Electronic Supplementary Material (ESI) for RSC Advances.

Supporting information for the manuscript entitled

Design and Synthesis of Conformationally Homogeneous Pseudo Cyclic Peptides through Amino Acid Insertion: Investigations on Their Self Assembly

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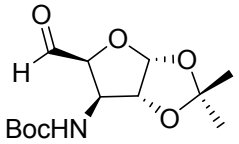
General Synthetic Experimental Details:

Solvents were dried over standard drying agents and freshly distilled prior to use. IR spectra between 400 and 4000 cm^{-1} were recorded with an FT-IR spectrometer using KBr pellets. Mass spectra were obtained under high resolution (HRMS). ^{1}H and ^{13}C NMR spectra were recorded in deuterated solvents on Bruker Avance (300 MHz) and Bruker (600 MHz) spectrometers. ^{1}H NMR multiplicity patterns are designated as singlet (s), doublet (d), triplet (t), or quartet (q); all first order splitting patterns are assigned. Splitting patterns that could not be interpreted or easily visualized are designated as multiplet (m) or broad (br). Column chromatographic separations were carried out on silica gel (60–120 mesh) and the cyclic peptides **1** and **2** were purified by preparative HPLC on Shimadzu UFLC (Model:LC-20AD) ODS-3-V, 250×4.6 mm, 5 μm (C-18/AR/25) with methanol:water (45:55) as mobile phase. 1-Hydroxybenzotriazole (HOBt) and 1-[3-(dimethylamino)propyl]-3-ethyl-carbodiimide hydrochloride (EDCI) were purchased from Spectrochem. All other reagents and solvents were purchased from Sigma-Aldrich or Merck.

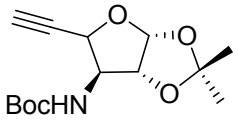
Preparation and Characterization of Compounds

3-Boc-Protected amino-3-deoxy-1,2-O-isopropylidene-α-D-xylo-furanosylaldehyde (4):



The 3-Boc protected amino-3-deoxy sugar diol (400 mg, 1.2 mmol) was dissolved in aqueous MeOH and sodium periodate (320 mg) was added portion wise at 0 °C. After 5 hr, the reaction mixture was filtered and evaporated, and the aqueous part was extracted with DCM (3×15 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to furnish the aldehyde (287 mg, 70%) as colourless oil which was used for the next step without further purification.

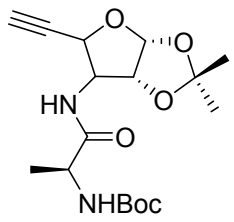
3-Boc-Protected amino-3-deoxy-1,2-O-isopropylidene α-D-xylo-furanosyl alkyne (5):



The mixture of aldehyde (287 mg, 1 mmol) and diazo 2-oxopropyl dimethyl phosphonate ester (231.6 mg, 1.2 mmol) was stirred in dry MeOH at 0 °C. After 5 min, K_2CO_3 (207 mg, 1.5 mmol) was added and the mixture was stirred at RT for 12 hr till the completion of reaction (TLC). The solvent was evaporated, and the residue was quenched with water and extracted with ethyl acetate (3×30 mL). The combined organic extract was dried over Na_2SO_4 and evaporated to afford the crude alkyne **5** which was purified by column chromatography using PE:EA (5:1) to a white solid (180 mg, two step yield 45%)**.**

^{1}HNMR ($CDCl_3$, 300 MHz, δ): 5.84 (d, J=3.6 Hz, 1H), 4.90 (m, 1H), 4.63 (m, 1H), 4.17 (m, 1H), 2.62 (s, 1H), 1.50 (s, 3H), 1.46 (s, 9H), 1.30 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**155.2, 112.3, 104.2, 84.0, 80.2, 69.3, 58.8, 28.3, 26.7, 26.1. **HRMS $(M+Na)^+$** Calculated for $C_{14}H_{21}NO_5Na$: 306.1317, found: 306.1322.

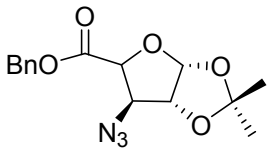
Boc-Protected sugar alkyne amide (6):



Compound **5** was stirred with TFA:DCM (1:5) at 0 °C for 1 hr, then at RT for another hour. After the completion of reaction, TFA and DCM were evaporated in high vac. To a stirred solution of Boc protected D-alanine (200 mg, 1.06 mmol) in dry DCM, EDC.HCl (202 mg, 1.06 mmol) and HOBt (143 mg, 1.06 mmol) were added at 0 °C. After stirring for 1hr at 0 °C, the deprotected sugar amine (300 mg, 1.06 mmol) was introduced to the reaction mixture and stirred for further 24 hr at room temperature under N_2. It was subsequently washed with 1(N) HCl (1×25 mL), 5% aq. $NaHCO_3$ (1×25 mL), and saturated NaCl solution (1×20 mL), and finally dried over Na_2SO_4. The organic layer was concentrated to give a yellow solid which was purified by column chromatography using PE:EA (1:1) as eluent to afford the corresponding Boc protected alkyne amide **6** as white solid (165 mg, 55%).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 6.45 (d, J=6.9 Hz, 1H), 5.84 (d, J=3.6 Hz, 1H), 4.95 (m, 1H), 4.59 (d, J=3.3 Hz, 1H), 4.41 (m, 1H), 4.16 (m, 1H), 2.61 (s, 1H), 1.51 (s, 3H), 1.45 (s, 9H), 1.38 (d, J = 6.9 Hz, 3H), 1.29 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**155.3, 112.4, 104.2, 83.6, 80.1, 69.0, 57.6, 31.0, 28.3, 26.6, 26.1, 18.1. **HRMS (M+Na)$^+$** Calculated for $C_{17}H_{26}N_2O_6Na$: 377.1689, Found: 377.1684.

Azidobenzyl sugar ester (7):

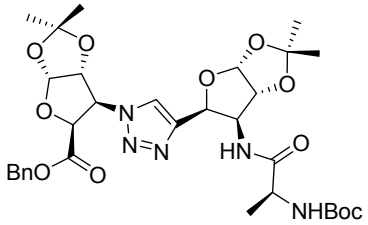


To a solution of sugar azido acid (500 mg, 2.1 mmol) in dry DMF at RT, benzyl bromide (525 mg, 3.0 mmol), $NaHCO_3$ (430 mg, 5.1 mmol) and catalytic amount of KI were added and left overnight. After completion of the reaction (TLC), it was extracted with DCM (3×20 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to yield the crude product which

was purified by column chromatography using PE:EA (10:1) to yield benzyl azido ester **7** as a colourless liquid (400 mg, 80%).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.38 (m, 5H), 6.03 (d, J=3.3 Hz, 1H), 5.23-5.33 (m, 2H), 4.86 (d, J=3.6 Hz, 1H), 4.66 (d, J=3.6 Hz, 1H), 4.26 (d, J=3.6 Hz, 1H), 1.54 (s, 3H), 1.33 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):** 167.0, 134.8, 128.8, 128.6, 112.8, 105.2, 82.9, 78.4, 67.4, 66.9, 26.7, 26.3. **HRMS $(M+Na)^+$** Calculated for $C_{15}H_{17}N_3O_5Na$: 342.1066, Found: 342.1063.

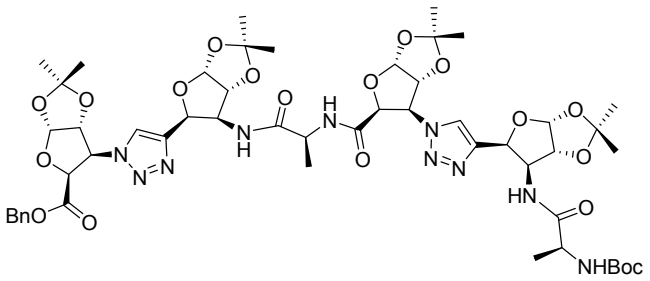
Boc-Protected benzyl ester dimer (8):



To a mixture of azido benzyl ester **7** (200 mg, 0.6 mmol) and Boc protected sugar alkyne **6** (350 mg, 1 mmol) in 2:1 tert-butanol:H_2O (35 mL), $CuSO_4.5H_2O$ (373.5 mg, 1.5 mmol) and TBTA (catalytic amount) were slowly added. Sodium L-ascorbate (396 mg, 2 mmol) was introduced to the reaction mixture; it was stirred for another 16 hr, quenched with saturated NaCl solution and extracted with DCM (3×25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford a yellow solid. The solid was purified by column chromatography (PE:EA, 1:2) to yield Boc protected benzyl ester **8** as white solid (161 mg, 46%).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.51 (s, 1H), 7.34-7.37 (m, 3H), 7.23-7.36 (m, 2H), 6.97 (d, J= 6.9 Hz, 1H), 6.31 (d, J= 3.3 Hz, 1H), 5.95 (d, J = 3.6 Hz, 1H), 5.37-5.42 (m, 2H), 5.12 (d, J= 4.2 Hz, 1H), 4.91-5.13 (m, 4H), 4.75 (d, J= 3.3 Hz, 1H), 4.39-4.42 (m, 1H), 4.06-4.11 (m, 1H), 1.62 (s, 3H), 1.60 (s, 3H), 1.57 (s, 6H), 1.44 (s, 9H), 1.25 (d, J = 6.9 Hz, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**172.9, 165.9, 155.3, 142.9, 134.3, 128.8, 128.7, 123.1, 113.2, 112.1, 105.6, 104.2, 84.2, 83.4, 80.1, 67.7, 66.4, 58.0, 28.3, 26.6, 26.1, 26.0. **HRMS $(M+Na)^+$** Calculated for $C_{32}H_{43}N_5O_{11}Na$: 696.2857, found: 696.2860.

Boc-Protected benzyl ester pentamer (11):



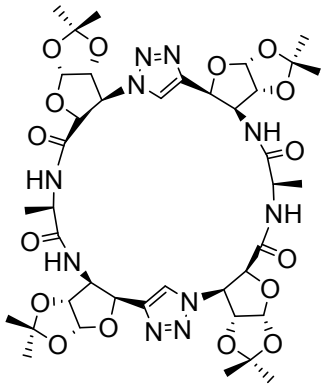
Compound **8** was divided into two parts. One part (60 mg, 0.08 mmol) was dissolved in EtOAc, 10% w/w Pd-C (15 mg) was added and the mixture was stirred for 2 hr under H_2 at one atmospheric pressure. After the completion of reaction (TLC), the mixture was filtered through a small celite pad, washed with MeOH (2×10 mL) and the combined filtrate was concentrated under reduced pressure to afford the corresponding acid as colorless semisolid **9** (50 mg, 85%). The other part was treated with 5:1 DCM:TFA at 0 °C for 1 hr, then at RT for another hour. After the completion of the reaction both TFA and DCM were evaporated to get Boc free amine **10**.

To a stirred solution of Boc protected acid **9** (50 mg, ca. 0.071 mmol) in dry CH_2Cl_2, EDC.HCl (14 mg, 0.071 mmol) and HOBt (9 mg, 0.071 mmol) were added at 0 °C. After stirring for 1 hr at 0 °C, the Boc free amine **10** (40 mg, ca. 0.071 mmol) and 0.4 mL DIEA were introduced to the reaction mixture and stirred for further 12 hr at room temperature under N_2. It was then washed with 1(N) HCl (1×25 mL), 5% aq. $NaHCO_3$ (1×25 mL), and saturated NaCl solution (1×20 mL), and dried over anhydrous Na_2SO_4. The organic layer was concentrated to give a yellow solid which was purified by column chromatography using 3% MeOH in DCM as eluent to afford the methyl ester **11** (27 mg, 55%) as a white solid.

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.66 (s, 1H), 7.58 (s, 1H), 7.36-7.49 (m, 4H), 6.94- 6.99 (m, 1H), 6.25-6.33 (m, 2H), 5.94-6.09 (m, 2H), 5.48-5.52 (m, 1H), 5.36-5.42 (m, 2H), 5.29-5.32 (m, 1H), 5.11-5.14 (m, 2H), 4.89-5.06 (m, 4H), 4.85 (d, J = 3.6 Hz, 1H), 4.73-4.78 (m, 1H), 4.57 (d, J = 3.6 Hz, 1H), 4.23-4.46 (m, 2H), 4.10-4.20 (m, 1H), 1.59 (s, 24 H), 1.45 (s, 9H), 1.25 (m, 6H).
^{13}C NMR ($CDCl_3$, 75 MHz, δ): 173.0, 165.8, 155.4, 142.6, 134.5, 128.9, 128.7, 123.5, 113.2,

112.1, 105.7, 104.3, 104.1, 84.1, 83.3, 79.4, 67.7, 66.4, 58.1, 39.6, 28.3, 26.6, 26.1. **HRMS (M+Na)$^+$** Calculated for $C_{52}H_{70}N_{10}O_{19}Na$: 1161.4716, Found: 1161.4712.

Cyclic compound (1):

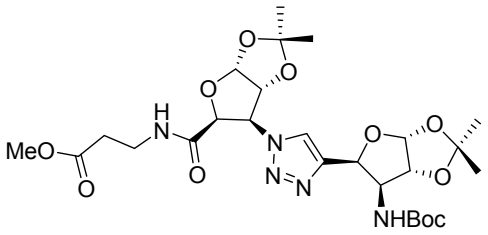


To a solution of compound **11** (60 mg, 0.05 mmol) in EtOAc, 10% w/w Pd-C (15 mg) was added and the mixture was stirred for 2 hr under H_2 at one atmospheric pressure. After the completion of reaction (TLC), the mixture was filtered through a small pad of celite, washed with MeOH (2×10 mL) and the combined filtrate was concentrated under reduced pressure to afford the corresponding acid as colorless semisolid.

To a stirred solution of Boc tetramer acid (40 mg, 0.04 mmol) in dry DCM, EDC.HCl (8 mg, 0.04 mmol) was added at 0 °C. After stirring at 0 °C for 10 min, pentafluoro phenol (1 to 2 drops) was introduced to the reaction mixture and stirred overnight at room temperature under N_2. It was washed subsequently with 1(N) HCl (1×25 mL) and saturated NaCl solution (1×20 mL), and dried over Na_2SO_4. After evaporating the solvent, the residue was washed with n-hexane four times to furnish the tetrameric Boc-pentaflourophenyl ester (85%) which was treated with 1:5 TFA:DCM, at 0 °C for 1hr then at RT for another 1 hr. After completion of the reaction, TFA and DCM were evaporated in high vac, 0.4 mL dry DIEA was added, and the reaction mixture was allowed to cyclize in dry acetonitrile solvent at 70-80 °C for 3 to 4 hr. Finally, the reaction mixture was extracted with EtOAc (3×10 mL) and dried over Na_2SO_4; the combined extract was concentrated under reduced pressure to afford the crude cyclic peptide **1** which was purified by RP-HPLC (C18 column, CH_3CN:H_2O).

^{1}H NMR (CD_3CN, 600 MHz, δ): 7.64 (s, 1H), 6.87 (d, J = 7.2 Hz, 1H), 6.40 (d, J = 7.2 Hz, 1H), 6.25 (d, J = 3.6 Hz, 1H), 6.14 (d, J = 3.6 Hz, 1H), 5.42 (d, J = 4.2 Hz, 1H), 5.32 (d, J = 4.2 Hz, 1H), 5.07 (d, J = 3.6 Hz, 1H), 4.93 (d, J = 4.2 Hz, 1H), 4.70 (d, J = 4.2 Hz, 1H), 4.32 (dd, J=5.4, J= 7.2,1H), 4.05-4.12 (m, 1H), 1.55 (s, 6H), 1.35 (s, 6H), 1.12 (s, 3H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**171.1, 166.1, 141.5, 139.3, 131.6, 125.6, 113.3, 111.9, 106.0, 104.3, 84.9, 82.6, 79.9, 65.4, 57.5, 48.1, 29.6, 29.3, 26.6, 26.2. **HRMS (M+Na)$^+$** Calculated for $C_{40}H_{54}N_{10}O_{16}Na$: 953.3617, Found: 953.3623.

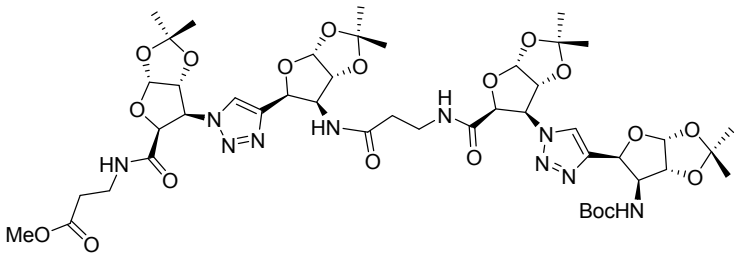
Boc-Protected methyl ester dimer (14):



To a mixture of azido sugar methyl ester **13** (214 mg, 1 mmol) and Boc protected sugar alkyne **5** (460 mg, 1.5 mmol) in 2:1 tert-butanol:H_2O (35 mL), $CuSO_4.5H_2O$ (373.5 mg, 1.5 mmol) and TBTA (catalytic amount) were slowly added. Sodium L-ascorbate (396 mg, 2 mmol) was introduced to the reaction mixture; it was stirred for another 16 hr, quenched with saturated NaCl solution and extracted with DCM (3×25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under vacuum to afford a yellow solid. The solid was purified by column chromatography (PE: EA, 1:2) to yield Boc protected methyl ester **14** as white solid (211 mg, 46%).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.63 (s, 1H), 6.72 (t, J = 3.6 Hz, 1H), 6.39 (d, J = 3.3 Hz, 1H), 5.92 (d, J = 3.6 Hz, 1H), 5.42 (d, J = 3.6 Hz, 1H), 5.30 (d, J = 4.2 Hz, 1H), 5.19-5.22 (m, 2H), 5.01 (d, J = 4.2 Hz, 1H), 4.45 (s, 1H), 4.23-4.26 (m, 1H), 3.68 (s, 3H), 3.18-3.27 (m, 2H), 2.24-2.32 (m, 1H), 1.62 (s, 6H), 1.57 (s, 6H), 1.39 (s, 9H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**171.9, 171.1, 166.1, 142.1, 125.0, 113.3, 112.0, 106.7, 103.9, 82.9, 80.3, 65.9, 60.3, 51.8, 34.0, 33.3, 29.6, 28.2, 26.8, 26.5, 26.3, 26.1. **HRMS (M+Na)$^+$** Calculated for $C_{26}H_{39}N_5O_{11}Na$: 620.2544, Found: 620.2538.

Boc-Protected methylester pentamer (17):



Compound **14** was divided into two parts. To a stirred solution of one part (60 mg, 0.10 mmol) in 15 mL THF:H_2O (3:1) at 0 °C, LiOH.H_2O (13.2 mg, 0.321 mmol) was added and stirred for 1 hr. The reaction mixture was acidified with aqueous sodium bisulphate solution and extracted with ethyl acetate (6×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish the corresponding acid **15** as white solid (57 mg, 95 %).

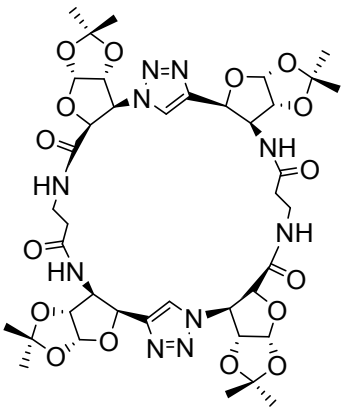
The other part (60 mg, 0.10 mmol) was treated with TFA:DCM (1:5) at 0 °C for 1 hr then at RT for another 1 hr; after the completion of the reaction TFA and DCM were evaporated in high vac to get Boc free amine **16** (50 mg, 82%)

To a stirred solution of Boc protected acid **15** (57 mg, ca. 0.10 mmol) in dry CH_2Cl_2, EDC.HCl (19 mg, 0.10 mmol) and HOBt (13 mg, 0.10 mmol) were added at 0 °C. After stirring for 1hr at 0 °C, the Boc free amine **16** (50 mg, ca. 0.10 mmol) and 0.4 mL DIEA were introduced to the reaction mixture and stirred for further 12 hr at room temperature under N_2. It was then successively washed with 1(N) HCl (1×25 mL), 5% aq. $NaHCO_3$ (1×25 mL), and saturated NaCl solution (1×20 mL), and dried over anhydrous Na_2SO_4. The organic layer was concentrated to give a yellow solid which was purified by column chromatography using 4% MeOH and DCM as eluent to afford the corresponding pentamer methyl ester **17** (31 mg, 55%) as white solid.

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 8.01 (s, 1H), 7.83 (s.1H), 7.66 (s, 1H), 6.59-6.73 (m, 2H), 6.38-6.43 (m, 2H), 6.04-6.15 (m, 2H), 5.90 (d, J = 3.3 Hz, 1H), 5.82 (d, J = 2.7Hz, 1H), 5.55 (d, J = 3.3 Hz, 1H), 5.50 (d, J = 3.3 Hz, 1H), 5.31-5.41 (m, 2H), 5.17-2.26 (m, 2H), 5.00-5.02 (m, 2H), 4.63-4.78 (m, 3H), 4.20-4.33 (m, 2H), 3.67 (s, 3H), 3.14-3.35 (m, 3H), 2.15-2.25 (m, 2H), 1.66 (s, 6H), 1.61 (s, 6H), 1.58 (s, 12H), 1.38 (s, 9H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**172.1, 170.2, 166.4, 142.5, 125.0, 113.4, 113.1, 106.9, 82.9, 80.6, 65.6, 60.4, 52.0, 34.3, 29.6, 28.2, 26.8, 26.6,

26.3, 26.1, 26.0. **HRMS (M+Na)$^+$** Calculated for $C_{46}H_{66}N_{10}O_{19}Na$: 1085.4403, Found: 1085.4398.

Cyclic compound (2):



To a stirred solution of compound **17** (60 mg, 0.05 mmol) in 15 mL THF:H_2O (3:1) at 0 °C, LiOH.H_2O (13.2 mg, 0.321 mmol) was added and the mixture stirred for 1 hr. The reaction mixture was acidified with aqueous sodium bisulphate solution and extracted with ethyl acetate (6×10 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish the corresponding acid as white semi solid (57 mg, 95 %).

To a stirred solution of Boc tetramer acid (40 mg, 0.03 mmol) in dry CH_2Cl_2, EDC.HCl (6 mg, 0.03 mmol) was added at 0 °C. After stirring at 0 °C for 10 min, pentafluoro phenol (1 to 2 drops) was introduced to the reaction mixture and stirred overnight at room temperature under N_2. It was diluted with DCM, washed with 1(N) HCl (1×25 mL) and saturated NaCl solution (1×20 mL), and dried over Na_2SO_4. After evaporating the solvent, the residue was washed with n-hexane four times to furnish the tetrameric Boc-pentaflourophenyl ester (85%) which was treated with TFA:DCM (1:5) at 0 °C for 1 hr, then at RT for another hour. After completion of the reaction TFA and DCM were evaporated, 0.4 mL dry DIEA was added to the reaction mixture and then heated in dry acetonitrile solvent at 70-80 °C for 3 to 4 hr. After the completion of reaction (TLC), the reaction mixture was extracted with EtOAc (3×5 mL) and dried over Na_2SO_4; the combined filtrate was concentrated under reduced pressure to afford the crude cyclic peptide **2** which was purified by RP-HPLC (C18 column/CH_3CN/H_2O).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.74 (s, 2H), 7.16 (d, J = 8.4 Hz, 2H), 6.78 (d, J = 3.9 Hz, 2H), 6.25 (d, J = 3.0 Hz, 2H), 6.16 (d, J = 3.6 Hz, 2H), 5.35 (d, J = 3.3 Hz, 2H), 5.31 (d, J = 5.1 Hz,

2H), 5.10 (d, J = 4.8 Hz, 2H), 4.85 (d, J = 3.3 Hz, 2H), 4.70-4.67 (m, 4H), 3.53-3.58 (m, 2H), 3.14-3.20 (m, 2H), 2.02-2.09 (m, 2H), 1.66-1.76 (m, 2H), 1.57 (s, 6H), 1.55 (s, 6H), 1.37 (s, 6H), 1.30 (s, 6H). **^{13}C NMR ($CDCl_3$, 75 MHz, δ):**171.0, 166.6, 141.9, 139.3, 131.7, 125.7, 113.6, 112.0, 106.4, 104.2, 84.4, 84.1, 80.1, 72.1, 66.1, 57.0, 29.5, 27.2, 26.6, 26.2. **HRMS $(M+Na)^+$** Calculated for $C_{40}H_{54}N_{10}O_{16}Na$: 953.3617, Found: 953.3611.

Structural Determination by Multidimensional NMR:

NMR Spectra (1D and 2D) of the pseudo cyclic peptides **1** and **2** were recorded in Bruker Avance-600 MHz with TCI CRYOPROBE in Acetonitrile-d_3 or (2:3) $CDCl_3$:CCl_4 or $CDCl_3$ using tetra methyl silane as internal standard and chemical shifts are shown in ppm. All the two dimensional NMR studies (DQF COSY, ROESY) were carried out in phase-sensitive mode. The 2D spectra were acquired with 2×256 or 2×192 free induction decays (FID) containing 16-32 scans with relaxation delays of 1.5 s. The ROESY experiments were performed with mixing time of 0.2 to 0.3 s and the TOCSY experiments were performed with mixing time of 0.02 s. The two dimensional data were processed with Gaussian apodization in both the dimensions. The spectra (One Dimensional, DQF-COSY and ROESY) are given below.

^{1}H-^{1}H ROESY cross peaks at 300 ms were assigned and integrated and the respective volumes were converted to distance restraints. When symmetric pairs of cross peaks were present, the larger peak volume was converted to the distance restraint. Cross-peaks were categorized as strong, medium, weak, and very weak based on their intensities. Inter-proton distances (r) were derived from the ROE intensities (S) with the known relationship $r= c(S)^{-1/6}$, where c is a coefficient determined on the basis of ROE corresponding to a known distance. The distance constraints were determined from volume integrals of ROESY cross peaks using reference distance 2.40 Å for vicinal cis-sugar ring protons. The conservative upper distances were fixed respectively as 3.5, 4.0, 4.5 and 6.0 Å and the lower distance limit was fixed at 2.0 Å. Corrections of 0.1 Å were applied to the upper bound distances derived from NOEs to account for any spin diffusion effect. The dihedral angles (φ) were calculated from the $^3J_{HN\text{-}H\beta}$ coupling constants measured from the ^{1}H-^{1}H DQF-COSY spectra using the modified Karplus[1] equation. The φ's thus obtained were used as dihedral restraints.

1. C. A. G. Haasnoot, F. A. A. M. de Leeuw, H. P. M. de Leeuw, C. Altona, *Org. Magn. Reson*. 1981, **15**, 43.

[1]H and [13]C NMR Spectra:

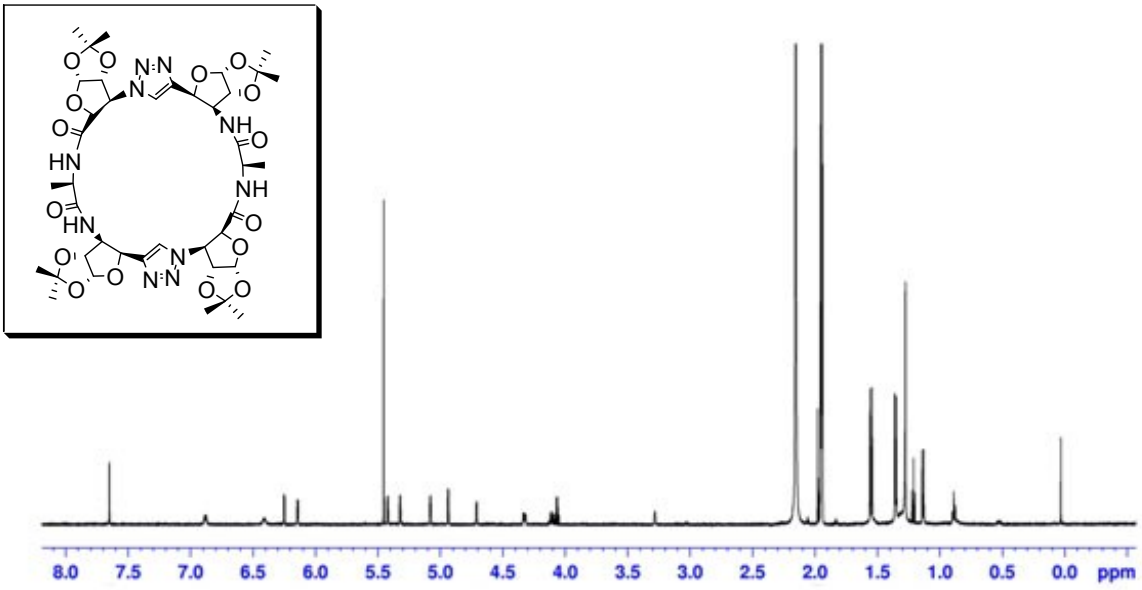


Fig 1:^{1}H NMR of macrocyclic peptide **1** at 298K in CD_3CN.

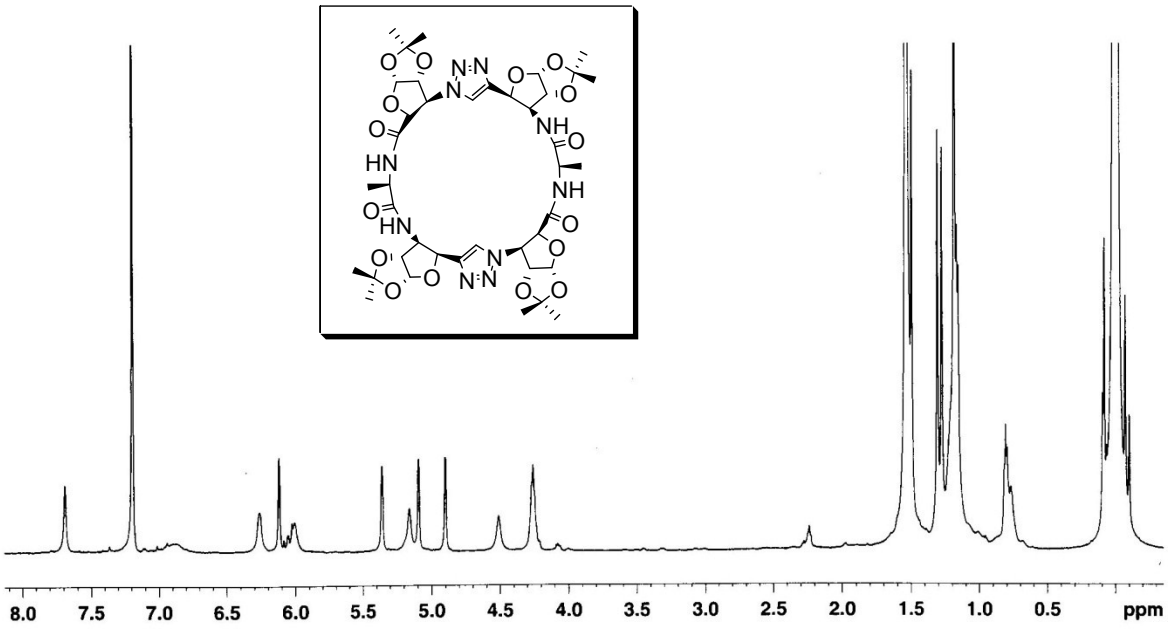


Fig 2: ^{1}H NMR of macrocyclic peptide **1** at 298 K in $CDCl_3$

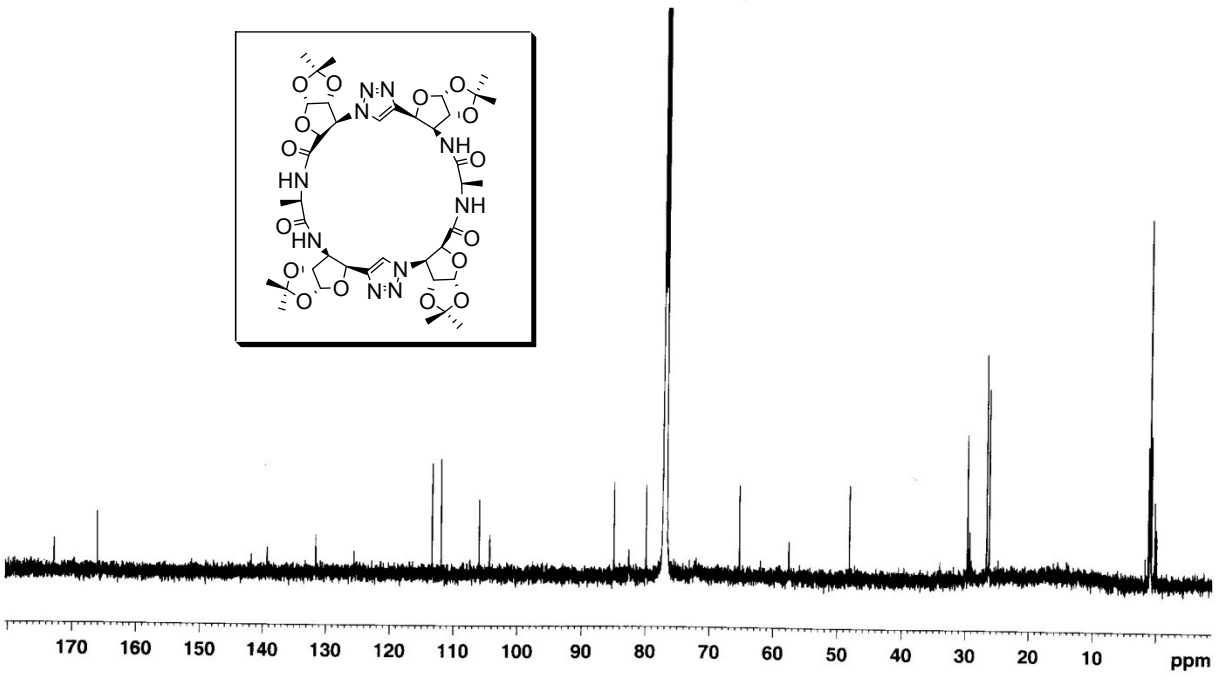


Fig 3: ^{13}C NMR of macrocyclic peptide **1** at 298 K in $CDCl_3$

2D NMR Study:

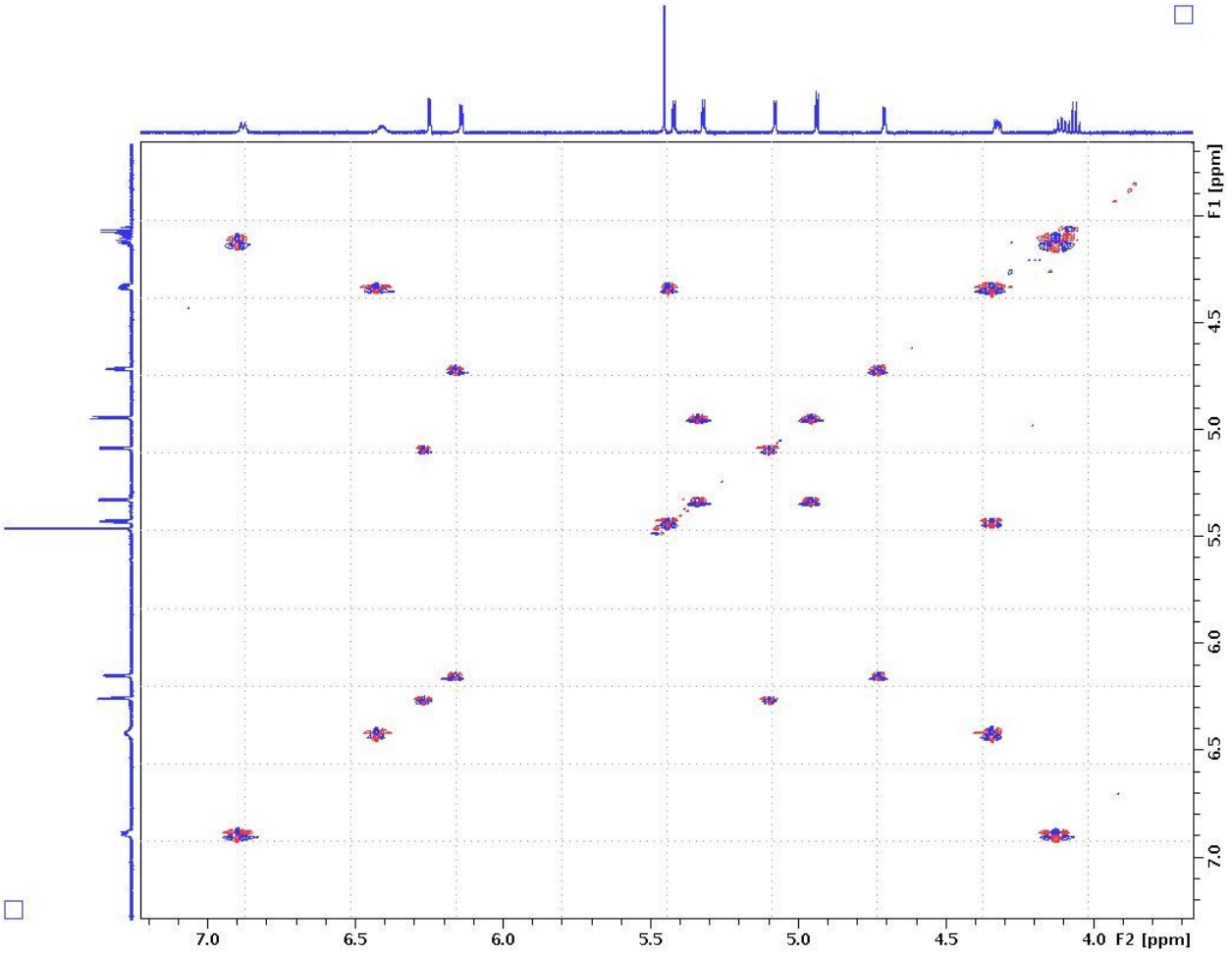


Fig 4: ^{1}H-^{1}H DQF-COSY Spectrum of the cyclic peptide **1** at 298 K in CD_3CN

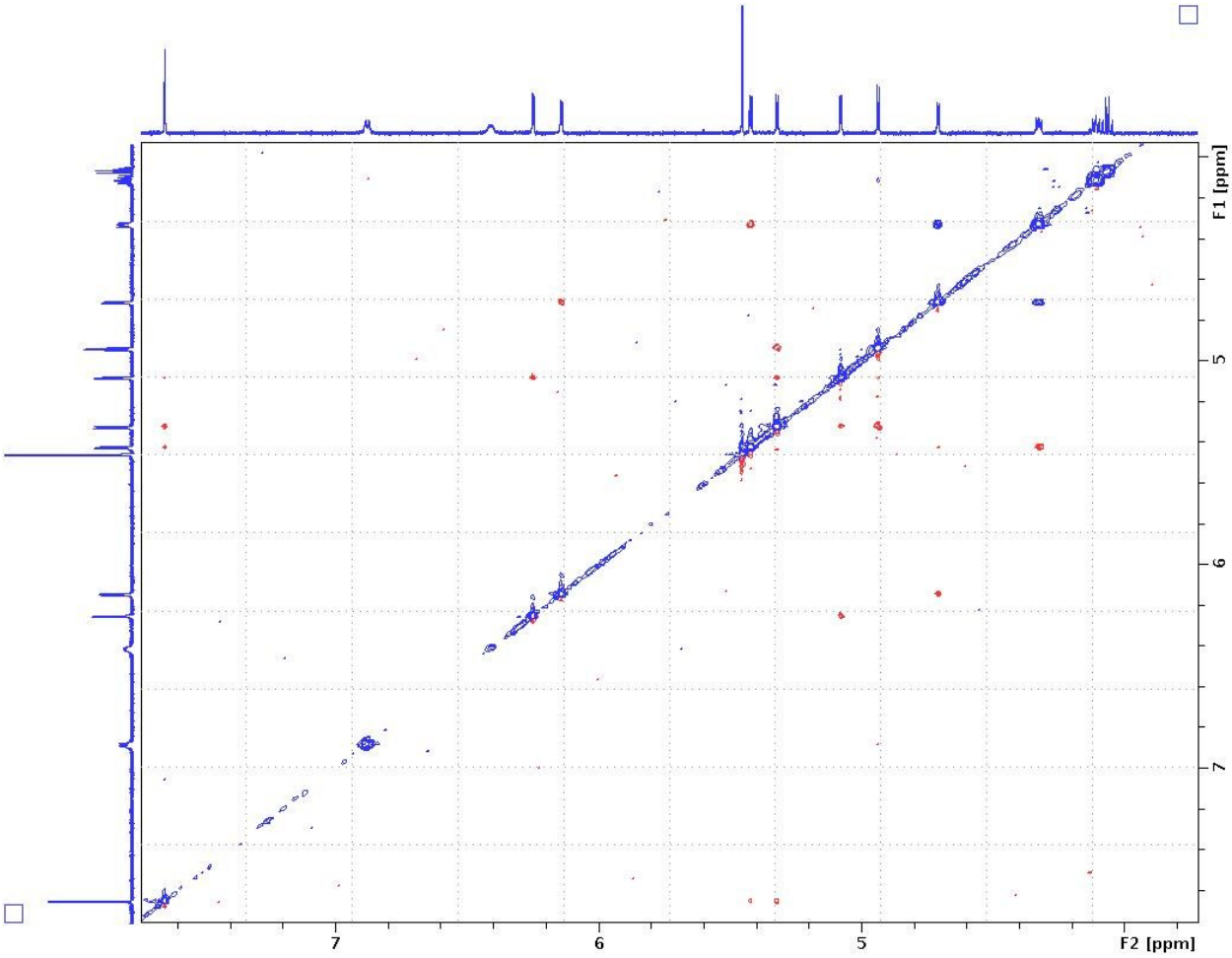


Fig 5: Partial ^{1}H-^{1}H ROESY Spectrum of the cyclic peptide **1** at 298 K in CD_3CN

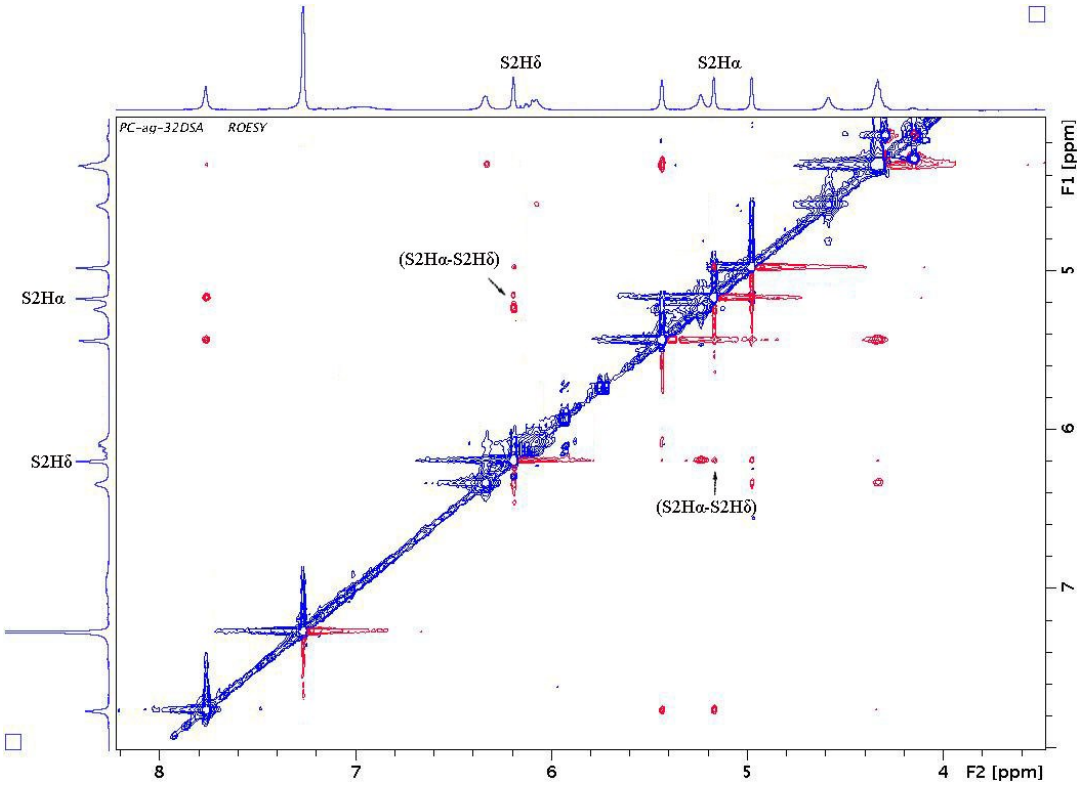


Fig 6: Partial ^{1}H-^{1}H ROESY Spectrum of the cyclic peptide **1** at 298 K in (2:3) $CDCl_3$:CCl_4 (600 MHz, 298 K).

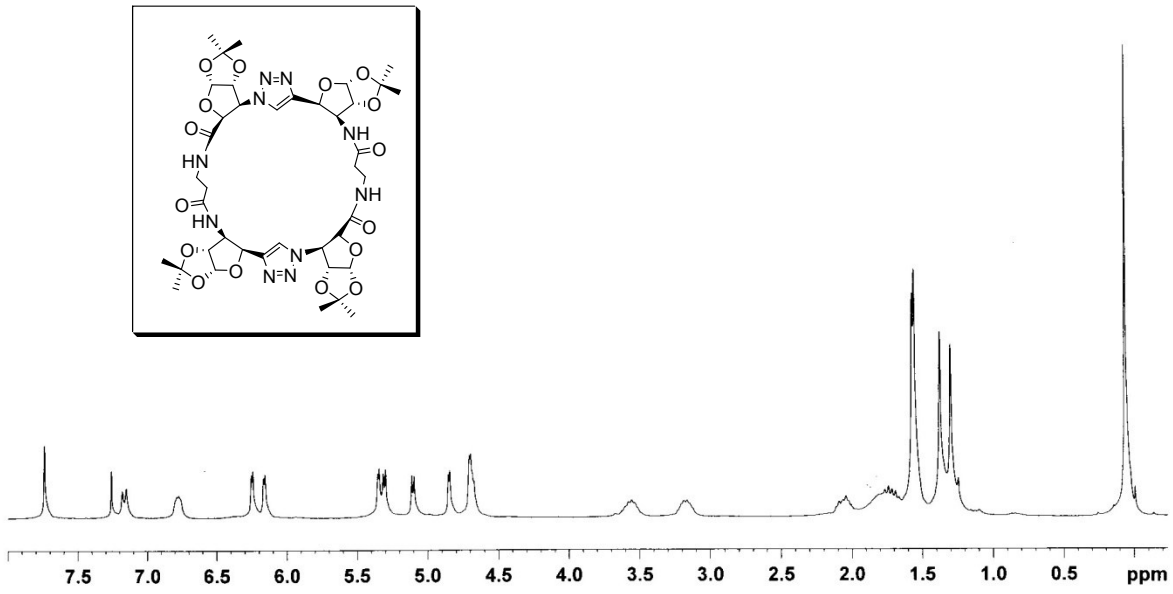


Fig 7: ^{1}H NMR of macrocyclic peptide **2** at 298 K in $CDCl_3$

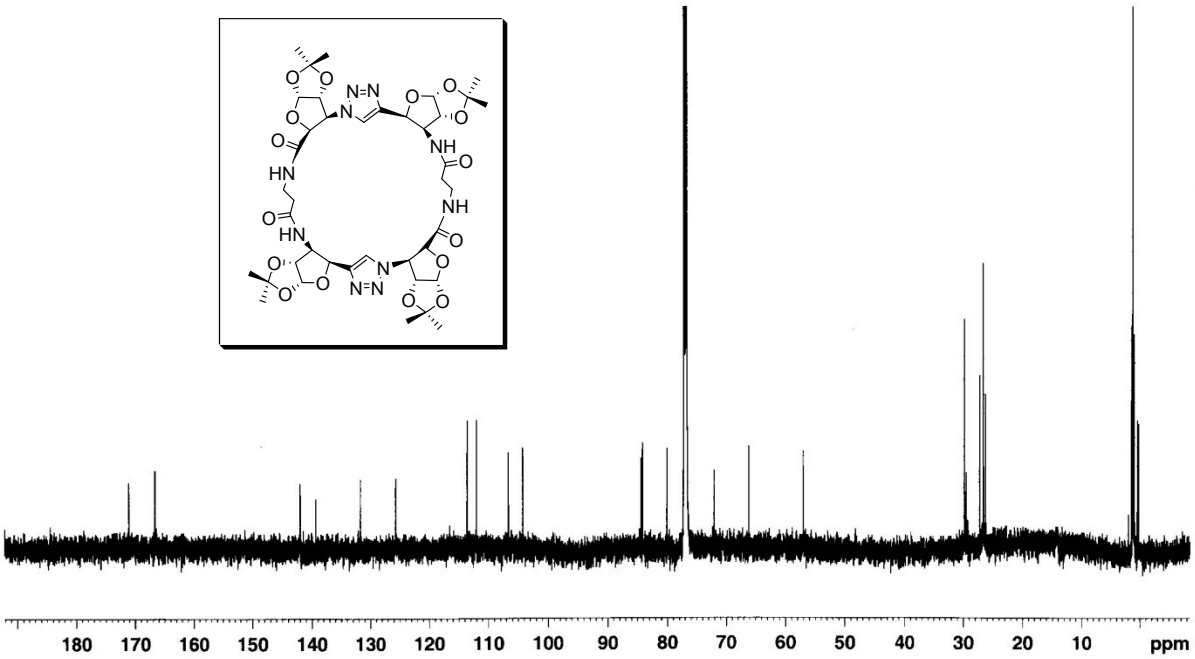


Fig 8: ^{13}C NMR of macrocyclic peptide **2** at 298 K in $CDCl_3$

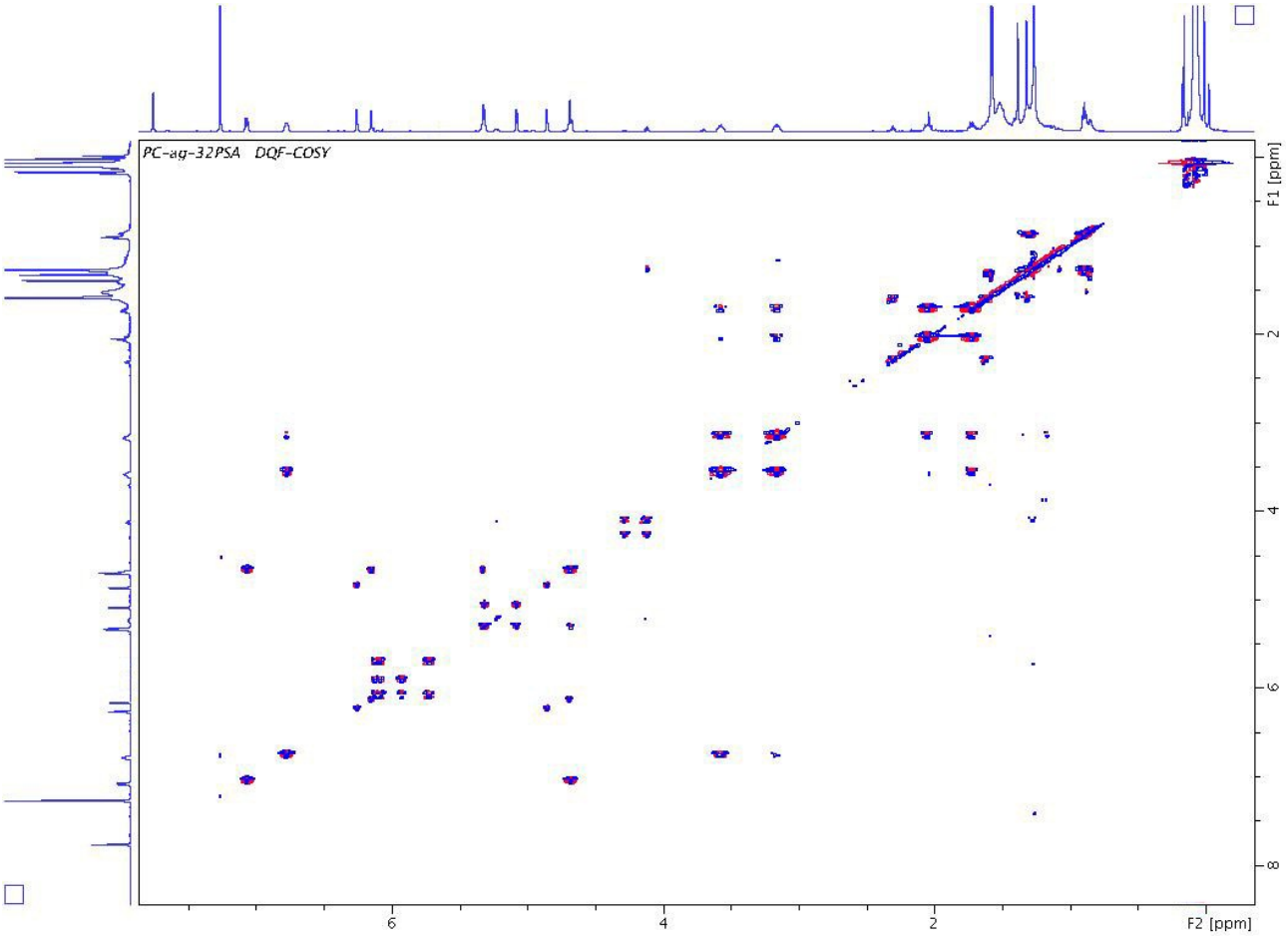


Fig 9: ^{1}H-^{1}H DQF-COSY Spectrum of the cyclic peptide **2** at 298 K in $CDCl_3$

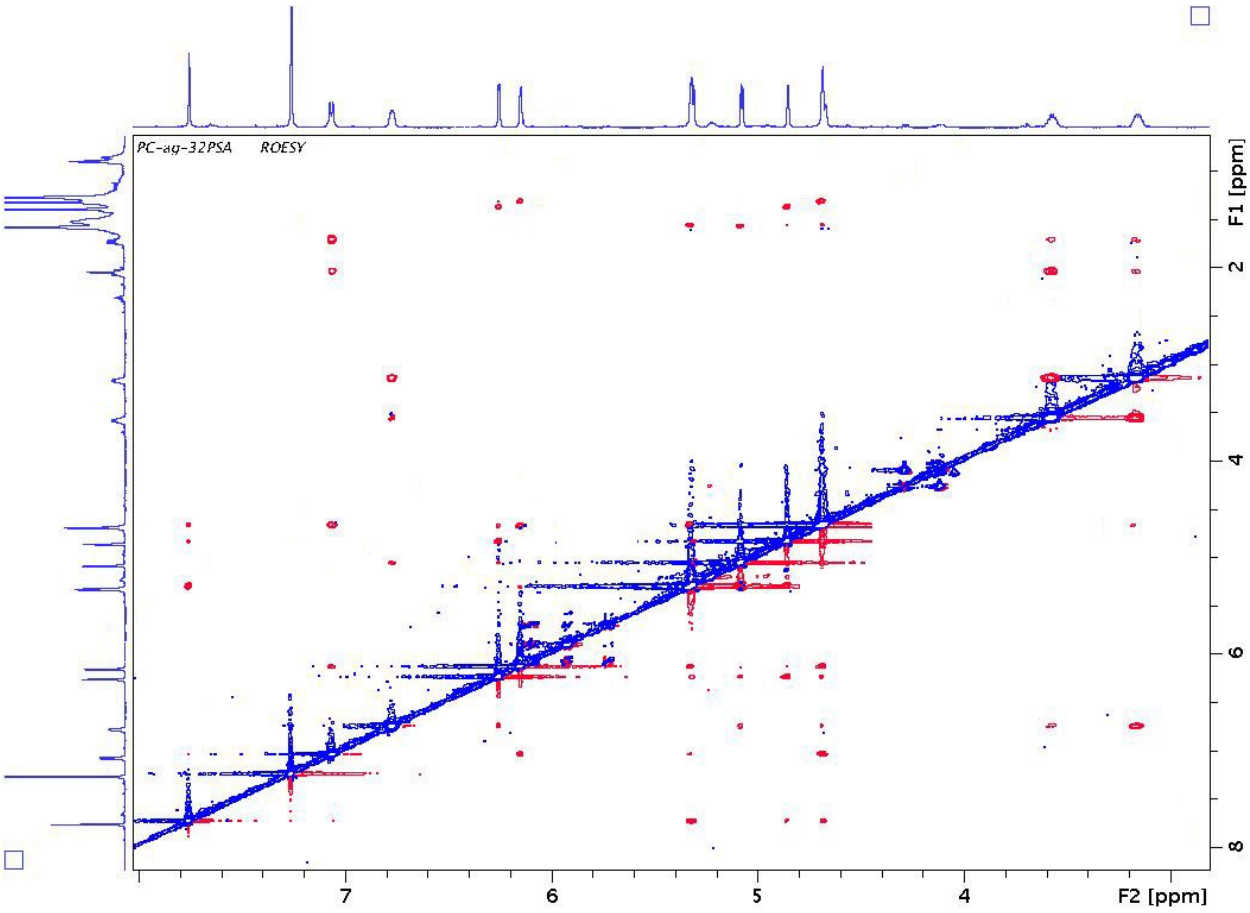


Fig 10: ^{1}H-^{1}H ROESY Spectrum of the cyclic peptide **2** at 298 K in $CDCl_3$

Conformational analysis

^{1}H NMR spectra of the macrocyclic peptide **1** were recorded in polar and nonpolar solvents (CD_3CN, CCl_4-$CDCl_3$ methanol-d_4). Spectra (CD_3CN) of all entries in Table-1 and spectra ($CDCl_3$) of entries Table-2 were assigned from the corresponding double-quantum-filtered 2D DQF-COSY as well as ROESY spectra.

Residue name	**Hα**	**Hβ**	**Hγ**	**Hδ**	**NH**	**N′H**	**TrH**
S_1	5.34 (d) $J_{Hα,Hβ}$=4.2	5.46 (d) $J_{Hβ,Hα}$=4.2	5.00 (d) $J_{Hγ,Hδ}$=3.6	6.14 (d) $J_{Hγ,Hδ}$=3.6			7.64 (s)
S_2	4.94 (d) $J_{Hα,Hβ}$=4.2	4.28 (dd) $J_{NH,Hβ}$=7.2 $J_{Hα,Hβ}$=4.2	4.60 (d) $J_{Hγ,Hδ}$=3.9	6.24(d) $J_{Hγ,Hδ}$=3.6	6.40 (d) $J_{NH,Hα}$=7.2		
Ala	4.05 (m)					6.87 (d) $J_{NH,Hβ}$=7.2	

Others: Methyl signals at 1.55, 1.35, 1.12.

Table 1: ^{1}H Chemical shifts (ppm) and coupling constants (Hz) of compound **1** (CD_3CN, 600 MHz, 300 K)

Residue	**Hα**	**Hβ**	**Hγ**	**Hδ**	**NH**	**N′H**	**TrH**
S1	5.10 (d) $J_{Hα,Hβ}$=4.8	5.31 (d) $J_{Hβ,Hα}$=5.1	4.85 (d) $J_{Hγ,Hδ}$=3.3	6.25 (d) $J_{Hγ,Hδ}$=3.0			7.74 (s)
S2	5.35 (d) $J_{Hα,Hβ}$=3.3	4.67 (m)	4.70 (d) $J_{Hγ,Hδ}$=3.0	6.16 (d) $J_{Hγ,Hδ}$=3.6	7.16 (d) $J_{NH,Hβ}$=8.4		
β-Ala	2.04 (m)	3.55 (m), 3.17 (m)				6.78 (dd) $J_{NH,Hβ}$=3.9 $J_{Hα,Hβ'}$=11.2	

Others: Methyl signals at1.57 ,1.55, 1.37, 1.30.

Table 2: ^{1}H Chemical shifts (ppm) and coupling constants (Hz) of compound **2** ($CDCl_3$, 600 MHz, 300 K)

Residue	Atom	Residue	Atom	Distance (Å)
Sugar (S_2)	NH	Sugar (S_2)	$C_\beta H$	2.7-3.05
Sugar (S_2)	NH	D-Ala	$C_\alpha H$	3.2-3.85
Sugar (S_1)	$C_\alpha H$	D-Ala	NH	3.7-4.3
D-Ala	NH	Sugar (S_1)	$C_\alpha H$	3.25-3.85
Triazole	CH	Sugar (S_1)	$C_\beta H$	3.1-3.45
Sugar (S_2)	$C_\alpha H$	Triazole	CH	2.95-3.2

Table 3: Inter proton distances of compound **1** calculated from NMR results.

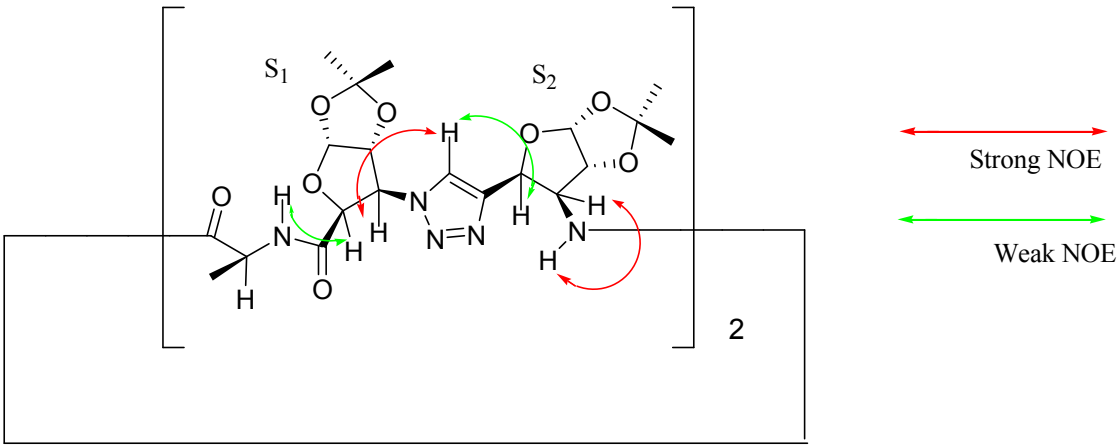


Fig 11: Strong and weak NOE connectivities of compound **1.**

SEM and AFM Images of Macrocyclic Peptide 1:

SEM image was achieved by SUPRA 35VP-30KV–resolution 2.5 nm, Carl Zeiss (Germany).

AFM Sample Preparation and Imaging

Aliquots (10 μL) of the sample **1** were deposited onto freshly cleaved muscovite Ruby mica sheet (ASTM V1 Grade Ruby Mica from MICAFAB) during 15-30 min. After 15 min, the sample was dried using a vacuum dryer. Sometimes the sample was gently washed with 0.5 mL Milli-Q water to remove the molecules that were not firmly attached to mica and the sample dried as mentioned above.

AAC mode AFM was performed using a Pico plus 5500 ILM AFM (Agilent Technologies USA) with a piezo scanner with maximum range of 9 μm. Micro fabricated silicon cantilevers used, 225 μm in length with a nominal spring force constant of 21-98 N/m, were from Nano sensors, USA. The cantilever oscillation frequency was tuned into resonance frequency, which was 150-300 kHz. The images (256 by 256 pixels) were captured with a scan size of between 0.5 and 5 μm at the scan speed rate of 0.5 lines/s. Images were processed by flattening using Pico view1.4 version software (Agilent Technologies, USA). Image manipulation has been done through Pico Image Advanced version software (Agilent Technologies, USA).

FT-IR Study:

FT-IR Measurements were made on a JASCO FT/IR-400 Spectrophotometer using 5-10 mM solution in $CHCl_3$ of compound **1** and **2** placed in a NaCl cell.

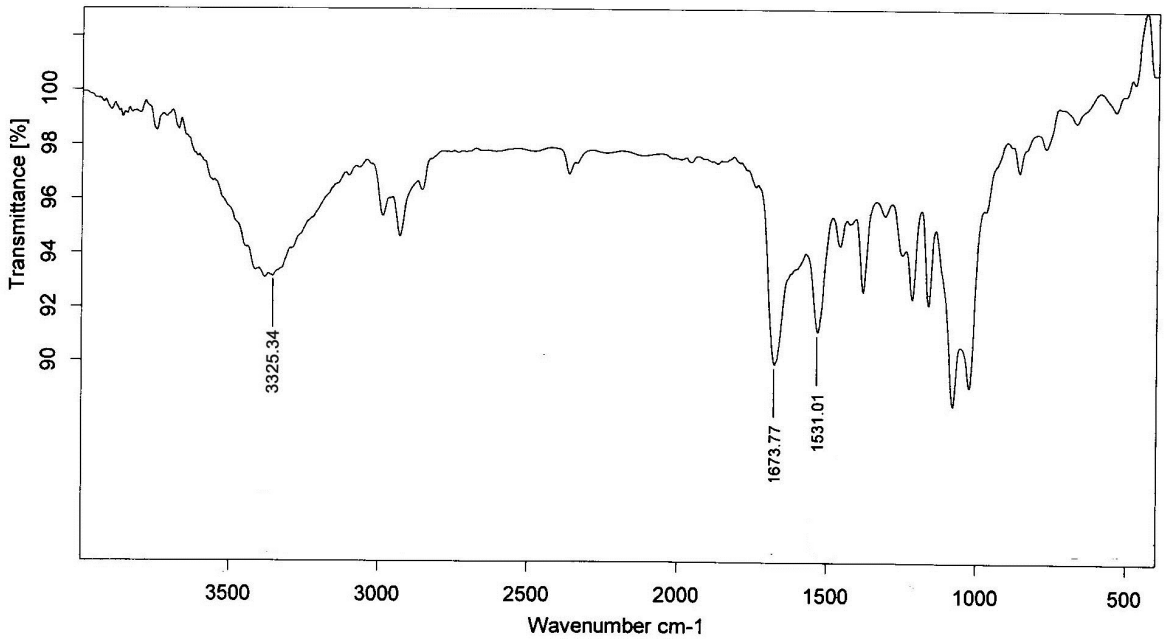


Fig 12: FT-IR spectrum of macrocyclic peptide **1** in $CHCl_3$ (20 mM)

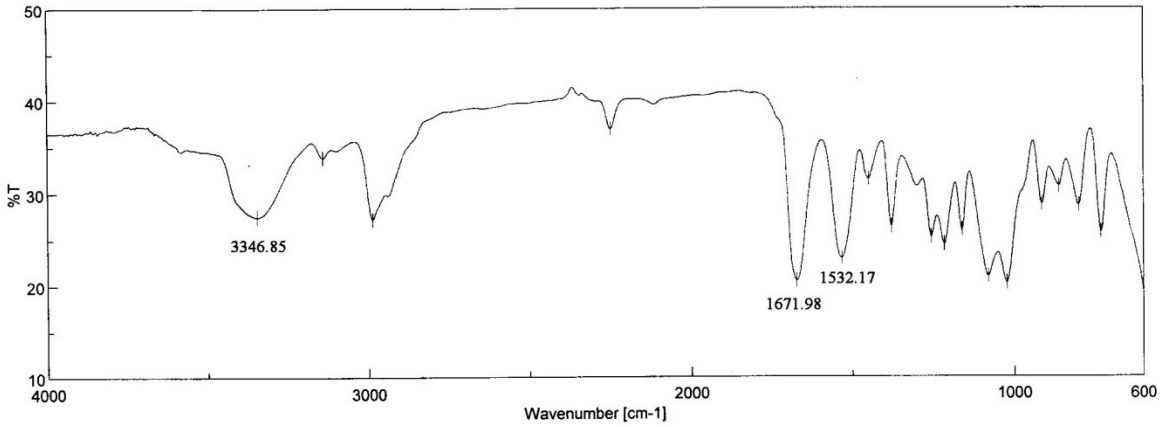


Fig 13: FT-IR Spectrum of macrocyclic peptide **2** in $CDCl_3$ (15 mM)

Molecular Modelling Studies

Construction of molecular model and structural analysis of different obtained conformations were achieved by Discovery studio 4.0. The Discover software was used for molecular modeling calculation and also energy minimization. The energy minimized structure was obtained by using a modified CHARMm force field. Structure refinement was carried out by incorporating NMR derived distance and torsion angle constraints. Energy minimization of each structure was carried out by the steepest descent method followed by conjugate gradient method, until an RMS deviation of 0.001 Kcal was arrived.

(1) B. R. Brooks, R. E. Bruccoleri, B. D. Olafson, D. J. States, S. Swaminathan, M. Karplus, *J. Comput. Chem.* 1983, **4**, 187.

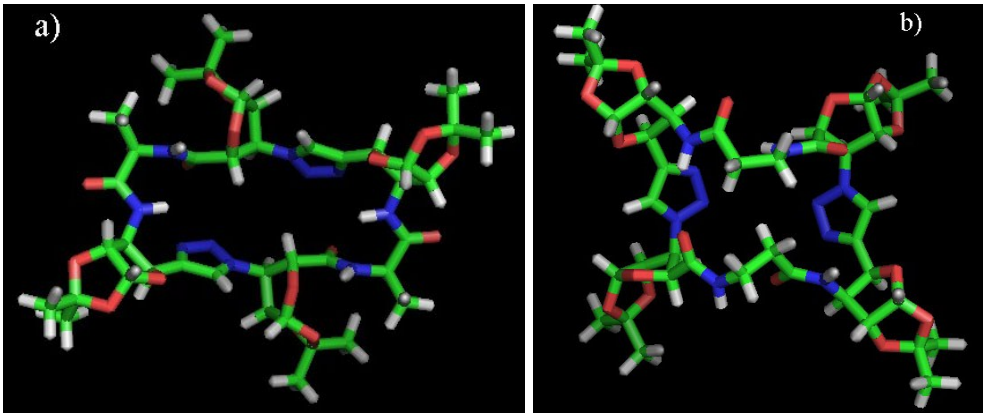


Fig 14: Possible energy minimized structures of a) pseudo cyclic peptide **1** and b) cyclic peptide **2**

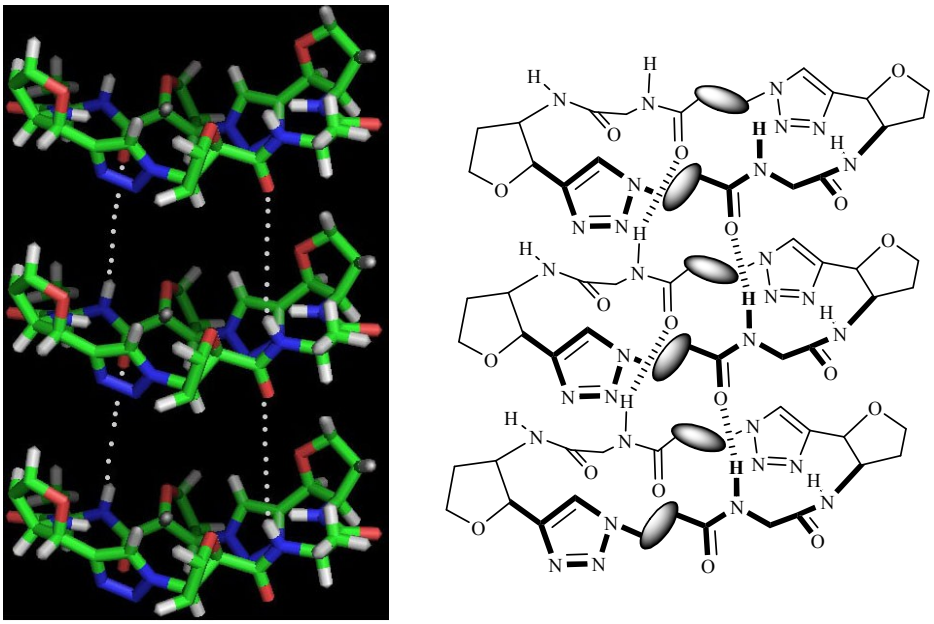


Fig 15: A typical schematic side view for self-assembly of compound **1** by molecular modeling: only S2 of upper two conformations and S1 of lower two conformations are shown, without isopropylidene moiety for the sake of clarity.

Co-ordinates of compound **1**

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HETATM   87  C18 KWH     5      -2.255  -9.825   4.309  1.00  0.00
C
HETATM   88 4H77 KWH     5      -1.785 -10.070   5.262  1.00  0.00
H
HETATM   89 5H77 KWH     5      -3.196 -10.371   4.245  1.00  0.00
H
HETATM   90 6H77 KWH     5      -2.485  -8.760   4.317  1.00  0.00
H
HETATM   91  C1  KWH     6      -2.216  -5.547   1.457  1.00  0.00
C
HETATM   92  N4  KWH     6      -1.948  -4.415   2.130  1.00  0.00
N
HETATM   93  N7  KWH     6      -2.400  -3.244   1.610  1.00  0.00
N
HETATM   94  N10 KWH     6      -3.091  -3.754   0.546  1.00  0.00
N
HETATM   95  C13 KWH     6      -2.934  -5.095   0.337  1.00  0.00
C
HETATM   96  C8  KWH     6      -3.970  -2.874  -0.268  1.00  0.00
C
HETATM   97  H10 KWH     6      -3.297  -5.693  -0.485  1.00  0.00
H
HETATM   98  C11 KWH     6      -3.615  -2.863  -1.763  1.00  0.00
C
HETATM   99  H41 KWH     6      -3.958  -1.870   0.159  1.00  0.00
H
HETATM  100  O14 KWH     6      -4.252  -4.025  -2.269  1.00  0.00
O
HETATM  101  C17 KWH     6      -5.462  -4.267  -1.568  1.00  0.00
C
HETATM  102  C20 KWH     6      -5.373  -3.471  -0.269  1.00  0.00
C
HETATM  103  N22 KWH     6      -4.553  -1.959  -3.781  1.00  0.00
N
HETATM  104  H87 KWH     6      -4.427  -2.916  -4.047  1.00  0.00
H
HETATM  105  C21 KWH     6      -4.180  -1.637  -2.523  1.00  0.00
C
HETATM  106 9H10 KWH     6      -2.537  -2.905  -1.926  1.00  0.00
H
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HETATM  107  O24 KWH     6      -4.287  -0.525  -2.020  1.00  0.00
O
HETATM  108  O22 KWH     6      -6.572  -3.730  -2.249  1.00  0.00
O
HETATM  109 9H24 KWH     6      -5.600  -5.335  -1.398  1.00  0.00
H
HETATM  110  O25 KWH     6      -6.354  -2.473  -0.394  1.00  0.00
O
HETATM  111 3H25 KWH     6      -5.593  -4.079   0.610  1.00  0.00
H
HETATM  112  C28 KWH     6      -7.282  -2.883  -1.372  1.00  0.00
C
HETATM  113  C25 KWH     6      -7.825  -1.664  -2.119  1.00  0.00
C
HETATM  114 3H26 KWH     6      -8.475  -1.964  -2.940  1.00  0.00
H
HETATM  115 4H26 KWH     6      -7.015  -1.068  -2.530  1.00  0.00
H
HETATM  116 5H26 KWH     6      -8.399  -1.021  -1.451  1.00  0.00
H
HETATM  117  C2  KWH     6      -8.406  -3.683  -0.704  1.00  0.00
C
HETATM  118 6H26 KWH     6      -9.122  -4.041  -1.444  1.00  0.00
H
HETATM  119 7H26 KWH     6      -8.945  -3.072   0.019  1.00  0.00
H
HETATM  120 8H26 KWH     6      -8.010  -4.552  -0.178  1.00  0.00
H
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Co-ordinates of compound **2**

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REMARK   Accelrys Discovery Studio PDB file
REMARK   Created:  2014-11-10T15:34:09Z
HETATM    1  N21 KWH     1       0.604  -5.308   1.731  1.00  0.00
N
HETATM    2 6H34 KWH     1       0.704  -5.148   0.746  1.00  0.00
H
HETATM    3  N22 KWH     1      -0.350  -0.680  -1.448  1.00  0.00
N
HETATM    4  N1  KWH     1      -0.710   0.180  -2.438  1.00  0.00
N
HETATM    5  N28 KWH     1       0.539  -1.439  -2.158  1.00  0.00
N
HETATM    6  C24 KWH     1       0.754  -1.048  -3.438  1.00  0.00
C
HETATM    7  C34 KWH     1      -0.084   0.053  -3.619  1.00  0.00
C
HETATM    8  C25 KWH     1       1.209  -2.609  -1.555  1.00  0.00
C
HETATM    9  N18 KWH     1       3.190  -4.121  -0.039  1.00  0.00
N
HETATM   10  C21 KWH     1       3.543  -2.931  -0.556  1.00  0.00
C
HETATM   11  O24 KWH     1       4.419  -2.207  -0.095  1.00  0.00
O
HETATM   12  C22 KWH     1       3.759  -4.599   1.214  1.00  0.00
C
HETATM   13  H57 KWH     1       2.556  -4.644  -0.606  1.00  0.00
H
HETATM   14  C1  KWH     1       2.996  -5.823   1.747  1.00  0.00
C
HETATM   15  H66 KWH     1       4.797  -4.856   0.995  1.00  0.00
H
HETATM   16  H67 KWH     1       3.761  -3.777   1.934  1.00  0.00
H
HETATM   17  C27 KWH     1       1.709  -5.477   2.512  1.00  0.00
C
HETATM   18  H71 KWH     1       2.770  -6.538   0.961  1.00  0.00
H
HETATM   19  H72 KWH     1       3.638  -6.350   2.453  1.00  0.00
H
HETATM   20  O30 KWH     1       1.715  -5.444   3.739  1.00  0.00
O
HETATM   21  C2  KWH     1       2.734  -2.571  -1.809  1.00  0.00
C
HETATM   22  O28 KWH     1       2.998  -3.536  -2.818  1.00  0.00
O
HETATM   23 0H34 KWH     1       3.076  -1.590  -2.138  1.00  0.00
H
HETATM   24  C31 KWH     1       1.820  -4.124  -3.327  1.00  0.00
C
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HETATM   25  C32 KWH     1       0.751  -3.861  -2.289  1.00  0.00
C
HETATM   26 7H35 KWH     1       0.943  -2.661  -0.497  1.00  0.00
H
HETATM   27  H13 KWH     1       1.419  -1.464  -4.181  1.00  0.00
H
HETATM   28  O32 KWH     1       1.944  -5.523  -3.360  1.00  0.00
O
HETATM   29 7H41 KWH     1       1.580  -3.726  -4.313  1.00  0.00
H
HETATM   30  O35 KWH     1       0.807  -5.016  -1.484  1.00  0.00
O
HETATM   31 1H42 KWH     1      -0.243  -3.775  -2.731  1.00  0.00
H
HETATM   32  C38 KWH     1       1.170  -6.088  -2.329  1.00  0.00
C
HETATM   33  C35 KWH     1       2.015  -7.109  -1.572  1.00  0.00
C
HETATM   34 3H43 KWH     1       2.268  -7.953  -2.213  1.00  0.00
H
HETATM   35 4H43 KWH     1       1.488  -7.500  -0.703  1.00  0.00
H
HETATM   36 5H43 KWH     1       2.951  -6.663  -1.241  1.00  0.00
H
HETATM   37  C3  KWH     1      -0.082  -6.718  -2.941  1.00  0.00
C
HETATM   38 6H43 KWH     1       0.180  -7.554  -3.589  1.00  0.00
H
HETATM   39 7H43 KWH     1      -0.622  -5.996  -3.548  1.00  0.00
H
HETATM   40 8H43 KWH     1      -0.759  -7.086  -2.172  1.00  0.00
H
HETATM   41  C1  KWH     3      -0.198   0.879  -4.869  1.00  0.00
C
HETATM   42  C4  KWH     3      -1.567   1.484  -5.167  1.00  0.00
C
HETATM   43  C7  KWH     3      -1.324   1.835  -6.633  1.00  0.00
C
HETATM   44  H9  KWH     3      -2.202   2.025  -7.248  1.00  0.00
H
HETATM   45  C10 KWH     3      -0.473   0.681  -7.144  1.00  0.00
C
HETATM   46  O13 KWH     3       0.023   0.039  -5.984  1.00  0.00
O
HETATM   47  N13 KWH     3      -2.602   0.458  -5.052  1.00  0.00
N
HETATM   48 4H24 KWH     3      -1.837   2.335  -4.541  1.00  0.00
H
HETATM   49 3H25 KWH     3      -2.399  -0.409  -4.592  1.00  0.00
H
HETATM   50  O24 KWH     3       0.585   1.278  -7.847  1.00  0.00
O
HETATM   51 0H86 KWH     3      -1.021  -0.024  -7.770  1.00  0.00
H
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HETATM   52  C27 KWH     3       0.567   2.672  -7.637  1.00  0.00
C
HETATM   53  O30 KWH     3      -0.456   2.938  -6.704  1.00  0.00
O
HETATM   54  C2  KWH     3       0.245   3.379  -8.956  1.00  0.00
C
HETATM   55 9H88 KWH     3       0.208   4.461  -8.826  1.00  0.00
H
HETATM   56 0H89 KWH     3      -0.723   3.051  -9.335  1.00  0.00
H
HETATM   57 1H89 KWH     3       0.997   3.156  -9.713  1.00  0.00
H
HETATM   58  C30 KWH     3       1.913   3.113  -7.061  1.00  0.00
C
HETATM   59 2H89 KWH     3       1.906   4.175  -6.815  1.00  0.00
H
HETATM   60 3H89 KWH     3       2.721   2.937  -7.771  1.00  0.00
H
HETATM   61 4H89 KWH     3       2.145   2.561  -6.152  1.00  0.00
H
HETATM   62  N32 KWH     3      -5.749  -2.103  -4.005  1.00  0.00
N
HETATM   63  C35 KWH     3      -6.070  -2.514  -2.773  1.00  0.00
C
HETATM   64  O38 KWH     3      -6.603  -1.801  -1.932  1.00  0.00
O
HETATM   65 9H55 KWH     3       0.570   1.652  -4.832  1.00  0.00
H
HETATM   66  C28 KWH     3      -5.497  -0.692  -4.257  1.00  0.00
C
HETATM   67  C31 KWH     3      -4.715  -0.563  -5.567  1.00  0.00
C
HETATM   68  H85 KWH     3      -6.457  -0.174  -4.292  1.00  0.00
H
HETATM   69  H86 KWH     3      -4.928  -0.309  -3.405  1.00  0.00
H
HETATM   70  C34 KWH     3      -3.827   0.679  -5.576  1.00  0.00
C
HETATM   71  H90 KWH     3      -4.066  -1.420  -5.725  1.00  0.00
H
HETATM   72  H91 KWH     3      -5.395  -0.520  -6.417  1.00  0.00
H
HETATM   73  O37 KWH     3      -4.211   1.733  -6.060  1.00  0.00
O
HETATM   74  H16 KWH     3      -5.424  -2.826  -4.613  1.00  0.00
H
HETATM   75  C1  KWH     5      -0.660  -5.913   2.175  1.00  0.00
C
HETATM   76  C4  KWH     5      -1.637  -6.177   1.024  1.00  0.00
C
HETATM   77  H9  KWH     5      -1.070  -5.289   2.970  1.00  0.00
H
HETATM   78  O7  KWH     5      -1.034  -7.245   0.334  1.00  0.00
O
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HETATM   79 9H56 KWH     5      -2.591  -6.515   1.433  1.00  0.00
H
HETATM   80  C10 KWH     5      -0.562  -8.164   1.302  1.00  0.00
C
HETATM   81  C13 KWH     5      -0.465  -7.371   2.603  1.00  0.00
C
HETATM   82 0H58 KWH     5       0.435  -7.597   3.174  1.00  0.00
H
HETATM   83  O12 KWH     5      -1.527  -9.159   1.538  1.00  0.00
O
HETATM   84 6H75 KWH     5       0.385  -8.603   0.988  1.00  0.00
H
HETATM   85  C15 KWH     5      -2.052  -9.028   2.842  1.00  0.00
C
HETATM   86  O18 KWH     5      -1.591  -7.789   3.335  1.00  0.00
O
HETATM   87  C2  KWH     5      -1.523 -10.163   3.723  1.00  0.00
C
HETATM   88 1H77 KWH     5      -1.874 -10.057   4.749  1.00  0.00
H
HETATM   89 2H77 KWH     5      -0.434 -10.159   3.739  1.00  0.00
H
HETATM   90 3H77 KWH     5      -1.849 -11.133   3.347  1.00  0.00
H
HETATM   91  C18 KWH     5      -3.580  -9.017   2.780  1.00  0.00
C
HETATM   92 4H77 KWH     5      -4.009  -8.874   3.772  1.00  0.00
H
HETATM   93 5H77 KWH     5      -3.963  -9.952   2.373  1.00  0.00
H
HETATM   94 6H77 KWH     5      -3.935  -8.207   2.145  1.00  0.00
H
HETATM   95  C1  KWH     6      -1.978  -5.058   0.076  1.00  0.00
C
HETATM   96  N4  KWH     6      -1.557  -3.783   0.048  1.00  0.00
N
HETATM   97  N7  KWH     6      -2.076  -2.980  -0.918  1.00  0.00
N
HETATM   98  N10 KWH     6      -2.882  -3.896  -1.537  1.00  0.00
N
HETATM   99  C13 KWH     6      -2.862  -5.143  -1.006  1.00  0.00
C
HETATM  100  H15 KWH     6      -3.404  -6.019  -1.329  1.00  0.00
H
HETATM  101  C8  KWH     6      -3.721  -3.518  -2.694  1.00  0.00
C
HETATM  102  C11 KWH     6      -5.227  -3.741  -2.405  1.00  0.00
C
HETATM  103  O14 KWH     6      -5.657  -4.825  -3.216  1.00  0.00
O
HETATM  104 5H38 KWH     6      -5.416  -3.969  -1.356  1.00  0.00
H
HETATM  105  C17 KWH     6      -3.448  -4.410  -3.901  1.00  0.00
C
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HETATM  106 0H39 KWH     6      -3.485  -2.480  -2.935  1.00  0.00
H
HETATM  107  C20 KWH     6      -4.606  -5.389  -3.970  1.00  0.00
C
HETATM  108  O18 KWH     6      -4.971  -5.441  -5.330  1.00  0.00
O
HETATM  109 9H43 KWH     6      -4.348  -6.378  -3.589  1.00  0.00
H
HETATM  110  O21 KWH     6      -3.552  -3.701  -5.112  1.00  0.00
O
HETATM  111 3H44 KWH     6      -2.485  -4.914  -3.864  1.00  0.00
H
HETATM  112  C24 KWH     6      -4.168  -4.543  -6.060  1.00  0.00
C
HETATM  113  C21 KWH     6      -3.098  -5.323  -6.828  1.00  0.00
C
HETATM  114 3H45 KWH     6      -2.443  -4.648  -7.378  1.00  0.00
H
HETATM  115 4H45 KWH     6      -3.555  -6.005  -7.546  1.00  0.00
H
HETATM  116 5H45 KWH     6      -2.482  -5.915  -6.150  1.00  0.00
H
HETATM  117  C2  KWH     6      -5.049  -3.724  -7.004  1.00  0.00
C
HETATM  118 1H46 KWH     6      -4.465  -2.965  -7.524  1.00  0.00
H
HETATM  119 2H46 KWH     6      -5.854  -3.225  -6.467  1.00  0.00
H
HETATM  120 3H46 KWH     6      -5.514  -4.364  -7.754  1.00  0.00
H
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