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Efficient and accelerated growth of multifunctional dendrimers using orthogonal thiol-ene and S_N2 reactions

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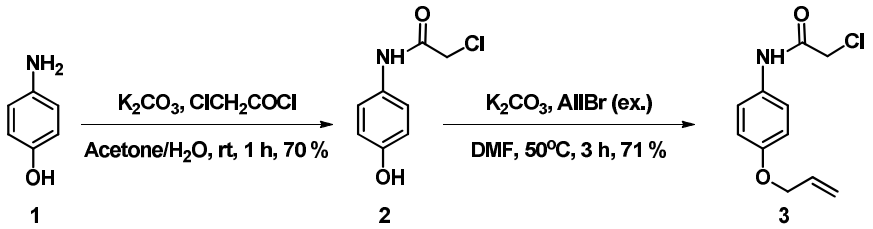
Contents

General Information:

All chemicals were purchased from commercial sources and were used without further purification. All reactions in organic medium were performed in standard oven dried glassware under an inert atmosphere of nitrogen using fresh dry solvents. Solvents and reagents were deoxygenated for thiol-ene reactions by purging with argon. Silica gel (60 Å, 40-63 μm) was used for column chromatography and TLC analysis was performed on commercial plates coated with silica gel 60 F_{254}. Visualization of the spots on TLC plates was achieved by UV radiation or 5% sulfuric acid in ethanol or mixture molybden-cerium solution (100 ml H_2SO_4, 900 ml H_2O, 25g $(NH_4)_6Mo_7O_{24}H_2O$, 10g $Ce(SO_4)_2$) and subsequent development by gentle warming with a heat-gun. ^{1}H NMR and ^{13}C NMR spectra were recorded at 300 or 600 MHz and 75 or 150 MHz, respectively. All NMR spectra were measured at 25°C in the 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), and "m"(multiplet) and broad resonances are indicated by "br". Residual protic solvent of $CDCl_3$ (^{1}H, δ7.26 ppm; ^{13}C, δ77.0 ppm), D_2O (^{1}H, δ4.79 ppm and 30.9 ppm for CH_3 of Acetone for ^{13}C spectra), DMSO-d_6 (^{1}H, δ2.50 ppm; ^{13}C, δ39.5 ppm) and MeOD-d_4 (^{1}H, δ 3.31 ppm; ^{13}C, δ 49.0 ppm) were used as the internal reference in the ^{1}H- and ^{13}C-NMR spectra. Fourier transform infrared (FTIR) spectra were measured as neat and the absorptions are given in wavenumbers (cm-1). Accurate mass measurements (HRMS) and low-resolution mass spectrometry were performed in positive electrospray mode or MALDI-TOF analysis. Either protonated molecular ions $[M+nH]^{n+}$, sodium adducts $[M+nNa]^{n+}$ or ammonium adducts $[M+NH_4]^+$ were used for empirical formula confirmation. Gel Permeation Chromatography (GPC) was performed using THF as the eluent, at 40^{o}C with a 1 mL/min flow rate on a Viscotek VE 2001 GPCmax (SEC System) with Wyatt DSP/Dawn EOS and refractive index RI/LS system as detectors. 2 PLGel mixed B LS (10 μm, 300×7.5 mm) and LS-MALLS detection with performances verified with polystyrene 100 kDa and 2000 kDa were used to determine the number-average molecular weight (M_n) and polydispersity index (M_W/M_n). Calculations were performed with Zimm Plot (model).

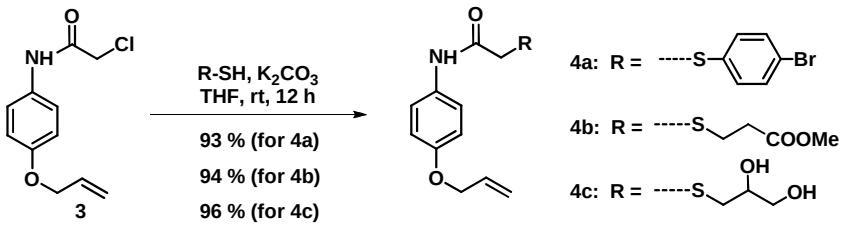
Experimental Part:



Scheme 1. Synthesis of bifunctional derivative **3**.

4-Chloroacetamidophenol (2): 4-Aminophenol (3.00 g, 27.5 mmol) was added into the suspension of K_2CO_3 (4.00 g, 30.2 mmol, 1.1 equiv) in acetone/water (40 mL, 3:1). After cooled to -10 ^oC, chloroacetyl chloride (3.29 mL, 41.25 mmol) was dropwise into the mixture during 30 min. The mixture was stirred at this temperature for 1 hour. Acetone was removed then under reduced pressure and the residue was diluted with EtOAc, washed with H_2O, brine, dried over Na_2SO_4, filtered, and the filtrate was concentrated followed by purification (SiO_2, CH_2Cl_2/MeOH = 98:2) afforded **2** as a brown solid. Yield (3.56 g, 70%). R_f = 0.27 (DCM/MeOH, 96:4); mp = 146^{o}C (non corrected) (Litt. 146^{o}C)[1]; ^{1}H NMR (600 MHz, DMSO-d_6): δ = 10.03 (s, 1H), 9.26 (s, 1H), 7.36 (d, 2H, J = 8.8 Hz), 6.71 (d, 2H, J = 8.8 Hz,), 4.18 (s, 2H); ^{13}C NMR (75 MHz, DMSO-d_6): δ = 173.4, 163.3, 139.6 , 130.7, 124.7, 53.0. ESI-HRMS Calcd. for $C_8H_8NO_2Cl$ 186.0316 $[M+H]^+$; found 186.0309.

2-Chloro-N-(4-allyloxyphenyl)acetamide (3): Allyl bromide (5.1 mL, 59 mmol) was added slowly to the suspension of **2** (2.20 g, 11.8 mmol) and potassium carbonate (3.25 g, 23.6 mmol) in DMF (20 mL) and stirred the reaction mixture at 50^{o}C for 3 h. The mixture was concentrated to dryness and the residue partitioned between ethyl acetate (100 mL) and water (75 mL). The organic phase collected and washed with NaCl (50 ml) and with the water (50 mL). The organic phase was dried (Na_2SO_4), filtered and the filtrate was concentrated followed by purification (SiO_2, CH_2Cl_2/MeOH = 98:2) afforded **3**, as a solid. Yield: (1.88 g, 71 %); R_f = 0.37 (Hexanes/EtOAc, 3:1); m.p. 138-140^{o}C; IR (neat) ν_{max} 3267, 3097, 1683, 1611, 1513, 1406, 1289, 1235, 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.14 (s, 1H), 7.43 (d, J = 9.0 Hz, 2H), 6.90 (d, J = 9.0 Hz, 2H), 6.11–5.98 (m, 1H), 5.44–5.37 (m, 1H), 5.31–5.27 (m, 1H), 4.53 (dt, J = 5.3, 1.4 Hz, 2H), 4.18 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 163.7, 156.0, 133.0, 129.8, 122.0, 121.9, 117.69, 115.1, 69.0, 42.8. ESI-HRMS Calcd. for $C_{11}H_{12}ClNO_2$ $[M+H]^+$ 226.0635, found 226.0616.



Scheme 2. S_N2 reactions on **3**.

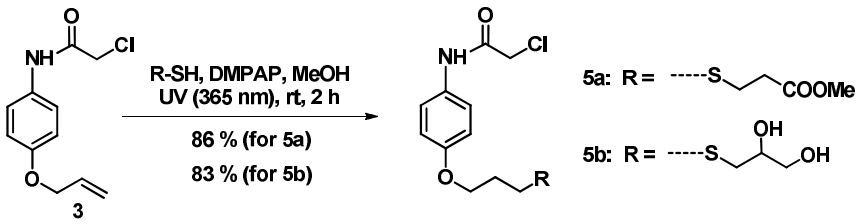
General procedure for selective S_N2 reaction: Thiol (0.6 mmol) was added into the suspension of potassium carbonate (1 mmol) and **3** (0.5 mmol) in DMF (4 mL). The reaction mixture was stirred at rt for 12 h. The mixture was concentrated to dryness and the residue partitioned between ethyl acetate (15 mL) and water (10 mL). The organic phase collected and washed with NaCl (10 ml) and with the water (10 mL). The organic phase was dried (Na_2SO_4), filtered and the filtrate was concentrated followed by purification (SiO_2) afforded the desired compounds.

***N*-(4-Allyloxyphenyl)-2-(4-bromophenylthio)acetamide (4a):** Yield: 93%; R_f = 0.41 (Hexanes/EtOAc, 3:1); m.p. 135-137^{o}C; IR (neat) ν_{max} 3320, 3254, 1651, 1535, 1512, 1474, 1253, 810 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.38 (s, 1H), 7.44–7.40 (m, 2H), 7.36–7.33 (m, 2H), 7.22–7.19 (m, 2H), 6.88–6.85 (m, 2H), 6.03-5.97 (m, 1H), 5.42-5.36 (m, 1H), 5.30-5.26 (m, 1H), 4.50 (dt, J = 5.2, 1.3 Hz, 2H), 3.72 (s, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 165.4, 155.8, 133.4, 133.1, 132.5, 130.3, 129.8, 121.8, 120.9, 117.7, 115.1, 69.1, 38.1. ESI-HRMS Calcd. for $C_{17}H_{16}BrNO_2S$ $[M+H]^+$ 380.0143, found 380.0138.

Methyl 3-(2-(4-allyloxyphenylamino)-2-oxoethylthio)propanoate (4b): Yield: 94%; R_f = 0.39 (EtOAc); m.p. 58-60^{o}C; IR (neat) ν_{max} 3302, 1733, 1655, 1533, 1508, 1412, 1219, 1172, 829 cm^{-1}; ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.68 (s, 1H), 7.66–7.36 (m, 2H), 7.13–6.73 (m, 2H), 6.07–6.02 (m, 1H), 5.42–5.39 (m, 1H), 5.29–5.27 (m, 1H), 4.52 (dt, J = 5.3, 1.5 Hz, 2H), 3.70 (s, 3H), 3.37 (s, 2H), 2.89 (t, J = 6.8 Hz, 2H), 2.67 (t, J = 6.8 Hz, 2H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 172.1, 166.3, 155.6, 133.2, 130.8, 121.5, 117.7, 115.0, 69.0, 52.0, 36.9, 33.7, 27.9. ESI-HRMS Calcd. for $C_{14}H_{19}NO_4S$ $[M+H]^+$ 310.1108, found 310.1104.

***N*-(4-Allyloxyphenyl)-2-(2,3-dihydroxypropylthio)acetamide (4c):** Yield: 96%; R_f = 0.31 (Hexanes/EtOAc, 3:2); m.p. 69-71^{o}C; IR (neat) ν_{max} 3296, 3081, 2921, 1651, 1541, 1508, 1413, 1234, 1023, 829 cm^{-1}; ^{1}H NMR (600 MHz, CD_3OD) δ 7.45 (d, J = 9.1 Hz, 2H), 6.89 (d, J = 9.1 Hz, 2H), 6.07–6.02 (m, 1H), 5.40–5.37 (m, 1H), 5.23–5.25 (m, 1H), 4.52 (dt, J = 5.2, 1.6 Hz,

2H), 3.82–3.80 (m, 1H), 3.60–3.54 (m, 2H), 3.40–3.35 (m, 2H), 2.88–2.85 (m, 1H), 2.74–2.70 (m, 1H); ^{13}C NMR (151 MHz, CD_3OD) δ 170.8, 157.0, 134.9, 132.7, 123.0, 117.4, 115.9, 72.7, 70.0, 65.9, 37.6, 37.1. ESI-HRMS Calcd. for $C_{14}H_{19}NO_4S$ $[M+H]^+$ 298.1113, found 298.1108.

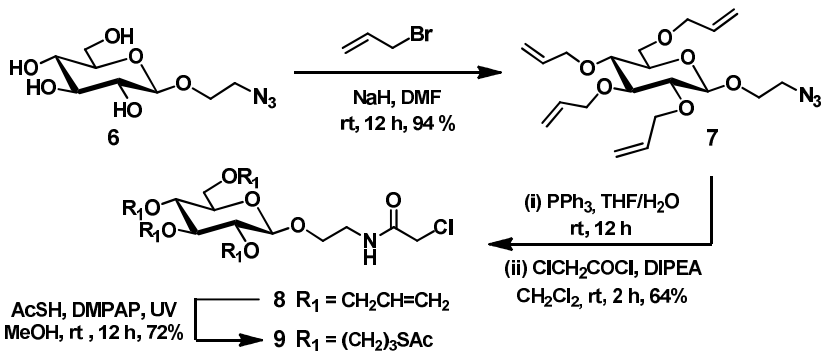


Scheme 3. Thiol-ene reactions on **3**.

General Procedure for selective thiol-ene reaction: Thiol (1 mmol) was added into a solution of 2,2-dimethoxy-2-phenylacetophenone (DMPA, 0.1 mmol) and **3** (0.5 mmol) in MeOH (or DMF) (1 mL). The reaction mixture was irradiated for 2 h with 365 nm light at room temperature *(classical glassware, UV lamp (365 nm, Model UVGL-58 MINERALIGHT® LAMP) in a cardboard box).* The mixture was concentrated to dryness and the residue was purified (SiO_2) to afford the desired compounds.

Methyl 3-(3-(4-(2-chloroacetamido)phenoxy)propylthio) propanoate (5a): Yield: 86%; R_f = 0.40 (Hexanes/EtOAc, 3:2); m.p. 58-60^{o}C; IR (neat) ν_{max} 3274, 3145, 3101, 2957, 1729, 1686, 1660, 1511, 1471, 1438, 1244, 1169, 826 cm^{-1}; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.44–7.41 (m, 2H), 6.89–6.80 (m, 2H), 4.17 (s, 2H), 4.03 (t, *J* = 6.0 Hz, 2H), 3.69 (s, 3H), 2.82–2.77 (m, 2H), 2.72 (t, *J* = 7.0 Hz, 2H), 2.61 (t, *J* = 7.0 Hz, 2H), 2.10–2.00 (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 172.3, 163.6, 163.5, 156.3, 129.8, 129.7, 122.0, 121.9, 114.9, 77.2, 66.4, 51.8, 42.8, 42.8, 34.6, 29.1, 28.6, 27.0. ESI-HRMS Calcd. for $C_{15}H_{20}ClNO_4S$ $[M+NH_4]^+$ 363.1140, found 363.1154.

2-Chloro-N-(4-(3-(2,3-dihydroxypropylthio)-propoxy)-phenyl) acetamide (5b): Yield: 83%; R_f = 0.43 (EtOAc); m.p. 97-98^{o}C; IR (neat) ν_{max} 3303, 2923, 2864, 1666, 1534, 1514, 1409, 1240, 1032, 823 cm^{-1}; ^{1}H NMR (300 MHz, MeOD) δ 7.47–7.44 (m, 2H), 6.90–6.87 (m, 2H), 4.15 (s, 2H), 4.04 (t, *J* = 6.1 Hz, 2H), 3.76–3.70 (m, 1H), 3.62–3.50 (m, 2H), 2.75–2.68 (m, 3H), 2.65–2.54 (m, 1H), 2.07–1.98 (m, 2H); ^{13}C NMR (75 MHz, MeOD) δ 167.1, 157.5, 132.1, 123.2, 115.7, 72.8, 67.6, 66.0, 44.0, 36.3, 30.5, 30.0. ESI-HRMS Calcd. for $C_{14}H_{20}ClNO_4S$ $[M+Na]^+$ 356.0694, found 356.0709.



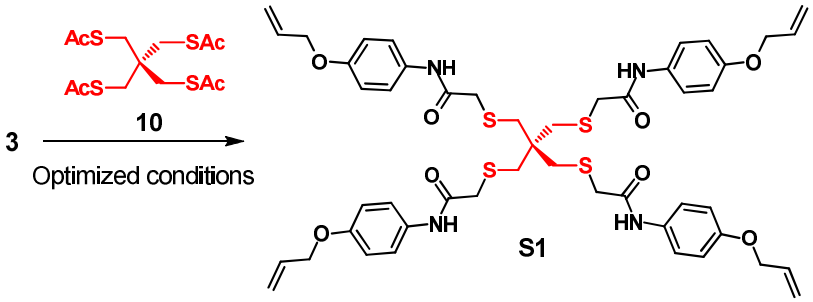
Scheme 4. Synthesis of glucose-derivative AB_4-type building block **6**.

2-Azidoethyl 2,3,4,6-tetra-*O*-allyl-β-D-glucopyranoside (7): Compound **6**[2] (985 mg, 3.95 mmol) in DMF (5 mL) was added to a suspension of NaH (1.264 g, 31.60 mmol, 8.0 equiv., 60 % in mineral oil) in a mixture of hexane/DMF (50 mL, 9:1, v/v). After stirring for 30 min. at room temperature, the reaction mixture was cooled to 0°C, and then allyl bromide (2.73 mL, 31.60 mmol, 8.0 equiv) was added slowly and stirred for 1h at 0°C and for 3h at room temperature. The mixture was then cooled with an ice bath; methanol (5 mL) was added slowly into the mixture to quench the excess sodium hydride. After concentration of the mixture to dryness, the residue was mixed with ethyl acetate (200 mL) and washed with brine (saturated NaCl, 50 mL), then washed with water (3x100 mL, with a little amount of hexane), the organic layer was dried over Na_2SO_4, filtered, and concentrated under reduced pressure followed by purification by silica gel column chromatography (Hexane/EtOAc = 85:15) to afford **7**, as a colorless oil. Yield: 1.52 g (94%); R_f = 0.39 (hexane/EtOAc 4:1); $[\alpha]_D$ -15.2 (*c* 1, MeOH); IR (neat) ν_{max} 3080, 2867, 2102, 1347, 1305, 1121, 1069, 994, 921 cm^{-1}; ^{1}H- NMR (300 MHz, $CDCl_3$) δ 5.93-5.71 (m, 4H), 5.27-5.04 (m, 8H), 4.41-3.91 (m, 10H), 3.68-3.58 (m, 3H), 3.50-3.25 (m, 5H), 3.24-3.13 (m, 1H); ^{13}C-NMR (75 MHz, $CDCl_3$) δ 135.1, 134.9, 134.6, 134.5, 116.8, 116.7, 116.6, 116.3, 103.3, 83.9, 81.3, 77.2, 74.7, 74.2, 73.6, 73. 4, 72.2, 68.7, 68.0, 50.8. ESI-HRMS Calcd. for $C_{20}H_{31}N_3O_6$ $[M+NH_4]^+$ 427.2557, found 427.2544.
(Following a procedure adapted from: J. Ni, H. Song, Y. Wang, N. M. Stamatos, L.-X. Wang. Toward a Carbohydrate-Based HIV-1 Vaccine: Synthesis and Immunological Studies of Oligomannose-Containing Glycoconjugates. *Bioconjugate Chem.* **2006**, *17*, 493-500.)

2-Chloroacetamido-ethyl 2,3,4,6-tetra-*O*-allyl-β-D-glucopyranoside (8): PPh_3 (3.55 g, 13.2 mmol) was added to a solution of **7** (1.8 g, 4.4 mmol) in THF:H_2O (3:1 20 mL) and stirred for 12

h at rt. The solvents were concentrated *in vacuo* and the crude residue was co-evaporated with toluene to remove the residual water. Chloroacetyl chloride (0.42 mL, 5.3 mmol) was added drop-wise to a solution of above crude residue and DIPEA (0.92 mL, 5.3 mmol) in CH_2Cl_2 (20 mL) and stirred at 0^oC for 30 min. and then for 2 hrs at rt. Upon reaction completion, the mixture was concentrated to dryness and residue was purified (SiO_2, Hexane/EtOAc = 1:1) to afford **8**, as a gum, which was solidified on standing. Yield: 1.29 g (64%); = 0.41 (Hexanes/EtOAc, 1:1); m.p. 54-56^oC; $[\alpha]_D$ +11.0 (*c* 0.4, MeOH); IR (neat) ν_{max} 3347, 2918, 2872, 1667, 1538, 1071, 996, 928 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 6.03–5.74 (m, 4H), 5.39–5.05 (m, 8H), 4.34–3.84 (m, 12H), 3.77–3.65 (m, 2H), 3.59–3.47 (m, 3H), 3.35–3.30 (m, 3H), 3.17 (t, *J* = 8.2 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 166.0, 135.1, 134.9, 134.7, 134.4, 117.2, 117.0, 116.8, 116.6, 103.4, 84.1, 81.4, 77.4, 74.6, 74.3, 73.7, 73.6, 72.4, 69.0, 68.7, 42.5, 40.0. ESI-HRMS Calcd. for $C_{22}H_{34}ClNO_7$ $[M+Na]^+$ 482.1916, found 482.1906.

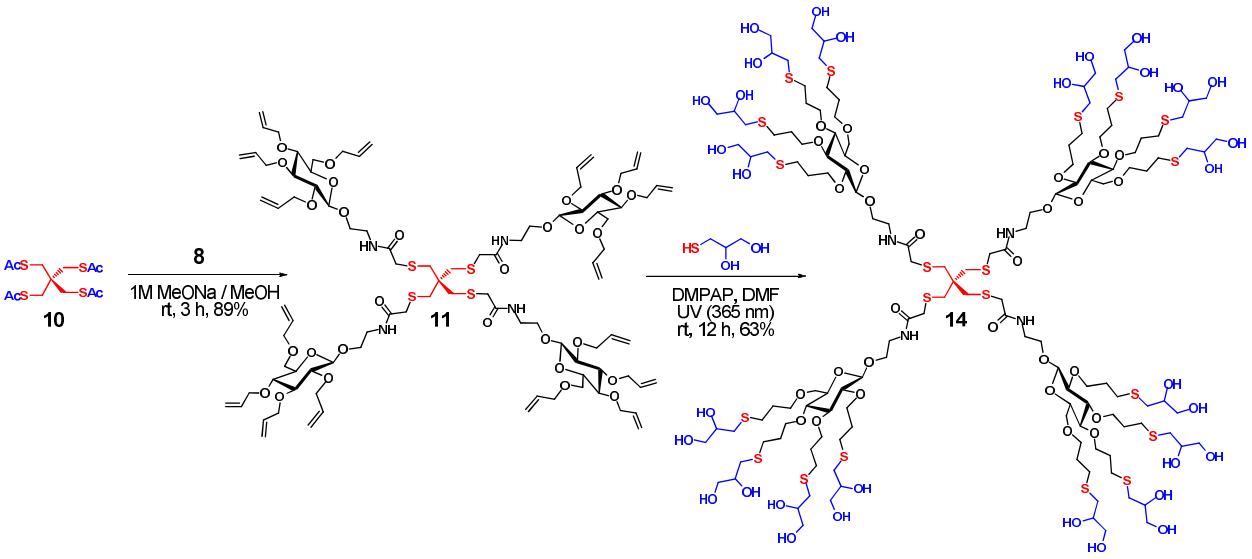
Compound 9: AcSH (0.14 mL, 2.0 mmol) was added into the solution of DMPAP (25.6 mg, 0.100 mmol) and **8** (102 mg, 0.22 mmol) in MeOH (2 mL). The reaction mixture was irradiated for 12 h with 365 nm light at room temperature. The mixture was concentrated to dryness and the residue was purified (SiO_2, Hexanes:EtOAc = 1:1) to afford **9** as an oil. Yield: 121 mg (72%); R_f = 0.41 (Hexanes/EtOAc, 1:3); $[\alpha]_D$ +23.4 (*c* 1, MeOH); ^1H NMR (300 MHz, $CDCl_3$) δ 7.08 (s, 1H), 4.20 (d, *J* = 7.7 Hz, 1H), 4.04 (s, 2H), 3.96–3.37 (m, 15H), 3.31–3.09 (m, 3H), 3.09–3.01 (m, 1H), 2.99–2.84 (m, 7H), 2.31–2.32 (m, 12H), 1.80–1.89 (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.7, 195.7, 195.6, 195.6, 166.1, 103.4, 84.5, 82.1, 77.9, 77.2, 74.6, 71.8, 71.1, 69.9, 69.7, 68.5, 42.6, 40.0, 30.6, 30.4, 30.2, 30.2, 29.6, 26.0, 25.9, 25.9. ESI-HRMS Calcd. for $C_{30}H_{50}ClNO_{11}S_4$ $[M+Na]^+$ 786.1853, found: 786.1827.



Entry	Basic conditions	Solvent	Yield
1	**1M MeONa**	**MeOH**	**88%**
2	K_2CO_3	MeOH	81%
3	K_2CO_3	MeOH/THF	77%
4	$NaOH/NaBH_4$	MeOH	85%
5	KCN	MeOH	73%

Scheme 5. Optimization's conditions for S_N2 reactions from tetra(thioacetylated) core **10** and chloroacetamide derivative **3**.

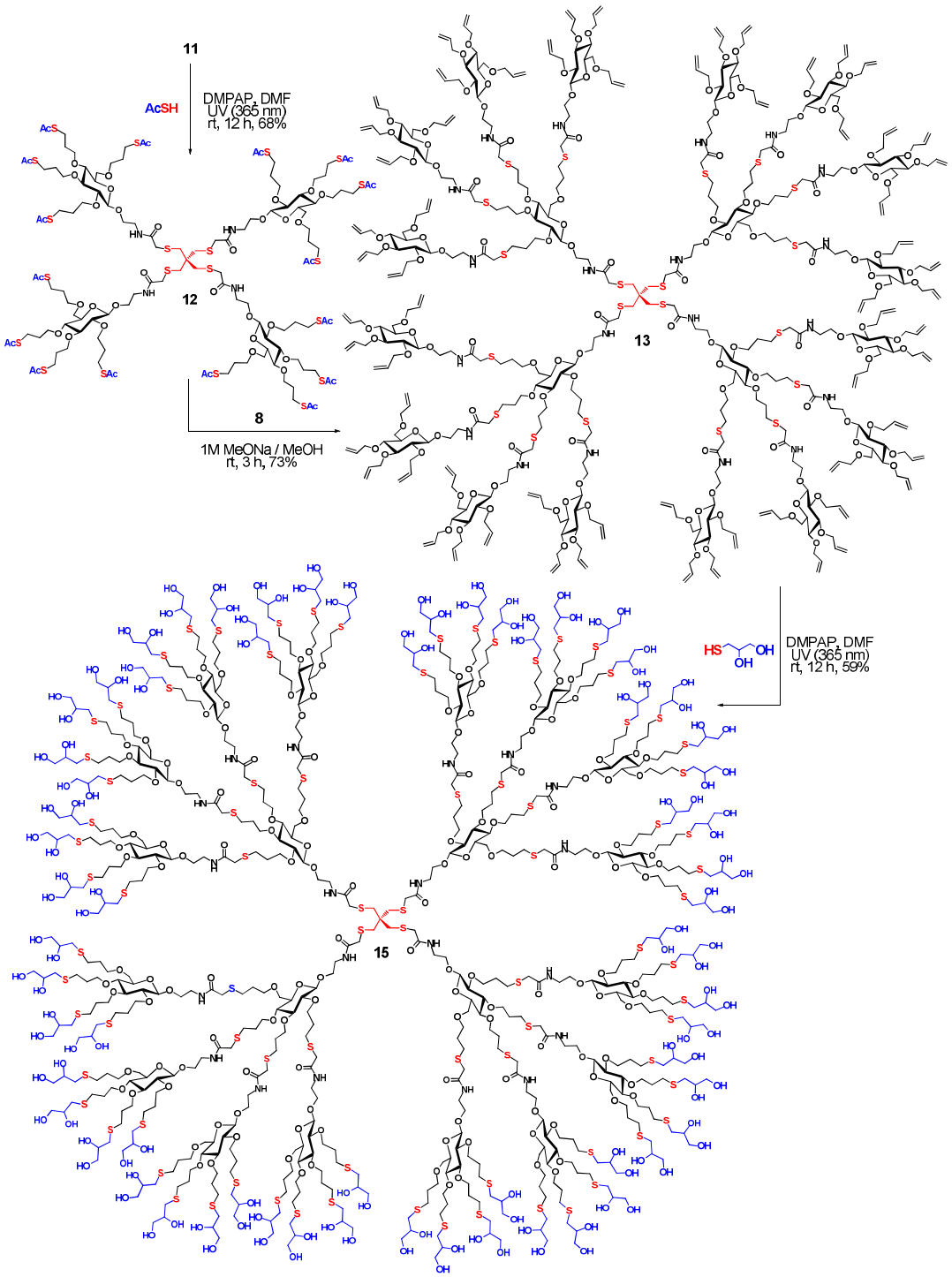
General conditions for S_N2 reactions' optimization: To a solution of tetra(thioacetylated) core **8** (20.0 mg, 54.3 µmol, 1.0 eq) in dry solvent (MeOH or THF/MeOH (1/1), 2 mL) was added base (MeONa, K_2CO_3, $NaOH/NaBH_4$ system or KCN, 8.0 eq) under a nitrogen atmosphere and at room temperature. After 5 minutes, 2-chloroacetamide derivative **3** (63.7 mg, 282 µmol, 5.2 eq) was incorporated to the mixture. The resulting yellowish solution was allowed to stirr at room temperature for 3 hours under a nitrogen atmosphere. An off-white coloration took place gradually with the formation of insoluble white species. Evaporation to dryness *in vacuo* with rotary evaporator and subsequent purification by column chromatography (SiO_2, CH_2Cl_2/MeOH 99.5:0.5 to 98:2) afforded desired tetraallylated compound **S1**. R_f = 0.18 (CH_2Cl_2/MeOH 97:3); m.p. = 186-188°C; ^{1}H NMR (600 MHz, DMSO-d_6) δ 9.93 (s, 4H), 7.49 (d, J = 9.1 Hz, 8H), 6.90 (d, J = 9.1 Hz, 8H), 6.08–6.03 (m, 4H), 5.42–5.39 (m, 4H), 5.29–5.27 (m, 4H), 4.53 (m, 8H), 3.38 (s, 8H), 2.94 (s, 8H); ^{13}C NMR (151 MHz, DMSO-d_6) δ 167.2, 154.2, 133.8, 132.2, 120.8, 117.3, 114.7, 68.3, 43.8, 38.7, 36.9; ESI-HRMS Calcd. for $C_{49}H_{56}N_4O_8S_4$ $[M+H]^+$ 957.3054, found 957.3056.



Scheme 6. Synthesis of polyol-terminated G(1)-dendrimer **14**.

Cluster 11: NaOMe in MeOH (1M, 0.23 mL) was added to a solution of **10**[3] (14 mg, 0.038 mmol) and chloride **8** (104 mg, 0.23 mmol) in MeOH stirred at rt for 3 h. Upon reaction completion, the solvents were concentrated *in vacuo* and residue was purified (SiO_2, EtOAc) to afford **11**, as a gum. Yield: 64 mg (89%); R_f = 0.64 (CH_2Cl_2/MeOH 9:1). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (t, *J* = 5.6 Hz, 4H), 5.98–5.80 (m, 16H), 5.29–5.12 (m, 32H), 4.34–3.95 (m, 36H), 3.89–3.81 (m, 4H), 3.78–3.67 (m, 8H), 3.60–3.30 (m, 24H), 3.23–3.15 (m, 12H), 2.76 (s, 8H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.8, 135.1, 135.1, 134.7, 134.4, 117.4, 117.0, 116.8, 116.6, 103.6, 84.1, 81.5, 77.2, 74.5, 74.3, 73.7, 73.6, 72.4, 69.1, 68.9, 44.0, 40.1, 38.7, 36.5. ESI-HRMS Calcd. for $C_{93}H_{144}N_4O_{28}S_4$ $[M+H]^+$ 1896.8972, found 1896.9005.

G(1)-Dendrimer 14: Thioglycerol (0.17 mL, 2 mmol) was added into the solution of DMPAP (10 mg, 0.04 mmol) and **11** (24 mg, 0.012 mmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at rt. The mixture was concentrated to dryness and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous phase was concentrated and the residue was dialyzed against 1kDa cut-off membrane followed by lyophilization, afforded **14** as viscous oil. Yield: 27 mg (63 %); ^{1}H NMR (600 MHz, D_2O) δ 4.31–4.29 (m, 4H), 4.03–4.00 (m, 4H), 3.80–3.19 (m, 120H), 3.03–2.81 (m, 28H), 2.69–2.46 (m, 52H), 1.93–1.76 (m, 32H); ^{13}C NMR (151 MHz, D_2O:CD_3OD) δ 172.5, 103.7, 84.7, 82.6, 78.9, 74.7, 73.2, 72.6, 72.1, 71.8, 70.7, 69.9, 69.2, 67.9, 66.7, 65.9, 65.4, 56.1, 55.3, 40.9, 39.5, 37.3, 35.4, 30.7, 30.3, 29.7, 24.2, 23.4.



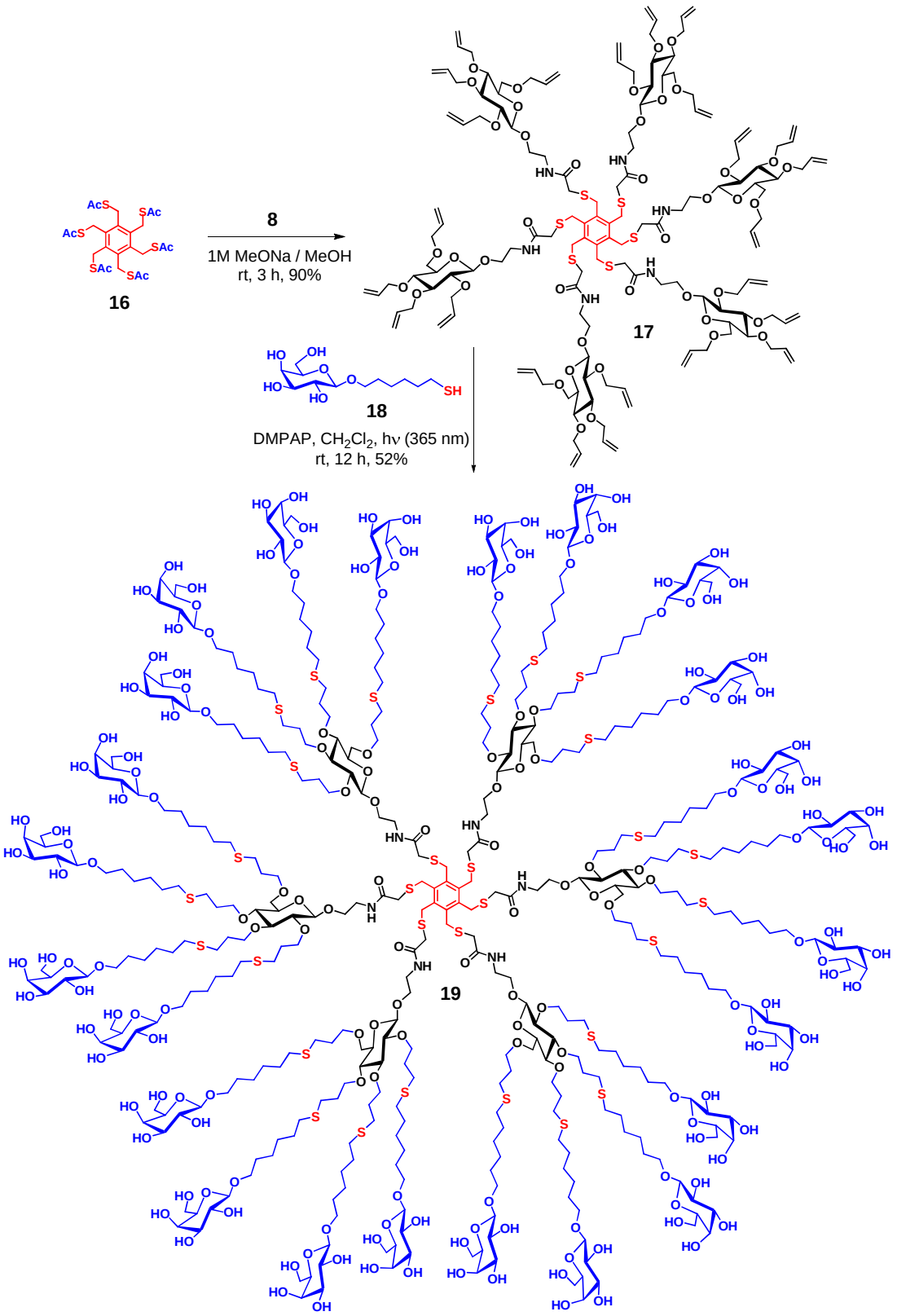
Scheme 7. Synthesis of polyol-terminated G(2)-dendrimer **15**.

Cluster 12: AcSH (0.43 mL, 0.60 mmol) was added into the solution of DMPAP (24 mg, 0.096 mmol) and **11** (24 mg, 0.012 mmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at room temperature. The mixture was concentrated to dryness and the

residue was purified (SiO_2, EtOAc/MeOH = 19:1) to afford **12** as an oil. Yield: 25 mg (68%); R_f = 0.14 (CH_2Cl_2/MeOH 24:1); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.16 (s, 4H), 4.20 (d, J = 7.7 Hz, 4H), 3.86–3.49 (m, 60H), 3.27–3.18 (m, 20H), 2.97–2.92 (m, 32H), 2.78 (s, 8H), 2.33 (s, 48H), 1.87–1.78 (m, 32H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 195.8, 195.7, 195.6, 195.5, 168.7, 103.5, 84.5, 82.0, 77.8, 77.2, 74.4, 71.8, 71.1, 69.8, 69.6, 68.8, 44.1, 40.0, 38.7, 36.6, 30.6, 30.6, 30.6, 30.4, 30.2, 29.5, 26.0, 25.9. ESI-HRMS Calcd. for $C_{125}H_{208}N_4O_{44}S_{20}$ $[M+2H]^{2+}$ 1556.9372, found 1556.9350.

Dendrimer 13: NaOMe in MeOH (1M, 0.21 mL) was added to a solution of **12** (16 mg, 5.14 μmol) and chloride **8** (94 mg, 0.205 mmol) in MeOH stirred at rt for 3 h. Upon reaction completion, the solvents were concentrated *in vacuo* and residue was purified (SiO_2, EtOAc:MeOH 9:1) to afford **11**, as a gum. Yield: 34 mg (73%); R_f = 0.55 (CH_2Cl_2/MeOH 9:1); ^{1}H NMR (300 MHz, MeOD) δ 8.02 (s, 20H), 6.01–5.88 (m, 64H), 5.34–5.12 (m, 128H), 4.37–4.03 (m, 152H), 3.92–3.84 (m, 40H), 3.72–3.61 (m, 80H), 3.45–3.34 (m, 100H), 3.22–3.12 (m, 48H), 2.86 (s, 8H), 2.74–2.68 (m, 32H), 1.92–1.83 (m, 32H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 169.3, 135.2, 135.1, 134.8, 134.5, 117.3, 117.0, 116.8, 116.7, 103.6, 84.1, 81.5, 77.2, 74.6, 74.37, 73.8, 73.6, 72.4, 70.9, 69.8, 69.1, 68.9, 42.7, 40.0, 35.7, 30.0, 29.7, 29.5, 29.1. GPC measurements (THF, 40^{o}C): PDI (M_w/M_n) 1.064.

G(2)-Dendrimer 15: Thioglycerol (0.082 mL, 0.96 mmol) was added into the solution of DMPAP (26.0 mg, 0.102 mmol) and **13** (30.0 mg, 3.20 μmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at rt. The mixture was concentrated to dryness and the residue was partitioned between ether (10 mL) and water (10 mL). The aqueous phase was concentrated and the residue was dialyzed against 1kDa cut-off membrane followed by lyophilization, afforded **15** as white solid. Yield: 31 mg (59%). ^{1}H NMR (600 MHz, D_2O) δ 4.54 (s, 20H), 4.25–4.22 (br s, 40H), 4.01–3.38 (m, 548H), 3.24–3.04 (m, 160H), 2.95–2.65 (m, 160H), 2.14–1.97 (m, 160 H); ^{13}C NMR (151 MHz, D_2O:Acetone) δ 172.6, 103.3, 84.3, 82.2, 78.4, 74.4, 72.2, 71.6, 70.8, 70.7, 70.4, 70.3, 70.1, 69.7, 68.9, 67.6, 67.6, 66.4, 65.6, 65.1, 64.9, 55.9, 55.0, 49.2, 49.0, 48.8, 42.0, 41.9, 40.4, 35.8, 35.2, 31.0, 30.4, 30.1, 29.4, 29.0, 23.8, 23.1; MALDI-TOF MS did not show molecular ions. We are investigating other matrices for this new family of dendrimers.



Scheme 8. Synthesis of galactodendrimer **19**.

Cluster 17: NaOMe in MeOH (1M, 0.13 mL) was added to a solution of **16**[3] (8.0 mg, 0.013 mmol) and chloride **8** (60 mg, 0.13 mmol) in MeOH (3 mL) and stirred at rt for 3 h. Upon reaction completion, the solvents were concentrated *in vacuo* and residue was purified (SiO_2, CH_2Cl_2: MeOH 1:19) to afford **17**, as a gum. Yield: 34 mg (90%); R_f = 0.18 (CH_2Cl_2/MeOH 24:1); ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.19 (t, *J* = 5.5 Hz, 6H), 5.95–5.83 (m, 24H), 5.25–5.13 (m, 48H), 4.33–4.20 (m, 30H), 4.17–4.12 (m, 18H), 4.08–4.01 (m, 12H), 3.98–3.95 (m, 6H), 3.88–3.84 (m, 6H), 3.81–3.77 (m, 6H), 3.67–3.65 (m, 6H), 3.58–3.54 (m, 12H), 3.47–3.42 (m, 6H), 3.37–3.29 (m, 30H), 3.19 (t, *J* = 8.3 Hz, 6H); ^{13}C NMR (151 MHz, $CDCl_3$) δ 169.4, 136.1, 135.1, 135.0, 134.7, 134.3, 117.4, 117.0, 116.7, 116.6, 103.6, 84.0, 81.4, 77.2, 74.4, 74.3, 73.7, 73.5, 72.3, 69.3, 68.8, 40.1, 36.7, 31.6. ESI-HRMS Calcd. for $C_{144}H_{216}N_6O_{42}S_6$ $[M+2Na]^{2+}$ 1469.6530, found 1469.6737.

Galactodendrimer 19: Thiogalactoside **18**[4] (245 mg, 0.829 mmol) was added into the solution of DMPAP (8 mg, 0.08 mmol) and **17** (16 mg, 0.006 mmol) in DMF (0.5 mL). The reaction mixture was irradiated for 12 h with 365 nm light at rt. The mixture was concentrated to dryness and the residue was partitioned between ethyl acetate (10 mL) and water (10 mL). The aqueous phase was concentrated and the residue was dialyzed against 2.5k cut-off membrane followed by lyophilization, afforded **19** as white solid. Yield: 29 mg (52 %); ^{1}H NMR (300 MHz, D_2O) δ 4.42–4.48 (m, 6 H), 4.36–4.33 (24 H), 3.95–3.10 (m, 324 H), 2.96–2.80 (m, 96 H), 2.11–1.95 (m, 48 H), 1.80–1.36 (192 H); ^{13}C NMR (151 MHz, D_2O:Acetone) δ 166.5, 130.1, 104.1, 103.5, 84.3, 82.2, 78.4, 75.7, 74.3, 73.6, 72.4, 71.5, 70.9, 70.3, 69.3, 68.8, 61.6, 57.6, 52.7, 51.4, 49.7, 48.3, 40.6, 31.7, 30.4, 29.3, 29.0, 28.4, 25.4, 23.9, 23.1, 22.7, 21.7; MALDI-TOF-MS Calcd. for $C_{432}H_{792}N_6O_{186}S_{30}$ $[M+Na]^+$ 10028.4, found 10027.9.

Surface plasmon resonance studies: The studies were conducted using a Biacore T200 SPR instrument with a CM5 sensor chip. A continuous flow of HEPES buffer (10 mm HEPES and 150 mm NaCl, pH 7.4) was maintained over the sensor surface at a flow rate of 10 μl/min. The CM5 sensor chip was activated with an injection of a solution containing *N*-ethyl-*N*′-(3-diethylaminopropyl) carbodiimide (EDC) (0.2 M) and *N*-hydroxysuccinimide (NHS) (0.05 M) for 7 minutes. PA-IL lectin (100 μg/mL) in NaOAc buffer (pH 4.2) was injected over the activated flow cell at flow rate of 10 μl/min for 10 minutes to achieve a ~1000 RU

immobilization. The immobilization procedure was completed by an injection of ethanolamine hydrochloride (1 M) (70 µL), followed by a flow of the buffer (100 µL/min.), in order to eliminate physically adsorbed compounds. Ethanol amine alone was used in one of the flow-cell as a reference. Glycodendrimer **19** was dissolved in running HEPES buffer and passed over flow cells of the PA-IL and ethanol amine (Association: 5 min and dissociation: 5 min). The sensor chip was regenerated with 2x5 minutes pulse of methyl-β-D-galactoside (100 mM) followed by an injection of running buffer for 5 minutes. Response units from the surface of PA-IL were subtracted from the surface of ethanol amine to eliminate non-specific interactions, as well as, bulk change in RU due to variation in refractive index of the medium. The primary subtracted sensorgrams were analyzed by 1:1 Langmuir model fitting, using the BIAevaluation software.

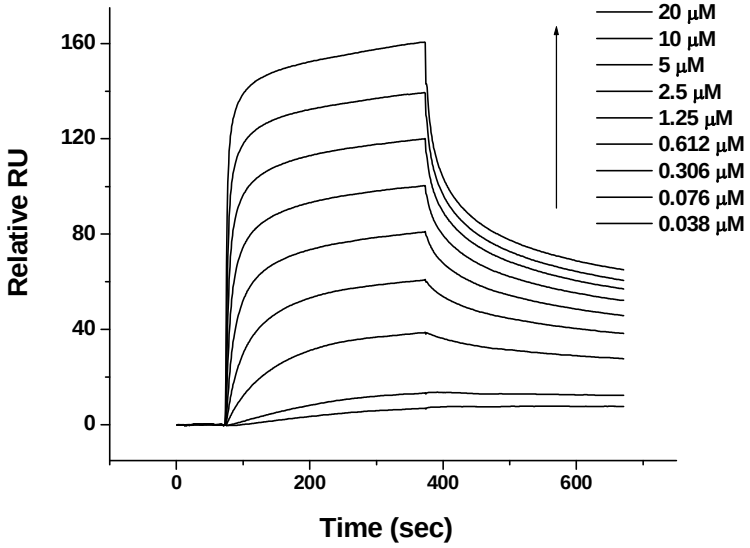


Figure 1. SPR sensorgrams for the interactions of glycodendrimer **19** (0.038 µM to 20 µM) with the surface bound PA-IL lectin (k_{on}:6.65e3 $M^{-1}s^{-1}$; k_{off}: 1.53e-3 s^{-1}. K_D: 230 nM).

References:

1. A. El Alaoui, F. Schmidt, M. Sarr, D. Decaudin, J.-C. Florent and L. Johannes, C*hem. Med. Chem.* 2008, **3**, 1687-1695.
2. (a) W. Wang, H. Wang, C. Ren, J. Wang, M. Tan, J. Shen, Z. Yang, P. G. Wang and L. Wang, *Carbohydr. Res.* 2011, **346**, 1013–1017; (b) S. Park and I. Shin, *Org. Lett.* 2007, **9**, 1675-1678.
3. Y. M. Chabre, C. Contino-Pépin, V. Placide, T. C. Shiao and R. Roy, *J. Org. Chem.* 2008, **73**, 5602-5605.
4. S. S. Mahajan and S. S. Iyer, *J. Carbohydr. Chem.* 2012, **31**, 447-465.

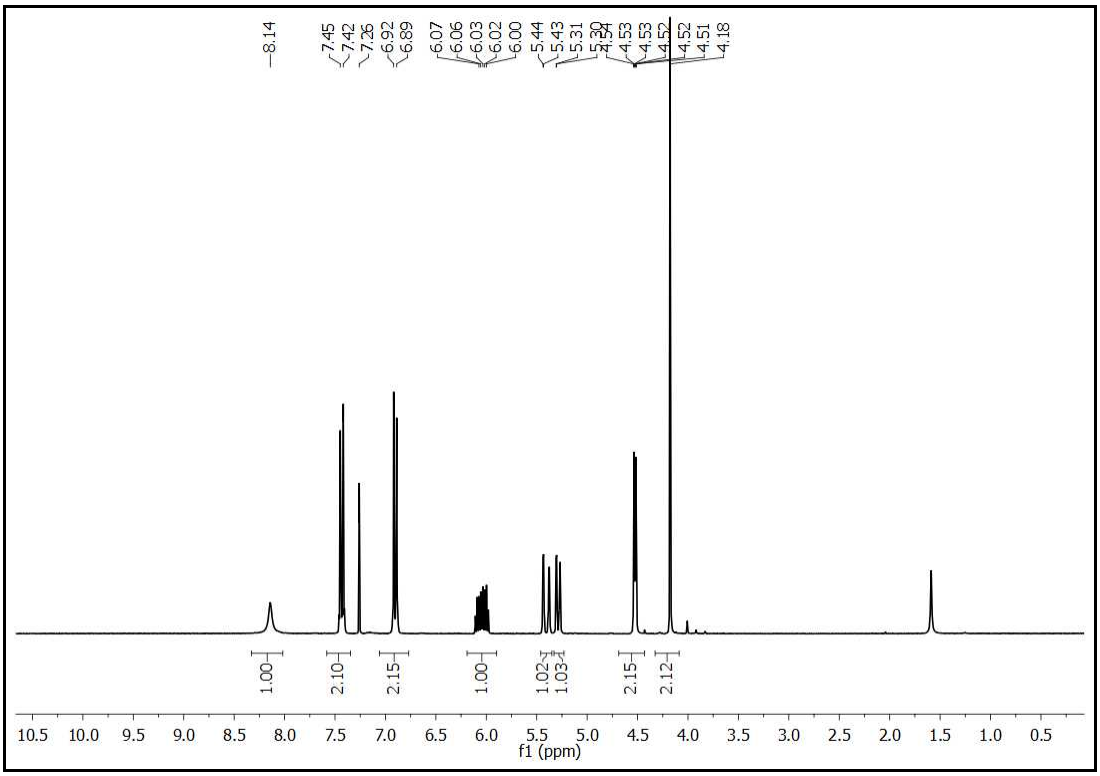


Figure 2. ^{1}H NMR spectrum of compound **3** ($CDCl_3$, 300 MHz).

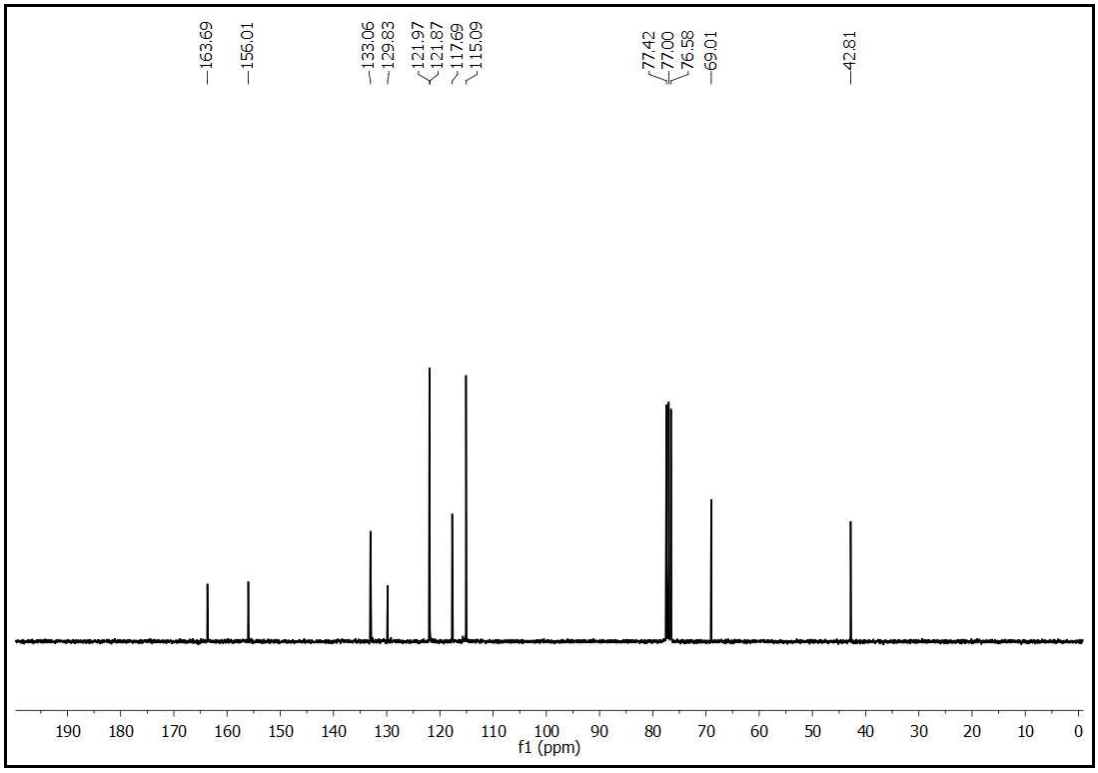


Figure 3. ^{13}C NMR spectrum of compound **3** ($CDCl_3$, 75 MHz).

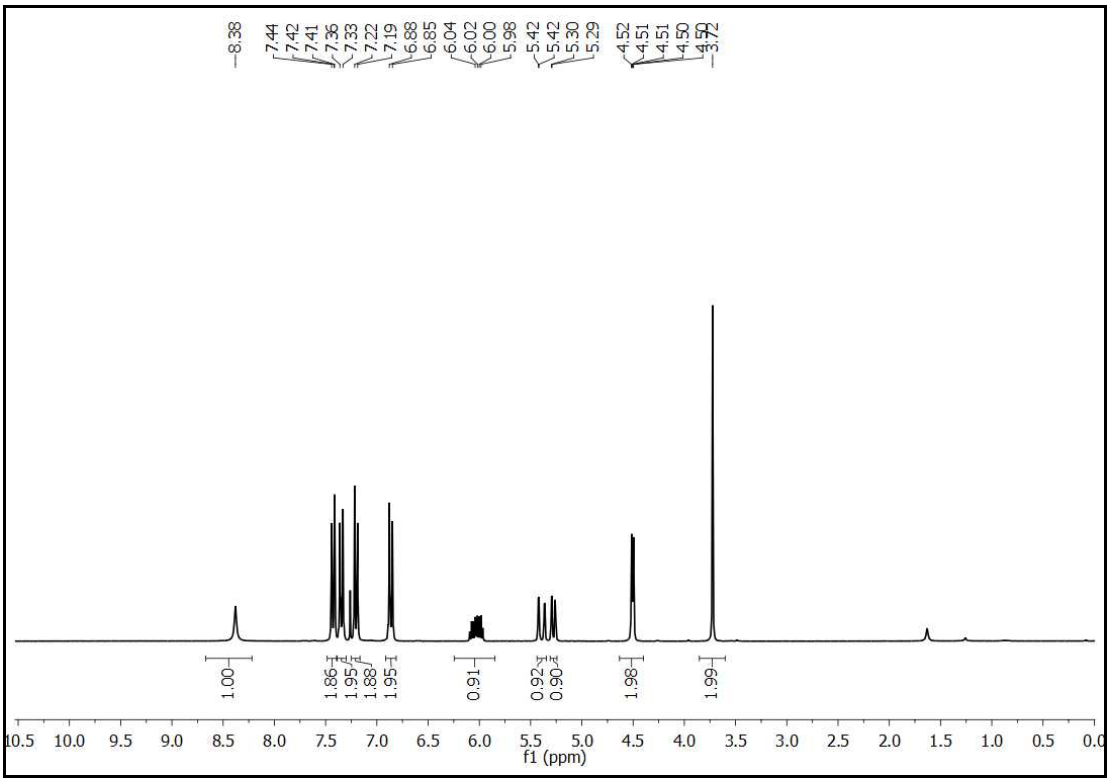


Figure 4. ^{1}H NMR spectrum of compound **4a** ($CDCl_3$, 300 MHz).

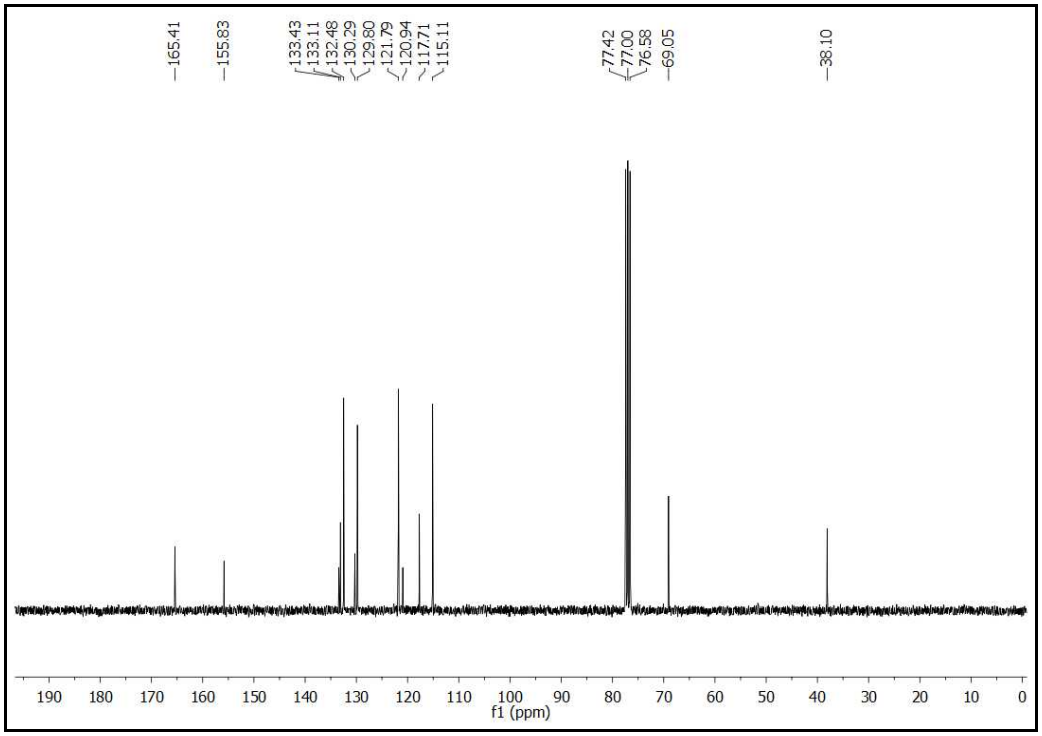


Figure 5. ^{13}C NMR spectrum of compound **4a** ($CDCl_3$, 75 MHz).

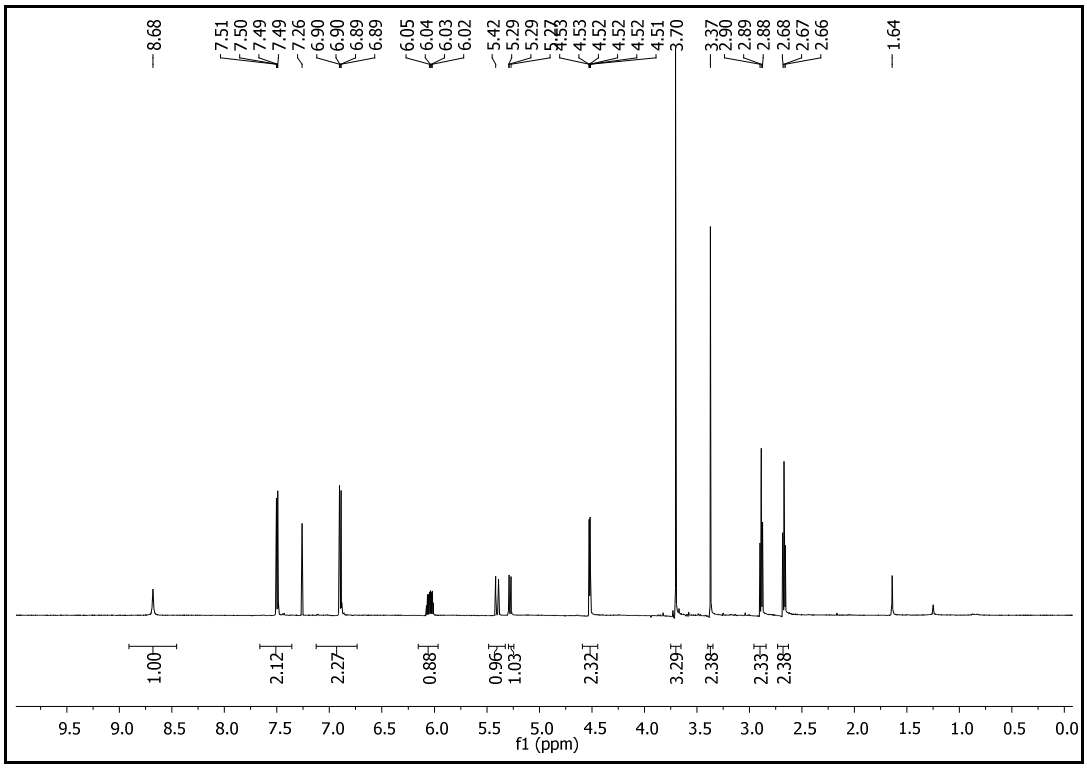


Figure 6. ^{1}H NMR spectrum of compound **4b** ($CDCl_3$, 600 MHz).

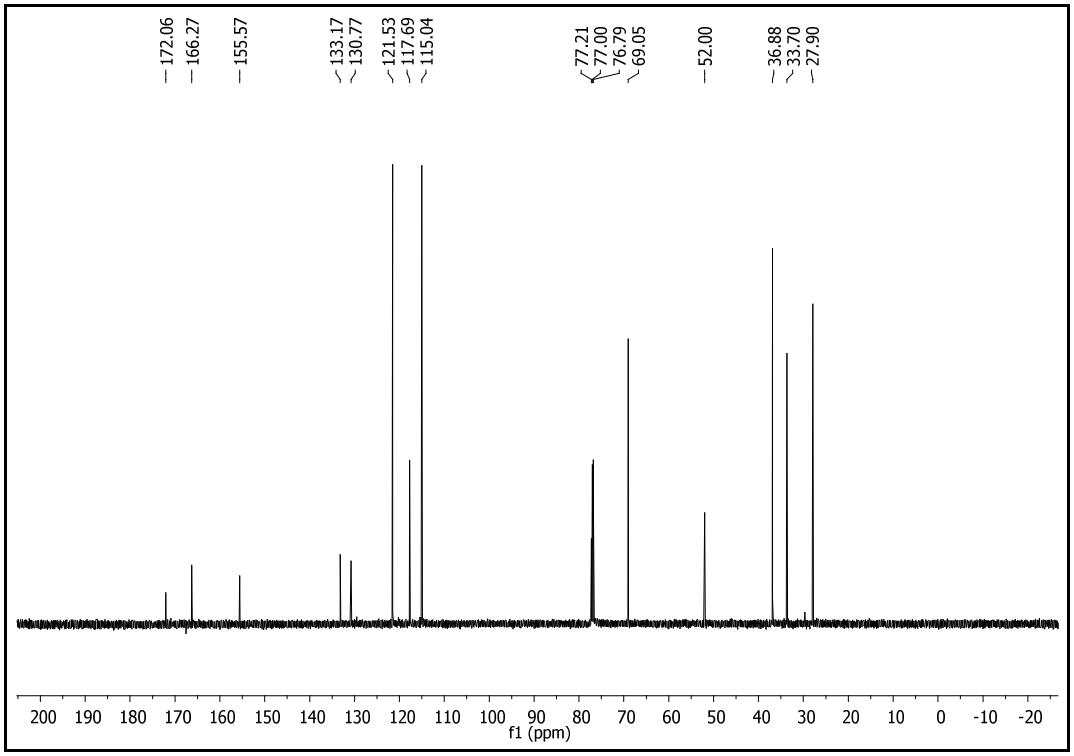


Figure 7. ^{13}C NMR spectrum of compound **4b** ($CDCl_3$, 151 MHz).

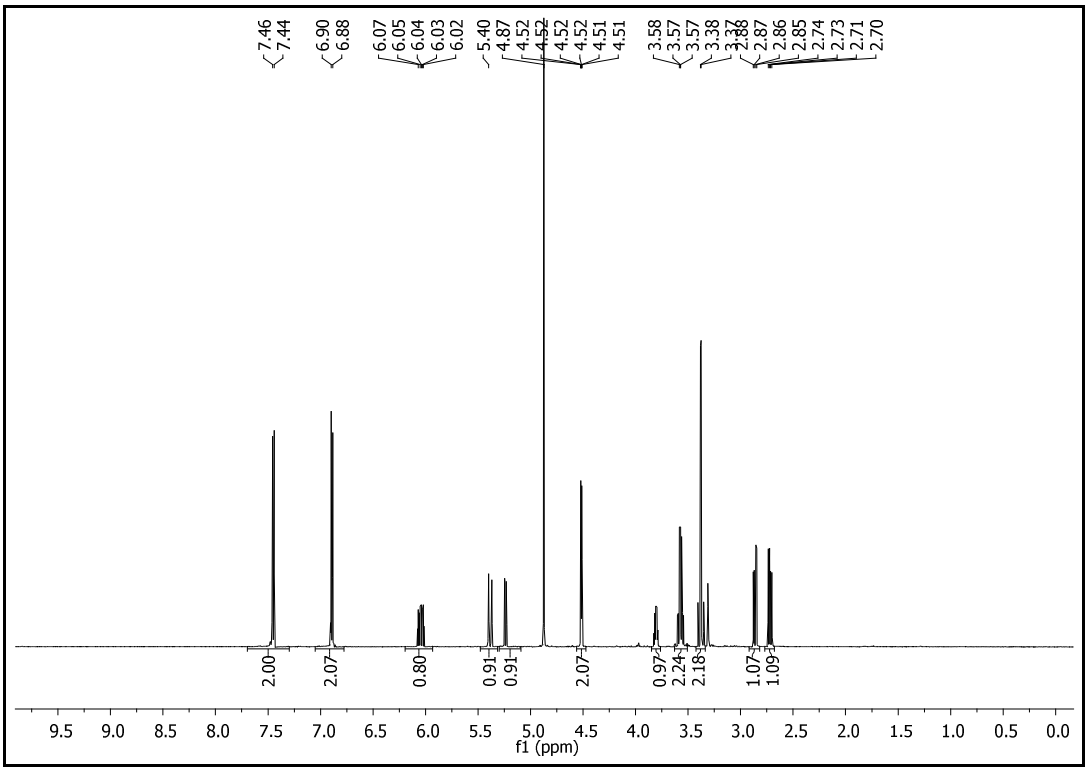


Figure 8. ^{1}H NMR spectrum of compound **4c** (CD_3OD, 600 MHz).

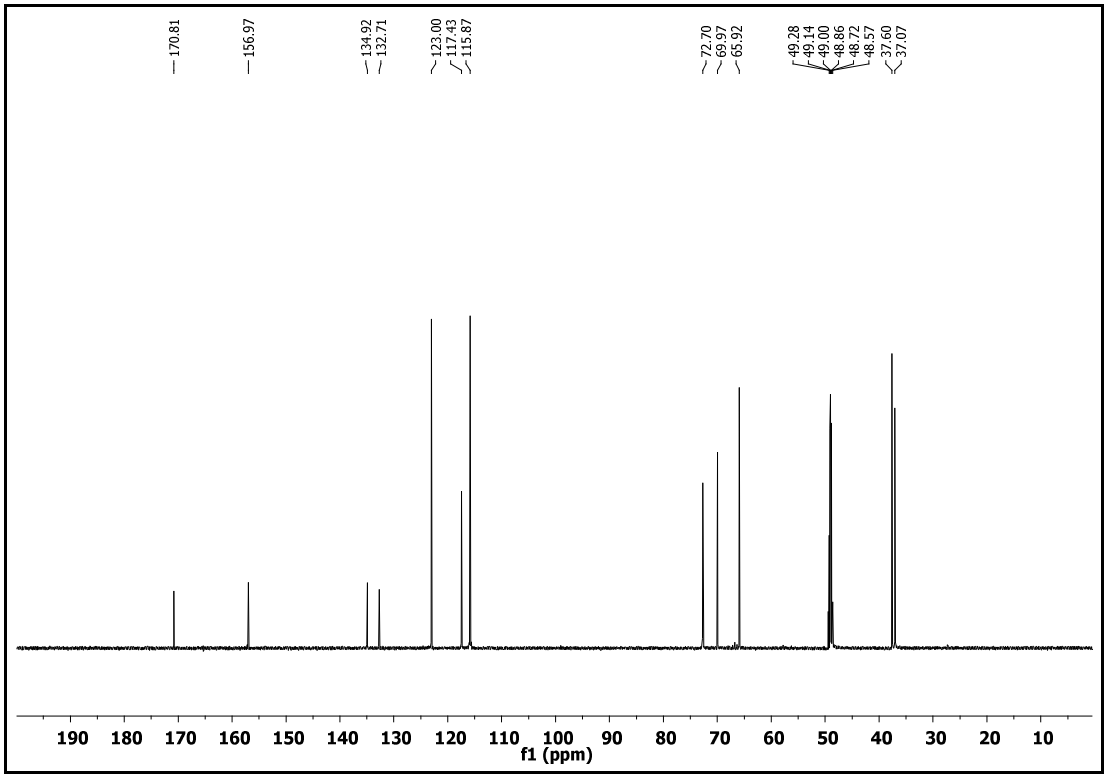


Figure 9. ^{13}C NMR spectrum of compound **4c** (CD_3OD, 151 MHz).

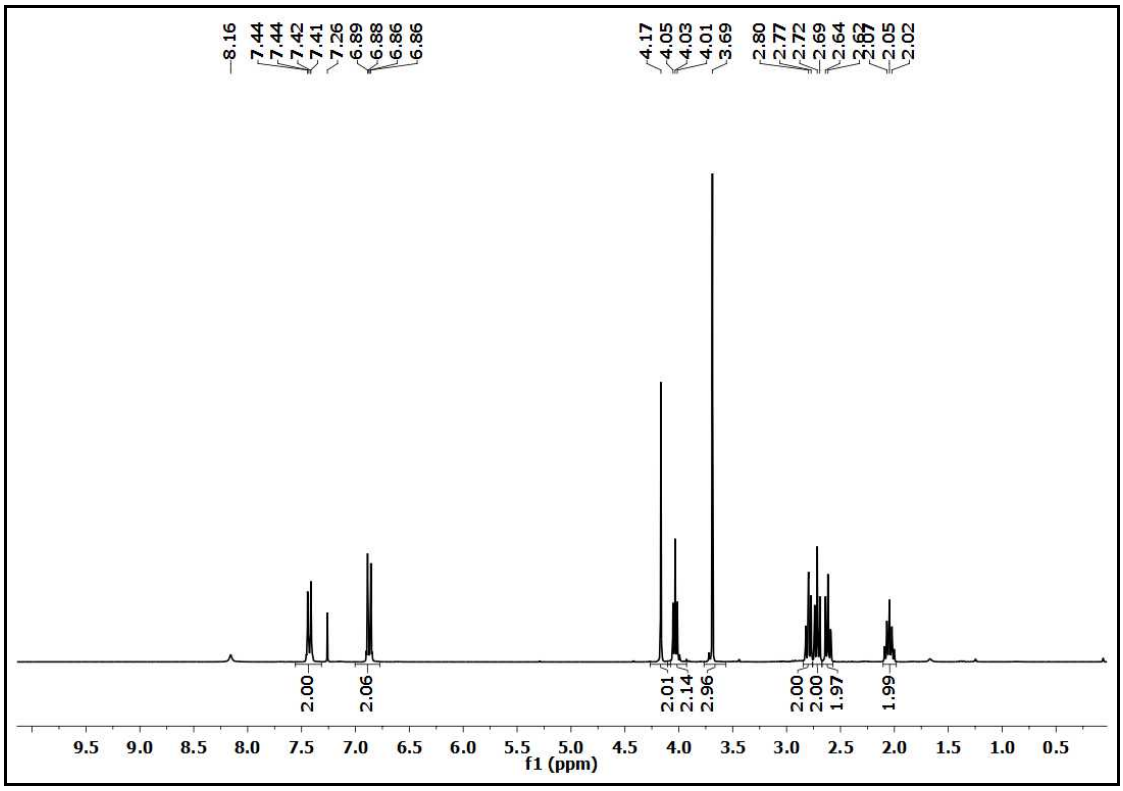


Figure 10. ^{1}H NMR spectrum of compound **5a** ($CDCl_3$, 300 MHz).

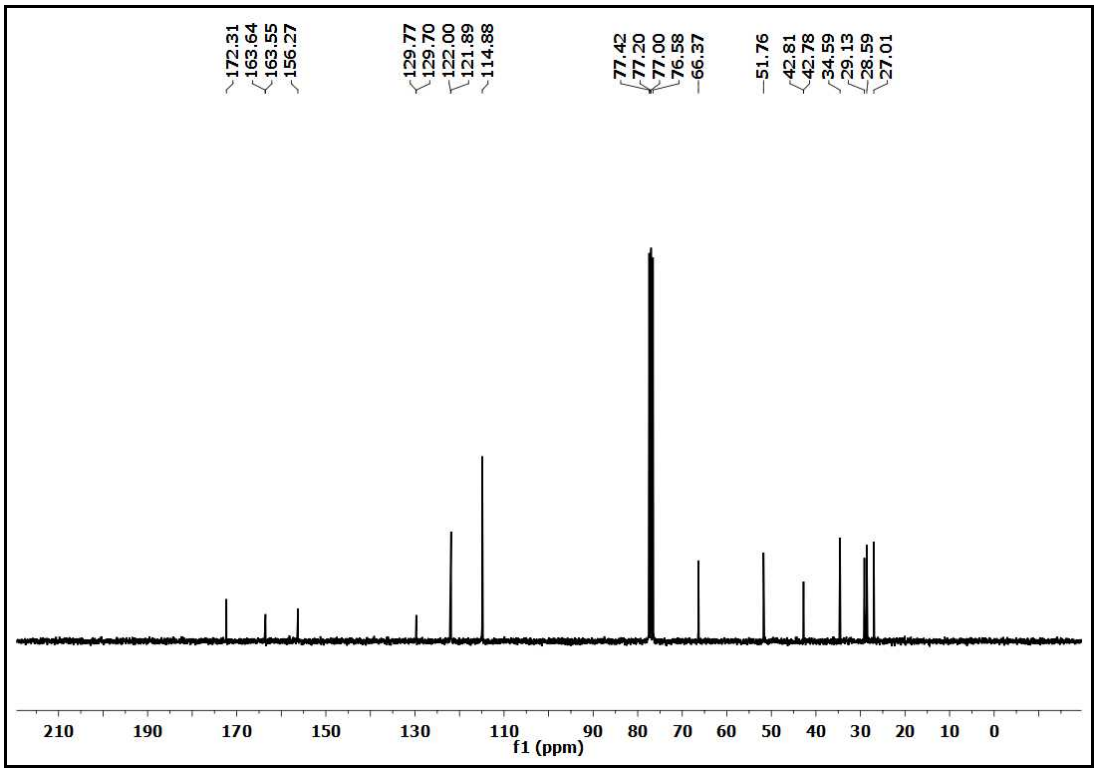


Figure 11. ^{13}C NMR spectrum of compound **5a** ($CDCl_3$, 75 MHz).

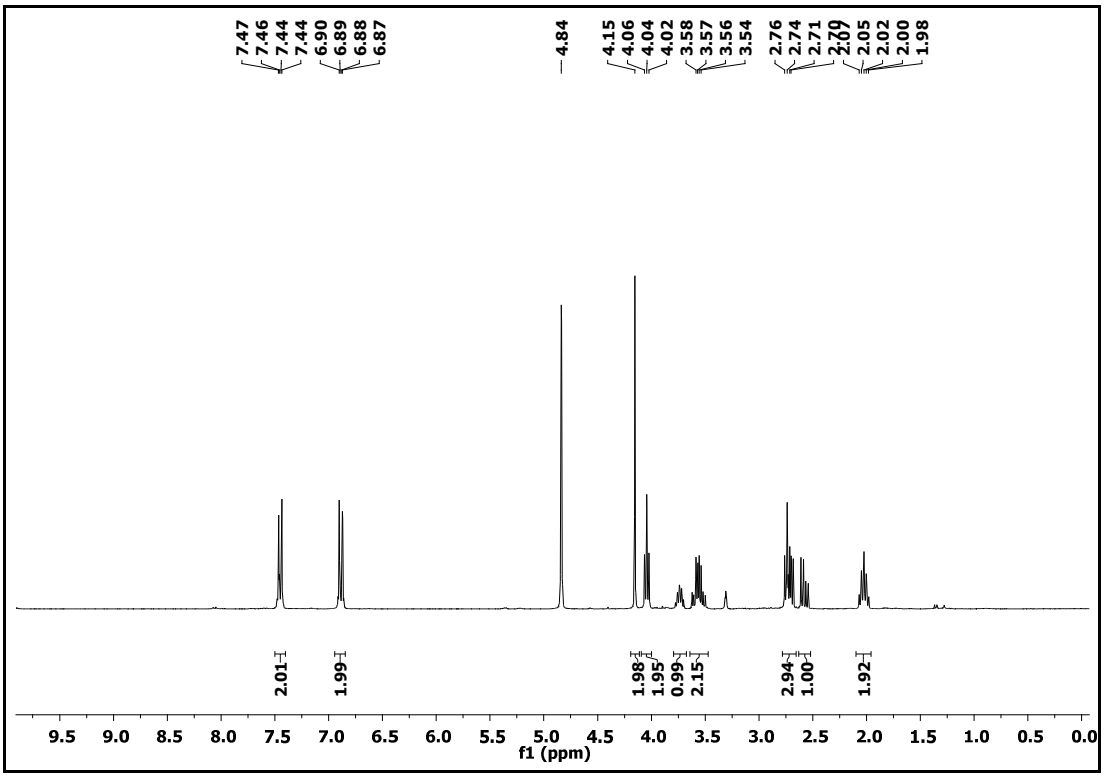


Figure 12. ^{1}H NMR spectrum of compound **5b** (CD_3OD, 300 MHz).

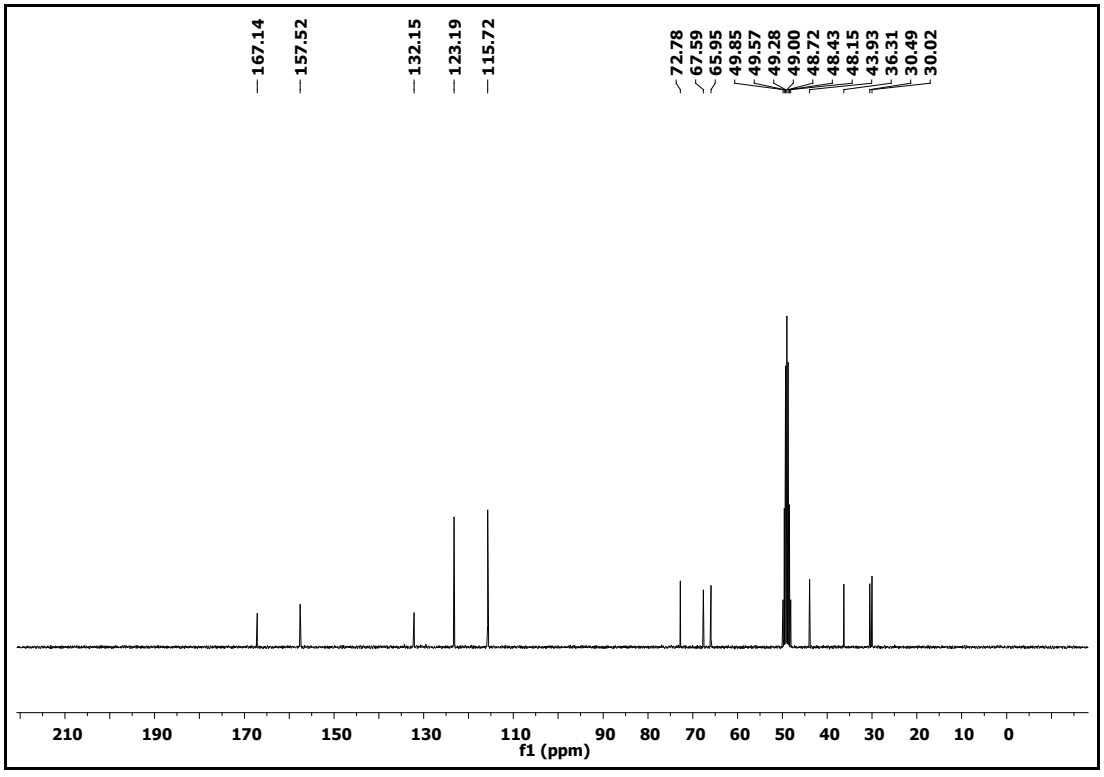


Figure 13. ^{13}C NMR spectrum of compound **5b** (CD_3OD, 75 MHz).

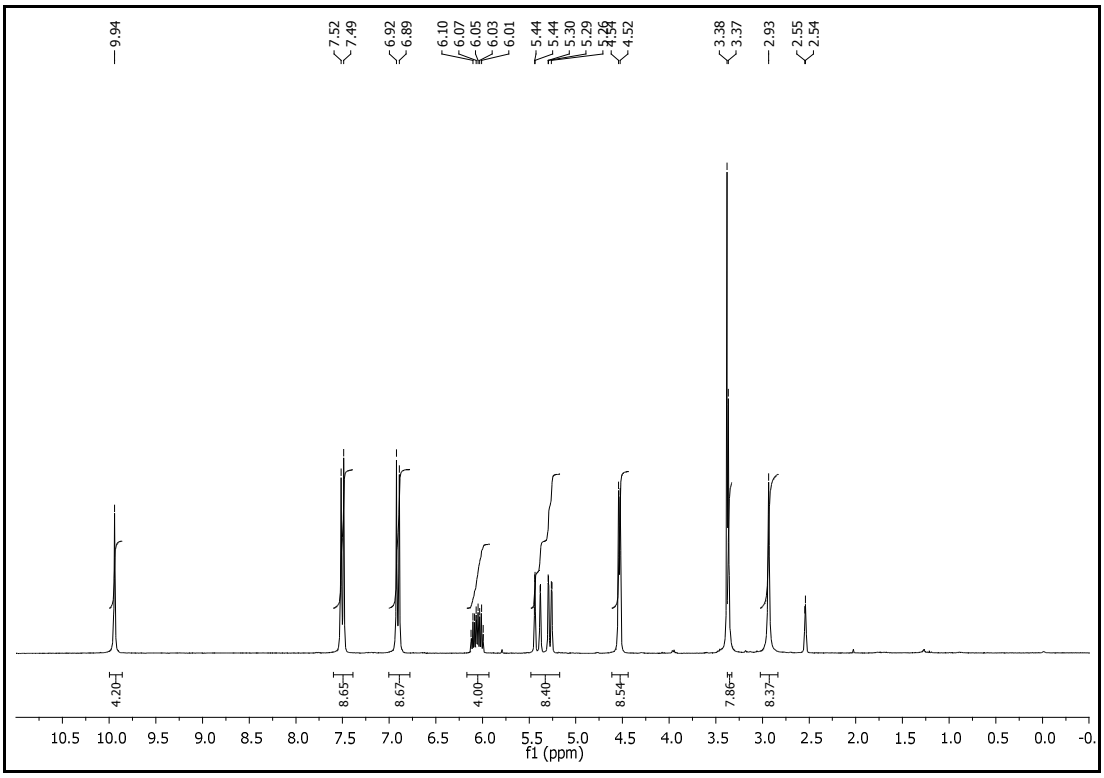


Figure 14. ^{1}H NMR spectrum of compound **S1** (DMSO-d_6, 300 MHz).

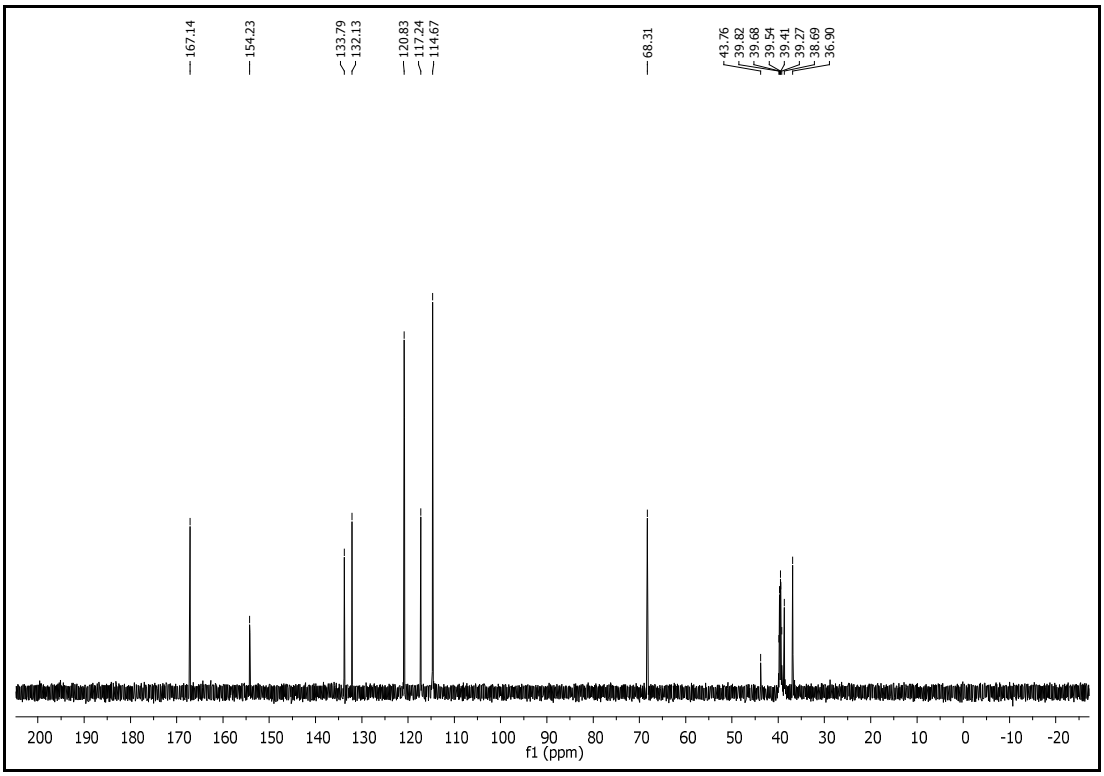
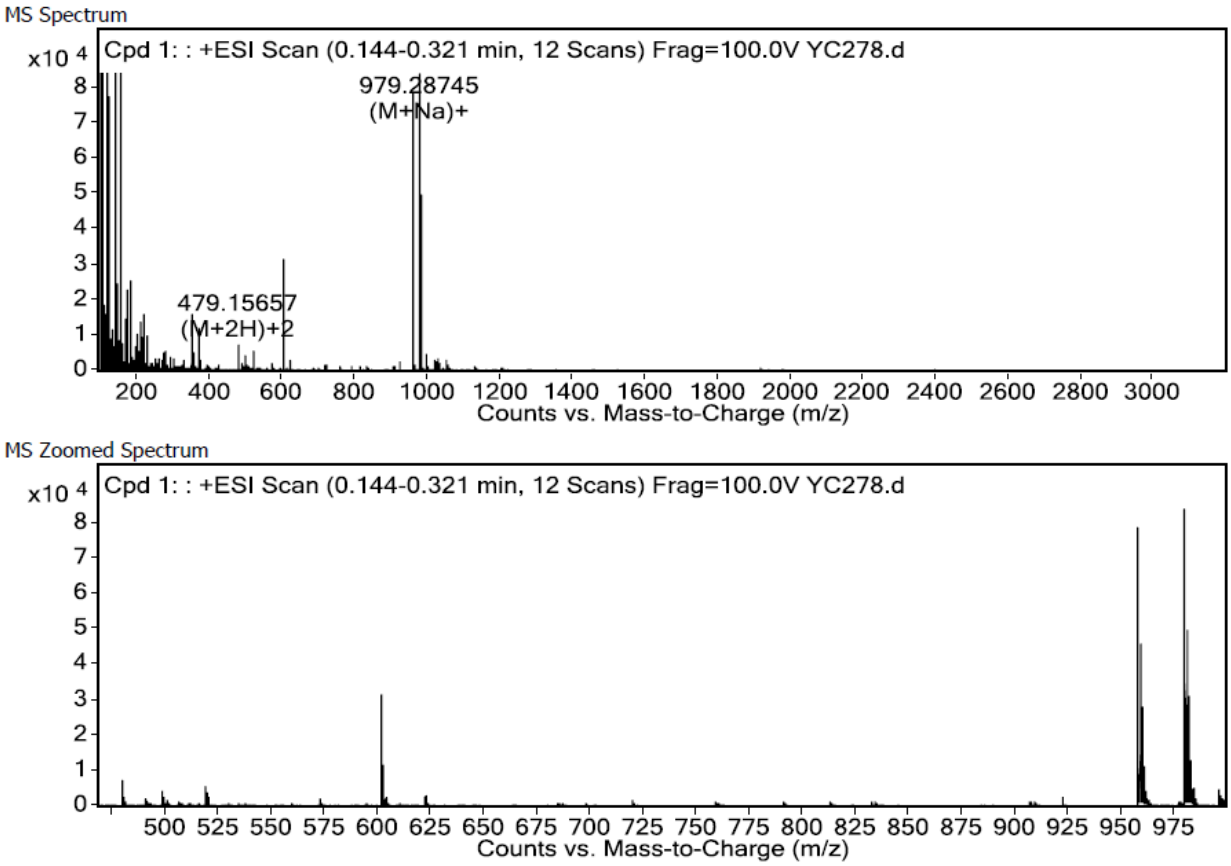


Figure 15. ^{13}C NMR spectrum of compound **S1** (DMSO-d_6, 151 MHz).



MS Spectrum Peak List

Ion	Ion Formula	Abund	*Expe. m/z*	*Calc. m/z*	Diff(ppm)
(M+H)+	C49H57N4O8S4	79659.9	957.30562	957.30537	0.26
(M+Na)+	C49H56N4NaO8S4	84255.1	979.28745	979.28732	0.13

Figure 16. HRMS (ESI^+) spectra of compound **S1**.

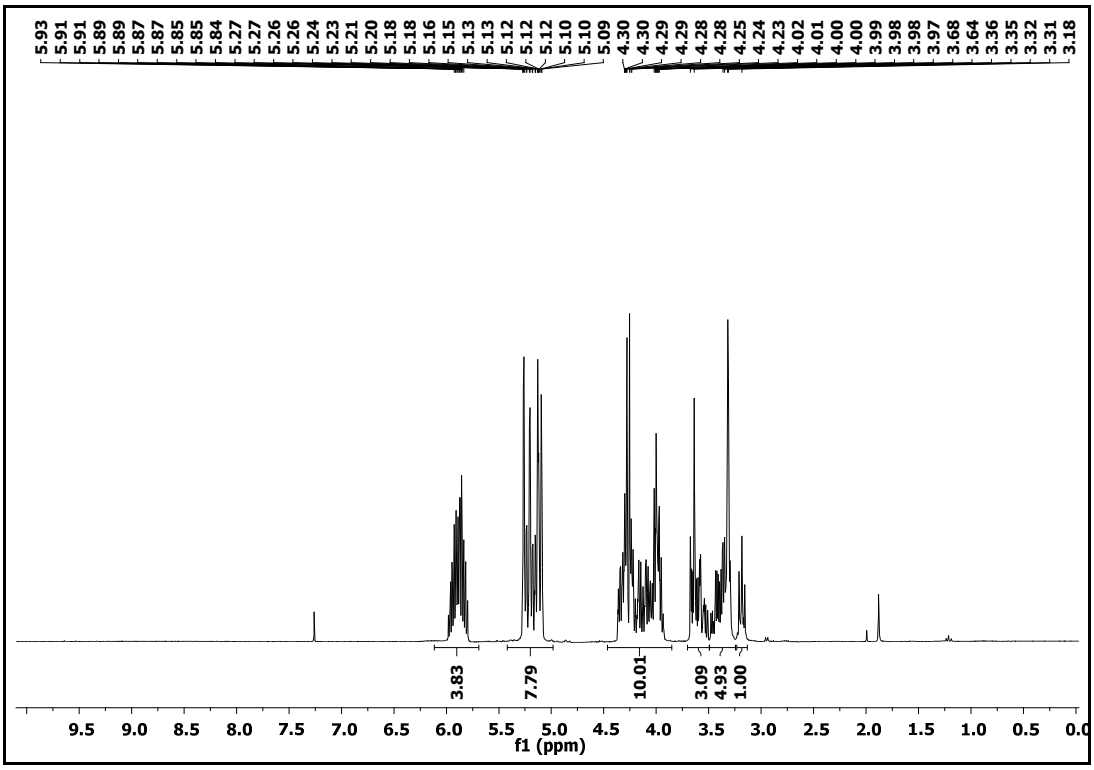


Figure 17. ^{1}H NMR spectrum of compound **7** ($CDCl_3$, 300 MHz).

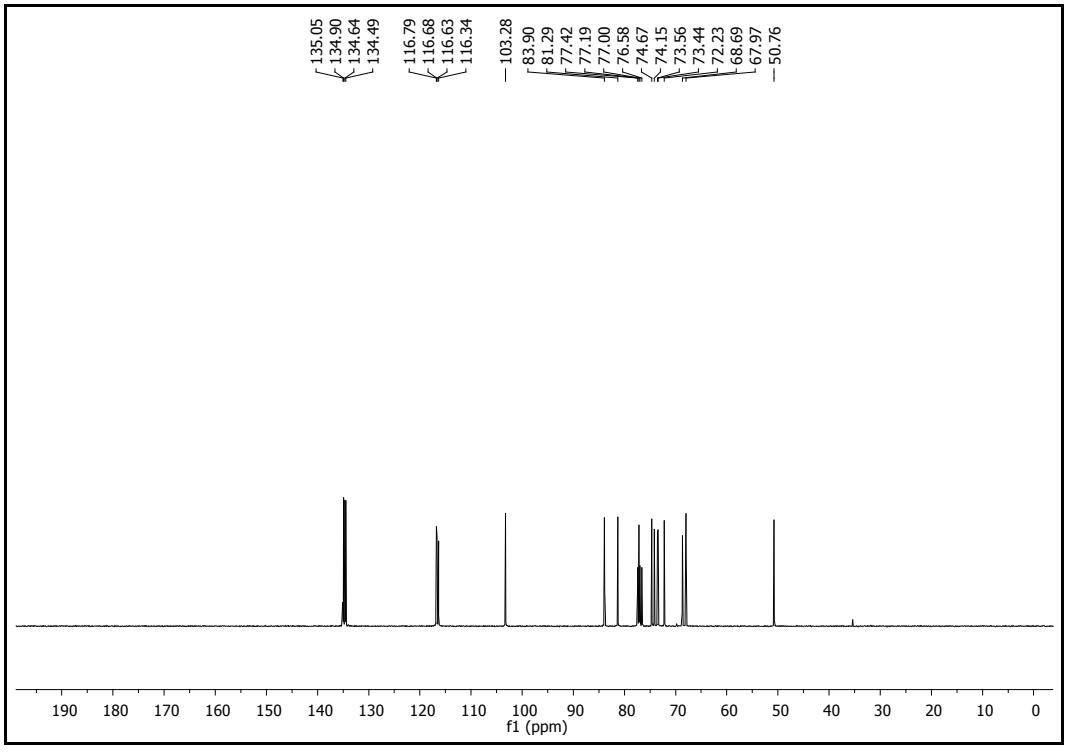


Figure 18. ^{13}C NMR spectrum of compound **7** ($CDCl_3$, 75 MHz).

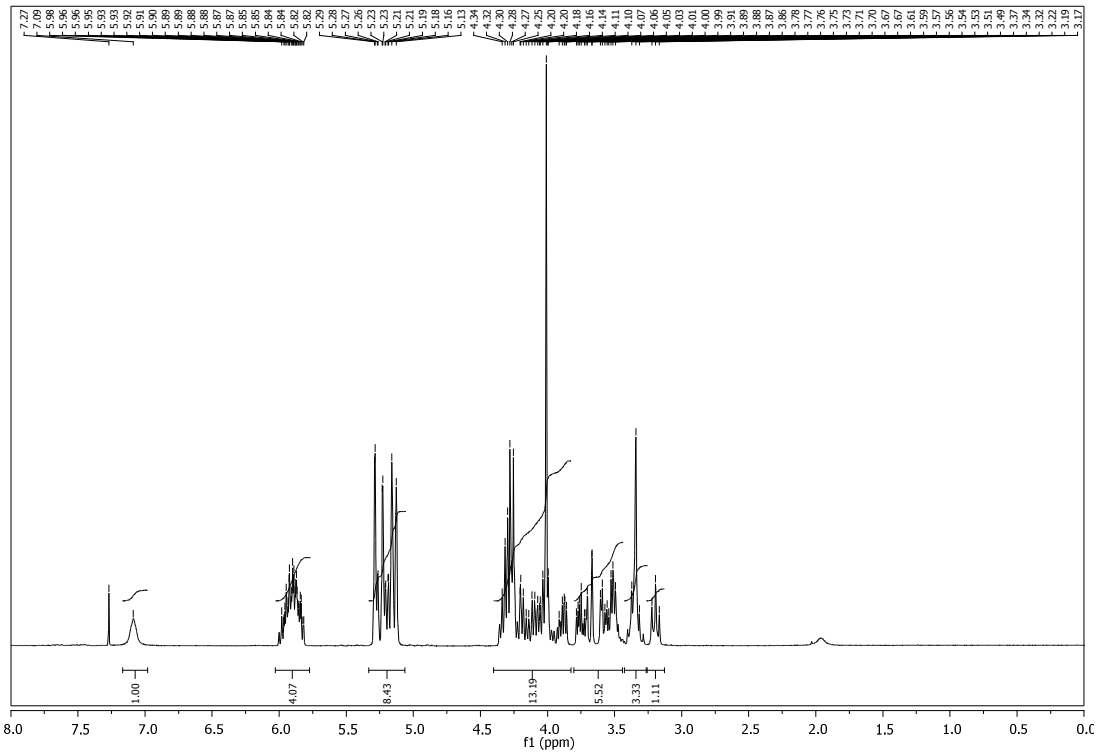


Figure 19. ^{1}H NMR spectrum of compound **8** ($CDCl_3$, 300 MHz).

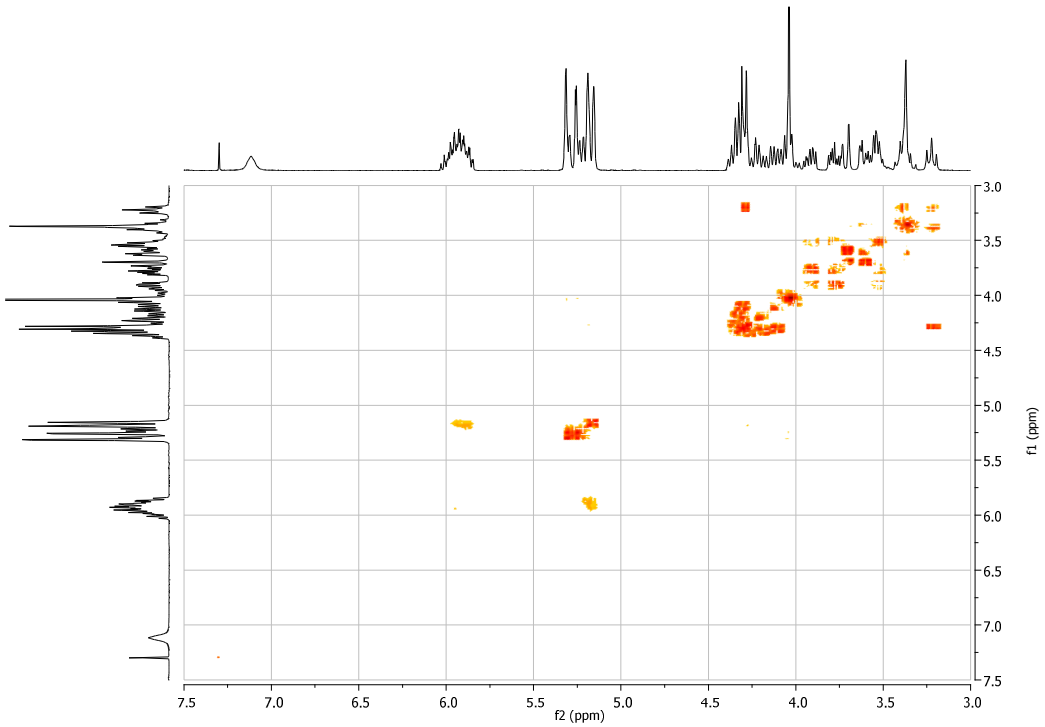


Figure 20. gCOSY spectrum of compound **8** ($CDCl_3$).

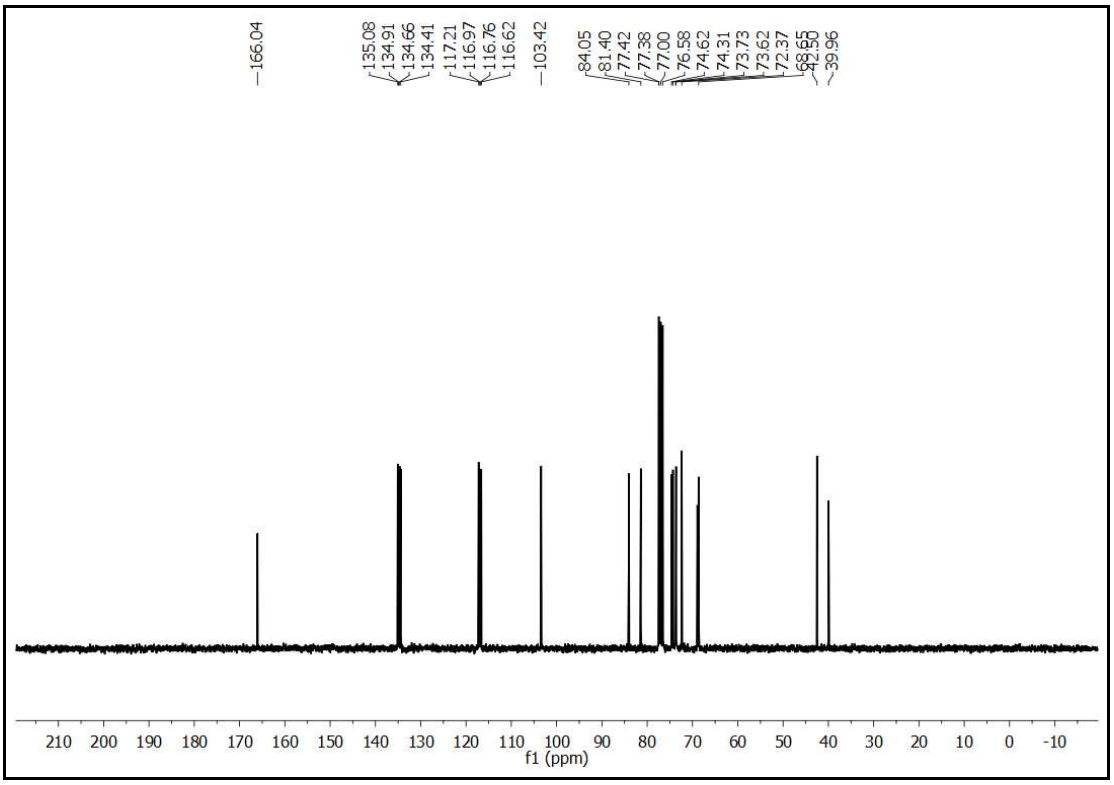


Figure 21. ^{13}C NMR spectrum of compound **8** ($CDCl_3$, 75 MHz).

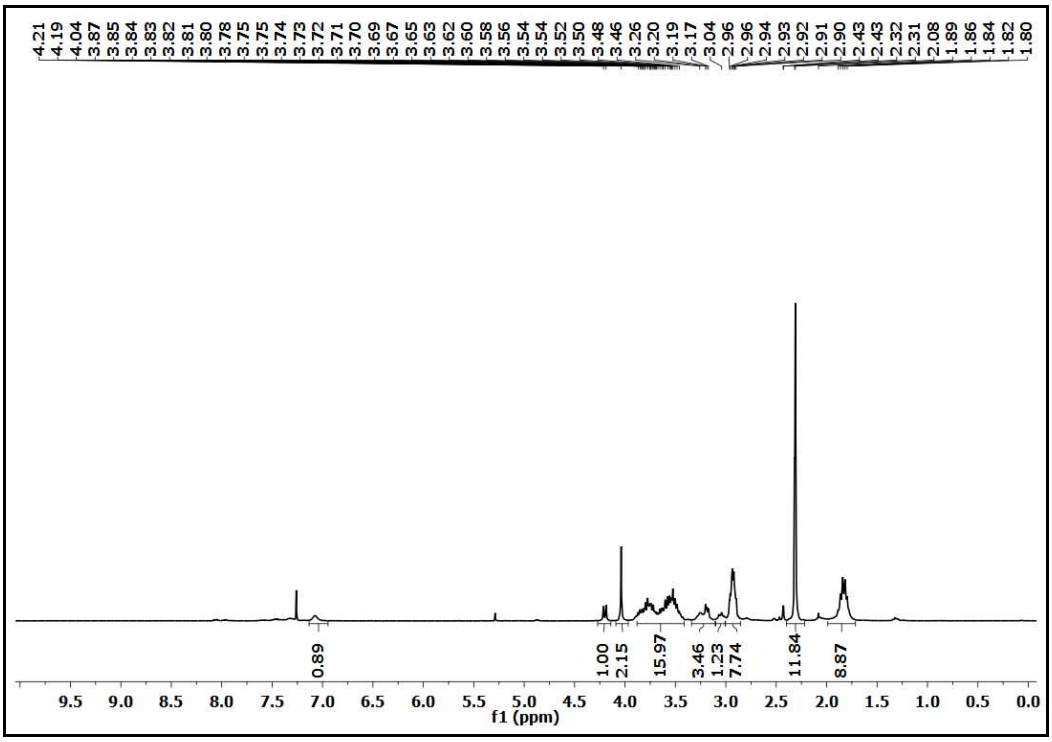


Figure 22. ^{1}H NMR spectrum of compound **9** ($CDCl_3$, 300 MHz).

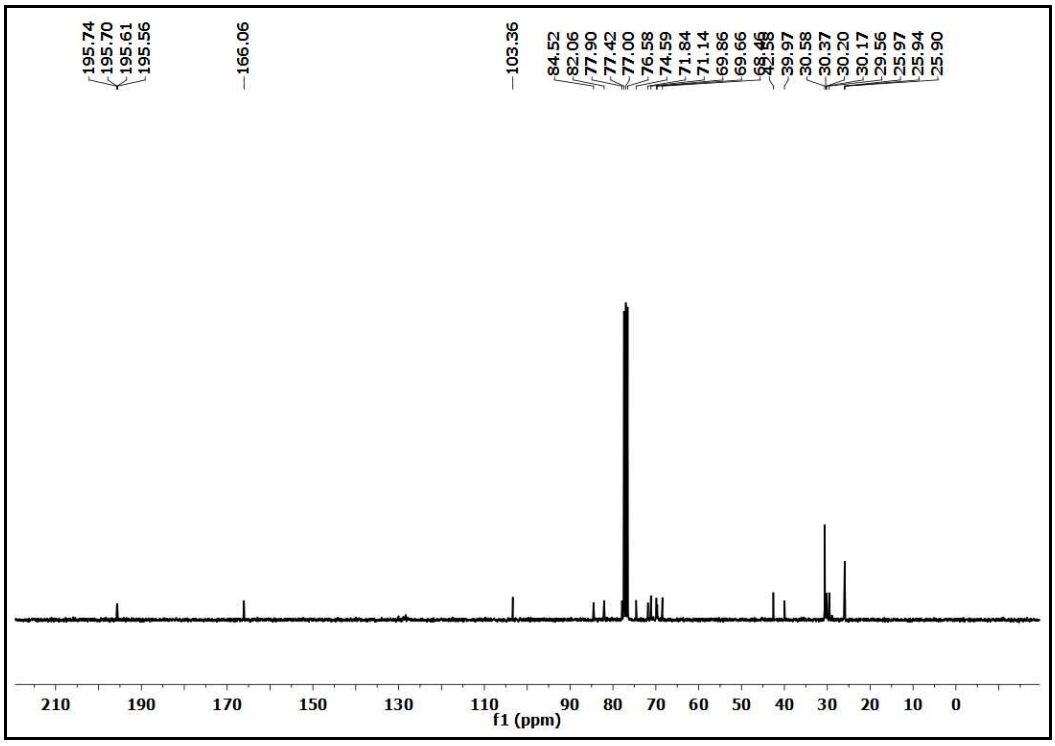


Figure 23. ^{13}C NMR spectrum of compound **9** ($CDCl_3$, 75 MHz).

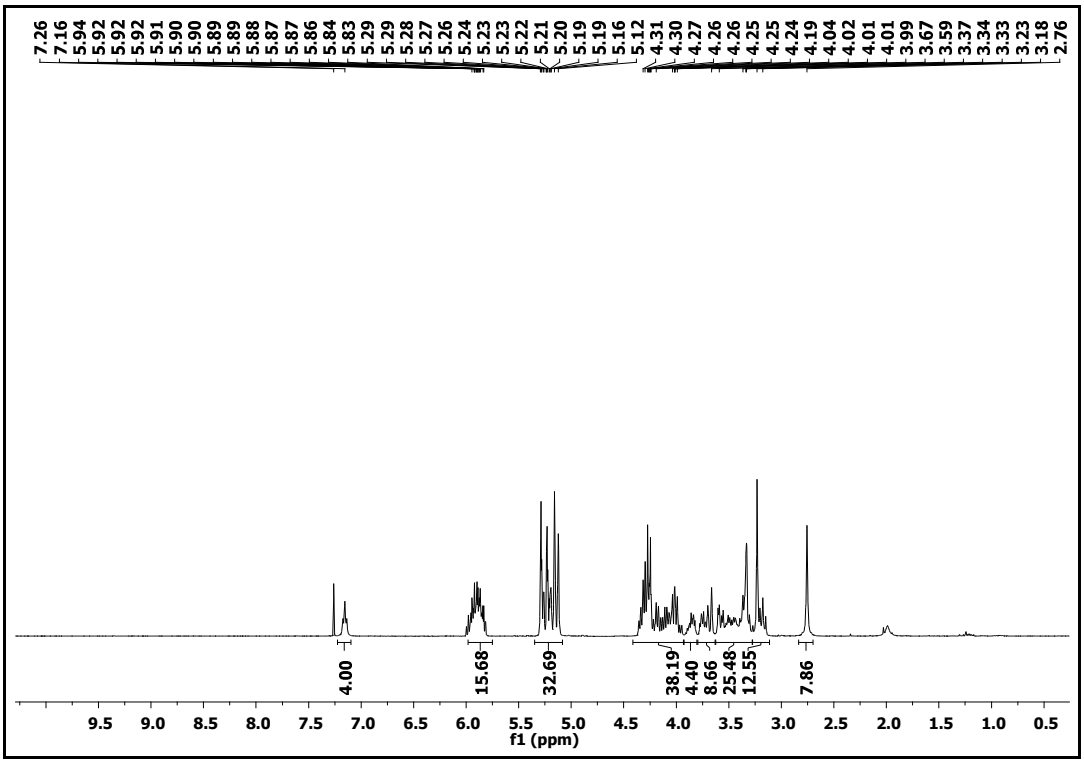


Figure 24. ^{1}H NMR spectrum of compound **11** ($CDCl_3$, 300 MHz).

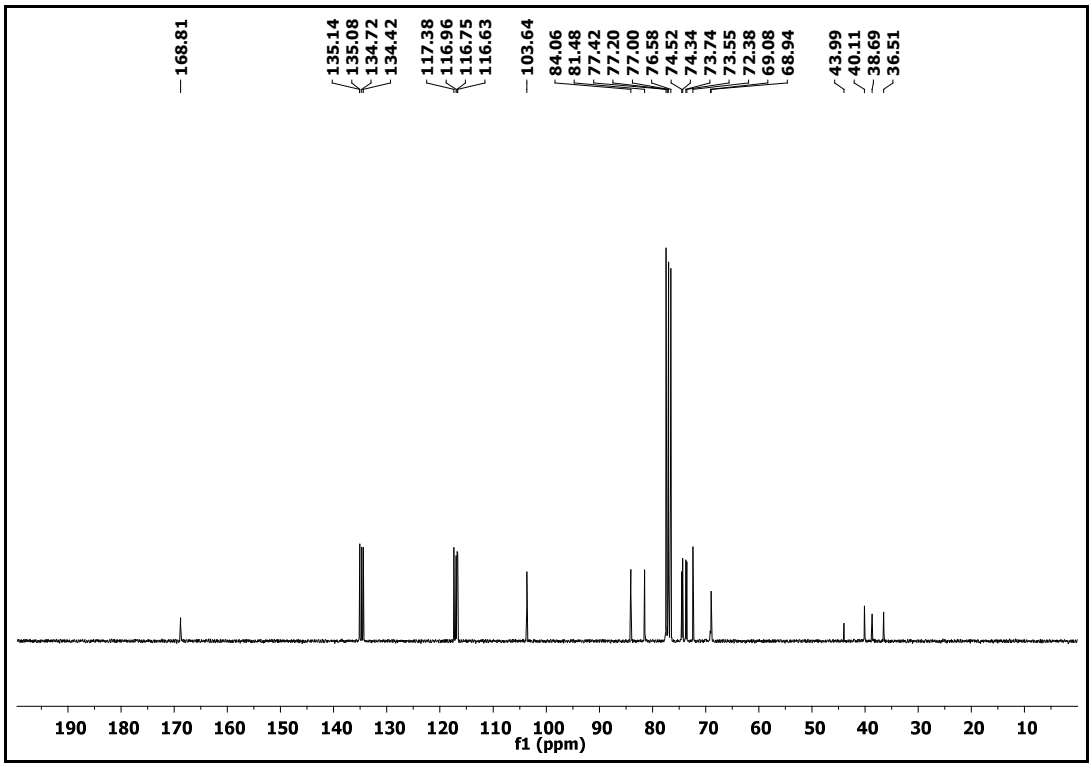


Figure 25. ^{13}C NMR spectrum of compound **11** ($CDCl_3$, 75 MHz).

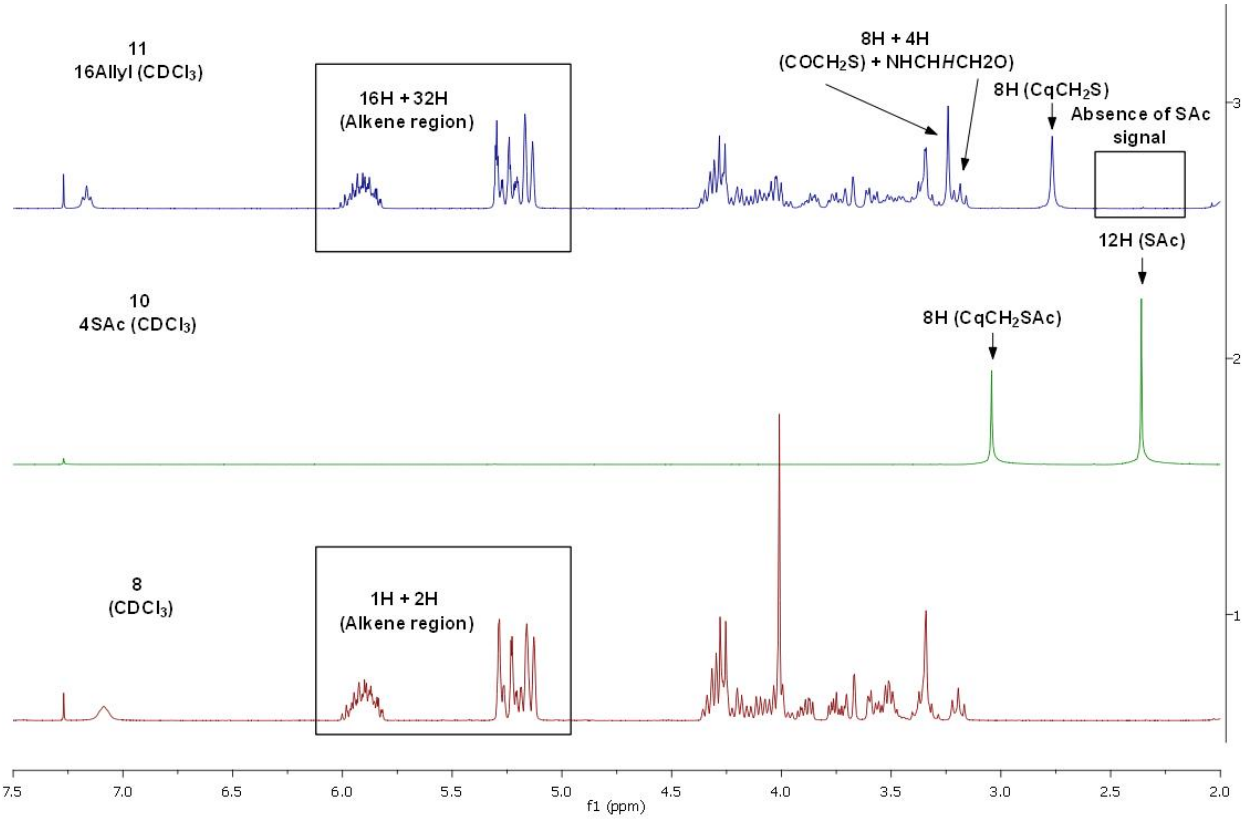
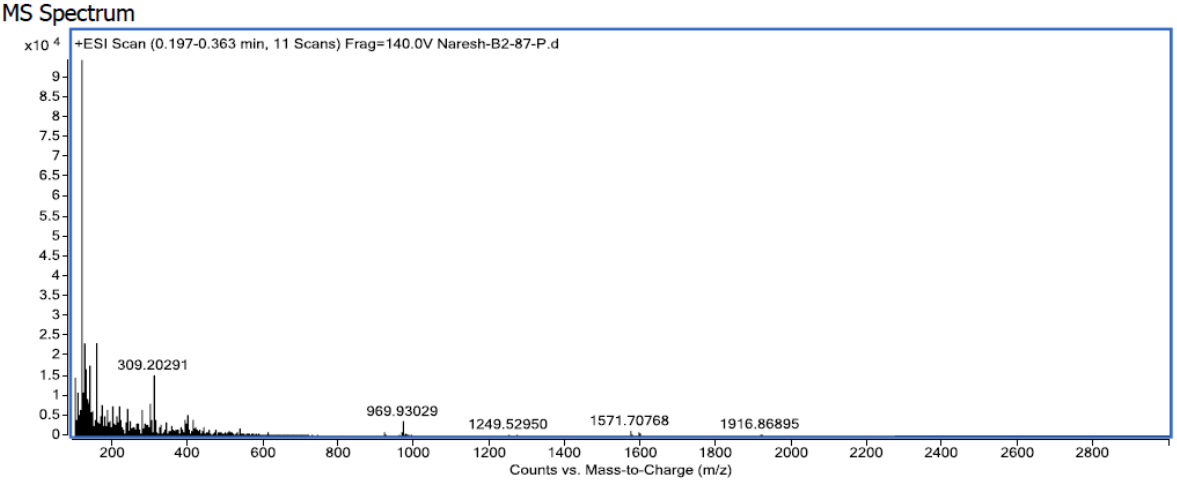
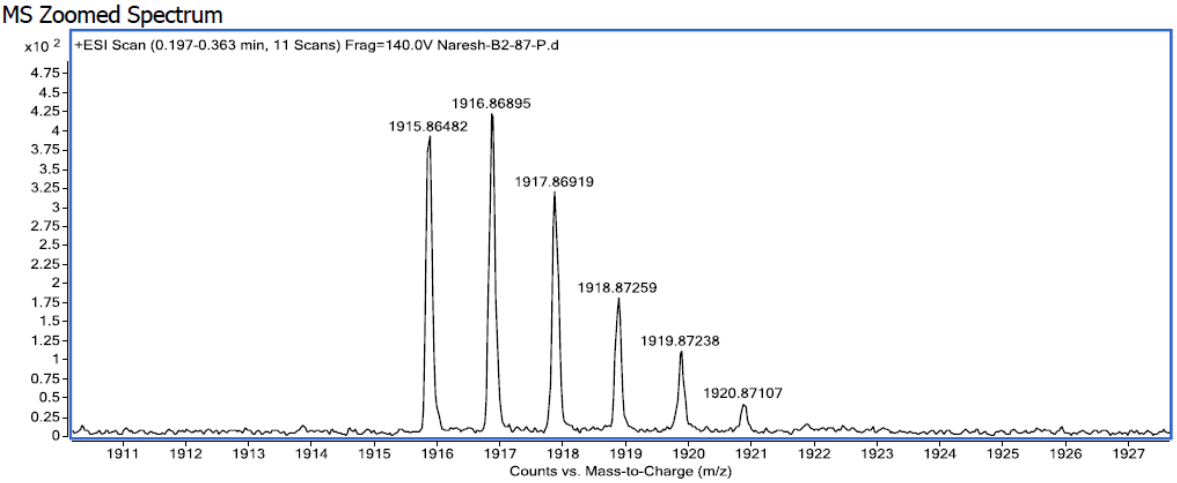


Figure 26. Comparison ^{1}H NMR spectra for the synthesis of **11** from **8** and **10** showing the appearance of core signals with corresponding integrations.

MS Spectrum



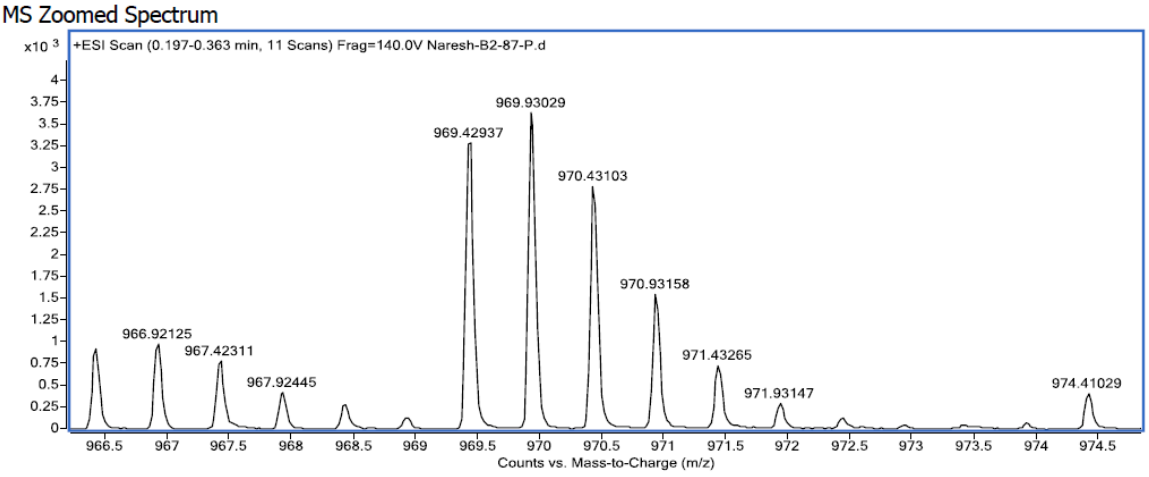
MS Zoomed Spectrum



MS Spectrum Peak List

Ion	Formula	Abund	Observed m/z	Calc m/z	Diff(ppm)
(M+Na)+	C93H144N4NaO28S4		1915.86482	1915.87421	4.9

MS Zoomed Spectrum



MS Spectrum Peak List

Ion	Formula	Abund	Observed m/z	Calc m/z	Diff(ppm)
(M+2Na)+2	C93H144N4Na2O28S4		969.42937	969.43172	2.42

Figure 27. HRMS (ESI$^+$) spectra of compound **11**.

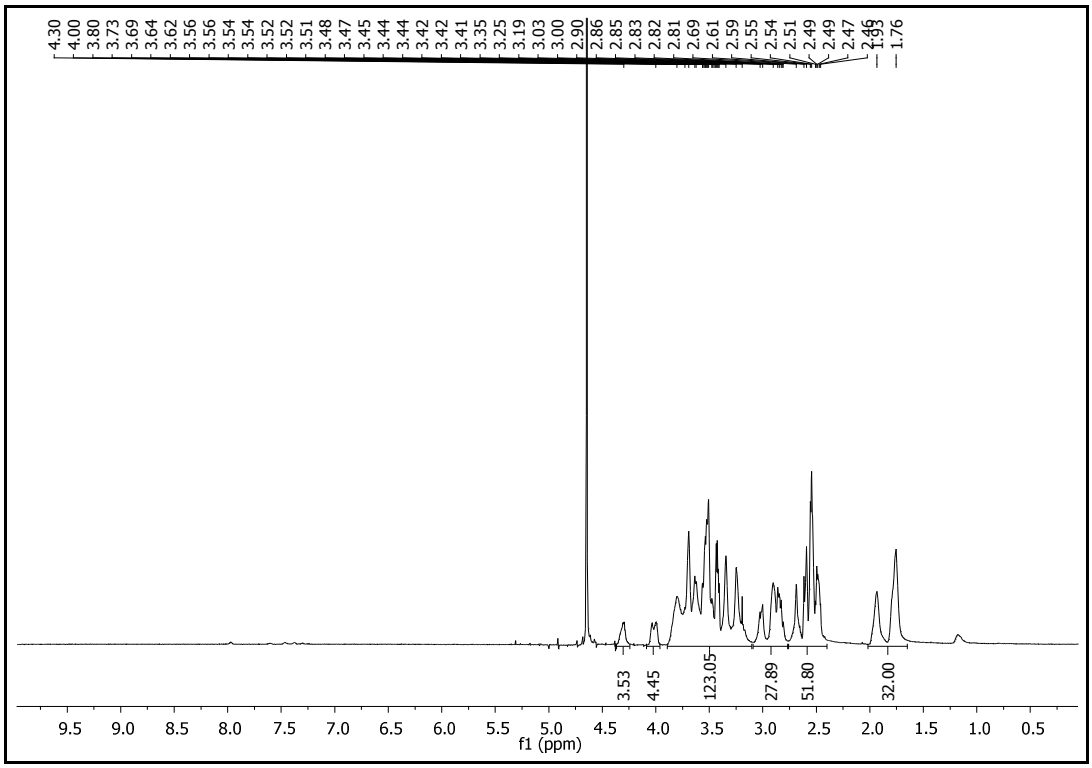


Figure 28. ^{1}H NMR spectrum of compound **14** (D_2O, 600 MHz).

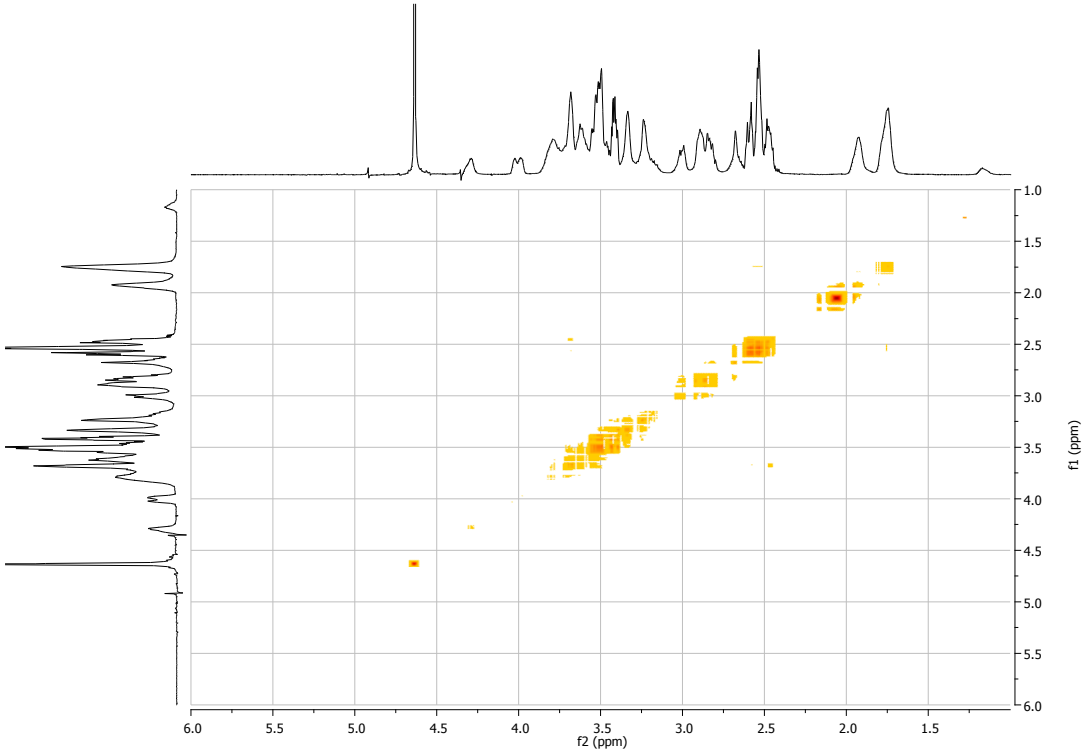


Figure 29. gCOSY spectrum of compound **14** (D_2O).

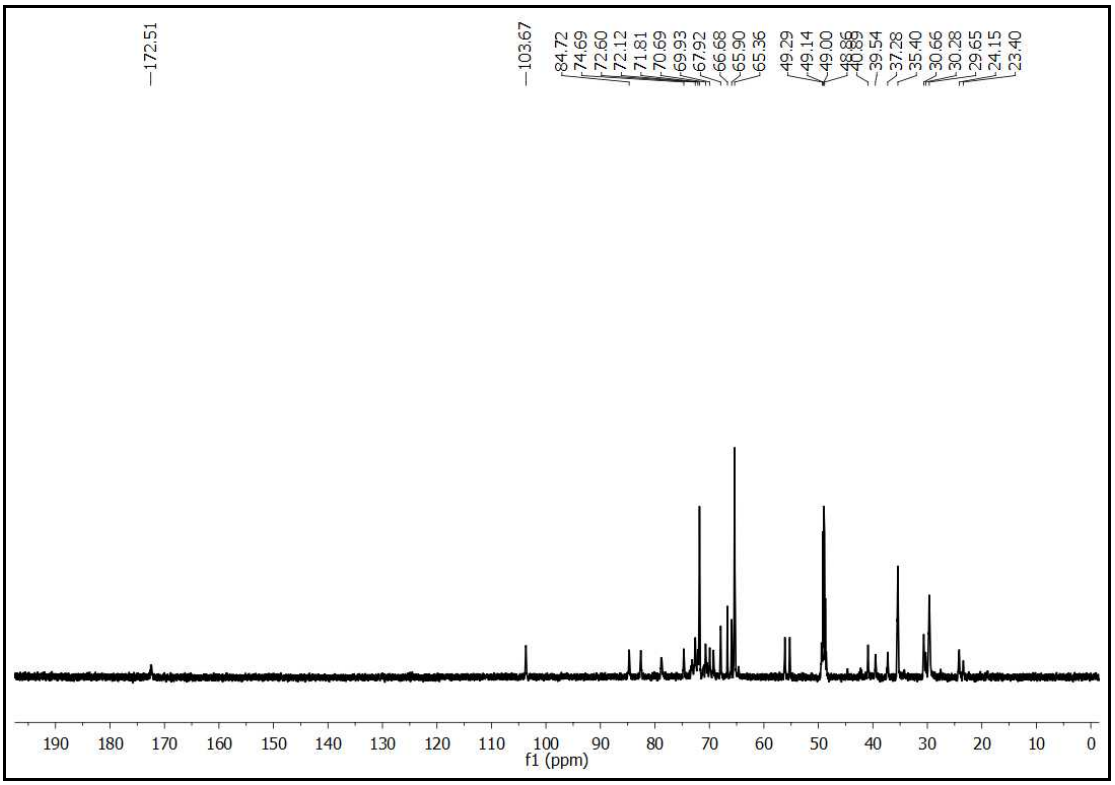


Figure 30. ^{13}C NMR spectrum of compound **14** (MeOD, 151 MHz).

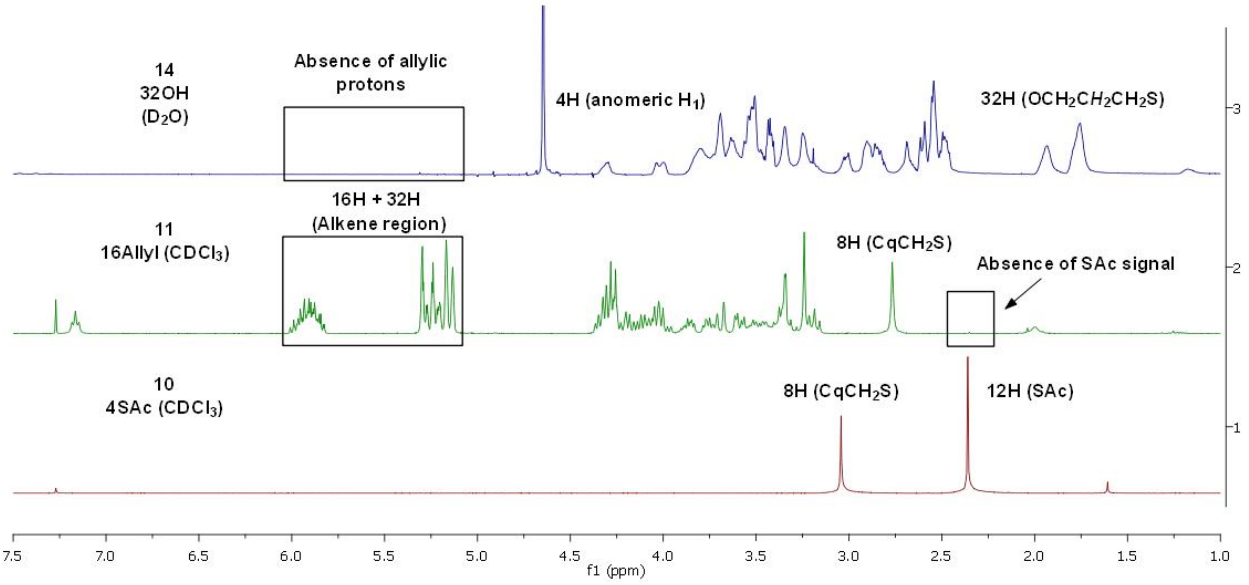


Figure 31. Sequence of ^{1}H NMR spectra for the synthesis of **14** from **10** showing the appearance and disappearance of main signals (chains and functional groups) with corresponding integrations.

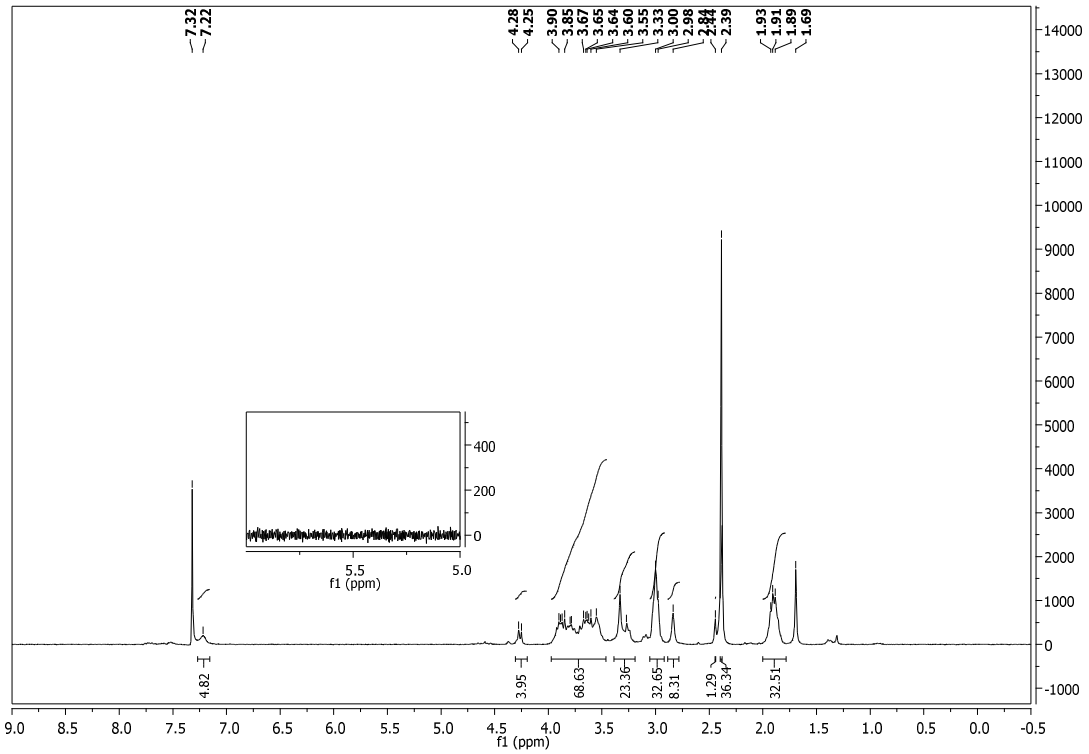


Figure 32. ^{1}H NMR spectrum of compound **12** ($CDCl_3$, 300 MHz).

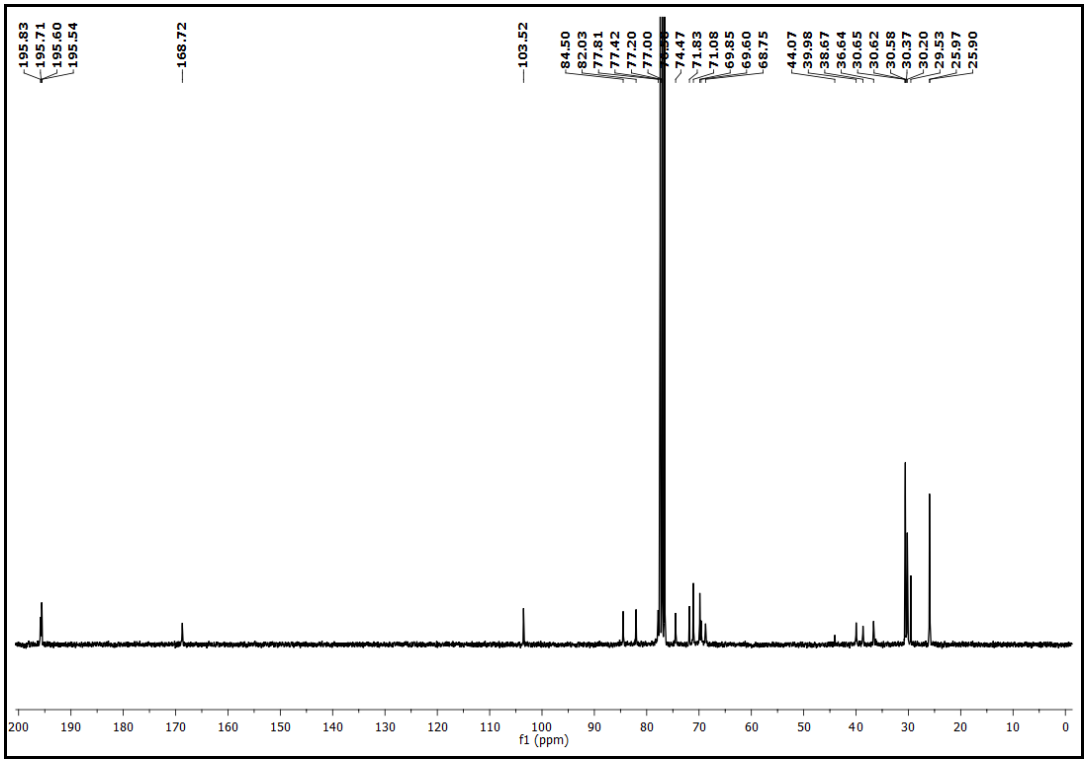
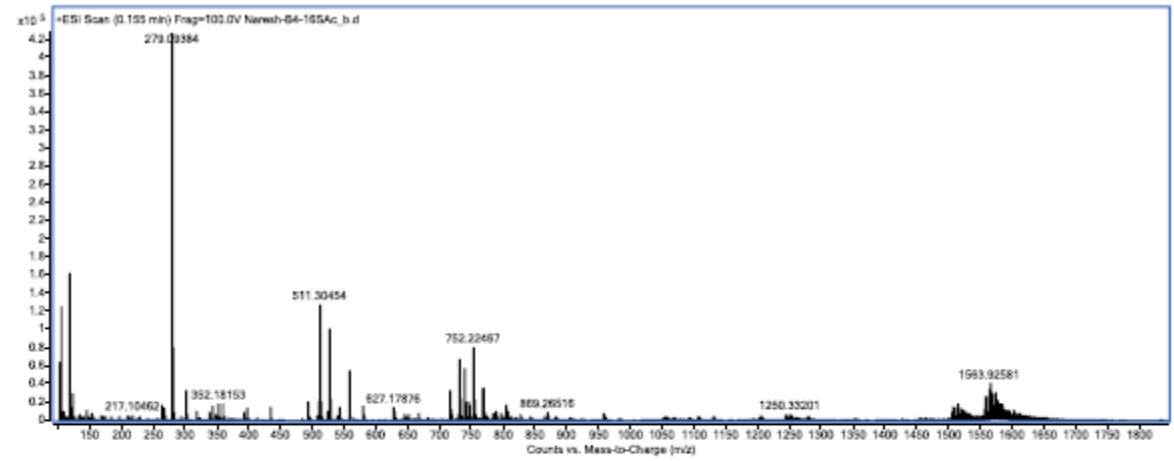
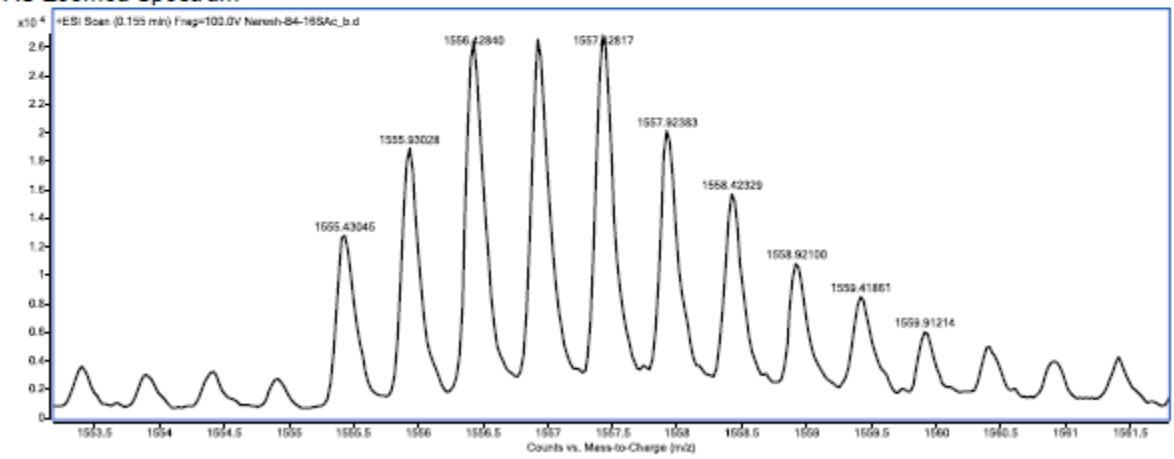


Figure 33. ^{13}C NMR spectrum of compound **12** ($CDCl_3$, 75 MHz).

MS Spectrum



MS Zoomed Spectrum



MS Spectrum Peak List

Ion	Ion Formula	Abund	*Expe. m/z*	*Calc. m/z*	Diff(ppm)
(M+2H)+2	C125H208N4O44S20		1555.43045	1555.43606	3.6

Figure 34. HRMS (ESI^+) spectra of compound **12**.

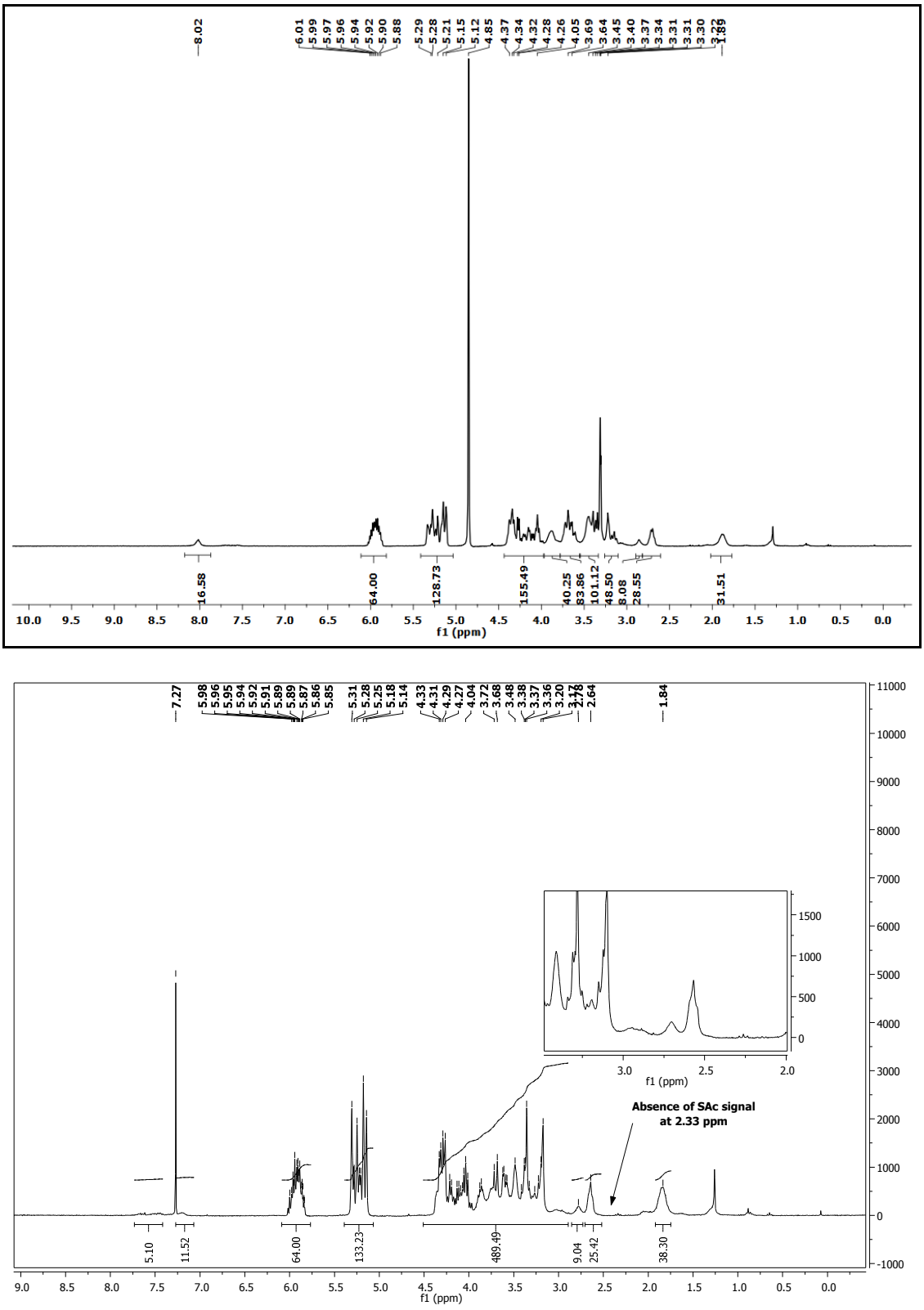


Figure 35. ^{1}H NMR spectrum of compound **13** (Top: CD_3OD, 300 MHz; Down: $CDCl_3$, 300 MHz).

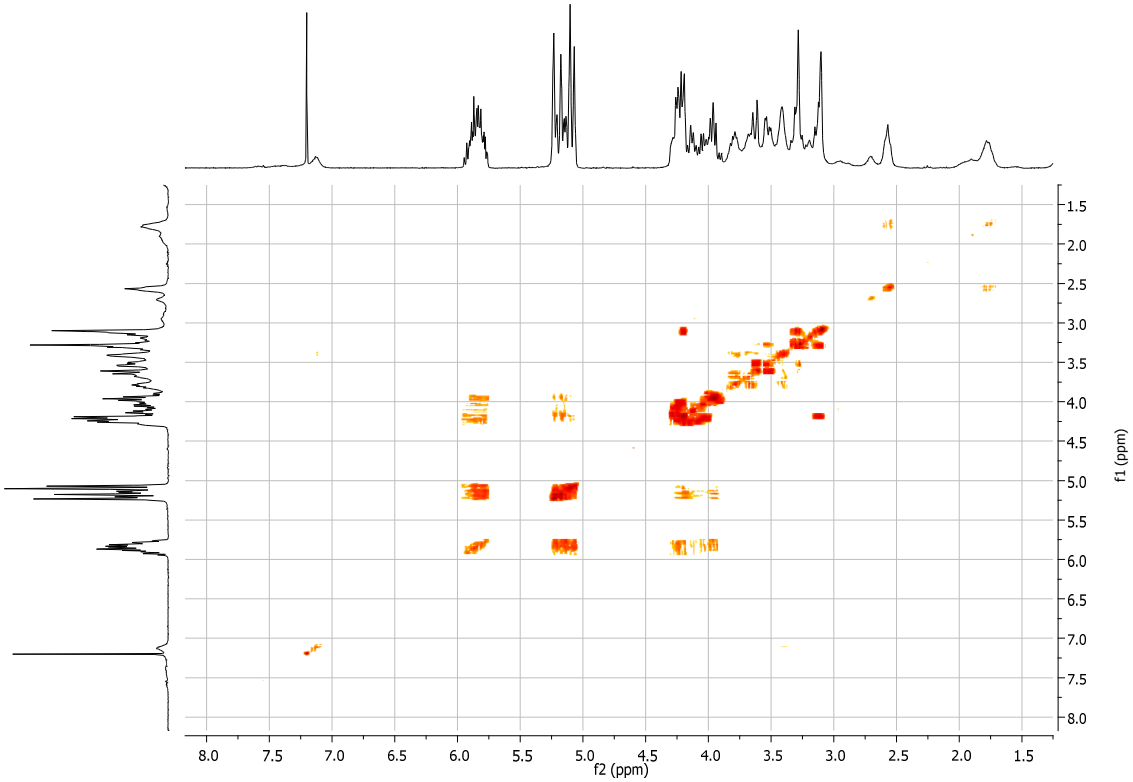


Figure 36. gCOSY spectrum of compound **13** ($CDCl_3$).

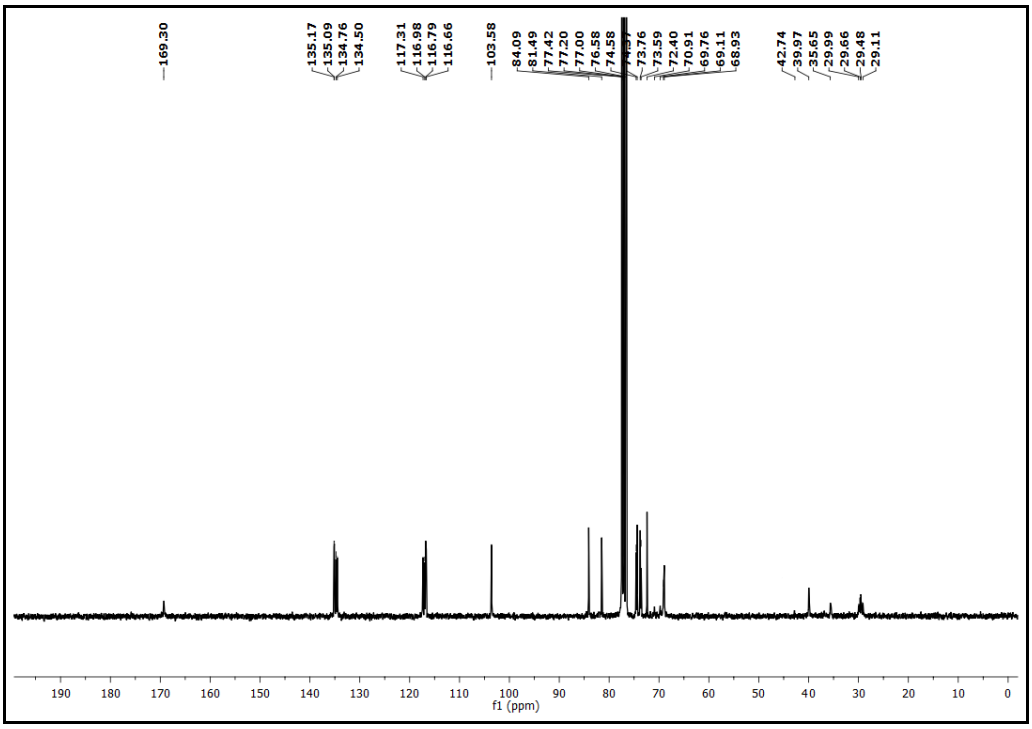
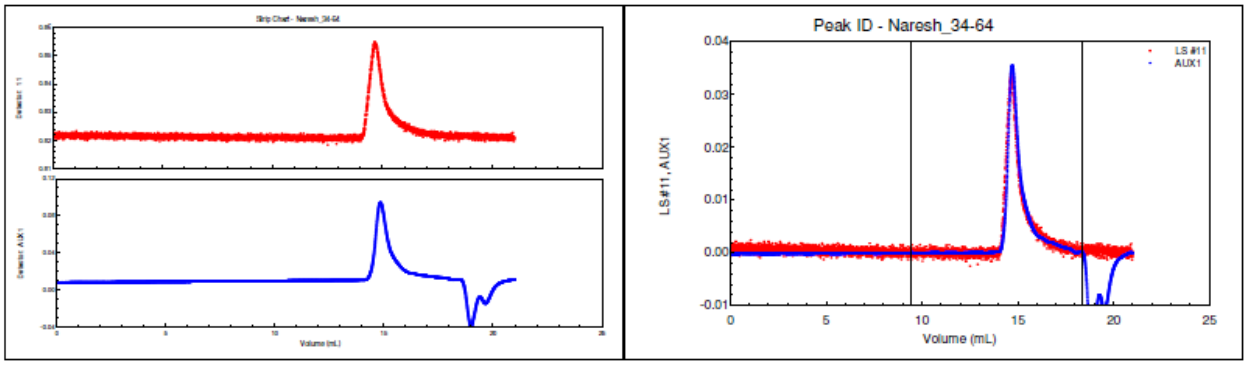


Figure 37. ^{13}C NMR spectrum of compound **13** ($CDCl_3$, 75 MHz).



Volume (mL)	:	9.438 - 18.325
Slices (used)	:	2134 (1015)
A2 (mol mL/g²)	:	0.000e+00
Fit degree	:	1
Injected Mass (g)	:	3.0600e-04
Calc. Mass (g)	:	3.0947e-04
dn/dc (mL/g)	:	0.063
Polydispersity(Mw/Mn)	:	1.064±0.150 (14%)
Polydispersity(Mz/Mn)	:	1.332±0.586 (44%)

Figure 38. GPC traces for compound **13**.

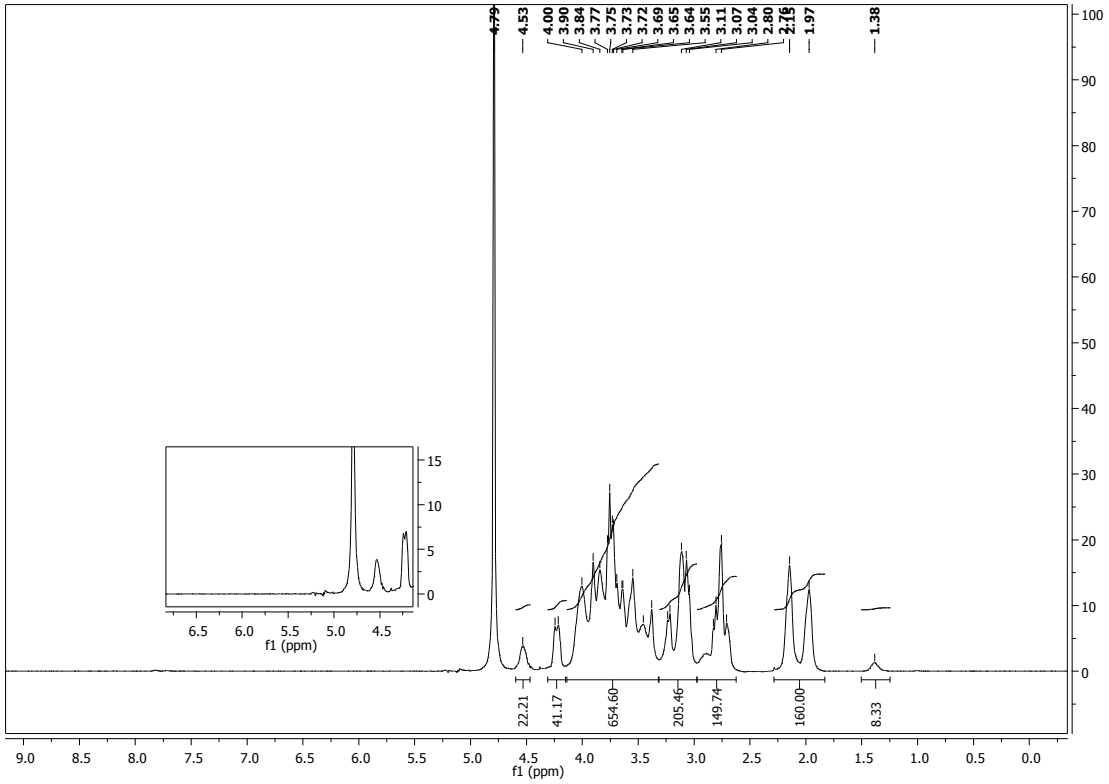


Figure 39. ^{1}H NMR spectrum of compound **15** (D_2O, 600 MHz).

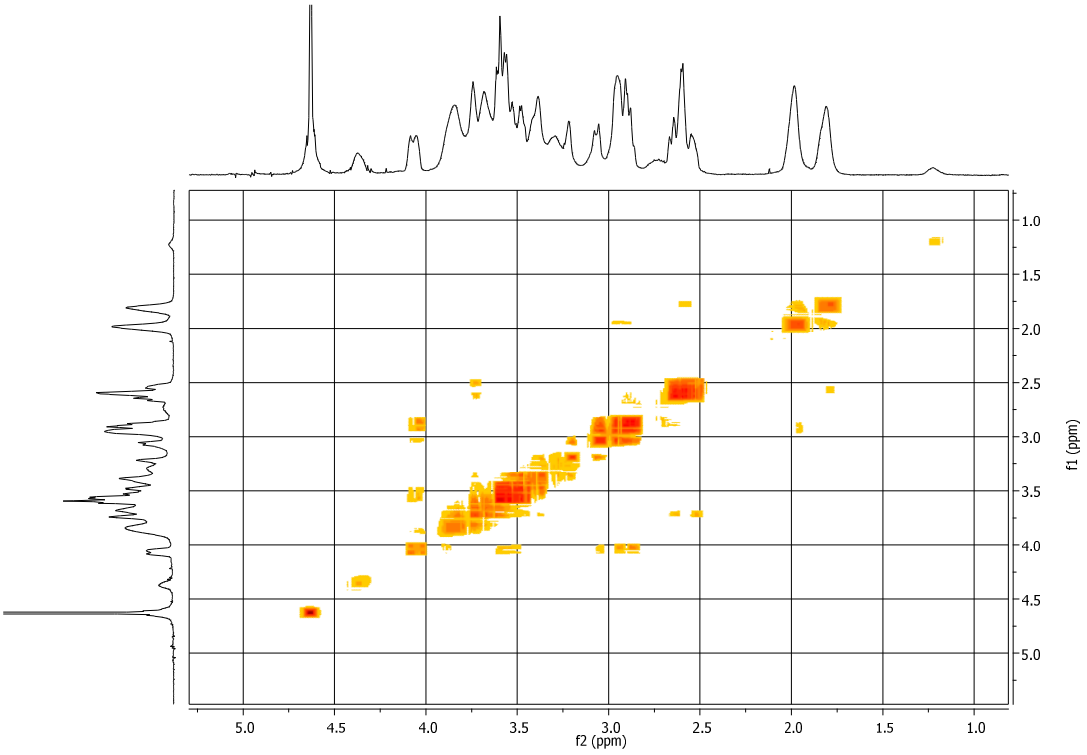


Figure 40. gCOSY trace of compound **15** (D_2O, 600 MHz).

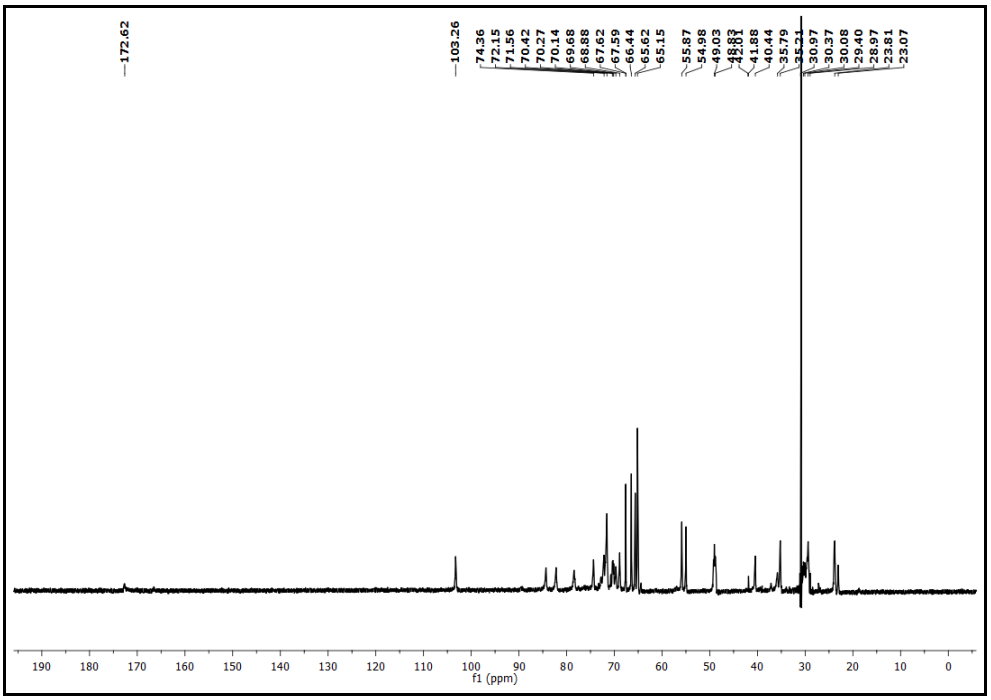


Figure 41. ^{13}C NMR spectrum of compound **15** (D_2O, 151 MHz, acetone as reference).

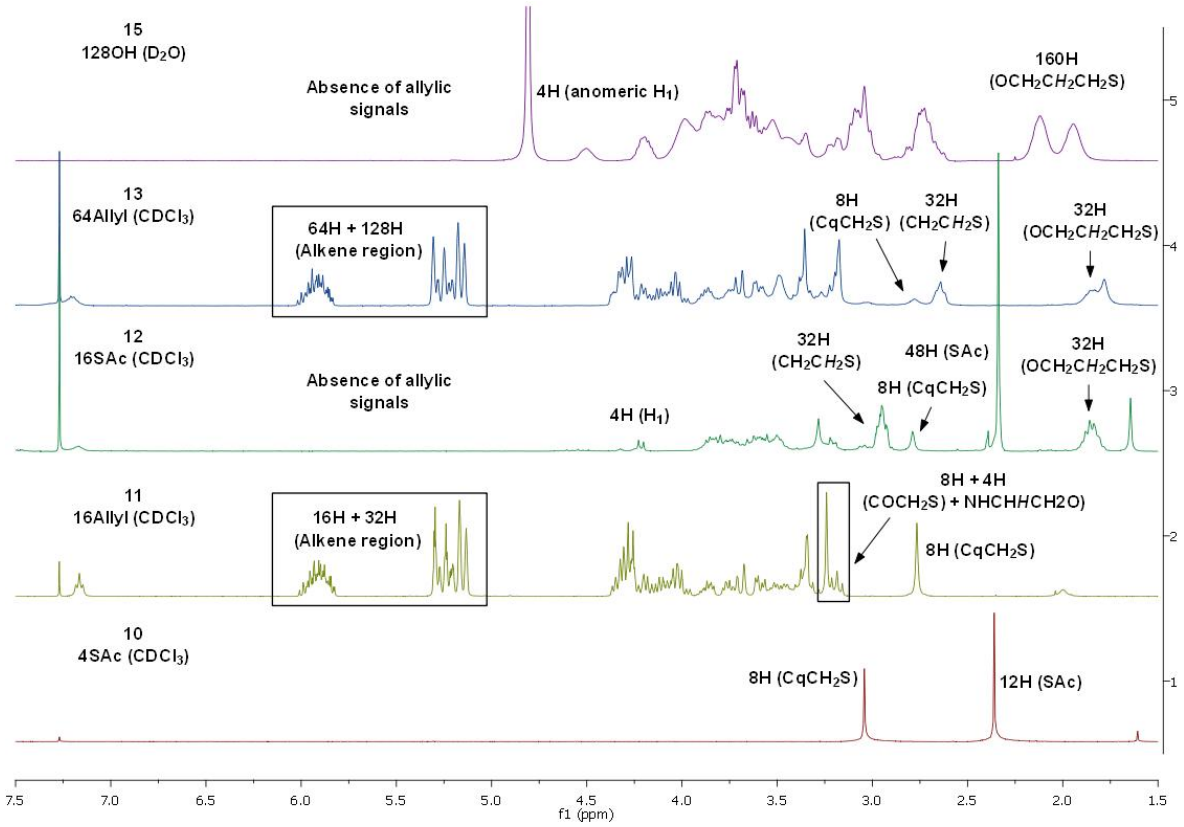


Figure 42. Sequence of ^{1}H NMR spectra for the synthesis of **15** from **10** showing the appearance and disappearance of main signals (chains and functional groups) with corresponding integrations.

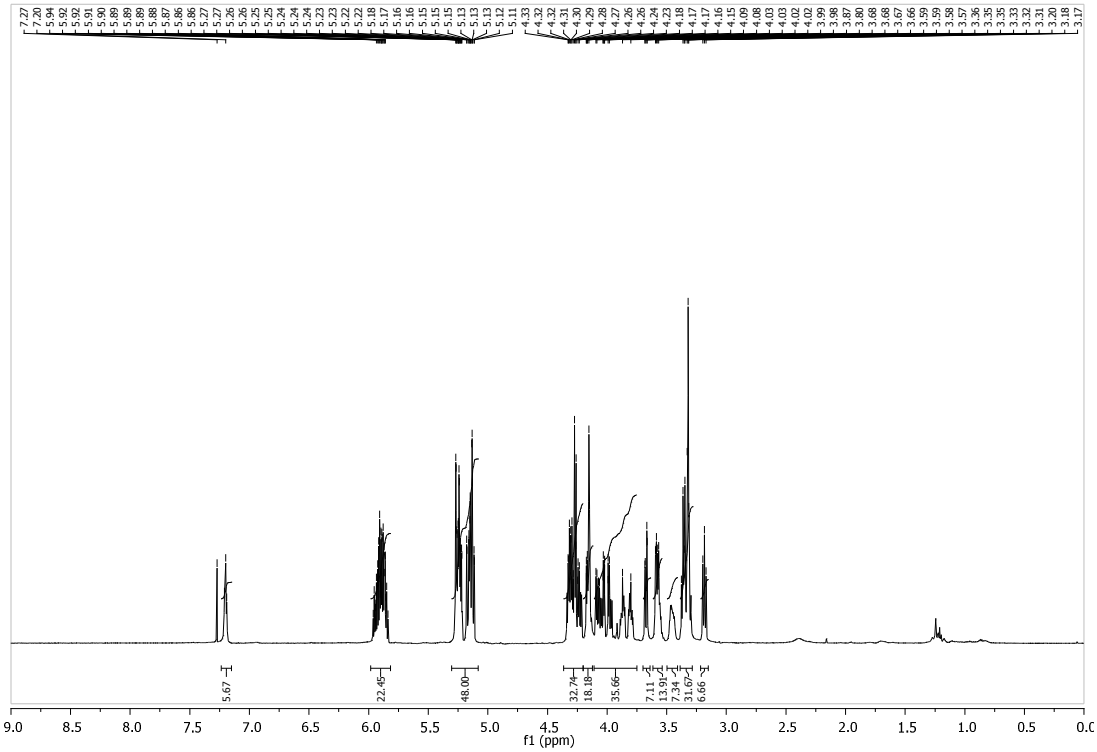


Figure 43. ^{1}H NMR spectrum of compound **17** ($CDCl_3$, 600 MHz).

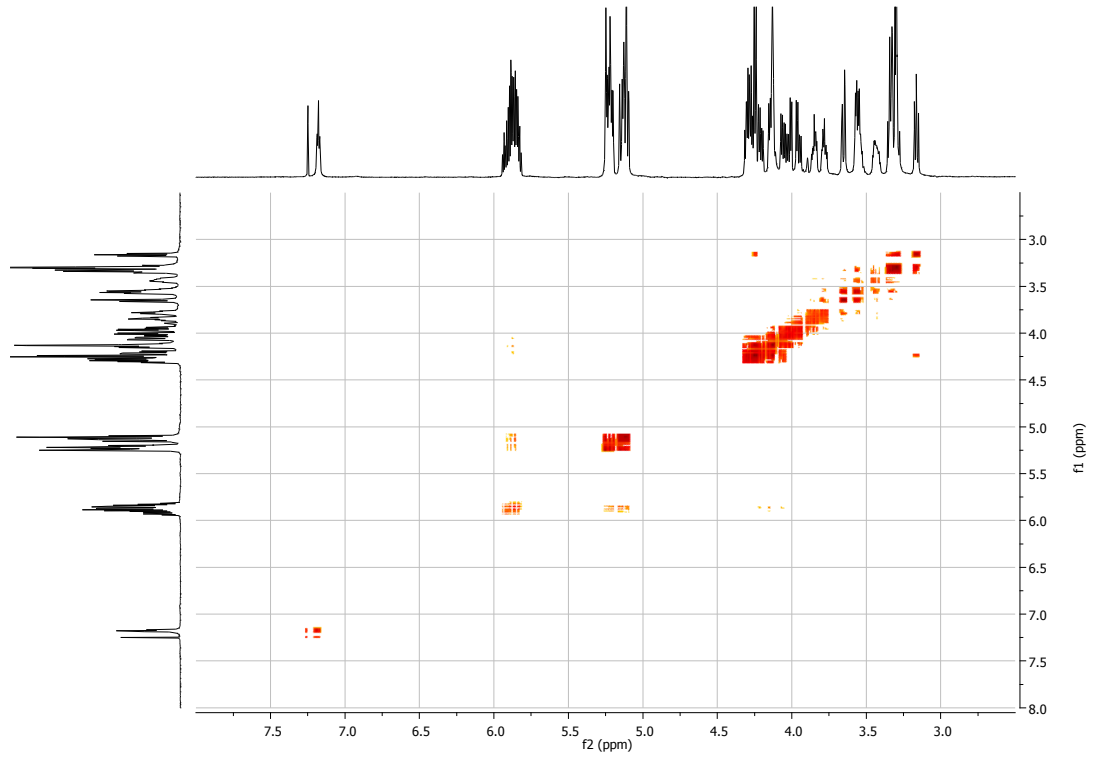


Figure 44. gCOSY spectrum of compound **17** ($CDCl_3$).

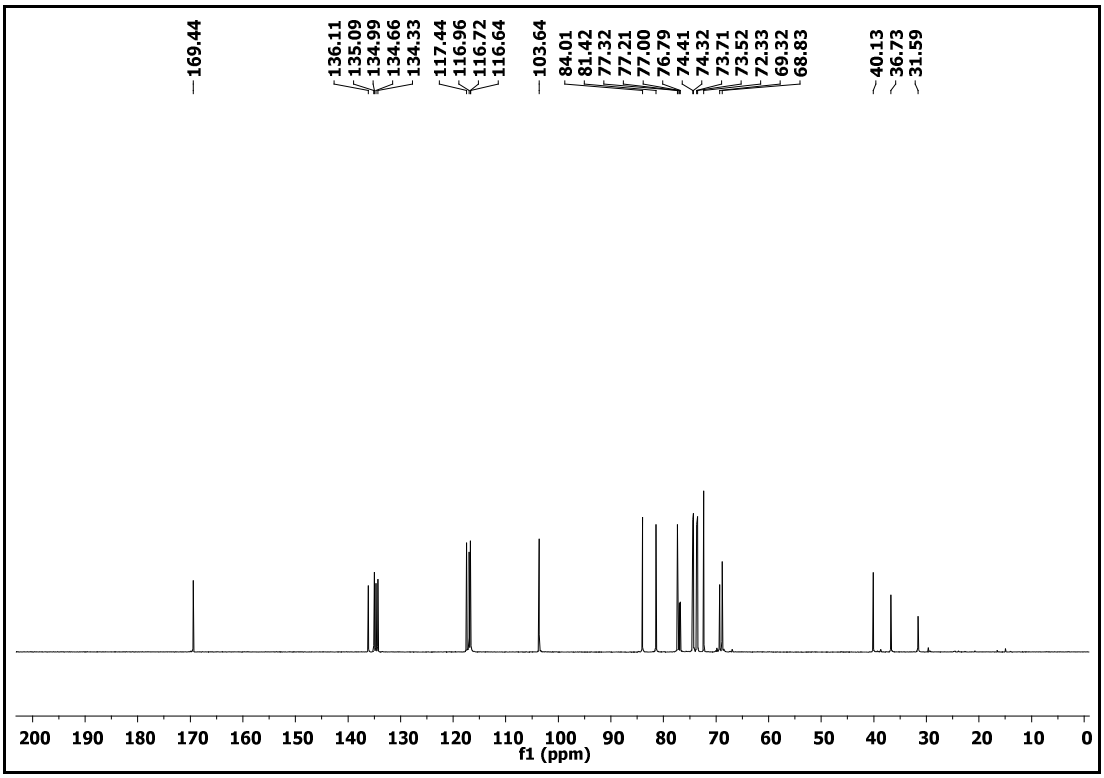


Figure 45. ^{13}C NMR spectrum of compound **17** ($CDCl_3$, 151 MHz).

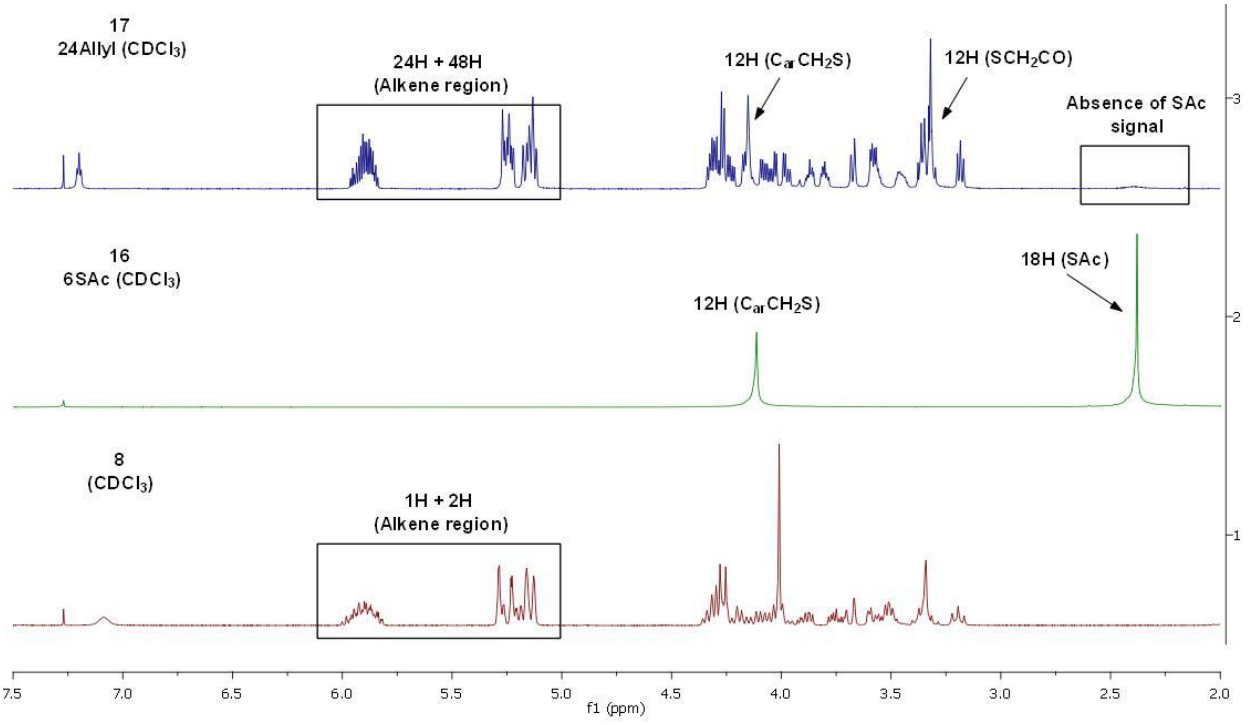
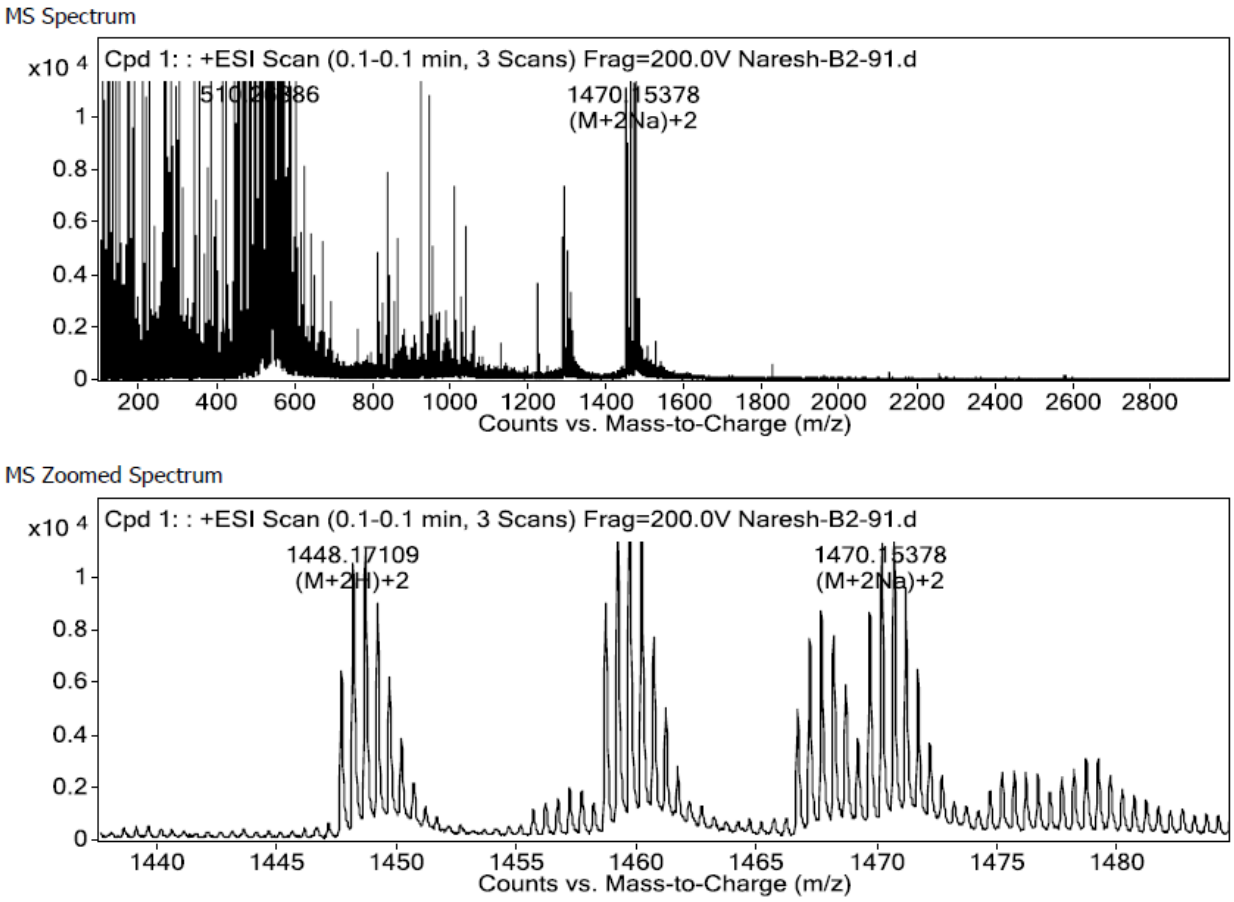


Figure 46. Comparison of ^{1}H NMR spectra for the synthesis of **17** from **8** and **10** showing the appearance and disappearance of main signals with corresponding integrations.



MS Spectrum Peak List

Ion	Formula	Abund	Observed m/z	Calc m/z	Diff(ppm)
(M+2H)+2	[12C]144H218N6[16O]42[32S]6	6479.9	1447.6696	1447.67102	-1.42
(M+2Na)+2	[12C]144H216N6Na2[16O]42[32S]6	8810.7	1469.65123	1469.65297	-1.73

Figure 47. HRMS (ESI^+) spectra of compound **17**.

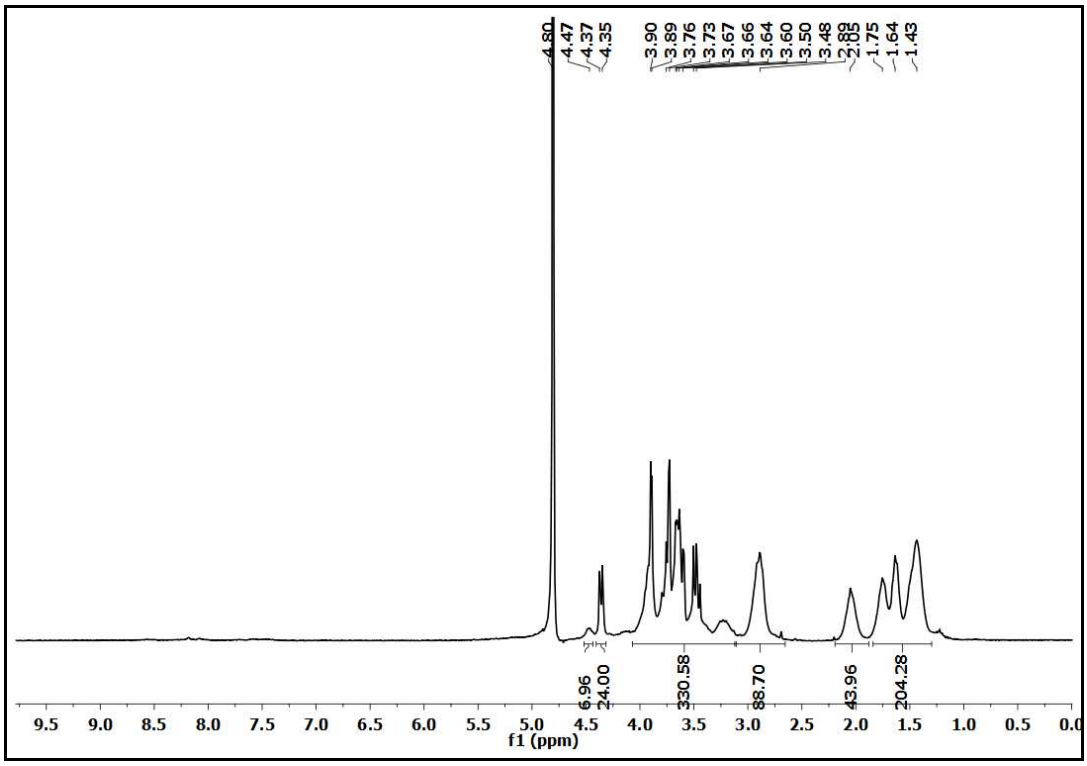


Figure 48. ^{1}H NMR spectrum of compound **19** (D_2O, 300 MHz).

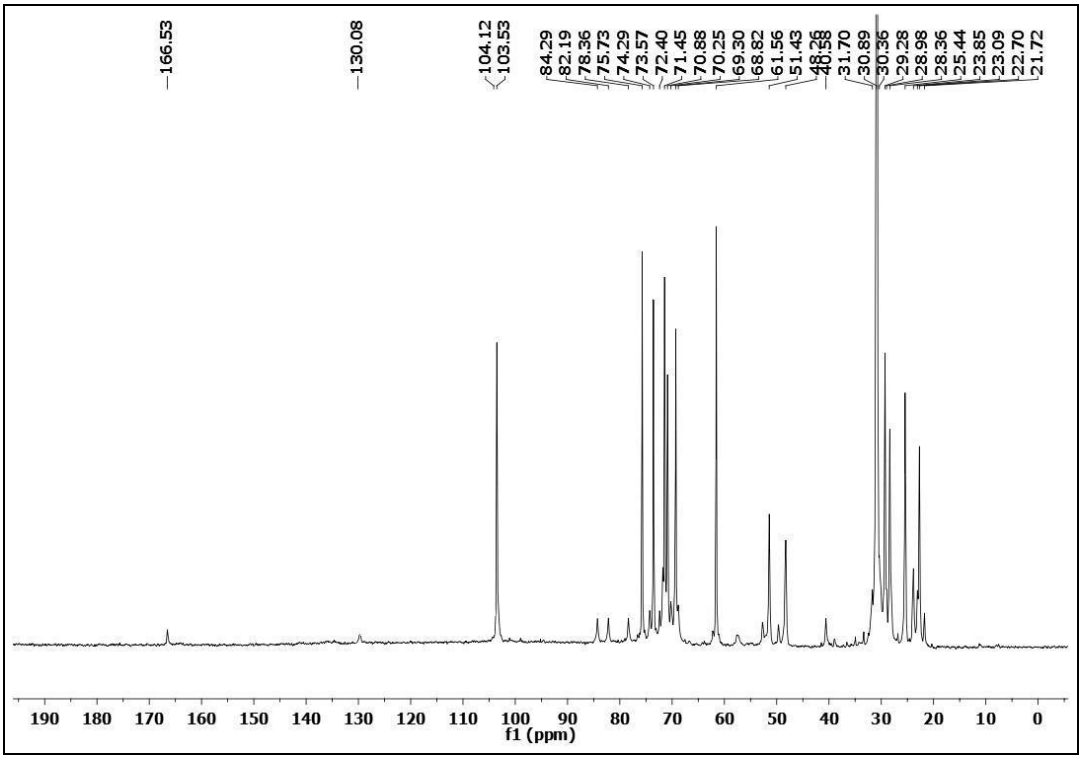


Figure 49. ^{13}C NMR spectrum of compound **19** (D_2O, 151 MHz).