Design and Synthesis of Regioisomeric Triazole/Amide Peptidomimetic Macrocycles and Their Dipole Moment Controlled Self-Assembly

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GENERAL EXPERIMENTAL INFORMATION

Solvents were dried over standard drying agents and freshly distilled prior to use. Melting points were determined in open capillaries and were not corrected. Optical rotations were measured in $CHCl_3$ solutions at room temperature using a cell of 1 dm length and λ= 589 nm. IR spectra between 400 and 4000 cm^{-1} were recorded with an FT-IR spectrometer as KBr pellets. Mass spectra were obtained under high resolution (HRMS). ^1H and ^{13}C NMR spectra were recorded in deuterated solvents on Bruker Avance-600 MHz. ^1H NMR multiplicity patterns are designated as singlet (s), doublet (d), triplet (t), 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 **2a** and **2b** were purified by preparative HPLC on Inertsil ODS-3-V, 250×4.6 mm, 5 μm (C-18/AR/25) with Acetonitrile: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 Aldrich or Merck.

TEM Imaging

TEM studies were performed with a JEOL-JEM 2010 electron microscope operating at 200 kV and equipped with a double tilt holder (±45°). Samples for electron microscopy were prepared by putting a drop of the nanotube suspension of **2a** in (4:1) CH_3CN: H_2O and **2b** in (2:3) $CDCl_3$:CCl_4 on two different Cu/carbon coated grids, drying overnight and negative staining with uranyl acetate.

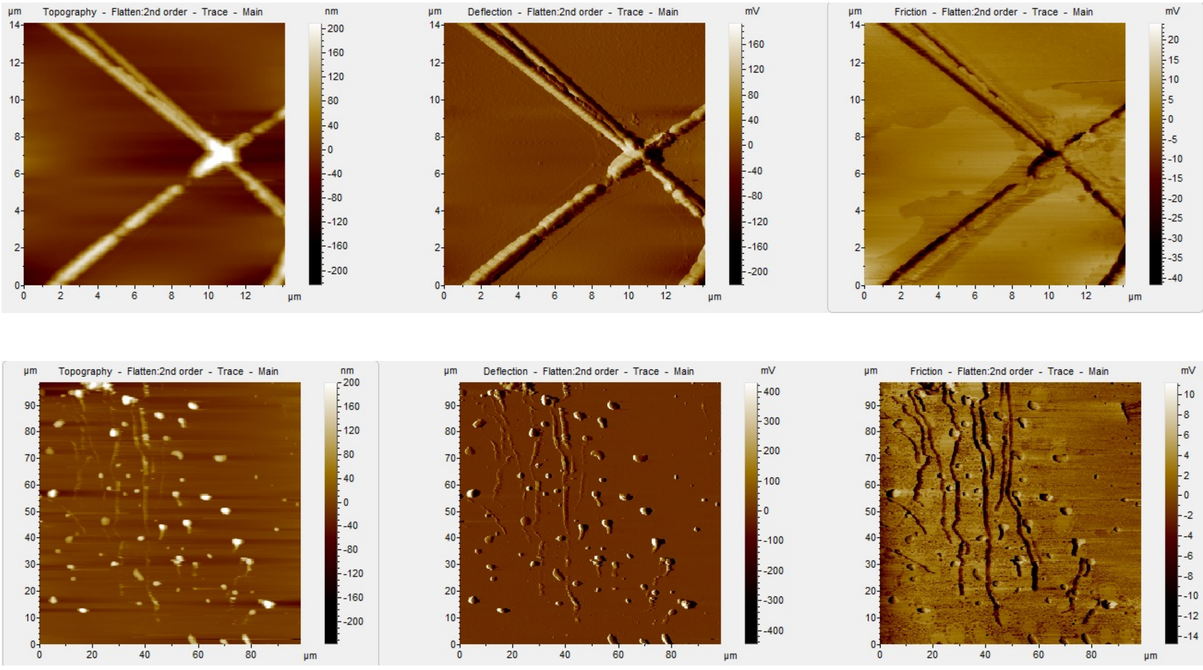
The selected area electron diffraction experiment was performed with the TEM operating in diffraction mode with the smallest selector aperture insertion which implies microcrystallinity of the self-assembled structures.

AFM Sample Preparation and Imaging

Aliquots (10 μL) of the samples **2a** and **2b** were deposited onto freshly cleaved muscovite Ruby mica sheet (ASTM V1 Grade Ruby Mica from MICAFAB) for 15-30 minutes. Mica sheets are basically negatively charged so nano materials bind strongly on the mica surface. After 15 min the sample was dried using 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 the 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 225 μm in length with a nominal spring force constant of 21-98 N/m were used from Nano sensors, USA. Cantilever oscillation frequency was tuned into resonance frequency. The cantilever resonance frequency 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).

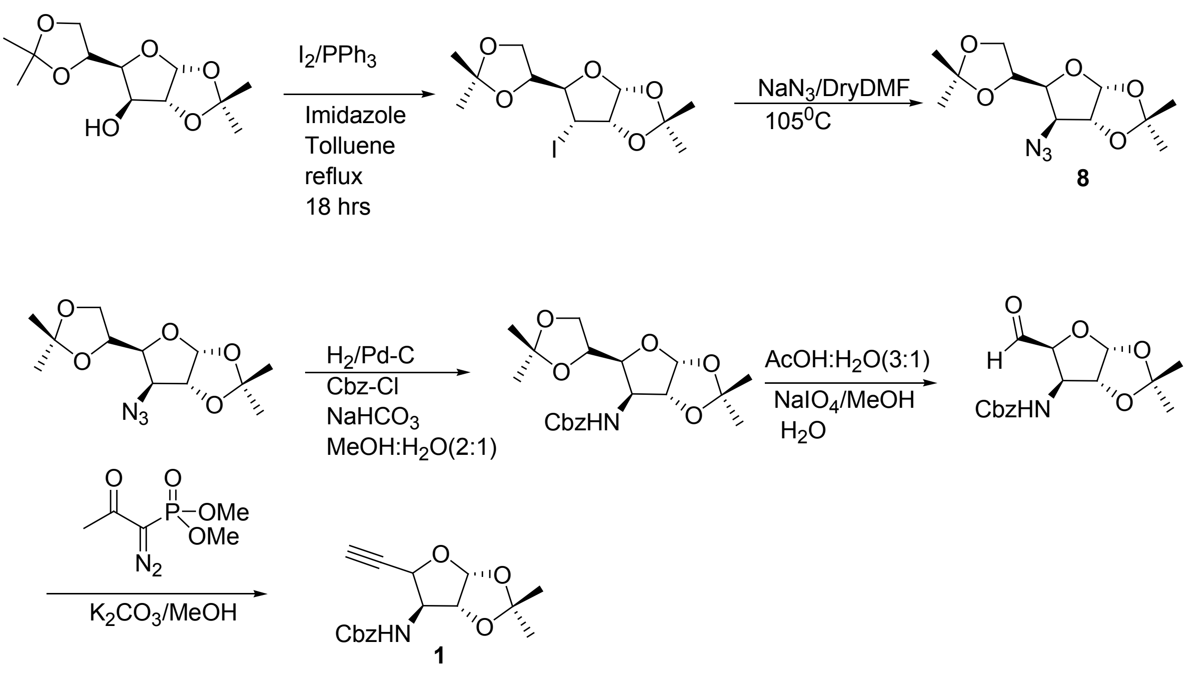


AFM images of **2a** and **2b** in (CH_3CN:H_2O) and (2:3) $CDCl_3$:CCl_4 respectively.

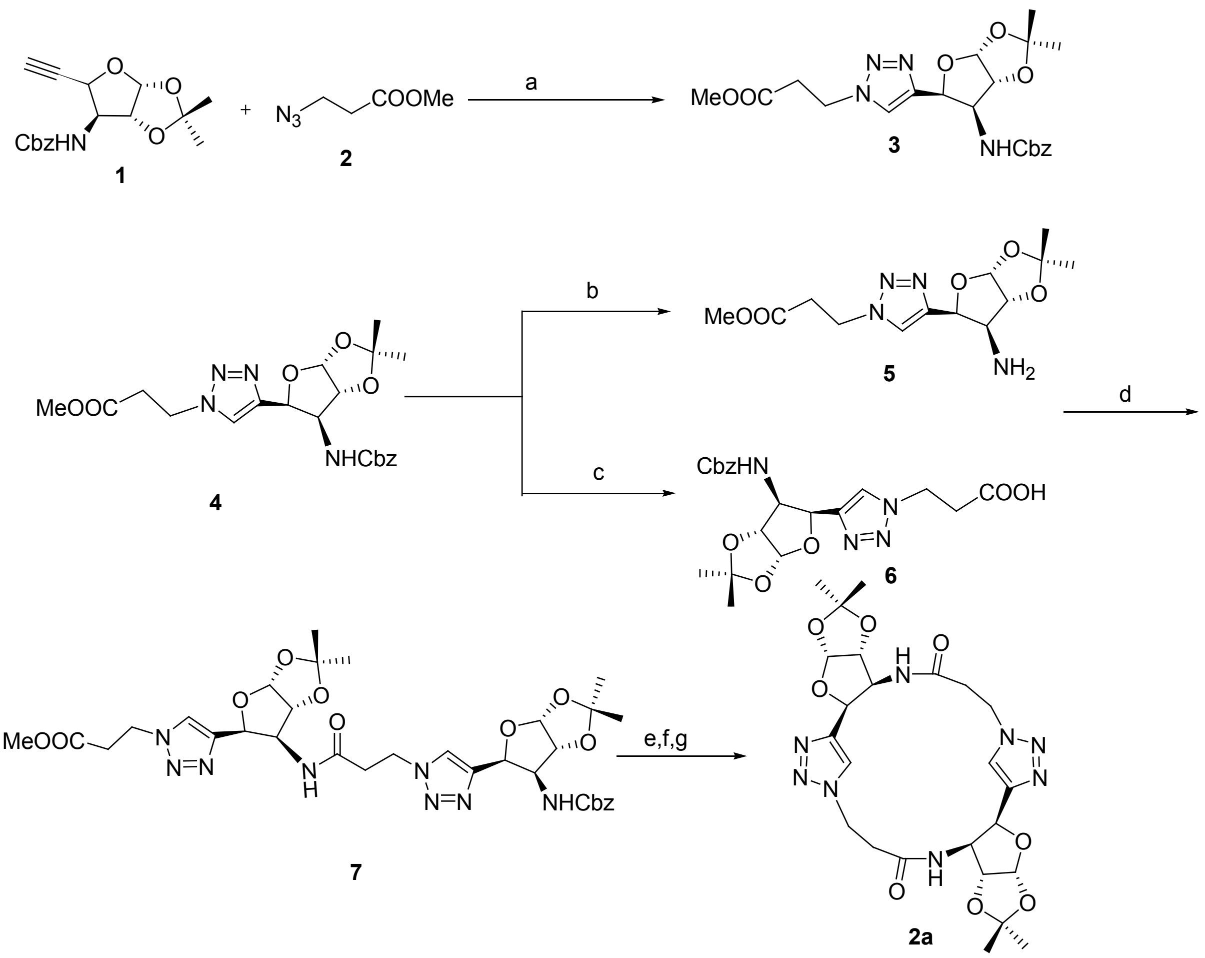
FT-IR Studies:

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

Preparation of compounds 1 and 8 :

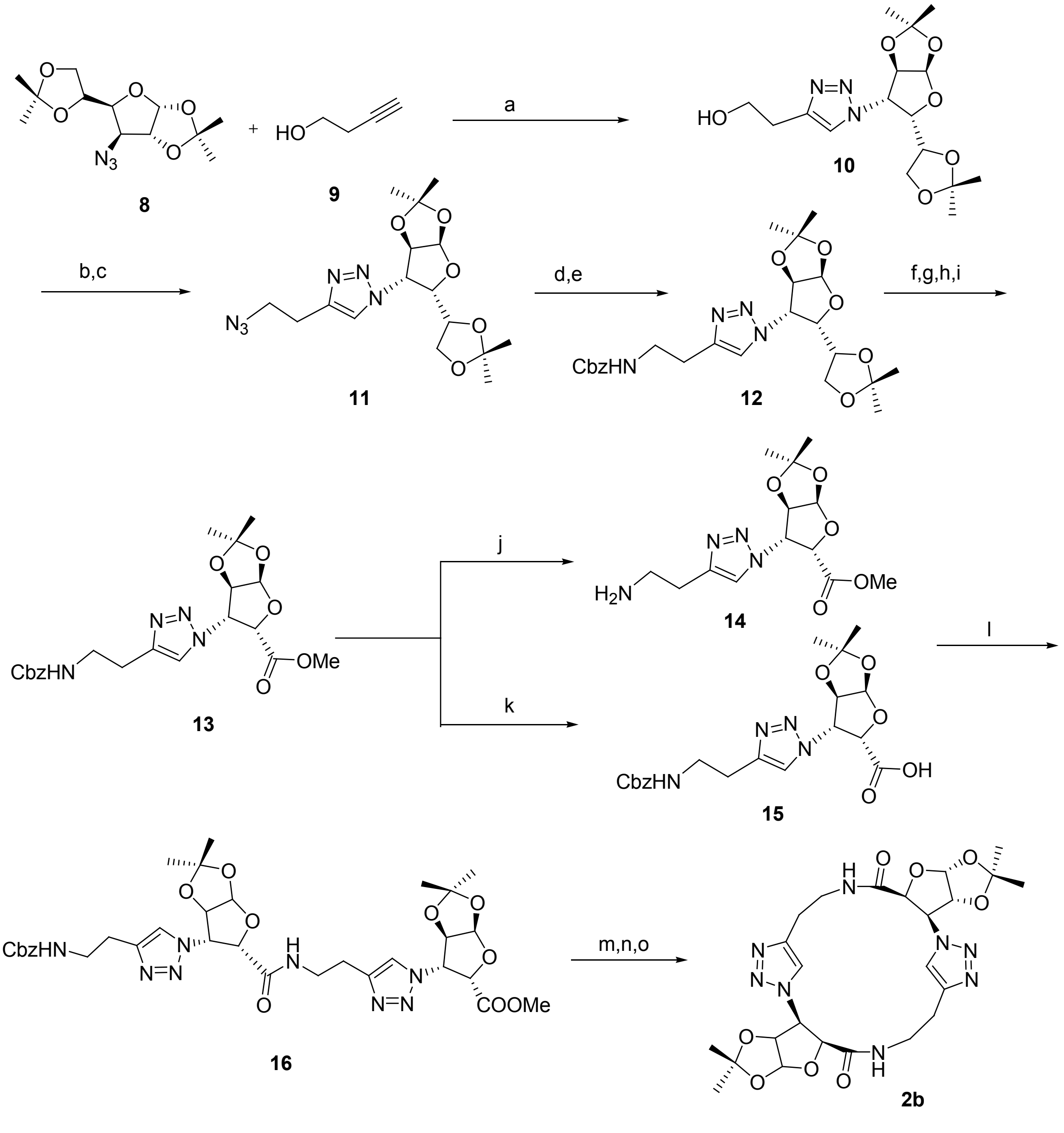


Synthetic Scheme for Peptidomimetic Macrocycle 2a:



Scheme 1. Synthesis of Peptidomimetic Macrocycle **2a**: a) $CuSO_4.5H_2O$, Na-L-Ascorbate, TBTA, ${}^tBuOH:H_2O(2:1)$ b) H_2, Pd-C, MeOH c) $LiOH.H_2O$, $THF:H_2O(3:1)$ d) EDC.HCl, HOBt, DCM e) LiOH, $THF:H_2O(3:1)$ f) EDC.HCl,Pfp-OH
g) H_2/Pd-C

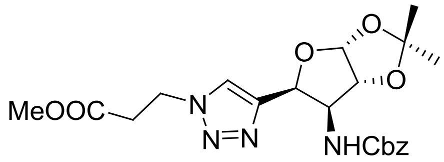
Synthetic Scheme for Peptidomimetic Macrocycle 2b:



Scheme 1. Synthesis of Peptidomimetic Macrocycle **2b:**a) $CuSO_4.5H_2O$, Na-L-Ascorbate, TBTA, ${}^tBuOH:H_2O(2:1)$ b) MsCl, Et_3N, DCM c) NaN_3, DMF d) $SnCl_2$, PhSH,Et_3N, CH_3CN e) CbzCl, $NaHCO_3$,$MeOH:H_2O(2:1)$ f) $AcOH:H_2O(3:1)$ g) $NaIO_4$, $MeOH:H_2O$ h) $NaClO_2$,Na_2HPO_4,H_2O_2(30%),CH_3CN i) MeI, $NaHCO_3$, DMF j) H_2, Pd-C, MeOH k) $LiOH.H_2O$, $THF:H_2O(3:1)$ l) EDC.HCl, HOBt, DCM m) LiOH, $THF:H_2O(3:1)$ n) H_2/Pd-C, EtOAc o) DPPA/Et_3N

Preparation and Characterization of Intermediates for 2a:

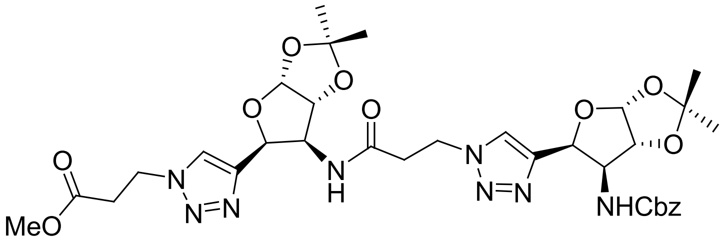
Cbz protected dimer methyl ester (3):



To a mixture of azido methyl ester (245 mg, 1 mmol) and alkyne (475.5 mg, 1.5 mmol) in tert-butanol was slowly added a solution of $CuSO_4.5H_2O$ (373.5 mg, 1.5 mmol) and TBTA (catalytic amount) in 2:1 tert-butanol:H_2O (35 mL). Sodium L-Ascorbate (990 mg, 5 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 Cbz dimer methyl ester (**3**) as Yellow viscous liquid (55%).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.70 (s, 1H), 7.34 (m, 5H), 5.95 (d, J = 3.6 Hz), 5.46 (d, J = 3.6 Hz), 5.04 (m, 3H), 4.82 (broad, 1H), 4.63 (t, J = 6.3 Hz, 2H), 3.68 (s, 3H), 2.94(t, J = 6.3 Hz, 2H) . **^{13}C NMR** ($CDCl_3$,75 MHz, δ): 170.9, 155.9, 136.2, 128.4, 128.1 124.2, 112.0, 104.1, 84.5, 72.4, 66.9, 59.3, 52.2, 45.6, 34.3, 31.7, 29.6, 29.3, 26.5, 26.0, 22.6. **HRMS**: $(M+Na)^+$ for $C_{21}H_{46}N_4O_7Na$ **:** calculated 446.1802, found: 446.1795.

Cbz protected tertramer methyl ester (7):



To a solution of compound **3** (60 mg, 0.107 mmol) in EtOAc:MeOH (1:1), 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 amino ester as colorless semisolid (**4**).

To a stirred solution of compound **4** (60 mg, 0.107 mmol) in 15 mL THF:H_2O (3:1) at 0^0C, 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 **5** as white solid (95 %).

To a stirred solution of compound **5** (50 mg, 0.092 mmol) in dry CH_2Cl_2 were added HOBt (12 mg, 0.092 mmol) and EDC.HCl (18 mg, 0.092 mmol) at 0^0C. After stirring for 1hr at 0^0C the amino ester (40 mg, 0.092 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 (1:2) PE:EA as eluent to afford the corresponding Cbz tetramer methyl ester **6** (67%) as white solid.

To the solution of compound **7** (30 mg, 0.032 mmol) in 25 mL THF:H_2O (3:1) at 0^0C, LiOH.H_2O (3.8 mg , 0.096 mmol) was added and the mixture was stirred for 1hr. After the completion of reaction (TLC) it was acidified by aqueous $NaHSO_4$ and extracted with ethyl acetate (3×25 mL). The combined organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to furnish the corresponding Cbz tetramer acid as white solid (95 %).

To a stirred solution of Cbz tetramer acid (25 mg, 0.026 mmol) in dry CH_2Cl_2 was added EDC.HCl (6 mg, 0.032 mmol) at 0^0C. After stirring at 0^0C for 10 min pentafluorophenol (10 mg, 0.039 mmol) 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 to furnish the Cbz tetramer pentaflourophenyl ester (85 %).

To a solution of compound Cbz tetramer pentaflourophenyl ester (20 mg, 0.018 mmol) in EtOAc, 10% (w/w) Pd-C (5 mg) was added and stirred for 12 hr under 1 atm Hydrogen pressure. After the completion of reaction (TLC) the reaction mixture was filtered through a small pad of celite and washed with MeOH (2×10 mL). The combined filtrate was concentrated under reduced pressure to afford the crude cyclic peptide which was purified by RP-HPLC (C_{18} column/CH_3CN/H_2O).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.71 (s, 2H), 7.33 (s, 5H), 7.17 (d, J = 5.1 Hz,1H), 6.10 (d, J = 4.2 Hz, 1H), 5.95 (d, J = 3.6 Hz, 1H), 5.93 (d, J = 3.6 Hz, 1H), 5.43 (d, J = 3.3 Hz, 1H), 5.39 (d, J = 3.3 Hz, 1H), 5.05 (m, 2H), 4.83(broad, 1H), 4.64 (m, 6H), 4.38 (m, 2H), 4.26 (broad, 1H), 3.69 (s, 3H), 2.95 (t, J = 12.0 Hz, 2H), 2.76 (m, 2H), 1.57 (s, 6H), 1.34 (s, 6H). **^{13}C NMR**

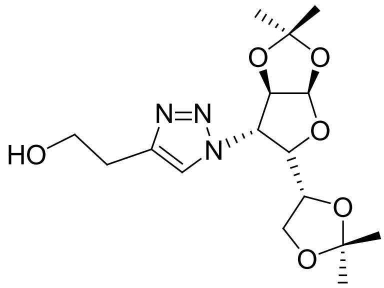
($CDCl_3$,75 MHz, δ): 171.0, 169.5, 156.0, 142.0, 136.2, 128.5, 128.1, 124.6, 124.5, 121.2, 111.9, 104.1, 84.5, 84.1, 72.2, 71.6, 66.8, 59.4, 58.3, 52.2, 45.7, 45.6, 35.9, 34.2, 26.6, 26.5, 26.08, 26.05. **HRMS** $(M+Na)^+$ calculated for $C_{33}H_{42}N_8O_{11}Na$: 726.2973, found: 726.2990.

Pseudo Cyclo-β-Peptide (2a):

^{13}C NMR ($CDCl_3$, 75 MHz, δ)**:** 171.7, 141.6, 126.7, 113.1, 104.9, 85.2, 73.1, 58.1, 46.8, 36.0, 26.6, 26.3, 24.4. **FTIR** (KBr, 298K): 3280 (amide A); 3159, 3098, 2990, 2925, 1672 (amide I); 1569 (amide I_{II}); 1435. **HRMS** $(M+Na)^+$ calculated for $C_{24}H_{32}N_8O_8Na$: 560.2343, observed: 560.2335.

Preparation and Characterization of Intermediates for 2b:

Triazolyl alcohol (10):



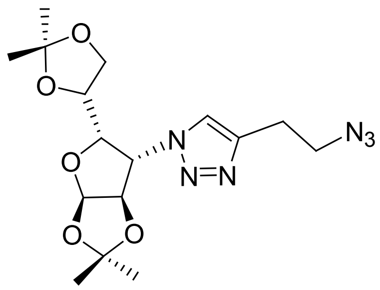
To a mixture of 3-azido (1,2;5,6) di-isopropylidene glucofuranose (500 mg, 1.75 mmol) and 3-butyn-1-ol (0.22 mL, 2.63 mmol) in tert-butanol, was slowly added a solution of $CuSO_4.5H_2O$ (655.2 mg, 2.63 mmol) and TBTA (catalytic amount) in 2:1 tert-butanol:H_2O (35 mL). Sodium L-Ascorbate (1.7 g, 8.75 mmol) was introduced to the reaction mixture; it was stirred for another 16 hr.After the completion of reaction the reaction mixture was quenched with saturated NaCl solution and extracted with DCM (3×25 mL). The combined organic layers were dried over Na_2SO_4 and concentrated.The crude product was purified by (3% MeOH in DCM) to yield triazolyl alcohol (**6**) as a colourless liquid (55%).

^{1}H NMR ($CDCl_3$, 600 MHz, δ): 7.66 (s, 1H), 6.24 (s, 1H), 5.17 (s,1H), 4.34 (dd, J=3.6, 9 Hz, 1H), 3.96 (m, 1H), 3.94 (m, 2H), 3.12 (m, 2H), 2.95 (m, 2H), 1.59 (s, 3H), 1.44 (s, 3H), 1.38 (s, 3H), 1.23 (s,3H).

^{13}C NMR ($CDCl_3$, 150 MHz, δ):112.5, 109.7, 106.3, 83.4, 80.4, 72.3, 67.5, 65.7, 61.6, 28.5, 26.9, 26.7, 26.1, 25.0.

HRMS $(M+Na)^+$ Calculated for $C_{16}H_{25}N_3O_6$: 355.3862, Found 355.3869.

Sugar Triazolyl Azide (11):



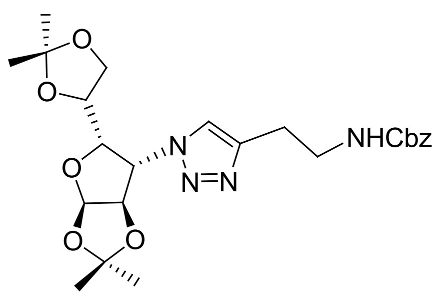
To a stirred solution of alcohol **6** (500 mg, 1.4 mmol) in dry DCM, triethyl amine (0.36 mL, 2.8 mmol) was added at 0^0C. After 15 minutes methane sulphonyl chloride (0.17 mL, 2.1 mmol) was added to the reaction mixture. It was stirred for another 1 hr at 0^0C. After the completion of reaction (TLC control) reaction mixture was poured in to ice-cold water and extracted by DCM (3×20 mL).The combined organic layer was evaporated under vacuum to give the crude mesyl ester which was dissolved in dry DMF. NaN_3 (125 mg, 3.2 mmol) was added to the solution. It was stirred at 70^0C for 2 hr. EtOAc was added to the reaction mixture and it was extracted with water (2×20 mL) followed by brine (1× 20 mL).The organic layer was dried over Na_2SO_4 and evaporated to yield the crude azide compound which was purified by column chromatography (PE:EA, 3:1) as white crystalline solid (80% over two steps).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.62 (s,1H), 6.24 (d, J=3.6 Hz, 1H), 5.21 (d, J=3.6 Hz, 1H), 4.99 (d, J=3.6 Hz, 1H), 4.32 (dd, J=3.6, 9.0 Hz, 1H), 3.94 (m, 2H), 3.81 (m, 2H), 3.27 (m, 1H), 3.22 (m, 2H), 3.12 (m, 2H), 1.59 (s, 3H), 1.45 (s, 3H), 1.38 (s, 3H), 1.23 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ): 143.7, 124.1, 112.4, 109.6, 106.3, 83.3, 80.6, 72.1, 67.5, 65.5, 43.6, 42.8, 29.0, 26.8, 26.7, 26.1, 24.9.

HRMS $(M+Na)^+$ Calculated for $C_{16}H_{24}N_6O_5Na$: 380.1808, Found: 380.1798.

Cbz-Protected Sugar Triazolyl Amine (12):



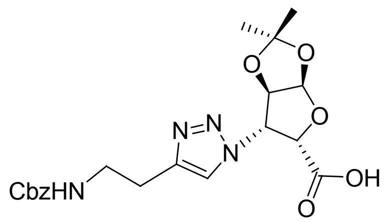
To a solution of triazolyl azide **11** (300 mg, 0.78 mmol) in acetonitrile, triethyl amine (0.35 mL, 1.58 mmol) and $SnCl_2.H_2O$ (166 mg, 1.2 mmol) were added. To this stirred solution PhSH (0.1 mL , 0.5 mmol) was added at room temperature. After the complete consumption of azide (TLC control), aqueous $NaHCO_3$ was added to the mixture and extracted with DCM (5×15 mL). The combined organic extract was dried over Na_2SO_4 and evaporated to give crude amine which was directly dissolved in MeOH:H_2O (2:1). To this solution $NaHCO_3$ (100 mg, 1.2 mmol) was added followed by Cbz-Cl at 0^0C. The stirring was continued for another 2 hr. After the completion of reaction the solvent was removed under reduced pressure and residue was extracted with EtOAc (3×20 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to give crude product which was again purified by column chromatography (PE:EA, 1:2) as white crystalline solid (60% over two steps).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.48 (s, 1H), 7.34 (m, 5H), 6.22 (d, J=3.6 Hz, 1H), 5.27 (broad, 1H), 5.15 (d, J=3.6 Hz, 1H), 5.08 (m, 2H), 4.95 (d, J=3.6 Hz, 1H), 4.32 (dd, J=3.6, 9 Hz, 1H), 3.93 (m, 2H), 3.55 (m, 2H), 3.09 (m, 1H), 2.94 (m, 2H), 1.43 (s, 3H), 1.37 (s, 3H), 1.25 (s, 3H), 1.20 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ): 175.3, 156.4, 144.7, 136.4, 128.5, 128.1, 128.0, 123.6, 112.5, 109.7, 106.3, 83.4, 80.4, 72.3, 67.4, 66.6, 65.5, 40.2, 29.6, 26.9, 26.7, 26.1, 25.8, 24.9.

HRMS $(M+Na)^+$ Calculated for $C_{16}H_{25}N_3O_6Na$: 488.2271, Found 488.2267.

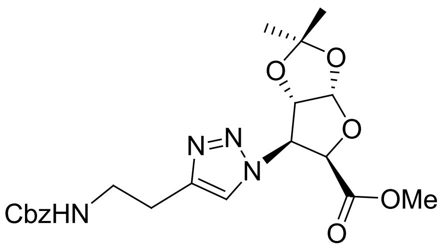
Cbz-Protected sugar Triazole Amino acid:



Compound **3** (300 mg, 0.6 mmol) was dissolved in AcOH:H_2O (3:1 v/v) and the reaction mixture was stirred overnight at RT. After completion of the reaction (TLC) the mixture was evaporated on a rotary evaporator and dried with azeotropic removal of water. The crude diol was dissolved in aqueous MeOH followed by the addition of sodium periodate (160 mg, 0.75 mmol, added portionwise) at 0^0C. After 5 h, the reaction mixture was filtered, evaporated, and the aqueous part was extracted with DCM (3×25 mL). The combined organic layer was dried over Na_2SO_4 and evaporated to furnish the aldehyde (70%) as colourless oil which was used for the next step without further purification.

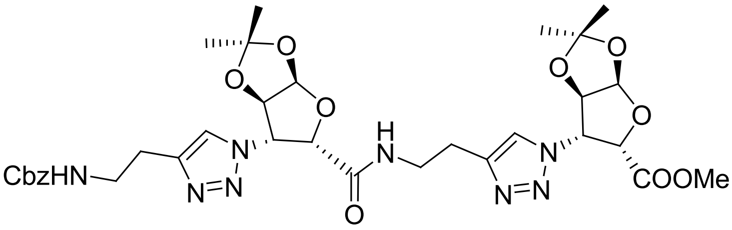
The aldehyde (200 mg, 0.48 mmol) was dissolved in acetonitrile (5 mL) and to this were added solutions of $NaClO_2$ (65 mg, 0.72 mmol) in 9 mL of water and NaH_2PO_4 (112 mg, 0.72 mmol) in 5 mL of water, and 30% H_2O_2 (0.1 mL, 2.4 mmol) at 0^0C. The reaction mixture was stirred overnight at room temperature, the solvent was removed under reduced pressure and the remaining content was basified by adding 5% aqueous solution of $NaHCO_3$. The aqueous phase was extracted with DCM (3×10 mL), and then acidified by $NaHSO_4$.The acidic layer was further extracted with EtOAc (4×15 mL) and dried over Na_2SO_4. Evaporation of solvent under reduced pressure gave the acid as white foam.

CBz-Protected Sugar Triazolyl Methyl Ester (13):



To a solution of acid **4** (100 mg, 0.23 mmol) in dimethyl formamide $NaHCO_3$ (40 mg, 0.46 mmol) and iodomethane (0.03 mL, 0.46 mmol) were added. The reaction was stirred for 4 h. EtOAc was added to the reaction mixture and it was extracted by aqueous $Na_2S_2O_3$ solution (2×15 mL) and brine (1×15 mL). The organic extract was dried over Na_2SO_4 and evaporated under reduced pressure to give the corresponding methyl ester as colourless liquid (90%).

Cbz Protected tetramer methyl ester (16):



To a solution of compound **5** (60 mg, 0.107 mmol) in EtOAc:MeOH (1:1), 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 amino ester as colorless semisolid (**6**).

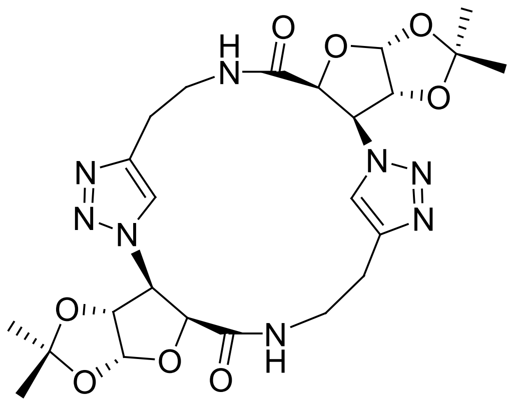
To a stirred solution of compound **4** (50 mg, 0.092 mmol) in dry CH_2Cl_2 were added HOBt (12 mg, 0.092 mmol) and EDC.HCl (18 mg, 0.092 mmol) at 0^0C. After stirring for 1hr at 0^0C, the amino ester **6** (40 mg, 0.092 mmol) was introduced to the reaction mixture and stirred for further 24 hr at room temperature under N_2. It was then subsequently washed with 1(N) HCl (1×25 mL), 5% aq. $NaHCO_3$ (1×25 mL), and saturated NaCl solution (1×20mL), then dried over Na_2SO_4. The organic layer was concentrated to give a yellow solid which was purified by column chromatography using 4% MeOH in DCM as eluent to afford the corresponding Cbz tetramer methyl ester **7** (55%) as white solid.

^{1}H NMR ($CDCl_3$, 600 MHz, δ): 7.44 (s, 1H), 7.34 (m, 5H), 7.32 (s, 1H), 6.53 (broad, 1H), 6.42 (d, J=3.6 Hz, 1H), 6.35 (d, J=3.6 Hz, 1H), 5.38 (m, 2H), 5.29 (d, J=4.2 Hz, 1H), 5.13 (m, 2H), 5.10 (m, 2H), 5.02 (m,1H), 4.96 (d, J=3.6 Hz, 1H), 3.58 (m, 1H), 3.55 (s, 3H), 3.52 (m, 2H), 3.32 (m, 1H), 3.25 (m, 1H), 2.89 (m, 2H), 2.57 (m, 1H), 2.36 (m, 1H) 1.58 (s, 3H), 1.56 (s, 3H), 1.38 (s, 3H), 1.36 (s, 3H).

^{13}C NMR ($CDCl_3$, 150 MHz, δ): 166.9, 166.3, 144.6, 136.5, 128.5, 128.0, 123.6, 121.7, 113.3, 113.1, 106.7, 105.9, 83.4, 83.1, 80.3, 78.2, 66.6, 66.2, 65.6, 52.6, 40.0, 37.7, 30.9, 26.9, 26.7, 26.3, 26.2, 25.7, 25.3.

HRMS $(M+Na)^+$ Calculated for $C_{16}H_{25}N_3O_6$: 726.2973, Found: 726.2968.

Pseudo-cyclo-β-peptide 2b:



To a solution of **16** in THF: H_2O (3:1) $LiOH.H_2O$ was added at 0^0C and stirring was continued for another 1 hr. After the completion of reaction the mixture was acidified by $NaHSO_4$ and extracted by EtOAc (4×10 mL).The combined organic layer was dried over Na_2SO_4 and evaporated under rotary to give the crude tetramer Cbz-protected acid (**17**) as white solid.

To a solution of **17** (30 mg, 0.040 mmol) in EtOAc:MeOH (1:1), 10% (w/w) Pd-C (10 mg) was added and stirred for 2 hr under 1 atmosphere Hydrogen pressure. After the completion of reaction (TLC) the reaction mixture was filtered through a small pad of celite which was then washed with MeOH (2×10 mL). The combined filtrate was concentrated under reduced pressure to afford the corresponding amino acid as colourless solid.

The crude product was dissolved in distilled acetonitrile (5 mL) at 0°C then DIEA (0.6 mmol) and DPPA (0.4 mmol) were added. The mixture was stirred for 48 h at room temperature. After evaporation of solvent under reduced pressure, the crude material was dissolved in ethyl acetate (20 mL) and washed with saturated $NaHCO_3$ solution (2 × 10 mL), saturated NH_4Cl solution (2 × 10 mL) then brine (10 mL). The organic layer was dried over Na_2SO_4 and evaporated under reduced pressure to afford the crude product which was purified by HPLC (C18 column/CH_3CN/H_2O).

^{13}C NMR ($CDCl_3$, 150 MHz, δ): 166.6, 144.9, 121.9, 112.9, 106.6, 82.3, 80.4, 65.7, 38.1, 26.7, 26.2, 24.0. $[\alpha]^{26}_{D}$ = 1.8 (c =1,$CHCl_3$). **HRMS** $(M+Na)^+$ calculated for $C_{24}H_{32}N_8O_8Na$: 560.2343, observed: 560.2352.

Structural Determination by Multidimensional NMR:

NMR Spectra (1D and 2D) of the Pseudo cyclic peptides **2a** and **2b** were recorded by Bruker Avance-600 MHz with TCI CYROPROBE in Acetonitrile-d_3 or (2:3) $CDCl_3$:CCl_4 using tetra methyl silane for $CDCl_3$ 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 1.5s. 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 in the supporting information.

^{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 A^0 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 ^1H-^1H DQF-COSY spectra using the modified Karplus[1] equation. The φ's thus obtained were used as dihedral restraints.

NMR Analysis:

^1H NMR spectra (CD_3CN+2% H_2O) of all entries in Table-1 were assigned from the corresponding double-quantum-filtered 2D DQF-COSY spectrum acquired at the concentration and temperature indicated. Spectra were acquired using Bruker-600MHz spectrometer as indicated for **2a** and **2b** and were referenced to residual $CHCl_3$ solvent peak (7.24 ppm). Signals for S and β-A are shown in the structures of **2a** and **2b**.

Residue name	NH/Tr	H_α	$H_{\alpha'}$	H_β	$H_{\beta'}$	H_γ	H_δ
S	7.76(d) $J_{NH,\beta}$=7.8	5.36(d) $J_{\alpha,\beta}$=3.6		4.22(dd) $J_{\beta,\alpha}$=3.6 $J_{\beta,NH}$=7.8		4.64 (d) $J_{\gamma,\delta}$=4.2	5.94(d) $J_{\delta,\gamma}$=4.2
β-A	7.61(s)	2.77(m)	2.84(m)	4.60(m)	4.40(m)		

Other Methyls: 1.20, 1.47

Table 1: [1]H NMR Chemical Shifts (ppm) (CD_3CN+2%H_2O, 600 MHz, 300K) and coupling constant (Hz) of pseudo-cyclo-β-peptide **2a**

Residue Name	NH/Tr-H	CαH	Cα[1]H	CβH	Cβ[1]H	CγH	CδH
S	7.31(s)	4.99 Jβ,α=3.6		5.12 Jβ,α=3.6		5.38 Jγ,δ=3.6	6.51 Jγ,δ=3.6
β-A	7.60(t) $J_{NH,\beta}$= 6.1 $J_{NH,\beta'}$=5.4	2.64(ddd) Jα,α'= 16 Jα,β'=9 Jα,β = 3	2.41(ddd) Jα,α'= 16 Jα',β=8.9 Jα',β' = 2.8	3.37(m)	3.29(m)		

Other Methyls: 1.60, 1.25; S= Sugar; β-A= β-Alanine

Table 2: [1]H NMR Chemical Shifts (ppm) ($CDCl_3$, 600 MHz, 300K) and coupling constant (Hz) of pseudo-cyclo-β-peptide **2b**

NMR Studies:

NMR Spectra of the Pseudo cyclic peptide were recorded by Bruker 600 MHz in CH_3CN-d_3 or (2:3) $CDCl_3$:CCl_4 (7 mM) using tetramethyl silane as internal standard and chemical shifts are shown in ppm.The dihedral angles (φ) were calculated from the $^{3}J_{HN\text{-}H\beta}$ coupling constants measured from the DQF-Cosy spectra using the modified Karplus equation[1].

Molecular Modeling studies:

Construction of molecular model and structural analysis of different obtained conformations were achieved by Insight-II. The Discover software was used for molecular modelling calculation and also energy minimization. The CVFF MSI version with default parameter was used as a force field throughout the calculation in chloroform (ε =4.8) and in vacuo (ε =1.8) respectively for **2b** and **2a**. Structure refinement was carried out by incorporating NMR derived distance and torsion angle constraints. Energy minimization of each structure was carried out by steepest descent method followed by conjugate gradient method, until an RMS deviation of 0.001 Kcal was arrived.

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

1D spectra of compound 2a:

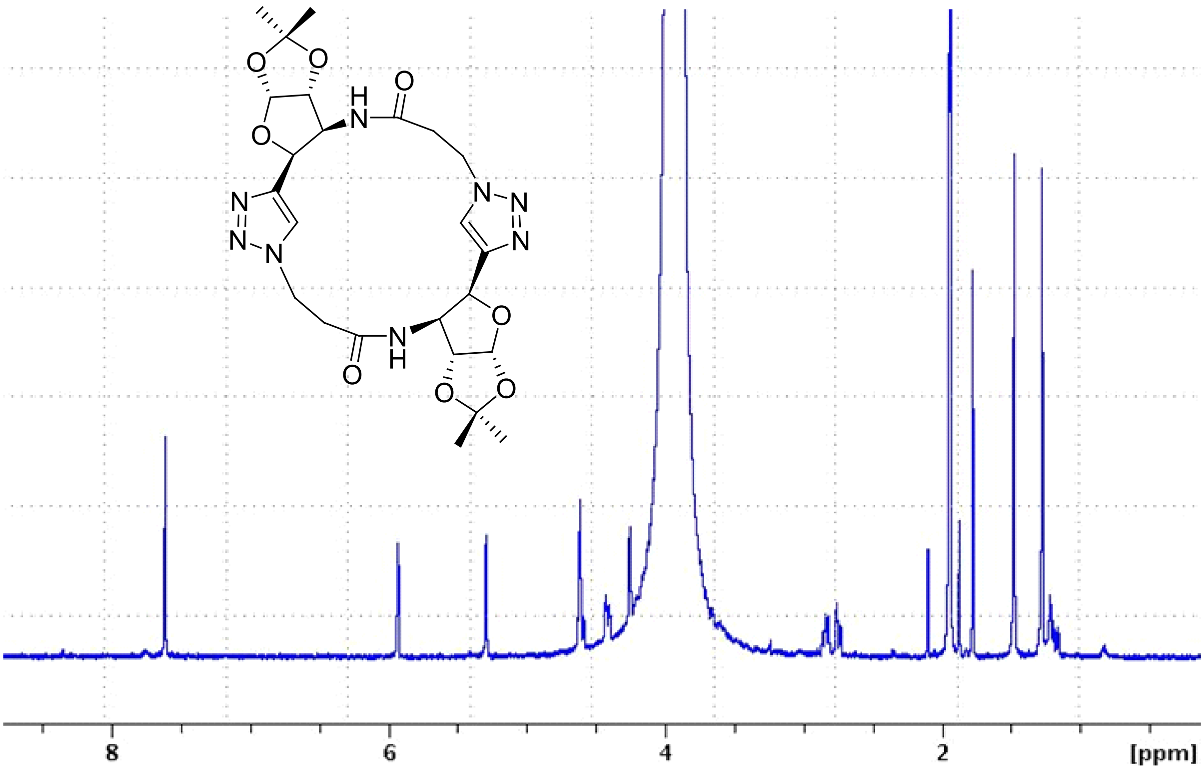


Fig.1 ^1H NMR of compound **2a** (CD_3CN +2%H_2O, 600MHz, 300K)

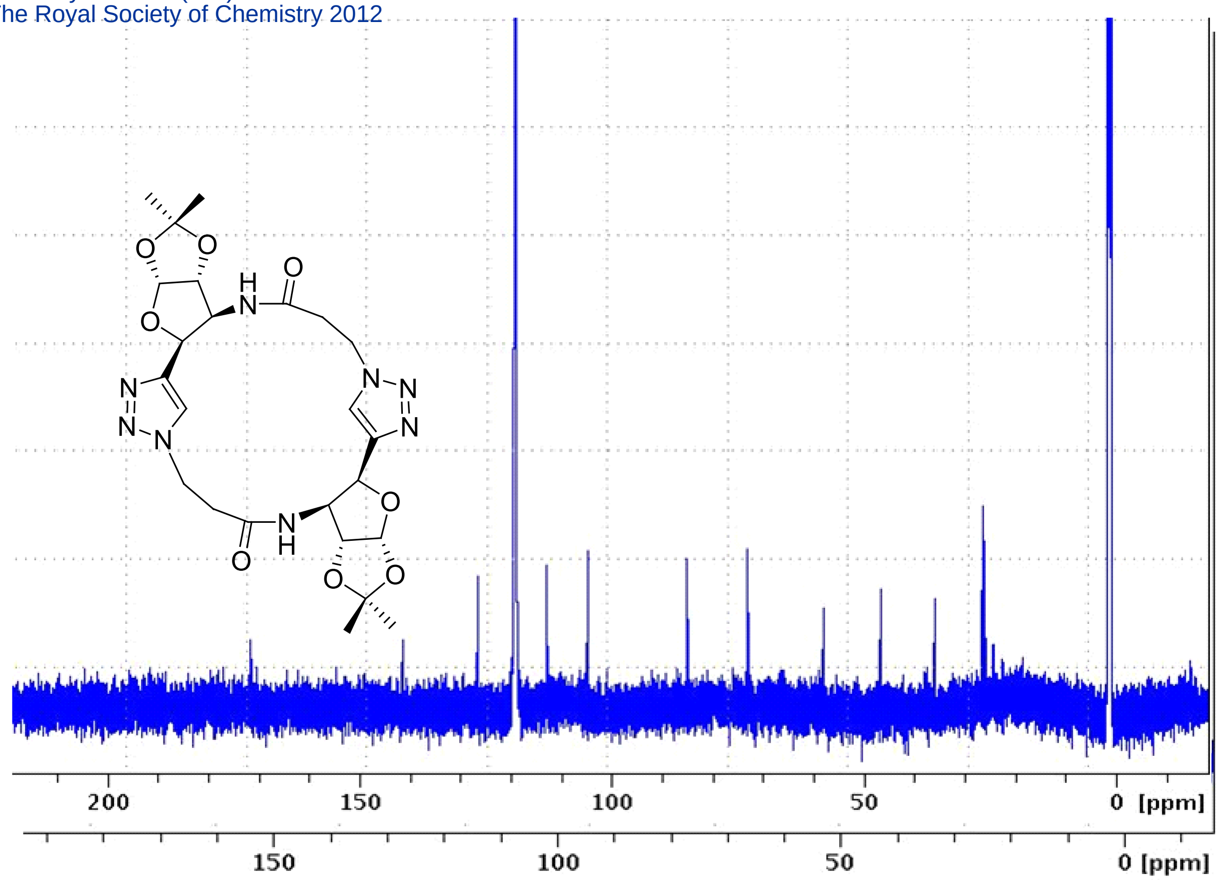


Fig.2 ^{13}CNMR spectrum of compound **2a** in CD_3CN+2%H_2O at 298K in 600 MHz

2D NMR of compound 2a:

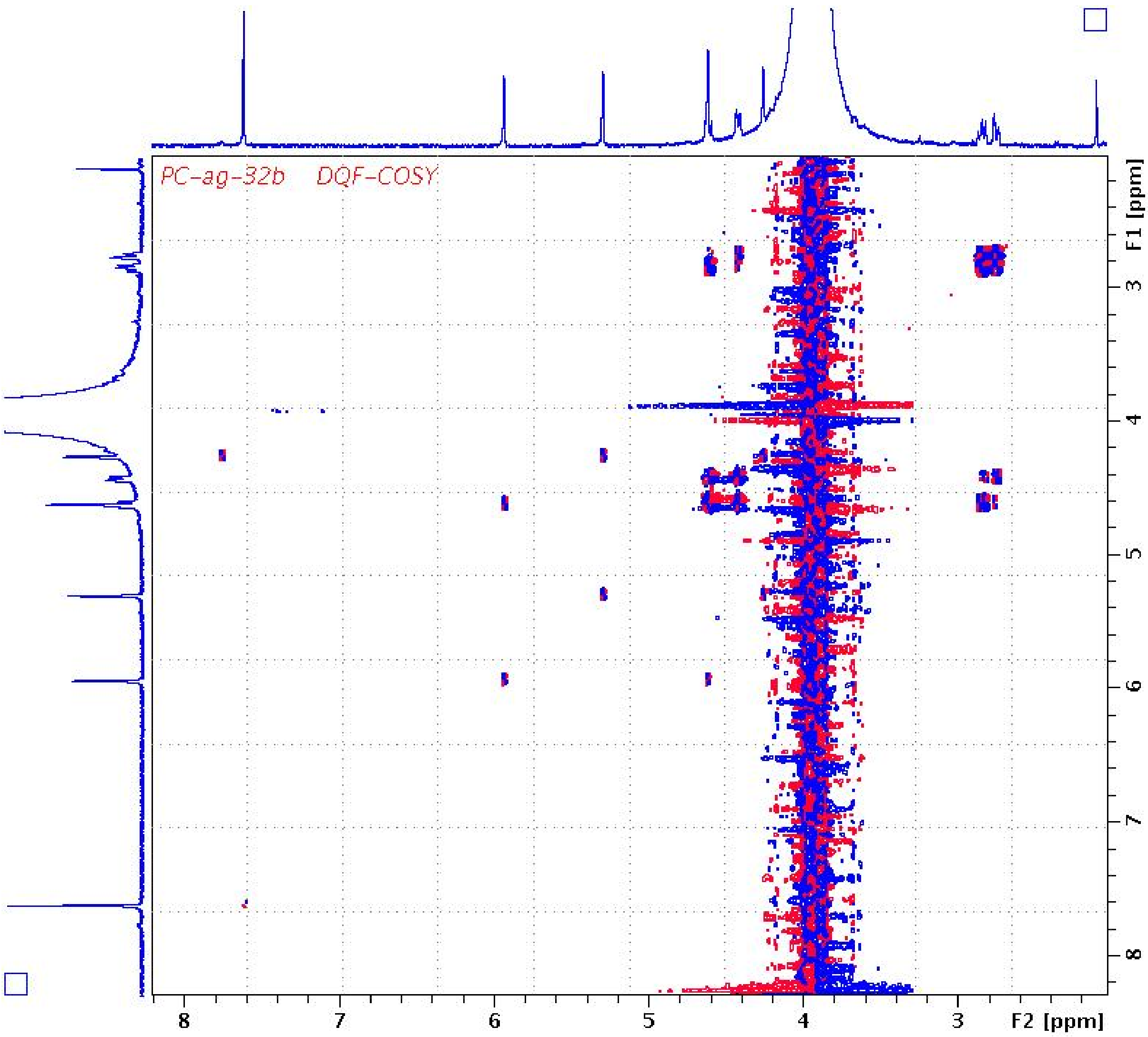


Fig.3 ^{1}H-^{1}H DQF-COSY of **2a** in CD_3CN+2%H_2O at 298K in 600MHz

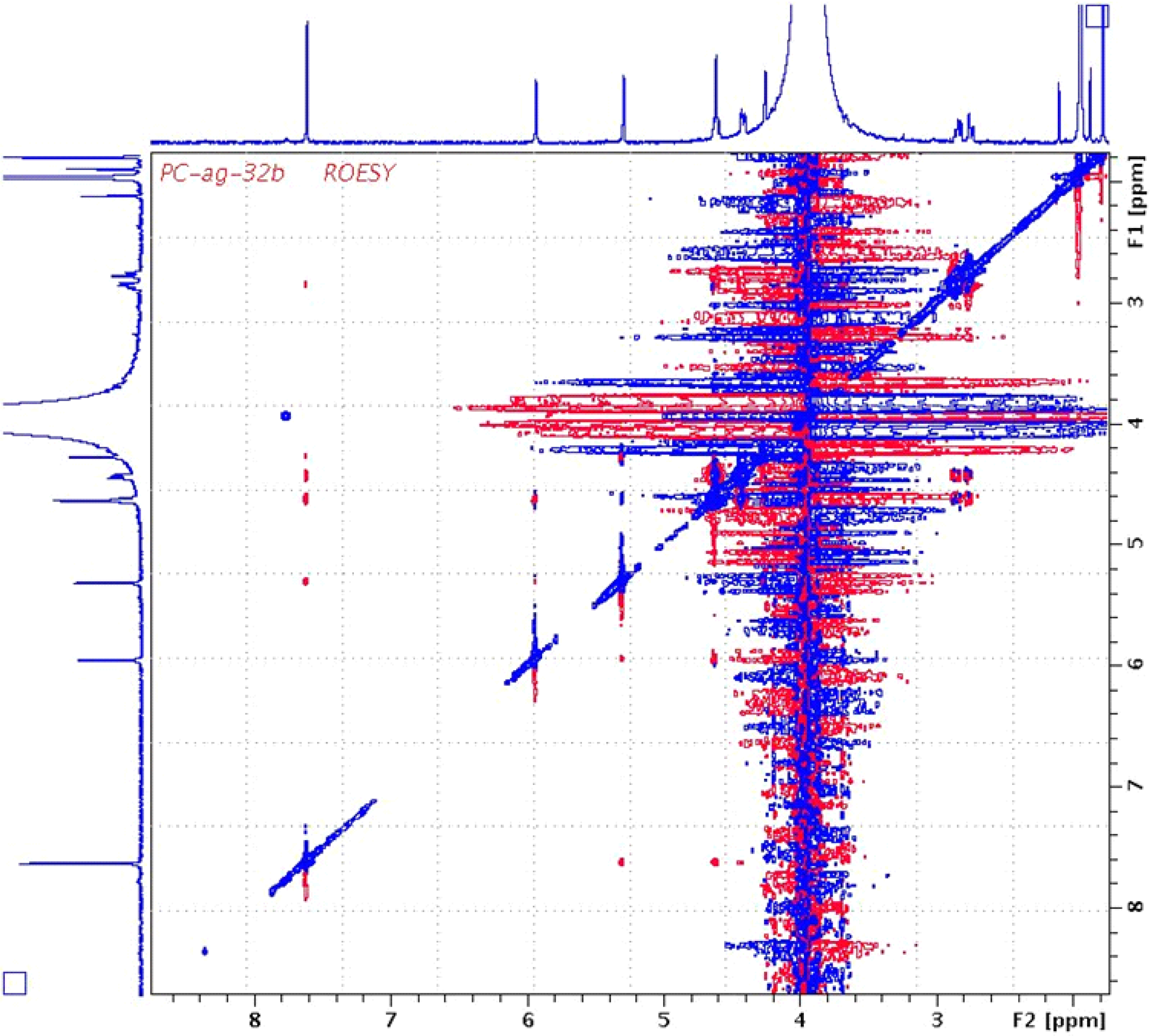


Fig.4. ^{1}H-^{1}H ROESY of compound **2a** in CD_3CN+2%H_2O at 300K in 600MHz

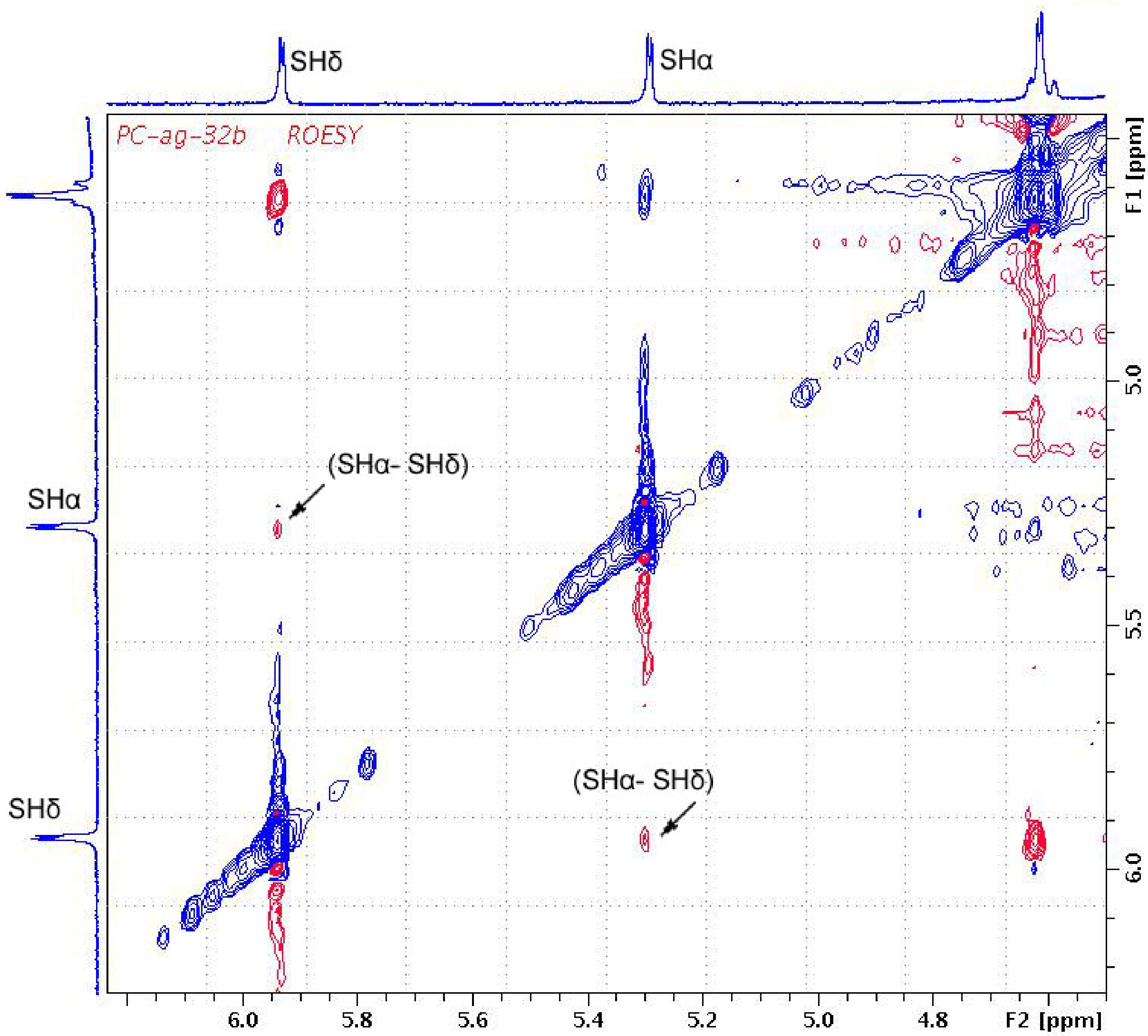


Fig.5 Selected region of ^{1}H-^{1}H ROESY of **2a** in (CD_3CN+2%H_2O) showing Parallel Homostacking between two sugar components as suggested by SH_{α}-SH_{δ} cross peaks.

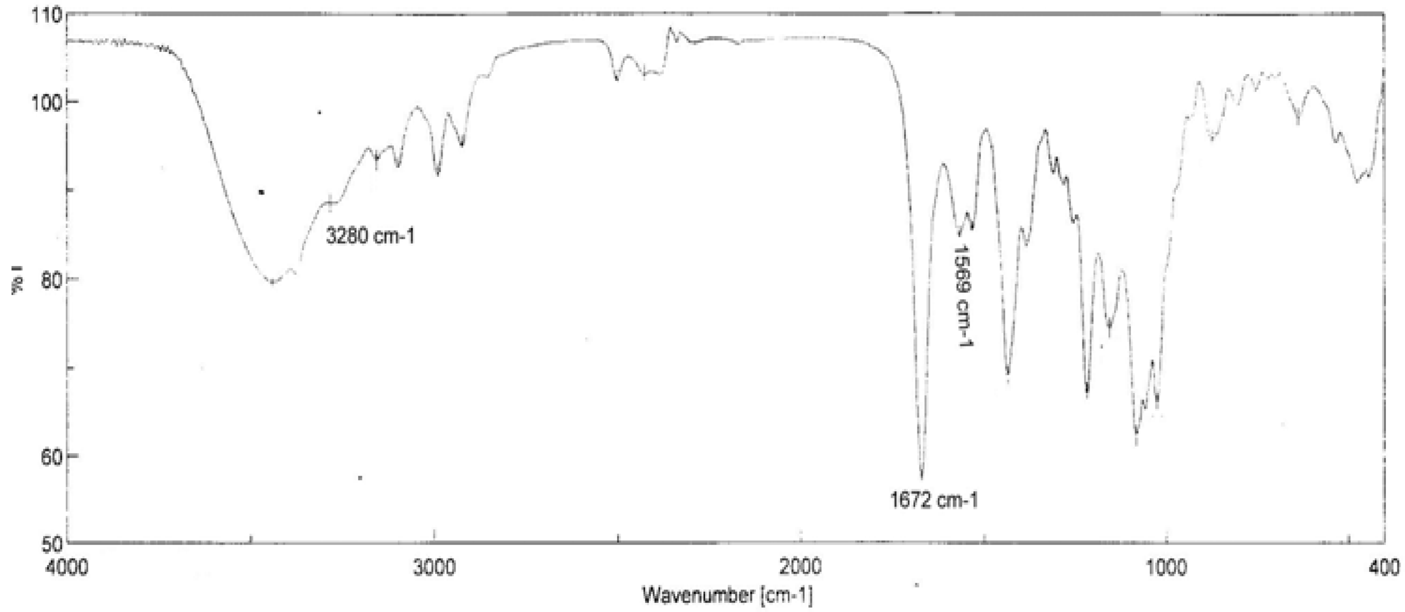


Fig.6: IR Spectrum of compound **2a** in KBr

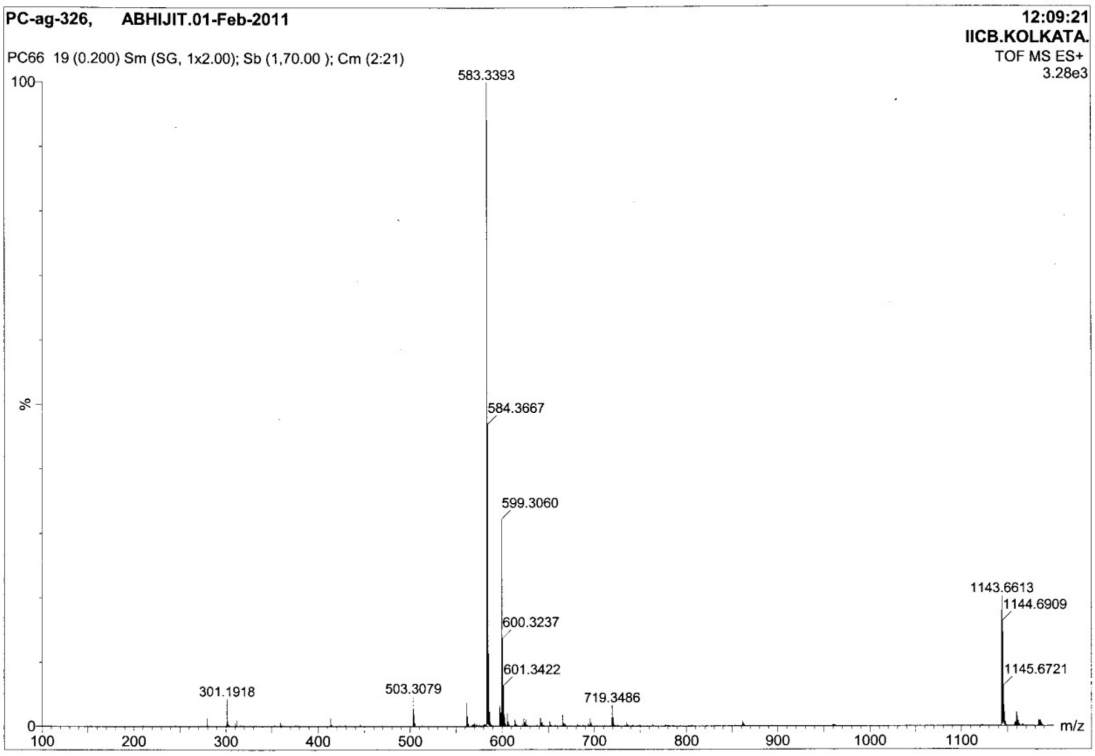


Fig.7: ESI mass Spectrum for compound **2a** in CH_3CN +2% H_2O showing Pseudomolecular monomeric and dimeric species

Electronic Supplementary Material (ESI) for Chemical Communications

1D NMR compound 2b:

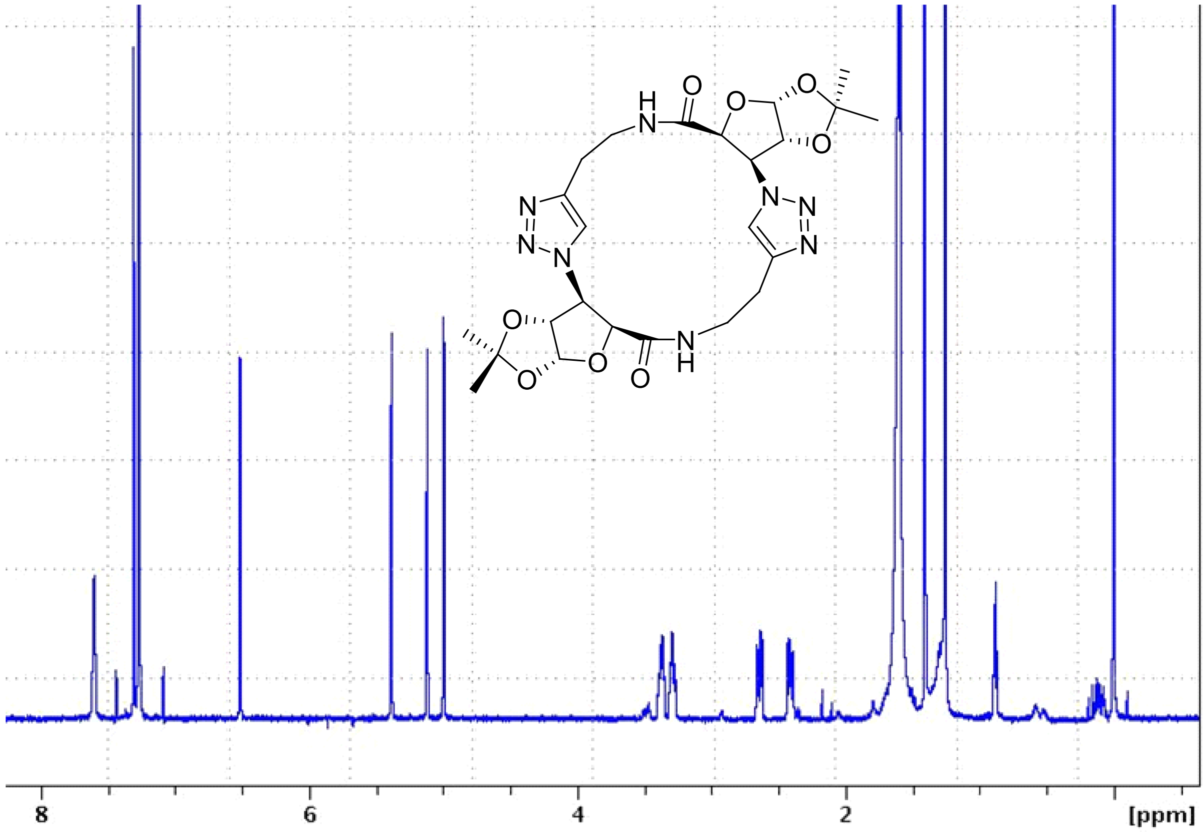


Fig.8: ^{1}H NMR Spectrum of compound **2b** in $CDCl_3$ at 298 in 600 MHz

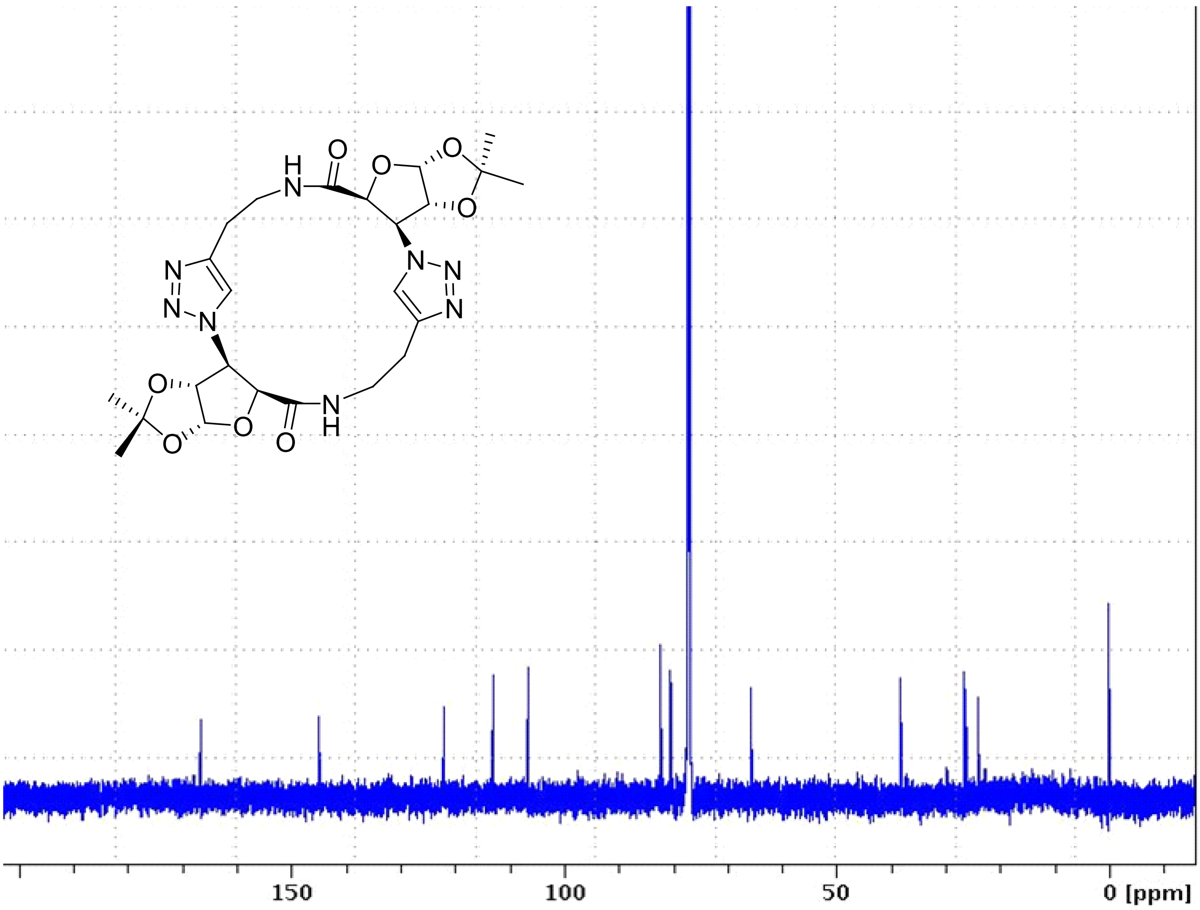
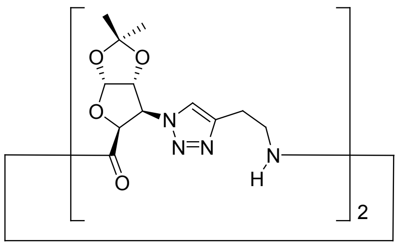


Fig.9: ^{13}C NMR of compound **2b** in $CDCl_3$ at 298K in 600MHz

Electronic Supplementary Material (ESI) for Chemical Communications

Concentration dependent NMR studies:



Compound 2b

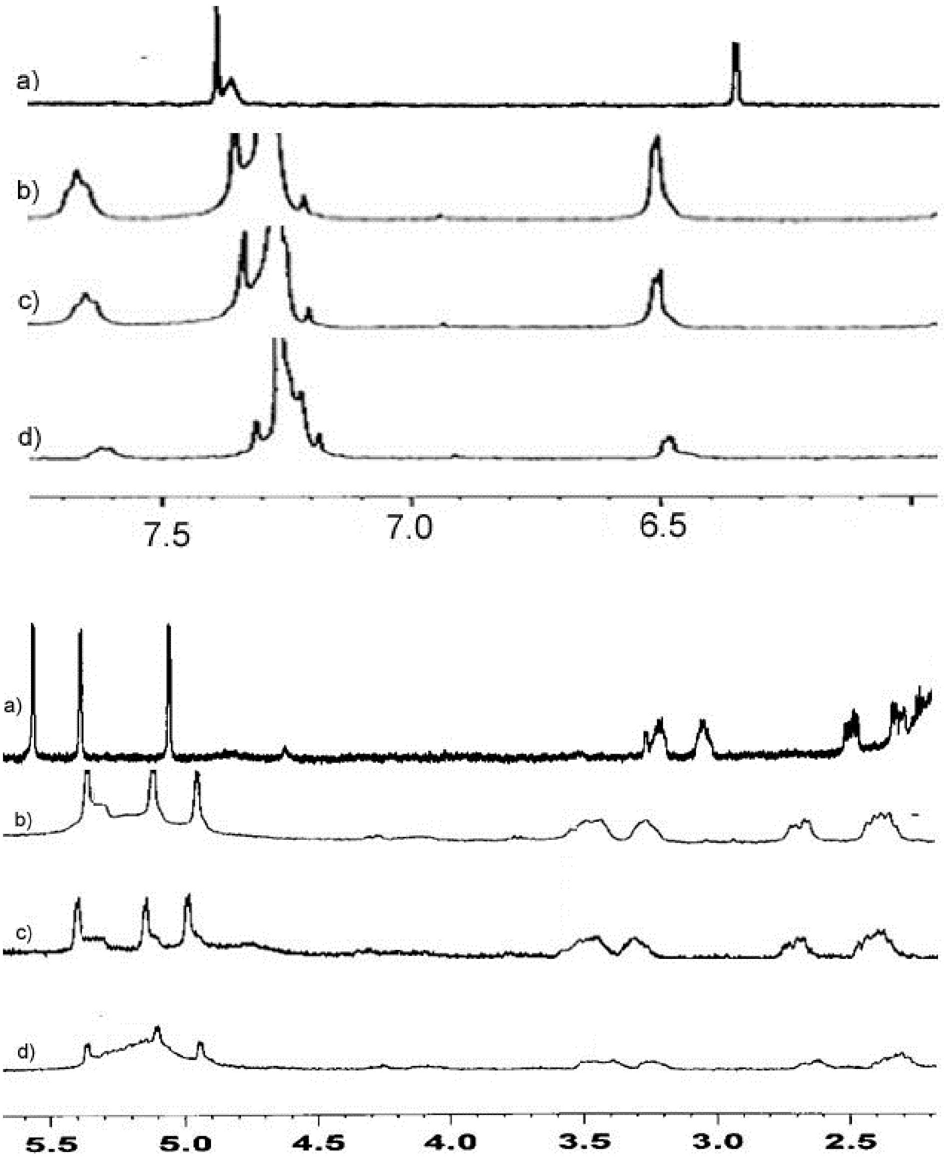


Fig.10: Selected Region of ^{1}H NMR Spectra of **2b**: a) 2 mM in CD_3CN at 298K, b) 2 mM in (2:3) $CDCl_3$:CCl_4, c) 0.5 mM, and d) 0.125 mM in (2:3) $CDCl_3$:CCl_4 at 243K.

FT-IR Studies:

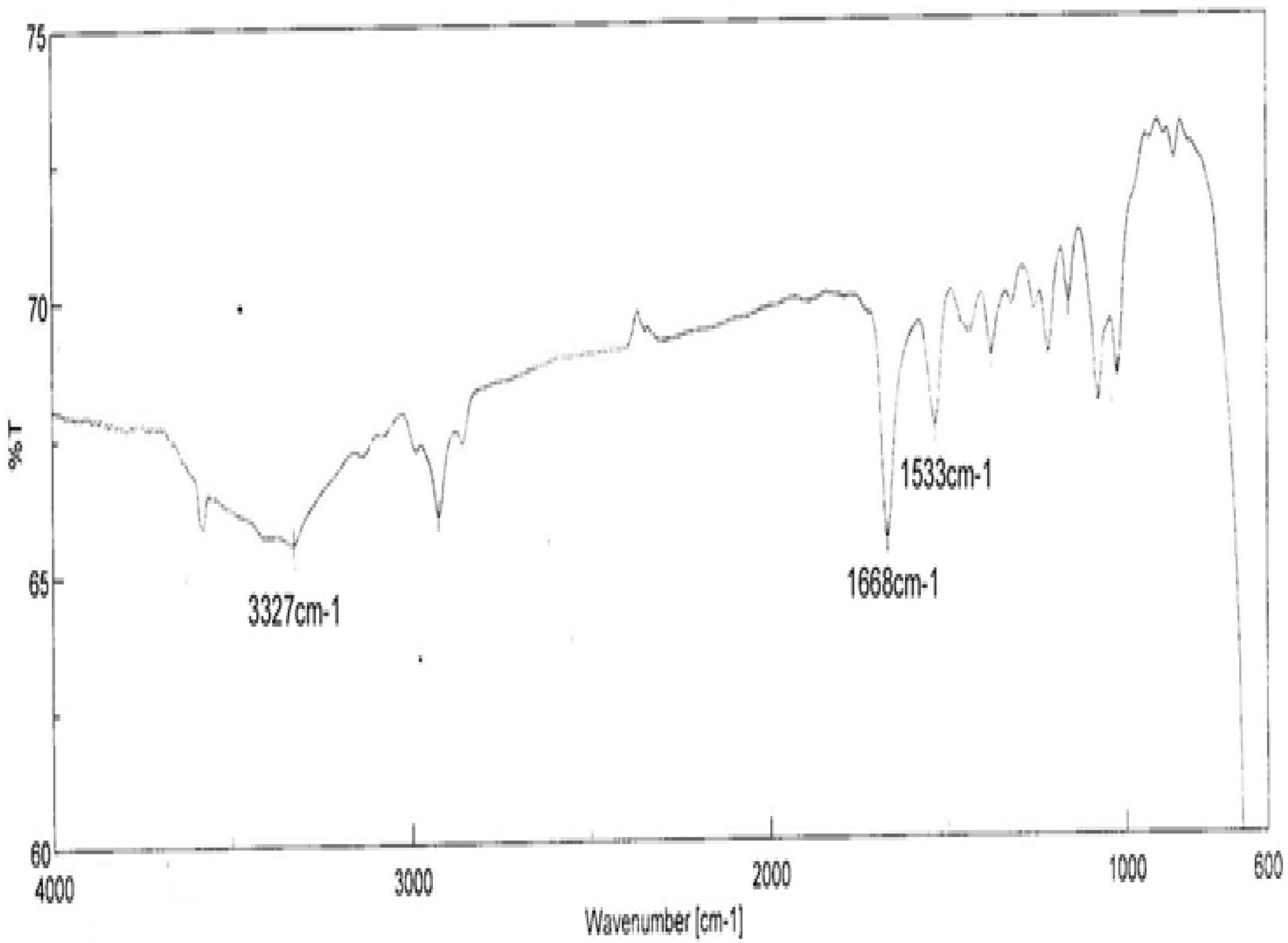


Fig.11: FT-IR Spectrum of 15 mM solution of compound **2b** in $CHCl_3$

2D NMR of compound 2b:

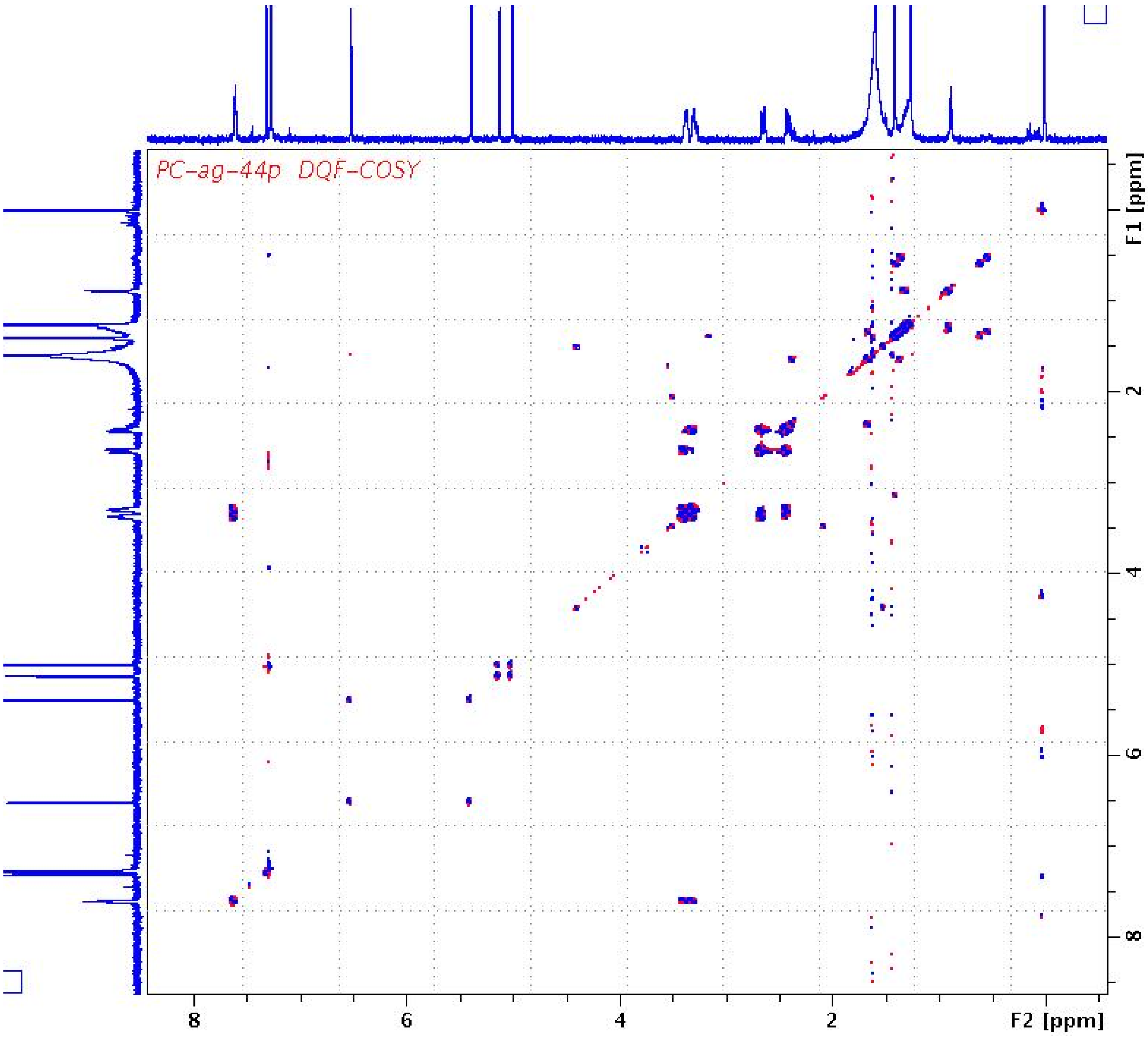


Fig.12. ^{1}H-^{1}H DQF-COSY of **2b** in $CDCl_3$ at 300K in 600MHz

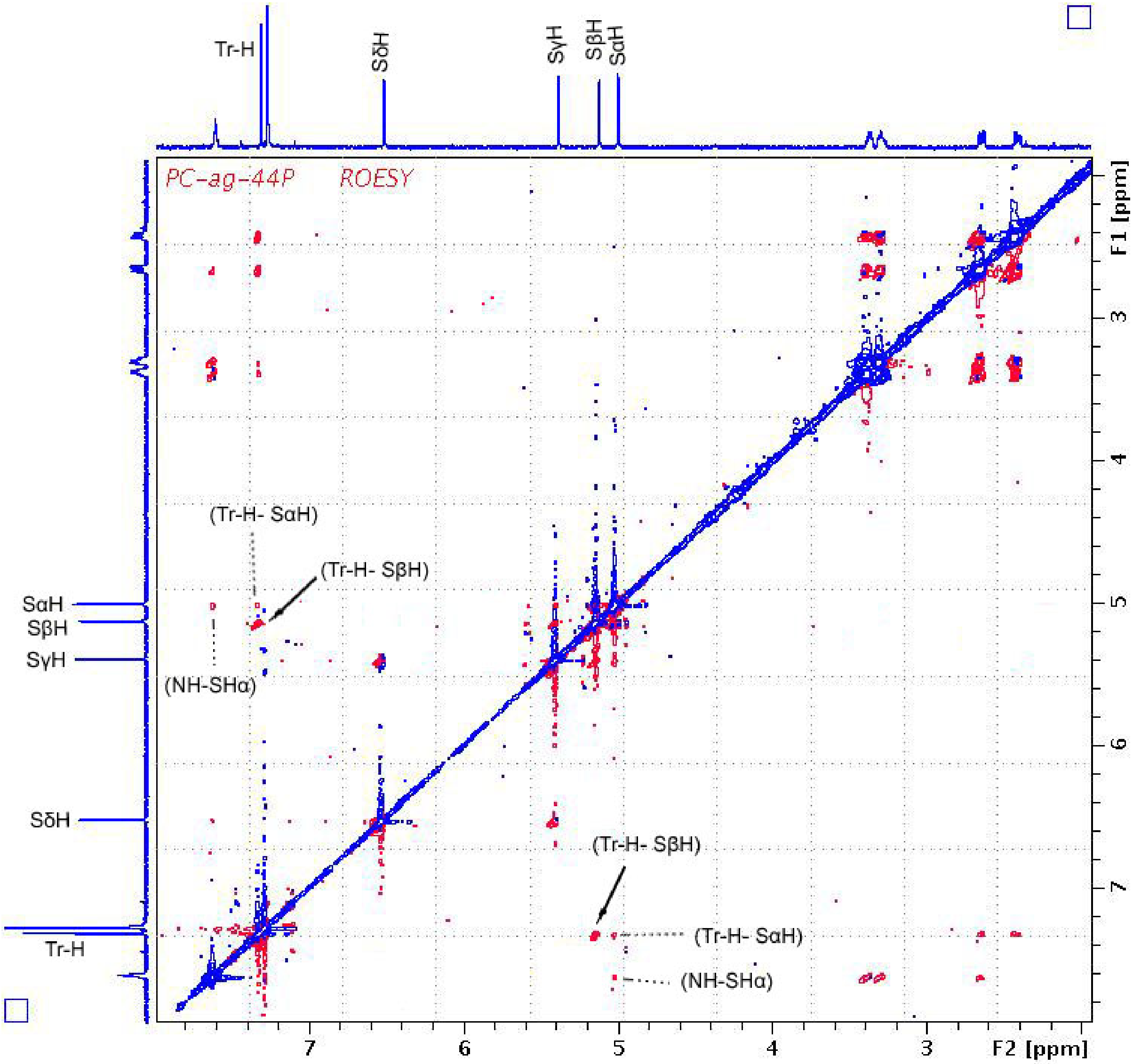


Fig.13: ^{1}H-^{1}H ROESY of **2b** in $CDCl_3$ at 300K in 600MHz

Structure Analysis by NMR spectroscopy:

NMR analysis of compound **2b** at 298K in $CDCl_3$ (600 MHz) indicates the ring conformation which resembles the D-,L,-homologous conformation of triazole/amide functional group. DQF COSY showing the coupling constants around 9 Hz and around 3Hz indicates the presence of gauche conformation in β-alanine moiety. Again the ROESY spectrum showed the cross-peaks between NH and Cα protons as weak whereas the cross-peak between triazole proton and Cβ-proton is very strong.

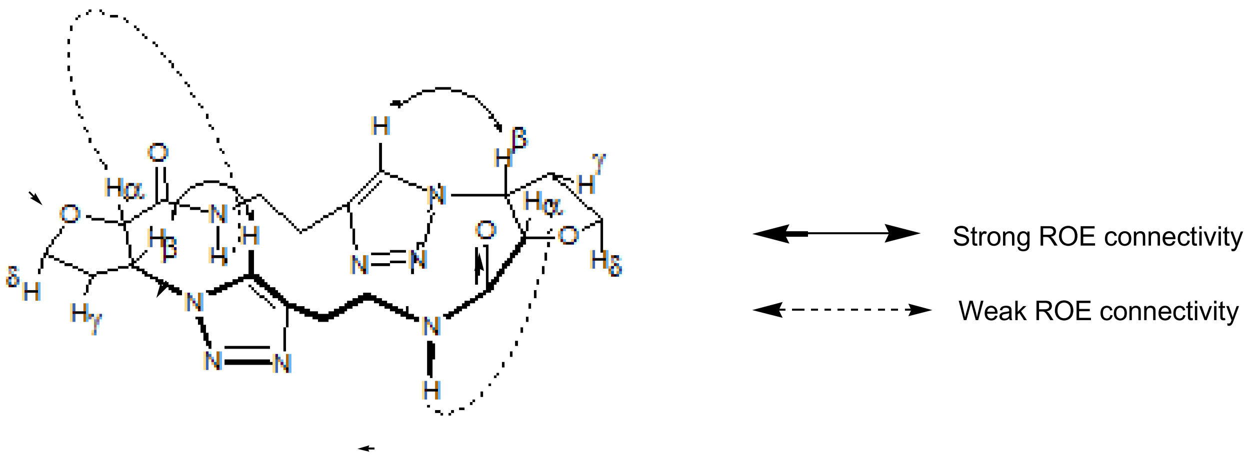


Fig.14. Summary of ROE connectivity observed in compound **2b** in $CDCl_3$ at 300K. The observed coupling constant and these ROE connectivities are used as conformational restraints in Molecular modeling studies in silicon graphics O_2 work station to achieve the minimized structure in chloroform.

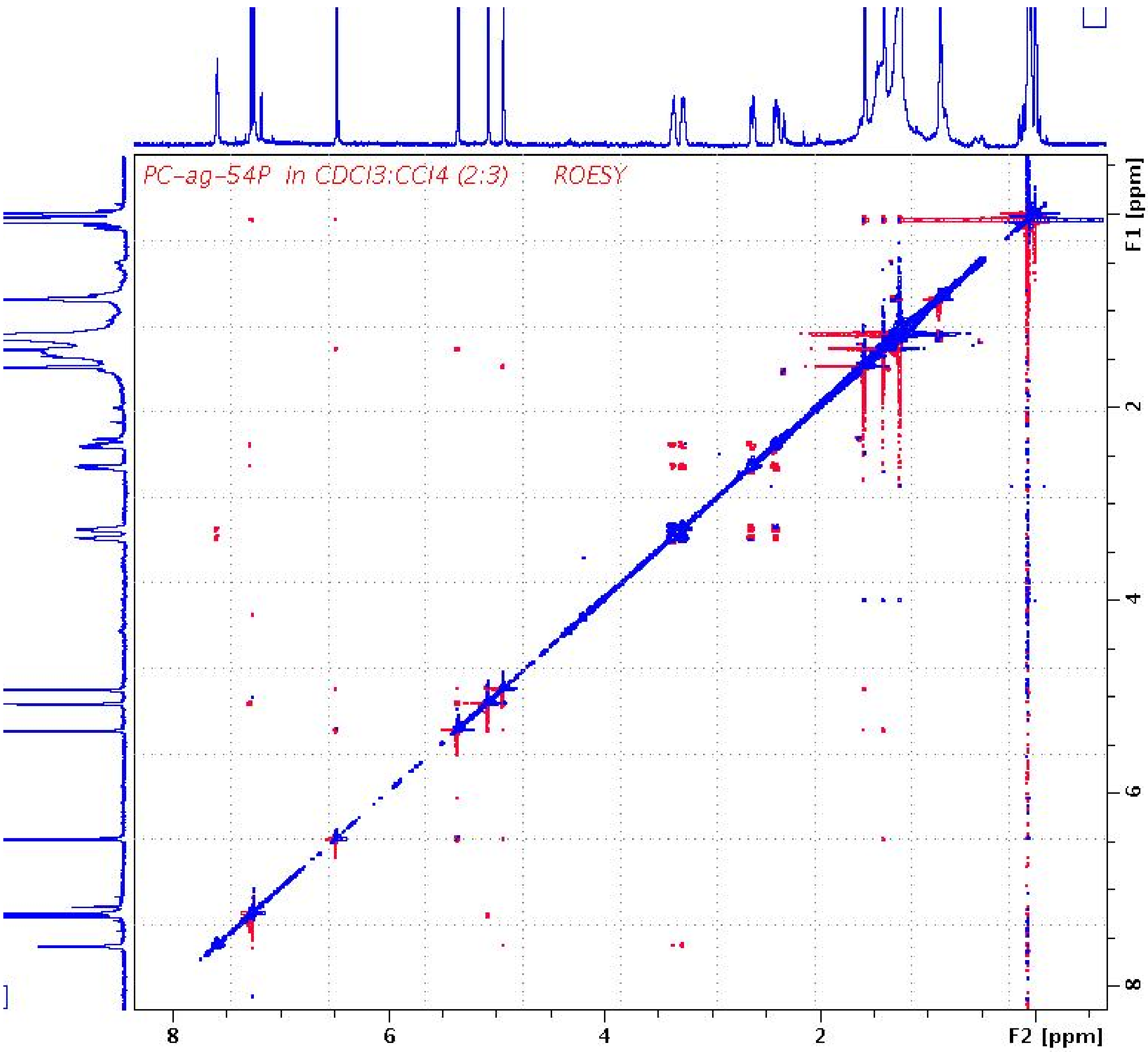


Fig.15: ^1H-^1H ROESY of **2b** in 2:3 ($CDCl_3$:CCl_4) at 300K in 600MHz

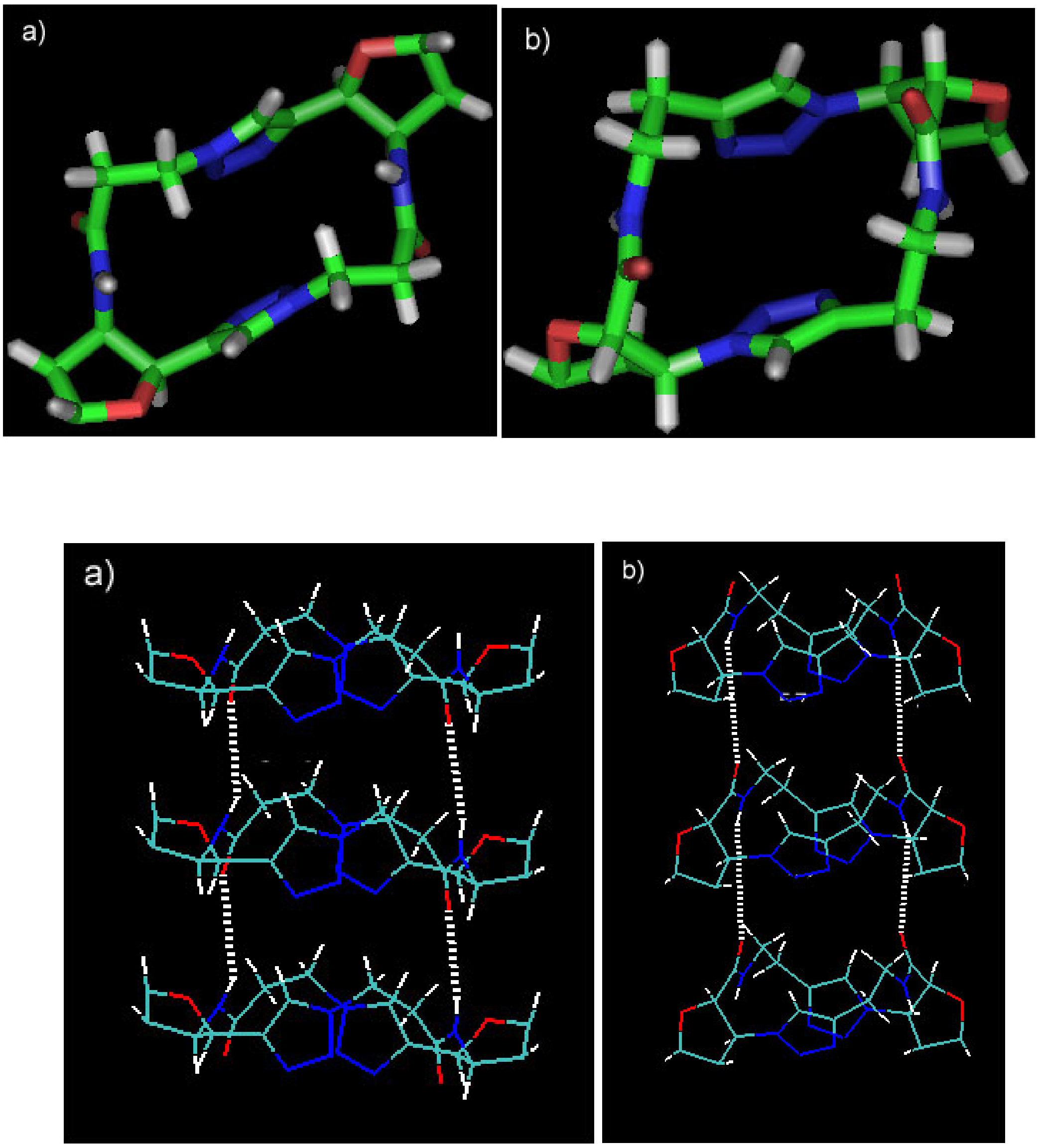


Fig.16: A typical schematic side view for self-assembly of compound a) for **2a** and b) for **2b** by molecular modeling without isopropylidene moiety for the sake of clarity.

Co-ordinates of energy minimized structure of compound 2a:

ATOM	1	O1	CPEN	1	4.532	1.389	-10.214	1.00	0.00	O
ATOM	2	C2	CPEN	1	4.498	0.840	-8.876	1.00	0.00	C
ATOM	3	C3	CPEN	1	5.079	-0.595	-9.000	1.00	0.00	C
ATOM	4	N32	CPEN	1	6.574	-0.651	-8.976	1.00	0.00	N
ATOM	5	C32	CPEN	1	7.249	-1.505	-8.205	1.00	0.00	C
ATOM	6	O32	CPEN	1	6.715	-2.449	-7.626	1.00	0.00	O
ATOM	7	C1	CPEN	1	8.762	-1.271	-8.077	1.00	0.00	C
ATOM	8	C4	CPEN	1	9.240	0.099	-7.509	1.00	0.00	C
ATOM	9	C13	CPEN	1	4.427	0.307	-11.162	1.00	0.00	C
ATOM	10	C33	CPEN	1	4.550	-1.001	-10.387	1.00	0.00	C
ATOM	11	H2	CPEN	1	3.430	0.737	-8.598	1.00	0.00	H
ATOM	12	H3	CPEN	1	4.634	-1.245	-8.217	1.00	0.00	H
ATOM	13	H32	CPEN	1	7.156	0.124	-9.302	1.00	0.00	H
ATOM	14	1H1	CPEN	1	9.207	-1.431	-9.075	1.00	0.00	H
ATOM	15	2H1	CPEN	1	9.181	-2.086	-7.457	1.00	0.00	H
ATOM	16	1H4	CPEN	1	10.316	0.210	-7.746	1.00	0.00	H
ATOM	17	2H4	CPEN	1	8.752	0.936	-8.044	1.00	0.00	H
ATOM	18	H13	CPEN	1	5.213	0.401	-11.935	1.00	0.00	H
ATOM	19	H33	CPEN	1	5.198	-1.735	-10.904	1.00	0.00	H
ATOM	20	N	PYRO	1B	4.935	1.624	-6.451	1.00	0.00	N
ATOM	21	N1	PYRO	1B	5.748	2.516	-5.848	1.00	0.00	N
ATOM	22	N2	PYRO	1B	6.425	3.246	-6.770	1.00	0.00	N
ATOM	23	C	PYRO	1B	6.025	2.777	-8.006	1.00	0.00	C
ATOM	24	C1	PYRO	1B	5.110	1.764	-7.809	1.00	0.00	C
ATOM	25	C2	PYRO	1B	7.482	4.257	-6.437	1.00	0.00	C
ATOM	26	C3	PYRO	1B	7.210	5.132	-5.176	1.00	0.00	C

ATOM	27	C4	PYRO	1B	7.367	4.471	-3.798	1.00	0.00	C
ATOM	28	N3	PYRO	1B	8.568	3.965	-3.510	1.00	0.00	N
ATOM	29	O	PYRO	1B	6.421	4.436	-3.014	1.00	0.00	O
ATOM	30	HC	PYRO	1B	6.404	3.105	-8.962	1.00	0.00	H
ATOM	31	1H2	PYRO	1B	8.457	3.741	-6.351	1.00	0.00	H
ATOM	32	2H2	PYRO	1B	7.605	4.937	-7.303	1.00	0.00	H
ATOM	33	1H3	PYRO	1B	7.869	6.019	-5.195	1.00	0.00	H
ATOM	34	2H3	PYRO	1B	6.188	5.549	-5.239	1.00	0.00	H
ATOM	35	H3	PYRO	1B	9.361	4.193	-4.126	1.00	0.00	H
ATOM	36	C1	CPEN	1C	9.758	3.763	-1.330	1.00	0.00	C
ATOM	37	C2	CPEN	1C	11.154	3.293	-1.730	1.00	0.00	C
ATOM	38	O3	CPEN	1C	10.999	2.180	-2.635	1.00	0.00	O
ATOM	39	C13	CPEN	1C	8.807	3.080	-2.328	1.00	0.00	C
ATOM	40	C33	CPEN	1C	9.607	1.789	-2.657	1.00	0.00	C
ATOM	41	H1	CPEN	1C	9.672	4.866	-1.329	1.00	0.00	H
ATOM	42	H2	CPEN	1C	11.734	4.100	-2.216	1.00	0.00	H
ATOM	43	H13	CPEN	1C	7.856	2.808	-1.823	1.00	0.00	H
ATOM	44	H33	CPEN	1C	9.456	1.087	-1.812	1.00	0.00	H
ATOM	45	N1	PYRO	1D	8.043	0.273	-4.051	1.00	0.00	N
ATOM	46	N2	PYRO	1D	7.970	-0.130	-5.336	1.00	0.00	N
ATOM	47	N3	PYRO	1D	9.055	0.293	-6.032	1.00	0.00	N
ATOM	48	C4	PYRO	1D	9.833	1.007	-5.142	1.00	0.00	C
ATOM	49	C5	PYRO	1D	9.201	1.005	-3.916	1.00	0.00	C
ATOM	50	H4	PYRO	1D	10.750	1.527	-5.375	1.00	0.00	H
ATOM	51	O	CPEN	1E	3.131	0.297	-11.763	1.00	0.00	O
ATOM	52	C	CPEN	1E	2.401	-0.833	-11.276	1.00	0.00	C
ATOM	53	C1	CPEN	1E	2.084	-1.771	-12.440	1.00	0.00	C
ATOM	54	C2	CPEN	1E	1.124	-0.348	-10.597	1.00	0.00	C

ATOM	55	O1	CPEN	1E	3.211	-1.520	-10.315	1.00	0.00	O
ATOM	56	1H13	CPEN	1E	1.535	-2.667	-12.098	1.00	0.00	H
ATOM	57	2H13	CPEN	1E	1.472	-1.268	-13.210	1.00	0.00	H
ATOM	58	3H13	CPEN	1E	3.010	-2.119	-12.928	1.00	0.00	H
ATOM	59	1H1	CPEN	1E	0.545	-1.188	-10.173	1.00	0.00	H
ATOM	60	2H1	CPEN	1E	1.358	0.342	-9.768	1.00	0.00	H
ATOM	61	3H1	CPEN	1E	0.472	0.198	-11.302	1.00	0.00	H
ATOM	62	O2	CPEN	1F	9.569	3.272	0.008	1.00	0.00	O
ATOM	63	C3	CPEN	1F	10.842	2.888	0.540	1.00	0.00	C
ATOM	64	C31	CPEN	1F	11.280	3.903	1.595	1.00	0.00	C
ATOM	65	C1	CPEN	1F	10.732	1.488	1.137	1.00	0.00	C
ATOM	66	O33	CPEN	1F	11.795	2.870	-0.526	1.00	0.00	O
ATOM	67	1H31	CPEN	1F	12.268	3.647	2.017	1.00	0.00	H
ATOM	68	2H31	CPEN	1F	11.359	4.914	1.159	1.00	0.00	H
ATOM	69	3H31	CPEN	1F	10.557	3.959	2.427	1.00	0.00	H
ATOM	70	1H1	CPEN	1F	11.697	1.147	1.552	1.00	0.00	H
ATOM	71	2H1	CPEN	1F	9.978	1.448	1.943	1.00	0.00	H
ATOM	72	3H1	CPEN	1F	10.431	0.756	0.368	1.00	0.00	H

Co-ordinates of energy minimized structure of compound 2b:

ATOM	1	C	CPEN	1	1.510	2.057	-8.721	1.00	0.00	C
ATOM	2	C1	CPEN	1	2.863	2.387	-8.050	1.00	0.00	C
ATOM	3	C2	CPEN	1	3.880	1.714	-9.020	1.00	0.00	C
ATOM	4	C3	CPEN	1	4.382	0.262	-8.749	1.00	0.00	C
ATOM	5	O	CPEN	1	5.577	0.069	-8.507	1.00	0.00	O
ATOM	6	N	CPEN	1	3.476	-0.726	-8.770	1.00	0.00	N
ATOM	7	C4	CPEN	1	3.812	-2.127	-8.438	1.00	0.00	C
ATOM	8	C5	CPEN	1	2.559	-2.937	-8.037	1.00	0.00	C
ATOM	9	C6	CPEN	1	1.845	1.950	-10.200	1.00	0.00	C
ATOM	10	O1	CPEN	1	3.273	1.816	-10.327	1.00	0.00	O
ATOM	11	H1	CPEN	1	1.079	1.107	-8.349	1.00	0.00	H
ATOM	12	H2	CPEN	1	3.019	3.479	-8.141	1.00	0.00	H
ATOM	13	H3	CPEN	1	4.784	2.352	-9.028	1.00	0.00	H
ATOM	14	H32	CPEN	1	2.515	-0.426	-8.965	1.00	0.00	H
ATOM	15	1H32	CPEN	1	4.284	-2.596	-9.322	1.00	0.00	H
ATOM	16	2H32	CPEN	1	4.570	-2.181	-7.630	1.00	0.00	H
ATOM	17	1H6	CPEN	1	2.821	-4.011	-8.080	1.00	0.00	H
ATOM	18	2H6	CPEN	1	1.770	-2.825	-8.806	1.00	0.00	H
ATOM	19	H13	CPEN	1	1.331	1.088	-10.667	1.00	0.00	H
ATOM	20	N	PYRO	1B	2.985	2.030	-6.583	1.00	0.00	N
ATOM	21	C	PYRO	1B	4.112	1.833	-5.803	1.00	0.00	C
ATOM	22	C1	PYRO	1B	3.708	1.592	-4.510	1.00	0.00	C
ATOM	23	N1	PYRO	1B	2.334	1.671	-4.481	1.00	0.00	N
ATOM	24	N2	PYRO	1B	1.924	1.945	-5.737	1.00	0.00	N
ATOM	25	C2	PYRO	1B	4.613	1.296	-3.311	1.00	0.00	C
ATOM	26	C3	PYRO	1B	4.997	-0.189	-3.145	1.00	0.00	C

ATOM	27	N3	PYRO	1B	3.861	-1.010	-2.676	1.00	0.00	N
ATOM	28	C4	PYRO	1B	3.895	-2.351	-2.671	1.00	0.00	C
ATOM	29	O	PYRO	1B	4.874	-2.999	-3.051	1.00	0.00	O
ATOM	30	HC	PYRO	1B	5.133	1.846	-6.157	1.00	0.00	H
ATOM	31	1H2	PYRO	1B	5.542	1.887	-3.417	1.00	0.00	H
ATOM	32	2H2	PYRO	1B	4.149	1.678	-2.382	1.00	0.00	H
ATOM	33	1H3	PYRO	1B	5.821	-0.269	-2.411	1.00	0.00	H
ATOM	34	2H3	PYRO	1B	5.405	-0.585	-4.096	1.00	0.00	H
ATOM	35	H3	PYRO	1B	3.011	-0.535	-2.340	1.00	0.00	H
ATOM	36	C1	CPEN	1C	1.354	-3.178	-3.070	1.00	0.00	C
ATOM	37	C2	CPEN	1C	2.624	-3.100	-2.178	1.00	0.00	C
ATOM	38	O3	CPEN	1C	2.135	-2.531	-0.936	1.00	0.00	O
ATOM	39	C13	CPEN	1C	0.445	-2.317	-2.183	1.00	0.00	C
ATOM	40	C33	CPEN	1C	0.731	-2.821	-0.754	1.00	0.00	C
ATOM	41	H1	CPEN	1C	0.972	-4.217	-3.054	1.00	0.00	H
ATOM	42	H2	CPEN	1C	2.942	-4.140	-1.966	1.00	0.00	H
ATOM	43	H13	CPEN	1C	0.683	-1.234	-2.311	1.00	0.00	H
ATOM	44	H33	CPEN	1C	1.062	-2.407	0.216	1.00	0.00	H
ATOM	45	N1	PYRO	1D	1.496	-2.751	-4.516	1.00	0.00	N
ATOM	46	C2	PYRO	1D	2.201	-3.337	-5.542	1.00	0.00	C
ATOM	47	C3	PYRO	1D	1.990	-2.618	-6.646	1.00	0.00	C
ATOM	48	N4	PYRO	1D	1.208	-1.654	-6.400	1.00	0.00	N
ATOM	49	N5	PYRO	1D	0.875	-1.696	-5.092	1.00	0.00	N
ATOM	50	H2	PYRO	1D	2.816	-4.222	-5.459	1.00	0.00	H
ATOM	51	O	CPEN	1E	0.570	3.132	-8.605	1.00	0.00	O
ATOM	52	C	CPEN	1E	0.467	3.799	-9.879	1.00	0.00	C
ATOM	53	C1	CPEN	1E	0.863	5.274	-9.712	1.00	0.00	C
ATOM	54	C2	CPEN	1E	-0.970	3.666	-10.411	1.00	0.00	C

ATOM	55	O1	CPEN	1E	1.383	3.168	-10.792	1.00	0.00	O
ATOM	56	1H13	CPEN	1E	0.815	5.822	-10.670	1.00	0.00	H
ATOM	57	2H13	CPEN	1E	0.205	5.796	-8.993	1.00	0.00	H
ATOM	58	3H13	CPEN	1E	1.898	5.369	-9.335	1.00	0.00	H
ATOM	59	1H1	CPEN	1E	-1.087	4.148	-11.399	1.00	0.00	H
ATOM	60	2H1	CPEN	1E	-1.256	2.605	-10.529	1.00	0.00	H
ATOM	61	3H1	CPEN	1E	-1.705	4.127	-9.725	1.00	0.00	H
ATOM	62	O	CPEN	1F	-0.950	-2.519	-2.406	1.00	0.00	O
ATOM	63	C	CPEN	1F	-1.518	-2.197	-1.139	1.00	0.00	C
ATOM	64	C1	CPEN	1F	-2.415	-3.349	-0.649	1.00	0.00	C
ATOM	65	C2	CPEN	1F	-2.300	-0.877	-1.231	1.00	0.00	C
ATOM	66	O1	CPEN	1F	-0.377	-2.022	-0.275	1.00	0.00	O
ATOM	67	1H13	CPEN	1F	-2.822	-3.148	0.359	1.00	0.00	H
ATOM	68	2H13	CPEN	1F	-3.271	-3.517	-1.328	1.00	0.00	H
ATOM	69	3H13	CPEN	1F	-1.855	-4.300	-0.591	1.00	0.00	H
ATOM	70	1H1	CPEN	1F	-2.707	-0.573	-0.249	1.00	0.00	H
ATOM	71	2H1	CPEN	1F	-1.655	-0.053	-1.586	1.00	0.00	H
ATOM	72	3H1	CPEN	1F	-3.149	-0.953	-1.936	1.00	0.00	H