Electronic Supplementary Information (ESI)

Self-assembly of lipidated pseudopeptidic triazolophanes to vesicles

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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. Amino acid L-Serine was purchased from SRL India. 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 (^{1}H) 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 using ESI technique. Circular Dichroism (CD) spectra were recorded on AVIV Model 410 spectropolarimeter equipped with a temperature controller. CD spectra were recorded using 1 mm length cell. MD simulations were performed on 320 processors SUN Microsystems clusters at Supercomputing Facility (SCFBio) at IIT Delhi.

Microscopic studies

(b) Scanning Electron Microscopy (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 ZEISS EVO 50 SEM.

(c) 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 (FESEM) combined with High-current ion column with Ga liquid-metal ion source.

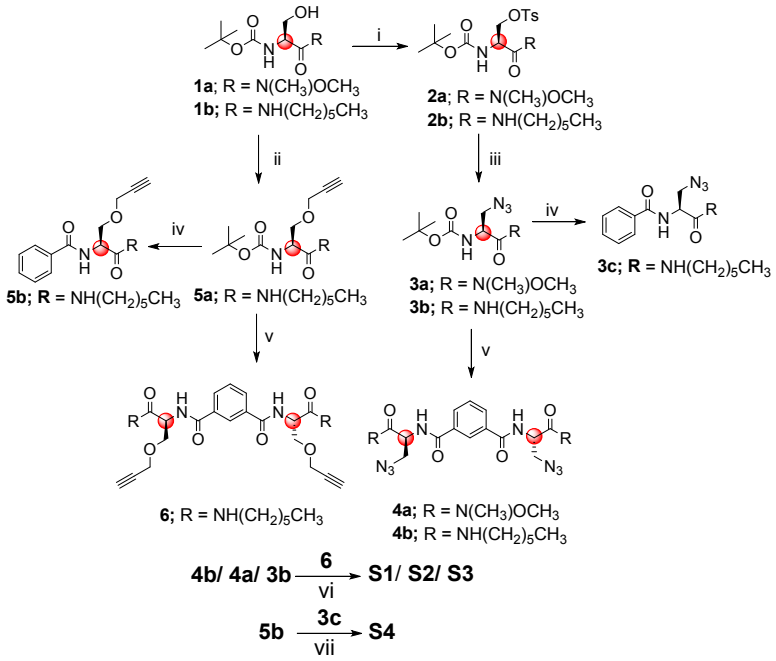
(d) Atomic Force Microscopy (AFM)

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

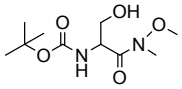
(e) High Resolution-Transmission Electron Microscopy (HR-TEM)

Samples for HR-TEM were prepared by dissolving the compound in 1:1 methanol and chloroform mixture. A 2µl 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 (20S-TWIN) electron microscope.

Scheme



Synthesis of **1a**



Boc-Serine (5.33 g, 26 mmol) was dissolved in 200 mL of dry CH_2Cl_2 and sequentially added N-Methoxy methylamine (2.8 g, 28.7 mmol) and Diisopropylethylamine (DIEA) (8.89 mL, 51.04 mmol). The reaction mixture was stirred at 0°C and HBTU (11.8 g, 31.1 mmol) was added in 4 equal parts over a time period of 1h. The reaction mixture was left stirred for 8h. Filtered the reaction mixture and the filtrate was diluted with 100 mL CH_2Cl_2, washed sequentially with 0.2 N H_2SO_4, $NaHCO_3$ (saturated) and water. The organic part was dried over Na_2SO_4 and evaporated to yield 7 g of the crude product. It was then chromatographed over silica gel (60-120 mesh) with $CHCl_3$:CH_3OH (97:3) as eluent to yield 3.59 g of the pure product.

Yield: 55.6%

Appearance: White crystalline solid

Melting point: 120-121°C

$[\alpha]_D^{30}$: -17.20 (c 0.104, CH_3OH)

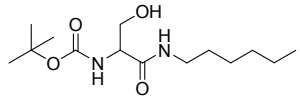
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H, -C(C<u>*H*</u>$_3$)$_3$), 2.65 (br s, 1H, -CH$_2$O<u>*H*</u>), 3.24 (s, 3H, -NC<u>*H*</u>$_3$), 3.81 (s+m, 5H, -OC<u>*H*</u>$_3$+-OC<u>*H*</u>$_2$), 4.81 (m, 1H, -NHC<u>*H*</u>C=O), 5.63 (br s, 1H, -N<u>*H*</u> Boc)

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.30, 32.08, 52.55, 61.53, 63.11, 79.84, 155.82, 171.08.

IR (KBr): 3441, 2981, 2934, 1697, 1650, 1512, 1461, 1393, 1368, 1266, 1169 cm^{-1}.

HRMS calcd for $C_{10}H_{20}N_2O_5Na$, m/z = 271.1270, obtained m/z = 271.1271

Synthesis of **1b**



Boc-Serine (2 g, 9.75 mmol) was dissolved in 100 mL of dry CH_2Cl_2 and sequentially added N-hydoxy succinimide (1.34 g, 11.6 mmol), DCC (2.4 g, 11.6 mmol), hexylamine (1.53 mL, 11.6 mmol) and triethylamine (3 mL, 21.5 mmol). The reaction mixture was left stirred for 24 h. Filtered the reaction mixture, washed the residue with CH_2Cl_2, the combined organic part was collected, dried over Na_2SO_4 and evaporated to yield 2.8 g of the crude product. The crude product was chromatographed over silica gel (60-120 mesh) with EtOAc-Hexane (3:7) to yield 2.3 g of the pure product.

Yield: 82%

Appearance: Yellow viscous liquid

$[\alpha]_D^{30}$: -13.89 (c 0.14, CH_3OH)

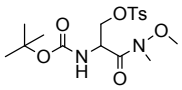
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (br t, 3H, C<u>*H*</u>$_3(CH_2)_3CH_2$-), 1.29 (br m, 6H, $CH_3(C$<u>*H*</u>$_2)_3$-), 1.46 (s, 9H, -C(C<u>*H*</u>$_3)_3$), 1.90 (s, 2H, -NHCH$_2$C<u>*H*</u>$_2$-), 3.25 (m, 2H, -NC<u>*H*</u>$_2$), 3.47 (br dd, 1H, Ser C<u>*H*</u>$_2$), 3.65 (br dd, 1H, Ser C<u>*H*</u>$_2$), 4.10 (m, 1H, -NHC<u>*H*</u>C=O-), 5.64 (br d, J = 6 Hz, 1H, -N<u>*H*</u> Boc), 6.76 (br s, 1H, -N<u>*H*</u>CH$_2$-)

^{13}C NMR (75 MHz, $CDCl_3$): δ 12.92, 21.45, 25.45, 27.25, 28.30, 30.39, 38.53, 54.19, 61.85, 79.40, 155.22, 170.18

IR (KBr): 3419, 3392, 2958, 2931, 2859, 1697, 1650, 1556, 1456, 1367, 1251, 1169, 1062 cm^{-1}

HRMS calcd for $C_{14}H_{28}N_2O_4Na$, m/z = 311.1947, obtained m/z = 311.1947

Synthesis of **2a**



1a (1.6 g, 6.44 mmol) was dissolved in dry CH_2Cl_2 and added triethylamine (1.8 mL, 12.9 mmol) and stirred for 10 minutes. Tosyl chloride (2.46 g, 12.9 mmol) in dry CH_2Cl_2 was added over a period of 20 minutes and stirred for 8 h. The reaction mixture was directly loaded on a column of silica gel (230-400 mesh) and eluted with $CHCl_3$:CH_3OH (97.8:2.2) to yield 0.975 g of pure product.

Yield: 38%

Appearance: Colorless viscous liquid.

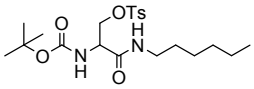
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.41 (s, 9H, -C(C<u>*H*</u>$_3)_3$), 2.45 (s, 3H, ArC<u>*H*</u>$_3$), 3.16 (s, 3H, -NC<u>*H*</u>$_3$), 3.71 (s, 3H, -OC<u>*H*</u>$_3$), 4.23 (m, 2H, Ser C<u>*H*</u>$_2$-), 4.86 (br s, 1H, -NHC<u>*H*</u>C=O), 5.37 (br d, 1H, -N<u>*H*</u> Boc), 7.34 (d, J = 7.8 Hz, 2H, ArC<u>*H*</u>), 7.77 (d, J = 7.8 Hz, 2H, ArC<u>*H*</u>)

^{13}C NMR (75 MHz, $CDCl_3$): δ 21.54, 28.17, 32.04, 50.25, 61.52, 68.75, 79.83, 127.90, 129.84, 132.46, 144.98, 154.92, 168.05

IR (KBr): 3426, 2928, 1759, 1713, 1668, 1497, 1365, 1178 cm^{-1}

HRMS calcd for $C_{17}H_{26}N_2O_7SNa$, m/z = 425.1358, obtained m/z = 425.1130.

Synthesis of **2b**



1b (0.23 g, 0.8 mmol), was dissolved in dry CH_2Cl_2 (25 mL), added 4-(Dimethylamino) pyrinine (DMAP) (0.058 g, 0.47 mmol) and triethylamine (0.56 mL, 4.02 mmol). To the above mixture at 0^oC, tosyl chloride (0.18 g, 0.94 mmol) in dry CH_2Cl_2 was added drop wise. The reaction mixture was stirred for 18 h, and evaporated to obtain crude product. It was charged on to a column of silica gel (100-200 mesh) and eluted with EtOAc:Hexane (2:3) to yield 0.162 g of **2b** and 0.072 g of dehydro alanine derivative.

Yield: 49.7%

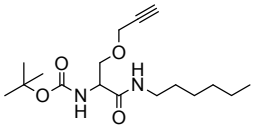
Appearance: Colorless viscous liquid

^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 6.5 Hz, 3H, C$\underline{H}_3(CH_2)_3CH_2$-), 1.29 (br s, 6H, -$CH_2(C\underline{H}_2)_3CH_3$), 1.46 (s, 9H, -C(C$\underline{H}_3)_3$), 1.89 (s, 2H, -NHC$H_2C\underline{H}_2$-), 2.46 (s, 3H, ArC$\underline{H}_3$), 3.22 (m, 2H, -NHC$\underline{H}_2$-), 4.18 (m, 1H, -NHC$\underline{H}$C=O), 4.36 (m, 2H, Ser C$\underline{H}_2$), 5.35 (br s, 1H, –N$\underline{H}$ Boc), 6.35 (br s, 1H, -N$\underline{H}CH_2$-), 7.36 (d, J = 8.1 Hz, 2H, ArC$\underline{H}$), 7.78 (d, J = 8.4 Hz, 2H, ArC$\underline{H}$)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.99, 21.66, 22.49, 26.43, 28.22, 29.30, 31.41, 39.77, 53.46, 69.02, 80.99, 128.02, 130.00, 132.18, 145.31, 155.27, 167.96

IR (KBr): 3330, 2958, 2929, 2856, 1685, 1661, 1544, 1518, 1456, 1367, 1305, 1244, 1172 cm^{-1}

Synthesis of **5a**



3a (0.1 g, 0.35 mmol), was dissolved in CH_2Cl_2 (20 mL), and added 2 mL of conc. NaOH (2 g/5 mL) and tetrabutylammonium bromide (TBABr) (0.028 g, 0.087 mmol), stirred for 20 minutes, added propargyl bromide (0.12 mL, 1.6 mmol) and stirred for 12 h. The reaction mixture was diluted with CH_2Cl_2 (100 mL), and washed thrice with water. The organic layer was separated, dried over Na_2SO_4, and evaporated to yield 0.12 g of the crude product. It was then chromatographed over silica gel (100-200mesh) with EtOAc:Hexane (1:1) to yield 0.05 g of **5a**.

Yield: 44%

Appearance: Colorless viscous liquid.

$[\alpha]_D^{30}$: -2.74 (c 0.109, CH_3OH)

^1H NMR (300 MHz, $CDCl_3$): δ 0.87 (br s, 3H, C$\underline{H}_3(CH_2)_3CH_2$-), 1.28 (br s, 6H, -$CH_2(C\underline{H}_2)_3CH_3$), 1.47 (s+m, 11H, -C(C$\underline{H}_3)_3$+-NHC$H_2C\underline{H}_2$-), 2.46 (s, 1H, -C≡C$\underline{H}$), 3.28 (m,

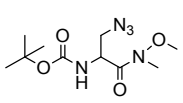
2H, -NHC$\underline{H_2}$-), 3.65 (m, 1H, Ser C$\underline{H_2}$-), 3.89 (m, 1H, SerC$\underline{H_2}$-), 4.10-4.23 (m, 3H, -NHC$\underline{H}$C=O+-OC$\underline{H_2}$C≡CH), 5.39 (br s, 1H, (-N$\underline{H}$ Boc), 6.41 (br s, 1H, -CON$\underline{H}$CH$_2$-)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.95, 22.49, 26.42, 28.27, 29.38, 31.41, 39.59, 53.89, 58.57, 69.56, 75.11, 78.97, 80.28, 155.47, 169.81.

IR (KBr): 3313, 2930, 2859, 2359, 1714, 1659, 1538, 1518, 1469, 1366, 1248, 1169, 1108 cm^{-1}

HRMS calcd for $C_{17}H_{30}N_2O_4Na$, m/z = 349.2103, obtained m/z = 349.2096.

Synthesis of **3a**



2a (3.53 g, 8.78 mmol) was dissolved in *N*, *N*–dimethylformamide (30 mL), and added NaN_3 (2.28 g, 35 mmol) and was stirred at 40-50^{o}C for 6 h. The reaction mixture was evaporated and directly loaded to a silica gel column and eluted with EtOAc:Hexane (3:7) to yield 2 g of the pure product.

Yield: 84 %

Appearance: Yellow viscous liquid

$[\alpha]_D^{38}$: +4.30 (c 0.093, CH_3OH)

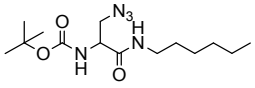
^{1}H NMR (300 MHz, $CDCl_3$): δ 1.45 (s, 9H, -C(C$\underline{H_3}$)$_3$), 3.25 (s, 3H, -NC$\underline{H_3}$), 3.57 (m, 2H, -C$\underline{H_2}$N$_3$), 3.78 (s, 3H, -N(OC$\underline{H_3}$)), 4.86 (m, 1H, -CH$_2$C$\underline{H}$C=O), 5.55 (br d, 1H, -N$\underline{H}$ Boc)

^{13}C NMR (75 MHz, $CDCl_3$): δ 28.13, 31.99, 50.55, 52.01, 61.52, 79.69, 155.05, 169.52

IR (KBr): 3430 (br), 2978, 2936, 2104, 1711, 1661, 1511, 1391, 1250, 1167, 1052 cm^{-1}

HRMS calcd for $C_{10}H_{19}N_5O_4Na$, m/z = 296.1335, obtained m/z = 296.1333

Synthesis of **3b**



2b (0.963 g, 2.18 mmol) was dissolved in DMF, added NaN_3 (2.4 g, 36.9 mmol). The reaction mixture was stirred at 40-50^{o}C for 6 h. The reaction mixture was filtered off through a filter paper, and passed through a sintered funnel containing silica gel. The filtrate was concentrated in reduced pressure and the crude material obtained was chromatographed over silica gel (100-200 mesh) using EtOAc:Hexane (1:4) yielded 0.283 g of the pure product.

Yield: 42%

Appearance: White solid upon standing

Melting point: 59-60^{o}C

$[\alpha]_D^{30}$: +8.40 (c 0.095, CH_3OH)

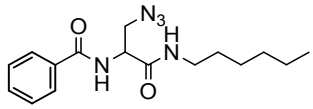
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.68 (br s, 3H, C<u>H</u>$_3$(CH$_2$)$_3$CH$_2$-), 1.27 (br s, 6H, CH$_3$(C<u>H</u>$_2$)$_3$CH$_2$-), 1.47 (s+m, 11H, -C(CH$_3$)$_3$+-NHCH$_2$C<u>H</u>$_2$-), 3.28 (m, 2H, -NHC<u>H</u>$_2$-), 3.52 (dd, J_1 = 11.8 Hz, J_2 = 5.5 Hz, 1H, SerC<u>H</u>$_2$-), 3.85 (dd, J_1 = 12.3 Hz, J_2 = 4.5 Hz, 1H, Ser C<u>H</u>$_2$-), 4.23 (m, 1H, -NHC<u>H</u>C=O), 5.28 (br s, 1H, -N<u>H</u> Boc), 6.29 (br s, 1H, -N<u>H</u> CH$_2$-)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.69, 22.27, 26.31, 28.04, 29.10, 31.22, 39.54, 52.44, 53.85, 80.06, 155.47, 169.49

IR (KBr): 3332, 3089, 2931, 2857, 2102, 1687, 1656, 1551, 1525, 1450, 1374, 1303, 1248, 1169, 1047, 1022 cm^{-1}

HRMS calcd for $C_{14}H_{27}N_5O_3Na$, m/z = 336.2012, obtained m/z = 336.2020

Compound **3c**



3b (0.214 g, 0.68 mmol) was dissolved in dry CH_2Cl_2 (0.8 mL), added TFA (0.8 mL, 10.45 mmol) and the reaction mixture was stirred for 4 h, afterwards it was subjected to vacuum. The amine thus obtained was dissolved in dry CH_2Cl_2 (25 mL) and added triethylamine (0.38 mL, 2.74 mmol) followed by the slow addition of benzoyl chloride (0.96 g, 0.68 mmol) in dry CH_2Cl_2 (10 mL). The reaction mixture was left stirred for 12 h, diluted with CH_2Cl_2 (50 mL), and washed sequentially with 2N H_2SO_4, $NaHCO_3$ and water. The organic layer was collected, dried over anhyd. Na_2SO_4 and evaporated to yield 0.192 g of **3c**

Yield: 88%

Appearance: Pale yellow solid

Melting point: 73- 75^{o}C

$[\alpha]_D^{30}$: +2.02 (c 0.099, CH_3OH)

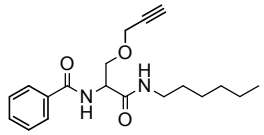
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.87 (br s, 3H, C<u>H</u>$_3$(CH$_2$)$_3$CH$_2$-), 1.27 (br s, 6H, CH$_3$(C<u>H</u>$_2$)$_3$CH$_2$-), 1.47 (m, 2H, -NHCH$_2$C<u>H</u>$_2$-), 3.3 (m, 2H, -NHC<u>H</u>$_2$CH$_2$-), 3.63-3.88 (m, 2H, SerC<u>H</u>$_2$-), 4.93 (m, 1H, -NHC<u>H</u>CO-), 6.97 (br t, 1H, -N<u>H</u>CH$_2$-), 7.37-7.6 (m, 4H, 3Ar<u>H</u>+1N<u>H</u>-), 7.81 (d, J = 7.5 Hz, 2H, Ar<u>H</u>).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.97, 22.49, 26.51, 29.26, 31.40, 39.94, 52.29, 52.83, 127.21, 128.68, 132.18, 133.21, 167.69, 169.06.

IR (KBr): 3299, 3087, 2930, 2861, 2099, 1719, 1638, 1529, 1447, 1296, 1214 cm^{-1}

HRMS calcd for $C_{16}H_{23}N_5O_2Na$, m/z = 340.1749, obtained m/z = 340.1755

Compound **5b**



5a (0.301 g, 0.92 mmol) was dissolved in dry CH_2Cl_2 (1.1 mL), added TFA (1.06 mL, 13.8 mmol) and the reaction mixture was stirred for 4 h. It was then subjected to high vacuum. The amine obtained was

dissolved in dry CH_2Cl_2 and added triethylamine (0.51 mL, 3.68 mmol) followed by benzoyl chloride (0.14 g, 0.99 mmol). The reaction mixture was left stirred for 12 h, diluted with CH_2Cl_2 (50 mL), washed sequentially with 2N H_2SO_4, $NaHCO_3$ and water. The organic layer was collected, dried over anhyd. Na_2SO_4 and evaporated to yield 0.283 g of **5b**

Yield: 93%

Appearance: Pale yellow solid.

Melting point: 98-99^oC

$[\alpha]_D^{30}$: +12.38 (c 0.105, CH_3OH)

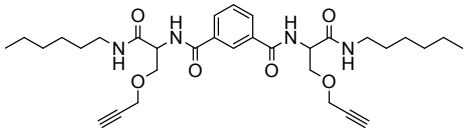
^1H NMR (300 MHz, $CDCl_3$): δ 0.88 (br s, 3H, C*H*$_3$(CH$_2$)$_3$CH$_2$-), 1.30 (br s, 6H, CH$_3$(C*H*$_2$)$_3$CH$_2$-), 1.53 (m, 2H, -NHCH$_2$C*H*$_2$-), 2.47 (s, 1H, -C≡C*H*), 3.30 (m, 2H, -NHC*H*$_2$-), 3.71 (m, 1H, Ser C*H*$_2$-), 4.06 (dd, J_1 = 9.15 Hz, J_2 = 4.2 Hz, 1H, Ser C*H*$_2$-), 4.25 (m, 2H, -OC*H*$_2$C≡CH), 4.71 (m, 1H, -NHC*H*C=O), 6.44 (br s, 1H, -N*H*), 7.16 (d, J = 5.4 Hz, 1H, -N*H*-), 7.48 (m, 3H, Ar*H*), 7.83 (d, J = 7.5 Hz, 2H, Ar*H*).

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.99, 22.52, 26.48, 29.36, 31.42, 39.79, 52.63, 58.68, 69.24, 75.30, 79.00, 127.16, 128.61, 131.93, 133.59, 167.32, 169.57

IR (KBr): 3297, 3095, 2928, 2860, 1716, 1629, 1533, 1462, 1366, 1323, 1255, 1215, 1158, 1104 cm^{-1}

HRMS calcd for $C_{19}H_{26}N_2O_3Na$, m/z = 353.1841, obtained m/z = 353.1847.

Synthesis of **6**



5a (0.76 g, 2.33 mmol) was dissolved in dry CH_2Cl_2 (2.6 mL), added TFA (2.6 mL, 34.9 mmol) and stirred for 4 h. It was then subjected to vacuum and the amine obtained was dissolved in dry CH_2Cl_2 (50 mL), added triethylamine (0.65 mL, 4.7 mmol), stirred for 5 minutes, and benzene dicarbonyl dichloride (0.237 g, 1.17 mmol) in dry CH_2Cl_2 (50 mL) was added dropwise over 10 minutes . The reaction mixture was stirred for 12 h, diluted with CH_2Cl_2 (50 mL), washed sequentially with 2 N H_2SO_4, $NaHCO_3$ and water. The organic part was collected, dried over anhyd. Na_2SO_4 and evaporated to yield 0.99 g of the crude product; which was chromatographed over silica gel (100-200 mesh) using EtOAc to yield 0.45 g of **6**

Yield: 66%

Appearance: White solid

Melting point: 160-161^oC

$[\alpha]_D^{30}$: +12.06 (c 0.116, CH_3OH)

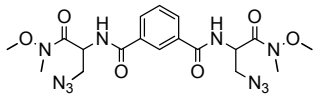
^{1}H NMR (300 MHz, $CDCl_3$): δ 0.89 (br s, 6H, C<u>*H*</u>$_3$(CH$_2$)$_3$CH$_2$-), 1.31 (br s, 12H, -(C<u>*H*</u>$_2$)$_3$CH$_3$), 1.54 (br s, 4H, -NHCH$_2$C<u>*H*</u>$_2$-), 2.54 (s, 2H, -C≡C<u>*H*</u>), 3.31 (m, 4H, -NHC<u>*H*</u>$_2$CH$_2$-), 3.75 (m, 2H, Ser C<u>*H*</u>$_2$), 4.04 (m, 2H, Ser C<u>*H*</u>$_2$), 4.27 (m, 4H -OC<u>*H*</u>$_2$-C≡CH), 4.76 (br m, 2H, -NHC<u>*H*</u>C=O), 6.52 (br s, 2H, -N<u>*H*</u>CH$_2$-), 7.34 (d, J = 5.7 Hz, 2H, Ser N<u>*H*</u>-), 7.54 (t, J = 7.7 Hz, 1H, ArC<u>*H*</u>), 7.99 (d, J = 7.5 Hz, 2H, 2ArC<u>*H*</u>), 8.29 (s, 1H, ArC<u>*H*</u>)

^{13}C NMR (75 MHz, $CDCl_3$): δ 14.03, 22.55, 26.49, 29.38, 31.43, 39.83, 52.76, 58.72, 69.12, 75.52, 78.94, 125.76, 129.05, 130.64, 134.03, 166.38, 169.43

IR (KBr): 3291, 3103, 3066, 2955, 2929, 2857, 2115, 1642, 1563, 1529, 1466, 1394, 1359, 1304, 1251, 1176, 1106, 1013 cm^{-1}

HRMS calcd for $C_{32}H_{46}N_4O_6Na$, m/z = 605.3315, obtained m/z = 605.3323

Synthesis of **4a**



3a (0.18 g, 0.659 mmol) was dissolved in dry CH_2Cl_2 (0.76 mL), and added TFA (0.76 mL, 9.9 mmol), and stirred for 4 h at 0^{o}C. It was subjected to vacuum and the amine obtained was dissolved in dry CH_2Cl_2 (50 mL) and added triethylamine (0.2 mL, 1.44 mmol), stirred for 5 minutes, and slowly added benzene dicarbonyl dichloride (0.067 g, 0.33 mmol) as a solution in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred for 12h at 0^{o}C, diluted with CH_2Cl_2 (50 mL), washed sequentially with 2N H_2SO_4, $NaHCO_3$ and water. The organic layer was collected, dried over anhyd. Na_2SO_4 and evaporated to yield 0.130 g of **4a**.

Yield: 83 %

Appearance: Yellow semi solid

$[\alpha]_D^{30}$: -2.82 (c 0.142, CH_3OH)

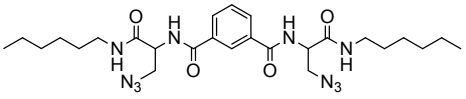
^{1}H NMR (300 MHz, $CDCl_3$): δ 3.30 (s, 6H, -NC<u>*H*</u>$_3$), 3.68-3.80 (m, 4H, N$_3$C<u>*H*</u>$_2$-), 3.85 (s, 6H, -OCH$_3$), 5.37 (br s, 2H, NHC<u>*H*</u>C=O), 7.52 (m, 3H, -N<u>*H*</u>-+ArC<u>*H*</u>), 7.99 (d, J = 7.8 Hz, 2H, ArC<u>*H*</u>), 8.33 (s, 1H, -Ar<u>*H*</u>)

^{13}C NMR (75 MHz, $CDCl_3$): δ 32.34, 50.19, 51.69, 61.86, 125.88, 128.86, 130.62, 133.64, 166.17, 169.52

IR (KBr): 3489, 3346, 3060, 3007, 2940, 2103, 1643, 1535, 1467, 1389, 1296, 1182 cm^{-1}

HRMS calcd for $C_{18}H_{24}N_{10}O_6Na$ m/z = 499.1778 obtained m/z = 499.1780

Synthesis of **4b**



3b (0.282 g, 0.9 mmol) was dissolved in dry CH_2Cl_2 (1.1 mL), and added TFA (1.1 mL, 14.28 mmol), and stirred for 4 h at 0^{o}C. The reaction mixture was subjected to vacuum and the amine obtained was dissolved in dry CH_2Cl_2 (50 mL), added triethylamine (0.37 mL, 2.69 mmol), stirred for 5

minutes, and then slowly added benzene dicarbonyl dichloride (0.914 g, 0.45 mmol) in dry CH_2Cl_2 (50 mL). The reaction mixture was stirred for 12 h at 0^oC, diluted with CH_2Cl_2 (50 mL), washed sequentially with 2 N H_2SO_4, $NaHCO_3$ and water. The organic layer was collected, dried over anhyd. Na_2SO_4 and evaporated to yield 0.212 g of the crude product; which was chromatographed over silica gel (100-200 mesh) using EtOAc as eluent to yield 0.14 g of **4b**

Yield: 56%

Appearance: White crystalline solid

Melting point: 169-170^oC

$[\alpha]_D^{30}$: +6.38 (c 0.094, CH_3OH)

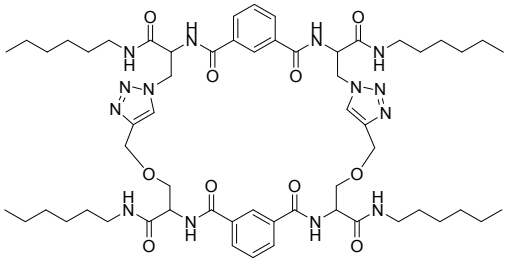
^1H NMR (300 MHz, $CDCl_3$): δ 0.89 (t, J = 6.5 Hz, 6H, C<u>*H*</u>$_3(CH_2)_3CH_2$-), 1.29 (br s, 12H, $CH_3(C$<u>*H*</u>$_2)_3CH_2$-), 1.53 (m, 4H, -$NHCH_2C$<u>*H*</u>$_2$-), 3.29 (m, 4H, -NHC<u>*H*</u>$_2$-), 3.67 (dd, J_1 = 12.3 Hz, J_2 = 6.6 Hz, 2H, Ser C<u>*H*</u>$_2$), 3.86 (dd, J_1 = 12.3 Hz, J_2 = 5.4 Hz, 2H, Ser C<u>*H*</u>$_2$-), 4.82 (q, J = 6.9 Hz, 2H, -NHC<u>*H*</u>C=O), 6.79 (t, J = 5.6 Hz, 2H, -N<u>*H*</u>CH_2-), 7.45 (t, J = 7.7 Hz, 1H, ArC<u>*H*</u>), 7.64 (d, J = 7.5 Hz, 2H, Ar C<u>*H*</u>), 7.93 (d, J = 7.8 Hz, 2H, -N<u>*H*</u>), 8.21 (s, 1H, ArC<u>*H*</u>)

^{13}C NMR (75 MHz, $CDCl_3$): δ 13.95, 22.50, 26.53, 29.28, 31.40, 40.01, 52.03, 53.18, 126.17, 128.86, 130.72, 133.71, 166.82, 169.21.

IR (KBr): 3284, 3081, 2930, 2858, 2100, 1639(br), 1553, 1515, 1473, 1455, 1361, 1306, 1271, 1238, 1147, 1104 cm^{-1}

HRMS calcd for $C_{26}H_{40}N_{10}O_4Na$ = 579.3132, obtained $C_{26}H_{40}N_{10}O_4Na$ = 579.3131

Synthesis of **S1**



The dialkyne **6** (0.05 g, 0.086 mmol), diazide **4b** (0.048 g, 0.086 mmol) and DIEA (0.02 mL, 0.162 mmol) were dissolved in 50 mL of Ethanol:Toluene (2:1) and added to a solution of $CuSO_4.5H_2O$ (0.0275 g, 0.11 mmol) and sodium ascorbate (0.085 g, 0.43 mmol) in 50 mL Ethanol:Toluene:Water (6:3:1) over a period of 10 h under argon. The reaction mixture was stirred for 24 h, and subjected to vacuum to obtain the solid, which was dissolved in CH_2Cl_2 (100 mL) and washed with NH_4Cl:NH_4OH (9:1) until the blue color disappeared. The organic layer was further washed with 2 N H_2SO_4 and $NaHCO_3$, dried over anhyd. Na_2SO_4 and evaporated to yield 0.0829 g of the product. The purification is done by precipitating from $CHCl_3$ by adding hexane.

Yield: 85%

Appearance: Pale brown solid.

Melting point: 239-240^{o}C

$[\alpha]_D^{38}$: -2.33 (c 0.086, CH_3OH)

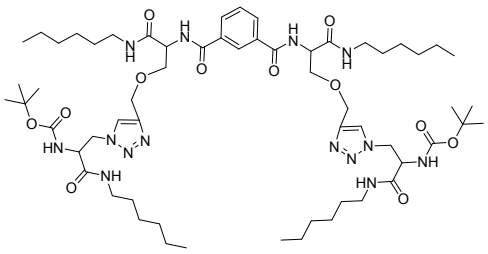
^{1}H NMR (300 MHz, DMSO-d_6): δ 0.763 (br s, 12H, C$\underline{H}_3(CH_2)_3CH_2$-), 1.16 (br s, 24H, $CH_3(C\underline{H}_2)_3CH_2$-), 1.29 (br s, 8H, -NHCH$_2$C$\underline{H}_2$-), 2.97 (br s, 8H, -NHC$\underline{H}_2$), 3.63 (br s, 4H, SerC$\underline{H}_2$-), 4.45 (br s, 4H, Ser C$\underline{H}_2$-), 4.60 (m, 4H, ser C$\underline{H}_2$-), 4.72 (m, 2H, -NHC$\underline{H}$C=O), 4.89 (m, 2H, -NHC$\underline{H}$C=O), 7.46 (m, 2H, -N$\underline{H}$), 7.75 (br d, J = 7.5 Hz, 1H, Ar$\underline{H}$), 7.86 (d, J = 7.2 Hz, 1H, Ar$\underline{H}$), 7.93 (m, 7H, 2-N$\underline{H}$+5Ar$\underline{H}$), 8.15 (m, 3H, trz $\underline{H}$ + Ar$\underline{H}$-), 8.29 (m, 2H, -N$\underline{H}$-), 8.50 (m, 2H, -N$\underline{H}$-), 8.79 (m, 2H, -N$\underline{H}$-)

^{13}C NMR (75 MHz, CD_3OD): δ 12.97, 22.21, 26.23, 28.87, 31.23, 39.38, 50.64, 53.71, 54.36, 68.82, 126.14, 128.51, 130.36, 130.60, 133.81, 167.72, 167.88, 168.86, 170.43

IR (KBr): 3444, 2929, 2858, 1646, 1539, 1468, 1376, 1273, 1108cm^{-1}

HRMS calcd for $C_{58}H_{86}N_{14}O_{10}Na$, m/z = 1161.6549 obtained m/z =1161.6536

Synthesis of **S3**



The dialkyne **6** (0.060 g, 0.104 mmol), the azide **3b** (0.065 g, 0.208 mmol) and DIEA (0.02 mL, 0.162 mmol) were dissolved in 50 mL of Ethanol: Toluene:Water (6:3:1) and added $CuSO_4.5H_2O$ (0.040 g, 0.162 mmol), and sodium ascorbate (0.085 g, 0.43 mmol) under argon. The reaction mixture was stirred for 24 h, subjected to vacuum to obtain the semi-solid, which is dissolved in CH_2Cl_2 (100 mL) and washed with NH_4Cl:NH_4OH (9:1) until the blue color disappeared. The organic layer was further washed with 2 N H_2SO_4 and $NaHCO_3$, dried over anhyd. Na_2SO_4 and evaporated to yield 0.085 g of the product. The crude product obtained was purified by precipitating by adding hexane to a saturated solution of compound in $CHCl_3$.

Yield: 67%

Appearance: Pale brown solid

Melting point: 119-120^{o}C

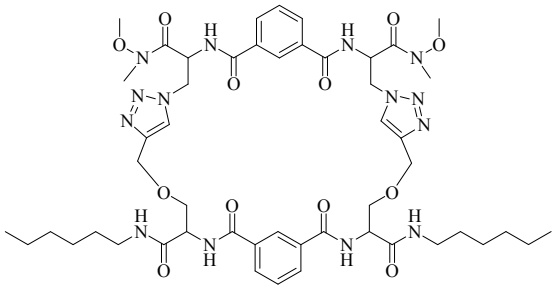
$[\alpha]_D^{30}$: +5.71 (c 0.105, CH_3OH)

^{1}H NMR (300 MHz, DMSO-d_6): δ 0.84 (br s, 12H, C$\underline{H}_3(CH_2)_3CH_2$-), 1.22 (br s, 24H, $CH_3(C\underline{H}_2)_3CH_2$-), 1.28 (s, 18H, -C$(CH_3)_3$), 1.34 (br s, 8H, -NHCH$_2C\underline{H}_2$-), 3.04 (m, 8H, -NHC$\underline{H}_2$), 3.73 (m, 8H, Ser C$\underline{H}_2$-), 4.3- 4.8 (m, 8H, 4 -NHC$\underline{H}$CO+4 -OC$\underline{H}_2$-), 7.11 (d, J = 7.2 Hz, 2H, -CON$\underline{H}$-), 7,57 (m, 1H, ArC$\underline{H}$), 7.94 (s, 2H, Triazole C$\underline{H}$), 8.05 (m, 5H, 3ArC$\underline{H}$-+ 2N$\underline{H}$-), 8.38 (m, 2H, -CON$\underline{H}$CH$_2$-), 8.62 (d, J = 6.9 Hz, 2H, -CON$\underline{H}$ CH$_2$-)

IR (KBr): 3443, 2829, 1645, 1541, 1367, 1275, 1261, 1165, 1109 cm^{-1}

HRMS calcd for $C_{60}H_{100}N_{14}O_{12}Na$, m/z = 1231.7543 obtained m/z = 1231.7519

Synthesis of **S2**



A solution of **6** (0.05 g, 0.086 mmol) and the diazide **4a** (0.041 g, 0.086 mmol) and DIEA (0.03 mL, 0.172 mmol) were dissolved in 50 mL of Ethanol:Toluene (2:1) was added to a solution of $CuSO_4.5H_2O$ (0.040 g, 0.162 mmol), and sodium ascorbate (0.085 g, 0.43 mmol) in 50 mL Ethanol:Toluene:Water (6:3:1) over a period of 10 h under argon. The reaction mixture was stirred for 24 h, and subjected to vacuum to obtain the solid which was dissolved in CH_2Cl_2 (100 mL) and washed sequentially with NH_4Cl:NH_4OH (9:1) until the blue color disappeared. The organic layer was further washed with 2 N H_2SO_4 and $NaHCO_3$, dried over anhyd. Na_2SO_4, evaporated to yield 0.097 g of the product. It was precipitated by adding hexane to a saturated solution of the compound in $CHCl_3$. The compound was chromatographed over silica gel (100-200 mesh) and eluted with CH_3OH:$CHCl_3$ (1:9) to yield 0.083 g of pure compound.

Yield: 91 %

Appearance: White solid

Melting point: 140-142^oC

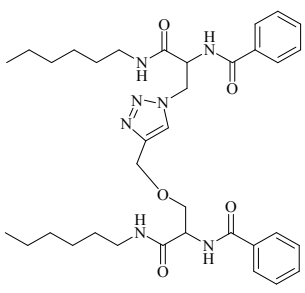
$[\alpha]_D^{37}$: -4.55 (c 0.066, CH_3OH)

^1H NMR (300 MHz, $DMSOd_6$): δ 0.83 (br s, 6H, C$\underline{H}_3(CH_2)_3CH_2$-), 1.22 (br s, 12H, -(C$\underline{H}_2)_3CH_3$), 1.34 (br s, 4H, -NHCH$_2C\underline{H}_2$), 2.95-3.20 (m, 10H, -NC$\underline{H}_3$+NHC$\underline{H}_2(CH_2)_4$-), 3.66 (s+m, 10H, -N(OC$\underline{H}_3$)+Ser C$\underline{H}_2$), 4.39-5.10 (m, 10H, Ser CH$_2$+triazoleC$\underline{H}_2$+2NHC$\underline{H}$C=O), 5.41 (br s, 2H, 2αCH), 7.55 (br s, 2H, -N$\underline{H}$), 7.7-8.3 (m, 8H, Ar$\underline{H}$+trz C$\underline{H}$-), 8.36 (br s, 2H, Ar$\underline{H}$), 8.6 (br s, 2H, N$\underline{H}$), 9.10 (br s, 2H, N$\underline{H}$)

IR (KBr): 3314, 3084, 2930, 2858, 1650, 1536, 1467, 1384, 1303, 1277, 1179, 1103 cm^{-1}

HRMS calcd for $C_{50}H_{70}N_{14}O_{12}Na$, m/z = 1081.5195, obtained m/z = 1081.5196

Compound **S4**



The alkyne **5b** (0.068 g, 0.207 mmol), was dissolved in 20 mL of CH_3CN and added DIEA (0.035 mL, 0.207 mmol), followed by azide **3c** (0.065 g, 0.207 mmol). Added CuI (0.008 g, 0.041 mmol) and the reaction mixture was stirred at room temperature for 30h. The reaction mixture was evaporated and the residue was dissolved in CH_2Cl_2 and washed with NH_4Cl:NH_4OH (9:1) until the blue color disappeared. The organic part was further washed with 2 N H_2SO_4, $NaHCO_3$, and dried over anhyd.Na_2SO_4 and evaporated to yield 0.11 g of the product.

The crude product was precipitated from $CHCl_3$ by adding hexane. It was chromatographed over silica gel (100-200 mesh) and eluted with EtOAc to yield 0.083 g of pure compound.

Yield: 61.9%

Melting point: 176-177^oC

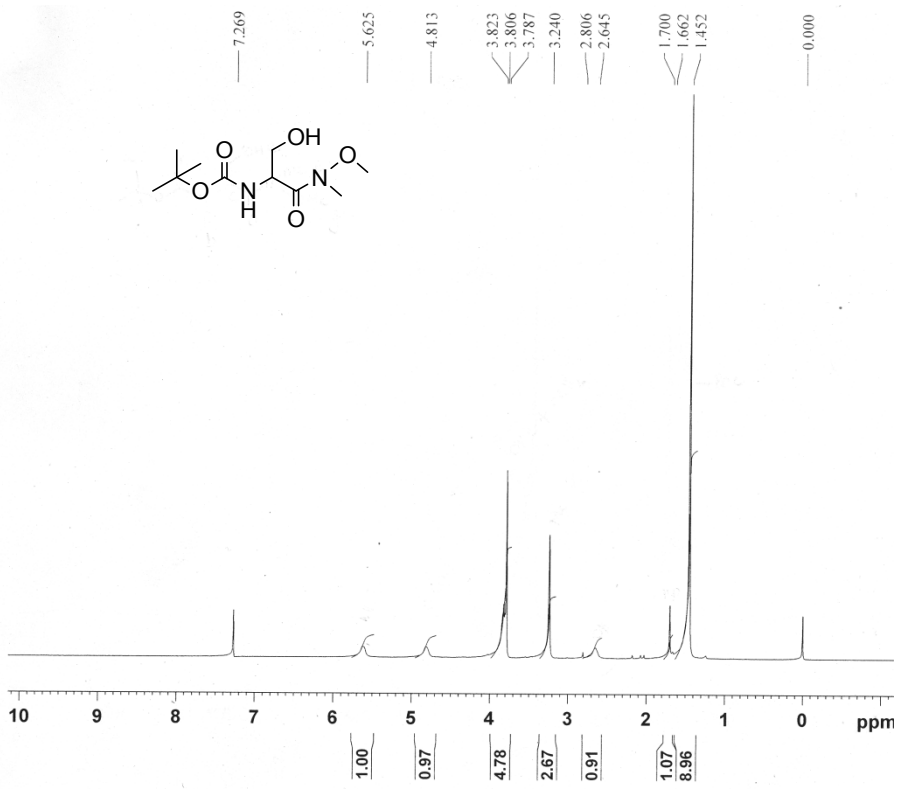
$[\alpha]_D^{37}$: -9.68 (c 0.093, CH_3OH)

^1H NMR (300 MHz, $CDCl_3$): δ 0.84(m, 6H, C$\underline{H}_3(CH_2)_4$-), 1.10-1.60 (br s+m, 16H, $CH_3(CH_2)_3C\underline{H}_2$-+$CH_3(C\underline{H}_2)_3CH_2$-), 3.00-3.30 (m, 4H, -NH(C$\underline{H}_2$)-), 3.62 (br dd, 1H, Ser C$\underline{H}_2$), 3.93 (br dd, 1H, serC$\underline{H}_2$), 4.44 (m, 1H, -NHC$\underline{H}$C=O), 4.69-4.85 (m, 3H, SerC$\underline{H}_2$+OC$\underline{H}_2$), 5.00-5.20 (m, 2H, -NHC$\underline{H}$C=O+-OC$\underline{H}_2$), 6.79 (br t, 1H, -N$\underline{H}CH_2$), 6.88 (br t, 1H, -N$\underline{H}CH_2$), 7.39 (m, 4H, trz C$\underline{H}$+ArCH-), 7.49 (m, 3H, ArC$\underline{H}$), 7.69 (m, 3H, ArC$\underline{H}$+-N$\underline{H}$-), 7.84 (m, 3H, ArC$\underline{H}$+-N$\underline{H}$-).

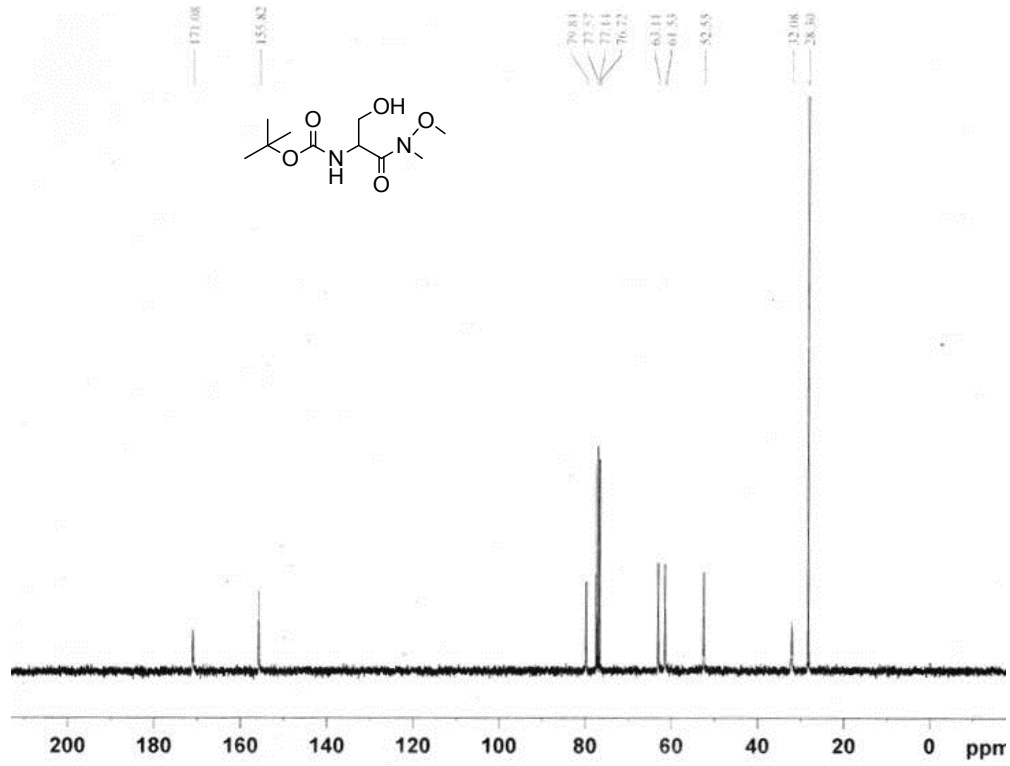
IR (KBr): 3303, 3070, 2927, 2858, 1637, 1533, 1460, 1381, 1322, 1231, 1149, 1108, 1049 cm^{-1}

HRMS: calcd for $C_{35}H_{49}N_7O_5Na$, m/z = 670.3693, obtained m/z = 670.3684.

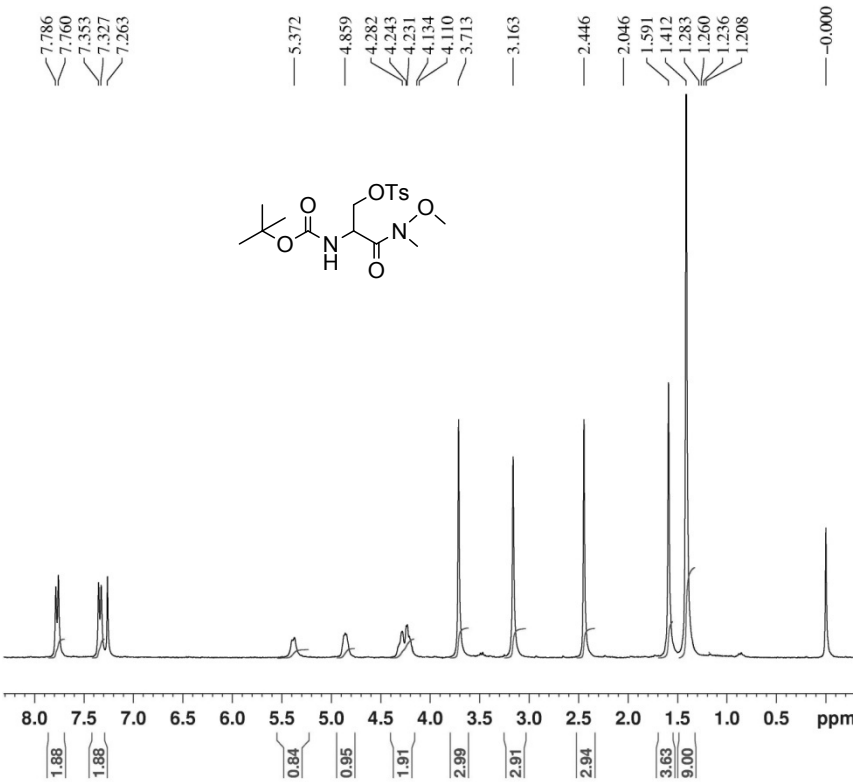
^1H NMR (300 MHz, $CDCl_3$) of **1a**



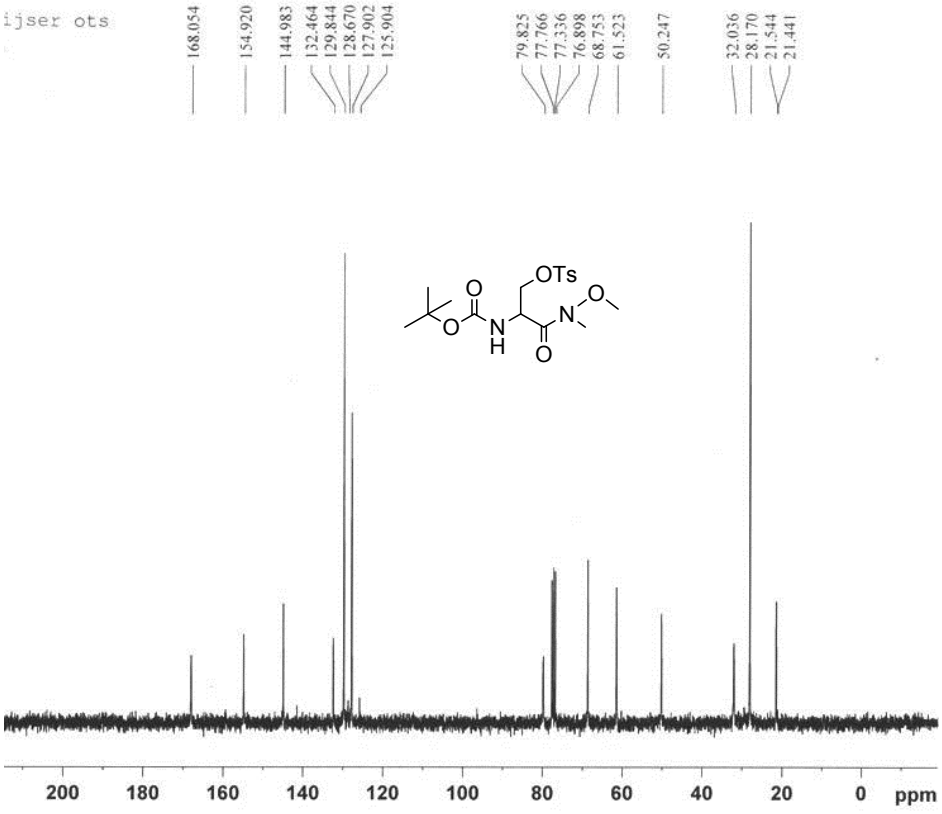
^{13}C NMR (75 MHz, $CDCl_3$) of **1a**



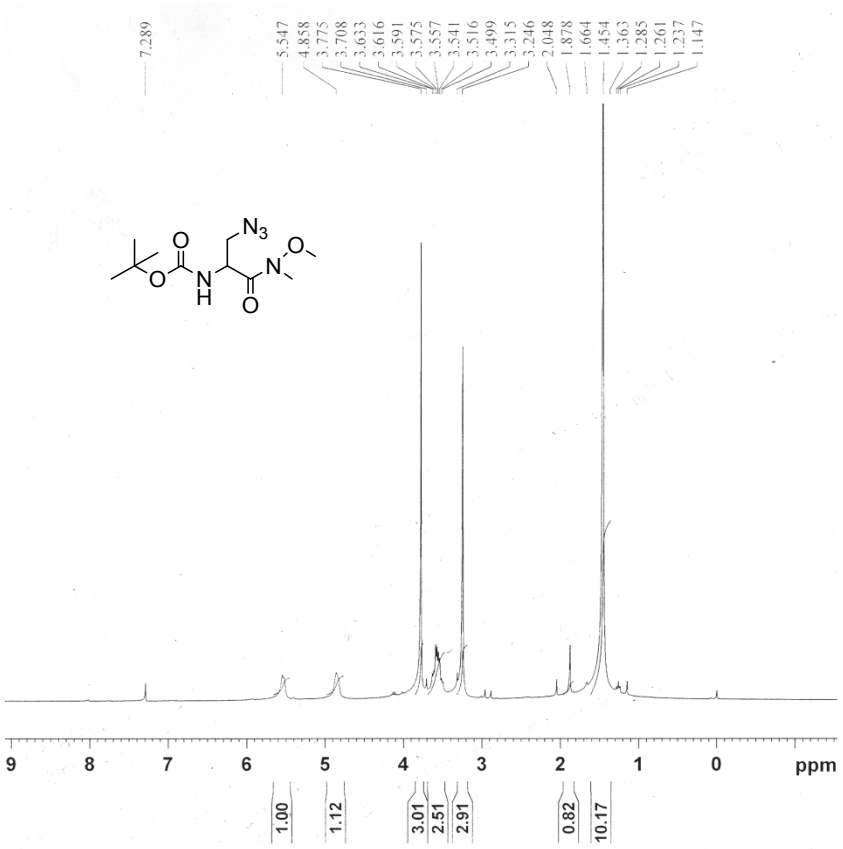
^{1}H NMR (300 MHz, $CDCl_3$) of **2a**



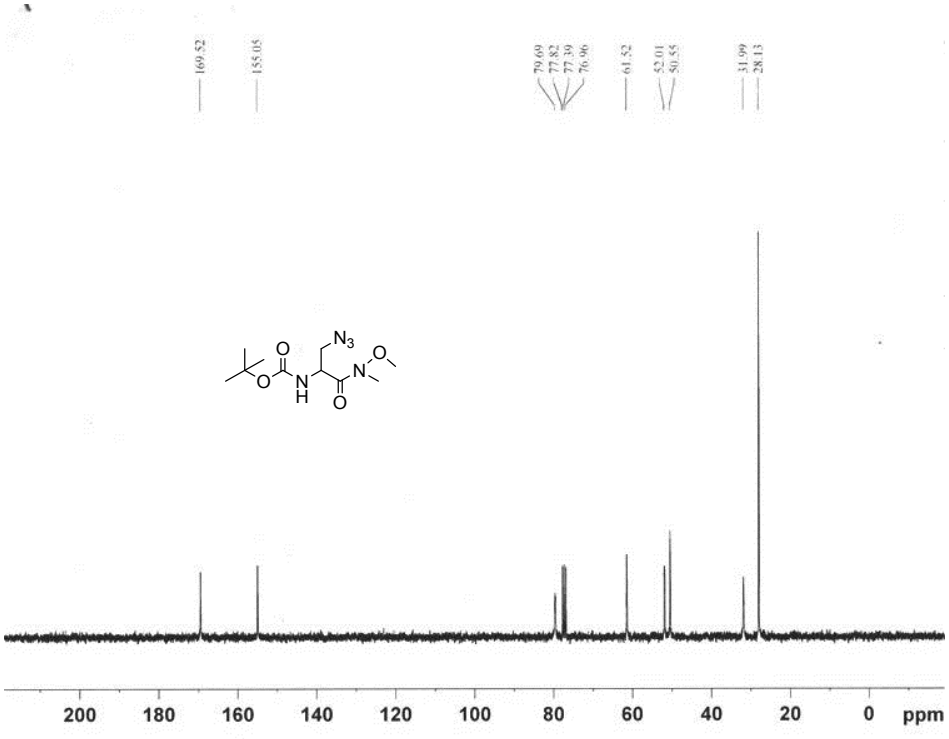
^{13}C NMR (75 MHz, $CDCl_3$) of **2a**



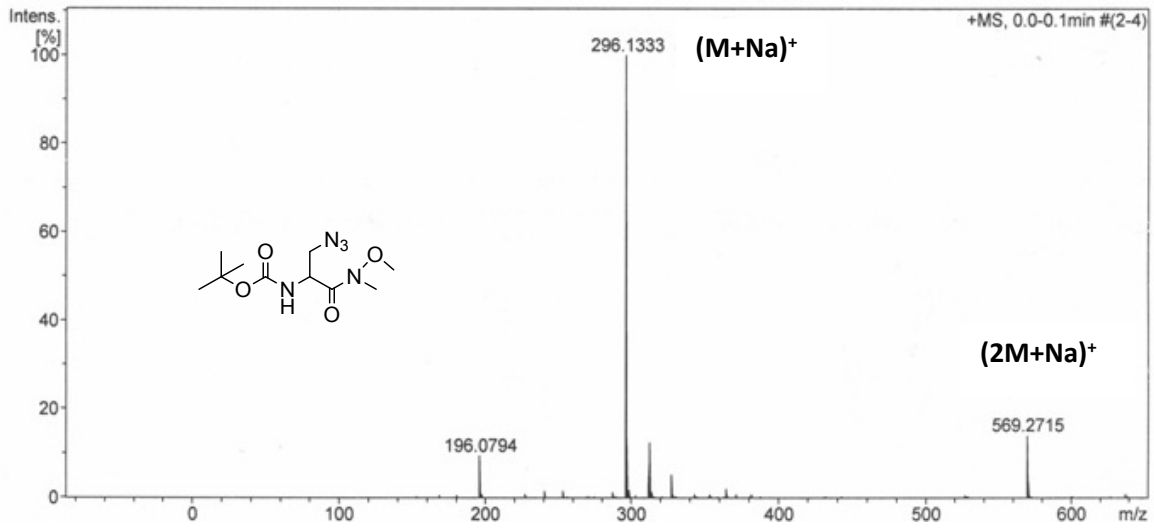
^{1}H NMR (300 MHz, $CDCl_3$) of **3a**



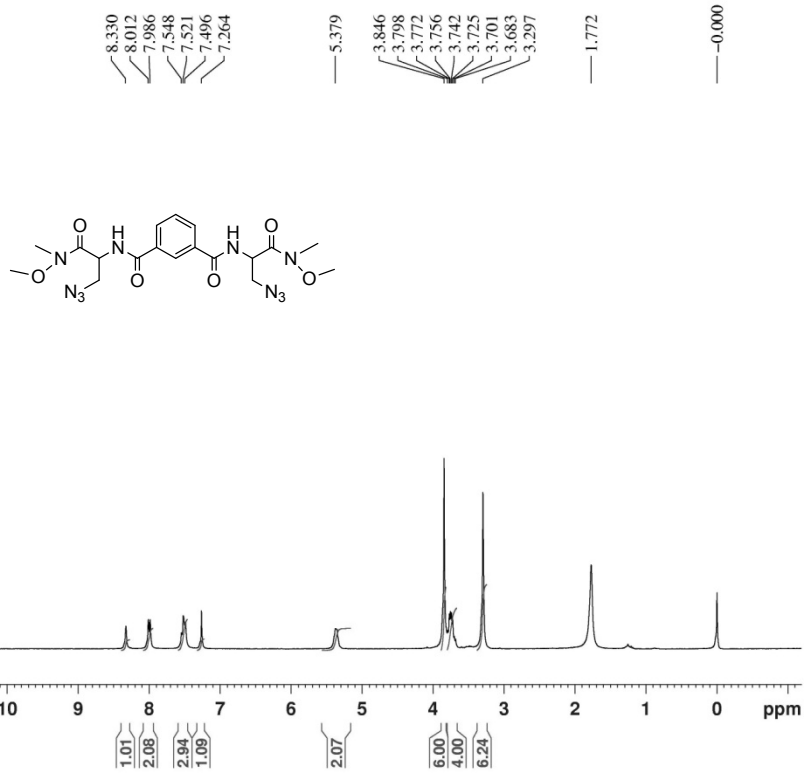
^{13}C NMR (75 MHz, $CDCl_3$) of **3a**



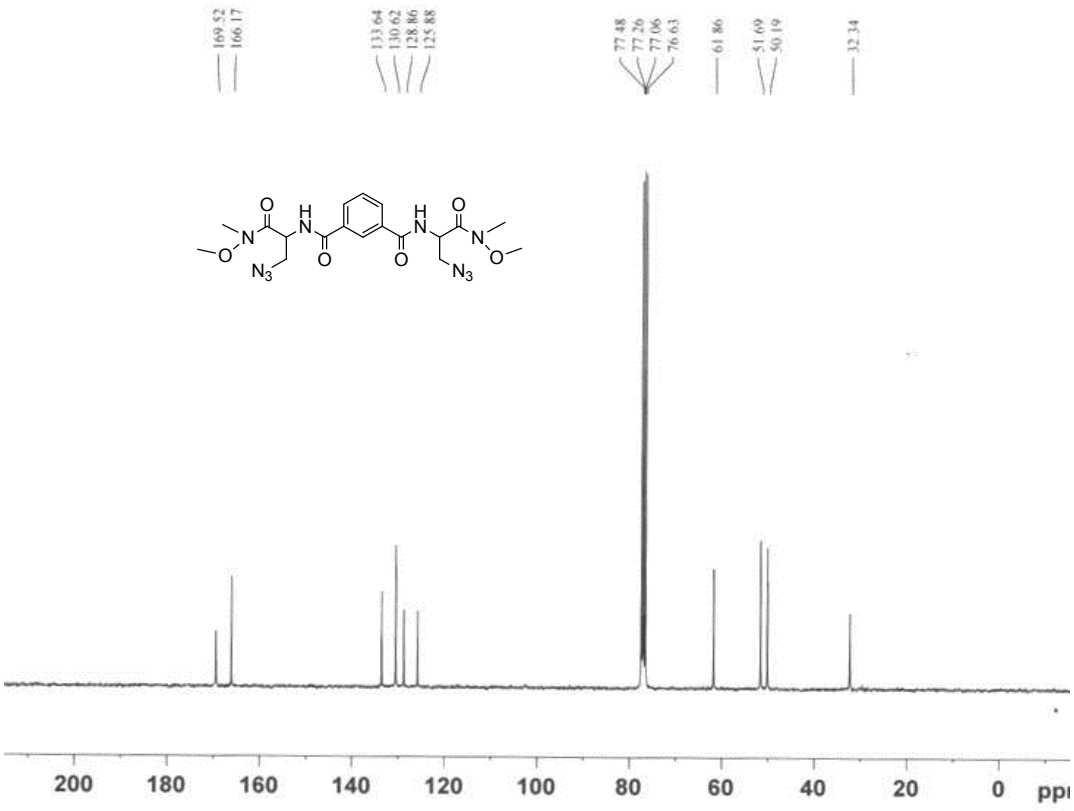
High Resolution Mass Spectrum of compound **3a**



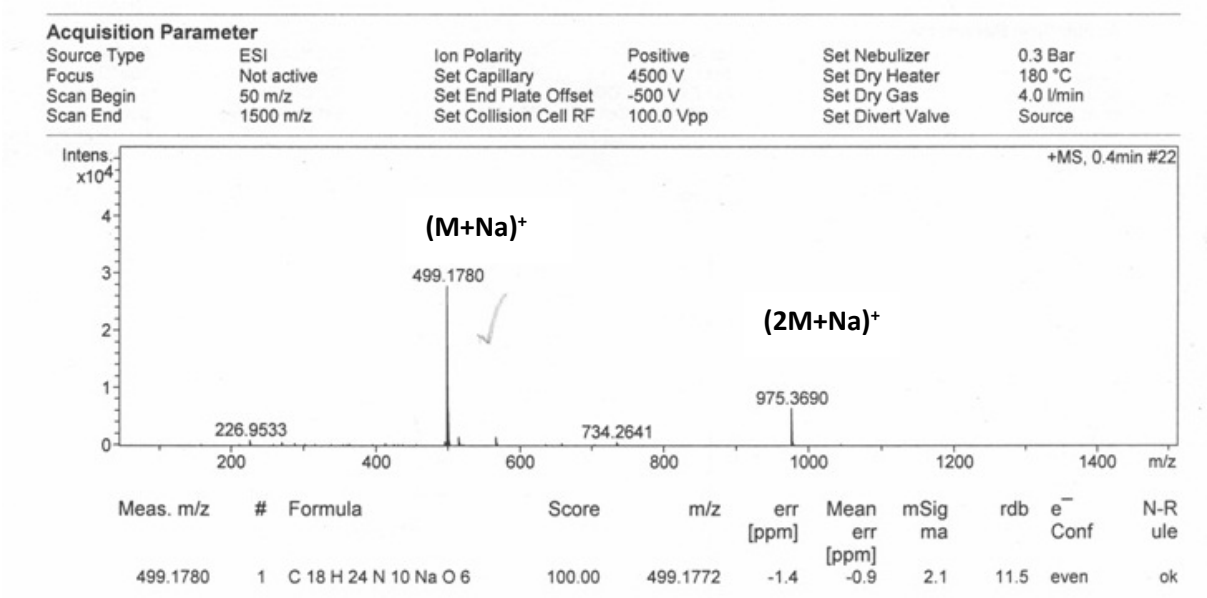
[1]H NMR (300 MHz, $CDCl_3$) of **4a**



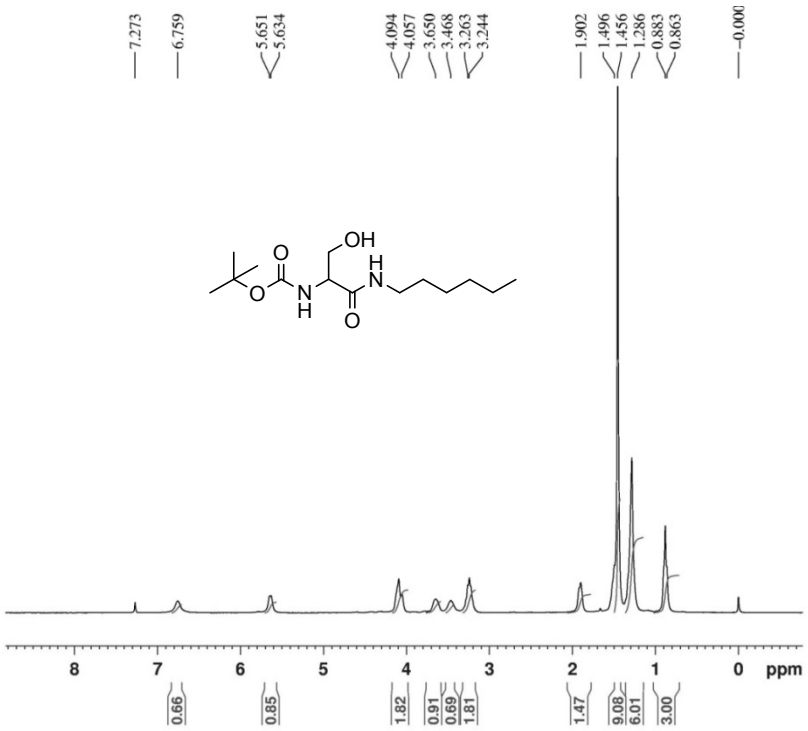
[13]C NMR (75 MHz, $CDCl_3$) of **4a**



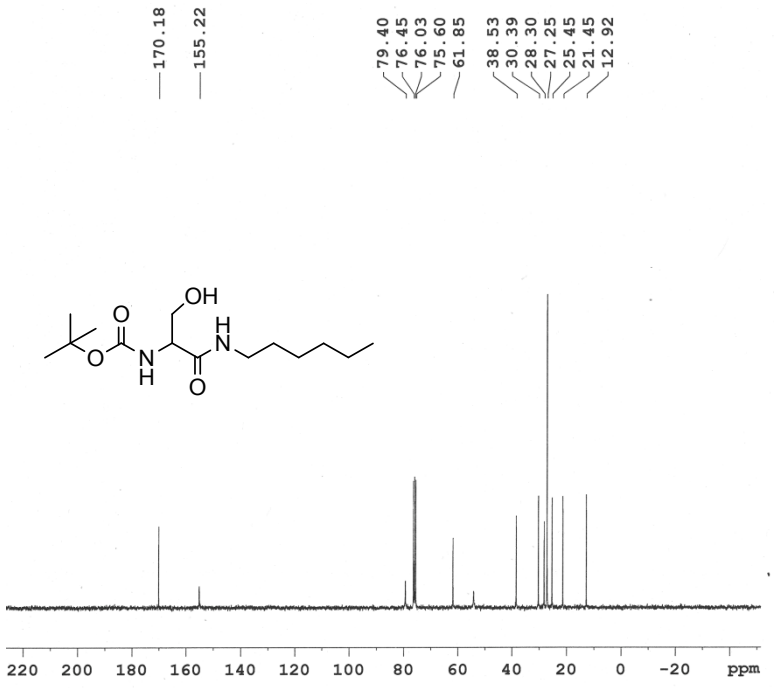
High Resolution Mass spectrum of **4a**



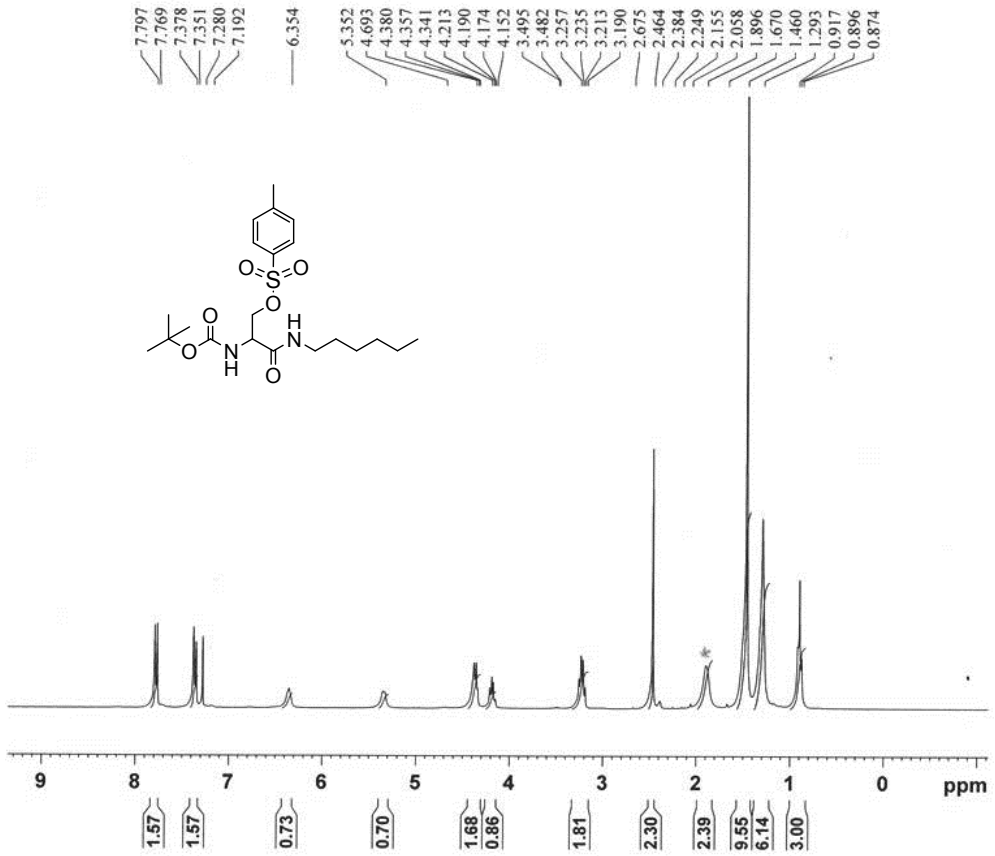
^{1}H NMR (300 MHz, $CDCl_3$) of **1b**



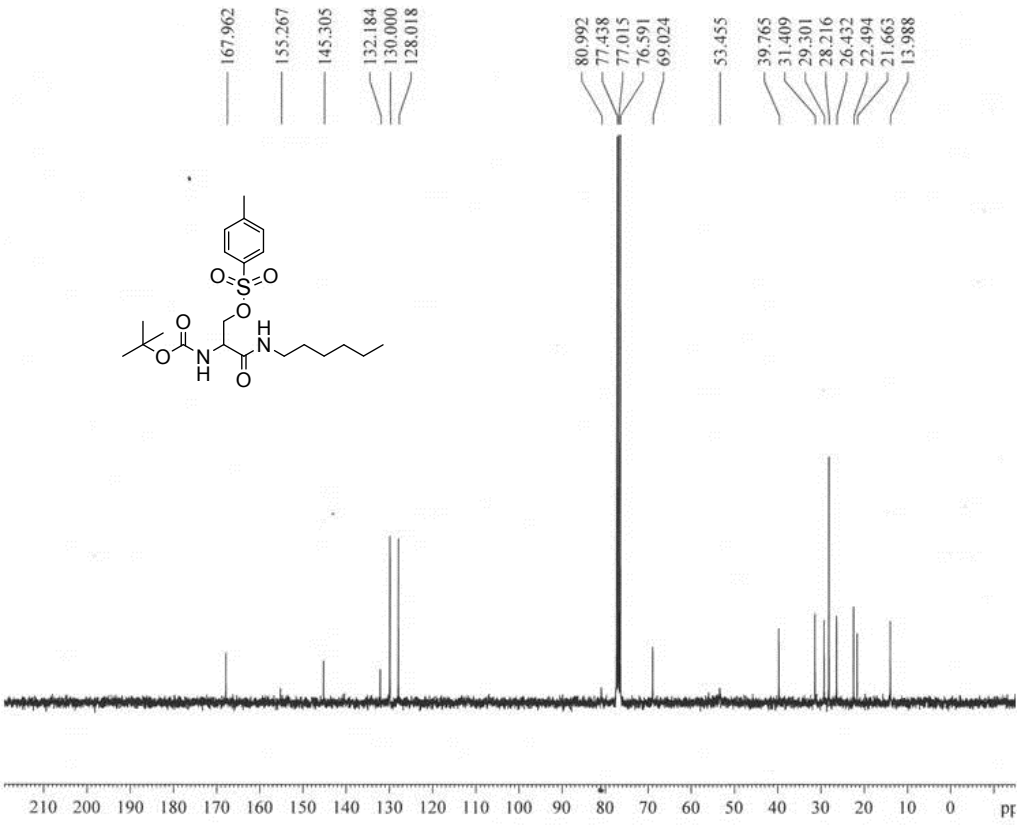
^{13}C NMR (75 MHz, $CDCl_3$) of **1b**



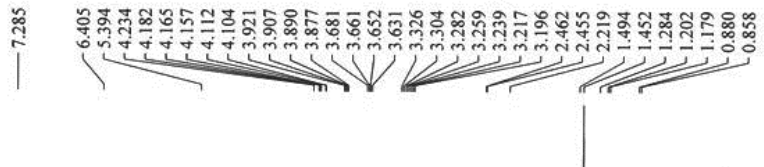
^{1}H NMR (300 MHz, $CDCl_3$) of **2b**



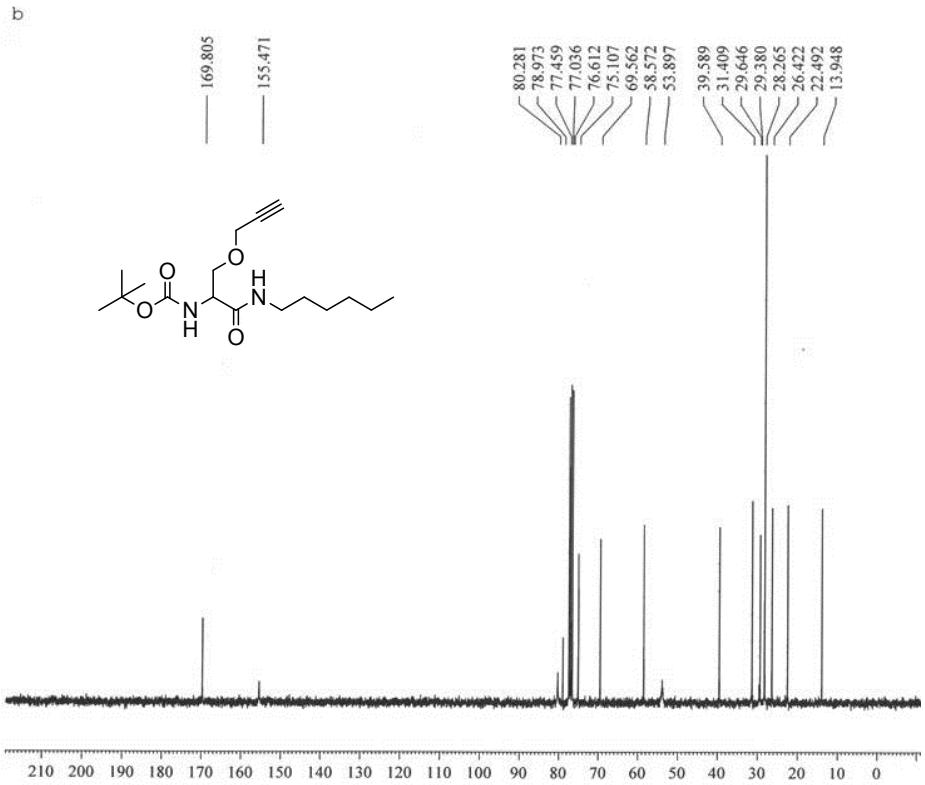
^{13}C NMR (75 MHz, $CDCl_3$) of **2b**



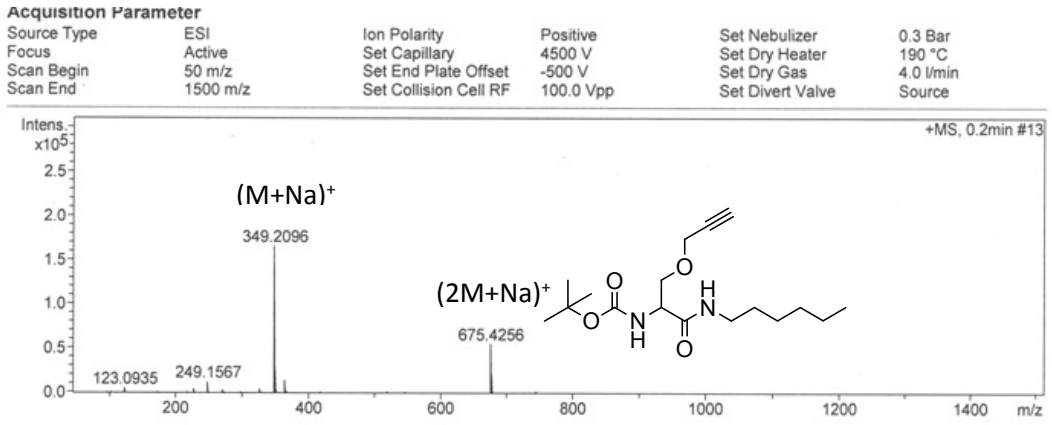
^{1}H NMR (300 MHz, $CDCl_3$) of **5a**



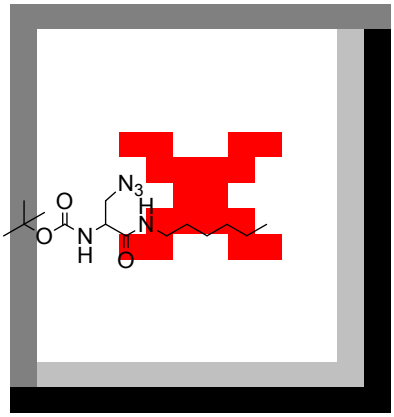
^{13}C NMR (75 MHz, $CDCl_3$) of **5a**



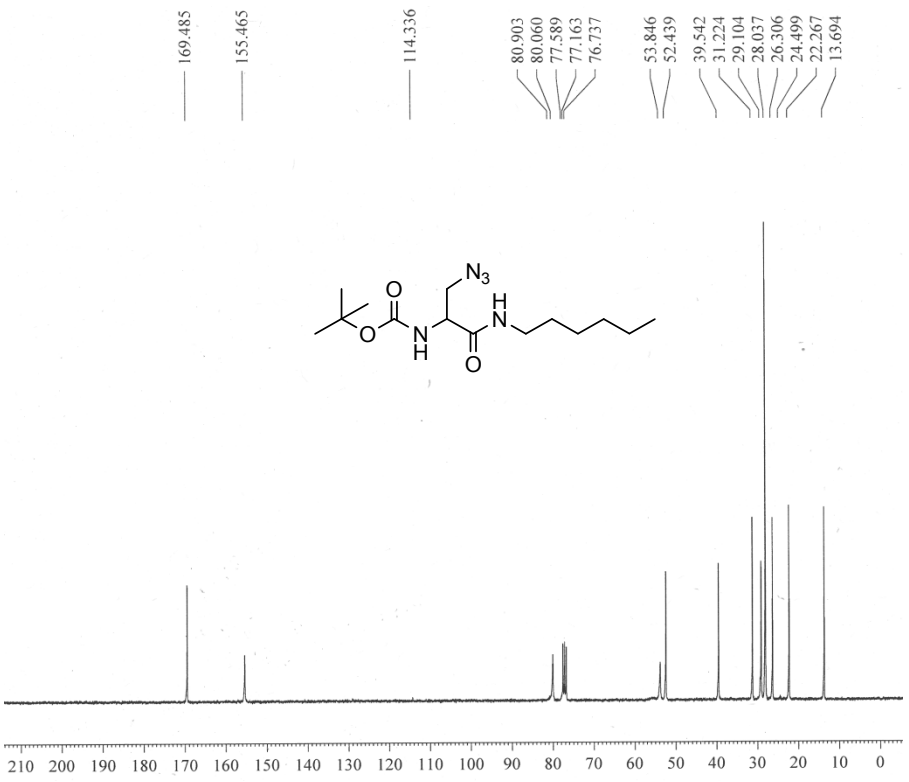
High Resolution Mass Spectra of **5a**



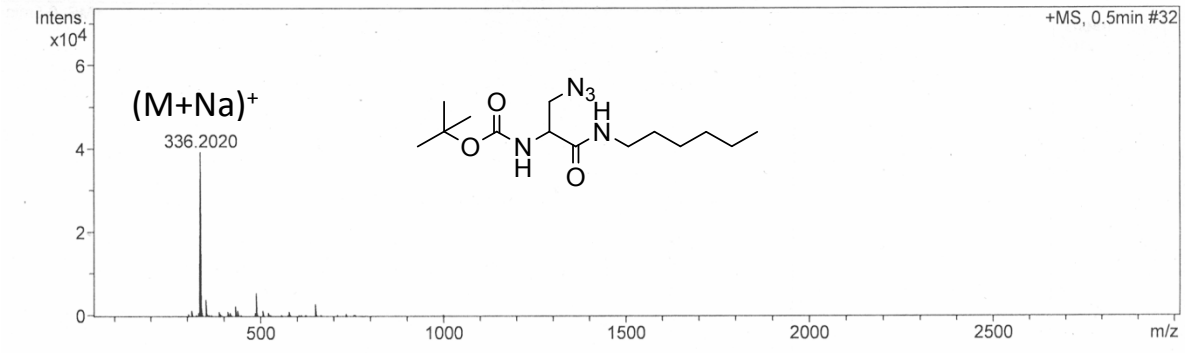
[1]H NMR (300 MHz, $CDCl_3$) of **3b**



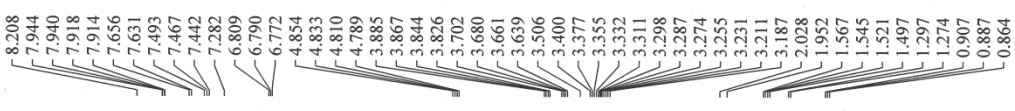
[13]C NMR (75 MHz, $CDCl_3$) of **3b**



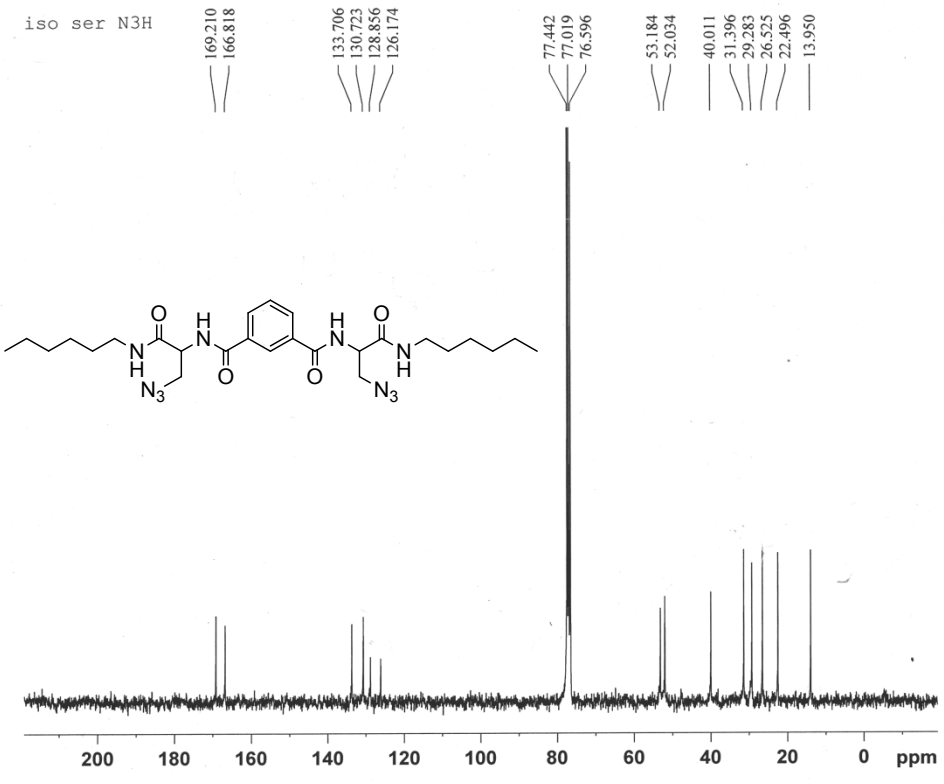
High Resolution Mass Spectrum of **3b**



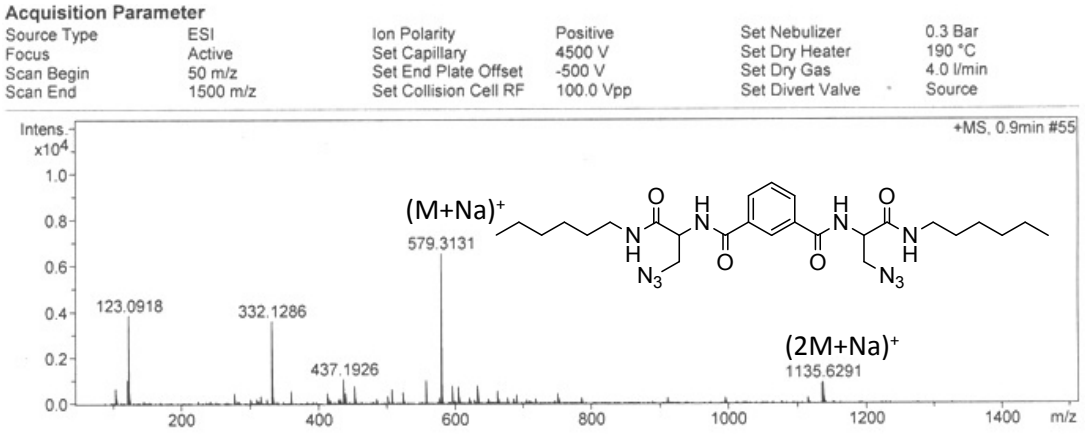
^{1}H NMR (300 MHz, $CDCl_3$) of **4b**



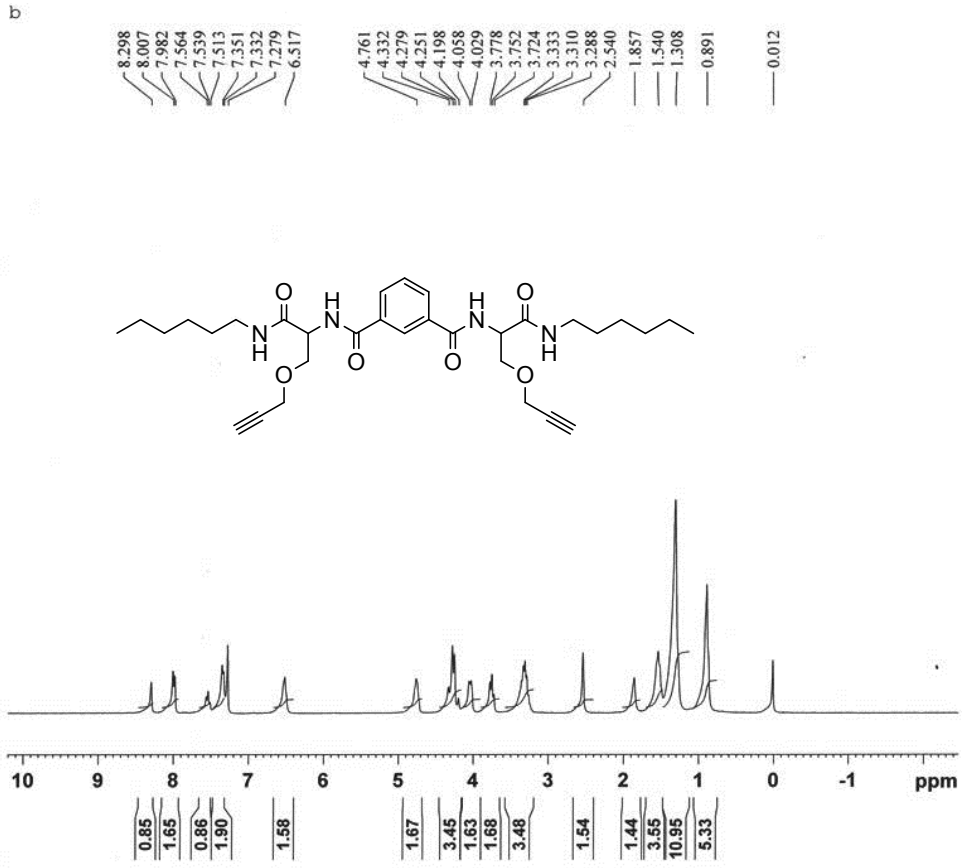
^{13}C NMR of (75 MHz, $CDCl_3$) of **4b**



High Resolution Mass Spectrum of **4b**

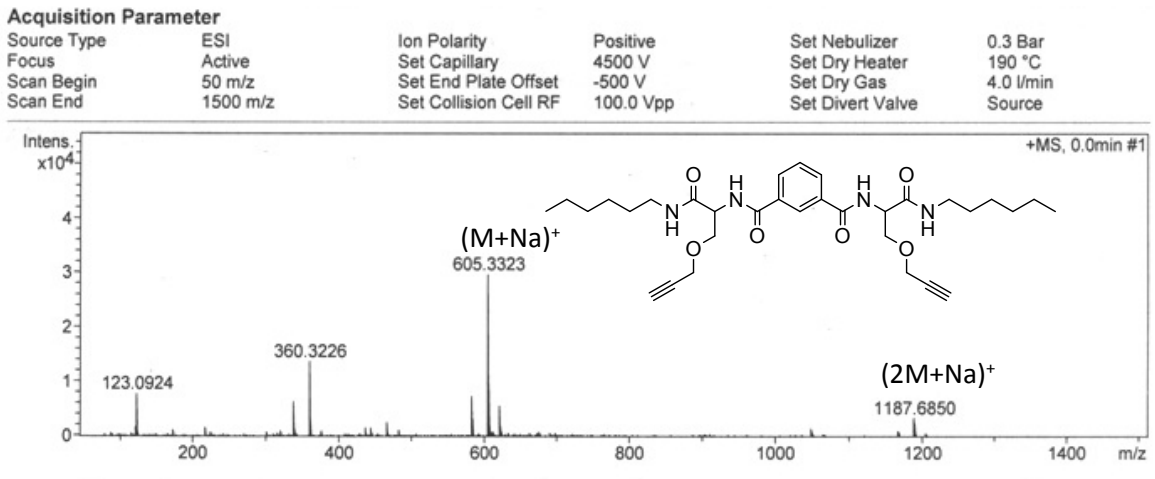


^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **6**

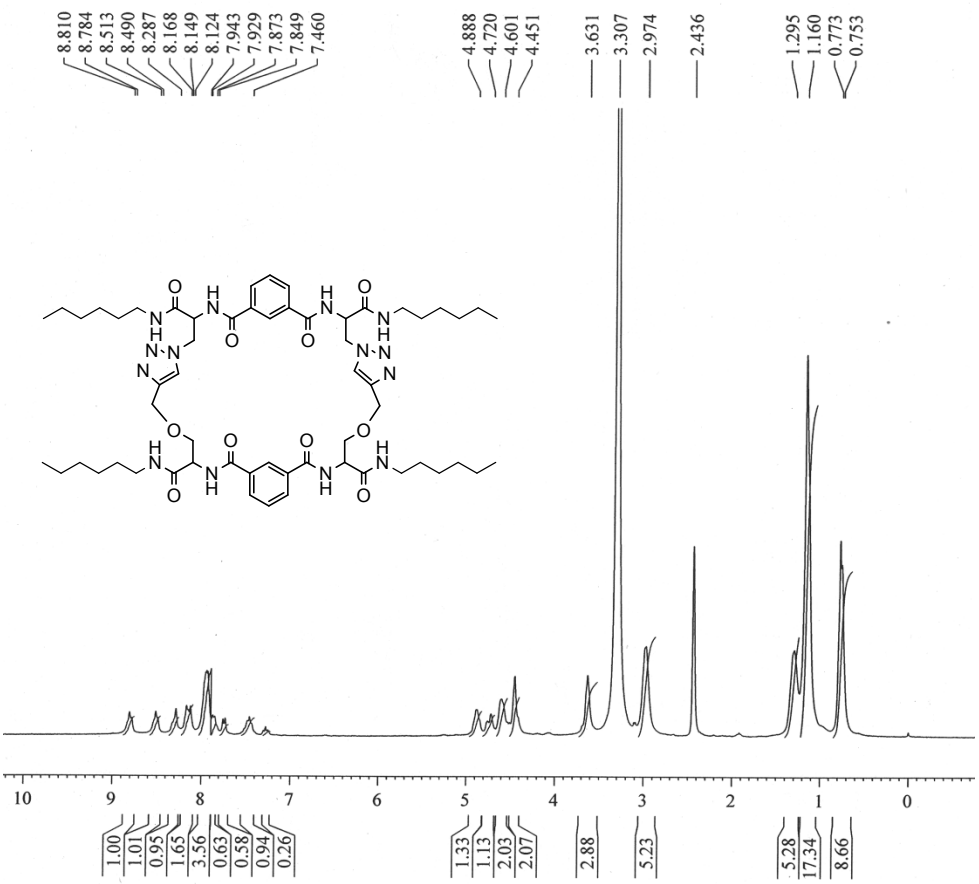


^{13}C NMR (75 MHz, $CDCl_3$) **6**

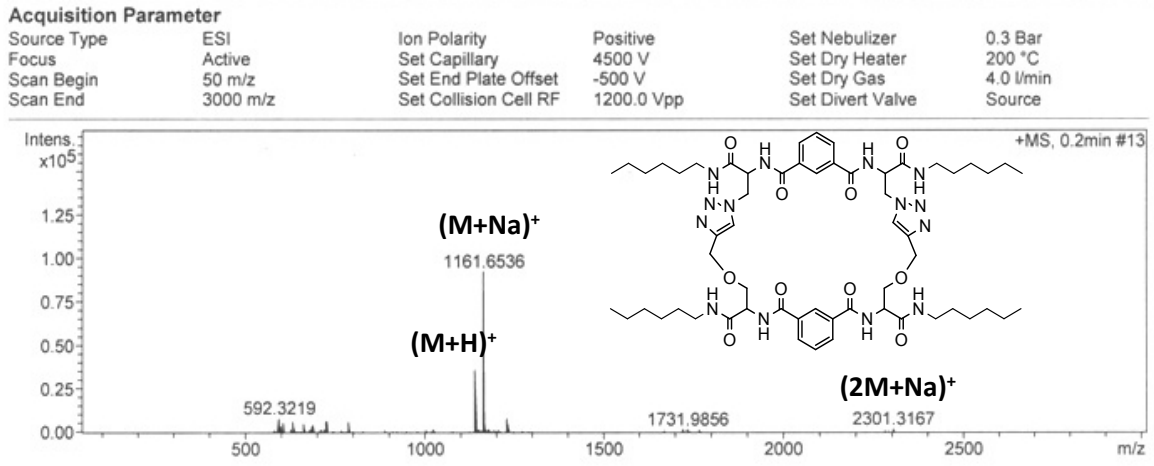
High Resolution Mass Spectrum of **6**



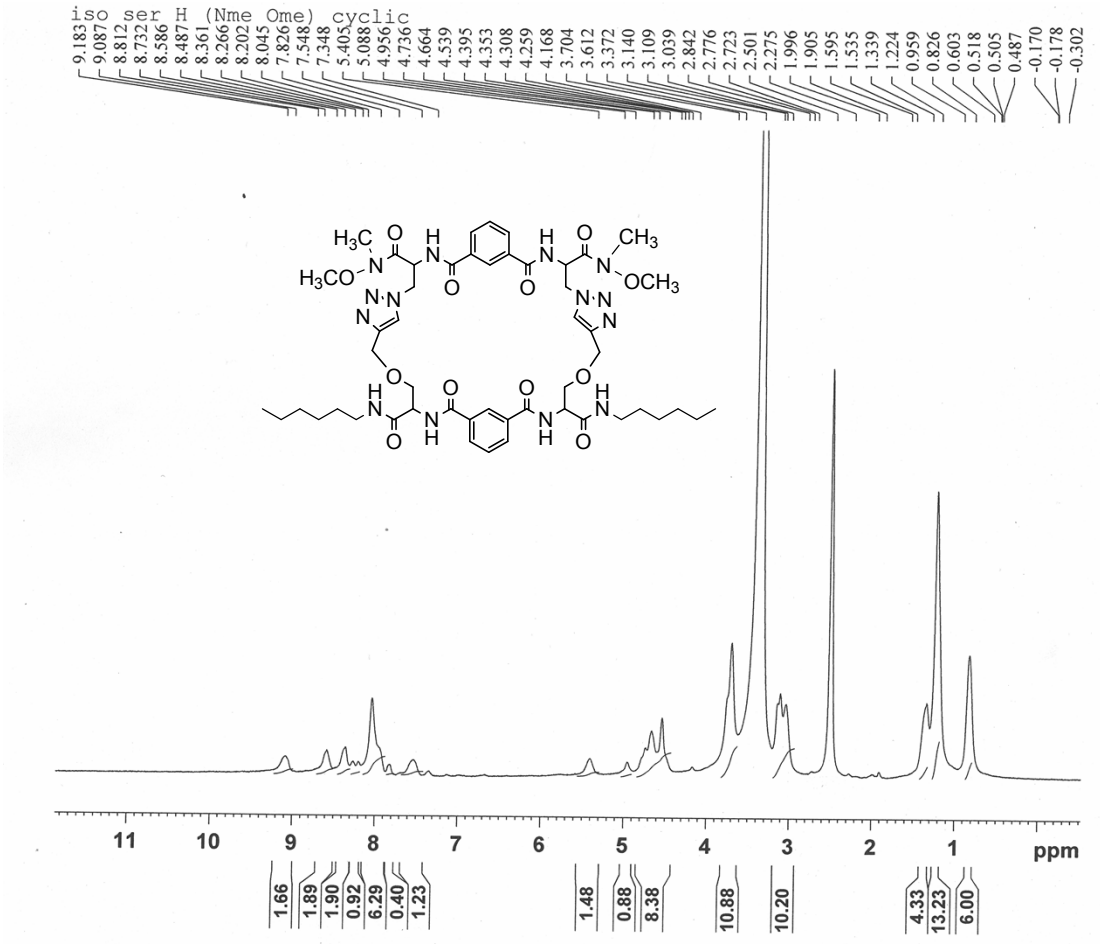
^{1}H NMR (300 MHz, DMSO-*d6*) spectrum of **S1**



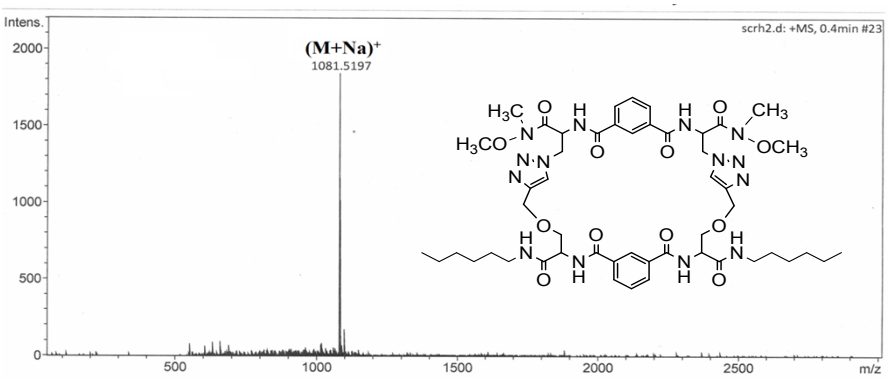
High Resolution Mass Spectrum of **S1**



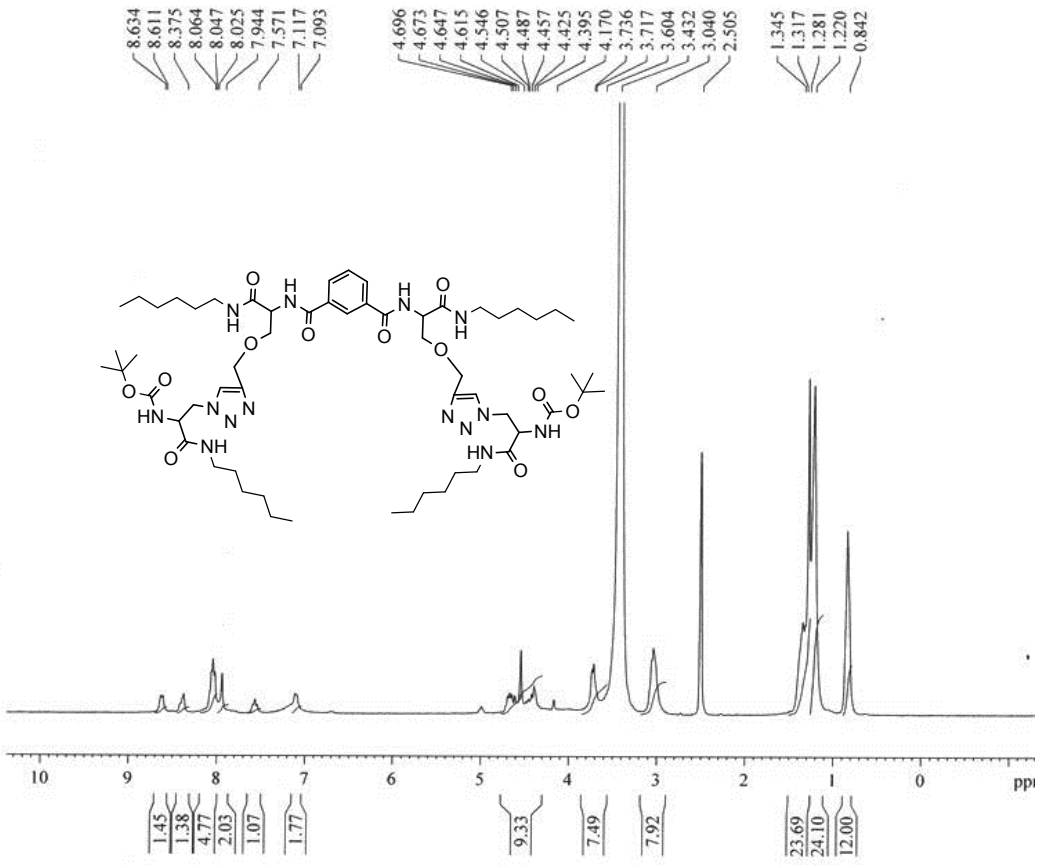
[1]H NMR (300 MHz, DMSO-*d6*) of **S2**



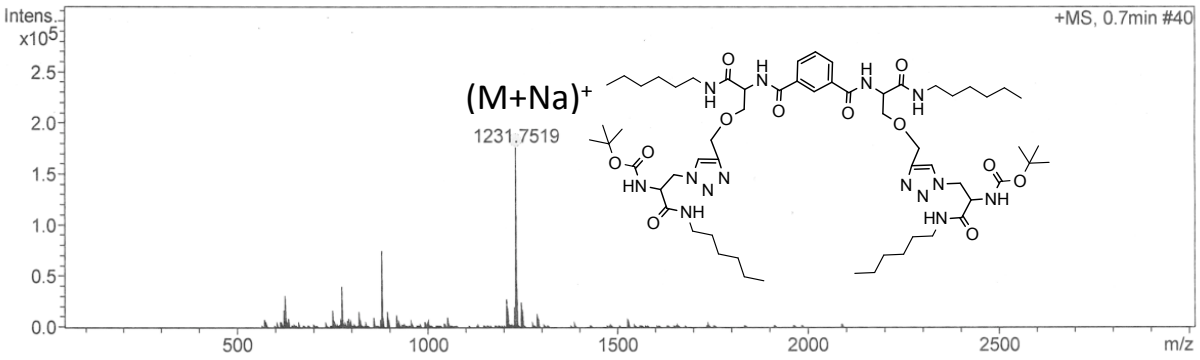
High Resolution Mass Spectrum of **S2**



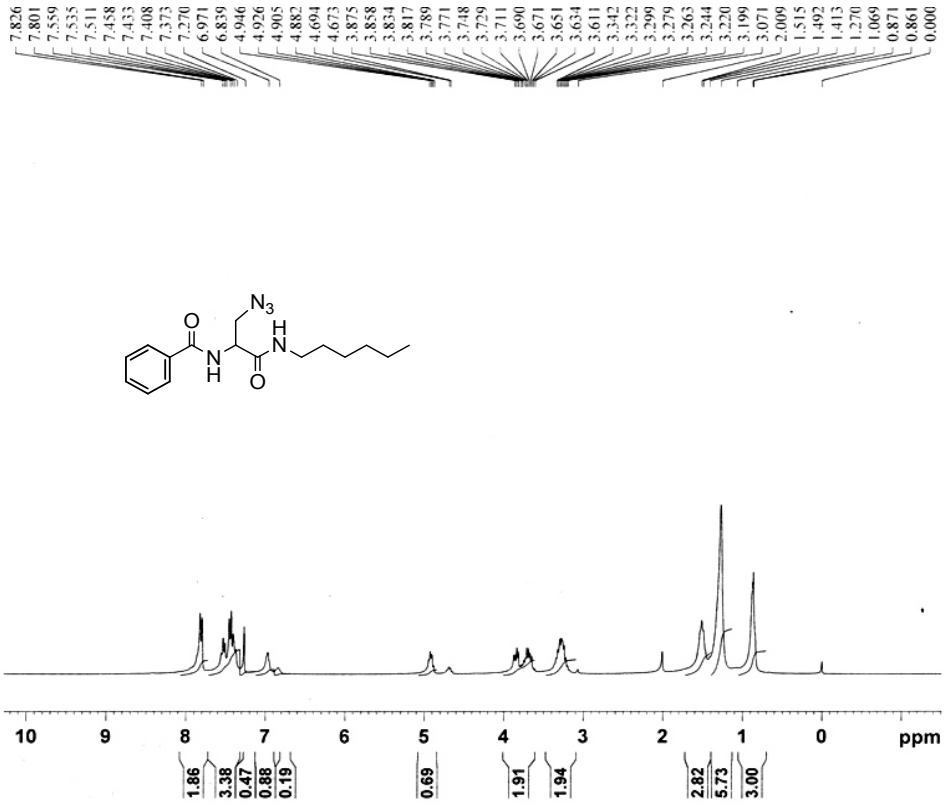
[1]H (300 MHz, DMSO-*d6*) NMR spectrum of **S3**



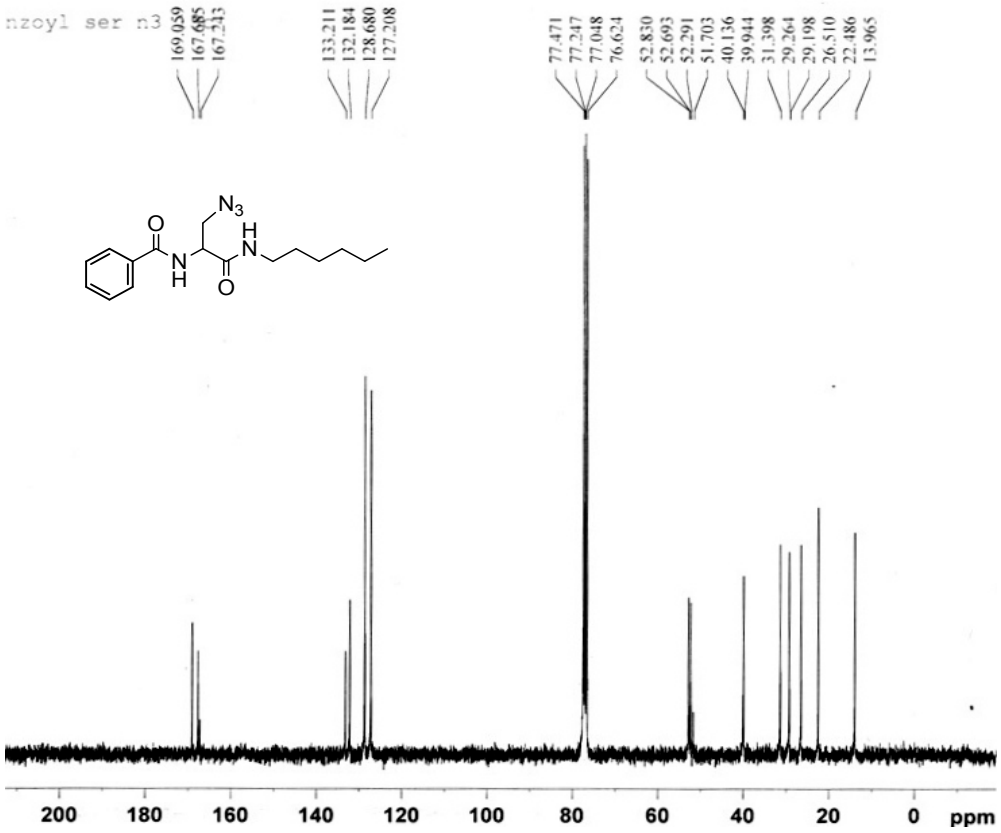
High Resolution Mass Spectrum of **S3**



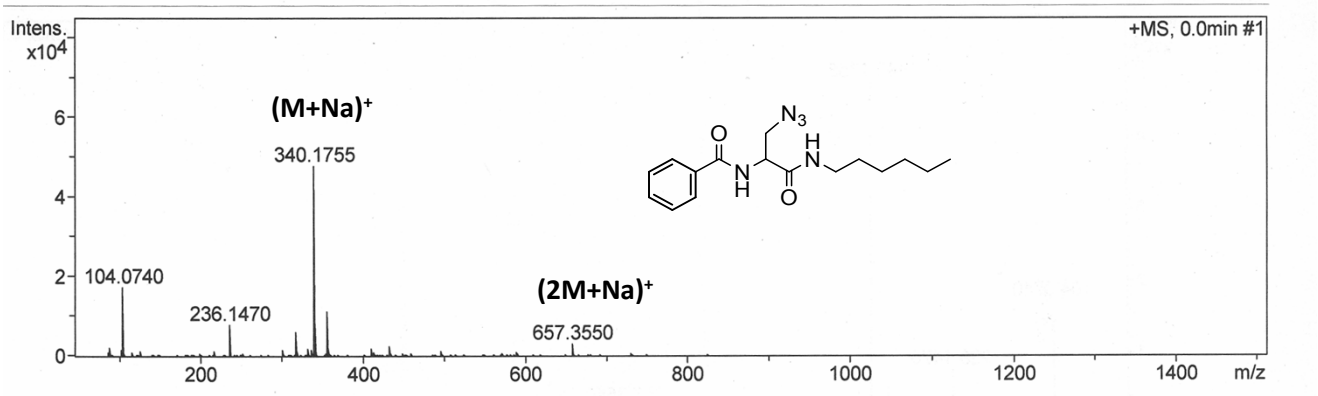
^{1}H NMR (300 MHz, $CDCl_3$) of **3c**



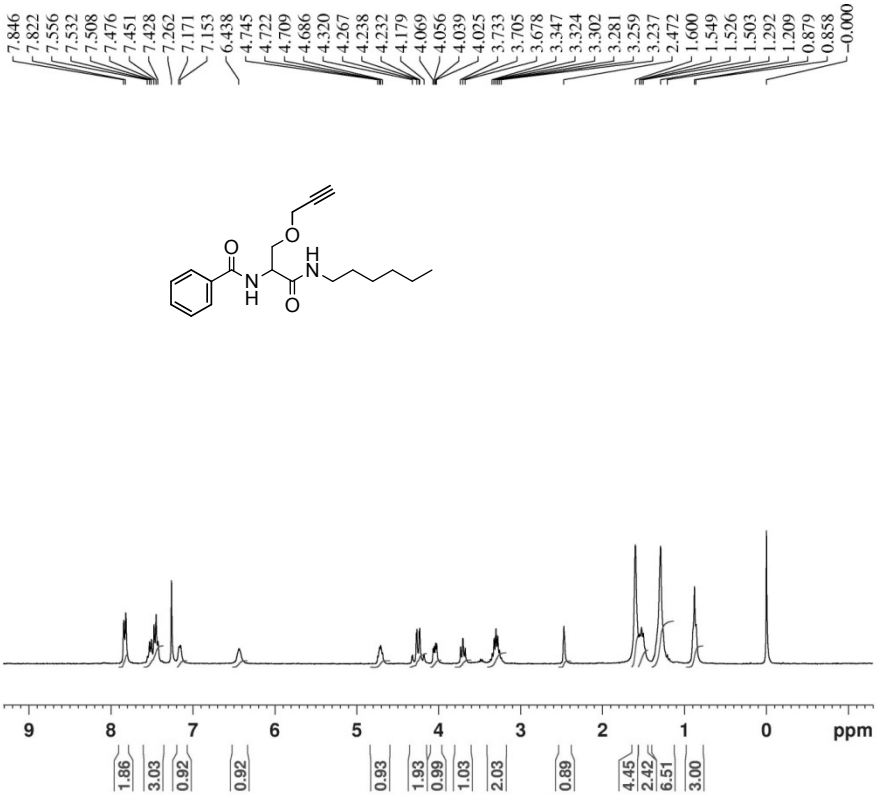
^{13}C NMR (75 MHz, $CDCl_3$) of **3c**



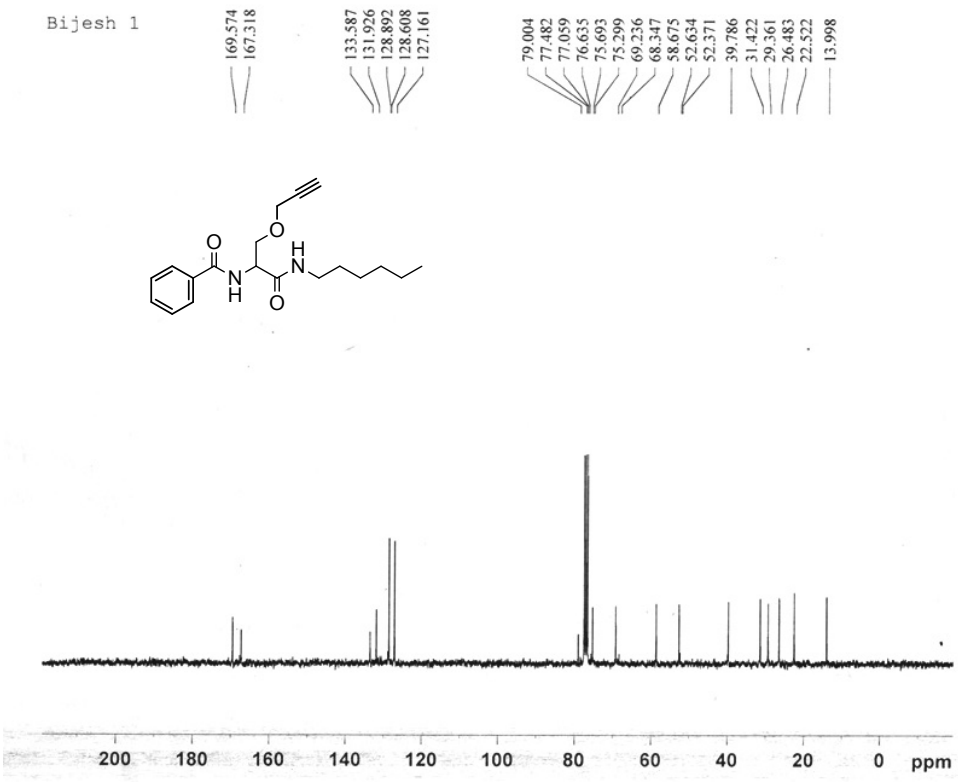
High Resolution Mass Spectrum of **3c**



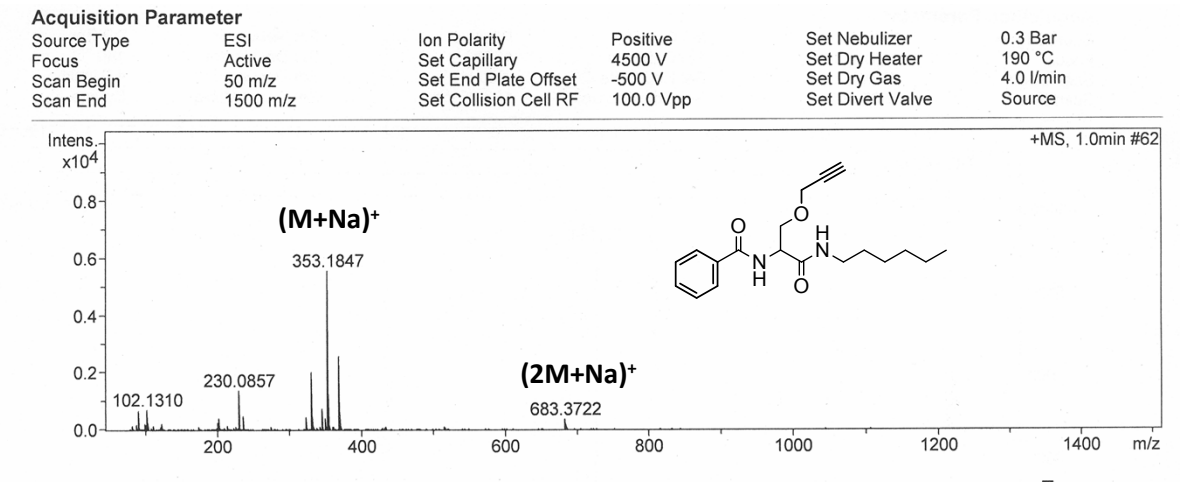
^{1}H NMR (300 MHz, $CDCl_3$) of **5b**



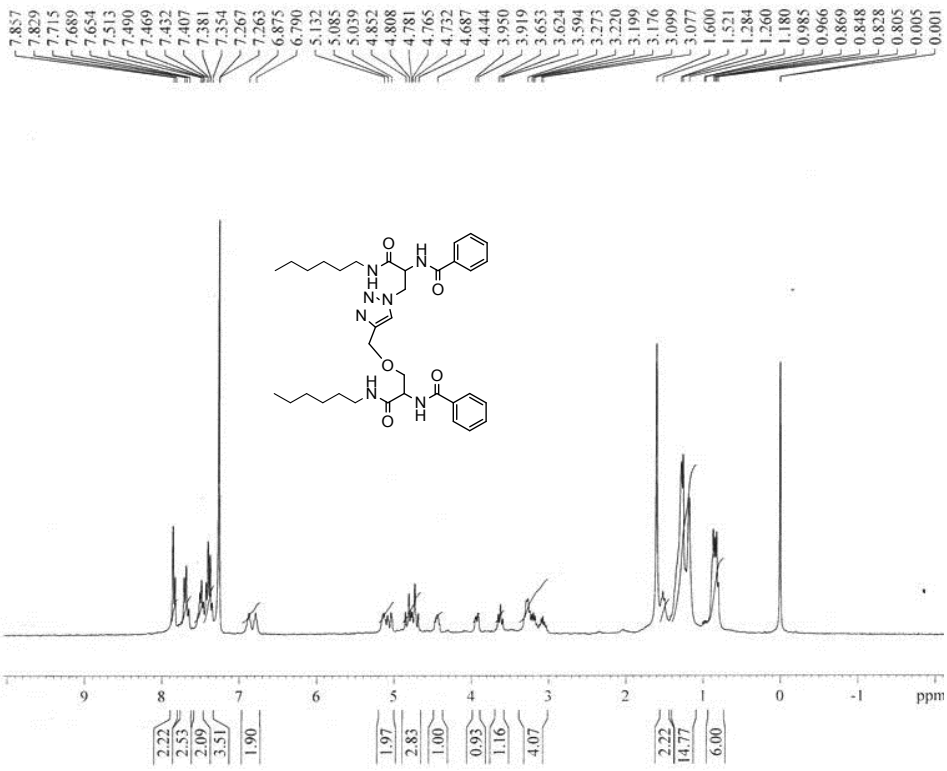
[1]H NMR (75 MHz, $CDCl_3$) of **5b**



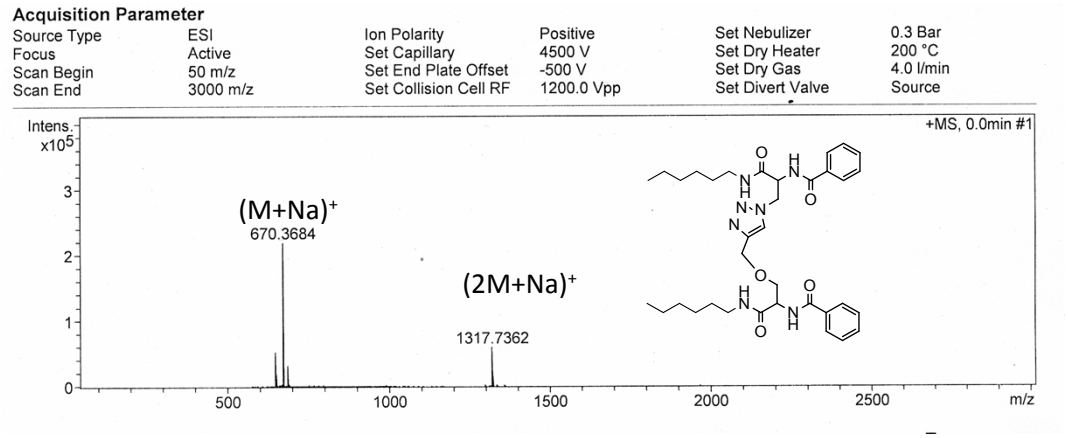
High Resolution Mass Spectrum of **5b**



^{1}H NMR (300 MHz, $CDCl_3$) of **S4**



High Resolution Mass Spectrum of **S4**



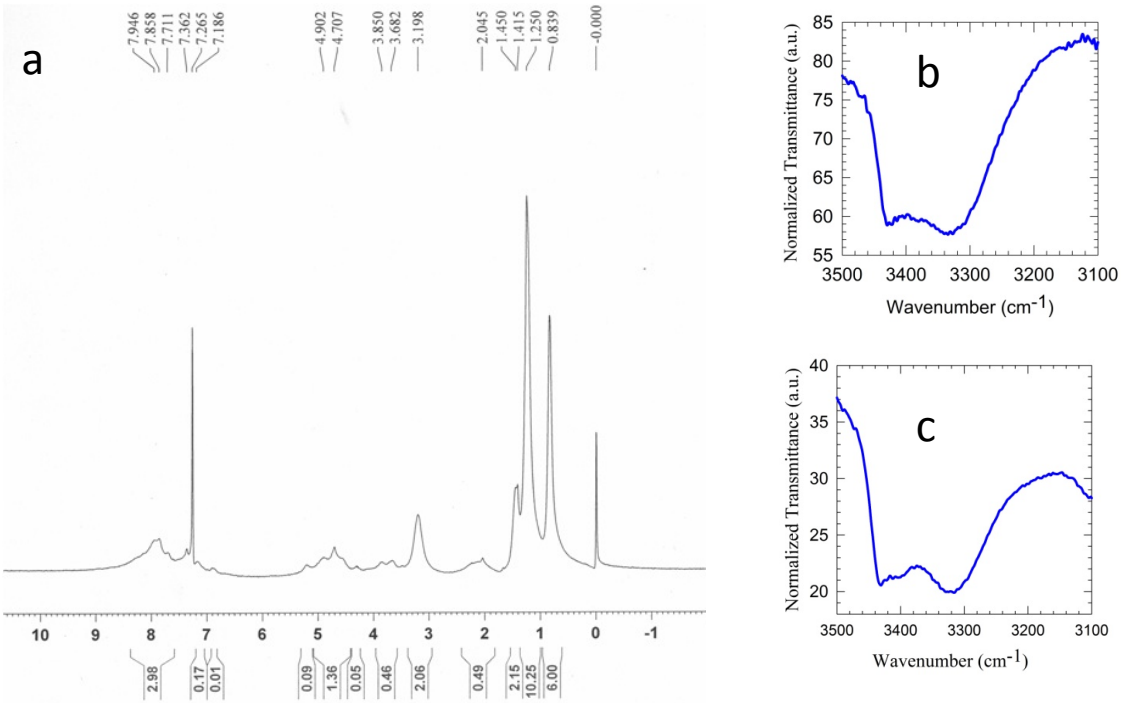


Figure S1 (a) ^{1}H NMR (300 MHz) spectra of **S1** in $CDCl_3$. The broadening of the amide NHs and aromatic protons is indicative of aggregation (b) FT-IR spectra of **S1** (5 mM) in $CHCl_3$ (c) FT-IR spectra of **4b** (10 mM) in $CHCl_3$.

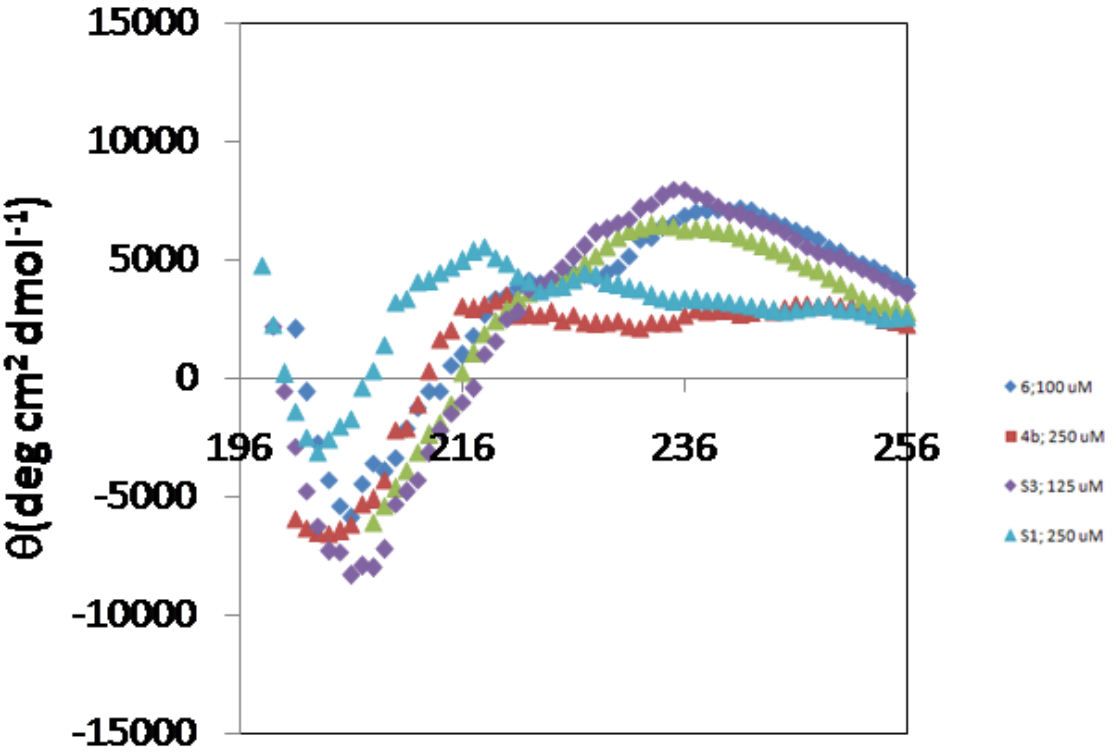


Figure S2 CD spectra of **4b**, **6**, **S1** and **S3** in methanol

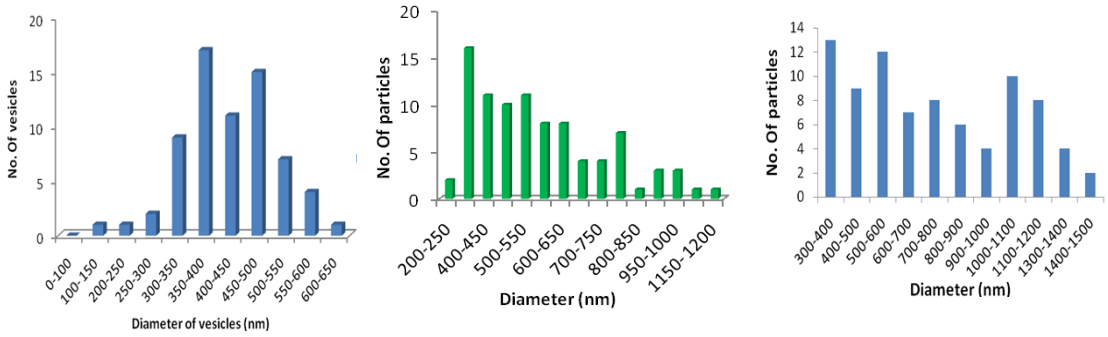


Figure S3 Histograms showing vesicle sizes of (a) **S1** (b) **S2** (c) **S3** measured from SEM

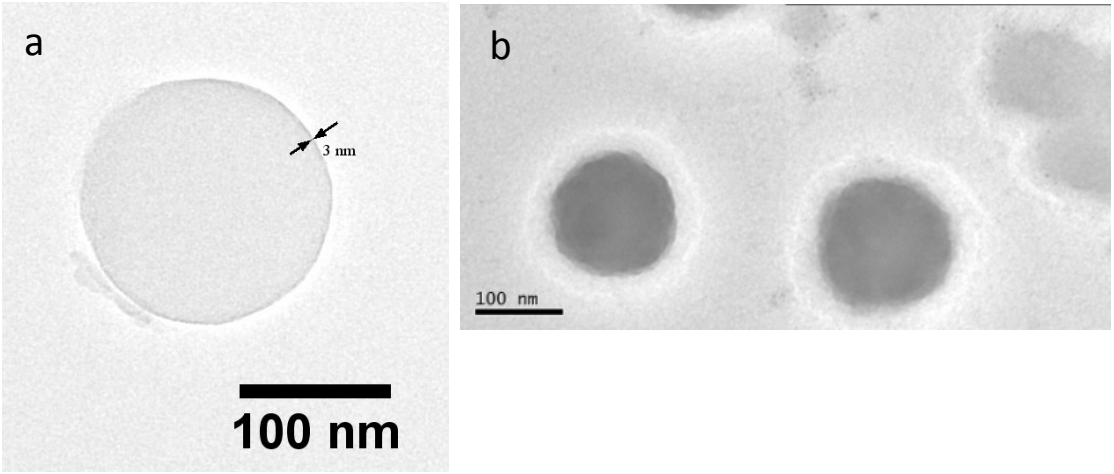


Figure S4 HR TEM images of (a) 0.5 mM solution of **S1** in $CHCl_3$:CH_3OH without staining (b) 0.5 mM solution of **S1** in $CHCl_3$:CH_3OH stained with phosphotungstic acid.

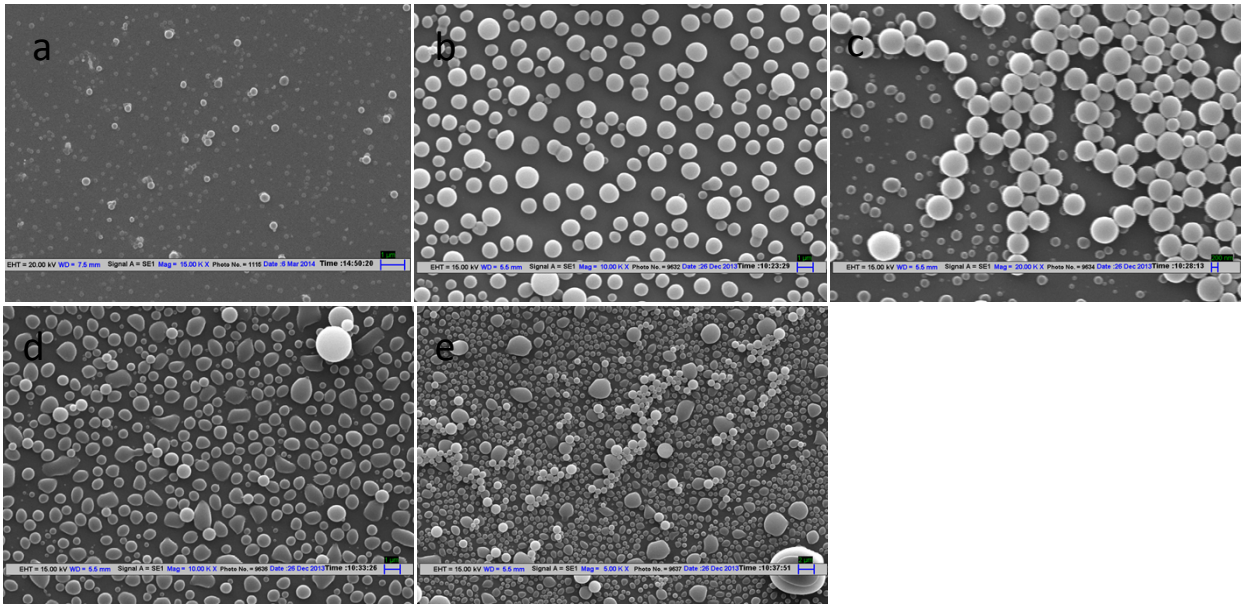


Figure S5 SEM images of **S1** in $CHCl_3$/CH_3OH (1:1) (a) 0.05 mM (Scale bar 1 μm) (b) 0.5 mM (Scale bar 1 μm) (c) 1 mM (Scale bar 200 nm) (d) 2 mM (Scale bar 1 μm) (e) 5 mM (Scale bar 2 μm)

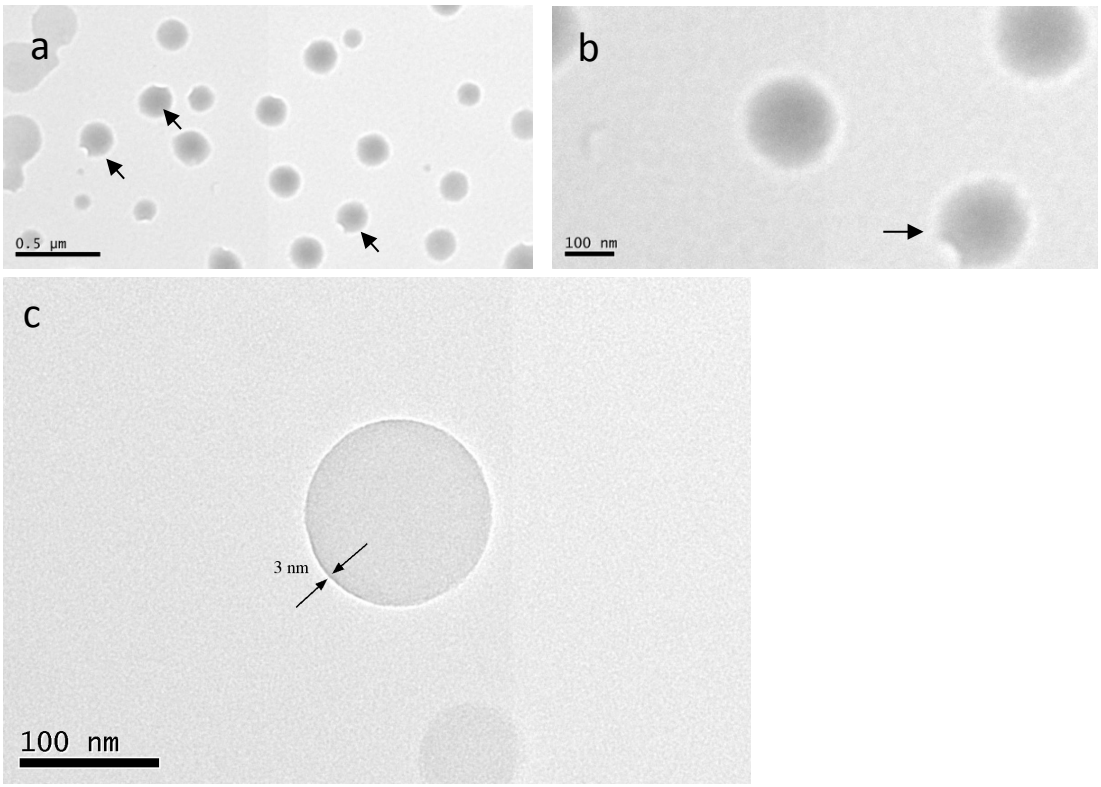


Figure S6 HRTEM images of 0.5 mM of **S2** in $CHCl_3$ / Methanol (1:1) showing (a-b) vesicles and pot-like structures (c) Selected vesicle showing the thickness of the wall.

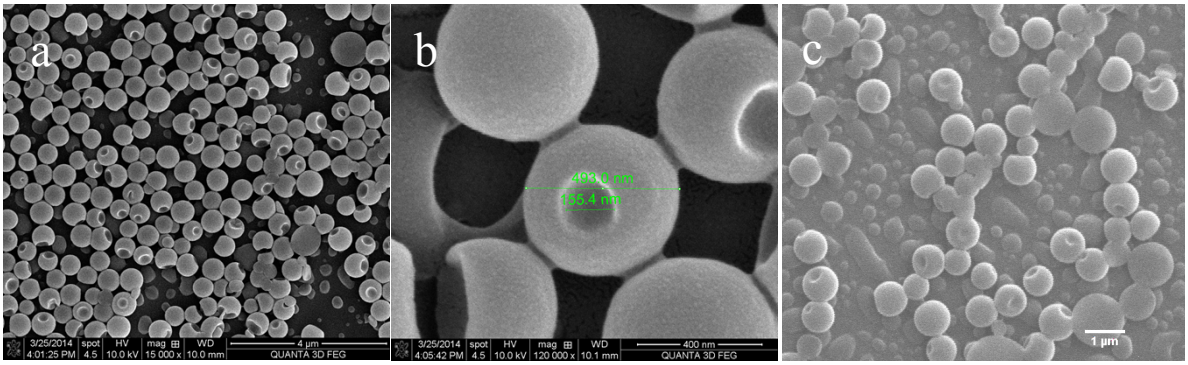


Figure S7 SEM images of (a) 0.5 mM solution of **S2** in $CHCl_3$:CH_3OH (1:1) (Scale bar 4 μm) (b) selected region from a showing the diameter of the orifice (Scale bar 430 nm) (c) 0.5 mM of **S2** solution in CH_3OH (scale bar 1 μm)

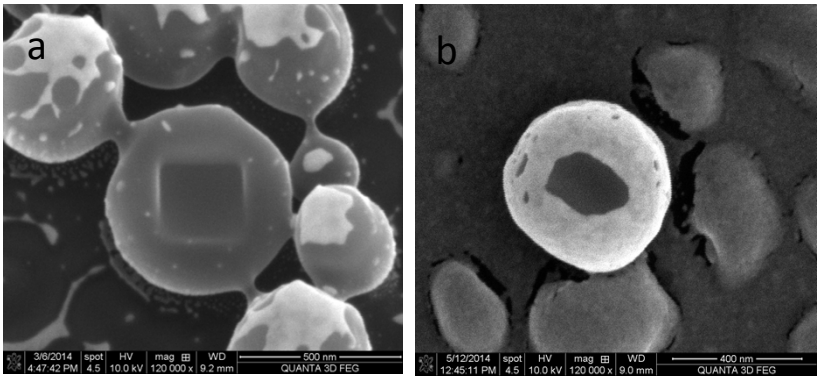


Figure S8 FIB-SEM images of (a) square inscribed on **S1** (Scale bar 500 nm) (b) circle inscribed on **S2** (Scale bar 400 nm)

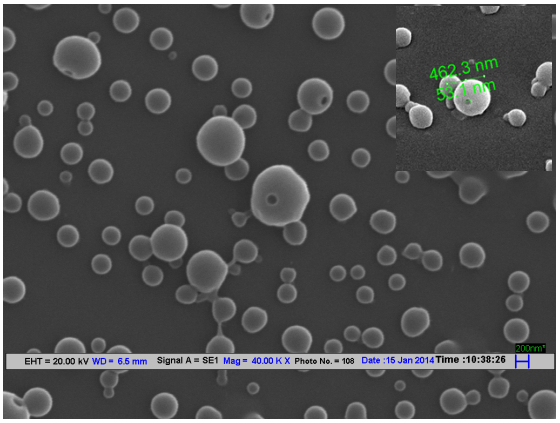


Figure S9 SEM images of 0.5 mM solution of **S3** in $CHCl_3$:CH_3OH (1:1) (Scale bar 200 nm)

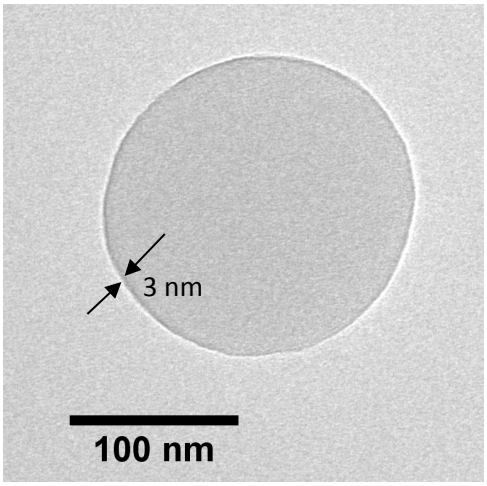


Figure S10 HR-TEM images of selected vesicle from **S3** showing dimension.

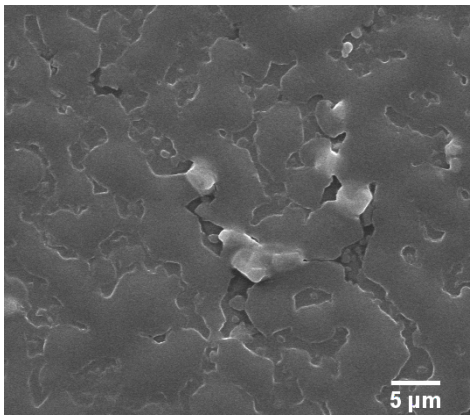


Figure S11 SEM image of a 0.5 mM solution of **S4** in $CHCl_3$:CH_3OH (1:1)

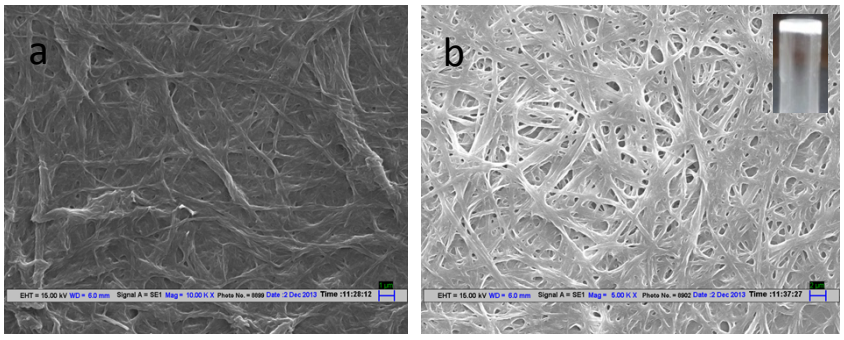


Figure S12 SEM images of (a) 1 mM solution of **6** in $CHCl_3$: Hexane (1:1) (b) Gel of **6**, 10.6 mM in $CHCl_3$: Hexane (1:1). Inset is the inverted vial with gel.

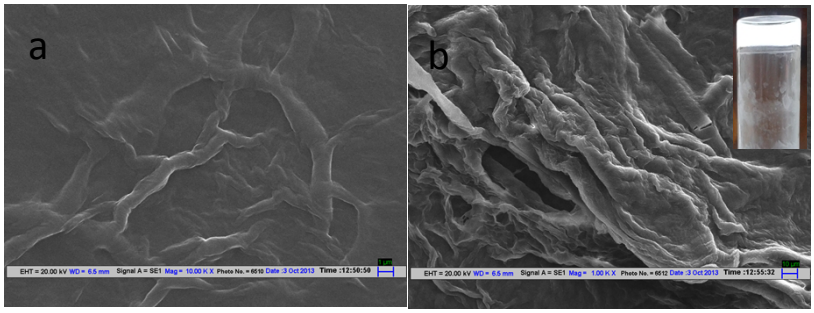


Figure S13 SEM images of (a) 1 mM solution of **4b** in $CHCl_3$: Hexane (1:1) (b) Gel of **4b** (9.9 mM) in $CHCl_3$: Hexane (1:3) Inset is the inverted vial with gel.

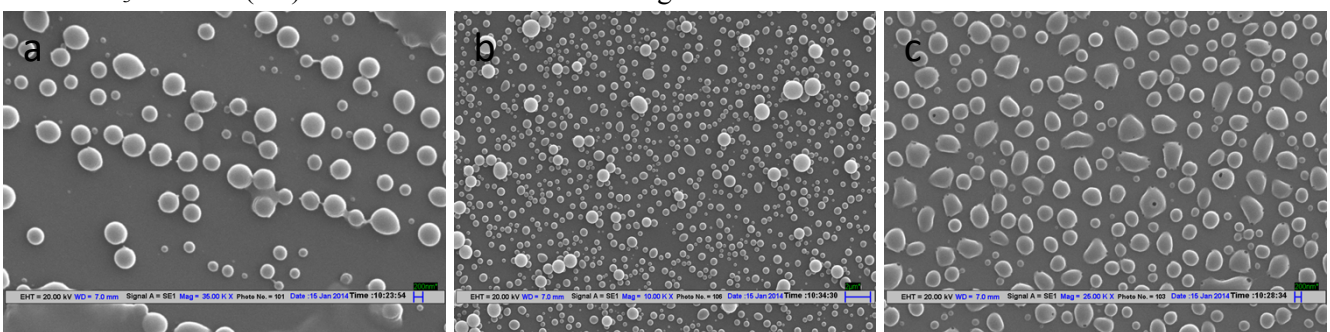
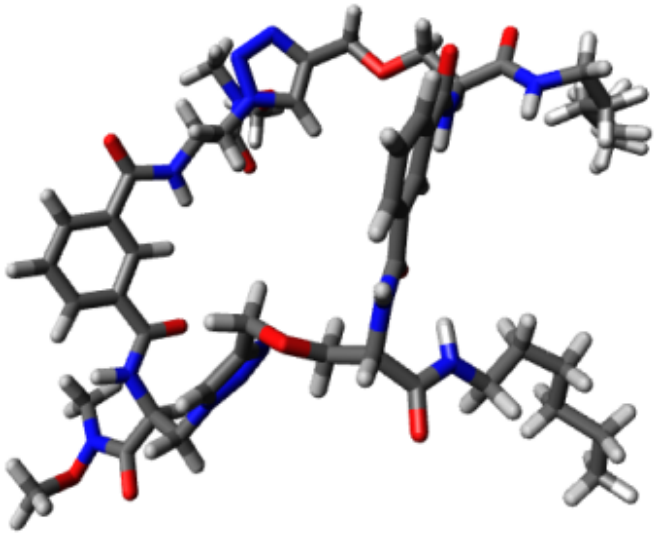


Figure S14 SEM images of 0.5 mM solution of **S1** in (a) CH_3OH (Scale bar 200 nm) (b) $CHCl_3$:CH_3OH (1:3) (Scale bar 2 μm) (c) $CHCl_3$:CH_3OH (3:1) (Scale bar 200 nm)

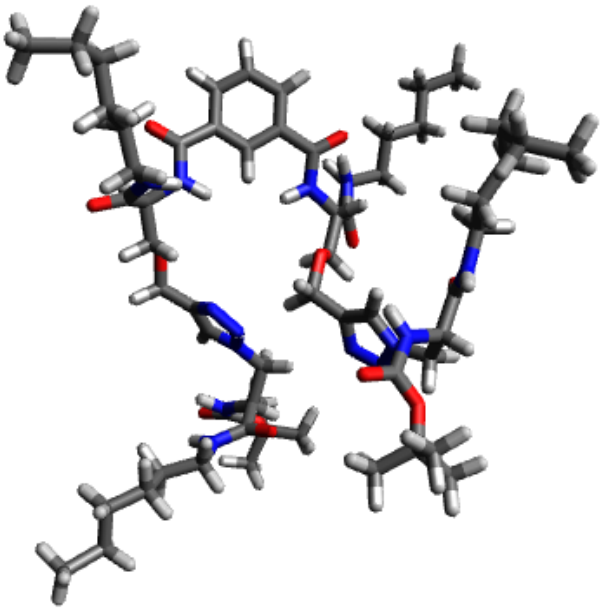
Molecular dynamics simulations

MD simulations were performed on a GPU clusters at Supercomputing Facility (SCFBio) at IIT Delhi. The AMBER 12 package[1] was used to prepare files for **S1**-**S3** and for performing Molecular Dynamics (MD) simulations. Molecules were solvated in an octahedron box of CH_3OH (methanol) 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 energy minimization and MD simulations of **S1** – **S3** were carried out with the aid of the SANDER module of the AMBER 12 program. At first, the simulation was affected with 1000 step minimization using the steepest descent algorithm followed by a 2000 step minimization using conjugate gradient to remove bad steric contacts. Topology and parameter files for the **S1**-**S3** 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 **S1**-**S3** with a fixed configuration of the solvent molecules in which the system was slowly heated from T = 10 to 300 K for 1ns. The entire system was then equilibrated at 300 K for 300 ps. The MD simulations were performed with a periodic boundary condition in the NPT ensemble at T=298.15 K with Berendsen temperature coupling and constant pressure P=1 atm with isotropic molecule-based scaling. 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. The coordinates of the trajectory was sampled every 10 ps for analysis of the energy stabilization.



(a)



(b)

Figure S15 (a) MD simulated structure of **S2** in CH_3OH (b) MD simulated structure of **S3** in CH_3OH

References

1. D. A. Case, T. A. Darden, T. E. Cheatham, III, C. L. Simmerling, J. Wang, R. E. Duke, R. Luo, R. C. Walker, W. Zhang, K. M. Merz, B. Roberts, S. Hayik, A. Roitberg, G. Seabra, J. Swails, A. W. Götz, I. Kolossváry, K. F.Wong, F. Paesani, J. Vanicek, R. M. Wolf, J. Liu, X. Wu, S. R. Brozell, T. Steinbrecher, H. Gohlke, Q. Cai, X. Ye, J. Wang, M. J. Hsieh, G. Cui, D. R. Roe, D. H. Mathews, M. G. Seetin, R. Salomon-Ferrer, C. Sagui, V. Babin, T. Luchko, S. Gusarov, A. Kovalenko, and P. A. Kollman (2012), AMBER 12, University of California, San Francisco.

2. W. D. Cornell, P. Cieplak, C. I. Bayly, I. R. Gould, K. M. Merz, D. M. Ferguson, D. C. Spellmeyer, T. Fox, J. W. Caldwell, and P. A. Kollman, *J. Am. Chem. Soc.*, 1995, **117**, 5179–5197.

3. U. Essmann, L. Perera, M. L. Berkowitz, T. Darden, H. Lee, and L. G. Pedersen, *J. Chem. Phys.*, 1995, **103**, 8577.