Electronic Supplementary Material (ESI) for Chemical Communications.

Design, Synthesis, and Evaluation of Heparan Sulfate Mimicking Glycopolymers for Inhibiting Heparanase Activity

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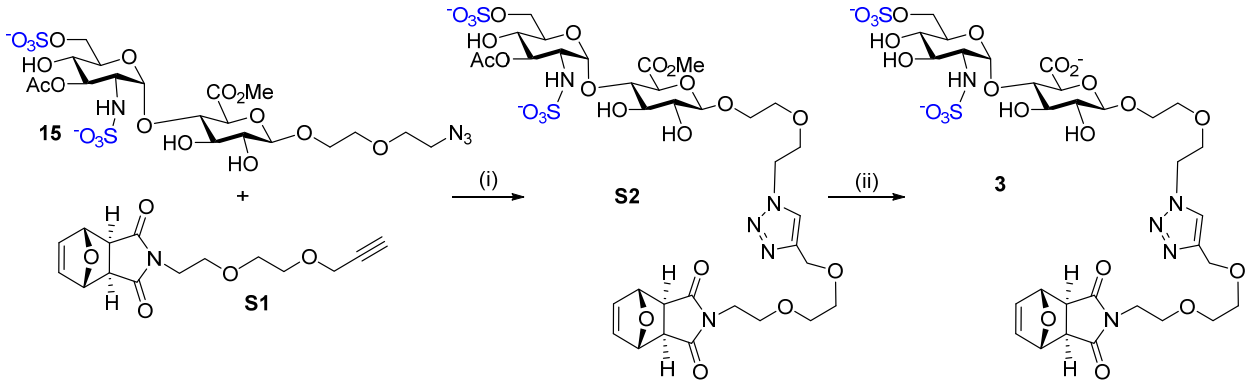
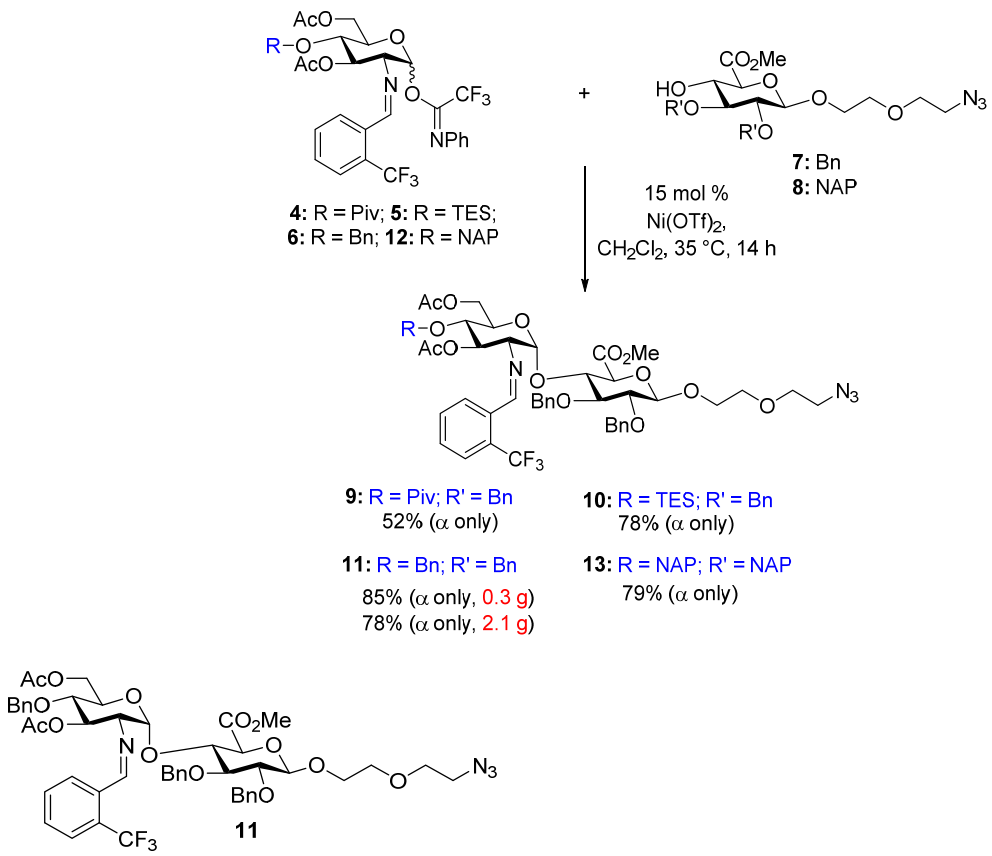
I. GENERAL INFORMATION

Methods and Reagents. All reactions were performed in dried flasks fitted with septa under a positive pressure of nitrogen atmosphere unless otherwise noted. Organic solutions were concentrated using a Buchi rotary evaporator below 40 °C at 25 torr. Analytical thin-layer chromatography (TLC) was routinely utilized to monitor the progress of the reactions and performed using pre-coated glass plates with 230-400 mesh silica gel impregnated with a fluorescent indicator (250 nm). Visualization was achieved using UV light, iodine, or ceric ammonium molybdate stain. Flash column chromatography was performed using 40-63 μm silica gel (SiliaFlash F60 from Silicycle). Dry solvents were obtained from a SG Waters solvent system utilizing activated alumina columns under an argon pressure. All other commercial reagents were used as received from Sigma Aldrich, Alfa Aesar, Acros Organics, TCI, and Combi-Blocks, unless otherwise noted.

Instrumentation. All new compounds were analyzed by NMR spectroscopy and High Resolution Mass spectrometry. All ^{1}H NMR spectra were recorded on either Bruker 400 or 500 MHz spectrometers. All ^{13}C NMR spectra were recorded on either Bruker 100 or 125 MHz NMR spectrometer. Chemical shifts are expressed in parts per million (δ scale) downfield from tetramethylsilane and are referenced to the residual proton in the NMR solvent ($CDCl_3$: δ 7.27 ppm, δ 77.16 ppm; CD_3OD-d_4: δ 3.31 ppm, δ 49.00 ppm; D_2O: δ 4.79 ppm). Data are presented as follows: chemical shift, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, and bs = broad singlet), integration, and coupling constant in hertz (Hz). High resolution (ESI-TOF) mass spectrometry was performed at the University of Iowa.



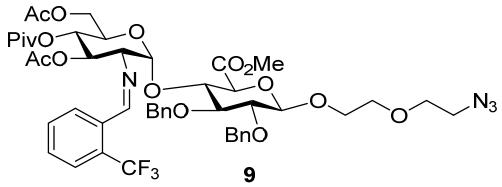
Scheme S1. Synthesis of monoantennary monomer 3. Reagents and conditions: (i) CuI, DBU, DMF, 50 °C, 68%;(ii) LiOH, H_2O, THF, 95%



For references on nickel catalyzed formation of 1,2-cis-aminoglycosides[i-iv]

A 50 mL oven-dried Schlenk flask was charged with donor **6** (2.13 g, 3.13 mmol, 2.0 equiv), acceptor **7** (784 mg, 1.57 mmol, 1.0 equiv), and CH_2Cl_2 (15 mL). A preformed solution of $Ni(OTf)_2$, which was generated in situ from a reaction of $NiCl_2$ (30.4 mg, 0.23 mmol, 15 mol %) and AgOTf (117.76 mg, 0.46 mmol, 30 mol %) in dichloromethane (1.0 mL) for 30 min, was added to the solution. The resulting mixture was stirred under argon at 35 °C overnight, filtered through Celite, concentrated *in vacuo*, and purified by silica gel flash chromatography (2/1 → 1/1 hexanes/ethyl acetate + 1% triethylamine) to give the desired disaccharide **S5** (1.32 g, 78%, α only) as yellow solid.

^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.48 (d, *J* = 2.5 Hz, 1H), 8.37 – 8.27 (m, 1H), 7.73 – 7.64 (m, 1H), 7.60 – 7.46 (m, 2H), 7.44 – 7.24 (m, 10H), 7.19 – 7.09 (m, 3H), 6.96 – 6.81 (m, 2H), 5.66 (dd, *J* = 10.3, 9.0 Hz, 1H), 5.56 (d, *J* = 3.6 Hz, 1H), 4.93 (d, *J* = 10.9 Hz, 1H), 4.84 (d, *J* = 11.4 Hz, 1H), 4.65 (dd, *J* = 11.2, 7.0 Hz, 2H), 4.62 – 4.54 (m, 3H), 4.38 – 4.33 (m, 2H), 4.24 (dd, *J* = 9.5, 8.6 Hz, 1H), 4.11 (d, *J* = 9.6 Hz, 1H), 4.09 – 4.04 (m, 1H), 3.91– 3.60 (m, 11H), 3.57 – 3.51 (m, 1H), 3.48 (dd, *J* = 10.4, 3.6 Hz, 1H), 3.35 (td, *J* = 4.8, 1.7 Hz, 2H), 2.13 (s, 3H), 1.81 (s, 3H).
^{13}C NMR ($CDCl_3$, 100 MHz): δ = 170.7, 169.3, 169.0, 160.1, 138.3, 138.1, 137.5, 133.0, 132.2, 130.7, 129.3, 128.5, 128.4, 128.3, 128.2, 128.0, 127.7, 126.9, 126.3, 125.5, 103.9, 98.4, 83.9, 81.5, 75.5, 75.4, 74.6, 74.5, 74.3, 74.2, 73.3, 72.3, 70.4, 70.0, 69.3, 69.2, 62.6, 52.6, 50.7, 20.9, 20.6.
HRMS (ESI): calc. for $C_{50}H_{56}N_4O_{14}F_3$ (M+H): 993.3745; found: 993.3739.



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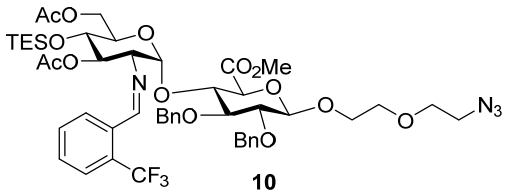
^{1}H NMR ($CDCl_3$, 500 MHz): δ = 8.46 (d, *J* = 2.4 Hz, 1H), 8.31 – 8.21 (m, 1H), 7.72 – 7.59 (m, 1H), 7.57 – 7.45 (m, 1H), 7.23 (s, 5H), 7.16 – 7.08 (m, 3H), 6.84 (d, *J* = 6.6 Hz, 2H), 5.63 (d, *J* = 3.7 Hz, 1H), 5.55 (t, *J* = 9.9 Hz, 1H), 5.09 (t, *J* = 9.9 Hz, 1H), 4.91 (d, *J* = 10.9 Hz, 1H), 4.82 (d, *J* = 11.3 Hz, 1H), 4.63 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 7.7 Hz, 1H), 4.54 (d, *J* = 11.3 Hz, 1H), 4.29 – 4.19 (m, 2H), 4.15 – 4.08 (m, 2H), 4.05 (ddd, *J* = 10.9, 4.8, 3.6 Hz, 2H), 3.86 (ddd, *J* = 10.3, 3.7, 1.7 Hz, 1H), 3.84 – 3.79 (m, 4H), 3.78 (d, *J* = 9.0 Hz, 1H), 3.74 – 3.67 (m, 2H), 3.64 (t, *J* = 5.1 Hz, 2H), 3.56 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.54 – 3.50 (m, 1H), 3.32 (td, *J* = 4.9, 2.3 Hz, 2H), 2.13 (s, 3H), 1.79 (s, 3H), 1.14 (s, 9H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 177.0, 170.8, 169.4, 169.2, 160.7, 138.1, 132.1, 130.9, 128.4, 128.2, 128.0, 127.8, 127.1, 126.4, 125.6 (q, $J_{C\text{-}F}$ = 6.0 Hz) 103.9, 98.2, 84.0, 81.6, 75.0, 74.6, 74.5, 74.1, 72.5, 70.4, 70.0, 69.3, 68.5, 67.9, 61.7, 52.5, 50.7, 38.9, 27.0, 20.8, 20.3.

HRMS (ESI): calc. for $C_{48}H_{58}N_4O_{15}F_3$ (M+H): 987.3851; found: 987.3850.



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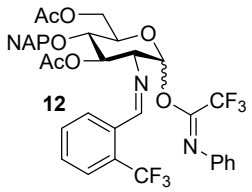
^{1}H NMR ($CDCl_3$, 400 MHz): δ = 8.43 (d, *J* = 2.4 Hz, 1H), 8.28 (dd, *J* = 5.4, 3.8 Hz, 1H), 7.68 – 7.60 (m, 1H), 7.55 – 7.45 (m, 2H), 7.22 (s, 5H), 7.13 – 7.05 (m, 3H), 6.83 (dd, *J* = 7.8, 1.7 Hz, 2H), 5.50 (d, *J* = 3.5 Hz, 1H), 5.43 (dd, *J* = 10.2, 8.8 Hz, 1H), 4.89 (d, *J* = 11.0 Hz, 1H), 4.79 (d, *J* = 11.4 Hz, 1H), 4.62 (d, *J* = 10.9 Hz, 1H), 4.58 (d, *J* = 8.2 Hz, 1H), 4.55 (d, *J* = 4.4 Hz, 1H), 4.38 (dd, *J* = 12.0, 2.1 Hz, 1H), 4.24 – 4.14 (m, 2H), 4.09 (d, *J* = 9.5 Hz, 1H), 4.07 – 4.00 (m, 1H), 3.85 (t, *J* = 9.2 Hz, 1H), 3.83 – 3.72 (m, 5H), 3.73 – 3.67 (m, 3H), 3.63 (t, *J* = 5.1 Hz, 2H), 3.50 (dd, *J* = 9.3, 7.5 Hz, 1H), 3.38 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.31 (td, *J* = 4.9, 1.8 Hz, 2H), 2.13 (s, 3H), 1.82 (s, 3H), 0.93 (t, *J* = 8.0 Hz, 9H), 0.55 (q, *J* = 7.9 Hz, 6H).

^{13}C NMR ($CDCl_3$, 125 MHz): δ = 170.8, 169.2, 159.8, 138.3, 138.2, 133.0, 132.2, 130.7, 128.6, 128.3, 128.2, 128.1, 128.0, 127.7, 126.9, 126.3, 125.5 (q, $J_{C\text{-}F}$ = 6.3 Hz), 103.9, 98.4, 84.0, 81.5, 75.2, 74.6, 74.5, 74.2, 73.7, 73.3, 70.7, 70.4, 70.0, 69.3, 69.2, 62.8, 52.5, 50.7, 21.0, 20.9, 6.8, 5.1.

HRMS (ESI): calc. for $C_{49}H_{64}N_4O_{14}F_3Si$ (M+H): 1017.4140; found: 1017.4148.



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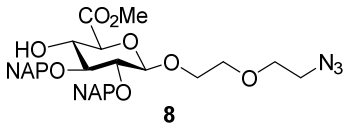
^{1}H NMR (CDCl$_3$, 500 MHz): δ 8.70 (s, 1H), 8.18 (d, *J* = 7.7 Hz, 1H), 7.98 – 6.80 (m, 15H, 6.07 (bs, 1H), 5.63 (s, 1H), 4.97 – 4.69 (m, 2H), 4.58 – 4.24 (m, 2H), 3.93 – 3.80 (m, 2H), 3.70 – 3.55 (m, 1H), 1.98 (s, 3H), 1.89 (s, 3H).
^{13}C NMR (CDCl$_3$, 126 MHz): δ 170.5, 169.4, 169.2, 161.7, 160.8, 143.3, 134.6, 133.4, 133.3, 133.2, 133.2, 133.2, 132.3, 131.0, 130.9, 129.7, 129.1, 128.8, 128.8, 128.7, 128.5, 128.5, 128.01, 127.99, 127.9, 127.8, 127.7, 127.1, 127.08, 126.4, 126.3, 126.28, 126.26, 126.0, 125.9, 125.7, 125.63, 125.59, 125.5, 125.2, 124.5, 123.0, 119.3, 95.9, 77.4, 77.1, 76.9, 75.1, 74.9, 74.9, 74.7, 74.6, 74.2, 74.0, 72.4, 72.1, 71.8, 62.5, 62.5, 20.6.
HRMS (ESI): calc. for $C_{37}H_{32}N_2F_6O_7Na$ $(M+Na)^+$: 753.2011; found: 753.2004.



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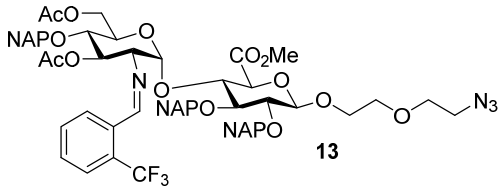
^{1}H NMR (CDCl$_3$, 500 MHz): δ 7.87 – 7.68 (m, 8H), δ 7.52 – 7.42 (m, 6H), 5.14 (d, *J* = 11.4 Hz, 1H), 5.08 (d, *J* = 11.6 Hz, 1H), 5.01 (d, *J* = 11.6 Hz, 1H), 4.92 (d, *J* = 11.4 Hz, 1H), 4.59 (d, *J* = 7.5 Hz, 1H), 4.14 – 4.04 (m, 1H), 3.93 (t, *J* = 9.1 Hz, 1H), 3.90 – 3.84 (m, 2H), 3.82 (s, 3H), 3.77 – 3.68 (m, 2H), 3.66 – 3.54 (m, 4H), 3.37 – 3.22 (m, 2H), 3.02 – 2.92 (m, 1H).
^{13}C NMR (CDCl$_3$, 126 MHz): δ 169.85, 136.03, 133.42, 133.41, 133.13, 133.11, 128.35, 128.17, 128.06, 128.03, 127.79, 126.80, 126.78, 126.28, 126.16, 126.03, 125.98, 104.21, 83.12, 81.18, 75.52, 74.86, 74.34, 71.94, 70.55, 70.07, 69.50, 52.79, 50.81.
HRMS (ESI): calc. for $C_{33}H_{35}N_3O_8Na$ $(M+Na)^+$: 624.2322; found: 624.2318.



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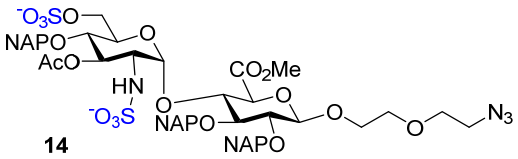
For references on nickel catalyzed formation of 1,2-cis-aminoglycosides[i-iv]

A 10 mL oven-dried Schlenk flask was charged with donor **12** (971.6 mg, 1.33 mmol, 2.0 equiv), acceptor **8** (400 mg, 0.67 mmol, 1.0 equiv), and CH_2Cl_2 (2.5 mL). A one third of preformed solution of $Ni(OTf)_2$, which was generated in situ from a reaction of $NiCl_2$ (39 mg, 0.1 mmol, 15 mol %) and AgOTf (153 mg, 0.6 mmol, 90 mol %) in dichloromethane (2.4 mL) for 30 min, 0.8 mL of catalyst solution was added to the reaction mixture. The resulting mixture was stirred under nitrogen at 35 °C overnight, quenched with triethylamine, filtered through celite and concentrated *in vacuo*. The crude product was purified by silica

gel flash chromatography (3/1 → 1/1 hexanes/ethyl acetate + 1% triethylamine) to give the desired disaccharide **7** (600 mg, 79%, α only) as yellow solid.

^{1}H NMR ($CDCl_3$, 500 MHz): δ 8.40 (d, *J* = 2.5 Hz, 1H), 8.27 (d, *J* = 7.7 Hz, 1H), 7.87 – 7.79 (m, 3H), 7.77 – 7.69 (m, 3H), 7.67 – 7.56 (m, 4H), 7.55 – 7.32 (m, 12H), 6.86 (dd, *J* = 8.4, 1.6 Hz, 1H), 5.71 (dd, *J* = 10.3, 9.1 Hz, 1H), 5.55 (d, *J* = 3.6 Hz, 1H), 5.07 (d, *J* = 11.2 Hz, 1H), 5.00 (d, *J* = 11.8 Hz, 1H), 4.84 (d, *J* = 11.8 Hz, 1H), 4.81 (d, *J* = 11.2 Hz, 1H), 4.76 (d, *J* = 11.6 Hz, 1H), 4.71 (d, *J* = 11.5 Hz, 1H), 4.64 (d, *J* = 7.6 Hz, 1H), 4.40 – 4.31 (m, 2H), 4.31 – 4.25 (m, 1H), 4.13 (d, *J* = 9.5 Hz, 1H), 4.08 (ddd, *J* = 11.1, 4.9, 3.6 Hz, 1H), 3.93 – 3.82 (m, 3H), 3.80 (s, 3H), 3.73 (ddt, *J* = 16.6, 14.2, 6.6 Hz, 3H), 3.67 – 3.59 (m, 3H), 3.45 (dd, *J* = 10.3, 3.6 Hz, 1H), 3.31 (td, *J* = 4.9, 2.2 Hz, 2H), 1.93 (s, 3H), 1.76 (s, 3H).
^{13}C NMR ($CDCl_3$, 125 MHz): δ 170.7, 169.3, 169.0, 160.2, 136.0, 135.6, 135.0, 133.2, 133.2, 133.2, 133.1, 133.1, 132.9, 132.6, 132.1, 130.7, 129.2, 128.5, 128.4, 128.0, 127.9, 127.9, 127.9, 127.8, 127.7, 127.6, 127.6, 127.5, 126.9, 126.9, 126.3, 126.2, 126.1, 125.9, 125.9, 125.8, 125.7, 125.5, 125.4, 125.0, 124.7, 124.5, 122.9, 104.0, 98.7, 83.9, 81.4, 75.9, 75.4, 74.7, 74.6, 74.4, 74.4, 73.4, 72.5, 70.4, 70.0, 69.5, 69.3, 62.6, 52.7, 50.7, 20.7, 20.6.
HRMS (ESI): calc. for $C_{62}H_{62}N_4F_3O_{14}$ $(M+H)^+$: 1143.4215; found: 1143.4222.



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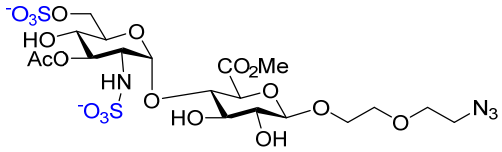
A 25 mL oven-dried Schlenk flask was charged with disaccharide **13** (300 mg, 0.26 mmol, 1 equiv.), anhydrous methanol (1.3 mL), and CH_2Cl_2 (250 μL). Sodium methoxide (14.2 mg, 0.26 mmol, 1 equiv.) was added and stirred at 25 °C for 1 h. Then 300 μL of acetone was added followed by 12 N HCl (330 μL, 15 equiv) and stirred at rt for 20 min. Reaction mixture was diluted with acetone and concentrated *in vacuo*. The crude intermediate was passed through a silica plug using 100% EtOAc →20:1 CH_2Cl_2:MeOH.

To the crude intermediate in a 25 mL oven-dried Schlenk flask was sequentially charged with anhydrous DMF (1.5 mL), $SO_3{\cdot}Me_3N$ (1.46 g, 10.48 mmol, 40 equiv.), and Et_3N (0.74 mL, 5.24 mmol, 20 equiv.) under nitrogen. The reaction mixture stirred at 55 °C for 3 d. The reaction progress was monitored by ESI negative mode mass spectrometry. The white solid filtered off, washed with CH_2Cl_2 and concentrated *in vacuo*. The crude product was purified using C-18 reverse phase silica gel flash chromatography (0 → 80% acetonitrile/water) to afford **14** (187.5 mg, 65% over 3 steps) as a white solid.

^{1}H NMR (CD_3OD, 500 MHz): δ 7.90 – 7.61 (m, 12H), 7.51 – 7.35 (m, 9H), 5.61 (d, *J* = 3.5 Hz, 1H), 5.29 – 5.23 (m, 1H), 5.14 (t, *J* = 11.4 Hz, 2H), 4.98 (t, *J* = 10.8 Hz, 2H), 4.80 (t, *J* = 12.1 Hz, 2H), 4.69 (d, *J* = 7.5 Hz, 1H), 4.41 (d, *J* = 10.0 Hz, 0H), 4.26 (d, *J* = 10.7 Hz, 1H), 4.15 – 4.08 (m, 2H), 3.96 (dt, *J* = 11.4, 4.2 Hz, 1H), 3.87 (t, *J* = 7.5 Hz, 1H), 3.84 – 3.74 (m, 6H), 3.67 – 3.61 (m, 2H), 3.59 – 3.50 (m, 3H), 3.40 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.22 (t, *J* = 5.0 Hz, 2H), 1.95 (s, 3H).
^{13}C NMR (CD_3OD, 125 MHz): δ 173.2, 170.9, 137.5, 137.3, 137.2, 134.8, 134.7, 134.5, 134.4, 134.3, 129.2, 129.0, 128.97, 128.94, 128.93, 128.8, 128.7, 128.6, 128.5, 128.1, 128.0, 127.7, 127.7, 127.4, 127.37, 127.1, 126.9, 126.87, 126.8, 126.7, 104.9, 99.5, 83.2, 82.8, 77.4, 76.9, 75.9, 75.7, 75.5, 75.1, 74.1, 71.8, 71.3, 70.9, 70.2, 66.7, 58.4, 53.4, 51.7, 21.4.
HRMS (ESI): calc. for $C_{52}H_{55}N_4O_{19}S_2$ $(M-H)^-$: 1103.2902; found: 1103.2896.



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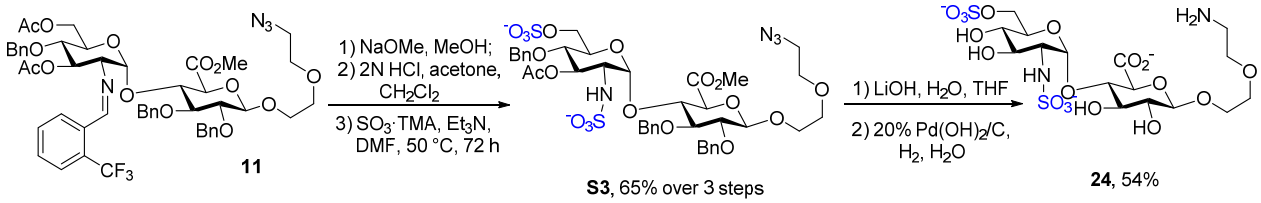
General 2-Naphthylmethyl Deprotection Procedure (Standard Procedure A)

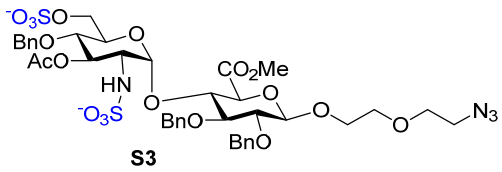
A 20 mL scintillation vial was charged with 2-naphthylmethyl protected sulfated disaccharide **14** (100 mg, 0.096 mmol, 1 equiv.), CH_2Cl_2 (1.2 mL), pH 7.4 1x PBS buffer (1.2 mL), recrystallized DDQ (142 mg, 0.63 mmol, 7 equiv.). An oversized was added and vial was wrapped in aluminum foil. Reaction mixture was stirred at rt overnight. Reaction completion was monitored for disappearance of the starting material by ESI mass spectrometry in negative mode. Upon completion, the reaction mixture was directly loaded onto a brand new 40 g Redisep Rf Gold column using minimal methanol to ensure all product was load and purified by silica gel flash chromatography on a Teledyne ISCO Flash Purification System (A-CH_2Cl_2 B-Methanol 0 → 20% B over 5 CV then 20 → 40% B over 20 CV) to afford the disaccharide **15** (41.9 mg, 75%) as a tan solid. Purification elution fractions were monitored for product by ESI mass spectrometry in negative mode.

^{1}H NMR (CD_3OD, 500 MHz): δ 5.56 (d, *J* = 3.6 Hz, 1H), 4.98 (dd, *J* = 10.9, 8.6 Hz, 1H), 4.48 (d, *J* = 7.8 Hz, 1H), 4.28 (dd, *J* = 10.9, 3.0 Hz, 1H), 4.21 (dd, *J* = 10.8, 1.9 Hz, 1H), 4.06 (d, *J* = 9.6 Hz, 1H), 4.00 – 3.90 (m, 2H), 3.84 (s, 3H), 3.80 – 3.61 (m, 9H), 3.53 – 3.40 (m, 3H), 2.14 (s, 3H).
^{13}C NMR (CD_3OD, 125 MHz): δ 173.6, 170.6, 104.6, 100.7, 80.3, 77.0, 76.1, 74.5, 74.4, 72.3, 71.3, 71.0, 70.1, 69.00, 67.1, 58.2, 54.5, 52.8, 21.2.
HRMS (ESI): calc. for $C_{19}H_{31}N_4O_{19}S_2$ $(M-H)^-$: 683.1024; found: 683.1012.



11 **S3**, 65% over 3 steps **24**, 54%

(i) 1) NaOMe, MeOH; 2) 2N HCl, acetone/CH_2Cl_2; 3) SO_3·TMA, Et_3N, DMF, 55 °C, 72 h, 65% (3 steps); (ii) 1) LiOH, H_2O, THF; 2) H_2, 20% $Pd(OH)_2$/C, H_20, 54% (2 steps)



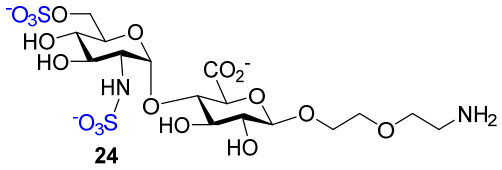
S3

A 25 mL oven-dried Schlenk flask was charged with disaccharide **11** (291 mg, 0.67 mmol, 1 equiv.) and anhydrous methanol (7 mL). Sodium methoxide (18 mg, 0.34 mmol, 0.5 equiv.) was then added and stirred at 25 °C for 2 h and monitored by TLC. The reaction mixture was neutralized with Amberlyst® 15 hydrogen

form, filtered, and concentrated to a yellow oil. The yellow oil was carried forward without any further purification. A 25 mL round bottom flask was charged with the yellow oil, aqueous hydrochloric acid (2 N, 3.1 mL, 6.1 mmol, 9 equiv.), and acetone (6 mL). The reaction mixture was stirred at 25 °C for 1 h then quenched with Et_3N (2 mL) and concentrated *in vacuo*. The crude product was then dissolved in dichloromethane (100 mL) and washed with water (2 x 40 mL). The aqueous layer was back extracted with dichloromethane (2 x 50 mL). The combined organic extracts were dried over anhydrous Na_2SO_4, concentrated *in vacuo*, and purified by silica gel flash chromatography (1/1 hexanes/ethyl acetate → ethyl acetate → 9/1 dichloromethane/methanol) to afford partially deprotected disaccharide **11a** (306 mg, 57% over two steps) as a white solid.

A 25 mL oven-dried Schlenk flask was sequentially charged with disaccharide **11a** (291 mg, 0.37 mmol, 1 equiv.), DMF (6 mL), $SO_3{\cdot}Me_3N$ (2.04 g, 14.64 mmol, 40 equiv.), and Et_3N (1.04 mL, 7.4 mmol, 20 equiv.). The reaction mixture stirred at 50 °C for 3 d. The reaction progress was monitored by ESI negative mode mass spectrometry. MeOH (6 mL) and Et_3N (2 mL) were added to the reaction mixture and stirred for 30 min. The reaction mixture was concentrated *in vacuo*. The residue was purified using C-18 reverse phase silica gel flash chromatography (0 → 80% acetonitrile/water) to afford **S3** (330 mg, 92%) as a white solid.

^{1}H NMR (CD_3OD, 500 MHz): δ = 7.62 – 7.06 (m, 15H), 5.54 (d, *J* = 3.5 Hz, 1H), 5.17 (dd, *J* = 10.9, 9.0 Hz, 2H), 4.97 (dd, *J* = 11.1, 9.0 Hz, 2H), 4.81 (dd, *J* = 11.0, 6.1 Hz, 4H), 4.67 (d, *J* = 7.5 Hz, 1H), 4.62 (dd, *J* = 11.2, 1.8 Hz, 2H), 4.33 (dd, *J* = 10.7, 2.1 Hz, 1H), 4.21 (dd, *J* = 10.7, 1.5 Hz, 1H), 4.16 – 4.06 (m, 2H), 4.00 – 3.92 (m, 1H), 3.86 – 3.75 (m, 5H), 3.72 (d, *J* = 7.5 Hz, 2H), 3.69 – 3.65 (m, 2H), 3.62 (t, *J* = 5.0 Hz, 2H), 3.46 (t, *J* = 7.9 Hz, 1H), 3.40 (dd, *J* = 10.8, 3.5 Hz, 1H), 3.27 (td, *J* = 4.8, 1.9 Hz, 2H), 2.00 (s, 3H)
^{13}C NMR (CD_3OD, 125 MHz): δ = 170.2, 168.0, 137.1, 136.8, 136.7, 126.8, 126.4, 126.3, 126.2, 125.8, 125.6, 125.5, 101.9, 96.7, 80.0, 79.8, 74.6, 74.1, 73.0, 72.8, 72.5, 72.2, 71.3, 68.8, 68.5, 68.1, 67.3, 63.8, 55.4, 50.5, 18.5.
HRMS (ESI): calc. for $C_{40}H_{49}N_4O_{19}S_2$ (M+H): 953.2432; found: 953.2427.

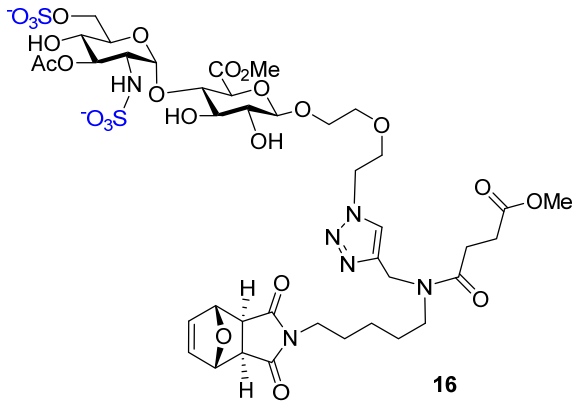


24

A 250 mL round bottom flask was charged with compound **S3** (90 mg, 0.095 mmol) and 2 mL of LiOH (0.25M) in water (60 mL), THF (16 mL). The entire reaction mixture was stirred for 4 h. The reaction progress was monitored by negative mode mass spectrometry. Solvents were removed on lyophilizer. The resulting residue was purified using C-18 reverse phase silica gel flash chromatography (0 → 80% acetonitrile/water) to afford (50 mg, 60%) as a white solid.

A 5 mL glass vial was charged with the compound (7 mg) after saponification, 20% $Pd(OH)_2/C$ (30 mg) and 400 μL water. The reaction mixture was subjected to hydrogenolysis at 150 psi of H_2 for 24 h at room temperature. The reaction mixture was filtered through a Millex- GS MCE membrane (pore size 0.22 μM, filter diameter 33 mm, and the membrane filter was washed with warm water (37 °C). The filtrate was passed through sodium ion exchange resin to afford compound **24** (5mg, 54% over two steps) as white solid.

^{1}H NMR (D_2O, 500 MHz): δ 5.71 (d, *J* = 3.8 Hz, 1H), 4.59 (d, *J* = 8.0 Hz, 1H), 4.38 (dd, *J* = 11.1, 2.9 Hz, 1H), 4.22 (dt, *J* = 11.1, 3.0 Hz, 1H), 4.08 (ddd, *J* = 11.8, 5.9, 2.9 Hz, 1H), 3.92 (m, 9H), 3.72 – 3.58 (m, 2H), 3.43 (t, *J* = 8.5 Hz, 1H), 3.32 (dd, *J* = 9.7, 3.8 Hz, 1H), 3.26 (t, *J* = 5.1 Hz, 2H).
^{13}C NMR (D_2O, 126 MHz): δ 175.1, 102.3, 97.2, 76.6, 76.5, 76.0, 72.9, 71.2, 69.8, 69.6, 69.2, 69.1, 66.5, 66.3, 58.0, 39.3.
HRMS (ESI): calc. for $C_{16}H_{29}N_2O_{18}S_2$ $(M-H)^-$: 601.0857; found: 601.0858.

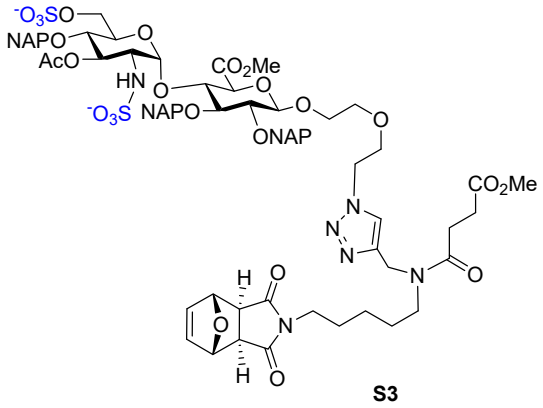


16

General "Click" Procedure (Standard Procedure B)

An oven-dried 10 mL Schlenk flask was charged with a solution of polymerizable scaffold **A** (10.9 mg, 0.027 mmol 1.2 equiv.) in CH_2Cl_2 and a solution of deprotected sulfated disaccharide **15** (15 mg, 0.023 mmol, 1 equiv.) in methanol. The mixture was then concentrated by rotary evaporation and placed *in vacuo* for 30 min. Under N_2, CuI (4.3 mg, 0.023 mmol, 1 equiv.) was added followed by anhydrous DMF (0.3 mL). Lastly the addition of DBU (4 μL, 0.027 mmol, 1.2 equiv.) by microsyringe. The resulting mixture was stirred overnight at 50 °C. The reaction mixture was monitored by ESI mass spectrometry in negative mode for complete consumption of **15**. Upon completion, the reaction mixture was directly loaded onto a brand new 24 g Redisep Rf Gold column using minimal methanol to ensure all product was load and purified by silica gel flash chromatography on a Teledyne ISCO Flash Purification System (A-CH_2Cl_2 B-Methanol 0 → 60% B over 20 CV) to afford the diantennary glycomonomer **16** (14.7 mg, 64%) as a tan solid. Purification elution fractions were monitored for product by ESI mass spectrometry in negative mode.

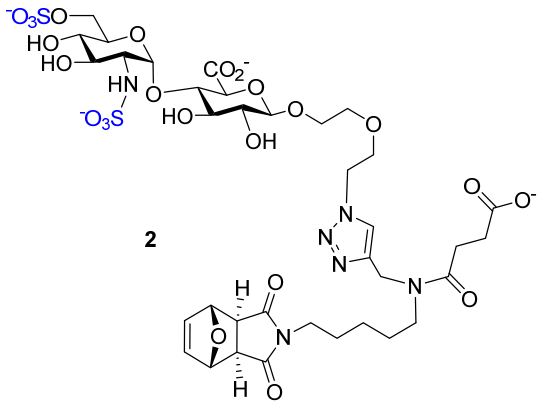
^{1}H NMR (CD_3OD, 500 MHz): δ 8.15 (s, 0.5H), 7.96 (s, 0.5H), 6.50 (s, 2H), 5.59 (s, 1H), 5.42 – 5.30 (m, 2H), 5.07 (s, 1H), 4.98 (t, *J* = 7.4 Hz 1H), 4.73 (s, 1H), 4.69 – 4.54 (m, 3H), 4.45 (d, *J* = 7.8 Hz, 1H), 4.33 – 4.15 (m, 2H), 4.09 – 4.01 (m, 1H), 3.95 – 3.62 (m, 18H), 3.48 – 3.38 (m, 4H), 3.22 – 3.10 (m, 1H), 2.90 (t, *J* = 6.5 Hz, 1H), 2.80 – 2.64 (m, 4H), 2.60 (t, *J* = 7.4 Hz, 1H), 2.14 (s, 3H), 1.80 – 1.52 (m, 4H), 1.42 – 1.26 (m, 2H).
^{13}C NMR (CD_3OD, 125 MHz): δ 175.3, 174.5, 174.4, 173.9, 173.5, 170.6, 138.0, 137.7, 127.4, 125.2, 104.7, 100.5, 81.9, 81.8, 81.2, 80.1, 80.1, 77.2, 77.2, 76.1, 74.5, 74.5, 72.4, 71.3, 70.3, 70.2, 69.0, 67.2, 61.6, 61.3, 61.1, 60.8, 58.8, 53.5, 52.3, 52.2, 51.4, 51.4, 51.1, 43.1, 43.0, 40.7, 30.2, 29.4, 29.1, 28.9, 28.0, 27.7, 27.7, 25.2, 25.1, 21.3.
HRMS (ESI): calc. for $C_{40}H_{59}N_6O_{25}S_2$ $(M-H+2)^-$: 1087.2971; found: 1087.2977.



S3

Synthesized Following Standard Procedure B

^{1}H NMR (CD_3OD, 500 MHz): δ 7.92 – 7.26 (m, 22H), 6.39 (d, *J* = 3.2 Hz, 2H), 5.59 (s, 1H), 5.27 (m, 3H), 5.15 (t, *J* = 12.2 Hz, 1H), 5.08 – 4.96 (m, 3H), 4.98 – 4.89 (m, 1H), 4.81 (d, *J* = 11.4 Hz, 1H), 4.76 – 4.65 (m, 2H), 4.53 – 4.33 (m, 5H), 4.29 (dd, *J* = 9.9, 4.1 Hz, 1H), 4.22 – 4.16 (m, 2H), 3.96 – 3.71 (m, 12H), 3.60 (s, 3H), 3.54 (t, *J* = 7.3 Hz, 1H), 3.47 (dd, *J* = 11.1, 3.1 Hz, 1H), 3.26 – 3.16 (m, 2H), 3.12 – 2.99 (m, 1H), 2.71 – 2.46 (m, 5H), 2.42 (td, *J* = 7.5, 2.1 Hz, 1H), 1.95 (s, 3H), 1.59 – 1.35 (m, 4H), 1.24 – 1.07 (m, 2H).
^{13}C NMR (CD_3OD, 125 MHz): δ 175.2, 174.4, 173.7, 173.3, 170.9, 138.0, 137.6, 137.5, 137.3, 137.2, 134.8, 134.7, 134.67, 134.5, 134.4, 134.35, 129.2, 129.1, 129.0, 128.9, 128.8, 128.7, 128.7, 128.6, 128.5, 128.0, 127.7, 127.6, 127.5, 127.4, 127.3, 127.1, 127.1, 127.0, 126.9, 126.7, 126.6, 126.57, 104.8, 99.9, 82.7, 82.5, 81.9, 81.1, 80.0, 77.9, 77.2, 76.1, 75.8, 75.0, 74.9, 74.4, 71.9, 71.4, 70.2, 66.9, 58.3, 53.5, 52.2, 52.2, 51.4, 51.0, 43.0, 40.7, 30.1, 30.0, 29.3, 29.0, 27.9, 27.7, 21.4.
HRMS (ESI): calc. for $C_{73}H_{83}N_4O_{19}S_2$ $(M\text{-}H+2)^-$: 1507.4849; found: 1507.4851.



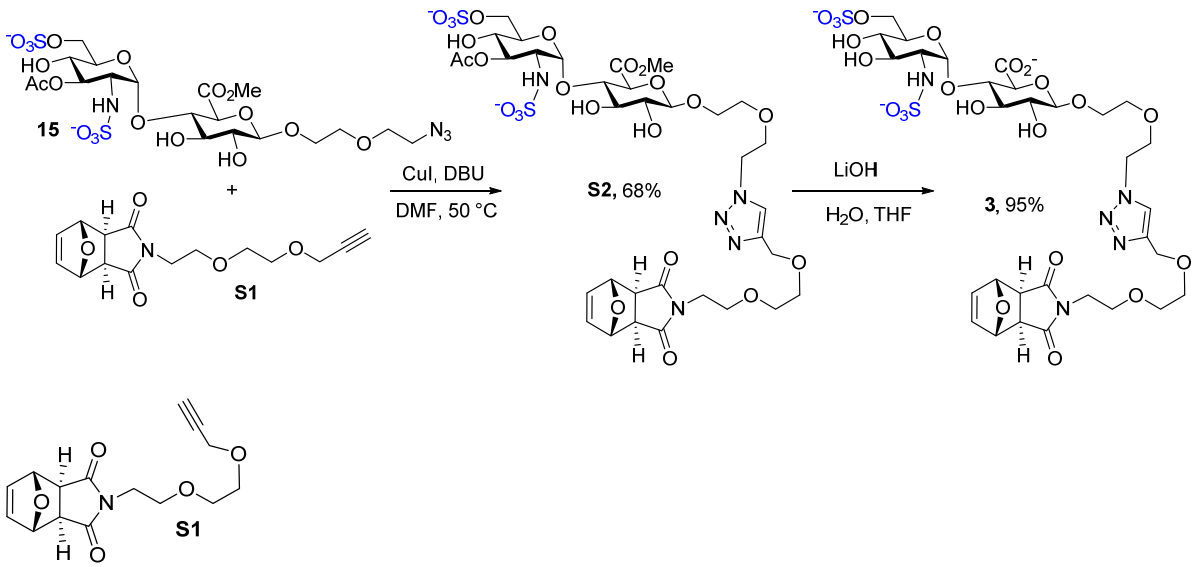
2

General Hydrolysis Procedure of Monomers (Standard Procedure C)

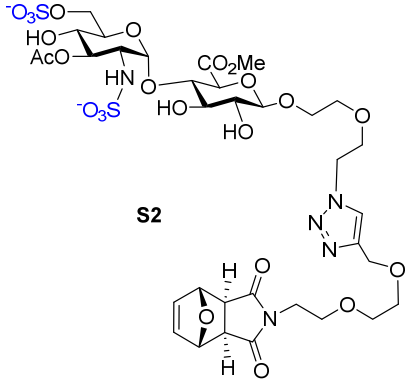
Diantennary monomer **16** (7.2 mg) was charged into a 3 dram scintillation vial along with 0.41 mL .25 M LiOH aqueous solution, 4.4 mL of water, and 1.2 mL of THF. Allowed to stir at room temperature for 24 h and monitored for completion of reaction by ESI mass spectrometry in negative mode. The reaction mixture was then frozen using liquid nitrogen and lyophilized to completion. Remaining solid was then dissolved in water and placed inside a dialysis cartridge (Float-A-Lyzer G2 Dialysis Device, Biotech, 0.1-0.5 kD MWCO, 1 ml, Cat. #: G235025) and dialyzed against 0.9% NaCl solution for 24 h (3 buffer changes) then against deionized water for 24 h (3 buffer changes). Finally sample was transferred into a 3 dram vial and

frozen by liquid nitrogen. Sample was then lyophilized to obtain fully deprotected diantennary **2** as a white solid (6.3 mg, 94%).

^{1}H NMR (D_2O, 500 MHz): δ 8.07 (s, 0.5H), 7.92 (s, 0.5H), 6.52 (d, *J* = 1.3 Hz, 2H), 5.65 (d, *J* = 3.8 Hz, 1H), 5.15 – 5.00 (m, 2H), 4.80 – 4.70 (m, 2H) 4.67 – 4.53 (m, 3H), 4.46 (d, *J* = 8.0 Hz, 1H), 4.35 (dd, *J* = 11.1, 2.1 Hz, 1H), 4.20 – 4.10 (m, 1H), 4.03 – 3.95 (m, 4H), 3.89 – 3.54 (m, 8H), 3.46 – 3.31 (m, 4H), 3.26 (dd, *J* = 9.9, 3.6 Hz, 1H), 3.21 – 3.06 (m, 1H), 2.91 (d, *J* = 7.3 Hz, 1H), 2.80 – 2.62 (m, 3H), 2.49 – 2.40 (m, 2H), 2.36 (d, *J* = 7.2 Hz, 1H), 1.69 – 1.41 (m, 4H), 1.39 – 1.11 (m, 2H).
^{13}C NMR (D_2O, 125 MHz): δ 175.3, 136.4, 135.9, 102.3, 97.3, 85.4, 82.4, 80.5, 76.8, 76.5, 76.2, 72.8, 71.2, 69.8, 69.7, 69.1, 68.9, 68.7, 66.4, 60.5, 58.0, 50.0, 48.8, 48.6, 46.8, 41.2, 39.9, 32.7, 29.4, 27.4, 26.1, 23.1.
HRMS (ESI): calc. for $C_{36}H_{53}N_6O_{24}S_2$ $(M-H+2)^-$: 1017.2553; found: 1017.2553.

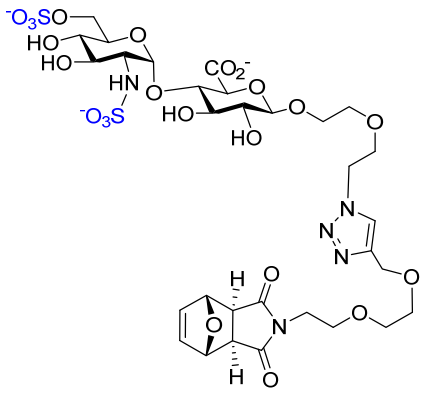


^{1}H NMR (500 MHz, $CDCl_3$): δ 6.5 (s, 2H), 5.26 (s, 2H), 4.17 (d, *J* = 2.4 Hz, 2H), 3.70 – 3.57 (m, 8H), 2.85 (s, 2H), 2.41 (t, *J* = 2.4 Hz, 1H).
^{13}C NMR (125 MHz, $CDCl_3$): δ 176.2, 136.7, 81.1, 74.6, 70.1, 69.2, 67.3, 47.6, 38.4.
HRMS (ESI): calc. for $C_{15}H_{18}NO_5$ $(M+H)^+$: 292.1185; found: 292.1192.



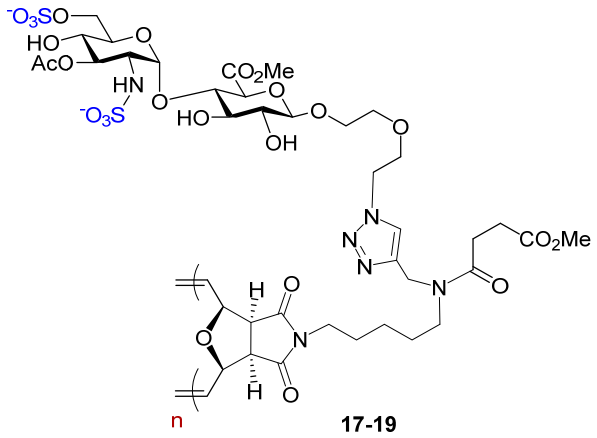
Synthesized Following Standard Procedure B

^{1}H NMR (CD_3OD, 500 MHz): δ 8.10 (s, 1H), 6.57 (s, 2H), 5.58 (d, *J* = 3.7 Hz, 1H), 5.25 – 5.12 (m, 2H), 4.96 (dd, *J* = 10.8, 8.8 Hz, 1H), 4.71 – 4.57 (m, 5H), 4.44 (d, *J* = 7.8 Hz, 1H), 4.31 – 4.13 (m, 2H), 4.04 (d, *J* = 9.6 Hz, 1H), 3.95 – 3.89 (m, 5H), 3.83 (s, 3H), 3.78 – 3.58 (m, 11H), 3.40 (m, 3H), 2.96 (s, 2H), 2.12 (s, 3H).
^{13}C NMR (CD_3OD, 125 MHz): δ 178.6, 173.5, 170.6, 137.66, 137.65, 126.1, 104.6, 100.5, 82.3, 80.1, 77.2, 76.1, 74.5, 74.47, 72.4, 71.3, 71.25, 70.7, 70.4, 70.1, 69.1, 68.3, 67.2, 65.0, 58.3, 53.5, 51.4, 39.3, 21.3.
HRMS (ESI): calc. for $C_{34}H_{48}N_5O_{24}S_2$ $(M-H)^-$: 974.2131; found: 974.2116.



3

^{1}H NMR (D_2O, 500 MHz): δ 8.12 (s, 1H), 6.49 (ddd, *J* = 65.6, 5.9, 1.8 Hz, 2H), 5.66 (d, *J* = 3.8 Hz, 1H), 5.12 (m, 2H), 4.85 – 4.74 (m,3), 4.65 (t, *J* = 5.1 Hz, 2H), 4.48 (d, *J* = 8.0 Hz, 1H), 4.37 (dd, *J* = 11.2, 2.5 Hz, 1H), 4.18 (dd, *J* = 11.1, 2.1 Hz, 1H), 4.05 – 3.93 (m, 3H), 3.92 – 3.55 (m, 14H), 3.49 – 3.20 (m, 4H), 2.79 – 2.69 (m, 2H).
^{13}C NMR (D_2O, 125 MHz): δ 178.8, 175.8, 175.0, 144.0, 137.4, 135.2, 125.6, 102.3, 97.3, 80.9, 80.6, 76.8, 76.5, 76.3, 72.8, 71.2, 69.8, 69.4, 69.1, 69.0, 68.9, 68.8, 68.75, 66.4, 63.1, 58.0, 50.1, 50.1, 47.3, 39.0, 23.4.
HRMS (ESI): calc. for $C_{31}H_{43}N_5O_{23}S_2Na$ $(M-2H+Na+2)^-$: 940.1688; found: 940.1681.



17-19

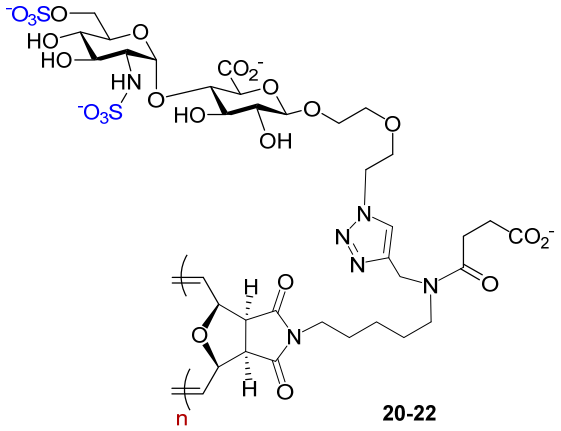
General Polymerization Procedure (Standard Procedure D)

To an oven-dried 10 mL Schlenk flask under N_2 was charged with a solution of diantennary monomer **16** (18 mg, 0.0166 mmol) in a degassed mixture of 2.5:1 1,2-dichloroethane:2,2,2-trifluoroethanol (DCE:TFE) (1 mL). The mixture was then concentrated by rotary evaporation and placed under vaccuum for 30 min.

Solvent mixture was degassed by freeze-pump-thaw method and repeated at least 5 times until bubbles subsided. In a glove box under an inert N_2 atmosphere, a conical 1 mL oven dried Schlenk was charged with 8.5 mg of Grubbs III catalyst **23** [$(H_2IMes)(3\text{-Br-py})_2(Cl)_2Ru{=}CHPh$] (G3), then sealed with glass stopper and removed from glove box. The catalyst **23** was then dissolved in 0.514 mL of degassed 2.5:1 DCE:TFE under N_2 to make a stock solution. Under N_2 monomer **16** was redissolved in the degassed 2.5:1 DCE:TFE (0.565 mL) mixture and a magnetic stir bar added. A 0.100 mL solution of the G3 stock solution (0.00149 mmol, 0.09 equiv.) was then rapidly injected to the monomer solution under N_2 and then sealed with a glass stopper (final concentration=0.025 M). The resulting solution was then lowered into a 55 °C oil bath and allowed to stir. After the solution became cloudy (1 h), the conversion of the monomer was monitored by ^{1}H NMR of a reaction aliquot in CD_3OD by observing the disappearance of the strained alkene peak at 6.4 ppm. Upon full conversion, the reaction was cooled to room temperature and stirred for 5 min. The reaction mixture was quenched with ethyl vinyl ether (10 drops) and allowed to stir for 30 min. The reaction mixture was then transferred into a 20 mL scintillation vial and concentrated *in vacuo* to a brown oil. The crude product was dissolved in a minimal amount of methanol and precipitated with an excess of diethyl ether. Precipitate was allowed to settle and the liquid was then decanted off (Note: if the precipitant was very fine, this solution was centrifuged, and the diethyl ether layer was decanted). The precipitate was then redissolved in excess methanol (2 mL) and reconcentrated until the polymer was in a minimal amount of methanol. This process was repeated two more times. On the final precipitation the polymer was not redissolved in methanol and placed *in vacuo* to yield diantennary polymer **19** as an off white solid (16.6 mg, 92%).

Since polymers are prone to form micelles, their DP cannot be determined by GPC analysis (please see page S30-S35 for our attempts to use GPC). As a result, the DP of glycopolymers was determined by ^{1}H end group analysis - Polymers of same scaffold showed no variation in ^{1}H NMR signals, only varying in the ratio of the GlcN anomeric peak (~5.5 ppm) and the phenyl end group (~7.4 ppm) which were used to find the DP.

^{1}H NMR (CD_3OD, 500 MHz): δ 8.14 (s, 0.5H), 7.94 (s, 0.5H), 7.53 – 7.21 (m, 1H, phenyl end group), 5.95 (s, 1H), 5.70 (s, 1H), 5.55 (s, 1H), 5.40 (s, 1H), 4.96 (t, *J* = 9.7 Hz, 1H), 4.70-4.50 (m, 4H), 4.44 (s, 1H), 4.29 – 4.12 (m, 2H), 4.03 (s, 2H), 3.95 – 3.56 (m, 19H), 3.48 – 3.32 (m, 4H), 3.02-2.97 (m, 1H), 2.96-2.92 (m, 1H), 2.90-2.22 (m, 4H), 2.11 (s, 3H), 1.70 – 1.52 (m, 4H), 1.39 – 1.16 (m, 2H).



20-22

General Hydrolysis Procedure for Polymers (Standard Procedure E)

Diantennary polymer **19** (16.6 mg) was charged into a 20 mL scintillation vial along with 1.4 mL of 0.25 M LiOH aqueous solution, 14.6 mL of water, and 3.9 mL of THF. The resulting solution was allowed to stir at room temperature for 24 h. The reaction mixture was then frozen using liquid nitrogen and lyophilized to completion. Remaining solid was then dissolved in water and placed inside a dialysis cartridge (Slide-A-Lyzer G2 Dialysis Cassettes, 3.5K MWCO, 3 mL, Cat. #: 87723) and dialyzed against 0.9% NaCl solution for 24 h (3 buffer changes) then against DI water for 24 h (3 buffer changes). Finally sample was transferred into a 3 dr vial and frozen by liquid nitrogen. Sample was then lyophilized to obtain fully deprotected diantennary **22** as a white solid (13.8 mg, 89%).

^{1}H NMR (D_2O, 500 MHz): δ 8.10 (s, 0.5H) 7.95 (s, 0.5H), 7.38 (m, 0.57H, phenyl end group), 6.03 (s, 2H), 5.66 (s, 1H), 5.15 (s, 1H), 4.80 – 4.70 (m, 2H), 4.68 – 4.42 (m, 4H), 4.38 (d, *J* = 10.9 Hz, 1H), 4.19 (d, *J* = 10.6 Hz, 1H), 3.98 – 3.10 (m, 18H), 2.79 – 2.53 (m, 6H), 1.51 (m, 4H), 1.20 (m, 2H).

^{13}C NMR (D_2O, 125 MHz): δ 174.9, 102.4, 97.5, 77.0, 76.8, 76.4, 72.8, 71.2, 69.9, 69.8, 69.1, 68.9, 68.8, 66.4, 58.0, 50.0, 48.5, 48.4, 43.1, 41.2, 29.1, 27.5, 23.6.

Since polymers are prone to form micelles, their DP cannot be determined by GPC analysis (please see page S30-S35 for our attempts to use GPC). As a result, the DP of glycopolymers was determined by ^{1}H end group analysis - Polymers of same scaffold showed no variation in ^{1}H NMR signals, only varying in the ratio of the GlcN anomeric peak (~5.5 ppm) and the phenyl end group (~7.4 ppm) which were used to find the DP.

*Due to the high sulfate contents, both elemental and MALDI analyses of these glycopolymers were not successful even after multiple attempts. As a result, the sulfate content was determined using the turbidimetric assay method reported by T. T. Terho and K. Hartiala "Method for Determination of the sulfate content of Glycosaminoglycans" Analytical Biochemistry, **1997**, 41, 471-476.*

Turbidimetric Sulfate Content Assay:

The quantity of sulfate in polymer **22** was determined by using sulfate assay kit (Sigma-Aldrich catalog # MAK132).

The hydrolysis of polymer was carried out in hydrochloric acid (3N) for 5.3 h at 100 °C. The reaction mixture was evaporated *in vacuo* at 65 °C. The residue was dissolved in a known amount of ultrapure water and the sulfate concentration was determined by using the sulfate assay kit. Standards were made according to the vendor's protocol ranging from 0 (blank) to 2.0 mM. Master reaction mixture was made just before the assay. A 200 μl solution of standards and sample were transferred to 96 well flat bottom clear plate and A 100 μl solutionof master reaction mix was then added to each well by a multichannel pipette and mixed well. In about 5 min later, optical density (OD) was measured at 600 nm. The OD measurement for each standard after blank subtraction were plotted against their concentrations (see Figure S1).

Result: Theoretical sulfate concentration = 1.76 mM (sulfate per disaccharide = 2); Found sulfate concentration: 1.64 mM (93.2%, sulfates per disaccharide = 1.86)

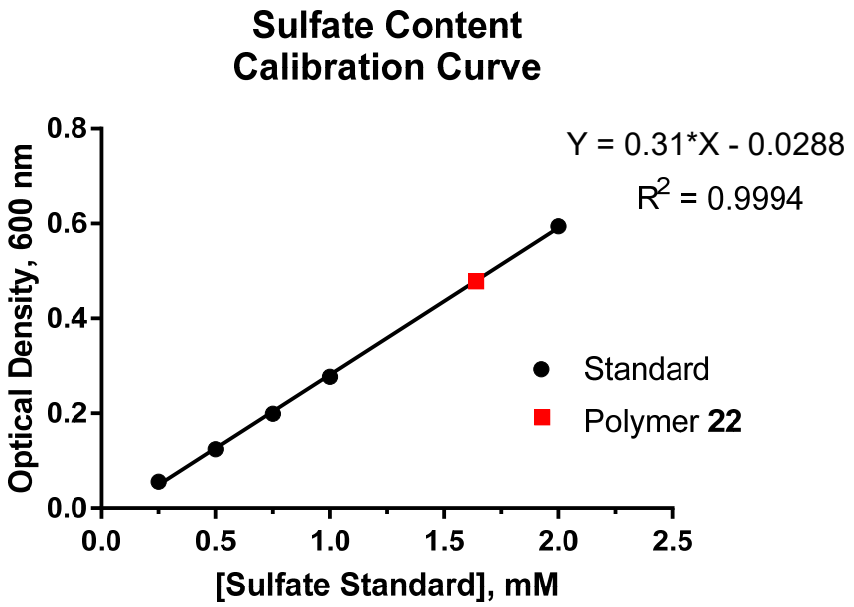


Figure S1. Measurement of sulfate content of glycopolymer 22.

Critical Micelle Concentration (CMC) Protocol

Fluorescence measurements were performed in an Aligent Technologies Cary Eclipse Fluorescence Spectrophotometer. A 15 μM stock solution of pyrene was formed in a 15:85 methanol:water mixture. A stock solution of polymer **22** was serially diluted in 1.5 mL Eppendorf tubes to a volume of 420 μL at 16 different concentrations with deionized water from 0 to 1 mg/mL. To each tube a 30 μL solution of the pyrene stock solution were added to bring the final pyrene concentration to 1 μM and a methanol concentration of <1%. Tubes were then covered in aluminum foil and mechanically agitated by an orbital shaker for 2 h at 100 RPM and then allowed to equilibrate for 18 h. Fluorescence emission spectra of the polymer solutions containing pyrene were recorded in a 400 μL microcuvette using an excitation wavelength of 335 nm, and the intensities I_1 and I_3 were measured at the wavelengths corresponding to the first and third vibronic bands located near 373 (I_1) and 384 (I_3) nm. A 2.5 nm slit width was used for both excitation and emission. All fluorescence measurements were carried out at 25.0 °C. The average ratio of I_1/I_3 for three trials was then plotted against the concentration of each polymeric sample using GraphPad Prism 7 (see Figure S2). The (CMC) was taken at the intersection of two calculated regression lines.

Result: Critical micelle concentration (CMC) of polymer **22** = 3.3 μM

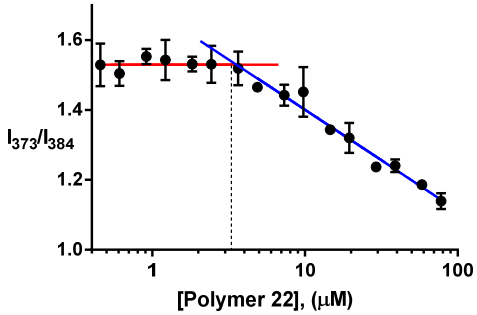


Figure S2. Measurement of CMC of glycopolymer 22.

Analyzing the CMC at Different Concentration of Polymer 22 in the Presence of Heparanase to determine whether heparanase could assist aggregation

Fluorescence measurements were performed in an Aligent Technologies Cary Eclipse Fluorescence Spectrophotometer. A 15 μM stock solution of pyrene was formed in a 15:85 methanol:Milli-Q water mixture. A stock solution of polymer **22** was serially diluted in 1.5 mL Eppendorf tubes to a volume of 82.5 μL at 7 different concentrations with Milli-Q water from 0 to 20 μM. To each tube 225 μL pH 5.5 0.2 M $NaCH_3CO_2$ buffer, 112.5 μL solution of heparanase (5.3 nM, R&D Systems) in pH 7.5 triz buffer (consisting of 20 mM TrisHCl, 0.15 M NaCl and 0.1% CHAPS) [*Note: These are the same conditions that we used in the FRET assay for studying heparanase inhibition*]. A 30 μL solution of the pyrene stock solution were added. This brought the final pyrene concentration to 1 μM and a methanol concentration of <1%, final heparanase concentration to 1.3 nM (*the same enzyme concentration used in the FRET assay*), and overall volume to 450 μL. Tubes were then covered in aluminum foil and mechanically agitated by an orbital shaker for 2 h at 100 RPM and then allowed to equilibrate for 18 h. Fluorescence emission spectra of the polymer solutions containing pyrene were recorded in a 400 μL microcuvette using an excitation wavelength of 335 nm, and the intensities I_1 and I_3 were measured at the wavelengths corresponding to the first and third vibronic bands located near 373 (I_1) and 384 (I_3) nm. A 2.5 nm slit width was used for both excitation and emission. All fluorescence measurements were carried out at 25.0 °C. The average ratio of I_1/I_3 for three trials was plotted against the concentration of each polymeric sample using GraphPad Prism 7 (see Figure S3).

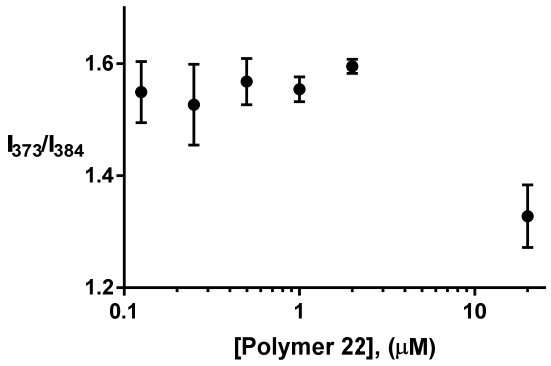


Figure S3. Measurement of fluorescence ratio of fluorogenic probe pyrene at different concentrations of glycopolymer 22 in the presence of heparanase.

There was no change in the fluorescence ratio (I_1/I_3) of fluorogenic probe pyrene (Figure S3), suggesting there was no aggregation. We also verify by conducting the experiment at higher polymer concentration (20 μM), the fluorescence ratio (I_1/I_3) was similar to the original ratio when calculated the CMC of glycopolymer **22** (Figures S2 vs S3), suggesting that micellar formation can occur in this buffer at high concentration.

Dynamic Light Scattering (DLS) Protocol

Micelle Z-average radiis and poly polydispersity were determined using a Wyatt DynaPro NanoStar dynamic light scattering instrument at a polymer concentration of 1 mg/mL. Samples were prepared in deionized water and filtered through a nylon 0.45 μm syringe filter (Millipore Millex-HN, 33 mm, Cat #: SLHN033NB). All measurements of polymers were the average of five runs carried out at 25.0 °C in a 4 μL microcuvette.

Entry	Polymer	DP_n	R_h (nm)	PDI
1	**20**	5	75.9	18.4
2	**21**	9	66.2	17.1
3	**22**	12	90.7	14.7

Table S1. DLS analysis of the distribution of hydrodynamic radiis of neo-glycopolymers 20-22 at a concentration of 1 mg/mL in water.

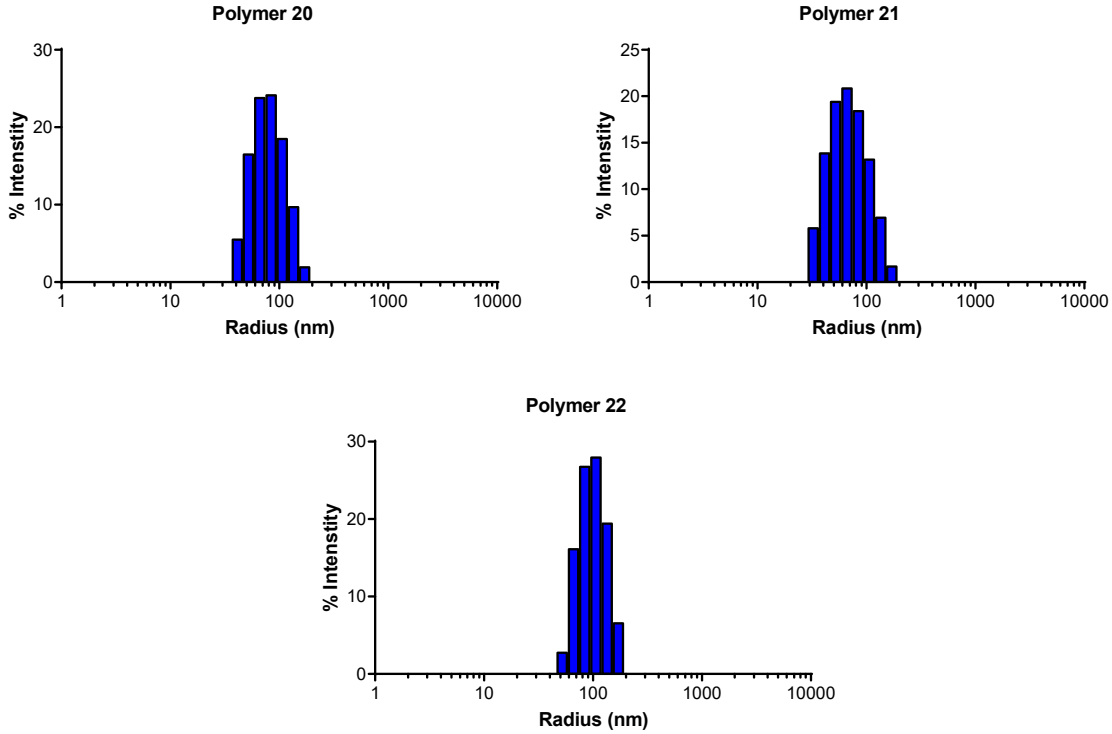
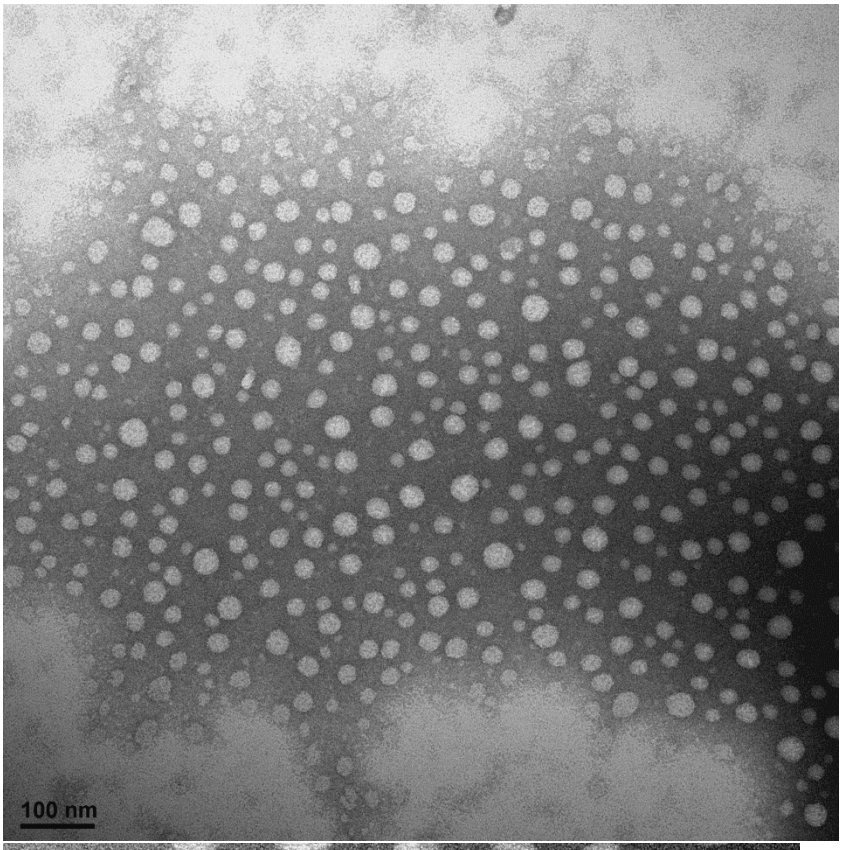
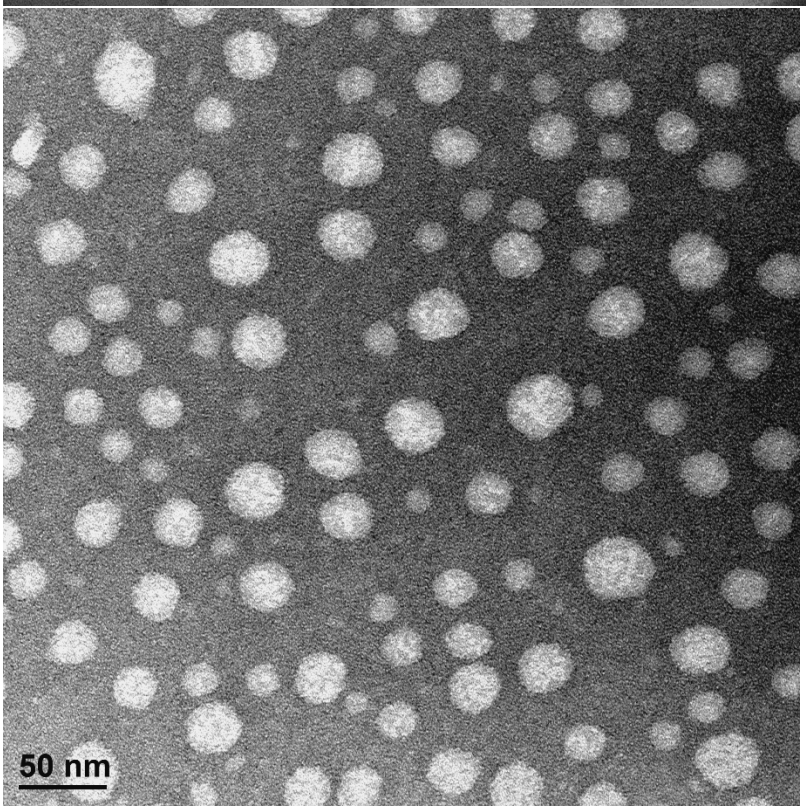


Figure S4. DLS histograms of the distribution of hydrodynamic radiis of neo-glycopolymers 20-22 at a concentration of 1 mg/mL in water.

Transmission Electron Microscopy (TEM) Protocol

TEM images were obtained using a JEOL1230 transmission electron microscope with a Gatan UltraScan 1000 2k x 2k CCD camera for acquiring digital images. Samples were prepared in deionized water and filtered through a nylon 0.45 µm syringe filter (Millipore Millex-HN, 33 mm, Cat #: SLHN033NB). 10 µL of the sample were placed onto formvar/carbon covered #400 copper mesh grids and allowed to sit for 1 min. Excess solution was then blotted off carefully with filter paper. The grids were then negatively stained by addition of 10 µL of freshly made 1% uranyl acetate solution. After 1 min, excess uranyl acetate solution was blotted off and the grids were allowed to air dry. Average particle size and distribution were then analyzed of five different grid areas by using the NIH ImageJ software.


100 nm


50 nm

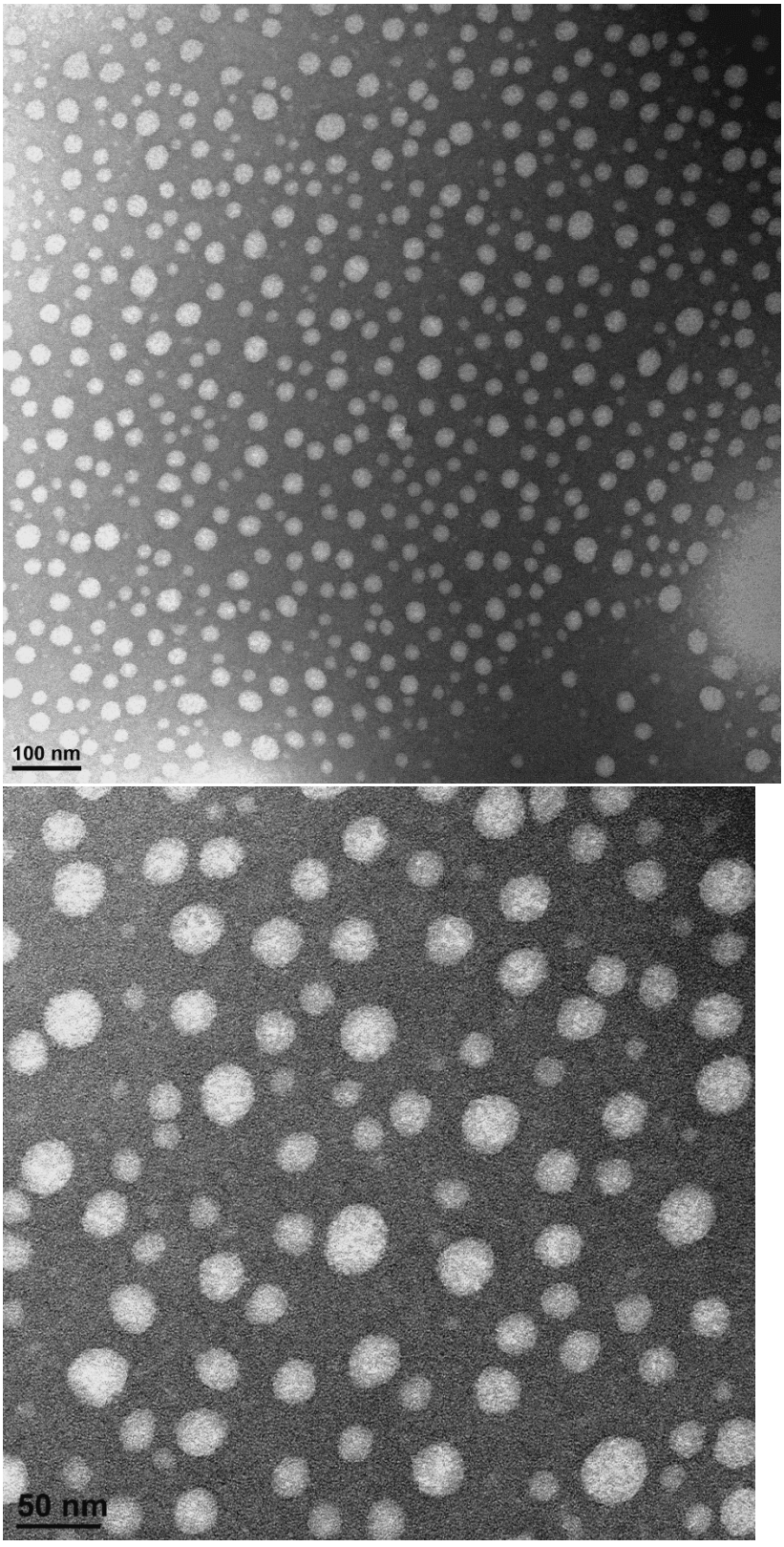


Figure S5. TEM images of spherical micelles of diantennary polymer 22 at a concentration of 1 mg/mL in water.

Two-Stage Chromogenic Assay to Evaluate FXa and FIIa Activity[vi]

BIOPHEN Heparin AntiXa (2 stages) USP/EP (Cat #: A221010-USP) kits from Aniara and BIOPHEN Heparin Anti-IIa (2 stages) USP/EP (Cat #: A221025-USP) were utilized to assess FXa and FIIa activity, respectively.

Factor Xa activity:

All the reagents were reconstituted and prepared according to the manufacturer's instructions and incubated at 37 °C for 15 min. Different concentrations of low molecular weight heparin (LMWH) or neo-glycopolymers (0.0002-166.7 µM; 40 µL) and ATIII (0.04 IU; 40 µL) were added to a deep-well block (Nunc 96 DeepWell 1.0 mL/well, clear), mixed, and incubated at 37 °C for 2 min. To the reaction mixture, FXa (0.32 µg; 40 µL) was added by multichannel pipette and was incubated at 37 °C for another 2 min (stage 1), then FXa specific chromogenic substrate (0.048 mmol; 40 µL) was added. The reaction was stopped by adding citric acid (240 µL; 20 g/L) exactly after 2 min. A 100 µl solution was then transferred to a clear 96-well microplate in triplicate, and absorbance at 405 nm was measured with a SpectraMax i3x Microplate Reader (Molecular Devices). The sample blank was measured by mixing the reagents in reverse order from that of the test, i.e. citric acid, FXa substrate, FXa, ATIII, and sample. The sample blank value was deducted from the absorbance measured for the corresponding assay.

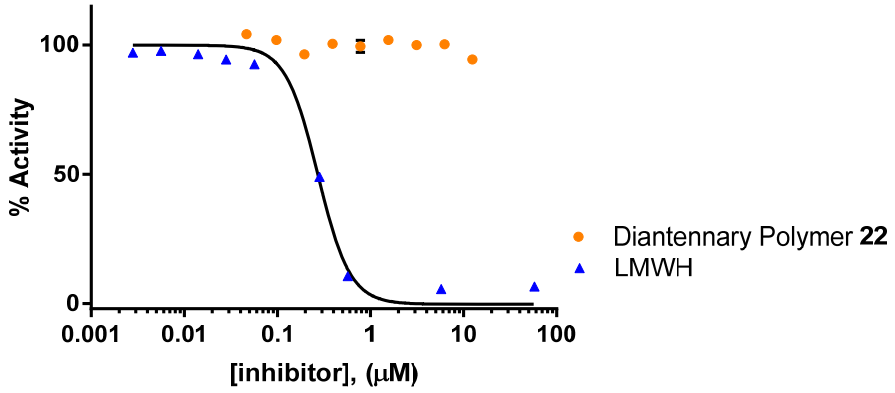


Figure S6. Biological activity of the inhibition of FXa by diantennary polymer 22 in comparison to LMWH.

Factor IIa activity:

All the reagents were reconstituted and prepared according to the manufacturer's instructions and incubated at 37 °C for 15 min. Different concentrations of heparin (0.0023-2.4 µM; 40 µL, MW-18 kDa, Sigma) or diantennary polymer **22** (90-1.4 µM; 40 µL) and ATIII (0.01 IU; 40 µL) were added to a deep-well block (Nunc 96 DeepWell 1.0 mL/well, clear), mixed, and incubated at 37 °C for 2 min. To the reaction mixture, FIIa (1.2 nkat; 40 µL) was added by multichannel pipette and was incubated at 37 °C for another 2 min (stage 1), then FIIa specific chromogenic substrate (0.048 mmol; 40 µL) was added. The reaction was stopped by adding citric acid (240 µL; 20 g/L) exactly after 2min. 100 µl was transferred to a 96-well microplate in triplicate, and absorbance at 405 nm was measured with SpectraMax i3x Microplate Reader (Molecular Devices). The sample blank was measured by mixing the reagents in reverse order from that of the test, i.e. citric acid, FXa substrate, FXa, ATIII, and sample. The sample blank value was deducted from the absorbance measured for the corresponding assay.

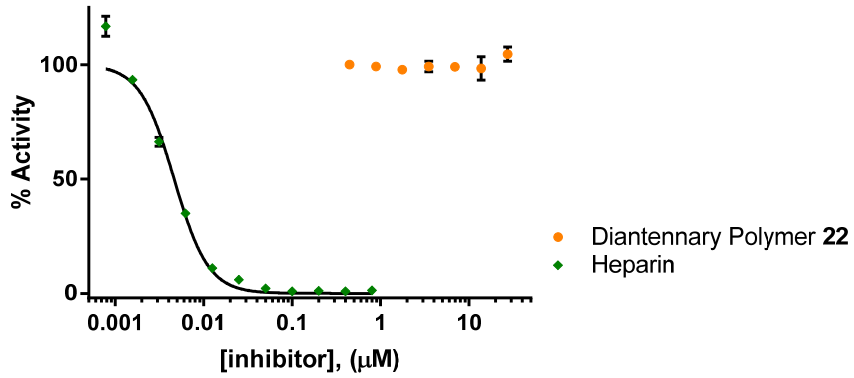


Figure S7. Biological activity of the inhibition of FIIa by diantennary polymer 22 in comparison to 18 kDa heparin.

Homogeneous Heparanase TR-FRET Assay:[vii]

A 42 μl of inhibitor solution in Milli-Q water (0.00016-4000μM) or just Milli-Q water (as a control), and 42 μl of heparanase (5.3 nM, R&D Systems) solution in pH 7.5 triz buffer (consisting of 20 mM TrisHCl, 0.15 M NaCl and 0.1% CHAPS) or just buffer as blank were added into microtubes. The mixture was pre-incubated at 37 °C for 10 min bringing the [heparanase] to 0.5 nM. A 84 μl solution of Biotin-Heparan sulfate-Eu cryptate (Cisbio, Cat #: 61BHSKAA) (58.6 ng in pH 5.5 0.2 M $NaCH_3CO_2$ buffer) was then added to the microtubes and incubated for 60 min at 37 °C. The enzyme reaction was stopped by adding 168 μl of Streptavidin-XLent! (Cisbio, Cat #: 611SAXLA) (1.0 μg/ml) solution in pH 7.5 dilution buffer (made of 0.1 M $NaPO_4$, 0.8 M KF, 0.1% BSA). After incubating for 15 min at room temperature, 100 μl/well of the reaction mixture was transferred to a 96 well microplate (Corning #3693 96 well, white polystyrene, half-area) in triplicates and HTRF emissions at 616 nm and 665 nm were measured by exciting at 340 nm using SpectraMax i3x Microplate Reader (Molecular Devices).

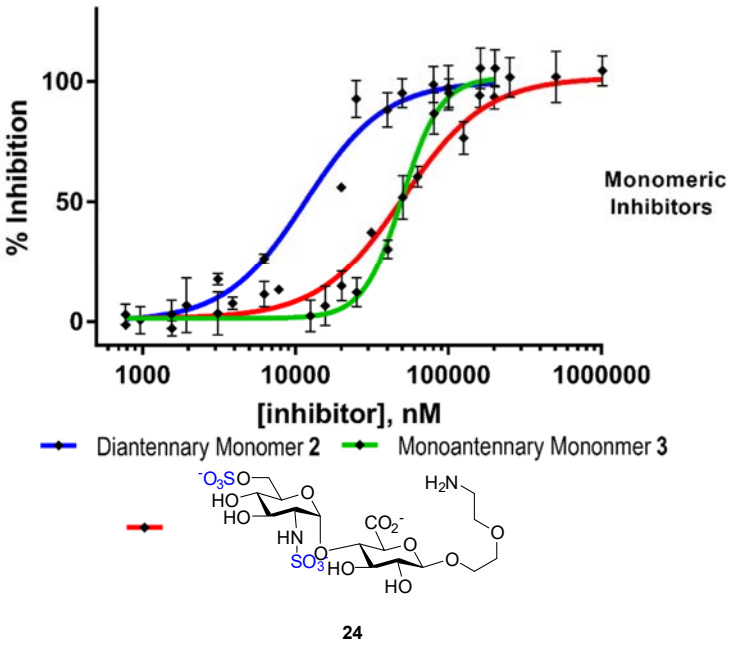
Henderson Tight-Binding Equation:

$$\%Inibition = 100\frac{E_I}{E_T} = 50\left(\frac{E_T + K_D + I_o - \sqrt{K_D^2 + E_T^2 + I_o^2 + 2E_TK_D + 2K_DI_o - 2E_TI_o}}{E_T}\right)$$

Control Inhibition TR-FRET Assay using Non-ionic Buffer (Tween-20):

A 42 μl of inhibitor solution in Milli-Q water (0.00016-4000μM) or just Milli-Q water (as a control), and 42 μl of heparanase (5.3 nM, R&D Systems) solution in pH 7.5 triz buffer (consisting of 20 mM TrisHCl, 0.15 M NaCl and 0.1% Tween-20) or just buffer as blank were added into microtubes. The mixture was pre-incubated at 37 °C for 10 min bringing the [heparanase] to 0.5 nM. A 84 μl solution of Biotin-Heparan sulfate-Eu cryptate (Cisbio, Cat #: 61BHSKAA) (58.6 ng in pH 5.5 0.2 M $NaCH_3CO_2$ buffer) was then added to the microtubes and incubated for 60 min at 37 °C. The enzyme reaction was stopped by adding 168 μl of Streptavidin-XLent! (Cisbio, Cat #: 611SAXLA) (1.0 μg/ml) solution in pH 7.5 dilution buffer made of 0.1 M $NaPO_4$, 0.8 M KF, 0.1% BSA. After incubating for 15 min at rt, 100 μl/well of the reaction mixture was transferred to a 96 well microplate (Corning #3693 96 well, white polystyrene, half-area) in triplicates and

HTRF emissions at 616 nm and 665 nm were measured by exciting at 340 nm using SpectraMax i3x Microplate Reader (Molecular Devices).



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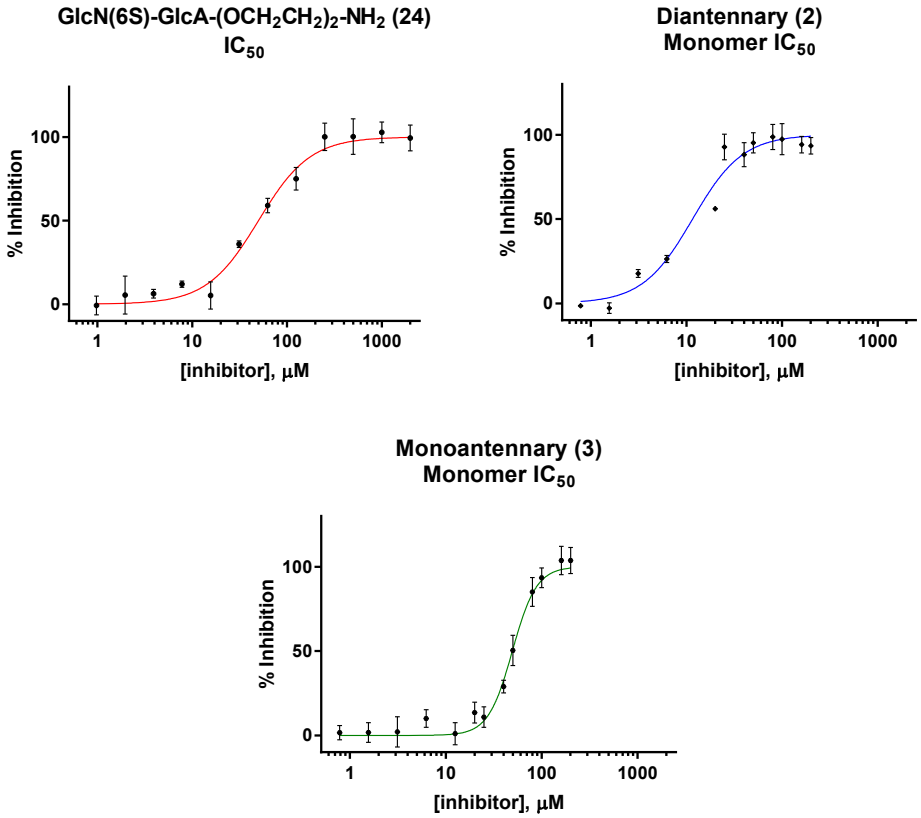


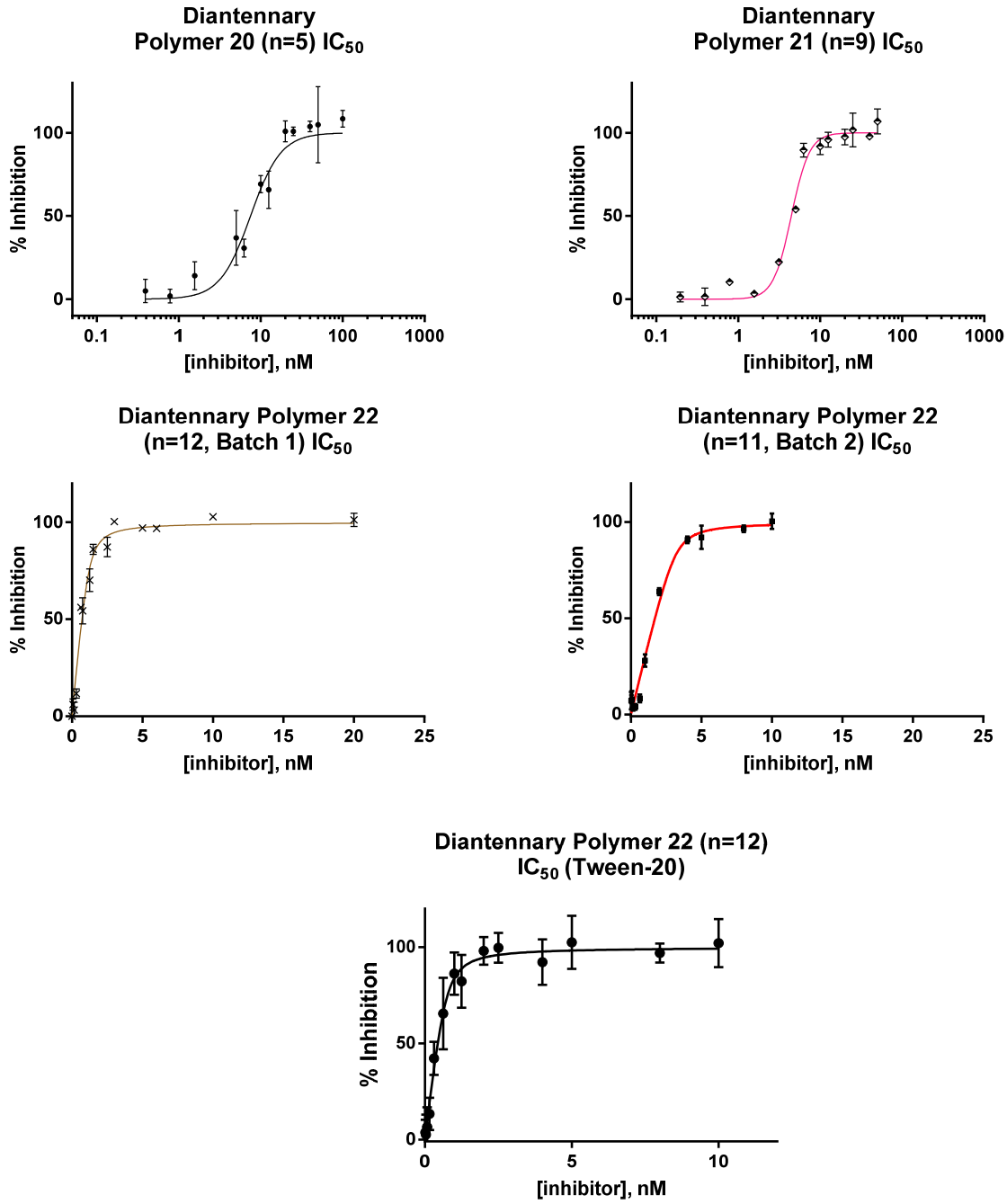


Figure S8. Inhibition of heparanase by glycomonomers and polymers of different designs and of different lengths.

Diantennary Polymer 22 Hydrolysis Assay[v]

Micro centrifuge tubes were pretreated for 2h at 37 °C by using a solution of phosphate buffered saline comprising of 0.05% Tween 20 (PBST) and 4% bovine serum albumin. Tubes were then washed three times

with PBST, dried, stored at 4 °C, and used for assay within a week. A 100 μM solution of diantennary polymer **22** or Fondaparinux with heparanase enzyme (3 nM) in pH 5.0 sodium acetate buffer (40 mM), were incubated at 37 °C in a microtube. The enzymatic reaction was stopped at different time points by adding equal volumes of reaction mixture and freshly made 1.69 mM WST-1 (Toronto Research Chemicals) in 0.1 M NaOH into a new microtube and developed at 60 °C for 60 min. A 200 μl (per well) solution of developed reaction solution was transferred to a clear 96-well microplate in triplicates and absorbance was measured at 584 nm with a SpectraMax Plus 384 Microplate Reader (Molecular Devices). For the controls, exactly the same procedure was followed for a 100 μM solution of diantennary polymer **22** or Fondaparinux without heparanase enzyme to rationalize non-enzymatic autohydrolysis.

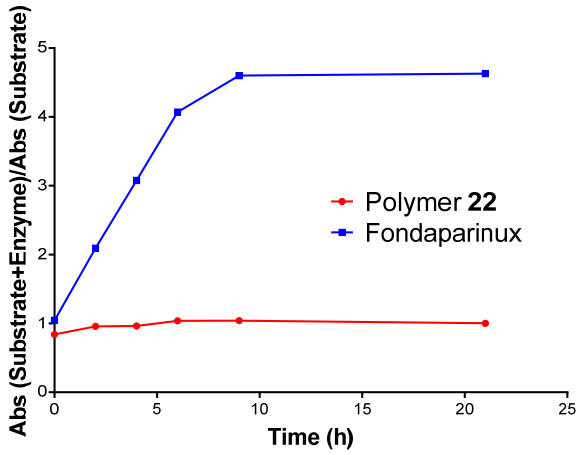


Figure S9. The hydrolytic potential over time of heparanase on **22** and Fondaparinux.

Docking Experiments

For the docking studies we used the apo heparanase structure (PDB code: 5E8M).[viii] The enzyme structure was imported into Yasara,[ix] cleaned, energy minimized *in vacuo*, and Glu225 was manually protonated. Ligands were constructed in a two-step method. The saccharide portion was first built using the Glycam GAGs builder (www.glycam.com) and then imported into the Avagadro molecular editing software (https://avogadro.cc/) where aliphatic portion was added. The ligand was then subjected to a steepest descent energy minimization and saved in the .pdb format. Global docking with each ligand was performed on the heparanase structure separately using the Autodock VINA default parameters in a simulation cell set built at least 10 Å from all the three sides of the enzyme. The set-up was done with the YASARA molecular modelling program (www.yasara.org) and the built-in docking simulation macro 'dock_run.mrc' for 100 docking runs using the AMBER14 force field for protein[x] and GLYCAM06[xi] and GAFF/Am1BCC for the synthetic saccharide ligand and a pose cluster RMSD of 5 Å for the docking conformations. Ligands and receptor residues were kept flexible during the docking runs. The most populated clusters of the 100 docking runs was subjected to further analysis.

MD Simulations

All the simulations were performed in the Yasara Structure version 16.4.6[x] with the built-in molecular dynamic simulation macro 'md_run.mrc'. The heparanase-ligand complexes were imported into Yasara and energy minimized *in vacuo*. Subsequently, a simulation cell was built with at least 10 Å from all the three sides of the enzyme-ligand complex molecule. AMBER14 force field was utilized with periodic boundary conditions. The force field parameters were done YASARA's 'AutoSMILES' feature and assigned the AMBER14 force field[x] for the amino acid residues and GLYCAM06[xi] oligosaccharide in conjunction with GAFF/AM1BCC for the atoms that were not part of GLYCAM. The simulation box was filled with TIP3P[xi] water as solvent. All simulated systems were neutralized at pH 7.4 by counter ions using 0.9% NaCl (concentration in mass percent, a physiological solution). Solvent density was 0.997 g/ml (water at 300 K). The pKa of titrable side chains was predicted and assigned to respective groups before running MD and Glu225 was manually protonated.

Following the minimization of the contents of the simulation box, a molecular dynamics simulation was performed for 25 ns. The MD simulations were run at 298K with Berendsen thermostat[xiii] and the pressure coupling was with manometer methodology as available in Yasara. The cut-off radius for long range electrostatics was set to 8 Å. The snapshots were saved at 25 ps intervals for the length of the 25 ns simulation. The equations of motion were integrated with a 1.25 fs timestep. To gain performance, the non-bonded Van der Waals and electrostatic forces were evaluated only every second step, and added with a scaling factor of 2. This straightforward multiple timestep algorithm is known as the 'impulse method'[xiv] or 'VERLET-I'.[xv] The pair list was updated every 10 steps (10 x 2.5 fs = 25 fs). Snapshots were then analyzed using the built-in 'md_analyze.mcr' macro for the RMSD of the Cα of the α-helices and β-strands and the ligand heavy atoms as distances of the catalytic residues from the scissile bond of the ligand.

All computations were carried out on the University of Iowa's Neon HPC cluster using a standard node with 16 processors 64 GB of memory.

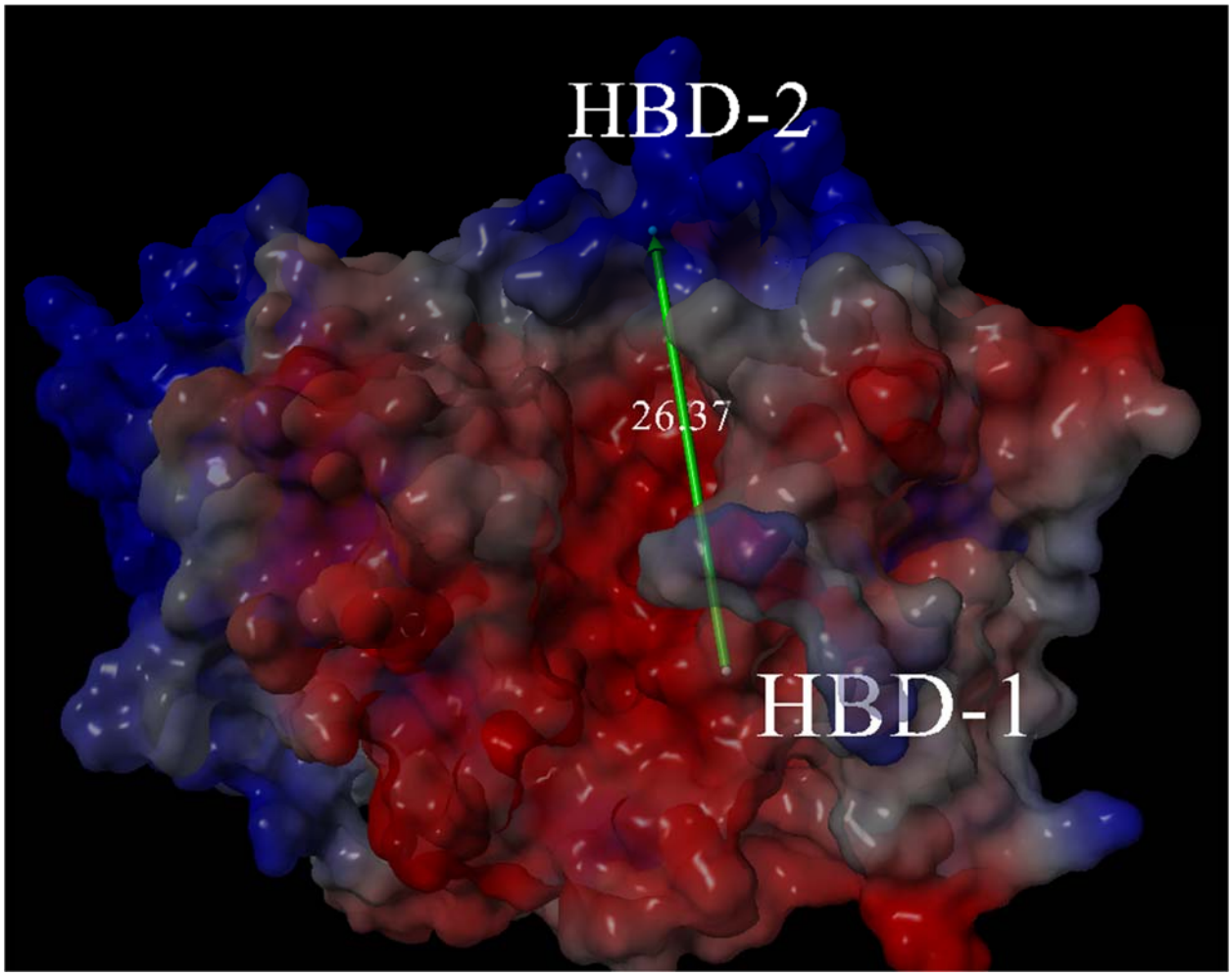
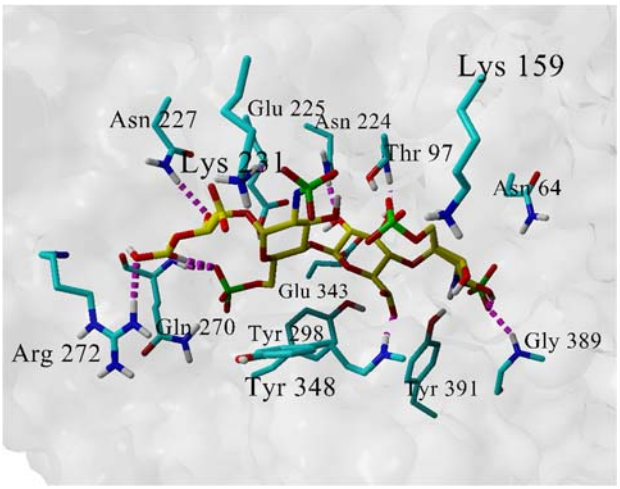
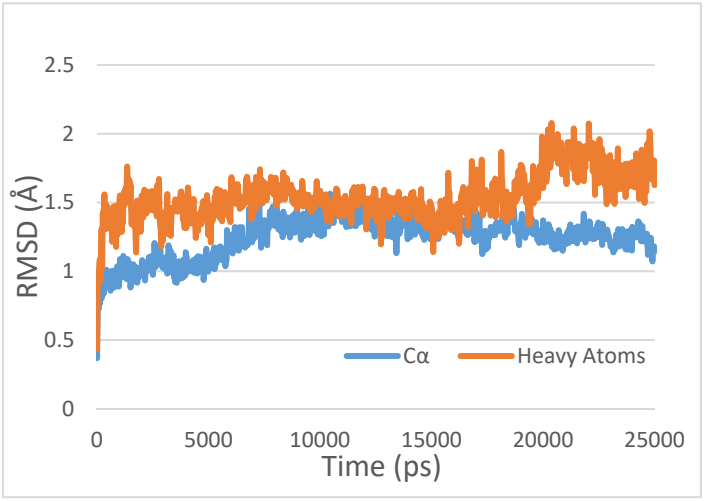
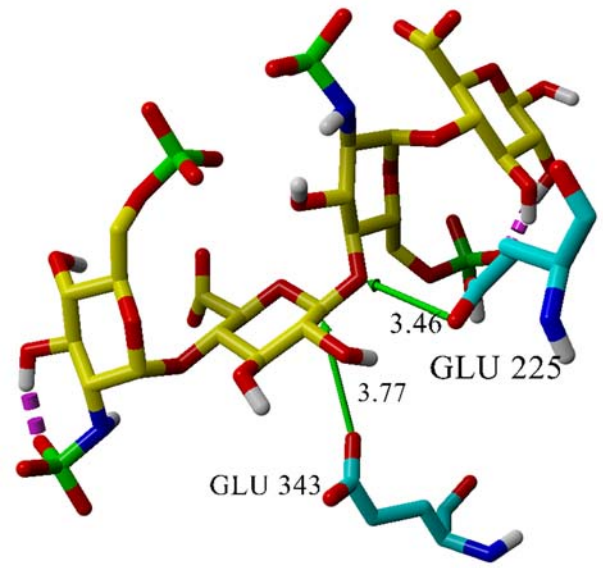


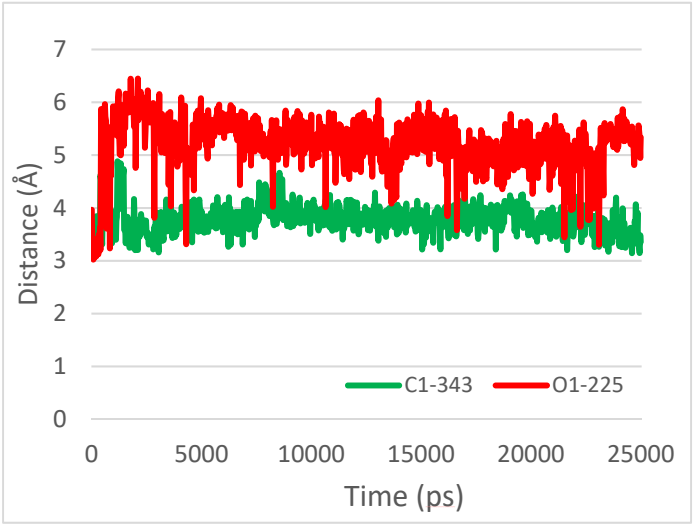
Figure S10. Electrostatic potential map of heparanase highlighting the distances between heparin binding domains. Positively charged basic residues (blue), negatively charged residues (red). Green arrow stretches directly through the active site cleft.

GlcNS(6S)α(1,4)GlcA β(1,4)GlcNS(6S)α(1,4)GlcA
Tetrasaccharide **1**

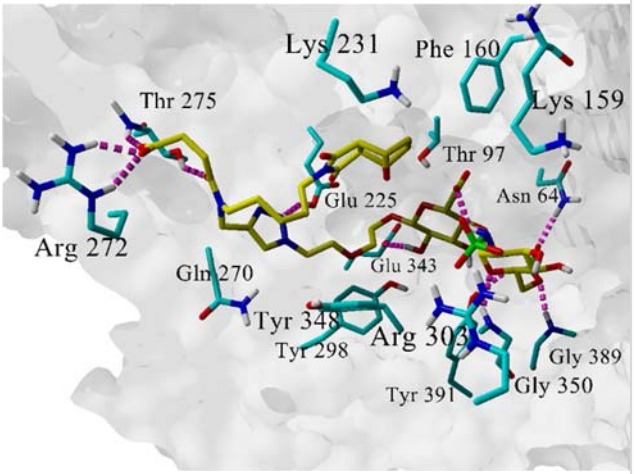


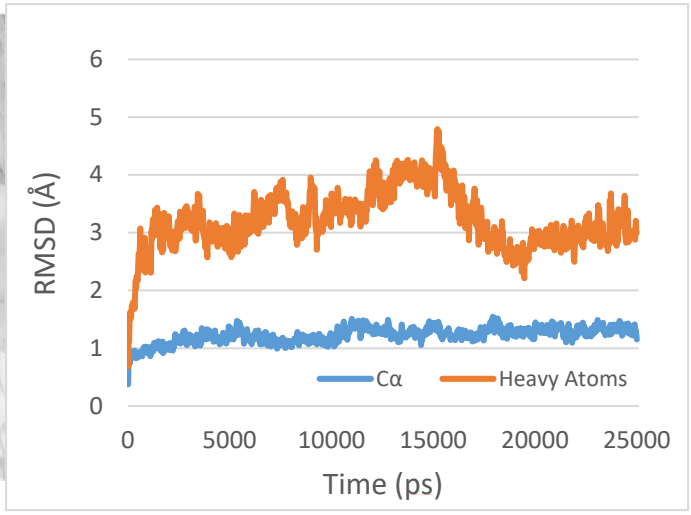


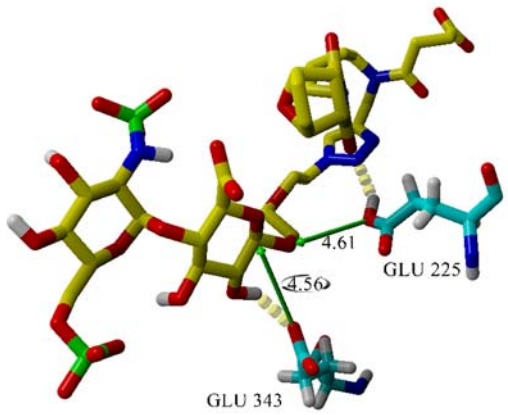


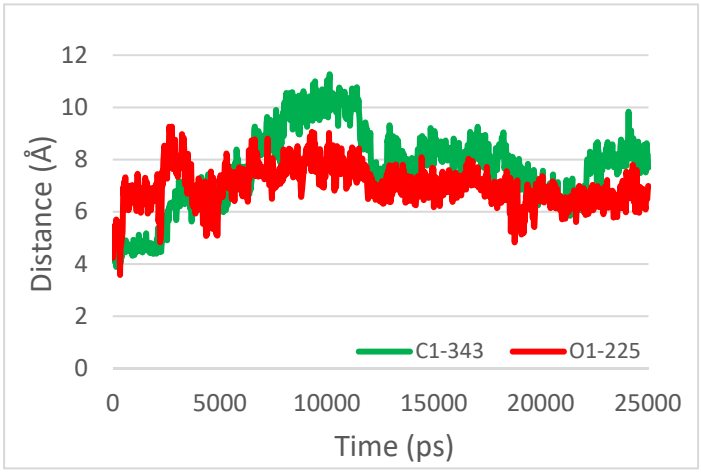


Diantennary Monomer **2**









Monoantennary Monomer **3**

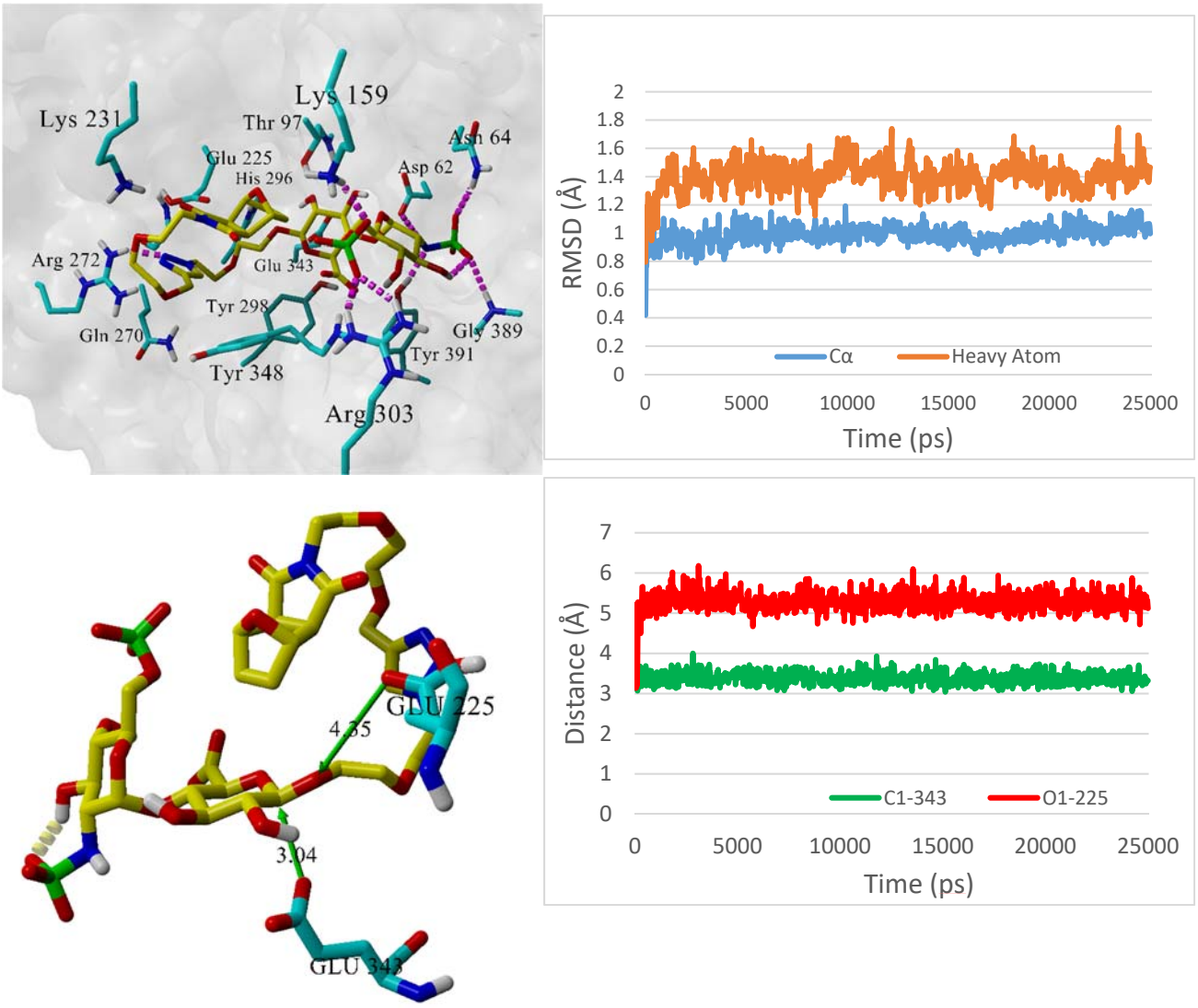
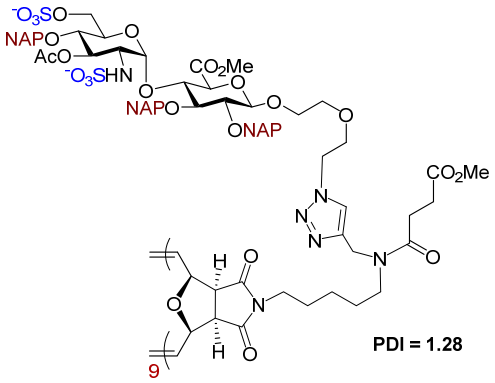


Figure S11. Analysis of computational docking studies and MD simulations. Top left: Snapshot of ligand (yellow) docked into human heparanase, showing hydrogen bonding network (magenta). Top right: Fluctuations in the RMSD during the MD simulation of 25 ns for Cα of the α-helices and β-strands (blue) and the ligand heavy atoms (orange). Bottom left: Initial distance (green arrow) and positioning between the catalytic residues (Glu225 and Glu343) and the scissile bond. Bottom right: Evolution of distances between the catalytic residues (Glu225 and Glu343) and the scissile bond over the course of 25 ns during the MD simulation.

GPC Analysis of Protected and Deprotected Glycopolymers.

Average polymer molecular weight (Mn) and polydispersity index (PDI) of the synthetic neoglycopolymers are determined by Gel Permeation Chromatography (GPC) using a Wyatt Dawn Heleos-II light scattering detector using either DMF with 0.05M LiBr or water with 6 mM $NaNO_3$ and 3 mM NaN_3 as the eluent. The eluent system utilized in GPC is indicated at top of the chromatogram. Columns were standardized using commercial polystyrene and dextran standards.

GPC Analyses of NAP-Protected Glycopolymers



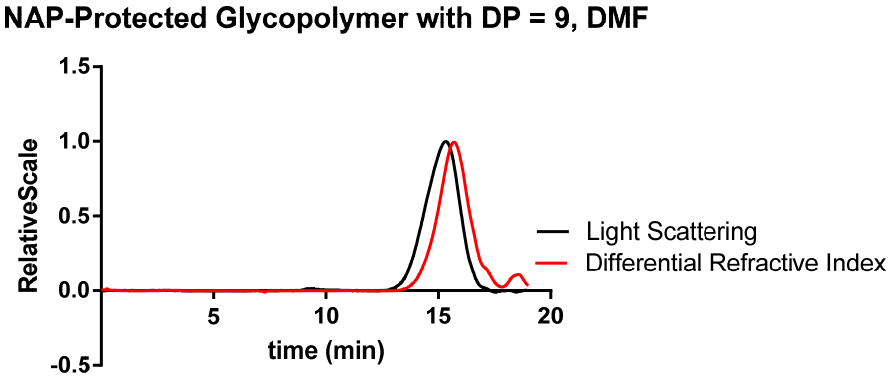
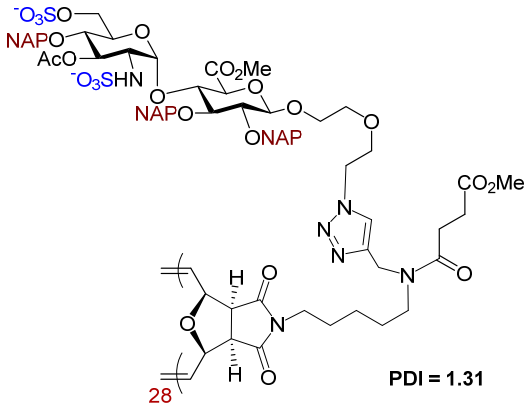


Figure S12. GPC chromatogram of the polymerization of NAP-protected monomer using 18 mol% Grubbs III catalyst.



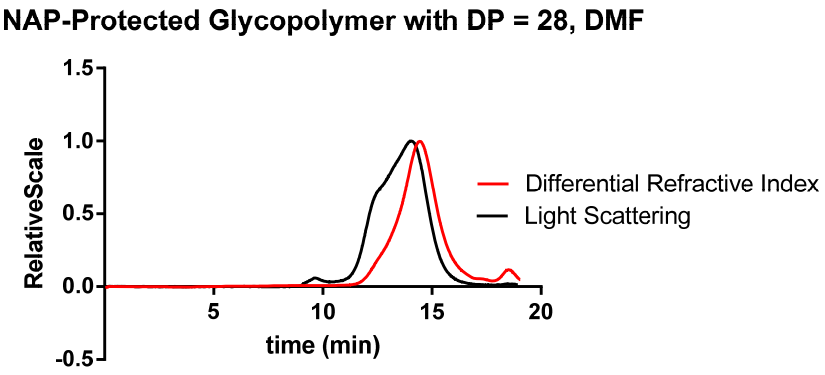
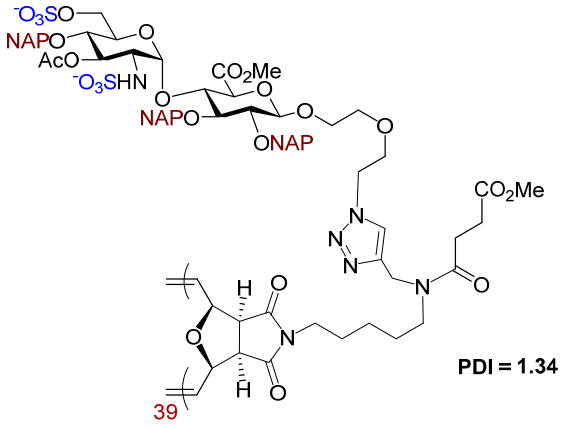


Figure S13. GPC chromatogram of the polymerization of NAP-protected monomer using 9 mol% Grubbs III catalyst.



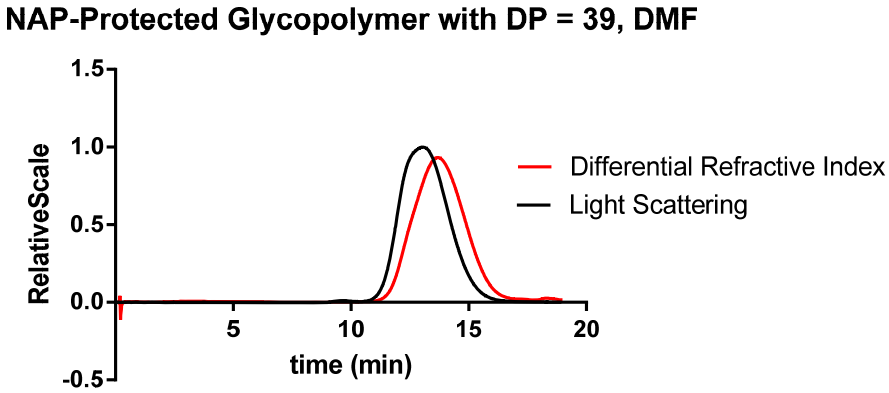


Figure S14. GPC chromatogram of the polymerization of NAP-protected monomer using 9 mol% Grubbs III catalyst.

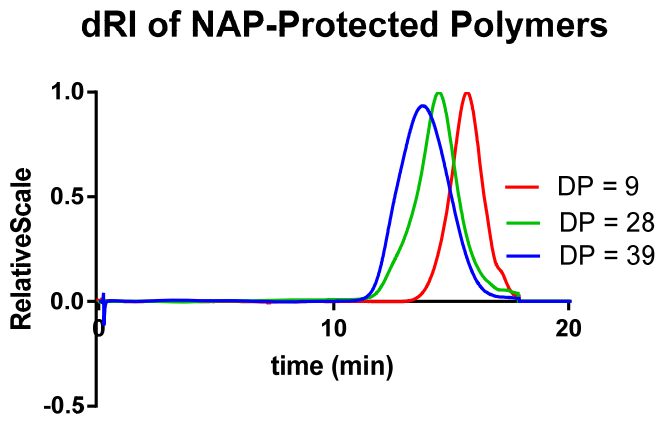
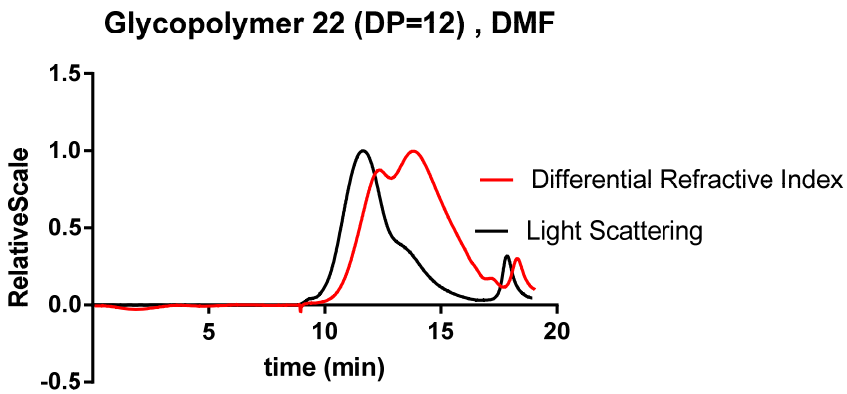


Figure S15. Combined GPC chromatogram of NAP-protected polymers.

From GPC analyses of these NAP-protected polymers (Figures S13 – S14), we were able to obtain three different degrees of polymerization (DP) which directly correlated with the different amount of catalyst used (high catalytic loading = short polymer, low catalytic loading = longer polymer). For these three polymers the light scattering and refractive index peaks were sharp and showed good overlay, indicative of a PDI of about 1.3 for all. The combined Figure S15 exemplifies the ability to separate based off of size with different length polymers having different retention times. However, all attempts to remove the NAP groups in these polymers led to only partial deprotection.

Attempted GPC Analyses of Unprotected Glycopolymers



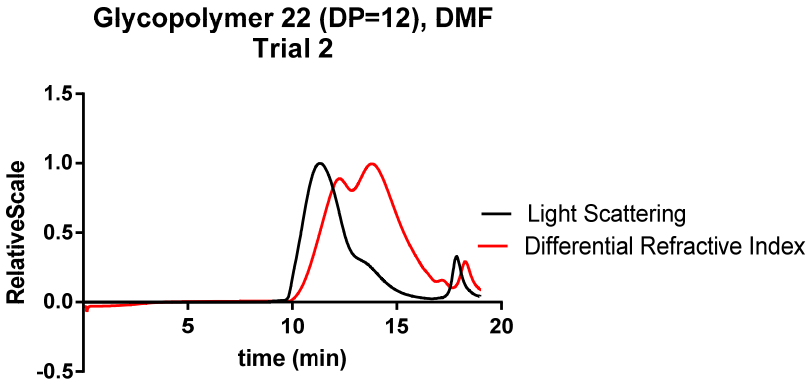


Figure S15. GPC chromatogram of the polymerization of NAP-deprotected monomer using 9 mol% Grubbs III catalyst.

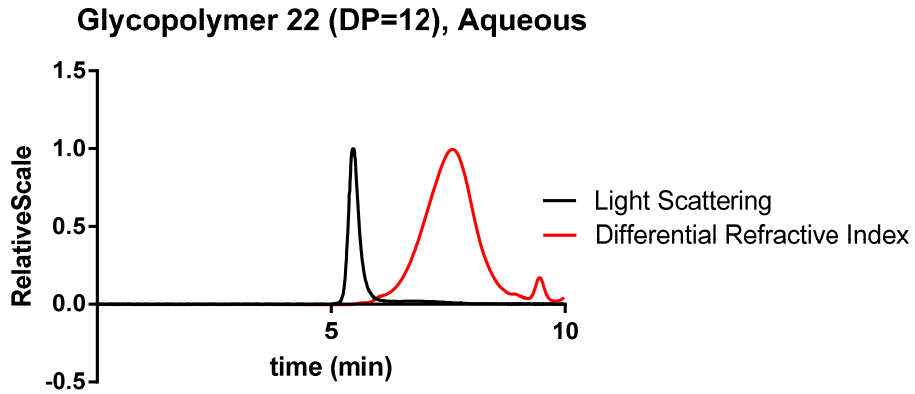


Figure S16. GPC chromatogram of the polymerization of NAP-deprotected monomer using 9 mol% Grubbs III catalyst.

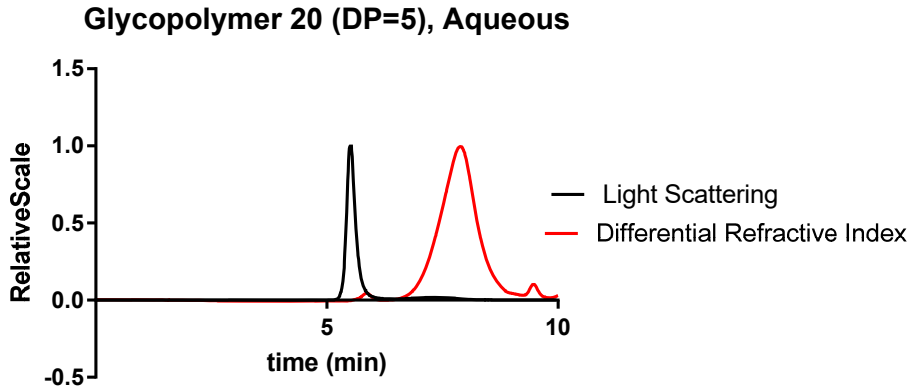


Figure S17. GPC chromatogram of the polymerization of NAP-deprotected monomer using 20 mol% Grubbs III catalyst.

*GPC analyses of these deprotected polymers with the DMF 0.05 M LiBr eluent system (see Figure S15 for glycopolymer **22**) resulted in the characterization of the micellar form of these polymers due to their now much greater amphiphilic nature. This is shown by broadness and the light scattering and refractive index peaks not overlapping. As well even though the molecular weight of the deprotected polymers (measured by ^{1}H NMR end group analysis) is much less than the NAP-protected polymers the retention time is shorter meaning the characterized sample has a very high molecular weight. Attempts to break up these aggregates by use of different salt concentrations only provided similar results. To increase the solubility of these polymers and break up these micelles we attempted to use an aqueous eluent system. Again, analysis of deprotected glycopolymers **20** and **22** in aqueous eluent system resulted in only characterization of the micelles (see Figures S16 and S17).* ***This is why we utilize ^{1}H NMR end group analysis to determine the PD of glycopolymers 20, 21, and 22 and turbidimeric assay to quantify the sulfate content***

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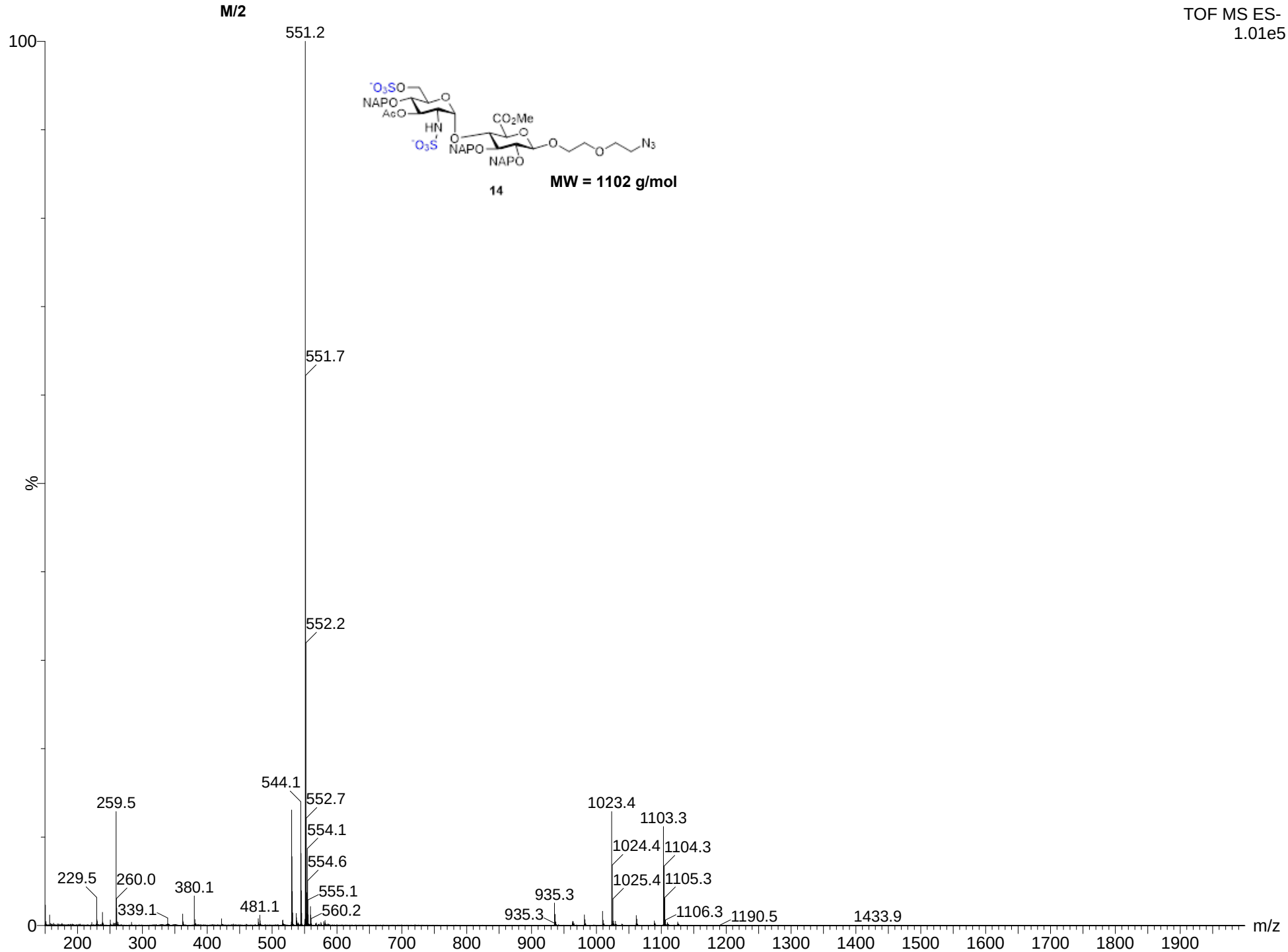
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100
%
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552.2
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554.6
555.1
560.2
259.5
229.5
260.0
339.1
380.1
481.1
935.3
935.3
1023.4
1024.4
1025.4
1103.3
1104.3
1105.3
1106.3
1190.5
1433.9
200
300
400
500
600
700
800
900
1000
1100
1200
1300
1400
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m/z
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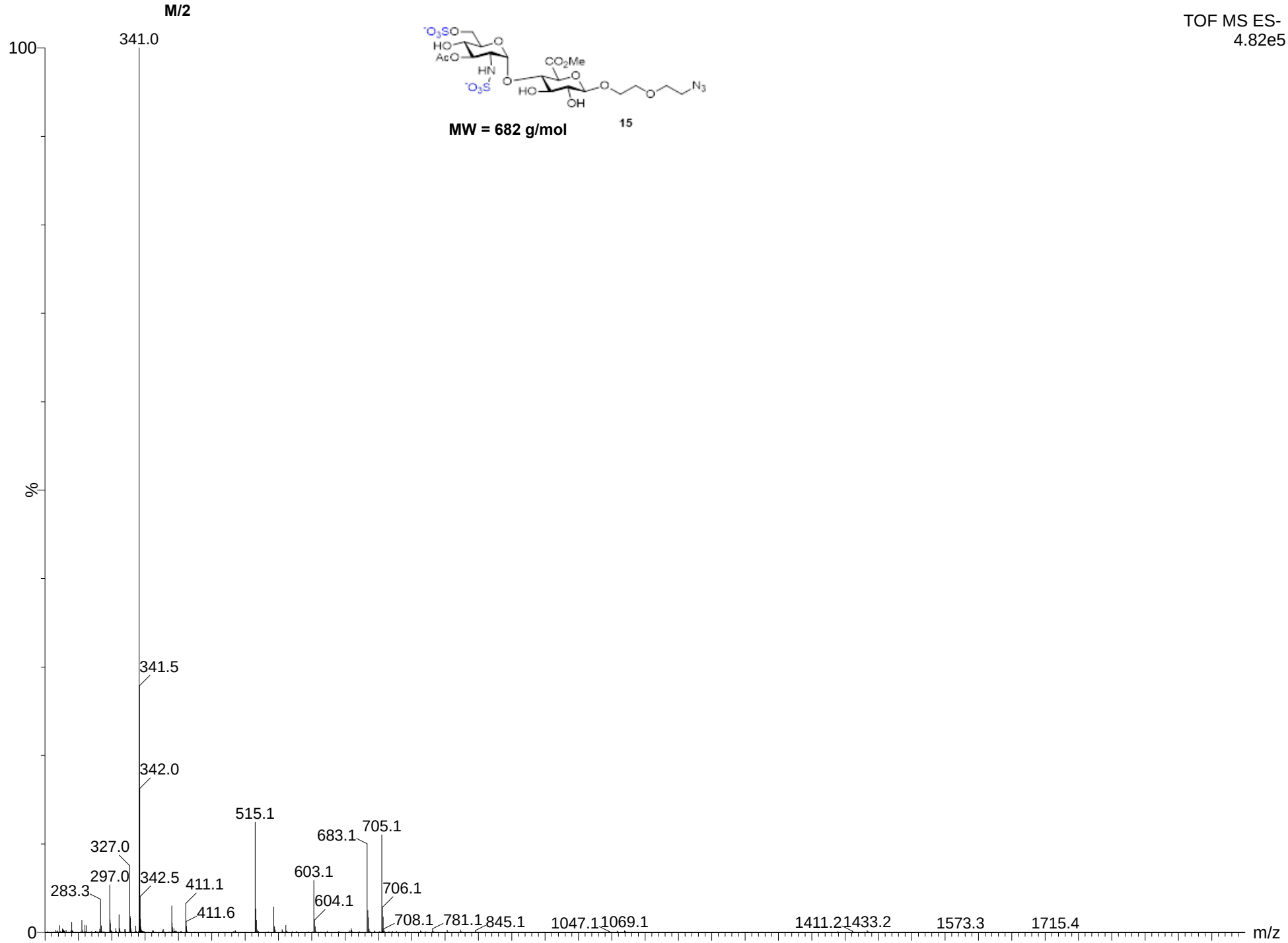
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603.1
706.1
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604.1
411.6
708.1
781.1
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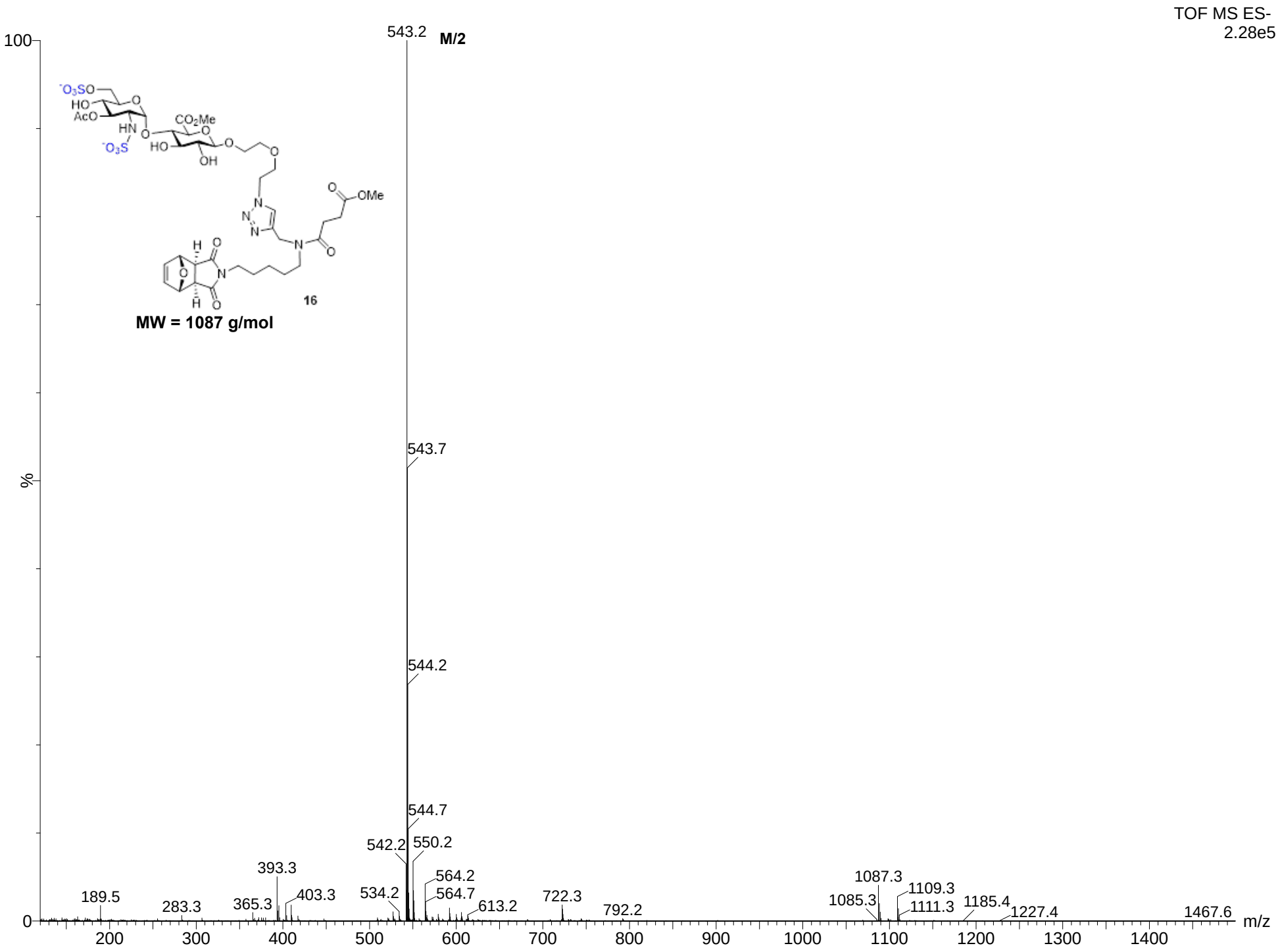
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534.2
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1467.6
m/z
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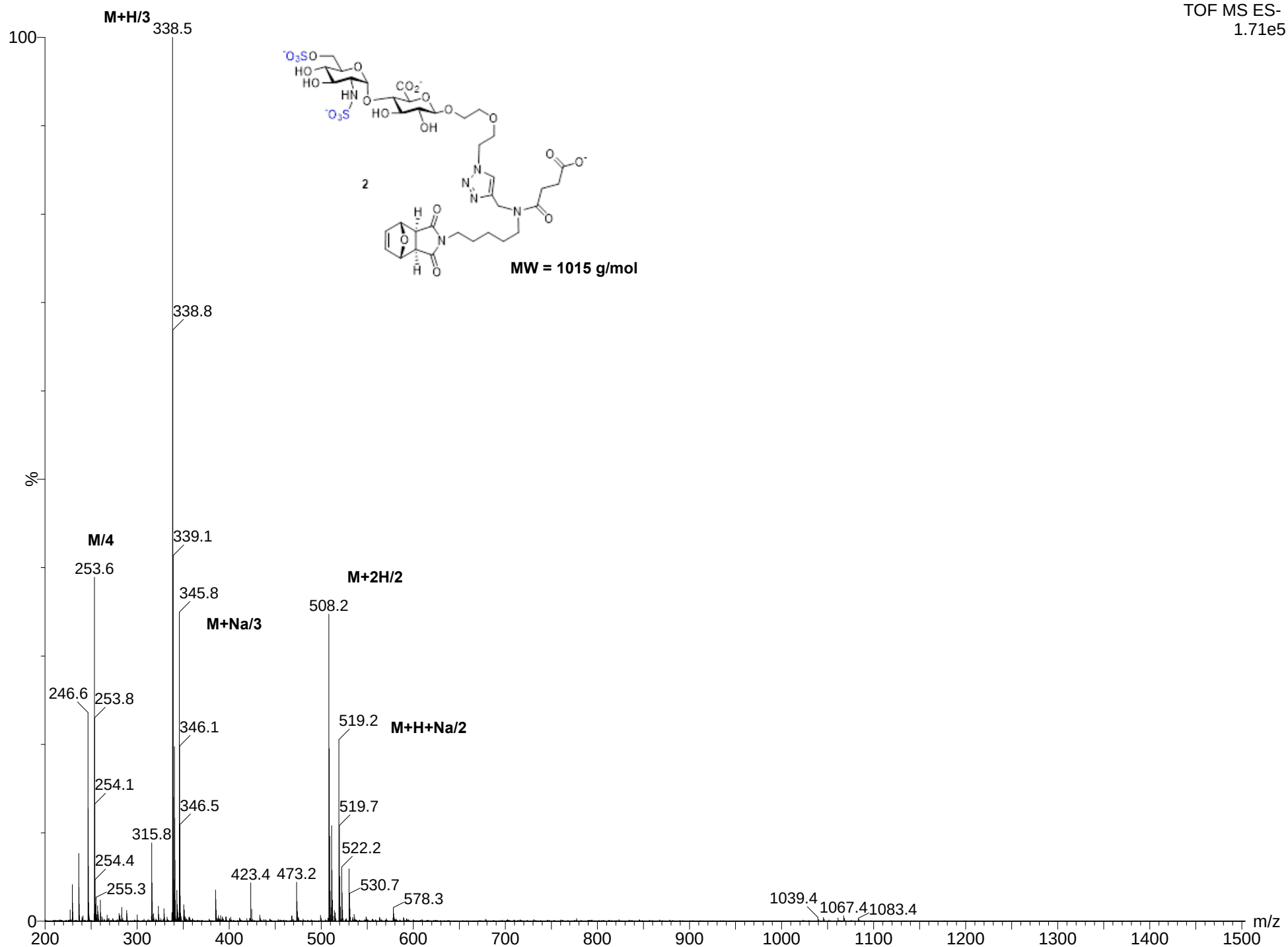
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%
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M+Na/3
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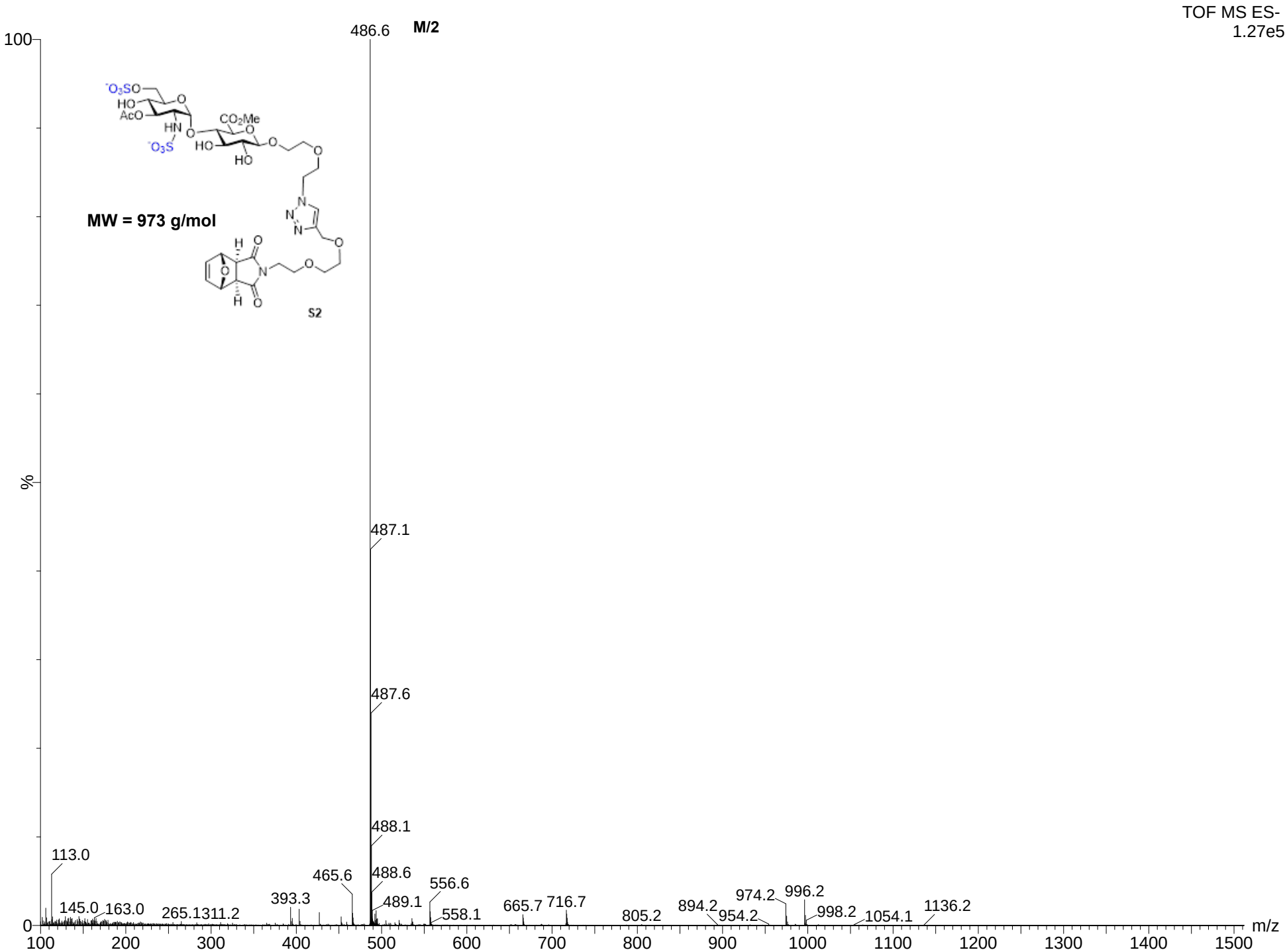
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998.2
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m/z
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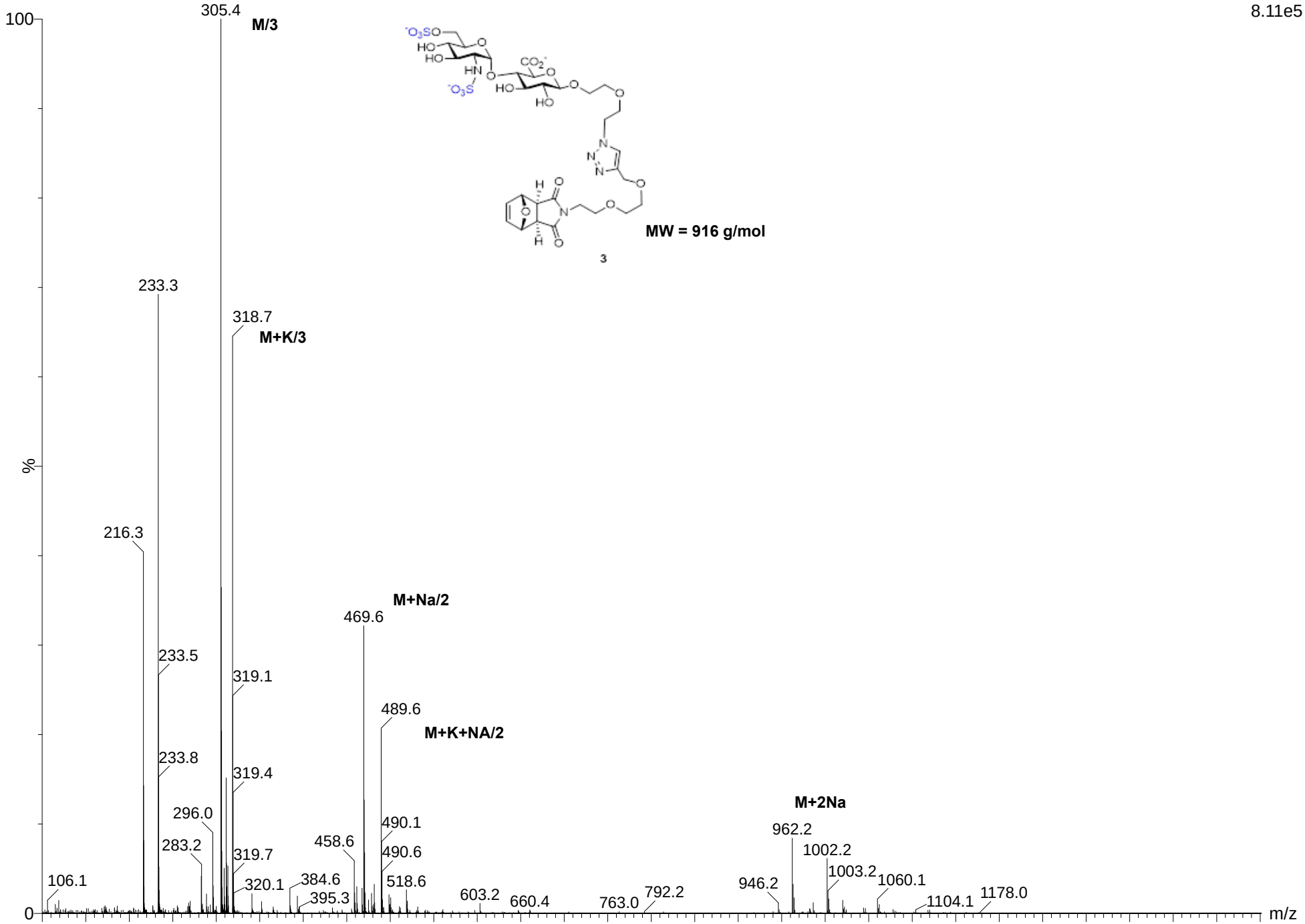

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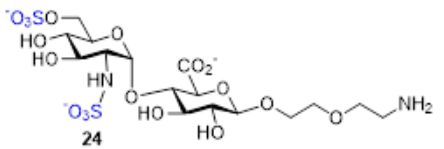
M/3



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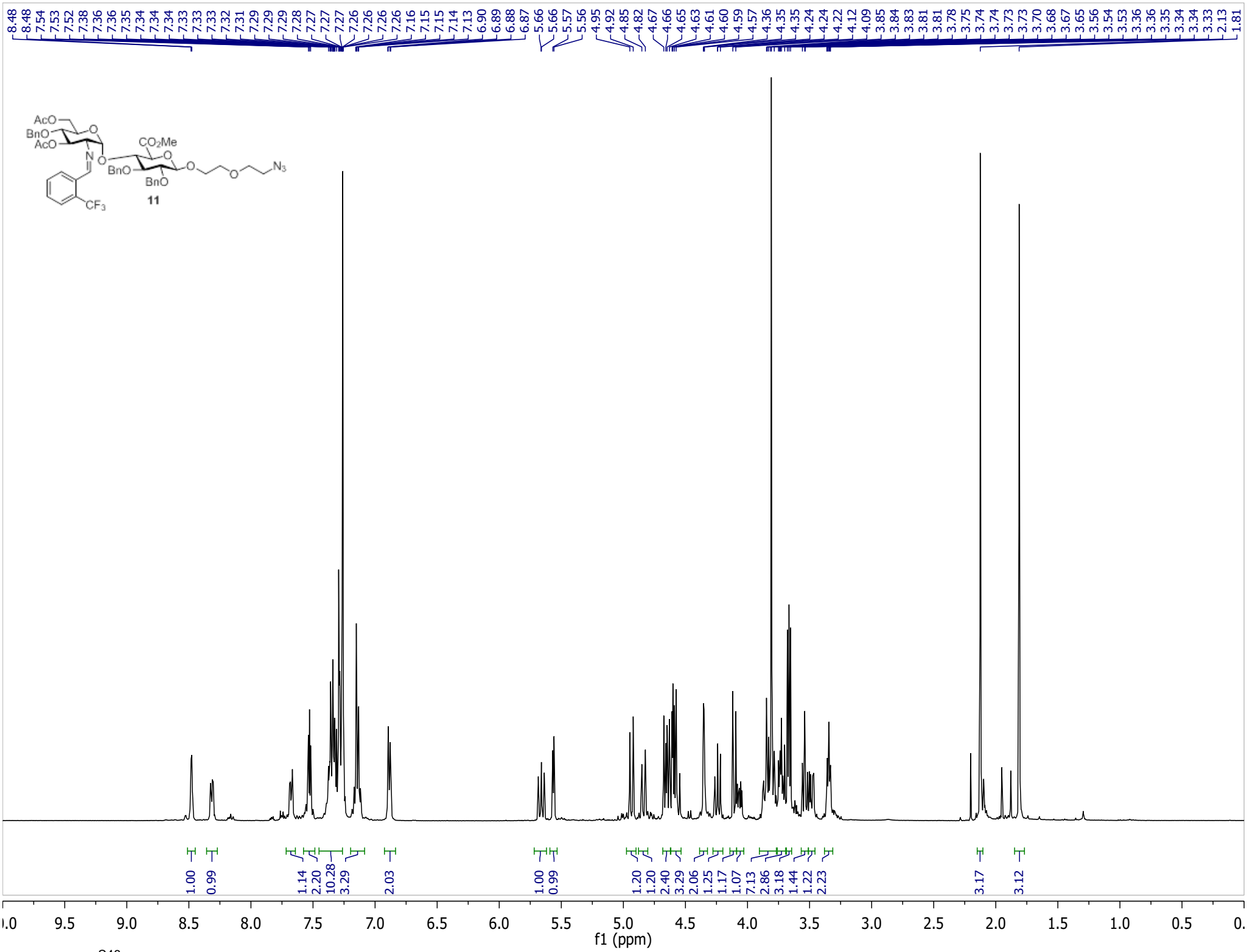
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BnO
BnO
O
O
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CF3
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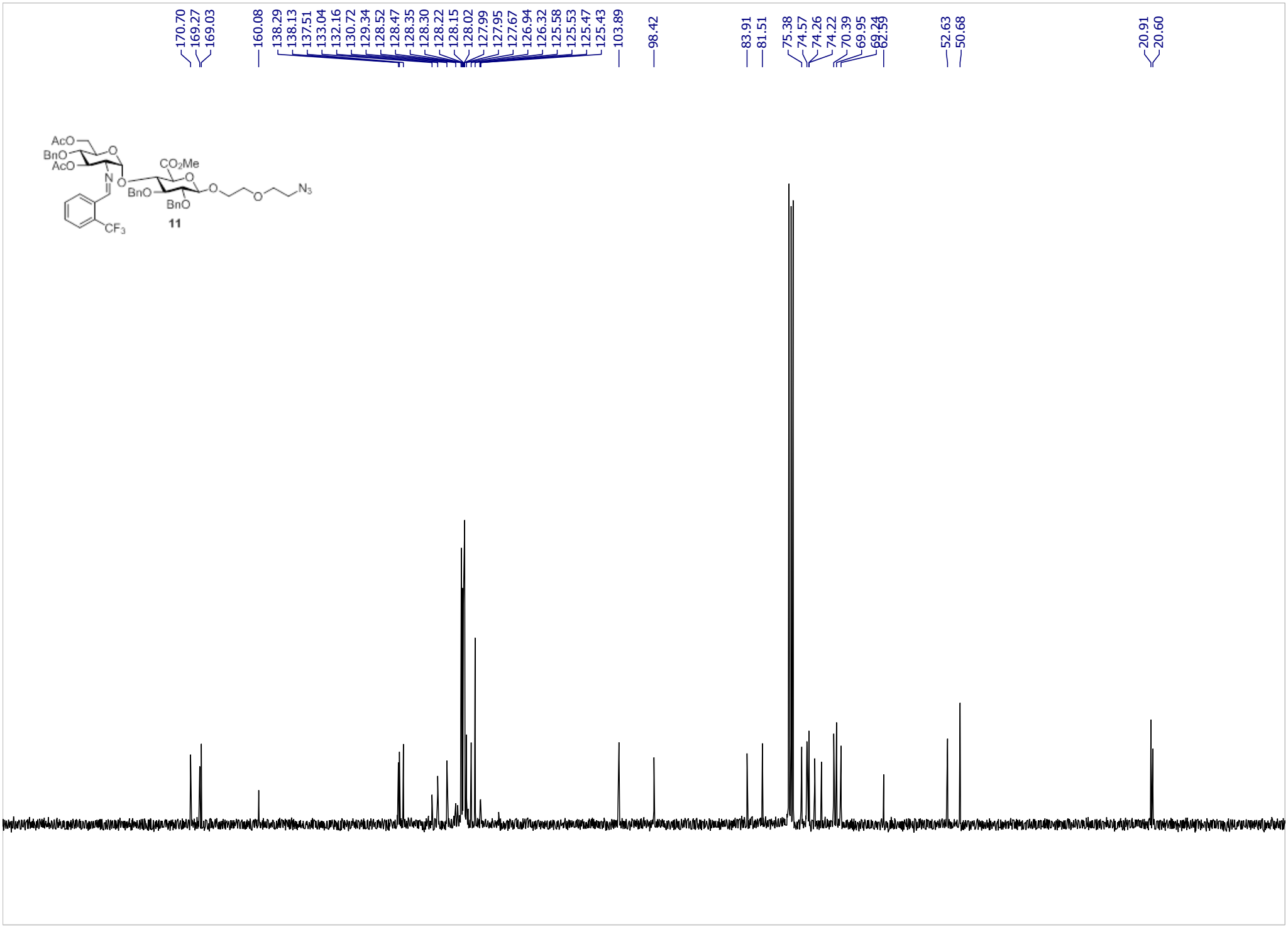
f1 (ppm)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98.42
83.91
81.51
75.38
74.57
74.26
74.22
70.39
69.95
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52.63
50.68
20.91
20.60
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BnO
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CO2Me
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O
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CF3
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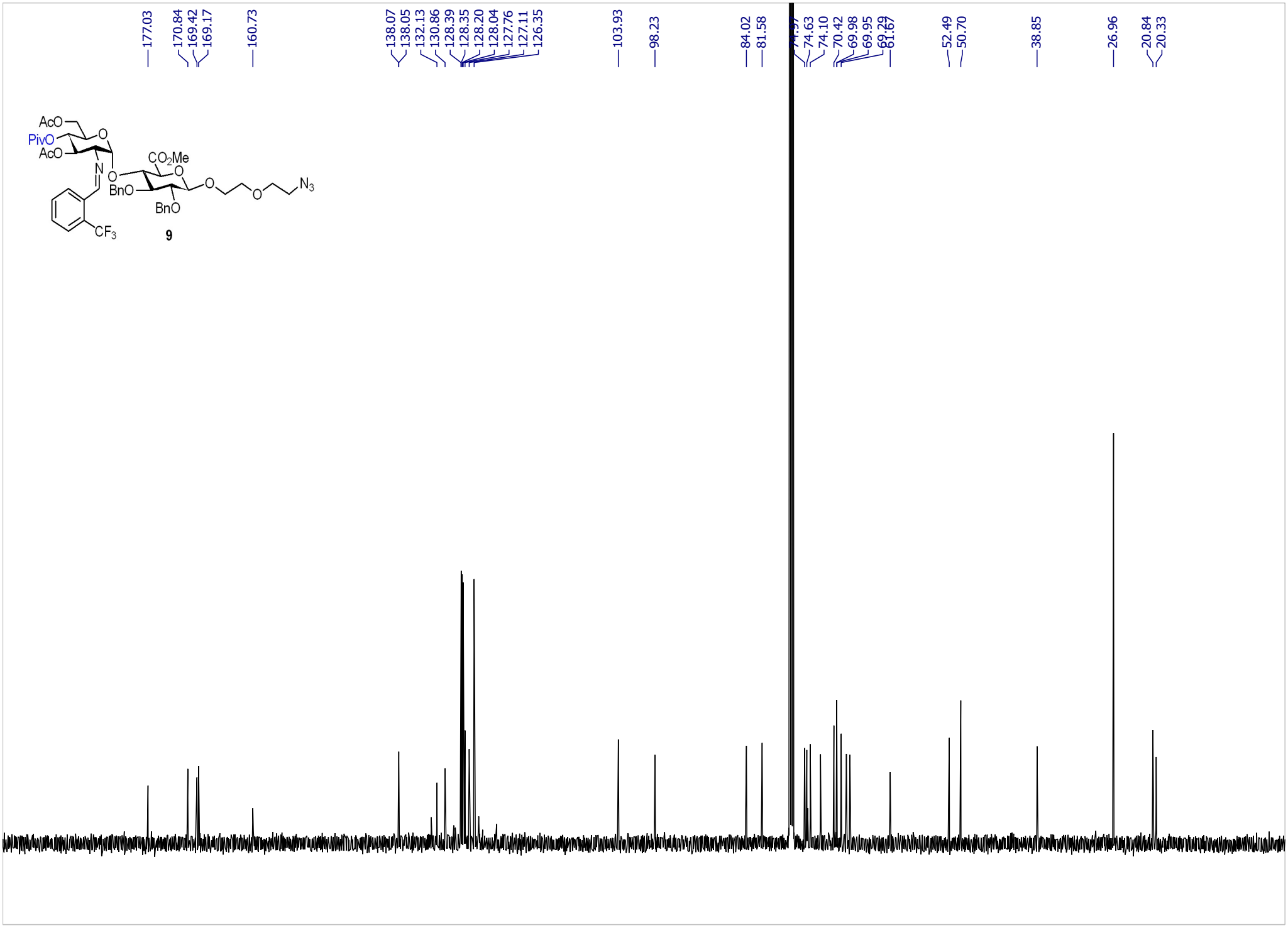
f1 (ppm)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26.96
20.84
20.33
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BnO
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O
N3
CF3
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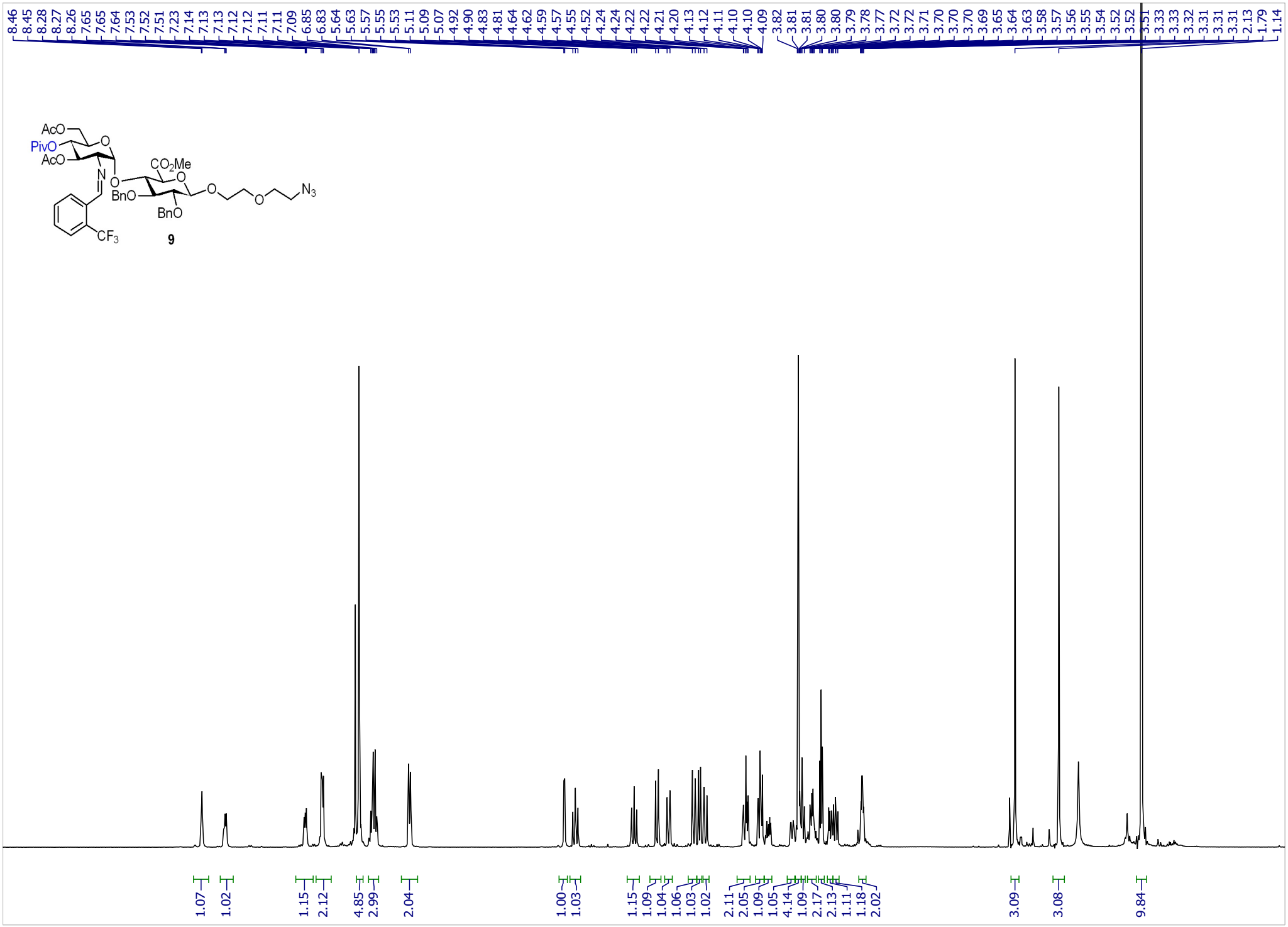
f1 (ppm)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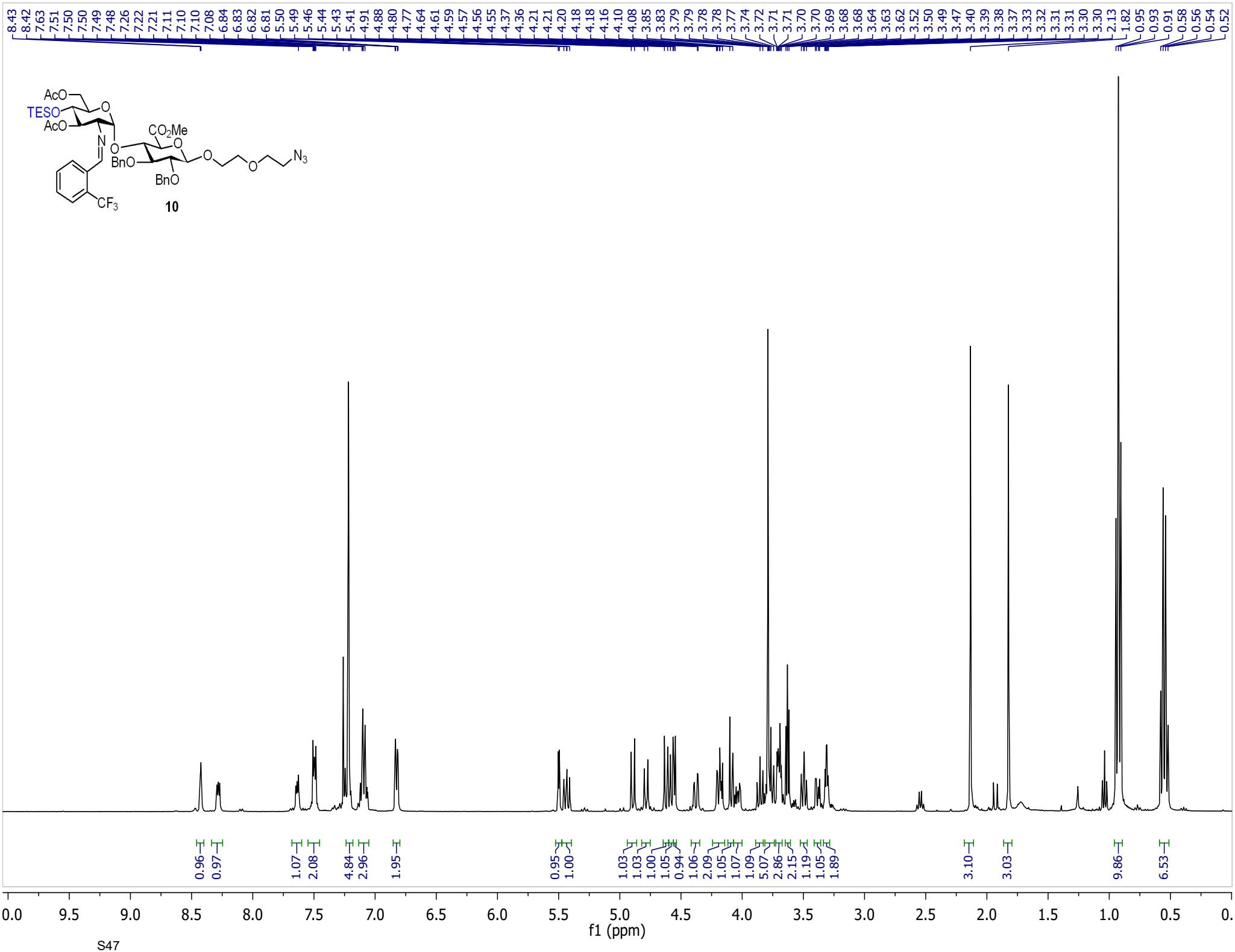
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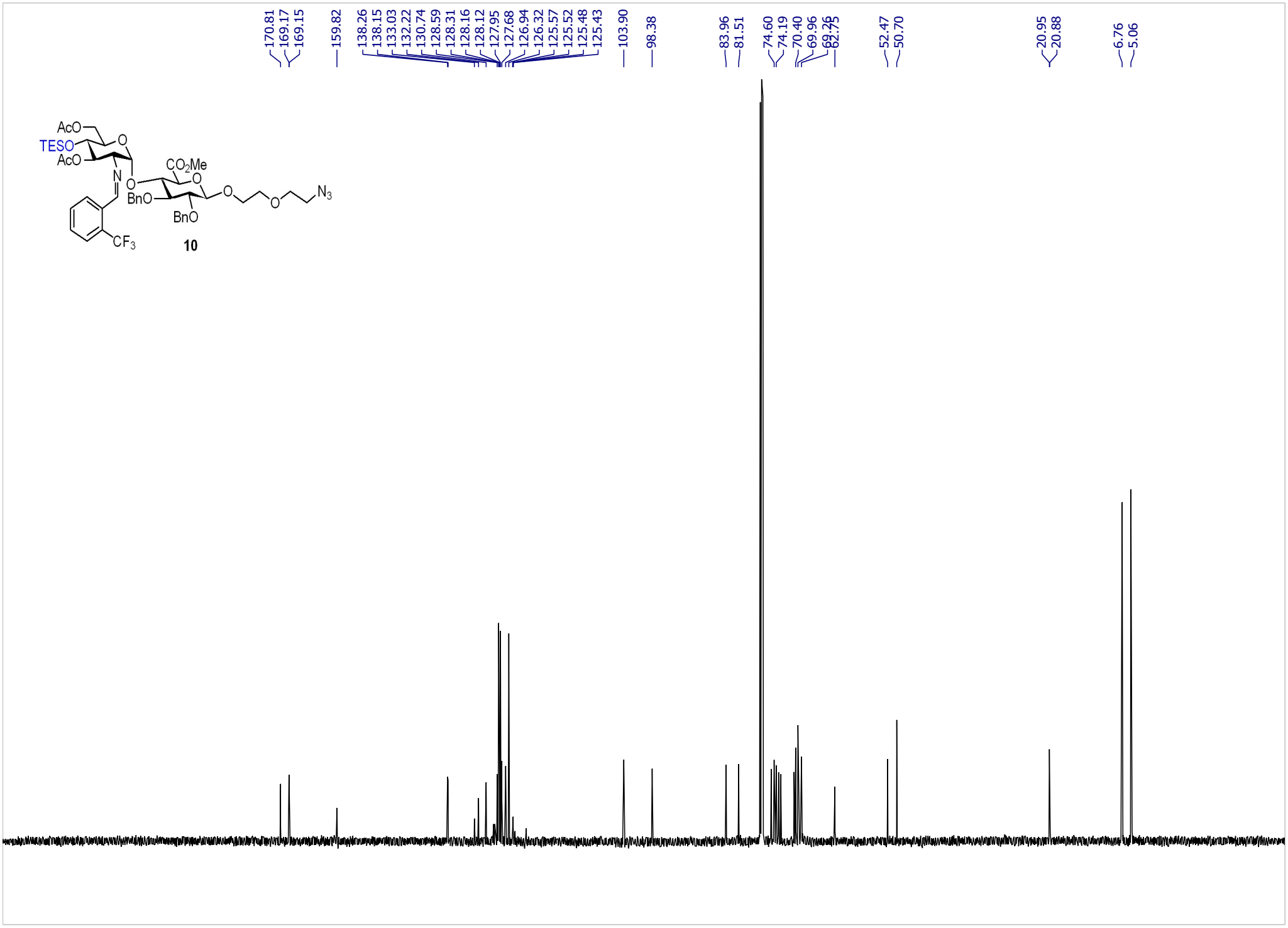
AcO
TESO
AcO
O
N
O
CO2Me
O
BnO
BnO
O
O
N3
CF3
10
0.96 0.97 1.07 2.08 4.84 2.96 1.95 0.95 1.00 1.03 1.03 1.00 1.05 0.94 1.06 2.09 1.05 1.07 1.09 5.07 2.86 2.15 1.19 1.05 1.89 3.10 3.03 9.86 6.53
0.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.
f1 (ppm)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74.60
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69.96
52.47
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20.95
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6.76
5.06
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TESO
AcO
N
O
CO2Me
O
BnO
BnO
O
O
N3
CF3
10
220
210
200
190
180
170
160
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10
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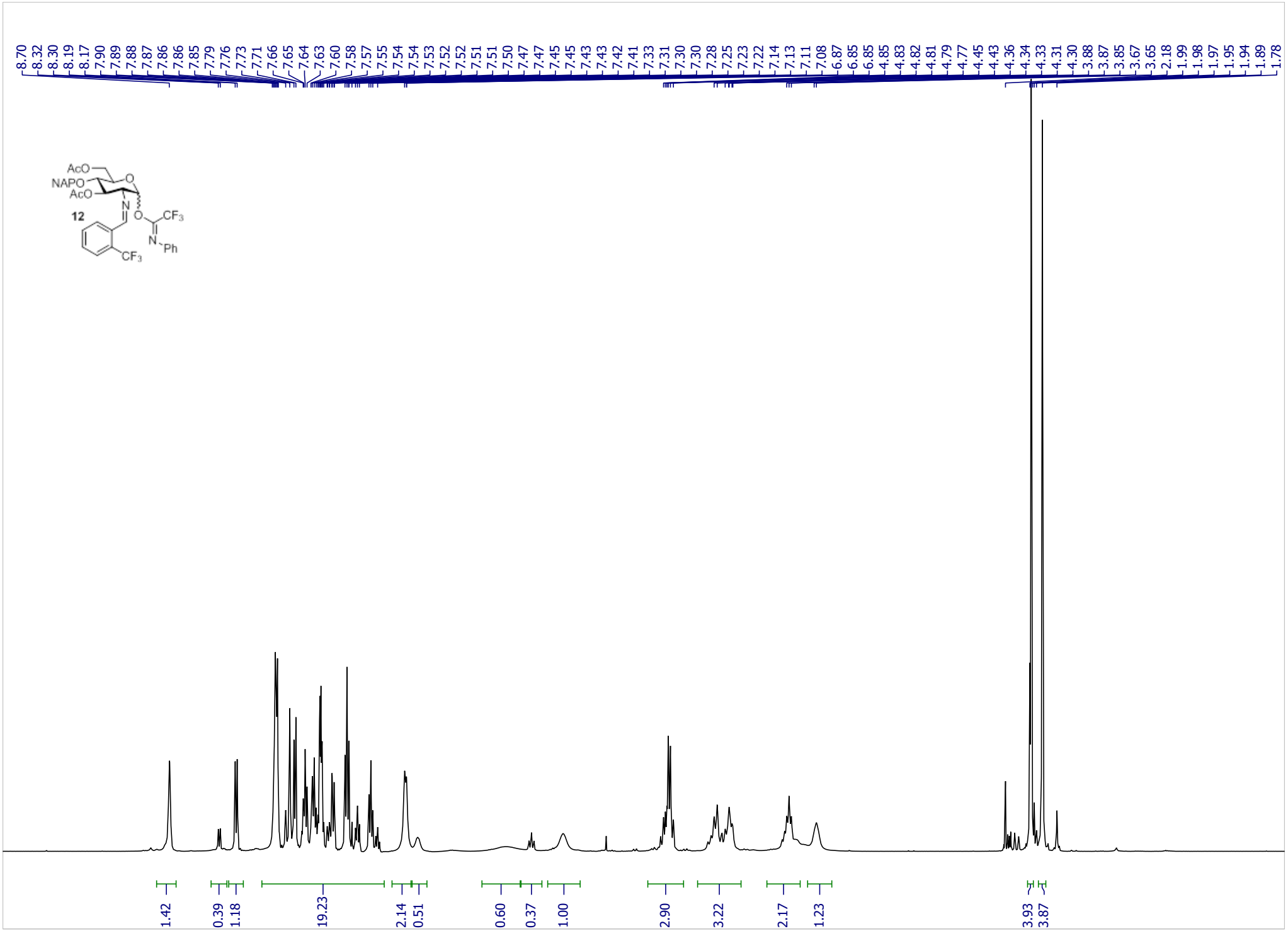
-10
-20
f1 (ppm)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AcO
NAPO
AcO
12
CF3
N
Ph
CF3
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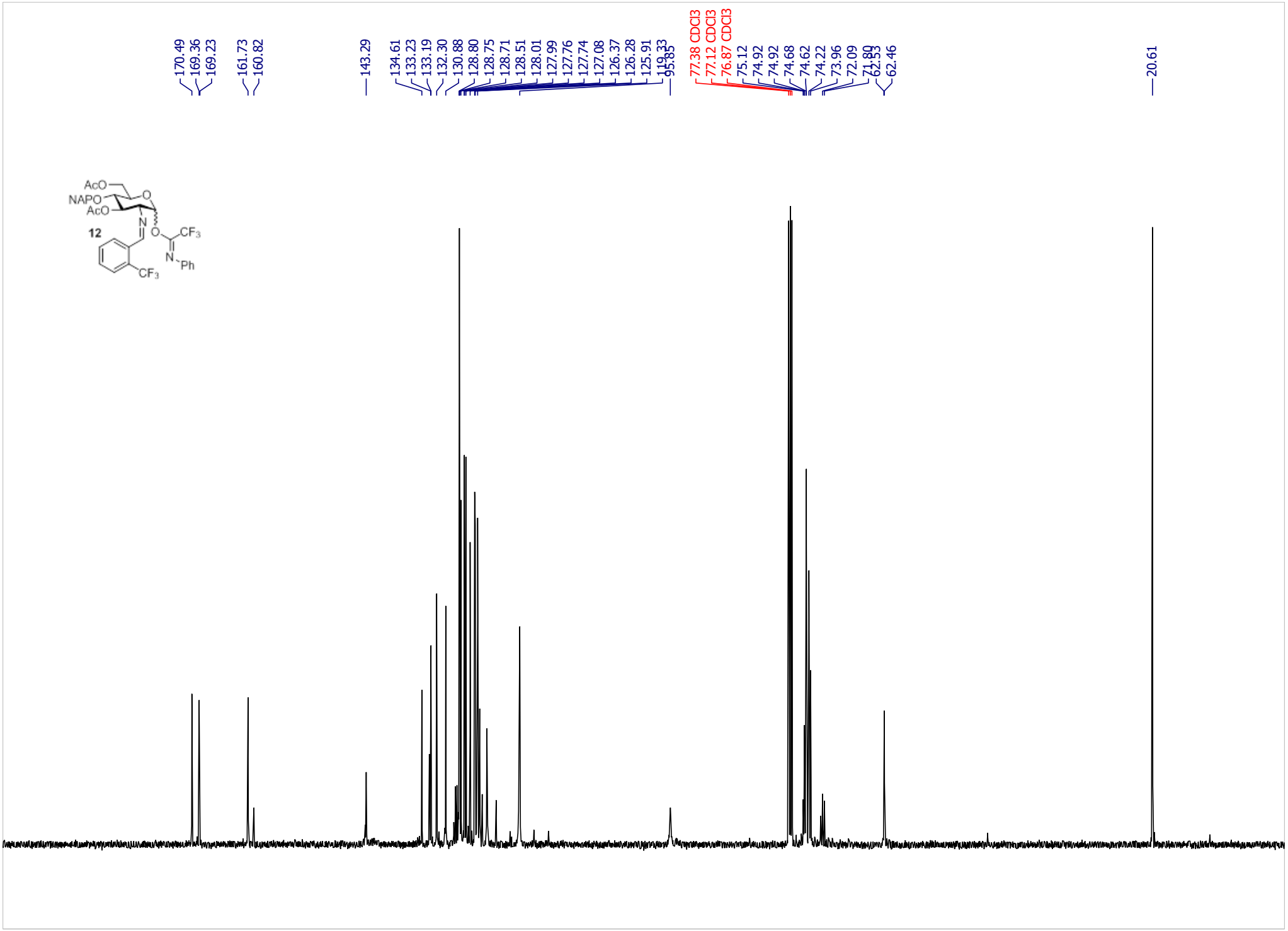
f1 (ppm)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119.33
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74.68
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62.46
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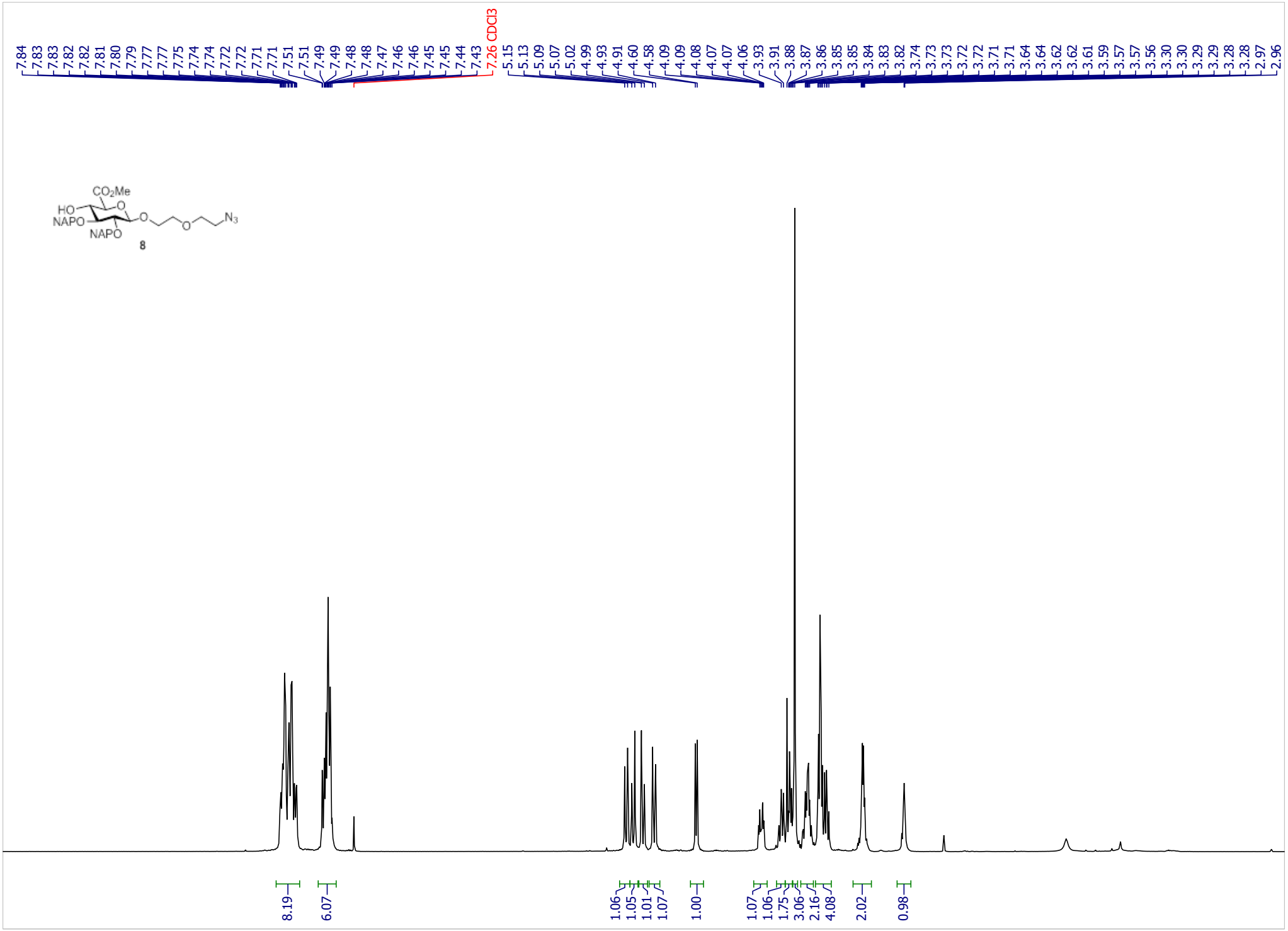
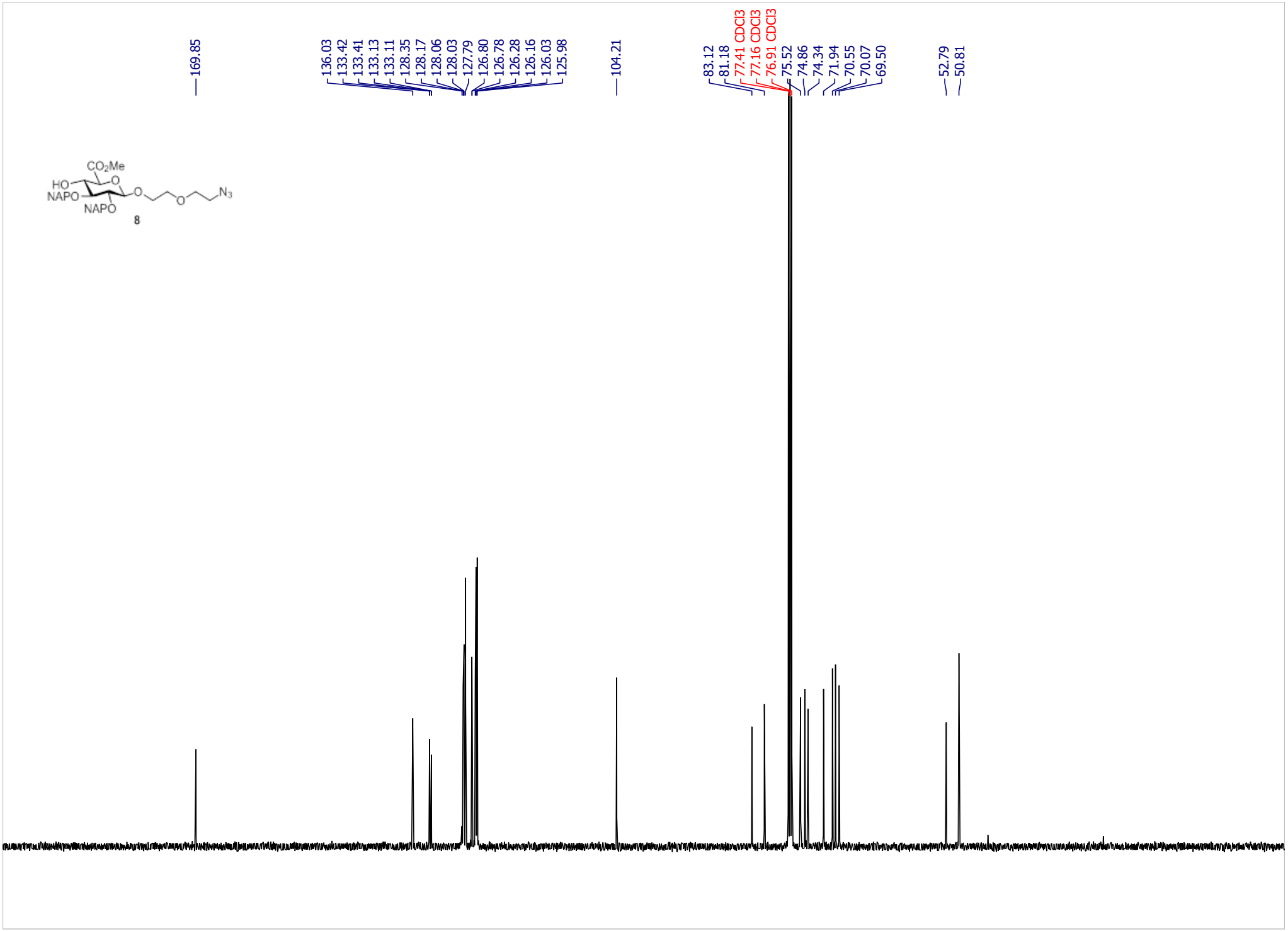
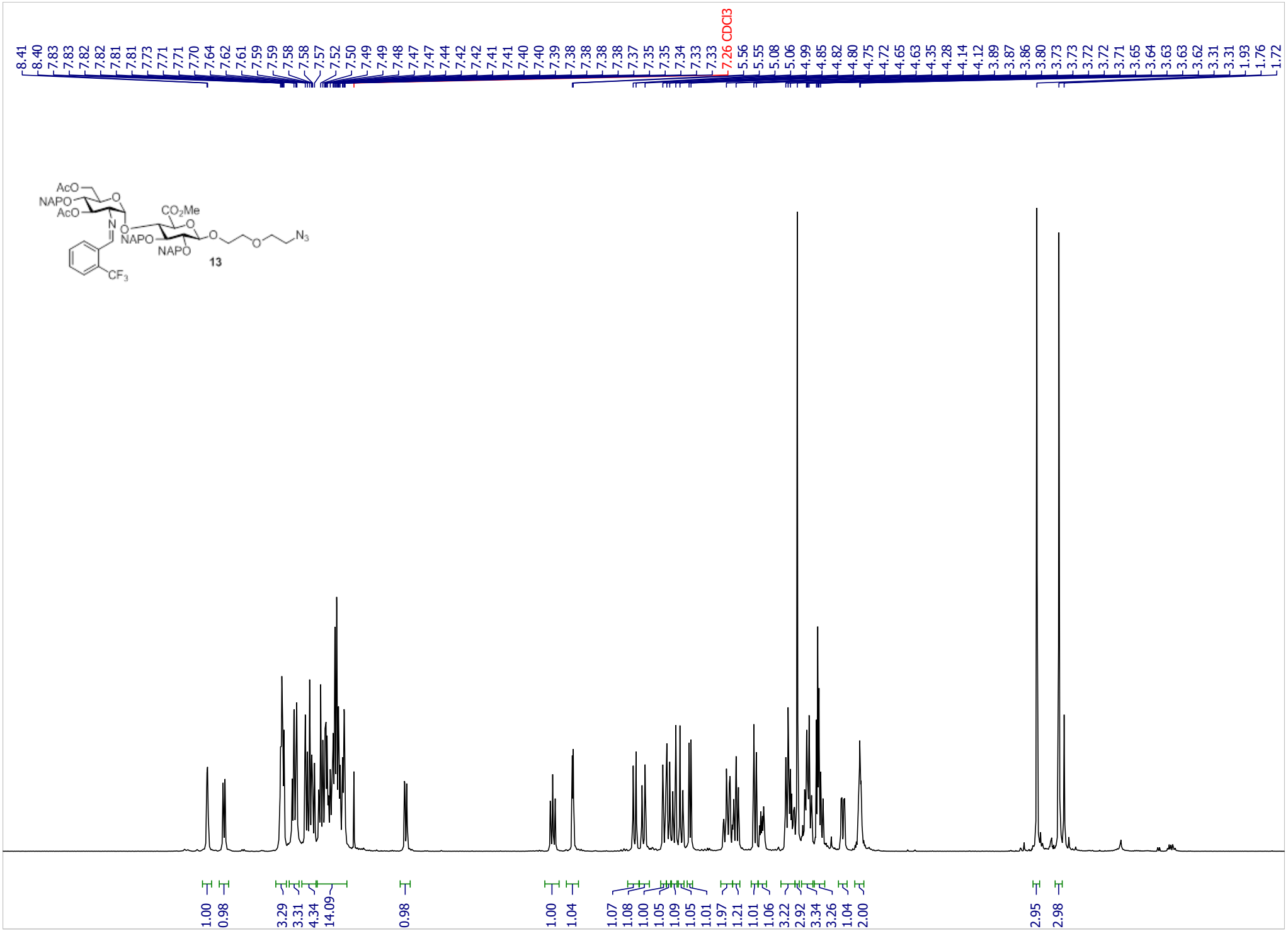
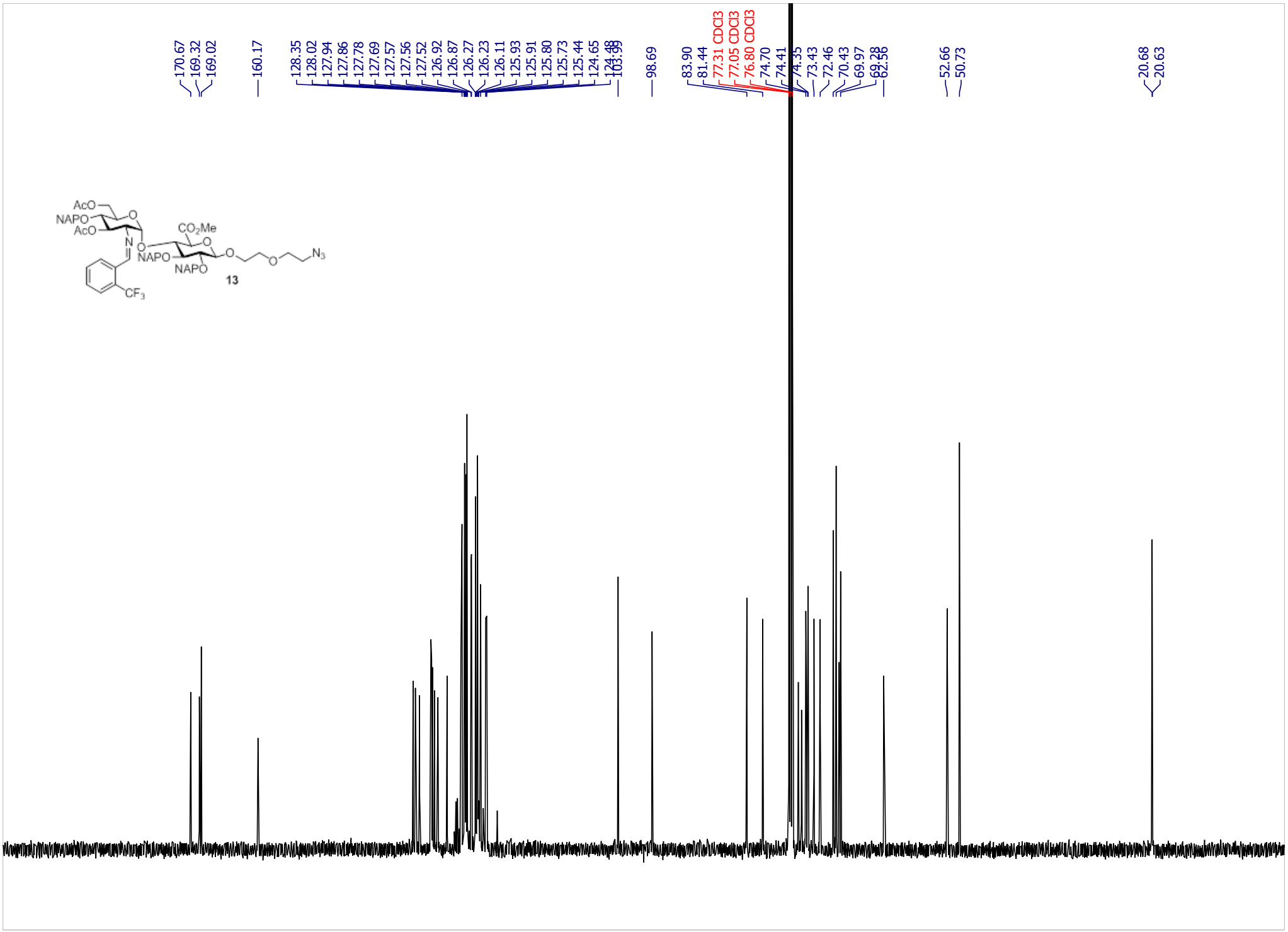
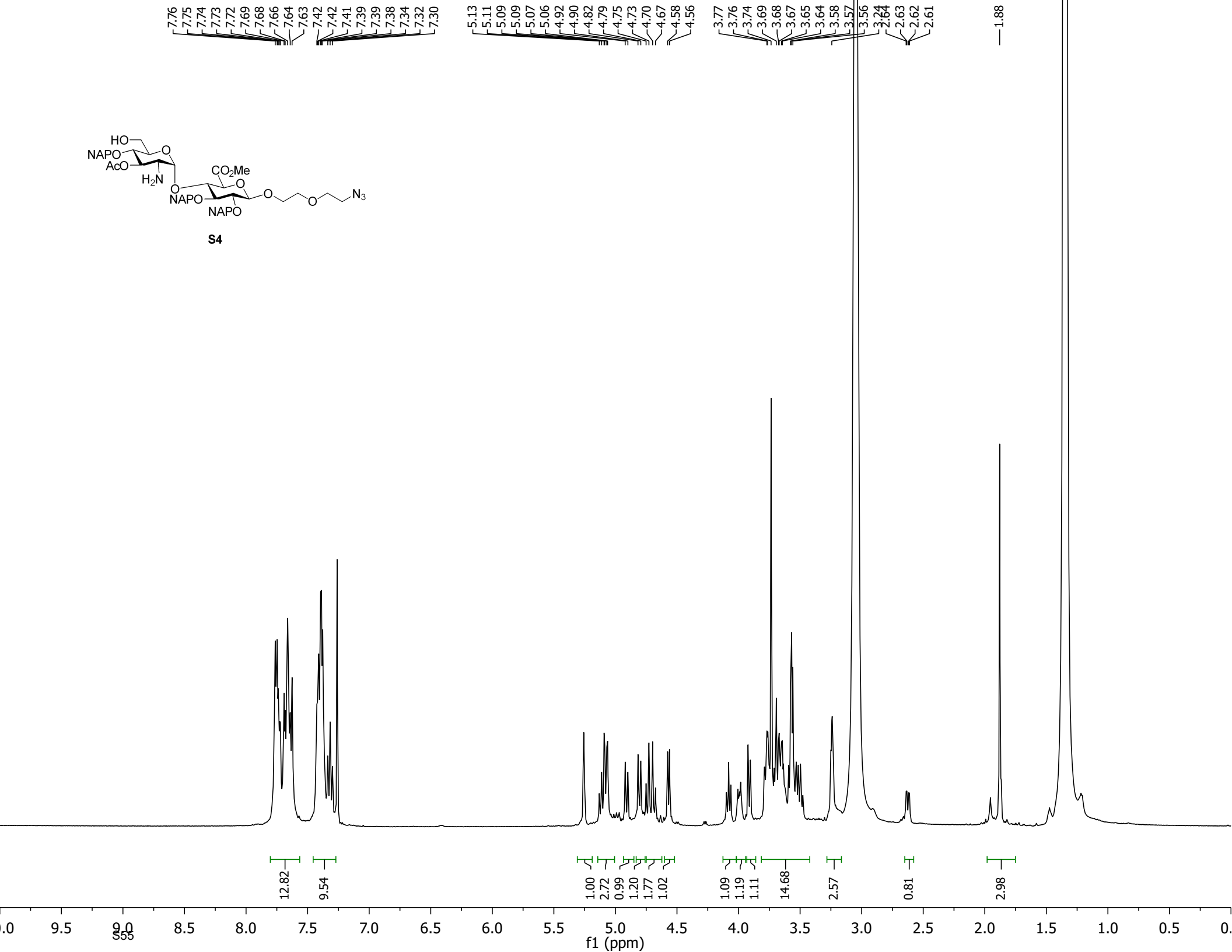
AcO
NAPO
AcO
12
N
O
CF3
N
Ph
CF3
f1 (ppm)

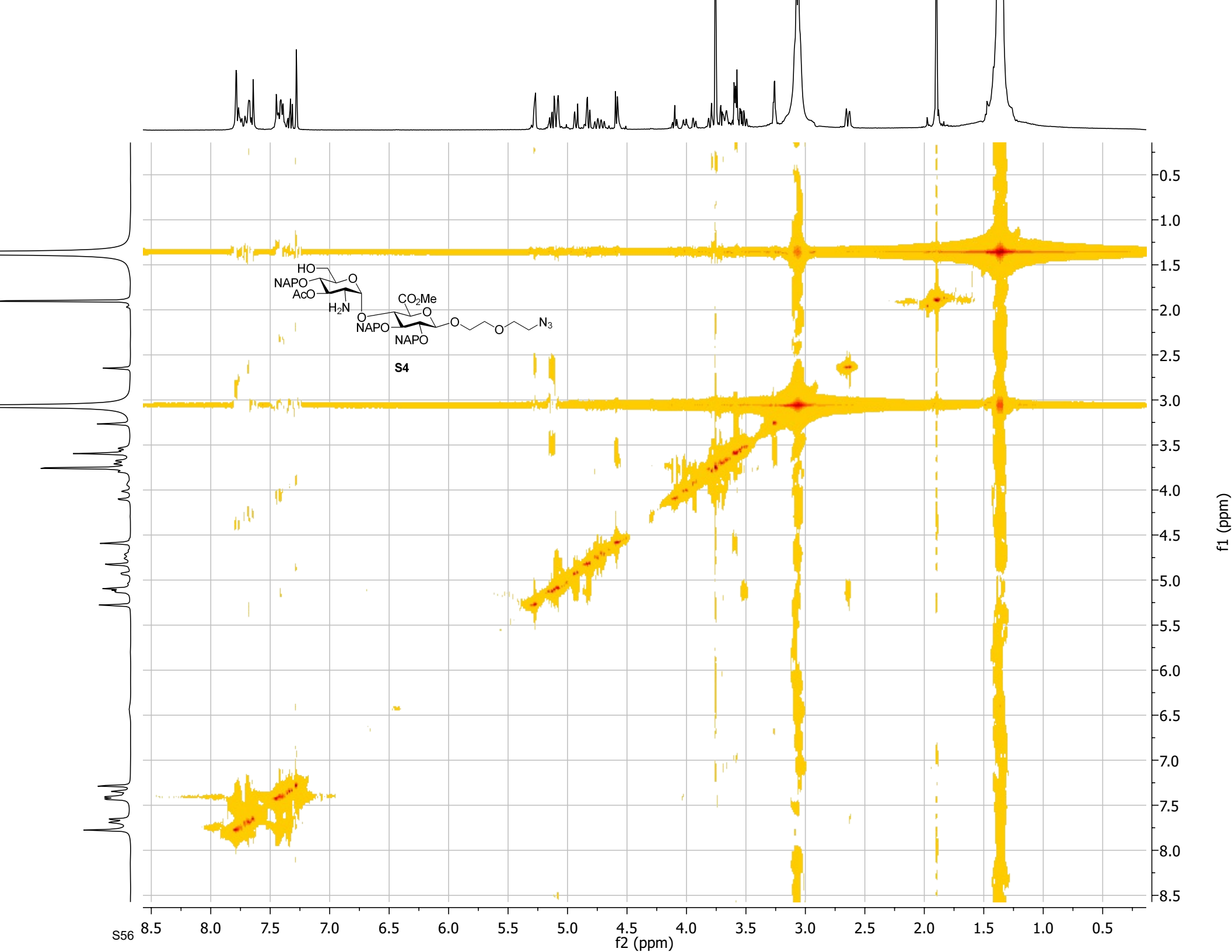

7.84 7.83 7.82 7.82 7.81 7.80 7.79 7.77 7.77 7.75 7.74 7.74 7.72 7.72 7.71 7.71 7.51 7.51 7.49 7.49 7.48 7.48 7.47 7.46 7.46 7.45 7.45 7.44 7.43 7.26 CDCl3
5.15 5.13 5.09 5.07 5.02 4.99 4.93 4.91 4.60 4.58 4.09 4.09 4.08 4.07 4.07 4.06 3.93 3.91 3.88 3.87 3.86 3.85 3.85 3.84 3.83 3.82 3.74 3.73 3.73 3.72 3.72 3.71 3.71 3.64 3.62 3.62 3.61 3.59 3.57 3.57 3.56 3.30 3.30 3.29 3.29 3.28 3.28 2.97 2.96
CO2Me
HO
NAPO
NAPO
O
O
O
N3
8
8.19
6.07
1.06
1.05
1.01
1.07
1.00
1.07
1.06
1.75
3.06
2.16
4.08
2.02
0.98
f1 (ppm)

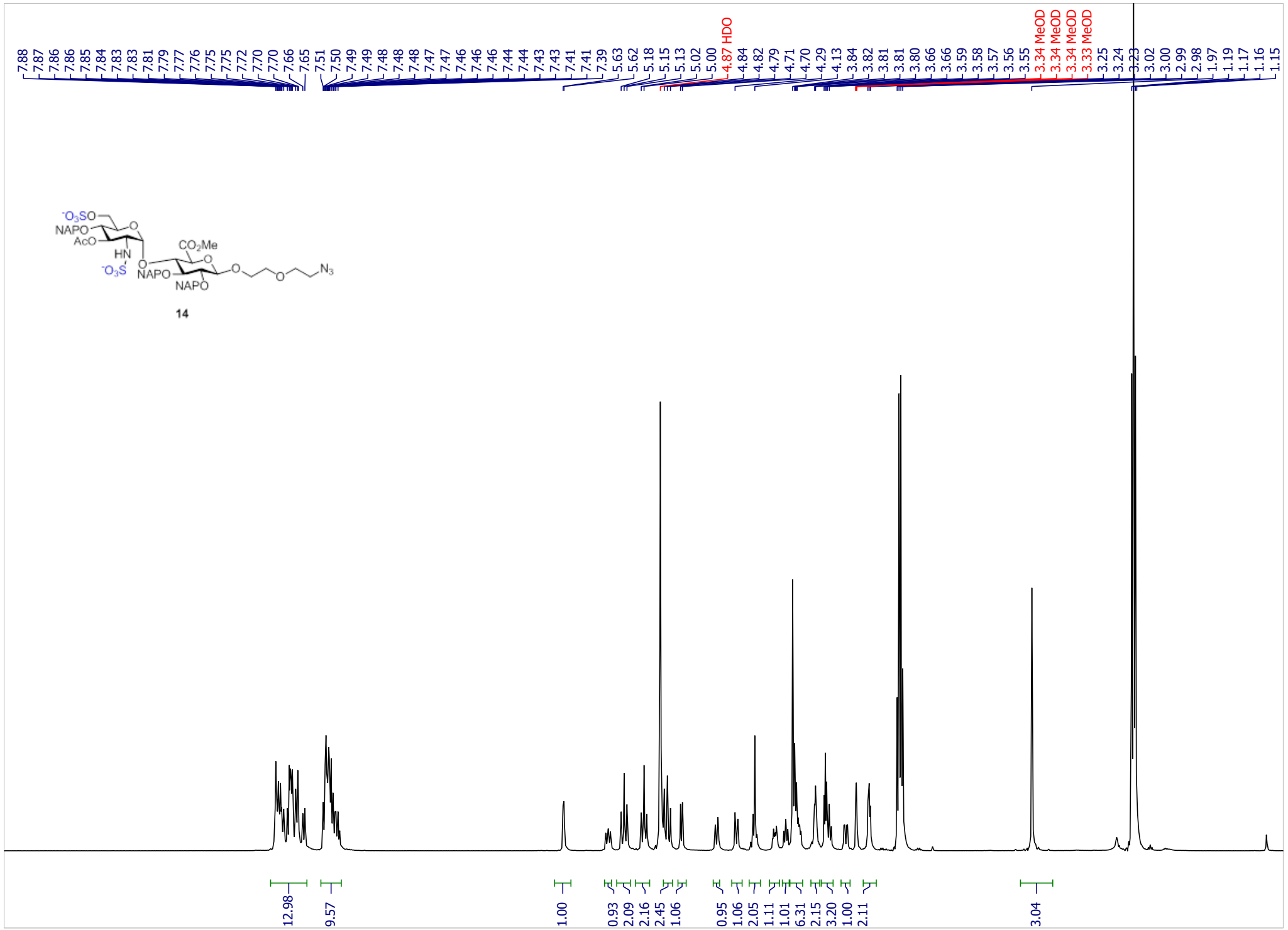

169.85
136.03
133.42
133.41
133.13
133.11
128.35
128.17
128.06
128.03
127.79
126.80
126.78
126.28
126.16
126.03
125.98
104.21
83.12
81.18
77.41 CDCl3
77.16 CDCl3
76.91 CDCl3
75.52
74.86
74.34
71.94
70.55
70.07
69.50
52.79
50.81
CO2Me
HO
NAPO
NAPO
O
O
O
N3
8
f1 (ppm)

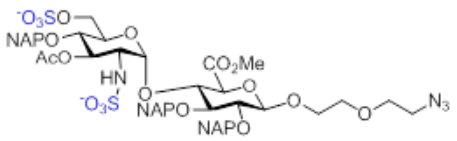

8.41 8.40 7.83 7.83 7.82 7.82 7.81 7.81 7.73 7.71 7.71 7.70 7.64 7.62 7.61 7.59 7.59 7.58 7.58 7.57 7.52 7.50 7.49 7.49 7.48 7.47 7.47 7.44 7.42 7.42 7.41 7.41 7.40 7.40 7.39 7.38 7.38 7.38 7.37 7.35 7.35 7.34 7.33 7.33 7.26 CDCl3 5.56 5.55 5.08 5.06 4.99 4.85 4.82 4.80 4.75 4.72 4.65 4.63 4.35 4.28 4.14 4.12 3.89 3.87 3.86 3.80 3.73 3.73 3.72 3.72 3.71 3.65 3.64 3.63 3.63 3.62 3.31 3.31 1.93 1.76 1.72
AcO
NAPO
AcO
N
O
NAPO
CO2Me
O
NAPO
O
O
O
N3
CF3
13
1.00 0.98 3.29 3.31 4.34 14.09 0.98 1.00 1.04 1.07 1.08 1.00 1.05 1.09 1.05 1.01 1.97 1.21 1.01 1.06 3.22 2.92 3.34 3.26 1.04 2.00 2.95 2.98
.0 9.5 9.0 8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)


170.67
169.32
169.02
160.17
128.35
128.02
127.94
127.86
127.78
127.69
127.57
127.56
127.52
126.92
126.87
126.27
126.23
126.11
125.93
125.91
125.80
125.73
125.44
124.65
98.69
83.90
81.44
77.31 CDCl3
77.05 CDCl3
76.80 CDCl3
74.70
74.41
74.35
73.43
72.46
70.43
69.97
52.66
50.73
20.68
20.63
AcO
NAPO
AcO
CO2Me
NAPO
NAPO
N3
CF3
13
f1 (ppm)


HO
NAPO
AcO
H2N
CO2Me
NAPO
NAPO
N3
S4
7.76 7.75 7.74 7.73 7.72 7.69 7.68 7.66 7.64 7.63 7.42 7.42 7.41 7.39 7.39 7.38 7.34 7.32 7.30
5.13 5.11 5.09 5.09 5.07 5.06 4.92 4.90 4.82 4.79 4.75 4.73 4.70 4.67 4.58 4.56
3.77 3.76 3.74 3.69 3.68 3.67 3.65 3.64 3.58 3.57 3.56 2.64 2.63 2.62 2.61
1.88
12.82
9.54
1.00
2.72
0.99
1.20
1.77
1.02
1.09
1.19
1.11
14.68
2.57
0.81
2.98
f1 (ppm)

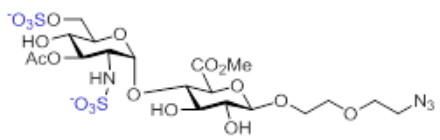

HO
NAPO
AcO
H_2N
O
NAPO
CO_2Me
O
NAPO
O
O
N_3
S4
f2 (ppm)
f1 (ppm)


7.88 7.87 7.86 7.86 7.85 7.84 7.83 7.83 7.81 7.79 7.77 7.76 7.75 7.75 7.72 7.70 7.70 7.66 7.65 7.51 7.50 7.49 7.49 7.48 7.48 7.48 7.47 7.47 7.46 7.46 7.46 7.44 7.44 7.43 7.43 7.41 7.41 7.39 5.63 5.62 5.18 5.15 5.13 5.02 5.00 4.87 HDO 4.84 4.82 4.79 4.71 4.70 4.29 4.13 3.84 3.82 3.81 3.81 3.80 3.66 3.66 3.59 3.58 3.57 3.56 3.55 3.34 MeOD 3.34 MeOD 3.34 MeOD 3.33 MeOD 3.25 3.24 3.23 3.02 3.00 2.99 2.98 1.97 1.19 1.17 1.16 1.15
$^{-}O_3SO$
NAPO
AcO
HN
$^{-}O_3S$
O
NAPO
NAPO
CO_2Me
O
O
O
N_3
14
12.98
9.57
1.00
0.93
2.09
2.16
2.45
1.06
0.95
1.06
2.05
1.11
1.01
6.31
2.15
3.20
1.00
2.11
3.04
f1 (ppm)


$^{-}O_3SO$
NAPO
AcO
HN
$^{-}O_3S$
O
NAPO
NAPO
CO_2Me
O
O
O
N_3

14

173.15
170.92
137.45
137.30
137.21
134.77
134.71
134.48
134.40
134.32
129.03
128.97
128.94
128.93
128.67
128.62
127.69
127.41
127.37
127.06
104.88
99.50
83.17
82.83
77.35
75.87
75.69
75.51
75.13
71.35
70.94
70.22
58.41
53.46
51.73
49.51 MeOD
49.34 MeOD
49.28 MeOD
49.17 MeOD
49.11 MeOD
49.00 MeOD
48.94 MeOD
48.83 MeOD
48.66 MeOD
48.49 MeOD
47.85
21.43
9.21
f1 (ppm)



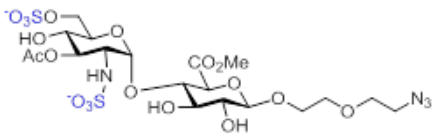
15

5.57 5.56 5.00 4.98 4.98 4.96 4.49 4.47 4.22 4.07 4.05 3.94 3.86 3.75 3.74 3.73 3.73 3.73 3.72 3.71 3.70 3.68 3.67 3.45 3.44 3.43 3.42 3.35 2.14

1.00 1.08 1.00 1.03 1.08 1.01 2.28 3.00 9.49 7.47 2.96

8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5 0.

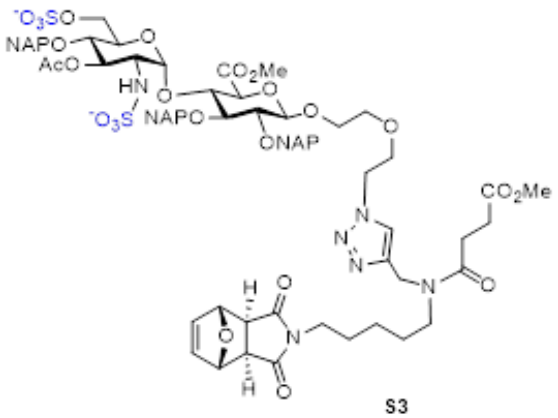
f1 (ppm)



15

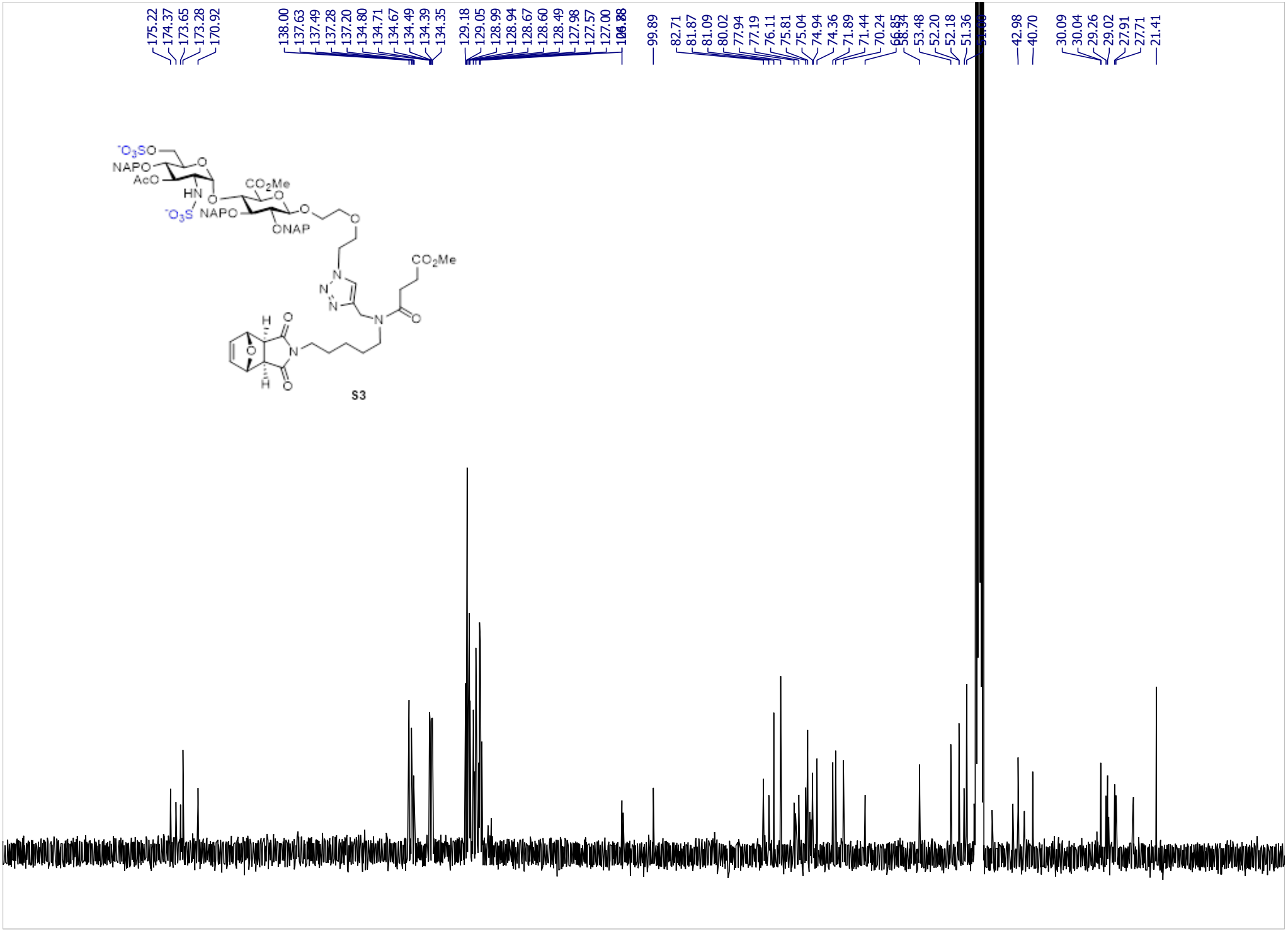
173.61
170.57
104.61
100.66
80.26
77.00
76.11
74.46
74.44
72.32
71.29
70.96
70.14
68.97
67.09
58.23
53.51
51.76
21.24

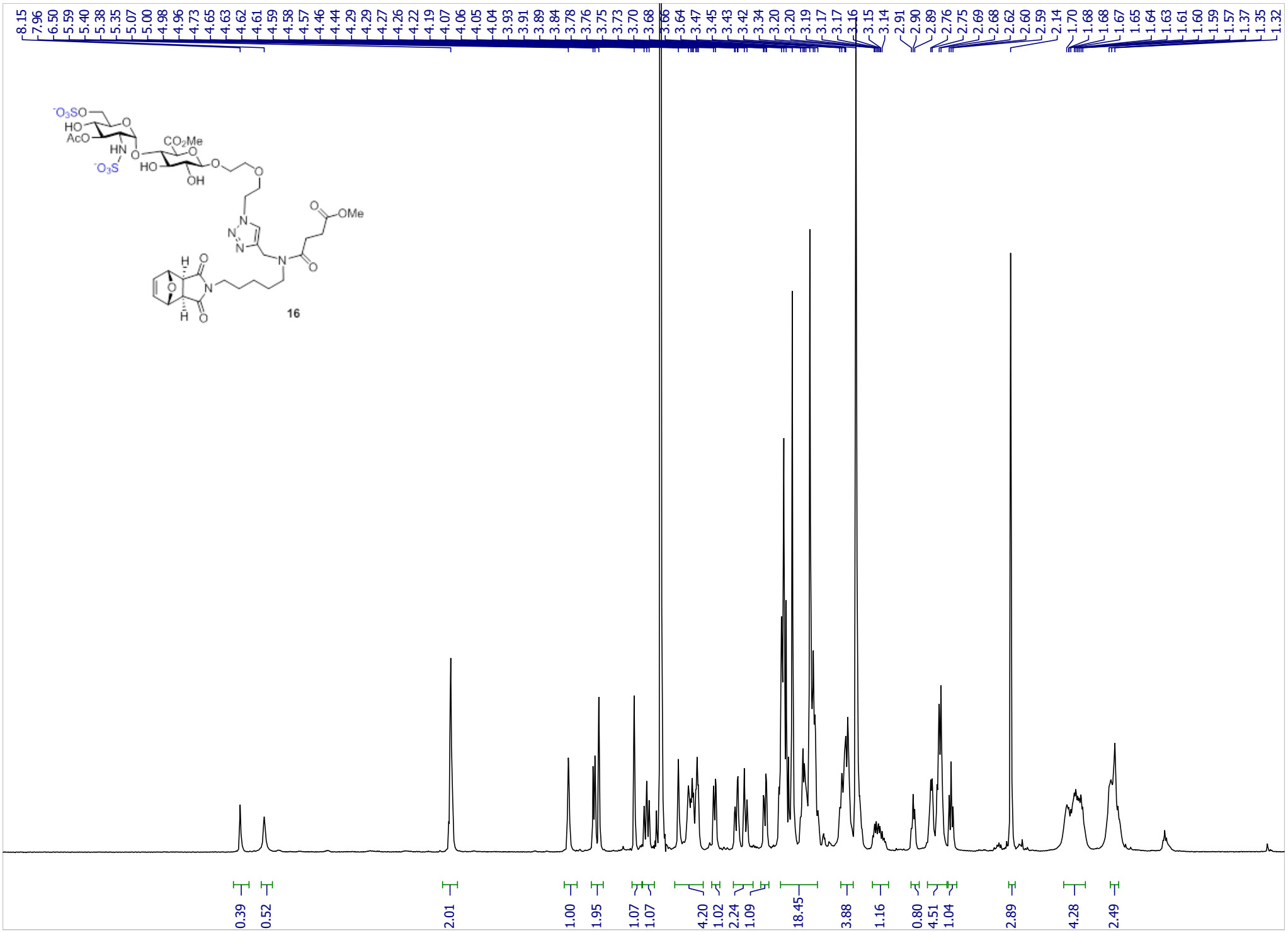
f1 (ppm)

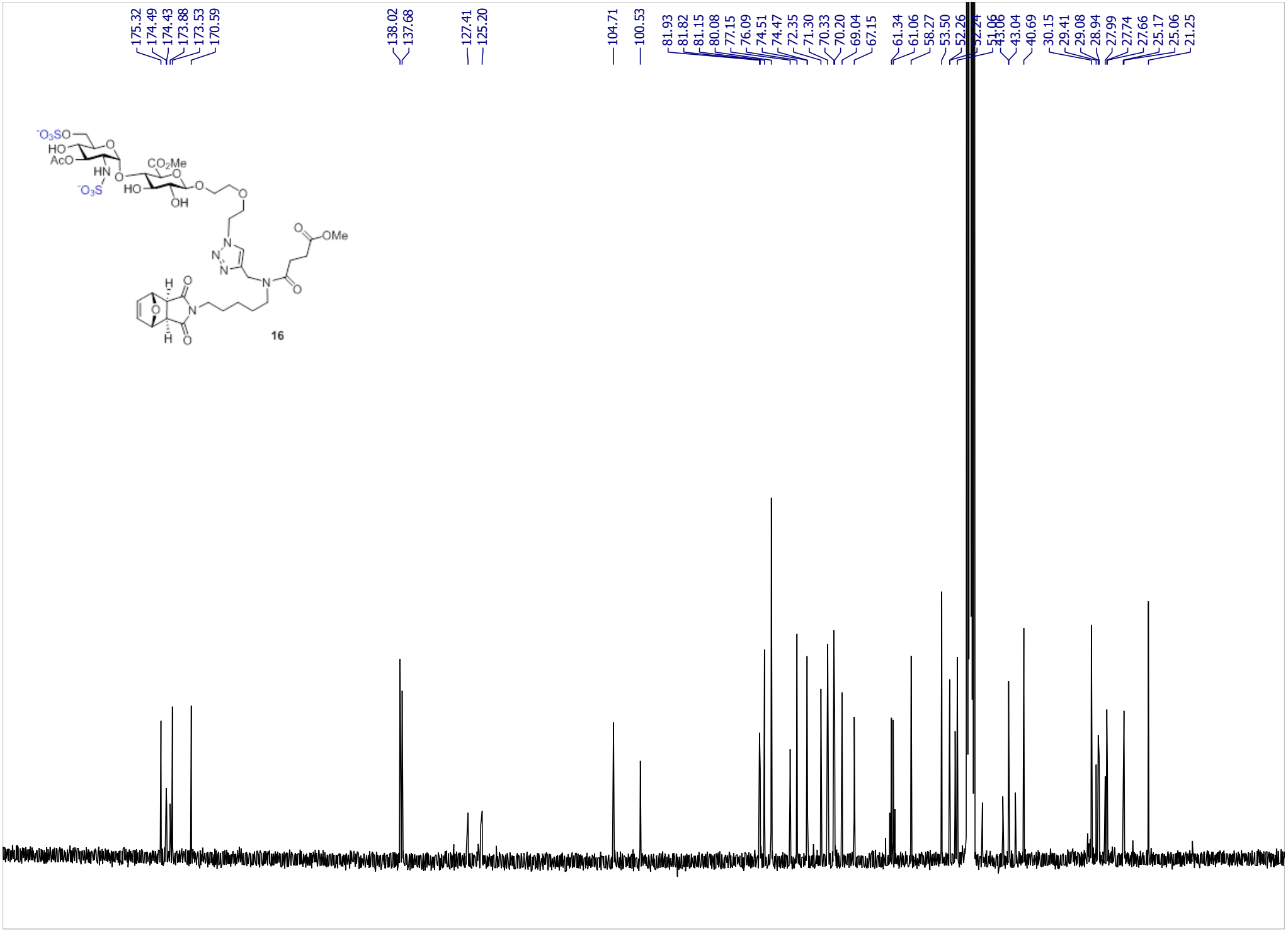


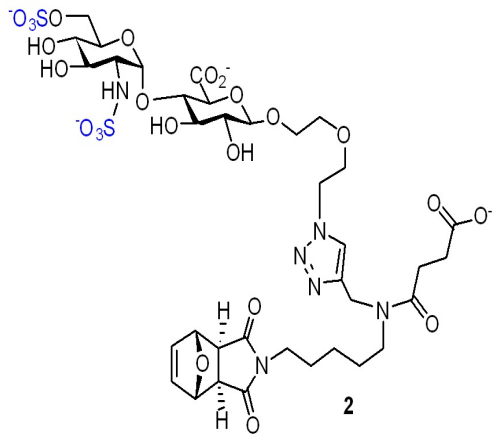
S3

f1 (ppm)


175.22
174.37
173.65
173.28
170.92
138.00
137.63
137.49
137.28
137.20
134.80
134.71
134.67
134.49
134.39
134.35
129.18
129.05
128.99
128.94
128.67
128.60
128.49
127.98
127.57
127.00
99.89
82.71
81.87
81.09
80.02
77.94
77.19
76.11
75.81
75.04
74.94
74.36
71.89
71.44
70.24
66.85
58.34
53.48
52.20
52.18
51.36
42.98
40.70
30.09
30.04
29.26
29.02
27.91
27.71
21.41
S3
f1 (ppm)

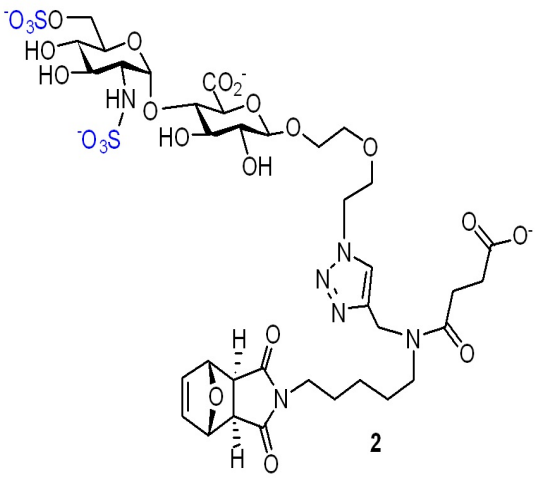

16
f1 (ppm)


175.32
174.49
174.43
173.88
173.53
170.59
138.02
137.68
127.41
125.20
104.71
100.53
81.93
81.82
81.15
80.08
77.15
76.09
74.51
74.47
72.35
71.30
70.33
70.20
69.04
67.15
61.34
61.06
58.27
53.50
52.26
52.24
51.06
43.06
43.04
40.69
30.15
29.41
29.08
28.94
27.99
27.74
27.66
25.17
25.06
21.25
16
f1 (ppm)



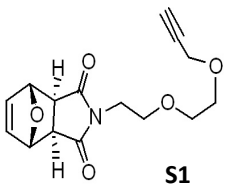
2

f1 (ppm)



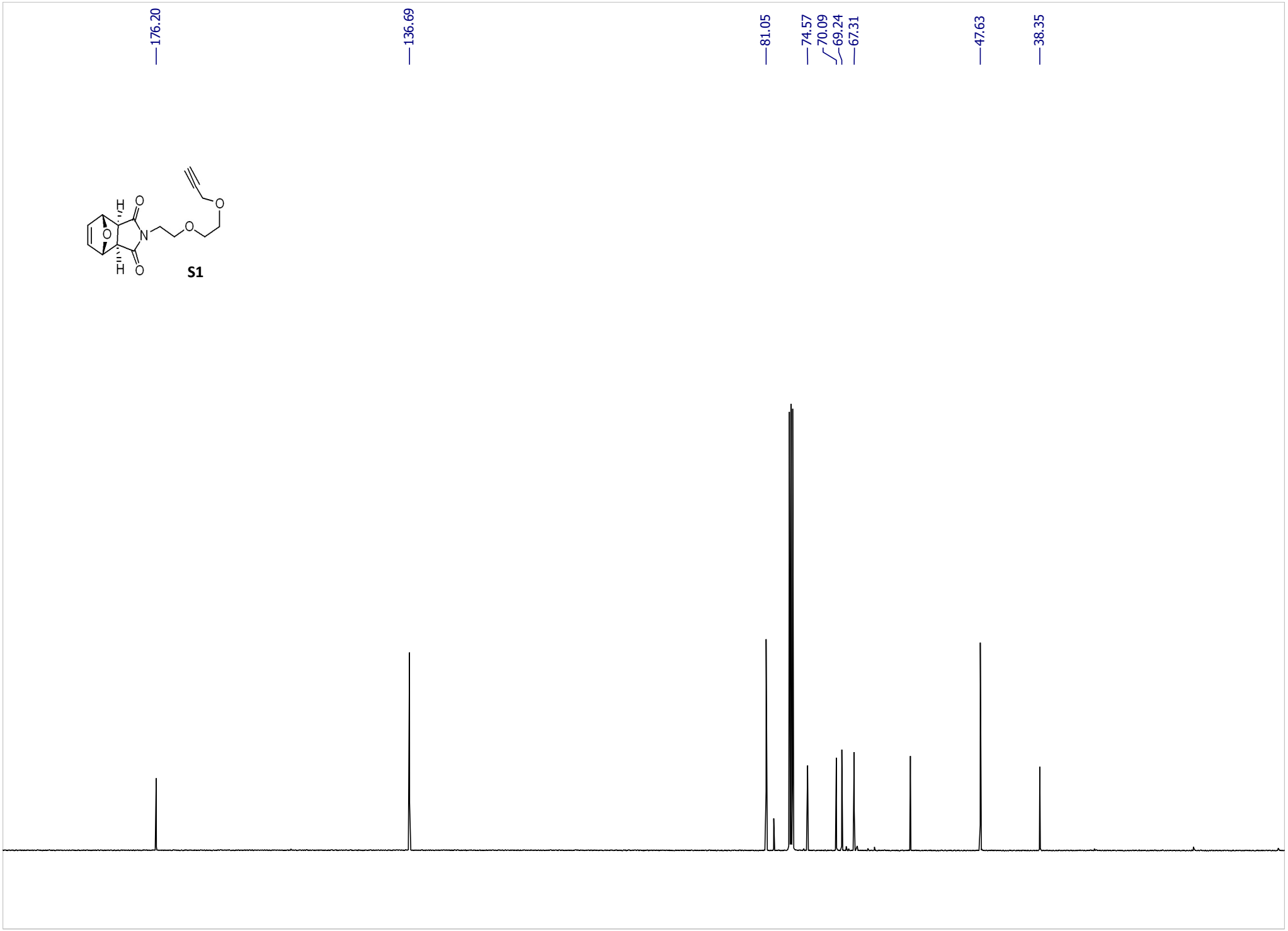
2

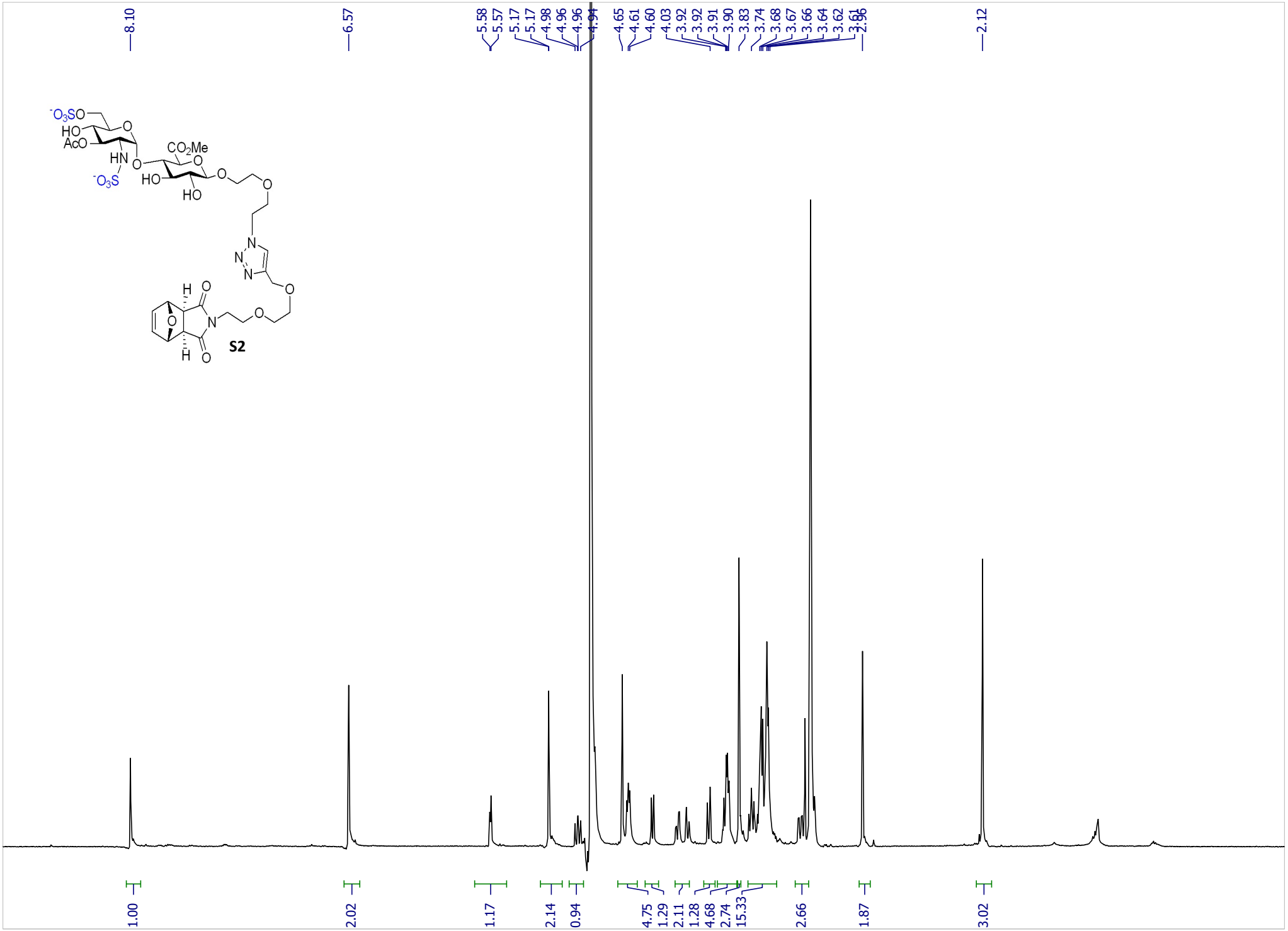
175.31
136.42
135.93
102.32
97.30
82.42
80.46
76.47
76.24
72.82
71.24
69.82
69.67
69.09
68.92
68.74
66.41
58.09
58.04
50.04
48.75
48.65
46.85
41.18
39.92
32.75
29.44
27.40
26.12
23.11
220 210 200 190 180 170 160 150 140 130 120 110 100 90 80 70 60 50 40 30 20 10 0 -10 -20
f1 (ppm)

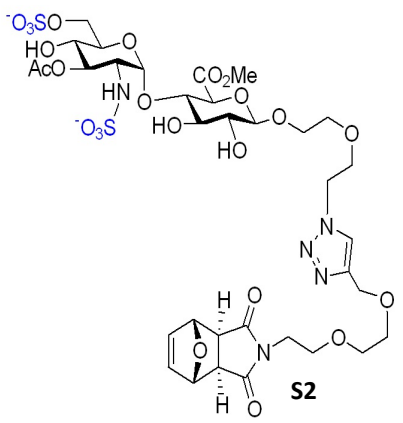


S1

6.50
5.26
4.17
4.16
3.70
3.70
3.69
3.68
3.64
3.64
3.63
3.62
3.61
3.61
2.85
2.42
2.41
2.41
2.01
1.97
2.01
8.40
2.05
0.85
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
0.
f1 (ppm)


176.20
136.69
81.05
74.57
70.09
69.24
67.31
47.63
38.35
S1
f1 (ppm)


8.10
6.57
5.58
5.57
5.17
5.17
4.98
4.96
4.96
4.94
4.65
4.61
4.60
4.03
3.92
3.92
3.91
3.90
3.83
3.74
3.68
3.67
3.66
3.64
3.62
3.61
2.96
2.12
S2
1.00
2.02
1.17
2.14
0.94
4.75
1.29
2.11
1.28
4.68
2.74
15.33
2.66
1.87
3.02
f1 (ppm)



S2

178.61
173.53
170.59
137.66
137.65
126.10
104.68
100.50
82.26
80.05
77.20
76.11
74.51
74.47
72.35
71.29
71.25
70.69
70.36
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67.15
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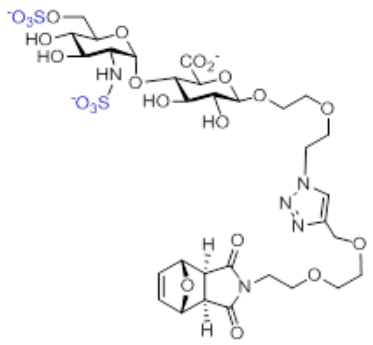
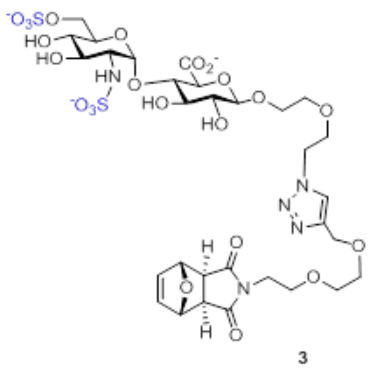
58.28
53.51
51.38
39.31
21.26

f1 (ppm)



3

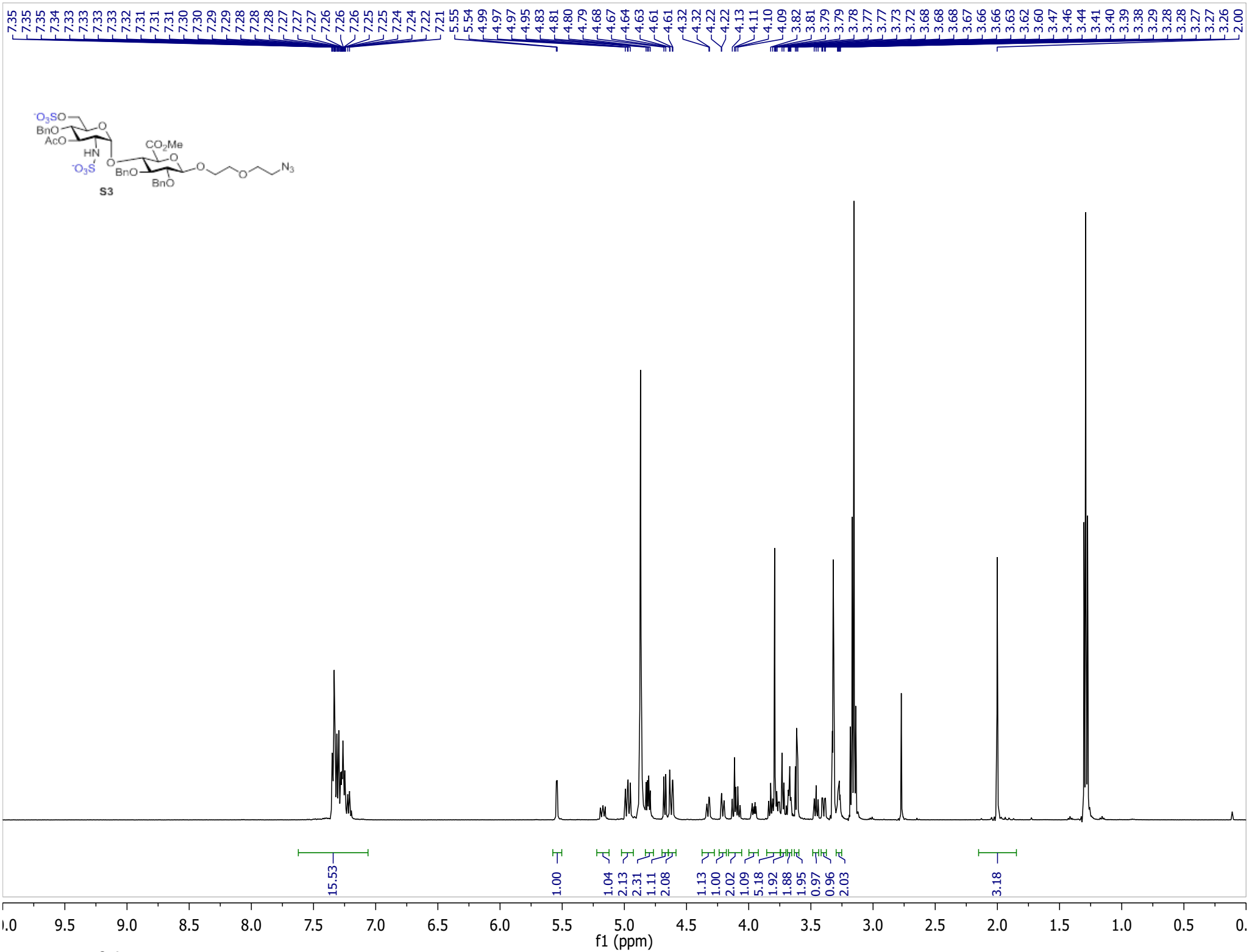
8.12 6.56 6.55 6.55 6.43 6.43 6.42 6.42 5.67 5.66 5.20 5.04 4.72 4.66 4.65 4.64 4.49 4.47 4.38 4.36 4.35 4.19 4.19 4.17 4.16 4.02 4.01 4.00 3.99 3.98 3.97 3.97 3.89 3.87 3.87 3.84 3.84 3.82 3.82 3.81 3.80 3.80 3.79 3.78 3.78 3.77 3.76 3.76 3.75 3.75 3.74 3.74 3.72 3.72 3.71 3.71 3.70 3.62 3.61 3.61 3.60 3.59 3.41 3.40 3.39 3.37 3.36 3.34 3.33 3.32 3.30 3.30 3.29 3.28 3.27 2.77 2.75 2.74 2.72
1.10
2.28
1.30
1.06
0.98
42.88
1.80
0.92
1.00
1.17
3.15
13.99
4.08
1.98
8.5 8.0 7.5 7.0 6.5 6.0 5.5 5.0 4.5 4.0 3.5 3.0 2.5 2.0 1.5 1.0 0.5
f1 (ppm)

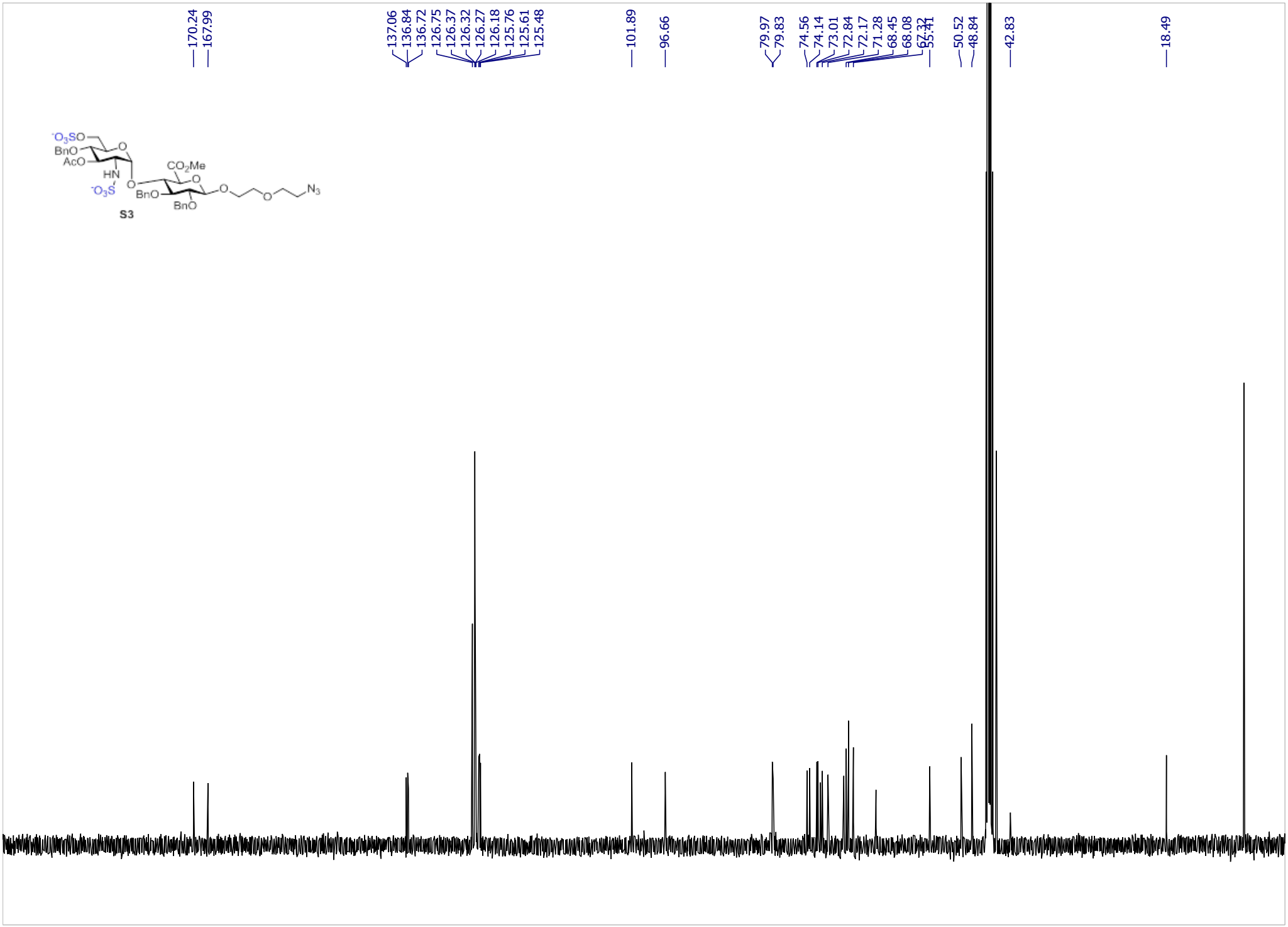


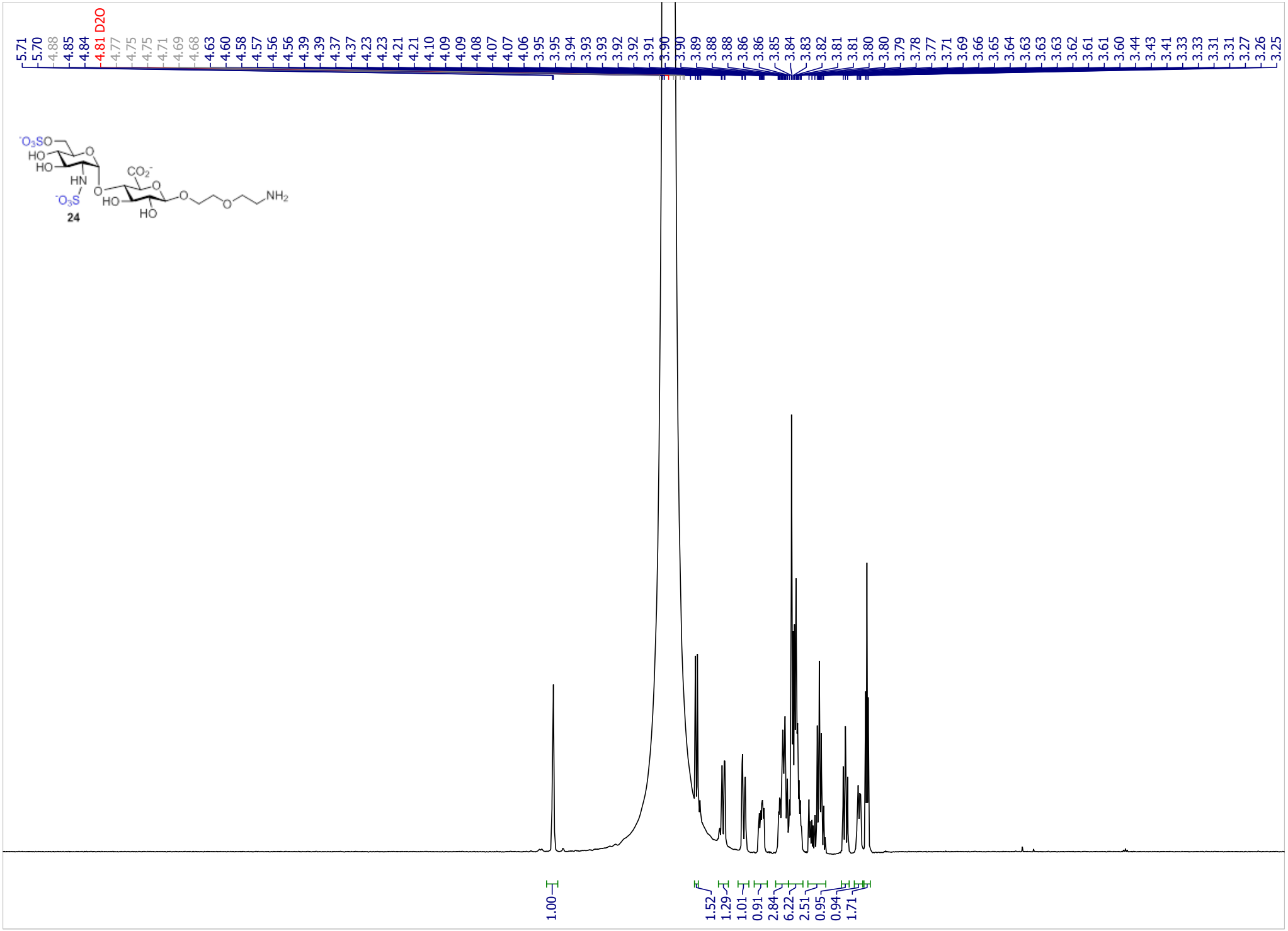
3

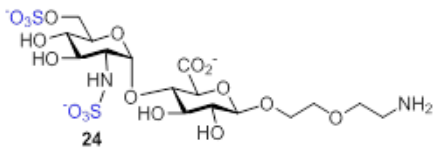
178.83
175.78
175.00
144.02
137.41
135.24
125.65
102.30
97.31
80.89
80.57
76.79
76.47
76.27
72.82
71.24
69.82
69.43
69.10
69.02
68.87
68.80
68.75
63.14
57.99
50.10
50.06
47.30
38.97
23.37

f1 (ppm)


7.35 7.35 7.35 7.34 7.33 7.33 7.33 7.32 7.31 7.31 7.30 7.30 7.29 7.29 7.28 7.28 7.28 7.27 7.27 7.27 7.26 7.26 7.26 7.25 7.25 7.24 7.24 7.22 7.21
5.55 5.54 4.99 4.97 4.97 4.95 4.83 4.81 4.80 4.79 4.68 4.67 4.64 4.63 4.61 4.61 4.32 4.32 4.22 4.22 4.13 4.11 4.10 4.09 3.82 3.81 3.79 3.79 3.78 3.77 3.77 3.73 3.72 3.68 3.68 3.67 3.66 3.66 3.63 3.62 3.60 3.47 3.46 3.44 3.41 3.40 3.39 3.38 3.29 3.28 3.28 3.27 3.27 3.26 2.00
S3
15.53
1.00
1.04
2.13
2.31
1.11
2.08
1.13
1.00
2.02
1.09
5.18
1.92
1.88
1.95
0.97
0.96
2.03
3.18
f1 (ppm)


170.24
167.99
137.06
136.84
136.72
126.75
126.37
126.32
126.27
126.18
125.76
125.61
125.48
101.89
96.66
79.97
79.83
74.56
74.14
73.01
72.84
72.17
71.28
68.45
68.08
67.32
55.41
50.52
48.84
42.83
18.49
S3
f1 (ppm)

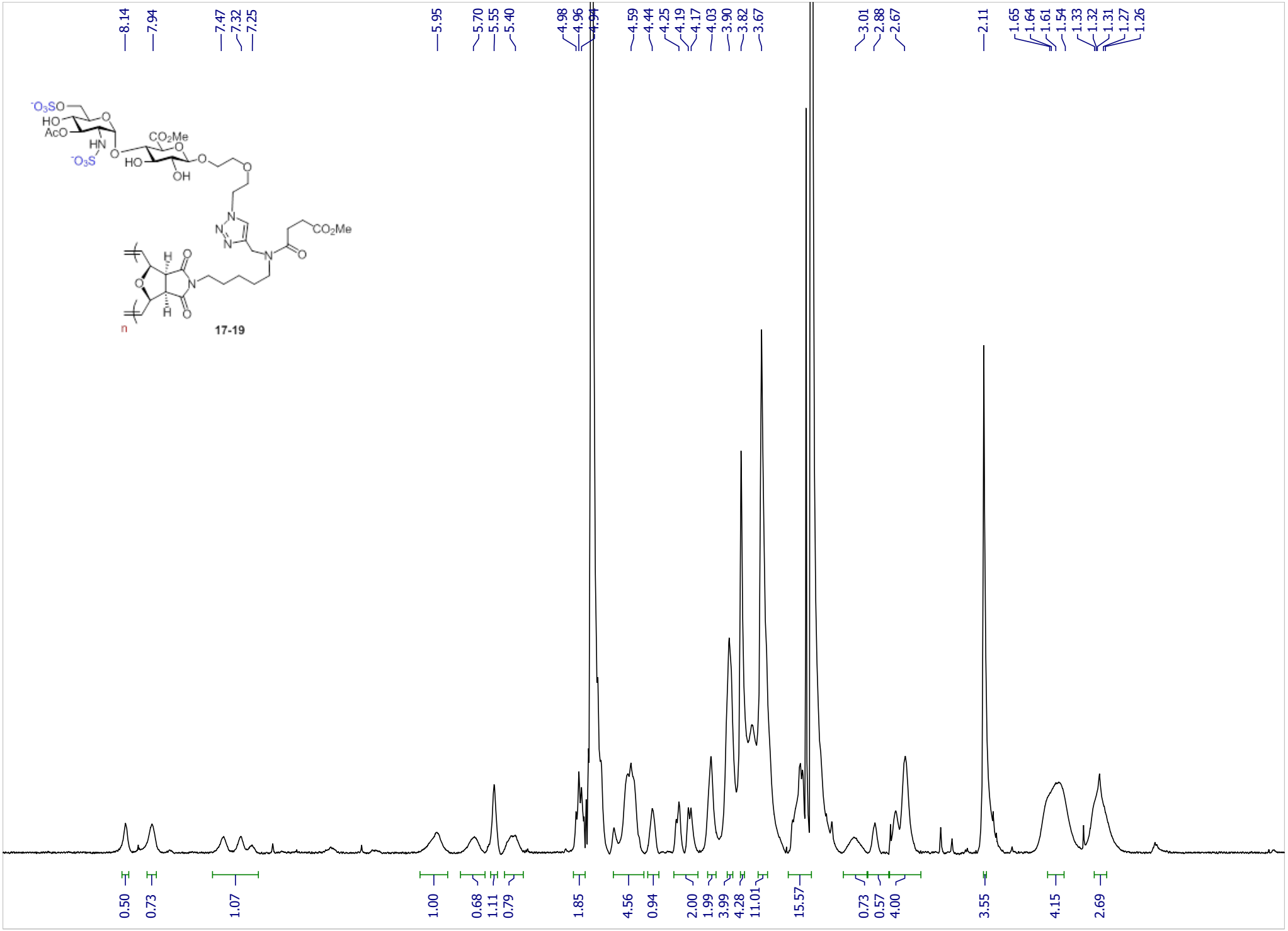

5.71 5.70 4.88 4.85 4.84 4.81 D2O 4.77 4.75 4.75 4.71 4.69 4.68 4.63 4.60 4.58 4.57 4.56 4.56 4.39 4.39 4.37 4.37 4.23 4.23 4.21 4.21 4.10 4.09 4.09 4.08 4.07 4.07 4.06 3.95 3.95 3.94 3.93 3.93 3.92 3.91 3.90 3.90 3.89 3.88 3.88 3.86 3.86 3.85 3.84 3.83 3.82 3.81 3.81 3.80 3.80 3.79 3.78 3.77 3.71 3.69 3.66 3.65 3.64 3.63 3.63 3.62 3.61 3.61 3.60 3.44 3.43 3.41 3.33 3.33 3.31 3.31 3.27 3.26 3.25
24
1.00
1.52
1.29
1.01
0.91
2.84
6.22
2.51
0.95
0.94
1.71
f1 (ppm)



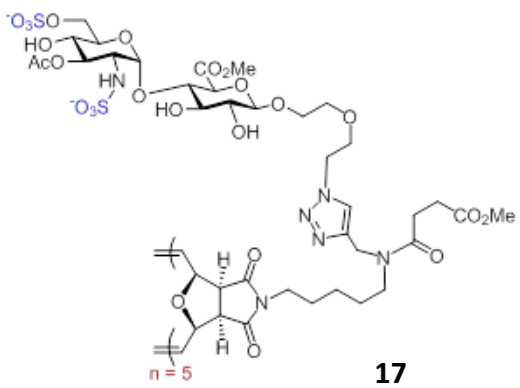
24

175.09
102.32
97.20
76.63
76.51
76.02
72.92
71.21
69.84
69.63
69.18
69.12
66.52
66.28
57.97
39.30

f1 (ppm)


8.14
7.94
7.47
7.32
7.25
5.95
5.70
5.55
5.40
4.98
4.96
4.94
4.59
4.44
4.25
4.19
4.17
4.03
3.90
3.82
3.67
3.01
2.88
2.67
2.11
1.65
1.64
1.61
1.54
1.33
1.32
1.31
1.27
1.26
0.50
0.73
1.07
1.00
0.68
1.11
0.79
1.85
4.56
0.94
2.00
1.99
3.99
4.28
11.01
15.57
0.73
0.57
4.00
3.55
4.15
2.69
f1 (ppm)

17-19

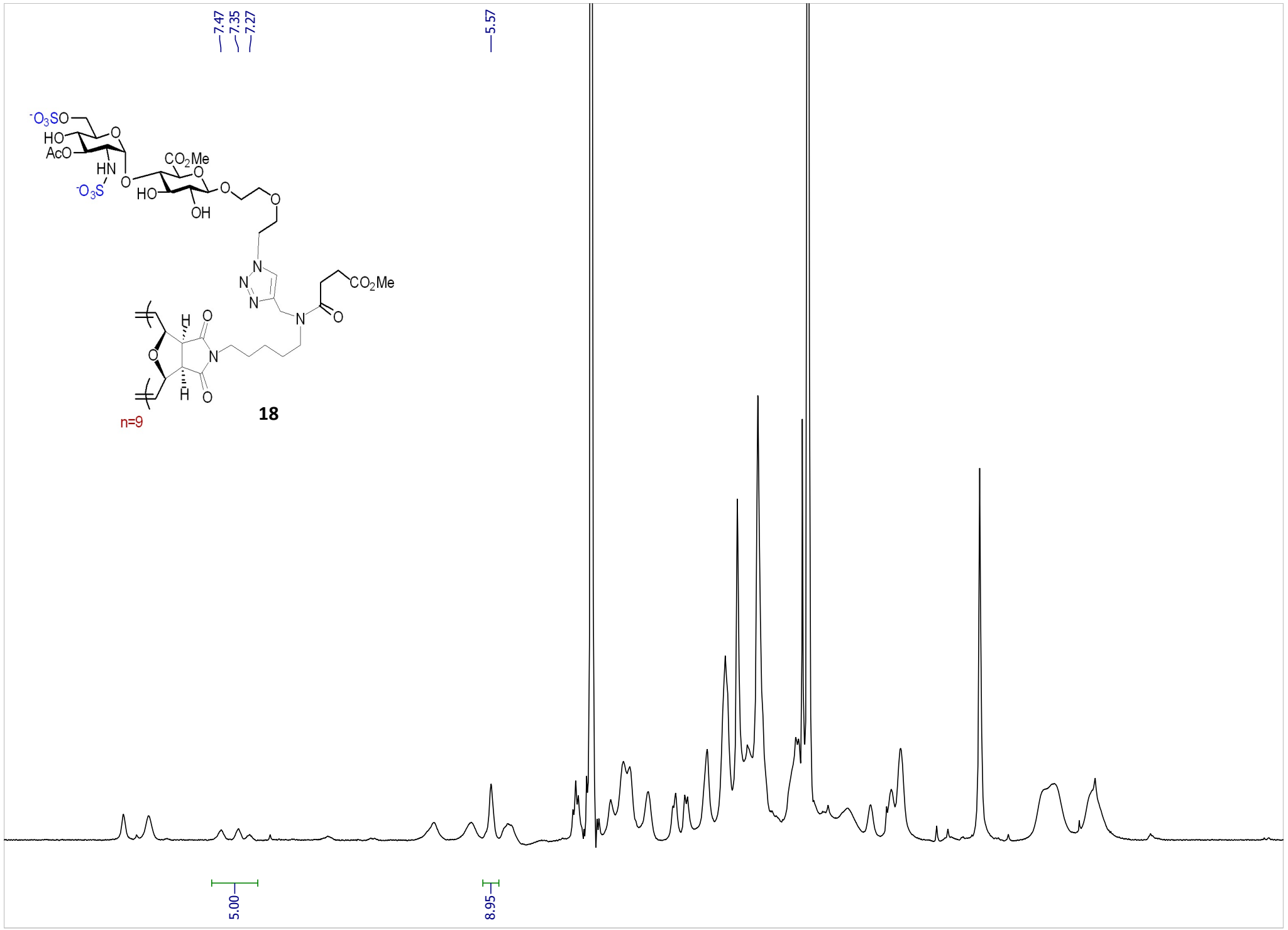


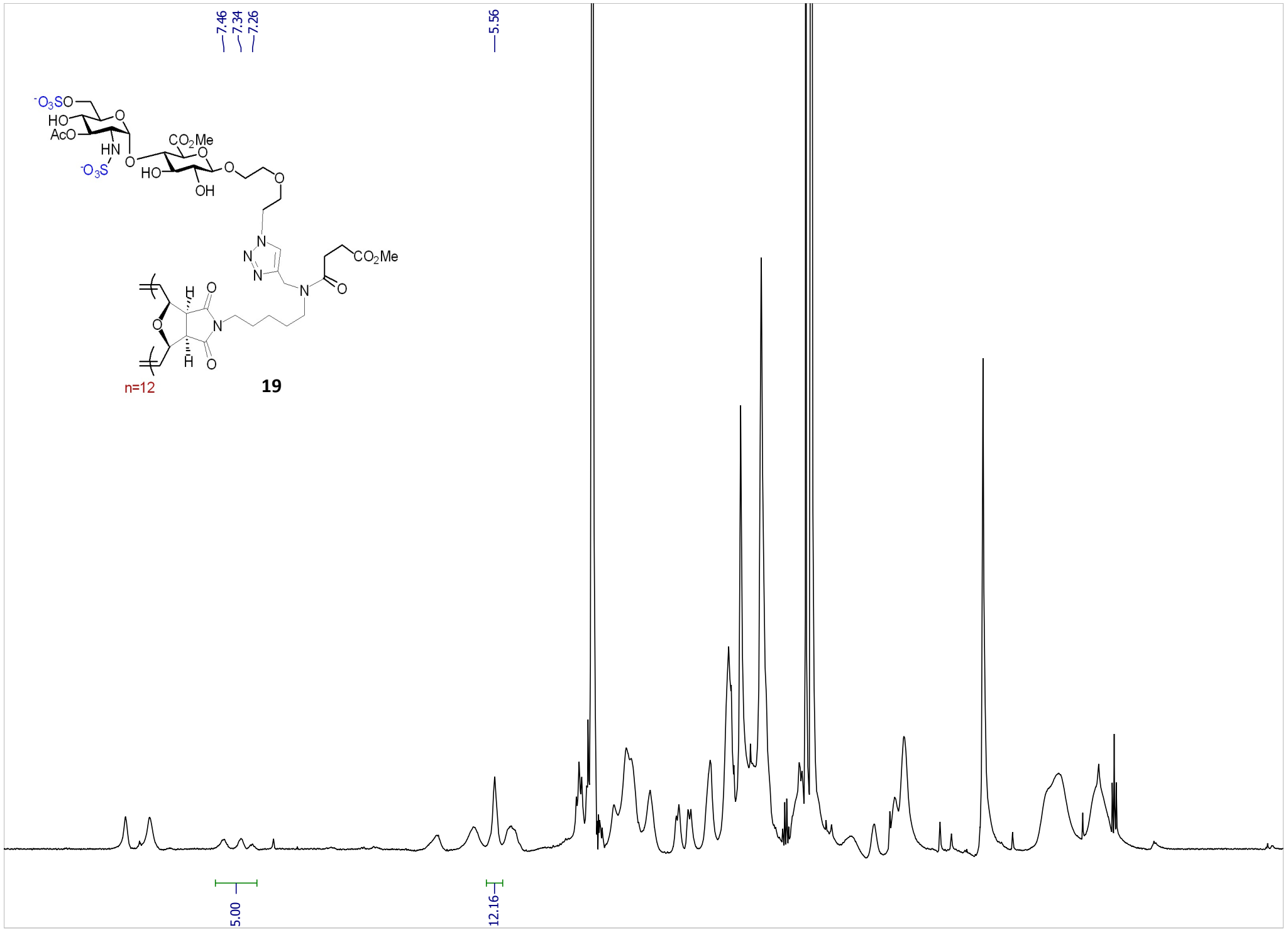
17

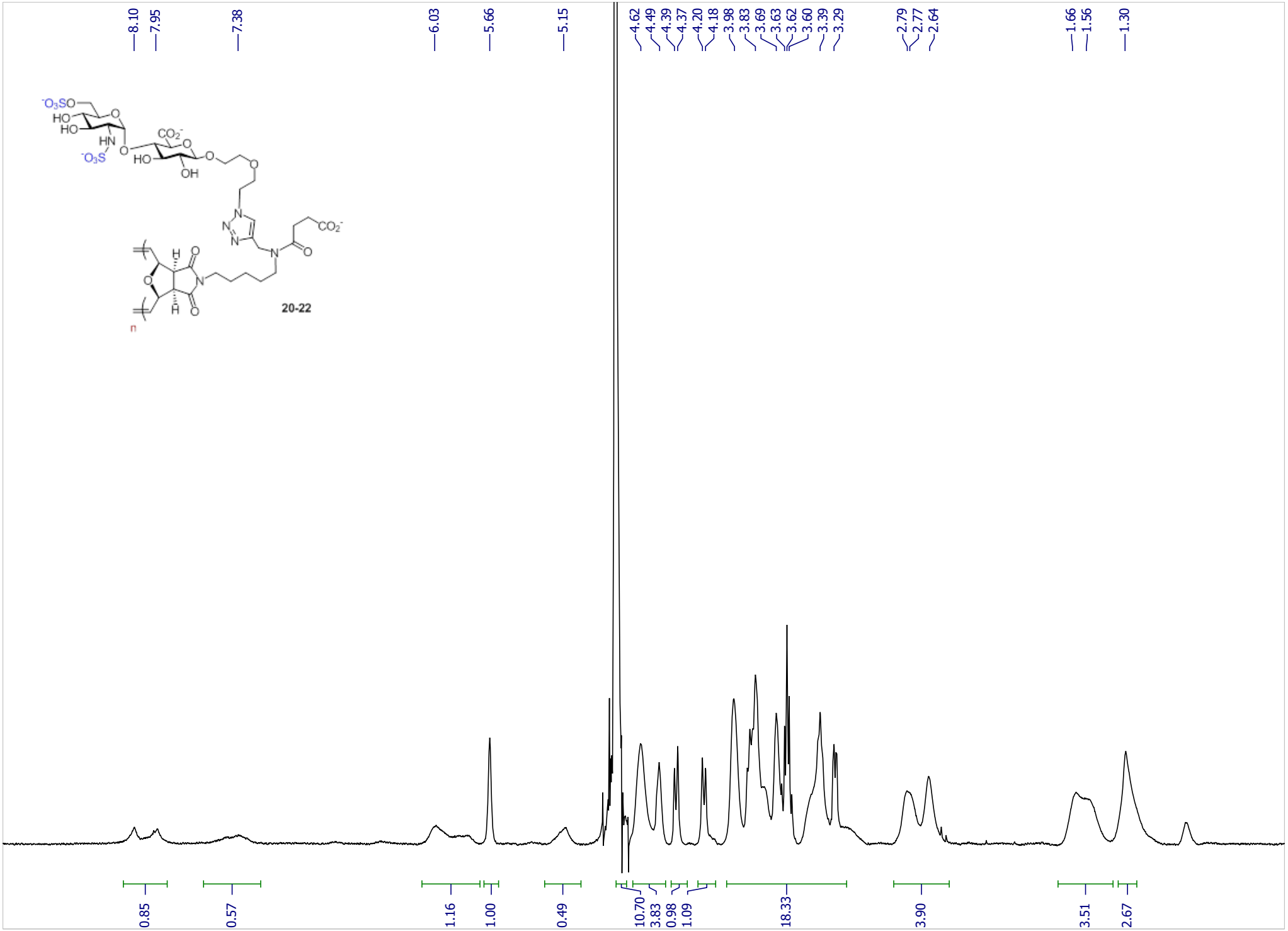
8.14 7.94 7.47 7.32 7.25 5.95 5.70 5.55 5.40 4.98 4.96 4.94 4.59 4.44 4.25 4.19 4.17 4.03 3.90 3.82 3.67 3.01 2.88 2.67 2.11 1.65 1.64 1.61 1.54 1.33 1.32 1.31 1.27 1.26

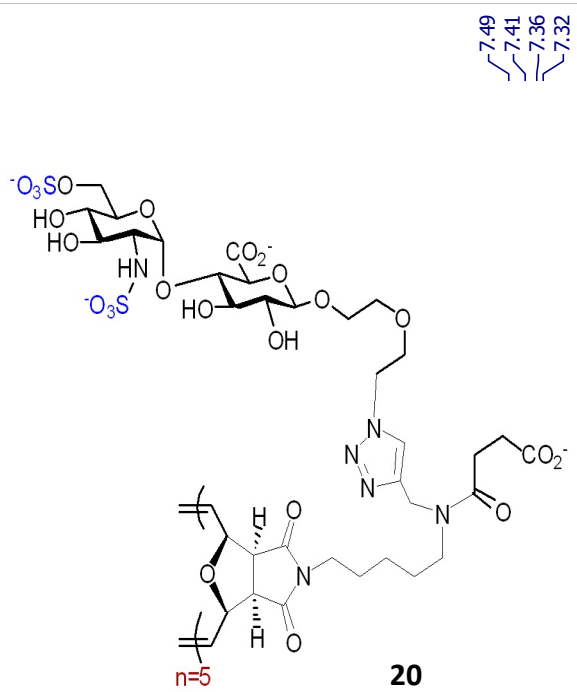
5.00 5.16

f1 (ppm)


7.47
7.35
7.27
5.57
$^{-}O_3SO$
HO
AcO
HN
$^{-}O_3S$
O
HO
CO_2Me
OH
N
N
N
CO_2Me
H
O
N
H
n=9
18
5.00
8.95
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

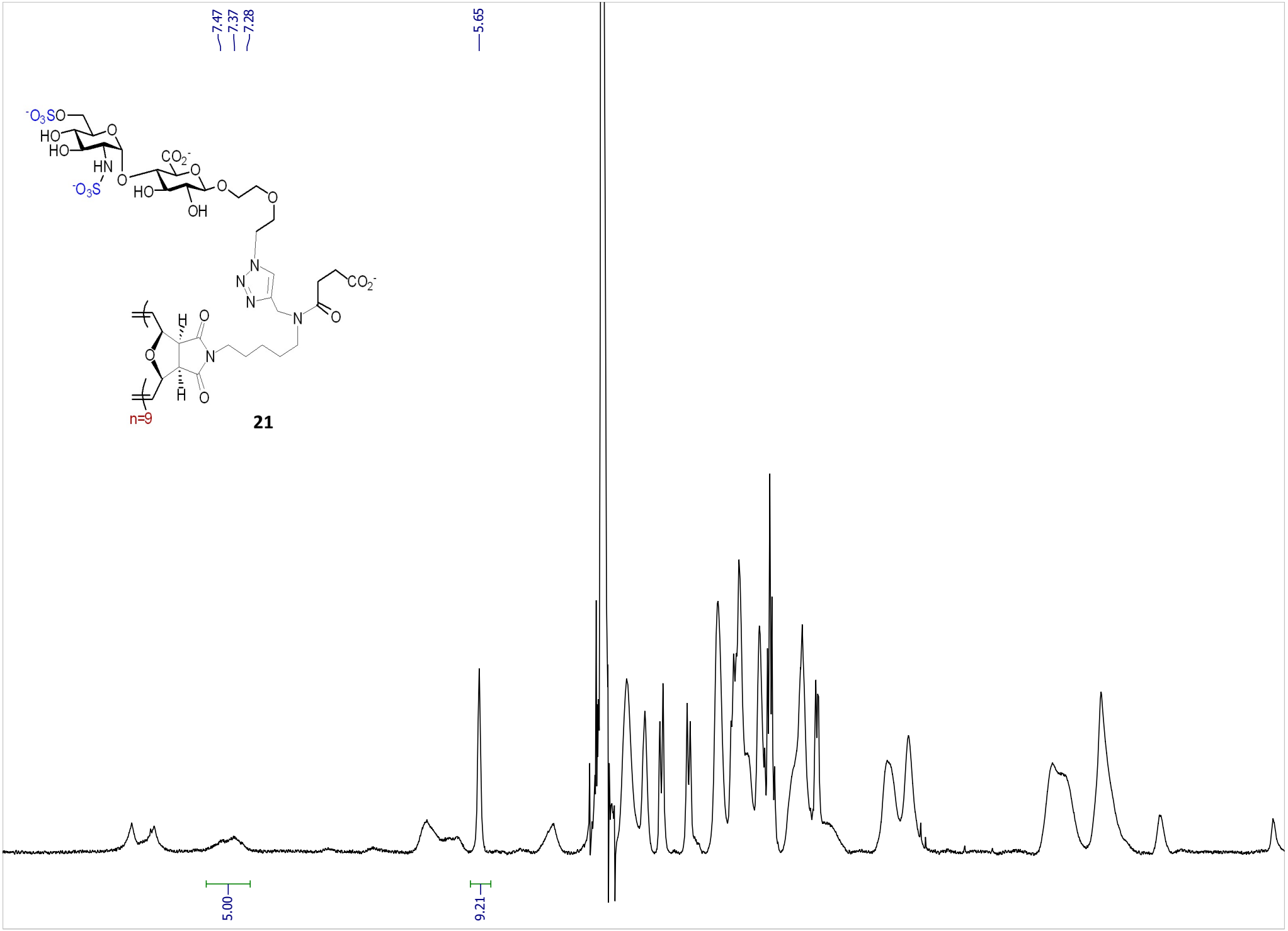

7.46
7.34
7.26
5.56
$^{-}O_3SO$
HO
AcO
HN
$^{-}O_3S$
O
CO_2Me
HO
OH
N
N
N
CO_2Me
O
H
O
N
O
H
O
n=12
19
5.00
12.16
.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

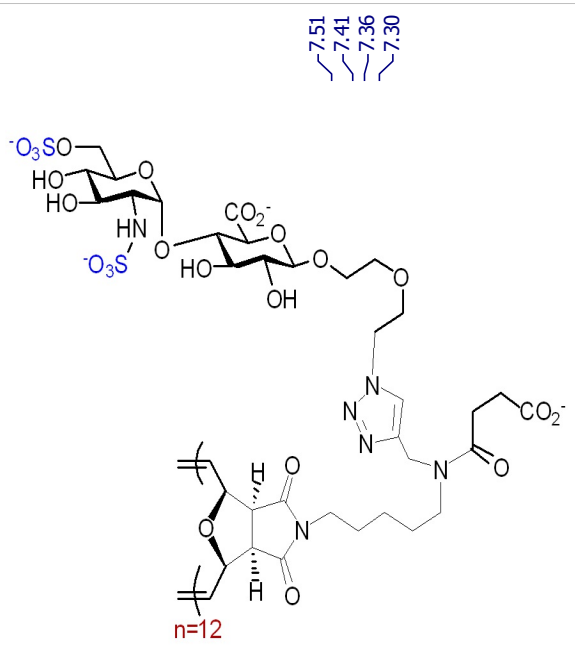

8.10
7.95
7.38
6.03
5.66
5.15
4.62
4.49
4.39
4.37
4.20
4.18
3.98
3.83
3.69
3.63
3.62
3.60
3.39
3.29
2.79
2.77
2.64
1.66
1.56
1.30
20-22
0.85
0.57
1.16
1.00
0.49
10.70
3.83
0.98
1.09
18.33
3.90
3.51
2.67
f1 (ppm)


n=5

20

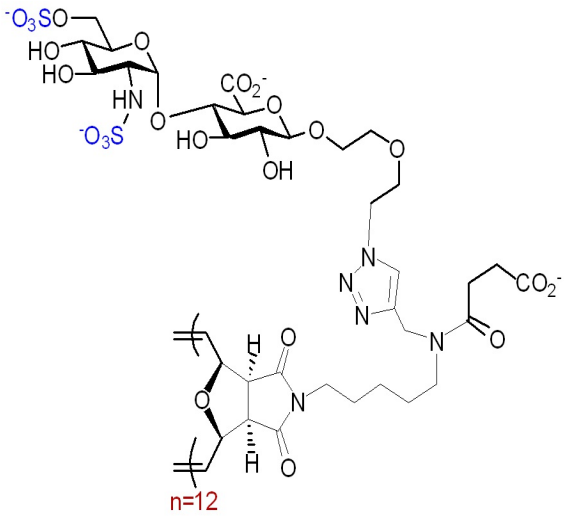
7.49
7.41
7.36
7.32
5.66
5.00
5.57
10.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


7.47
7.37
7.28
5.65
21
n=9
5.00
9.21
f1 (ppm)


n=12

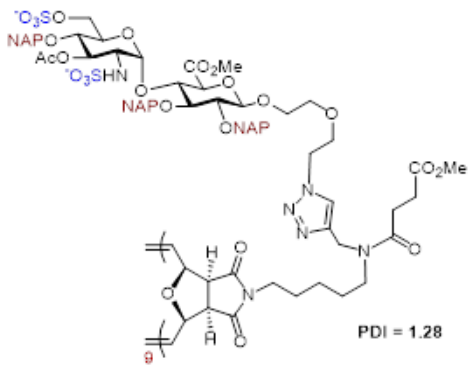
22

7.51
7.41
7.36
7.30
5.65
5.00
12.04
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)

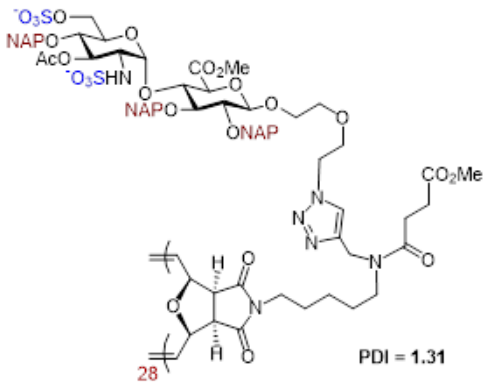

n=12

22

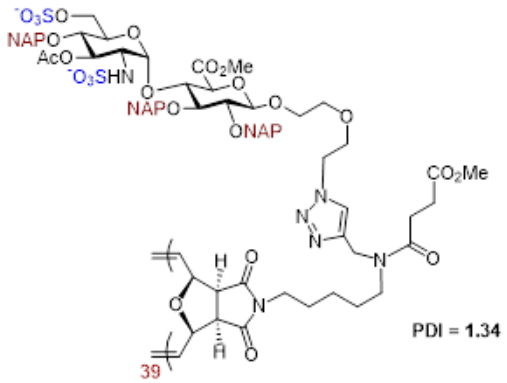
174.98
102.36
97.48
77.04
76.82
76.42
72.84
71.22
69.86
69.78
69.11
68.91
68.79
66.41
58.01
50.04
48.54
48.45
43.13
41.19
29.09
27.48
23.60
210
200
190
180
170
160
150
140
130
120
110
100
90
80
70
60
50
40
30
20
10
f1 (ppm)



f1 (ppm)


$^{-}O_3SO$
NAPO
AcO
$^{-}O_3SHN$
CO_2Me
NAPO
ONAP
CO_2Me
28
PDI = 1.31

7.86
7.82
7.70
7.64
7.45
7.38
5.95
5.62
5.32
5.16
5.02
4.68
4.59
4.46
4.31
4.16
4.09
3.86
3.82
3.57
3.49
3.19
3.15
2.85
2.54
1.97
1.42
1.12
21.00
0.88
1.86
3.82
2.93
2.17
5.12
2.62
7.98
7.22
2.04
1.29
2.51
2.84
3.94
1.25
0.0
9.5
9.0
8.5
8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0
1.5
1.0
0.5
f1 (ppm)


$^{-}O_3SO$
NAPO
AcO
$^{-}O_3SHN$
CO_2Me
NAPO
ONAP
CO_2Me
PDI = 1.34
39

7.83
7.79
7.67
7.61
7.56
7.42
7.34
5.89
5.58
5.29
5.14
5.01
4.99
4.96
4.87
4.64
4.55
4.41
4.28
4.14
4.07
3.82
3.78
3.67
3.53
3.48
3.46
3.10
2.81
2.51
2.45
1.94
1.37
1.05
21.00
0.98
1.98
4.44
3.09
2.62
5.92
2.52
6.50
3.28
6.95
2.47
1.67
3.88
3.02
7.99
2.63
f1 (ppm)