Efficient solid-phase based synthesis of jasplakinolide analogs by intramolecular azide/alkyne cycloaddition

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Supplementary Information

Table of contents

General methods

All solvents, when not purchased in suitable purity or dryness, were distilled using standard methods [1]. Deionized water was used for all experiments. Thin Layer Chromatography (TLC) was carried out on Merck precoated silica gel plates (60F-254) using ultraviolet light irradiation at 254 nm or $KMnO_4$ solution as staining reagent (1 g $KMnO_4$, 6.6 K_2CO_3, 1.7 mL 5% NaOH solution, 100 mL H_2O). Silica gel chromatography was performed using silica gel from J. T. Baker or Merck (particle size 40-60 µm) under approximately 0.5 bar pressure.

^{1}H- and ^{13}C-NMR spectra were recorded on Bruker DRX 500 (500 MHz (^{1}H) and 125.7 MHz (^{13}C)), Bruker DRX 400 (400 MHz (^{1}H) and 100.5 MHz (^{13}C)) and Varian Mercury 400 (400 MHz (^{1}H) and 100.6 MHz (^{13}C)) spectrometers. Chemical shifts are expressed in parts per million (ppm) and the spectra are calibrated to residual solvent signals of $CDCl_3$ (7.26 ppm (^{1}H) and 77.0 ppm (^{13}C)) and DMSO (2.50 ppm (^{1}H) and 39.43 ppm (^{13}C)), respectively. Coupling constants are given in Hertz (Hz) and the following notations indicate the multiplicity of the signals: s (singlet), d (doublet), t (triplet), q (quartet), m (multiple), br (broad signal).

Optical rotations were measured in a Schmidt + Haensch Polartronic HH8 polarimeter at 589 nm, with concentrations given in g/100mL.

Fourier transform infrared spectroscopy (FT-IR) spectra were obtained with a Bruker Tensor 27 spectrometer (ATR, neat). Wavenumbers v are given in cm^{-1}.

Preparative HPLC was performed on a Waters machine using a Macherey Nagel C18 gravity 5 µm Reversed Phase column. The separations were started at 10 % MeCN (with 0.1% TFA) in H_2O (with 0.1% TFA), and the MeCN proportion was linearly increased to 100 % over 20 min with a flow of 20 $mL \cdot min^{-1}$.

High Resolution Mass Spectra were recorded on a Jeol SX 102 A (FAB; matrix m-nitrobenzylalcohol) or Thermo Electron LTQ Orbitrap (ESI; source voltage 3.8 kV) spectrometer.

Melting points were determined with a Büchi Melting Point B-540 apparatus (uncorrected).

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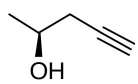
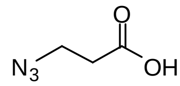
[1] Armarego, W. L. F.; Chai, C. L. L. *Purification of Laboratory Chemicals*, 5th Ed, Elsevier, 2002.

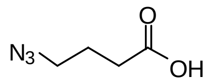
All reagents were purchased from commercial suppliers (Acros, Aldrich, Novabiochem, Fluka) and used without purification. The following building blocks were prepared according to known procedures: homopropargylic alcohol **9k**[2] as well as the azido building blocks **7a**[3] and **7b**[4].



9k



7a



7b

[2] C. Dimitriadis, M. Gill, M.F. Harte, *Tetrahedron: Asymmetry* **1997**, *8*, 2153-2158.
[3] C. Grandjean, A. Boutonnier, C. Guerreiro, J.-M. Fournier, L.A. Mulard, *J. Org. Chem.*, **2005**, *70*, 7123-7132.
[4] N. Khoukhi, M. Vaultier, R. Carrie, *Tetrahedron*, **1987**, *43*, 1811-1822.

General Procedures

A general procedure for the synthesis of acid 3 (procedure 1) [5]

To a suspension of 2-Cl-trityl chloride resin (280 mg) in DCM (3 mL) were added Fmoc-β-AlaOH (**5**, R^1 = H, 0.225 g, 0.72 mmol), Diisopropylethylamine (DIPEA, 0.48 mL, 2.89 mmol). After shaken for 1h, the resin was filtered, and the residue resin sites were capped with a mixture of DCM/MeOH/DIPEA (17:2:1, 3 × 3 mL, 3 min for each time). After filtration, the resin was washed with DCM (3 × 4 mL), and dried in vacuo. The loading was determined by quantitative Fmoc analysis to be 0.98 mmol/g.

The resin was subjected to Fmoc-peptide synthesis using the following conditions:

(1) Fmoc deprotection: 20% piperidine in DMF (8 mL) for 30 min, followed by washing with DMF (4 × 4 mL) and DCM (4 × 4 mL).

(2) Coupling conditions: (a) Fmoc-D-TrpOH (0.358 g, 0.84 mmol), HOBt (0.129 g, 0.84 mmol), and DIC (0.13 mL, 0.84 mmol) in DMF (8 mL), 1.5 h. (b) Fmoc-L-AlaOH (0.261 g, 0.84 mmol), HOBt (0.129 g, 0.84 mmol), and DIC (0.13 mL, 0.84 mmol) in DMF (8 mL), 1.5 h. (c) azido acid, **7** (3 equiv), HOBt (0.129 g, 0.84 mmol), and DIC (0.13 mL, 0.84 mmol) in DMF (8 mL), 1.5 h. Following all the couplings the resin was filtered and washed with DMF (6 × 4 mL) and DCM (6 × 4 mL).

*The above procedure gave polymer-bound peptide **8**.*

On-resin 1,3-dipolar cycloaddition reaction: polymer-bound peptide **8** (0.14 mmol, 1 equiv) was treated with alkyne **9** (5 equiv), DIPEA (10 equiv) and CuI (0.1 equiv) in degassed THF (4 mL) for 16 h at rt. Resin was filtered and washed with THF (4 × 4 mL) and DCM (4 × 4 mL).

Acidic Cleavage: Resin (0.14 mmol) was treated with a mixture of acetic acid, trifluoroethanol and DCM (1:1:8, 2 × 4 mL, each 1h). After filtration, the combined filters were condensed under reduced pressure to give acid **3** (>68% overall yield).

A typical procedure for the macrolactonization of 3 (procedure 2)

[5] (a) K. Barlos, D. Gatos, J. Kallitsis, G. Papaphotiu, P. Sotiriu, Y. Wenqing, W. Schafer, *Tetrahedron Lett.* **1989**, *30*, 3943-3946. (b) I. R. Marsh, M. Bradley, *J. Org. Chem.* **1997**, *62*, 6199-6203.

To a solution of seco acid **3d** (42 mg, 0.08 mmol) in DCM/DMF (40 mL/2 mL) at room temperature was added DIPEA (0.16 mL, 0.93 mmol), DMAP (117 mg, 0.96 mmol) and 2,4,6-trichlorobenzoyl chloride (75 μL, 0.48 mmol). The resulting mixture was stirred for 26 h, and sat. aq. NH_4Cl solution (8 mL) was added. The aqueous phase was extracted with DCM (2 × 10 mL), and the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration, the solvent was removed under reduced pressure and the residue was purified by preparative HPLC to give 24 mg (59%) of cyclic peptide **2d** as a white solid. In cases of seco acids **3e-3g**, the crude products from macrolactonization were treated with TBAF (2 eq.) in THF at 0 °C for 2h. Removal of the solvent gave a residue, which was purified by preparative HPLC to give **2e-2g**, respectively.

A general procedure for the preparation of azido acid 10 (procedure 3)

The polymer-bound peptide **8** (0.14 mmol), prepared according to Fmoc-peptide synthesis described in procedure 1, was treated with a mixture of acetic acid, trifluoroethanol and DCM for 2 h. (1:1:8, 2 × 4 mL, each 1h). After filtration, the combined filters were condensed under reduced pressure to give azido acid **10**.

A typical procedure for the preparation of azido alkyne 4 by esterification (procedure 4)

To a solution of azido acid **10a** (R_1 = H, n = 1, 0.291 g, 0.66 mmol) in DCM/DMF (16 mL/2.5 mL) propargyl alcohol (0.15 mL, 2.57 mmol), EDC (0.253 g, 1.32 mmol), DMAP (0.161 g, 1.32 mmol) and DIPEA (0.22 mL, 1.32 mmol) were added. The reaction mixture was stirred at room temperature for 8 h, and quenched with sat. aq. NH_4Cl (5 mL) solution. The aqueous phase was extracted with DCM (8 mL × 2), the combined organic layers were washed with brine and dried with $MgSO_4$. After filtration and removal of the solvent, the residue was purified by silica gel chromatography (cyclohexane/EA 1:1 to DCM/MeOH 25:1 to DCM/MeOH 20:1) to give 0.220 g (70%) of **4a** as a white solid.

A typical procedure for the preparation of azido alkyne 4 by amide bond formation (procedure 5)

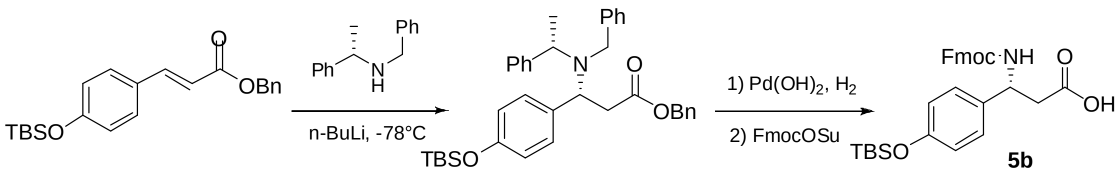
To a solution of azido acid **10b** (R^1 = H, R^2 = H, n = 2, 0.150 g, 0.33 mmol) in DCM/DMF (7 mL/1.4 mL) propargyl amine (0.085 mL, 1.32 mmol), EDC (0.126 g, 0.66 mmol) and DIPEA (0.11 mL, 0.66 mmol) were added. The reaction mixture was stirred overnight at room temperature for 8 h, and the precipitate was collected to give 0.130 g (80%) of **4l** as a white solid.

A typical procedure for the Cu(I)-catalyzed intramolecular 1,3-dipolar cycloaddition reaction of azido alkyne 4 (procedure 6)

4a (100 mg, 0.21 mmol) was dissolved in a small amount of DMSO (ca 0.2 mL) and diluted with CH_3CN/THF (160 mL/40 mL). Argon was bubbled through the resulting solution for 30 min. DIPEA (0.11 mL, 0.64 mmol), 2,6-lutidine (47 µL, 0.40 mmol) and CuI (14 mg, 0.07 mmol) were added. After stirring at room temperature for 14 h the reaction mixture was filtered and the volatiles were removed. (In case of **4i**, the resulting residue was treated with 1.1 equiv of TBAF in THF at 0 °C for 15 min, and then THF was removed under reduced pressure) The residue was purified by preparative HPLC to give 87 mg (87%) of cyclic peptide **2a** as a white solid.

Analytical Data

Synthesis of (*R*)-*N*-Fmoc-*O*-TBS-β-tyrosine 5b[6]



n-Butyllithium (2.5 M solution in hexane, 5.4 mL, 13.7 mmol, 1.5 equiv) was added dropwise to a stirred solution of (*S*)-*N*-benzyl-*N*-α-methylbenzylamine (2.9 mL,13.7 mmol, 1.6 equiv) in anhydrous THF (60 mL) at -78 °C under Argon. After 30 min, a solution of benzyl (*E*)-3-(4-*tert*-butyldimethylsilyloxyphenyl)prop-2-enoate (3.320 g, 9.0 mmol) in anhydrous THF (20 mL) was added dropwise. The mixture was stirred at -78 °C for 2 h before addition of sat. aq. NH_4Cl (20 mL). The aqueous phase was extracted with Ethyl acetate (EA, 3 × 10 mL). The combined organic phases were washed with brine and dried over $MgSO_4$. After filtration and concentration, the residue was purified by column chromatography on silica gel (cyclohexane/EA, 20:1 then 10:1) to give benzyl (*R*)-3-(benzyl((*S*)-1-phenylethyl)amino)-3-(4-*tert*-butyldimethylsilyloxyphenyl) propanoate (3.215 g, 62%) as a yellow syrup. $[\alpha]_D$ –0.64 (c 0.9, $CHCl_3$); ^{1}H-NMR (500 MHz, $CDCl_3$) ppm 7.40 (d, 2H, *J* = 7.4 Hz), 7.34-7.27 (m, 5H), 7.25-7.15 (m, 8H), 7.13 (dd, 2H, *J* = 7.0, 2.5 Hz), 6.79 (d, 2H, *J* = 8.5 Hz), 4.92 (d, 1H, *J* = 12.4 Hz), 4.89 (d, 1H, *J* = 12.4 Hz), 4.41 (dd, 1H, *J* = 9.6, 5.4 Hz), 3.99 (q, 1H, *J* = 6.8 Hz), 3.69 (d, 1H, *J* = 15.0 Hz), 3.65 (d, 1H, *J* = 15.0 Hz), 2.68 (dd, 1H, *J* = 14.7, 5.4 Hz), 2.60 (dd, 1H, *J* = 14.7, 9.6 Hz), 1.21 (d, 3H, *J* = 6.8 Hz), 0.99 (s, 9H), 0.19 (s, 6H). ^{13}C NMR (100 MHz, $CDCl_3$) 171.7, 154.7, 144.2, 141.5, 135.8, 134.2, 129.1, 128.4, 128.09, (two more carbons are overlapped in this region) 128.06, 128.01, 127.8, 126.8, 126.5, 119.7, 66.0, 58.8, 56.8,

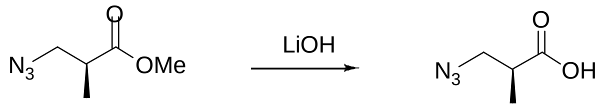
[6] (a) S. G. Davies, O. Ichihara *Tetrahedron: Asymmetry* **1991**, *2*, 183. (b) S. G. Davies, N. M. Garrido, D. Kruchinin, O. Ichihara, L. J. Kotchie, P. D. Price, A. J. P. Mortimer, A. J. Russell, A. D. Smith, *Tetrahedron: Asymmetry* **2006**, *17*, 1973-1811.

50.6, 37.5, 26.8, 25.6, 16.1, -4.4.HRMS (FAB) Calcd. for $C_{37}H_{45}NO_3Si$ 579.3169; Found 579.3177

$Pd(OH)_2$ on Carbon (0.917 g) was added to a solution of benzyl (*R*)-3-(benzyl((*S*)-1-phenylethyl)amino)-3-(4-*tert*-butyldimethylsilyloxyphenyl)propanoate (3.670g, 6.3 mmol) in EtOH (50 mL). The mixture was stirred under 6 bar H2 for 20 h at rt, and 6 mL of AcOH was added to dissolve the precipitate. After filtration through Celite® and wash with EtOH, the filtrate was concentrated under reduced pressure and the residue was triturated with EtOH (5 mL) to give, after filtration, (*R*)-3-amino-3-(4-*tert*-butyldimethylsilyloxyphenyl)propanoic acid (1.480 g, 79%) as a white solid. $[\alpha]_D$ +8.0 (c 0.92, MeOH), ^{1}H NMR (400 MHz, CD_3OD) 7.35 (d, 2H, *J* = 8.5 Hz), 6.90 (d, 2H, *J* = 8.5 Hz), 4.47 (dd, 1H, *J* = 9.7, 4.5 Hz), 2.76 (dd, 1H, *J* = 16.7, 9.7 Hz), 2.64 (dd, 1H, *J* = 4.5, 16.7 Hz), 1.00 (s, 9H), 0.20 (s, 6H); ^{13}C-NMR (100 MHz, CD_3OD) 177.3, 157.7, 131.4, 129.6, 121.8, 53.93, 41.3, 26.2, 19.1, -4.3; IR(neat) 2930, 2857, 1628, 1610, 1554, 1538, 1511, 1298, 1262, 919, 836, 783; HRMS (FAB) Calcd. for $C_{15}H_{26}NO_3Si$ ($M+H^+$) 296.1682; Found 296.1667

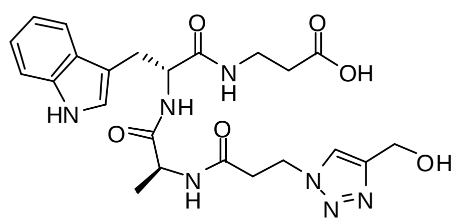
To as suspension of (*R*)-3-amino-3-(4-*tert*-butyldimethylsilyloxyphenyl)propanoic acid (1.020 g, 3.45 mmol) in a mixture of dioxane and water (1:1, 34 mL) at 0 °C were added $NaHCO_3$ (1.259 g, 13.79 mmol) and FmocOSu (1.397 g, 4.14 mmol). The mixture was stirred at 0 °C for 1 h, then allowed to stir at rt for 4 h, acidified to pH = 2 with 6 N HCl, and extracted with EA (2 × 30 mL). The combined organic phases were washed with brine, and dried over $MgSO_4$. After filtration and concentration, the residue was purified by column chromatography on silica gel (DCM then DCM/MeOH 20:1) to give (*R*)-*N*-Fmoc-*O*-TBS-β-tyrosine **5b** (1.706 g, 95%) as a white foam-like solid. $[\alpha]_D$ +21.4 (c 1.2, $CHCl_3$); ^{1}H-NMR (500 MHz, CD_3OD) 7.78 (d, 2H, *J* = 7.5 Hz), 7.62 (d, 2H, *J* = 7.3 Hz), 7.36 (m, 2H), 7.27 (m, 2H), 7.21 (d, 2H, *J* = 8.2 Hz), 6.79 (d, 2H, *J* = 8.4 Hz), 5.05 (t, 1H, *J* = 6.9 Hz), 4.32 (m, 2H), 4.19 (t, 1H, *J* = 6.7 Hz), 2.79 (dd, 1H, *J* = 15.5, 8.6 Hz), 2.71 (dd, 1H, *J* = 15.5, 6.3 Hz), 0.99 (s, 9H), 0.19 (s, 6H); ^{13}C-NMR (100 MHz, CD_3OD) 174.3, 158.0, 156.2, 145.2, 142.5, 136.3, 128.7, 128.6, 128.1, 126.2, 121.1, 120.9, 67.7, 52.8, 48.4, 42.1, 26.2, 19.0, -4.2; IR (neat) 2953, 2930, 2857, 1708, 1608, 1252, 912, 838, 738; HRMS (FAB) Calcd. for $C_{30}H_{35}NO_5Si$ 517.2284; Found 517.2294

(*S*)-3-azido-2-methylpropanoic acid, 7j



At 0 °C 0.14 g (2.1 mmol) of LiOH·H_2O was added to a solution of 0.30 g (2.1 mmol) (*S*)-methyl-3-azido-2-methylpropanoate[7] in THF/H_2O (2:1) and stirred for 4 h at rt followed by treatment with diethyl ether. The aqueous layer was separated, acidified to pH 2 with 4 N aqueous HCl and extracted with three times with diethyl ether. The combined organic layers were washed with brine, dried with $MgSO_4$ and concentrated under reduced pressure to give 0.17 g (1.3 mmol; 63 %) of **7j** as a colorless oil. $[\alpha]_D$ +11.9 (c 3.7, $CHCl_3$). ^{1}H-NMR (400 MHz, $CDCl_3$) 10.7 (br s, 1H), 3.57 (dd, 1H, *J* = 12.2, 7.2 Hz), 3.43 (dd, 1H, *J* = 12.2, 5.7 Hz), 2.73 (m, 1H), 1.27 (d, 3H, *J* = 7.2 Hz).^{13}C-NMR (100 MHz, $CDCl_3$) 180.4, 53.5, 39.7, 14.7.

Seco Acid 3a

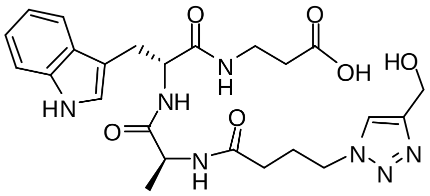


Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 3-azidopropanoic acid, and prop-2-yn-1-ol. Polymer-bound peptide **8a** (0.20 mmol), after on-resin cycloaddition, gave 83 mg (0.17 mmol, 84 % overall yield) of **3a** as a slightly yellow solid.

[7] A.K. Ghosh, A. Bischoff, *Eur. J. Org. Chem.*, **2004**, 2131-2141.

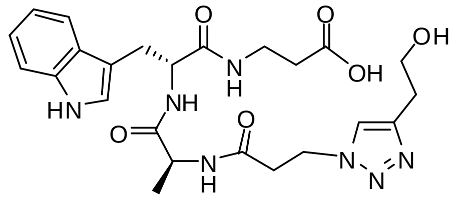
^{1}H-NMR (500 MHz, DMSO-d^6) 10.80 (s, 1H), 8.21 (d, 1H, *J* =7.0 Hz), 8.18 (d, 1H, *J* =8.3 Hz), 8.02 (t, 1H, *J* =5.4 Hz), 7.86 (s, 1H), 7.58 (s, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (s, 1H), 7.04 (t, 1H, *J* = 7.5 Hz), 6.96 (t, 1H, *J* = 7.4 Hz), 4.58-4.46 (m, 2H), 4.48 (s, 2H), 4.45-4.38 (m, 1H), 4.28-4.18 (m, 1H), 3.33-3.22 (m, 2H), 3.14 (dd, 1H, *J* = 4.2, 14.5 Hz), 2.90 (dd, 1H, *J* = 9.4, 14.5 Hz), 2.80-2.64 (m, 2H), 2.34 (t, 2H, *J* = 6.6 Hz), 0.95 (d, 3H, *J* = 7.0 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 171.8, 171.1, 168.9, 147.7, 135.9, 127.2, 123.5, 122.7, 120.7, 118.3, 118.0, 111.1, 110.1, 54.9, 53.3, 48.3, 45.4, 35.2, 35.1, 34.1, 27.6, 17.8. IR 3292(br), 1717, 1643, 1538, 1178, 746 cm^{-1}. HRMS (ESI) Calcd. for $C_{23}H_{30}N_7O_6$ (MH^+) 500.2252; Found 500.2246.

Seco Acid 3b



Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 4-azidobutanoic acid, and prop-2-yn-1-ol. Polymer-bound peptide **8b** (0.19 mmol), after on-resin cycloaddition, gave 70 mg (0.14 mmol, 74 % overall yield) of **3b** as a slightly yellow solid.
^{1}H-NMR (400 MHz, DMSO-d^6+D_2O 35:1) 7.95 (br s, 1H), 7.56 (d, 1H, *J* = 7.3 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.08 (s, 1H), 7.04 (t, 1H, *J* = 7.4 Hz), 6.95 (t, 1H, *J* = 7.3 Hz), 4.48 (s, 2H), 4.39 (m, 1H), 4.30 (m, 2H), 4.18 (m , 1H), 3.25 (m, 2H), 3.20-3.07 (m, 1H), 2.95-2.82 (m, 1H), 2.48-2.25 (m, 2H), 2.15-2.05 (m, 2H), 2.05-1.92 (m, 2H), 0.97 (d, 3H, *J* = 6.8 Hz). HRMS (ESI) Calcd. for $C_{24}H_{32}N_7O_6$ (MH^+) 514.2409; Found 514.2402.

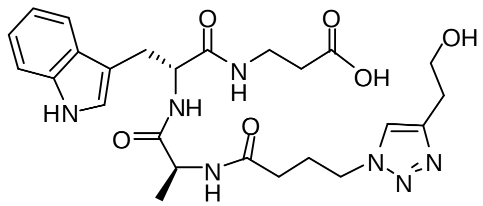
Seco Acid 3c



Prepared according procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 3-azidopropanoic acid, and but-3-yn-1-ol. Polymer-bound peptide **8a** (0.17 mmol), after on-resin cycloaddition, gave 83 mg (0.16 mmol, 95 % overall yield) of **3c** as a slightly yellow solid.

^{1}H-NMR (400 MHz, DMSO-d^6+D_2O 35:1) 7.75 (br s, 1H), 7.56 (d, 1H, *J* = 7.8 Hz), 7.30 (d, 1H, *J* = 7.8 Hz), 7.08 (s, 1H), 7.04 (t, 1H, *J* = 7.7 Hz), 6.95 (t, 1H, *J* = 7.3 Hz), 4.47 (m, 2H), 4.39 (m, 1H), 4.18 (m, 1H), 3.60 (m, 2H), 3.25 (m, 2H), 3.14 (m, 1H), 2.88 (m, 1H), 2.80-2.60 (m, 4H), 2.48-2.25 (m, 2H), 0.93 (d, 3H, *J* = 6.8 Hz). HRMS (ESI) Calcd. for $C_{24}H_{32}N_7O_6$ (MH^+) 514.2409; Found 514.2402.

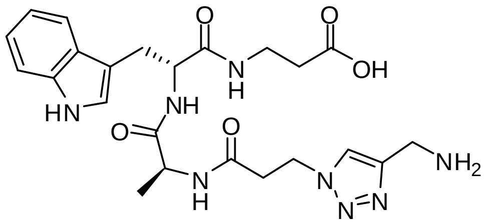
Seco Acid 3d



Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 4-azidobutanoic acid, and but-3-yn-1-ol. Polymer-bound peptide **8b** (0.19 mmol), after on-resin cycloaddition, gave 102 mg (0.19 mmol, quant.) of **3d** as a slightly yellow solid.

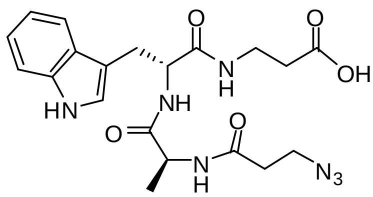
^{1}H-NMR (400 MHz, DMSO-d^6+D_2O 35:1) 7.80 (br s, 1H), 7.54 (d, 1H, *J* = 8.0 Hz), 7.30 (d, 1H, *J* = 8.0 Hz), 7.08 (s, 1H), 7.04 (t, 1H, *J* = 7.5 Hz), 6.95 (t, 1H, *J* = 7.5 Hz), 4.37 (m, 1H), 4.24 (m, 2H), 4.13 (q , 1H, *J* = 6.8 Hz), 3.60 (m, 2H), 3.23 (m, 2H), 3.14 (dd, 1H, *J* = 4.1, 14.6 Hz), 2.87 (dd, 1H, *J* = 9.8, 14.6 Hz), 2.80-2.65 (m, 2H), 2.48-2.25 (m, 2H), 2.15-2.05 (m, 2H), 2.05-1.87 (m, 2H), 0.96 (d, 3H, *J* = 6.8 Hz). HRMS (ESI) Calcd. for $C_{25}H_{34}N_7O_6$ (MH^+) 528.2565; Found 528.2562.

ω-Amino Acid 3h



Prepared according to procedure 1. The following 5 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, 3-azidopropanoic acid, and propargyl amine. 0.375 g of the trityl resin (0.375 mmol), after peptide synthesis, gave Polymer-bound peptide **8a** (0.20 mmol), after on-resin cycloaddition, gave 89 mg (0.18 mmol, 89 % overall yield) of **3h** as a slightly yellow solid.
$[\alpha]_D$ -4.5 (c 0.31, DMSO). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.84 (s, 1H), 8.28 (d, 2H, *J* = 6.3 Hz), 8.03-7.95 (m, 2H), 7.57 (d, 1H, *J* = 7.9 Hz), 7.30 (d, 1H, *J* = 8.1 Hz), 7.09 (s, 1H), 7.03 (t, 1H, *J* = 7.2 Hz), 6.95 (t, 1H, *J* = 7.4 Hz), 4.54 (t, 2H, J = 6.3 Hz), 4.43-4.35 (m, 1H), 4.26-4.17 (m, 1H), 3.29-3.20 (m, 2H), 3.18 (dd, 1H, *J* = 4.0, 5.0 Hz), 2.89 (dd, 1H, *J* = 9.8, 14.6 Hz), 2.7 (t, 2H, *J* = 6.4 Hz), 2.28-2.18 (m, 2H), 0.94 (d, 3H, *J* = 7.0 Hz). IR 3403, 3284, 1661, 1634, 1544, 1183, 1130, 745, 722 cm^{-1}. HRMS (ESI) Calcd. for $C_{23}H_{31}N_8O_5$ (MH^+) 499.2412; Found 499.2405.

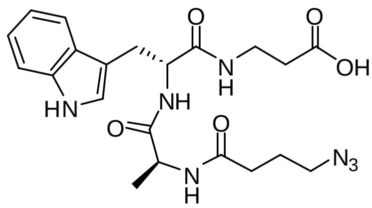
Azido Acid 10a



Prepared according to procedure 3. The following 4 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, and 3-azidopropanoic acid. 0.375 g (0.375 mmol) of the trityl resin, after peptide synthesis, gave 0. 156 g (94%) of **10a** as a slightly yellow solid.

mp = 171°C (dec.). $[\alpha]_D$ –5.5 (c 0.7, MeOH). ^{1}H-NMR (500 MHz, CD_3OD) 7.58 (d, 1H, *J* = 8.0 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.10-7.05 (m, 3H), 7.00 (t, 1H, *J* = 8.0 Hz), 4.59 (dd, 1H, *J* = 5.4, 8.6 Hz), 4.20 (q, 1H, *J* = 7.2 Hz), 3.58-3.52 (m, 1H), 3.50-3.44 (m, 1H), 3.42-3.36(m, 2H), 3.33 (dd, 1H, *J* = 5.5, 14.7 Hz), 2.45-2.37 (m, 4H), 1.12 (d, 3H, *J* = 7.2 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.8, 171.9, 171.3, 169.4, 136.0, 127.2, 123.5, 120.8, 118.4, 118.1, 111.2, 110.1, 53.3, 48.4, 46.8, 34.9, 34.2, 33.6, 27.7, 17.9; IR 3402, 3288, 2982, 2127, 1697, 1661, 1641, 1542, 1437, 744 cm^{-1}; HRMS (FAB) Calcd. for $C_{20}H_{26}N_7O_5$ (MH^+) 444.1995; Found 444.1984.

Azido Acid 10b

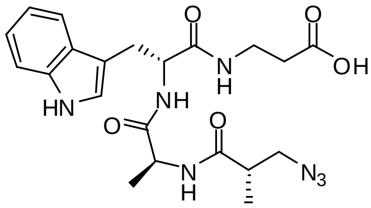


Prepared according to procedure 3. The following 4 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, and 4-azidobutanoic acid. 0.625 g (0.625 mmol) of the trityl resin, after peptide synthesis, gave 0. 223 g (78%) of **10b** as a slightly yellow solid.

mp = 144°C (dec.). $[\alpha]_D$ -35 (c 0.89, MeOH). ^{1}H-NMR (400 MHz, DMSO-d^6) 12.23 (s, 1H), 10.80 (s, 1H), 8.13 (d, 1H, *J* = 8.3 Hz), 8.08 (d, 1H, *J* = 6.8 Hz), 8.02 (t, 1H, *J* = 5.4 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.08 (d, 1H, *J* = 1.9 Hz), 7.04 (t, 1H, *J* = 7.5 Hz), 6.96 (t, 1H, *J* = 7.3 Hz), 4.41 (dt, 1H, *J* = 4.5, 9.0 Hz), 4.27-4.14 (m, 1H), 3.33-3.20 (m, 4H), 3.15 (dd, 1H, *J* = 4.3, 14.6 Hz), 2.89 (dd, 1H, *J* = 9.6, 14.6 Hz), 2.37 (t, 2H, *J* = 7.2 Hz), 2.17 (t, 2H, *J* = 7.3 Hz), 1.77-1.66 (m, 2H), 0.98 (d, 3H, *J* =

7.04 Hz). IR 3402, 3303, 2103, 1725, 1438, 1539, 1248, 743 cm^{-1}; HRMS (FAB) Calcd. for $C_{21}H_{28}N_7O_5$ (MH^+) 458.2152; Found 458.2153.

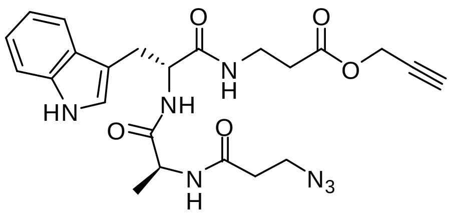
Azido Acid 10j



Prepared according to procedure 3. The following 4 building blocks were used sequentially, Fmoc-β-AlaOH, Fmoc-D-TrpOH, Fmoc-L-AlaOH, and (*S*)-3-azido-2-methylpropanoic acid. 0.500 g (0.5 mmol) of the trityl resin, after peptide synthesis, gave 0.160 g (70%) of **10j** as a slightly yellow solid.

$[\alpha]_D$ +5.0 (c 1.9, DMSO). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.78 (s, 1H), 8.15 (d, 1H, *J* = 7.1 Hz), 8.07 (d, 1H, *J* = 8.4 Hz), 8.01 (t, 1H, *J* = 5.5 Hz), 7.58 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.08 (d, 1H, *J* = 2.1 Hz), 7.04 (t, 1H, *J* = 8.0 Hz), 6.96 (t, 1H, *J* = 7.4 Hz), 4.44 (dt, 1H, *J* = 4.9, 8.9 Hz), 4.31-4.17 (m, 1H), 3.43 (dd, 1H, *J* = 8.1, 12.0 Hz), 3.30-3.20 (m, 3H), 3.13 (dd, 1H, *J* = 4.7, 14.6 Hz), 2.88 (dd, 1H, *J* = 9.3, 14.6 Hz), 2.65-2.54 (m, 2H), 2.35 (t, 2H, *J* = 7.2 Hz), 1.02-0.98 (m. 6H). ^{13}C-NMR (125 MHz, DMSO-d^6) 175.0, 174.6, 173.7, 173.1, 137.9, 129.2, 125.4, 122.7, 120.3, 120.0, 113.1, 112.0, 55.4, 55.2, 50.3, 41.2, 36.8, 35.5, 29.7, 19.7, 17.1. HRMS (FAB) Calcd. for $C_{21}H_{27}N_7O_5$ (M^+) 457.2053; Found 457.2073.

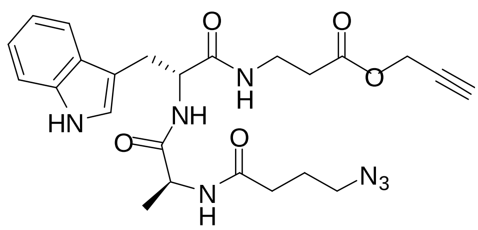
Azido Alkyne 4a



Following procedure 4, 291 mg (0.66 mmol) of azido acid **10a** were subjected to esterification reaction conditions to give 220 mg (0.46 mmol, 70 %) of **4a** as a slightly yellow solid.

mp = 197°C (dec.). $[\alpha]_D$ –3.7 (c 0.6, MeOH). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.19 (d, 2H, *J* = 6.9 Hz), 8.06 (t, 1H, *J* = 5.4 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz,), 7.09 (d, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 6.97 (t, 1H, *J* = 7.3 Hz), 4.69 (d, 2H, *J* = 2.4 Hz), 4.42 (dt, 1H, *J* = 4.8, 8.9 Hz), 4.34-4.18 (m, 1H), 3.54 (t, 1H, *J* = 2.4 Hz), 3.53-3.40 (m, 2H), 3.35-3.21 (m, 2H), 3.14 (dd, 1H, *J* = 4.5, 14.5 Hz), 2.97-2.81 (m, 1H), 2.48 (t, 2H, *J* = 7.1 Hz), 2.39 (m, 2H), 0.99 (d, 3H, *J* = 7.02 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 171.9, 171.3, 170.4, 169.4, 135.9, 127.1, 123.5, 120.7, 118.3, 118.1, 111.1, 110.0, 78.3, 77.6, 53.2, 51.7, 48.3, 46.8, 34.6, 34.1, 33.1, 27.6, 17.8. IR 3402, 3294, 2108, 1743, 1639, 1539, 1169, 743 cm^{-1}. HRMS (ESI) Calcd. for $C_{23}H_{28}N_7O_5$ (MH^+) 482.2146; Found 482.2142.

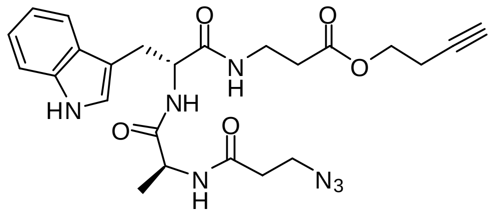
Azido Alkyne 4b



Following procedure 4, 209 mg (0.46 mmol) of azido acid **10b** were subjected to esterification reaction conditions to give 187 mg (0.39 mmol, 82 %) of **4b** as a white solid.

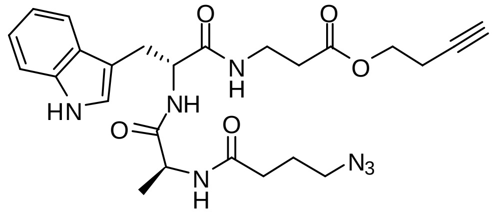
mp = 198°C (dec.). $[\alpha]_D$ +0.56 (c 1.5, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.15 (d, 1H, *J* = 8.3 Hz), 8.13-7.99 (m, 2H), 7.57 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.96 (t, 1H, *J* = 7.1 Hz), 4.69 (d, 2H, *J* = 2.4 Hz), 4.40 (dt, 1H, *J* = 4.7, 9.0 Hz), 4.32-4.13 (m, 1H), 3.55 (t, 1H, *J* = 2.4 Hz), 3.37-3.20 (m, 4H), 3.20-3.05 (m, 1H), 2.89 (dd, 1H, *J* = 9.5, 14.6 Hz), 2.47 (t, 2H, *J* = 7.0 Hz), 2.17 (t, 2H, *J* = 7.3 Hz), 1.86-1.60 (m, 2H), 0.99 (d, 3H, *J* = 7.0 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.1, 171.35, 171.33, 170.4, 135.9, 127.1, 123.4, 120.7, 118.3, 118.1, 111.1, 110.0, 78.3, 77.6, 53.3, 51.7, 50.1, 48.3, 34.6, 33.1, 31.7, 27.5, 24.3, 17.6; IR 3402, 3305, 2103, 1734, 1660, 1638, 1536, 1179, 744 cm^{-1}. HRMS (ESI) Calcd. for $C_{24}H_{30}N_7O_5$ (MH^+) 496.2303; Found 496.2299.

Azido Alkyne 4c



Following procedure 4, 134 mg (0.30 mmol) of azido acid **10a** were subjected to esterification reaction conditions to give 80 mg (0.16 mmol, 53 %) of **4c** as a white solid. mp = 240°C (dec.). $[\alpha]_D$ -38.0 (c 0.51, MeOH). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.19 (d, 2H, *J* = 7.3 Hz), 8.04 (t, 1H, *J* = 5.5 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 1.8 Hz), 7.05 (t, 1H, *J* = 7.4 Hz), 6.96 (t, 1H, *J* = 7.3 Hz), 4.41 (dt, 1H, *J* = 4.7, 9.0 Hz), 4.33-4.19 (m, 1H), 4.15-4.02 (m, 2H), 3.57-3.39 (m, 2H), 3.34-3.21 (m, 2H), 3.13 (dd, 1H, *J* = 4.5, 14.6 Hz), 2.94-2.83 (m, 2H), 2.48-2.28 (m, 4H), 0.99 (d, 3H, *J* = 7.01 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 171.9, 171.3, 170.9, 169.4, 135.9, 127.1, 123.5, 120.7, 118.3, 118.0, 111.1, 110.0, 80.7, 72.4, 61.7, 53.2, 48.3, 46.8, 34.7, 34.1, 33.4, 27.6, 18.2, 17.8. IR 3404, 3302, 2108, 1727, 1660, 1640, 1542, 1183, 744 cm^{-1}. HRMS (ESI) Calcd. for $C_{24}H_{30}N_7O_5$ (MH^+) 496.2303; Found 496.2298.

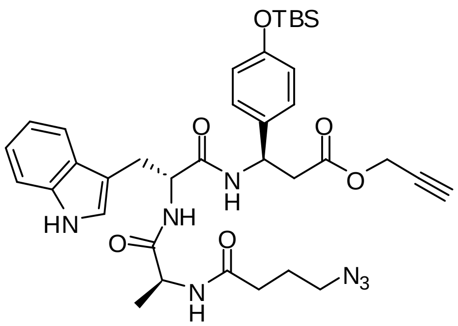
Azido Alkyne 4d



Following procedure 4, 209 mg (0.46 mmol) of azido acid **10b** were subjected to esterification reaction conditions to give 166 mg (0.33 mmol, 71 %) of **4d** as a white solid.

mp = 186°C (dec.). $[\alpha]_D$ –4.1 (c 0.58, MeOH). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.15 (d, 1H, *J* = 8.3 Hz), 8.08 (d, 1H, *J* = 6.8 Hz), 8.03 (t, 1H, *J* = 5.5 Hz), 7.57 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.96 (t, 1H, *J* = 7.2 Hz), 4.40 (dt, 1H, *J* = 4.6, 9.0 Hz), 4.30-4.14 (m, 1H), 4.09 (t, 2H, *J* = 6.7 Hz), 3.35-3.19 (m, 4H), 3.15 (dd, 1H, *J* = 4.4, 14.6 Hz), 3.00-2.79 (m, 2H), 2.45 (t, 2H, *J* = 7.1 Hz), 2.17 (t, 2H, *J* = 7.3 Hz), 1.83-1.61 (m, 2H), 0.99 (d, 3H, *J* = 7.04 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.2, 171.4, 171.3, 170.9, 136.0, 127.2, 123.5, 120.767, 118.3, 118.1, 111.8, 110.1, 80.7, 72.5, 61.8, 53.3, 50.2, 48.4, 34.8, 33.4, 31.7, 27.5, 24.4, 18.2, 17.6. IR 3403, 3301, 2101, 1725, 1659, 1639, 1537, 1181, 744 cm^{-1}. HRMS (FAB) Calcd. for $C_{25}H_{32}N_7O_5$ (MH^+) 510.2465; Found 510.2437.

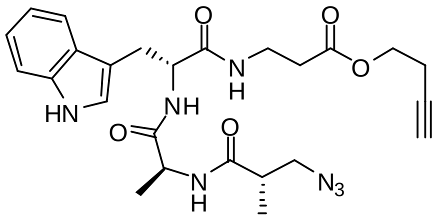
Azido Alkyne 4i



Following procedure 4, 209 mg (0.31 mmol) of azido acid **10i** were subjected to esterification reaction conditions to give 187 mg (0.27 mmol, 82 %) of **4i** as a white solid.

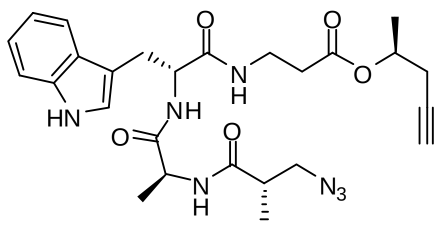
$[\alpha]_D$ +11.4 (c 0.33, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.35 (d, 1H, *J* = 8.5 Hz), 8.28 (d, 1H, *J* = 8.1 Hz), 8.18 (d, 1H, *J* = 6.1 Hz), 7.54 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.10 (d, 2H, *J* = 8.5 Hz), 7.07 (d, 1H, *J* = 2.0 Hz), 7.04 (t, 1H, *J* = 7.2 Hz), 6.95 (t, 1H, *J* = 7.3 Hz), 6.72 (d, 2H, *J* = 8.5 Hz), 5.20 (q, 1H, *J* = 7.9 Hz), 4.66 (d, 2H, *J* = 2.4 Hz), 4.40 (ddd, 1H, *J* = 4.3, 8.4, 9.4 Hz), 4.24-4.15 (m, 1H), 3.53 (t, 1H, *J* = 2.4 Hz), 3.27 (t, 2H, *J* = 6.9 Hz), 3.18 (dd, 1H, *J* = 4.1, 14.6 Hz), 2.89-2.82 (m, 3H), 2.23-2.09 (m, 2H), 1.77-1.58 (m, 2H), 1.00 (d, 3H, *J* = 7.0 Hz), 0.94 (s, 9H), 0.17 (s, 6H). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.5, 171.6, 170.3, 169.4, 153.9, 135.9, 134.5, 127.4 (2x), 127.1, 123.4, 120.7, 119.3 (2x), 118.2, 118.1, 111.1, 110.1, 78.2, 77.7, 53.5, 51.7, 50.1, 48.7, 40.4, 35.7, 31.6, 27.1, 25.4 (3x), 24.2, 17.8, 17.2, -4.6. HRMS (FAB) Calcd. for $C_{36}H_{47}N_7O_6Si$ 701.3358; Found 701.3383**.**

Azido Alkyne 4j



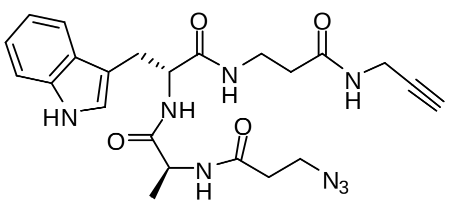
Following procedure 4, 100 mg (0.22 mmol) of azido acid **10j** were subjected to esterification reaction conditions to give 69 mg (0.14 mmol, 62 %) of **4j** as a white solid. [α]$_D$ +6.6 (c 1.9, DMSO). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.79 (d, 1H, *J* = 1.2 Hz), 8.16 (d, 1H, *J* = 7.1 Hz), 8.09 (d, 1H, *J* = 8.4 Hz), 8.02 (t, 1H, *J* = 5.6 Hz), 7.57 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.09 (d, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.97 (t, 1H, *J* = 7.1 Hz), 4.44 (dt, 1H, *J* = 5.0, 8.8 Hz), 4.30-4.20 (m, 1H), 4.09 (t, 2H, *J* = 6.6 Hz), 3.43 (dd, 1H, *J* = 8.1, 12.0 Hz), 3.33-3.22 (m, 3H), 3.13 (dd, 1H, *J* = 4.8, 14.6 Hz), 2.89 (dd, 1H, *J* = 9.6, 14.7 Hz), 2.85 (t, 1H, *J* = 2.7 Hz), 2.64-2.56 (m, 1H), 2.52-2.48 (m, 2H), 2.43 (t, 2H, *J* = 7.1 Hz), 1.01 (d, 3H, *J* = 8.3 Hz), 1.00 (d, 3H, *J* = 7.07 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 172.9, 171.7, 171.1, 170.8, 135.9, 127.1, 123.4, 120.6, 118.2, 118.0, 111.0, 109.9, 80.6, 72.3, 61.7, 53.4, 53.2, 48.2, 39.1, 34.6, 33.3, 27.6, 18.1, 17.7, 15.1. IR 3280, 3083, 2930, 2104, 1729, 1631, 1546, 1176, 741, 658 cm^{-1}. HRMS (FAB) Calcd. for $C_{25}H_{32}N_7O_5$ (MH$^+$) 510.2465; Found 510.2467.

Azido Alkyne 4k



Following procedure 4, 100 mg (0.22 mmol) of azido acid **10j** were subjected to esterification reaction conditions to give 74 mg (0.14 mmol, 65 %) of **4k** as a white solid. $[\alpha]_D$ −1.1 (c 2.7, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.78 (d, 1H, *J* = 1.5 Hz), 8.15 (d, 1H, *J* = 7.1 Hz), 8.07 (d, 1H, *J* = 8.3 Hz), 8.00 (t, 1H, *J* = 5.6 Hz), 7.57 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 2.0 Hz), 7.05 (t, 1H, *J* = 7.0 Hz), 6.97 (t, 1H, *J* = 7.0 Hz), 4.93-4.82 (m, 1H), 4.44 (dt, 1H, *J* = 4.9, 8.6 Hz), 4.30-4.18 (m, 1H), 3.43 (dd, 1H, *J* = 8.1, 12.0 Hz), 3.35-3.20 (m, 3H), 3.14 (dd, 1H, *J* = 4.7, 14.5 Hz), 2.89 (dd, 1H, *J* = 9.6, 14.9 Hz), 2.85 (t, 1H, *J* = 2.6 Hz), 2.66-2.54 (m, 1H), 2.46 (td, 2H, *J* = 2.6, 5.5 Hz), 2.40 (t, 2H, *J* = 7.1 Hz), 1.24 (d, 3H, *J* = 6.3 Hz), 1.02 (d, 3H, *J* = 7.5 Hz), 1.00 (d, 3H, *J* = 7.0 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6)173.0, 171.8, 171.2, 170.4, 135.9, 127.1, 123.4, 120.7, 118.3, 118.0, 111.1, 109.9, 80.1, 72.9, 68.2, 53.4, 53.2, 48.3, 39.2, 34.7, 33.7, 27.7, 24.7, 18.7, 17.7, 15.1. IR 3284, 3079, 2930, 2105, 1724, 1633, 1543, 1156, 1059, 740, 654 cm^{-1}. HRMS (FAB) Calcd. for $C_{26}H_{34}N_7O_5$ (MH^+) 524.2622; Found 524.2646.

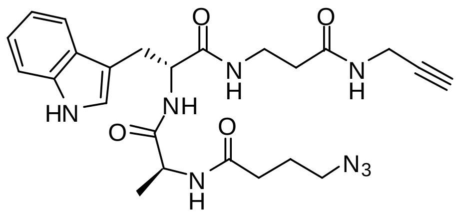
Azido Alkyne 4h



Following procedure 5, 90 mg (0.20 mmol) of azido acid **10a** gave 74 mg (0.15 mmol, 74 %) of **4h** as a white solid.

mp = 240°C (dec.). [α]$_D$ +150 (c 0.54, DMSO/MeOH 1:1). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.78 (s, 1H), 8.31 (t, 1H, J = 5.5 Hz, NH), 8.18-8.11 (m, 2H, NH), 8.02 (t, 1H, J = 5.5 Hz), 7.58 (d, 1H, J = 7.7 Hz), 7.31 (d, 1H, 7.7 Hz), 7.08 (s, 1H), 7.04 (t, 1H, J = 7.6 Hz), 6.96 (t, 1H, J = 7.4 Hz), 4.45-4.37 (m, 1H), 4.29-4.22 (m, 1H), 3.88-3.82 (m, 2H), 3.57-3.48 (m, 1H), 3.48-3.41 (m, 1H), 3.29-3.19 (m, 2H), 3.12 (dd, 1H, J = 4.4, 14.6 Hz), 3.09 (t, 1H, J = 2.5 Hz), 2.88 (dd, 1H, J = 9.6, 14.6 Hz), 2.46-2.34 (m, 2H), 2.32-2.22 (m, 2H), 0.97 (d, 3H, J = 7.0 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 171.8, 171.2, 169.9, 169.3, 135.9, 127.2, 123.5, 120.7, 118.3, 118.0, 111.1, 110.0, 81.1, 72.8, 53.2, 48.3, 46.8, 35.3, 34.8, 34.2, 34.1, 27.7, 17.9. IR 3403, 3290, 2107, 1668, 1638, 1538, 744 cm^{-1}. HRMS (FAB) Calcd. for $C_{23}H_{29}N_8O_4$ (MH$^+$) 481.2312; Found 481.2298.

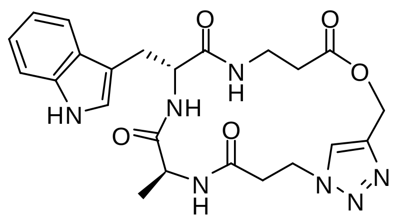
Azido Alkyne 4l



Following procedure 5, 150 mg (0.33 mmol) of azido acid **10b** gave 130 mg (0.26 mmol, 80 %) of **4l** as a white solid.

mp = 239°C (dec.). [α]$_D$ -21.0 (c 0.55, DMSO). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.78 (s, 1H), 8.30 (t, 1H, *J* = 5.3 Hz), 8.09 (d, 1H *J* = 8.4 Hz), 8.05 (d, 1H, *J* = 6.9 Hz), 8.00 (t, 1H, *J* = 5.6 Hz), 7.58 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.08 (d, 1H, *J* = 1.7 Hz), 7.05 (t, 1H, *J* = 8.7 Hz), 6.96 (t, 1H, *J* = 7.29 Hz), 4.42 (dt, 1H, *J* = 4.5, 9.0 Hz), 4.27-4.15 (m, 1H), 3.85 (dd, 2H, *J* = 2.4, 5.3 Hz), 3.34-3.19 (m, 4H), 3.14 (dd, 1H, *J* = 4.3, 14.6 Hz), 3.08 (t, 1H, *J* = 2.40 Hz), 2.89 (dd, 1H, *J* = 9.5, 14.6 Hz), 2.33-2.22 (m, 2H), 2.17 (t, 2H, *J* = 7.3 Hz), 1.76-1.68 (m, 2H), 0.98 (d, 3H, *J* = 7.05 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 172.0, 171.2, 171.1, 169.8, 135.9, 127.1, 123.4, 120.7, 118.3, 118.0, 111.1, 110.0, 81.0, 72.8, 53.2, 50.1, 48.3, 35.2, 34.8, 31.7, 27.6, 27.6, 24.3, 17.6. HRMS (ESI) Calcd. for $C_{24}H_{31}N_8O_4$ (MH$^+$) 495.2463; Found 495.2458.

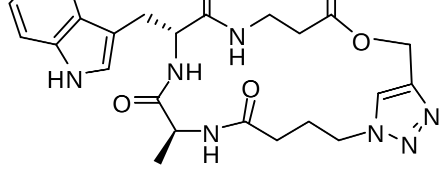
Cyclic Peptide 2a



76 mg (0.15 mmol) of seco acid **3a** were subjected to macrolactonization conditions as described in procedure 2 to give 26 mg (0.054 mmol, 37 %) of **2a** as a white solid.

When 100 mg (0.21 mmol) of azido alkyne **4a** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 87 mg (0.18 mmol, 87 %) of the same product (**2a**) were obtained.
mp = 140°C (dec.). $[\alpha]_D$ –11.6 (c 0.6, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.20 (d, 1H, J = 4.3 Hz), 8.18 (d, 1H, J = 4.9 Hz), 7.96 (t, 1H, J = 5.4 Hz), 7.78 (s, 1H), 7.59 (d, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 8.0 Hz), 7.13 (d, 1H, J = 1.5 Hz), 7.04 (t, 1H, J = 7.3 Hz), 6.96 (t, 1H, J = 7.3 Hz), 5.08 (q, 2H, J = 12.9 Hz), 4.70-4.59 (m, 2H), 4.58-4.49 (m, 2H), 4.47-4.38 (m, 2H), 4.38-4.27 (m, 2H), 3.48-3.34 (m, 1H), 3.25-3.14 (m, 1H), 3.08 (dd, 1H, J = 4.1, 14.5 Hz), 2.81-2.68 (m, 1H), 2.68-2.57 (m, 1H), 0.86 (d, 3H, J = 7.0 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 171.9, 171.6, 171.5, 168.9, 141.8, 136.0, 127.1, 124.3, 123.7, 120.8, 118.4, 118.1, 111.2, 110.1, 57.6, 53.2, 47.6, 46.1, 35.4, 34.9, 33.6, 27.4, 18.0. IR 3292, 1734, 1644, 1531, 1167, 745 cm^{-1}. HRMS (FAB) Calcd. for $C_{23}H_{28}N_7O_5$ (MH^+) 482.2152; Found 482.2138.

Cyclic Peptide 2b

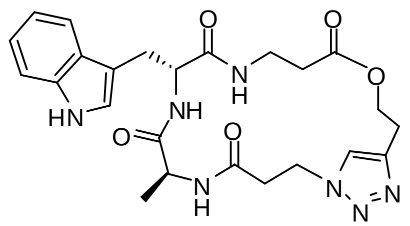


51 mg (0.10 mmol) of seco acid **3b** were subjected to macrolactonization conditions as described in procedure 2 to give 14 mg (0.028 mmol, 28 %) of **2b** as a white solid.

When 98 mg (0.20 mmol) of azido alkyne **4b** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 64 mg (0.13 mmol, 65 %) of the same product (**2b**) were obtained.

mp = 63°C (dec.). $[\alpha]_D$ –19.0 (c 0.8, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.14 (dd, 1H, J = 4.4, 6.1 Hz), 8.07 (d, 1H, J = 7.5 Hz), 8.03 (d, 1H, J = 8.3 Hz), 7.63-7.56 (m, 2H), 7.30 (d, 1H, J = 8.0 Hz), 7.12 (d, 1H, J = 1.8 Hz), 7.04 (t, 1H, J = 7.4 Hz), 6.96 (t, 1H, J = 7.3 Hz), 5.22 (d, 1H, J = 13.1 Hz), 5.09 (d, 1H, J = 13.1 Hz), 4.50-4.41 (m, 2H), 4.33-4.23 (m, 2H), 3.18-3.07 (m, 2H), 2.93 (dd, 1H, J = 9.8, 14.5 Hz), 2.66-2.53 (m, 1H), 2.16-2.04 (m, 1H), 2.03-1.89 (m, 3H), 2.46 (t, 2H, J = 5.6 Hz), 0.94 (d, 3H, J = 7.1 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 172.0, 171.4, 171.2, 170.9, 142.5, 135.9, 127.1, 124.1, 123.6, 120.7, 118.3, 118.0, 111.1, 109.9, 58.0, 53.1, 47.9, 47.6, 34.8, 33.9, 31.1, 27.6, 25.3, 17.0. IR 3284, 1734, 1646, 1534, 1166, 746 cm^{-1}. HRMS (FAB) Calcd. for $C_{24}H_{30}N_7O_5$ (MH^+) 496.2308; Found 496.2283.

Cyclic Peptide 2c

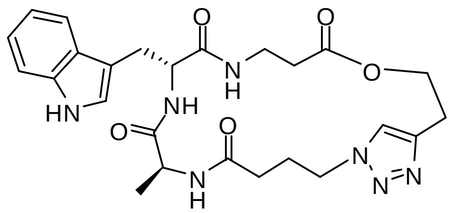


57 mg (0.11 mmol) of seco acid **3c** were subjected to macrolactonization conditions as described in procedure 2 to give 25 mg (0.050 mmol, 45 %) of **2c** as a white solid.

When 60 mg (0.12 mmol) of azido alkyne **4c** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 55 mg (0.11 mmol, 92 %) of the same product (**2c**) was obtained.

mp = 115°C (dec.). $[\alpha]_D$ +1.9 (c 0.8, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.29 (d, 1H, J = 8.6 Hz), 8.26 (d, 1H, J = 6.5 Hz) 8.01 (t, 1H, J = 5.6 Hz), 7.68 (s, 1H), 7.60 (d, 1H, J = 7.8 Hz), 7.30 (d, 1H, J = 8.0 Hz), 7.09 (s, 1H), 7.13 (d, 1H, J = 1.8 Hz), 7.04 (t, 1H, J = 7.3 Hz), 7.00 (t, 1H, J = 7.3 Hz), 4.62-4.47 (m, 2H), 4.43-4.32 (m, 2H), 4.20-4.12 (m, 1H), 4.10-4.03 (m, 1H), 3.47-3.38 (m, 1H), 3.20-3.10 (m, 2H), 2.97-2.83 (m, 3H), 2.66-2.59 (m, 2H), 2.46 (t, 2H, J = 5.6 Hz), 0.92 (d, 3H, J = 7.1 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.1, 171.6, 171.3, 169.7, 143.6, 135.9, 127.1, 123.5, 123.0, 120.7, 118.3, 118.0, 111.1, 110.3, 63.0, 53.5, 48.5, 45.8, 35.0, 34.8, 33.9, 26.8, 24.9, 17.1. IR 3274, 1730, 1651, 1542, 1176, 746 cm^{-1}. HRMS (FAB) Calcd. for $C_{24}H_{30}N_7O_5$ (MH^+) 496.2308; Found 496.2297.

Cyclic Peptide 2d



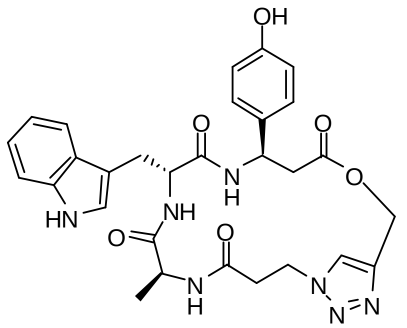
42 mg (0.080 mmol) of seco acid **3d** were subjected to macrolactonization conditions as described in procedure 2 to give 24 mg (0.047 mmol, 59 %) of **2d** as a white solid.

When 100 mg (0.20 mmol) of azido alkyne **4d** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6, 82 mg (0.16 mmol, 82 %) of the same product (**2d**) was obtained.

mp = 64°C (dec.). $[\alpha]_D$ –9.0 (c 0.6, DMSO). ^{1}H NMR (500 MHz, DMSO-d^6) 10.80 (s, 1H), 8.28 (d, 1H, *J* = 8.2 Hz), 8.26 (d, 1H, *J* = 6.4 Hz), 7.93 (t, 1H, *J* = 5.7 Hz), 7.81 (s, 1H), 7.56 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.13 (d, 1H, *J* = 2.1 Hz), 7.05 (ddd, 1H, *J* = 0.9, 7.5, 8.0 Hz), 6.97 (ddd, 1H, *J* = 0.8, 7.2, 7.9 Hz), 4.36-4.29 (m, 3H), 4.27-4.21 (m, 2H), 4.19-4.14 (m, 1H), 3.31-3.24 (m, 1H), 3.24-3.18 (m, 2H), 2.95 (t, 2H, *J* = 5.5 Hz), 2.90 (dd, 1H, *J* = 10.0, 14.8 Hz), 2.42 (td, 1H, *J* = 7.3, 14.8 Hz), 2.32 (td, 1H, *J* = 6.5, 13.6 Hz), 2.14-2.08 (m, 1H), 2.07-2.00 (m, 1H), 1.98-1.92 (m, 1H), 1.90-1.84

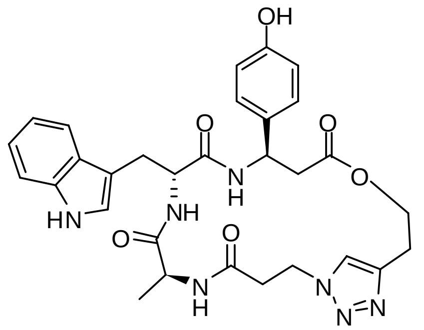
(m, 1H), 1.00 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (125 MHz, DMSO-d^6) 172.4, 171.7, 171.3, 170.8, 143.4, 135.9, 127.1, 123.3, 123.1, 120.7, 118.2, 118.1, 111.2, 110.3, 62.5, 53.8, 48.5, 48.1, 34.6, 33.6, 31.4, 26.8, 26.2, 24.6, 16.4. IR 3292, 1732, 1646, 1540, 1174, 746 cm^{-1}. HRMS (FAB) Calcd. for $C_{25}H_{31}N_7O_5$ 509.2387; Found 509.2402

Cyclic Peptide 2e



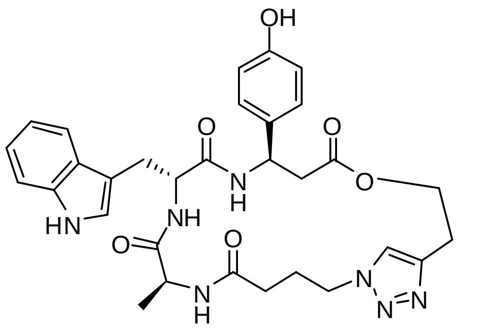
87 mg (0.15 mmol) of seco acid **3e** were subjected to macrolactonization conditions as described in procedure 2 to give 11 mg (0.019 mmol, 15 %) of **2e** as a white solid.
mp = 231°C (dec.). $[\alpha]_D$ –24.6 (c 0.47, DMSO). ^{1}H NMR (400 MHz, DMSO-d^6) 10.76 (d, 1H, *J* = 1.7 Hz,), 9.29 (s, 1H), 8.68 (d, 1H, *J* = 8.5 Hz), 8.26 (d, 1H, *J* = 8.2 Hz), 8.20 (d, 1H, *J* = 8.0 Hz), 7.75 (s, 1H), 7.59 (d, 1H, *J* = 7.9 Hz), 7.30 (d, 1H, *J* = 8.1 Hz), 7.13-6.99 (m, 4H), 6.94 (t, 1H, *J* = 7.4 Hz), 6.68 (d, 2H, *J* = 8.5 Hz), 5.23 (ddd, 1H, *J* = 3.3, 8.5, 11.9 Hz), 5.06 (dd, 2H, *J* = 12.8, 33.3 Hz), 4.73-4.52 (m, 2H), 4.52-4.29 (m, 2H), 3.02 (dd, 1H, *J* = 5.0, 14.7 Hz), 2.93-2.78 (m, 2H), 2.68 (dd, 1H, *J* = 4.6, 16.1 Hz), 2.66-2.52 (m, 2H), 0.97 (d, 3H, *J* = 7.1 Hz). ^{13}C NMR (100 MHz, DMSO-d^6) 171.8, 170.1, 169.9, 169.2, 156.0, 141.7, 135.8, 132.5, 127.2, 126.9 (2x), 124.3, 123.6, 120.6, 118.4, 117.9, 114.9 (2x), 111.0, 109.6, 58.2, 53.0, 48.2, 47.6, 46.2, 41.5, 35.4, 27.5, 17.0. IR 1731, 1651, 1516, 1174, 746 cm^{-1}. HRMS (ESI) Calcd. for $C_{29}H_{32}N_7O_6$ (MH^+) 574.2409; Found 574.2407.

Cyclic Peptide 2f



87 mg (0.14 mmol) of seco acid **3f** were subjected to macrolactonization conditions as described in procedure 2 to give 23 mg (0.039 mmol, 32 %) of **2f** as a white solid.
mp = 146°C (dec.). $[\alpha]_D$ +6.1 (c 1.1, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.76 (d, 1H, *J* = 1.5 Hz), 9.33 (s, 1H), 8.50 (d, 1H, *J* = 9.0 Hz), 8.19 (t, 2H, *J* = 8.3 Hz), 7.60 (d, 1H, *J* = 7.9 Hz), 7.56 (s, 1H), 7.30 (d, 1H, *J* = 8.0 Hz), 7.11 (d, 2H, *J* = 8.5 Hz), 7.08 (d, 1H, *J* = 1.9 Hz), 7.03 (t, 1H, *J* = 7.6 Hz), 6.94 (t, 1H, *J* = 7.5 Hz), 6.69 (d, 2H, *J* = 8.5 Hz), 5.28-5.19 (m, 1H), 4.64-4.54 (m, 2H), 4.56-4.46 (m, 1H), 4.35-4.25 (m, 1H), 4.22-4.07 (m, 2H), 3.08 (dd, 1H, *J* = 4.1, 14.8 Hz), 2.97-2.81 (m, 2H), 2.78 (dd, 1H, *J* = 4.7, 15.0 Hz), 2.72-2.52 (m, 4H), 0.87 (d, 3H, *J* = 7.0 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 171.6, 170.6, 170.2, 169.2, 156.1, 142.9, 135.9, 132.1, 127.0 (3x), 123.7, 122.5, 120.6, 118.3, 117.9, 114.9 (2x), 111.0, 109.8, 63.0, 53.1, 48.8, 47.6, 46.2, 41.3, 36.0, 27.6, 24.7, 18.0; IR 3293, 1732, 1654, 1516, 1173, 747 cm^{-1}. HRMS (ESI) Calcd. for $C_{30}H_{34}N_7O_6$ (MH^+) 588.2565; Found 588.2563.

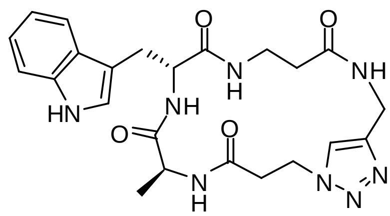
Cyclic Peptide 2g



95 mg (0.15 mmol) of seco acid **3g** were subjected to macrolactonization conditions followed by TBS deprotection as described in procedure 2 to give 20 mg (0.033 mmol, 26 %) of **2g** as a white solid.

mp = 127°C (dec.). $[\alpha]_D$ –0.73 (c 0.69, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.77 (d, 1H, *J* = 1.9 Hz), 8.53 (d, 1H, *J* = 8.6 Hz), 8.08 (d, 1H, *J* = 7.4 Hz), 7.98 (d, 1H, *J* = 8.3 Hz), 7.65 (s, 1H), 7.55 (d, 1H, *J* = 7.9 Hz), 7.30 (d, 1H, *J* = 8.6 Hz), 7.08-6.98 (m, 4H), 6.94 (t, 1H, *J* = 7.4 Hz), 6.67 (d, 2H, *J* = 8.4 Hz), 5.12 (q, 1H, *J* = 8.1 Hz), 4.57-4.44 (m, 1H), 4.37-4.28 (m, 1H), 4.29-4.13 (m, 4H), 3.06 (dd, 1H, *J* = 4.6, 14.8 Hz), 2.96-2.78 (m, 2H), 2.75 (dd, 1H, *J* = 6.3, 15.3 Hz), 2.66 (dd, 1H, *J* = 8.9, 15.3 Hz), 2.18-2.02 (m, 2H), 2.04-1.83 (m, 2H), 0.98 (d, 3H, *J* = 6.9 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 171.7, 170.9, 170.5, 169.8, 156.2, 142.8, 135.9, 131.8, 127.3 (2x), 127.1, 123.5, 123.3, 120.6, 118.3, 118.0, 114.9 (2x), 111.1, 109.7, 62.5, 53.0, 48.8, 48.1, 47.4, 41.1, 31.2, 27.5, 25.3, 24.7, 16.8. IR 3292, 1732, 1650, 1517, 1174, 747 cm^{-1}. HRMS (ESI) Calcd. for $C_{31}H_{36}N_7O_6$ (MH^+) 602.2722; Found 602.2719.

Cyclic Peptide 2h

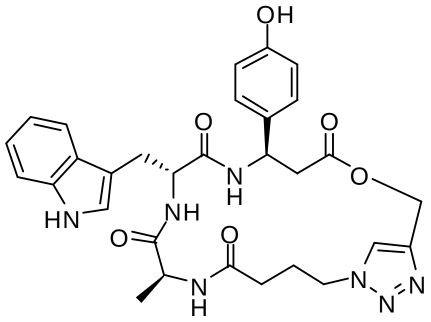


30 mg (0.062 mmol) of azido alkyne **4h** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 21 mg (0.044 mmol, 70 %) of **2h** as a white solid.

mp = 158°C (dec.). $[\alpha]_D$ –4.1 (c 0.4, MeOH). ^{1}H NMR (400 MHz, DMSO-d^6) 10.80 (s, 1H), 8.19 (d, 2H, *J* = 6.9 Hz), 8.06 (t, 1H, *J* = 5.4 Hz), 7.58 (d, 1H, *J* = 7.8 Hz), 7.31 (d, 1H, *J* = 8.0 Hz), 7.09 (d, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 7.2 Hz), 6.97 (t, 1H, *J* = 7.3 Hz), 4.69 (d, 2H, *J* = 2.4 Hz), 4.42 (dt, 1H, *J* = 4.8, 8.9 Hz), 4.32-4.22 (m, 1H), 3.54 (t, 1H, *J* = 2.44 Hz), 3.53-3.40 (m, 2H), 3.34-3.21 (m, 2H), 3.14 (dd, 1H, *J* = 4.5, 14.5 Hz), 2.89 (dd, 1H, *J* = 9.5, 14.6 Hz), 2.47 (d, 1H, *J* = 7.1 Hz), 2.45-2.33 (m, 2H), 0.99 (d, 3H,

J = 7.0 Hz). ^{13}C NMR (100 MHz, DMSO-d^6) 171.9, 171.4, 170.7, 169.1, 145.0, 136.0, 127.1, 123.6, 122.6, 120.7, 118.3, 118.1, 111.1, 110.1, 53.4, 47.6, 46.0, 35.8, 35.0, 34.5, 34.4, 27.4, 18.2. IR 3278, 1641, 1538, 1200, 744. HRMS (FAB) Calcd. for $C_{23}H_{29}N_8O_4$ (MH$^+$) 481.2312; Found 481.2344.

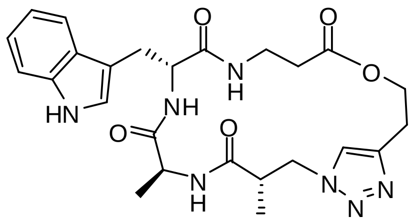
Cyclic Peptide 2i



68 mg (0.097 mmol) of azido alkyne **4i** were subjected to intramolecular cycloaddition reaction conditions followed by TBS deprotection as described in procedure 6 to give 36 mg (0.061 mmol, 63 %) of **2i** as a white solid.

mp = 158°C (dec.). [α]$_D$ –21.5 (c 0.6, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.77 (d, 1H, *J* = 2.2 Hz,), 9.35 (br s, 1H), 8.84 (d, 1H, *J* = 9.1 Hz), 8.16 (d, 1H, *J* = 8.2 Hz), 8.01 (d, 1H, *J* = 8.9 Hz), 7.65 (d, 1H, *J* = 8.1 Hz), 7.53 (s, 1H), 7.30 (dd, 1H, *J* = 0.6, 8.0 Hz), 7.12 (d, 2H, *J* = 8.6 Hz), 7.08 (d, 1H, *J* = 2.1 Hz), 7.04 (t, 1H, *J* = 7.5 Hz), 6.96 (t, 1H, *J* = 7.5 Hz), 6.70 (d, 2H, *J* = 8.6 Hz), 5.28 (ddd, 1H, *J* = 3.2, 9.1, 12.5 Hz), 5.15 (dd, 2H, *J* = 12.7, 27.4 Hz), 4.55-4.45 (m, 3H), 4.29-4.18 (m, 1H), 2.96 (dd, 1H, *J* = 3.8, 14.5 Hz), 2.88-2.80 (m, 2H), 2.68 (dd, 1H, *J* = 12.1, 15.6 Hz), 2.12-1.94 (m, 3H), 1.84-1.72 (m, 1H), 0.92 (d, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.0, 170.7, 170.4, 169.9, 156.2, 141.9, 135.8, 132.6, 127.0, 126.9 (2x), 125.3, 123.9, 120.6, 118.5, 118.0, 115.0 (2x), 111.0, 109.6, 58.3, 53.2, 48.5, 47.2, 47.1, 41.6, 30.2, 27.9, 25.0, 17.7. IR 3291, 1732, 1649, 1516, 1162, 746 cm^{-1}. HRMS (FAB) Calcd. for $C_{30}H_{34}N_7O_6$ (MH$^+$) 588.2565; Found 588.2562.

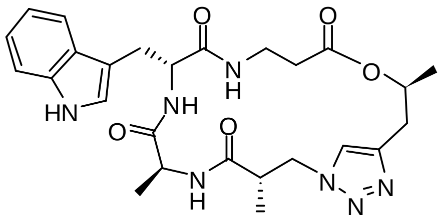
Cyclic Peptide 2j



60 mg (0.12 mmol) of azido alkyne **4j** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 45 mg (0.088 mmol, 75 %) of **2j** as a white solid.

mp = 126°C (dec.). $[\alpha]_D$ +4.3 (c 2.3, DMSO). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.79 (s, 1H), 8.30-8.17 (m, 2H), 8.03 (t, 1H, *J* = 5.7 Hz), 7.65-7.54 (m, 2H), 7.31 (d, 1H, *J* = 8.1 Hz), 7.14 (d, 1H, *J* = 1.8 Hz, 1H), 7.04 (t, 1H, *J* = 7.5 Hz), 6.96 (t, 1H, *J* = 7.4 Hz), 4.52-4.34 (m, 4H), 4.25-4.14 (m, 1H), 4.09-3.98 (m, 1H), 3.48-3.36 (m, 1H), 3.32-3.21 (m, 1H), 3.16 (dd, 1H, *J* = 4.3, 14.6 Hz), 2.97-2.91 (m, 1H), 2.92-2.82 (m, 2H), 2.82-2.76 (m, 1H), 2.50-2.39 (m, 2H), 1.04 (d, 3H, *J* = 7.0 Hz), 0.92 (d, 3H, *J* = 7.1 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 173.0, 172.0, 171.5, 171.3, 143.7, 135.9, 127.1, 123.5, 122.9, 120.7, 118.3, 118.0, 111.1, 110.2, 63.0, 53.4, 52.1, 48.3, 40.0, 34.7, 33.9, 27.0, 25.0, 17.4, 15.3. IR 3294, 1730, 1650, 1536, 1172, 745 cm^{-1}. HRMS (FAB) Calcd. for $C_{25}H_{31}N_7O_5$ (M^+) 509.2387; Found 509.2374.

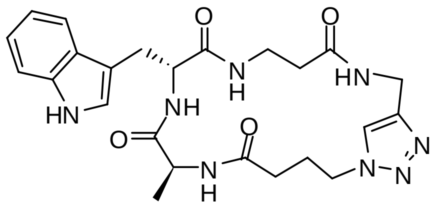
Cyclic Peptide 2k



60 mg (0.11 mmol) of azido alkyne **4k** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 41 mg (0.078 mmol, 70 %) of **2k** as a white solid.

mp = 127°C (dec.). $[\alpha]_D$ –6.8 (c 2.1, DMSO). ^{1}H-NMR (500 MHz, DMSO-d^6) 10.80 (s, 1H), 8.26 (d, 2H, *J* = 7.6 Hz), 7.85 (t, 1H, *J* = 5.6 Hz), 7.69 (s, 1H), 7.55 (d, 1H, *J* = 7.9 Hz), 7.31 (d, 1H, *J* = 8.1 Hz), 7.11 (d, 1H, *J* = 1.9 Hz), 7.05 (t, 1H, *J* = 7.5 Hz), 6.96 (t, 1H, *J* = 7.4 Hz), 5.08-4.96 (m, 1H), 4.54-4.34 (m, 3H), 4.20-4.08 (m, 1H), 3.46-3.35 (m, 1H), 3.35-3.25 (m, 1H), 3.21 (dd, 1H, *J* = 4.7, 14.7 Hz), 2.99-2.90 (m, 2H), 2.89-2.84 (m, 1H), 2.81 (dd, 1H, *J* = 7.3, 15.1 Hz), 2.44 (t, 2H, *J* = 5.5 Hz), 1.22 (d, 3H, *J* = 6.3 Hz), 1.04 (d, 3H, *J* = 7.0 Hz), 0.99 (d, 3H, *J* = 7.2 Hz). ^{13}C-NMR (125 MHz, DMSO-d^6) 173.2, 172.0, 171.2, 170.7, 142.6, 135.9, 127.1, 123.6, 123.3, 120.7, 118.1, 118.1, 111.1, 110.2, 69.7, 53.9, 52.1, 48.6, 40.0, 34.8, 34.2, 31.2, 26.7, 19.4, 17.1, 15.1. IR 3292, 2980, 1727, 1651, 1537, 1177, 745 cm^{-1}. HRMS (ESI) Calcd. for $C_{26}H_{34}N_7O_5$ (MH^+) 524.2616; Found 524.2609.

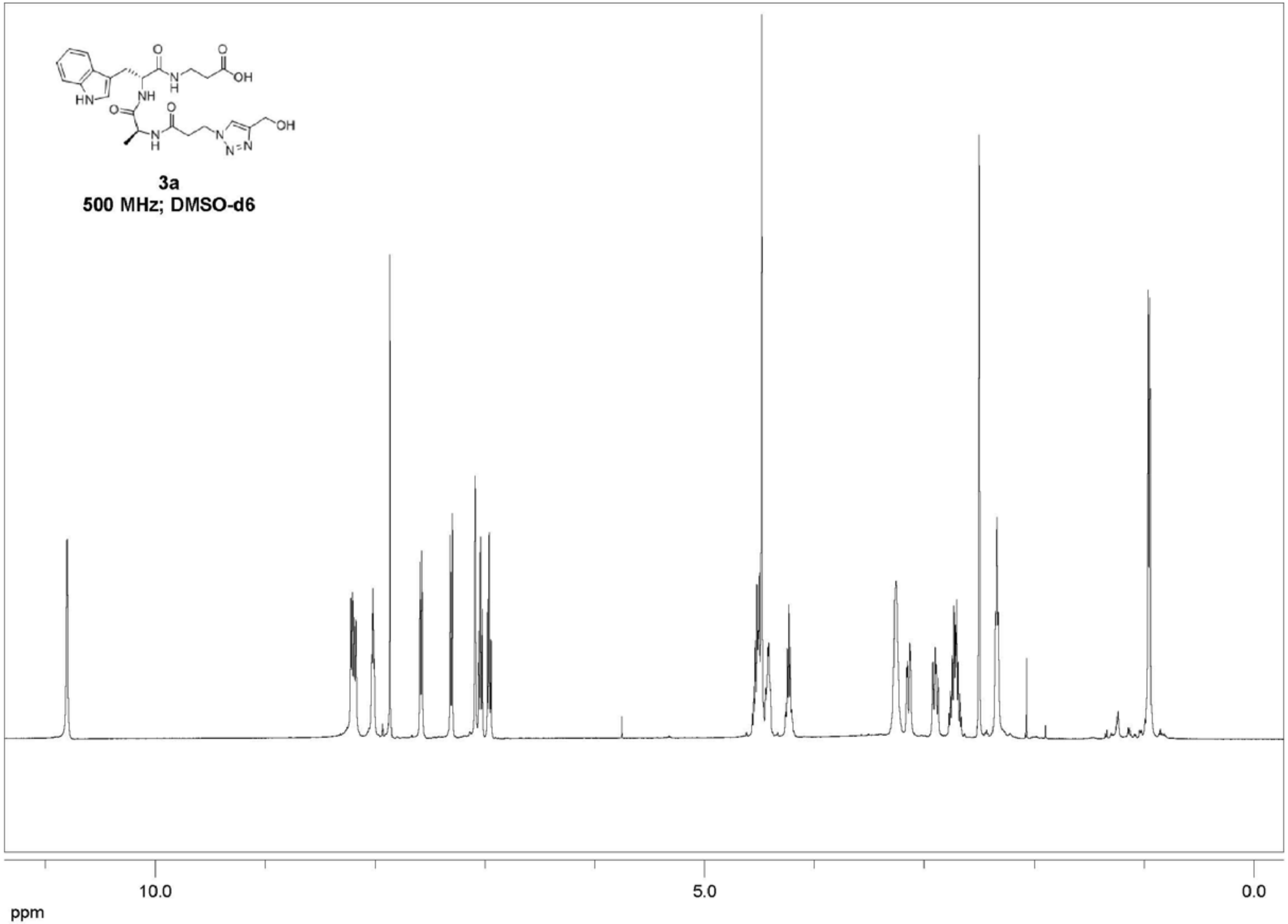
Cyclic Peptide 2l



70 mg (0.14 mmol) of azido alkyne **4l** were subjected to intramolecular cycloaddition reaction conditions as described in procedure 6 to give 40 mg (0.081 mmol, 57 %) of **2l** as a white solid.

mp = 236°C (dec.). $[\alpha]_D$ –22.9 (c 0.28, DMSO). ^{1}H-NMR (400 MHz, DMSO-d^6) 10.78 (s, 1H), 8.32 (t, 1H, *J* = 5.7 Hz), 8.18 (t, 1H, *J* = 5.5 Hz), 8.09 (d, 1H, *J* = 7.4 Hz), 7.99 (d, 1H, *J* = 8.5 Hz), 7.62 (d, 1H, *J* = 7.8 Hz), 7.41 (s, 1H), 7.29 (d, 1H, *J* = 8.0 Hz), 7.13 (s, 1H), 7.03 (t, 1H, *J* = 7.3 Hz), 6.95 (t, 1H, *J* = 7.4 Hz), 4.69-4.36 (m, 3H), 4.36-4.16 (m, 2H), 4.13 (dd, 1H, *J* = 4.4, 15.6 Hz), 3.61-3.39 (m, 1H), 3.33-3.13 (m, 1H), 3.13 (dd, 1H, *J* = 4.0, 14.5 Hz), 2.94 (dd, 1H, *J* = 9.9, 14.5 Hz), 2.48-2.33 (m, 1H), 2.27 (dd, 1H, *J* = 6.7, 13.8 Hz), 2.21-1.76 (m, 4H), 0.92 (d, 3H, *J* = 7.1 Hz). ^{13}C-NMR (100 MHz, DMSO-d^6) 172.0, 171.5, 171.2, 170.6, 145.7, 135.9, 127.1, 123.6, 122.6, 120.6, 118.4, 117.9, 111.0, 109.9, 52.9, 47.9, 47.2, 35.4, 35.2, 34.6, 31.3, 27.7, 25.8, 16.8; IR 3292, 1634, 1543, 1236, 1053, 744 cm^{-1}. HRMS (ESI) Calcd. for $C_{24}H_{31}N_8O_4$ (MH^+) 496.2463; Found 496.2457.

^{1}H-NMR spectra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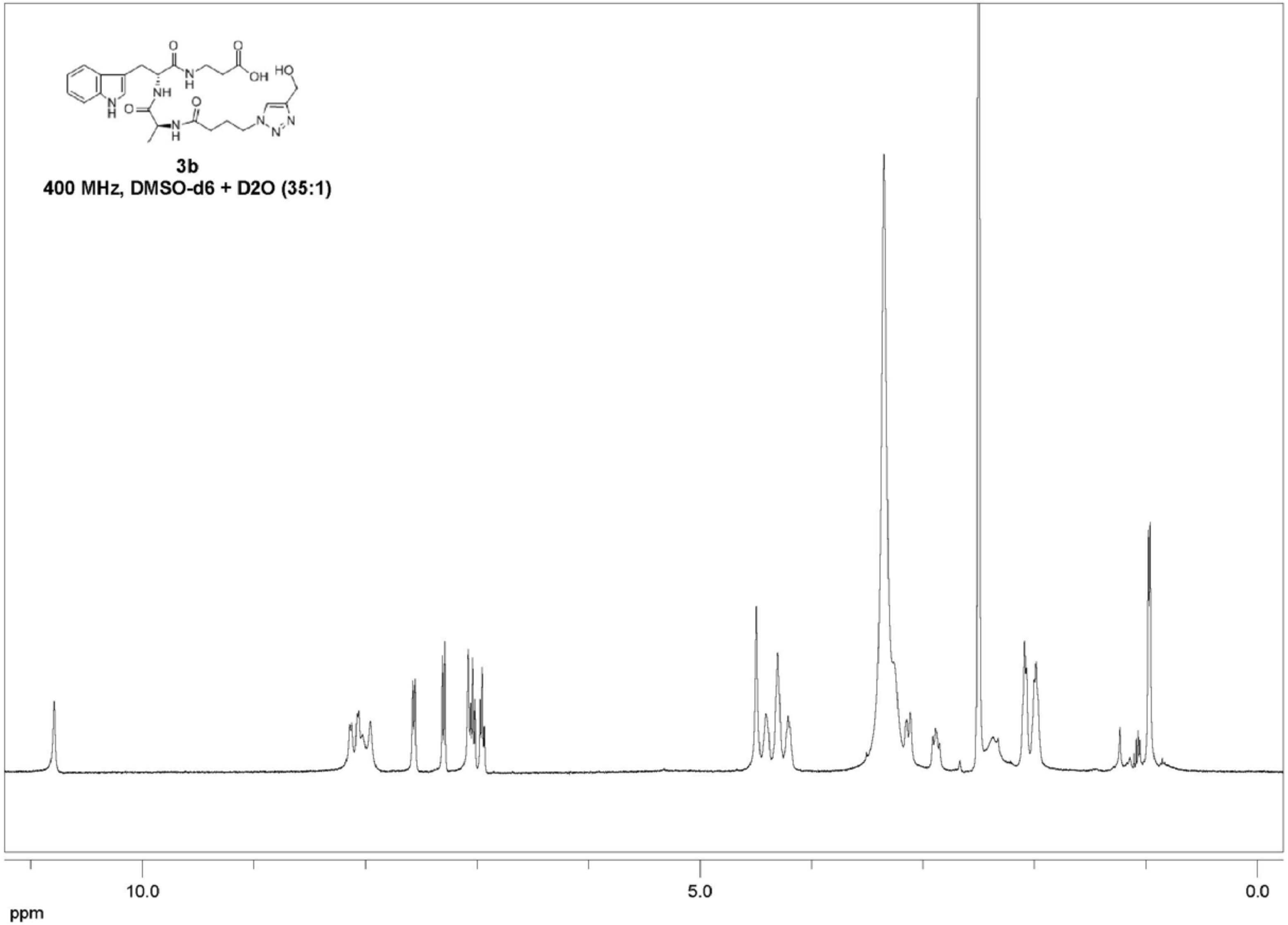
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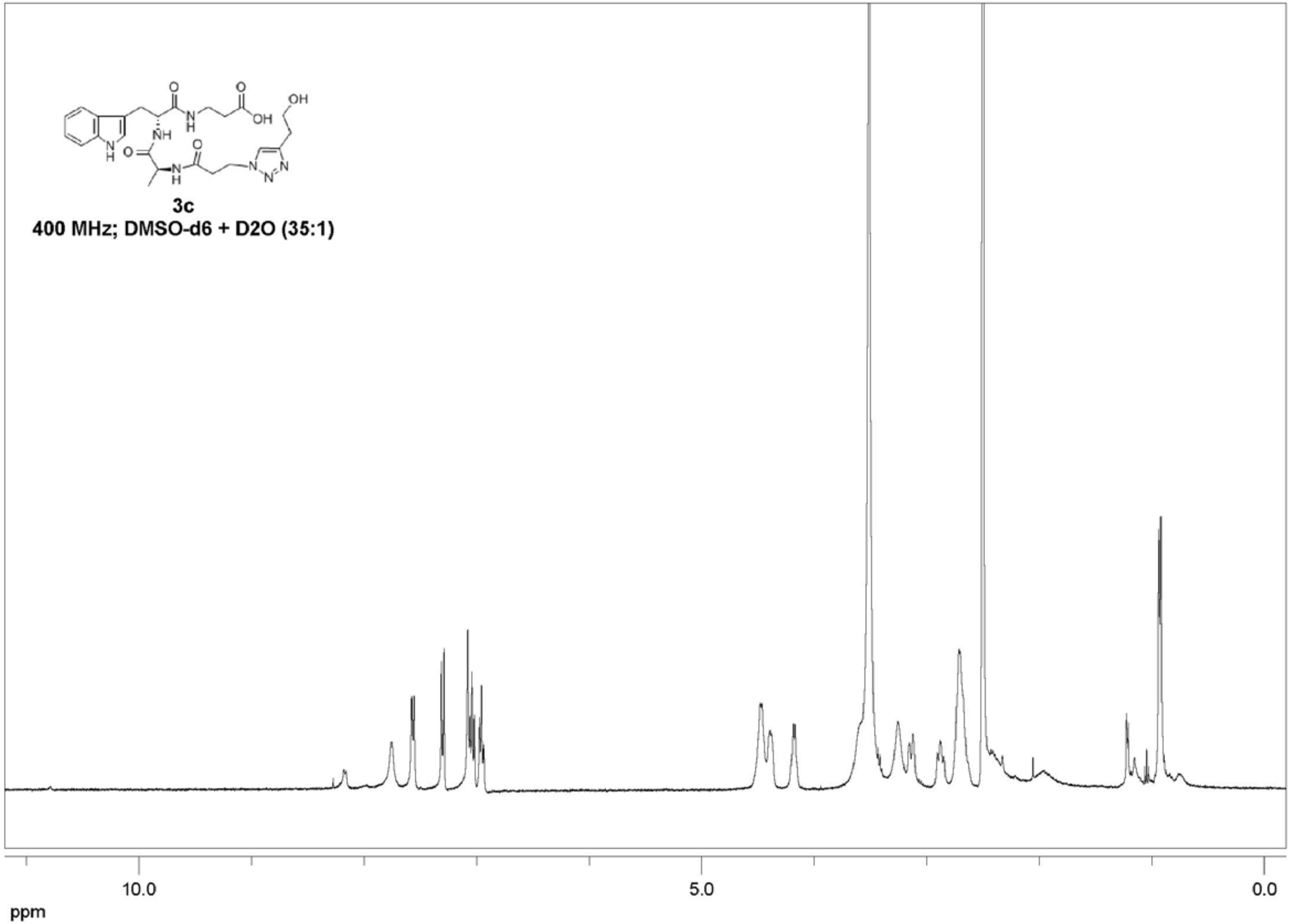
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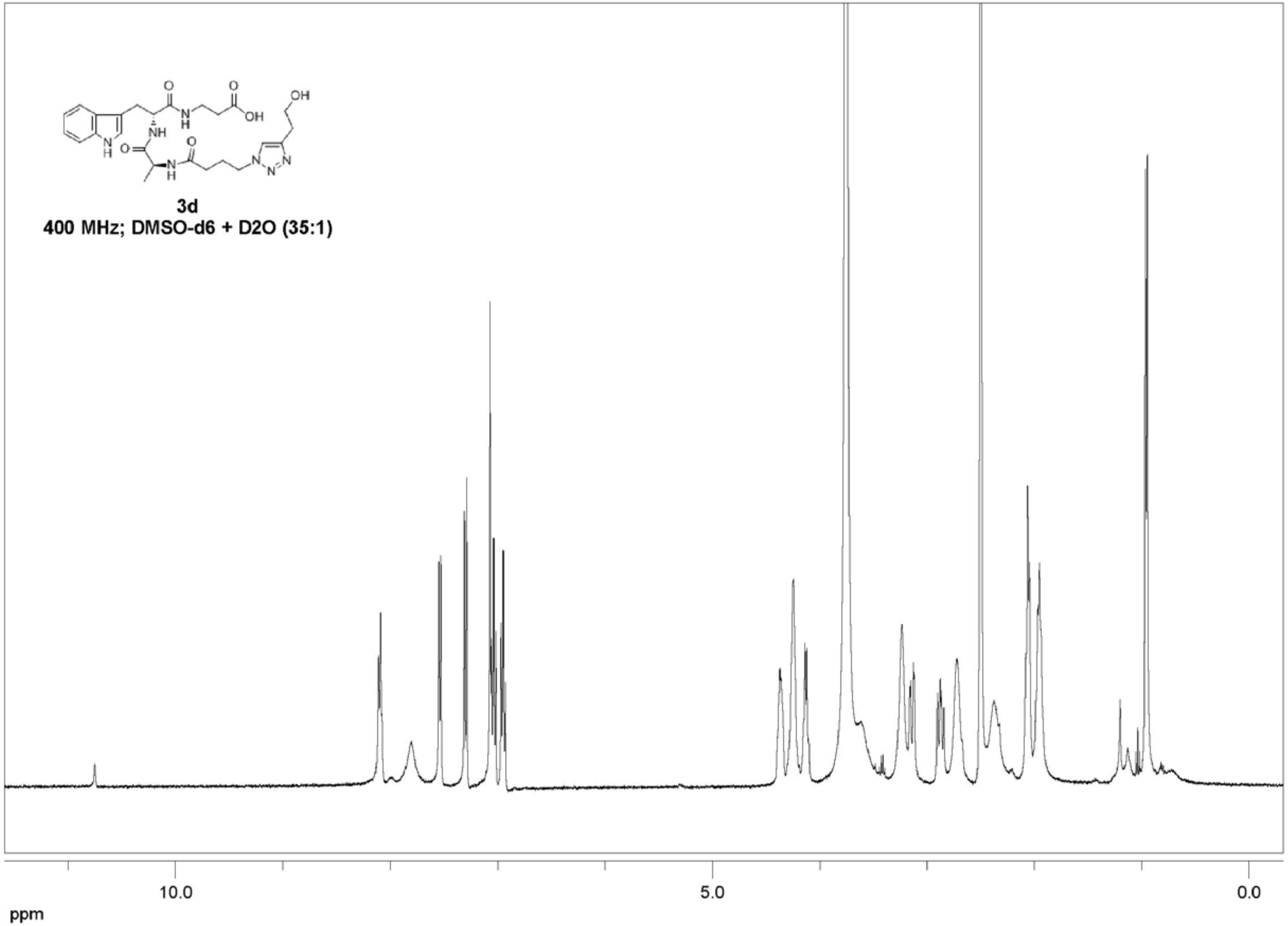
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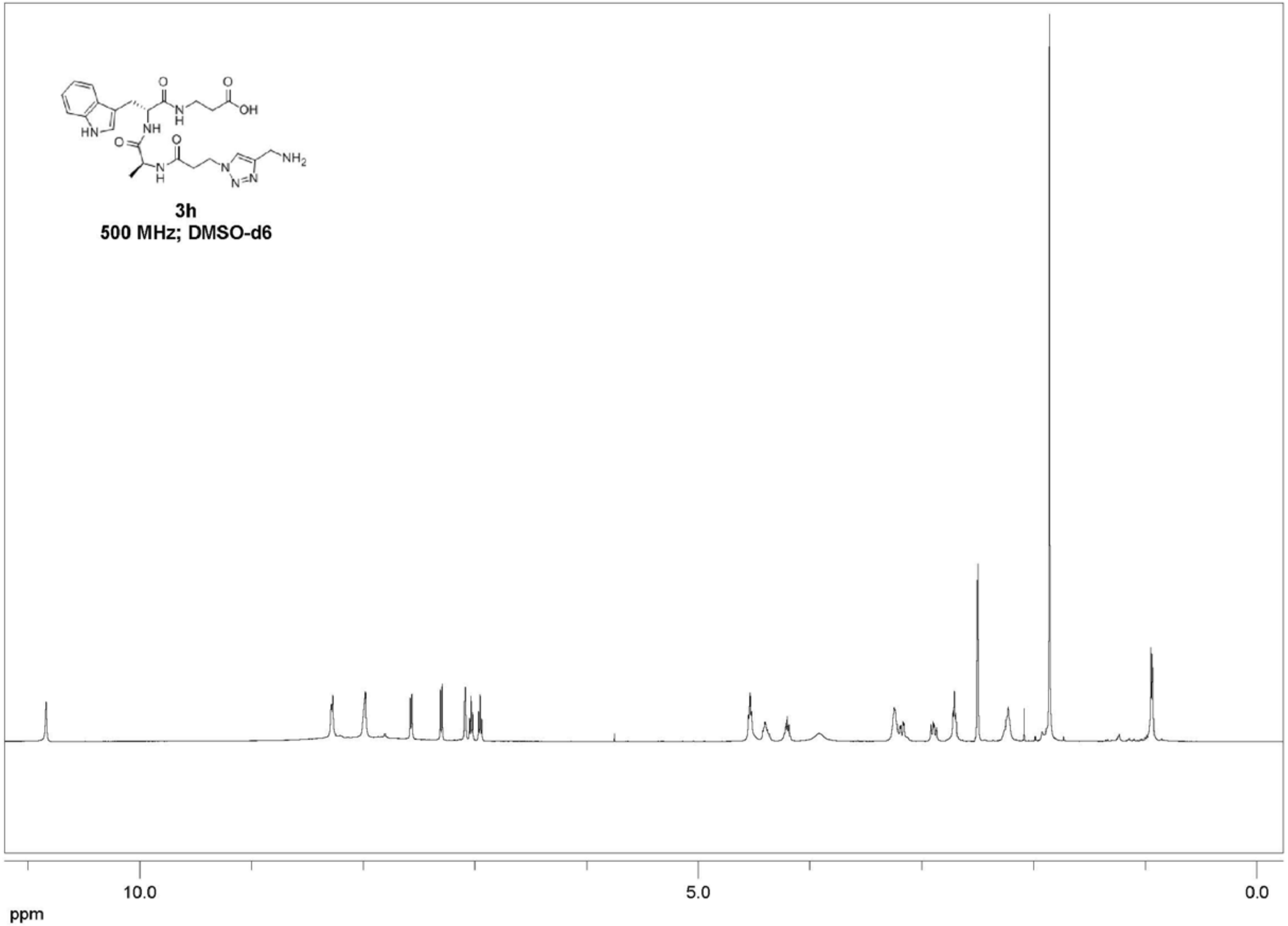
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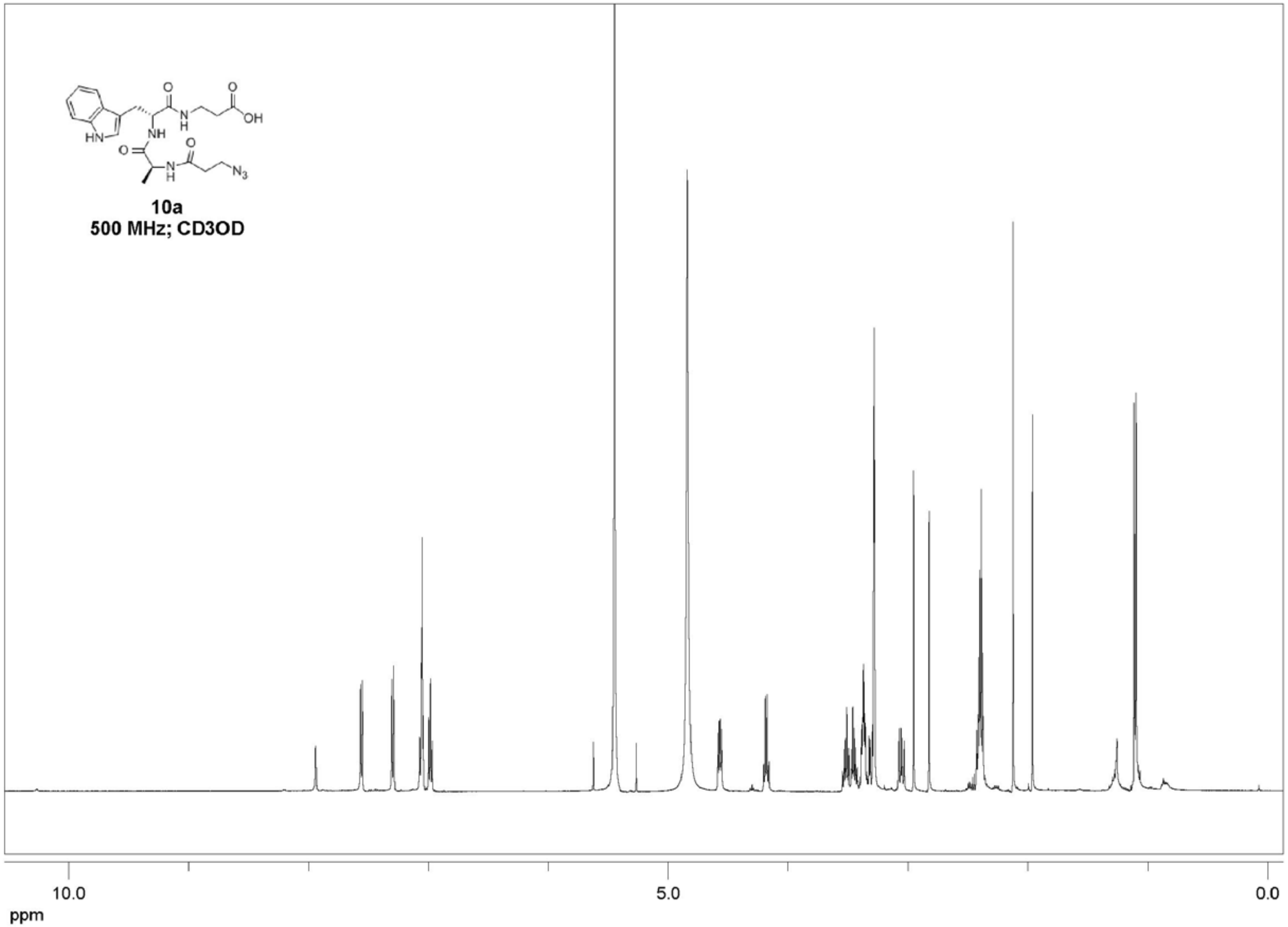
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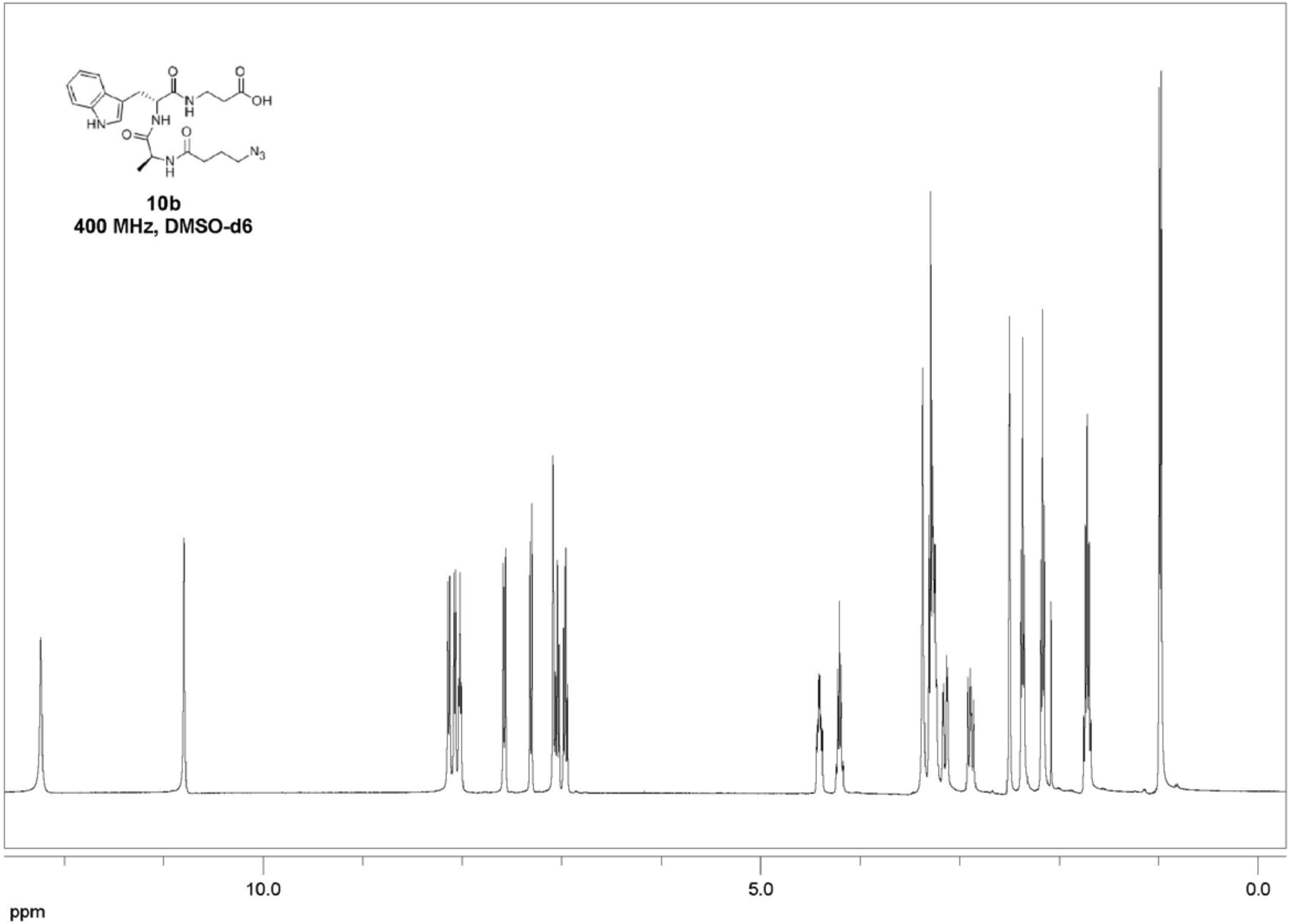
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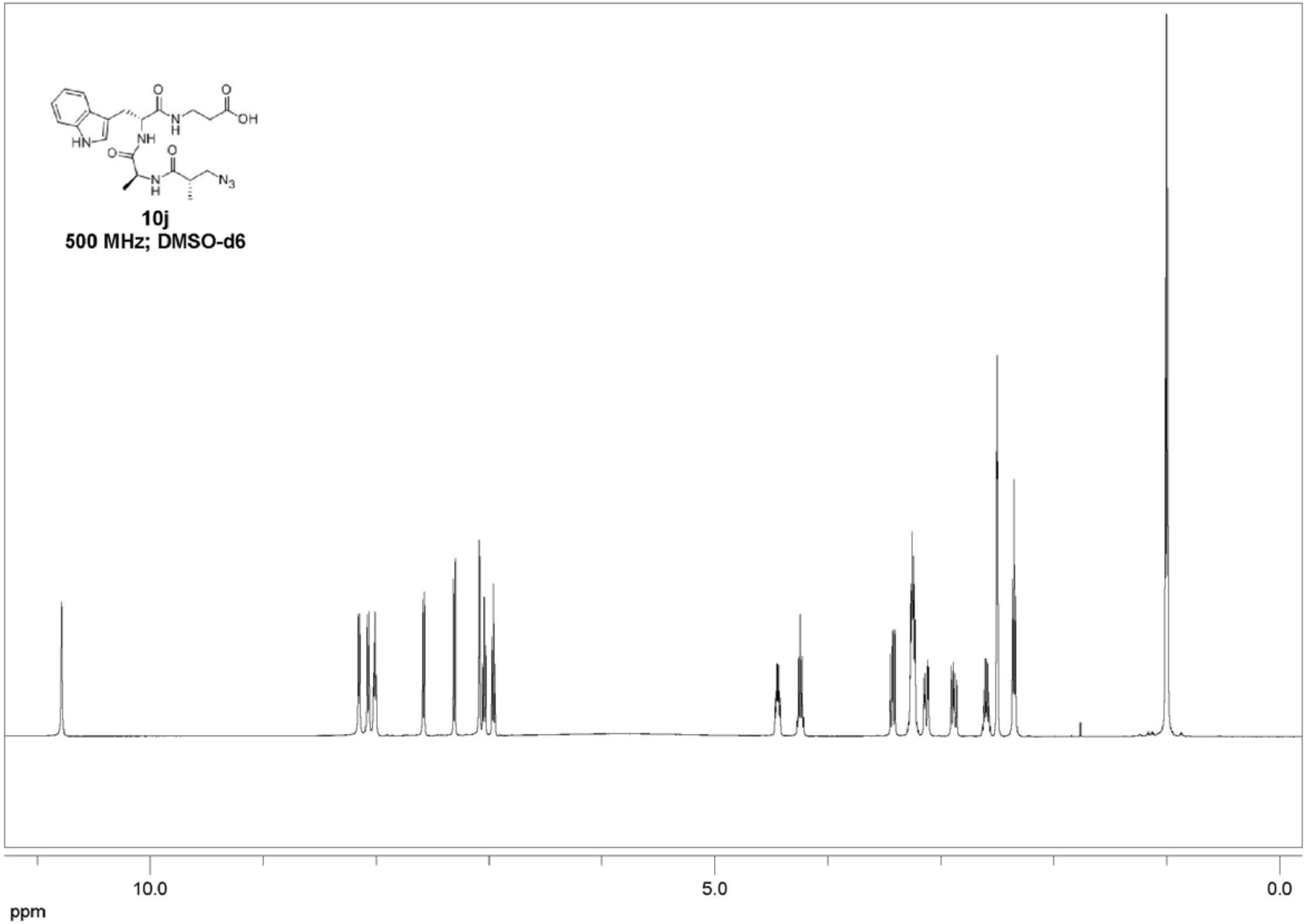
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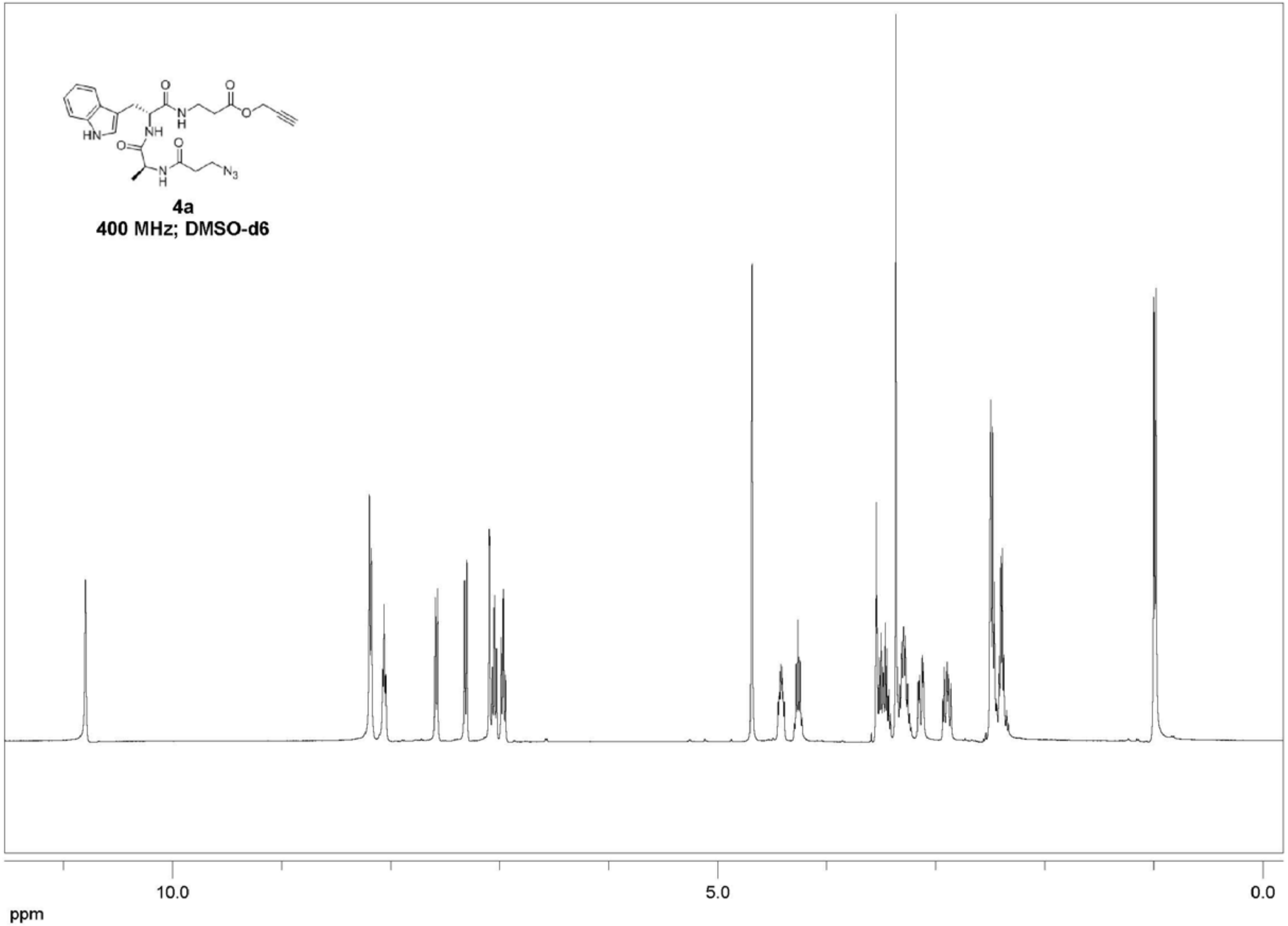
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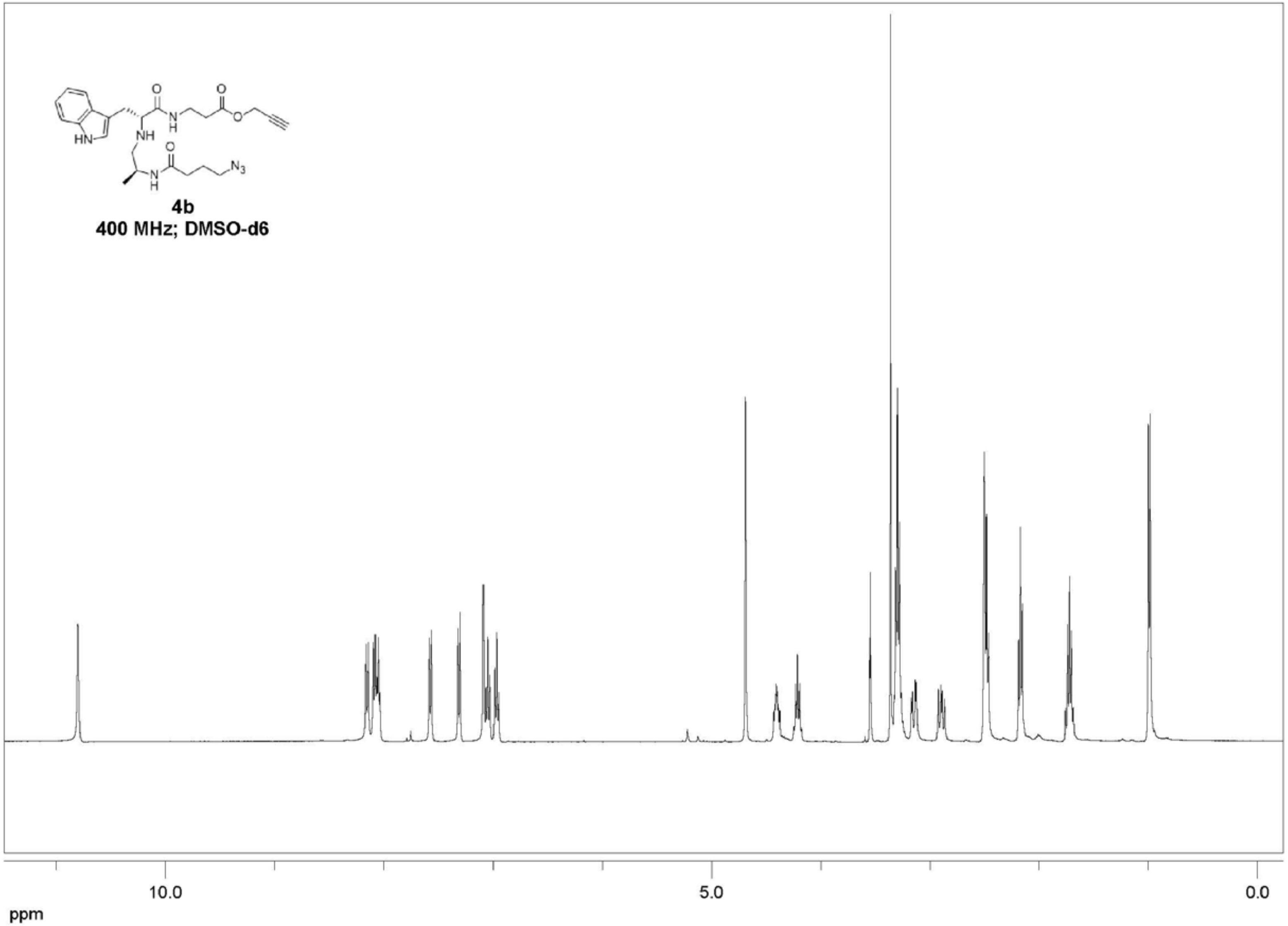
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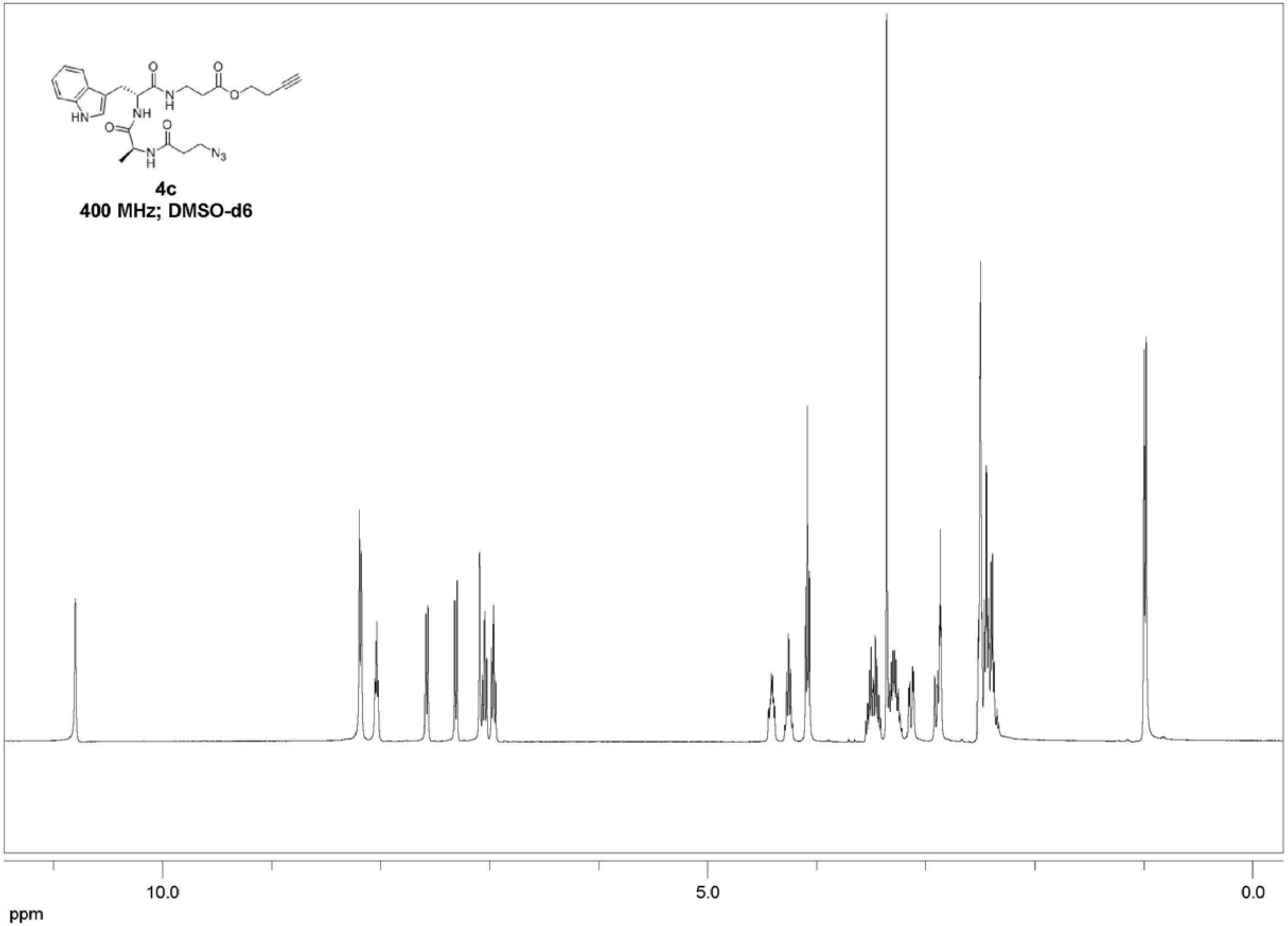
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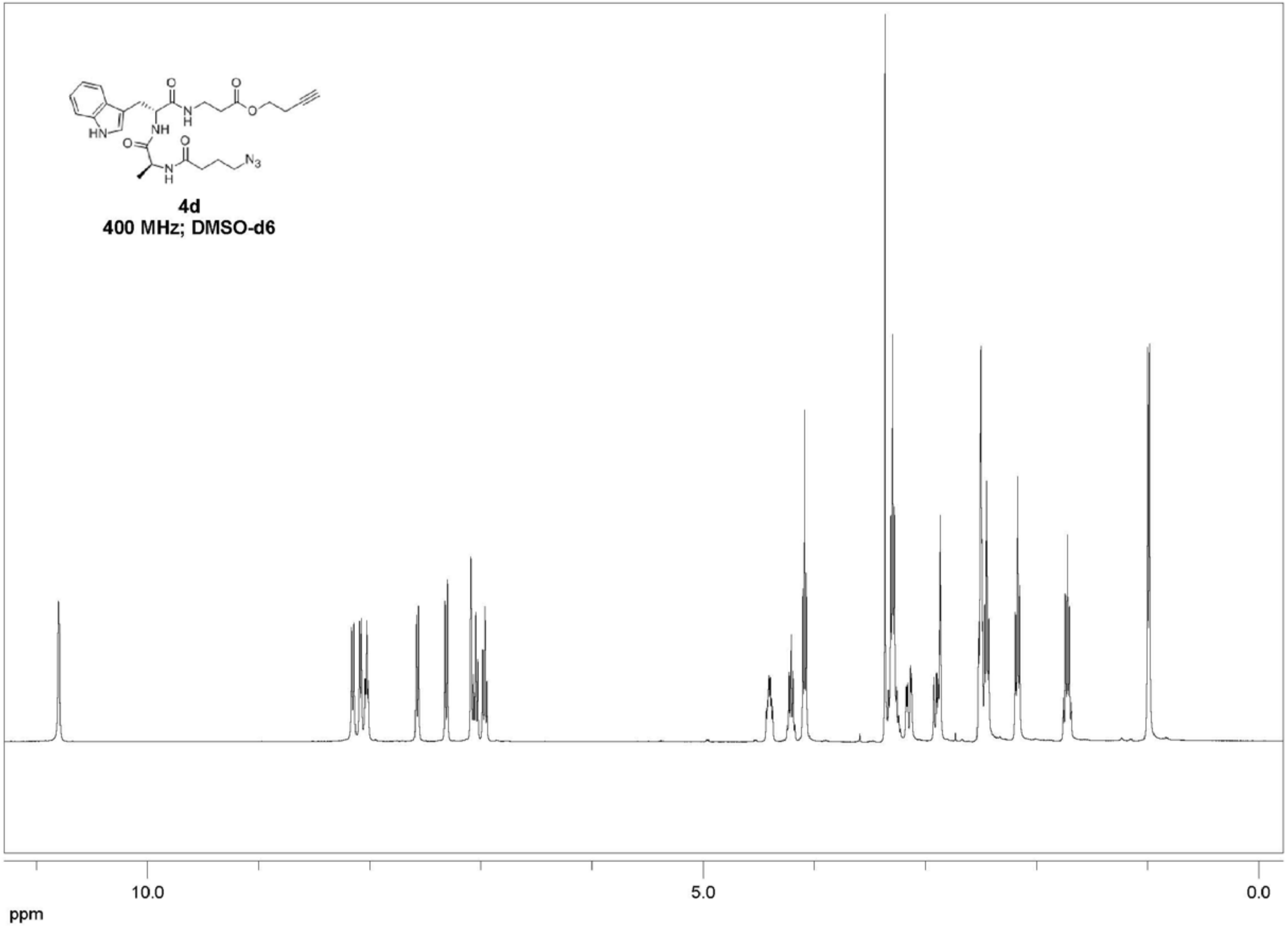
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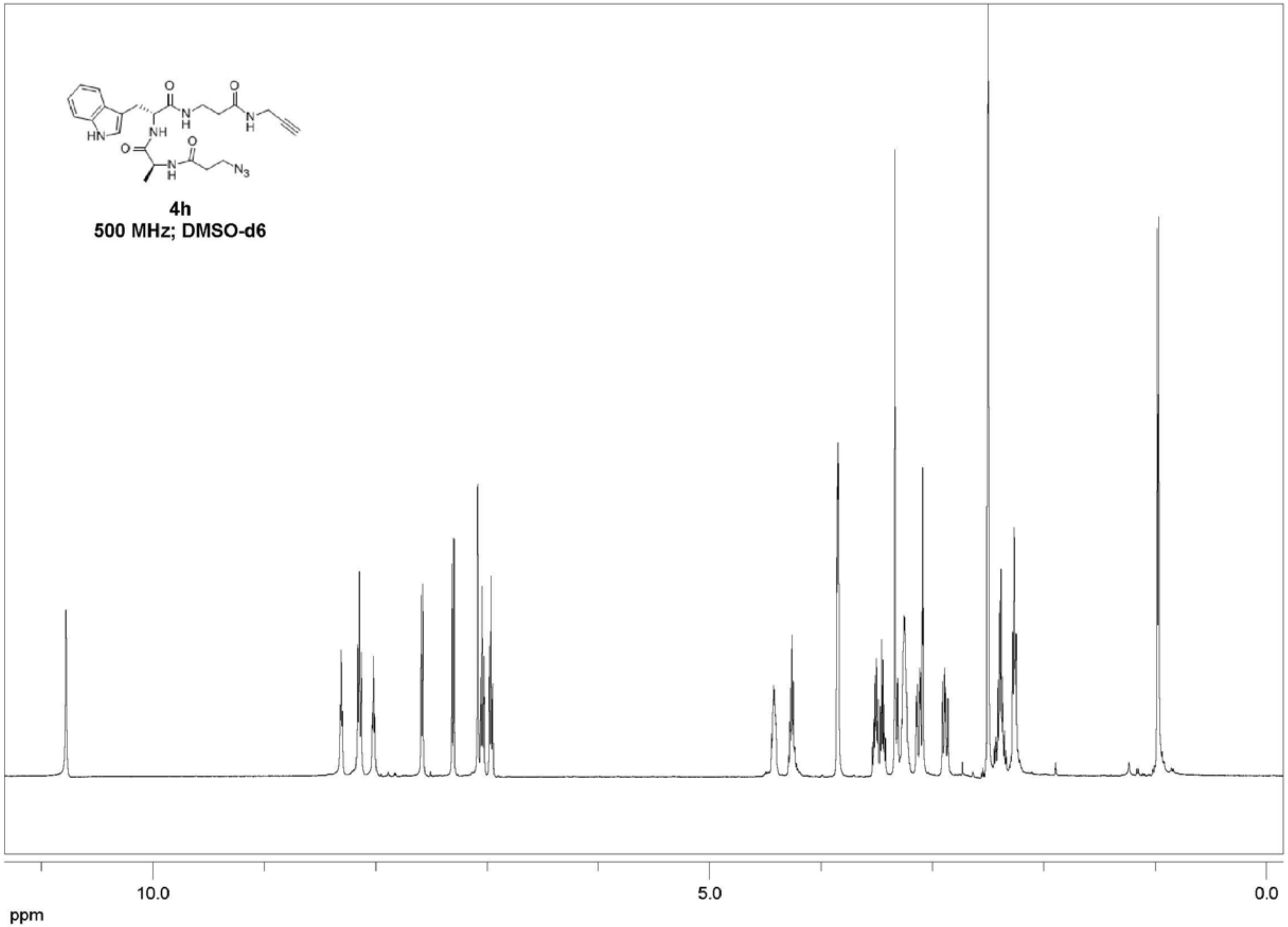
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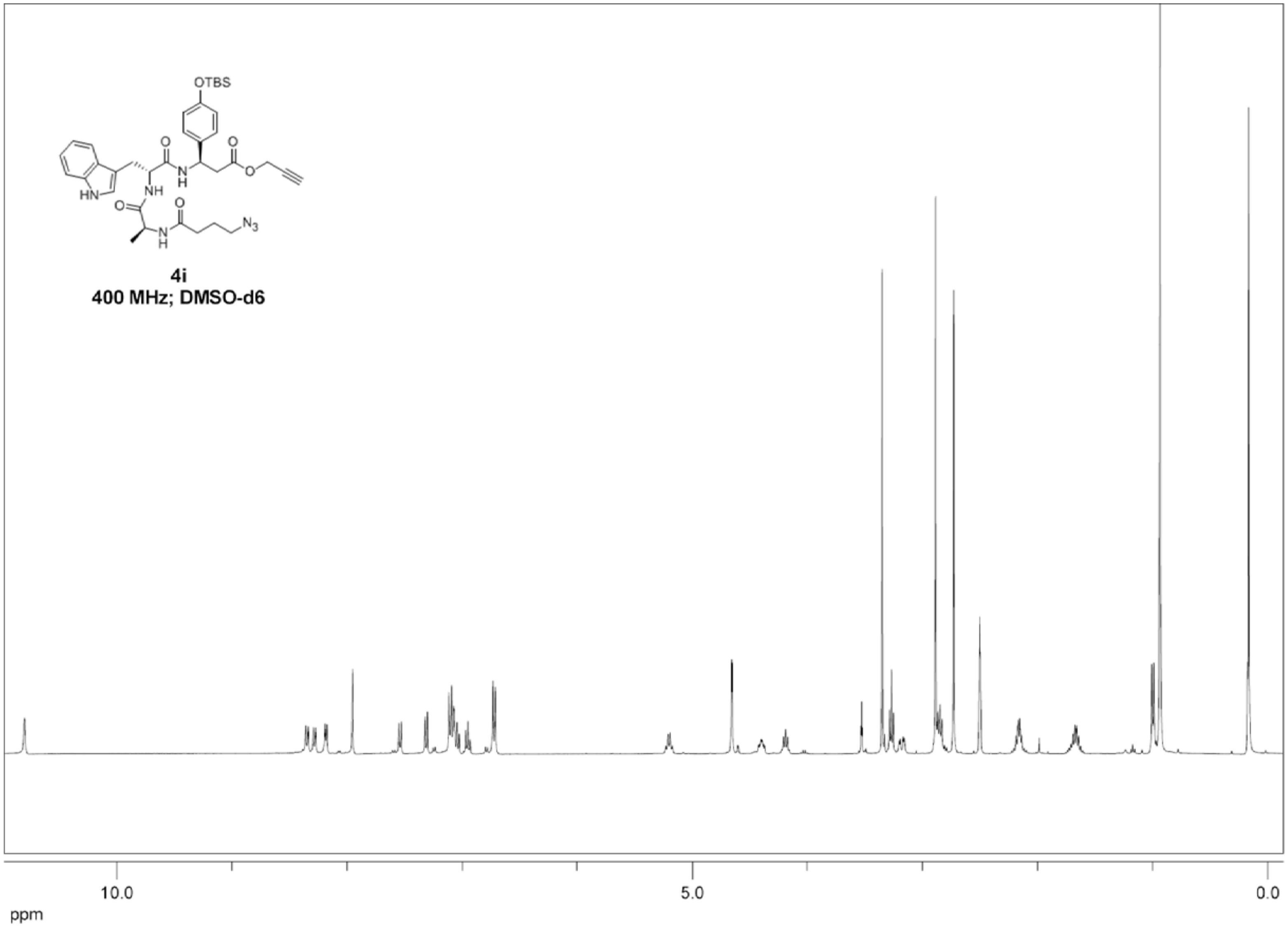
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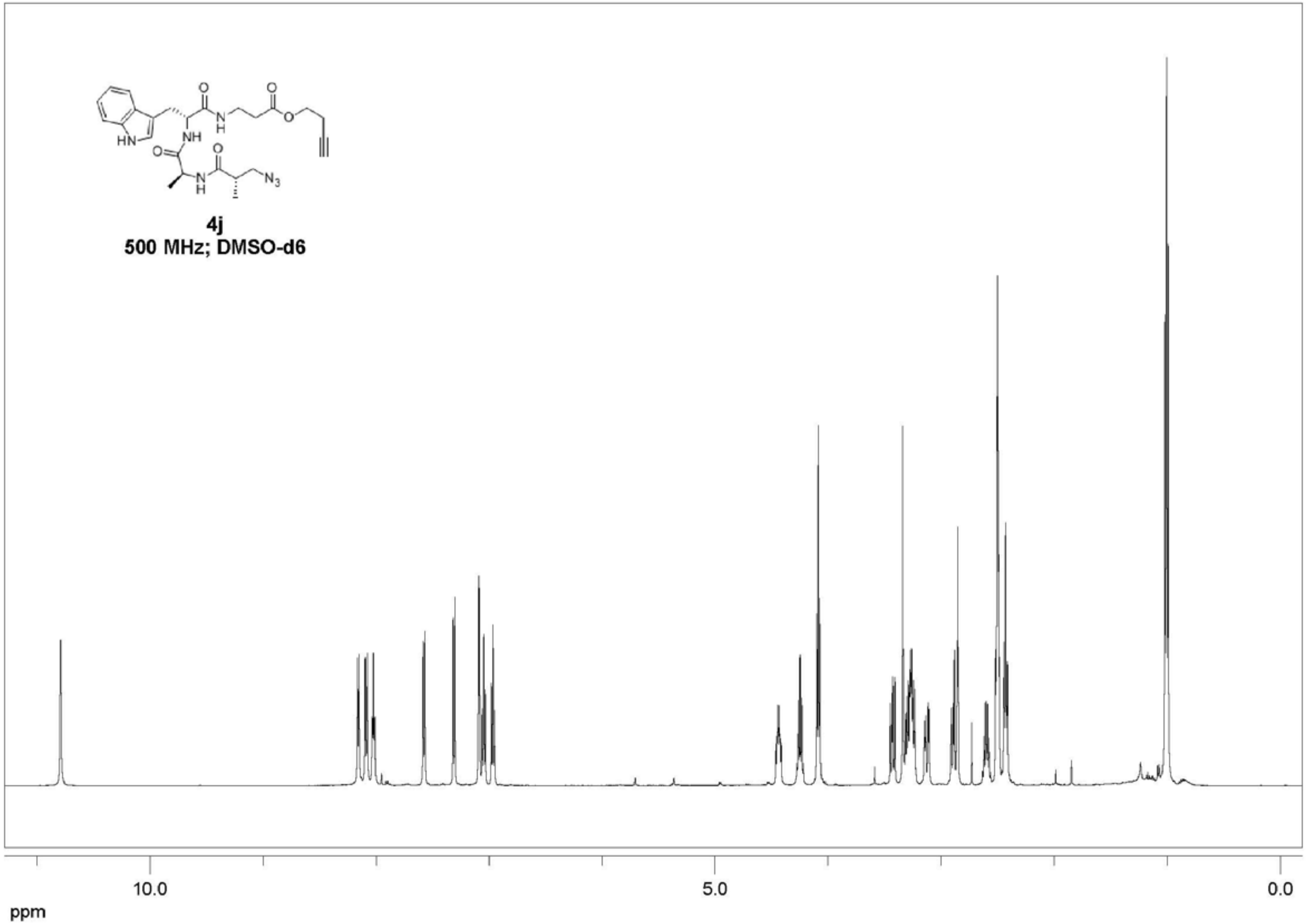
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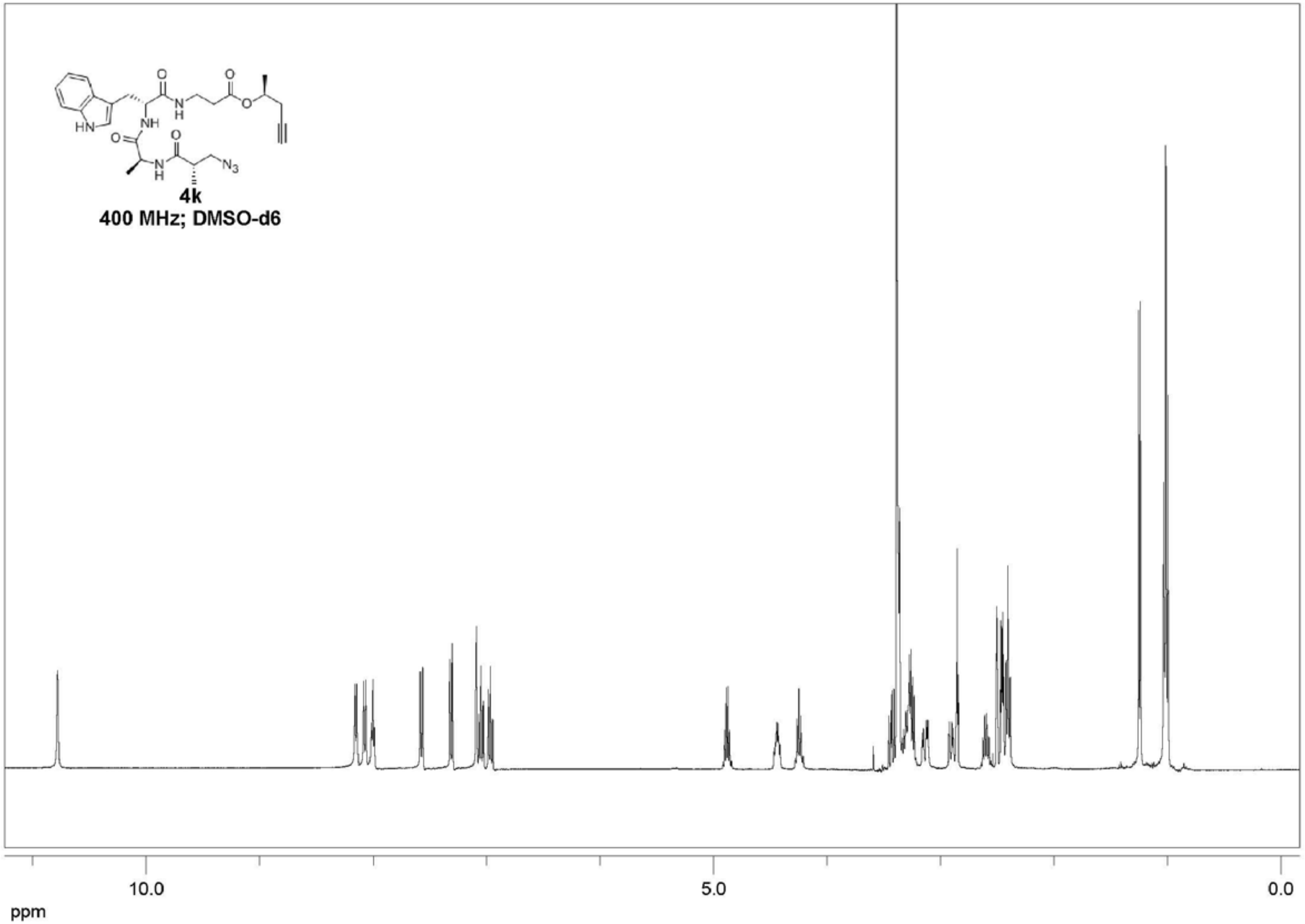
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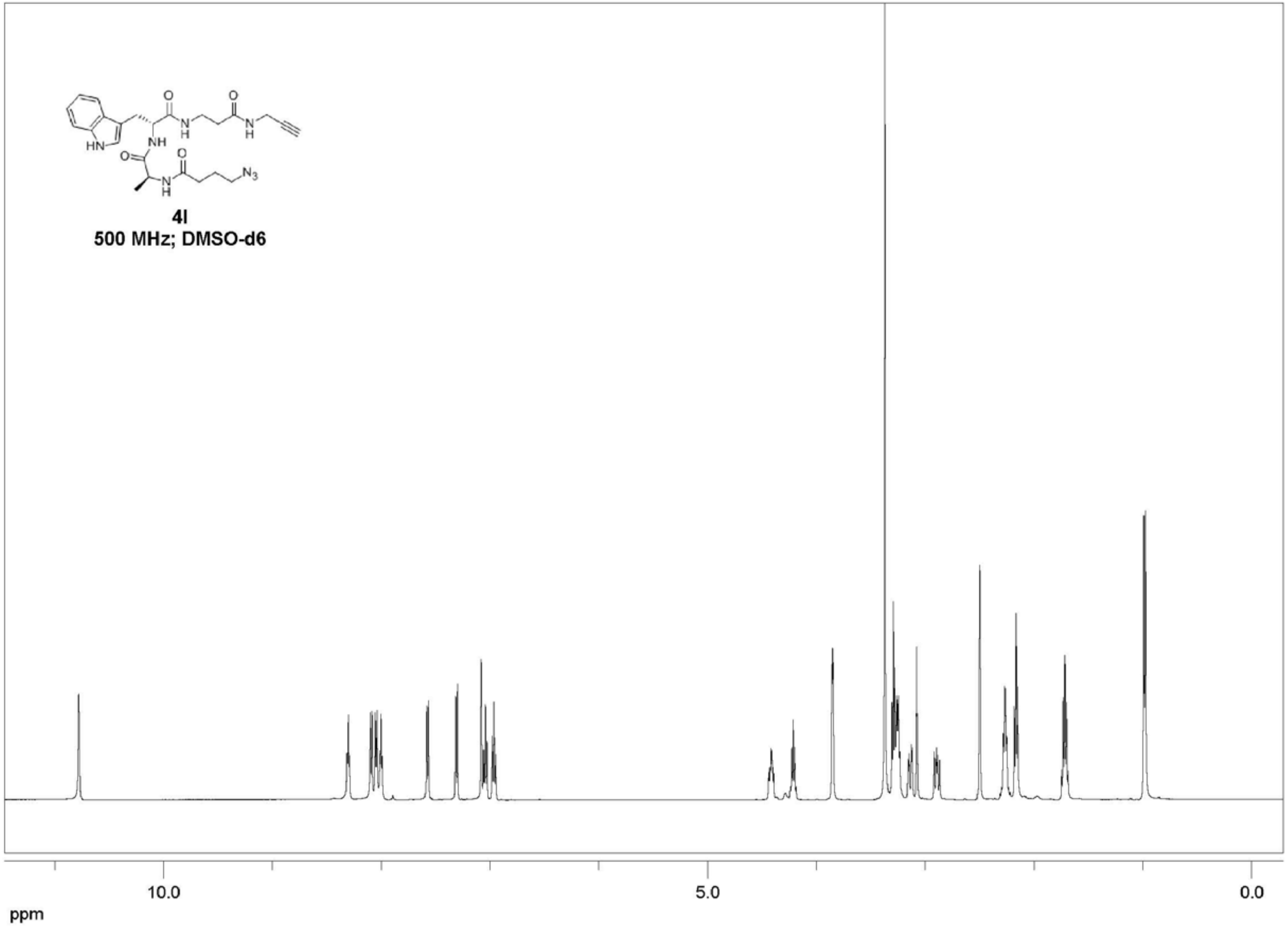
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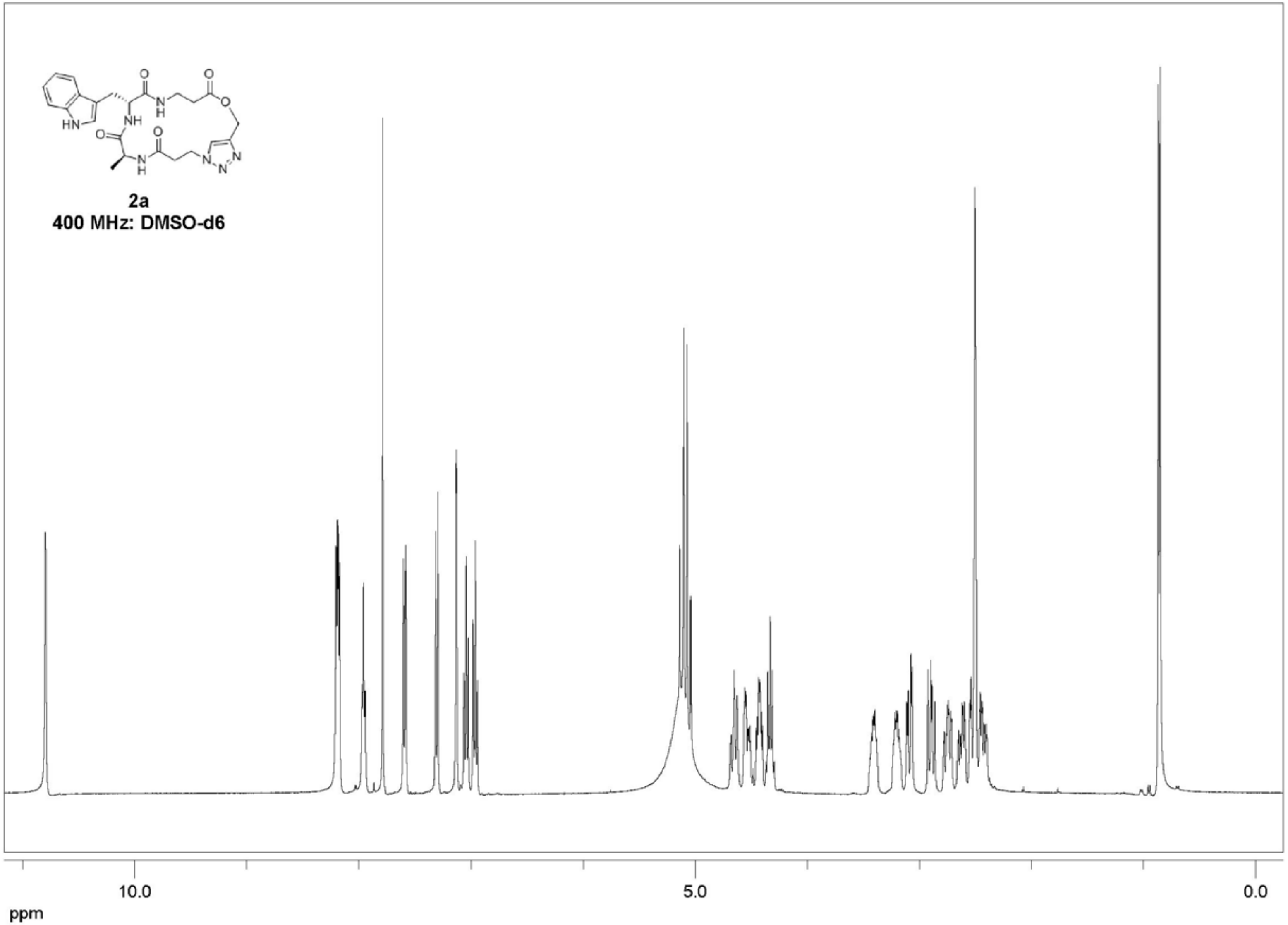
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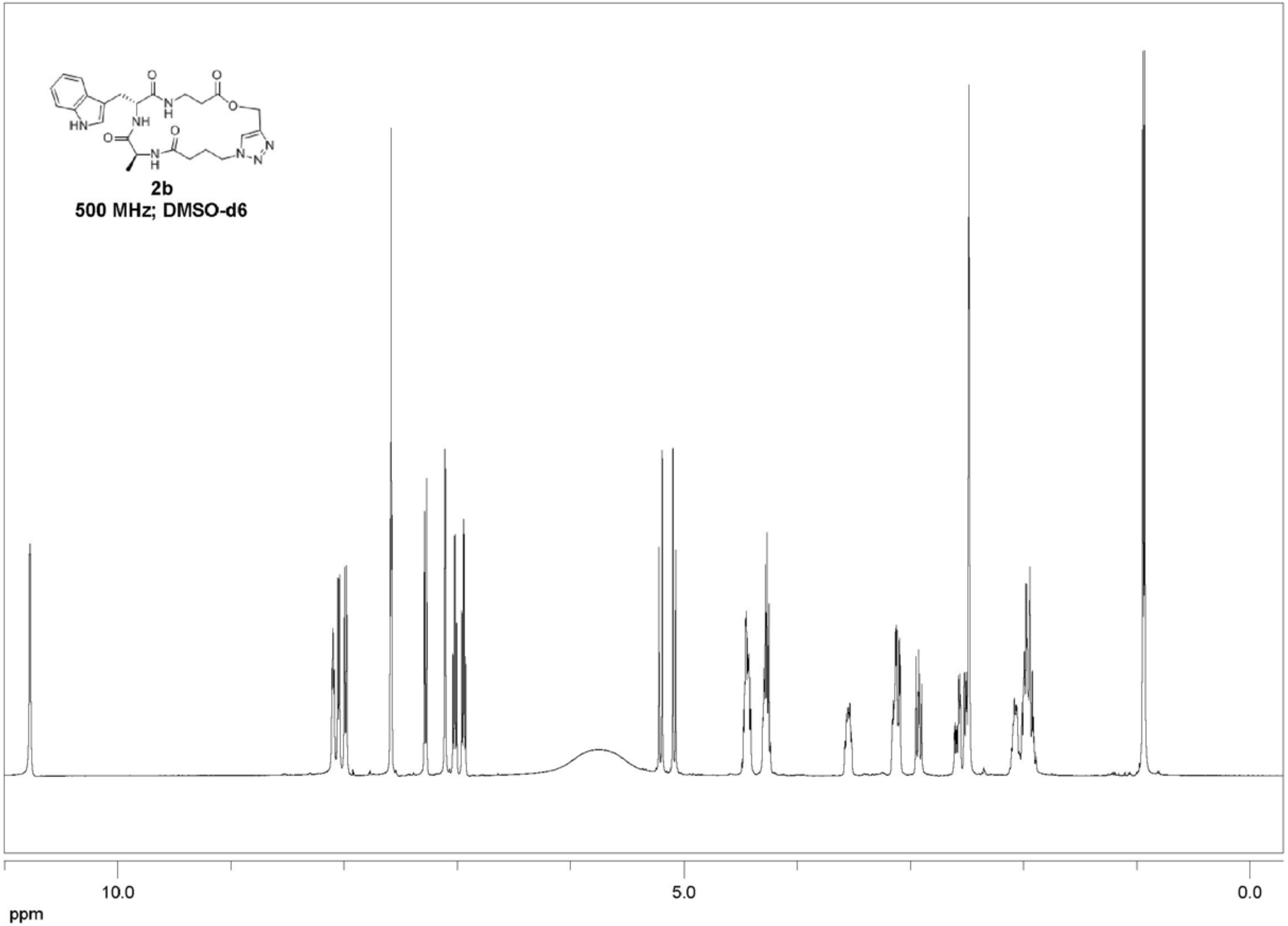
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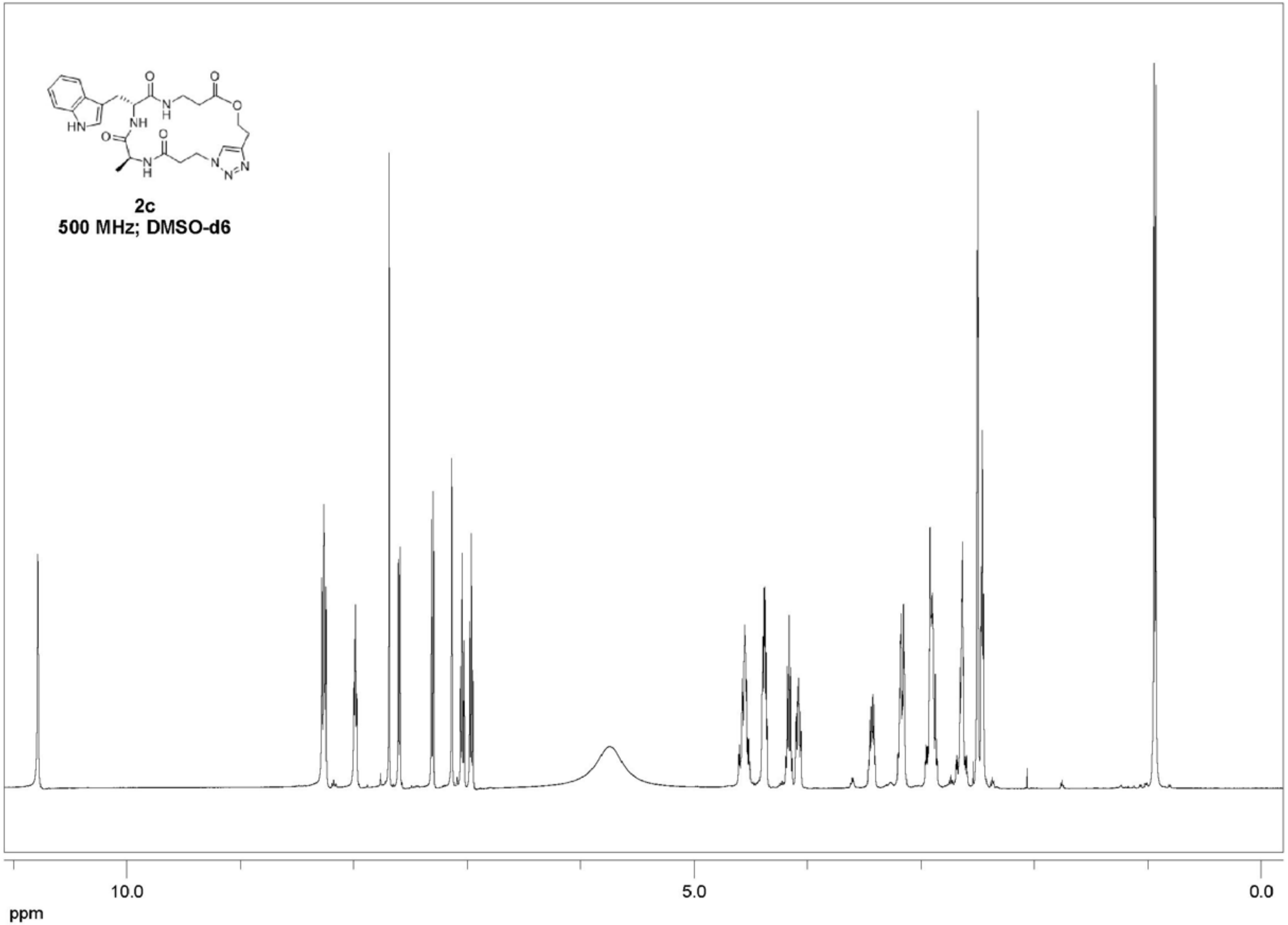
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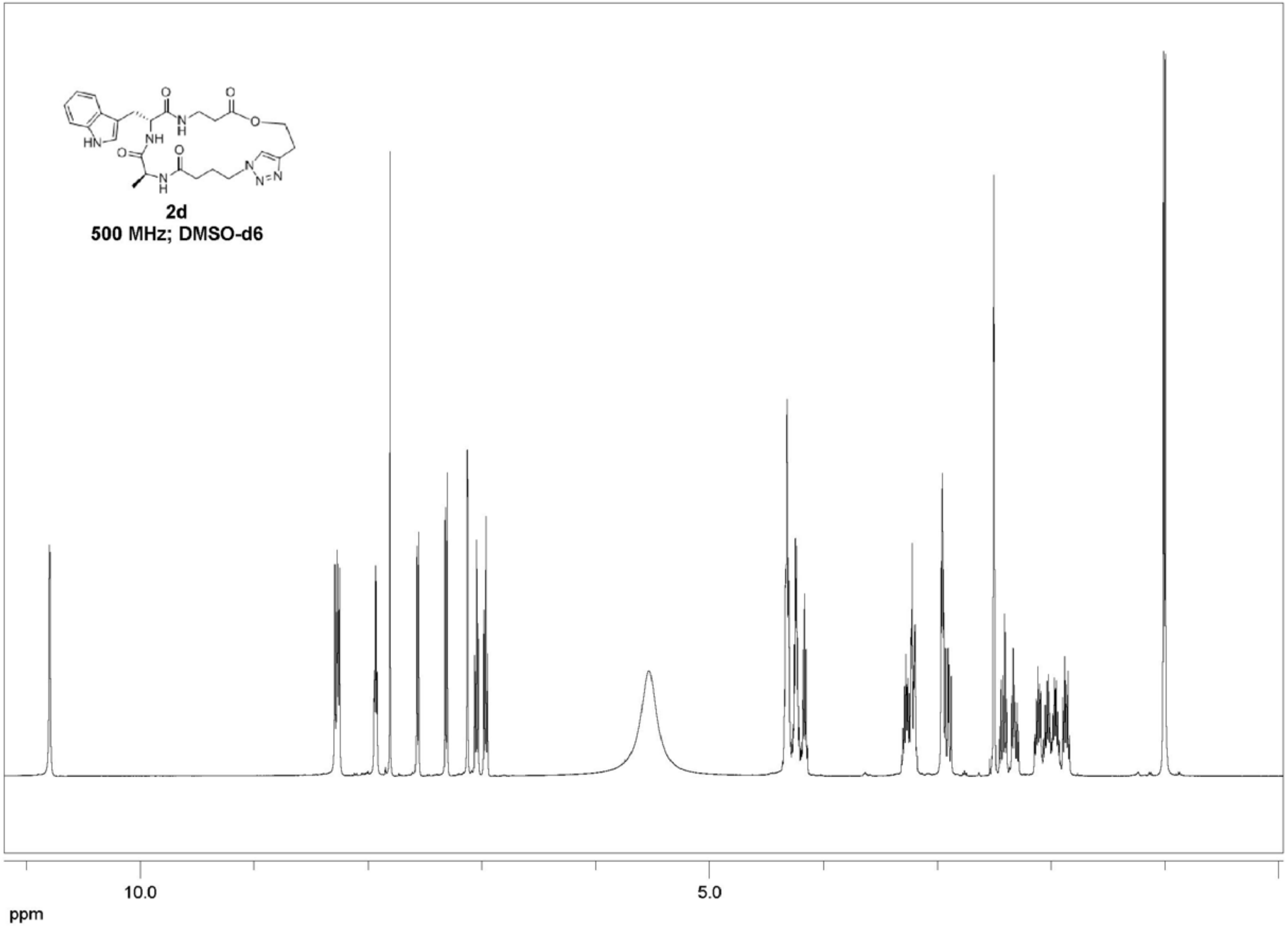
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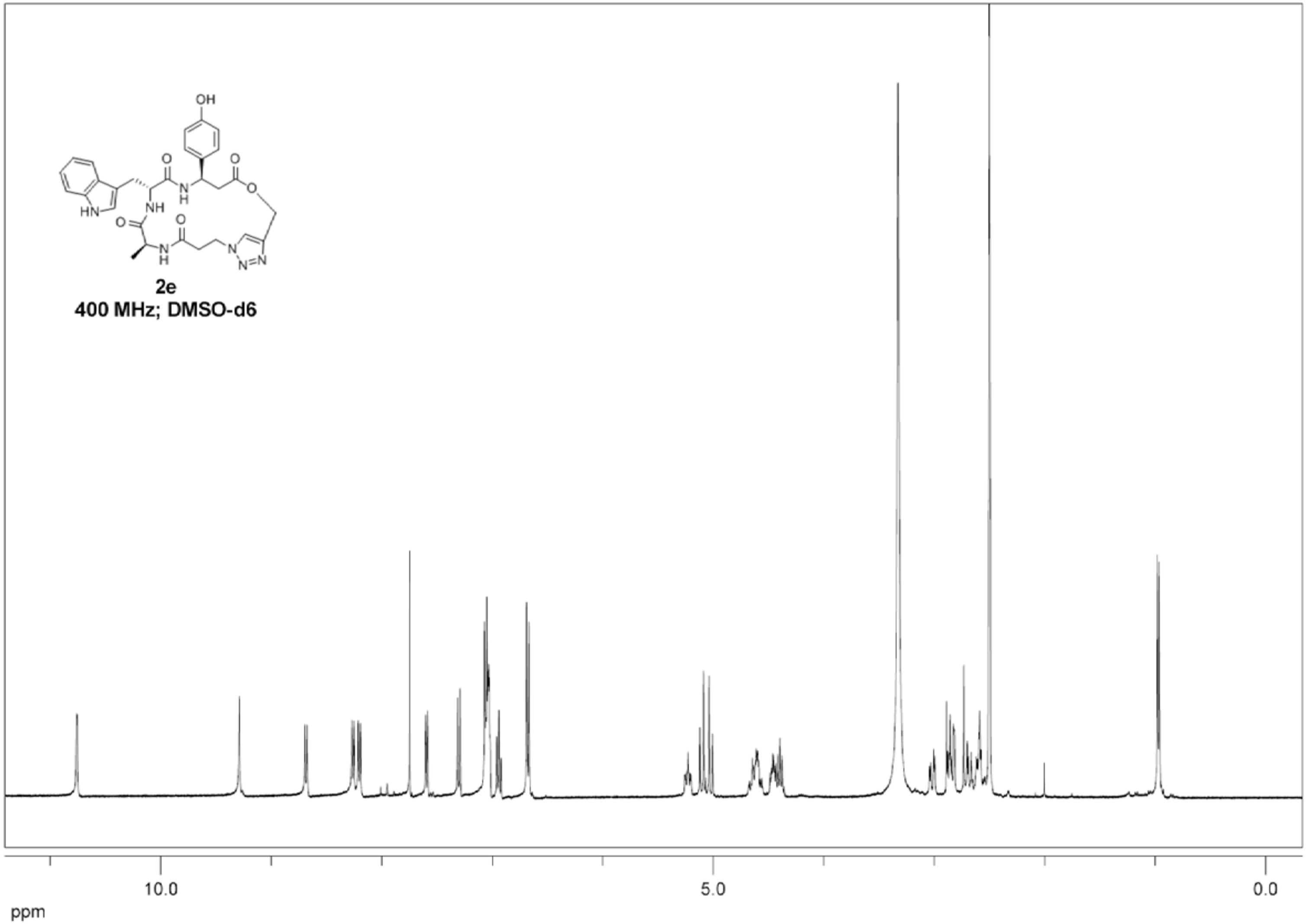
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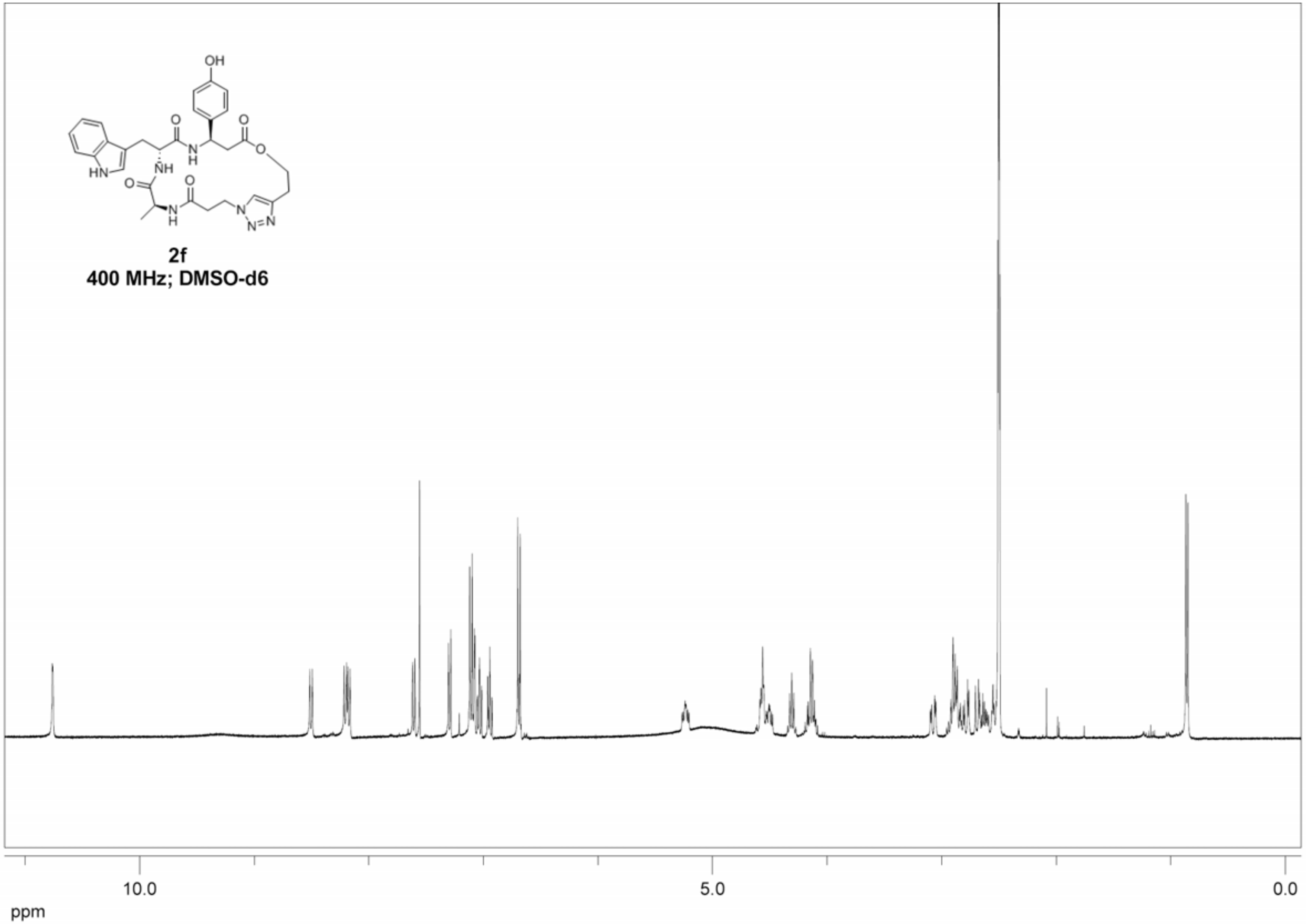
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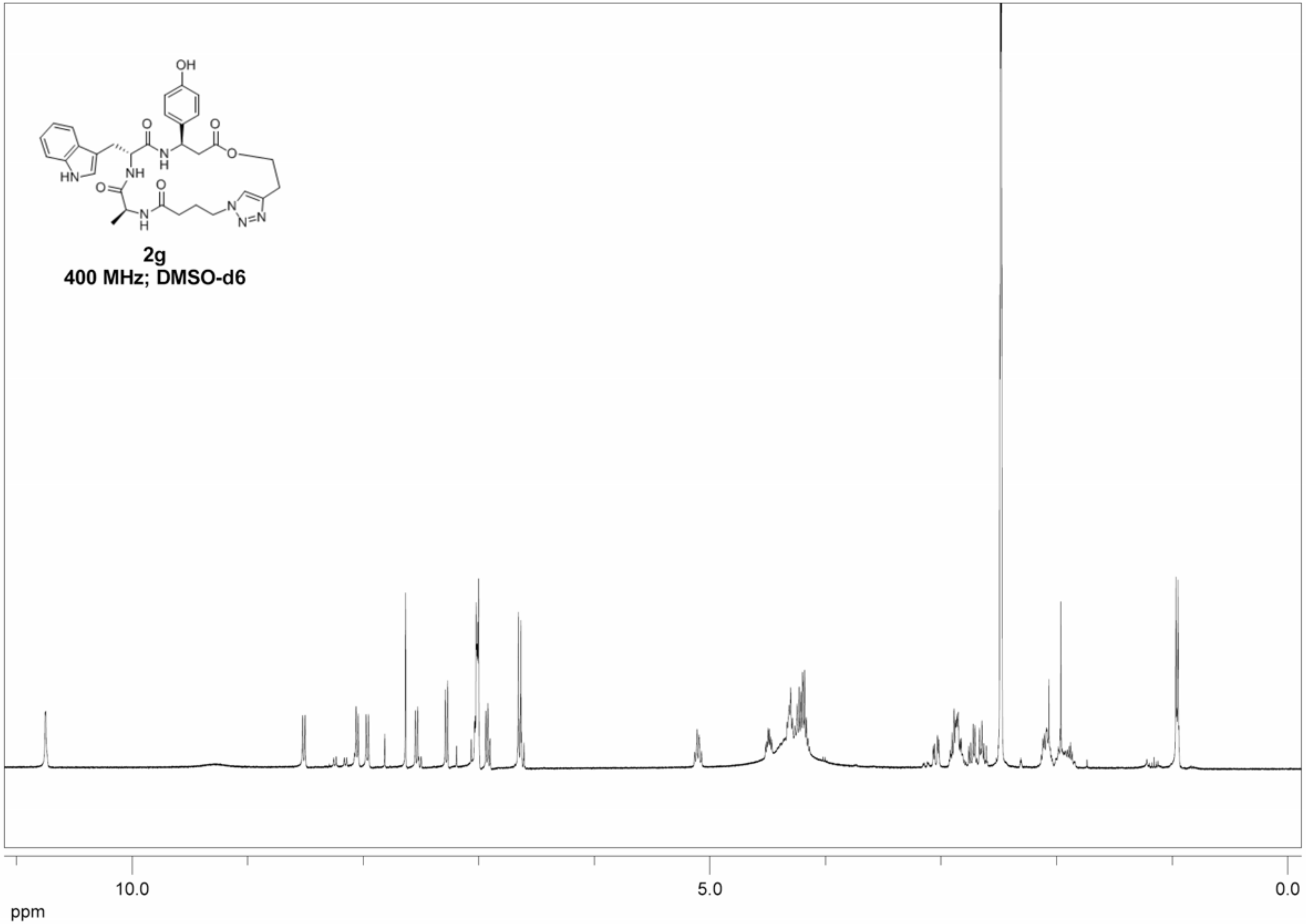
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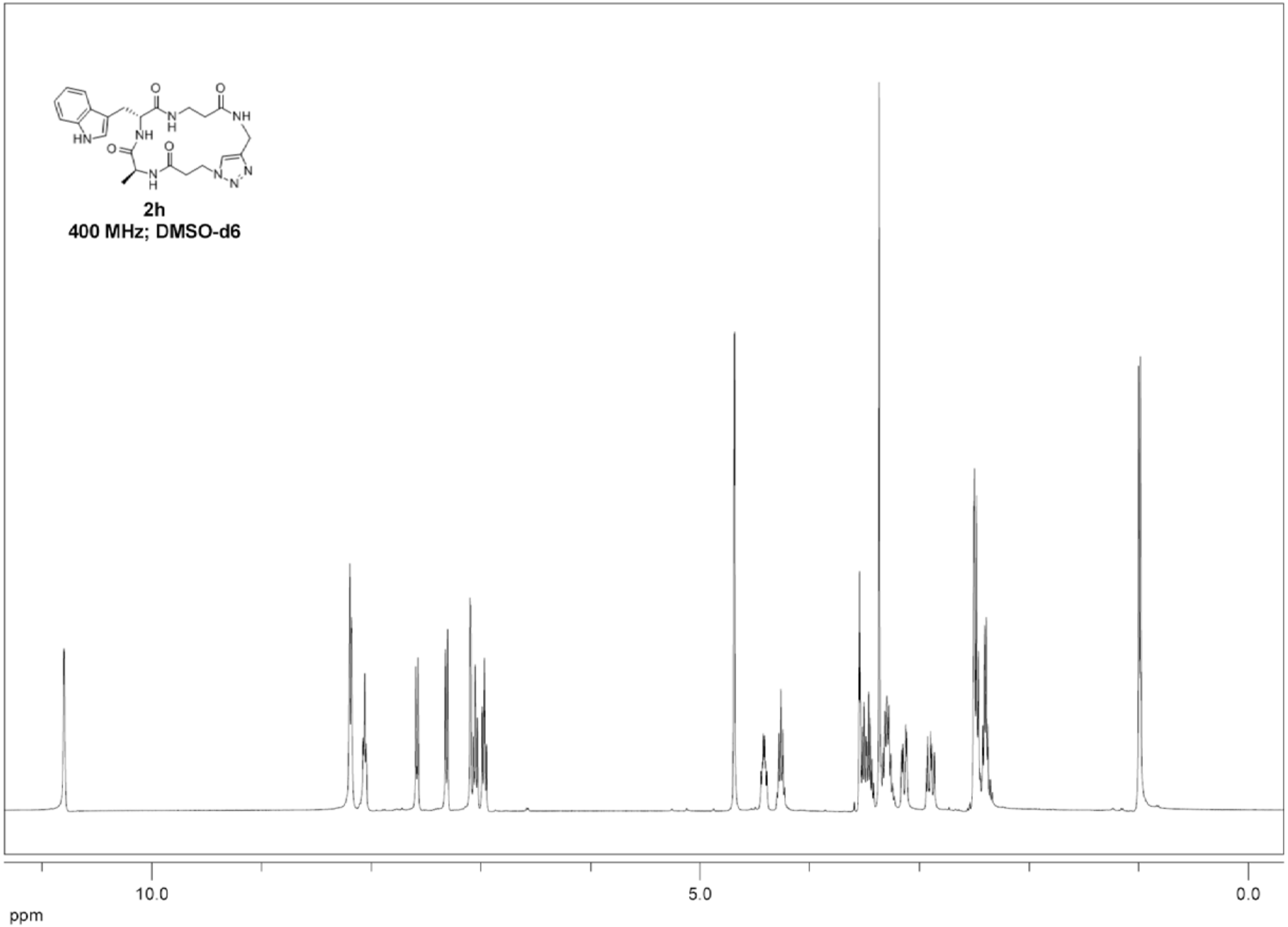
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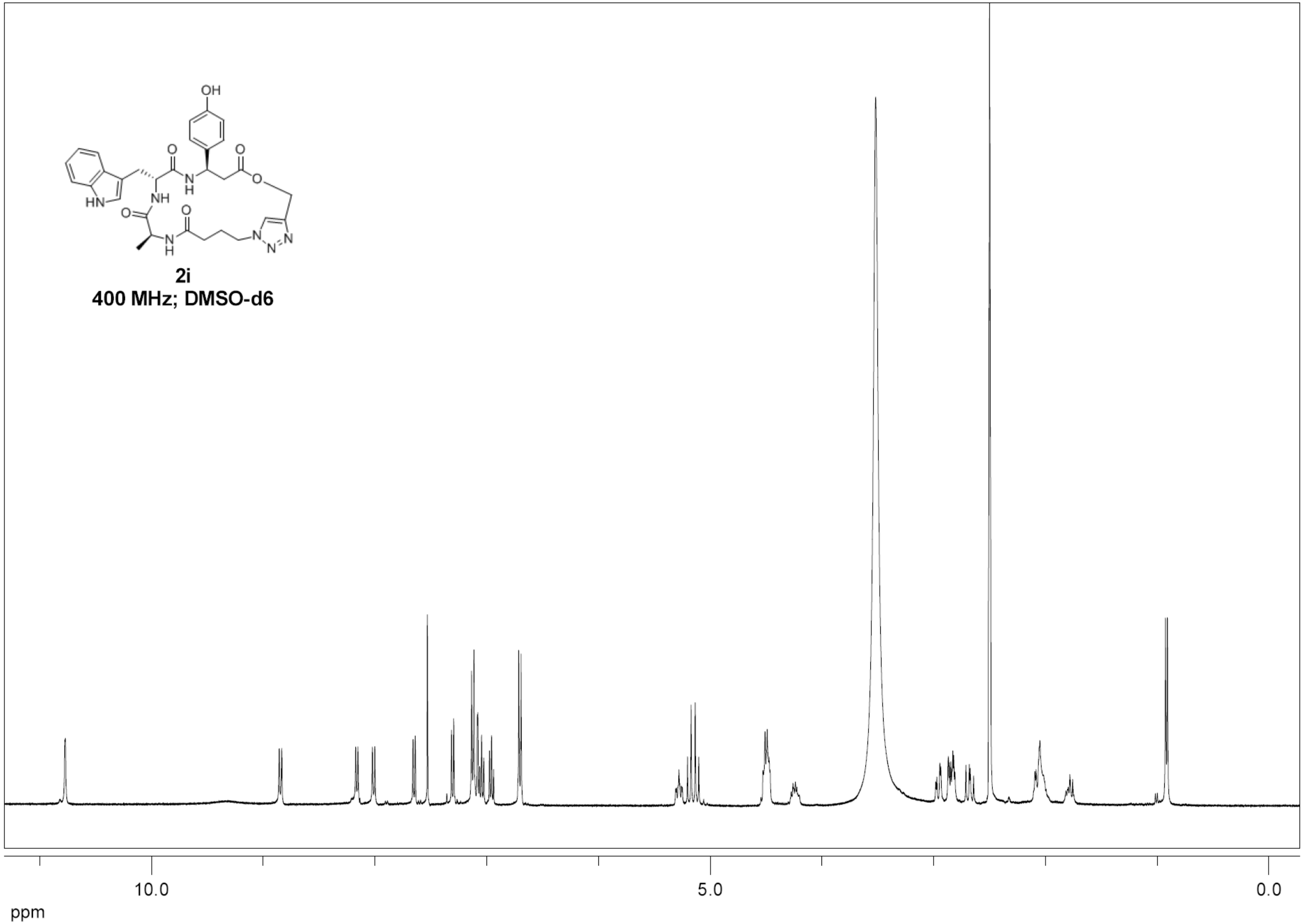
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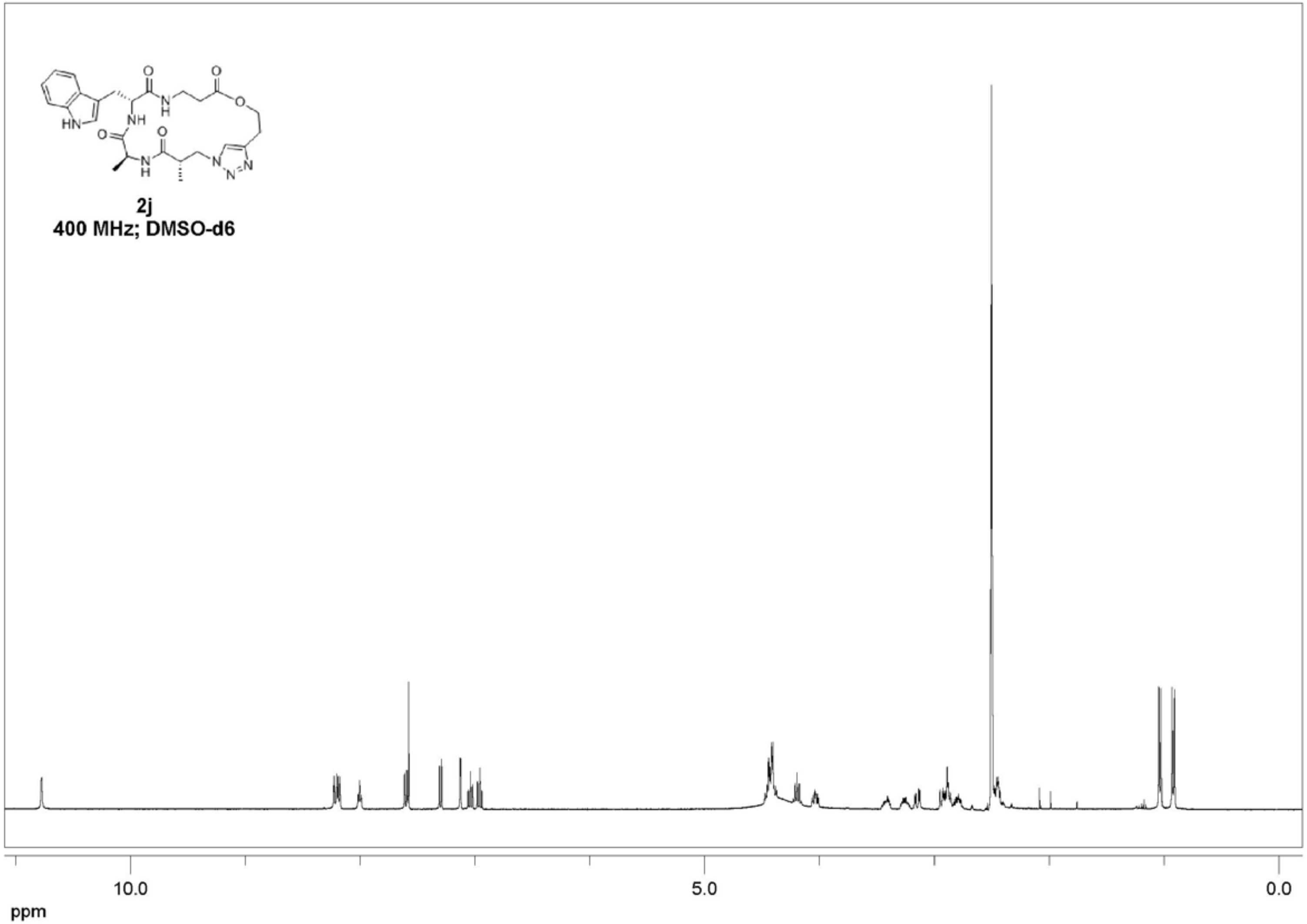
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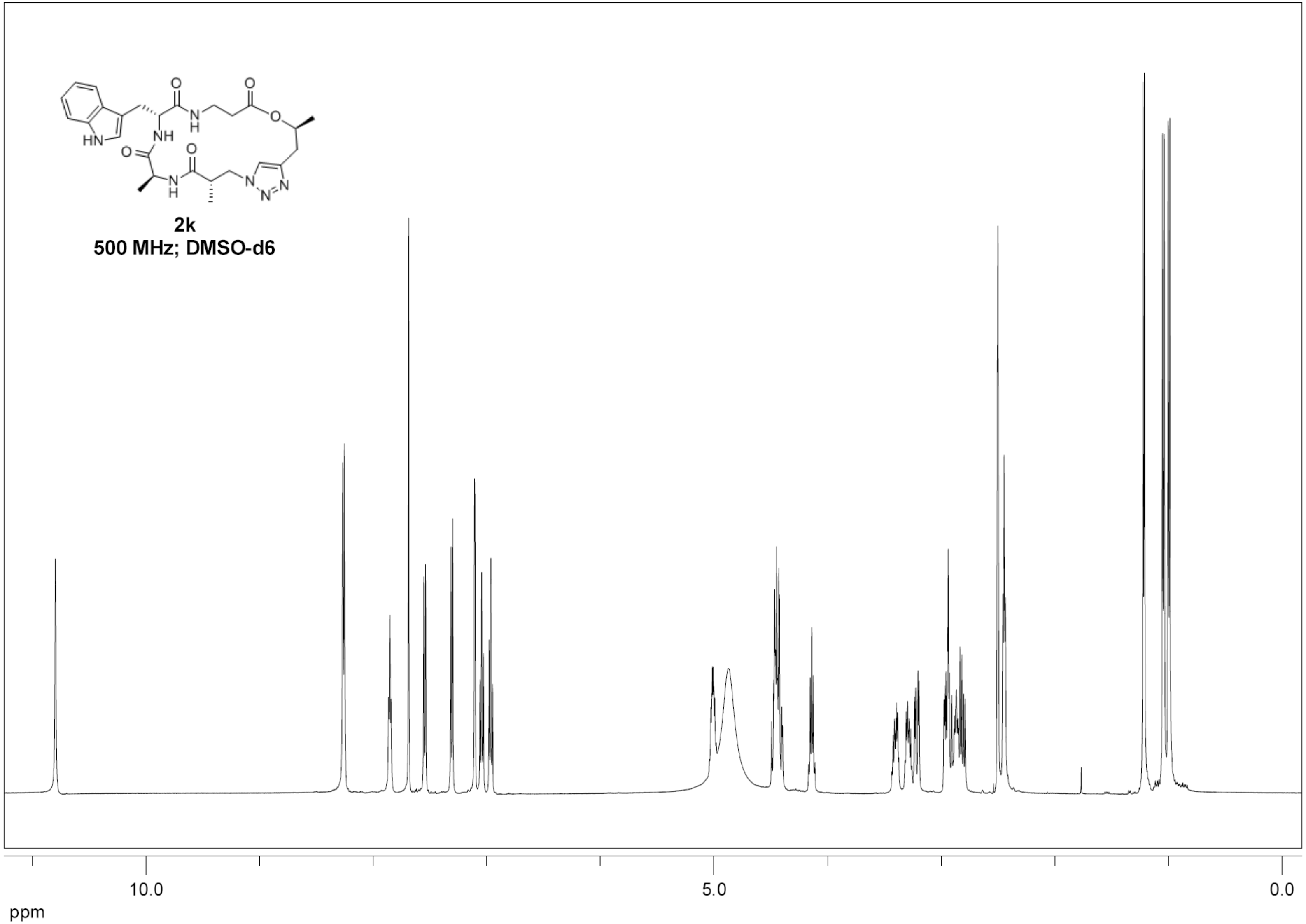
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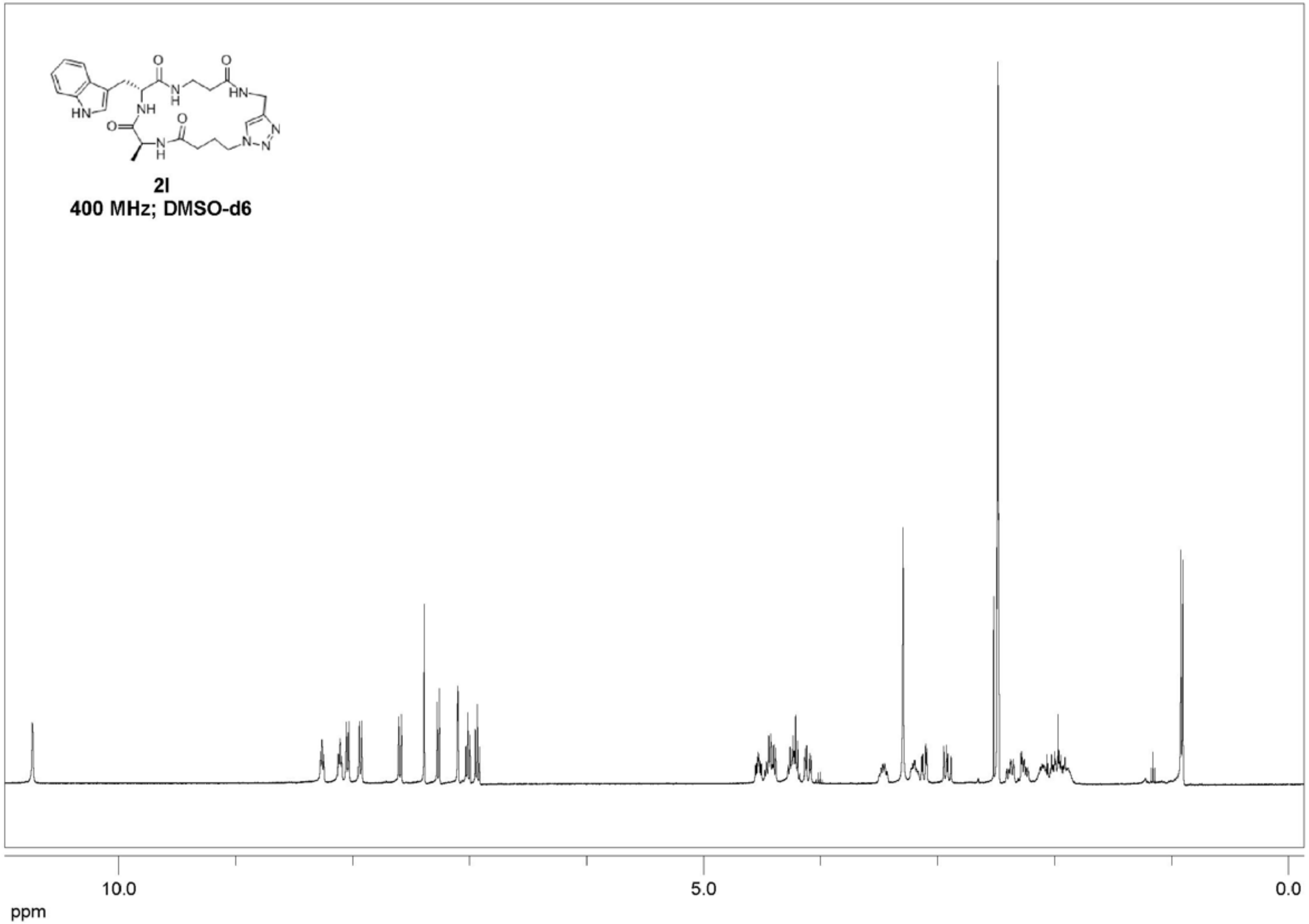
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