Accelerated Synthesis of Large Generation Triazine Dendrimers Using Microwave Assisted Reactions: A 24 Hours Challenge

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Contributions

A.E.E. guided the synthetic efforts, overseeing the contributions of F.R-C. (a visiting scholar from the group of R.R.) and undergraduate M.J.Z. E.E.S. contributed to the oversight and communication of the project.

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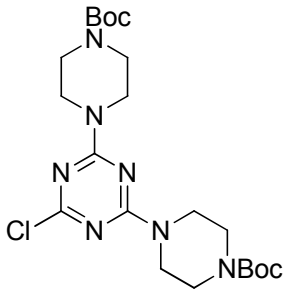
General Experimental

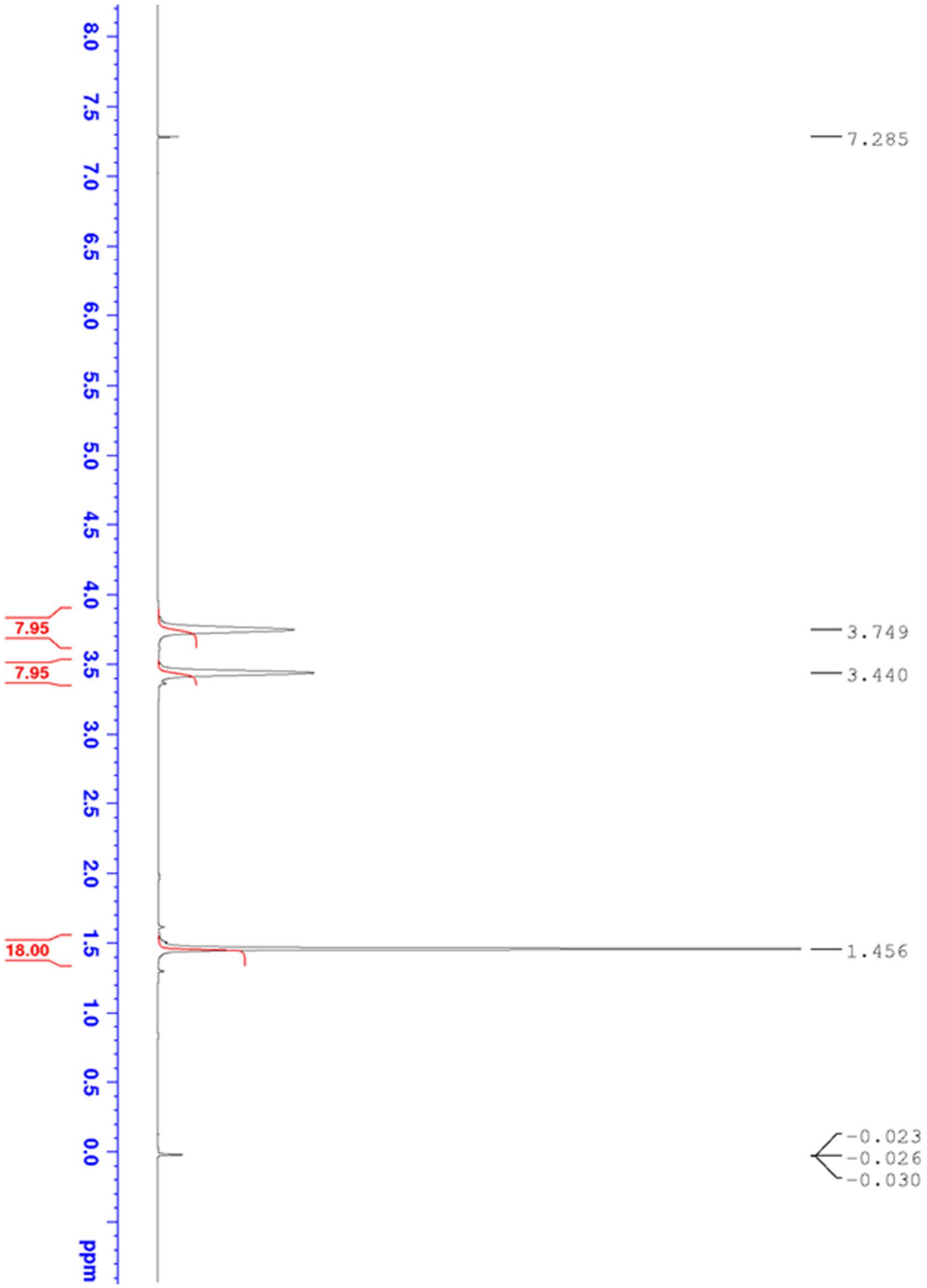
Microwave. A CEM SP Discovery microwave was utilized for these experiments. Reactions were performed in dynamic mode wherein microwave power (250 watts) is modulated to maintain the set-point temperature—here either 60 ^{o}C or 95 ^{o}C.

Automated chromatography. A CombiFlash RF automatic chromatographer (Teledyne ISCO) was used up to Generation 3 dendrimer. The separations were performed using a solid loading method in a 25 g preloaded cartridge.

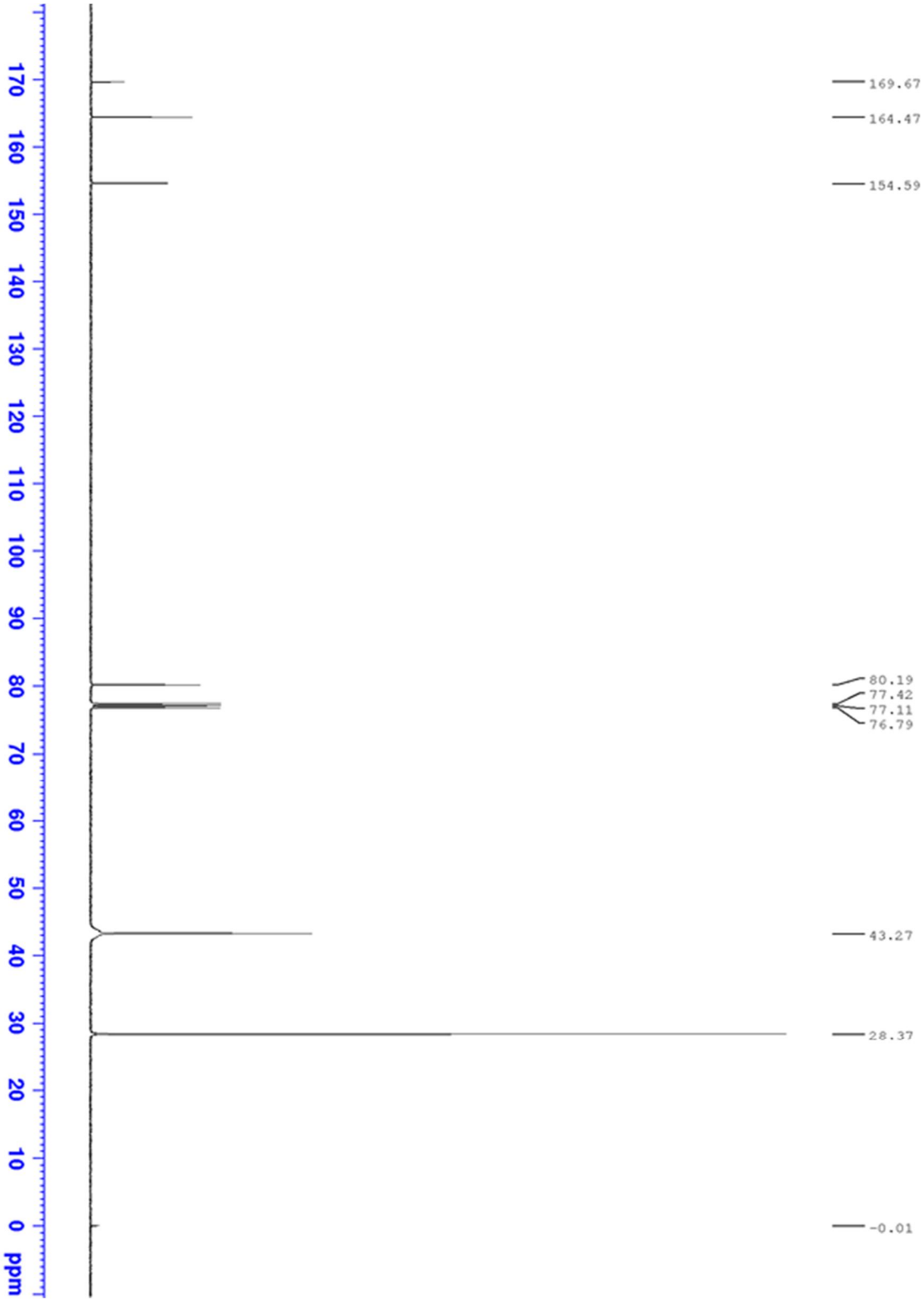
Compound 1. 1-Boc-piperazine (11.14 g, 60 mmol) was added to a solution of cyanuric chloride (5.02 g, 27 mmol) in THF (200mL). Afterwards DIPEA (19 mL, 0.109 mol) was added dropwise. The solution was stirred for 2 minutes in order to allow reagents to mix. Then, the solution was separated in multiple vessels and irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The crude product was purified by precipitations hexanes/EtOAc to give **1** (10.83 g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (br, 8H, NC**H₂**CH_2NBoc), 3.44 (br, 8H, NCH_2C**H₂**NBoc), 1.45 (s, 18H, C(C**H₃**)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 169.6, 164.4 (**C**$_3N_3$), 156.5 (**C**O), 80.1 (**C**$(CH_3)_3$), 43.2 (N**C**H_2**C**H_2N), 28.3 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{21}H_{34}ClN_7O_4$ 483.2361, found 484.3702 $(M + H)^+$.



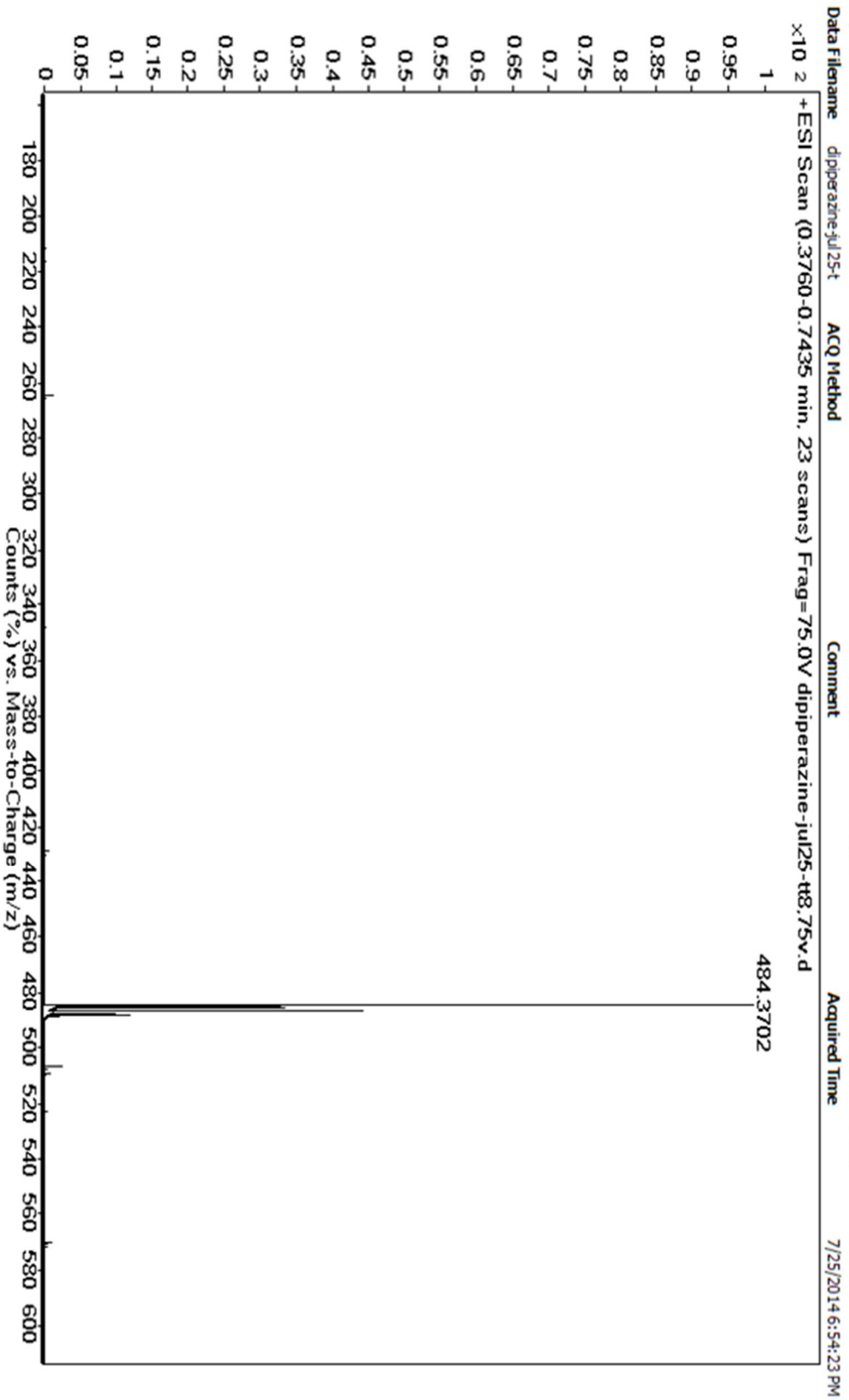
SI Figure 1. ^{1}HNMR



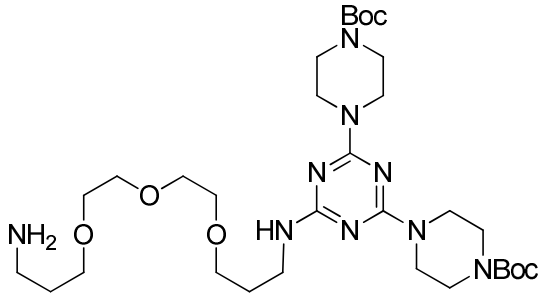
SI Figure 2. ^{13}CNMR



SI Figure 3. Mass Spectra



Compound 2. A solution of **1** (3g, 6 mmol) with 4,7,10-trioxa-1,13-tridecanediamine (13.65mL, 62 mmol) and Cs_2CO_3 (4g, 12 mmol) in 40 mL of 1,4 dioxane was stirred for 2 minutes. Then, the solution was separated in multiple vessels and irradiated in the microwave while stirring for 30 minutes at 95ºC and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The solvent system (in column volumes) used was the following: 5CV (100%DCM), 5CV (95:5= DCM: MeOH), 5CV (90:10= DCM: MeOH), 5CV (85:15= DCM: MeOH), 5CV (80:20= DCM: MeOH) to give **2** (3.26 g, 79%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 8H, NC**H**$_2$C**H**$_2$NBoc), 3.67-3.57 (m, 12H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 10H, NHC**H**$_2$CH$_2$CH$_2$O, NCH$_2$C**H**$_2$NBoc), 2.81 (t, 2H, OCH$_2$CH$_2$C**H**$_2$NH$_2$), 1.84 (m, 2H, OCH$_2$C**H**$_2$CH$_2$NH), 1.76 (m, 2H, OCH$_2$C**H**$_2$CH$_2$NH$_2$), 1.47 (s, 18H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.5 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O), 70.1 (O**C**H$_2$**C**H$_2$O), 69.5 (two lines, NHCH$_2$CH$_2$**C**H$_2$O, O**C**H$_2$CH$_2$CH$_2$NH$_2$), 43.8 (piperazine), 39.4 (NH**C**H$_2$CH$_2$CH$_2$O), 38.2 (OCH$_2$CH$_2$**C**H$_2$NH$_2$), 32.6 (OCH$_2$**C**H$_2$CH$_2$NH$_2$), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.6 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{31}H_{57}N_9O_7$ 667.4381, found 668.5915$(M + H)^+$.



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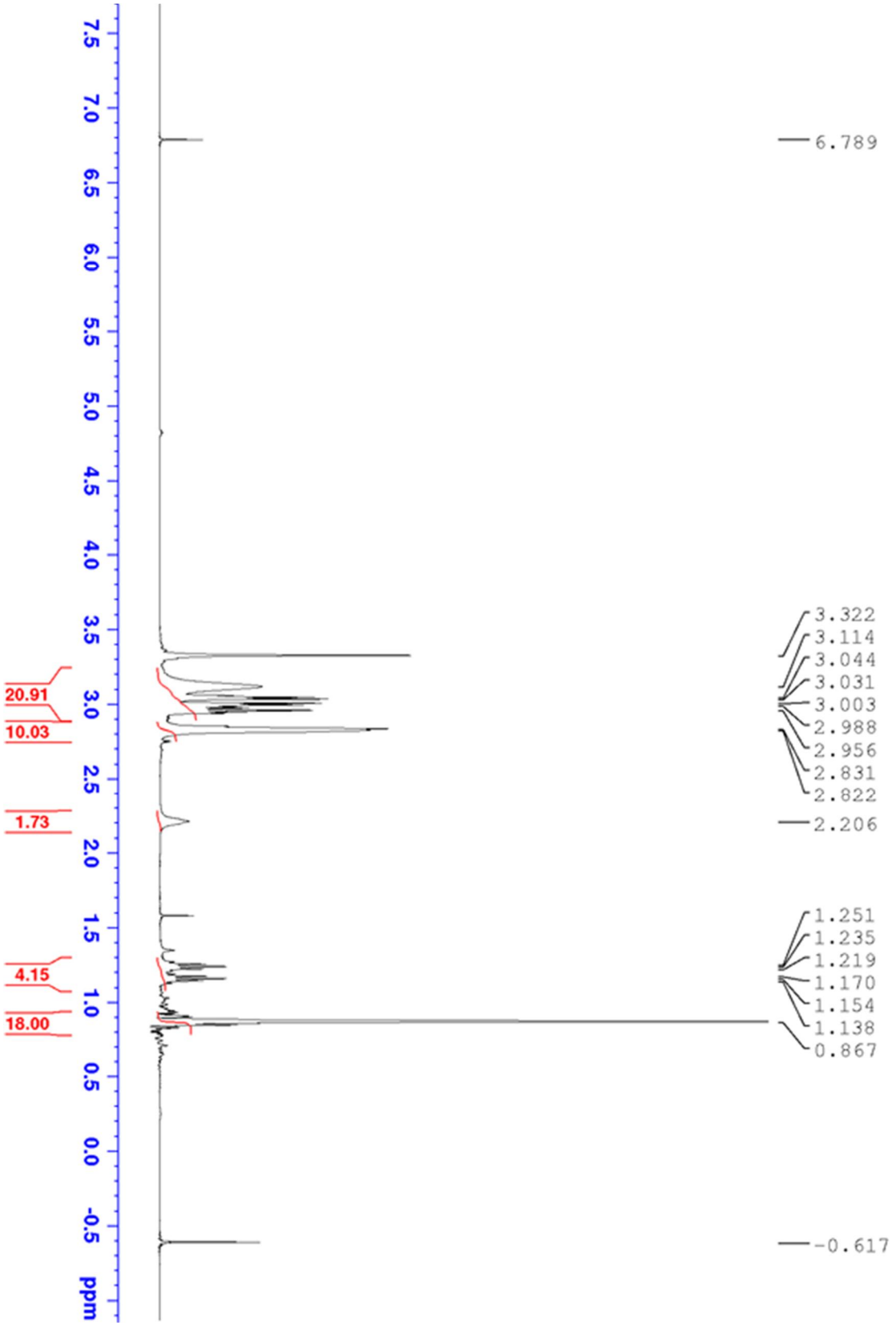
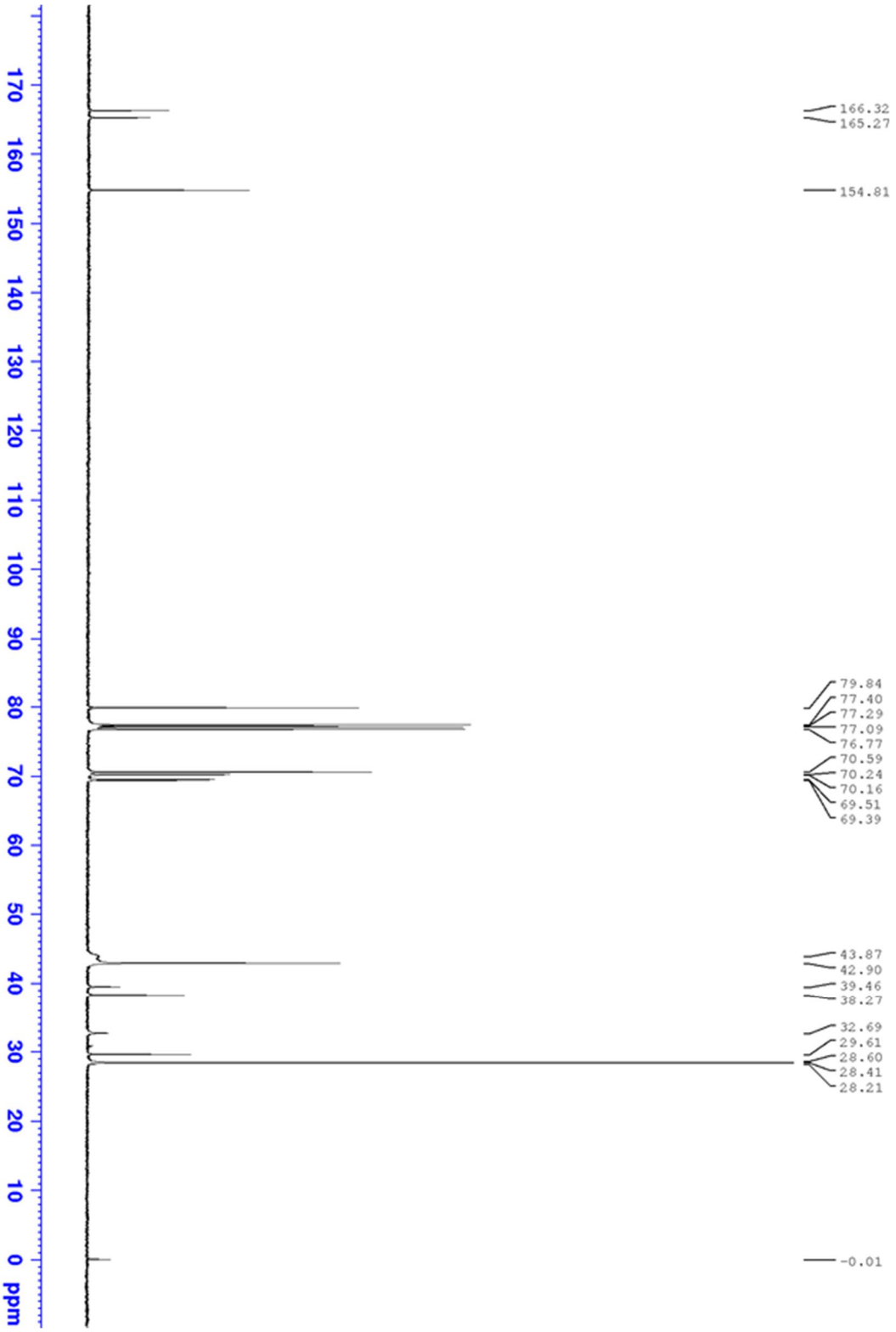
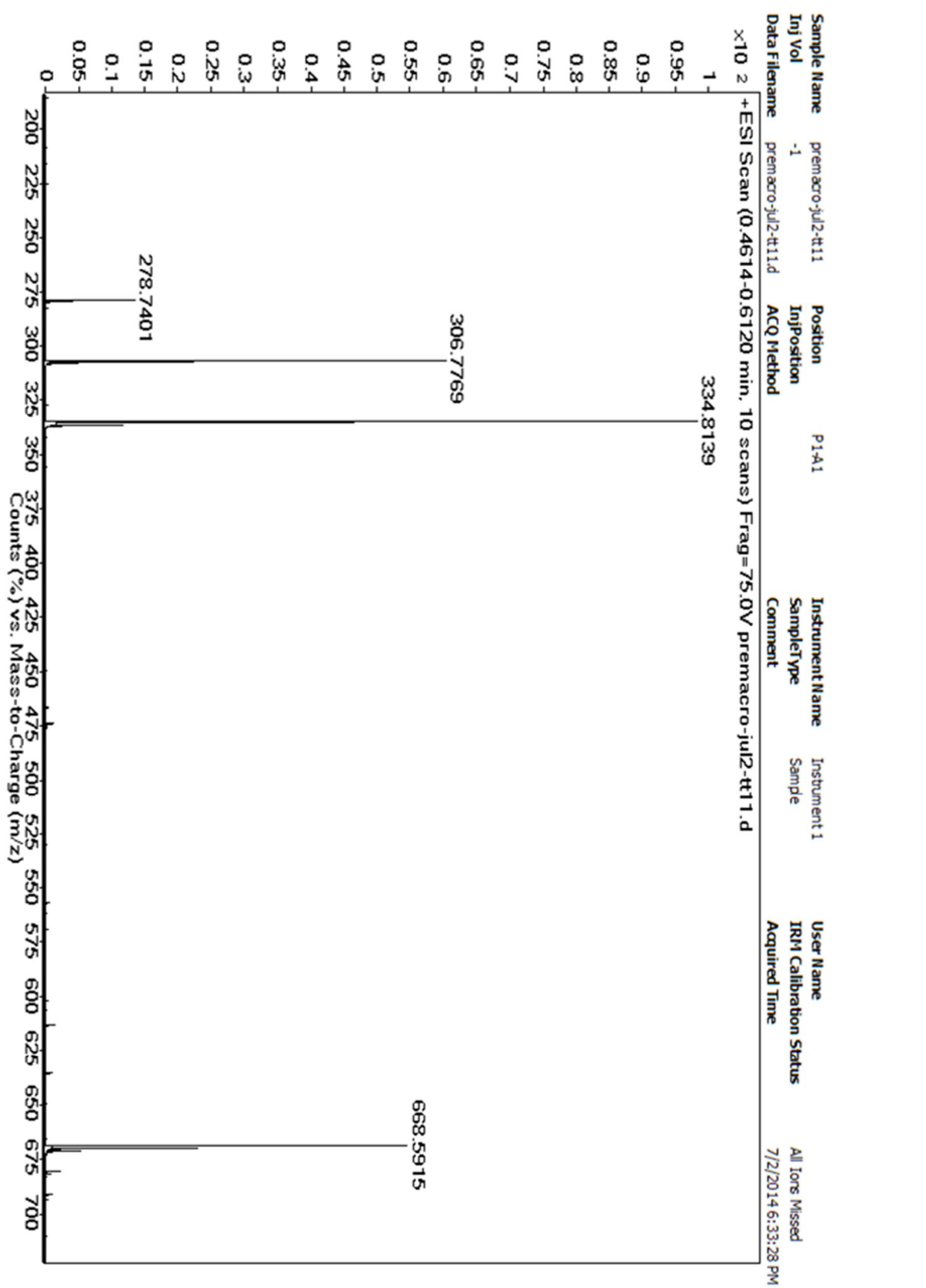


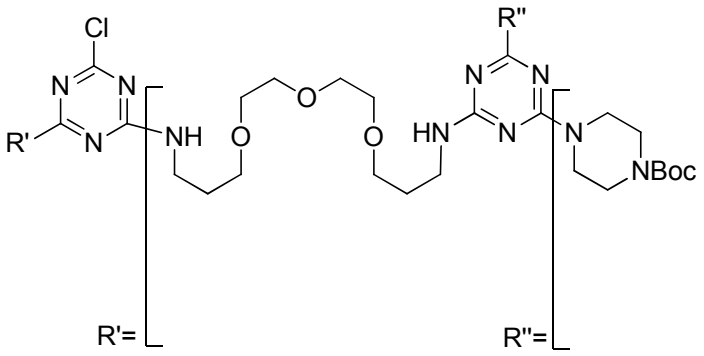
SI Figure 5. ^{13}CNMR



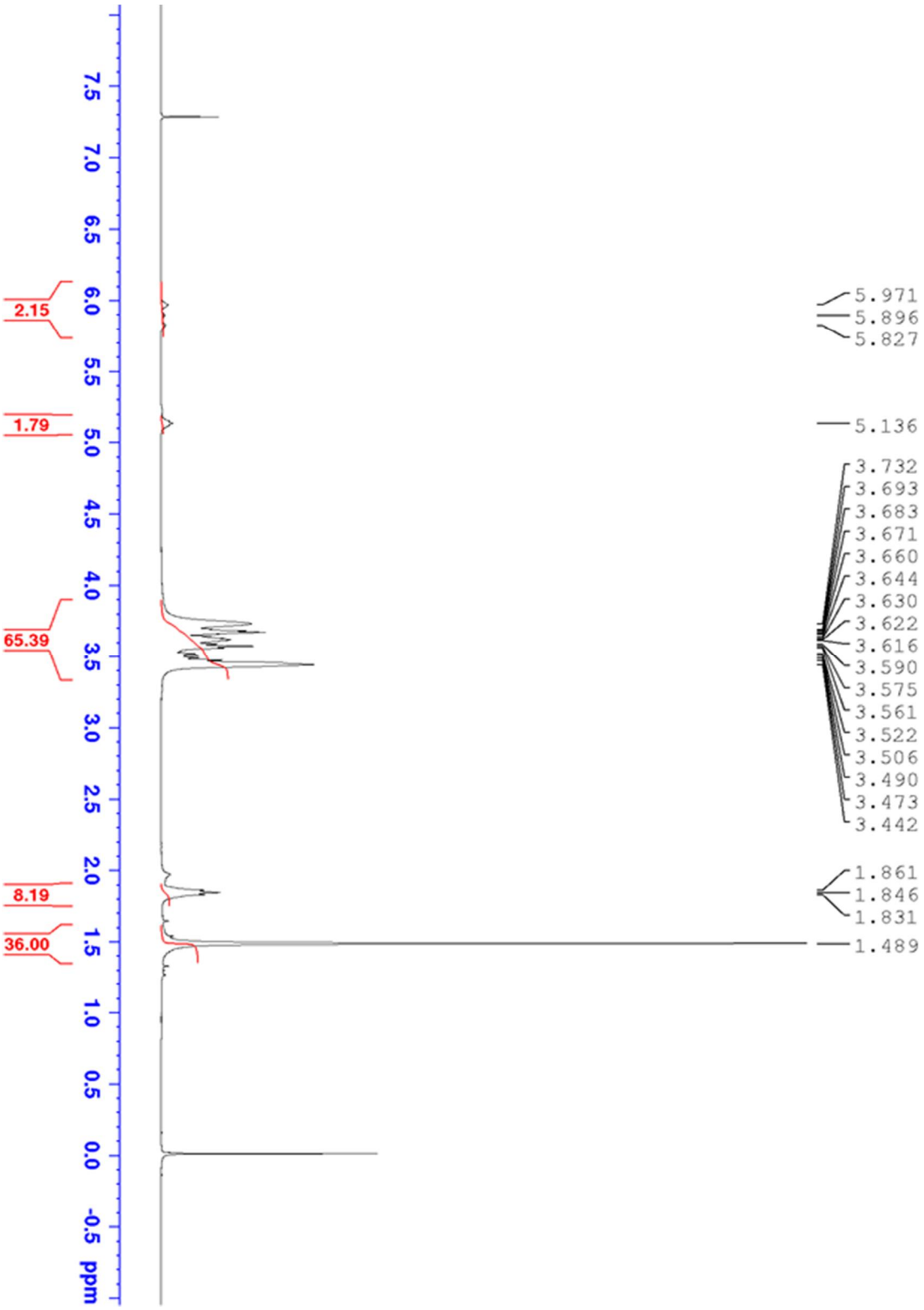
SI Figure 6. Mass Spectra



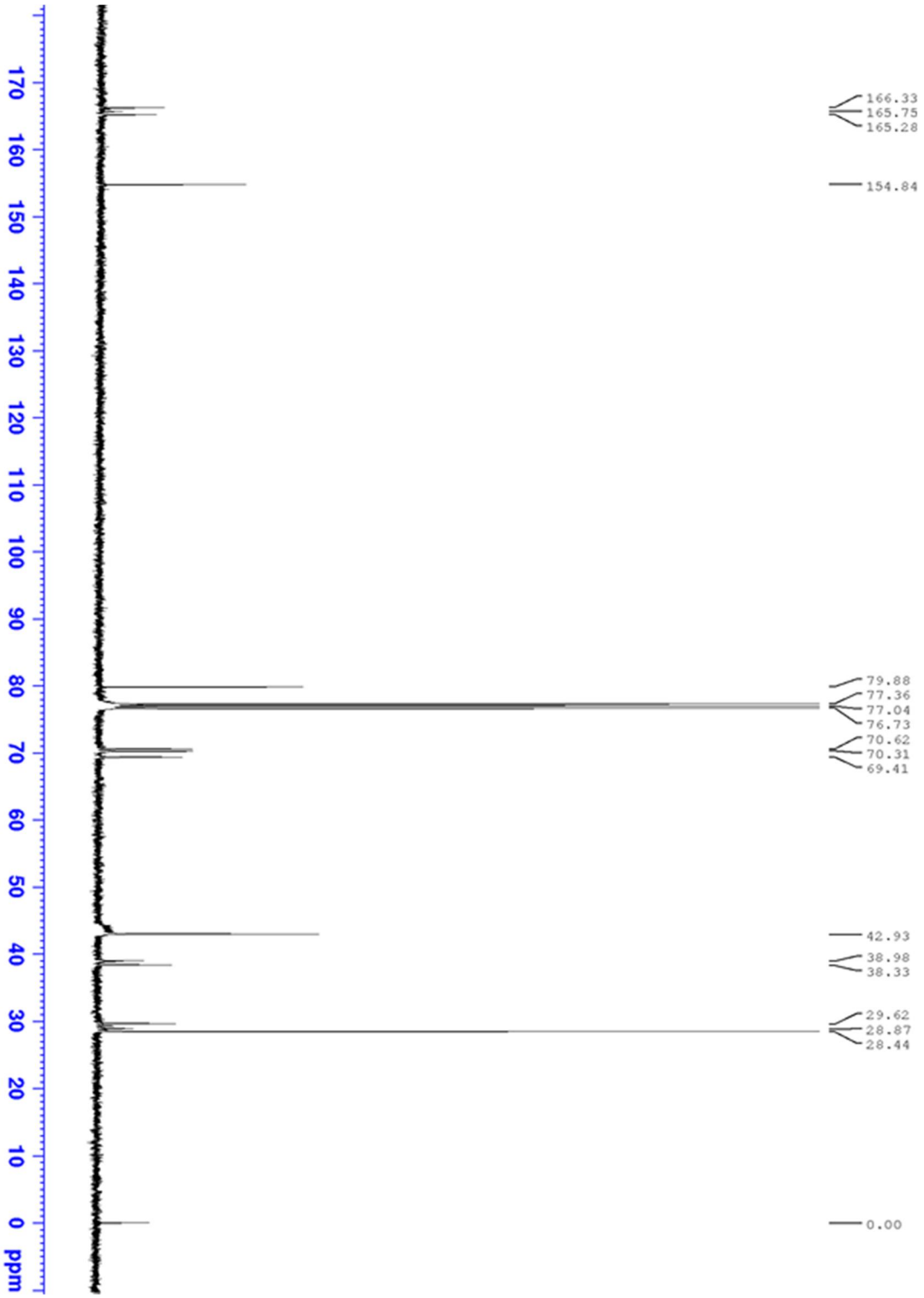
Compound 3 (macromonomer). Compound **2** (3.26 g, 4.8 mmol) was added to a solution of cyanuric chloride (0.411 g, 2.2 mmol) in THF (20mL). Afterwards DIPEA (3.2 mL, 18 mmol) was added dropwise, and the solution was sonicated for 2 minutes in order to allow reagents to mix. Then, the solution was irradiated in the microwave while stirring for 10 minutes at 60ºC using dynamic mode. The solvent system (in column volumes) used was the following: 5 CV (100% DCM), 5 CV (95:5= DCM: MeOH), 5CV (90:10= DCM: MeOH), 5CV (85:15= DCM: MeOH), 5 CV (80:20= DCM: MeOH) to give **3** (3.07g, 95%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 16H, NC**H**$_2$$CH_2$NBoc), 3.69-3.57 (m, 24H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 24H, C_3N_3-NHC**H**$_2$$CH_2CH_2O$, NCH_2C**H**$_2$NBoc), 1.86 (m, 8H, OCH_2C**H**$_2$$CH_2$NH), 1.48 (s, 36H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3 (**C**$_3N_3$), 165.7 (**C**$_3N_3$), 165.2 (**C**$_3N_3$), 154.8 (**C**O), 79.8 (**C**$(CH_3)_3$), 70.6 (O**C**H_2**C**H_2O), 70.3 (O**C**H_2**C**H_2O), 69.4 ($NHCH_2CH_2$**C**H_2O), 42.9 (piperazine), 38.9 (NH**C**$H_2CH_2CH_2O$), 38.3 (NH**C**$H_2CH_2CH_2O$), 29.6 ($NHCH_2$**C**H_2CH_2O), 28.8 ($NHCH_2$**C**H_2CH_2O), 28.4 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{65}H_{112}ClN_{21}O_{14}$ 1445.8386, found 1447.1735 $(M + H)^+$.



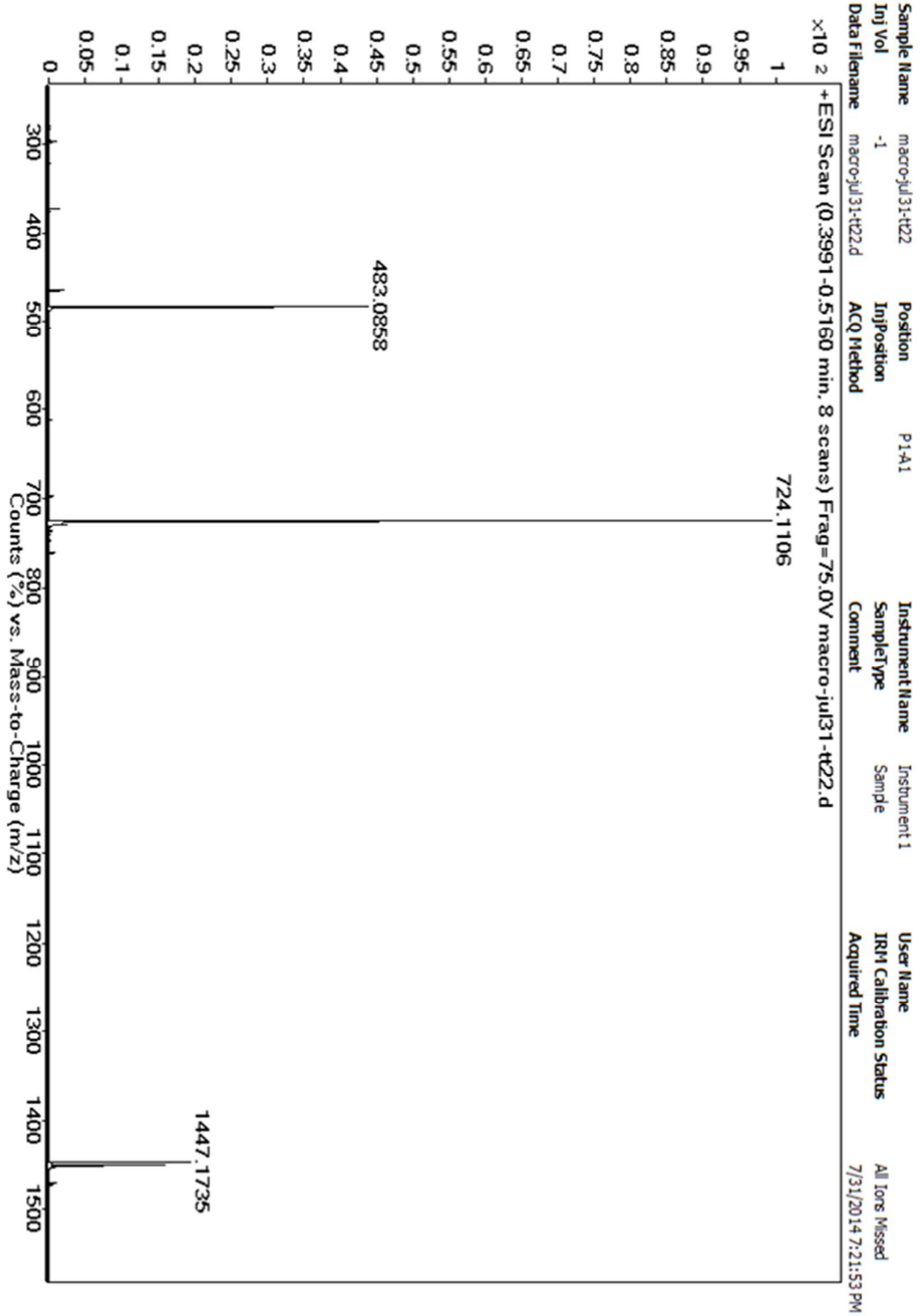
SI Figure 7. ^{1}HNMR



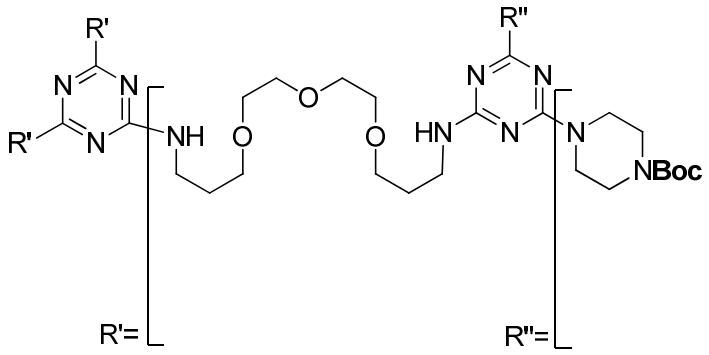
SI Figure 8. ^{13}CNMR



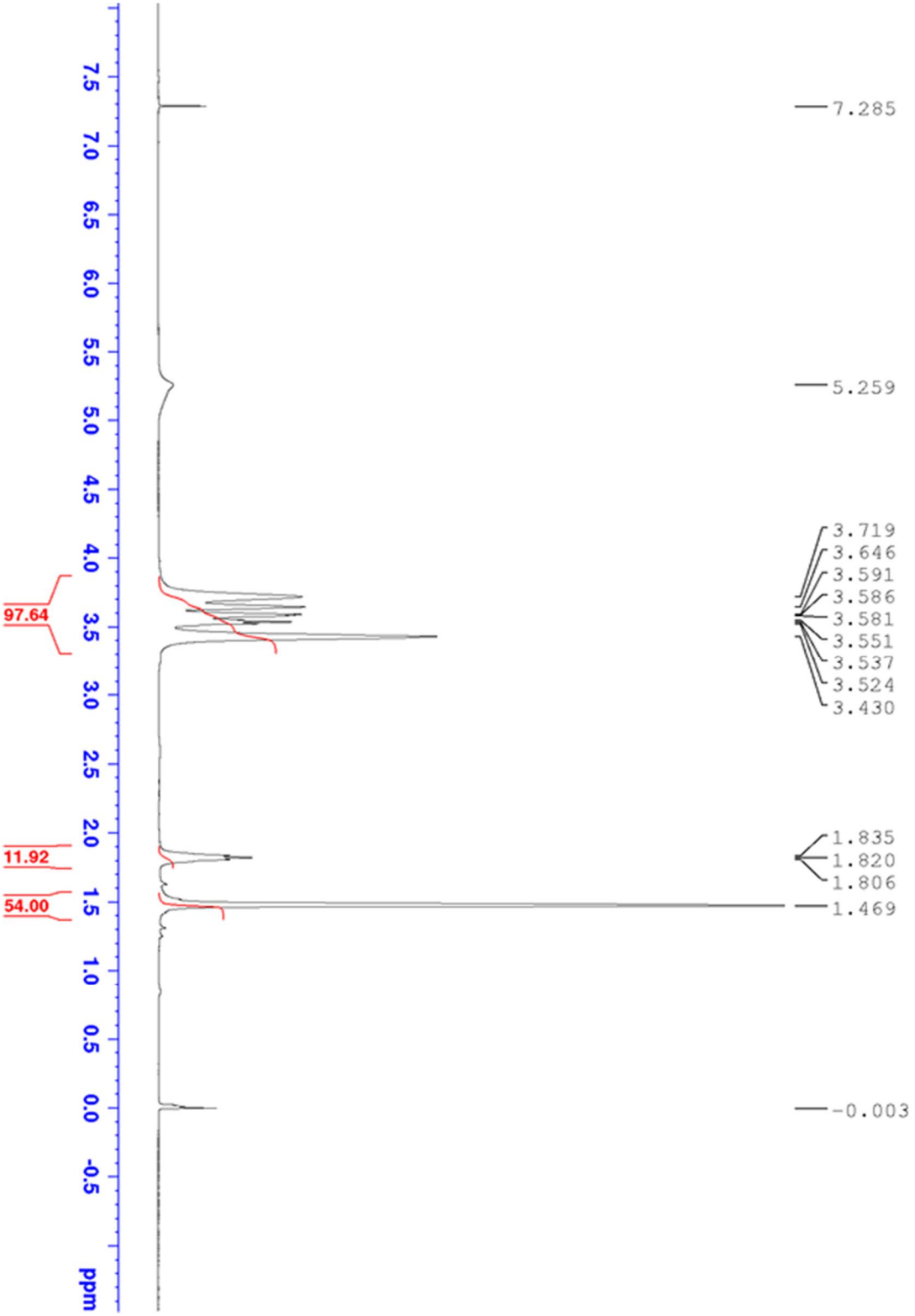
SI Figure 9. Mass Spectra



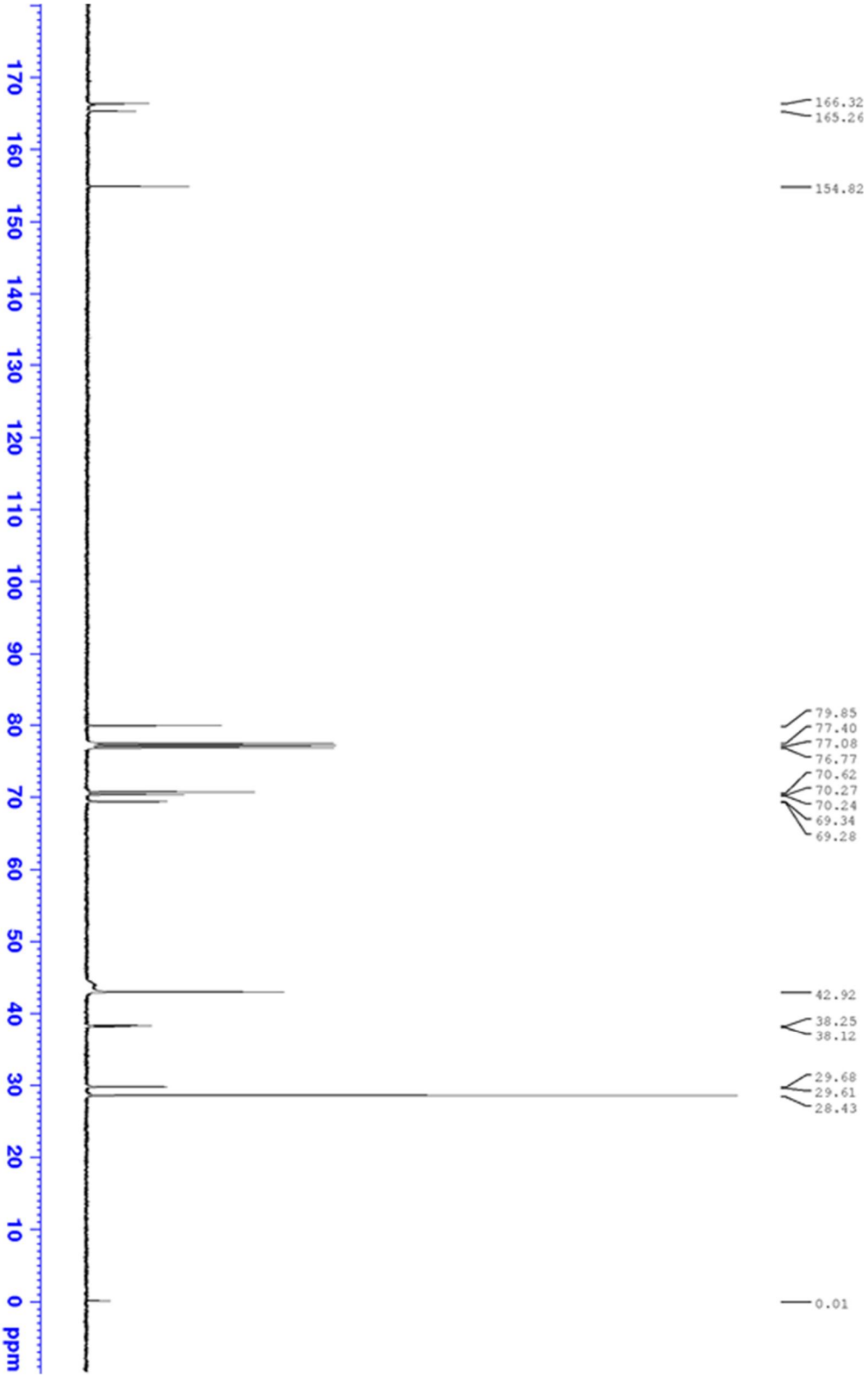
Compound 4 (G1-Boc) A solution of **3** (0.743g, 0.5 mmol) with **2** (1.042g, 2 mmol) and Cs_2CO_3 (1.066g, 3 mmol) in 5mL of 1,4 dioxane and 0.5mL MeOH was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 2 hours 30 minutes at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by automated chromatography. The solvent system (in column volumes) used was the following: 20CV (100% DCM), 5CV (90:10= DCM: MeOH) to give **4** (0.709g, 66%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 24H, NC**H**$_2$CH$_2$NBoc), 3.64-3.52 (m, 36H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$) 3.43 (br, 36H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.83 (m, 12H, OCH$_2$C**H**$_2$CH$_2$NH), 1.46 (s, 54H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.26 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.2 (two lines, NHCH$_2$CH$_2$**C**H$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{96}H_{168}N_{30}O_{21}$ 2077.3000, found 2079.6681 $(M + H)^+$.



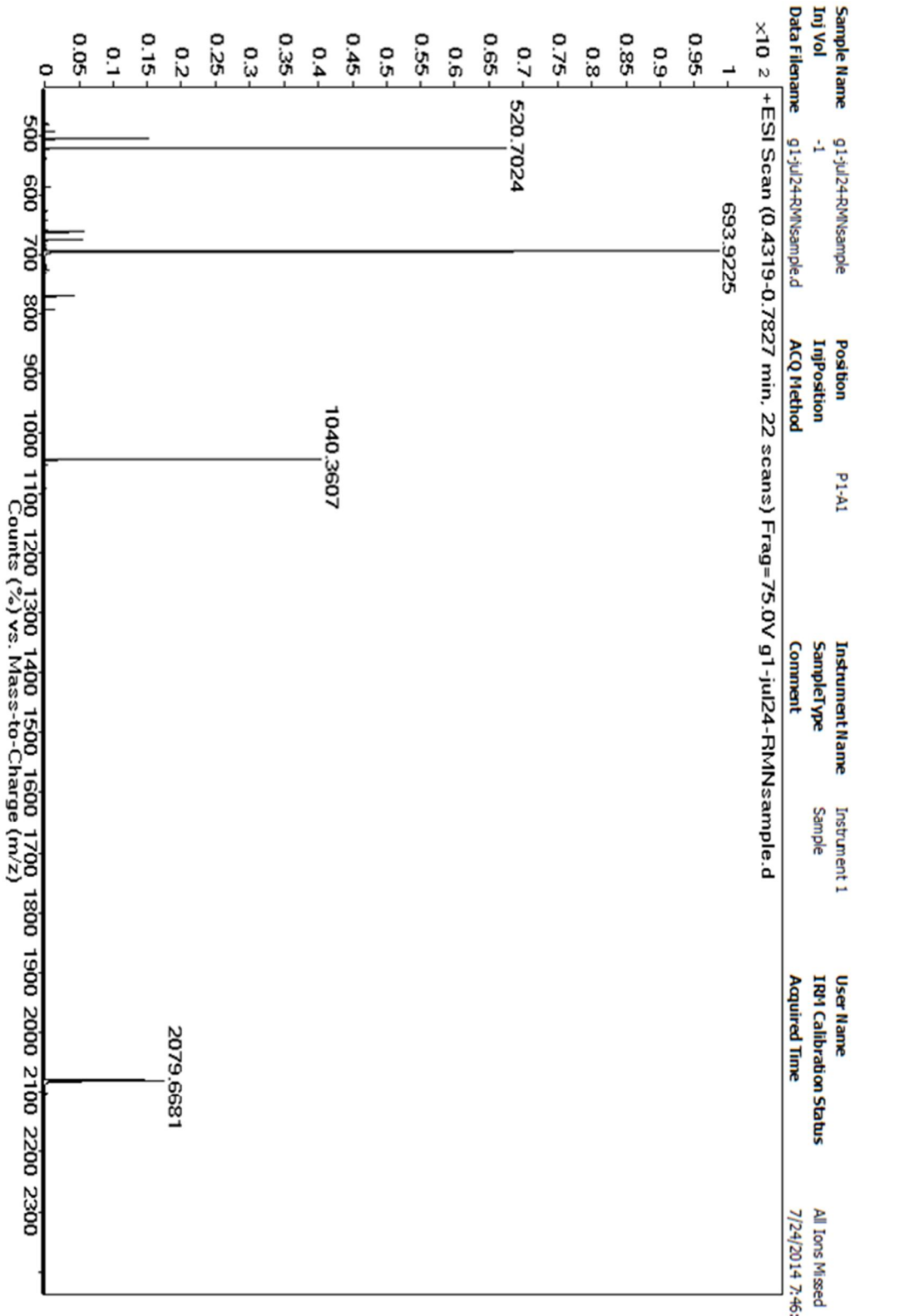
SI Figure 10. ^{1}HNMR



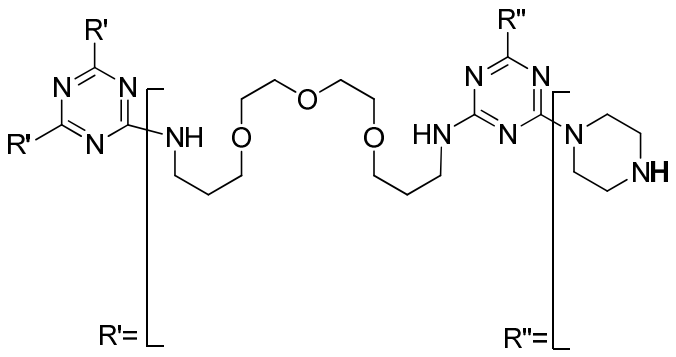
SI Figure 11. ^{13}CNMR



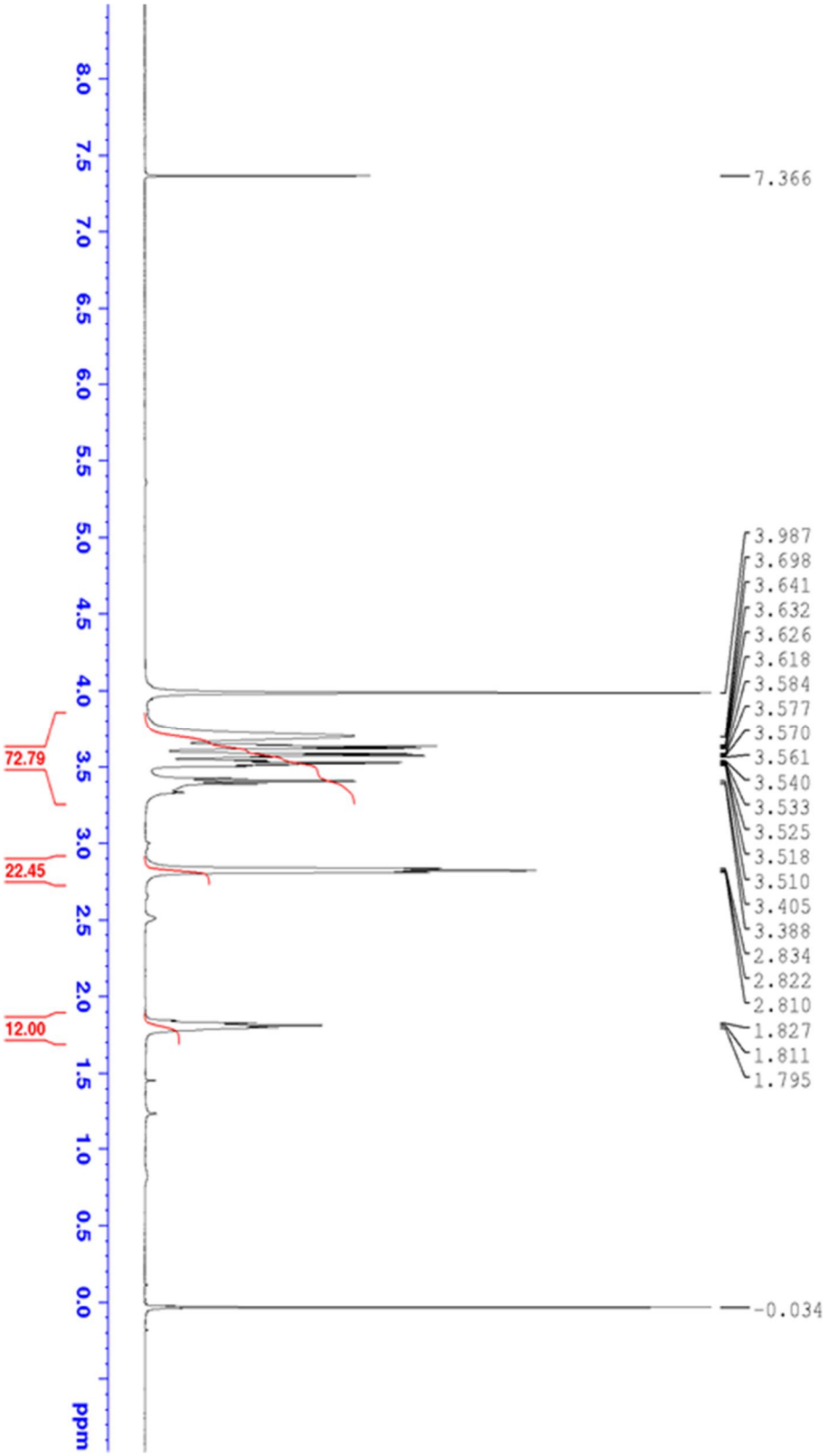
SI Figure 12. Mass Spectra



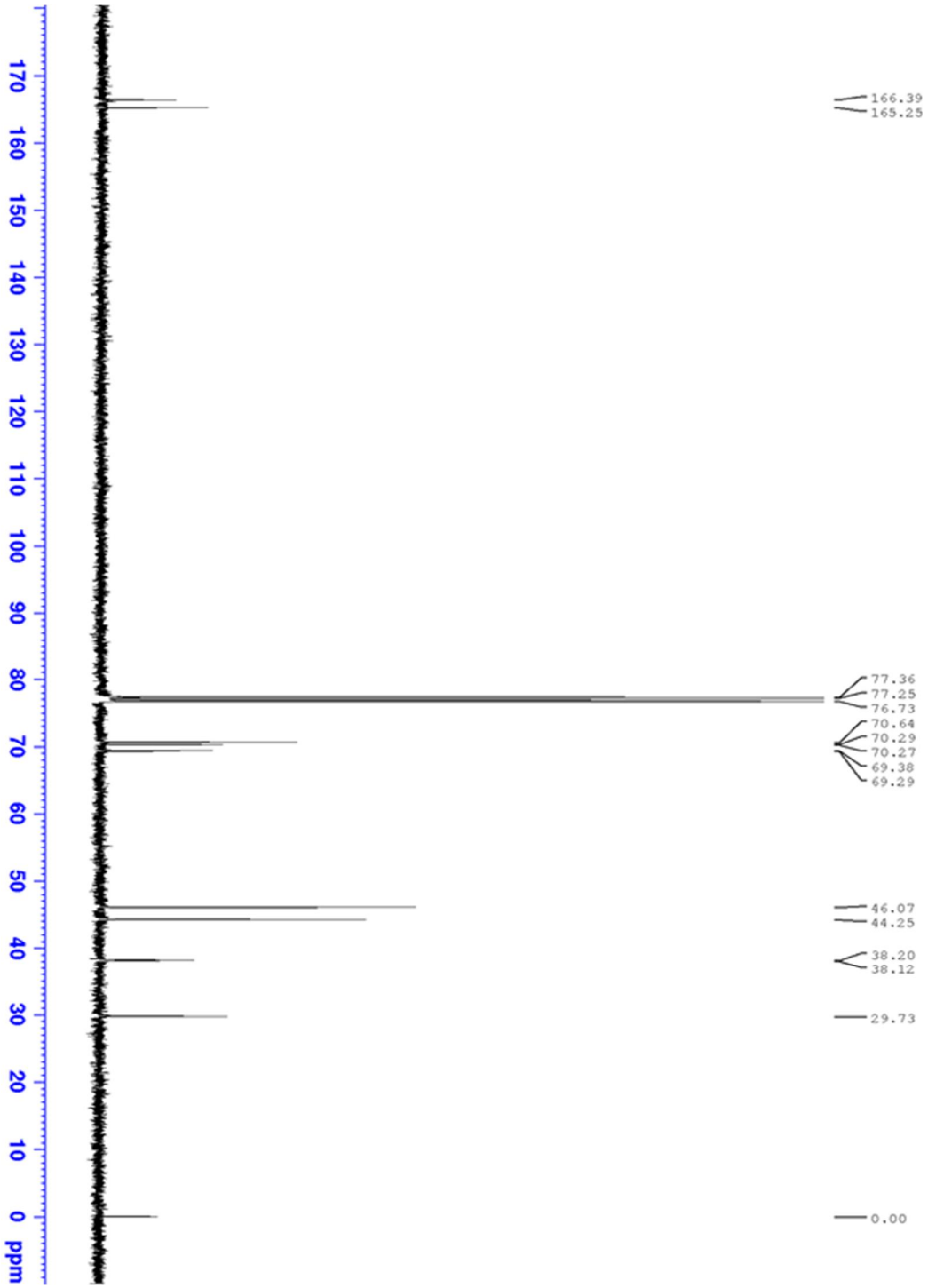
Compound 5 (G1 deprotected). A solution of **4** (0.800 g, 0.385 mmol) in concentrated HCl (3 mL) and 1,4 dioxane (6 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **5** (0.571 g, quantitative) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.69 (br, 24H, NC**H**$_2$$CH_2NH$), 3.64-3.51 (m, 36H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$) 3.40 (br, 12H, C_3N_3-NHC**H**$_2$$CH_2CH_2O$), 2.83 (br, 24H, HNC**H**$_2$$CH_2N$), 1.82 (m, 12H, OCH_2C**H**$_2$$CH_2NH$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$$N_3$), 70.6 (O**C**$H_2$**C**$H_2O$), 70.2 (two lines, O**C**H_2**C**H_2O), 69.3 ($NHCH_2CH_2$**C**H_2O), 69.2 ($NHCH_2CH_2$**C**H_2O), 46.0 (NCH_2**C**H_2NH), 44.2 (N**C**H_2CH_2NH), 38.2 (NH**C**$H_2CH_2CH_2O$), 38.1 (NH**C**$H_2CH_2CH_2O$), 29.6 ($NHCH_2$**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{66}H_{120}N_{30}O_9$ 1476.9855, found 1478.2639 $(M + H)^+$.



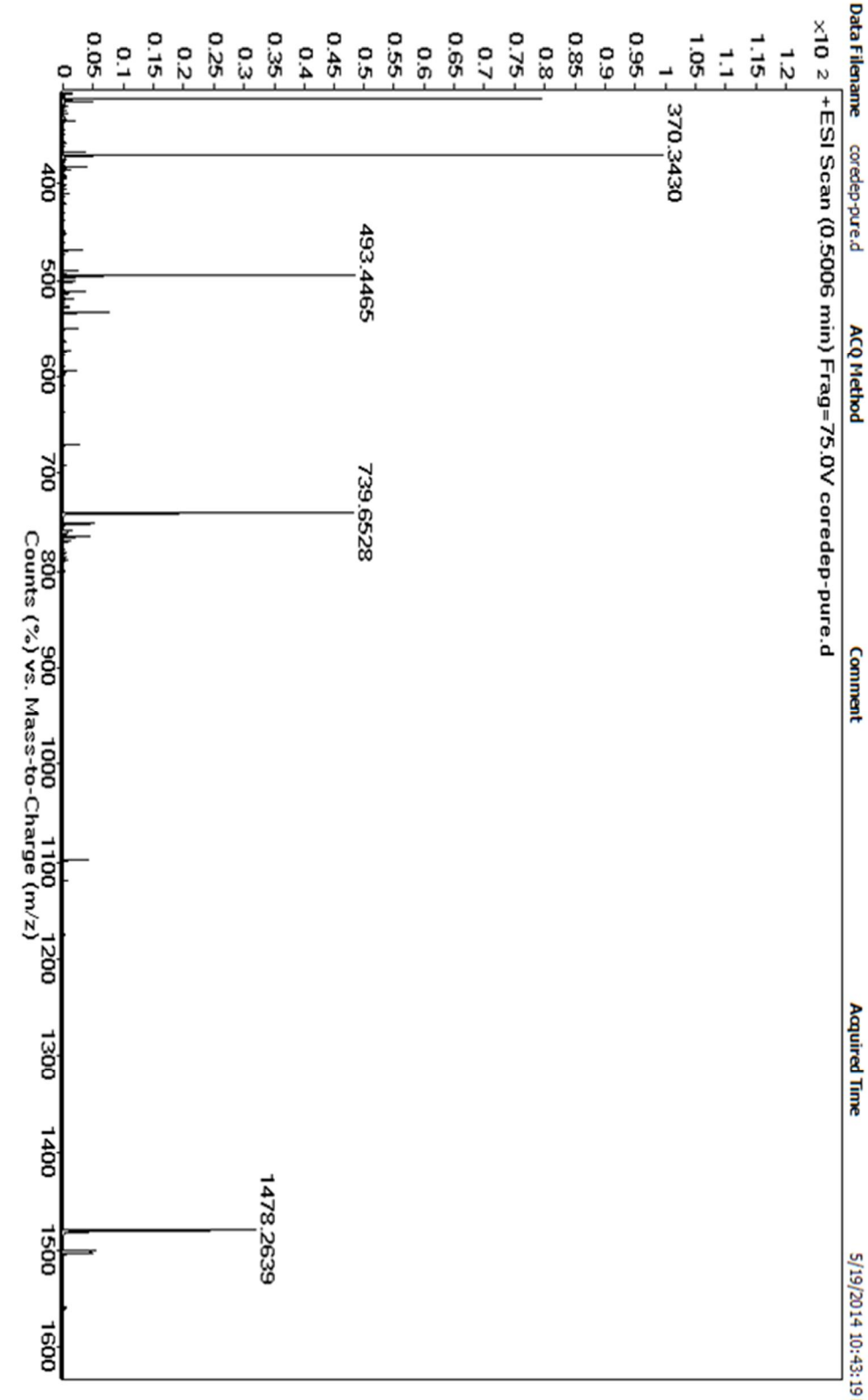
SI Figure 13. ^{1}HNMR



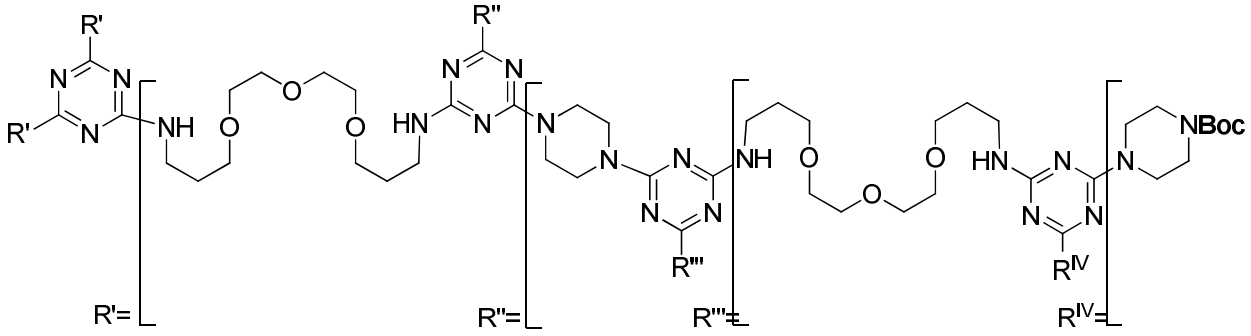
SI Figure 14. ^{13}CNMR



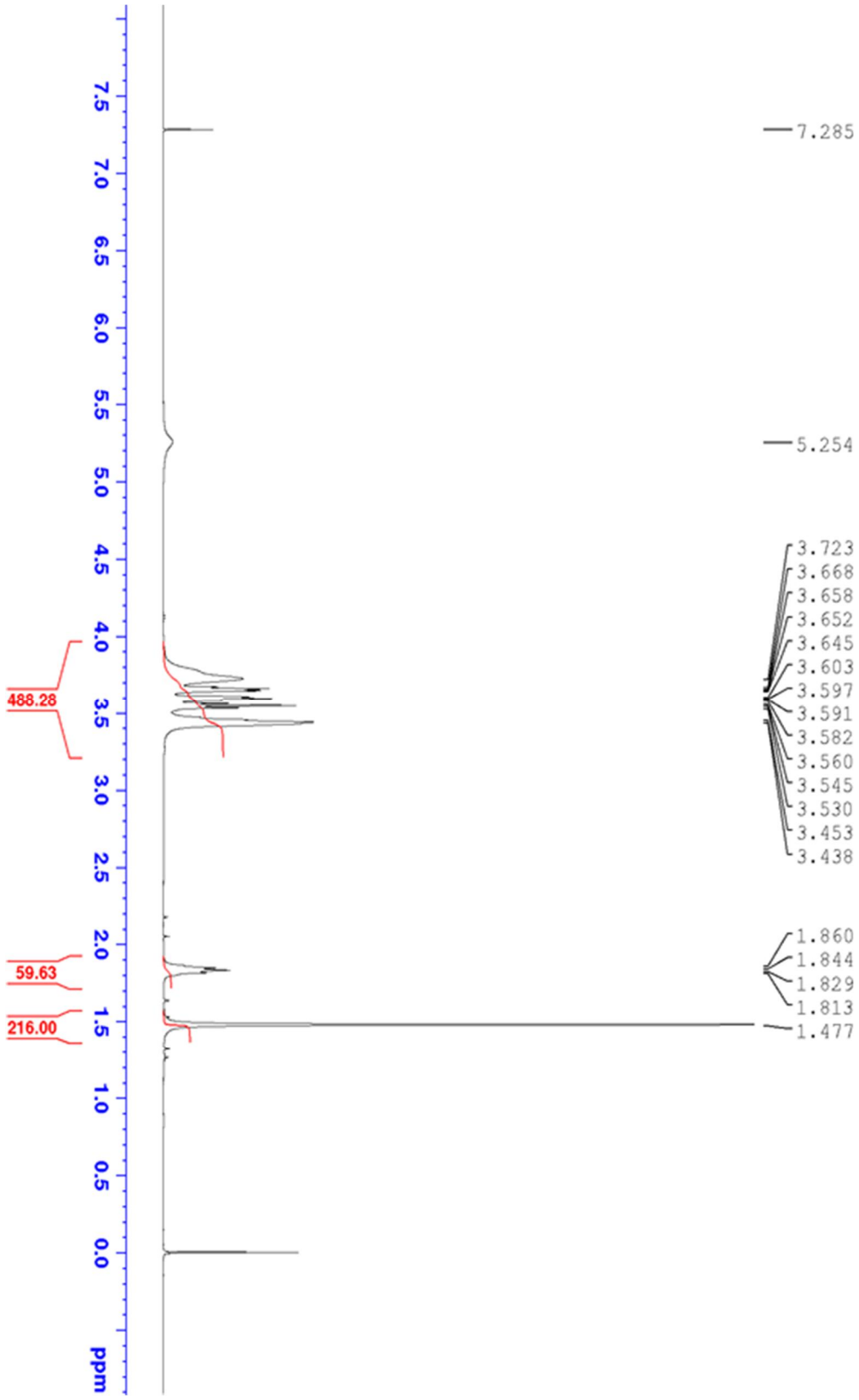
SI Figure 15. Mass Spectra



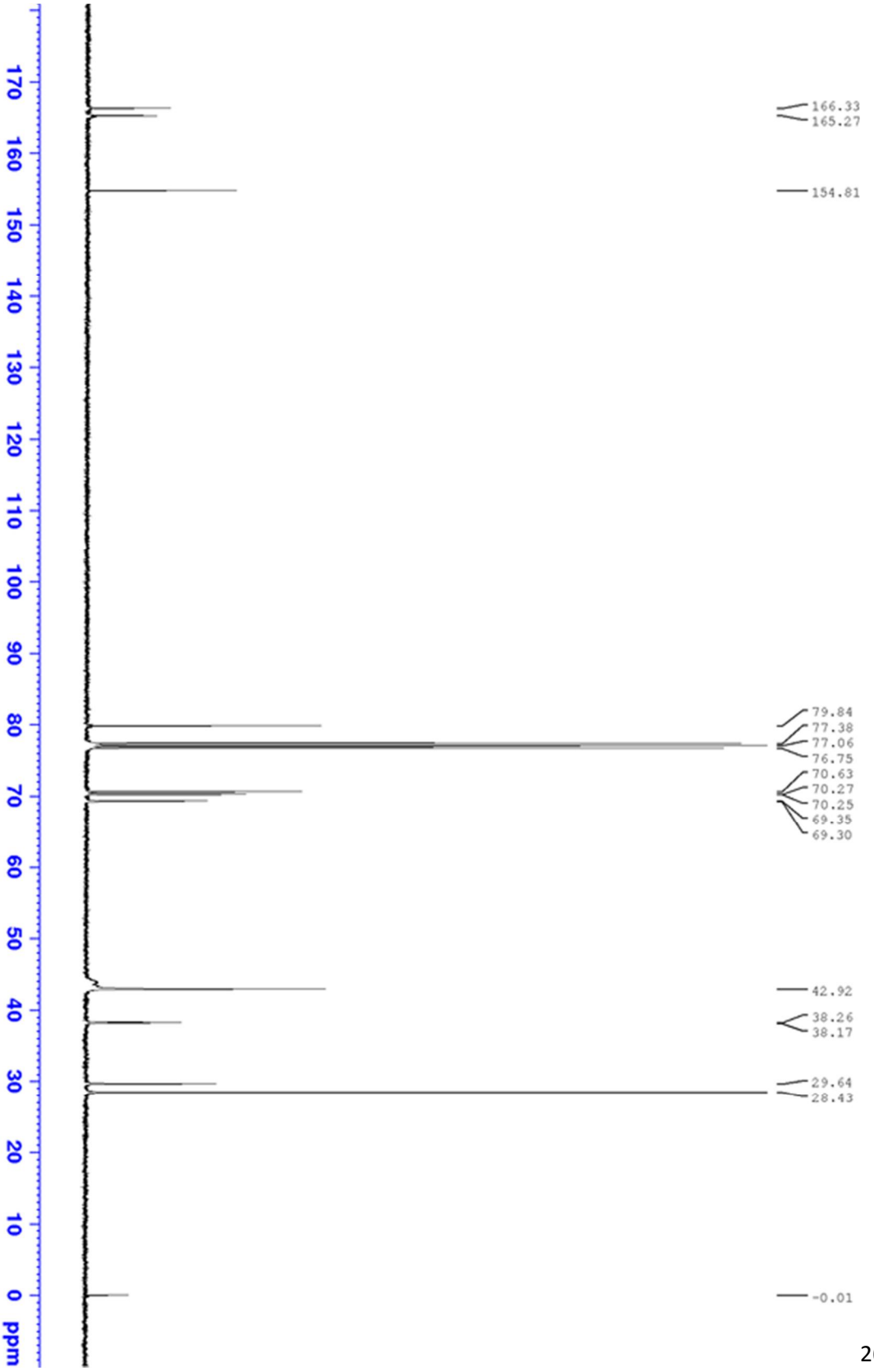
Compound 6 (G3-Boc). A solution of **3** (2.35g, 1.624 mmol) with **5** (0.200g, 0.135 mmol) and DIPEA (0.42mL, 2.44 mmol) in 4mL of 1,4 dioxane and 0.5mL MeOH was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 4 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by automated chromatography. The solvent system (in column volumes) used was the following: 5CV (99:1= EtoAc:MeOH), 5CV (98:2= EtoAc: MeOH), 5CV (100% DCM) to give **6** (1.1g, 82%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (br, 144H, NC**H**$_2$$CH_2$NBoc, N**C**$H_2$**C**$H_2$N), 3.66-3.53 (m, 180H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.45 (br, 156H, C_3N_3-NHC**H**$_2$$CH_2$$CH_2$O, BocNC**H**$_2$$CH_2$N), 1.86 (m, 60H, O$CH_2$C**H**$_2$$CH_2$NH), 1.47 (s, 216H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.26 (**C**$_3$$N_3$), 154.8 (**C**O), 79.8 (**C**$(CH_3)_3$), 70.6 (O**C**H_2**C**H_2O), 70.2 (two lines, O**C**H_2**C**H_2O), 69.3 (two lines, NH$CH_2$$CH_2$**C**$H_2$O), 42.9 (piperazine), 38.2 (NH**C**$H_2$$CH_2$$CH_2$O), 38.1 (NH**C**$H_2$$CH_2$$CH_2$O), 29.6 (NH$CH_2$**C**$H_2$$CH_2$O), 28.4 (C(**C**$H_3)_3$); MS (ESI-TOF) calcd for $C_{456}H_{786}N_{156}O_{93}$ 9936.16, found 9944.5803 $(M + H)^+$.



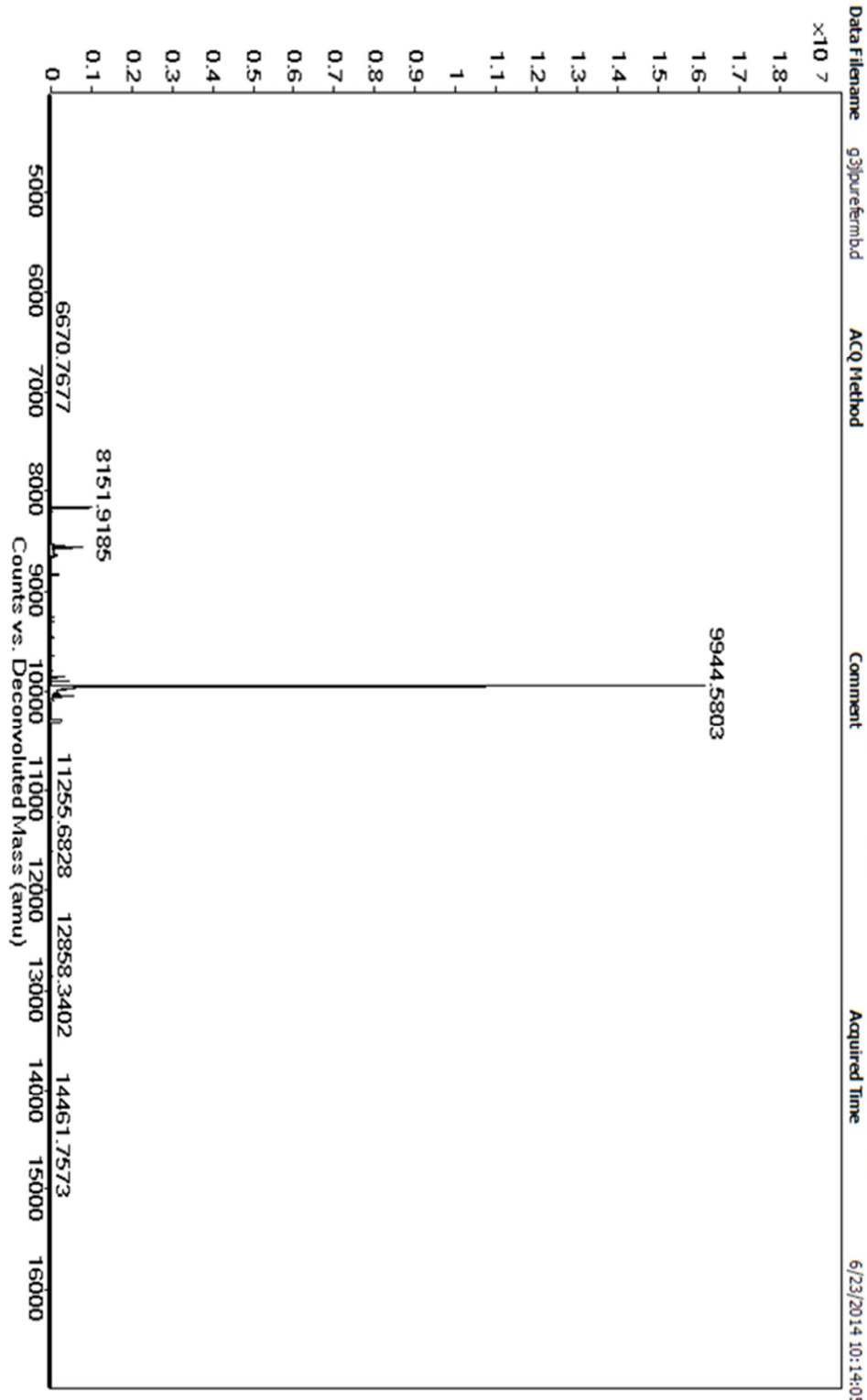
SI Figure 16. ^{1}HNMR



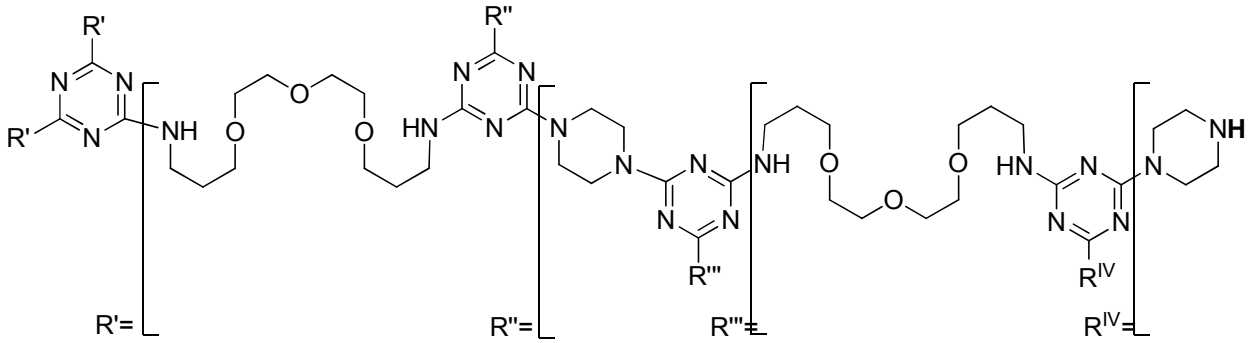
SI Figure 17. ^{13}CNMR



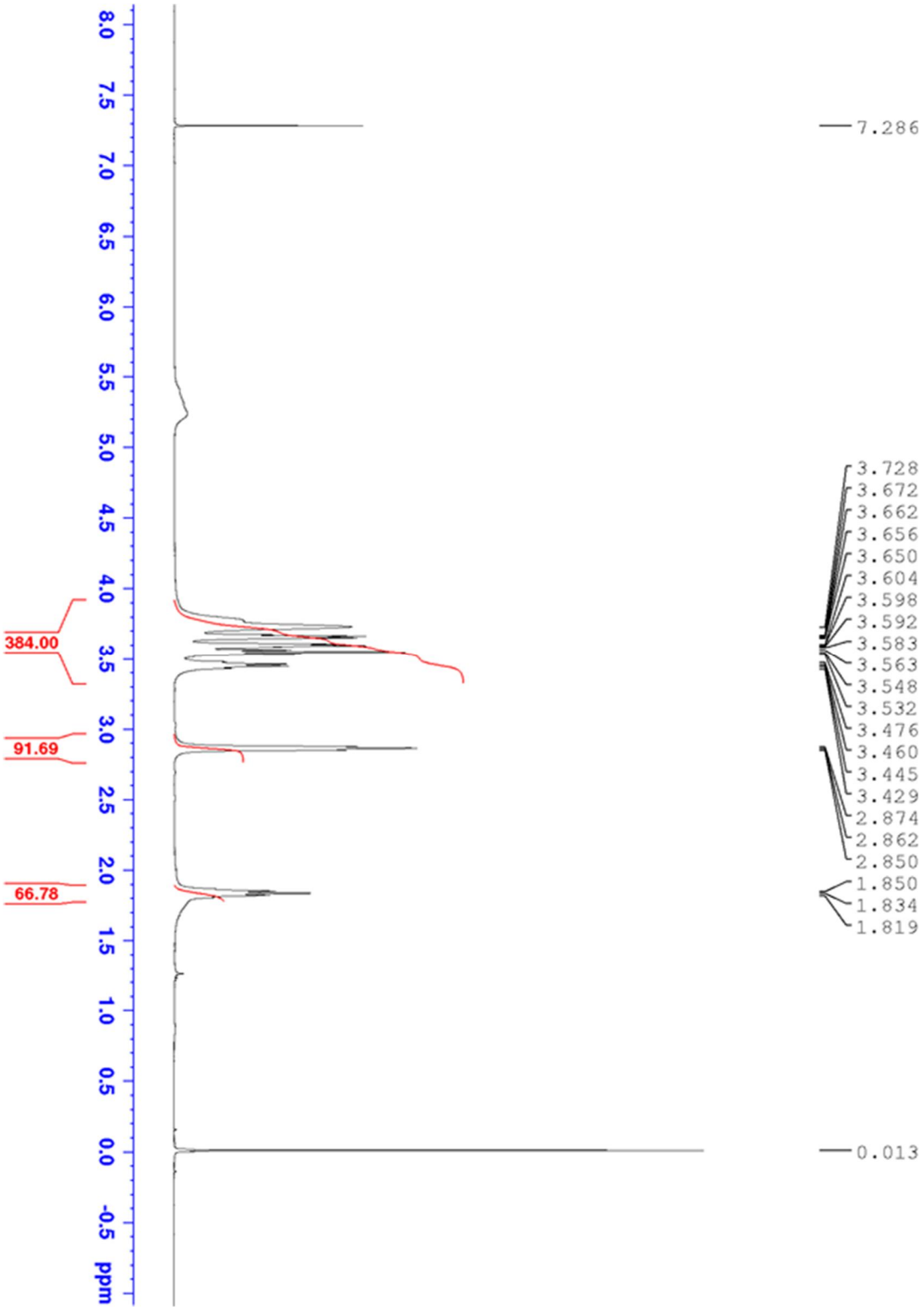
SI Figure 18. Mass Spectra



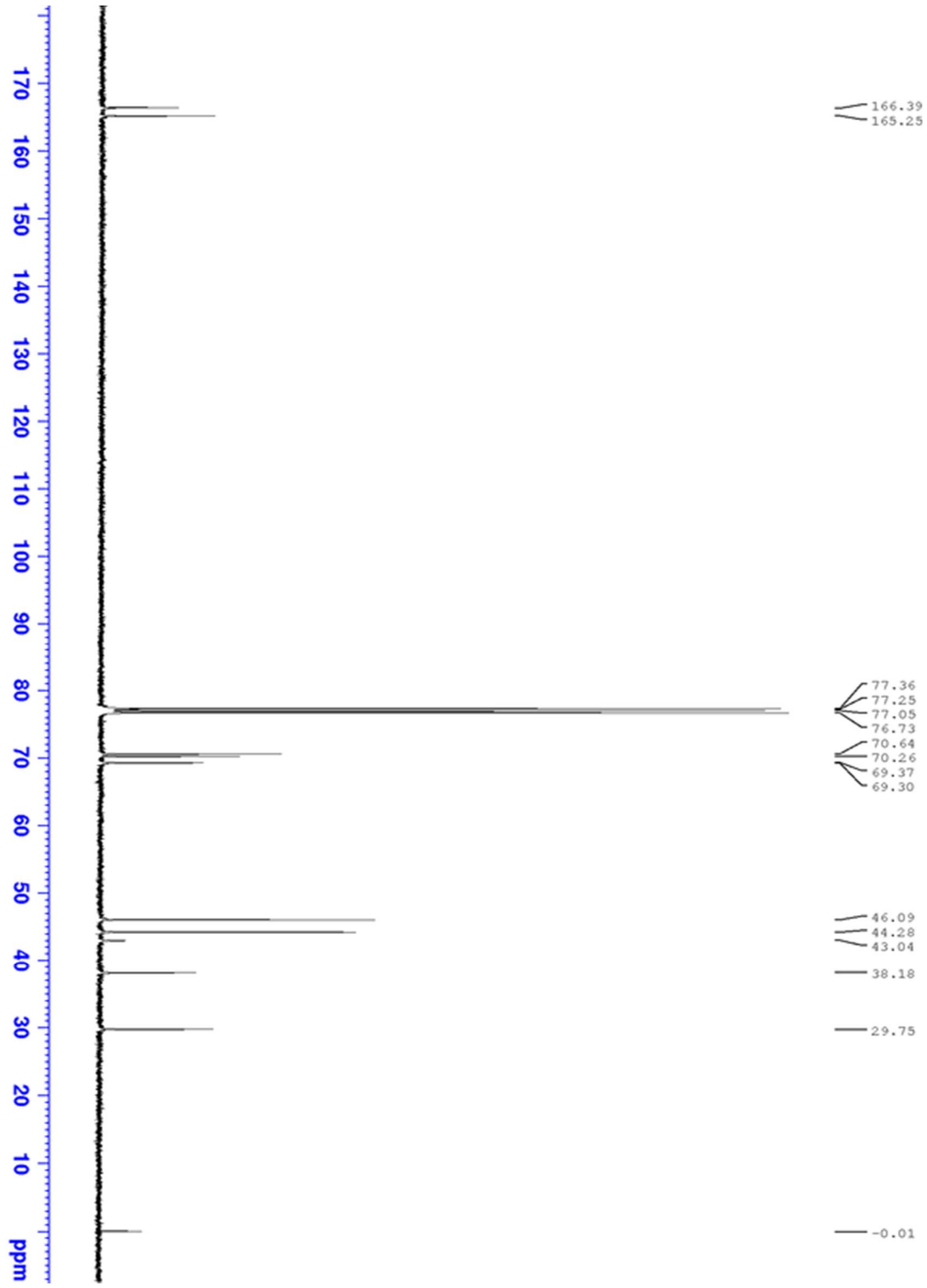
Compound 7 (G3 deprotected). A solution of **6** (0.650 g, 65.4 μmol) in concentrated HCl (3 mL) and dioxane (6 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for two periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **7** (0.493 g, quantitative) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.72 (br, 144H, NC**H**$_2$CH_2NH, NC**H**$_2$C**H**$_2$N), 3.67-3.53 (m, 180H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.47 (br, 60H, C_3N_3-NHC**H**$_2$CH_2CH_2O), 2.87 (br, 96H, HNC**H**$_2$CH_2N), 1.85 (m, 60H, OCH_2C**H**$_2$CH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (O**C**H_2**C**H_2O), 70.2 (O**C**H_2**C**H_2O), 69.3 (two lines, NHCH_2CH_2**C**H_2O), 46.0 (NCH_2**C**H_2NH), 44.2 (N**C**H_2CH_2NH), 43.0 (N**C**H_2**C**H_2N), 38.1 (NH**C**H_2CH_2CH_2O), 29.6 (NHCH_2**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{336}H_{594}N_{156}O_{45}$ 7534.90, found 7541.6290 $(M + H)^+$.



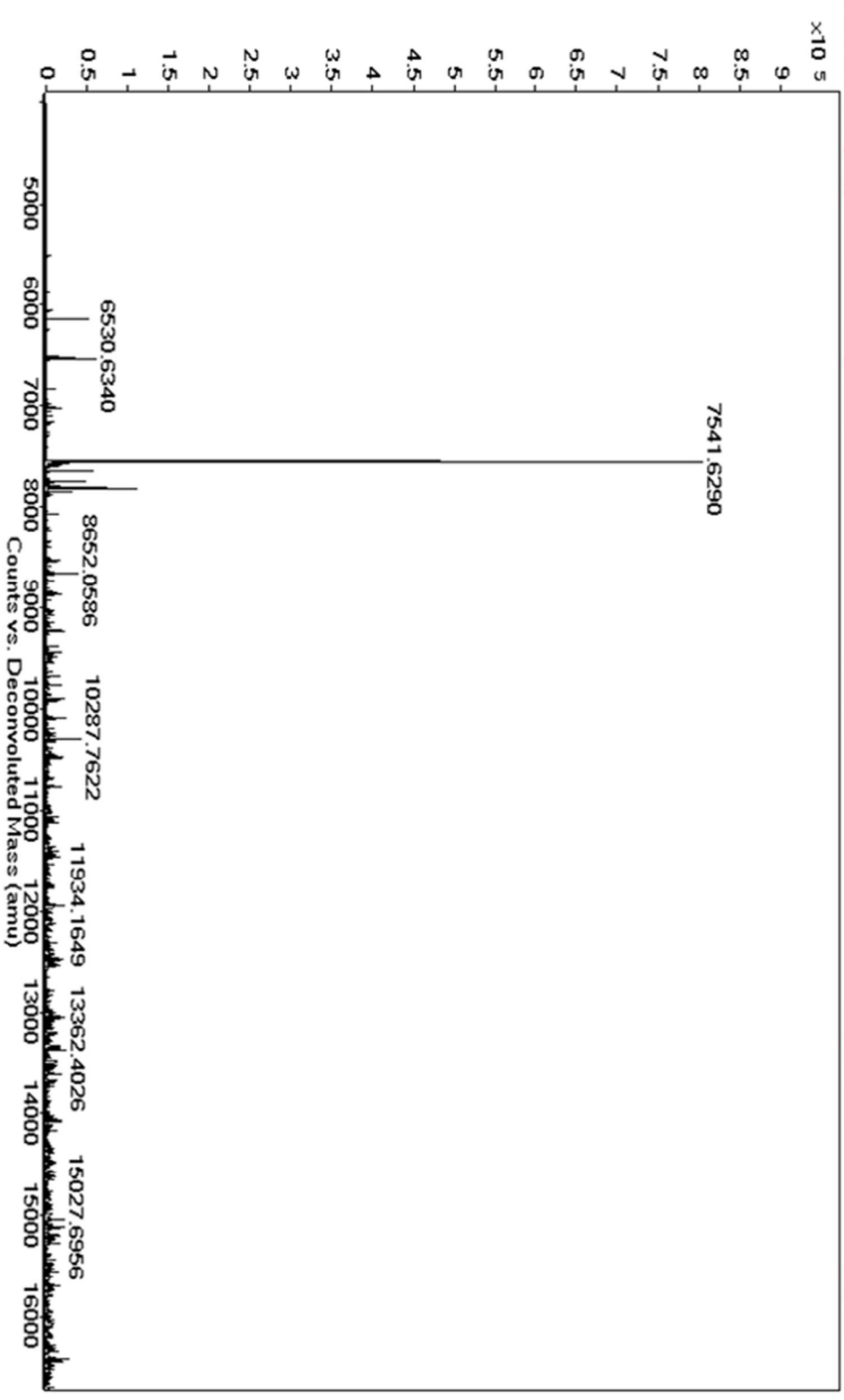
SI Figure 19. ^{1}HNMR



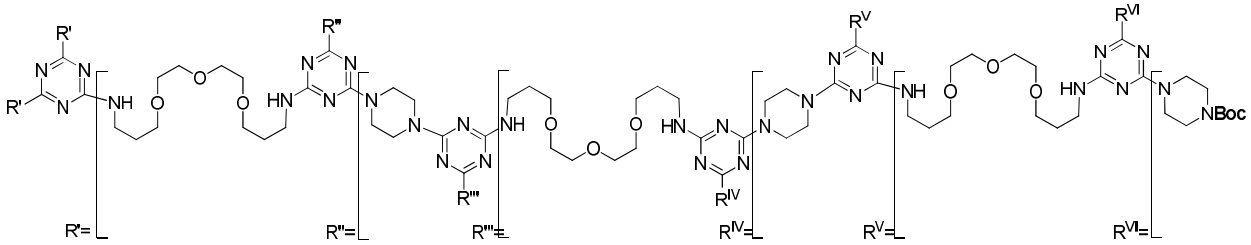
SI Figure 20. ^{13}CNMR



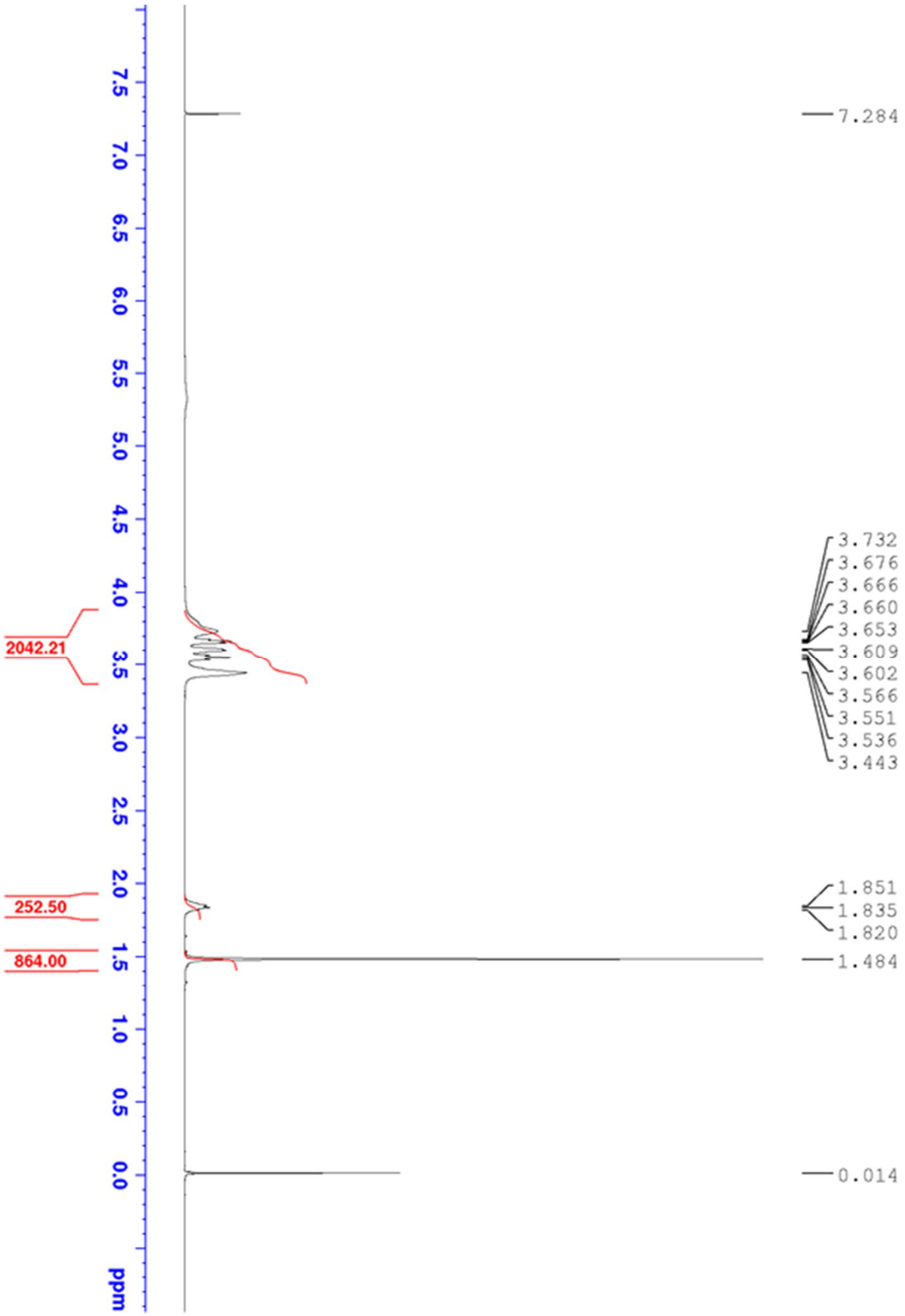
SI Figure 21. Mass Spectra



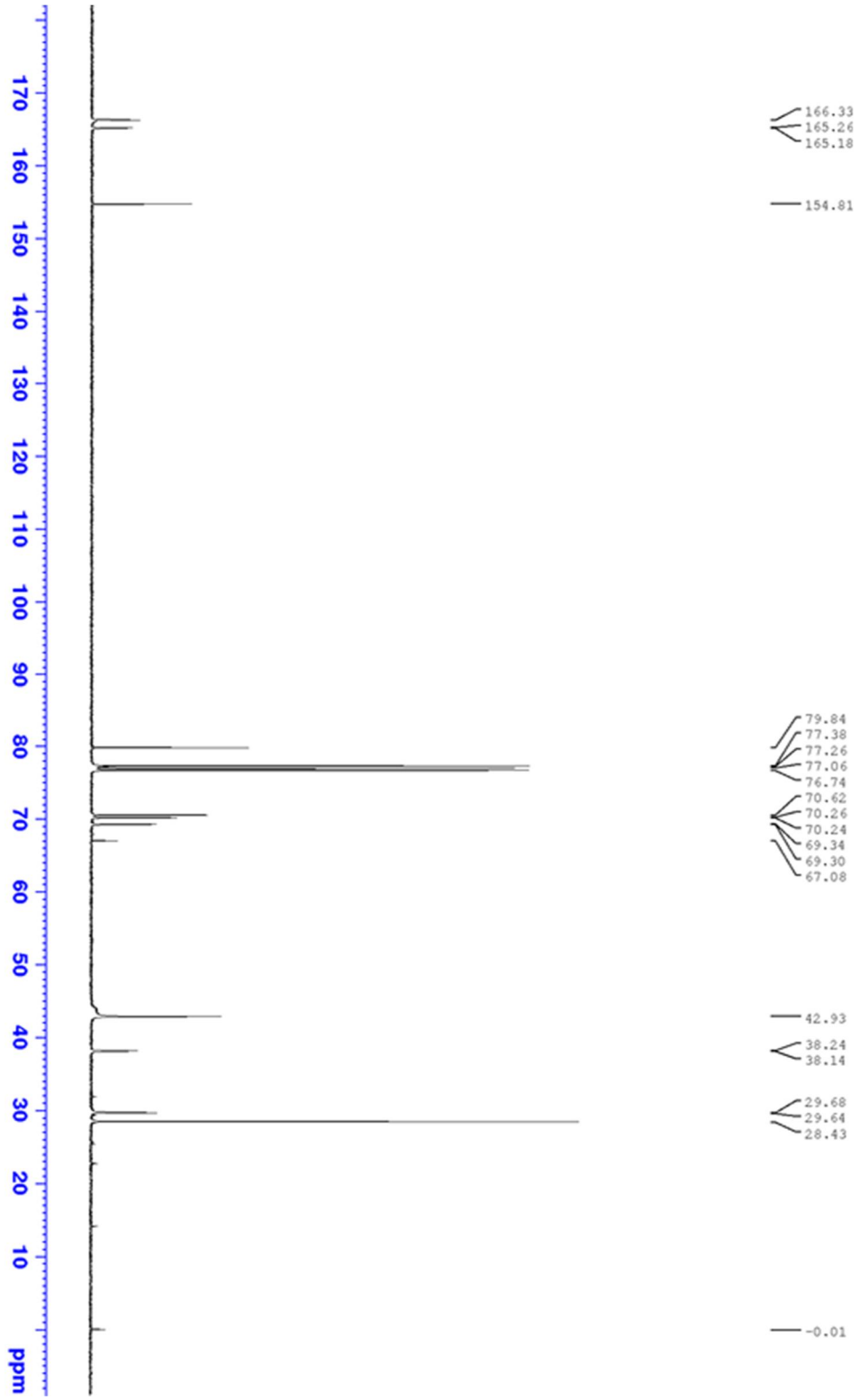
Compound 8 (G5-Boc). A solution of **3** (1.84g, 1.274 mmol) with **7** (0.200g, 26.53 μmol) and DIPEA (0.33mL, 1.89 mmol) in 6mL of 1,4 dioxane, 0.5mL MeOH and 0.5mL H_2O was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 4 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by several washes with a solution of 98:2= EtoEt:MeOH to give **8** (0.76g, 75%) as a white solid.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 624H, NC**H**$_2$CH$_2$NBoc, N**C**H$_2$**C**H$_2$N), 3.67-3.53 (m, 756H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 636H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.85 (m, 252H, OCH$_2$C**H**$_2$CH$_2$NH), 1.48 (s, 864H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2, 165.1 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.3 (two lines, NHCH$_2$CH$_2$**C**H$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (two lines, NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{1896}H_{3258}N_{660}O_{381}$ 41371.59, found 41404.7224 $(M + H)^+$.



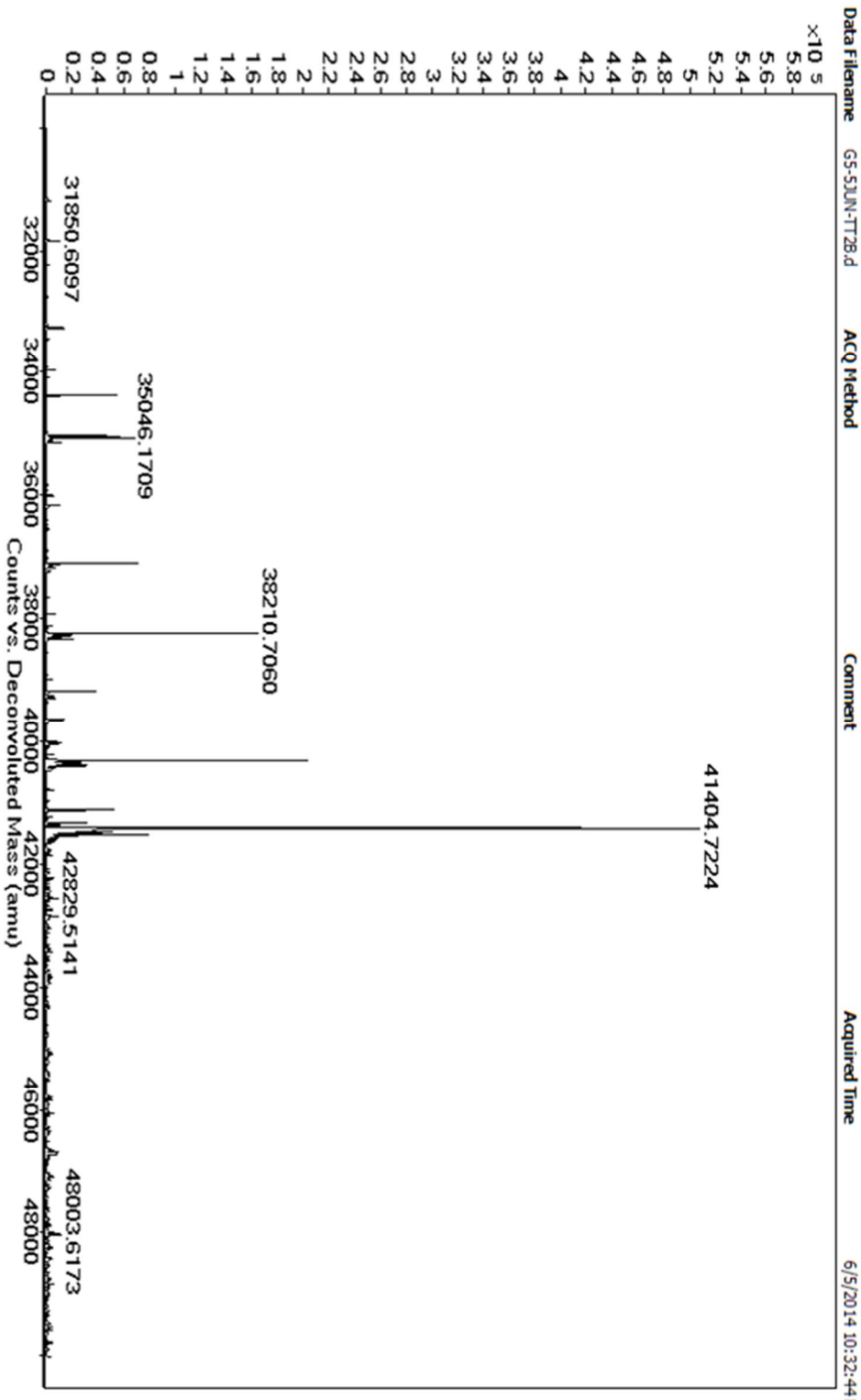
SI Figure 22. ^{1}HNMR



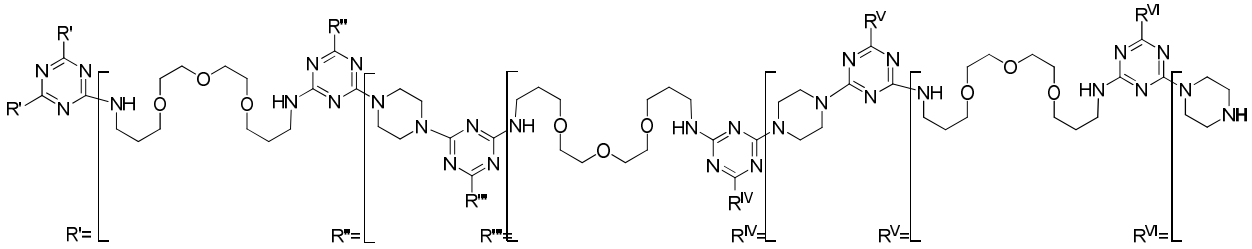
SI Figure 23. ^{13}CNMR



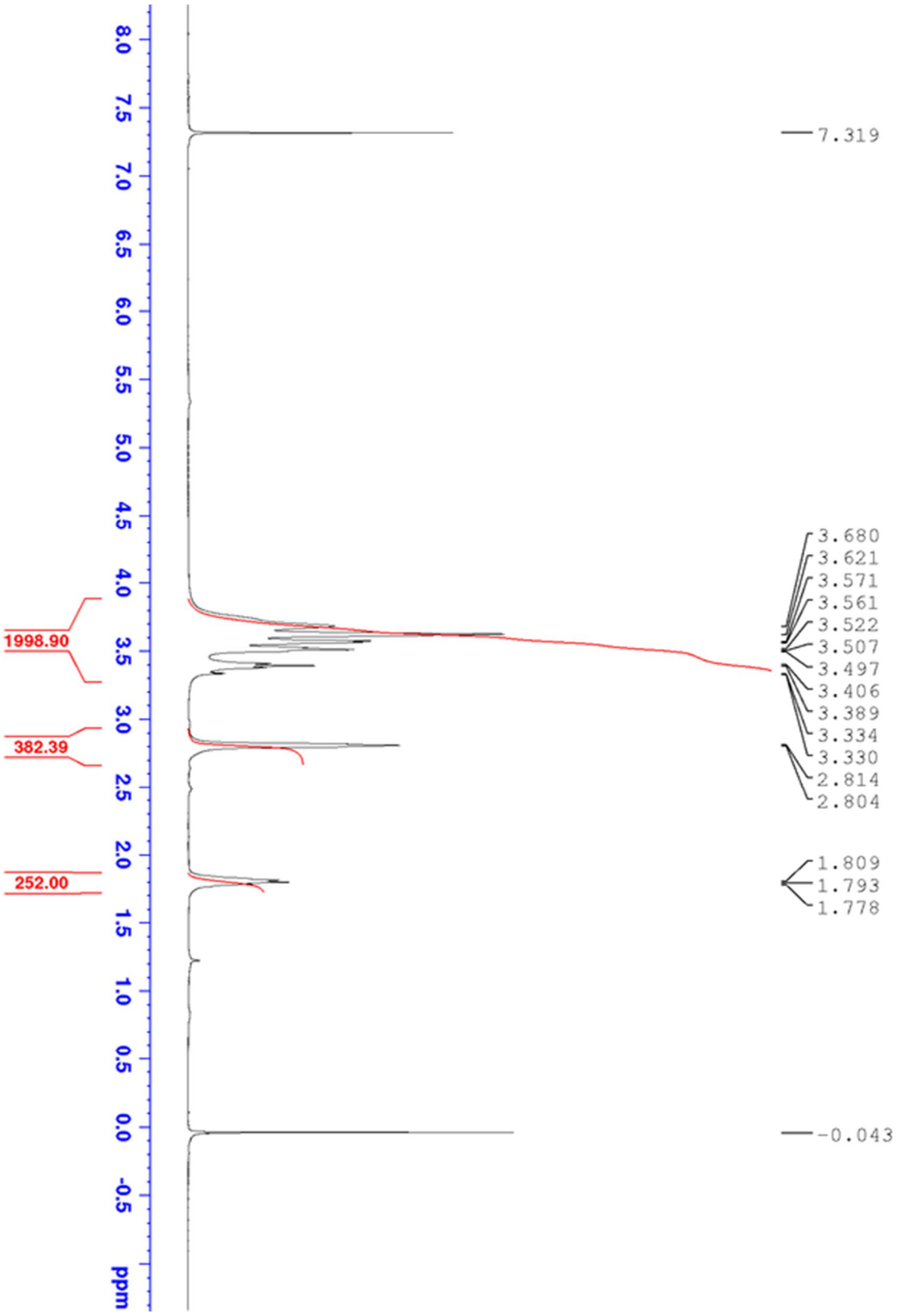
SI Figure 24. Mass Spectra



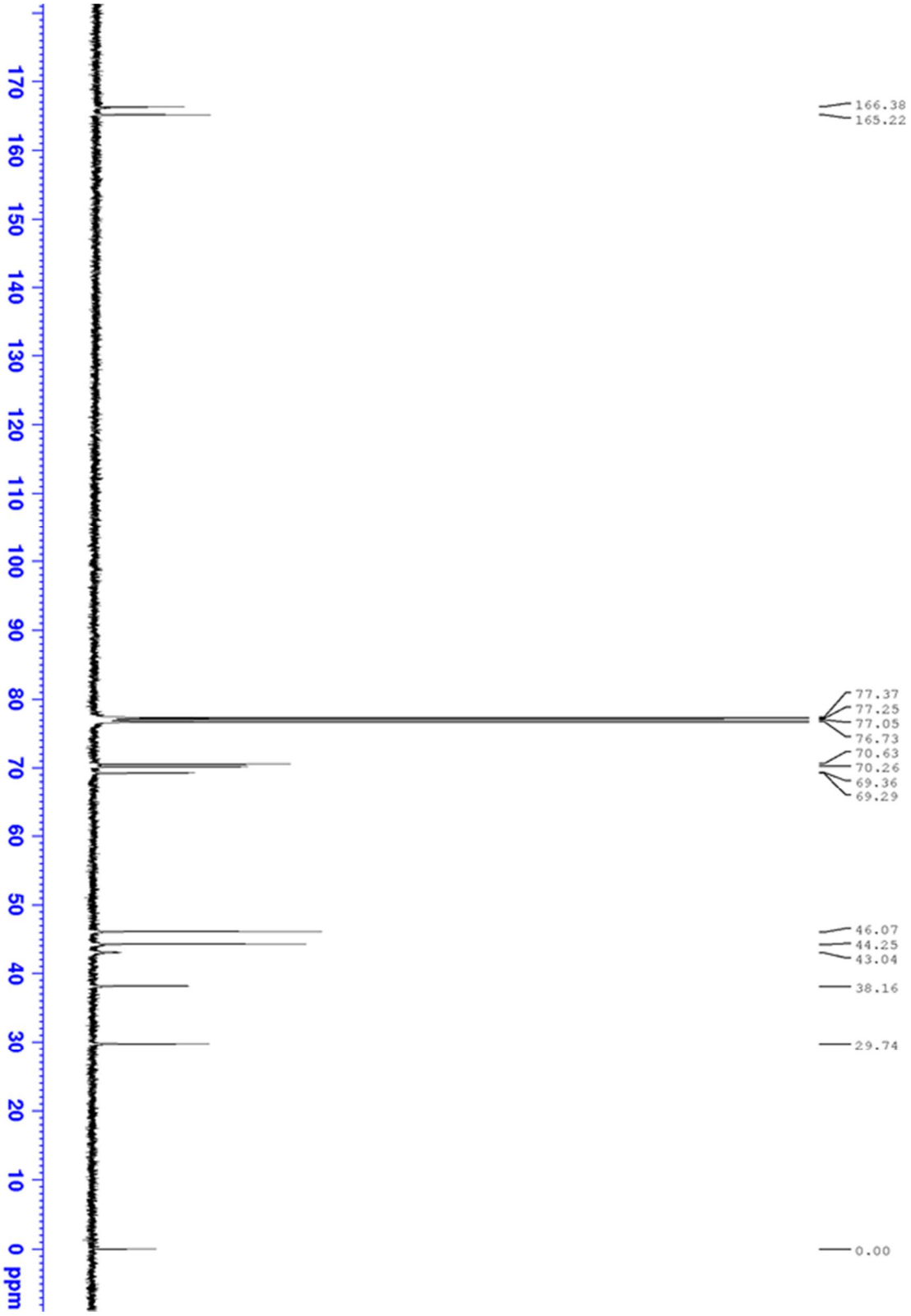
Compound 9 (G5 deprotected). A solution of **8** (0.400 g, 9.67μmol) in concentrated HCl (2 mL) and dioxane (4 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for three periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **9** (0.307g, quantitative) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.68 (br, 624H, NC**H**$_2$CH$_2$NH, NC**H**$_2$C**H**$_2$N), 3.62-3.49 (br m, 756H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.40 (br, 252H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O), 2.81 (br m, 384H, HNC**H**$_2$CH$_2$N), 1.80 (m, 252H, OCH$_2$C**H**$_2$CH$_2$NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O), 69.3 (NHCH$_2$CH$_2$**C**H$_2$O), 69.2 (NHCH$_2$CH$_2$**C**H$_2$O), 46.0 (NCH$_2$**C**H$_2$NH), 44.2 (N**C**H$_2$CH$_2$NH), 43.0 (N**C**H$_2$**C**H$_2$N), 38.1 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O); MS (ESI-TOF) calcd for $C_{1416}H_{2490}N_{660}O_{189}$ 31766.55, found 31792.1374 $(M + H)^+$.



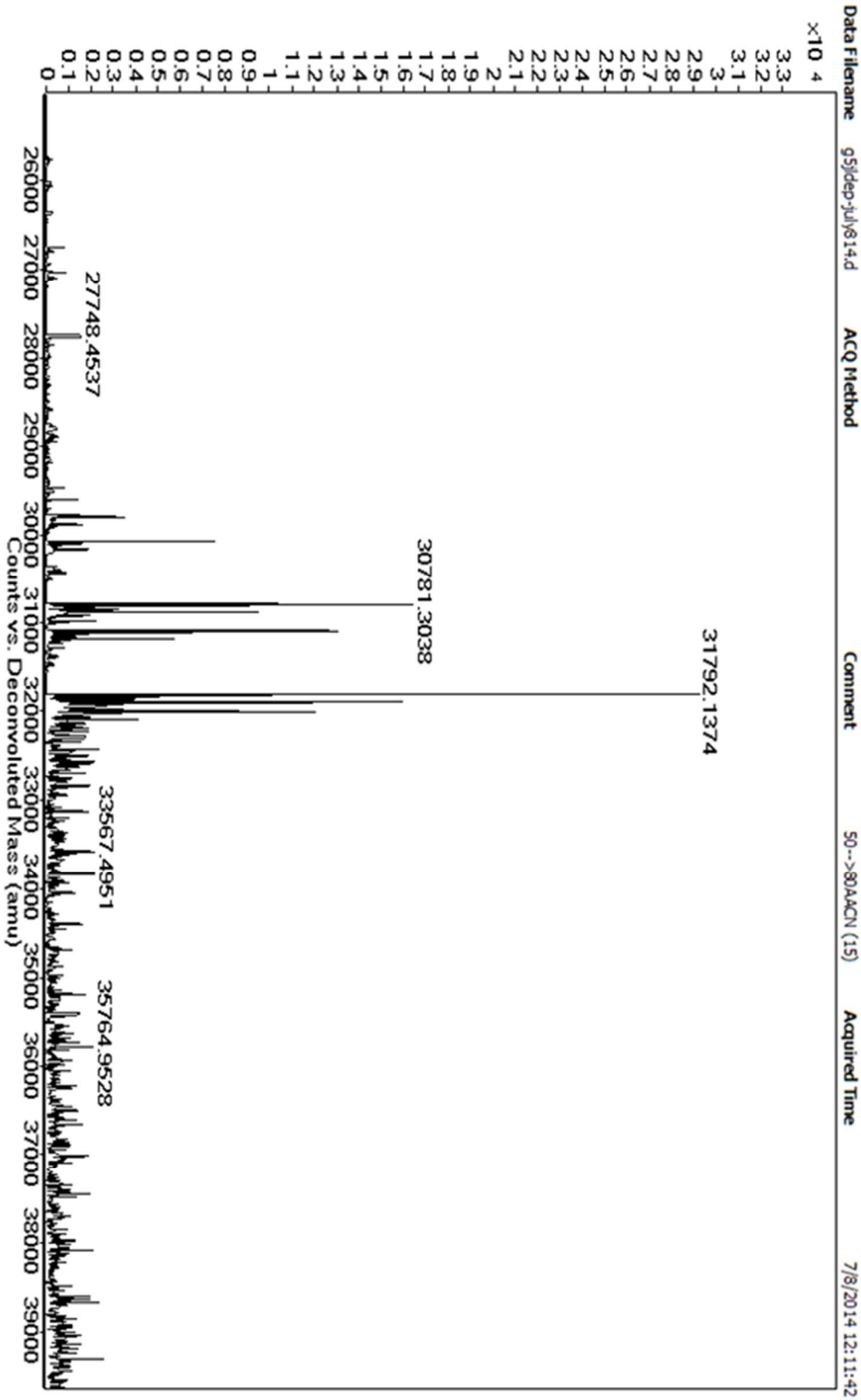
SI Figure 25. ^{1}HNMR



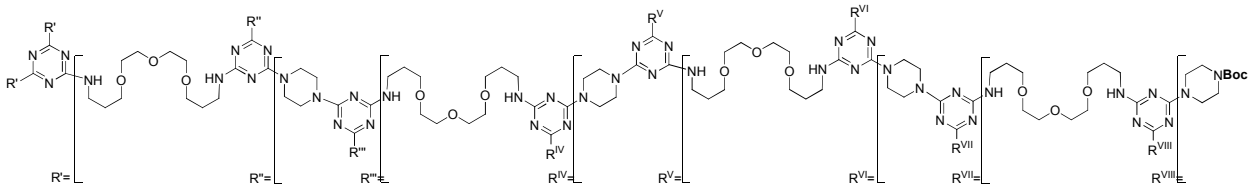
SI Figure 26. ^{13}CNMR



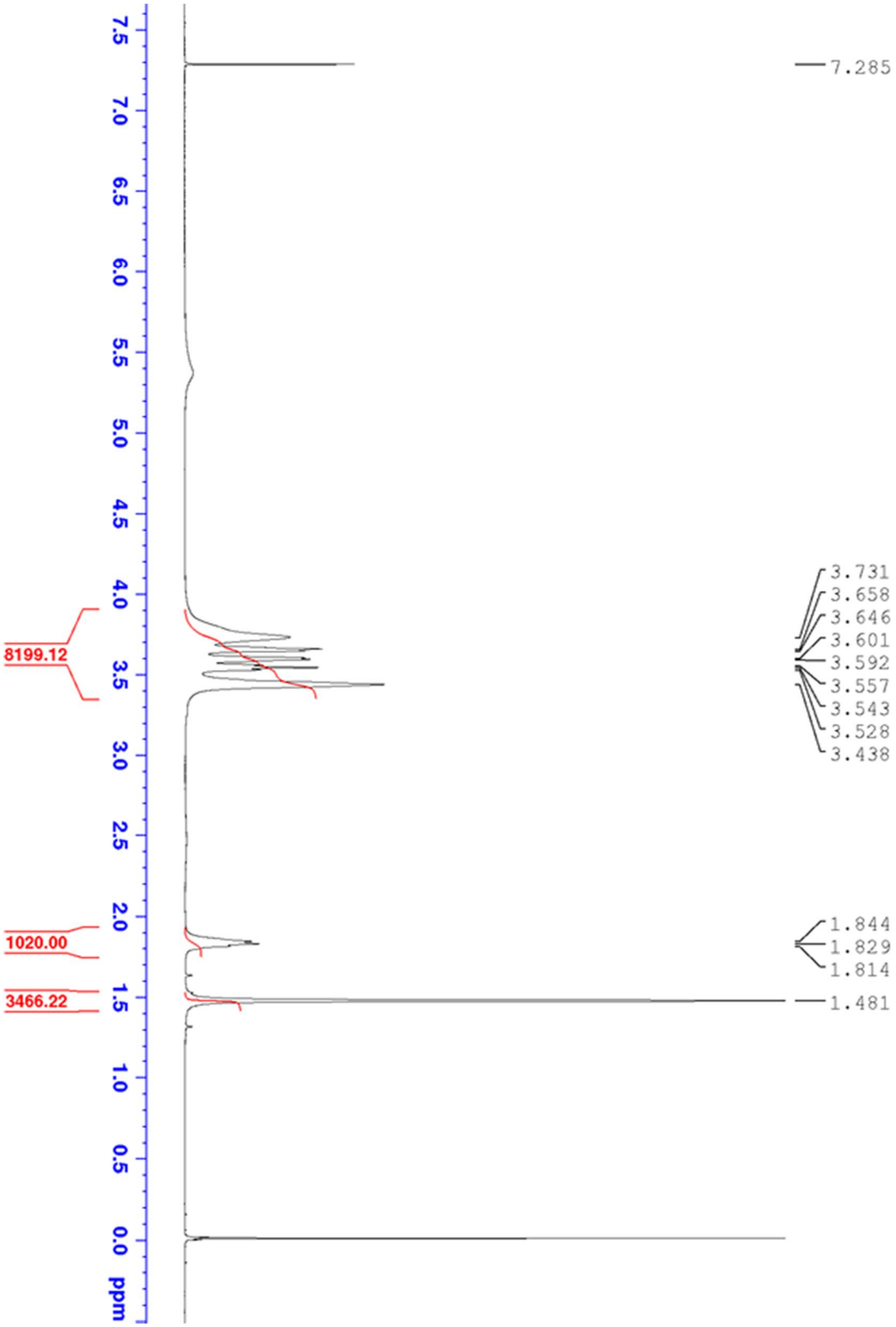
SI Figure 27. Mass Spectra



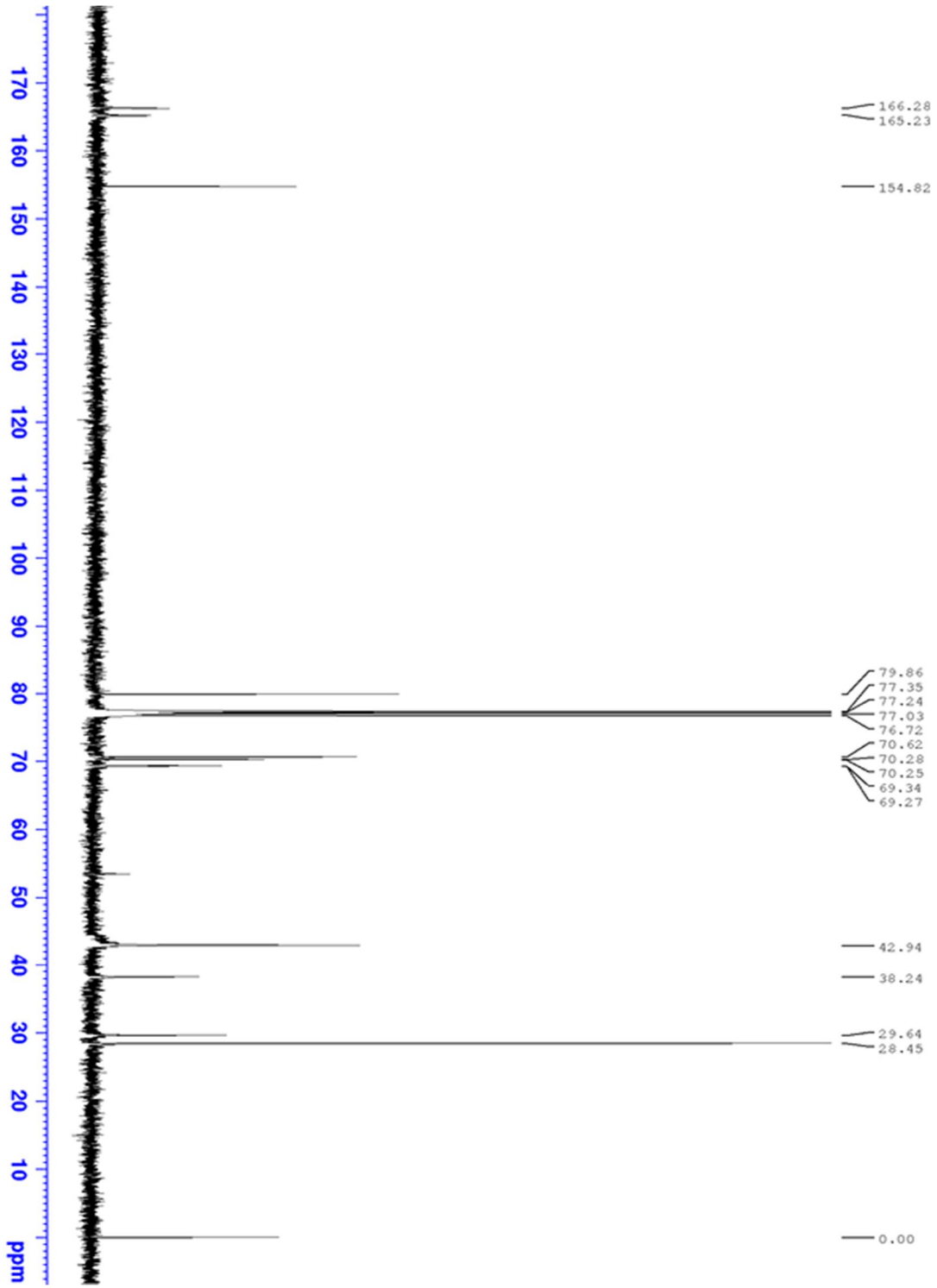
Compound 10 (G7-Boc). A solution of **3** (1.75g, 1.2 mmol) with **9** (0.200g, 6.3 μmol) and DIPEA (0.33mL, 1.89 mmol) in 7mL of 1,4 dioxane, 1mL MeOH and 0.5mL H_2O was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 6 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by several washes with a solution of 97:3= EtoEt:MeOH to give **10** (0.850g, 81%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.73 (br, 2544H, NC**H**$_2$CH$_2$NBoc, N**C**H$_2$**C**H$_2$N), 3.65-3.52 (m, 3060H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.43 (br, 2556H, C_3N_3-NHC**H**$_2$CH$_2$CH$_2$O, BocNC**H**$_2$CH$_2$N), 1.84 (m, 1020H, OCH$_2$C**H**$_2$CH$_2$NH), 1.48 (s, 3456H, C(C**H**$_3$)$_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 154.8 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (two lines, O**C**H$_2$**C**H$_2$O), 69.3 (NHCH$_2$CH$_2$**C**H$_2$O), 69.2 (NHCH$_2$CH$_2$**C**H$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (ESI-TOF) calcd for $C_{7656}H_{13146}N_{2676}O_{1533}$ 167113.30, not found.



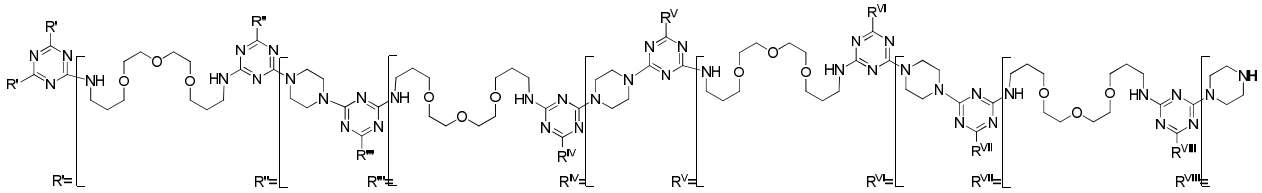
SI Figure 28. ^{1}HNMR



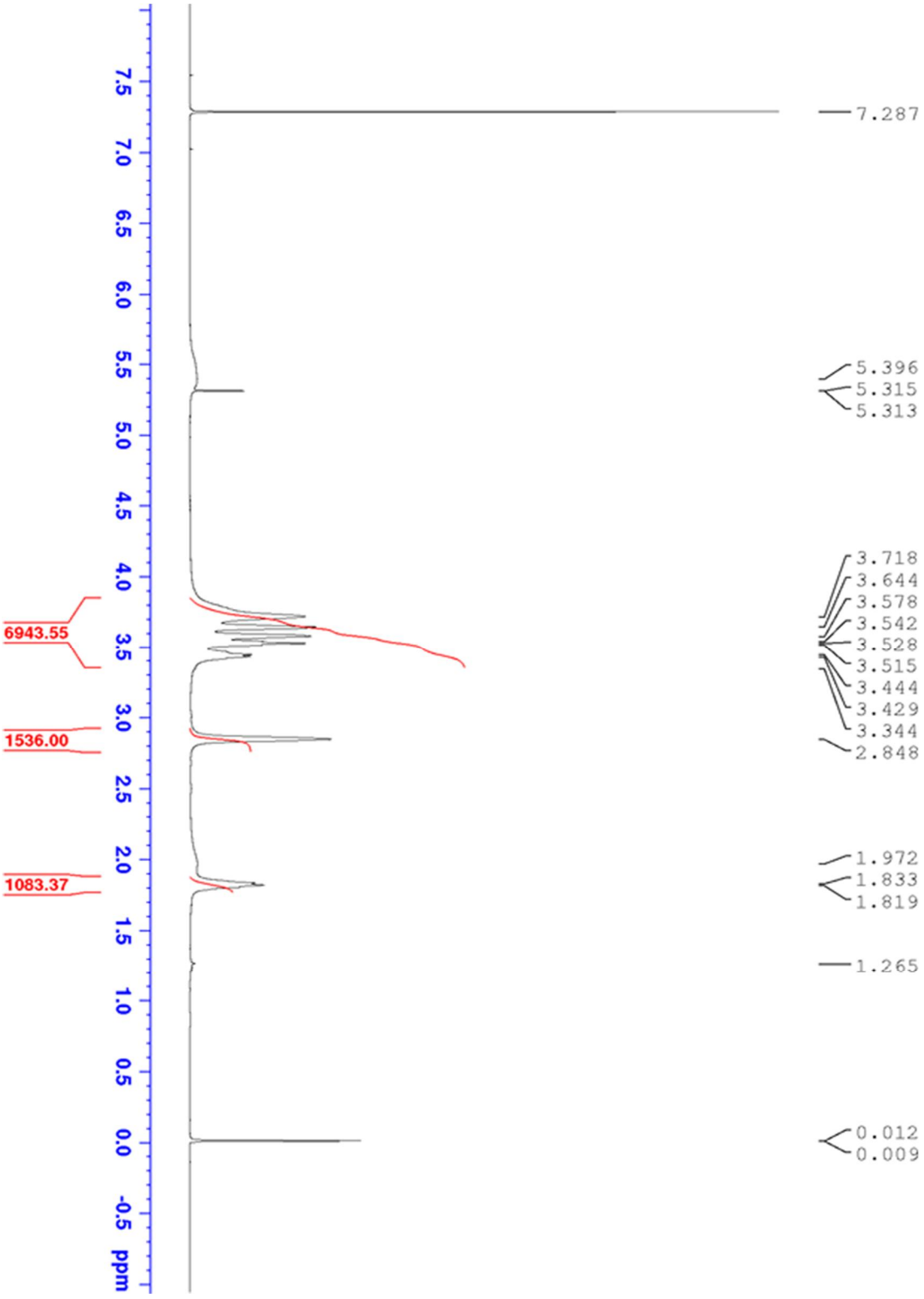
SI Figure 29. ^{13}CNMR



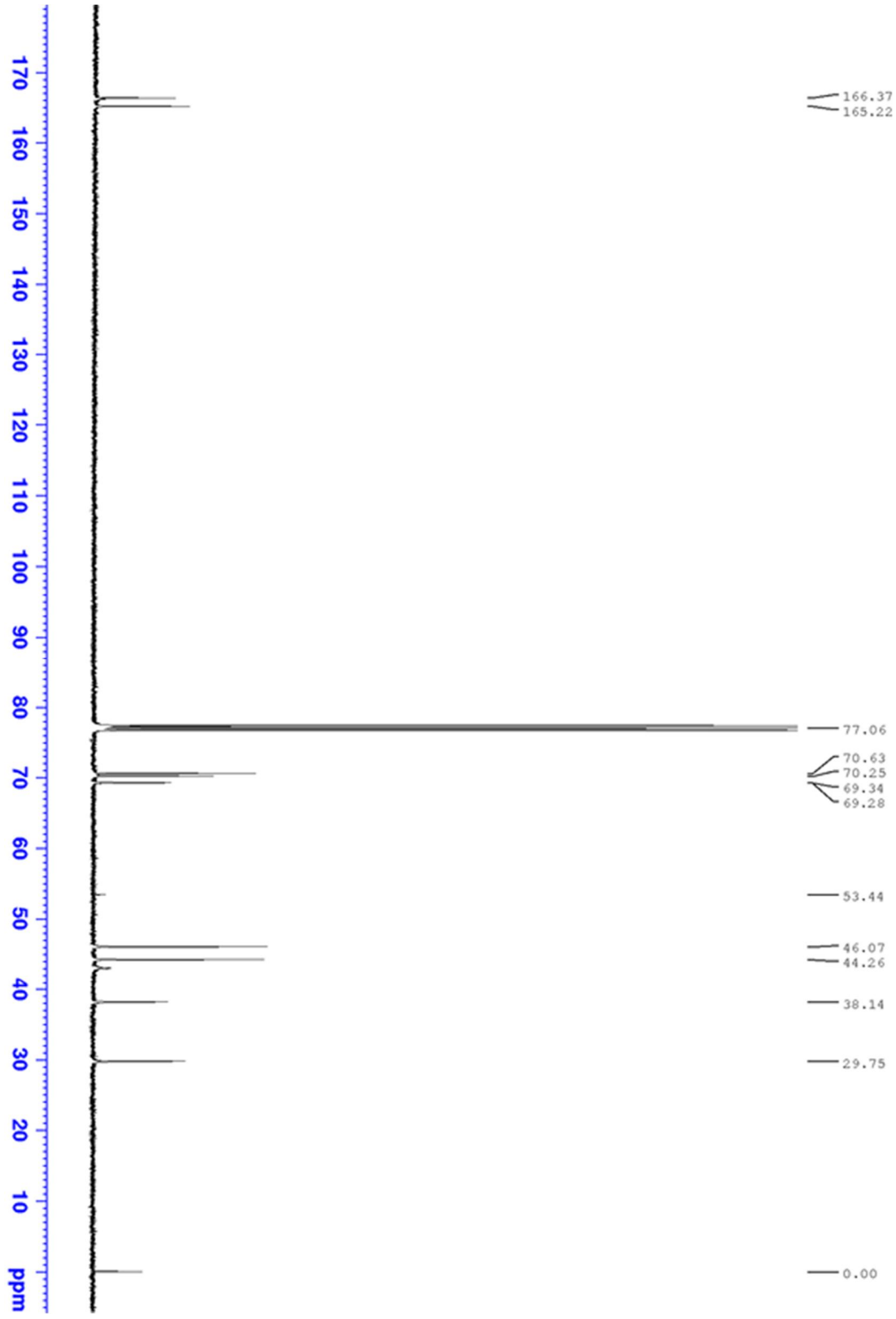
Compound 11 (G7 deprotected). A solution of **10** (0.390 g, 2.3 μmol) in concentrated HCl (2.5 mL) and dioxane (5 mL) was stirred for 1 min at room temperature and then was irradiated in the microwave while stirring for three periods of 3 minutes at 60ºC using dynamic mode and then evaporated with air. The residue was dissolved in dichloromethane, washed with 5 M NaOH (aq), dried over $MgSO_4$, filtered, and evaporated under vacuum to give **9** (0.270g, 90%) as a white solid. ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 2544H, NC**H**$_2$CH_2NH, NC**H**$_2$C**H**$_2$N), 3.64-3.51 (br m, 3060H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$), 3.44 (br, 1020H, C_3N_3-NHC**H**$_2$CH_2CH_2O), 2.84 (br, 1536H, HNC**H**$_2$CH_2N), 1.83 (m, 1020H, OCH_2C**H**$_2$CH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.2 (**C**$_3$N$_3$), 70.6 (O**C**H_2**C**H_2O), 70.2 (O**C**H_2**C**H_2O), 69.3 (NHCH_2CH_2**C**H_2O), 69.2 (NHCH_2CH_2**C**H_2O), 46.0 (NCH_2**C**H_2NH), 44.2 (N**C**H_2CH_2NH), 43.0 (N**C**H_2**C**H_2N), 38.1 (NH**C**H_2CH_2CH_2O), 29.7 (NHCH_2**C**H_2CH_2O); MS (MALDI-TOF) calcd for $C_{5736}H_{10074}N_{2676}O_{765}$ 128693.17, not found.



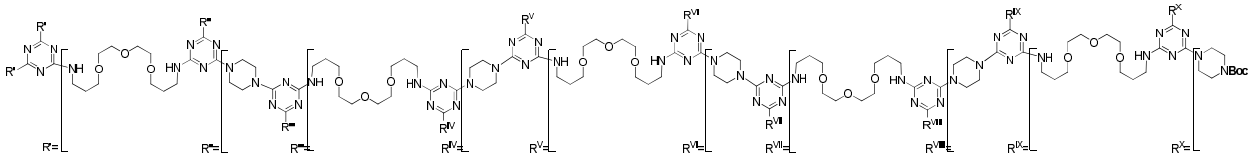
SI Figure 30. ^{1}HNMR



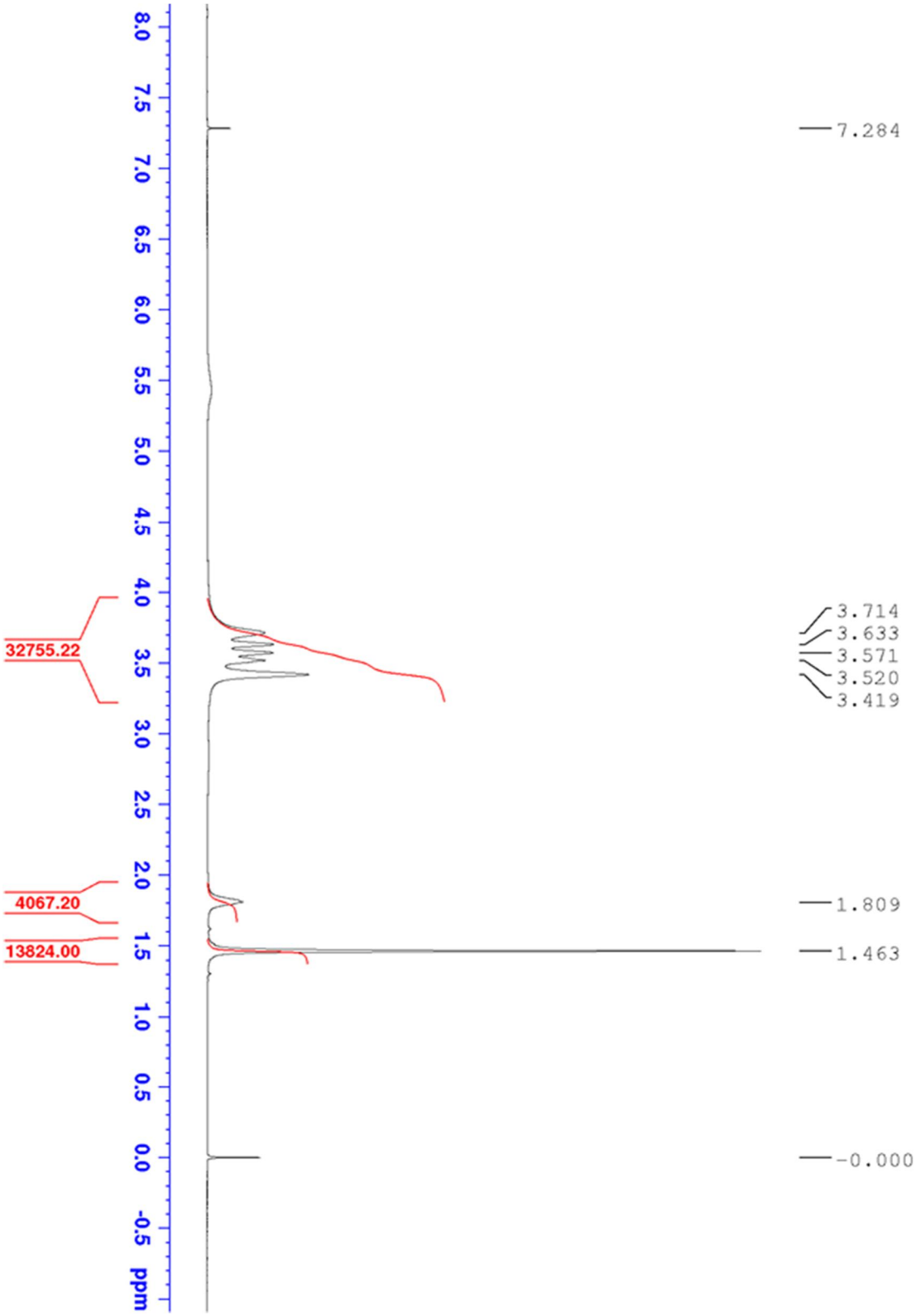
SI Figure 31. ^{13}CNMR



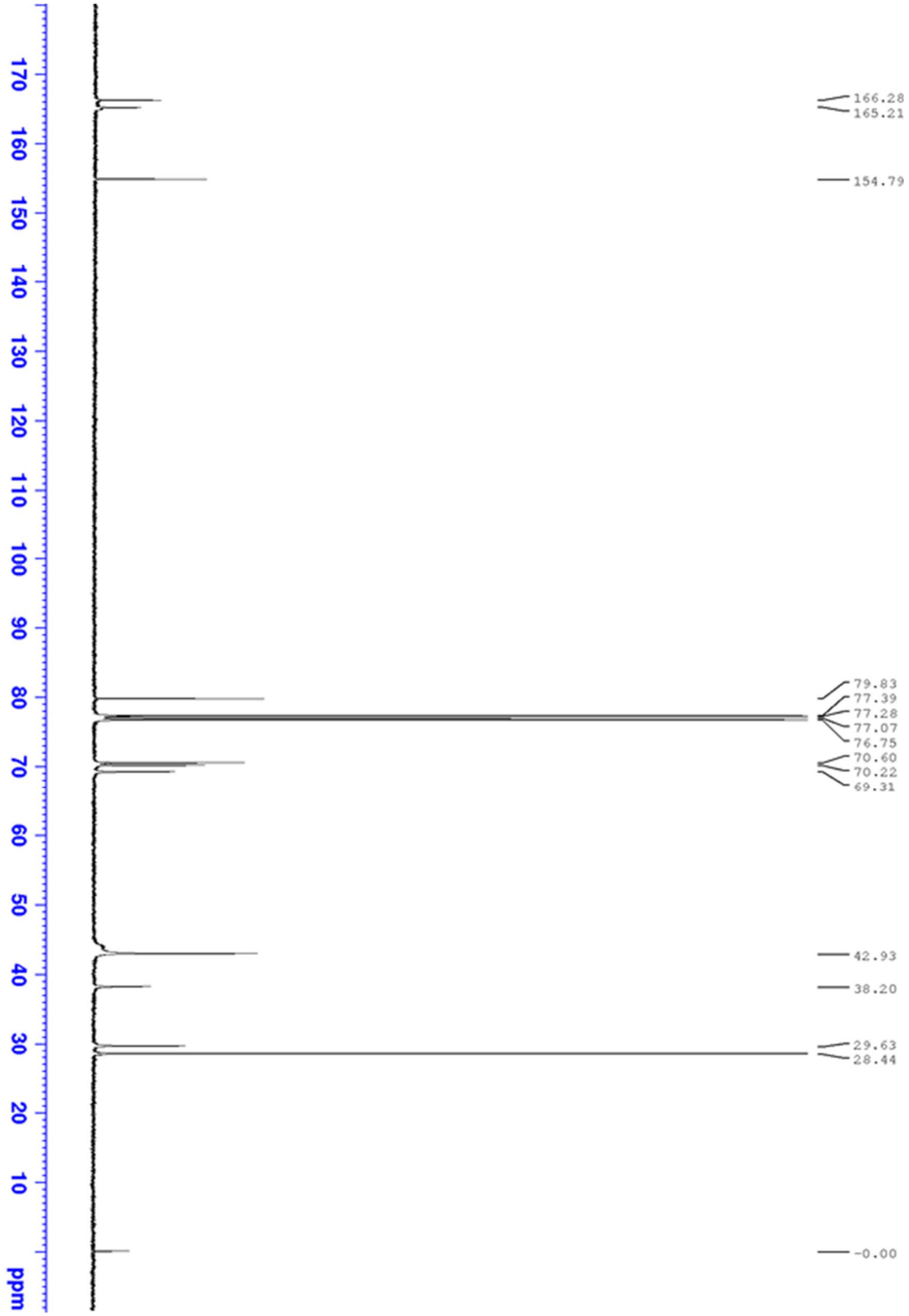
Compound 12 (G9-Boc). A solution of **3** (0.430g, 0.30 mmol) with **11** (0.050g, 0.39 μmol) and DIPEA (0.08mL, 0.46 mmol) in 3mL of 1,4 dioxane, 1mL MeOH and 0.5mL H_2O was stirred for 2 minutes. Then, the solution was irradiated in the microwave while stirring for 6 hours at 95ºC using dynamic mode and then evaporated under vacuum. The residue was dissolved in dichloromethane, washed with brine solution and dried over $MgSO_4$, filtered, and evaporated under vacuum. The crude was purified by several washes with MeOH to give **10** (0.209g, 80%) as a white wax.^{1}H NMR (400 MHz, $CDCl_3$) δ 3.71 (br, 10224H, NC**H**$_2$CH$_2$NBoc, N**C**H$_2$**C**H$_2$N), 3.63-3.52 (br m, 12276H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**), 3.41 (br, 10236H, C_3N_3-NHC**H$_2$**CH$_2$CH$_2$O, BocNC**H$_2$**CH$_2$N), 1.80 (m, 4092H, OCH$_2$C**H$_2$**CH$_2$NH), 1.46 (s, 13824H, C(C**H$_3$**)$_3$);^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 165.2 (**C**$_3$N$_3$), 154.7 (**C**O), 79.8 (**C**(CH$_3$)$_3$), 70.6 (O**C**H$_2$**C**H$_2$O), 70.2 (O**C**H$_2$**C**H$_2$O), 69.3 (NHCH$_2$CH$_2$**C**H$_2$O), 42.9 (piperazine), 38.2 (NH**C**H$_2$CH$_2$CH$_2$O), 29.6 (NHCH$_2$**C**H$_2$CH$_2$O), 28.4 (C(**C**H$_3$)$_3$); MS (MALDI-TOF) calcd for $C_{30696}H_{52698}N_{10740}O_{6141}$ 670080.15, not found.



SI Figure 32. ^{1}HNMR



SI Figure 33. ^{13}CNMR



==== Shimadzu LabSolutions GPC Calibration Curve ====

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Ch# : Channel 1
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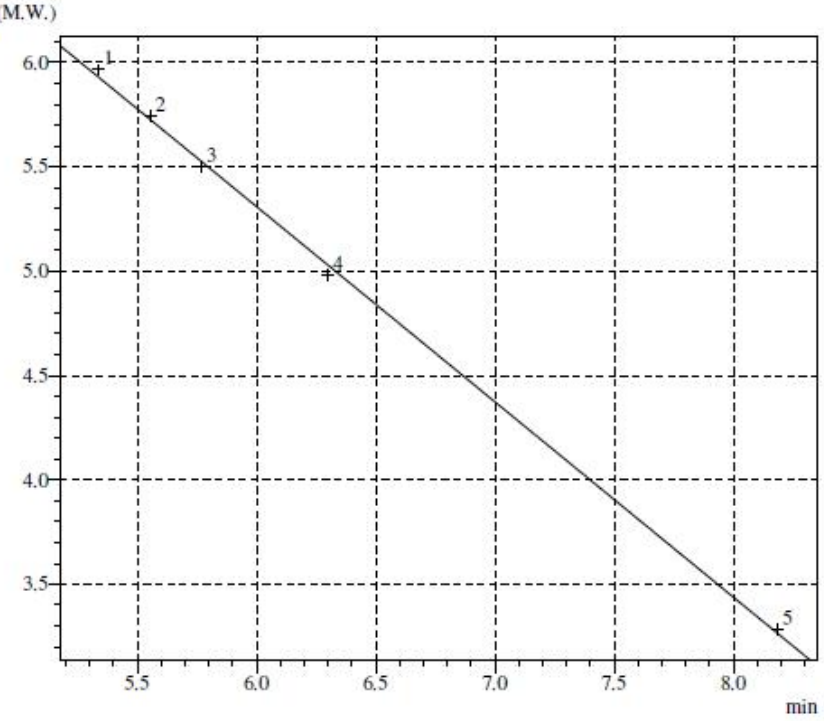
Curve Fit Type : Linear
Function : f(x)=-0.9359686*x+10.92512
R^2=0.9989695 Dispersion=0.03092953



#	Time(min)	Molecular Weight	Error(%)	Active	Virtual
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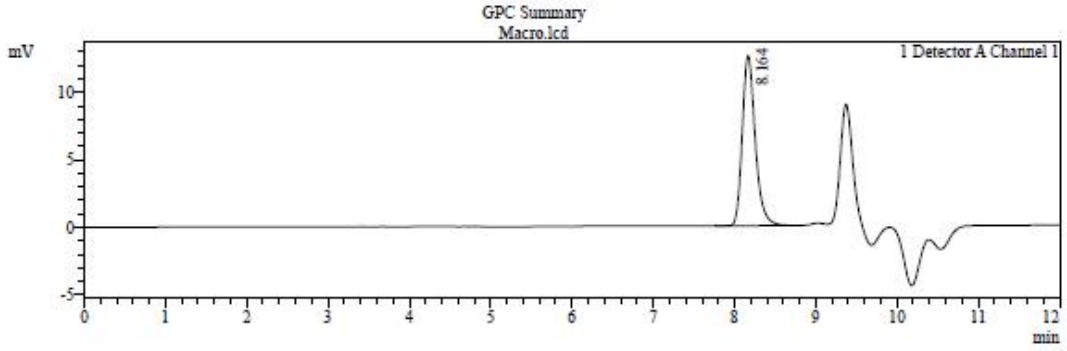
2	5.555	554000	3.8991	Enabled	Disabled
3	5.768	319000	-5.3836	Enabled	Disabled
4	6.298	96000	-11.8336	Enabled	Disabled
5	8.184	1920	4.1750	Enabled	Disabled

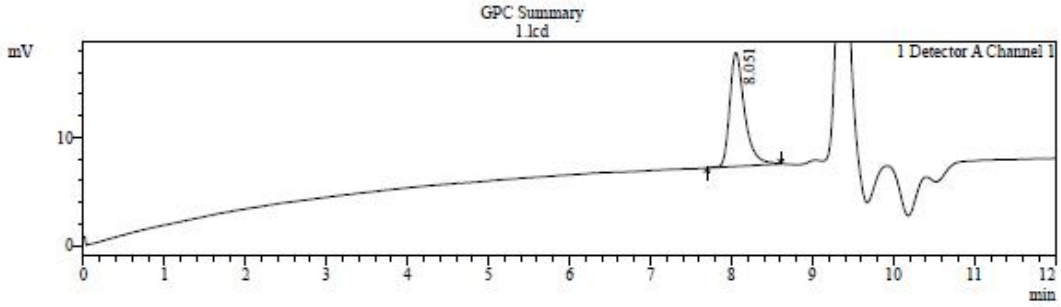
Macromonomer



Chromatogram Detector 1 Ch1

Sample Name	#	Title	Mn	Mw	Mz	Mz1	Mv
Macro	1	Macro.lcd	1809	1871	1927	1980	0
		Average	1809	1871	1927	1980	0
		%RSD	0.000	0.000	0.000	0.000	0.000
		Maximum	1809	1871	1927	1980	0
		Minimum	1809	1871	1927	1980	0
		SD	0	0	0	0	0

G1-BOC



Chromatogram Detector 1 Ch1

Sample Name	#	Title	Mn	Mw	Mz	Mz1	Mv
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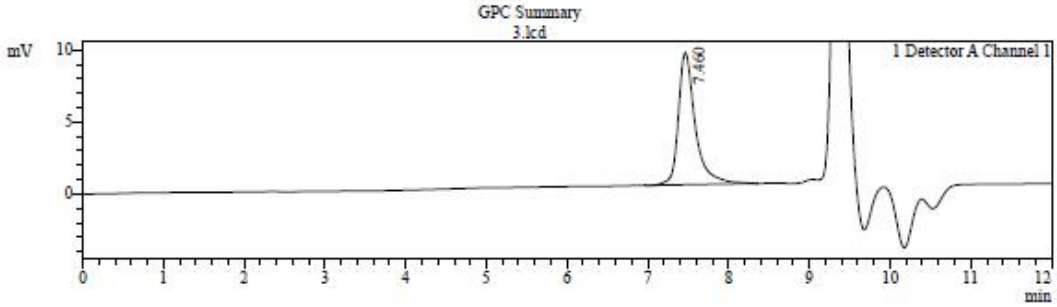
		Average	2215	2331	2431	2521	0
		%RSD	0.000	0.000	0.000	0.000	0.000
		Maximum	2215	2331	2431	2521	0
		Minimum	2215	2331	2431	2521	0
		SD	0	0	0	0	0

G3-BOC



Chromatogram Detector 1 Ch1

Sample Name	#	Title	Mn	Mw	Mz	Mz1	Mv
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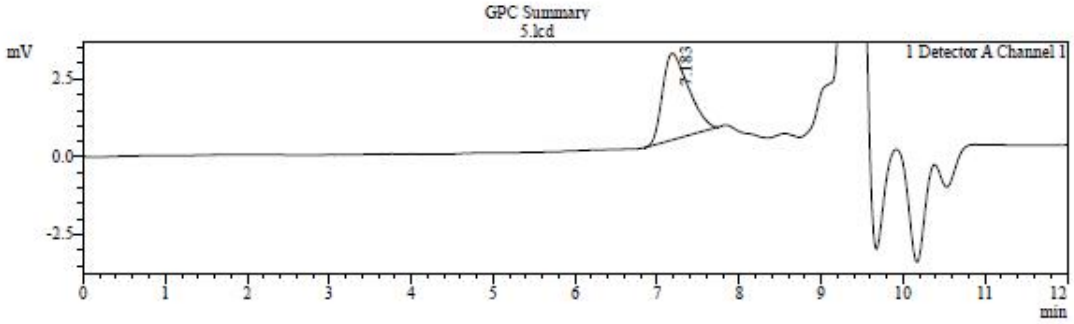
		%RSD	0.000	0.000	0.000	0.000	0.000
		Maximum	7477	8221	8789	9298	0
		Minimum	7477	8221	8789	9298	0
		SD	0	0	0	0	0

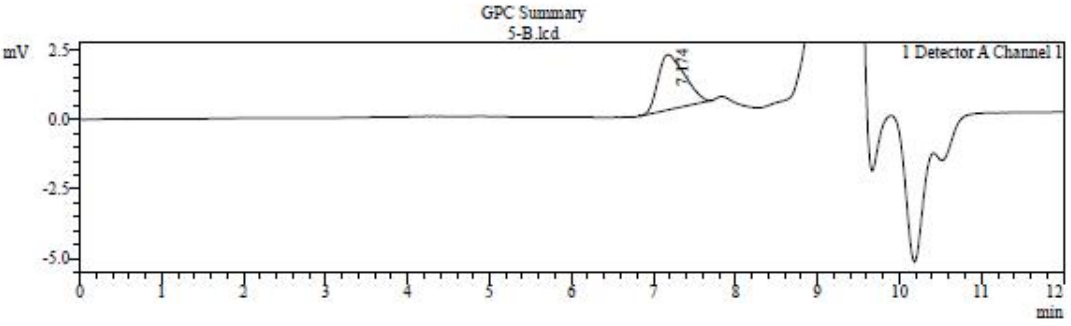
G5-BOC



Chromatogram Detector 1 Ch1

#	Title	Mn	Mw	Mz	Mz1	Mv
1	5.lcd	13141	14577	15929	17157	0
	Average	13141	14577	15929	17157	0
	%RSD	0.000	0.000	0.000	0.000	0.000
	Maximum	13141	14577	15929	17157	0
	Minimum	13141	14577	15929	17157	0
	SD	0	0	0	0	0

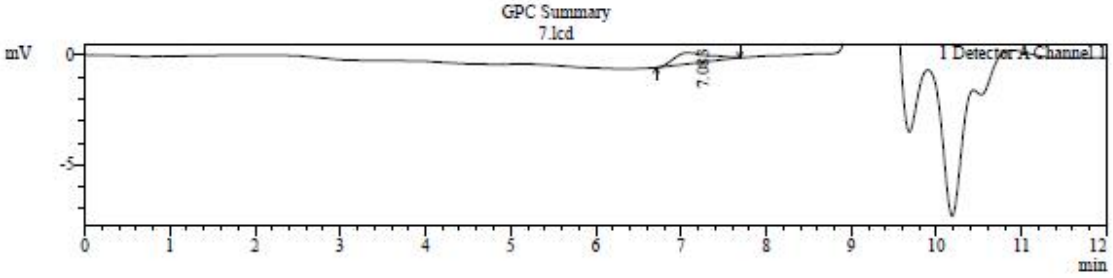
G5-BOC longer time of irradiation



Chromatogram Detector 1 Ch1

Sample Name	#	Title	Mn	Mw	Mz	Mz1	Mv
5-B	1	5-B.lcd	13476	14901	16276	17547	0
		Average	13476	14901	16276	17547	0
		%RSD	0.000	0.000	0.000	0.000	0.000
		Maximum	13476	14901	16276	17547	0
		Minimum	13476	14901	16276	17547	0
		SD	0	0	0	0	0

G7-BOC



Chromatogram Detector 1 Ch1

Sample Name	#	Title	Mn	Mw	Mz	Mzl	Mv
7	1	7.lcd	15652	18517	21208	23537	0
		Average	15652	18517	21208	23537	0
		%RSD	0.000	0.000	0.000	0.000	0.000
		Maximum	15652	18517	21208	23537	0
		Minimum	15652	18517	21208	23537	0
		SD	0	0	0	0	0