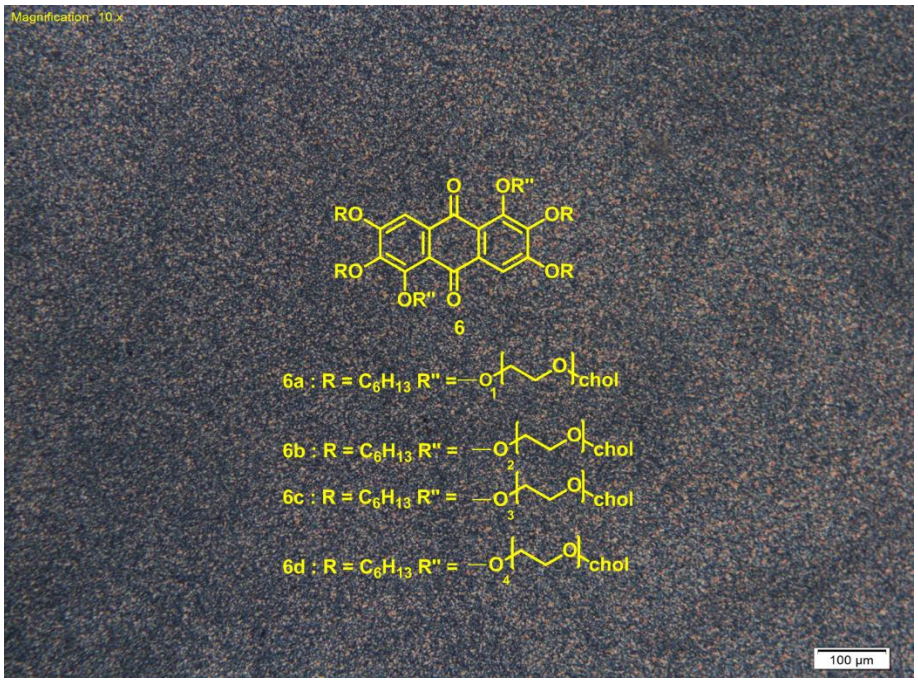
Chapter-4

Synthesis and characterization of cholesterol functionalized amphiphilic anthraquinones

Abstract

This chapter describes the synthesis of cholesterol functionalized anthraquinone discs with ethylene glycol (EG) spacers. The influence of mesomorphic properties as a function of the length of the ethylene glycol spacer is studied. These compounds were explored for lyotropic behavior with respect to water and formamide. The water-based systems were found to be non-mesomorphic. On the other hand, the formamide based systems were found to be liquid crystalline.



publication based on this work: Manuscript under Preparation

4.1 Introduction:

Cholesterol (cholest-5-en-3β-ol) belongs to the lipid family and is one of the vital structural components of cell membranes. The chemical structure of cholesterol shows that it is a rigid and almost planar molecule with a steroidal skeleton (constituting four fused rings; three six-membered and one five-membered). The presence of a hydrophilic hydroxy headgroup on the A-ring, together with a hydrophobic hydrocarbon body, provides the amphiphilicity to the molecule.

4.2 Literature review of cholesterol functionalized columnar phases:

Cholesterol benzoates synthesized by Reinitzer was one of the first compounds to be reported for mesomorphic behavior. Since then cholesterol moiety has become unavoiding member among the liquid crystal community [1,2]. It is a very tedious job to cover all the reports on cholesterol-based mesogenic compounds. This section gives a very brief account of the mesogenicity of cholesterol derivatives. Most of the cholesterol derivatives reported are nematic or smectic in nature[3]. There are reports of cholesterol functionalized disc-shaped chromophores some of them were reported to be liquid crystalline whereas others are not. The reports on the columnar phase involving cholesterol derivatives are countable in number.

Ajayghosh et al. have synthesized perylene diimides functionalized with cholesterol through urea linkage with various bay substituents (**Figure1**) In the gel state the molecule tend to show photo functional properties[4].

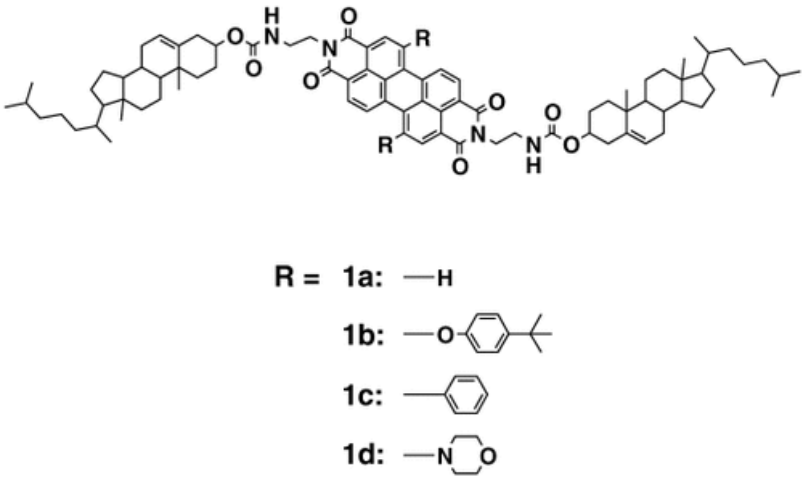


Figure1: Cholesterol functionalized perylenes[4]

Gupta et al. have documented the preparation of perylene based cholesterol tetramer and they were found to show monotropic cholesteric phase[5] . There is one more recent report on perylenes-cholesterol conjugates which was studied for their mesomorphic potential as a function of position and no cholesterol motif. It was shown that the enhancement of mesomorphic potential when there is a long spacer separating both perylenes and cholesterol units [6] (**Figure 2**).

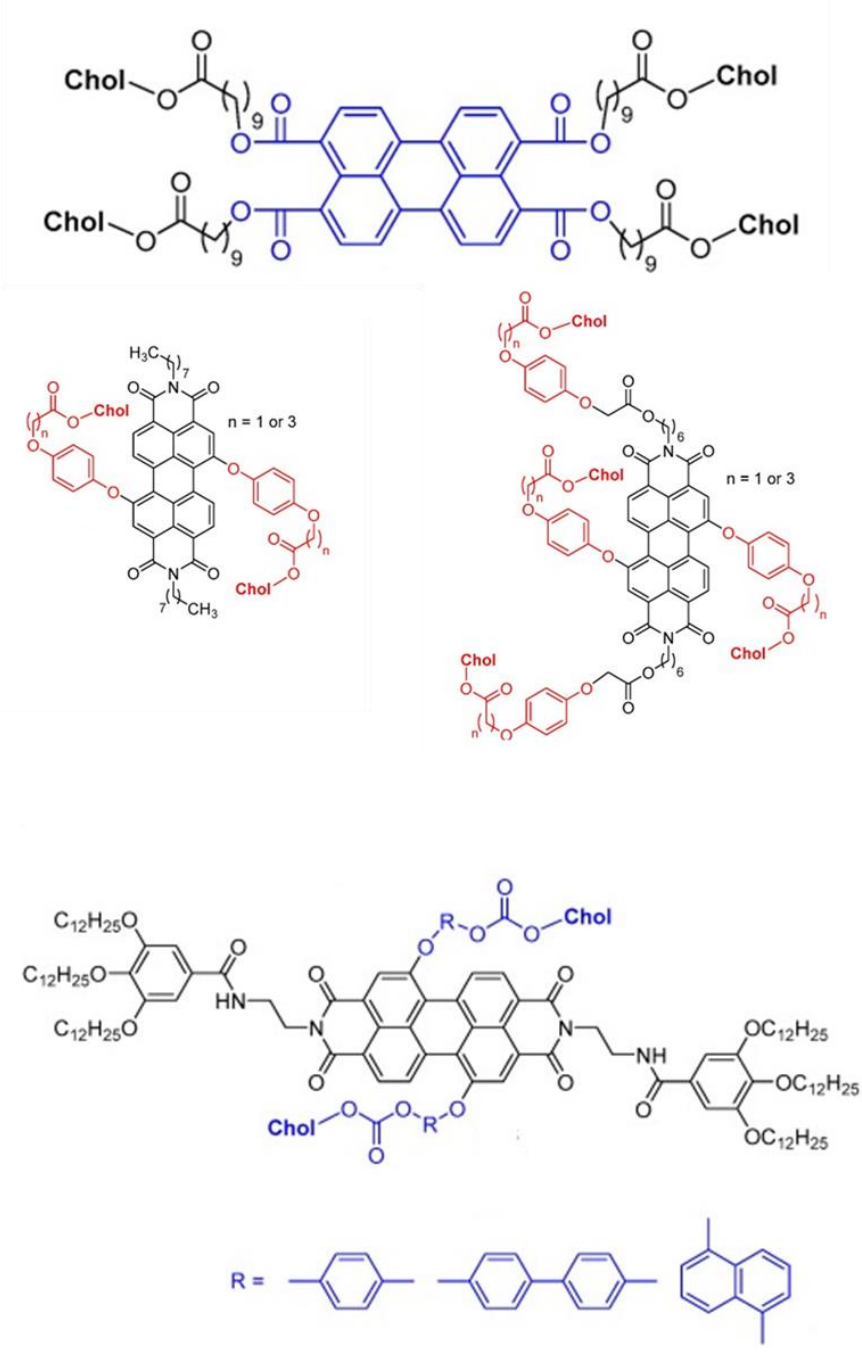


Figure 2: Liquid crystalline perylene-cholesterol hybrids[5,6]

Oligothiophenes with functionalization of cholesterol have been found to show thermochromism in their gel state [7] (**Figure3**).

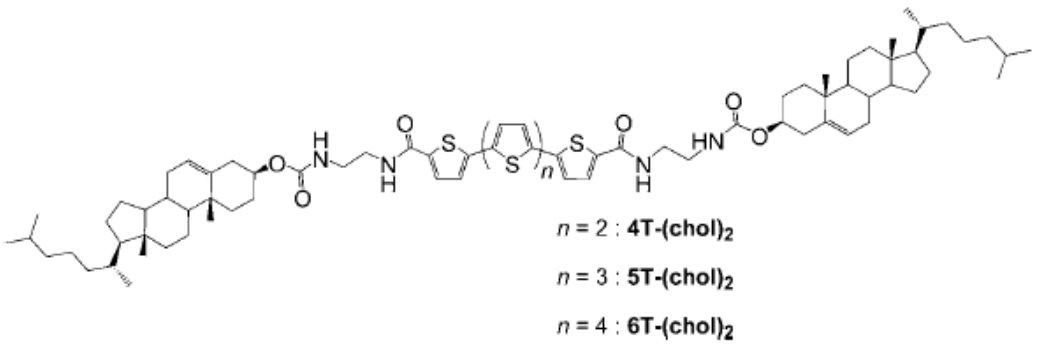


Figure3: Cholesterol functionalized thiophenes[7]

Ghosh et al. have studied the self-assembly behavior of oligo (*p*-phenylenevinylene) s (OPVs) that are mono- or disubstituted with cholesterol moieties. They were found to form pseudo-J and pseudo-H aggregates, respectively which lead to coiled and twisted helical structures with diverse properties[4] (**Figure 4**).

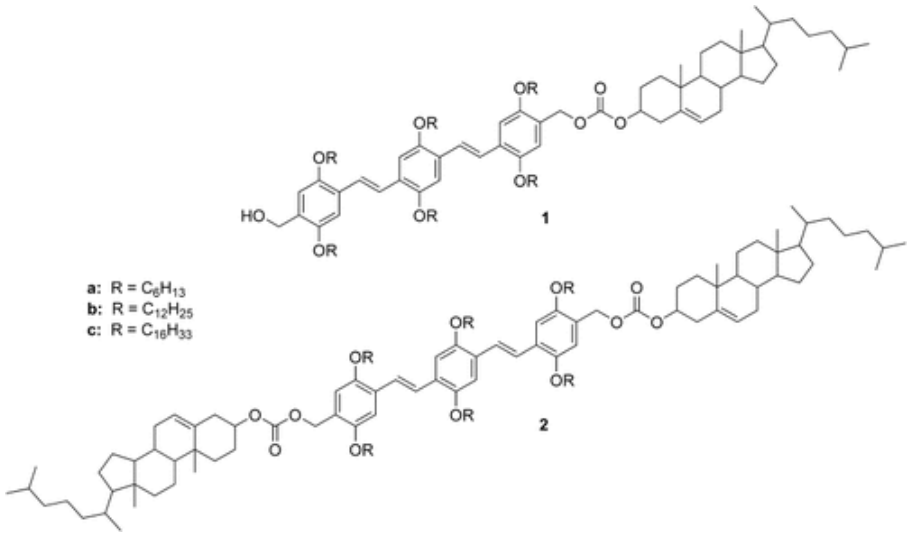


Figure 4: OPV functionalized cholesterols[4]

George et al. have reported the unusual excimer emission of cholesterol functionalized naphthalene diimide (**Figure 5**) through carbonate linkage in both solid and self-assembled states [8].

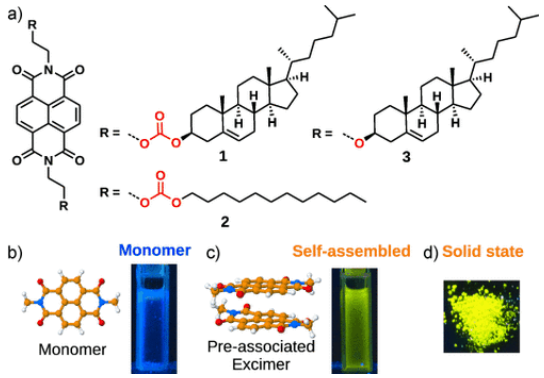


Figure 5: Cholesterol functionalized naphthalene diimides[8]

Kanvah et al. synthesized cholesterol conjugated cyano stilbenes. The cyanostilbene conjugate was found to exhibit excellent aggregation-induced emissive properties in the self-assembled state [9](**Figure 6)**. Pal et al. have reported room temperature cholesteric behavior of pentaalkynylbenzene-cholesterol dyads (**Figure7**) [10].

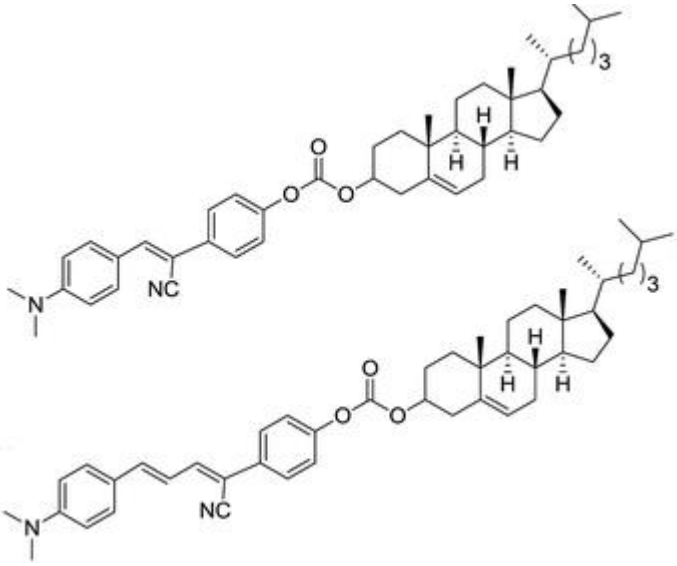


Figure 6: Cholesterol functionalized cyanostilbenes[9]

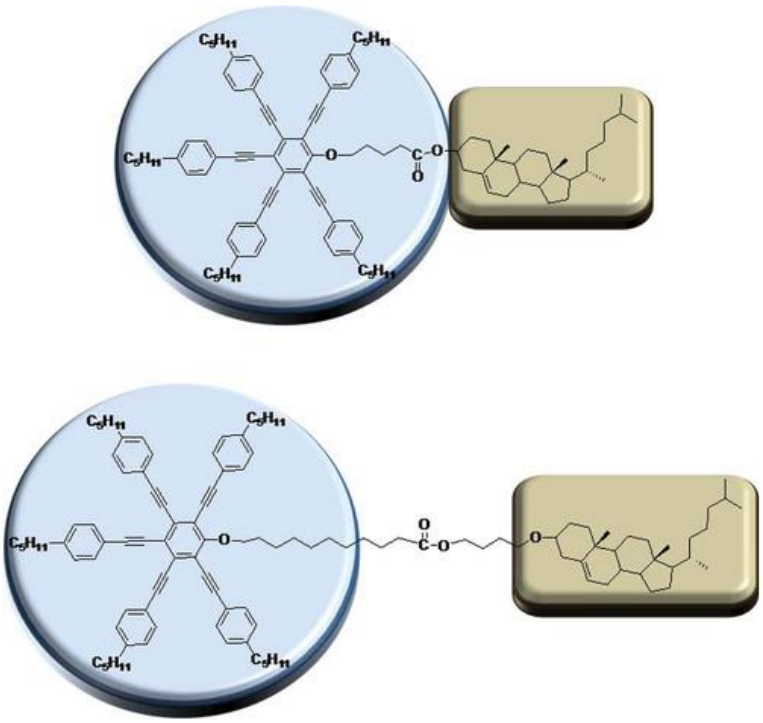


Figure 7: Cholesterol functionalized pentaalkynylbenzene[10]

Sougata et al. have studied the self-assembly behavior of cholesteryl derivatives of pyrimidines. They have shown that the compounds were found to show gelation in dodecane and butanol. The compounds were found to show hexagonal phase on complexation with alkali metal ions [11](**Figure 8**).

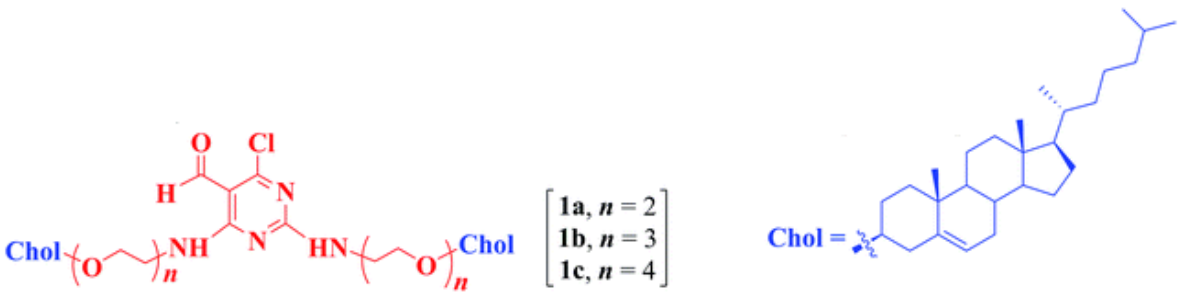


Figure 8: Cholesterol functionalized pyrimidines[11]

Yang et al have synthesized symmetric hairpin-shaped cholesterol tetramers bridged by rigid or hydrogen-bonding Schiff-base spacers. The compounds exhibit mesomorphic properties showing hexagonal order (**Figure 9**). This strategy reveals the criteria for the formation of the columnar phase from cholesteryl derivative by forming tetramers with rigid central core or core with H-bonding ability [12].

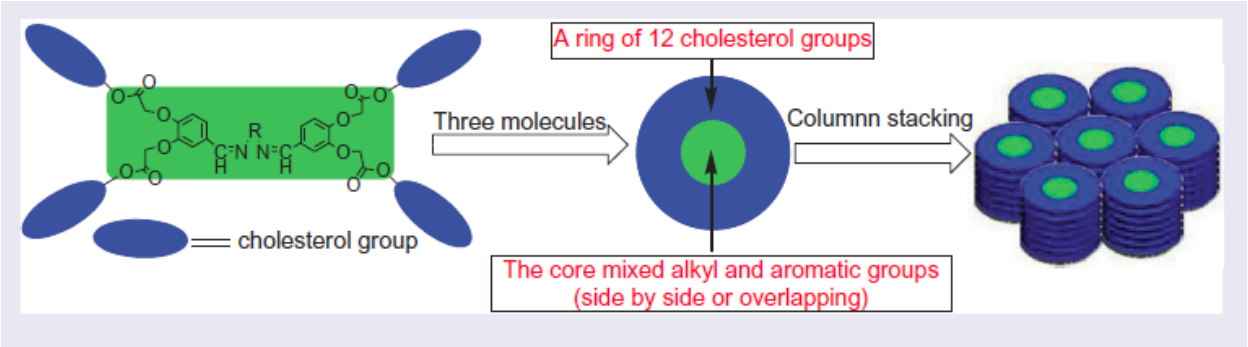


Figure 9: Cholesterol tetramer[12]

Yang et al. have successfully synthesized the functionalization of cholesterol in the anthraquinone core through conventional synthetic chemistry. The compounds were found to assemble in columns with hexagonal symmetry. Further, the CD spectra showed the chirality of cholesterol moiety has been transferred to the columns as there is good CD signal in their mesophase regime [13](**Figure10**).

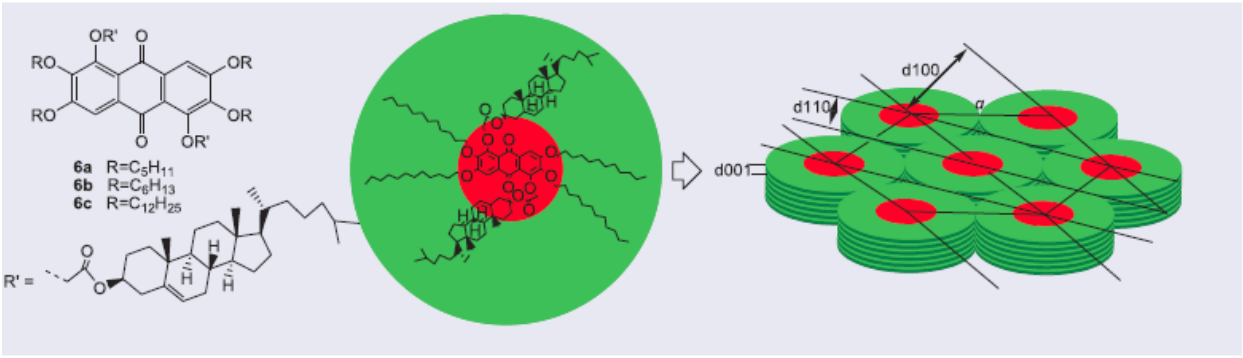


Figure 10: Cholesterol functionalized anthraquinones[13]

Liquid crystalline gelators have been prepared using Tetraphenylethene with cholesterols connected through azobenzenes. The compounds showed smectic phases with excellent gelation ability [14] (**Figure11**).

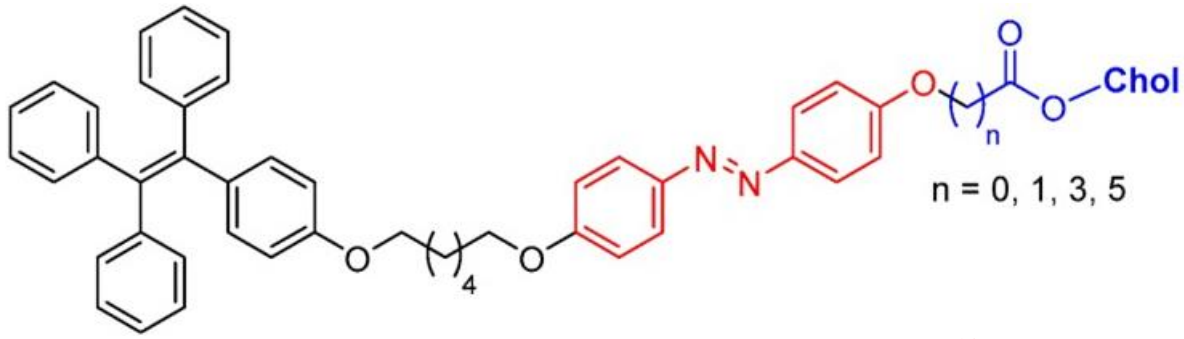


Figure 11: Cholesterol functionalized tetraphenylethene [14]

Trimers involving Cholesterol, triazine, BODIPY units have been prepared and studied for their mesomorphism, the mesomorphic behavior was found to be dependent on the number of cholesterol units. The compound with one cholesterol unit showed nematic phases whereas the compound with two cholesterol units showed hexagonal columnar phase[15](**Figure12**).

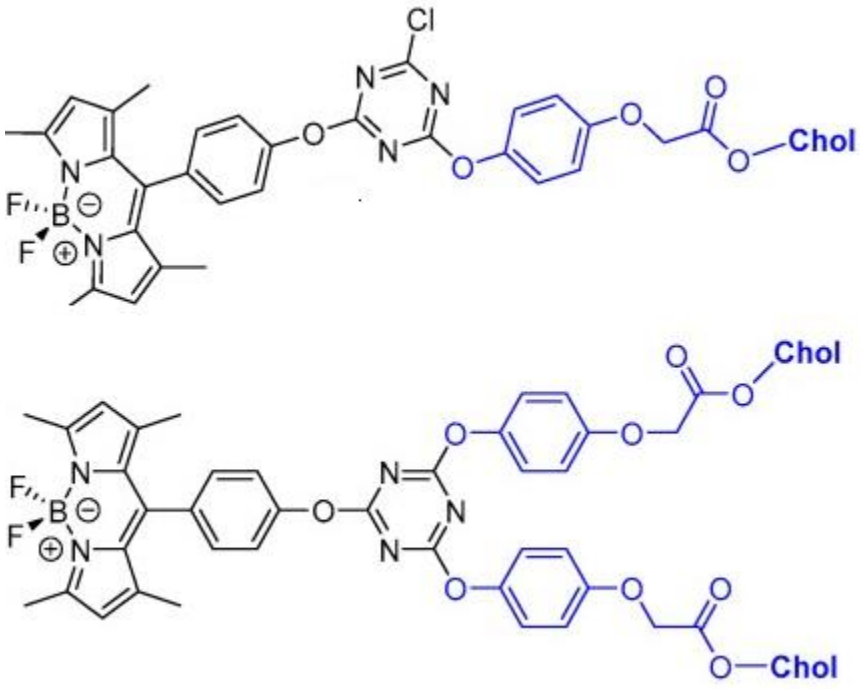


Figure 12: Cholesterol functionalized Triazines[15]

Pal et al. have reported cholesterol-based tetramers containing azobenzenes. The compounds showed a cholesteric phase [16]. These compounds were found to be resistant to photoisomerization. (**Figure13**).

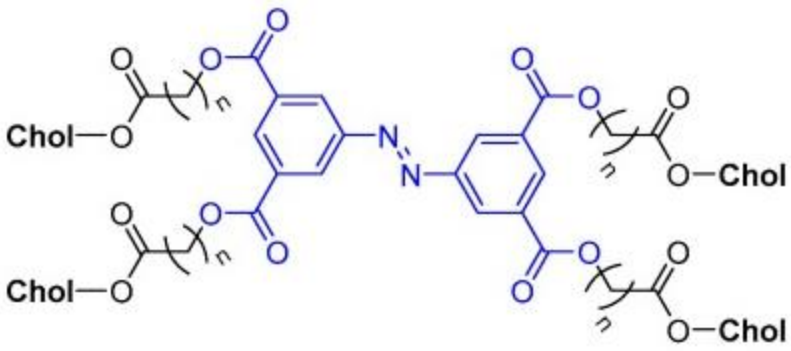


Figure 13: Cholesterol functionalized with azobenzenes[16]

Guo et al. synthesized calixarene –cholesterol conjugates and studied their mesomorphic character. They were found to show columnar phases. Further, this calixarene functionalized with cholesterol was explored with imine linkage. The imine linked compounds too were mesomorphic. It was demonstrated that the mesophase behavior can be fine-tuned by complexation with metal ions[17]. (**Figure14**)

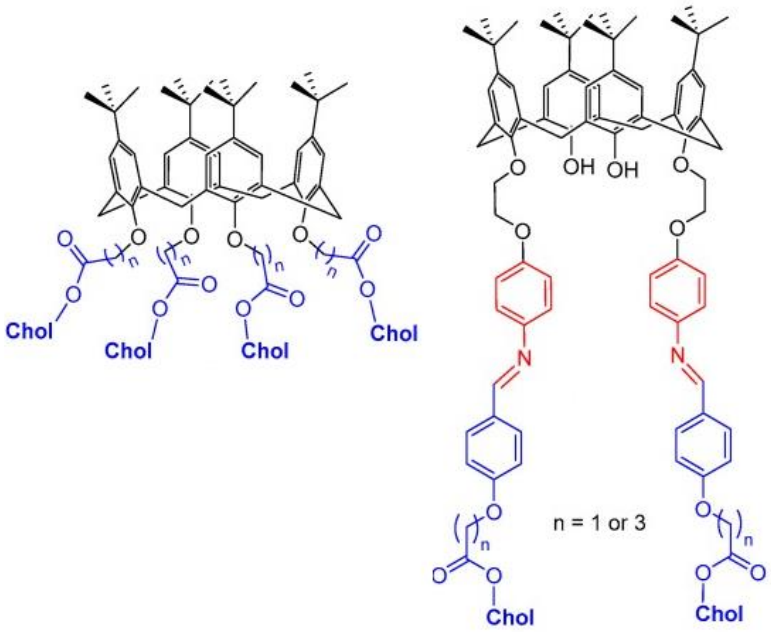


Figure 14: Cholesterol-calixarene hybrids[17]

This is a recent account of the formation of columnar structure from cholesterol-based ionic liquid crystals (**Figure15**). Constituting the hexamethylene tetra amine cationic central core and cholesterol derivative with different counterions. The ionic liquid formed showed smectic mesophase with excellent ionic conductivity[18].

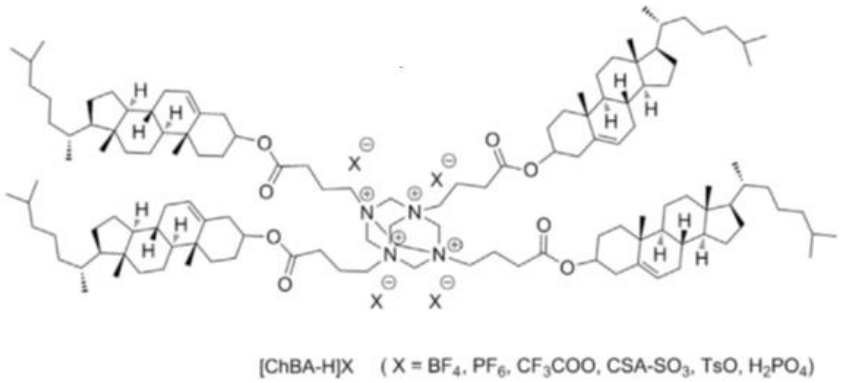


Figure15: Cholesterol-based ionic liquid crystals[18]

4.3 Results and Discussion:

4.3.1 Synthesis:

The cholesterol functionalized anthraquinones were synthesized by following the synthetic pathway shown in the figure 16. Gallic acid was commercially obtained from SD fine chemicals and used without further purification. Rufigallol was synthesized by acid-catalyzed condensation of gallic acid as reported by Grimshaw et al. [19] The obtained red solid was used as such for further steps. Rufigallol was alkylated at hydroxyl groups of 2,3,7,6 positions. The tetra alkylated product was confirmed by NMR and elemental analysis.

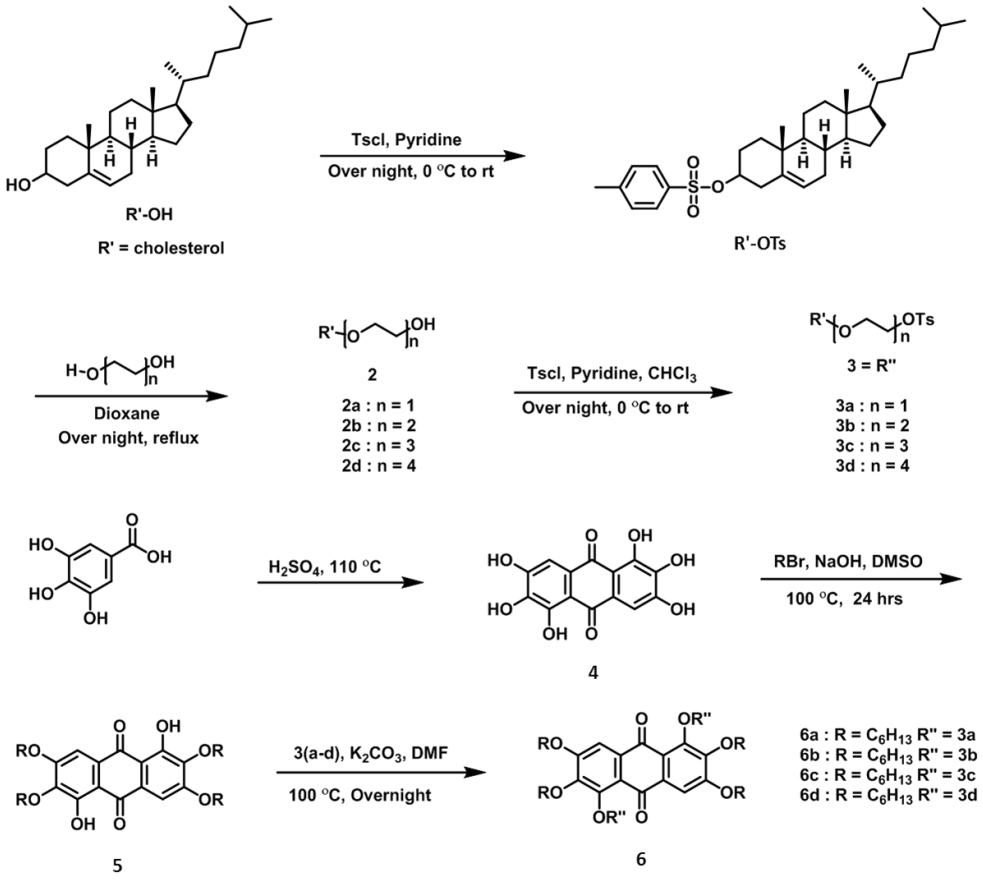


Figure 16: Synthetic scheme for cholesterol amphiphile

Cholesterol was first tosylated using tosyl chloride and pyridine. The tosylated cholesterol was alkylated with oligo ethylene glycols (EG) by heating in dioxane medium, the obtained product was subjected to tosylation in order to activate the hydroxyl group. The tetra alkylated anthraquinone (AQ) derivatives were alkylated at hydroxyl groups at 1,5positions with cholesterol

containing EG spacers tosylates through Williamson etherification. All compounds were purified by column chromatography on silica gel (100-200 mesh) followed by repeated crystallization using suitable analytical grade solvents. The structure of final compounds were confirmed through NMR, Elemental analysis. TGA thermograms suggest that all the compounds have good thermal stability (**Figure17**).

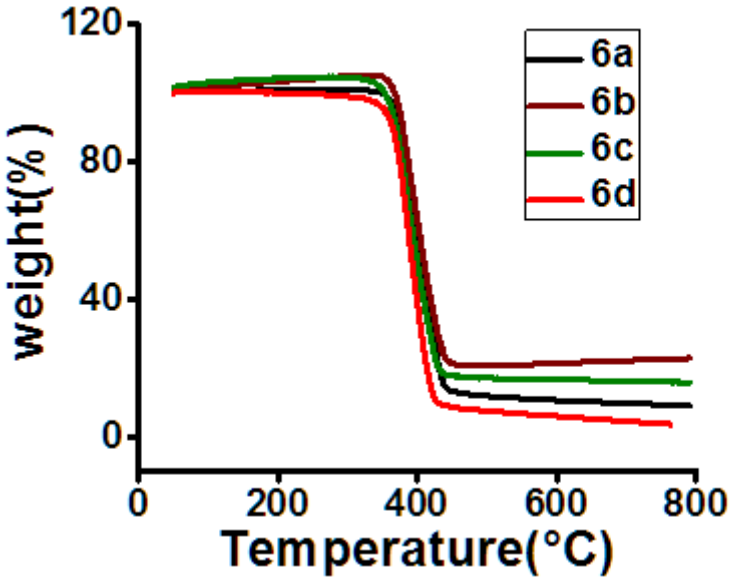


Figure 17: TGA thermograms of compounds 6a-d.

4.3.2 Mesomorphic characteristics:

Mesomorphic properties of all the compounds were analysed using POM, DSC, and SAXS. It was found that compounds 6a & 6d were non-mesomorphic. The compound 6a was crystal whereas the compound 6d was oily liquid. The other two compounds 6b &6c were mesomorphic. POM images suggest the presence of columnar order (**Figure18**). DSC thermograms confirm the above observation (**Figure19**). The thermal behaviour of all the compounds is given in the table1. These compound were not crystalizing even after reaching -30^{o}C as shown by DSC.

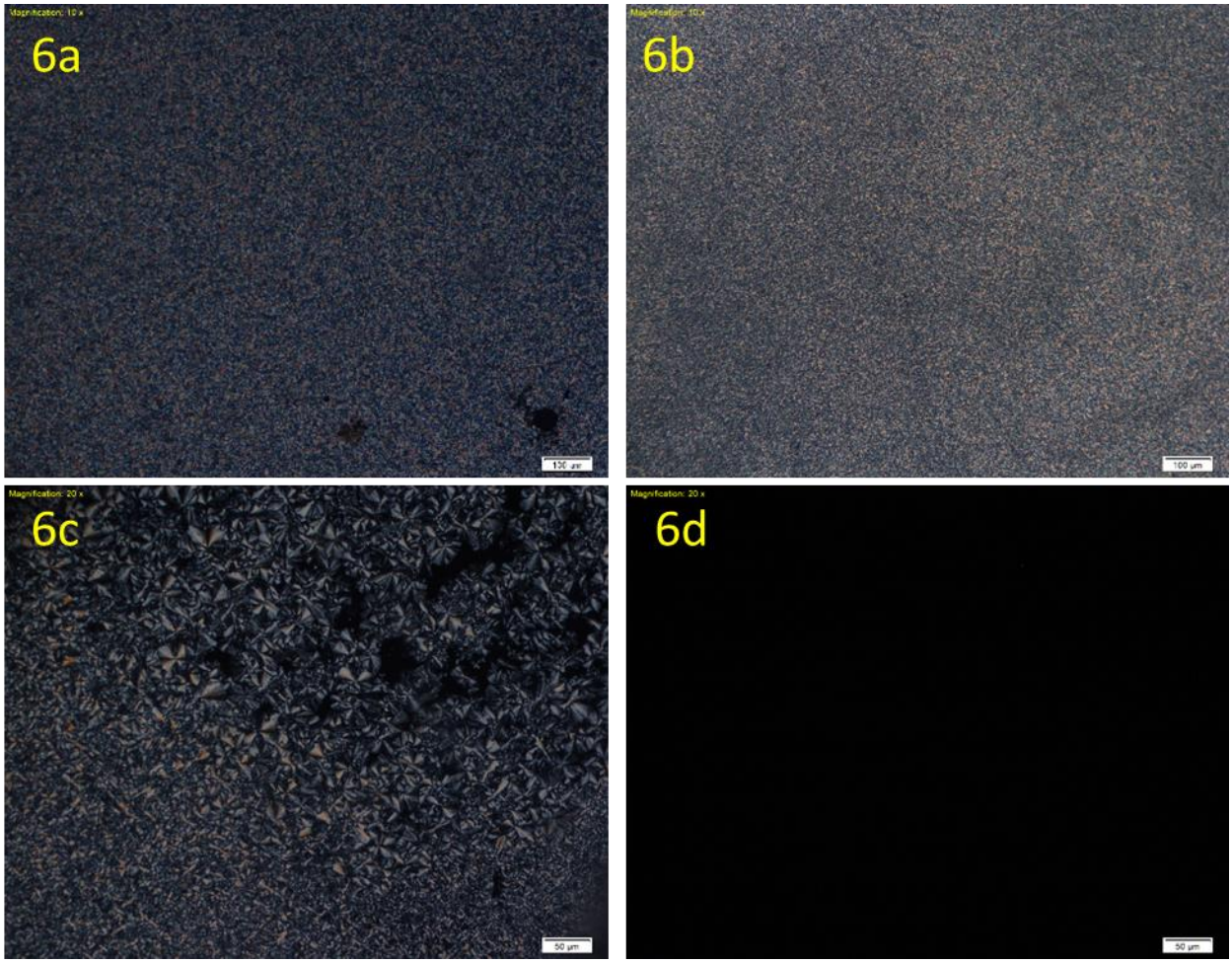


Figure 18: POM images of 6a at 90°C; 6b at 35°C; 6c at 40°C; 6d at 30°C

The structure of columnar phase was further elucidated through SAXS. The peaks in small-angle region were indexed to a centered rectangular lattice as all the indexed peaks followed the condition h+k=2n. The lattice parameters, area, volume are given in the table. After analyzing the lattice parameters the number of molecules occupying a single slice of the column was found to be 2. (**Figure20, Table 2**)

The non mesomorphic behavior of compound 4a is quite straight forward as in a discotic amphiphile the relative amount of hydrophilic and hydrophobic part should be sufficient to impart mesogenicity. The above argument can again be suitable for explaining the nonmesogenic behavior of compound 6d. The tetraaethylenoxy spacer has very high hydrophilicity in the compound which disrupt the mesomorphism.

From the diffraction results followed by detailed indexation, the following model was proposed for molecular arrangement in the columnar phase as shown in figure 21.

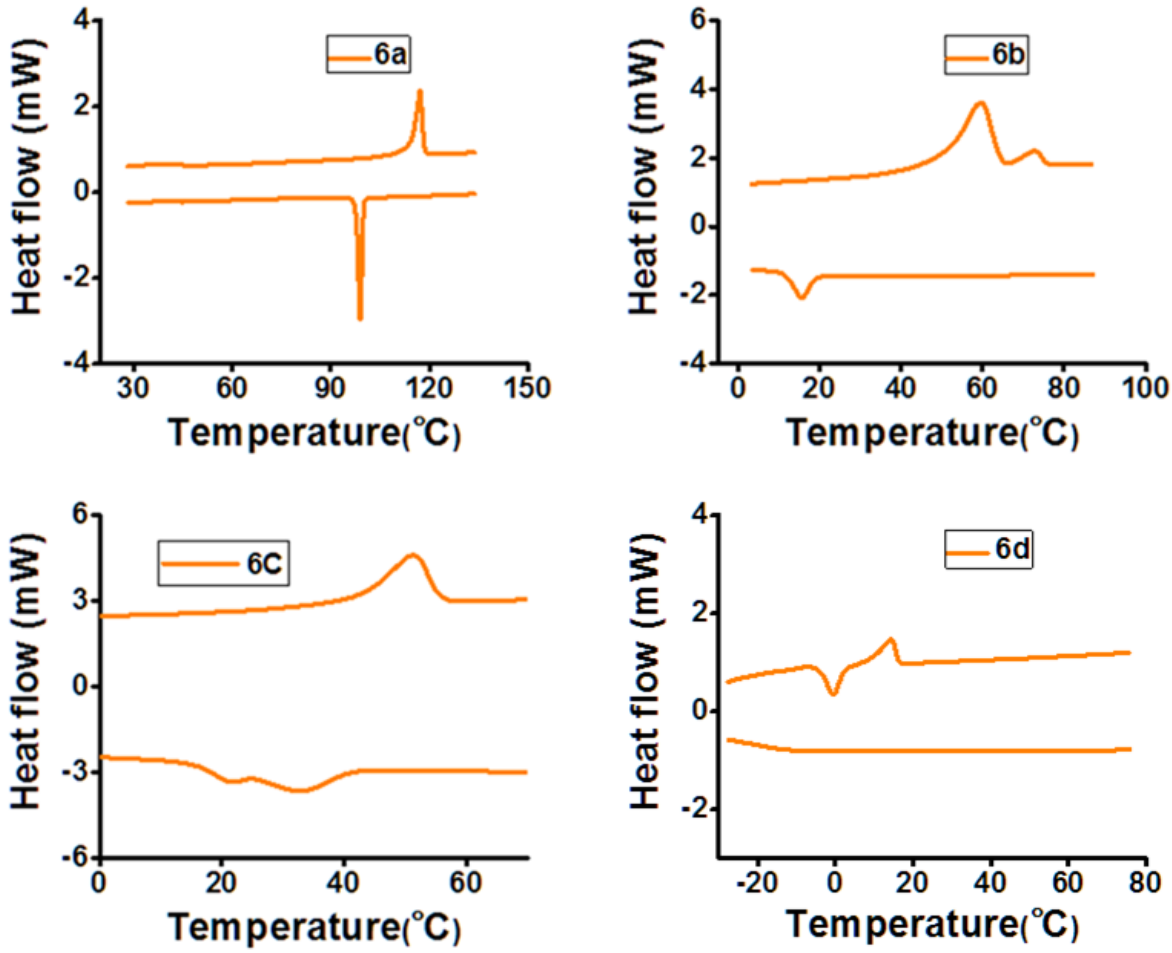


Figure 19: DSC thermograms of compounds 6a-d

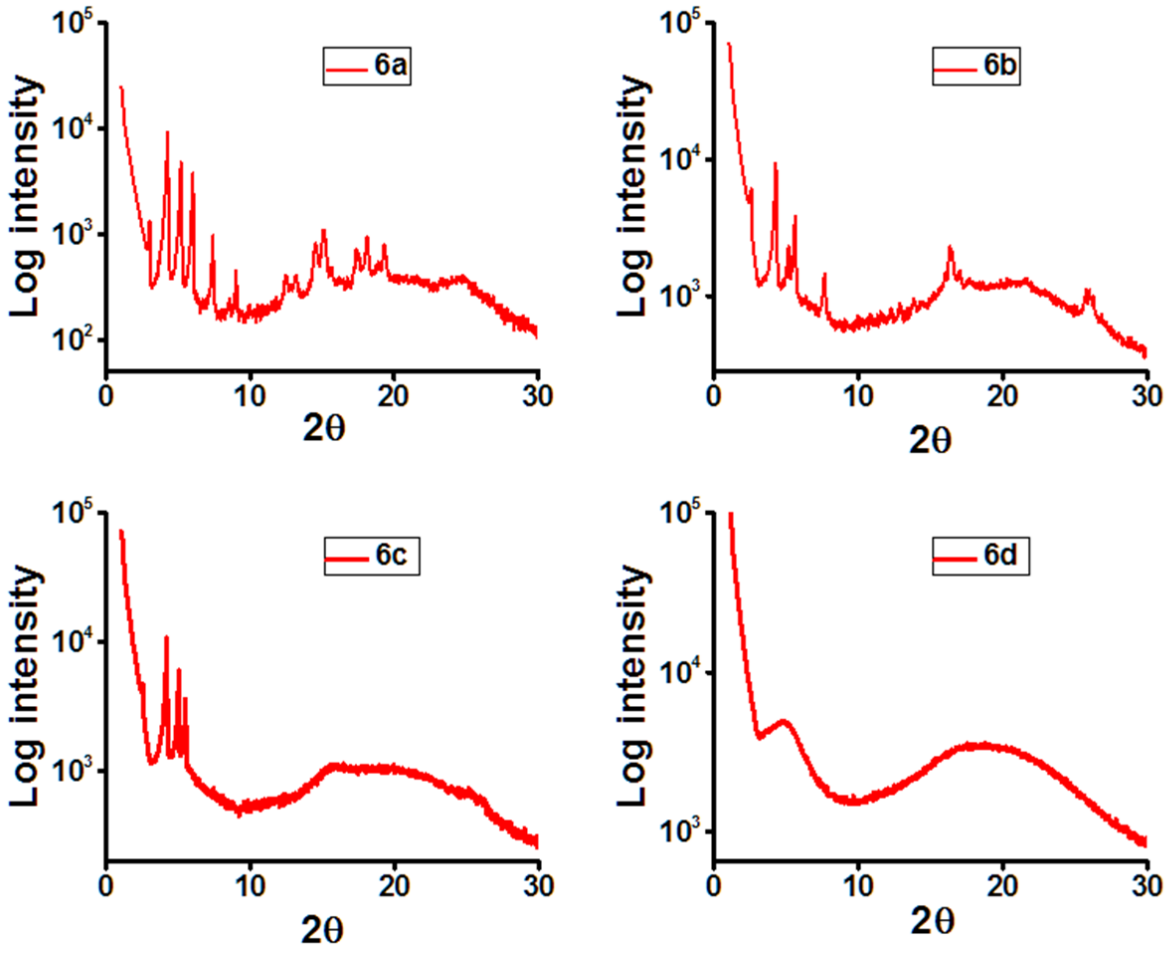


Figure 20: X-ray diffractograms of 6a (70°C); 6b (65°C); 6c (40°C); 6d (25°C)

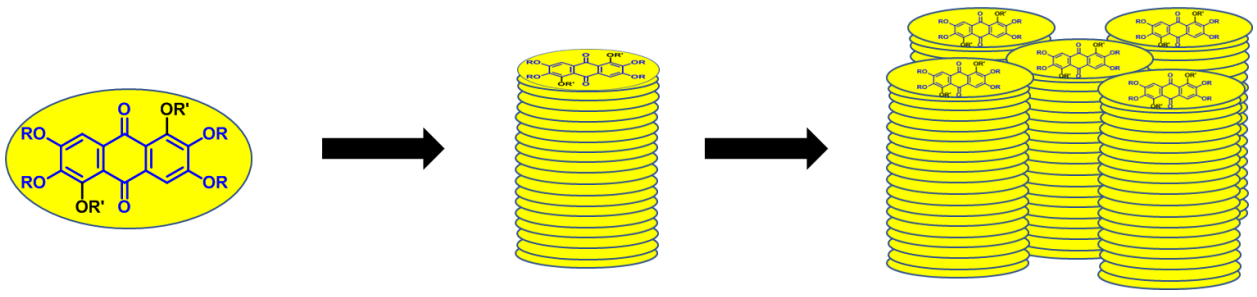


Figure 21: Proposed model for packing of molecule sin columnar phase

Table 1: Thermal behaviour of compounds

. [a] Phase transition temperatures (°C) and the corresponding energy changes ($kJmol^{-1}$)

Compd.	Phase sequence	
	Heating	Cooling
6a	Cr 117.17 (33.69) I	I 98.4 (34.57) Cr
6b	Col_r 72.03 (26.76) I	I 65 (24.52) Col_r
6c	Col_r 52.18 (16.65) I	I 37.58 (12.95) Col_r

COMPOUND	**Phase (temperature in °C)**	**Spacing (Å)**		**Index**	**parameters**
		d obs	**d cal**		
6b	**Rectangular (65°C)**	34.21 20.74 17.07 15.71 11.55 5.40 5.21 3.43	34.21 19.75 17.10 15.74 11.40 5.44 5.18 3.63	20 11 04 13 60 40 04	a=68.42 Å b=21.76 Å S= 1488.8192 $Å^2$ V=5106.6498 $Å^3$ Z= 1.98
6c	**Rectangular (45°C)**	34.74 21.13 17.60 16.05 11.85 5.72 3.53	34.74 21.13 17.52 16.28 11.40 5.80 3.6	20 11 04 13 60 40	a=69.48 Å b= 22.18 Å S= 1541.0664 $Å^2$ V= 5439.964 $Å^3$ Z= 1.99

Table 2: d-spacings of compounds

4.3.3 Lyotropic Behaviour

The compounds are made up of both hydrophilic and hydrophobic groups. This prompted us to look for the lyotropic behavior in these compounds. There are reports of cholesterol with EO chains attached to chromophore having excellent gelation ability forming fiber-like structures[9,11]. We checked for mesomorphism in aqueous medium by dispersing the compounds in 5wt% composition in water resulted in a viscous liquid. XRD studies confirm that they are not liquid crystalline (**Figure22**)

The compound **6a** was completely precipitated. The other compounds were fluids and did not show any mesomorphic behavior which was justified from XRD. The compounds were tested for mesomorphism in the formamide medium. Only **6b &6c** showed mesomorphic rectangular phase They were birefringent under POM as shown in figure 23. It was further confirmed by XRD studies (**Figure24**)

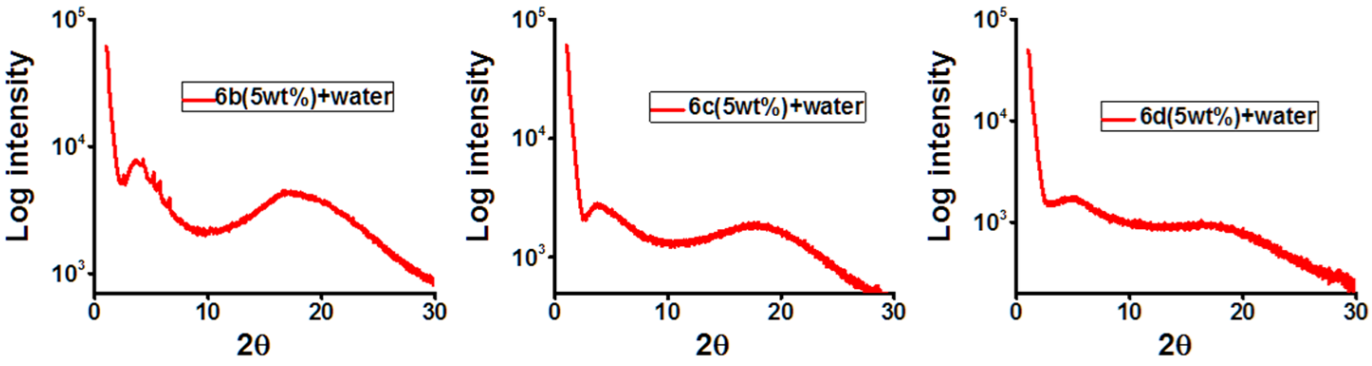


Figure 22: Diffractograms of 6b-d (5wt%) in water

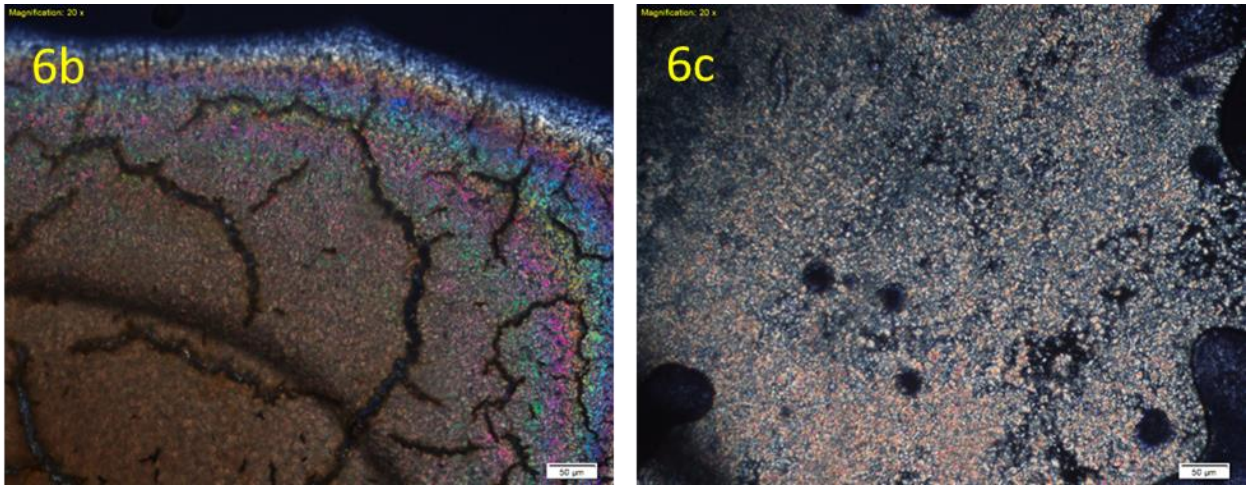


Figure 23: POM images of 6b (5wt %) in formamide at 35°C; 6c(5wt%)in formamide at 40°C

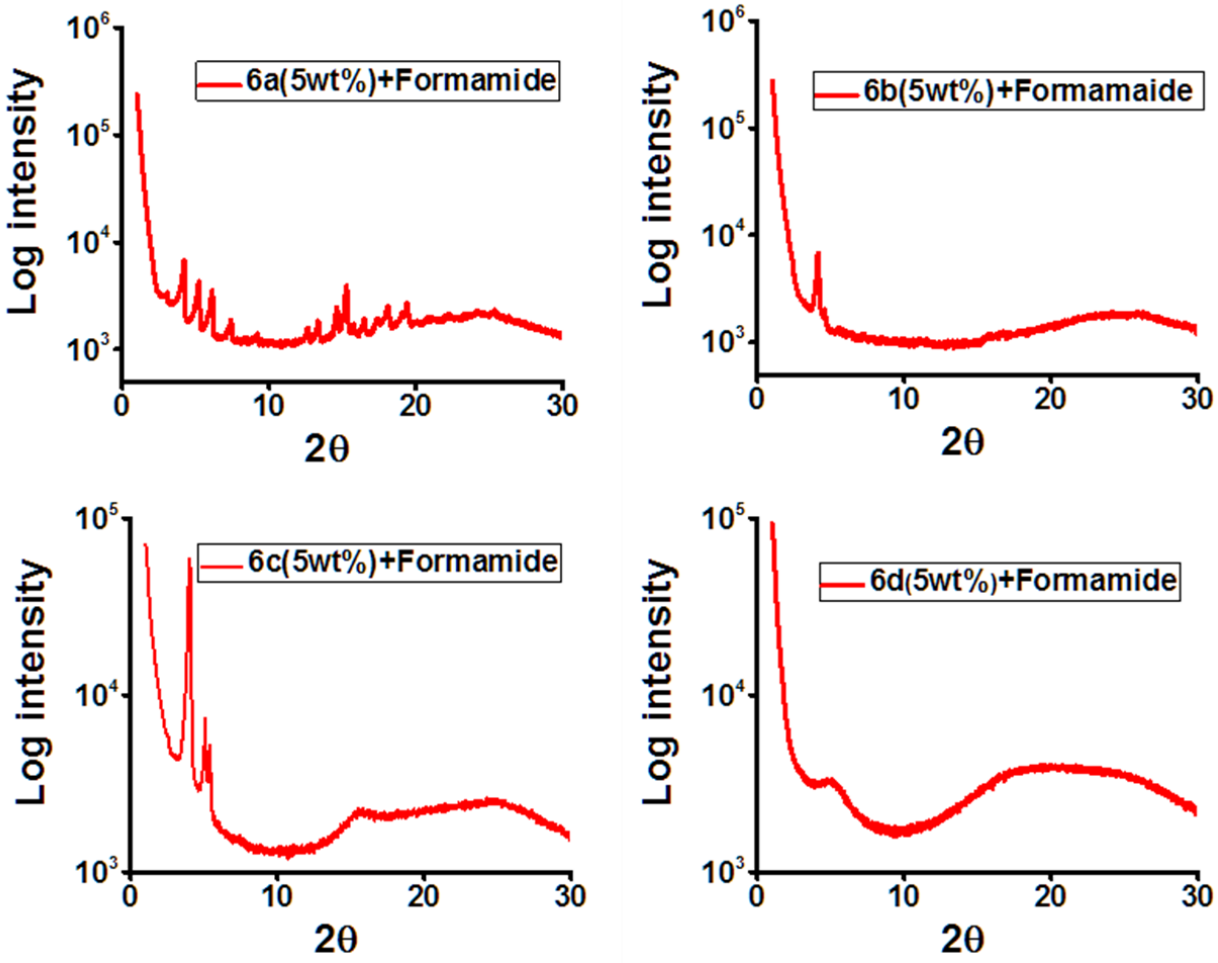


Figure 24: X-ray diffractograms of 6a 5wt%in formamide (RT); 6b 5wt%in formamide (RT); 6c 5wt%in formamide (RT); 6d 5wt%in formamide (RT)

4.4 Conclusions

Anthraquinones with cholesterol functionalization with ethylene glycol spacer has been synthesized. The compounds were found to have good thermal stability. The length of ethyleneoxy spacer influences the mesomorphic order in these compounds. The lower and higher homologs were solid and liquid respectively. The other two compounds were showing the columnar phase. They form rectangular phase in the formamide medium also.

4.5 Experimental section

All the chemicals and reagents are purchased from Sigma Aldrich and used directly. The solvents are AR grade and they were distilled and dried using corresponding protocols before usage. The crude products were subjected to column chromatography using silica gel (100-200 mesh) and recrystallized using suitable solvents. All the intermediates and final products structure were confirmed by NMR, Mass, Elemental analysis. ^{1}H NMR and ^{13}C NMR (Nuclear magnetic resonance spectroscopy) were recorded by Bruker 500MHz instrument using $CDCl_3$ as solvent and trimethyl silane as internal standard. Chemical shift values are given in ppm and the solvent $CDCl_3$ peaks appear at ^{1}H NMR: δ = 7.23 ppm and ^{13}C NMR δ = 77.0 ppm. Peak multiplicity is given as s = singlet, d = doublet, t = triplet, m = multiplet, b = broad peak. Elemental analysis was done by using the Elementar Vario MICRO Select instrument. Samples were placed between the glass slides and kept inside Mettler FP82HT hot stage which is controlled by Mettler FP90 central processor and the liquid crystal textures were recorded using Olympus BX51 polarizing optical microscope (Olympus, Tokyo, Japan). Mettler Toledo DSC instrument was used to record the phase transition temperatures of all the compounds. The peak temperatures are given in ^{o}C and corresponding enthalpy values are given in J g^{-1}. Panalytical (Empyrean) Cu-Kα (1.54Å) X-ray diffractometer was used to further confirm the mesophase structure of all compounds. The thermal stability of all the compounds was studied using TGA 4000 thermogravimetric analysis instrument.

General procedure for the synthesis of cholesterol tosylate:

Chol-OTS: To an ice-cooled solution of cholesterol (1) (2.5 g, 6.47 mmol, 1eq) in dry pyridine (5 ml) and chloroform (5 ml), *p*-tosyl chloride (1.47 g, 7.76 mmol, 1.1 eq) was added. A catalytic amount of DMAP was also added. The reaction mixture was then allowed to stir at 0 °C for 6 h. Solvent was evaporated. Then, EtOAc (35 ml) was added, and the reaction mixture was washed with 1 N HCl (2 × 50 ml), water (50 ml), and brine (saturated NaCl) (50 ml); the organic layer was separated and dried over anhydrous Na_2SO_4. The solvent was evaporated to leave a residue. From the residue, cholest-5-en-3*β*-tosylate (2) was recrystallized using chloroform and methanol. Yield: 90% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.65 (s, 3H), 0.86 – 0.96 (m, 11H), 1.01 - 1.12 (m, 12H), 1.21 - 1.58 (m, 18H), 1.66 – 1.73 (m, 1H), 1.79 – 1.82 (m, 3H), 1.92 – 2.0 (m,2H), 2.25 – 2.27 (m, 1H), 2.44 (s, 4H), 4.31 (bs, 1H), 5.30 (s, 1H), 7.33 (d, *J* = 7.5 Hz, 2H), 7.79 (d, *J* = 7.5 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ ppm = 11.84, 18.71, 19.15, 21.00, 21.63, 22.56, 22.81,

23.81, 24.25, 28.01, 28.19, 28.64, 31.76, 31.86, 35.76, 36.17, 36.35, 36.90, 38.88, 39.51, 39.67, 42.30, 49.93, 56.12, 56.66, 82.41, 123.52, 127.64, 129.74, 134.75, 138.88, 144.38 ; Elemental analysis: C, 75.82; H, 9.83; S, 5.60 calculated (%): C, 75.51; H, 9.69; S, 5.93 (expt. %).

General procedure for the synthesis of compounds 2a-d:

To a suspension of cholest-5-ene-3β-tosylate (1eq) in anhydrous dioxane (25 mL), oligo ethylene glycol (25 eq), was added and the mixture was stirred under reflux for overnight in an inert atmosphere. The solution was cooled and the solvent removed in vacuo. The white residue was partitioned between $CHCl_3$ (20 mL) and water (20 mL), washed sequentially with saturated $NaHCO_3$ (2 × 10 mL), water (10 mL), and saturated brine (10 mL), and dried over anhydrous Na_2SO_4, and the solvent was removed in vacuo. The residue was purified by column chromatography on silica gel (60−120 mesh) using ethyl acetate/hexanes.

Compound 2a : cholesterol tosylate (5g, 9.24mmol, 1eq), dioxane (25mL) ethylene glycol (12.92ml, 231.1mmol, 25eq) Yield: 70% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.86 – 0.98 (m, 10H), 1.00 – 1.07 (m, 5H), 1.09 – 1.18 (m, 7H), 1.22 – 1.34 (m, 4H), 1.41 - 1.58 (m, 7H), 1.82 – 2.08 (m, 6H), 2.18 – 2.23 (m, 1H), 2.36 – 2.39 (m, 1H), 3.20 (bm, 1H), 3.59 (bs, 2H), 3.72 (bs, 2H), 5.35 (s, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.86, 18.73, 19.37, 21.08, 22.56, 22.82, 23.85, 24.29, 28.01, 28.23, 28.42, 31.90, 31.95, 35.79, 36.20, 36.86, 37.19, 39.11, 39.52, 39.79, 42.11, 50.19, 56.19, 56.78, 62.07, 69.00, 79.46, 121.75, 140.70 ; Elemental analysis: C, 80.42; H, 11.28 calculated (%): C, 80.87; H, 11.70 (expt. %).

Compound 2b : cholesterol tosylate (5g, 9.24mmol, 1eq), dioxane (25 mL), diethylene glycol (21.89mL, 231.1 mmol, 25 eq) Yield: 60% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.86 – 0.94 (m, 10H), 0.99 – 1.15 (m, 12H), 1.22 – 1.34 (m, 4H), 1.41 - 1.59 (m, 7H), 1.82 – 2.02 (m, 7H), 2.19 – 2.24 (m, 1H), 2.36 – 2.39 (m, 1H), 3.20 (bm, 1H), 3.63 – 3.73 (m, 8H), 5.34 (s, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85, 18.72, 19.37, 21.07, 22.56, 22.81, 23.83, 24.28, 28.00, 28.23, 28.32, 31.89, 31.94, 35.78, 36.20, 36.86, 37.20, 38.97, 39.52, 39.79, 42.32, 50.19, 56.18, 56.78, 61.83, 67.40, 70.77, 72.59, 79.62, 121.71, 140.74 ; Elemental analysis: C, 78.82; H, 11.98 calculated (%): C, 78.43; H, 11.46 (expt. %).

Compound 2c : cholesterol tosylate (5g, 9.24mmol, 1eq), dioxane (25 mL) , triethylene glycol (31.55 mL, 231.1 mmol, 25 eq) Yield: 50%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.85 – 1.14 (m, 22H), 1.22 – 1.59 (m, 12H), 1.83 – 2.01 (m, 5H), 2.19 – 2.23 (m, 1H), 2.35 – 2.38 (m, 1H), 3.18 – 3.19 (bm, 1H), 3.61 – 3.73 (m, 12H), 5.34 (s, 1H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85, 18.72, 19.37, 21.07, 22.55, 22.81, 23.83, 24.29, 28.00, 28.23, 28.30, 31.89, 31.94, 35.78, 36.19, 36.86, 37.22, 38.98, 39.52, 39.79, 42.32, 50.19, 56.17, 56.78, 61.74, 67.21, 70.32, 70.60, 70.85, 72.61, 79.56, 121.60 , 140.88 ; Elemental analysis: C, 76.63; H, 11.62 calculated (%): C, 76.40; H, 11.27 (expt. %).

Compound 2d: cholesterol tosylate (5g, 9.24mmol, 1eq), dioxane (9 mL) tetra ethylene glycol (39.9mL, 231.1mmol, 25 eq) Yield: 60%. ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.86 – 0.91 (m, 10 H), 0.99 (s, 6H), 1.02 – 1.14 (m, 7H), 1.24 – 1.26 (m, 3H), 1.32 – 1.57 (m, 7H), 1.83 – 2.01 (m, 5H), 2.20 – 2.23 (m, 1H), 2.35 – 2.38 (m, 1H), 2.71 (s, 1H), 3.17 – 3.18 (bm, 1H), 3.61 – 3.72 (m, 16H), 5.33 (s, 1H); ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 7.89, 14.76, 15.39, 17.10, 18.61, 18.86, 19.87, 20.32, 24.03, 24.27, 27.92, 27.98, 31.82, 32.24, 32.88, 33.25, 34.95, 35.55, 35.83, 38.35, 46.22, 52.21, 52.81, 57.64, 63.21, 66.21, 66.51, 66.54, 66.61, 66.85, 68.83, 75.59, 117.61, 136.88 ; Elemental analysis: C, 74.92; H, 11.43 calculated (%): C, 74.68; H, 11.10 (expt. %).

General procedure for the synthesis of compounds 3a-d:

The alcohol **2a-d** (1eq) was taken in dry $CHCl_3$ (150 mL), pyridine (20 mL) was added, and the mixture was cooled to 0 °C. To the cold solution, *p*-toluenesulfonyl chloride (2 equiv) was added and allowed to stir for 3 h at room temperature. The reaction mixture was poured into cold dilute HCl (25 mL of 6 N HCl) and extracted with $CHCl_3$ (2 × 15 mL). The combined organic layers were dried over Na_2SO_4 (anhydrous), and the solvent was removed in vacuo. The concentrated product was purified through silica gel column chromatography.

Compound 3a : compound 2a (3.8g, 8.8 mmol, 1eq), chloroform 150ml, TsCl (3.36g, 17.64 mmol, 2eq), pyridine (19ml) Yield: 80% ; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.86 – 0.91 (m, 11H), 0.96 – 1.00 (m, 7H), 1.05 – 1.14 (m, 7H), 1.22 – 1.57 (m, 13H), 1.78 – 1.83 (m, 3H), 1.94 – 2.01 (m, 2H), 2.06 – 2.11 (m, 1H), 2.22 – 2.25 (m, 1H), 2.44 (s, 3H), 3.09 – 3.10 (bm, 1H), 3.65 (d, *J*= 3.50 Hz, 2H), 4.14 (d, *J*= 3.50 Hz, 2H), 5.31 (s, 1H), 7.33 (d, *J*= 7.50 Hz, 2H), 7.80 (d, *J*= 7.50 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85, 18.72, 19.33, 21.06, 21.63, 22.56, 22.82, 22.83, 24.28, 28.01, 28.18, 28.22, 31.88, 31.93, 35.78, 36.20, 36.79, 37.09, 38.87, 39.52, 39.77, 42.32, 50.15, 56.17, 56.76, 65.37, 69.66, 79.59, 121.79, 128.00, 129.76, 133.24, 140.56, 144.67 ; Elemental analysis: C, 74.20; H, 9.96 calculated (%): C, 73.93; H, 9.65; S, 5.48 (expt. %).

Compound 3b : Compound 2b (2.6g, 5.47 mmol, 1eq), chloroform 100ml, TsCl (2.68g, 10.95 mmol, 2eq), pyridine (13ml) Yield: 80% ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.85 – 1.15 (m, 23H), 1.24 – 1.36 (m, 4H), 1.43 – 1.62 (m,9H), 1.78 – 1.88 (m, 3H), 1.94 – 2.04 (m, 2H), 2.15 – 2.20 (m, 1H), 2.31 – 2.35 (m, 1H), 2.44 (s, 3H), 3.10 - 3.16 (m, 1H), 3.56 (s, 4H), 3.69 (t, *J*= 5.00 Hz , 2H), 4.16 (t, *J*= 5.00 Hz, 2H), 5.33 (m, 1H), 7.33 (d, *J*= 8.00 Hz, 2H), 7.80 (d, *J*= 8.5 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.86, 18.72, 19.38, 21.07, 21.66, 22.57, 22.82, 23.83, 24.30, 28.02, 28.24, 28.34, 31.90, 31.95, 35.79, 36.19, 36.87, 37.22, 39.04, 39.52, 39.79, 42.33, 50.19, 56.16, 56.78, 67.28, 68.70, 69.27, 71.07, 79.56, 121.63, 128.00, 129.81, 133.04, 140.88, 144.75 ; Elemental analysis: C, 72.84; H, 10.03; S, 5.14 calculated (%): C, 72.57; H, 9.62; S 5.10 (expt. %).

Compound 3c : Compound 2c (4.58g, 8.8 mmol, 1eq), chloroform 150ml, TsCl (3.36g, 17.66 mmol, 2eq), pyridine (22 ml) Yield: 75%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.86 – 0.93 (m, 11H), 0.99 – 1.15 (m, 13H), 1.22 – 1.59 (m, 12H), 1.83 – 2.08 (m, 6H), 2.17 – 2.22 (m, 1H), 2.34 – 2.37 (m, 1H), 2.44 (s, 3H), 3.16 – 3.17 (bm, 1H), 3.59 – 3.60 (m, 8H), 3.69 (d, *J*= 3.50 Hz ,2H), 4.16 (d, *J*= 3.50 Hz , 2H), 5.33 (s, 1H), 7.34 (d, *J*= 7.50 Hz, 2H), 7.80 (d, *J*= 8.5 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85, 18.72, 19.36, 20.57, 21.06, 21.62, 22.56, 22.81, 23.82, 24.28, 27.98, 28.22, 28.34, 31.89, 31.93, 35.77, 36.19, 36.85, 37.23, 39.05, 39.51, 39.78, 42.31, 50.18, 56.16, 56.76, 67.25, 68.67, 69.23, 70.53, 70.72,70.91,79.49, 121.54,

127.96, 129.79, 133.09, 140.90, 144.71 ; Elemental analysis: C, 71.49; H, 9.82; S, 4.69 calculated (%): C, 71.39; H, 9.59; S, 4.76 (expt. %).

Compound 3d : compound 2d (5g, 8.8 mmol, 1eq), chloroform 150ml, TsCl (3.38 g, 17.76 mmol, 2eq), pyridine (25 ml) Yield: 70%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 3H), 0.85 – 0.92 (m, 10H), 0.99 – 1.15 (m, 12H), 1.32 – 1.34 (m, 4H), 1.45 – 1.51 (m, 7H), 1.80 – 2.02 (m, 6H), 2.17 – 2.22 (m, 1H), 2.34 – 2.38 (m, 1H), 2.44 (s, 3H), 3.14 – 3.20 (m, 1H), 3.58 – 3.69 (m, 14H), 4.14 - 4.16 (m, 2H), 5.32 – 5.33 (m, 1H), 7.34 (d, *J*= 8.50 Hz, 2H), 7.79 (d, *J*= 8.5 Hz, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85, 18.72, 19.38, 21.06, 21.64, 22.56, 22.82, 23.82, 24.29, 28.00, 28.23, 28.35, 31.89, 31.94, 35.78, 36.19, 36.86, 37.23, 39.05, 39.51, 39.78, 42.32 , 50.18, 56.15, 56.77, 67.27, 68.67, 69.23, 70.51, 70.57, 70.61, 70.74, 70.88 ,79.48, 121.55, 127.98, 129.81, 133.04, 140.94, 144.75 ; Elemental analysis: C, 70.64; H, 9.88; S, 4.62 calculated (%): C, 70.35; H, 9.56; S, 4.47 (expt. %).

General procedure for the synthesis of compounds 6 a-d:

The mixture of compound **5** (1 eq), compound **3a-d** (3 eq), K_2CO_3 (10eq) and KI (catalytic) was stirred and refluxed in 50 mL of dry DMF for 24 h. TLC tests indicated that the raw materials were used out. The solution was cooled to room temperature and neutralized by adding dilute hydrochloric acid (1 M). The residue was treated with water and followed by extraction with chloroform. The organic layer was partitioned. The solvent was removed under reduced pressure to give a yellow solid, which was purified by silica gel column chromatography (eluent: petroleum ether (60–90°C)/ethyl acetate = 9:1, V/V).

Compound 6a : Compound 5 (0.5g , 0.858 mmol, 1eq), compound 3a (1.38g, 2.574 mmol, 3eq), K_2CO_3 (1.185g, 8.58 mmol, 10 eq), Yield: 50% ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 6H), 0.85 – 0.93 (m, 35H), 0.96 – 1.16 (m, 26H), 1.31 – 1.57 (m, 62H), 1.78 – 2.01 (m, 19H), 2.15 – 2.20 (m, 2H), 2.34 – 2.37 (m, 2H), 3.21 – 3.27 (m, 2H), 3.88 – 3.93 (m, 4H), 3.09 (t, *J*= 5.00 Hz, 4H), 4.14 (t, *J*= 5.00 Hz ,4H), 4.24 (t, *J*= 5.00 Hz, 4H), 5.28 – 5.29 (m, 2H), 7.56 (s, 2H)

; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85, 14.03, 14.10, 18.72, 19.37, 21.07, 22.57, 22.61, 22.68, 22.82, 23.83, 24.29, 25.68, 25.74, 28.02, 28.24, 28.31, 29.08, 30.29, 31.55, 31.72, 31.90, 31.95, 35.79, 36.19, 36.86, 37.23, 39.05, 39.52, 39.80, 42.32, 50.21, 56.17, 56.80, 67.32, 69.13, 73.41, 74.13, 79.29, 106.96, 120.36, 121.42, 132.49, 141.09, 146.74, 153.61, 157.34, 181.14 ; Elemental analysis: C, 78.20; H, 10.26 calculated (%): C, 78.64; H, 10.45 (expt. %).

Compound 6b: Compound 5 (0.7g , 1.09 mmol, 1eq), compound 3b (2.060g, 3.276 mmol, 3eq), K_2CO_3 (1.5g, 11 mmol, 10 eq), Yield: 50%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s, 6H), 0.85 – 0.91 (m, 34H), 0.98 – 1.15 (m, 25H), 1.25 – 1.57 (m, 35H), 1.77 – 2.01 (m, 18H), 2.17 – 2.22 (m, 2H), 2.34 – 2.37 (m, 2H), 3.16 - 3.20 (m, 2H), 3.62 – 3.67 (m, 4H), 3.70 – 3.72 (m, 4H), 3.96 (t, *J*= 5.00 Hz, 4H), 4.08 (t, *J*= 6.50 Hz, 4H), 4.14 (t, *J*= 6.5 Hz, 4H), 4.24 (t, *J*= 5.50 Hz, 4H), 5.31 – 5.32 (m, 2H), 7.57 (s, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85,14.10, 14.13, 18.72, 19.38, 21.07, 22.57, 22.63, 22.68, 22.82, 23.84, 24.29, 26.00, 26.02, 28.02, 28.24, 28.36, 29.06, 29.12, 29.23, 30.35, 31.80, 31.90, 31.91, 31.95, 35.79, 36.20, 36.86, 37.26, 39.08, 39.52, 39.79, 42.32, 50.19, 56.17, 56.79, 67.36, 69.16, 70.57, 70.80, 73.00, 74.16, 79.51, 107.07, 120.27, 121.51, 132.47, 140.98, 146.84, 153.46, 157.37, 181.05 ; Elemental analysis: C, 77.45; H, 10.45 calculated (%): C, 77.27; H, 10.38 (expt. %).

Compound 6c: Compound 5 (0.8 g , 1.24 mmol, 1eq), compound 3c (2.52 g, 3.74 mmol, 3eq), K_2CO_3 (1.92 g, 11 mmol, 10 eq), Yield: 50% ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.66 (s, 6H), 0.85 – 0.91 (m, 34H), 0.98 – 1.01 (m, 12H), 1.06 – 1.14 (m, 14H), 1.26 – 1.37 (m, 36H), 1.38 – 1.52 (m, 24H), 1.70 (bs, 3H), 1.76 – 2.01 (m, 19H), 2.17 – 2.22 (m, 2H), 2.33 – 2.37 (m, 2H), 3.15 – 3.20 (m, 2H), 3.63 (bs, 8H), 3.66 – 3.69 (m, 4H), 3.74 – 3.76 (m, 4H), 3.95 (t, *J*= 5.5 Hz, 4H), 4.08 (t, *J*= 6.50 Hz, 4H), 4.15 (t, *J*= 6.50 Hz, 4H), 4.24 (t, *J*= 5 Hz, 4H), 5.31 – 5.32 (m, 2H), 7.57 (s, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.86,14.10, 14.13, 18.72, 19.38, 21.07, 22.57, 22.63, 22.68, 22.82, 23.84, 24.29, 24.98, 26.02, 28.02, 28.24, 28.36, 29.05, 29.11, 29.21, 30.34, 31.80, 31.90, 31.95, 35.80, 36.20, 36.87, 37.25, 39.07, 39.53, 39.79, 42.32, 50.19, 56.17, 56.79, 67.32, 69.18, 70.55, 70.60, 70.66, 70.95, 73.00, 74.16, 79.50, 107.10, 120.26, 121.52, 132.47, 140.98, 146.86, 153.45, 157.39, 181.04 ; Elemental analysis: C, 76.50; H, 10.48 calculated (%): C, 76.05; H, 10.38 (expt. %).

Compound 6d: Compound 5 (0.7g, 1.09 mmol, 1eq), compound 3d (2.351g, 3.276 mmol, 3eq), K_2CO_3 (1.92 g, 11 mmol, 10 eq). Yield: 50%; ^{1}H NMR (500 MHz, $CDCl_3$): δ (ppm) = 0.67 (s,

6H), 0.85 – 0.91 (m, 34H), 0.98 – 1.15 (m, 25H), 1.25 – 1.57 (m, 35H), 1.77 – 2.01 (m, 18H), 2.17 – 2.22 (m, 2H), 2.34 – 2.37 (m, 2H), 3.16 - 3.20 (m, 2H), 3.62 – 3.67 (m, 4H), 3.70 – 3.72 (m, 4H), 3.96 (t, *J*= 5.00 Hz, 4H), 4.08 (t, *J*= 6.50 Hz, 4H), 4.14 (t, *J*= 6.5 Hz, 4H), 4.24 (t, *J*= 5.50 Hz, 4H), 5.31 – 5.32 (m, 2H), 7.57 (s, 2H) ; ^{13}C NMR (125 MHz, $CDCl_3$): δ (ppm) = 11.85,14.10, 14.13, 18.72, 19.38, 21.07, 22.57, 22.63, 22.68, 22.82, 23.84, 24.29, 26.00, 26.02, 28.02, 28.24, 28.36, 29.06, 29.12, 29.23, 30.35, 31.80, 31.90, 31.91, 31.95, 35.79, 36.20, 36.86, 37.26, 39.08, 39.52, 39.79, 42.32, 50.19, 56.17, 56.79, 67.36, 69.16, 70.57, 70.80, 73.00, 74.16, 79.51, 107.07, 120.27, 121.51, 132.47, 140.98, 146.84, 153.46, 157.37, 181.05 ; Elemental analysis: C, 74.34; H, 10.53 calculated (%): C, 74.96; H, 10.25 (expt. %).

4.6 Spectra of compounds:

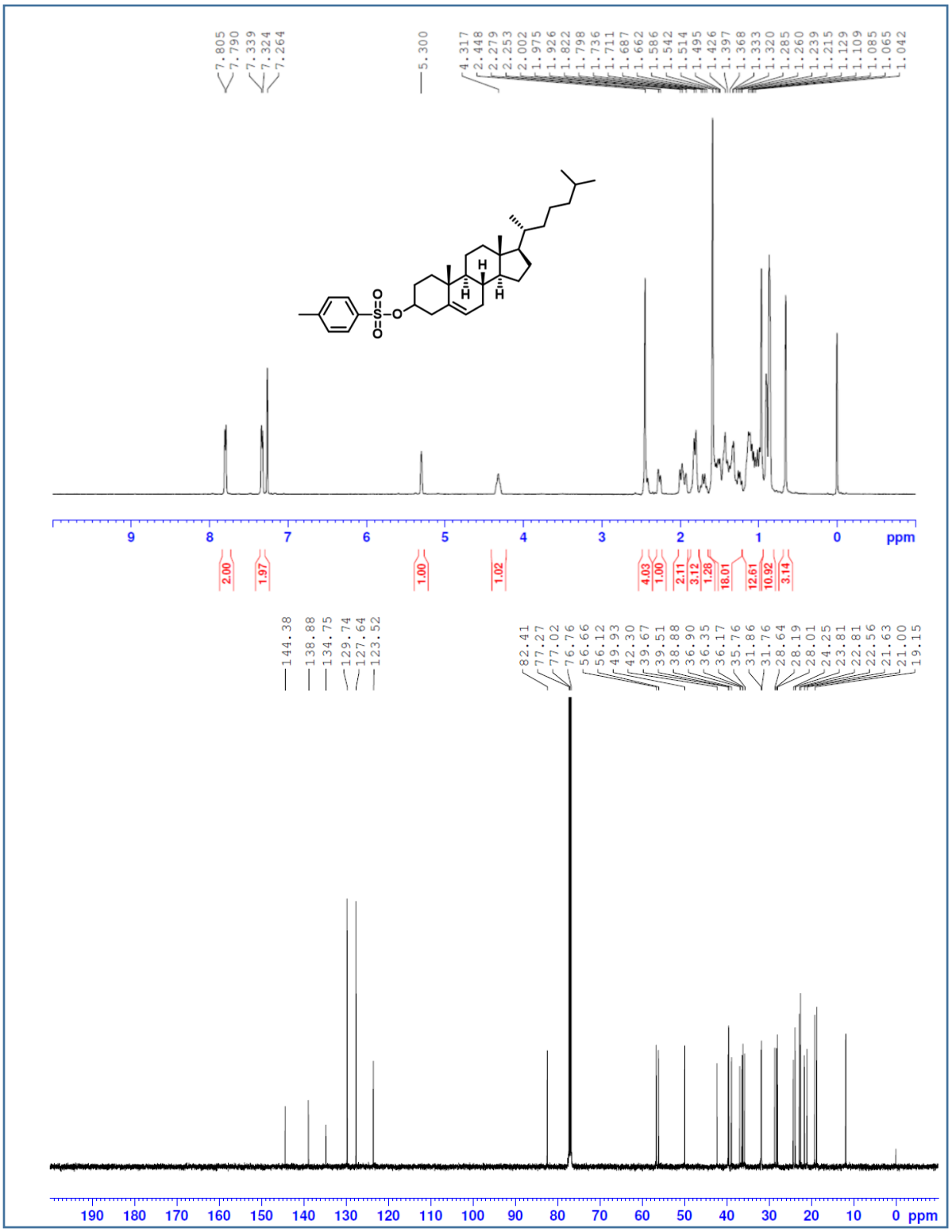


Figure 25: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **R'- OTs (R'=cholesterol)**

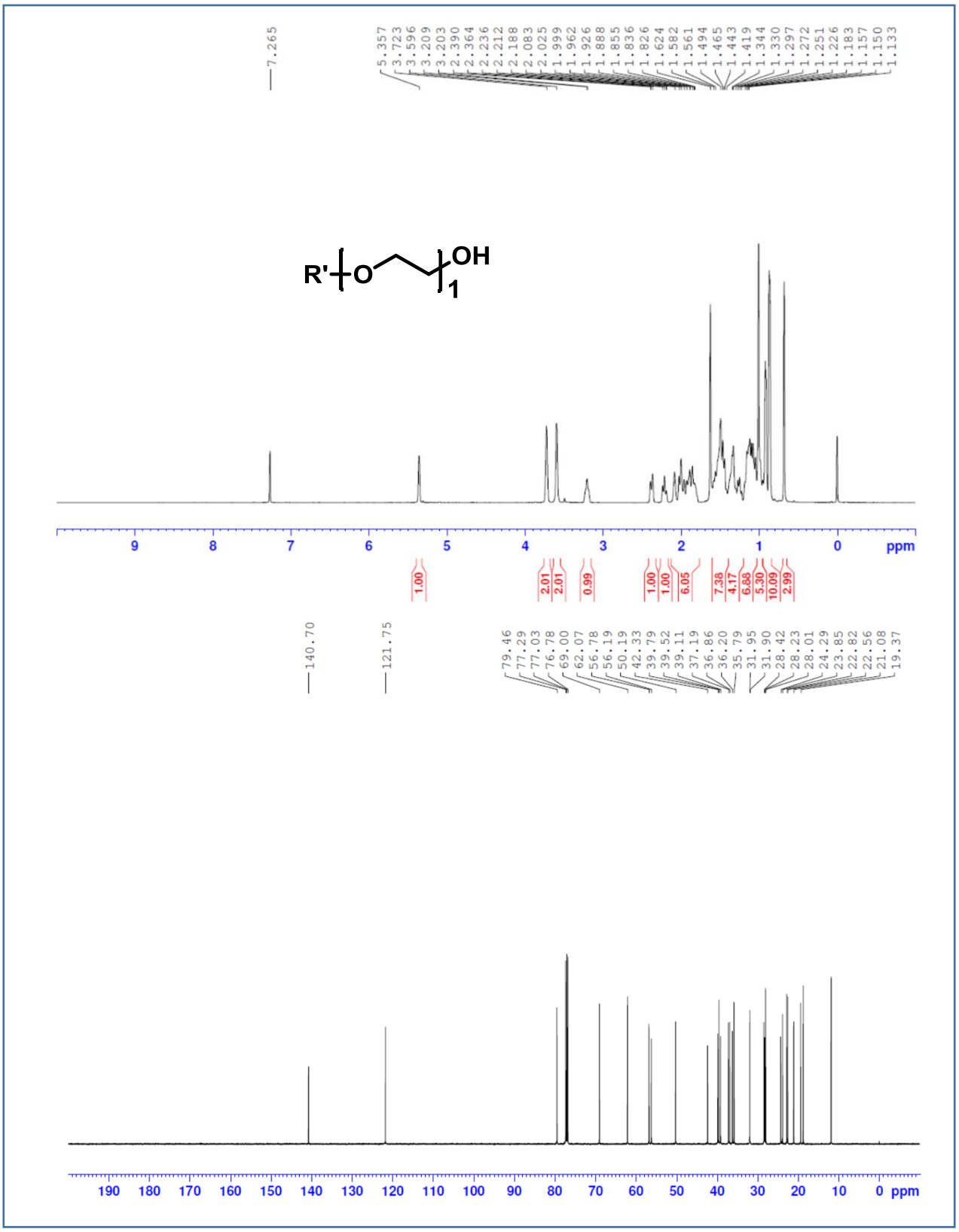


Figure 26: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **2a**

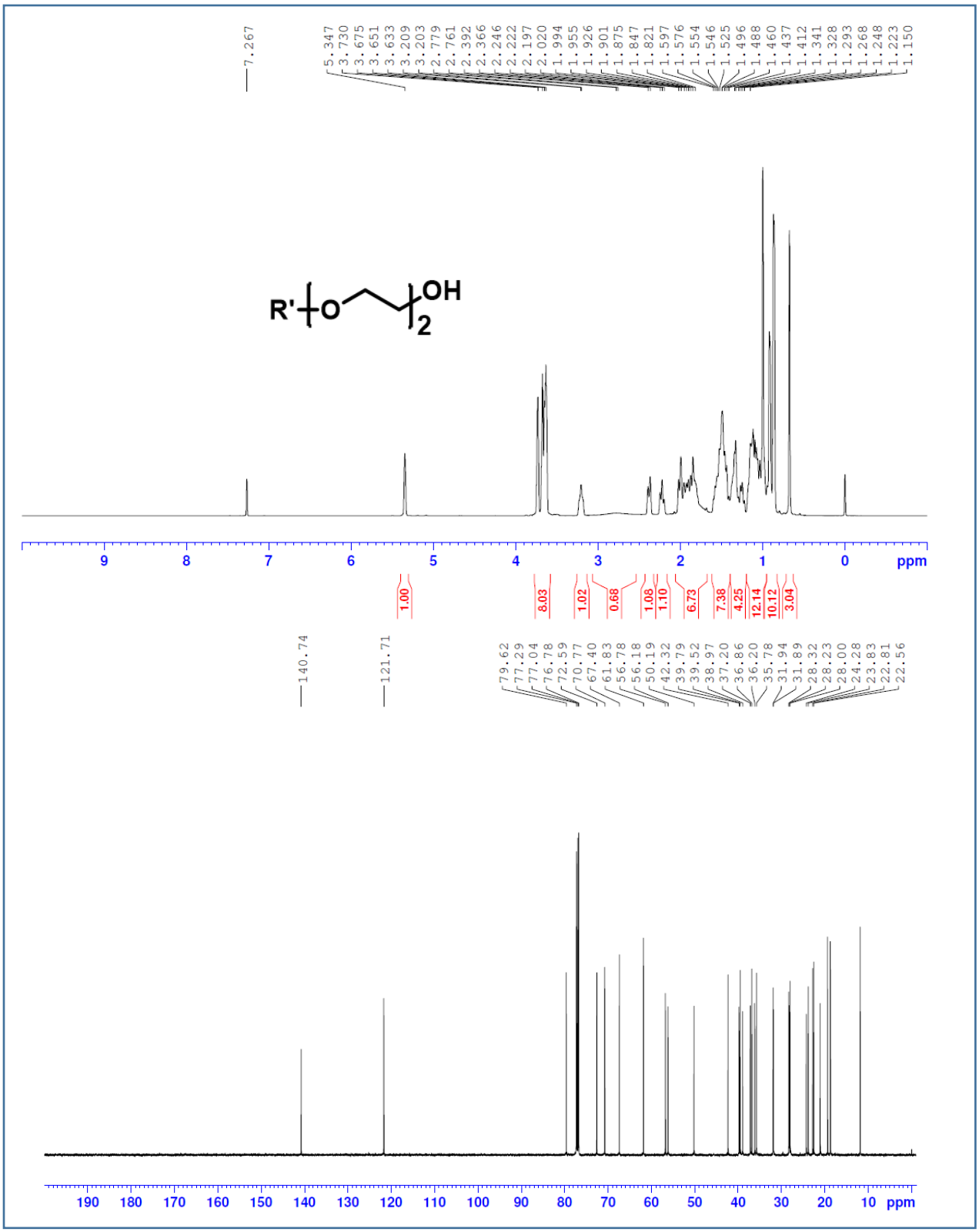


Figure 27: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **2b**

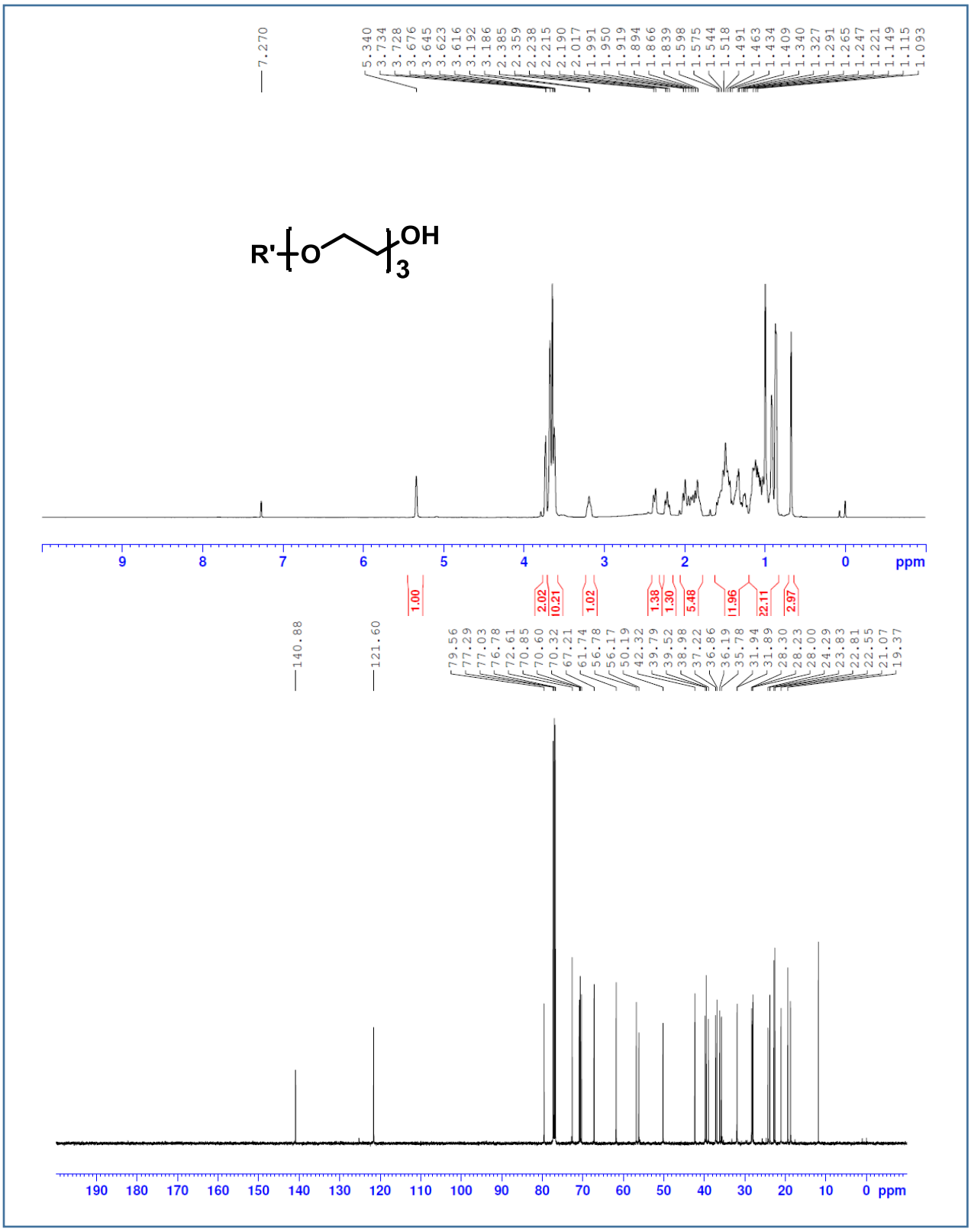


Figure 28: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **2c**

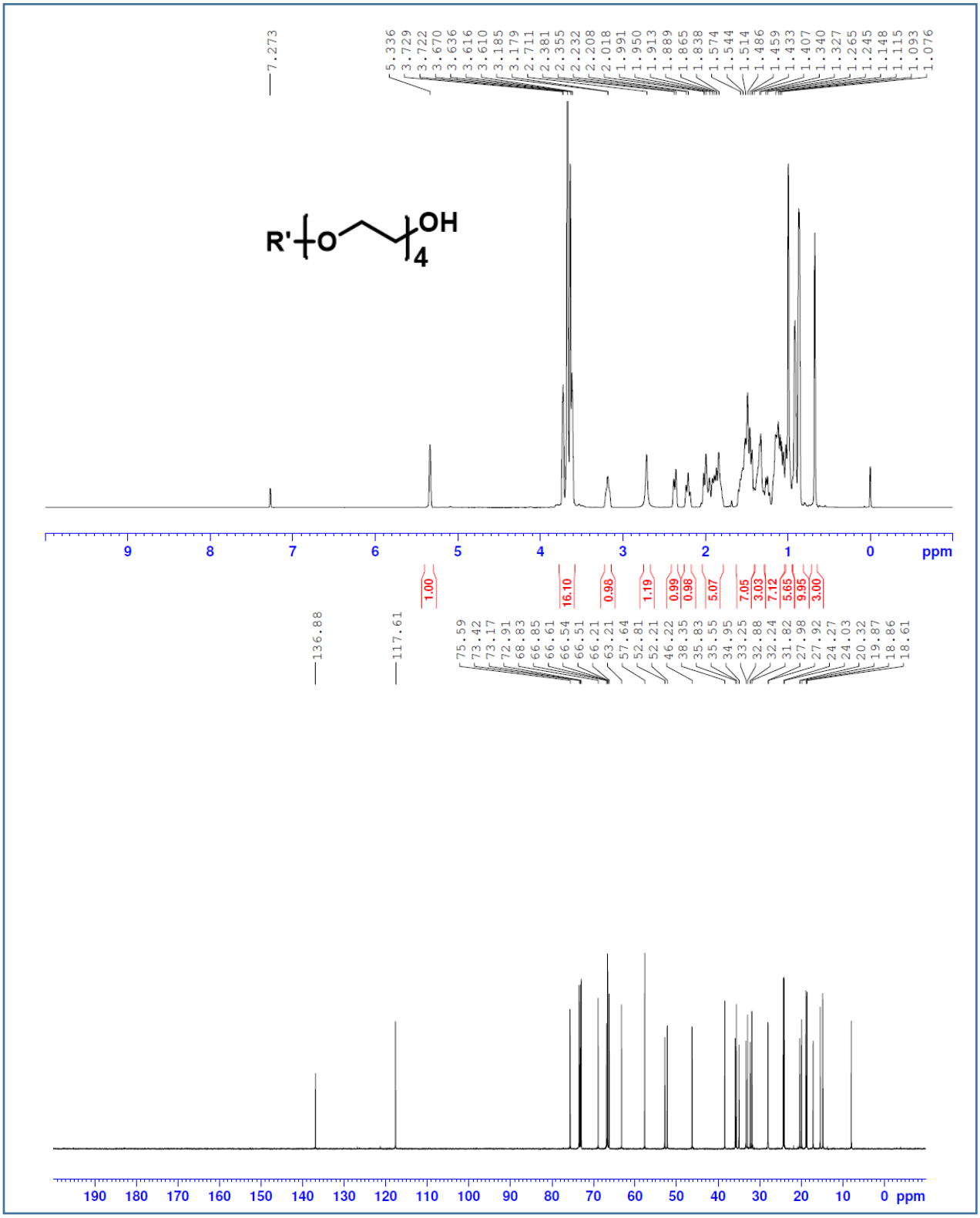


Figure 29: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **2d**

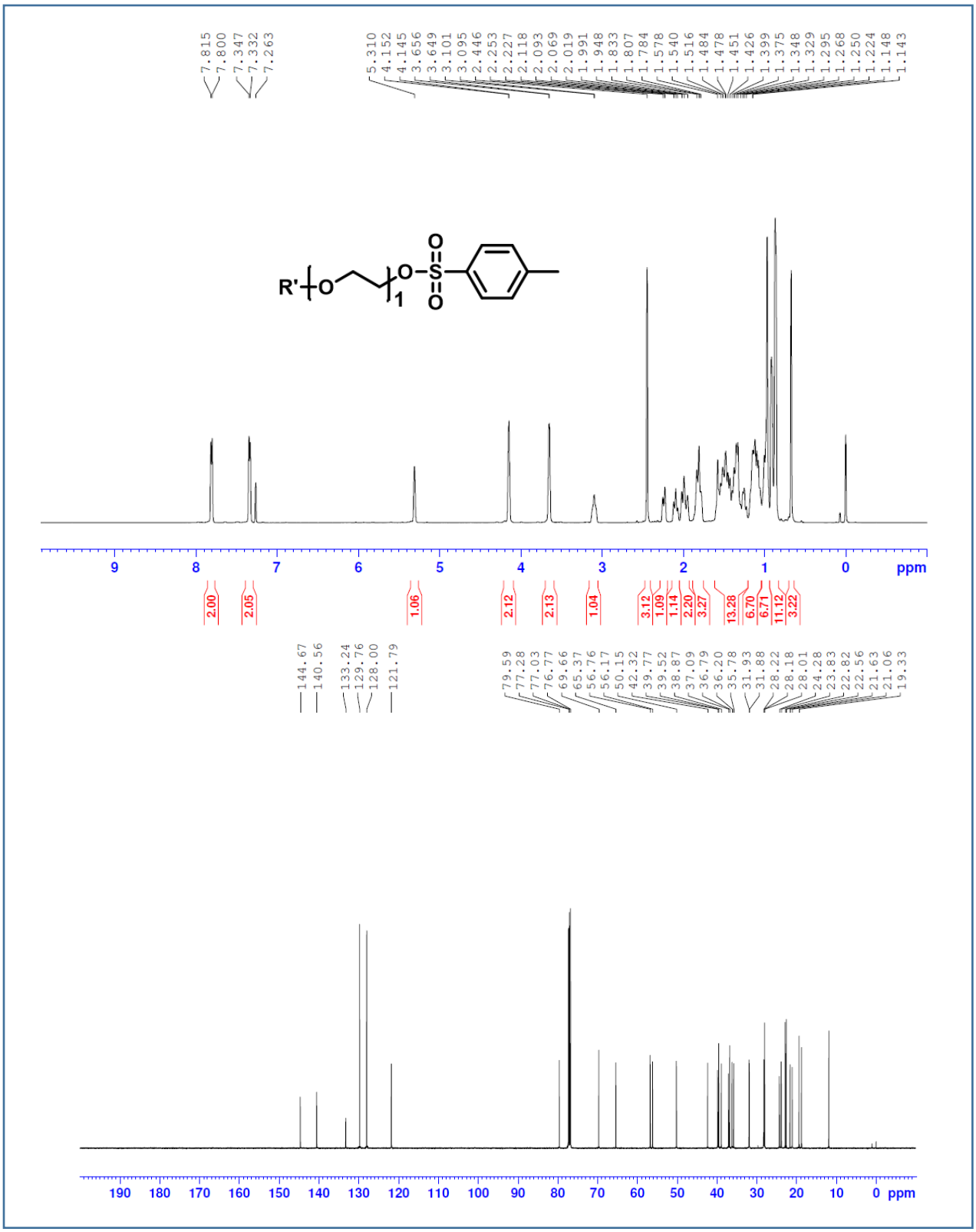


Figure 30: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **3a**

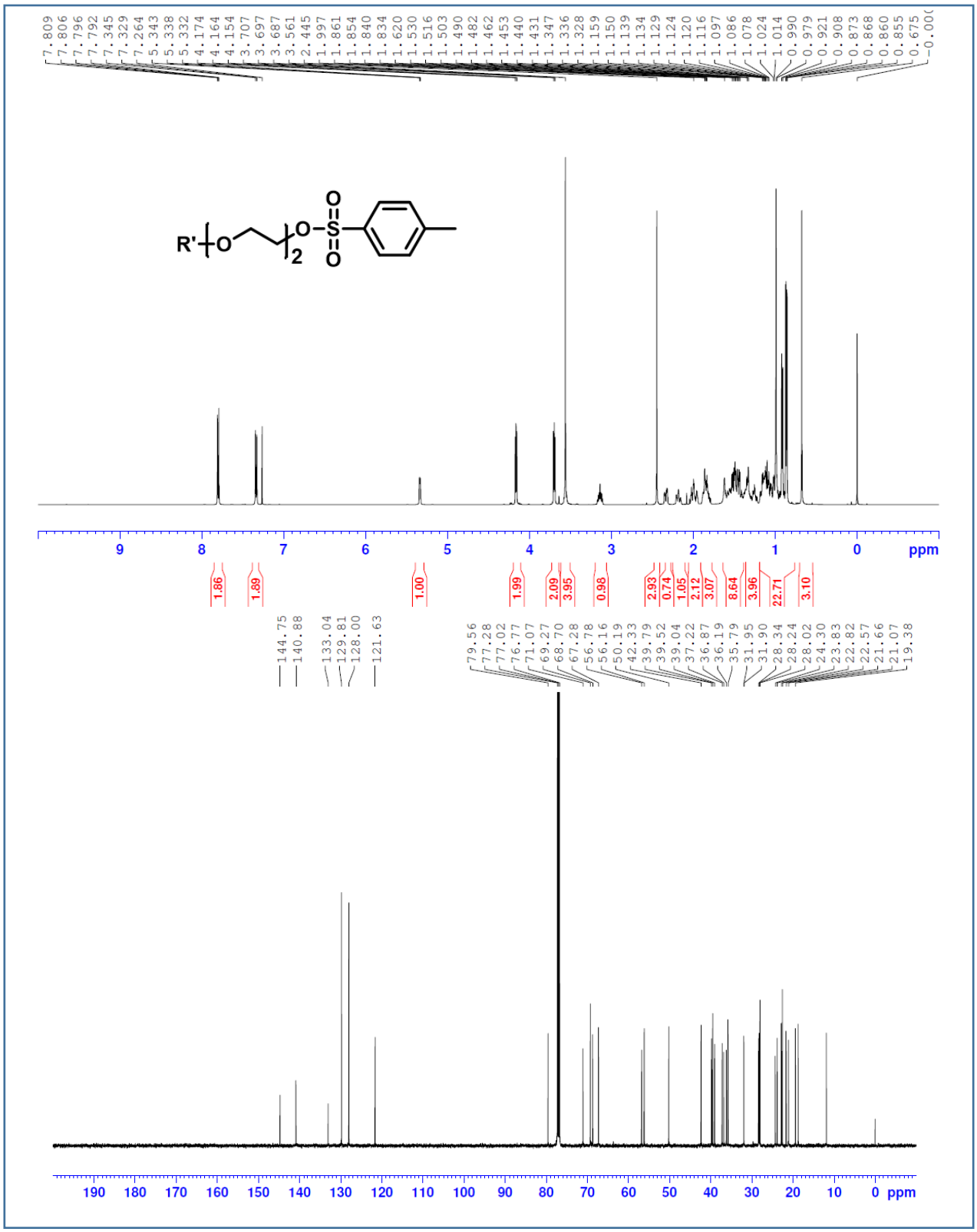


Figure 31: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **3b**

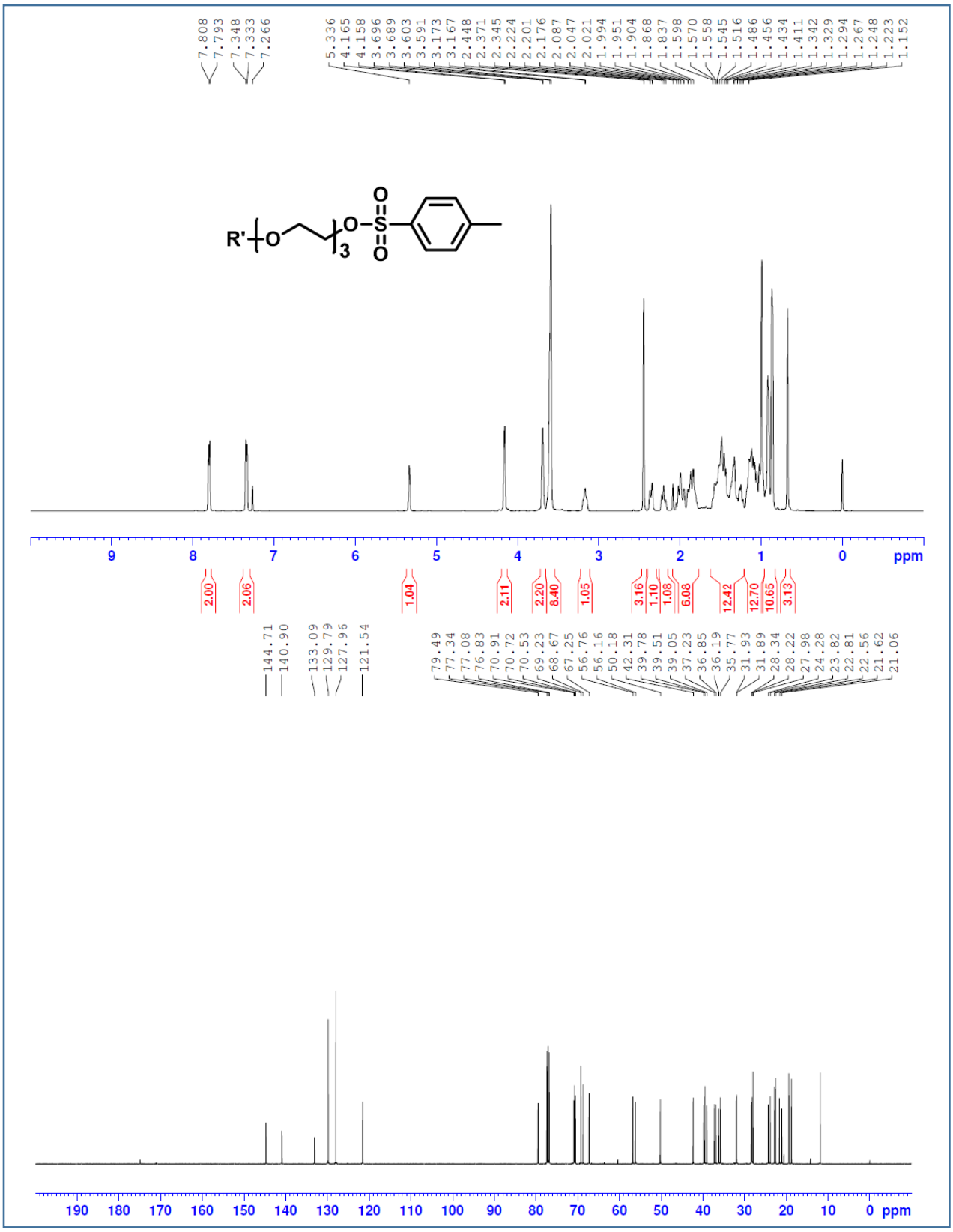


Figure 32: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **3**c

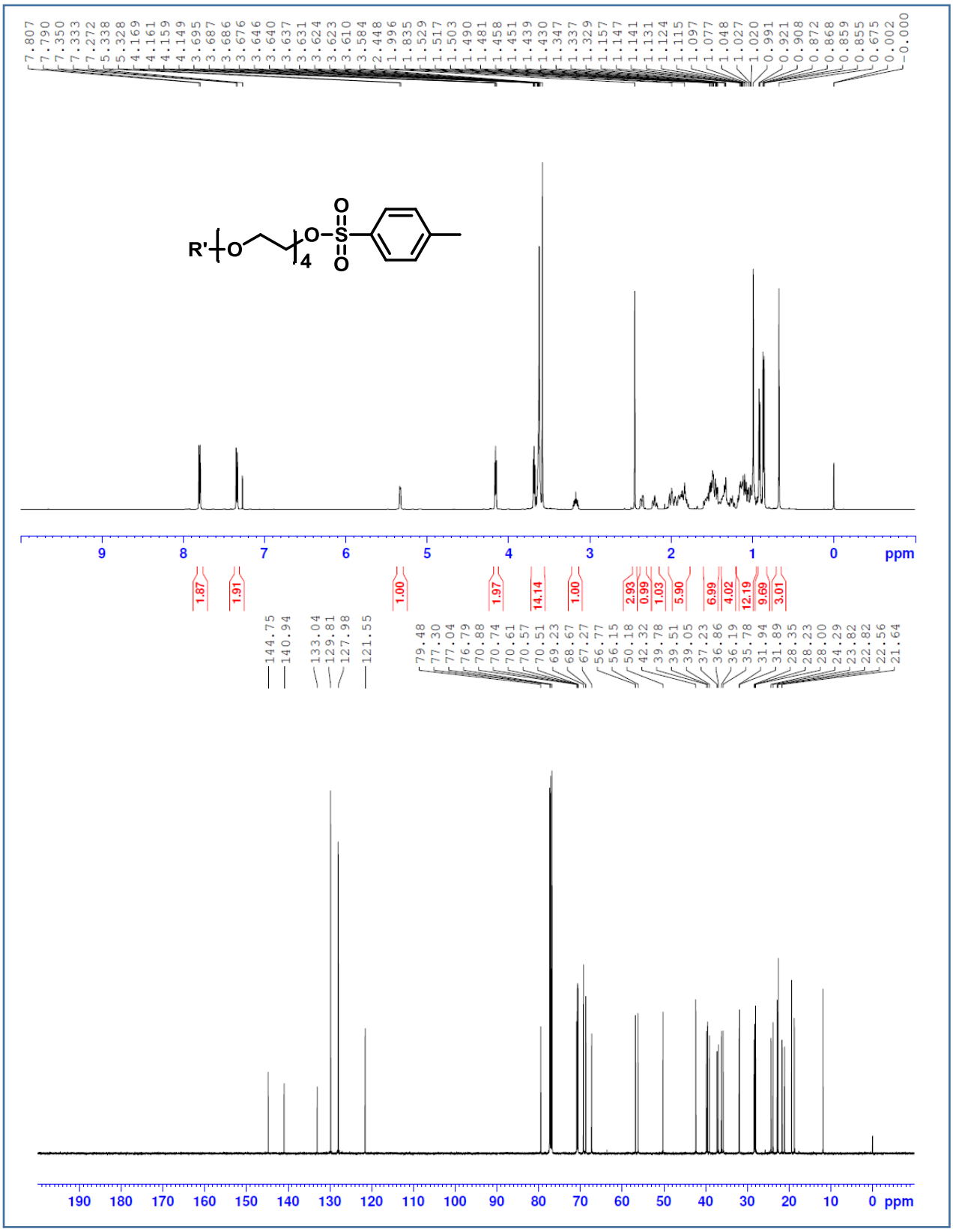


Figure 33: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **3d**

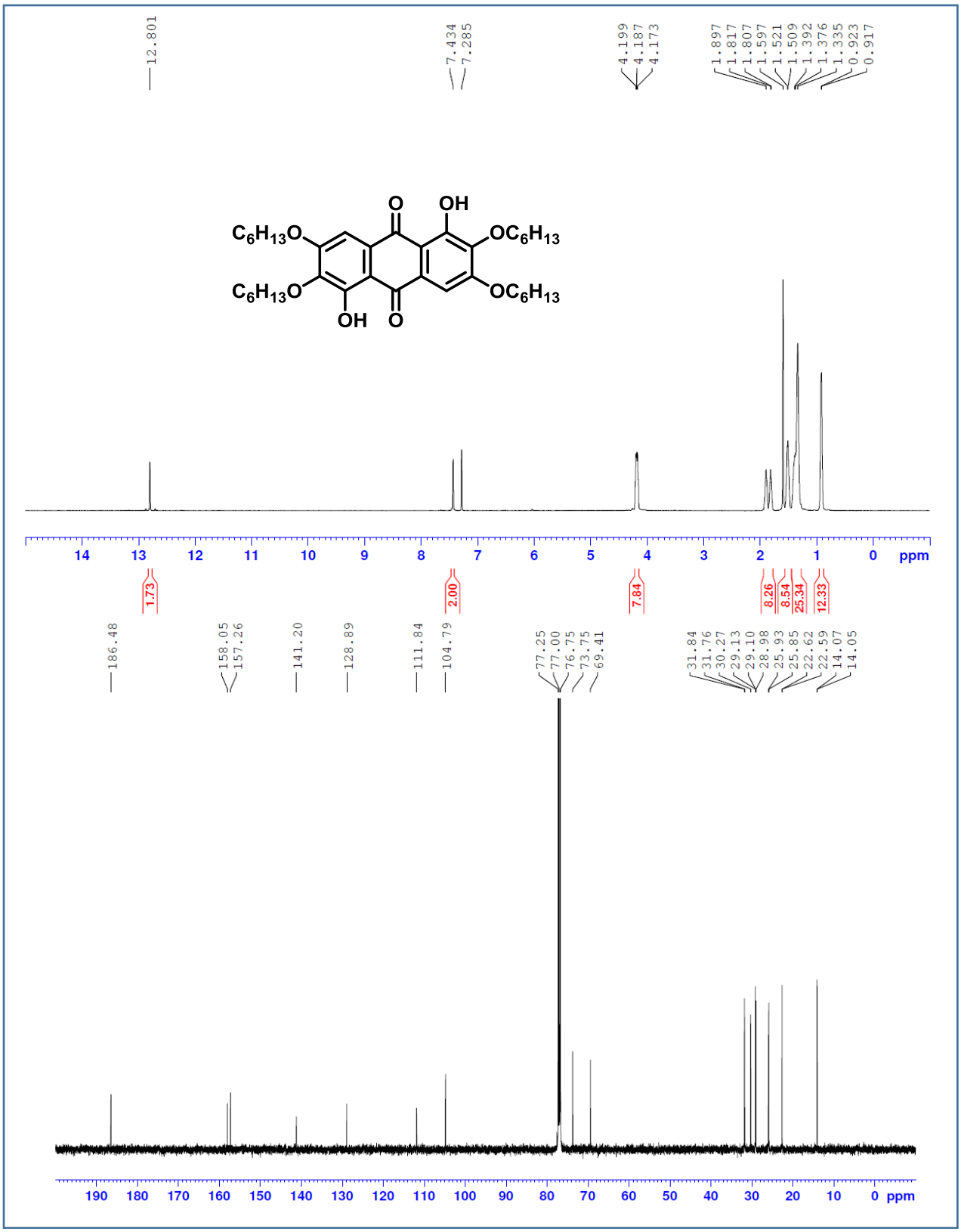


Figure 34: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **5**

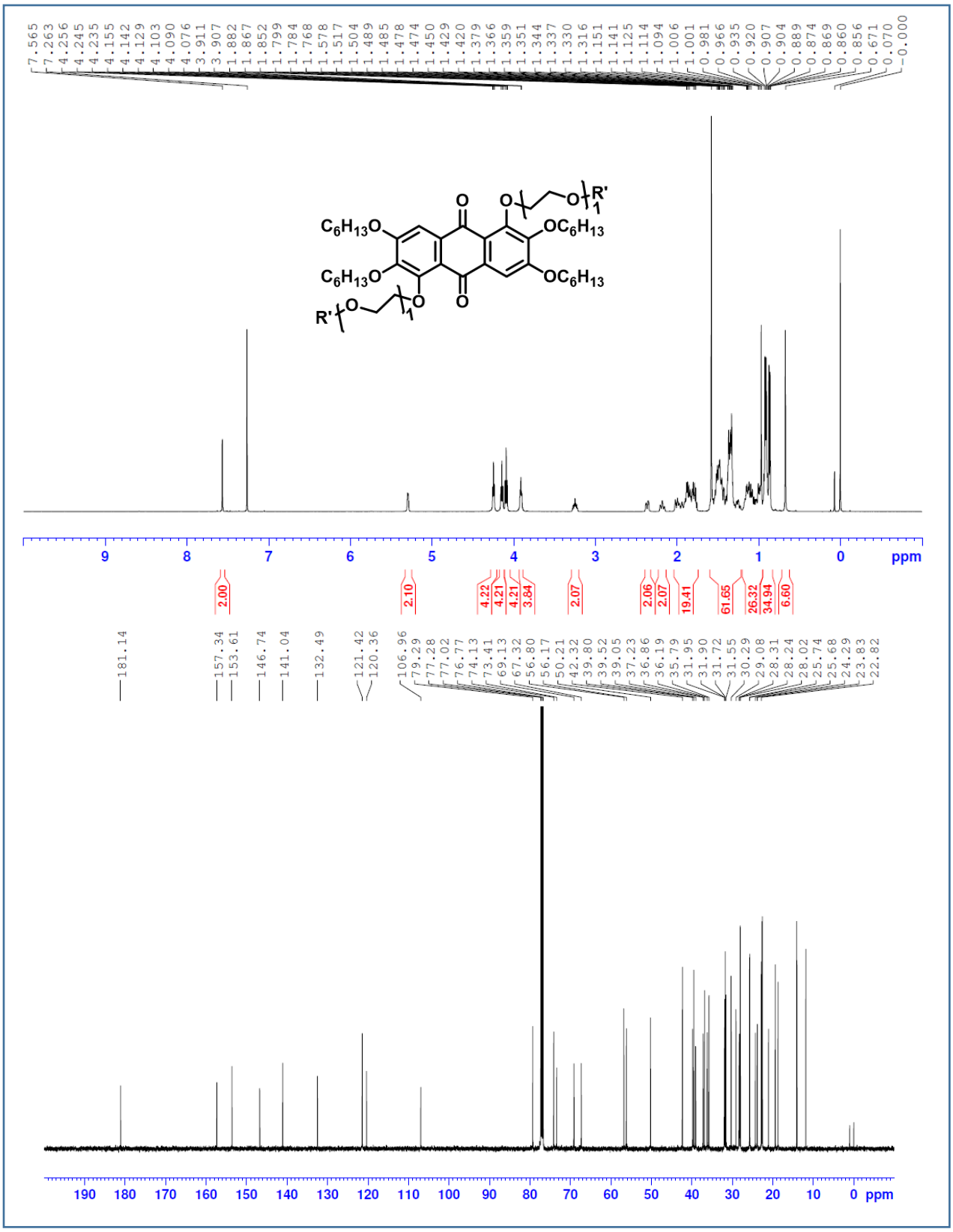


Figure 35: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **6a**

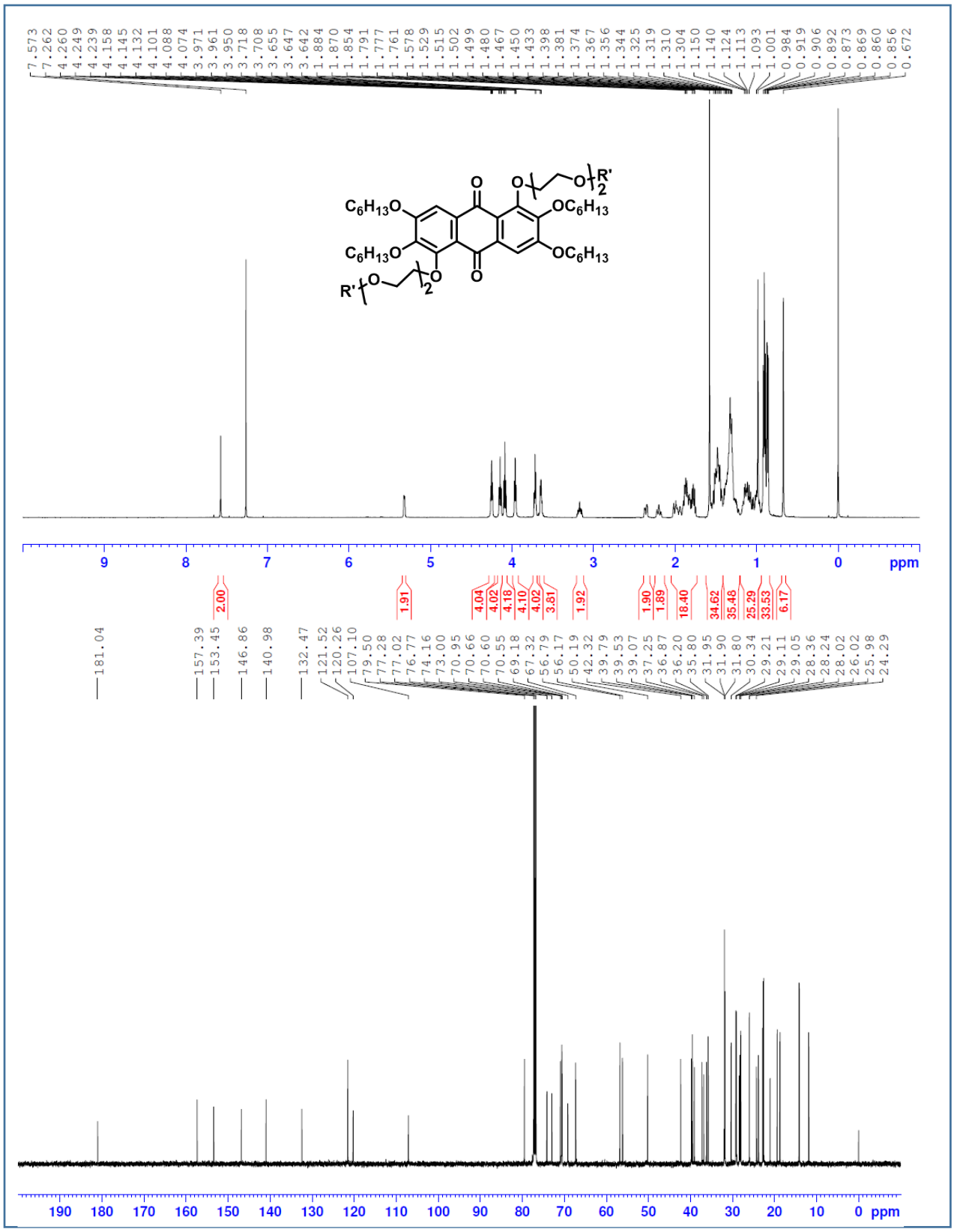


Figure 36: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **6b**

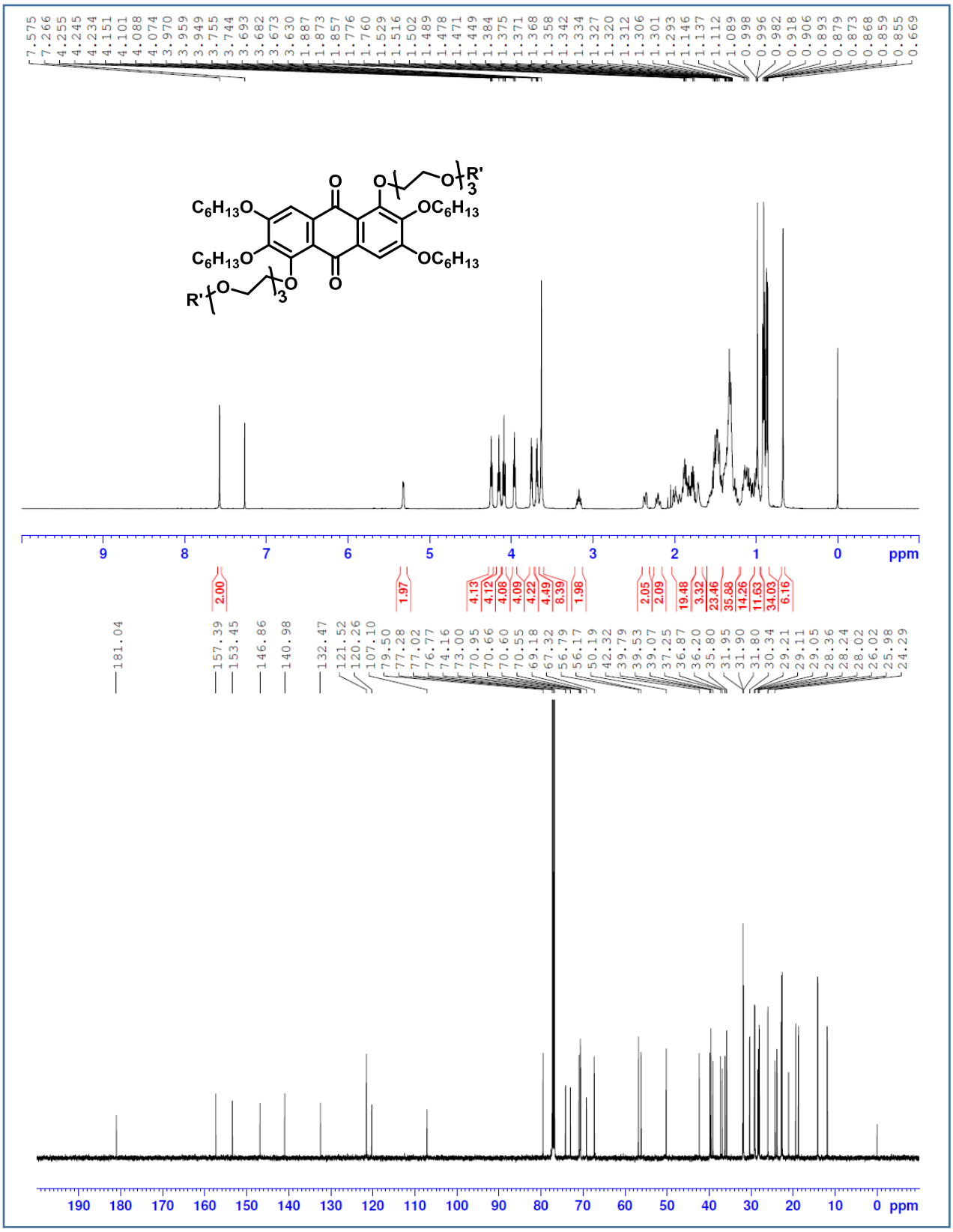


Figure 37: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **6c**

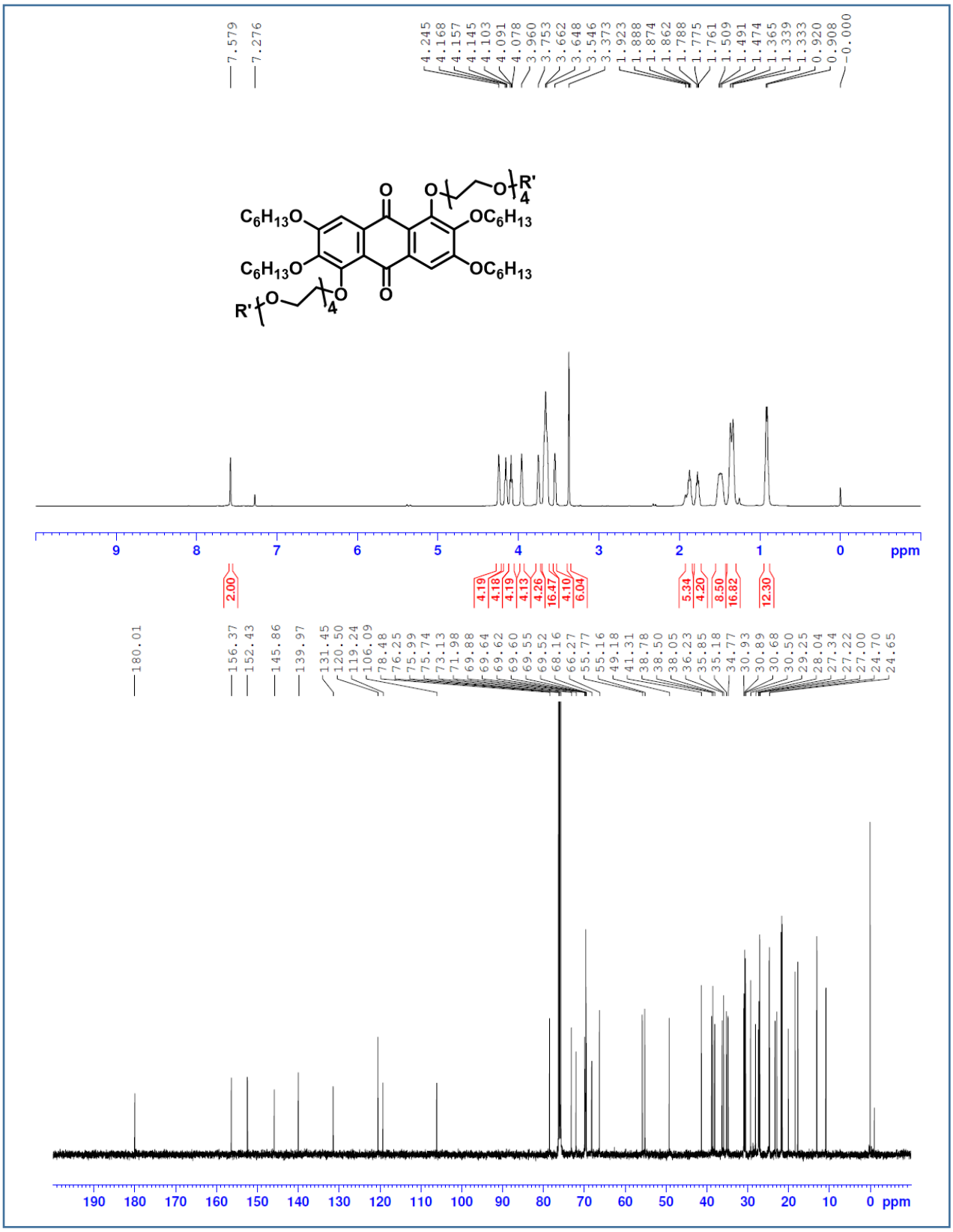


Figure 38: ^{1}H (top) and ^{13}C-NMR (bottom) spectra of **6d**

4.7 References and Notes

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