Supporting Information

Conformationally Homogeneous Heterocyclic Pseudo-Tetrapeptides as Three-Dimensional Scaffolds for Rational Drug Design: Mapping the Structural Basis Set and Application to the Design of Receptor-Selective Somatostatin Analogues

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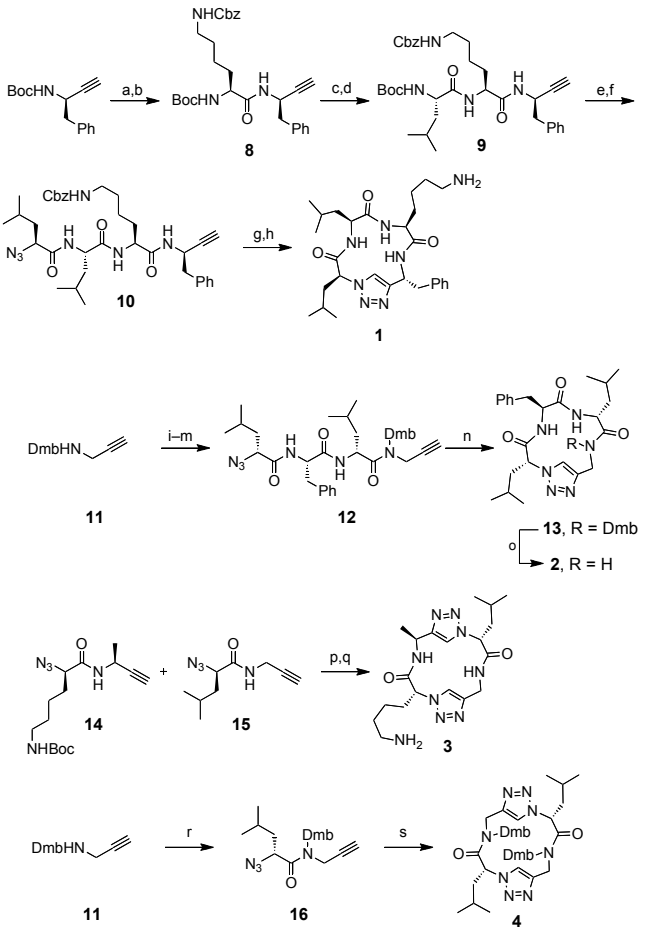
1. General experimental information.

All amino acid starting materials were purchased from Novabiochem. 2-(7-Aza-1H-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate (HATU) was purchased from Applied Biosystems. 1-Hydroxybenzotriazole (HOBt) and *N*-(3-dimethylaminopropyl)-*N*'-ethylcarbodiimide hydrochloride (EDC•HCl) were purchased from ACROS. TBTA was synthesized according to the method of Sharpless and coworkers.[S1] All other reagents were purchased from Aldrich or Fischer Scientific unless otherwise noted and used without further purification. All NMR spectra were obtained on a Varian Inova-400 MHz, Bruker AMX-400 MHz, Bruker AMX-500 MHz, or Bruker DRX-600 MHz instrument (sometimes equipped with a cryo probe). In all cases the solvent peak was used as an internal reference for ^{1}H and ^{13}C calibration: $CDCl_3$ = 7.26 ppm and 77.0 ppm and DMSO-d_6 = 2.49 ppm and 39.5 ppm, respectively. Analytical and preparative RP-HPLC were carried out with C_{18} columns using gradients of solvent A (99:1:0.1 [water/acetonitrile/TFA]) and solvent B (10:90:0.1 [water/acetonitrile/TFA]). Room temperature (RT) is defined as 22 °C.

2. Synthesis and characterization of peptides 1–4.

We have previously reported the feasibility of cyclic pseudo-hexapeptide synthesis via tandem dimerization/ macrocyclization steps involving 1,3-dipolar cycloadditions with pseudo-tripeptide substrates.[S2] To explore the scope of this synthetic strategy toward triazole-containing tetrapeptides, we examined the Cu^{I}-catalyzed oligomerization/cyclization of linear tetrapeptide and dipeptide substrates. Subjecting linear pseudo tetrapeptide **12** to copper(I) iodide, followed by removal of the backbone dimethoxybenzyl protecting groups (introduced to enhance solubility), gave cyclic pseudo-tetrapeptide **2** as the major isolated product (31%) (Scheme S1). This reaction also gave significant amounts of larger oligomers as seen by HPLC analysis and insoluble material present in the final crude product mixture. In contrast, Cu^{I}-catalyzed cyclooligomerization of dipeptide **16** gave cyclic dimer pseudo-tetrapeptide **4** as the major isolated product in good efficiency (67%). The effects of reaction conditions including solvent, Cu(I) source, and base as well as addition of reducing agents and Cu(I)-stabilizing ligand were investigated for these reactions. The highest conversion and purity for compounds **2** and **4** were obtained using 1 mM peptide in MeCN, DIEA (2 eq), 2,6-lutidine (2 eq), and CuI (2 eq). While such reactions also proceeded with catalytic CuI, the addition of two equivalents was required to ensure full conversion within a reasonable timeframe (12 hours). Compound **3** was synthesized to confirm that non-symmetric bis-triazole tetrapeptides could be prepared by mixing equimolar amounts of two different azido/alkyne-terminated dipeptide substrates. Indeed, a mixture of dipeptides **14** and **15** gave the cyclic heterodimer **3** in a yield that, while modest, is nevertheless impressive considering the simplicity of the azide-alkyne dipeptide starting materials.

To explore the possibility of constructing triazole-modfied cyclic tetrapeptides bearing side chains at each of the four



Scheme S1. Reagents and conditions: (a) TFA; (b) Boc-Lys(Cbz), HBTU, DIEA (83%, two steps); (c) TFA; (d) Boc-Leu, HBTU, DIEA (70%, two steps); (e) TFA; (f) N_3-Leu, EDC•HCl, HOBT, DIEA, 0 °C (36%, two steps); (g) CuI, 2,6-lutidine, DIEA, TBTA; (h) TFA, TMSOTf, *m*-cresol (55%, two steps); (i) Boc-D-Leu, HBTU, DIEA; (j) TFA; (k) Boc-Phe, HBTU, DIEA; (l) TFA; (m) N_3-D-Leu, HATU, DIEA, 0 °C; (n) CuI, 2,6-lutidine, DIEA (23%); (o) TFA, TMSOTf, anisole (quant); (p) CuI, 2,6-lutidine, DIEA; (q) TFA (8%, two steps); (r) N_3-D-Leu, HATU, DIEA, 0 °C (66%); (s) CuI, 2,6-lutidine, DIEA (66%).

stereogenic carbons in the backbone, we set out to prepare compound **1**. Boc-D-Phe was converted to the chiral properglyamine using a reported procedure,[S3] deprotected, and coupled to Boc-Lys(Cbz) to give dipeptide **8**. Sequential peptide extension with Boc-Leu and then N_3-Leu yielded linear tetrapeptide **10**. Attempts to cyclize **10** using conditions as described above for compounds **2** and **4** gave negligible quantities of the desired product, instead leading to the predominant formation of the cyclic pseudo-octapeptide. We found that addition of the Cu(I) ligand TBTA to the reaction favored the cyclic tetrapeptide as the major product and consequently greatly improved the yield of **1**. Following cleavage of the lysine side chain Cbz protecting group, cyclic tetrapeptide **1** was isolated in 55 % yield (over two steps from **10**).

Taken together, the syntheses of compounds **1**–**4** highlight the generality of azide-alkyne cycloaddition for preparing cyclic pseudo-tetrapeptides.

S1.) Chan, T.R.; Hilgraf, R.; Sharpless, K.B.; Fokin, V.V. *Org. Lett.* **2004**, *6(17)*, 2853.

S2.) van Maarseveen, J. H.; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503.

S3.) Corey, E. J.; Fuchs, P. L. *Tetrahedron Lett.* **1972**, 3769.

General procedure for Cu-mediated peptide cyclization for compounds 2 and 4: The azido-alkyne terminated peptide (1 eq.) was dissolved in acetonitrile to a concentration of 1 mM. The solution was degassed by Ar bubbling for 20 minutes. Diisopropylethylamine (2 eq.), 2,6-lutidine (2 eq.), and CuI (2 eq.) were added sequentially. The reaction was stirred for 12 hr at room temperature under Ar. The reaction mixture was then concentrated to a residue and purified by preparative RP-HPLC. Residual water and TFA from the preparative HPLC were removed by solvent exchange with acetonitrile (x3) followed by $CHCl_3$ (x3).

Dipeptide 8: Boc-D-Phe-alkyne was prepared in four steps from Boc-D-Phe as described in the literature for the L-enantiomer.[S4] To remove the Boc group, this alkyne (140 mg, 0.571 mmol) was dissolved in 1:1 TFA / CH_2Cl_2 (6 mL). The reaction was allowed to stand for 30 min at room temperature. The solution was concentrated, and the resulting residue exchanged with $CHCl_3$ (x3) and dried under high vacuum. In a second flask, Boc-Lys(Cbz)-OH (261 mg, 0.685 mmol) and HBTU (238 mg, 0.628 mmol) were dissolved in DMF (10 mL). Diisopropylethylamine (300 μL, 1.72 mmol) was added, and the solution stirred at room temperature for 10 min. A solution of the crude deprotected Phe alkyne from above in DMF (2 mL) with diisopropylethylamine (100 μL, 0.574 mmol) was then added. The reaction was allowed to stir at room temperature for 3 hr. The solution was concentrated under high vacuum, redissolved in EtOAc, and washed successively with 5% aq. $NaHCO_3$ (x2), 5% aq. $KHSO_4$ (x2), and satd. NH_4Cl. The organic layer was dried with $MgSO_4$, concentrated, purified by silica column eluted with 1:1 hexanes / EtOAc to yield 240 mg (83%) of the product as a gummy solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.31 (d, J = 8 Hz, 1H), 7.35-7.15 (overlapping m, 10 H), 6.67 (d, J = 8 Hz, 1H), 4.99 (s, 2H), 4.70 (m, 1H), 3.83 (m, 1H), 3.23 (d, J = 2 Hz, 1H), 2.95-2.80 (overlapping m, 4H), 1.35 (s, 9H), 1.29 (m, 4H), 1.07 (m, 2H); ^{13}C NMR (150 MHz, MeOD) δ 173.7, 158.7, 157.4, 138.3, 138.0, 130.5, 129.3, 129.2, 128.8, 128.7, 127.7, 80.3, 73.1, 67.2, 55.5, 43.3, 42.4, 41.4, 41.3, 33.1, 30.3, 28.7, 23.6; HRMS (m/z) $[M+H]^+$ obsd. = 508.2812 (calc. = 508.2806).

Tripeptide 9: Linear dipeptide **8** (235 mg, 0.462 mmol) was dissolved in 1:1 TFA / CH_2Cl_2 (6 mL). The reaction was allowed to stand for 30 min at room temperature. The solution was concentrated, and the resulting residue exchanged with $CHCl_3$ (3×) and dried under high vacuum. In a second flask, Boc-Leu-OH·H_2O (138 mg, 0.554 mmol) and HBTU (193 mg, 0.508 mmol) were dissolved in DMF (10 mL). Diisopropylethylamine (240 μL, 1.38 mmol) was added, and the solution stirred at room temperature for 10 min. A solution of the crude deprotected dipeptide alkyne **8** from above in DMF (2 mL) with diisopropylethylamine (82 μL, 0.470 mmol) was then added. The reaction was allowed to stir at room temperature for 3 hr. The solution was concentrated under high vacuum, redissolved in EtOAc, and washed successively with 5% aq. $NaHCO_3$ (2×), 5% aq. $KHSO_4$ (x2), and satd. NH_4Cl. The organic layer was dried with $MgSO_4$, concentrated, purified by silica column eluted with 1:2 hexanes / EtOAc to yield 198 mg (70%) of the product as a gummy solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ 8.45 (d, J = 8 Hz, 1H), 7.58 (d, J = 8 Hz, 1H), 7.4-7.1 (overlapping m, 11H), 6.92 (d, J = 8 Hz, 1H), 4.98 (s, 2H), 4.70 (m, 1H), 4.17 (m, 1H), 3.92 (m, 1H), 3.21 (d, J = 3 Hz, 1H), 2.9-2.8 (m, 4H), 1.56 (m, 1H), 1.4-1.2 (m, 15H), 1.00 (m, 2H), 0.84 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 173.0, 170.3, 156.5, 155.8, 136.5, 136.2, 129.5, 129.5, 128.4, 128.2, 128.0, 128.0, 126.8, 82.4, 80.1, 72.0, 66.5, 53.2, 52.6, 42.3, 41.3, 41.0, 40.3, 31.4, 29.6, 29.2, 28.2, 28.2, 24.6, 22.9, 22.1, 21.7; HRMS (m/z) $[M+H]^+$ obsd. = 621.3656 (calc. = 621.3646).

Linear tetrapeptide 10: Peptide **9** (192 mg, 0.309 mmol) was dissolved in 1:1 TFA / CH_2Cl_2 (6 mL). The reaction was allowed to stand for 30 min at room temperature. The solution was concentrated, and the resulting residue exchanged with $CHCl_3$ (x3) and dried under high vacuum. The crude residue was dissolved in CH_2Cl_2 (10 mL). Diisopropylethylamine (215 μL, 1.236 mmol), HOBT·H_2O (52 mg, 0.340 mmol), and N_3-L-Leu[S5] (53 mg, 0.340 mmol) were added. The solution was cooled to 0°C and EDC·HCl (65 mg, 0.340 mmol) was added. The solution was stirred at 0°C for 1 hr then at room temperature for 2 hr. The reaction was then diluted with EtOAc, and washed successively with 5% aq. $KHSO_4$ (x3), 5% aq. $NaHCO_3$ (x3), and satd. NH_4Cl. The organic layer was dried with $MgSO_4$, concentrated, and purified by silica column eluted with 1:2 hexanes / EtOAc to yield 74 mg (36%) of the product as a gummy solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.41 (d, J = 8 Hz, 1H), 8.33 (d, J = 8 Hz, 1H), 7.90 (d, J = 8 Hz, 1H), 7.35-7.15 (overlapping m, 10H), 4.98 (s, 2H), 4.70 (m, 1H), 4.34 (dd, J = 16, 8 Hz, 1H), 4.12 (m, 1H), 3.75 (t, J = 7 Hz, 1H), 3.22 (d, J = 2 Hz, 1H), 2.95-2.80 (m, 4H), 1.60-1.20 (m, 10H), 1.02 (m, 2H), 0.95-0.80 (overlapping d, 12H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.1, 170.3, 170.1, 156.6, 136.5, 136.1, 129.5, 128.4, 128.3, 128.0, 126.9, 72.0, 66.6, 62.6, 62.3, 52.7, 51.5, 42.2, 41.6, 41.4, 41.1, 40.9, 40.2, 31.5, 29.3, 24.9, 24.7, 23.0, 22.9, 22.1, 21.9, 21.6; HRMS (m/z) $[M+H]^+$ obsd. = 660.3869 (calc. = 660.3868).

Cyclic peptide 1: Linear azido-alkyne terminated peptide **10** (30 mg, 45 μmol) was dissolved in acetonitrile (230 mL) and the solution degassed by bubbling Ar for 15 min. To this solution were sequentially added diisopropylethylamine (16 μL, 91 μmol), 2,6-lutidine (11 μL, 91 μmol), *tris*-(benzyltriazolylmethyl)-amine (48 mg, 91 μmol), and CuI (17 mg, 91 μmol). The reaction was stirred at room temperature under an Ar atmosphere for 3 days. The reaction was then concentrated to a residue and treated with TFA / TMSOTf / *m*-cresol (2 mL of an 8:1:1 solution by volume). After 30 min at room temperature, the suspension was diluted with Et_2O (45 mL) and centrifuged. The supernatant was discarded, and the solid pellet dried under vacuum. Purification by preparative HPLC on a C_{18} column yielded 16 mg (55% assuming a salt with one molecule of trifluoroacetate per peptide) of the product as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 8.62 (d, J = 10 Hz, 1H), 7.97 (s, 1H), 7.89 (d, J = 10 Hz, 1H), 7.59 (br s, 3H), 7.31 (d, J = 7 Hz, 2H), 7.27 (t, J = 7 Hz, 2H), 7.25 (d, J = 8 Hz, 1H), 7.18 (t, J = 7 Hz, 1H), 5.25 (m, 1H), 5.09 (t, J = 8 Hz, 1H), 4.28 (m, 1H), 4.02 (dd, J = 16, 8 Hz, 1H), 3.34 (dd, J = 14, 6 Hz, 1H), 3.12 (dd, J = 14, 10 Hz, 1H), 2.69 (br t, J = 7 Hz, 2H), 2.22 (m, 1H), 1.99 (m, 1H), 1.60-1.30 (m, 8H), 1.16-1.02 (m, 2H), 0.96 (d, J = 4 Hz, 3H), 0.95 (d, J = 4 Hz, 3H), 0.89 (d, J = 7 Hz, 3H), 0.82 (d, J = 7 Hz, 3H); ^{13}C NMR (150 MHz, $CDCl_3$) δ 170.98, 170.95, 166.8, 150.8, 138.6, 129.2, 128.8, 128.1, 126.2, 65.3, 54.0, 52.7, 48.4, 38.6, 37.2, 26.8, 24.9, 24.7, 22.7, 22.2, 22.1, 22.0, 21.4, 36.2, 30.6; HRMS (m/z) $[M+H]^+$ obsd. = 526.3508 (calc. = 526.3500).

Dmb-propargylamine hydrochloride 11: Propargylamine (1.0 g, 18.1 mmol) and 2,4-dimethoxy benzaldehyde (2.5 g, 15.1 mmol) were dissolved in dry methanol (50 mL) and stirred for 2

S4.) Reginato, G.; Mordini, A.; Messina, F.; DegIInnocenti, A.; Poli, G. *Tetrahedron* **1996**, *52* 10985.

S5.) Lundquist, J. T. I. V.; Pelletier, J. C., *Org. Lett.* **2001,** *3*, 781-783.

hr. To the resulting clear solution sodium borohydride (1.0 g, 27.0 mmol) was carefully added portionwise. The suspension was stirred for 2 hr. After dilution with ether (100 mL), 2 M NaOH (20 mL) was added to quench the reaction. The reaction mixture was transferred to a separation funnel and the organic layer was washed with water (x2) and dried (brine and $MgSO_4$). After filtration the volatiles were evaporated under vacuum and the sticky residue was dissolved in methanol (25 mL). To this 12 M HCl (2 mL) was added, and the volatiles were removed under reduced pressure. The residue was dissolved in 1:4 MeOH / EtOAc (40 mL) followed by saturation with hexanes (in the case no crystallization occurs additional ether may be added). The resulting crystals were collected by filtration and dried to give the product (2.3 g, 55%) as its HCl salt. ^{1}H NMR (500 MHz, CD_3OD) d 7.30 (d, *J* = 8 Hz, 1H), 6.64 (d, *J* = 2 Hz, 1H), 6.58 (dd, *J* = 8, 2 Hz, 1H), 4.23 (s, 2H), 3.91 (s, 3H), 3.90 (d, *J* = 3 Hz, 2H), 3.83 (s, 3H), 3.27 (t, *J* = 3 Hz, 1H); ^{13}C NMR (100 MHz, DMSO-d_6) d 161.5, 158.7, 132.5, 111.4, 104.8, 98.2, 79.4, 74.9, 55.6, 55.3, 43.4, 35.0; ESI-MS (m/z) $[M+H]^+$ obsd. = 206.1 (calc. = 206.1).

General procedure for solution-phase peptide synthesis used to prepare 12 and 15: Couplings were carried out as follows: to a stirred solution of carboxylic acid component (1.1 eq.) in 4:1 CH_2Cl_2 / DMF at a concentration ~0.4 M was added DIEA (2.2 eq.). The solution was cooled to 0 ºC and HATU or HBTU (1 eq.) was added in one portion. After 10 minutes at 0 ºC, a solution of the amine component (1 eq.) in DMF at a concentration of ~0.5 M was added. The reactions were typically stirred for 3 hr at 0 ºC. Work-up was accomplished by diluting the reaction mixture with EtOAc followed by successive washing with 0.5 M $KHSO_4$ (x3) and brine. After drying with $MgSO_4$ and filtration, the solvents were removed under vacuum and the residue was purified by flash chromatography. Fmoc deprotections were carried out by dissolving the peptide in 2:1 acetonitrile / diethylamine and stirring for 1 h. After concentration of the solution under vacuum, the residue was exchanged with acetonitrile and used directly in the subsequent coupling step.

Protected linear tetrapeptide 12: Prepared from secondary amine **11**, Fmoc-D-Leu, Fmoc-Phe, and N_3-D-Leu by the general solution phase peptide synthesis conditions described above. Due to complexity arising from *cis-trans* isomerization about tertiary amide, the ^{1}H NMR was not assigned. The full spectrum can be found in Figure S2. ^{1}H NMR (400 MHz, $CDCl_3$) see Figure S2; ^{13}C NMR (150 MHz, $CDCl_3$) δ 171.81, 171.07, 169.89, 169.64, 169.58, 161.16, 160.53, 158.85, 136.25, 136.21, 130.84, 130.50, 129.19, 128.65, 127.08, 116.54, 115.14, 104.14, 103.84, 98.62, 98.35, 78.59, 78.45, 72.68, 71.80, 62.64, 55.35, 55.29, 55.23, 55.16, 54.47, 54.36, 47.93, 47.85, 45.39, 43.75, 42.90, 42.05, 41.02, 41.05, 38.84, 38.78, 36.52, 33.22, 24.90, 24.51, 24.47, 23.47, 23.39, 22.90, 22.87, 21.48, 21.47, 21.43; HRMS (m/z) $[M+Na]^+$ obsd. = 627.3254 (calc. = 627.3265).

Protected cyclic peptide 13: Prepared from azide-alkyne tetrapeptide **12** (61 mg, 0.10 mmol) by the general Cu-mediated cyclization procedure as described above. Purification by preparative RP-HPLC yielded 14 mg (23%) of the product. Due to complexity arising from *cis-trans* isomerization about tertiary amide, the ^{1}H NMR was not assigned. The full spectrum can be found in Figure S2. ^{1}H NMR (600 MHz, $CDCl_3$) see Figure S2; ^{13}C NMR (150 MHz, $CDCl_3$) δ 172.2, 170.1, 167.7, 161.0, 158.8, 135.8, 130.7, 129.0, 128.9, 128.5, 128.4, 126.9, 116.8, 103.7, 98.8, 62.5, 55.4, 55.3, 54.8, 48.1, 47.5, 41.8, 38.2, 37.7, 36.8, 24.6, 24.3, 22.9, 22.6, 21.8, 21.6; HRMS (m/z) $[M+H]^+$ obsd. = 605.3447 (calc. = 605.3446).

Cyclic peptide 2: Prepared by dissolving peptide **13** in 8:1:1 by volume TFA / trimethylsilyltrifluoromethanesulfonate (TMSOTf) / anisole to a concentration of ~0.2 M. The mixture was allowed to stand at room temperature for 30 min. The product was precipitated by addition of cold ether. The suspension was centrifuged, the supernatant discarded, and the resulting solid washed with ether (x3). Drying the resulting pellet under high vacuum gave **2** in quantitative yield. ^{1}H NMR (600 MHz) d 8.34 (d, *J* = 10 Hz, 1H), 8.19 (overlapping d, 2H), 7.47 (s, 1H), 7.21 (m, 2H), 7.15 (m, 3H), 5.24 (t, *J* = 7 Hz, 1H), 4.57 (dd, *J* = 18, 8 Hz, 1H), 4.53 (dd, *J* = 14, 8 Hz, 1H), 4.14 (dd, *J* = 15, 9 Hz, 1H), 3.85 (dd, *J* = 15, 4 Hz, 1H), 2.83 (dd, *J* = 14, 8 Hz, 1H), 2.74 (dd, *J* = 14, 8 Hz, 1H), 1.91 (m, 2H), 1.44 (m, 1H), 1.33 (m, 2H), 1.23 (m, 1H), 0.89 (d, *J* = 7 Hz, 3H), 0.86 (d, *J* = 7 Hz, 3H), 0.77 (d, *J* = 7 Hz, 3H), 0.68 (d, *J* = 7 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) d 171.0, 169.3, 166.9, 147.2, 137.1, 128.9, 127.9, 126.2, 61.5, 53.9, 51.1, 37.8, 36.9, 36.4, 34.9, 24.4, 23.8, 22.4, 22.2, 22.0, 22.0; HRMS (m/z) $[M+H]^+$ obsd. = 455.2754 (calc. = 455.2765).

Dipeptide 14: Boc-Ala-alkyne (130 mg, 0.768 mmol), prepared according to a literature procedure,[S4] was dissolved in 1:1 TFA / CH_2Cl_2 (10 mL). The reaction was allowed to stand for 20 min at room temperature and concentrated. The resulting residue was exchanged with $CHCl_3$ (x3) and used directly in the next step. The crude amino alkyne from above, diisopropylethylamine (534 μL, 3.07 mmol), N_3-D-Lys(Boc)[S5] (230 mg, 0.845 mmol), and HOBT·H_2O (129 mg, 0.845 mmol) were dissolved in CH_2Cl_2 (20 mL). The solution was cooled to 0°C and EDC·HCl (162 mg, 0.845 mmol) was added at once. After stirring for 1 hr at 0°C and 2 hr at room temperature, the reaction was concentrated, diluted with EtOAc (150 mL), and washed successively with 5% aq. $NaHCO_3$ (x2), 5% aq. $KHSO_4$ (x2), and brine. The organic layer was dried with $MgSO_4$, concentrated, and purified by flash chromatography (1:1 hexanes / EtOAc) to yield 197 mg (79%) of the product as a white solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 6.61 (d, *J* = 8 Hz, 1H), 4.75 (m, 1H), 4.61 (br s, 1H), 3.95 (dd, *J* = 7, 5 Hz, 1H), 3.10 (m, 2H), 2.27 (d, *J* = 2 Hz, 1H), 1.95-1.81 (m, 2H), 1.55-1.35 (m, 16H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 168.2, 155.9, 83.5, 70.7, 63.8, 40.1, 36.9, 31.6, 29.5, 28.3, 22.3, 21.9; HRMS (m/z) $[M+Na]^+$ obsd. = 346.1848 (calc = 346.1849).

Dipeptide 15: N_3-D-Leu, prepared from D-Leu as previously described for the L-enantiomer,[S5] (300 mg, 1.91 mmol) and propargylamine (72 μL, 1.91 mmol) were reacted according to the general HATU coupling procedure outlined above to yield 253 mg (68%) of the product. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.57 (br s, 1H), 4.03 (m, 2 H), 3.95 (dd, *J* = 9, 4 Hz, 1H), 2.23 (t, *J* = 3 Hz, 1H), 1.90-1.60 (m, 3H), 0.95 (dd, *J* = 6, 4 Hz, 6H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 78.8, 71.9, 62.7, 41.1, 29.1, 24.9, 22.9, 21.4; HRMS (m/z) $[M-H]^-$ obsd. = 193.1090 (calc. = 193.1095).

Cyclic tetrapeptide 3: Dipeptide **14** (16 mg, 0.05 mmol) and dipeptide **15** (10 mg, 0.05 mmol) were dissolved in acetonitrile (100 mL). The solution was degassed by Ar bubbling for 20 min, after which diisopropylethylamine (35 μL, 0.2 mmol), 2,6-lutidine (23 μL, 0.2 mmol), and CuI (38 mg, 0.2 mmol) were added. The reaction was stirred at room temperature under Ar for 24 hr and then concentrated under vacuum. The resulting residue was suspended in 1:1 TFA / $CHCl_3$ (10 mL), allowed to stand for 30 min, and then concentrated under vacuum. Purification by preparative RP-HPLC yielded 2 mg (8% assuming a salt with 2 eq. of TFA) of the product as a white solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.07 (dd, *J* = 7, 5 Hz, 1H), 8.91 (d, *J* = 8 Hz, 1H), 7.64 (br s, 3H), 7.29 (s, 1H), 7.24 (s, 1H), 5.12 (t, *J* = 8 Hz, 1H),

5.00 (m, 2H), 4.53 (dd, J = 14, 7 Hz, 1H), 3.88 (dd, J = 14, 5 Hz, 1H), 2.76 (m, 2H), 2.04 (m, 1H), 1.98-1.86 (m, 3H), 1.53 (m, 2H), 1.48 (d, J = 7 Hz, 3H), 1.39 (m, 1H), 1.30-1.15 (m, 2H), 0.91 (d, J = 7 Hz, 3H), 0.88 (d, J = 7 Hz, 3H); ^{13}C NMR (150 MHz, DMSO-d_6) δ 167.5, 166.2, 148.9, 145.2, 120.1, 119.2, 62.6, 61.5, 41.1, 38.5, 37.9, 34.4, 29.6, 26.6, 24.3, 22.1, 22.0, 16.8; HRMS (m/z) $[M+H]^+$ obsd. = 418.2683 (calc. = 418.2673).

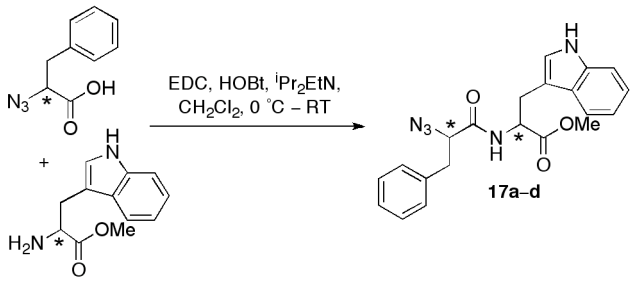
Protected dipeptide 16: To a stirred solution of N_3-D-Leu[S5] (0.325 g, 2.07 mmol) in 4:1 CH_2Cl_2 / DMF (5 mL) was added DIEA (0.721 mL, 4.14 mmol). The solution was cooled to 0 ºC and HATU (780 mg, 2.05 mmol) was added in one portion. After 10 minutes, a solution of N-(2,4-dimethoxybenzyl)-propargylamine hydrochloride **11** (0.50 g, 2.07 mmol) and DIEA (0.360 mL, 2.01 mmol) dissolved in DMF (3 mL) was added, and the reaction was stirred for 3 hours at 0 ºC. Work-up was accomplished by diluting the reaction mixture with EtOAc followed by washing sequentially with 0.2 M $KHSO_4$ (x3) and brine. After drying with $MgSO_4$ and filtration, the solvent was removed under vacuum and the residue was purified by flash chromatography (1:1 EtOAc / hexanes) to give the 468 mg (66 %) of the product as a viscous oil. Ratio of integration in ^{1}H NMR indicates a 70:30 mixture of two conformers likely resulting from cis-trans rotamers about the tertiary amide bond. In regions where the two conformations are well separated, resonances are assigned partial proton integration for each. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 8 Hz, 0.3 H), 7.06 (d, J = 9 Hz, 0.7 H), 6.50-6.40 (m, 2H), 4.70-4.30 (overlapping d, 2.6H), 4.11 (dd, J = 10, 4 Hz, 0.7H), 4.06 (dd, J = 19, 3 Hz, 0.3 H), 4.0-3.8 (overlapping m, 1.4H), 3.78 (overlapping s, 6H), 2.25 (t, J = 3 Hz, 0.3H), 2.20 (t, J = 3 Hz, 0.7H), 2.0-1.5 (overlapping m, 3H), 1.0-0.8 (overlapping d, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.57, 169.75, 160.94, 160.51, 158.63, 158.33, 131.19, 129.57, 116.54, 115.29, 104.10, 103.86, 98.56, 98.19, 78.47, 72.51, 71.90, 56.93, 56.68, 55.22, 55.13, 45.44, 43.79, 39.46, 39.12, 36.19, 33.75, 24.92, 22.92, 22.75, 21.66, 21.36; HRMS (m/z) $[M+H]^+$ obsd. = 345.1808 (calc. = 345.1921).

Protected cyclic peptide 4: Prepared from azide-alkyne dipeptide **16** (103 mg, 0.30 mmol) by the general Cu-mediated cyclization procedure as described above. Purification by preparative RP-HPLC yielded 68 mg (66%) of the product. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.70 (s, 2H), 7.25 (d, J = 8 Hz, 2H), 6.50-6.45 (overlapping s and dd, 4H), 6.0 (dd, J = 9, 6 Hz, 2H), 5.06 (d, J = 15 Hz, 2H), 4.82 (d, J = 15 Hz, 2H), 3.88 (d, J = 15 Hz, 2H), 3.83 (s, 6H), 3.80 (s, 6H), 3.88 (d, J = 15 Hz, 2H), 2.12 (m, 2H), 1.95 (m, 2H), 1.41 (m, 2H), 0.98 (d, J = 7 Hz, 6H), 0.84 (d, J = 7 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 167.3, 161.3, 159.0, 143.8, 131.4, 121.1, 115.8, 103.9, 99.1, 58.4, 55.4, 46.5, 40.1, 39.9, 24.6, 22.7, 22.0; HRMS (m/z) $[M+H]^+$ obsd. = 689.3754 (calc. = 689.3769).

3. Synthesis and characterization of peptides 7a–7h and *ent*-7a–*ent*-7h.

The threonine-derived alkyne[S6] and the phenylalanine-derived azide[S5] were synthesized as described in the literature. Some racemization was observed in the preparation of the threonine-derived alkyne (varying between 7% and 12%). Alternative preparation of the threonine-derived alkyne via Corey-Fuchs homologation[S3] avoids this racemization, but the overall yield of the alkyne was significantly reduced. The stereochemistry assigned to the molecules below refers to that of the parent amino acid. We note in the case of Thr that, following homologation, the assigned stereochemistry changes although no inversion of the stereocenter takes place.

General procedure for azido esters (17a–d). Methyl ester protected amino acid (1.77 mmol, 1.2 eq) was dissolved in DCM (10 mL) and diisopropylethylamine (DIEA) was added (4.32 mmol, 3.0 eq). The reaction mixture was cooled to 0 °C (15 min) followed by addition of EDC (1.58 mmol, 1.1 eq), HOBt (1.58 mmol, 1.1eq), and the azido acid (1.44mmol, 1 eq) in that order. The reaction was allowed to run at 0 °C for 30 min at which time the reaction was allowed to warm to RT. After 2.5 h at RT the reaction mixture was transferred to a separation funnel using DCM (40 mL), and the organic layer was extracted once each with 5% $KHSO_4$ (aq, 30 mL), 5% $NaHCO_3$ (aq, 30 mL), H_2O (30 mL) and brine (30 mL). The organic layer was then dried with $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude product was purified by flash chromatography using EtOAc:hexanes (1:1) as eluent. The eluent was removed under vacuum to leave a clear, colorless oil which was subsequently dissolved in $CHCl_3$ and evaporated under vacuum (x3) to yield a white solid.



N_3-L-Phe-L-Trp-OMe (17a). White solid (529 mg, 92%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.89 (s, 1H), 8.68 (d, J = 8 Hz, 1H), 7.48 (d, J = 8 Hz, 1H), 7.34-7.27 (m, 3H), 7.24-7.22 (m, 3H), 7.10 (d, J = 2 Hz, 1H), 7.06 (t, J = 15, 7 Hz, 1H), 6.98 (t, J = 15, 7 Hz, 1H), 4.59-4.54 (m, 1H), 4.05-4.02 (m, 1H), 3.58 (s, 3H), 3.20-3.05 (m, 2H), 3.06-2.84 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 168.0, 136.0, 135.9, 129.6, 128.7, 127.3, 127.2, 122.7, 122.3, 119.6, 118.5, 111.2, 109.5, 65.1, 52.6, 52.4, 38.1, 27.6 ppm. ESI-TOF (m/z) $[M+Na]^+$ obsd. = 414.1540 (calc. = 414.1537).

N_3-L-Phe-D-Trp-OMe (17b). White solid (547 mg, 95%). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.80 (s, 1H), 8.66 (d, J = 8 MHz, 1H), 7.47 (d, J = 8 MHz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.27-7.21 (m, 3H), 7.16-7.15 (m, 2H), 7.05 (t, J = 15, 7 Hz, 1H), 7.02 (d, J = 2 Hz, 1H), 6.98 (t, J = 15, 7 Hz, 1H), 4.57-4.53 (m, 1H), 4.04-4.01 (m, 1H), 3.60 (s, 3H), 3.13-2.99 (m, 2H), 2.89-2.76 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.5, 168.5, 136.0, 135.9, 129.1, 128.4, 127.1, 126.9, 122.8, 122.0, 119.3, 118.1, 111.3, 109.0, 65.0, 52.9, 52.2, 38.2, 27.3 ppm. ESI-TOF (m/z) $[M+Na]^+$ obsd. = 414.1539 (calc. = 414.1537).

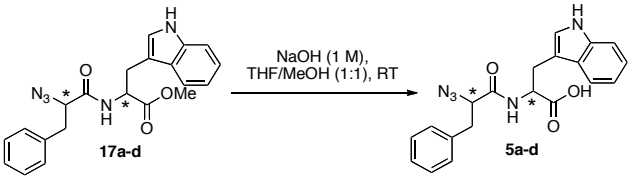
N_3-D-Phe-L-Trp-OMe (17c). White solid (541 mg, 94%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.85 (s, 1H), 8.67 (d, J = 8 Hz, 1H), 7.46 (d, J = 8 Hz, 1H), 7.31 (d, J = 8 Hz, 1H), 7.27-7.19 (m, 3H), 7.16-7.14 (m, 2H), 7.07 (t, J = 15, 7 Hz, 1H), 7.01 (d, J = 2 Hz, 1H), 6.99 (t, J = 15, 7 Hz, 1H), 4.58-4.52 (m, 1H), 4.03-4.00 (m, 1H), 3.60 (s, 3H), 3.13-2.97 (m, 2H), 2.89-2.75 (m, 2H) ppm.

S6.) Roth, G.J.; Liepold, B.; Muller, S.G.; Bestmann, H.J. *Synthesis*. **2004**, *1*, 59.

^{13}C NMR (150 MHz, $CDCl_3$) δ: 171.5, 168.5, 136.1, 136.0, 129.3, 128.6, 127.3, 127.1, 122.7, 122.2, 119.5, 118.3, 111.3, 109.4, 65.4, 53.9, 53.4, 39.5, 27.4 ppm. ESI-TOF (*m/z*) $[M+H]^+$ obsd. = 392.1713 (calc. = 392.1717).

N_3-D-Phe-D-Trp-OMe (17d). White solid (540 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.88 (s, 1H), 8.67 (d, *J* = 8 Hz, 1H), 7.47 (d, *J* = 8 Hz, 1H), 7.33 (d, *J* = 8 Hz, 1H), 7.31-7.27 (m, 3H), 7.24-7.22 (m, 2H), 7.10 (d, *J* = 2 Hz, 1H), 7.05 (t, *J* = 15, 7 Hz, 1H), 6.98 (t, *J* = 15, 7 Hz, 1H), 4.58-4.54 (m, 1H), 4.05-4.02 (m, 1H), 3.57 (s, 3H), 3.20-3.07 (m, 2H), 3.07-2.84 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.8, 168.1, 136.0, 135.7, 129.3, 128.4, 127.2, 127.0, 122.7, 122.8, 121.9, 118.2, 111.2, 108.8, 64.6, 52.6, 52.2, 37.8, 27.4 ppm. ESI-TOF (*m/z*) $[M+H]^+$ obsd. = 392.1710 (calc. = 392.1717).

General procedure for saponification of 17a-d to give azido acids (5a-d). The azido ester protected dipeptide **17** (0.884 mmol, 1 eq) was dissolved in THF/MeOH (1:1, 8 mL). A 1M solution of NaOH (aq, 2.21 mmol, 2.5 eq) was added to the reaction vessel slowly, and the reaction was left stirring at room temperature for 1 h. The vessel was then put on ice and acidified using 5% $KHSO_4$ (aq). The organic solvent was removed under vacuum, followed by addition of EtOAc (30 mL) to the aqueous slurry, and extraction with H_2O (2 x 15 mL) and brine (15 mL). The organic layer was dried with $MgSO_4$, filtered, and the solvent removed under vacuum to leave a clear oil. The oil was dissolved in $CHCl_3$, then evaporated under vacuum (x3) to leave analytically pure azido acid dipeptide product **5** as a white solid.



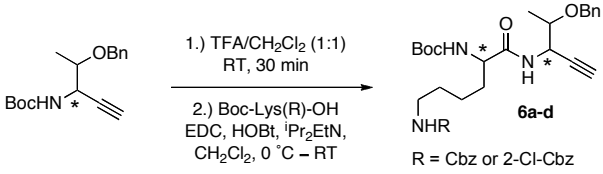
N_3-L-Phe-L-Trp-OH (5a). White solid (327 mg, 98%). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.86 (s, 1H), 8.51 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.33-7.28 (m, 3H), 7.26-7.22 (m, 3H), 7.09 (d, *J* = 2 Hz, 1H), 7.05 (t, *J* = 15, 7 Hz, 1H), 6.97 (t, *J* = 15, 7 Hz, 1H), 4.54-4.49 (m, 1H), 4.06-4.02 (m, 1H), 3.22-2.82 (m, 4H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.2, 168.9, 136.0, 135.8, 129.6, 128.6, 127.4, 127.3, 123.0, 122.3, 119.6, 118.6, 111.3, 109.1, 64.9, 52.8, 38.1, 27.2 ppm. ESI-TOF $[M+Na]^+$ obsd. = 400.1378 (calc. = 400.1380).

N_3-L-Phe-D-Trp-OH (5b). White solid (315 mg, 94%). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.83 (s, 1H), 8.52 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H) 7.25-7.20 (m, 3H), 7.15-7.14 (m, 2H), 7.04 (t, *J* = 15, 8 Hz, 1H), 7.00 (d, *J* = 3 Hz, 1H), 6.97 (t, *J* = 15, 7 Hz, 1H), 4.53-4.48 (m, 1H), 4.03-4.00 (m, 1H), 3.15-2.97 (m, 2H), 2.87-2.74 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.9, 169.5, 136.0, 135.9, 129.2, 128.6, 127.3, 127.1, 123.1, 122.1, 119.6, 118.2, 111.4, 109.0, 65.1, 53.2, 38.5, 27.0 ppm. ESI-TOF $[M+Na]^+$ obsd. = 400.1385 (calc. = 400.1380).

N_3-D-Phe-L-Trp-OH (5c). White solid (330 mg, quant.). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 10.83 (s, 1H), 8.54 (d, *J* = 8 Hz, 1H), 7.52 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H) 7.25-7.14 (m, 5H), 7.05 (t, *J* = 15, 8 Hz, 1H), 7.01 (d, *J* = 3 Hz, 1H), 6.97 (t, *J* = 15, 7 Hz, 1H), 4.53-4.48 (m, 1H), 4.03-4.00 (m, 1H), 3.16-2.96 (m, 2H), 2.87-2.73 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 174.9, 169.7, 136.1, 135.8, 129.3, 128.6, 127.3, 127.2, 123.2, 122.2, 119.6, 118.2, 111.5, 108.9, 65.1, 53.2, 38.5, 27.1 ppm. ESI-TOF $[M+Na]^+$ obsd. = 400.1380 (calc. = 400.1380).

N_3-D-Phe-D-Trp-OH (5d). White solid (323 mg, 97%). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.82 (s, 1H), 8.50 (d, *J* = 8 Hz, 1H), 7.51 (d, *J* = 8 Hz, 1H), 7.31 (d, *J* = 8 Hz, 1H) 7.30-7.28 (m, 2H), 7.23-7.21 (m, 3H), 7.08 (d, *J* = 3 Hz, 1H), 7.05 (t, *J* = 15, 8 Hz, 1H), 6.95 (t, *J* = 15, 7 Hz, 1H), 4.53-4.49 (m, 1H), 4.05-4.02 (m, 1H), 3.21-3.05 (m, 2H), 3.06-2.82 (m, 2H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 175.3, 170.0, 136.6, 136.3, 130.1, 129.1, 127.9, 127.8, 123.8, 122.7, 120.2, 119.0, 111.9, 109.4, 65.2, 53.6, 38.5, 27.7 ppm. ESI-TOF $[M+Na]^+$ obsd. = 400.1378 (calc. = 400.1380).

Standard amino acid to amino alkyne coupling (6a-d). Boc protected amino alkyne (1.73 mmol, 1.2 eq) was dissolved in TFA:DCM (1:1) and stirred at room temperature for 30 min. The solvent was removed under vacuum, and the resulting residue was dissolved in $CHCl_3$ and evaporated to dryness (x3) to remove any trace TFA. The residue (deprotected amino alkyne) was then dissolved in DCM (10 mL) and DIEA was added (4.32 mmol, 3.0 eq). The reaction mixture was cooled to 0 °C (15 min) followed by addition of EDC (1.58 mmol, 1.1 eq), HOBt (1.58 mmol, 1.1eq), and the amino acid (1.44 mmol, 1 eq) in that order. The reaction was allowed to run at 0 °C for 30 min at which time the reaction warmed to RT. After 2.5 h at RT, the reaction mixture was transferred to a separation funnel using DCM (40 mL), and the organic layer was extracted once each with 5% $KHSO_4$ (aq, 30 mL), 5% $NaHCO_3$ (aq, 30 mL), H_2O (30 mL) and brine (30 mL). The organic layer was then dried with $MgSO_4$, filtered, and concentrated under vacuum. The resulting crude product was purified by flash chromatography using EtOAc:hexanes (1:1) as eluent. Eluent was removed under vacuum to leave a yellowish oil which was subsequently dissolved in $CHCl_3$ and evaporated under vacuum (x3) to yield a white flaky solid.



Boc-L-Lys(Z)-L-Thr(Bn)-CCH (6a). yellowish white solid (683 mg, 86% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.12 (d, *J* = 10 Hz, 1H), 7.37-7.27 (m, 8H), 7.27-7.26 (m, 1H), 7.26-7.25 (m, 1H), 6.84 (d, *J* = 10 Hz, 1H), 4.99 (s, 2H), 4.73-4.71 (m, 1H), 4.54 (s, 2H), 3.91-3.88 (m, 1H), 3.61-3.56 (m, 1H), 3.21 (d, *J* = 2 Hz, 1H), 2.95-2.93 (m, 2H), 1.51-1.45 (m, 2H), 1.35 (s, 9H), 1.29 (bs, 2H), 1.23-1.21 (m, 2H), 1.15 (d, *J* = 5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 172.1, 157.0, 156.1, 138.6, 137.0, 128.9, 128.8, 128.6, 128.5, 128.2, 128,1, 81.6, 80.4, 75.8, 72.4, 71.9, 67.0, 54.6, 45.7, 40.9, 32.2, 29.9, 28.7, 22.9, 16.7 ppm. ESI-TOF (*m/z*) $[M+H]^+$ obsd. = 552.3066 (calc. = 552.3088).

Boc-L-Lys(Z)-D-Thr(Bn)-CCH (6b). white solid (702 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.18 (d, *J* = 6 Hz, 1H), 7.36-7.27 (m, 8H), 7.26-7.24 (m, 1H), 7.22-7.19 (m, 1H), 6.84 (d, *J* = 8 Hz, 1H), 4.98 (s, 2H), 4.73-4.70 (m, 1H), 4.52 (s, 2H), 3.91-3.88 (m, 1H), 3.57-3.52 (m, 1H), 3.24 (d, *J* = 2 Hz, 1H), 2.93-2.89 (m, 2H), 1.50-1.42 (m, 2H), 1.35 (s, 9H), 1.31-1.19 (m, 4H), 1.17 (d, *J* = 5 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 156.5, 155.5, 138.0, 136.5, 128.4, 128.2, 128.0, 127.8, 127.6, 127.6, 81.3, 81.3, 75.4, 71.7, 71.4, 66.5, 54.4, 45.1, 40.2, 31.6,

29.4, 28.2, 22.4, 16.2 ppm. ESI-TOF (*m/z*) $[M+H]^+$ obsd. = 552.3068 (calc. = 552.3088).

Boc-D-Lys(2-Cl-Z)-L-Thr(Bn)-CCH (6c). white solid (743 mg, 88% yield). ^{1}H NMR (400 MHz, DMSO-d_6) δ: 8.18 (d, *J* = 9 Hz, 1H), 7.47-7.43 (m, 2H), 7.36-7.31 (m, 6H), 7.27-7.25 (m, 1H), 6.85 (d, *J* = 8 Hz, 1H), 5.06 (s, 2H), 4.74-4.70 (m, 1H), 4.53 (s, 2H), 3.91-3.88 (m, 1H), 3.57-3.53 (m, 1H), 3.25 (d, *J* = 2 Hz, 1H), 2.94-2.91 (m, 2H), 1.50-1.42 (m, 2H), 1.35 (s, 9H), 1.33-1.20 (m, 4H), 1.13 (d, *J* = 6 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.6, 156.3, 155.6, 137.9, 134.2, 133.3, 129.5, 129.3, 129.1, 128.2, 127.6, 127.5, 126.7, 81.1, 79.9, 75.3, 71.7, 71.3, 63.7, 54.3, 45.0, 40.2, 31.6, 29.2, 28.1, 22.3, 16.1 ppm. ESI-TOF (*m/z*) $[M+Na]^+$ obsd. = 608.2497 (calc. = 608.2498).

Boc-D-Lys(2-Cl-Z)-D-Thr(Bn)-CCH (6d). white solid (698 mg, 83% yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 8.09 (d, *J* = 9 Hz, 1H) 7.45-7.41 (m, 2H), 7.34-7.29 (m, 6H), 7.25-7.23 (m, 1H), 6.82 (d, *J* = 8 Hz, 1H), 5.04 (s, 2H), 4.71-4.68 (m, 1H) 4.52 (s, 2H), 3.92-3.87 (m, 1H), 3.60-3.56 (m, 1H), 3.19 (d, *J* = 3 Hz, 1H), 2.93-2.91 (m, 2H), 1.48-1.43 (m, 2H), 1.32 (s, 9H), 1.28 (bs, 2H), 1.21-1.20 (m, 2H), 1.15 (d, *J* = 6 Hz, 3H) ppm. ^{13}C NMR (125 MHz, $CDCl_3$) δ: 171.5, 156.2, 155.6, 137.9, 134.2, 133.3, 129.6, 129.3, 129.1, 128.2, 127.6, 127.5, 126.7, 79.9, 75.2, 71.8, 71.3, 70.8, 63.6, 54.0, 45.0, 40.4, 31.6, 29.2, 28.1, 22.3, 16.0 ppm. ESI-TOF (*m/z*) $[M+Na]^+$ obsd. = 586.2674 (calc. = 586.2678).

Parallel synthesis of cyclic pseudo-tetrapeptides (7a–7h and *ent*-7a–*ent*-7h): Boc protected amino alkyne (**6**) (0.027 mmol, 1 eq) was dissolved in TFA/DCM (1:1) and stirred at RT for 30 minutes. The solvent was removed under vacuum, and the residue was subsequently dissolved in $CHCl_3$ and evaporated to dryness (x3) to remove any excess TFA. The crude residue (deprotected amino alkyne dipeptide) was then dissolved in DMF (1 mL), followed by addition of the azido acid dipeptide (**5**) (0.030 mmol, 1.1 eq), and, lastly, DIEA (0.3 mmol, 3 eq) was added in one portion. The solution was cooled to 0 °C (10 min). At 0 °C HATU (0.030 mmol, 1.1 eq) was added in one portion. The reaction was held at 0 °C for 30 minutes, then left at RT for 3 h. After 3 h the linear tetramer was quantified by integrating an HPLC trace using Ac-Trp-OH as a standard (λ = 280 nm, ε_{Trp} = 5690 $M^{-1}\bullet cm^{-1}$). Additional DMF was added to give a final concentration of 1 mM. 2,6-Lutidine (2 eq), DIEA (10 eq), and TBTA (2 eq) were added to the solution. The reaction was degassed by bubbling argon for 30 minutes. CuI (2 eq) was added in one portion to the reaction vessel and the reaction was left at ambient temperature under argon overnight. The DMF was then removed under vacuum with heating (≤ 40 °C). The resulting brown residue was transferred to an HF vessel as a slurry using DCM. Anisole (500 μL) was added as a scavenger, and the vessel was purged with N_2. The residue was treated with HF (~10 mL) at –76 °C and then warmed to 0 °C and left for 1 h. The HF was removed by bubbling N_2, and the resulting solid was transferred with TFA (2 mL) and precipitated with ether (40 mL) leaving a suspension of a white solid. The white solid was isolated via centriguation and removal of the supernatant. The resulting solid was purified via RP-HPLC (25–55% solvent B) and lyophilized leaving the triazole substituted cyclic tetrapeptide **7** as a white fluffy solid. Yields were determined via UV (λ = 280 nm, ε_{Trp} = 5690 $M^{-1}\bullet cm^{-1}$) and are based on dipeptide starting material (4 steps). Tetramer formation was confirmed via isotopic distribution of HRMS.

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-L-Lys-L-Thr] (7a).** White solid (36% cyclization yield, 24% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.88 (s, 1H), 8.28 (s, 1H), 8.20 (d, *J* = 10 Hz, 1H), 7.83 (d, *J* = 9 Hz, 1H), 7.78 (d, *J* = 9 Hz, 1H), 7.63 (bs, 3H), 7.53 (d, *J* = 8 Hz, 1H), 7.36 (d, *J* = 8 Hz, 1H), 7.16-7.06 (m, 7H), 6.98 (t, *J* = 16, 8 Hz, 1H), 5.21-5.17 (m, 2H), 4.56-4.53 (m, 1H), 4.45-4.42 (m, 1H), 4.26-4.23 (m, 1H), 3.98-3.94 (m, 1H), 3.58-3.43 (m, 2H), 3.11-3.08 (m, 2H), 2.73-2.71 (m, 2H), 1.80-1.76 (m, 1H), 1.62-1.60 (m, 1H), 1.51-1.48 (m, 2H), 1.21-1.16 (m, 2H), 1.14 (d, *J* = 6 Hz, 3H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3079 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-L-Trp-L-Lys-L-Thr] (7b).** White solid (59% cyclization yield, 20% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.86 (s, 1H), 8.42 (d, *J* = 8 Hz, 1H), 8.16 (s, 1H), 7.92 (d, *J* = 9 Hz, 1H), 7.68 (bs, 3H), 7.59 (d, *J* = 10 MHz, 1H), 7.46 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.25-7.19 (m, 5H), 7.07-7.04 (m, 2H), 6.96 (t, *J* = 15, 8 Hz, 1H), 5.45 (t, *J* = 15, 7 Hz, 1H), 5.15 (d, *J* = 5 Hz, 1H), 4.67-4.65 (m, 1H), 4.43-4.41 (m, 1H), 4.08-4.05 (m, 1H), 3.77-3.74 (m, 1H), 3.55 (d, *J* = 5 Hz, 2H), 3.06-2.93 (m, 2H), 2.66-2.63 (m, 2H), 1.77-1.72 (m, 1H), 1.59-1.54 (m, 1H), 1.46-1.42 (m, 2H), 1.14 (d, *J* = 6 Hz, 3H), 1.10-1.05 (m, 2H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3082 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-L-Lys-L-Thr] (7c).** White solid (90% cyclization yield, 48% overall yield). ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.78 (s, 1H), 8.63 (d, *J* = 10 Hz, 1H), 7.94 (d, *J* = 10 Hz, 1H), 7.81 (s, 1H), 7.65 (bs, 3H), 7.52 (d, *J* = 8 Hz, 1H), 7.33-7.13 (m, 8H), 7.07-7.02 (m, 2H), 6.95 (t, *J* = 15, 7 Hz, 1H), 5.44-5.41 (m, 1H), 4.66-4.57 (m, 2H), 4.07-4.03 (m, 2H), 3.53-3.48 (m, 1H), 3.28-3.00 (m, 2H), 2.79-2.75 (m, 2H), 2.66-2.63 (m, 2H), 1.59-1.54 (m, 2H) 1.42-1.39 (m, 2H), 1.10 (d, *J* = 6 Hz, 3H), 1.05-1.03 (m, 2H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3083 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-D-Lys-L-Thr] (7d).** White solid (80% cyclization yield, 21% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.75 (s, 1H), 8.26 (d, *J* = 8 Hz, 1H), 8.20 (d, *J* = 9 Hz, 1H), 7.89 (s, 1H), 7.60 (bs, 3H), 7.50 (d, *J* = 8 Hz, 1H), 7.33-7.18 (m, 7H), 7.05-7.03 (m, 2H), 6.95 (t, *J* = 15, 7 Hz, 1H), 5.24 (t, *J* = 17, 8 Hz, 1H), 4.71-4.69 (m, 1H), 4.52-4.48 (m, 1H), 4.17-4.13 (m, 1H), 4.04-4.00 (m, 1H), 3.75-3.52 (m, 2H), 3.17-3.02 (m, 2H), 2.68-2.65 (m, 2H), 1.55-1.50 (m, 1H), 1.42-1.36 (m, 3H), 1.18 (d, *J* = 6 Hz, 3H), 1.03-0.98 (m, 2H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3090 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-D-Trp-D-Lys-L-Thr] (7e).** White solid (31% cyclization yield, 20% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.95 (s, 1H), 8.26 (d, *J* = 9 Hz, 1H), 8.09 (d, *J* = 10 Hz, 1H), 7.73 (bs, 3H), 7.65 (s, 1H), 7.54 (d, *J* = 8 Hz, 1H), 7.40-7.31 (m, 3H), 7.24 (d, *J* = 8 Hz, 1H), 7.13-6.98 (m, 5H), 6.77 (d, *J* = 8 Hz, 1H), 5.02-5.00 (m, 1H), 4.82-4.79 (m, 1H), 4.58-4.50 (m, 1H), 4.23-4.19 (m, 1H), 4.30 (bs, 1H) 3.97-3.92 (m, 1H), 3.88-3.85 (m, 1H), 3.06-3.01 (m, 3H), 2.76-2.72 (m, 2H), 1.62-1.60 (m, 1H), 1.54-1.50 (m, 2H), 1.47-1.39 (m, 1H), 1.21-1.16 (m, 2H), 1.12 (d, *J* = 7 Hz, 3H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3081 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-D-Lys-L-Thr] (7f).** White solid (64% cyclization yield, 30% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.81 (s, 1H), 8.13-8.09 (m, 2H), 7.68 (bs, 3H), 7.49 (s, 1H), 7.45 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 9 Hz, 1H), 7.19-7.15 (m, 3H), 7.08-7.02 (m, 5H), 6.96 (t, *J* = 14, 7 Hz, 1H), 5.35 (t, *J* = 14, 7 Hz, 1H), 4.71-4.69 (m, 1H), 4.63-4.61 (m, 1H), 4.14-4.11 (m, 1H), 3.94-3.90 (m, 1H), 3.30-3.21 (m, 2H), 3.05-2.90 (m, 2H), 2.76-2.68 (m, 2H), 1.57-1.54 (m, 1H), 1.49-1.44 (m, 2H), 1.37-1.33 (m, 1H), 1.10-1.07 (m, 5H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3083 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-D-Lys-D-Thr] (7g).** White solid (36% cyclization yield, 22% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.74 (s, 1H), 7.97 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.80 (d, *J* = 9 Hz, 1H), 7.63 (bs, 3H), 7.49 (d, *J* = 8 Hz, 1H), 7.32-7.27 (m, 5H), 7.24-7.20 (m, 2H), 7.04 (t, *J* = 15, 7 Hz, 1H), 6.96-6.93 (m, 2H), 5.26-5.23 (m, 1H), 5.10 (bs, 1H), 4.68-4.66 (m, 1H), 4.39-4.35 (m, 1H), 4.12-4.07 (m, 2H), 3.75-3.67 (m, 2H), 3.13-2.79 (m, 2H), 2.70-2.66 (m, 2H), 1.61-1.55 (m, 1H), 1.47-1.39 (m, 3H), 1.20-1.12 (m, 1H), 1.10 (d, *J* = 6 Hz, 3H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3074 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-L-Lys-D-Thr] (7h).** White solid (86% cyclization yield, 59% overall yield). ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.81 (s, 1H), 8.68 (d, *J* = 12 Hz, 1H), 8.45 (d, *J* = 10 Hz, 1H), 7.82 (s, 1H), 7.62 (bs, 3H), 7.46 (d, *J* = 12 Hz, 1H), 7.30-7.20 (m, 7H), 7.09 (d, *J* = 2 Hz, 1H), 7.04 (t, *J* = 17, 9 Hz, 1H), 6.94 (t, *J* = 17, 9 Hz, 1H), 5.45 (t, *J* = 18, 9 Hz, 1H), 5.12-5.11 (m, 1H), 4.74-4.71 (m, 1H), 4.60-4.55 (m, 1H), 4.12-4.07 (m, 1H), 3.90-3.88 (m, 1H), 3.62-3.55 (m, 2H), 3.07-2.81 (m, 2H), 2.63-2.59 (m, 2H), 1.48-1.45 (m, 1H), 1.38-1.29 (m, 3H), 1.15 (d, *J* = 8 Hz, 3H), 0.89-0.85 (m, 2H) ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3086 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-D-Trp-D-Lys-D-Thr] (*ent*-7a).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.89 (s, 1H), 8.38 (s, 1H), 8.18 (d, *J* = 8 Hz, 1H), 7.92 (d, *J* = 8 Hz, 1H), 7.70-7.64 (m, 4H), 7.53 (d, *J* = 8 Hz, 1H), 7.36 (d, *J* = 7 Hz, 1H), 7.15-7.06 (m, 7H), 6.98 (t, *J* = 16, 8 Hz, 1H), 5.20-5.15 (m, 2H), 4.61-4.59 (m, 1H), 4.46-4.42 (m, 1H), 4.20-4.15 (m, 1H), 4.05-4.00 (m, 1H), 3.56-3.43 (m, 2H), 3.14-3.06 (m, 2H), 2.73-2.71 (m, 2H), 1.80-1.76 (m, 1H), 1.65-1.62 (m, 1H), 1.53-1.49 (m, 2H), 1.23-1.19 (m, 2H), 1.13 (d, *J* = 6 Hz, 3H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.172.5, 171.6, 167.5, 151.1, 137.5, 136.8, 130.2, 129.7, 128.3, 128.2, 124.9, 123.3, 122.3, 119.7, 119.4, 112.8, 110.8, 69.0, 67.4, 57.9, 56.3, 56.0, 39.9, 35.8, 30.8, 28.2, 27.8, 23.6, 22.2 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3090 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-D-Lys-D-Thr] (*ent*-7b).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.85 (s, 1H), 8.39 (d, *J* = 8 Hz, 1H), 8.09 (s, 1H), 7.87 (d, *J* = 8 Hz, 1H), 7.64-7.60 (m, 4H), 7.46 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H), 7.25-7.16 (m, 5H), 7.06-7.04 (m, 2H), 6.96 (t, *J* = 15, 8 Hz, 1H), 5.45 (t, *J* = 15, 7 Hz, 1H), 5.15 (bs, 1H), 4.67-4.65 (m, 1H), 4.44-4.40 (m, 1H), 4.08-4.07 (m, 1H), 3.75-3.73 (m, 1H), 3.56-3.53 (m, 2H), 3.06-2.88 (m, 2H), 2.66-2.63 (m, 2H), 1.77-1.73 (m, 1H), 1.58-1.54 (m, 1H), 1.45-1.42 (m, 2H), 1.14 (d, *J* = 6 Hz, 3H), 1.09-1.07 (m, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.171.2, 170.6, 166.5, 149.1, 137.5, 136.2, 129.1, 128.4, 127.0, 126.6, 123.1, 122.2, 121.0, 118.3, 118.1, 111.4, 109.3, 66.0, 64.2, 56.4, 55.7, 53.7, 38.6, 32.4, 29.2, 27.0, 26.5, 22.3, 20.7 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3083 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-L-Trp-D-Lys-D-Thr] (*ent*-7c).** White solid. ^{1}H NMR (500 MHz, DMSO-d_6) δ: 10.80 (s, 1H), 8.64 (d, *J* = 10 Hz, 1H), 7.96 (d, *J* = 9 Hz, 1H), 7.81 (s, 1H), 7.69 (bs, 3H), 7.52 (d, *J* = 8 Hz, 1H), 7.32 (d, *J* = 8 Hz, 1H) 7.30-7.15 (m, 6H), 7.07-7.02 (m, 2H), 6.97 (t, *J* = 14, 7 Hz, 1H), 5.44-5.41 (m, 1H), 4.66-4.60 (m, 2H), 4.06-4.05 (m, 2H), 3.57-3.48 (m, 1H), 3.25-3.01 (m, 2H), 2.78-2.75 (m, 2H), 2.66-2.63 (m, 2H), 1.59-1.54 (m, 2H) 1.42-1.39 (m, 2H), 1.10 (d, *J* = 6 Hz, 3H), 1.05-1.03 (m, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.171.2, 168.9, 167.0, 148.9, 136.6, 136.0, 128.9, 128.0, 127.0, 126.5, 122.9, 122.7, 120.8, 118.1, 118.1, 111.2, 109.6, 66.1, 63.6, 54.9, 54.2, 53.2, 38.4, 35.6, 29.0, 27.1, 26.1, 21.9, 20.8 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3084 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-D-Trp-L-Lys-D-Thr] (*ent*-7d).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.78 (s, 1H), 8.31 (d, *J* = 8 Hz, 1H), 8.29 (d, *J* = 9 Hz, 1H), 7.89 (s, 1H), 7.61 (bs, 3H), 7.50 (d, *J* = 8 Hz, 1H), 7.36-7.18 (m, 7H), 7.05-7.03 (m, 2H), 6.94 (t, *J* = 14, 7 Hz, 1H), 5.24 (t, *J* = 17, 8 Hz, 1H), 5.15 (d, *J* = 5 Hz, 1H) 4.70-4.68 (m, 1H), 4.51-4.48 (m, 1H), 4.15-4.14 (m, 1H), 4.04-4.00 (m, 1H), 3.76-3.53 (m, 2H), 3.16-3.03 (m, 2H), 2.68-2.65 (m, 2H), 1.55-1.49 (m, 1H), 1.42-1.31 (m, 3H), 1.18 (d, *J* = 6 Hz, 3H), 1.02-0.97 (m, 2H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.170.4, 170.2, 169.8, 149.2, 136.0, 135.9, 129.0, 128.3, 127.1, 126.7, 123.1, 122.2, 120.7, 118.2, 118.1, 111.1, 109.6, 68.0, 65.9, 54.0, 52.8, 52.2, 38.5, 34.0, 27.8, 26.5, 26.2, 21.7, 20.7 ppm.. ESI-TOF $[M+H]^+$ obsd. = 587.3083 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-L-Lys-D-Thr] (*ent*-7e).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.92 (s, 1H), 8.24 (d, *J* = 9 Hz, 1H), 8.07 (bs, 1H), 7.73 (bs, 3H), 7.65 (s, 1H), 7.55 (d, *J* = 8 Hz, 1H), 7.39 (d, *J* = 8 Hz, 1H) 7.22 (bs, 1H), 7.10-6.98 (m, 6H), 6.78 (d, *J* = 7 Hz, 1H), 5.02-5.00 (m, 1H), 4.82-4.79 (m, 2H), 4.58-4.54 (m, 1H), 4.23-4.21 (m, 1H), 3.97-3.92 (m, 1H), 3.88-3.85 (m, 1H), 3.06-3.01 (m, 3H), 2.76-2.72 (m, 2H), 1.62-1.60 (m, 1H), 1.54-1.50 (m, 2H), 1.47-1.39 (m, 1H), 1.21-1.16 (m, 2H), 1.12 (d, *J* = 7 Hz, 3H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.171.4, 170.5, 166.8, 149.9, 136.2, 135.2, 129.0, 128.3, 127.3, 126.7, 123.7, 122.7, 121.0, 118.3, 118.1, 111.5, 109.7, 67.7, 66.3, 56.9, 54.6, 52.8, 38.7, 34.6, 30.5, 27.0, 26.8, 22.3, 20.8 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3089 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-L-Trp-L-Lys-D-Thr] (*ent*-7f).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.84 (s, 1H), 8.17-8.10 (m, 2H), 7.63 (bs, 3H), 7.50 (s, 1H), 7.45 (d, *J* = 9 Hz, 1H), 7.33 (d, *J* = 9 Hz, 1H), 7.19-7.16 (m, 3H), 7.08-7.02 (m, 4H), 6.96 (t, *J* = 15, 7 Hz, 1H), 5.35 (t, *J* = 14, 7 Hz, 1H), 4.70-4.67 (m, 1H), 4.63-4.59 (m, 1H), 4.14-4.10 (m, 1H), 3.93-3.91 (m, 1H), 3.40-3.21 (m, 2H), 3.05-2.90 (m, 2H), 2.71-2.68 (m, 2H), 1.56-1.53 (m, 1H), 1.48-1.44 (m, 2H), 1.37-1.33 (m, 1H), 1.10-1.07 (m, 5H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.171.3, 170.2, 166.3, 149.5, 136.4, 136.0, 129.0, 128.2, 127.1, 126.5, 123.3, 122.0, 120.9, 118.3, 118.1, 111.4, 109.6, 66.5, 63.4, 56.7, 54.9, 53.0, 38.7, 36.3, 30.2, 26.9, 26.8, 22.3, 20.8 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3082 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-D-L-Trp-L-Lys-L-Thr] (*ent*-7g).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.73 (s, 1H), 7.97 (s, 1H), 7.93 (d, *J* = 8 Hz, 1H), 7.79 (d, *J* = 9 Hz, 1H), 7.63 (bs, 3H), 7.49 (d, *J* = 8 Hz, 1H), 7.32-7.17 (m, 7H), 7.04 (t, *J* = 15, 7 Hz, 1H), 6.96-6.93 (m, 2H), 5.26-5.23 (m, 1H), 5.10 (bs, 1H), 4.68-4.66 (m, 1H), 4.39-4.35 (m, 1H), 4.12-4.07 (m, 2H), 3.76-3.67 (m, 2H), 3.13-2.80 (m, 2H), 2.70-2.66 (m, 2H), 1.61-1.55 (m, 1H), 1.46-1.43 (m, 3H), 1.20-1.12 (m, 1H), 1.10 (d, *J* = 6 Hz, 3H) ppm; ^{13}C NMR (151 MHz, DMSO-d_6) δ:.171.3, 168.8, 167.7, 149.4, 136.3, 136.1, 129.3, 128.3, 127.2, 126.3, 124.0, 123.3, 120.8, 118.2, 118.2, 111.3, 110.0, 67.8, 66.1, 54.9, 53.9, 53.6, 38.6, 32.9, 39.4, 26.3, 26.3, 22.1, 20.6 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3085 (calc. = 587.3089).

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-L-Trp-D-Lys-L-Thr] (*ent*-7h).** White solid. ^{1}H NMR (600 MHz, DMSO-d_6) δ: 10.81 (s, 1H), 8.68 (d, *J* = 10 Hz, 1H), 8.45 (d, *J* = 8 Hz, 1H), 7.82 (s, 1H), 7.61 (bs, 3H), 7.46 (d, *J* = 8 Hz, 1H), 7.30-7.20 (m, 7H), 7.09 (d, *J* = 2 Hz, 1H), 7.04 (t, *J* = 14, 7 Hz, 1H), 6.94 (t, *J* = 15, 8 Hz, 1H), 5.45 (t, *J* = 14, 8 Hz, 1H), 5.12 (bs, 1H), 4.73-4.71 (m, 1H), 4.59-4.55 (m, 1H), 4.11-4.08 (m, 1H), 3.90 (bs, 1H), 3.62-3.55 (m, 2H), 3.06-2.81 (m, 2H), 2.63-2.59 (m, 2H), 1.49-1.45 (m, 1H), 1.38-1.29 (m, 3H), 1.15 (d, *J* = 6 Hz, 3H), 0.88-0.84 (m, 2H) ppm; ^{13}C NMR

(151 MHz, DMSO-d_6) δ:.170.3, 170.1, 166.5, 148.9, 137.2, 135.3, 129.1, 128.4, 127.1, 126.5, 124.1, 122.9, 120.9, 118.3, 118.2, 111.1, 109.4, 66.3, 64.4, 53.7, 52.7, 52.2, 38.5, 31.8, 27.7, 27.3, 26.6, 21.6, 20.7 ppm. ESI-TOF $[M+H]^+$ obsd. = 587.3078 (calc. = 587.3089).

4. Determination of somatostatin receptor affinity profiles.

The compounds were tested for their ability to bind to the five human sst receptor subtypes in complete displacement experiments using the universal SRIF radioligand [^{125}]-[Leu^8, D-Trp^{22}, Tyr^{25}]-SRIF-28. CHO-K1 and CCL39 cells stably expressing the human sst_1-sst_5 receptors were grown as described previously.[S7] Cell membrane pellets were prepared and receptor autoradiography was done as described in detail previously.[S7] SRIF-28 was run in parallel as control. IC_{50} values were calculated after quantification of the data using a computer assisted image processing system.[S7] The data are shown in Table 1 of the manuscript.

5. Structural determinations and analysis.

Crystal Structure of 4

Crystals were obtained by vapor phase diffusion of hexanes into a solution of **4** in chloroform and contained residual TFA from preparative HPLC purification. Diffraction data were collected at 296 K on a Bruker SMART APEX diffractometer equipped with a graphite monochromator using Mo_{Ka} radiation (l = 0.71073 Å). Crystal data for **4**·CF_3CO_2H: colorless crystal 0.16 × 0.22 × 0.28 mm^3, orthorhombic, $C222_1$, a = 15.269(3), b = 29.564(6), c = 18.535(4) Å, $a = b = g$ = 90°, V = 8367(3) Å^3, r_{calcd} = 1.275 gm cm^{-3}, m = 0.099 mm^{-1}, 2.76° < 2q < 50°, 31327 (7380) observed (independent) reflections. Full-matrix least squares refinement against F^2 using SHELXTL-PC gave a final structure with R_1 = 0.0860 (0.2170), wR_2 = 0.1505 (0.2620) for 4140 reflections with $I > 2s$ (all reflections), GOF (F^2) = 1.004. Non-hydrogen atoms were refined anisotropically and hydrogen atoms were fixed at calculated positions relative to C, N, and O atoms. CCDC 698625 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/conts/retrieving.html (or from the Cambridge Crystallographic Data Centre, 12, Union Road, Cambridge CB21EZ, UK; fax: (+44)1223-336-033; or deposit@ccdc.cam.ac.uk).

Structural Determinations by Multidimensional NMR

NMR structural determinations were carried out for compounds **1**–**3** and **7a**–**7h**; the structures of the enantiomers (***ent*-7a**–***ent*-7h**) were modelled with Insight II ("reflect" command) using a representative structure from each series of accepted structures. All experiments were carried out in ~7–9 mM solution of peptide in DMSO-d_6 on a Bruker DRX-600 MHz instrument. Two-dimensional experiments were obtained using 2048 data points in the direct dimension and 512 data points in the indirect dimension. All 2-D experiments were taken under a regulated temperature of 22 °C with the exceptions of **1** (27 °C), **2** (40 °C), and **7f** (27 °C) for improved peak separations. TOCSY or COSY spectra were obtained for initial peak assignment. ROESY spectra were taken using a mixing time of 200 ms. Integration was performed using the program NEASY followed by peak sorting and normalization via Microsoft Excel. Using the equation $I = cr^{-6}$, where I is peak intensity, r is distance between protons, and c is a constant, the rOe measurements were converted to a scale of strong (≤2.7 Å), medium (≤3.5 Å) and weak (≤4.5 Å) rOe using the rOe of two geminal CH_2 protons as a standard. In cases where there were no suitable geminal couplings present, the distance between two vicinal protons was used as the standard. Structure calculation was carried out using Crystallography & NMR System (CNS). A patch was written to modify an amide bond to a 1,4-disubstituted-1,4-(1,2,3-triazole) using known bond geometries from the Cambridge Structural Database. A survey of the ROESY spectra at high intensity gave no evidence of *cis* amide bonds as evidenced by the absence of C_α–C_α or C_α–C_β couplings across residues. To further investigate the possibility of *cis-trans* isomerization of the amide bonds, additional calculations in which the amide bonds were allowed to isomerize were performed. However, no structures that matched the distance restraints were found, so the calculations were subsequently carried out using a fixed *trans* amide bond conformation. Two sets of molecular dynamic annealing calculations were performed. The first set of 50 calculations did not use rOe restraints and were performed as a control to confirm that diverse conformations were sampled during the calculations. The second set of 50 were performed using the rOe distance restraints and were used as trial structures. Those of the 50 trial structures that did not violate the rOe data by more than ± 0.2 Å (accepted structures) were used to represent the solution structure. In some cases, violations were found involving the triazole proton (HT) or the Trp sidechain (Trp HE3 and Trp HD1) with the amide backbone, and were attributed to flipping of the triazole ring or the indole side chain between two mutually exclusive structures (see Figure S1 for atom naming). Those structures in which the triazole proton or the specific Trp side chain protons have been omitted from the calculation are noted. The calculations for **7e** yielded three additional accepted structures indicative of a fast rotation of the amide bond between Trp and Lys. Though these three structures were accepted by the program, the structures were omitted due to the absence of an expected rOe between the Trp HA and the Lys HN even at high intensity.

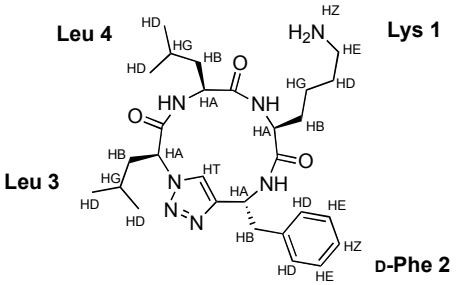
S7.) J. C. Reubi, J. C. Schaer, B. Waser, S. Wenger, A. Heppeler, J. Schmitt, and H. R. Mäcke, *Eur. J. Nuclear Med.* **2000**, *27*, 273-282.

Root Mean Square Deviation Calculations:
The "fit" command in MacPYMOL was used for pairwise fitting. The obtained RMSD values used for cutoffs as described in the manuscript are listed in the table below.

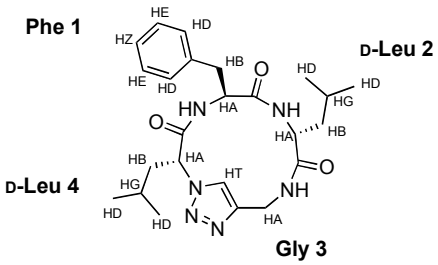
Fitting onto ***ent*-7g** used atoms PHE (Cα, Cβ); TRP (Cβ); LYS (Cβ).
Fitting onto ***ent*-7f** used atoms PHE (Cα, Cβ); TRP (backbone N, Cβ); LYS (Cβ, carbonyl C); THR (Cα).
Fitting onto **7h** used atoms PHE (Cα); TRP (Cα, Cβ); LYS (Cα, Cβ); THR (Cα).

Table S1. Compilation of peptide RMSD values from pairfitting analyses.

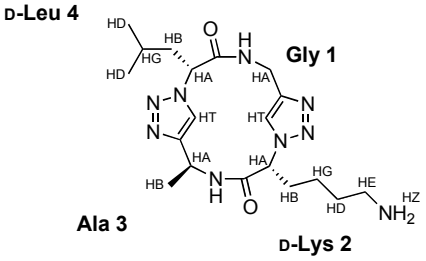
Compound	RMSD (Å)		
	***ent*-7g**	***ent*-7f**	**7h**
7a	0.956	1.014	0.653
7b	0.602	0.523	0.983
7c	0.857	1.136	0.385
7d	0.392	0.705	1.407
7e	0.598	0.464	0.962
7f	0.759	0.742	0.650
7g	0.417	0.701	1.359
7h	0.830	1.229	~
***ent*-7a**	0.679	0.509	0.936
***ent*-7b**	0.753	0.810	0.765
***ent*-7c**	0.665	0.562	1.186
***ent*-7d**	0.096	0.984	0.192
***ent*-7e**	0.885	0.961	0.719
***ent*-7f**	0.567	~	0.952
***ent*-7g**	~	0.938	0.275
***ent*-7h**	0.639	0.581	1.366



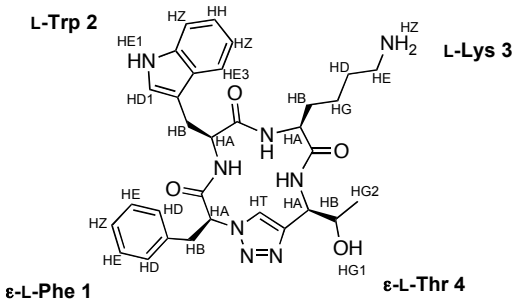
compound **1**



compound **2**



compound **3**



compound **7a**

Figure S1. Depiction of residue numbering and atom naming for compounds **1–3** and **7a**. Compounds **7a**–**7h** and ***ent*-7a**–***ent*-7h** all use the same numbering and naming scheme.

The NOE tables below report the observed rOe measurements: strong ≤ 2.7 Å, medium ≤ 3.5 Å, weak ≤ 4.5 Å. The atom labels used are those used by the program NEASY; see Figure S1 for atom labelling. For compounds **7a**–**7h** and ***ent*-7a**–***ent*-7h**, the proton THR HG1 is the threonine OH proton and was omitted from all calculations; the number of accepted structures (out of 50 possible) are shown in brackets above each table.

Compound 1

Res	Atom	Res	Atom	NOE
1	HA	2	HN	s
1	HN	4	HN	s
2	HB#	2	HA	s
3	HB#	4	HN	s
3	HB#	3	HA	s
2	HB#	2	HA	s
2	HB#	2	HN	s
3	HB#	3	HA	s
3	HB#	4	HN	s
1	HN	2	HT	s
1	HA	1	HN	m
3	HB#	2	HT	m
4	HA	4	HN	m
1	HB#	1	HA	m
3	HG	3	HA	m
2	HA	2	HN	m
2	HA	2	HT	m
2	HA	2	HB#	m
3	HB#	2	HT	m
2	HB#	2	HB#	m
2	HB#	2	HB#	m
2	HB#	2	HN	m
3	HA	2	HT	m
1	HB#	1	HD##	m
2	HT	2	HN	m
3	HD##	3	HA	m
4	HD##	4	HA	m
4	HA	1	HN	m
2	HN	2	HB#	w
2	HB#	2	HT	w
1	HA	2	HT	w
1	HA	4	HA	w
2	HA	2	HB#	w
2	HB#	2	HT	w
4	HA	3	HA	w
2	HB#	2	HB#	w
1	HB#	1	HN	w
1	HB#	1	HD##	w
4	HA	2	HT	w
2	HB#	2	HB#	w
1	HA	2	HA	w
2	HN	1	HN	w
2	HA	1	HN	w

The "#" sign indicates diastereotopic protons that were either overlapping or not stereospecifically assigned; residue numbers and atom naming used are indicated in the figure preceding NOE tables.

Compound 2

Res	Atom	Res	Atom	NOE
2	HN	1	HA	s
2	HA	3	HN	s
1	HA	2	HN	s
4	HA	1	HN	s
3	HA^1	3	HN	s
1	$HB^{\#}$	1	HA	s
1	$HB^{\#}$	1	HA	s
4	$HB^{\#}$	4	HA	m
2	$HB^{\#}$	2	HA	m
1	HN	1	HA	m
1	HA	1	HN	m
4	HA	3	HT	m
1	$HB^{\#}$	1	HN	m
1	$HB^{\#}$	1	HN	m
2	$HB^{\#}$	2	HN	m
1	HA	1	$HB^{\#}$	m
2	$HB^{\#}$	2	HA	m
1	$HB^{\#}$	1	HA	m
2	HG	2	HA	m
4	HG	4	HA	m
3	HT	1	HN	m
2	$HB^{\#}$	2	HA	m
3	HT	3	HA^2	w
4	$HB^{\#}$	4	HA	w
2	HG	2	HN	w
4	$HB^{\#}$	3	HT	w
3	HA^1	3	HT	w
1	HA	2	HA	w
2	HA	3	HT	w
1	HA	1	$HB^{\#}$	w
1	HB#	1	HN	w

Glycine protons HA^1 and HA^2 are pro-(*S*) and pro-(*R*) respectively; the "#" sign indicates diastereotopic protons that were either overlapping or not stereospecifically assigned; residue numbers and atom naming used are indicated in the figure preceding NOE tables.

Compound 3

Res	Atom	Res	Atom	NOE
3	HN	2	HA	s
4	HA	1	HN	s
1	HA^1	1	HN	s
3	HT	3	HA	m
1	HA^2	1	HT	m
2	$HE^{\#}$	2	$HZ^{\#}$	m
3	HN	3	HA	m
4	HA	3	HT	m
1	HA^2	1	HN	m
4	HG	4	HA	m
3	$HB^{\#}$	3	HN	m
3	HT5	4	HA	m
4	$HD^{\#}$	4	HA	m
1	HT	2	HA	m
2	$HD^{\#}$	2	$HZ^{\#}$	w
1	HN	3	HT	w
3	HN	3	HT	w
3	HN	1	HT	w
1	HN	1	HT	w
1	HA^1	1	HT	w

Glycine protons HA^1 and HA^2 are pro-(*S*) and pro-(*R*) respectively; the "#" sign indicates diastereotopic protons that were either overlapping or not stereospecifically assigned; residue numbers and atom naming used are indicated in the figure preceding NOE tables.

Compound 7a

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-L-Lys-L-Thr]**

Accepted structures: [30/50]

prot		res	Hs	prot		res	Hs	integration	corrected	calc dist	
HB	3	LYS	1	HB	3	LYS	1	405600	405600	1.8	2.7
HB	4	THR	1	HG1	4	THR	1	163900	163900	2.0	2.7
HB	1	PHE	1	HA	1	PHE	1	109600	109600	2.2	2.7
HB	1	PHE	1	HN	2	TRP	1	108200	108200	2.2	2.7
HB#	2	TRP	2	HA	2	TRP	1	197100	98550	2.2	2.7
HB	1	PHE	1	HA	1	PHE	1	84720	84720	2.3	2.7
HA	3	LYS	1	HN	3	LYS	1	76190	76190	2.3	2.7
HB	2	TRP	1	HE3	2	TRP	1	72630	72630	2.3	2.7
HB	1	PHE	1	HN	2	TRP	1	71270	71270	2.4	2.7
HB	3	LYS	1	HA	3	LYS	1	65790	65790	2.4	2.7
HN	2	TRP	1	HN	3	LYS	1	61840	61840	2.4	2.7
HA	3	LYS	1	HN	4	THR	1	60120	60120	2.4	2.7
HT	4	THR	1	HN	2	TRP	1	59640	59640	2.4	2.7
HA	2	TRP	1	HN	3	LYS	1	58740	58740	2.4	2.7
HB	3	LYS	1	HA	3	LYS	1	57200	57200	2.4	2.7
HG2#	4	THR	3	HB	4	THR	1	169600	56533.3333	2.4	2.7
HA	2	TRP	1	HD1	2	TRP	1	55440	55440	2.5	2.7
HA	2	TRP	1	HE3	2	TRP	1	53630	53630	2.5	2.7
HA	4	THR	1	HN	4	THR	1	50740	50740	2.5	2.7
HB	1	PHE	1	HT	4	THR	1	50270	50270	2.5	2.7
HB	1	PHE	1	HT	4	THR	1	44620	44620	2.5	2.7
HG#	3	LYS	2	HA	3	LYS	1	84780	42390	2.6	2.7
HB#	2	TRP	2	HN	2	TRP	1	81560	40780	2.6	2.7
HA	1	PHE	1	HD#	1	PHE	2	77870	38935	2.6	2.7
HA	1	PHE	1	HT	4	THR	1	36420	36420	2.6	2.7
HG2#	4	THR	3	HA	4	THR	1	107400	35800	2.6	2.7
HA	2	TRP	1	HN	2	TRP	1	35460	35460	2.6	2.7
HB	1	PHE	1	HD#	1	PHE	2	70130	35065	2.6	2.7
HT	4	THR	1	HN	3	LYS	1	34520	34520	2.7	2.7
HB	1	PHE	1	HD#	1	PHE	2	67350	33675	2.7	2.7
HB#	2	TRP	2	HN	3	LYS	1	61460	30730	2.7	2.7
HB#	2	TRP	2	HD1	2	TRP	1	58030	29015	2.7	2.7
HG2#	4	THR	3	HG1	4	THR	1	85630	28543.3333	2.7	2.7
HE#	3	LYS	2	HZ#	3	LYS	3	134500	22416.6667	2.9	3.5
HB	3	LYS	1	HN	4	THR	1	20920	20920	2.9	3.5
HB	3	LYS	1	HN	3	LYS	1	19850	19850	2.9	3.5
HD#	3	LYS	2	HA	3	LYS	1	38550	19275	2.9	3.5
HB	3	LYS	1	HN	4	THR	1	17900	17900	3.0	3.5
HA	4	THR	1	HG1	4	THR	1	17440	17440	3.0	3.5
HB	4	THR	1	HN	4	THR	1	15230	15230	3.0	3.5
HT	4	THR	1	HN	4	THR	1	13530	13530	3.1	3.5
HD#	3	LYS	2	HZ#	3	LYS	3	54820	9136.66667	3.3	3.5
HB	3	LYS	1	HN	3	LYS	1	6034	6034	3.5	3.5

The triazole HT, Trp HE3, and Trp HD1 protons were omitted from calculations for this peptide. The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7b

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-L-Trp-L-Lys-L-Thr]**

Accepted structures: [28/50]

prot		res	Hs	prot		res	Hs	integration	corrected	calc dist	
HB	2	TRP	1	HB	2	TRP	1	1163000	1163000	1.8	2.7
HB	3	LYS	1	HB	3	LYS	1	773700	773700	1.9	2.7
HA	1	PHE	1	HN	2	TRP	1	499100	499100	2.0	2.7
HB	4	THR	1	HA	4	THR	1	355000	355000	2.1	2.7
HB	4	THR	1	HG1	4	THR	1	289000	289000	2.2	2.7
HA	1	PHE	1	HT	4	THR	1	232600	232600	2.3	2.7
HA	3	LYS	1	HN	3	LYS	1	222500	222500	2.3	2.7
HA	2	TRP	1	HN	3	LYS	1	218300	218300	2.3	2.7
HB#	1	PHE	2	HA	1	PHE	1	427100	213550	2.3	2.7
HB	2	TRP	1	HA	2	TRP	1	208900	208900	2.3	2.7
HB	2	TRP	1	HA	2	TRP	1	201400	201400	2.4	2.7
HA	2	TRP	1	HD1	2	TRP	1	160500	160500	2.4	2.7
HB	2	TRP	1	HN	2	TRP	1	142800	142800	2.5	2.7
HA	4	THR	1	HN	4	THR	1	138200	138200	2.5	2.7
HG2#	4	THR	3	HB	4	THR	1	385800	128600	2.5	2.7
HB	3	LYS	1	HA	3	LYS	1	114800	114800	2.6	2.7
HB	3	LYS	1	HA	3	LYS	1	113400	113400	2.6	2.7
HB	2	TRP	1	HD1	2	TRP	1	-108900	108900	2.6	2.7
HN	4	THR	1	HT	4	THR	1	100500	100500	2.6	2.7
HB	3	LYS	1	HN	4	THR	1	98600	98600	2.7	2.7
HB	3	LYS	1	HN	4	THR	1	98120	98120	2.7	2.7
HB	2	TRP	1	HE3	2	TRP	1	93620	93620	2.7	2.7
HT	4	THR	1	HN	2	TRP	1	90120	90120	2.7	2.7
HB	2	TRP	1	HN	2	TRP	1	90100	90100	2.7	2.7
HA	1	PHE	1	HD#	1	PHE	2	176400	88200	2.7	2.7
HD1	2	TRP	1	HE1	2	TRP	1	86890	86890	2.7	2.7
HB#	1	PHE	2	HD#	1	PHE	2	344700	86175	2.7	2.7
HG2#	4	THR	3	HA	4	THR	1	254000	84666.66667	2.7	2.7
HA	2	TRP	1	HE3	2	TRP	1	82210	82210	2.7	2.7
HA	2	TRP	1	HN	2	TRP	1	81220	81220	2.7	2.7
HN	3	LYS	1	HN	2	TRP	1	75710	75710	2.8	3.5
HG#	3	LYS	2	HA	3	LYS	1	146000	73000	2.8	3.5
HD#	3	LYS	2	HE#	3	LYS	2	278100	69525	2.8	3.5
HN	4	THR	1	HN	3	LYS	1	66950	66950	2.8	3.5
HA	3	LYS	1	HN	4	THR	1	63940	63940	2.9	3.5
HB	4	THR	1	HN	4	THR	1	61770	61770	2.9	3.5
HN	3	LYS	1	HT	4	THR	1	58560	58560	2.9	3.5
HB	2	TRP	1	HE3	2	TRP	1	51980	51980	3.0	3.5
HG#	3	LYS	2	HB	3	LYS	1	97700	48850	3.0	3.5
HB	2	TRP	1	HD1	2	TRP	1	45780	45780	3.0	3.5
HG#	3	LYS	2	HB	3	LYS	1	91350	45675	3.0	3.5
HG#	3	LYS	2	HD#	3	LYS	2	181100	45275	3.0	3.5
HB	4	THR	1	HT	4	THR	1	38240	38240	3.1	3.5
HG#	3	LYS	2	HE#	3	LYS	2	149100	37275	3.1	3.5
HE#	3	LYS	2	HZ#	3	LYS	3	210500	35083.33333	3.2	3.5
HG2#	4	THR	3	HG1	4	THR	1	86020	28673.33333	3.3	3.5
HD#	3	LYS	2	HA	3	LYS	1	49690	24845	3.3	3.5
HG1	4	THR	1	HT	4	THR	1	22200	22200	3.4	3.5
HZ2	2	TRP	1	HE1	2	TRP	1	17920	17920	3.5	3.5
HB#	1	PHE	2	HT	4	THR	1	28540	14270	3.7	4.5
HA	4	THR	1	HT	4	THR	1	12180	12180	3.8	4.5
HD#	3	LYS	2	HZ#	3	LYS	3	53100	8850	4.0	4.5
HB	2	TRP	1	HN	3	LYS	1	8810	8810	4.0	4.5

The triazole HT proton was omitted from calculations for this peptide. The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7c

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-L-Lys-L-Thr]**

Accepted structures: [18/50]

prot		res	Hs	prot		res	Hs	integration	corrected	calc dist	
HB	2	TRP	1	HB	2	TRP	1	-4613000	4613000	1.8	2.7
HB	1	PHE	1	HB	1	PHE	1	-4220000	4220000	1.8	2.7
HA	2	TRP	1	HN	3	LYS	1	-1416000	1416000	2.1	2.7
HA	1	PHE	1	HN	2	TRP	1	-1259000	1259000	2.2	2.7
HB	4	THR	1	HA	4	THR	1	-883400	883400	2.3	2.7
HB	3	LYS	1	HA	3	LYS	1	-658200	658200	2.4	2.7
HB	1	PHE	1	HA	1	PHE	1	-614700	614700	2.5	2.7
HB	2	TRP	1	HA	2	TRP	1	-543100	543100	2.5	2.7
HN	4	THR	1	HT	4	THR	1	-480100	480100	2.6	2.7
HB	4	THR	1	HN	4	THR	1	-469600	469600	2.6	2.7
HB	1	PHE	1	HA	1	PHE	1	-449100	449100	2.6	2.7
HN	4	THR	1	HN	3	LYS	1	-421500	421500	2.6	2.7
HB	3	LYS	1	HA	3	LYS	1	-392500	392500	2.7	2.7
HB	2	TRP	1	HA	2	TRP	1	-369000	369000	2.7	2.7
HA	4	THR	1	HN	4	THR	1	-351600	351600	2.7	2.7
HB	3	LYS	1	HN	3	LYS	1	-289100	289100	2.8	3.5
HA	2	TRP	1	HE3	2	TRP	1	-274400	274400	2.8	3.5
HA	2	TRP	1	HD1	2	TRP	1	-263300	263300	2.8	3.5
HB	3	LYS	1	HN	4	THR	1	-253400	253400	2.9	3.5
HB	3	LYS	1	HN	4	THR	1	-242500	242500	2.9	3.5
HD1	2	TRP	1	HE1	2	TRP	1	-235400	235400	2.9	3.5
HA	2	TRP	1	HN	2	TRP	1	-223300	223300	2.9	3.5
HG2#	4	THR	3	HA	4	THR	1	-666600	222200	2.9	3.5
HA	2	TRP	1	HT	4	THR	1	-211800	211800	2.9	3.5
HB	2	TRP	1	HN	2	TRP	1	-210100	210100	2.9	3.5
HA	1	PHE	1	HD#	1	PHE	2	-345300	172650	3.0	3.5
HB	2	TRP	1	HE3	2	TRP	1	-169900	169900	3.1	3.5
HB	3	LYS	1	HN	3	LYS	1	-169000	169000	3.1	3.5
HB	2	TRP	1	HN	2	TRP	1	-167400	167400	3.1	3.5
HB	2	TRP	1	HD1	2	TRP	1	-164600	164600	3.1	3.5
HA	1	PHE	1	HT	4	THR	1	-160400	160400	3.1	3.5
HT	4	THR	1	HN	3	LYS	1	-152800	152800	3.1	3.5
HB	1	PHE	1	HD#	1	PHE	2	-300900	150450	3.1	3.5
HB	1	PHE	1	HD#	1	PHE	2	-270500	135250	3.2	3.5
HB	2	TRP	1	HE3	2	TRP	1	-129600	129600	3.2	3.5
HB	1	PHE	1	HT	4	THR	1	-125200	125200	3.2	3.5
HG#	3	LYS	2	HB	3	LYS	1	-246000	123000	3.2	3.5
HB	4	THR	1	HT	4	THR	1	-106200	106200	3.3	3.5
HB	3	LYS	1	HN	3	LYS	1	-104100	104100	3.3	3.5
HB	2	TRP	1	HD1	2	TRP	1	-90500	90500	3.4	3.5
HG#	3	LYS	2	HE#	3	LYS	2	-349300	87325	3.4	3.5
HB	1	PHE	1	HT	4	THR	1	-80050	80050	3.5	3.5
HE#	3	LYS	2	HZ#	3	LYS	3	-470700	78450	3.5	3.5
HZ2	2	TRP	1	HE1	2	TRP	1	-56400	56400	3.7	4.5
HD#	3	LYS	2	HZ#	3	LYS	3	-313400	52233.33333	3.7	4.5
HT	4	THR	1	HN	2	TRP	1	-50380	50380	3.7	4.5
HG2#	4	THR	3	HN	4	THR	1	-126200	42066.66667	3.9	4.5
HG#	3	LYS	2	HZ#	3	LYS	3	-31570	5261.666667	5.4	4.5

The triazole HT proton was omitted from calculations for this peptide. The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7d

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-D-Lys-L-Thr]**

Accepted structures: [40/50]

prot		res	Hs	prot		res	Hs	integration	corrected	calc dist	
HB	1	PHE	1	HB	1	PHE	1	-1440000	-1440000	1.8	2.7
HA	3	LYS	1	HN	4	THR	1	-763400	-763400	2.0	2.7
HA	2	TRP	1	HN	3	LYS	1	-614500	-614500	2.0	2.7
HB	4	THR	1	HA	4	THR	1	-471800	-471800	2.1	2.7
HB	1	PHE	1	HA	1	PHE	1	-322800	-322800	2.3	2.7
HB	1	PHE	1	HN	2	TRP	1	-298200	-298200	2.3	2.7
HB	3	LYS	1	HA	3	LYS	1	-197300	-197300	2.5	2.7
HB	3	LYS	1	HA	3	LYS	1	-194800	-194800	2.5	2.7
HB	2	TRP	1	HA	2	TRP	1	-188800	-188800	2.5	2.7
HB	2	TRP	1	HA	2	TRP	1	-185200	-185200	2.5	2.7
HT	4	THR	1	HN	2	TRP	1	-165100	-165100	2.5	2.7
HB	1	PHE	1	HN	2	TRP	1	-154400	-154400	2.6	2.7
HB	1	PHE	1	HA	1	PHE	1	-153900	-153900	2.6	2.7
HB	3	LYS	1	HN	3	LYS	1	-148100	-148100	2.6	2.7
HA	2	TRP	1	HD1	2	TRP	1	-141400	-141400	2.6	2.7
HG2#	4	THR	3	HB	4	THR	1	-417600	-139200	2.6	2.7
HN	4	THR	1	HT	4	THR	1	-120500	-120500	2.7	2.7
HB	4	THR	1	HN	4	THR	1	-113100	-113100	2.7	2.7
HG#	3	LYS	2	HA	3	LYS	1	-222300	-111150	2.7	2.7
HG2#	4	THR	3	HA	4	THR	1	-315800	-105266.6667	2.7	2.7
HB	1	PHE	1	HT	4	THR	1	-102900	-102900	2.7	2.7
HD1	2	TRP	1	HE1	2	TRP	1	-98960	-98960	2.7	2.7
HB	2	TRP	1	HN	2	TRP	1	-96790	-96790	2.8	3.5
HB	2	TRP	1	HE3	2	TRP	1	-93710	-93710	2.8	3.5
HB	2	TRP	1	HD1	2	TRP	1	-84820	-84820	2.8	3.5
HB	1	PHE	1	HT	4	THR	1	-83900	-83900	2.8	3.5
HB	1	PHE	1	HD#	1	PHE	2	-161900	-80950	2.8	3.5
HA	2	TRP	1	HE3	2	TRP	1	-79540	-79540	2.9	3.5
HB	3	LYS	1	HE#	3	LYS	2	-143700	-71850	2.9	3.5
HA	4	THR	1	HN	4	THR	1	-70980	-70980	2.9	3.5
HA	1	PHE	1	HD#	1	PHE	2	-140100	-70050	2.9	3.5
HB	1	PHE	1	HD#	1	PHE	2	-137800	-68900	2.9	3.5
HB	3	LYS	1	HN	3	LYS	1	-65630	-65630	2.9	3.5
HB	2	TRP	1	HN	2	TRP	1	-64990	-64990	2.9	3.5
HA	2	TRP	1	HN	2	TRP	1	-64160	-64160	3.0	3.5
HA	3	LYS	1	HN	3	LYS	1	-56330	-56330	3.0	3.5
HA	1	PHE	1	HN	2	TRP	1	-54450	-54450	3.0	3.5
HD#	3	LYS	2	HE#	3	LYS	2	-217200	-54300	3.0	3.5
HE#	3	LYS	2	HZ#	3	LYS	3	-281700	-46950	3.1	3.5
HG#	3	LYS	2	HB	3	LYS	1	-84560	-42280	3.2	3.5
HB	2	TRP	1	HE3	2	TRP	1	-41570	-41570	3.2	3.5
HA	1	PHE	1	HT	4	THR	1	-35600	-35600	3.3	3.5
HB	4	THR	1	HT	4	THR	1	-34120	-34120	3.3	3.5
HG#	3	LYS	2	HE#	3	LYS	2	-124000	-31000	3.3	3.5
HB	2	TRP	1	HD1	2	TRP	1	-29980	-29980	3.4	3.5
HG#	3	LYS	2	HN	3	LYS	1	-56180	-28090	3.4	3.5
HA	4	THR	1	HT	4	THR	1	-25070	-25070	3.5	3.5
HG#	3	LYS	2	HD#	3	LYS	2	-96610	-24152.5	3.5	3.5
HG2#	4	THR	3	HN	4	THR	1	-64520	-21506.66667	3.5	3.5
HD#	3	LYS	2	HZ#	3	LYS	3	-108200	-18033.33333	3.7	4.5

The triazole HT, Trp HE3, and Trp HD1 protons were omitted from calculations for this peptide. The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7e

***cyclo*[1,4-(1,2,3-triazole)-D-Phe-D-Trp-D-Lys-L-Thr]**

Accepted structures: [27/50]

prot	res		Hs	prot	res		Hs	integration	corrected	calc dist	
HB	1	PHE	1	HB	1	PHE	1	194300	194300	1.8	2.7
HB	3	LYS	1	HB	3	LYS	1	68260	68260	2.1	2.7
HB	4	THR	1	HA	4	THR	1	63260	63260	2.1	2.7
HA	3	LYS	1	HN	4	THR	1	53700	53700	2.2	2.7
HB	1	PHE	1	HA	1	PHE	1	33110	33110	2.4	2.7
HN	3	LYS	1	HN	2	TRP	1	28430	28430	2.4	2.7
HB#	2	TRP	2	HN	2	TRP	1	50420	25210	2.5	2.7
HB#	2	TRP	2	HA	2	TRP	1	42970	21485	2.5	2.7
HB	4	THR	1	HN	4	THR	1	19940	19940	2.6	2.7
HB	3	LYS	1	HA	3	LYS	1	16710	16710	2.6	2.7
HA	4	THR	1	HN	4	THR	1	15720	15720	2.7	2.7
HG2#	4	THR	3	HA	4	THR	1	38260	12753.33333	2.8	3.5
HB	3	LYS	1	HA	3	LYS	1	11340	11340	2.8	3.5
HB	1	PHE	1	HD#	1	PHE	2	21440	10720	2.9	3.5
HG2#	4	THR	3	HB	4	THR	1	30530	10176.66667	2.9	3.5
HA	1	PHE	1	HD#	1	PHE	2	19560	9780	2.9	3.5
HA	3	LYS	1	HN	3	LYS	1	9547	9547	2.9	3.5
HG#	3	LYS	2	HA	3	LYS	1	17760	8880	2.9	3.5
HB#	2	TRP	2	HN	3	LYS	1	16440	8220	3.0	3.5
HA	1	PHE	1	HT	4	THR	1	8172	8172	3.0	3.5
HB	1	PHE	1	HA	1	PHE	1	7462	7462	3.0	3.5
HT	4	THR	1	HN	4	THR	1	6505	6505	3.1	3.5
HA	2	TRP	1	HN	2	TRP	1	6458	6458	3.1	3.5
HN	3	LYS	1	HT	4	THR	1	5990	5990	3.1	3.5
HA	4	THR	1	HT	4	THR	1	4563	4563	3.3	3.5
HB	4	THR	1	HT	4	THR	1	3041	3041	3.5	3.5
HN	2	TRP	1	HT	4	THR	1	2981	2981	3.5	3.5
HG#	3	LYS	2	HE#	3	LYS	2	10160	2540	3.6	4.5

The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7f

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-D-Lys-L-Thr]**

Accepted structures: [26/50]

prot		res	Hs	prot		res	Hs	integration	corrected	calc dist	
HB	1	PHE	1	HB	1	PHE	1	964000	964000	1.8	2.7
HB	3	LYS	1	HB	3	LYS	1	537500	537500	1.9	2.7
HA	3	LYS	1	HN	4	THR	1	357300	357300	2.1	2.7
HA	1	PHE	1	HN	2	TRP	1	256400	256400	2.2	2.7
HB	4	THR	1	HA	4	THR	1	146800	146800	2.4	2.7
HB	2	TRP	1	HA	2	TRP	1	141500	141500	2.4	2.7
HB	1	PHE	1	HA	1	PHE	1	138700	138700	2.4	2.7
HB	1	PHE	1	HA	1	PHE	1	133100	133100	2.4	2.7
HB	2	TRP	1	HA	2	TRP	1	125700	125700	2.5	2.7
HB	4	THR	1	HN	4	THR	1	107900	107900	2.5	2.7
HB	3	LYS	1	HA	3	LYS	1	107000	107000	2.5	2.7
HA	2	TRP	1	HN	3	LYS	1	99530	99530	2.6	2.7
HT	4	THR	1	HN	4	THR	1	92620	92620	2.6	2.7
HA	3	LYS	1	HN	3	LYS	1	91750	91750	2.6	2.7
HB	2	TRP	1	HN	2	TRP	1	75920	75920	2.7	2.7
HG2#	4	THR	3	HA	4	THR	1	214900	71633.33333	2.7	2.7
HB	2	TRP	1	HD1	2	TRP	1	70520	70520	2.7	2.7
HB	3	LYS	1	HA	3	LYS	1	67740	67740	2.7	2.7
HD1	2	TRP	1	HE1	2	TRP	1	67020	67020	2.7	2.7
HG#	3	LYS	2	HA	3	LYS	1	127000	63500	2.8	3.5
HB	1	PHE	1	HD#	1	PHE	2	104600	52300	2.9	3.5
HG2#	4	THR	3	HA	4	THR	1	145800	48600	2.9	3.5
HB	2	TRP	1	HE3	2	TRP	1	46260	46260	2.9	3.5
HA	2	TRP	1	HE3	2	TRP	1	46110	46110	2.9	3.5
HB	2	TRP	1	HN	2	TRP	1	46000	46000	2.9	3.5
HD#	3	LYS	2	HE#	3	LYS	2	181300	45325	2.9	3.5
HA	1	PHE	1	HD#	1	PHE	2	88430	44215	2.9	3.5
HA	2	TRP	1	HN	2	TRP	1	44180	44180	2.9	3.5
HA	4	THR	1	HN	4	THR	1	41660	41660	3.0	3.5
HA	1	PHE	1	HT	4	THR	1	39270	39270	3.0	3.5
HB	3	LYS	1	HN	3	LYS	1	38510	38510	3.0	3.5
HB	1	PHE	1	HD#	1	PHE	2	72480	36240	3.0	3.5
HB	1	PHE	1	HT	4	THR	1	34810	34810	3.1	3.5
HG#	3	LYS	2	HB	3	LYS	1	67270	33635	3.1	3.5
HB	3	LYS	1	HN	3	LYS	1	32590	32590	3.1	3.5
HB	4	THR	1	HT	4	THR	1	32330	32330	3.1	3.5
HB	2	TRP	1	HE3	2	TRP	1	32000	32000	3.1	3.5
HG#	3	LYS	2	HD#	3	LYS	2	115500	28875	3.2	3.5
HA	3	LYS	1	HT	4	THR	1	24400	24400	3.2	3.5
HG#	3	LYS	2	HE#	3	LYS	2	96330	24082.5	3.3	3.5
HE#	3	LYS	2	HZ#	3	LYS	3	125800	20966.66667	3.3	3.5
HG#	3	LYS	2	HB	3	LYS	1	41120	20560	3.3	3.5
HD#	3	LYS	2	HA	3	LYS	1	32720	16360	3.5	3.5
HA	4	THR	1	HT	4	THR	1	14240	14240	3.6	4.5
HD#	3	LYS	2	HZ#	3	LYS	3	62380	10396.66667	3.7	4.5
HG2#	4	THR	3	HN	4	THR	1	29520	9840	3.8	4.5
HB	3	LYS	1	HD#	3	LYS	2	12810	6405	4.1	4.5

The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7g

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-L-Trp-D-Lys-D-Thr]**

Accepted structures: [49/50]

prot	res		Hs	prot	res		Hs	integration	corrected	calc dist	
HB	2	TRP	1	HB	2	TRP	1	3062000	3062000	1.8	2.7
HB	4	THR	1	HA	4	THR	1	648800	648800	2.3	2.7
HB	3	LYS	1	HA	3	LYS	1	603000	603000	2.3	2.7
HB	2	TRP	1	HA	2	TRP	1	450200	450200	2.4	2.7
HA	4	THR	1	HN	4	THR	1	438800	438800	2.4	2.7
HA	3	LYS	1	HN	4	THR	1	397400	397400	2.5	2.7
HB#	1	PHE	2	HA	1	PHE	1	708900	354450	2.5	2.7
HB#	1	PHE	2	HN	2	TRP	1	687300	343650	2.5	2.7
HN	4	THR	1	HN	3	LYS	1	337000	337000	2.5	2.7
HB	3	LYS	1	HA	3	LYS	1	328400	328400	2.6	2.7
HB	2	TRP	1	HA	2	TRP	1	325200	325200	2.6	2.7
HA	1	PHE	1	HT	4	THR	1	315400	315400	2.6	2.7
HG2#	4	THR	3	HB	4	THR	1	815800	271933.333	2.6	2.7
HA	2	TRP	1	HN	3	LYS	1	255700	255700	2.7	2.7
HA	2	TRP	1	HN	2	TRP	1	247600	247600	2.7	2.7
HA	1	PHE	1	HD#	1	PHE	2	495200	247600	2.7	2.7
HB#	1	PHE	2	HD#	1	PHE	2	733100	183275	2.8	3.5
HA	3	LYS	1	HN	3	LYS	1	183000	183000	2.8	3.5
HB	3	LYS	1	HN	4	THR	1	179400	179400	2.8	3.5
HG2#	4	THR	3	HA	4	THR	1	530000	176666.667	2.8	3.5
HN	3	LYS	1	HT	4	THR	1	157900	157900	2.9	3.5
HB	3	LYS	1	HN	3	LYS	1	151800	151800	2.9	3.5
HB	4	THR	1	HT	4	THR	1	137700	137700	3.0	3.5
HB	2	TRP	1	HN	2	TRP	1	126100	126100	3.0	3.5
HB	3	LYS	1	HN	3	LYS	1	118200	118200	3.0	3.5
HA	1	PHE	1	HN	2	TRP	1	117300	117300	3.0	3.5
HE#	3	LYS	2	HZ#	3	LYS	3	525500	87583.3333	3.2	3.5
HB	2	TRP	1	HN	2	TRP	1	86340	86340	3.2	3.5
HG#	3	LYS	3	HE#	3	LYS	2	469600	78266.6667	3.2	3.5
HA	4	THR	1	HT	4	THR	1	69900	69900	3.3	3.5
HA	2	TRP	1	HT	4	THR	1	45060	45060	3.6	4.5
HD#	3	LYS	2	HZ#	3	LYS	3	208000	34666.6667	3.7	4.5

The triazole HT proton was omitted from calculations for this peptide. The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

Compound 7h

***cyclo*[1,4-(1,2,3-triazole)-L-Phe-D-Trp-L-Lys-D-Thr]**

Accepted structures: [23/50]

prot		res	Hs	prot		res	Hs	integration	corrected	calc dist	
HB	2	TRP	1	HB	2	TRP	1	3062000	3062000	1.8	2.7
HA	3	LYS	1	HN	4	THR	1	1412000	1412000	2.0	2.7
HA	2	TRP	1	HN	3	LYS	1	1192000	1192000	2.1	2.7
HA	1	PHE	1	HN	2	TRP	1	1080000	1080000	2.1	2.7
HB	4	THR	1	HA	4	THR	1	867000	867000	2.2	2.7
HA	1	PHE	1	HT	1	PHE	1	475900	475900	2.4	2.7
HB	2	TRP	1	HD1	2	TRP	1	-429800	429800	2.4	2.7
HB	2	TRP	1	HA	2	TRP	1	421400	421400	2.4	2.7
HB#	1	PHE	2	HA	1	PHE	1	781900	390950	2.5	2.7
HB	3	LYS	1	HA	3	LYS	1	353400	353400	2.5	2.7
HB	3	LYS	1	HA	3	LYS	1	336200	336200	2.5	2.7
HB	2	TRP	1	HA	2	TRP	1	296400	296400	2.6	2.7
HB	3	LYS	1	HN	3	LYS	1	295000	295000	2.6	2.7
HB	4	THR	1	HG1	4	THR	1	285400	285400	2.6	2.7
HN	4	THR	1	HT	1	PHE	1	264100	264100	2.6	2.7
HT	1	PHE	1	HN	2	TRP	1	260400	260400	2.7	2.7
HG2#	4	THR	3	HB	4	THR	1	738400	246133.3333	2.7	2.7
HB	4	THR	1	HN	4	THR	1	189800	189800	2.8	3.5
HG#	3	LYS	2	HA	3	LYS	1	378600	189300	2.8	3.5
HA	4	THR	1	HN	4	THR	1	185300	185300	2.8	3.5
HA	3	LYS	1	HN	3	LYS	1	171300	171300	2.8	3.5
HB	2	TRP	1	HN	2	TRP	1	168600	168600	2.9	3.5
HD1	2	TRP	1	HE1	2	TRP	1	168300	168300	2.9	3.5
HA	2	TRP	1	HN	2	TRP	1	165600	165600	2.9	3.5
HA	1	PHE	1	HD#	1	PHE	2	330200	165100	2.9	3.5
HG2#	4	THR	3	HA	4	THR	1	493800	164600	2.9	3.5
HB#	1	PHE	2	HD#	1	PHE	2	641000	160250	2.9	3.5
HB	2	TRP	1	HN	2	TRP	1	159700	159700	2.9	3.5
HB	2	TRP	1	HD1	2	TRP	1	151100	151100	2.9	3.5
HG#	3	LYS	2	HB	3	LYS	1	174700	87350	3.2	3.5
HB	3	LYS	1	HN	3	LYS	1	82580	82580	3.2	3.5
HE#	3	LYS	2	HZ#	3	LYS	3	471000	78500	3.2	3.5
HB	4	THR	1	HT	1	PHE	1	70640	70640	3.3	3.5
HG#	3	LYS	2	HE#	3	LYS	2	275900	68975	3.3	3.5
HA	4	THR	1	HT	1	PHE	1	55690	55690	3.4	3.5
HG#	3	LYS	2	HN	3	LYS	1	103200	51600	3.5	3.5
HG2#	4	THR	3	HN	4	THR	1	136000	45333.33333	3.6	4.5
HG2#	4	THR	3	HG1	4	THR	1	67290	22430	4.0	4.5
HB#	1	PHE	2	HT	1	PHE	1	26210	13105	4.4	4.5

The "#" signs indicates diastereotopic protons that were either overlapping or not stereospecifically assigned.

5. Analysis of compounds as mimics of various β-turn motifs.

The pharmacophoric region of somatostatin adopts a type II' β-turn, but several other β-turn types are known and represent appealing targets for drug design. To assess the potential of the triazole-modified cyclic tetrapeptides as mimics of common β-turn motifs, we first tabulated dihedral angles for each of our reported structures (Table S1) using the dihedral angle measurement tool in MacPymol. These angles were compared to the dihedral angles of idealized β-turn motifs[S8] (Table S2) to identify peptides that would likely serve as close mimics of the particular β-turn types. For each β-turn motif examined, several of the identified peptides were subsequently pairfit to the structure of the β-turn (constructed using the mean dihedral angles reported in ref. S8 and Table S2). The overlay giving the lowest RMSD value for the C_α and C_β atoms of residues *i* + 1 and *i* + 2 for each β-turn type is presented in Figure S2.

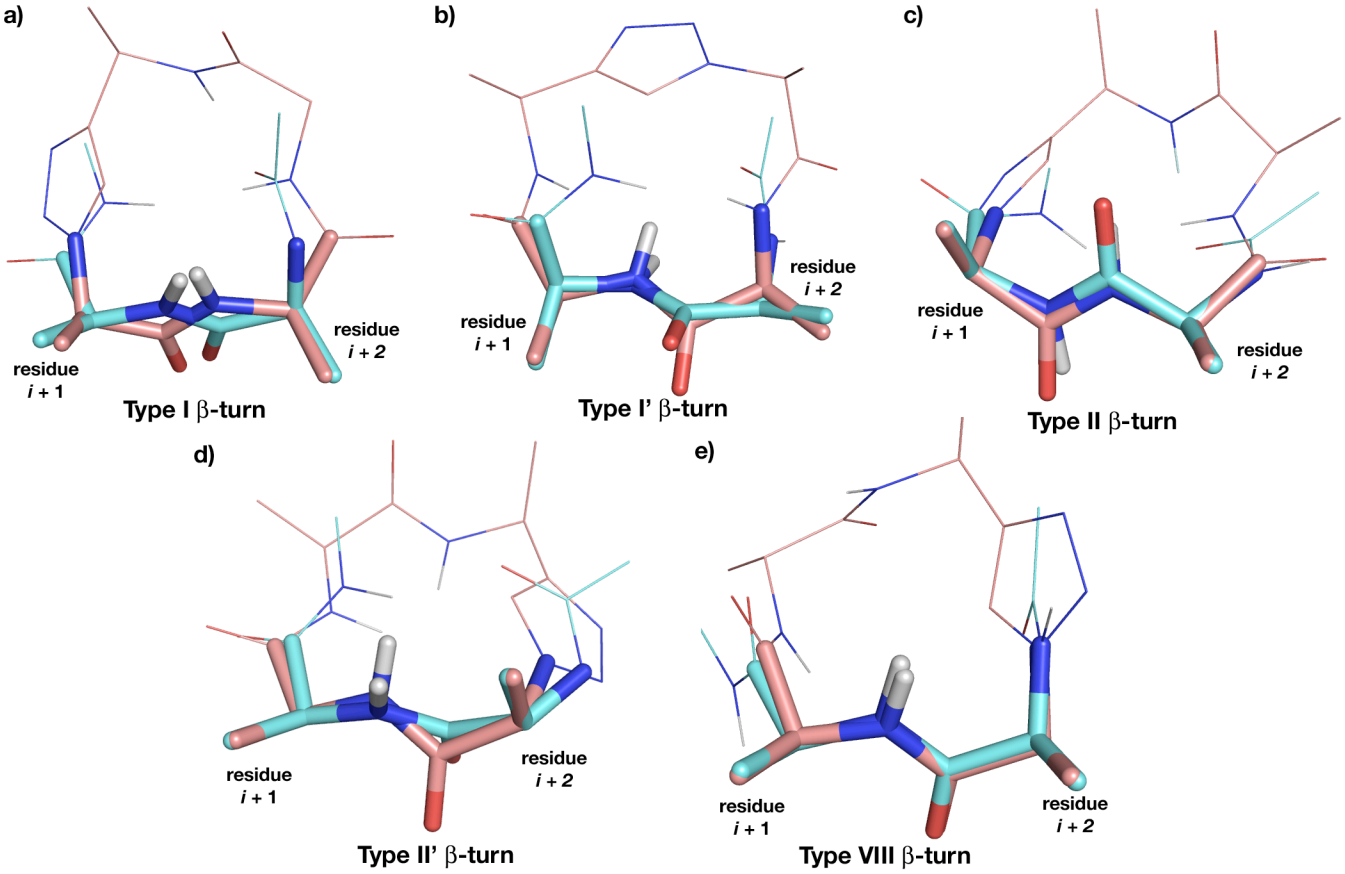


Figure S2. Overlays of triazole-containing pseudo-tetrapeptides with idealized structures of various β-turn motifs. In all panels, the β-turn is colored cyan while the triazole-modified peptide is colored pink. (a) Overlay of a type I β-turn onto peptide *ent*-**7a** (RMSD = 0.232 Å for C_α and C_β atoms of residues *i* + 1 and *i* + 2). Note that the turn motif and peptide have opposite N→C orientations in this overlay. (b) Overlay of a type I' β-turn onto peptide **7a** (RMSD = 0.314 Å for C_α and C_β atoms of residues *i* + 1 and *i* + 2). (c) Overlay of a type II β-turn onto peptide *ent*-**7a** (RMSD = 0.057 Å for C_α and C_β atoms of residues *i* + 1 and *i* + 2). Note that the turn motif and peptide have opposite N→C orientations in this overlay. (d) Overlay of a type II' β-turn onto peptide **7a** (RMSD = 0.081 Å for C_α and C_β atoms of residues *i* + 1 and *i* + 2). (e) Overlay of a type VIII β-turn onto peptide **7d** (RMSD = 0.105 Å for C_α and C_β atoms of residues *i* + 1 and *i* + 2).

S8.) E. G. Hutchinson and J. M. Thornton, Protein Sci. **1994**, *3*, 2207-2216.

Table S2. Compilation of peptide phi (Φ) and psi (Ψ) dihedral angles.[a]

		Phe	Trp		Lys		Thr
Compound	**Chirality**	***Ψ***	***Φ***	***Ψ***	***Φ***	***Ψ***	***Φ***
7a	LLLL	-66	-144	37	143	61	112
7b	DLLL	82	-109	55	142	-92	-72
7c	LDLL	41	-147	86	-80	-67	-92
7d	LLDL	-46	-127	85	-105	73	-107
7e	DDDL	-65	-106	-55	-119	92	-81
7f	LDDL	52	-130	85	74	85	-84
7g	LLDD	-34	-143	79	-111	45	140
7h	LDLD	81	-109	78	-114	92	-73
***ent*-7a**	DDDD	-66	-144	37	143	61	112
***ent*-7b**	LDDD	81	-109	55	142	-92	-72
***ent*-7c**	DLDD	41	-147	86	-80	-67	-92
***ent*-7d**	DDLD	-46	-127	85	-105	73	-107
***ent*-7e**	LLLD	-65	-106	-55	-119	92	-81
***ent*-7f**	DLLD	52	-130	85	74	85	-84
***ent*-7g**	DDLL	-34	-143	79	-111	45	140
***ent*-7h**	DLDL	81	-109	78	-114	92	-73
		Leu	**Leu**		**Lys**		**Phe**
1	LLLD	-64	-110	-46	-129	90	-85
		Leu	**Phe**		**Leu**		**Gly**
2	DLD~	41	-130	84	-103	73	-105

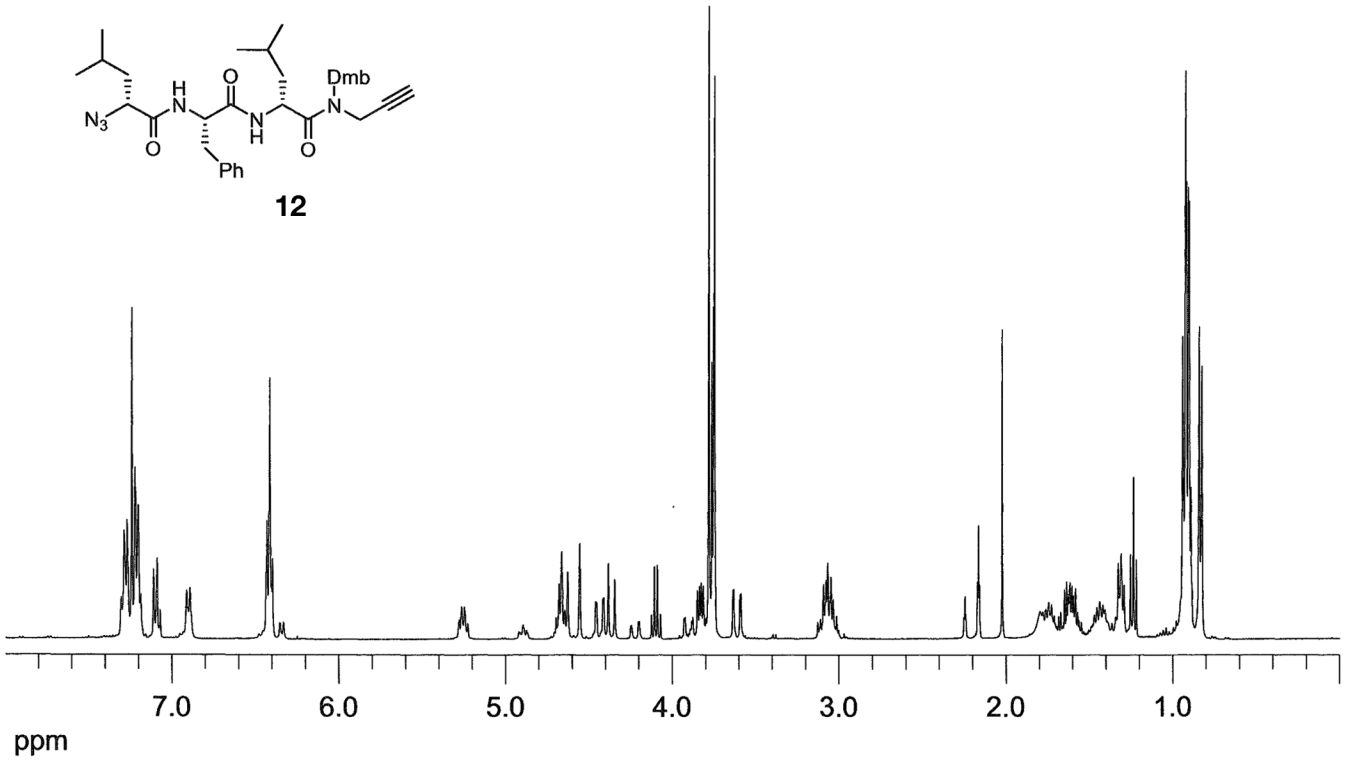
[a] For amino acids having D-chirality, the transformation (Φ, Ψ) → (-Φ, -Ψ) was applied, following the convention for reporting dihedral angles of D-amino acids. For a discussion of this convention, see ref S9.

Table S3. Phi (Φ) and psi (Ψ) dihedral angles for mean and idealized β-turn motifs (taken from ref. S8).[a]

	***i* + 1**		***i* + 2**	
β-turn	***Φ***	***Ψ***	***Φ***	***Ψ***
type I	-64 (-60)	-27 (-30)	-90 (-90)	-7 (0)
type I'	55 (60)	38 (30)	78 (90)	6 (0)
type II	-60 (-60)	131 (120)	84 (80)	1 (0)
type II'	60 (60)	-126 (-120)	-91 (-80)	1 (0)
type VIII	-72 (-60)	-33 (-30)	-123 (-120)	121(120)

[a] Mean dihedral angles and idealized dihedral angles are reported, with the idealized values in parentheses.

S9.) J. B. O. Mitchell and J. Smith, *Proteins: Structure, Function, and Genetics* **2003**, *50*, 563-571.



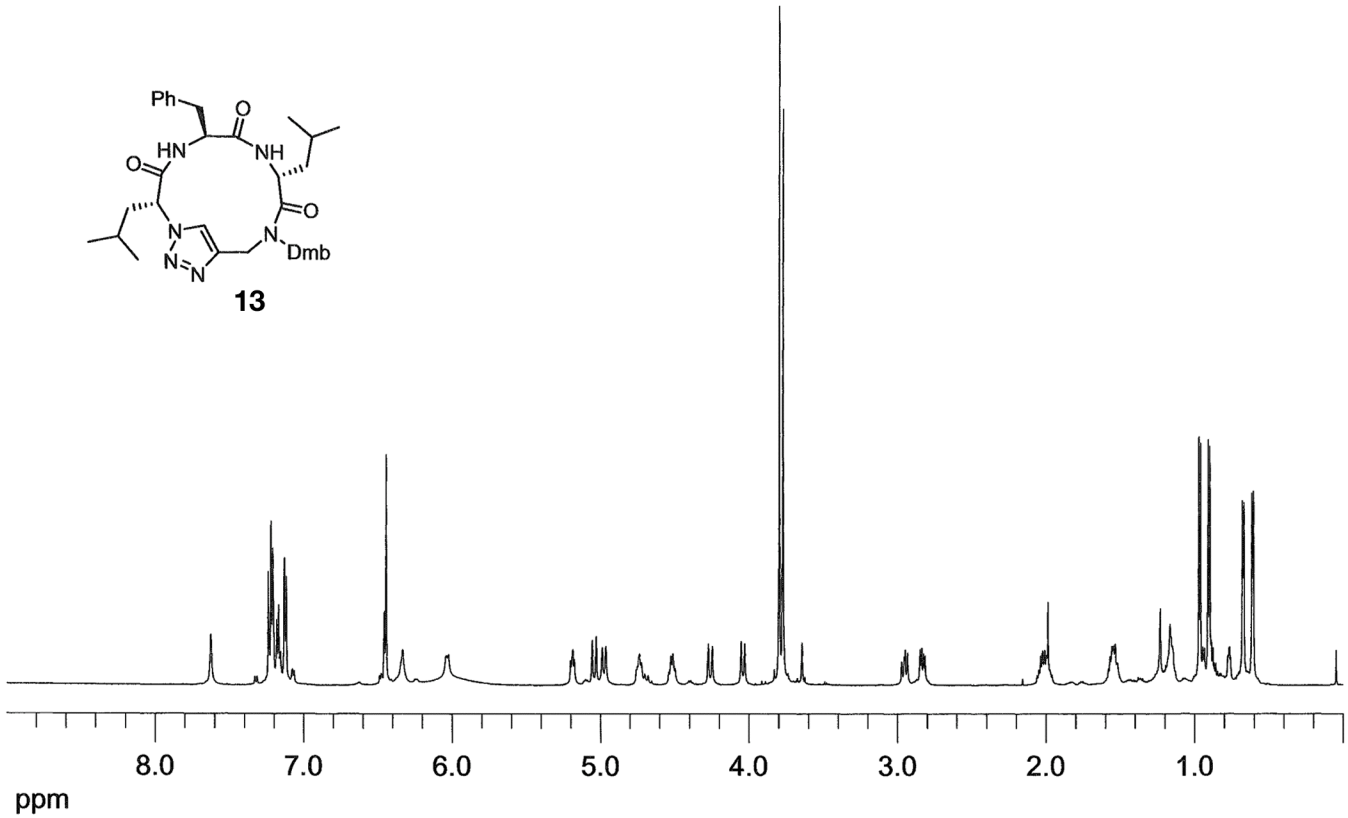
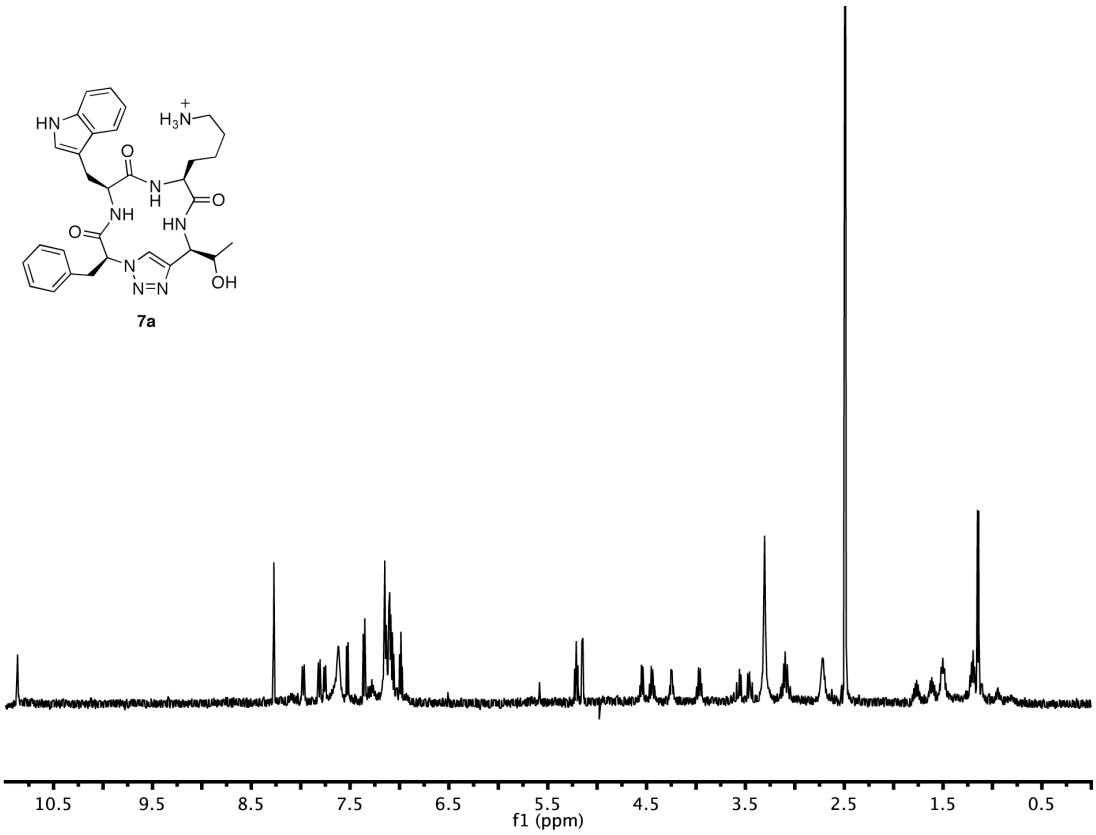


Figure S3. ^{1}H NMR spectra for compounds **12** and **13**.



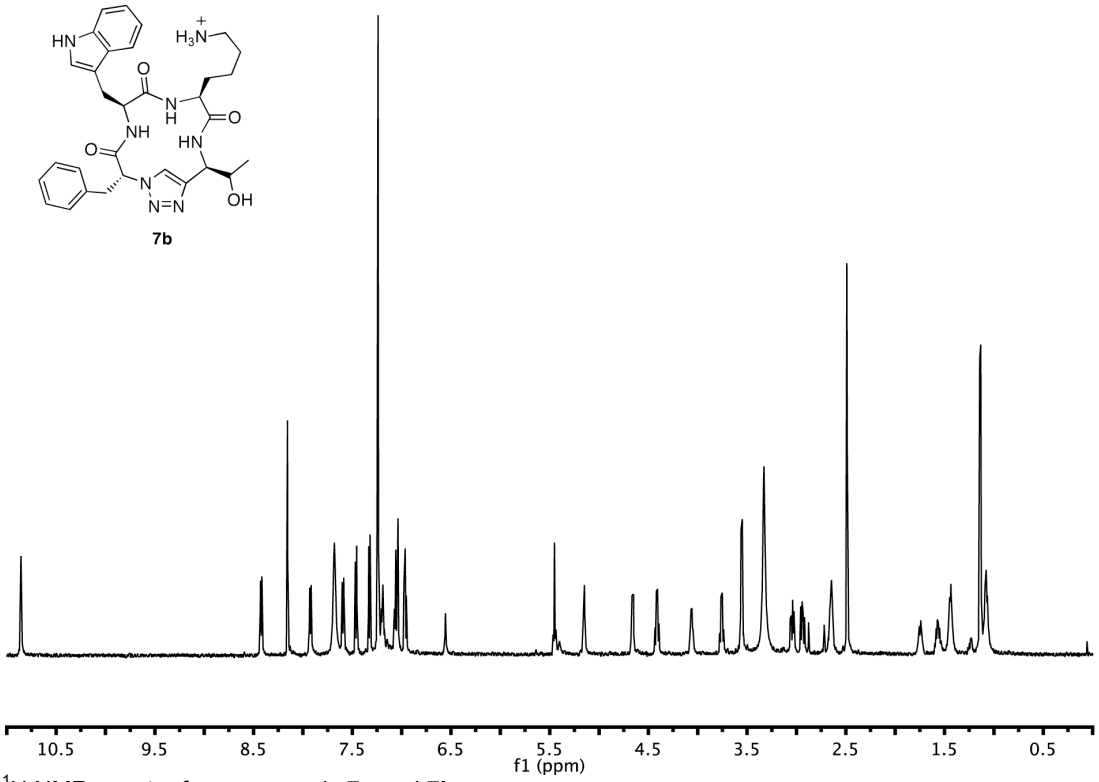
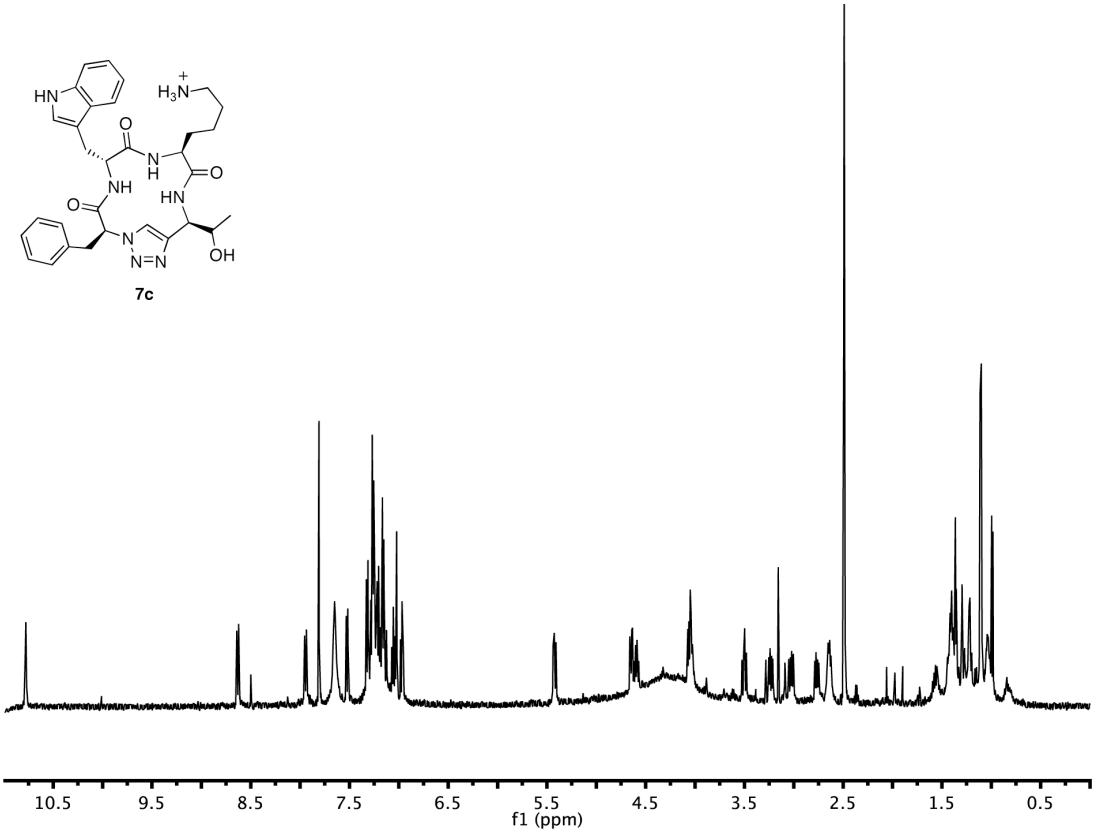
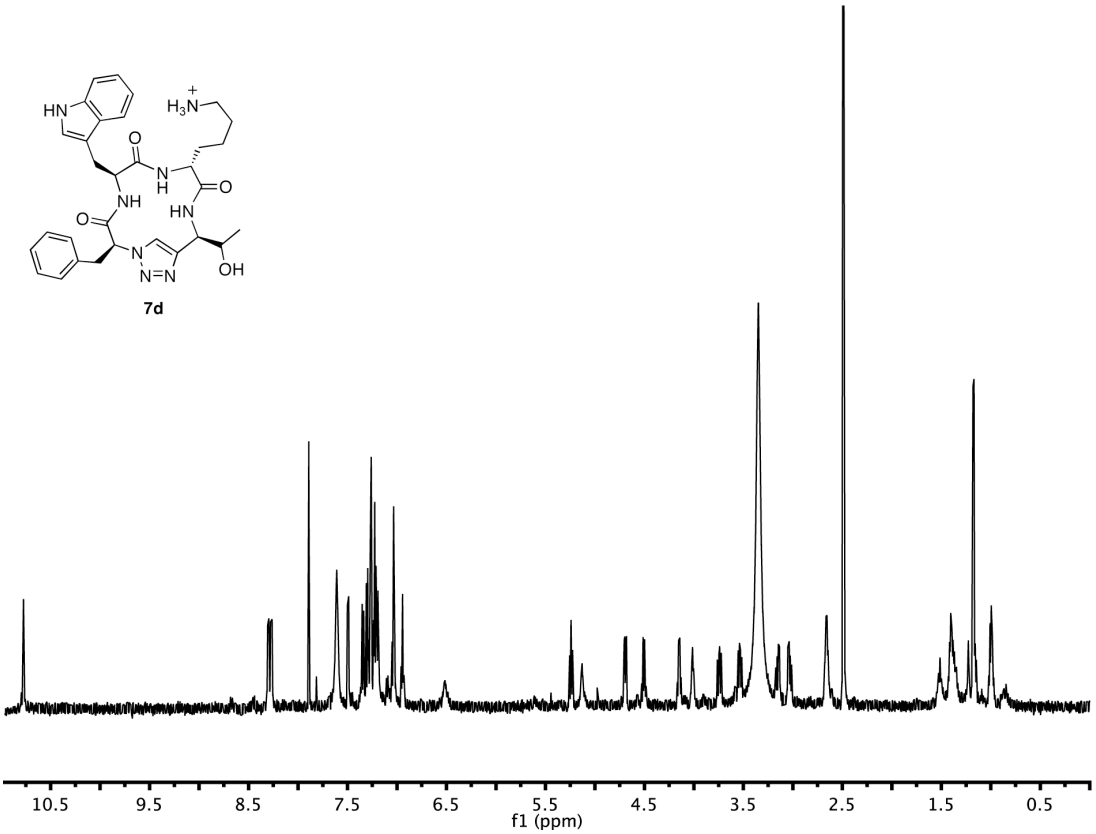


Figure S4. ^{1}H NMR spectra for compounds **7a** and **7b**.



7c



7d

Figure S5. ^{1}H NMR spectra for compounds **7c** and **7d**.

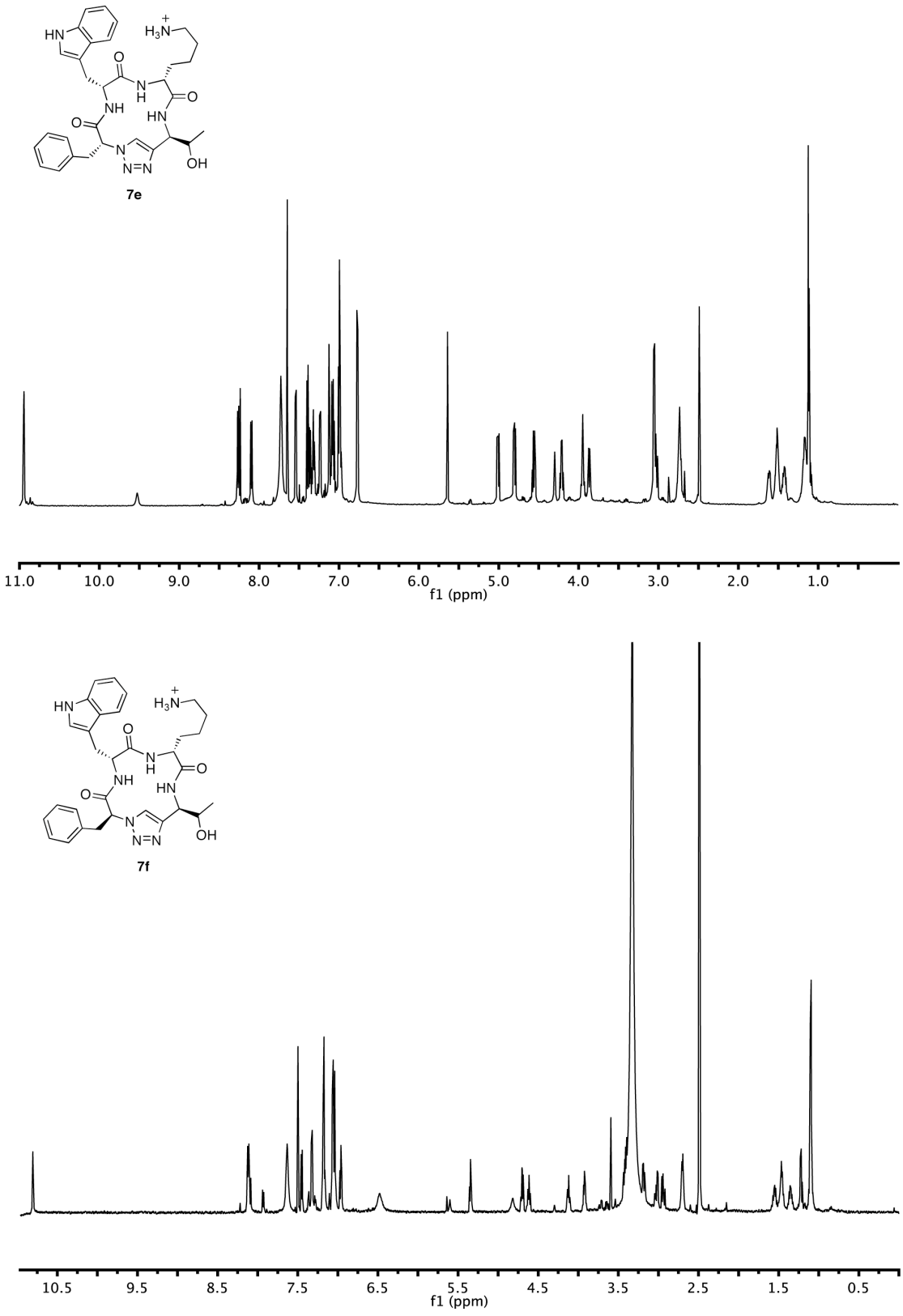
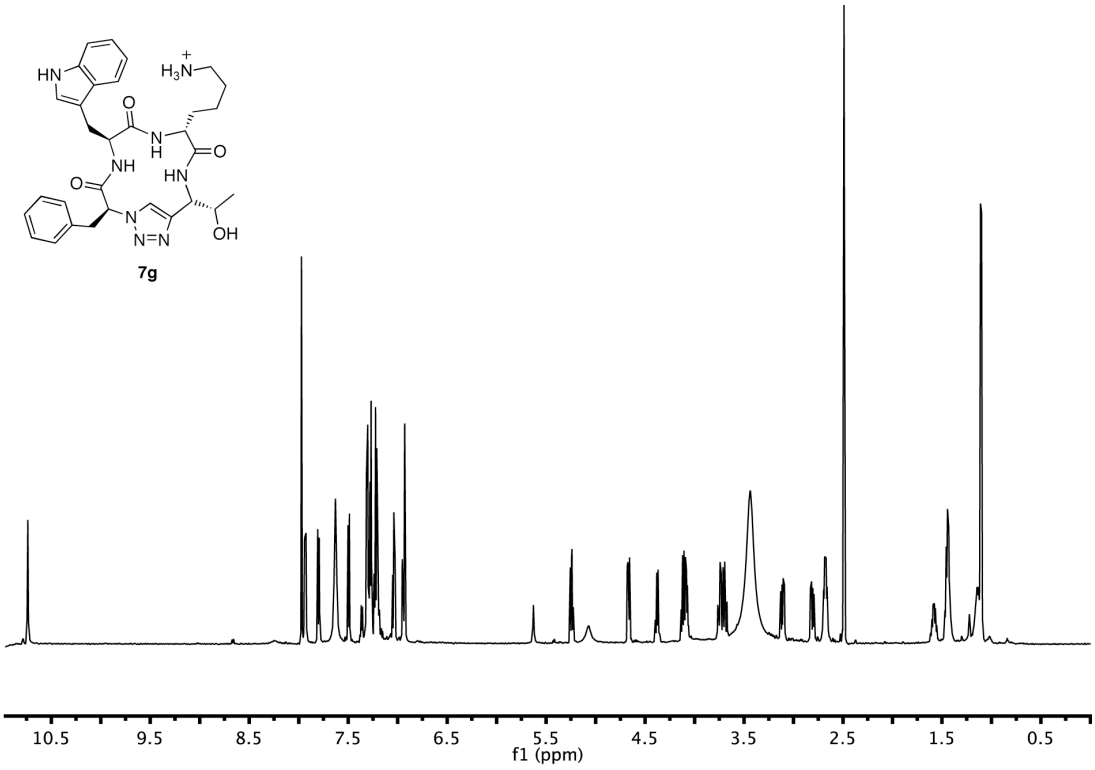


Figure S6. ^{1}H NMR spectra for compounds **7e** and **7f**.



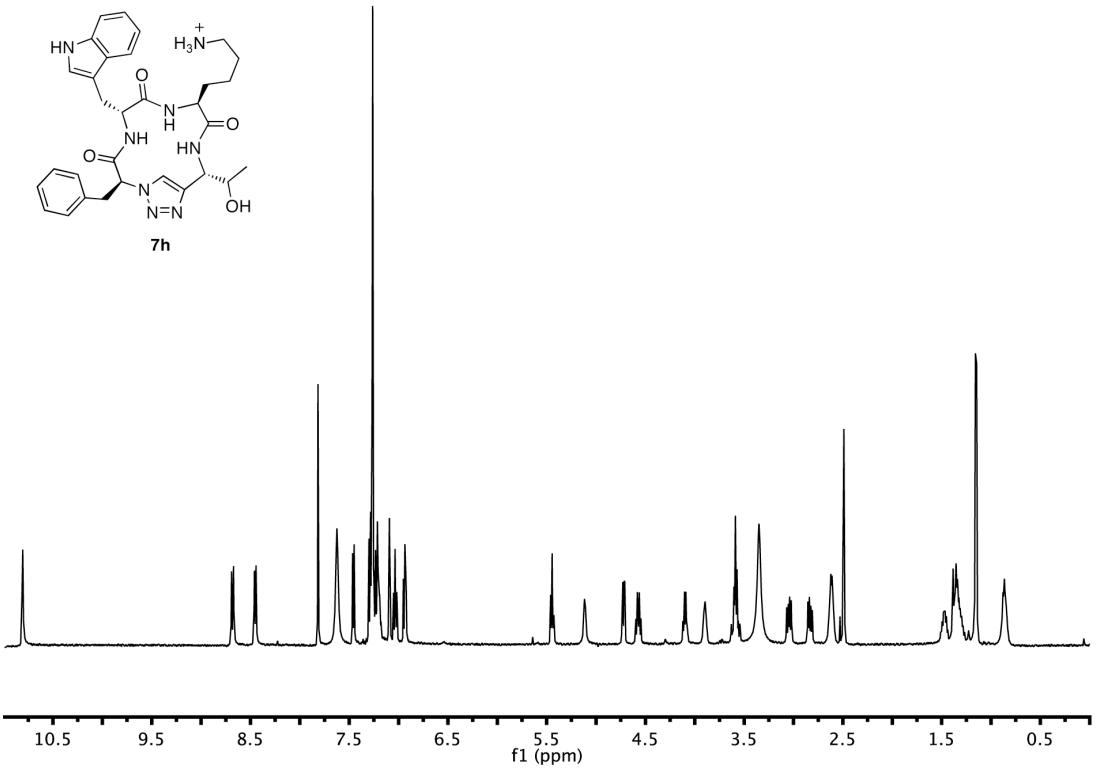


Figure S7. ^{1}H NMR spectra for compounds **7g** and **7h**.