Electronic Supplementary Material (ESI) for RSC Advances.

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF TRIAZINE DENDRIMERS WITH DABCO GROUPS

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Contributions

A majority of the synthesis work was accomplished by R.S.S. Z.M.A. contributed to the synthetic effort. Both R.S.S. and Z.M.A. collected the biological data. Z.M.A. maintained the cell preparations. H.H.C. contributed to the design of the study and one synthetic compound. S.M.G. supervised the biological assays. E.E.S. supervised the synthetic efforts. R.S.S. and Z.M.A. assembled the manuscript. S.M.G. and E.E.S. supervised communication of the efforts.

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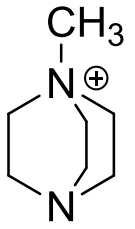
General Experimental

Microwave: A CEM SP Discovery microwave was utilized for these experiments. Reactions were performed in dynamic mode wherein microwave power is modulated to maintain the set point temperature.

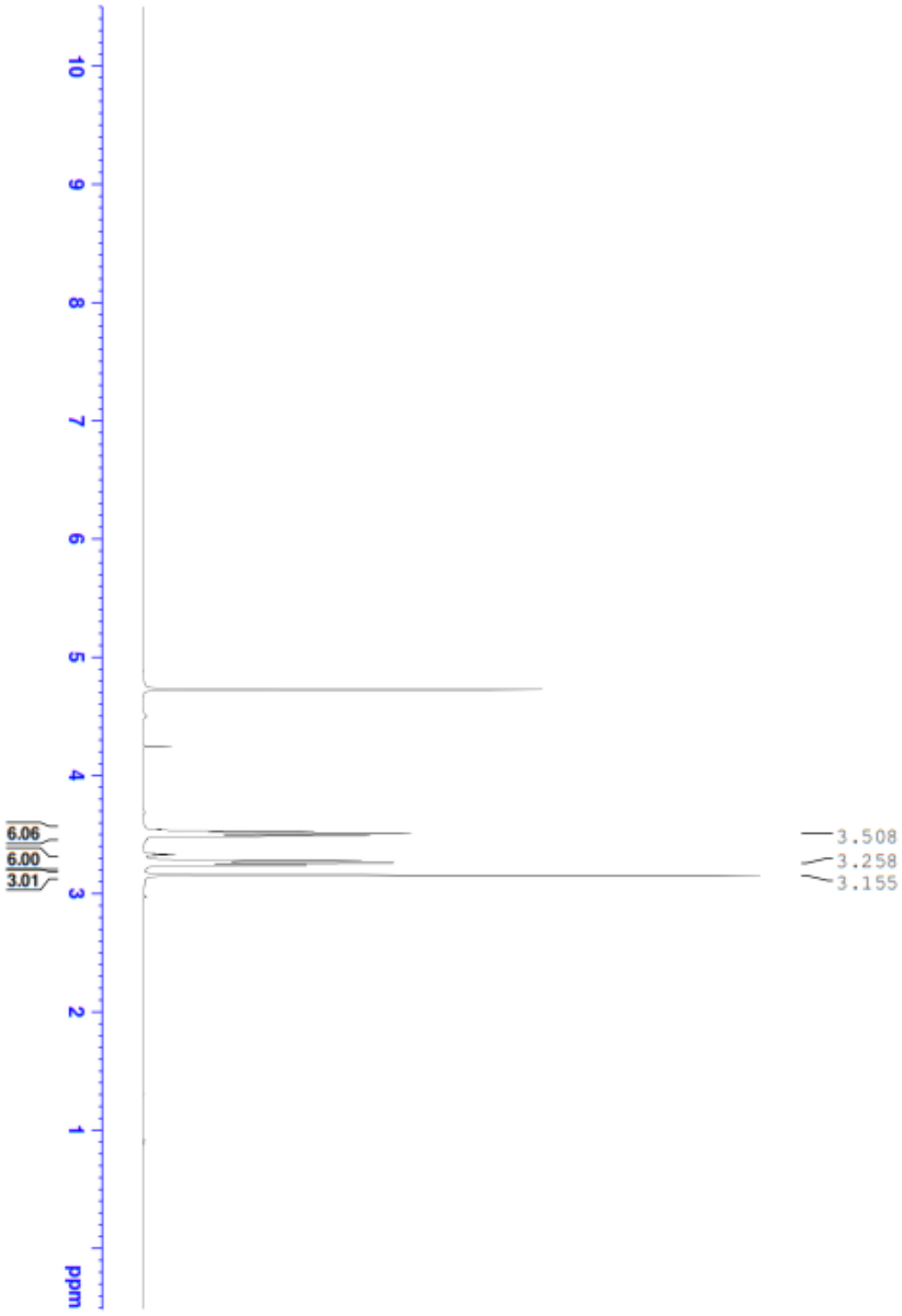
Automated Chromatography: A Combiflash RF Automated Chromatographer (Teledyne ISCO) was used for these experiments. All the purifications were performed using a solid loading method.

Compound **1-Me:**

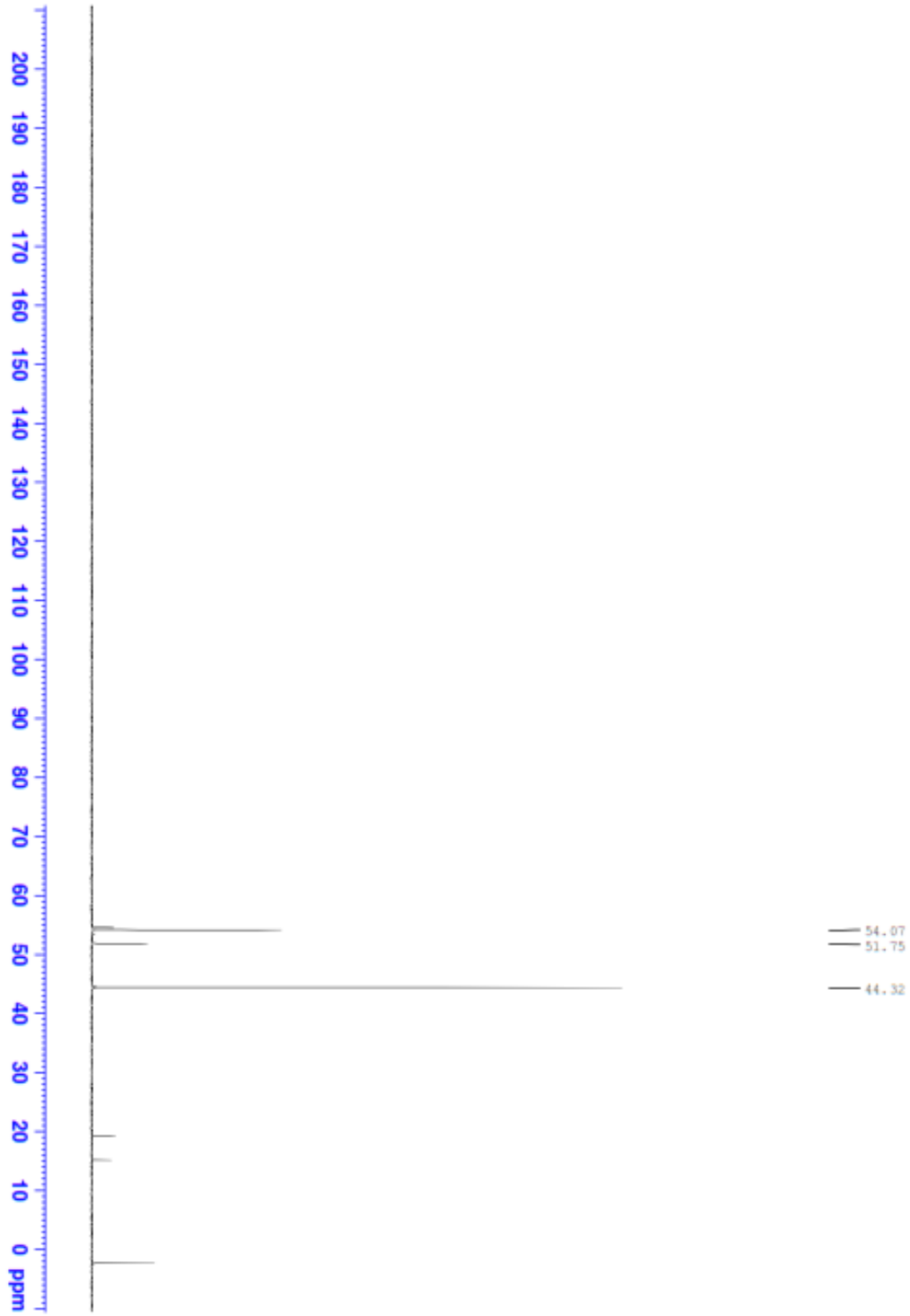
Methyl iodide (0.5 ml, 8.9 mmol) was added slowly to a solution of DABCO (1 g, 8.9 mmol) in hexane (25 ml) at 0^{o}C and stirred for 1 hr at room temperature. The solvent was evaporated, and residue was washed with hexanes (100 ml) and dried to yield a pale yellow solid (1.02 g, 90%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.50 (t, 6H, DABCO), δ 3.25 (t, 6H, DABCO), δ 3.15 (t, 3H, -C**H$_3$**); ^{13}C NMR (100 MHz, D_2O) 54.0, 44.3 (DABCO), 51.7 (-**C**H_3).



SI Figure 1. ^{1}H NMR spectrum of **1-Me**

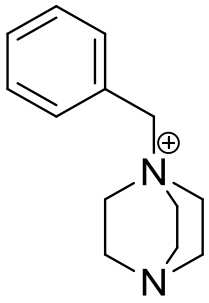


SI Figure 2. ^{13}C NMR spectrum of compound **1-Me**

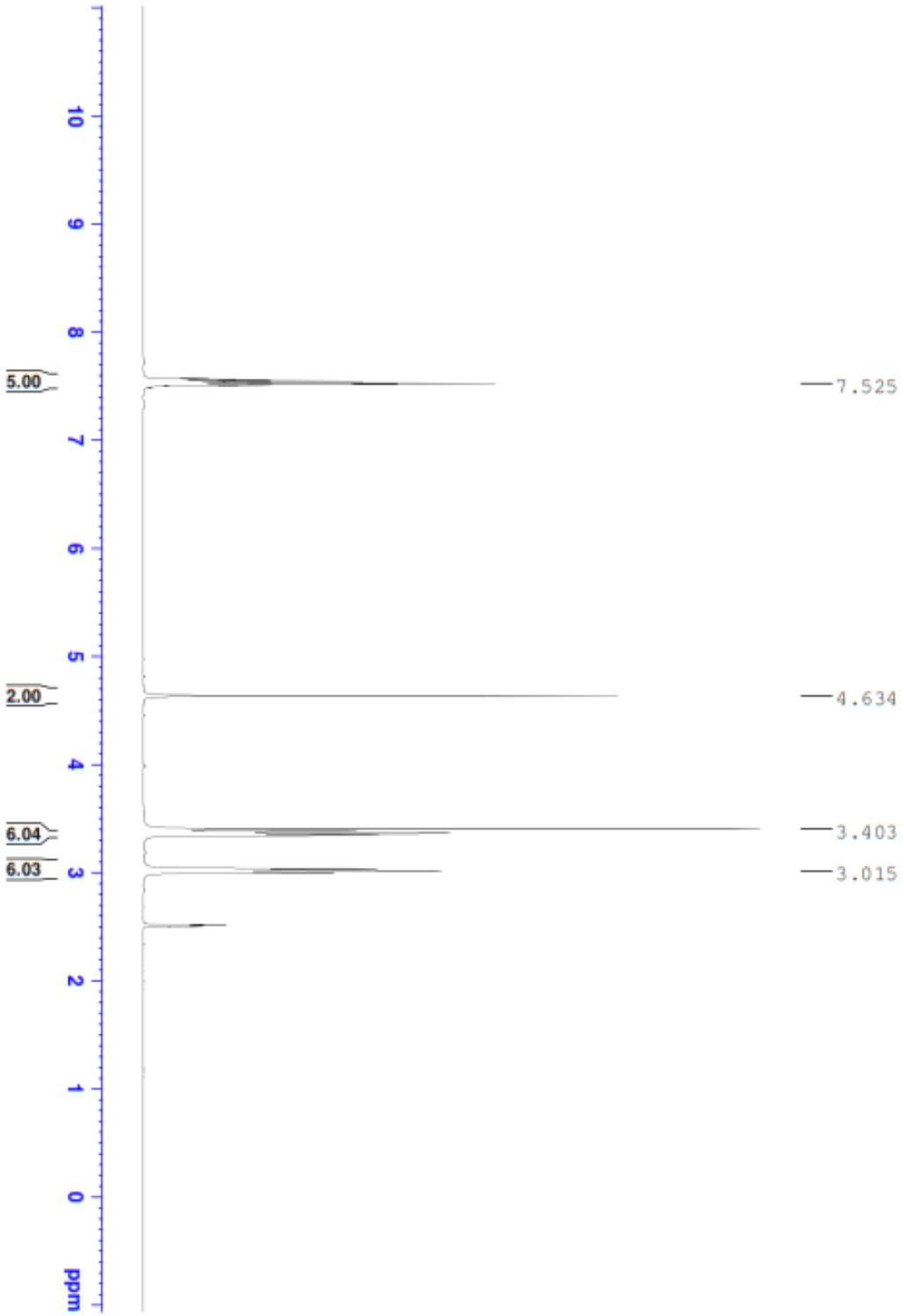


Compound **1-Bz:**

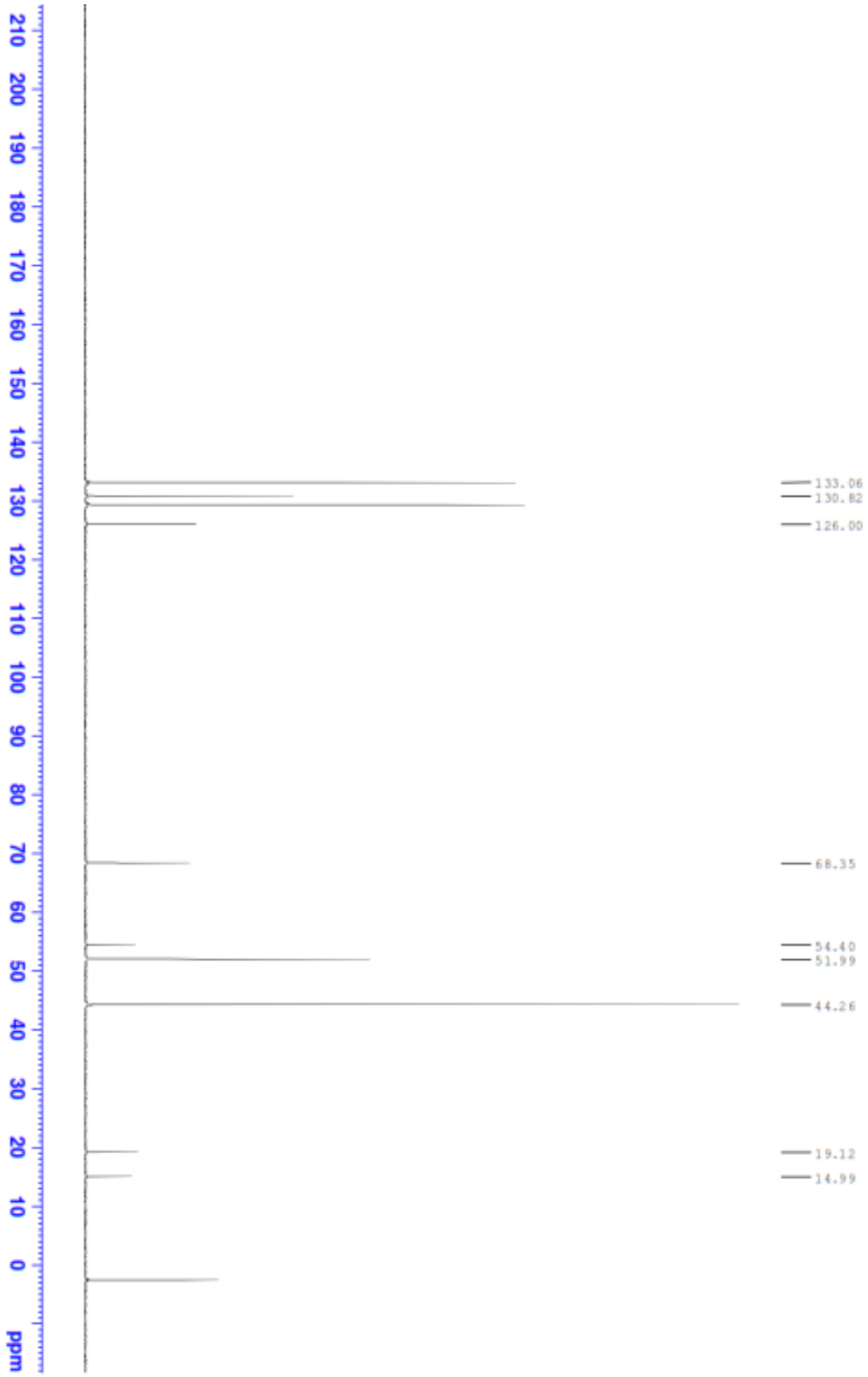
Benzyl Chloride (5.13 ml, 44.6 mmol) is added slowly to the solution of DABCO (5.03 g, 44.6 mmol) in THF (50 ml) at room temperature and a white precipitate is formed after 10 min. The solvent was evaporated and the precipitate was washed with ethyl acetate and hexane and dried to yield a white solid (10.25 g, 96.24%). ^{1}H NMR (400 MHz, DMSO) δ 7.52 ($C_6\mathbf{H_5}$), δ 4.63 ($C_\mathbf{6}H_5$-C$\mathbf{H_2}$), δ 3.40 (t, 6H, DABCO), δ 3.01 (t, 6H, DABCO); ^{13}C NMR (100 MHz, D_2O) 133.0, 130.8, 129.2, 126.0 ($\mathbf{C_6}H_5$-), 68.3 ($\mathbf{C_6}H_5$-$\mathbf{C}H_2$), 51.9, 44.2 (DABCO).



SI Figure 3. ^{1}H NMR spectrum of compound **1-Bz**

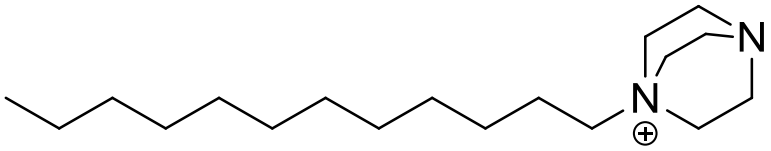


SI Figure 4. ^{13}C NMR spectrum of compound **1-Bz**

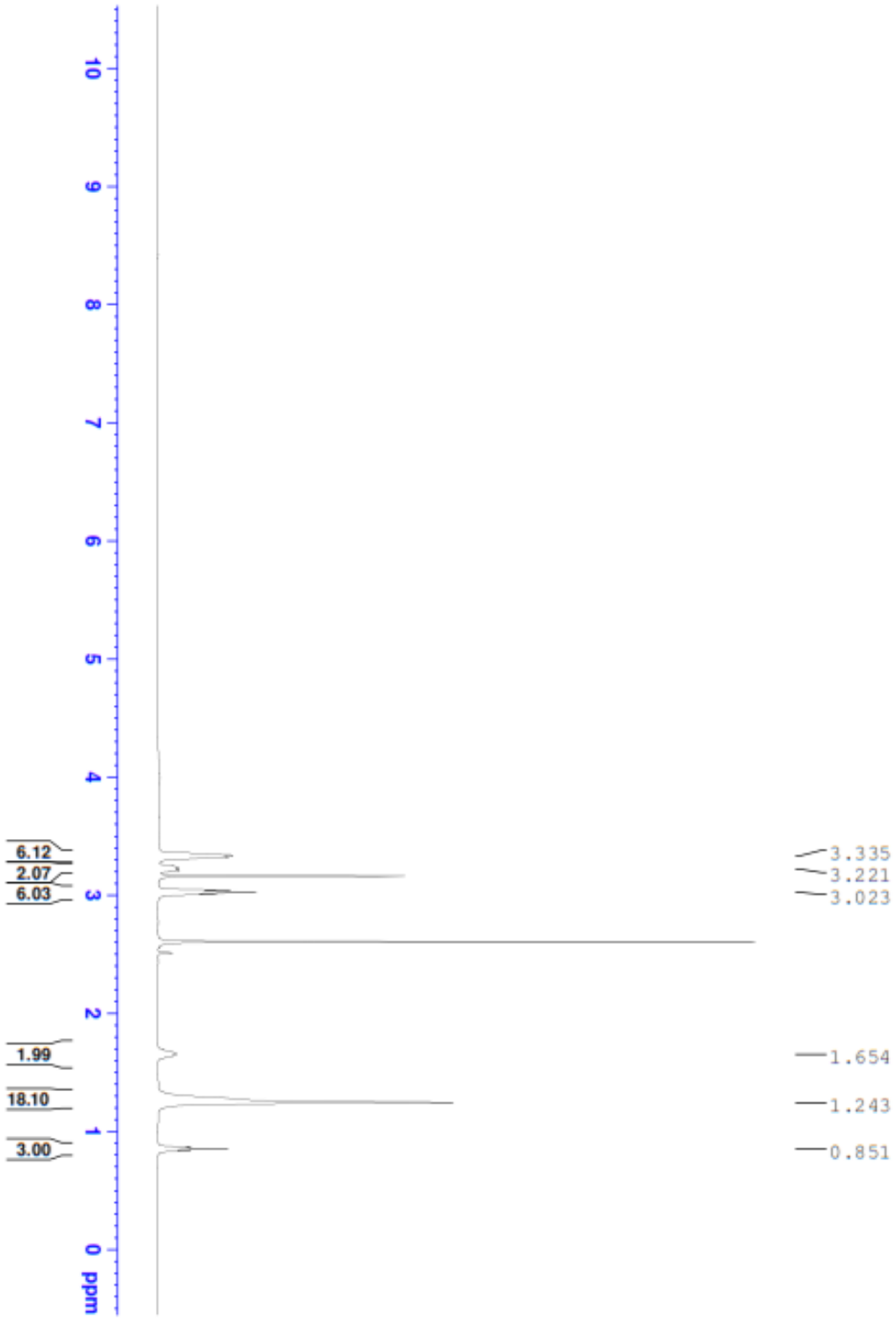


Compound **1-C12:**

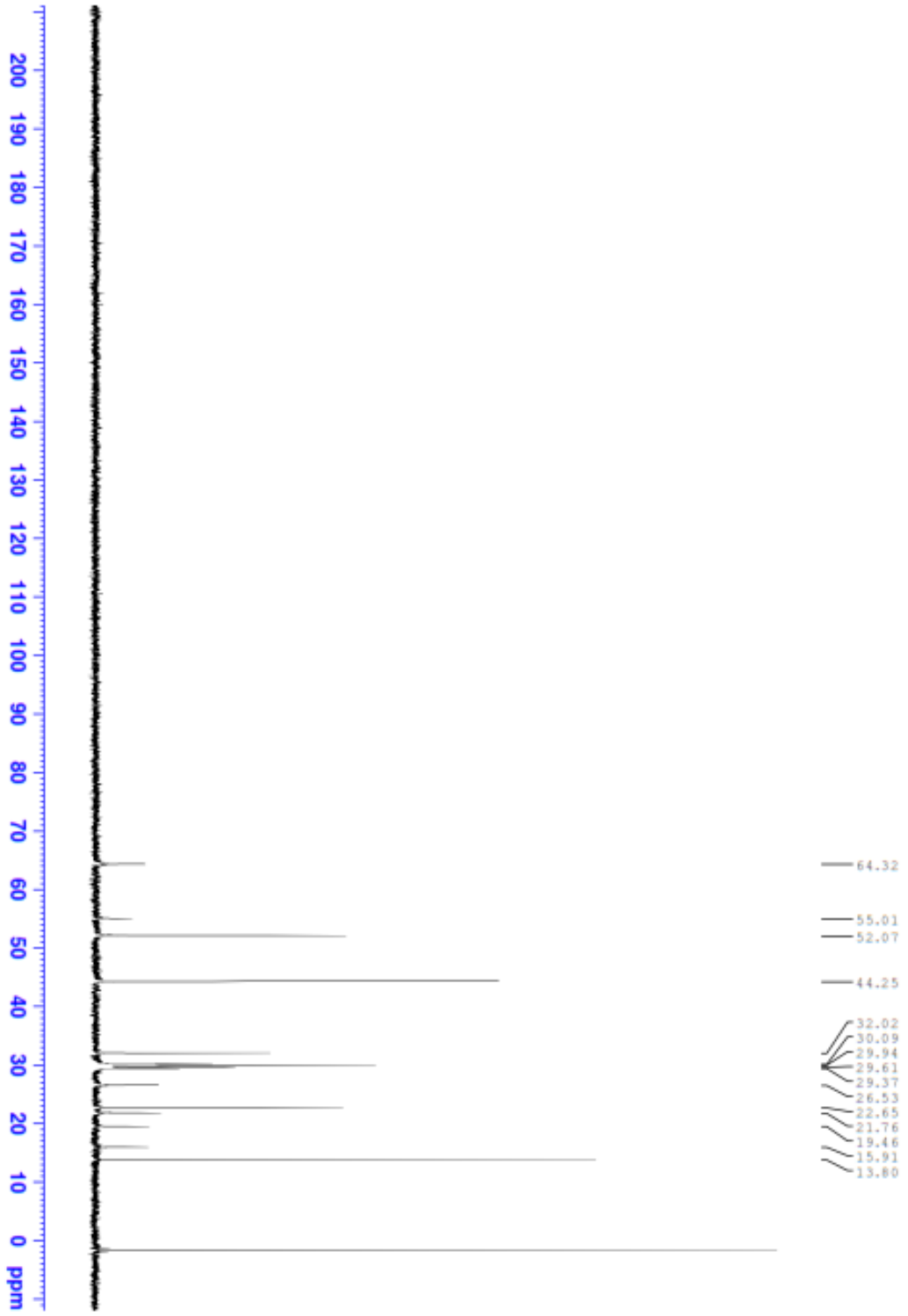
1-Bromododecane (2.5 ml, 10.4 mmol) was added slowly to a solution of DABCO (2.3 g, 20.8 mmol) in methanol (21 ml) at 0°C and stirred for 24 hrs at room temperature. The solvent was evaporated, and the residue was washed with (100 ml) portions of diethyl ether and dichloromethane to yield a pale white solid (5.04 g, 86%). ^{1}H NMR (400 MHz, DMSO) δ 3.33 (t, 6H, DABCO), δ 3.22 (t, 2H, -$CH_3(CH_2)_9CH_2C\mathbf{H_2}$-), δ 3.02 (t, 6H, DABCO), δ 1.65 (m, 2H, $CH_3(CH_2)_9C\mathbf{H_2}CH_2$-), δ 1.24 (m, 18H, $CH_3(C\mathbf{H_2})_9CH_2CH_2$-), δ 0.85 (t, 3H, -$C\mathbf{H_3}$); ^{13}C NMR (100 MHz, D_2O) 64.8 ($CH_3(CH_2)_9CH_2\mathbf{C}H_2$-), 52.0, 44.2 (DABCO), 32.0 ($CH_3(CH_2)_9\mathbf{C}H_2CH_2$-), 29.9, 29.6, 26.5, 22.6, 21.7, 19.4, 15.9 ($CH_3(\mathbf{C}H_2)_9CH_2CH_2$), 13.8 ($\mathbf{C}H_3(CH_2)_9CH_2CH_2$-).



SI Figure 5. ^{1}H NMR spectrum of compound **1-C12**

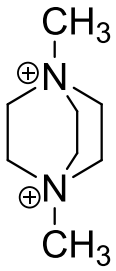


SI Figure 6. ^{13}C NMR spectrum of compound **1-C12**

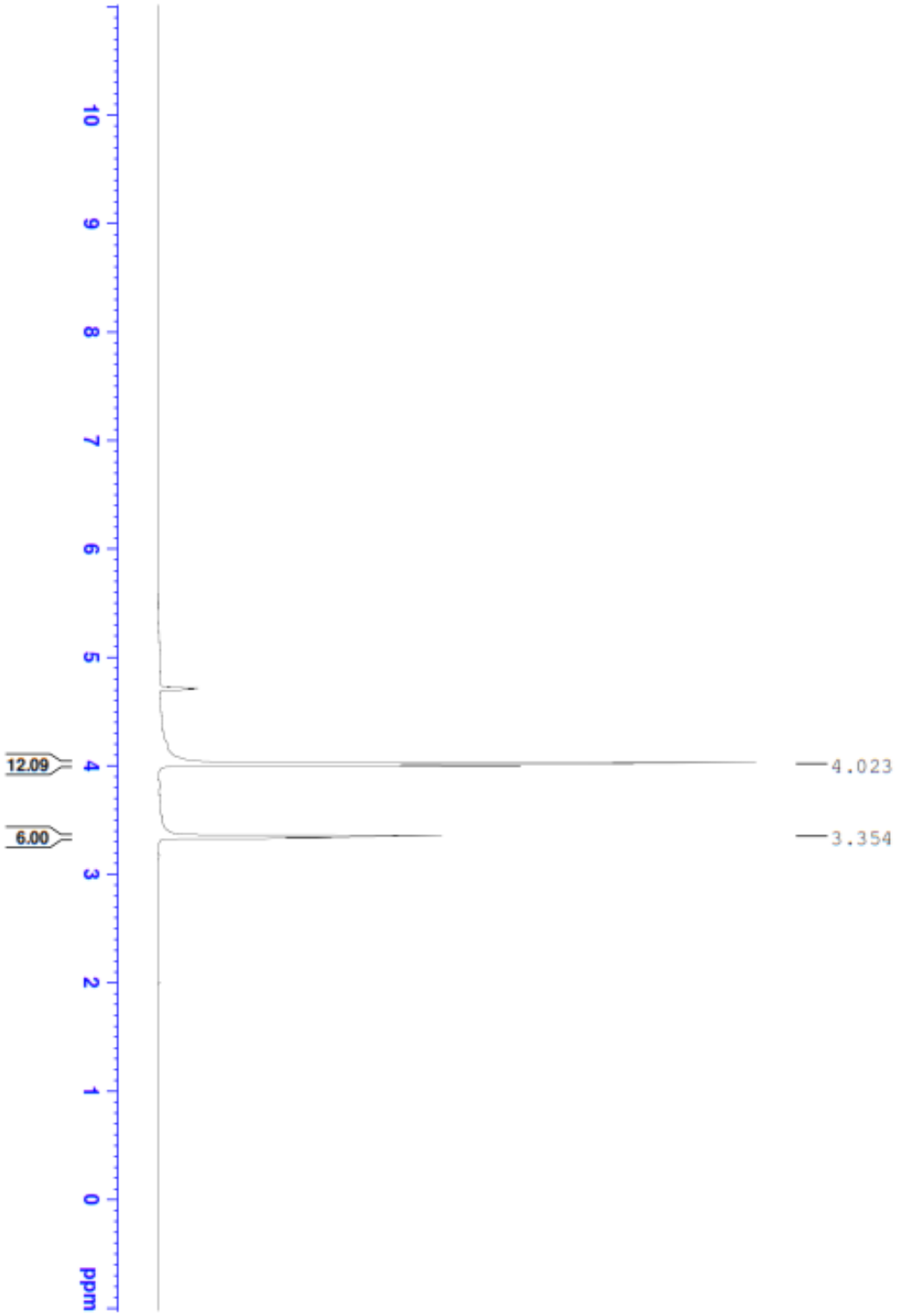


Compound **1-(Me)$_2$:**

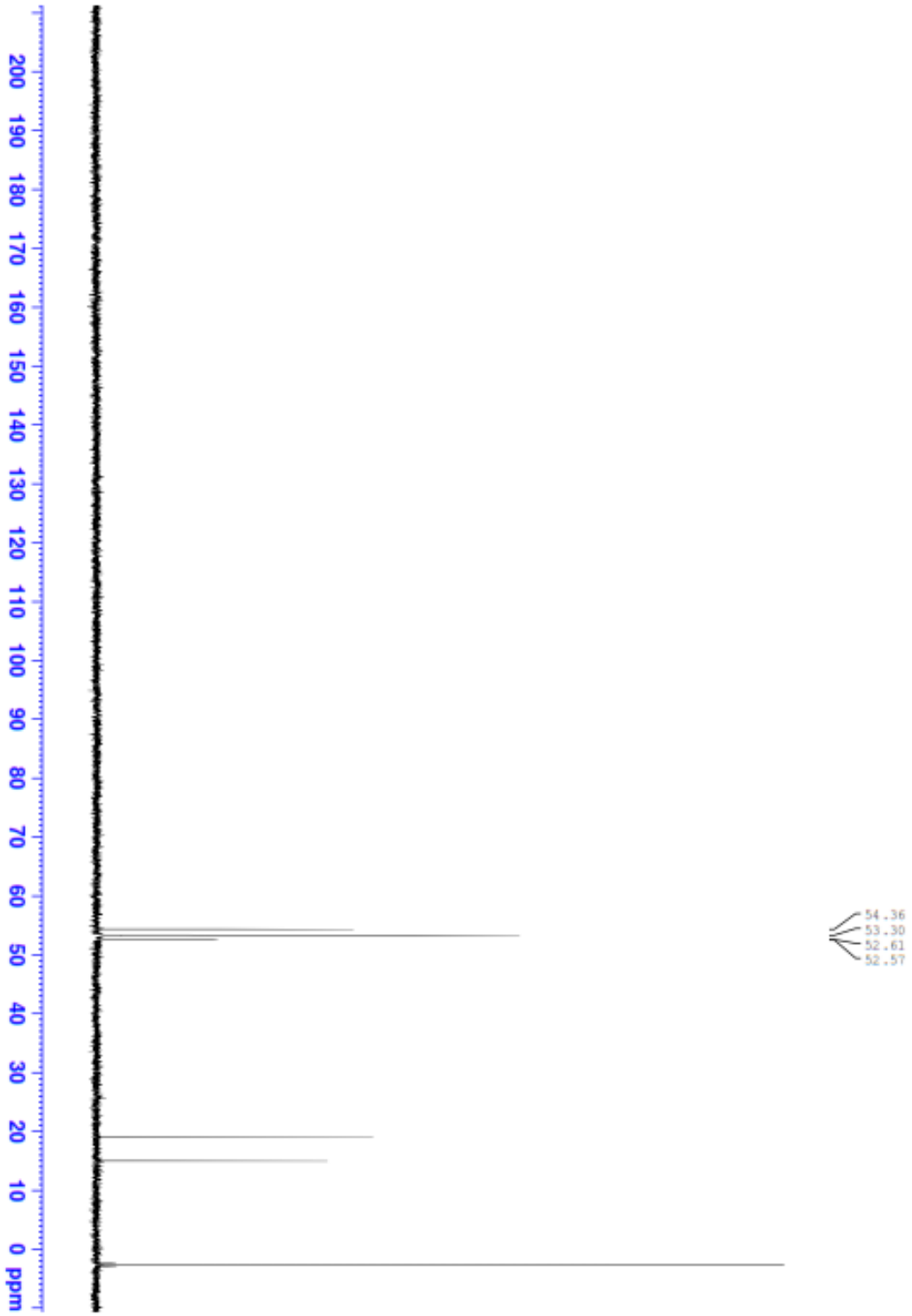
Methyl iodide (0.025 ml, 0.4 mmol) was added slowly to a solution of **1-Me** (50 mg, 0.4 mmol) in Acetonitrile (2 ml) at 0^{o}C and stirred for 1 hr at room temperature. The solvent was evaporated and the precipitate was washed with portions (10 ml) of diethyl ether and acetonitrile to yield a white solid (41.53 mg, 73%). ^{1}H NMR (400 MHz, D_2O) δ 4.02 (t, 12H, DABCO), δ 3.35 (t, 6H, -C**H$_3$**); ^{13}C NMR (100 MHz, D_2O) 54.3, 53.3 (DABCO), 52.5 (-**C**H_3).



SI Figure 7. ^{1}H NMR spectrum of compound **1-(Me)$_2$**

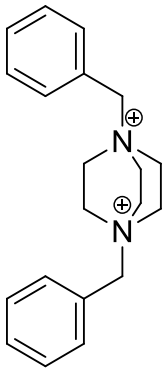


SI Figure 8. ^{13}C NMR spectrum of compound **1-(Me)$_2$**

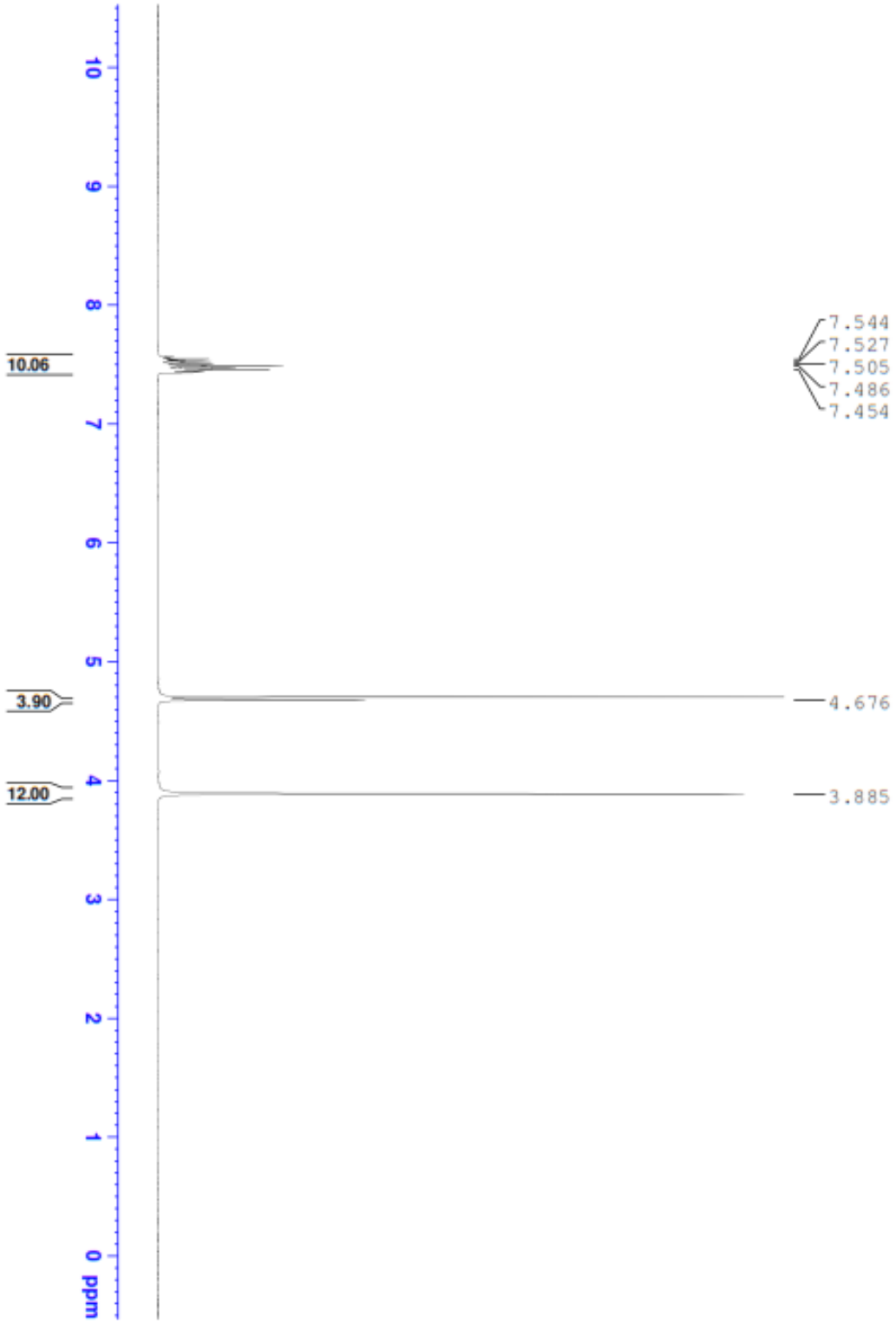


Compound **1-(Bz)$_2$:**

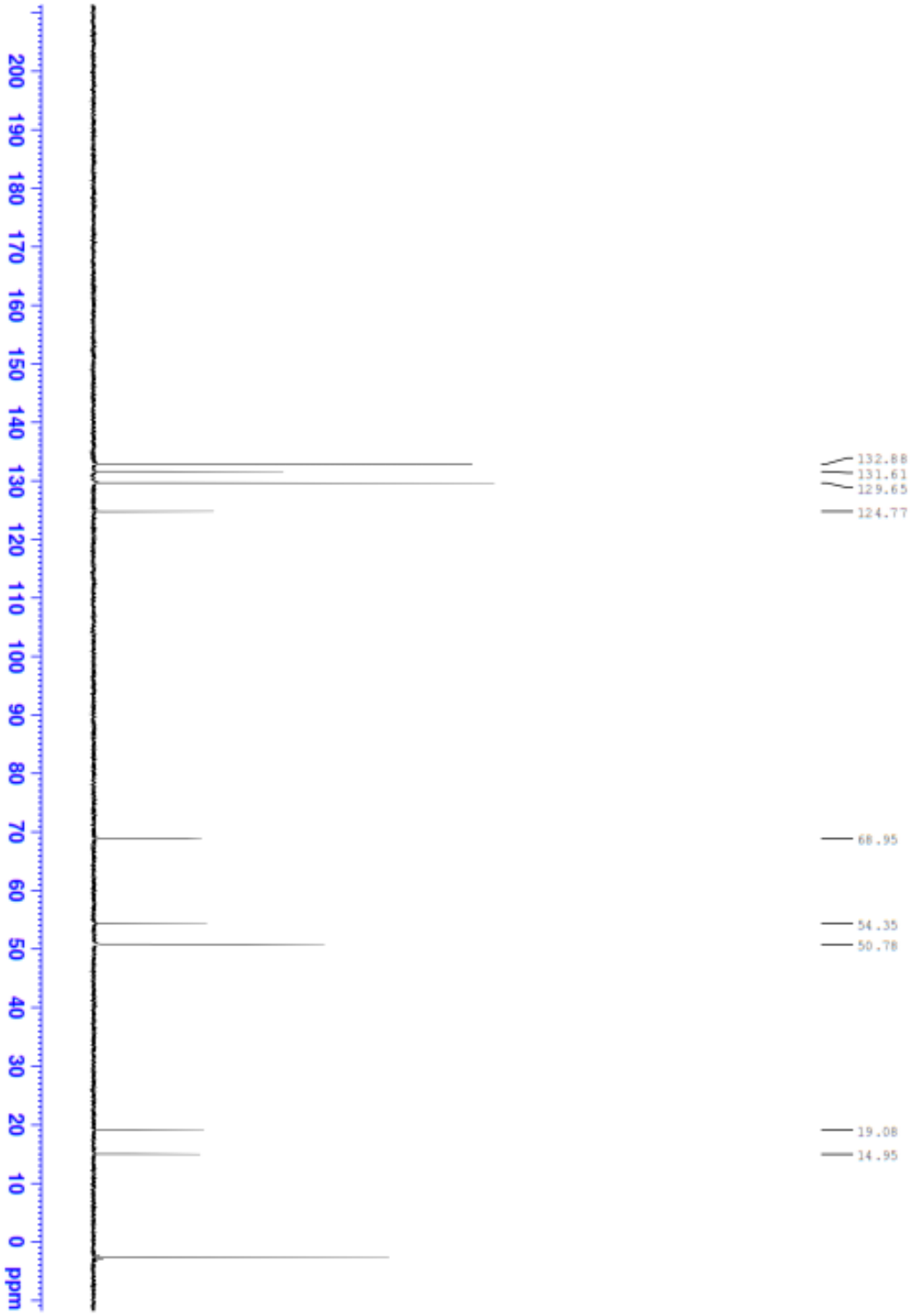
Benzyl Chloride (0.04 ml, 0.33mmol) was added slowly to a solution of **1-Bz** (60 mg, 0.33 mmol) in THF (3 ml) and stirred for 48 hrs at room temperature. The solvent was evaporated and the precipitate was washed with portions (10 ml) of diethyl ether and acetonitrile to yield a white solid (66.24 mg, 75%). ^{1}H NMR (400 MHz, D_2O) δ 7.54 (10H, C_6**H$_5$**), δ 4.67 (s, 4H, C_6H_5-C**H$_2$**), δ 3.88 (t, 6H, DABCO); ^{13}C NMR (100 MHz, D_2O) 132.8, 131.6, 129.6, 124.7 (**C$_6$**H_5-), 68.9 (**C$_6$**H_5-**C**H_2), 54.3, 50.7 (DABCO).



SI Figure 9. ^{1}H NMR spectrum of compound **1-(Bz)$_2$**

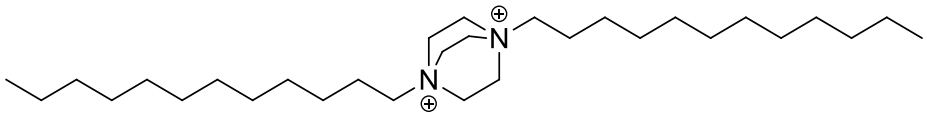


SI Figure 10. ^{13}C NMR spectrum of compound **1-(Bz)$_2$**

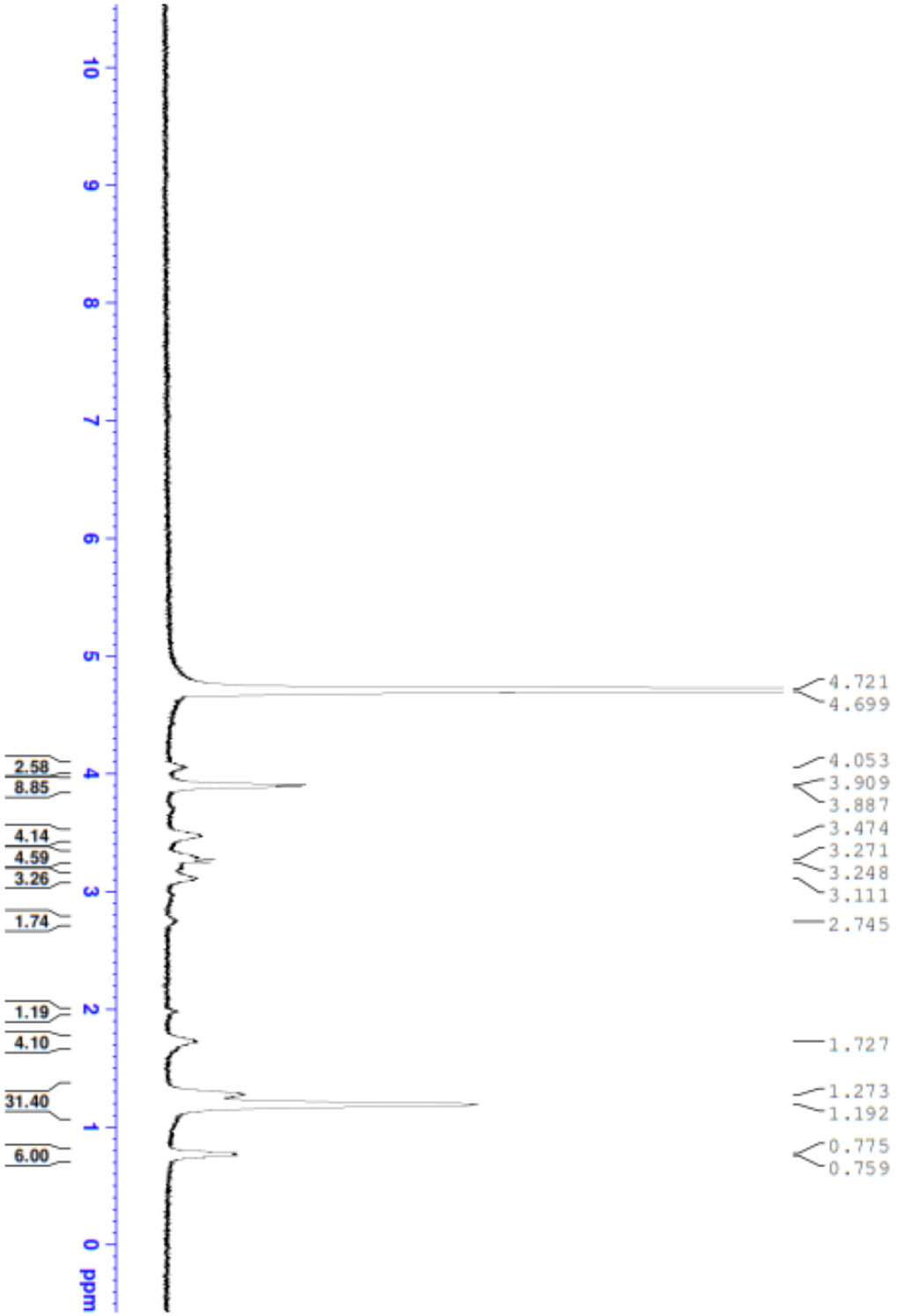


Compound **1-(C12)$_2$**

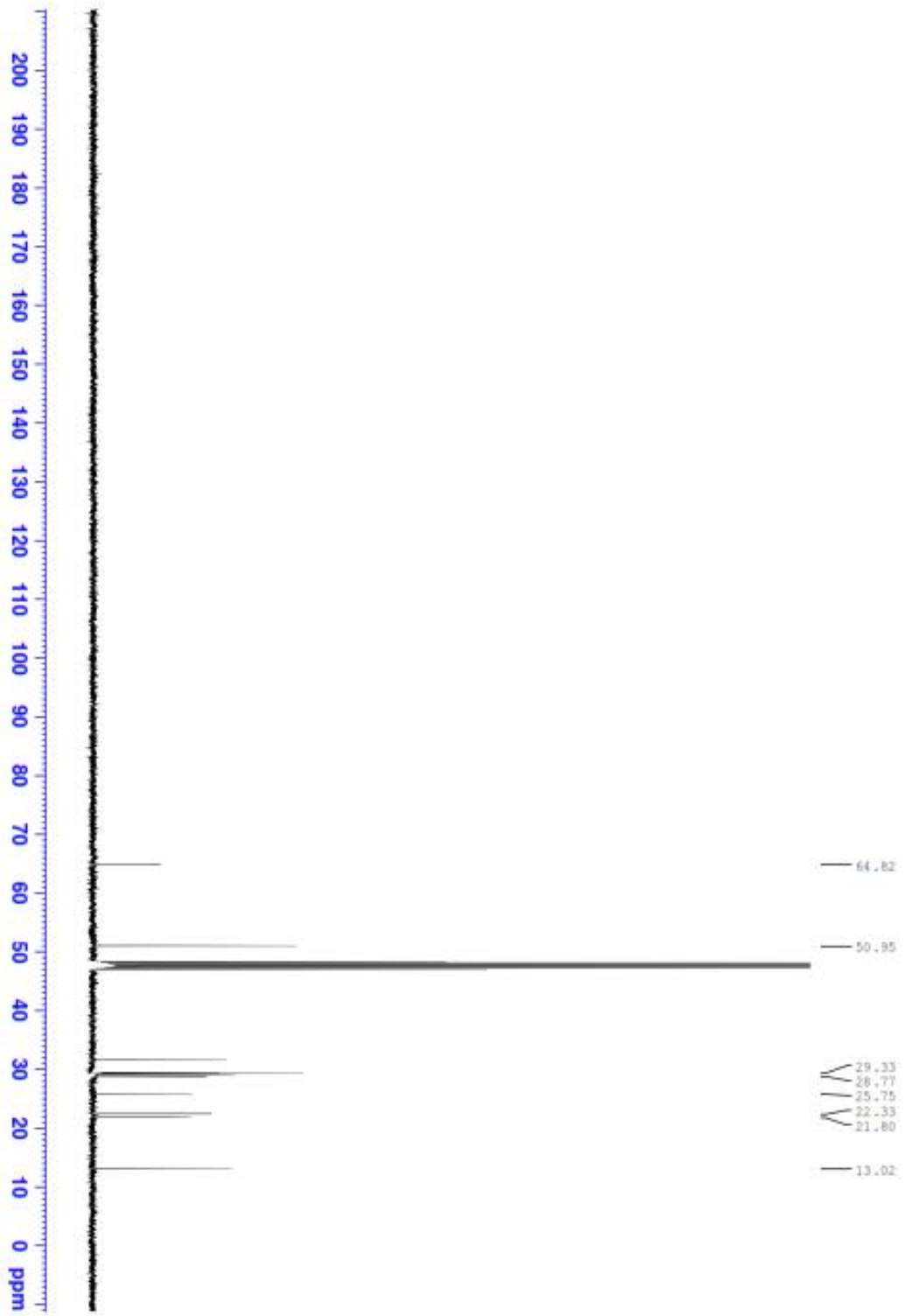
1-Bromododecane (0.05 ml, 0.2 mmol) was added slowly to a solution of **1-C12** (50 mg, 0.18 mmol) in Acetonitrile (2 ml) at 0^{o}C and stirred for 48 hrs at room temperature. The solvent was evaporated and the precipitate was washed with portions (10 ml) of diethyl ether and acetonitrile to yield a white solid (42.2 mg, 52%). ^{1}H NMR (400 MHz, D_2O)) δ 4.05 (t, 12H, DABCO), δ 3.47 (m, 4H, -$CH_3(CH_2)_9CH_2C\mathbf{H_2}$-), δ 3.24 (m, 4H, $CH_3(CH_2)_8C\mathbf{H_2}CH_2CH_2$ δ 1.72 (m, 4H, $CH_3(CH_2)_9C\mathbf{H_2}CH_2$-), δ 1.27 (m, 32H, $CH_3(C\mathbf{H_2})_8CH_2CH_2CH_2$-), δ 0.77 (t, 6H, -$C\mathbf{H_3}$). ^{13}C NMR (100 MHz, CD_3OD) 64.8 ($CH_3(CH_2)_9CH_2\mathbf{C}H_2$-), 50.9 (DABCO), 32.0 ($CH_3(CH_2)_9\mathbf{C}H_2CH_2$-), 29.3, 28.7, 25.7, 22.3, 21.8 ($CH_3(\mathbf{C}H_2)_9CH_2CH_2$-), 13.0 ($C\mathbf{H_3}(CH_2)_9CH_2CH_2$-).



SI Figure 11. ^{1}H NMR spectrum of compound **1-(C12)$_2$**

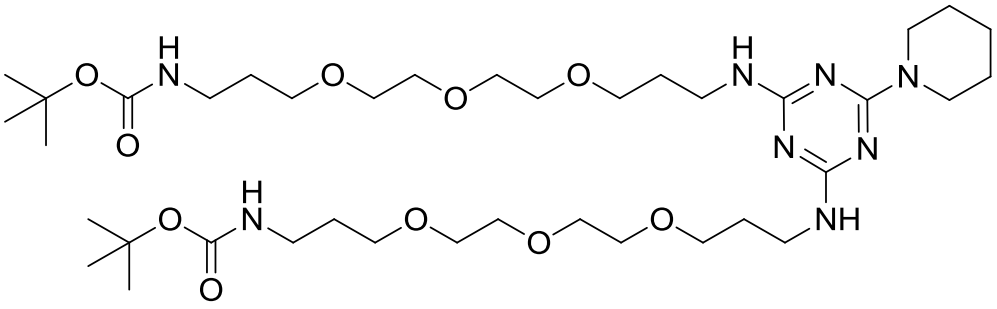


SI Figure 12. ^{13}C NMR spectrum of compound **1-(C12)$_2$**

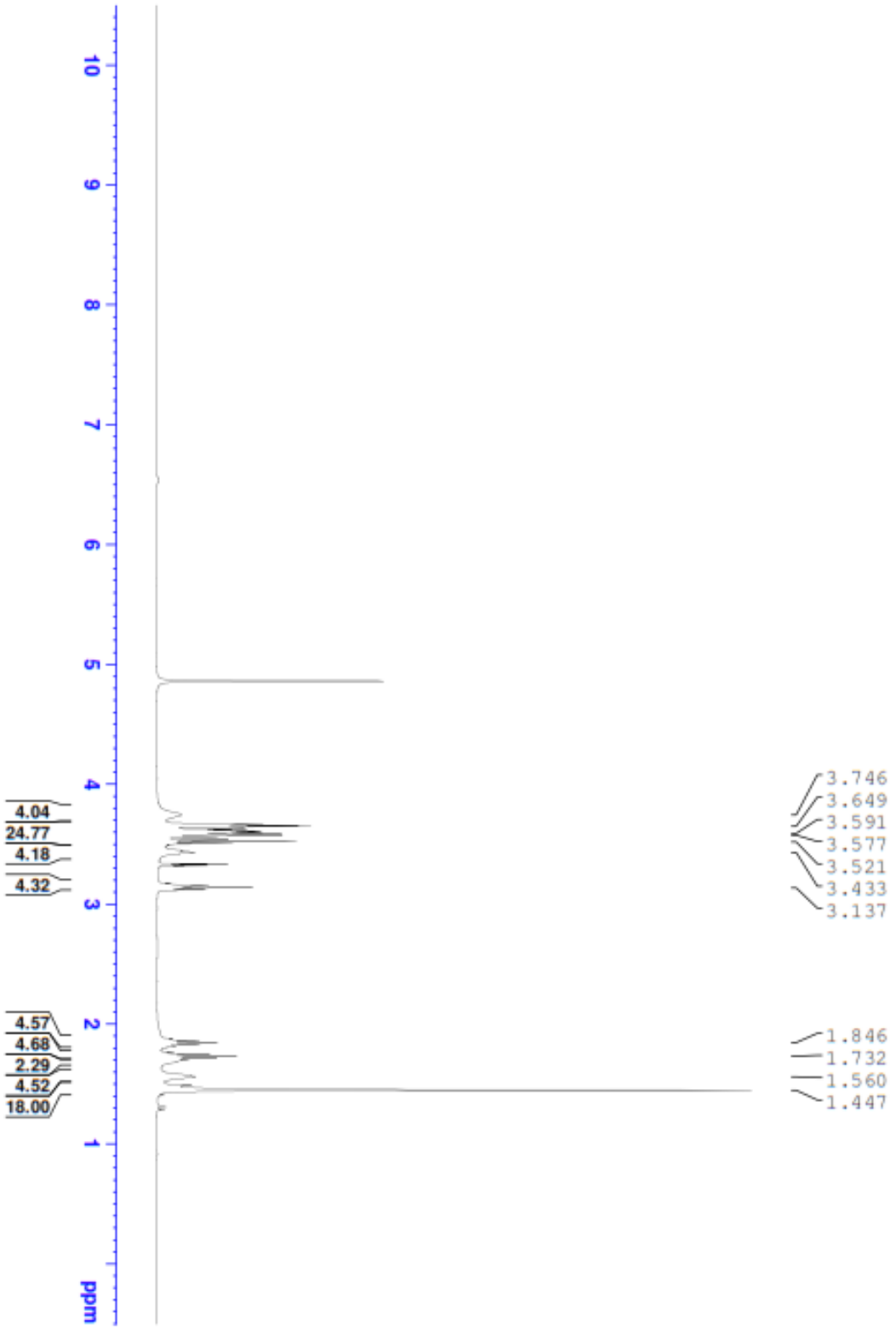


Compound **8a:**

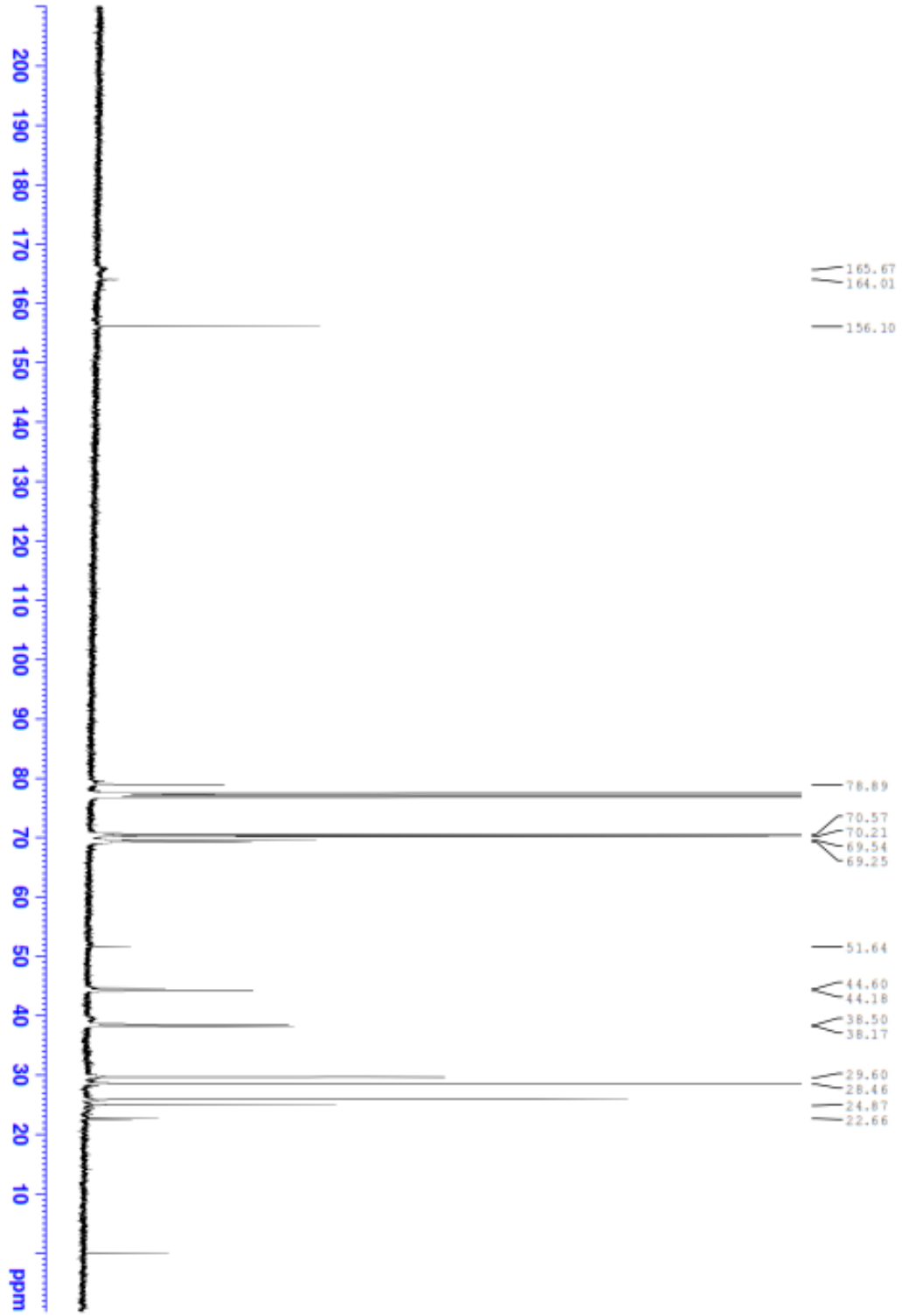
A solution of **7** (1.5 g, 2 mmol) with piperidine (510 mg, 6 mmol) and DIPEA (1.04 ml, 6 mmol) was stirred for 2 minutes in 20 ml of acetonitrile. The solution was irradiated in the microwave at 75ºC for 45 min. The solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and evaporated under vacuum. The crude product was purified using automated chromatography to yield a pale yellow oil (1.44 g 90%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.74 (t, 4H,-$CH_2C\mathbf{H_2}$-N-$C\mathbf{H_2}CH_2CH_2$-), δ 3.64-3.52 (t, 24H, $C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}$), δ 3.43 (m, 4H, C_3N_3-NHC$\mathbf{H_2}CH_2CH_2O$); δ 3.13 (m, 4H, -C(O)-NHC$\mathbf{H_2}CH_2CH_2O$), δ 1.84-1.73 (m, 8H, -$OCH_2C\mathbf{H_2}CH_2$-NH-), δ 1.63-1.56 (m, 6H, -$C\mathbf{H_2}CH_2$-N-$CH_2C\mathbf{H_2}C\mathbf{H_2}$-), 1.44 (s, 18H, -C($C\mathbf{H_3}$)$_3$); 13C NMR (100 MHz, $CDCl_3$) 165.6 ($\mathbf{C}_3N_3$), 164.0 (**C**O), 156.1 ($\mathbf{C}_3N_3$), 78.8 -**C**$(CH_3)_3$), 70.5 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 70.2 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 69.5 ($NHCH_2CH_2\mathbf{C}H_2O$), 69.2 ($NHCH_2CH_2\mathbf{C}H_2O$), 51.6 (-$CH_2\mathbf{C}H_2$-N-$\mathbf{C}H_2CH_2$-), 44.6, 44.1 ($NH\mathbf{C}H_2CH_2CH_2O$), 38.5, ($NH\mathbf{C}H_2CH_2CH_2O$), 38.1, 29.6 ($NHCH_2\mathbf{C}H_2CH_2O$), 28.4 (C($\mathbf{C}H_3)_3$), 24.8 (-$\mathbf{C}H_2CH_2$-N-$CH_2\mathbf{C}H_2$-), 22.6 (-$CH_2CH_2$-N-$CH_2CH_2\mathbf{C}H_2$-); MS (ESI-TOF) calcd for $C_{38}H_{72}N_8O_{10}$ 801.03, found 801.59 $(M)^+$.



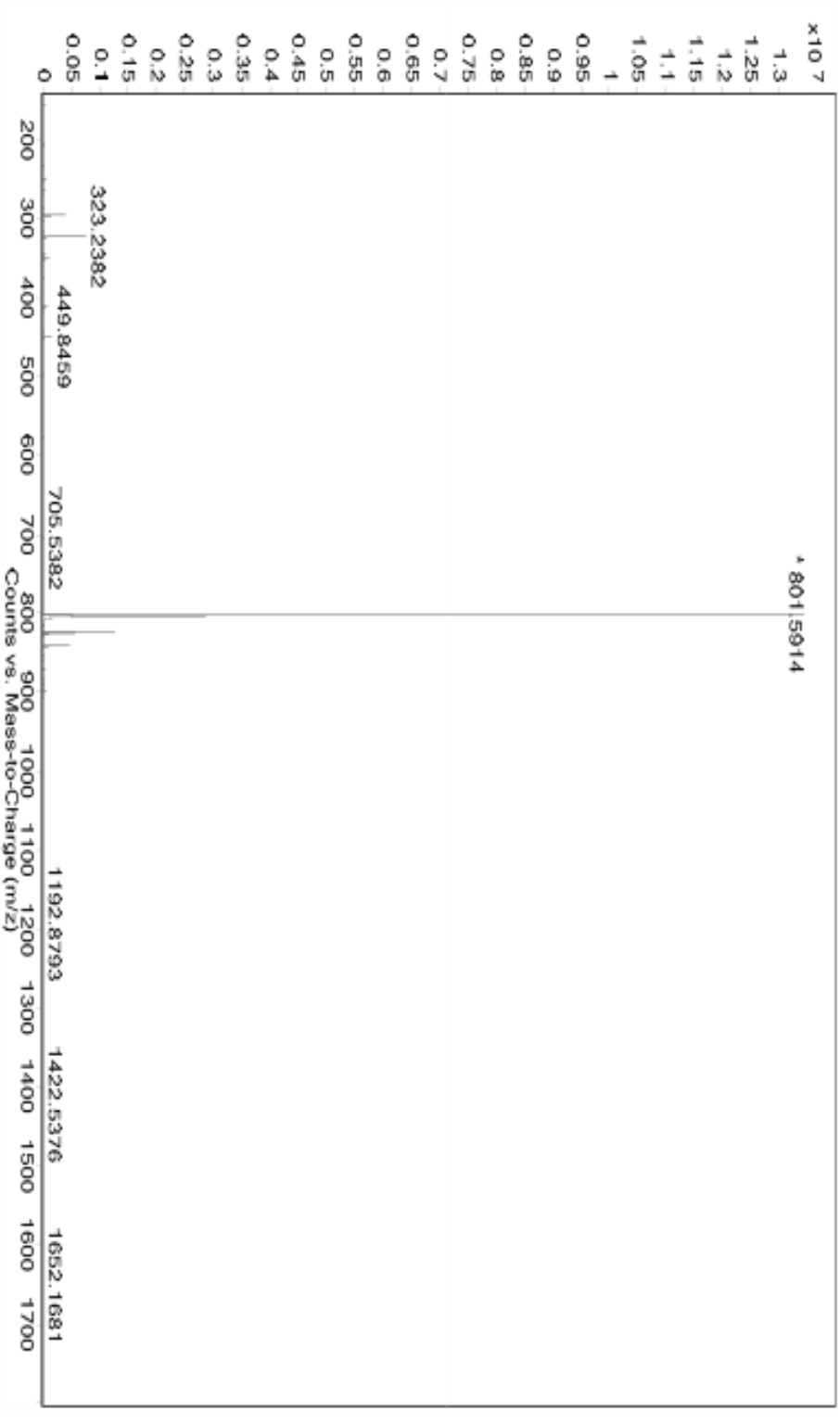
SI Figure 13. ^{1}H NMR spectrum of compound **8a.**



SI Figure 14. ^{13}C NMR spectrum of compound **8a.**

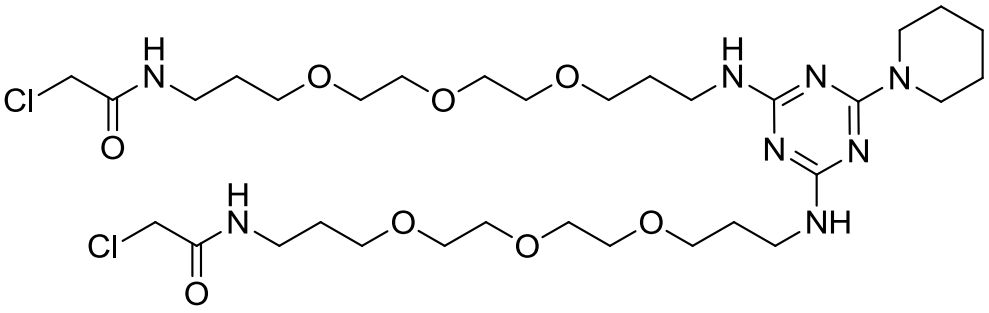


SI Figure 15. Mass spectrum of compound **8a.**

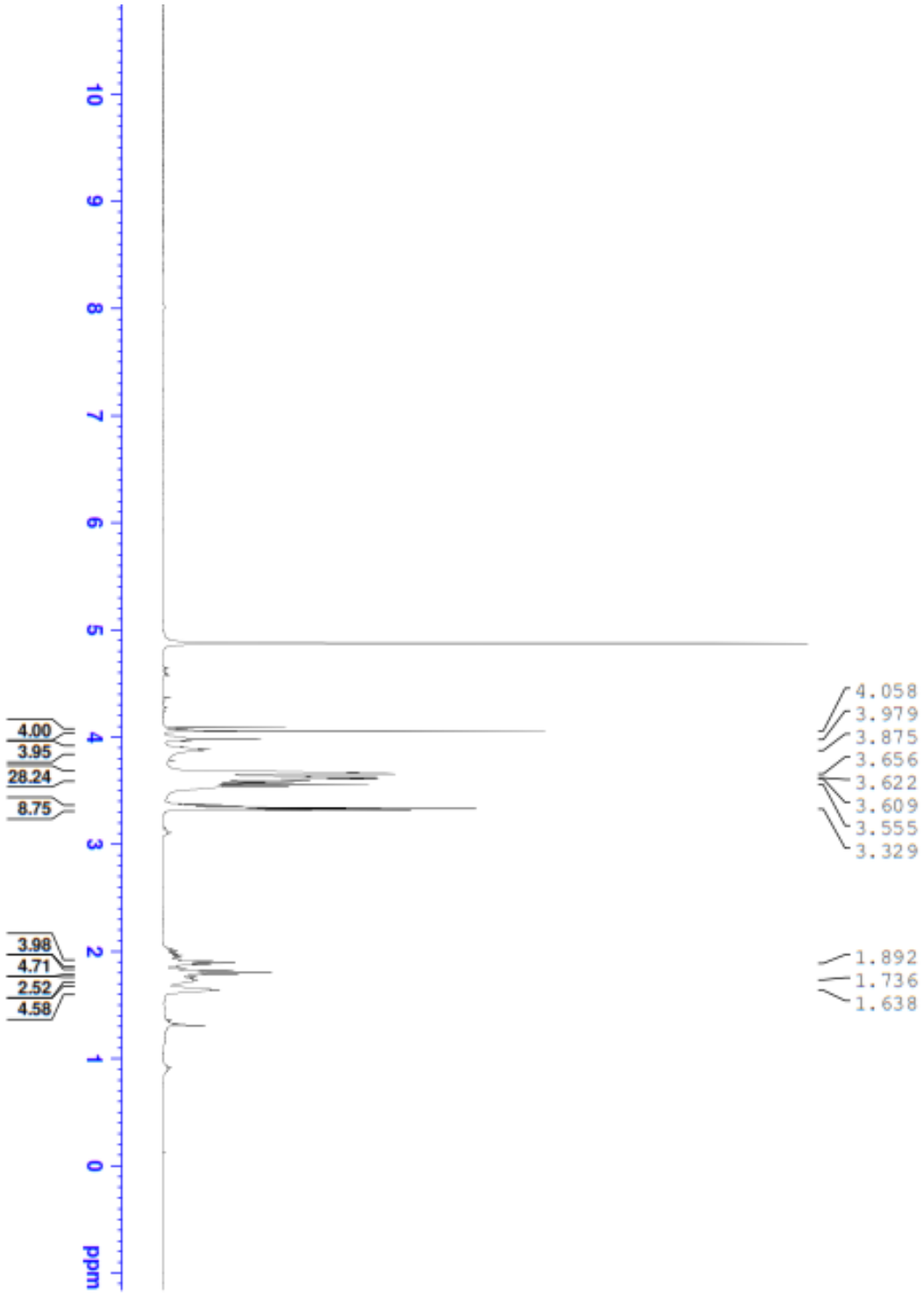


Compound **8c:**

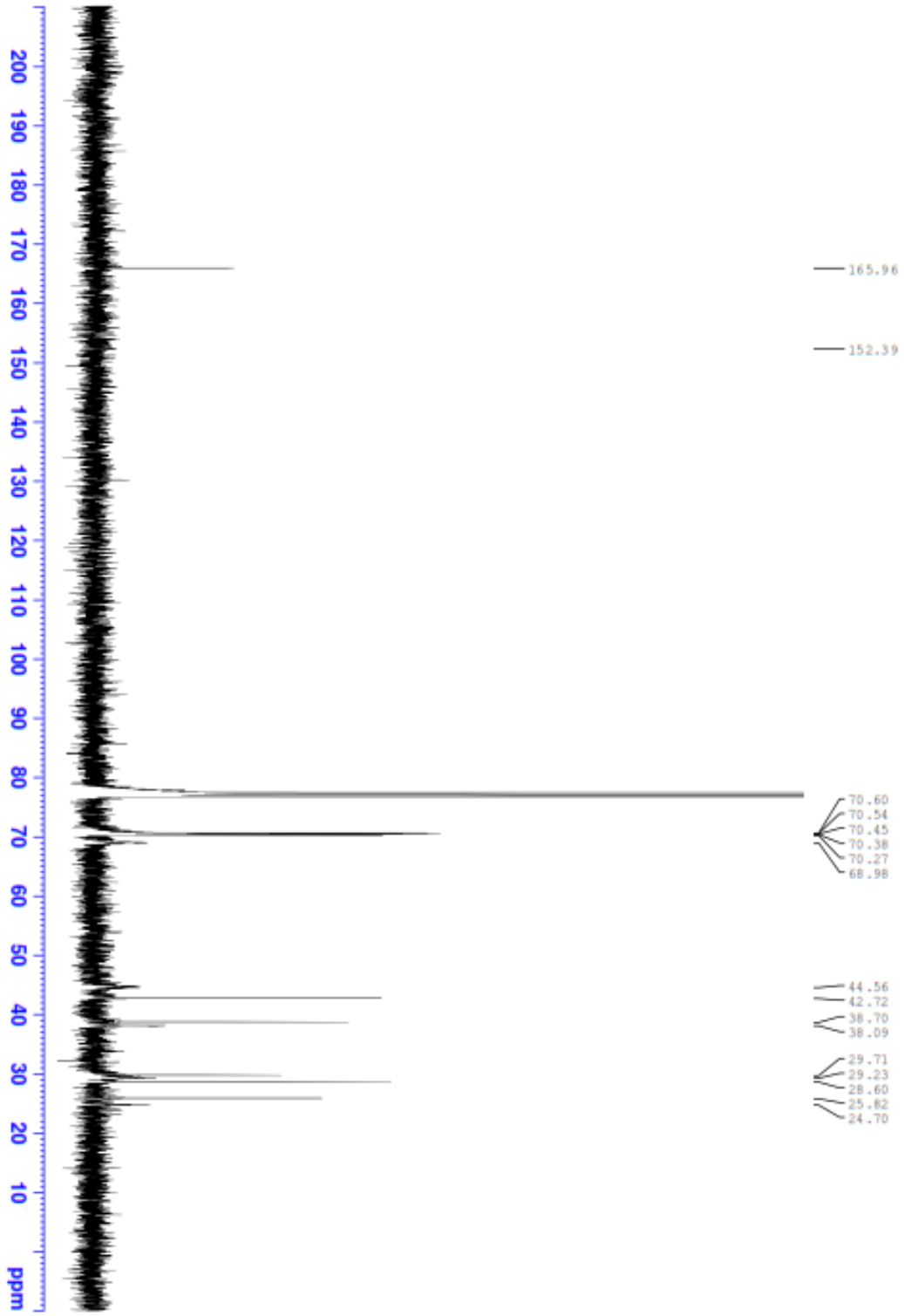
Chloroacetyl chloride (0.32 ml, 3.99 mmol) was added drop wise to a solution of **8b** (800 mg, 1.33 mmol) and DIPEA (0.694 ml, 3.99 mmol) in dichloromethane (20 ml) at 0ºC. The solution was stirred for 2 hrs at room temperature. Then the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and evaporated under vacuum. The crude was purified using automated chromatography to yield a clear oil (270 mg 27%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.05 (s, 4H, -NHC(O)C**H$_2$**Cl), δ 3.87 (t, 4H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2CH_2-), δ 3.65-3.55 (t, 24H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**), δ 3.32 (m, 8H, -C(O)-NHC**H$_2$**CH_2CH_2O, C_3N_3-NHC**H$_2$**CH_2CH_2O); δ 1.89-1.73 (m, 8H, -OCH_2C**H$_2$**CH_2), δ 1.63 (m, 6H, -C**H$_2$**CH_2-N-CH_2C**H$_2$**C**H$_2$**-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 165.9, (**C**$_3N_3$), 152.3 (**C**O), 70.6 (O**C**H_2**C**H_2O), 70.3, 70.4 (O**C**H_2**C**H_2O), 68.9 (NHCH_2CH_2**C**H_2O), 44.5 (-CH_2**C**H_2-N-**C**H_2CH_2-), 42.7 ((CO)**C**H_2Cl), 38.7, 37.0 (NH**C**$H_2CH_2CH_2$O), 29.7, 28.6 (NHCH_2**C**H_2CH_2O); 25.8 (-**C**H_2CH_2-N-CH_2**C**H_2-), 24.7 (-CH_2CH_2-N-CH_2CH_2**C**H_2); MS (ESI-TOF) calcd for $C_{32}H_{58}Cl_2N_8O_8$ 753.76, found 753.45 $(M)^+$.



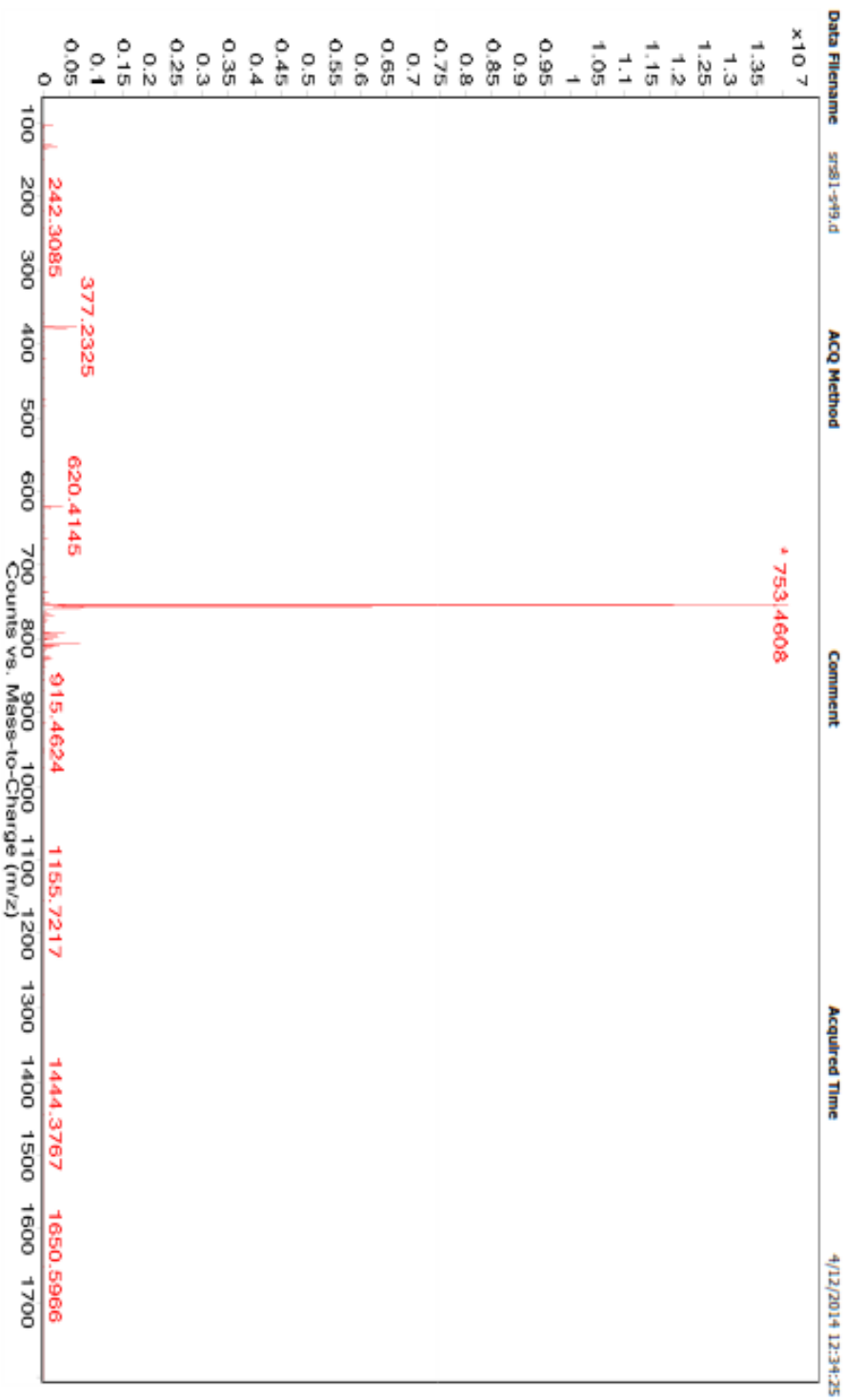
SI Figure 16. ^{1}H NMR spectrum of compound **8c**



SI Figure 17. ^{13}C NMR spectrum of compound **8c**

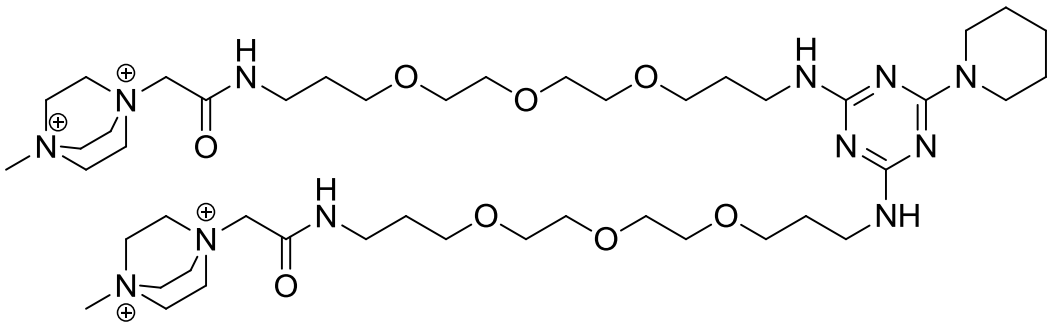


SI Figure 18. Mass spectrum of compound **8c**

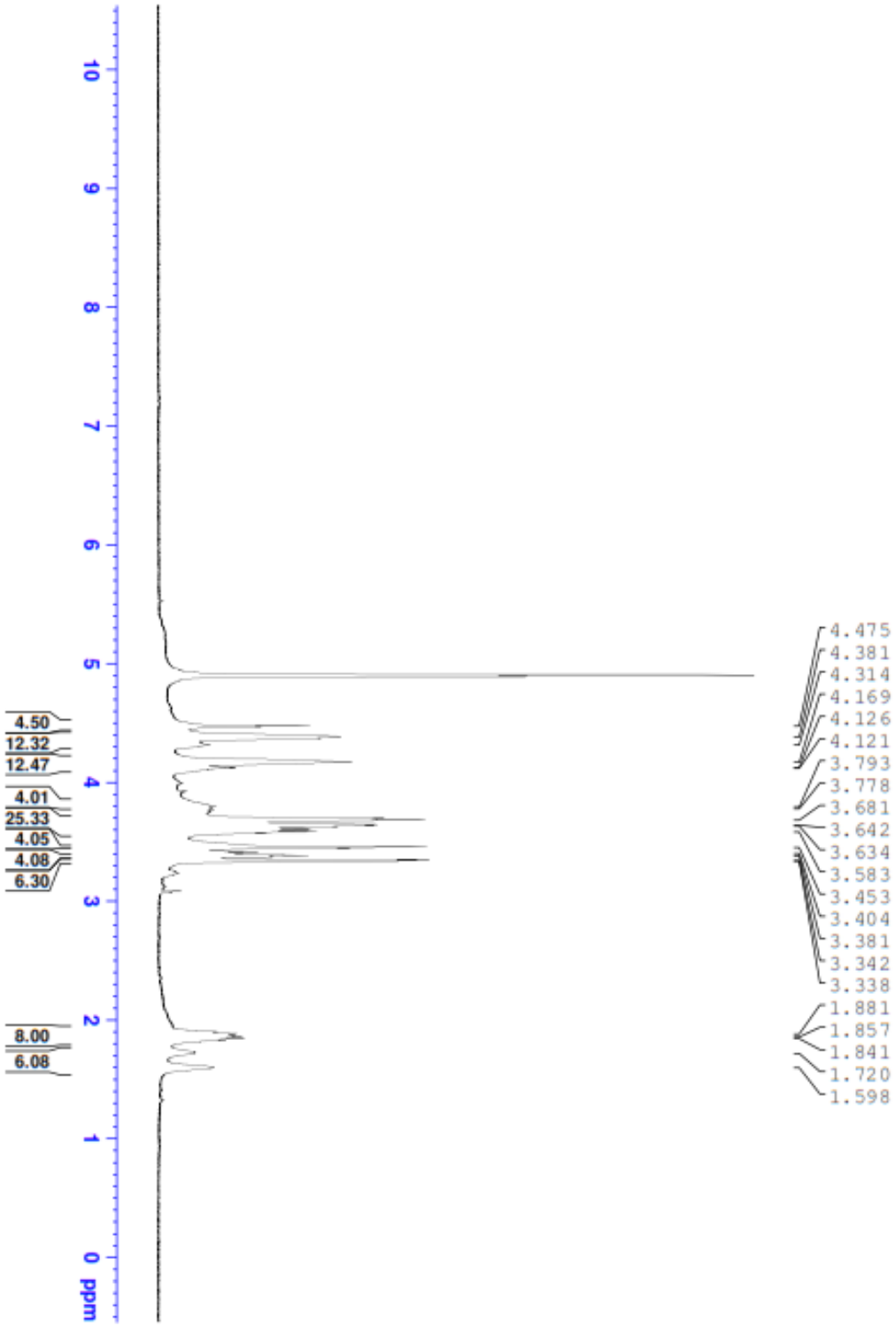


Compound **2-Me:**

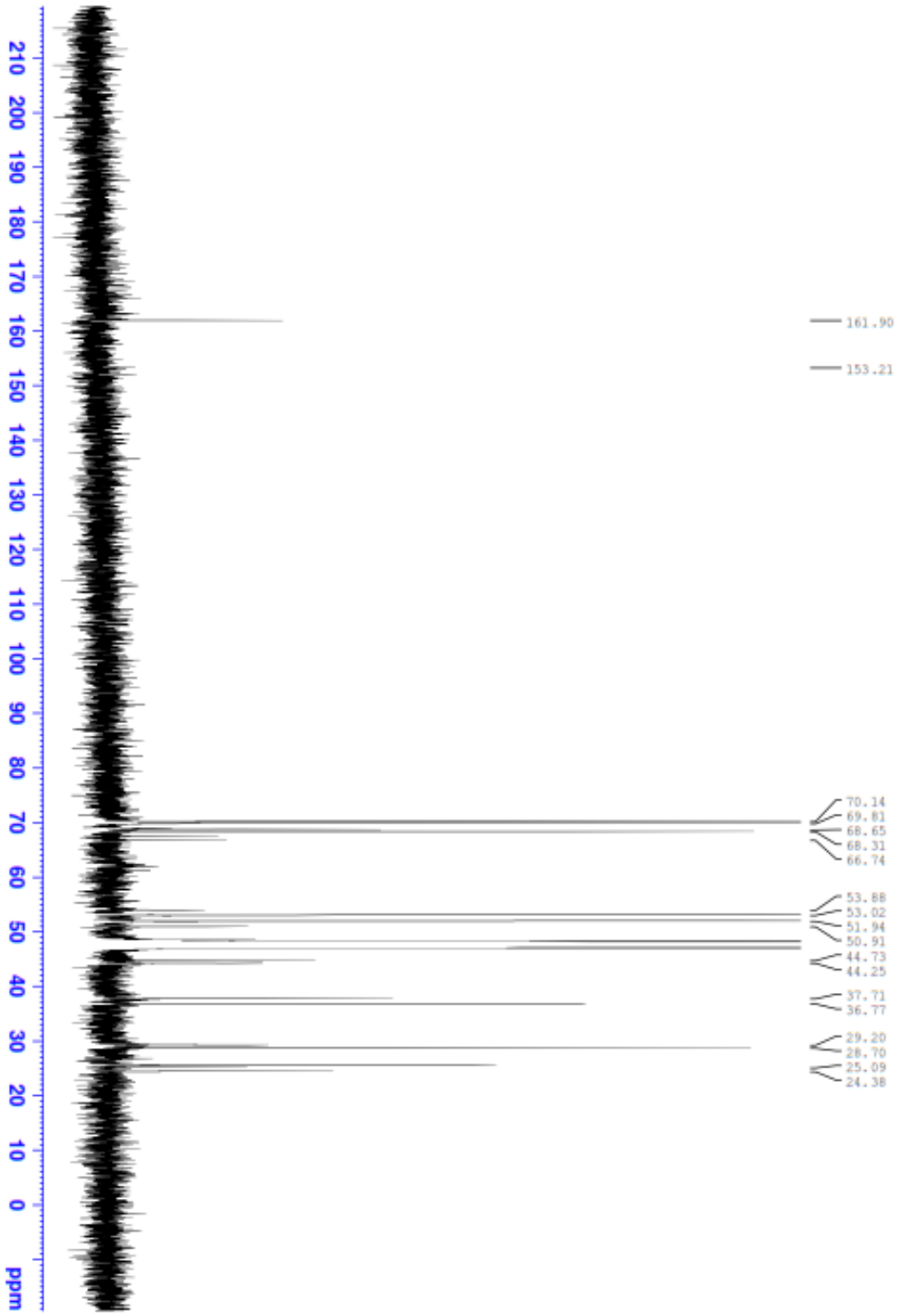
1-Me (23 mg, 0.18 mmol) was added to a solution of **8c** (45 mg, 0.06 mmol) in methanol (1 ml). The above solution was stirred for 2 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was further washed with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to give a pale yellow solid (42 mg, 73%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.47 (s, 4H, -NHC(O)C**H$_2$**-), δ 4.38-4.16 (t, 24H, DABCO), δ 3.79 (t, 4H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2CH_2-), δ 3.68-3.58 (m, 24H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**), δ 3.45 (m, 4H, -C(O)-NHC**H$_2$**CH_2CH_2O), 3.38 (m, 4H, C_3N_3-NHC**H$_2$**CH_2CH_2O); δ 3.33 (-C**H$_3$**), δ 1.88-1.84 (m, 8H, -OCH_2C**H$_2$**CH_2), δ 1.72-1.59 (m, 6H, -C**H$_2$**CH_2-N-CH_2C**H$_2$**C**H$_2$**-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 161.9, (**C**$_3N_3$), 153.2 (**C**O), 70.1 (O**C**H_2**C**H_2O), 69.8 (O**C**H_2**C**H_2O), 68.5 (NHCH_2CH_2**C**H_2O), 66.7 (NHCH_2CH_2**C**H_2O), 66.7 ((CO)**C**H_2Cl), 53.0, 51.9 (DABCO), 50.9 (**C**H3) 44.7, 44.2 (-CH_2**C**H_2-N-**C**H_2CH_2-), 29.2, 28.7 (NH**C**$H_2CH_2CH_2O$), 25.0, 24.3 (-**C**H_2CH_2-N-CH_2**C**H_2**C**H_2-).



SI Figure 19. ^{1}H NMR spectrum of compound **2-Me**

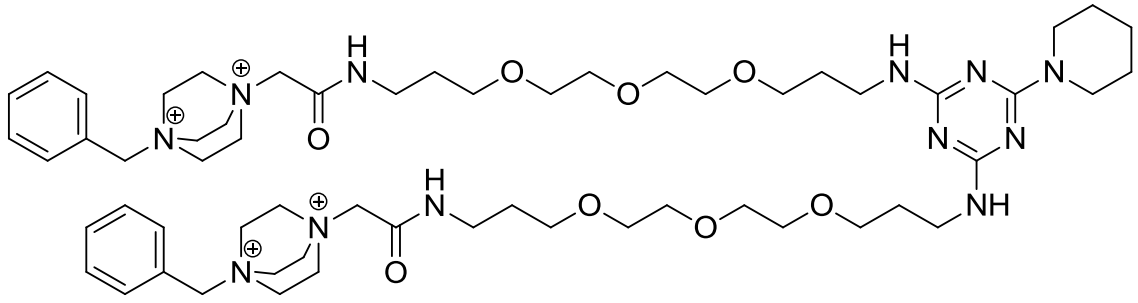


SI Figure 20. ^{13}C NMR spectrum of compound **2-Me**

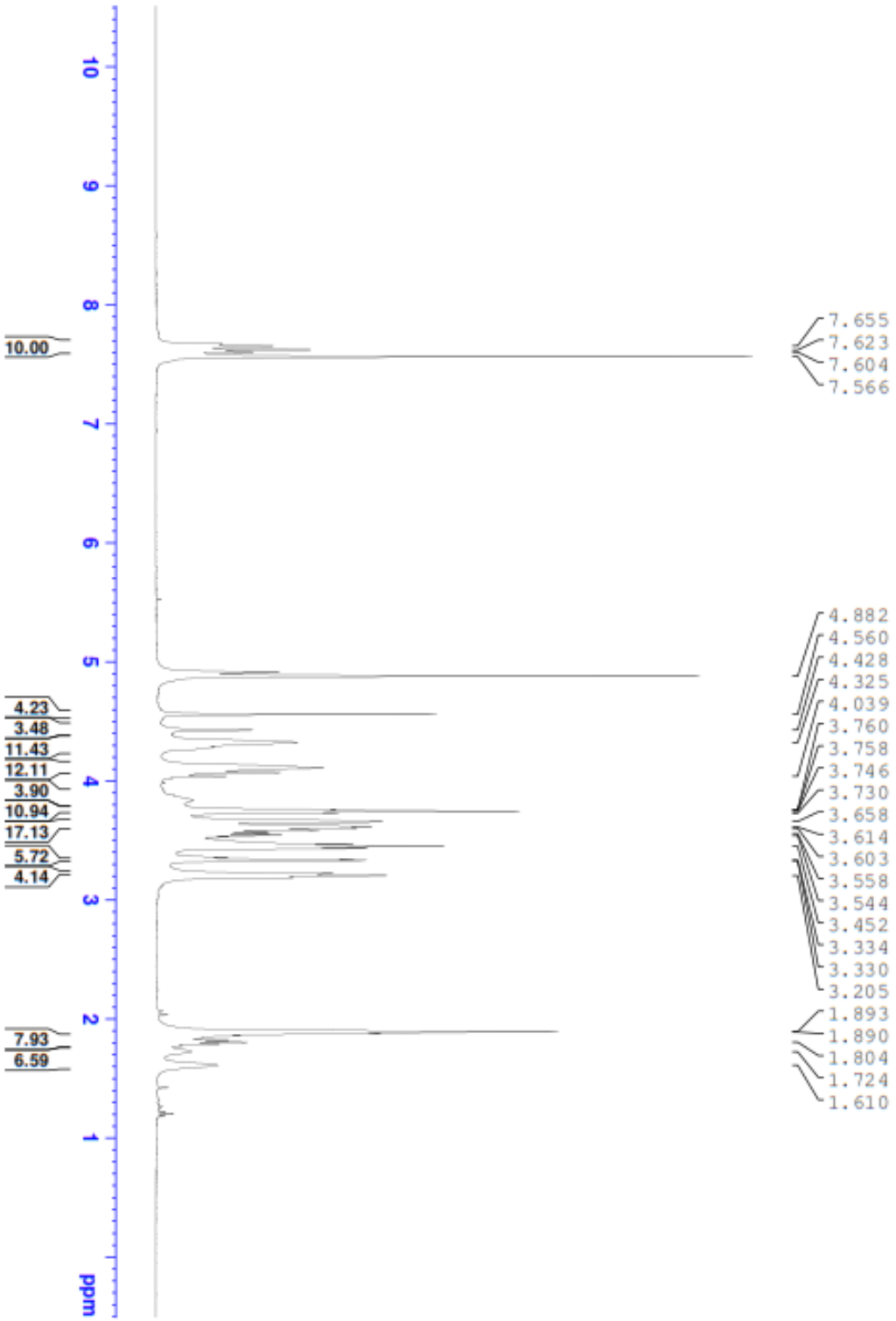


Compound **2-Bz:**

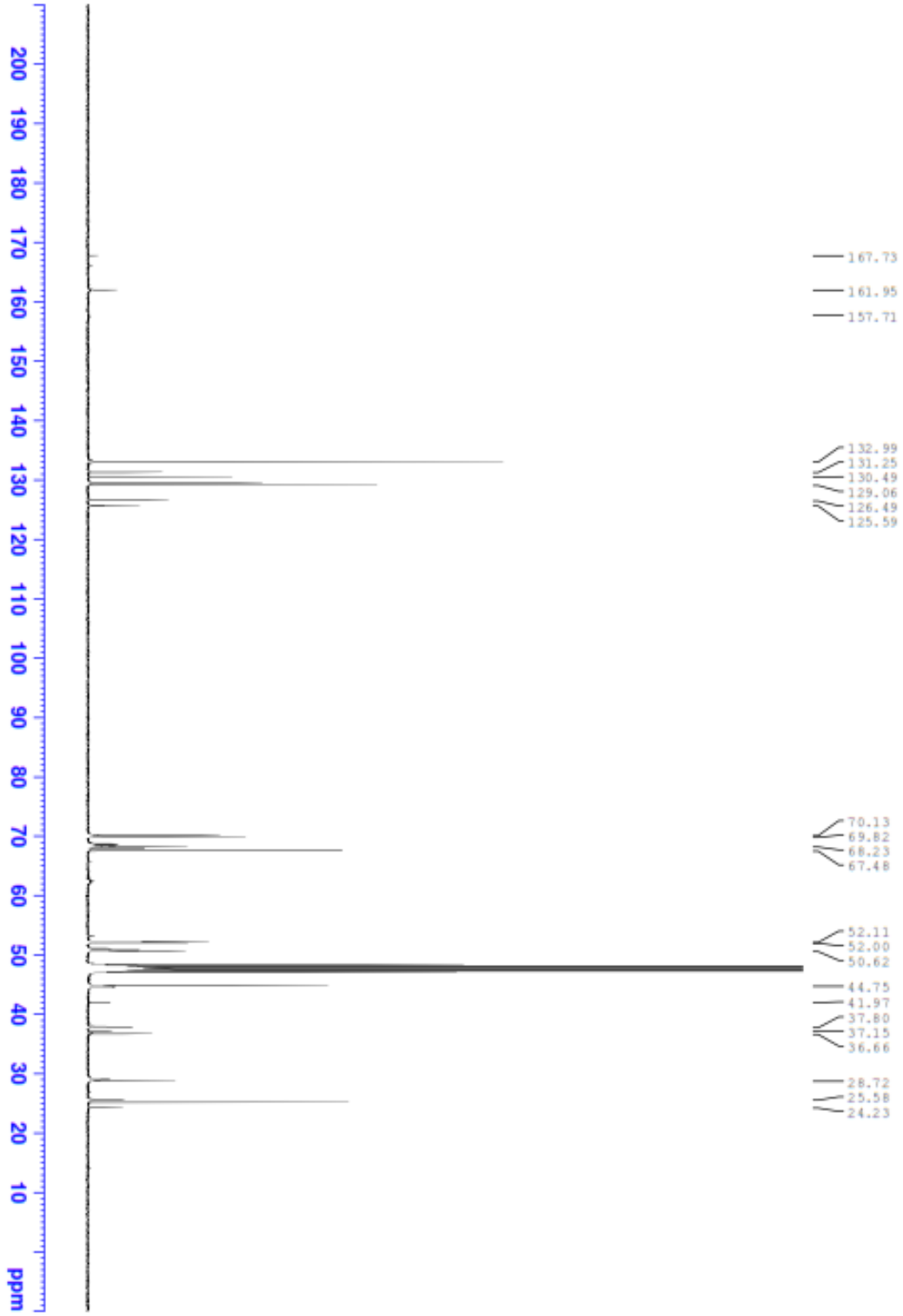
1-Bz (41 mg, 0.2 mmol) was added to a solution of **8c** (50 mg, 0.07 mmol) in methanol (1 ml). The solution was stirred for 2 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was further washed with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to give a white solid (43 mg 58%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.65-7.60 (d, 10H, $C_6\mathbf{H}_5$-), δ 4.56 (s, C_6H_5-$C\mathbf{H_2}$), δ 4.42 (s, 4H, -NHC(O)$C\mathbf{H_2}$-), δ 4.32-4.03 (t, 24H, DABCO), δ 3.75 (t, 4H, -$CH_2C\mathbf{H_2}$-N-$C\mathbf{H_2}CH_2CH_2$-), δ 3.61-3.45 (t, 24H, $C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}$), δ 3.33-3.20 (t, 8H, C(O)-NH$C\mathbf{H_2}CH_2CH_2O$, C_3N_3-NH$C\mathbf{H_2}CH_2CH_2O$); δ 1.88-1.84 (m, 8H, -$OCH_2C\mathbf{H_2}CH_2$), δ 1.72-1.61 (m, 6H, -CH_2CH_2-N-$CH_2C\mathbf{H_2}C\mathbf{H_2}C\mathbf{H_2}$-); ^{13}C NMR (100 MHz, CD_3OD) δ 167.7, 161.9 ($\mathbf{C}_3N_3$), 157.7 (**C**O), 131.2, 130.4, 129.0, 126.4 ($\mathbf{C_6}H_5$-), 70.1 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 69.8 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 68.2 ($\mathbf{C_6}H_5$-$CH_2$), 67.5, 67.4 ($NHCH_2CH_2\mathbf{C}H_2O$), 62.5 ((CO)$\mathbf{C}H_2Cl$), 52.1, 50.6 (DABCO), 44.7, 41.9 (-$\mathbf{C}H_2\mathbf{C}H_2$-N-$\mathbf{C}H_2\mathbf{C}H_2$-), 37.8, 36.6 ($NH\mathbf{C}H_2CH_2CH_2O$), 28.8 ($NHCH_2\mathbf{C}H_2CH_2O$); 25.6, 24.2 (-$\mathbf{C}H_2CH_2$-N-$CH_2\mathbf{C}H_2\mathbf{C}H_2$-).



SI Figure 21. ^{1}H NMR spectrum of compound **2-Bz**

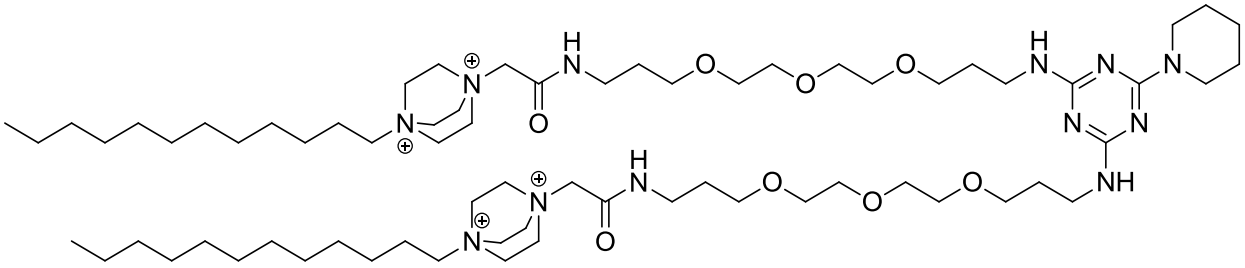


SI Figure 22. ^{13}C NMR spectrum of compound **2-Bz**

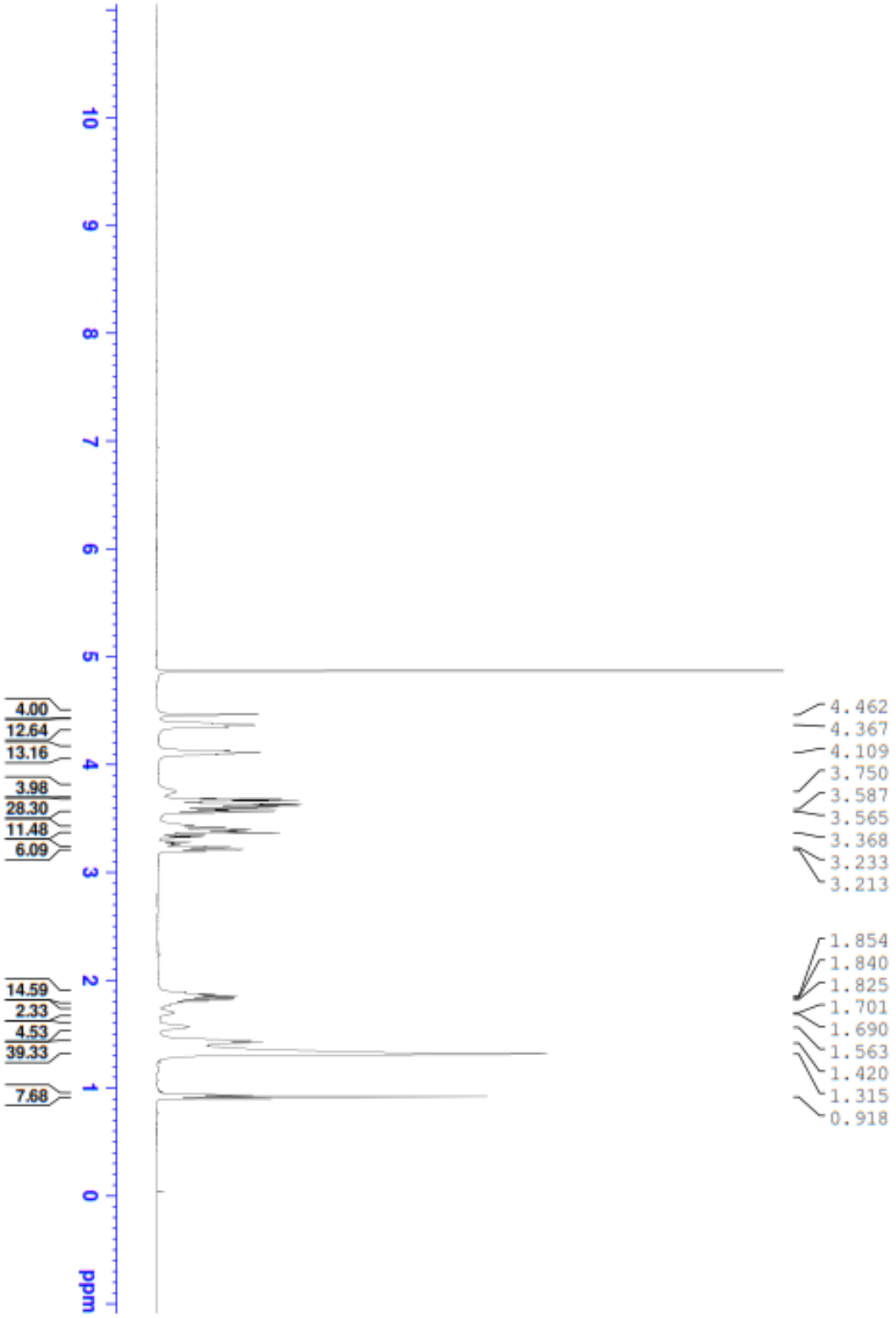


Compound 2-C12:

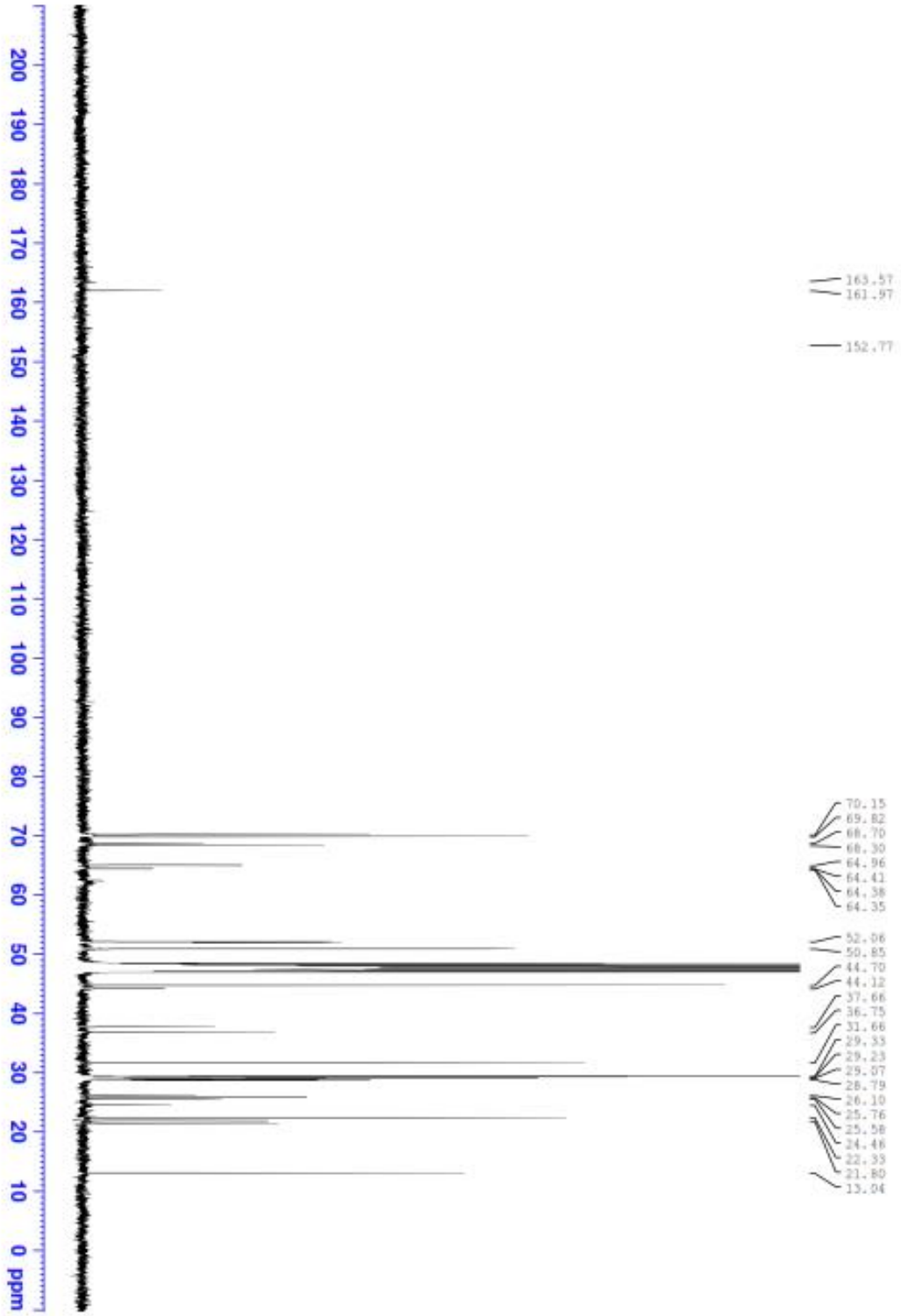
1-C12 (45mg, 0.16mmol) was added to a solution of **8c** (40mg, 0.05) in methanol (1ml). The above solution was stirred for 2days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product is further washed with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to give a white solid (54 mg, 81%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.46 (s, 4H, -NHC(O)C**H$_2$**-), δ 4.36-4.10 (t, 24H, DABCO), δ 3.75 (t, 4H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2CH_2-), δ 3.58-3.56 (t, 24H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**), δ 3.36-3.23 (m, 8H, -NHC**H$_2$**CH_2CH_2O) δ 3.21 (m, 4H, -CH3$(CH_2)_9$C**H$_2$**CH_2), δ 1.85-1.82 (m, 12H, -OCH_2C**H$_2$**CH_2. -CH3$(CH_2)_9CH_2$C**H$_2$-**), δ 1.70-1.56 (t, 6H, -C**H$_2$** C**H$_2$**CH_2-N-C**H$_2$**C**H$_2$**-) 1.42-1.31 (m, 36H, -CH3(C**H$_2$)$_9$**CH_2CH_2-), 0.91 (t, 6H, C**H$_3$**$(CH_2)_9CH_2CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 163.5, 161.9 (**C**$_3N_3$), 152.7 (**C**O), 70.1 (O**C**H_2**C**H_2O), 69.8 (O**C**H_2**C**H_2O), 68.7 (NHCH_2CH_2**C**H_2O), 68.3 (NHCH_2CH_2**C**H_2O), 64.9 ((CO)**C**H_2Cl), 64.3 (**C$_{12}$**H_{25}) 52.0, 50.8 (DABCO), 44.7, 44.1 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 37.6, 36.7 (NH**C**$H_2CH_2CH_2O$), 31.6, 29.3, 29.2, 29.1 (CH_3(**C**H_2)$_9$$CH_2CH_2$-), 26.1, 25.7, 24.4 ($CH_3(CH_2)_9CH_2$**C**$H_2$-**,** $CH_3(CH_2)_9$**C**H_2CH_2-**,** -NHCH_2**C**H_2CH_2O), 22.3, 21.8 (-**C**H_2CH_2-N-CH_2**C**H_2**C**H_2, 13.0 (**C**$H_3(CH_2)_9CH_2CH_2$-).



SI Figure 23. ^{1}H NMR spectrum of compound **2-C12**

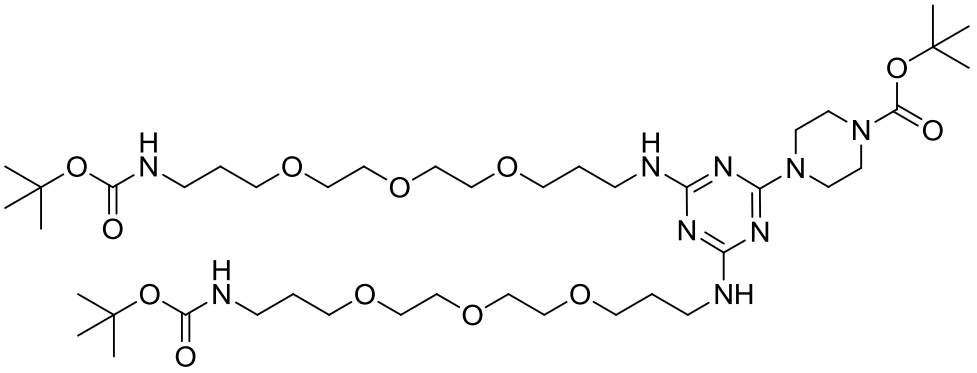


SI Figure 24. ^{13}C NMR spectrum of compound **2-C12**

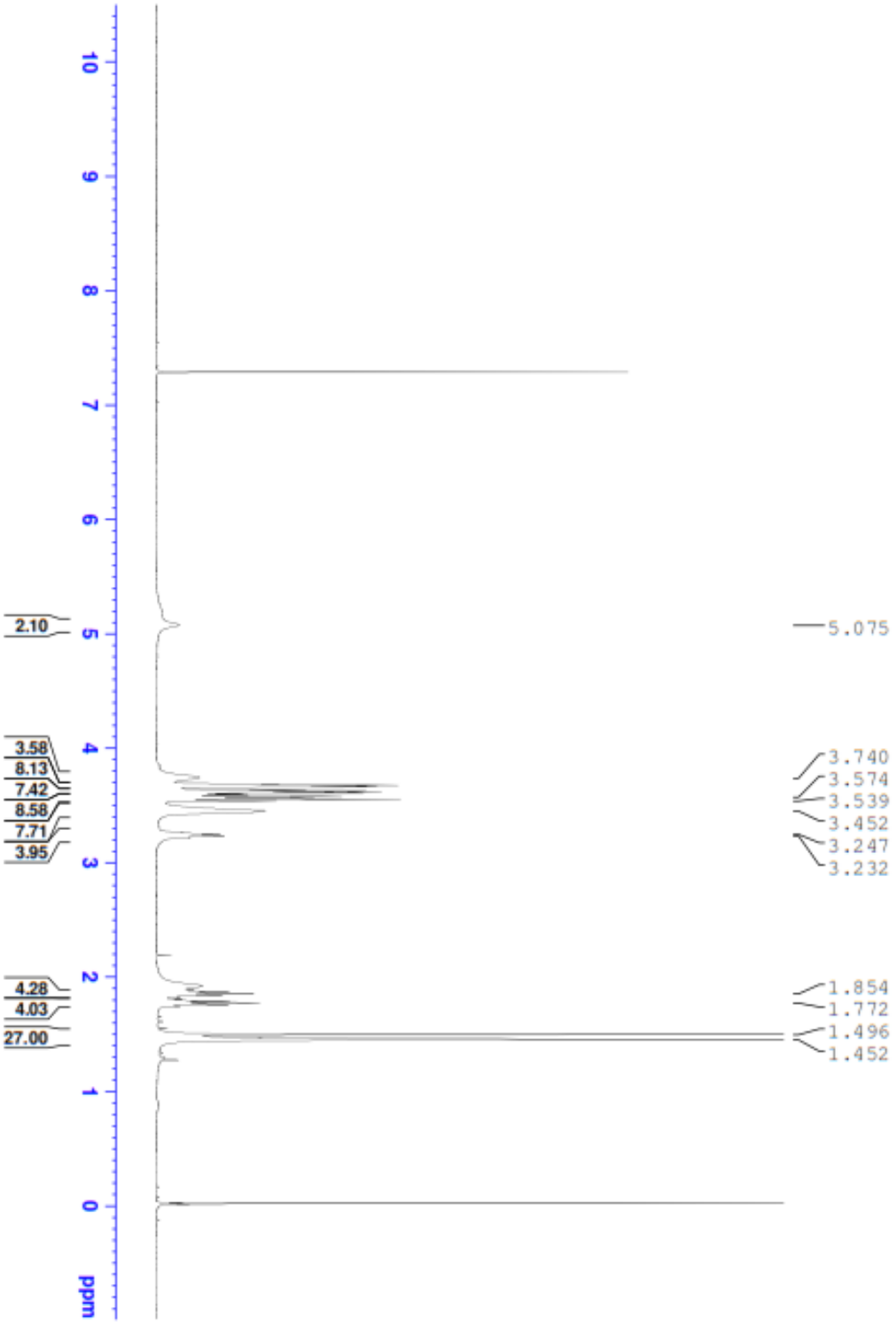


Compound **9a:**

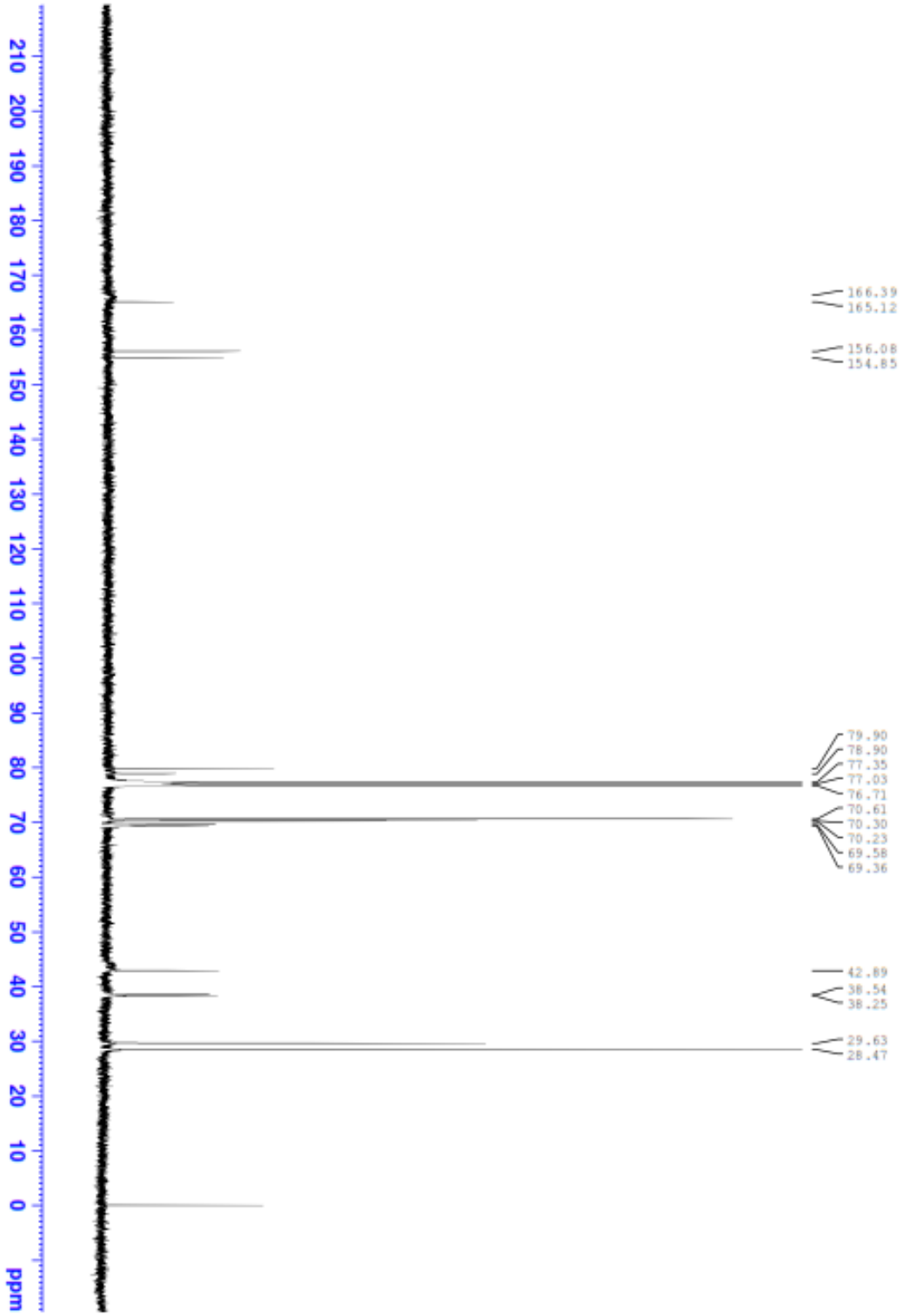
A solution of **7** (1.5 g, 2 mmol) with N-Boc piperazine (1.1 g, 6 mmol) and DIPEA (1.04 ml, 6 mmol) in 20 ml of acetonitrile was stirred for 2 minutes. Then, the solution was irradiated in the microwave at 80ºC for 45 min of stirring. The solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and evaporated under vacuum. The crude was purified using automated chromatography to yield a clear oil (1.64 g, 91%). ^{1}H NMR (400 MHz, $CDCl_3$) δ 3.74 (t, 4H, -$CH_2C\mathbf{H_2}$-N-$C\mathbf{H_2}CH_2$-Piperazine), δ 3.57-3.53 (br, m, 20H, $CH_2OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OCH_2$, $C\mathbf{H_2}CH_2$-N-$CH_2C\mathbf{H_2}$-Piperazine), δ 3.45 (t, 8H, -$NHCH_2CH_2C\mathbf{H_2}O$-), 3.22 (m, 4H, -$NHC\mathbf{H_2}CH_2CH_2O$-), 1.85-1.77 (m, 8H, $OCH_2C\mathbf{H_2}CH_2$), 1.52 (s, 27H, -$C(C\mathbf{H_3})_3$); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.3, 165.1 ($\mathbf{C}_3N_3$), 156.08, 154.85 (**C**O), 79.9, 78.9 $\mathbf{C}(CH_3)_3$), 70.6, 70.3 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 69.5 ($NHCH_2CH_2\mathbf{C}H_2O$), 69.3 ($NHCH_2CH_2\mathbf{C}H_2O$), 42.8 (-$\mathbf{C}H_2\mathbf{C}H_2$-N-$\mathbf{C}H_2\mathbf{C}H_2$-), 38.5, 38.2 ($NH\mathbf{C}H_2CH_2CH_2O$), 29.6 ($NHCH_2\mathbf{C}H_2CH_2O$), 28.4 ($C(\mathbf{C}H_3)_3$); MS (ESI-TOF) calcd for $C_{42}H_{79}N_9O_{12}$, 902.13, found 902.65 $(M)^+$.



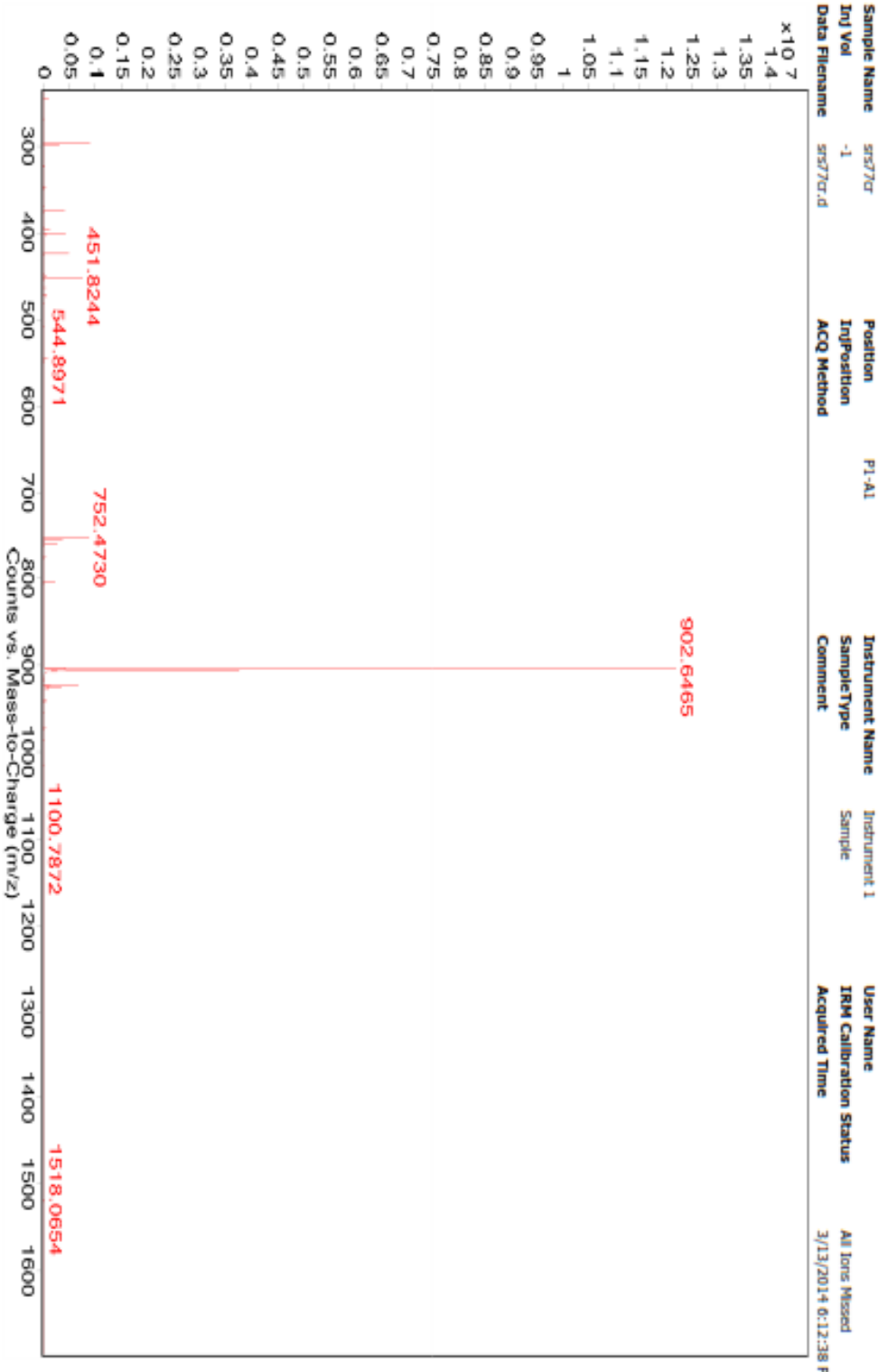
SI Figure 25. ^{1}H NMR spectrum of compound **9a.**



SI Figure 26. ^{1}H NMR spectrum of compound **9a**

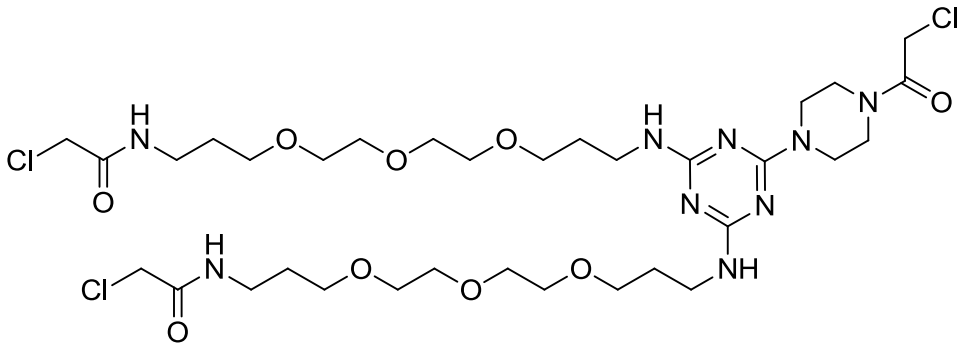


SI Figure 27. Mass spectrum of compound **9a.**

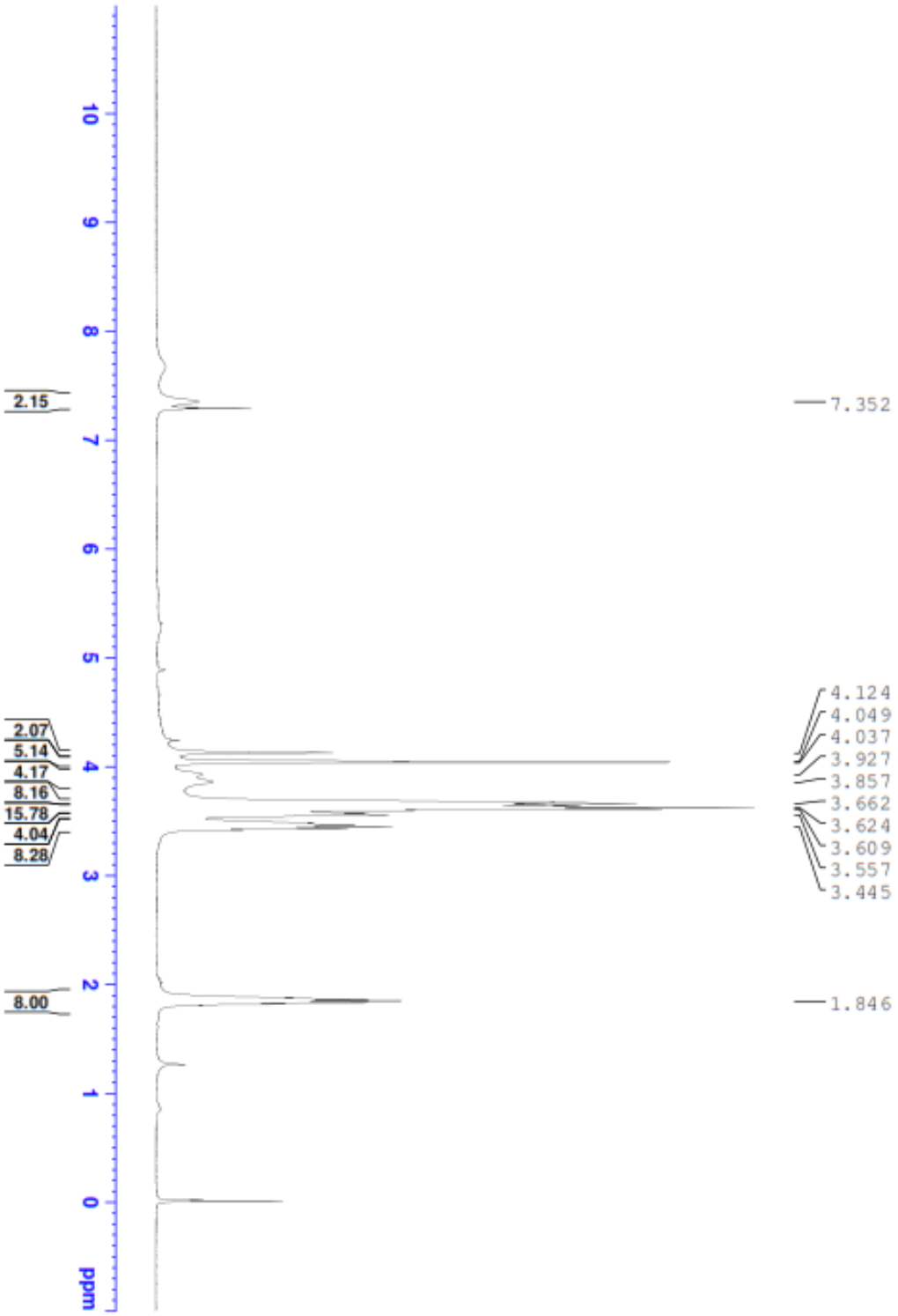


Compound **9c:**

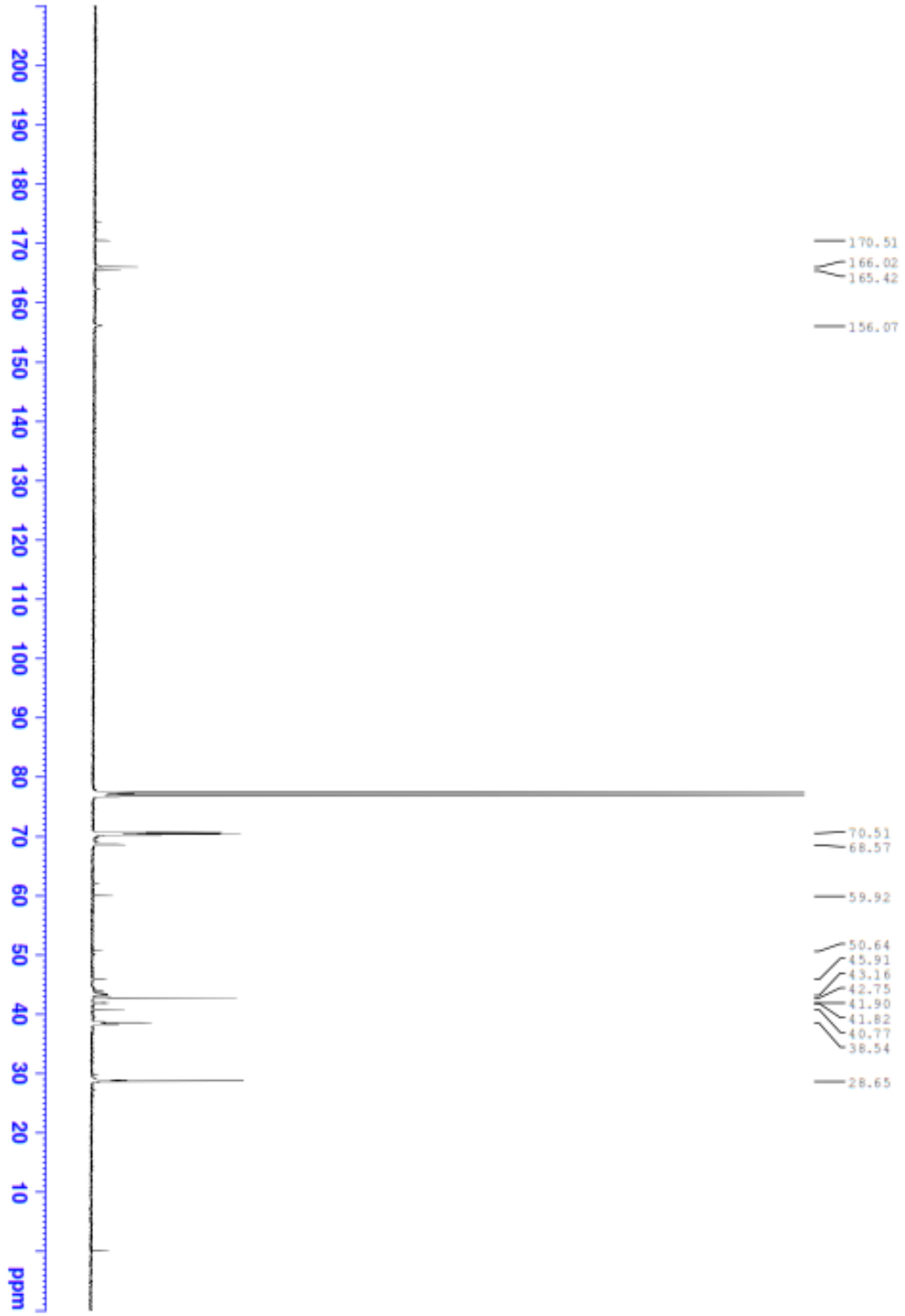
Chloroacetyl chloride (0.4 ml, 4.8 mmol) was added drop wise to the solution of **9b** (700 mg, 1.2 mmol) and DIPEA (0.625 ml, 3.6 mmol) in dichloromethane (12 ml) at 0ºC. The above solution was stirred for 2 hrs at room temperature. Then the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and evaporated under vacuum. The crude was purified using automated chromatography to yield a pale yellow oil (270 mg 27%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.04 (s, 6H, -NH-C(O)C**H$_2$**Cl), δ 3.92-3.85 (t, 4H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2-Piperazine), δ 3.66-3.60 (br, m, 24H, CH_2OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OCH_2, -OCH_2CH_2C**H$_2$**NH), δ 3.55 (m, 4H, -C**H$_2$**CH_2-N-CH_2C**H$_2$**-), δ 3.44 (t, 8H, C**H$_2$**OCH_2CH_2OCH_2CH_2OC**H$_2$**), 1.84 (m, 8H, OCH_2C**H$_2$**CH_2); ^{13}C NMR (100 MHz, $CDCl_3$) δ 170.5, 166.0 (**C**$_3$N$_3$), 165.4, 156.0 (**C**O), 70.5 (O**C**H_2**C**H_2O), 68.5 (CH_2CH_2**C**H_2O), 59.9 (CH_2**C**H_2-N-**C**H_2CH_2-),, 50.64 (**C**H_2CH_2-N-CH_2**C**H_2-), 43.9, 42.7 ((CO)**C**H_2Cl) 38.5 (**C**$H_2CH_2CH_2$O), 28.6 (NHCH_2**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{33}H_{58}Cl_3N_9O_9$ 831.23, found 832.42 $(M + H)^+$.



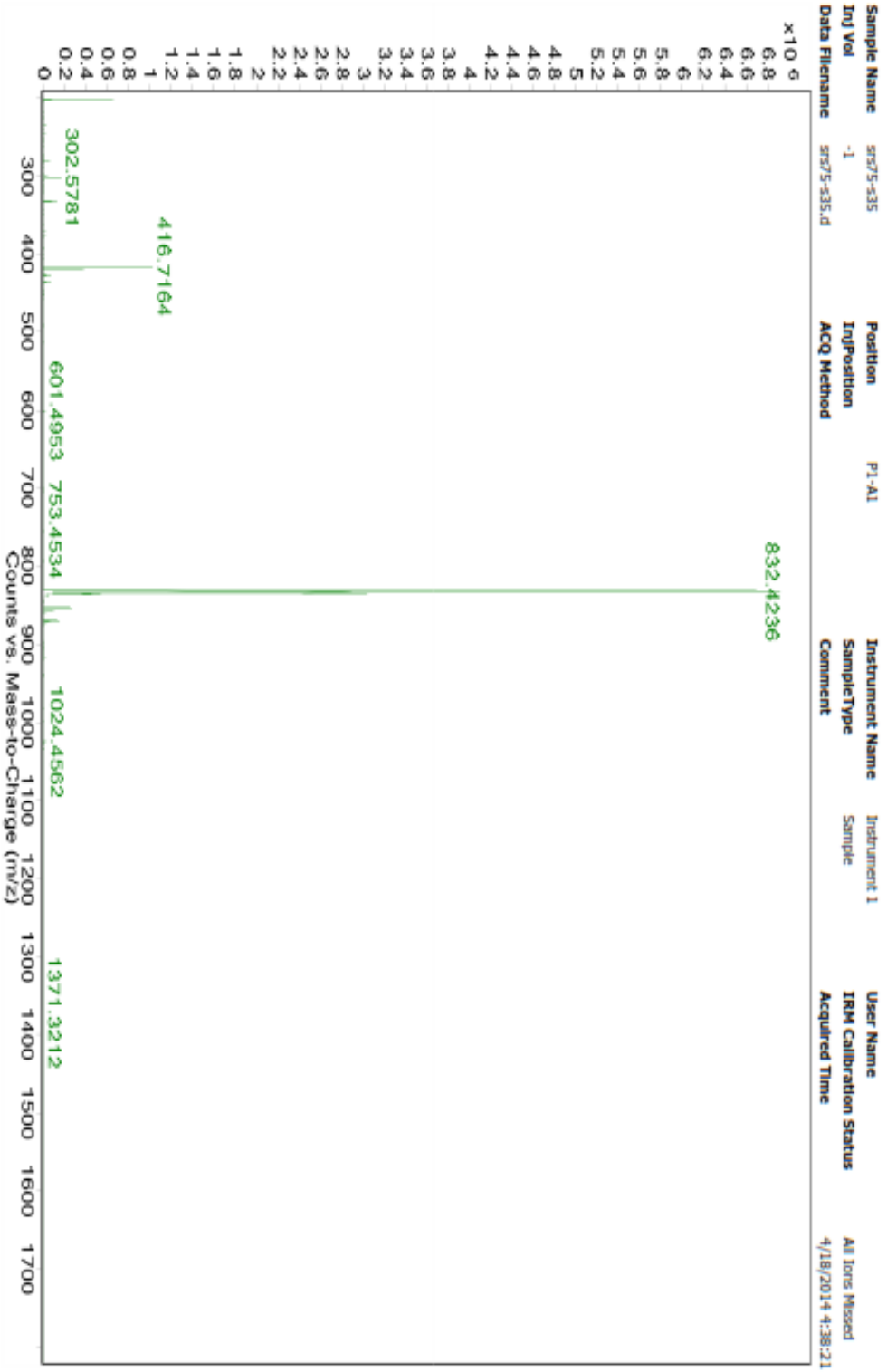
SI Figure 28. ^{1}H NMR spectrum of compound **9c**



SI Figure 29. ^{13}C NMR spectrum of compound **9c**

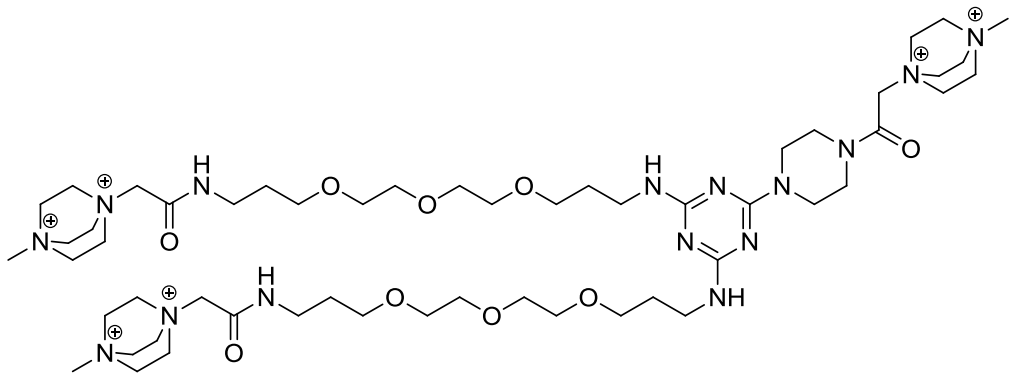


SI Figure 30. Mass spectrum of compound **9c**

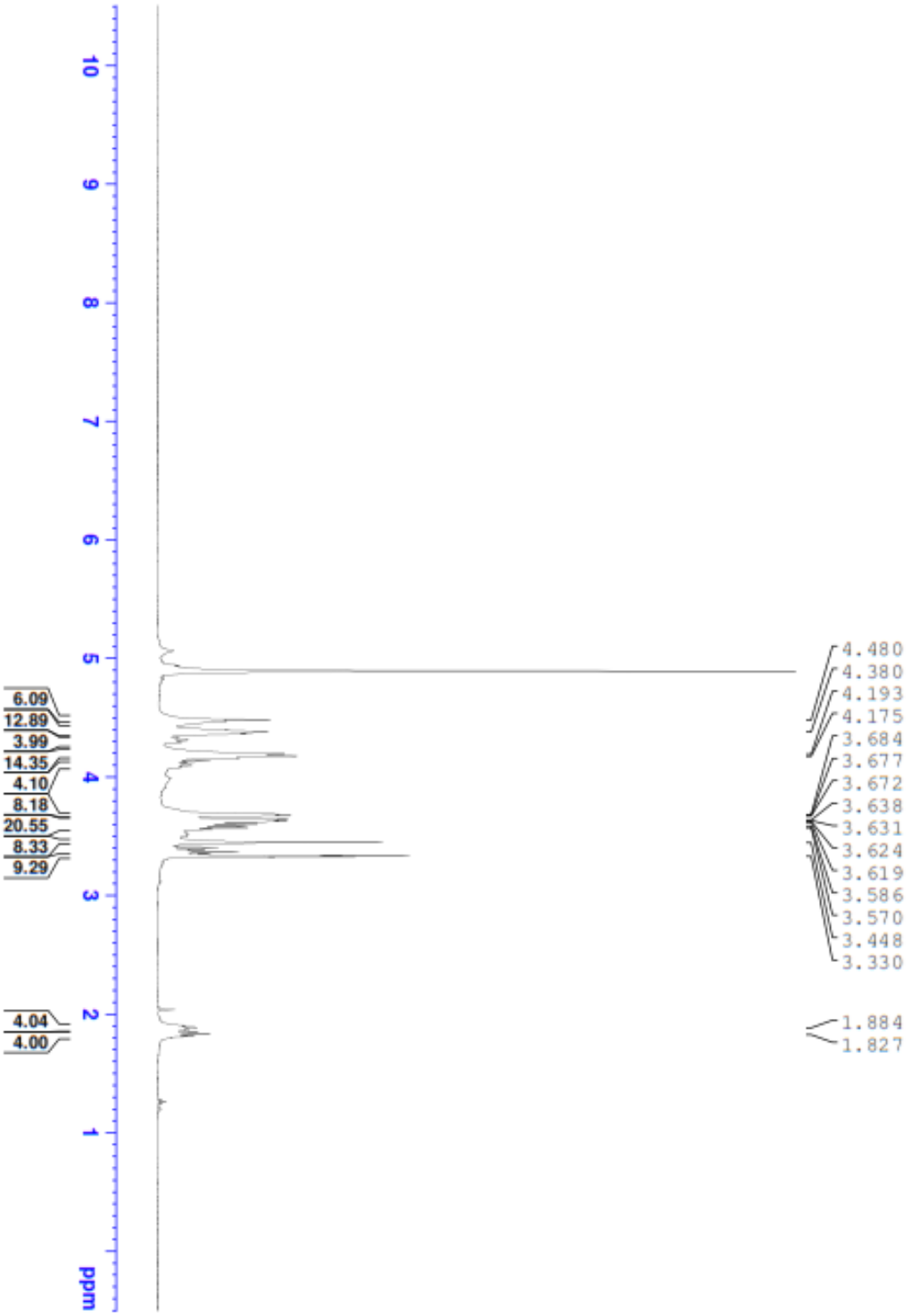


Compound **3-Me:**

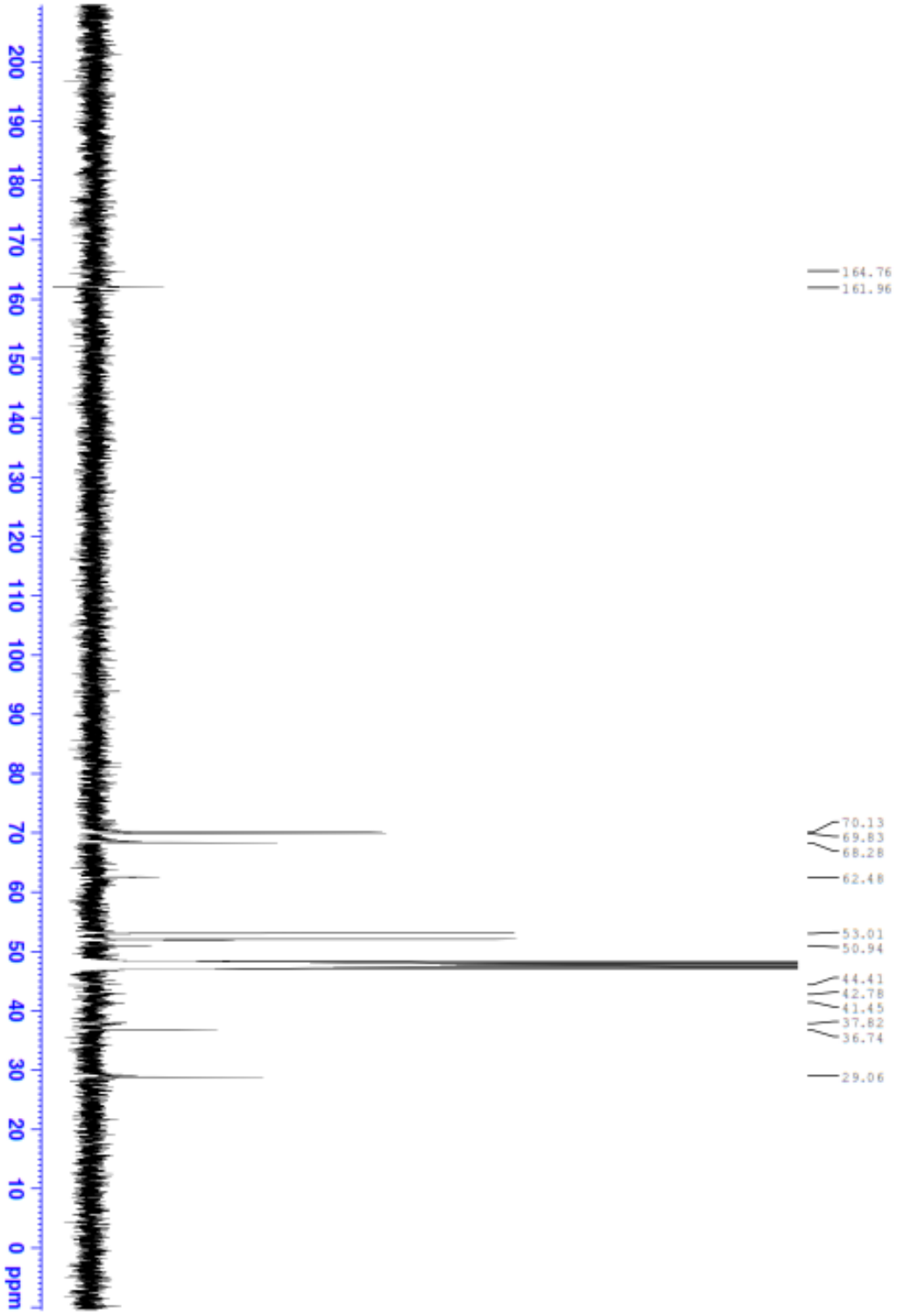
1-Me (35 mg, 0.28 mmol) was added to a solution of **9c** (50 mg, 0.06 mmol) in methanol (1 ml). The solution was stirred for 2 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was washed further with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to give a pale yellow solid (52 mg 78%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.48 (s, 6H, -NHC(O)C**H$_2$**), δ 4.38 (t, 12H, DABCO), δ 4.19 (t, 4H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2-Piperazine) δ 4.17 (t, 24H, DABCO) , δ 3.68-3.58 (m, 32H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, NHC**H$_2$**CH_2CH_2O, -CH_2C**H$_2$**-N-C**H$_2$**CH_2-Piperazine), δ 3.44-3.36 (m, 4H, NHC**H$_2$**CH_2CH_2O), δ 3.33 (s, 9H,-C**H$_3$**), δ 1.88-1.82 (m, 8H, -OCH_2C**H$_2$**CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 164.7 (**C**O), 161.9, 161.2 (**C**$_3$$N_3$), 157.4 (**C**O), 70.13, 69.8 (O**C**H_2**C**H_2O), 68.2 (NHCH_2CH_2**C**H_2O), 62.4 ((CO)**C**H_2Cl), 53.0, 52.1 (DABCO), 50.9 (-**C**H_3), 42.7, 37.8 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 36.7 (NH**C**$H_2$$CH_2CH_2O$), 29.1, 28.7, (NHC$H_2$**C**$H_2$$CH_2O$);



SI Figure 31. ^{1}H NMR spectrum of compound **3-Me**

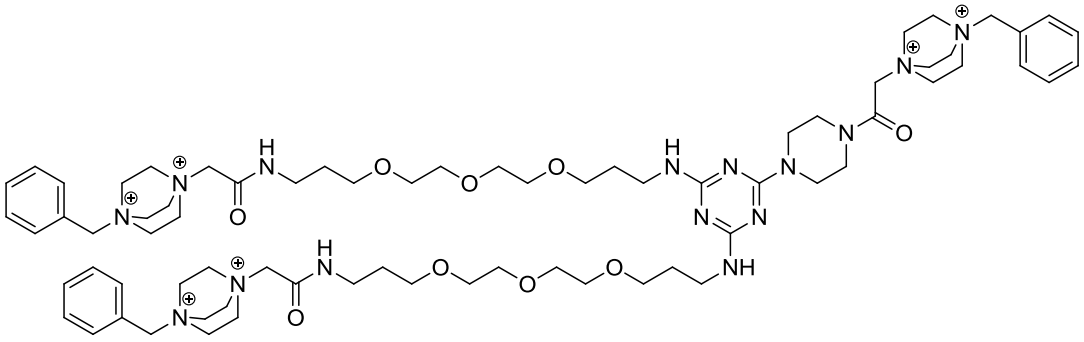


SI Figure 32. ^{13}C NMR spectrum of compound **3-Me**

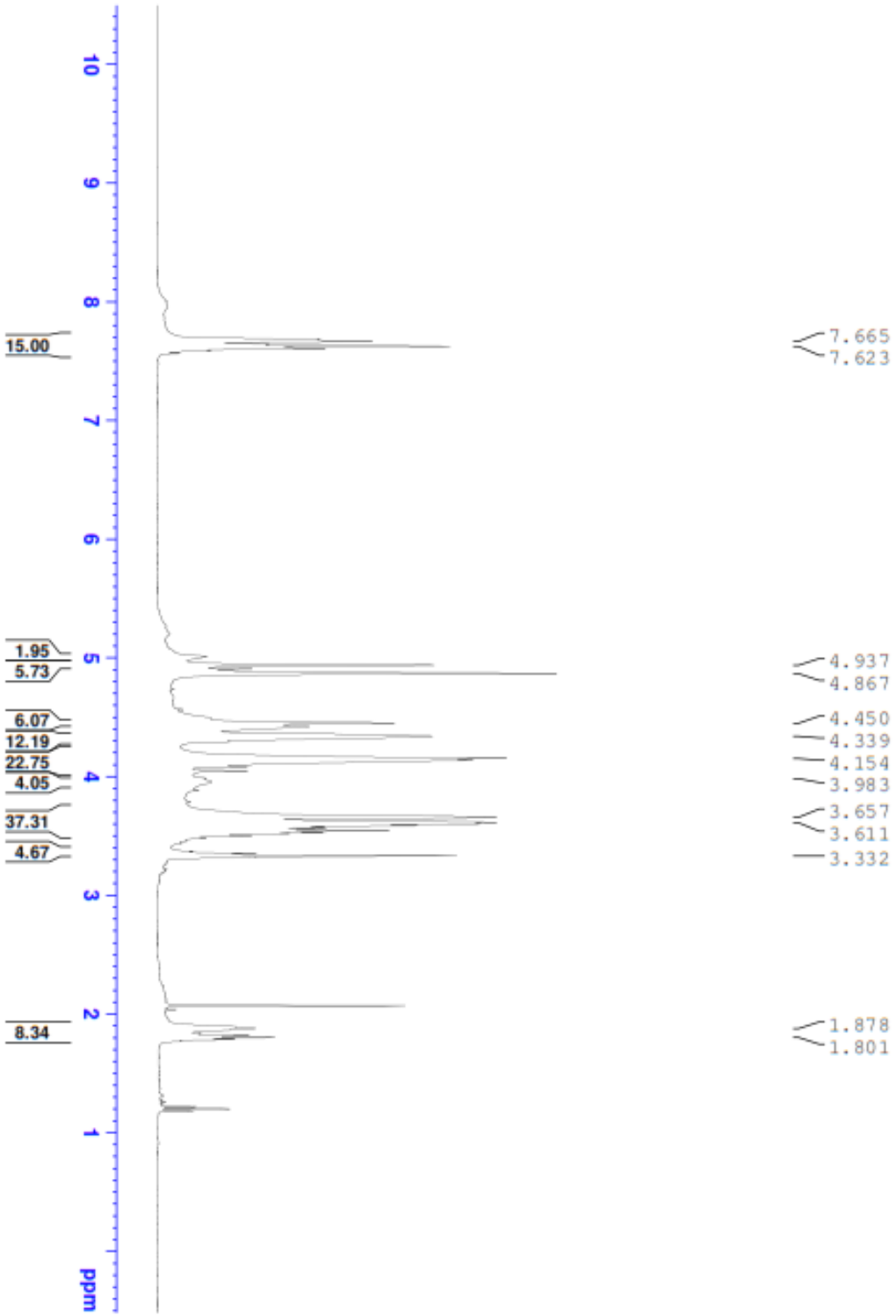


Compound **3-Bz:**

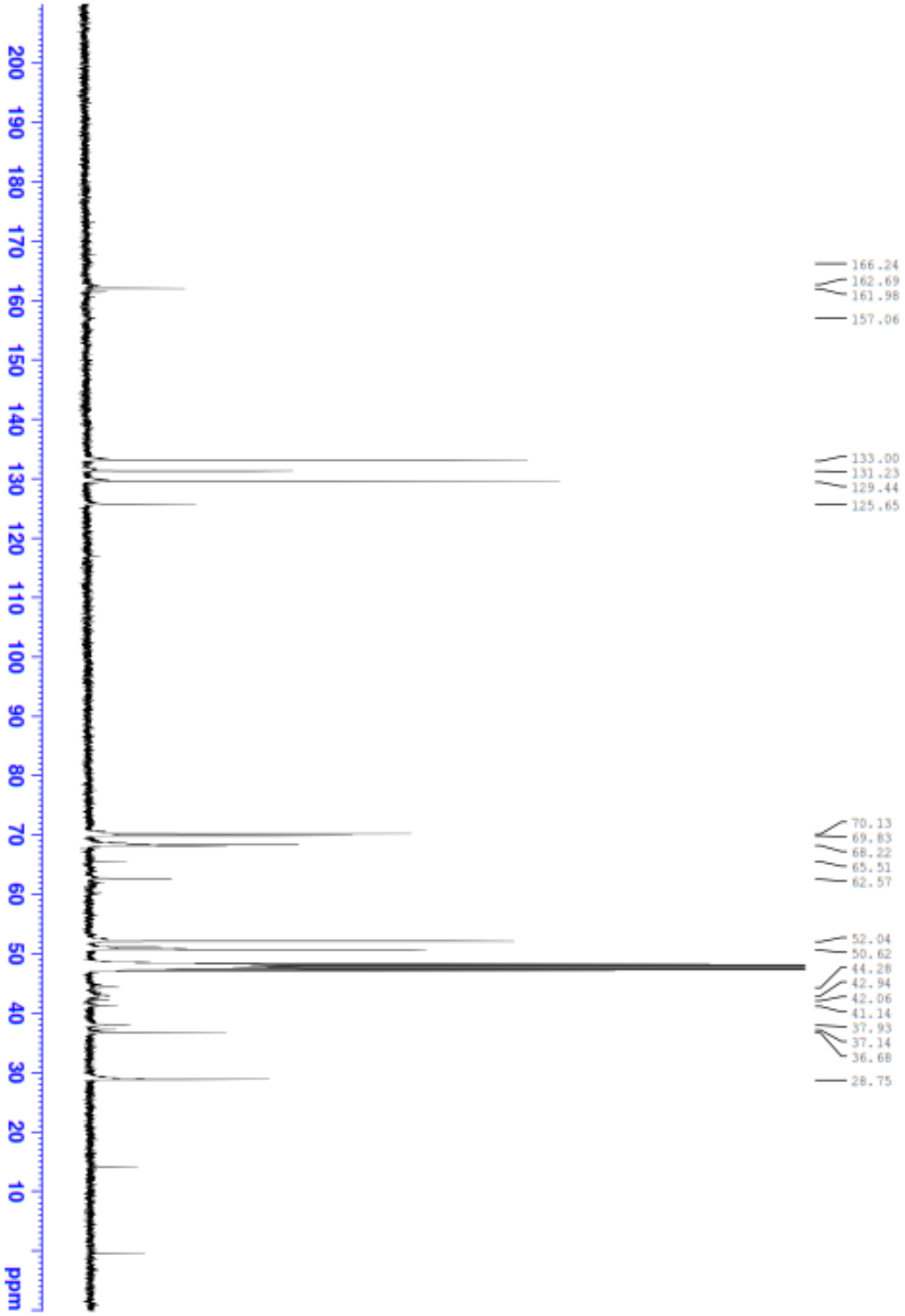
1-Bz (44 mg, 0.27 mmol) was added to a solution of **9c** (40 mg, 0.05 mmol) in methanol (1 ml). The above solution was stirred for 2 days at 55^0C and 1 day at room temperature. The crude product was purified by precipitation with methanol and acetonitrile. The final product is further washed with acetonitrile, diethyl ether and ethyl acetate to give a white solid (62 mg 91%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.68-7.60 (d, 15H, C_6**H**$_5$-), δ 4.86 (s, 6H, C_6H_5-C**H**$_2$-), δ 4.45 (s, 6H, -NHC(O)C**H**$_2$-), δ 4.33-4.15 (t, 36H, DABCO), δ 3.98 (t, 4H, -CH_2C**H**$_2$-N-C**H**$_2$$CH_2CH_2$-Piperazine), δ 3.65-3.61 (m, 32H, C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$C**H**$_2$OC**H**$_2$, C(O)-NHC**H**$_2$$CH_2CH_2O$, -$CH_2$C**H**$_2$-N-C**H**$_2$$CH_2$-Piperazine); δ 3.33 (m, 4H, C_3N_3-NHC**H**$_2$$CH_2CH_2O$) δ 1.87-1.80 (m, 8H, -$OCH_2$C**H**$_2$$CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 165.2 (**C**O), 162.6, 161.9 (**C**$_3N_3$), 157.0 (**C**O), 133.0, 131.2, 129.4, 125.6 (**C**$_6$$H_5$-), 70.1 (O**C**$H_2$**C**$H_2$O), 69.8 (O**C**$H_2$**C**$H_2$O), 68.2 ($NHCH_2CH_2$**C**$H_2$O), 65.5 (**C**$_6$$H_5$-$CH_2$), 62.5 ((CO)**C**$H_2$Cl), 52.0, 50.6 (DABCO), 42.9, 37.9 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 37.1, 36.6 (NH**C**$H_2CH_2CH_2O$), 28.7, ($NHCH_2$**C**H_2CH_2O);



SI Figure 33. ^{1}H NMR spectrum of compound **3-Bz**

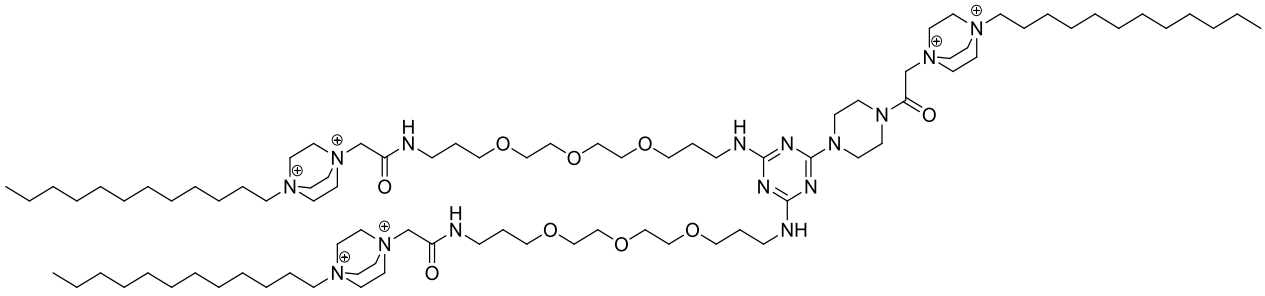


SI Figure 34. ^{13}C NMR spectrum of compound **3-Bz**

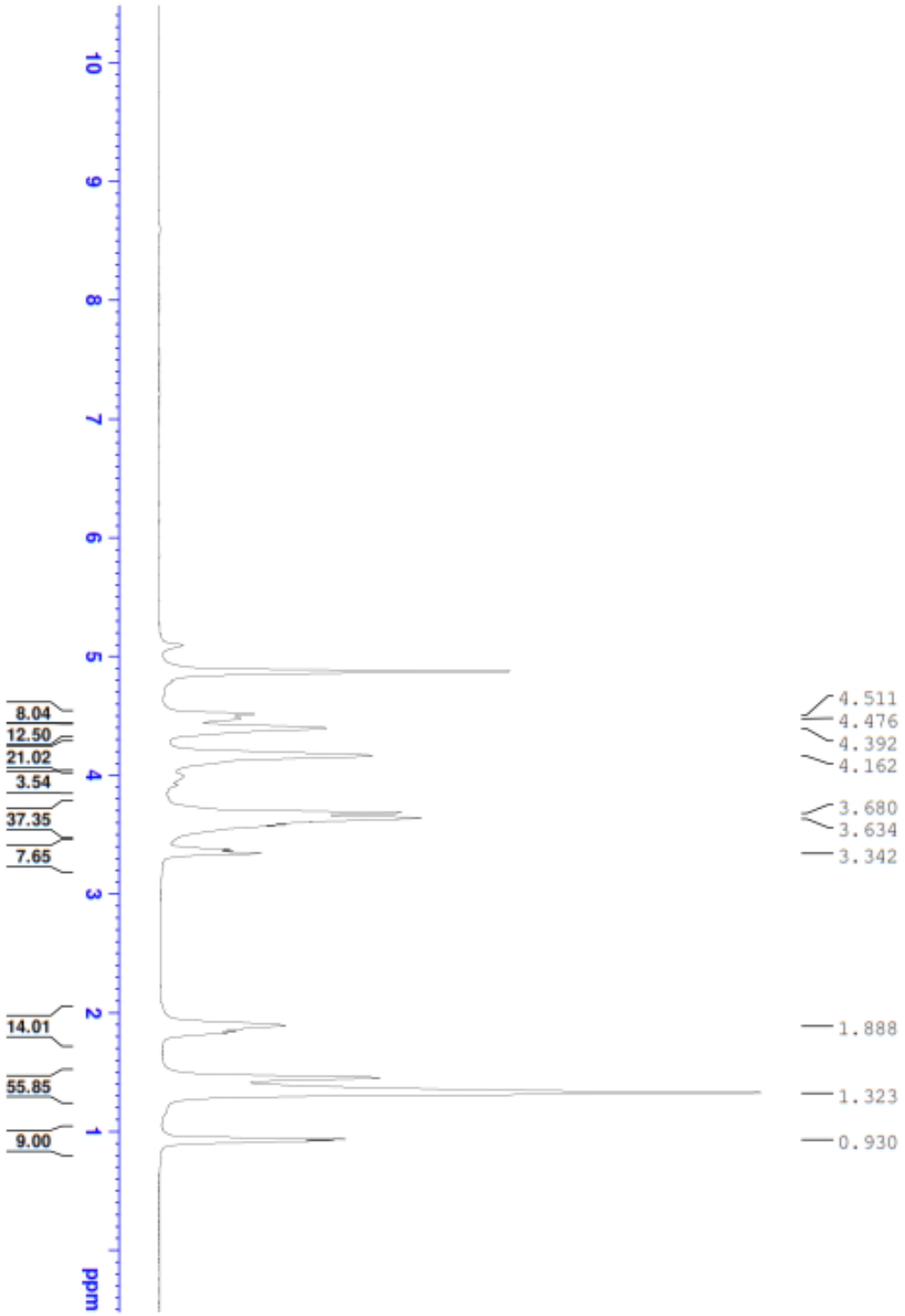


Compound **3-C12:**

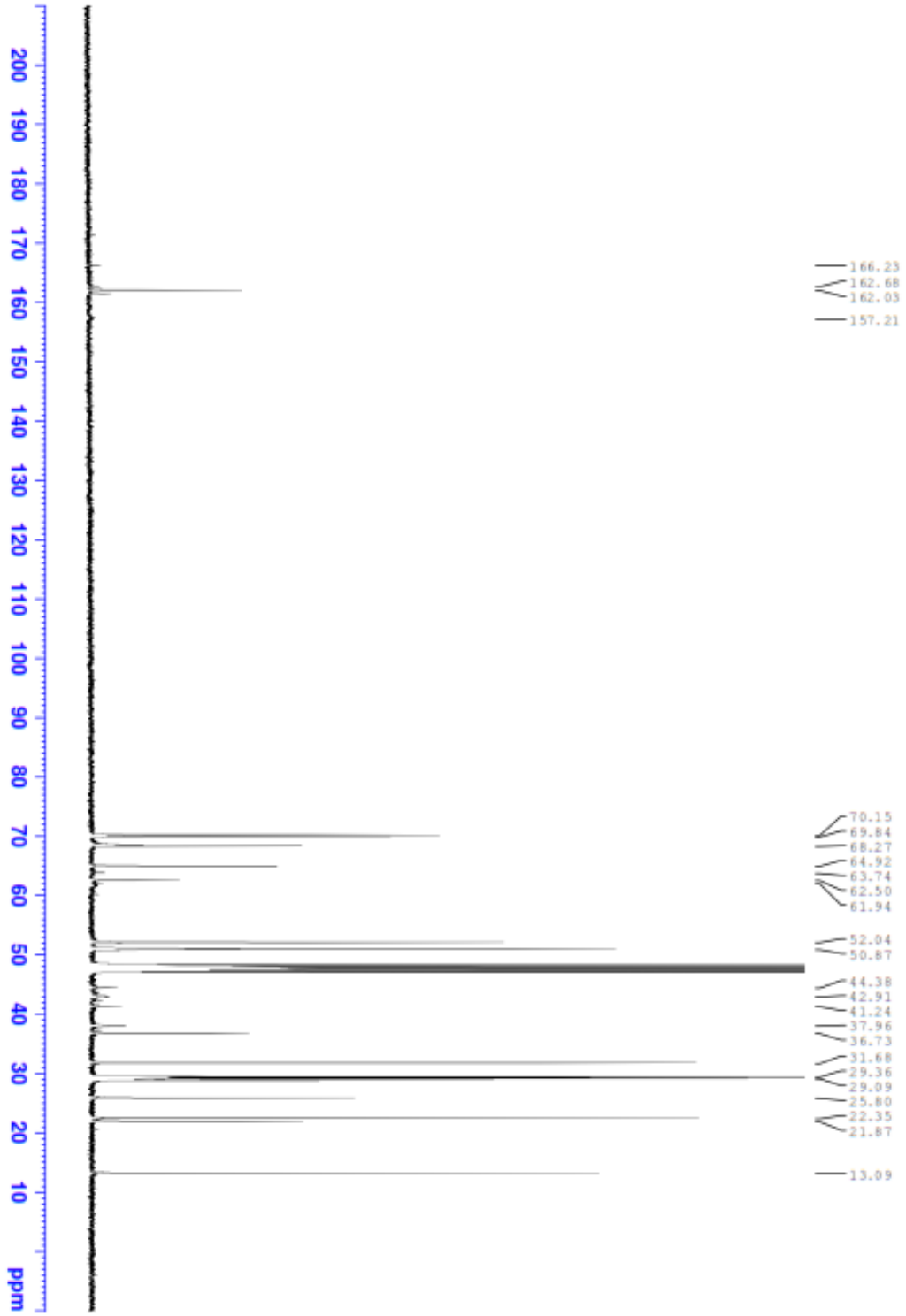
1-C12 (63 mg, 0.26 mmol) was added to a solution of **9c** (40 mg, 0.05 mmol) in methanol (1 ml). The solution was stirred for 2 days at 55^0C and 1 day at room temperature. The crude product was purified by precipitation with methanol and acetonitrile. The final product was further washed with acetonitrile, diethyl ether and ethyl acetate to give a white solid (60 mg, 76%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.51 (s, 6H, -NHC(O)C**H$_2$**-), δ 4.47-4.16 (t, 36H, DABCO), δ 3.98 (t, 4H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2CH_2-Piperazine), δ 3.68-3.63 (m, 32H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C(O)-NHC**H$_2$**CH_2CH_2O, -CH_2C**H$_2$**-N-C**H$_2$**CH_2-Piperazine); δ 3.34 (m, 8H, C_3N_3-NHC**H$_2$**CH_2CH_2O, -CH3$(CH_2)_9$C**H$_2$**CH_2), δ 1.88 (m, 14H, -OCH_2C**H$_2$**CH_2, -CH3(C**H$_2$**)$_9$$CH_2$C**H$_2$**-), 1.32 (m, 54H, -CH3(C**H$_2$**)$_9$$CH_2CH_2$-), 0.93 (t, 12H, C**H$_3$**$(CH_2)_9CH_2CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 166.2 (**C**O), 162.6, 162.0 (**C**$_3N_3$), 157.0 (**C**O), 70.15, 69.8 (O**C**H_2**C**H_2O), 68.2 (NHCH_2CH_2**C**H_2O), 64.9 ((CO)**C**H_2Cl), 62.5 (**C$_{12}$**H_{25}) 52.0, 50.8 (DABCO), 42.9, 37.9 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 36.7 (NH**C**$H_2CH_2CH_2O$), 31.6 (CH_3(**C**H_2)$_9$$CH_2CH_2$-),29.3, 29.0 (NH$CH_2$**C**$H_2CH_2O$), 25.8, 22.3, 21.8 (-CH3$(CH_2)_9$**C**H_2**C**H_2), 13.0 (**C**$H_3(CH_2)_9CH_2CH_2$);



SI Figure 35. ^{1}H NMR spectrum of compound **3-C12**

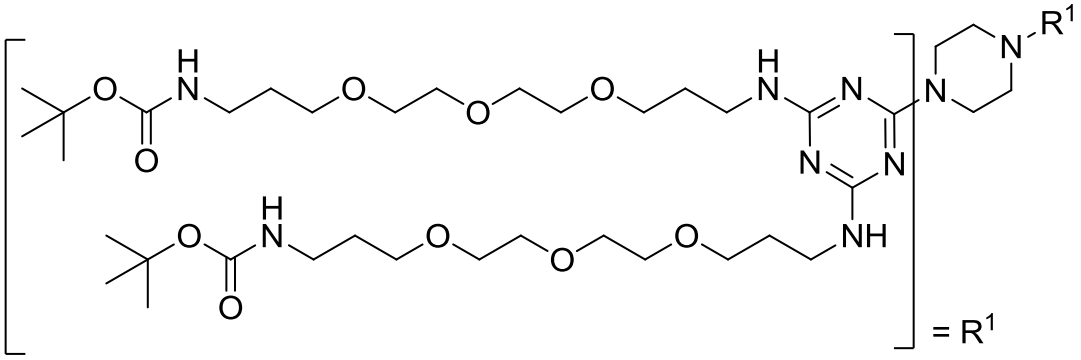


SI Figure 36. ^{13}C NMR spectrum of compound **3-C12**

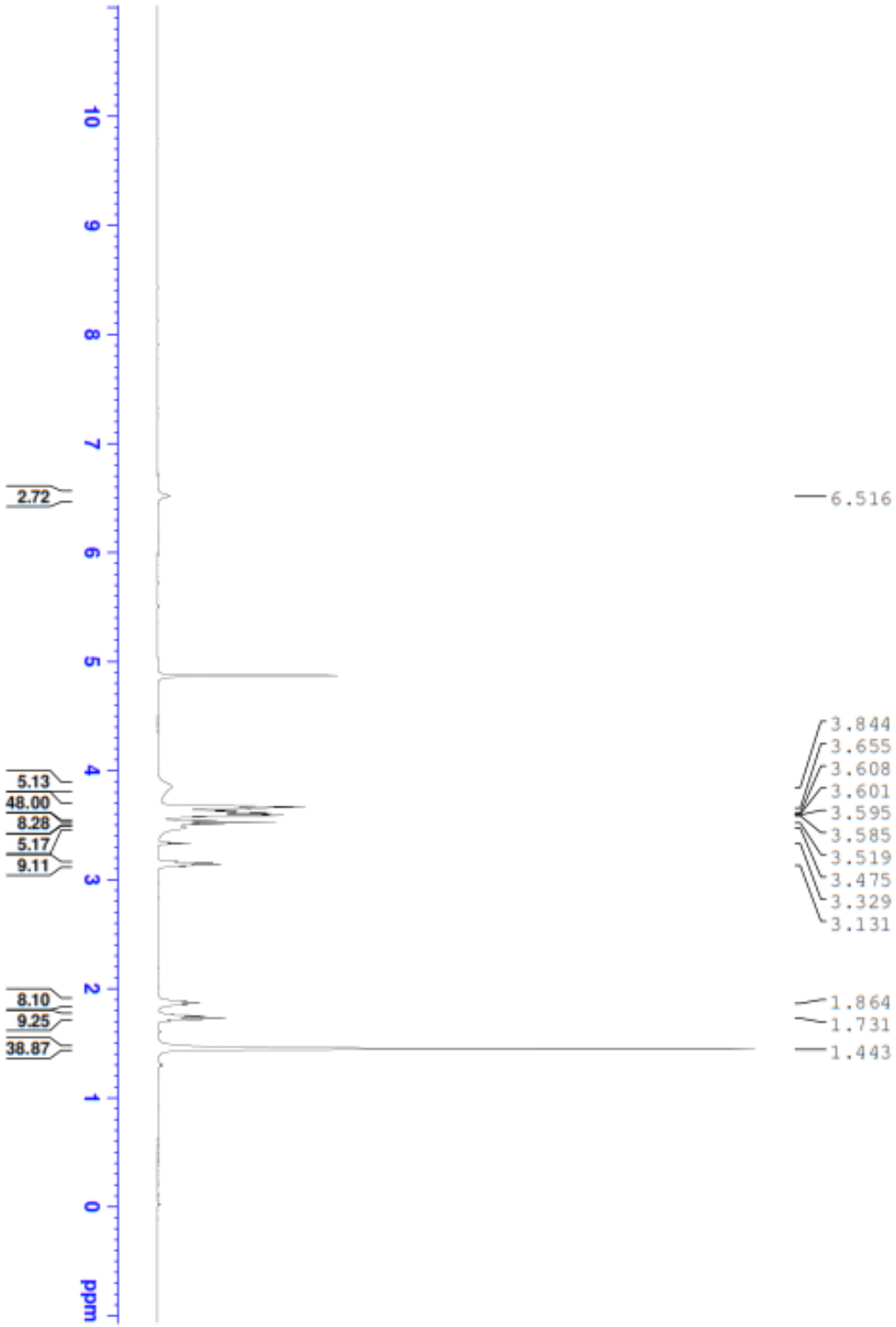


Compound **10a:**

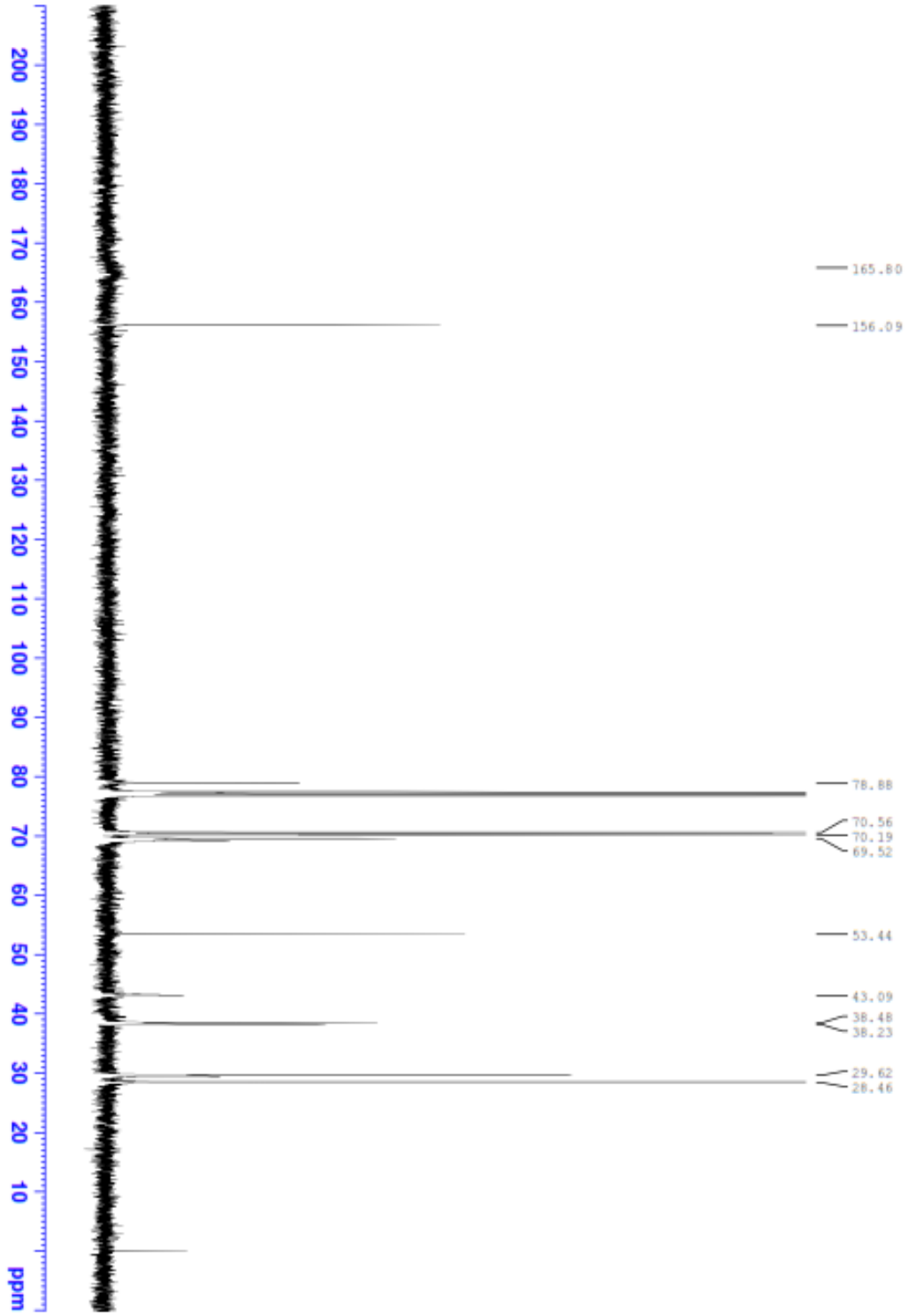
A solution of **7** (1.03 g, 1.37 mmol), piperazine (65 mg, 0.75mmol) and DIPEA (710 mg, 5.5 mmol) was dissolved in 7 ml of 4:1 mixture of THF and methanol. This solution was irradiated in microwave at 95^0C for 30 min. Then the solvent was evaporated under vacuum. The residue was dissolved in ethyl acetate and extracted with 1M HCl and dried over MgSO4, filtered, and then evaporated under vacuum to yield a clear oil (785 mg, 68%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.84 (t, 8H, -$CH_2C\mathbf{H_2}$-N-$C\mathbf{H_2}CH_2$-Piperazine), δ 3.65-3.58 (br, m, 48H, $C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}$), δ 3.51 (t, 8H, -$OCH_2CH_2C\mathbf{H_2}$NH), δ 3.13 (m, 8H -$OCH_2CH_2C\mathbf{H_2}$NH-), 1.86-1.73 (m, 16H, $OCH_2C\mathbf{H_2}CH_2$-); 1.44 (s, 36H, $C(C\mathbf{H_3})_3$); ^{13}C NMR (100 MHz, CD_3OD) δ 165.8 (**C**O), 156.09 ($\mathbf{C}_3N_3$), 78.8 $\mathbf{C}(CH_3)_3$), 70.5, 70.1 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 69.5 ($\mathbf{C}H_2OCH_2CH_2O\mathbf{C}H_2$), 53.44 ($NHCH_2CH_2\mathbf{C}H_2O$), 43.09 (-$\mathbf{C}H_2\mathbf{C}H_2$-N-$\mathbf{C}H_2\mathbf{C}H_2$-), 38.4, 38.2 ($NH\mathbf{C}H_2CH_2CH_2O$), 29.6 ($NHCH_2\mathbf{C}H_2CH_2O$), 28.4 ($C(\mathbf{C}H_3)_3$); MS (ESI-TOF) calcd for $C_{70}H_{132}N_{16}O_{20}$, 1517.89, found 1517.99, 759.51.



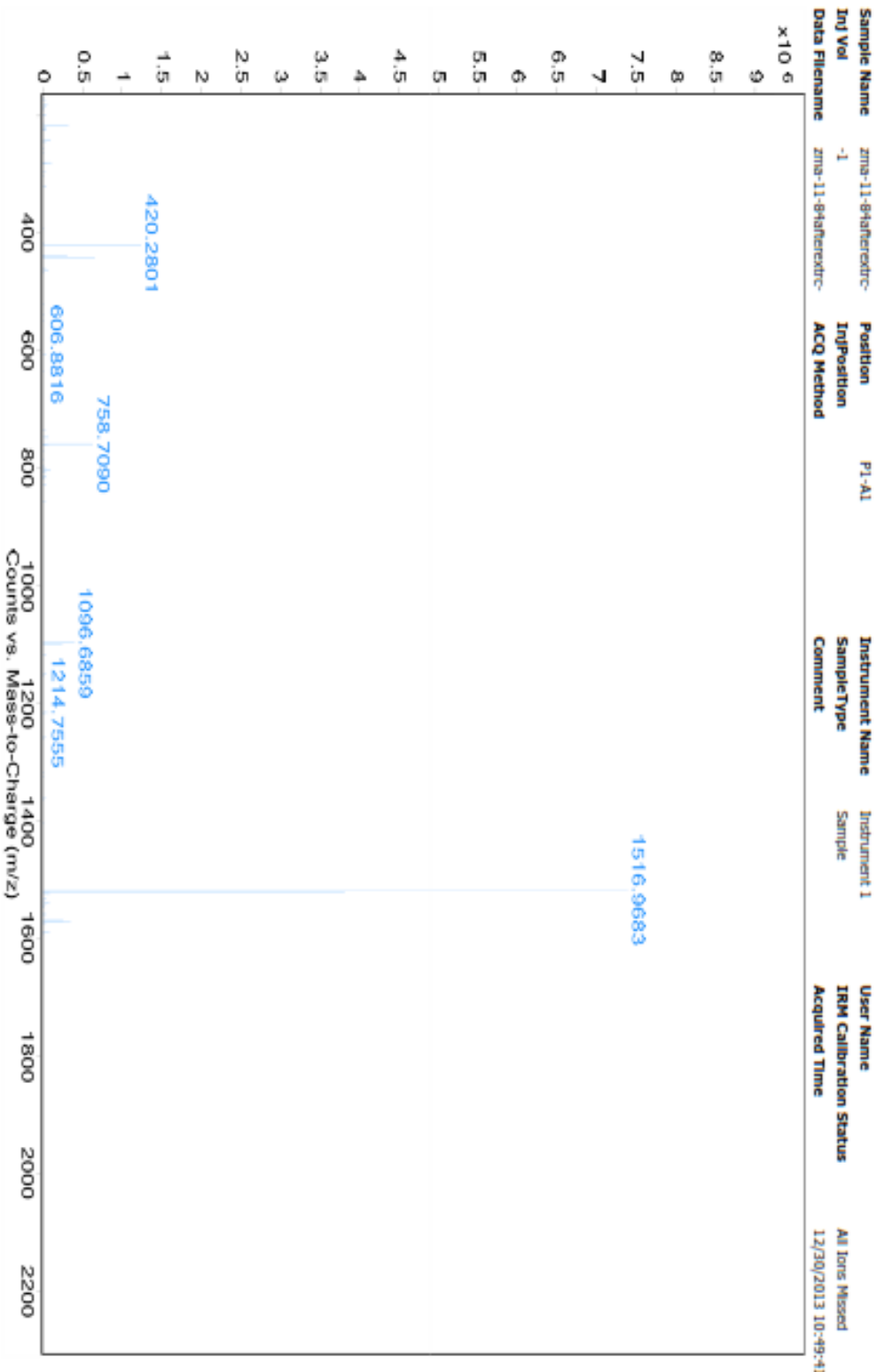
SI Figure 37. ^{1}H NMR spectrum of compound **10a**



SI Figure 38. ^{13}C NMR spectrum of compound **10a**

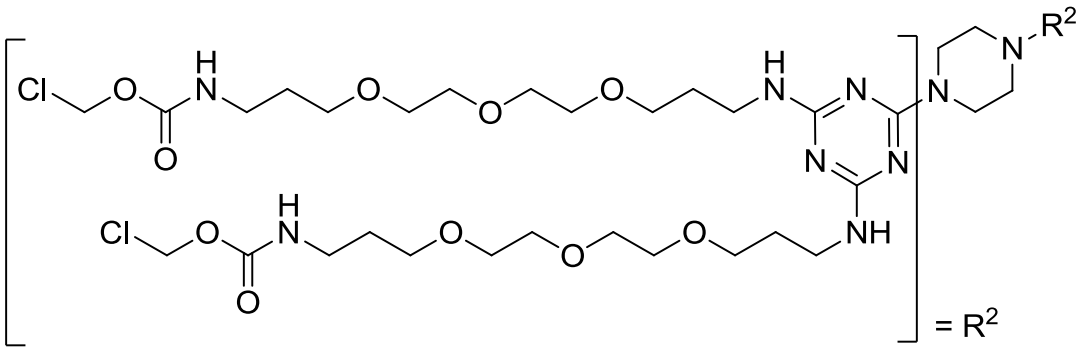


SI Figure 39. Mass spectrum of compound **10a**

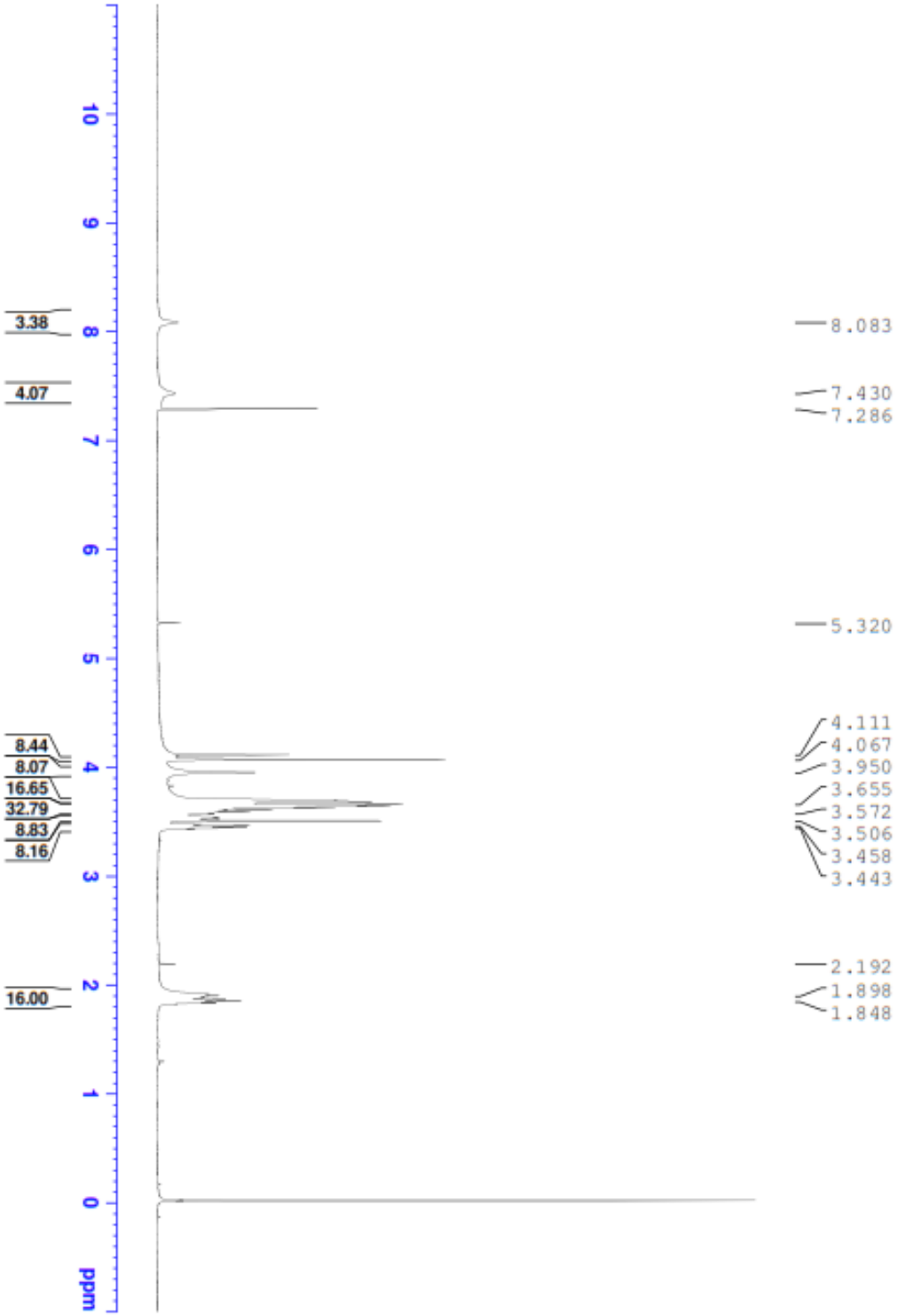


Compound **10c:**

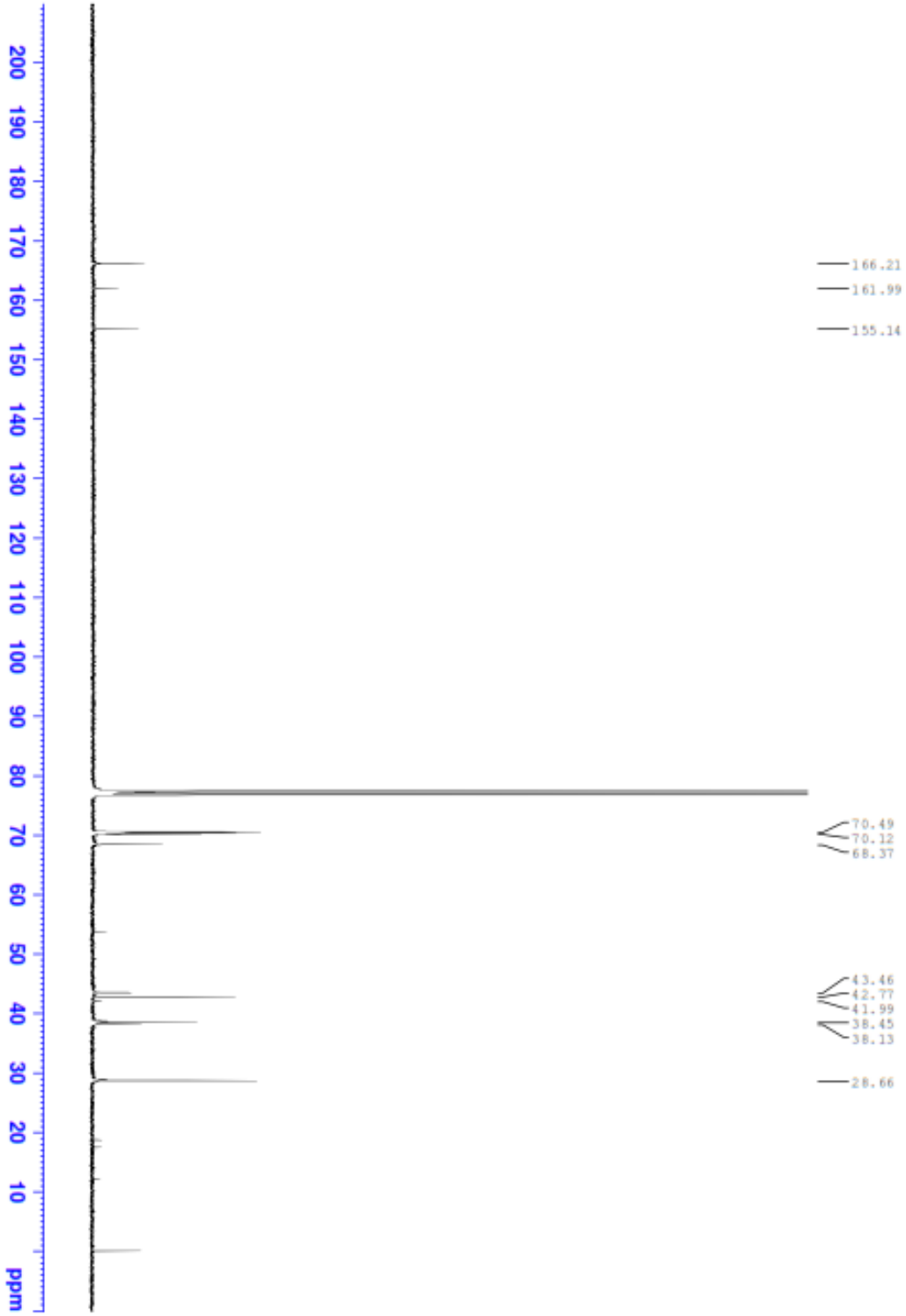
Chloroacetyl chloride (0.352 ml, 0.45 mmol) was added drop wise to the solution of **10b** compound (540 mg, 0.29 mmol) in dichloromethane (6 ml) at 0ºC and was stirred for 2 hrs. Then the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and then evaporated under vacuum. The crude was purified using automated chromatography to yield a clear oil (446 mg 69 %). ^{1}H NMR (400 MHz, $CDCl_3$) δ 4.11 (s, 8H, -NHC(O)C**H$_2$**Cl), δ 4.06 (t, 8H, -C**H$_2$**C**H$_2$**-N-C**H$_2$**C**H$_2$**-Piperazine) δ 3.95 (t, 16H, OCH_2CH_2OC**H$_2$**), δ 3.65 (t, 32H, OC**H$_2$**C**H$_2$**O), δ 3.57 (m, 8H -OCH_2CH_2C**H$_2$**NH), δ 3.50 (m, 8H -OCH_2CH_2C**H$_2$**NH-), 1.89-1.84 (m, 16H, -OCH_2C**H$_2$**CH_2NH); ^{13}C NMR (100 MHz, $CDCl_3$) δ 166.2, 161.9 (**C**$_3N_3$), 155.14, (**C**O), 70.49 (O**C**H_2**C**H_2O), 68.37 (OCH_2CH_2OC**H$_2$**), 43.4 (NH**C**$H_2CH_2CH_2O$), 42.7 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 38.4, 38.1 (NH**C**$H_2CH_2CH_2O$), 28.6 ($NHCH_2$**C**H_2CH_2O); MS (ESI-TOF) calcd for $C_{58}H_{104}Cl_4N_{16}O_{16}$, 1423.36, found 1423.692, 712.347.



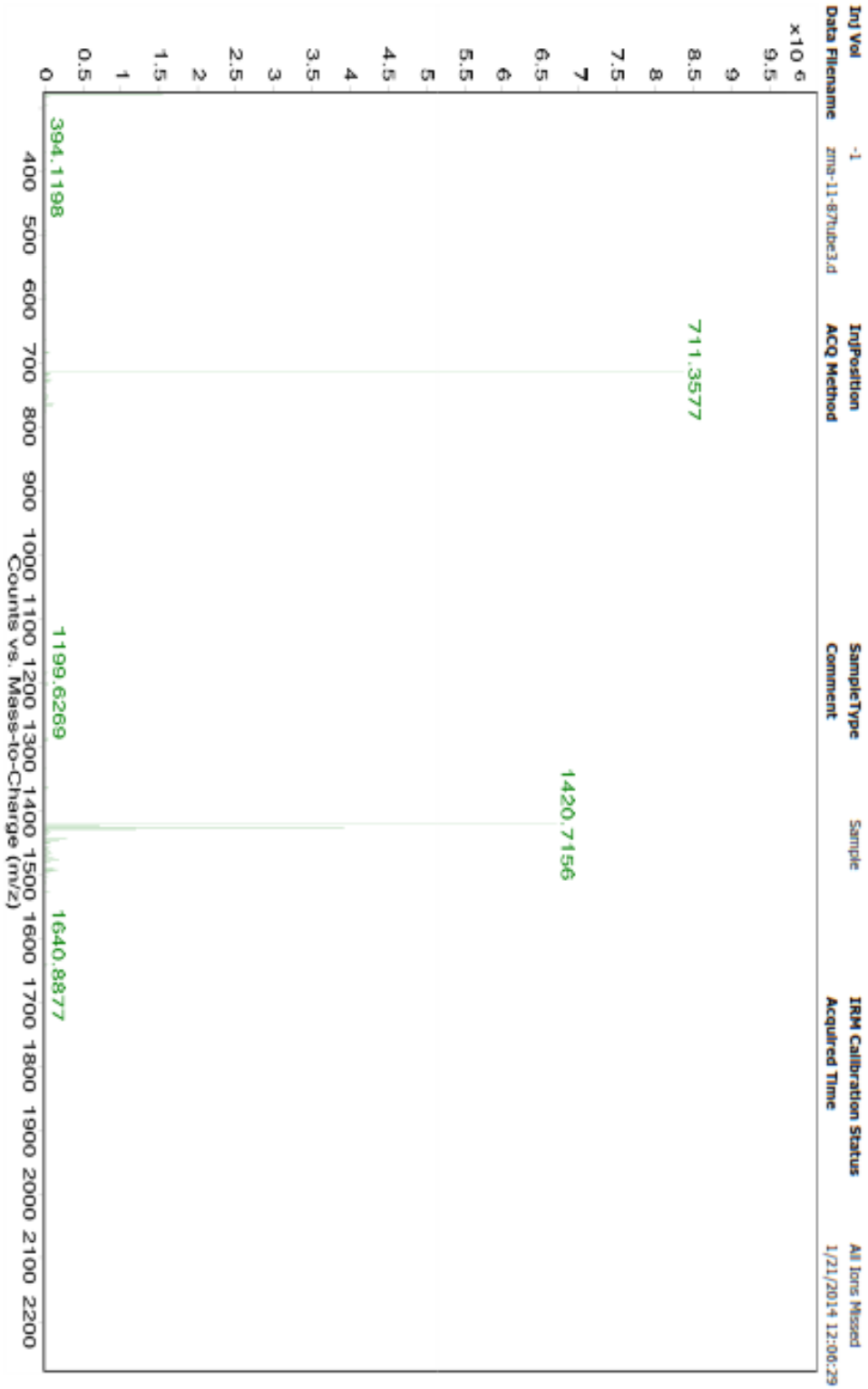
SI Figure 40. ^{1}H NMR spectrum of compound **10c**



SI Figure 41. ^{13}C NMR spectrum of compound **10c**

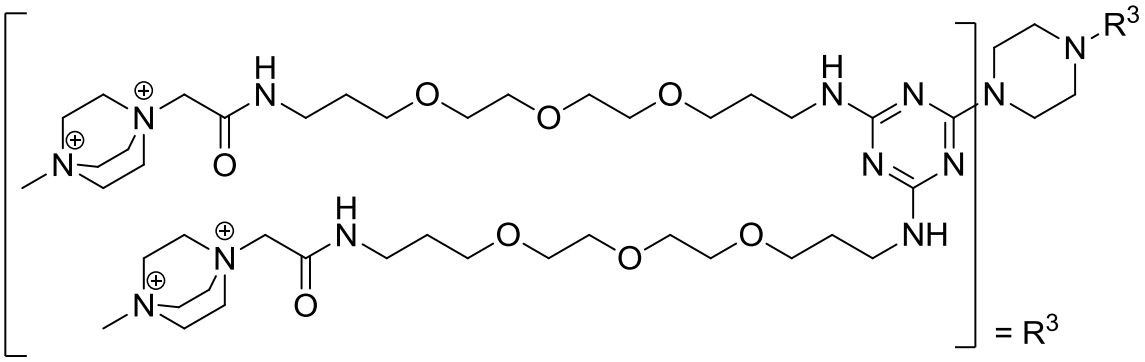


SI Figure 42. Mass spectrum of compound **10c**

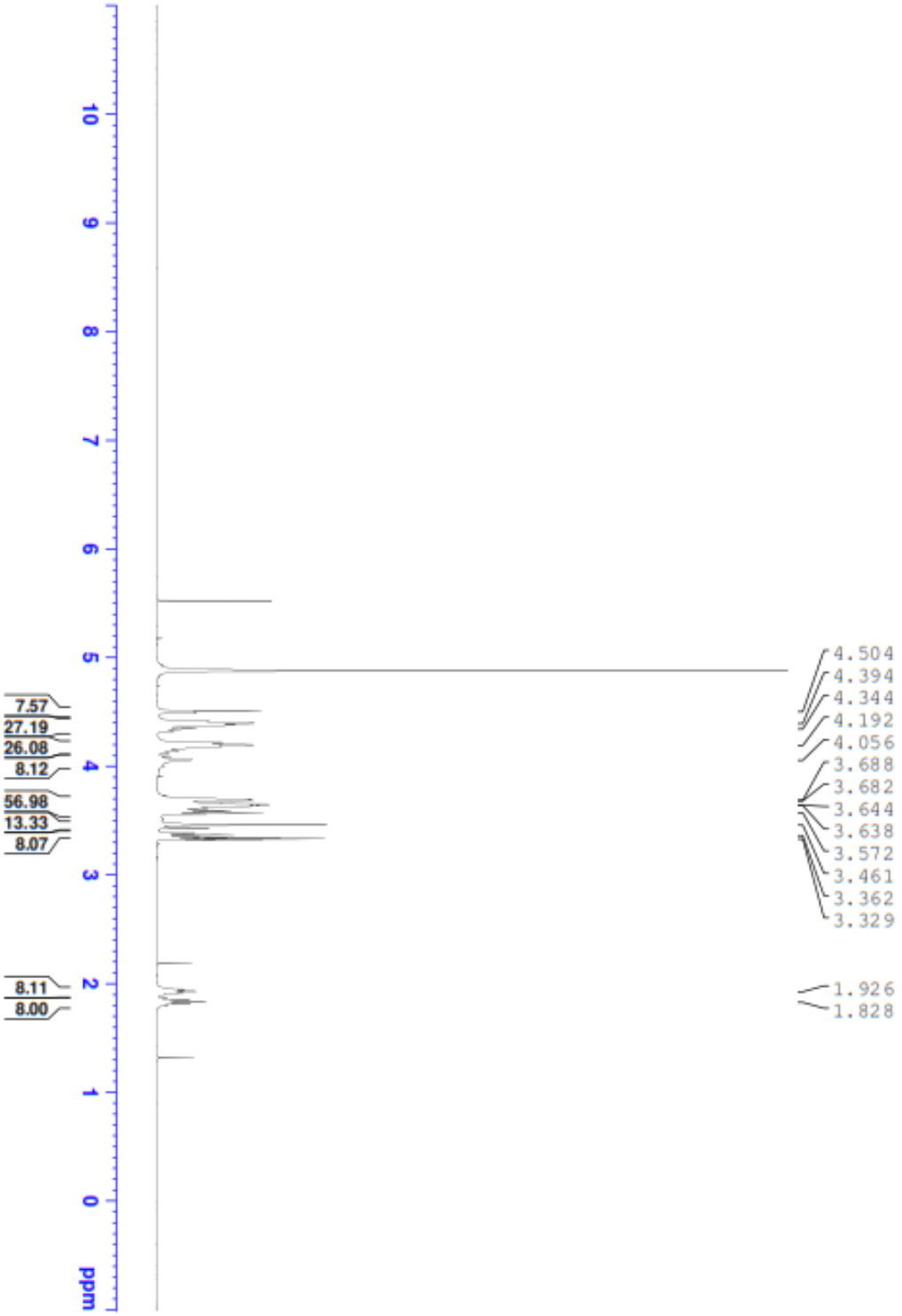


Compound **4-Me**

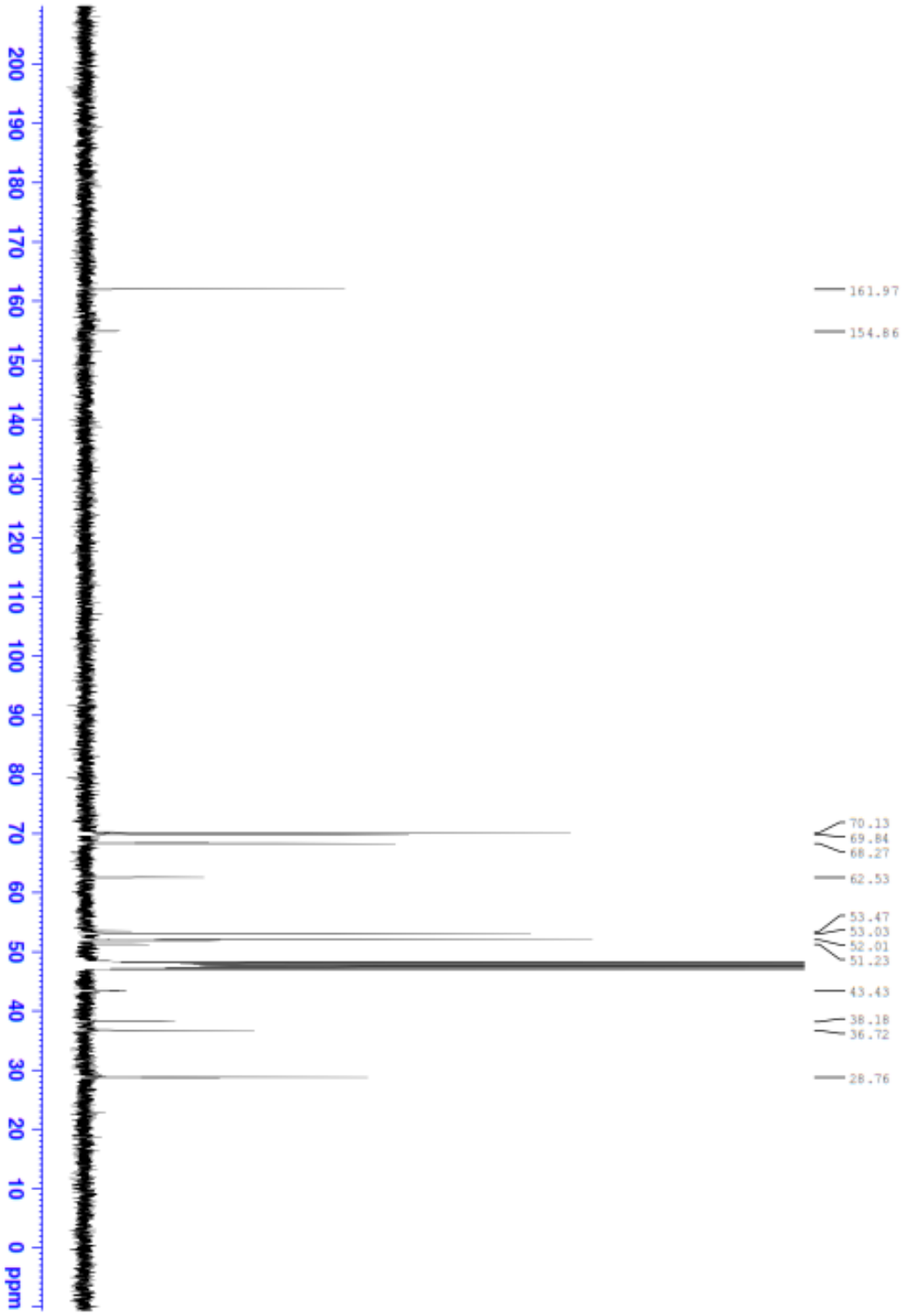
1-Me (31 mg, 0.24 mmol) was added to a solution of **10c** (50 mg, 0.04 mmol) in methanol (1 ml). The above solution was stirred for 2 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was washed further with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to give a pale yellow solid (60 mg 73%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.50 (s, 8H, -NHC(O)C**H$_2$**-), δ 4.39-4.19 (t, 48H, DABCO), δ 4.05 (t, 8H, -C**H$_2$**C**H$_2$**-N-C**H$_2$**C**H$_2$**-Piperazine), δ 3.68-3.57 (t, 56H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), δ 3.46 (s, 12H, -C**H$_3$**), δ 3.36 (t, 8H, $NHCH_2$**C**H_2CH_2O), δ 1.92-1.82 (m, 8H, -OCH_2C**H$_2$**CH_2);^{13}C NMR (100 MHz, CD_3OD) δ 161.9 (**C**$_3N_3$), 154.8 (**C**O), 70.1, 69.8 (O**C**H_2**C**H_2O), 68.2 ($NHCH_2CH_2$**C**H_2O), 62.5 ((CO)**C**H_2Cl), 53.0, 52.0 (DABCO), 51.2 (-C**C**H_3), 43.4, (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 38.1, 36.7 (NH**C**$H_2CH_2CH_2O$), 28.7, ($NHCH_2$**C**H_2CH_2O);



SI Figure 43. ^{1}H NMR spectrum of compound **4-Me**

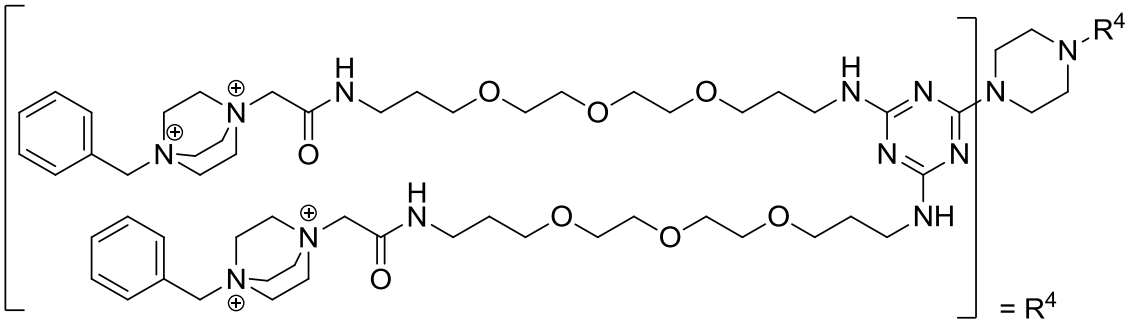


SI Figure 44. ^{13}C NMR spectrum of compound **4-Me**

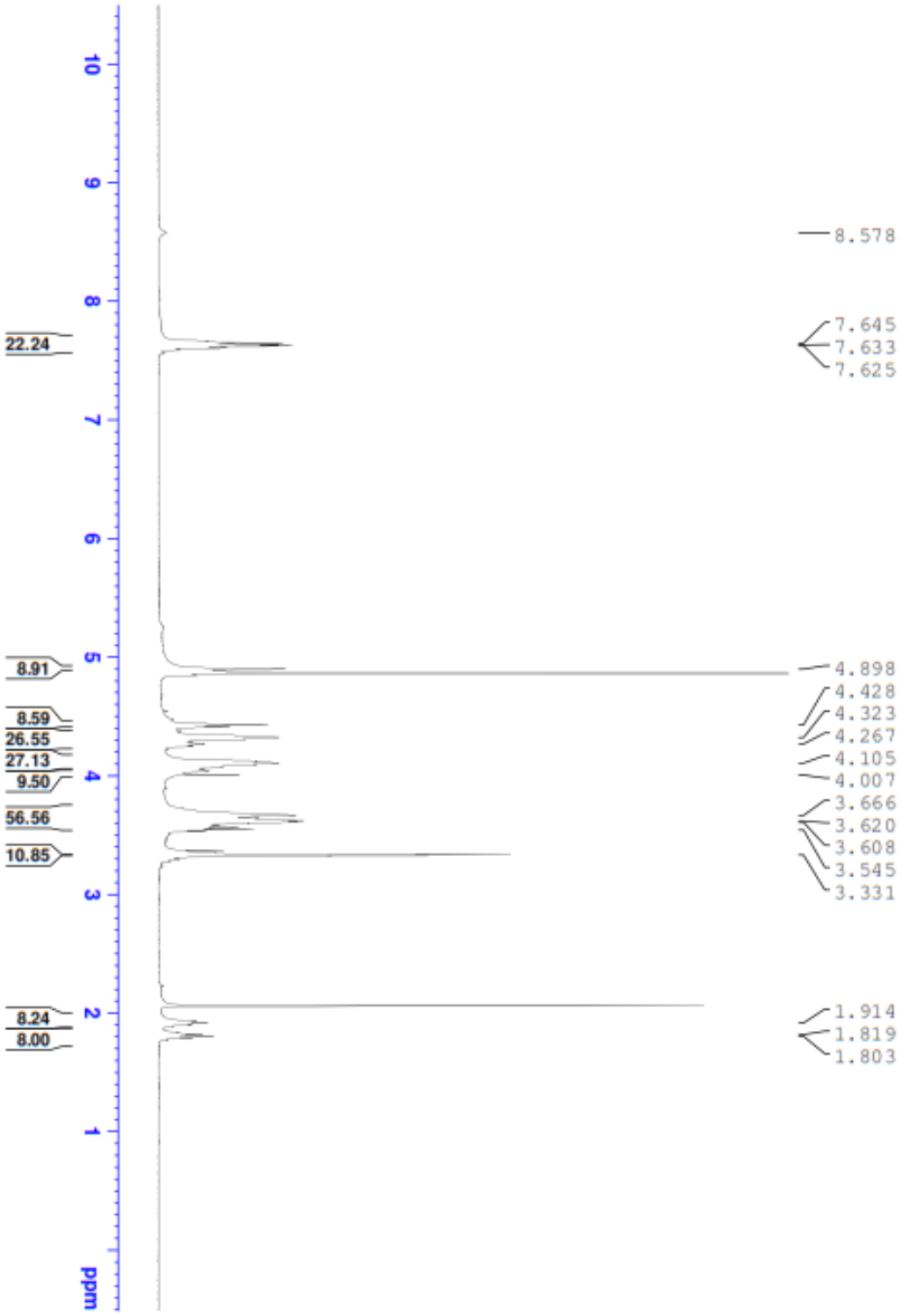


Compound **4-Bz:**

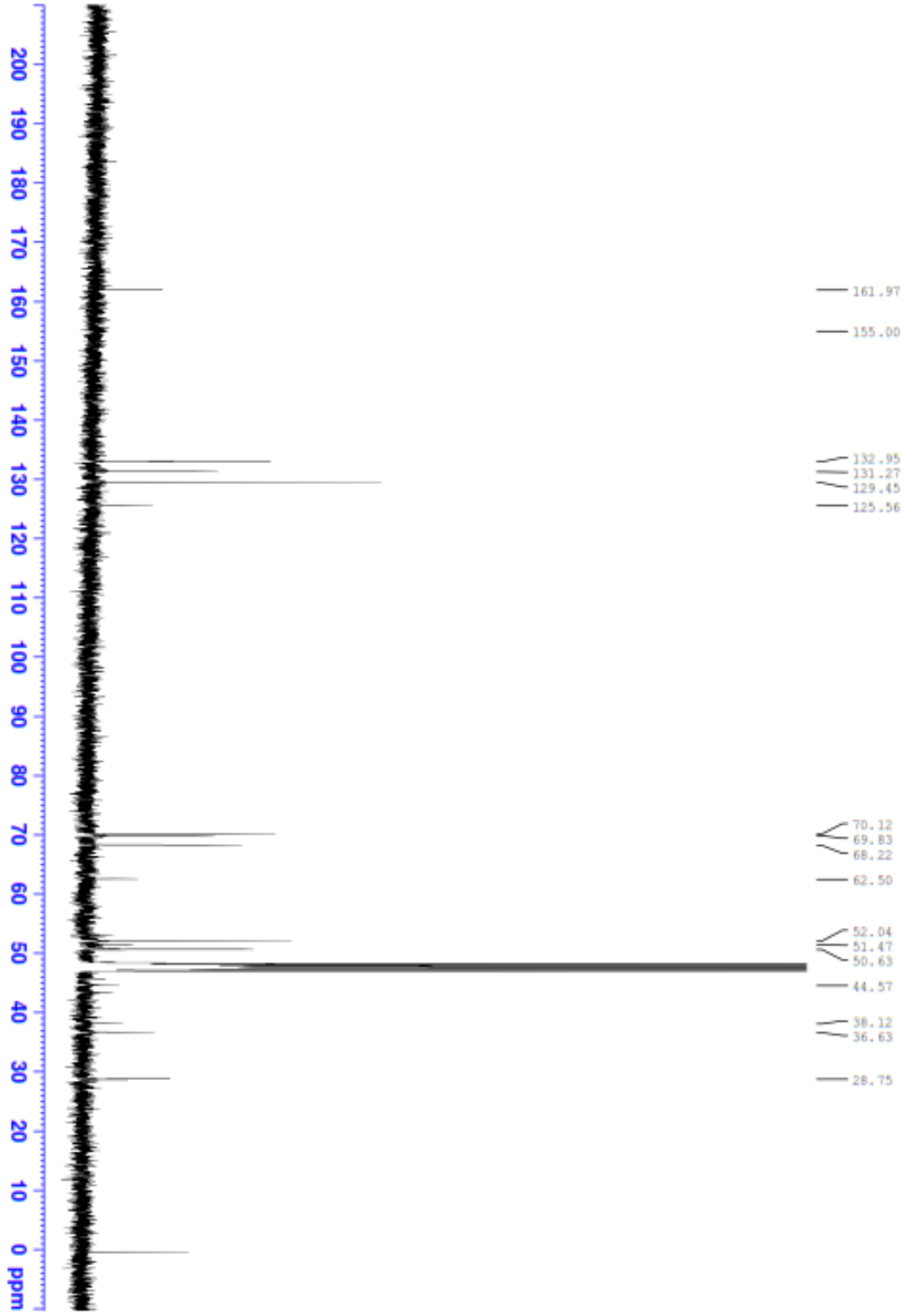
1-Bz (65 mg, 0.32 mmol) was added to a solution of **10c** (75mg, 0.05 mmol) in methanol (1 ml). The solution was stirred for 2 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was washed further with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to yield a white solid (82 mg, 79%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.64-7.62 (d, 20H, $C_6\mathbf{H_5}$-), δ 4.89 (s, 8H, C_6H_5-C$\mathbf{H_2}$-), δ 4.42 (s, 8H, -NHC(O)C$\mathbf{H_2}$-), δ 4.32-4.10 (t, 48H, DABCO), δ 4.00 (t, 8H, -C$\mathbf{H_2}$C$\mathbf{H_2}$-N-C$\mathbf{H_2}$C$\mathbf{H_2}$-Piperazine), δ 3.66-3.54 (t, 56H, C$\mathbf{H_2}$OC$\mathbf{H_2}$C$\mathbf{H_2}$OC$\mathbf{H_2}$C$\mathbf{H_2}$OC$\mathbf{H_2}$, C_3N_3-NHC$\mathbf{H_2}$$CH_2CH_2O$), δ 3.36 (t, 8H, $NHCH_2$**C**H_2CH_2O), δ 1.81-1.80 (m, 8H, -OCH_2C$\mathbf{H_2}$$CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 161.9, (**C**$_3N_3$), 155.0 (**C**O), 132.9, 131.2, 129.4, 125.5, (**C$_6$**H_5-), 70.1, 69.83 (O**C**H_2**C**H_2O), 68.2 ($NHCH_2CH_2$**C**H_2O), 62.5 ((CO)**C**H_2Cl)), 52.0 (**C$_6$**H_5-CH_2), 51.4, 50.6 (DABCO), 44.5, 43.3 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 38.1, 36.6 (NH**C**$H_2CH_2CH_2O$), 28.7, ($NHCH_2$**C**H_2CH_2O);



SI Figure 45. ^{1}H NMR spectrum of compound **4-Bz**

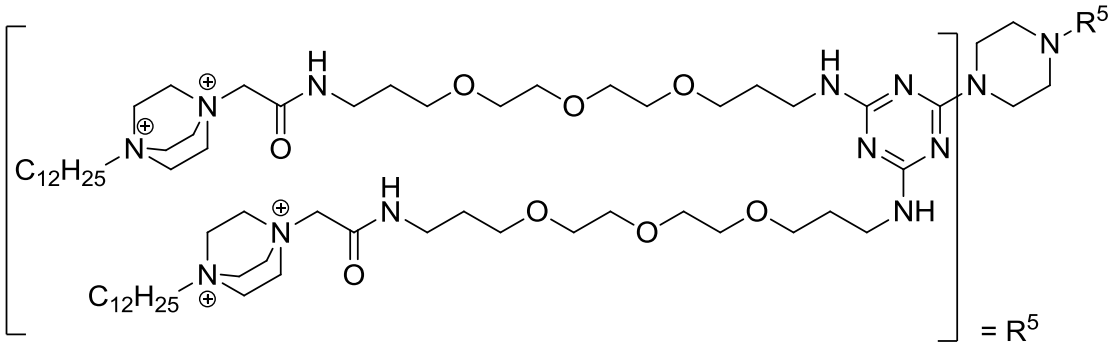


SI Figure 46. ^{13}C NMR spectrum of compound **4-Bz**

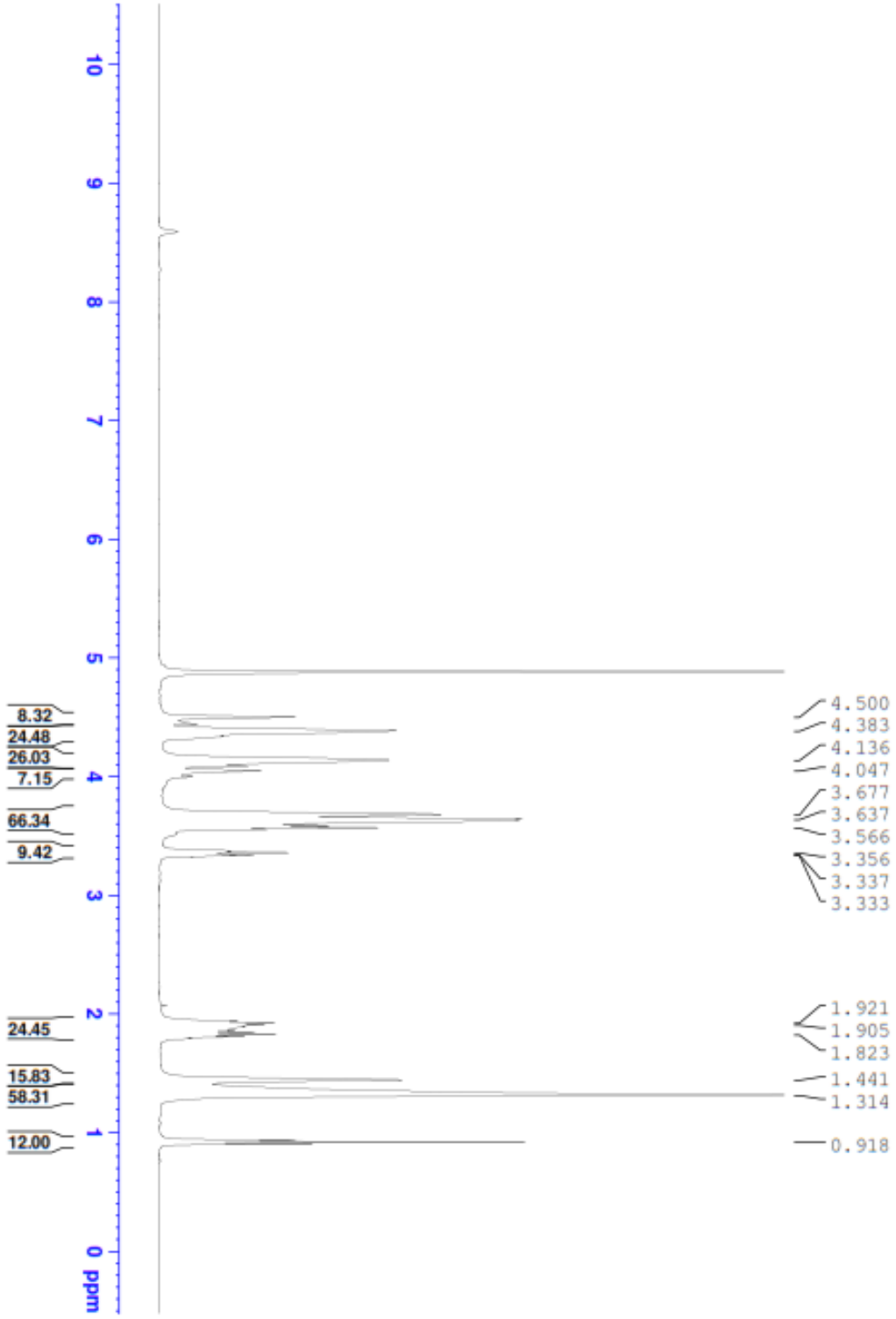


Compound **4-C12:**

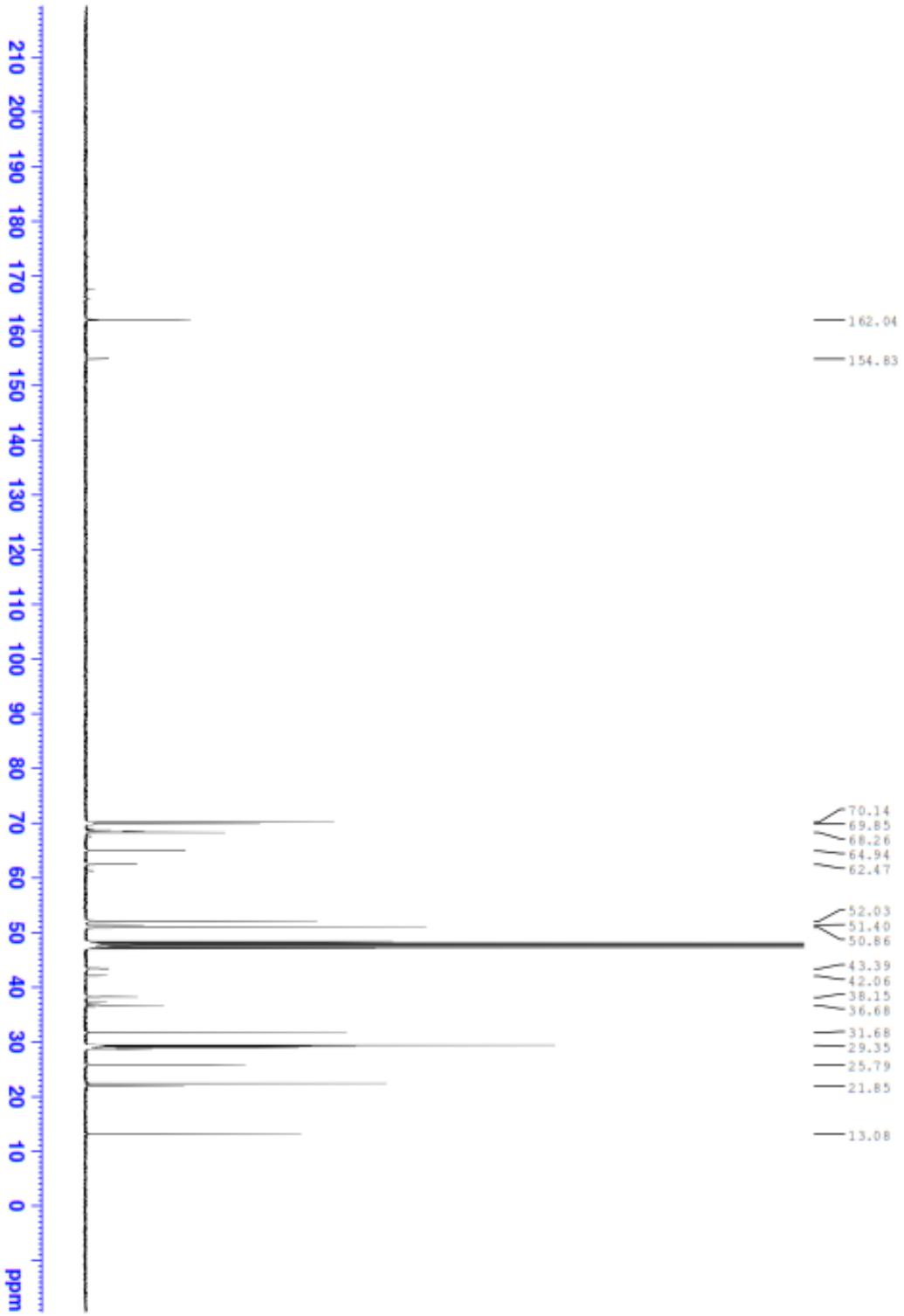
1-C12 (89 mg, 0.32 mmol) was added to a solution of **10c** (75 mg, 0.05 mmol) in methanol (1 ml). The above solution was stirred for 2 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was washed further with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to yield a white solid (93 mg, 79%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.50 (s, 8H, -NHC(O)C**H$_2$**-), δ 4.38-4.13 (t, 48H, DABCO), δ 4.04 (t, 8H, -C**H$_2$**C**H$_2$**-N-C**H$_2$**C**H$_2$**-Piperazine), δ 3.67-3.56 (t, 64H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O, -$CH3(CH_2)_9CH_2$C**H$_2$**-), δ 3.33 (t, 8H, $NHCH_2$**C**H_2CH_2O), δ 1.92-1.82 (m, 24H, -OCH_2C**H$_2$**CH_2, -$CH3(CH_2)_9$C**H$_2$**CH_2), 1.44-1.31 (m, 72H, -$(CH3(CH_2)_9CH_2CH_2$-), 0.91 (t, 12H, C**H$_3$**$(CH_2)_9CH_2CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 162.0 (**C**$_3N_3$), 154.8 (**C**O), 70.1, 69.8 (O**C**H_2**C**H_2O), 68.2 ($NHCH_2CH_2$**C**H_2O), 64.9 ((CO)**C**H_2Cl), 62.4 (**C$_{12}$**H_{25}) 52.0, 50.8 (DABCO), 43.3, 42.0 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 38.1 (NH**C**$H_2CH_2CH_2O$), 36.6 ($NHCH_2$**C**H_2CH_2O), 31.6, 29.3, 28.8 ($CH3$(**C**H_2)$_9$$CH_2CH_2$-), 25.7, 22.3 (-$CH3(CH_2)_9$**C**$H_2$**C**$H_2$), 13.0 (**C**$H_3(CH_2)_9CH_2CH_2$);



SI Figure 47. ^{1}H NMR spectrum of compound **4-C12**

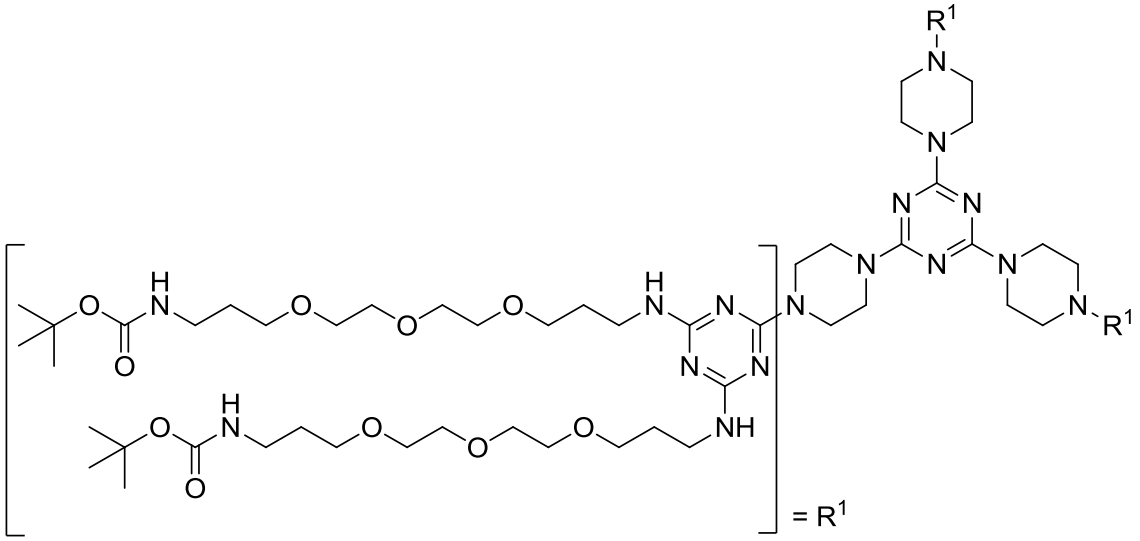


SI Figure 48. ^{13}C NMR spectrum of compound **4-C12**

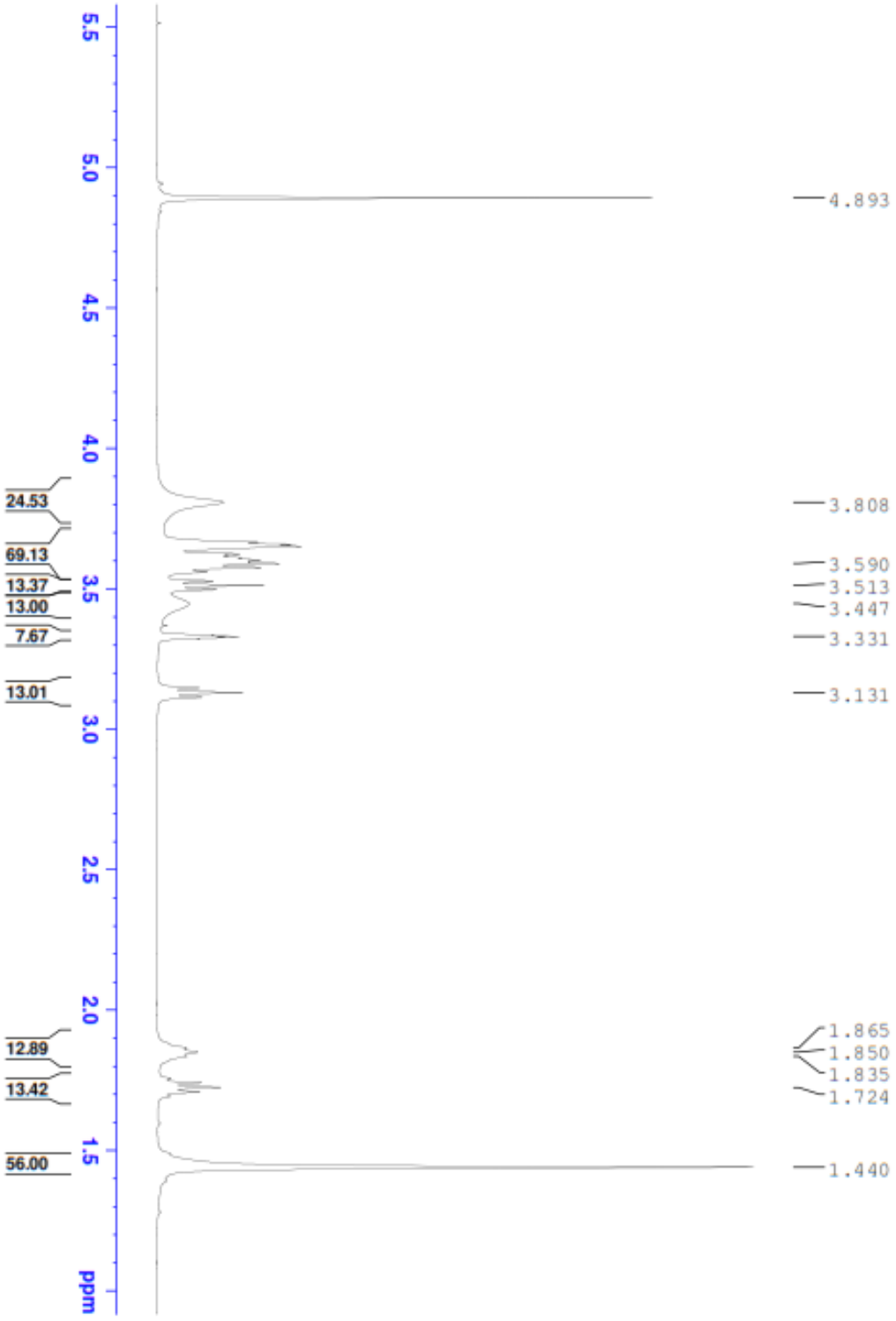


Compound **11a:**

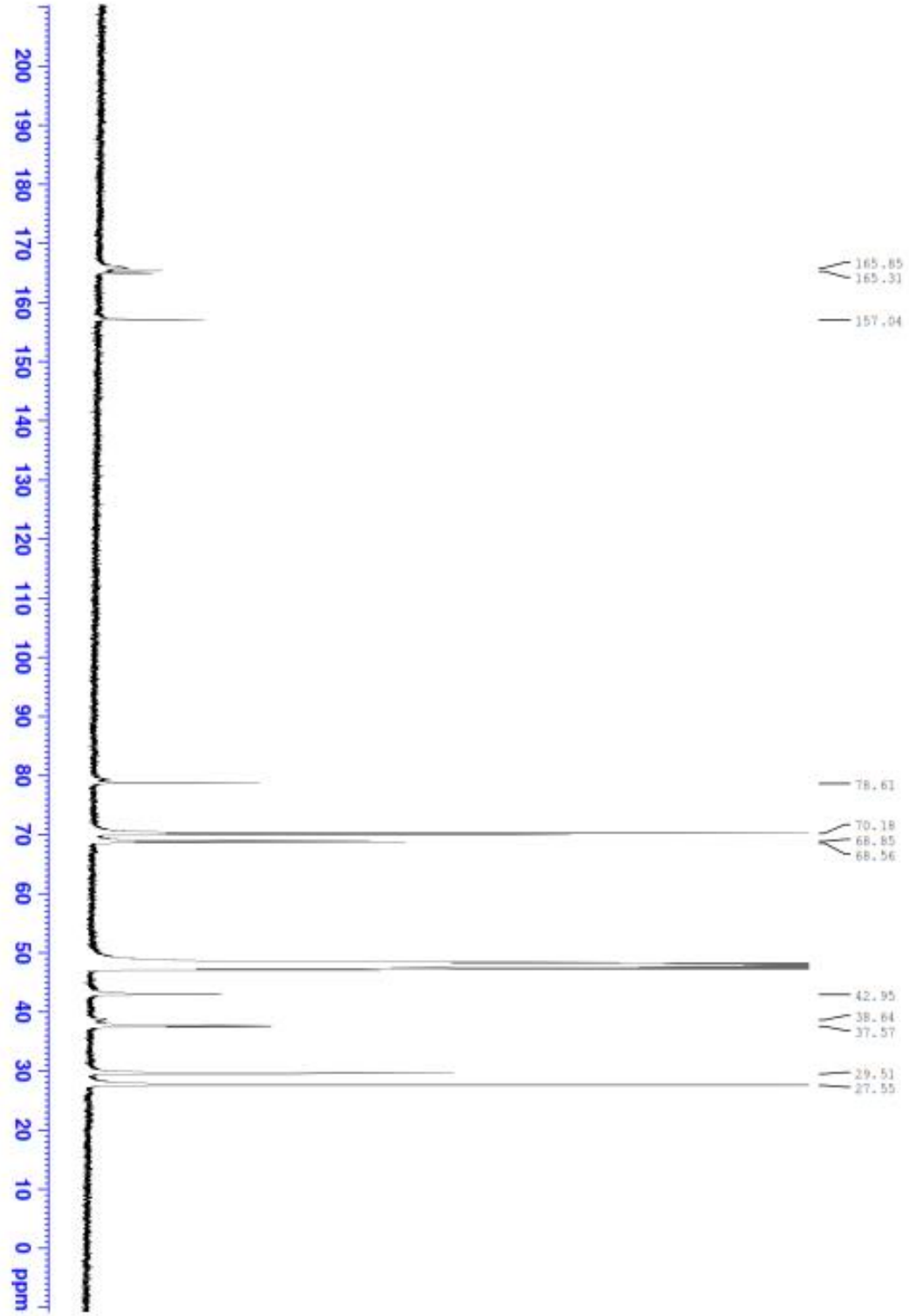
A solution of **7** (750 mg, 0.23 mmol) with 1- tert-butoxycarbonyl piperazine (778 mg, 1.03 mmol) and DIPEA (0.1789 ml, 1.03 mmol) in 20 ml of acetonitrile was stirred for 2 minutes. Then, the solution was irradiated in the microwave at 85ºC for 60 min of stirring. The solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and then evaporated under vacuum. The crude product was purified using automated chromatography to yield a clear oil (338 mg, 91%). ^{1}H NMR (400 MHz, CD_3OD) δ 3.80 (t, 24H, -$CH_2C\mathbf{H_2}$-N-$C\mathbf{H_2}CH_2$-Piperazine), δ 3.65-3.51 (br, m, 72H, $C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}$), δ 3.44 (m, 12H -$OCH_2CH_2C\mathbf{H_2}$NH), δ 3.13 (m, 12H -$OCH_2CH_2C\mathbf{H_2}$NH-), 1.86-1.72 (m, 24H, $OCH_2C\mathbf{H_2}CH_2$-); 1.44 (s, 54H, $C(C\mathbf{H_3})_3$);
^{13}C NMR (100 MHz, CD_3OD) δ 165.8, 165.3, 164.9 ($\mathbf{C}_3N_3$), 157.0 (**C**O), 78.6 $\mathbf{C}(CH_3)_3$), 70.1 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 69.8 ($O\mathbf{C}H_2\mathbf{C}H_2O$), 68.8 ($NHCH_2CH_2\mathbf{C}H_2O$), 68.5 ($NHCH_2CH_2\mathbf{C}H_2O$), 42.9 (-$CH_2C\mathbf{H_2}$-N-$C\mathbf{H_2}CH_2$-), 37.5 ($NH\mathbf{C}H_2CH_2CH_2O$), 29.5 ($NHCH_2\mathbf{C}H_2CH_2O$), 27.5 ($C(\mathbf{C}H_3)_3$); MS (ESI-TOF) calcd for $C_{114}H_{210}N_{30}O_{30}$, 2481.07, found 2480.8115 $(M)^+$.



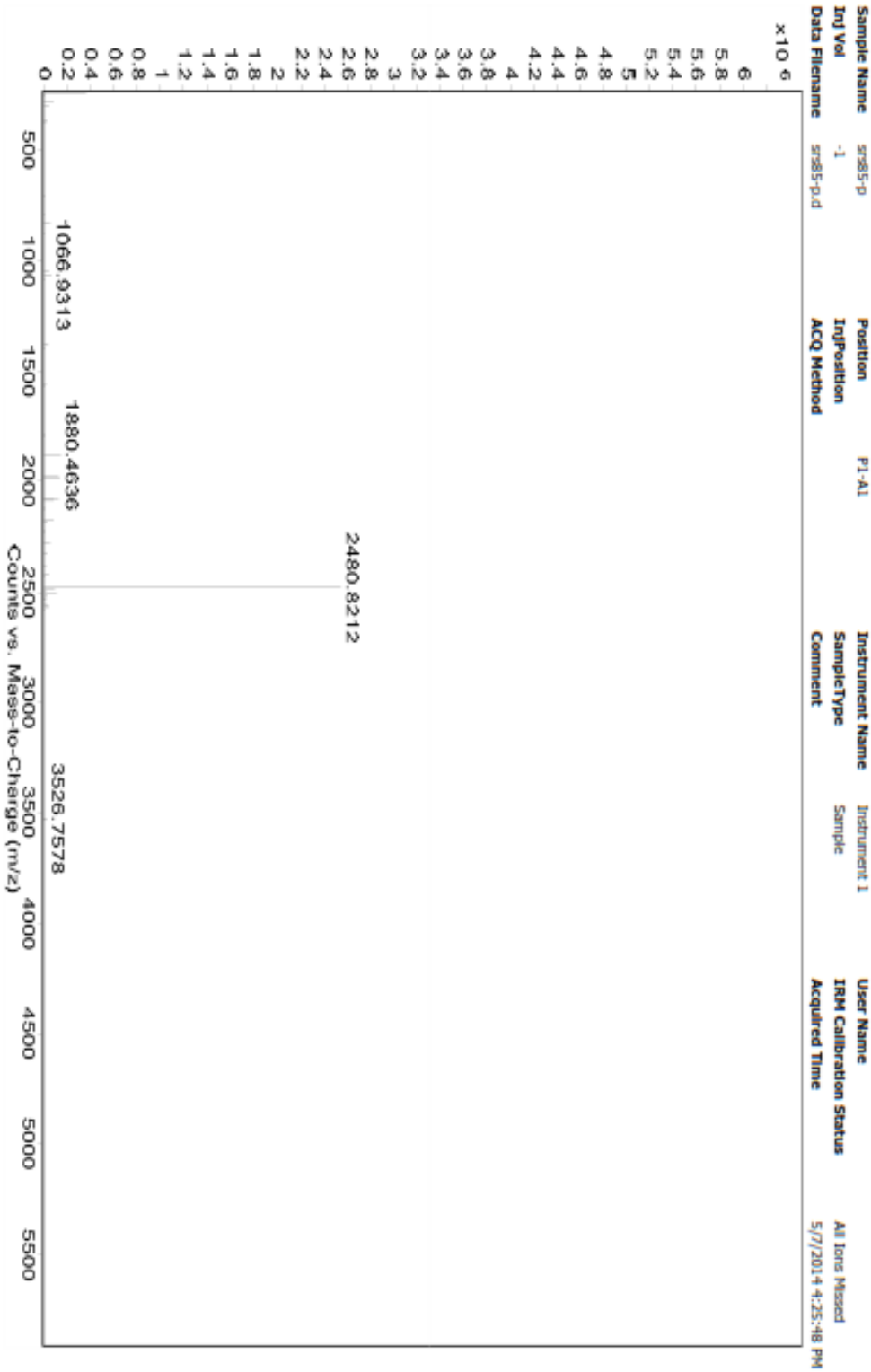
SI Figure 49. ^{1}H NMR spectrum of compound **11a**



SI Figure 50. ^{13}C NMR spectrum of compound **11a**

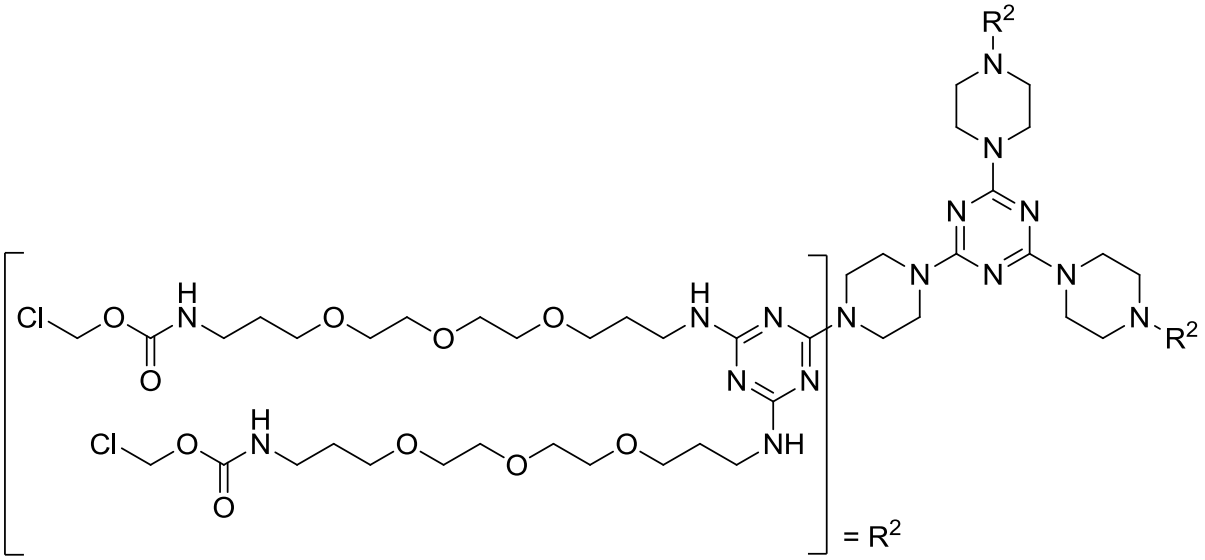


SI Figure 51. Mass spectrum of compound **11a**

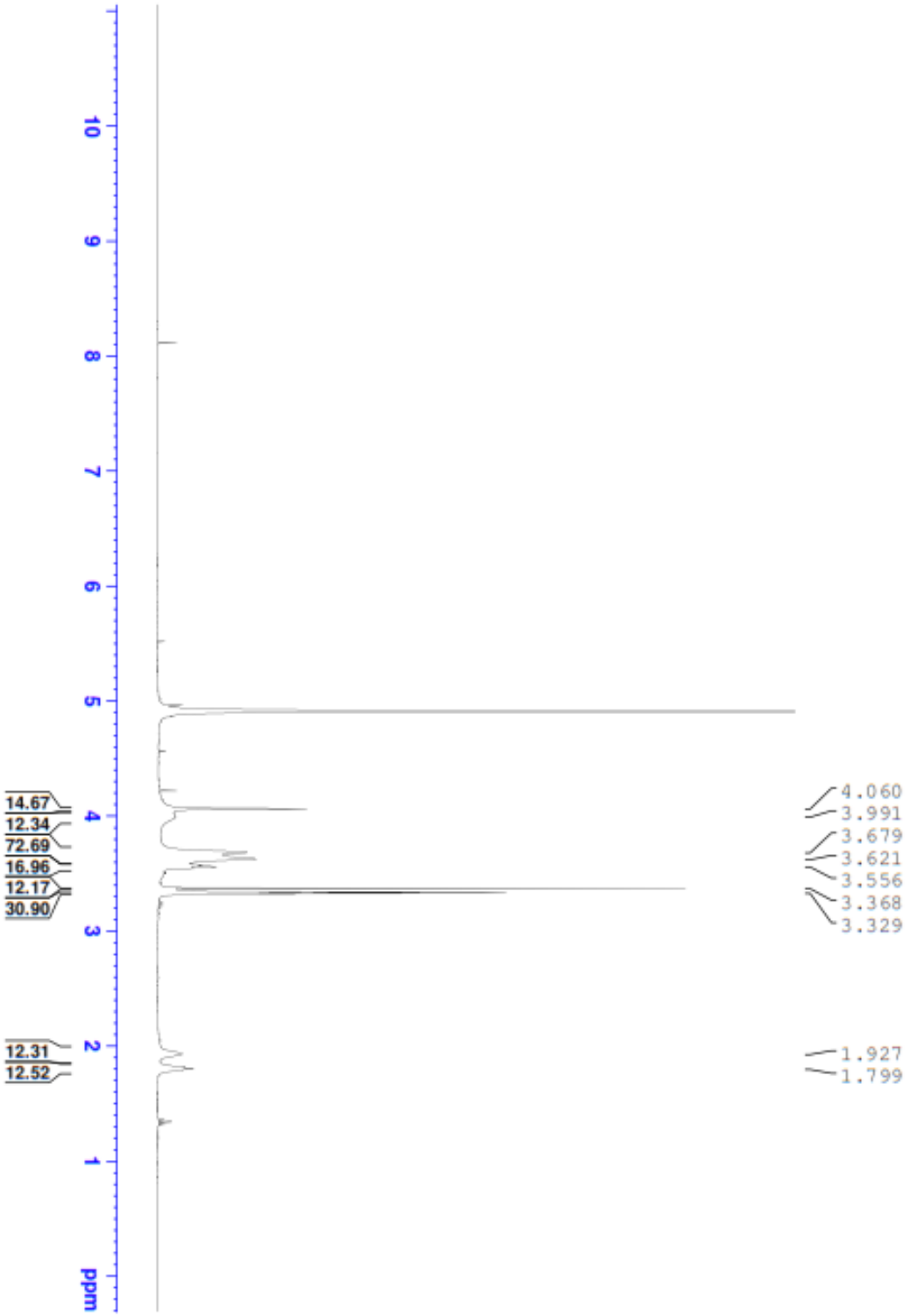


Compound **11c:**

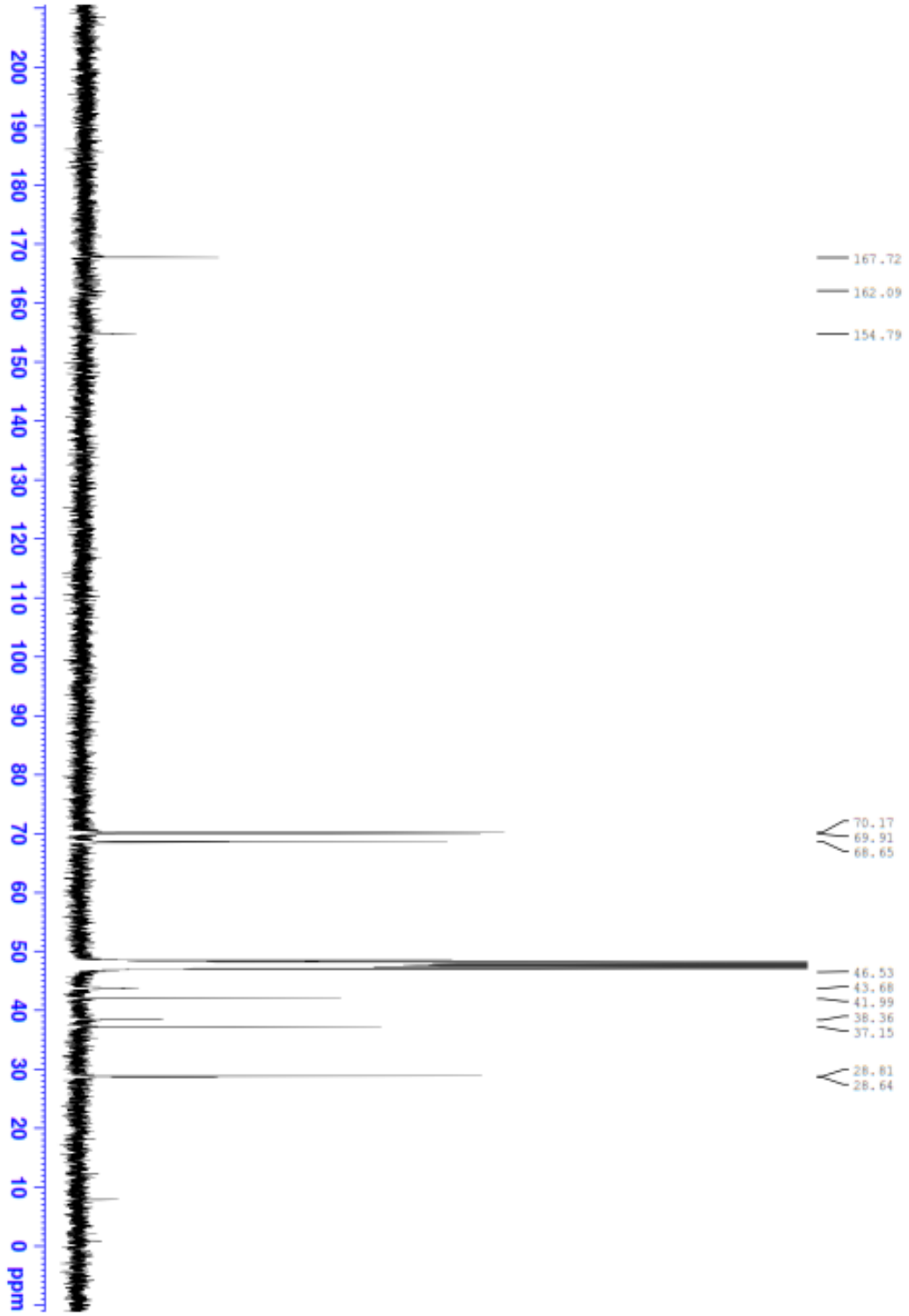
Chloroacetyl chloride (0.15ml, 1.9mmol) was added drop wise to the solution of **11b** (540mg, 0.29mmol) and DIPEA (0.303ml, 1.74mmol) in dichloromethane (5ml) at 0ºC. The above solution was stirred for 2 hrs at room temperature. Then the solvent was evaporated under vacuum. The residue was dissolved in dichloromethane and extracted with brine solution and dried over MgSO4, filtered, and then evaporated under vacuum. The crude product was purified using automated chromatography to yield a clear oil (120 mg 18%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.06 (s, 12H, -NHC(O)C**H$_2$**Cl), δ 3.99 (t, 12H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2-Piperazine), δ 3.67-3.62 (br, m, 72H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**), δ 3.55 (m, 12H -OCH_2CH_2C**H$_2$**NH), δ 3.36 (m, 12H -OCH_2CH_2C**H$_2$**NH-), δ 3.32 (t, 12H, -CH_2C**H$_2$**-N-C**H$_2$**CH_2-Piperazine), 1.92-1.79 (m, 24H, OCH_2C**H$_2$**CH_2-); ^{13}C NMR (100 MHz, $CDCl_3$) δ 167.7, 162.0 (**C**$_3$N$_3$), 154.7 (**C**O), 70.1 (O**C**H_2**C**H_2O), 69.9 (O**C**H_2**C**H_2O), 68.6 (-$NHCH_2CH_2$**C**H_2O-), 68.5 ($NHCH_2CH_2$**C**H_2O), 43.6 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-piperazine), 41.9 ((CO)**C**H_2Cl), 38.3, 37.1 (NH**C**$H_2CH_2CH_2$O), 28.8, 28.6 (-$NHCH_2$**C**H_2CH_2O-); MS (ESI-TOF) calcd for $C_{96}H_{168}N_{30}O_{24}$, 2339.27, found 2339.344 $(M)^+$.



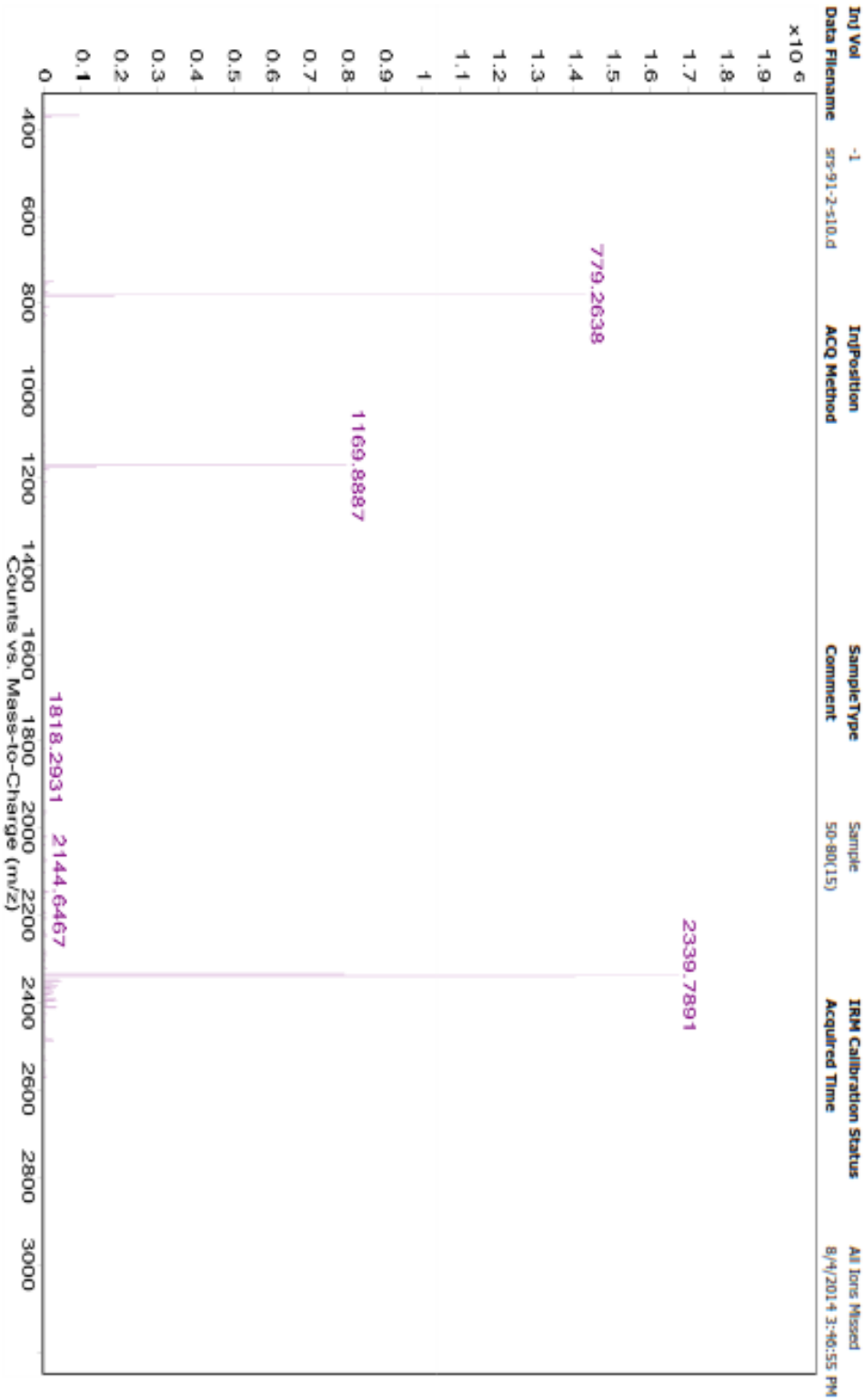
SI Figure 52. ^{1}H NMR spectrum of compound **11c**



SI Figure 53. ^{13}C NMR spectrum of compound **11c**

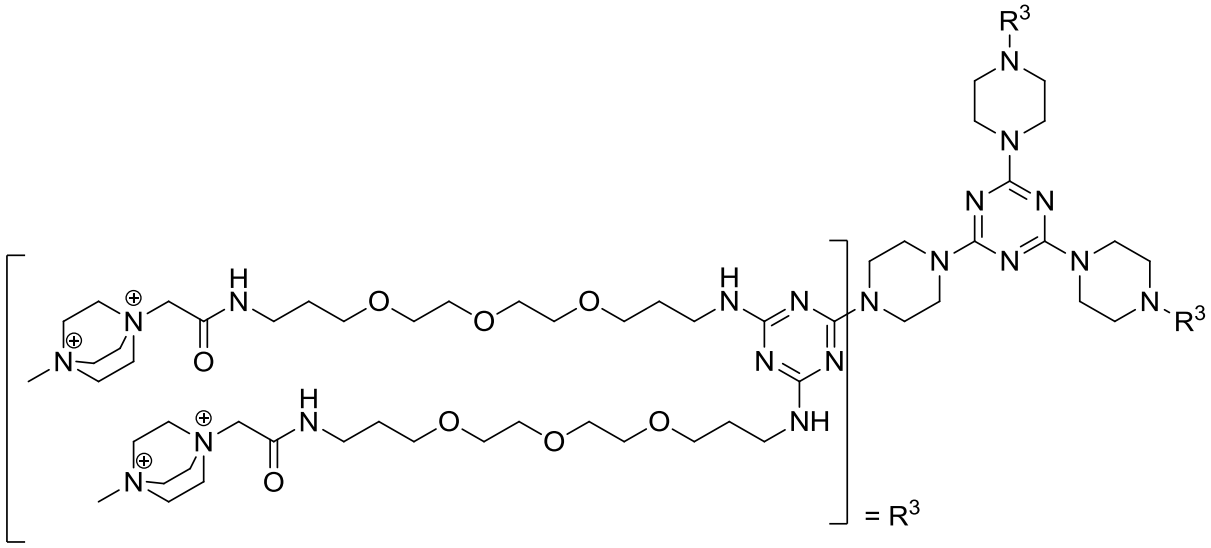


SI Figure 54. Mass spectrum of compound **11c**

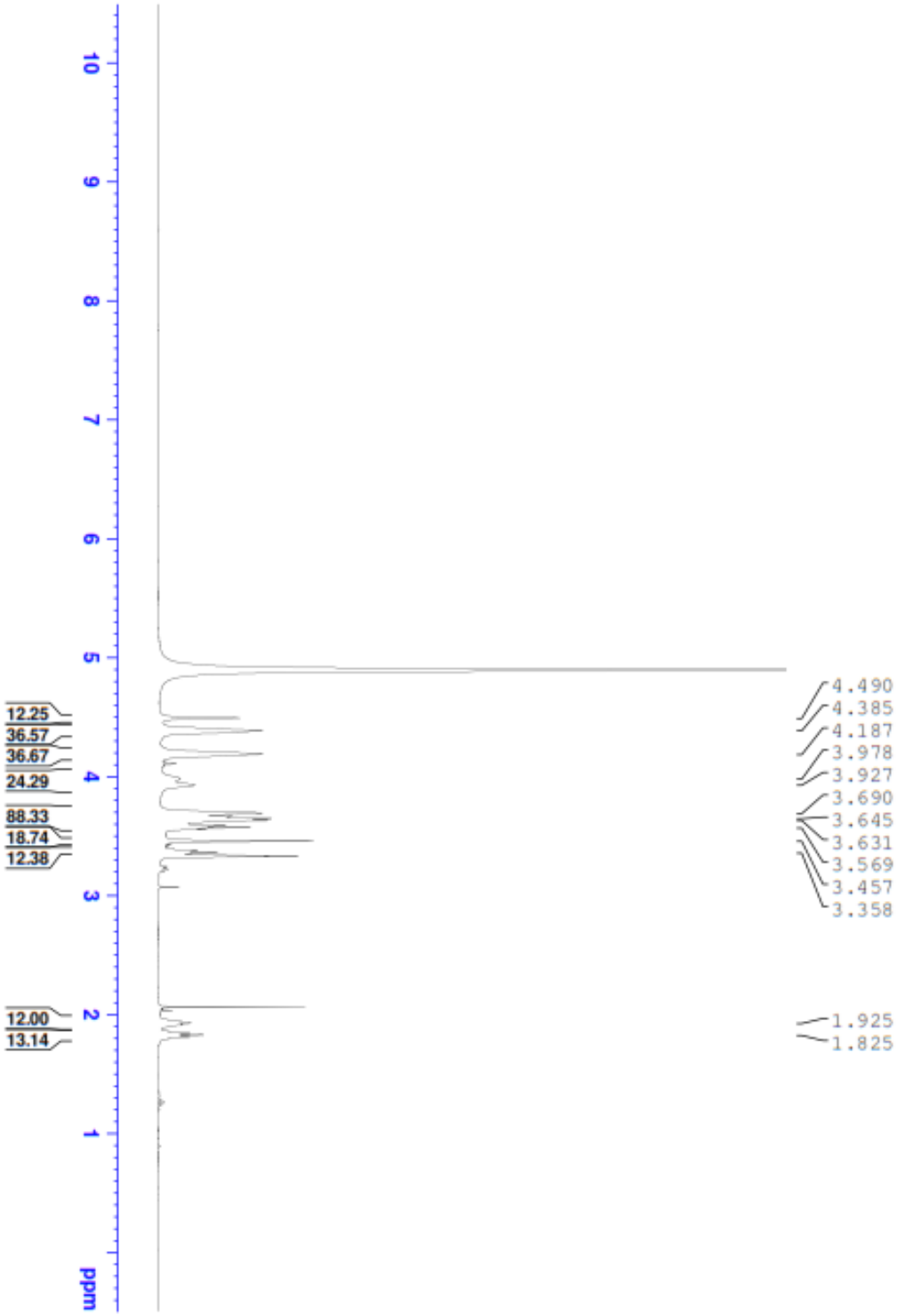


Compound **6-Me**

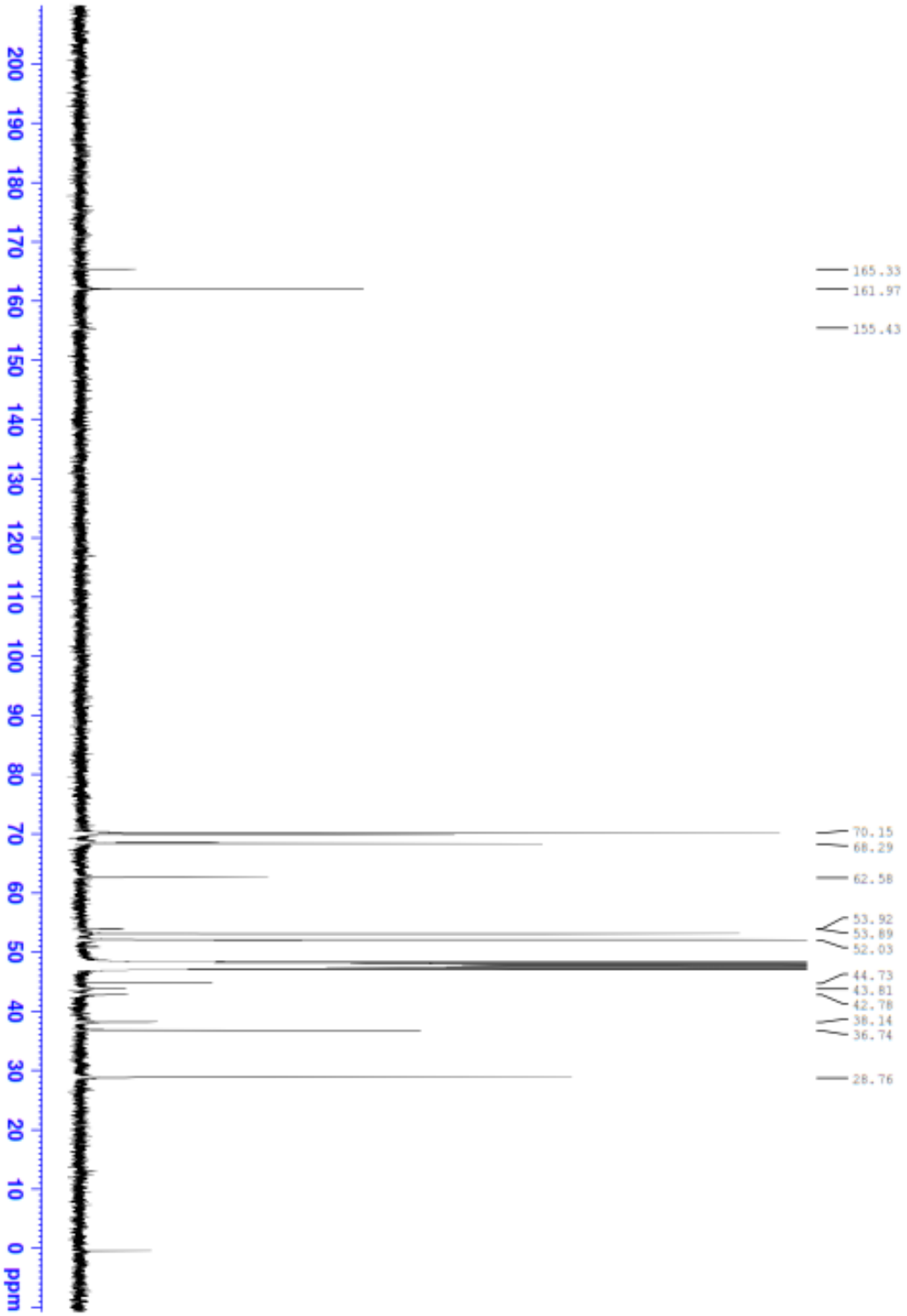
1-Me (20 mg, 0.154 mmol) was added to a solution of **11c** (40 mg, 0.018 mmol) in methanol (0.4 ml). The above solution was stirred for 5 days at room temperature. The crude product was purified by precipitation with methanol and acetonitrile. The final product is further washed with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to yield a pale yellow solid (40.05 mg, 77%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.49 (s, 12H, -NHC(O)C**H$_2$**-), δ 4.38-4.18 (t, 72H, DABCO), δ 3.97-3.92 (t, 24H, -C**H$_2$**C**H$_2$**-N-C**H$_2$**C**H$_2$**-Piperazine), δ 3.69-3.63 (t, 84H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O), δ 3.56 (s, 18H, -C**H$_3$**), δ 3.35 (t, 12H, NHC**H$_2$**CH_2CH_2O), δ 1.92-1.82 (m, 24H, -OCH_2C**H$_2$**CH_2); ^{13}C NMR (100 MHz, CD_3OD) δ 165.3, 161.9 (**C**$_3N_3$), 155.4 (**C**O), 70.1 (O**C**H_2**C**H_2O), 69.8 (O**C**H_2**C**H_2O), 68.2 (NHCH_2CH_2**C**H_2O), 62.5 ((CO)**C**H_2Cl), 53.8, 52.0 (DABCO), 44.7 (-**C**H_3), 43.8, 42.7 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 38.1, 36.7 (NH**C**$H_2CH_2CH_2O$), 28.7, (NHCH_2**C**H_2CH_2O);



SI Figure 55. ^{1}H NMR spectrum of compound **6-Me**

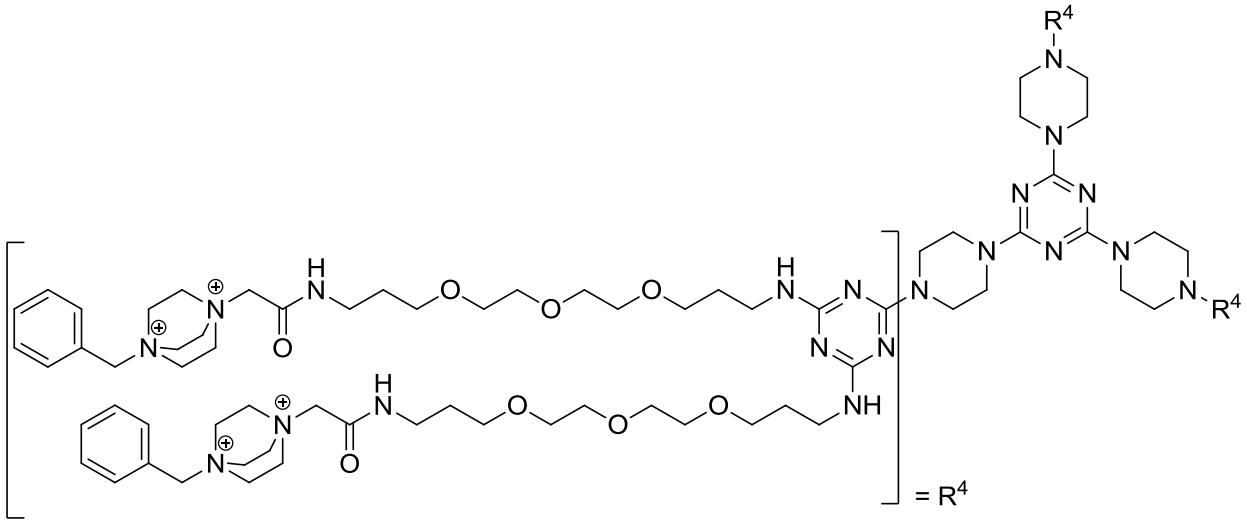


SI Figure 56. ^{13}C NMR spectrum of compound **6-Me**

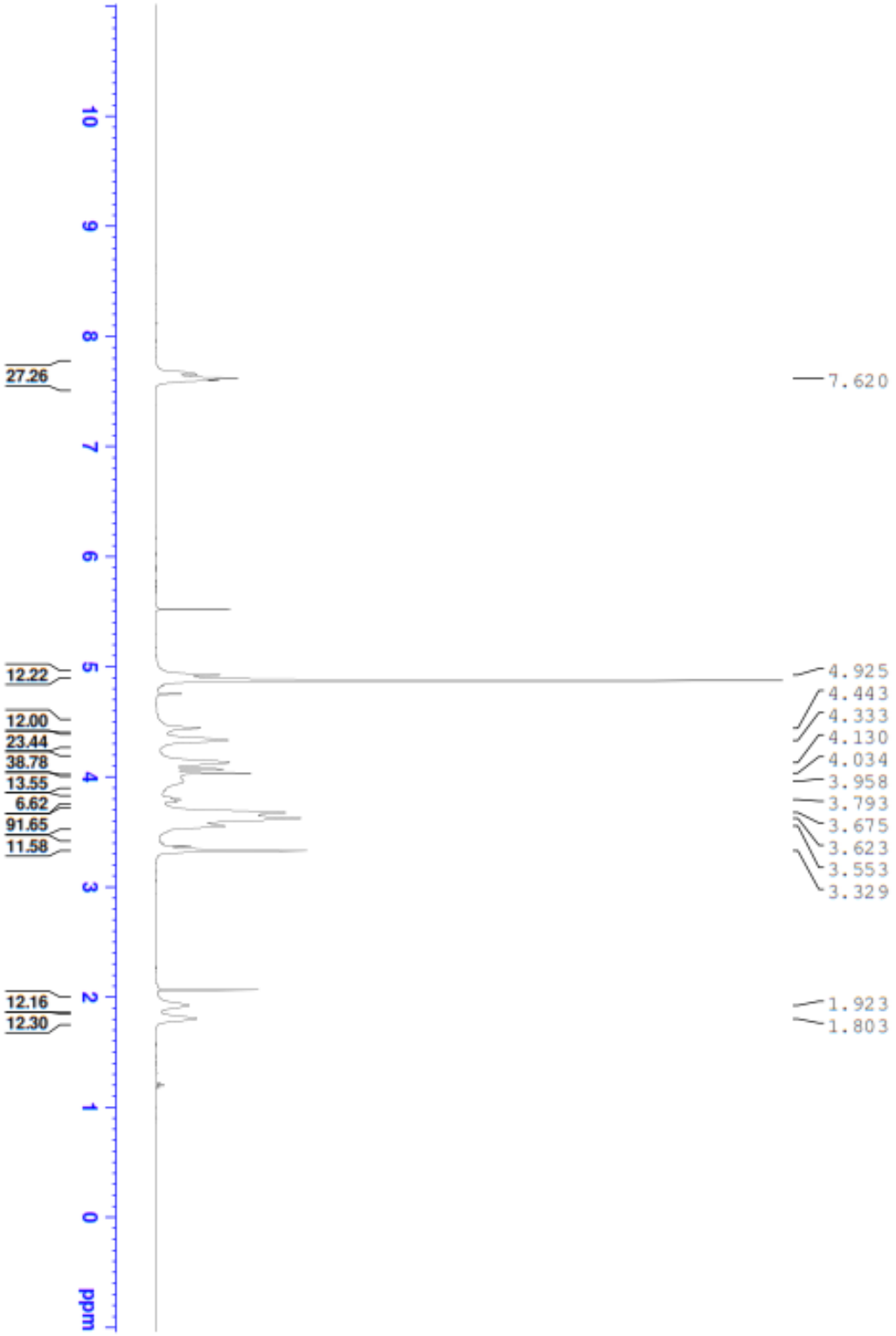


Compound **6-Bz**

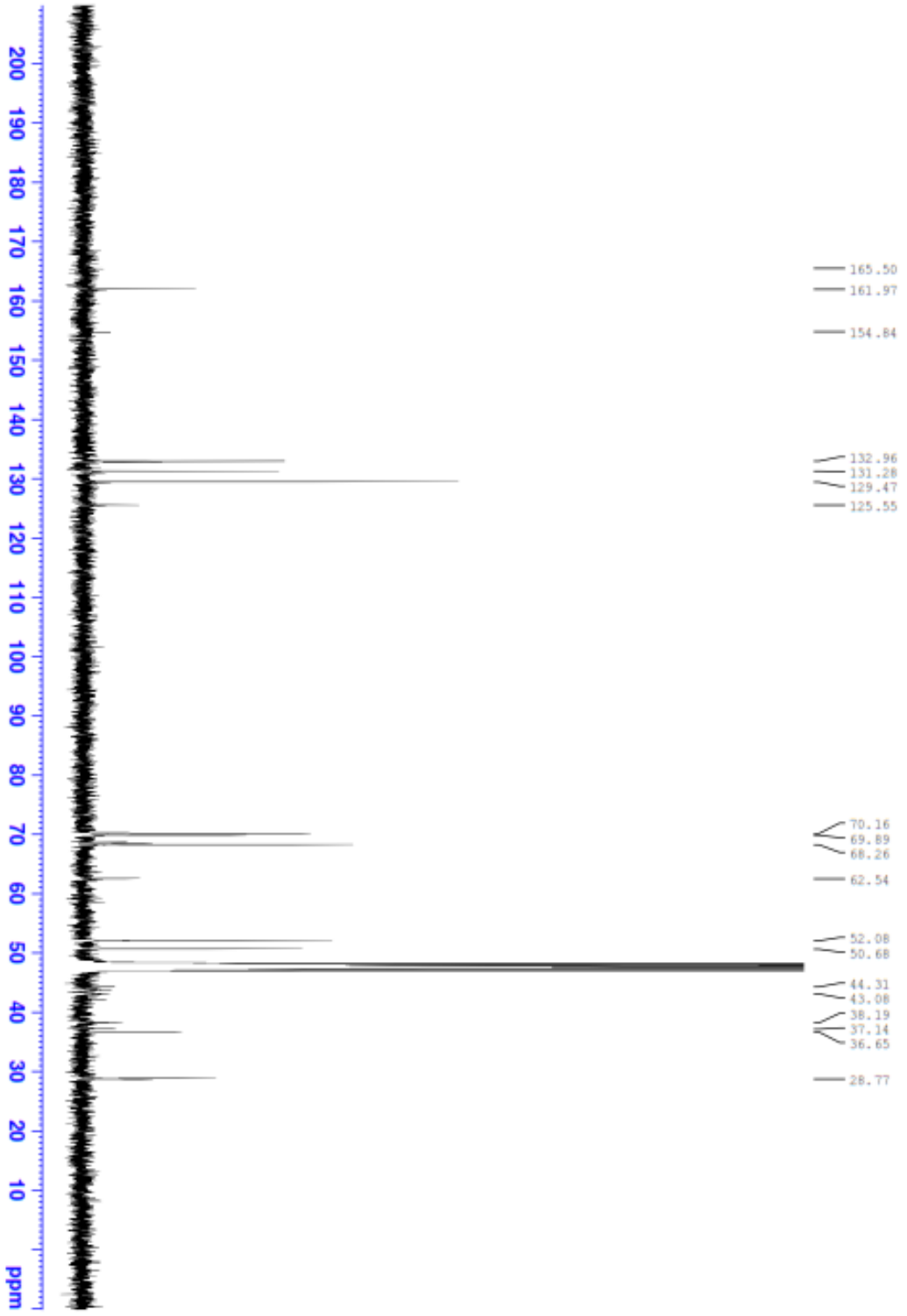
1-Bz (24 mg, 0.115 mmol) was added to a solution of **11c** (30 mg, 0.013 mmol) in methanol (0.4 ml). The above solution was stirred for 5 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product was washed further with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to give a white solid (10.8 mg 25%). ^{1}H NMR (400 MHz, CD_3OD) δ 7.62 (d, 30H, $C_6\mathbf{H_5}$-), δ 4.92 (s, 12H, C_6H_5-$C\mathbf{H_2}$-),δ 4.44 (s, 12H, -NHC(O)$C\mathbf{H_2}$-), δ 4.33-4.13 (t, 72H, DABCO), δ 3.95 (t, 12H, -$C\mathbf{H_2}C\mathbf{H_2}$-N-$C\mathbf{H_2}C\mathbf{H_2}$-), δ 3.67-3.55 (t, 96H, $C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}C\mathbf{H_2}OC\mathbf{H_2}$, -NHC$\mathbf{H_2}CH_2CH_2O$-, -$C\mathbf{H_2}C\mathbf{H_2}$-N-$C\mathbf{H_2}C\mathbf{H_2}$-), δ 3.32 (t, 12H, -NHC$\mathbf{H_2}CH_2CH_2O$-), δ 1.92-1.80 (m, 24H, -$OCH_2C\mathbf{H_2}CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 165.9, ($\mathbf{C}_3N_3$), 158.6 (**C**O), 132.9, 131.2, 129.4, 125.5 ($\mathbf{C_6}H_5$-), 70.1, 69.8 (O$\mathbf{C}H_2\mathbf{C}H_2$O), 68.2 ($C_6H_5$-$CH_2$), 62.5 ((CO)$\mathbf{C}H_2$Cl), 52.0, 50.6 (DABCO), 44.3, 43.0 (-$\mathbf{C}H_2\mathbf{C}H_2$-N-$\mathbf{C}H_2\mathbf{C}H_2$-), 38.1, 37.1 (NH$\mathbf{C}H_2CH_2CH_2O$), 28.7, ($NHCH_2\mathbf{C}H_2CH_2O$).



SI Figure 57. ^{1}H NMR spectrum of compound **6-Bz**

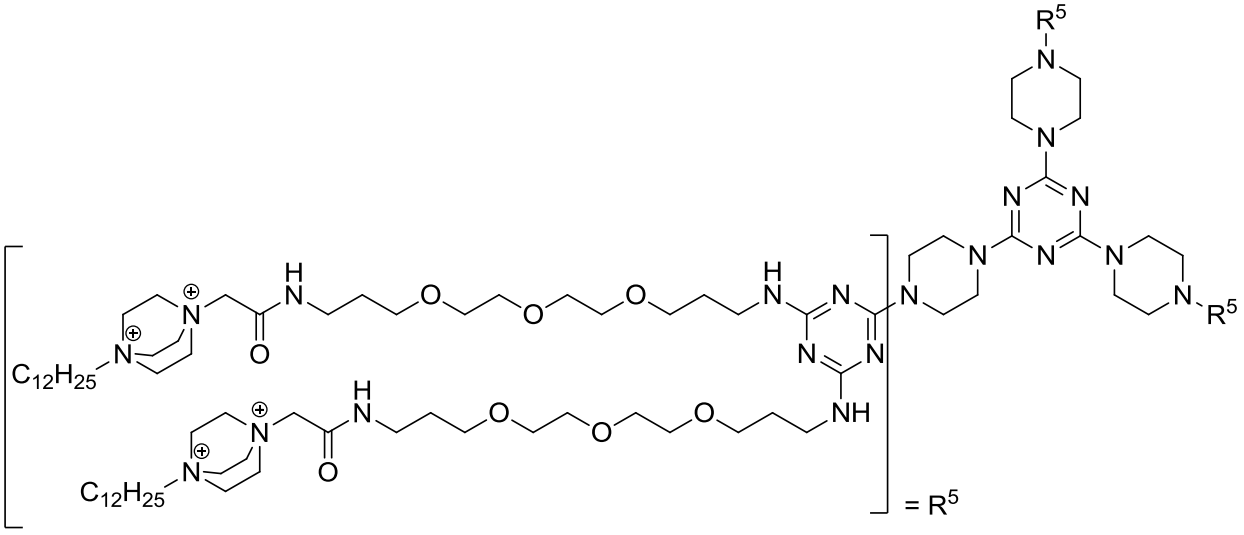


SI Figure 58. ^{13}C NMR spectrum of compound **6-Bz**

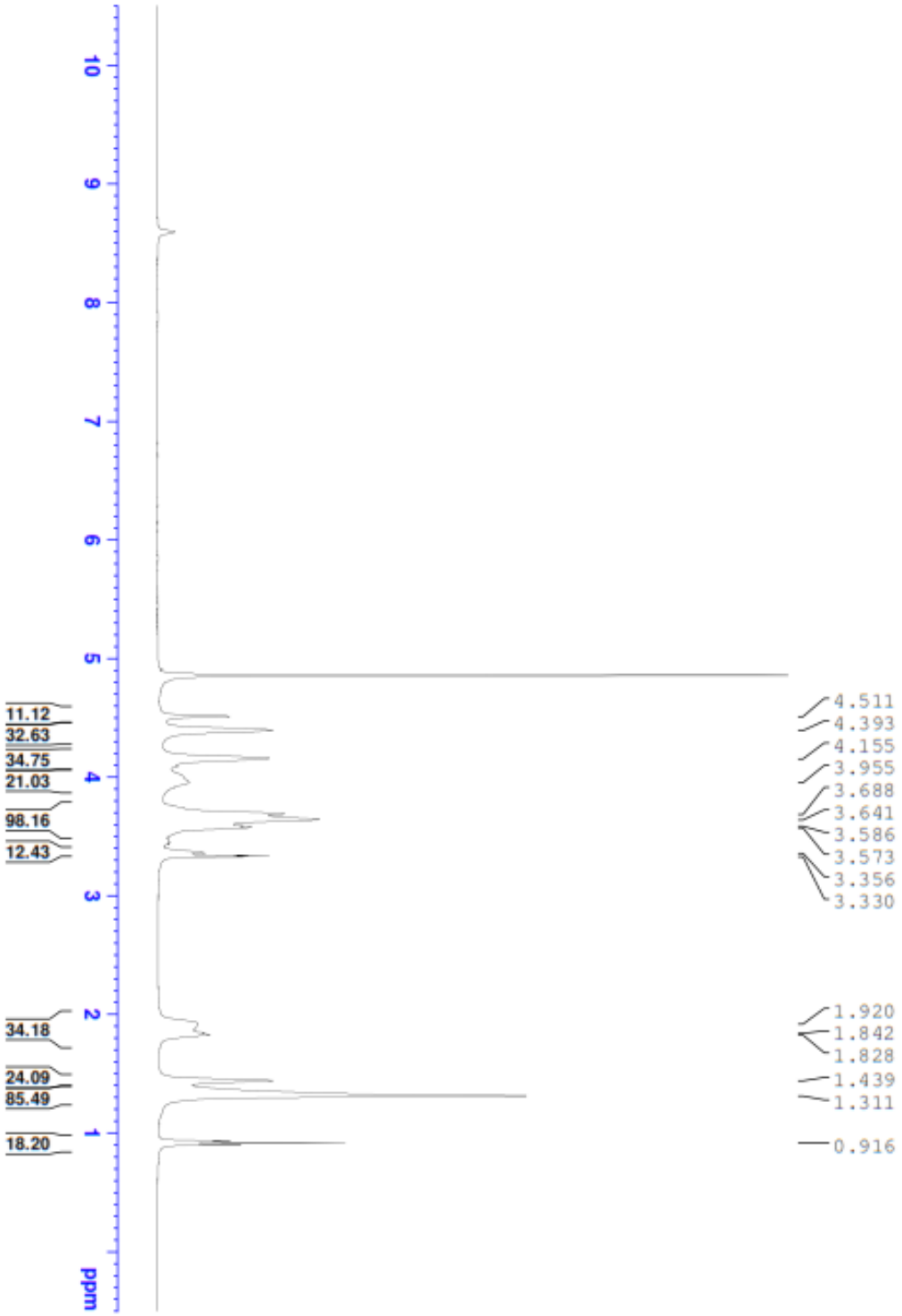


Compound **6-C12**

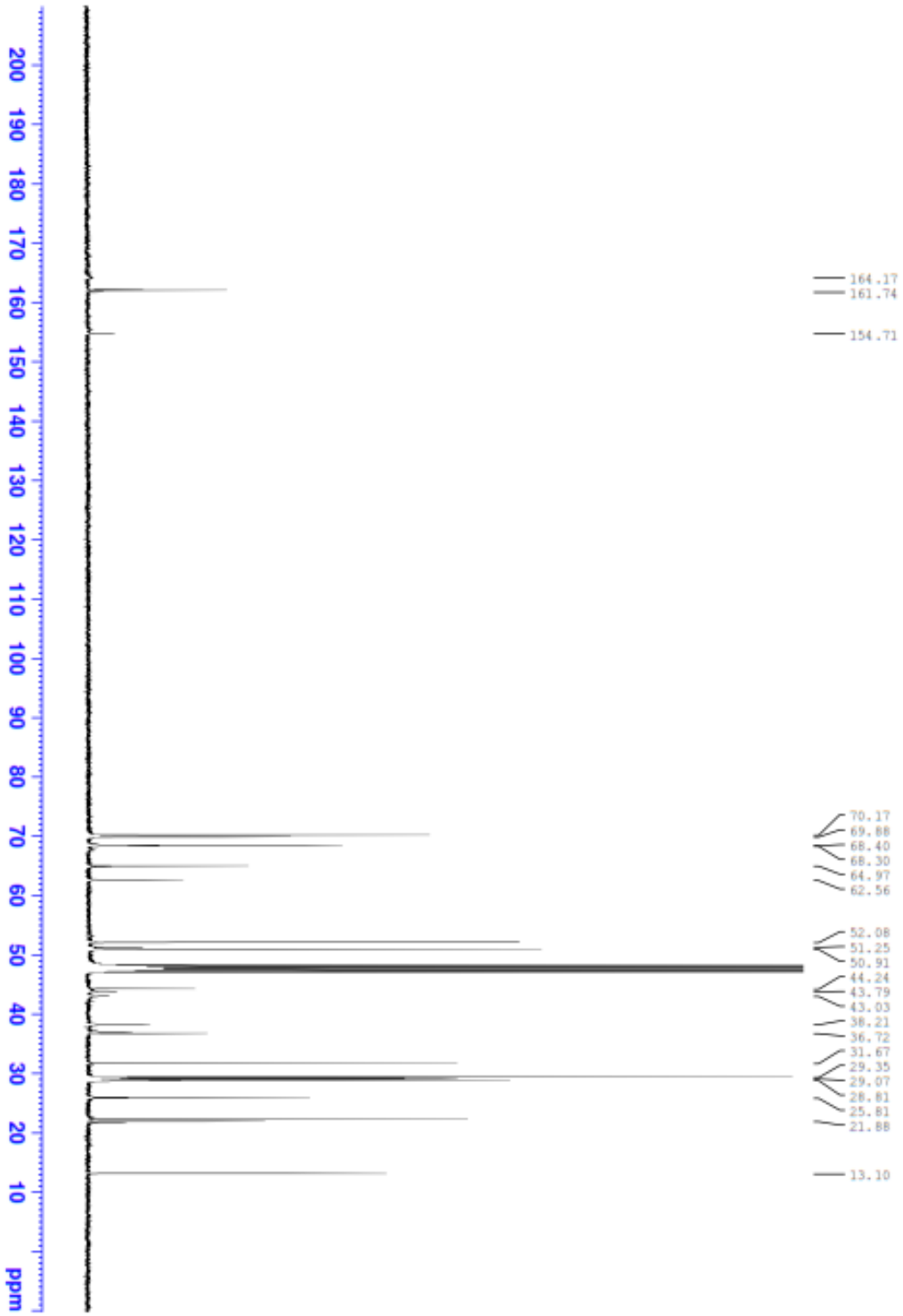
1-C12 (33mg, 0.115mmol) was added to a solution of **11c** (30 mg, 0.013 mmol) in methanol (0.4 ml). The above solution was stirred for 5 days at 55^0C. The crude product was purified by precipitation with methanol and acetonitrile. The final product is further washed with acetonitrile, diethyl ether, ethyl acetate and tetrahydrofuran to yield a white solid (44.6 mg, 90%). ^{1}H NMR (400 MHz, CD_3OD) δ 4.51 (s, 12H, -NHC(O)C**H$_2$**-), δ 4.39-4.15 (t, 72H, DABCO), δ 3.95 (t, 24H, -C**H$_2$**C**H$_2$**-N-C**H$_2$**C**H$_2$**-Piperazine), δ 3.64-3.57 (t, 96H, C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**C**H$_2$**OC**H$_2$**, C_3N_3-NHC**H$_2$**CH_2CH_2O, -$CH3(CH_2)_9CH_2$C**H$_2$**-), δ 3.35 (t, 12H, NHC**H$_2$****C**H_2CH_2O), δ 1.92-1.82 (m, 36H, -OCH_2C**H$_2$**CH_2, -$CH3(CH_2)_9$C**H$_2$**CH_2), 1.43-1.31 (m, 108H, $CH3(C$**H$_2$)$_9$**CH_2CH_2-), 0.91 (t, 18H, C**H$_3$**$(CH_2)_9CH_2CH_2$); ^{13}C NMR (100 MHz, CD_3OD) δ 161.7, 161.7 (**C**$_3$N$_3$), 154.7 (**C**O), 70.1, 69.8 (O**C**H_2**C**H_2O), 68.3 ($NHCH_2CH_2$**C**H_2O), 64.9 ((CO)**C**H_2Cl), 62.5 (**C$_{12}$**H_{25}) 52.0, 50.9 (DABCO), 43.7, 43.0 (-**C**H_2**C**H_2-N-**C**H_2**C**H_2-), 38.2, 36.7 (NH**C**$H_2CH_2CH_2O$), 31.6 ($NHCH_2$**C**H_2CH_2O), 29.3, 29.0, 28.8 (CH_3(**C**H_2)$_9$$CH_2CH_2$-), 25.8 ($CH_3(CH_2)_9CH_2$**C**$H_2$-), 21.8 ($CH_3(CH_2)_9$**C**$H_2CH_2$-**),** 13.1 (**C**$H_3(CH_2)_9CH_2CH_2$-);



SI Figure 59. ^{1}H NMR spectrum of compound **6-C12**

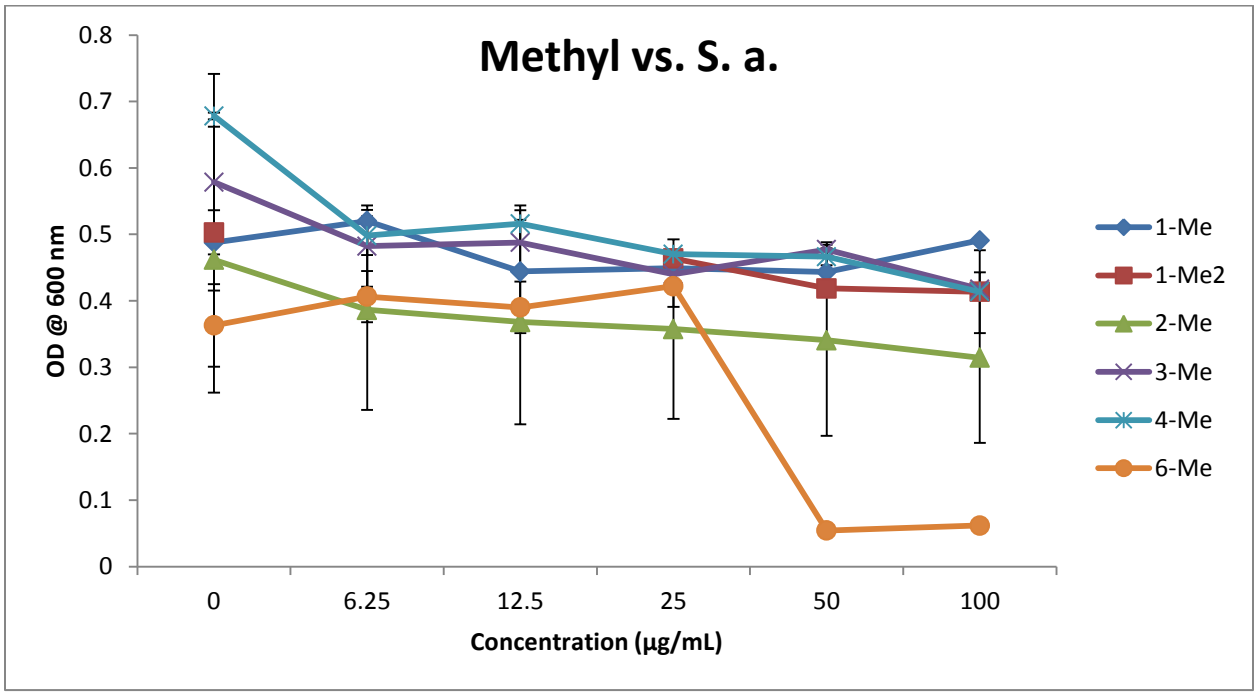


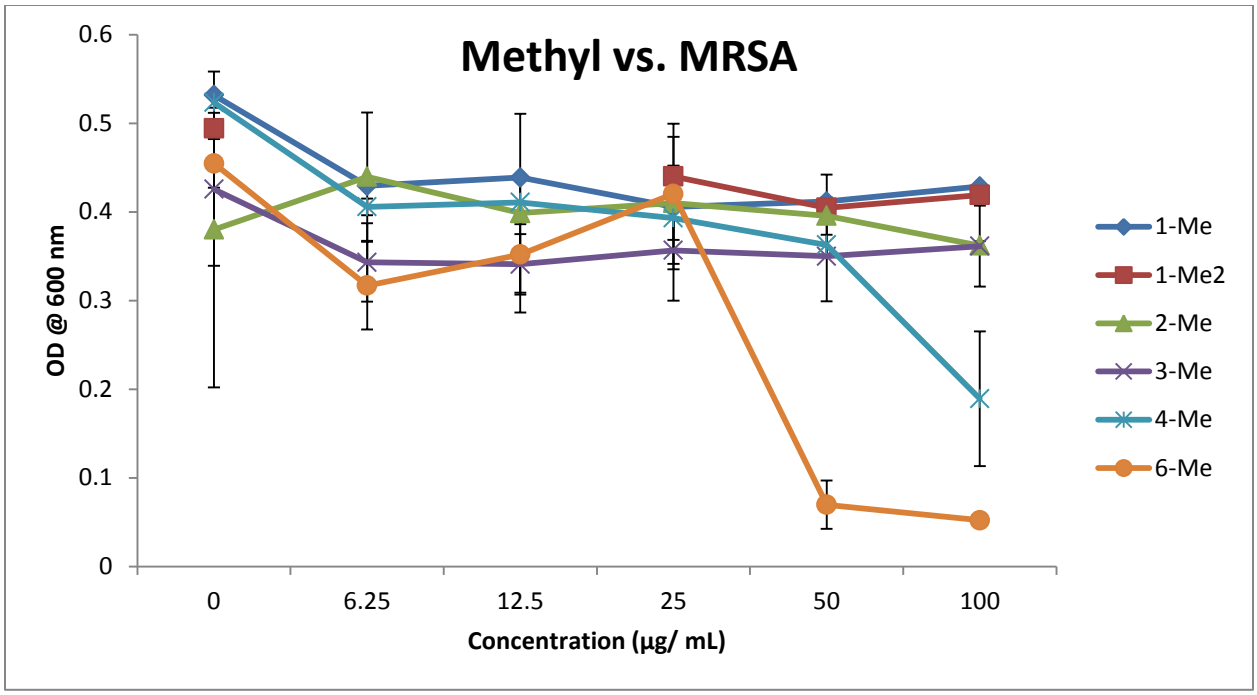
SI Figure 60. ^{13}C NMR spectrum of compound **6-C12**

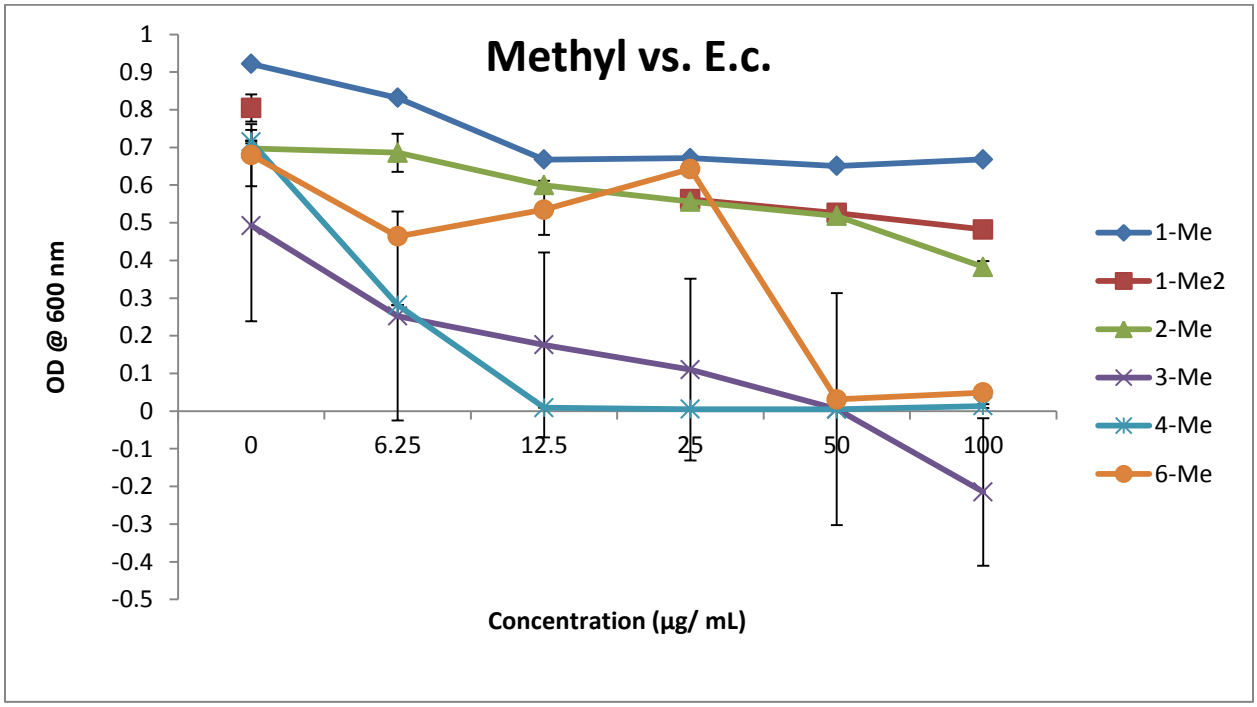


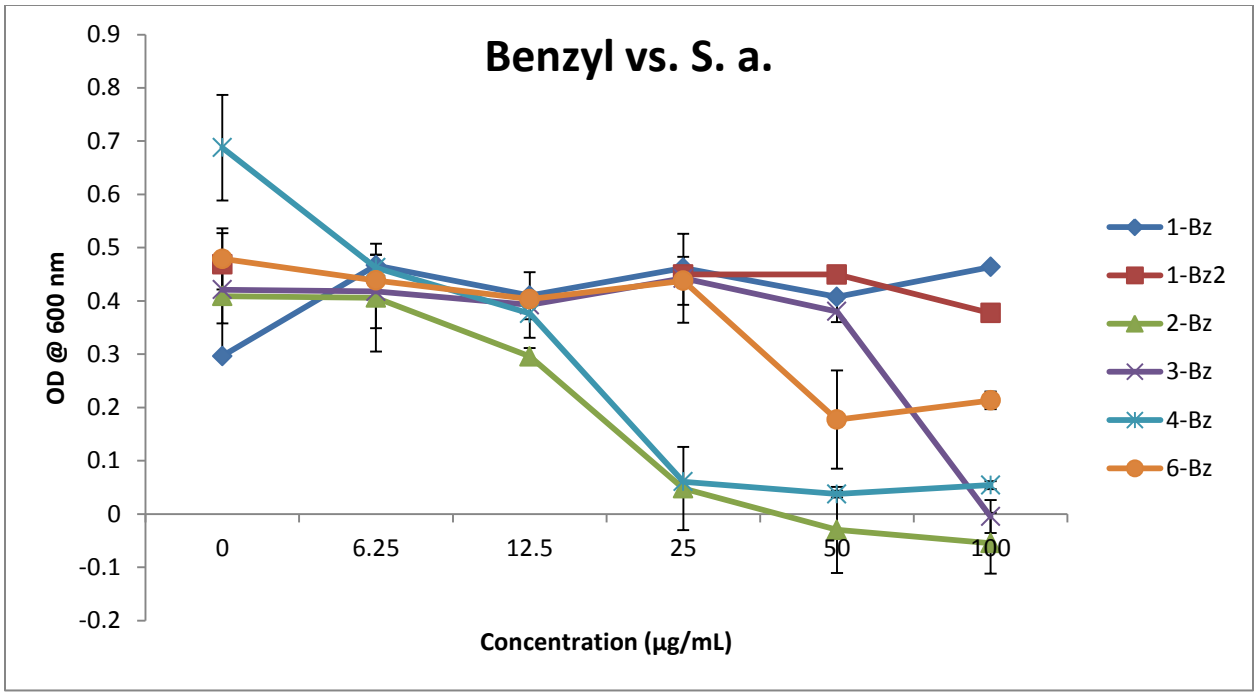
Graphical representation of MIC values of all compounds:

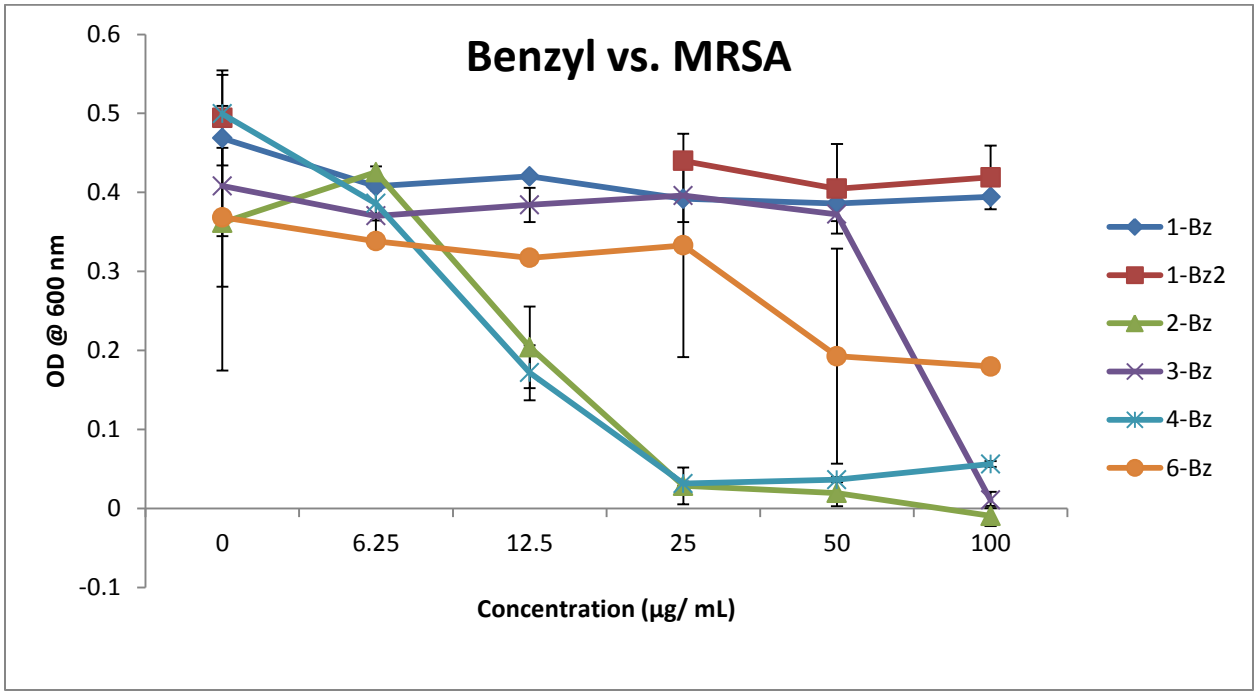
MIC values and optical density (OD) values of all compounds are reported against three strains of bacteria. Error bars represent standard error of the mean. Standard error of the mean was not calculated for any 1-X compound, 1-$(X)_2$ compounds at 6.25 and 12.5 (µg/ mL) or 6-X compounds at 6.25 and 12.5 (µg/ mL). OD readings of these compounds followed clear patterns of activity. E.g. if 6-X did not show activity at 25 (µg/ mL) it was not assessed at lower concentrations.

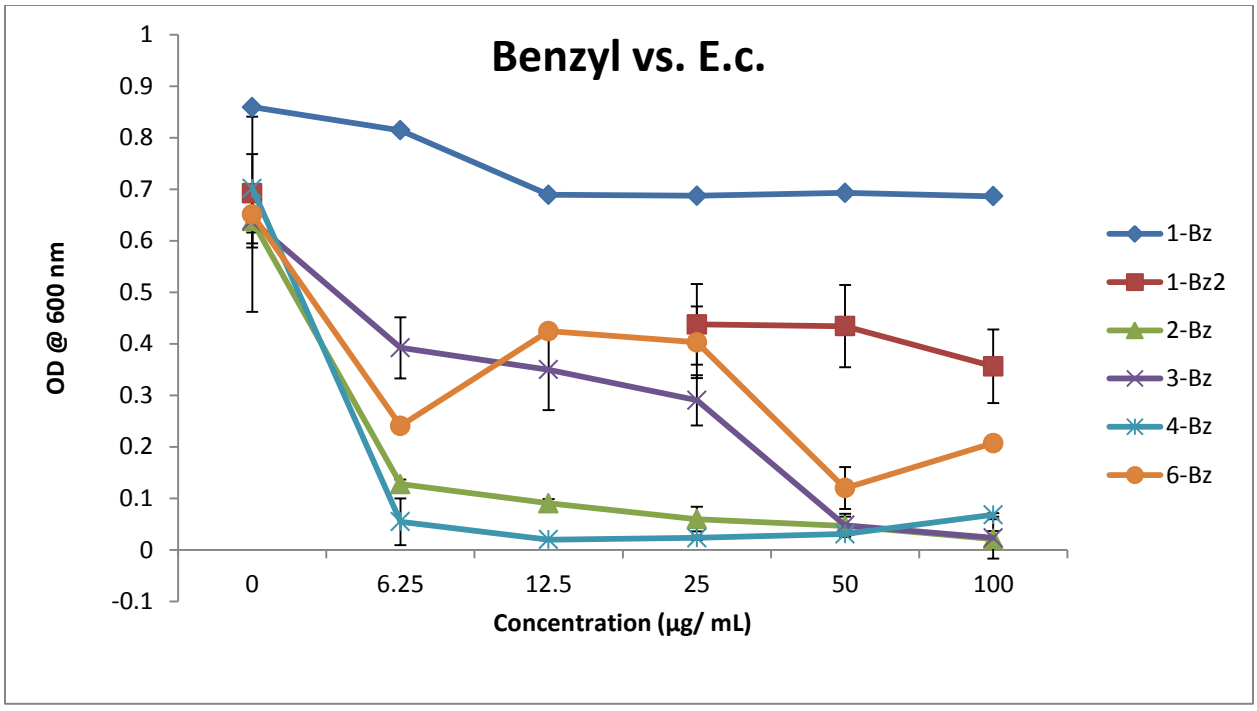


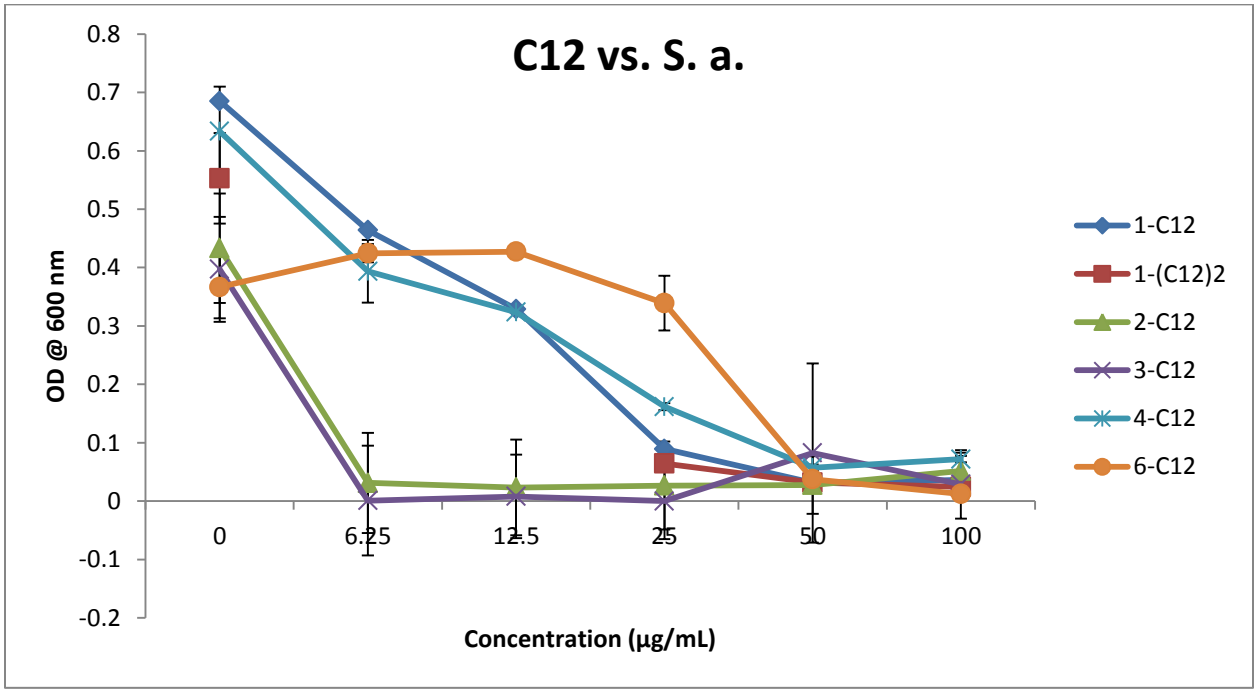

Methyl vs. MRSA
OD @ 600 nm
0.6
0.5
0.4
0.3
0.2
0.1
0
0
6.25
12.5
25
50
100
Concentration (µg/ mL)
1-Me
1-Me2
2-Me
3-Me
4-Me
6-Me

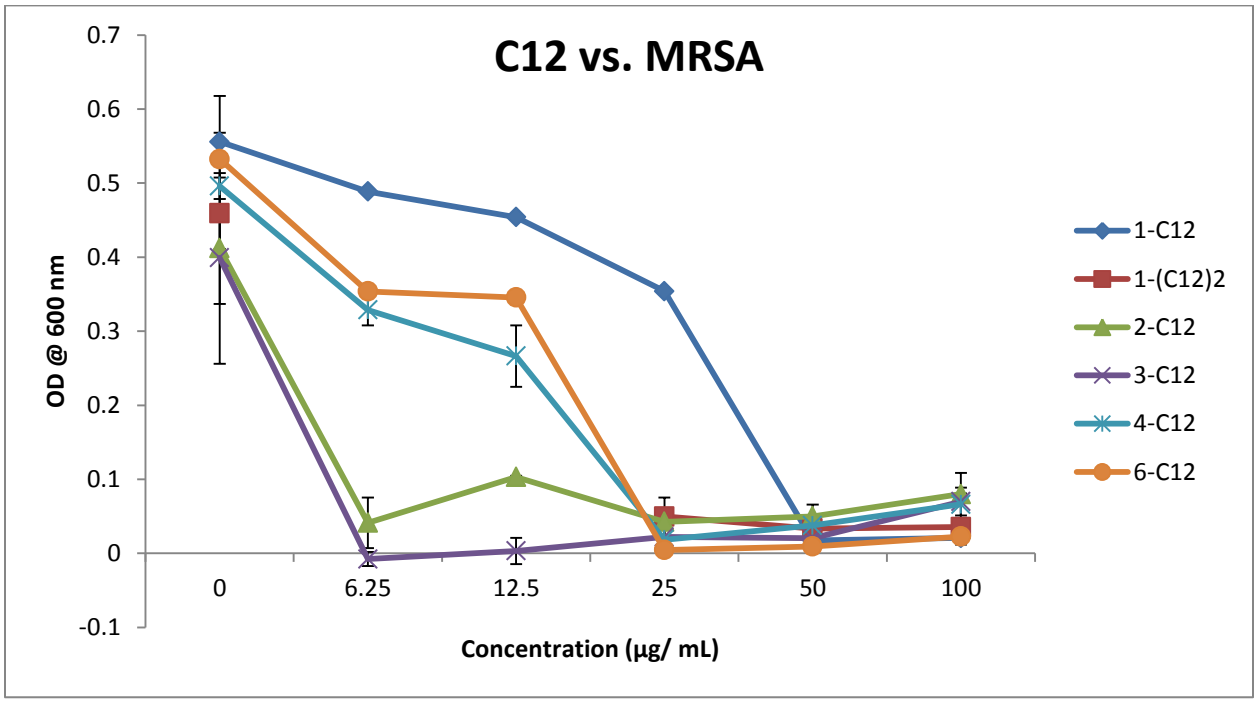

Methyl vs. E.c.
OD @ 600 nm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
-0.3
-0.4
-0.5
0
6.25
12.5
25
50
100
Concentration (µg/ mL)
1-Me
1-Me2
2-Me
3-Me
4-Me
6-Me

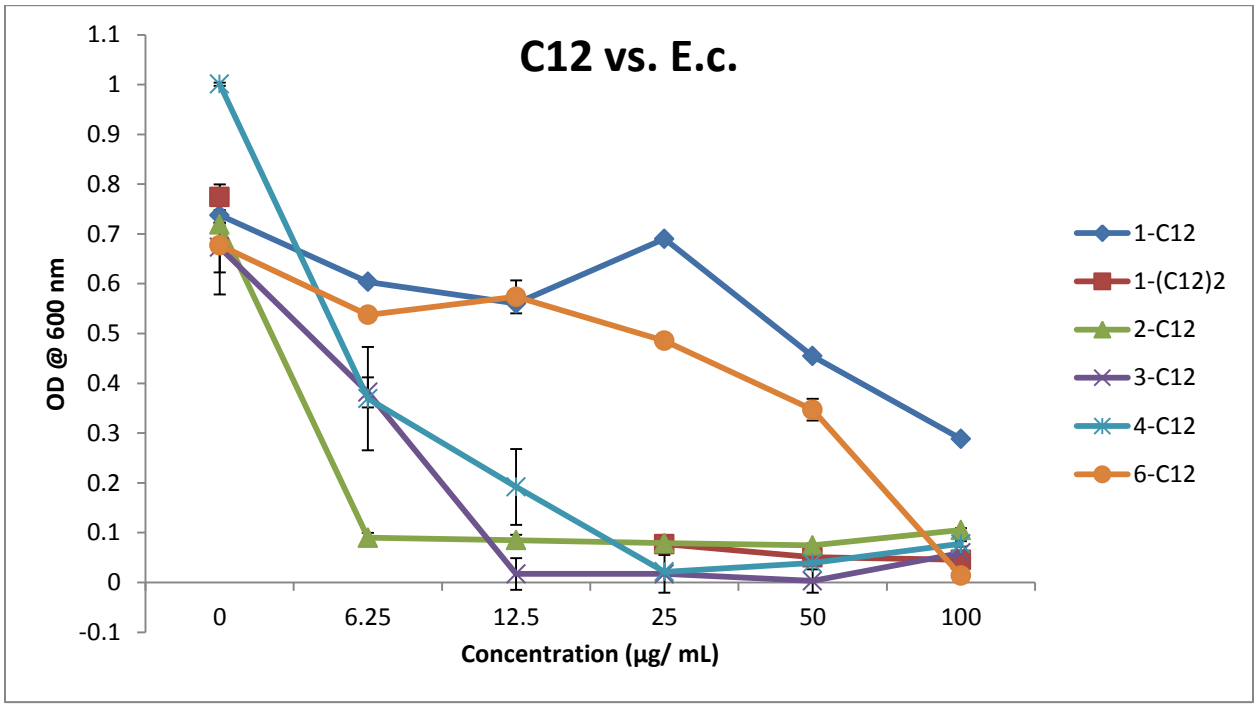

Benzyl vs. S. a.
OD @ 600 nm
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
0
6.25
12.5
25
50
100
Concentration (µg/mL)
1-Bz
1-Bz2
2-Bz
3-Bz
4-Bz
6-Bz


Benzyl vs. MRSA
OD @ 600 nm
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0
6.25
12.5
25
50
100
Concentration (µg/ mL)
1-Bz
1-Bz2
2-Bz
3-Bz
4-Bz
6-Bz


Benzyl vs. E.c.
OD @ 600 nm
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0
6.25
12.5
25
50
100
Concentration (µg/ mL)
1-Bz
1-Bz2
2-Bz
3-Bz
4-Bz
6-Bz


C12 vs. S. a.
OD @ 600 nm
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
-0.2
0
6.25
12.5
25
50
100
Concentration (µg/mL)
1-C12
1-(C12)2
2-C12
3-C12
4-C12
6-C12


C12 vs. MRSA
OD @ 600 nm
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0
6.25
12.5
25
50
100
Concentration (µg/ mL)
1-C12
1-(C12)2
2-C12
3-C12
4-C12
6-C12


C12 vs. E.c.
OD @ 600 nm
1.1
1
0.9
0.8
0.7
0.6
0.5
0.4
0.3
0.2
0.1
0
-0.1
0
6.25
12.5
25
50
100
Concentration (µg/ mL)
1-C12
1-(C12)2
2-C12
3-C12
4-C12
6-C12