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SUPPORTING INFORMATION

Low generation anionic dendrimers modulate islet amyloid polypeptide self-assembly and inhibit pancreatic β-cell toxicity

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General approach for synthesis of low generation dendrimers:

All reactions in organic medium were performed in standard oven dried glassware under an inert atmosphere of nitrogen using freshly distilled solvents. Solvents and reagents were deoxygenated when necessary by purging with nitrogen. Water used for lyophilization of final dendrimers was nanopure grade, purified through Barnstead NANOPure II Filter with Barnstead MegOhm-CM Sybron meter. All reagents were used as supplied without prior purification unless otherwise stated, and obtained from Sigma-Aldrich Chemical Co. Ltd. Reactions were monitored by analytical thin-layer chromatography using silica gel 60 F254 precoated plates (E. Merck). Purifications were performed by flash column chromatography using silica gel from Silicycle (60 Å, 40-63 µm) with the indicated eluent.

^{1}H NMR and ^{13}C NMR spectra were recorded at 300 or 600 MHz and 75 or 150 MHz, respectively, on a Bruker spectrometer (300 MHz) and (600 MHz). All NMR spectra were measured at 25°C in indicated deuterated solvents. Proton and carbon chemical shifts (δ) are reported in ppm and coupling constants (J) are reported in Hertz (Hz). The resonance multiplicity in the ^{1}H NMR spectra are described as "s" (singlet), "d" (doublet), "t" (triplet), "quint" (quintuplet) and "m" (multiplet) and broad resonances are indicated by "br". Residual protic solvent of $CDCl_3$ (^{1}H, δ 7.27 ppm; ^{13}C, δ 77.0 ppm (central resonance of the triplet)), D_2O (^{1}H, δ 4.79 ppm and 30.9 ppm for CH_3 of Acetone for ^{13}C spectra), MeOD (^{1}H, δ 3.31 ppm and ^{13}C, δ 49.0 ppm). 2D Homonuclear correlation 1H-1H COSY experiments were used to confirm NMR peak assignments. Fourier transform infrared (FTIR) spectra were obtained with Thermo-scientific, Nicolet model 6700 equipped with ATR. The absorptions are given in wavenumbers (cm^{-1}). The intensity of the bands is described as s (strong), m (medium) or w (weak).

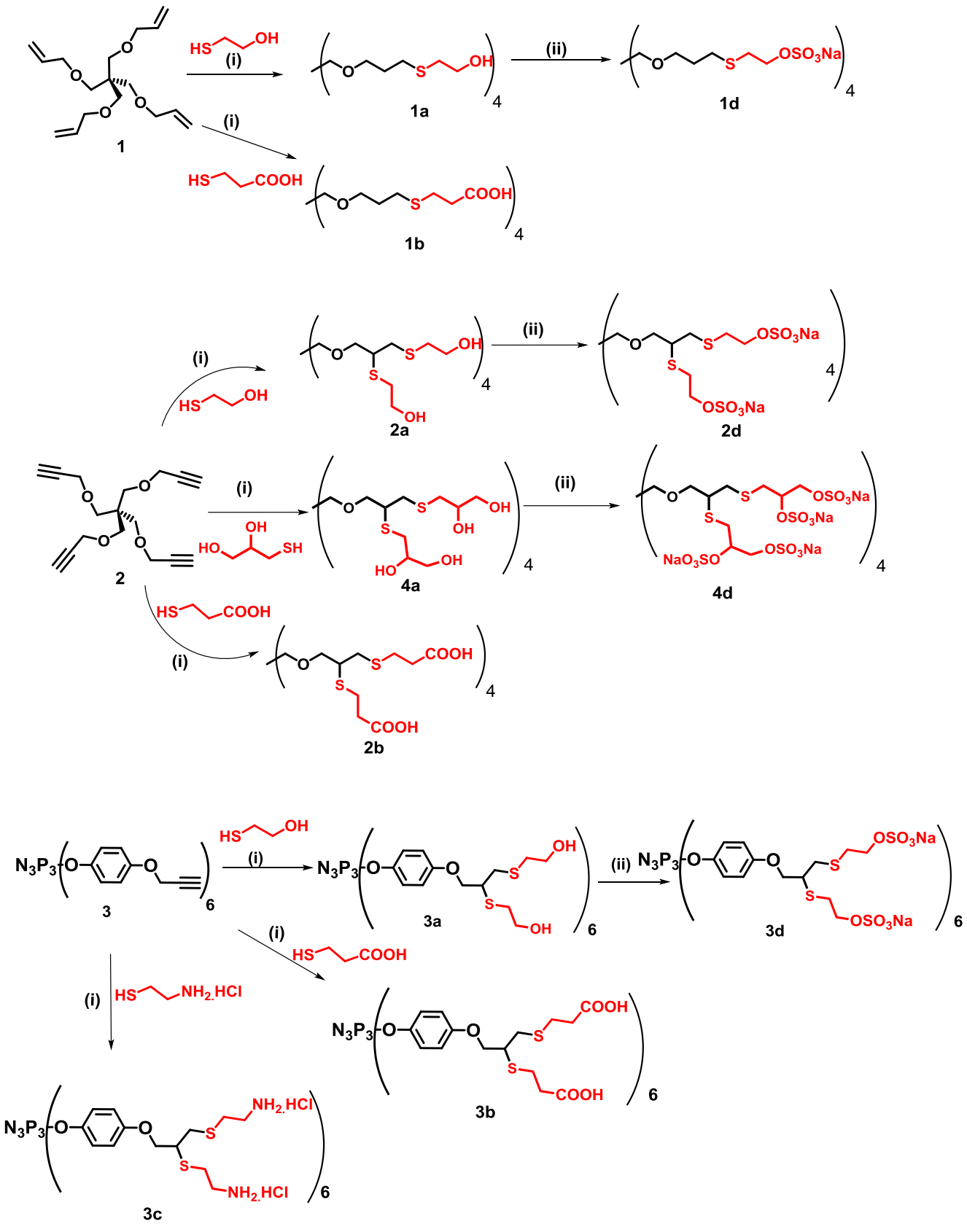
Accurate mass measurements (HRMS) were performed on a LC-MSD-ToF instrument from Agilent Technologies in positive electrospray mode. Low-resolution mass spectra were performed on the same apparatus or on a LCQ Advantage ion trap instrument from Thermo Fisher Scientific in positive electrospray mode (Plateforme analytique pour molécules organiques (Université du Québec à Montréal), Québec, Canada). Either protonated molecular ions $[M+nH]^{n+}$ or adducts $[M+nX]^{n+}$ (X = Na, K, NH_4) were used for empirical formula confirmation. MALDI-TOF experiments were performed on an Autoflex III from Brucker Smarteam in linear positive mode (Mass Spectrometry Laboratory (McGill University)) to afford adducts $[M+nX]^{n+}$ (X = Na, K or Li). Samples were solubilized in H_2O for a final concentration of 6 mg/mL. Dihydroxybenzoic acid (DHB) was used as the matrix. Cationization was eased by the use of the corresponding sodium salt (2mg/mL).

Results and discussion of low generation dendrimers synthesis:

Starting from tetrakis-allylpentaerythritol core (1; Scheme 1), we first performed radical induced photolytic addition of 2-mercaptoethanol under standard thiol-ene click conditions to obtain compound (**1a**).[1] The reaction of (1) with 3-mercaptopropionic acid using similar conditions provided tetra-carboxylic acid derivative (**1b**) in decent yield (78%). In the NMR spectrum of the product (**1b**) signals analogous to allylic group from parent core molecule disappeared completely and a singlet was observed corresponding to carboxylic acid around 11.36 δ which confirming the 100% completion of the reaction. I.R spectrum also showed strong O-H stretching band in at 2800-3000 cm^{-1}. Tetrahydroxylated compound (**1a**) was further subjected to sulfation using sulphur trioxide pyridine complex in DMF at $60^{o}C$ for 24 h. The resulting tetra-sulfated compound (**1d**) was isolated in 71% yield; after purification of the reaction mixture by dialysis. The ^{1}H NMR spectrum of (**1d**) showed a downfield shift from 3.74 to 4.25 ppm for -CH_2- peak present adjacent to hydroxyl group. HRMS (ESI-MS) also confirmed the desired product with a sharp dominant peak at 1016.0075 (calculated 1016.0095).

For the enhancement of number of surface groups we further utilized thiol-yne click reaction to build dendrimers. Thiol-yne click is radical initiated hydrothiolation reaction where two thiols are added over an alkyne bond; and due to this advantage it is an effective tool for rapid construction of complex macromolecules. The photoaddition of 2-mercaptoethanol , 1-thioglycerol and 3-mercaptopropionic acid to tetrapropargylated pentaerythritol (2) yielded G1 dendrimers **2a**[1], **4a**, **2b** harboring 8,16 hydroxyl groups and 8 carboxylic acids, respectively. The ^{1}H NMR spectra clearly illustrated completion of click reaction by entire disappearance of propargyl function from core around 2.5 ppm. Hydroxyl terminated dendrimers **2a** and **4a** were finally transformed into sulfates 2d and 4d using sulphur trioxide pyridine complex. Degree of sulfation was calculated with the help of ^{1}H NMR spectra. We observed for dendrimer **2d** which consists of 8 hydroxyl groups, only six were converted to sulfates. The CH_2 which are alpha to hydroxyl group shifted downfield from 3.79 to 4.21 ppm but this downfield shift is experienced by only 12 protons. It is observed that two CH_2 are still unmoved or unchanged from their previous position. In the case of dendrimer **4d** we found that only 12 hydroxyl groups are transformed into sulfates and leaving 4 of the secondary OHs are not transformed to sulfates as we observed downfield signal at 4.70 ppm corresponding to 4 protons (CH-OH).

We further selected rigid hexapropargyl cyclotriphosphazene core for our next series of (G1) dendrimers. Once again thiol-yne reaction was performed using commercially available 2-mercaptoethanol, 3-mercaptopropionic acid and cysteamine hydrochloride which provided us dendrimers with 12 peripheral hydroxyl (**3a**), carboxylic acid (**3b**)[1] and amine (**3c**) groups in decent yields. Upon completion signals due to propargyllic protons were not found in any case which confirmed defect free products. Moreover a singlet was observed in ^{13}P NMR of these products which determines the monodispersity of these dendrimers. High resolution mass spectrometry (ESI) confirmed the formation of products with dominant signal at calculated values. Finally polyhydroxy (**G1**) dendrimer **3a** was subjected to sulfation using excess of SO_3.Py in DMF for 36 hours to yield sulfated dendrimer (**3d**). ^1H NMR spectrum suggests that only 9-10 OH groups were converted to sulfates as we observed 2 to 3 $–CH_2-$ groups still unmoved from their previous position of 3.70 δ. All the dendrimers were achieved rapidly in decent yields with ease, bypassing any protection /deprotection steps without intensive purification procedures. The additional advantage of these hydroxyl, carboxylic acid and amine based dendrimers comes from the fact that all the dendrimers have terminal reactive functionalities on the surface which can be easily utilised as a platform for the preparation of highly branched dendritic structures. This work is under investigation and will be covered in future.



Scheme 1. Reaction conditions and reagents: (*i*) DMPAP (10 mol%),UV 365 nm, DMF, rt, 12 h; (*ii*) SO_3.Py, DMF, 60°C, 24-36 h.

Synthesis and characterization of low generation dendrimers:

General procedure for thiol-ene, thiol-yne click reaction and sulfation:

Procedure A for thiol-ene:

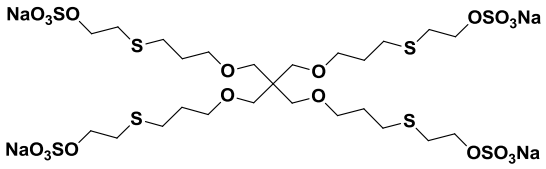
To a stirred solution of alkene derivative (1.0 eq.), 2,2'-dimethoxy-2-phenylacetophenone (DMPA) (10 mol %) in dry DMF (0.2 ml/mmol) was added thiol derivative (excess per alkene) under nitrogen. The vial was then purged with N_2 for 10 min and irradiated for 12 hrs using UV lamp at room temperature *(classical glassware, UV lamp (365 nm, Model UVGL-58 MINERALIGHT® LAMP) in a cardboard box)*. Upon completion of the reaction, the solvent was removed under vacuum and the residue was subsequently washed three times with diethyl ether to remove excess of thiol and disulphide formed during the reaction, affording a clear viscous liquid. The crude product was further purified by column chromatography over silica gel or through dialysis.

Procedure B for thiol-yne:

To a stirred solution of alkyne derivative (1.0 eq.), 2,2'-dimethoxy-2-phenylacetophenone (DMPA) (10 mol %) in dry DMF (0.2 ml/mmol) was added thiol derivative (excess per alkyne) under nitrogen. The vial was then purged with N_2 for 10 min and irradiated for 12 hrs using UV lamp at room temperature *(classical glassware, UV lamp (365 nm, Model UVGL-58 MINERALIGHT® LAMP) in a cardboard box)*. Upon completion of the reaction, the solvent was removed under vacuum and the residue was subsequently washed three times with diethyl ether to remove excess of thiol and disulphide formed during the reaction, affording a clear viscous liquid. The crude product was further purified by column chromatography over silica gel or through dialysis.

Procedure C for Sulfation:

To a solution of polyhydroxy compound in 10 ml dry DMF, sulfur trioxide pyridine complex (6 eq. per hydroxyl) was added, and the mixture was stirred over 24- 36 h at 60 ^{o} C. After removal of the solvent, crude mixture was redissolved in distilled water and 1M NaOH solution was added until a pH of 10 was reached. Crude mixture was further purified by dialysis in water (MWCO: 500-2000 based on M.Wt). Dialysed products were lyophilized.



Synthesis of compound 1d:

Compound **1a** (500mg, 0.821 mmol) and sulfur trioxide pyridine complex (2612mg, 16.42 mmol, 5 eq. per hydroxyl) were reacted together following the procedure C. Crude mixture was further purified by dialysis against water using 500 molecular weight cut-off dialysis tubing. Dialysed product was lyophilized to yield compound **1d,** yield**:** 71%.

^{1}H NMR (300 MHz, D_2O): δ (ppm) 4.32 - 4.16 (m, 8H), 3.68 – 3.57 (m, 8H), 3.47 (br s, 8H), 2.94 (t, *J* = 5.7 Hz, 8H), 2.74 (d, *J* = 6.1 Hz, 8H), 1.95 (d, *J* = 6.7 Hz, 8H).

^{13}C NMR (151 MHz, D_2O): δ (ppm): 70.4, 68.3, 63.0, 31.2, 29.1, 28.8.

HRMS (ESI^{+}-TOF): Calculated for $C_{25}H_{48}Na_4O_{20}S_8$: 1016.0095, found: 1016.0075.

IR (cm^{-1}): 3459, 2920, 2863, 1634, 1107, 1067, 973, 883, 750.

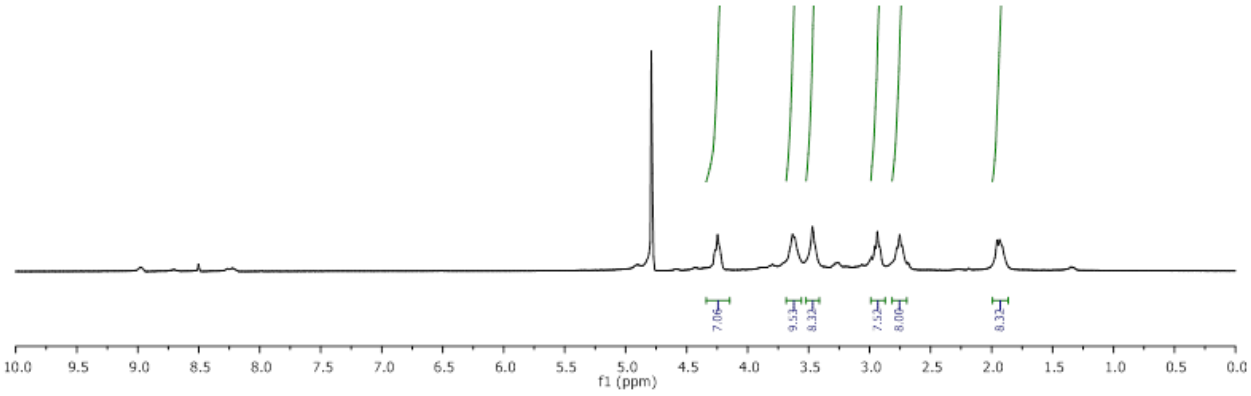


Figure S1. ^{1}HNMR spectrum of compound **1d** (D_2O, 300 MHz).

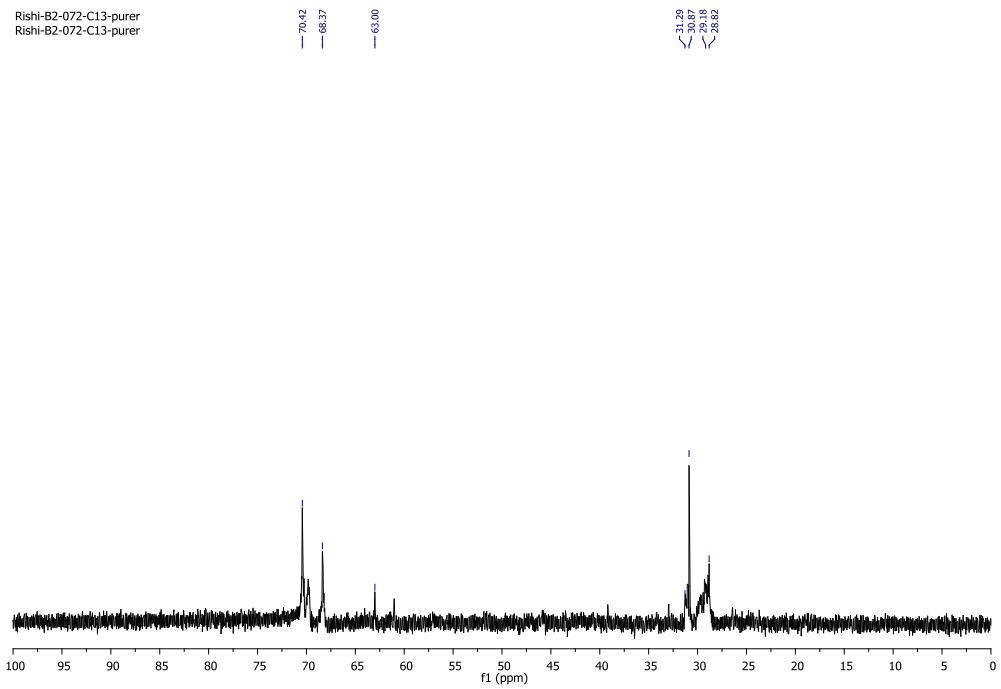


Figure S2. ^{13}CNMR spectrum of compound **1d** (D_2O, 151 MHz).

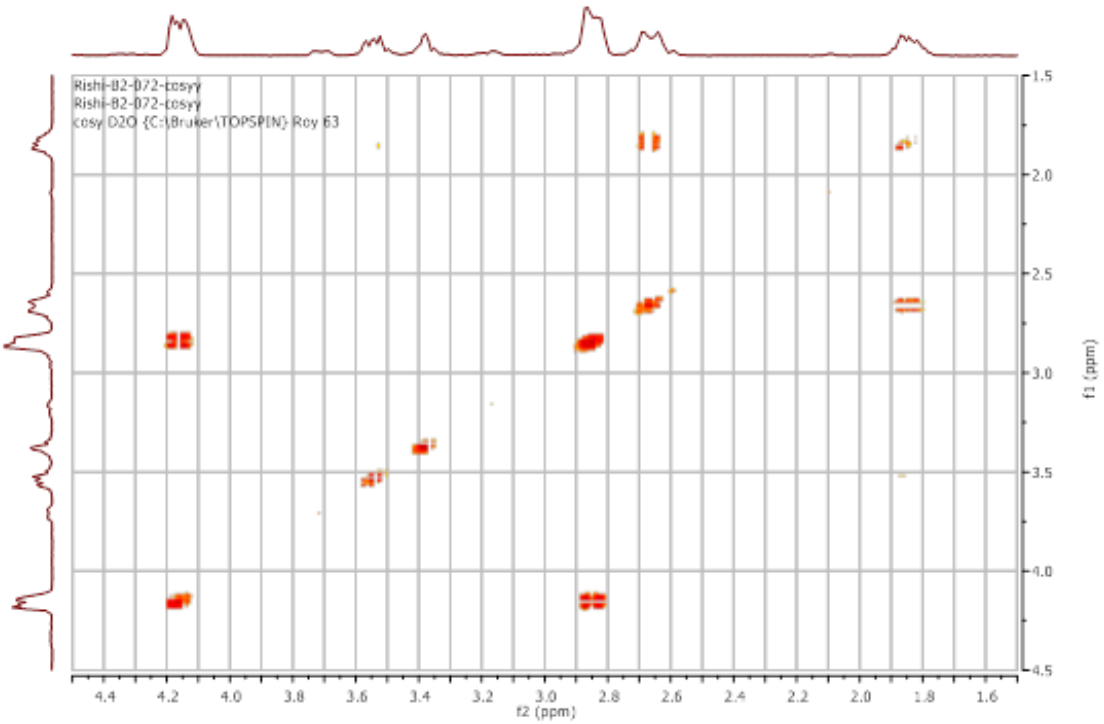


Figure S3. COSY spectrum of compound **1d.**

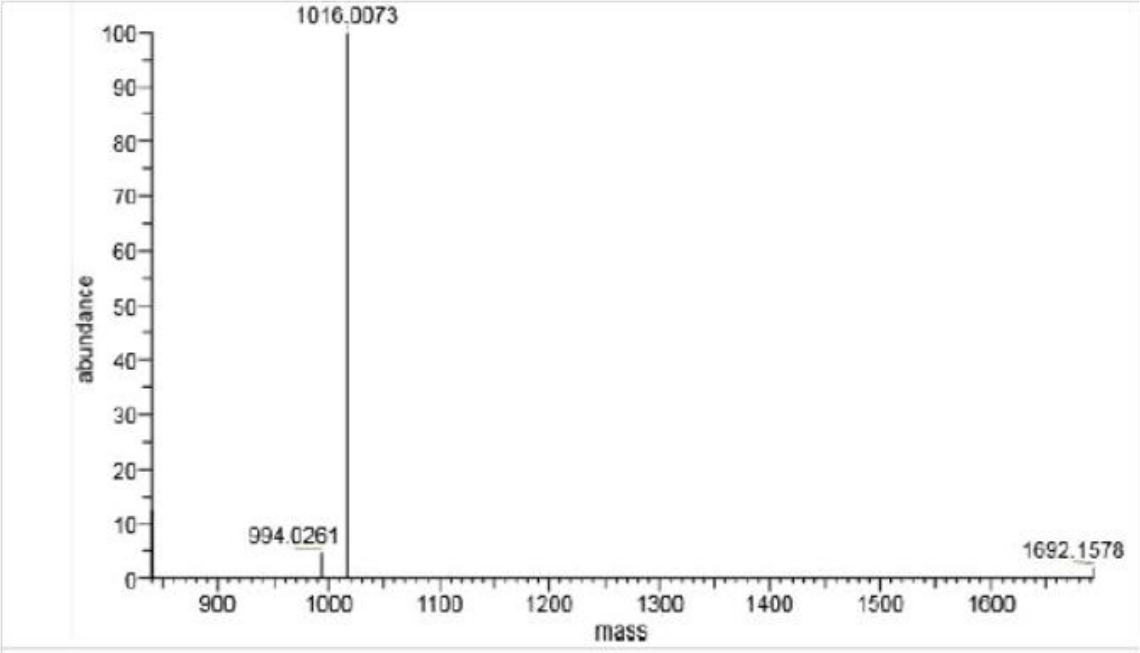


Figure S4. HRMS analysis (ESI^+) for compound **1d.**

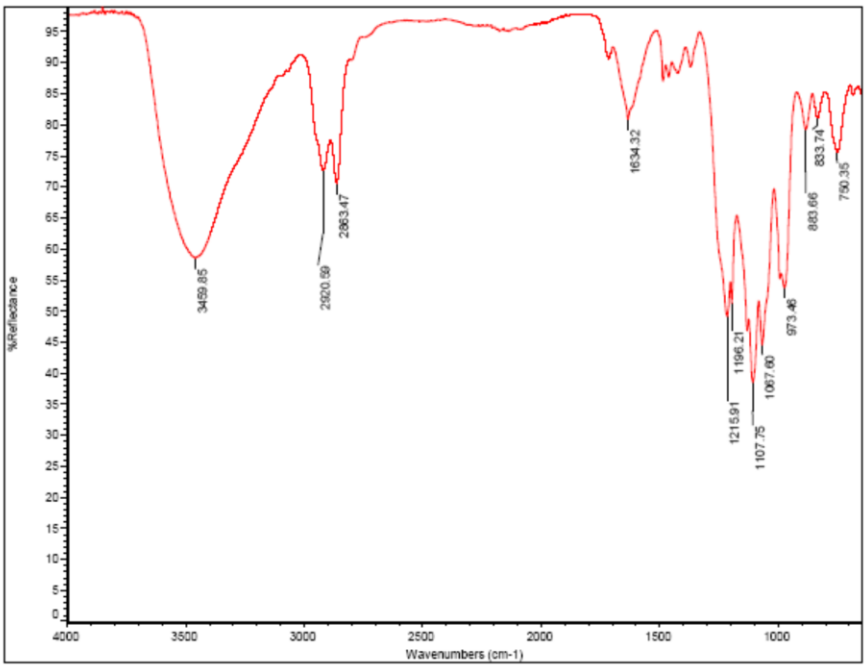
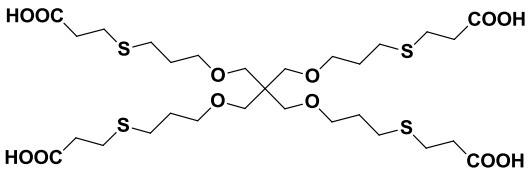


Figure S5. IR spectrum of compound **1d.**



Synthesis of compound 1b:
Tetraallyl pentaerythritol **1** (500 mg, 1.68 mmol) and 3-mercaptopropanoic acid (2.9 ml, 33.7mmol, 5 eq. per site) were reacted according to procedure **A**. Crude mixture was purified by passing through a column of silica gel using 4-8% MeOH in DCM as eluents. The final compound was recovered as white solid. (yield:78%).
^{1}H NMR (300 MHz, $CDCl_3$) δ 11.36 (s, 4H), 3.46 (t, *J* = 5.5 Hz, 8H), 3.36 (d, *J* = 8.0 Hz, 8H), 2.85 – 2.72 (m, 8H), 2.71 – 2.54 (m,16H), 1.91 – 1.71 (m, 8H,).
^{13}C NMR (151 MHz, CDCl3): δ178.0, 69.8, 69.5, 45.4, 35.1, 29.6, 29.0, 26.8.
IR (cm^{-1}): 2934, 2871, 1655, 1420, 1108, 927.

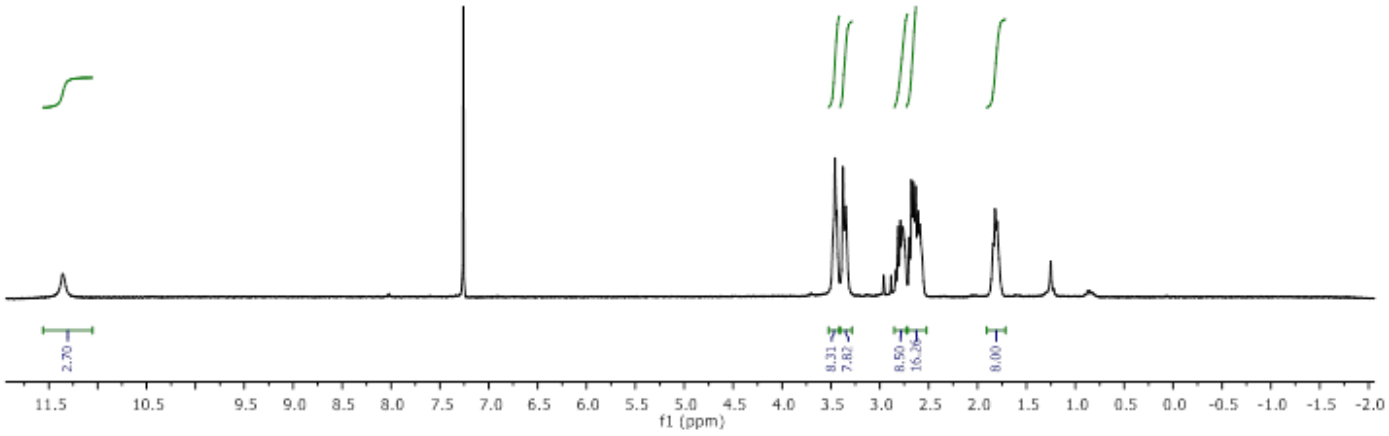


Figure S6 ^{1}HNMR spectrum of compound **1b** ($CDCl_3$, 300 MHz)

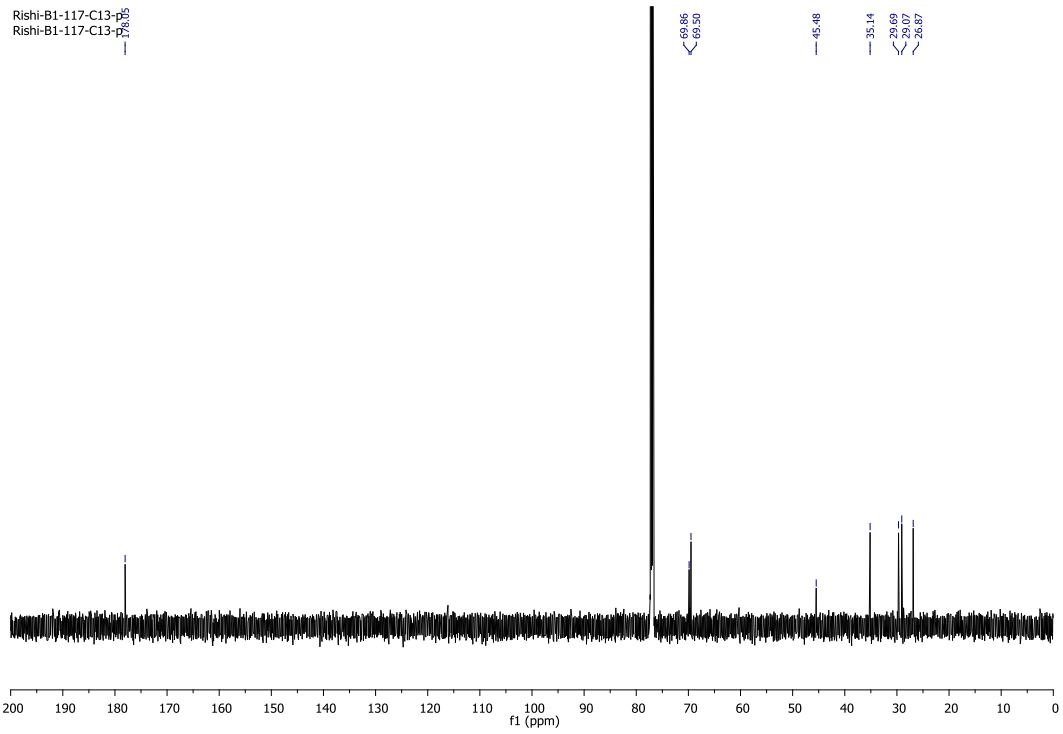


Figure S7. ^{13}C NMR spectrum of compound **1b** (CD_3Cl_3, 151 MHz)

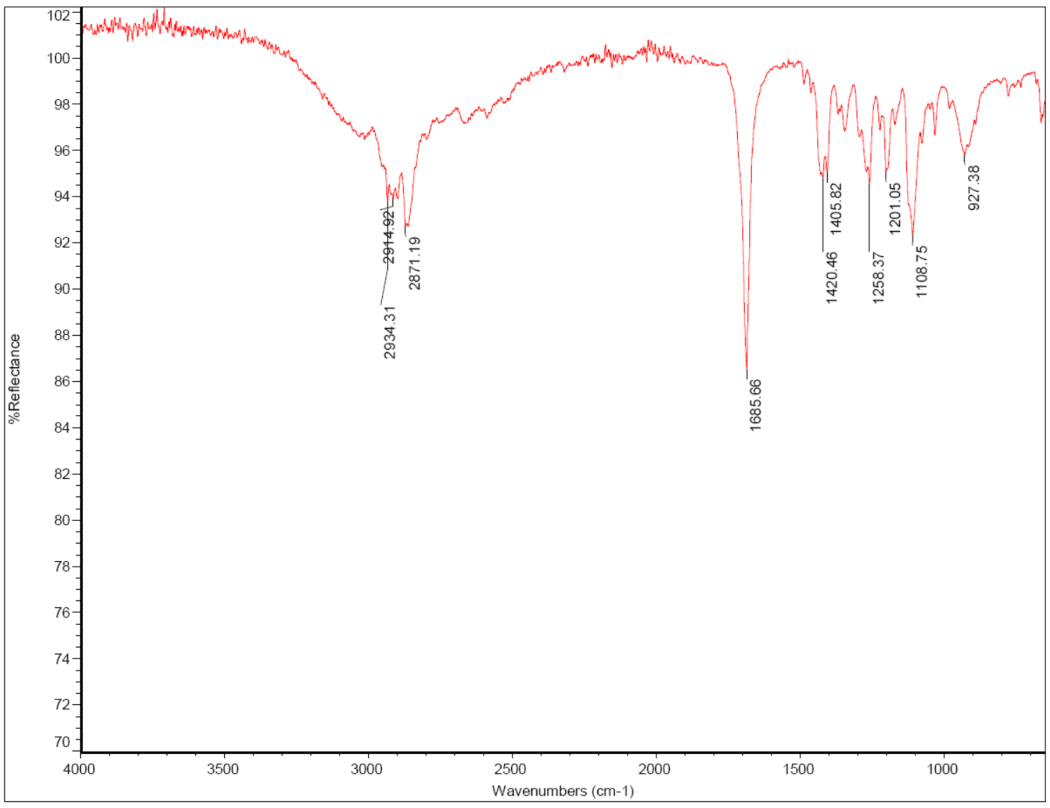
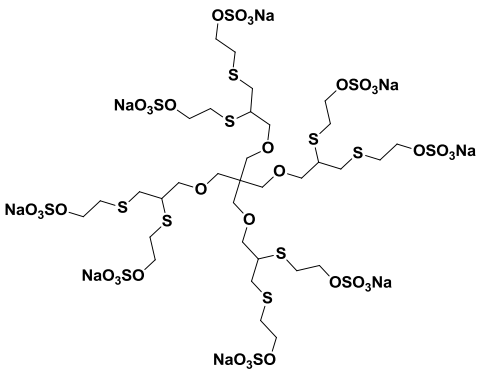


Figure S8. IR spectrum of compound **1b.**



Synthesis of compound 2d :

Polyhydroxyl dendrimer **2a** (220 mg, 0.240 mmol) and sulfur trioxide pyridine complex (1526mg, 9.60 mmol, 5 eq. per hydroxyl) were reacted together according to procedure **C**. Crude mixture was further purified by dialysis in water using dialysis tubing of 1000 molecular weight cut-off. Dialysed product was lyophilized to yield pure product **2d**, **yield:** 74%

^{1}H NMR (300 MHz, D_2O) δ 4.21 (t, *J* = 6.0 Hz, 12H), 3.84 - 3.63 (m, 12H), 3.48 (s, 8H), 3.23 (s, 4H), 3.07 – 2.85 (m, 24H).

^{13}C NMR (75 MHz, D_2O): δ (ppm) 148.1, 142.0, 128.3, 73.5, 69.0, 46.2, 35.2, 32.2.

IR (cm^{-1}): 3468, 2922, 1634, 1417, 1223, 1115, 1070, 972.

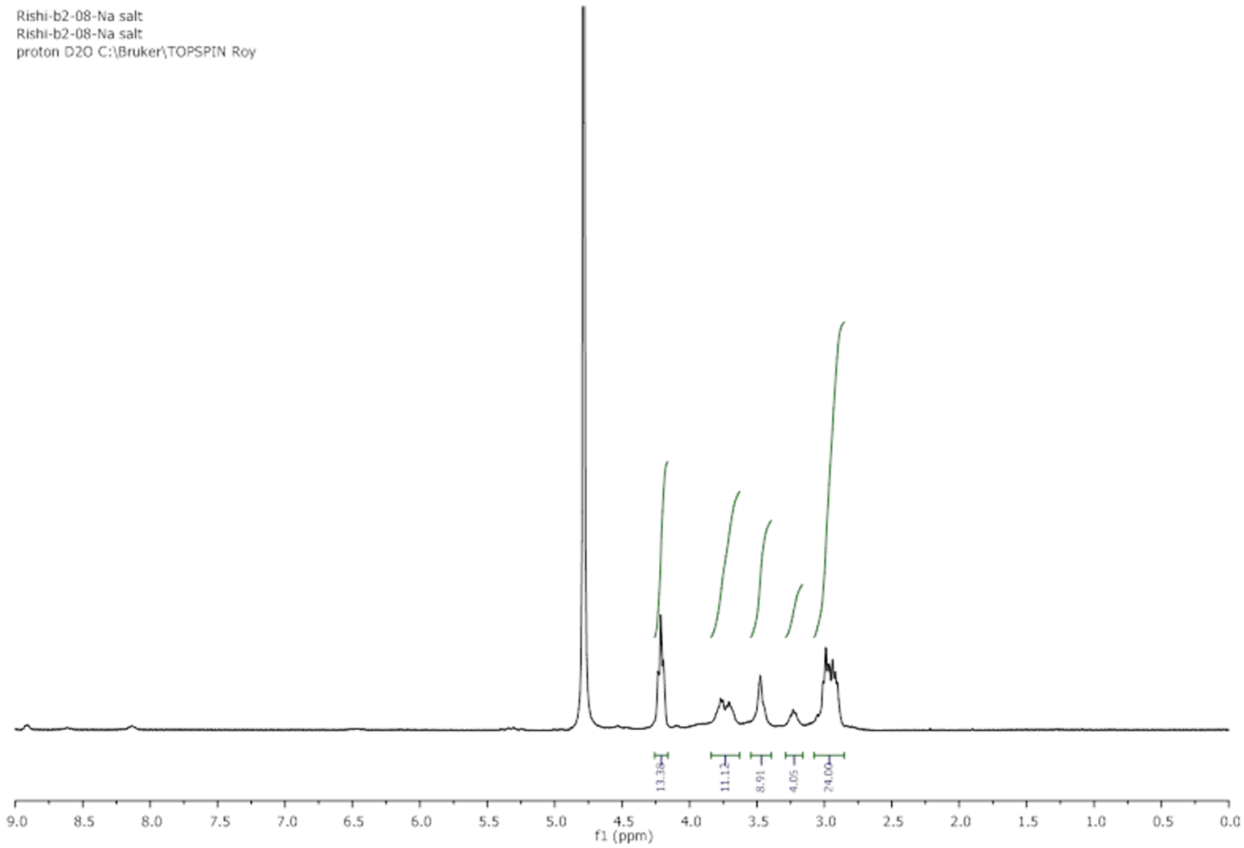


Figure S9. ^{1}HNMR spectrum of compound **2d** (D_2O, 300 MHz).

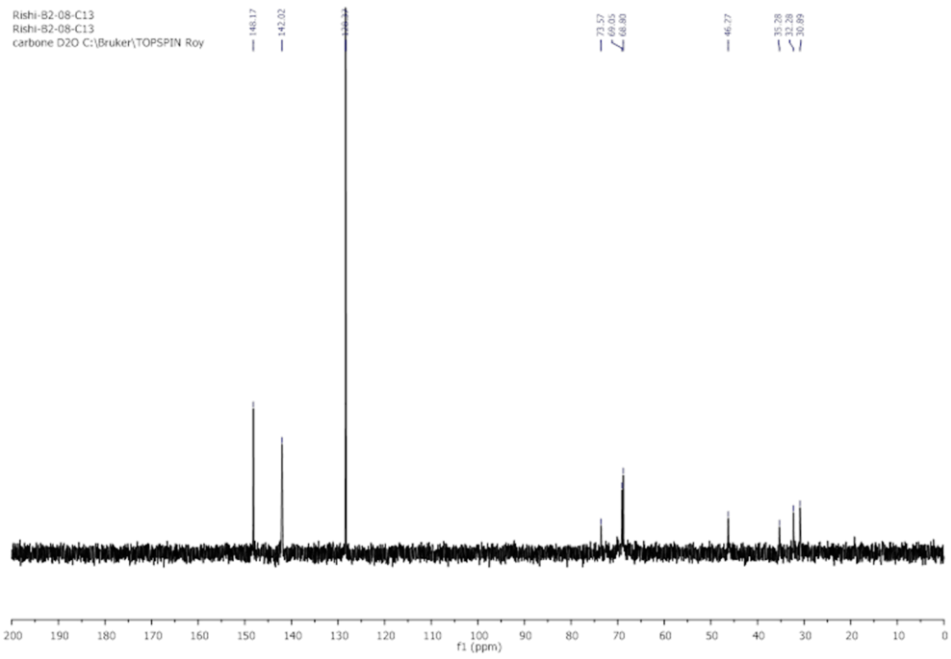


Figure S10. ^{13}CNMR spectrum of compound **2d** (D_2O, 75 MHz).

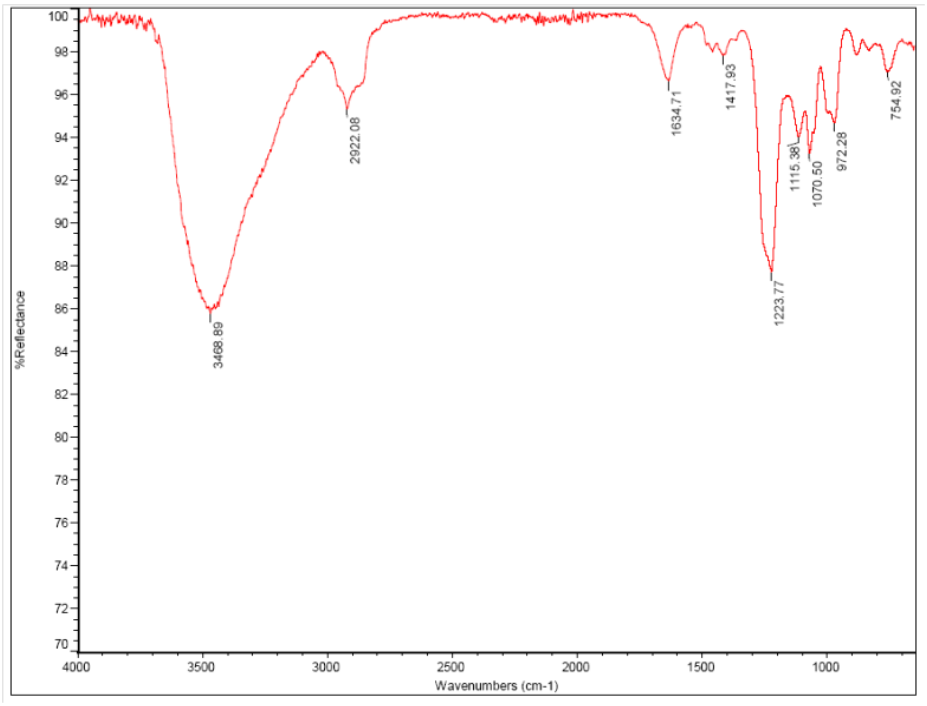
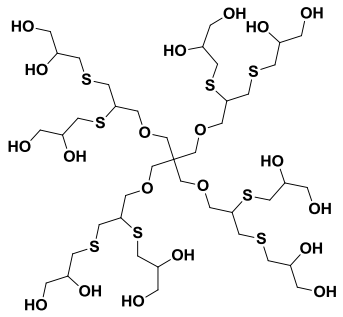


Figure S11. IR spectrum of compound **2d.**



Synthesis of compound 4a:

Tetrapropargyl pentaerythritol **(2)** (0.330 mg, 1.14 mmol), and 1-thioglycerol (4.2 ml, 48.5 mmol, 10.6 eq. per site) were reacted together according to **procedure B** to give crude mixture which was washed with diethyl ether. The residue was dissolved in 4 ml of water and washed with ethyl acetate (3x15 ml) and finally aqueous layer was lyophilized to obtain the pure product **4a** as an oil (yield: 990 mg; 75%).

^{1}H NMR (600 MHz, D2O) δ 3.90 – 3.82 (m, 8H), 3.81 – 3.72 (m, 4H), 3.72 – 3.64 (m, 12H), 3.60 – 3.54 (m, 8H), 3.48 (s, 8H), 3.21 – 3.13 (m, 4H,), 3.02 – 2.89 (m, 8H,), 2.87 – 2.76 (m, 8H,), 2.76 – 2.65 (m, 8H,).

^{13}C NMR (151 MHz, D2O) δ 73.3, 71.8, 71.7, 71.5, 69.9, 64.9, 46.3, 36.1, 35.4, 34.5.

IR : 3328.2 cm-1 (hydroxyl group)

HRMS (ESI^{+}-TOF): For $C_{41}H_{85}O_{20}S_8$ calculated: 1153.3394 found:1153.3393 (M+H).

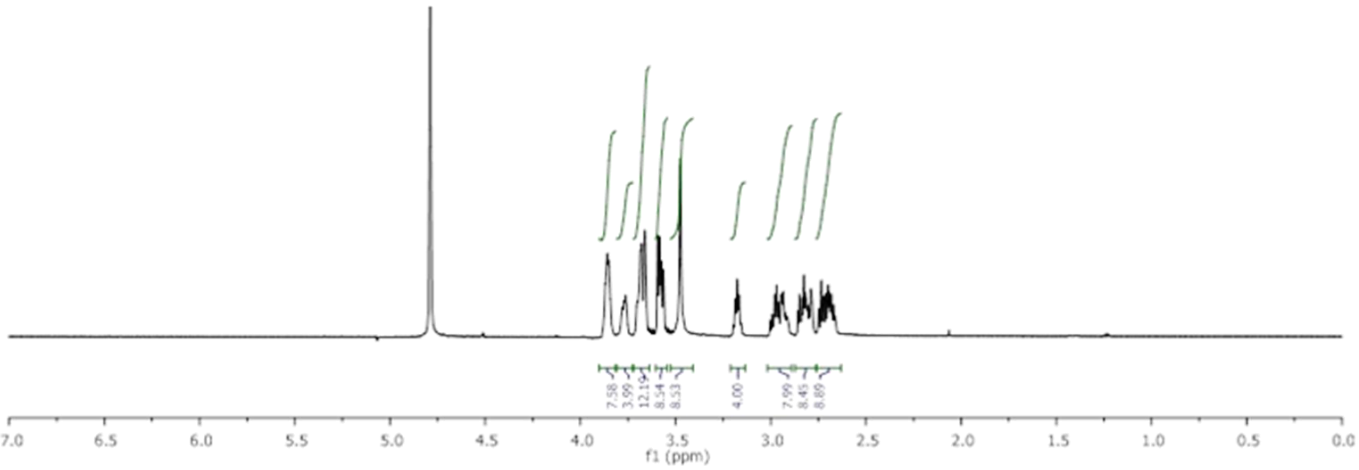


Figure S12 ^{1}HNMR spectrum of compound **4a** (D_2O, 600 MHz)

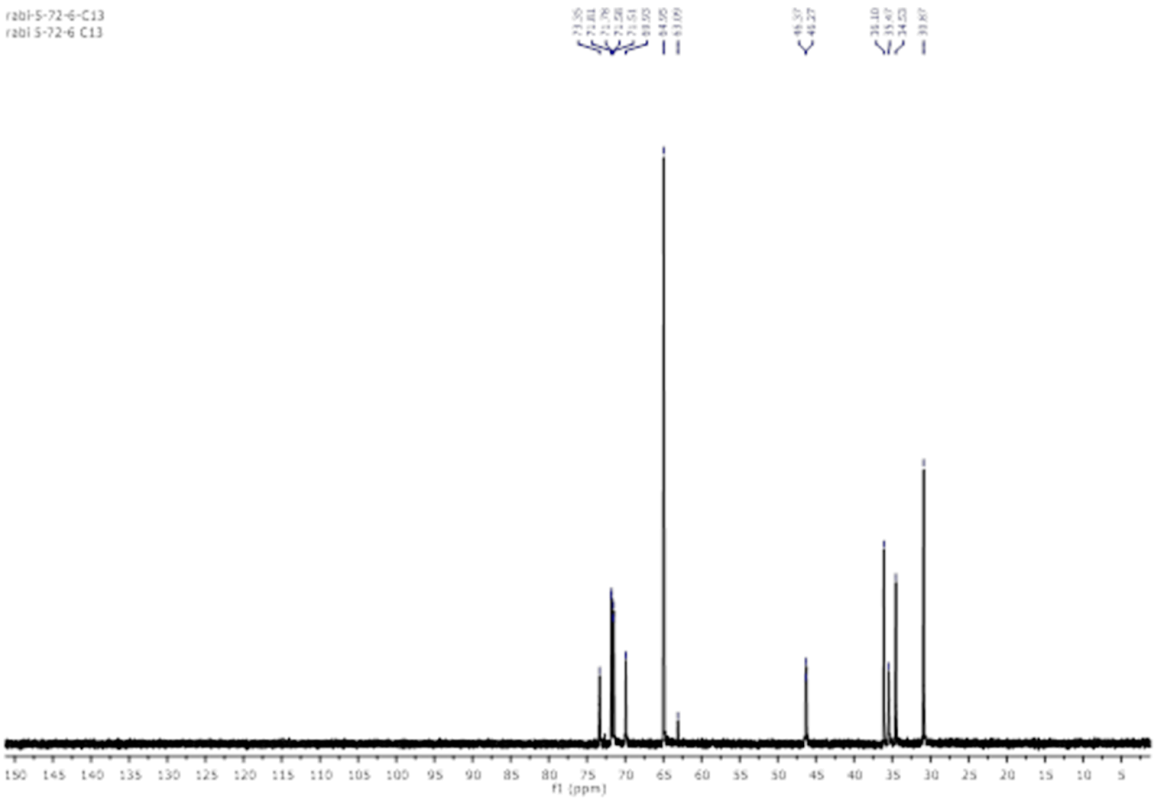


Figure S13 ^{13}C NMR spectrum of compound **4a** (D_2O, 151 MHz)

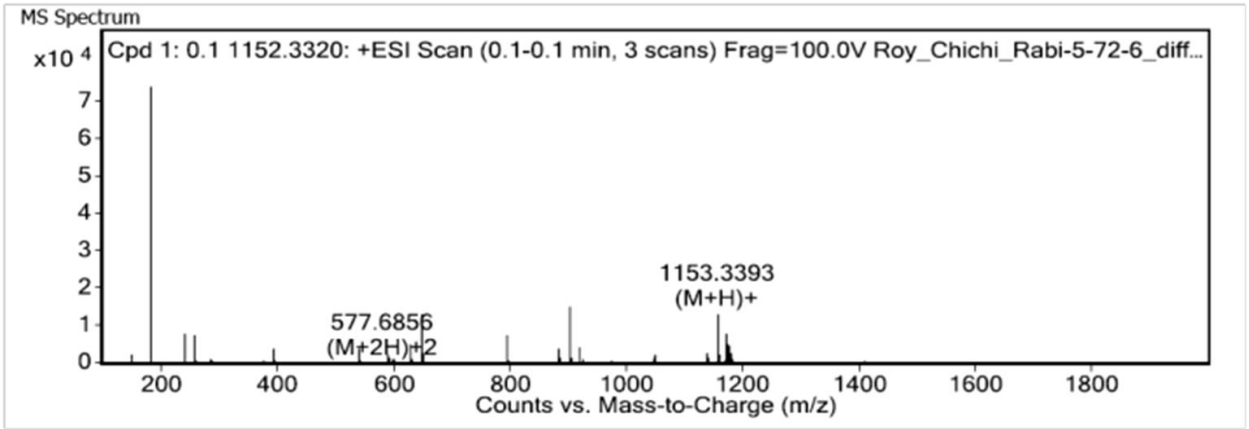


Figure S14 HRMS analysis (ESI^+) for compound **4a.**

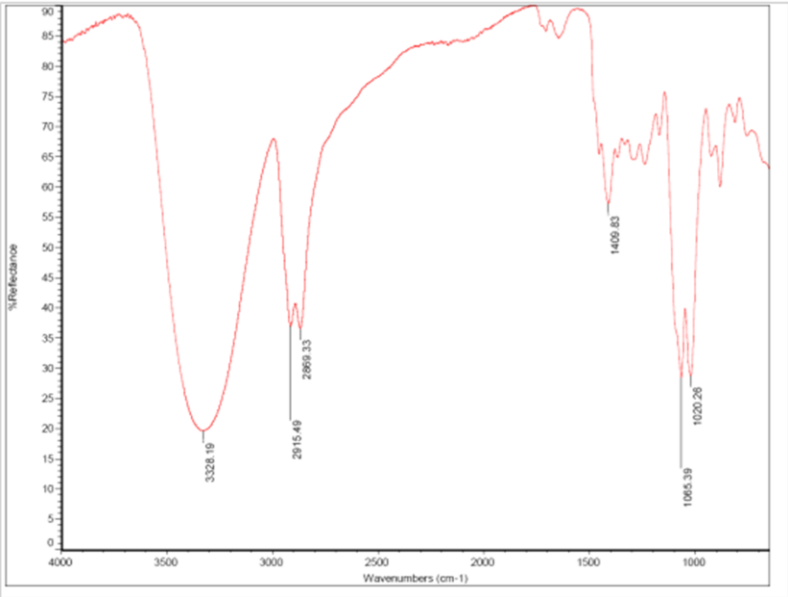
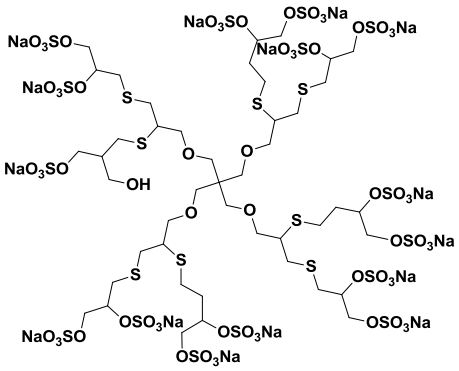


Figure S15. IR spectrum of compound **4a.**



Synthesis of compound 4d:

Polyhydroxy dendrimer **4a** (200 mg, 0.173 mmol) and sulfur trioxide pyridine complex (2.2 g, 13.84 mmol, 5 eq. per hydroxyl) were reacted together following the procedure C. Crude mixture was further purified by dialysis in water using 1000 cut-off dialysis tubing. Dialysed product was lyophilized to yield compound **4d**, y**ield:** 76%

^{1}H NMR (300 MHz, D_2O): δ (ppm) ^{1}H NMR (300 MHz, D_2O) δ 4.73-4.66 (m, 4H, HO-CH), 4.41-4.26 (m, 8H), 4.22-4.02 (m, 8H), 3.95 – 3.65 (m, 12H), 3.49 (s, 2H), 3.31-3.16 (m, 4H,), 3.12 – 2.67 (m, 24H,).

^{13}C NMR (75 MHz, D_2O): δ (ppm) ^{13}C NMR (75 MHz, D_2O) δ 76.8, 73.0, 70.9, 69.4, 69.1, 67.9, 46.2, 35.5, 34.0, 33.4, 31.7.

IR (cm^{-1}): 3443, 2917, 1636, 1216, 1063, 994, 918.

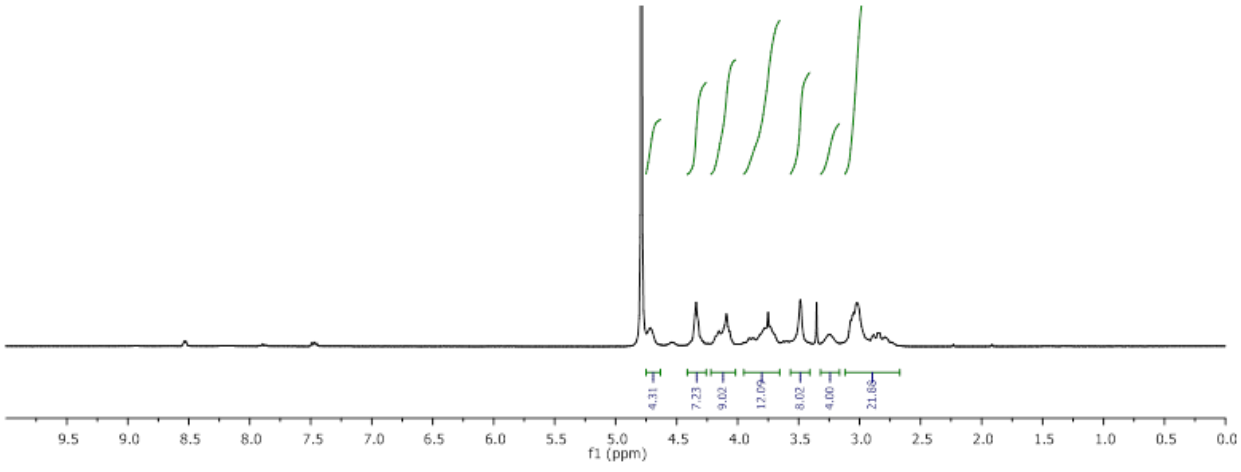


Figure S16 ^{1}HNMR spectrum of compound **4d** (D_2O, 300 MHz)

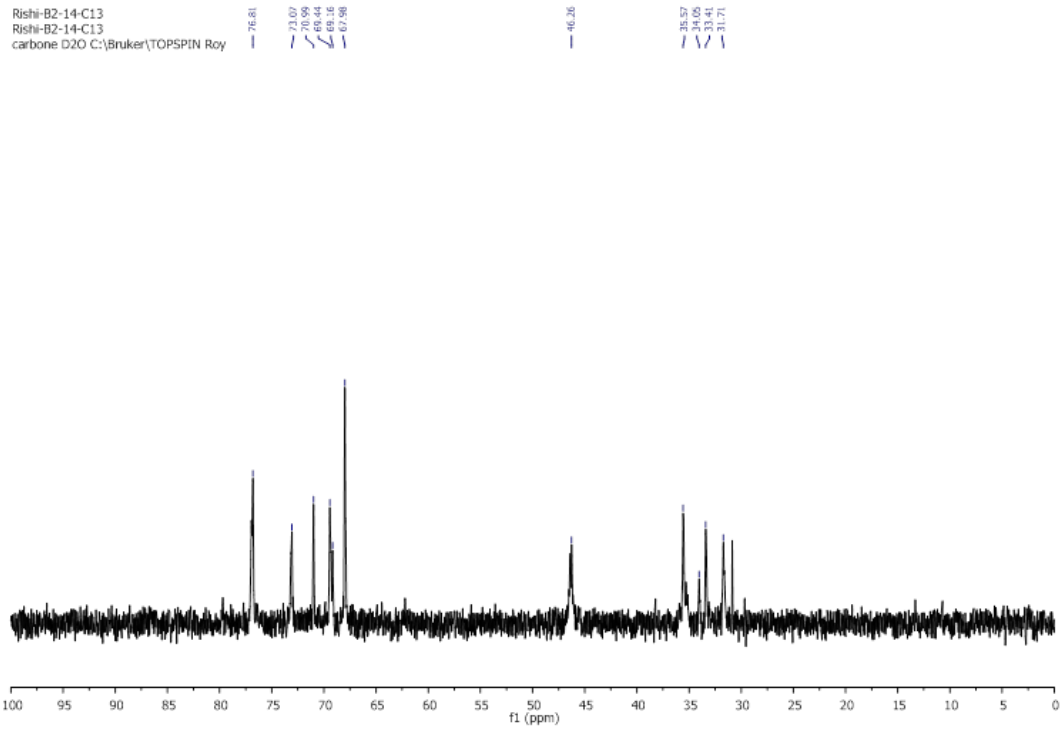


Figure S17 ^{13}C NMR spectrum of compound **4d** (D_2O, 75 MHz)

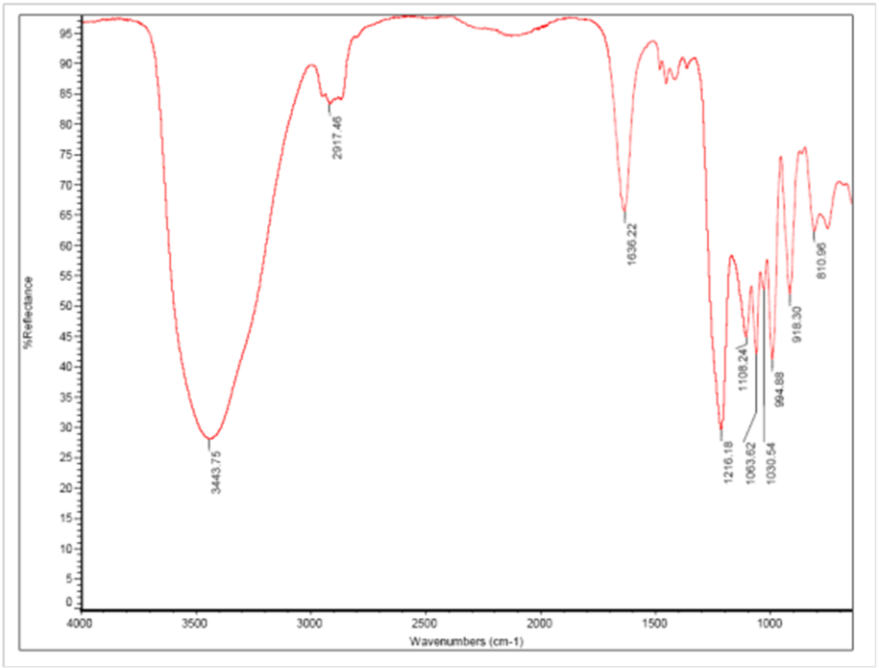
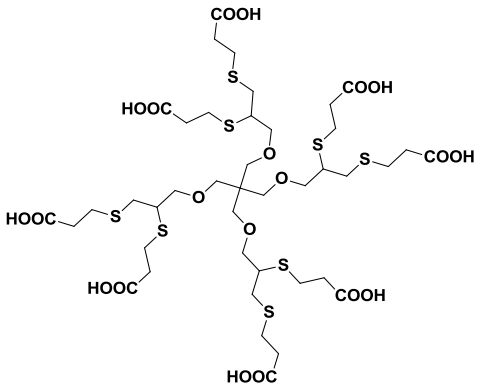


Figure S18. IR spectrum of compound **4d.**



Synthesis of compound 2b:

Tetrapropargyl pentaerythritol (**2)** (100mg, 0.347mmol) and 3-mercaptopropanoic acid (0.183ml, 13.888mmol, 5 eq. per site) were reacted according to procedure **B**. Crude mixture was passed through a silica coloumn and 5% methanol in DCM was used as an eluent to get rid of disulfide. The final compound (**2b**) was recovered using 10% H_2O in acetone as white solid. (yield:78%).

^{1}H NMR (300 MHz, D_2O) δ 3.83 – 3.63 (m, 8H), 3.49 (s, 8H), 3.21-3.11 (m, 4H), 3.01-2.83 (m, 24H), 2.67 (t, *J* = 7.0 Hz, 16H).

^{13}C NMR (75 MHz, D_2O) δ 178.11, 73.41, 69.85, 45.87, 36.28, 36.0, 34.80, 28.43, 26.98.

HRMS (ESI$^+$-TOF): For $C_{41}H_{68}NaO_{20}S_8$ found:1159.1963 $(M+Na)^+$; calculated: 1159.1961

IR (cm^{-1}): 3323, 2946, 2830, 1019.

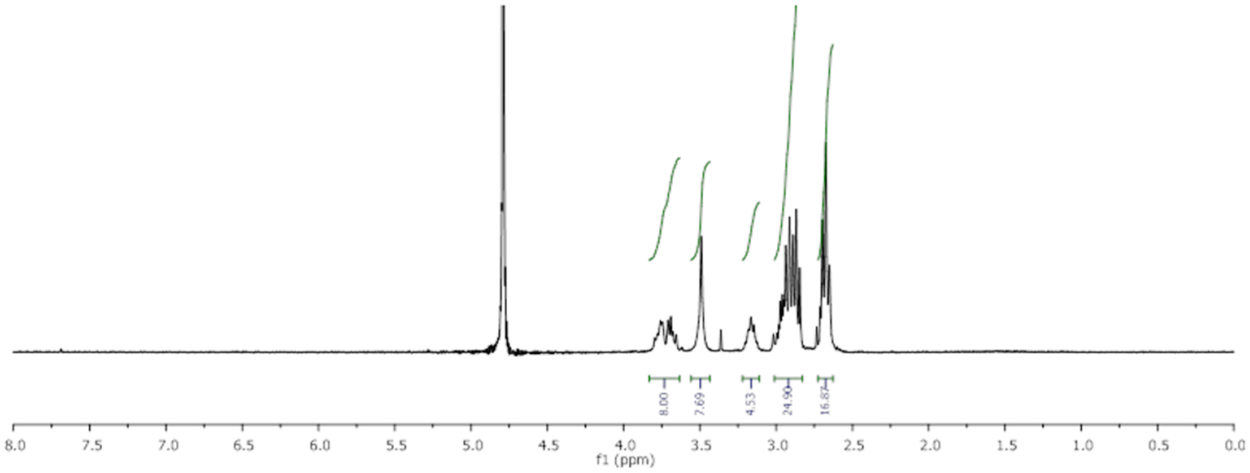


Figure S19 ^{1}HNMR spectrum of compound **2b** (D_2O, 300 MHz)

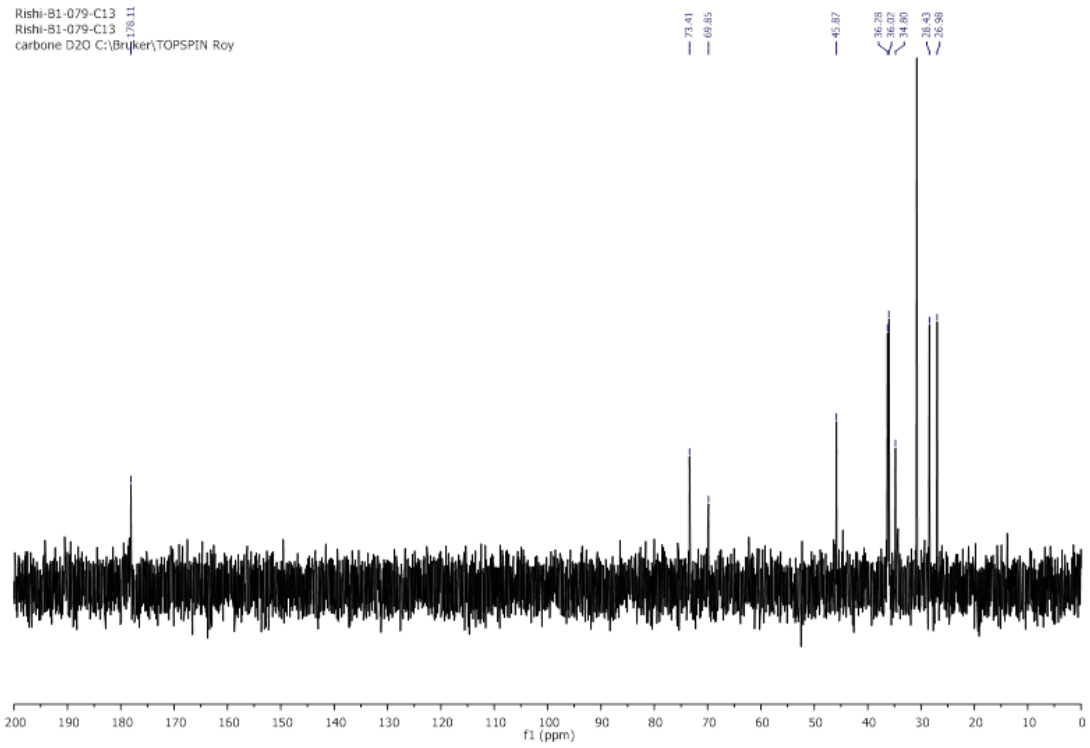


Figure S20 ^{13}C NMR spectrum of compound **2b** (D_2O, 75 MHz)

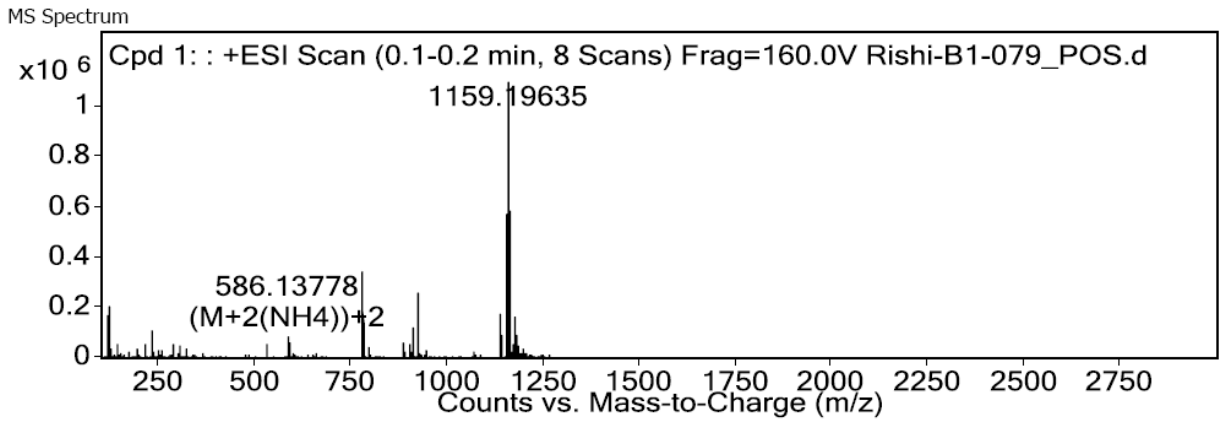


Figure S21 HRMS analysis (ESI^+) for compound **2b**

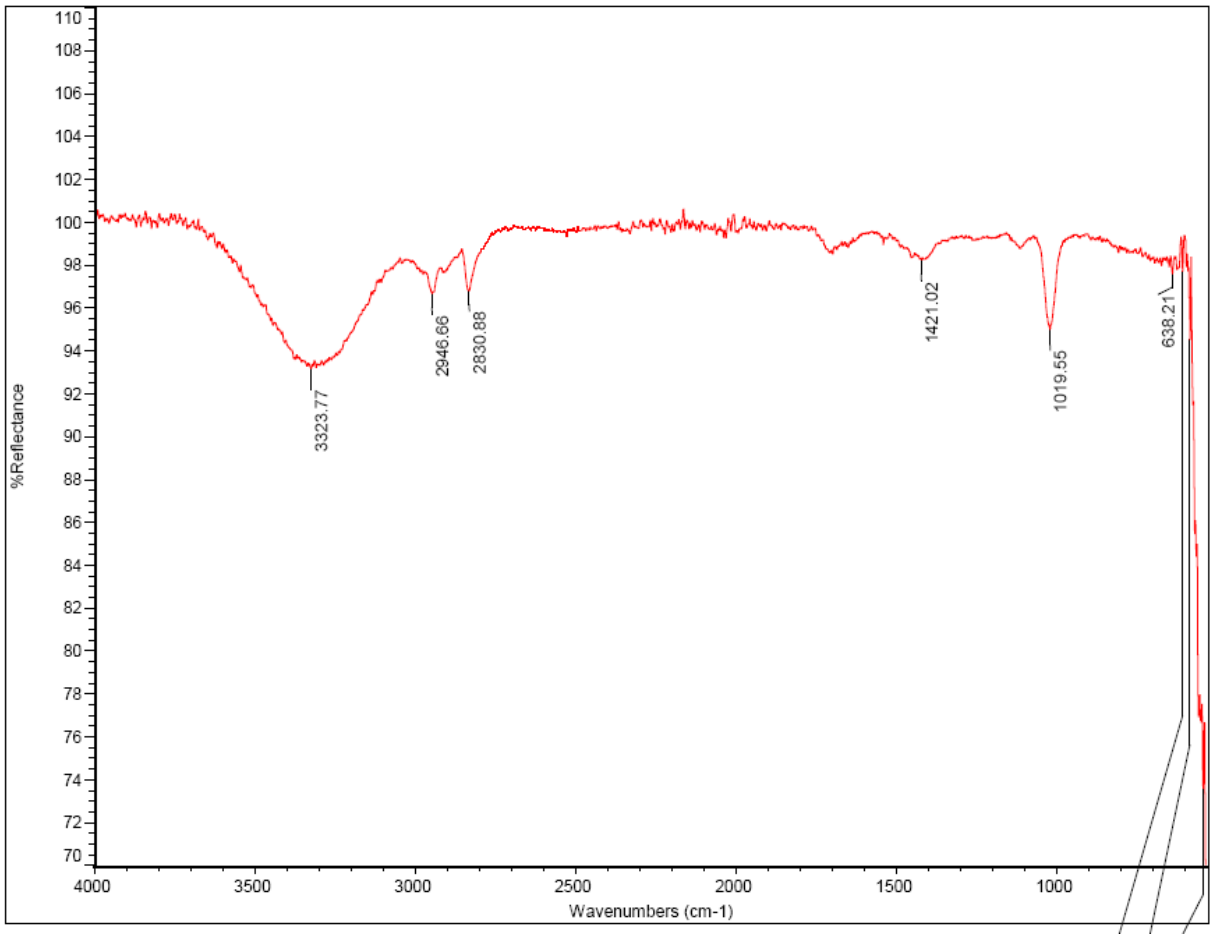
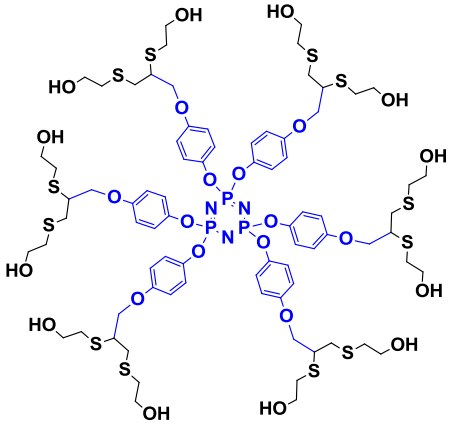


Figure S22. IR spectrum of compound **2b**



Synthesis of compound 3a:

Hexapropargylated P_3N_3 core **(3)** (100 mg, 0.0983 mmol, 1.0 eq.) 2-mercaptoethanol **(**0.413 ml, 5.89 mmol, 10 eq. per site) and AIBN (0.1 mmol, 15mg) were dissolved in methanol (2ml) and heated together at 70^{o}C in a sealed tube for 10 hrs. Solvent was evaporated and crude mixture was washed with diethylether. The crude mixture was dissolved in minimum amount of methanol followed by dilution with water and placed in a dialysis bag of 1000 molecular weight cut-off. Dialysis was performed for 5-6 hrs and finally lyophilization afforded the compound **3a**, **yield: 83%**.

^{1}H NMR (300 MHz, CD_3OD) : δ 6.76 (dd, *J* = 20.5, 9.2 Hz,24H, ArH), 4.23 (ddd, *J* = 31.1, 9.7, 5.2 Hz, 12H, Ph-OCH_2), 3.72 (dt, *J* = 11.3, 6.6 Hz, 24H, OH-CH_2), 3.29 – 3.20 (m, 6H, CH), 3.06 – 2.96 (m, 12H, CH-CH_2), 2.83 (t, *J* = 6.6 Hz, 12H, SH-CH_2), 2.72 (t, *J* = 6.6 Hz, 12H, SH-CH_2).

^{31}P NMR (122 MHz, CD_3OD) δ 10.45 (s).

^{13}C NMR (151 MHz, CD_3OD): δ 157.8, 145.5, 123.0, 116.5, 71.3, 63.0, 62.6, 45.9, 36.3, 35.9, 35.2

HRMS (ESI^+-TOF): Calculated for $C_{78}H_{115}N_3O_{24}P_3S_{12}$ [M+H]$^+$: 1956.4467, found: 1956.3749 $(M+NH_4)^+$-(H_2O).

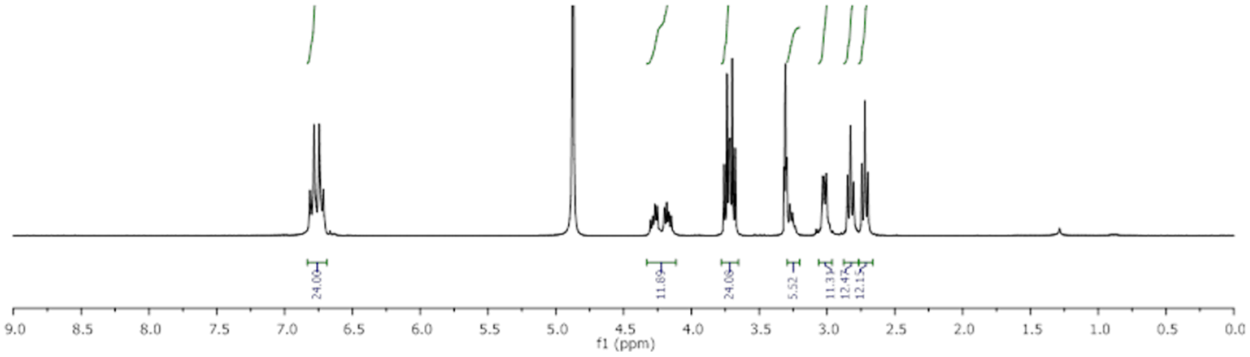


Figure S23. ^{1}HNMR spectrum of compound **3a** (CD_3OD, 300 MHz)

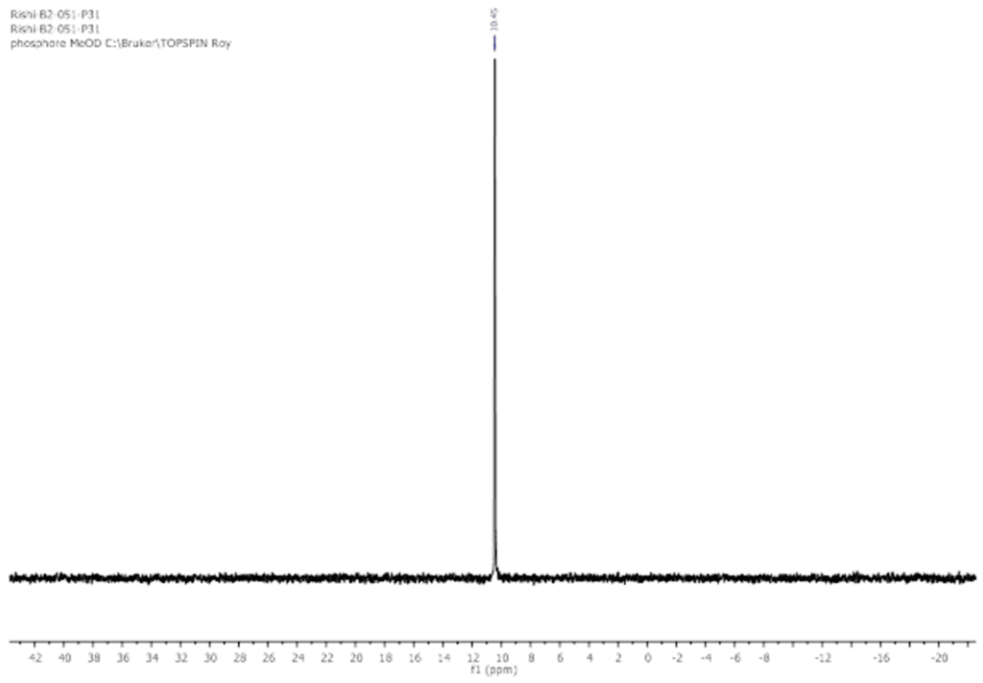


Figure S24. ^{13}P NMR spectrum of compound **3a** (122 MHz, CD_3OD).

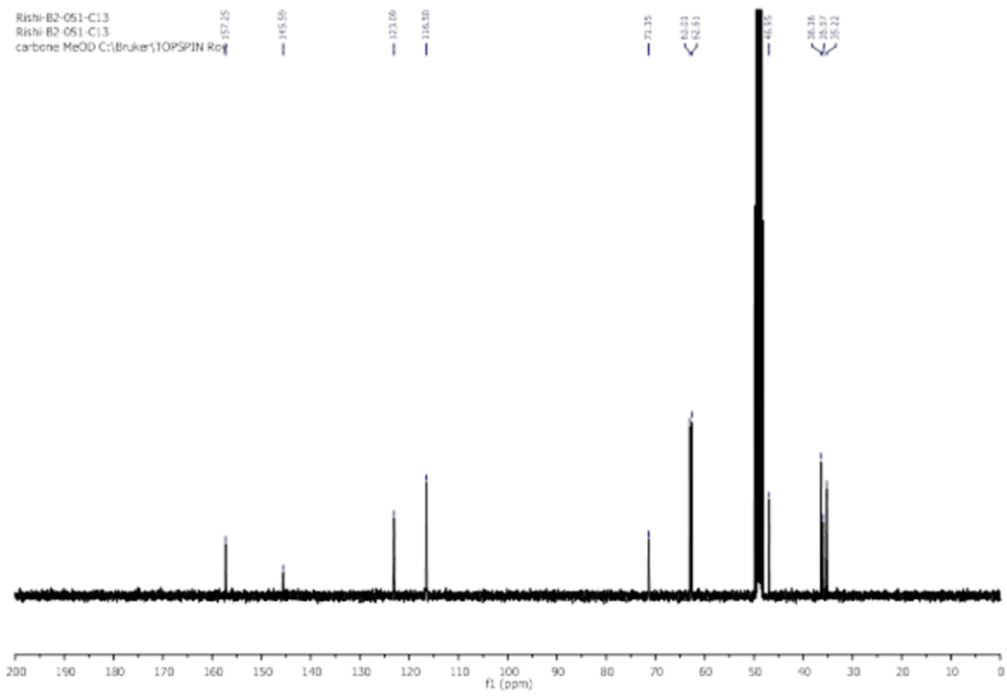


Figure S25 ^{13}C NMR spectrum of compound **3a** (CD_3OD, 75 MHz)

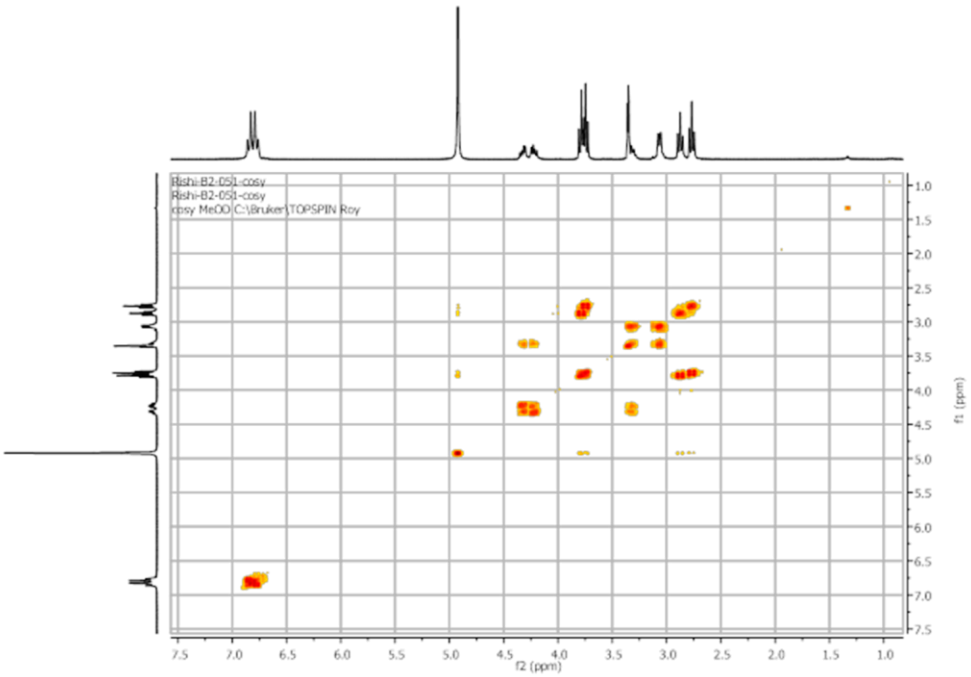


Figure S26. COSY spectrum of compound **3a**

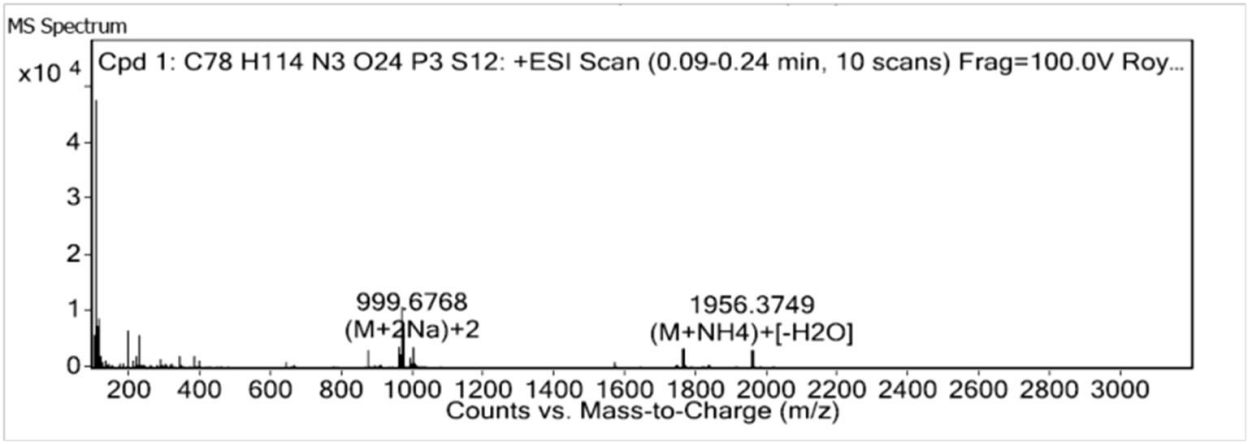
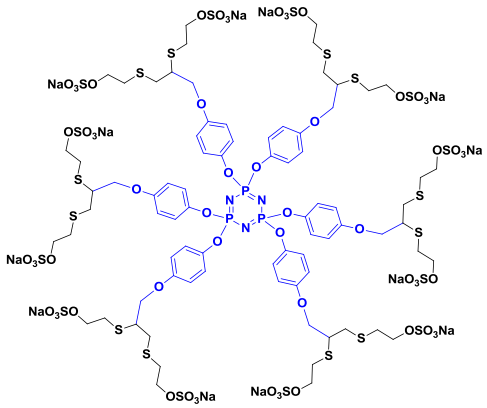


Figure S27. HRMS analysis (ESI^+) for compound **3a**



Synthesis of compound 3d:

Polyhydroxy dendrimer **3a** (100mg, 0.055 mmol) and sulfur trioxide pyridine complex (488mg, 3.06 mmol, 5 eq. per hydroxyl) were reacted together following the procedure **C**. Crude mixture was further purified by dialysis in water using dialysis tubing 1000 molecular weight cut-off. Dialysed product was lyophilized to yield compound **3d**, **yield:** 80%

^{1}H NMR (300 MHz, D_2O) : δ (ppm) 6.93-6.50 (m, 24H), 4.38-3.95 (m, 28H), 3.84-3.52 (m, 6H), 3.40-2.65 (m, 42H).

^{13}C NMR (75 MHz, D_2O): δ (ppm) 122.5, 116.2, 70.4, 68.8, 68.5, 45.6, 36.4, 34.8, 31.9.

^{31}P NMR (122 MHz, D_2O): δ 10.77 (s).

IR (cm^{-1}): 2981, 2937, 2865, 1634, 1500, 1461, 1220, 1188, 1167, 1053, 953, 880, 831.

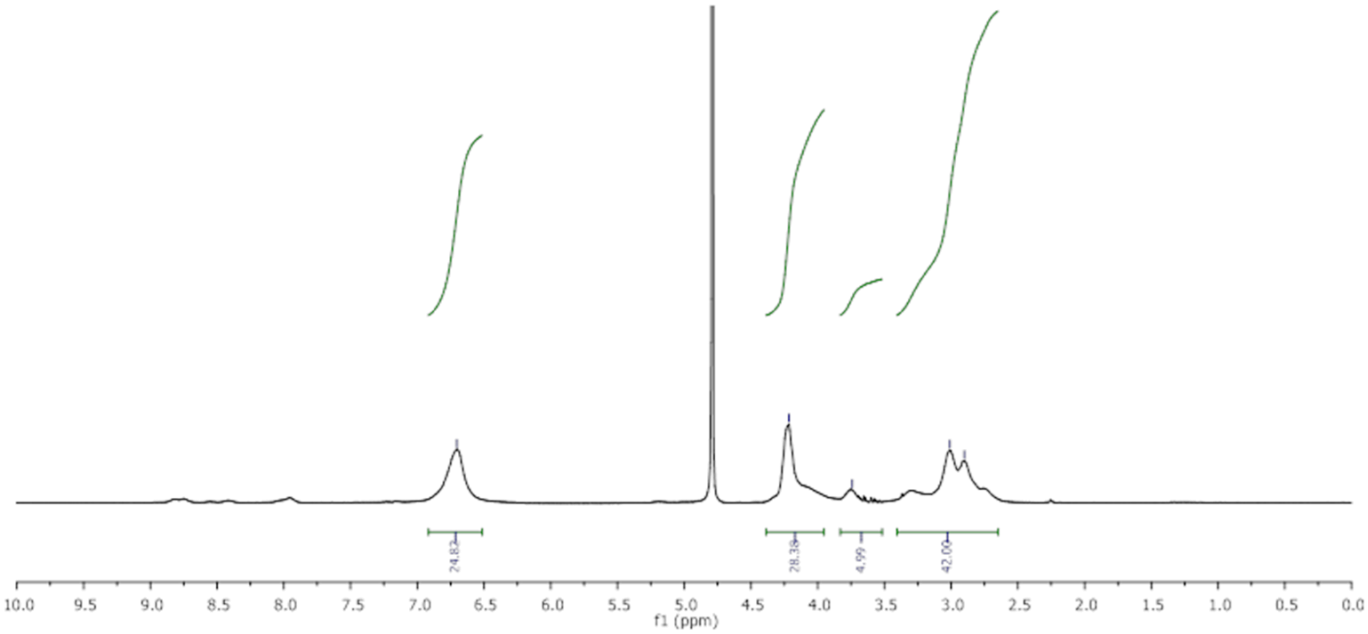


Figure S28. ^{1}HNMR spectrum of compound **3d** (D_2O, 300 MHz)

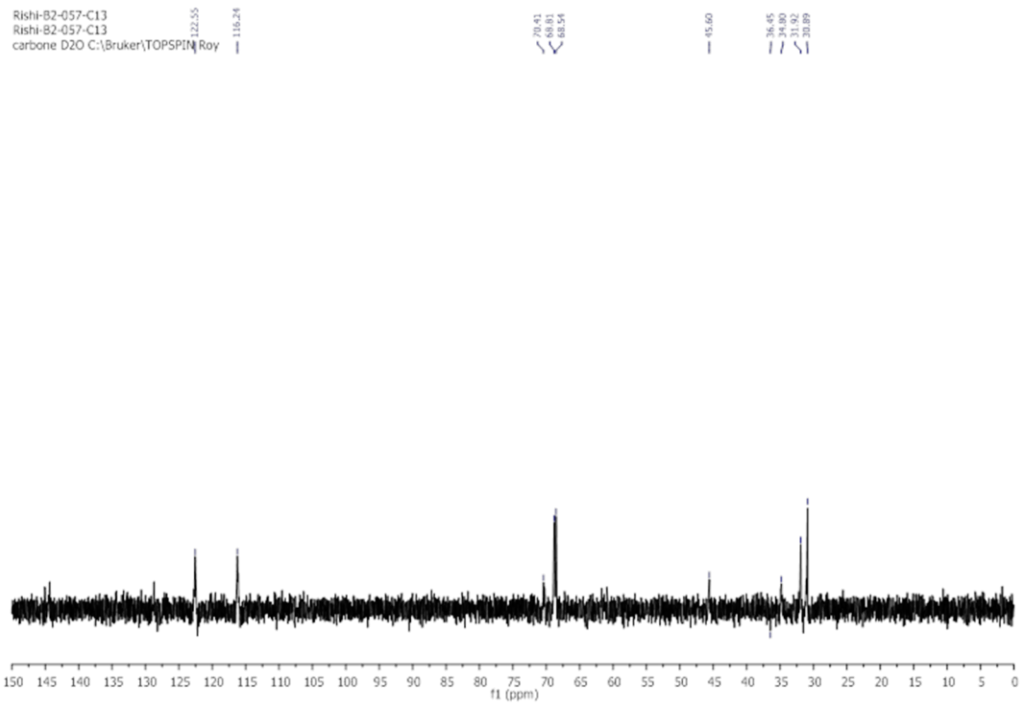


Figure S29. ^{13}CNMR spectrum of compound **3d** (D_2O, 75 MHz)

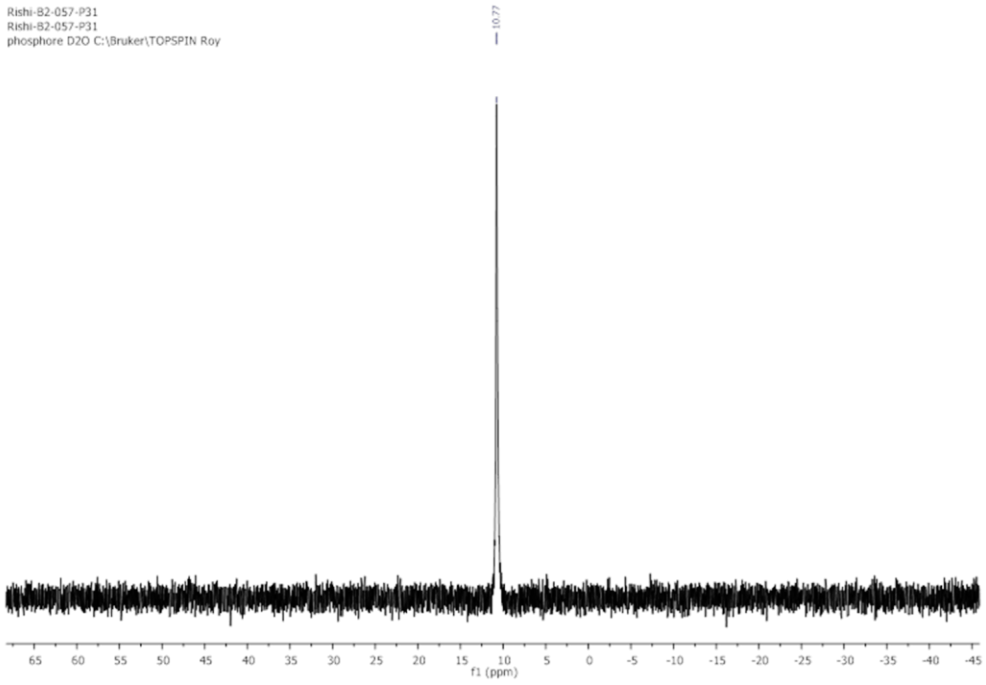


Figure S30. ^{13}PNMR spectrum of compound **3d** (D_2O, 122 MHz)

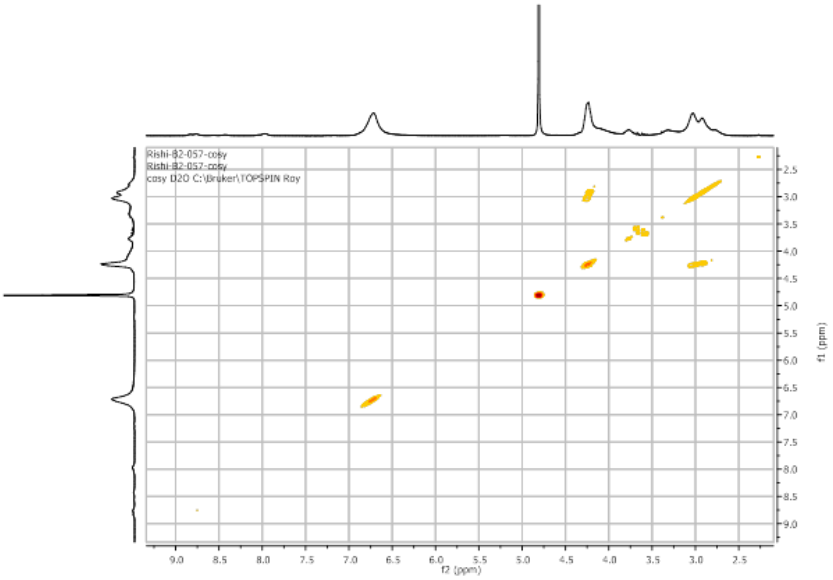


Figure S31. COSY spectrum of compound **3d**

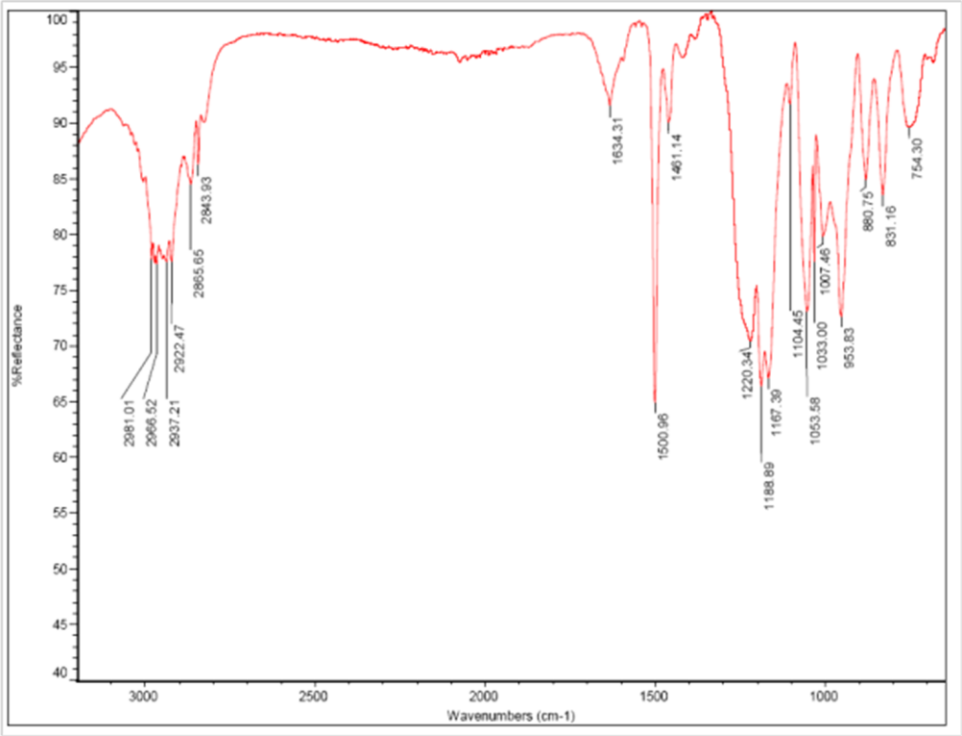
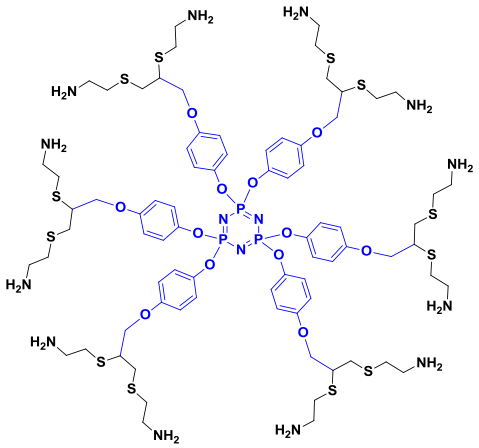


Figure S32. IR spectrum of compound **3d**



Synthesis of compound 3c:

Hexapropargylated P_3N_3 core **(3)** (100 mg, 0.0983 mmol, 1.0 eq.) 2-aminoethanethiol hydrochloride (0.804 mg, 7.0 mmol, 12 eq. per acetylene) and AIBN (0.196 mmol, 13 mg) were dissolved in methanol (2 ml) and heated together at 70^{o}C in a sealed tube for 10 hrs. Solvent was evaporated and crude mixture was washed with diethyl ether. The crude mixture was dissolved in minimum volume of methanol followed by dilution with water and placed in a dialysis bag of 1000 molecular weight cut-off. Dialysis was performed for 8-10 hrs and finally lyophilization afforded the compound **3c**, **Yield: 69%**.

^{1}H NMR (300 MHz, D_2O): δ 6.91 (dd, *J* = 30.9, 8.7 Hz, 24H), 4.42 – 4.28 (m, 12H), 3.49 – 3.38 (m, 6H), 3.28 (dt, *J* = 10.7, 6.8 Hz, 24H), 3.15 – 3.00 (m, 24H), 2.95 (t, *J* = 6.8 Hz, 12H).

^{13}C NMR (75 MHz, D_2O): δ 122.6, 116.6, 70.5, 45.3, 39.7, 39.1, 34.1, 30.0, 28.9.

^{31}P NMR (122 MHz, D_2O): δ 10.59 (s).

HRMS (ESI^{+}-TOF): Calculated for $C_{78}H_{127}N_{15}O_{12}P_3S_{12}$ [M+H]$^{+}$: 1944.6296, found: 972.7893 (M+2)$^{+}$.

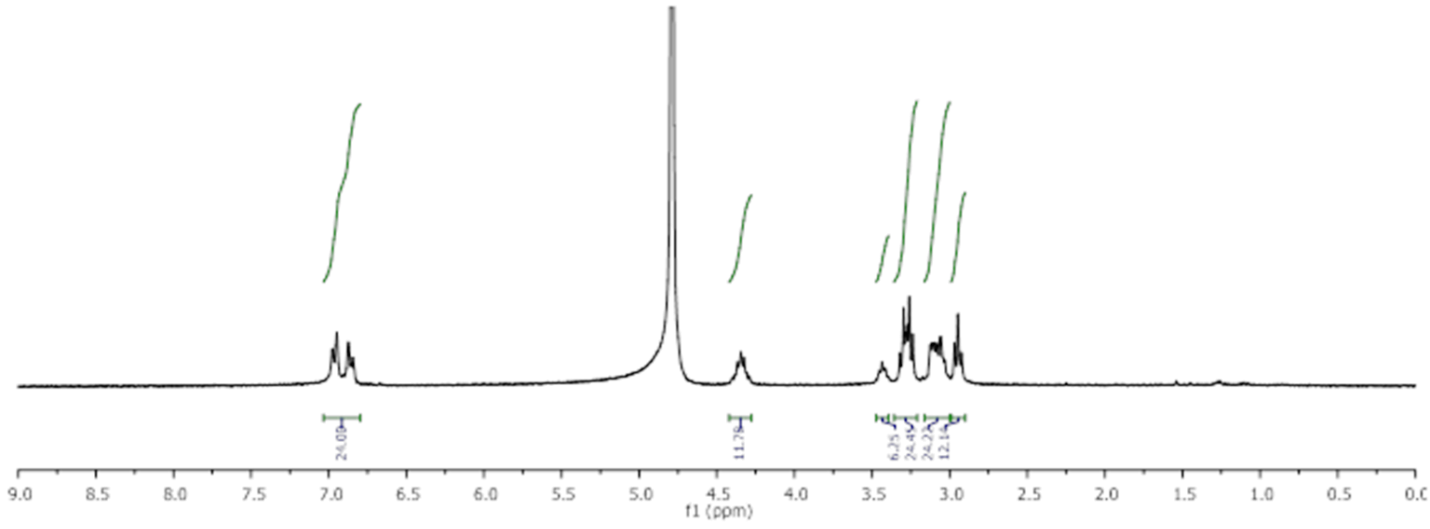


Figure S33. ^{1}HNMR spectrum of compound **3c** (D_2O, 300 MHz)

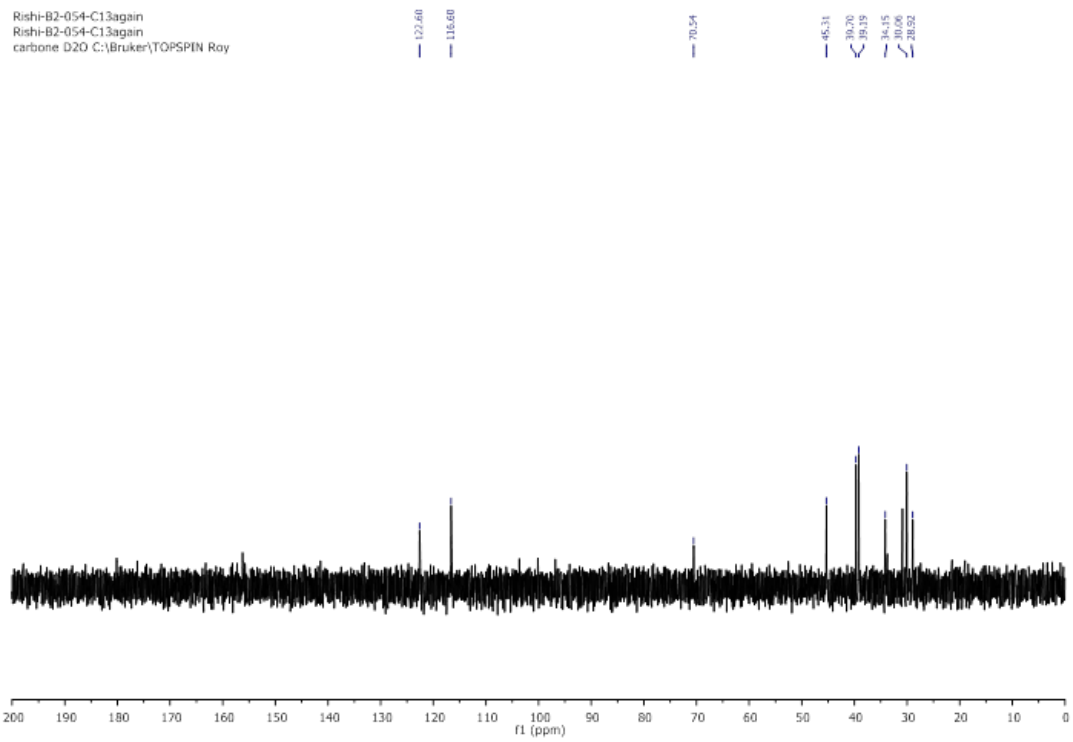


Figure S34. ^{13}CNMR spectrum of compound **3c** (D_2O, 75 MHz)

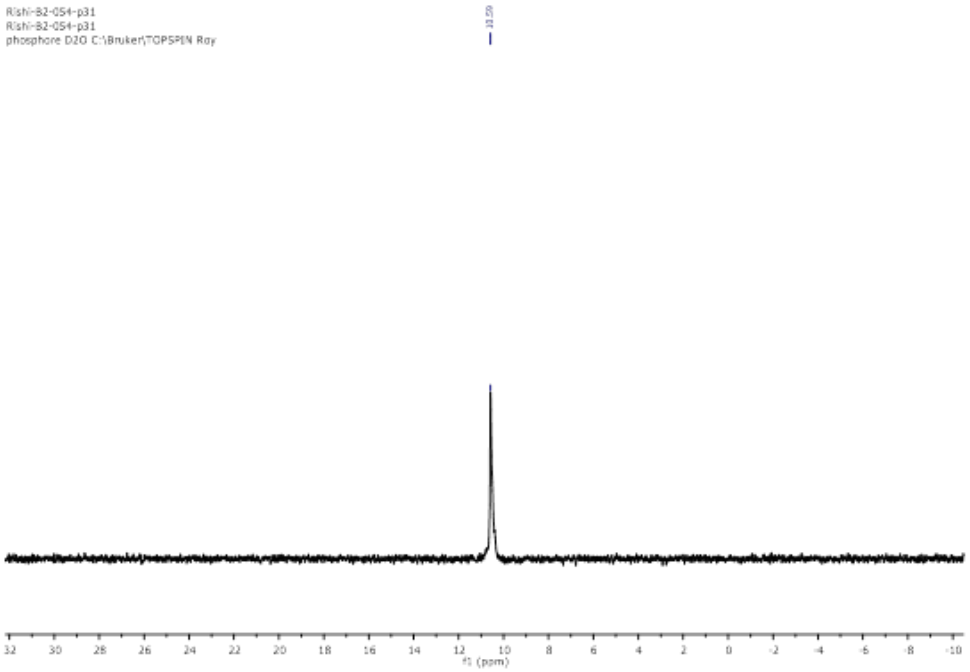


Figure S35. ^{13}PNMR spectrum of compound **3c** (D_2O, 122 MHz)

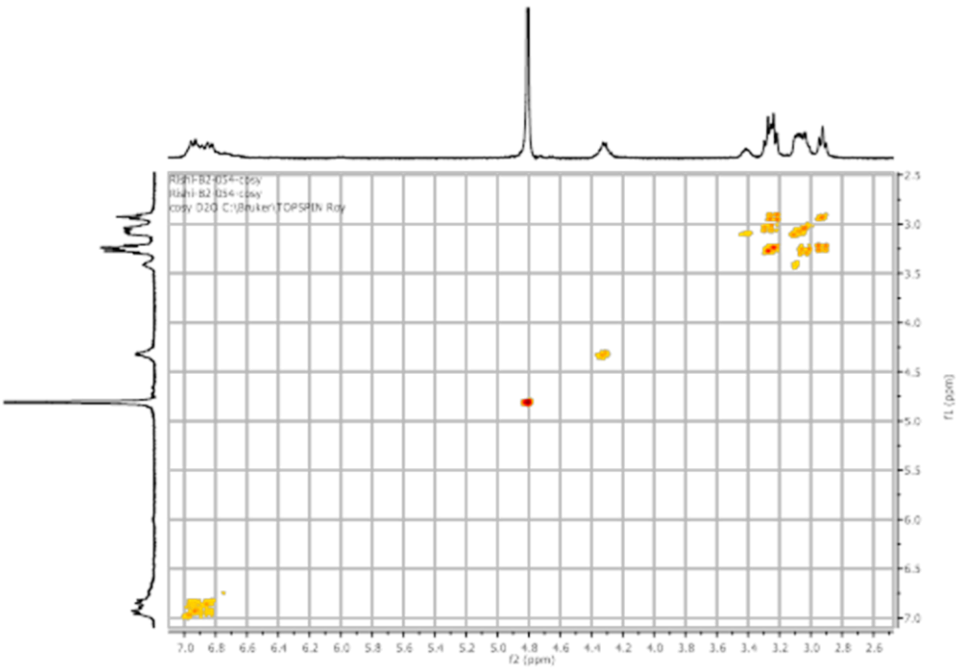
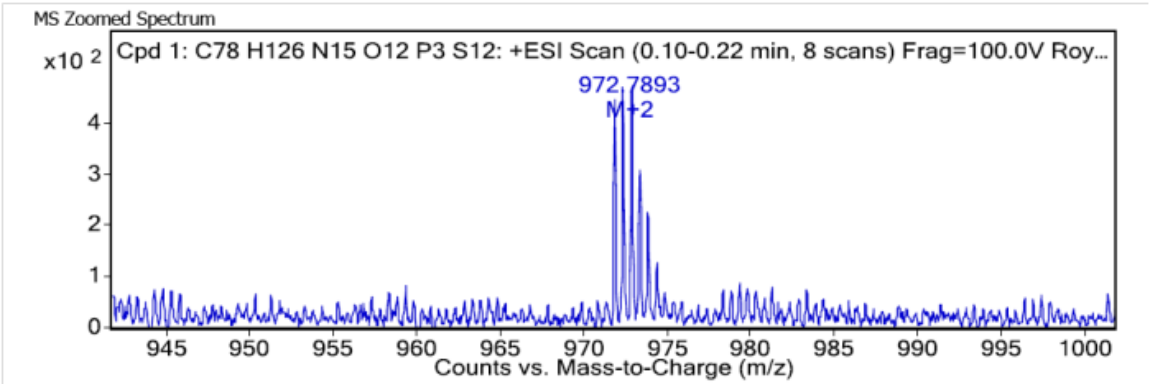


Figure S36. COSY spectrum of compound **3c**



MS Spectrum Peak List

m/z	*Calc m/z*	Diff(ppm)	z	Abund	Formula	Ion
358.1047				1095		
358.5083				15204		
358.7088				14595		
358.9088				14354		
359.1095				9555		
359.3088				5704		
359.5084				2919		
359.7088				1439		
362.1051				1153		
971.7846	971.7783	6.5	2	458	C78 H126 N15 O12 P3 S12	M+2

--- End Of Report ---

Figure S37. HRMS analysis (ESI^+) for compound **3c**

Peptide synthesis, cyclisation purification and characterization: IAPP was synthesised by solid phase peptide synthesis based on Fmoc chemistry and 2-(6-Chloro-1-H-benzotriazole-1-yl)-1,1,3,3-tetramethylaminium hexafluorophosphate (HCTU) coupling strategy using a tribute infrared (IR) synthesizer. Two oxazolidine pseudoproline dipeptide derivatives were incorporated: Fmoc-Ser-Ser($\psi^{Me,Me}$pro)-OH was incorporated at positions Ser-19 and Ser-20 whereas Fmoc-Leu-Ser($\psi^{Me,Me}$pro)-)-OH was inserted at positions Leu-27 and Ser-28[2]. Cleavage from the resin was achieved with a mixture of TFA/ethanedithiol/phenol/water (92/2.5/3/2.5) and after TFA evaporation, the peptide was precipitated with diethylether, washed several times with diethylether, solubilized in 20% acetic acid (v/v) before being lyophilized. Crude IAPP was purified by preparative reversed-phase high performance liquid chromatography (RP-HPLC) using a linear gradient of ACN in H_2O/TFA (0.06% v/v) To increase the solubility, crude IAPP was dissolved in 35% acetic acid (v/v) before being injected on a C18 (5 μm, 100 Å) column (250 x 21.2 mm). Collected fractions were analyzed by analytical RP-HPLC using a C18 (3.6 μm) column (250 mm x 4.6 mm) and a linear gradient of ACN in H_2O/TFA (0.06% v/v). Fractions were also analysed by 'time of flight' mass spectrometry using a LC/MS-TOF (Agilent) to confirm the identity of the peptide. Fractions corresponding to the desired peptide were pooled and lyophilized before cyclisation was performed. Disulfide bond formation between Cys-2 and Cys-7 was achieved by dimethyl sulfoxide (DMSO) oxidation[3]. Purified IAPP was dissolved in 100% DMSO at a final concentration of 2 mg/mL and the sample was gently stirred for 20 hours at room temperature. After incubation, 50% acetic acid (v/v) was added to the peptide mixture to a final ratio of 9:1 (50% acetic acid:DMSO) and IAPP was re-purified by RP-HPLC as above-described. Fractions corresponding to the desired product and with purity higher than 95%, confirmed by analytical RP-HPLC, were finally pooled and lyophilized.

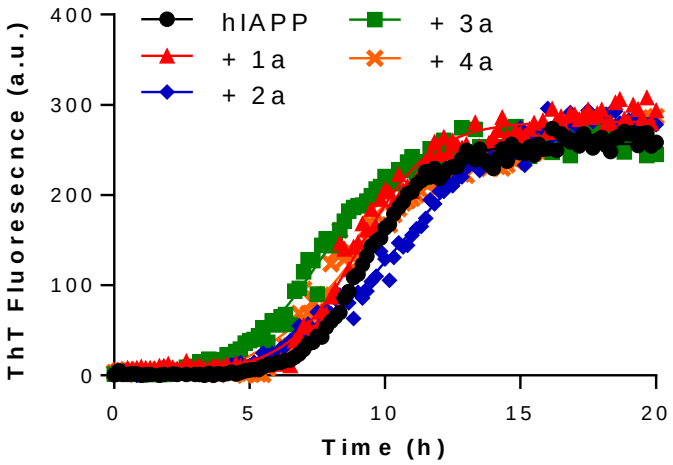


Figure S38. Effects of polyhydroxyl low generation dendrimers on IAPP amyloid fibril formation monitored by ThT fluorescence. IAPP (12.5 μM) was incubated in 20 mM Tris, pH 7.4, at 25°C without agitation in the absence (●) or in the presence of 1 eq. of compound 1a (▲), compound 2a (♦), compound 3a (■) or compound 4a (×). ThT fluorescence was measured every 10 min over the course of 20 h, with excitation at 440 nm and emission at 485 nm.

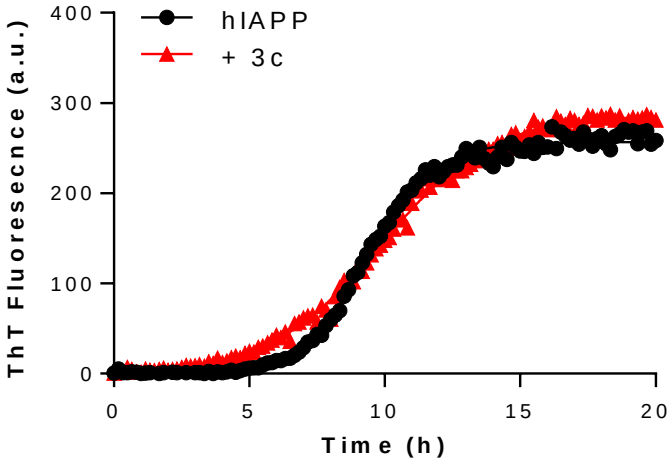
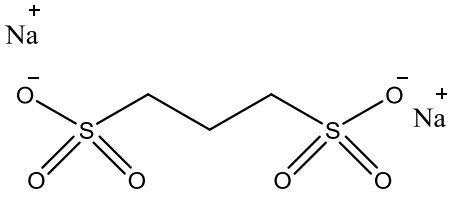


Figure S39. Effect of polyamine G1 dendrimer on IAPP amyloid fibril formation monitored by ThT fluorescence. IAPP (12.5 μM) was incubated in 20 mM Tris, pH 7.4, at 25°C without agitation in the absence (•) or in the presence of 1 eq. of compound 3c (▲). ThT fluorescence was measured every 10 min over the course of 20 h, with excitation at 440 nm and emission at 485 nm.

(A)



(B)

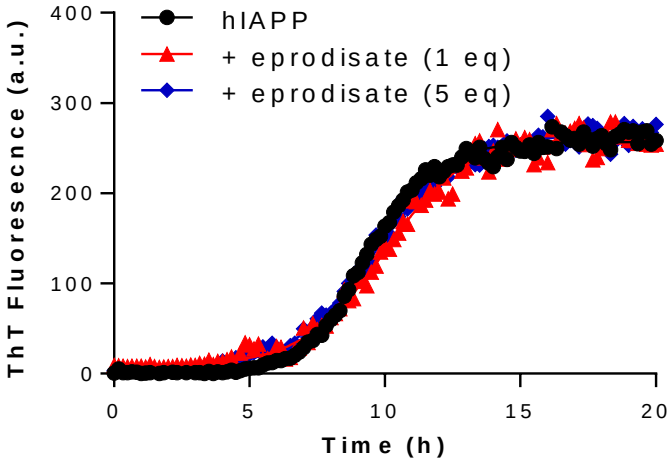


Figure S40. Effect of the glycosaminoglycan mimetic, eprodisate (sodium propane-1,3-disulfonate) on IAPP amyloid fibril formation monitored by ThT fluorescence. (A) Chemical structure of eprodisate. (B) IAPP (12.5 μM) was incubated in 20 mM Tris, pH 7.4, at 25°C without agitation in the absence (•) or in the presence of 12.5 μM (▲) or 62.5 μM (♦) of eprodisate. ThT fluorescence was measured every 10 min over the course of 20 h, with excitation at 440 nm and emission at 485 nm.

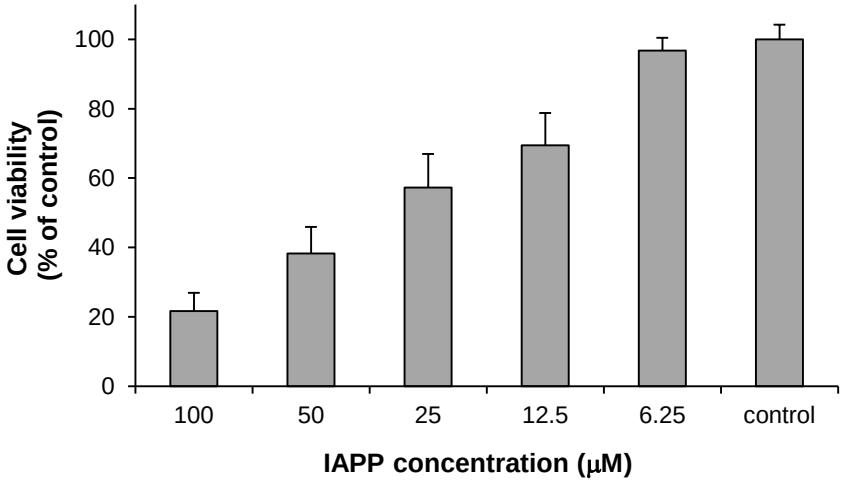


Figure S41. Concentration-effect of IAPP on the viability of INS-1 pancreatic β-cells. INS-1 cells were treated with concentrations of IAPP ranging from 100 to 6.25 μM for 24 h. and cell viability was measured by the resazurin reduction assay and compared to cells treated with vehicle only (100% cell viability).

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2. Abedini, A.; Raleigh, D. P., Incorporation of pseudoproline derivatives allows the facile synthesis of human IAPP, a highly amyloidogenic and aggregation-prone polypeptide. *Organic letters* **2005,** *7* (4), 693-6.

3. Abedini, A.; Singh, G.; Raleigh, D. P., Recovery and purification of highly aggregation-prone disulfide-containing peptides: application to islet amyloid polypeptide. *Analytical biochemistry* **2006,** *351* (2), 181-6.