Supporting Information

Oligo-glycerol based non-ionic amphiphilic nanocarriers for lipase mediated controlled drug release

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1. Experimental section

1.1 Materials

All the chemicals and solvents were purchased from commercially available sources such as Sigma-Aldrich Chemicals, USA, Sisco Research Laboratories (SRL) Pvt. Ltd., India, and Spectrochem Pvt. Ltd., India. Immobilized *Candida antarctica* lipase (Novozym 435) was purchased from Julich Chiral Solution GmbH (Julich, Germany). All the dyes and drugs used for encapsulation were obtained in maximum purity from Fluka Chemie GmbH, (Buchs, Switzerland) and Sigma-Aldrich Chemicals, USA. Silica gel (100-200 mesh) was used for the column chromatography. The solvents used for reactions as well as column chromatography were dried and distilled prior to use. The progress of the reaction was monitored by pre-coated TLC plate (Merck silica gel, $60F_{254}$) and ceric stain was used for visualisation of the spots. The physiochemical characterization and transport analysis were performed using Milli-Q water.

1.2 Methods and Instrumentation

The IR spectra of the samples were recorded using either Perkin-Elmer FT-IR model 9 or Compact FT-IR Spectrometer ALPHA II from Bruker. The UV-Vis spectra (200-800 nm) were recorded on a Cary-300 series UV-Vis spectrophotometer (Agilent technologies). Fluorescence measurements (450-800 nm) were performed on a Cary Eclipse fluorescence spectrophotometer (Agilent Technologies) with a slit width 5 nm. ^{1}H and ^{13}C NMR spectra were recorded on JEOL 400 and 100.5 MHz spectrometer, respectively; the solvent residual peak was used for referencing. The chemical shift values are on δ scale and coupling constant (*J*) values are in Hertz.

1.2.1 Gel permeation chromatography

The molecular weights M_w, M_n and M_z of the synthesized amphiphiles were recorded using Waters GPC system equipped with a Waters 515 HPLC pump, a refractive index detector, using Styragel HR columns, with THF as an eluent at a flow rate of 1.2 mL min^{-1} and molecular weight calibration carried using polystyrene standards.

1.2.2 Critical aggregation concentration (CAC) measurements

The CAC of the diglycerol based amphiphiles was investigated using Cary Eclipse fluorescence spectrophotometer and 'Nile red' as a model dye.[1] For CAC calculation, a stock solution of the dye was prepared at a concentration of 1 mg mL^{-1} (3.14 x 10^{-3} M) in THF. Then 20 µL of stock solution of Nile red was added in each of the 10 sample vials and THF was allowed to evaporate. Meanwhile, a stock solution of amphiphile was prepared in Milli-Q water at a concentration of 1 mM and stirred for 1 h. Two-fold serial dilution of the amphiphilic stock solution was carried out to obtain the different concentrations, which were then transferred to the sample vials having a thin dry film of Nile red and kept for overnight stirring.[2] The solution was filtered through 0.45 µm polytetrafluoroethylene (PTFE) filter to remove non-encapsulated dye and fluorescence measurements were made. The plot of fluorescence intensity maxima values against log [amphiphile concentration] for different samples gives the CAC values.

1.2.3 Dynamic light scattering (DLS) measurements and Transmission Electron Microscopy (TEM)

Malvern Zetasizer Nano ZS Analyser containing thermostated sample chamber having 4 mW He-Ne laser, λ = 633 nm, using back scattering detection (scattering angle $\theta = 173^{o}$) with an avalanche photodiode as a detector, was used for investigating the nanostructures formed in the aqueous solution (Milli-Q water) at a concentration of 5 mg mL^{-1} well above their CAC values. The measurements were performed using disposable micro BRAND UV-Cuvettes. The DLS samples were prepared by stirring for 24 h and then filtered through 0.45 µm PTFE filter. Measurements were obtained in triplicates with 10 runs per single measurement and their mean values were used. The nanoparticles formed were further analyzed by transmission electron microscopy (TEM) using a TECNAI G2-30 U-TWIN TEM instrument (FEI, Eindhoven, The Netherlands) with an acceleration voltage of 200 kV. The sonicated aqueous solution of the sample was drop-coated and dried onto formvar-coated 200 mesh copper grids (Ted Pella, USA) and analyzed by TEM.

1.2.4 Drug/Dye encapsulation and quantification

Nile red and nimodipine encapsulation was performed by the thin film method, using UV-vis and fluorescence spectrophotometer.[2] The study was carried out by taking 5 mg of amphiphile in 1 mL of water, and 0.12 mg Nile red and 4 mg nimodipine were taken in two separate vials and each dissolved in 1 mL of THF. After evaporation of THF a thin layer of dye/drug was formed and then 1 mL of aqueous solution of amphiphile was added to it. Then the solution was kept for stirring at room temperature for 24 h and then free dye/drug was filtered through 0.45

μm PTFE filter and the fluorescence and UV-vis measurements were carried out. Then the encapsulated dye and drug samples were lyophilized and re-dissolved in a known quantity of anhydrous methanol (Nile red) or anhydrous ethanol (Nimodipine) and the absorption spectrum recorded (220-800 nm) using standard disposable PMMA UV-vis cuvettes with a path length of 1 cm from PLASTIBRAND. The fluorescence spectra were recorded using a variable slit system from 575 to 800 nm and excitation wavelength of 550 nm for Nile red. Origin 8 software was used for data analysis.

1.2.5 Cytotoxicity study and confocal laser scanning microscopy (CLSM)

Cytotoxicity of the compounds was analysed by the Cell Counting Kit 8 (CCK-8) from Sigma-Aldrich Chemie GmbH (Taufkirchen, Germany) according to the manufactures' instructions. In short, HeLa cell lines (DSMZ no.: ACC 57) cultured in DMEM medium supplemented with 2% glutamine, 100 U/mL penicillin, 100 μg/mL streptomycin (all from Gibco BRL, Eggenstein, Germany), and 10% fetal calf serum (Biochrom AG, Berlin, Germany) and incubated overnight at 37 °C and 5% CO_2. Then, compounds were added in serial dilutions. SDS (1%) and PBS treated cells served as a control. For background subtraction, wells without cells but only sample were used. Cells were incubated for another day at 37 °C before the CCK-8 solution was added. After approximately 2 h, absorbance was measured at a measurement wavelength of 450 nm and a reference wavelength of 650 nm with a Tecan plate reader (Infinite® PRO 200, TECAN-reader Tecan Group Ltd., Männedorf, Switzerland). Measurements were done in triplicates and repeated three times. The cell viability was calculated by setting the non-treated control to 100% and the non-cell control to 0% after subtracting the background using the GraphPad Prism software.

For cLSM, HeLa cells were seeded in 8-well ibidi μ-slides (27.000 cells/well) in (DMEM). After 1 day, the compounds were added at a final sample concentration of 0.5 mg ml^{-1} and the cells were grown for another day. Cell nuclei were stained with 1μg/ml Hoechst 33342 (Life Technologies GmbH, Darmstadt, Germany). Confocal images were taken with an inverted confocal laser scanning microscope Leica DMi 6000 CSB SP8 (Leica, Wetzlar, Germany) with a 63x 1.4 HC PL APO CS2 oil immersion objective using the manufacturer's given LAS X software.

1.2.6 Enzyme triggered release study

The enzyme-responsive behaviour of the synthesized amphiphiles was studied using fluorescence measurements using Nile red as a model dye. The encapsulated sample was prepared by the similar procedure as used in quantification. After removing the non-encapsulated dye through 0.45 μm PTFE filter, few drops of *n*-butanol for trapping the acid liberated from

ester hydrolysis of the amphiphile, and 200 wt. % of the Novozym 435 were added. The final solution was incubated at 37 ^{o}C and 200 rpm under dark conditions.

1.3 Synthetic procedures

Non-ionic mPEG and diglycerol based amphiphiles were synthesized *via* Cu (I) catalysed Huisgen 1, 3-dipolar cycloaddition reaction (**Scheme 3**). The hydrophobic and hydrophilic units, in turn, were synthesized by following **Schemes 1** and **2** depicted in the manuscript.

1.3.1 Synthesis of 4,4'-(oxybis(methylene))bis(2,2-dimethyl-1,3-dioxolane) (**1**)

To synthesize protected diglycerol, in a round bottom flask solketal (10 g, 75.67 mmol) was dissolved in DCM (70 mL) and then triethyl amine (2.5 equiv, 19.12 g, 189.16 mmol) was added and stirred, then mesyl chloride (1.5 equiv, 12.93 g, 113.5 mmol) was added drop-wise in ice cold conditions and stirred for 2 h. After completion of the reaction water (100 mL) was added in the reaction mixture and then compound was extracted with DCM (3 x 100 mL). The combined organic layer was dried over anhydrous sodium sulphate and evaporated *in vacuo* to obtain the mesylated solketal. Then further reaction of this this mesylated solketal (15.9 g, 1.2 equiv) with solketal (8.3 g, 1.0 equiv) in toluene at 70 ^{o}C for 40 h using potassium hydroxide (5.28 g, 1.5 equiv) as a base and TBAB (2.4 g, 10 wt. %) as a phase transfer catalyst. Reaction was monitored on thin layer chromatography (Ethyl acetate : Petroleum ether) and after completion of the reaction, toluene was evaporated and reaction mixture was extracted with ethyl acetate (3 × 100 ml) and then crude compound was obtained by evaporation of solvent. The compound was purified by column chromatography using silica gel (100-200 mesh) (Ethyl acetate : Petroleum ether) and the compound was obtained in 70 % yield as a viscous liquid.

1.3.1.1 Compound **1** was obtained as a viscous liquid in 70 % yield by the following general procedure; IR ($CHCl_3$) υ: 2986, 2877, 1374, 1212, 1049, 842 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ): 1.33 (6 H, s, H-a), 1.39 (6 H, s, H-b), 3.45-3.60 (4 H, m, H-6a & H-5a), 3.68-3.73 (2 H, m, H-6b), 4.00-4.04 (2 H, m, H-5b), 4.22-4.28 (2 H, m, H-4); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 25.44 (CH_3-a) , 26.83 (CH_3-b), 66.71 (C-6), 72.65 (C-5), 74.74 (C-4), 109.51 (C-2).

1.3.2 Synthesis of 3,3'-oxybis(propane-1,2-diol) (**2**)

Diglycerol (**2**) was synthesized in 95 % yield by the hydrolysis of protected diglycerol by using Dowex 50WX8. Compound (**1**) (10 g) was dissolved in methanol (100 mL) and then Dowex 50wx8 (5.0 g) was added to it. Then reaction mixture was stirred for 12 h at 50 ^{o}C. After completion of the reaction Dowex was filtered off and methanol was evaporated on rotary-evaporator.

1.3.2.1 Compound **1** was hydrolysed to give compound **2** as a viscous liquid in 95 % yield by the following general procedure; IR (CH_3OH) υ: 3301, 2941, 2830, 1020 cm^{-1}; ^1H NMR (400 MHz, D_2O, TMS, δ): 3.33-3.50 (8 H, m, H-1, H-3), 3.71-3.76 (2 H, m, H-2); ^{13}C NMR (100.5 MHz, D_2O, TMS, δ): 62.49 (C-1), 70.39 (C-2), 71.99 (C-3).

1.3.3 Synthesis of 2,6-dihydroxyheptane-1,7-diyl diacetate **(3)**

The dihydroxy compound **3** was obtained *via* chemo-enzymatic pathway using commercially available vinyl acetate and a lipase Novozym 435. Compound **2** (5.0 g, 1.0 equiv) was taken in round bottom flask and then enzyme (1.5 g, 10 wt. %) and vinyl acetate (6.93 mL, 2.5 equiv) were added and reaction was stirred in incubator shaker at 35 ^oC for 12 h. After completion of the reaction, Novozym 435 was filtered off and the compound was purified by column chromatography using silica gel (100-200 mesh) (chloroform: methanol) and the compound was obtained in 70 % yield as a viscous liquid.

1.3.4 Synthesis of diethyl 4,4'-((oxybis(1-acetoxypropane-3,2-diyl))bis(oxy))dibenzoate **(4)**

To a stirred solution of compound **3** (1.0 g, 3.9 mmol), ethyl,4-hydroxybenzoate (1.45 g, 8.8 mmol) and triphenylphosphine (2.62 g, 10.0 mmol) in anhydrous THF (20 mL), DIAD (1.78 g, 8.8 mmol) in THF (5 mL) was added dropwise. The reaction mixture was stirred for 15 h at 40 °C. The progress of the reaction was monitored by TLC (ethyl acetate/petroleum ether, 1:1, *v*/*v*). After completion of the reaction, the reaction mixture was concentrated under reduced pressure and the desired compound was extracted with ethyl acetate (3 × 40 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuuo. The obtained crude product was purified through column chromatography using petroleum ether/ethyl acetate to give the desired compound **4** in 70 % yield.

1.3.5 Synthesis of diethyl 4,4'-((oxybis(1-hydroxypropane-3,2-diyl))bis(oxy))dibenzoate **(5)**

The title compound **5** was synthesized as a viscous liquid in 65% yield. Compound **4** (2.0 g, 1.0 equiv) was hydrolyzed by K_2CO_3 (2.52 g, 5.0 equiv) in the ethanol as a solvent. The reaction was stirred for 12 h at 25 ^oC. On completion of the reaction, the ethanol was evaporated under reduced pressure and the desired compound was extracted with chloroform (3 x 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuuo. The obtained crude product was purified through column chromatography using chloroform/methanol to give the desired compound **5**.

1.3.6 Synthesis of compound **6** and **7**

Compound **5** (2.0 g, 1.0 equiv) was complete hydrolyzed by KOH (0.97 g, 4 equiv) in ethanol (70 mL). The reaction mixture was stirred for 12 h at 80 ^oC. After completion of the reaction the

reaction mixture was neutralized by 2 N HCl to yield compound **6**. Considering 100 % yield the compound **6** (1.75 g, 1.0 equiv) was dissolved in DMF (50 mL) and then K_2CO_3 (3.0 g, 5.0 equiv) was added to it and stirred for half an hour. Then propargyl bromide (1.12 mL, 3 eq.) was added to the reaction mixture and the reaction was stirred for 12 h at 50 ^oC. The progress of the reaction was monitored on TLC. On completion of the reaction, the reaction mixture was concentrated under reduced pressure and the desired compound was extracted with chloroform (3 × 100 mL). The combined organic layer was dried over anhydrous Na_2SO_4 and concentrated in vacuuo. The obtained crude product was purified through column chromatography using chloroform/methanol to give the desired compound **7**.

1.3.6.1 Compound **6** was propargylated using propargyl bromide and give compound **7** as a viscous liquid in 70 % yield by the following general procedure; IR ($CHCl_3$) υ: 3459, 3289, 2918, 2860, 2123, 1756, 1608, 1511, 1461, 1352, 1285, 1253, 1107, 948, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, δ): 2.44 (2 H, broad, OH), 2.51 (2 H, t, ^4J(H,H) = 4Hz, H-3''), 3.87-3.92 (8 H, m, H-1' & 3'), 4.48-4.56 (2 H, m, H-2'), 4.88 (4 H, d, ^4J(H,H) = 4 Hz, H-1''), 6.97 (4 H, d, $^{Ortho}J$(H,H) = 8.4 Hz, H-3), 7.98 (4 H, d, $^{Ortho}J$(H,H) = 8.3 Hz, H-2); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 52.34, 60.83, 68.95, 70.69, 72.52, 75.01, 77.99, 114.26, 122.30, 132.05, 162.59, 165.38; HRMS: *m/z* $[M + H]^+$ Calculated for $C_{26}H_{26}O_9$: 483.1655; found: 483.2326.

1.3.7 Synthesis of compounds **8** and **9**

To a stirred solution of compound **7** (500 mg, 1.0 equiv), dodecanoic acid/ pentadecanoic acid (456 mg/ 553 mg, 2.2 eq.) in the anhydrous DCM (30 mL), *N*-(3-dimethylaminopropyl)-*N*-ethyl-carbodiimide hydrochloride (EDC.HCl) (495 mg, 2.5 equiv.) followed by 4-dimethylaminopyridine (DMAP) (152 mg, 1.2 equiv.) at 0 ^oC was added. The reaction mixture was stirred at 25 ^oC for 12 h. On completion of the reaction the solvent was evaporated under reduced pressure and the resulting product was extracted with ethyl acetate (3 x 50 mL) and dried over anhydrous sodium sulphate. Removal of solvent and subsequent purification by column chromatography using silica gel (Ethyl acetate: Petroleum ether :: 1: 50). Compound **8**/**9** was obtained in 75% yield as a viscous liquid.

1.3.7.1 The reaction of compound **7** with dodecanoic acid give compound **8** as a yellow viscous liquid by the following general procedure in 75 % yield. IR ($CHCl_3$) υ: 3305, 2923, 2854, 2248, 1716, 1605, 1508, 1461, 1370, 1282, 1249, 1101, 948, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, δ): 0.86 (6 H, t, ^3J(H,H) = 8 Hz, H-l), 1.22 (32 H, bs, H-d – H-k), 1.53-1.56 (4 H, m, H-c), 2.26 (4 H, t, ^3J(H,H) = 8 Hz, H-b), 2.50 (2 H, t, ^4J(H,H) = 2 Hz, H-3''), 3.71-3.74 (4 H, s, H-3'),

4.25-4.29 (4 H, m, H-1'), 4.65-4.69 (2 H, m, H-2'), 4.89 (4 H, d, ^{4}J(H,H) = 2 Hz, H-1''), 6.94 (4 H, d, $^{Ortho}J$(H,H) = 8.7 Hz, H-3), 7.97 (4 H, d, $^{Ortho}J$(H,H) = 8.7 Hz, H-2,); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 14.20, 22.76, 24.91, 29.43, 31.98, 34.95, 52.38, 62.76, 70.67, 74.94, 75.07, 77.97, 115.45, 122.68, 132.00, 162.16, 165.43, 173.60; HRMS: *m/z* $[M + H]^+$ Calculated for $C_{50}H_{70}O_{11}$: 847.4996; found: 847.6331.

1.3.7.2 The reaction of compound **7** with pentadecanoic acid give compound **9** as a yellow viscous liquid by the following general procedure in 75 % yield. IR ($CHCl_3$) υ: 3306, 2924, 2854, 2240, 1717, 1605, 1508, 1461, 1370, 1251, 1169, 1102, 947, 850, 633 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ): 0.86 (6 H, t, ^{3}J(H,H) = 8 Hz, H-o), 1.22-1.24 (48 H, m, H-d – H-n), 1.51-1.59 (4 H, m, H-c), 2.26 (4 H, t, ^{3}J(H,H) = 8 Hz, H-b), 2.50 (2 H, t, ^{4}J(H,H) = 2.9 Hz, H-3''), 3.67-3.79 (4 H, m, H-3'), 4.26-4.32 (4 H, m, H-1'), 4.62-4.75 (2 H, m, H-2'), 4.89 (4 H, d, ^{4}J(H,H) = 2.4 Hz, H-1''), 6.94 (4 H, d, $^{Ortho}J$(H,H) = 8.9 Hz, H-3), 7.97 (4 H, d, $^{Ortho}J$(H,H) = 8.9 Hz, H-2); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 14.24, 22.73, 24.86, 29.33, 29.73, 32.07, 34.31, 52.32, 62.84, 70.82, 75.01, 77.92, 115.42, 122.57, 131.99, 162.09, 165.50, 173.62; HRMS: *m/z* $[M + H]^+$ Calculated for $C_{56}H_{82}O_{11}$: 931.5935; found: 931.5976.

1.3.8 Synthesis of compounds **13** and **14**

To a stirred solution of compound **10** (500 mg), mPEG-350/mPEG-550 acids **(11/12)** (2.2 eq., 3.42/5.40 g) in anhydrous DCM (50 mL), EDC.HCl (2.5 equiv., 2.45 g) followed by DMAP (1.2 equiv., 1.56 g) at 0 ^{o}C was added.[3] Then reaction mixture was stirred at 35 ^{o}C for 12 h. On completion of reaction the solvent was evaporated under reduced pressure and the resulting product was extracted with chloroform (3 × 100 mL) and dried over anhydrous sodium sulphate. Removal of solvent and subsequent purification by column chromatography using silica gel (methanol:chloroform :: 1: 50). Compound **13/14** was obtained in 80% yield as a viscous liquid.

1.3.9 Synthesis of compound **15/16/17/18**

The compound having hydrophilic unit (**13/14**) and hydrophobic unit (**8/9**) (0.5 g, 1 equiv.) were dissolved in DMF in round bottom flask. Then bromotris(triphenylphosphine) copper (I) catalyst (5 mg) and DIPEA were added. The resultant mixture was allowed to stir at 60 ^{o}C for 24 h. On completion solvent was evaporated under reduced pressure and the product was extracted with chloroform (3 x 100 ml) and dried over anhydrous sodium sulphate. Then product was purified by column chromatography using silica gel (100-200 mesh) in 3% methanol in chloroform to get pure compound (**15/16/17/18**).

1.3.9.1 The click reaction of compound **8** with compound **14** gives compound **15** as a yellow viscous liquid in 75 % yield was synthesised by the following general procedure. IR ($CHCl_3$) υ: 2916, 2865, 1744, 1605, 1510, 1456, 1351, 1248, 1095, 946, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, δ): 0.84 (6 H, t, ^3J(H,H) = 6.8 Hz, H-l), 1.21 (32 H, s, H-d – H-k), 1.48-1.59 (4 H, m, H-c), 2.25 (4 H, t, ^3J(H,H) = 7.5 Hz, H-b), 3.36 (12 H, bs, H-11''), 3.48-3.74 (198 H, m, -OCH_2CH_2 of PEG 550 & H-1'b), 3.98 (2 H, d, ^3J(H,H) = 8.3 Hz, H-1'a), 4.06-4.29 (18 H, m, H-8'' & H-10'' & H-3'a), 4.54-4.67 (6 H, m, H-2' & H-7'' & H-3'b), 5.39 (4 H, s, H-6''), 6.79-6.89 (4 H, m, H-3), 7.82-7.88 (4 H, m, H-2), 7.99 (2 H, s, H-5''); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 14.24, 22.62, 24.86, 29.29, 31.83, 33.93, 59.02, 61.58, 62.15, 63.12, 68.32, 70.83, 71.76, 74.93, 115.29,122.84, 124.47, 131.77, 142.65, 161.79, 165.87, 170.21, 173.40; GPC (THF, 1.2 mL min^{-1}): M_w = 3562 g mol^{-1}, M_n = 3440 g mol^{-1}, M_z = 3680 g mol^{-1}, polydispersity index (PDI) = 1.035.

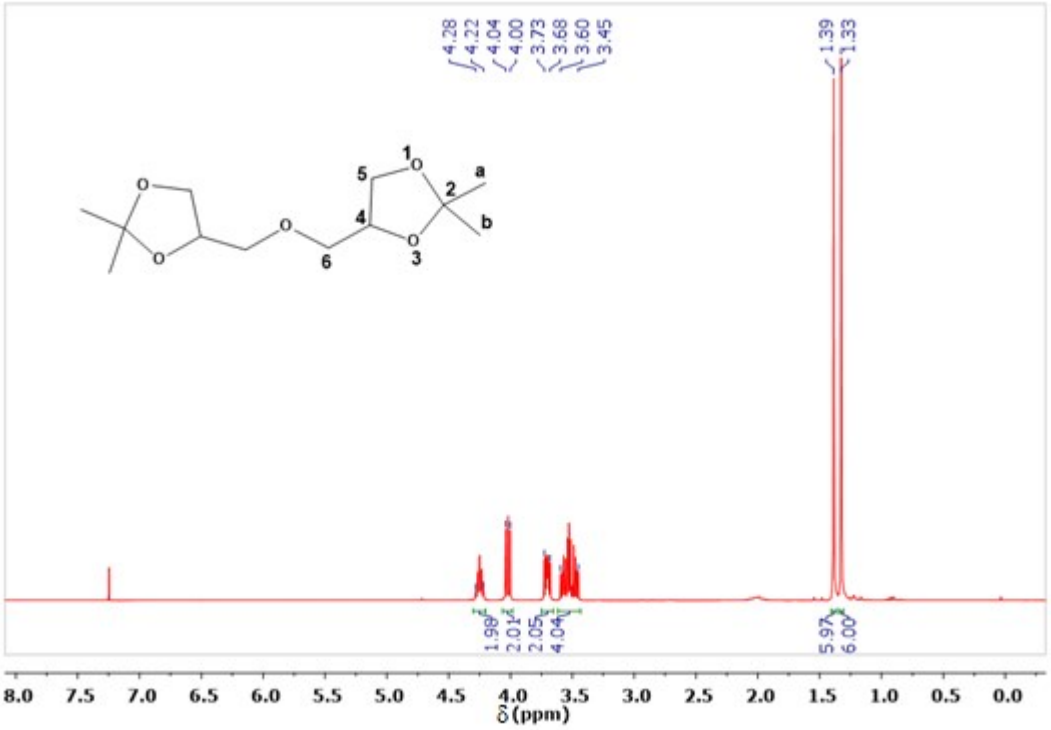
1.3.9.2 The click reaction of compound **9** with compound **14** gives compound **16** as a yellow viscous liquid in 75 % yield was synthesised by the following general procedure. IR ($CHCl_3$) υ: 2918, 2863, 1743, 1605, 1510, 1457, 1352, 1248, 1095, 948, 850 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, δ): 0.83 (6 H, t, ^3J(H,H) = 6.8 Hz, H-o), 1.19 (44 H, s, H-d – H-n), 1.48-1.53 (4 H, m, H-c), 2.22 (4 H, t, ^3J(H,H) = 7.5 Hz, H-b), 3.33 (12 H, s, H-11''), 3.49-3.65 (194 H, m, -OCH_2CH_2 of PEG 550 region & H-1'b), 3.96 (2 H, d, ^3J(H,H) = 8.3 Hz, H-1'a), 4.08-4.21 (18 H, m, H-8'' & H-10'' & H-3'a), 4.58-4.60 (6 H, m, H-7'' & H-2' & H-3'b), 5.37 (4 H, s, H-6''), 6.84 (4 H, d, $^{Ortho}J$(H,H) = 9 Hz, H-3), 7.85 (4 H, d, $^{Ortho}J$(H,H) = 9.2 Hz, H-2), 7.97 (2 H, s, H-4''); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 14.54, 22.75, 24.88, 29.41, 31.97, 34.10, 57.89, 59.09, 61.19, 62.62, 68.48, 70.59, 71.96, 115.40,122.44, 124.59, 131.88, 142.69, 161.90, 165.95, 170.31, 173.56; GPC (THF, 1.2 mL min^{-1}): M_w = 3580 g mol^{-1}, M_n = 3458 g mol^{-1}, M_z = 3700 g mol^{-1}, polydispersity index (PDI) = 1.035.

1.3.9.3 The click reaction of compound **8** with compound **13** gives compound **17** as a yellow viscous liquid in 70 % yield was synthesised by the following general procedure. IR ($CHCl_3$) υ: 2919, 2863, 1741, 1605, 1510, 1458, 1351, 1249, 1097, 948, 851 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$, TMS, δ): 0.84 (6 H, t, ^3J(H,H) = 6.4 Hz, H-l), 1.20 (32 H, s, H-d – H-k), 1.49-1.56 (4 H, m, H-c), 2.24 (4 H, t, ^3J(H,H) = 7.5 Hz, H-b), 3.34 (12 H, s, H-11''), 3.34-3.72 (84 H, m, H = -OCH_2CH_2 of PEG 350 region & H-1'b), 3.97 (2 H, d, ^3J(H,H) = 8.3 Hz, H-1'a), 4.11-4.22 (18 H, m, H-8'' & H-10'' & H-3'a), 4.50-4.59 (6 H, m, H-7'' & H-2' & H-3'b), 5.39 (4 H, s, H-6''), 6.75-6.95 (4 H, m, H-3), 7.83-7.93 (6 H, m, H-2 & H-4''); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 14.20, 22.75, 24.89, 29.15, 29.41, 31.97, 34.10, 59.09, 61.42, 62.62, 68.43, 70.60, 71.97, 115.40, 122.91, 124.89, 131.99, 142.85, 161.91, 166.09, 170.17, 173.56; GPC (THF, 1.2 mL

min^{-1}): M_w = 2429 g mol^{-1}, M_n = 2382 g mol^{-1}, M_z = 2481 g mol^{-1}, polydispersity index (PDI) = 1.019.

1.3.9.4 The click reaction of compound **9** with compound **13** gives compound **18** as a yellow viscous liquid in 70 % yield was synthesised by the following general procedure. IR ($CHCl_3$) υ: 2915, 2868, 1744, 1666, 1607, 1456, 1352, 1249, 1095, 946, 850 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$, TMS, δ): 0.84 (6 H, t, ^3J(H,H) = 6.7 Hz, H-o), 1.21 (44 H, s, H-d – H-n), 1.52-1.55 (4 H, m, H-c) 2.24 (4 H, t, ^3J(H,H) = 7.5 Hz, H-b), 3.35 (12 H, s, H-11''), 3.51-3.70 (93 H, m, -OCH_2CH_2 of PEG 350 region & H-1'b), 3.97 (2 H, s, H-1'a), 4.11-4.24 (18 H, m, H-8'' & H-10'' & H-3'a), 4.60 (6 H, s, H-7'' & H-2' & H-3'b), 5.41 (4 H, s, H-6''), 6.80-6.95 (4 H, m, H-3), 7.87-8.00 (6 H, m, H-2 & H-4''); ^{13}C NMR (100.5 MHz, $CDCl_3$, TMS, δ): 14.18, 22.73, 24.88, 29.40, 31.96, 33.92, 59.02, 61.14, 62.81, 68.31, 70.29, 71.94, 115.42, 122.77, 131.90, 161.93, 166.32, 170.43, 173.56; GPC (THF, 1.2 mL min^{-1}): M_w = 2486 g mol^{-1}, M_n = 2416 g mol^{-1}, M_z = 2556 g mol^{-1}, polydispersity index (PDI) = 1.028.

2. Figures



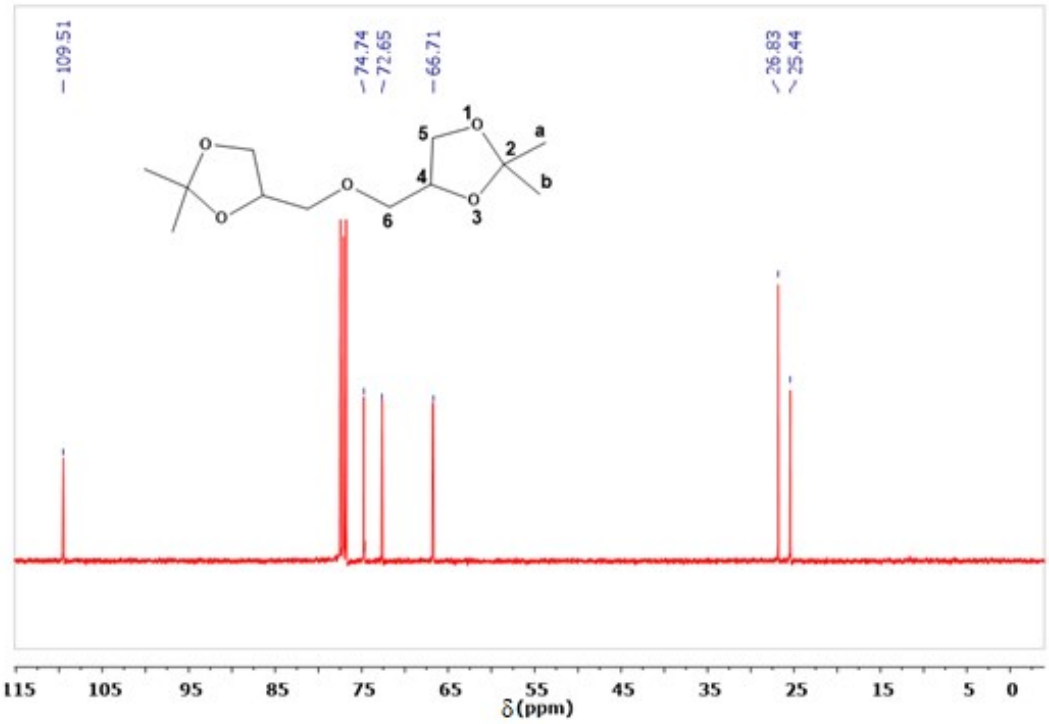
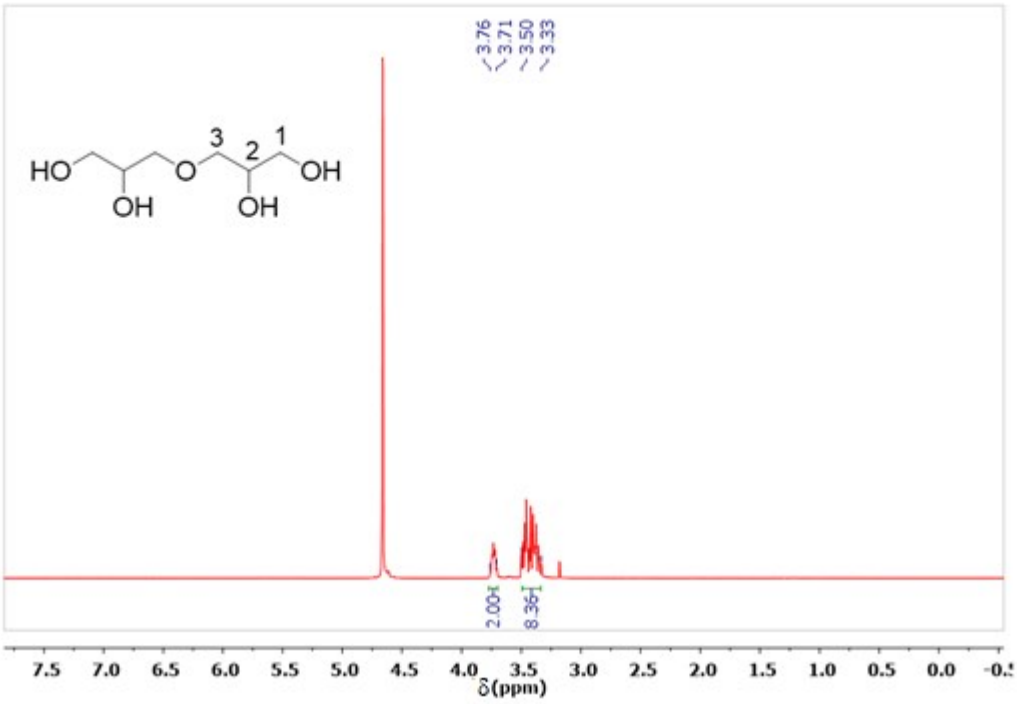


Figure S1. ^{1}H & ^{13}C NMR spectra of 4,4'-(oxybis(methylene))bis(2,2-dimethyl-1,3-dioxolane) **(1)**



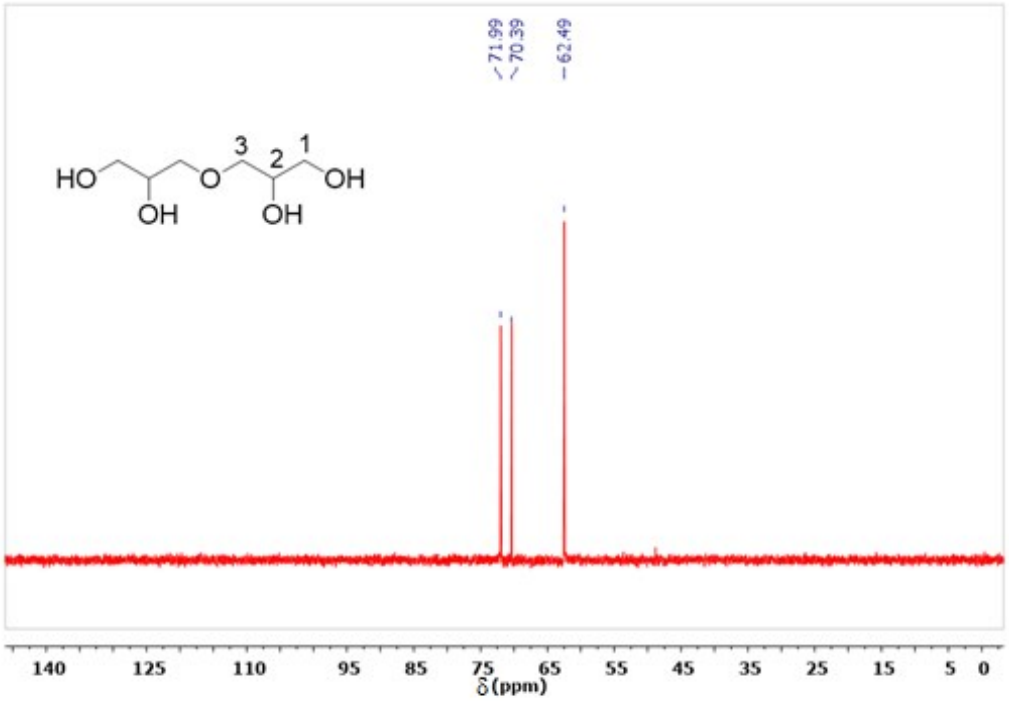
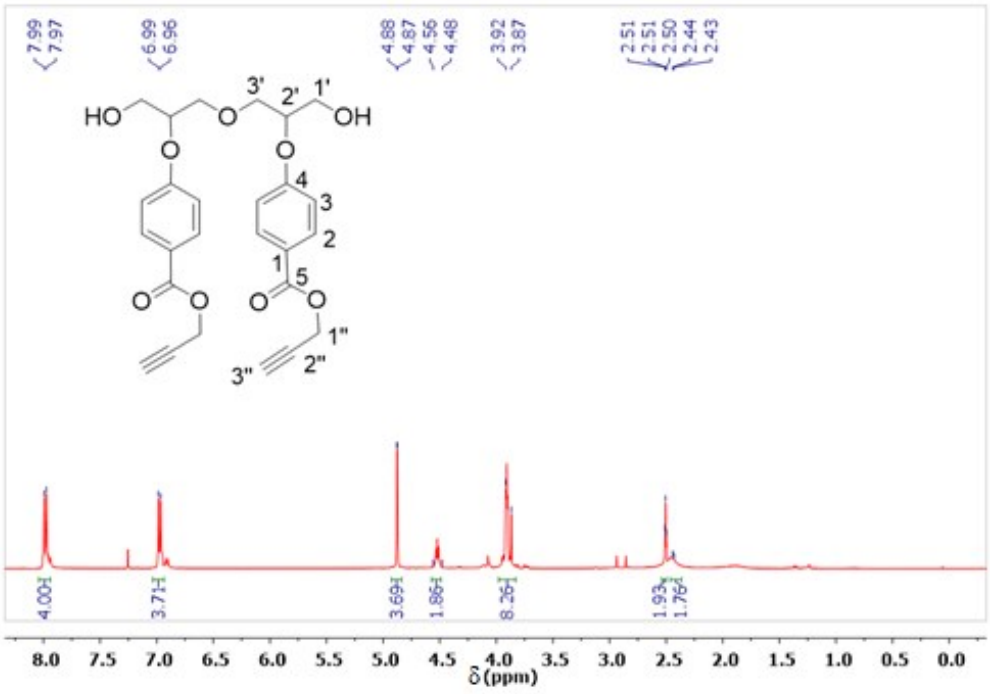


Figure S2. ^{1}H & ^{13}C NMR spectra of 3, 3'-oxybis(propane-1,2-diol) **(2)**



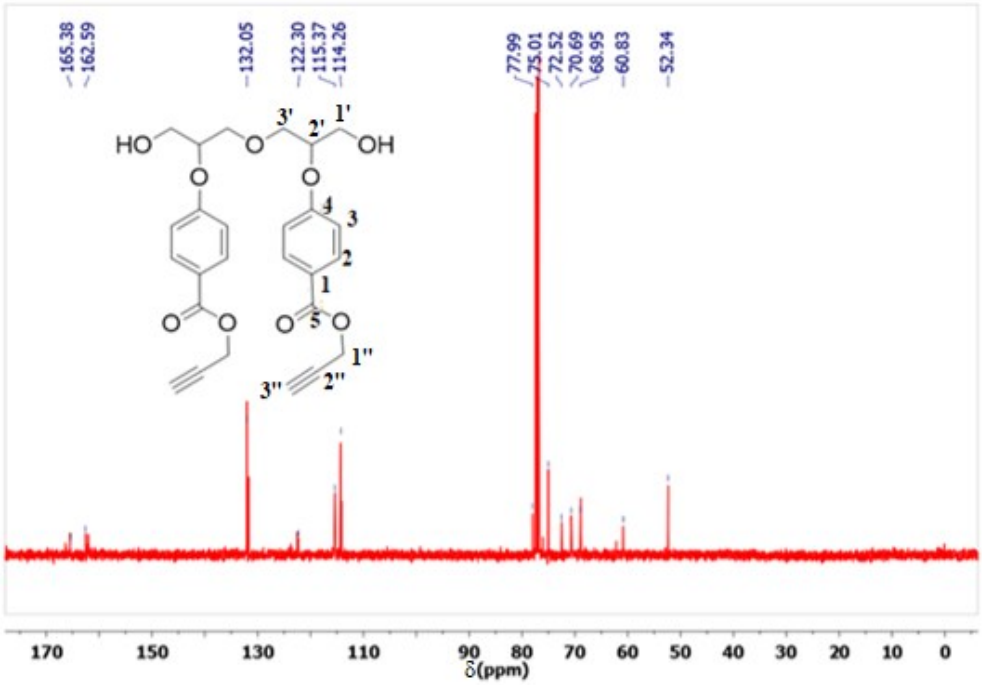
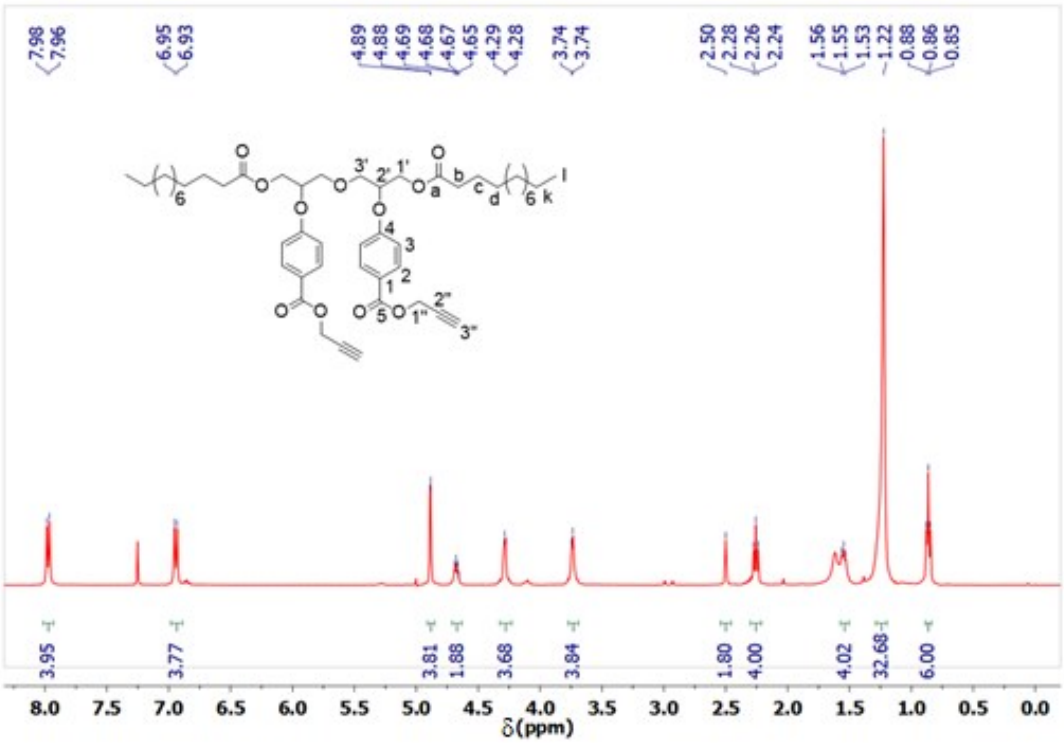


Figure S3. ^{1}H & ^{13}C NMR spectra of di(prop-2-yn-1-yl) 4,4'-((oxybis(1-hydroxypropane-3,2-diyl))bis(oxy))dibenzoate (**7**)



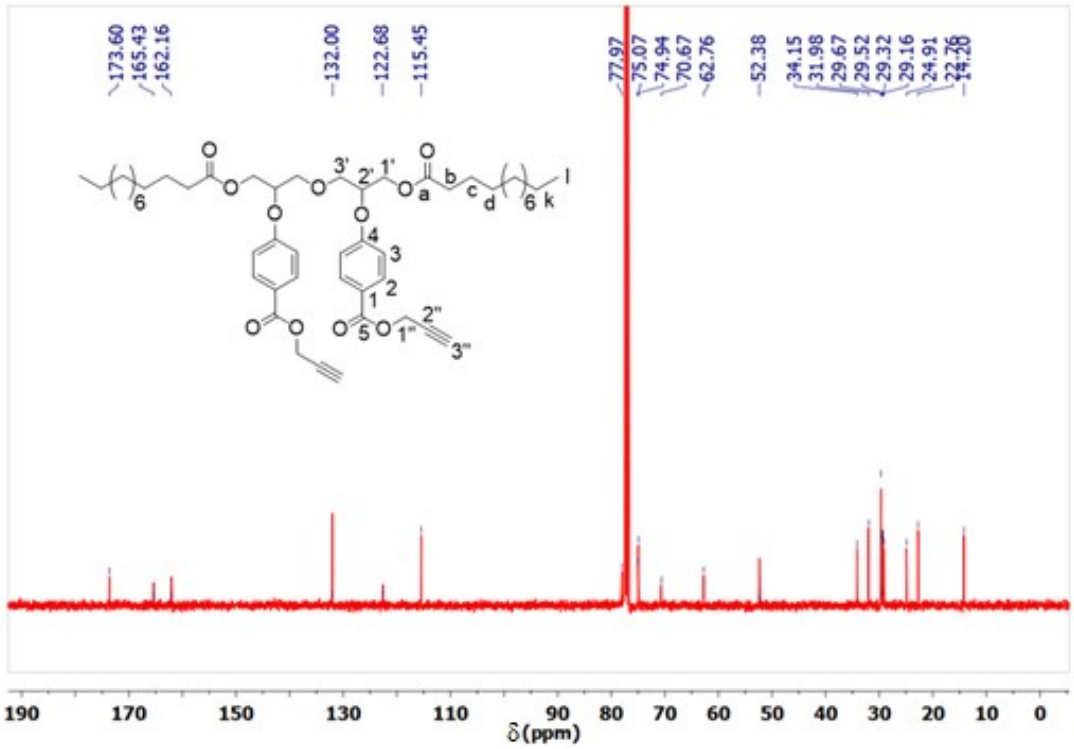
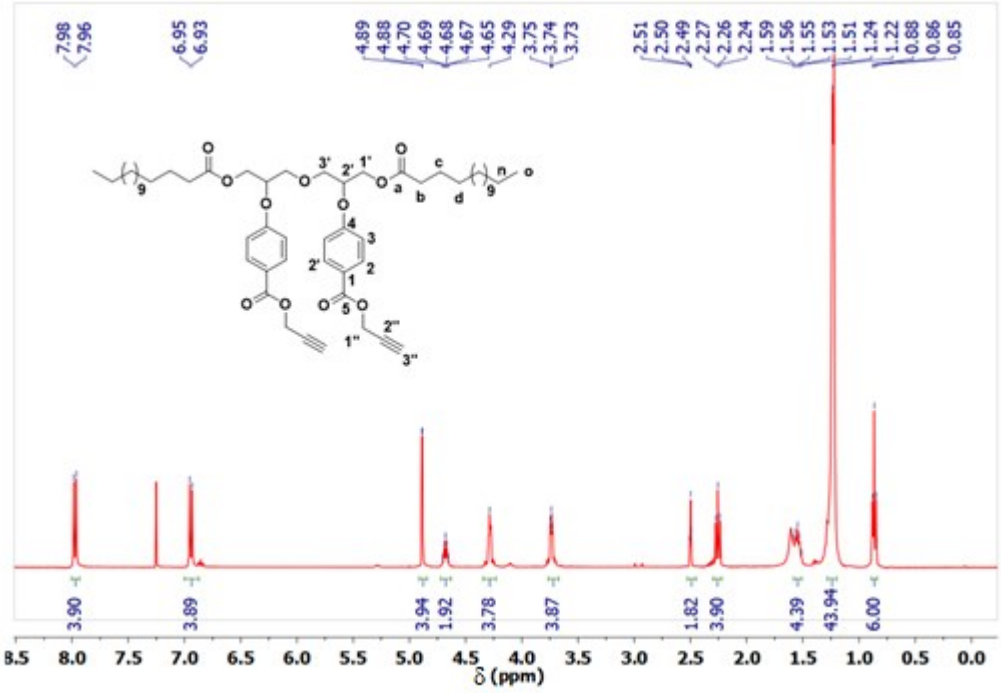


Figure S4. ^{1}H & ^{13}C NMR spectra of di(prop-2-yn-1-yl) 4,4'-((oxybis(1-(dodecanoyloxy)propane-3,2-diyl))bis(oxy))dibenzoate (**8**)



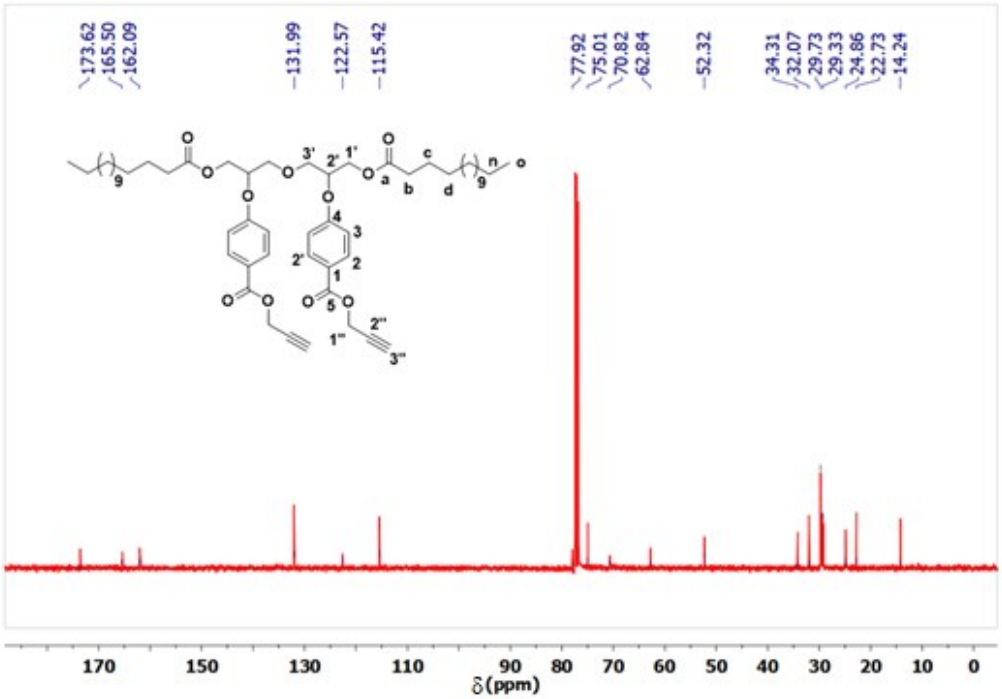
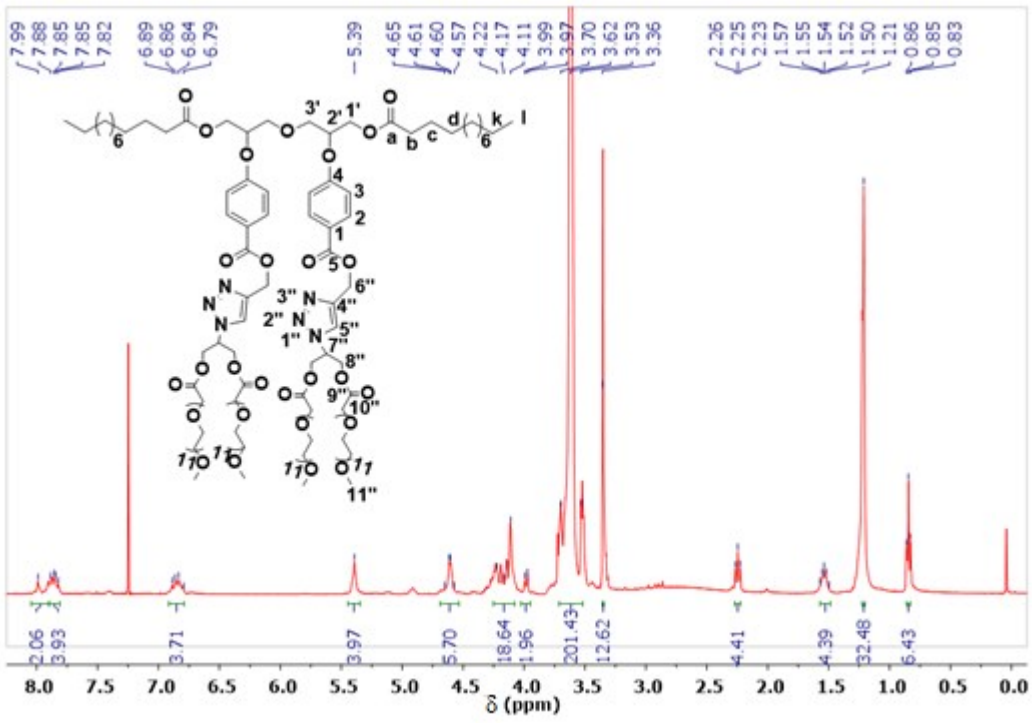


Figure S5. ^{1}H & ^{13}C NMR spectra of di(prop-2-yn-1-yl) 4,4'-((oxybis(1-(pentadecanoyloxy)propane-3,2-diyl))bis(oxy))dibenzoate (**9**)



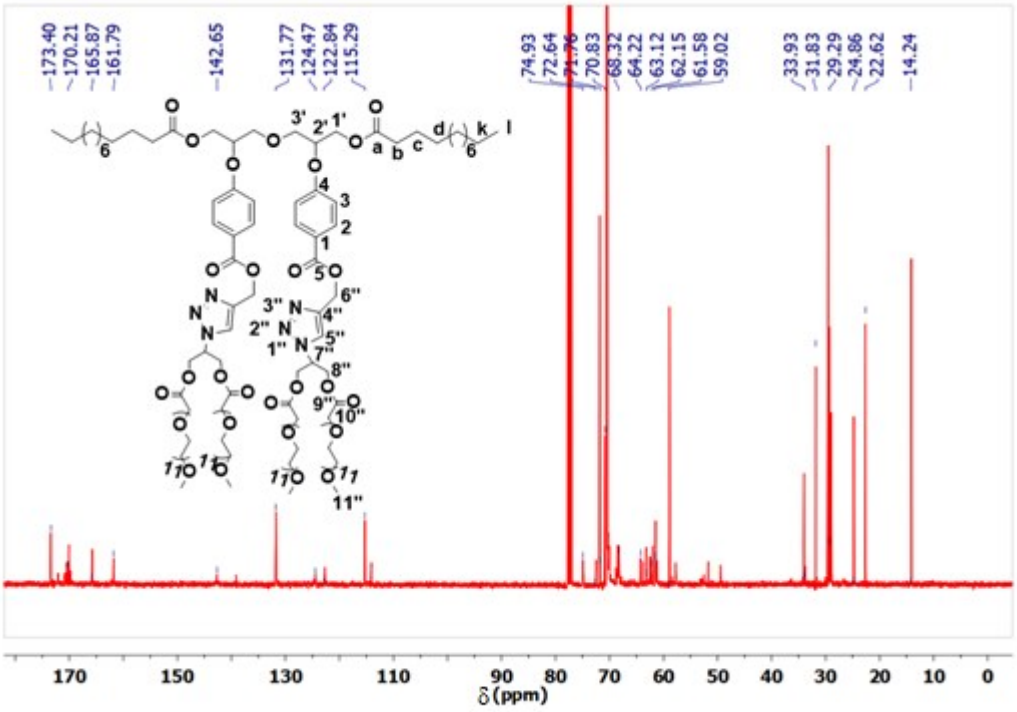
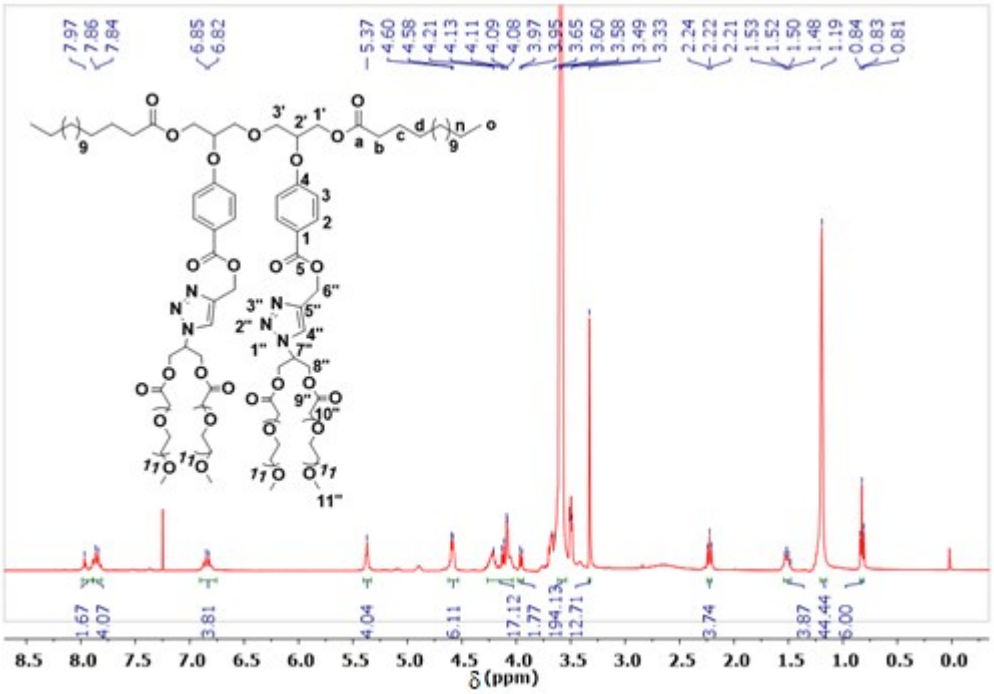


Figure S6. ^{1}H & ^{13}C NMR spectra of compound **15**.



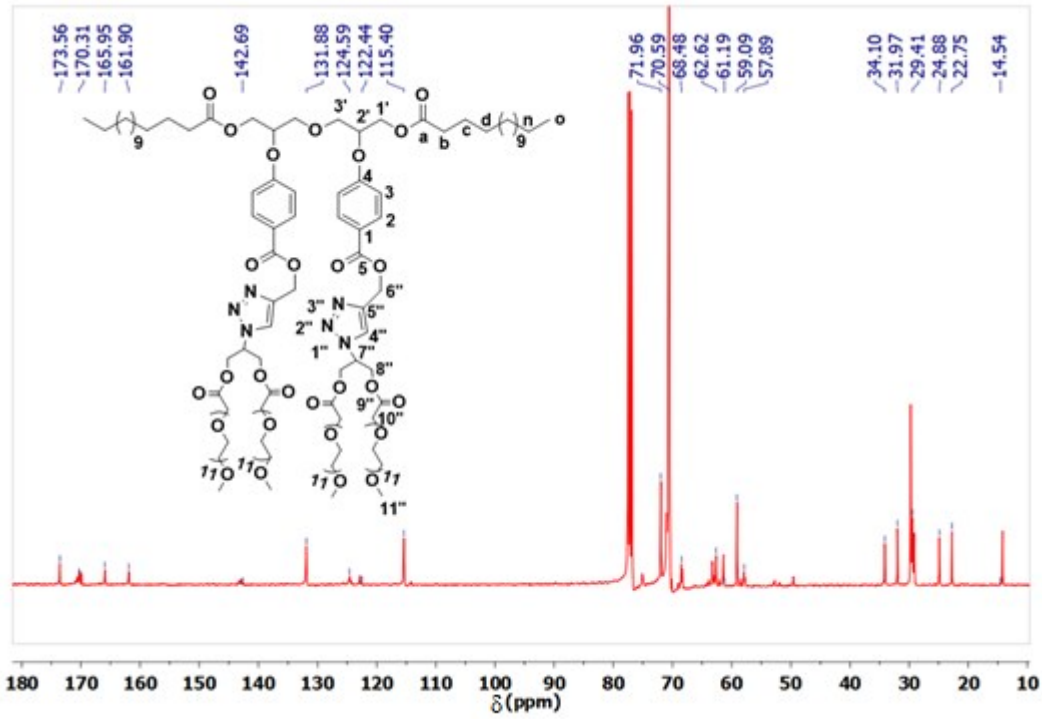
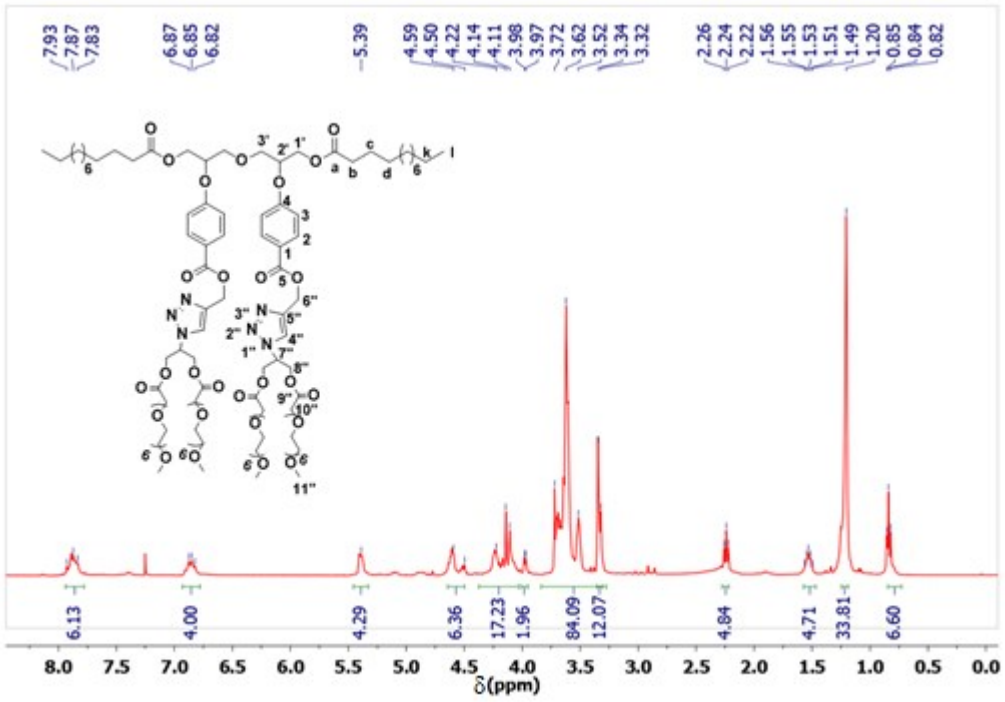


Figure S7. ^{1}H & ^{13}C NMR spectra of **16**



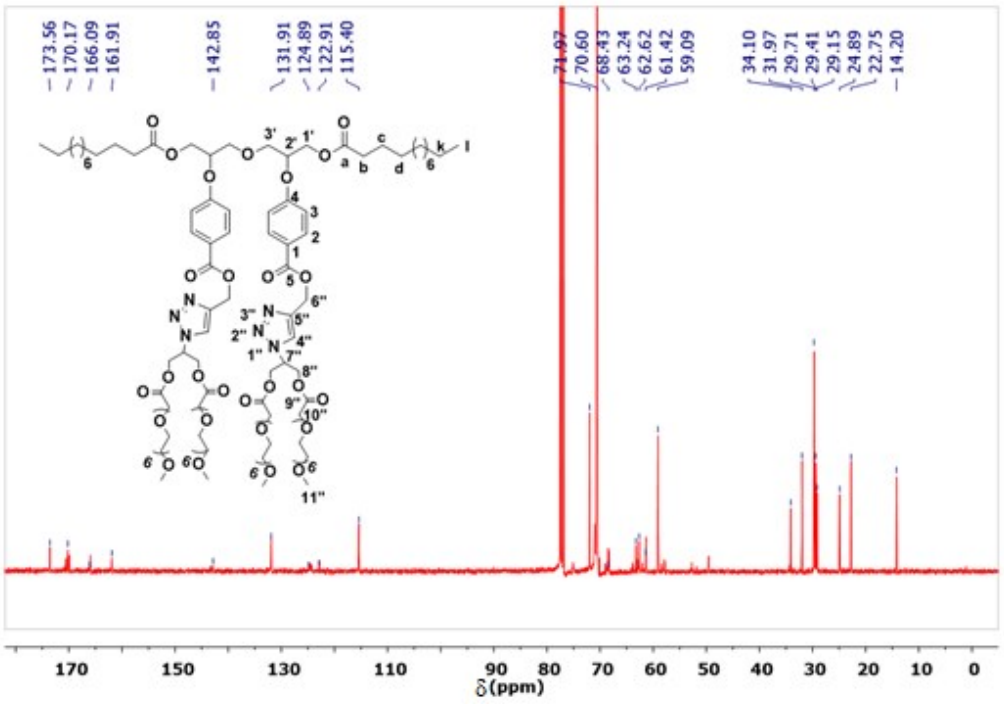
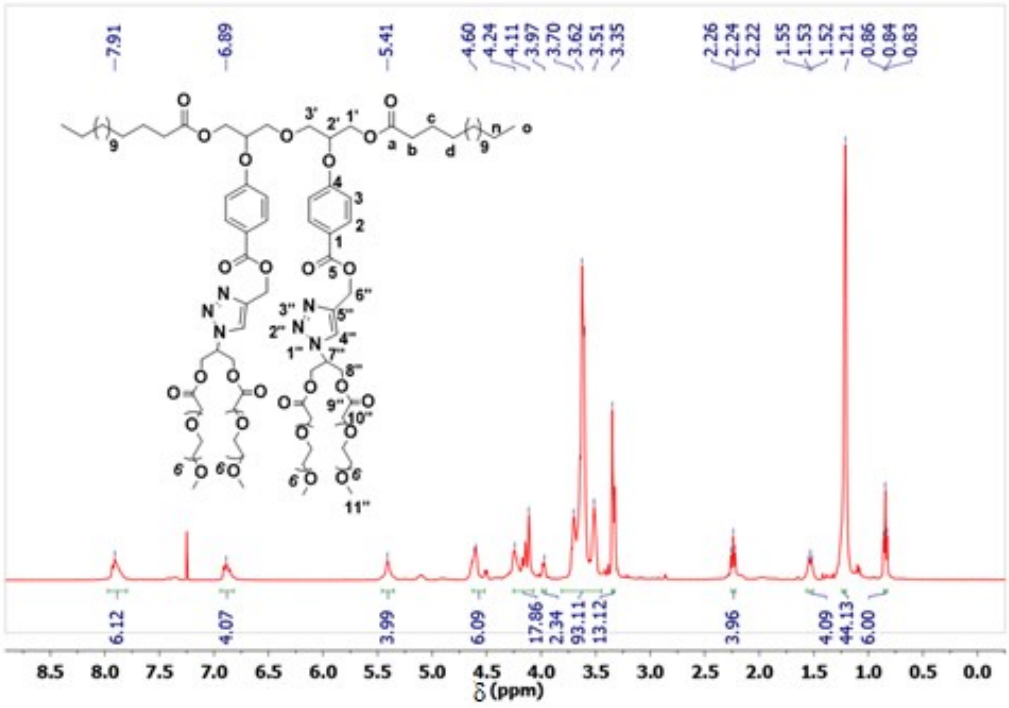


Figure S8. ^{1}H & ^{13}C NMR spectra of **17**



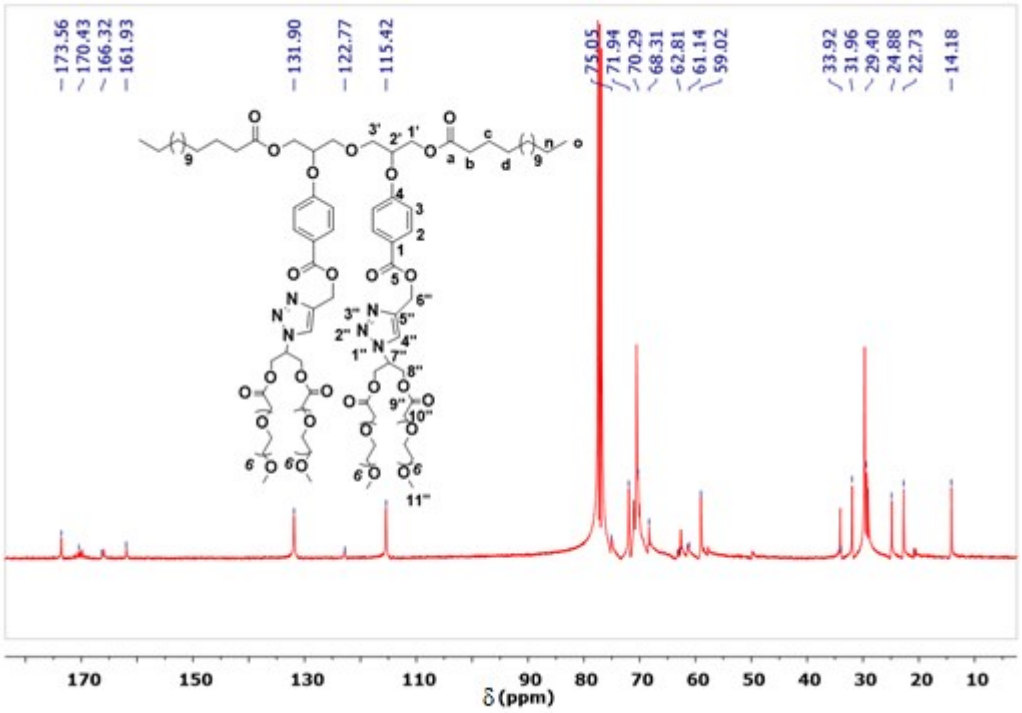
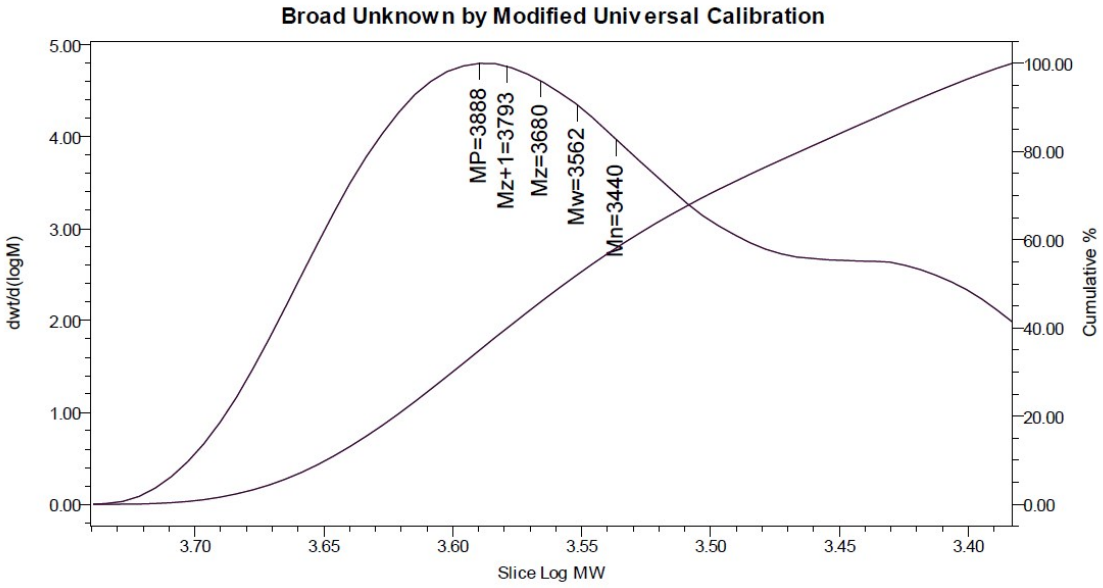
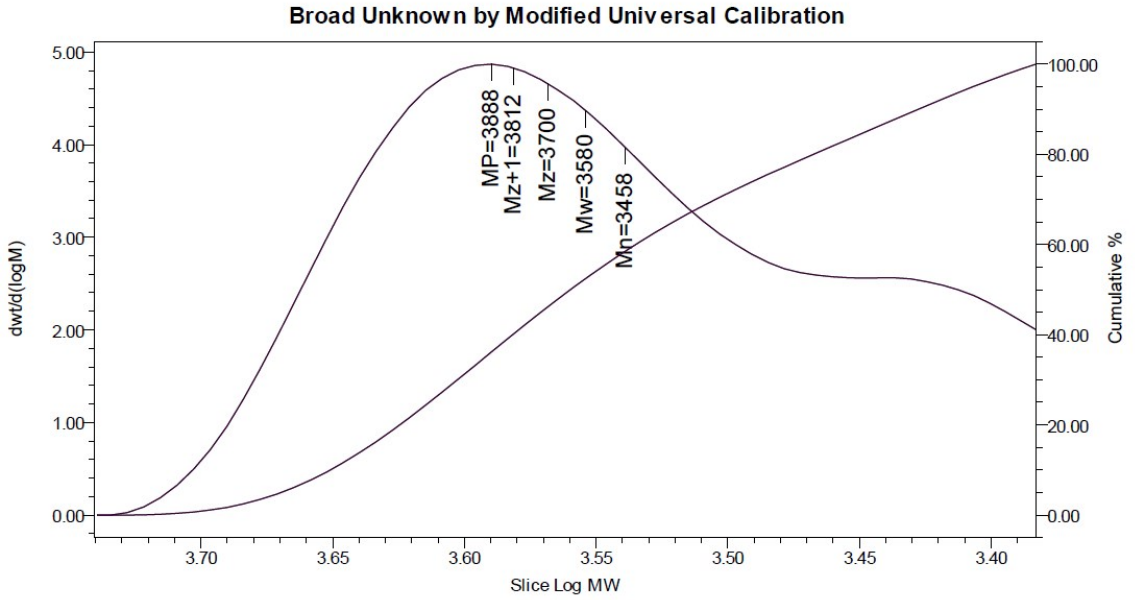


Figure S9. ^{1}H & ^{13}C NMR spectra of **18**



(a)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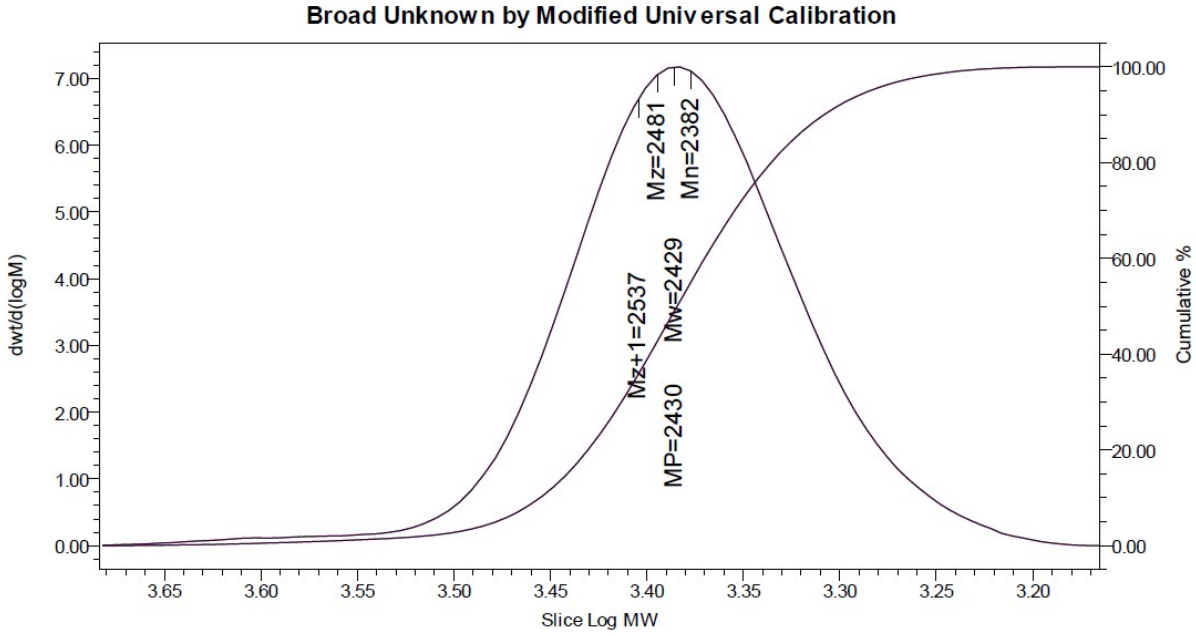
(b)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Cumulative %
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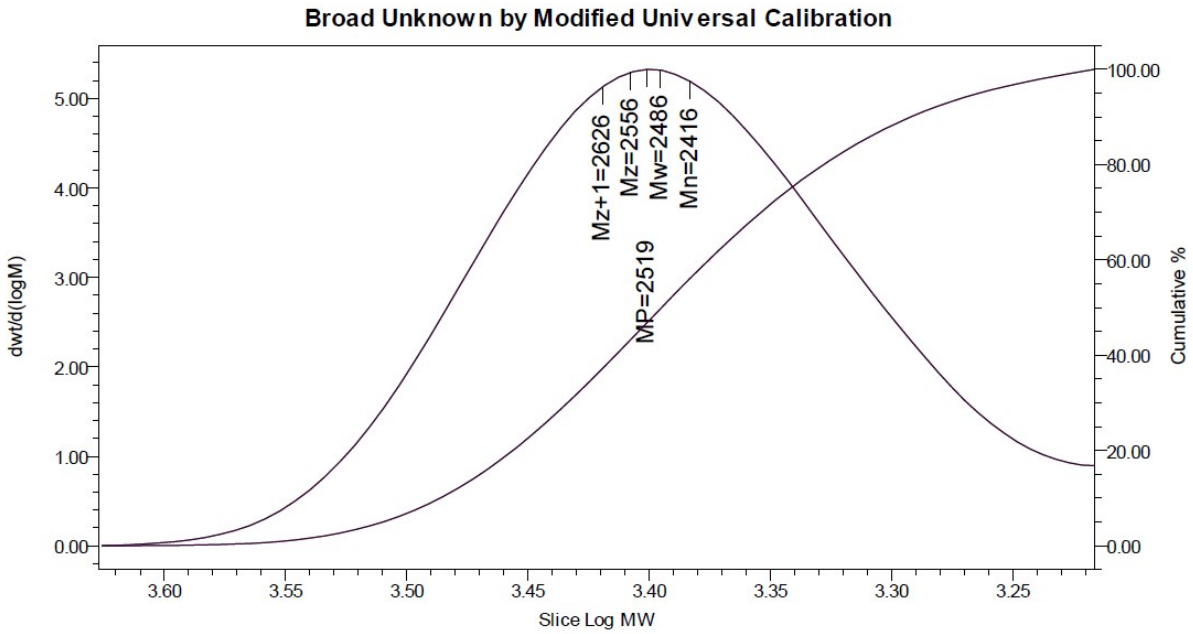
(c)



(d)

Figure S10. Gel permeation chromatogram of amphiphiles (a) **15** (b) **16** (c) **17** (d) **18**

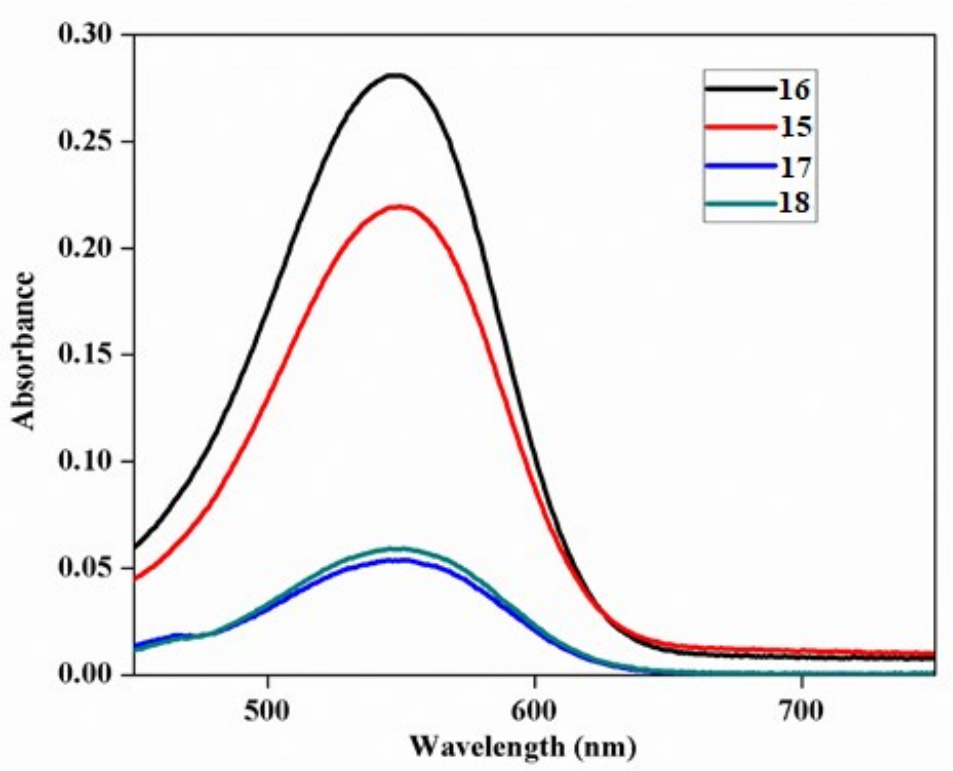


Figure S11. UV-vis spectra for quantification of Nile red encapsulation in amphiphiles **15-18**.

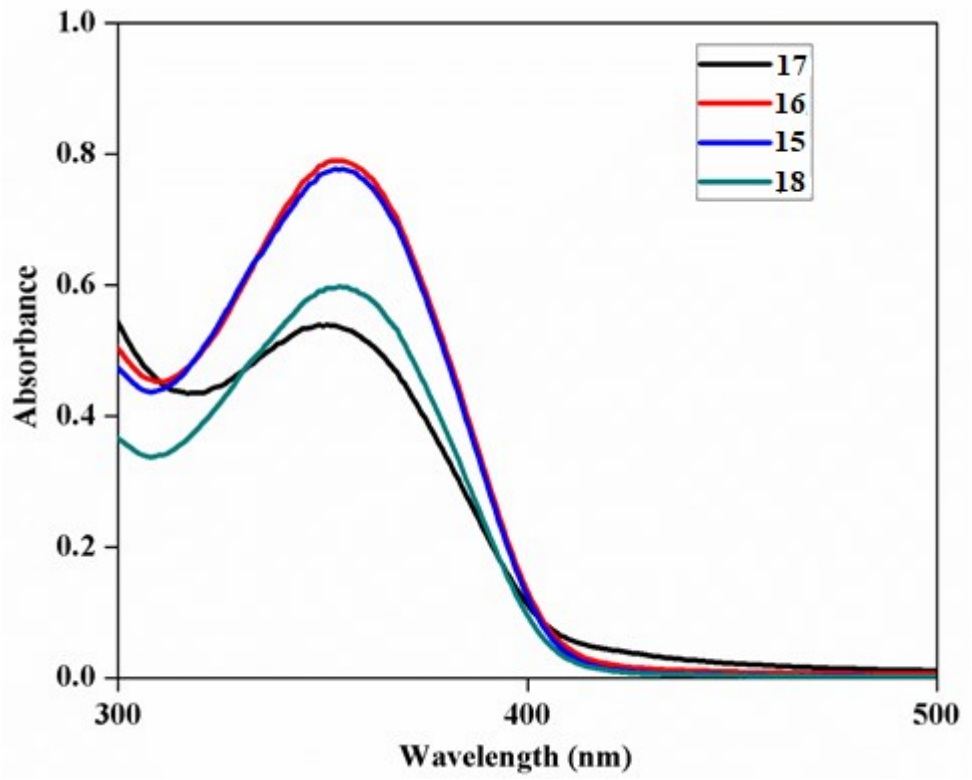


Figure S12. UV-vis spectra for quantification of nimodipine encapsulation in amphiphiles **15-18**

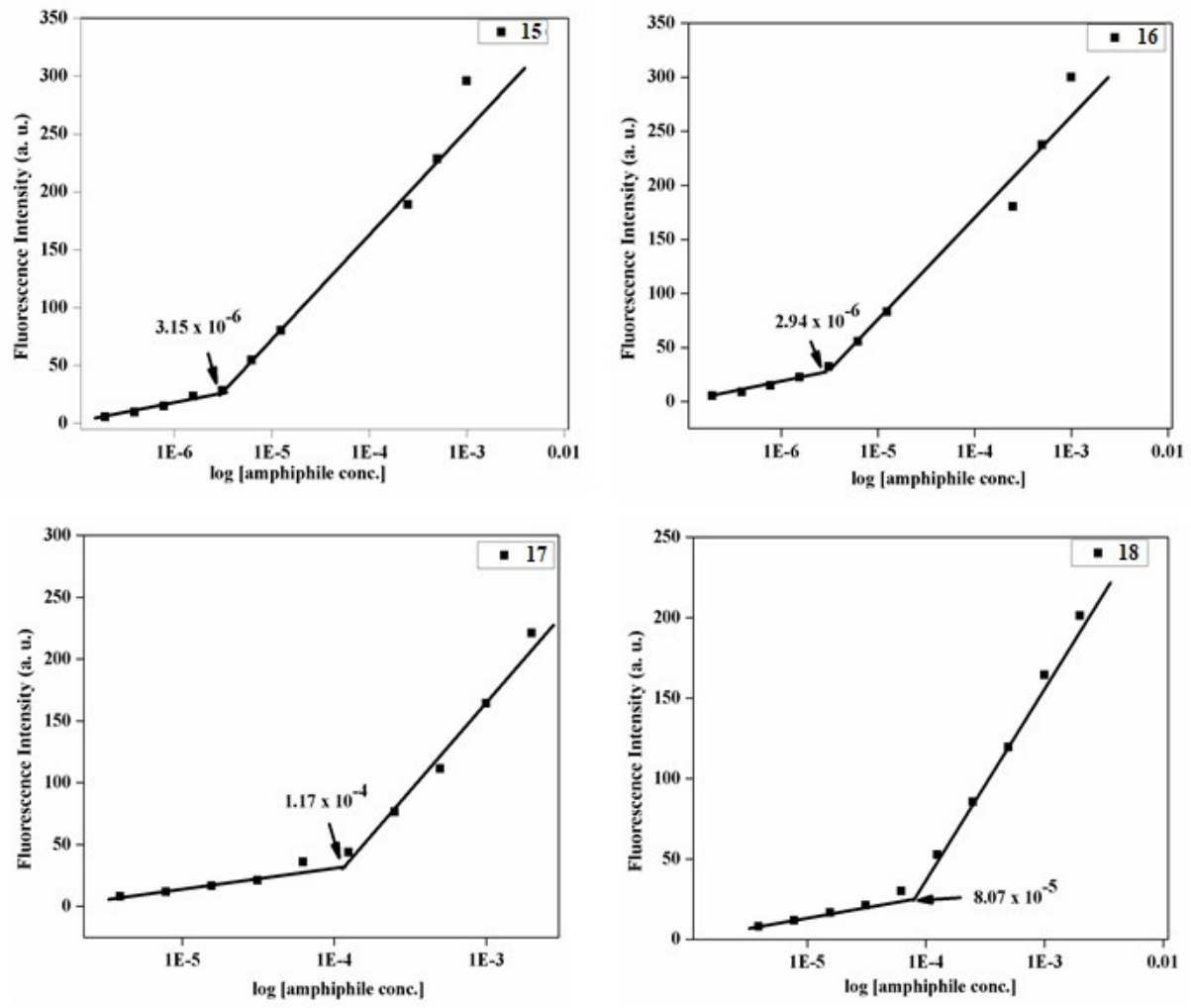


Figure S13. CAC plots of amphiphiles **15-18**.

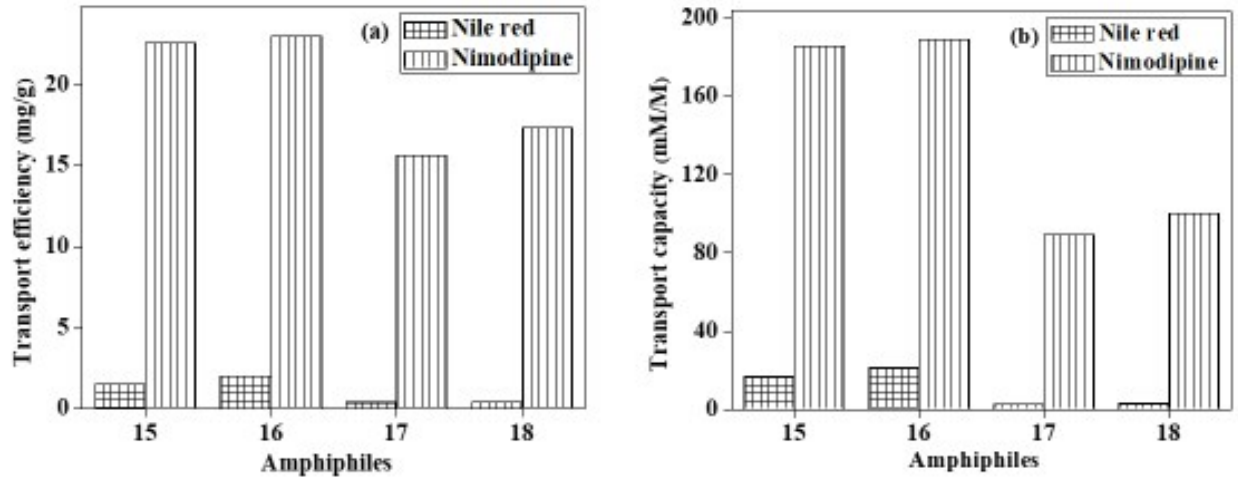


Figure S14. (a**)** Transport efficiency and **(**b**)** transport capacity of amphiphiles **15-18** for Nile red and nimodipine.

3. References

1. A. C. Rodrigo, A. Barnard, J. Cooper, D. K. Smith, *Angew. Chem. Int. Ed*. **2011**, *50*, 4675.
2. E. Fleige, B. Ziem, M. Grabolle, R. Haag, U. Resch-Genger, *Macromolecules* **2012**, *45*, 9452.
3. S. Gupta, B. Schade, S. Kumar, C. Böttcher, S. K. Sharma, R. Haag, *Small* **2013**, *9*, 894.