tRational Construction of Triazole/Urea Based Peptidomimetic Macrocycles as Pseudo-cyclo-β-peptides and Studies on Their Chirality Controlled Self-Assembly

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Supporting Information

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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 in $CHCl_3$ in NaCl cell. Mass spectra were obtained under high resolution (HRMS). ^1H and ^{13}C NMR spectra were recorded in deuterated solvents on Bruker Avance-300 MHz and Varian Inova-600 MHz spectrometers. ^1H 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 **16a,b** 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-[3-(Dimethylamino)propyl]-3-ethyl-carbodiimide.HCl (EDCI) and 1-hydroxybenzotriazole (HOBt) 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 suspension of **16b** in (4:1) CH_3CN:H_2O on Cu/carbon coated grids, drying overnight, and subjecting to negative staining with uranyl acetate.

FT-IR Studies

FT-IR Measurements were made on a JASCO FT/IR-400 Spectrophotometer using 20 mM solution in $CHCl_3$ of the compound placed in an NaCl cell.

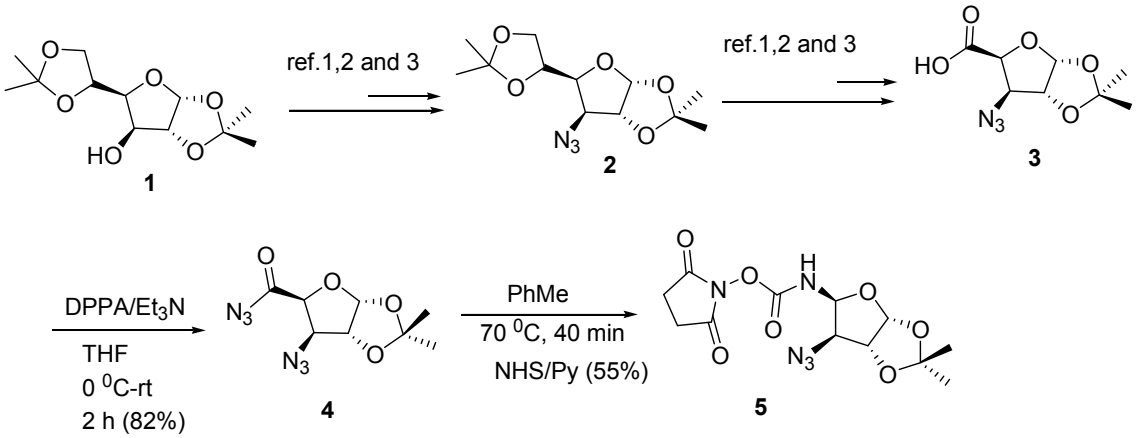
AFM Sample Preparation and Imaging:

Aliquots (10 μL) of the solutions of the samples **16a** and **16b** in (2:3) $CDCl_3$:CCl_4 and CH_3CN: H_2O (4:1) respectively were deposited onto freshly cleaved muscovite Ruby mica sheets (ASTM V1 Grade Ruby Mica from MICAFAB) and left for 15-30 min. 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 dried.

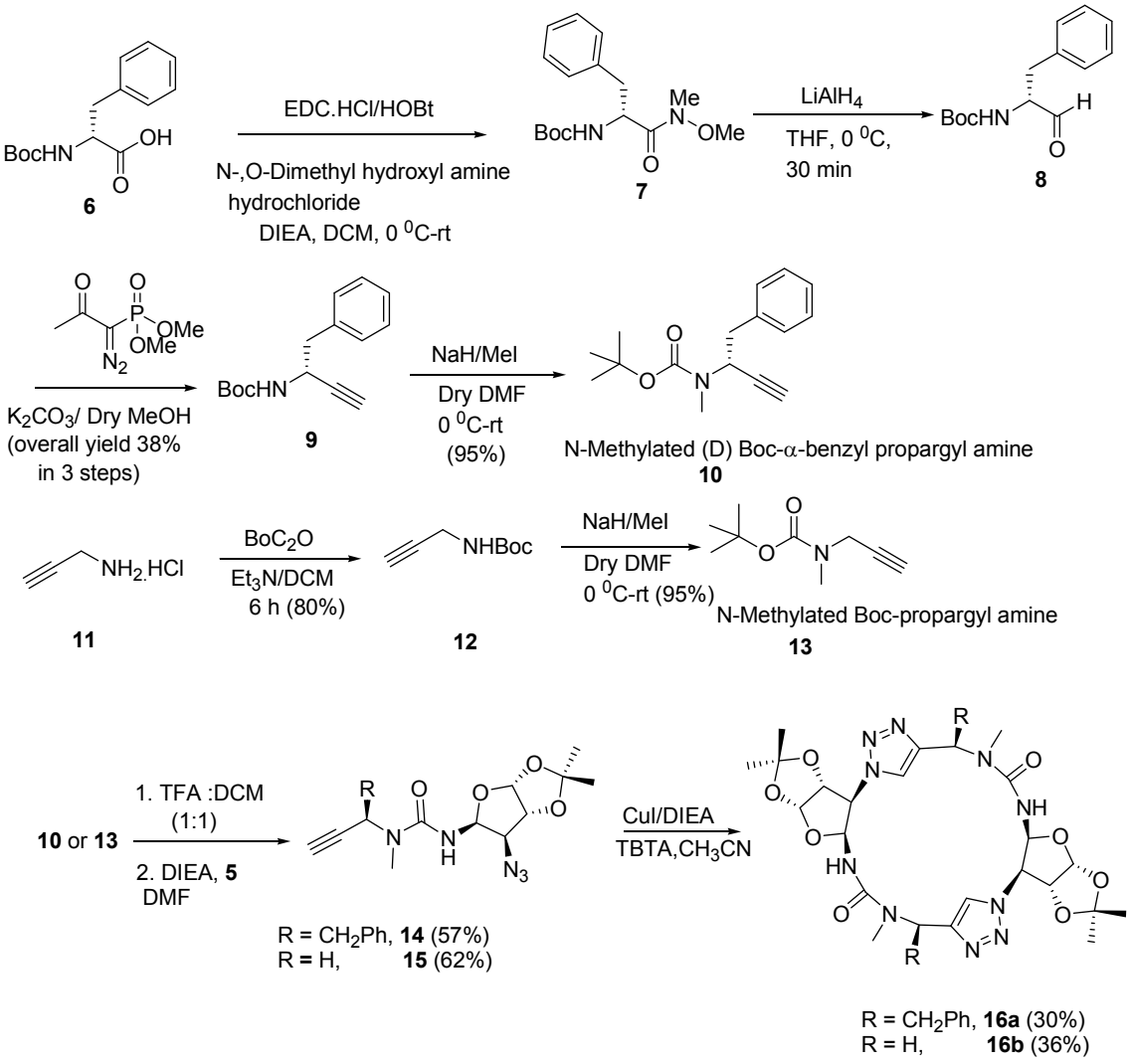
AAC mode AFM was performed using a Pico plus 5500 ILM AFM (Agilent Technologies USA) with a piezo scanner with maximum range of 9 μm. Micro fabricated silicon cantilevers 225 μm in length with a nominal spring force constant of 21-98 N/m were obtained from Nano sensors, USA. Cantilever oscillation frequency 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 Picoview1.4 version software (Agilent Technologies, USA). Image manipulation has been done through Pico Image Advanced version software (Agilent Technologies, USA).

Synthesis of activated cis-furanoid-β-azido succinimidyl carbamate ester 5[1]***:***



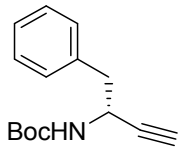
1. a) Hennig, A.; Fischer, L; Guichard, G; Matile, S. *J. Am. Chem. Soc.* **2009**, *131*, 16889. b) Fischer, L; Decossas, M; Briand, J.-P.; Didierjean, C; Guichard, G. *Angew. Chem., Int. Ed.* **2009**, *48*, 1625 and references therein. c) Fischer, L; Guichard, G. *Org. Biomol. Chem.* **2010**, *8*, 3101.
2. (a) Ghorai, A.; Padmanaban, E.; Mukhopadhyay, C.; Achari, B.; Chattopadhyay, P. *Chem. Commun.* **2012**, *48*, 11975. b) Ghorai, A.; Gayen, A.; Kulsi, G.; Padmanaban, E.; Laskar, A.; Achari, B,; Mukhopadhyay, C.; Chattopadhyay, P. *Org. Lett.* **2011**, *13*, 5512–5515.
3. Jagannadh, B.; Reddy, M. S.; Lohitha Rao, C.; Prabhakar,A.; Jagadeesh, B.; Chandrasekhar, S. *Chem. Commun*. **2006**, 4847

Synthesis of N-methylated chiral (α-benzyl propargyl) and achiral (propargyl) amines and peptidomimetic macrocycles (16a and b):



Preparation and Characterisation of Compounds:

(*R*) and (*S*)-tert-butyl (1-phenylbut-3-yn-2-yl)carbamate (9)[4]:



Commercially available Boc-D-phenyl alanine **6** (500 mg, 1.886 mmol), HOBt.H_2O (280 mg, 2.07 mmol), and *N*,*O*-dimethylhydroxylamine.HCl (201 mg, 2.072 mmol) were suspended in CH_2Cl_2 (20 mL). DIEA (0.7 mL, 12.04 mmol) was added and the solution cooled to 0 °C under argon. EDC.HCl (412 mg, 2.08 mmol) was added and the reaction was allowed to stir at rt over 2 h. The reaction mixture was then diluted with EtOAc and washed successively with 5% aq. $KHSO_4$ (2×), 5% aq. $NaHCO_3$ (2×), and brine (2×). The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to yield the Weinreb amide **7** as oil (441 mg) which was directly used in the next step. The amide was dissolved in THF (25 mL) and cooled to 0 °C under argon. $LiAlH_4$ (286 mg, 7.53 mmol) was added at once and the suspension was stirred for 30 min at 0 °C. The reaction was quenched by slow addition of 5% aq. $KHSO_4$. The mixture was diluted with EtOAc; the organic layer was separated and washed successively with 5% aq. $KHSO_4$ (2×), 5% aq. $NaHCO_3$ (3×) and brine (3×). It was then dried with anhydrous Na_2SO_4 and concentrated to yield the aldehyde as oil (321 mg) which was used directly in the next step. K_2CO_3 (600 mg, 4.34 mmol) and p-toluenesulfonyl azide (800 mg, 4.06 mmol) were suspended in anhydrous acetonitrile (15 mL) under argon. Dimethyl-(2-oxopropyl)-phosphonate (360 mg, 2.17 mmol) was added, and the reaction mixture was stirred for 2 h. The crude aldehyde was dissolved in MeOH (3 mL) and added to the reaction mixture of diazophosphonate ester. After stirring overnight, the solution was concentrated to a residue, diluted with EtOAc, and washed successively with water (2×) and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated to yield the crude product which was purified by column chromatography using (15:1) PE:EA to yield **9** (196 mg, 38% yield over 3 steps) as white amorphous solid.

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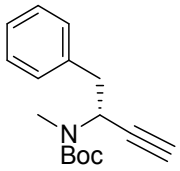
4. (a) Ohira, S. *Synth. Commun.* **1989**, *19*, 561. (b) De Luca, L.; Giacomelli, G.; Taddei, M. *J. Org. Chem.* **2001**, *66*, 2534.

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.28 (m, 5H), 4.68 (br, 2H), 2.99 (m, 2H), 2.27 (s, 1H), 1.42 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ): 154.5, 136.3, 129.8, 128.3, 126.9, 82.7, 80.0, 72.7, 43.1, 41.7, 29.7, 28.3.

HRMS $(M+Na)^+$ for $C_{15}H_{19}NO_2Na$**:** calculated 268.1416, found 268.1421.

(*R*)-tert-butyl methyl (1-phenylbut-3-yn-2-yl)carbamate (10):



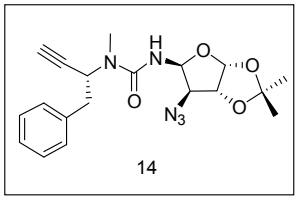
NaH (15 mg, 0.6 mmol) was added to a stirred solution of compound **9** (100 mg, 0.4 mmol) in dry DMF. After 15 min, MeI (0.8 mmol, 0.05 mL) was added and the reaction mixture was allowed to stir overnight at 0 ^{0}C. The reaction was quenched by slow addition of 5% $KHCO_3$ and the mixture was then diluted with EtOAc. The organic layer was separated and washed successively with $Na_2S_2O_3$ and brine. Then it was dried over anhydrous Na_2SO_4 and concentrated to yield yellow oil. Compound **10** was eluted as a colourless liquid (197 mg, 95% yield) in (20:1) PE: EA eluates by column chromatography.

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.26 (m, 5H), 5.06 (br, 1H), 2.93 (m, 5H), 2.35 (s, 1H), 1.36 (s, 9H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ): 154.1, 136.3, 129.2, 128.3, 126.6, 79.9, 73.0, 49.1, 40.2, 30.1, 29.6, 28.1.

HRMS $(M+Na)^+$ for $C_{15}H_{19}NO_2Na$**:** calculated 282.1572, found: 282.1566.

***N*-Methylated ureido-(azide/alkyne) precursor 14:**



14

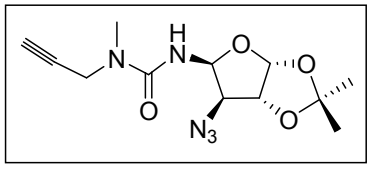
The sugar azido acid **3** (195 mg, 0.84 mmol) was dissolved in dry THF under Ar at 0 ^{0}C. After the addition of triethyl amine (95 mg, 0.41 mmol) and DPPA (257 mg, 0.93 mmol), the reaction mixture was allowed to stir for 40 min. Then it was diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the sugar acyl azide (85 mg) which was used without purification. Toluene was added under Ar, and the resulting solution was heated to 70 °C under stirring. After the gas evolution had stopped, N-hydroxysuccinimide (80 mg, 0.69 mmol) and pyridine (294 mg, 3.72 mmol) were added. The mixture was stirred at 70 °C for 30 min. Then solvent was removed under vacuum to get a dark red coloured semisolid which was directly used for the next step. In another R.B. flask the Boc protected amino alkyne **10** (47 mg, 0.183 mmol) was dissolved in 1:1 DCM:TFA under Ar and stirred for 30 min to remove Boc. The resulting TFA salt of the amine was neutralised with DIEA. The N-hydroxy succinimide sugar azidoester (62 mg, 0.18 mmol) was dissolved in dry DMF at rt and the amine was added as solution in dry DMF. The reaction was allowed to stir overnight at rt. Then it was diluted with EtOAc and washed successively with 5% $KHSO_4$, 5% $NaHCO_3$, and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to get a red oily liquid. Purification was done by silica-gel column chromatography using (3:1) PE:EA as eluent to get **14** as a white amorphous solid (40 mg, 57% yield over two steps).

^{1}H NMR ($CDCl_3$, 300 MHz, δ): 7.26 (m, 5H), 6.04 (dd, *J*=3.3, 6.6 Hz, 1H), 5.84 (d, *J*=3.9 Hz, 1H), 5.37 (m, 2H), 4.64 (t, *J*=9.9 Hz, 1H), 4.02 (t, *J*=6.0 Hz, 1H), 2.99 (m, 2H), 2.89 (s, 3H), 2.32 (s, 1H), 1.57 (s, 3H), 1.33 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ): 154.9, 136.5, 129.3, 128.4, 126.8, 112.6, 102.3, 82.0, 81.8, 73.8, 65.9, 49.2, 40.1, 30.0, 26.8, 26.4.

HRMS $(M+Na)^+$ for $C_{19}H_{23}N_5O_4Na$**:** calculated 408.1750, found: 408.1744.

***N*-Methylated ureido-(azide/alkyne) precursor 15:**



The sugar azido acid **3** (195 mg, 0.84 mmol) was dissolved in dry THF under Ar at 0 ^{0}C. After the addition of triethyl amine (0.1 mL, 0.41 mmol) and DPPA (257 mg, 0.93 mmol), the reaction mixture was allowed to stir for 40 min. Then it was diluted with DCM, washed with brine, dried over anhydrous Na_2SO_4, and concentrated under reduced pressure to yield the sugar acyl azide (85 mg) which was used without purification. Toluene was added under Ar, and the resulting solution was heated to 70 °C under stirring. After the gas evolution had stopped *N*-hydroxysuccinimide (80 mg, 0.69 mmol) and pyridine (294 mg, 3.72 mmol) were added. The mixture was stirred at 70 ^{o}C for 30 min. Then solvent was removed under vacuum to get a dark red coloured semisolid which was directly used for the next step. In another R.B. flask the Boc protected amino alkyne **13** (28 mg, 0.181 mmol) was dissolved in (1:1) DCM:TFA under Ar and stirred for 30 min to remove Boc. The resulting TFA salt of the deprotected amine was neutralised with DIEA. *N*-hydroxy succinimidosugar azidocarbamate **5** was dissolved in dry DMF at RT and the amine was added by dissolving in dry DMF. The reaction was allowed to stir overnight at RT. Then it was diluted with EtOAc and washed with 5% $KHSO_4$, 5% $NaHCO_3$ and brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under vacuum to get a red coloured oil. Purification was done by silica-gel column chromatography using (2:1) PE:EA as eluent to get **15** as a colourless semi-solid (33 mg, 62% yield over two steps).

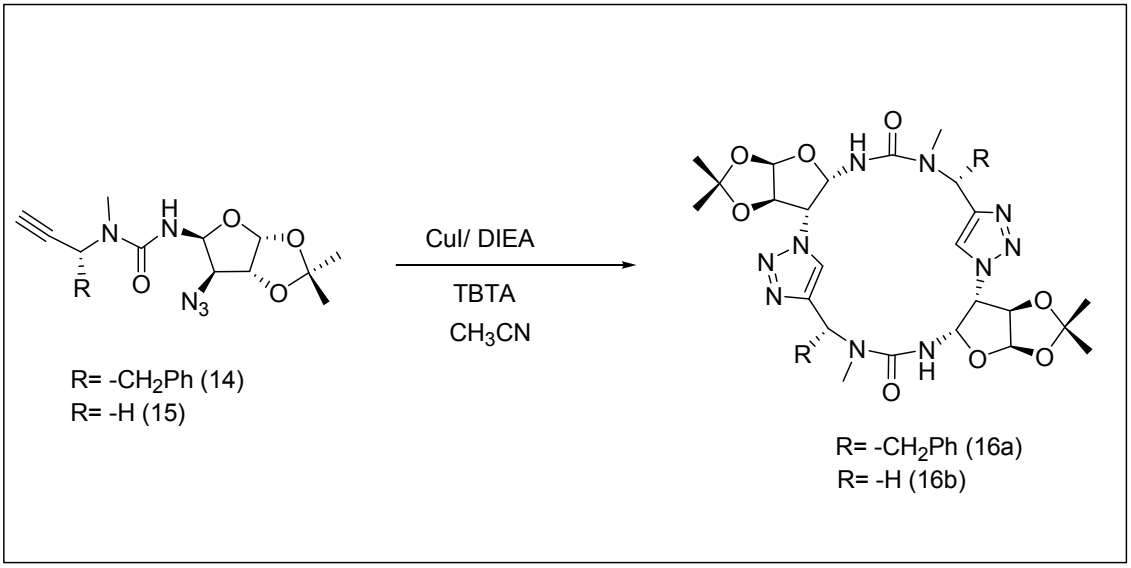
^{1}H NMR ($CDCl_3$, 300 MHz, δ): 6.06 (dd, *J* =3.3, 9.9 Hz, 1H), 5.85 (d, *J*=3.6 Hz, 1H), 5.39 (d, *J*= 9.9 Hz, 1H), 4.66 (d, *J*=3.6 Hz, 1H), 4.57 (d, *J*=3.6 Hz, 1H), 4.12 (m, 2H), 3.08 (s, 3H), 2.32 (s, 1H), 1.55 (s, 3H), 1.34 (s, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz, δ): 155.6, 112.7, 102.4, 82.1, 81.9, 72.4, 66.0, 37.8, 33.7, 29.6, 26.8, 26.5.

HRMS $(M+Na)^+$ for $C_{12}H_{17}N_5O_4Na$**:** calculated 318.1281, found: 318.1286.

General procedure for Cu(I)-mediated tandem dimerization-macrocyclization[5] of N-methylated ureido-(azido/alkyne) derivatives:

The azido-alkyne terminated peptide (1 eq) was dissolved in acetonitrile to a concentration of 1 mM. The solution was degassed by Ar bubbling for 20 min. Diisopropyl ethylamine (2 eq), TBTA (0.5 eq) and CuI (2 eq) were added sequentially. The reaction was stirred for 12 h at room temperature under Ar. After the completion of reaction the mixture was diluted with EtOAc, and washed with 9:1 aq.NH_4Cl:NH_3 (1×15 mL) and then brine (1×15 mL). The organic layer was dried over Na_2SO_4 and evaporated in a rotary to yield a yellow solid which was purified by RP-HPLC. The main product was the dimer (**16a/b**) which was eluted with (60:40) CH_3CN:H_2O. The higher oligomers were eluted subsequently in traces and were not analysed further.



Structural determination by multidimensional NMR:

NMR Spectra (1D and 2D) of the pseudo cyclic peptides **16a** and **16b** were recorded in a Bruker Avance-600 MHz instrument with TCI CYROPROBE in Acetonitrile-d_3, $CDCl_3$, or (2:3) $CDCl_3$:CCl_4 using tetramethyl 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

5. Maarseveen, J ; Horne, W. S.; Ghadiri, M. R. *Org. Lett.* **2005**, *7*, 4503.

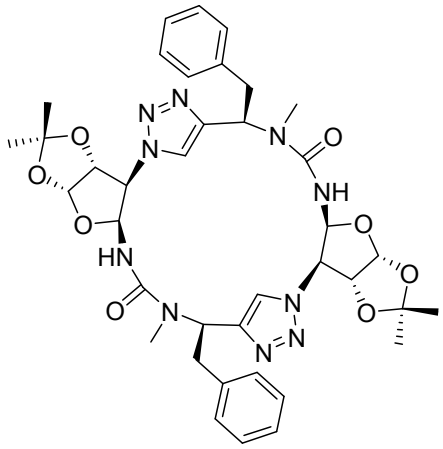
decays (FID) containing 16-32 scans with relaxation delays of 1.5 s. The ROESY experiments were performed with mixing time of 0.2 to 0.3 sec. and the TOCSY experiments were performed with mixing time of 0.02 s. The two dimensional data were processed with Gaussian apodization in both the dimensions. 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 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 $^{3}J_{HN\text{-}CH\alpha}$ coupling constants measured from the ^{1}H-^{1}H DQF-COSY spectra using the modified Karplus equation. The φ values thus obtained were used as dihedral angle constraints.

^{1}H NMR Chemical Shifts (ppm) ($CDCl_3$, 600 MHz, 300K) and coupling constants (Hz) of pseudo-cyclo-β-peptide 16a:

Residue name	NH/Tr	H_α	H_α	H_β	$H_{\beta'}$	H_γ	H_δ
S	4.15(d) $J_{NH,\alpha}$=4.6	5.89(m)		5.30(d) $J_{\beta,\alpha}$=4.2		5.18 (d) $J_{\gamma,\delta}$=4.2	5.94(d) $J_{\delta,\gamma}$=4.2
Phe-Al	7.42(s)	5.89(m)		3.42(m)	3.15(m)		

Other signals: 1.25, 1.39 (2×Me), 2.45 (N-Me), 7.36-7.08 m (aromatic protons)



16a

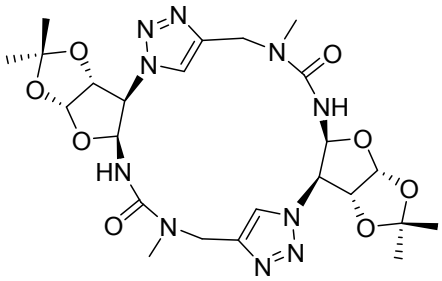
^{13}C NMR ($CDCl_3$, 150 MHz, δ) 154.9 , 144.9 , 137.3 , 129.1 , 128.8 , 128.5 , 126.5 , 124.7, 113.0, 103.8, 86.1 , 83.0 , 65.4, 49.5, 36.9, 28.4, 27.0, 26.6.

HRMS (M+Na)$^+$ for $C_{38}H_{46}N_{10}O_8Na$**:** calculated 793.0098, found: 793.0005.

^{1}H NMR Chemical Shifts (ppm) (CD_3CN, 600 MHz, 300K) and coupling constants (Hz) of pseudo-cyclo-β-peptide 16b:

Residue name	NH/Tr	H_α	$H_{\alpha'}$	H_β	$H_{\beta'}$	H_γ	H_δ
S	6.12 (d, $J_{NH,CH\alpha}$=10.2	6.04(b,s)		5.2(d, $J_{CH\alpha,CH\beta}$=3.6		5.12(b,s)	6.18 (d, $J_{CH\gamma,CH\delta}$=3.0
Gly-moiety	7.55 (s)	4.33 (m)	4.12 (m)				

Other signals (Methyls): 1.57, 1.37, 2.64 (N-Me)



16b

^{13}C NMR (CD_3CN, 150 MHz, δ): 157.6, 144.8, 125.9, 113.5, 104.8, 86.3, 83.8, 66.4, 44.1, 34.5, 27.3, 26.6.

HRMS $(M+Na)^+$ for $C_{24}H_{34}N_{10}O_8Na$**:** calculated 613.2561, found: 613.2568.

Molecular Modelling studies:

Construction of molecular models and structural analysis of different obtained conformations were achieved using Insight-II. The Discover software was used for molecular modelling calculation and also energy minimization. The CFF-91 MSI version with default parameter was used as a force field throughout the calculation, in chloroform and in vacuo respectively for **16a** and **16b**. 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.

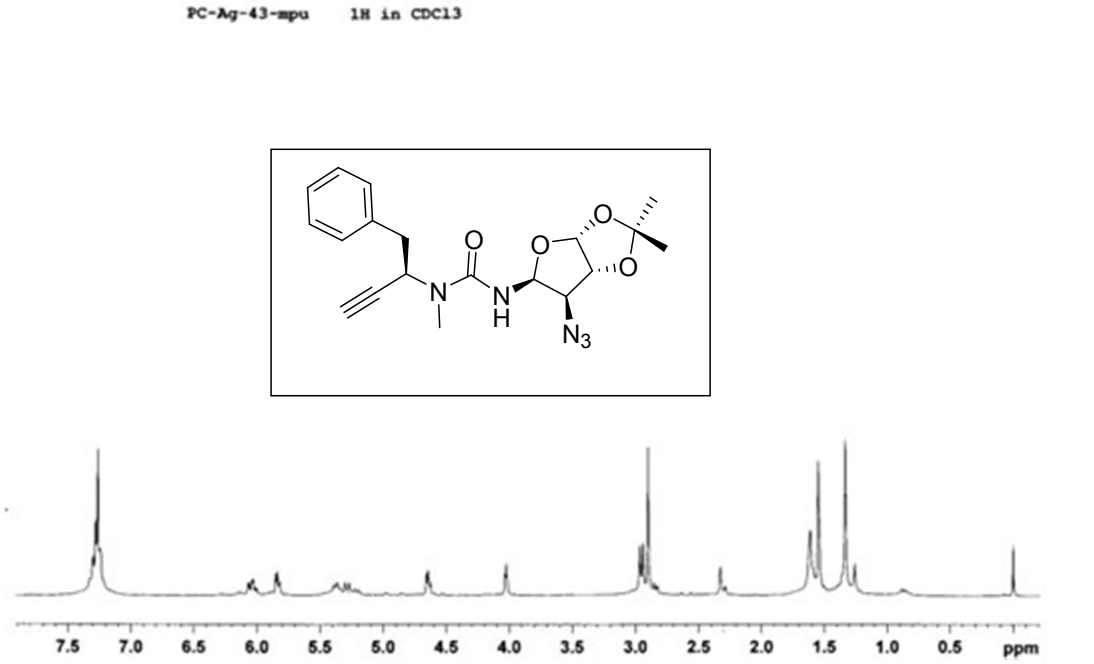


Fig. 1: ^{1}H NMR of **14** in $CDCl_3$ at 298K

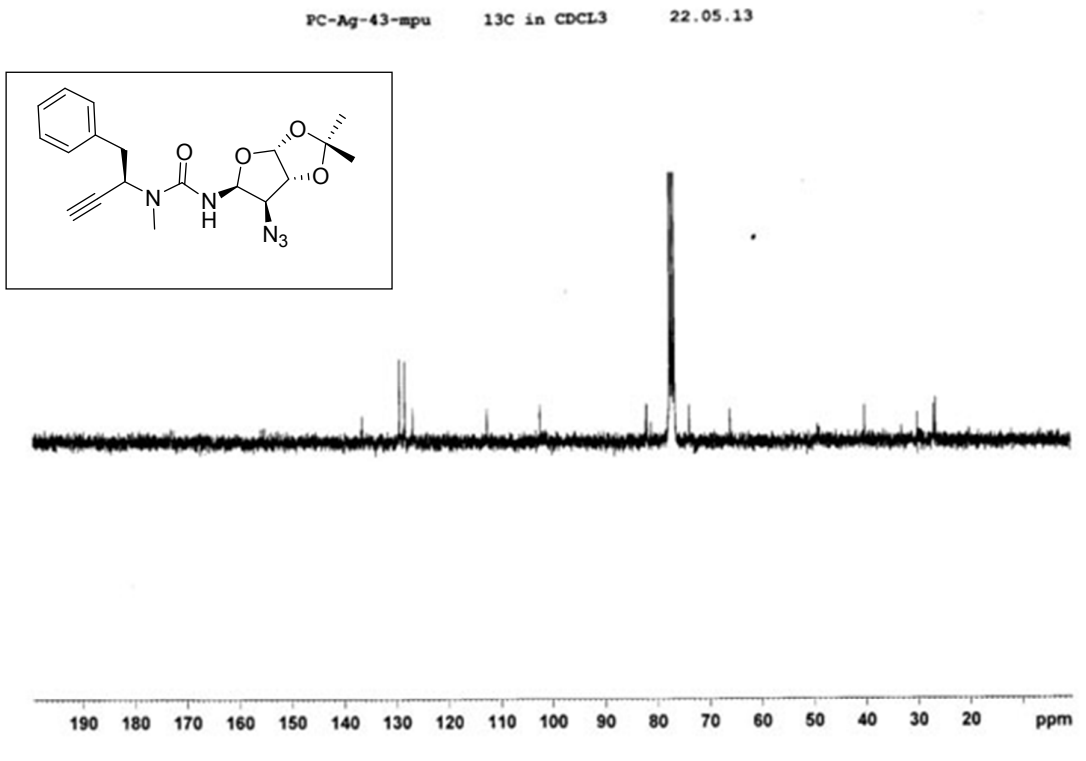


Fig. 2: ^{13}C NMR of **14** in $CDCl_3$ at 298K

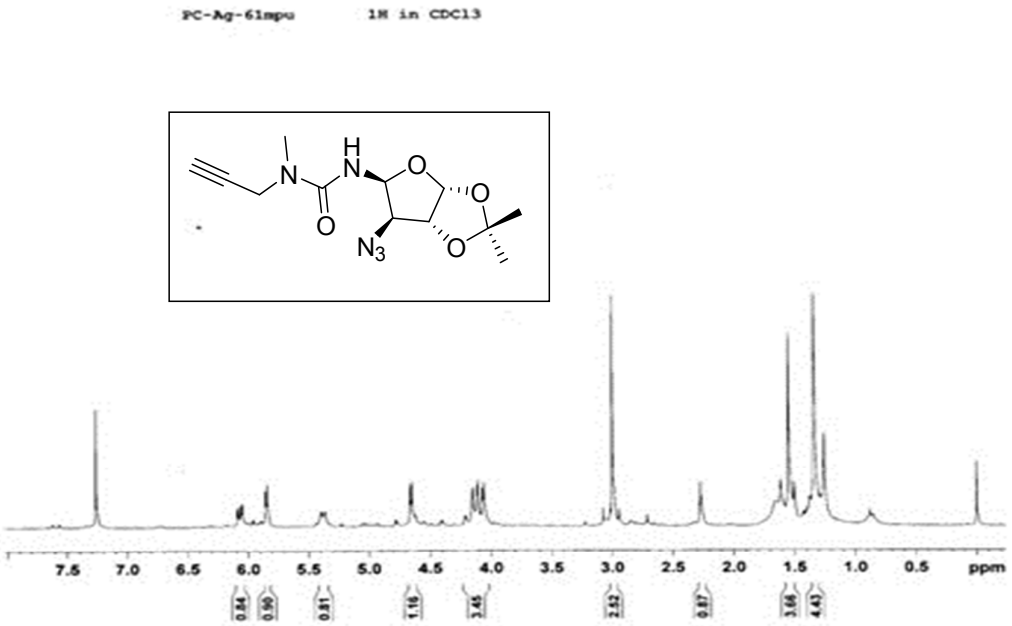


Fig. 3: ^{1}H NMR of **15** in $CDCl_3$ at 298K

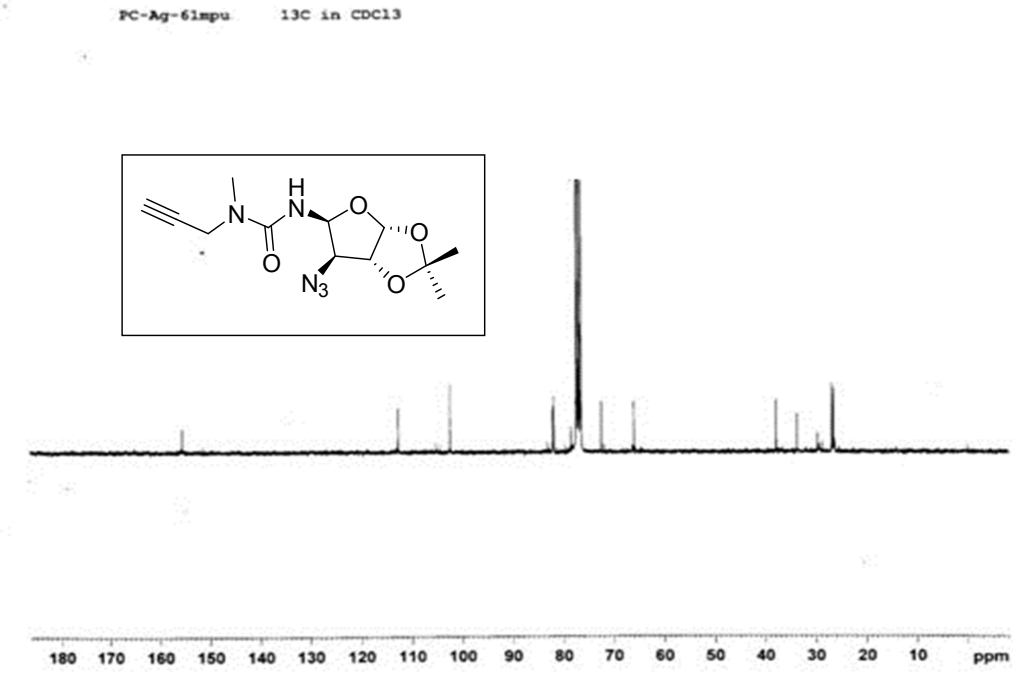


Fig. 4: ^{13}C NMR of **15** in $CDCl_3$ at 298K

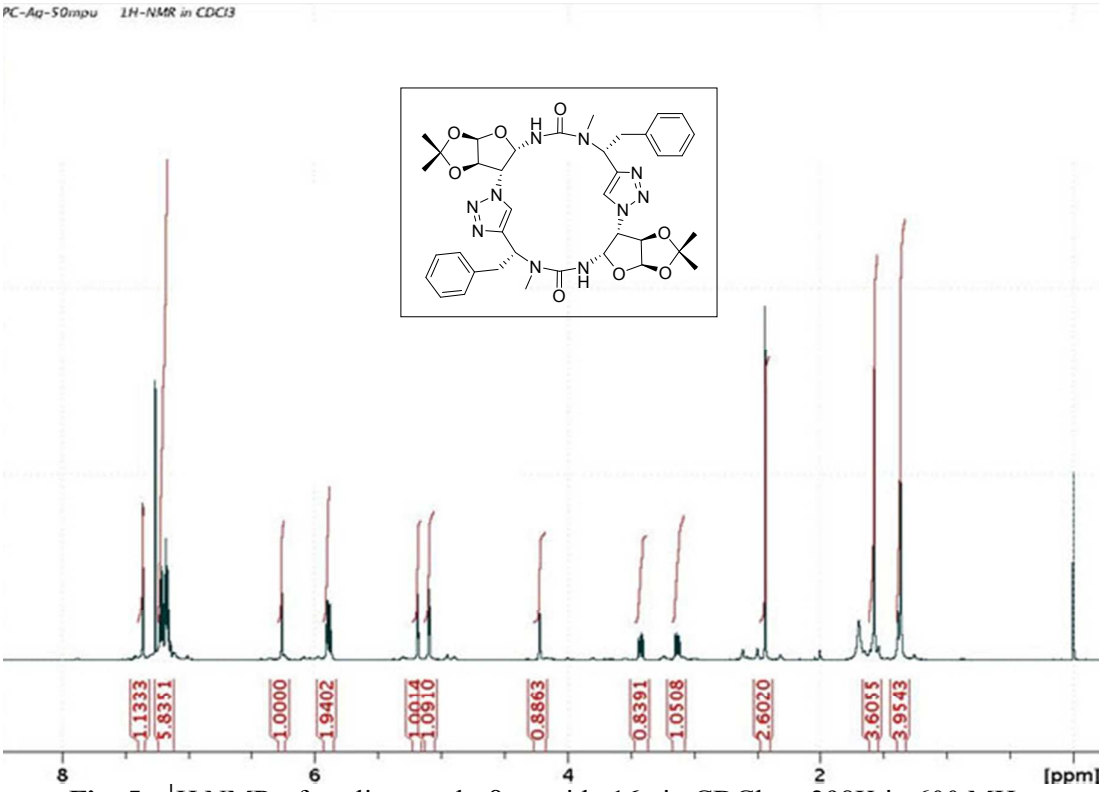


Fig. 5: ^{1}H NMR of cyclic pseudo-β-peptide **16a** in $CDCl_3$ at 298K in 600 MHz

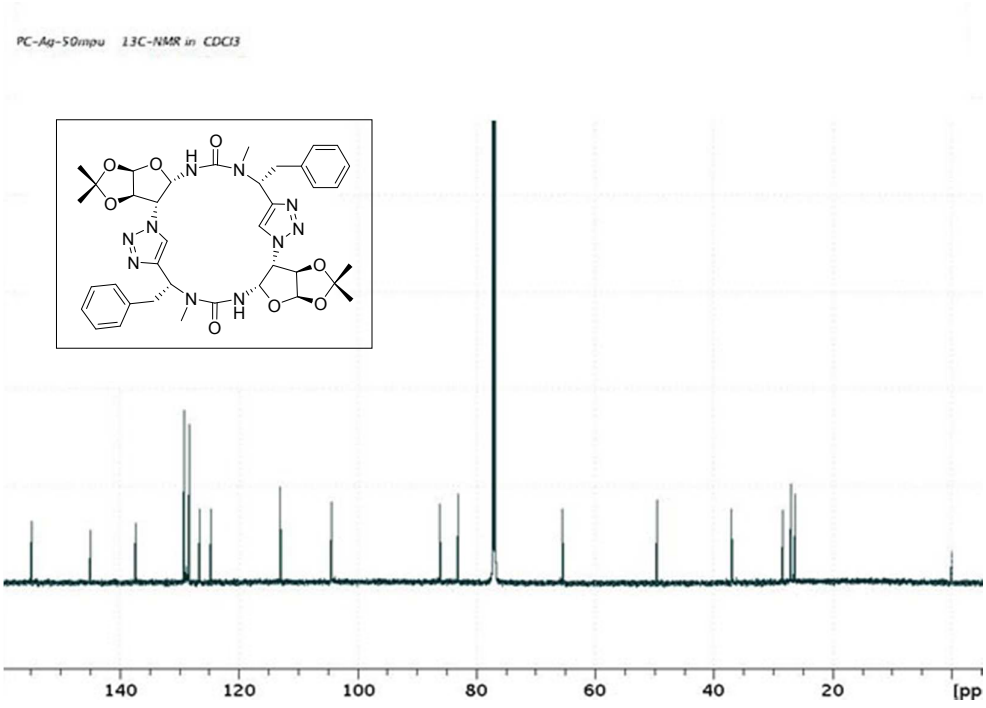


Fig. 6: ^{13}C NMR of pseudo cyclic-β-peptide **16a** (20 mM) in $CDCl_3$ at 298K at 150 MHz.

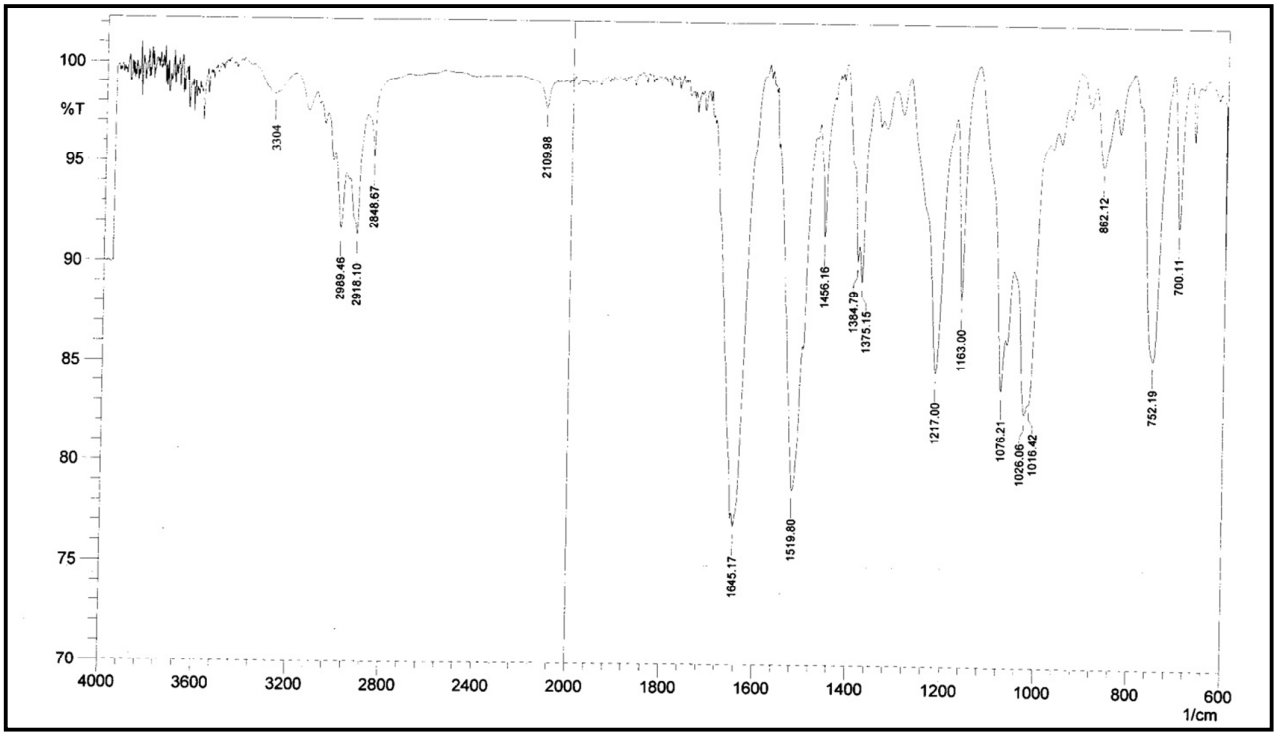


Fig. 7: FT-IR spectrum of pseudo-cyclo-β-peptide **16a** in $CDCl_3$ (20 mM)

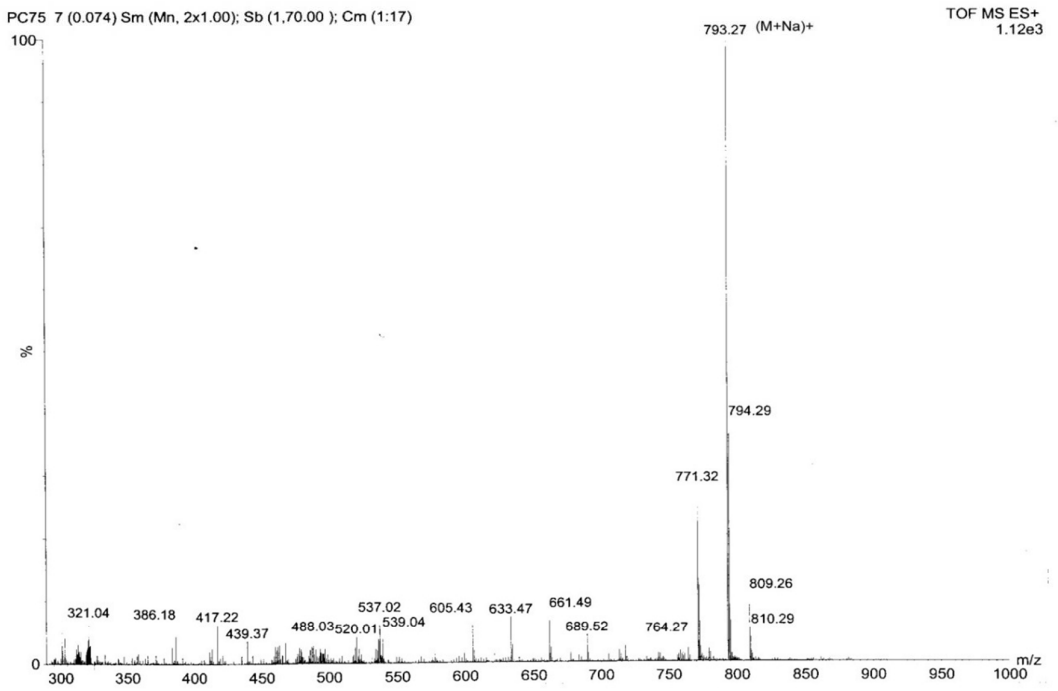


Fig. 8: ESI-Mass spectrum of HPLC pure cyclo-dimer **16a**

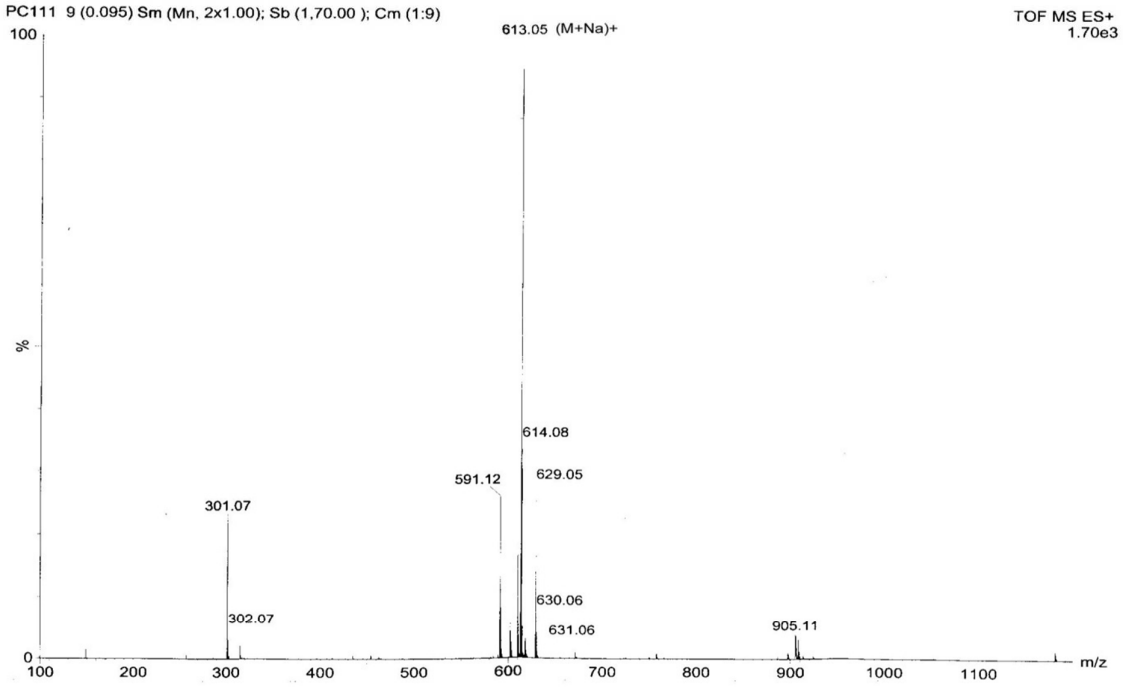


Fig. 9: ESI-Mass spectrum of HPLC pure cyclo-dimer **16b**.

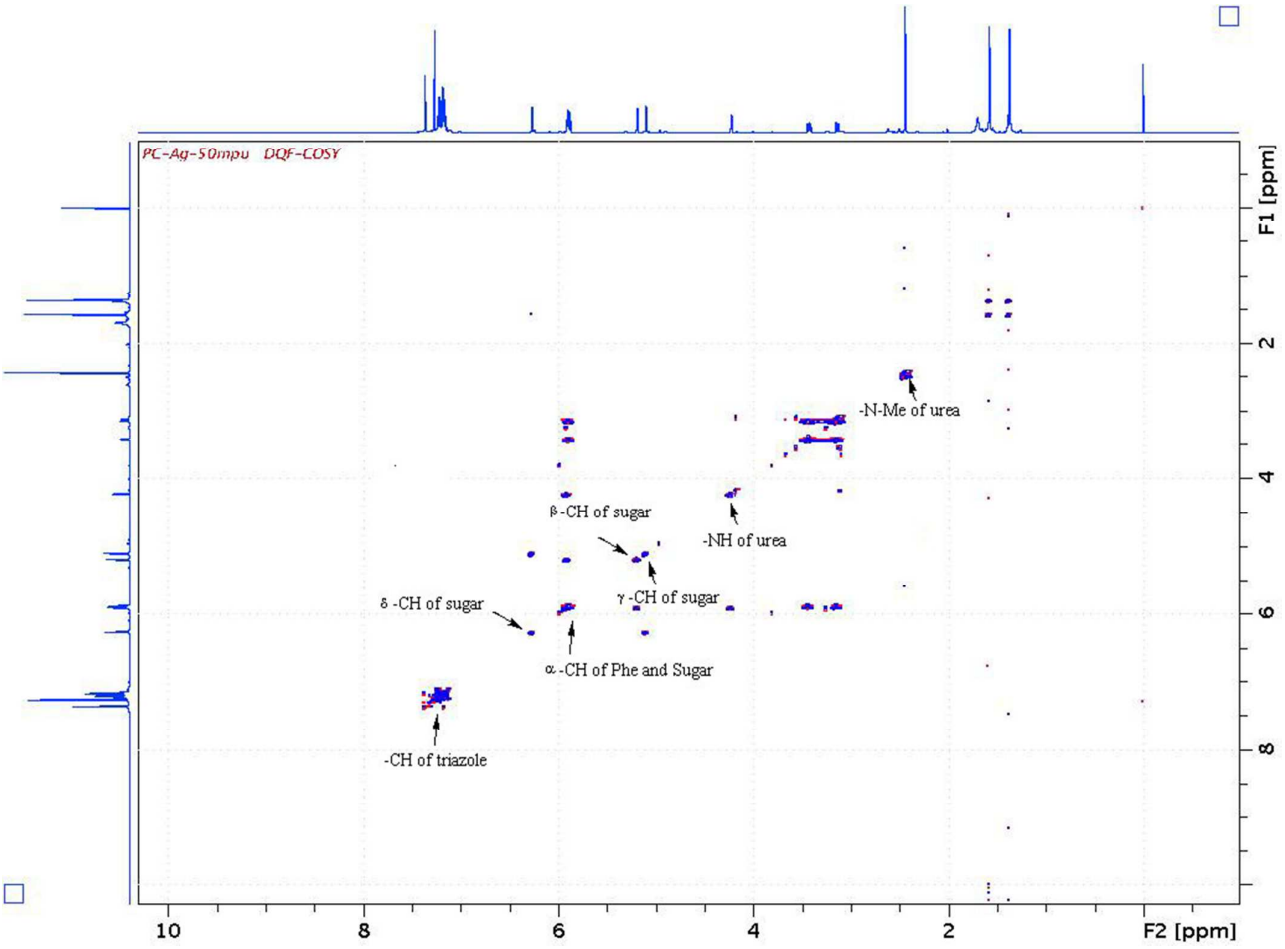


Fig. 10: ^{1}H-^{1}H DQF-COSY spectrum of pseudo cyclic-β-peptide **16a** (20 mM) in $CDCl_3$ at 298K at 600 MHz

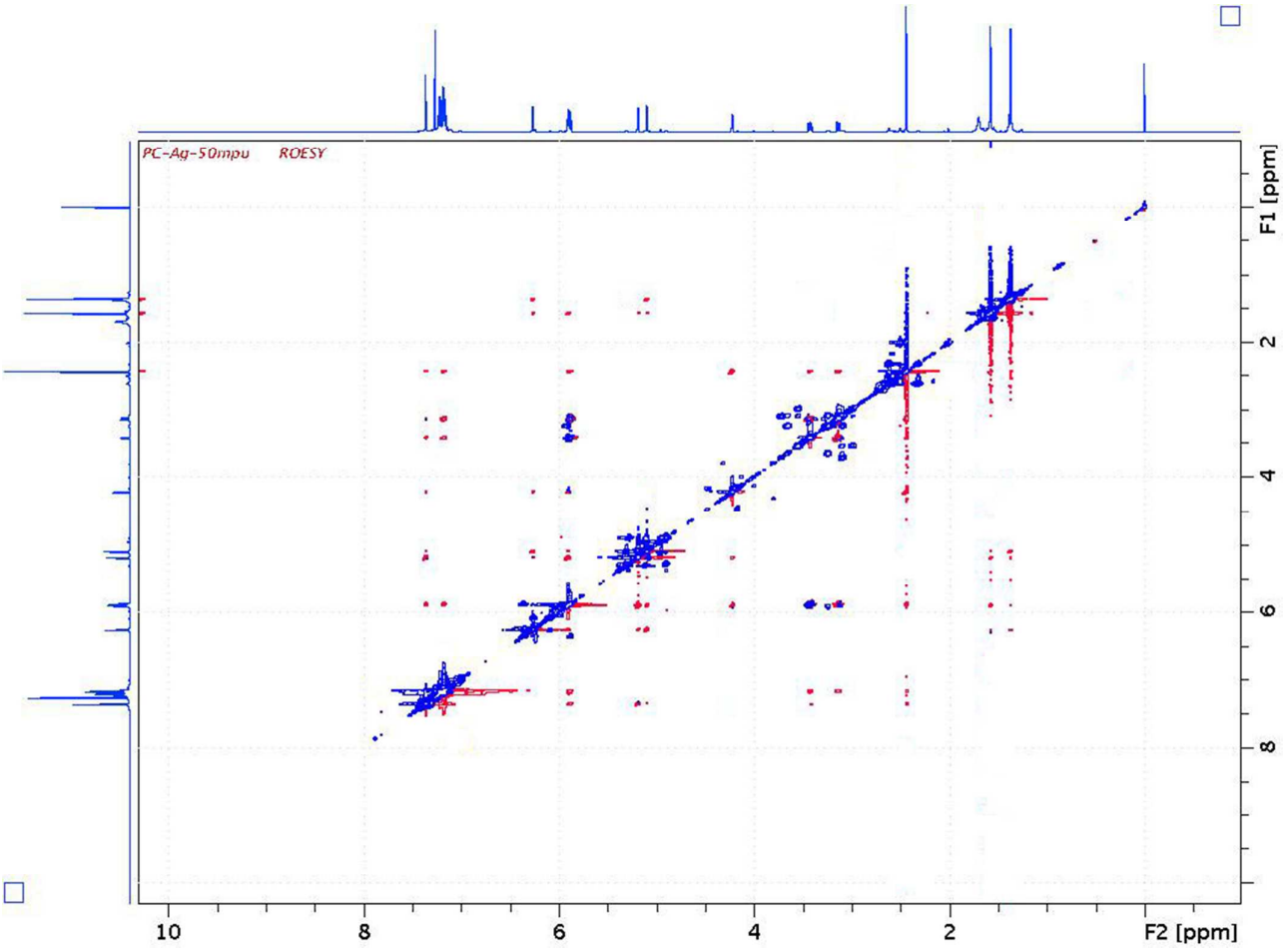


Fig. 11: ^{1}H-^{1}H ROESY spectrum of pseudo cyclic-β-peptide **16a** in $CDCl_3$ (20 mM) at 298K at 600 MHz

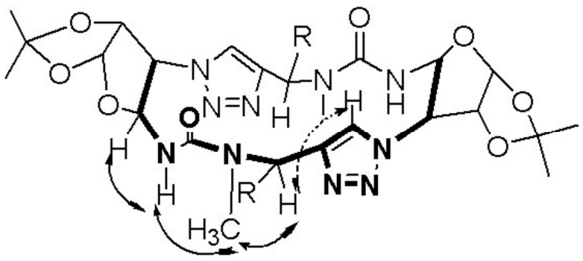


Fig. 12a: Summary of representative NOE connectivities observed for compound **16a** in $CDCl_3$ at 298K.

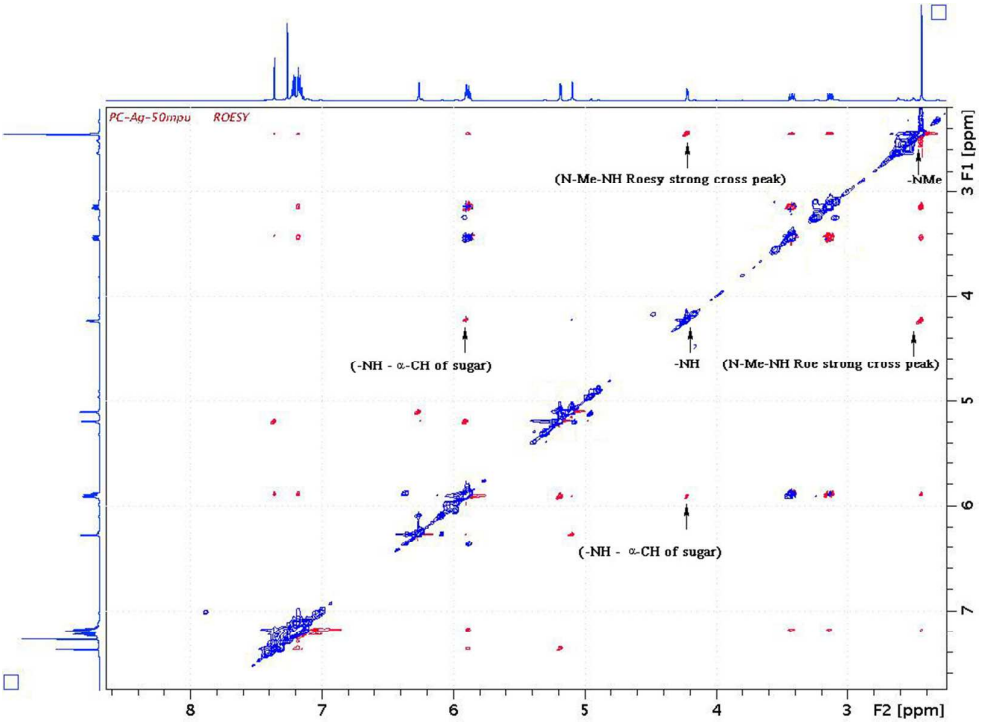


Fig. 12b: NMR analysis (DQF-COSY as well as ROESY) of compound **16a** (20 mM) in $CDCl_3$ at 298K (600 MHz) depicting a ring conformation in solution phase

a) The weak cross peak in ROESY spectrum between triazole-CH and $^{\alpha}$CH of phenyl alanine residue is indicative of an antiperiplanar arrangement between these protons. The ureido amide proton exhibits a small coupling constant (4.6 Hz) as evidenced by weak cross coupling in DQF-COSY spectrum.

b)Part of ROESY spectrum showing strong NOE correlations of NMe with $^{\alpha}$CH proton of phenylalanine residue as well as NH protons. A summary of NOE connectivity is shown in **Fig. 12a**.

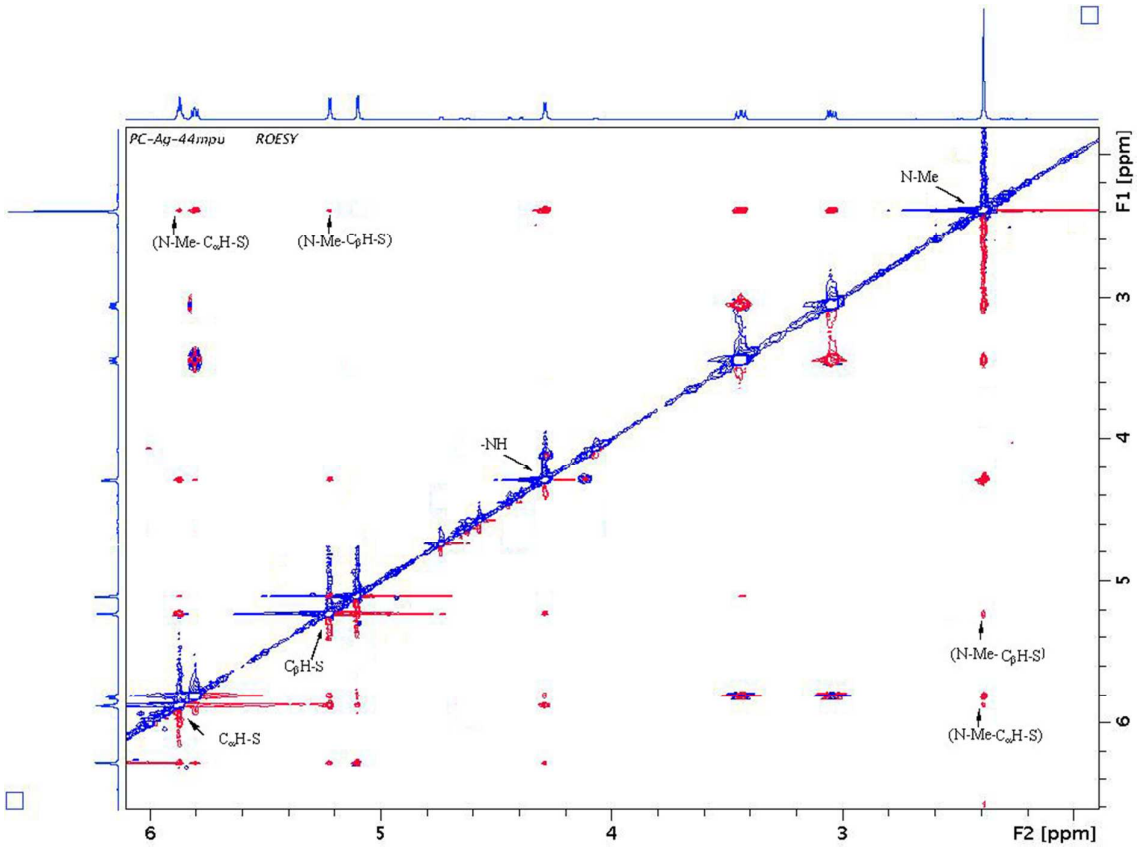
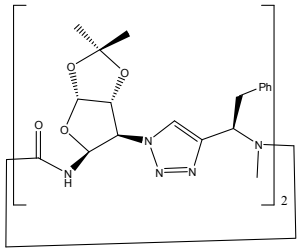


Fig.13: Selected region of the ROESY spectrum of self-assembled macrocycle **16a**, showing dimer formation by cross-peaks of N-Me with *S*-CH_α as well as *S*-CH_β (600 MHz, 298K, 2:3 $CDCl_3$:CCl_4).



Compound 16a

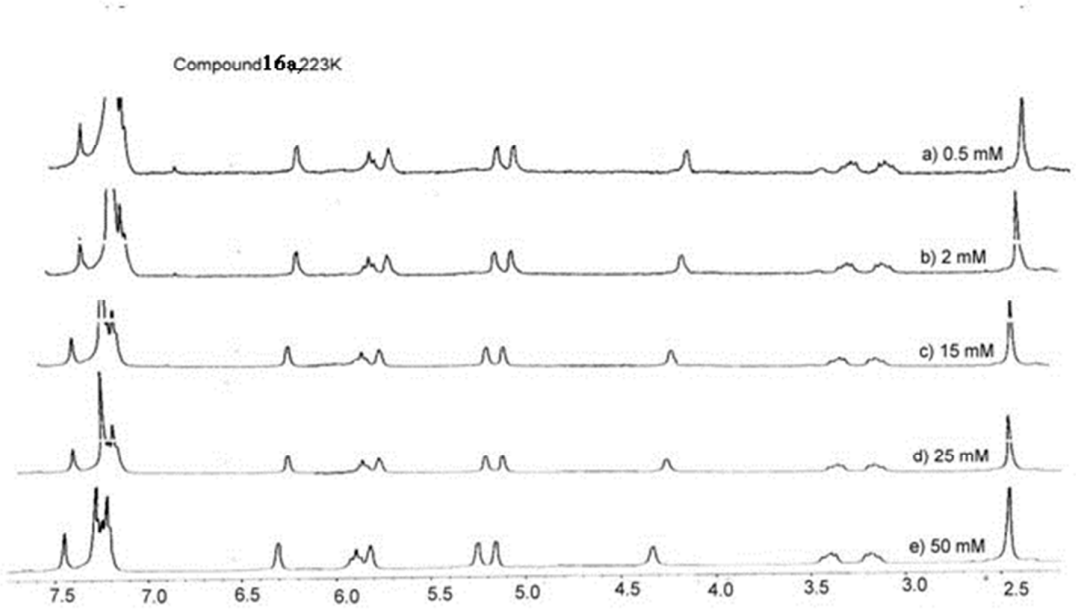


Fig. 14: Concentration dependence of chemical shifts of ureido-NH proton of **16a** in $CDCl_3$ at 223 K (300 MHz).

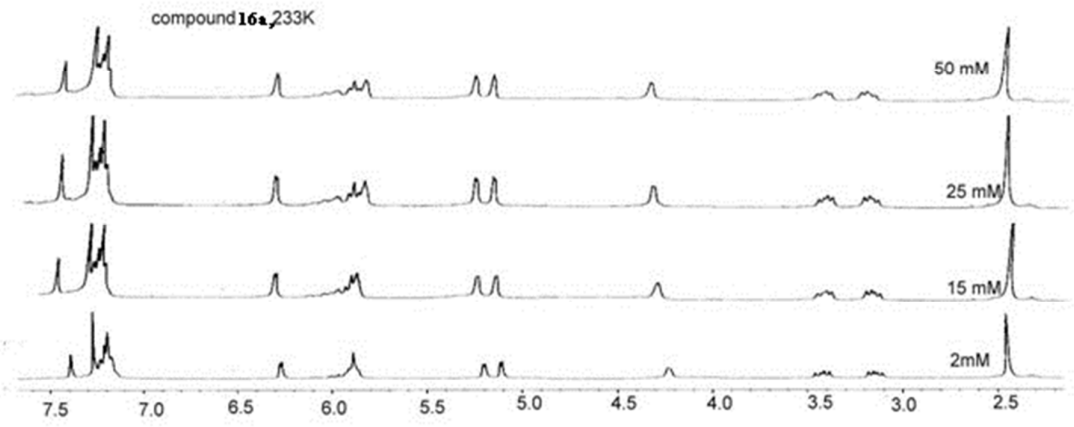


Fig. 15: Concentration dependence of chemical shifts of ureido-NH proton of **16a** in $CDCl_3$ at 233 K (300 MHz).

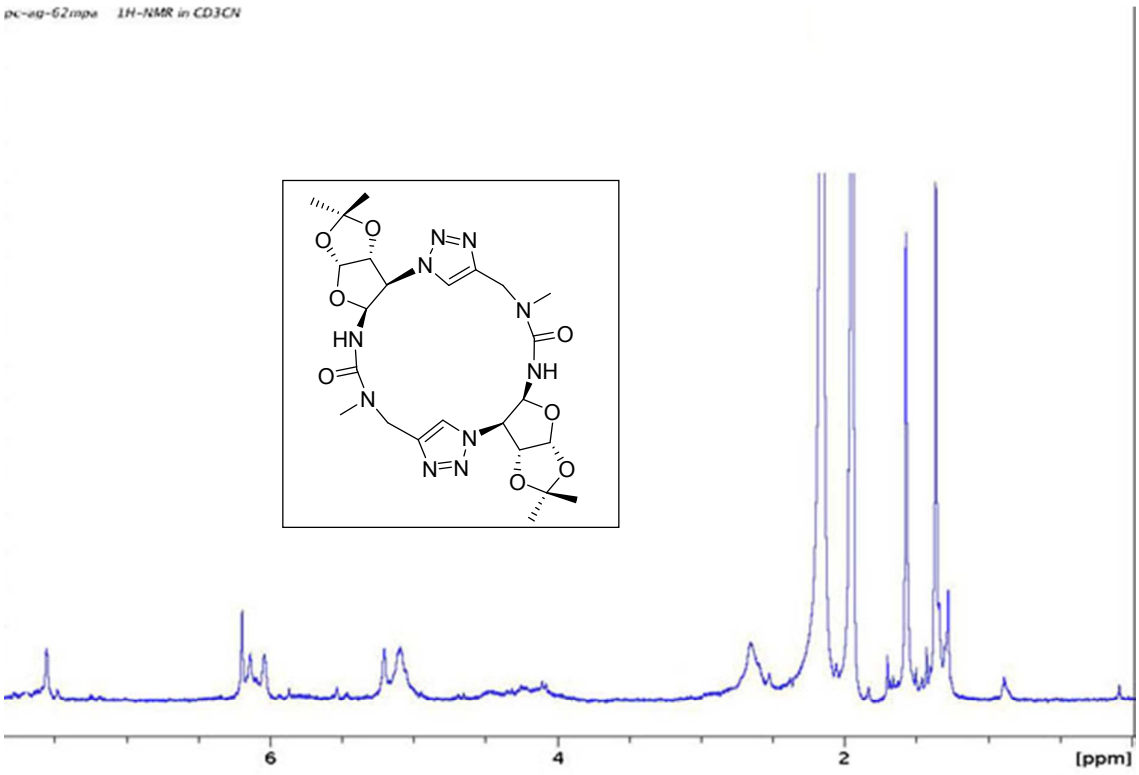


Fig. 16: ^{1}H NMR of pseudo-cyclo-β-peptide **16b** (2 mM) in CD_3CN at 298 K and 600 MHz.

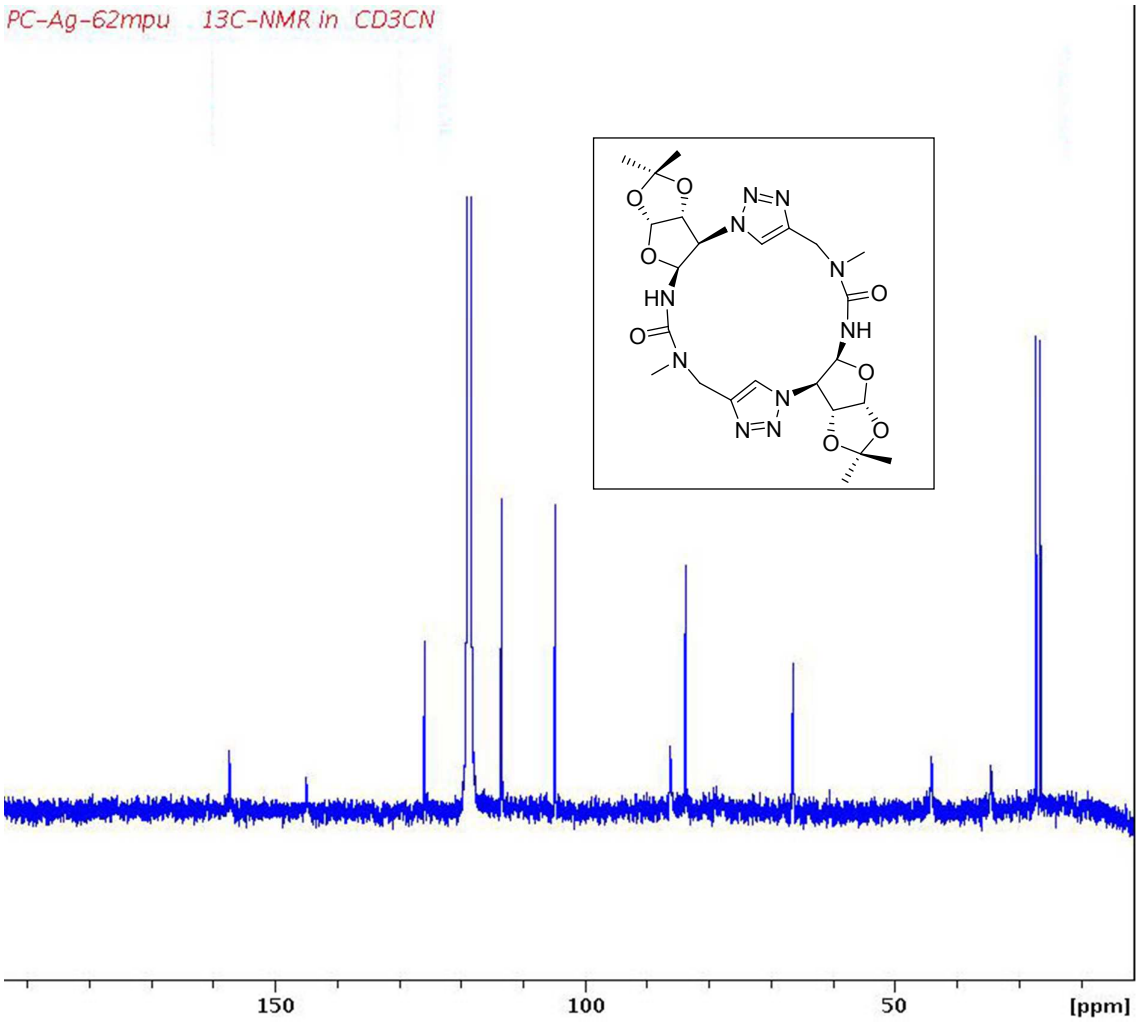


Fig. 17: ^{13}C NMR of pseudo-cyclo-β-peptide **16b** (2 mM) in CD_3CN at 298K and 600 MHz.

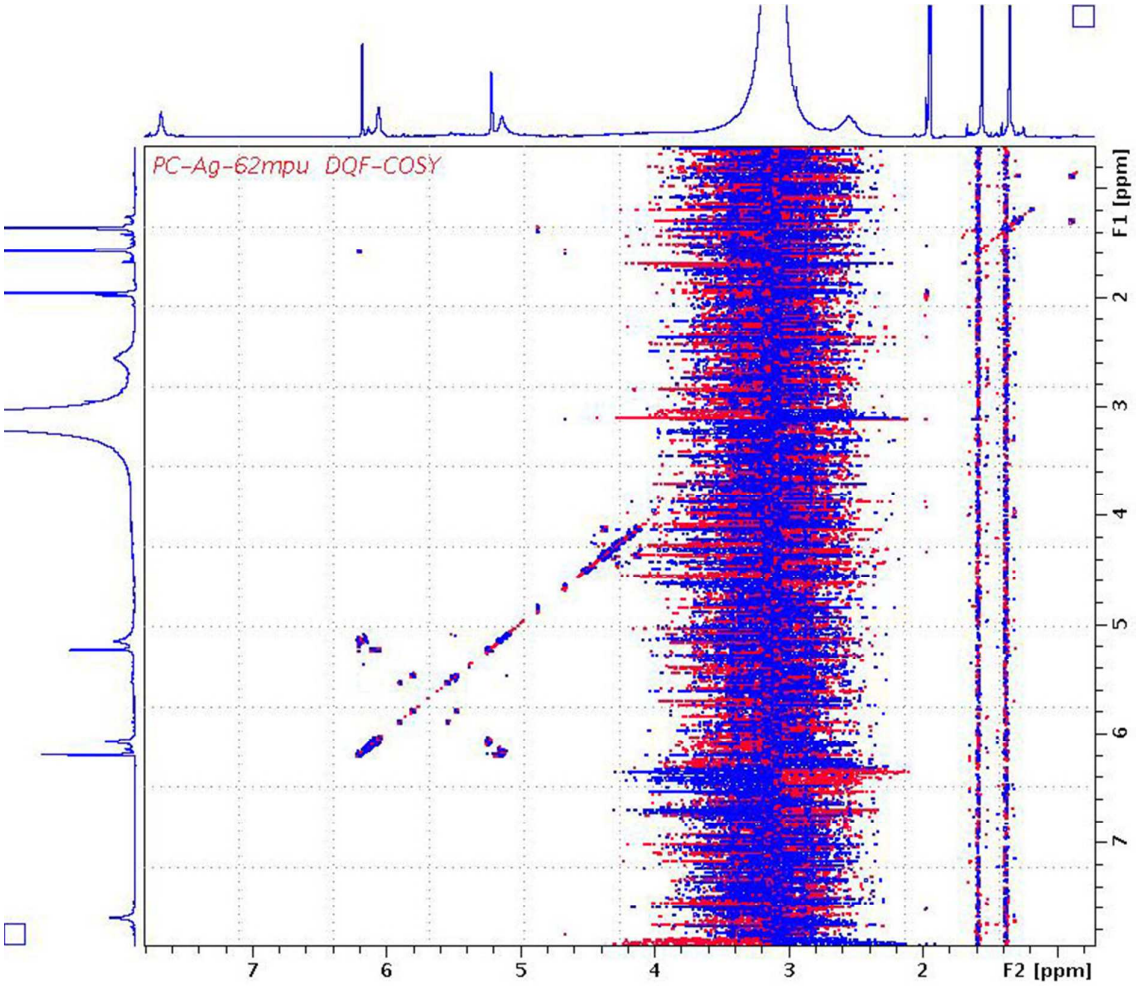


Fig. 18: 1H-1H DQF-COSY spectrum of **16b** (2 mM) in CD_3CN (2% H_2O) at 298K.

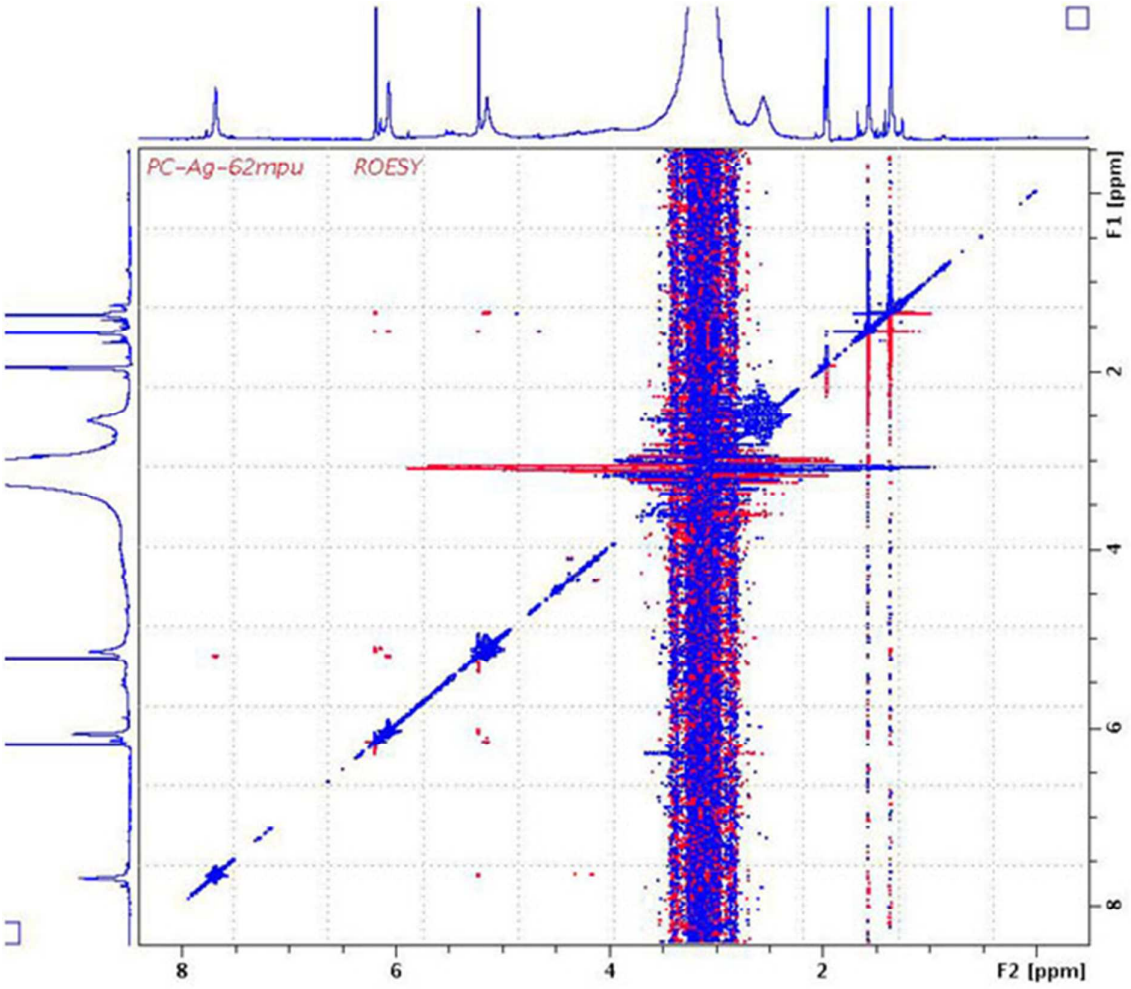


Fig. 19: ^{1}H-^{1}H ROESY spectrum of **16b** (2 mM) in CD_3CN (2% H_2O) at 298K.

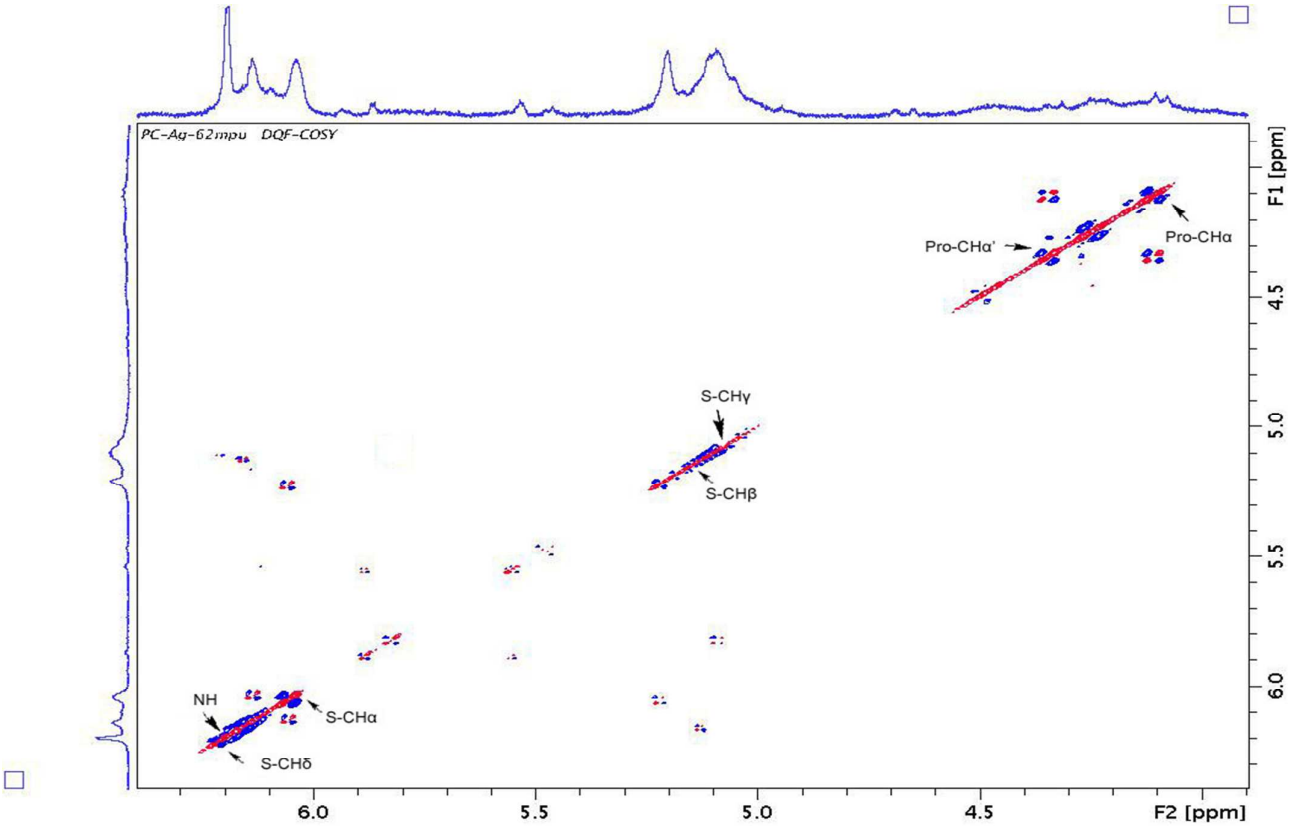


Fig. 20: Partial ^{1}H-^{1}H DQF-COSY spectrum of pseudo-cyclo-β-peptide **16b** (2 mM) in CD_3CN (2% H_2O) at 298K in 600 MHz.

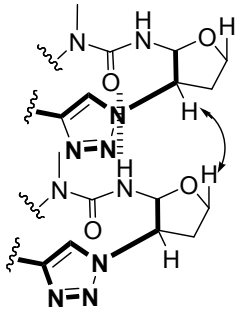


Fig. 21: Triazole/urea β-conformation of **16b** and their parallel stacking via (β,β) H-bonding detected by Roesy spectrum (see **Fig. 22**)

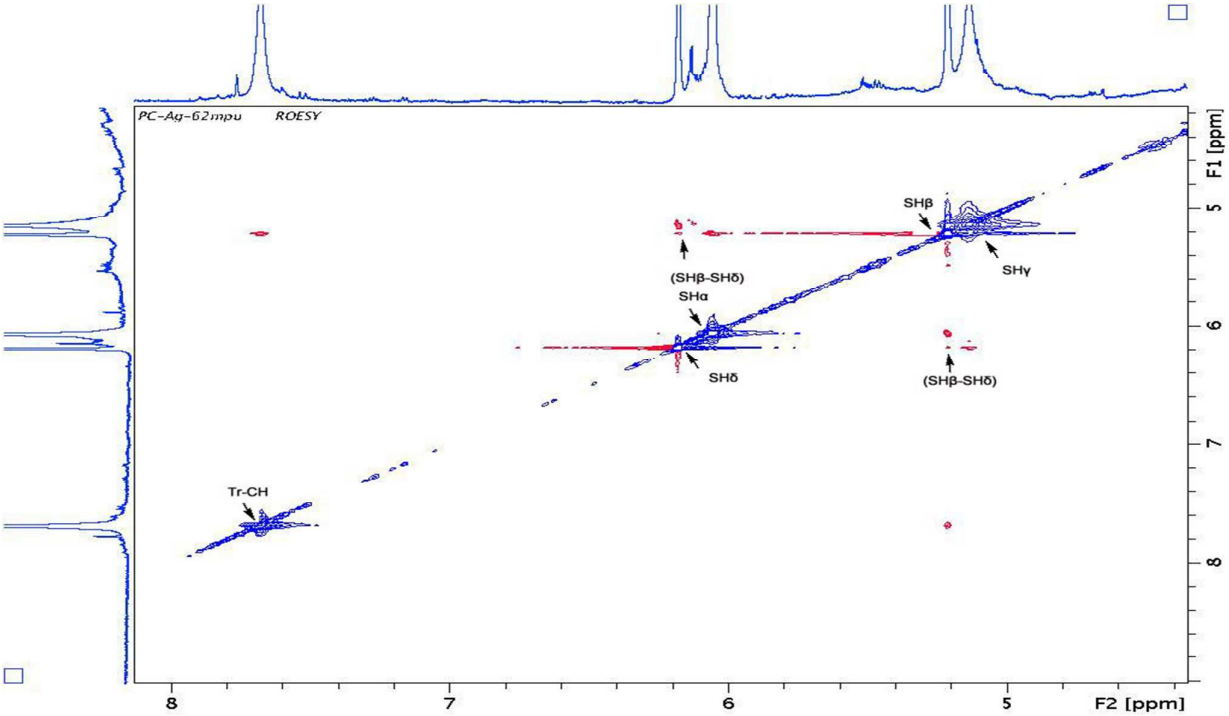


Fig. 22: Partial ^{1}H-^{1}H Roesy spectrum of pseudo-cyclo-β-peptide **16b** (2 mM) in CD_3CN (2% H_2O) at 298 K and 600 MHz

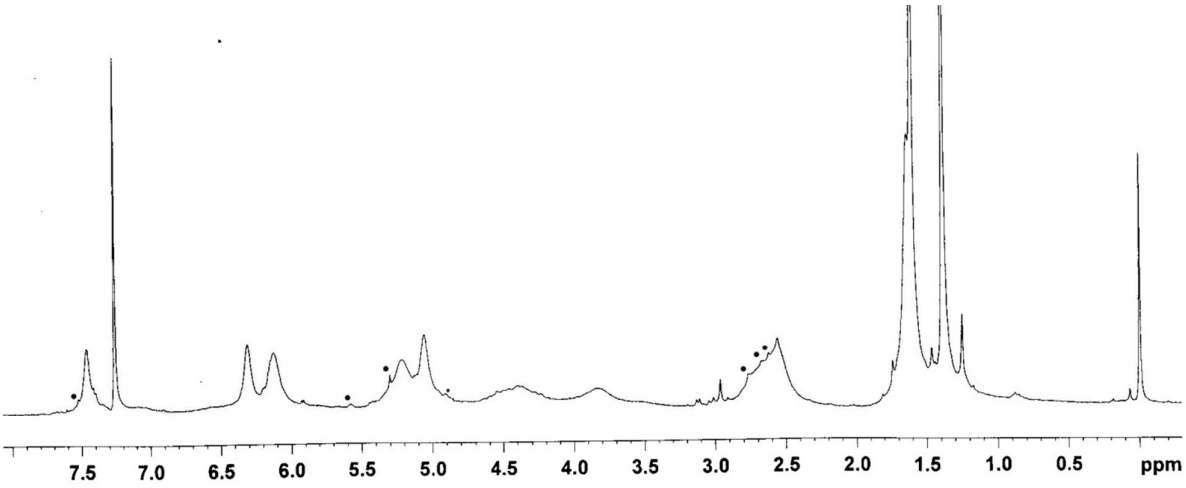


Fig. 23: ^{1}H NMR spectrum of **16b** (15 mM) in $CDCl_3$ at 298K showing significant broadening of all protons due to intermolecular hydrogen bonding arising due to several supramolecular species existing in exchange on NMR time scale.

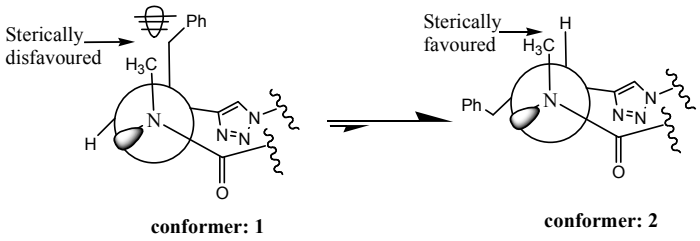


Fig. 24: Possible conformers of macrocyles derived from D-phenyl alanine (conformer 2), and L-amino acid based product (conformer 1); the latter is disfavoured due to axial orientation of the side chain.

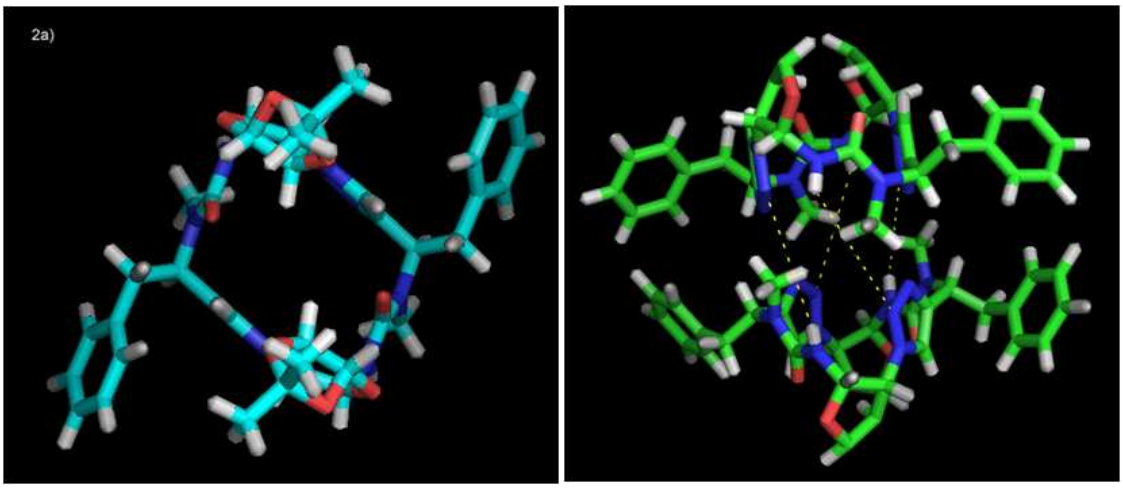


Fig. 25: Energy minimized structure of **16a** and typical side view (excluding isopropylidene moiety) of dimer formation by molecular modelling.

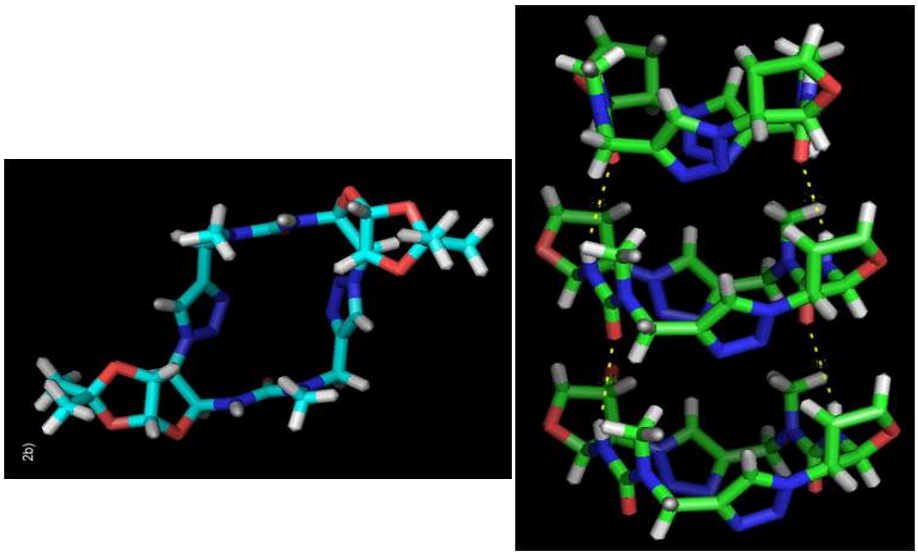


Fig. 26: Energy minimized conformation of **16b** and typical side view (excluding isopropylidene moiety) of dimer formation by molecular modelling.

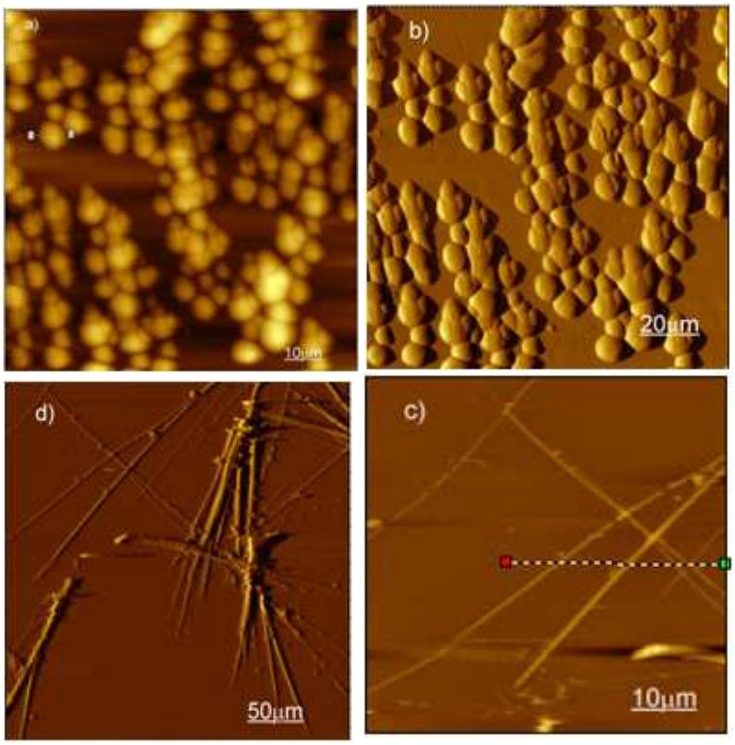


Fig. 27: AFM images in (2:3) $CDCl_3$:CCl_4 for **16a** (a and b) and (4:1) CH_3CN:H_2O for **16b** (c and d).

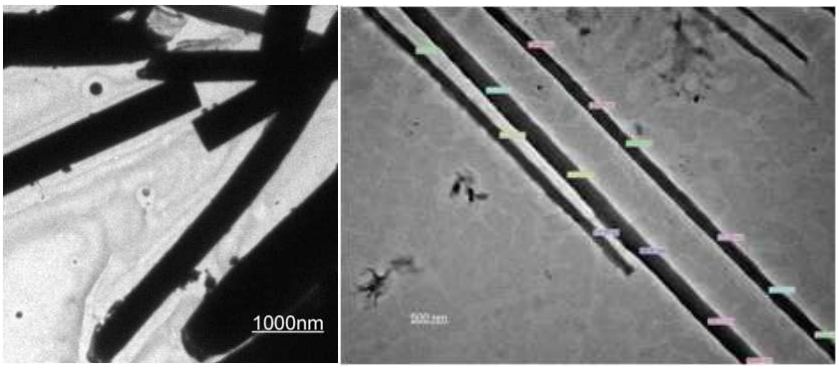


Fig. 28: TEM images of peptidomimetic macrocycle **16b** in CH_3CN:H_2O (4:1)

Coordinates of compound 16a derived by molecular modelling:

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ATOM      1  C9  CPEN    1C      4.539   3.572 -10.219  1.00  0.00
C
ATOM      2  C92 CPEN    1C      5.442   2.368  -9.872  1.00  0.00
C
ATOM      3  N91 CPEN    1C      3.074   3.289 -10.032  1.00  0.00
N
ATOM      4 1CN9 CPEN    1C      2.175   3.359 -11.221  1.00  0.00
C
ATOM      5 2C91 CPEN    1C      2.531   3.042  -8.738  1.00  0.00
C
ATOM      6 2N91 CPEN    1C      1.140   2.871  -8.650  1.00  0.00
N
ATOM      7 2O91 CPEN    1C      3.239   2.985  -7.751  1.00  0.00
O
ATOM      8  H9  CPEN    1C      4.684   3.718 -11.306  1.00  0.00
H
ATOM      9 1H92 CPEN    1C      5.416   2.149  -8.794  1.00  0.00
H
ATOM     10 2H92 CPEN    1C      5.049   1.459 -10.360  1.00  0.00
H
ATOM     11 H912 CPEN    1C      0.644   2.861  -9.511  1.00  0.00
H
ATOM     12 1HN9 CPEN    1C      1.617   2.417 -11.343  1.00  0.00
H
ATOM     13 1HN9 CPEN    1C      1.452   4.183 -11.112  1.00  0.00
H
ATOM     14 1HN9 CPEN    1C      2.731   3.532 -12.157  1.00  0.00
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N
ATOM     18  C3  PYRO    1B      2.774  10.100  -9.032  1.00  0.00
C
ATOM     19  C32 PYRO    1B      3.487   8.843  -6.958  1.00  0.00
C
ATOM     20  N32 PYRO    1B      4.807   9.119  -7.350  1.00  0.00
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ATOM     21 2O32 PYRO    1B      3.247   8.209  -5.948  1.00  0.00
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ATOM     22  H2  PYRO    1B      0.417   9.518  -8.302  1.00  0.00
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ATOM     23 1H22 PYRO    1B      0.776  10.710  -6.161  1.00  0.00
H
ATOM     24 2H22 PYRO    1B      0.973   9.188  -5.320  1.00  0.00
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ATOM     25 HN32 PYRO    1B      4.914   9.702  -8.148  1.00  0.00
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H
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ATOM     32  C13 CPEN    1D      6.295   6.984  -6.861  1.00  0.00
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ATOM     39  C13 CPEN    1E      7.416   5.987  -3.979  1.00  0.00
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ATOM     41  C1  CPEN    1E      7.050   5.586  -2.533  1.00  0.00
C
ATOM     42  O33 CPEN    1E      7.393   7.409  -4.142  1.00  0.00
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ATOM     45 1H   CPEN    1E      9.127   5.764  -5.321  1.00  0.00
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ATOM     46 1H1  CPEN    1E      7.743   6.049  -1.814  1.00  0.00
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ATOM     47 2H1  CPEN    1E      6.027   5.902  -2.274  1.00  0.00
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ATOM     52  N4  PYRO    1G      0.208   6.940  -8.754  1.00  0.00
N
ATOM     53  N5  PYRO    1G      0.057   5.681  -8.376  1.00  0.00
N
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H
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C
ATOM     57  C3  PYRO    1H      5.012   4.840  -9.546  1.00  0.00
C
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C
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C
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C
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O
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H
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ATOM     70  O2  CPEN    1       1.105   4.165  -4.056  1.00  0.00
O
ATOM     71  C3  CPEN    1       0.554   3.021  -3.394  1.00  0.00
C
ATOM     72  C31 CPEN    1       1.519   2.541  -2.288  1.00  0.00
C
ATOM     73  C1  CPEN    1      -0.793   3.402  -2.756  1.00  0.00
C
ATOM     74  O33 CPEN    1       0.314   1.988  -4.356  1.00  0.00
O
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H
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ATOM     80 3H1  CPEN    1      -1.502   3.753  -3.523  1.00  0.00
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C
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ATOM     83  C3  BENZ    1J     -1.612   8.585  -5.236  1.00  0.00
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ATOM     84  C4  BENZ    1J     -1.022   9.533  -6.076  1.00  0.00
C
ATOM     85  C5  BENZ    1J     -1.865  10.382  -6.799  1.00  0.00
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ATOM     88  H2  BENZ    1J     -3.431   7.722  -4.469  1.00  0.00
H
ATOM     89  H3  BENZ    1J     -0.977   7.920  -4.654  1.00  0.00
H
ATOM     90  H5  BENZ    1J     -1.427  11.136  -7.450  1.00  0.00
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ATOM     91  H6  BENZ    1J     -3.888  10.957  -7.276  1.00  0.00
H
ATOM     92  C1  BENZ    1I      9.191   3.155  -9.820  1.00  0.00
C
ATOM     93  C2  BENZ    1I      9.533   3.026 -11.170  1.00  0.00
C
ATOM     94  C3  BENZ    1I      8.544   2.674 -12.097  1.00  0.00
C
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C
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H
```

Coordinates of compound 16b derived by molecular modelling:

```
ATOM      1  C9  CPEN    1C      5.321   4.504  -8.368  1.00  0.00
C
ATOM      2 1H9  CPEN    1C      6.216   3.887  -8.183  1.00  0.00
H
ATOM      3 2H9  CPEN    1C      4.874   4.076  -9.283  1.00  0.00
H
ATOM      4  C   CPEN    1D      7.229  10.406  -7.897  1.00  0.00
C
ATOM      5  N   CPEN    1D      5.950  10.590  -7.174  1.00  0.00
N
ATOM      6  C1  CPEN    1D      4.706  10.536  -7.812  1.00  0.00
C
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ATOM      7  N1  CPEN    1D      3.549  10.671  -6.998  1.00  0.00
N
ATOM      8  C2  CPEN    1D      3.658  10.854  -5.523  1.00  0.00
C
ATOM      9  C3  CPEN    1D      2.190  10.524  -7.607  1.00  0.00
C
ATOM     10  O   CPEN    1D      4.623  10.379  -9.017  1.00  0.00
O
ATOM     11  O1  CPEN    1D      8.196  11.200  -7.194  1.00  0.00
O
ATOM     12  C4  CPEN    1D      8.921  10.292  -6.353  1.00  0.00
C
ATOM     13  C5  CPEN    1D      7.802   8.917  -7.948  1.00  0.00
C
ATOM     14  C6  CPEN    1D      8.386   8.874  -6.512  1.00  0.00
C
ATOM     15  HC  CPEN    1D      7.148  10.849  -8.902  1.00  0.00
H
ATOM     16  HN  CPEN    1D      5.961  10.789  -6.201  1.00  0.00
H
ATOM     17 1H2  CPEN    1D      2.668  10.951  -5.049  1.00  0.00
H
ATOM     18 2H2  CPEN    1D      4.165   9.992  -5.061  1.00  0.00
H
ATOM     19 3H2  CPEN    1D      4.230  11.765  -5.285  1.00  0.00
H
ATOM     20 1H3  CPEN    1D      1.469  11.136  -7.041  1.00  0.00
H
ATOM     21 2H3  CPEN    1D      2.193  10.965  -8.619  1.00  0.00
H
ATOM     22  H4  CPEN    1D      8.915  10.699  -5.328  1.00  0.00
H
ATOM     23  H5  CPEN    1D      8.651   8.910  -8.653  1.00  0.00
H
ATOM     24  H6  CPEN    1D      7.600   8.591  -5.793  1.00  0.00
H
ATOM     25  O1  CPEN    1E      9.509   8.029  -6.259  1.00  0.00
O
ATOM     26  C13 CPEN    1E     10.663   8.870  -6.388  1.00  0.00
C
ATOM     27 1C13 CPEN    1E     11.611   8.282  -7.448  1.00  0.00
C
ATOM     28  C1  CPEN    1E     11.402   8.949  -5.035  1.00  0.00
C
ATOM     29  O33 CPEN    1E     10.259  10.172  -6.826  1.00  0.00
O
ATOM     30 1H13 CPEN    1E     12.501   8.920  -7.570  1.00  0.00
H
ATOM     31 H    CPEN    1E     11.944   7.271  -7.164  1.00  0.00
H
ATOM     32 1H   CPEN    1E     11.107   8.211  -8.426  1.00  0.00
H
ATOM     33 1H1  CPEN    1E     12.287   9.599  -5.115  1.00  0.00
H
ATOM     34 2H1  CPEN    1E     10.751   9.354  -4.245  1.00  0.00
H
```

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ATOM     35 3H1  CPEN    1E     11.733   7.946  -4.721  1.00  0.00
H
ATOM     36  N1  PYRO    1H      6.883   7.814  -8.358  1.00  0.00
N
ATOM     37  C2  PYRO    1H      6.829   6.559  -7.826  1.00  0.00
C
ATOM     38  C3  PYRO    1H      5.787   5.920  -8.594  1.00  0.00
C
ATOM     39  N4  PYRO    1H      5.271   6.784  -9.540  1.00  0.00
N
ATOM     40  N5  PYRO    1H      5.978   7.884  -9.327  1.00  0.00
N
ATOM     41  H2  PYRO    1H      7.458   6.206  -7.021  1.00  0.00
H
ATOM     42  C   CPEN    1F      0.131   6.099  -6.198  1.00  0.00
C
ATOM     43  C1  CPEN    1F      0.235   6.122  -4.651  1.00  0.00
C
ATOM     44  C2  CPEN    1F     -0.181   4.701  -4.291  1.00  0.00
C
ATOM     45  C3  CPEN    1F      0.664   4.611  -6.422  1.00  0.00
C
ATOM     46  N   CPEN    1F      2.130   4.422  -6.335  1.00  0.00
N
ATOM     47  C4  CPEN    1F      2.969   4.487  -7.452  1.00  0.00
C
ATOM     48  N5  CPEN    1F      4.365   4.346  -7.228  1.00  0.00
N
ATOM     49  C52 CPEN    1F      4.912   4.144  -5.857  1.00  0.00
C
ATOM     50  O   CPEN    1F      2.516   4.660  -8.570  1.00  0.00
O
ATOM     51  O1  CPEN    1F      0.100   3.806  -5.377  1.00  0.00
O
ATOM     52  H1  CPEN    1F      1.257   6.398  -4.345  1.00  0.00
H
ATOM     53  H2  CPEN    1F      0.272   4.281  -3.378  1.00  0.00
H
ATOM     54  HN  CPEN    1F      2.546   4.210  -5.457  1.00  0.00
H
ATOM     55 1H52 CPEN    1F      6.010   4.044  -5.866  1.00  0.00
H
ATOM     56 2H52 CPEN    1F      4.662   4.999  -5.209  1.00  0.00
H
ATOM     57 3H52 CPEN    1F      4.500   3.228  -5.404  1.00  0.00
H
ATOM     58  H3  CPEN    1F      0.295   4.181  -7.366  1.00  0.00
H
ATOM     59  HC  CPEN    1F     -0.942   6.112  -6.460  1.00  0.00
H
ATOM     60  N1  PYRO    1       0.781   7.210  -6.955  1.00  0.00
N
ATOM     61  C2  PYRO    1       1.066   8.458  -6.484  1.00  0.00
C
ATOM     62  C3  PYRO    1       1.668   9.109  -7.624  1.00  0.00
C
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ATOM     63  N4  PYRO    1       1.715   8.259  -8.710  1.00  0.00
N
ATOM     64  N5  PYRO    1       1.170   7.154  -8.223  1.00  0.00
N
ATOM     65  H2  PYRO    1       0.854   8.799  -5.481  1.00  0.00
H
ATOM     66  C   CPEN    1B     -1.758   6.118  -3.543  1.00  0.00
C
ATOM     67  C1  CPEN    1B     -3.073   6.717  -4.074  1.00  0.00
C
ATOM     68  C2  CPEN    1B     -1.831   6.020  -2.004  1.00  0.00
C
ATOM     69  O   CPEN    1B     -1.590   4.823  -4.130  1.00  0.00
O
ATOM     70  O1  CPEN    1B     -0.662   6.960  -3.922  1.00  0.00
O
ATOM     71 1H1  CPEN    1B     -3.245   7.723  -3.660  1.00  0.00
H
ATOM     72 2H1  CPEN    1B     -3.048   6.801  -5.172  1.00  0.00
H
ATOM     73 3H1  CPEN    1B     -3.928   6.078  -3.802  1.00  0.00
H
ATOM     74 1H2  CPEN    1B     -1.988   7.018  -1.564  1.00  0.00
H
ATOM     75 2H2  CPEN    1B     -2.663   5.368  -1.696  1.00  0.00
H
ATOM     76 3H2  CPEN    1B     -0.900   5.607  -1.583  1.00  0.00
H
```