Electronic Supplementary Information

Expanded triazolophanes: A topological analysis of vesicular assembly

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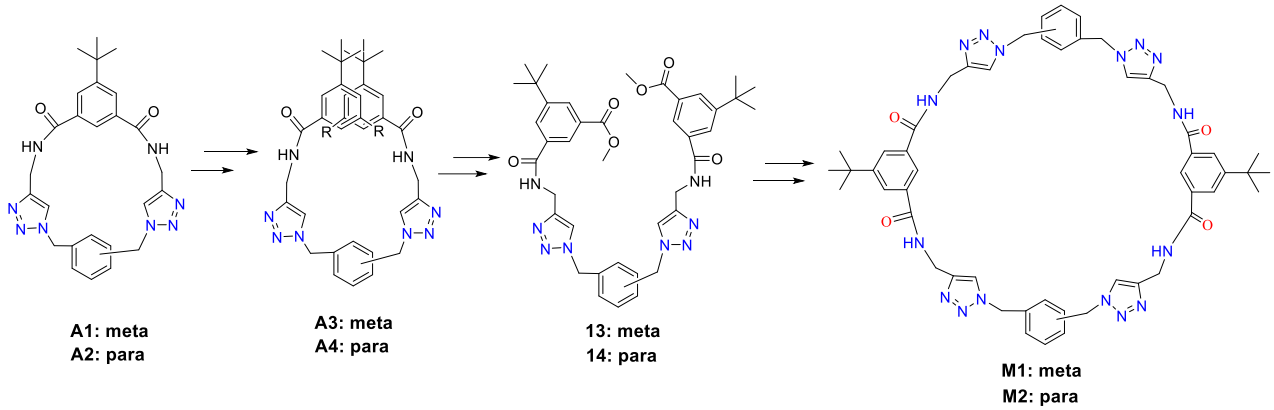
General Information

The materials and reagents used in the experiments were obtained from Sigma-Aldrich (USA) or Alfa Aesar (India). Progress of the chemical reactions was monitored using thin-layer chromatography on silica gel plates procured from Merck USA. The compounds were purified through column chromatography using silica gel with 100-200 mesh size. All solvents employed in the reactions were distilled or dried from appropriate drying agents prior to use. The FT-IR were recorded on Nicolet Protégé 460 spectrometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were recorded on Bruker-DPX- 300MHz spectrometer. Compounds were dissolved in deuterated solvents, and tetramethylsilane is used as an internal standard. Coupling constants are reported in Hz and the ^{1}H NMR data are presented as s (singlet), d (doublet), br (broad), br d (broad doublet), t (triplet), q (quartet), m (multiplet). High-resolution mass spectrometry (HRMS) was done on a Bruker MicrO-TOF-QII model with ESI technique. Melting points were recorded using a Fisher-Johns melting point apparatus.

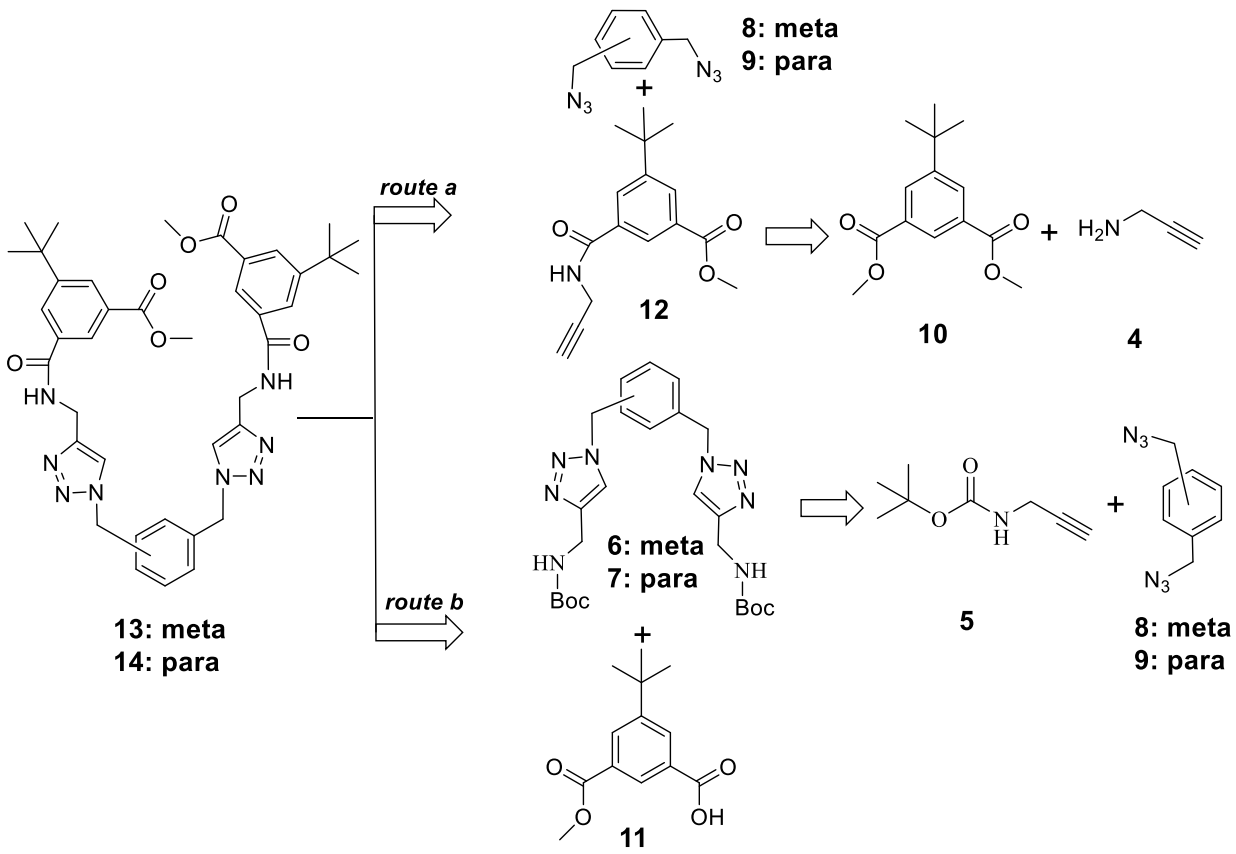
Synthetic schemes



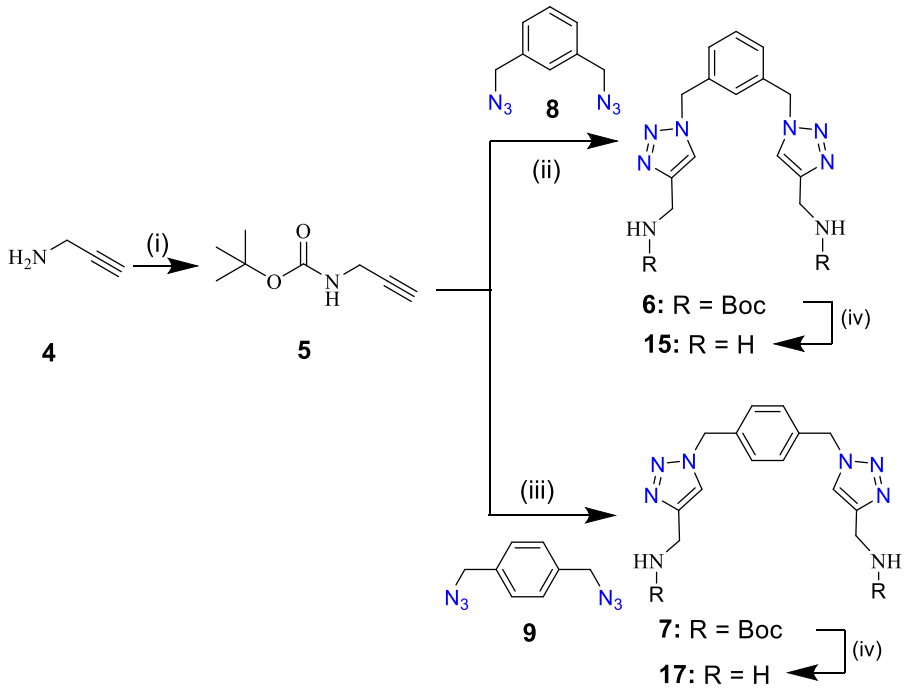
Scheme S1: Evolution of large ring cyclic molecules **M1-M2** from smaller triazophanes.[1]

Synthesis of **3**

The p-xylene dibromide was treated with sodium azide in acetone at room temperature to obtain the corresponding mono-azido product **1** after silica gel column chromatography. Monoazide **1** was further treated with dipropargyldiamide **2** in the presence of Cu (I) to obtain the intermediate **3**. The intermediate **3** was found to be insoluble, moreover the monoazide **1** was found to be highly lachrymatory, and hence we avoided this synthetic route.

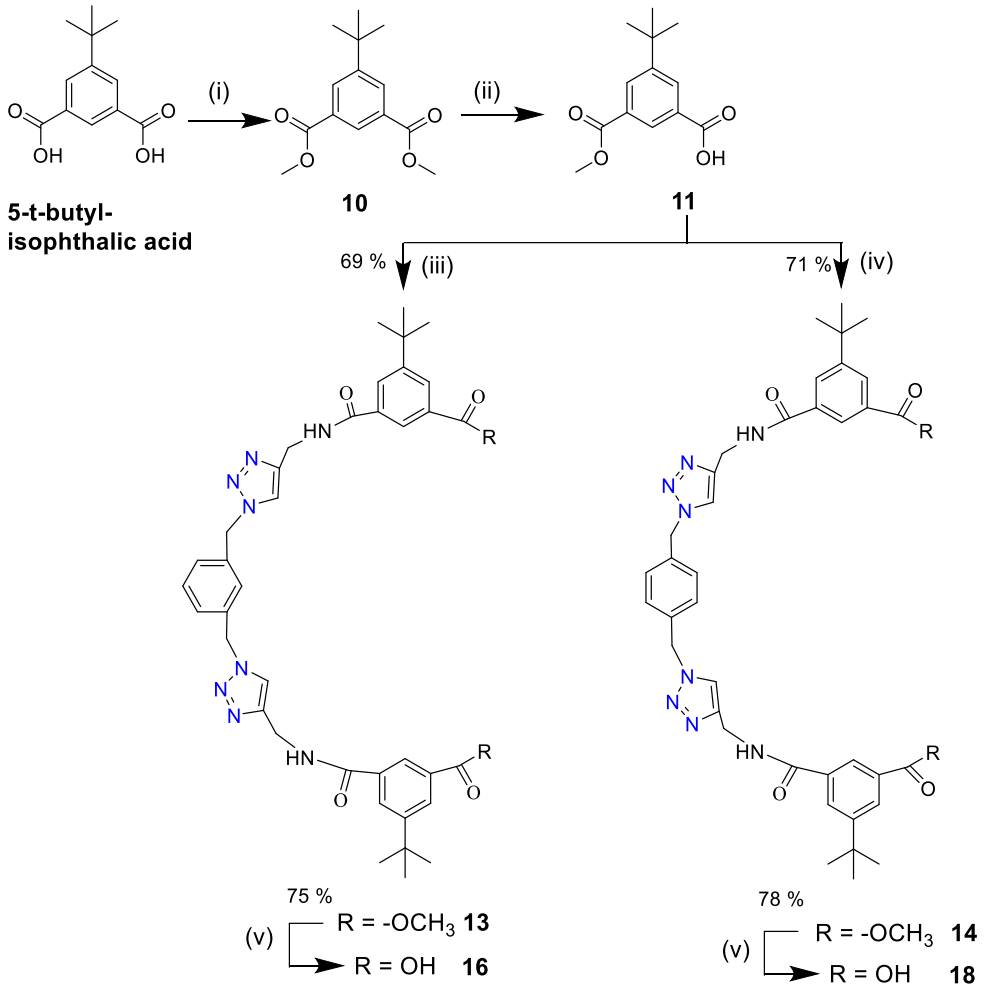


Scheme S2: *Disconnection* of precursors **13** and **14**.



Scheme S3: Synthesis of amines **15** and **17**. Reagents and conditions: (i) $(Boc)_2O$, Dry $CHCl_3$, RT/12 h; (ii) **8**, DIPEA, CH_3CN, CuI, RT/24 h; (iii) **9**, DIPEA, CH_3CN, CuI, RT/24 h; (iv) HCl; EtOH, RT/4 h.

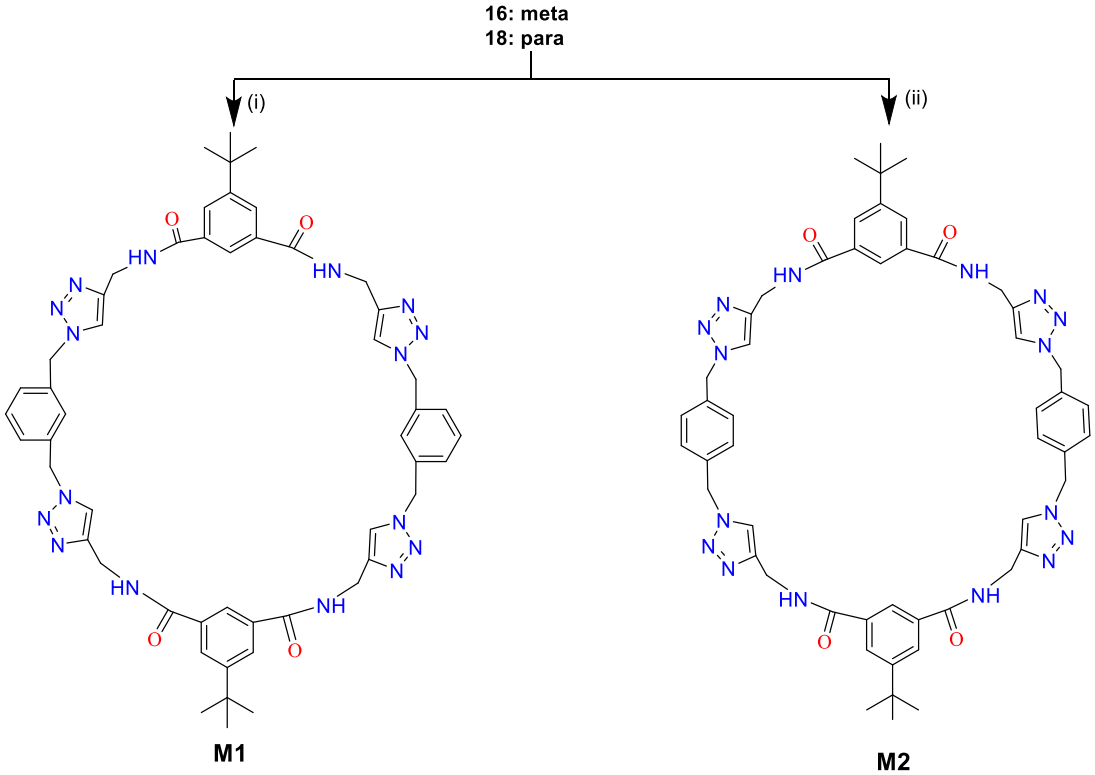
The diester **10** was synthesized by refluxing corresponding dicarboxylic acid with methanol and conc. H_2SO_4. The mono acid derivative **11** was prepared from diester derivative **11** under controlled hydrolysis (1eq NaOH in methanol). Amines **15** and **17** were further reacted with mono acid derivative **11** to yield precursors **13** and **14** with embodying two triazole moieties in their structures.



Scheme S4: Synthesis of precursors **13**, **14**, **16** and **18**. Reagents and conditions: (i) H_2SO_4, MeOH, reflux/24 h; (ii) 1N NaOH (1eq), MeOH, RT/24 h; (iii) $SOCl_2$, DMF, reflux/12 h and **15**, Et_3N, Dry CH_2Cl_2, RT/12 h; (iv) $SOCl_2$, DMF, reflux/12 h and **17**, Et_3N, Dry CH_2Cl_2, RT/12 h; (v) 0.5 N KOH, THF, RT/24 h.

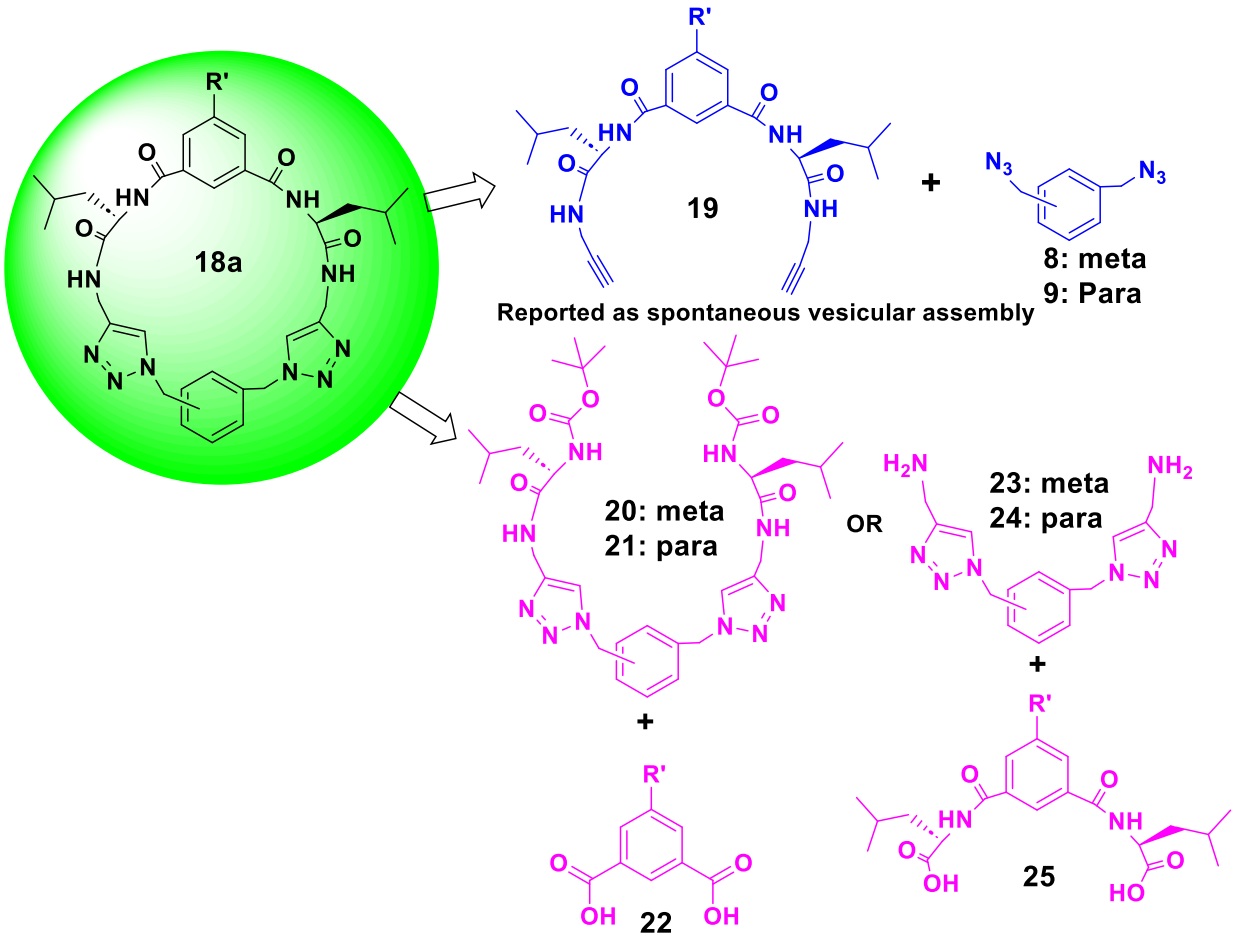
Table S1: Different conditions utilized for the synthesis of **M1** and **M2**.

S.NO	Reagent Used	Time (h)	Reaction Conditions	Yield (%)
1	DCC	24	DCM and Et_3N at RT	No reaction Starting material recovered
2	HBTU	12	DCM and Et_3N at RT	No reaction Starting material recovered
3	EDC.HCl	12	DCM and Et_3N at RT	No reaction Starting material recovered
4	HATU	12	DCM and DIPEA at RT	35

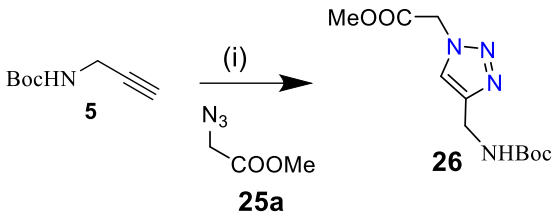


Scheme S5: Synthesis of expanded macrocycles **M1** and **M2**.

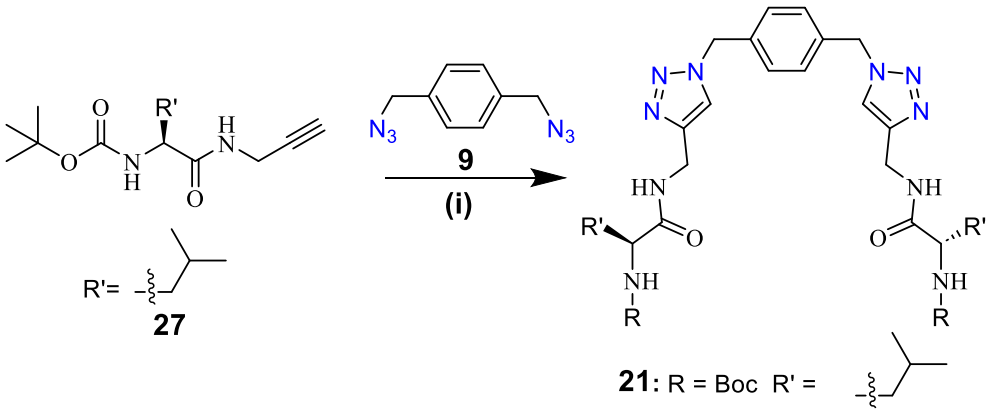
Reagents and conditions: (i) **Table S1**, **15**, HATU, DIPEA, CH_2Cl_2, DMF, RT/12 h; (ii) **17**, HATU, DIPEA, CH_2Cl_2, DMF, RT/12 h.



Scheme S6: Design of acyclic molecules based on simple triazolophanes.[1]



Scheme S7: Synthesis of acyclic molecule **26**. Reagents and conditions: (i) DIPEA, CH_3CN, CuI, RT/24 h



Scheme S8: Synthesis of acyclic molecule **21**. Reagents/conditions: (i) DIPEA, CH_3CN, CuI, RT/24 h.

Methods: -

1. **Scanning Electron Microscopy (SEM):**

SEM images were recorded using ZEISS EVO Series Scanning Electron Microscope EVO 50 operating at an accelerating voltage of 0.2 − 30 kV. For SEM, a 10 μL aliquot of the sample solution (1mM) was drop-casted on a glass cover slip, dried and coated with ∼10 nm of gold. FE-SEM iamges were recorded using FEI Quanta 3D FEG High resolution scanning electron microscope (FE-SEM) combined with High-current ion column with Ga liquid-metal ion source.

2. **Atomic Force Microscopy (AFM):**

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

3. **High Resolution-Transmission Electron Microscopy (HR-TEM):**

HR-TEM images were recorded on a TECHNAI G2 (20S-TWIN) electron microscope operated at an accelerating voltage of 200 kV. Samples were prepared by drop-casting the sample on 200 square mesh carbon-coated copper grids.

4. **Details of molecular simulation studies:**

The initial structure of **M1** was drawn in Gaussview and optimized using the Gaussian09 software[2] at the HF/6-31G level of theory. The optimized structure was then solvated in a 1:1 mixture of methanol and chloroform and simulated in the NPT ensemble at temperature 300 K and pressure 1 bar. From this simulation trajectory we observed that this molecule is very

flexible and spans a large conformational space. To understand the self-assembly process, we simulated a system with randomly placed **M1** monomers in the solvent mixture. The **M1** molecules were found to aggregate and form dimers and multimers that were stabilized by the formation of π-stacks and hydrogen bonds. In principle, we expect that these monomers aggregate to form large stable stacks. However, to observe such stacks formation, we need to simulate much bigger system for long time. Alternatively, we could construct a preformed stack and check its dynamical behavior in the solvent. Towards this goal, we constructed a stack of sixteen monomers and simulated it in the solvent mixture. From this simulation, we observed that the stack has an intrinsic curvature that leads to the formation of toroids.

The Charmm General Force Field (CGenFF) was used for both the solute and solvent molecules. The steepest descent algorithm was used for minimizing the initial configurations. The systems were thermally equilibrated by an NVT simulation at temperature 300 K. The system's volume was subsequently equilibrated by running a short NPT simulation. In these simulations, the temperature was controlled at 300 K by using the V-rescale thermostat. In the equilibration NPT simulation, the pressure was controlled at 1 bar using the Berendsen barostat. Finally, long production simulations in the NPT ensemble were carried out keeping the same thermostat but changing the barostat to Parrinello-Rahman. We have used a timestep of 0.5 and 1 fs in the equilibration and production simulations, respectively. All simulations were carried out using GROMACS-2021.4 software package. The Figures were generated using the VMD software.[3]

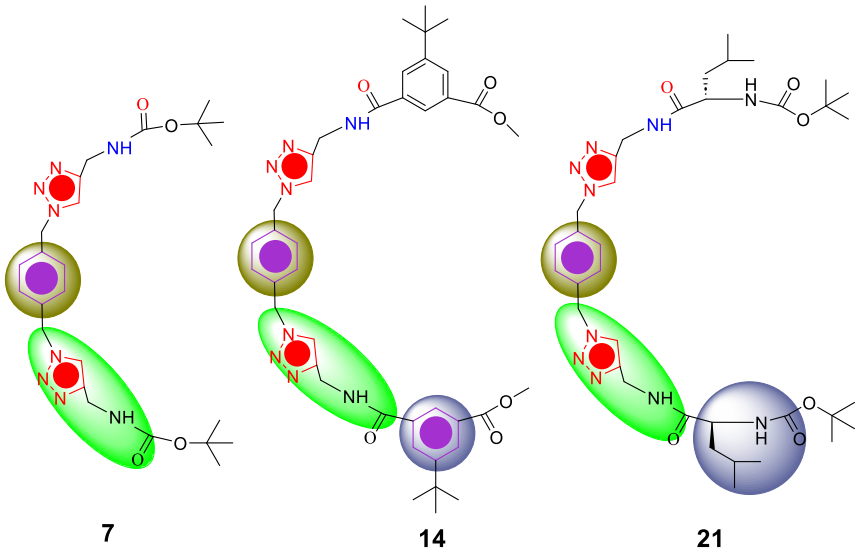


Fig. S1: Structures of acyclic molecules **7, 14** and **21.**

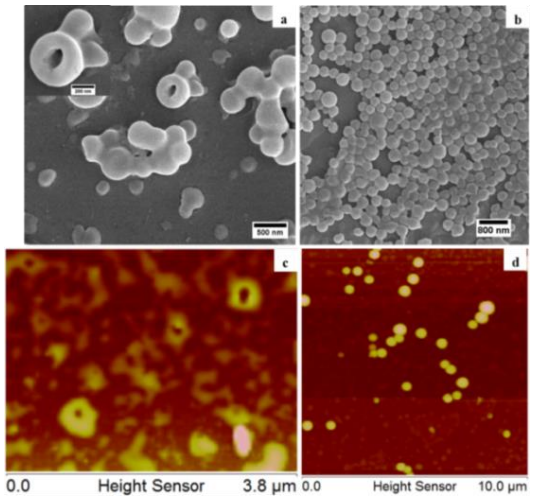


Fig. S2: FE-SEM images of **13** (a) at 0.5 mM showing toroids (Inset: magnified toroid) (b) at 1 mM showing vesicles. AFM of (c) **13** at 0.5 mM showing toroids (d) at 1 mM showing the vesicles.

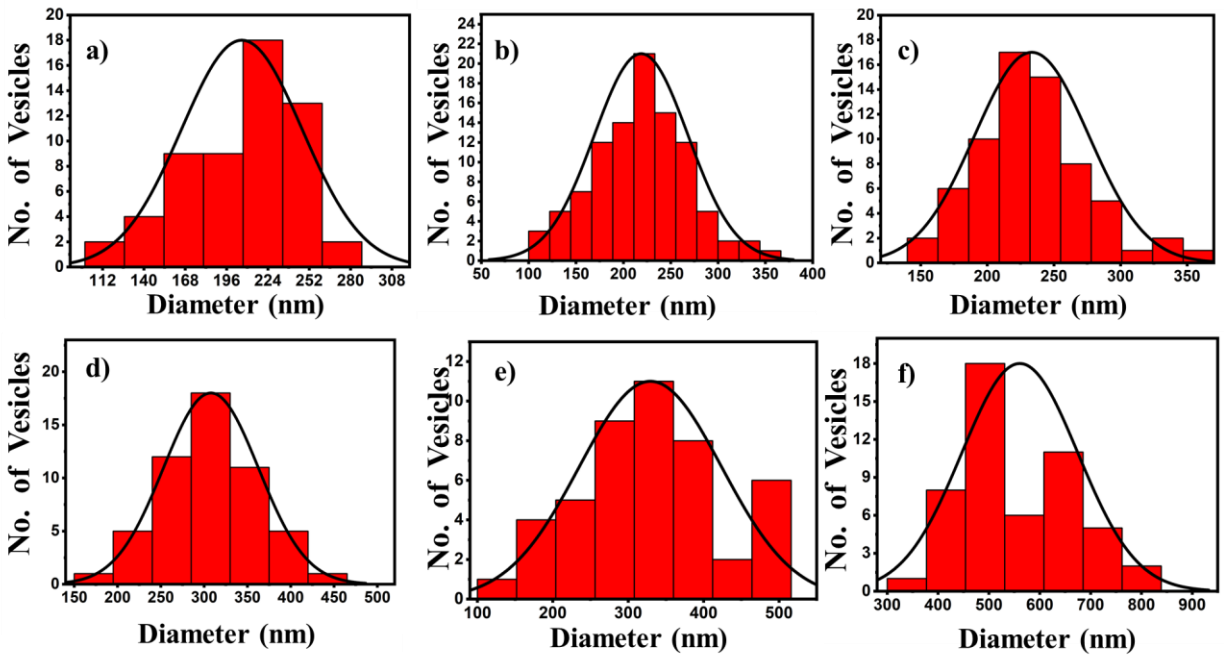


Fig. S3: Histograms based on SEM images (a) Size distributions of diameters of vesicles at 1 mM of **M1** in a mixture of methanol: chloroform (1:1); (b) Size distribution of diameters of vesicles at 0.5 mM of **14** in a mixture of methanol: chloroform (1:1); (c) Size distributions in diameters of vesicles at 1 mM of **14**; (d) Size distribution of diameters of toroids at 0.5 mM of **13** in a mixture of methanol: chloroform (1:1); (e) Size distribution of diameters of vesicles at 1 mM of **13** in a mixture of methanol: chloroform (1:1); (f) Size distribution of diameters of vesicles at 1 mM of **21** in a mixture of methanol: chloroform (1:1).

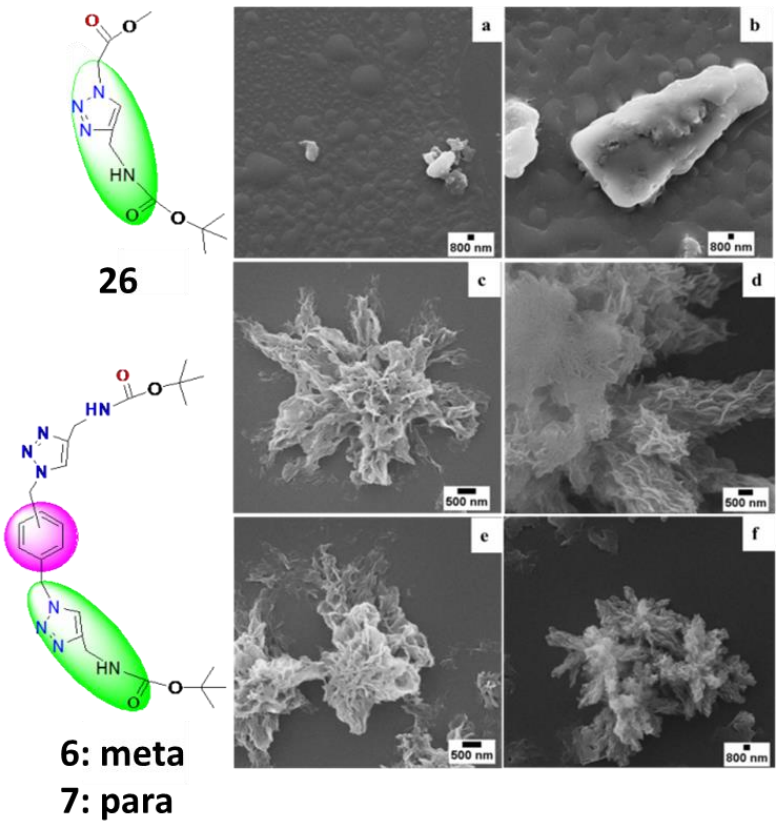
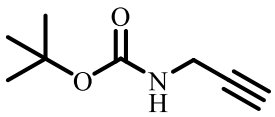


Fig S4*:* (a-b) SEM images of **26** at 0.5 mM and 1 mM (c-d) SEM images of **6** at 0.5 mM and 1 mM (e-f) SEM images of **7** at 0.5 mM and 1 mM.

Experimental section:

Synthesis of 5:



5

To an ice-cooled solution of propargyl amine **4** (2.5 g, 45.38 mmol) in $CHCl_3$ (150 mL) was added $(Boc)_2O$ (9.90 g, 45.38 mmol) slowly and stirred for 12 h.The reaction mixture was evaporated in vacuo and dissolved in ethyl acetate (150 mL). The EtOAc part was washed with water; the organic layer was dried over Na_2SO_4 and evaporated in vaccuo to afford 5 g of **5**.

Yield:71%

Mp: 119-121 ^oC

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.46 (s, 9H), 2.23 (t, J = 2.25 Hz, 1H), 3.93 (br d, 2H), 4.74 (br s, 1H).

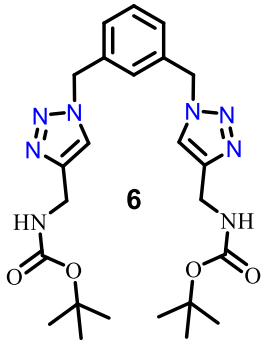
^{13}C NMR (75 MHz, $CDCl_3$): δ 28.3, 30.3, 71.1, 79.8, 80.2, 155.3.

IR(KBr): 3327, 2980, 2926, 2859, 2129, 1691, 1532, 1452, 1366, 1282, 1167 cm^{-1}.

HRMS: Calcd for $C_8H_{13}NO_2Na$ m/z = 178.0838, obtained m/z = 178.0834.

General method for the synthesis of 6 and 7

To an ice cold solution of Boc-propargylamine **5** (1.5 g, 9.67 mmol) in dry acetonitrile was added diisopropylethylamine (DIEA) (2.0 mL, 11.60 mmol), and the diazide (910 mg, 4.83 mmol) under an N_2 atmosphere. CuI (184 mg, 0.97 mmol) was added and the reaction mixture was stirred for 24 h under N_2 atmosphere. The solvent was evaporated and the residue was dissolved in chloroform and washed with an aqueous solution of NH_4Cl + NH_4OH (9:1), 2N H_2SO_4, saturated solution of $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain 1.73 g of **6** and 1.78 g of **7**.



Yield: 72 %

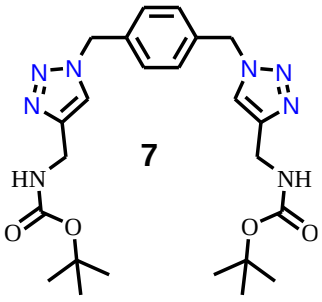
Mp: 93-96 ^{o}C

^{1}H NMR (300 MHz, CDCl$_3$): δ 1.42 (s, 18H), 4.38 (d, J = 6 Hz, 4H), 5.19 (br s, 2H), 5.48 (s, 4H), 7.11 (s, 1H), 7.22 (d, J = 8.1 Hz, 2H), 7.37 (t, J =7.7 Hz, 1H), 7.44 (s, 2H).

^{13}C NMR (75 MHz, CDCl$_3$): δ 28.3, 36.1, 53.6, 79.7, 121.9, 127.3, 128.1, 129.9, 135.8, 146.1, 155.9.

IR (KBr): 3387, 3125, 2977, 1694, 1518, 1448, 1368, 1259, 1168, 1044 cm^{-1}.

HRMS: calcd for $C_{24}H_{34}N_8O_4Na$ m/z = 521.2595, found m/z = 521.2569.



Yield: 74 %

Mp: 184-185^{o}C

^{1}H NMR (300 MHz , CDCl$_3$): δ 1.42 (s, 18H), 4.36 (d, J = 5.7 Hz, 4H), 5.10 (br s, 2H), 5.49 (s, 4H), 7.25 (m, 4H), 7.44 (s, 2H).

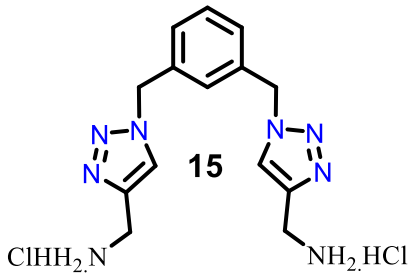
^{13}C NMR (75 MHz, CDCl$_3$): δ 28.2, 35.6, 52.3, 77.9, 122.7, 128.3, 136.1, 145.8, 155.5.

IR (KBr): 3413, 3132, 2977, 1688, 1513, 1368, 1272, 1170, 1057 cm^{-1}.

HRMS: calcd for $C_{24}H_{34}N_8O_4Na$ m/z = 521.2595, found m/z = 521.259.

General method for the synthesis of 15 and 17

To an ice cold solution of **6** or **7** (2 g, 4.01 mmol) was added HCl (g) in ethanol (20 mL) and left stirred for 4 h. The reaction mixture was then evaporated and the resulting product was dissolved in acetone (20 mL) and stirred for 15 min. It was filtered and the residue was dried to obtain 1.2 g of **15** and **17**.



Yield: 81 %

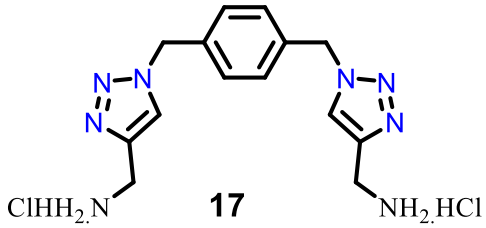
Mp: above 260 ^{o}C

^{1}H NMR (300 MHz, D_2O): δ 4.34 (s, 4H), 5.56 (s, 4H), 7.20 – 7.45 (br m, 4H), 8.17 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 53.6, 125.6, 127.5, 128.3, 129.9, 135.6, 140.0.

IR (KBr): 3431, 2920, 1590, 1505, 1443, 1226, 1131, 1084 cm^{-1}.

HRMS: calcd for $C_{14}H_{19}N_8$ m/z = 299.1727, found m/z = 299.1726.



Yield: 81 %

Mp: above 260 ^{o}C

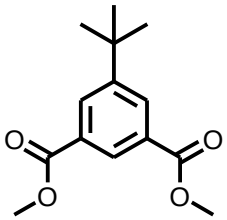
^{1}H NMR (300 MHz , $CDCl_3$): δ 4.36 (s, 4H), 5.70 (s, 4H), 7.41 (s, 4H), 8.17 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 34.0, 53.5, 125.5, 128.7, 135.2, 140.0.

IR (KBr): 3422, 3007, 1593, 1504, 1224, 1088 cm^{-1}.

HRMS: calcd for $C_{14}H_{19}N_8$ m/z = 299.1727, found m/z = 299.1725.

Synthesis of 10



To a stirred, homogeneous solution of 5-*t*-butyl-isophthalic acid (2 g, 9.01 mmol) in 100 mL of dry MeOH was added 1 mL conc. H_2SO_4 and the resulting solution was refluxed for 24 h at 90 ºC. Methanol was evaporated; the white residue obtained was dissolved in 75 mL of $CHCl_3$ and washed with aqueous $NaHCO_3$ solution. The organic layer was dried over Na_2SO_4 and evaporated to yield 1.9 g of 5-*t*-butyl-isophthalic acid dimethyl ester **10**.

Mp: 98-100 ºC

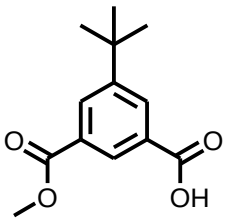
Yield: 84 %.

^{1}H NMR ($CDCl_3$, 300 MHz): δ 1.38 (s, 9H), 3.95 (s, 6H), 8.26 (d, J = 1.2 Hz, 2H) 8.50 (s, 1H)

^{13}C NMR ($CDCl_3$, 75 MHz): δ 31.1, 34.9, 52.2, 127.9, 130.3, 130.8, 152.1, 166.5.

IR (KBr): 2965, 1721, 1600, 1450, 1332, 1250 cm^{-1}.

Synthesis of 11



5-*t*-butyl-isophthalic acid dimethyl ester **10** (2 g, 8 mmol) was dispersed in 150 mL of dry MeOH under ice-cooled condition. To this non-homogenous solution was added 1 M aqueous solution of NaOH (12 mL) portion wise in 0.5 h intervals over a period of 12 h. The ice bath was removed after completion of the addition and the suspension was left stirred vigorously at RT for 12 h. The solvent was evaporated and the white solid obtained was dissolved in CH_2Cl_2 and washed with an aqueous $NaHCO_3$ solution, dried over Na_2SO_4, concentrated to yield the unreacted starting material. The aqueous layer was acidified with 2N HCl to pH 2, yielding a milky white suspension, which was then extracted with ethyl acetate. The ethyl acetate part was washed with water, dried over Na_2SO_4 and filtered and evaporated. The crude compound was purified by column chromatography using 5% EtOAc/hexane to get 1.7 g of **11**.

Yield: 90 %

Mp: 114-116 ^{o}C

^{1}H NMR ($CDCl_3$, 300 MHz): 1.39 (s, 9H), 3.96 (s, 3H), 8.33 (d, J = 1.5 Hz, 2H) 8.56 (s, 1H).

IR (KBr): 3437, 2956, 1726, 1595, 1441, 1270, 1143 cm^{-1}.

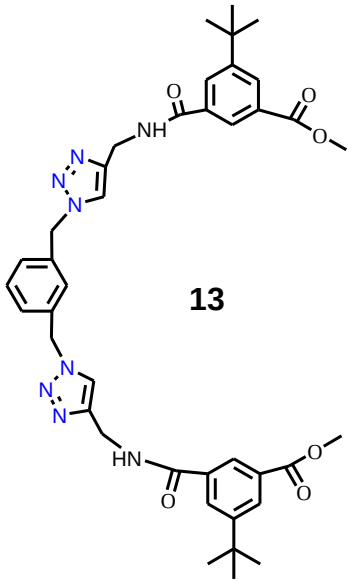
General method of synthesis of 13 and 14

(i) **Synthesis of acid chloride 11a**

5-*t*-Butylisophthalic acid monomethyl ester **11** (1 g, 4.23 mmol) was dissolved in freshly distilled $SOCl_2$ (3 mL) and DMF (0.5 mL), refluxed at 85-90 ^{o}C for 4 h. The reaction mixture was subjected to high vacuum to remove excess $SOCl_2$ and the acid chloride of **11** (**11a**) was obtained as 1 g of white solid.

(ii) **Synthesis of 13** and **14**

Amine salt **15** or **17** (727 mg, 1.96 mmol) was dissolved in dry CH_2Cl_2 (10 mL), added triethylamine (NEt_3) (1.36 mL, 9.82 mmol); stirred for 5 min at 0 ^{o}C and the acid chloride of **11** (1 g, 3.93 mmol) in dry CH_2Cl_2 (60 mL) was added dropwise. The reaction mixture was stirred for 12 h at room temperature, 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. The crude compound was purified by column chromatography using MeOH/ $CHCl_3$ to yield 995 mg of **13** and 1.02 g of **14.**



13

Yield: 69 %

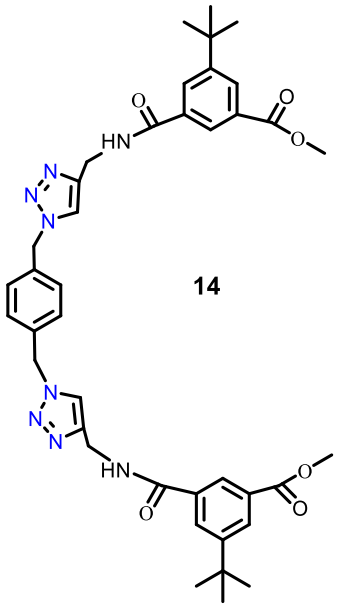
Mp: 163-165 ^{o}C

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 18H), 3.90 (s, 6H), 4.72 (d, J = 5.1 Hz, 4H), 5.48 (s, 4H), 6.79 (s, 1H), 7.24 (s, 2H), 7.35 (d, J = 6.9 Hz, 1H), 7.45 (br s, 2H), 7.55 (s, 2H), 8.12 (s, 2H), 8.18 (s, 2H), 8.24 (s, 2H).

^{13}C NMR (75 MHz, $CDCl_3$): δ 31.1, 35.0, 35.4, 52.2, 53.6, 122.7, 122.9, 125.2, 128.1, 129.1, 129.6, 129.8, 130.2, 134.1, 135.8, 145.5, 152.3, 166.6, 167.1

IR (KBr): 3304, 2958, 1722, 1640, 1545, 1442, 1250 cm^{-1}.

HRMS: calcd for $C_{40}H_{46}N_8O_6Na$ m/z = 757.3433, found m/z = 757.3436.



Yield: 71 %

Mp: 202-204 ºC

^{1}H NMR (300 MHz, $CDCl_3$): δ 1.34 (s, 18H), 3.91 (s, 6H), 4.69 (d, J = 5.7 Hz, 4H), 5.49 (s, 4H), 7.15 (t, J = 5.5 Hz, 2H), 7.26 (s, 4H), 7.58 (s, 2H), 8.07 (t, J = 1.6 Hz, 2H), 8.17(br m, 4H).

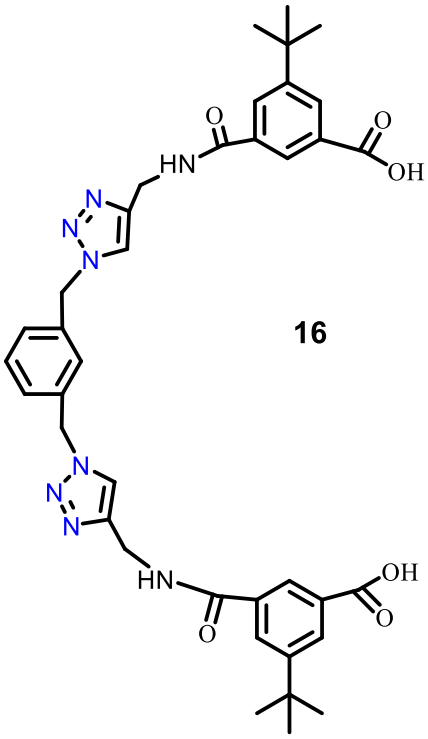
^{13}C NMR (75 MHz, $CDCl_3$): δ 29.6, 31.1, 35.0, 52.2, 53.6, 122.9, 125.2, 128.7, 129.1, 129.5, 130.1, 134.1, 135.2, 145.4, 152.2, 166.6, 167.0.

IR (KBr): 3493, 3322, 3064, 2962, 1724, 1641, 1546, 1445, 1328, 1260, 1123, 1046 cm^{-1}.

HRMS: calcd for $C_{40}H_{46}N_8O_6Na$ m/z = 757.3433, found m/z = 757.3413.

General method for synthesis of 16 and 18

13/14 (990 mg, 1.35 mmol) was dissolved in THF (45 mL) and 0.5 M KOH solution (45 ml) was added to the reaction vessel, and allowed to stir at room temperature for 24 h. THF was removed under reduced pressure and then acidified with 2 N HCl solution. The product was extracted from the aqueous solution with ethyl acetate and dried over anhydrous Na_2SO_4, filtered and evaporated to yield 714 mg of **16** and 743 mg of **18**.



16

Yield: 75 %

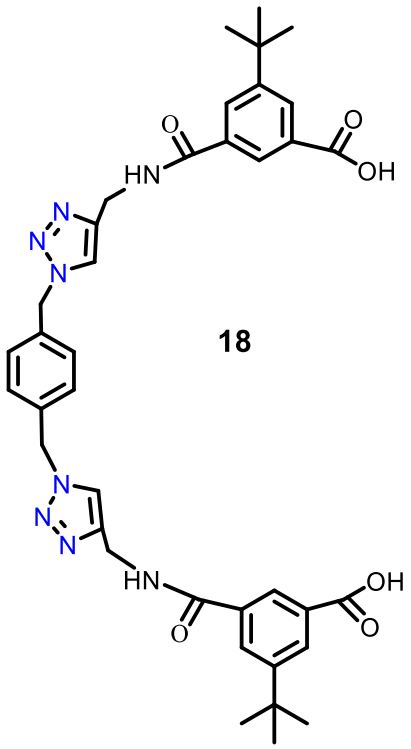
Mp: 242-244 ºC

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.33 (s, 18H), 4.52 (s, 4H), 5.55 (s, 4H), 7.26 (m, 2H), 7.35 (s, 2H), 8.08 (br m, 6H), 8.30 (s, 2H), 9.22 (s, 2H), 13.09 (br s, 2H).

^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 30.9, 34.6, 34.9, 52.5, 123.2, 125.8, 127.7, 127.8, 128.4, 128.5, 129.2, 130.8, 134.3, 136.6, 145.2, 151.4, 165.5, 167.1.

IR (KBr): 3455, 2963, 2938, 1731, 1689, 1601, 1446, , 1367, 1270, 1146 cm^{-1}.

HRMS: calcd for $C_{38}H_{42}N_8O_6Na$ m/z = 729.3120, found m/z = 729.3119.



18

Yield: 78 %

Mp: 248-250 ºC

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.32 (s, 18H), 4.51 (d, J = 5.1 Hz, 4H), 5.54 (s, 4H), 7.31 (s, 4H), 8.00-8.20 (m, 6H), 8.30 (s, 2H), 9.21 (s, 2H), 13.07 (br s, 2H).

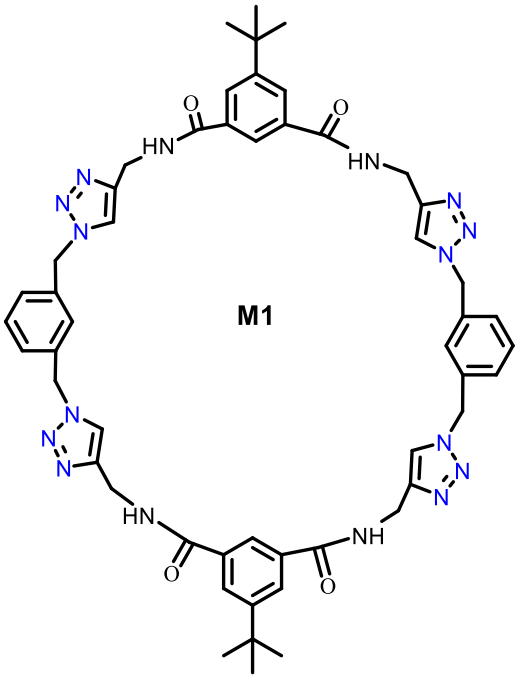
^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 30.9, 34.6, 34.9, 52.3, 123.1, 125.8, 128.4, 130.8, 134.2, 136.0, 145.3, 151.4, 165.5, 167.1.

IR (KBr): 3344, 2962, 1652, 1542, 1450, 1279, 1131, 1063 cm^{-1}.

HRMS: calcd for $C_{38}H_{42}N_8O_6Na$ m/z = 729.3119, found m/z = 729.3109.

General method for synthesis of M1 and M2:

To an ice-cooled solution of **16** or **18** (250 mg, 0.35 mmol) in DMF (2 mL) and CH_2Cl_2 (130 mL), under nitrogen was added diisopropyl ethylamine (0.14 mL, 0.78 mmol), and HATU (295 mg, 0.78 mmol) and allowed to stir for 10 min. To this reaction mixture, was added Compound **15** or **17** (131 mg, 0.35 mmol) and stirred under N_2 atmosphere for 24 h. The reaction mixture was evaporated and dissolved in $CHCl_3$ (100 mL) washed sequentially with an aqueous $NaHCO_3$ solution, aqueous 2 N H_2SO_4, and finally with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to yield 120 mg of **M1** and 96 mg of **M2**.



Yield: 35%

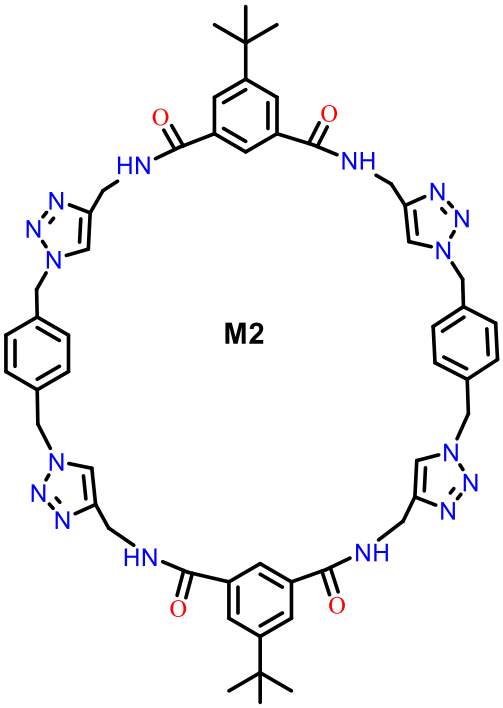
Mp: Above 260 ºC

^{1}H NMR (300 MHz, DMSO-*d*$_6$): δ 1.31 (s, 18H), 4.49 (d, J = 5.1 Hz, 8H), 5.54 (s, 8H), 7.23 (d, J = 7.5 Hz, 4H), 7.32 (t, J = 5.4 Hz, 4H), 7.99 (br m, 7H), 8.15 (s, 2H), 8.31 (s, 1H), 9.07 (t, J = 5.0 Hz, 4H).

^{13}C NMR (75 MHz, DMSO-*d*$_6$): δ 29.4, 31.4, 35.2, 35.3, 52.9, 123.6, 124.4, 127.3, 128.1, 128.2, 129.7, 134.5, 137.1, 145.7, 151.6, 166.4.

IR (KBr): 3445, 3257, 3120, 2956, 1652, 1536, 1460, 1328, 1273, 1173, 1129, 1057 cm^{-1}.

HRMS: Calcd for $C_{52}H_{56}N_{16}O_4Na$ m/z = 991.4563, found m/z = 991.4568.



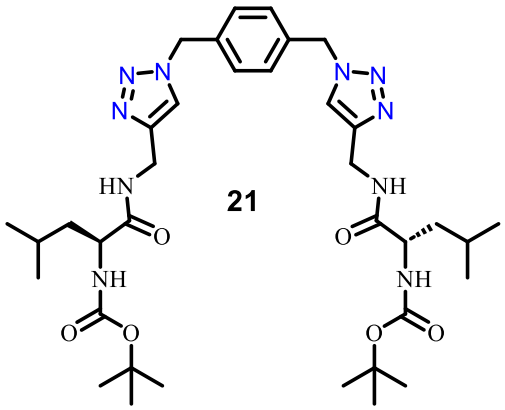
Yield: 28%

Mp: Above 260 ºC

IR (KBr): 3442, 3278, 3108, 2930, 2855, 1642, 1574, 1464, 1366, 1328, 1282, 1224, 1129, 1055 cm^{-1}.

HRMS: Calcd for $C_{52}H_{56}N_{16}O_4Na$ m/z = 991.4563, found m/z = 991.4576.

Synthesis of 21:



To an ice cold solution of Boc-Leu-propargylamine **27** (500 mg, 1.86 mmol) in dry acetonitrile was added DIEA (0.75 mL, 4.09 mmol), followed by p-xylylenediazide (174 mg, 0.93 mmol) under N_2 atmosphere. CuI (35 mg, 0.19 mmol) was added and the reaction mixture was stirred for 24 h under an N_2 atmosphere. The solvent was evaporated and the residue was dissolved in chloroform and washed with an aqueous solution of NH_4Cl + NH_4OH (9:1), 2N H_2SO_4, saturated solution of $NaHCO_3$ and water. The organic layer was dried over anhydrous Na_2SO_4 and evaporated to obtain 900 mg of the product.

Yield: 66 %

Mp: 65-67 ^oC

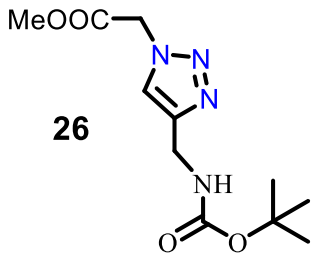
^{1}H NMR ($CDCl_3$, 300 MHz): δ 0.89 (br d, 12H), 1.38 (s, 18 H), 1.59 (m, 4H), 2.10 (br s, 2H), 4.15 (br s, 2H), 4.55 (br m, 4H), 5.20-5.65 (br m, 5H), 6.75 (br s, 1H), 7.35 (br m, 5H), 7.51 (m, 3H).

^{13}C NMR ($CDCl_3$, 75 MHz): δ 21.8, 23.0, 24.7, 28.3, 34.9, 41.5, 53.5, 79.9, 122.6, 127.9, 136.0, 145.5, 155.8, 173.3.

IR (KBr): 3351, 3141, 2967, 1691, 1521, 1376, 1262, 1166, 1042 cm^{-1}.

HRMS: Calcd for $C_{36}H_{57}N_{10}O_6$ m/z = 725.4457, obtained m/z = 725.4459.

Synthesis of 26



26

To an ice-cooled solution of **5** (2 g, 12.89 mmol) in 100 ml of dry acetonitrile under nitrogen was added diisopropyl ethylamine (3.66 mL, 28.35 mmol), azido-acetic acid methyl ester **25** (1.7 g, 15.47 mmol) and CuI (294 mg, 1.547 mmol). The reaction mixture was stirred under N_2 atmosphere for 24 h. The reaction mixture was evaporated and dissolved in EtOAc (50mL) washed sequentially with aqueous NH_4CI + NH_4OH (9:1) solution, 0.2 N H_2SO_4, and finally with water. The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to yield 2.2 g of **26**.

Yield: 61 %.

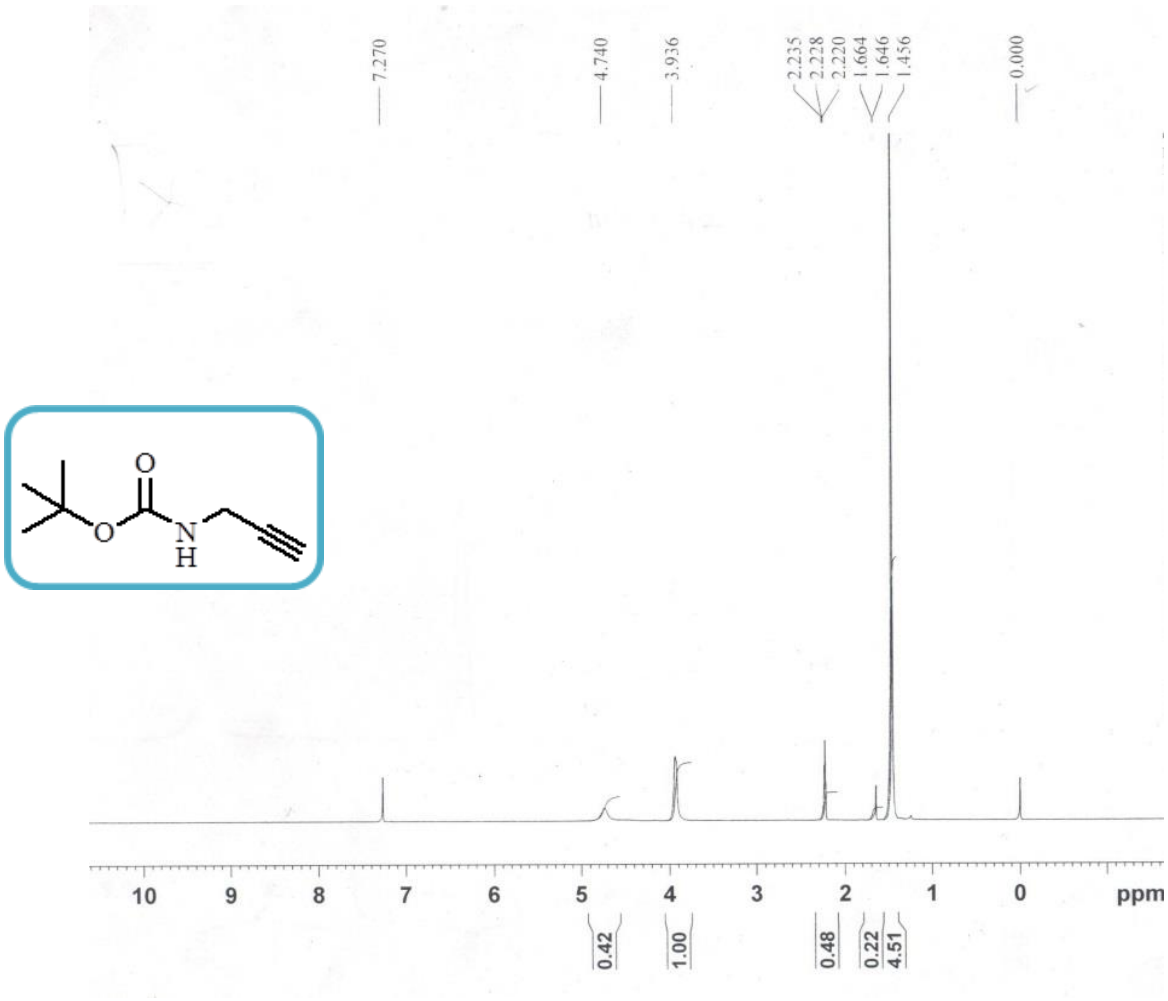
Mp: 159-161 ^oC

^{1}H NMR (300 MHz, DMSO-d_6): δ 1.39 (s, 9H), 3.71 (s, 3H), 4.18 (d, J = 5.7 Hz, 2H) 5.38 (s, 2H), 7.39 (br s, 1H), 7.89 (s, 1H).

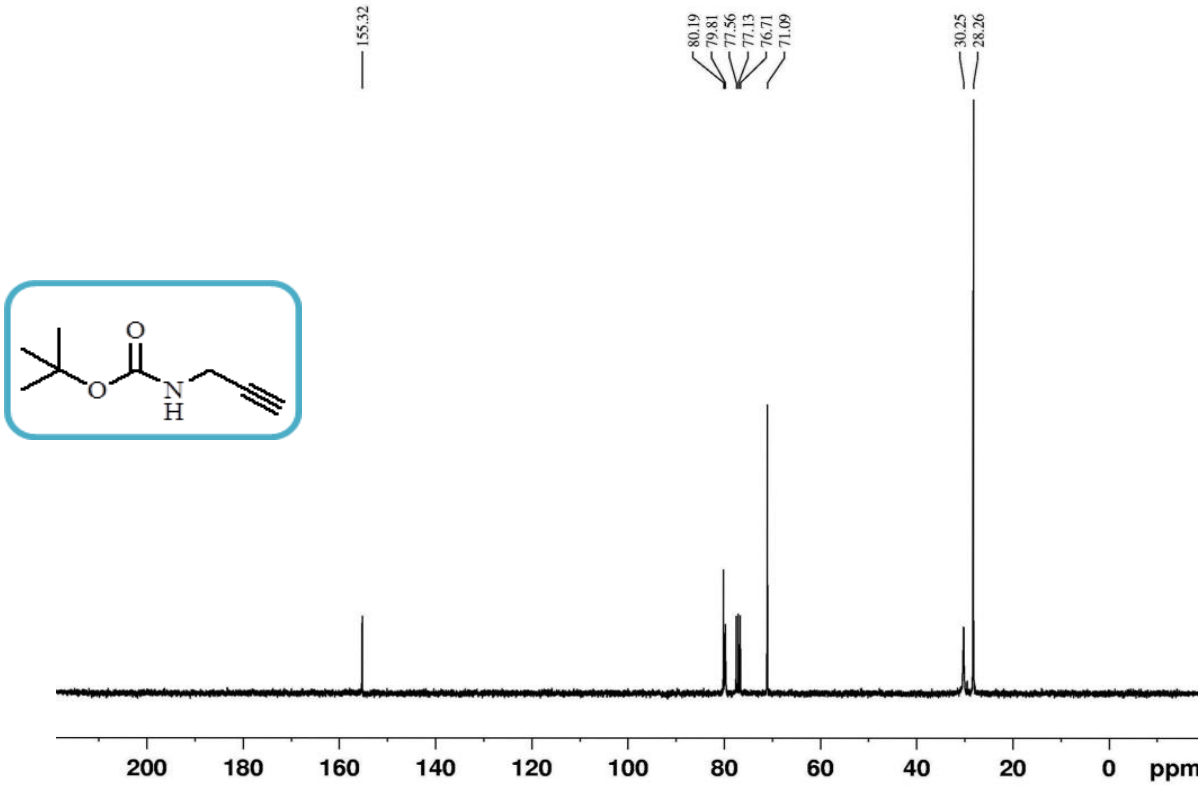
^{13}C NMR ((75 MHz, DMSO-d_6): δ 28.7, 36.1, 50.7, 52.9, 78.4, 124.4, 146.2, 156.1, 168.2.

IR (KBr): 3439, 2925, 2856, 1749, 1687, 1537, 1453, 1371, 1242, 1171 cm^{-1}.

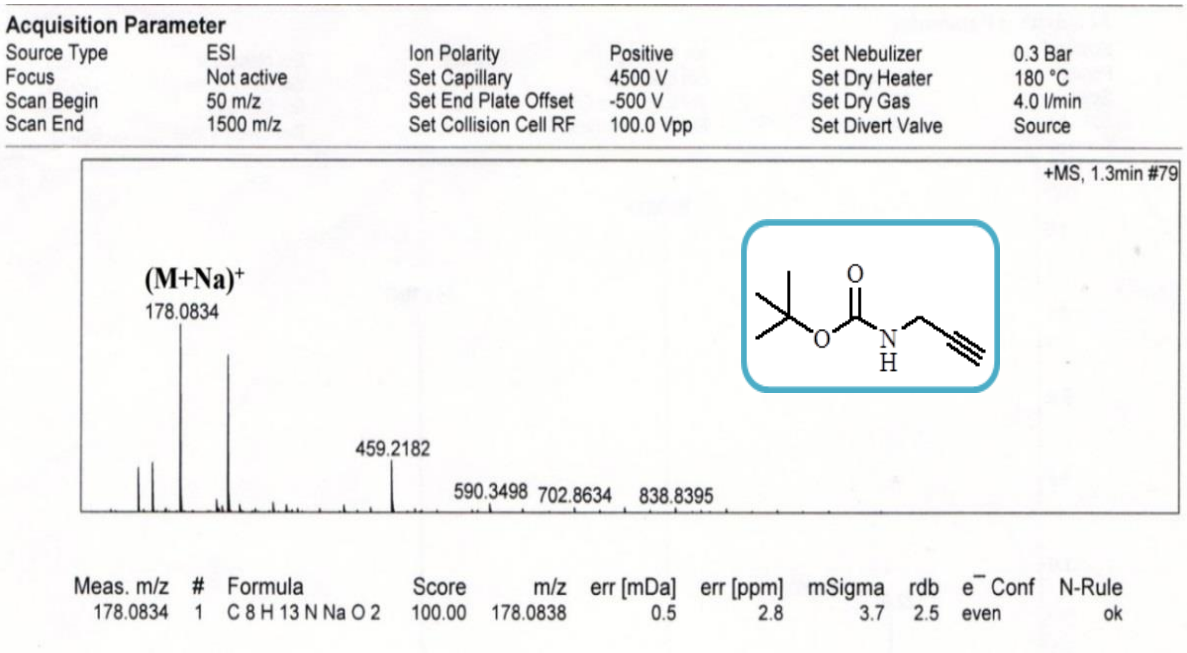
HRMS: Calcd for $C_{11}H_{18}N_4O_4Na$ m/z = 293.1226, obtained m/z = 293.1226.



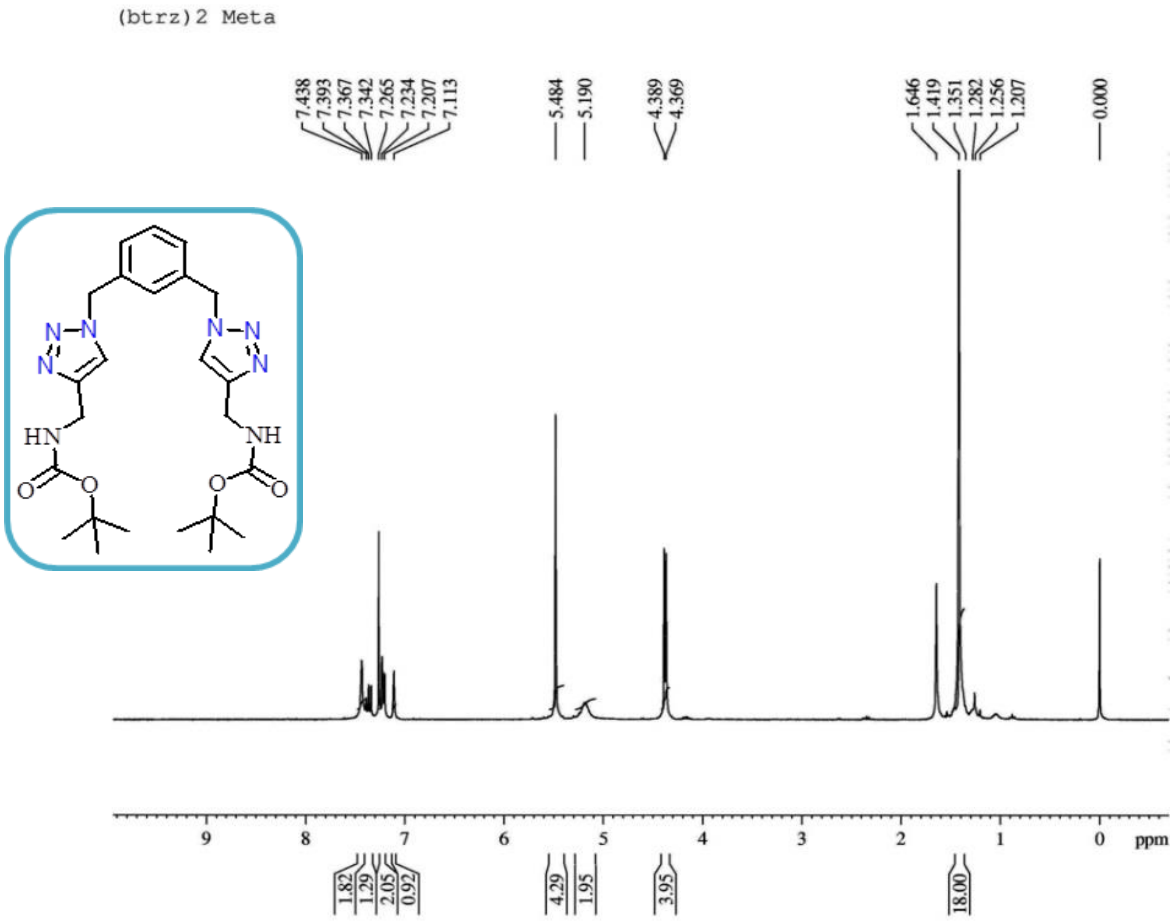
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **5**



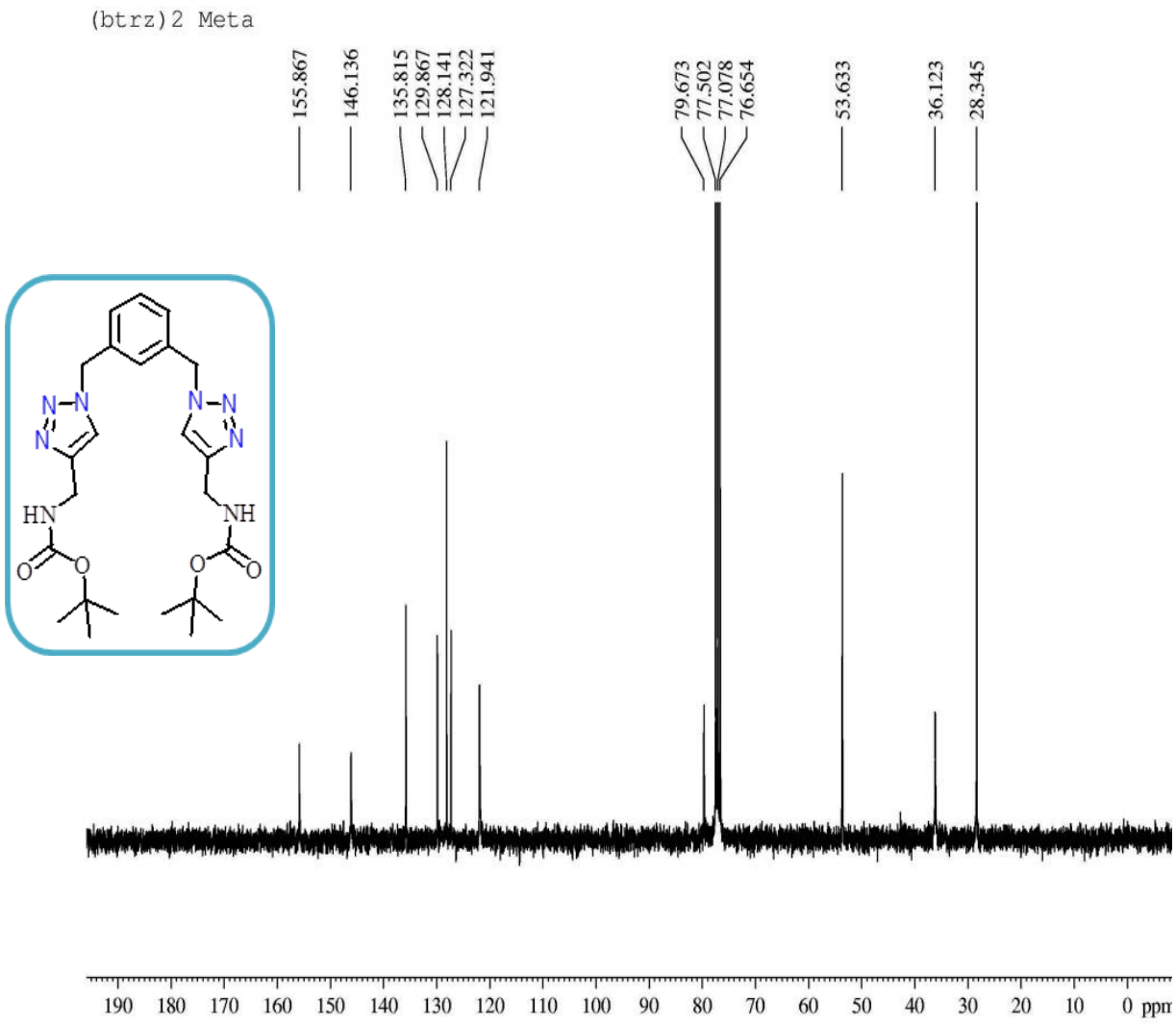
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **5**



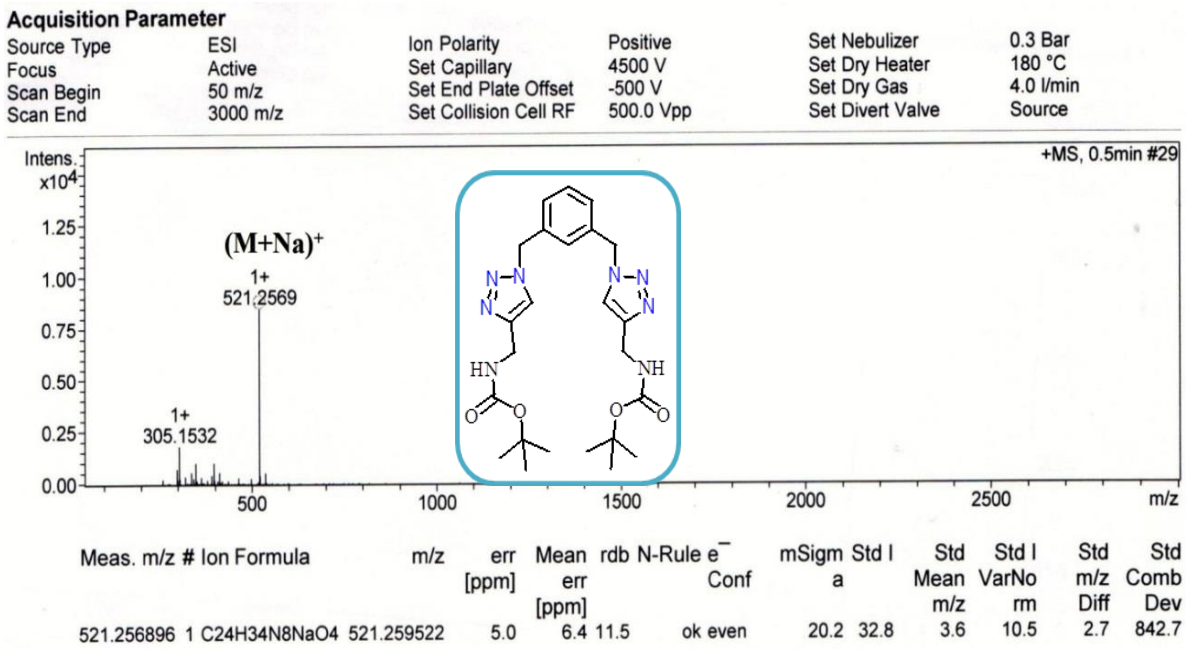
Mass spectrum of **5**



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

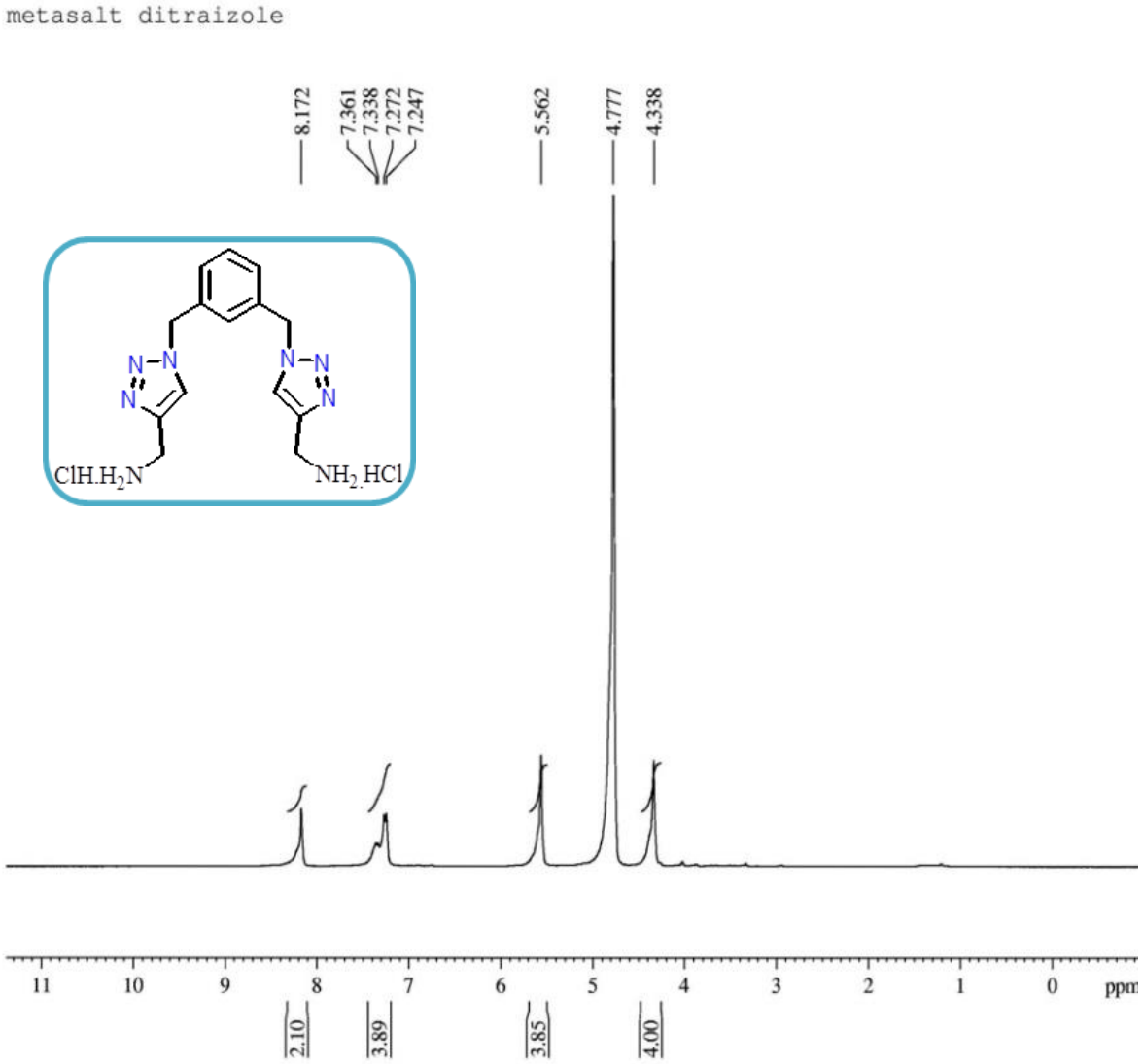


^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **6**

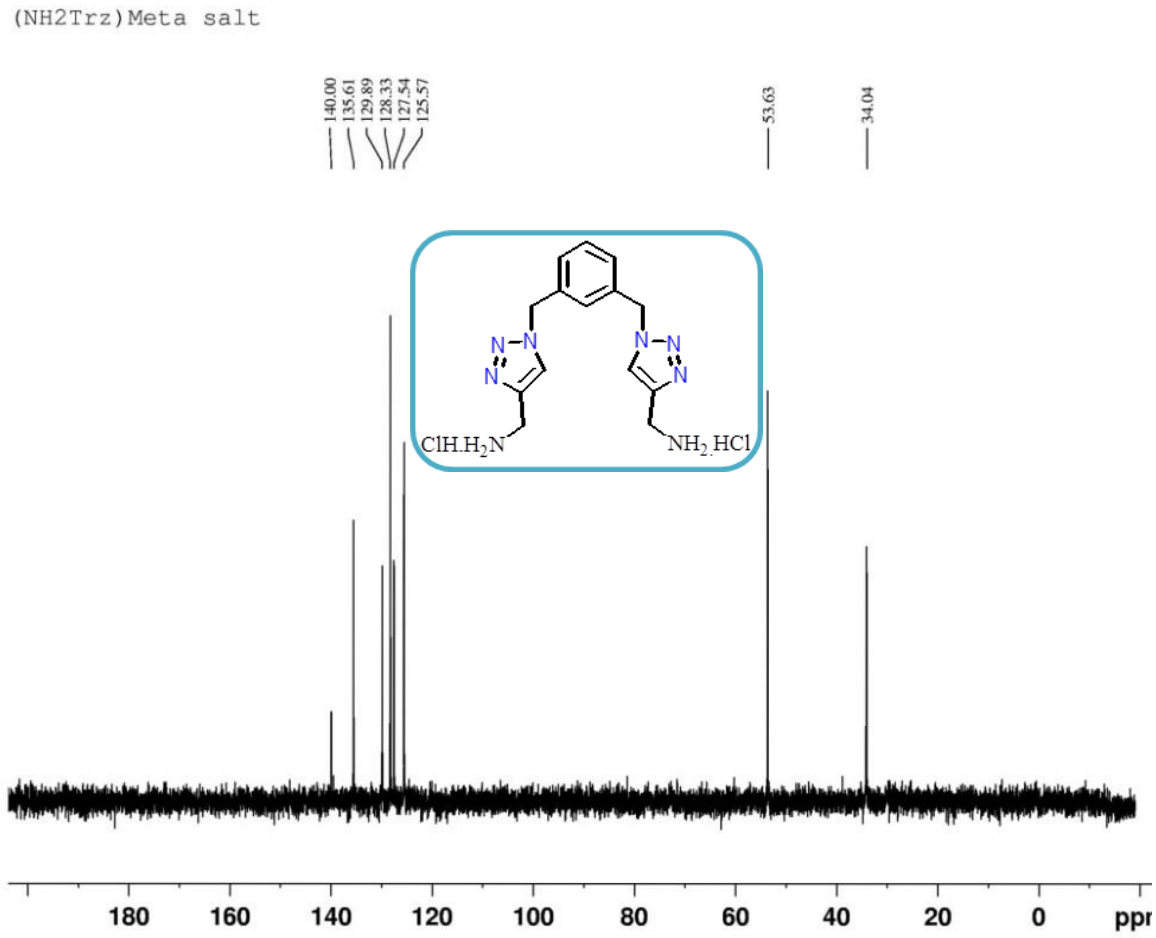


Meas. m/z	#	Ion Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
521.256896	1	C24H34N8NaO4	521.259522	5.0	6.4	11.5	ok	even	20.2	32.8	3.6	10.5	2.7	842.7

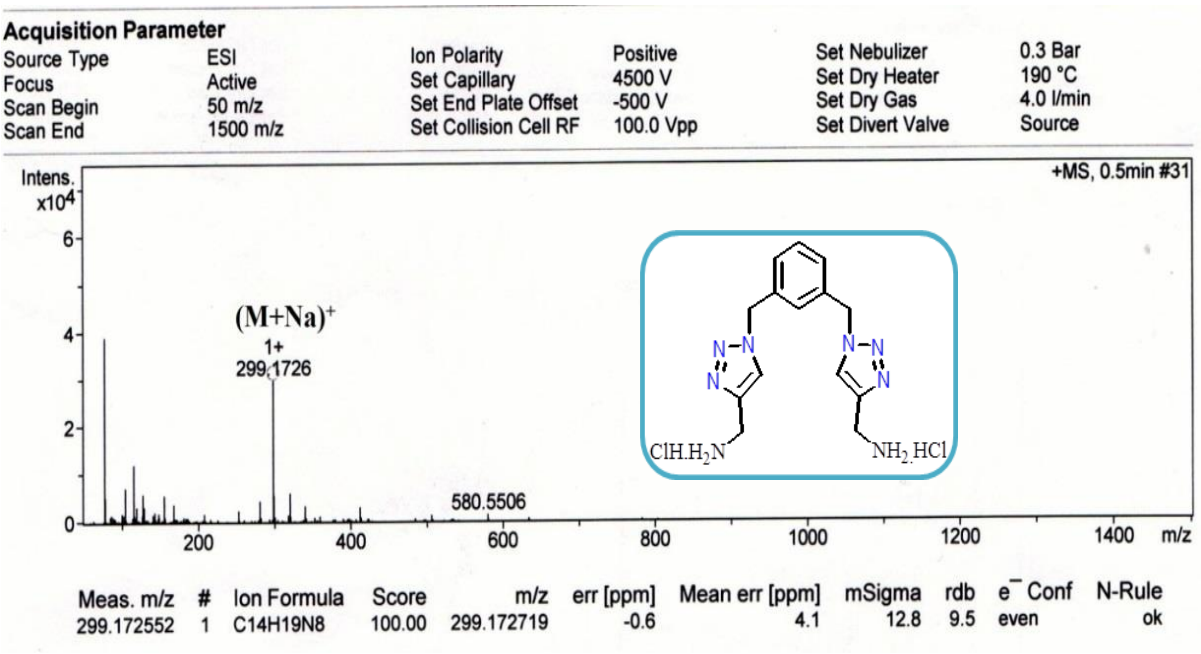
Mass spectrum of **6**



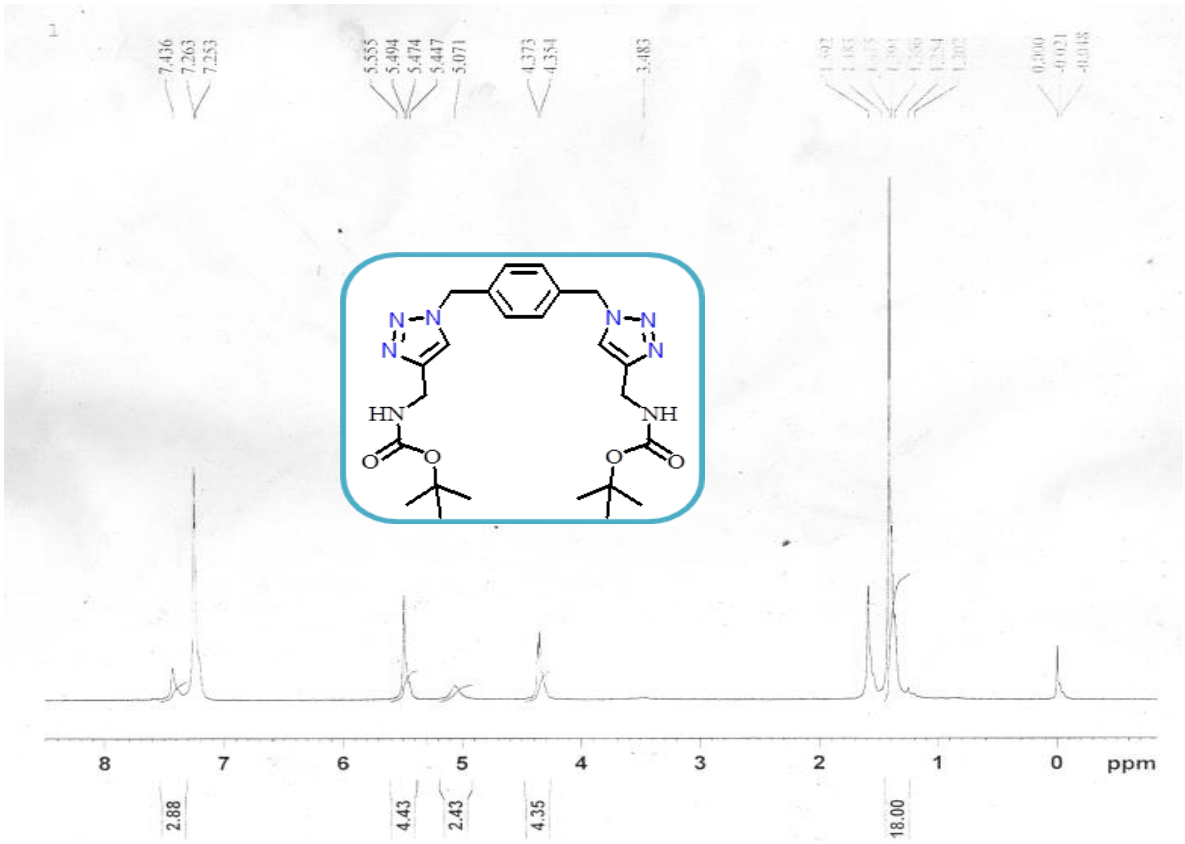
^{1}H NMR (300 MHz, D_2O) spectrum of **15**



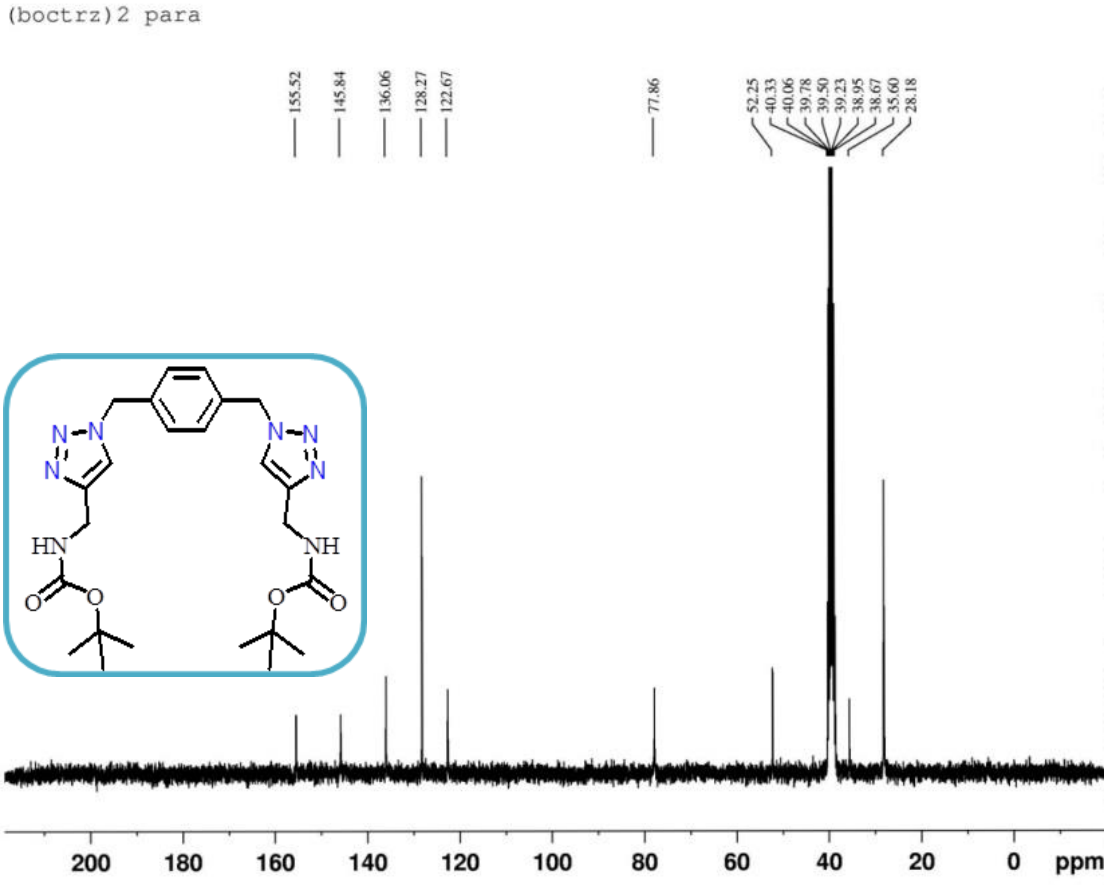
^{13}C NMR (75 MHz, D_2O) spectrum of **15**



Mass spectrum of **15**



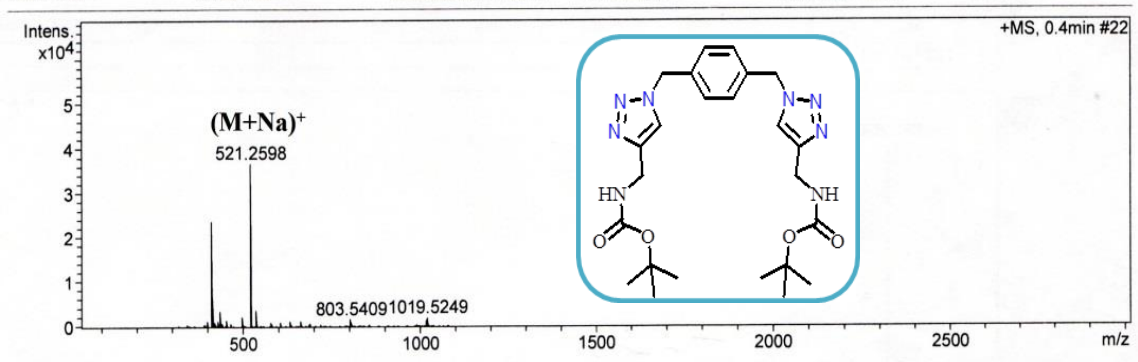
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **7**



^{13}C NMR (75 MHz, DMSO-*d6*) spectrum of **7**

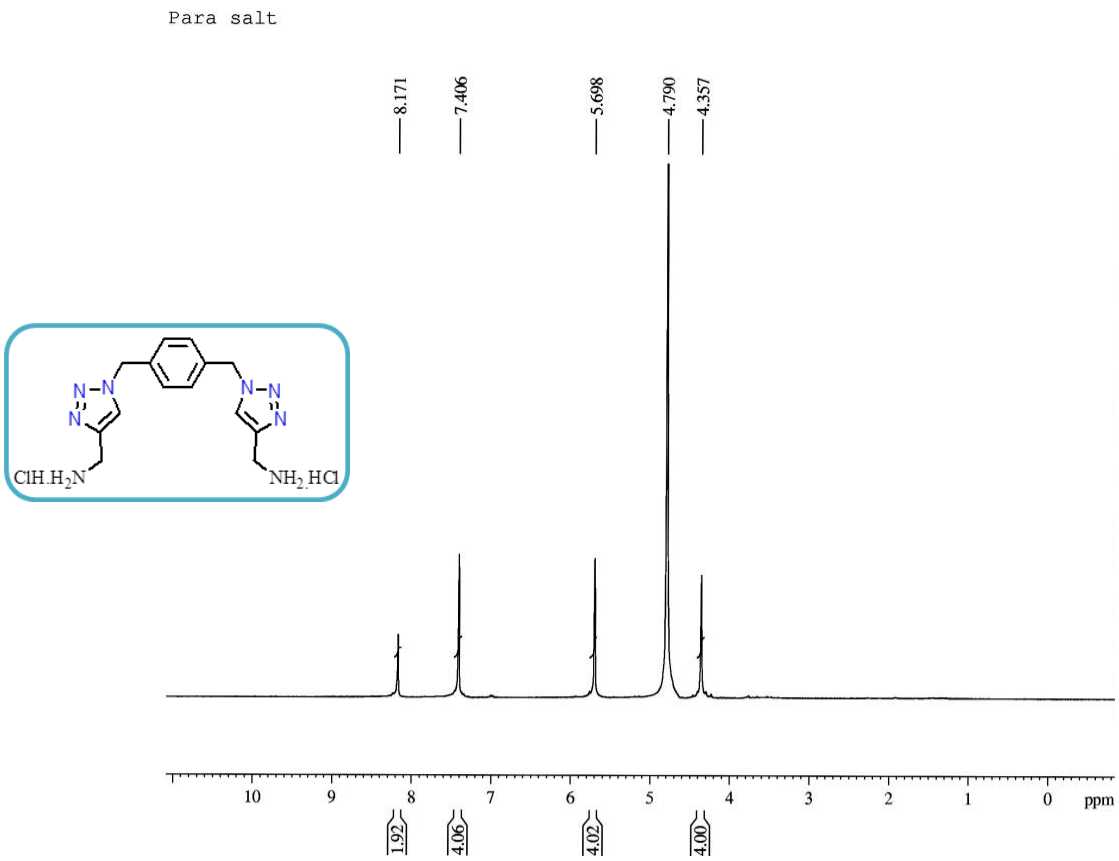
Acquisition Parameter

Source Type	ESI	Ion Polarity	Positive	Set Nebulizer	0.3 Bar
Focus	Active	Set Capillary	4500 V	Set Dry Heater	180 °C
Scan Begin	50 m/z	Set End Plate Offset	-500 V	Set Dry Gas	4.0 l/min
Scan End	3000 m/z	Set Collision Cell RF	600.0 Vpp	Set Divert Valve	Source

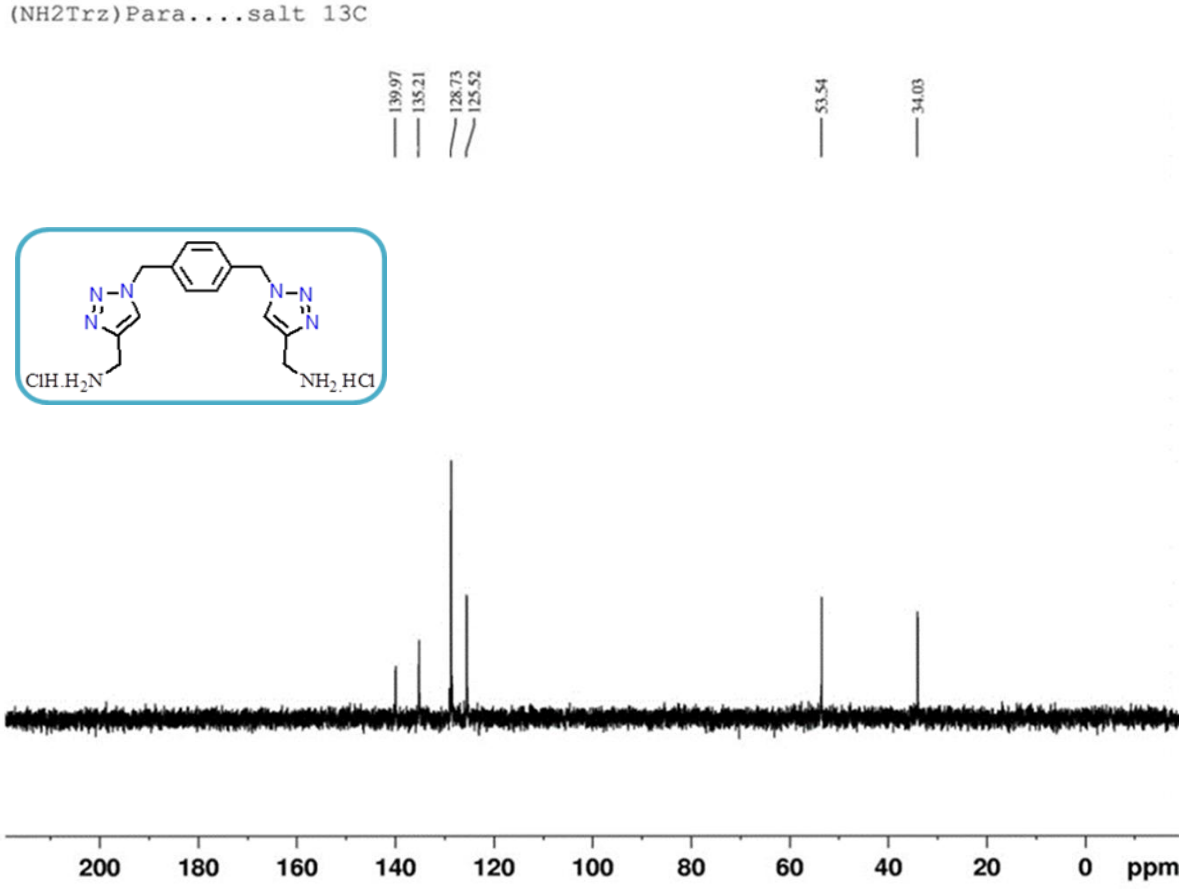


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I Var Norm	Std m/z Diff	Std Comb Dev
521.2598	1	C 24 H 34 N 8 Na O 4	521.2595	-0.4	-0.1	11.5	ok	even	3.3	4.6	0.4	2.0	0.6	842.7

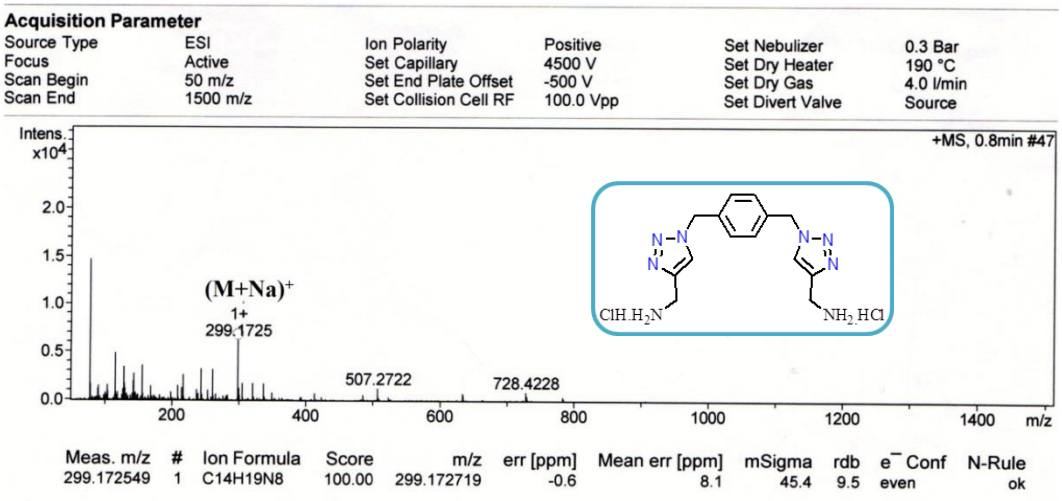
Mass spectrum of **7**



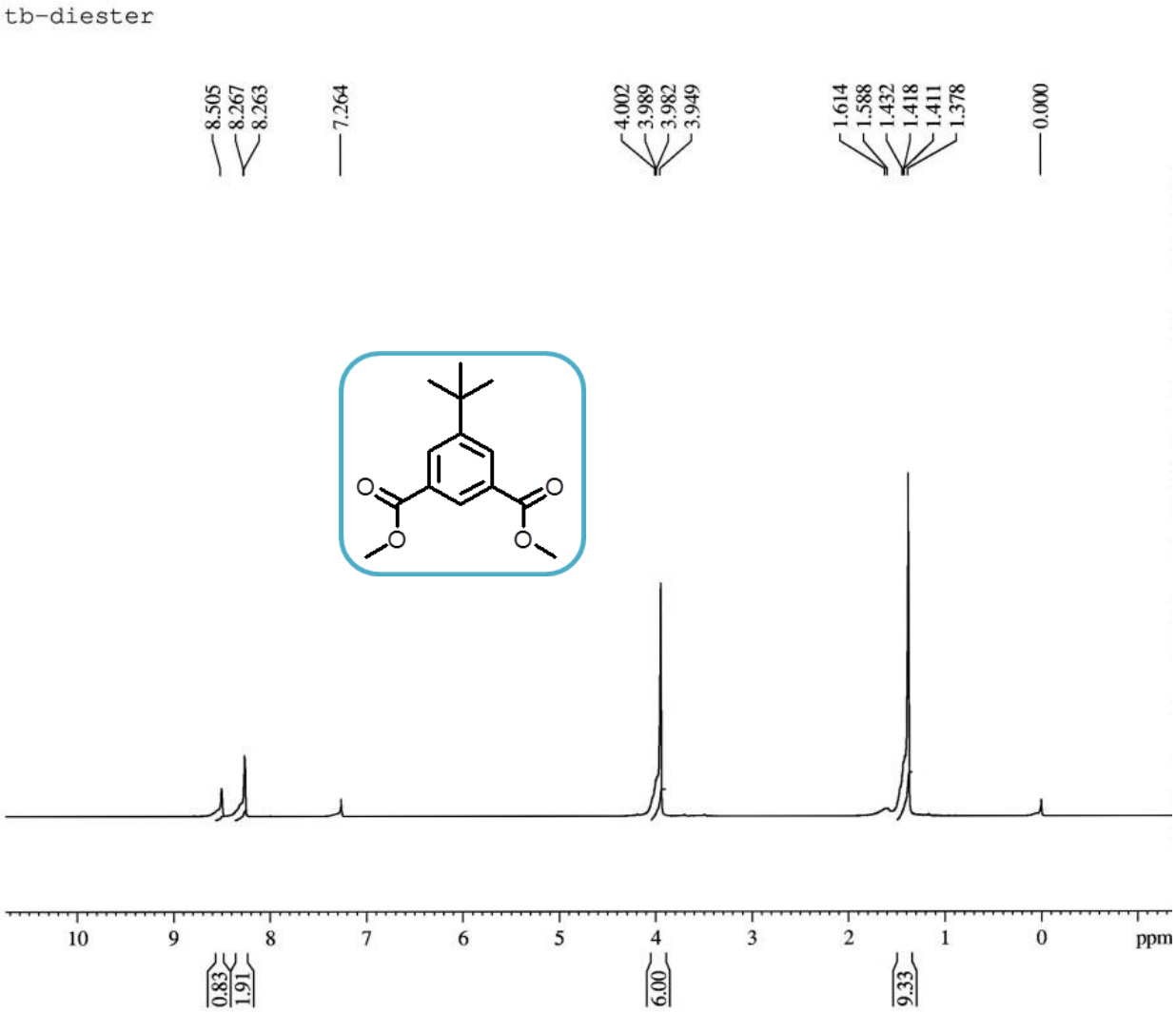
^{1}H NMR (300 MHz, D_2O) spectrum of **17**



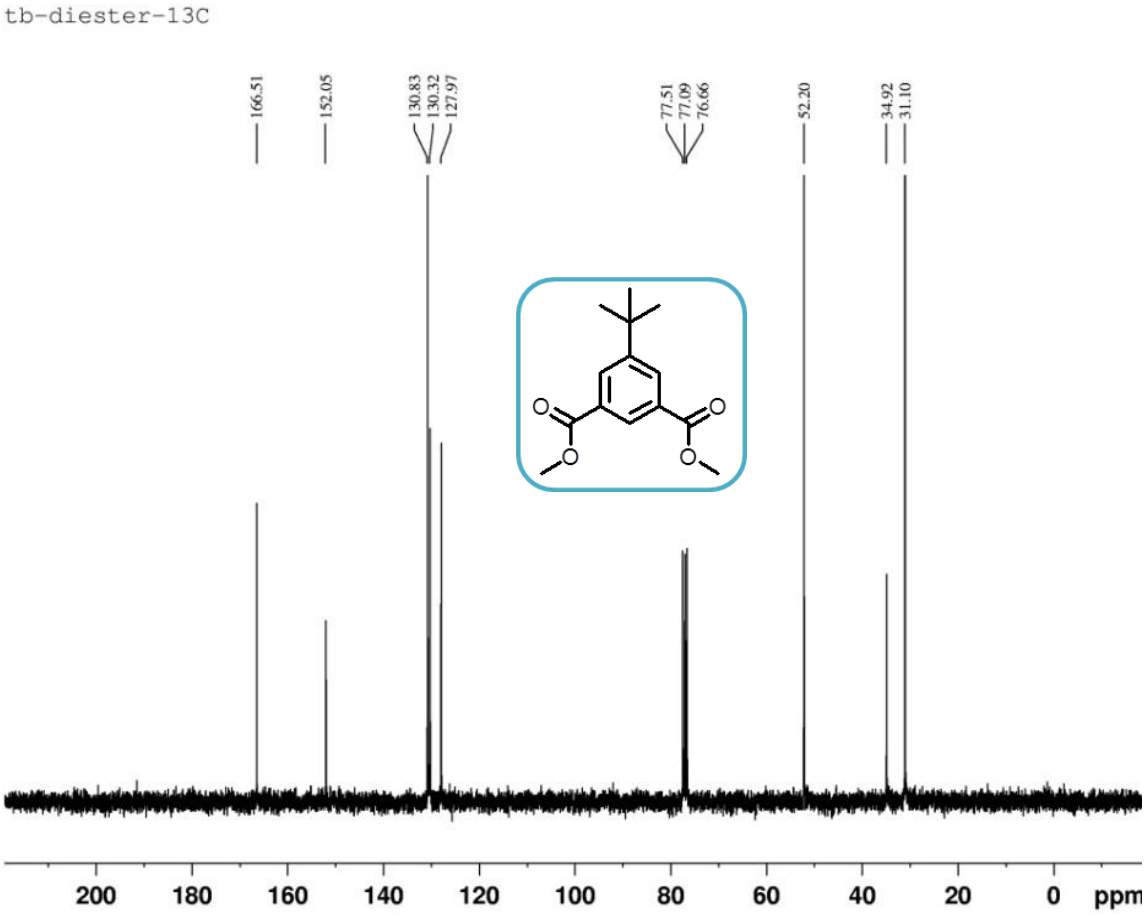
^{13}C NMR (75 MHz, D_2O) spectrum of **17**



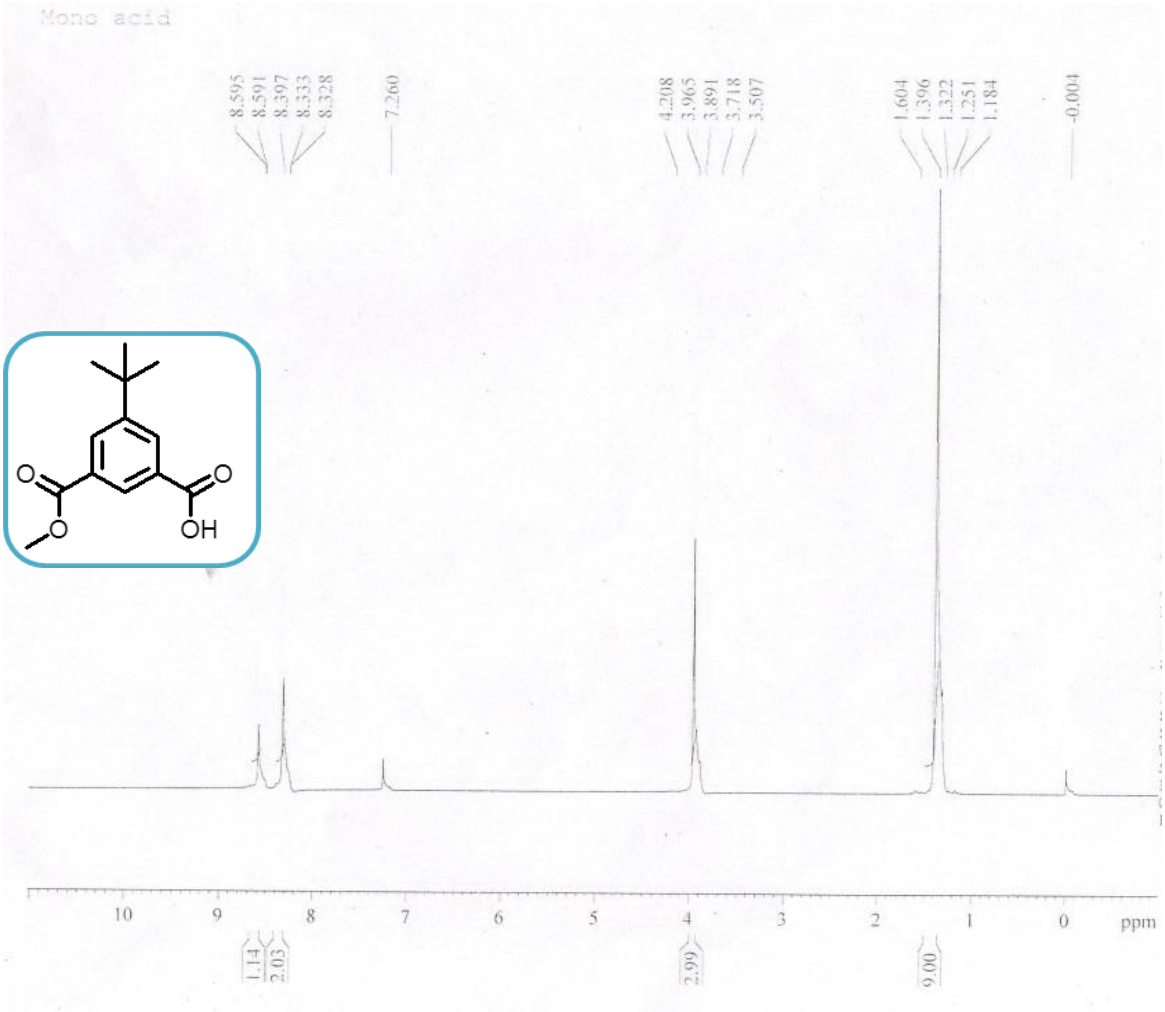
Mass spectrum of **17**



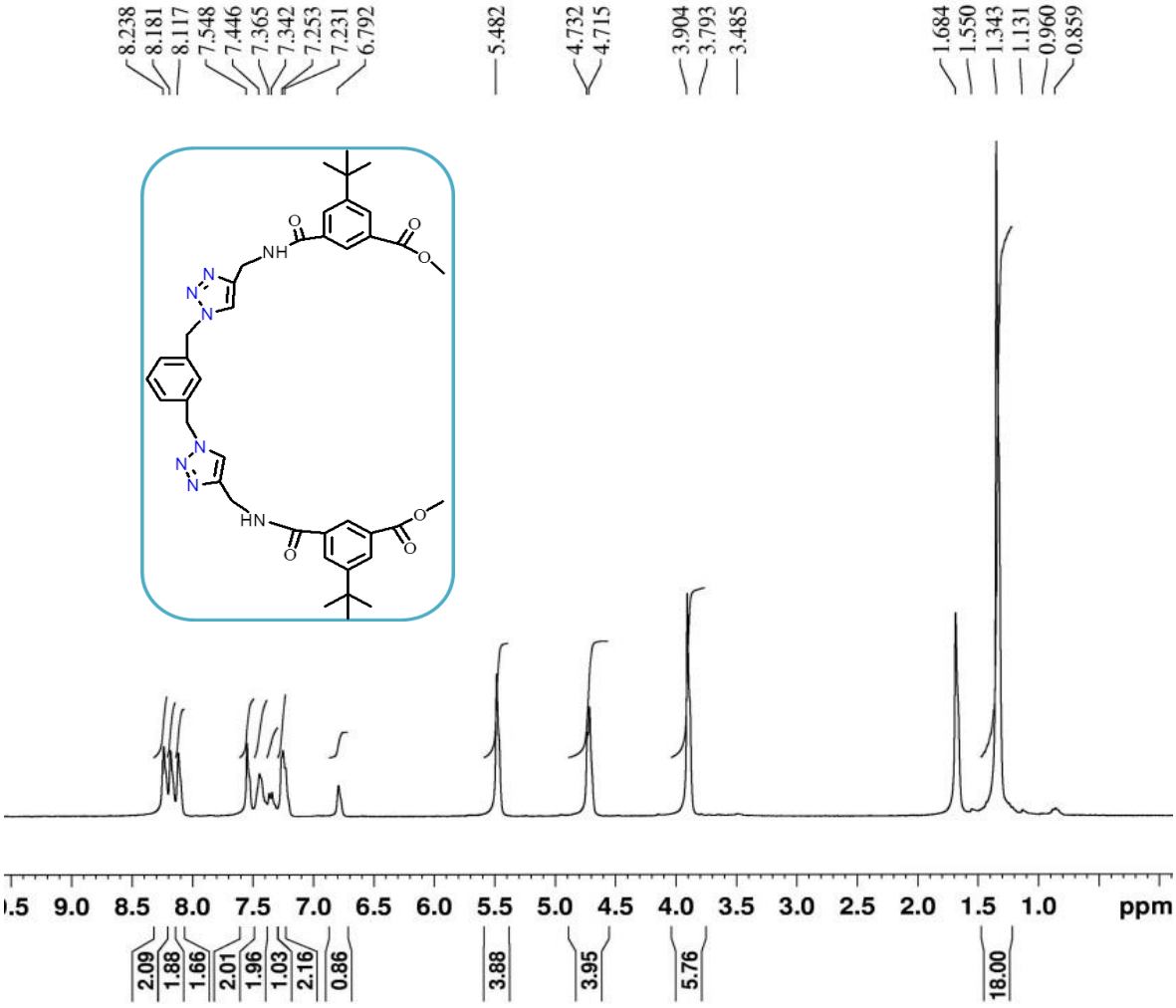
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **10**



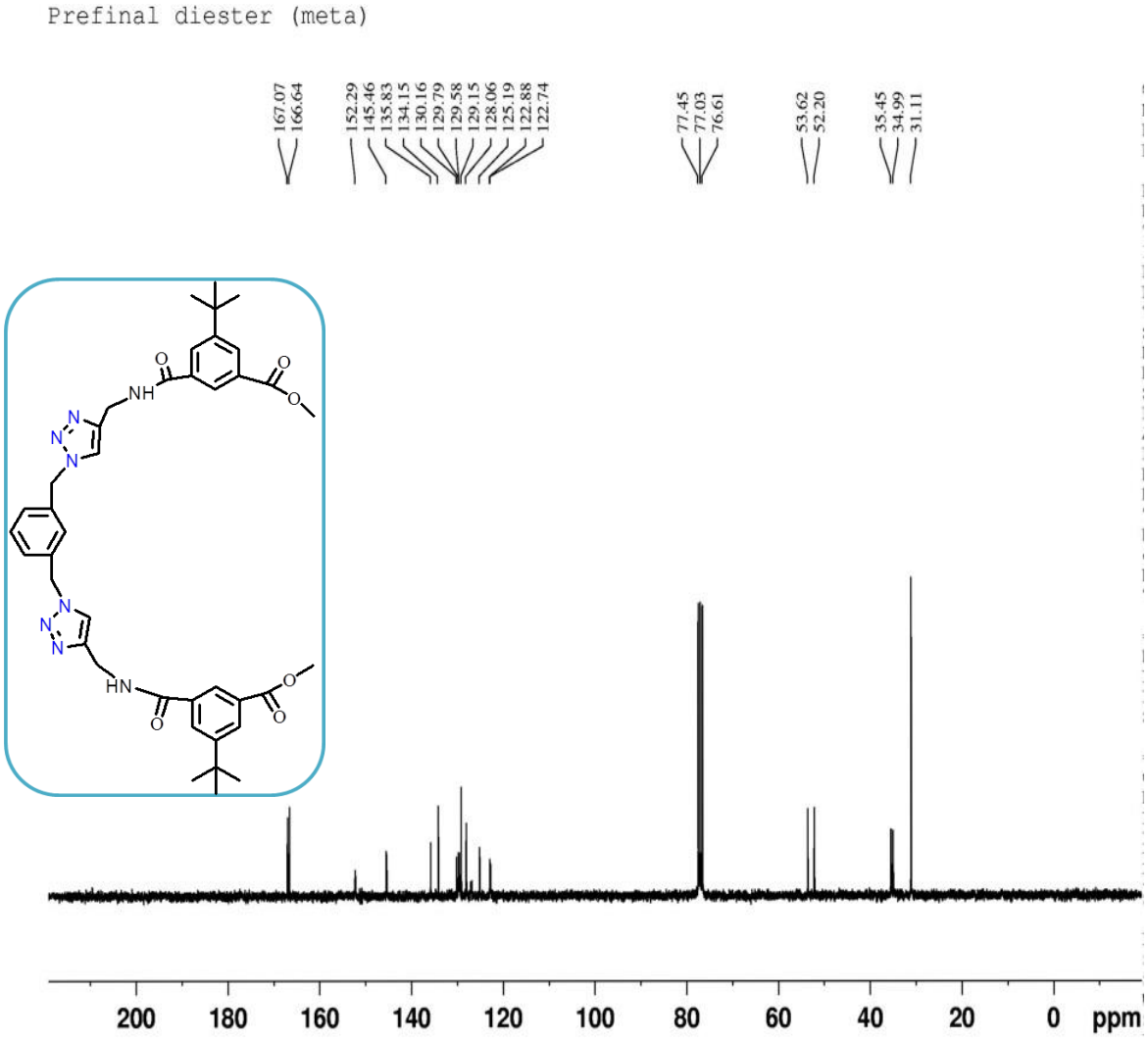
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **10**



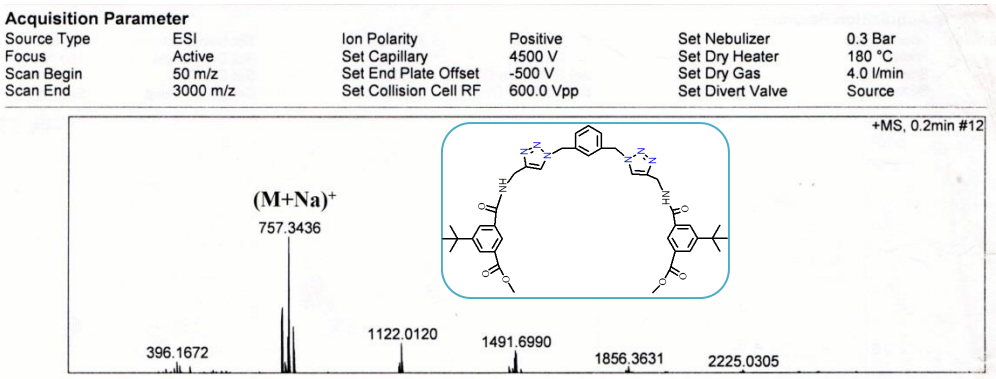
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **11**



^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **13**

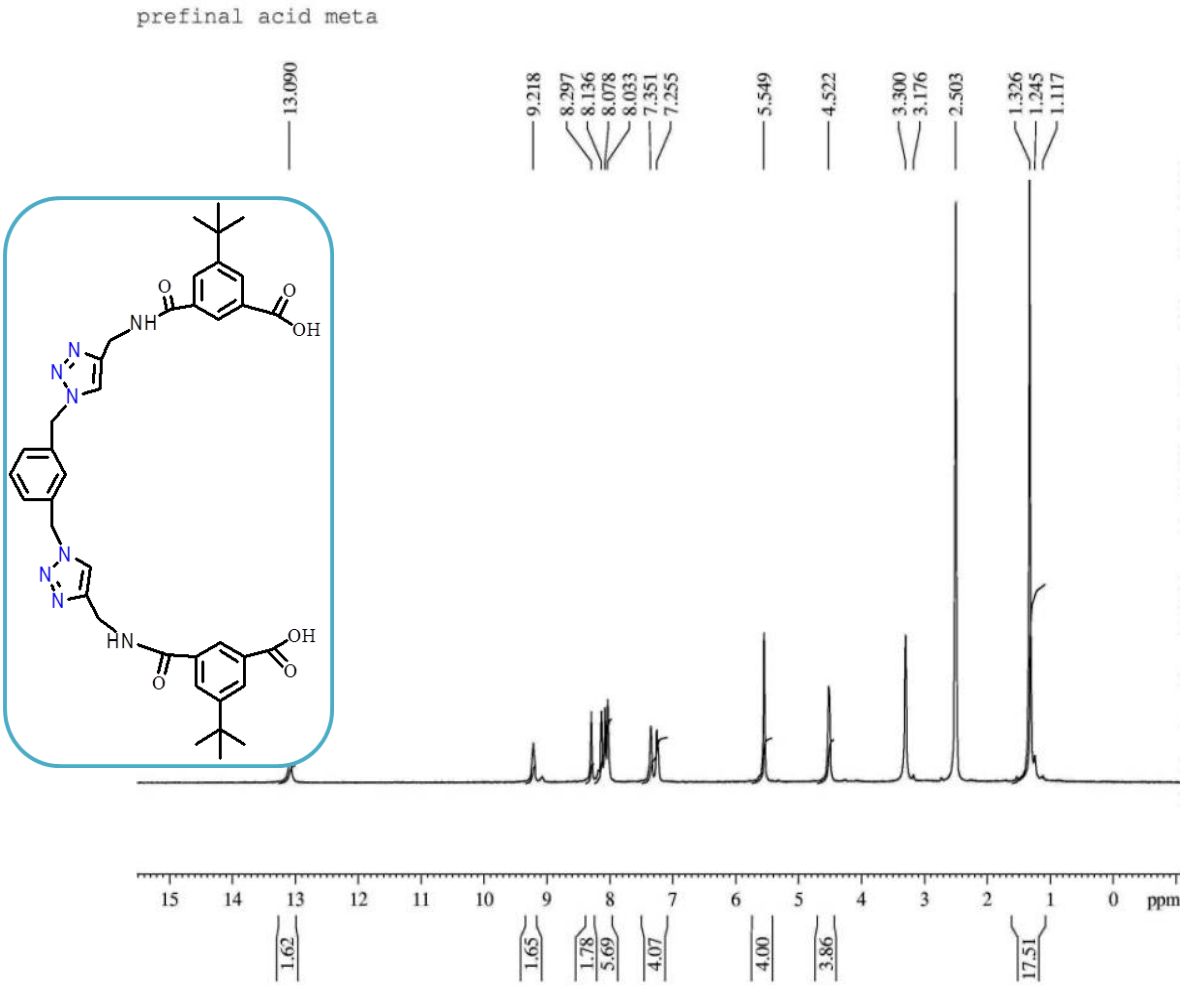


^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **13**

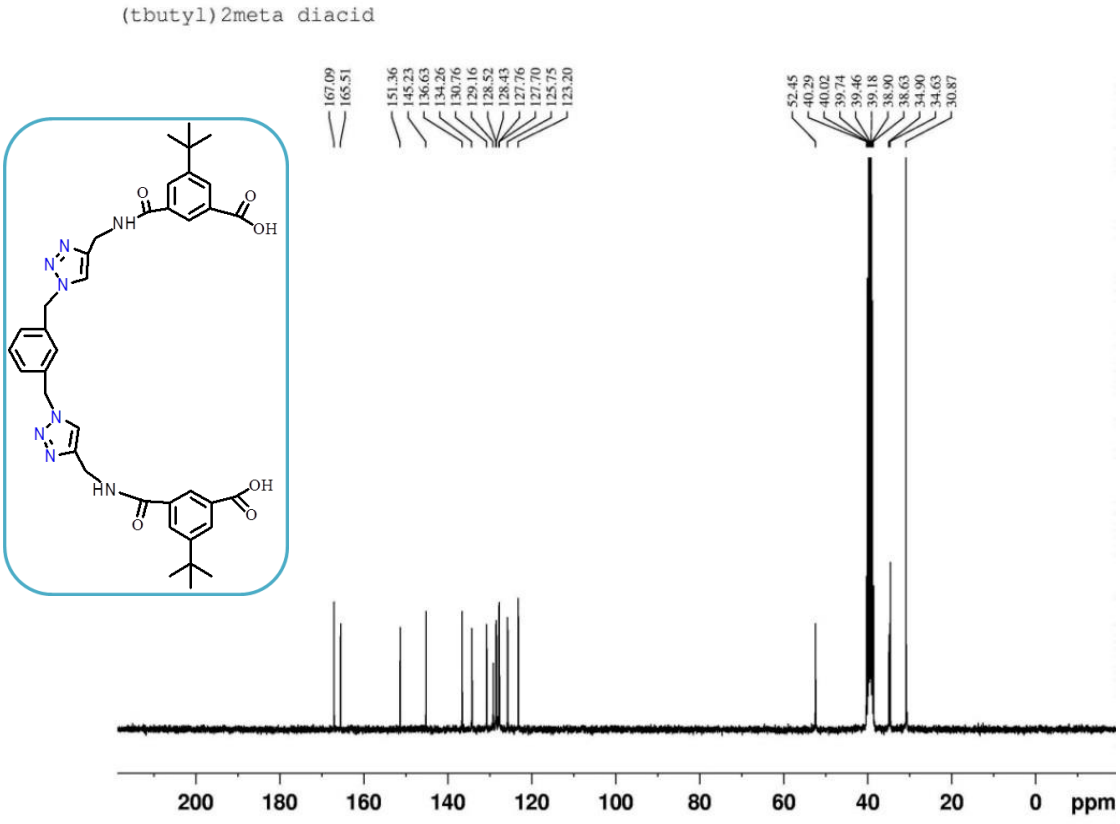


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I VarNorm	Std m/z Diff	Std Comb Dev
757.3436	1	C 40 H 46 N 8 Na O 6	757.3433	-0.4	-0.4	21.5	ok	even	233.9	410.4	0.5	142.2	0.5	842.7

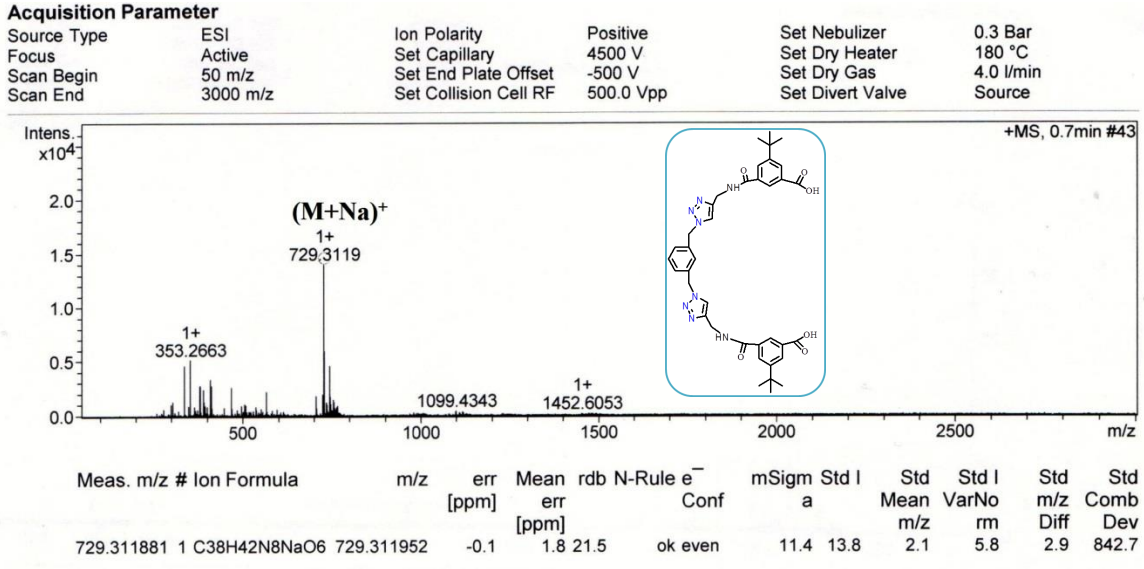
Mass spectrum of **13**



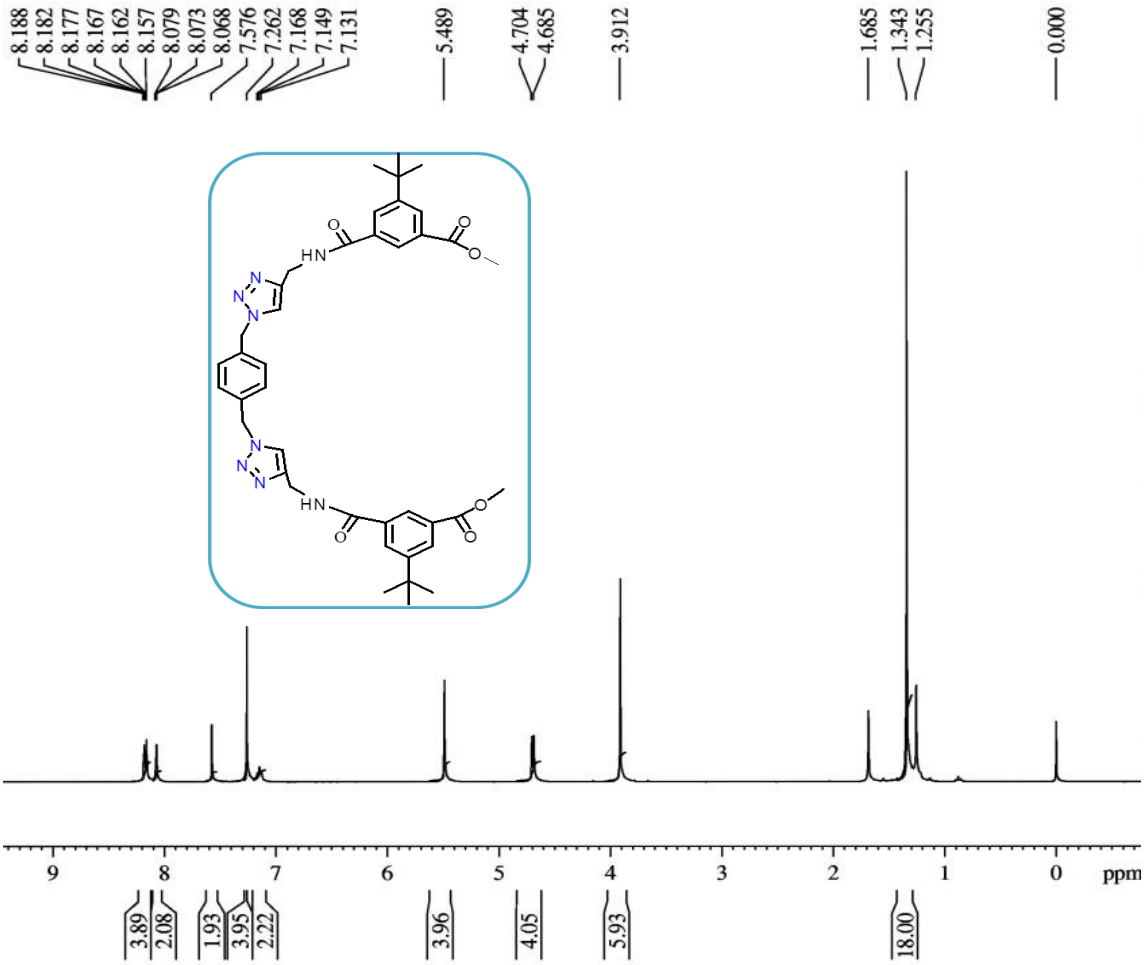
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **16**



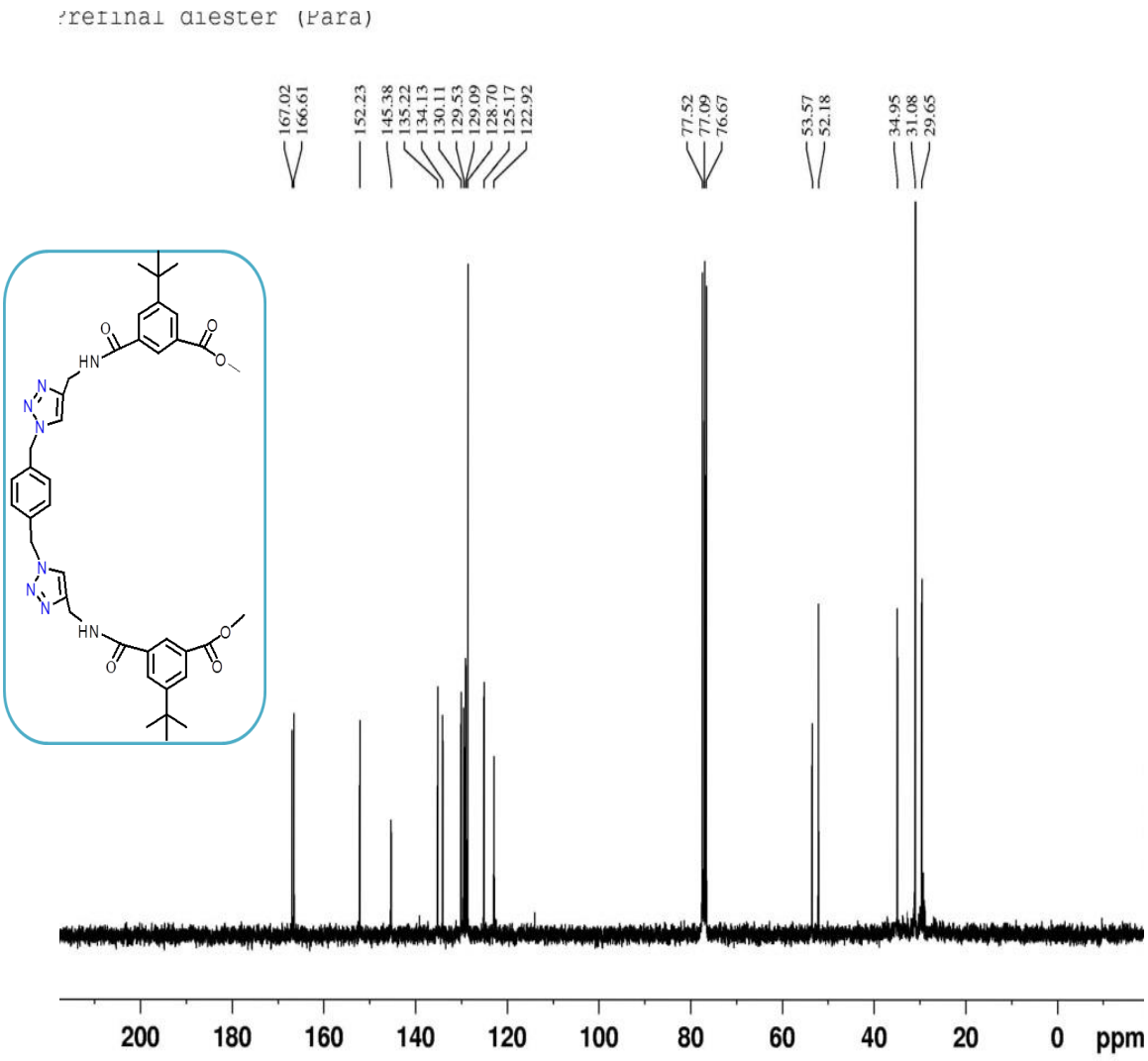
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **16**



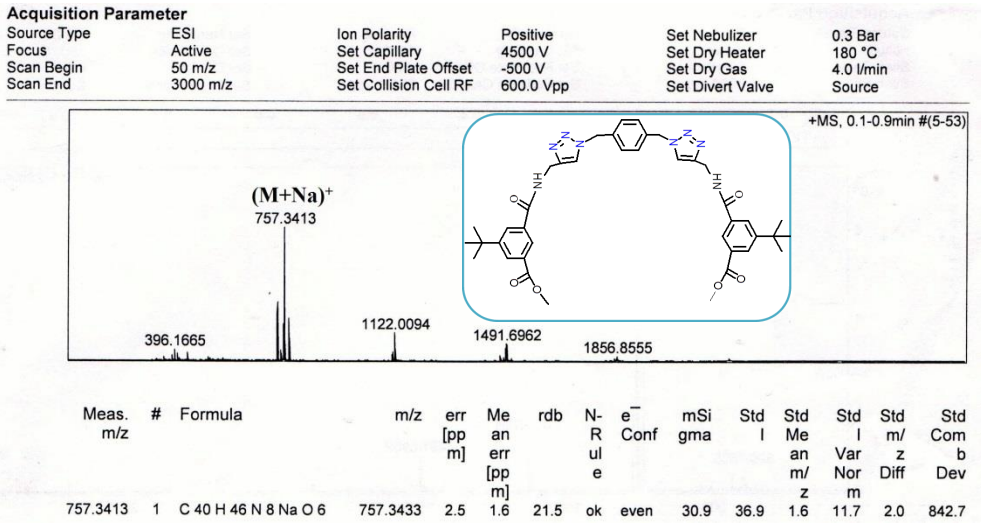
Mass spectrum of **16**



^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **14**

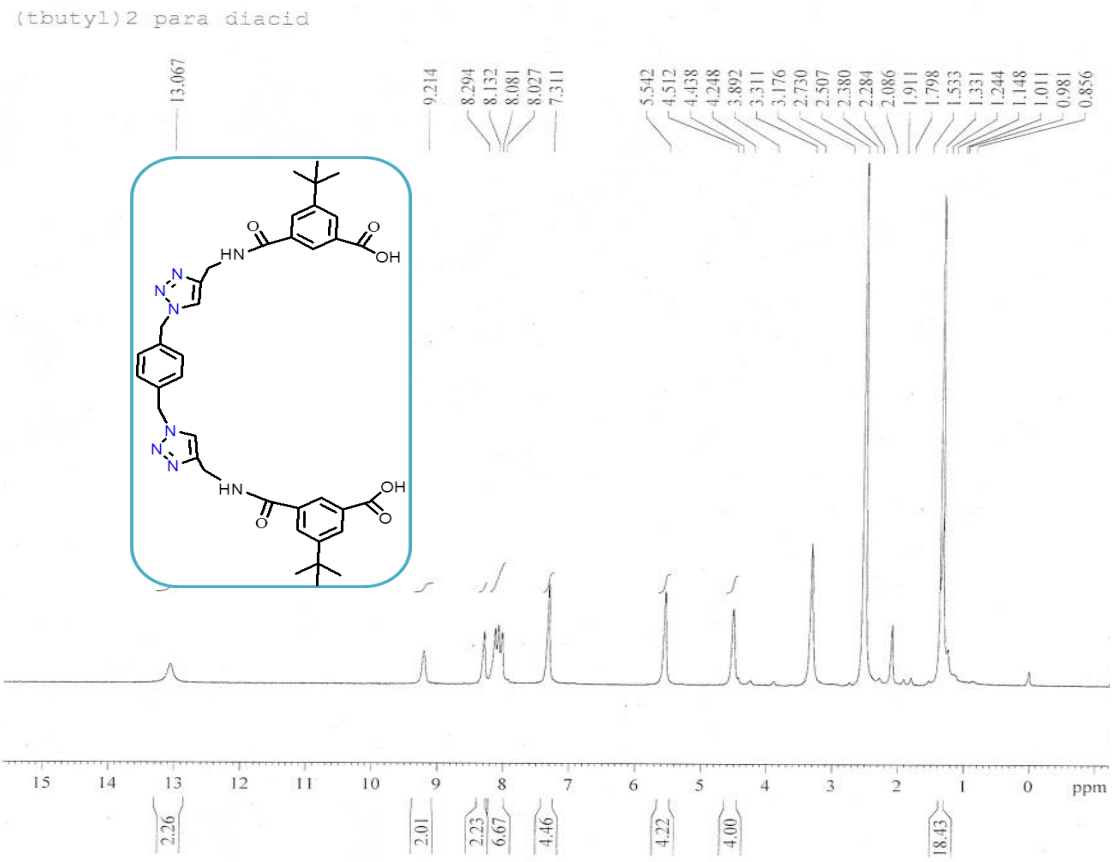


^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **14**

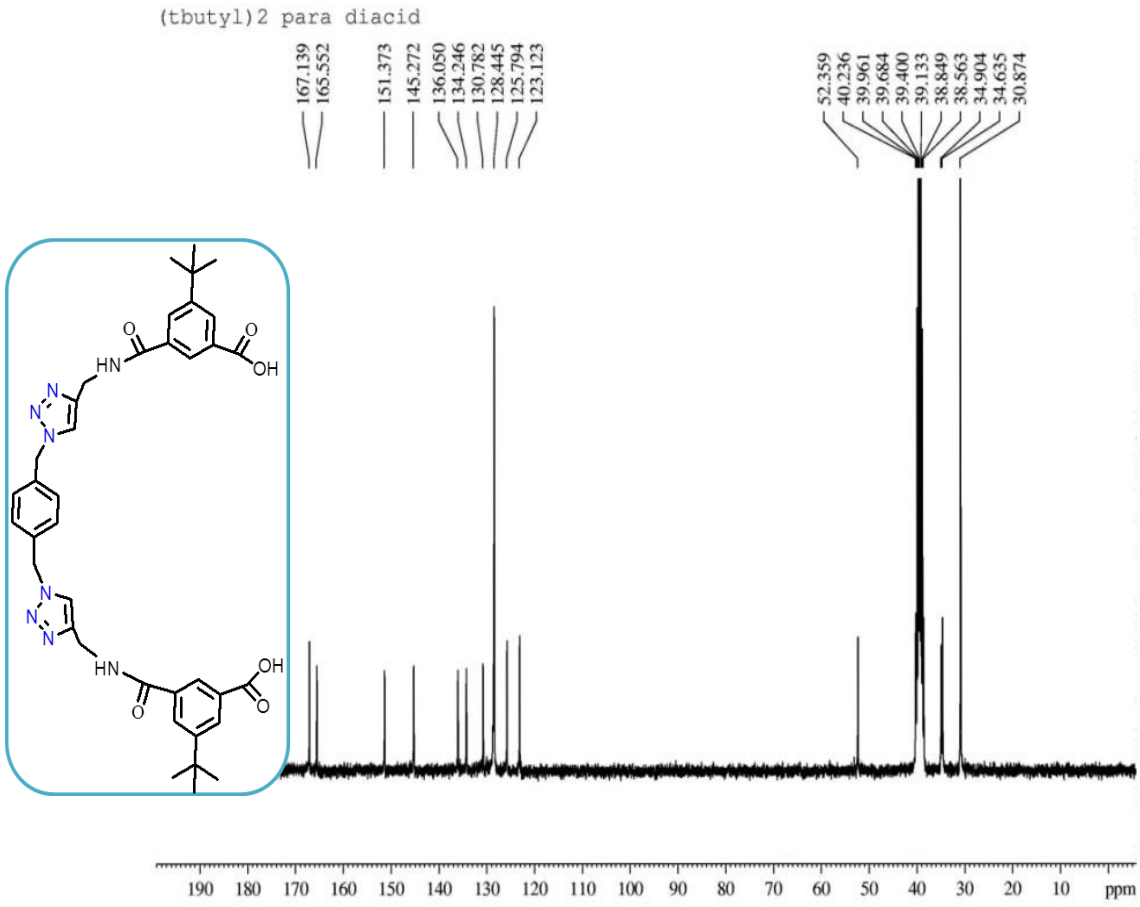


Meas. m/z	#	Formula	m/z	err [ppm]	Mean err [ppm]	rdb	N-Rule	e⁻ Conf	mSigma	Std I	Std Mean m/z	Std I Var Norm	Std m/z Diff	Std Comb Dev
757.3413	1	C 40 H 46 N 8 Na O 6	757.3433	2.5	1.6	21.5	ok	even	30.9	36.9	1.6	11.7	2.0	842.7

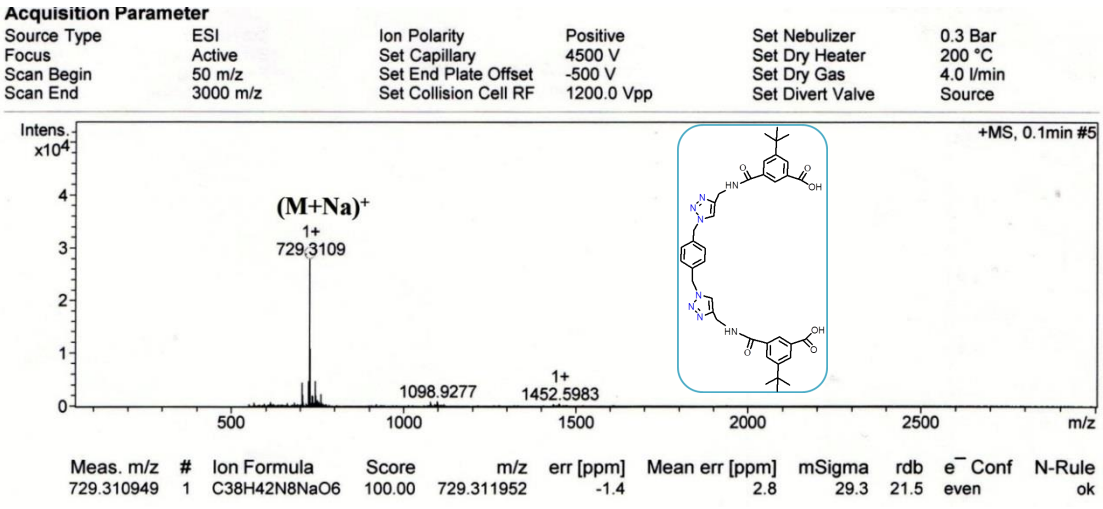
Mass spectrum of **14**



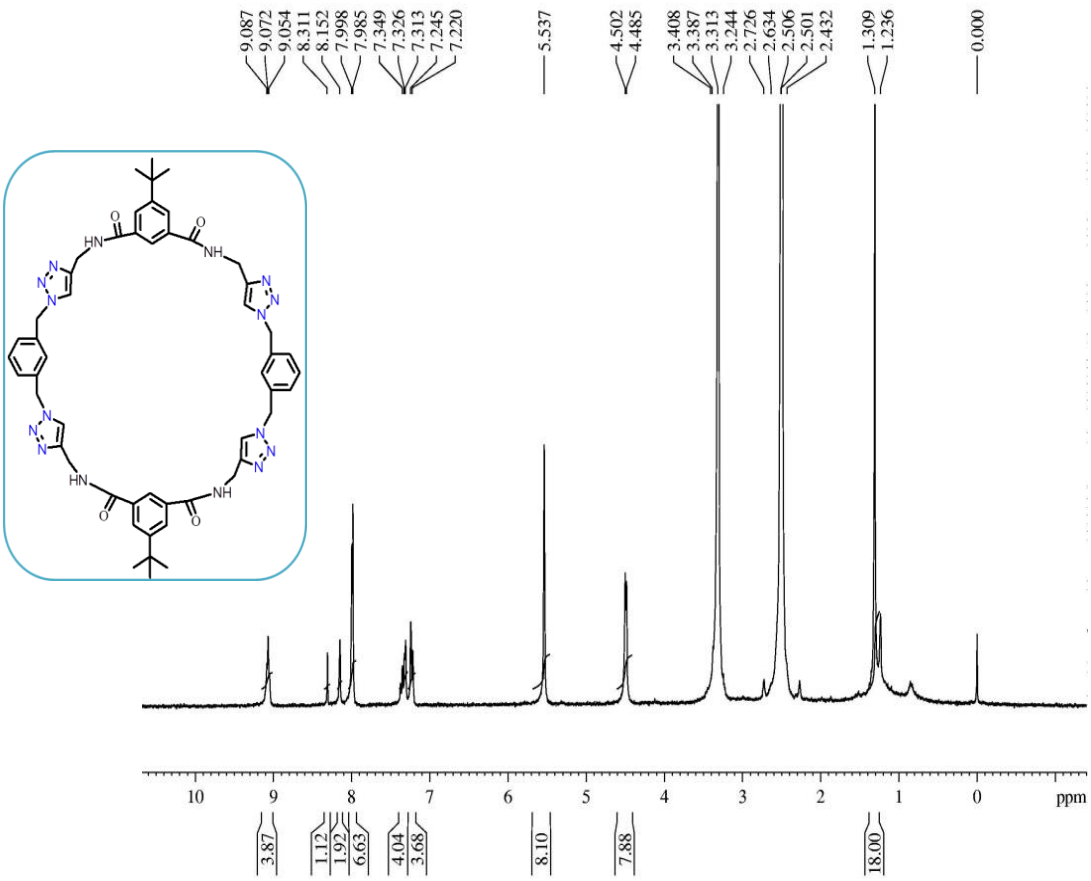
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **18**



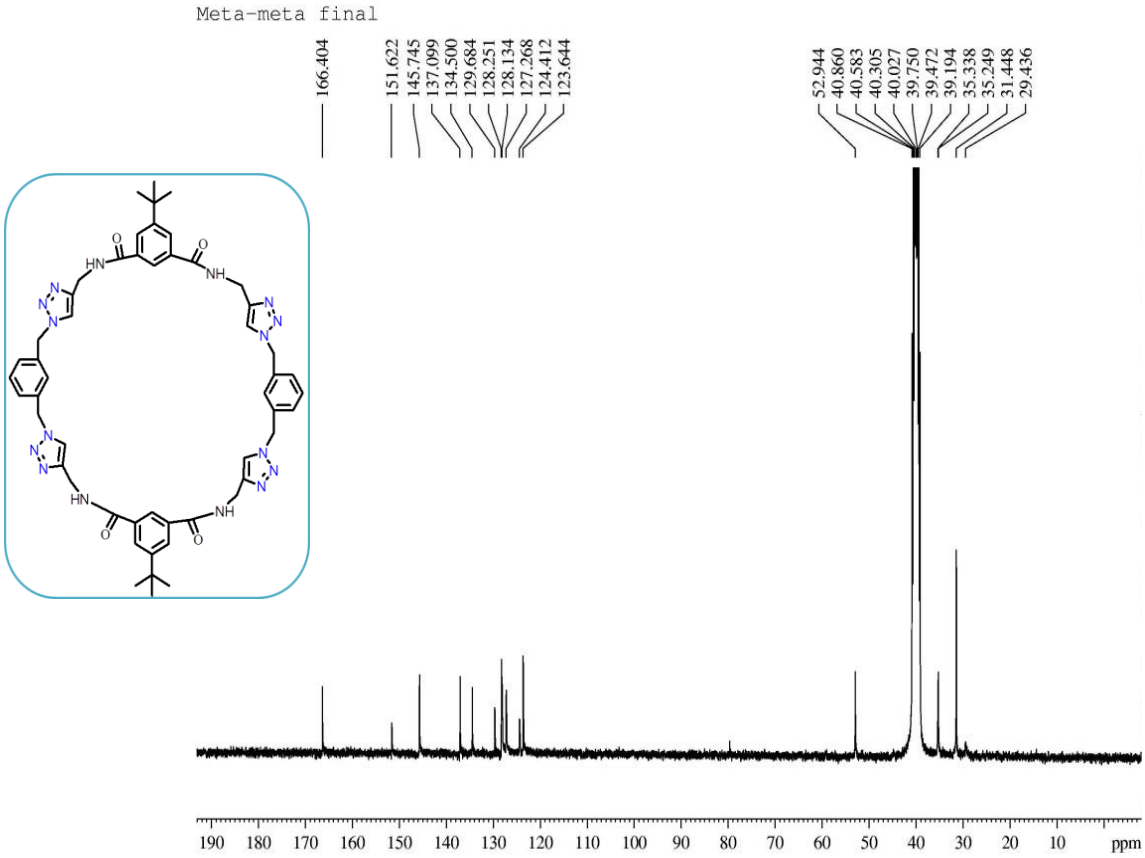
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **18**



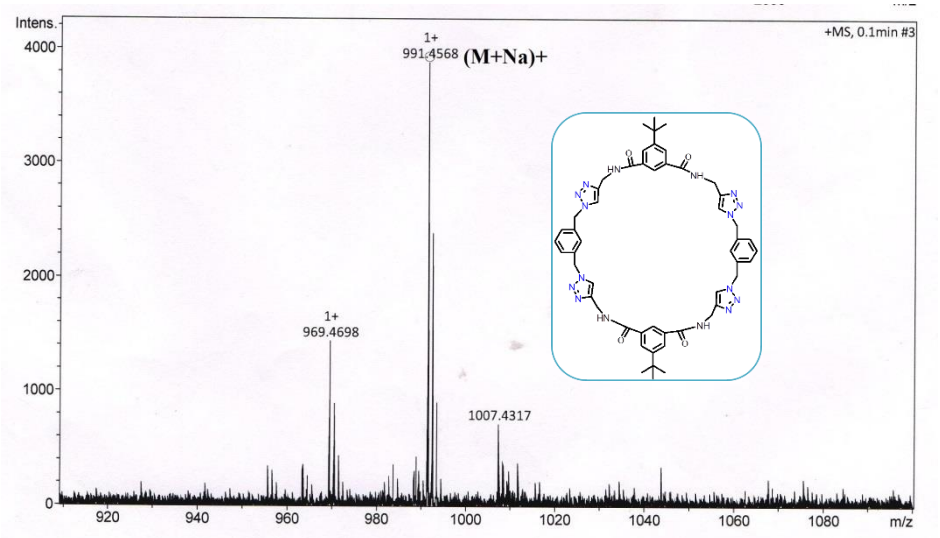
Mass spectrum of **18**



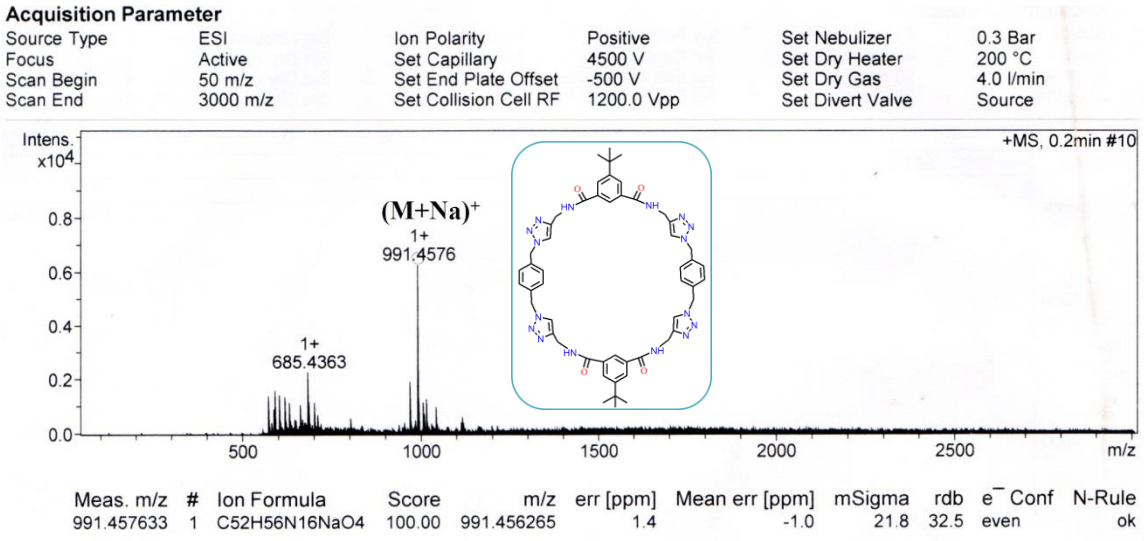
^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **M1**



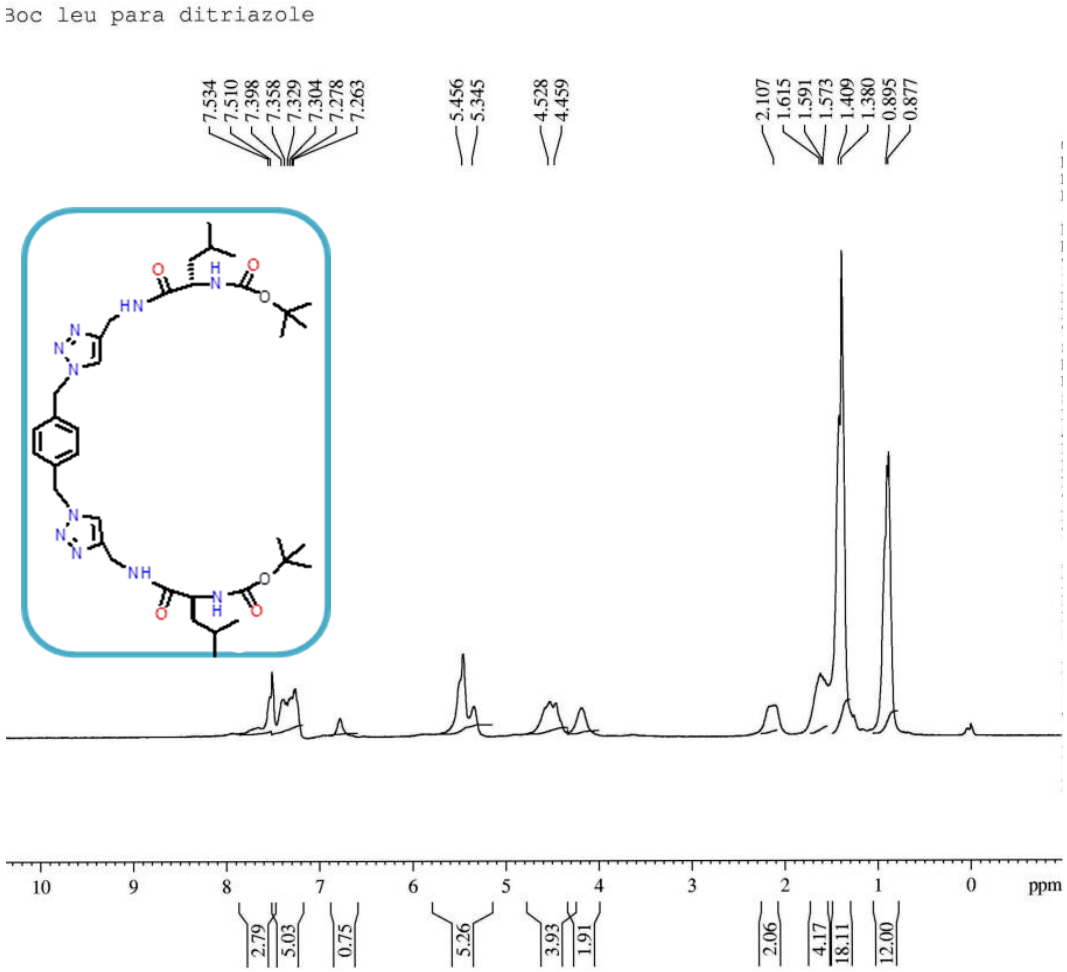
^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **M1**



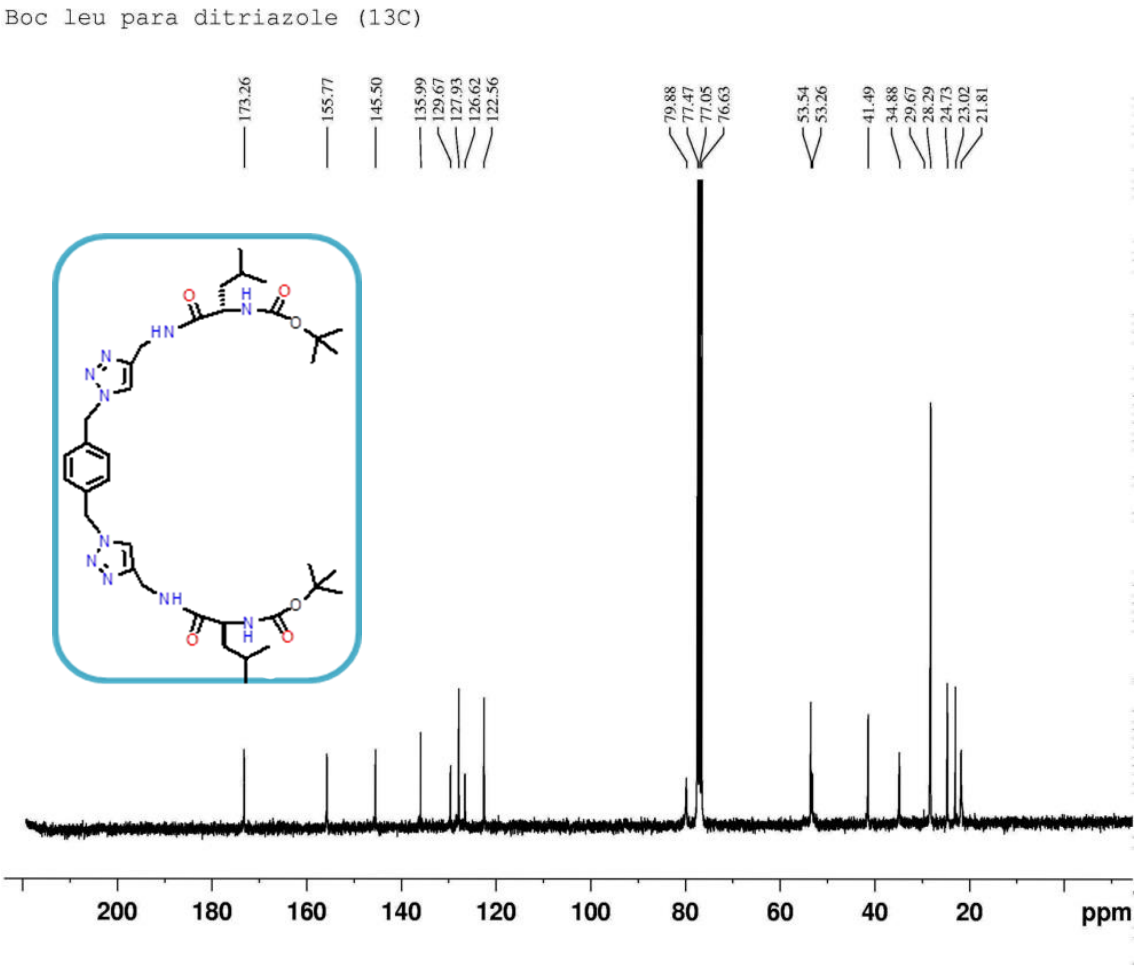
Mass spectrum of **M1**



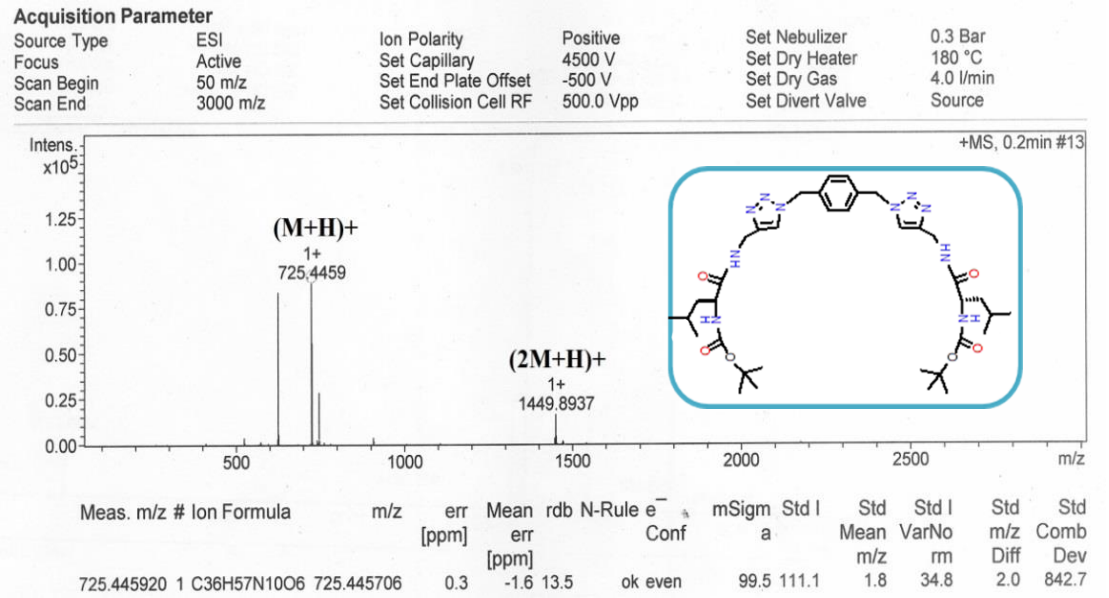
Mass spectrum of **M2**



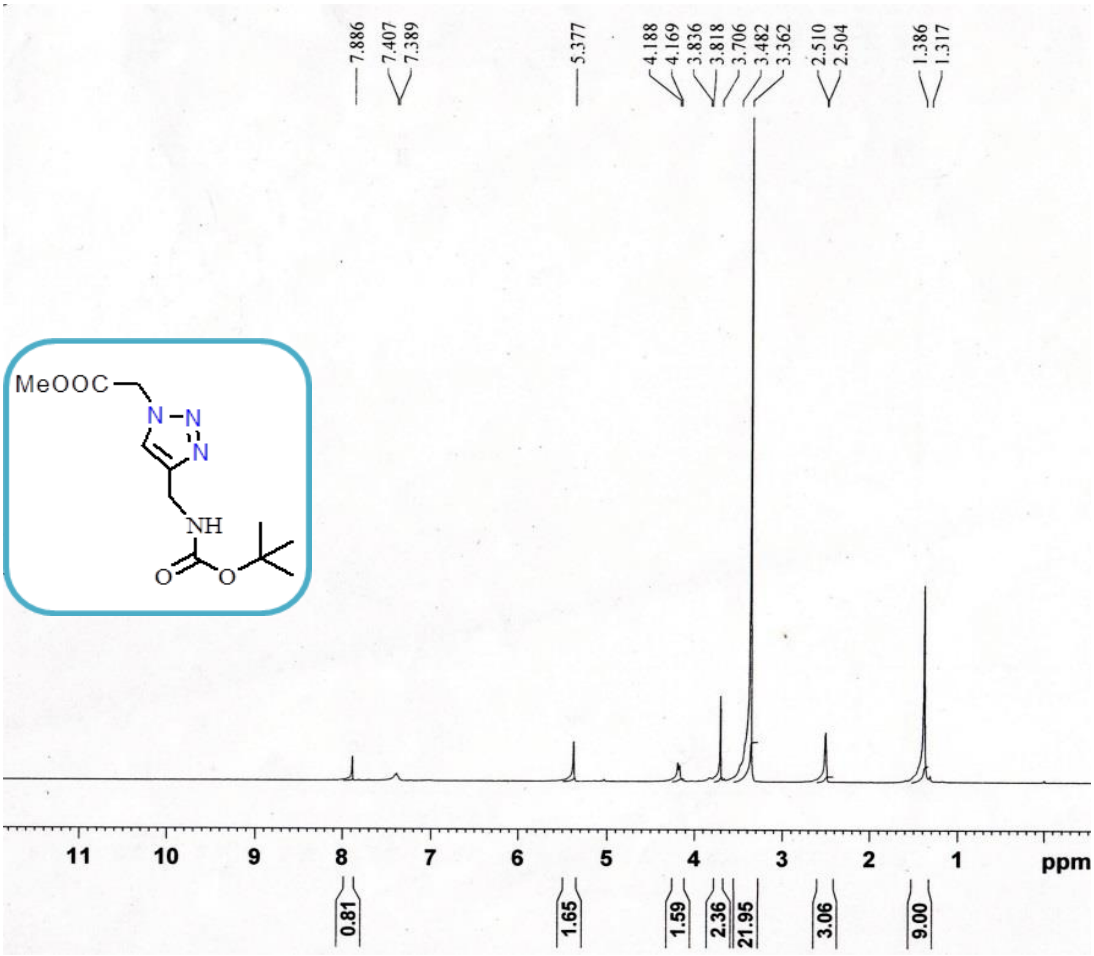
^{1}H NMR (300 MHz, $CDCl_3$) spectrum of **21**



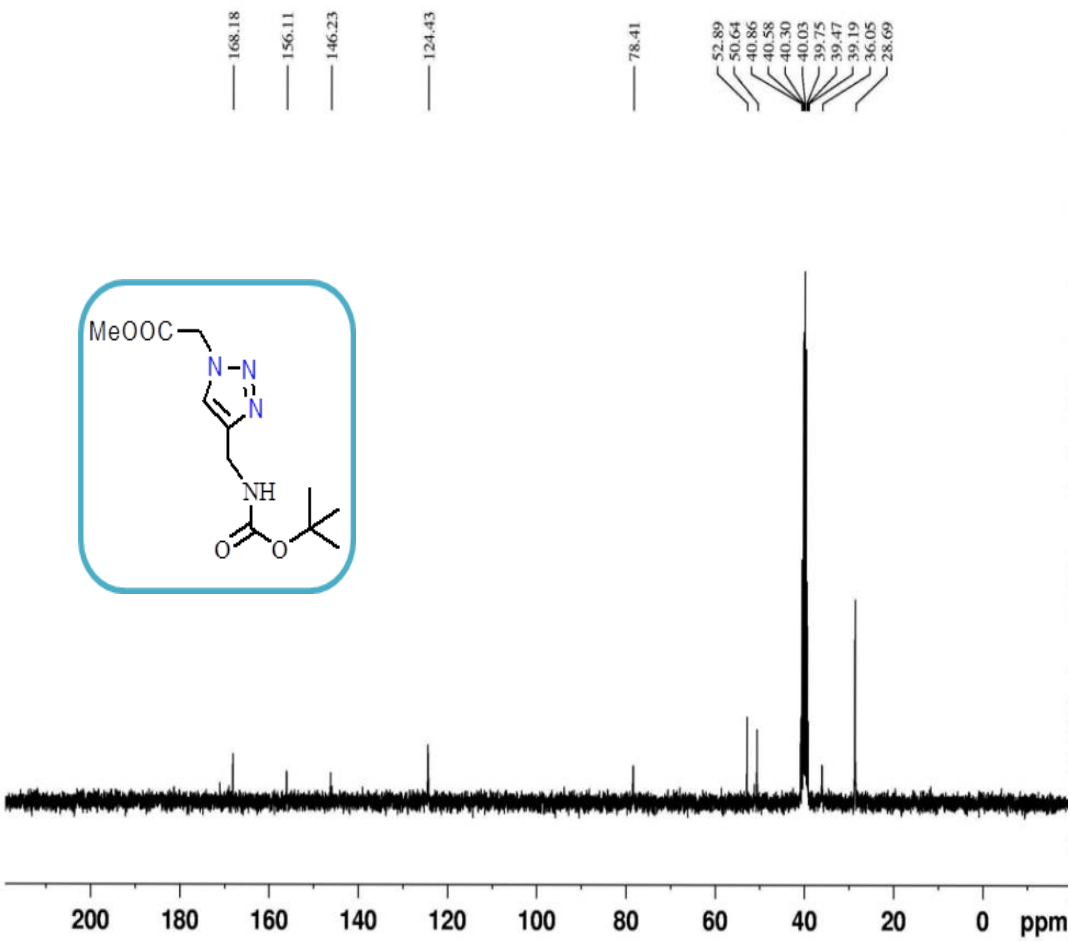
^{13}C NMR (75 MHz, $CDCl_3$) spectrum of **21**



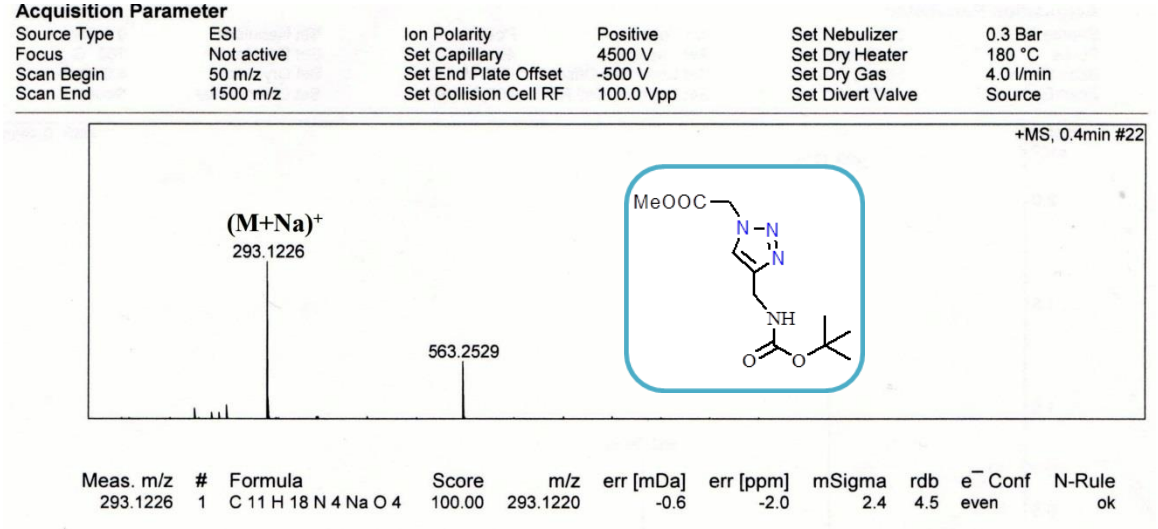
Mass spectrum of **21**



^{1}H NMR (300 MHz, DMSO-d_6) spectrum of **26**



^{13}C NMR (75 MHz, DMSO-d_6) spectrum of **26**



Mass spectrum of **26**

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