Supporting Information for

Photoredox Ni-Catalyzed Peptide C(sp^2)–O Cross-Coupling: From Intermolecular Reactions to Side Chain-to-Tail Macrocyclization

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General considerations

All oxygen- and moisture-sensitive manipulations were carried out under an inert atmosphere (N_2 or Ar) using either standard Schlenk techniques or a glove box. Acetonitrile (MeCN) and dimethyl sulfoxide (DMSO) were purchased from Acros Organics and stored with 4 Å molecular sieves. Toluene was purchased from Acros Organics and used as received. *N*-Methyl-2-pyrrolidone (NMP), *N*,*N*-dimethylformamide (DMF), dichloromethane (DCM), diethyl ether (Et_2O) were purchased from Fisher Scientific and used without further purification. All other chemicals were purchased from commercial sources and used as received. Flash chromatography was performed using automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with either prepacked silica gel cartridge (RediSep Rf Gold® Normal Phase Silica high performance Flash columns) (eluent: (3:1 ethyl acetate:ethanol)/hexane) or C18 cartridge (RediSep Rf Gold® Reversed-phase C18) (eluent: MeCN/water, 0.1% TFA or 0.1% NH_4OH). Unless otherwise noted, final products were purified by preparative reverse-phase HPLC (column: SunFire® Prep C18 19 x 150 mm, 5 µm OBD™ for eluent of MeCN/water, 0.1% TFA and XBridge® Prep C18 19 x 150 mm, 5 µm OBD™ for eluent of MeCN/water, 0.1% NH_4OH).

All NMR spectra were recorded on a Bruker BioSpin spectrometer (500 MHz or 600 MHz for ^1H and 125 MHz or 151 MHz for ^{13}C) or a Bruker AVANCE III NMR spectrometer (600 MHz for ^1H and 151 MHz for ^{13}C) equipped with a 1.7 mm MicroCryoProbeTM TXI probe at 298 K. Deuterated solvents (DMSO-d_6, methanol-d_4) were purchased from Cambridge Isotope Labs. All NMR chemical shifts are reported in ppm relative to residual solvent for ^1H and ^{13}C NMR. Chemical shifts are reported in parts per million (ppm) in the scale relative to DMSO-d_6, 2.50 ppm for ^1H NMR and 39.52 for ^{13}C NMR; methanol-d_4, 3.31 ppm for ^1H NMR and 49.00 for ^{13}C NMR. Signals are quoted as singlet (s), doublet (d), triplet (t), quartet (q), quintet (quint), multiplet (m), and broad singlet (br s). Coupling constants are reported in Hz. The NMR yields were determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene (TMB) as an internal standard (the singlet corresponding to the three arene protons of TMB was used as a reference and corresponding product peaks that do not overlap with other peaks from starting materials or byproducts were integrated). All data were analyzed using MestReNova v11 (from Mestrelab Research S.L.). In some cases (e.g., the linear precursors for macrocyclization in methanol-d_4), exchangeable proton signals do not appear or integration of the corresponding peaks appears to be relatively small. In these cases, the integrations were reported if they appear and denoted with prime (‘). 2D NMR spectra (HSQC, HMBC, COSY) were included for cyclic products in addition to 1D NMR (^1H, ^{13}C).

The reactions were monitored by an Agilent Technologies UHPLC-LC/MS system (column: CORTECS® C18 2.1 x 50 mm, 2.7 µm, eluent: MeCN/water, 0.05% TFA). UV detection was carried out at 210 nm. For HRMS of final products, LC/MS analysis was performed on a Waters Acquity UPLC system, consisting of a binary pump, a sample manager, a TUV detector and a Waters

Synapt G1 Mass Spectrometer (Waters, Milford, MA) under positive ESI conditions. The output signal was monitored and processed using MassLynx software designed by Waters (Milford, MA). The separation was carried out on a Waters BEH C18 column (2.1 x 150 mm, 1.7 µm particle size). The mobile phase consisted of 10 mM ammonium formate adjusted to pH 9 with ammonium hydroxide in water (mobile phase A) and acetonitrile (mobile phase B). The injection volume was 2 µL. Analytes were eluted using a gradient method consisting of an initial hold at 5% mobile phase B for 0.5 min, followed by a linear gradient to 95% B over 12 min, then a hold at 95% B for 1.5 min. The flow rate was 0.5 mL/min, and the column temperature was set at 45 °C. UV detection was carried out at 215 nm. The eluent was introduced directly into the mass spectrometer by electrospray. Source temperature and desolvation temperature were set at 100 °C and 350 °C, respectively. Nitrogen was used as both cone gas (30 liters/h) and desolvation gas (600 liters/h), and argon was used as collision gas. The capillary and cone voltages were set to 1 KV and 20 V respectively. Leucine enkephalin was used as the lock mass (m/z of 556.2772) for accurate mass calibration and was introduced using the LockSpray interface at 100 µl/min at a concentration of 0.5 µM in 50% aqueous acetonitrile. In mass spectrometry scanning, data were acquired in centroid mode from m/z 100 to 1500.

Synthesis of substrates

General procedure A:

Peptides were prepared by Fmoc solid-phase peptide synthesis (SPPS) utilizing an automated peptide synthesizer (Symphony® X from Gyros Protein Technologies) as follows. A 45 mL peptide synthesis vessel was charged with resin (0.25-0.40 mmol scale). The resin was swelled in 1:1 DMF:DCM (12 mL) for 10 minutes, followed by washed with DMF (8 mL). Coupling was run at ambient temperature for 30 minutes using 2.75-5.20 equiv. of the Fmoc protected amino acids (0.20 M in DMF), 2.5-5.0 equiv. HATU (0.50 M in DMF), and 5.00-10.0 equiv. of NMM (1.0 M of *N*-methylmorpholine in DMF). Between each coupling and deprotection sequence, the resin was washed with 5 x 12.5 mL DMF for 50 seconds. Fmoc deprotection was carried out using 20% piperidine in DMF (3 x 10 mL) for 3 minutes each. After coupling of the last residue, the Fmoc group was deprotected by 3 x 10.0 mL 20% piperidine in DMF and the resin was washed with 5 x 12.5 mL DMF, followed by *N*-terminal capping with 5.0 equiv. capping reagents (0.1 M solution in NMP) and 10.0 equiv. *N*,*N*-diisopropylethylamine (DIPEA). Final washing was done with 5 x 12.5 mL DMF, followed by 3 x 12.5 mL DCM.

General procedure B:

Peptides were prepared by Fmoc solid-phase peptide synthesis utilizing an automated peptide synthesizer (Biotage® Initiator+ Alstra™) as follows. A 30 mL peptide synthesis vessel was charged with resin (0.50 mmol scale). The resin was swelled in 1:1 DMF:DCM (15 mL) for 10 minutes, followed by washed with DMF (10 mL). Coupling was run at 60 °C for 30 minutes using 5.0 equiv. of the Fmoc protected amino acids (0.50 M in DMF), 4.9 equiv. HATU (0.50 M in DMF), and 10.0 equiv. of DIPEA (4.0 M in NMP). Between each coupling and deprotection sequence, the resin was washed with 4 x 6 mL DMF for 45 seconds. Fmoc deprotection was carried out using 20% piperidine in DMF (2 x 9 mL), first for 3 minutes and second for 10 minutes. After coupling of the last sequence, Fmoc group was deprotected by 2 x 9 mL 20% piperidine in DMF and the resin was washed with 4 x 6 mL DMF, followed by *N*-terminal capping with 10.0 equiv. capping reagents (5 mL of 1.0 M solution in NMP) and 20.0 equiv. DIPEA (2.5 mL of 4.0 M solution in NMP). At the completion, the resin was washed with 4 x 10 mL DMF, followed by 3 x 10 mL DCM.

Resin used for SPPS and corresponding cleavage methods:

For the synthesis of substrates **1**, **2k**, **2l**, **2m**, **2n**, **5**, **6**, **11**, **13, 14**, **16**, and **18**, Rink Amide MBHA resin (100-200 mesh, Novabiochem®, 0.52 meq/g or 0.78 meq/g loading) was used. The resin was cleaved by a treatment with a solution of 95:2.5:2.5 trifluoroacetic acid (TFA):triisopropylsilane (TIS):water (10 mL/0.250 mmol) at room temperature for 3 hours.

For the synthesis of substrates **7**, **8**, **9**, **10** and **17** (protected peptide amides), Sieber amide resin (9-Fmoc-aminoxanthen-3-yloxy polystyrene resin, 100-200 mesh, ChemImpex, 0.60 meq/g loading) was used. The resin was cleaved by a treatment with 1% TFA in DCM (10 mL/0.250 mmol) at room temperature for 2 x 1 hour and neutralized with pyridine before concentration.

For the synthesis of substrate **12**, 2-chlorotrityl resin preloaded with L-Leu (H-Leu-2-ClTrt resin, ChemImpex, 0.662 meq/g) was used. The resin was cleaved by a treatment with 10% TFA in DCM (10 mL/0.250 mmol) at room temperature for 2 x 1 hour.

For the synthesis of substrate **15**, 2-chlorotrityl resin preloaded with L-Phe (H-Phe-2-ClTrt resin, ChemImpex, 0.74 meq/g) was used. The resin was cleaved by a treatment with 10% TFA in DCM (10 mL/0.250 mmol) at room temperature for 2 x 1 hour.

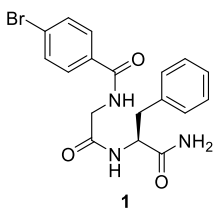
The cleaved solution was concentrated under reduced pressure and triturated with cold Et_2O. The crude material was then further purified by flash chromatography.

Amino acids and capping reagents used for SPPS:

Fmoc-protected amino acids: Fmoc-Phe-OH, Fmoc-Gly-OH, Fmoc-Leu-OH, Fmoc-Ala-OH, Fmoc-Pro-OH, Fmoc-D-Pro-OH, Fmoc-Ser(*t*Bu)-OH, Fmoc-Ser(Trt)-OH, Fmoc-D-Ser(*t*Bu)-OH, Fmoc-Thr(*t*Bu)-OH, Fmoc-Tyr(*t*Bu)-OH, Fmoc-Trp(Boc)-OH, Fmoc-Glu(*t*Bu)-OH, Fmoc-Gln(Trt)-OH, Fmoc-Lys(Boc)-OH, Fmoc-Met-OH.

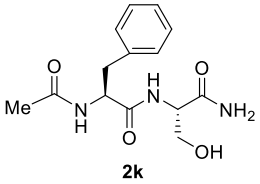
Capping reagents: 3-bromobenzoyl chloride, 4-bromobenzoyl chloride, acetic anhydride

Substrates in Table 2



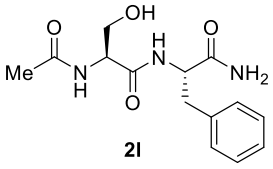
1

Using Rink Amide MBHA resin (8 x 0.25 mmol, 481 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 4-bromobenzoyl chloride (8 x 1.25 mmol, 0.1 M in NMP) and DIPEA (8 x 2.50 mmol). After cleavage and trituration with Et_2O, the crude material was precipitated in methanol and a white solid was isolated after filtration (**1**, 715 mg, 88%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.81 (t, *J* = 5.6 Hz, 1H), 8.08 (d, *J* = 8.3 Hz, 1H), 7.80 (d, *J* = 8.4 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.42 (s, 1H), 7.25 – 7.19 (m, 4H), 7.19 – 7.14 (m, 1H), 7.12 (s, 1H), 4.44 (td, *J* = 8.8, 4.6 Hz, 1H), 3.90 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.75 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.4 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.83, 168.56, 165.62, 137.97, 133.04, 131.32, 129.44, 129.13, 128.03, 126.22, 125.11, 53.78, 42.64, 37.47; MS (ESI+) 404.05 ($C_{18}H_{18}BrN_3O_3$, M+H$^+$).



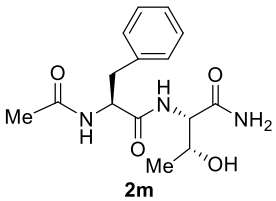
2k

Using Rink Amide MBHA resin (8 x 0.30 mmol, 577 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with acetic anhydride (8 x 1.50 mmol, 0.1 M in NMP) and DIPEA (8 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with C18 cartridge (eluent: MeCN/water, 0.1% TFA) to afford a white solid (**2k**, 497 mg, 71%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.12 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 7.9 Hz, 1H), 7.29 – 7.22 (m, 4H), 7.21 – 7.13 (m, 1H), 7.09 (d, *J* = 3.1 Hz, 2H), 4.87 (br s, 1H), 4.53 (ddd, *J* = 9.9, 8.5, 4.4 Hz, 1H), 4.18 (dt, *J* = 7.9, 5.3 Hz, 1H), 3.61 (dd, *J* = 10.7, 5.5 Hz, 1H), 3.55 (dd, *J* = 10.7, 5.0 Hz, 1H), 3.03 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.73 (dd, *J* = 13.8, 10.1 Hz, 1H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 171.82, 171.30, 169.26, 138.06, 129.15, 128.00, 126.19, 61.62, 55.03, 54.07, 37.42, 22.46; MS (ESI+) 294.14 ($C_{14}H_{19}N_3O_4$, M+H$^+$).



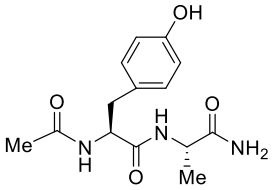
2l

Using Rink Amide MBHA resin (4 x 0.25 mmol, 481 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with acetic anhydride (4 x 1.25 mmol, 0.1 M in NMP) and DIPEA (4 x 2.50 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with C18 cartridge (eluent: MeCN/water, 0.1% TFA) to afford a white solid (**2l**, 165 mg, 45%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 7.97 (d, *J* = 8.3 Hz, 1H), 7.91 (d, *J* = 7.6 Hz, 1H), 7.35 (s, 1H), 7.27 – 7.15 (m, 6H), 4.39 (td, *J* = 9.1, 4.4 Hz, 1H), 4.23 (q, *J* = 6.3 Hz, 1H), 3.53 – 3.41 (m, 2H), 3.07 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.82 (dd, *J* = 13.9, 9.4 Hz, 1H), 1.83 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.89, 170.10, 169.57, 138.03, 129.13, 128.06, 126.24, 61.74, 55.10, 53.90, 36.98, 22.55; MS (ESI+) 294.14 ($C_{14}H_{19}N_3O_4$, M+H$^+$).



2m

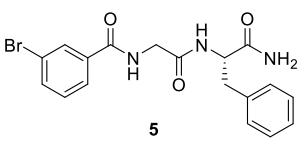
Using Rink Amide MBHA resin (12 x 0.30 mmol, 385 mg each, 0.78 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with acetic anhydride (12 x 1.50 mmol, 0.1 M in NMP) and DIPEA (12 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with C18 cartridge (eluent: MeCN/water, 0.1% TFA) to afford a white solid (**2m**, 667 mg, 60 %). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.18 (d, *J* = 7.8 Hz, 1H), 7.69 (d, *J* = 8.2 Hz, 1H), 7.36 – 7.22 (m, 4H), 7.22 – 7.15 (m, 1H), 7.09 (s, 1H), 7.01 (s, 1H), 4.89 (br s, 1H), 4.64 – 4.50 (m, 1H), 4.14 – 3.98 (m, 2H), 3.03 (dd, *J* = 13.7, 3.7 Hz, 1H), 2.81 – 2.70 (m, 1H), 1.76 (s, 3H), 1.01 (d, *J* = 5.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.14, 171.58, 169.43, 138.12, 129.18, 128.06, 126.25, 66.26, 58.05, 54.20, 37.03, 22.43, 20.10; MS (ESI+) 308.15 ($C_{15}H_{21}N_3O_4$, M+H$^+$).



2n

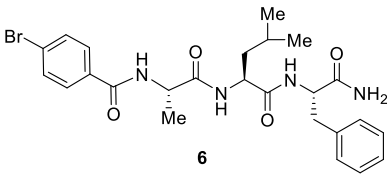
Using Rink Amide MBHA resin (4 x 0.30 mmol, 577 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with acetic anhydride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with C18 cartridge (eluent: MeCN/water, 0.1% TFA) to afford a white solid (**2n**, 341 mg, 97%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 7.97 (dd, *J* = 16.5, 7.8 Hz, 2H), 7.14 (s, 1H), 7.06 – 6.83 (m, 3H), 6.59 (d, *J* = 8.3 Hz, 2H), 4.35 (td, *J* = 9.4, 4.4 Hz, 1H), 4.14 (p, *J* = 7.1 Hz, 1H), 2.85 (dd, *J* = 13.9, 4.1 Hz, 1H), 2.56 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.72 (s, 3H), 1.17 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 174.03, 171.07, 169.20, 155.69, 130.02, 128.06, 114.82, 54.34, 47.98, 36.64, 22.49, 18.32; MS (ESI+) 294.14 ($C_{14}H_{19}N_3O_4$, M+H$^+$).

Substrates in Table 3



5

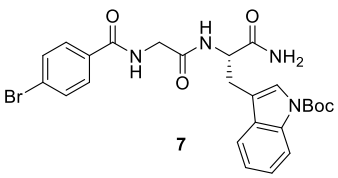
Using Rink Amide MBHA resin (4 x 0.30 mmol, 577 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was precipitated in methanol and a white solid was isolated after filtration (**5**, 212 mg, 44%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.86 (t, *J* = 5.8 Hz, 1H), 8.09 (d, *J* = 8.4 Hz, 1H), 8.04 (s, 1H), 7.85 (d, *J* = 7.8 Hz, 1H), 7.75 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 7.9 Hz, 1H), 7.41 (s, 1H), 7.27 – 7.19 (m, 4H), 7.19 – 7.15 (m, 1H), 7.12 (s, 1H), 4.44 (td, *J* = 8.8, 4.6 Hz, 1H), 3.90 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.76 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.89, 168.57, 165.14, 137.99, 136.12, 134.13, 130.63, 130.09, 129.16, 128.07, 126.47, 126.26, 121.66, 53.84, 42.73, 37.46; MS (ESI+) 404.05 ($C_{18}H_{18}BrN_3O_3$, M+H$^+$).



6

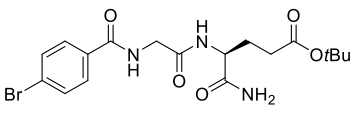
Using Rink Amide MBHA resin (2 x 0.50 mmol, 962 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure B. N-Terminus was capped with 4-bromobenzoyl chloride (2 x 5.0 mmol, 1.0 M in NMP) and DIPEA (2 x 10.0 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with C18 cartridge (eluent: MeCN/water, 0.1% TFA) to afford a white solid (**6**, 254 mg, 48%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (d, *J* = 7.0 Hz, 1H), 7.99 (d, *J* = 7.9 Hz, 1H), 7.83 (d, *J* = 8.6 Hz, 2H), 7.72 (d, *J* = 8.2 Hz, 1H), 7.68 (d, *J* = 8.5 Hz, 2H), 7.31 (s, 1H), 7.22 (d, *J* = 6.9 Hz, 2H), 7.17 (d, *J* = 7.3 Hz, 3H), 7.09 (s, 1H), 4.41 (qd, *J* = 8.6, 7.9, 4.3 Hz, 2H), 4.25 – 4.13 (m, 1H), 3.02 (dd, *J* = 13.9, 5.1 Hz, 1H), 2.82 (dd, *J* = 13.8, 8.9 Hz, 1H), 1.53 (dt, *J* = 13.0, 6.6 Hz, 1H), 1.44 –

1.34 (m, 2H), 1.30 (d, *J* = 7.2 Hz, 3H), 0.84 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.65, 172.37, 171.54, 165.42, 137.71, 133.11, 131.23, 129.69, 129.13, 128.01, 126.22, 125.10, 53.42, 51.51, 49.25, 37.48, 24.10, 22.94, 21.67, 17.55; MS (ESI+) 531.15 ($C_{25}H_{31}BrN_4O_4$, M+H$^+$).



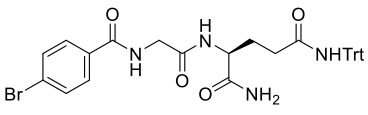
7

Using Sieber amide resin (4 x 0.30 mmol, 500 mg each, 0.6 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 4-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was precipitated in Et_2O and a white solid was isolated after filtration (**7**, 360 mg, 55%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.79 (t, *J* = 5.6 Hz, 1H), 8.21 (d, *J* = 8.2 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.79 (d, *J* = 8.4 Hz, 2H), 7.68 (t, *J* = 6.8 Hz, 3H), 7.51 (s, 2H), 7.31 (t, *J* = 7.6 Hz, 1H), 7.23 (t, *J* = 7.4 Hz, 1H), 7.20 (s, 1H), 4.55 (td, *J* = 8.5, 5.2 Hz, 1H), 3.93 (dd, *J* = 16.3, 5.8 Hz, 1H), 3.80 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.14 (dd, *J* = 14.7, 4.5 Hz, 1H), 2.95 (dd, *J* = 14.7, 8.9 Hz, 1H), 1.61 (s, 9H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.93, 168.76, 165.66, 149.07, 134.62, 133.10, 131.32, 130.36, 129.45, 125.11, 124.27, 123.85, 122.47, 119.38, 116.71, 114.63, 83.51, 52.40, 42.68, 27.72, 27.23; MS (ESI+) 543.12 ($C_{25}H_{27}BrN_4O_5$, M+H$^+$).



8

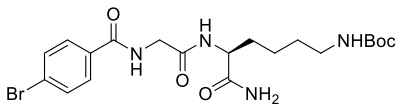
Using Sieber amide resin (4 x 0.30 mmol, 500 mg each, 0.6 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 4-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**8**, 139 mg, 26%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.86 (t, *J* = 5.7 Hz, 1H), 8.05 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 1H), 7.11 (s, 1H), 4.21 (td, *J* = 8.5, 5.0 Hz, 1H), 3.91 (dd, *J* = 5.6, 3.3 Hz, 2H), 2.31 – 2.14 (m, 2H), 2.03 – 1.84 (m, 1H), 1.84 – 1.63 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 173.08, 171.73, 168.83, 165.78, 133.12, 131.36, 129.47, 125.15, 79.72, 51.62, 42.79, 31.35, 27.77, 27.25; MS (ESI+) 464.08 ($C_{18}H_{24}BrN_3O_5$, M+Na$^+$).



9

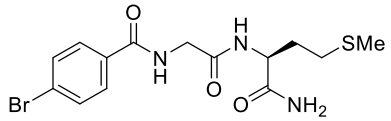
Using Sieber amide resin (4 x 0.30 mmol, 500 mg each, 0.6 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 4-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was precipitated in methanol and a white solid was isolated after filtration (**9**, 393 mg, 52%). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.85 (t, *J* = 5.2 Hz, 1H), 8.59 (s, 1H), 8.06 (d, *J* = 8.0 Hz, 1H), 7.81 (d, *J* = 8.1 Hz, 2H), 7.68 (d, *J* = 8.2 Hz, 2H), 7.35 – 7.22 (m, 7H), 7.22 – 7.13 (m, 9H), 7.09 (s, 1H), 4.32 – 4.09 (m, 1H), 3.92 (d, *J* = 5.2 Hz, 2H), 2.40 – 2.24 (m,

2H), 1.97 – 1.83 (m, 1H), 1.79 – 1.61 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.36, 171.57, 168.82, 165.85, 144.93, 133.13, 131.37, 129.49, 128.55, 127.50, 126.35, 125.18, 69.23, 52.22, 42.89, 32.72, 28.02; MS (ESI+) 649.14 ($C_{33}H_{31}BrN_4O_4$, M+Na$^+$).



10

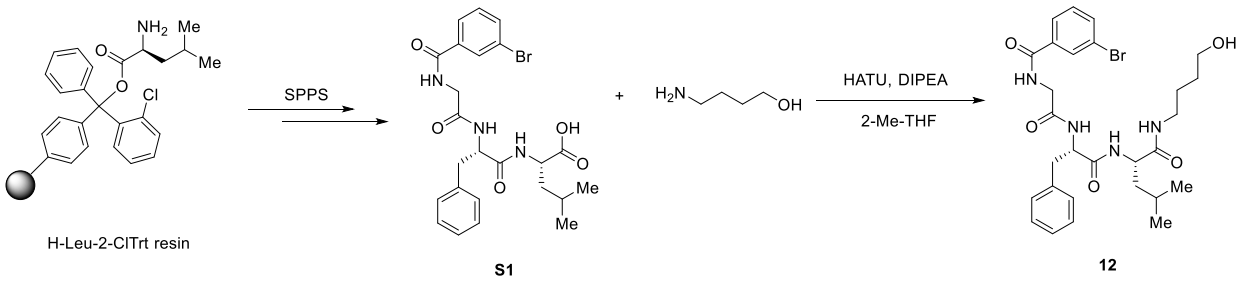
Using Sieber amide resin (2 x 0.30 mmol, 500 mg each, 0.6 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 4-bromobenzoyl chloride (2 x 1.50 mmol, 0.1 M in NMP) and DIPEA (2 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane), followed by precipitation in Et_2O to afford a white solid (**10**, 253 mg, 87%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.85 (t, *J* = 5.7 Hz, 1H), 8.00 (d, *J* = 8.1 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.69 (d, *J* = 8.4 Hz, 2H), 7.33 (s, 1H), 7.04 (s, 1H), 6.75 (t, *J* = 5.1 Hz, 1H), 4.17 (td, *J* = 8.4, 4.7 Hz, 1H), 3.98 – 3.83 (m, 2H), 2.87 (q, *J* = 6.5 Hz, 2H), 1.73 – 1.61 (m, 1H), 1.56 – 1.45 (m, 1H), 1.44 – 1.29 (m, 11H), 1.29 – 1.15 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.64, 168.68, 165.72, 155.57, 133.13, 131.35, 129.47, 125.13, 77.36, 52.37, 42.72, 39.80, 31.66, 29.26, 28.30, 22.74; MS (ESI+) 507.12 ($C_{20}H_{29}BrN_4O_5$, M+Na$^+$).



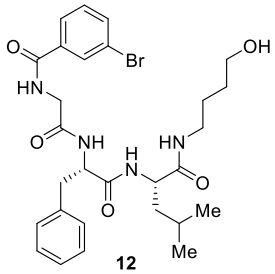
11

Using Rink Amide MBHA resin (2 x 0.40 mmol, 770 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 4-bromobenzoyl chloride (2 x 2.0 mmol, 1.0 M in NMP) and DIPEA (2 x 4.0 mmol). After cleavage and trituration with Et_2O, the crude material was precipitated in methanol and a white solid was isolated after filtration (**11**, 124 mg, 40%). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.86 (t, *J* = 5.7 Hz, 1H), 8.09 (d, *J* = 8.2 Hz, 1H), 7.82 (d, *J* = 8.5 Hz, 2H), 7.70 (d, *J* = 8.5 Hz, 2H), 7.33 (s, 1H), 7.11 (s, 1H), 4.29 (td, *J* = 8.7, 4.5 Hz, 1H), 4.00 – 3.83 (m, 2H), 2.48 – 2.33 (m, 2H), 2.03 (s, 3H), 2.00 – 1.90 (m, 1H), 1.84 – 1.68 (m, 1H); ^{13}C NMR (125 MHz, DMSO): δ 173.12, 168.85, 165.73, 133.08, 131.33, 129.45, 125.11, 51.62, 42.80, 31.59, 29.67, 14.61; MS (ESI+) 388.04 ($C_{14}H_{18}BrN_3O_3S$, M+H$^+$).

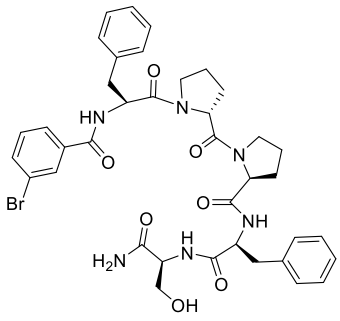
Substrates in Figure 3



Scheme S1. Synthesis of 4-aminobutan-1-ol C-terminally modified precursor **12** for macrocyclization.

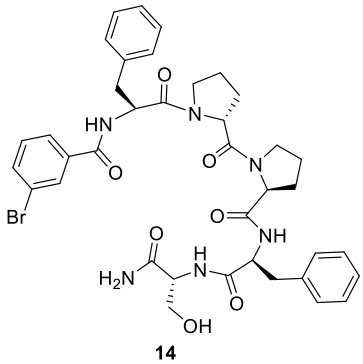


Using 2-chlorotrityl resin preloaded with L-Leu (6 x 0.30 mmol, 453 mg each, 0.662 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (6 x 1.50 mmol, 0.1 M in NMP) and DIPEA (6 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material **S1** was directly used without further purification in the next step. To a 40 mL vial (28 x 95mm, 24-414 Thread, with Red Pressure Relief Cap, CG-4912-06), **S1** (476.5 mg, 0.919 mmol) and HATU (349 mg, 0.919 mmol) were added, followed by 2-Me-THF (15 mL). DIPEA (0.321 mL 1.838 mmol) and 4-aminobutan-1-ol (0.093 ml, 1.011 mmol) were subsequently added to the vial and the reaction mixture was stirred at room temperature for 20 hours. The reaction mixture was concentrated under reduced pressure, and the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**12**, 329 mg, overall 31%). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.95' (t, *J* = 5.2 Hz, 0.05H), 8.64' (d, *J* = 3.6 Hz, 0.1H), 8.33' (d, *J* = 8.3 Hz, 0.1H), 8.17' (d, *J* = 6.7 Hz, 0.3H), 7.95 (s, 1H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.66 (d, *J* = 7.9 Hz, 1H), 7.46 (t, *J* = 5.4 Hz, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.23 – 7.07 (m, 5H), 4.56 (dd, *J* = 8.4, 5.0 Hz, 1H), 4.38 – 4.24 (m, 1H), 3.99 (d, *J* = 16.1 Hz, 1H), 3.84 (d, *J* = 16.1 Hz, 1H), 3.45 (s, 2H), 3.31 (s, 1H), 3.21 – 3.06 (m, 2H), 3.06 – 2.90 (m, 2H), 1.75 – 1.63 (m, 1H), 1.63 – 1.48 (m, 2H), 1.47 – 1.35 (m, 4H), 0.89 (d, *J* = 6.2 Hz, 3H), 0.85 (d, *J* = 6.1 Hz, 3H); ^{13}C NMR (125 MHz, methanol-d_4): δ 174.37, 173.37, 172.47, 168.84, 137.92, 136.54, 135.90, 131.70, 131.40, 130.14, 129.54, 127.88, 127.16, 123.48, 62.45, 56.55, 53.53, 44.67, 41.49, 40.20, 37.86, 30.72, 26.57, 25.72, 23.57, 21.74; MS (ESI+) 589.19 ($C_{28}H_{37}BrN_4O_5$, M+H$^+$).



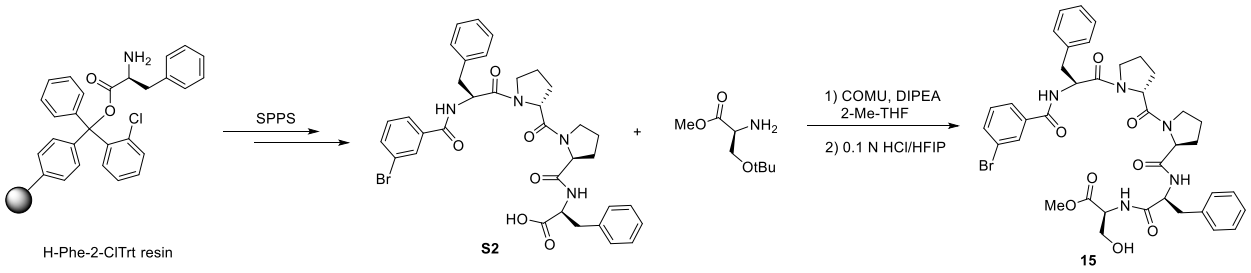
13

Using Rink Amide MBHA resin (6 x 0.30 mmol, 577 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (6 x 1.50 mmol, 0.1 M in NMP) and DIPEA (6 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**13**, 883 mg, 60%). ^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.65 (d, *J* = 7.8 Hz, 1H), 7.90 (s, 1H), 7.74 – 7.63 (m, 3H), 7.61 (d, *J* = 7.2 Hz, 1H), 7.36 (d, *J* = 7.2 Hz, 2H), 7.34 – 7.22 (m, 8H), 7.22 – 7.16 (m, 2H), 5.14 (q, *J* = 7.6 Hz, 1H), 4.45 (t, *J* = 7.3 Hz, 1H), 4.42 – 4.34 (m, 1H), 4.27 (dd, *J* = 8.7, 3.4 Hz, 1H), 4.15 – 4.07 (m, 1H), 3.94 (td, *J* = 9.8, 3.8 Hz, 1H), 3.86 (d, *J* = 4.5 Hz, 2H), 3.66 (q, *J* = 7.9 Hz, 1H), 3.60 (q, *J* = 8.7 Hz, 1H), 3.43 – 3.36 (m, 1H), 3.29 – 3.22 (m, 1H), 3.14 – 2.98 (m, 3H), 2.15 – 1.96 (m, 3H), 1.88 – 1.74 (m, 2H), 1.74 – 1.65 (m, 1H), 1.65 – 1.56 (m, 1H), 1.45 – 1.31 (m, 1H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.65, 174.59, 174.53, 173.30, 172.19, 167.65, 139.28, 138.17, 136.79, 135.77, 131.68, 131.37, 130.52, 130.16, 129.52, 129.50, 127.99, 127.82, 127.47, 123.39, 63.07, 62.61, 59.90, 57.70, 57.29, 57.19, 54.64, 49.85, 38.99, 37.05, 30.24, 29.37, 26.41, 24.85; MS (ESI+) 775.24 ($C_{38}H_{43}BrN_6O_7$, M+H$^+$).

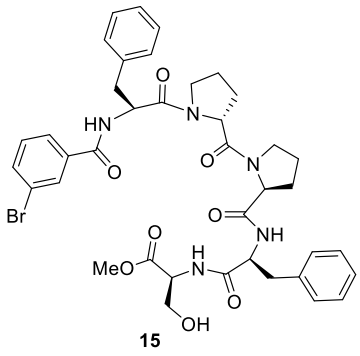


14

Using Rink Amide MBHA resin (4 x 0.30 mmol, 577 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**14**, 205 mg, 22%). ^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.68' (d, *J* = 9.0 Hz, 0.5H), 8.02 (s, 1H), 7.91' (d, *J* = 8.1 Hz, 0.8H), 7.76 (d, *J* = 7.8 Hz, 1H), 7.72' (d, *J* = 7.1 Hz, 0.7H), 7.66 (d, *J* = 8.0 Hz, 1H), 7.43 – 7.29 (m, 7H), 7.27 – 7.15 (m, 4H), 5.32 – 5.22 (m, 1H), 4.60 (t, *J* = 7.7 Hz, 1H), 4.50 (ddd, *J* = 11.0, 8.1, 5.3 Hz, 1H), 4.38 (dd, *J* = 8.7, 2.5 Hz, 1H), 4.25 – 4.17 (m, 1H), 4.04 (dd, *J* = 11.9, 3.4 Hz, 1H), 3.99 – 3.91 (m, 1H), 3.87 (dd, *J* = 12.0, 3.6 Hz, 1H), 3.69 – 3.57 (m, 2H), 3.52 – 3.43 (m, 1H), 3.40 (dd, *J* = 13.6, 6.2 Hz, 1H), 3.35 – 3.27 (m, 2H), 3.27 – 3.17 (m, 1H), 2.29 – 2.15 (m, 1H), 2.14 – 1.98 (m, 2H), 1.94 – 1.77 (m, 3H), 1.77 – 1.66 (m, 1H), 1.41 – 1.25 (m, 1H).; ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.62, 174.08, 174.00, 173.70, 171.81, 167.90, 139.17, 138.96, 137.31, 135.58, 131.72, 131.27, 130.74, 130.19, 129.54, 129.19, 127.85, 127.60, 127.48, 123.31, 63.38, 62.34, 60.60, 57.33, 57.24, 56.49, 54.49, 48.90, 38.55, 37.25, 30.34, 29.48, 26.60, 24.64; MS (ESI+) 775.24 ($C_{38}H_{43}BrN_6O_7$, M+H$^+$).

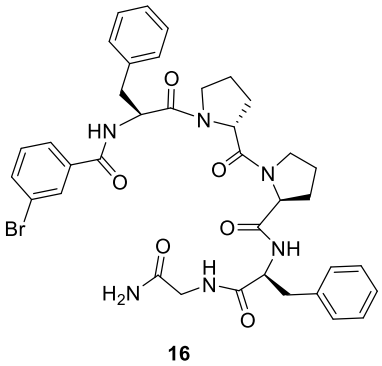


Scheme S2. Synthesis of substrate **15** containing methyl ester motif.



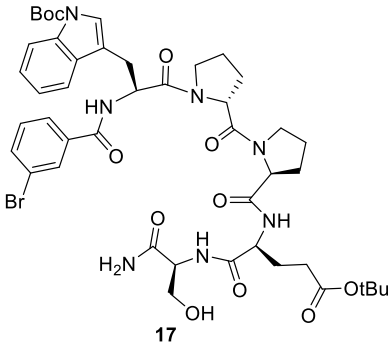
Using 2-chlorotrityl resin preloaded with L-Phe (4 x 0.30 mmol, 405 mg each, 0.74 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material **S2** was directly used without further purification in the next step. To a 40 mL vial (28 x 95mm, 24-414 Thread, with Red Pressure Relief Cap, CG-4912-06), **S2** (487.6 mg, 0.707 mmol) and COMU ((1-Cyano-2-ethoxy-2-oxoethylidenaminooxy)dimethylamino-morpholino-carbenium hexafluorophosphate) (303 mg, 0.707 mmol) were added, followed by 2-Me-THF (12 mL). DIPEA (0.494 mL 2.83 mmol) and O-*tert*-butyl-L-serine methyl ester hydrochloride (165 mg, 0.778 mmol) were subsequently added to the vial and the reaction mixture was stirred at room temperature for 14 hours. At the completion of the reaction, the reaction mixture was diluted in ethyl acetate (15 mL) and washed with water, followed by brine to remove excess O-*tert*-butyl-L-serine methyl ester. The organic layers were dried over sodium sulfate and concentrated. The crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid. This material was then resubjected to a 15 mL of 0.1 N HCl solution in HFIP and the reaction mixture was stirred at room temperature for 1 hour. At the completion of the deprotection, the reaction mixture was concentrated under reduced pressure, and the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**15**, 206 mg, two steps 37%). ^{1}H NMR (500 MHz, methanol-d_4): δ 7.93 (s, 1H), 7.75 (dt, *J* = 7.8, 1.3 Hz, 1H), 7.68 (ddd, *J* = 8.0, 1.9, 0.9 Hz, 1H), 7.41 (d, *J* = 7.1 Hz, 2H), 7.38 – 7.27 (m, 7H), 7.26 – 7.21 (m, 2H), 5.28 (t, *J* = 7.5 Hz, 1H), 4.67 (dd, *J* = 11.5, 4.7 Hz, 1H), 4.55 (t, *J* = 7.3 Hz, 1H), 4.36 (dd, *J* = 8.7, 2.7 Hz, 1H), 4.18 (t, *J* = 3.9 Hz, 1H), 3.96 (td, *J* = 9.3, 3.2 Hz, 1H), 3.84 – 3.71 (m, 2H), 3.64 (s, 3H), 3.68 – 3.52 (m, 3H), 3.28 (d, *J* = 7.2 Hz, 1H), 3.24 – 3.09 (m, 3H), 2.20 – 1.96 (m, 3H), 1.93 – 1.74 (m, 3H), 1.70 – 1.63 (m, 1H), 1.27 – 1.22

(m, 1H); ^{13}C NMR (125 MHz, methanol-d_4): δ 174.35, 173.39, 173.31, 171.75, 171.71, 167.97, 139.37, 138.44, 137.28, 135.73, 131.76, 131.28, 130.64, 130.38, 129.54, 129.47, 127.91, 127.76, 127.62, 123.34, 62.96, 62.35, 59.85, 56.52, 55.75, 54.25, 52.72, 49.51, 48.83, 39.16, 37.78, 30.32, 29.38, 26.49, 24.53; MS (ESI+) 790.24 ($C_{39}H_{44}BrN_5O_8$, M+H$^+$).



16

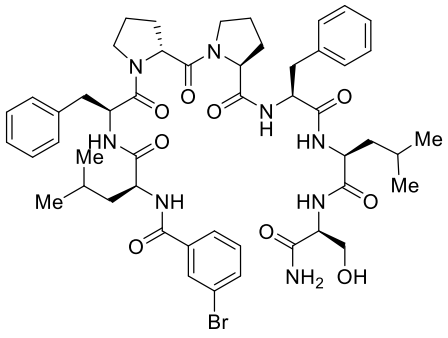
Using Rink Amide MBHA resin (2 x 0.40 mmol, 770 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (2 x 2.00 mmol, 0.1 M in NMP) and DIPEA (2 x 4.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**16**, 555 mg, 93%). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.69' (d, *J* = 7.9 Hz, 0.7H), 7.95' (t, *J* = 1.7 Hz, 1H), 7.89' (d, *J* = 7.2 Hz, 0.7H), 7.86' (t, *J* = 6.0 Hz, 0.7H), 7.78 (d, *J* = 7.8 Hz, 1H), 7.65 (d, *J* = 8.0 Hz, 1H), 7.42 (d, *J* = 7.2 Hz, 2H), 7.37 – 7.27 (m, 7H), 7.26 – 7.20 (m, 2H), 5.25 – 5.16 (m, 1H), 4.52 – 4.42 (m, 2H), 4.32 (dd, *J* = 8.6, 2.8 Hz, 1H), 3.89 (td, *J* = 9.7, 3.3 Hz, 1H), 3.70 – 3.63 (m, 3H), 3.56 (q, *J* = 9.2 Hz, 1H), 3.48 – 3.41 (m, 1H), 3.31 – 3.26 (m, 1H), 3.25 – 3.13 (m, 3H), 2.11 (dq, *J* = 12.1, 6.9 Hz, 1H), 2.07 – 1.96 (m, 2H), 1.88 – 1.80 (m, 1H), 1.79 – 1.65 (m, 3H), 1.32 – 1.25 (m, 1H); ^{13}C NMR (125 MHz, methanol-d_4): δ 174.31, 174.08, 174.01, 173.58, 171.70, 167.71, 139.26, 138.34, 137.03, 135.68, 131.73, 131.33, 130.57, 130.24, 129.52, 129.44, 127.88, 127.84, 127.46, 123.35, 62.21, 59.90, 57.25, 57.15, 54.46, 43.29, 38.89, 37.45, 37.41, 30.26, 29.25, 26.35, 24.65; MS (ESI+) 745.23 ($C_{37}H_{41}BrN_6O_6$, M+H$^+$).



17

Using Sieber amide resin (4 x 0.30 mmol, 500 mg each, 0.6 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (4 x 1.50 mmol, 0.1 M in NMP) and DIPEA (4 x 3.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**17**, 171 mg, 15%). ^{1}H NMR (500 MHz, methanol-d_4): δ 8.61' (d, *J* = 8.0 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 7.93 (t, *J* = 1.7 Hz, 1H), 7.84' (d, *J* = 7.4 Hz, 1H), 7.72 (d, *J* = 7.9 Hz, 1H), 7.67 (d, *J* = 7.0 Hz, 2H), 7.65' (s, 1H), 7.57 (s, 1H), 7.35 (t, *J* = 7.9 Hz, 1H), 7.31 (t, *J* = 8.4 Hz, 1H), 7.26 (t, *J* = 7.5 Hz, 1H), 5.21 (q, *J* = 7.6 Hz, 1H), 4.39 (dd, *J* = 8.4, 3.9 Hz, 1H), 4.34 (t, *J* = 7.2 Hz, 1H), 4.22 – 4.15 (m, 1H), 4.11 – 4.02 (m, 2H), 3.89 – 3.80 (m, 2H), 3.72 – 3.63 (m, 2H), 3.47 – 3.40 (m, 1H), 3.36 – 3.31 (m, 1H), 3.19 (dd, *J* = 14.3, 7.4 Hz, 1H), 2.50 – 2.40 (m, 1H), 2.40 – 2.32 (m, 1H), 2.32 – 2.26 (m, 1H), 2.12 – 1.94 (m, 7H), 1.87 – 1.78 (m, 1H), 1.64 (s,

9H), 1.62 – 1.58 (m, 1H), 1.43 (s, 9H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 175.11, 175.03, 174.68, 174.38, 174.12, 173.68, 172.18, 167.78, 150.83, 136.75, 136.68, 135.88, 131.68, 131.65, 131.43, 127.51, 125.64, 125.50, 123.71, 123.41, 120.07, 117.14, 116.22, 84.96, 82.09, 63.04, 62.94, 60.13, 57.62, 55.01, 53.45, 53.35, 33.00, 30.52, 29.34, 28.43, 28.41, 28.37, 26.99, 26.94, 26.26, 25.52; MS (ESI+) 952.28 ($C_{45}H_{58}BrN_7O_{11}$, M+H$^+$).



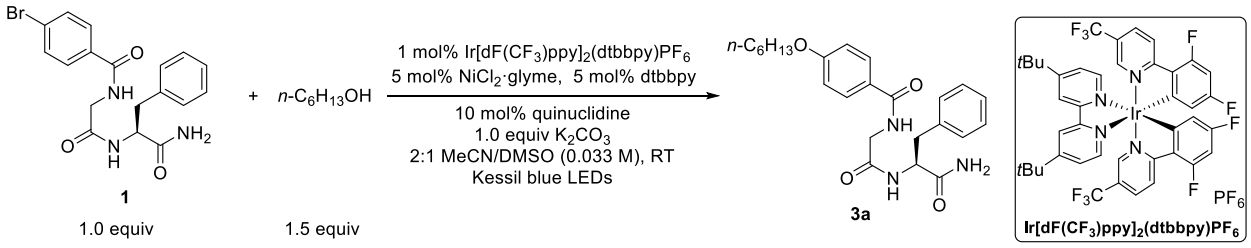
18

Using Rink Amide MBHA resin (2 x 0.40 mmol, 770 mg each, 0.52 meq/g), peptide synthesis was carried out following general procedure A. N-Terminus was capped with 3-bromobenzoyl chloride (2 x 2.00 mmol, 0.1 M in NMP) and DIPEA (2 x 4.00 mmol). After cleavage and trituration with Et_2O, the crude material was purified by automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane) to afford a white solid (**18**, 437 mg, 55%). ^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.57 (d, *J* = 9.0 Hz, 1H), 8.49 (d, *J* = 8.4 Hz, 1H), 8.35 (d, *J* = 7.4 Hz, 1H), 8.07 (d, *J* = 7.7 Hz, 1H), 8.03 (t, *J* = 1.7 Hz, 1H), 7.90 – 7.83 (m, 2H), 7.69 (d, *J* = 8.7 Hz, 1H), 7.45 (d, *J* = 7.2 Hz, 2H), 7.39 (dt, *J* = 16.3, 7.9 Hz, 1H), 7.36 – 7.15 (m, 10H), 5.20 – 5.11 (m, 1H), 4.95 (td, *J* = 8.9, 5.5 Hz, 1H), 4.72 – 4.63 (m, 1H), 4.56 (q, *J* = 5.7 Hz, 2H), 4.48 – 4.39 (m, 2H), 3.86 – 3.73 (m, 3H), 3.71 – 3.61 (m, 1H), 3.57 – 3.49 (m, 2H), 3.29 (d, *J* = 4.5 Hz, 1H), 3.22 (dd, *J* = 13.4, 8.1 Hz, 1H), 3.03 (dd, *J* = 13.4, 6.2 Hz, 1H), 2.22 – 2.09 (m, 2H), 2.02 – 1.82 (m, 3H), 1.81 – 1.60 (m, 9H), 0.98 (t, *J* = 6.2 Hz, 6H), 0.92 (t, *J* = 6.0 Hz, 6H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.82, 174.71, 174.31, 174.07, 174.00, 173.59, 171.19, 168.39, 139.29, 138.20, 137.43, 135.62, 131.75, 131.38, 130.59, 130.42, 129.50, 129.47, 127.81, 127.77, 127.64, 123.38, 63.03, 61.96, 59.65, 56.79, 54.03, 53.80, 53.54, 48.34, 41.87, 41.53, 39.36, 38.37, 30.28, 29.20, 26.29, 26.21, 25.97, 24.39, 23.59, 23.28, 22.70, 22.33; MS (ESI+) 1001.41 ($C_{50}H_{65}BrN_8O_9$, M+H$^+$).

Reaction optimization by batch reactions

In addition to the multi-parameter reaction condition optimization using nanomole-scale high-throughput experimentation, we initially optimized the reaction of coupling of **1** and *n*-hexanol by batches. Selected examples are shown in Table S1. The reaction was run on a 0.1 mmol scale of **1** in an 8 mL vial (2 Dram, 17 x 60mm, 15-425 Thread, with Red Pressure Relief Cap, CG-4912-02) using Kessil® lamp (H150-BLUE) as a blue LED source (2 reactions/lamp, irradiated from 6.5 cm away) with a fan.

Table S1. Reaction time, temperature, base screen.



	variations	time (h)	yield (%)[a]
	conditions above	14	25
	conditions above	**24**	**79**
	30 °C	24	25[b]
Base	DBU	14	0
	K_2HPO_4	24	4
	TMG	24	1
	BTMG	24	0
	MTBD	24	0[c]
	P2Et	24	0
	P1-*t*-Oct	24	0
	1.5 equiv K_2CO_3	24	39

[a]Yields were determined by ^{1}H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard. [b]Major protodebrominated starting material was observed. [c]Ar-Ar major side product was formed.

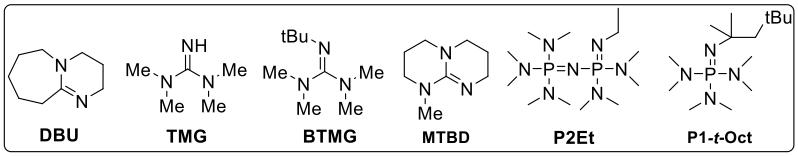
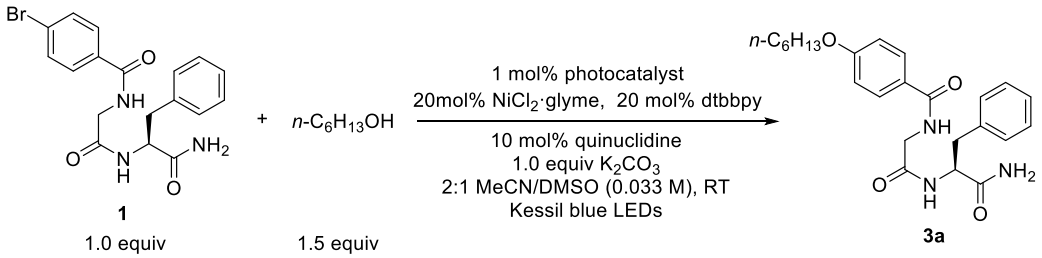
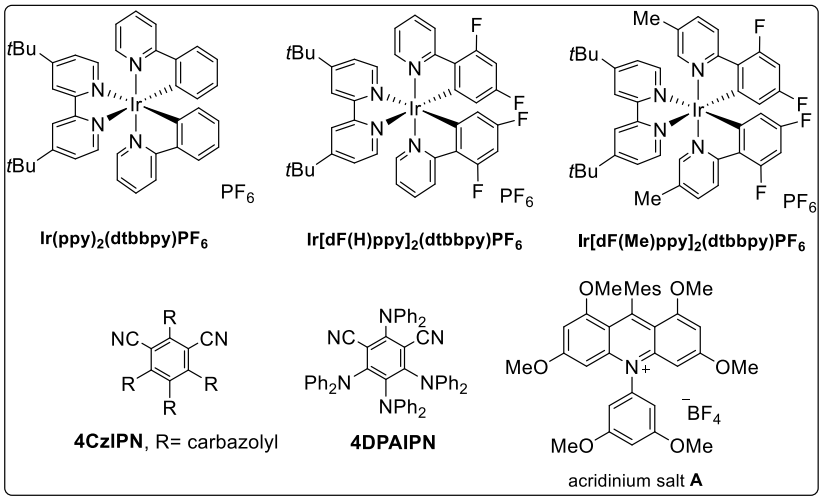


Table S2. Photocatalyst screen.



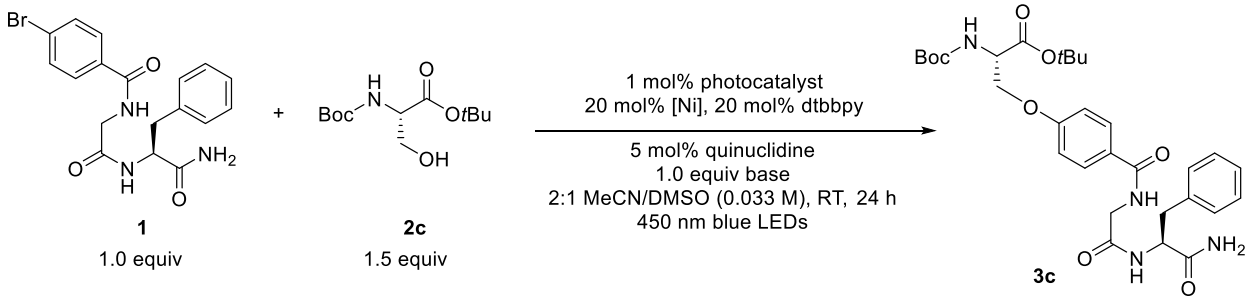
photocatalyst	time (h)	yield (%)[a]
$Ir(ppy)_2(dtbbpy)PF_6$	24	0
$Ir[dF(H)ppy]_2(dtbbpy)PF_6$	24	46
$Ir[dF(Me)ppy]_2(dtbbpy)PF_6$	24	37
4CzIPN	24	9
4DPAIPN	24	57
acridinium salt **A**	24	0

[a]Yields were determined by ^1H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard.



Further optimization in coupling reactions of **1** and **2c** was explored. The reaction was run on a 0.1 mmol scale of **1** in an 8 mL vial (2 Dram, 17 x 60mm, 15-425 Thread, with Red Pressure Relief Cap, CG-4912-02) using either MSD photoreactor or Penn Optical photoreactor (m1) (at 450 nm, 100% light intensity, fan speed of 5200–5500 rpm, 1000 rpm stirring speed).

Table S3. Photocatalyst, nickel source, base screen.



photocatalyst	[Ni]	base	yield (%)[a]
$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	$NiCl_2$·glyme	K_2CO_3	25[b]
$Ir[dF(H)ppy]_2(dtbbpy)PF_6$	$NiCl_2$·glyme	K_2CO_3	13[b]
4DPAIPN	$NiCl_2$·glyme	K_2CO_3	61[b]
$Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$	$NiBr_2$·glyme	K_2CO_3	61
4DPAIPN	**$NiBr_2$·glyme**	**K_2CO_3**	**81**
4DPAIPN	$NiBr_2$·glyme	Li_2CO_3	0
4DPAIPN	$NiBr_2$·glyme	2 equiv K_2CO_3	42

[a]Yields were determined by ^{1}H NMR spectroscopy against 1,3,5-trimethoxybenzene as an internal standard. [b]ArCl side product was observed.

Nanomole-scale HTE optimization

Reaction experimental design was accomplished using Freeslate Library Studio® 8.4. Advantage™ 384-well collection plates (Analytical-Sales, Cat. No. 38120, polypropylene, square well, 120 µL, clear) were used as source plates for stock solutions and analytical plates. The nanomole-scale reaction was run using Corning® 1536-well plates (Corning®, Cat. No. 3730, 1536-well x 12.5 µL well Echo™ qualified flat bottom microplate) inside a glove box with a constant nitrogen purge. Dosing of reaction components from the source plates into the reaction plates was carried out in the glove box using a Mosquito® HTS liquid handling robot with the TTP Labtech Mosquito software. Inorganic bases were predosed from a suspension (0.5 M in *t*-amyl alcohol) to the reaction plates and dried in the oven to remove solvent prior to dispensing other reaction components. Once the dosing was completed, the reaction plates were sealed with Photoredox Nano Nest (Analytical-Sales, Cat. No. 1536050, open block, for LED excitation) and mixed for 5 min using PharmaRAM II (Resodyn™ Acoustic Mixers). The reaction plate was irradiated with blue LED at 450 nm, with fan cooling for 18 h. Upon completion of reaction, the reaction was quenched with 1% AcOH in DMSO solution in the glove box using Matrix PlateMate™ 2x2 with ControlMate™ software. The quenching solution (101.5 µL) was dispensed into each well of the analytical plates and 4 µL of the solution was transferred into each well of reaction plates containing reaction mixture of 1 µL. From the reaction plates containing total volume of 5 µL, 2.5 µL was transferred back to the analytical plates, giving total volume of 100 µL per well. The analytical plates were taken out of the glove box and sealed, vigorously mixed, and subjected to analysis using a Waters Acquity UPLC-MS (column: CORTECS UPLC C18+ column (30 × 2.1mm, 1.6µm), eluent: MeCN/water, 2 mM ammonium formate, adjusted to pH 3.5 with formic acid). UPLC-MS data were processed using Virscidian Analytical Studio Professional 4.8. Details in reaction set up for nanomole-scale High-Throughput Experimentation can be found in previous reports.[1,2,3]

The reaction was screened for 4 x 240 reaction conditions (two solvents (NMP, DMF), two Nickel sources ($NiCl_2$·glyme, $NiBr_2$·glyme), five bases (Cs_2CO_3, K_3PO_4, K_2CO_3, BTMG, DBU), four ligands (dtbbpy, dOMebpy, tMePhene, tButpy), six photocatalysts ($Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, $Ir[dF(H)ppy]_2(dtbbpy)PF_6$, $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$, $Ru(bpy)_3(PF_6)_2$, 4CzIPN, 4DPAIPN), two quinuclidine loadings (5 mol%, 10 mol%)). At the end of the reaction, 4 x 384-well plates were used as analytical plates for a 1526-well reaction plate. Among these reactions, reactions in NMP with $NiBr_2$·glyme showed the best results and the corresponding 240 reactions were analyzed to generate a heat map (Figure 2). The reaction conversion was calculated using the UV peak area at 210 nm, using the following equation: (area of product)/(area of product, starting material ArBr, ArH, ArOH, Ar-NMP adduct) x 100%. (dtbbpy= 4,4'-di-*tert*-butyl-2,2'-dipyridyl, dOMebpy= 4,4'-dimethoxy-2,2'-bipyridine, tMePhene= 3,4,7,8-tetramethyl-1,10-phenanthroline, tButpy=4,4',4''-tri-*tert*-butyl-2,2':6',2''-terpyridine).

Stock solution preparation:

Total 48 stock solutions were prepared (1 mL each of 2 x 24 solutions in either anhydrous NMP or DMF) as follows:

ArBr **1** (1.0 equiv, 0.125 M)

ArBr **1** + BTMG (1.0 equiv **1**, 0.125 M + 1.0 equiv BTMG, 0.125 M)

ArBr **1** + DBU (1.0 equiv 1, 0.125 M + 1.0 equiv DBU, 0.125 M)

Alcohol **2c** (1.5 equiv, 0.25 M)

$NiCl_2$·glyme + dtbbpy (0.2 equiv $NiCl_2$·glyme, 0.05 M + 0.2 equiv dtbbpy, 0.05 M)

$NiCl_2$·glyme + dOMebpy (0.2 equiv $NiCl_2$·glyme, 0.05 M + 0.2 equiv dOMebpy, 0.05 M)

$NiCl_2$·glyme + tMePhene (0.2 equiv $NiCl_2$·glyme, 0.05 M + 0.2 equiv tMePhene, 0.05 M)

$NiCl_2$·glyme + tButpy (0.2 equiv $NiCl_2$·glyme, 0.05 M + 0.2 equiv tButpy, 0.05 M)

$NiBr_2$·glyme + dtbbpy (0.2 equiv $NiBr_2$·glyme, 0.05 M + 0.2 equiv dtbbpy, 0.05 M)

$NiBr_2$·glyme + dOMebpy (0.2 equiv $NiBr_2$·glyme, 0.05 M + 0.2 equiv dOMebpy, 0.05 M)

$NiBr_2$·glyme + tMePhene (0.2 equiv $NiBr_2$·glyme, 0.05 M + 0.2 equiv tMePhene, 0.05 M)

$NiBr_2$·glyme + tButpy (0.2 equiv $NiBr_2$·glyme, 0.05 M + 0.2 equiv tButpy, 0.05 M)

Quinuclidine + $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.05 equiv quinuclidine, 0.025 M + 0.05 equiv $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, 0.025 M)

Quinuclidine + $Ir[dF(H)ppy]_2(dtbbpy)PF_6$ (0.05 equiv quinuclidine, 0.025 M + 0.05 equiv $Ir[dF(H)ppy]_2(dtbbpy)PF_6$, 0.025 M)

Quinuclidine + $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$ (0.05 equiv quinuclidine, 0.025 M + 0.05 equiv $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$, 0.025 M)

Quinuclidine + $Ru(bpy)_3(PF_6)_2$ (0.05 equiv quinuclidine, 0.025 M + 0.05 equiv $Ru(bpy)_3(PF_6)_2$, 0.025 M)

Quinuclidine + 4CzIPN (0.05 equiv quinuclidine, 0.025 M + 0.05 equiv 4CzIPN, 0.025 M)

Quinuclidine + 4DPAIPN (0.05 equiv quinuclidine, 0.025 M + 0.05 equiv 4DPAIPN, 0.025 M)

Quinuclidine + $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$ (0.1 equiv quinuclidine, 0.05 M + 0.05 equiv $Ir[dF(CF_3)ppy]_2(dtbbpy)PF_6$, 0.025 M)

Quinuclidine + $Ir[dF(H)ppy]_2(dtbbpy)PF_6$ (0.1 equiv quinuclidine, 0.05 M + 0.05 equiv $Ir[dF(H)ppy]_2(dtbbpy)PF_6$, 0.025 M)

Quinuclidine + $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$ (0.1 equiv quinuclidine, 0.05 M + 0.05 equiv $Ir[dF(Me)ppy]_2(dtbbpy)PF_6$, 0.025 M)

Quinuclidine + $Ru(bpy)_3(PF_6)_2$ (0.1 equiv quinuclidine, 0.05 M + 0.05 equiv $Ru(bpy)_3(PF_6)_2$, 0.025 M)

Quinuclidine + 4CzIPN (0.1 equiv quinuclidine, 0.05 M + 0.05 equiv 4CzIPN, 0.025 M)

Quinuclidine + 4DPAIPN (0.1 equiv quinuclidine, 0.05 M + 0.05 equiv 4DPAIPN, 0.025 M)

Each of the stock solutions was manually dispensed into 384-well plates as shown in Figure S1.

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
A																								
B																								
C										5% quinuclidine + Ir[dF(CF3)ppy]2(dtbbpy)PF6														
D										5% quinuclidine + Ir[dF(H)ppy]2(dtbbpy)PF6														
E										5% quinuclidine + Ir[dF(Me)ppy]2(dtbbpy)PF6														
F										5% quinuclidine + Ru(bpy)3(PF6)2														
G										5% quinuclidine + 4CzIPN														
H										5% quinuclidine + 4DPAIPN														
I										10% quinuclidine + Ir[dF(CF3)ppy]2(dtbbpy)PF6														
J										10% quinuclidine + Ir[dF(H)ppy]2(dtbbpy)PF6														
K										10% quinuclidine + Ir[dF(Me)ppy]2(dtbbpy)PF6														
L										10% quinuclidine + Ru(bpy)3(PF6)2														
M	ArBr	ArBr + BTMG	ArBr + DBU	DMF	NiCl2 + dtbbpy	NiCl2 + dOMebpy	NiCl2 + tMePhene	NiCl2 + tButpy	DMF	10% quinuclidine + 4CzIPN	alcohol	NiBr2 + dtbbpy	NiBr2 + dOMebpy	NiBr2 + tMePhene	NiBr2 + tButpy									
N										10% quinuclidine + 4DPAIPN														
O																								
P																								

Figure S1. 384-Well source plate design.

Dosing into reaction plates:

Reaction components from the source plates into the reaction plates were handled by multi-aspiration of 0.4 µL of 'ArBr **1** + (base)' solution, 0.2 µL of 'Ni + ligand' solution, 0.1 µL of 'quinuclidine + photocatalyst' solution, followed by 0.3 µL of 'alcohol **2c**' solution in sequence using Mosquito® to give total volume of 1 µL per well.

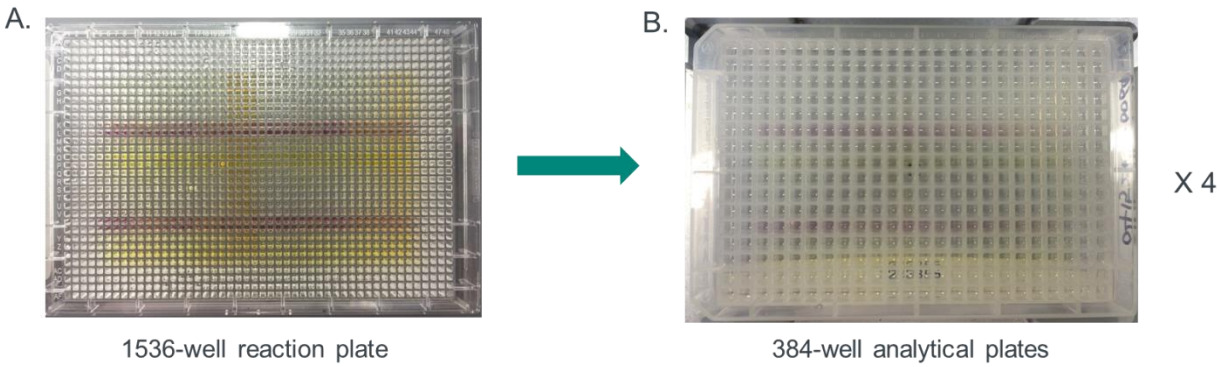


Figure S2. A. A 1536-well reaction plate (nano scale; 0.02 mg ArBr, 1 µL per well), 40 x 24 (960) wells used for photoredox set up. **B.** A 384-well analytical plate.

Proposed mechanisms for Ni-catalyzed photoredox C–O cross-coupling

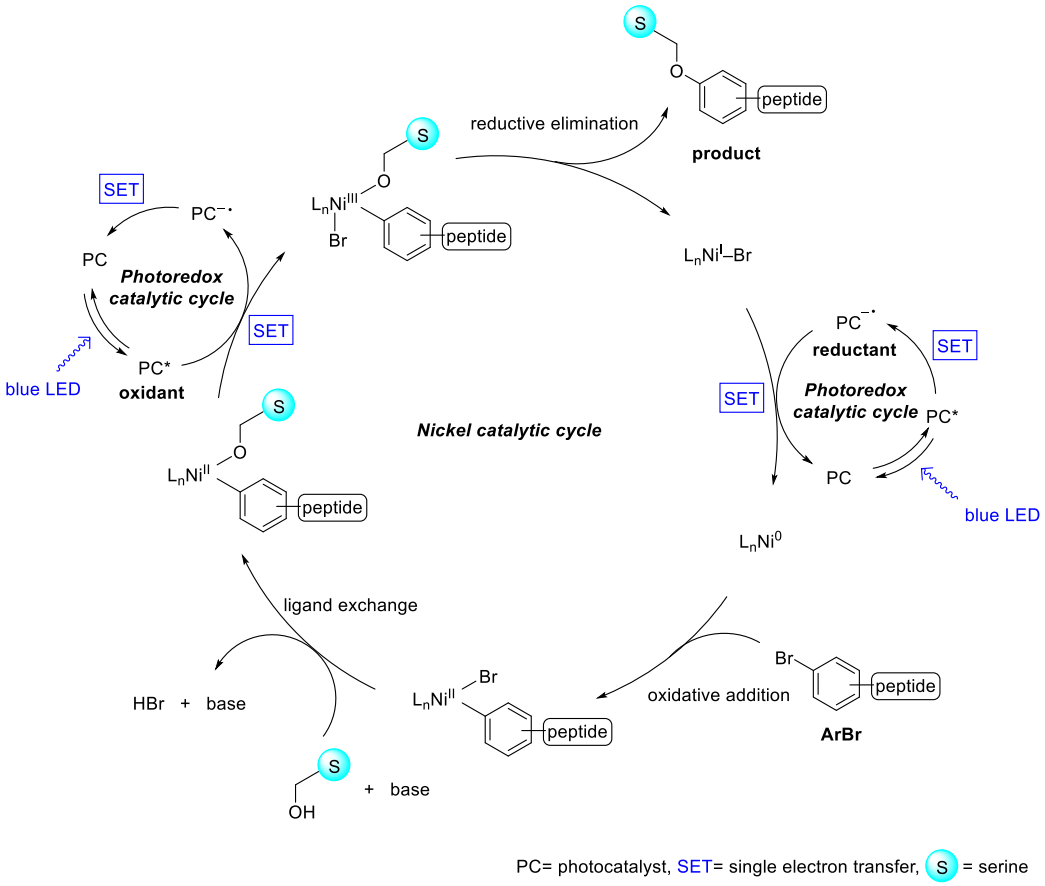
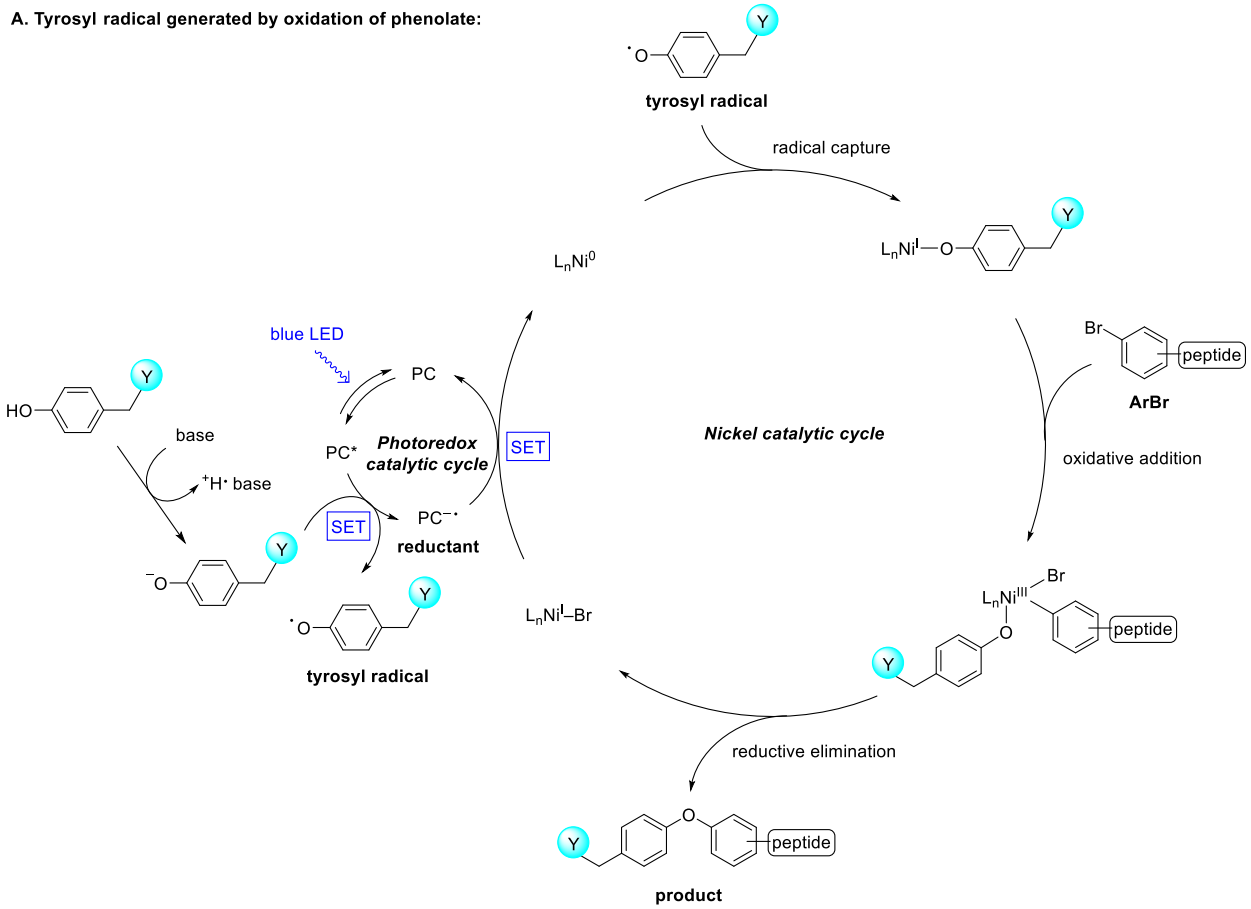


Figure S3. Proposed Ni/photoredox dual catalytic cycle for peptide C(sp^3)–O–C(sp^2) coupling (modified from the previously reported work for small molecule C–O coupling[4]).

A. Tyrosyl radical generated by oxidation of phenolate:



PC= photocatalyst, SET= single electron transfer, Y = tyrosine

B. Tyrosyl radical generated by proton-coupled electron transfer (PCET):

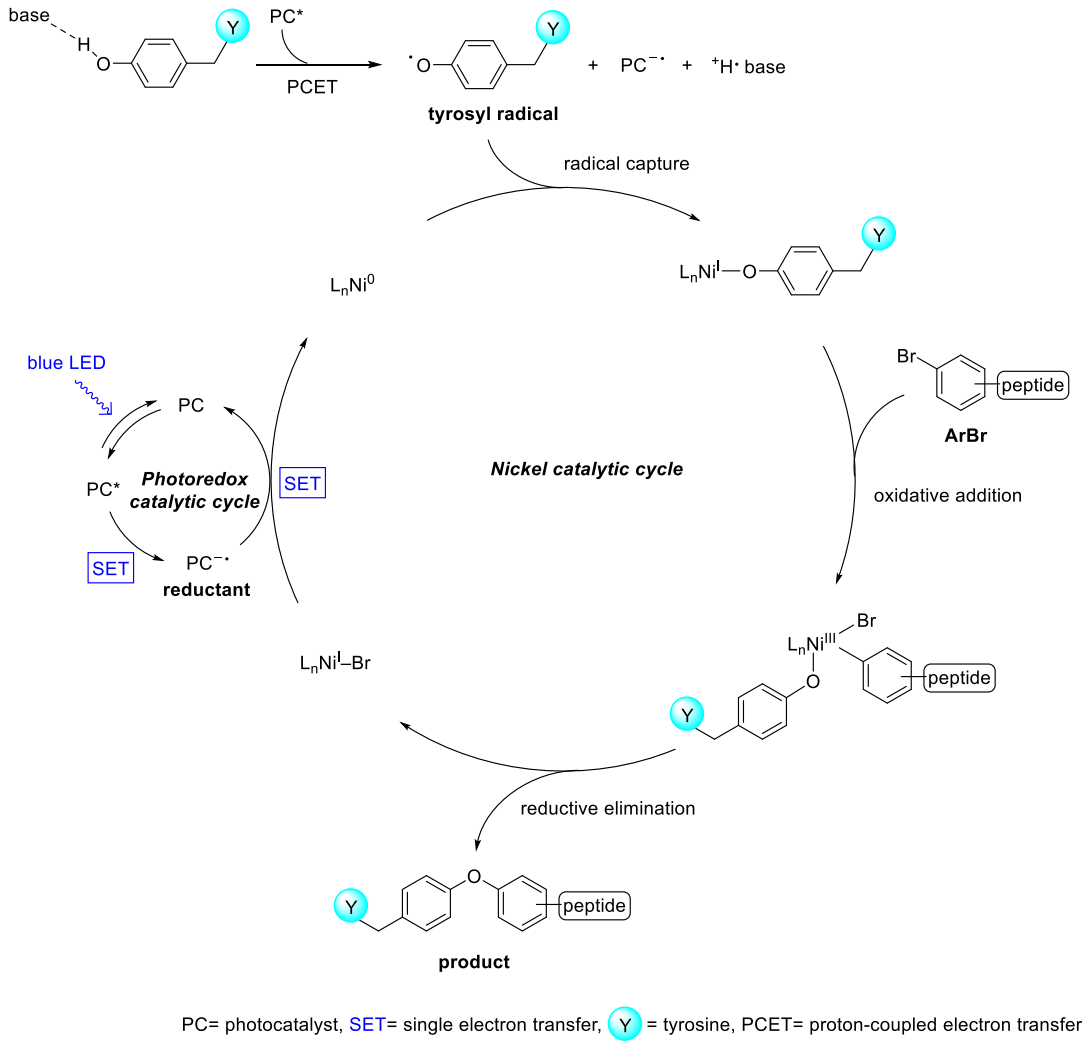


Figure S4. Alternative proposed mechanisms for peptide C(sp^2)–O–C(sp^2) coupling. **A.** Tyrosyl radical generated by oxidation of phenolate. **B.** Tyrosyl radical generated by proton-coupled electron transfer (PCET).

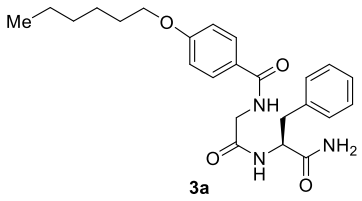
Ni-Catalyzed photoredox C–O coupling (Intermolecular Reaction)

General procedure C:

Prior to setting up reactions, all peptide substrates were dried by co-evaporation with toluene to remove residual water. The reaction was set up under a flow of argon. To an 8 mL vial (2 Dram, 17 x 60mm, 15-425 Thread, with Red Pressure Relief Cap, CG-4912-02) equipped with a stir bar, containing aryl bromide (0.100 mmol) and potassium carbonate (13.8 mg, 1.00 equiv, 0.100 mmol), a solution of 4DPAIPN (0.797 mg, 0.0100 equiv, 1.00 µmol) and quinuclidine (0.556 mg, 0.0500 equiv, 5.00 µmol) in MeCN (0.600 mL) was added. Then, a solution of $NiBr_2$·glyme (6.17 mg, 0.200 equiv, 0.0200 mmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) (5.37 mg, 0.200 equiv, 0.0200 mmol) in MeCN (1.40 mL), followed by alcohol (1.50-3.00 equiv, 0.150-0.300 mmol) dissolved in DMSO (1.00 mL) were added to the reaction mixture. The vial was sparged with Ar for 15 minutes and sealed with parafilm, and then placed in MSD photoreactor or Penn Optical photoreactor and irradiated with 100% LED exposure for 24 hours (at 450 nm, stirring speed of 1000 rpm, fan speed of 5200–5500 rpm). After 24 hours, the reaction mixture was filtered through an Acrodisc® syringe filter. The filtrate was then concentrated under reduced pressure using a Biotage® V-10 evaporator. A 100 µL of TMB standard solution (0.100 M in DMSO-d_6) was added to the concentrated crude materials. The reaction yield was analyzed by ^{1}H NMR and reported in Table 2 and Table 3. Isolated yields are reported in the following after purification by either preparative reverse-phase HPLC or automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco).

A 5X stock solution of "4DPAIPN + quinuclidine" (4.00 mg 4DPAIPN + 2.80 mg quinuclidine dissolved in 3.00 mL MeCN) was prepared and 0.600 mL of this solution was used. A 2.5X stock solution of "$NiBr_2$·glyme + dtbbpy" (15.4 mg $NiBr_2$·glyme and 13.4 mg dtbbpy dissolved in 3.50 mL MeCN) was prepared and 1.40 mL of this solution was used.

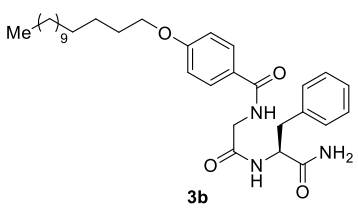
Products in Table 2



3a

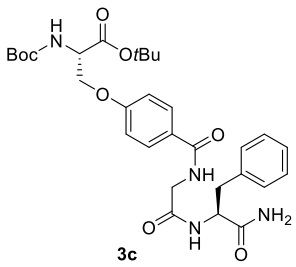
Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and *n*-hexanol **2a** (19.0 µL, 0.150 mmol) afforded the desired product, **3a** (26.0 mg, 60%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (t, *J* = 5.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.28 – 7.18 (m, 4H), 7.19 – 7.14 (m, 1H), 7.12 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.43 (td, *J* = 8.9, 4.6 Hz, 1H), 4.02 (t, *J* = 6.5 Hz, 2H), 3.87 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.86 – 1.61 (m, 2H), 1.55 – 1.37 (m, 2H), 1.37 – 1.20 (m, 4H), 0.87 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.88, 168.97, 166.15, 161.16, 137.97,

129.18, 129.16, 128.06, 126.24, 125.97, 113.94, 67.69, 53.76, 42.73, 37.45, 30.99, 28.56, 25.15, 22.08, 13.93; HRMS (ESI+) 426.2341 (calcd for 426.2387 $C_{24}H_{31}N_3O_4$, M + H^+).



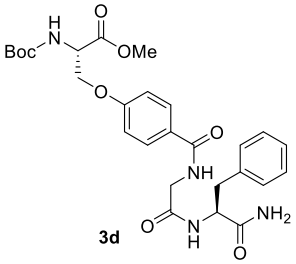
3b

Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and 1-tetradecanol **2b** (32.2 mg, 0.150 mmol) afforded the desired product, **3b** (27.3 mg, 51%) as a white solid after purification using automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with silica gel cartridge (eluent: (3:1 ethyl acetate:ethanol)/hexane). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.57 (t, *J* = 5.8 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.25 – 7.18 (m, 4H), 7.18 – 7.14 (m, 1H), 7.12 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.43 (td, *J* = 8.9, 4.6 Hz, 1H), 4.01 (t, *J* = 6.5 Hz, 2H), 3.87 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.72 (dd, *J* = 16.2, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.7, 4.5 Hz, 1H), 2.80 (dd, *J* = 13.8, 9.2 Hz, 1H), 1.71 (p, *J* = 6.6 Hz, 2H), 1.45 – 1.35 (m, 2H), 1.23 (s, 20H), 0.85 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.89, 168.98, 166.14, 161.16, 137.97, 129.17, 129.17, 128.07, 126.25, 125.96, 113.93, 67.69, 53.77, 42.73, 37.46, 31.31, 29.06, 29.06, 29.03, 29.03, 28.99, 28.99, 28.76, 28.72, 28.59, 25.48, 22.12, 13.99; HRMS (ESI+) 538.3650 (calcd for 538.3639 $C_{32}H_{47}N_3O_4$, M+H^+).

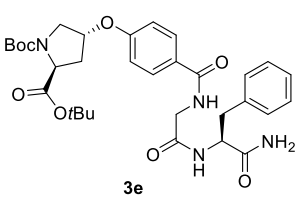


3c

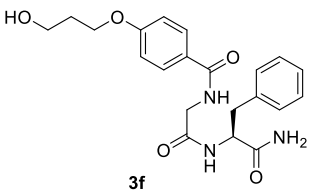
Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **3c** (37.2 mg, 64%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). The scale-up reaction was carried out in a 40 mL vial with **1** (202 mg, 0.500 mmol), **2c** (196 mg, 0.750 mmol), potassium carbonate (69.0 mg, 0.500 mmol), 4DPAIPN (20.0 mg, 25.0 µmol), quinuclidine (2.78 mg, 25.00 µmol), $NiBr_2$·glyme (31.0 mg, 0.100 mmol), and dtbbpy (27.0 mg, 0.100 mmol) in 15 mL of 2:1 MeCN/DMSO for 48 h. A white solid **3c** (178 mg, 61%) was isolated by purification using automated column chromatography (CombiFlash® Rf Flash Chromatography System from Teledyne Isco) with C18 cartridge, followed by preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60 (t, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.33 (d, *J* = 7.7 Hz, 1H), 7.25 – 7.19 (m, 4H), 7.16 (dd, *J* = 8.8, 4.6 Hz, 1H), 7.12 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.43 (td, *J* = 8.9, 4.6 Hz, 1H), 4.33 – 4.26 (m, 1H), 4.26 – 4.19 (m, 2H), 3.88 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.81 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.39 (s, 18H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.84, 168.97, 168.90, 166.02, 160.52, 155.38, 137.96, 129.17, 129.13, 128.03, 126.55, 126.20, 114.06, 81.12, 78.40, 67.45, 54.02, 53.73, 42.71, 37.44, 28.15, 27.61; HRMS (ESI+) 585.2918 (calcd for 585.2919 $C_{30}H_{40}N_4O_8$, M+H^+).



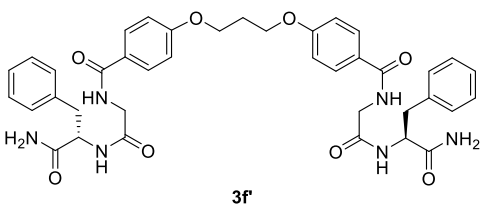
Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2d** (32.9 mg, 0.150 mmol) afforded the desired product, **3d** (21.3 mg, 39%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^1H NMR (500 MHz, DMSO-d_6): δ 8.60 (t, *J* = 5.6 Hz, 1H), 8.04 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.48 (d, *J* = 8.1 Hz, 1H), 7.42 (s, 1H), 7.24 – 7.19 (m, 4H), 7.17 (dd, *J* = 9.2, 4.6 Hz, 1H), 7.12 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.53 – 4.45 (m, 1H), 4.45 – 4.39 (m, 1H), 4.26 (d, *J* = 5.5 Hz, 2H), 3.87 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.1, 5.8 Hz, 1H), 3.67 (s, 3H), 3.02 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.39 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.85, 170.40, 168.89, 165.99, 160.43, 155.40, 137.97, 129.13, 128.03, 126.61, 126.21, 114.13, 78.57, 67.17, 53.76, 53.27, 52.18, 42.69, 37.44, 28.13; HRMS (ESI+) 543.2442 (calcd for 543.2449 $C_{27}H_{34}N_4O_8$, $M+H^+$).



Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2e** (86 mg, 0.300 mmol) afforded the desired product, **3e** (25.2 mg, 41%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^1H NMR (500 MHz, DMSO-d_6): δ 8.61 (t, *J* = 5.8 Hz, 1H), 8.02 (d, *J* = 8.3 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.25 – 7.19 (m, 4H), 7.16 (dd, *J* = 8.6, 4.6 Hz, 1H), 7.12 (s, 1H), 7.01 (d, *J* = 8.8 Hz, 2H), 5.15 – 5.05 (m, 1H), 4.43 (td, *J* = 8.9, 4.6 Hz, 1H), 4.23 – 4.11 (m, 1H), 3.88 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.69 – 3.52 (m, 3H), 3.02 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.28 – 2.12 (m, 1H), 1.43 (s, 9H), 1.36 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.89, 171.41, 168.92, 166.02, 159.12, 153.15, 137.97, 129.33, 129.16, 128.06, 126.68, 126.24, 114.92, 80.90, 79.37, 74.71, 58.01, 53.77, 51.84, 42.73, 37.46, 35.95, 27.91, 27.64; HRMS (ESI+) 611.3101 (calcd for 611.3075 $C_{32}H_{42}N_4O_8$, $M+Na^+$).

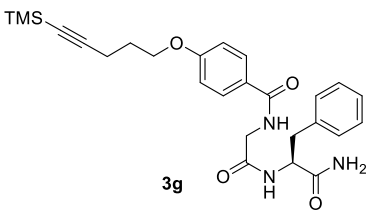


Following general procedure C, the reaction between **1** (81.0 mg, 0.200 mmol) and **2f** (7.23 µL, 0.100 mmol) afforded the desired products, **3f** (17.5 mg, 44%) and **3f'** (2.0 mg, 3%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^1H NMR (500 MHz, DMSO-d_6): δ 8.58 (t, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.25 – 7.19 (m, 4H), 7.19 – 7.14 (m, 1H), 7.12 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.43 (td, *J* = 8.8, 4.6 Hz, 1H), 4.09 (t, *J* = 6.4 Hz, 2H), 3.87 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.56 (t, *J* = 6.2 Hz, 2H), 3.02 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.87 (p, *J* = 6.3 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.88, 168.96, 166.14, 161.17, 137.97, 129.18, 129.15, 128.06, 126.24, 125.99, 113.93, 64.83, 57.22, 53.76, 42.73, 37.45, 32.02; HRMS (ESI+) 400.1853 (calcd for 400.1867 $C_{21}H_{25}N_3O_5$, $M+H^+$).



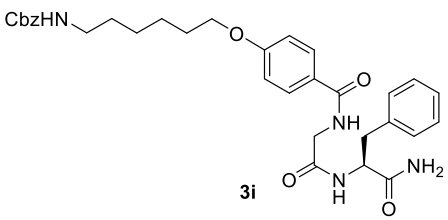
3f'

^{1}H NMR (500 MHz, DMSO-d_6): δ 8.58 (t, *J* = 5.8 Hz, 2H), 8.03 (d, *J* = 8.4 Hz, 2H), 7.83 (d, *J* = 8.8 Hz, 4H), 7.42 (s, 2H), 7.24 – 7.19 (m, 8H), 7.19 – 7.14 (m, 2H), 7.12 (s, 2H), 7.03 (d, *J* = 8.8 Hz, 4H), 4.43 (td, *J* = 8.9, 4.6 Hz, 2H), 4.21 (t, *J* = 6.2 Hz, 4H), 3.87 (dd, *J* = 16.3, 5.9 Hz, 2H), 3.72 (dd, *J* = 16.3, 5.7 Hz, 2H), 3.02 (dd, *J* = 13.8, 4.5 Hz, 2H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 2H), 2.21 (p, *J* = 6.2 Hz, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.86, 168.93, 166.08, 160.92, 137.96, 129.20, 129.14, 128.05, 126.22, 126.21, 113.99, 64.47, 53.75, 42.71, 37.44, 28.48; HRMS (ESI+) 723.3121 (calcd for 723.3137 $C_{39}H_{42}N_6O_8$, M+H$^+$).



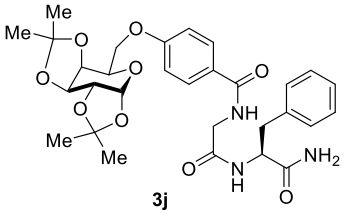
3g

Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2g** (36 µL, 0.200 mmol) afforded the desired product, **3g** (18.5 mg, 39%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.58 (t, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.24 – 7.19 (m, 4H), 7.19 – 7.14 (m, 1H), 7.12 (s, 1H), 7.00 (d, *J* = 8.8 Hz, 2H), 4.44 (td, *J* = 8.8, 4.6 Hz, 1H), 4.09 (t, *J* = 6.2 Hz, 2H), 3.88 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.03 (dd, *J* = 13.7, 4.6 Hz, 1H), 2.81 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.39 (t, *J* = 7.1 Hz, 2H), 1.89 (p, *J* = 6.6 Hz, 2H), 0.11 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.84, 168.92, 166.05, 160.90, 137.96, 129.18, 129.14, 128.03, 126.20, 126.17, 113.93, 106.97, 84.80, 66.19, 53.73, 42.70, 37.44, 27.56, 15.84, 0.11; HRMS (ESI+) 480.2308 (calcd for 480.2313 $C_{26}H_{33}N_3O_4Si$, M+H$^+$).



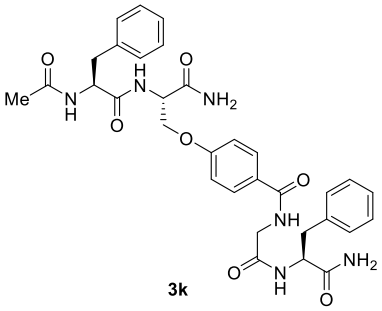
3i

Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2i** (37.7 mg, 0.150 mmol) afforded the desired product, **3i** (16.2 mg, 28%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.58 (t, *J* = 5.8 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.38 – 7.28 (m, 5H), 7.26 – 7.19 (m, 5H), 7.17 (dd, *J* = 9.1, 4.6 Hz, 1H), 7.13 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 5.00 (s, 2H), 4.43 (td, *J* = 8.9, 4.6 Hz, 1H), 4.01 (t, *J* = 6.4 Hz, 2H), 3.87 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.07 – 2.95 (m, 3H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.76 – 1.64 (m, 2H), 1.47 – 1.36 (m, 4H), 1.35 – 1.27 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.87, 168.96, 166.12, 161.14, 156.11, 137.98, 137.32, 129.17, 129.15, 128.34, 128.05, 127.74, 127.72, 126.22, 125.98, 113.92, 67.62, 65.08, 53.75, 42.72, 40.21, 37.44, 29.32, 28.52, 25.96, 25.17; HRMS (ESI+) 575.2838 (calcd for 575.2864 $C_{32}H_{38}N_4O_6$, M+H$^+$).



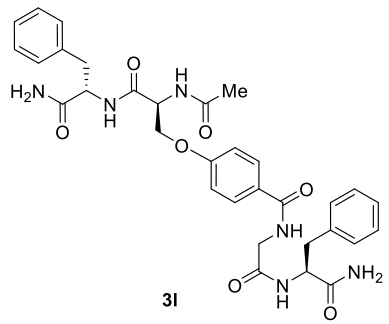
3j

Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2j** (52.1 mg, 0.200 mmol) afforded the desired product, **3j** (28.4 mg, 49%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.59 (t, *J* = 5.7 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.7 Hz, 2H), 7.42 (s, 1H), 7.28 – 7.14 (m, 5H), 7.12 (s, 1H), 7.03 (d, *J* = 8.7 Hz, 2H), 5.49 (d, *J* = 4.9 Hz, 1H), 4.65 (dd, *J* = 7.8, 2.1 Hz, 1H), 4.43 (td, *J* = 8.8, 4.7 Hz, 1H), 4.39 – 4.27 (m, 2H), 4.23 (dd, *J* = 9.3, 3.4 Hz, 1H), 4.12 – 3.95 (m, 2H), 3.87 (dd, *J* = 16.2, 5.8 Hz, 1H), 3.77 – 3.71 (m, 1H), 3.02 (dd, *J* = 13.7, 4.4 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.38 (s, 6H), 1.29 (d, *J* = 12.6 Hz, 6H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.90, 168.96, 166.08, 160.61, 137.98, 129.17, 128.07, 126.25, 114.19, 108.60, 107.96, 95.67, 92.83, 70.34, 70.04, 69.76, 66.92, 65.80, 55.17, 53.79, 42.75, 37.46, 25.97, 25.81, 24.86, 24.32; HRMS (ESI+) 584.2607 (calcd for 584.2603 $C_{30}H_{37}N_3O_9$, M+H$^+$).



3k

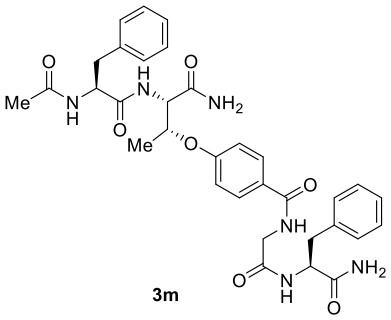
Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **3k** (33.1 mg, 54%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.60 (t, *J* = 5.8 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.04 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.36 (s, 1H), 7.29 (s, 1H), 7.25 – 7.16 (m, 10H), 7.12 (s, 1H), 7.02 (d, *J* = 8.8 Hz, 2H), 4.63 – 4.53 (m, 2H), 4.43 (td, *J* = 8.8, 4.6 Hz, 1H), 4.27 – 4.18 (m, 2H), 3.88 (dd, *J* = 16.1, 5.8 Hz, 1H), 3.73 (dd, *J* = 16.2, 5.7 Hz, 1H), 3.08 – 2.99 (m, 2H), 2.84 – 2.70 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.88, 171.71, 170.48, 169.38, 168.93, 166.05, 160.65, 137.97, 129.21, 129.16, 128.30, 128.20, 128.06, 128.03, 127.31, 126.53, 126.24, 114.15, 67.88, 54.05, 53.77, 52.36, 42.72, 37.45, 37.41, 22.45; HRMS (ESI+) 617.2717 (calcd for 617.2718 $C_{32}H_{36}N_6O_7$, M+H$^+$).



3l

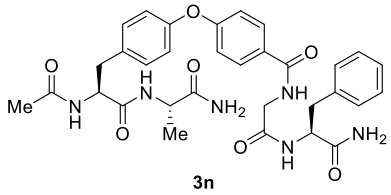
Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2l** (44.0 mg, 0.150 mmol) afforded the desired product, **3l** (20.1 mg, 33%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.59 (t, *J* = 5.8 Hz, 1H), 8.32 (d, *J* = 7.5 Hz, 1H), 8.11 (d, *J* = 8.2 Hz, 1H), 8.03 (d, *J* = 8.4 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.42 (s, 1H), 7.31 (s, 1H), 7.23 – 7.16 (m, 11H), 7.12 (s, 1H), 6.96 (d, *J* = 8.9 Hz, 2H), 4.62 (q, *J* = 5.7 Hz, 1H), 4.48 – 4.40 (m, 2H), 4.11 (d, *J* = 5.6 Hz, 2H), 3.90 – 3.84 (m, 1H), 3.73 (dd, *J* = 16.2, 5.7 Hz, 1H), 3.04 (td, *J* = 14.4, 4.6 Hz, 2H), 2.90 – 2.76 (m, 2H), 1.87 (s, 3H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.88, 172.55, 169.96, 168.93, 168.83, 166.05, 160.56, 137.97, 137.86, 133.91, 131.40, 129.16, 128.31,

128.06, 127.32, 126.52, 126.25, 114.11, 67.64, 53.91, 53.78, 52.69, 42.71, 37.47, 37.22, 22.54; HRMS (ESI+) 617.2715 (calcd for 617.2718 $C_{32}H_{36}N_6O_7$, M+H$^+$).



3m

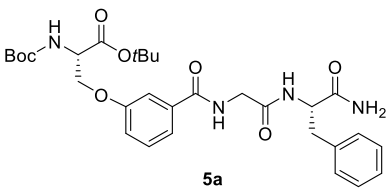
Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2m** (92 mg, 0.300 mmol) afforded the desired product, **3m** (14.3 mg, 23%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.58 (t, *J* = 5.7 Hz, 1H), 8.22 (d, *J* = 8.2 Hz, 1H), 8.10 (d, *J* = 8.9 Hz, 1H), 8.02 (d, *J* = 8.4 Hz, 1H), 7.82 (d, *J* = 8.6 Hz, 2H), 7.42 (s, 1H), 7.31 – 7.16 (m, 12H), 7.12 (s, 1H), 7.02 (d, *J* = 8.7 Hz, 2H), 4.95 (dd, *J* = 6.1, 3.6 Hz, 1H), 4.67 (td, *J* = 9.9, 4.5 Hz, 1H), 4.51 – 4.39 (m, 2H), 3.87 (dd, *J* = 16.3, 5.8 Hz, 1H), 3.73 (dd, *J* = 16.3, 5.6 Hz, 1H), 3.08 – 3.00 (m, 2H), 2.83 – 2.74 (m, 2H), 1.75 (s, 3H), 1.18 (d, *J* = 6.2 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.91, 172.05, 170.85, 169.52, 168.95, 166.11, 159.87, 138.04, 138.04, 137.97, 137.97, 129.20, 129.17, 128.08, 126.50, 126.28, 126.26, 115.28, 73.79, 56.34, 54.02, 53.78, 42.74, 37.45, 36.95, 22.39, 15.95; HRMS (ESI+) 631.2877 (calcd for 631.2875 $C_{33}H_{38}N_6O_7$, M+H$^+$).



3n

Following general procedure C, the reaction between **1** (40.4 mg, 0.100 mmol) and **2n** (44.0 mg, 0.150 mmol) afforded the desired product, **3n** (24.2 mg, 39%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.67 (t, *J* = 5.7 Hz, 1H), 8.11 (d, *J* = 8.3 Hz, 1H), 8.05 (d, *J* = 8.0 Hz, 2H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.43 (s, 1H), 7.30 (d, *J* = 8.4 Hz, 2H), 7.23 – 7.20 (m, 5H), 7.18 – 7.16 (m, 1H), 7.13 (s, 1H), 7.04 – 6.98 (m, 4H), 6.97 (s, 1H), 4.56 – 4.47 (m, 1H), 4.47 – 4.39 (m, 1H), 4.19 (p, *J* = 7.1 Hz, 1H), 3.89 (dd, *J* = 16.3, 6.0 Hz, 1H), 3.75 (dd, *J* = 16.2, 5.8 Hz, 1H), 3.06 – 2.98 (m, 2H), 2.81 (dd, *J* = 13.7, 9.3 Hz, 1H), 2.73 (dd, *J* = 13.7, 9.9 Hz, 1H), 1.77 (s, 3H), 1.22 (d, *J* = 7.1 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 174.07, 172.91, 170.86, 169.33, 168.86, 165.91, 159.90, 153.96, 137.98, 134.13, 130.95, 129.51, 129.18, 128.09, 127.33, 126.27, 119.26, 117.16, 54.05, 53.80, 48.06, 42.74, 37.48, 36.89, 22.51, 18.37; HRMS (ESI+) 617.2659 (calcd for 617.2718 $C_{32}H_{36}N_6O_7$, M+H$^+$).

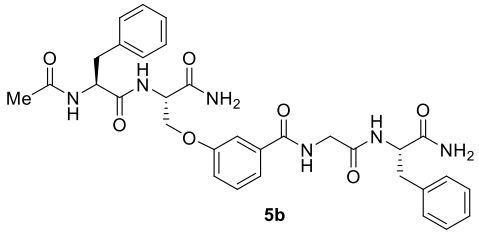
Products in Table 3



5a

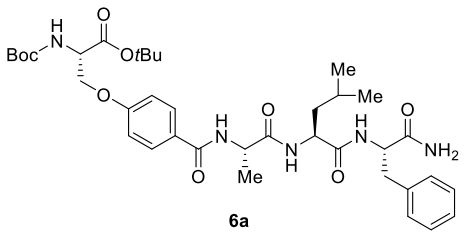
Following general procedure C, the reaction between **5** (40.4 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **5a** (24.3 mg, 42%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.73 (t, *J* = 5.7 Hz, 1H), 8.05 (d, *J* = 8.4 Hz, 1H), 7.46 (d, *J* = 7.7 Hz, 1H), 7.43 – 7.35 (m, 3H), 7.32 (d, *J* = 7.9 Hz, 1H), 7.21

(d, *J* = 4.2 Hz, 4H), 7.17 (dd, *J* = 8.9, 4.5 Hz, 1H), 7.10 (dd, *J* = 14.3, 6.0 Hz, 2H), 4.44 (td, *J* = 8.8, 4.7 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.24 – 4.18 (m, 2H), 3.90 (dd, *J* = 16.2, 5.8 Hz, 1H), 3.75 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.02 (dd, *J* = 13.8, 4.6 Hz, 1H), 2.80 (dd, *J* = 13.7, 9.3 Hz, 1H), 1.40 (s, 18H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.83, 169.03, 168.69, 166.12, 158.04, 155.38, 137.95, 135.32, 129.47, 129.14, 128.03, 126.21, 120.01, 117.81, 113.19, 81.09, 78.39, 67.46, 54.10, 53.77, 42.68, 37.48, 28.16, 27.63; HRMS (ESI+) 585.2920 (calcd for 585.2915 $C_{30}H_{40}N_4O_8$, M+Na$^+$).



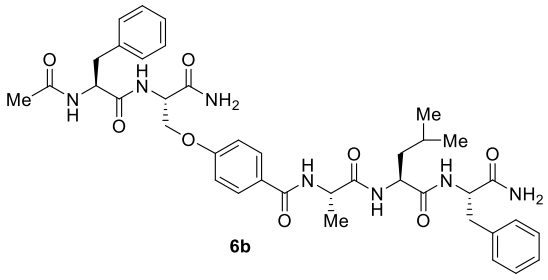
5b

Following general procedure C, the reaction between **5** (40.4 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **5b** (25.1 mg, 41%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.76 (t, *J* = 5.8 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.07 (d, *J* = 8.4 Hz, 1H), 7.51 – 7.35 (m, 5H), 7.31 – 7.20 (m, 9H), 7.19 – 7.14 (m, 2H), 7.14 – 7.09 (m, 2H), 4.65 – 4.54 (m, 2H), 4.44 (td, *J* = 8.9, 4.6 Hz, 1H), 4.27 – 4.17 (m, 2H), 3.90 (dd, *J* = 16.3, 5.9 Hz, 1H), 3.75 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.07 – 3.00 (m, 2H), 2.85 – 2.70 (m, 2H), 1.74 (s, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.83, 171.64, 170.51, 169.36, 168.69, 166.15, 158.14, 137.94, 135.30, 129.49, 129.13, 129.13, 129.13, 128.03, 128.03, 128.00, 126.22, 120.04, 117.82, 113.23, 67.91, 54.03, 53.76, 52.44, 42.69, 37.45, 37.40, 22.42; HRMS (ESI+) 617.2722 (calcd for 617.2718 $C_{32}H_{36}N_6O_7$, M+H$^+$).



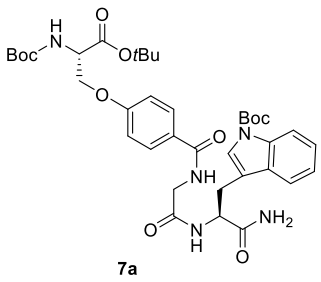
6a

Following general procedure C, the reaction was carried out with **6** (26.6 mg, 0.0500 mmol), **2c** (19.6 mg, 0.0750 mmol), potassium carbonate (6.91 mg, 0.050 mmol), 4DPAIPN (0.40 mg, 0.50 µmol), quinuclidine (0.28 mg, 2.5 µmol), $NiBr_2$·glyme (1.54 mg, 5.00 µmol), and dtbbpy (1.34 mg, 5.00 µmol) in 1.5 mL of 2:1 MeCN/DMSO. The desired product, **6a** (16.5 mg, 46%) was isolated as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.39 (d, *J* = 6.9 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.87 (d, *J* = 8.7 Hz, 2H), 7.73 (d, *J* = 8.3 Hz, 1H), 7.33 (d, *J* = 7.8 Hz, 1H), 7.29 (s, 1H), 7.25 – 7.14 (m, 5H), 7.10 (s, 1H), 6.99 (d, *J* = 8.8 Hz, 2H), 4.48 – 4.36 (m, 2H), 4.33 – 4.14 (m, 4H), 3.03 (dd, *J* = 13.9, 4.9 Hz, 1H), 2.83 (dd, *J* = 13.8, 8.9 Hz, 1H), 1.58 – 1.46 (m, 1H), 1.39 (s, 18H), 1.37 – 1.34 (m, 2H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.67, 172.66, 171.54, 168.97, 165.82, 160.51, 155.38, 137.74, 129.41, 129.10, 127.98, 126.57, 126.18, 113.95, 81.11, 78.40, 67.46, 54.01, 53.45, 51.51, 49.19, 37.43, 28.15, 27.61, 24.08, 22.92, 21.64, 17.56; HRMS (ESI+) 712.3923 (calcd for 712.3916 $C_{37}H_{53}N_5O_9$, M+Na$^+$).



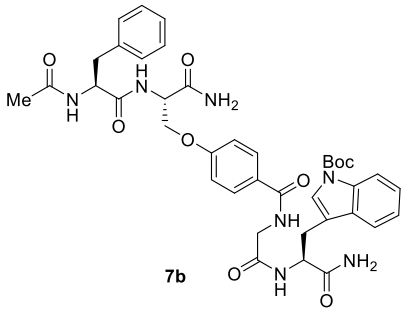
6b

Following general procedure C, the reaction was carried out with **6** (26.6 mg, 0.0500 mmol), **2k** (22.0 mg, 0.0750 mmol), potassium carbonate (6.91 mg, 0.050 mmol), 4DPAIPN (0.40 mg, 0.50 µmol), quinuclidine (0.28 mg, 2.5 µmol), $NiBr_2$·glyme (3.09 mg, 10.0 µmol), and dtbbpy (2.68 mg, 10.0 µmol) in 1.5 mL of 2:1 MeCN/DMSO. The desired product, **6b** (10.3 mg, 28%) was isolated as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.39 (d, *J* = 6.9 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.14 (d, *J* = 8.2 Hz, 1H), 7.95 (d, *J* = 7.8 Hz, 1H), 7.88 (d, *J* = 8.7 Hz, 2H), 7.74 (d, *J* = 8.3 Hz, 1H), 7.36 (s, 1H), 7.29 (s, 2H), 7.27 – 7.20 (m, 6H), 7.20 – 7.14 (m, 4H), 7.10 (s, 1H), 7.01 (d, *J* = 8.7 Hz, 2H), 4.62 – 4.53 (m, 2H), 4.45 – 4.37 (m, 2H), 4.27 – 4.14 (m, 3H), 3.08 – 2.99 (m, 2H), 2.83 (dd, *J* = 13.8, 9.0 Hz, 1H), 2.74 (dd, *J* = 13.7, 10.1 Hz, 1H), 1.74 (s, 3H), 1.56 – 1.49 (m, 1H), 1.42 – 1.33 (m, 2H), 1.30 (d, *J* = 7.1 Hz, 3H), 0.83 (d, *J* = 6.6 Hz, 3H), 0.78 (d, *J* = 6.5 Hz, 3H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.73, 172.71, 171.71, 171.59, 170.50, 169.39, 165.83, 160.66, 137.96, 137.75, 129.46, 129.17, 129.13, 128.04, 128.03, 126.55, 126.26, 126.23, 114.05, 67.90, 54.05, 53.49, 52.37, 51.55, 49.22, 40.50, 37.46, 24.11, 22.95, 22.46, 21.67, 17.61; HRMS (ESI+) 744.3796 (calcd for 744.3715 $C_{39}H_{49}N_7O_8$, M+H$^+$).



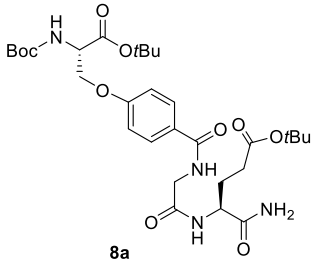
7a

Following general procedure C, the reaction between **7** (54.3 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **7a** (32.5 mg, 45%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 8.57 (t, *J* = 5.8 Hz, 1H), 8.17 (d, *J* = 8.3 Hz, 1H), 8.01 (d, *J* = 8.2 Hz, 1H), 7.81 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.50 (d, *J* = 4.0 Hz, 2H), 7.36 – 7.28 (m, 2H), 7.23 (t, *J* = 7.5 Hz, 1H), 7.18 (s, 1H), 6.98 (d, *J* = 8.8 Hz, 2H), 4.54 (td, *J* = 8.6, 4.9 Hz, 1H), 4.34 – 4.26 (m, 1H), 4.26 – 4.18 (m, 2H), 3.91 (dd, *J* = 16.4, 5.8 Hz, 1H), 3.76 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.13 (dd, *J* = 14.8, 4.6 Hz, 1H), 2.94 (dd, *J* = 14.8, 8.9 Hz, 1H), 1.61 (s, 9H), 1.39 (s, 18H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 172.90, 169.04, 168.96, 166.01, 160.49, 155.38, 149.05, 134.60, 130.34, 129.15, 126.61, 124.25, 123.80, 122.45, 119.35, 116.72, 114.60, 114.04, 83.48, 81.12, 78.41, 67.46, 54.02, 52.36, 42.68, 28.15, 27.70, 27.61, 27.18; HRMS (ESI+) 724.3541 (calcd for 724.3552 $C_{37}H_{49}N_5O_{10}$, M+Na$^+$).



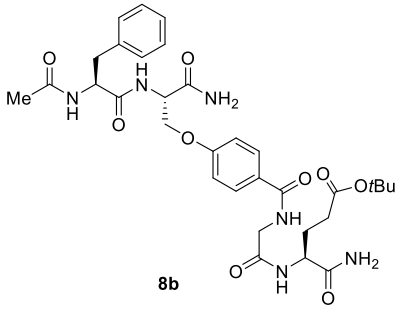
7b

Following general procedure C, the reaction between **7** (54.3 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **7b** (34.9 mg, 46%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^1H NMR (500 MHz, DMSO-d_6): δ 8.57 (t, *J* = 5.7 Hz, 1H), 8.34 (d, *J* = 7.8 Hz, 1H), 8.16 (dd, *J* = 17.1, 8.2 Hz, 2H), 8.02 (d, *J* = 8.2 Hz, 1H), 7.83 (d, *J* = 8.8 Hz, 2H), 7.68 (d, *J* = 7.8 Hz, 1H), 7.54 – 7.47 (m, 2H), 7.36 (s, 1H), 7.34 – 7.28 (m, 2H), 7.28 – 7.21 (m, 5H), 7.21 – 7.15 (m, 2H), 7.01 (d, *J* = 8.9 Hz, 2H), 4.63 – 4.50 (m, 3H), 4.27 – 4.18 (m, 2H), 3.91 (dd, *J* = 16.3, 5.8 Hz, 1H), 3.76 (dd, *J* = 16.3, 5.7 Hz, 1H), 3.14 (dd, *J* = 14.8, 4.6 Hz, 1H), 3.04 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.94 (dd, *J* = 14.8, 8.9 Hz, 1H), 2.74 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.75 (s, 3H), 1.62 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 172.91, 171.69, 170.46, 169.34, 169.05, 166.01, 160.61, 149.06, 137.96, 134.61, 130.35, 129.19, 129.15, 128.02, 126.57, 126.23, 124.27, 123.81, 122.47, 119.36, 116.74, 114.61, 114.12, 92.82, 83.51, 67.87, 55.15, 54.03, 52.38, 42.68, 37.41, 27.72, 22.44; HRMS (ESI+) 756.3348 (calcd for 756.3352 $C_{39}H_{45}N_7O_9$, $M+H^+$).



8a

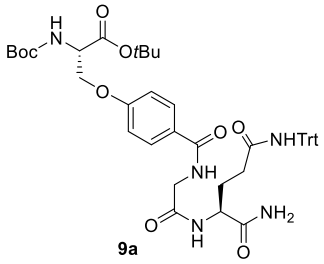
Following general procedure C, the reaction between **8** (44.2 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **8a** (25.4 mg, 41%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^1H NMR (500 MHz, DMSO-d_6): δ 8.64 (t, *J* = 5.7 Hz, 1H), 8.00 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.36 – 7.29 (m, 2H), 7.11 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.35 – 4.26 (m, 1H), 4.26 – 4.17 (m, 3H), 3.93 – 3.82 (m, 2H), 2.21 (t, *J* = 9.5 Hz, 2H), 1.99 – 1.88 (m, 1H), 1.72 (dt, *J* = 13.3, 7.5 Hz, 1H), 1.39 (s, 18H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.08, 171.73, 169.13, 168.99, 166.14, 160.55, 155.41, 129.19, 126.62, 114.09, 81.16, 79.71, 78.44, 67.49, 54.04, 51.56, 42.80, 31.33, 28.18, 27.76, 27.64, 27.23; HRMS (ESI+) 623.3327 (calcd for 623.3287 $C_{30}H_{46}N_4O_{10}$, $M+Na^+$).



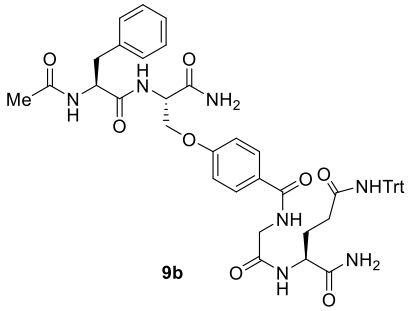
8b

Following general procedure C, the reaction between **8** (44.2 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **8b** (31.6 mg, 48%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^1H NMR (500 MHz, DMSO-d_6): δ 8.64 (t, *J* = 5.6 Hz, 1H), 8.35 (d, *J* = 7.7 Hz, 1H), 8.15 (d, *J* = 8.1 Hz, 1H), 8.01 (d, *J* = 8.1 Hz, 1H), 7.85 (d, *J* = 8.7 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.28 – 7.21 (m, 4H), 7.20 – 7.14 (m, 1H), 7.11 (s, 1H), 7.03 (d, *J* = 8.6 Hz, 2H), 4.63 – 4.53 (m, 2H), 4.27 – 4.17 (m, 3H), 3.93 – 3.83 (m, 2H), 3.04 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.74 (dd, *J* = 13.8, 10.0 Hz, 1H), 2.21 (t, *J* = 7.9 Hz, 2H), 1.99 – 1.88 (m, 1H), 1.75 (s, 3H), 1.73 – 1.68 (m, 1H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.08, 171.73, 170.48, 169.37, 169.14, 166.68,

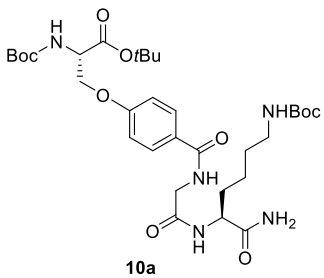
166.13, 160.65, 137.97, 129.16, 128.03, 127.32, 126.59, 126.25, 114.17, 79.72, 67.89, 54.05, 52.36, 51.57, 42.80, 37.42, 31.34, 27.77, 27.24, 22.45; HRMS (ESI+) 655.3044 (calcd for 655.3086 $C_{32}H_{42}N_6O_9$, M+H$^+$).



Following general procedure C, the reaction between **9** (62.8 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **9a** (30.2 mg, 37%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.64 – 8.55 (m, 2H), 8.00 (d, J = 7.8 Hz, 1H), 7.83 (d, J = 7.1 Hz, 2H), 7.33 (d, J = 7.4 Hz, 1H), 7.30 – 7.23 (m, 7H), 7.21 – 7.14 (m, 9H), 7.07 (s, 1H), 6.99 (d, J = 7.4 Hz, 2H), 4.33 – 4.14 (m, 4H), 3.92 – 3.85 (m, 2H), 2.34 – 2.26 (m, 2H), 1.89 (d, J = 8.3 Hz, 1H), 1.72 – 1.62 (m, 1H), 1.40 (s, 18H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.29, 171.51, 169.05, 168.97, 166.12, 160.51, 155.38, 144.91, 129.17, 128.51, 127.44, 126.61, 126.28, 114.06, 81.13, 78.41, 69.17, 67.46, 54.01, 52.11, 42.85, 32.67, 28.16, 27.98, 27.62; HRMS (ESI+) 808.4016 (calcd for 808.3916 $C_{45}H_{53}N_5O_9$, M+Na$^+$).

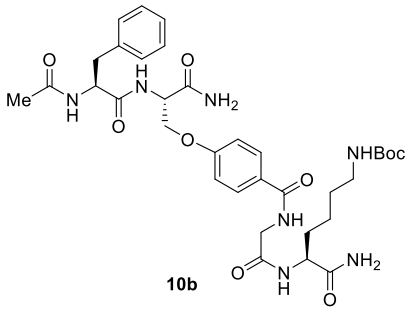


Following general procedure C, the reaction between **9** (62.8 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **9b** (11.6 mg, 14%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 – 8.57 (m, 2H), 8.34 (d, J = 7.8 Hz, 1H), 8.14 (d, J = 8.2 Hz, 1H), 8.00 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.8 Hz, 2H), 7.36 (s, 1H), 7.31 – 7.23 (m, 12H), 7.21 – 7.14 (m, 10H), 7.07 (s, 1H), 7.01 (d, J = 8.8 Hz, 2H), 4.63 – 4.54 (m, 2H), 4.27 – 4.19 (m, 2H), 4.16 (td, J = 8.6, 5.2 Hz, 1H), 3.92 – 3.85 (m, 2H), 3.04 (dd, J = 13.8, 4.4 Hz, 1H), 2.74 (dd, J = 13.8, 10.1 Hz, 1H), 2.34 – 2.26 (m, 2H), 1.95 – 1.84 (m, 1H), 1.74 (s, 3H), 1.71 – 1.62 (m, 1H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.28, 171.69, 171.51, 170.45, 169.32, 169.05, 166.10, 160.61, 144.90, 137.96, 129.19, 129.14, 128.51, 128.01, 127.44, 126.57, 126.29, 126.22, 114.13, 69.16, 67.87, 54.02, 52.33, 52.11, 42.83, 37.41, 32.67, 27.99, 22.44; HRMS (ESI+) 840.3720 (calcd for 840.3715 $C_{47}H_{49}N_7O_8$, M+Na$^+$).

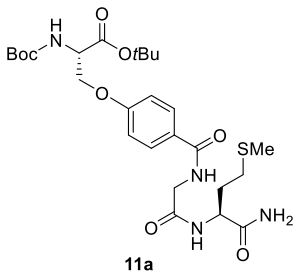


Following general procedure C, the reaction between **10** (48.5 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **10a** (26.8 mg, 40%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.62 (t, J = 5.6 Hz, 1H), 7.94 (d, J = 8.1 Hz, 1H), 7.84 (d, J = 8.6 Hz, 2H), 7.32 (d, J = 6.3 Hz, 2H), 7.03 (s, 1H), 7.00 (d, J = 8.6 Hz, 2H), 6.75 (t, J = 5.0 Hz, 1H), 4.35 – 4.27 (m, 1H), 4.27 – 4.19 (m, 2H), 4.16 (q, J = 8.3 Hz, 1H), 3.88 (qd, J = 16.3, 5.7 Hz, 2H), 2.87 (q, J = 6.5 Hz, 2H), 1.73

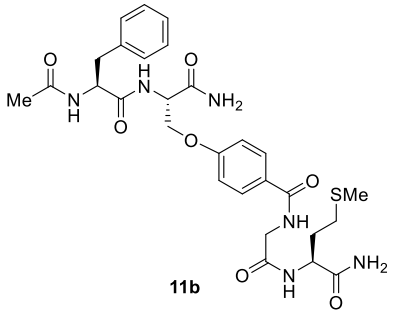
– 1.61 (m, 1H), 1.57 – 1.45 (m, 2H), 1.45 – 1.38 (m, 1H), 1.39 (s, 9H), 1.39 (s, 9H), 1.37 (s, 9H), 1.27 – 1.17 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.61, 168.97, 168.96, 166.07, 160.52, 155.55, 155.39, 129.18, 126.62, 114.07, 81.13, 78.41, 77.34, 67.46, 54.03, 52.30, 42.73, 31.64, 29.24, 28.29, 28.16, 27.93, 27.62, 22.71; HRMS (ESI+) 666.3692 (calcd for 666.3709 $C_{32}H_{51}N_5O_{10}$, M+Na$^+$).



Following general procedure C, the reaction between **10** (48.5 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **10b** (34.3 mg, 49%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.63 (t, *J* = 5.8 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 7.94 (d, *J* = 8.2 Hz, 1H), 7.85 (d, J = 8.9 Hz, 2H), 7.39 – 7.28 (m, 3H), 7.28 – 7.22 (m, 4H), 7.21 – 7.15 (m, 1H), 7.03 (d, *J* = 8.8 Hz, 2H), 7.03 (s, 1H), 6.76 (t, *J* = 5.4 Hz, 1H), 4.63 – 4.52 (m, 2H), 4.28 – 4.19 (m, 2H), 4.16 (td, *J* = 8.5, 4.9 Hz, 1H), 3.94 – 3.80 (m, 2H), 3.04 (dd, *J* = 13.9, 4.4 Hz, 1H), 2.87 (q, *J* = 6.7 Hz, 2H), 2.74 (dd, *J* = 13.8, 10.0 Hz, 1H), 1.75 (s, 3H), 1.70 – 1.62 (m, 1H), 1.55 – 1.46 (m, 1H), 1.37 (s, 9H), 1.34 (m, 2H), 1.29 – 1.17 (m, 2H); ^{13}C NMR (125 MHz, DMSO-d_6): δ 173.63, 171.70, 170.47, 169.35, 168.97, 166.06, 160.63, 155.56, 137.96, 129.15, 128.02, 127.31, 126.59, 126.24, 114.15, 77.36, 67.87, 54.03, 52.31, 42.73, 37.41, 31.65, 29.25, 28.30, 22.71, 22.45; HRMS (ESI+) 698.3529 (calcd for 698.3508 $C_{34}H_{47}N_7O_9$, M+H$^+$).



Following general procedure C, the reaction between **11** (38.8 mg, 0.100 mmol) and **2c** (39.2 mg, 0.150 mmol) afforded the desired product, **11a** (17.3 mg, 30%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^{1}H NMR (500 MHz, DMSO-d_6): δ 8.65 (t, *J* = 5.7 Hz, 1H), 8.05 (d, *J* = 8.2 Hz, 1H), 7.84 (d, *J* = 8.7 Hz, 2H), 7.33 (d, *J* = 10.9 Hz, 2H), 7.11 (s, 1H), 7.00 (d, *J* = 8.7 Hz, 2H), 4.35 – 4.26 (m, 2H), 4.26 – 4.19 (m, 2H), 4.00 – 3.79 (m, 2H), 2.48 – 2.31 (m, 2H), 2.02 (s, 3H), 1.99 – 1.92 (m, 1H), 1.83 – 1.72 (m, 1H), 1.39 (s, 9H), 1.38 (s, 9H); ^{13}C NMR (125 MHz, DMSO): δ 173.20, 169.22, 169.00, 166.17, 160.55, 155.42, 129.20, 126.60, 114.10, 81.16, 78.45, 67.48, 54.04, 51.64, 42.87, 31.58, 29.69, 28.18, 27.64, 14.63; HRMS (ESI+) 569.2613 (calcd for 569.2640 $C_{26}H_{40}N_4O_8S$, M+H$^+$).



11b

Following general procedure C, the reaction between **11** (38.8 mg, 0.100 mmol) and **2k** (44.0 mg, 0.150 mmol) afforded the desired product, **11b** (23.8 mg, 40%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH). ^1H NMR (500 MHz, DMSO-d_6): δ 8.66 (t, *J* = 5.7 Hz, 1H), 8.35 (d, *J* = 7.8 Hz, 1H), 8.15 (d, *J* = 8.2 Hz, 1H), 8.06 (d, *J* = 8.2 Hz, 1H), 7.86 (d, *J* = 8.8 Hz, 2H), 7.35 (d, *J* = 11.0 Hz, 2H), 7.31 – 7.22 (m, 5H), 7.20 – 7.15 (m, 1H), 7.11 (s, 1H), 7.03 (d, *J* = 8.9 Hz, 2H), 4.64 – 4.52 (m, 2H), 4.29 (td, *J* = 8.8, 4.5 Hz, 1H), 4.26 – 4.19 (m, 2H), 3.95 – 3.81 (m, 2H), 3.04 (dd, *J* = 13.8, 4.4 Hz, 1H), 2.74 (dd, *J* = 13.8, 10.0 Hz, 1H), 2.48 – 2.36 (m, 2H), 2.02 (s, 3H), 2.00 – 1.92 (m, 1H), 1.83 – 1.77 (m, 1H), 1.75 (s, 3H); ^{13}C NMR (125 MHz, DMSO): δ 173.19, 171.71, 170.47, 169.34, 169.21, 166.13, 160.65, 137.97, 129.21, 129.16, 128.02, 126.57, 126.24, 114.15, 67.88, 54.02, 52.35, 51.62, 42.86, 37.42, 31.58, 29.68, 22.44, 14.62; HRMS (ESI+) 601.2457 (calcd for 601.2439 $C_{28}H_{36}N_6O_7S$, $M+H^+$).

Macrocyclization

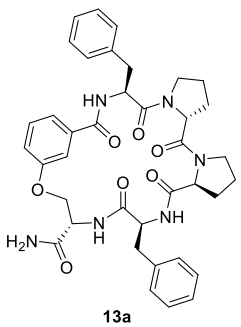
General procedure D:

Prior to setting up reactions, all peptide substrates were dried by co-evaporation with toluene to remove residual water. The reaction was set up under a flow of argon. To a 20 mL vial (28 x 57mm, 24-414 Thread, with Red Pressure Relief Cap, CG-4912-05) equipped with a stir bar, a linear peptide precursor (0.0500 mmol), potassium carbonate (6.91 mg, 1.00 equiv, 0.0500 mmol), and 4DPAIPN (3.98 mg, 0.100 equiv, 5.00 µmol) were weighed out and 6.20 mL MeCN was added. To the reaction mixture, a solution of quinuclidine (0.278 mg, 0.0500 equiv, 2.50 µmol) dissolved in MeCN (0.150 mL) was added. Then, a solution of $NiBr_2$·glyme (3.09 mg, 0.200 equiv, 0.0100 mmol) and 4,4'-di-*tert*-butyl-2,2'-bipyridine (dtbbpy) (2.68 mg, 0.200 equiv, 0.0100 mmol) dissolved in MeCN (0.350 mL) was added to the reaction mixture, followed by 3.30 mL DMSO. The vial was sparged with Ar for 15 minutes and sealed with parafilm, and then placed in MSD photoreactor and irradiated with 100% LED exposure for 24 hours (at 450 nm, stirring speed of 1000 rpm, fan speed of 5500 rpm). After 24 hours, the reaction mixture was filtered through an Acrodisc® syringe filter. The filtrate was then concentrated under reduced pressure using a Biotage® V-10 evaporator. The crude material was purified by preparative reverse-phase HPLC, followed by SFC separation (CELERIS™ Arginine 5 µm, 21.1 x 250 mm from Regis Technologies, mobile phase: MeOH/MeCN, 0.1% NH_4OH) if necessary.

A 10X stock solution of "quinuclidine" (2.80 mg quinuclidine dissolved in 1.50 mL MeCN) was prepared and 0.150 mL of this solution was used. A 5X stock solution of "$NiBr_2$·glyme + dtbbpy" (15.4 mg $NiBr_2$·glyme and 13.4 mg dtbbpy dissolved in 1.75 mL MeCN) was prepared and 0.350 mL of this solution was used.

Products in Figure 3

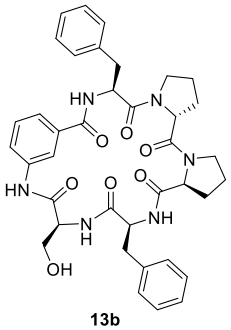
Following general procedure D, the intramolecular reaction of **13** (38.8 mg, 0.0500 mmol) afforded the desired products, **13a** (C–O product, 15.5 mg, 45%) and **13b** (C–N product, 7.8 mg, 22%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA).



13a

^{1}H NMR (600 MHz, DMSO-d_6): δ 8.67 (s, 1H), 8.66 (s, 1H), 8.20 (s, 1H), 7.76 (s, 1H), 7.52 – 7.45 (m, 2H), 7.43 (s, 1H), 7.40 – 7.35 (m, 3H), 7.34 – 7.26 (m, 6H), 7.23 – 7.18 (m, 2H), 7.09 (s, 1H), 5.35 (d, *J* = 7.6 Hz, 1H), 4.93 – 4.87 (m, 1H), 4.52 – 4.47 (m, 2H), 4.37 (t, *J* = 10.0 Hz, 1H), 4.20 (d, *J* = 6.8 Hz, 1H), 3.98 (d, *J* = 10.8 Hz, 1H), 3.82 – 3.76 (m, 1H), 3.64 – 3.58 (m, 1H), 3.50 – 3.45 (m, 1H), 3.34 (dd, *J* = 12.4, 7.4 Hz, 2H), 3.24 (t, *J* = 11.9 Hz, 1H), 3.11 (d, *J* = 9.2 Hz, 1H), 3.04 (dd, *J* = 13.2, 6.0 Hz, 1H), 2.11 – 2.02 (m, 1H), 1.97 – 1.90 (m, 1H),

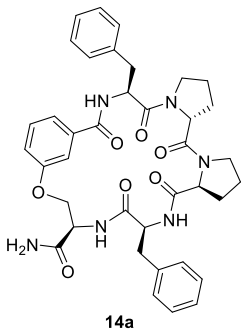
1.88 – 1.81 (m, 1H), 1.75 – 1.68 (m, 2H), 1.67 – 1.61 (m, 1H), 1.60 – 1.54 (m, 1H), 1.11 – 1.05 (m, 1H); ^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 172.16, 170.95, 170.41, 170.30, 168.74, 164.76, 157.20, 137.84, 137.84, 134.49, 129.88, 129.31, 129.23, 128.34, 128.21, 126.43, 126.39, 121.07, 121.02, 110.96, 67.58, 60.17, 57.60, 52.80, 51.33, 50.72, 47.49, 46.76, 37.66, 36.62, 29.12, 27.98, 25.05, 22.93; HRMS (ESI+) 695.3228 (calcd for 695.3188 $C_{38}H_{42}N_6O_7$, M+H$^+$).



13b

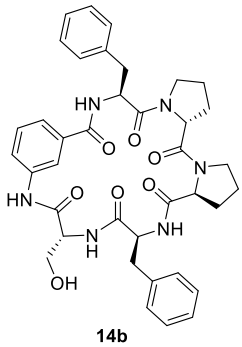
^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 7.82 (d, *J* = 6.5 Hz, 1H), 7.72 – 7.66 (m, 1H), 7.54 – 7.48 (m, 1H), 7.45 (d, *J* = 7.5 Hz, 2H), 7.41 (d, *J* = 7.8 Hz, 1H), 7.35 (dt, *J* = 15.1, 7.3 Hz, 6H), 7.25 (t, *J* = 7.4 Hz, 2H), 5.22 (dd, *J* = 9.1, 5.1 Hz, 1H), 4.82 – 4.76 (m, 1H), 4.60 (br s, 1H), 4.45 – 4.33 (m, 2H), 3.83 – 3.69 (m, 2H), 3.60 (br s, 1H), 3.52 (dd, *J* = 9.4, 8.4 Hz, 1H), 3.48 – 3.40 (m, 1H), 3.29 – 3.16 (m, 4H), 3.11 (br s, 1H), 2.06 (dq, *J* = 12.5, 7.2 Hz, 1H), 2.00 – 1.90 (m, 1H), 1.90 – 1.70 (m, 3H), 1.70 – 1.62 (m, 1H), 1.61 – 1.48 (m, 1H), 1.07 – 0.92 (m, 1H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.86, 173.40, 173.27, 173.11, 170.49, 168.89, 139.06, 138.38, 138.00, 136.23, 136.13, 130.73, 130.70, 130.64, 130.57, 129.60, 129.44, 128.36, 128.10, 127.84, 62.95, 61.62, 59.50, 55.19, 55.03, 54.80, 48.75, 48.26, 40.64, 39.14, 30.14, 29.16, 26.15, 24.08. HRMS (ESI+) 695.3131 (calcd for 695.3188 $C_{38}H_{42}N_6O_7$, M+H$^+$).

Following general procedure D, the intramolecular reaction of **14** (38.8 mg, 0.0500 mmol) afforded the desired products, **14a** (C–O product, 14.0 mg, 40%) and **14b** (C–N product, 9.5 mg, 27%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA), followed by SFC separation (MeOH/MeCN, 0.1% NH_4OH).



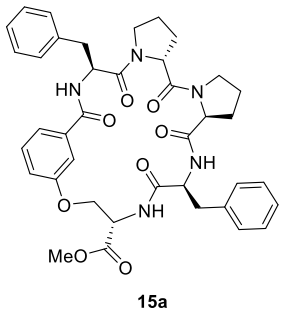
14a

^{1}H NMR (600 MHz, DMSO-*d*$_6$): δ 8.97 (d, *J* = 7.7 Hz, 1H), 8.42 (d, *J* = 8.7 Hz, 1H), 7.82 (s, 1H), 7.72 (s, 1H), 7.58 (d, *J* = 9.5 Hz, 1H), 7.53 (d, *J* = 7.6 Hz, 1H), 7.42 – 7.37 (m, 3H), 7.35 (s, 1H), 7.33 – 7.27 (m, 6H), 7.24 – 7.20 (m, 2H), 7.17 (d, *J* = 8.0 Hz, 1H), 5.15 (q, *J* = 7.7 Hz, 1H), 4.88 (td, *J* = 10.5, 4.6 Hz, 1H), 4.39 – 4.31 (m, 3H), 4.18 (d, *J* = 8.3 Hz, 1H), 4.02 (dd, *J* = 11.6, 3.2 Hz, 1H), 3.76 – 3.71 (m, 1H), 3.48 – 3.39 (m, 2H), 3.24 – 3.05 (m, 5H), 2.04 – 1.97 (m, 1H), 1.94 (tt, *J* = 12.3, 6.4 Hz, 1H), 1.79 – 1.67 (m, 2H), 1.67 – 1.55 (m, 3H), 0.98 – 0.86 (m, 1H); ^{13}C NMR (151 MHz, DMSO-*d*$_6$): δ 172.23, 170.67, 170.29, 170.12, 168.48, 165.35, 156.84, 138.15, 137.14, 134.54, 129.75, 129.45, 129.42, 128.38, 128.14, 126.72, 126.43, 121.57, 121.47, 113.20, 68.51, 59.80, 57.56, 52.88, 52.88, 50.74, 47.19, 46.60, 39.02, 38.36, 28.89, 28.06, 24.99, 22.69; HRMS (ESI+) 695.3228 (calcd for 695.3188 $C_{38}H_{42}N_6O_7$, M+H$^+$).



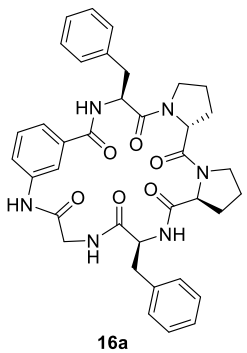
14b

^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 7.80 (d, *J* = 8.1 Hz, 1H), 7.53 – 7.47 (m, 1H), 7.46 – 7.27 (m, 8H), 7.26 – 7.18 (m, 3H), 7.16 (d, *J* = 7.1 Hz, 1H), 5.30 (t, *J* = 6.5 Hz, 1H), 4.62 (t, *J* = 7.2 Hz, 1H), 4.51 (dd, *J* = 11.3, 4.8 Hz, 1H), 4.37 (d, *J* = 8.7 Hz, 1H), 4.21 (t, *J* = 3.3 Hz, 1H), 4.01 – 3.93 (m, 1H), 3.89 (dd, *J* = 11.3, 4.9 Hz, 1H), 3.81 (dd, *J* = 11.9, 3.2 Hz, 1H), 3.72 – 3.65 (m, 1H), 3.65 – 3.57 (m, 1H), 3.53 – 3.44 (m, 1H), 3.39 (dd, *J* = 13.5, 6.3 Hz, 1H), 3.29 – 3.24 (m, 1H), 3.21 (dd, *J* = 13.4, 8.4 Hz, 1H), 2.31 – 2.17 (m, 1H), 2.13 – 2.01 (m, 2H), 1.97 – 1.78 (m, 3H), 1.77 – 1.66 (m, 1H), 1.42 – 1.23 (m, 2H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.62, 174.57, 174.13, 173.75, 171.92, 169.56, 139.24, 139.10, 135.15, 132.73, 130.81, 130.76, 130.64, 130.26, 129.56, 129.44, 129.23, 128.78, 127.87, 127.48, 63.42, 62.36, 60.53, 57.20, 56.59, 54.34, 48.66, 48.49, 38.77, 37.41, 30.37, 29.50, 26.62, 24.66. HRMS (ESI+) 695.3149 (calcd for 695.3188 $C_{38}H_{42}N_6O_7$, M+H$^+$).



15a

Following general procedure D, the intramolecular reaction of **15** (39.5 mg, 0.0500 mmol) afforded the desired product, **15a** (C–O product, 14.8 mg, 42%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, DMSO-*d*$_6$): δ 9.00 (d, *J* = 7.9 Hz, 1H), 8.45 (d, *J* = 9.5 Hz, 1H), 7.79 (s, 1H), 7.52 (d, *J* = 9.3 Hz, 1H), 7.46 – 7.04 (m, 13H), 5.32 (q, *J* = 7.8 Hz, 1H), 4.75 (q, *J* = 9.3 Hz, 1H), 4.67 – 4.60 (m, 1H), 4.52 (t, *J* = 7.0 Hz, 1H), 4.50 – 4.41 (m, 1H), 4.23 (d, *J* = 8.3 Hz, 1H), 4.04 (d, *J* = 12.3 Hz, 1H), 3.81 (t, *J* = 8.2 Hz, 1H), 3.68 – 3.61 (m, 1H), 3.67 (s, 3H), 3.58 – 3.48 (m, 1H), 3.41 – 3.28 (m, 2H), 3.26 – 3.18 (m, 1H), 3.13 – 3.04 (m, 2H), 2.20 – 2.05 (m, 1H), 2.01 – 1.92 (m, 1H), 1.92 – 1.84 (m, 1H), 1.82 – 1.57 (m, 4H), 1.21 – 1.11 (m, 1H); ^{13}C NMR (125 MHz, DMSO-*d*$_6$): δ 171.63, 170.99, 170.40, 169.48, 168.95, 164.86, 156.35, 137.78, 137.56, 134.87, 130.09, 129.24, 129.22, 128.22, 128.15, 126.39, 126.31, 121.26, 121.09, 110.99, 66.68, 60.13, 57.64, 52.91, 52.53, 51.26, 49.38, 47.50, 46.78, 37.24, 36.27, 29.02, 27.95, 25.02, 23.01; HRMS (ESI+) 710.3524 (calcd for 710.3184 $C_{39}H_{43}N_5O_8$, M+H$^+$).

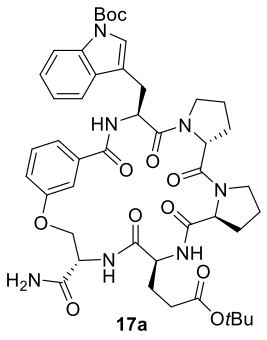


16a

Following general procedure D, the intramolecular reaction of **16** (37.3 mg, 0.0500 mmol) using 4DPAIPN (8.0 mg, 10.0 µmol) with 48 h reaction time afforded the desired product, **16a** (C–N product, 13.7 mg, 41%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA), followed by SFC separation (MeOH/MeCN, 0.1% NH_4OH). ^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.77' (s, 0.5H), 7.87 (s, 1H), 7.82 (d, *J* = 9.1 Hz, 1H), 7.70 (d, *J* = 7.6 Hz, 1H), 7.49 (t, *J* = 7.8 Hz, 1H), 7.41 (d, *J* = 7.5 Hz, 3H), 7.38 – 7.29 (m, 5H), 7.27 – 7.21 (m, 2H), 5.31 – 5.22 (m, 1H), 4.84 – 4.77 (m, 1H), 4.52 (t, *J* = 7.2 Hz, 1H), 4.40 (d, *J* = 7.7 Hz, 1H), 3.94 (d, *J* = 15.2 Hz, 1H), 3.80 (d, *J* = 14.0 Hz, 2H), 3.60 – 3.53 (m, 1H), 3.49 (q, *J* = 9.3 Hz, 1H), 3.30 – 3.16 (m, 5H),

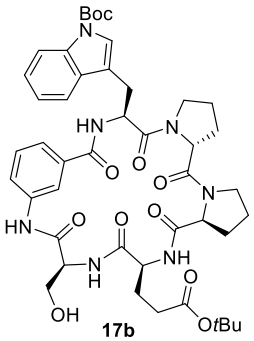
2.10 (dq, *J* = 13.0, 6.9 Hz, 1H), 2.04 – 1.96 (m, 1H), 1.95 – 1.86 (m, 1H), 1.80 (dq, *J* = 13.0, 6.9 Hz, 2H), 1.75 – 1.65 (m, 2H), 1.22 – 1.03 (m, 1H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 173.45, 173.41, 173.15, 172.92, 170.75, 168.98, 138.93, 138.86, 138.37, 136.36, 130.64, 130.56, 130.54, 130.29, 129.52, 129.48, 127.91, 127.84, 127.08, 126.98, 61.89, 59.50, 55.25, 54.27, 49.17, 48.76, 48.39, 39.85, 38.71, 30.32, 29.13, 26.11, 24.31; HRMS (ESI+) 665.3040 (calcd for 665.3082 $C_{37}H_{40}N_6O_6$, M+H$^+$).

Following general procedure D, the intramolecular reaction of **17** (43.7 mg, 0.0500 mmol) afforded the desired products, **17a** (C–O product, 10.7 mg, 25%) and **17b** (C–N product, 8.6 mg, 20%) as as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% NH_4OH).



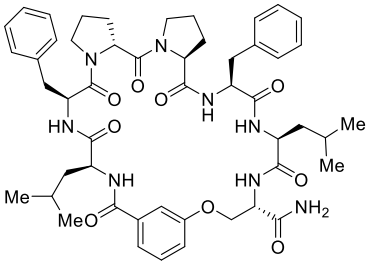
17a

^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.08 (d, *J* = 8.2 Hz, 1H), 7.98 (s, 1H), 7.71 (d, *J* = 7.6 Hz, 1H), 7.57 (s, 1H), 7.43 (d, *J* = 7.6 Hz, 1H), 7.33 (t, *J* = 7.9 Hz, 1H), 7.31 – 7.27 (m, 1H), 7.25 – 7.21 (m, 1H), 7.11 – 7.07 (m, 1H), 5.34 (t, *J* = 7.5 Hz, 1H), 4.76 (dd, *J* = 7.1, 5.2 Hz, 1H), 4.53 (dd, *J* = 8.2, 2.3 Hz, 1H), 4.51 – 4.42 (m, 4H), 4.12 – 4.05 (m, 1H), 3.69 – 3.61 (m, 1H), 3.61 – 3.50 (m, 2H), 3.40 – 3.33 (m, 1H), 3.20 (dd, *J* = 14.4, 7.0 Hz, 1H), 2.51 – 2.40 (m, 1H), 2.34 – 2.21 (m, 2H), 2.21 – 2.14 (m, 1H), 2.13 – 1.93 (m, 6H), 1.90 – 1.81 (m, 1H), 1.75 – 1.68 (m, 1H), 1.66 (s, 9H), 1.42 (s, 9H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.11, 174.06, 173.87, 173.42, 173.04, 171.30, 169.30, 158.66, 150.98, 136.71, 135.94, 131.85, 130.93, 125.50, 125.31, 123.63, 122.61, 121.97, 120.17, 117.56, 116.11, 112.46, 84.88, 82.02, 67.90, 62.28, 59.67, 54.11, 52.71, 52.62, 47.86, 46.93, 32.66, 30.78, 29.19, 28.44, 28.39, 28.25, 28.10, 26.39, 24.99; HRMS (ESI+) 872.4191 (calcd for 872.4189 $C_{45}H_{57}N_7O_{11}$, M+H$^+$).



17b

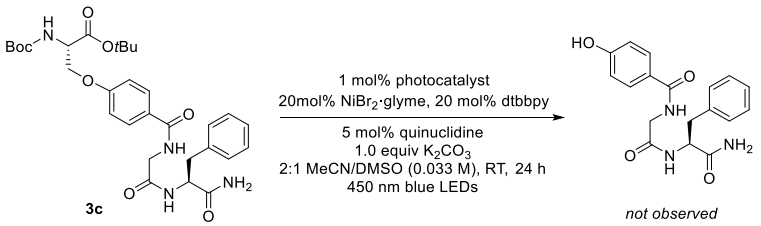
^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.10 (d, *J* = 8.0 Hz, 1H), 7.75 (d, *J* = 7.6 Hz, 2H), 7.71 (s, 1H), 7.56 (s, 1H), 7.50 (t, *J* = 7.2 Hz, 2H), 7.34 – 7.25 (m, 2H), 5.30 – 5.19 (m, 1H), 4.63 (s, 1H), 4.59 – 4.54 (m, 1H), 4.53 – 4.48 (m, 1H), 4.36 (t, *J* = 6.7 Hz, 1H), 4.04 – 3.95 (m, 1H), 3.77 (s, 1H), 3.68 – 3.54 (m, 2H), 3.52 – 3.44 (m, 1H), 3.30 – 3.24 (m, 2H), 3.17 (s, 1H), 2.43 (t, *J* = 8.1 Hz, 2H), 2.27 – 2.17 (m, 2H), 2.16 – 2.01 (m, 4H), 1.99 – 1.86 (m, 2H), 1.82 – 1.74 (m, 1H), 1.66 (s, 9H), 1.42 (s, 9H), 1.40 – 1.38 (m, 1H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 173.87, 173.87, 173.57, 173.57, 173.10, 170.81, 169.27, 150.89, 136.56, 136.70, 136.37, 131.80, 130.66, 125.63, 125.63, 125.53, 125.53, 123.64, 120.37, 118.31, 117.16, 116.16, 84.99, 81.95, 62.69, 61.91, 59.59, 53.60, 53.15, 48.83, 48.49, 32.50, 30.27, 30.12, 29.45, 29.09, 29.05, 28.41, 28.40, 25.92, 25.18; HRMS (ESI+) 872.4278 (calcd for 872.4189 $C_{45}H_{57}N_7O_{11}$, M+H$^+$).



18a

Following general procedure D, the intramolecular reaction of **18** (50.1 mg, 0.0500 mmol) using 4DPAIPN (8.0 mg, 10.0 µmol) afforded the desired product, **18a** (C–O product, 12.3 mg, 27%) as a white solid after purification using preparative reverse-phase HPLC (eluent: MeCN/water, 0.1% TFA). ^{1}H NMR (500 MHz, methanol-*d*$_4$): δ 8.66' (d, *J* = 7.6 Hz, 0.9H), 8.20 (s, 1H), 8.15' (d, *J* = 7.6 Hz, 0.7H), 7.94' (d, *J* = 8.7 Hz, 0.9H), 7.74 (d, *J* = 7.2 Hz, 1H), 7.39 (t, *J* = 8.5 Hz, 2H), 7.36 – 7.26 (m, 8H), 7.25 – 7.20 (m, 3H), 7.19 – 7.13 (m, 2H), 7.07 (d, *J* = 8.0 Hz, 1H), 5.15 – 5.08 (m, 1H), 5.05 – 4.98 (m, 1H), 4.81 (dd, *J* = 11.9, 3.1 Hz, 1H), 4.72 – 4.66 (m, 1H), 4.51 – 4.45 (m, 2H), 4.40 (dt, *J* = 10.4, 6.5 Hz, 1H), 4.30 – 4.21 (m, 2H), 3.62 (t, *J* = 7.9 Hz, 1H), 3.49 – 3.43 (m, 1H), 3.42 – 3.34 (m, 4H), 3.29 – 3.25 (m, 1H), 2.91 (dd, *J* = 13.6, 6.1 Hz, 1H), 2.09 – 2.02 (m, 1H), 2.00 – 1.93 (m, 1H), 1.90 – 1.82 (m, 2H), 1.79 – 1.70 (m, 5H), 1.65 – 1.57 (m, 3H), 1.37 – 1.29 (m, 1H), 1.18 – 1.11 (m, 1H), 1.00 (d, *J* = 6.6 Hz, 3H), 0.97 (d, *J* = 6.7 Hz, 3H), 0.95 (d, *J* = 6.4 Hz, 3H), 0.92 (d, *J* = 5.8 Hz, 3H); ^{13}C NMR (125 MHz, methanol-*d*$_4$): δ 174.97, 174.25, 174.11, 173.79, 173.45, 171.99, 170.36, 170.32, 158.50, 138.95, 138.72, 136.63, 130.89, 130.46, 130.16, 129.64, 129.31, 128.00, 127.60, 121.53, 121.49, 113.24, 67.70, 61.59, 60.52, 57.97, 55.30, 54.01, 53.84, 51.37, 48.75, 48.16, 41.97, 41.17, 38.93, 37.50, 30.16, 29.00, 26.31, 26.07, 24.57, 23.10, 22.94, 22.24; HRMS (ESI+) 921.4910 (calcd for 921.4869 $C_{50}H_{64}N_8O_9$, M+H$^+$).

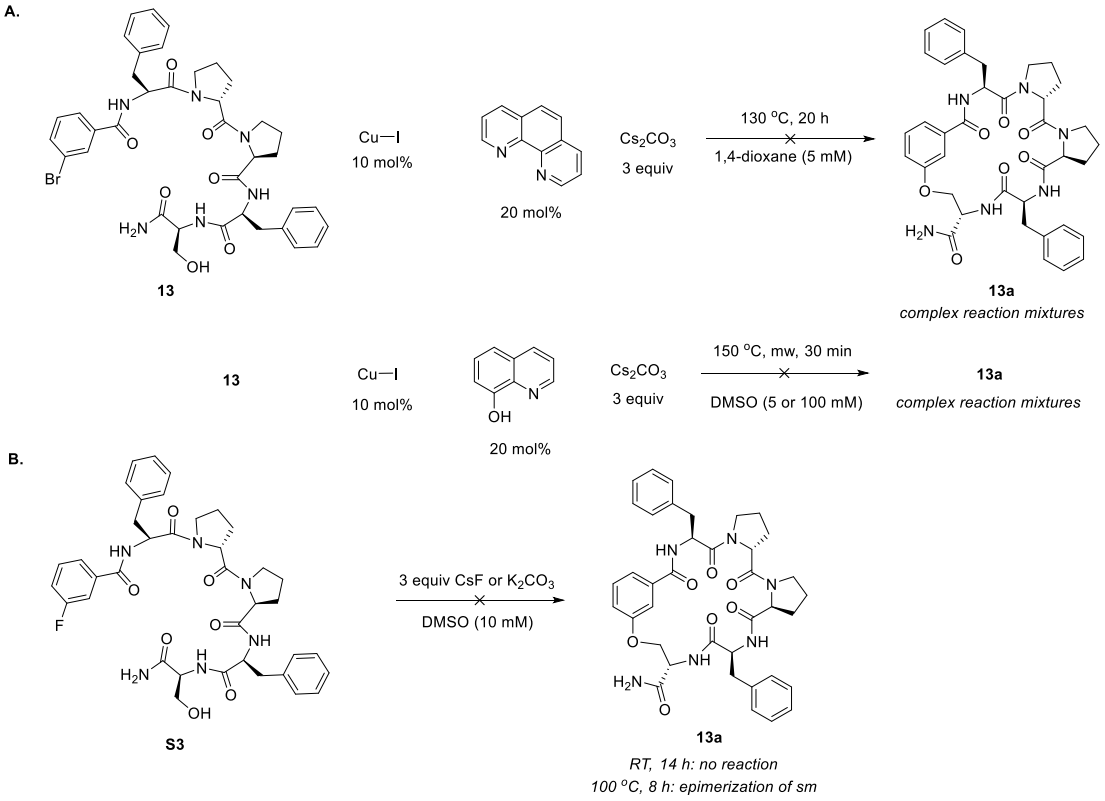
Product stability experiments



Scheme S3. Stability test of C–O coupling product **3c**.

To examine the origin of the phenol side product, we conducted product stability experiments where the desired product **3c** was resubjected to the reaction condition. As a result, we found that **3c** is stable under the reaction condition, ruling out possibility of phenol being produced by β-elimination, releasing ArOH. This confirms that residual phenol product observed in the reaction is coming from the reaction between **1** and existing water.

Alternative methods attempted for macrocyclization



Scheme S4. Macrocyclization attempt under Ullmann (**A**) and S_NAr (**B**) conditions.

We also attempted other methods traditionally utilized in macroetherification (Ullmann reaction and S_NAr). However, we found that there was no desired product observed and the starting material **13** decomposed under harsh Ullmann reaction conditions (Scheme S4, **A**).[5,6] In S_NAr conditions[7,8], the reaction of **S3** did not afford the desired product at room temperature and epimerization of the starting material **S3** was observed at higher temperature (Scheme S4, **B**).

Conformational sampling

For computational modeling to predict lowest energy conformations of two proposed designs for macrocyclization, conformational sampling was utilized and a hundred thousand conformations were generated by using our in-house implementation of the distance geometry approach. Phenylalanine was replaced by alanine for simplicity in calculation. For design 1 (Figure 3), compound **12** showed highly flexible structures resulting in 51 conformations within 2 kcal/mol compared to the lowest energy (54.1 kcal/mol). In the case of compound **13** containing D-Pro–L-Pro motif, 10 conformations were found within the 2kcal/mol ranges with the lowest energy being 97.2 kcal/mol. In this pool, 9 out of 10 conformations showed intramolecular hydrogen bonding interactions between the backbone amides orienting two arms in antiparallel directions.

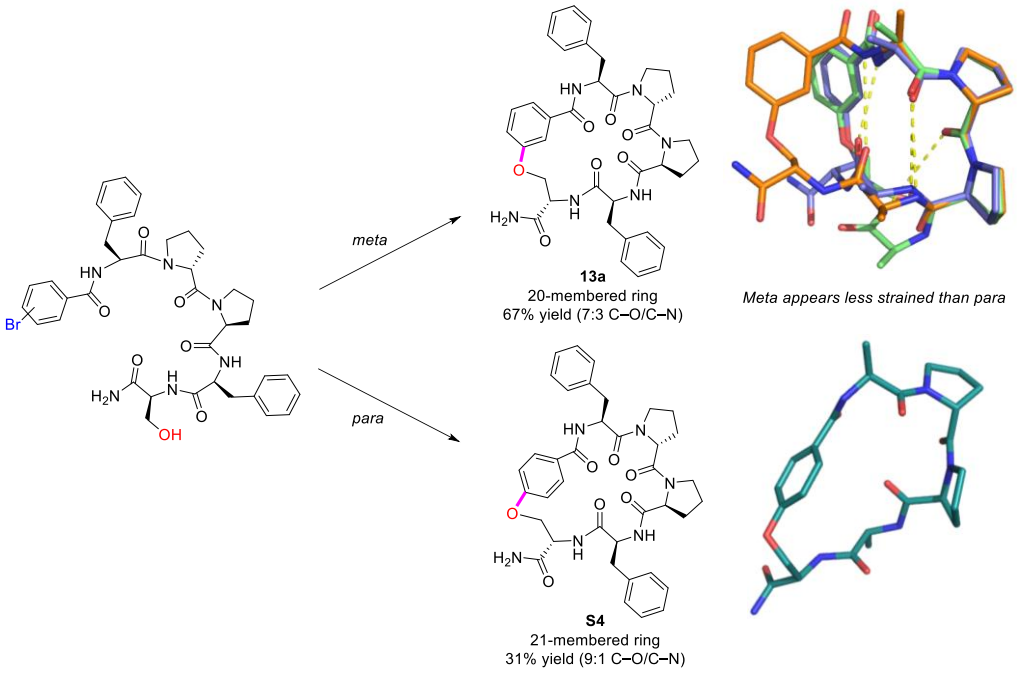


Figure S5. Computational modeling and experimental data for *meta* vs. *para* substituted macrocycles.

The macrocyclic conformations were also explored in addition to the two proposed designs. The 20-membered ring (**13a**, *meta*) showed organized hydrogen bonding interactions (yellow dashed lines), while 21-membered ring (**S4**, *para*) has a distorted conformation with a loss of intramolecular H-bond network due to its connectivity.

References

(1) A. B. Santanilla, E. L. Regalado, T. Pereira, M. Shevlin, K. Bateman, L.-C. Campeau, J. Schneeweis, S. Berritt, Z.-C. Shi, P. Nantermet, Y. Liu, R. Helmy, C. J. Welch, P. Vachal, I. W. Davies, T. Cernak, S. D. Dreher, *Science*, 2015, **347**, 49.

(2) N. J. Gesmundo, B. Sauvagnat, P. J. Curran, M. P. Richards, C. L. Andrews, P. J. Dandliker, T. Cernak, *Nature*, 2018, **557**, 228.

(3) S. Lin, S. Dikler, W. D. Blincoe, R. D. Ferguson, R. P. Sheridan, Z. Peng, D. V. Conway, K. Zawatzky, H. Wang, T. Cernak, I. W. Davies, D. A. DiRocco, H. Sheng, C. J. Welch, S. D. Dreher, *Science*, 2018, **361**, eaar6236.

(4) J. A. Terrett, J. D. Cuthbertson, V. W. Shurtleff, D. W. C. MacMillan, *Nature*, 2015, **524**, 330.

(5) H. Uchiro, R. Kato, Y. Arai, M. Hasegawa, Y. Kobayakawa, *Org. Lett*. 2011, **13**, 6268.

(6) J. C. Collins, K. A. Farley, C. Limberakis, S. Liras, D. Price, K. James, *J. Org. Chem.* 2012, **77**, 11079.

(7) D. L. Boger, S. Miyazaki, S. H. Kim, J. H. Wu, S. L. Castle, O. Loiseleur, Q. Jin, *J. Am. Chem. Soc.* 1999, **121**, 10004.

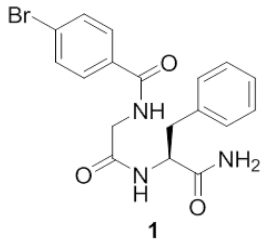
(8) D. A. Evans, M. R. Wood, B. W. Trotter, T. I. Richardson, J. C. Barrow, J. L. Katz, *Angew. Chem. Int. Ed*. 1998, **37**, 2700.

Worksheet from Library Studio for preparation of stock solutions in HTE

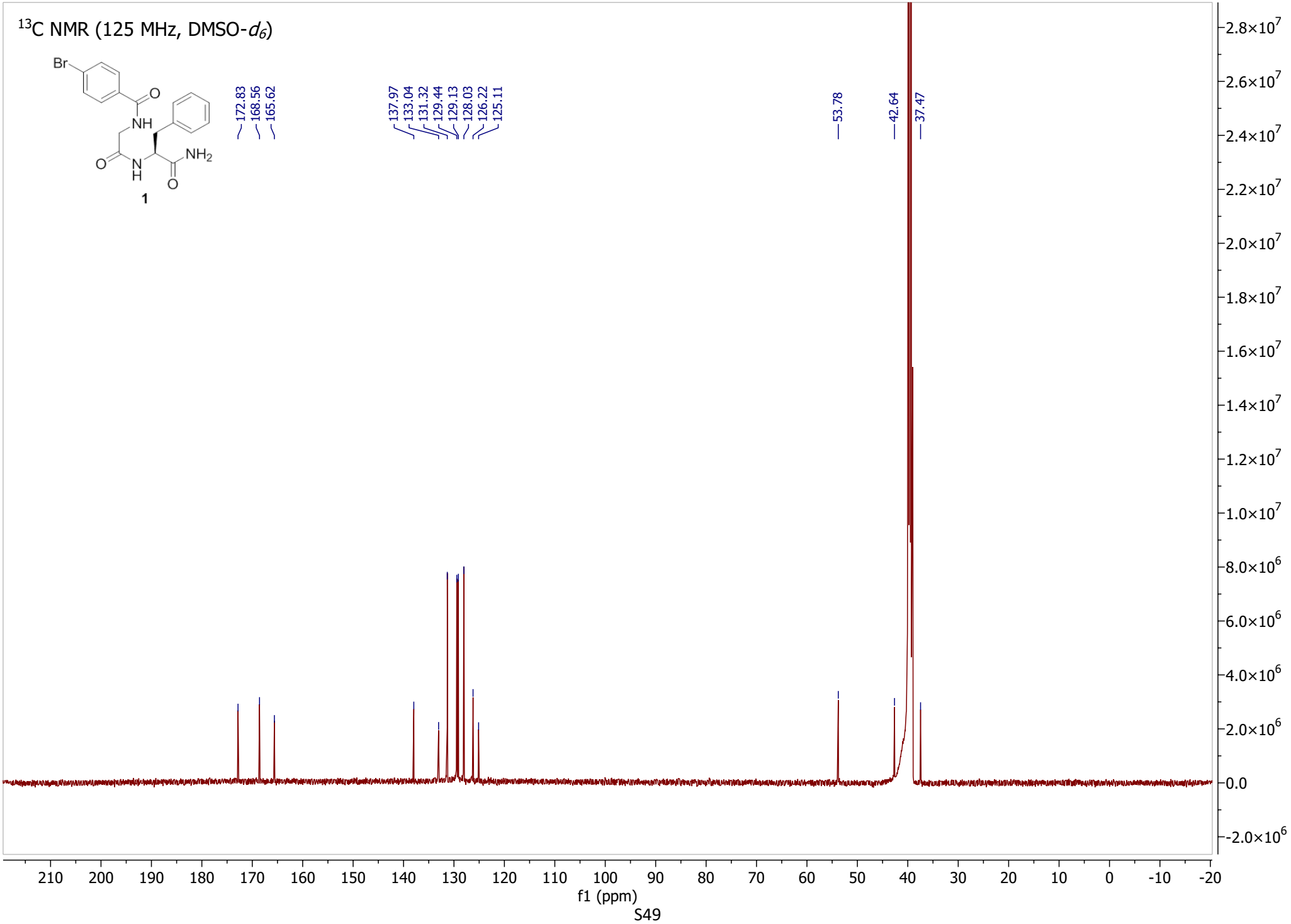
Mapped Source			Chemical				
Name	Amount	Actual	Name	d (g/ml)	Amount	Actual	Actual Conc.
ArBr_DMF	0.400 µl	1000.000 µl	ArBr	1.000	50.532 mg		0.125 mol/l
			DMF	0.948	0.949 ml		remainder
Boc-Ser-OtBu_s	0.300 µl	1000.000 µl	Boc-Ser-OtBu	1.000	65.329 mg		0.250 mol/l
			DMF	0.948	0.935 ml		remainder
Ir[dF(CF3)ppy]2 (dtbbpy)PF6_s_5%quin	0.100 µl	1000.000 µl	Ir[dF(CF3)ppy]2 (dtbbpy)PF6	1.000	28.048 mg		0.025 mol/l
			quinuclidine	1.000	2.780 mg		0.025 mol/l
			DMF	0.948	0.969 ml		remainder
ArBr_DBU_DMF	0.400 µl	1000.000 µl	ArBr	1.000	50.532 mg		0.125 mol/l
			DBU	1.018	19.030 mg		0.125 mol/l
			DMF	0.948	0.931 ml		remainder
NiCl2(dme) _dtbbpy_dmf	0.200 µl	1000.000 µl	NiCl2(dme)	1.000	10.986 mg		0.050 mol/l
			dtbbpy	1.000	13.420 mg		0.050 mol/l
			DMF	0.948	0.976 ml		remainder
Ir[dF(H)ppy]2(dtbbpy) PF6_5%qui	0.100 µl	1000.000 µl	Ir[dF(H)ppy]2 (dtbbpy)PF6	1.000	24.648 mg		0.025 mol/l
			quinuclidine	1.000	2.780 mg		0.025 mol/l
			DMF	0.948	0.973 ml		remainder
Ir[dF(Me)ppy]2(dtbbpy) PF6_5%qui	0.100 µl	1000.000 µl	Ir[dF(Me)ppy]2 (dtbbpy)PF6	1.000	25.349 mg		0.025 mol/l
			quinuclidine	1.000	2.780 mg		0.025 mol/l
			DMF	0.948	0.972 ml		remainder
Ru(bpy)3(PF6)2_5%qui	0.100 µl	1000.000 µl	Ru(bpy)3(PF6)2	1.000	21.489 mg		0.025 mol/l
			quinuclidine	1.000	2.780 mg		0.025 mol/l
			DMF	0.948	0.976 ml		remainder
4CzIPN_5%qui	0.100 µl	1000.000 µl	4CzIPN	1.000	19.722 mg		0.025 mol/l
			quinuclidine	1.000	2.780 mg		0.025 mol/l
			DMF	0.948	0.977 ml		remainder
4DPAIPN_5%qui	0.100 µl	1000.000 µl	4DPAIPN	1.000	19.924 mg		0.025 mol/l
			quinuclidine	1.000	2.780 mg		0.025 mol/l
			DMF	0.948	0.977 ml		remainder
Ir[dF(CF3)ppy]2 (dtbbpy)PF6_s_10% quin	0.100 µl	1000.000 µl	Ir[dF(CF3)ppy]2 (dtbbpy)PF6	1.000	28.048 mg		0.025 mol/l
			quinuclidine	1.000	5.559 mg		0.050 mol/l
			DMF	0.948	0.966 ml		remainder
Ir[dF(H)ppy]2(dtbbpy) PF6_s_10%quin	0.100 µl	1000.000 µl	Ir[dF(H)ppy]2 (dtbbpy)PF6	1.000	24.648 mg		0.025 mol/l
			quinuclidine	1.000	5.559 mg		0.050 mol/l
			DMF	0.948	0.970 ml		remainder
Ir[dF(Me)ppy]2(dtbbpy) PF6_s_10%quin	0.100 µl	1000.000 µl	Ir[dF(Me)ppy]2 (dtbbpy)PF6	1.000	25.349 mg		0.025 mol/l

Mapped Source			Chemical				
Name	Amount	Actual	Name	d (g/ml)	Amount	Actual	Actual Conc.
			quinuclidine	1.000	5.559 mg		0.050 mol/l
			DMF	0.948	0.969 ml		remainder
Ru(bpy)3(PF6)2_s_10% quin	0.100 µl	1000.000 µl	Ru(bpy)3(PF6)2	1.000	21.489 mg		0.025 mol/l
			DMF	0.948	0.973 ml		remainder
			quinuclidine	1.000	5.559 mg		0.050 mol/l
4CzIPN_s_10%quin	0.100 µl	1000.000 µl	4CzIPN	1.000	19.722 mg		0.025 mol/l
			quinuclidine	1.000	5.559 mg		0.050 mol/l
			DMF	0.948	0.975 ml		remainder
4DPAIPN_s_10%quin	0.100 µl	1000.000 µl	4DPAIPN	1.000	19.924 mg		0.025 mol/l
			quinuclidine	1.000	5.559 mg		0.050 mol/l
			DMF	0.948	0.975 ml		remainder
NiCl2(dme)_OMe	0.200 µl	1000.000 µl	NiCl2(dme)	1.000	10.986 mg		0.050 mol/l
			dOMebpy	1.000	10.812 mg		0.050 mol/l
			DMF	0.948	0.978 ml		remainder
NiCl2(dme)_phen	0.200 µl	1000.000 µl	NiCl2(dme)	1.000	10.986 mg		0.050 mol/l
			tMePhene	1.000	11.816 mg		0.050 mol/l
			DMF	0.948	0.977 ml		remainder
NiCl2(dme)_tButpy	0.200 µl	1000.000 µl	NiCl2(dme)	1.000	10.986 mg		0.050 mol/l
			tBu-tpy	1.000	20.080 mg		0.050 mol/l
			DMF	0.948	0.969 ml		remainder
NiBr2(dme)_dtbbpy	0.200 µl	1000.000 µl	NiBr2(dme)	1.000	15.431 mg		0.050 mol/l
			dtbbpy	1.000	13.420 mg		0.050 mol/l
			DMF	0.948	0.971 ml		remainder
NiBr2(dme)_OMe	0.200 µl	1000.000 µl	NiBr2(dme)	1.000	15.431 mg		0.050 mol/l
			dOMebpy	1.000	10.812 mg		0.050 mol/l
			DMF	0.948	0.974 ml		remainder
NiBr2(dme)_phen	0.200 µl	1000.000 µl	NiBr2(dme)	1.000	15.431 mg		0.050 mol/l
			tMePhene	1.000	11.816 mg		0.050 mol/l
			DMF	0.948	0.973 ml		remainder
NiBr2(dme)_tButpy	0.200 µl	1000.000 µl	NiBr2(dme)	1.000	15.431 mg		0.050 mol/l
			tBu-tpy	1.000	20.080 mg		0.050 mol/l
			DMF	0.948	0.964 ml		remainder
ArBr_BTMG	0.400 µl	1000.000 µl	ArBr	1.000	50.532 mg		0.125 mol/l
			BTMG	0.840	21.410 mg		0.125 mol/l
			DMF	0.948	0.924 ml		remainder

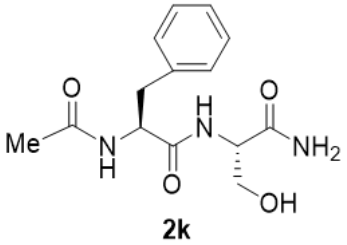
^{1}H NMR (500 MHz, DMSO-d_6)



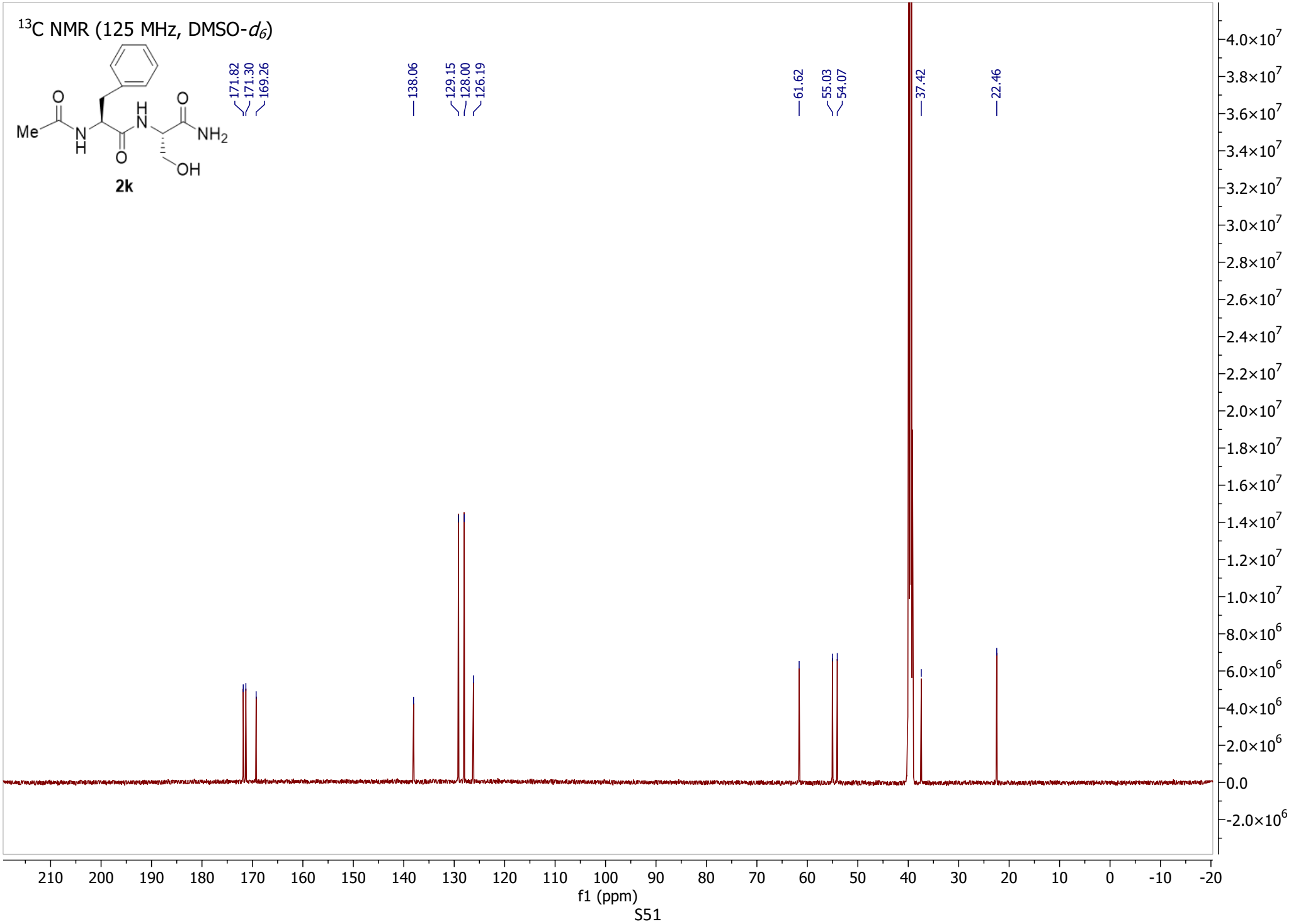
1


^{13}C NMR (125 MHz, DMSO-d_6)
Br
O
NH
O
N
H
NH$_2$
O
1
172.83
168.56
165.62
137.97
133.04
131.32
129.44
129.13
128.03
126.22
125.11
53.78
42.64
37.47
2.8×10^7
2.6×10^7
2.4×10^7
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

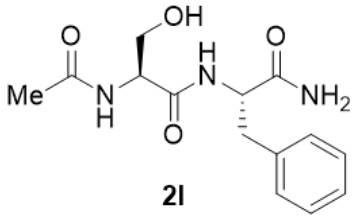
^{1}H NMR (500 MHz, DMSO-d_6)



2k

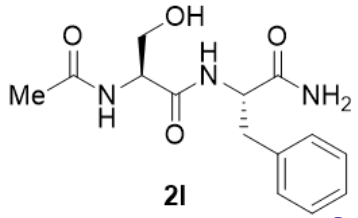

^{13}C NMR (125 MHz, DMSO-d_6)
Me
O
N
H
O
H
N
O
NH$_2$
OH
2k
171.82
171.30
169.26
138.06
129.15
128.00
126.19
61.62
55.03
54.07
37.42
22.46
4.0×10^7
3.8×10^7
3.6×10^7
3.4×10^7
3.2×10^7
3.0×10^7
2.8×10^7
2.6×10^7
2.4×10^7
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



2l

^{13}C NMR (125 MHz, DMSO-d_6)

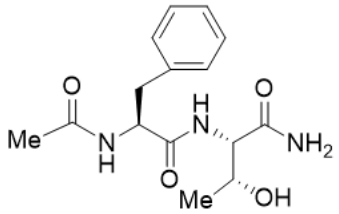


2l

172.89
170.10
169.57
138.03
129.13
128.06
126.24
61.73
55.10
53.90
36.98
22.55

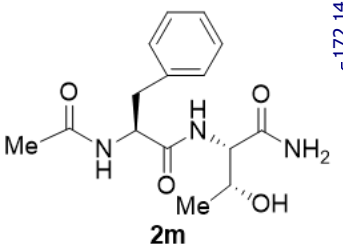
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



2m

^{13}C NMR (125 MHz, DMSO-d_6)



2m

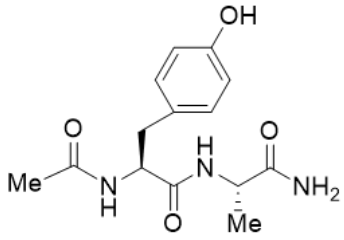
172.14
171.58
169.43
138.12
129.18
128.06
126.25
66.26
58.05
54.20
37.03
22.43
20.10

5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

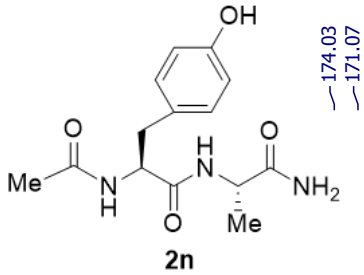
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



2n

^{13}C NMR (125 MHz, DMSO-d_6)

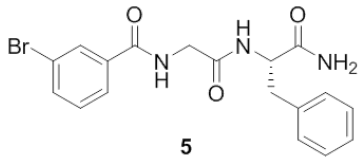


2n

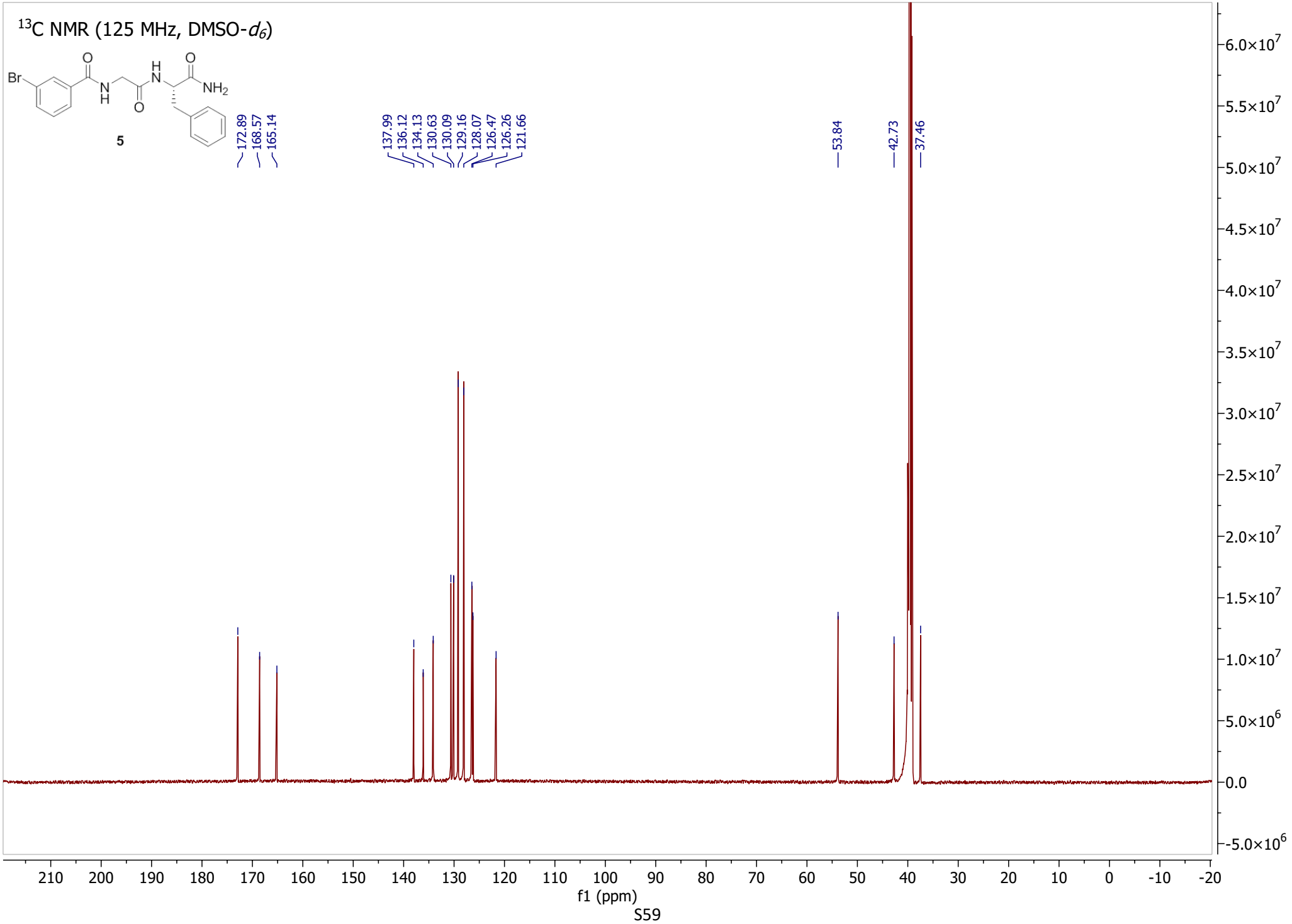
174.03
171.07
169.20
155.69
130.02
128.06
114.82
54.34
47.98
36.64
22.49
18.32

f1 (ppm)

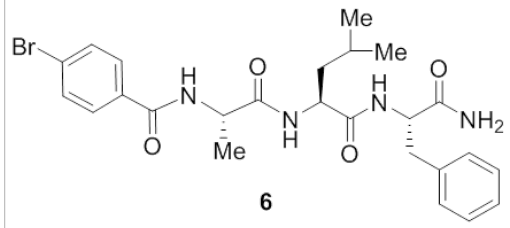
^{1}H NMR (500 MHz, DMSO-d_6)



5

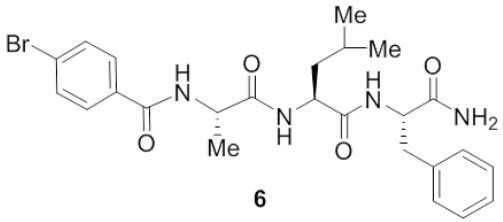

^{13}C NMR (125 MHz, DMSO-d_6)
Br
O
N
H
O
H
N
O
NH$_2$
5
172.89
168.57
165.14
137.99
136.12
134.13
130.63
130.09
129.16
128.07
126.47
126.26
121.66
53.84
42.73
37.46
6.0×10^7
5.5×10^7
5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
-5.0×10^6
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



6

^{13}C NMR (125 MHz, DMSO-d_6)



6

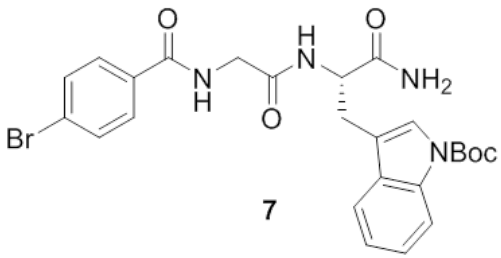
172.65
172.37
171.54
165.42
137.71
133.11
131.23
129.69
129.13
128.01
126.22
125.10
53.42
51.51
49.25
37.48
24.10
22.94
21.67
17.55

3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

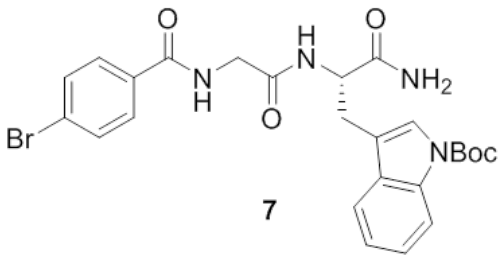
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



7

^{13}C NMR (125 MHz, DMSO-d_6)



7

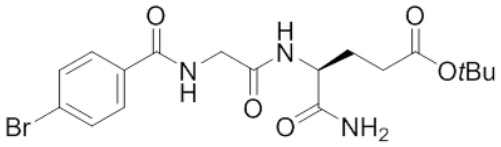
172.93
168.76
165.66
149.07
134.62
133.10
131.32
130.36
129.45
125.11
124.27
123.85
122.47
119.38
116.71
114.63
83.51
52.40
42.68
27.72
27.23

1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

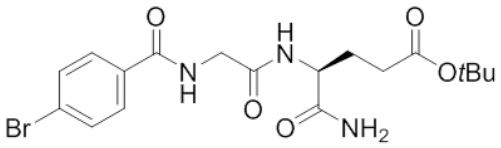
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



8

^{13}C NMR (125 MHz, DMSO-d_6)



8

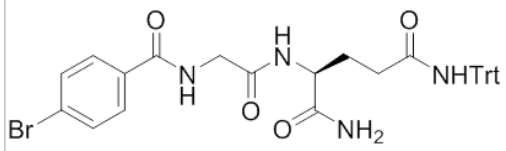
173.08
171.73
168.83
165.78
133.12
131.36
129.47
125.15
79.72
51.62
42.79
31.35
27.77
27.25

1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

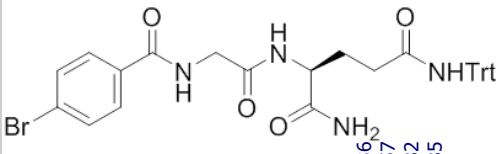
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



9

^{13}C NMR (125 MHz, DMSO-d_6)

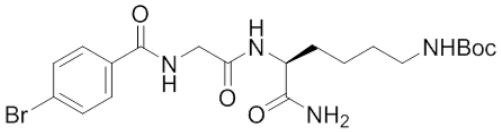


9

173.36
171.57
168.82
165.85
144.93
133.13
131.37
129.49
128.55
127.50
126.35
125.18
69.23
52.22
42.89
32.72
28.02

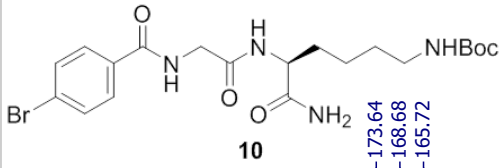
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



10

^{13}C NMR (125 MHz, DMSO-d_6)



10

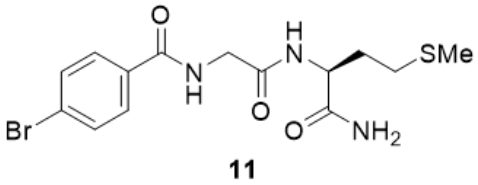
173.64
168.68
165.72
155.57
133.13
131.35
129.47
125.13
77.36
52.37
42.72
39.80
31.66
29.26
28.30
22.74

2.00E+08
1.90E+08
1.80E+08
1.70E+08
1.60E+08
1.50E+08
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

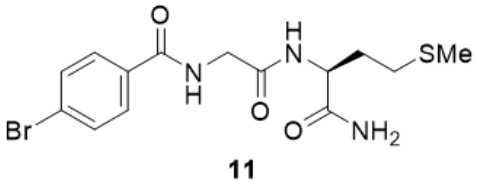
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



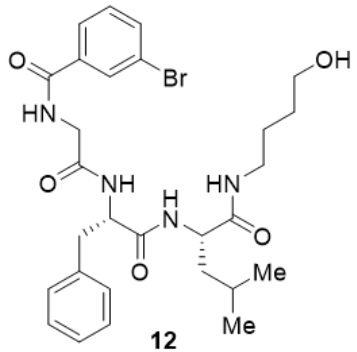
11

^{13}C NMR (125 MHz, DMSO-d_6)



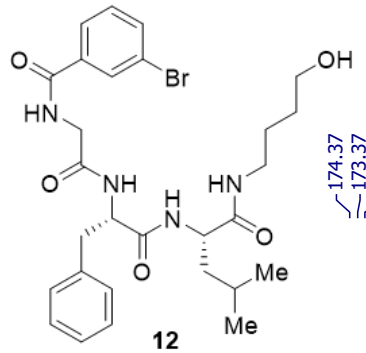
11

^{1}H NMR (500 MHz, methanol-d_4)



12

^{13}C NMR (125 MHz, methanol-d_4)



12

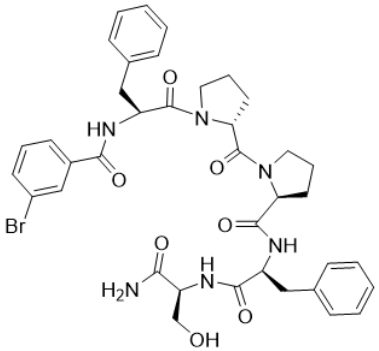
174.37
173.37
172.47
168.84
137.92
136.54
135.90
131.70
131.40
130.14
129.54
127.88
127.16
123.48
62.45
56.55
53.53
44.67
41.49
40.20
37.86
30.72
26.57
25.72
23.57
21.74

1.10×10^{8}
1.00×10^{8}
9.00×10^{7}
8.00×10^{7}
7.00×10^{7}
6.00×10^{7}
5.00×10^{7}
4.00×10^{7}
3.00×10^{7}
2.00×10^{7}
1.00×10^{7}
0.00
-1.00×10^{7}

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

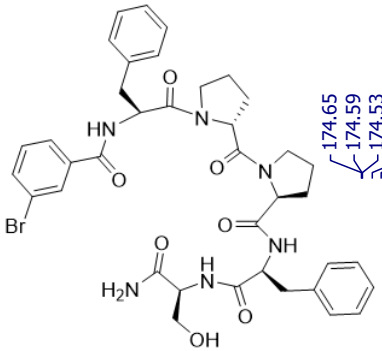
f1 (ppm)

^{1}H NMR (500 MHz, methanol-d_4)



13

^{13}C NMR (125 MHz, methanol-d_4)



13

174.65
174.59
174.53
173.30
172.19
167.65

139.28
138.17
136.79
135.77
131.68
131.37
130.52
130.16
129.52
129.50
127.99
127.82
127.47
123.39

63.07
62.61
59.90
57.70
57.29
57.19
54.64
49.85

38.99
37.05

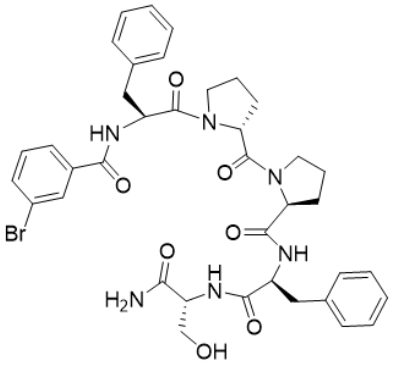
30.24
29.37
26.41
24.85

1.20×10^8
1.10×10^8
1.00×10^8
9.00×10^7
8.00×10^7
7.00×10^7
6.00×10^7
5.00×10^7
4.00×10^7
3.00×10^7
2.00×10^7
1.00×10^7
0.00
-1.00×10^7

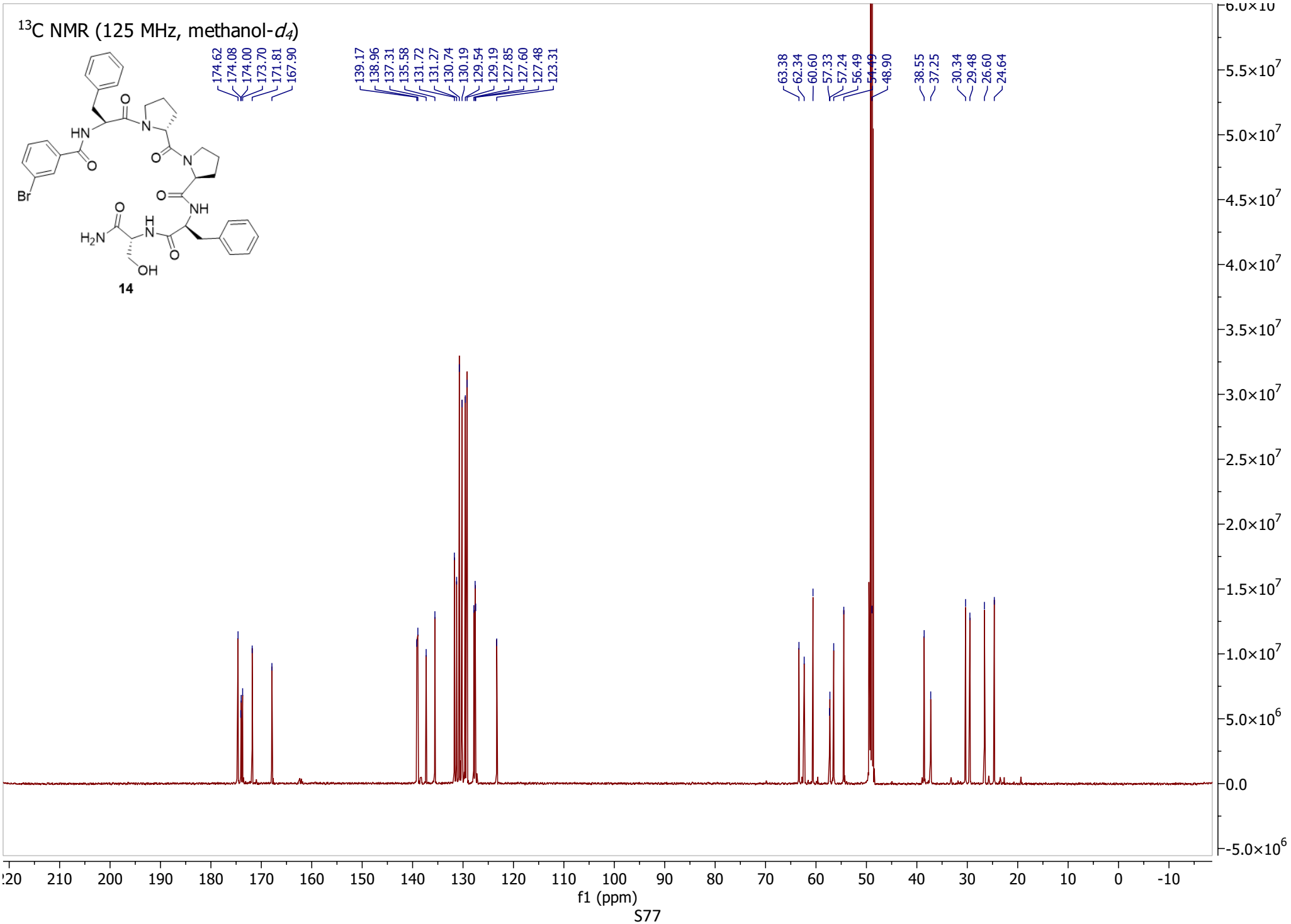
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

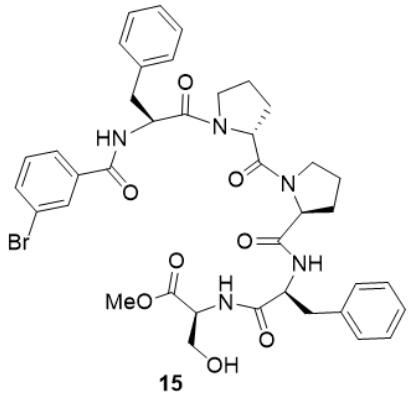
^{1}H NMR (500 MHz, methanol-d_4)



14

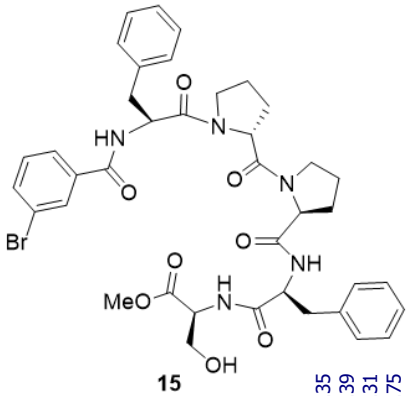

^{13}C NMR (125 MHz, methanol-d_4)
174.62
174.08
174.00
173.70
171.81
167.90
139.17
138.96
137.31
135.58
131.72
131.27
130.74
130.19
129.54
129.19
127.85
127.60
127.48
123.31
63.38
62.34
60.60
57.33
57.24
56.49
54.49
48.90
38.55
37.25
30.34
29.48
26.60
24.64
14
f1 (ppm)

^{1}H NMR (500 MHz, methanol-d_4)



15

^{13}C NMR (125 MHz, methanol-d_4)



15

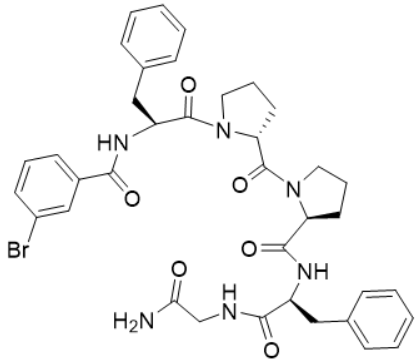
174.35
173.39
173.31
171.75
171.71
167.97
139.37
138.44
137.28
135.73
131.76
131.28
130.64
130.38
129.54
129.47
127.91
127.76
127.62
123.34
62.96
62.35
59.85
56.52
55.75
54.25
52.72
49.51
48.83
39.16
37.78
30.32
29.38
26.49
24.53

16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000

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

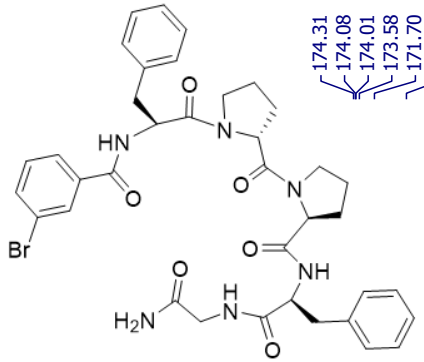
f1 (ppm)

^{1}H NMR (500 MHz, methanol-d_4)



16

^{13}C NMR (125 MHz, methanol-d_4)



16

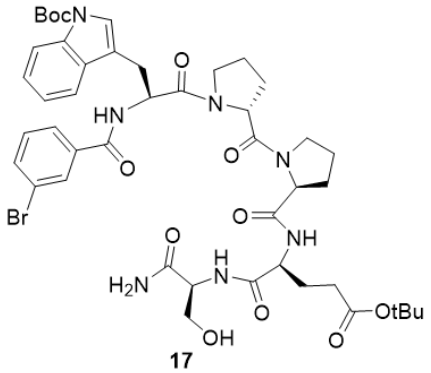
174.31
174.08
174.01
173.58
171.70
167.71
139.26
138.34
137.03
135.68
131.73
131.33
130.57
130.24
129.52
129.44
127.88
127.84
127.46
123.35
62.21
59.90
57.25
57.15
54.46
43.29
38.89
37.45
37.41
30.26
29.25
26.35
24.65

3.8×10^7
3.6×10^7
3.4×10^7
3.2×10^7
3.0×10^7
2.8×10^7
2.6×10^7
2.4×10^7
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6

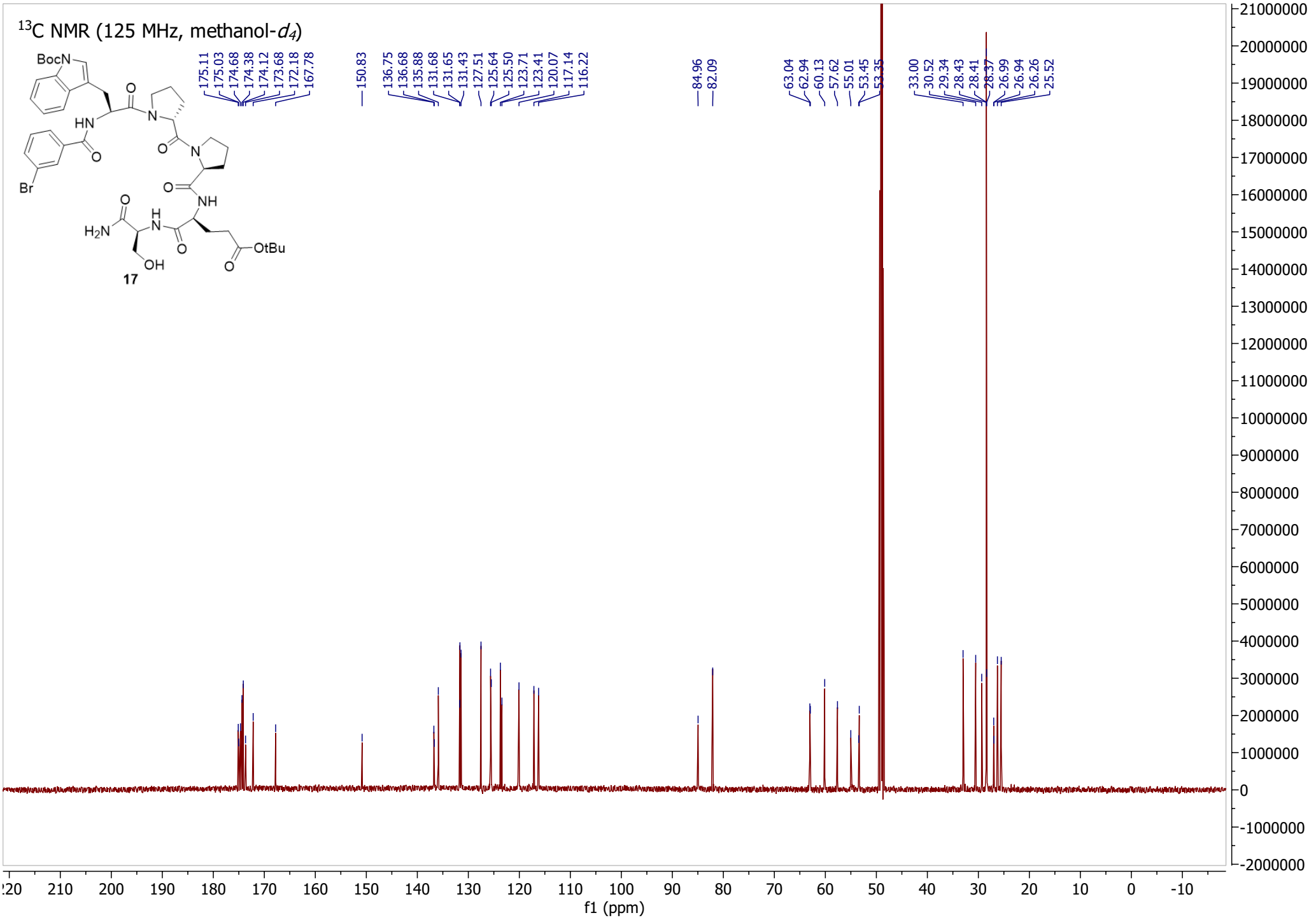
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

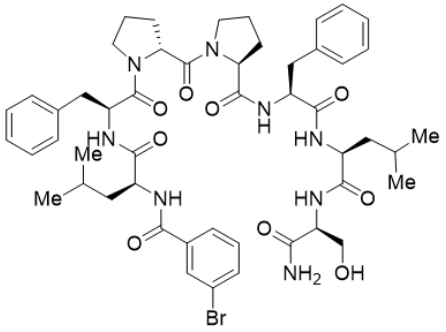
^{1}H NMR (500 MHz, methanol-d_4)



17

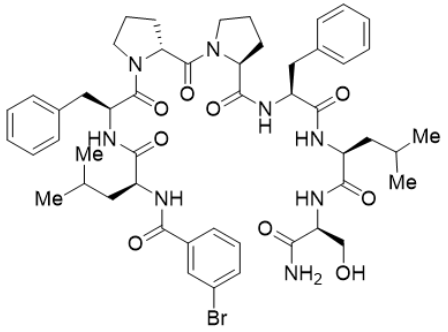

^{13}C NMR (125 MHz, methanol-d_4)
BocN
HN
O
N
O
Br
NH
H_2N
H
OH
OtBu
17
175.11
175.03
174.68
174.38
174.12
173.68
172.18
167.78
150.83
136.75
136.68
135.88
131.68
131.65
131.43
127.51
125.64
125.50
123.71
123.41
120.07
117.14
116.22
84.96
82.09
63.04
62.94
60.13
57.62
55.01
53.45
53.35
33.00
30.52
29.34
28.43
28.41
28.37
26.99
26.94
26.26
25.52
21000000
20000000
19000000
18000000
17000000
16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
-2000000
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)

^{1}H NMR (500 MHz, methanol-d_4)



18

^{13}C NMR (125 MHz, methanol-d_4)



18

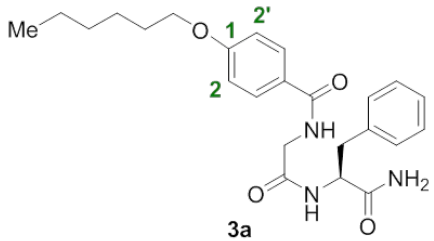
174.82
174.71
174.31
174.07
174.00
173.59
171.19
168.39
139.29
138.20
137.43
135.62
131.75
131.38
130.59
130.42
129.50
129.47
127.81
127.77
127.64
123.38
63.03
61.96
59.65
56.79
54.03
53.80
53.54
48.34
41.87
41.53
39.36
38.37
30.28
29.20
26.29
26.21
25.97
24.39
23.59
23.28
22.70
22.33

3.4×10^7
3.2×10^7
3.0×10^7
2.8×10^7
2.6×10^7
2.4×10^7
2.2×10^7
2.0×10^7
1.8×10^7
1.6×10^7
1.4×10^7
1.2×10^7
1.0×10^7
8.0×10^6
6.0×10^6
4.0×10^6
2.0×10^6
0.0
-2.0×10^6

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)

Crude reaction for determination of NMR yield



3a

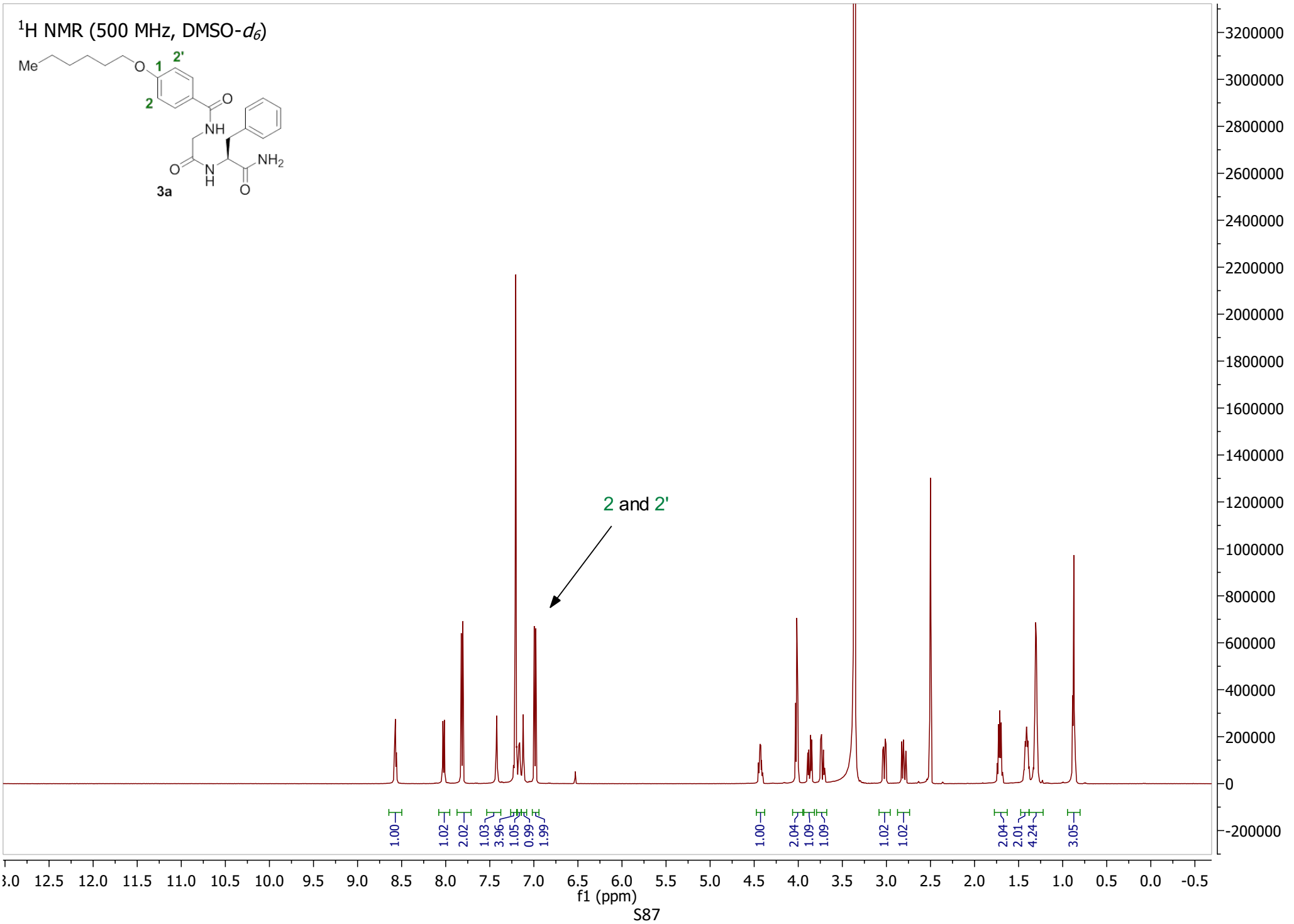
two arene protons (2 and 2')

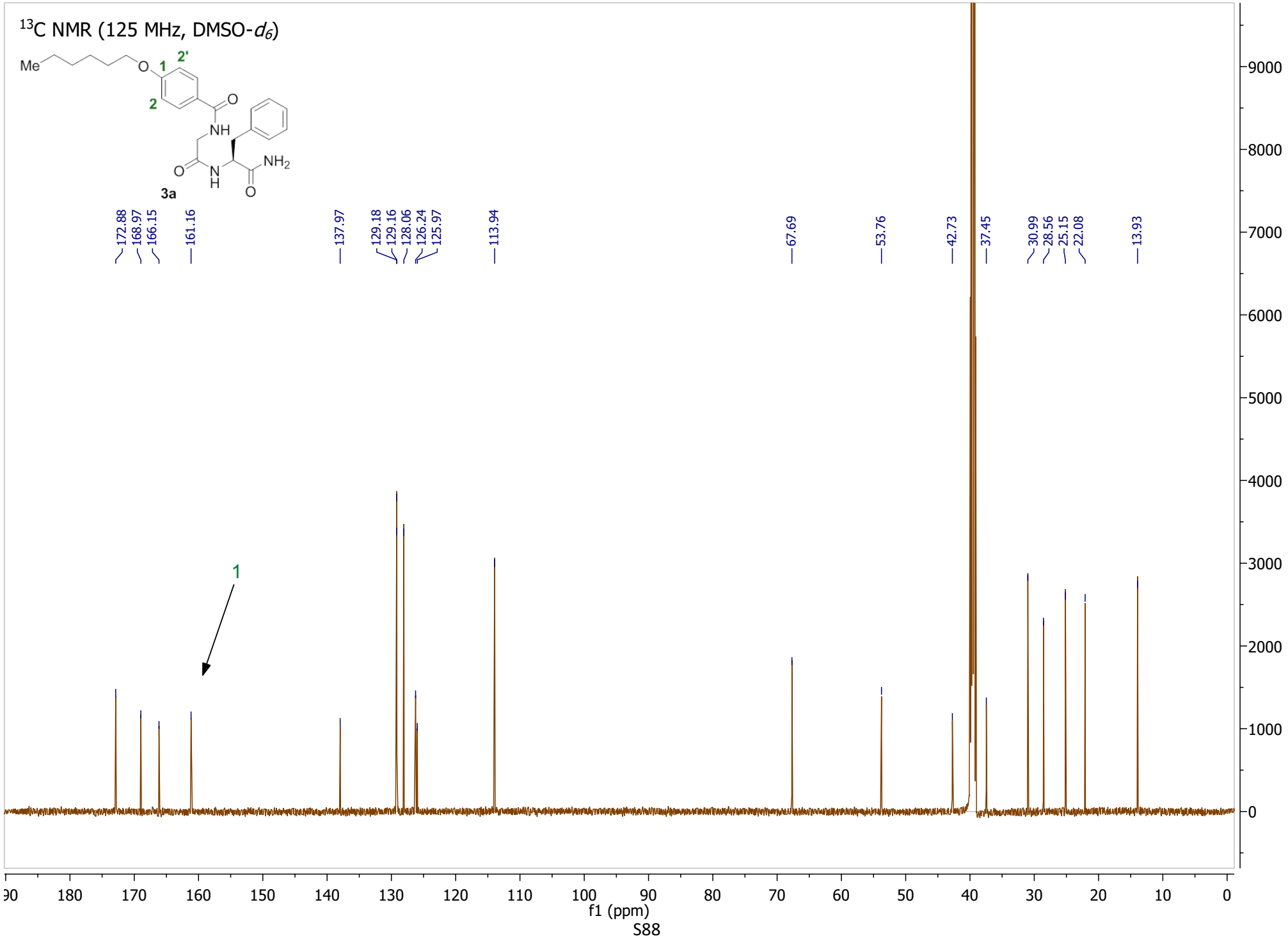
three arene protons of TMB

19.34

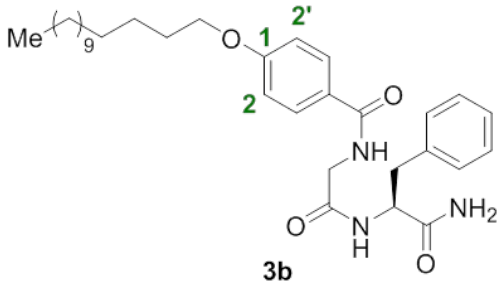
3.00

f1 (ppm)


^{1}H NMR (500 MHz, DMSO-d_6)
Me
O
1
2'
2
O
NH
O
N
H
NH$_2$
O
3a
2 and 2'
1.00
1.02
2.02
1.03
3.96
1.05
0.99
1.99
1.00
2.04
1.09
1.09
1.02
1.02
2.04
2.01
4.24
3.05
3200000
3000000
2800000
2600000
2400000
2200000
2000000
1800000
1600000
1400000
1200000
1000000
800000
600000
400000
200000
0
-200000
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


13C NMR (125 MHz, DMSO-d6)
Me
O
1
2'
2
O
NH
O
N
H
NH2
O
3a
172.88
168.97
166.15
161.16
137.97
129.18
129.16
128.06
126.24
125.97
113.94
67.69
53.76
42.73
37.45
30.99
28.56
25.15
22.08
13.93
1
9000
8000
7000
6000
5000
4000
3000
2000
1000
0
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
f1 (ppm)

Crude reaction for determination of NMR yield



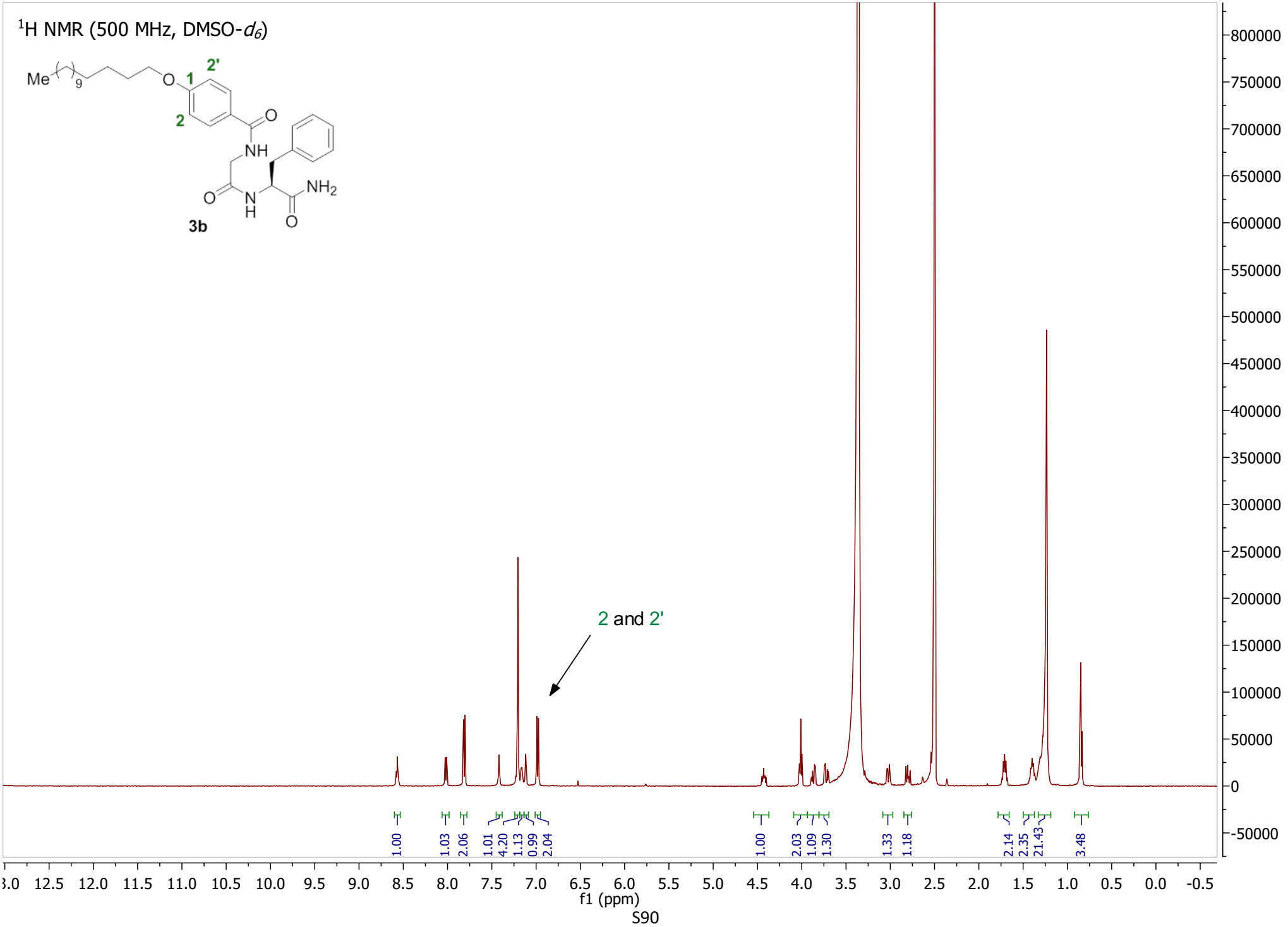
two arene protons (2 and 2')

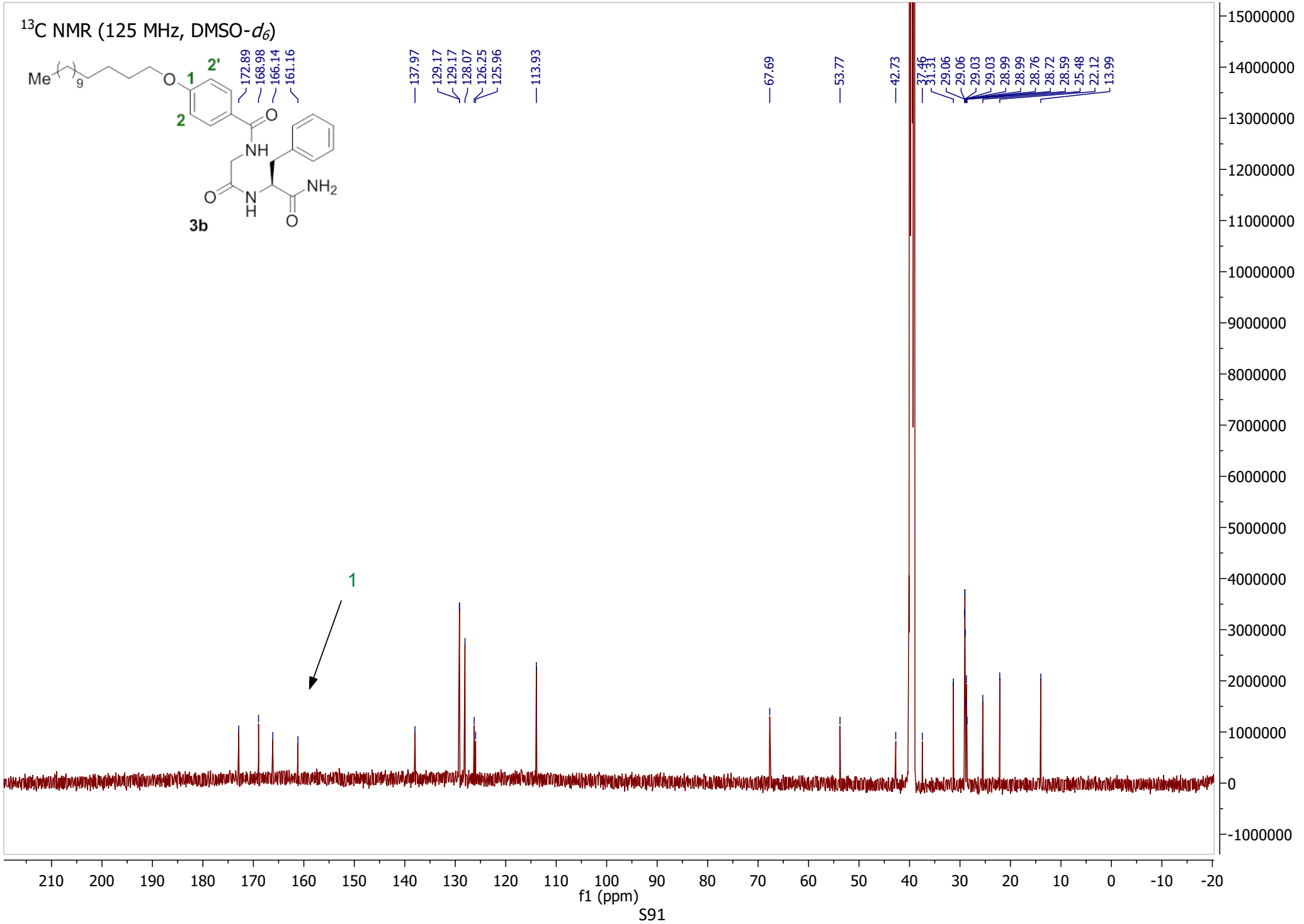
three arene protons of TMB

11.56

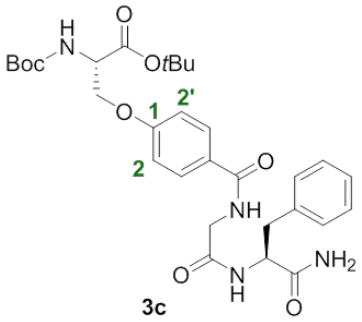
3.00

f1 (ppm)


^{1}H NMR (500 MHz, DMSO-d_6)
Me
9
O
1
2'
2
O
NH
O
N
H
NH$_2$
O
3b
2 and 2'
1.00
1.03
2.06
1.01
4.20
1.13
0.99
2.04
1.00
2.03
1.09
1.30
1.33
1.18
2.14
2.35
21.43
3.48
800000
750000
700000
650000
600000
550000
500000
450000
400000
350000
300000
250000
200000
150000
100000
50000
0
-50000
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


13C NMR (125 MHz, DMSO-d6)
Me
9
O
1
2'
2
O
NH
O
N
H
NH2
O
3b
172.89
168.98
166.14
161.16
137.97
129.17
129.17
128.07
126.25
125.96
113.93
67.69
53.77
42.73
37.46
31.31
29.06
29.06
29.03
29.03
28.99
28.99
28.76
28.72
28.59
25.48
22.12
13.99
1
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
0
-10
-20
f1 (ppm)

Crude reaction for determination of NMR yield



two arene protons (2 and 2')

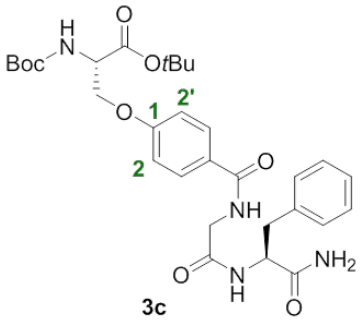
three arene protons of TMB

16.15

3.00

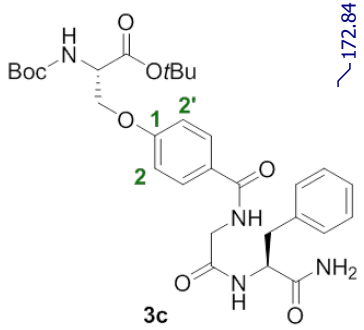
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



3c

^{13}C NMR (125 MHz, DMSO-d_6)



172.84
168.97
168.90
166.02
160.52
155.38
137.96
129.17
129.13
128.03
126.55
126.20
114.06
81.12
78.40
67.45
54.02
53.73
42.71
37.44
28.15
27.61

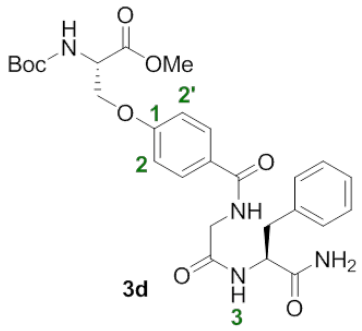
1

5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06

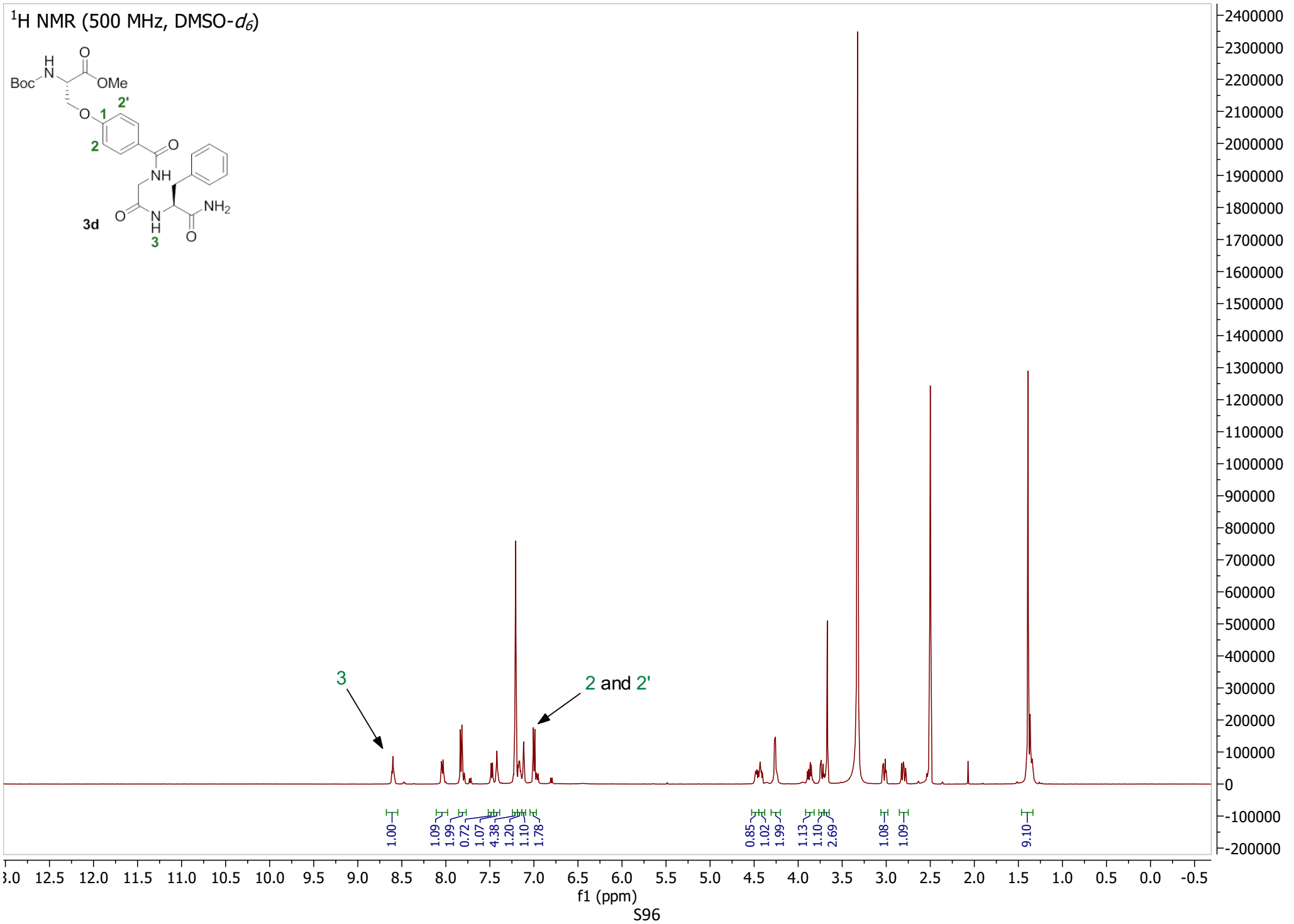
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

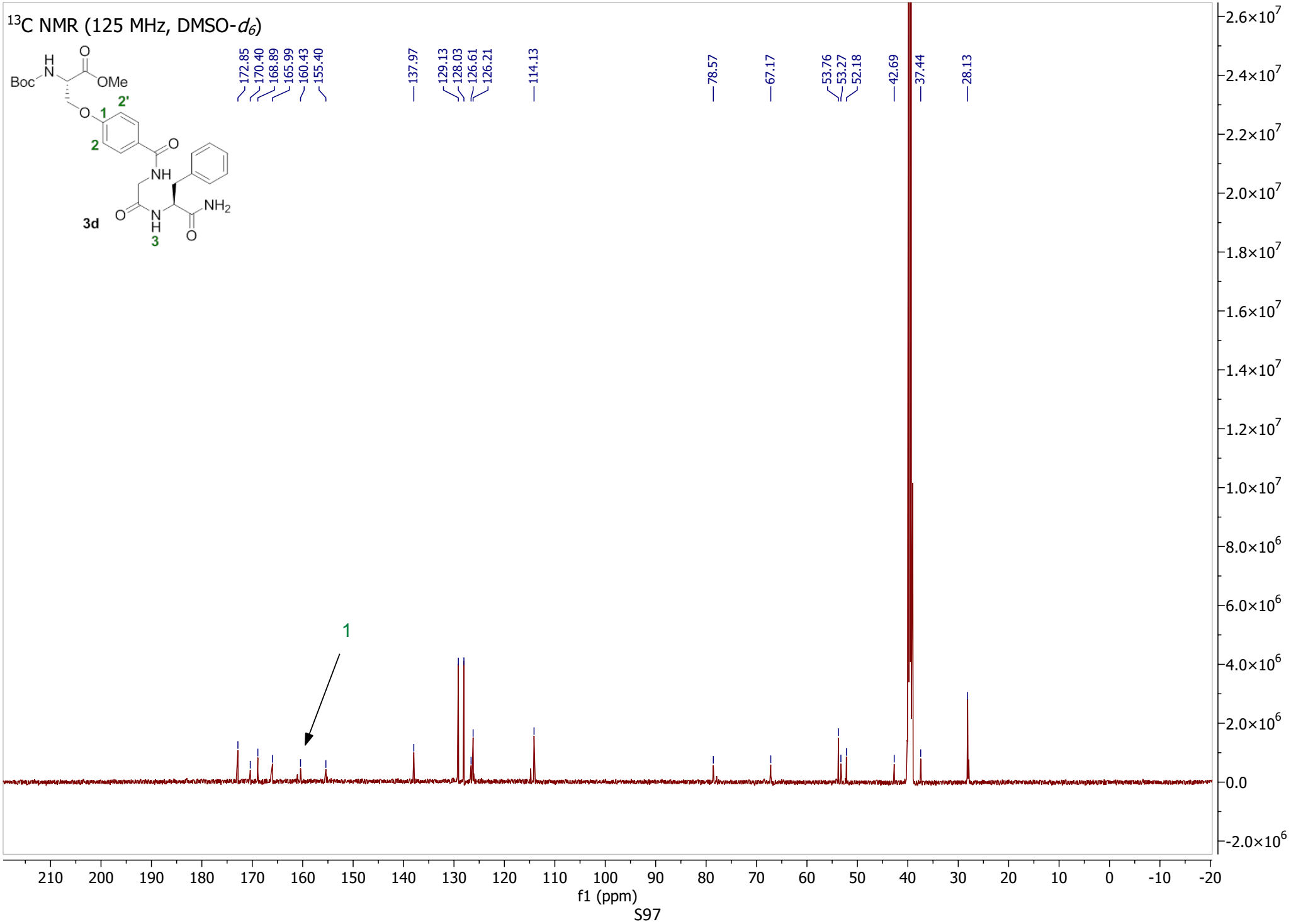
f1 (ppm)

Crude reaction for determination of NMR yield

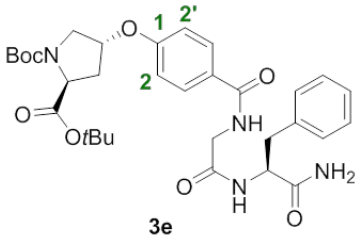


3d


^{1}H NMR (500 MHz, DMSO-d_6)
Boc
OMe
NH
NH$_2$
3d
3
2 and 2'
1.00
1.09
1.99
0.72
1.07
4.38
1.20
1.10
1.78
0.85
1.02
1.99
1.13
1.10
2.69
1.08
1.09
9.10
f1 (ppm)


^{13}C NMR (125 MHz, DMSO-d_6)
Boc
OMe
NH
NH$_2$
3d
172.85
170.40
168.89
165.99
160.43
155.40
137.97
129.13
128.03
126.61
126.21
114.13
78.57
67.17
53.76
53.27
52.18
42.69
37.44
28.13
1
f1 (ppm)

Crude reaction for determination of NMR yield



3e

two arene protons (2 and 2')

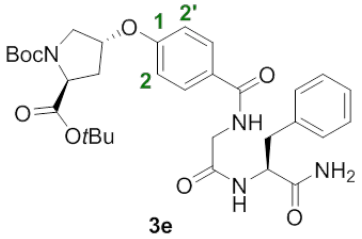
three arene protons of TMB

10.45

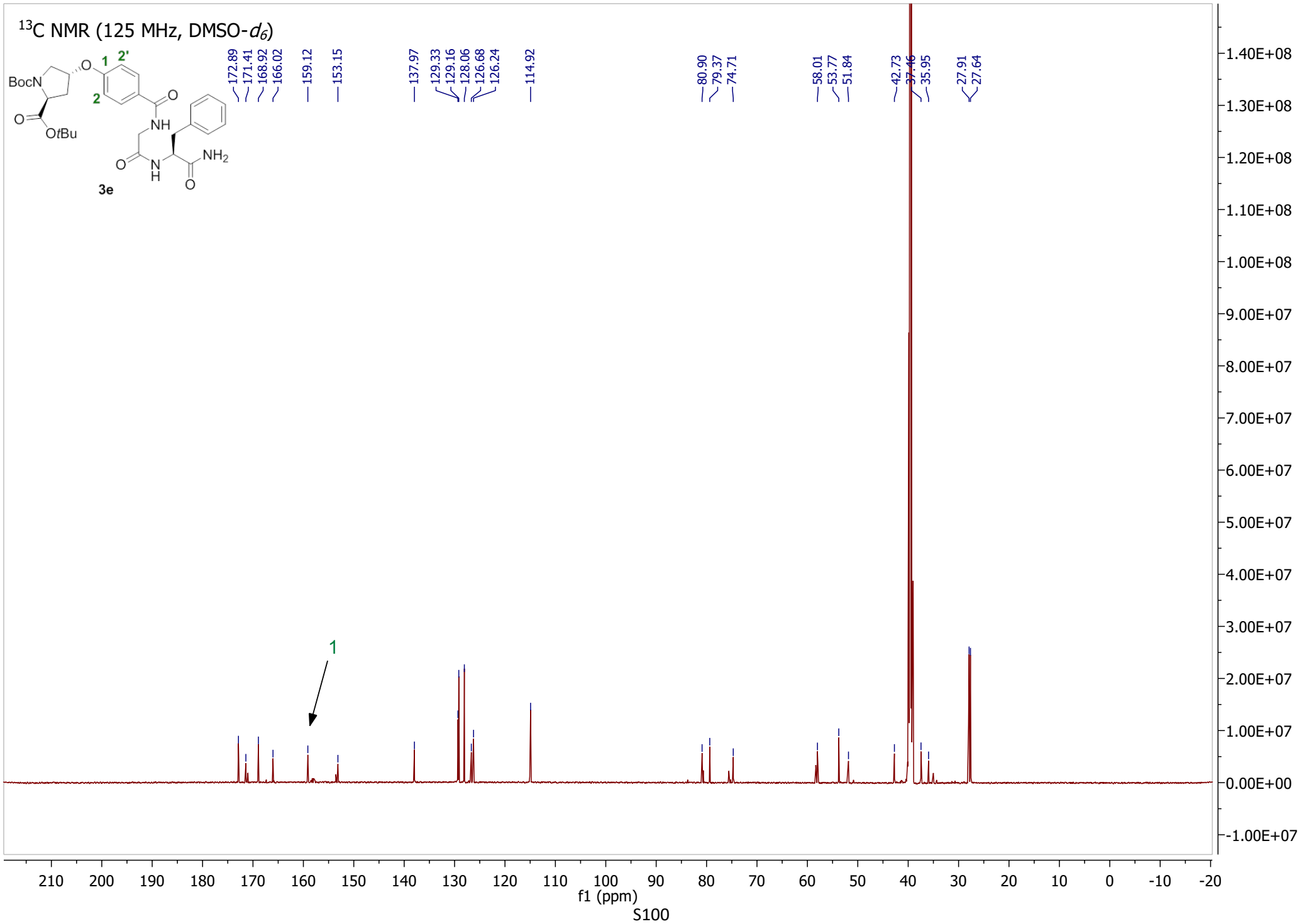
3.00

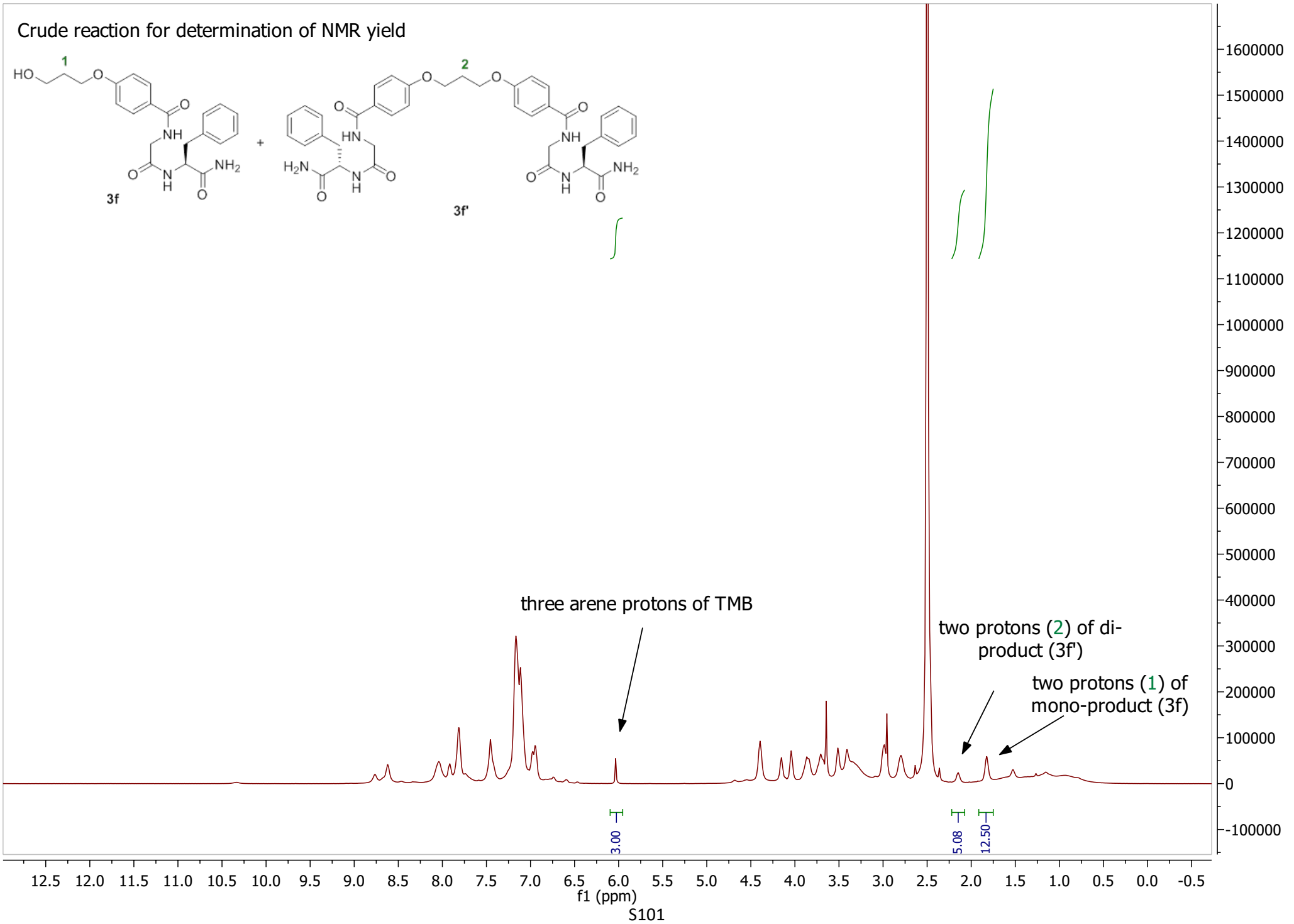
f1 (ppm)

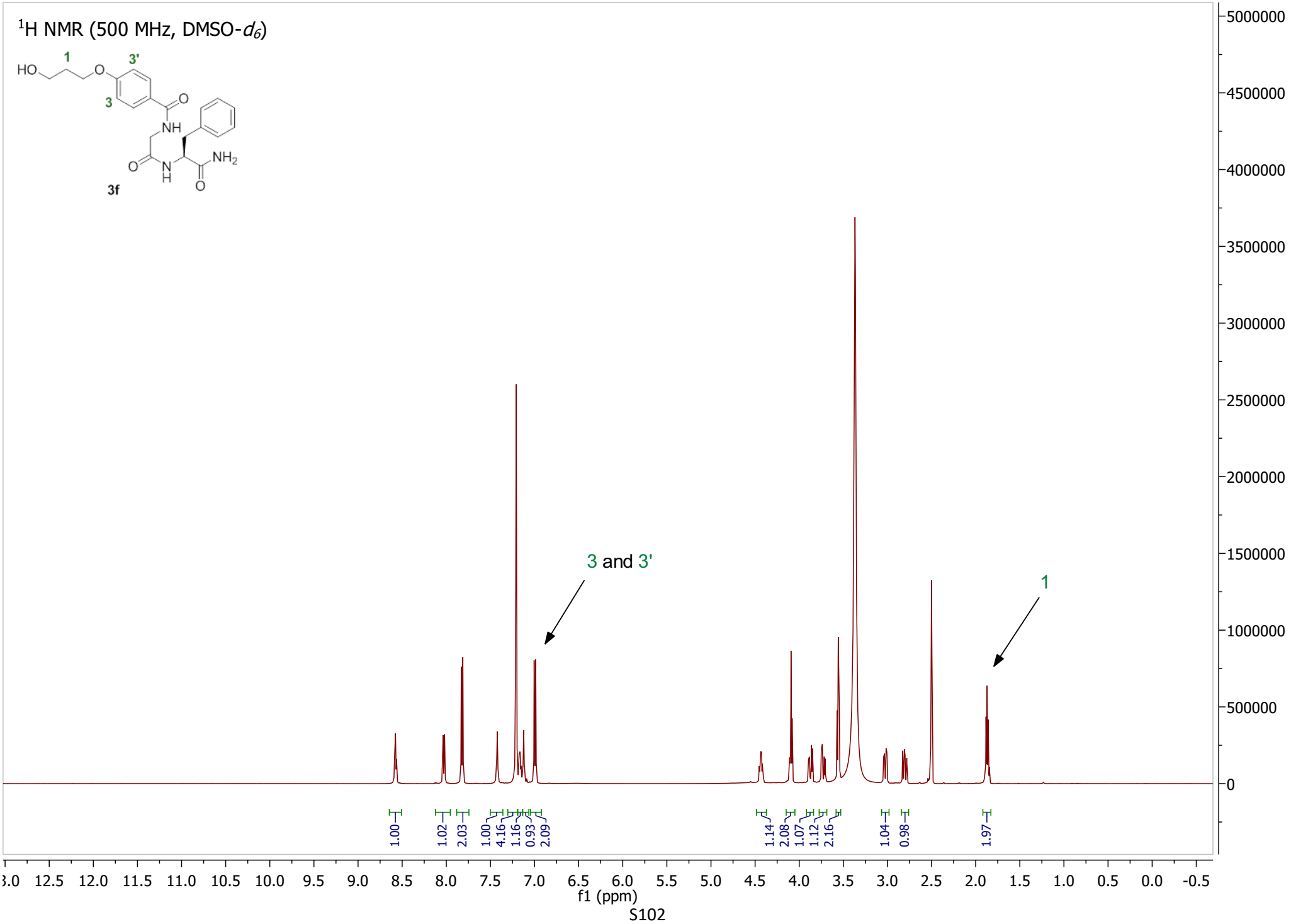
^{1}H NMR (500 MHz, DMSO-d_6)



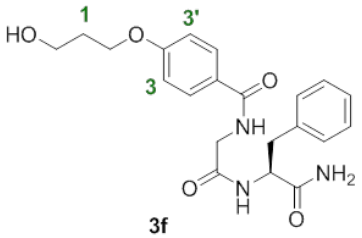
3e


^{13}C NMR (125 MHz, DMSO-d_6)
BocN
O
OtBu
1
2
2'
NH
N
H
NH$_2$
3e
172.89
171.41
168.92
166.02
159.12
153.15
137.97
129.33
129.16
128.06
126.68
126.24
114.92
80.90
79.37
74.71
58.01
53.77
51.84
42.73
37.46
35.95
27.91
27.64
1
1.40E+08
1.30E+08
1.20E+08
1.10E+08
1.00E+08
9.00E+07
8.00E+07
7.00E+07
6.00E+07
5.00E+07
4.00E+07
3.00E+07
2.00E+07
1.00E+07
0.00E+00
-1.00E+07
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)


Crude reaction for determination of NMR yield
1
2
3f
3f'
three arene protons of TMB
two protons (2) of di-product (3f')
two protons (1) of mono-product (3f)
3.00
5.08
12.50
f1 (ppm)


^{1}H NMR (500 MHz, DMSO-d_6)
HO
1
O
3'
3
O
NH
O
N
H
NH$_2$
O
3f
3 and 3'
1
1.00
1.02
2.03
1.00
4.16
1.16
0.93
2.09
1.14
2.08
1.07
1.12
2.16
1.04
0.98
1.97
5000000
4500000
4000000
3500000
3000000
2500000
2000000
1500000
1000000
500000
0
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

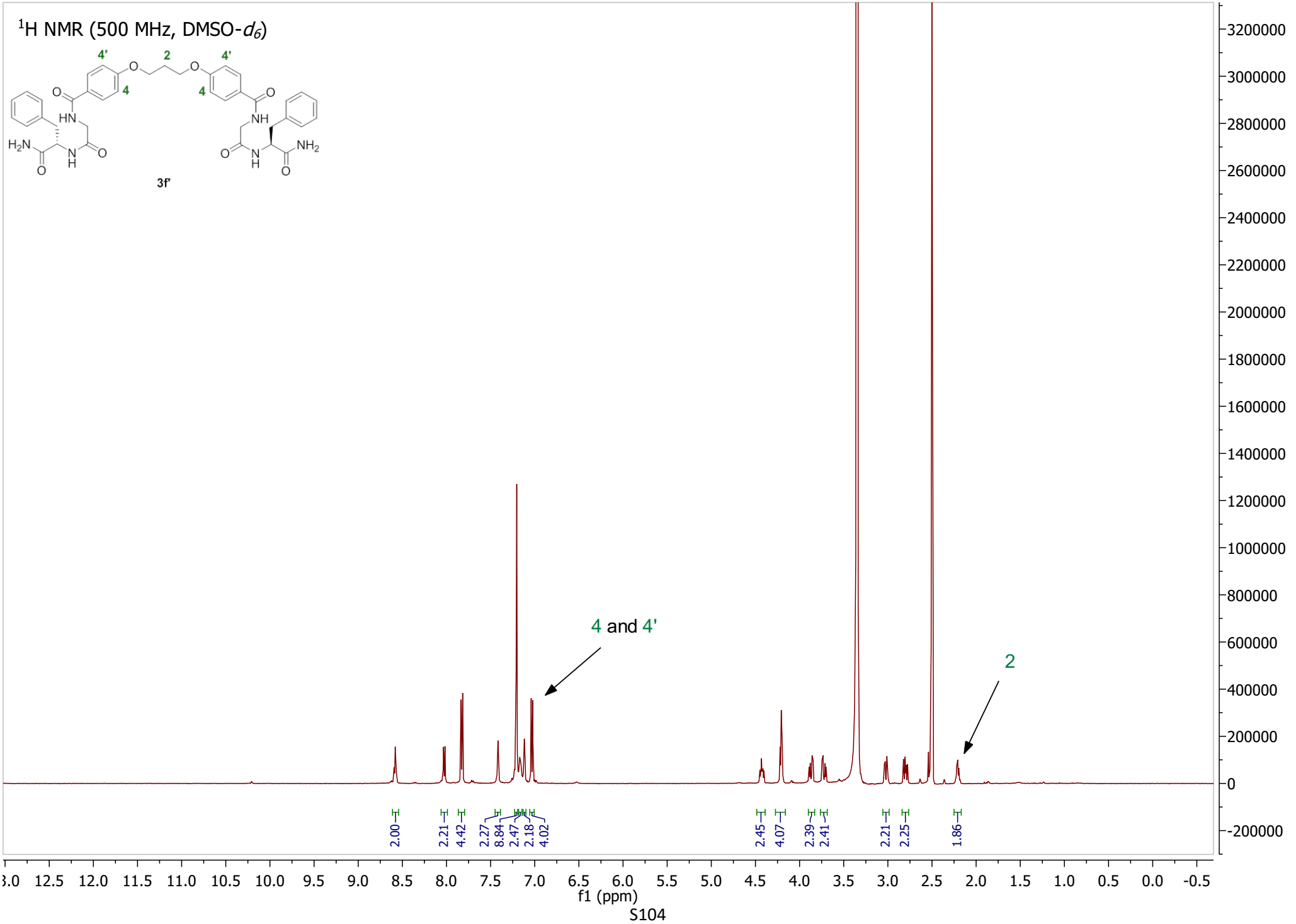
^{13}C NMR (125 MHz, DMSO-d_6)



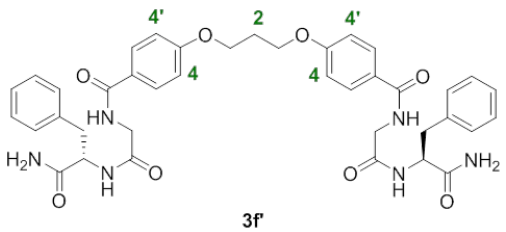
3f

172.88
168.96
166.14
161.17
137.97
129.18
129.15
128.06
126.24
125.99
113.93
64.83
57.22
53.76
42.73
37.45
32.02

f1 (ppm)


^{1}H NMR (500 MHz, DMSO-d_6)
4'
2
4'
4
4
3f'
4 and 4'
2
2.00
2.21
4.42
2.27
8.84
2.47
2.18
4.02
2.45
4.07
2.39
2.41
2.21
2.25
1.86
f1 (ppm)

^{13}C NMR (125 MHz, DMSO-d_6)

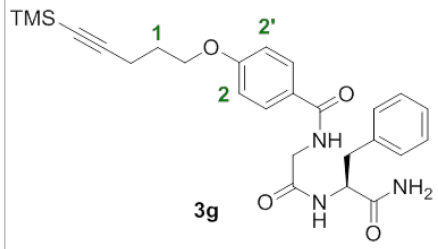


3f'

172.86
168.93
166.08
160.92
137.96
129.20
129.14
128.05
126.22
126.21
113.99
64.47
53.75
42.71
37.44
28.48

f1 (ppm)

Crude reaction for determination of NMR yield



3g

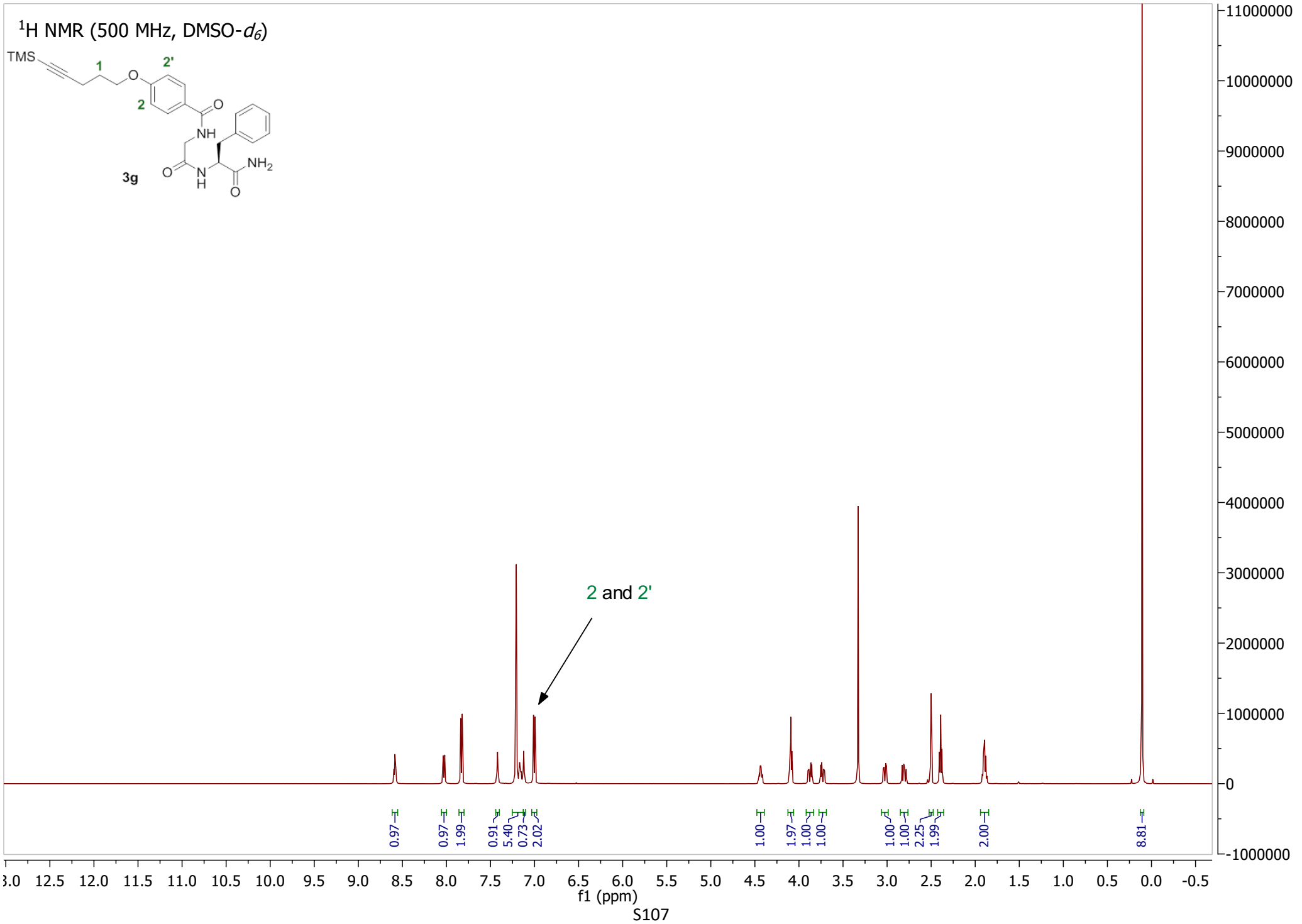
three arene protons of TMB

two protons (1)

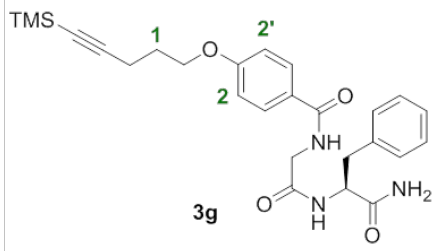
3.00

12.47

f1 (ppm)


^{1}H NMR (500 MHz, DMSO-d_6)
TMS
1
2'
2
O
NH
O
N
H
NH$_2$
O
O
3g
2 and 2'
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000
0.97
0.97
1.99
0.91
5.40
0.73
2.02
1.00
1.97
1.00
1.00
1.00
1.00
2.25
1.99
2.00
8.81
12.5
12.0
11.5
11.0
10.5
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.0
-0.5
f1 (ppm)

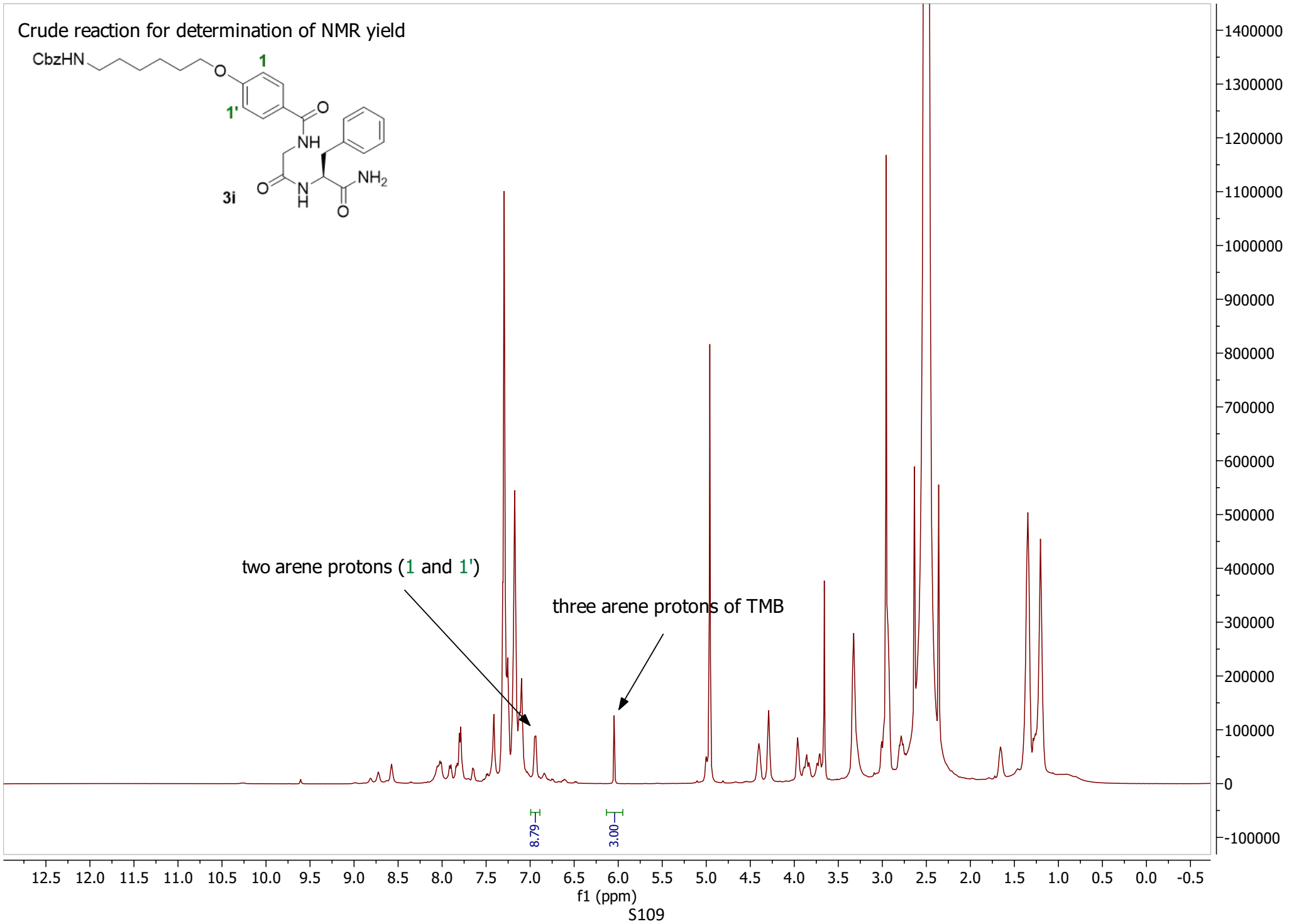
^{13}C NMR (125 MHz, DMSO-d_6)

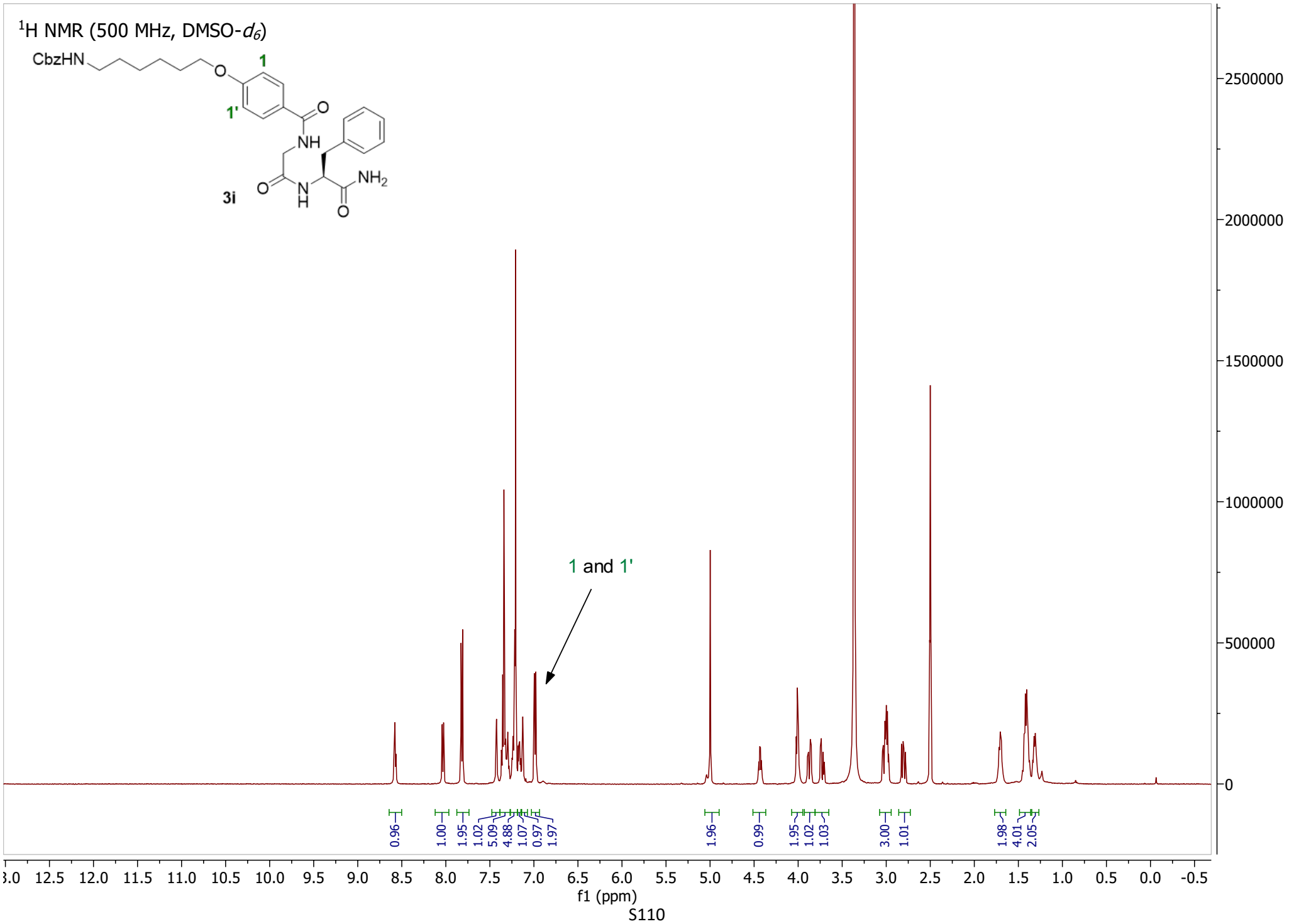


3g

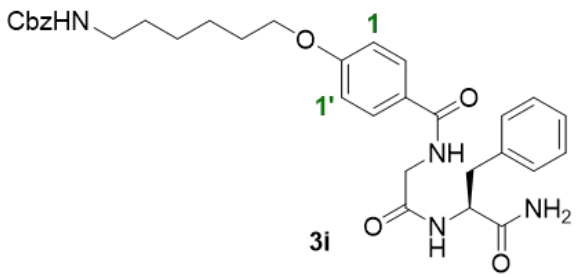
172.84
168.92
166.05
160.90
137.96
129.18
129.14
128.03
126.20
126.17
113.93
106.97
84.80
66.19
53.73
42.70
37.44
27.56
15.84
0.11

f1 (ppm)


Crude reaction for determination of NMR yield
CbzHN
O
1
1'
O
NH
O
N
H
NH2
O
3i
two arene protons (1 and 1')
three arene protons of TMB
8.79
3.00
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)


1H NMR (500 MHz, DMSO-d6)
CbzHN
O
1
1'
O
NH
O
N
H
NH2
O
3i
1 and 1'
2500000
2000000
1500000
1000000
500000
0
0.96
1.00
1.95
1.02
5.09
4.88
1.07
0.97
1.97
1.96
0.99
1.95
1.02
1.03
3.00
1.01
1.98
4.01
2.05
12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

^{13}C NMR (125 MHz, DMSO-d_6)

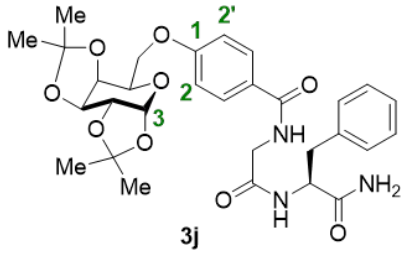


3i

172.87
168.96
166.12
161.14
156.11
137.98
137.32
129.17
129.15
128.34
128.05
127.74
127.72
126.22
125.98
113.92
67.62
65.08
53.75
42.72
40.21
37.44
29.32
28.52
25.96
25.17

f1 (ppm)

Crude reaction for determination of NMR yield



3j

two arene protons (2 and 2')

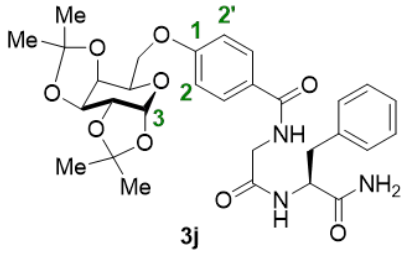
three arene protons of TMB

10.80

3.00

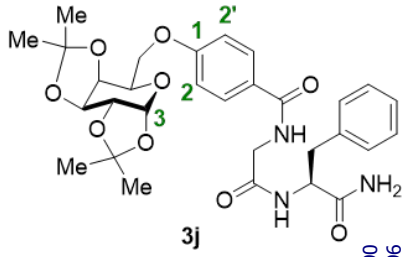
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



3j

^{13}C NMR (125 MHz, DMSO-d_6)



3j

172.90
168.96
166.08
160.61
137.98
129.17
128.07
126.25
114.19
108.60
107.96
95.67
92.83
70.34
70.04
69.76
66.92
65.80
55.17
53.79
42.75
37.46
25.97
25.81
24.86
24.32

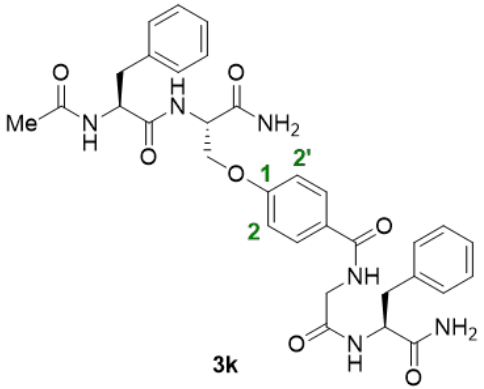
1

5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

Crude reaction for determination of NMR yield



3k

two arene protons (2 and 2')

three arene protons of TMB

11.97

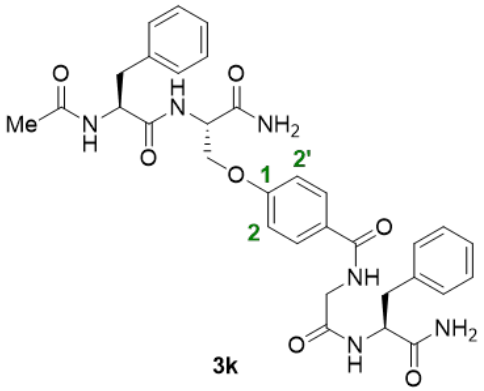
3.00

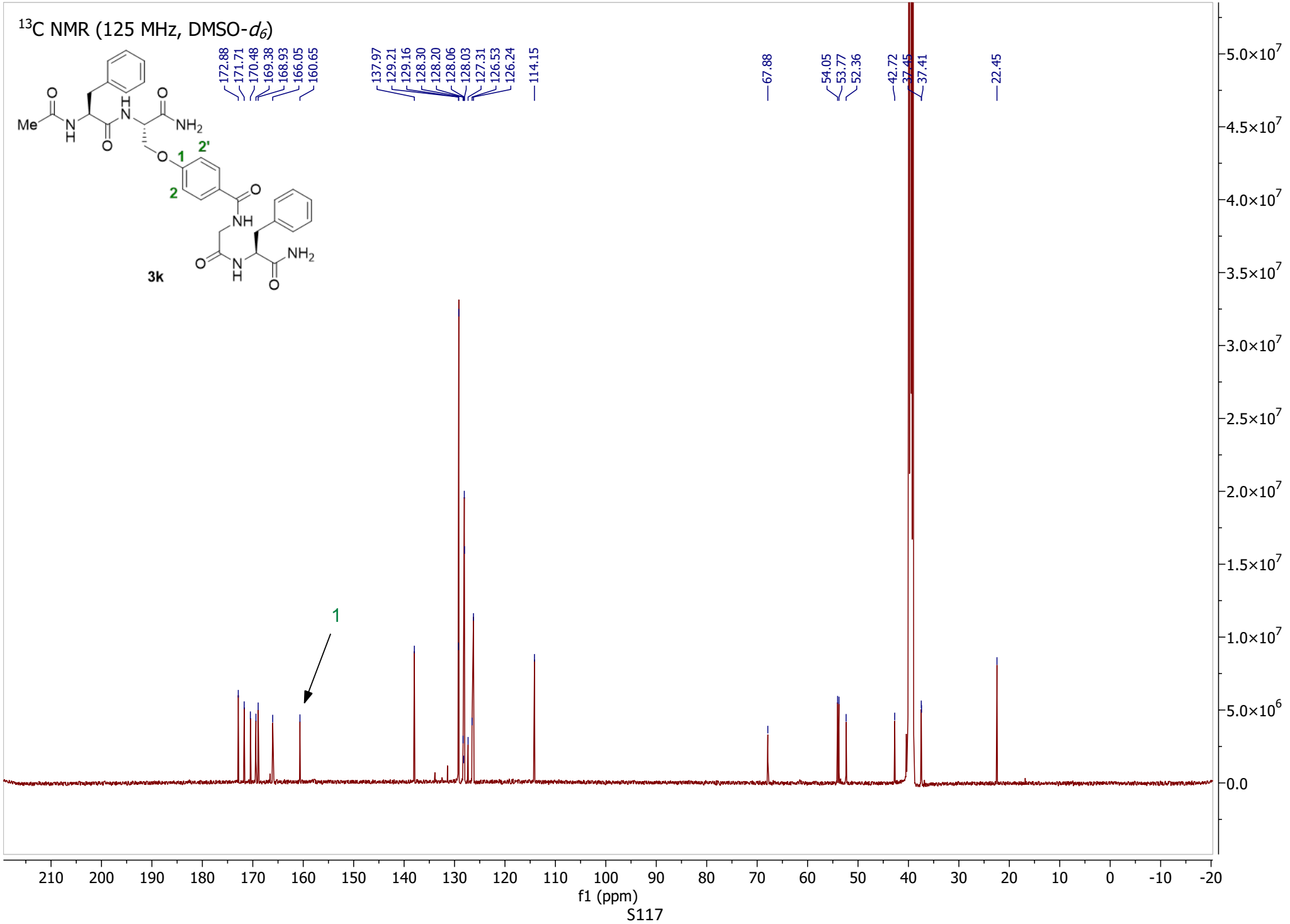
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0

12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5

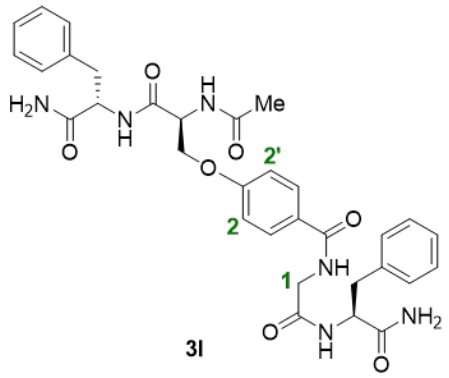
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)

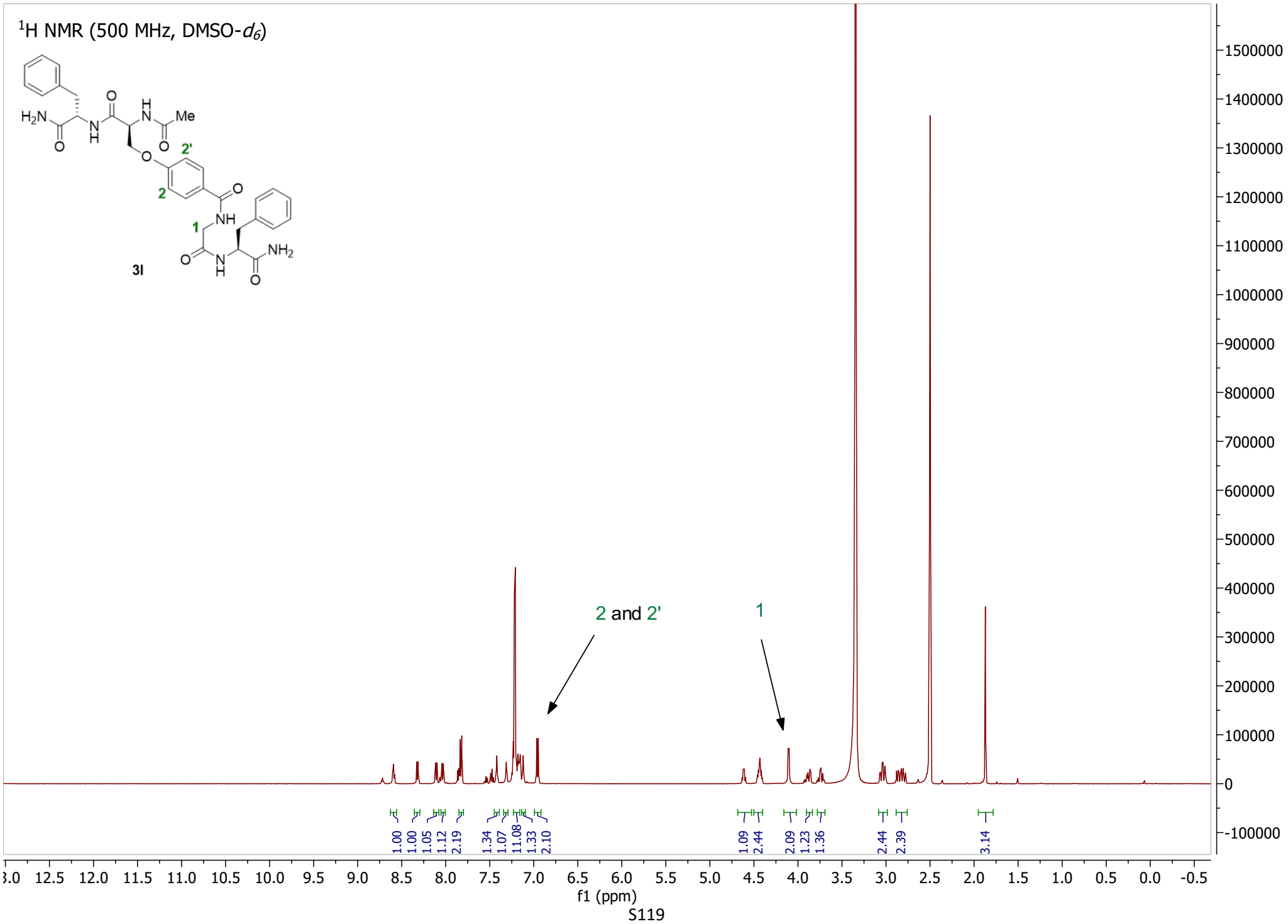



^{13}C NMR (125 MHz, DMSO-d_6)
172.88
171.71
170.48
169.38
168.93
166.05
160.65
137.97
129.21
129.16
128.30
128.20
128.06
128.03
127.31
126.53
126.24
114.15
67.88
54.05
53.77
52.36
42.72
37.45
37.41
22.45
Me
NH2
O
NH
1
2
2'
3k
1
5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

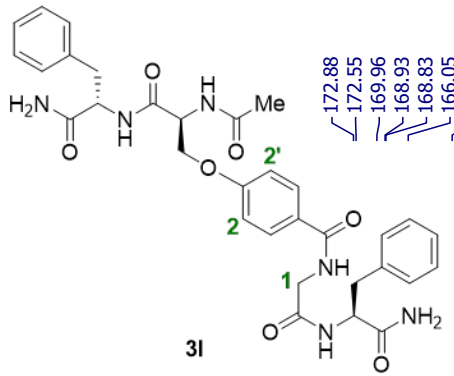
Crude reaction for determination of NMR yield



3l


^{1}H NMR (500 MHz, DMSO-d_6)
3l
2 and 2'
1
1.00
1.00
1.05
1.12
2.19
1.34
1.07
11.08
1.33
2.10
1.09
2.44
2.09
1.23
1.36
2.44
2.39
3.14
f1 (ppm)

^{13}C NMR (125 MHz, DMSO-d_6)



3l

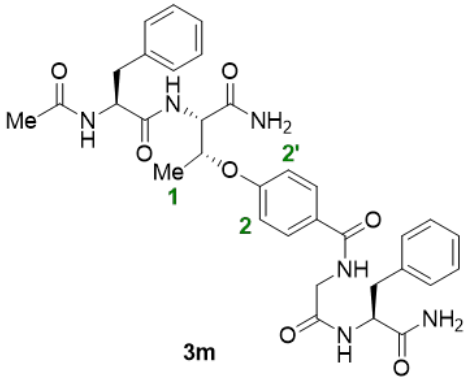
172.88 172.55 169.96 168.93 168.83 166.05 160.56 137.97 137.86 133.91 131.40 129.16 128.31 128.06 127.32 126.52 126.25 114.11 67.64 53.91 53.78 52.69 42.71 37.47 37.22 22.54

4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

Crude reaction for determination of NMR yield



3m

three arene protons of TMB

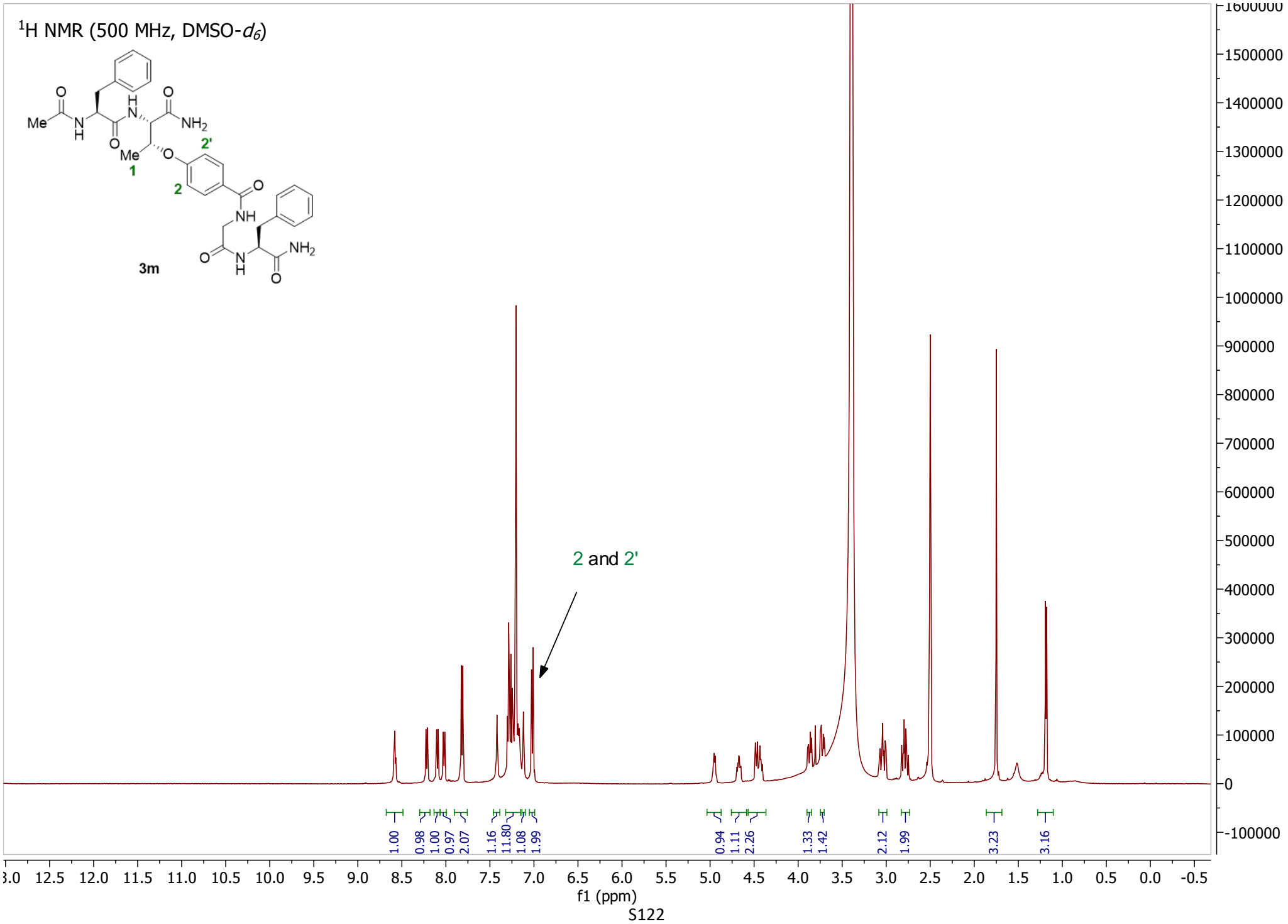
three protons (1)

3.00

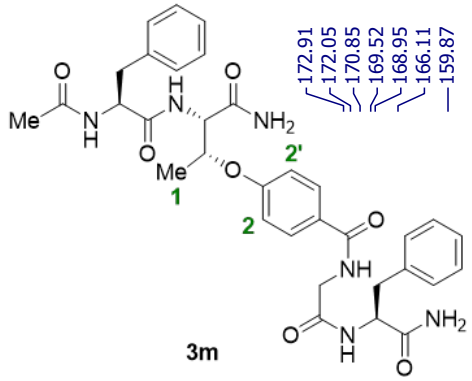
7.57

f1 (ppm)

S121


1H NMR (500 MHz, DMSO-d6)
Me
O
N
H
O
H
N
O
NH2
2'
Me
1
O
2
O
NH
O
N
H
NH2
O
3m
2 and 2'
1.00
0.98
1.00
0.97
2.07
1.16
11.80
1.08
1.99
0.94
1.11
2.26
1.33
1.42
2.12
1.99
3.23
3.16
f1 (ppm)

^{13}C NMR (125 MHz, DMSO-d_6)



3m

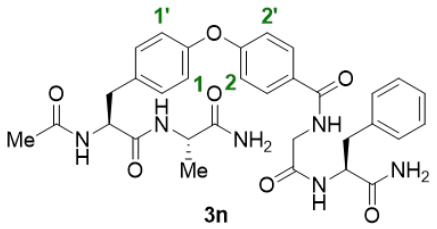
172.91
172.05
170.85
169.52
168.95
166.11
159.87
138.04
138.04
137.97
137.97
129.20
129.17
128.08
126.50
126.28
126.26
115.28
73.79
56.34
54.02
53.78
42.74
37.45
36.95
22.39
15.95

15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000

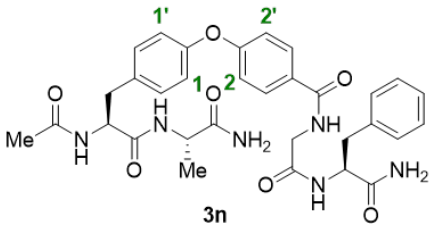
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



^{13}C NMR (125 MHz, DMSO-d_6)

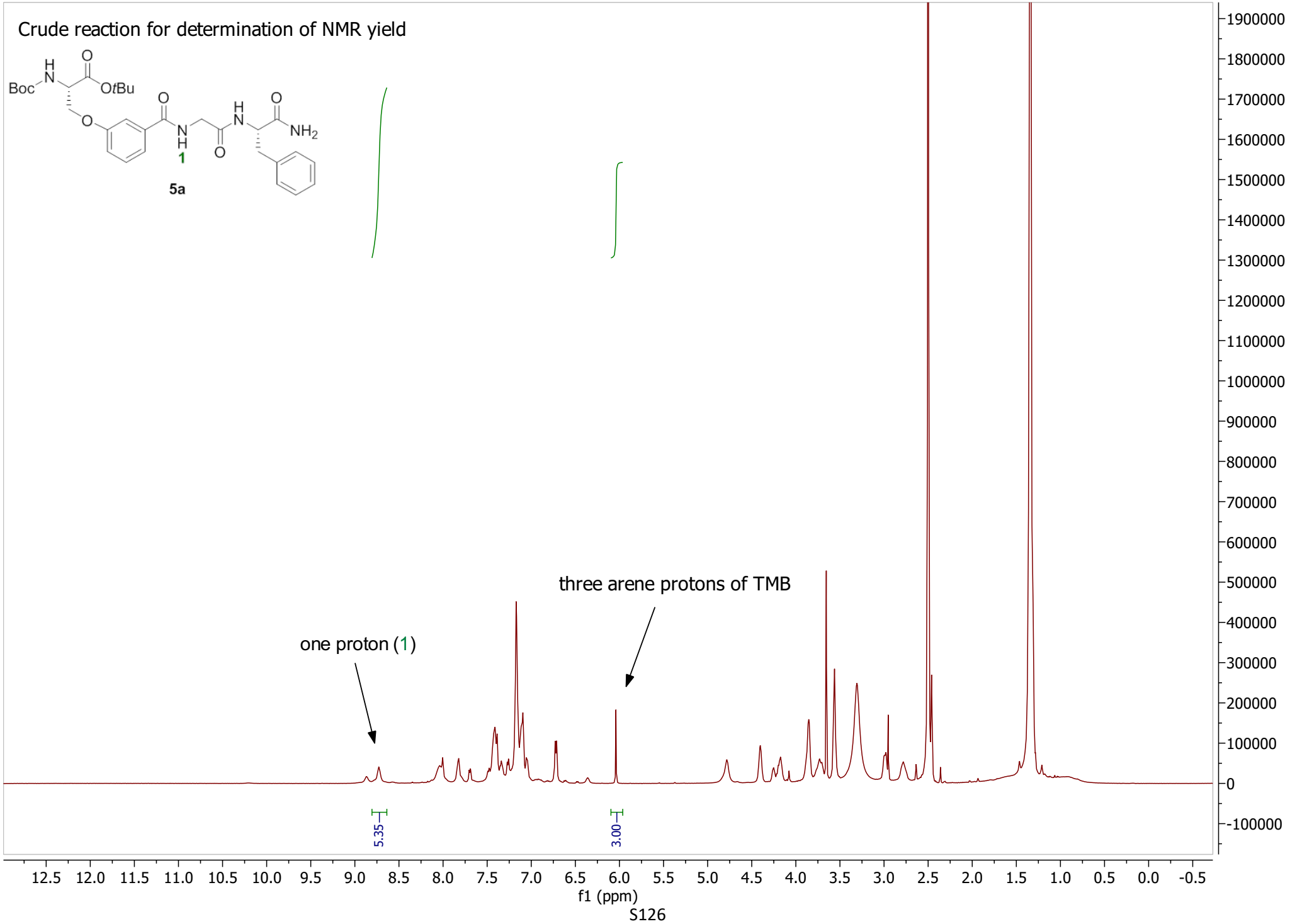


174.07
172.91
170.86
169.33
168.86
165.91
159.90
153.96
137.98
134.13
130.95
129.51
129.18
128.09
127.33
126.27
119.26
117.16
54.05
53.80
48.06
42.74
37.48
36.89
22.51
18.37

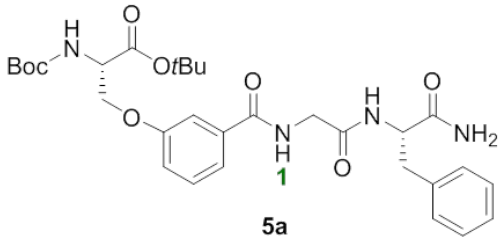
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

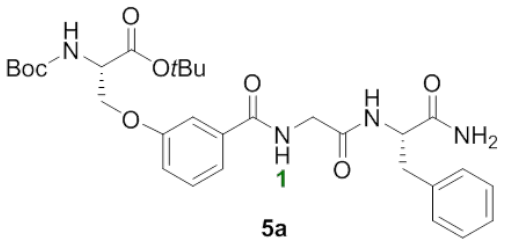

Crude reaction for determination of NMR yield
Boc
OtBu
NH2
1
5a
one proton (1)
three arene protons of TMB
5.35
3.00
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



5a

^{13}C NMR (125 MHz, DMSO-d_6)

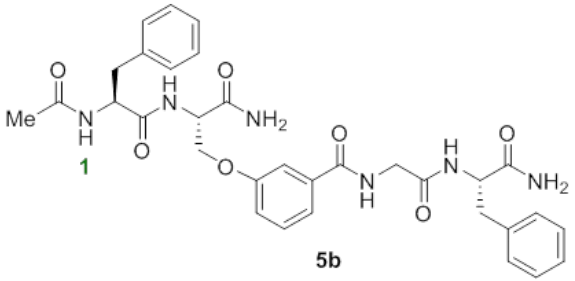


5a

172.83
169.03
168.69
166.12
158.04
155.38
137.95
135.32
129.47
129.14
128.03
126.21
120.01
117.81
113.19
81.09
78.39
67.46
54.10
53.77
42.68
37.48
28.16
27.63

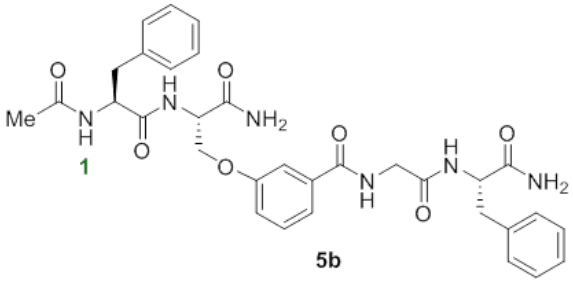
f1 (ppm)

Crude reaction for determination of NMR yield

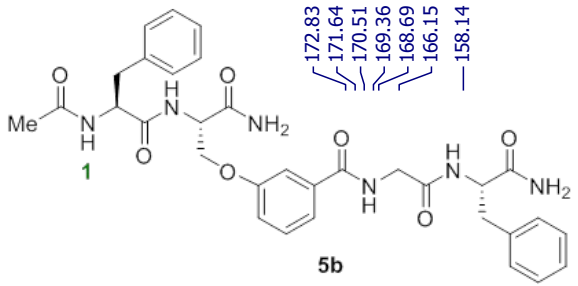


5b

^{1}H NMR (500 MHz, DMSO-d_6)



^{13}C NMR (125 MHz, DMSO-d_6)



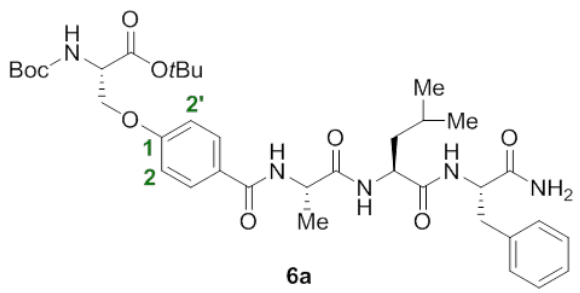
172.83
171.64
170.51
169.36
168.69
166.15
158.14
137.94
135.30
129.49
129.13
128.03
128.00
126.22
120.04
117.82
113.23
67.91
54.03
53.76
52.44
42.69
37.45
37.40
22.42

6.0E+07
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

Crude reaction for determination of NMR yield



6a

two protons (2 and 2')

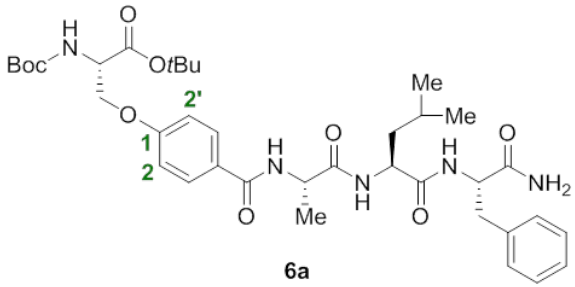
three arene protons of TMB

12.66

3.00

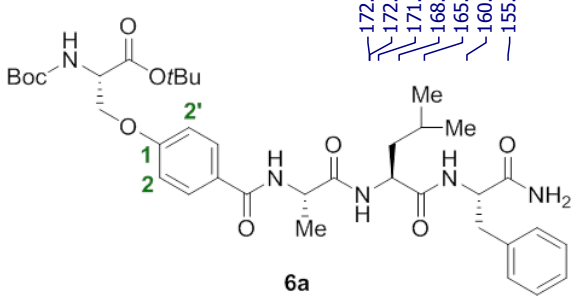
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



6a

^{13}C NMR (125 MHz, DMSO-d_6)



6a

172.67 172.66 171.54 168.97 165.82 160.51 155.38 137.74 129.41 129.10 127.98 126.57 126.18 113.95 81.11 78.40 67.46 54.01 53.45 51.51 49.19 37.43 28.15 27.61 24.08 22.92 21.64 17.56

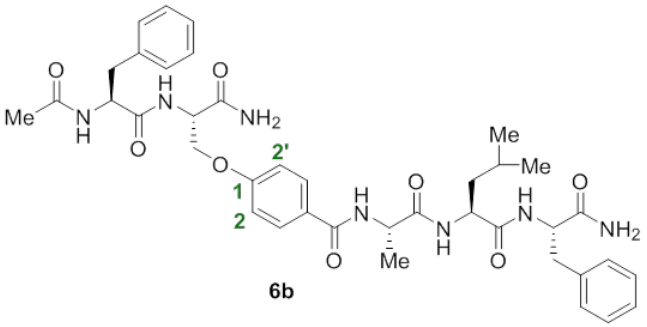
1

2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

Crude reaction for determination of NMR yield



6b

two protons (2 and 2')

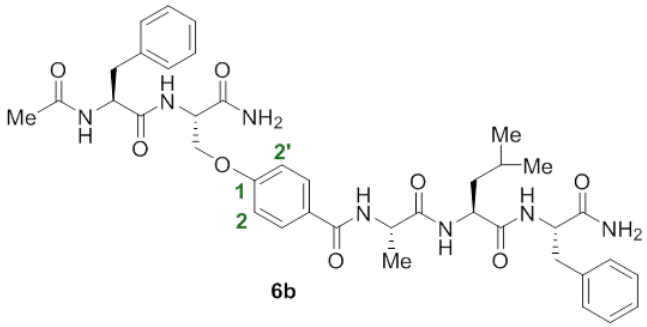
three arene protons of TMB

10.04

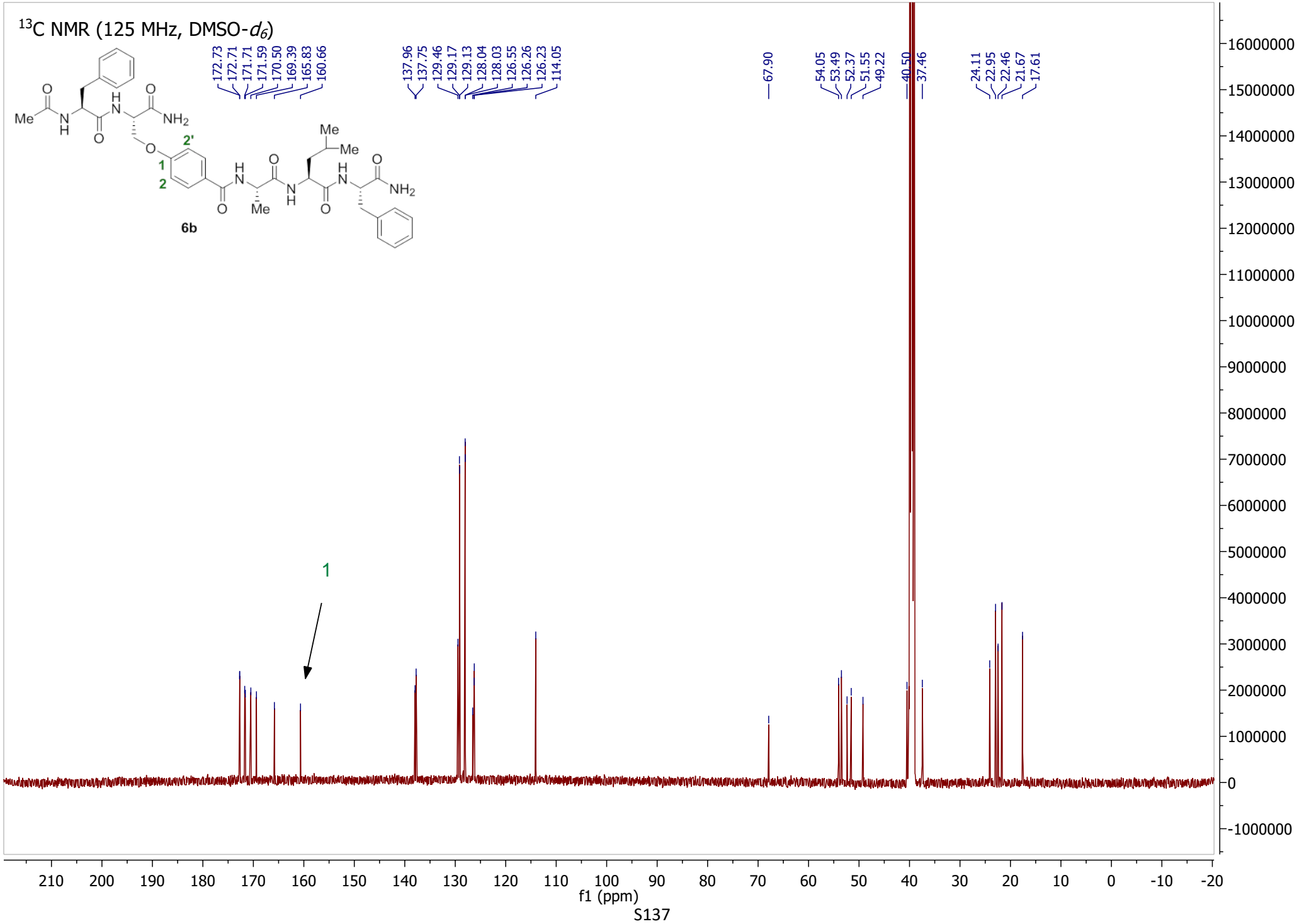
3.00

f1 (ppm)

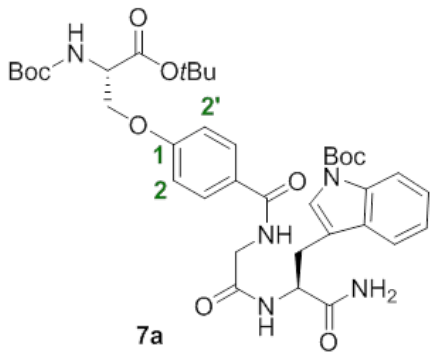
^{1}H NMR (500 MHz, DMSO-d_6)



6b


^{13}C NMR (125 MHz, DMSO-d_6)
172.73
172.71
171.71
171.59
170.50
169.39
165.83
160.66
137.96
137.75
129.46
129.17
129.13
128.04
128.03
126.55
126.26
126.23
114.05
67.90
54.05
53.49
52.37
51.55
49.22
40.50
37.46
24.11
22.95
22.46
21.67
17.61
6b
1
f1 (ppm)

Crude reaction for determination of NMR yield



two protons (2 and 2')

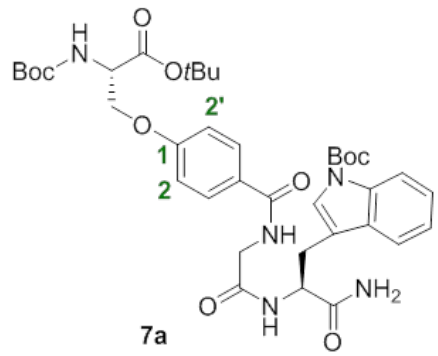
three arene protons of TMB

12.64

3.00

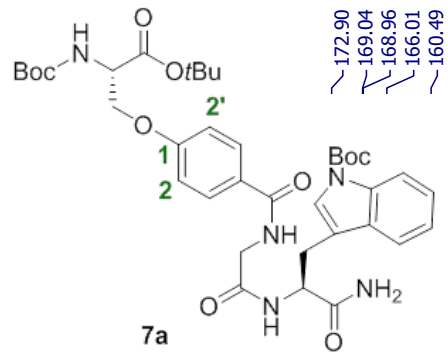
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



7a

^{13}C NMR (125 MHz, DMSO-d_6)



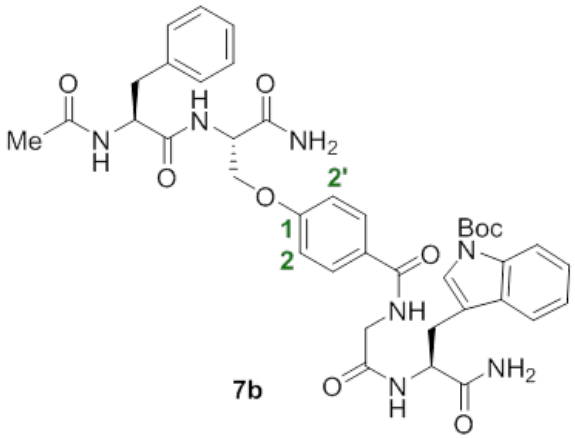
7a

172.90 169.04 168.96 166.01 160.49 155.38 149.05 134.60 130.34 129.15 126.61 124.25 123.80 122.45 119.35 116.72 114.60 114.04 83.48 81.12 78.41 67.46 54.02 52.36 42.68 28.15 27.70 27.61 27.18

1

f1 (ppm)

Crude reaction for determination of NMR yield



7b

two protons (2 and 2')

three arene protons of TMB

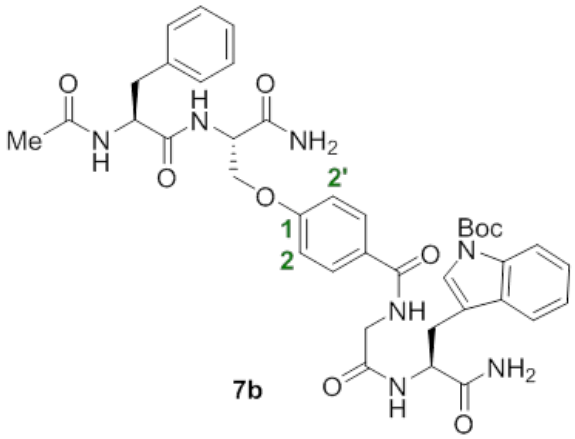
12.83

3.00

f1 (ppm)

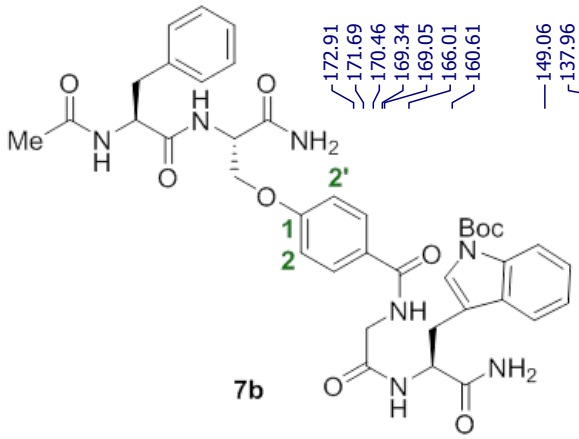
S141

^{1}H NMR (500 MHz, DMSO-d_6)



7b

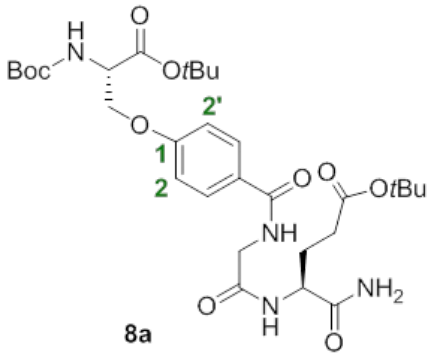
^{13}C NMR (125 MHz, DMSO-d_6)



7b

172.91 171.69 170.46 169.34 169.05 166.01 160.61 149.06 137.96 134.61 130.35 129.19 129.15 128.02 126.57 126.23 124.27 123.81 122.47 119.36 116.74 114.61 114.12 92.82 83.51 67.87 55.15 54.03 52.38 42.68 37.41 27.72 22.44

Crude reaction for determination of NMR yield



two protons (2 and 2')

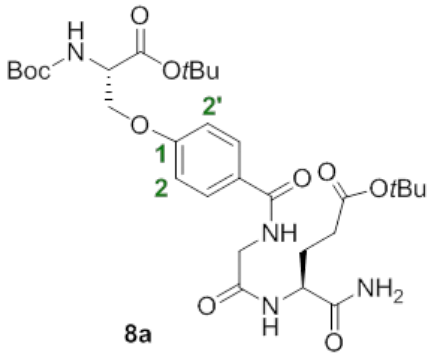
three arene protons of TMB

12.05

3.00

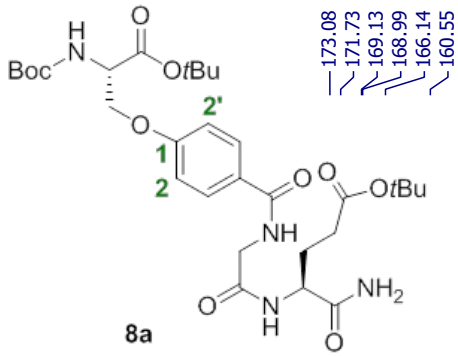
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



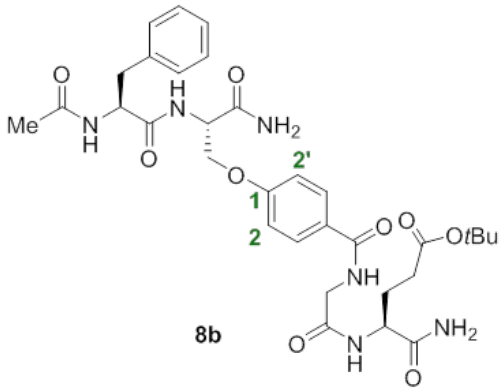
8a

^{13}C NMR (125 MHz, DMSO-d_6)



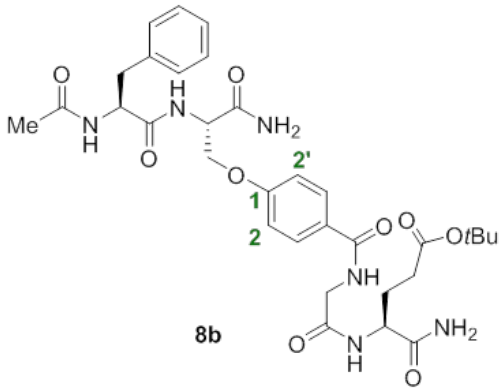
173.08, 171.73, 169.13, 168.99, 166.14, 160.55, 155.41, 129.19, 126.62, 114.09, 81.16, 79.71, 78.44, 67.49, 54.04, 51.56, 42.80, 31.33, 28.18, 27.76, 27.64, 27.23

Crude reaction for determination of NMR yield

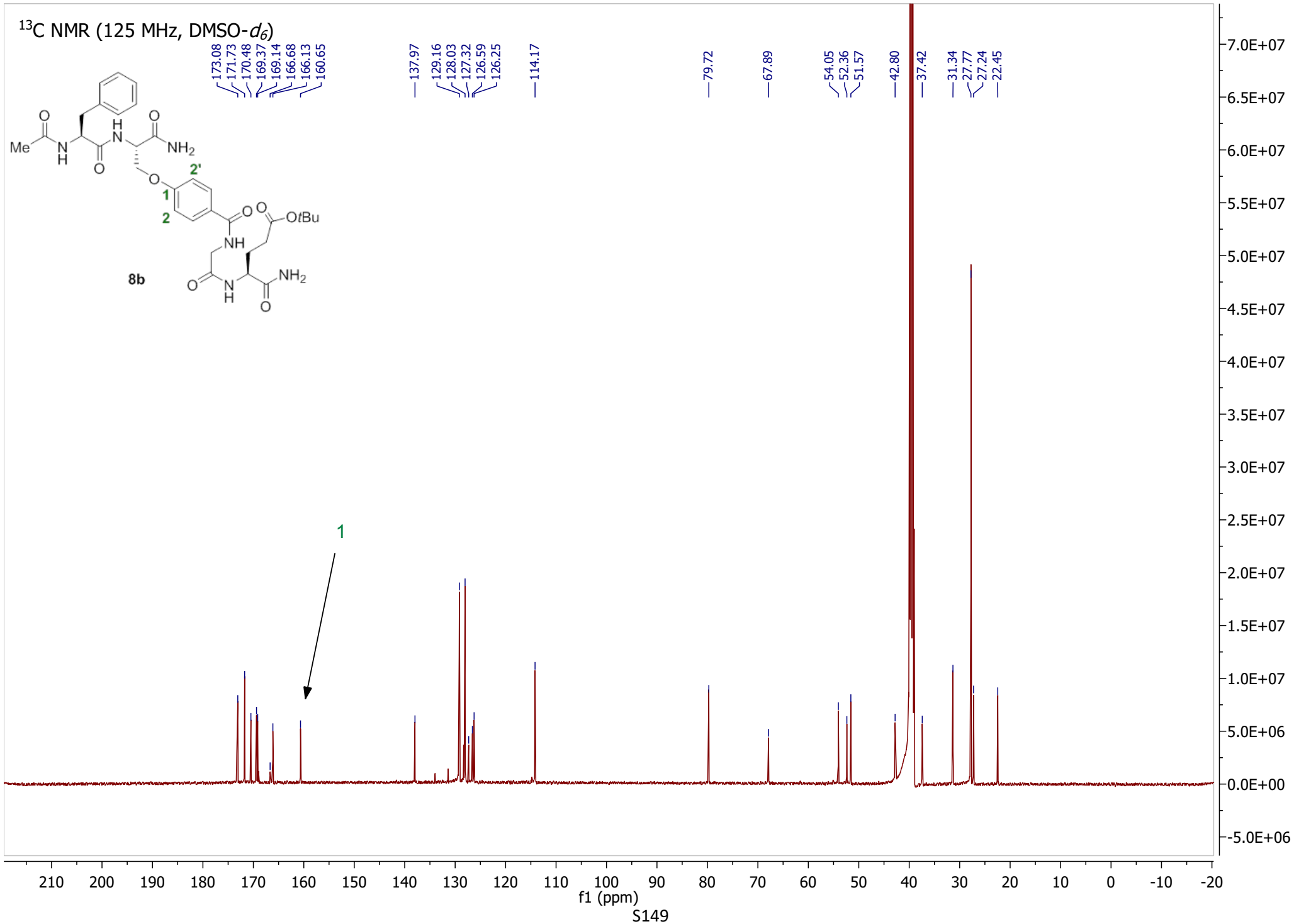


8b

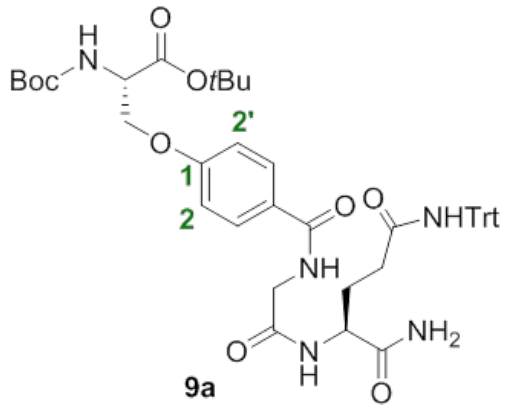
^{1}H NMR (500 MHz, DMSO-d_6)



8b


^{13}C NMR (125 MHz, DMSO-d_6)
173.08
171.73
170.48
169.37
169.14
166.68
166.13
160.65
137.97
129.16
128.03
127.32
126.59
126.25
114.17
79.72
67.89
54.05
52.36
51.57
42.80
37.42
31.34
27.77
27.24
22.45
Me
NH2
2'
1
2
OtBu
8b
1
7.0E+07
6.5E+07
6.0E+07
5.5E+07
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
-5.0E+06
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

Crude reaction for determination of NMR yield



two protons (2 and 2')

three arene protons of TMB

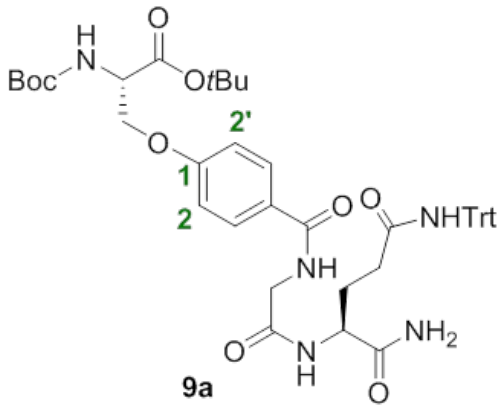
15.57

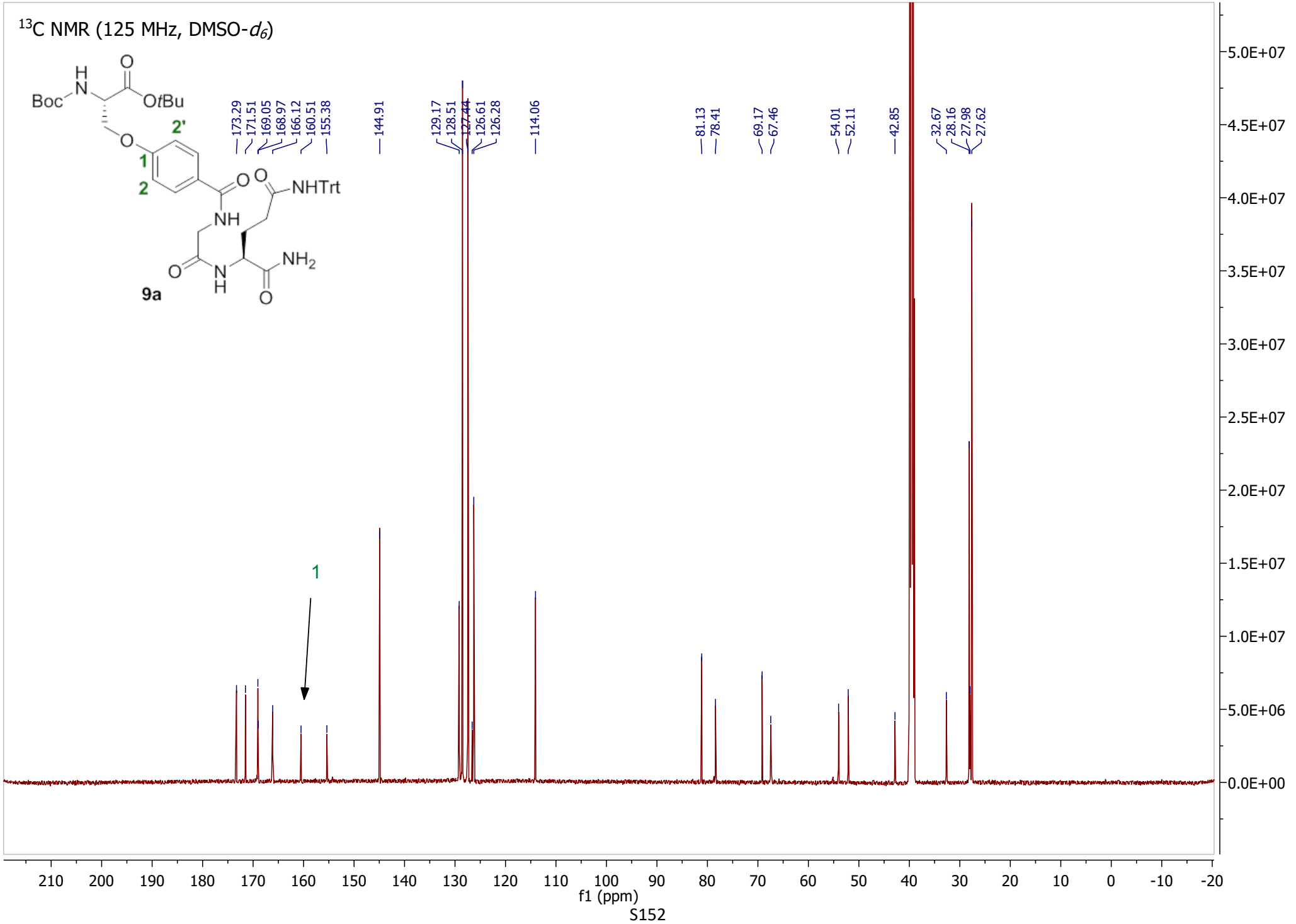
3.00

f1 (ppm)

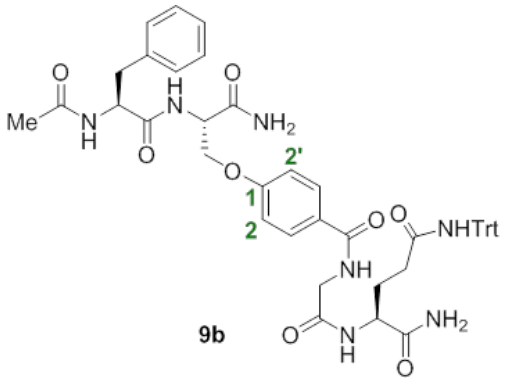
S150

^{1}H NMR (500 MHz, DMSO-d_6)



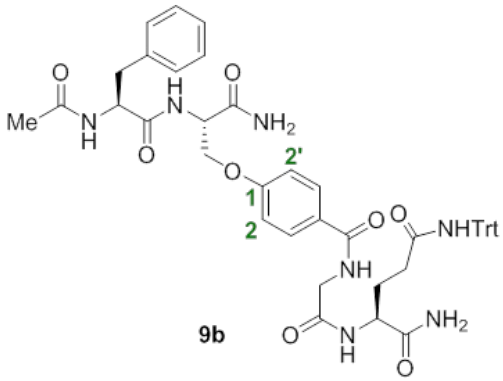

^{13}C NMR (125 MHz, DMSO-d_6)
Boc
OtBu
2'
1
2
NHTrt
NH
NH2
9a
173.29
171.51
169.05
168.97
166.12
160.51
155.38
144.91
129.17
128.51
127.44
126.61
126.28
114.06
81.13
78.41
69.17
67.46
54.01
52.11
42.85
32.67
28.16
27.98
27.62
1
5.0E+07
4.5E+07
4.0E+07
3.5E+07
3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

Crude reaction for determination of NMR yield

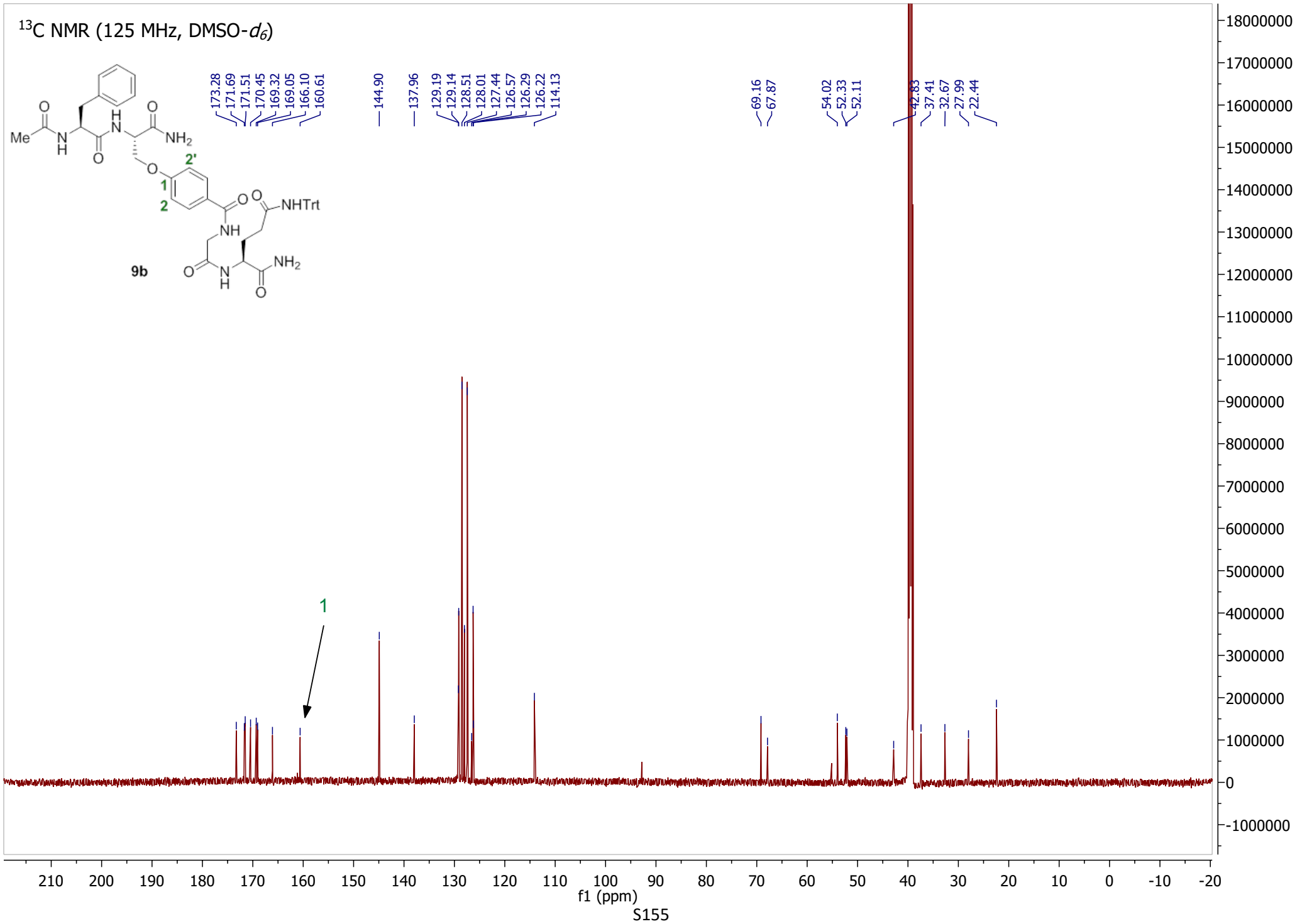


9b

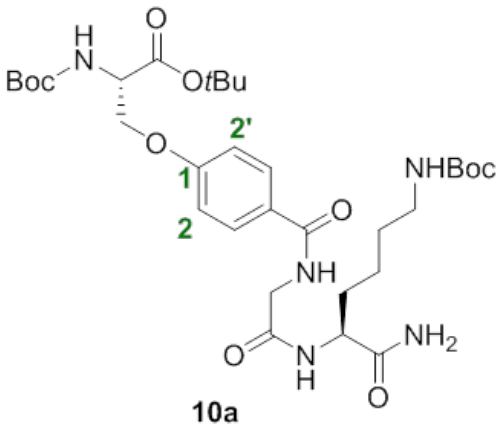
^{1}H NMR (500 MHz, DMSO-d_6)



9b

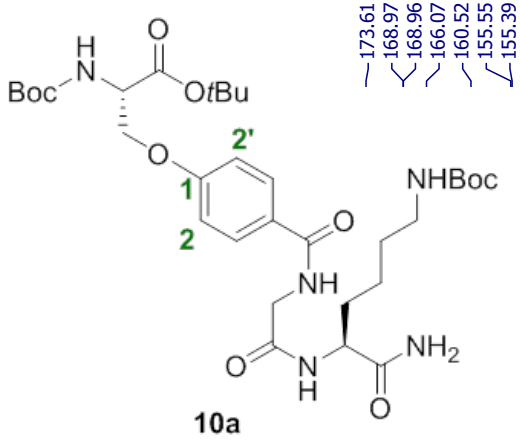

^{13}C NMR (125 MHz, DMSO-d_6)
9b
173.28
171.69
171.51
170.45
169.32
169.05
166.10
160.61
144.90
137.96
129.19
129.14
128.51
128.01
127.44
126.57
126.29
126.22
114.13
69.16
67.87
54.02
52.33
52.11
42.83
37.41
32.67
27.99
22.44
1
f1 (ppm)

^{1}H NMR (500 MHz, DMSO-d_6)



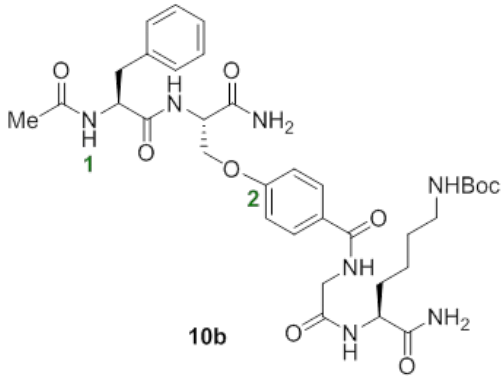
10a

^{13}C NMR (125 MHz, DMSO-d_6)



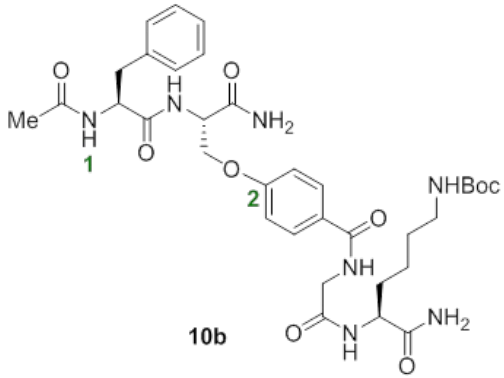
10a

Crude reaction for determination of NMR yield



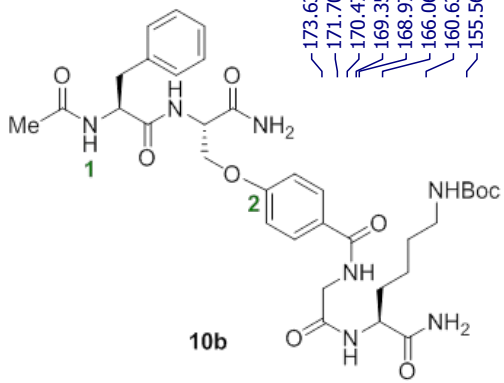
10b

^{1}H NMR (500 MHz, DMSO-d_6)



10b

^{13}C NMR (125 MHz, DMSO-d_6)



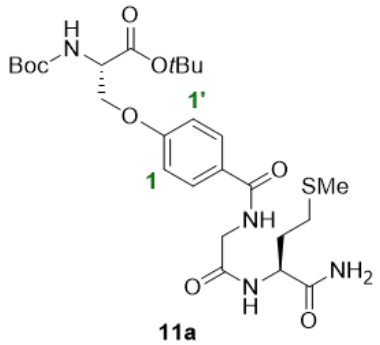
173.63
171.70
170.47
169.35
168.97
166.06
160.63
155.56
137.96
129.15
128.02
127.31
126.59
126.24
114.15
77.36
67.87
54.03
52.31
42.73
37.41
31.65
29.25
28.30
22.71
22.45

2

3.0E+07
2.5E+07
2.0E+07
1.5E+07
1.0E+07
5.0E+06
0.0E+00

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

^{1}H NMR (500 MHz, DMSO-d_6)



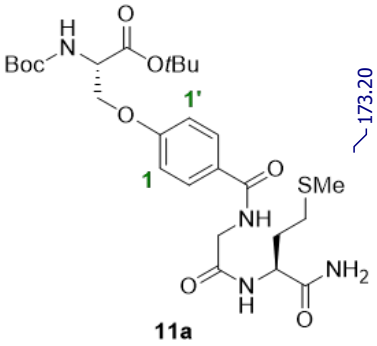
11a

1 and 1'

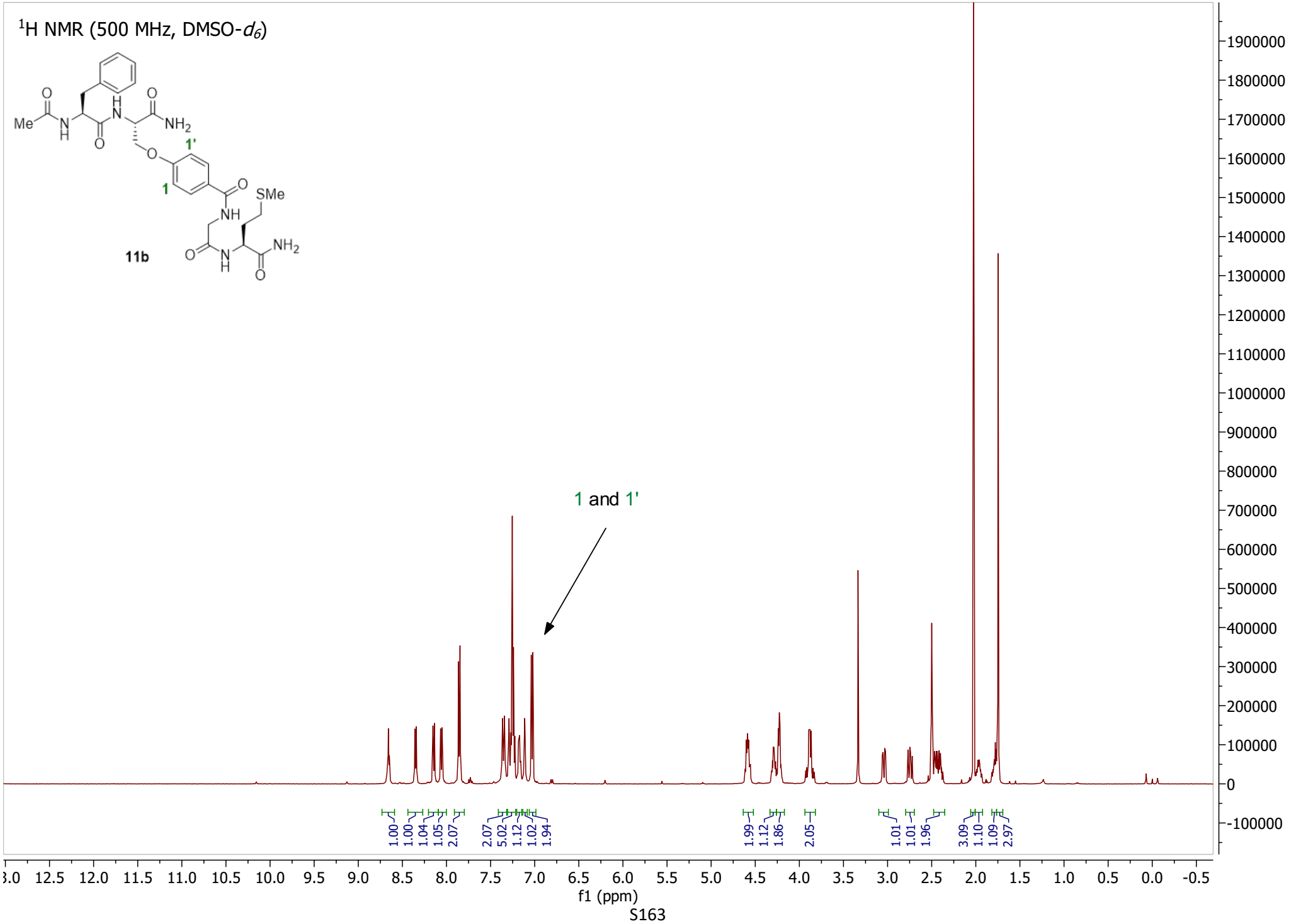
1.00 1.01 2.08 1.90 1.06 2.16 2.14 1.99 2.10 1.94 3.14 1.09 1.05 18.56

f1 (ppm)

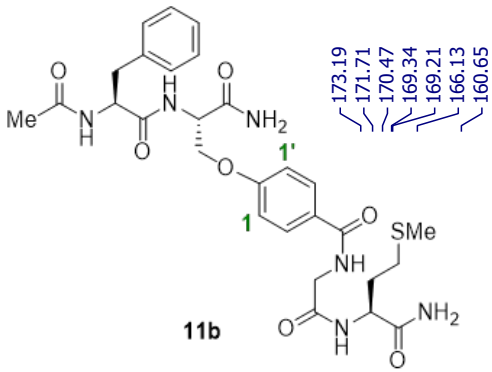
^{13}C NMR (125 MHz, DMSO-d_6)



173.20
169.22
169.00
166.17
160.55
155.42
129.20
126.60
114.10
81.16
78.45
67.48
54.04
51.64
42.87
31.58
29.69
28.18
27.64
14.63


^{1}H NMR (500 MHz, DMSO-d_6)
Me
NH
O
NH
O
NH$_2$
1'
O
1
SMe
NH
O
NH
O
NH$_2$
11b
1 and 1'
1.00
1.00
1.04
1.05
2.07
2.07
5.02
1.12
1.02
1.94
1.99
1.12
1.86
2.05
1.01
1.01
1.96
3.09
1.10
1.09
2.97
1900000
1800000
1700000
1600000
1500000
1400000
1300000
1200000
1100000
1000000
900000
800000
700000
600000
500000
400000
300000
200000
100000
0
-100000
3.0 12.5 12.0 11.5 11.0 10.5 10.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.0 -0.5
f1 (ppm)

^{13}C NMR (125 MHz, DMSO-d_6)



11b

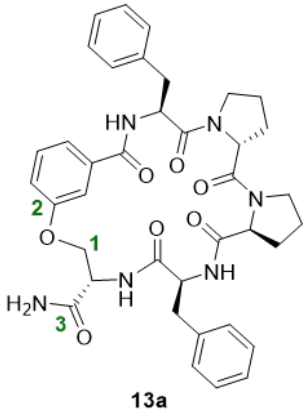
173.19 171.71 170.47 169.34 169.21 166.13 160.65 137.97 129.21 129.16 128.02 126.57 126.24 114.15 67.88 54.02 52.35 51.62 42.86 37.42 31.58 29.68 22.44 14.62

5500000 5000000 4500000 4000000 3500000 3000000 2500000 2000000 1500000 1000000 500000 0 -500000

210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

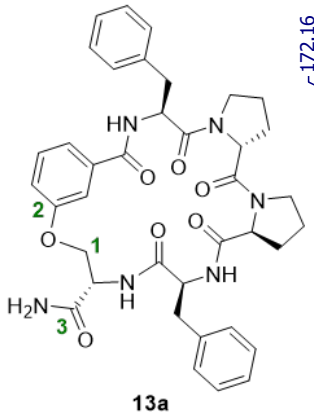
f1 (ppm)

^{1}H NMR (600 MHz, DMSO-d_6)



13a

^{13}C NMR (151 MHz, DMSO-d_6)



13a

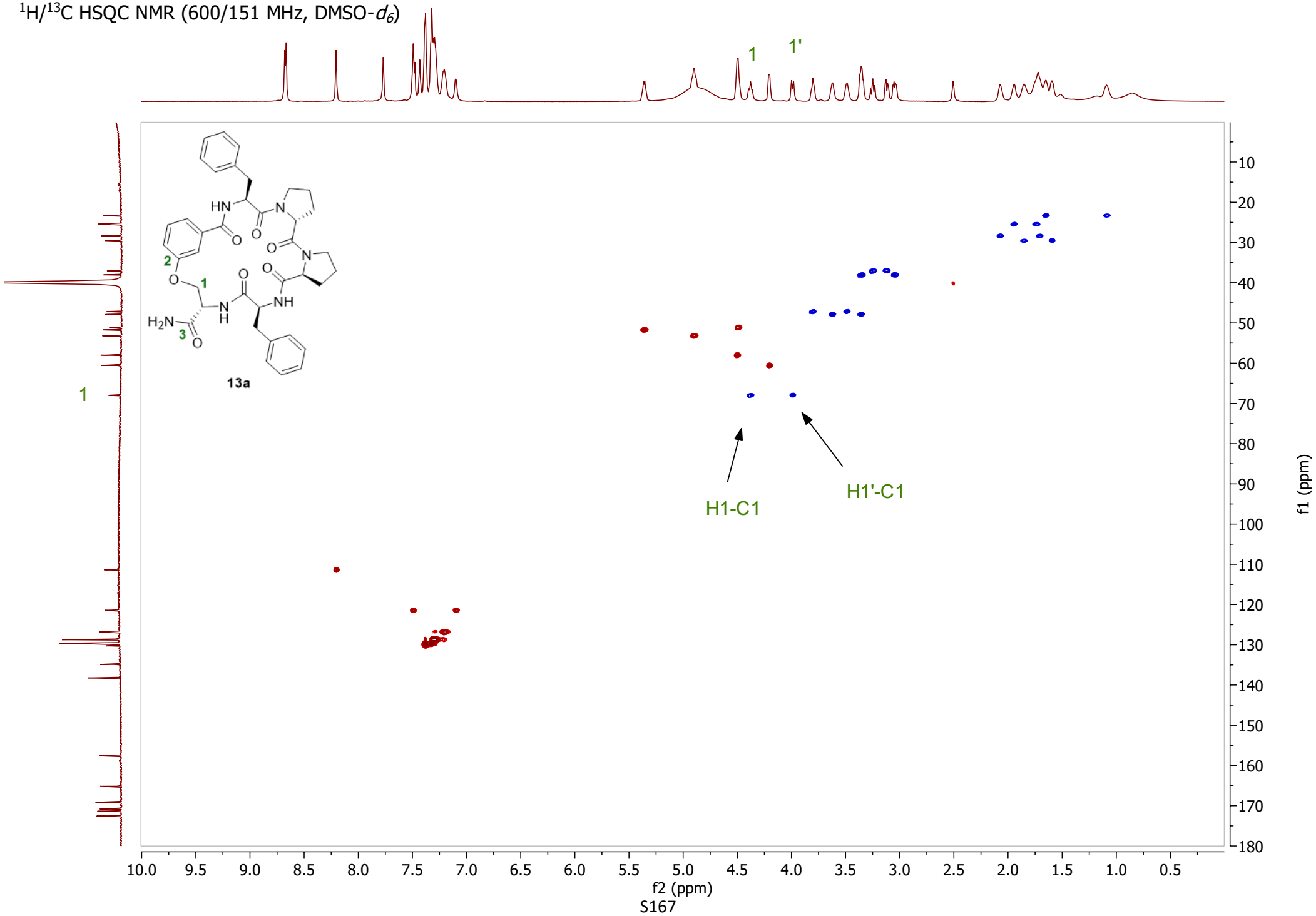
172.16 170.95 170.41 170.30 168.74 164.76 157.20 137.84 134.49 129.88 129.31 129.23 128.34 128.21 126.43 126.39 121.07 121.02 110.96 67.58 60.17 57.60 52.80 51.33 50.72 47.49 46.76 37.66 36.62 29.12 27.98 25.05 22.93

110000 100000 90000 80000 70000 60000 50000 40000 30000 20000 10000 0

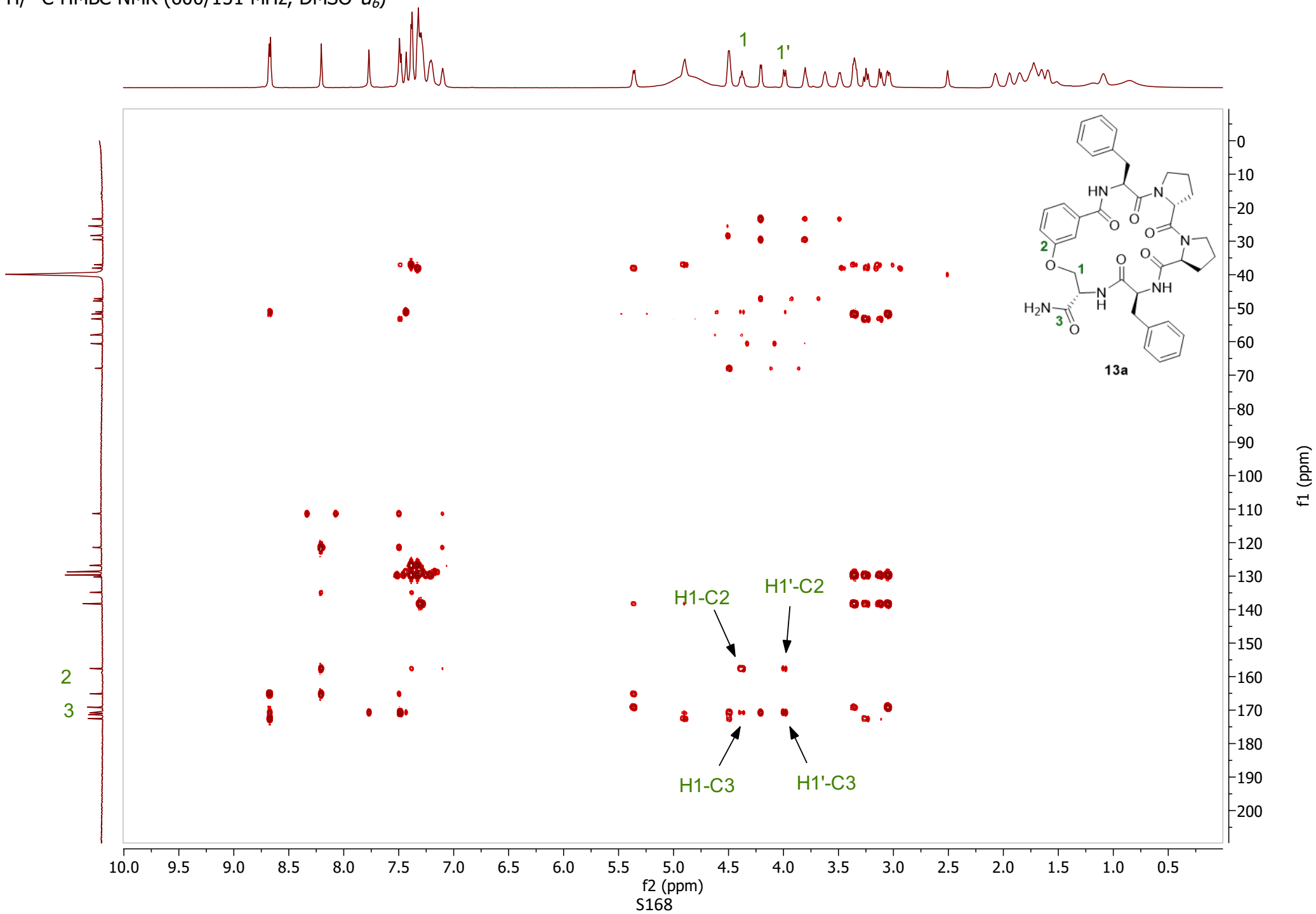
200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0

f1 (ppm)

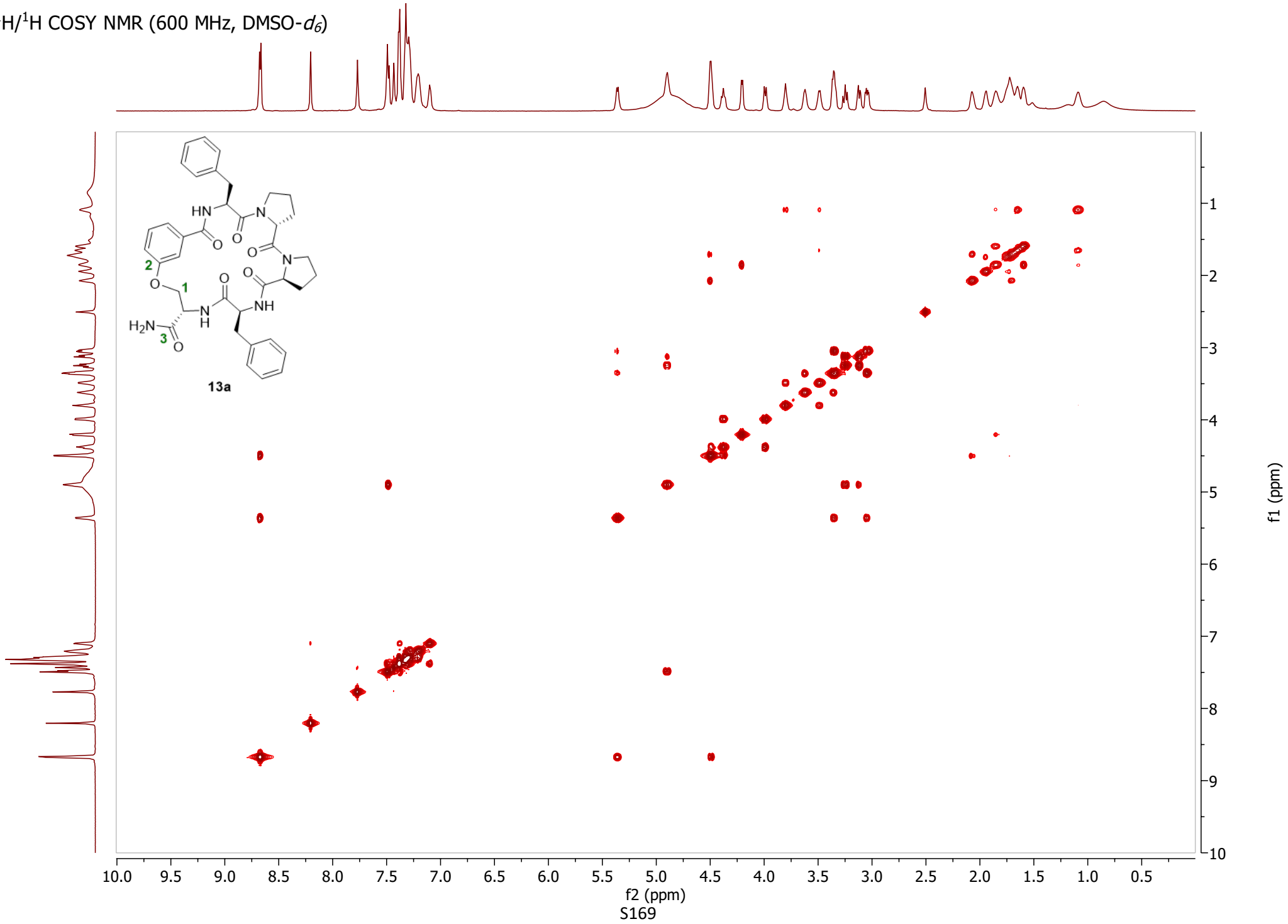
$^{1}H/^{13}C$ HSQC NMR (600/151 MHz, DMSO-d_6)



$^{1}H/^{13}C$ HMBC NMR (600/151 MHz, DMSO-d_6)

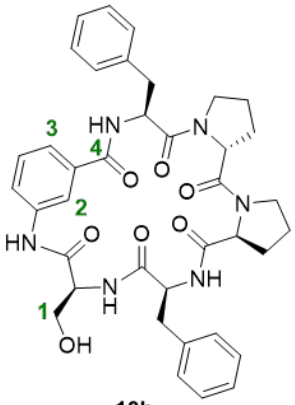


$^{1}H/^{1}H$ COSY NMR (600 MHz, DMSO-d_6)



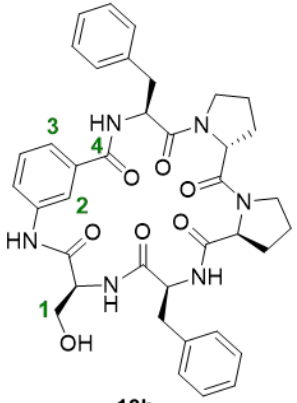
S169

^{1}H NMR (500 MHz, methanol-d_4)



13b

^{13}C NMR (125 MHz, methanol-d_4)



13b

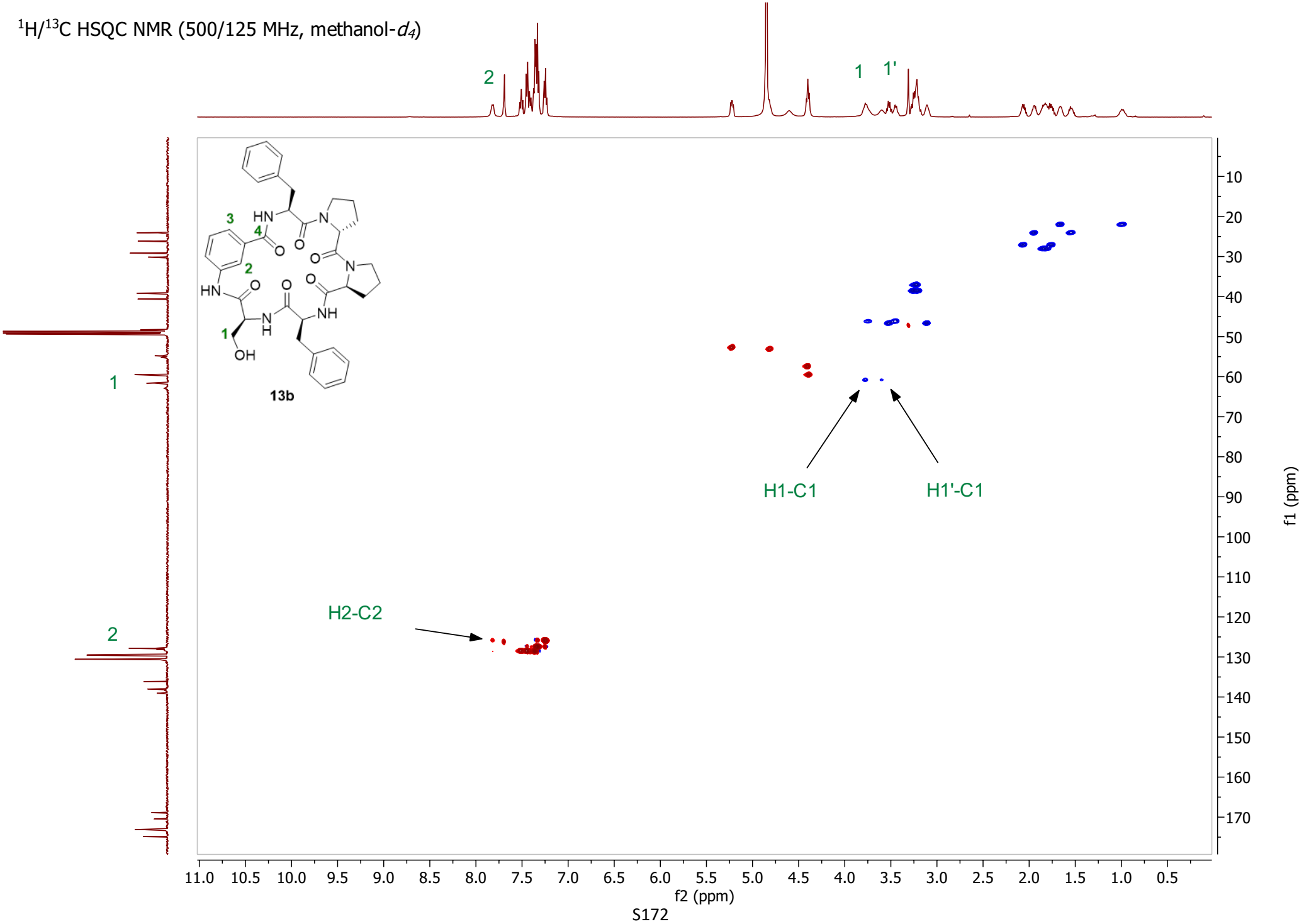
174.86 173.40 173.27 173.11 170.49 168.89

139.06 138.38 138.00 136.23 136.13 130.73 130.70 130.64 130.57 129.60 129.44 128.36 128.10 127.84

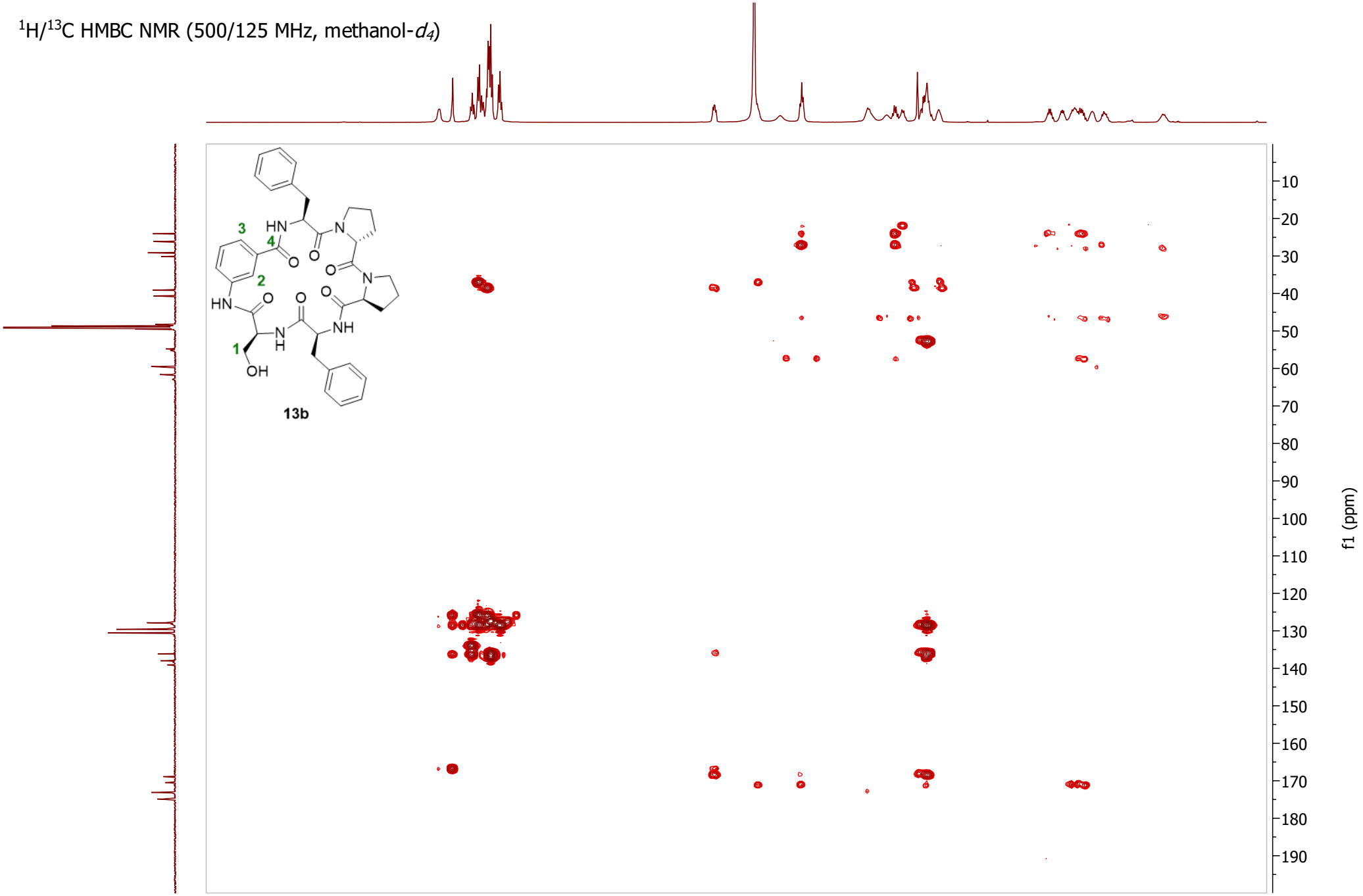
62.95 61.62 59.50 55.19 55.03 54.80 48.75 48.26 40.64 39.14 30.14 29.16 26.15 24.08

f1 (ppm)

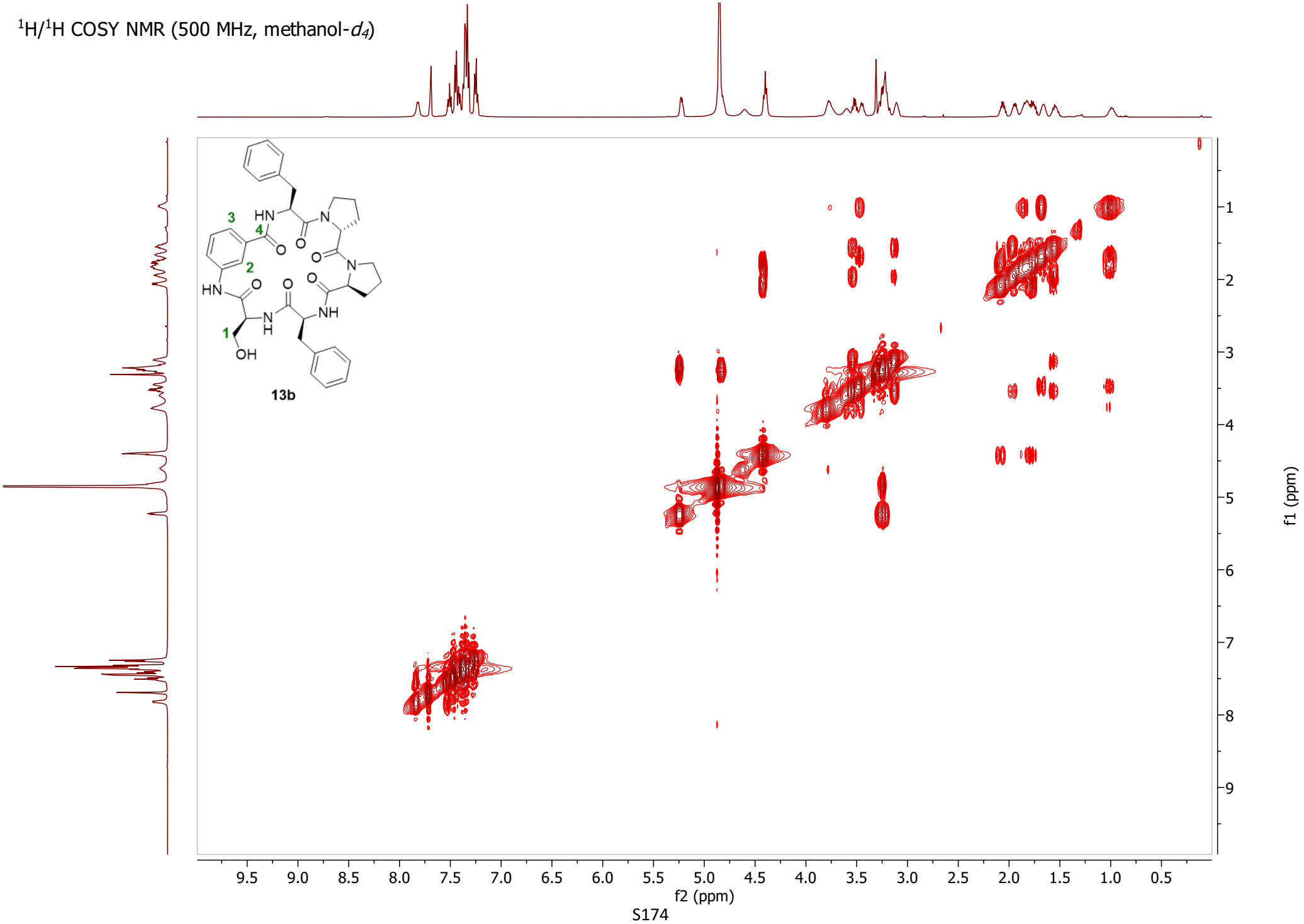
$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, methanol-d_4)



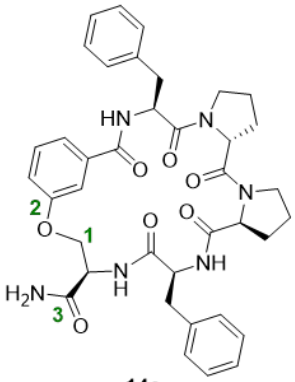
$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, methanol-d_4)



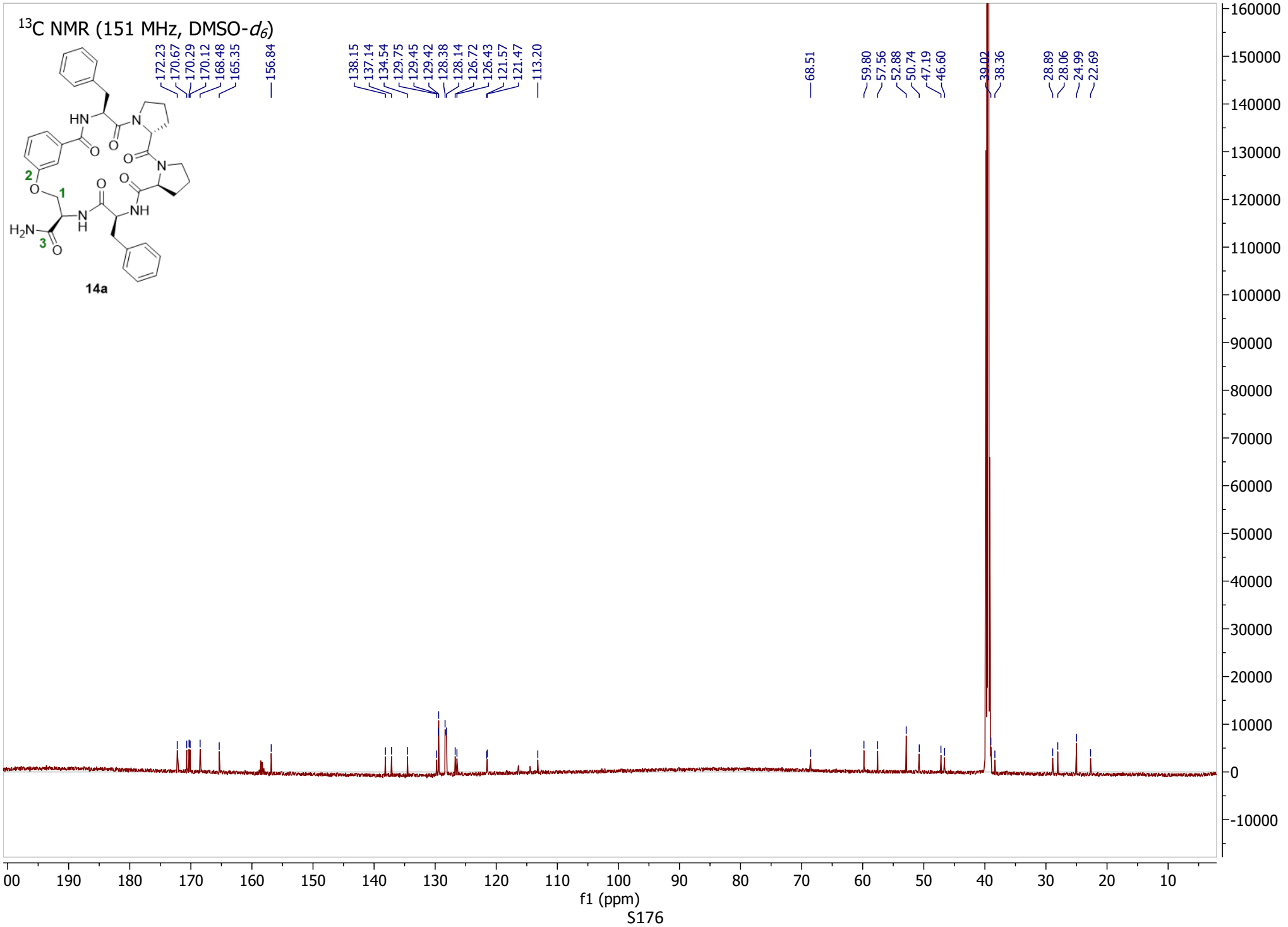
$^{1}H/^{1}H$ COSY NMR (500 MHz, methanol-d_4)



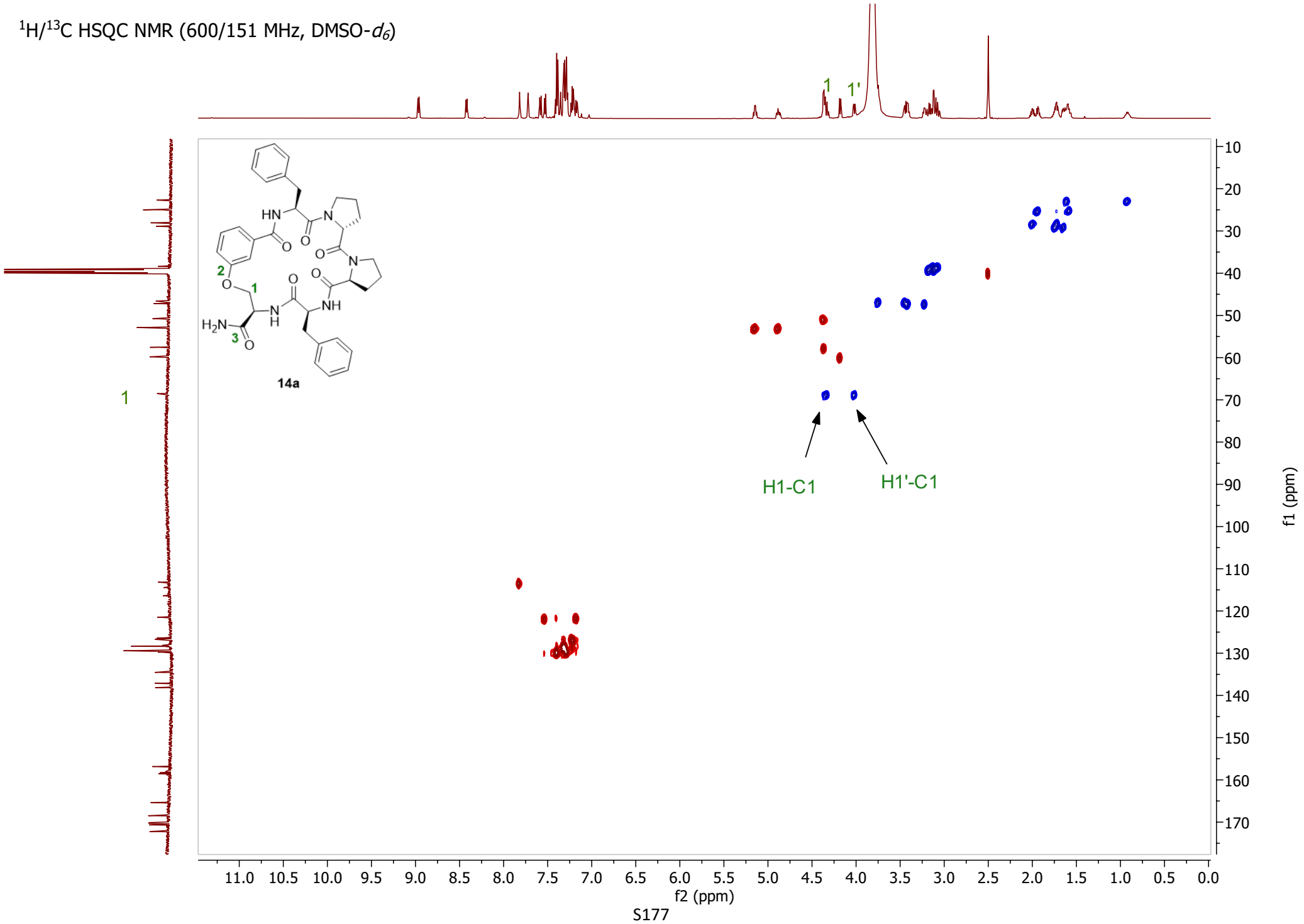
^{1}H NMR (600 MHz, DMSO-d_6)



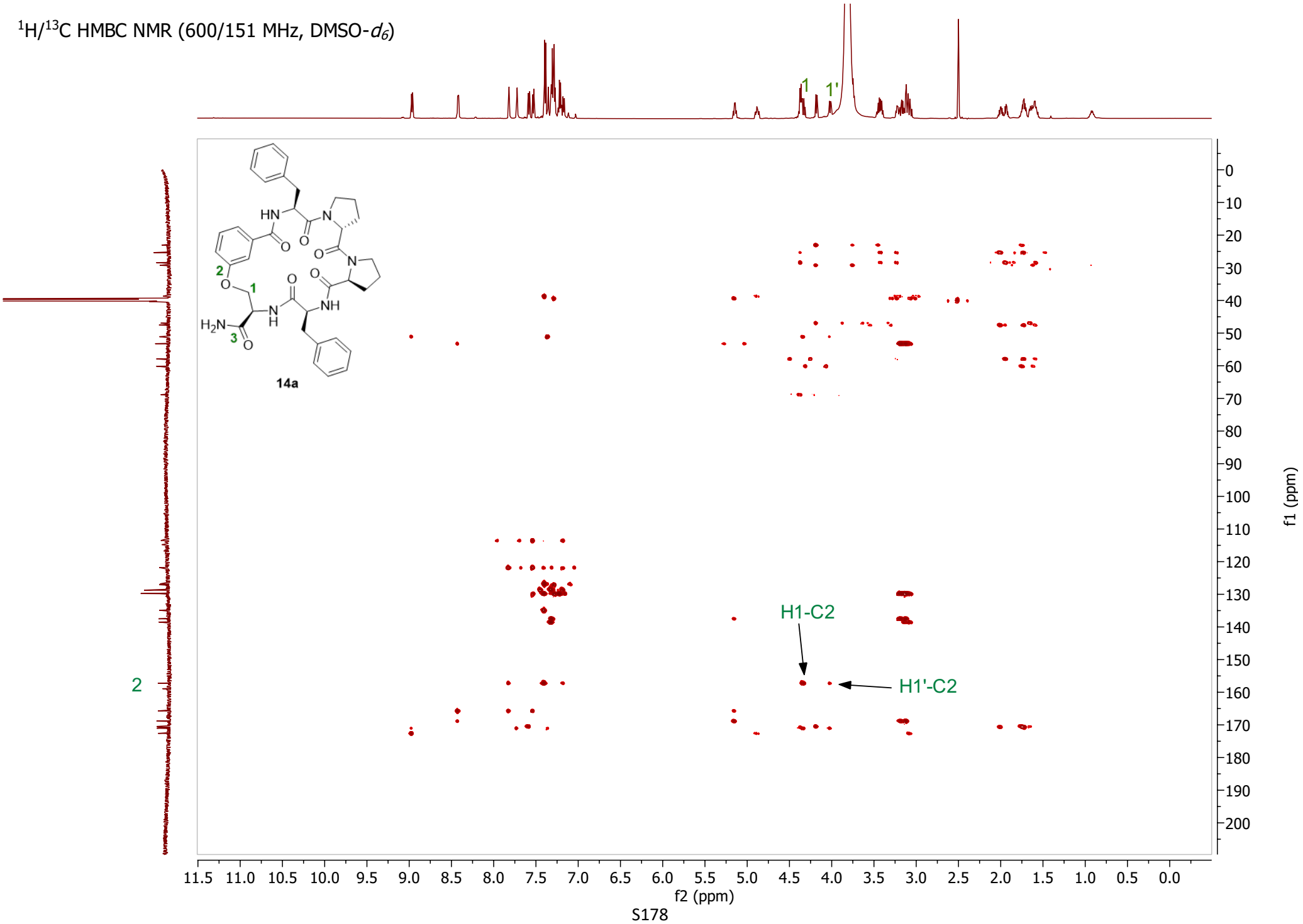
14a


^{13}C NMR (151 MHz, DMSO-d_6)
172.23
170.67
170.29
170.12
168.48
165.35
156.84
138.15
137.14
134.54
129.75
129.45
129.42
128.38
128.14
126.72
126.43
121.57
121.47
113.20
68.51
59.80
57.56
52.88
50.74
47.19
46.60
39.02
38.36
28.89
28.06
24.99
22.69
14a
f1 (ppm)

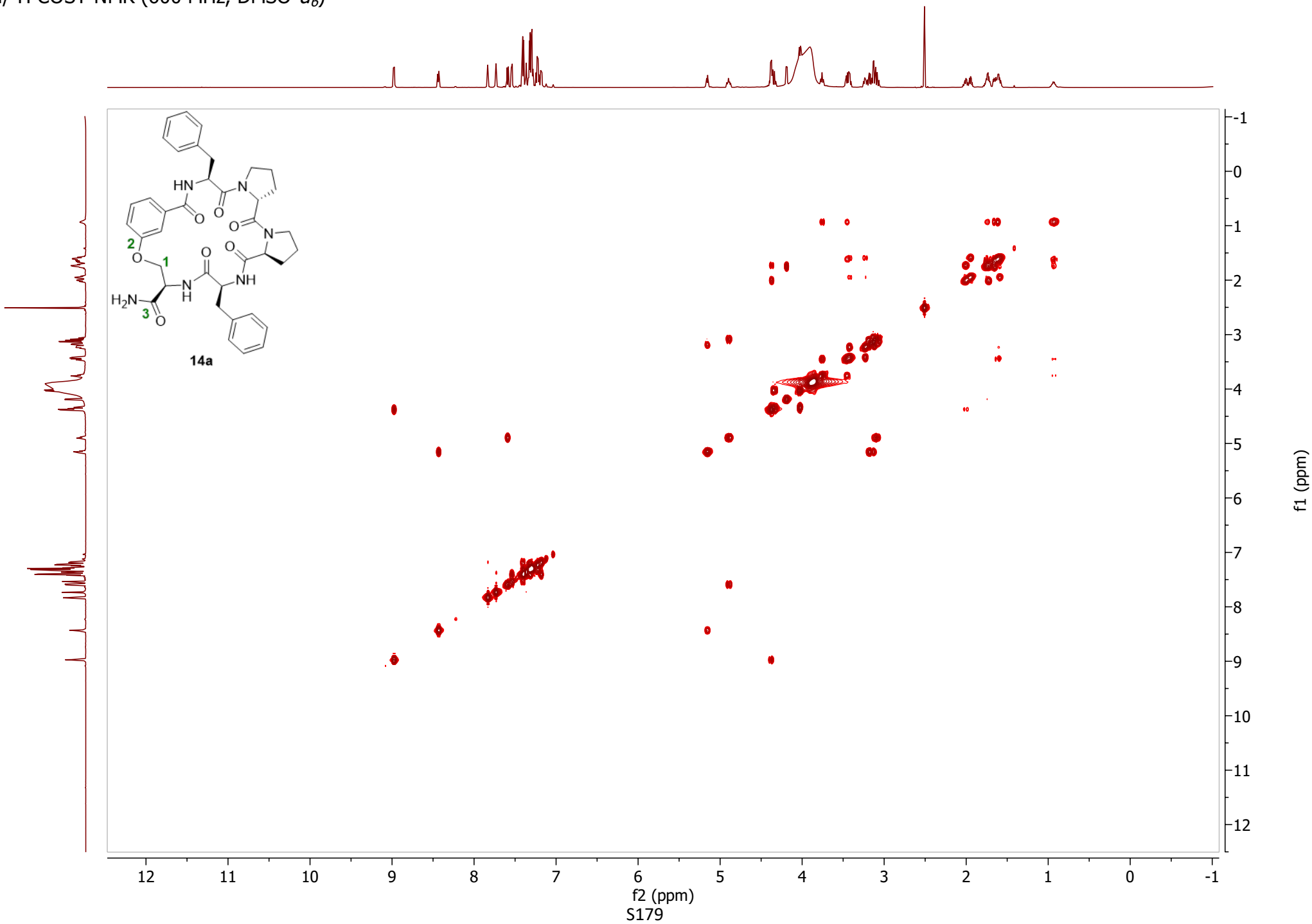
$^{1}H/^{13}C$ HSQC NMR (600/151 MHz, DMSO-d_6)



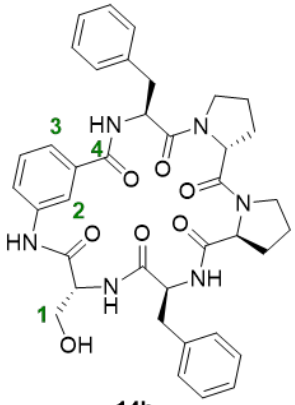
$^{1}H/^{13}C$ HMBC NMR (600/151 MHz, DMSO-d_6)



$^{1}H/^{1}H$ COSY NMR (600 MHz, DMSO-d_6)

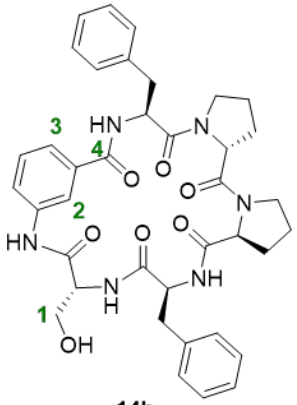


^{1}H NMR (500 MHz, methanol-d_4)



14b

^{13}C NMR (125 MHz, methanol-d_4)



14b

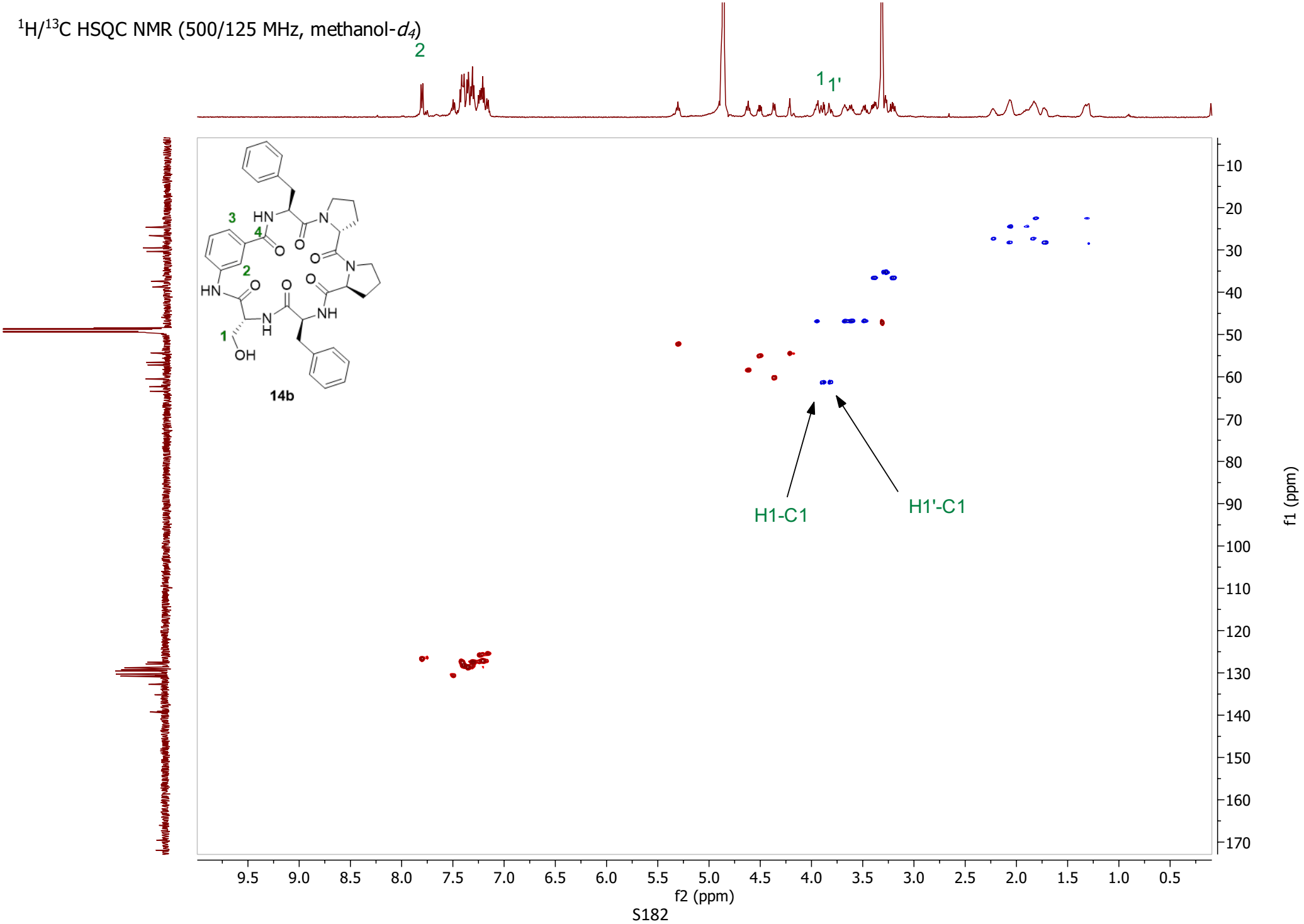
174.62
174.57
174.13
173.75
171.92
169.56
139.24
139.10
135.15
132.73
130.81
130.76
130.64
130.26
129.56
129.44
129.23
128.78
127.87
127.48
63.42
62.36
60.53
57.20
56.59
54.34
48.66
48.49
38.77
37.41
30.37
29.50
26.62
24.66

10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0

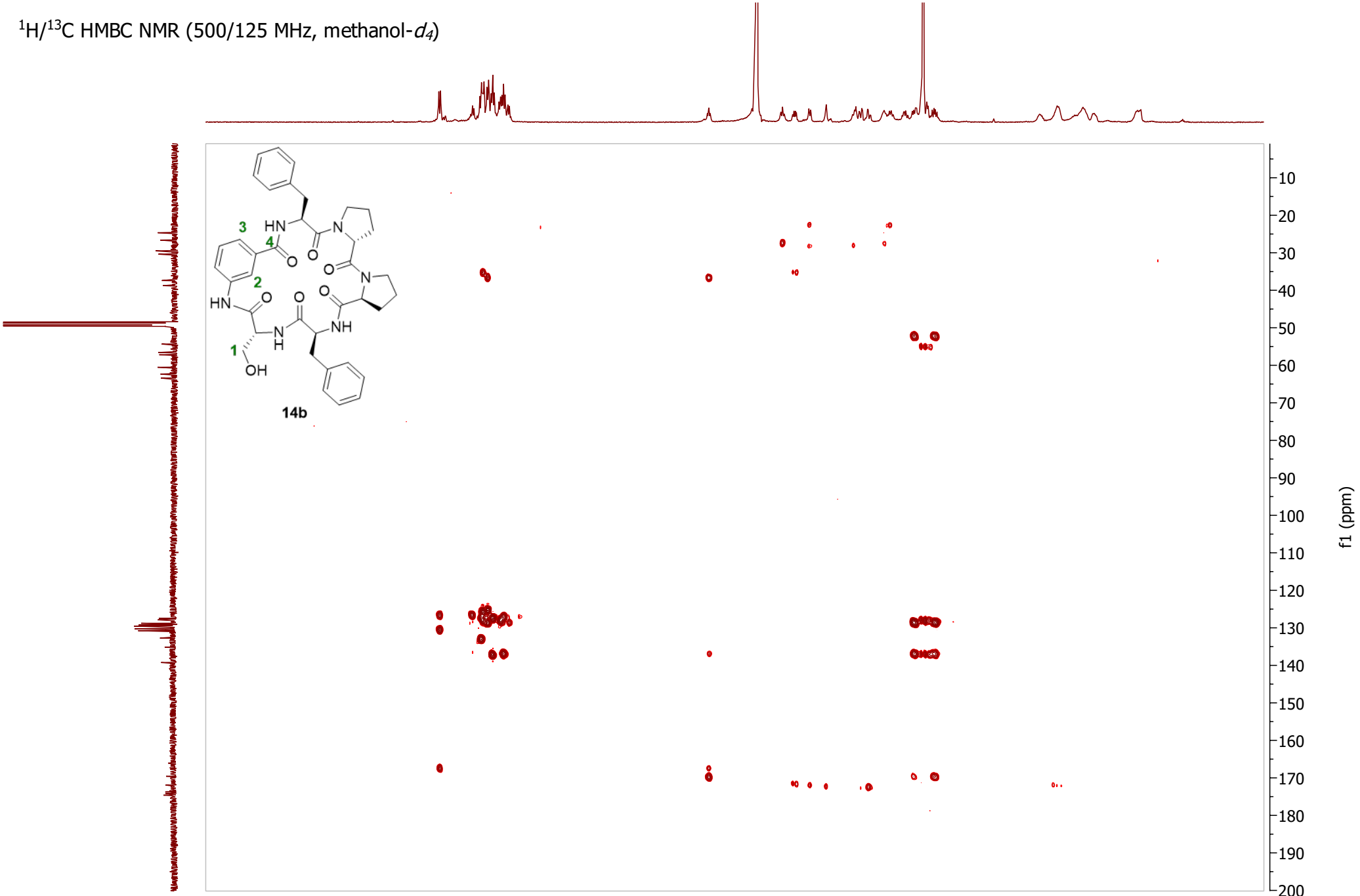
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

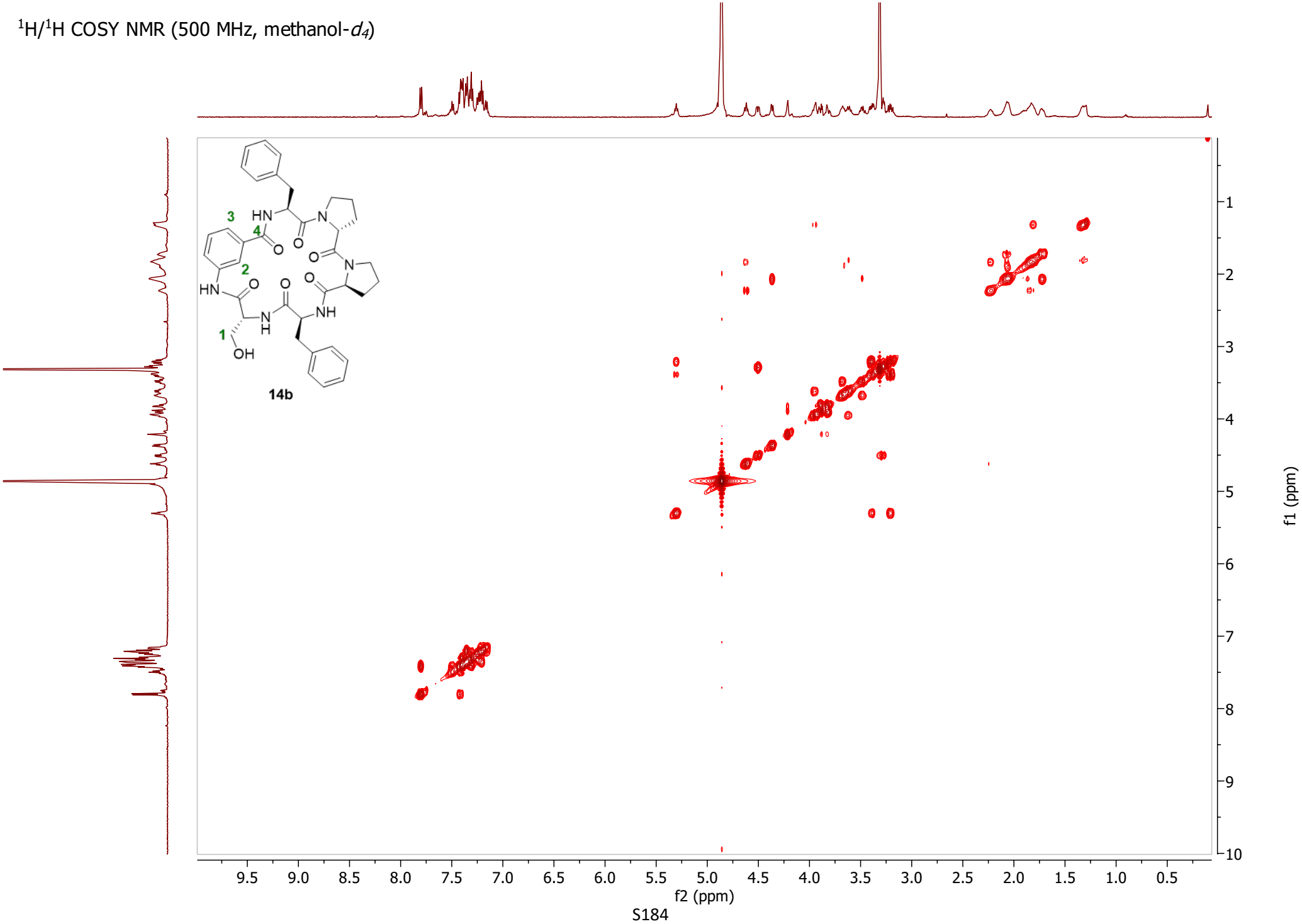
$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, methanol-d_4)



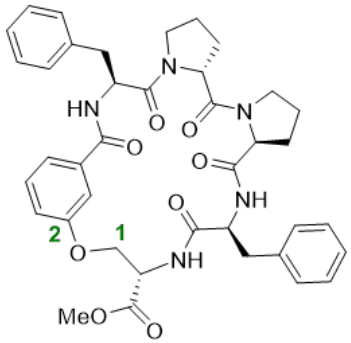
$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, methanol-d_4)



$^{1}H/^{1}H$ COSY NMR (500 MHz, methanol-d_4)

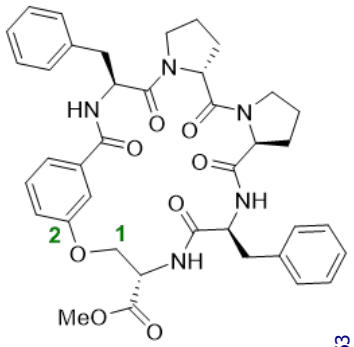


^{1}H NMR (500 MHz, DMSO-d_6)



15a

^{13}C NMR (125 MHz, DMSO-d_6)



15a

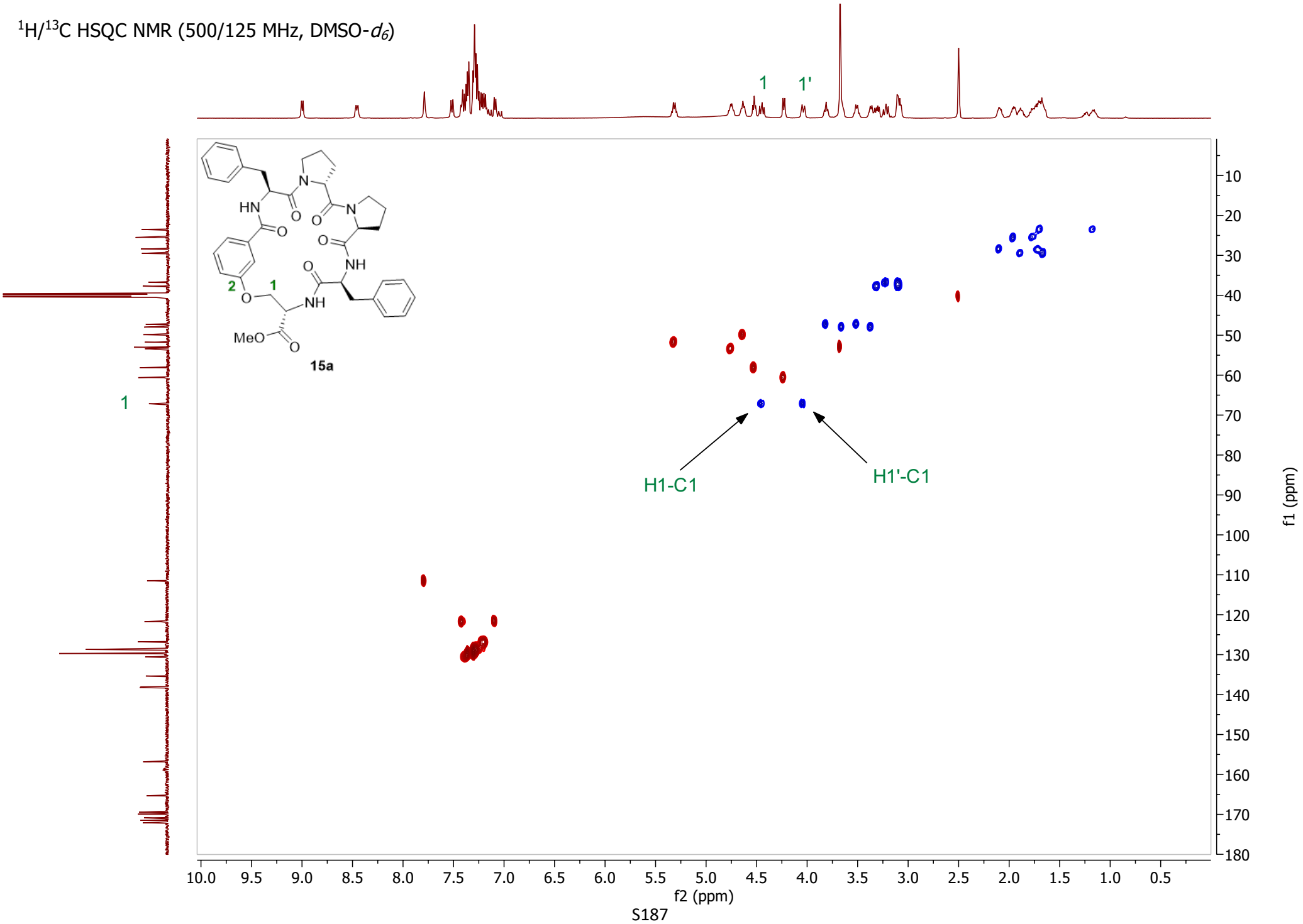
171.63
170.99
170.40
169.48
168.95
164.86
156.35
137.78
137.56
134.87
130.09
129.24
129.22
128.22
128.15
126.39
126.31
121.26
121.09
110.99
66.68
60.13
57.64
52.91
52.53
51.26
49.38
47.50
46.78
37.24
36.27
29.02
27.95
25.02
23.01

13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000

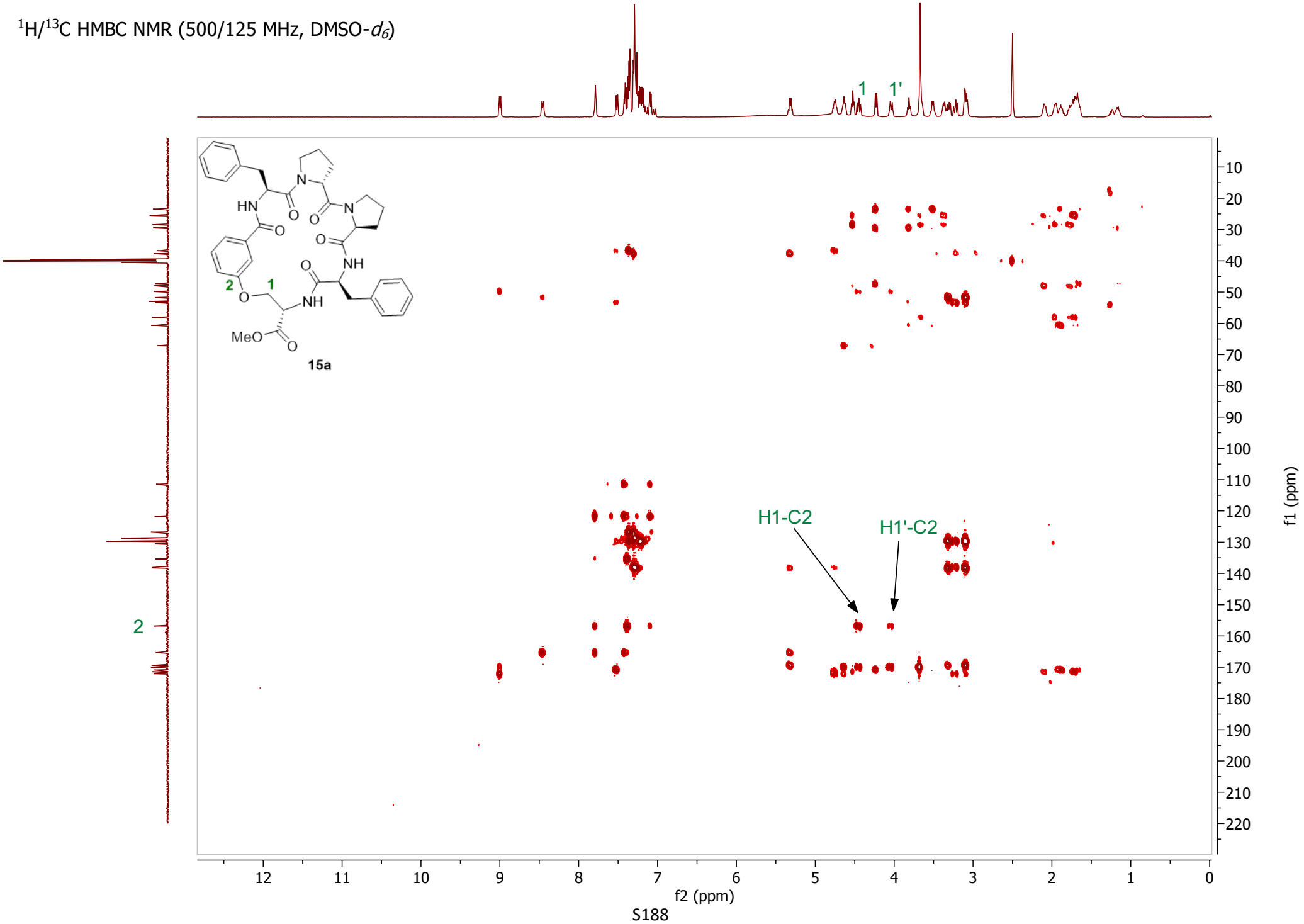
210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20

f1 (ppm)

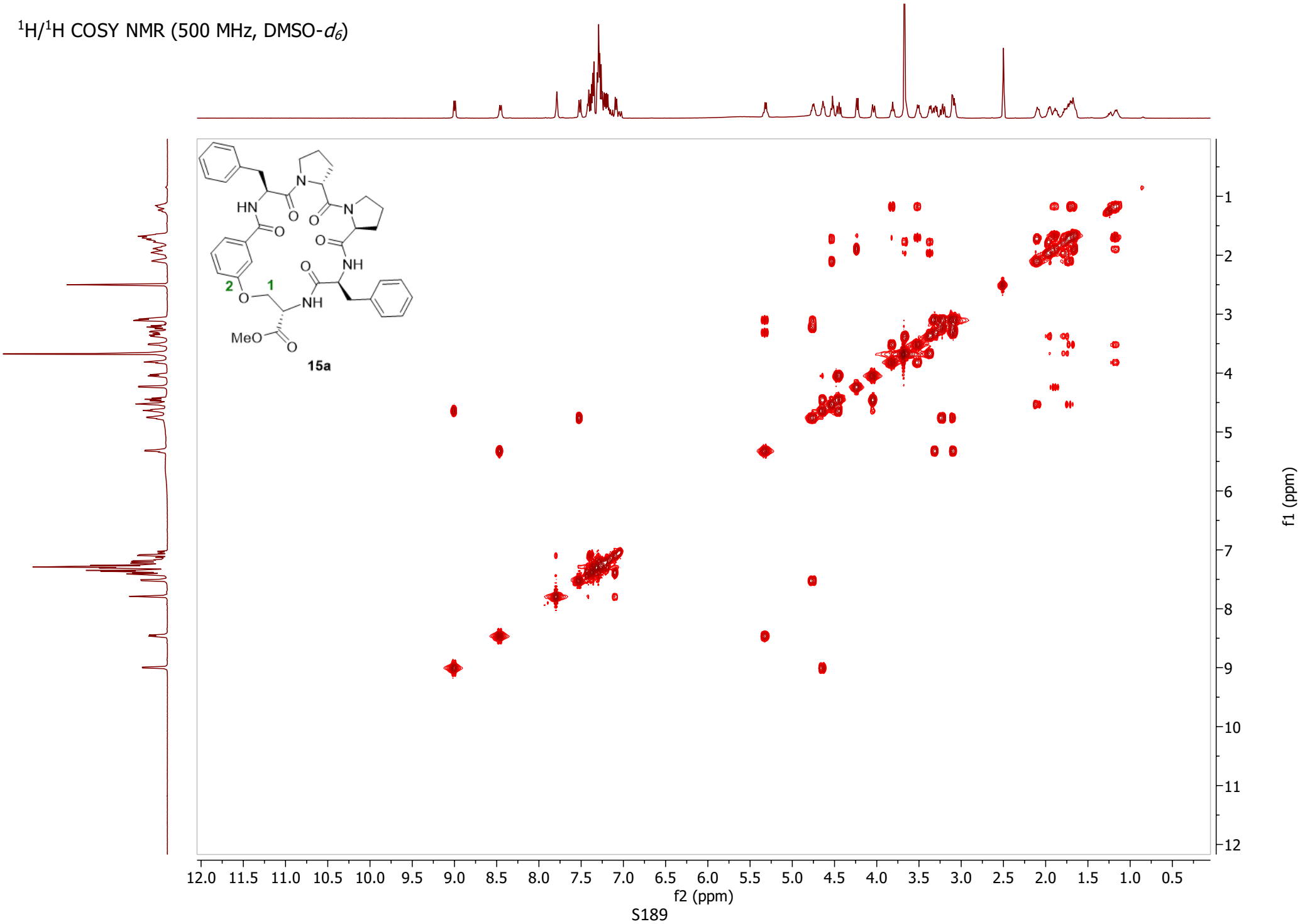
$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, DMSO-d_6)



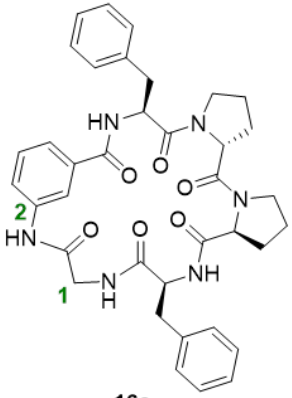
$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, DMSO-d_6)



$^{1}H/^{1}H$ COSY NMR (500 MHz, DMSO-d_6)

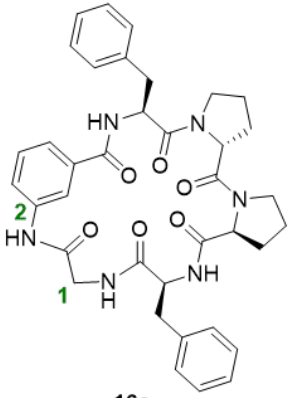


^{1}H NMR (500 MHz, methanol-d_4)



16a

^{13}C NMR (125 MHz, methanol-d_4)



16a

173.45
173.41
173.15
172.92
170.75
168.98
138.93
138.86
138.37
136.36
130.64
130.56
130.54
130.29
129.52
129.48
127.91
127.84
127.08
126.98
61.89
59.50
55.25
54.27
49.17
48.76
48.39
39.85
38.71
30.32
29.13
26.11
24.31

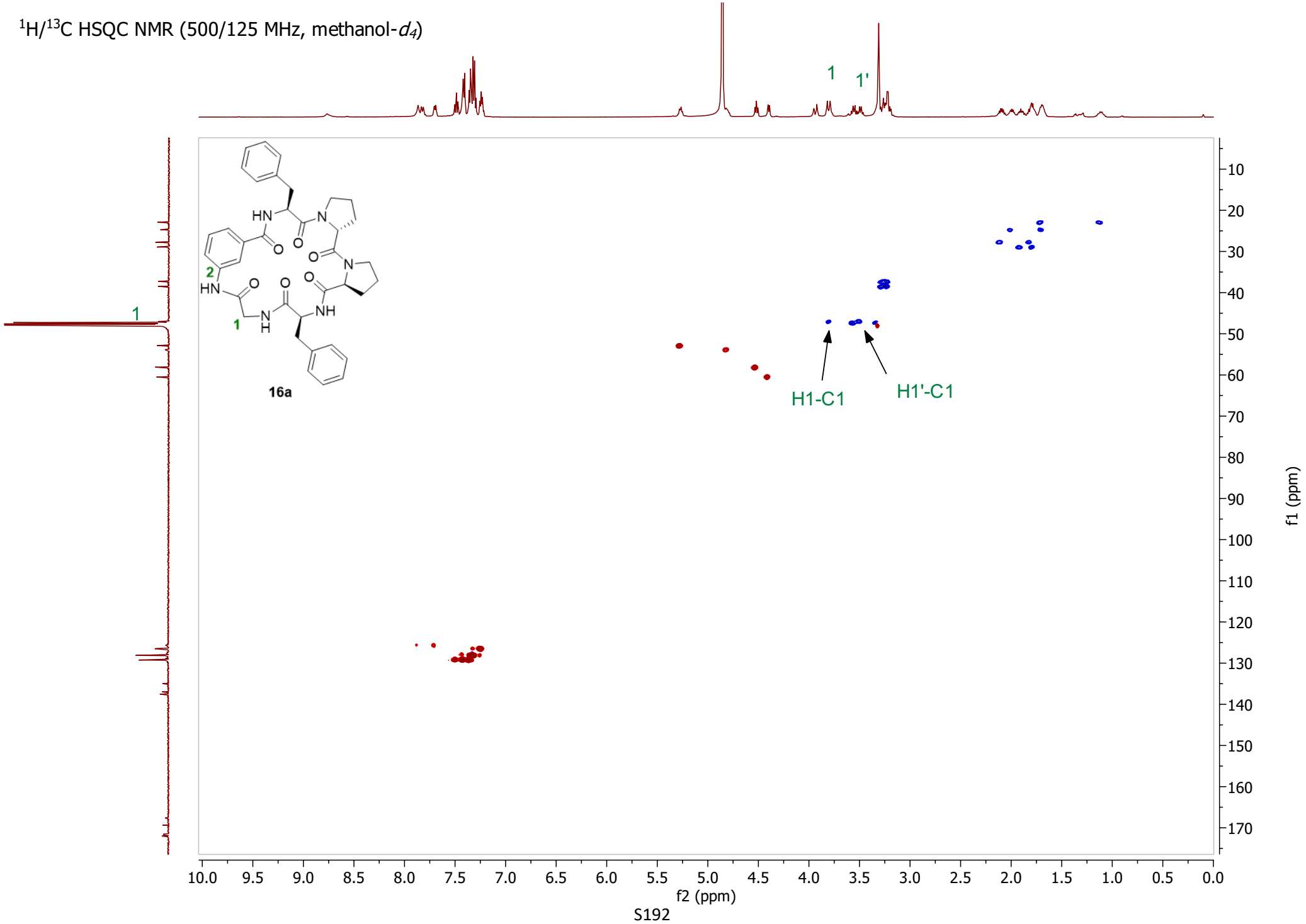
2
1

6.0×10^7
5.5×10^7
5.0×10^7
4.5×10^7
4.0×10^7
3.5×10^7
3.0×10^7
2.5×10^7
2.0×10^7
1.5×10^7
1.0×10^7
5.0×10^6
0.0
-5.0×10^6

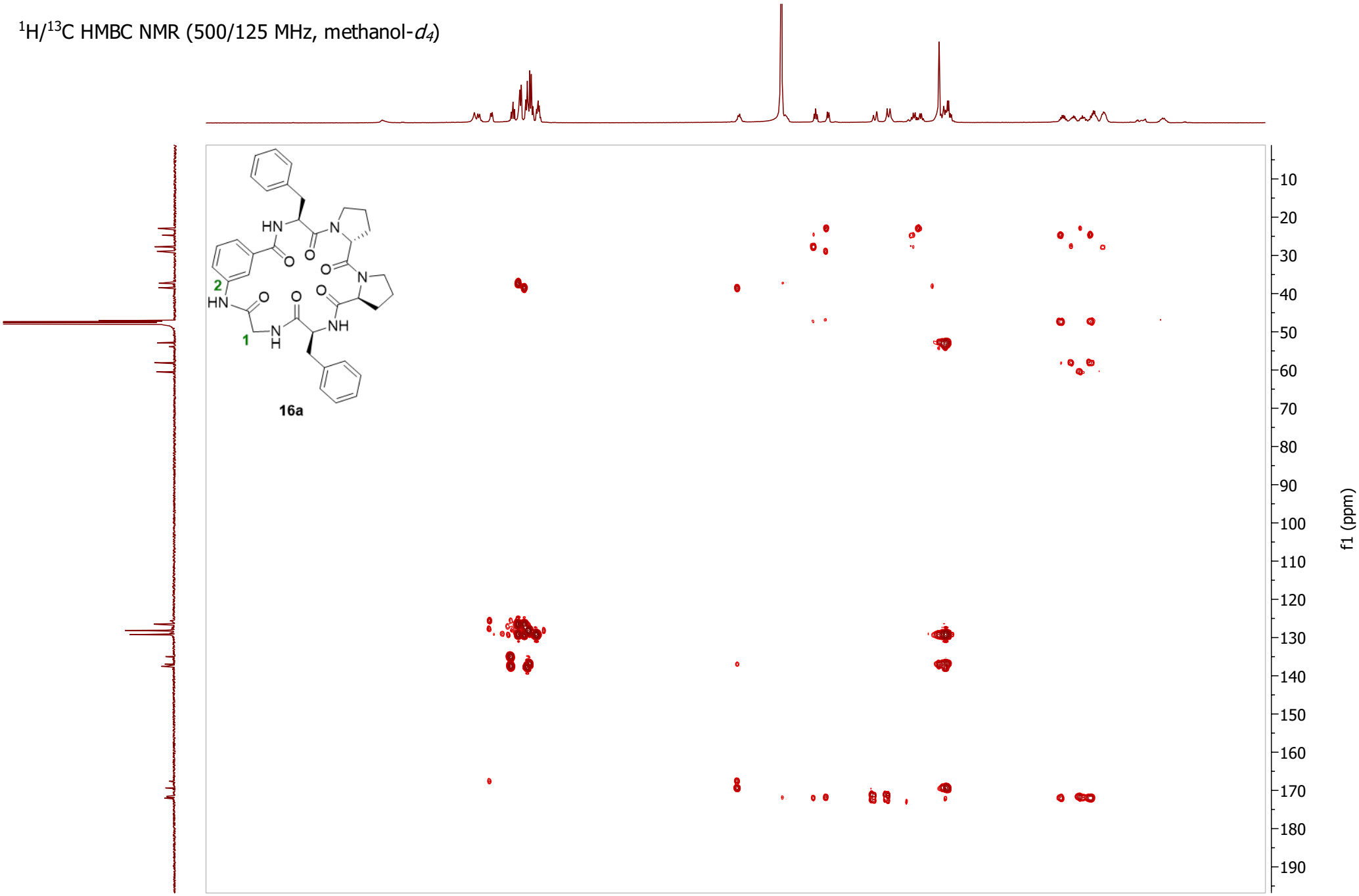
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

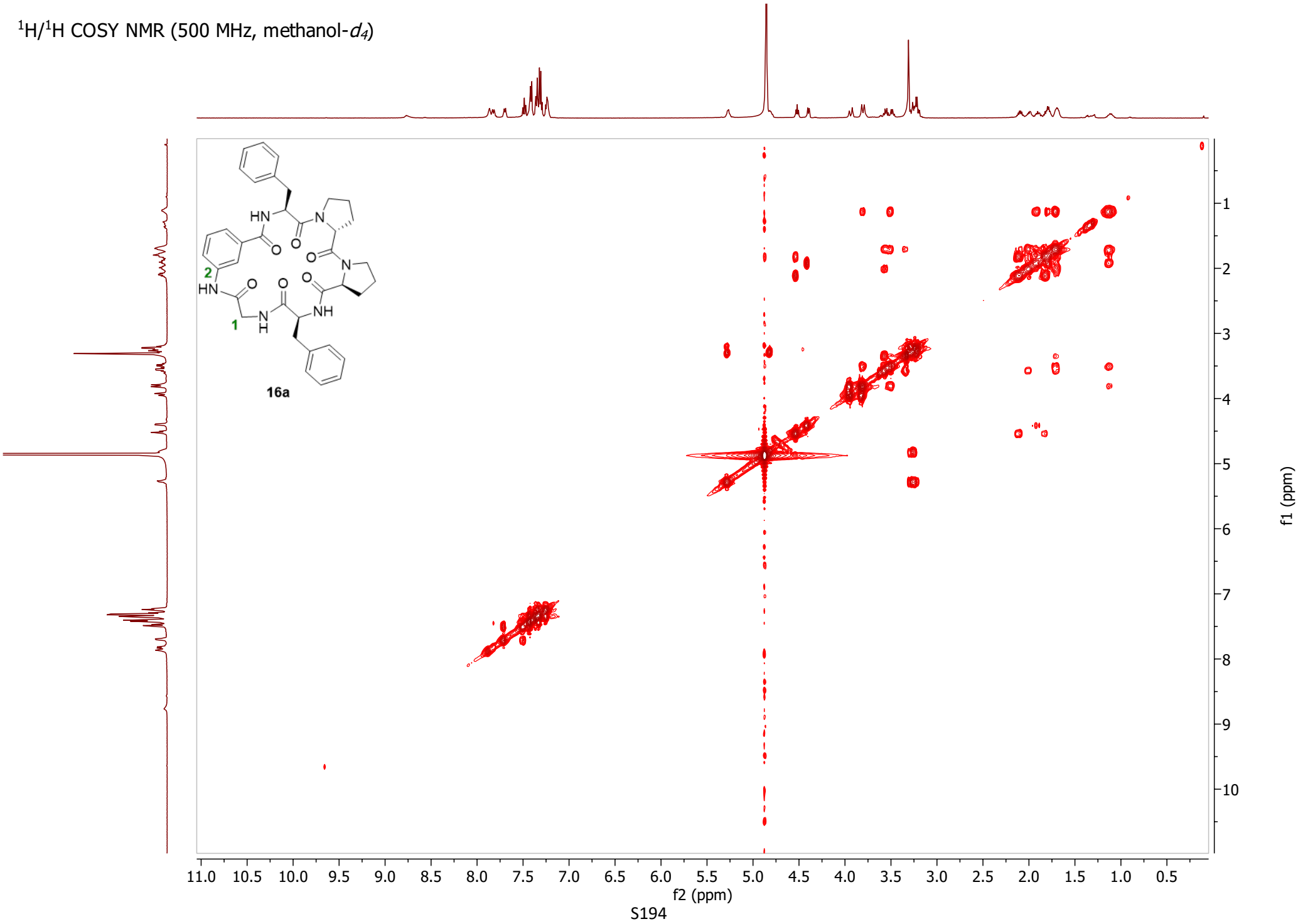
$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, methanol-d_4)



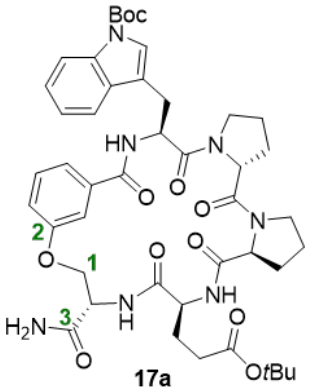
$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, methanol-d_4)



$^{1}H/^{1}H$ COSY NMR (500 MHz, methanol-d_4)

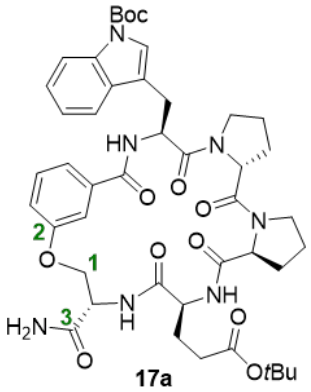


^{1}H NMR (500 MHz, methanol-d_4)



17a

^{13}C NMR (125 MHz, methanol-d_4)



17a

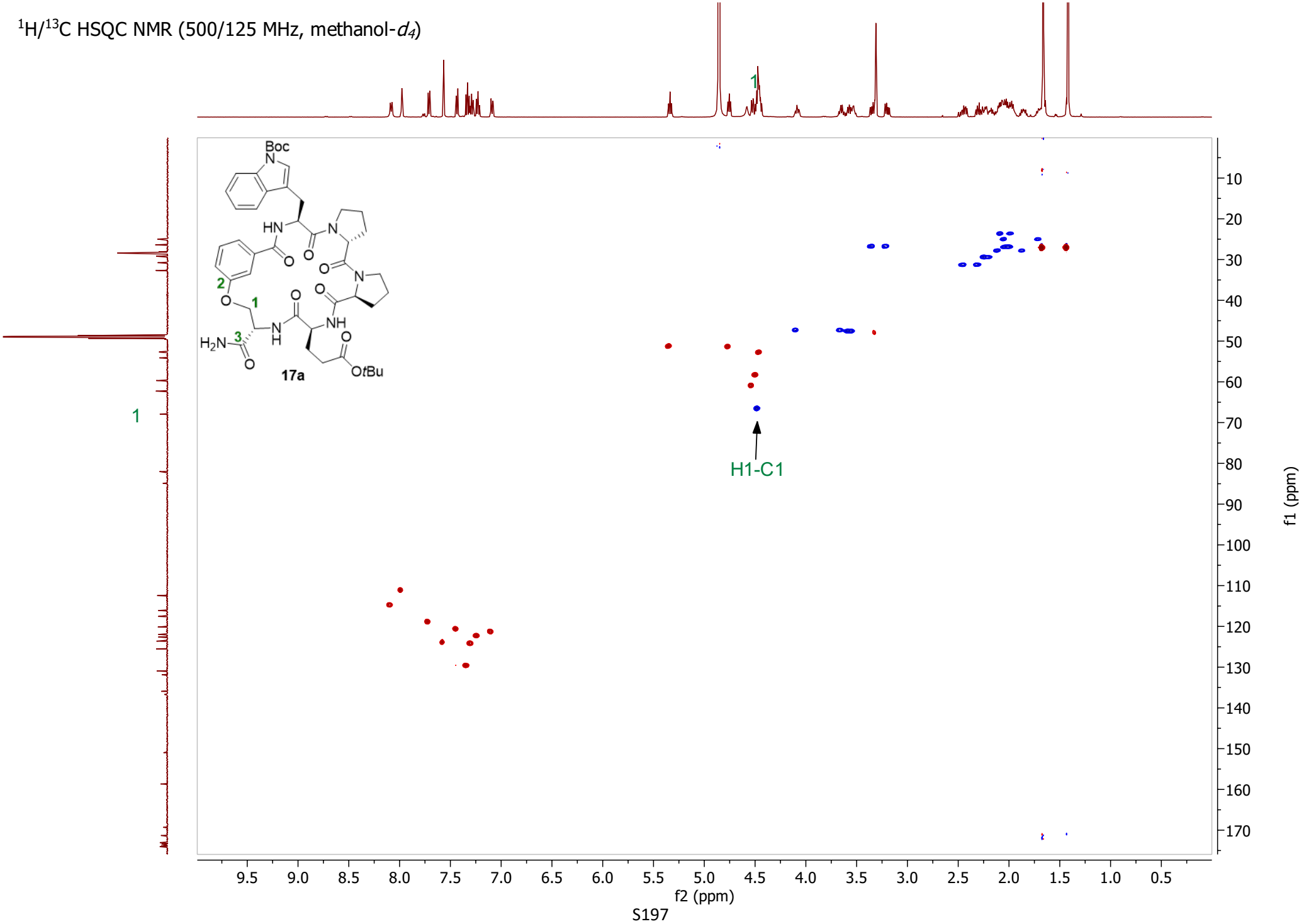
174.11
174.06
173.87
173.42
173.04
171.30
169.30
158.66
150.98
136.71
135.94
131.85
130.93
125.50
125.31
123.63
122.61
121.97
120.17
117.56
116.11
112.46
84.88
82.02
67.90
62.28
59.67
54.11
52.71
52.62
47.86
46.93
32.66
30.78
29.19
28.44
28.39
28.25
28.10
26.39
24.99

14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000

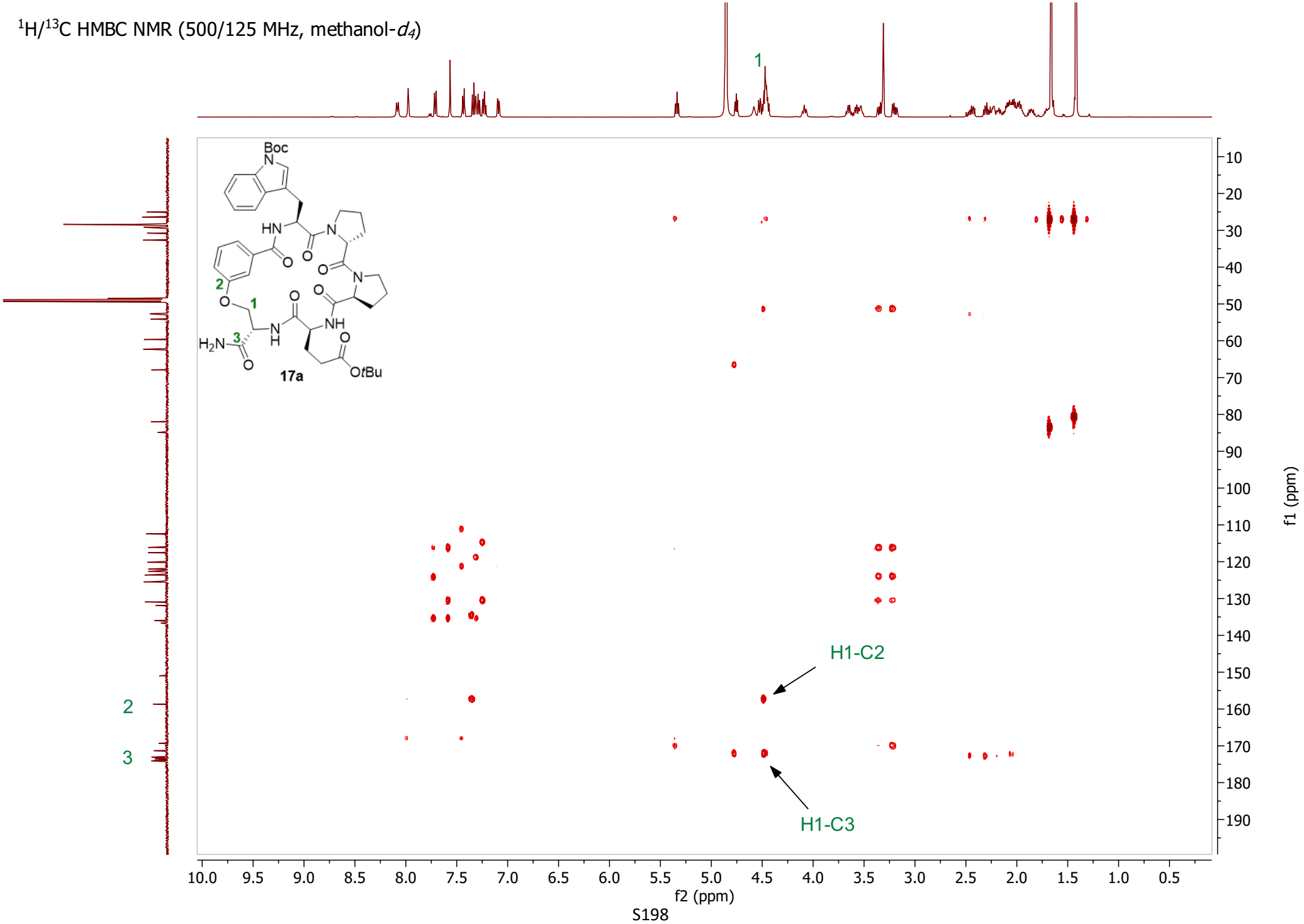
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

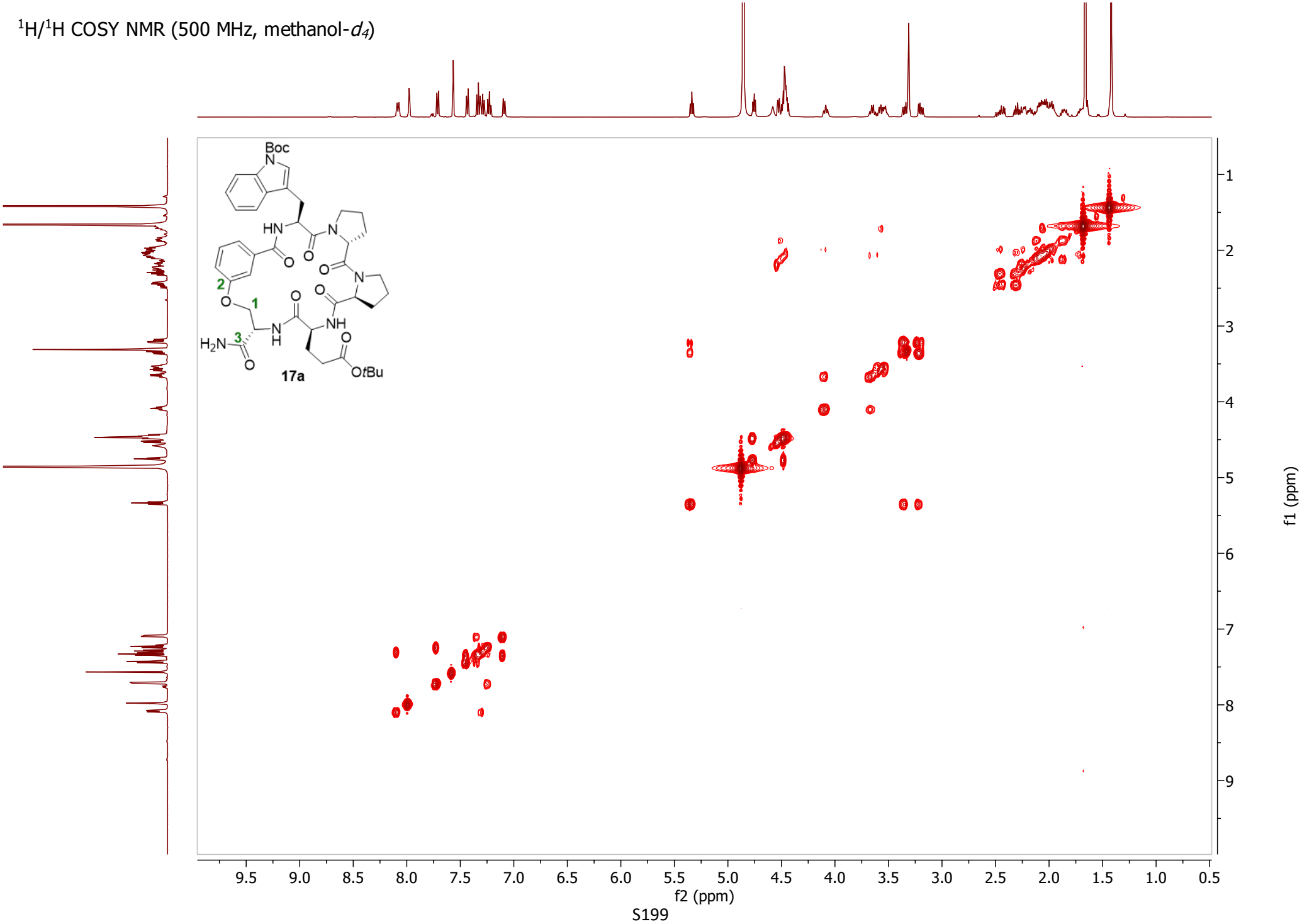
$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, methanol-d_4)



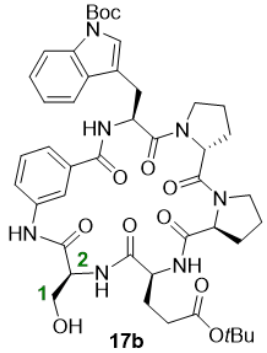
$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, methanol-d_4)



$^{1}H/^{1}H$ COSY NMR (500 MHz, methanol-d_4)

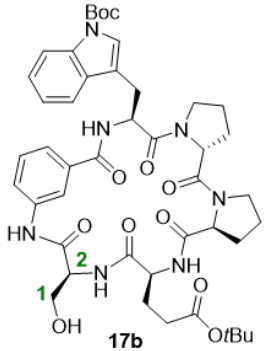


^{1}H NMR (500 MHz, methanol-d_4)



17b

^{13}C NMR (125 MHz, methanol-d_4)

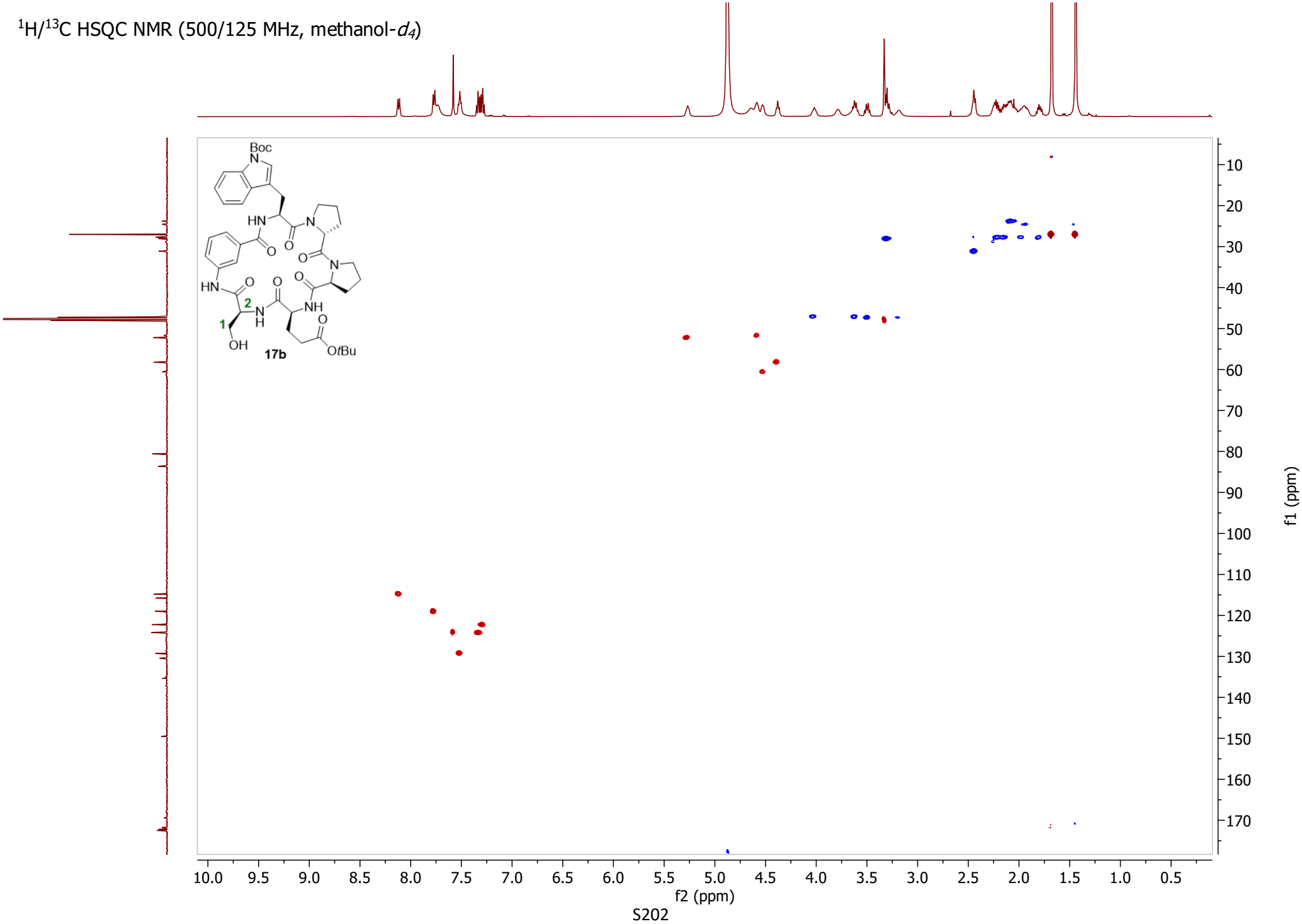


17b

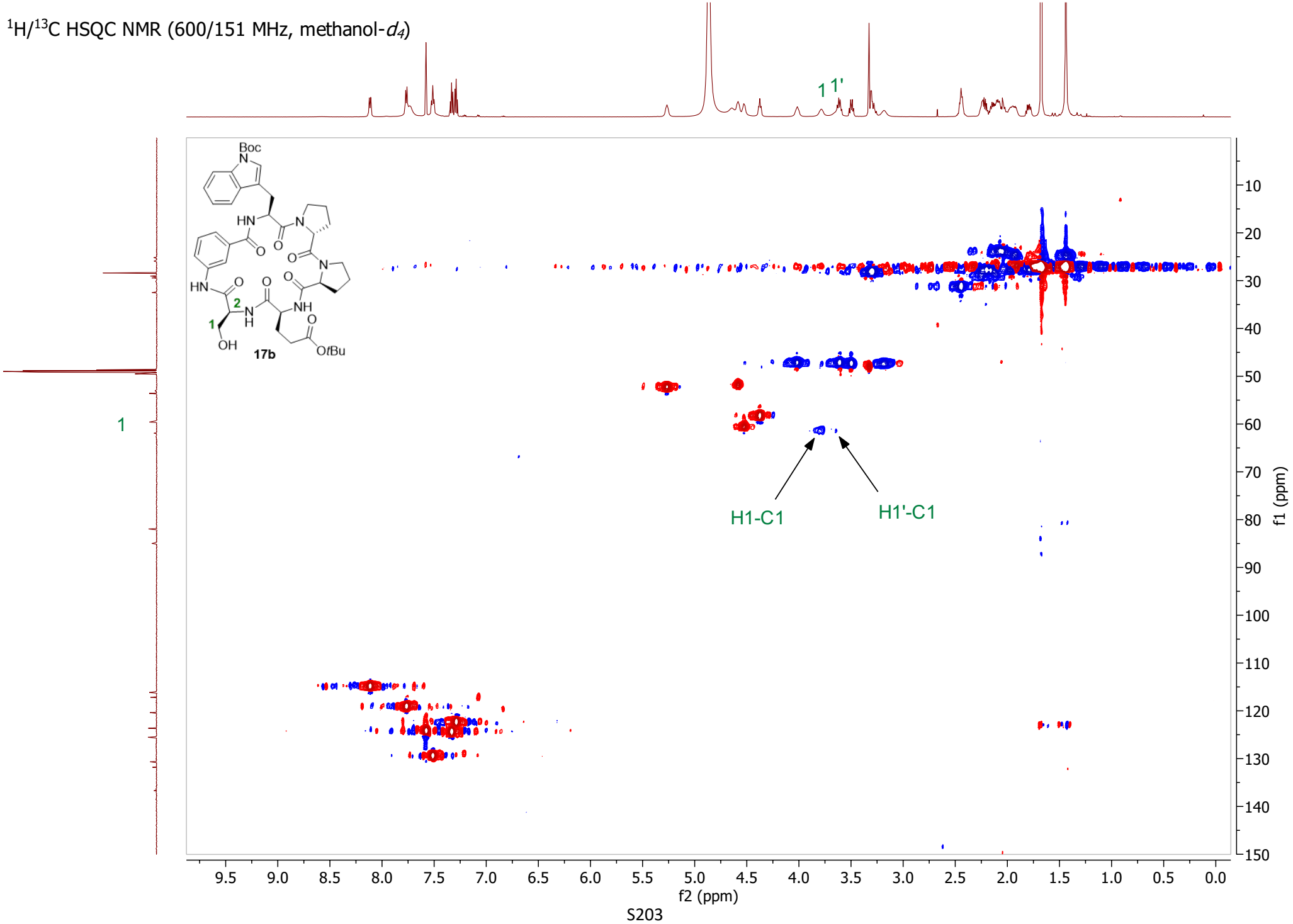
173.87
173.57
173.10
170.81
169.27
150.89
138.56
136.70
136.37
131.80
130.66
125.63
125.53
123.64
120.37
118.31
117.16
116.16
84.99
81.95
62.69
61.91
59.59
53.60
53.15
48.83
48.49
32.50
30.27
30.12
29.45
29.09
29.05
28.41
28.40
25.92
25.18

f1 (ppm)

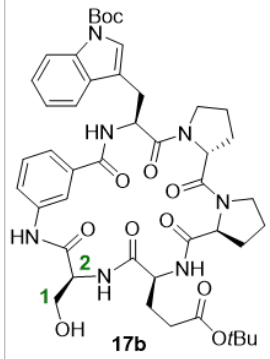
$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, methanol-d_4)



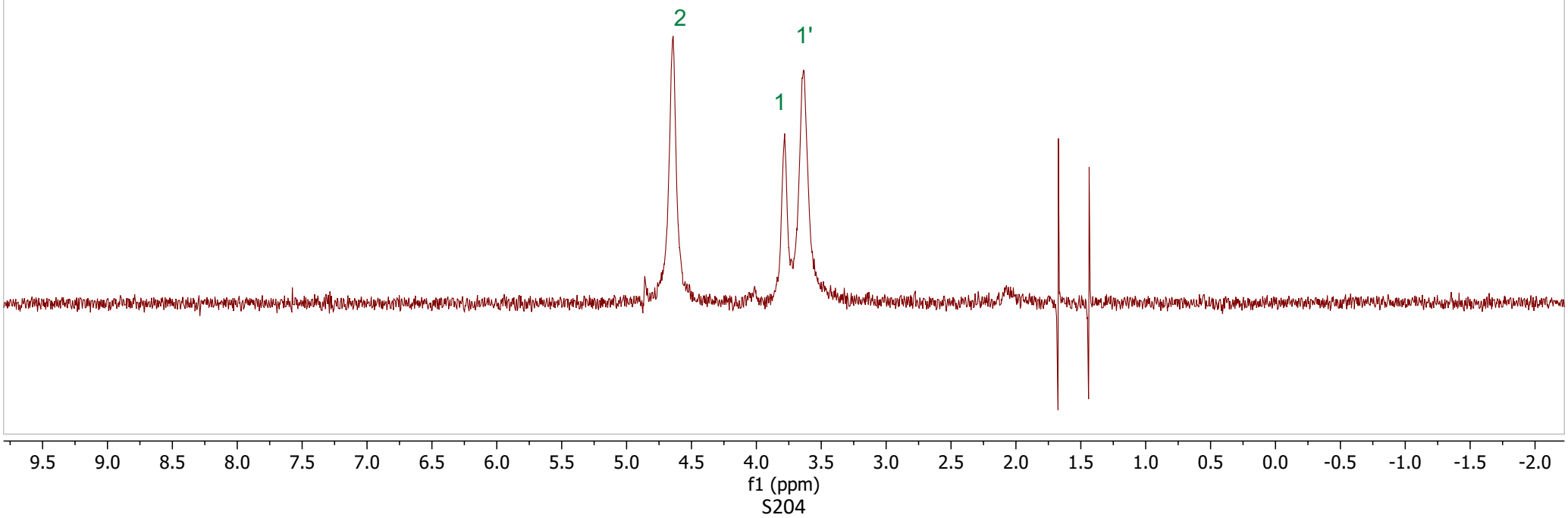
$^{1}H/^{13}C$ HSQC NMR (600/151 MHz, methanol-d_4)



^{1}H selective 1D TOCSY NMR (600 MHz, methanol-d_4)

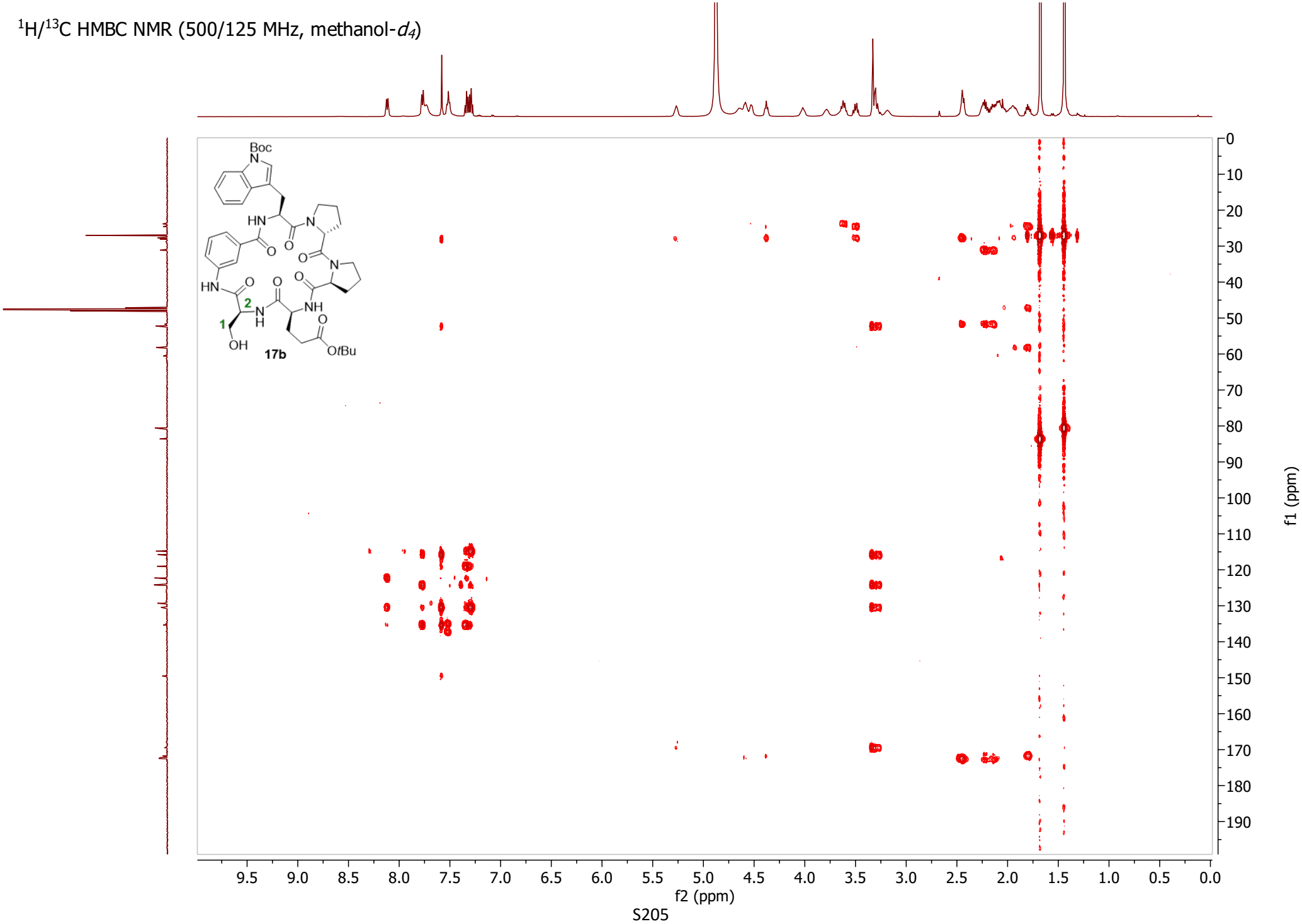


17b

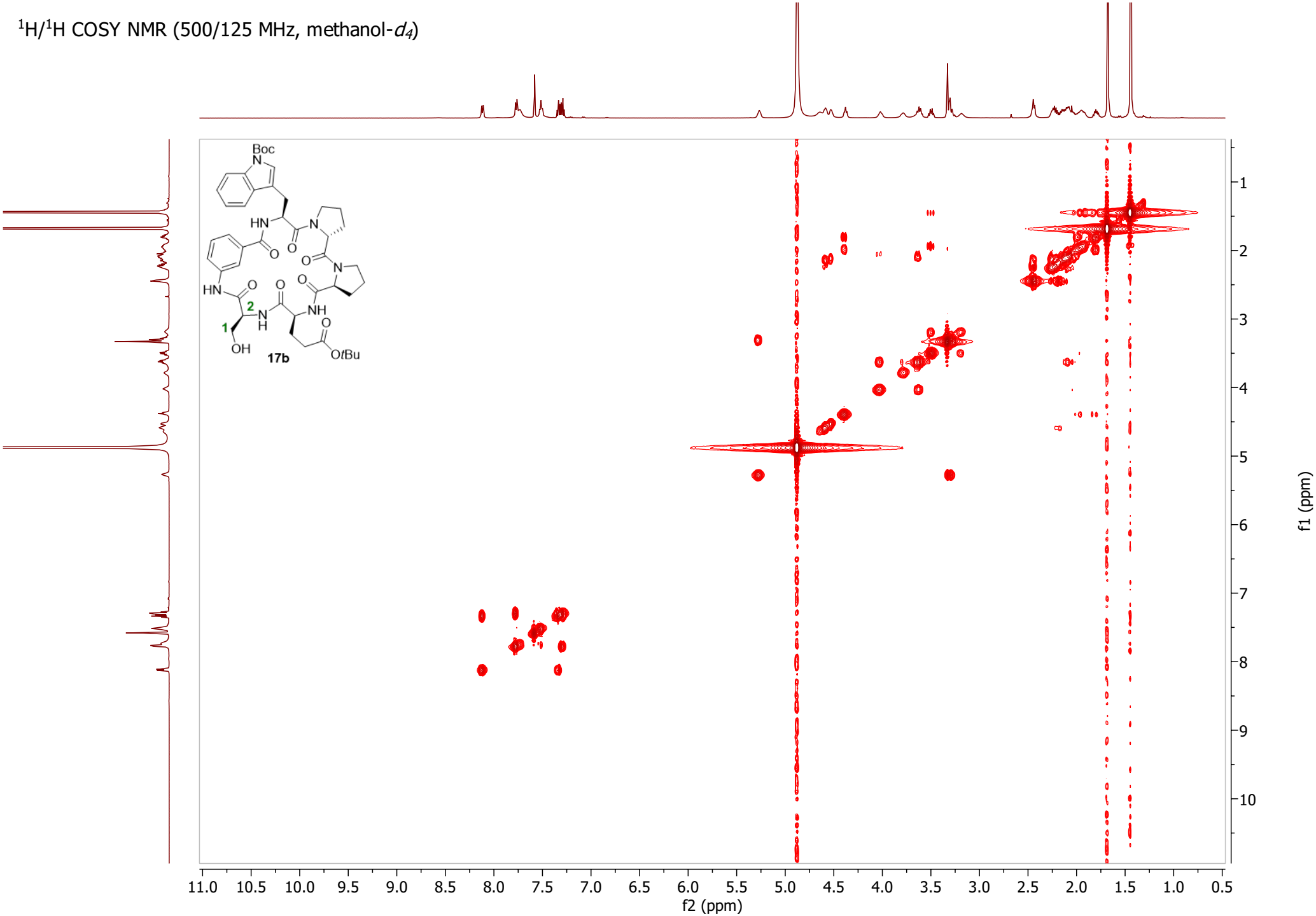


S204

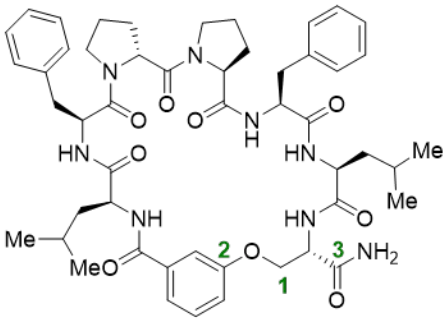
$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, methanol-d_4)



$^{1}H/^{1}H$ COSY NMR (500/125 MHz, methanol-d_4)

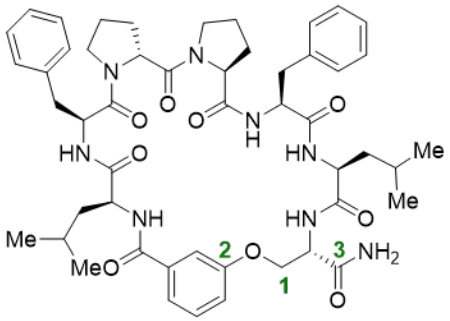


^{1}H NMR (500 MHz, methanol-d_4)



18a

^{13}C NMR (125 MHz, methanol-d_4)



18a

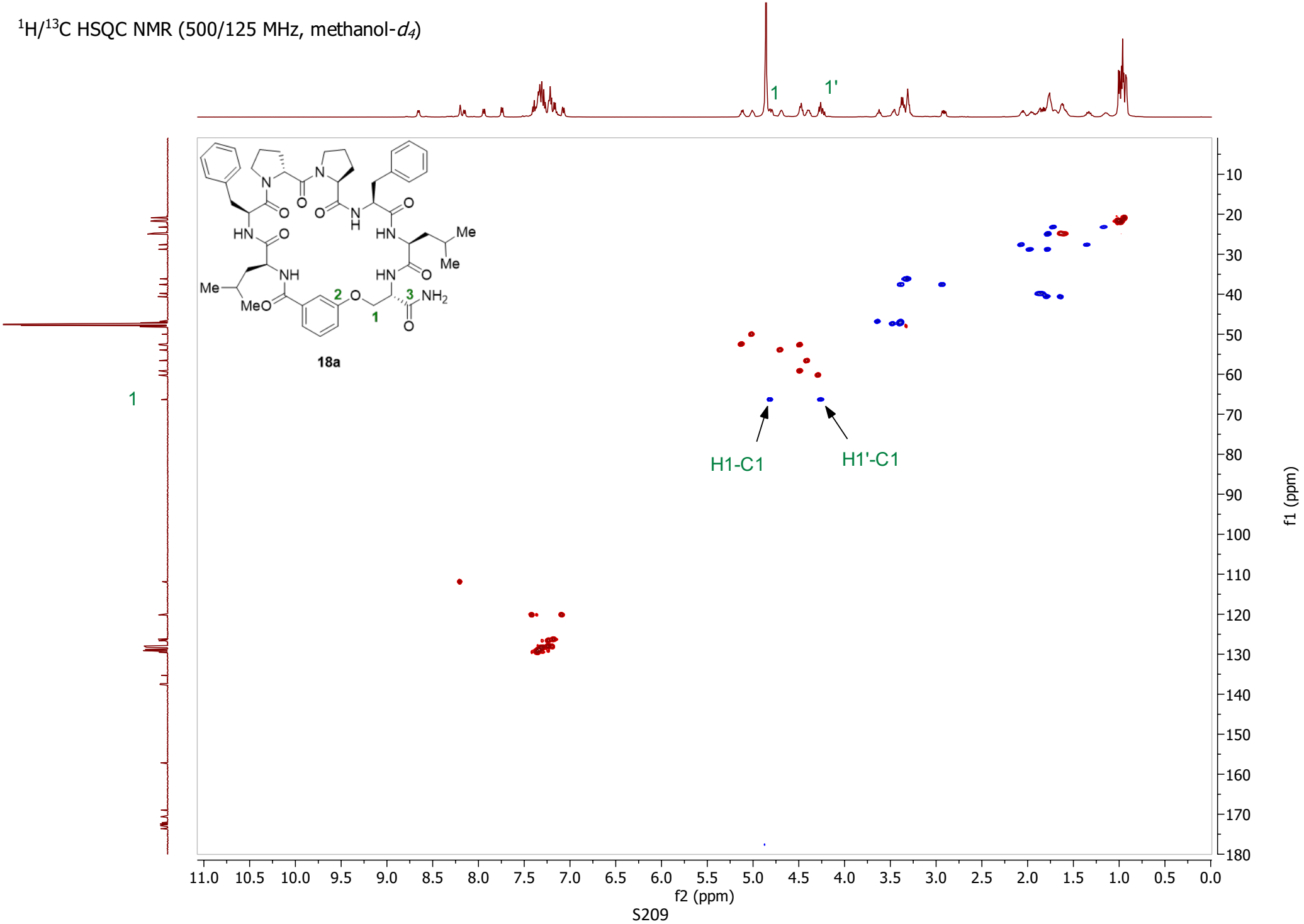
174.97
174.25
174.11
173.79
173.45
171.99
170.36
170.32
158.50
138.95
138.72
136.63
130.89
130.46
130.16
129.64
129.31
128.00
127.60
121.53
121.49
113.24
67.70
61.59
60.52
57.97
55.30
54.01
53.84
51.37
48.75
48.16
41.97
41.17
38.93
37.50
30.16
29.00
26.31
26.07
24.57
23.10
22.94
22.24

16000000
15000000
14000000
13000000
12000000
11000000
10000000
9000000
8000000
7000000
6000000
5000000
4000000
3000000
2000000
1000000
0
-1000000

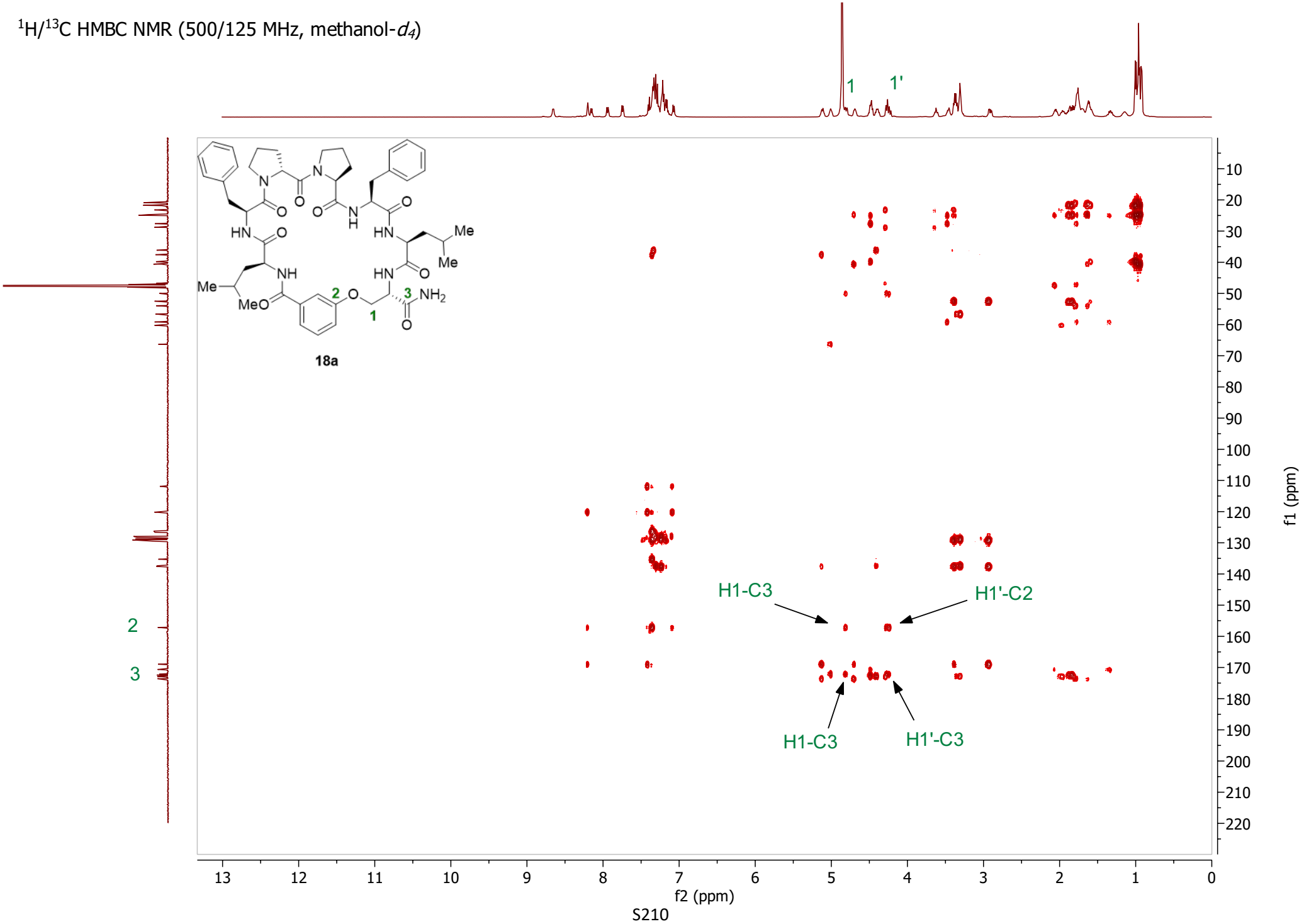
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10

f1 (ppm)

$^{1}H/^{13}C$ HSQC NMR (500/125 MHz, methanol-d_4)



$^{1}H/^{13}C$ HMBC NMR (500/125 MHz, methanol-d_4)



$^{1}H/^{1}H$ COSY NMR (500 MHz, methanol-d_4)