Supplementary Data

Solid-phase S_N2 Macrocyclization Reactions To Form β-Turn Mimics

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Experimental

General Methods. All α-amino acids had the L-configuration, except where otherwise indicated. All chemicals were obtained from commercial suppliers and used without further purification. Di-*iso*-propylcarbodiimide (DIC), *N*-hydroxybenzotriazole (HOBt), di-*iso*-propylethylamine (DIEA), *N*-methylmorpholine (NMM), TFA, CH_2Cl_2, DMF, thionyl chloride, piperidine, tetrabutylammonium fluoride (TBAF), and tri-*iso*-propylsilane (TIS) were purchased from Aldrich or ACROS. Rink amide MBHA resin was obtained from NovaBiochem. TentaGel S RAM FMOC resin was purchased from Advanced ChemTech. Except for FMOC-Cys(Mmt)-OH and FMOC-Orn(Mtt)-OH which were purchased from NovaBiochem, all other α-amino acids were obtained either from Advanced ChemTech or from Chem-Impex.

Reverse phase high performance liquid chromatography (RP-HPLC) was carried out on Vydac C-18 columns of the following dimensions: 25 x 0.46 cm for analysis, and 25 x 2.2 cm for preparative work. All HPLC experiments were performed using gradient conditions. The eluants used were: solvent A (H_2O with 0.1% TFA) and solvent B (CH_3CN with 0.1% TFA). Flow rates used were 1.0 mL/min for analytical, and 6 mL/min for preparative HPLC.

All NMR spectra were recorded on a Varian instruments at 500 MHz or 300 MHz (^1H), and 75 MHz (^{13}C). NMR chemical shifts are expressed in ppm relative to internal solvent peaks, and coupling constants were measured in Hz.

General Experimental Procedure for Preparation of the Macrocyclic Peptidomimetics. Compound 1a. TentaGel S RAM resin (0.2 mmol, 0.30 mmol/g) was swelled in DMF (10 mL/g) in a manual solid phase synthesis shaker for 30 min, then rinsed with DMF (2 x *ca.* 10 mL/g, for each washing cycle throughout). The FMOC group on the resin was removed by treating the resin with 20% piperidine in DMF (2 x 10 min). After the resin was rinsed liberally with DMF, MeOH, and CH_2Cl_2 (last washing by CH_2Cl_2), FMOC-Cys(Mmt)-OH (2 equiv), DIC (4 equiv), HOBt (4 equiv), and NMM (5 equiv) were added in CH_2Cl_2/DMF (v/v,

4:1). After 1.5 h of gentle shaking, a ninhydrin test on a small sample of beads gave a negative result. The reaction mixture was drained and the resin was rinsed with DMF (4x). The above deprotection/coupling cycles were repeated to introduce FMOC-Lys(BOC)-OH and FMOC-Glu(O^{t}Bu)-OH consecutively. The 2-bromomethylbenzoic acid moiety was introduced to the *N*-terminus of the tripeptide-resin by treating with 2-bromomethylbenzoyl chloride (2 equiv) and DIEA (4 equiv) in CH_2Cl_2 for 60 min. The side-chain protecting group (Mmt) of Cys was removed by treatment with 1% TFA and 4% TIS in CH_2Cl_2 (4 x 5 min, or until no colour). After the resin was rinsed with CH_2Cl_2 (3x) and DMF (3x). The macrocyclization step was carried out by treating the supported peptide with diisopropylethylamine (DIEA, 10 equiv) in DMF (10 mL) at 25 ˚C. After gentle shaking for 20 h, the peptide-resin was washed liberally with DMF, H_2O, MeOH, and CH_2Cl_2, then dried *in vacuo* for 4 h. The peptide was cleaved from the resin by treatment with a mixture of 90% TFA, 5% TIS, and 5% H_2O for 4 h. The cleavage solution was separated from the resin by filtration. After most of the cleavage cocktail (about 90%) was evaporated *in vacuo*, the crude peptide was triturated using anhydrous ethyl ether, dissolved in H_2O, and then lyophilized to give the crude product. The purity of this crude material was determined by analytical HPLC (SSI system, 5-40% B in 30 min) to be *ca.* 77% based on absorption at 215 nm. Preparative HPLC (Rainin System) was carried out to provide a white powder (30 mg, 25%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 12.2 (b, 1H), 8.61 (d, J = 7.5, 1H), 7.94 (d, J = 8.1, 1H), 7.80-7.m, 4H), 7.47-7.37 (m, 4H), 7.34 (s, 1H), 7.24 (s, 1H), 4.44-4.34 (m, 1H), 4.34-4.19 (m, 2H), 4.02 (d, J = 11.4, 1H), 3.77 (d, J = 11.4, 1H), 3.00-2.82 (m, 2H), 2.82-2.68 (m, 2H), 2.58-2.48 (m, 2H), 2.24-1.90 (m, 2H), 1.90-1.76 (m, 1H), 1.65-1.45 (m, 2H), 1.38-1.18 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 173.8, 171.9, 171.6, 170.7, 169.7, 136.4, 136.2, 130.5, 130.0, 127.3, 127.1, 35.2, 33.9, 30.5, 29.1, 26.7, 26.4, 22.4. Analytical HPLC: single peak, retention time = 11.8 min (5-30% B in 30 min). MALDI MS: calc'd for $C_{22}H_{31}N_5O_6S$ (MH^+) 494.2, found 494.1.

Compound 1b. TentaGel S RAM resin (0.2 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude

material was subjected to preparative HPLC separation and lyophilization to give a white powder (25 mg, 21%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 8.57 (d, J = 8.1, 1H), 8.07 (d, J = 8.1, 1H), 7.74 (b, 3H), 7.64 (d, J = 8.7, 1H), 7.46-7.39 (m, 3H), 7.39-7.34 (m, 2H), 7.25 (s, 1H), 4.50-4.36 (m, 1H), 4.25-4.10 (m, 2H), 4.02 (d, J = 11.7, 1H), 3.85 (d, J = 11.7, 1H), 2.96-2.72 (m, 4H), 1.94-1.77 (m, 2H), 1.68-1.48 (m, 4H), 1.38-1.20 (m, 3H), 0.96-0.85 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 171.8, 171.7, 170.9, 169.8, 137.2, 136.1, 130.6, 130.0, 127.3, 127.2, 59.8, 52.8, 52.7, 35.4, 35.3, 33.9, 29.0, 26.8, 25.5, 22.8, 15.7, 10.8. Analytical HPLC: single peak, retention time = 17.4 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{23}H_{35}N_5O_4S$ (MH^+) 478.2, found 478.3.

Compound 1c. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to analytical HPLC and shown to process two major products; one with a percentage of 63% (MS showed it is the desired product), and another one with a percentage of 30% (MS showed it is the cyclic dimer). This crude material was subjected to preparative HPLC separation and lyophilization to give two white powder compounds (monomer: 10 mg, 15%; dimer: 5 mg, 8%). Analytical data for the monomer **1c**: ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C), δ 12.6 (b, 1H), 8.67 (d, J = 8.4, 1H), 7.69 (d, J = 8.7, 1H), 7.50-7.32 (m, 6H), 7.30 (s, 1H), 4.70-4.62 (m, 1H), 4.46-4.36 (m, 1H), 4.27 (t, J = 8.7, 1H), 4.20 (d, J = 10.8, 1H), 3.79 (d, J = 10.8, 1H), 3.05 (dd, J = 12.2, 3.6, 1H), 2.86-2.68 (m, 3H), 1.98-1.85 (m, 1H), 1.43-1.32 (m, 1H), 1.16-1.00 (m, 1H), 0.90-0.78 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 171.6, 171.5, 171.0, 170.5, 169.1, 136.4, 136.3, 130.7, 130.3, 127.7, 127.4, 56.9, 52.7, 51.8, 36.8, 36.6, 35.1, 33.9, 24.1, 15.8, 11.4. Analytical HPLC: single peak, retention time = 19.7 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{21}H_{28}N_4O_6S$ (MH^+) 465.2, found 464.7.

Analytical data for the dimer **6c:** ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C), δ 12.4 (b, 2H), 8.77 (d, J = 8.4, 2H), 8.34 (d, J = 7.5, 2H), 7.55 (d, J = 8.7, 2H), 7.45 (d, J = 1.8, 4H), 7.39 (d, J = 1.8, 4H), 7.23 (s, 2H), 7.12 (s, 2H), 4.87-4.76 (m, 2H),

4.40-4.30 (m, 4H), 4.05 (d, J = 13.2, 2H), 3.88 (d, J = 13.2, 2H), 2.81 (dd, J = 16.5, 4.8, 2H), 2.74-2.60 (m, 6H), 1.84-1.67 (m, 2H), 1.52-1.38 (m, 2H), 1.18-1.00 (m, 2H), 0.93-0.75 (m, 12H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.2, 172.1, 170.9, 170.4, 168.8, 137.6, 135.8, 130.4, 130.1, 128.2, 127.0, 56.8, 52.9, 50.8, 37.6, 36.4, 33.6, 33.4, 24.3, 15.3, 11.4. Analytical HPLC: single peak, retention time = 19.4 min (8-70% B in 30 min). MALDI MS: calc'd for $C_{42}H_{56}N_8O_{12}S_2$ (MNa^+) 951.4, found 951.4.

Compound 1d. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (20 mg, 27%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 8.52 (d, J = 8.4, 1H), 8.05 (d, J = 7.8, 1H), 7.63 (d, J = 8.7, 1H), 7.54 (t, J = 5.7, 1H), 7.40-7.32 (m, 3H), 7.32-7.26 (m, 2H), 7.18 (s, 1H), 7.40-6.70 (very broad peak, 4H), 4.40-4.30 (m, 1H), 4.21-4.04 (m, 2H), 3.95 (d, J = 11.7, 1H), 3.80 (d, J = 11.7, 1H), 3.12-3.00 (m, 2H), 2.90-2.74 (m, 2H), 1.90-1.72 (m, 2H), 1.66-1.50 (m, 3H), 1.50-1.32 (m, 2H), 1.26-1.14 (m, 1H), 0.90-0.80 (m, 6H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 171.8, 171.7, 170.8, 169.7, 156.9, 137.2, 136.0, 130.4, 129.8, 127.1, 127.0, 59.8, 52.8, 52.7, 35.3, 35.1, 33.9, 26.9, 25.6, 25.4, 15.6, 10.7. Analytical HPLC: single peak, retention time = 19.2 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{23}H_{35}N_7O_4S$ (MH^+) 506.3, found 506.3.

Compound 1e. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (30 mg, 44%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 9.14 (d, J = 5.7, 1H), 8.97 (dd, J = 7.2, 4.5, 1H), 7.80 (d, J = 9.0, 1H), 7.60 (t, J = 5.7, 1H), 7.42-7.35 (m, 2H), 7.31 (s, 1H), 7.30-7.22 (m, 2H), 7.15 (s, 1H), 7.42-6.80 (very broad peak, 4H), 4.45-4.35 (m, 1H), 4.24 (dd, J = 13.8, 7.2, 1H), 4.00 (dd, J = 16.8, 7.8, 1H), 3.80 (d, J = 12.6, 1H), 3.62 (d, J = 12.6, 1H), 3.47 (dd, J = 16.8, 4.5, 1H), 3.10 (dd, J = 24.9, 6.9, 1H), 2.95 (dd, J = 15.0, 9.0, 1H), 2.56 (dd, J = 15.0, 3.3, 1H), 1.75-1.35 (m, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.7, 172.2, 171.3, 169.1, 156.9, 136.9,

136.5, 130.9, 129.9, 126.8, 126.3, 54.9, 54.7, 43.1, 32.8, 31.4, 26.8, 25.3. Analytical HPLC: single peak, retention time = 10.2 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{19}H_{27}N_7O_4S$ (MH^+) 450.2, found 450.2.

Compound 1f. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (20 mg, 25%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 9.2 (b, 1H), 8.52 (d, J = 7.5, 1H), 7.90 (d, J = 8.7, 1H), 7.67 (b, 3H), 7.51 (d, J = 9.3, 1H), 7.45-7.35 (m, 5H), 7.22 (s, 1H), 6.98 (d, J = 8.7, 2H), 6.64 (d, J = 8.7, 2H), 4.45-4.35 (m, 2H), 4.13 (dd, J = 15.0, 7.8, 1H), 4.04 (d, J = 11.7, 1H), 3.80 (d, J = 11.7, 1H), 3.04 (dd, J = 13.2, 7.2, 1H), 2.93 (dd, J = 12.9, 3.3, 1H), 2.86-2.65 (m, 4H), 1.68-1.55 (m, 1H), 1.55-1.38 (m, 3H), 1.38-1.16 (m, 1H), 1.14-0.98 (m, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 171.9, 171.7, 170.6, 169.7, 155.8, 136.7, 136.4, 130.7, 130.2, 130.0, 128.5, 127.3, 127.2, 115.0, 55.3, 54.3, 52.9, 38.8, 35.5, 34.4, 34.0, 30.7, 26.7, 22.5. Analytical HPLC: single peak, retention time = 14.8 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{26}H_{33}N_5O_5S$ (MH^+) 528.2, found 528.0.

Compound 1g. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (18 mg, 27%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 9.23 (d, J = 6.6, 1H), 8.83 (dd, J = 7.8, 4.2, 1H), 7.76 (d, J = 9.0, 1H), 7.40 (d, J = 3.6, 1H), 7.34-7.24(m, 2H), 7.22 (s, 1H), 7.18 (d, J = 7.5, 1H), 7.12 (d, J = 8.1, 2H), 6.69 (d, J = 8.4, 2H), 4.45-4.35 (m, 2H), 4.03 (dd, J = 16.8, 8.1, 1H), 3.94 (d, J = 12.3, 1H), 3.63 (d, J = 12.3, 1H), 3.38 (dd, J = 17.1, 4.5, 1H), 3.03 (dd, J = 15.0, 8.4, 1H), 2.86 (d, J = 7.5, 2H), 2.61 (dd, J = 14.4, 3.6, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.3, 172.2, 171.1, 169.0, 156.0, 136.7, 136.4, 130.9, 130.2, 130.0, 127.8, 126.9, 126.5, 115.2, 56.9, 54.1, 43.0, 38.6, 34.8, 33.0, 31.8. Analytical HPLC: single peak, retention time = 16.5 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{22}H_{24}N_4O_5S$ (MNa^+) 479.2, found 479.1.

Compound 1h. TentaGel S RAM resin (0.10 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (10 mg, 23%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 9.06 (d, J = 6.3, 1H), 7.74 (b, 3H), 7.52-7.36(m, 6H), 7.29 (s, 1H), 7.15 (s, 1H), 5.10 (b, 1H), 4.41-4.30 (m, 2H), 4.28-4.17 (m, 2H), 4.18 (d, J = 11.4, 1H), 3.82 (d, J = 11.4, 1H), 3.06 (dd, J = 13.8, 7.8, 1H), 2.93-2.75 (m, 3H), 1.92-1.75 (m, 2H), 1.68-1.43 (m, 4H), 1.05 (d, J = 6.6, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.9, 171.8, 170.3, 170.1, 136.7, 135.9, 131.2, 130.7, 128.1, 127.4, 64.9, 57.9, 56.2, 52.9, 34.3, 33.6, 30.5, 26.7, 22.9, 20.6. Analytical HPLC: single peak, retention time = 9.5 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{21}H_{31}N_5O_5S$ (MH^+) 466.2, found 465.8.

Compound 1i. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to analytical HPLC and shown to process two major products; one with a percentage of 76% (MS showed it is the desired product), and another one with a percentage of 21% (MS showed it is the cyclic dimer). This crude material was subjected to preparative HPLC separation and lyophilization to give two white powder compounds (monomer: 14 mg, 24%; dimer: 3 mg, 5%). Analytical data for the monomer **1i**: ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 9.05-8.96 (m, 2H), 7.85 (d, J = 9.0, 1H), 7.46-7.28 (m, 5H), 7.22 (s, 1H), 4.43 (dt, J = 8.7, 3.3, 1H), 4.12 (dd, J = 8.4, 6.0, 1H), 4.02 (dd, J = 16.8, 7.5, 1H), 3.94 (dd, J = 8.7, 2.1, 1H), 3.88 (d, J = 12.6, 1H), 3.68(d, J = 12.6, 1H), 3.54 (dd, J = 17.1, 4.8, 1H), 3.04 (dd, J = 15.0, 9.0, 1H), 2.63 (dd, J = 14.8, 3.3, 1H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.4, 171.6, 171.4, 169.2, 137.0, 136.7, 130.9, 130.0, 126.9, 126.3, 65.0, 62.8, 54.8, 43.1, 32.9, 31.4, 20.4. Analytical HPLC: single peak, retention time = 9.5 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{17}H_{22}N_4O_5S$ (MH^+) 395.2, found 394.9.

Analytical data for the cyclic dimer **6i**: ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 8.23 (d, J = 9.0, 1H), 8.15 (t, J = 5.7, 1H), 8.05 (d, J = 8.1, 1H), 7.50 (d, J = 6.9, 1H), 7.46-7.32 (m, 4H), 7.20 (s, 1H), 4.38-4.24 (m, 2H), 4.16-4.05 (m, 1H), 3.98 (d, J = 13.2, 2H), 3.86 (d, J = 13.2, 2H), 3.88-3.82(m, 1H), 2.78 (dd, J = 13.5, 4.8, 1H), 2.66

(dd, J = 13.5, 8.4, 1H), 1.19 (d, J = 6.3, 3H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.2, 170.7, 169.4, 169.0, 137.1, 136.2, 130.6, 130.0, 128.3, 127.0, 66.7, 60.0, 52.8, 42.4, 33.4, 33.3, 20.3. Analytical HPLC: single peak, retention time = 16.5 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{34}H_{44}N_8O_{10}S_2$ (MH^+) 789.3, found 788.6.

Compound 1j. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (10 mg, 17%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 9.04 (t, J = 5.4, 1H), 8.30 (d, J = 8.4, 1H), 7.75 (d, J = 8.4, 1H), 7.42-7.28(m, 5H), 7.27 (s, 1H), 7.19 (s, 1H), 6.89 (s, 1H), 4.65 (dd, J = 14.7, 6.3, 1H), 4.42-4.32 (m, 1H), 4.09 (d, J = 11.7, 1H), 3.91 (dd, J = 15.0, 6.6, 1H), 3.88 (d, J = 11.7, 1H), 3.66 (dd, J = 15.0, 5.1, 1H), 2.98-2.82 (m, 2H), 2.68-2.54 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.2, 171.8, 170.6, 170.2, 169.4, 136.3, 136.1, 130.9, 130.1, 127.4, 127.2, 53.0, 49.5, 44.3, 35.4, 34.6, 33.7. Analytical HPLC: single peak, retention time = 8.9 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{17}H_{21}N_5O_5S$ (MNa^+) 430.1, found 430.1.

Compound 1k. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (25 mg, 35%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 12.0 (b, 1H), 8.76 (d, J = 6.3, 1H), 8.11 (d, J = 8.1, 1H), 7.72 (d, J = 9.0, 1H), 7.42-7.30 (m, 5H), 7.27 (s, 1H), 7.21 (s, 1H), 6.86 (s, 1H), 4.52 (dd, J = 14.4, 6.3, 1H), 4.41-4.32 (m, 1H), 4.21 (dd, J = 14.4, 7.2, 1H), 3.97 (d, J = 12.0, 1H), 3.86 (d, J = 12.0, 1H), 2.96-2.80 (m, 2H), 2.64 (dd, J = 16.2, 6.6, 1H), 2.56 (dd, J = 15.9, 6.3, 1H), 2.37 (t, J = 7.5, 2H), 1.98-1.82 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 173.9, 172.4, 171.9, 171.7, 170.4, 170.2, 136.6, 136.4, 130.5, 130.0, 127.2, 127.0, 55.1, 54.0, 49.9, 46.0, 35.5, 34.0, 33.8, 30.4, 26.1. Analytical HPLC: single peak, retention time = 8.5 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{20}H_{25}N_5O_7S$ (MNa^+) 522.2, found 522.0.

Compound 1l. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a

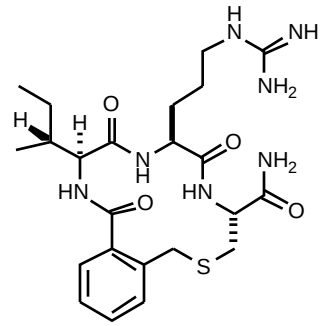
white powder (26 mg, 37%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 8.75 (d, J = 6.9, 1H), 8.03 (d, J = 8.4, 1H), 7.75 (d, J = 9.3, 1H), 7.46-7.27 (m, 7H), 7.23 (s, 1H), 7.00 (s, 1H), 6.85 (s, 1H), 4.60-4.48 (m, 2H), 4.42-4.33 (m, 1H), 4.04 (d, J = 12.0, 1H), 3.88 (d, J = 12.0, 1H), 2.95-2.84 (m, 2H), 2.65-2.50 (m, 4H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 172.4, 171.9, 171.3, 171.0, 170.4, 169.8, 136.5, 136.4, 130.6, 130.1, 127.3, 127.1, 53.6, 52.6, 49.9, 36.7, 35.5, 34.6, 33.9. Analytical HPLC: single peak, retention time = 6.5 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{19}H_{24}N_6O_6S$ (MNa^+) 487.2, found 487.0.

Compound 1m. TentaGel S RAM resin (0.15 mmol, 0.30 mmol/g) was used to prepare this compound. After the peptide was cleaved from the resin, the crude material was subjected to preparative HPLC separation and lyophilization to give a white powder (28 mg, 31%). ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 8.63 (d, J = 7.2, 1H), 7.89 (d, J = 7.5, 1H), 7.75 (d, J = 8.7, 1H), 7.68 (b, 3H), 7.48 (s, 1H), 7.44-7.30 (m, 5H), 7.22 (s, 1H), 7.04 (s, 1H), 4.60 (dd, J = 15.3, 8.7, 1H), 4.42-4.31 (m, 1H), 4.18 (dd, J = 13.5, 7.5, 1H), 4.11 (d, J = 11.1, 1H), 3.82 (d, J = 11.1, 1H), 2.95 (dd, J = 12.9, 3.0, 1H), 2.88-2.70 (m, 3H), 2.62-2.52 (m, 2H), 1.86-1.72(m, 1H), 1.70-1.42 (m, 3H), 1.38-1.15 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 171.9, 171.6, 171.2, 170.9, 169.5, 136.5, 135.4, 130.8, 130.2, 127.4, 127.3, 52.9, 52.8, 52.7, 40.8, 37.1, 35.5, 34.0, 29.1, 26.9, 22.5. Analytical HPLC: single peak, retention time = 9.8 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{21}H_{30}N_6O_5S$ (MH^+) 479.2, found 478.8.

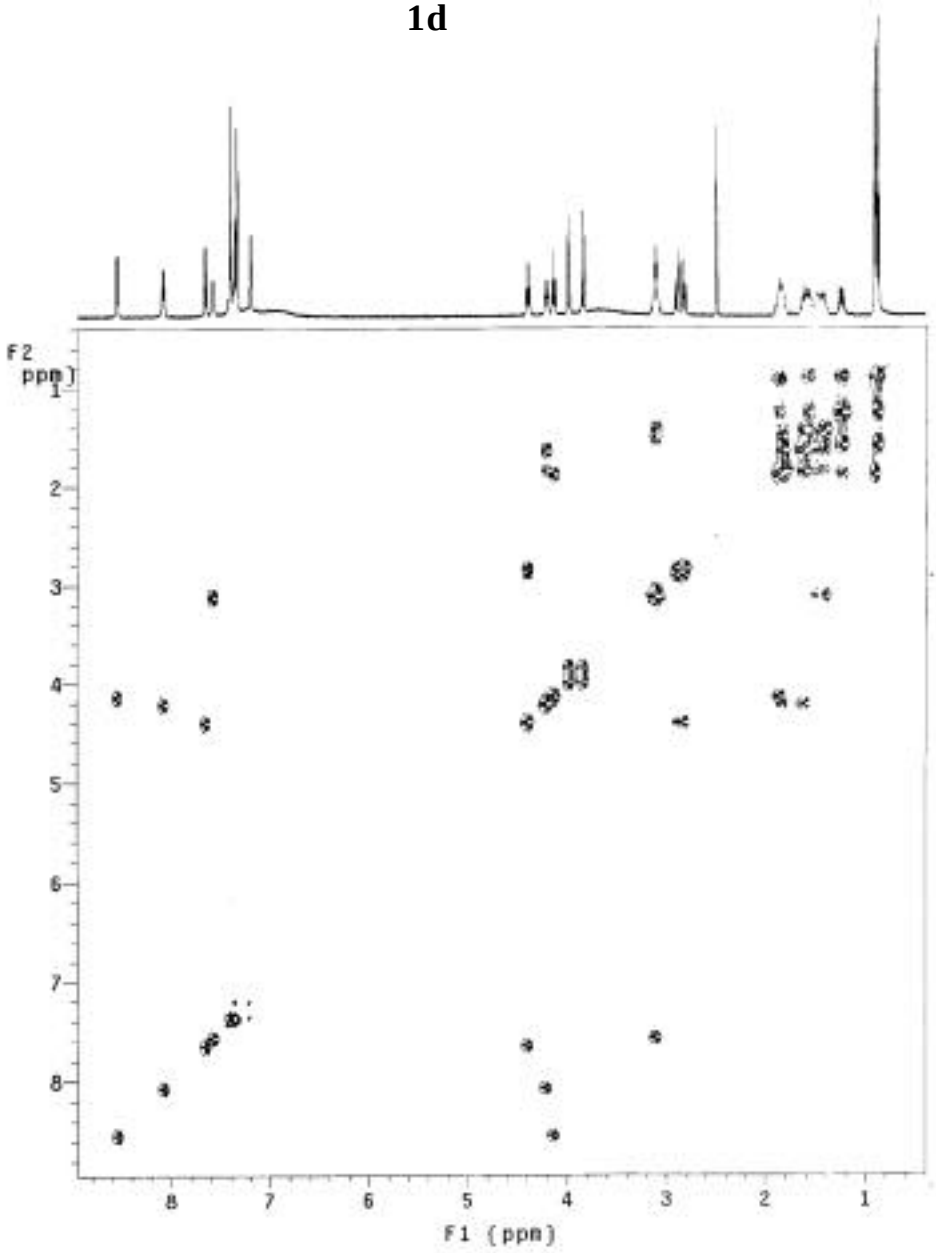
Preparation of The Linear Peptidomimetic 4. Rink amide MBHA resin (0.2 mmol, 0.65 mmol/g) was swelled in DMF (10 mL/g) in a manual solid phase synthesis shaker for 30 min, then rinsed with DMF (2 x *ca.* 10 mL/g, for each washing cycle throughout). The FMOC protecting group on the Rink handle was removed by treating the resin with 20% piperidine in DMF (2 x 10 min). After the resin was rinsed liberally with DMF, MeOH, and CH_2Cl_2 (the last washing by CH_2Cl_2), FMOC-Ser(Trt)-OH (2 equiv), DIC (4 equiv), HOBt (4 equiv), and NMM (5 equiv) were added in CH_2Cl_2/DMF (v/v, 4:1). After 1.5 h of gentle shaking, a ninhydrin test on a small sample of beads gave a negative result. The reaction mixture was drained and the resin

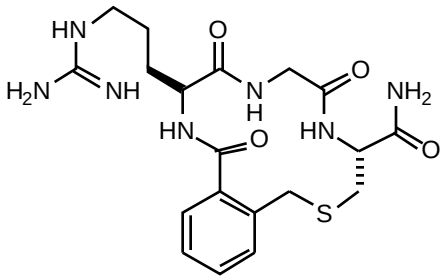
was rinsed with DMF (4x). The above deprotection/coupling cycles were repeated to introduce FMOC-Lys(BOC)-OH and FMOC-Glu(O^{t}Bu)-OH consecutively. The 2-bromomethylbenzoic acid moiety was introduced to the *N*-terminus of the tripeptide-resin by treating with 2-bromomethylbenzoyl chloride (2 equiv) and DIEA (4 equiv) in CH_2Cl_2 for 45 min. The side-chain protecting group (Trt) of Ser was removed by treatment with 1% TFA and 4% TIS in CH_2Cl_2 (4 x 5 min). After the resin was rinsed with CH_2Cl_2 (3x) and DMF (3x), the macrocyclization was attempted to carry out by treating the supported peptide with tetramethylguanidine (TMG, 10 equiv) in DMF at 25 ˚C. After gentle shaking for 20 h, the peptide-resin was washed liberally with DMF, H_2O, MeOH, and CH_2Cl_2, then dried *in vacuo* for 4 h. The peptide was cleaved from the resin by treatment with a mixture of 90% TFA, 5% TIS, and 5% H_2O for 4 h. The cleavage solution was separated from the resin by filtration. After most of the cleavage cocktail (about 90%) was evaporated by passing N_2, the crude peptide was precipitated using anhydrous ethyl ether, dissolved in H_2O (or a mixture of CH_3CN and H_2O), and then lyophilized to give the crude product (99 mg). The purity of this crude material was determined by analytical HPLC (SSI system, 5-40% B in 30 min) to be *ca*. 97% based on absorption at 215 nm. Preparative HPLC (Rainin System) was carried out to provide a white powder (35 mg obtained from 75 mg crude, 48%). NMR results demonstrated that this product is the benzolactam linear peptide. ^{1}H NMR (300 MHz, DMSO-d_6, 25 °C) δ 12.2 (b, 1H), 8.33 (d, J = 7.8, 1H), 7.88 (d, J = 7.8, 1H), 7.73 (d, J = 7.5, 1H), 7.68 (b, 3H), 7.66-7.60 (m, 2H), 7.57-7.48 (m, 1H), 7.31 (s, 1H), 7.12 (s, 1H), 4.87 (dd, J = 9.9, 4.2, 1H), 4.69 (d, J = 17.7, 1H), 4.54 (d, J = 17.7, 1H), 4.33-4.18 (m, 2H), 3.68-3.54 (m, 2H), 2.77-2.64 (m, 2H), 2.30-2.14 (m, 3H), 2.12-1.98 (m, 1H), 1.77-1.64 (m, 1H), 1.63 -1.44 (m, 3H), 1.37-1.23 (m, 2H). ^{13}C NMR (DMSO-d_6, 75 MHz, 25 °C) δ 174.6, 172.2, 171.5, 170.8, 168.1, 142.6, 132.0, 131.7, 128.0, 123.7, 123.0, 61.8, 55.3, 54.1, 52.9, 47.5, 45.7, 32.0, 30.9, 26.7, 25.8, 22.3. Analytical HPLC: homogeneous single peak, retention time = 9.8 min (5-40% B in 30 min). MALDI MS: calc'd for $C_{22}H_{31}N_5O_7$ (MH^+) 478.2, found 478.8.

Representative 2-D COSY NMR Spectra



1d





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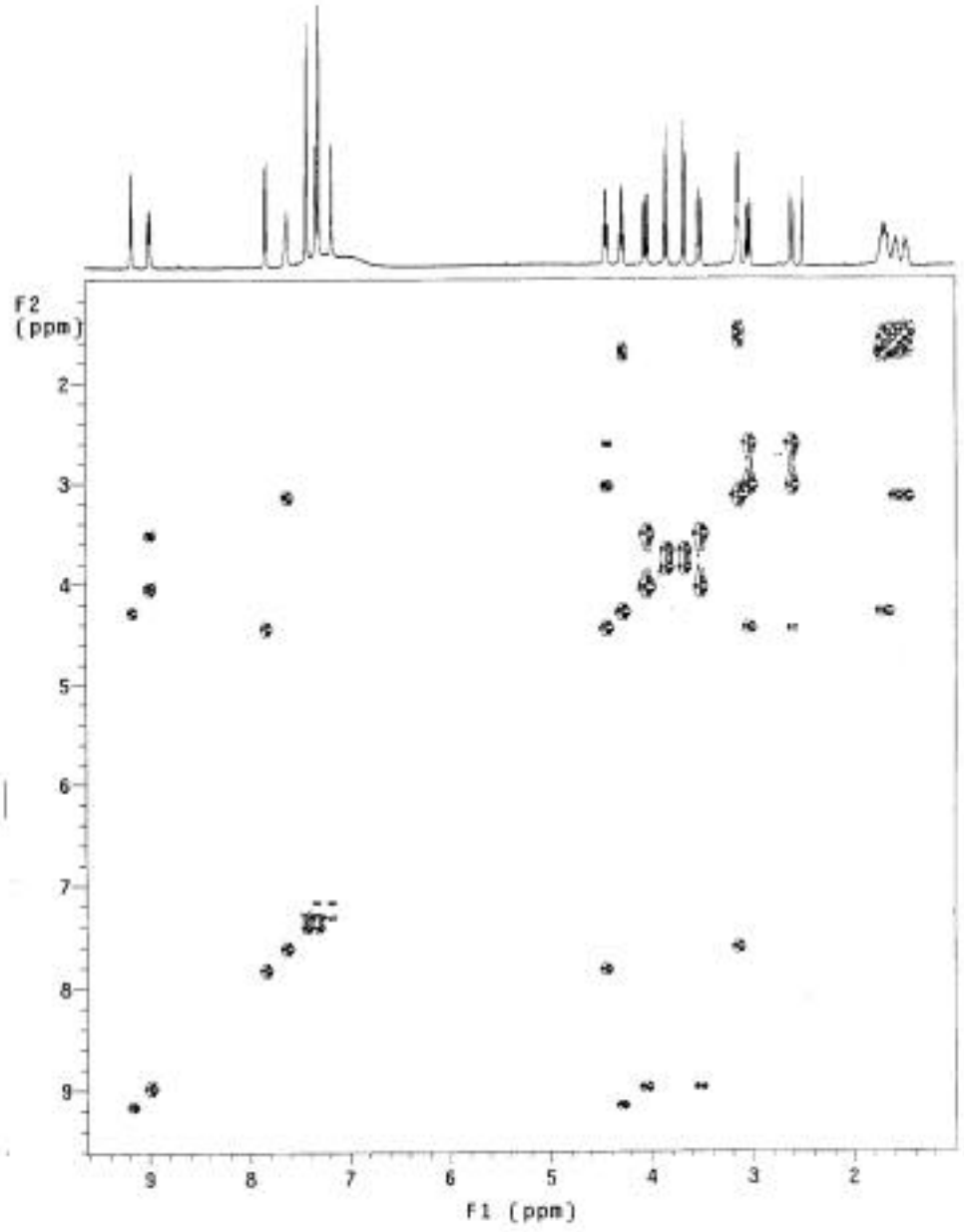

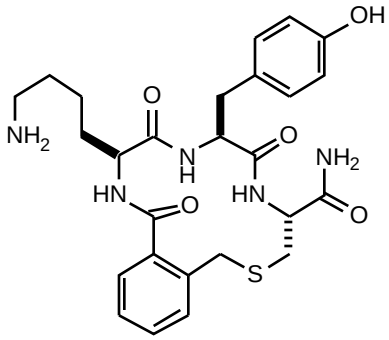

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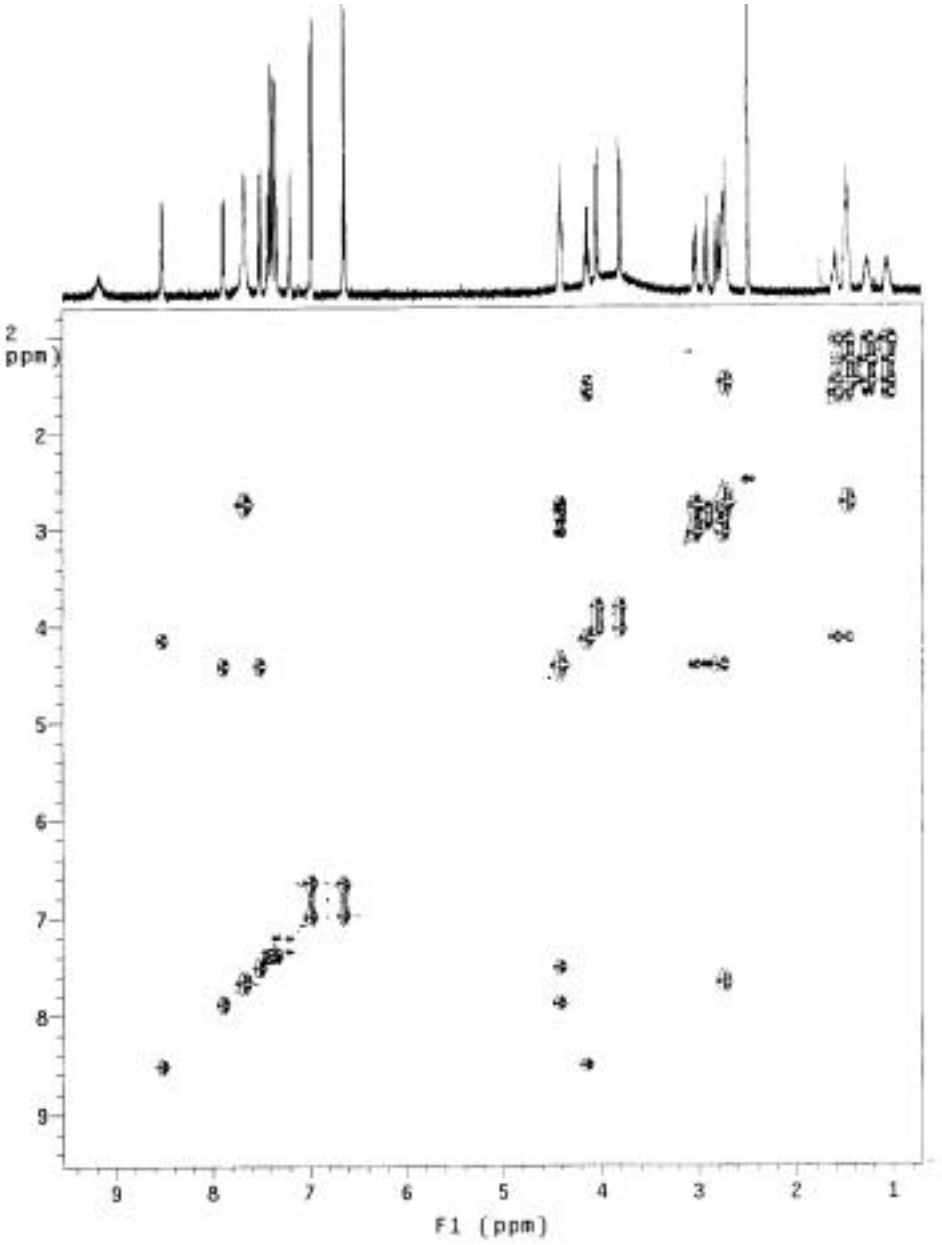

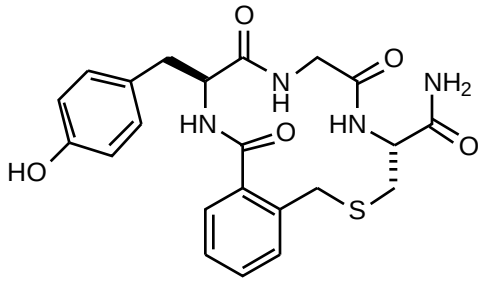

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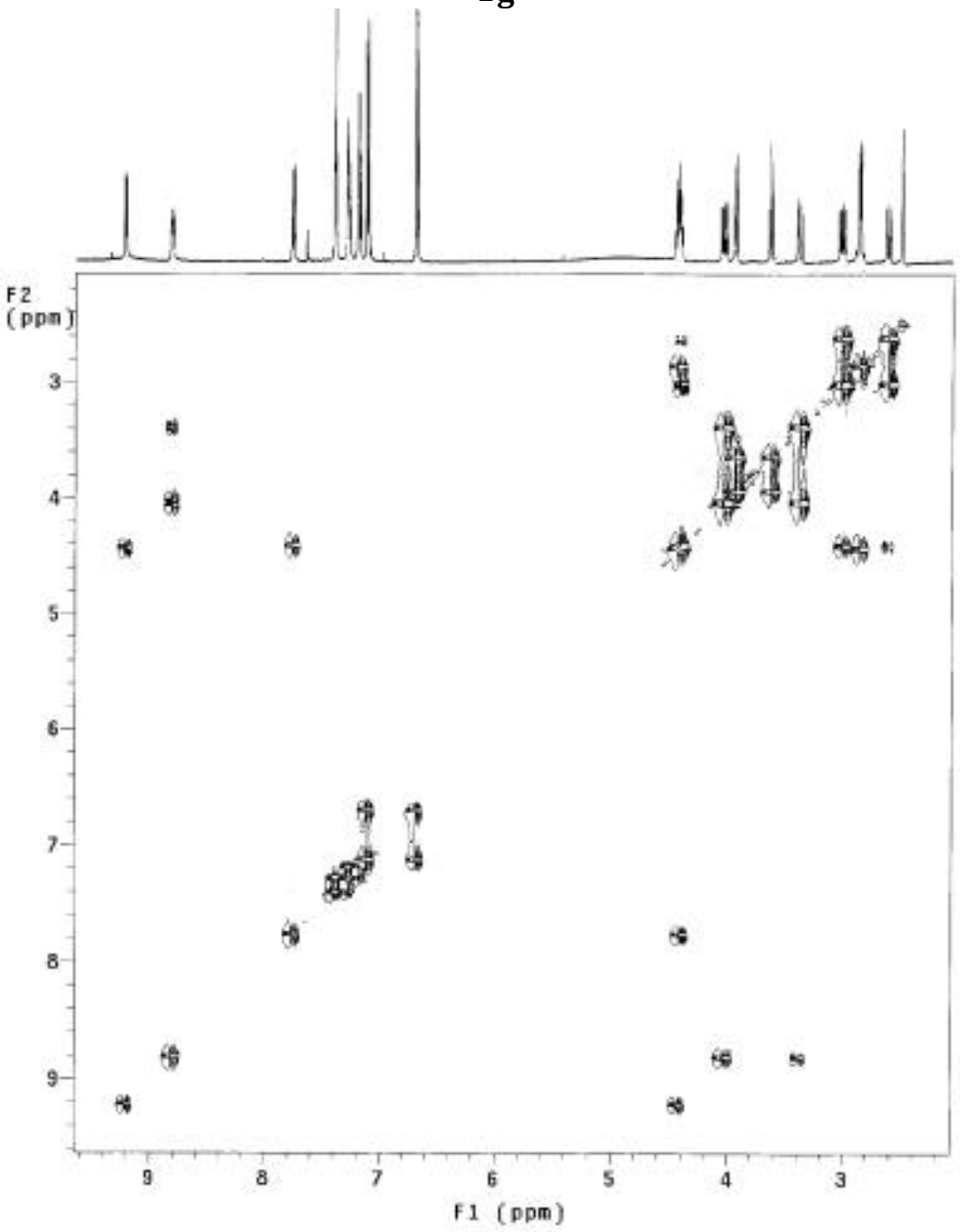

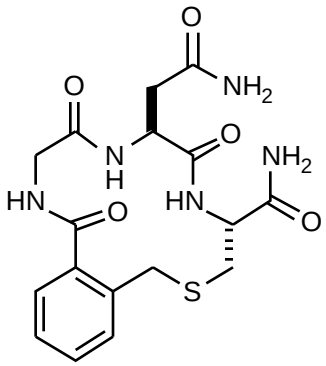

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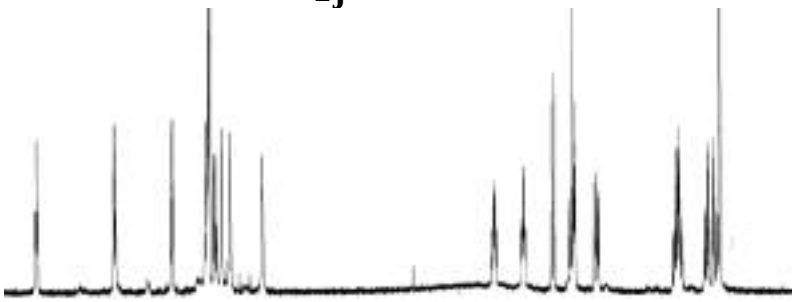
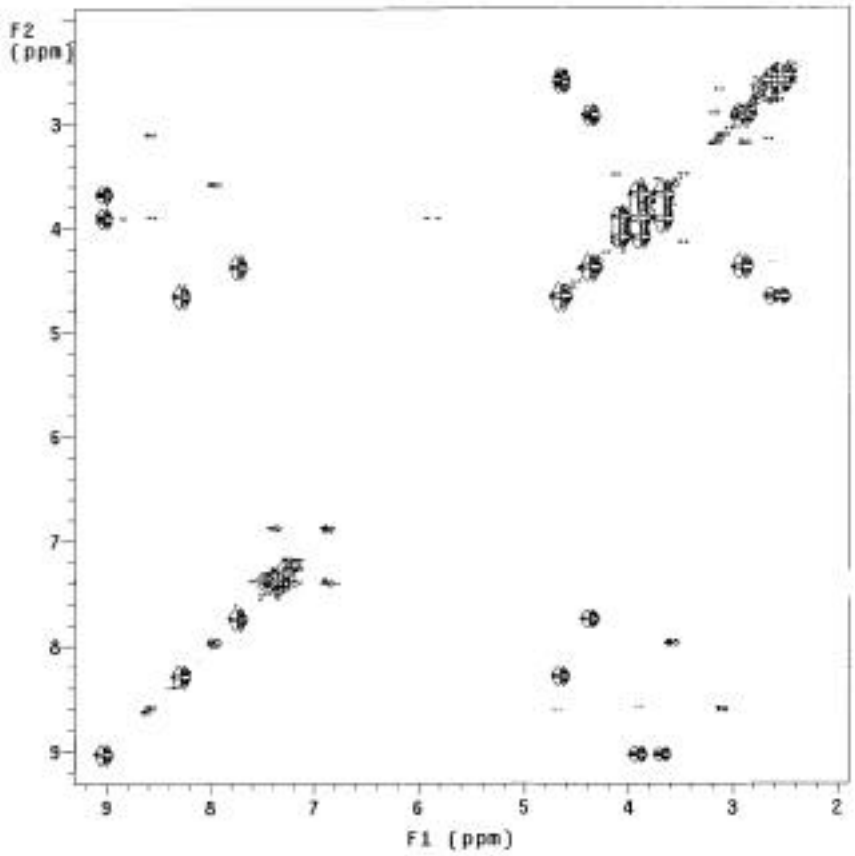
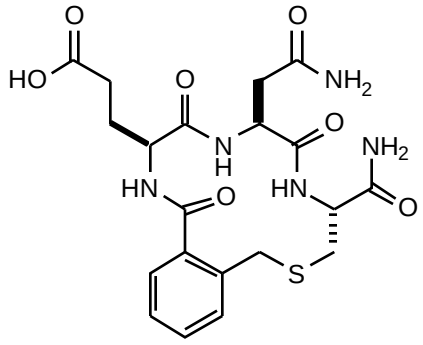
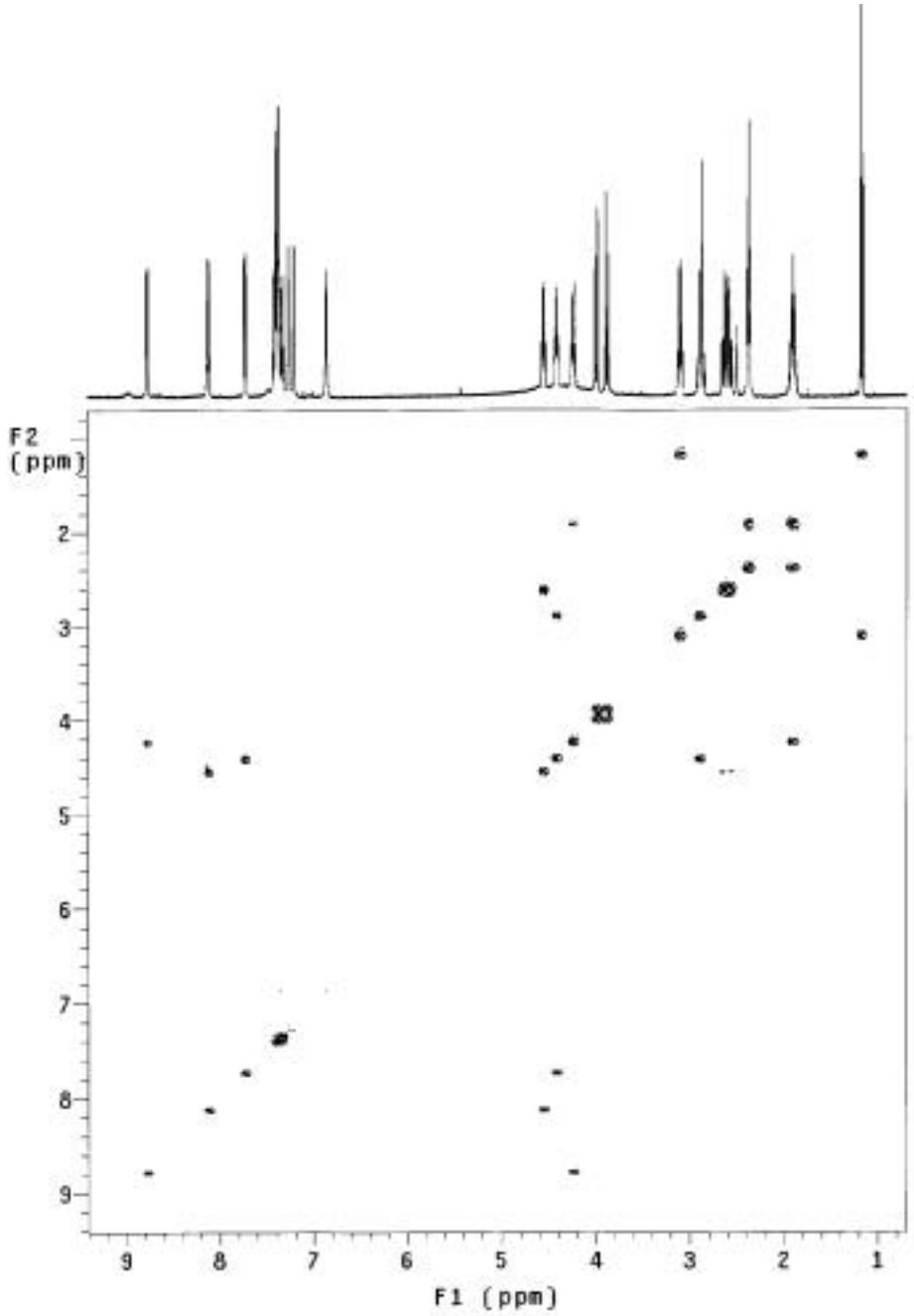
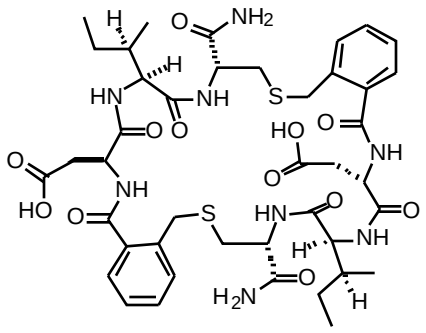




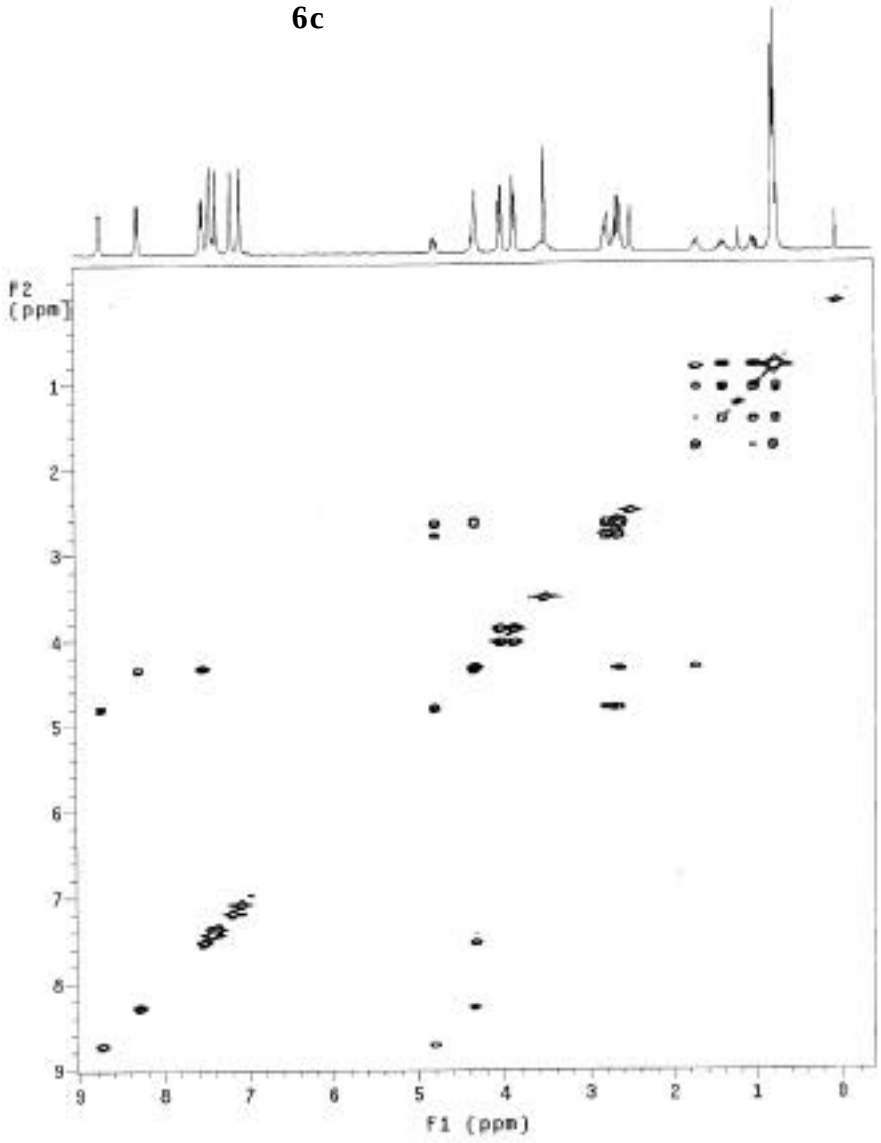


1k

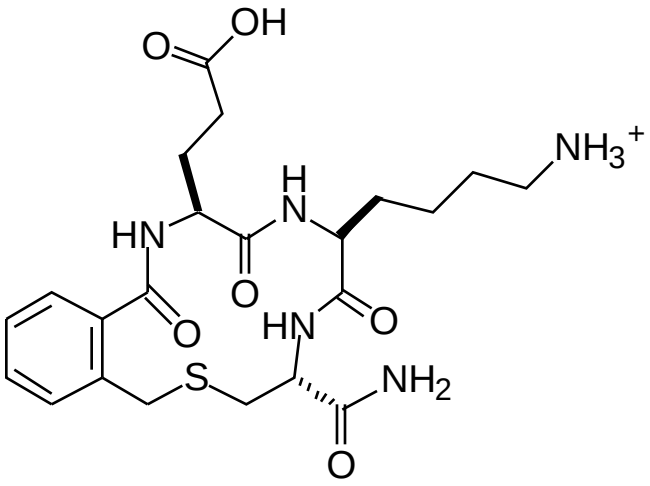




6c



Summary of QMD and Conformational Studies of 1a



1a

Key ROE contacts

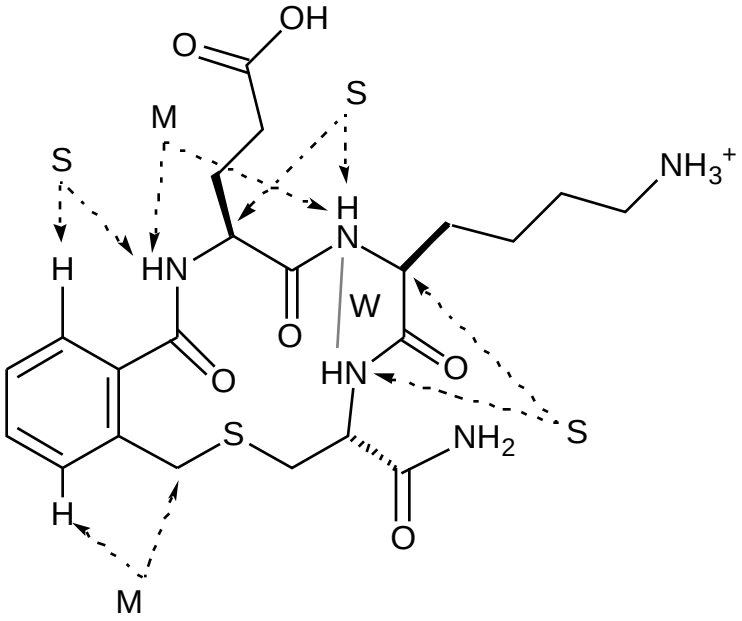
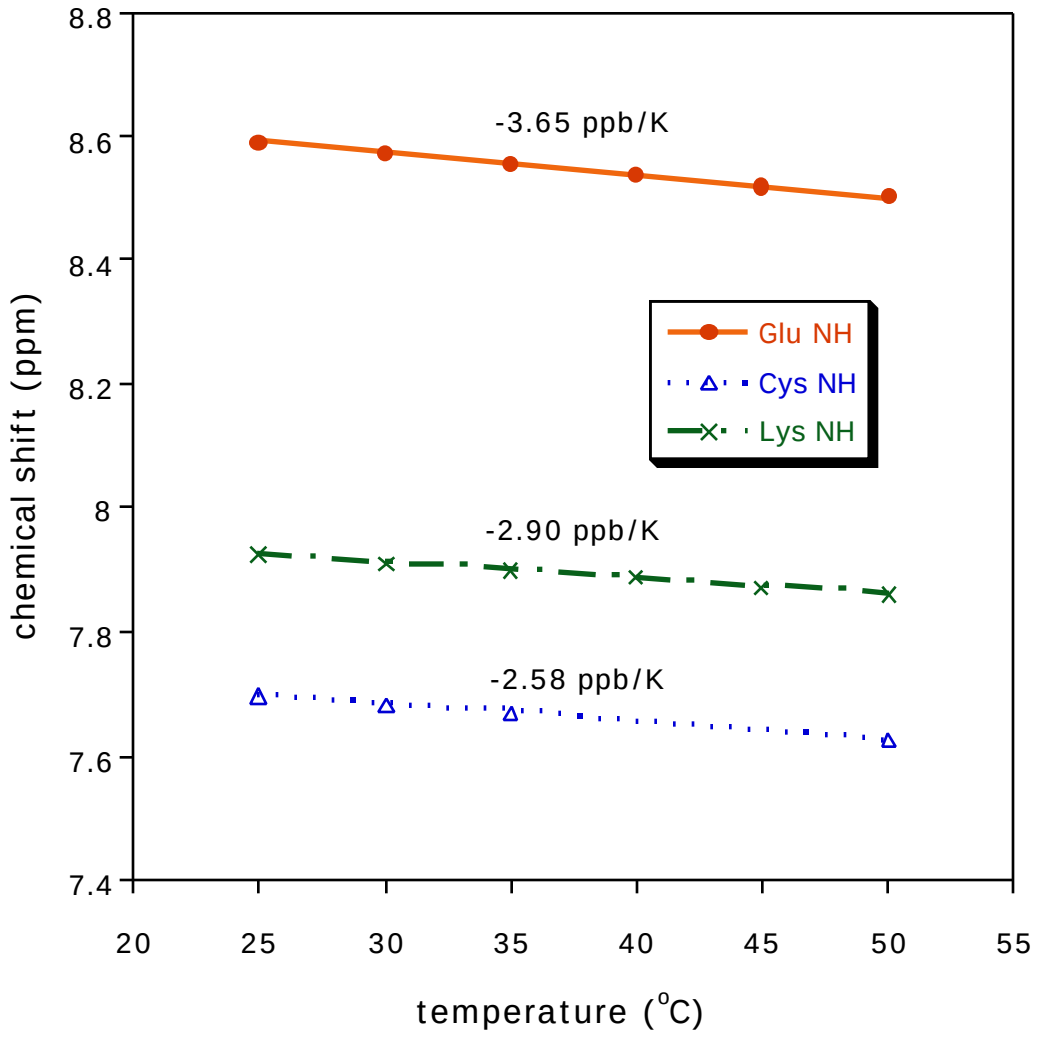


Table 1. Chemical Shift, Coupling Constants, and Temperature Coefficient Data for **1a**

sequence	proton	δ (ppm)	^{3}J (Hz)	temperature coefficient (ppb/K)
Glu	NH	8.592 (d)	6.99	-3.65
	α	4.267 (m)		
	β	1.957 (m)		
	β	1.957 (m)		
	γ	2.395 (m)		
	OH	12.10 (b)		
Lys	NH	7.917 (d)	8.49	-2.9
	α	4.267 (m)		
	β	1.45-1.60 (m)		
	β	1.81 (m)		
	γ	1.270 (m)		
	δ	1.536 (m)		
	ε	2.747 (m)		
	NHε	7.431 (m)		
Cys	NH	7.690 (d)	9.49	-2.58
	α	4.384 (m)		
	β	2.80-2.96		
	β	2.80-2.96 (m)		
C termini	NH	7.208 (s)		
	NH	7.311 (s)		
Ar	H3-H6	7.30-7.42 (m)		
benzyl	H	3.812, 4.076 (AB q)		

Figure1. temperature coefficient of 1a



QMD Data For Compound 1a

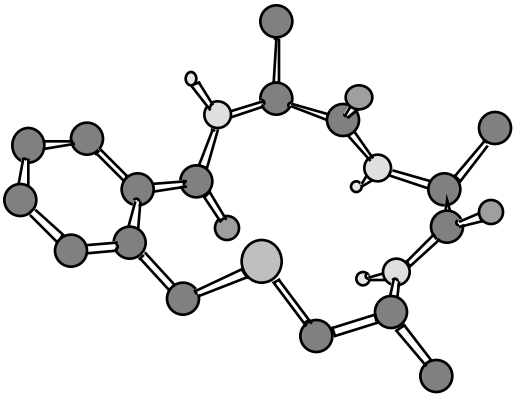
Table 2. QMD study of **1a** (RMSD threshold 0.75 Å)

residue	dihderal angle (˚)	family 1	family 2	family 3	family 4
		lowest energy conformer	lowest energy conformer	lowest energy conformer	lowest energy conformer
Glu	φ	-70 ˚	-75 ˚	-67 ˚	-79˚
	ψ	118 ˚	-24 ˚	-54 ˚	-31 ˚
Lys	φ	63˚	-61˚	-156 ˚	-124˚
	ψ	47˚	-25 ˚	45 ˚	-27˚
number in family		61	79	17	9
lowest energy conformer (kcal/mol)		0.1100	-0.7230	0.2847	1.2293
distance (Å) O_i-N$\underline{H}_{i+3}$		2.914	2.329	3.978	4.046
type of turn[a]		βII	βIII	–	–

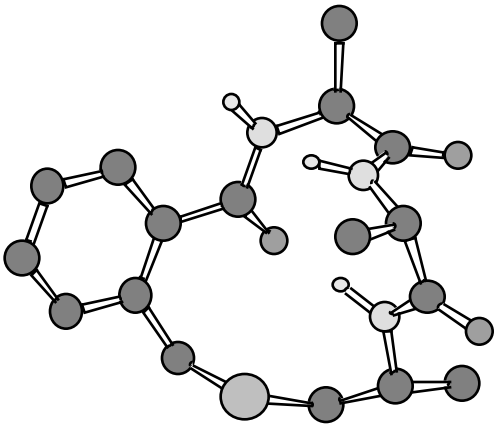
[a] turn- type was determined according to data from P. Y. Chou and G. D. Fasman, J. Mol. Biol. 115, 135-175, 1997; C. M. Wilmot and J. M. Thornton, J. Mol. Biol. 203, 221-232, 1988; J. S. Richardon, Adv. Protein Chem. 34, 167-339,1981.
βI: −60, −30, −60, −30; βII: −60, 120, 80, 0; βIII: −60, −30, −60,.−30

Figure 2. Lowest Energy Backbone Conformations For Compound **1a**

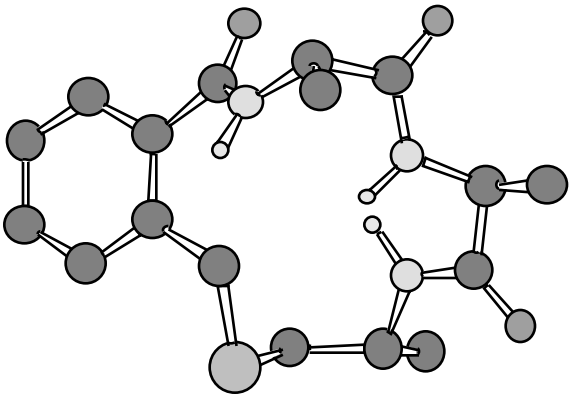
family 1



family 2



family 3



family 4

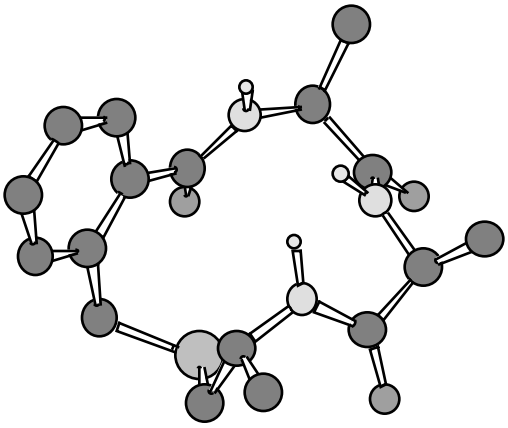
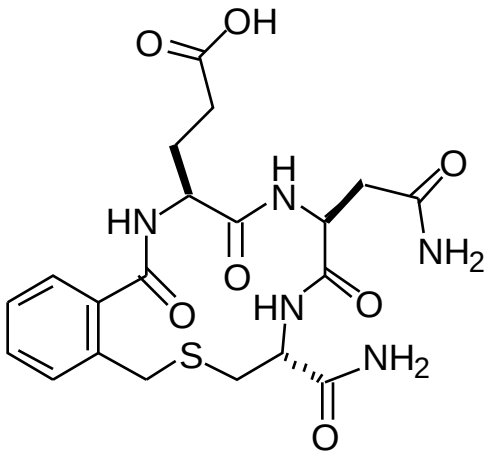


Table 3. Comparison of Observed Coupling Constants for **1a** with Angles Obtained from the Lowest Energy Conformer in F2 from QMD Data Study

N<u>H</u> – Cα	$^{3}J_{obs}$ (Hz)	calculated angles[a] (degrees)	φ from F2 (degrees)
Glu	6.99	-82.1	-75.0
Lys	8.49	-95.7	-61.0
Cys	9.49	-110.1	62.4

[a] the dihedral angle was obtained by solving Bystrov-Karplus equation with A = 6.4, B = -1.4 and C = 1.9

Summary of QMD and Conformational Studies For Compound 1k



1k

Key ROE contacts

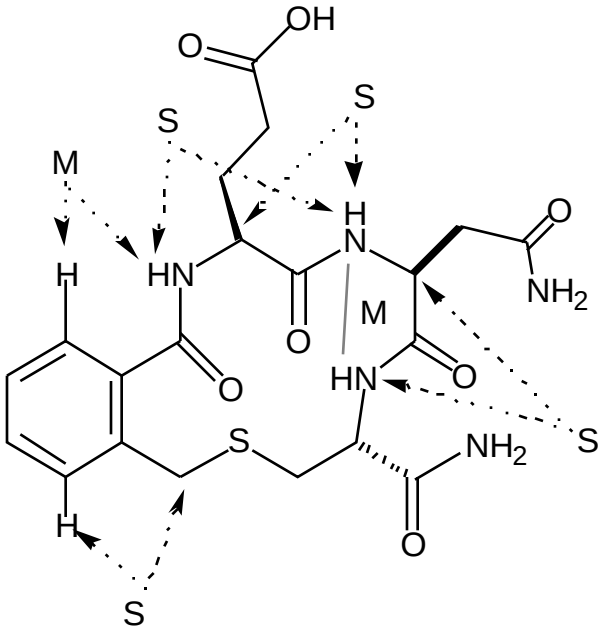
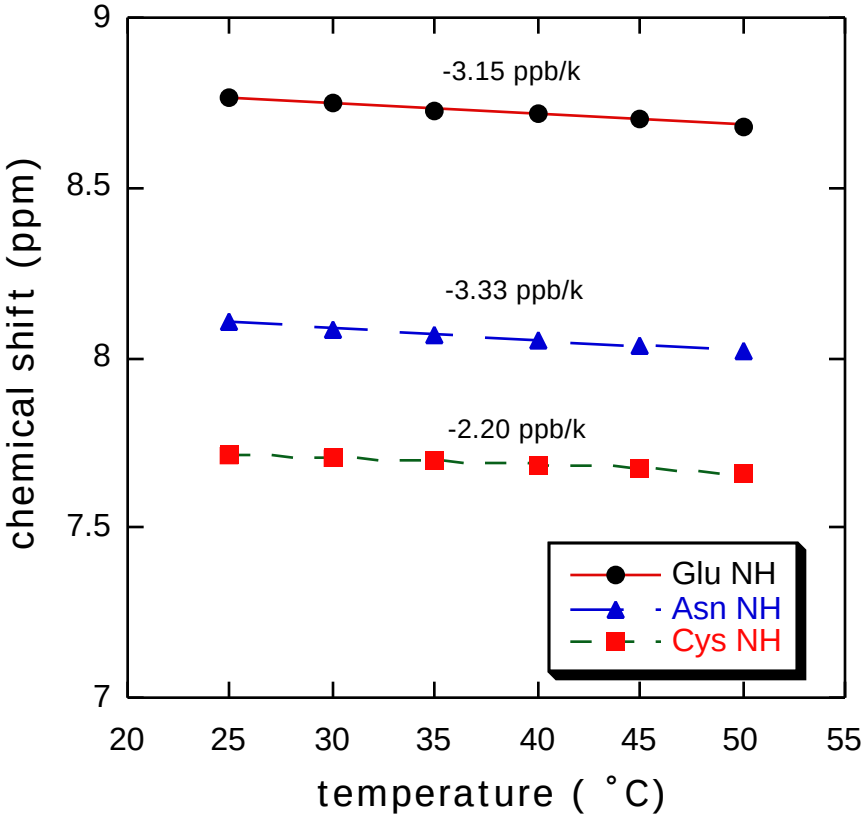


Table 4. Chemical Shifts, Coupling Constants and Temperature Coefficients Data for **1k**

sequence	proton	δ (ppm)	^{3}J (Hz)	temperature coefficient (ppb/K)
Glu	NH	8.770 (d)	6.50	-3.15
	α	4.235 (m)		
	β	1.923 (m)		
	β	1.923 (m)		
	γ	2.385(m)		
	OH	12.10 (b)		
Asn	NH	8.115 (d)	8.50	-3.33
	α	4.557 (m)		
	β	2.555-2.657 (m)		
	NH γ	6.861 (s)		
	NH γ	7.316 (s)		
Cys	NH	7.727 (d)	9.00	-2.20
	α	4.410 (m)		
	β	2.88-2.90 (m)		
	β	2.88-2.90 (m)		
C termini	NH	7.211(s)		
	NH	7.272 (s)		
Ar	H3-H6	7.38-7.42 (m)		
benzyl	H	3.878, 3.990 (AB q)		

Figure 3. temperature coefficient of 1k



QMD Data For 1k

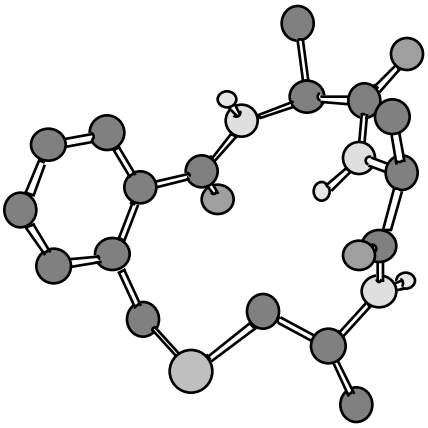
Table 5. QMD study of **1k** (RMSD threshold 0.75 Å)

residue	dihderal angle (˚)	family 1	family 2	family 3	family 4
		lowest energy conformer	lowest energy conformer	lowest energy conformer	lowest energy conformer
Glu	φ	-65.89 ˚	-87.24˚	-79.07 ˚	-72.30˚
	ψ	-27.67 ˚	-50.61˚	-52.32 ˚	-121.7 ˚
Asn	φ	-71.57˚	-133.0 ˚	-111.4 ˚	62.70˚
	ψ	-25.67˚	84.98˚	97.81˚	47.21˚
number in family		85	27	62	31
lowest energy conformer (kcal/mol)		1.0415	2.8018	1.9268	0.9289
distance (Å) O_i-$N\underline{H}_{i+3}$		2.217	4.723	4.796	2.904
type of turn[a]		βIII	βVIII	βVIII	–

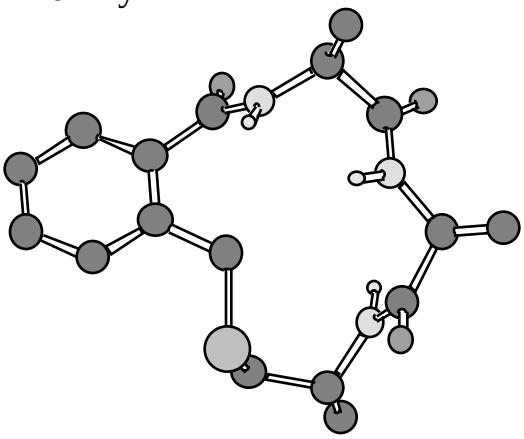
[a] Turn type is determined according to data from P. Y. Chou and G. D. Fasman, J. Mol. Biol. 115, 135-175, 1997; C. M. Wilmot and J. M. Thornton, J. Mol. Biol. 203, 221-232, 1988; J. S. Richardon, Adv. Protein Chem. 34, 167-339,1981.
βI: −60, −30, −60, −30; βII: −60, 120, 80, 0; βIII: −60, −30, −60,.−30

Figure 4. Lowest Energy Backbone Conformations For Compound **1k**.

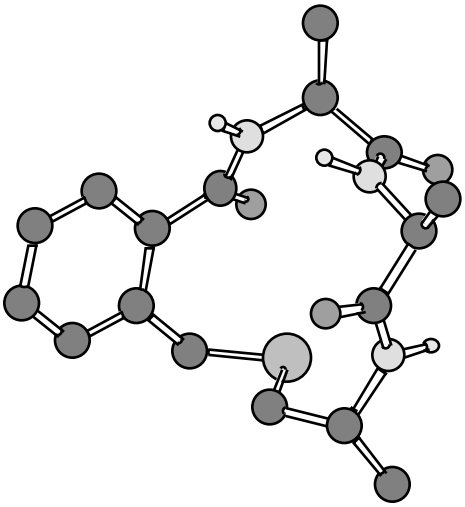
family 1



family 2



family 3



family 4

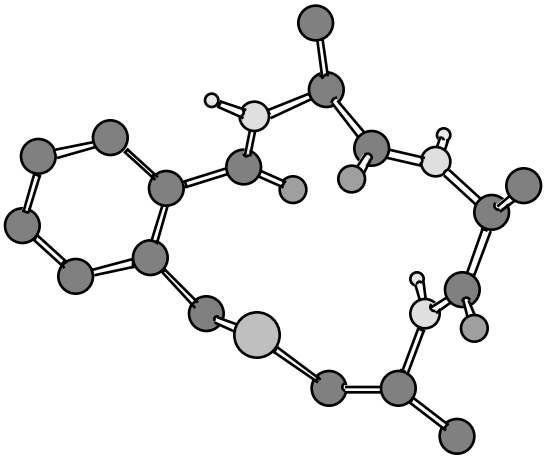


Table 6. Comparison of Observed Coupling Constants for **1k** with Angles Obtained from the Lowest Energy Conformer in F1 from QMD Data Study

NH – Cα	$^3J_{obs}$ (Hz)	calculated angles[a] (degrees)	φ from F1 (degrees)
Glu	6.5	44.6, 75.4, -78.19	-65.9
Asn	8.5	-95.8	-71.6
Cys	9.0	-101.7	-106.0

[a] the dihedral angle was obtained by solving Bystrov-Karplus equation with A = 6.4, B = -1.4 and C = 1.9