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PII: S0040-4020(15)30071-5

DOI: 10.1016/j.tet.2015.09.043

Reference: TET 27140

To appear in: *Tetrahedron*

Received Date: 29 July 2015

Revised Date: 18 September 2015

Accepted Date: 21 September 2015

Please cite this article as: Verma RP, Shandilya A, Haridas V, Peptide dendrimers with designer core for directed self-assembly, *Tetrahedron* (2015), doi: 10.1016/j.tet.2015.09.043.

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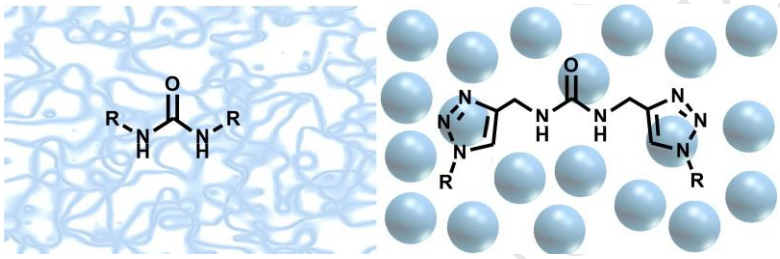

Tetrahedron
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Peptide dendrimers with designer core for directed self-assembly

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ARTICLE INFO

Article history:
Received
Received in revised form
Accepted
Available online

Keywords:
Peptide
Dendrimer
Click reaction
Triazole
Urea

ABSTRACT

A series of designer peptide dendrimers with urea and urea-triazole cores were synthesized. Urea cored dendrimers assembled into fibrillar morphology, while dendrimers with urea-triazole core assembled into vesicular morphology. The core-dependent self-assembly behaviour is studied by ultramicroscopy, X-ray crystallography and supported by molecular dynamics simulation.

1. Introduction

Peptide dendrimers serve as models for proteins and therefore have innumerable possibilities for applications in the area of biology and nanotechnology. Peptide dendrimers are particularly attractive because of the use of amino acid building blocks and their potential to self-assemble due to the presence of several peptide bonds in their structure. The synthesis and purification of peptide dendrimers are difficult due to the presence of a large number of functional groups on their surface and their branched architecture. The challenges involved in the synthesis and their several applications make peptide dendrimers, very interesting candidates for the chemists. Over the last two decades, there have been significant developments in the area of functional dendrimers.[1-3] The design of functional dendrimers is a challenge, since the central core and surface functional groups are of critical in determining the topology and properties of these branched molecules.[4-5] Apart from this, the stitching of two large peptide fragments without racemization using a clean reaction poss a challenge.[6-7]

Here, in this paper, we report the urea and urea-triazole as central cores in the design of self-assembling peptide dendrimers. We envisioned that a carbonyl unit is one of the smallest structural entity that can be used for linking two peptide dendrons through their N-termini. The resultant linkage of dendrons through N-terminals by a carbonyl unit results in a urea core which has additional benefits,

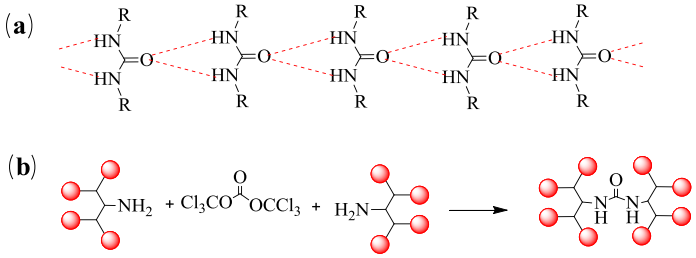

Figure 1: (a) Extended hydrogen bonding present in urea-type molecules (b) Cartoon representation of the synthesis of urea cored peptide dendrimers.

such as strong intrinsic self-assembly and anionic guest binding properties.[8-9] The urea linkage can arrange the dendrimers in a supramolecular arrangement as a result of the urea α-type hydrogen bonding pattern (Fig. 1a).[10] Hence urea unit is one of the minimal and benign structural entities that can be envisaged as a central core for the design of self-assembling dendrimers.

In the second design, we introduced a urea-triazole unit with the notion that it will induce a curvature to the overall assembly (Fig. 3a). The hydrogen bonding ability of urea along with the pentagonal shape of triazole will induce a unique self-assembling pattern. Cycloaddition of azides and alkynes in the presence of Cu(I) salt to give triazoles is an effective synthetic strategy with several applications.[11]

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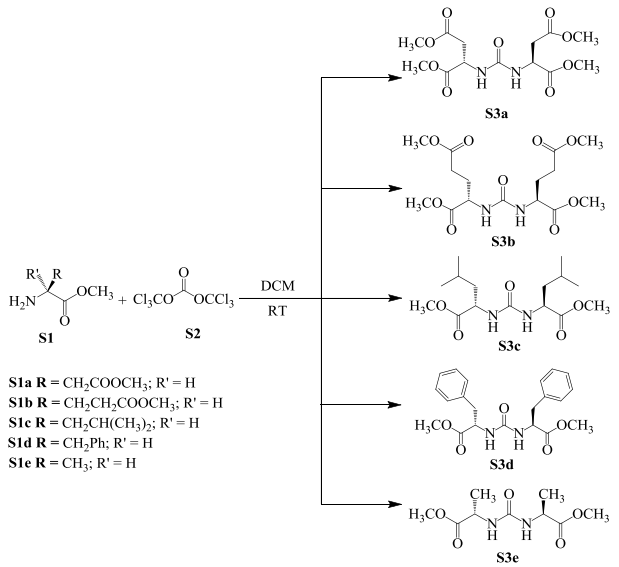
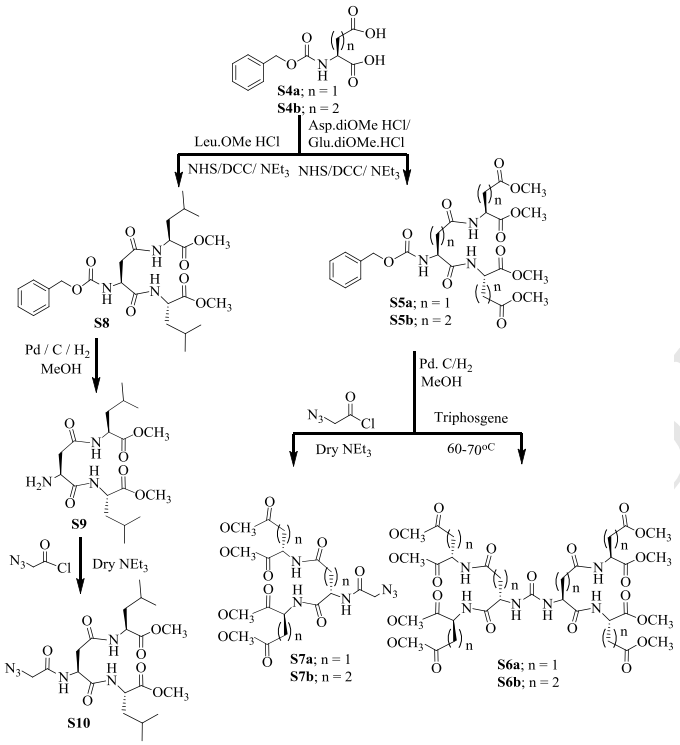


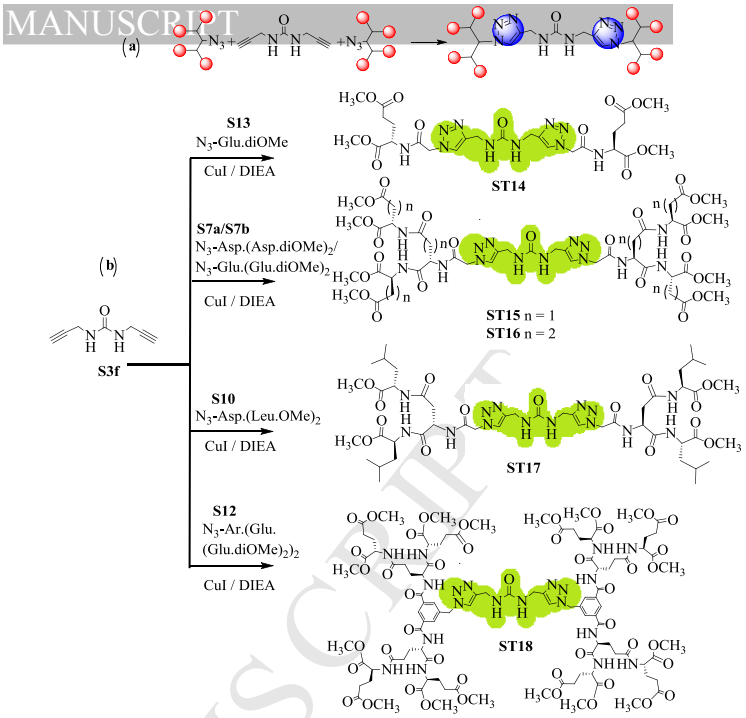
Scheme 1. Synthesis of first generation urea cored dendrimers **S3a-e**.



Scheme 2. Synthesis of dendrons **S7a-b**, **S10** and second generation urea dendrimers **S6a-b**.

2. Results and Discussion

The first generation urea-based dendrimers were synthesized by reacting several C-protected amino acids with triphosgene in dichloromethane (Scheme 1). Compounds **S3a-e** (Scheme 1) were obtained in ~ 60-64 % yield by reacting the corresponding amino acid methyl esters with triphosgene. Glutamic acid and aspartic acid are good choices for the synthesis of peptide dendrimers because these residues have additional carboxylic acid group in its structure; hence, can act as branching units.[6] The N^{α} Z-Glu/Asp acids **S4a**/**S4b** were reacted with the dimethyl esters of Asp/Glu to produce dendrons with four methyl esters on the surface **S5a**/**S5b** (Scheme 2). In the similar way, Asp-Leu based dendron **S8** was also synthesized. Deprotection of dendrons **S5a-b** using Pd/C/H_2 followed by treatment with triphosgene yielded urea cored dendrimers (**S6a-b**) in ~ 68-70 % yield (Scheme 2). The bidirectional linking ability, easy reaction and atom economy are attributes of this reaction.



Scheme 3. (a) Cartoon representation of synthesis of urea-triazole cored peptide dendrimers, (b) synthesis of first (**ST14**) and second (**ST15-ST18**) generation urea-triazole cored peptide dendrimers.

In the next step, we have undertaken the synthesis of urea-triazole cored peptide dendrimers. Dialkyne units on both sides of urea were introduced by reacting propargyl amine with triphosgene to generate urea-based dialkyne **S3f**. In order to equip dendrons for the dipolar cycloaddition reaction, an azide group was attached to the N-terminus of the dendron. The N-terminal benzyloxycarbonyl group (Z) of **S5a**, **S5b** and **S8** was deprotected using H_2/Pd/C and coupled to azidoacetyl chloride to generate the dendrons **S7a**, **S7b** and **S10** in ~70 % yield (Scheme 2). Urea cored dialkyne **S3f** was reacted with dendrons equiped with azide to generate a series of urea-triazole cored dendrimers **ST14-ST18** (Scheme 3).

Higher generation dendrimer **ST18** was synthesized to demonstrate the versatility of this approach (Scheme 3). The reaction of H_2N-Glu.(Glu.diOME)(Glu.diOME) with 5-azidomethylbenzene-1,3-dicarbonyldichloride afforded the dendron carrying an azide functionality **S12** (Scheme S1, Supplementary data).[12] This **S12** upon reaction dialkyne afforded **ST18**. The post reaction work up afforded reasonably pure compounds and further purification was done by passing the compounds through small silica gel column to afford pure dendrimers.

We envisioned that the peptide dendrimers with a urea core will assemble as a result of urea-type hydrogen bonds that may lead to fibrillar morphology.[13] Dendrimers with urea and urea-triazole cores were evaluated for their self-assembling properties by X-ray crystallography and various ultramicroscopic techniques like Scanning Electron Microscopy (SEM), Transmission Electron Microscopy (TEM) and Atomic Force Microscopy (AFM) (Figs. 2-4 and Figs. S1-S5, Supplementary data). The X-ray structures revealed that **S3a**, **S3b** and **S3e** form supramolecular arrays as a result of intermolecular hydrogen bonding between the urea core (Table S1, Supplementary data). The first generation dendrimers (**S3a**, **S3b** and **S3e**) were crystallized from 1:1 $CHCl_3$+EtOAc at room temperature (Tables S2-S4, Supplementary data). X-ray structures revealed that the molecules are arranged in a contiguous sheet assembly held together by six-membered hydrogen bonded ring between the urea COs and NHs (Figs. S2-S5, Supplementary data).

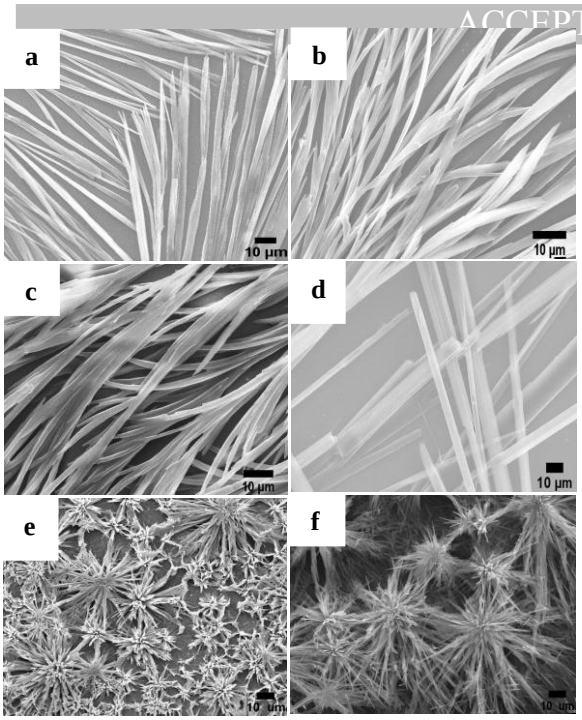


Figure 2: SEM images of (a) **S3a** (b) **S3b** (c) **S3c** (d) **S3e** (e) **S6a** and (f) **S6b**.

Initially, urea cored first generation dendrimers **S3a-e** were studied using ultramicroscopy. SEM images of **S3a-d** showed tape-like self-assembly, while **S3e** showed rigid flat-tape morphology in $CHCl_3$+MeOH (Fig. 2a-c, 2d and Fig. S1a, Supplementary data). The widths of individual tapes were in the range of ~ 1-10 µm. Self-assembly of dendrimers of varying size were investigated in order to study the effect of molecular size and shape on the self-assembling pattern.[14] The long tape-like structure observed in the first generation dendrimers (**S3a-e**) might be arising due to intermolecular association of molecules from hydrogen bonds. X-ray crystallographic analysis also revealed an extended assembly. The higher generation urea cored dendrimers (**S6a-b**) revealed different morphological features compared to first generation dendrimers. Interestingly, higher generation dendrimers (**S6a-b**) showed fibers ~ 300-500 nm which were bundled together to form a flower-like morphology in $CHCl_3$+MeOH (Fig. 2e-f). Higher generation dendrimers **S6a** and **S6b** showed fibrillar, but flower like assembly, and is attributed to the fact that the bulky dendron on both sides of the core may sterically disallow extended arrangement as observed in the lower generation dendrimers (Fig. 2e-f).

We also envisioned that dendrimers with a self-assembling core might gelate organic solvents due to their large size, surface area and hydrogen bonding capabilities.[15] Gels are promising materials for several biomedical applications.[16] Dendritic gels can be used for controlled release of molecules, hence useful in drug delivery applications.Therefore, all the urea cored dendrimers were screened for gelation in organic solvents. It was found that the second generation dendrimers **S6a** and **S6b** both showed gelation in organic solvents. It is noteworthy that peptide dendrimers **S6a-b** displayed gelling properties, when hexane was slowly added to homogeneous solutions of **S6a** and **S6b** in chloroform separately. Gelation ability of the dendrimers was tested in various solvents by the vial inversion method (Fig. 3b, inset, Table S5, Supplementary data). The gels of **S6a-b** were examined by SEM, TEM and AFM. The organgels from **S6a-b** have fibrous morphologies with fibers wound around each other to form entangled ribbon networks with fibers having widths mostly in the range of ~ 0.2-1.0 µm. The fibrous morphology is evident from TEM, AFM and SEM images (Fig. 3a-d).

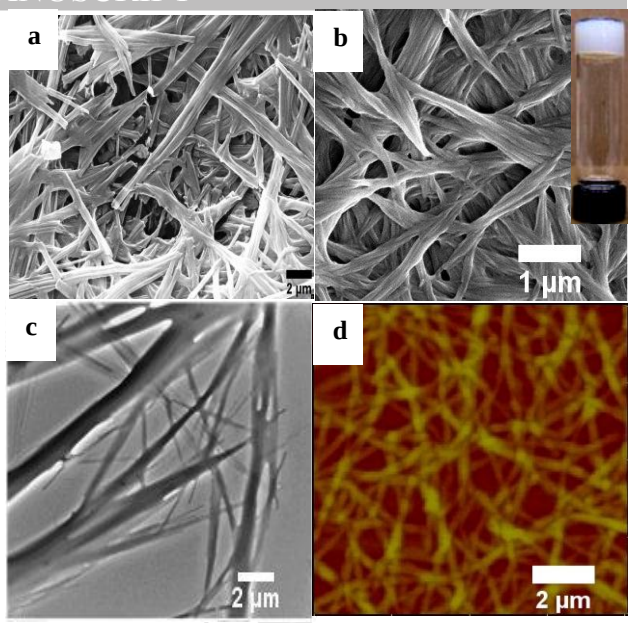


Figure 3: (a) SEM image of gel from **S6a** (b) FE-SEM image of gel from **S6b**, Inset shows photograph of the gel from **S6b** in (7.2 mM of **S6b** chloroform: hexane, 6:4) in an inverted tube (c) TEM image of gel from **S6b** (d) AFM image in tapping mode of gel made from **S6b**.

In the next step, we turned our attention to urea-triazole based dendrimers. The first generation dendrimer **ST14**, the second generation dendrimers **ST15-16**, the leucine containing dendrimer **ST17** and structurally more complex **ST18** were designed and synthesized. SEM, AFM and TEM images of both lower and higher generation Asp/Glu dendrimers **ST14-17** showed vesicular assembly in $CHCl_3$+MeOH (Fig. 4 and Fig. S1b-e Supplementary data). The diameters of the vesicles are in the range of 0.5-2.0 µm. Dendrimer **S18** was insoluble in $CHCl_3$+MeOH, hence ultramicroscopy was not recorded.

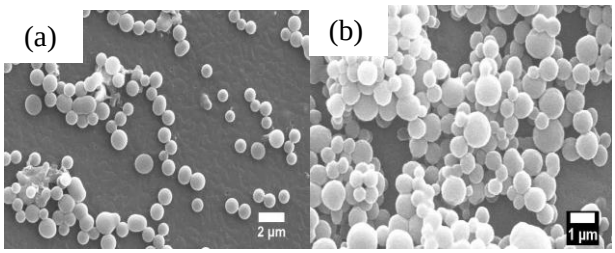


Figure 4: (a) SEM image of **ST14** (b) SEM images of **ST17**.

Molecular Dynamics (MD) simulations using Amber (ff99SB) force field were performed on these dendrimers to rationalize the observed self-assembly behavior.[17] In order to carefully analyze the factors responsible for the unique core-dependent self-assembly, we first investigated the conformation of the core units. The results of molecular modeling revealed that the urea cored and urea-triazole cored dendrimers adopted different conformations (Fig. S6-S7, Supplementary data). The urea cored dendrimers **S3b** and **S6b** adopted an extended conformation (Figs. S6a-b and S7a, Supplementary data), while the urea-triazole cored dendrimers **ST14** and **ST16** showed a turn conformation (Figs. S6c-d and S7b, Supplementary data).

An 80 Å cubic box, containing approximately 4000 solvent molecules ($CHCl_3$ + MeOH) and 300 urea cored molecules **S3b** were randomly placed. After heating, 10 ns of equilibration, and 90 ns of production run resulted in several small and large clusters of these

molecules. The simulation clearly revealed that dendrimers assembled into ordered structures instead of disordered aggregates.

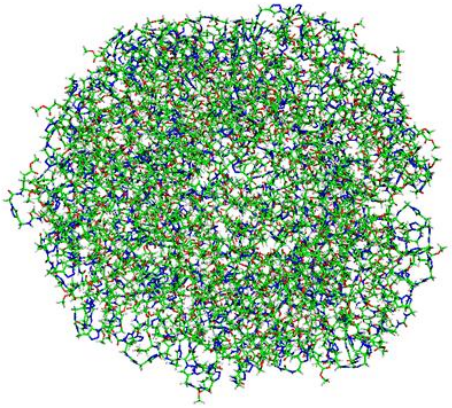


Figure 5: The vesicular assembly of urea-triazole cored dendrimer **ST14** (front view). The fully formed vesicle is presented. The red color represents oxygen, the blue nitrogen and green carbon backbone.

The extended conformation of urea cored molecules facilitated the fibrillar assembly (Fig. S8, Supplementary data). On the other hand the urea-triazole cored molecule **ST14** adopted turn architecture, which further assembled to vesicles with the solvent molecules (mostly MeOH) inside. In a similar way, 400 urea-triazole cored dendrimers **ST14** were fixed inside 100 Å cubic box and were arranged in such a way that nonpolar groups interacted with chloroform and hydrophilic groups interacted with methanol. Interestingly, complete and incomplete vesicles were apparent after 100 ns of MD simulations (Fig. 5 and S9, Supplementary data).

3. Conclusions

We have designed and synthesized a variety of urea and urea-triazole cored dendrimers. Our investigations revealed that the dendrimer core can inculcate unique self-assembly patterns to the dendrimers. Urea-based dendrimers showed fibrous morphology and gelling properties, while urea-triazole based dendrimers displayed a vesicular assembly. Ultra microscopy and X-ray structure analysis provided connvincing evidences and MD simulations supported the experimental findings. The studies presented in this paper points to the fact that core unit has a profound role on self-assembly, hence designer cores will be a new paradigm for the dendrimer design.

4. Experimental Section

4.1 General method of synthesis of urea derivatives of amino acids: S3a-e

A solution of amino acid methyl ester (2.00 mmol) in dry dicholoromethane was added drop-wise to a stirred solution of triphosgene (0.74 mmol) in two phase solution of dry CH_2Cl_2 (20 mL) and saturated solution of $NaHCO_3$ (40 mL). After 5 min. of stirring, a solution of aminoacid methyl ester (2.00 mmol) was added further in to the reactiom mixture and stirred for additional 4 h. The organic phase was then washed with water, dried with anhydrous Na_2SO_4 and evaporated to give crude product, which was purified by column chromatography. ***S3a.*** Yield: 62 %. mp: 95-96 ^oC; $[\alpha]_D$ = + 57.64 (*c* 0.085, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 2.84 (dd, 2H, J = 17.4, 4.5 Hz), 3.04 (dd, 2H, J = 17.4, 4.5 Hz), 3.70 (s, 6H), 3.75 (s, 6H), 4.74-4.80 (m, 2H), 5.59 (d, 2H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 36.9, 49.3, 51.9, 52.7, 156.5, 171.7, 172.1; IR (KBr): 3372, 3003, 2961, 1734, 1631, 1554, 1447, 1355, 1301, 1216, 1160 cm^{-1}; HRMS: Calcd for $C_{13}H_{20}N_2O_9Na$ m/z 371.1067, found m/z 371.1070.

S3b. Yield: 62 %. mp: 110-112 ^oC; $[\alpha]_D$ = + 52.24 (*c* 0.080, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.96 (br s, 2H), 2.16 (br s, 2H), 2.42 (s, 4H), 3.68 (s, 6H), 3.76 (s, 6H), 4.51 (br s, 2H), 5.63 (d, 2H, J = 4.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 27.9, 29.9, 51.7, 52.3, 52.4, 156.8, 173.4, 173.5; IR (KBr): 3282, 3148, 3049, 2955, 1739, 1647, 1594, 1439, 1407, 1217, 1175, 1050 cm^{-1}; HRMS: Calcd for $C_{15}H_{24}N_2O_9Na$ m/z 399.1380, found m/z 399.1386.

S3c. Yield: 60 %. mp: 58-62 ^oC; $[\alpha]_D$ = + 10.00 (*c* 0.20, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz,) δ 0.93 (m, 12H), 1.44-1.73 (m, 6H), 3.73 (s, 6H), 4.45-4.52 (m, 2H), 5.07 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 22.0, 22.8, 24.7, 42.2, 51.5, 52.2, 156.9, 174.9; IR (KBr): 3357, 3136, 2960, 2874, 1754, 1713, 1626, 1575, 1443, 1374, 1277, 1245, 1172, 1097, 1027 cm^{-1}; HRMS: Calcd for $C_{15}H_{29}N_2O_5$ m/z 317.2076, found m/z 317.2108.

S3d. Yield: 66 %. mp: 186-190 ^oC; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.99 (d, 4H, J = 5.7 Hz), 3.62 (s, 6H), 4.80 (q, 2H, J = 13.9 Hz), 5.45 (d, 2H, J = 7.8 Hz), 7.07 (d, 4H, J = 6.6 Hz), 7.17-7.27 (m, 6H); IR (KBr): 3322, 2959, 1741, 1698, 1654, 1533, 1439, 1358, 1319, 1259, 1174, 1020 cm^{-1}; HRMS: Calcd for $C_{21}H_{24}N_2O_5Na$ m/z 407.1577, found m/z 407.1572.

S3e. Yield: 64 %. mp: 186-190 ^oC; $[\alpha]_D$ = + 07.69 (*c* 0.10, $CHCl_3$). ^1H NMR ($CDCl_3$, 300 MHz) δ 1.39 (d, 6H, J = 7.2 Hz), 3.77 (s, 6H), 4.44-4.54 (m, 2H), 5.36 (d, 2H, J = 7.5 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 25.5, 52.4, 56.0, 156.0, 176.9; IR (KBr): 3368, 3336, 2989, 2954, 1738, 1643, 1563, 1466, 1435, 1388, 1293, 1219, 1152 cm^{-1}; HRMS: Calcd for $C_9H_{16}N_2O_5Na$ m/z 255.0957, found m/z 255.0955.

4.2 Synthesis of dialkyne S3f

A solution of propargyl amine (10 mL, 0.15 mmol) in dry dicholoromethane was added drop-wise to a stirred solution of triphosgene (0.016 g, 0.056 mmol) in two phase solution of dry CH_2Cl_2 (20 mL) and saturated solution of $NaHCO_3$ (40 mL). After 5 min. of stirring, a solution of propargyl amine (10 mL, 0.15 mmol) was added further in to the reactiom mixture and stirred for additional 4 h. The organic phase was then washed with water, dried with anhydrous Na_2SO_4 and evaporated to give crude product, which was purified by column chromatography.Yield: 46 %. mp: 186-188 ^oC; ^1H NMR (300 MHz, DMSO-d_6): δ 3.05 (br s, 2H), 3.79 (br d, 4H), 6.35 (br s, 2H); ^{13}C NMR (DMSO-d_6, 75 MHz): δ 28.8, 72.5, 82.3, 156.9; IR (KBr): 3324, 3149, 3010, 2923, 2117, 1618, 1426, 1357, 1297, 1256, 1062 cm^{-1}; HRMS: Calcd for $C_7H_9N_2O$ m/z 137.0715, found m/z 137.0710.

4.3 Synthesis of dendrons

4.3.1 Synthesis of ***S5a.*** To a well-stirred and ice-cooled solution of Z-Aspartic acid **S4a** (1.50 g, 5.62 mmol) in 70 mL dry CH_2Cl_2 was added N-hydroxysuccinimide (1.42 g, 12.35 mmol), DCC (2.54 g, 12.35 mmol), Asp.diOMe.HCl (2.44 g, 14.02 mmol), NEt_3 (1.7 mL, 12.35 mmol). After stirring for 24 h at RT, the reaction mixture was filtered. The residue was washed with CH_2Cl_2 (4 X 20 mL) and the combined filtrates were washed sequentially with 2 N H_2SO_4, water and 5 % aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4 and evaporated in vacuo to afford 2.90 g of **S5a**. Yield: 93 %. ^1H NMR ($CDCl_3$, 300 MHz) δ 2.55-3.30 (m, 6H), 3.68 (s, 6H), 3.73 (s, 6H), 4.62 (br, 1H), 4.80-4.85 (m, 2H), 5.12 (s, 2H), 6.29 (d, 1H, J = 7.8 Hz), 6.90 (d, 1H, J = 8.4 Hz), 7.35 (s, 5H), 7.64 (d, 1H, J = 7.8 Hz); IR (KBr): 3307, 3084, 2955, 2854, 1739, 1698, 1648, 1545, 1438, 1366, 1300 cm^{-1}; HRMS calcd for $C_{24}H_{31}N_3O_{12}Na$ m/z 576.1805, found m/z 576.1793.

4.3.2 Synthesis of ***S5b.*** To a well-stirred and ice-cooled solution of Z-Glutamic acid **S4b** (1.7 g, 5.75 mmol), N-hydroxysuccinimide (1.45 g, 12.65 mmol) and DCC (2.61 g, 12.65mmol) in dry CH_2Cl_2 (100 mL) was added a solution of H_2N-Glu.OMe.HCl (2.68 g, 12.65 mmol), NEt_3 (1.7 mL, 13.31 mmol). After stirring for 24 h at RT, the reaction mixture was filtered. The residue was washed with CH_2Cl_2 (4 × 20 mL) and the combined filtrates were washed sequentially

with 2 N H_2SO_4, water and 5 % aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, evaporated in vacuo and the crude product was chromatographed on a column of silica gel using EtOAc/hexane as eluents to afford the dendron **S5b**. Yield: 75 %. mp: 116-118 ^oC; $[\alpha]_D$ = -40.4 (*c* 0.5, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.80-2.10 (br s, 3H), 2.10-2.35 (m, 3H), 2.35-2.51 (br m, 6H), 3.68 (s, 3H), 3.69 (s, 3H), 3.77 (s, 3H), 3.79 (s, 3H), 4.06 (br 1H), 4.60-4.85 (br m, 2H), 5.08 (s, 2H), 5.33 (d, 1H, J = 5.4 Hz), 7.34 (s, 5H), 7.67 (d, 1H, J = 7.8 Hz), 8.03 (d, 1H, J = 7.8 Hz); IR (KBr): 3301, 3059, 2953, 1737, 1693, 1652, 1536, 1440, 1387, 1334, 1276, 1250, 1215, 1176, 1055, 1000 cm^{-1}; HRMS calcd for $C_{27}H_{37}N_3O_{12}Na$ m/z 618.2264, found m/z 618.2273.

4.3.3 Synthesis of ***S8.*** To a well-stirred and ice-cooled solution of Z-Aspartic acid **S4a** (1.6 g, 5.99 mmol), N-hydroxysuccinimide (1.72 g, 14.97 mmol) and DCC (3.09 g, 14.97 mmol) in dry CH_2Cl_2 (20 mL) was added a dichloromethane solution of H_2N-Leu.OMe.HCl (2.72 g, 14.97 mmol) and NEt_3 (2.1 mL, 14.97 mmol). After stirring for 24 h at RT, the reaction mixture was filtered. The residue was washed with CH_2Cl_2 (4 × 20 mL) and the combined filtrates were washed sequentially with 2 N H_2SO_4, water and 5 % aqueous $NaHCO_3$. The organic layer was dried over anhydrous Na_2SO_4, evaporated in vacuo and the crude product was chromatographed on a column of silica gel using EtOAc/hexane as eluents to afford the dendron **S8**. Yield: 94 %. mp: 143-144 ^oC; $[\alpha]_D$ = -40.4 (*c* 0.5, MeOH); ^1H NMR ($CDCl_3$, 300 MHz) δ 0.90 (m, 12H), 1.57 (m, 6H), 2.63 (dd, 1H, J = 15.3, 7.0 Hz), 2.87 (br d, 1H), 3.70 (s, 3H), 3.71 (s, 3H), 4.55 (m, 3H), 5.11 (s, 2H), 6.40 (d, 1H, J = 7.2 Hz), 6.71 (d, 1H, J = 7.5 Hz), 7.31 (m, 6H); ^{13}C NMR ($CDCl_3$, 75 MHz,) δ 21.6, 21.7, 22.6, 22.7, 24.7, 33.8, 38.0, 40.7, 41.0, 50.9, 51.0, 51.4, 52.1, 52.2, 67.0, 127.9, 128.0, 128.4, 136.1, 156.0, 170.6, 170.8, 173.2, 173.5; IR (KBr): 3298, 3076, 2956, 2878, 1740, 1702, 1653, 1542, 1441, 1362, 1257, 1141 cm^{-1}; HRMS calcd for $C_{26}H_{39}N_3O_8Na$ m/z 544.2635, found m/z 544.2636.

4.3.4 Synthesis of ***S9.*** To an ice-cooled solution of Z-Asp.(Leu.OMe)Leu.OMe **S8** (0.65 g, 1.24 mmol) in 10 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.25 w/w), and H_2 was bubbled through the reaction mixture for 1.5 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated to yield 0.442 g of the NH_2-Asp (Leu.OMe)Leu.OMe **S9**. Yield: 92 %. ^1H NMR ($CDCl_3$, 300 MHz) δ 0.95 (m, 12H), 1.58 (m, 6H), 1.91 (m, 2H), 2.51 (dd, 1H, J = 14.7, 7.5 Hz), 2.75 (dd, 1H, J = 14.5, 4.4 Hz), 3.73 (s, 6H), 4.53 (m, 2H), 4.58 (m, 1H) 6.99 (br d, 1H), 7.84 (d, 1H, J = 8.4 Hz); IR (KBr): 3324, 3188, 3077, 2960, 1752, 1679, 1525, 1443, 1375, 1313, 1242 cm^{-1}; HRMS calcd for $C_{18}H_{33}N_3O_6K$ m/z 426.2006, found m/z 426.2007.

4.4 Synthesis of urea cored dendrimers

4.4.1 Synthesis of ***S6a.*** To an ice-cooled solution of Z-Asp-(Asp.diOMe)Asp.diOMe **S5a** (1.0 g, 1.87 mmol) in 20 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.5 w/w), and H_2 was bubbled through the reaction mixture for 2 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated. The residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and NEt_3 (~ 0.1 ml) was added and divided into two equivalent parts. One part (0.39 g, 0.93 mmol) was added drop wise to the stirring solution of triphosgene (0.09 g, 0.33 mmol) in a mixture of CH_2Cl_2 (20 mL) and saturated solution of $NaHCO_3$ (40 mL). The second part (0.39 g, 0.93 mmol) was added in the reaction mixture after 5 min. and stirred it for additional 4 h. The organic phase was then washed with water, dried with anhydrous Na_2SO_4 and evaporated to give crude product. The solid obtained was purified by silica gel column chromatography using EtOAc/hexane to give the urea product. Yield: 70 %. mp: 148-150 ^oC; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.95-2.41 (m, 12H), 3.67 (s, 12H), 3.75 (s, 12H), 4.50 (br m, 2H), 4.68 (br m, 4H), 5.37 (d, 2H, J = 6.0 Hz), 7.68 (d, 4H, J = 6.0 Hz); IR (KBr): 3291, 3076, 2953, 1740, 1646, 1546, 1442, 1384, 1246, 1172 cm^{-1}; HRMS calcd for $C_{33}H_{48}N_6O_{21}H$ m/z 865.2951, found m/z 865.2934.

4.4.2 Synthesis of ***S6b.*** To an ice-cooled solution of Z-Glu-(Glu.diOMe)Glu.diOMe **S5b** (1.0 g, 1.68 mmol) in 20 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.5 w/w), and H_2 was bubbled through the reaction mixture for 2 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated. The residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and NEt_3 (~ 0.1 mL) was added and divided into two equal parts. One part (0.38 g, 0.84 mmol) was added drop wise to the stirring solution of triphosgene (0.08 g, 0.31 mmol) in mixture of CH_2Cl_2 (20 mL) and saturated solution of $NaHCO_3$ (40 mL). A solution of second part (0.38 g, 0.84 mmol) was added in the reaction mixture and stirred it for additional 4 h. The organic phase was then washed with water, dried with anhydrous Na_2SO_4 and evaporated to give crude product. The solid obtained was directly loaded in column and purified by silica gel column chromatography using EtOAc/hexane to give the urea product. Yield: 68 %. mp: 184-186 ^oC; ^1H NMR ($CDCl_3$, 300 MHz) δ 1.90-2.08 (br m, 6H), 2.12-2.33 (br m, 6H), 2.37-2.57 (m, 12H), 3.67 (s, 6H), 3.68 (s, 6H), 3.75 (s, 6H), 3.78 (s, 6H), 4.18-4.30 (m, 2H), 4.57-4.61 (m, 2H), 4.68-4.72 (m, 2H), 5.73 (d, 2H, J = 7.8 Hz), 7.68 (d, 4H, J = 8.4 Hz); IR (KBr): 3346, 3283, 2956, 1735, 1687, 1614, 1535, 1445, 1395, 1202, 1133 cm^{-1}; HRMS calcd for $C_{39}H_{60}N_6O_{21}H$ m/z 949.3890, found m/z 949.3889.

4.5 Synthesis of azide linked dendrons

4.5.1 Synthesis of N_3*-Asp-(Asp.diOMe)Asp.diOMe* ***S7a.*** To an ice-cooled solution of Z-Asp-(Asp.diOMe)Asp.diOMe **S5a** (0.221 g, 0.41 mmol) in 10 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.5 w/w), and H_2 was bubbled through the reaction mixture for 1.5 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated. The residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and NEt_3 (0.057 mL, 0.41 mmol) was added, followed by the slow addition of azidoacetyl chloride (0.048 g, 0.41 mmol) over a period of 0.5 h. The reaction mixture was left stirred at room temperature for 12 h. The solvent was removed in vacuo, the solid obtained was dissolved in ethyl acetate (50 mL), washed, with 2 N H_2SO_4, water and 5 % aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, evaporated and purified by silica gel column chromatography using EtOAc/hexane to give the desired product **S7a**. Yield: 72 %. mp: 135-136 ^oC; ^1H NMR ($CDCl_3$, 300 MHz) δ 2.60-3.20 (m, 6H), 3.70 (s, 6H), 3.75 (s, 3H), 3.76 (s, 3H), 4.02 (s, 2H), 4.82 (m, 3H), 6.85 (d, 1H, J = 7.4 Hz), 7.65 (d, 1H, J = 7.5 Hz), 7.87 (d, 1H, J = 7.0 Hz); IR (KBr): 3310, 2959, 2854, 2111, 1741, 1666, 1644, 1536, 1436, 1373, 1281 cm^{-1}; HRMS calcd for $C_{18}H_{27}N_6O_{11}$ m/z 503.1738, found m/z 503.1732.

4.5.2 Synthesis of N_3*-Glu-(Glu.diOMe)Glu.diOMe* ***S7b.*** To an ice-cooled solution of Z-Glu-(Glu.diOMe)Glu.diOMe **S5b** (1.72 g, 2.8 mmol) in 20 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.5 w/w), and H_2 was bubbled through the reaction mixture for 1.5 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated. The residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and NEt_3 (0.39 mL, 2.8 mmol) was added, followed by the slow addition of azidoacetyl chloride (0.33 g, 2.80 mmol) over a period of 0.5 h. The reaction mixture was left stirred at room temperature for 12 h. The solvent was removed in vacuo, the solid obtained was dissolved in ethyl acetate (50 mL), washed, with 2 N H_2SO_4, water, and 5 % aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, evaporated and purified by silica gel column chromatography using EtOAc/hexane to give the desired peptide dendron **S7b**. Yield: 72 %. mp: 138-140 ^oC; $[\alpha]_D$ = + 09.70 (*c* 0.268, $CHCl_3$); ^1H NMR ($CDCl_3$, 300 MHz) δ 1.85-2.20 (m, 3H), 2.20-2.38 (br m, 3H), 2.38-2.65 (br m, 6H), 3.68 (s, 3H), 3.69 (s, 3H), 3.78 (s, 6H), 3.92 (s, 2H), 4.29 (br m, 1H), 4.67-4.74

(br m, 2H), 6.83 (d, 1H, J = 6.8 Hz), 7.65 (d, 1H, J = 8.7 Hz), 8.07 (d, 1H, J = 8.4 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 26.5, 26.6, 28.8, 29.9, 30.2, 31.9, 51.4, 51.6, 51.7, 51.8, 51.9, 52.2, 52.8, 52.9, 166.3, 171.1, 172.5, 172.8, 173.9, 174.0; IR (KBr): 3289, 3073, 2956, 2104, 1735, 1645, 1545, 1440, 1385, 1212, 1173, 1123, 1070, 983 cm^{-1}; HRMS calcd for $C_{21}H_{32}N_6O_{11}Na$ m/z 567.2027, found m/z 567.2028.

4.5.3 Synthesis of N_3-Asp(Leu.OMe)$_2$ ***S10.*** To an ice-cooled solution of Z-Asp-(Leu.OMe)Leu.OMe **S8** (0.7 g, 1.34 mmol) in 10 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.5 w/w), and H_2 was bubbled through the reaction mixture for 1.5 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated. The residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and NEt_3 (0.19 mL, 1.34 mmol) was added, followed by the slow addition of azidoacetyl chloride (0.16 g, 1.34 mmol) over a period of 0.5 h. The reaction mixture was left stirred at room temperature for 12 h. The solvent was removed in vacuo, the solid obtained was dissolved in ethyl acetate (50 mL), washed, with 2 N H_2SO_4, water, and 5 % aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, evaporated and purified by silica gel column chromatography using EtOAc/hexane to give the desired product **S10**. Yield: 72 %. mp: 94-95 ^{o}C; $[\alpha]_{D\,=}$ +09.70 (*c* 0.268, $CHCl_3$); ^{1}H NMR ($CDCl_3$, 300 MHz) δ 0.92 (t, 12H, J = 6.3 Hz), 1.54-1.72 (m, 6H), 2.64 (dd, 1H, J = 15, 7.5 Hz), 2.87 (dd, 1H, J = 15, 7.5 Hz), 3.72 (s, 3H), 3.73 (s, 3H), 4.00 (m, 2H), 4.50-4.62 (m, 2H), 4.47-4.82 (br m, 1H), 6.87 (d, 1H, J = 7.2 Hz), 7.64 (d, 1H, J = 7.5 Hz), 7.89 (d, 1H, J = 7.2 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 21.5, 21.7, 22.7, 24.8, 37.9, 39.6, 39.9, 40.2, 40.4, 40.9, 49.6, 51.0, 51.2, 52.3, 52.4, 167.0, 170.3, 170.6, 173.3, 173.5; IR (KBr): 3289, 3079, 2959, 2873, 2104, 1746, 1647, 1549, 1437, 1369, 1249, 1209, 1154, 1021 cm^{-1}; HRMS calcd for $C_{20}H_{34}N_6O_7Na$ m/z 493.2387, found m/z 493.2381.

4.5.4 Synthesis of N_3-Ar-(Glu-(Glu.diOMe)Glu.diOMe)$_2$ ***S12.*** To an ice-cooled solution of Z-Glu-(Glu.diOMe)Glu.diOMe **S5b** (1.72 g, 2.8 mmol) in 20 mL of dry MeOH was admixed with 10 % Pd/C, (peptide/catalyst 1:0.5 w/w), and H_2 was bubbled through the reaction mixture for 1.5 h. After completion of the reaction, the solution was filtered, and the filtrate was evaporated. The residue obtained was dissolved in dry dichloromethane. The solution was cooled in an ice-bath and NEt_3 (0.39 mL, 2.8 mmol) was added, followed by the slow addition of 5-(azidomethyl) benzene-1,3-dicarbonyl dichloride (0.359 g, 1.40 mmol) over a period of 0.5 h. The reaction mixture was left stirred at room temperature for 24 h. The solvent was removed in vacuo, the solid obtained was dissolved in ethyl acetate (50 mL), washed, with 2 N H_2SO_4, water, and 5 % aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, evaporated and purified by silica gel column chromatography using EtOAc/hexane to give the desired dendron N_3-Ar-(Glu-(Glu.diOMe)Glu.diOMe)$_2$ **S12**. Yield: 64 %. mp: 160-161 ^{o}C; ^{1}H NMR ($CDCl_3$, 300 MHz) δ 1.90-2.17 (br m, 6H), 2.17-2.34 (br m, 6H), 2.41-2.67 (br m, 12H), 3.65 (s, 6H), 3.68 (s, 6H), 3.76 (s, 12H), 4.40 (s, 2H), 4.48-4.61 (br m, 2H), 4.62-4.83 (br m, 4H), 7.51-7.75 (m, 4H), 7.88 (s, 2H), 8.09 (br m, 2H), 8.17 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 24.9, 25.5, 26.6, 28.3, 29.7, 30.1, 30.2, 32.1, 33.9, 49.1, 51.6, 51.7, 51.8, 52.8, 52.9, 53.0, 53.9, 125.2, 130.1, 134.3, 136.7, 165.7, 172.0, 172.8, 172.9, 173.0, 173.8, 173.9; IR (KBr): 3294, 3076, 2955, 2091, 1738, 1642, 1545, 1441, 1384, 1212, 1171 cm^{-1}; HRMS calcd for $C_{47}H_{65}N_9O_{22}Na$ m/z 1130.4136, found m/z 1130. 4147.

4.5.5 Synthesis of N_3-Glu.di.OMe ***S13.*** NH_2-Glu.di.OMe.HCl (0.500 g, 2.36 mmol) was dissolved in 10 mL dicholomethane. The solution was cooled in an ice-bath and NEt_3 (1.8 mL, 11.8 mmol) was added, followed by the slow addition of azidoacetyl chloride (0.28 g, 2.36 mmol) over a period of 0.5 h. The reaction mixture was left stirred at room temperature for 12 h. The solvent was removed in vacuo, the solid obtained was dissolved in ethyl acetate (50 mL), washed, with 2 N H_2SO_4, water, and 5 % aqueous $NaHCO_3$ solution. The organic layer was dried over anhydrous Na_2SO_4, evaporated and purified by silica gel column chromatography using EtOAc/hexane to give the desired product N_3Glu.OMe$_2$ **S13**. Yield: 82 %. ^{1}H NMR ($CDCl_3$, 300 MHz) δ 2.03-2.46 (m, 4H), 3.70 (s, 3H), 3.78 (s, 3H), 4.01 (s, 2H), 4.62-4.69 (m, 1H), 6.98 (br s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz,) δ 27.0, 29.9, 51.6, 51.9, 52.4, 52.6, 166.8, 171.7, 173.1; IR (KBr): 3347, 2955, 2925, 2854, 2110, 1739, 1670, 1533, 1441, 1374, 1210 cm^{-1}; HRMS calcd for $C_9H_{14}N_4O_5Na$ m/z 281.0856, found m/z 281.0860.

4.6 Synthesis of urea-triazole cored dendrimers

4.6.1 Synthesis of ***ST14.*** To an ice-cooled solution of dialkyne **S3f** (0.03 g, 0.22 mmol) in 20 mL of dry acetonitrile under argon atmosphere was added diisopropylethylamine (0.038 mL, 0.22 mmol), N_3-Glu.OMe$_2$ **S13** (0.113 g, 0.44 mmol) and CuI (0.004 g, 0.022 mmol). The reaction mixture was stirred under argon atmosphere for 17 h. The reaction mixture was evaporated, the solid thus obtained was washed with 0.2 N H_2SO_4, water, NH_4Cl / NH_4OH (9:1) solution and finally with water. The residue obtained was dried and crystallized from a mixture of chloroform and methanol to give the symmetrical dendrimer **ST14**. Yield: 70 %. mp: 184-186 ^{o}C; ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.88-2.23 (m, 8H), 3.56 (s, 6H), 3.61 (s, 6H), 4.32 (br s, 6H), 5.23 (s, 4H), 6.56 (d, 2H, J = 6.3 Hz), 7.87 (s, 2H), 8.24 (d, 2H, J = 5.7 Hz); IR (KBr): 3324, 3071, 2956, 2855, 1738, 1664, 1538, 1442, 1376, 1212 cm^{-1}; HRMS calcd for $C_{25}H_{36}N_{10}O_{11}Na$ m/z 675.2463, found m/z 675.2449.

4.6.2 Synthesis of ***ST15.*** To an ice-cooled solution of dialkyne **S3f** (0.015 g, 0.11 mmol) in 20 mL of dry acetonitrile under argon atmosphere was added diisopropylethylamine (0.019 mL, 0.11 mmol), N_3-Asp-(Asp.diOMe)Asp.diOMe **S7a** (0.11 g, 0.22 mmol) and CuI (0.002 g, 0.011 mmol). The reaction mixture was stirred under argon atmosphere for 17 h. The reaction mixture was evaporated, the solid thus obtained was washed with 0.2 N H_2SO_4, water, NH_4Cl / NH_4OH (9:1) solution and finally with water. The residue obtained was dried and crystallized from a mixture of chloroform and methanol to give symmetrical dendrimer **ST15**. Yield: 67 %. mp: 202-204 ^{o}C; $[\alpha]_{D\,=}$ - 11.21 (*c* 0.106, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 2.55-2.88 (br m, 12H), 3.60 (s, 12H), 3.62 (s, 12H), 4.26 (br s, 4H), 4.55-4.70 (br m, 6H), 5.00-5.20 (br m, 4H), 6.42 (br s, 2H), 7.83 (s, 2H), 8.46 (br s, 4H), 8.57 (d, 2H, J = 5.7 Hz); ^{13}C NMR ($CDCl_3$, 75 MHz) δ 34.5, 34.9, 35.2, 36.7, 48.0, 48.1, 49.0, 50.8, 51.2, 51.7, 123.4, 145.2, 157.2, 164.8, 168.4, 169.9, 170.0, 170.4, 170.6 ; IR (KBr): 3286, 3086, 2955, 1734, 1652, 1552, 1439, 1370, 1298, 1226, 1173, 1052 cm^{-1}; HRMS calcd for $C_{43}H_{60}N_{14}O_{23}Na$ m/z 1163.3848, found m/z 1163.3807.

4.6.3 Synthesis of ***ST16.*** To an ice-cooled solution of dialkyne **S3f** (0.015 g, 0.11 mmol) in 20 mL of dry acetonitrile under argon atmosphere was added diisopropylethylamine (0.019 mL, 0.11 mmol), N_3-Glu-(Glu.diOMe)Glu.diOMe **S7b** (0.119 g, 0.22 mmol) and CuI (0.002 g, 0.011 mmol). The reaction mixture was stirred under Ar atmosphere for 17 h. The reaction mixture was evaporated, the solid thus obtained was washed with 0.2 N H_2SO_4, water, NH_4Cl / NH_4OH (9:1) solution and finally with water. The residue obtained was dried and crystallized from a mixture of chloroform and methanol to give symmetrical dendrimer **ST16**. Yield: 65 %. mp: 180-182 ^{o}C; $[\alpha]_D$ = - 30.15 (*c* 0.126, MeOH); ^{1}H NMR (DMSO-d_6, 300 MHz) δ 1.61-2.00 (br m, 12H), 2.07-2.20 (br m, 4H), 2.27-2.36 (br m, 8H), 3.51 (s, 12H), 3.56 (s, 12H), 4.14-4.32 (br m, 10H), 5.06 (s, 4H), 6.31-6.40 (br m, 2H), 7.70 (s, 2H), 8.21 (d, 2H, J = 7.8 Hz), 8.39 (d, 2H, J = 7.8 Hz), 8.49 (d, 2H, J = 7.5 Hz); ^{13}C NMR (DMSO-d_6, 75 MHz) δ 26.4, 26.5, 28.8, 30.1, 30.2, 31.7, 35.5, 51.7, 52.0, 52.5, 52.6, 124.6, 146.2, 158.3, 166.0, 171.7, 172.3, 172.5, 172.9, 173.2; IR (KBr): 3295, 2926, 2855, 1739, 1646, 1542, 1442, 1380, 1214, 1173 cm^{-1}; HRMS calcd for $C_{49}H_{72}N_{14}O_{23}Na$ m/z 1247.4792, found m/z 1247.4796.

4.6.4 Synthesis of ***ST17.*** To an ice-cooled solution of dialkyne **S3f** (0.015 g, 0.11 mmol) in 20 mL of dry acetonitrile under argon

atmosphere was added diisopropylethylamine (0.019 mL, 0.11 mmol), N_3-Asp-(Leu.OMe)Leu.OMe **S10** (0.103 g, 0.16 mmol) and CuI (0.002 g, 0.011 mmol). The reaction mixture was stirred under Ar atmosphere for 17 h. The reaction mixture was evaporated, the solid thus obtained was washed with 0.2 N H_2SO_4, water, NH_4Cl / NH_4OH (9:1) solution and finally with water. The residue obtained was dried and crystallized from a mixture of chloroform and methanol to give symmetrical dendrimer **ST17**. Yield: 65 %. mp: 196-198 ^oC; $[\alpha]_D$ = - 30.15 (*c* 0.126, MeOH); ^1H NMR (DMSO-d_6, 300 MHz) δ 0.75-0.96 (br m, 24H), 1.18-1.30 (br m, 4H), 1.42-1.72 (br m, 8H), 2.53 (br m, 4H), 3.61 (s, 6H), 3.64 (s, 6H), 4.27 (br s, 8H), 4.57 (br m, 2H) 4.95-5.21 (br m, 4H), 6.54 (br s, 2H), 7.83 (d, 2H, J = 8.4 Hz), 8.30 (d, 4H, J = 7.8 Hz), 8.57 (d, 2H, J = 7.2 Hz); IR (KBr): 3296, 2958, 1742, 1649, 1548, 1462, 1233, 1125 cm^{-1}; HRMS calcd for $C_{47}H_{76}N_{14}O_{15}Na$ m/z 1099.5507, found m/z 1099.5504.

*4.6.5 Synthesis of **ST18.*** To an ice-cooled solution of dialkyne **S3f** (0.010 g, 0.07 mmol) in 20 mL of dry acetonitrile under argon atmosphere was added diisopropylethylamine (0.012 mL, 0.07 mmol), N_3-Ar-(Glu-(Glu.diOMe)Glu.diOMe)$_2$ **S12** (0.155 g, 0.14 mmol) and CuI (0.001 g, 0.0053 mmol). The reaction mixture was stirred under Ar atmosphere for 24 h. The reaction mixture was evaporated, the solid thus obtained was washed with 0.2 N H_2SO_4, water, NH_4Cl /NH_4OH (9:1) solution and finally with water. The residue obtained was dried and crystallized from a mixture of chloroform and methanol to give dendrimer **ST18**. Yield: 43 %. mp: 160-161 ^oC; ^1H NMR (DMSO-d_6, 300 MHz) δ 1.75-2.12 (m, 24H), 2.21-2.45 (m, 24H), 3.57 (s, 24H), 3.59 (s, 24H), 4.08-4.37 (br m, 12H), 4.44-4.58 (br m, 4H), 5.65 (br s, 4H), 6.40 (br s , 2H), 7.80 (d, 5H, J = 7.2 Hz), 8.29 (br m, 7H), 8.44 (d, 4H, J = 6.3 Hz), 8.64 (d, 4H, J = 6.0 Hz); IR (KBr): 3316, 2926, 2854, 1737, 1650, 1540, 1442, 1376, 1213 cm^{-1}; HRMS calcd for $C_{101}H_{138}N_{20}O_{45}Na$ m/z 2350.4147, found $[M/2+Na]^+$ 1198.4463.

Acknowledgements

This work was supported by DST-New Delhi. We thank DST -FIST for mass spectral and single crystal XRD facilities at IITD. We thank Department of Textile Technology, Department of Physics and NRF IIT-Delhi for SEM images, AFM images and TEM studies respectively. We also thank Prof. B. Jayaram, IITD for the help in MD simulation. RPV thanks Council of Scientific & Industrial Research (CSIR) New Delhi for the fellowship and Oil and Natural Gas Corporation (ONGC) for the support.

Supplementary data

^1H NMR, ^{13}C NMR, and HRMS of all new compounds. Supplementary data related to this article can be found online at doi:xxxxxxxxxxxxx

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SUPPLEMENTARY INFORMATION

Peptide dendrimers with designer core for directed self-assembly

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Experimental section

(a) Synthesis and characterization

All reagents were used without further purification. All solvents employed in the reactions were distilled or dried from appropriate drying agents prior to use. All amino acids used were of L-configuration. Progress of reactions was monitored by thin layer chromatography (TLC). Purification of compounds was done by silica gel column chromatography. Silica gel G (Merck) was used for TLC and silica gels with 100-200 mesh was used for column chromatography. Melting points were recorded on a Fisher-Scientific melting point apparatus and were uncorrected. Optical rotations were measured with a Rudolph Research Analytical Autopol® V Polarimeter; where concentrations are given in gram/100 mL. IR spectra were recorded on a Nicolet, Protégé 460 spectrometer as KBr pellets. ^{1}H NMR spectra were recorded on Brucker-DPX-300 spectrometer using tetramethylsilane as an internal standard. Coupling constants are in Hz and the ^{1}H NMR data are reported as s (singlet), d (doublet), br (broad), t (triplet) and m (multiplet), dd (double doublet). High Resolution mass spectra (HRMS) were recorded in Bruker MicrO-TOF-QII model and AB Sciex, 1011273/A model using ESI technique. MD simulations were performed on 320 processors SUN Microsystems clusters at Supercomputing Facility (SCFBio) at IIT Delhi.

(b) Gelation Study

The dendrimer was dissolved in a more polar solvent and the less polar solvent was added to initiate the gel formation. The gel formation is assessed by the tube inversion method.

(c) Preparation of gel from S6a-b

In a typical procedure, 20 mg of **S6a-b** was dissolved in 0.3 mL chloroform and added 0.2 mL hexane to get the gel.

Microscopic studies

(d) Scanning Electron Microscopy (SEM)

A 10 μl aliquot of the sample solution was applied on a sticky carbon tape and it was then coated with ~ 10 nm of gold. SEM images were recorded using a CARL ZEISS EVO 50 SEM.

(e) Field Emission-Scanning Electron Microscopy (FE-SEM)

A 10μl aliquot of the sample solution was put on a fresh piece of glass, which is attached to a stub via carbon tape. The sample was dried at room temperature and coated with ~10nm of gold. Samples were analyzed using FEI Quanta 3D FEG High resolution scanning electron microscope combined with High-current ion column with Ga liquid-metal ion source.

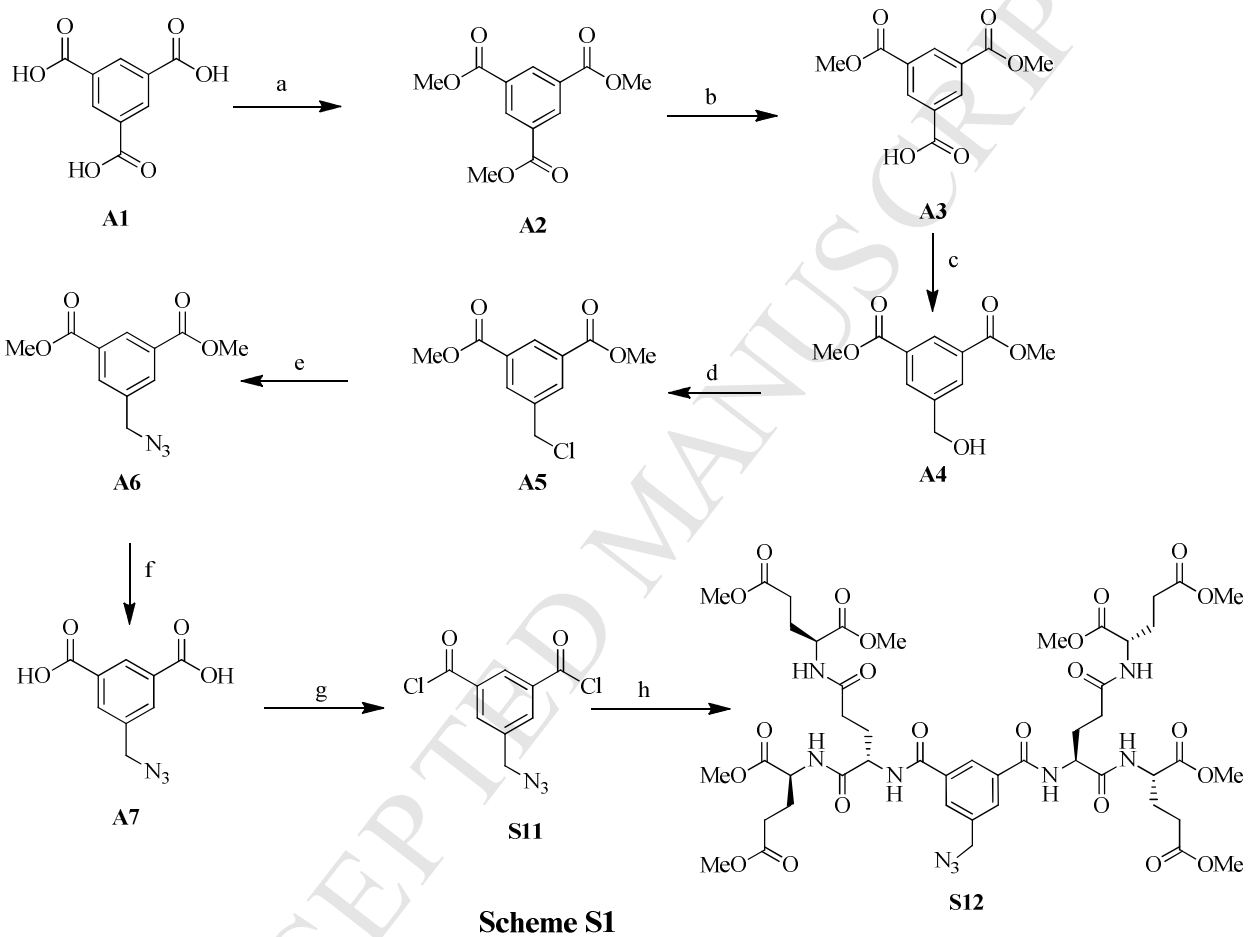
(f) Atomic Force Microscopy (AFM)

Bruker Dimension Icon atomic force microscope was used for imaging. Tapping mode is used for the analysis. About 10 μl aliquot of the sample solution was transferred onto a freshly cleaved mica and allowed to dry and imaged using AFM.

(g) High Resolution-Transmission Electron Microscopy (HR-TEM)

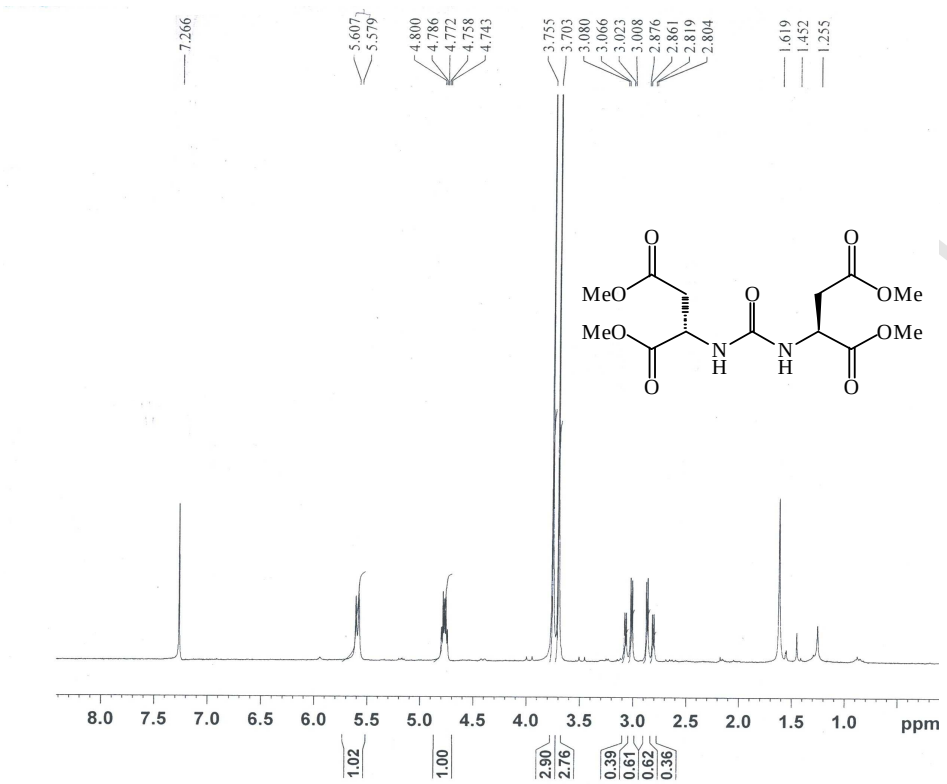
Samples for HR-TEM were prepared by dissolving the compound in 1:1 methanol and chloroform mixture. A 2 μl aliquot of the sample solution was placed on a 200 mesh copper grid. It was then stained with 2 % phosphotungstate in water for 2 min. and the

excess fluid was removed using a filter paper and samples were viewed using a TECHNAI G2 (20STWIN) electron microscope.

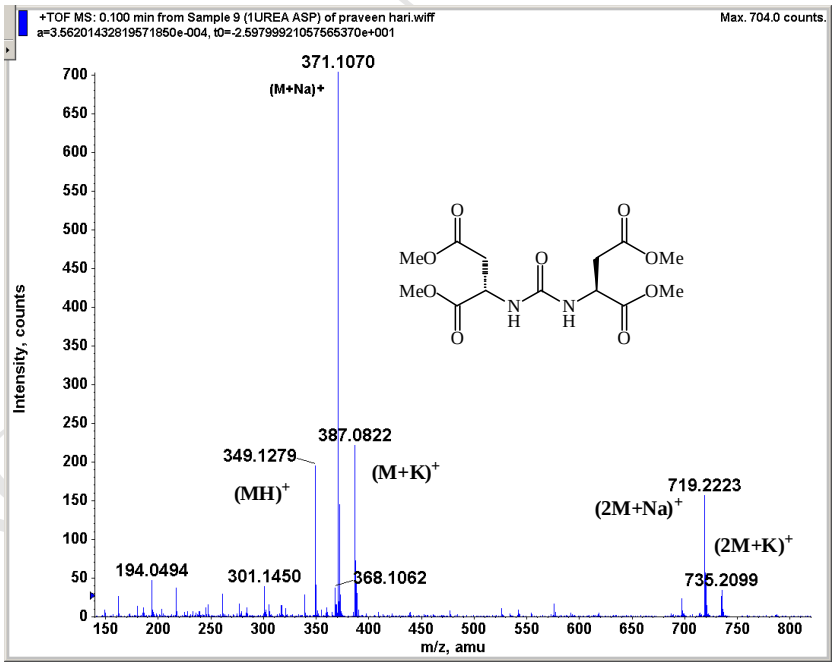


Scheme S1

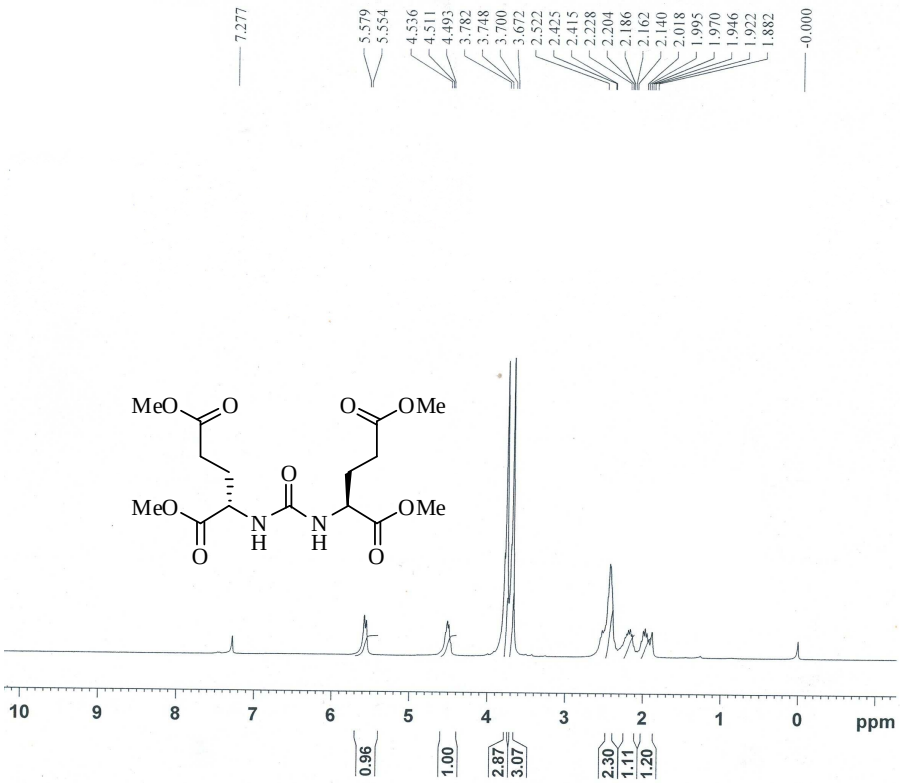
(a) $MeOH/H_2SO_4$; (b) 1 equiv. of NaOH; (c) $BH_3.Me_2S$; (d) $SOCl_2$, reflux; (e) NaN_3; (f) 2M NaOH; (g) $SOCl_2$, reflux (h) Dry NEt_3, $NH_2Glu_3OMe_4$



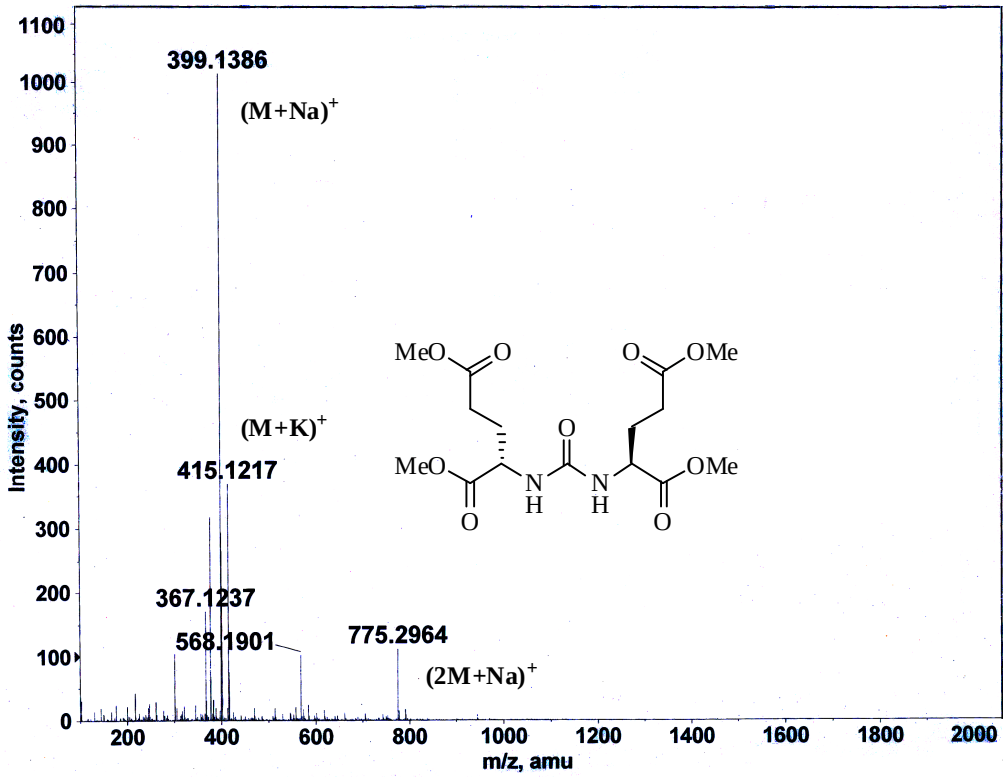
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S3a**



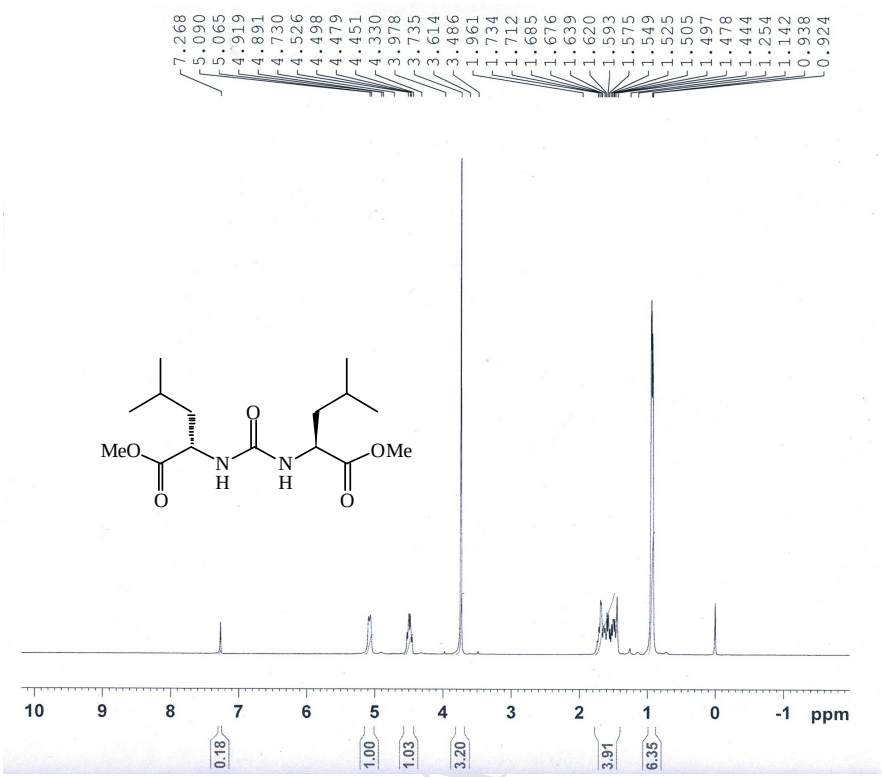
ESI-MS of compound **S3a**



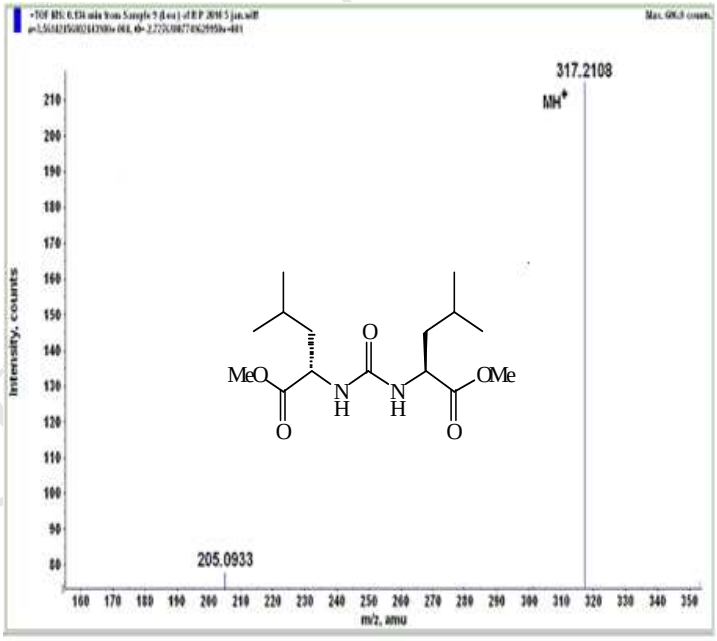
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S3b**



ESI-MS of compound **S3b**



^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S3c**



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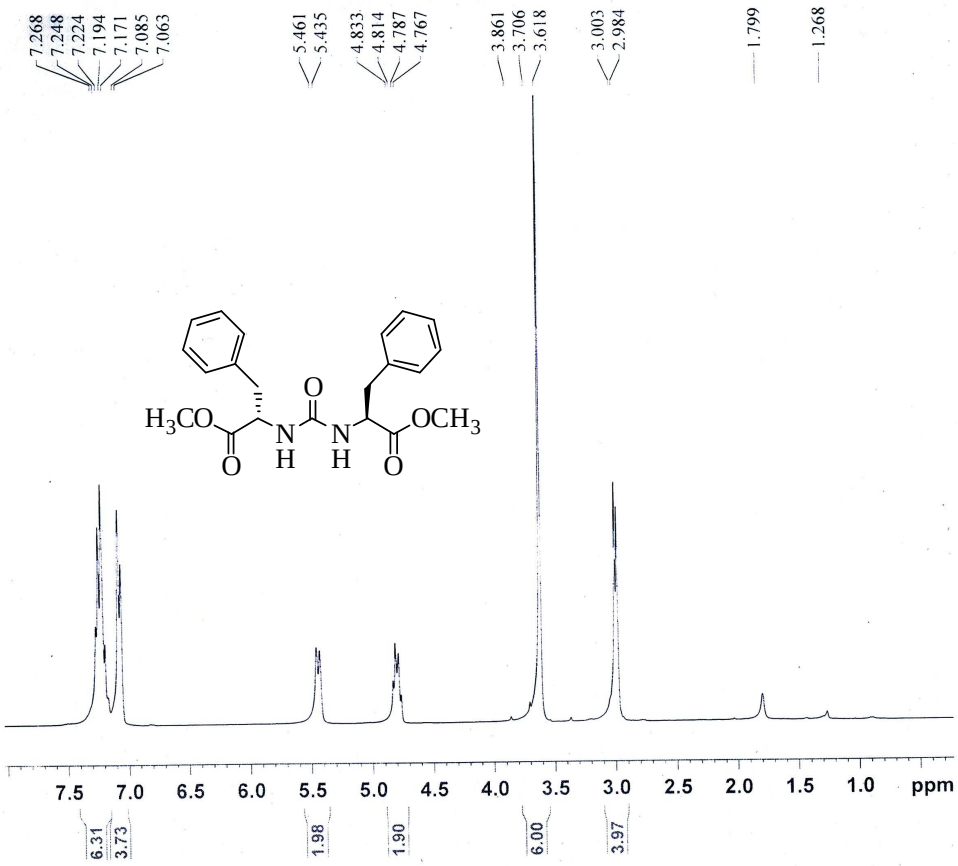
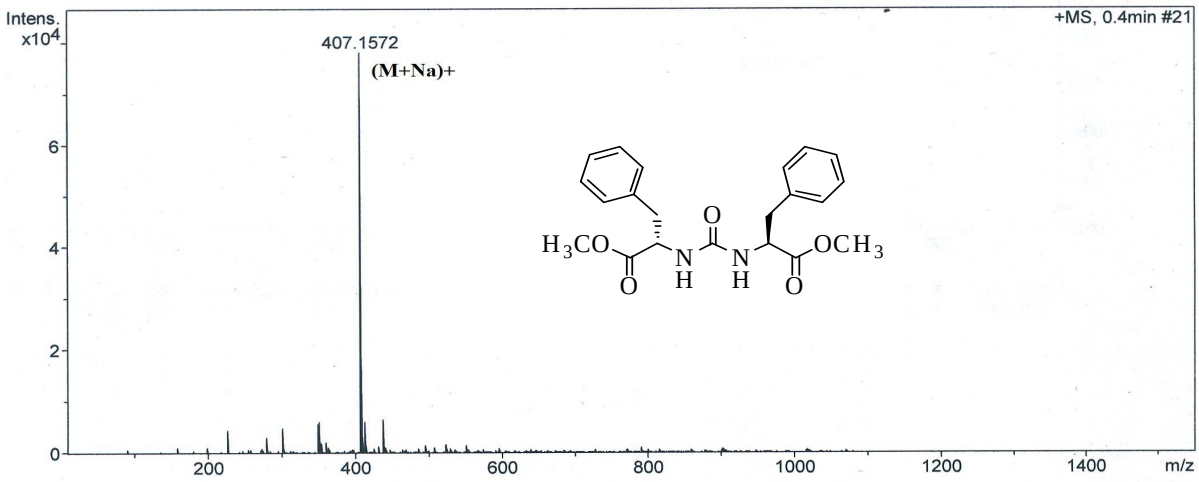


^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S3d**



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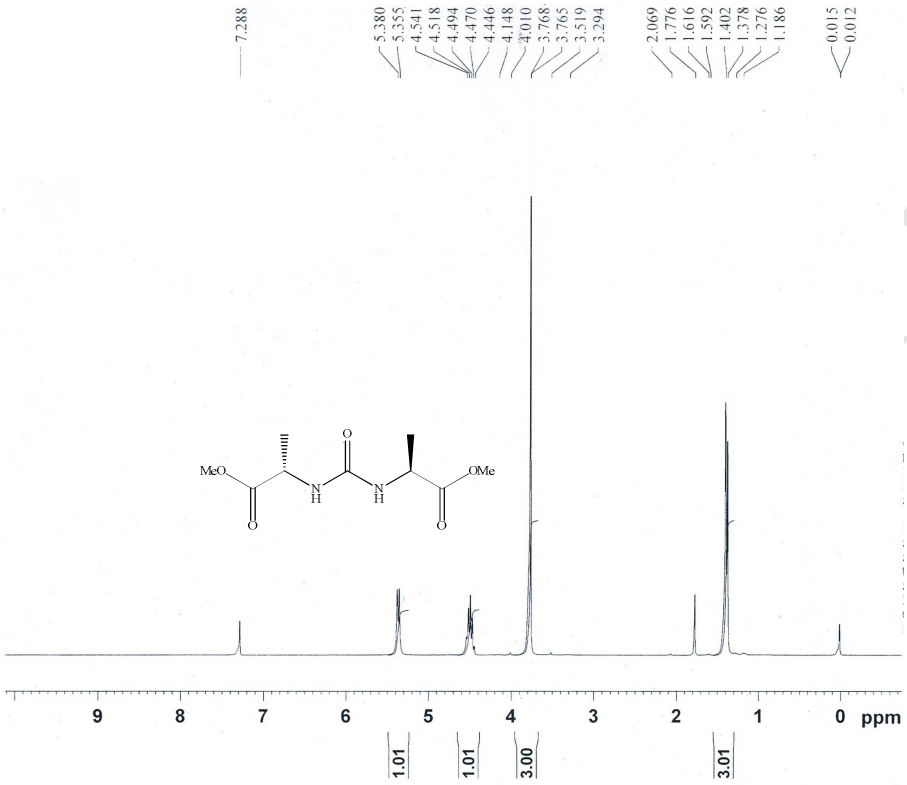
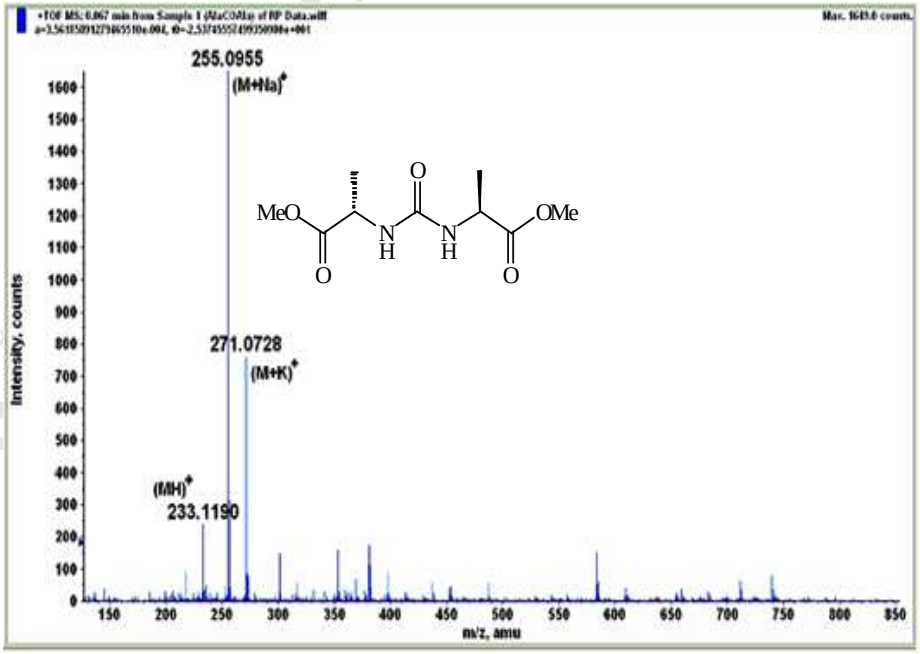


^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S3e**



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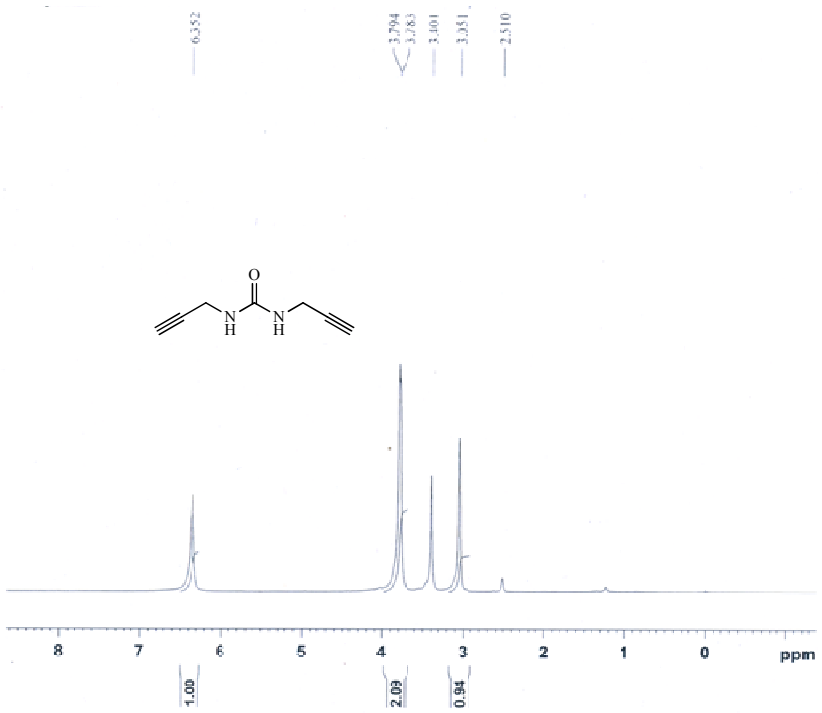
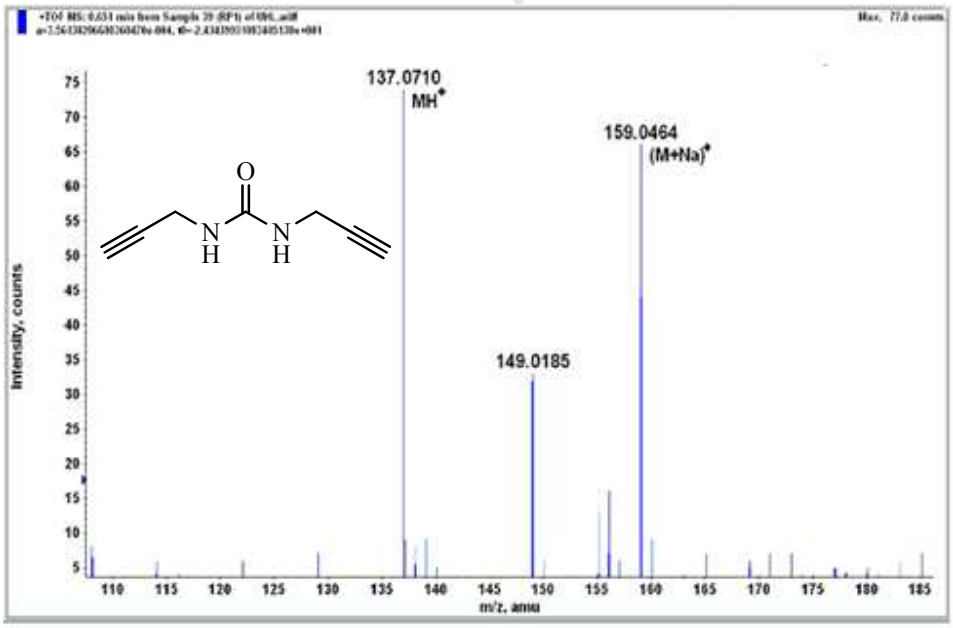


^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of **S3f**



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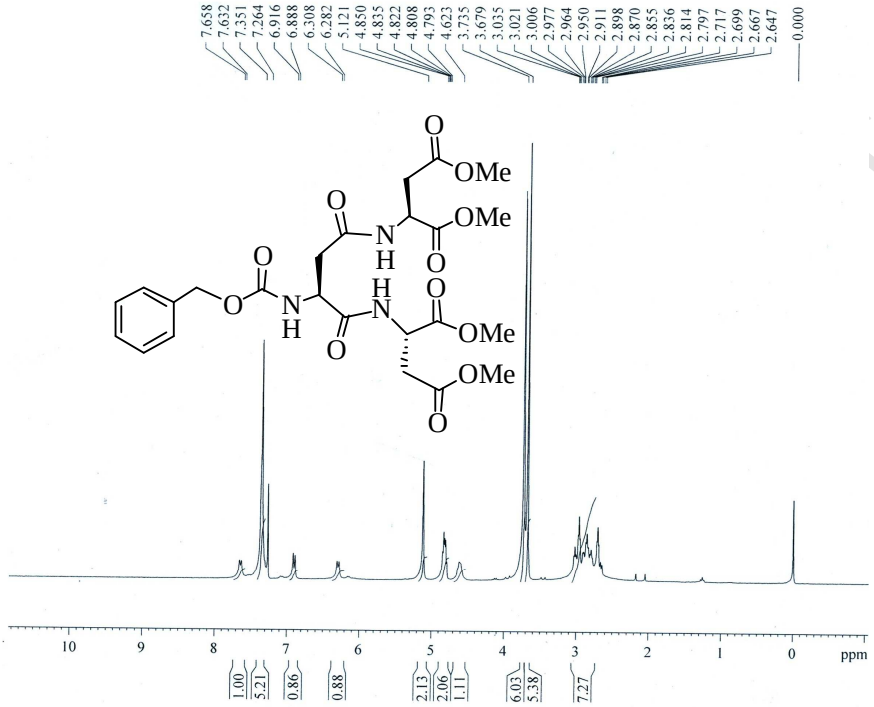
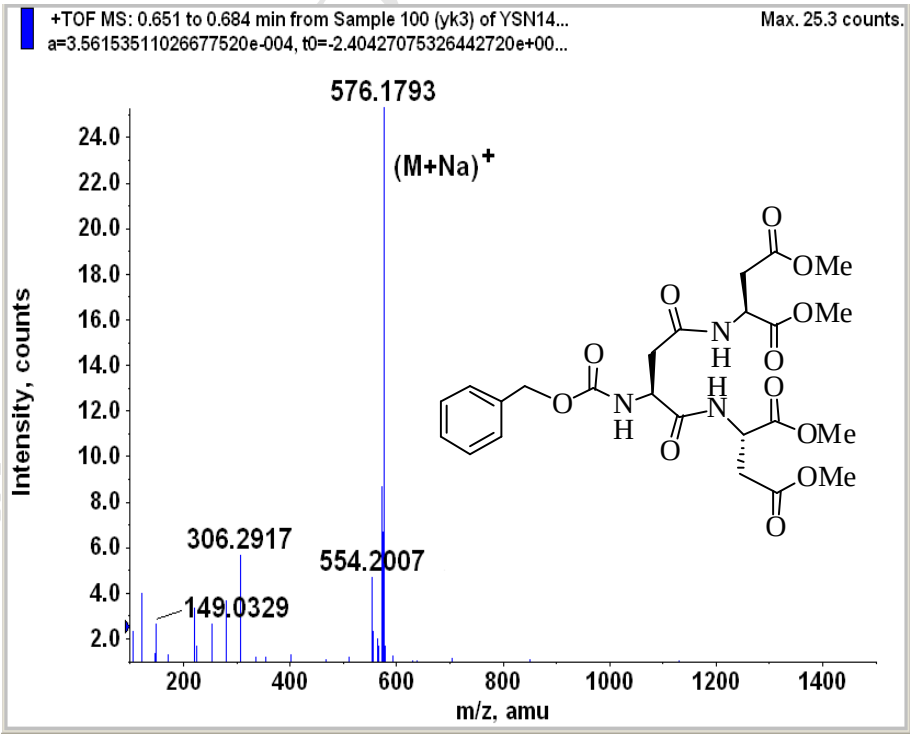


^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S5a**



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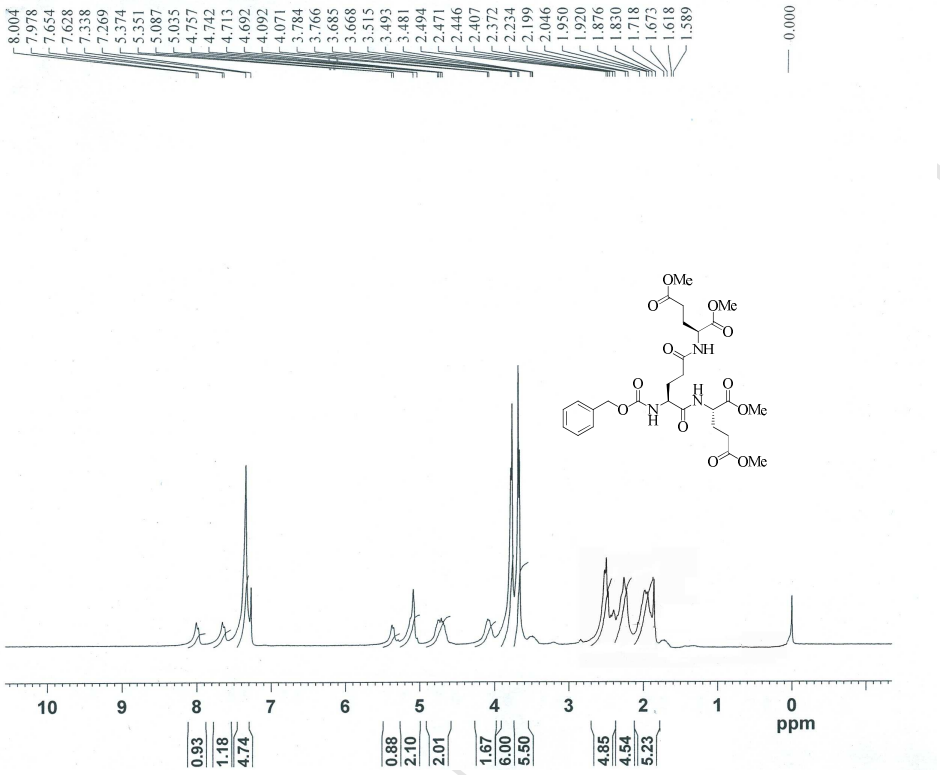

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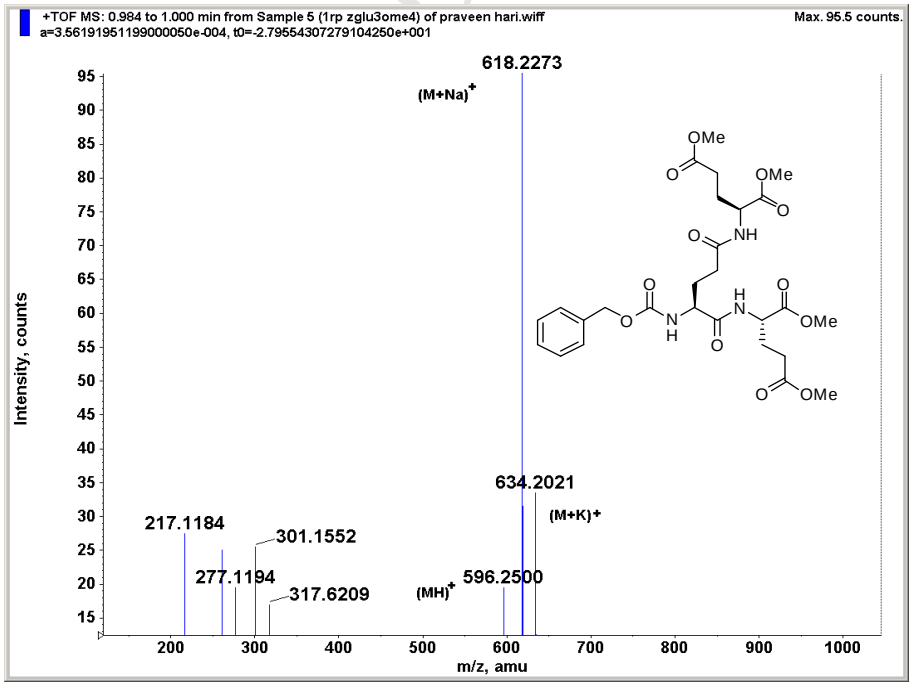

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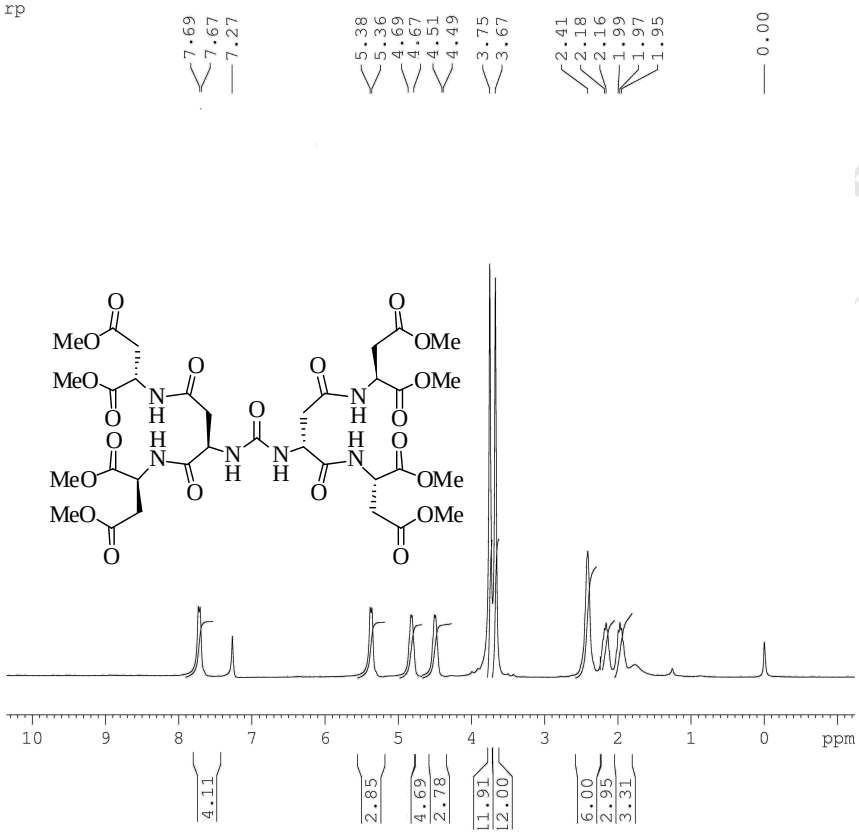

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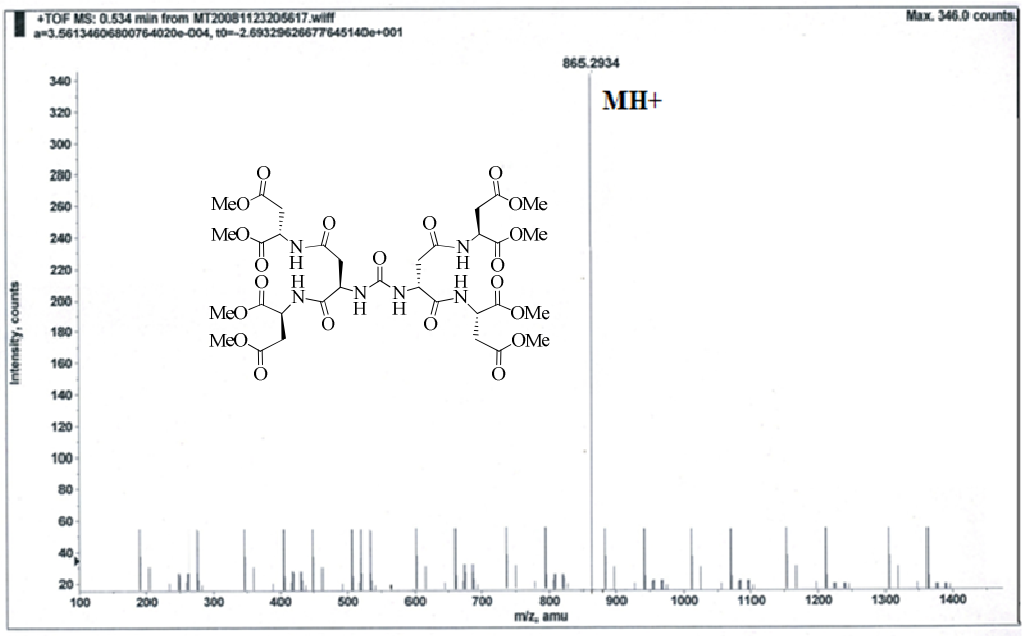

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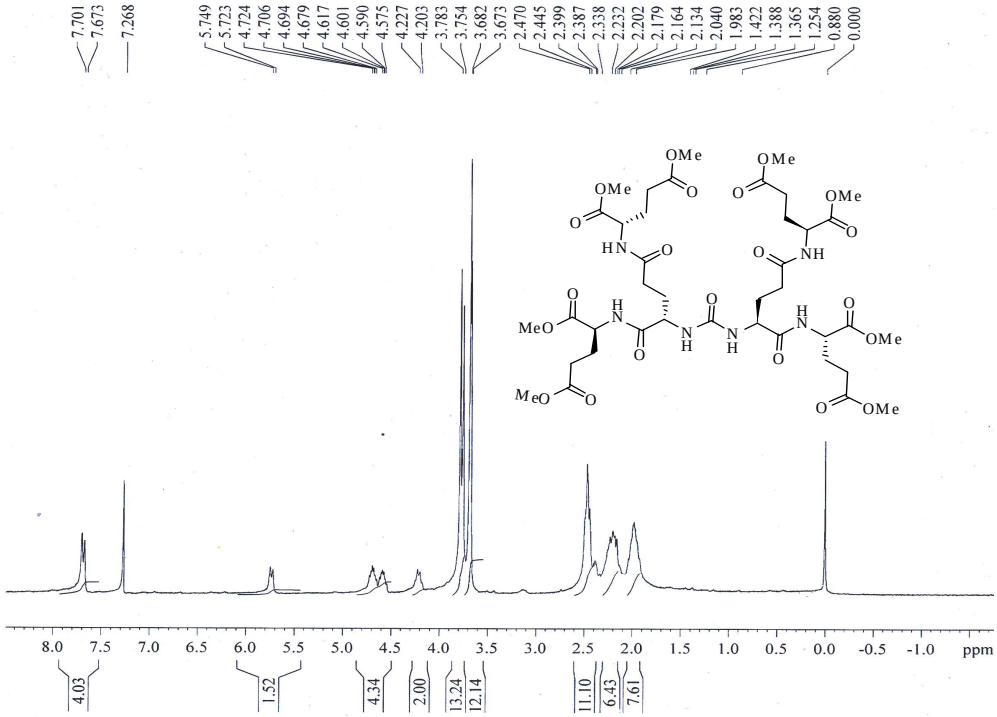

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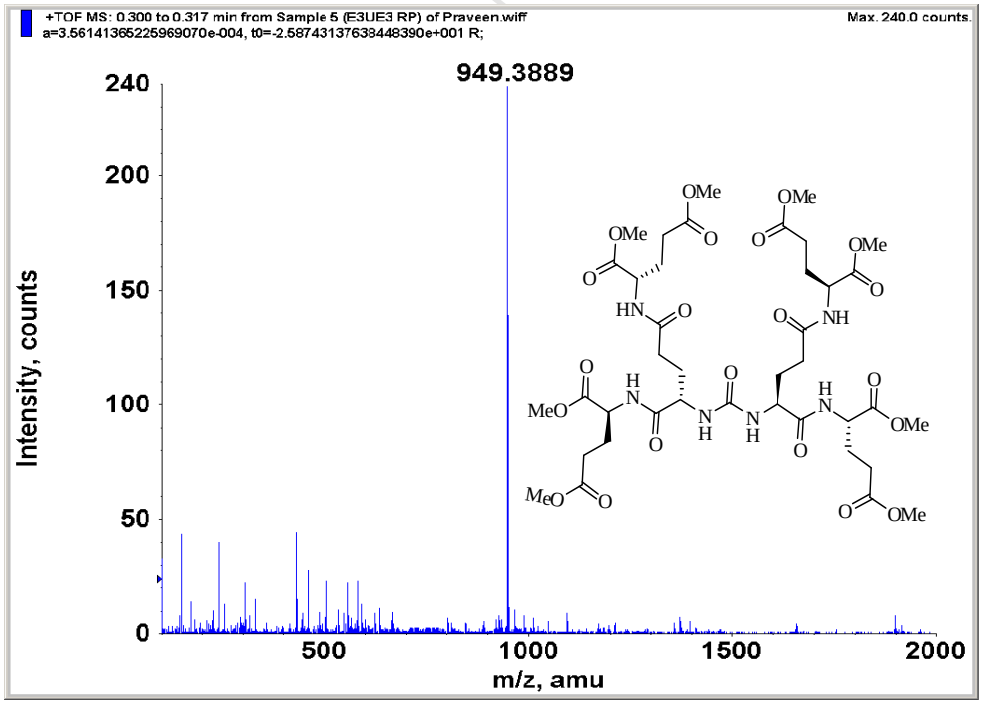

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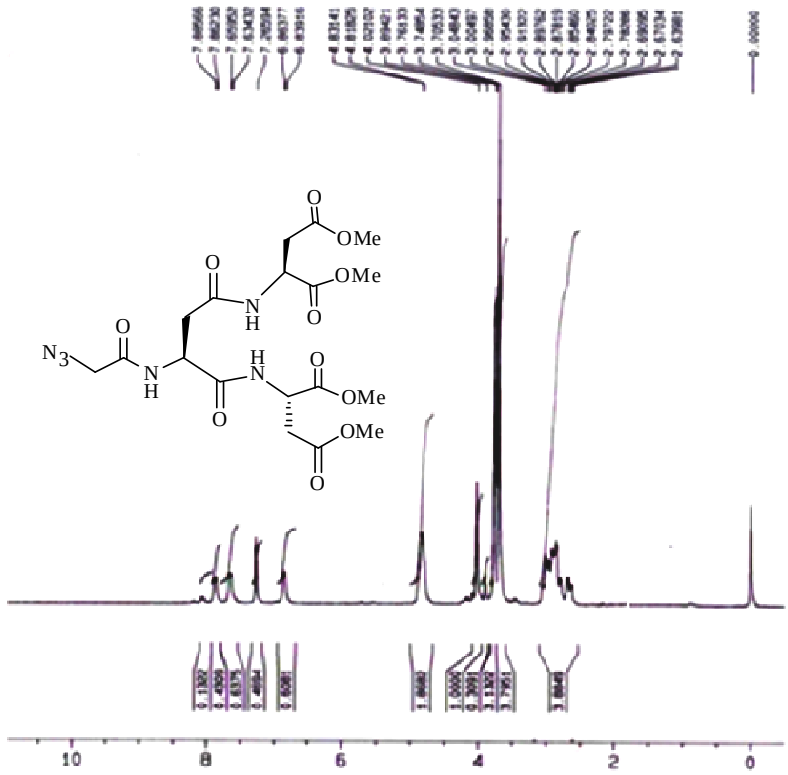

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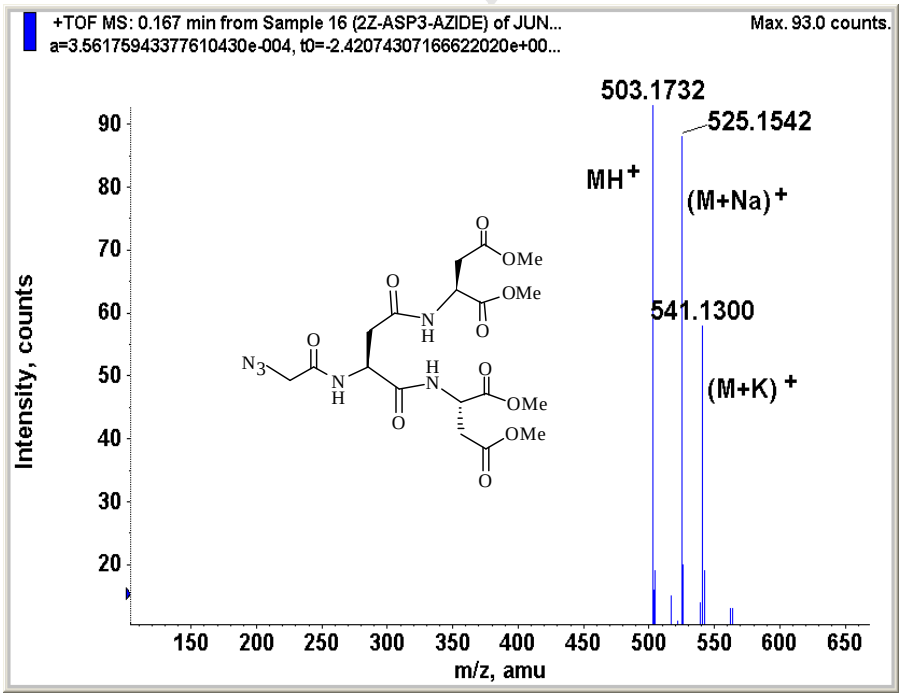

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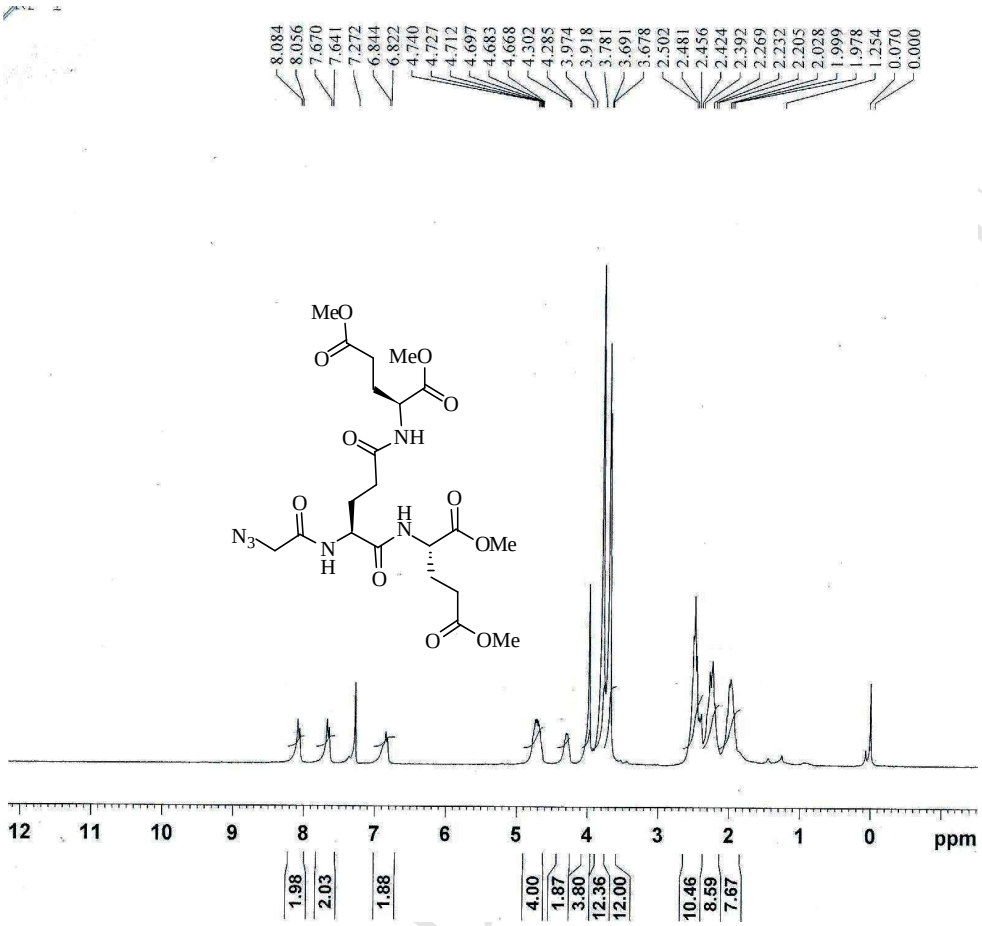

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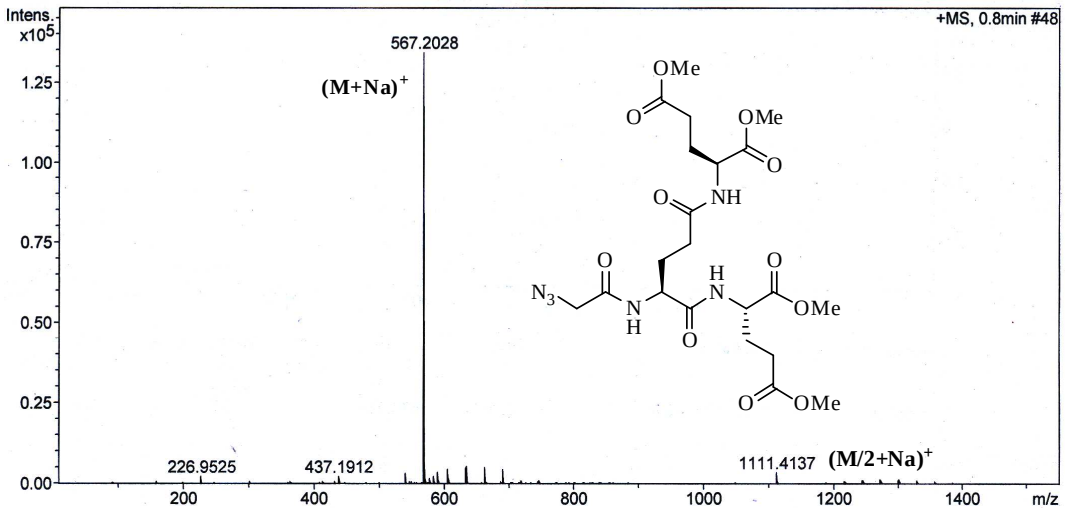

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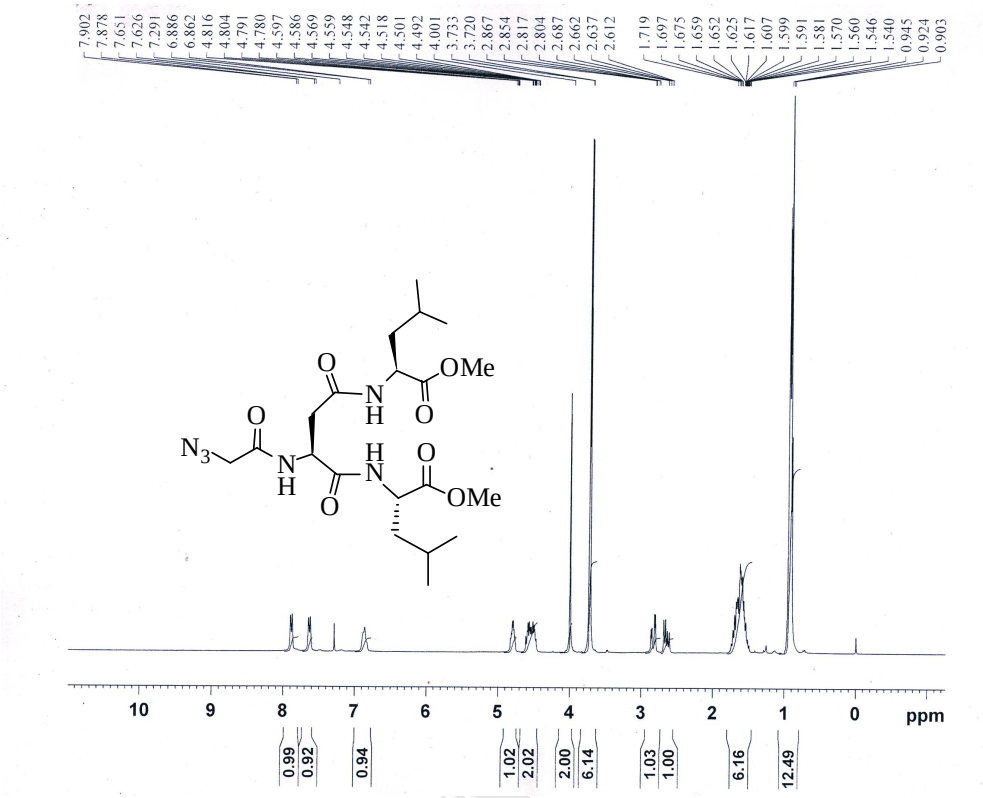
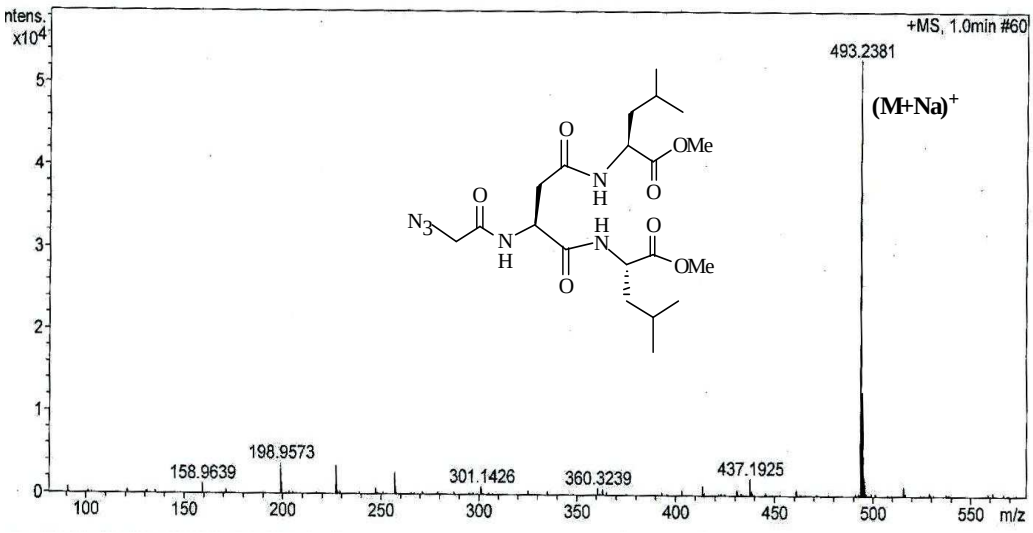
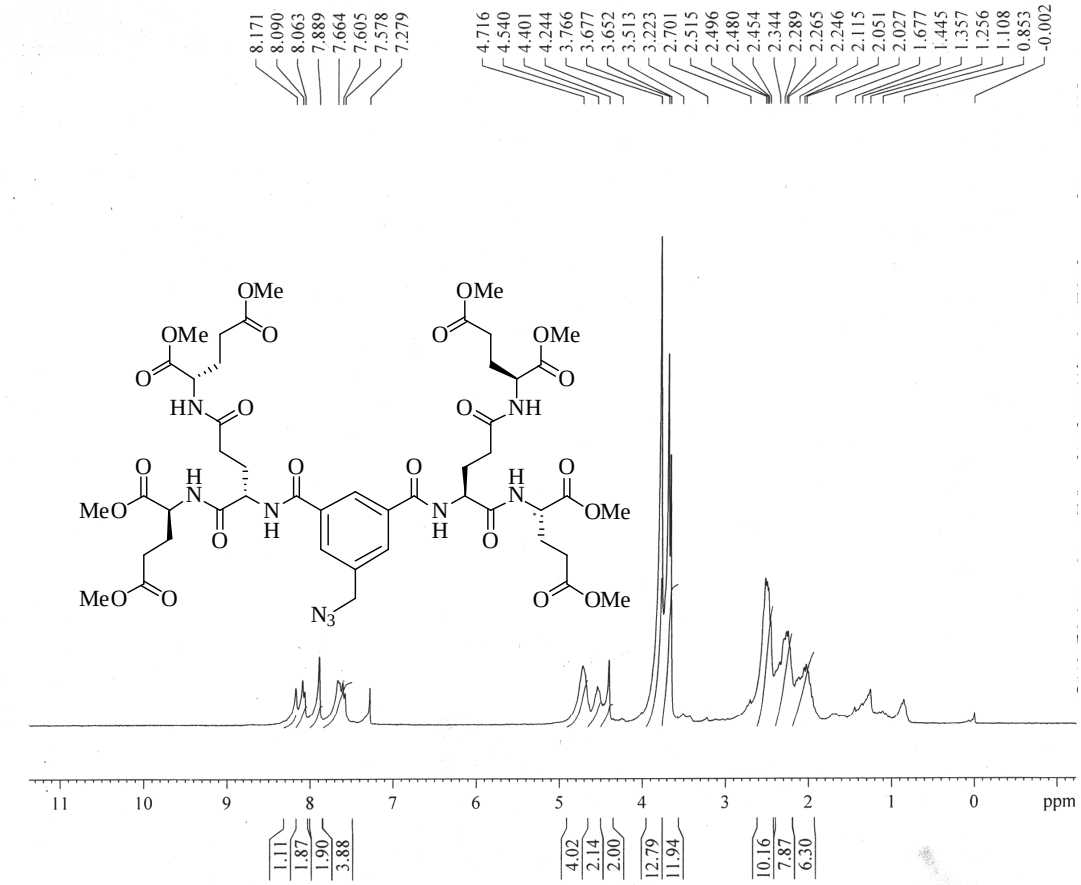


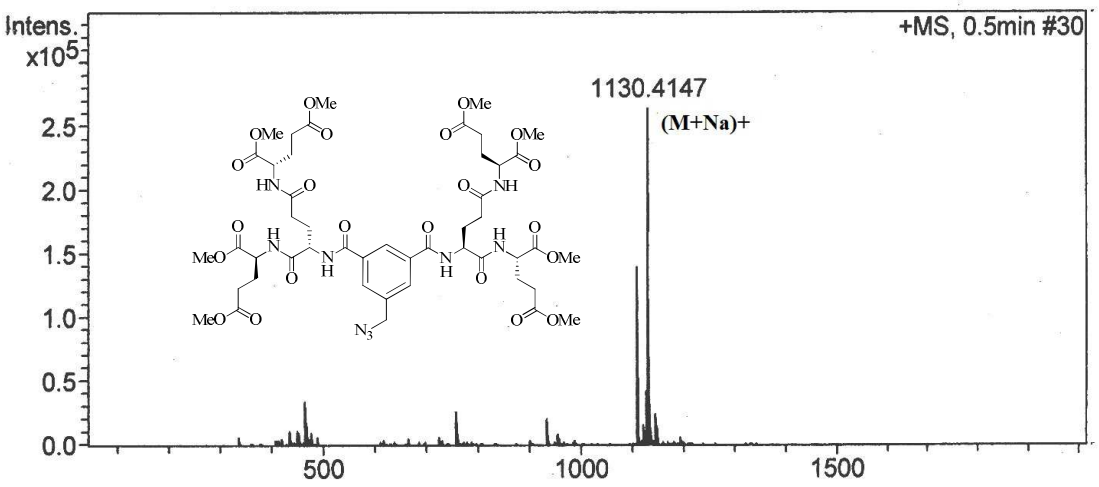
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S10**



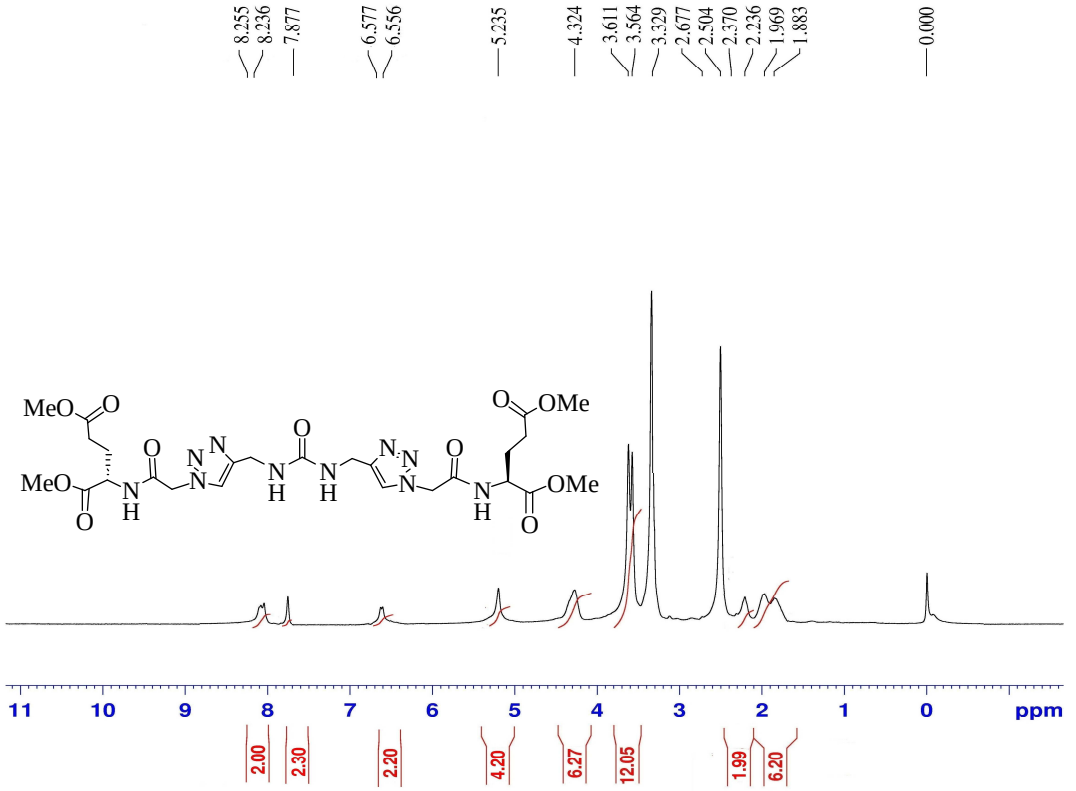
ESI-MS of compound **S10**



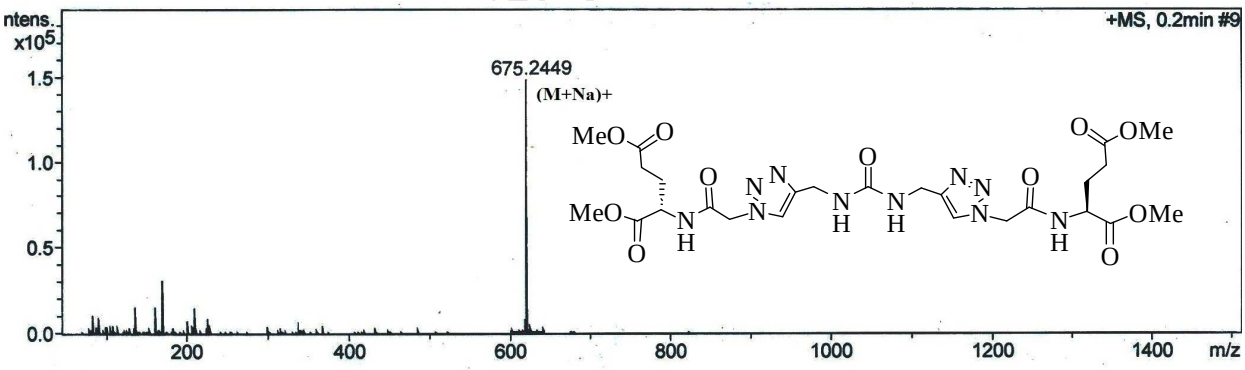
^{1}H NMR ($CDCl_3$, 300 MHz) spectrum of **S12**



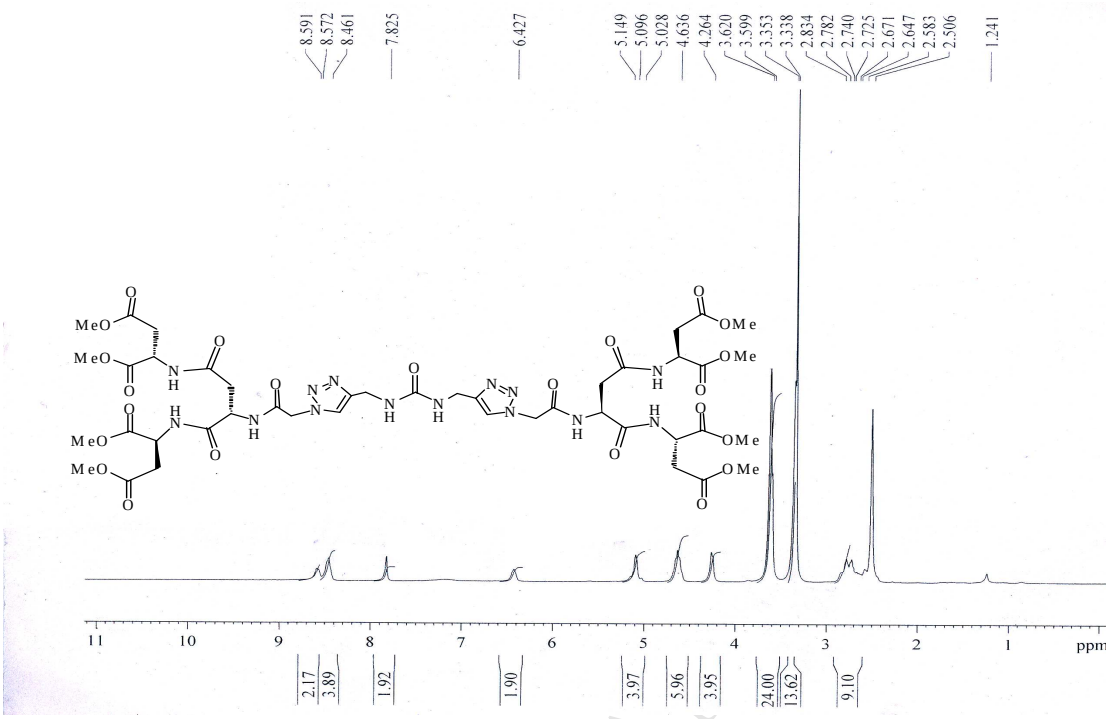
ESI-MS of compound **S12**



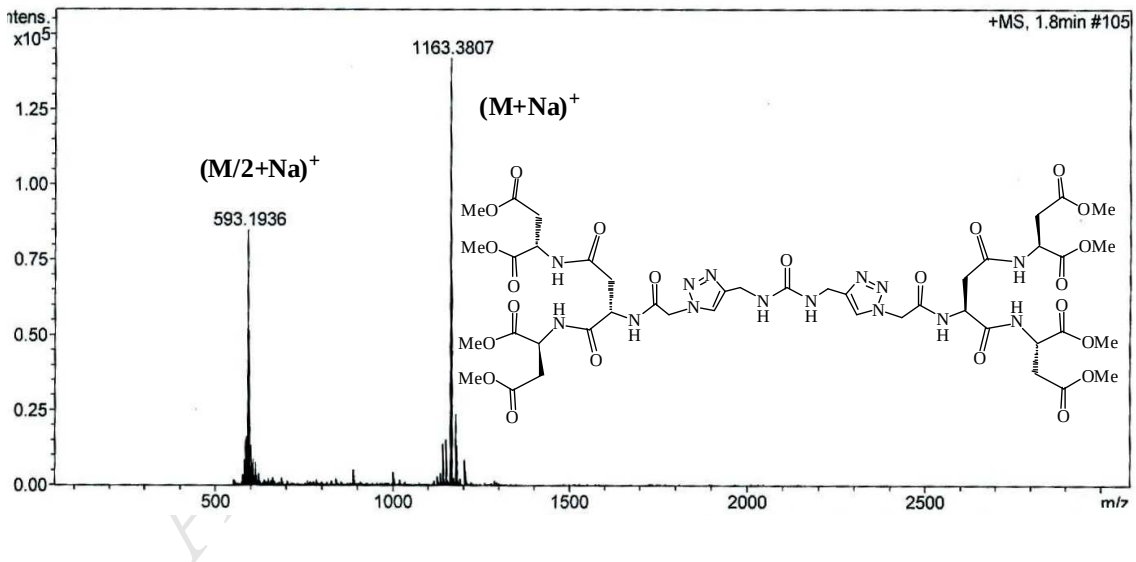
^{1}H NMR (DMSO-d$_6$, 300 MHz) spectrum of **ST14**



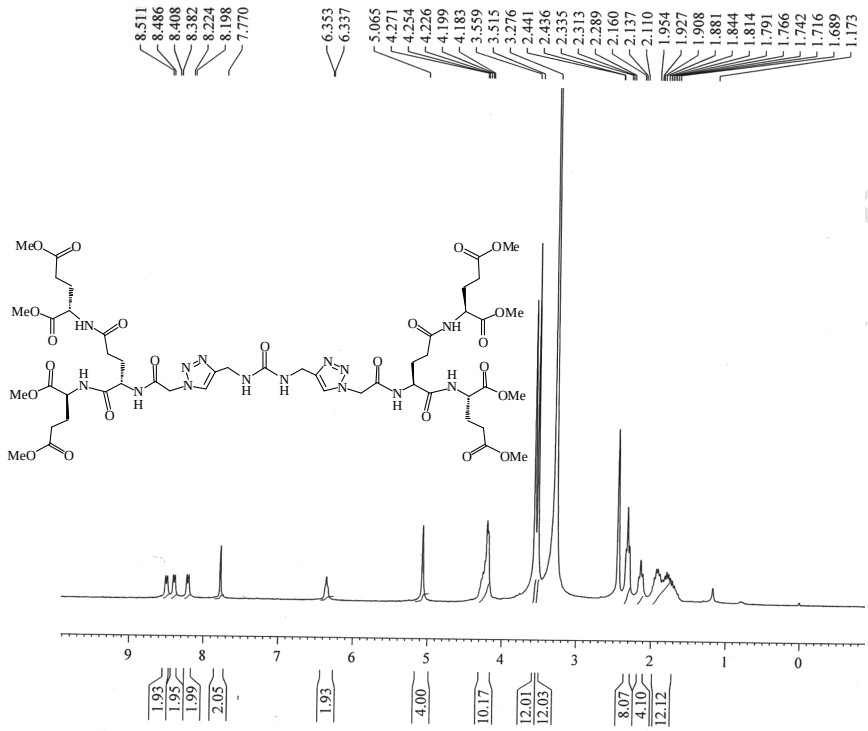
ESI-MS of compound **ST14**



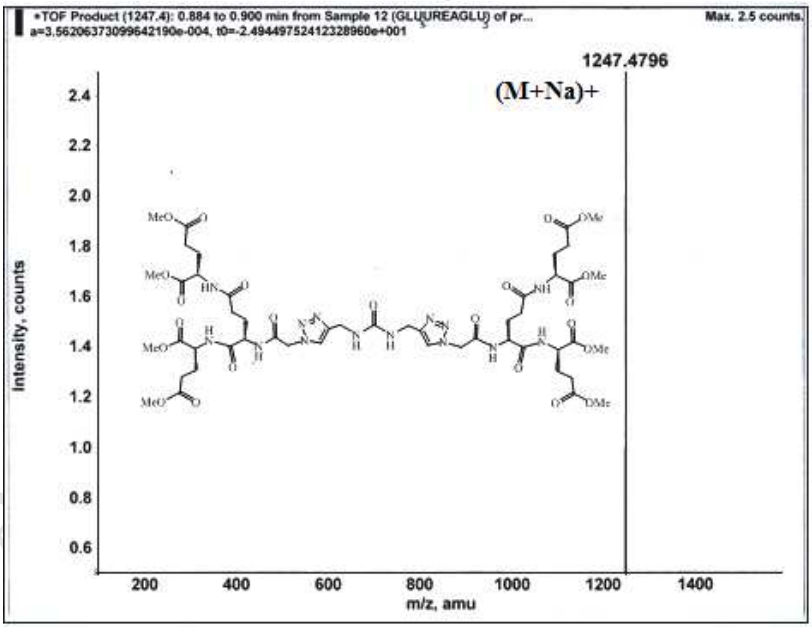
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of **ST15**



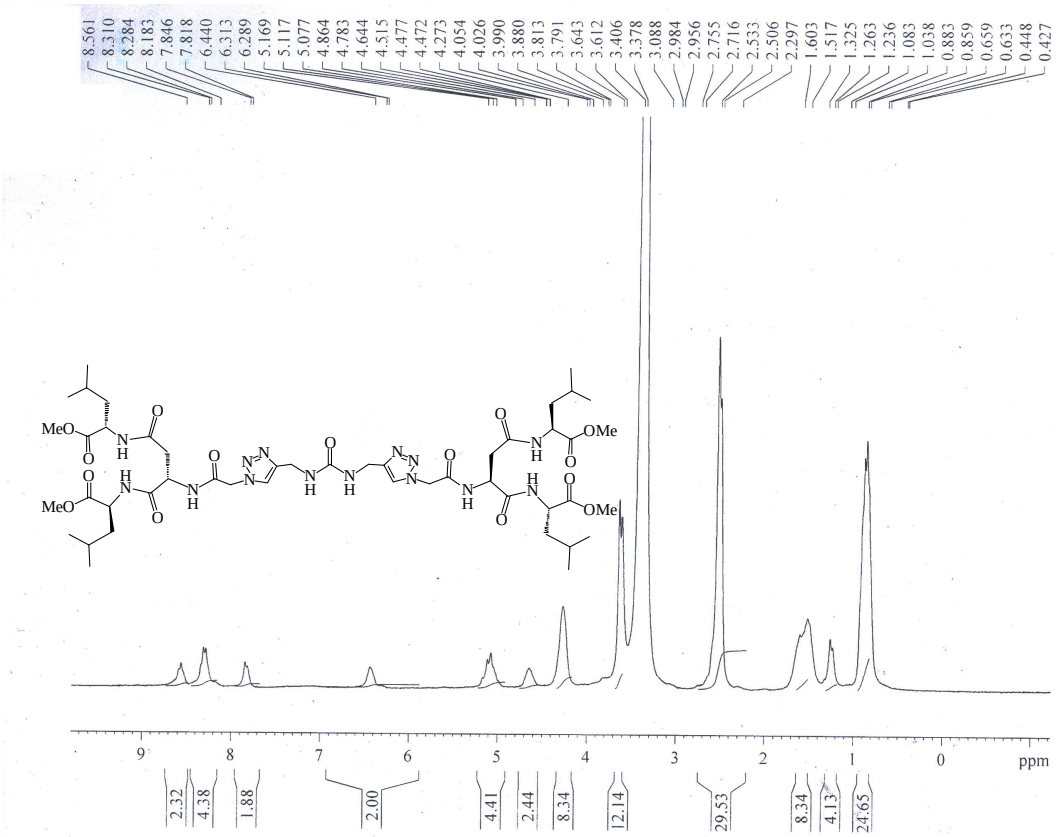
ESI-MS of compound **ST15**



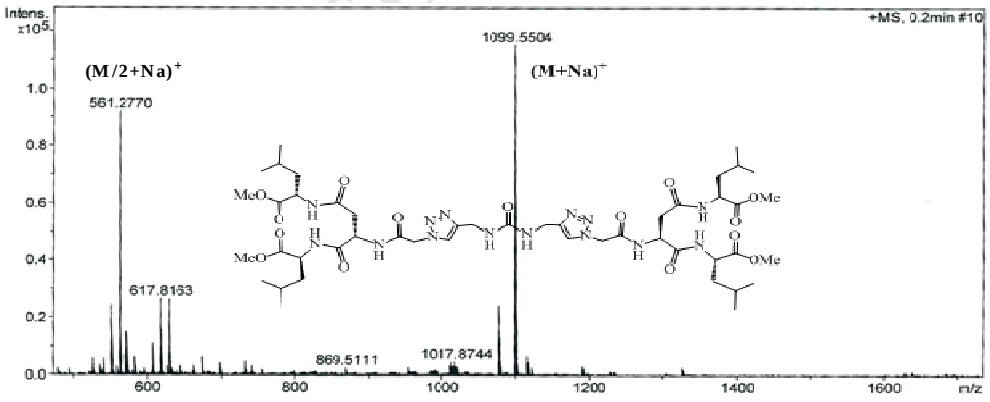
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of **ST16**



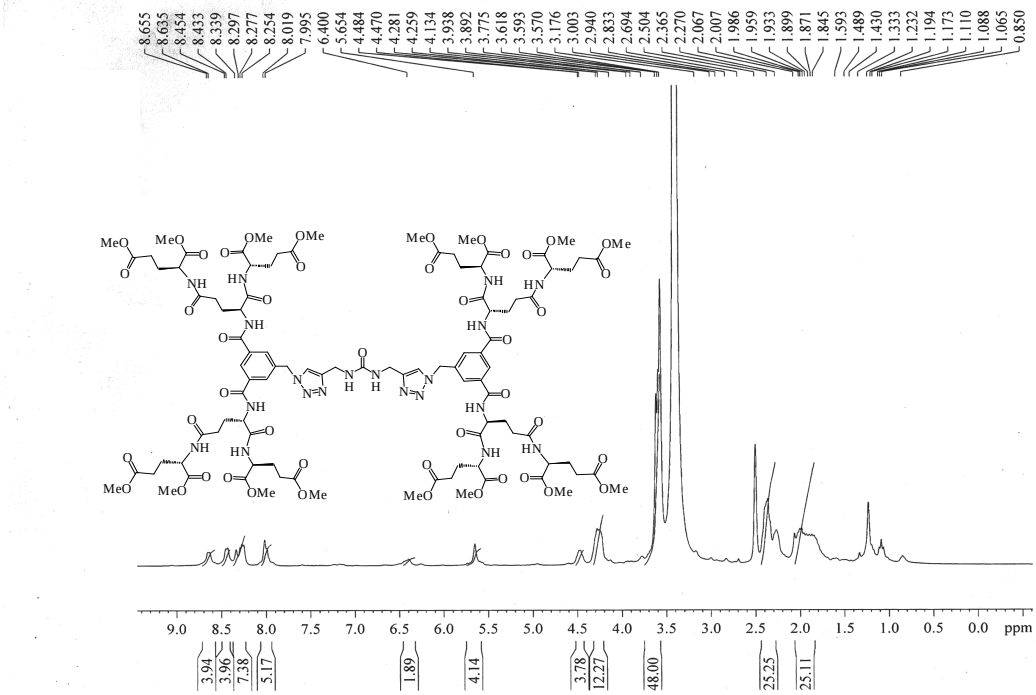
ESI-MS of compound **ST16**



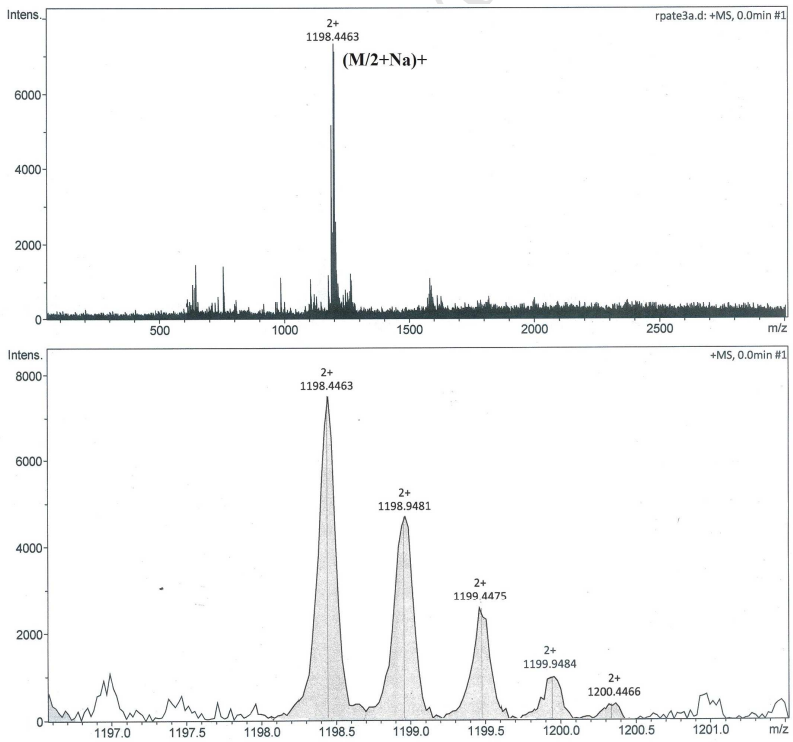
^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of **ST17**



ESI-MS of compound **ST17**



^{1}H NMR (DMSO-d_6, 300 MHz) spectrum of **ST18**



ESI-MS of compound **ST18**

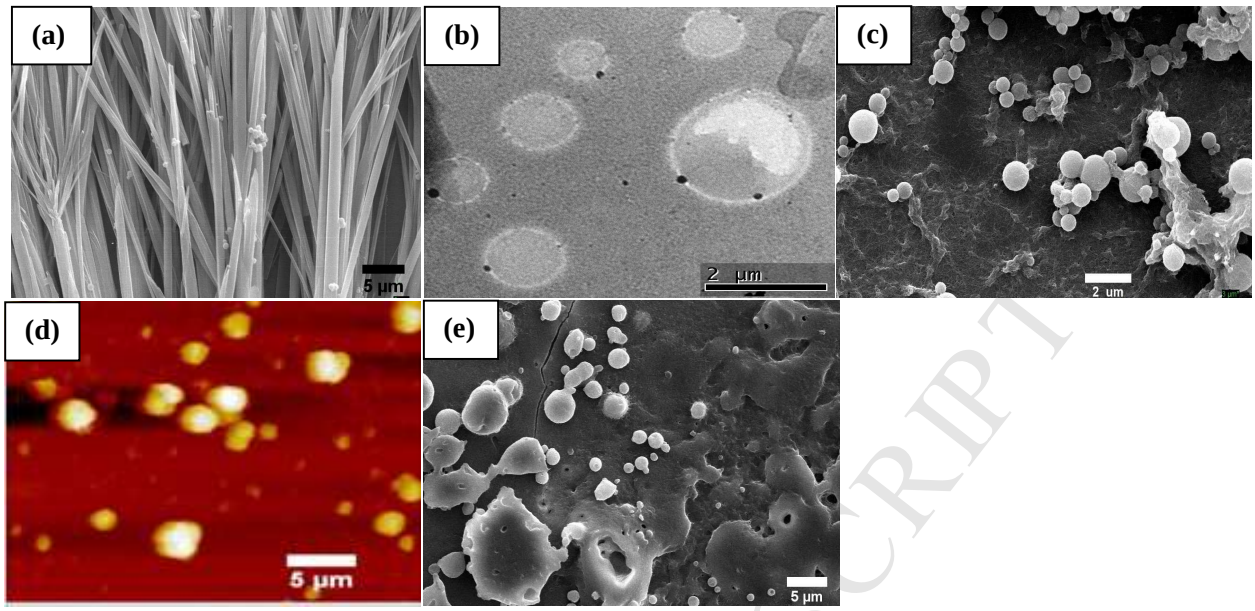


Figure S1: SEM image of (a) **S3d** (b) HR-TEM image of **ST14** in (1:1) $CHCl_3$:CH_3OH (c) SEM image of **ST15** (d) AFM image of **ST15** in tapping mode (e) SEM image of **ST16**

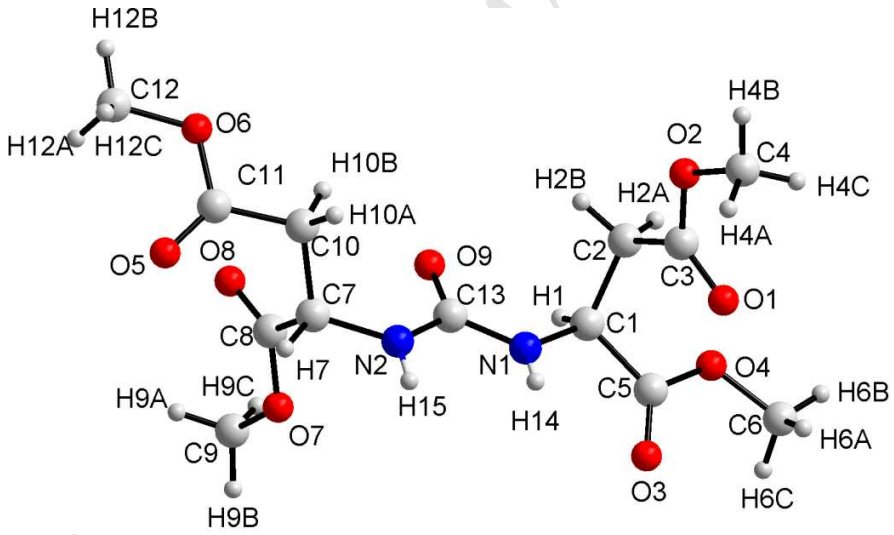


Figure S2: X-ray crystal structure of **S3a** indicating the atom labels.

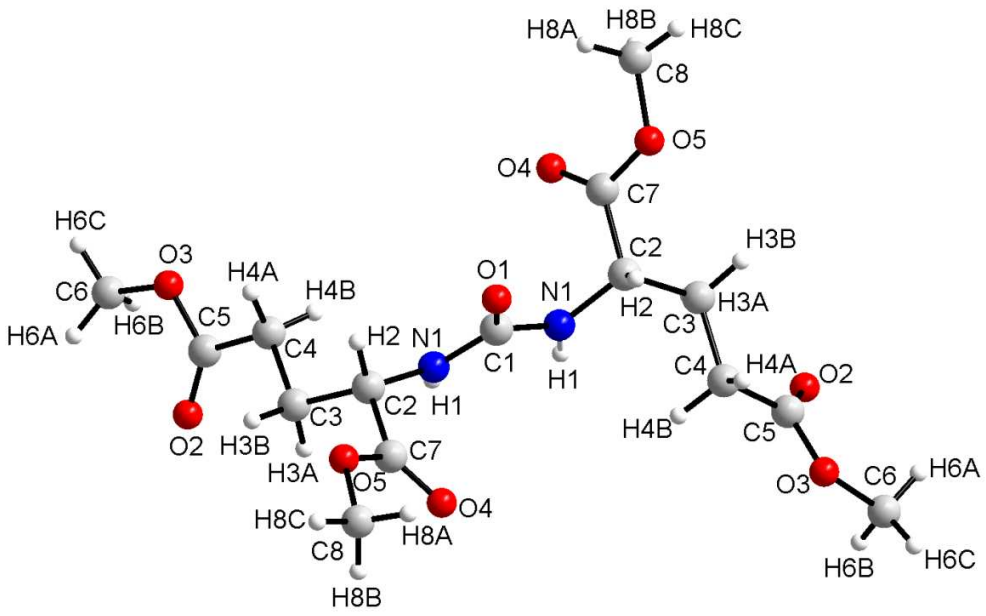


Figure S3: X-ray crystal structure of **S3b** indicating the atom labels.

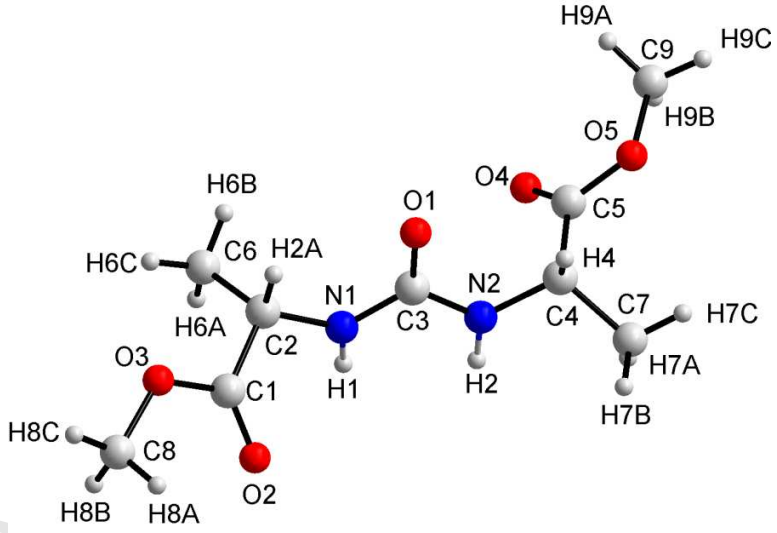


Figure S4: X-ray crystal structure of **S3e** indicating the atom labels.

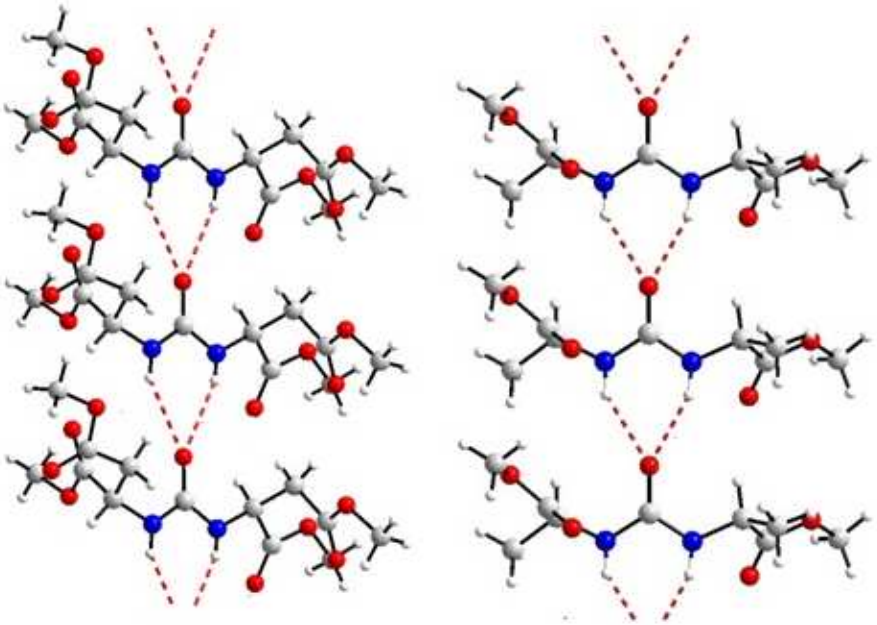


Figure. S5: X-ray structure of (a) **S3a** and (b) **S3e** showing intermolecular H bonding.

Compound	**type**	**Donor**	**H label**	**Acceptor**	**DH----A (Å)**	**D----A (Å)**	**∢DHA**
S3a	Inter	N1	H14	O9	2.495	3.199	154.08^{o}
		N2	H15	O9	2.418	3.167	152.36^{o}
S3b	Inter	N1	H1	O1	2.223	2.993	148.95^{o}
		N1	H1	O1	2.223	2.993	148.95^{o}
S3e	Inter	N1	H1	O1	2.112	2.913	154.85^{o}
		N2	H2	O1	2.169	2.941	149.24^{o}

Table S1 : Hydrogen bond distances and angles of **S3a**, **S3b** and **S3e**.

X-ray Crystallographic studies

Crystal Data of S3a (CCDC 1051349)

Empirical formula	$C_{13}H_{20}N_2O_9$
Formula weight	348.31
Crystal system	Monoclinic
space group	$P2_1$
a [Å]	4.9241(8)
b [Å]	11.2488(19)
c [Å]	15.418(3)
α [deg]	90.00
β [deg]	96.569(3)
γ [deg]	90.00
Z	2
V [Å^3]	848.4(2)
D_{calc} [g/cm^3]	1.363
μ [mm^{-1}]	0.116
max/min transm	0.983/0.977
θ range (deg)	1.33-24.99
reflections collected	8124
independent/(R_{int})	2979 (0.0323)
observed ($I > 2\sigma(I)$)	2723
goodness-of-fit on F^2	1.211
$R(F)$	0.0635
$R_\omega(F^2)$	0.1276
Δρ max/min (eÅ^{-3})	0.171 /-0.179

Table S2

Crystal Data of S3b (CCDC 1051350)

Empirical formula	$C_{15}H_{24}N_2O_9$
Formula weight	376.36
Crystal system	Monoclinic
space group	$C2_y$
a [Å]	21.028(16)
b [Å]	4.716(8)
c [Å]	9.580(8)
α [deg]	90.00
β [deg]	111.92(16)
γ [deg]	90.00
Z	2
V [Å^3]	881.3(12)
D_{calc} [g/cm^3]	1.418
μ [mm^{-1}]	0.118
max/min transm	0.983/0.977
θ range (deg)	2.09-25
reflections collected	1073
independent/(R_{int})	1042 (0.0091)
observed ($I > 2\sigma(I)$)	952
goodness-of-fit on F^2	1.177
$R(F)$	0.0510
$R_\omega(F^2)$	0.1282
Δρ max/min (eÅ^{-3})	0.238 /-0.230

Table S3

Crystal Data of S3e (CCDC 1051366)

Empirical formula	$C_9H_{16}N_2O_5$
Formula weight	232.24
Crystal system	Monoclinic
space group	$P2_1$
a [Å]	4.657(2)
b [Å]	12.775(6)
c [Å]	10.399(5)
α [deg]	90.00
β [deg]	100.012(9)
γ [deg]	90.00
Z	2
V [Å^3]	609.3(5)
D_{calc} [g/cm^3]	1.266
μ [mm^{-1}]	0.103
max/min transm	0.988/0.982
θ range (deg)	2.55-24.99
reflections collected	2132
independent/(R_{int})	2132 (0.0285)
observed ($I > 2\sigma(I)$)	1875
goodness-of-fit on F^2	1.102
$R(F)$	0.0665
$R_\omega(F^2)$	0.1638
Δρ max/min (eÅ^{-3})	0.270/ -0.186

Table S4

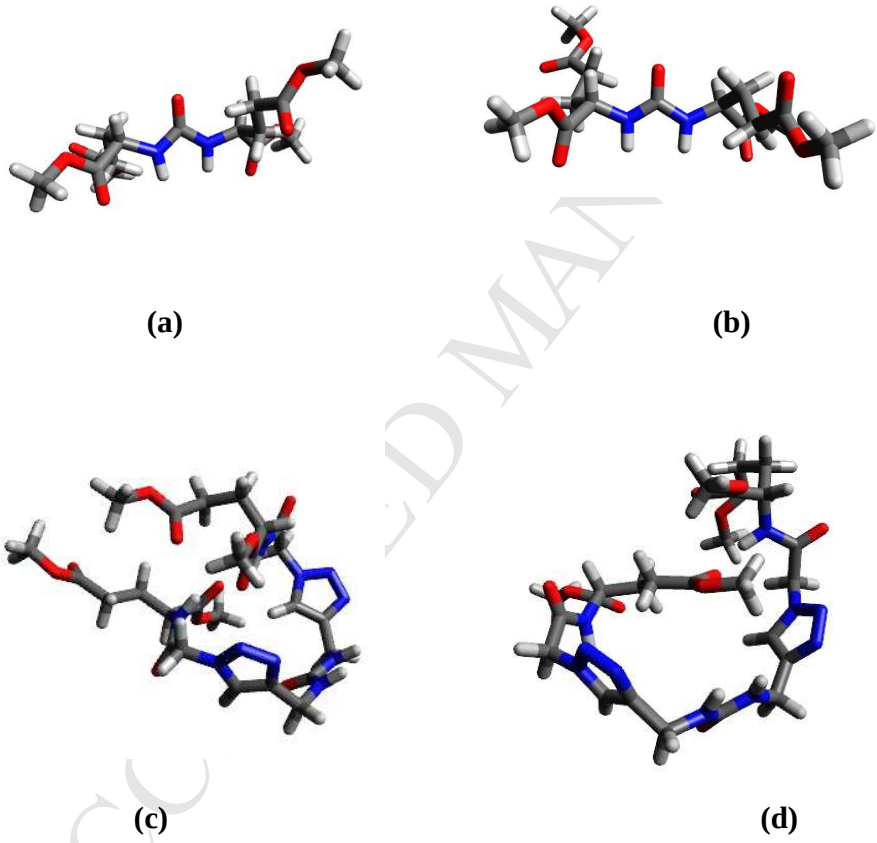
Solvent	Critical gel concentration (g/mL)
Chloroform	No gel
Ethyl Acetate	No gel
Methanol	No gel
Acetonitrile	No gel
THF	No gel
Acetone	No gel
Dichloromethane	No gel
Ethanol	No gel
Water	Insoluble
Chloroform:Hexane (6:4)	Gel (0.0072)
Ethyl acetate:Hexane (1:1)	No gel

Table S5: Gelation study of **S6a-b** in various solvents.

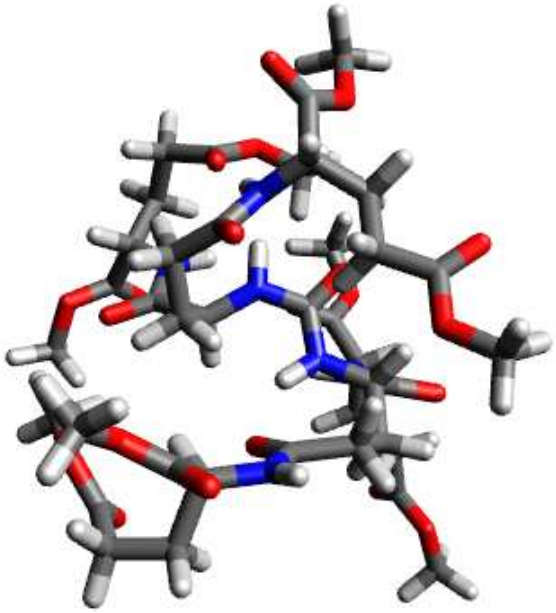
Molecular dynamics simulations

Molecular dynamics (MD) simulations were performed on a GPU clusters at Supercomputing Facility (SCFBio) at IIT Delhi. The AMBER 14 package[1] was used to prepare files for **S6b**, **ST14** and **ST16** and for performing MD simulations. Molecules were solvated in an octahedron box of CH_3OH (methanol) and $CHCl_3$ with a 10 Å distance between the molecular surface and the box boundary. The partial atomic charges for the molecules were obtained using "antechamber" module of AMBER. The partial atomic charges for the ligands were obtained after optimization at the Hartree-Fock level with 6-31G* basis set and subsequent single-point calculation of the electrostatic potential to which the charge were fitted using RESP procedure. The energy minimization and MD simulations of **S3b**, **S6b**, **ST14** and **ST16** were carried out with the aid of the SANDER module of the AMBER 14 program. At first, the simulation was affected with 1000 step minimization using the steepest descent algorithm followed by a 1500 step minimization using conjugate gradient to remove bad steric contacts. Topology and parameter files for the **S3b**, **S6b**, **ST14** and **ST16** were prepared using "gaff" based on the atom types of the force field model developed by Cornell et al.[2] Then the system was equilibrated with solvent molecules at 300 K. Next step involved the equilibration of the molecules **S3b**, **S6b**, **ST14** and **ST16** with a fixed configuration of the solvent molecules in which the system was slowly heated from T = 10 to 310 K for 1ns. The entire system was then equilibrated at 300 K for 10 ns. The MD simulations were performed with a periodic boundary condition in the NPT ensemble at T = 310 K with Berendsen temperature coupling and constant pressure P = 1 atm with

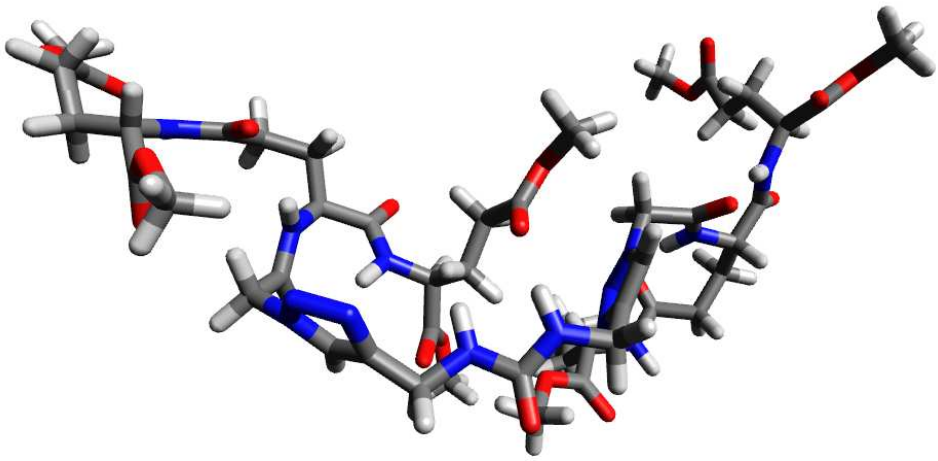
isotropic molecule-based scaling. The simulation was then carried out under NPT conditions for 150 ns. A 2 femto second (fs) time step was used for integrating the equations of motion. We used a time step of 2 fs and a nonbonding interaction cutoff radius of 12 Å. The Particle Mesh Ewald (PME) method[3] was used to treat long-range electrostatic interactions. Convergence of energy, density were monitored**.** The coordinates of the trajectory was sampled every 100 ps for analysis of the energy stabilization.



Figures S6: Energy minimum structures obtained after performing MD simulation of (a) **S3b** in chloroform (b) **S3b** in methanol (c) urea-triazole cored **ST14** in chloroform (d) **ST14** in methanol.



(a)



(b)

Figures S7: MD simulated structure of (a) second generation urea cored dendrimer in chloroform **S6b** (b) second generation urea-triazole cored dendrimer **ST16** in chloroform.

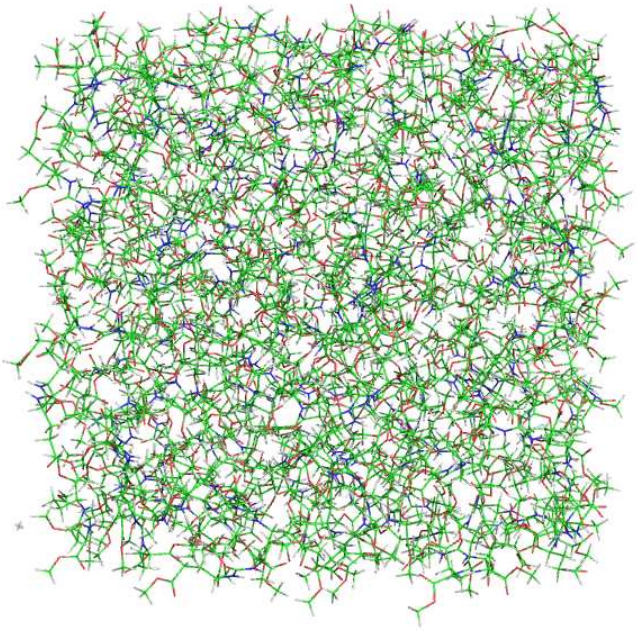


Figure S8: Fibrillar assembly formed from urea cored molecule **S3b**. The simulation was performed in chloroform : Methanol using AMBER (ff99SB) force field.

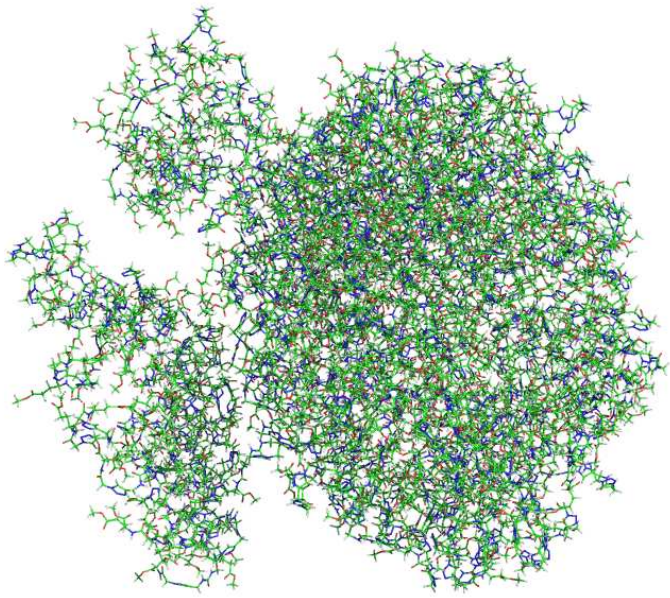


Figure S9: The urea-triazole cored dendrimer **ST14** assembly in a mixture of chloroform and methanol. The assembly was simulated using AMBER (ff99SB) force field. The results of the simulation show a completely formed vesicle with partially formed curved surface.

References

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2. Cornell, W. D.; Cieplak, P.; Bayly, C. I.; Gould, I. R.; Merz, K. M.; Ferguson, D. M.; Spellmeyer, D. C.; Fox, T.; Caldwell, J. W.; Kollman, P. A. *J. Am. Chem. Soc*. **1995**, *117*, 5179–5197.
3. Essmann, U.; Perera, L.; Berkowitz, M. L.; Darden, T.; Lee, H.; Pedersen, L. G. *J.Chem. Phys.* **1995**, *103*, 8577.