Diazido Macrocyclic Sulfates as a Platform for the Synthesis of Sequence-Defined Polymers for Antibody Drug Conjugates

Neil L. Forsythe, Mikayla F. Tan, and Heather D. Maynard

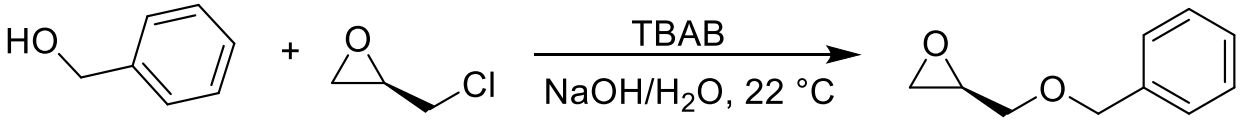
Department of Chemistry and Biochemistry, University of California, Los Angeles, California 90095-1569

Supporting Information – Table of Contents

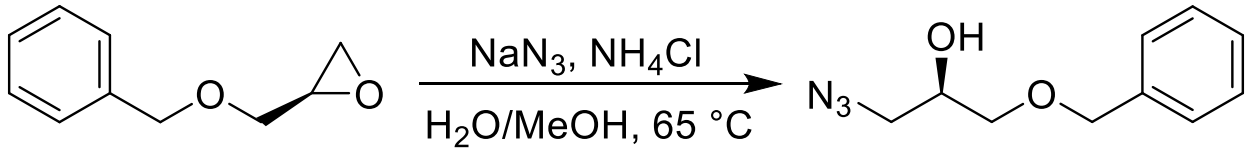
Materials.
R-(-)-Epichlorohydrin was purchased from Oakwood Chemicals. All other chemicals were purchased from Fisher Scientific and were used without purification unless otherwise noted. Herceptin® was purchased from the UCLA pharmacy as a lyophilize powder. Before conjugations the protein was buffer exchanged into PBS (pH=7.4). Whole molecule (Anti-Human IgG (whole molecule)−Peroxidase antibody produced in rabbit) imaging antibodies were purchased from Sigma-Aldrich. Recombinant Human ErbB2/Her2 was purchased from R&D Solutions. Zeba® desalting columns were purchased from Fisher Scientific. PNGase F was purchased from New England BioLabs.

Analytical Techniques.
Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker DRX 500 MHz, Bruker AV 500 MHz, and Bruker AV 600 MHz spectrometer. Mass spectrometry for both proteins and small molecules was obtained on an Agilent Q-TOF 6530 LC/MS. Analytical size exclusion chromatography was performed on an AKTA pure with a UV and Wyatt miniDawn Treos light scattering detectors using a Wyatt WTC-020S5 column. Preparatory reverse phase high performance liquid chromatography (RP-HPLC) was performed on an Agilent 1290 Infinity II system with an open bed sampler/fraction collector equipped with a UV detector using a Luna 5 µm C18 100A column (5 µm, 250 x 21.2 mm). Small molecule purification was done via flash chromatography on a Biotage Isolera One auto-column system. UV-Vis measurements were conducted on a SpectraMax iD3 plate reader. As a safety precaution, all azides were handled behind the protection of a blast shield.

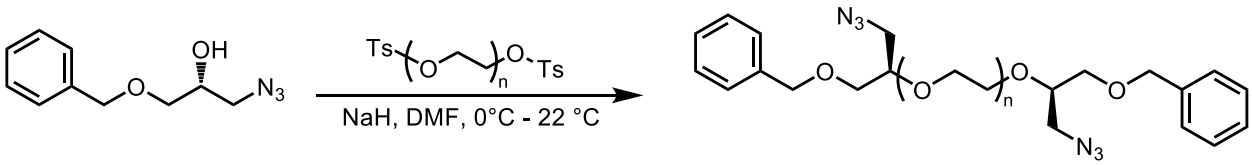
Experimental Methods



(R)-2-((Benzyloxy)methyl)oxirane.[1] To a round-bottom flask, NaOH (110 g, 2.9 mol, 13 equivalents) and tetrabutylammonium bromide (3.9 g, 12 mmol, 0.055 equivalents) were dissolved in 180 mL of water and cooled to 0 °C. Next, (R)-(-)-epichlorohydrin (26 mL, 0.33 mol, 1.5 equivalents) was added to the vigorously stirring solution. Benzyl alcohol (23 mL, 0.22 mol, 1.0 equivalents) was then added dropwise to the solution and the reaction was allowed to proceed for 3 h. The reaction mixture was then added to a separatory funnel and extracted three times with ether and dried with magnesium sulfate ($MgSO_4$). The crude was then purified via Biotage with an 8:2 hexanes:ethyl acetate (EtOAc) isocratic mobile phase to yield the product as a clear oil (25.9 g, 71%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.35 (m, *J* = 4.4 Hz, 5H), 4.64 – 4.53 (m, 2H), 3.78 (dd, *J* = 11.4, 3.0 Hz, 1H), 3.44 (dd, *J* = 11.4, 5.9 Hz, 1H), 3.20 (m, 1H), 2.81 (m, 1H), 2.63 (dd, *J* = 5.0, 2.7 Hz, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 137.92, 128.46, 127.79, 73.35, 70.84, 50.89, 44.32. IR: ν = 3031, 2999, 2860, 1736, 1453, 1244, 1092, 845, 736.



(R)-1-Azido-3-(benzyloxy)propan-2-ol.[2] In a round-bottom flask, (R)-benzyl oxirane (36 g, 0.22 mol, 1 equivalent), ammonium chloride (23 g, 0.44 mol, 2 equivalents), and sodium azide (43 g, 0.66 mol, 3 equivalents) were suspended in 200 mL of methanol and 50 mL of H_2O. The reaction was heated to 65 °C and allowed to proceed for 12 h. Methanol (MeOH) was then removed via rotary evaporation and the product was then extracted three times with diethyl ether. The organic layers were dried with $MgSO_4$ and concentrated to yield the product as a clear oil (32.95g, 73%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.39 – 7.31 (m, 5H), 4.57 (s, 2H), 3.97 (m, 1H), 3.57 – 3.48 (m, 2H), 3.43 – 3.35 (m, 2H), 2.45 (broad s, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 137.59, 128.57, 128.01, 127.88, 73.59, 71.36, 69.71, 53.51. IR: ν = 3424, 2866, 2095, 1453, 1275, 1088, 1074, 737, 697.



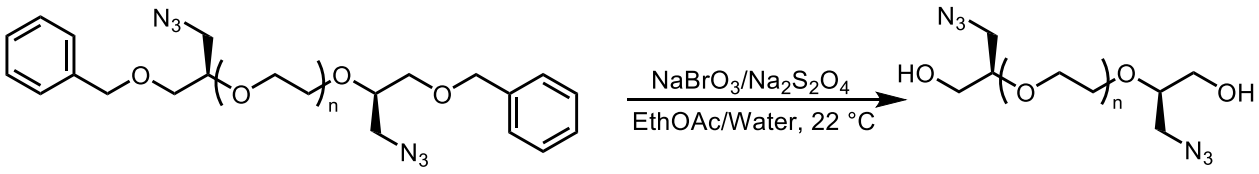
General Procedure of Dibenzylated azido PEGs (using dibenzyl-azido tetraethylene glycol as example). (R)-1-Azido-3-(benzyloxy)propan-2-ol (5.03 g, 24.3 mmol, 2.05 equivalents) was dissolved in dry dimethylformamide (DMF) (0.5 M) and cooled to 0 °C. Sodium hydride (60% dispersion, 2.37 g, 59.2 mmol, 5 equivalents) was added portion wise and the reaction was allowed to stir for 5 min. Diethylene glycol ditosylate (4.91 g, 11.8 mmol, 1 equivalents) was then added and reaction was allowed to proceed for 8 h 22 °C. Methanol was then added slowly to the reaction to quench remaining sodium hydride, and the solution was added to a separatory funnel. 100 mL of water (H_2O) was then added to the separatory funnel and the crude was extracted from DMF/H_2O three times with hexanes. The pooled hexanes layers were then dried with $MgSO_4$ and evaporated. The crude was then purified via flash chromatography with a hexanes:ether gradient (0% ether to 100% ether) to yield the product as a clear oil (2.51 g, 44%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.38 – 7.27 (m, 10H), 4.53 (s, 4H), 3.79 – 3.75 (m, 2H), 3.74 – 3.63 (m, 8H), 3.56 (dd, J = 9.9, 4.9 Hz, 2H), 3.51 (dd, J = 10.0, 5.9 Hz, 2H), 3.37 (d, J = 5.1 Hz, 4H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 137.92, 128.44, 127.78, 127.69, 78.53, 73.49, 70.85, 69.91, 69.53, 51.97. IR: ν = 2867, 2094, 1738, 1453, 1365, 1277, 1092, 736 cm^{-1}. HRMS (ESI) calculated for $C_{24}H_{32}N_6O_5$ $[M+NH_4]^+$ = 502.2777, observed = 502.2832.

Dibenzyl-Azido pentaethylene glycol. Product isolated as a clear oil (43%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.40 – 7.27 (m, 10H), 4.53 (s, 4H), 3.82 – 3.62 (m, 14H), 3.59 – 3.48 (m, 4H),

3.37 (d, J = 5.1 Hz, 4H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 137.92, 128.44, 127.78, 127.69, 78.54, 73.50, 70.79, 70.66, 69.92, 69.52, 51.98. IR: ν = 2866, 2094, 1453, 1277, 1092, 736, 697 cm^{-1}. HRMS (ESI) calculated for $C_{10}H_{18}N_6O_7S$ [M+NH_4] = 546.3040, observed = 546.3168.

Dibenzyl-Azido hexaethylene glycol. Product isolated as a clear oil (47%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.39 – 7.26 (m, 10H), 4.53 (s, 4H), 3.82 – 3.60 (m, 18H), 3.59 – 3.48 (m, 4H), 3.37 (d, J = 5.2 Hz, 4H). ^{13}C NMR (126 MHz, chloroform-*d*) δ ^{13}C NMR (126 MHz, Chloroform-*d*) δ 137.92, 128.44, 127.78, 127.69, 78.54, 73.50, 70.78, 70.65, 70.59, 69.92, 69.52, 51.98. IR: ν = 2865, 2095, 1738, 1453, 1278, 1094, 736 cm^{-1}. HRMS (ESI) calculated for $C_{28}H_{40}N_6O_7$ [M+NH_4]$^+$ = 590.3302, observed = 590.3405.

Dibenzyl-Azido heptaethylene glycol. Product isolated as a clear oil (41%). ^{1}H NMR (500 MHz, chloroform-*d*) δ 7.38 – 7.26 (m, 10H), 4.53 (s, 4H), 3.78 (m, 2H), 3.74 – 3.61 (m, 20H), 3.58 – 3.49 (m, 4H), 3.37 (d, J = 5.2 Hz, 4H).^{13}C NMR (126 MHz, chloroform-*d*) δ 137.92, 128.44, 127.77, 127.69, 78.54, 73.49, 70.79, 70.65, 70.59, 69.92, 69.53, 51.98. IR: ν = 2866, 2095, 1738, 1614, 1453, 1278, 1097, 737 cm^{-1}. HRMS (ESI) calculated for $C_{30}H_{44}N_6O_8$ [M+NH_4]$^+$ = 634.3564, observed = 634.3706.



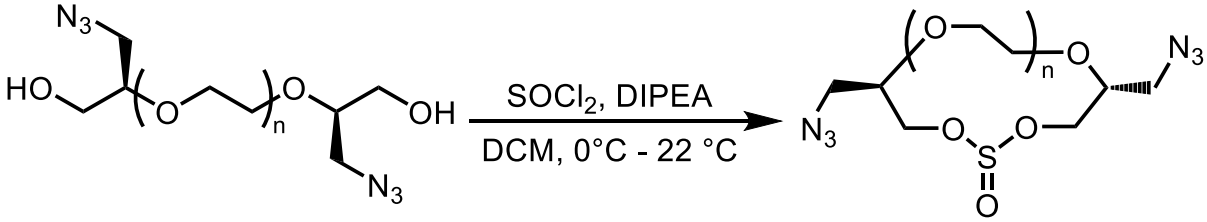
General Debenzylation Procedure (using tetraethylene glycol diazide as an example). Dibenzylazide tetraethylene glycol (21.79 g, 44.97 mmol, 1 equivalent) was dissolved in 50 mL of EtOAc in a round-bottom flask. Sodium bromate (20.36 g, 134.9 mmol, 3 equivalents) was dissolved in 100 mL of water and added to the vigorously stirring solution. Sodium dithionite (23.49 g, 134.9 mmol, 3 equivalents) was dissolved in water and added to an addition funnel. The dithionite solution was added slowly over the course of 2 h (caution: reaction auto-heats rapidly if solution is added too quickly). After addition, the reaction was allowed to stir at 22 °C for 1 h. The biphasic solution was then transferred to a separatory funnel and the organic layer was collected. The aqueous layer was the extracted three times with EtOAc and the pooled organic layers were dried with $MgSO_4$ and concentrated to yield the crude. The resulting oil was then purified via flash chromatography with a first isocratic 100% EtOAc mobile phase over 5 column volumes to elute the UV active byproducts followed by an isocratic dichloromethane (DCM)+5% MeOH mobile phase to elute the product as a clear oil (12.51 g, 91 %). ^{1}H NMR (600 MHz, chloroform-*d*) δ 3.91 – 3.86 (m, 2H), 3.83 – 3.70 (m, 6H), 3.63 – 3.52 (m, 6H), 3.41 (dd, J = 12.9, 7.4 Hz, 2H), 3.22 (dd, J = 12.9, 4.2 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 80.76, 70.61, 69.39, 62.42, 51.67. IR: ν = 3408, 2921, 2092, 1447, 1343, 1274, 1104, 1069, 954, 833 cm^{-1}. HRMS (ESI) calculated for $C_{10}H_{20}N_6O_5$ [M+Na]$^+$ = 327.1392, observed: 327.1417.

Pentaethylene glycol diazide. Product isolated as a clear oil (74%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 3.84 (m, 2H), 3.78 (m, 2H), 3.74 – 3.51 (m, 16H), 3.41 (dd, J = 12.9, 7.3 Hz, 2H),

3.23 (dd, J = 12.9, 4.1 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 80.50, 70.82, 70.27, 69.59, 62.18, 51.75. IR: ν = 3433, 2873, 2093, 1739, 1447, 1346, 1275, 1100, 1071, 947, 837 cm^{-1}. HRMS (ESI) calculated for $C_{12}H_{24}N_6O_6$ [M+NH$_4$] = 366.2101, observed = 366.2139.

*Hexaethylene glycol diazide***.** Product isolated as a clear oil (75%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 3.87 (m, 2H), 3.76 (m, 2H), 3.72 – 3.55 (m, 18H), 3.39 (dd, J = 12.9, 6.9 Hz, 2H), 3.26 (dd, J = 12.8, 4.0 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 80.49, 70.93, 70.49, 70.38, 69.68, 62.24, 51.74. IR: ν = 3433, 2872, 2094, 1738, 1450, 1347, 1275, 1096, 1074, 947, 837 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_{28}N_6O_7$ [M+H]$^+$ = 393.2097, observed = 393.2175.

*Heptaethylene glycol diazide***.** Product isolated as a clear oil (80%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 3.88 (ddd, J = 11.3, 4.3, 2.6 Hz, 2H), 3.79 – 3.54 (m, 24H), 3.39 (dd, J = 12.9, 7.0 Hz, 2H), 3.33 (s, 2H), 3.26 (dd, J = 12.9, 4.1 Hz, 2H). ^{13}C NMR (126 MHz, chloroform-*d*) δ 80.45, 70.89, 70.48, 70.45, 70.40, 69.71, 62.27, 51.76. IR: ν = 3421, 2873, 2094, 1450, 1346, 1277, 1094, 947 cm^{-1}. HRMS (ESI) calculated for HRMS (ESI) calculated for $C_{16}H_{32}N_6O_8$ [M+H]$^+$ = 437.2359, observed = 437.2495.



General Procedure for Macrocyclic Sulfite Synthesis (using tetraethylene glycol diazide macrocyclic sulfite as an example).[3] To a round-bottom flask, tetraethylene glycol diazide (2.85 g, 9.37 mmol, 1 equivalent) and diisopropylethylamine (DIPEA, 7.9 mL, 45 mmol, 4.8 equivalents) was dissolved in DCM (60 mM) under argon. The reaction was cooled to 0 °C and thionyl chloride (1 molar solution in DCM, 18.7 mL, 18.7 mmol, 2 equivalents) was added dropwise over the course of 1 h. The reaction was then allowed to stir for 1 h at 22 °C before the addition of cold brine. The solution was then transferred to a separatory funnel and the organic layer was collected. The aqueous layer was then extracted three times with DCM and the pooled organic layers were dried with $MgSO_4$. The crude was then concentrated and purified via flash chromatography with a hexanes:EtOAc gradient (0-100% EtOAc) to yield the product as black oil (2.35 g, 72%). Note: macrocyclic sulfites show some degradation on silica, therefore dry loading can lead to decreased yields. ^{1}H NMR (400 MHz, chloroform-*d*) δ 4.30 (dd, J = 10.7, 5.9 Hz, 1H), 4.21 (dd, J = 10.5, 4.7 Hz, 1H), 4.13 (dd, J = 10.5, 4.6 Hz, 1H), 3.97 – 3.68 (m, 9H), 3.63 – 3.54 (m, 2H), 3.47 – 3.31 (m, 4H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 77.90, 77.60, 70.72, 70.62, 70.53, 70.47, 62.47, 61.05, 51.74, 51.65. IR: ν = 2924, 2871, 2093, 1448, 1293, 1275, 1202, 1116, 956, 738 cm^{-1}. HRMS (ESI) calculated for $C_{10}H_{18}N_6O_6S$ [M+NH$_4$]$^+$ = 368.1352, observed: 368.1417.

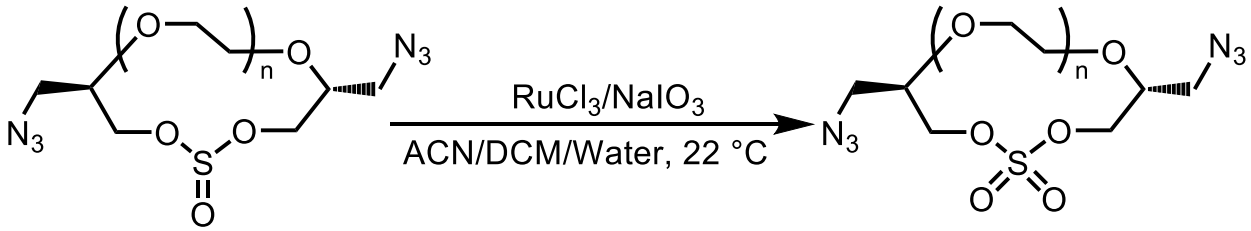
Pentaethylene glycol diazide macrocyclic sulfite. Product isolated as a black oil (64%). ^{1}H NMR (400 MHz, acetonitrile-d_3) δ 4.15 (dd, J = 11.5, 4.7 Hz, 1H), 4.11 – 3.98 (m, 3H), 3.82 – 3.66 (m, 6H), 3.55 (m, 8H), 3.43 – 3.28 (m, 4H). ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 77.35, 77.07, 70.55,

70.44, 70.32, 70.29, 70.20, 70.07, 62.49, 61.32, 51.22, 51.10. IR: ν = 2875, 2094, 1735, 1450, 1347, 1277, 1203, 1106, 949, 731 cm^{-1}. HRMS (ESI) calculated for $C_{12}H_{22}N_6O_7S$ $[M+Na]^+$ = 417.1168, observed 417.1124.

Hexaethylene glycol diazide macrocyclic sulfite. Product isolated as a black oil (53%). ^1H NMR (400 MHz, acetonitrile-d_3) δ 4.15 – 3.99 (m, 4H), 3.86 – 3.79 (m, 2H), 3.77 – 3.67 (m, 4H), 3.61 – 3.51 (m, 12H), 3.45 – 3.30 (m, 4H). ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 77.02, 76.82, 70.74, 70.64, 70.32, 70.30, 70.27, 70.23, 69.56, 69.52, 62.29, 61.08, 50.96, 50.90. IR: ν = 2872, 2100, 1738, 1452, 1350, 1296, 1206, 1114, 955, 832, 746 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_{26}N_6O_8S$ $[M+Na]^+$ = 461.1430, observed = 461.1364.

Heptaethylene glycol diazide macrocyclic sulfite. Product isolated as a black oil (34%). ^1H NMR (500 MHz, Acetonitrile-d_3) δ 4.12 – 3.97 (m, 4H), 3.80 (m, 2H), 3.74 (m, 4H), 3.62 – 3.54 (m, 16H), 3.48 – 3.33 (m, 4H). ^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 77.20, 77.13, 70.62, 70.58, 70.39, 70.37, 70.25, 69.68, 69.66, 61.68, 61.36, 50.91. IR: ν = 2870, 2098, 1755, 1450, 1348, 1295, 1204, 1112, 955, 743 cm^{-1}. HRMS (ESI) calculated for $C_{16}H_{30}N_6O_9S$ $[M+NH_4]^+$ = 500.2138, observed = 500.2230.

Tetraethylene glycol macrocyclic sulfite.[3] Product isolated as a black oil (82 %). ^1H NMR (300 MHz, chloroform-*d*) δ 4.39 (m, *J* = 2H), 4.21 – 4.08 (m, 2H), 3.91 – 3.65 (m, 12H). ^{13}C NMR (126 MHz, ccetonitrile-d_3) δ 70.35, 70.14, 69.25, 62.04. IR: ν = 2868, 1638, 1449, 1200, 1113, 1013, 929, 875, 710 cm^{-1}.



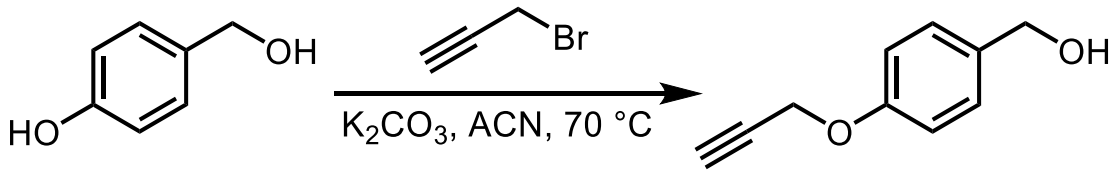
General Procedure for Macrocyclic Sulfite Oxidation (using tetraethylene glycol diazide macrocyclic sulfate as an example), adapted from Zhang *et al*.[3] To a round-bottom flask, tetraethylene glycol diazide macrocyclic sulfite (2.35 g, 6.71 mmol, 1 equivalent) was dissolved in 1:1:2 acetonitrile:DCM:water (70 mM) and stirred vigorously. Next, ruthenium chloride (70 mg, 335 µmol, 0.05 equivalents) and sodium periodate (14.3 g, 67.1 mmol, 10 equivalents) were added sequentially and the reaction was allowed to proceed at 22 °C for 4 h. The solution was then transferred to separatory funnel and the organic layer was collected. The aqueous layer was then extracted with DCM three times and the pooled organic layers were then dried with $MgSO_4$ and the solution was filtered through celite. The resulting filtrate was concentrated and purified via flash chromatography with a hexanes:EtOAc gradient (0 to 100% ethyl acetate) to yield the product as a white solid (2.22g, 90%). ^1H NMR (400 MHz, chloroform-*d*) δ 4.45 (dd, *J* = 10.1, 5.3 Hz, 2H), 4.33 (dd, *J* = 10.1, 4.7 Hz, 2H), 3.96 – 3.89 (m, 2H), 3.88 – 3.70 (m, 6H), 3.61 – 3.52 (m, 2H), 3.46 – 3.34 (m, 4H). ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 76.47, 72.36, 70.15, 70.07, 50.73. IR: ν = 2941, 2879, 2095, 1737, 1448, 1400, 1192, 1014, 924, 861, 831 cm^{-1}. HRMS (ESI) calculated for $C_{10}H_{18}N_6O_7S$ $[M+NH_4]^+$ = 389.0855, observed = 389.0879.

Pentaethylene glycol diazide macrocyclic sulfate. Product isolated as a clear oil (59%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 4.39 (dd, *J* = 5.0, 0.9 Hz, 4H), 3.92 – 3.76 (m, 6H), 3.72 – 3.57 (m, 8H), 3.49 – 3.35 (m, 4H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 81.55, 77.62, 75.74, 75.68, 75.65, 56.01. IR: ν = 2874, 2097, 1738, 1451, 1393, 1277, 1193, 1106, 960, 929, 858 cm^{-1}. HRMS (ESI) calculated for $C_{12}H_{22}N_6O_8S$ $[M+Na]^+$ = 433.1117, observed = 433.1057.

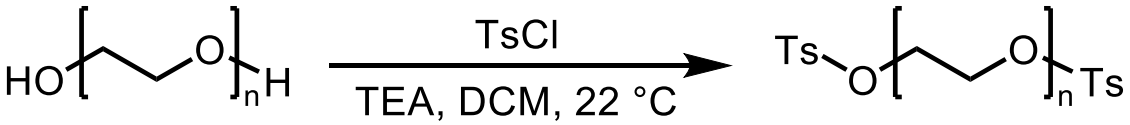
Hexaethylene glycol diazide macrocyclic sulfate. Product isolated as a clear oil (60%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 4.45 – 4.35 (m, 4H), 3.96 (m, 2H), 3.90 – 3.77 (m, 4H), 3.75 – 3.60 (m, 12H), 3.42 (d, *J* = 5.4 Hz, 4H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 76.33, 72.11, 71.34, 70.69, 70.62, 70.02, 51.00. IR: ν = 2872, 2098, 1737, 1713, 1450, 1392, 1194, 1104, 997, 980, 862 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_{26}N_6O_9S$ $[M+Na]^+$ = 477.1379, observed = 477.1254.

Heptaethylene glycol diazide macrocyclic sulfate. Product isolated as a clear oil (88%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 4.44 – 4.34 (m, 4H), 3.91 (m,2H), 3.87 – 3.78 (m, 4H), 3.70 – 3.61 (m, 16H), 3.51 – 3.38 (m, 4H). ^{13}C NMR (101 MHz, acetonitrile-d_3) δ 76.23, 72.42, 70.58, 70.26, 70.25, 70.15, 69.74, 50.49. IR: ν = 2873, 2098, 1738, 1451, 1394, 1194, 1105, 994, 926, 861 cm^{-1}. HRMS (ESI) calculated for $C_{16}H_{30}N_6O_{10}S$ $[M+NH_4]^+$ = 516.2087, observed = 516.2138.

Tetraethylene glycol macrocyclic sulfate.[3] Product isolated as a clear oil (61%). ^{1}H NMR (400 MHz, Chloroform-*d*) δ 4.51 – 4.44 (m, 4H), 3.88 – 3.81 (m, 4H), 3.72 – 3.61 (m, 8H). ^{13}C NMR (126 MHz, Acetonitrile-d_3) δ 72.90, 70.33, 70.13, 68.09. IR: ν = 2871, 1729, 1287, 1191, 1124, 1004, 920 cm^{-1}.



(4-(Prop-2-yn-1-yloxy)phenyl)methanol Synthesis.[4] To a round-bottom flask with a stir bar, K_2CO_3 (14 g, 100 mmol, 5 equivalents) and 4-(hydroxymethyl)phenol (2.5 g, 20 mmol, 1 equivalent) were added and suspended in 30 mL of acetonitrile. Propargyl bromide (80% in toluene, 2.7 mL, 24 mmol, 1.2 equivalents) was then added dropwise and the reaction was stirred at 70 °C for 5 h. The reaction was then cooled, filtered through celite, concentrated, and dissolved in dichloromethane. The remaining insoluble precipitate was then filtered through a 0.45 μM filter and concentrated to yield the pure product as an orange oil (1.47 g, 45%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.32 (d, *J* = 8.7 Hz, 2H), 6.98 (d, *J* = 8.7 Hz, 2H), 4.70 (d, *J* = 2.4 Hz, 2H), 4.64 (s, 2H), 2.52 (t, *J* = 2.4 Hz, 1H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 157.16, 134.09, 128.61, 115.03, 78.52, 75.56, 65.01, 55.87. IR: ν = 3283, 2922, 2871, 1739, 1609, 1509, 1212, 1022, 1008, 811 cm^{-1}. HRMS (ESI) calculated for $C_{10}H_{10}O_2$ $[M+H]^+$ = 163.0759, observed = 163.0717.



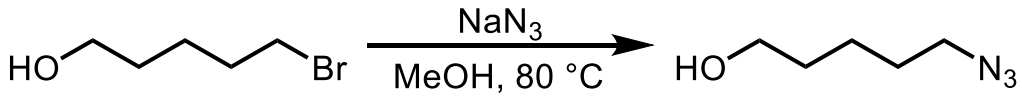
General Ditosylation Procedure (using diethylene glycol ditosylate as an example). Diethylene glycol (7.0 mL, 73 mmol, 1 equivalent), triethylamine (30 mL, 0.22 mol, 3 equivalents), and tosyl

chloride (31 g, 0.16 mol, 2.2 equivalents) were dissolved in 150 mL of dichloromethane in a round-bottom flask. The reaction was allowed to proceed for 4 h and the crude was transferred to a separatory funnel. The organic layer was then washed with water once, followed by one wash with 1 M HCl. The organic layer was dried over $MgSO_4$ and dried to yield the crude solid. The product was then recrystallized by first dissolving in hot toluene followed by a slow addition of 14 mL of petroleum ether. The crystalized product was then collected via filtration and washed with cold toluene (20.54 g, 68%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.79 (d, *J* = 8.3 Hz, 2H), 7.35 (d, *J* = 7.9 Hz, 2H), 4.13 – 4.06 (m, 2H), 3.64 – 3.59 (m, 2H), 2.45 (s, 3H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 144.98, 132.87, 129.92, 127.97, 69.01, 68.77, 21.68. IR: ν = 2900, 1597, 1351, 1170, 1017, 916, 814 cm^{-1}. HRMS (ESI) calculated for $C_{18}H_{22}O_7S_2$ $[M+H]^+$ = 415.0885, observed = 415.0992.

Triethylene glycol ditosylate. Product purified via flash chromatography with a 7:3 hexanes:EtOAc isocratic mobile phase to yield the product was a white solid (56%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (d, *J* = 8.3 Hz, 4H), 7.34 (d, *J* = 7.9 Hz, 4H), 4.17 – 4.09 (m, 4H), 3.68 – 3.62 (m, 4H), 3.52 (s, 4H), 2.44 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 144.86, 132.97, 129.85, 127.97, 70.70, 69.21, 68.76, 21.66. IR: ν = 2876, 1597, 1451, 1351, 1173, 914, 814, 772, 661 cm^{-1}. HRMS (ESI) calculated for $C_{20}H_{26}O_8S_2$ $[M+H]^+$ = 459.1147, observed = 459.1175.

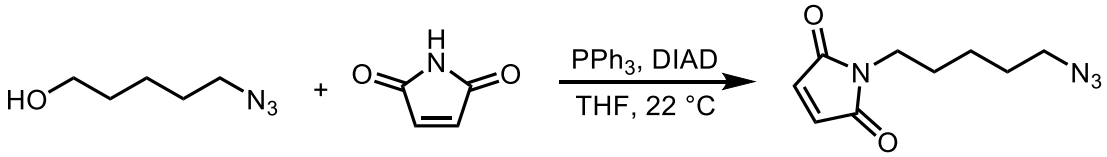
Tetraethylene glycol ditosylate. Product purified via flash chromatography with a 7:3 hexanes:EtOAc isocratic mobile phase to yield the product as a clear oil (56%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 7.79 (d, *J* = 8.3 Hz, 4H), 7.33 (d, *J* = 8.0 Hz, 4H), 4.18 – 4.13 (m, 4H), 3.71 – 3.66 (m, 4H), 3.60 – 3.52 (m, 8H), 2.44 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 144.82, 132.99, 129.84, 127.98, 70.75, 70.56, 69.27, 68.70, 21.66. IR: ν = 2873, 1737, 1597, 1451, 1351, 1173, 913, 814, 771 cm^{-1}. HRMS (ESI) calculated for $C_{22}H_{30}O_9S_2$ $[M+H]^+$ = 503.1409, observed = 503.1497.

Pentaethylene glycol ditosylate. Product purified via flash chromatography with a 0-100% hexanes:EthOAc gradient (0% ethyl acetate to 100%) to yield the product was a clear oil. ^{1}H NMR (300 MHz, chloroform-*d*) δ 7.79 (d, *J* = 8.3 Hz, 4H), 7.34 (d, *J* = 7.9 Hz, 4H), 4.17 – 4.13 (m, 4H), 3.70 – 3.64 (m, 4H), 3.59 (d, *J* = 6.4 Hz, 12H), 2.44 (s, 6H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 144.83, 133.01, 129.85, 127.99, 70.76, 70.61, 70.52, 69.28, 68.68, 21.65. IR: ν = 2871, 1734, 1597, 1352, 1174, 1095, 1012, 915, 815, 772, 661 cm^{-1}. HRMS (ESI) calculated for $C_{24}H_{34}O_{10}S_2$ $[M+H]^+$ = 547.1671, observed = 547.1776.

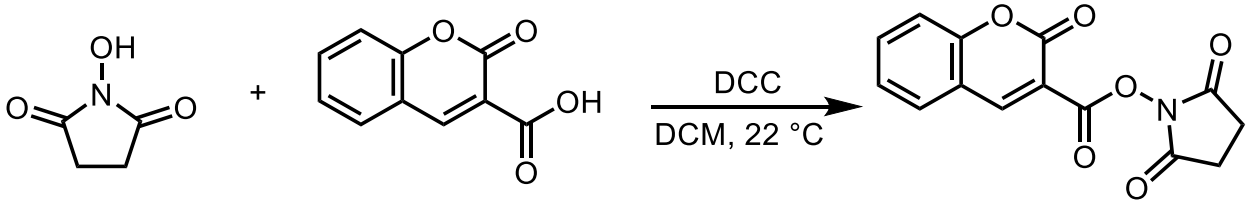


5-Azido-pentan-1-ol.[5] To a scintillation vial with a stir bar, sodium azide (1.41 g, 21.7 mmol, 3 equivalents) and 5-bromopentan-1-ol (1.21 g, 7.24 mmol, 1 equivalent) was added. The reagents were dissolved in 10 mL of methanol and the reaction was heated to 80 °C for 10 h. The reaction was then cooled and the crude was dry-loaded onto silica. The product was then purified via flash chromatography with a hexanes:EtOAc gradient (0% EtOAc to 100% EtOAc) to yield the product as a clear oil (574 mg, 61%). ^{1}H NMR (400 MHz, chloroform-*d*) δ 3.65 (t, *J* = 6.4 Hz, 2H), 3.28 (t, *J* = 6.9 Hz, 2H), 1.69 – 1.55 (m, 4H), 1.49 – 1.39 (m, 2H). ^{13}C NMR (101 MHz, chloroform-*d*)

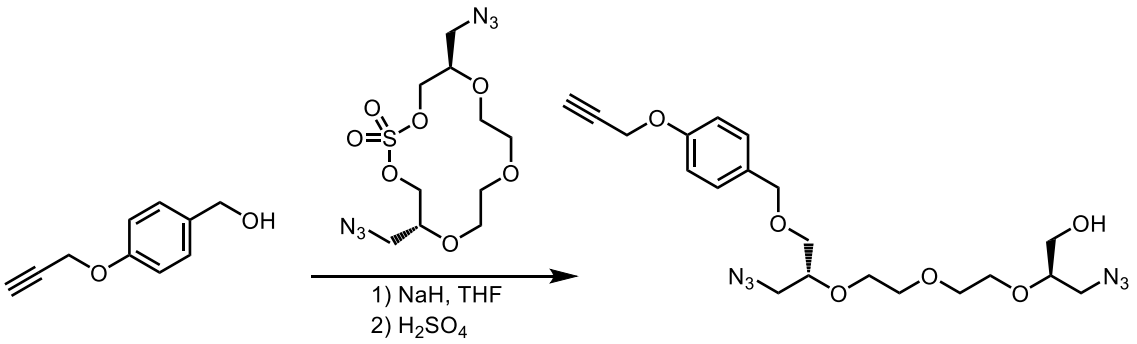
δ 62.60, 51.40, 32.17, 28.66, 23.01. IR: ν = 3325, 2936, 2865, 2090, 1455, 1348, 1259, 1052 cm^{-1}.



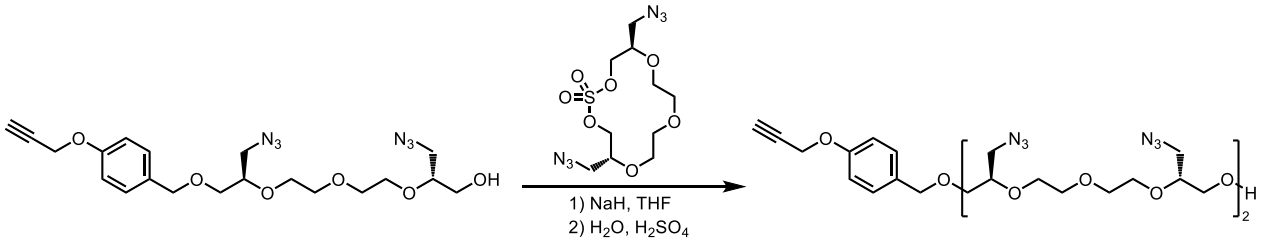
5-Azidopentyl-1-maleimide. Triphenylphosphine (305 mg, 1.16 mmol, 1 equivalent) was dissolved in dry THF (5 mL) and cooled to 0 °C. DIAD (226 µL, 1.16 mmol, 1 equivalent) was added then dropwise and reaction was allowed to stir for 15 min at 0 °C. 5-azido-pentan-1-ol (150 mg, 1.16 mmol, 1 equivalent) was then added and reaction was allowed to stir for an additional 15 min at 0 °C. Finally, maleimide (135 mg, 1.39 mmol, 1.2 equivalents) was added and reaction was allowed to stir at 23 °C for 2 h. The product was then concentrated and purified via flash chromatography with a hexanes:EtOAc gradient (0% EtOAc to 50% EtOAc) to yield the product as an oil (119 mg, 49 %). Note: The final product degrades if stored under concentrated conditions. Therefore, after purification, the final material was only concentrated to 10 mg/mL in the hexanes/ EtOAc mixture and dried immediately before use by blowing a stream of air over an aliquoted solution. ^{1}H NMR (600 MHz, chloroform-*d*) δ 6.70 (s, 2H), 3.53 (t, *J* = 7.2 Hz, 2H), 3.26 (t, *J* = 6.9 Hz, 2H), 1.66 – 1.58 (m, 4H), 1.41 – 1.32 (m, 2H).^{13}C NMR (126 MHz, chloroform-*d*) δ 170.82, 134.09, 51.18, 37.53, 28.33, 28.06, 23.86. IR: ν = 2942, 2095, 1703, 1409, 1147, 828, 695 cm^{-1}. HRMS (ESI) calculated for $C_9H_{12}N_4O_2$ $[M+Na]^+$ = 231.0857, observed = 231.0855.



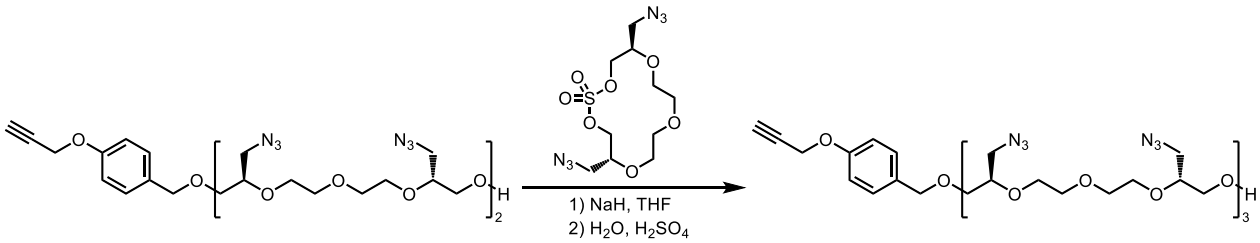
Coumarin-3-carboxylic acid N-succinimidyl ester.[6] Coumarin-3-carboxylic acid (1.0 g, 5.3 mmol, 1 equivalents), dicyclohexylcarbodiimide (DCC, 1.6 g, 7.9 mmol, 1.5 equivalents), and N-hydroxysuccinimide (0.91 g, 7.9 mmol, 1.5 equivalents) was dissolved in 10 mL of DCM in a scintillation vial. The reaction was allowed proceed at 22 °C for 12 h. The reaction was then filtered, concentrated, and purified via flash chromatography with a DCM:EtOAc gradient (0% EtOAc to 50% EtOAc). ^{1}H NMR (300 MHz, acetonitrile-d_3) δ 8.94 (s, 1H), 7.90 – 7.79 (m, 2H), 7.52 – 7.41 (m, 2H), 2.88 (s, 4H). ^{13}C NMR (101 MHz, chloroform-*d*) δ 168.84, 151.94, 136.06, 130.25, 125.36, 117.36, 117.19, 25.68 cm^{-1}. HRMS (ESI) calculated for $C_{14}H_9NO_6$ $[M+H]^+$ = 288.0508, observed = 288.0549.



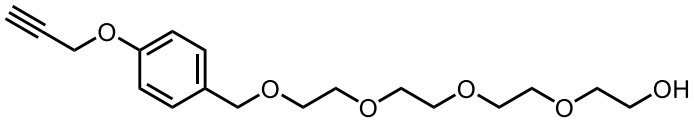
General macrocyclic sulfate ring opening procedure (using tetraethylene glycol diazide macrocyclic sulfate as an example). (4-(Prop-2-yn-1-yloxy)phenyl)methanol (184 mg, 1.14 mmol, 1 equivalent) was dissolved in dry THF (0.3 M) and cooled to 0 °C. Sodium hydride (60 % dispersion in mineral oil, 136 mg, 3.41 mmol, 3 equivalents) was then added and the reaction was stirred for 5 min at 0 °C. Tetraethylene glycol diazide macrocyclic sulfate (625 mg, 1.71 mmol, 1.5 equivalents) was then added and the reaction was allowed to proceed for 12 h at 22 °C. Water (72 µL, 3.98 mmol, 3.5 equivalents) was then added to the stirring mixture dropwise followed by sulfuric acid (90.9 µL, 1.71 mmol, 1.5 equivalents). The reaction was stirred for a further 4 h at 22 °C. The contents were then transferred to a separatory funnel along with 25 mL of DCM and 15 mL of H_2O. The organic layer was collected and the aqueous layer was further extracted 3 times with DCM. The pooled organic layers were dried with $MgSO_4$ and concentrated to yield the crude. The product was then purified via flash chromatography with a DCM:MeOH gradient (0% MeOH to 5% MeOH) to yield the product as an orange oil (402 mg, 79%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 6.96 (d, *J* = 8.7 Hz, 2H), 4.70 (d, *J* = 2.4 Hz, 2H), 4.47 (s, 2H), 3.92 – 3.82 (m, 1H), 3.81 – 3.50 (m, 13H), 3.41 – 3.34 (m, 3H), 3.25 (dd, *J* = 12.9, 4.2 Hz, 1H), 2.53 (t, *J* = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{20}H_{28}N_6O_6$ $[M+NH_4]^+$ = 466.2414, observed = 466.2540.



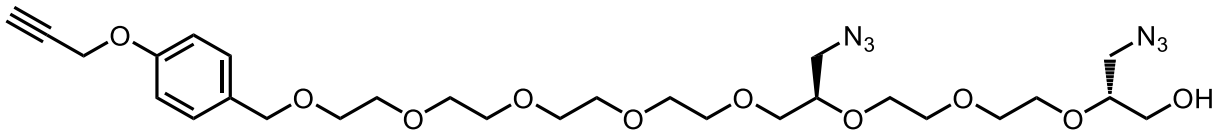
Propargylbenzy (tetra-azide octaethylene glycol). Purified product was isolated as a brown oil (83%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 6.96 (d, *J* = 8.7 Hz, 2H), 4.70 (d, *J* = 2.4 Hz, 2H), 4.47 (s, 2H), 3.89 (m, 2H), 3.82 – 3.47 (m, 41H), 3.42 – 3.30 (m, 10H), 3.26 (dd, *J* = 12.8, 4.3 Hz, 2H), 2.53 (t, *J* = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{30}H_{46}N_{12}O_{10}$ $[M+NH_4]^+$ = 752.3803, observed = 752.3873.



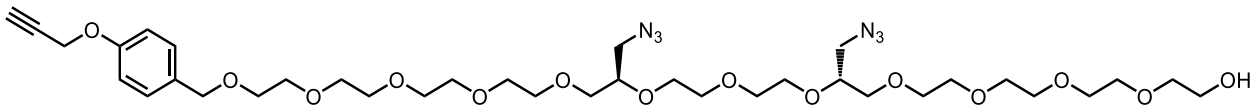
Propargylbenzy (hexa-azide dodecaethylene glycol). Purified product was isolated as a brown oil (87%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 6.96 (d, *J* = 8.6 Hz, 2H), 4.70 (d, *J* = 2.4 Hz, 2H), 4.47 (s, 2H), 3.89 (m, 2H), 3.83 – 3.46 (m, 67H), 3.42 – 3.24 (m, 18H), 2.53 (t, *J* = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{40}H_{64}N_{18}O_{14}$ $[M+NH_4]^+$ = 1038.5193, observed = 1038.5292.



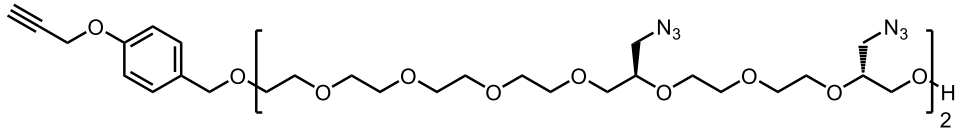
Propargylbenzy (tetraethylene glycol). Purified product was isolated as a brown oil (80%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.29 (d, *J* = 8.8 Hz, 2H), 6.95 (d, *J* = 8.7 Hz, 2H), 4.69 (d, *J* = 2.4 Hz, 2H), 4.50 (s, 2H), 3.74 – 3.70 (m, 2H), 3.67 (m, 10H), 3.63 – 3.60 (m, 4H), 2.52 (t, *J* = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{18}H_{26}O_6$ $[M+NH_4]^+$ = 356.2073, observed = 356.2057.



Propargylbenzy (diazide octaethylene glycol). Purified product was isolated as a brown oil (45%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.69 (d, *J* = 2.4 Hz, 2H), 4.50 (s, 2H), 3.88 (m, 1H), 3.83 – 3.47 (m, 37H), 3.42 – 3.35 (m, 3H), 3.27 – 3.23 (m, 1H), 2.52 (t, *J* = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{28}H_{44}N_6O_{10}$ $[M+NH_4]^+$ = 642.3462, observed = 642.3544.

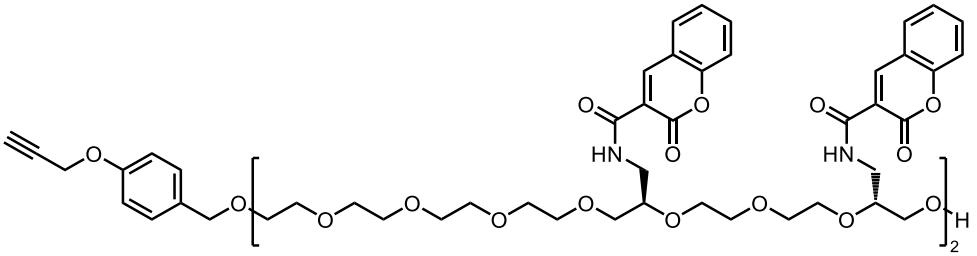


Propargylbenzy (diazide dodeca-ethylene glycol). Purified product was isolated as a brown oil (42%). ^{1}H NMR (500 MHz, chloroform-*d*) δ 6.94 (d, *J* = 8.6 Hz, 2H), 4.68 (d, *J* = 2.4 Hz, 2H), 4.50 (s, 2H), 3.81 – 3.47 (m, 48H), 3.42 – 3.31 (m, 4H), 2.52 (t, *J* = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{36}H_{60}N_6O_{14}$ $[M+NH_4]^+$ = 818.4511, observed = 818.4574.

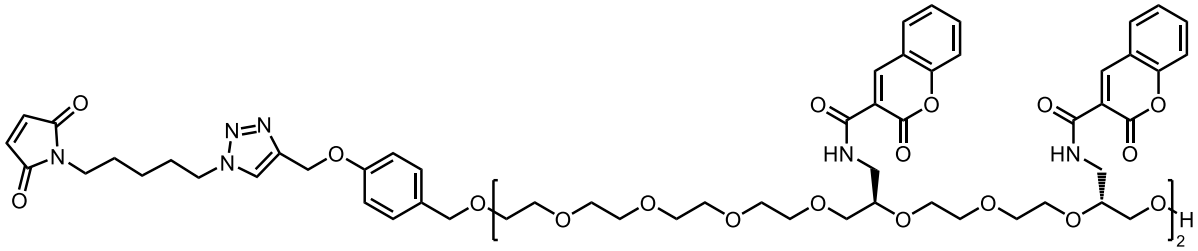


Propargylbenzy (tetra-azide hexadeca-ethylene glycol). Purified product was isolated as a brown oil (68%). ^{1}H NMR (600 MHz, chloroform-*d*) δ 7.28 (d, *J* = 8.5 Hz, 2H), 6.95 (d, *J* = 8.6 Hz, 2H), 4.69 (d, *J* = 2.4 Hz, 2H), 4.50 (s, 2H), 3.92 – 3.87 (m, 1H), 3.83 – 3.48 (m, 89H), 3.43 – 3.32 (m,

9H), 3.26 (dd, J = 12.8, 4.2 Hz, 1H), 2.53 (t, J = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{46}H_{78}N_{12}O_{18}$ $[M+NH_4]^+$ = 1104.5900, observed = 1104.3670.



Propargylbenzy (tetra-azide hexadeca-ethylene glycol) reduction and coumarin addition. Propargylbenzy (tetra-azide hexadeca-ethylene glycol) (17 mg, 16 µmol, 1 equivalent) and triphenylphosphine (41 mg, 160 µmol, 10 equivalents) were dissolved in 700 µL of THF and 200 µL of water in a dram vial. The reduction was allowed to proceed for 12 h at 22 °C. Solvent was then removed under vacuum. To the solid, coumarin-3-carboxylic acid N-succinimidyl ester (44 mg, 150 µmol, 10 equivalents) and N,N-diisopropylethylamine (16 µL, 92 µmol, 6 equivalents) were added. The reagents were then dissolved in 0.5 mL of dimethyl sulfoxide (DMSO) and the reaction allowed to proceed for 4 h at 22 °C. The crude reaction was then diluted with acetonitrile, filtered, and purified via preparatory high-performance liquid chromatography (HPLC) with a 50-100% acetonitrile gradient (elution time: 9.2 min) and lyophilized to yield the product as a clear oil (6.6 mg, 26%). ^{1}H NMR (500 MHz, chloroform-*d*) δ 9.08 (s, 4H), 8.86 (d, J = 11.1 Hz, 4H), 7.71 – 7.59 (m, 9H), 6.92 (d, J = 8.2 Hz, 2H), 4.67 (d, J = 2.4 Hz, 2H), 4.48 (s, 2H), 3.88 – 3.48 (m, 79H), 2.52 (t, J = 2.4 Hz, 1H). HRMS (ESI) calculated for $C_{86}H_{102}N_4O_{30}$ $[M+H]^+$ = 1671.6657, observed = 1671.6698.



Maleimide (tetra-coumarin hexadeca-ethylene glycol). An aliquoted stock solution of the 5-azidopentyl-1-maleimide (2.27 mg, 10.9 µmol, 5 equivalents) was added to a dram vial and dried with a stream of air. A stock solution (18.2 mg/mL in DMF) of propargylbenzy (tetra-coumarin hexadeca-ethylene glycol) was then added (3.64 mg, 2.18 µmol, 1 equivalents) and the reaction was diluted to a total volume of 400 µL. Stock solutions of copper(II)sulfate (3.5 mg/mL) and sodium ascorbate (4.3 mg/mL) were prepared in water. Aliquots of both copper(II)sulfate (174 µg, 1.09 µmol, 0.5 equivalents) and ascorbic acid (216 µg, 1.09 µmol, 0.5 equivalents) were then added and reaction was allowed to stir for 15 min at 22 °C. An additional 0.5 equivalents of copper(II)sulfate and ascorbic acid were added every 15 min until a total of 2 equivalents of each was added. The reaction was allowed to stir at 22 °C for 4 h. The reaction was then diluted with acetonitrile and product was purified via preparatory HPLC with a 50-100% acetonitrile gradient (elution time: 8.6 min) and lyophilized to yield the product as white residue (2.3 mg, 56%). ^{1}H

NMR (500 MHz, acetonitrile-d_3) δ 8.89 (t, J = 5.6 Hz, 4H), 8.78 (dd, J = 10.2, 5.5 Hz, 4H), 7.84 – 7.71 (m, 5H), 7.71 – 7.62 (m, 4H), 7.41 – 7.31 (m, 9H), 7.21 (d, J = 8.3 Hz, 2H), 6.92 (d, J = 8.4 Hz, 2H), 6.71 (s, 2H), 5.07 (s, 2H), 4.41 (s, 2H), 4.31 (t, J = 7.1 Hz, 2H), 3.79 – 3.68 (m, 12H), 3.67 – 3.44 (m, 67H). HRMS (ESI) calculated for $C_{95}H_{114}N_8O_{32}$ $[M+H]^+$ = 1879.7617, observed = 1879.7776.

Trastuzumab Conjugation Protocol. Trastuzumab (1 mg, 0.0068 μmol, 1 equivalent) was buffer exchanged into phosphate buffered saline (PBS, pH=7.4) + 10 mM ethylenediaminetetraacetic acid (EDTA) via 5 cycles of centrifugal (100 MW cutoff) filtration. The Trastuzumab solution was then concentrated to 10 mg/mL and tris(2-carboxyethyl)phosphine (TCEP, 19 μg, 0.068 μmol, 10 equivalents) was then added via a freshly prepared stock solution and reduction was allowed to proceed at 37 °C for 1 hr. Excess TCEP was then removed with a desalting ZEBA® column (7 MWCO cutoff). A stock solution of the maleimide (tetra-coumarin hexadeca-ethylene glycol) was prepared in DMF and added (0.25 mg, 0.14 μmol, 20 equivalents, 20% final DMF concentration). The conjugation was allowed to proceed for 12 h. Precipitate was removed via centrifugation and the supernatant was run through a ZEBA® column. Remaining small molecule reagents were then removed via centrifugal filtration (10 total washes) with PBS. The final yield of the conjugation was 22%. The conjugate was digested with PNGase F according to manufactures instructions before LCMS analysis. The coumarin-to-antibody ratio was determined by comparing the abundances of modified and unmodified antibody fragments.

Indirect ELISA Protocol.[7] To the wells of a high-binding 96 well plate, 100 μL of a 1 μg/mL solution (diluted in 0.1 M carbonate buffer, pH 9.6) of recombinant human epidermal growth factor receptor 2 (Her2) was added. The plate was covered with foil and incubated at 4 °C for 12 h. The following day, the solution was aspirated and the plate was washed four times with ELISA wash buffer (PBS + 0.3% Tween 20). To the wells, 200 μL of blocking buffer (1% bovine serum albumin, BSA, in PBS, filtered with 0.22 μM filter) was added and incubated at 22 °C for 2 h. Again, 4 washes were performed with wash buffer before adding 100 μL of antibody or conjugate samples at appropriate dilution (dilution buffer = 1% BSA in PBS). The plate was incubated at 22 °C for 1 h before repeating the aspiration and wash procedure. Whole molecule anti-Human IgG (whole molecule)−Peroxidase antibody produced in rabbit (diluted 1:40,000 in dilution buffer) was then added (100 μL per well) and the plate was incubated at 37 °C for 45 min. After aspirating and washing the plate a final time, 100 μL of TMB (3,3',5,5'-Tetramethylbenzidine) substrate solution was added to the wells via a multichannel pipette and the plate was incubated in the dark for ~5 min. After sufficient development of blue color, 50 μL of 1 M sulfuric acid was added and absorbance of each well was measured at 450 nm.

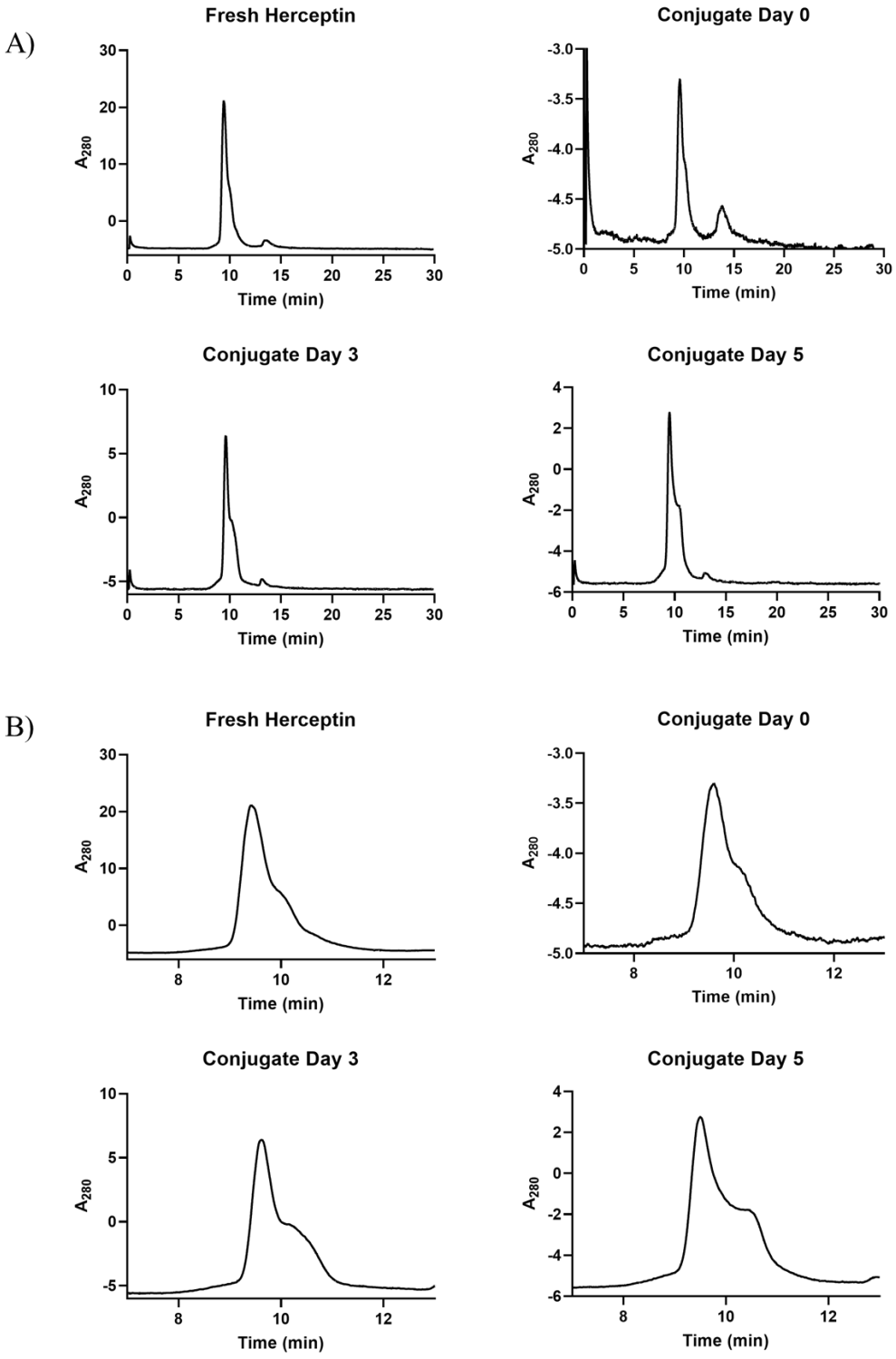
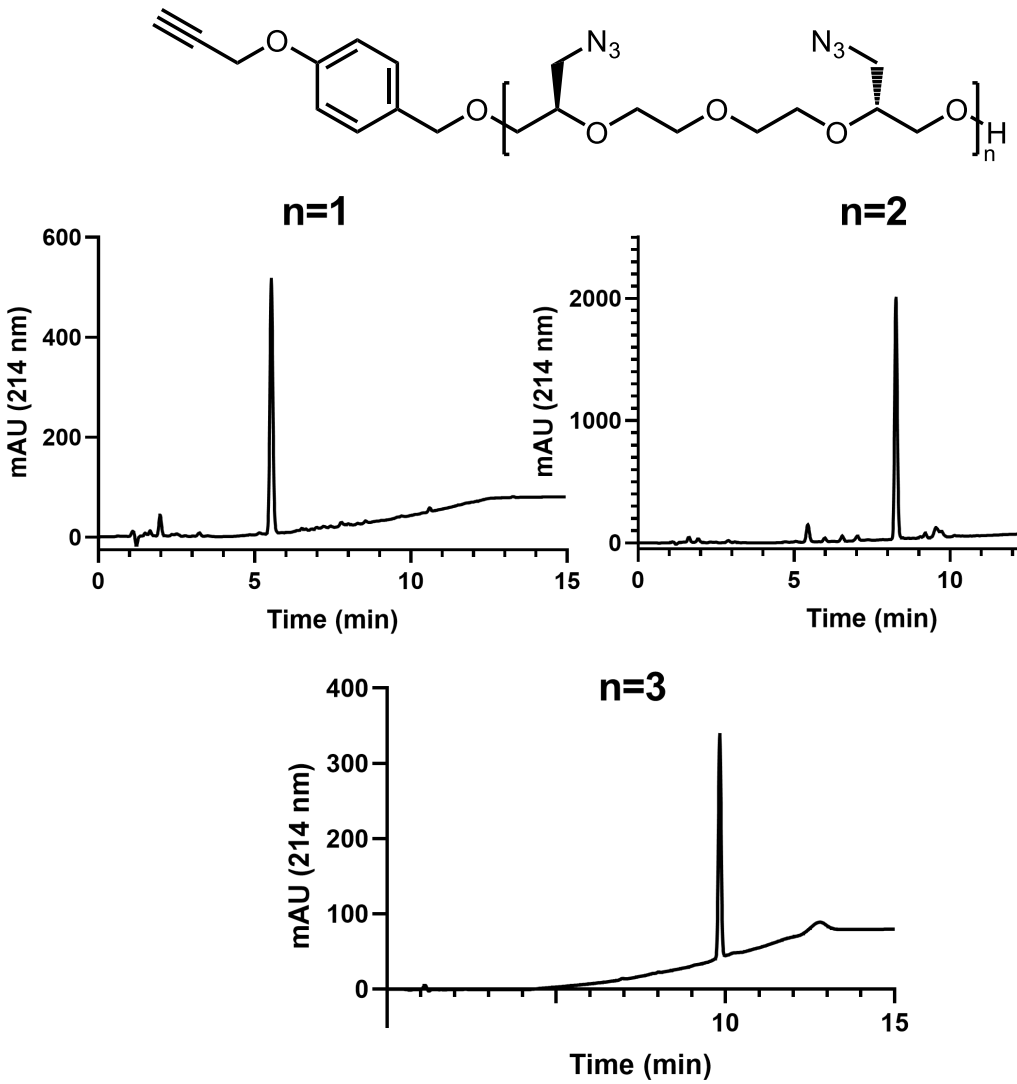


Figure S1. Full (A) and zoomed in (B) size exclusion chromatograms (SEC) of fresh Herceptin and coumarin-Herceptin conjugate after 0, 3, and 5 days at 22 °C. The main antibody peak eluted at 10 minutes followed by a salt/impurity peak at 14 minutes.

HPLC and Mass Spectrometry Spectra of Oligomers and Intermediates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1000
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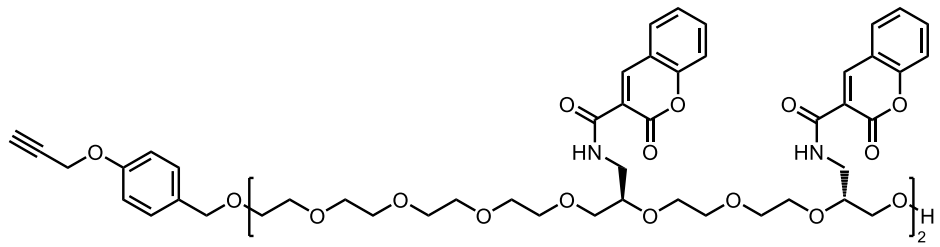
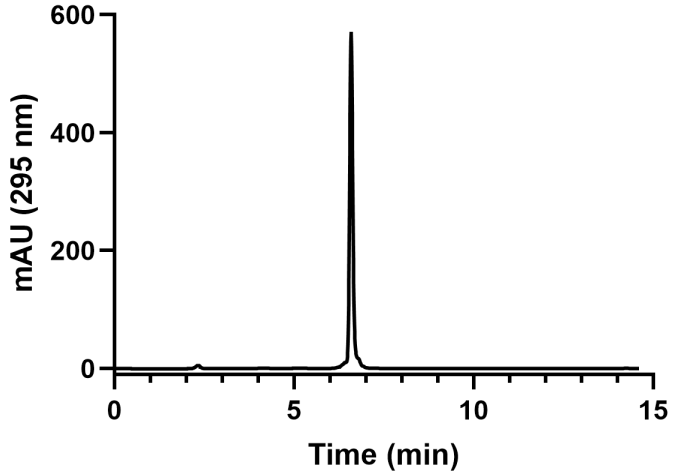
15




600
400
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mAU (295 nm)
0
5
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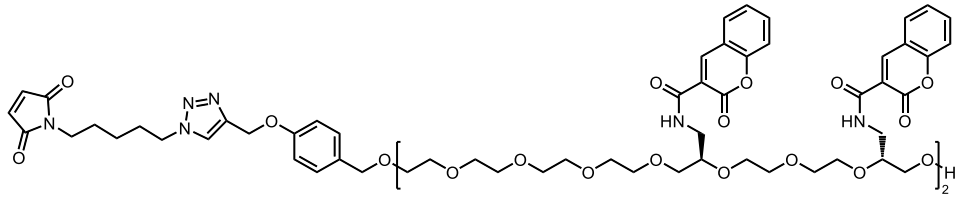
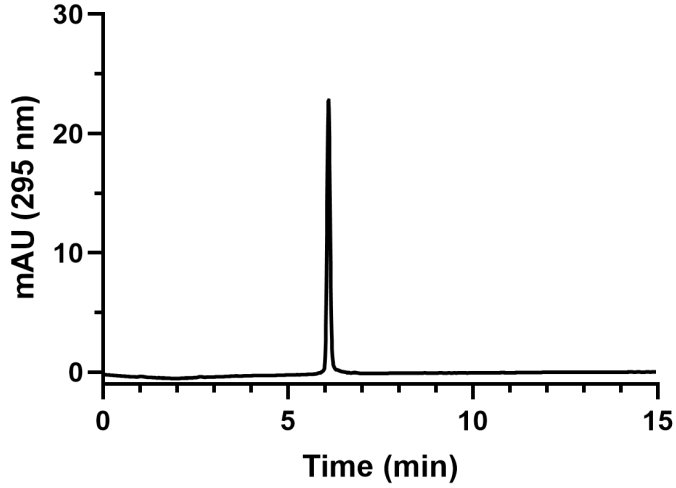
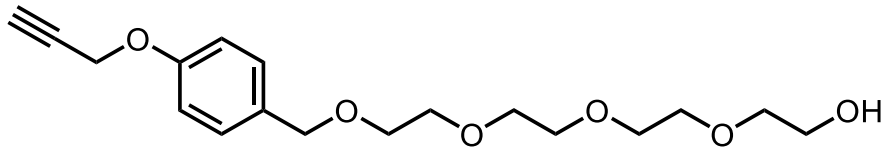
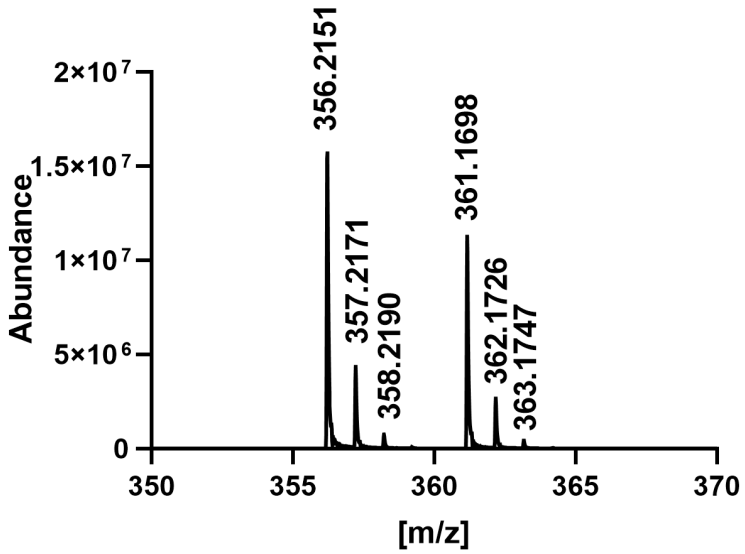
15
Time (min)

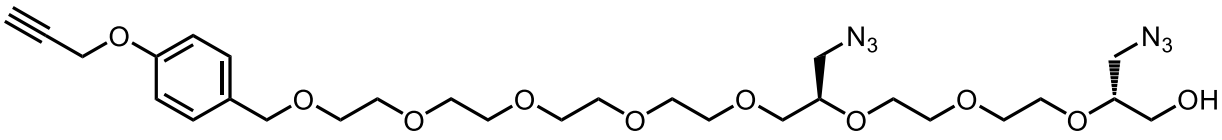



30
20
10
0
mAU (295 nm)
0
5
10
15
Time (min)

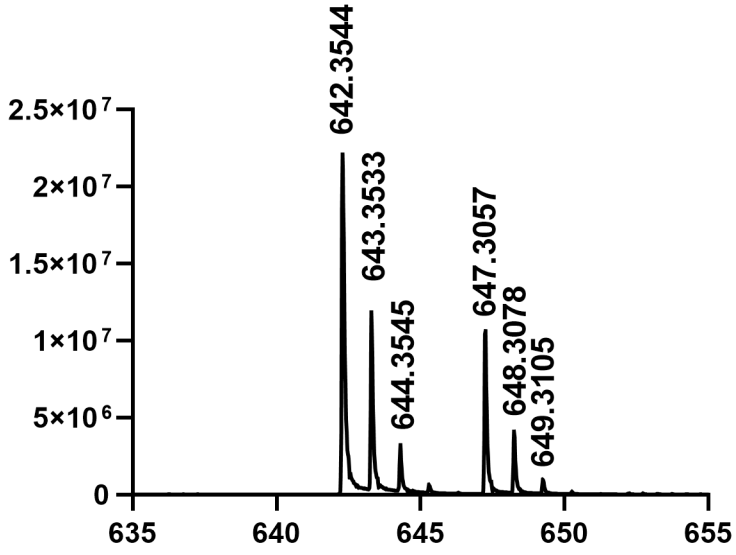


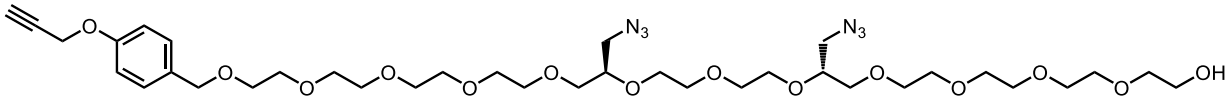
Calculated for $C_{18}H_{26}O_6$: $[M+NH_4]^+ = 356.2073$, $[M+Na]^+ = 361.1627$



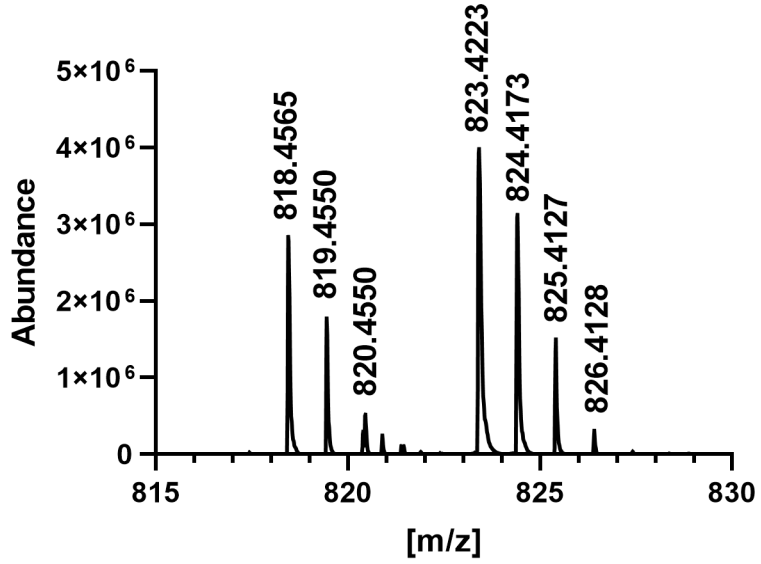


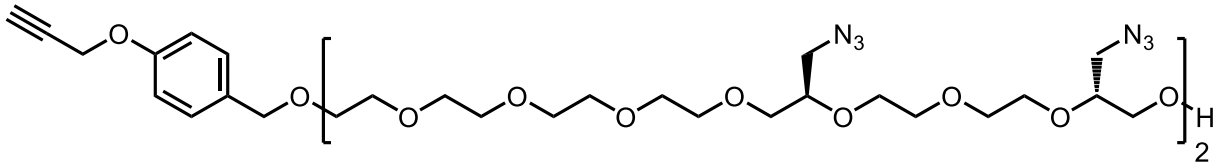
Calculated for $C_{28}H_{44}N_6O_{10}$ $[M+NH_4]^+ = 647.3016$, $[M+Na]^+ = 647.30166$



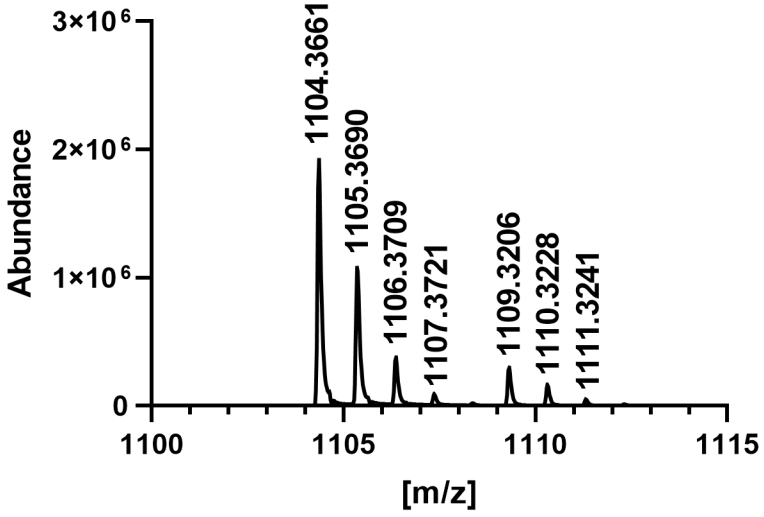


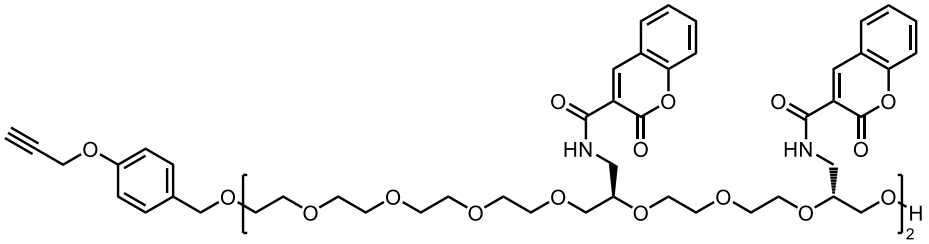
Calculated for $C_{36}H_{60}N_6O_{14}$: $[M+NH_4]^+$ = 818.4511, $[M+Na]^+$ = 823.4065



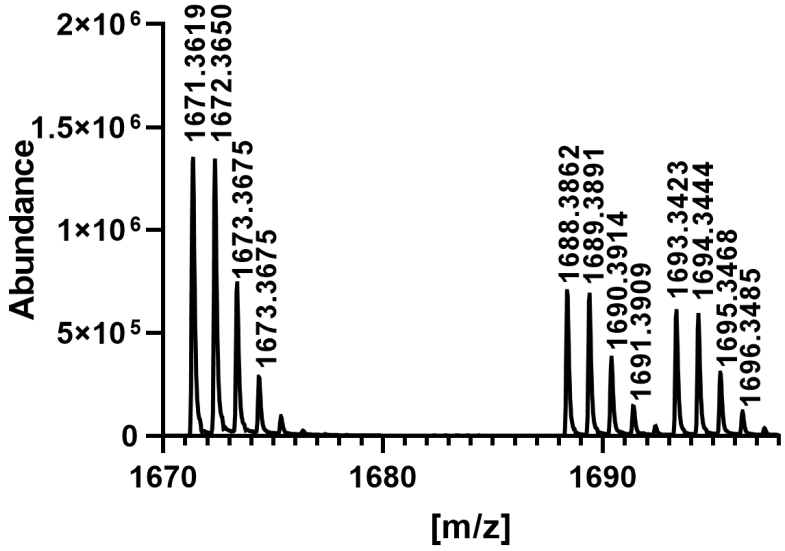


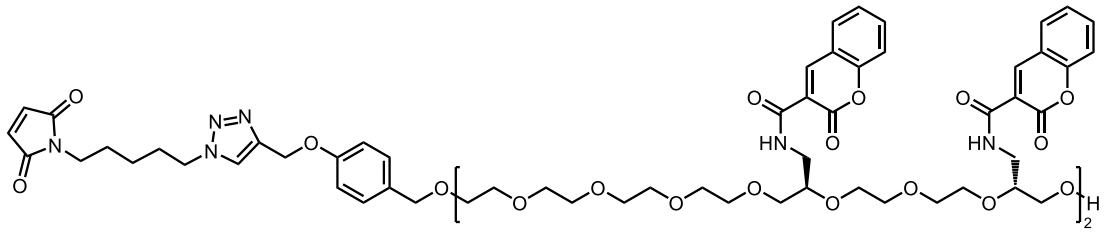
Calculated for $C_{46}H_{78}N_{12}O_{18}$: $[M+NH_4]^+$ = 1104.5900 , $[M+Na]^+$= 1109.5454



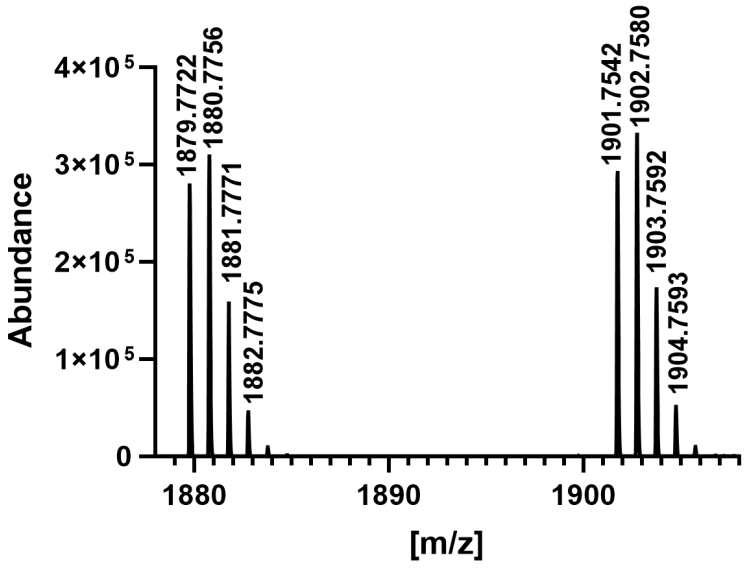


Calculated for $C_{86}H_{102}N_4O_{30}$ $[M+H]^+$ = 1671.6657, $[M+NH_4]^+$= 1688.6922, $[M+Na]^+$= 1693.6476

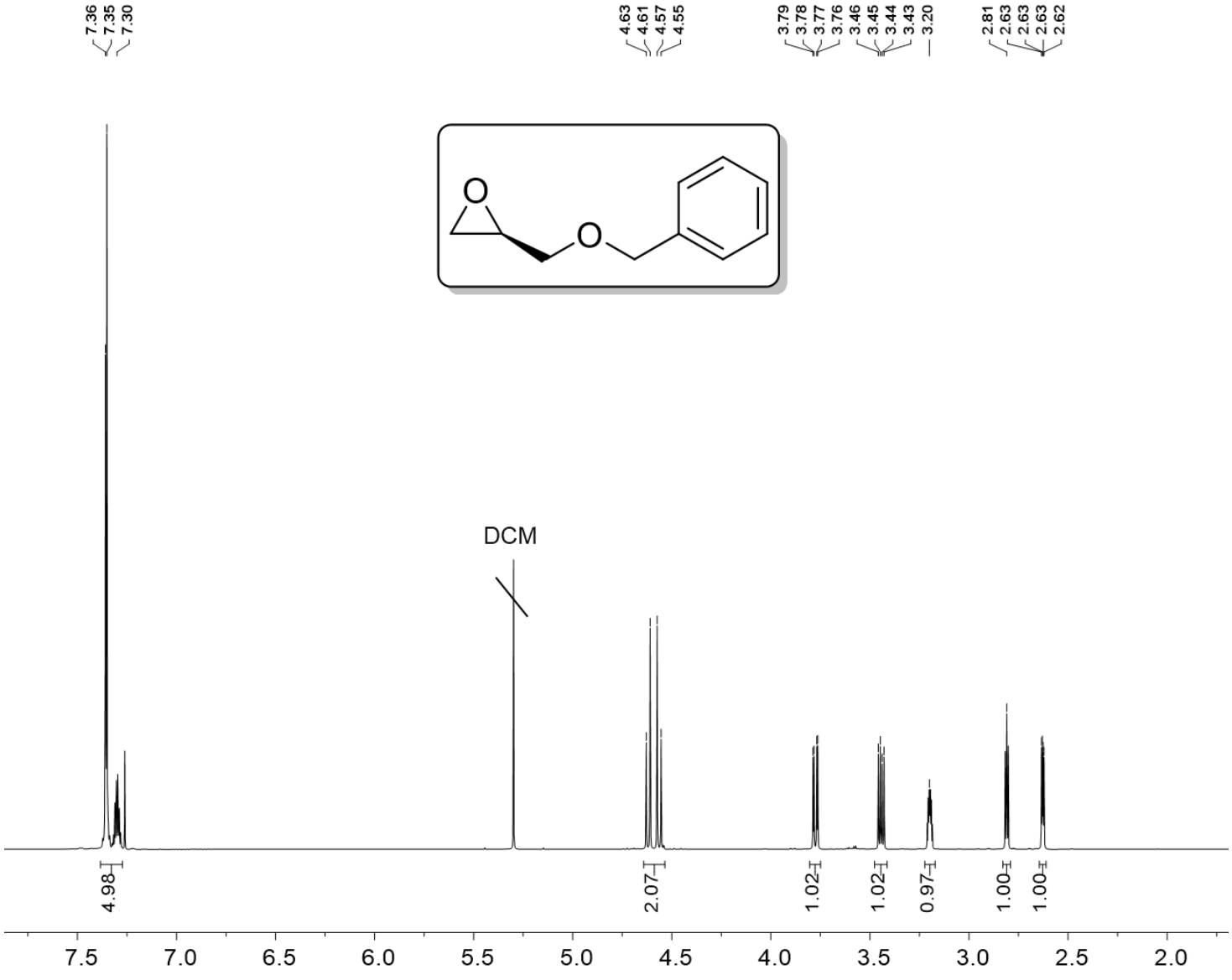


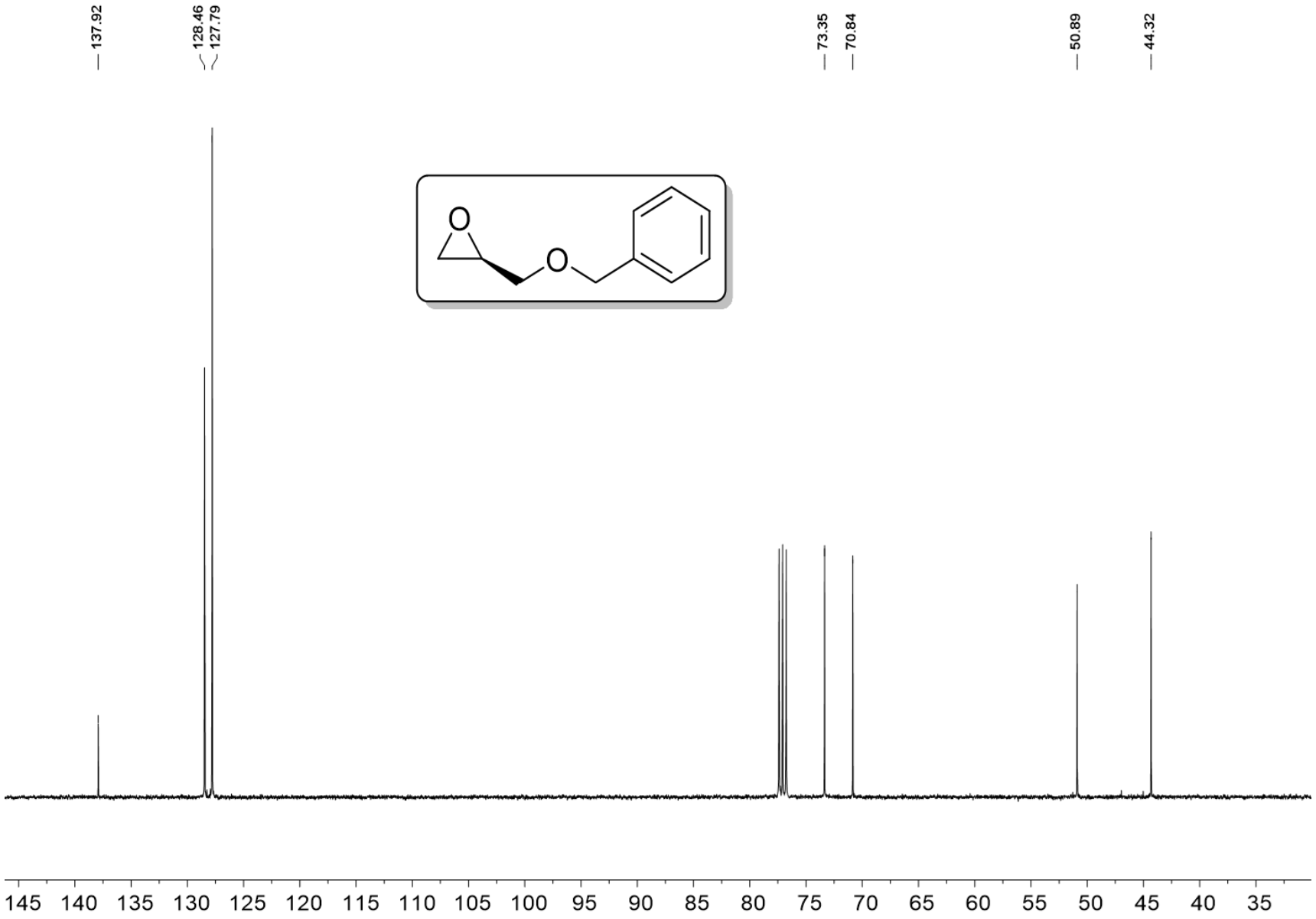


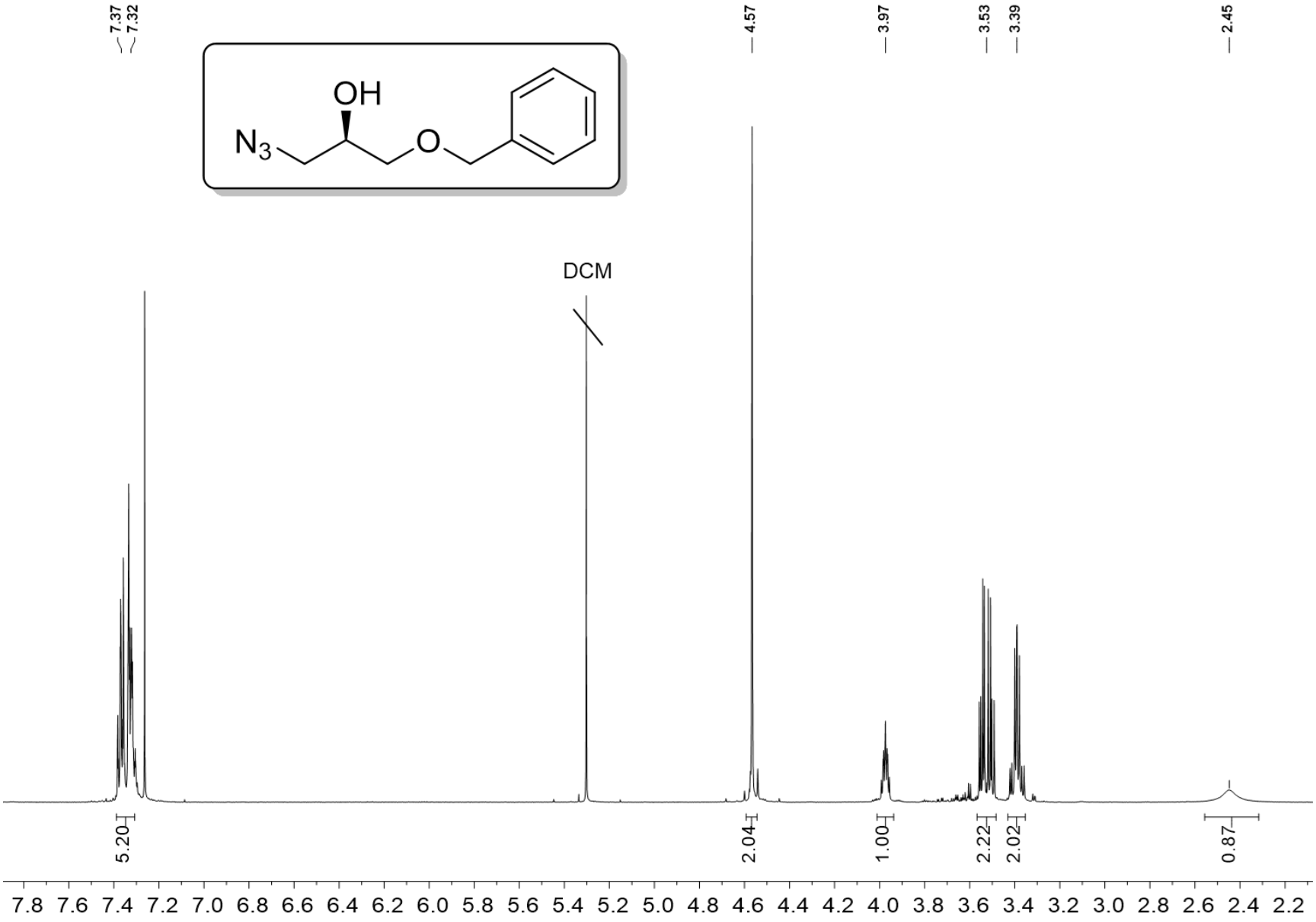
Calculated for $C_{95}H_{114}N_8O_{32}$: $[M+H]^+$ = 1879.7617, $[M+Na]^+$ = 1901.7436

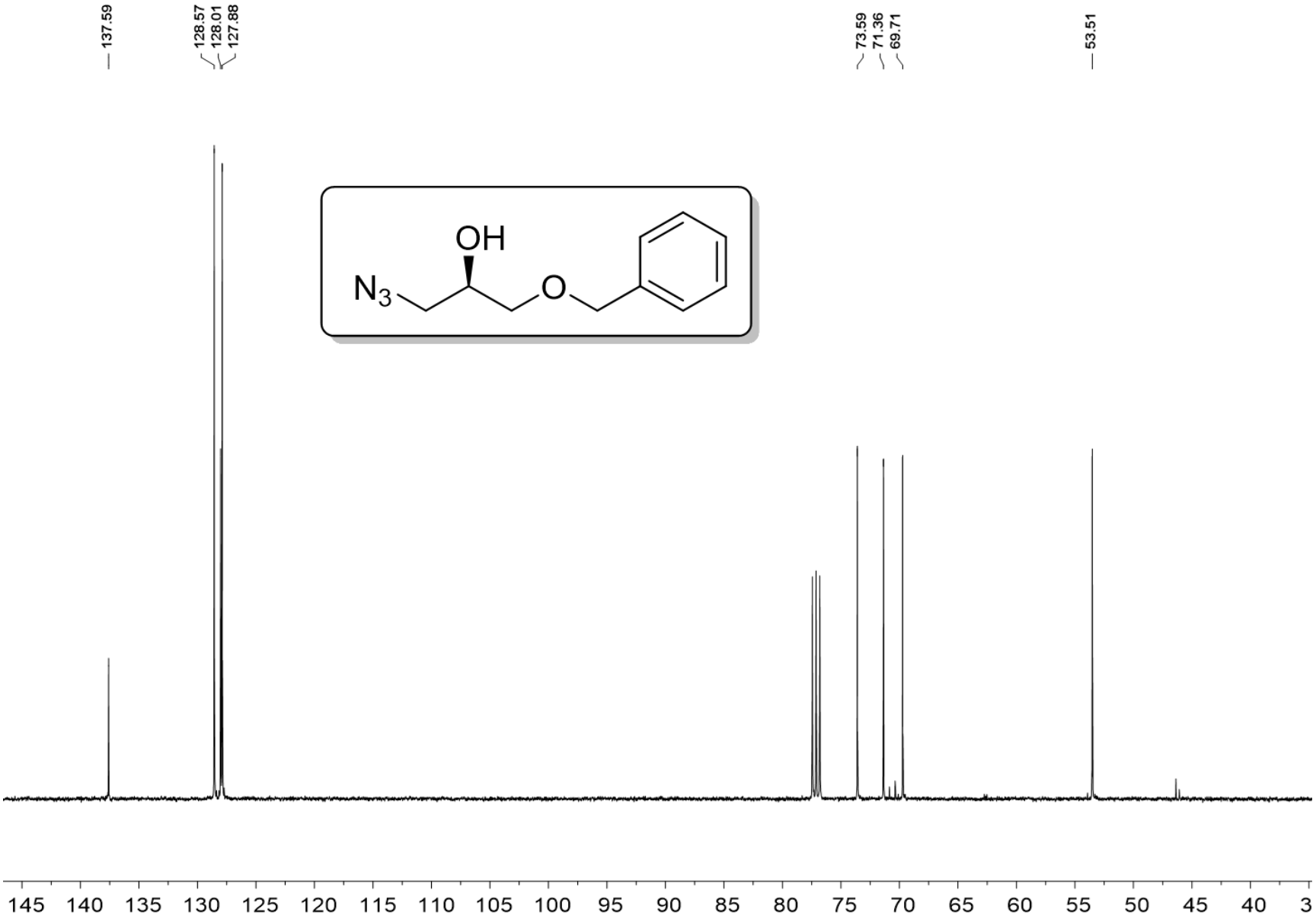


^{1}H and Carbon NMRs


7.36
7.35
7.30
4.63
4.61
4.57
4.55
3.79
3.78
3.77
3.76
3.46
3.45
3.44
3.43
3.20
2.81
2.63
2.63
2.63
2.62
O
O
DCM
4.98
2.07
1.02
1.02
0.97
1.00
1.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5
2.0


137.92
128.46
127.79
73.35
70.84
50.89
44.32
O
O
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35


7.37
7.32
4.57
3.97
3.53
3.39
2.45
OH
N3
O
DCM
5.20
2.04
1.00
2.22
2.02
0.87
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2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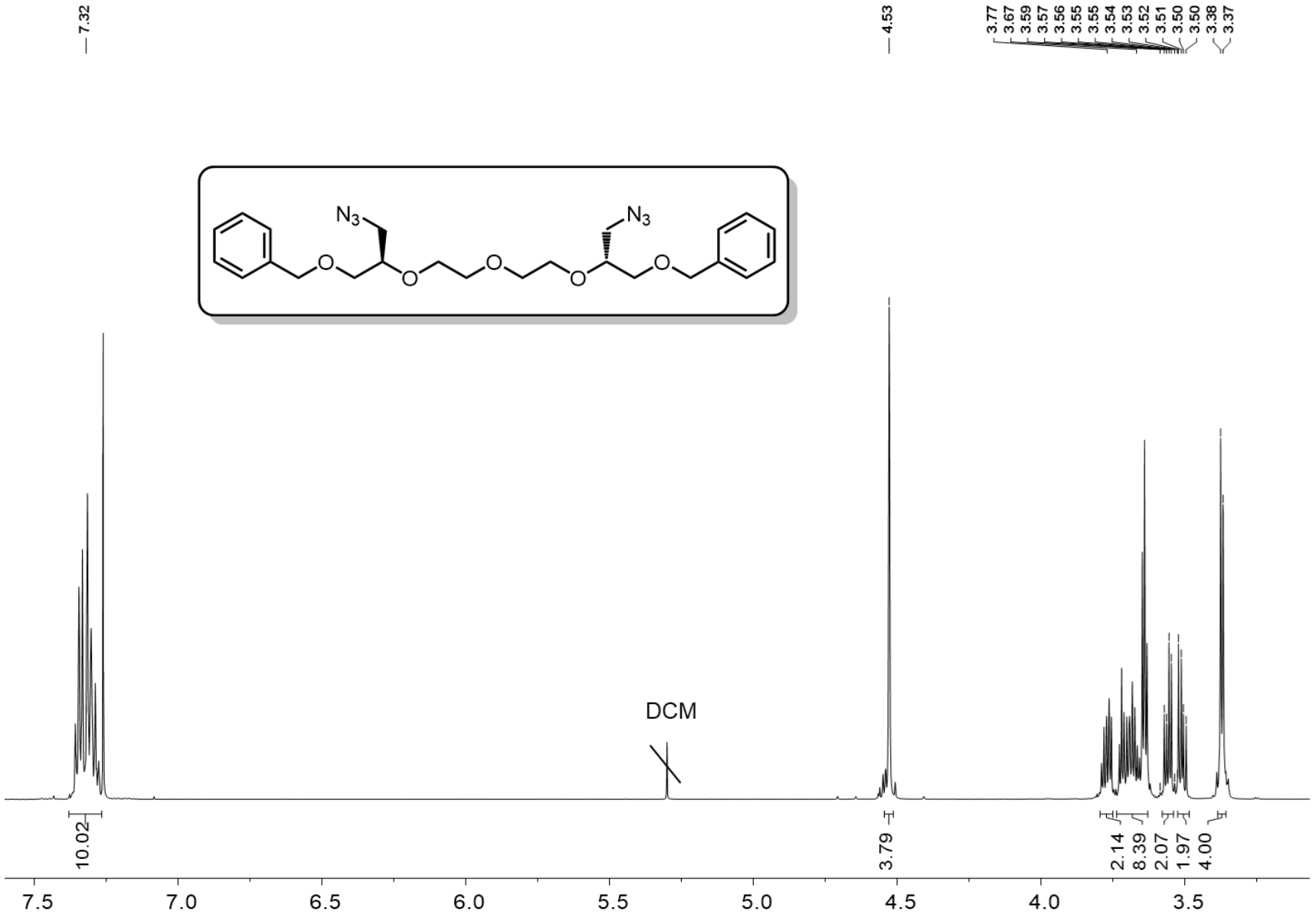
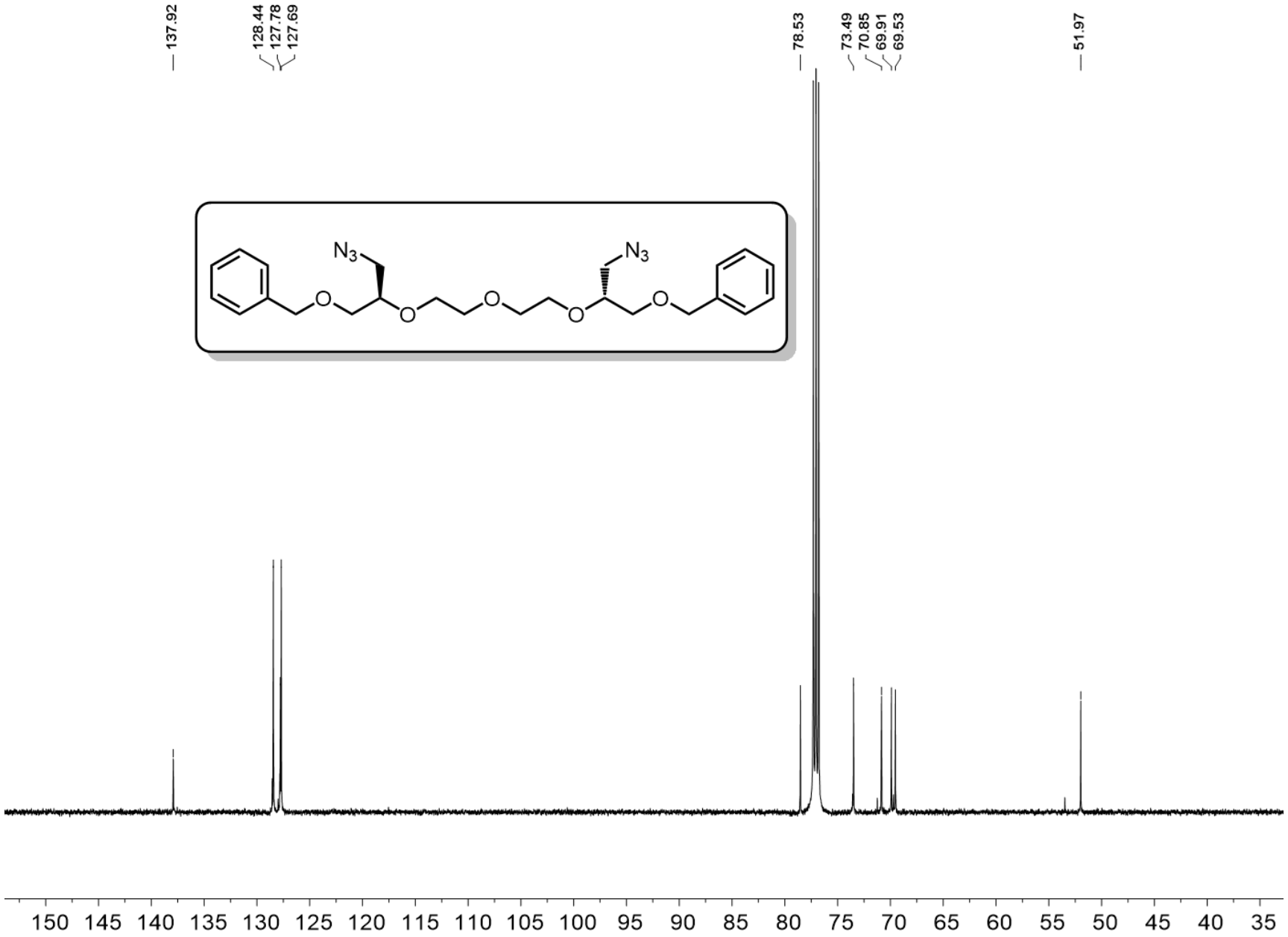
128.57
128.01
127.88
73.59
71.36
69.71
53.51
OH
N3
O
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 3


7.32
4.53
3.77
3.67
3.59
3.57
3.56
3.55
3.55
3.54
3.53
3.52
3.51
3.50
3.50
3.38
3.37
N3
N3
O
O
O
O
O
DCM
10.02
3.79
2.14
8.39
2.07
1.97
4.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5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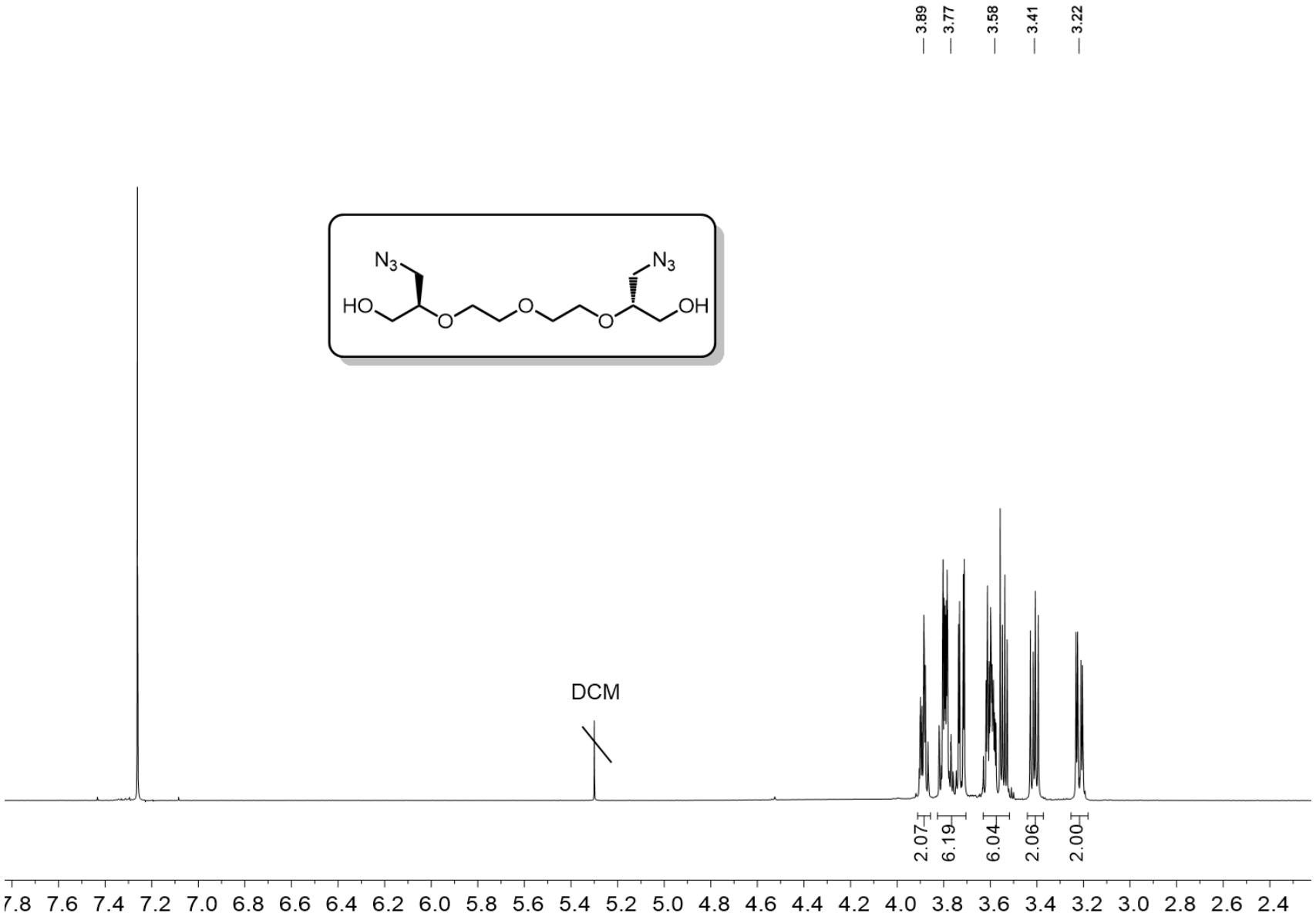
128.44
127.78
127.69
78.53
73.49
70.85
69.91
69.53
51.97
N3
N3
O
O
O
O
O
150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35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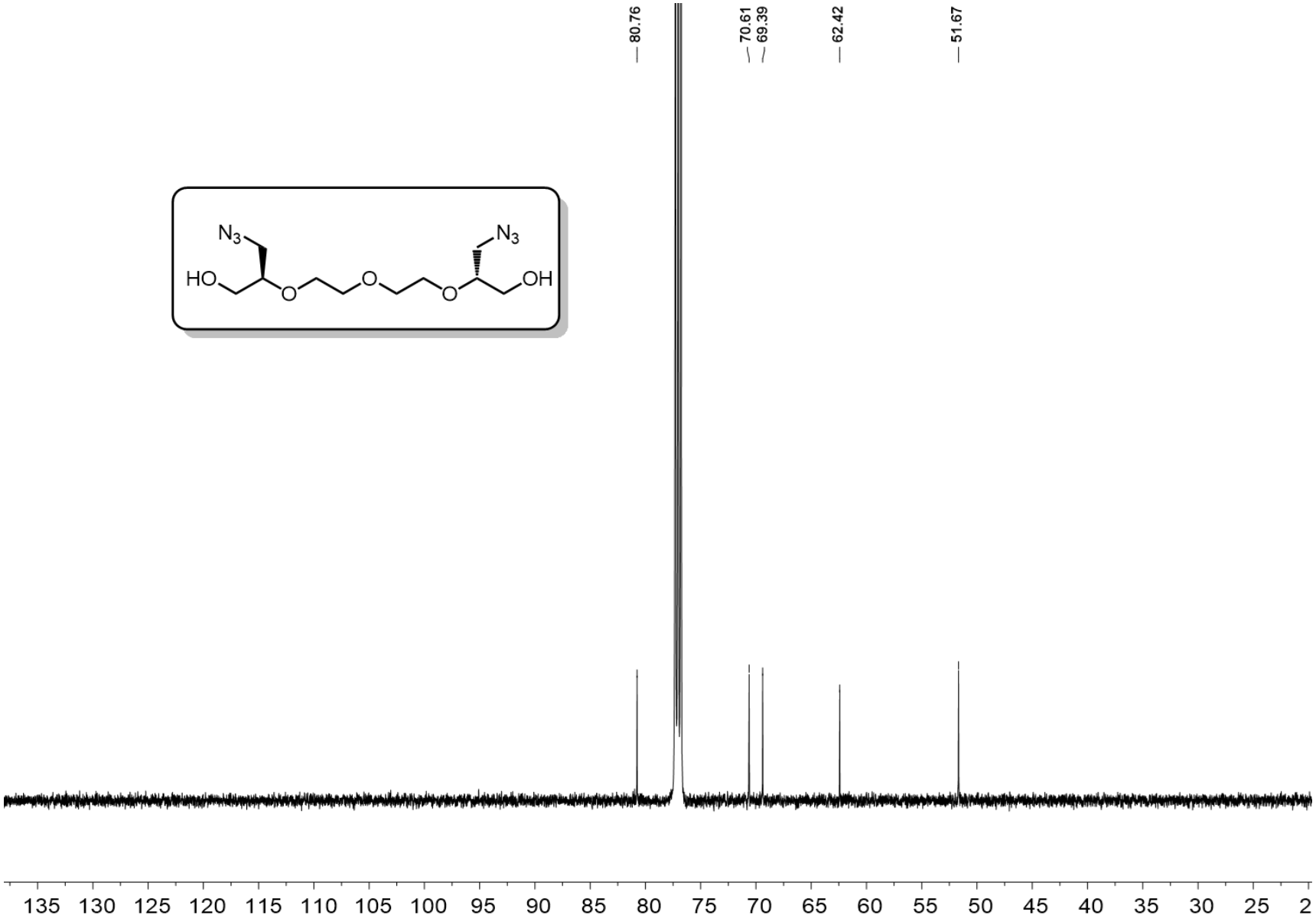
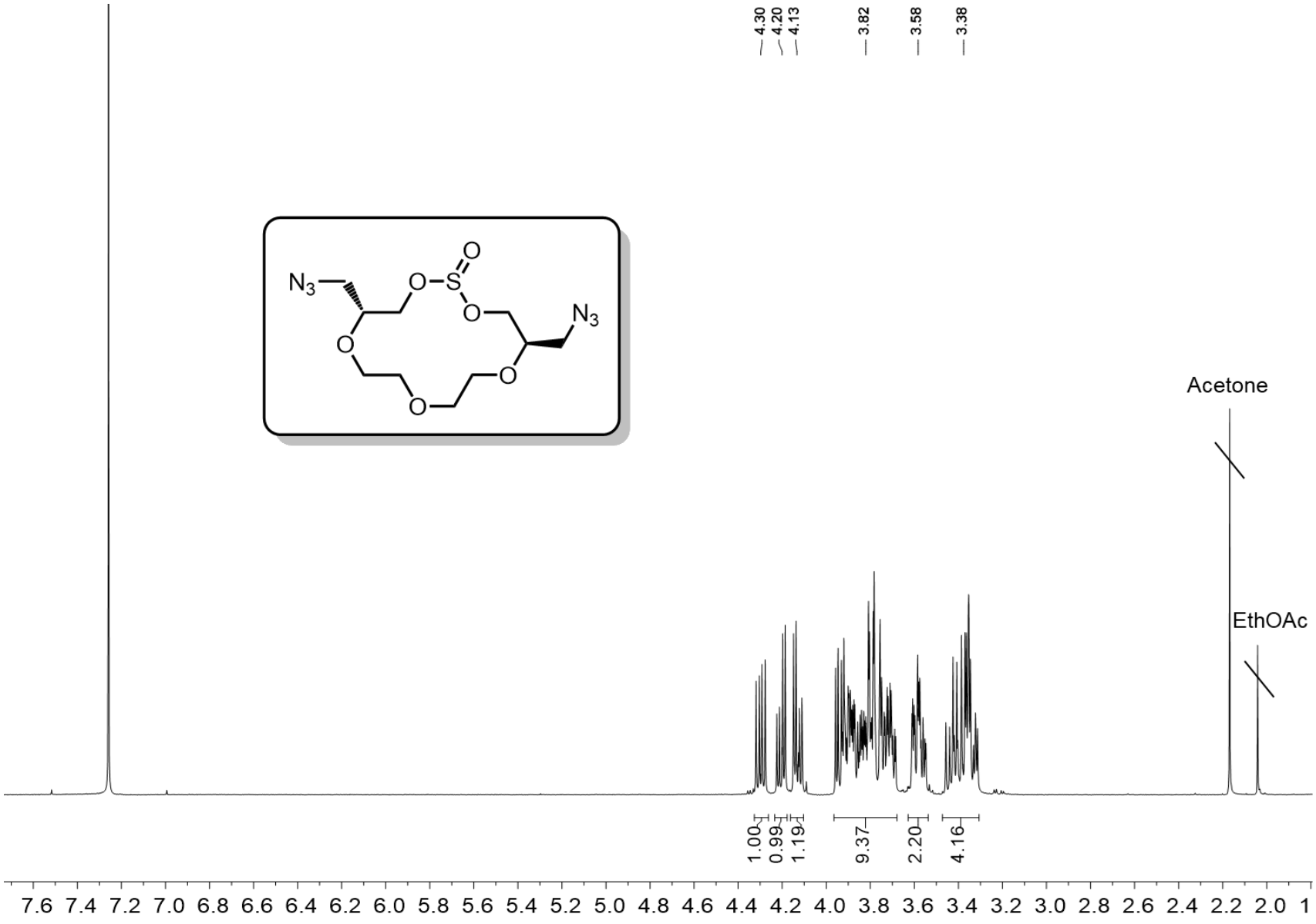
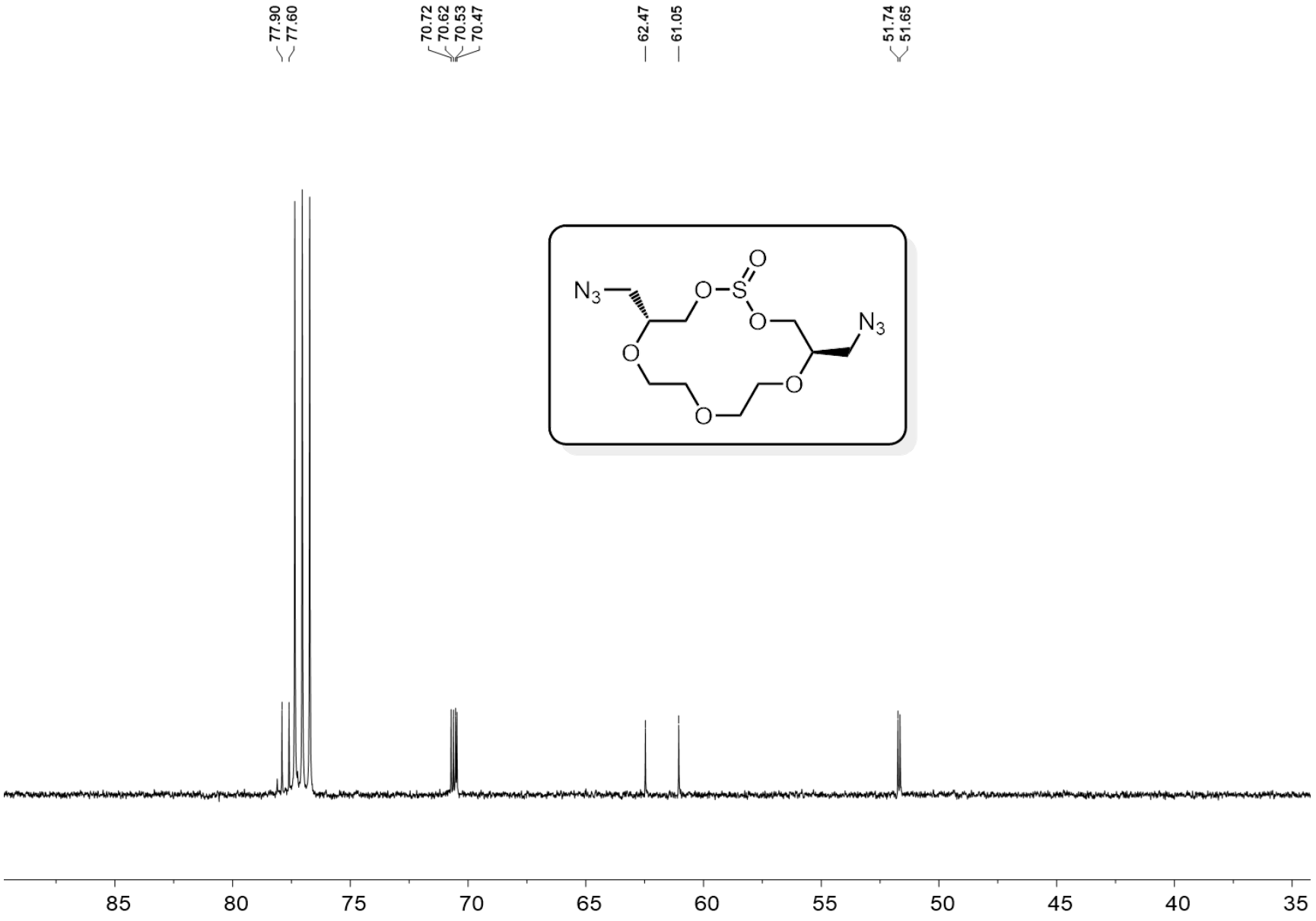
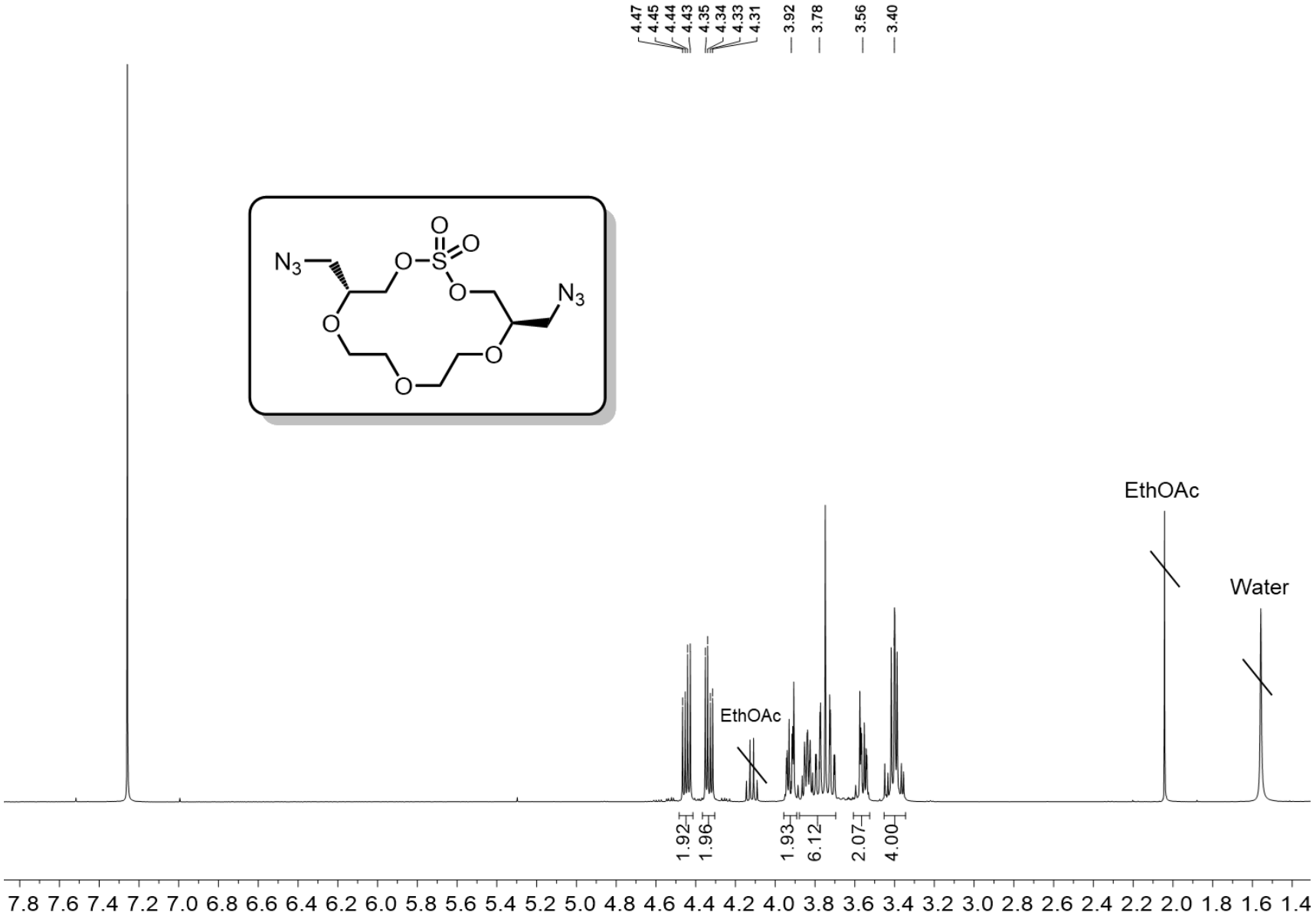
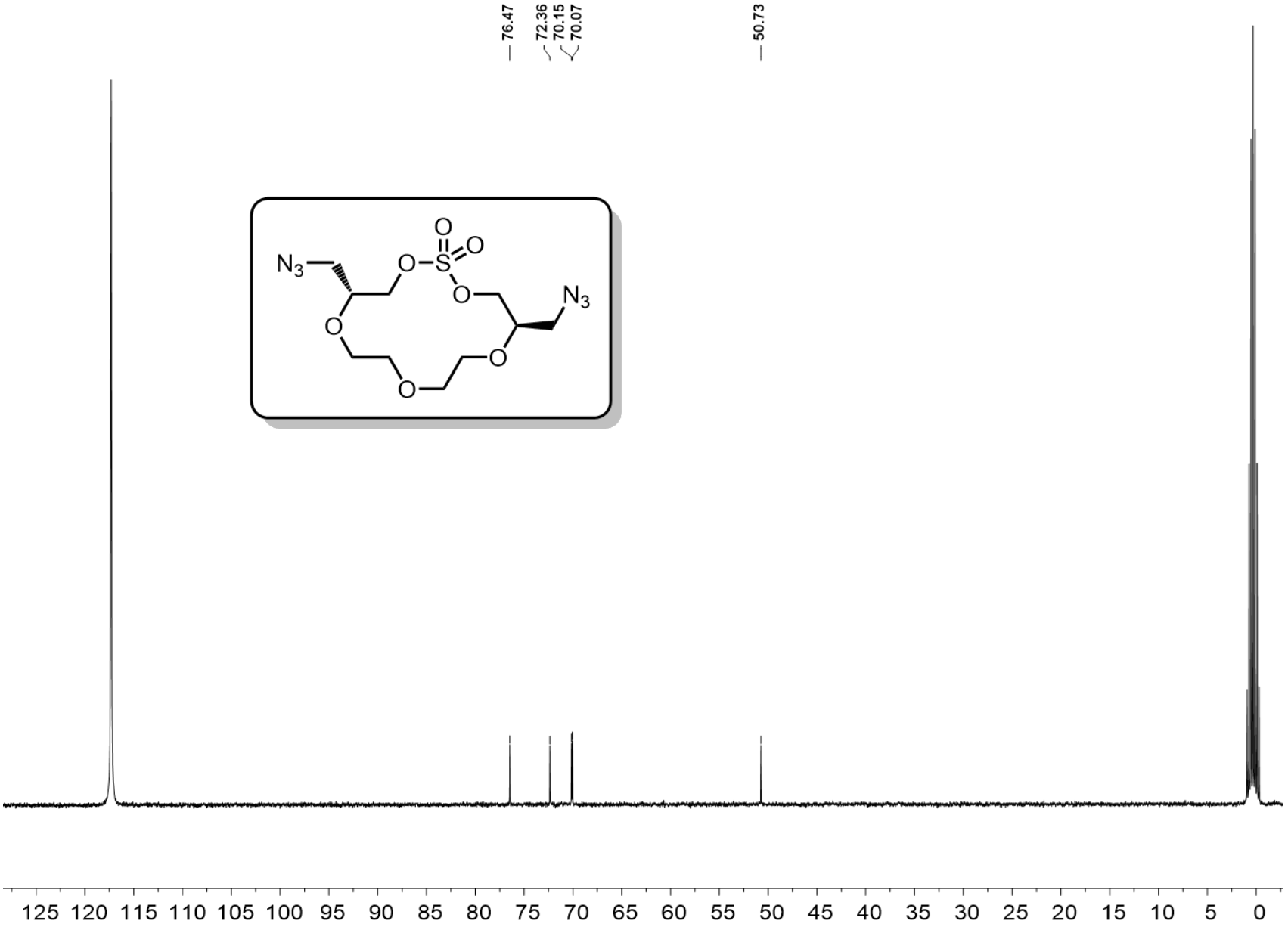
3.77
3.58
3.41
3.22
N3
N3
HO
OH
O
O
O
DCM
2.07
6.19
6.04
2.06
2.00
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4


80.76
70.61
69.39
62.42
51.67
N3
N3
HO
OH
O
O
O
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 2


4.30
4.20
4.13
3.82
3.58
3.38
Acetone
EthOAc
1.00
0.99
1.19
9.37
2.20
4.16
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1


77.90
77.60
70.72
70.62
70.53
70.47
62.47
61.05
51.74
51.65
N3
O
S
O
O
O
O
O
N3
85
80
75
70
65
60
55
50
45
40
35


4.47
4.45
4.44
4.43
4.35
4.34
4.33
4.31
3.92
3.78
3.56
3.40
N3
O
S
O
O
O
O
O
O
N3
EthOAc
Water
EthOAc
1.92
1.96
1.93
6.12
2.07
4.00
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6 1.4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72.36
70.15
70.07
50.73
N3
O
S
O
O
O
O
O
O
O
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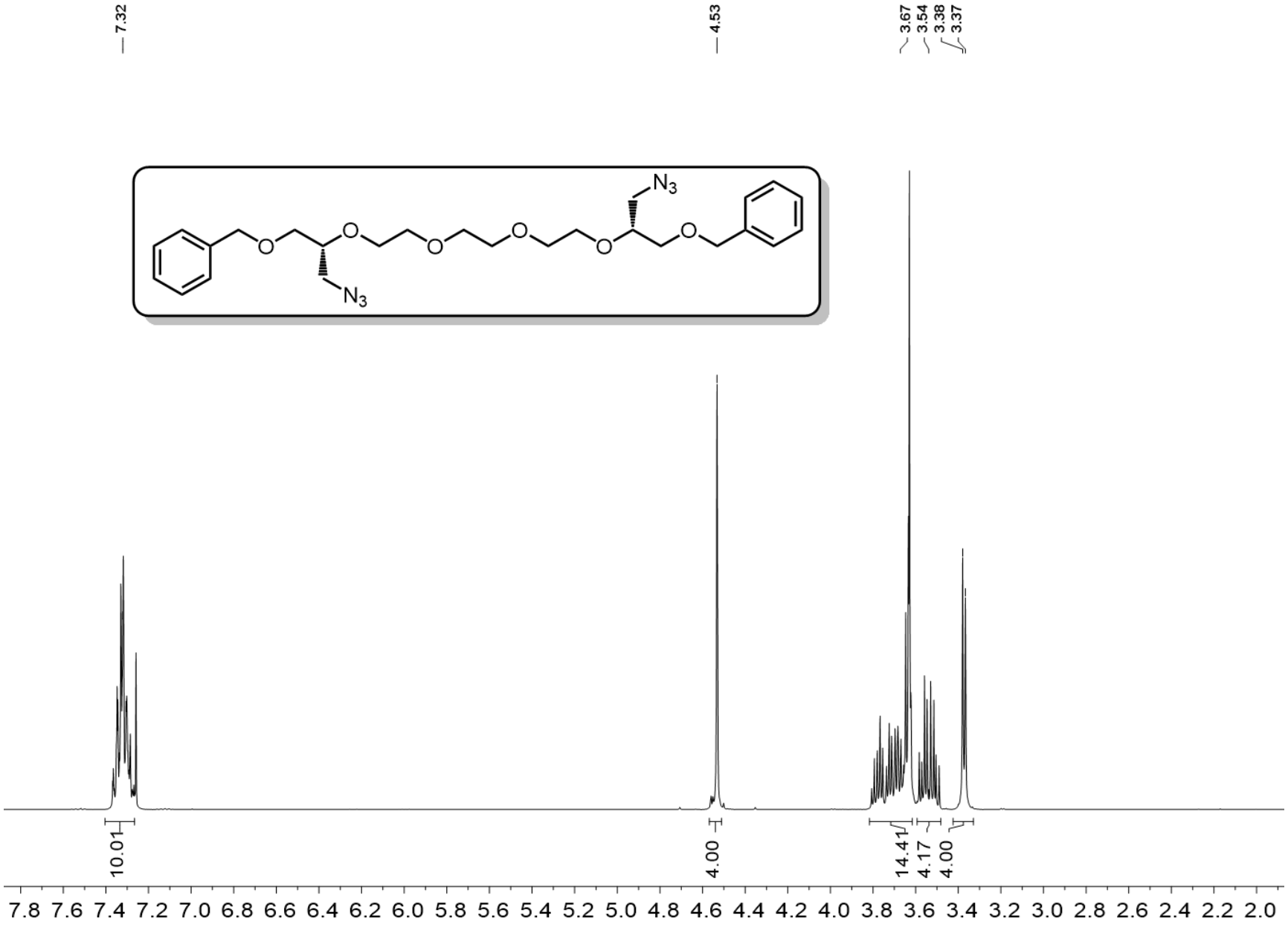
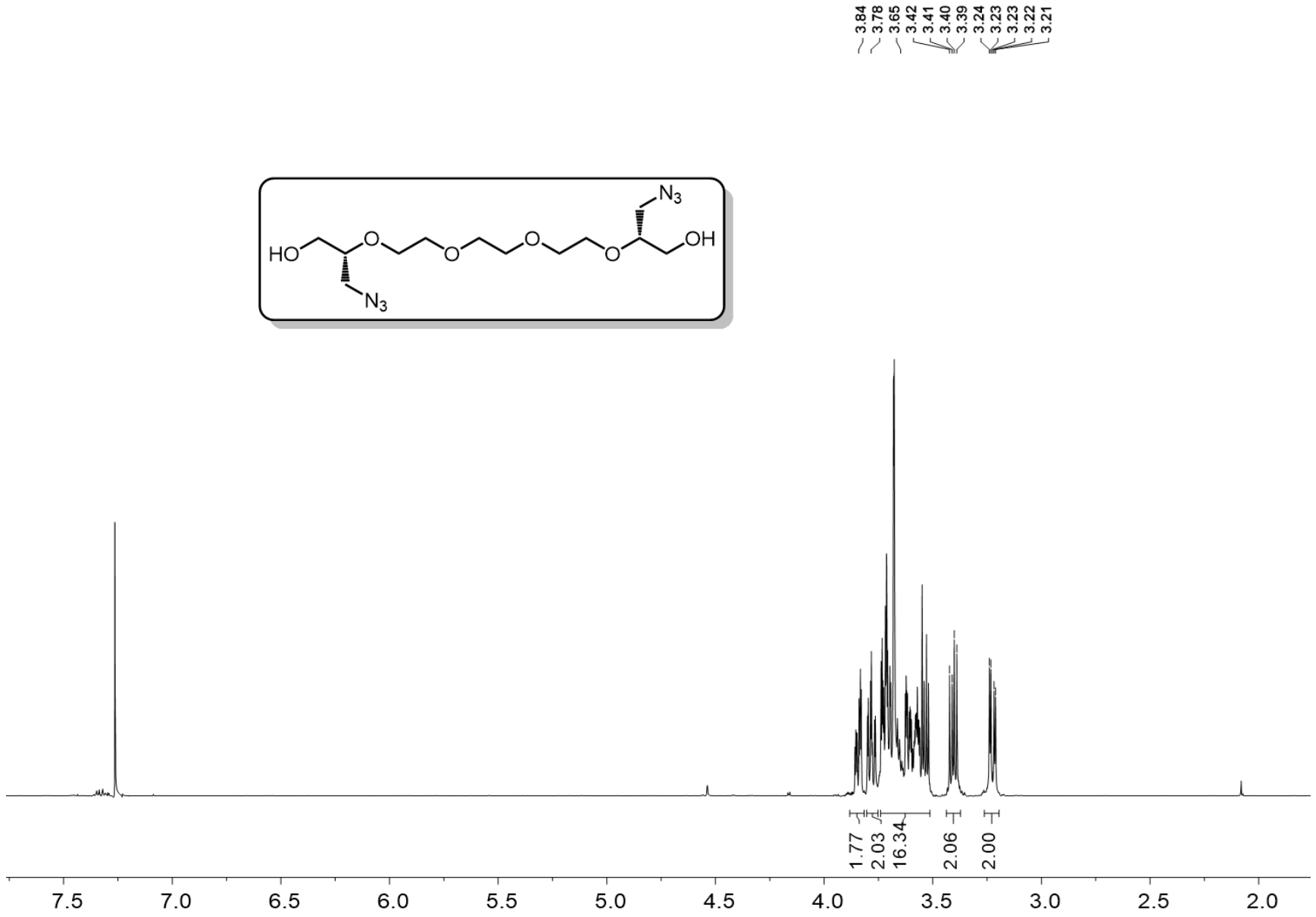
125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0


7.32
4.53
3.67
3.54
3.38
3.37
N3
N3
O
O
O
O
O
O
10.01
4.00
14.41
4.17
4.00
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0


137.92
128.44
127.78
127.69
78.54
73.50
70.79
70.66
69.92
69.52
51.98
N3
N3
55 150 145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40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3.78
3.65
3.42
3.41
3.40
3.39
3.24
3.23
3.23
3.22
3.21
HO
OH
N3
N3
1.77
2.03
16.34
2.06
2.00
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
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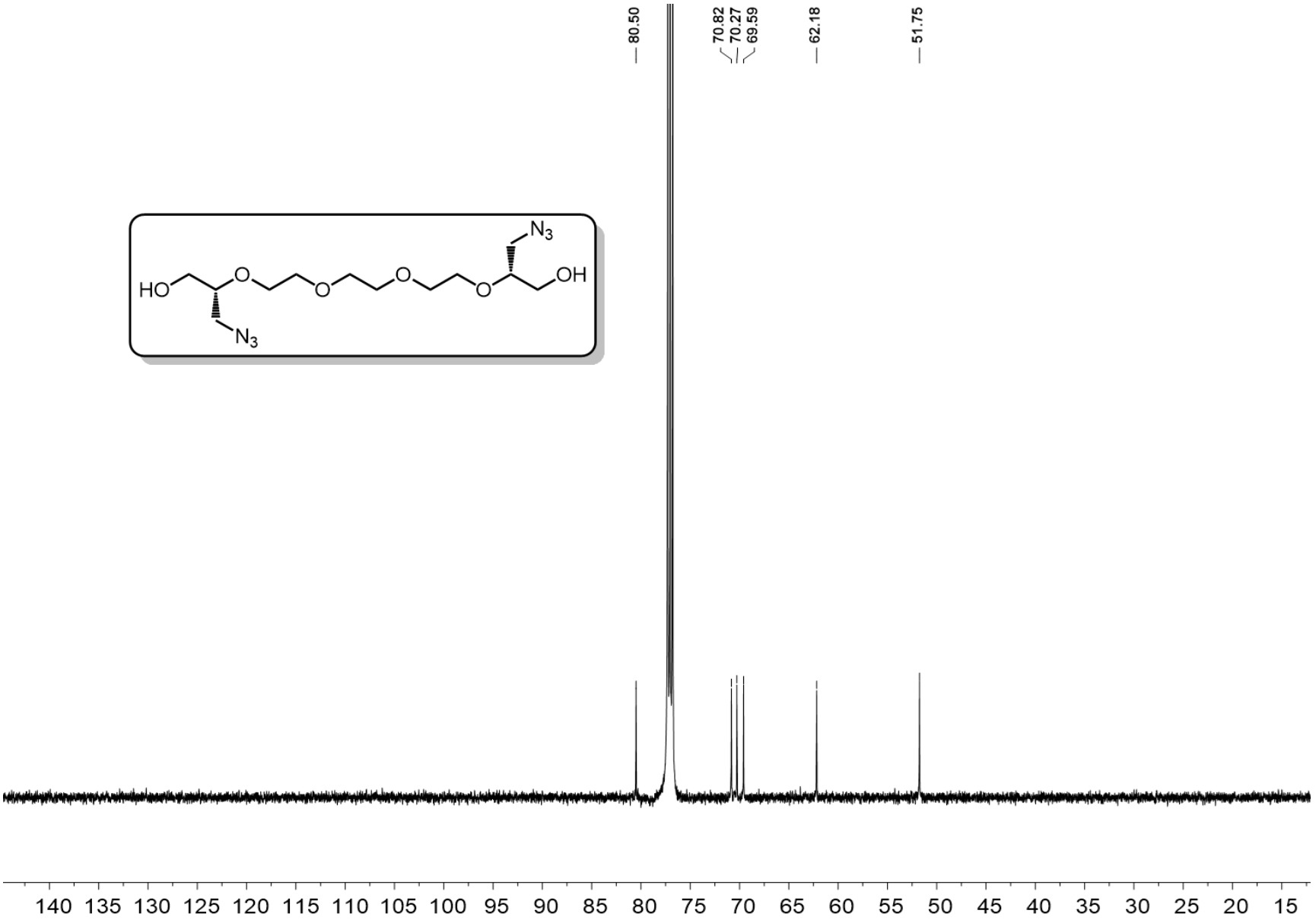
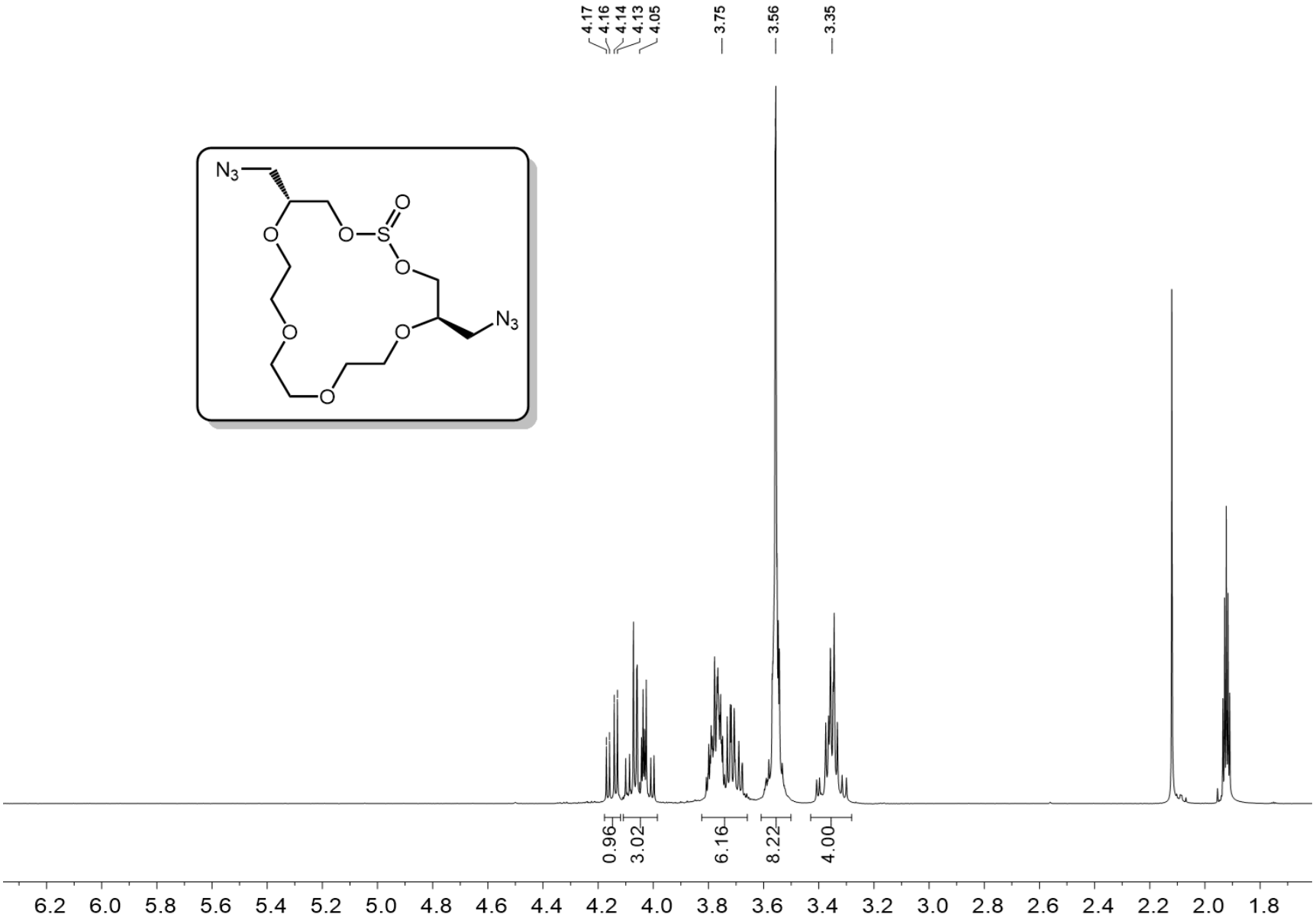

80.50
70.82
70.27
69.59
62.18
51.75
HO
O
O
O
O
OH
N3
N3
140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15


4.17
4.16
4.14
4.13
4.05
3.75
3.56
3.35
N3
O
O
S
O
O
O
O
O
N3
0.96
3.02
6.16
8.22
4.00
6.2
6.0
5.8
5.6
5.4
5.2
5.0
4.8
4.6
4.4
4.2
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3.4
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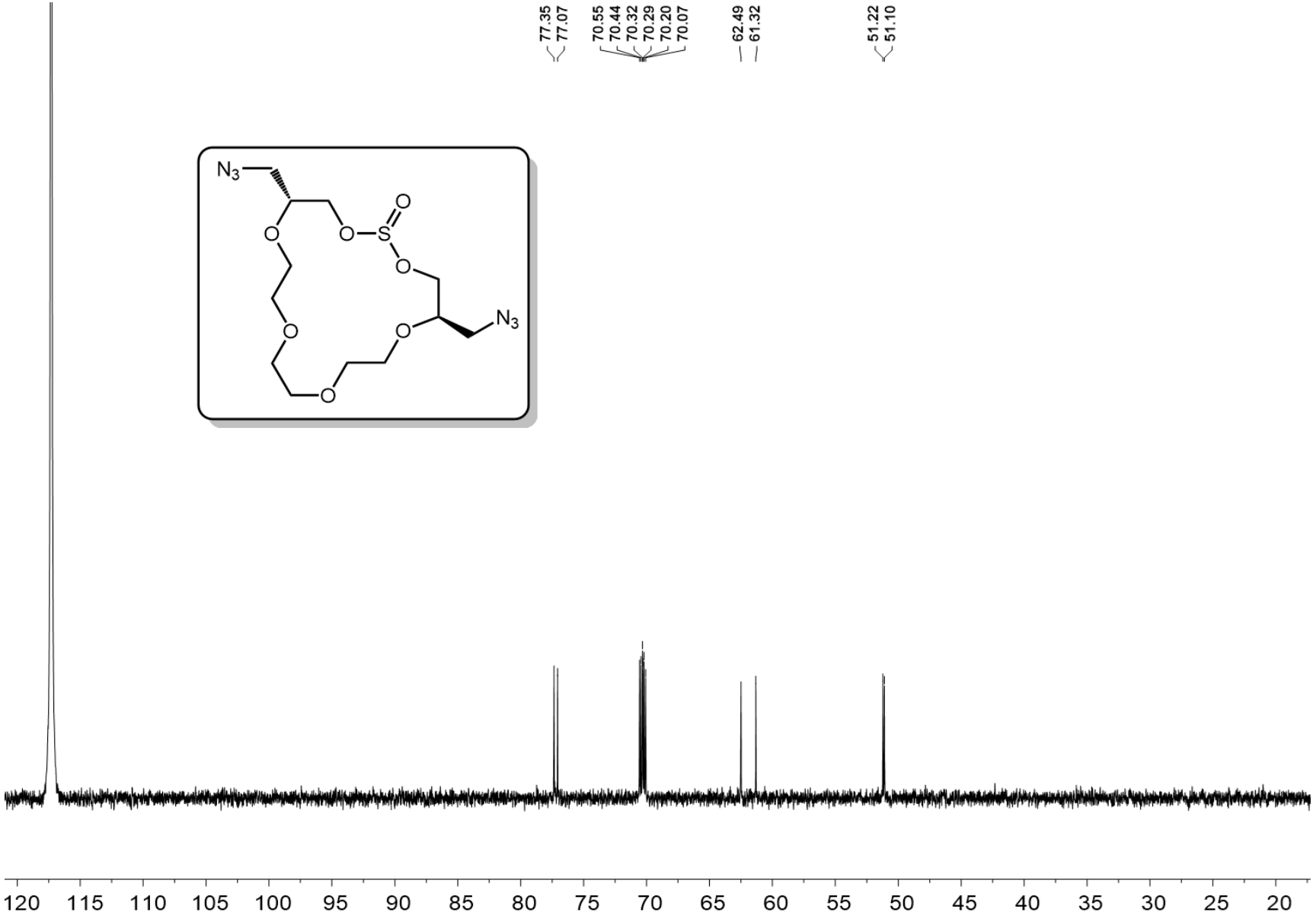
2.6
2.4
2.2
2.0
1.8


77.35
77.07
70.55
70.44
70.32
70.29
70.20
70.07
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61.32
51.22
51.10
N3
O
O
O
S
O
O
O
O
N3
120
115
110
105
100
95
90
85
80
75
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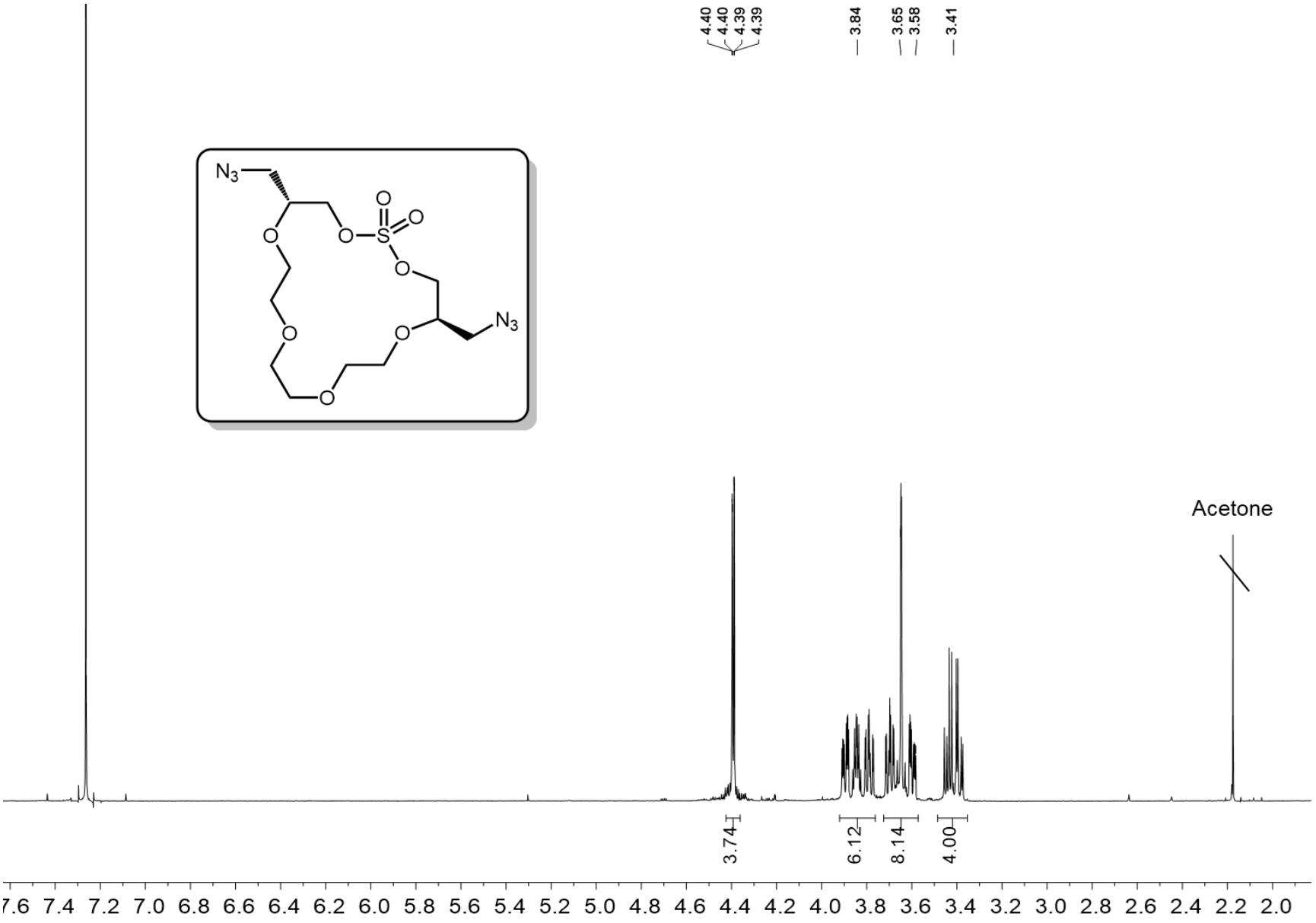
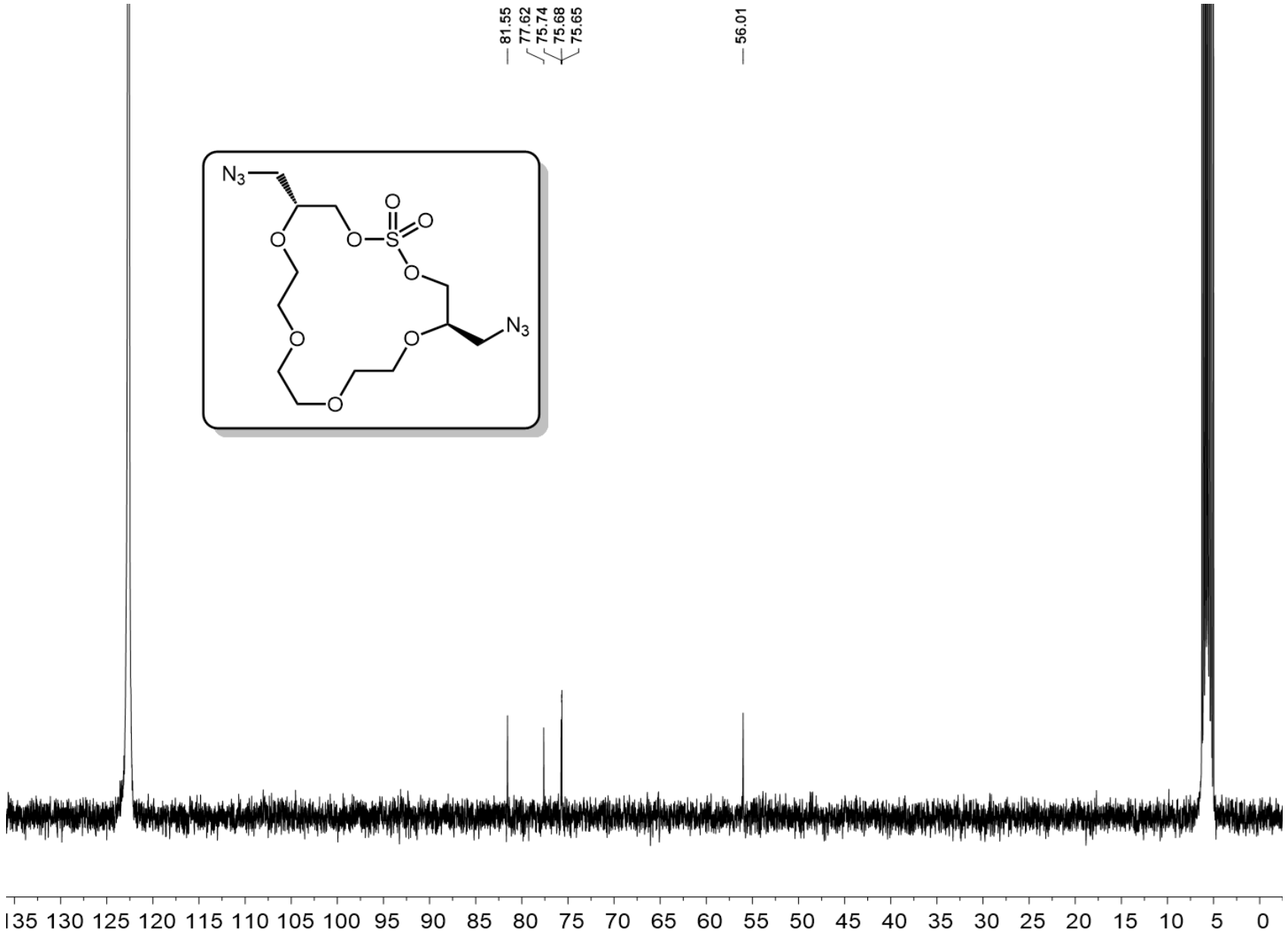
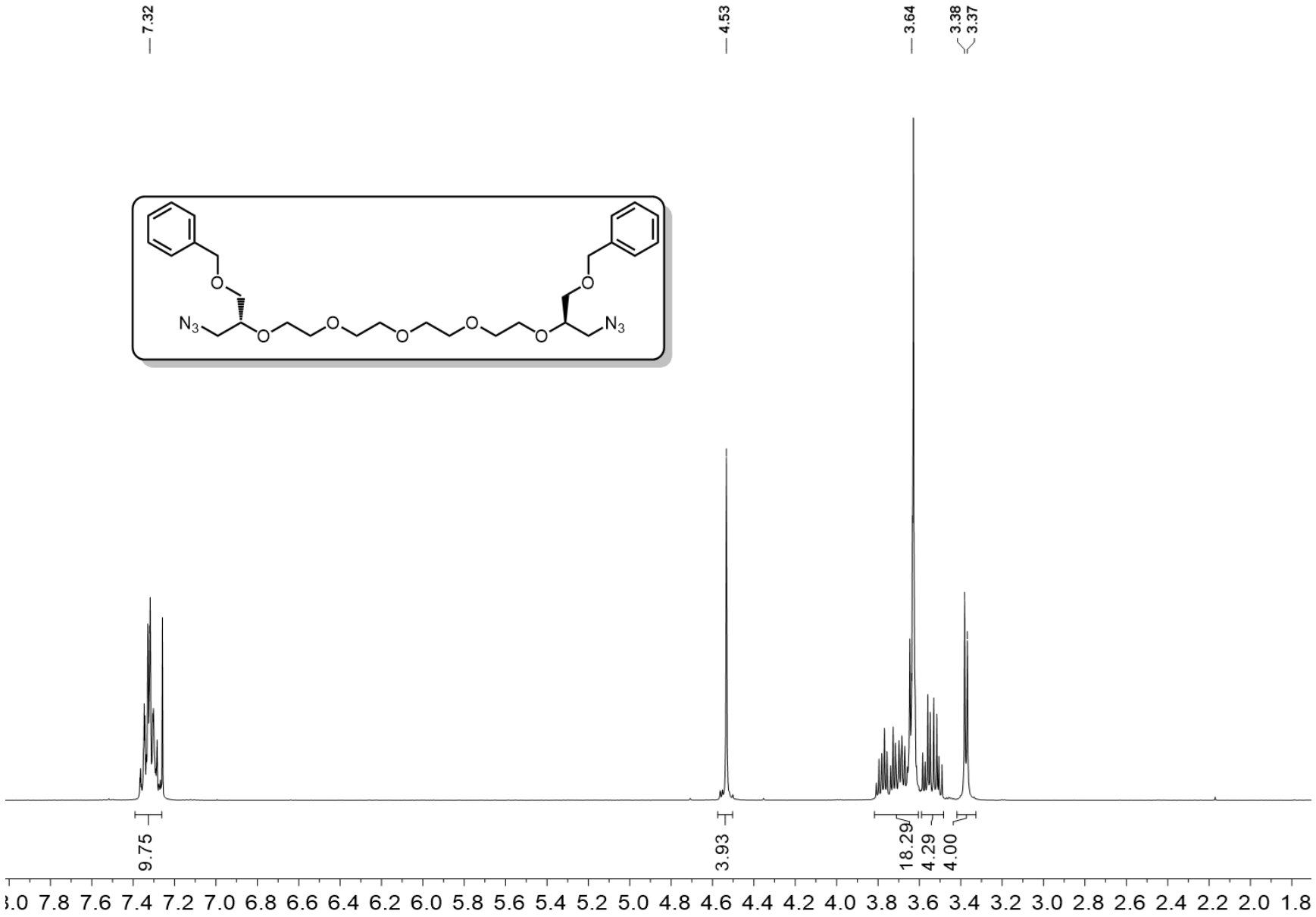
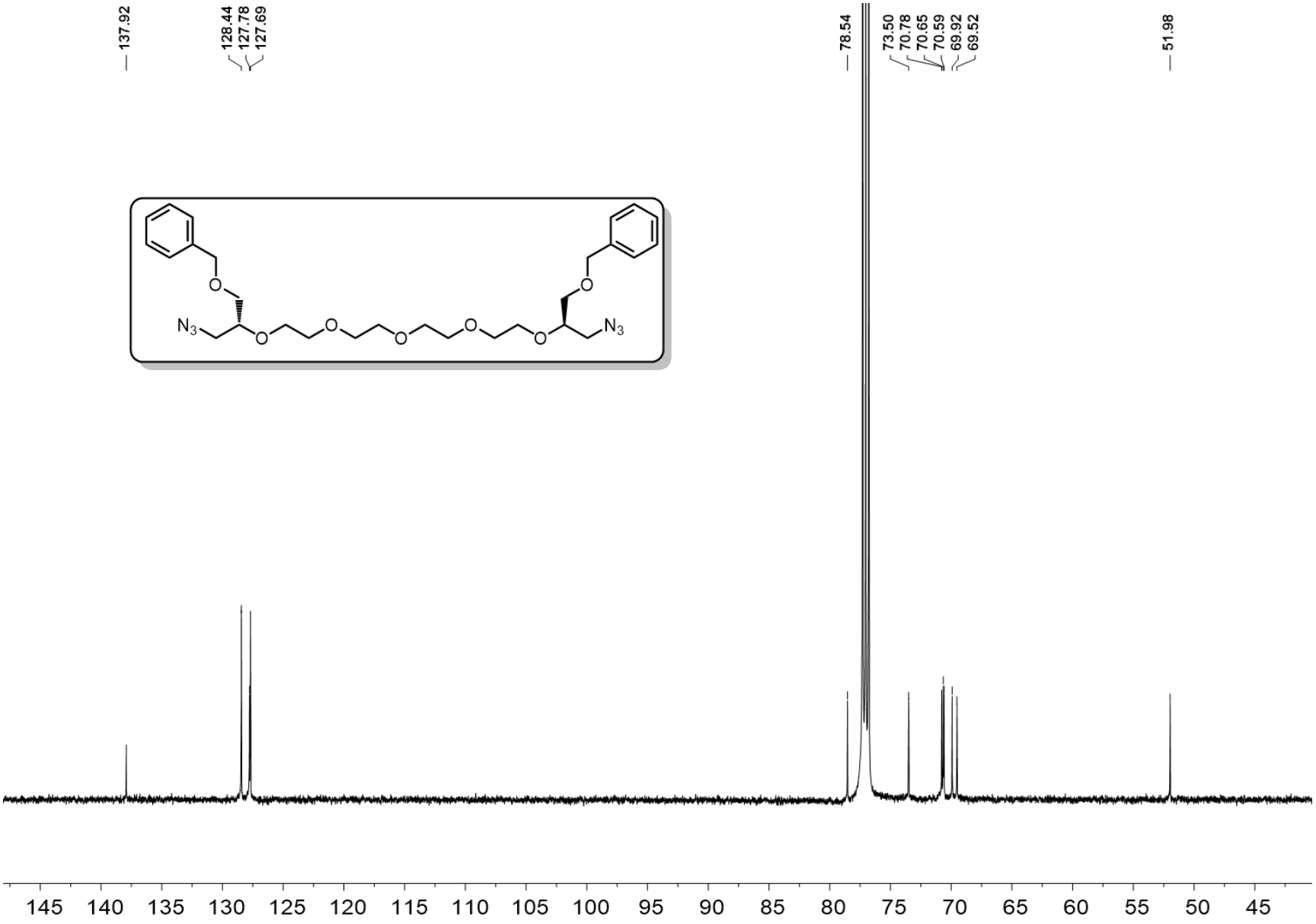
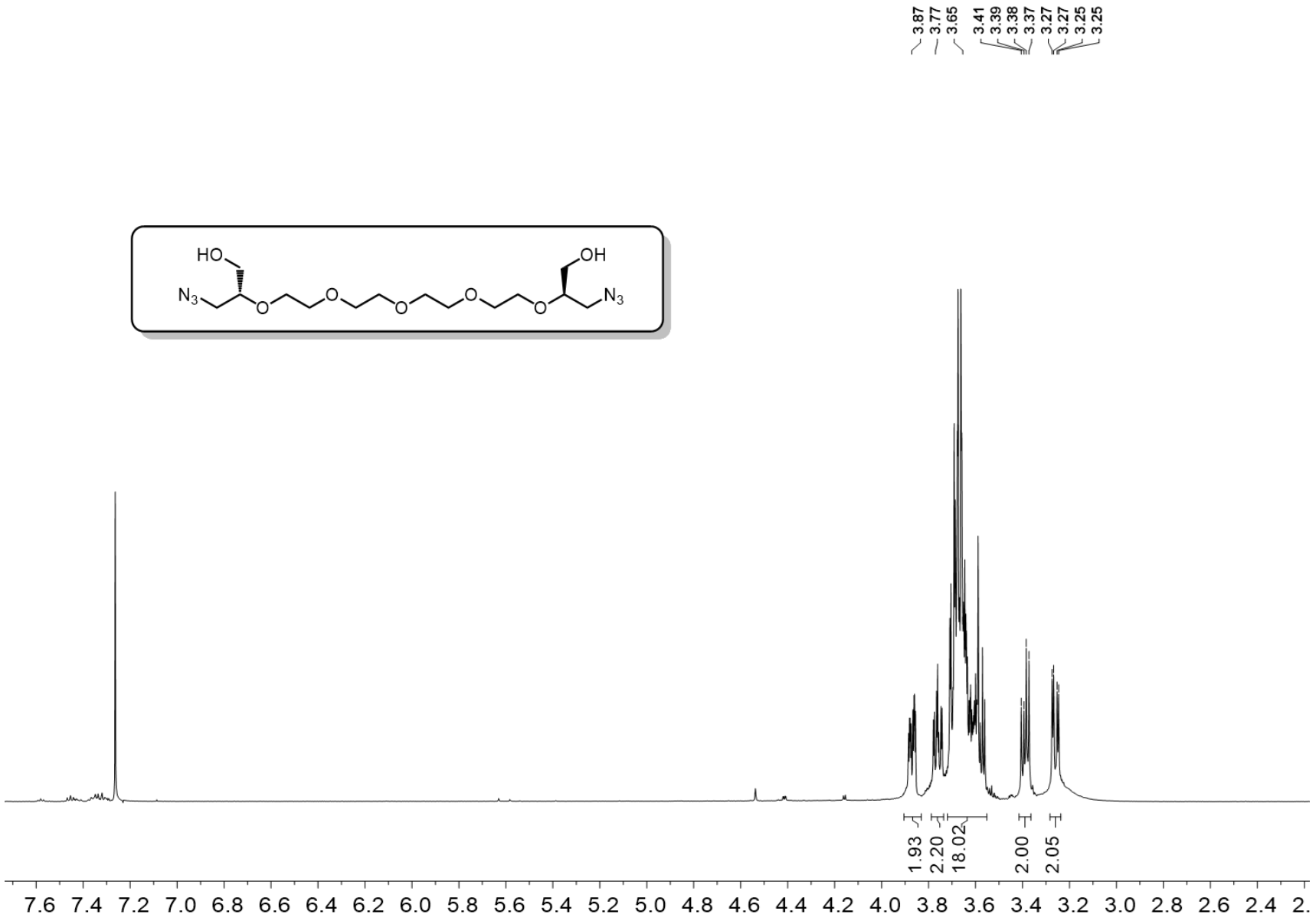
65
60
55
50
45
40
35
30
25
20


4.40
4.40
4.39
4.39
3.84
3.65
3.58
3.41
Acetone
3.74
6.12
8.14
4.00
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0


81.55
77.62
75.74
75.68
75.65
56.01
N3
O
O
O
O
S
O
O
O
O
O
N3
135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45 40 35 30 25 20 15 10 5 0


7.32
4.53
3.64
3.38
3.37
9.75
3.93
18.29
4.29
4.00
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8


137.92
128.44
127.78
127.69
78.54
73.50
70.78
70.65
70.59
69.92
69.52
51.98
N3
N3
O
145 140 135 130 125 120 115 110 105 100 95 90 85 80 75 70 65 60 55 50 45


3.87
3.77
3.65
3.41
3.39
3.38
3.37
3.27
3.27
3.25
3.25
HO
OH
N3
N3
O
O
O
O
O
1.93
2.20
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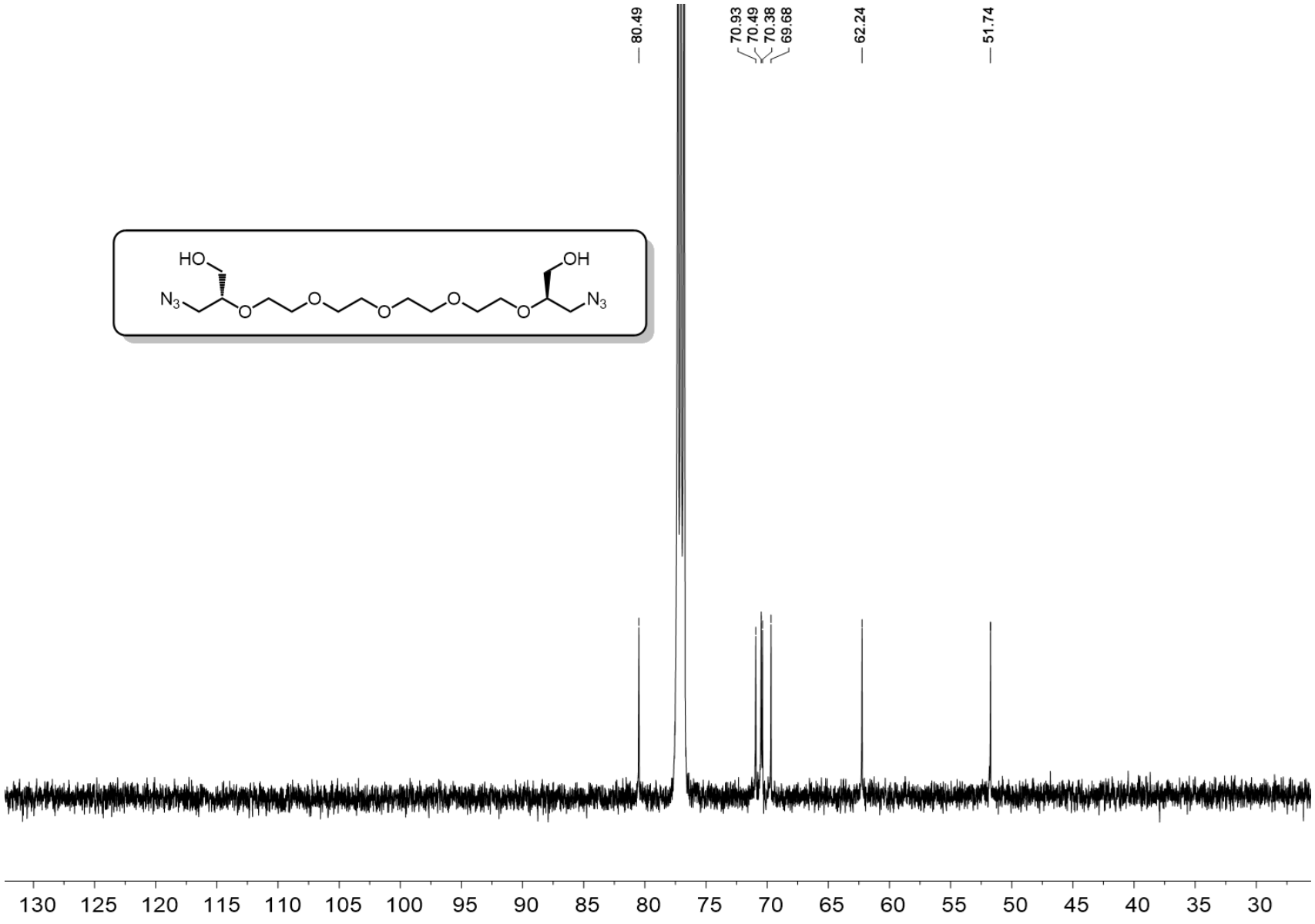
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.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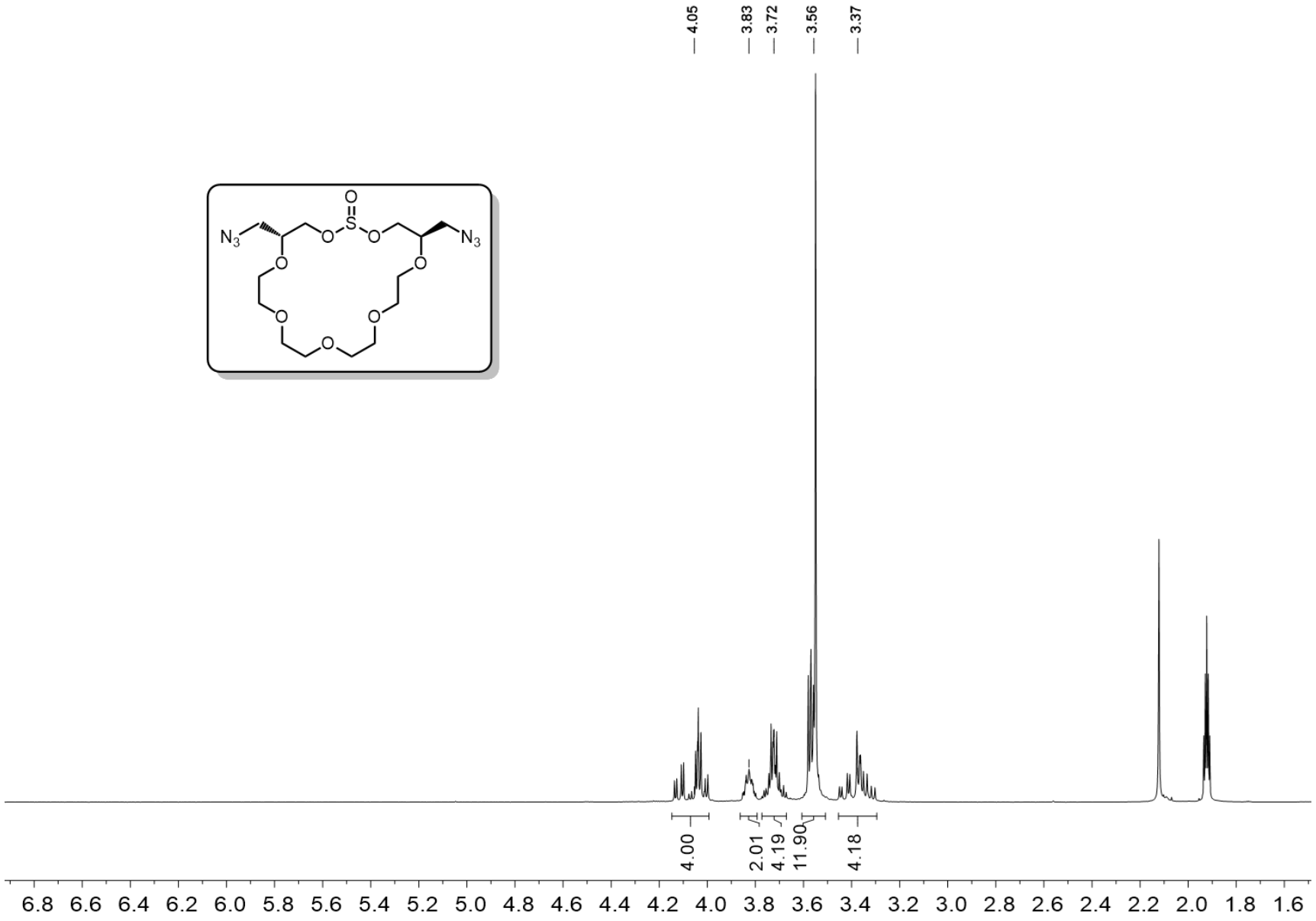
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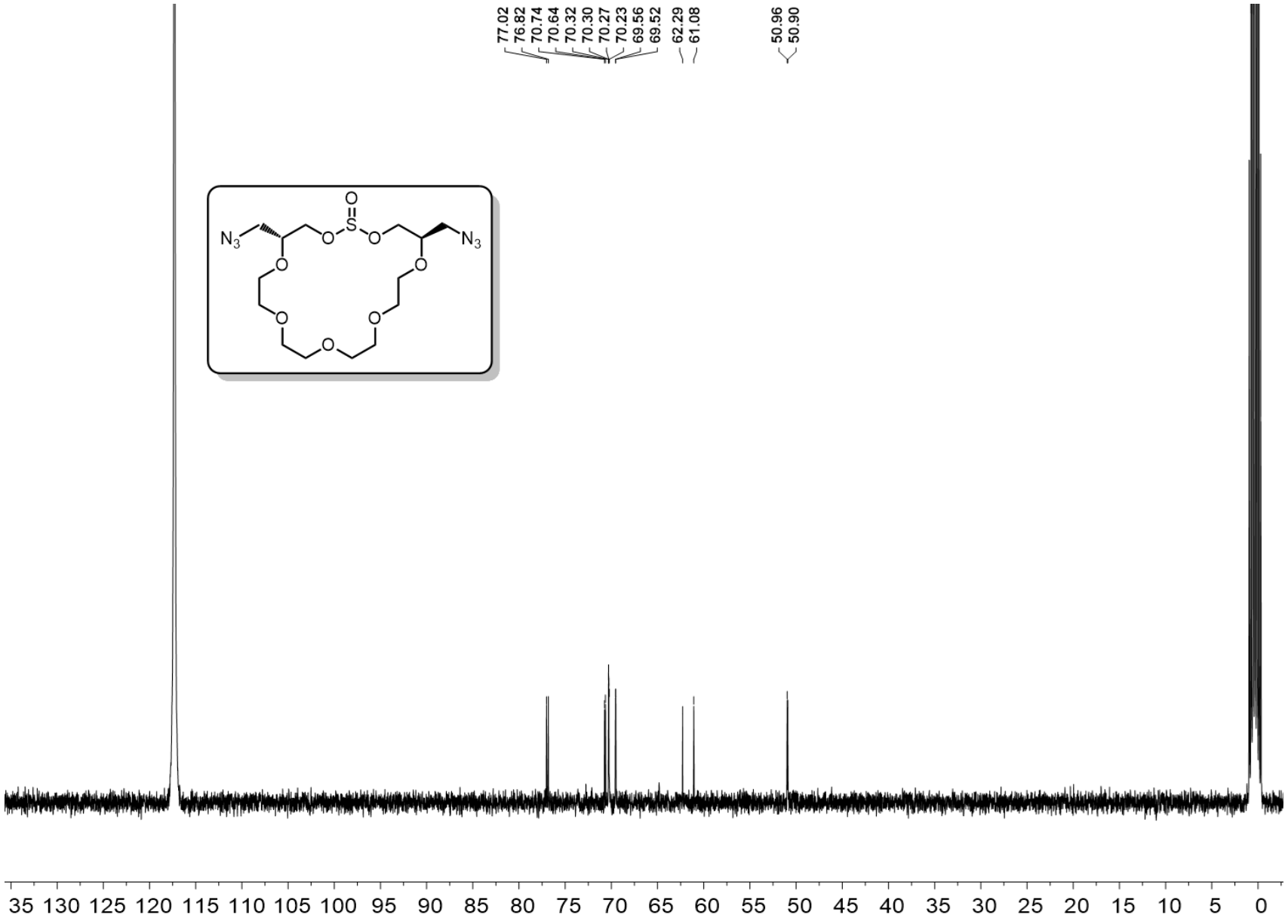
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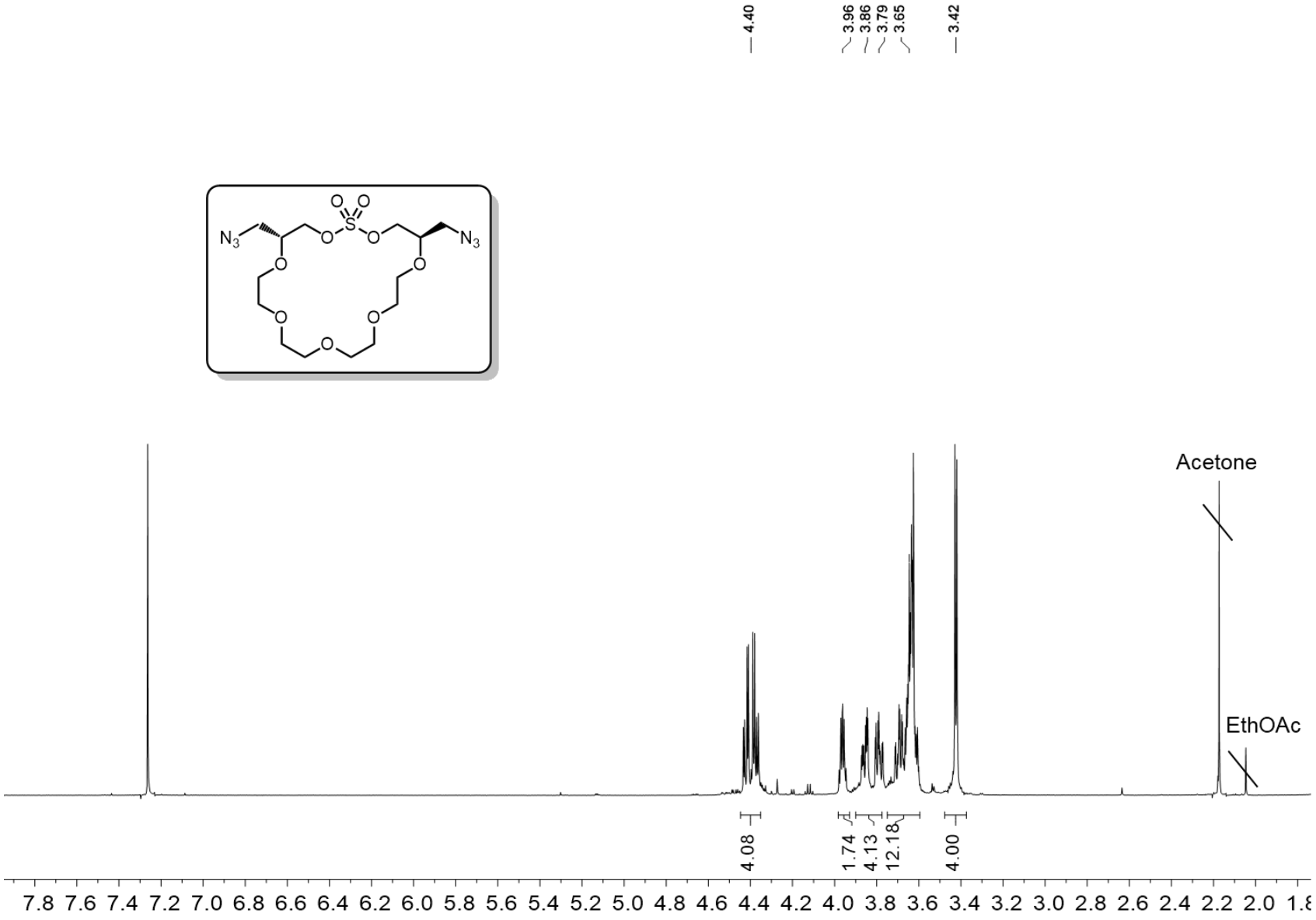
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EthOAc
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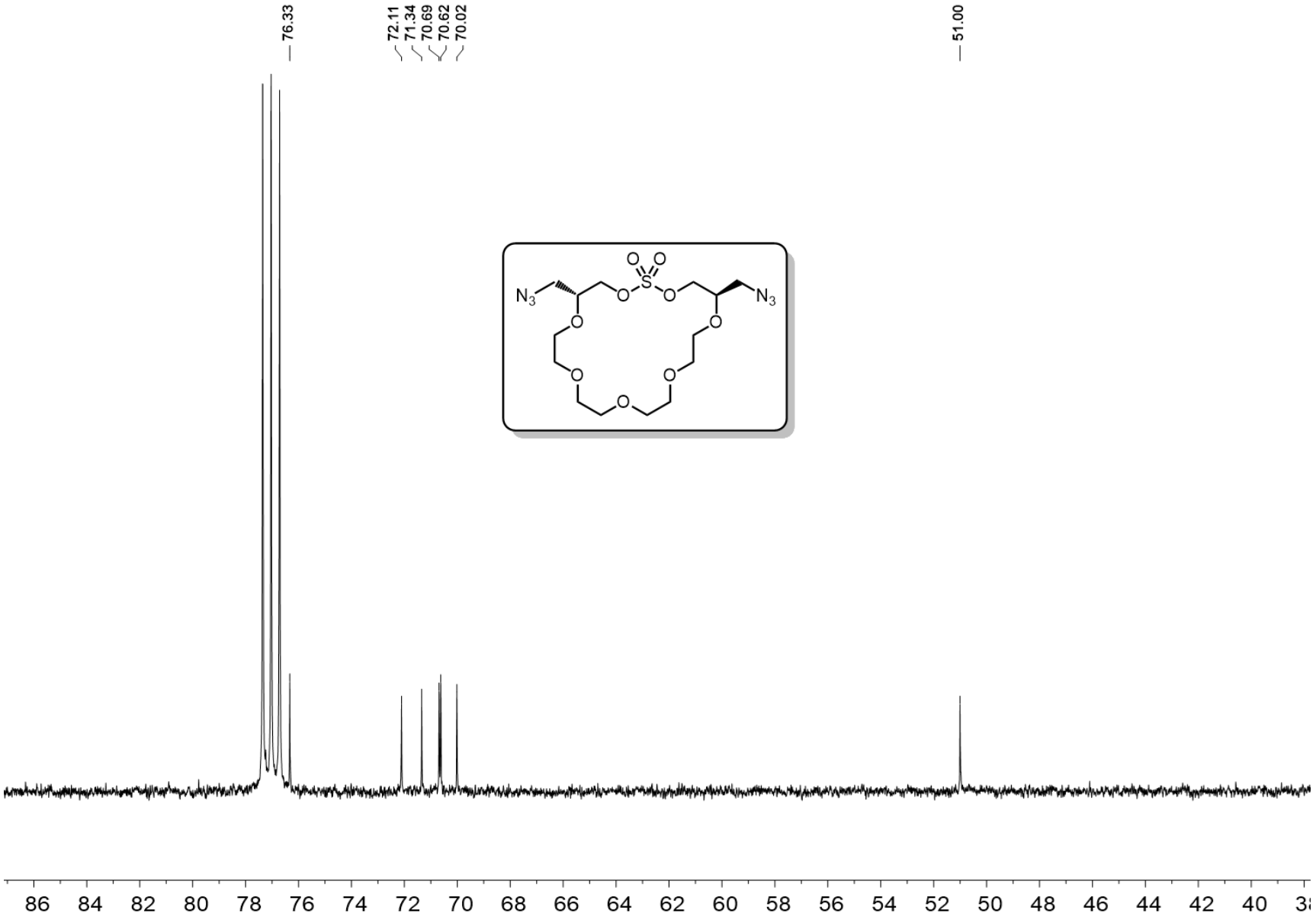
4.00
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0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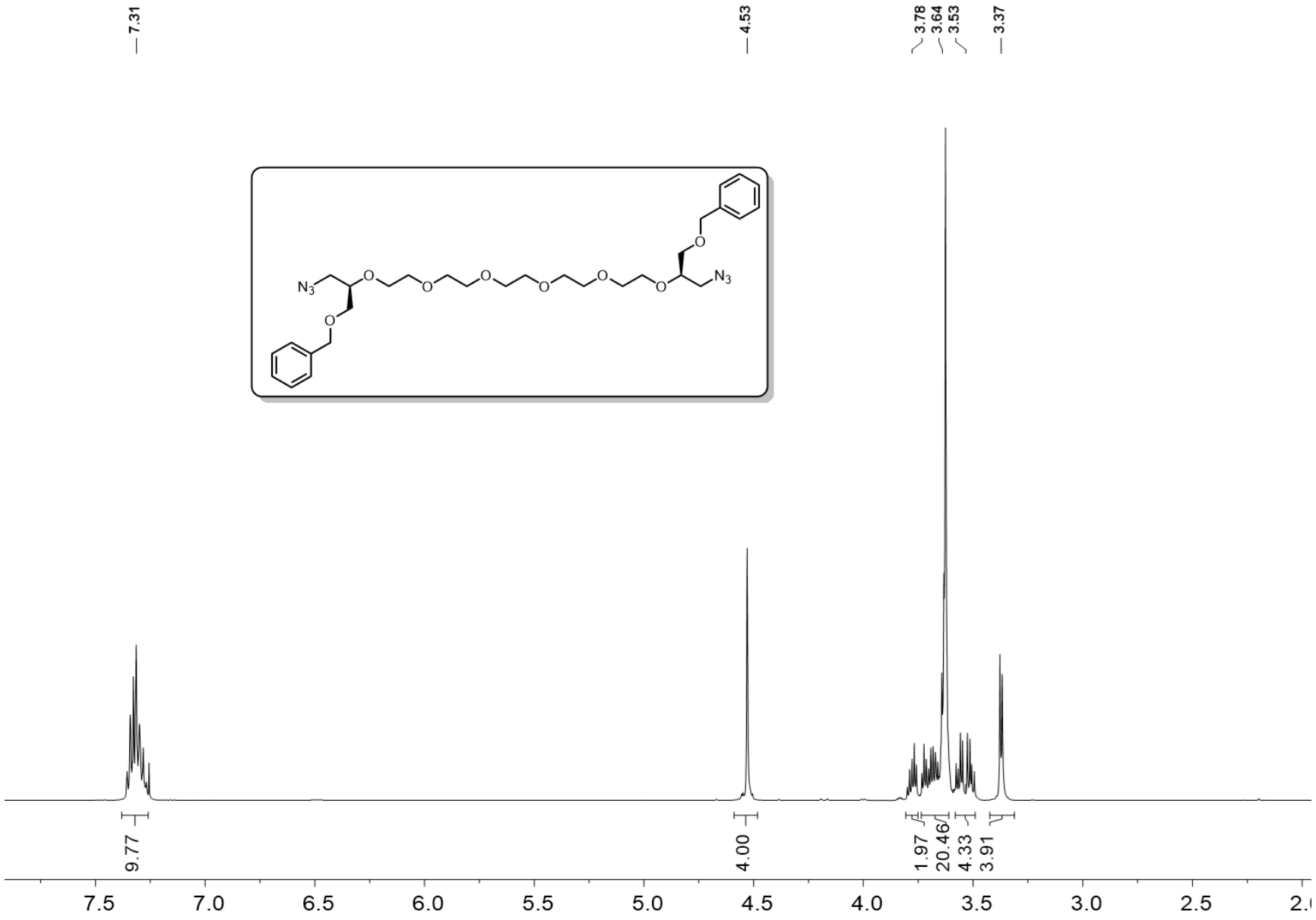
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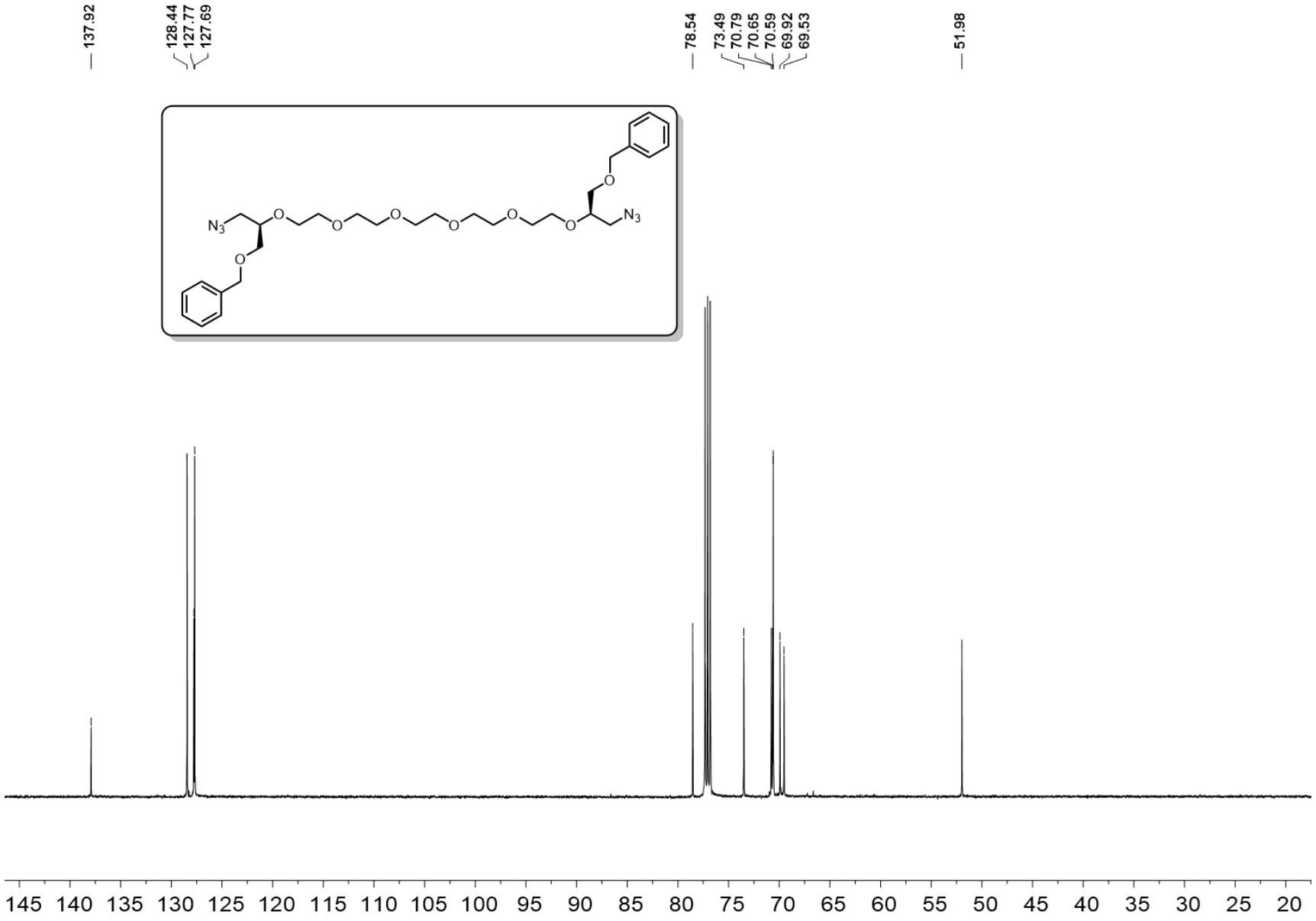
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N3
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3.88
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HO
N3
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24.30
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1.84
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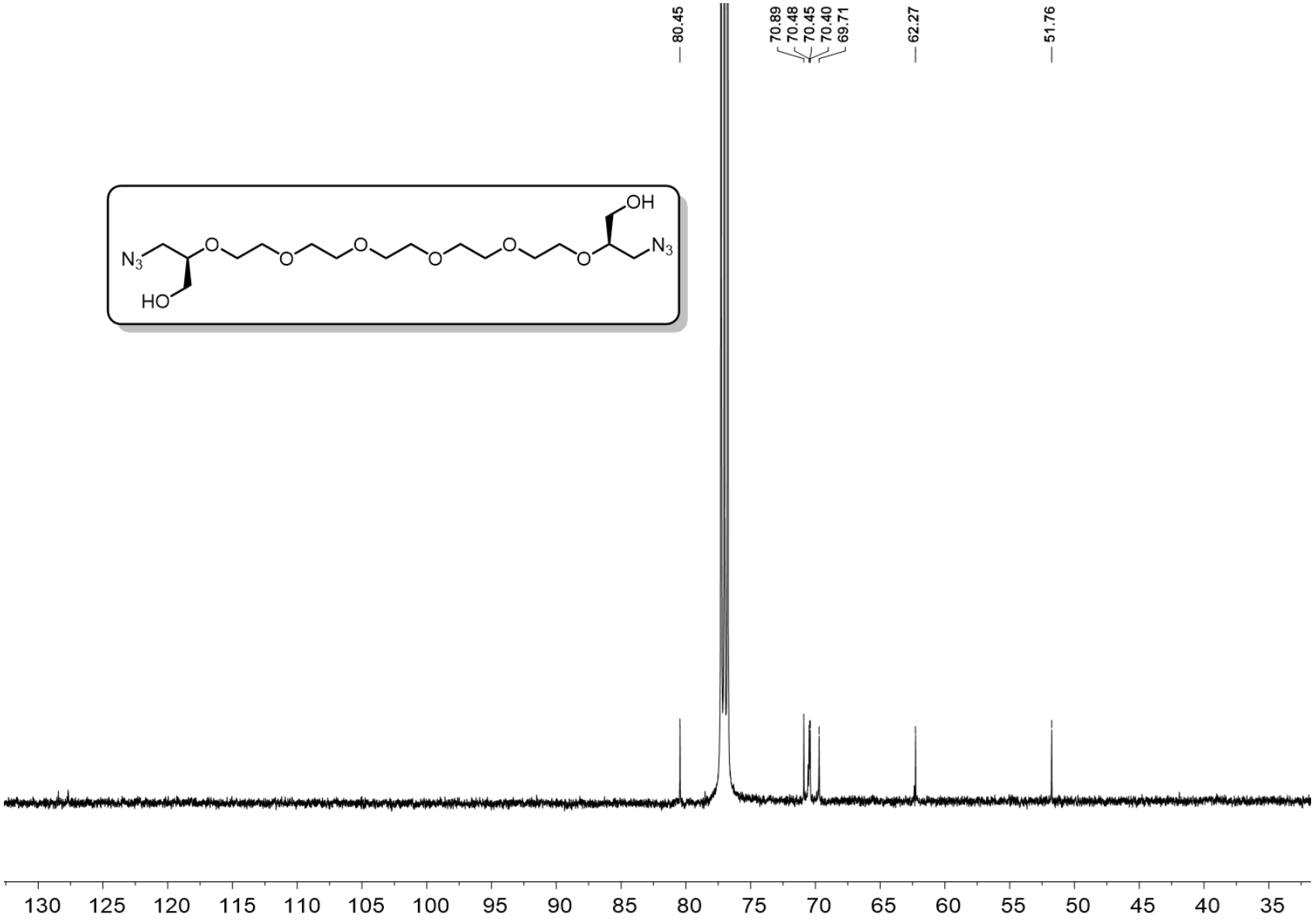
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N3
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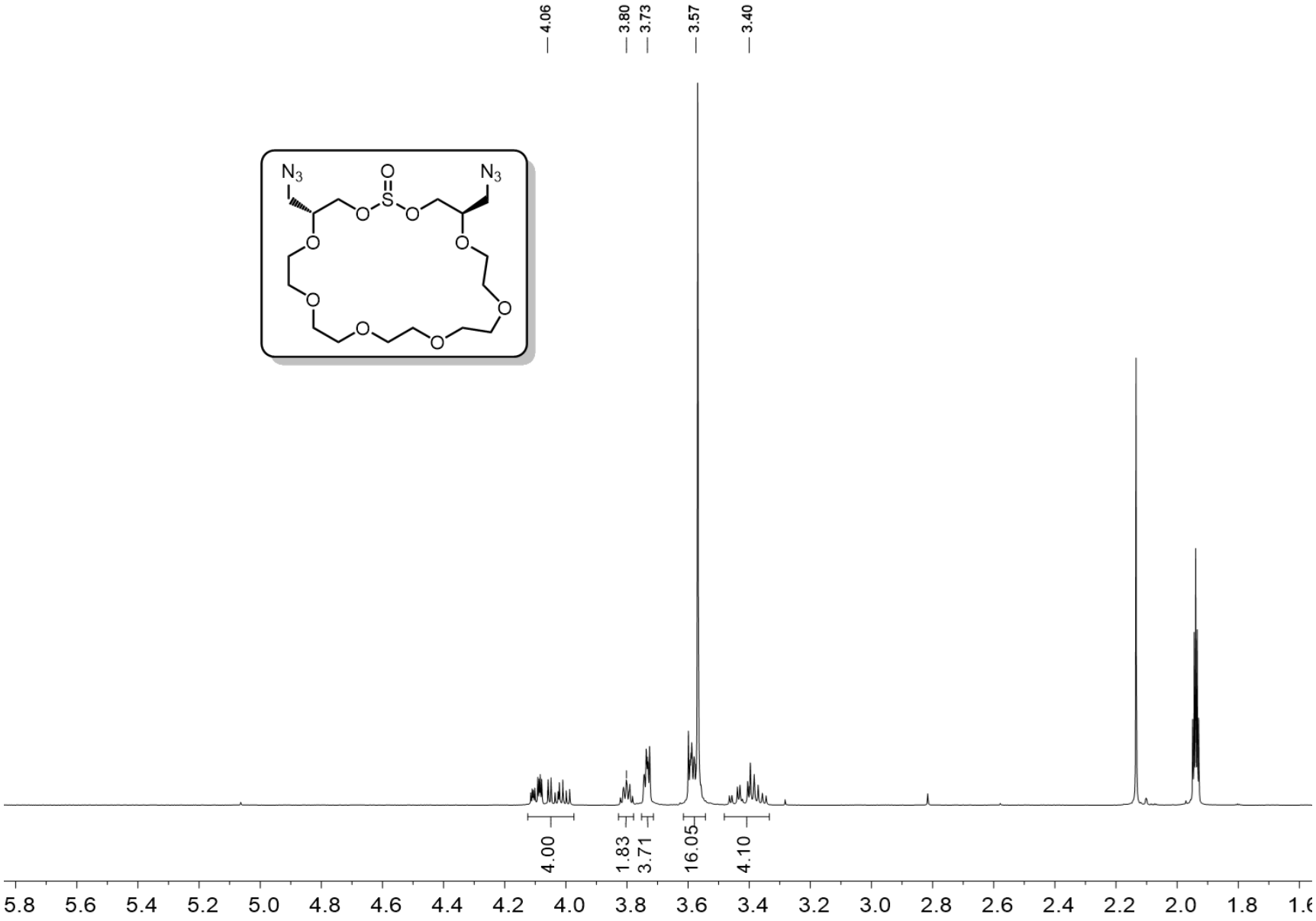
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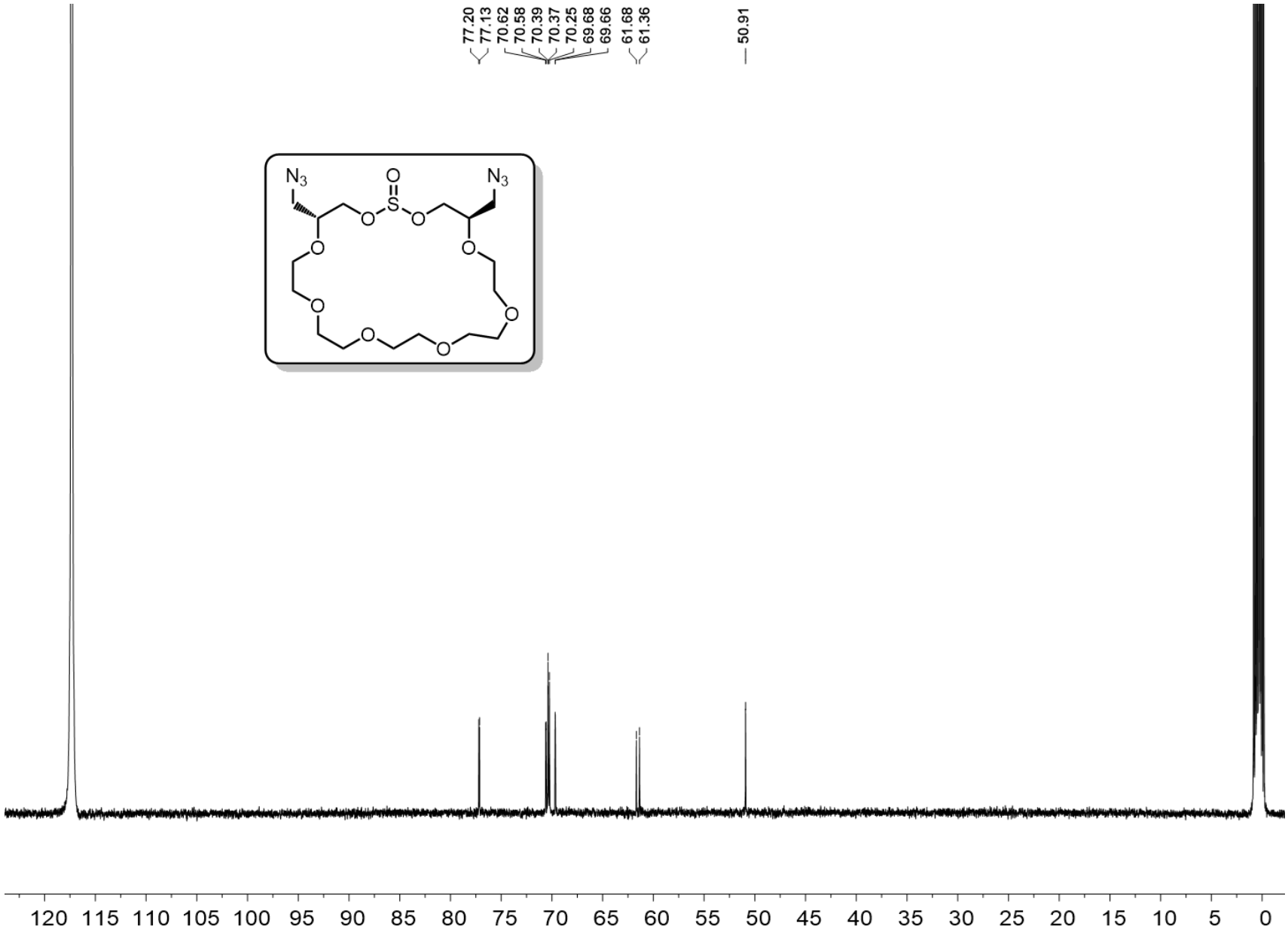
1.8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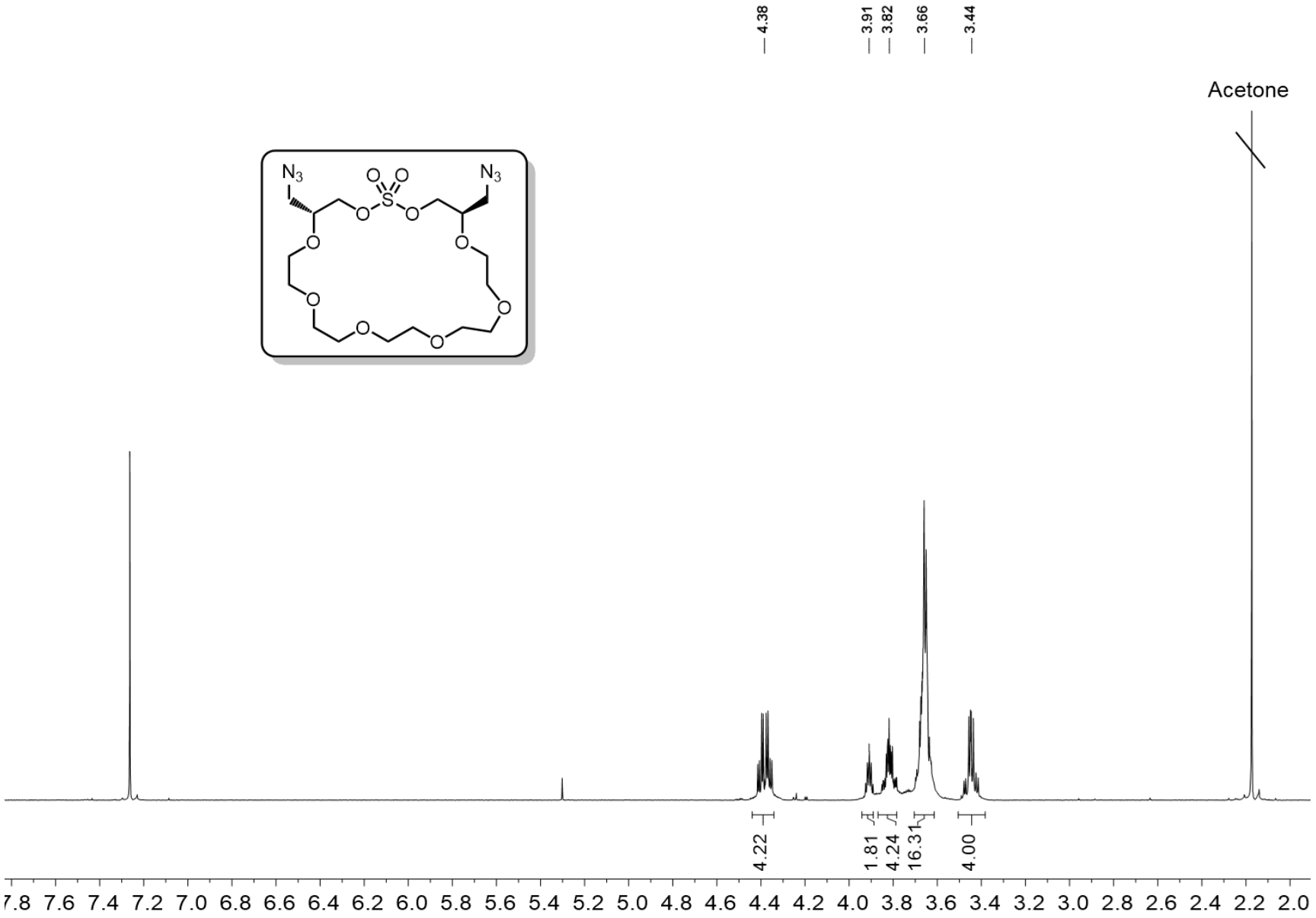
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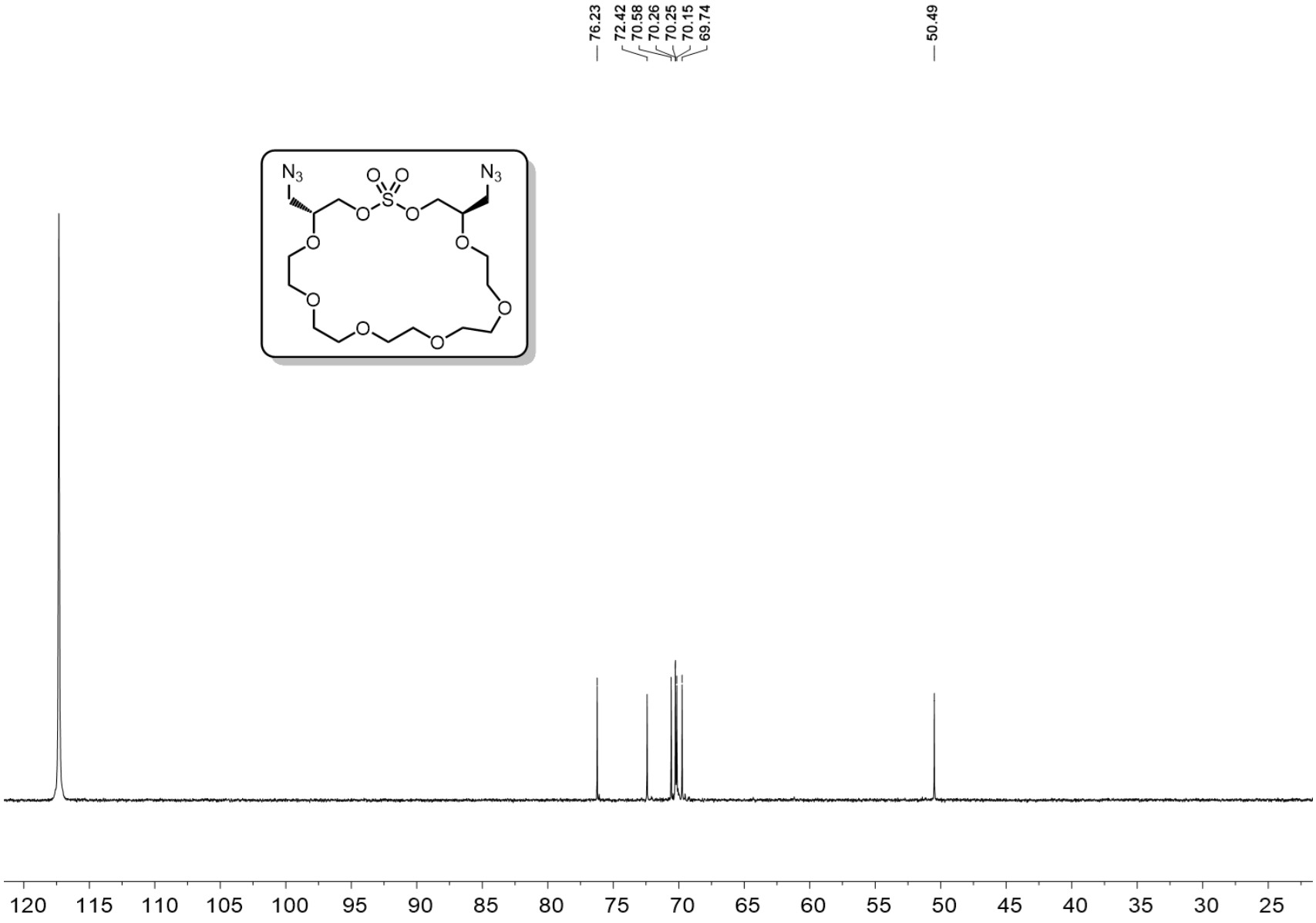
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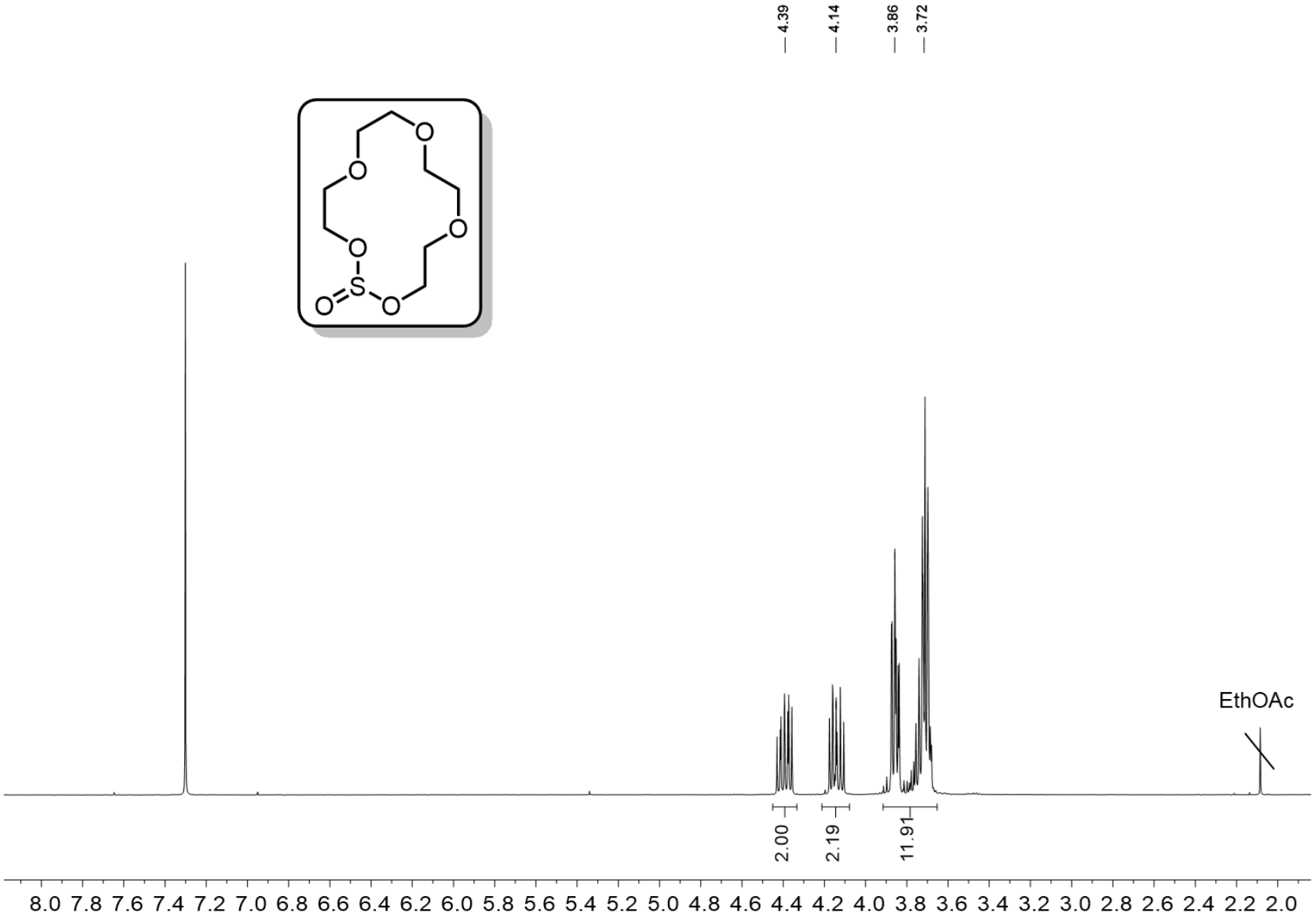
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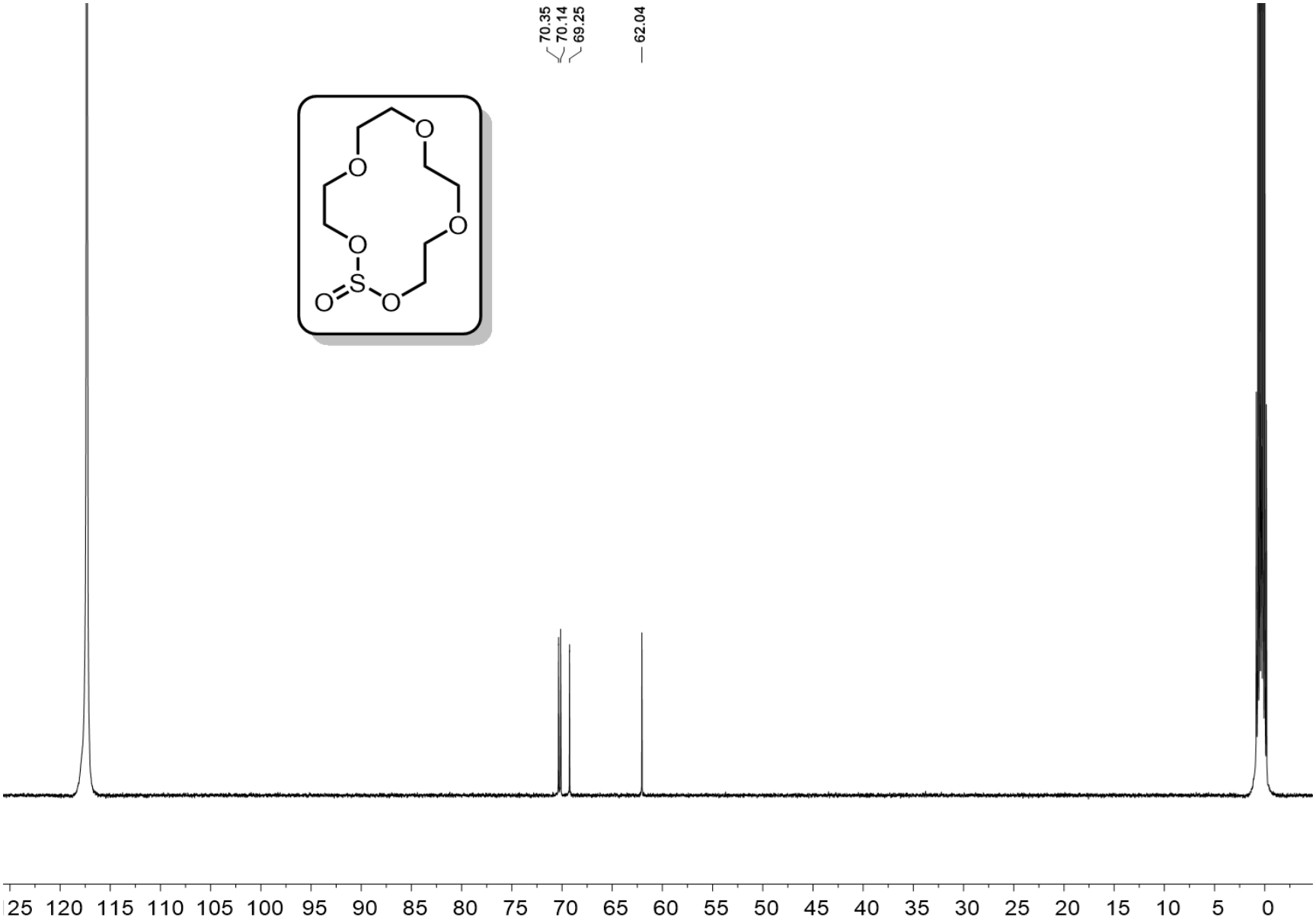
2.19
11.91
8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0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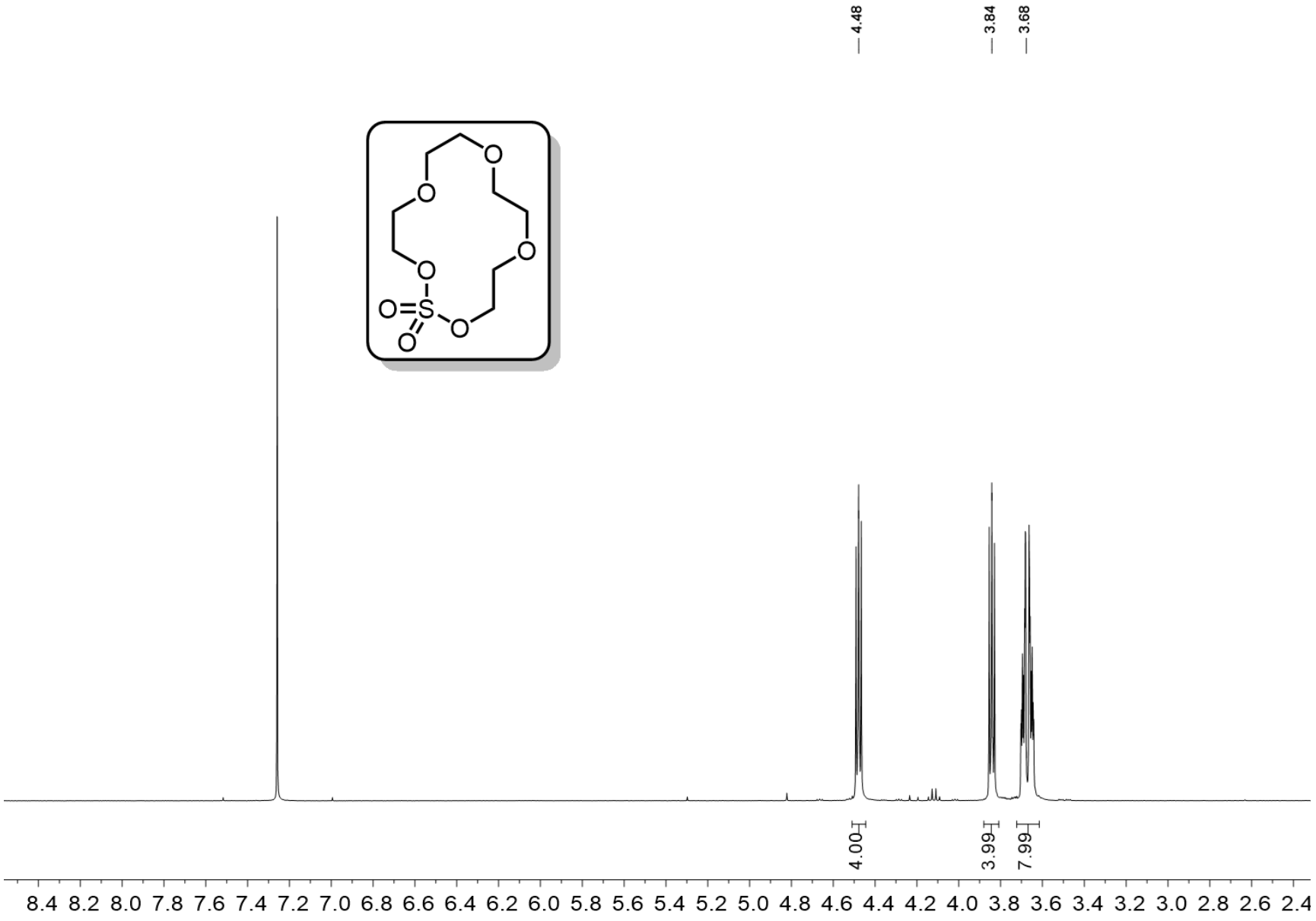
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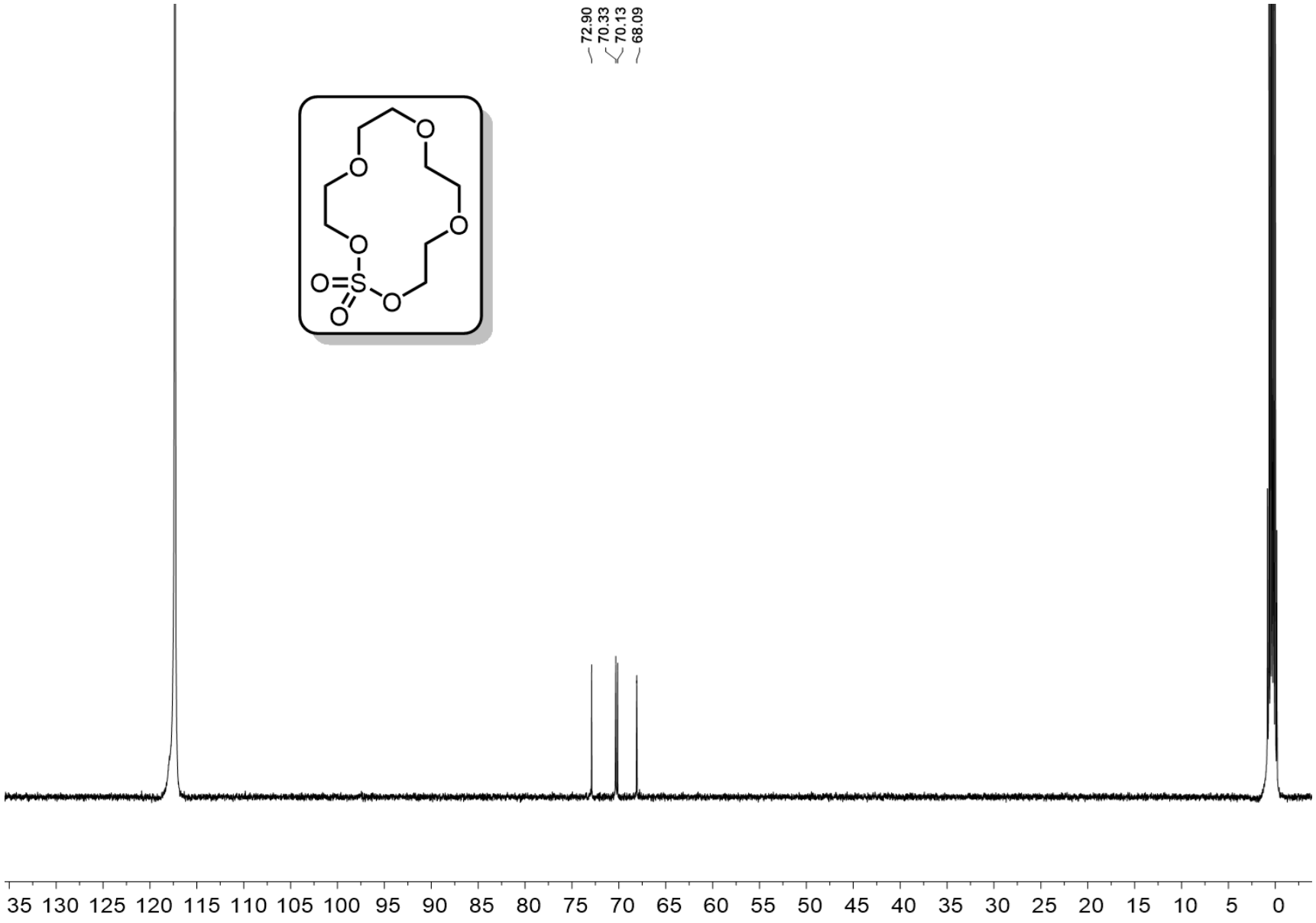
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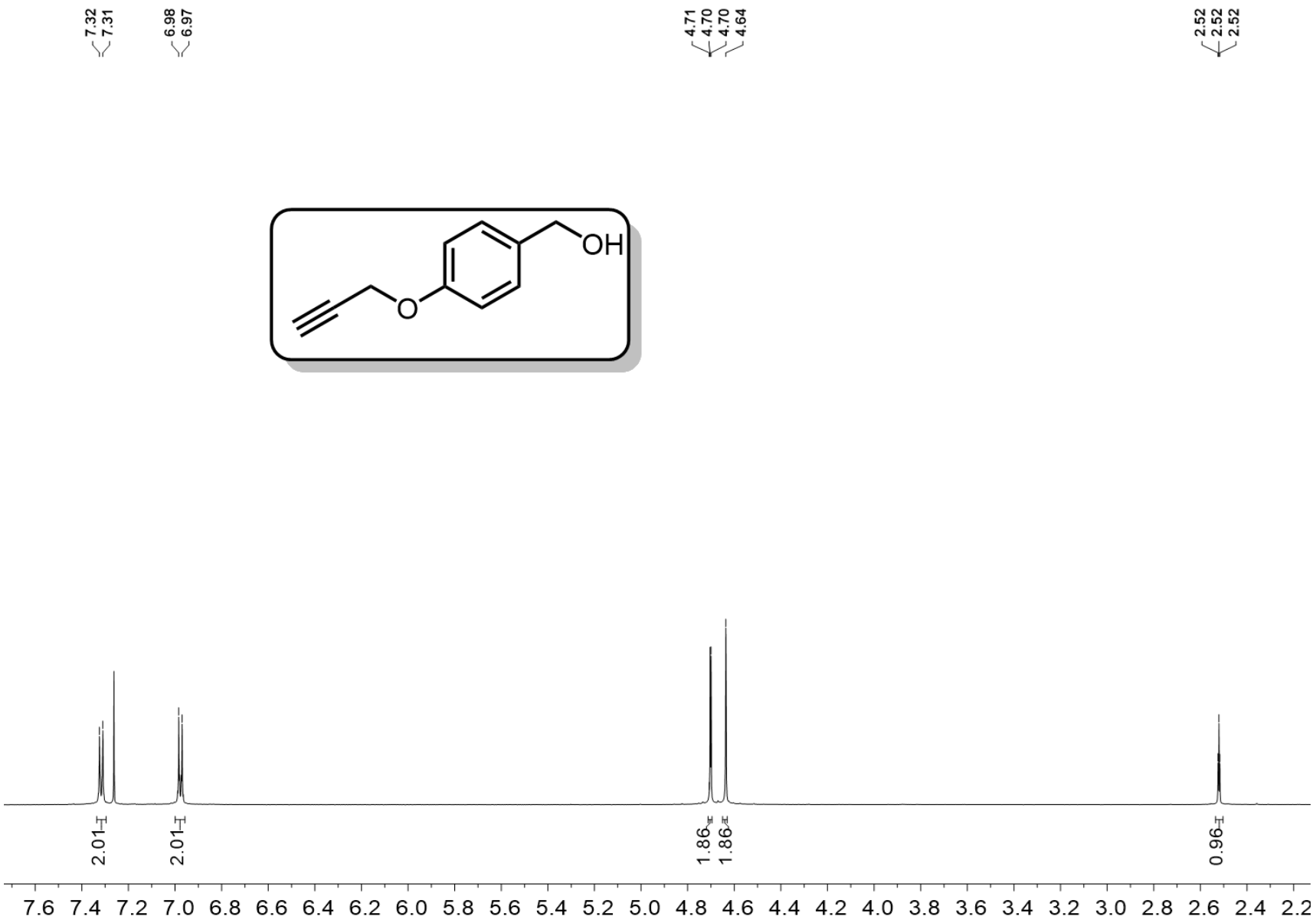
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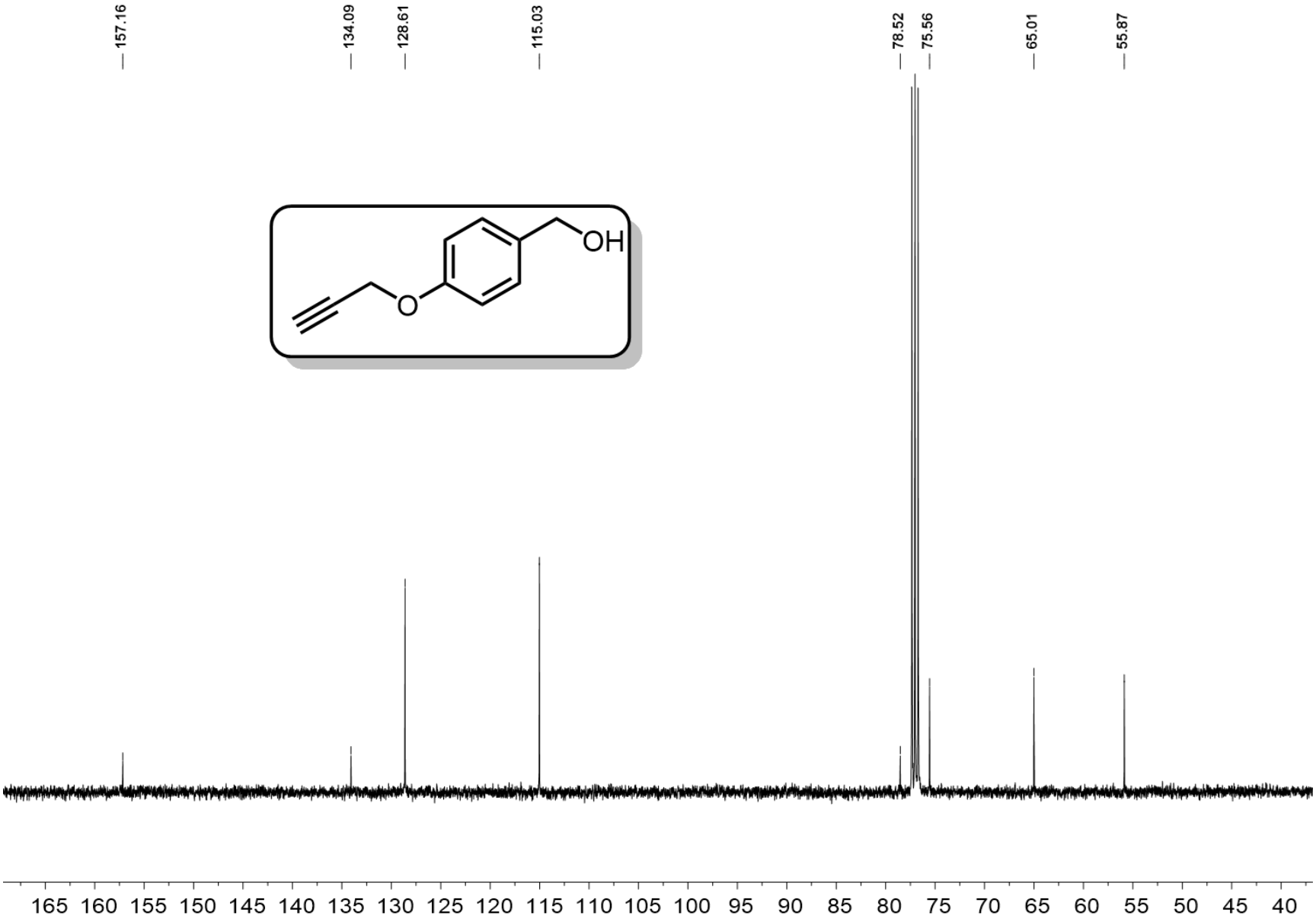
2.01
1.86
1.86
0.96
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2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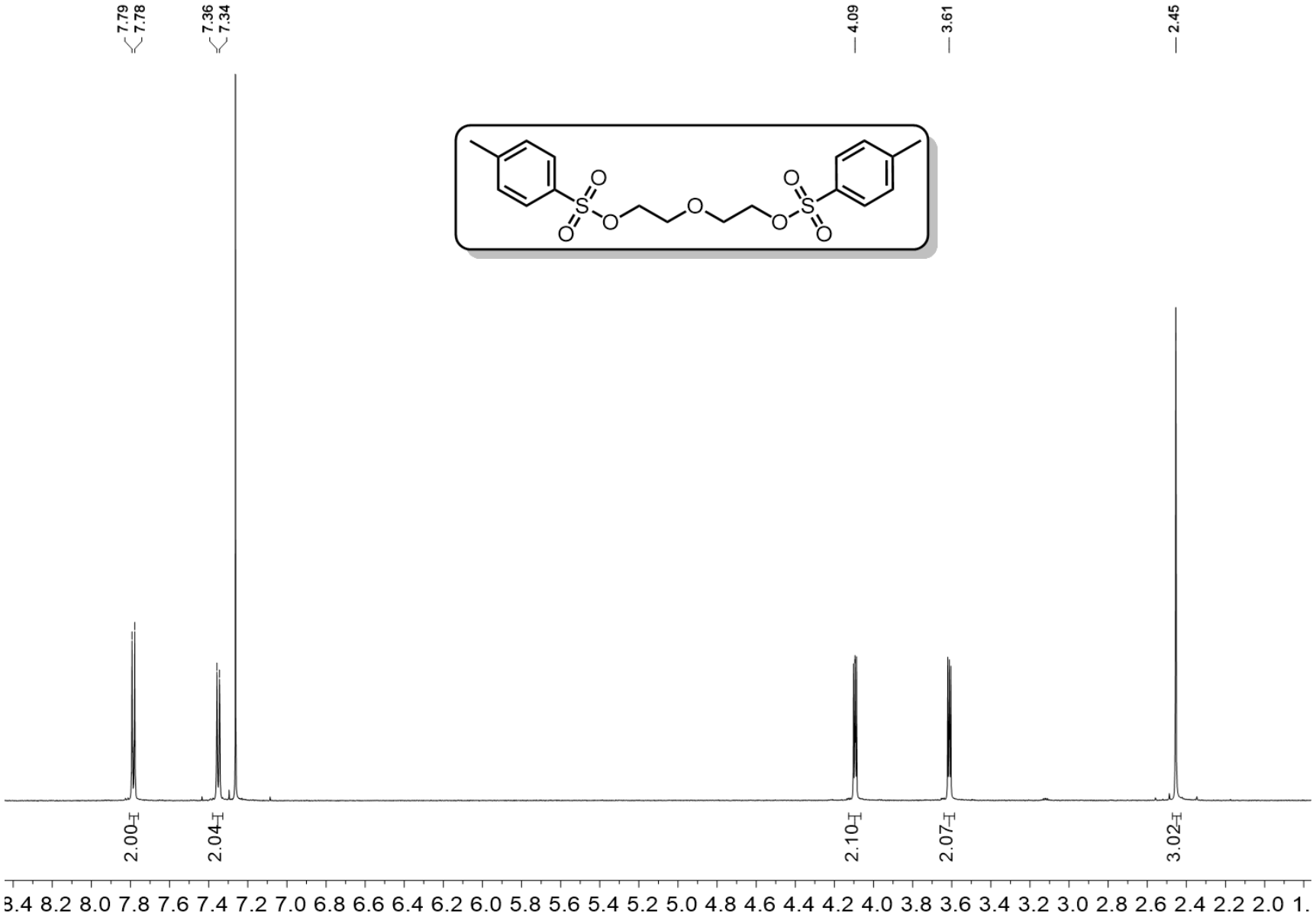
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2.07
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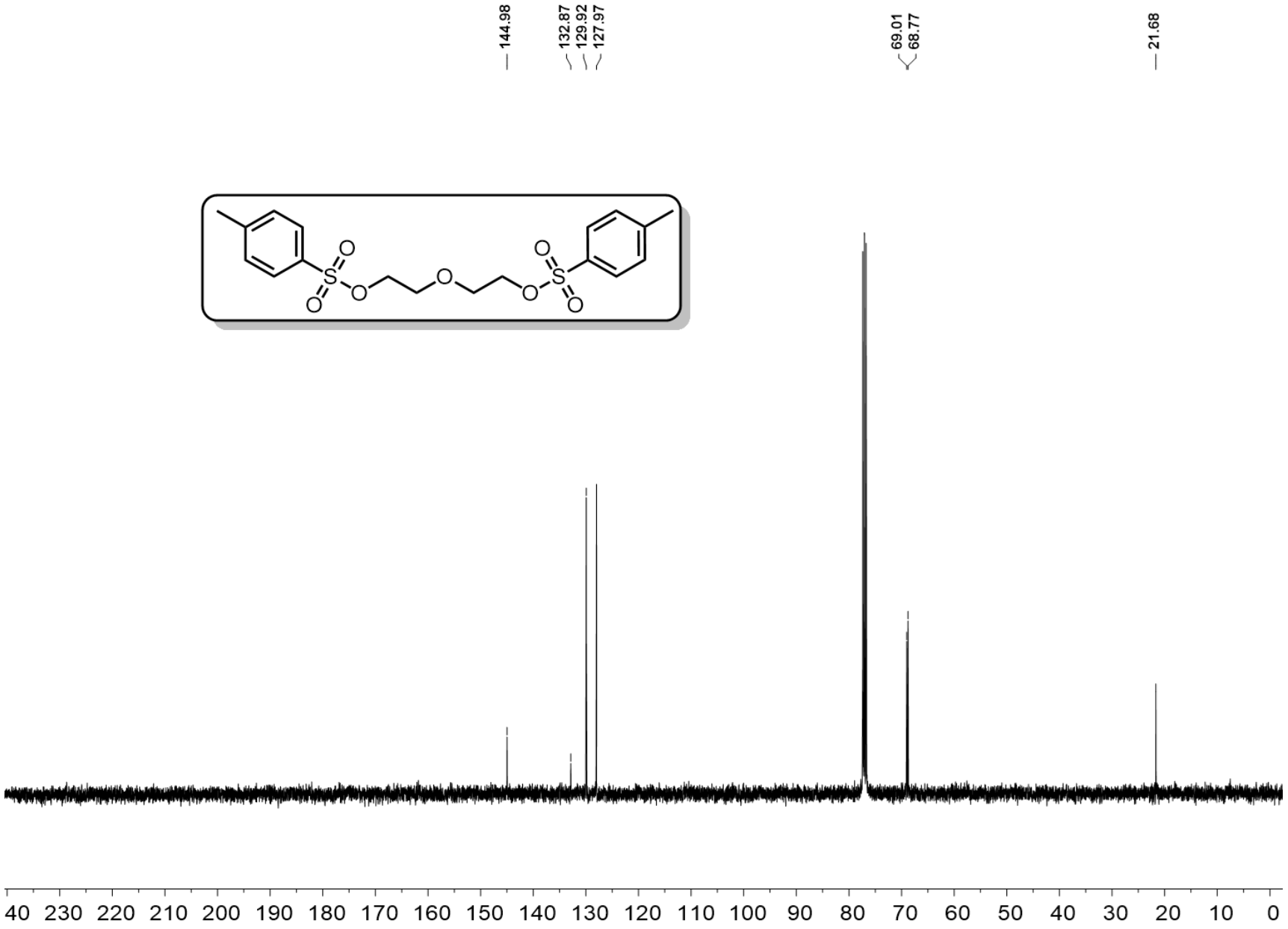
8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.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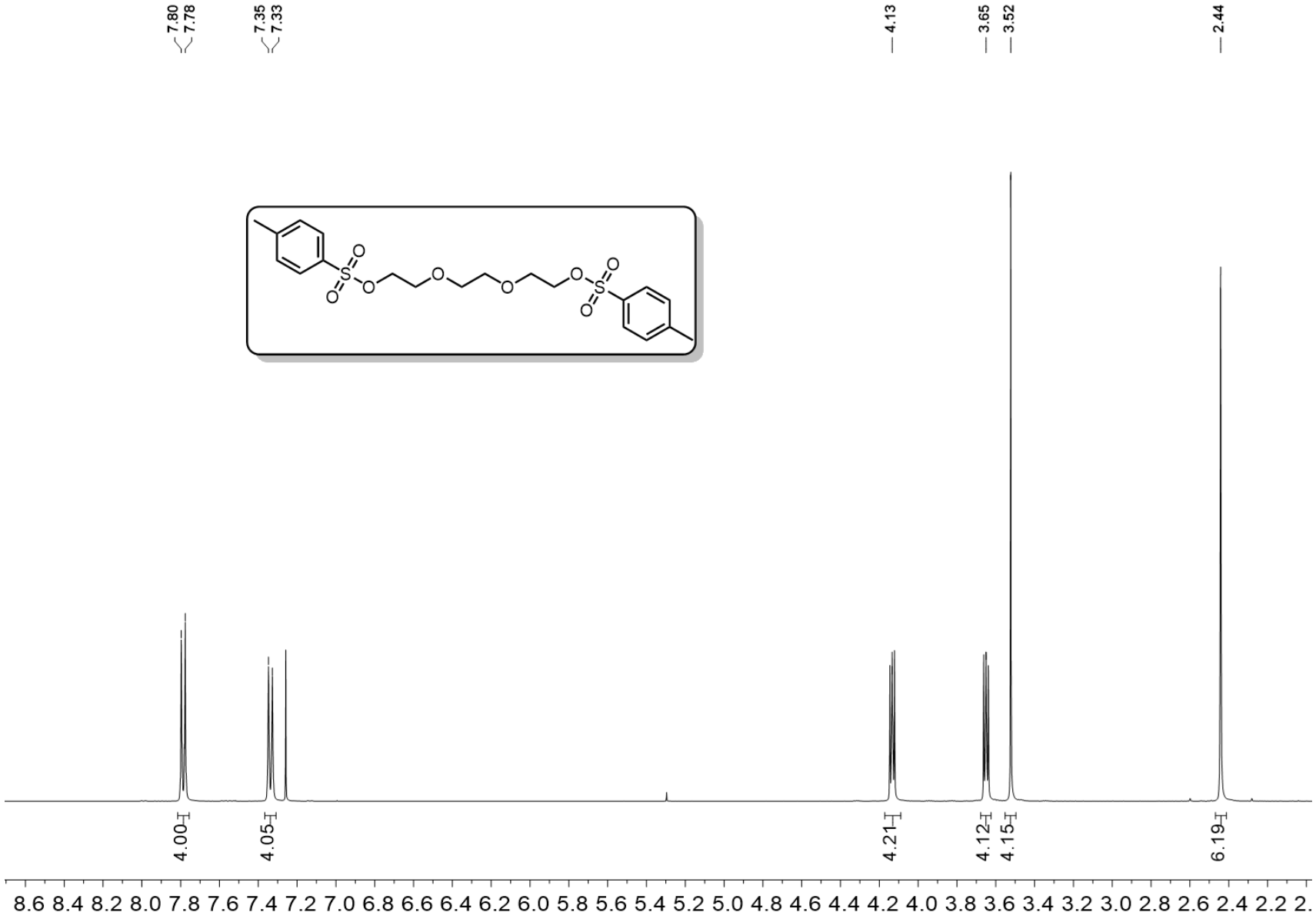
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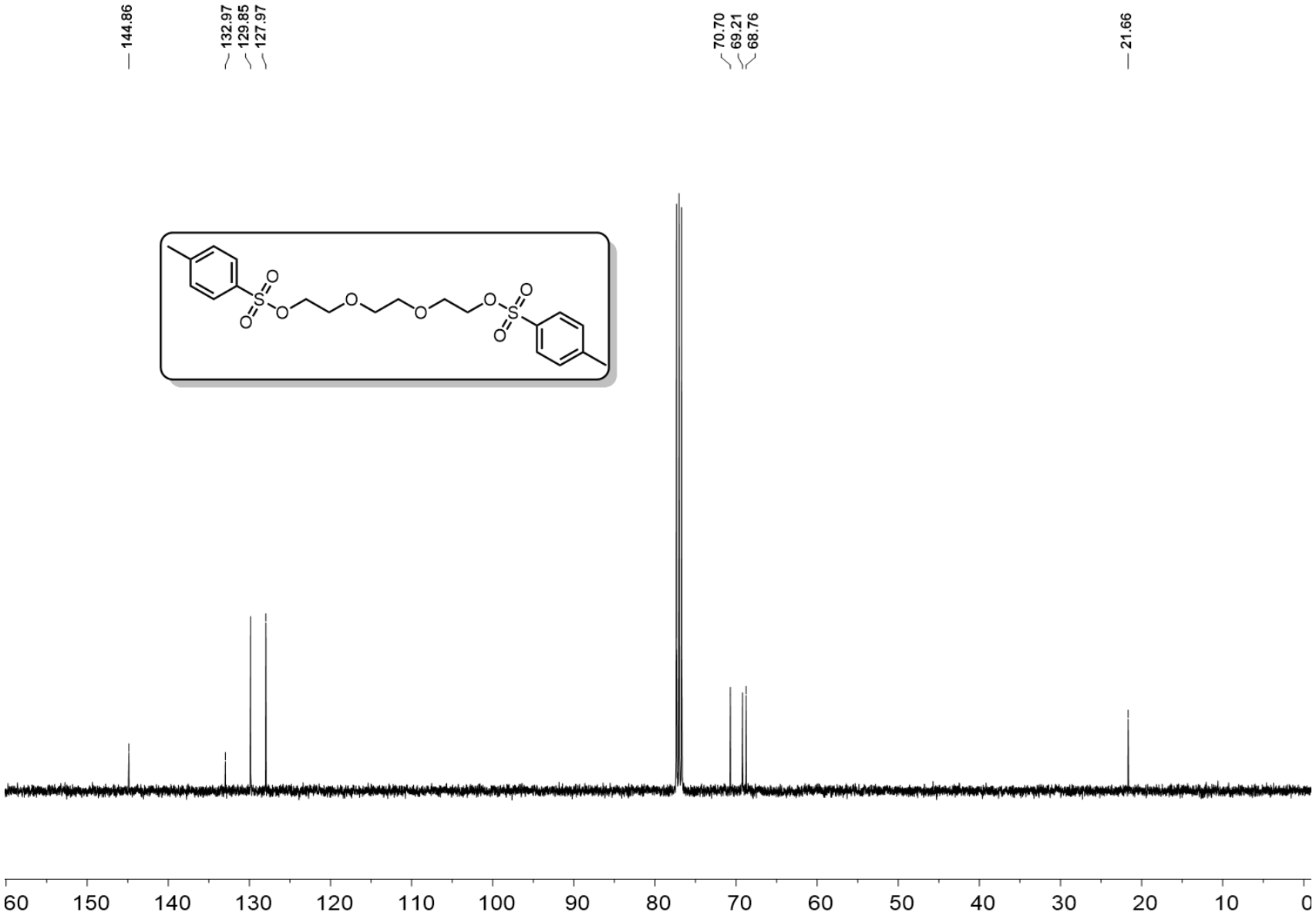
6.19
8.6 8.4 8.2 8.0 7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.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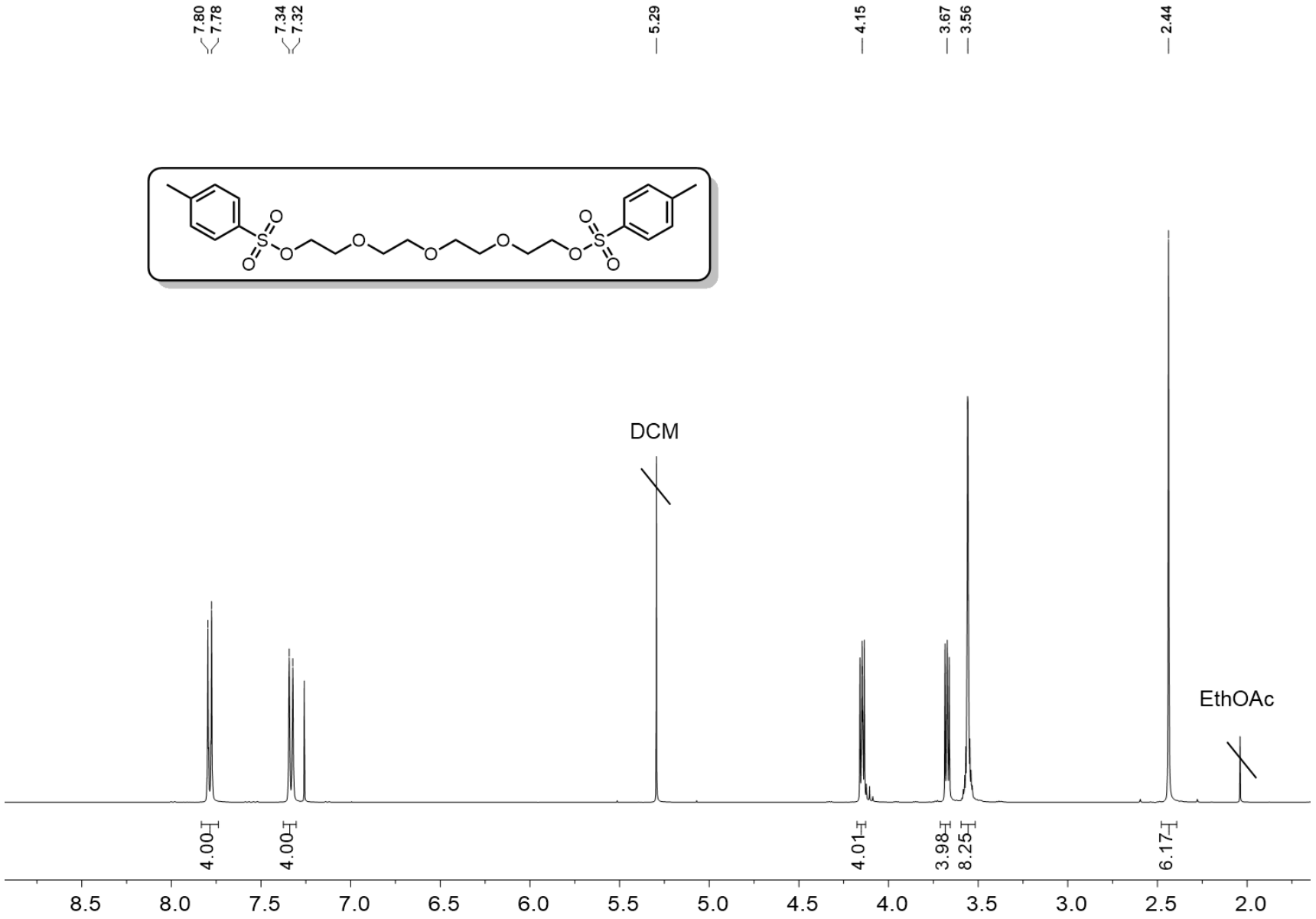
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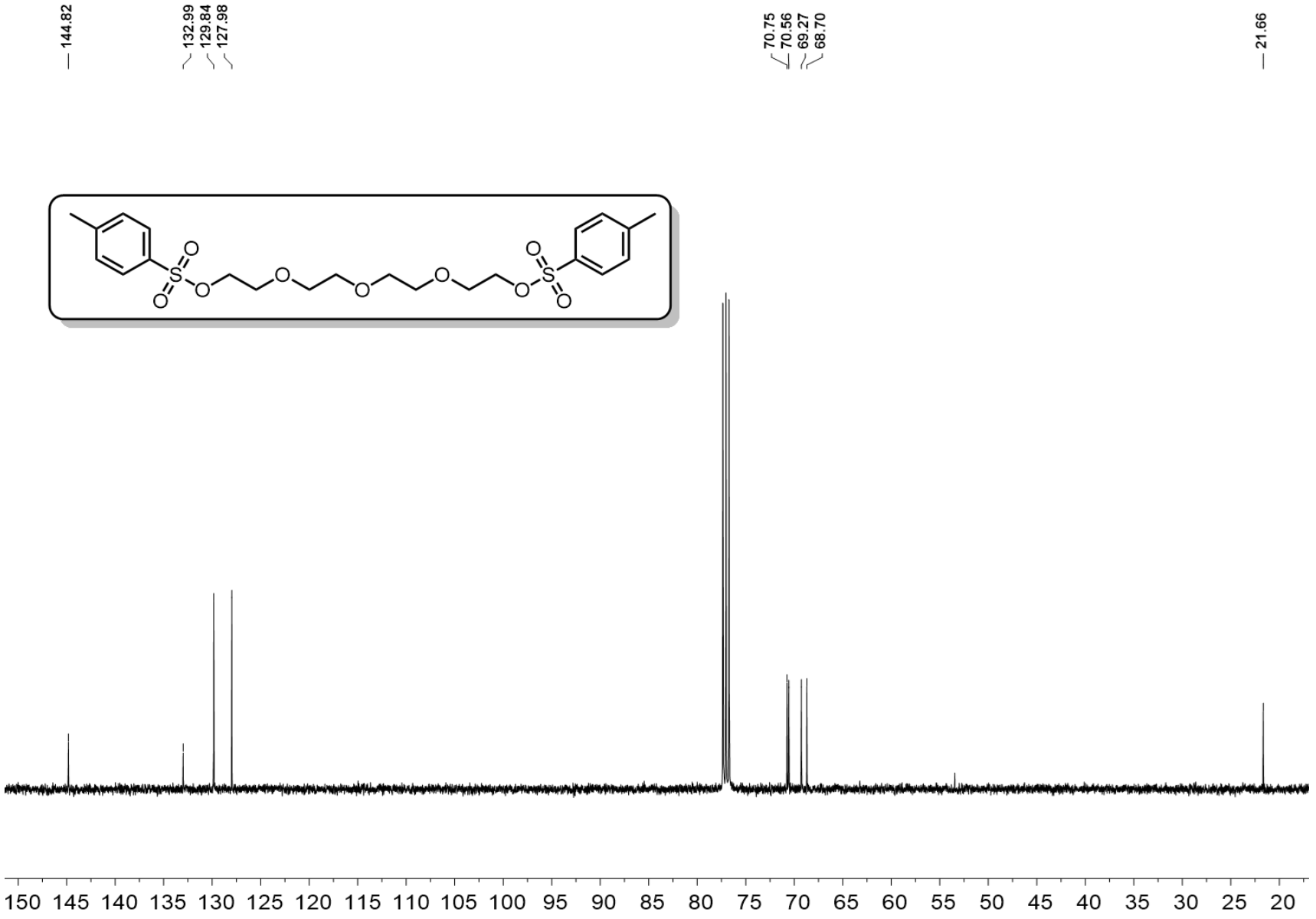
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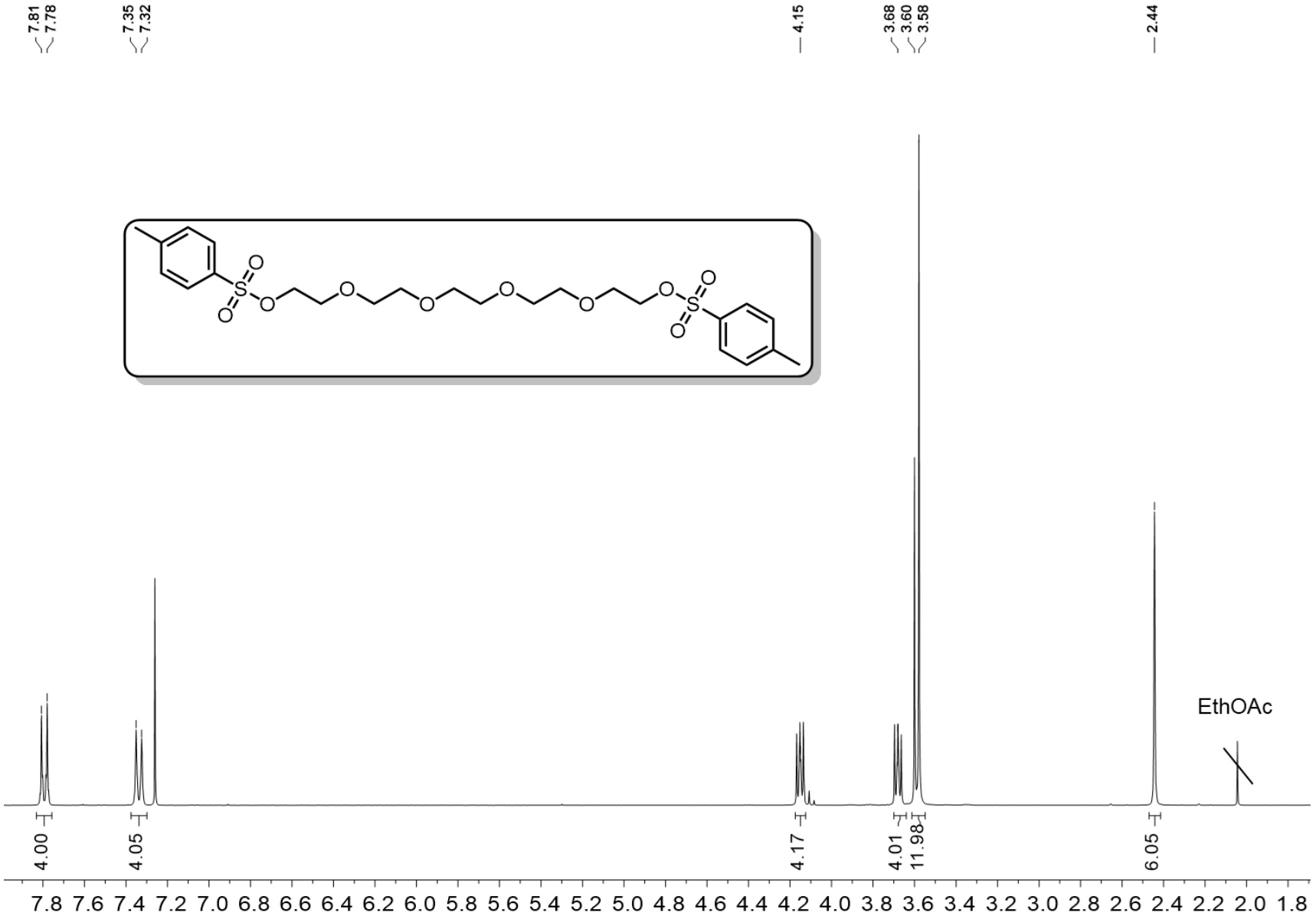
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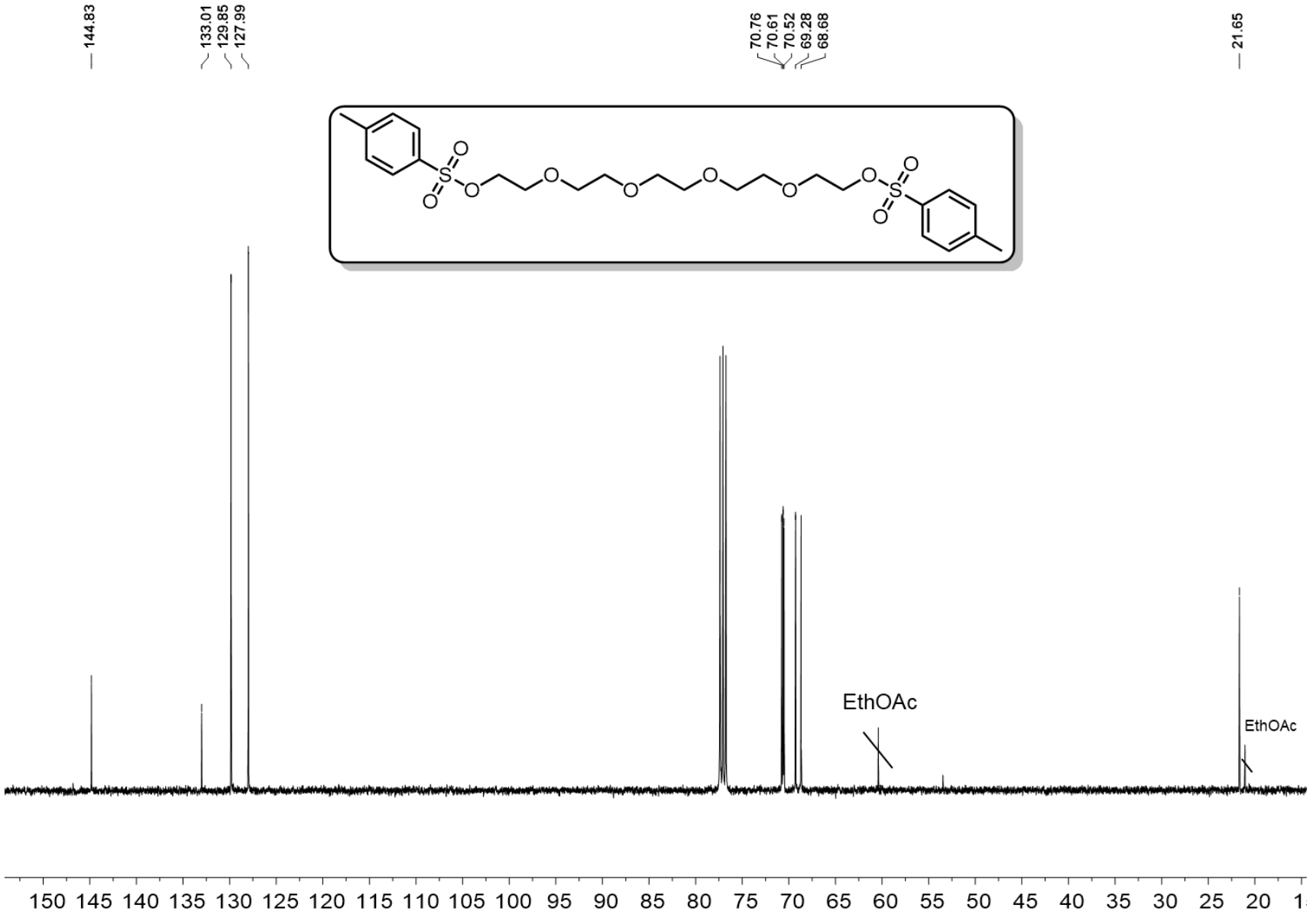
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8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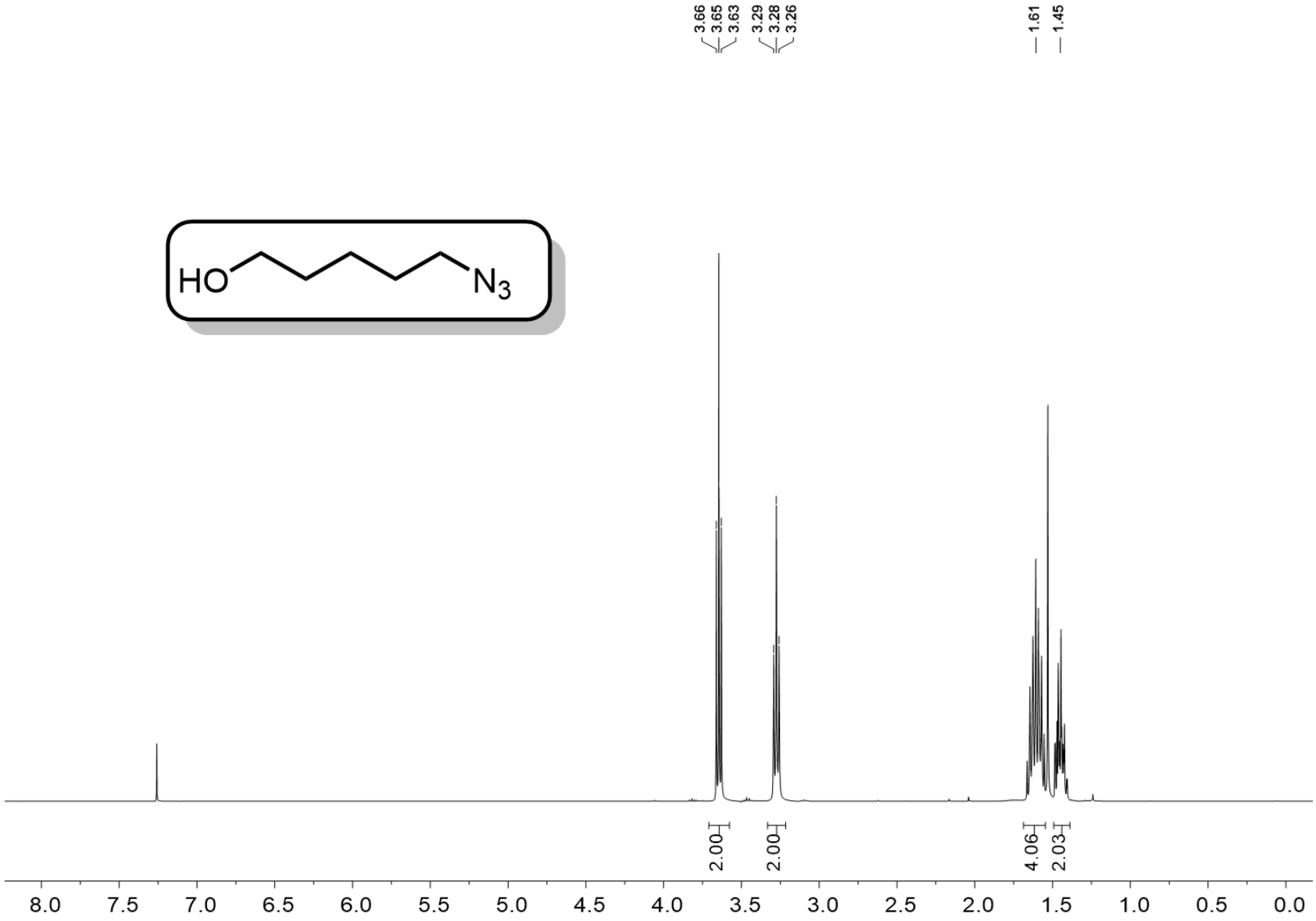
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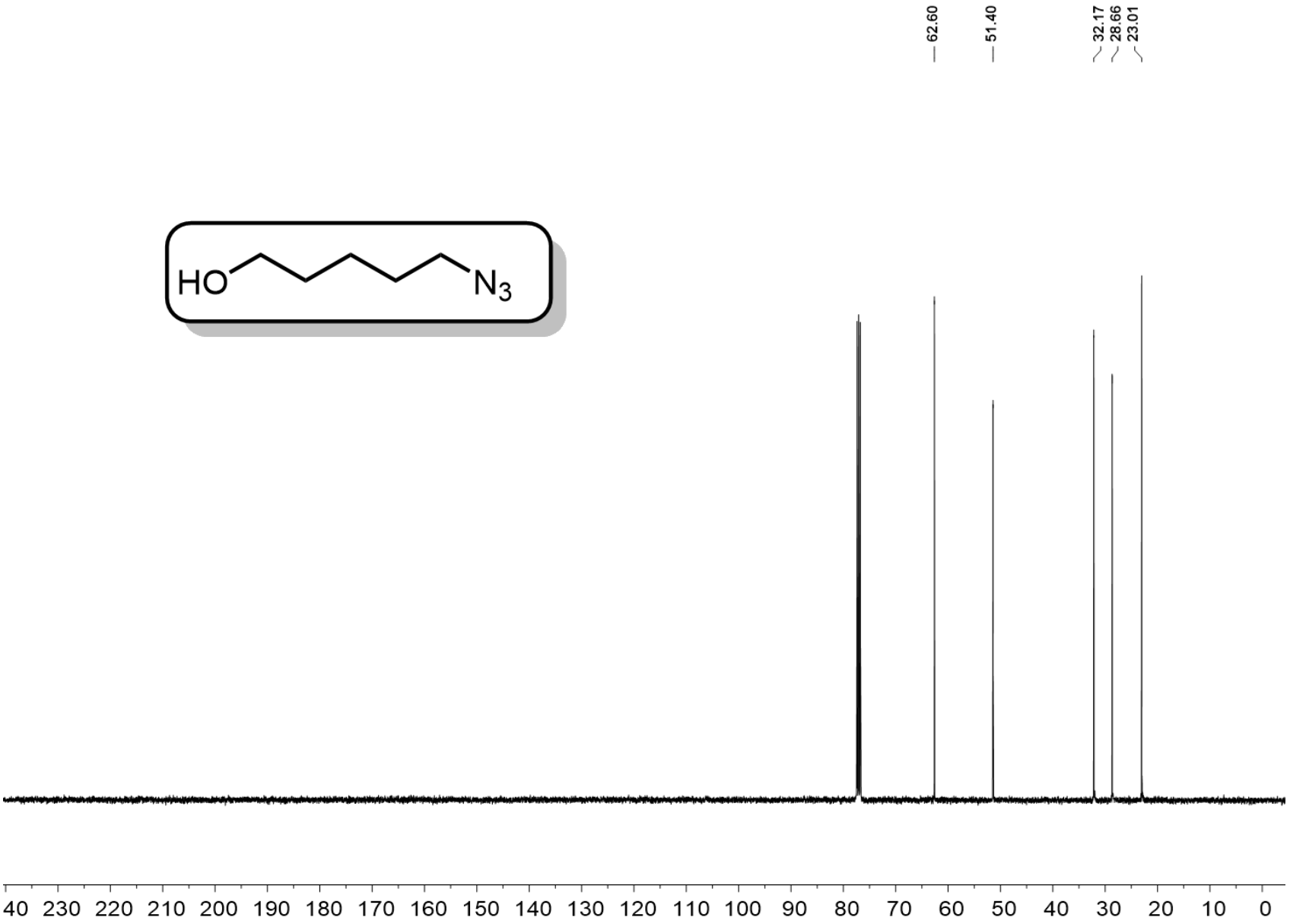
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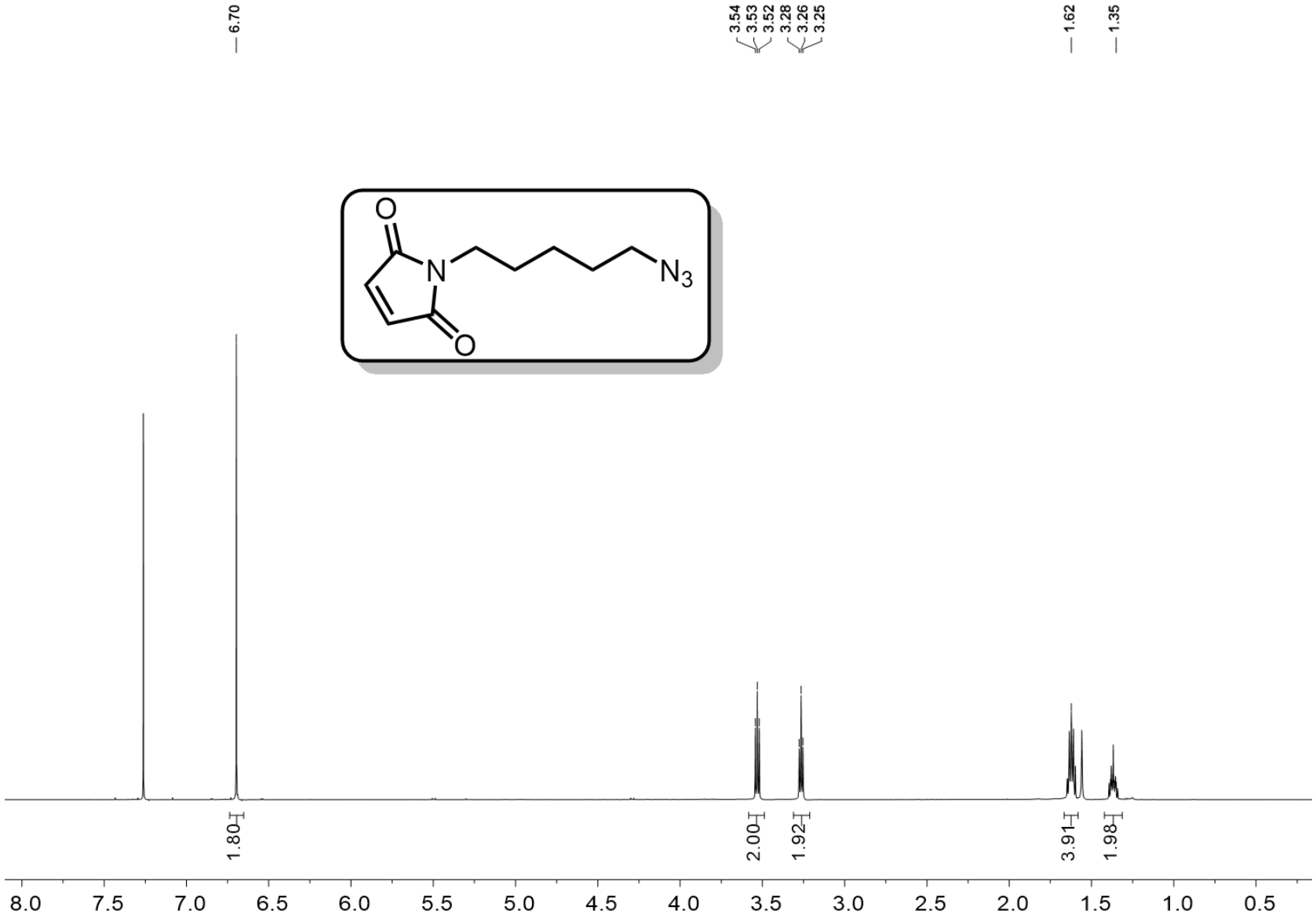
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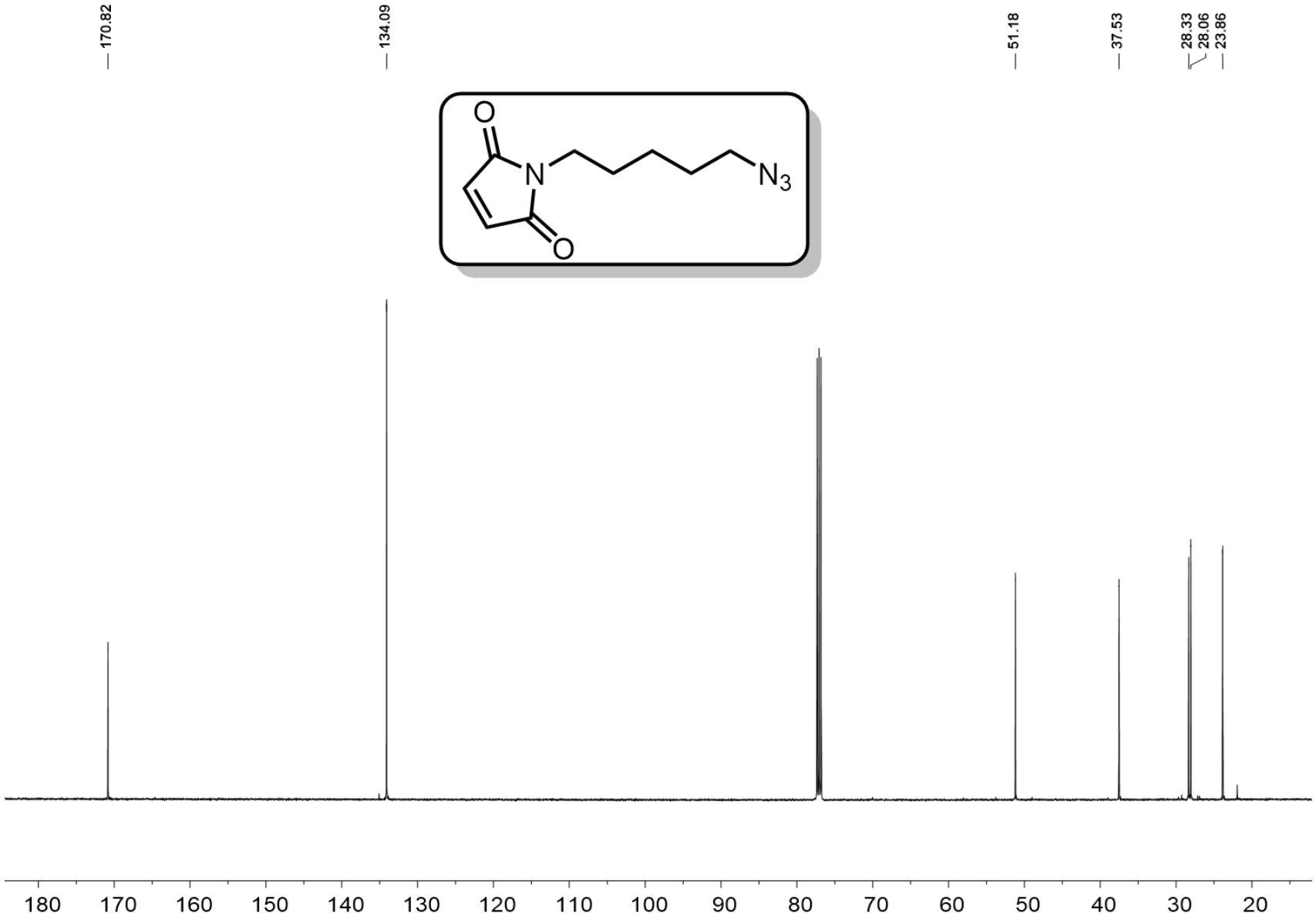
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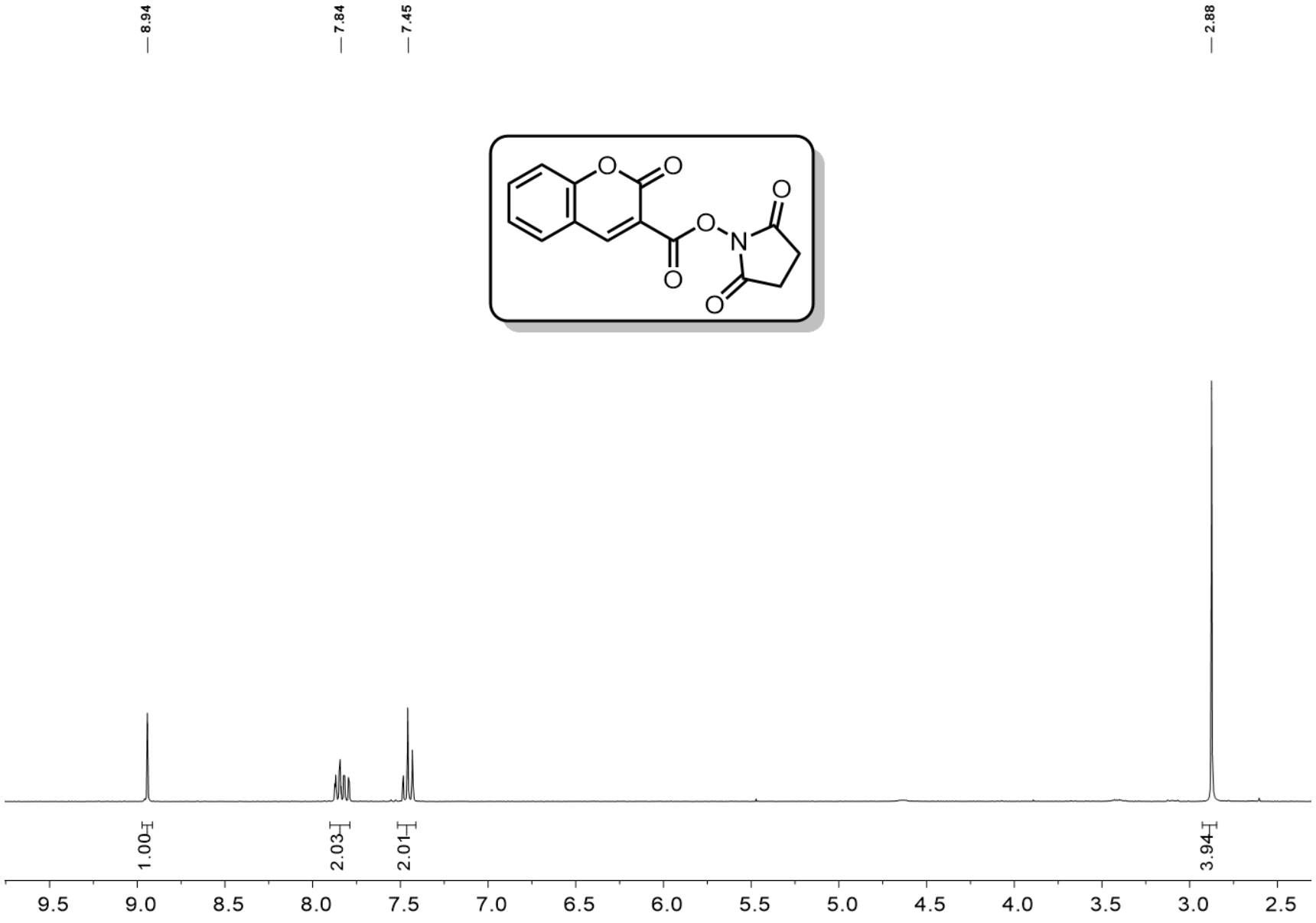
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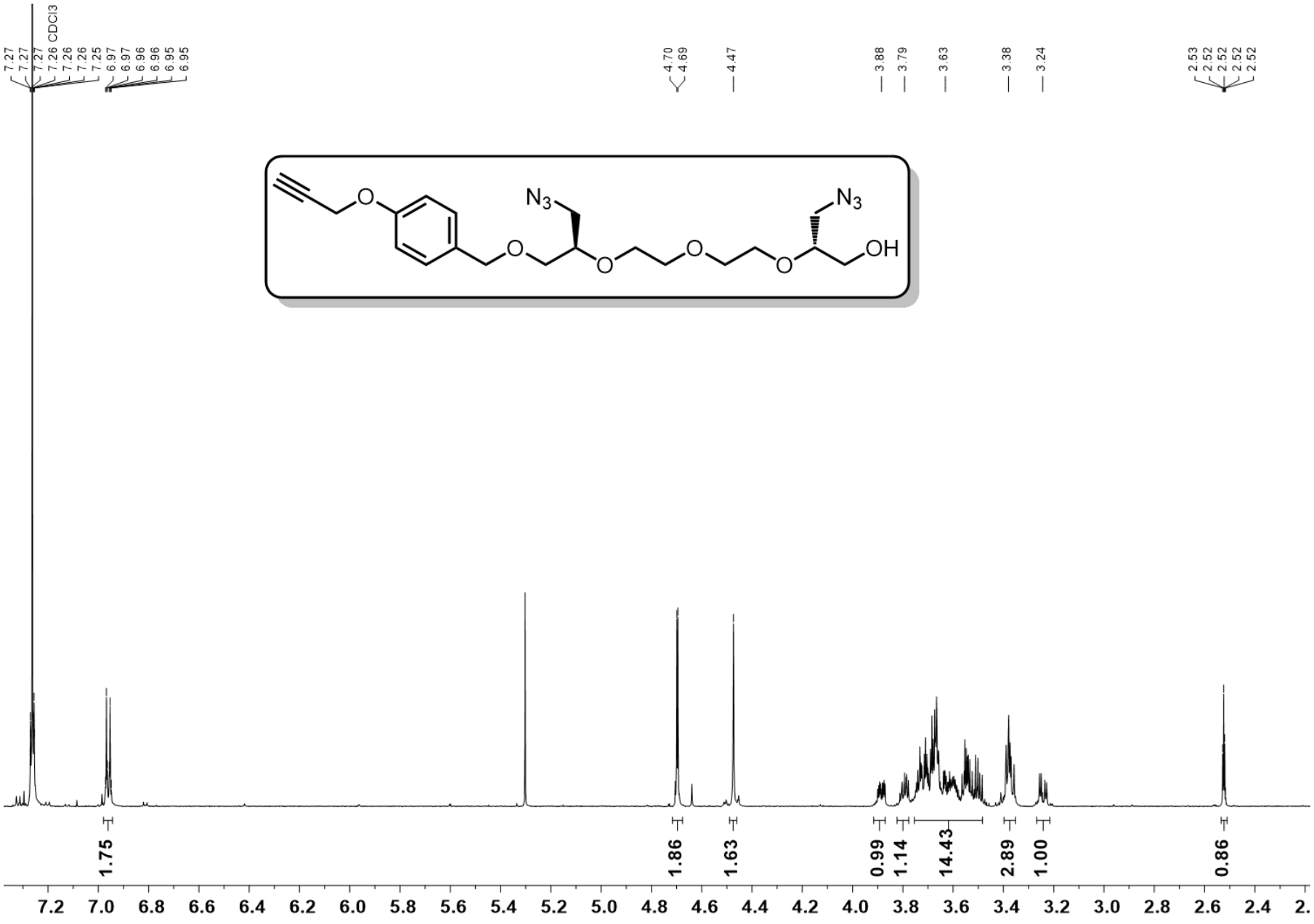
3.0
2.5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CDCl3
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4.69
4.47
3.88
3.79
3.63
3.38
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2.52
2.52
2.52
N3
N3
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O
O
O
O
OH
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1.63
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1.14
14.43
2.89
1.00
0.86
7.2
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6.4
6.2
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5.8
5.6
5.4
5.2
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4.6
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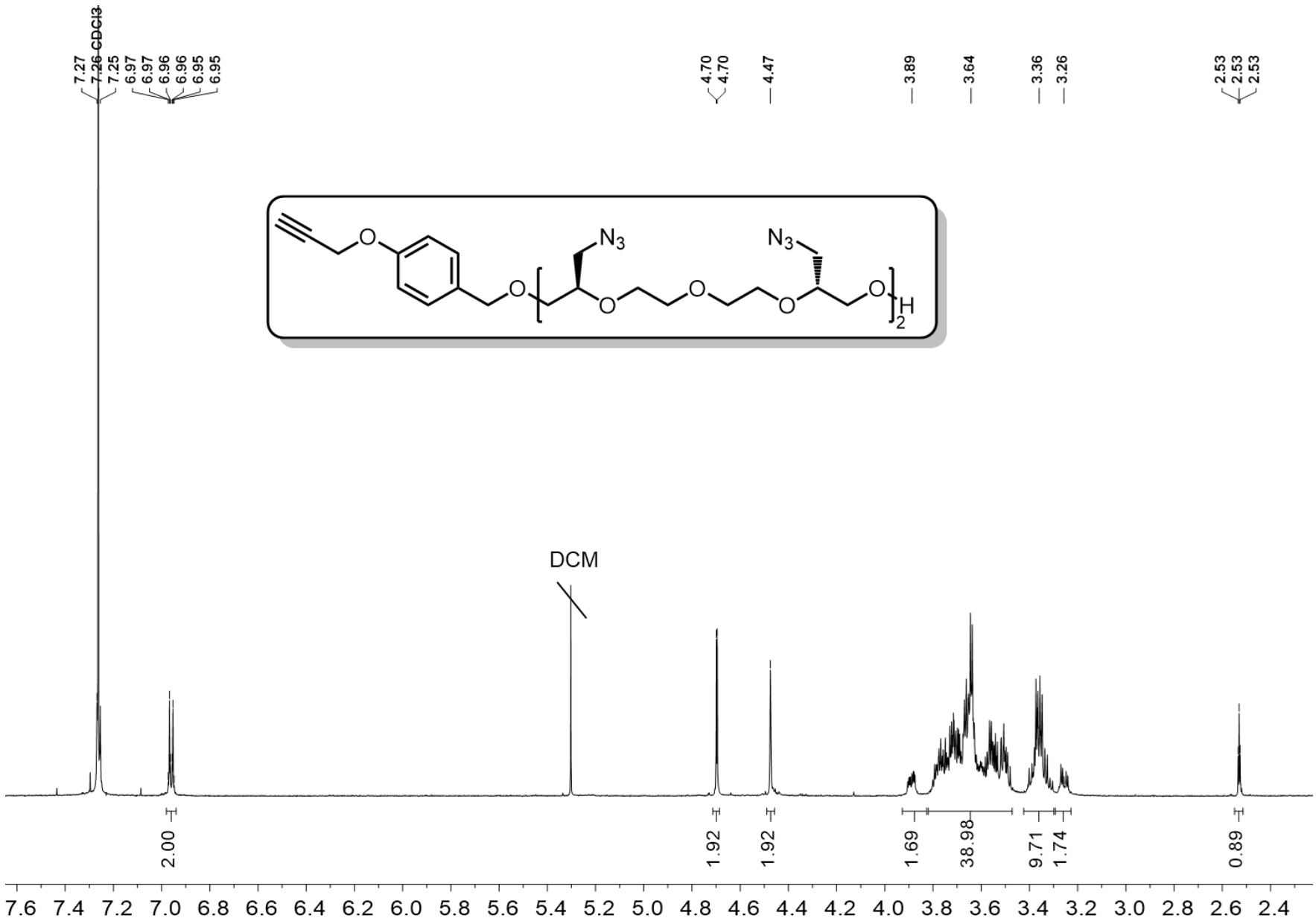
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4.47
3.89
3.64
3.36
3.26
2.53
2.53
2.53
N3
N3
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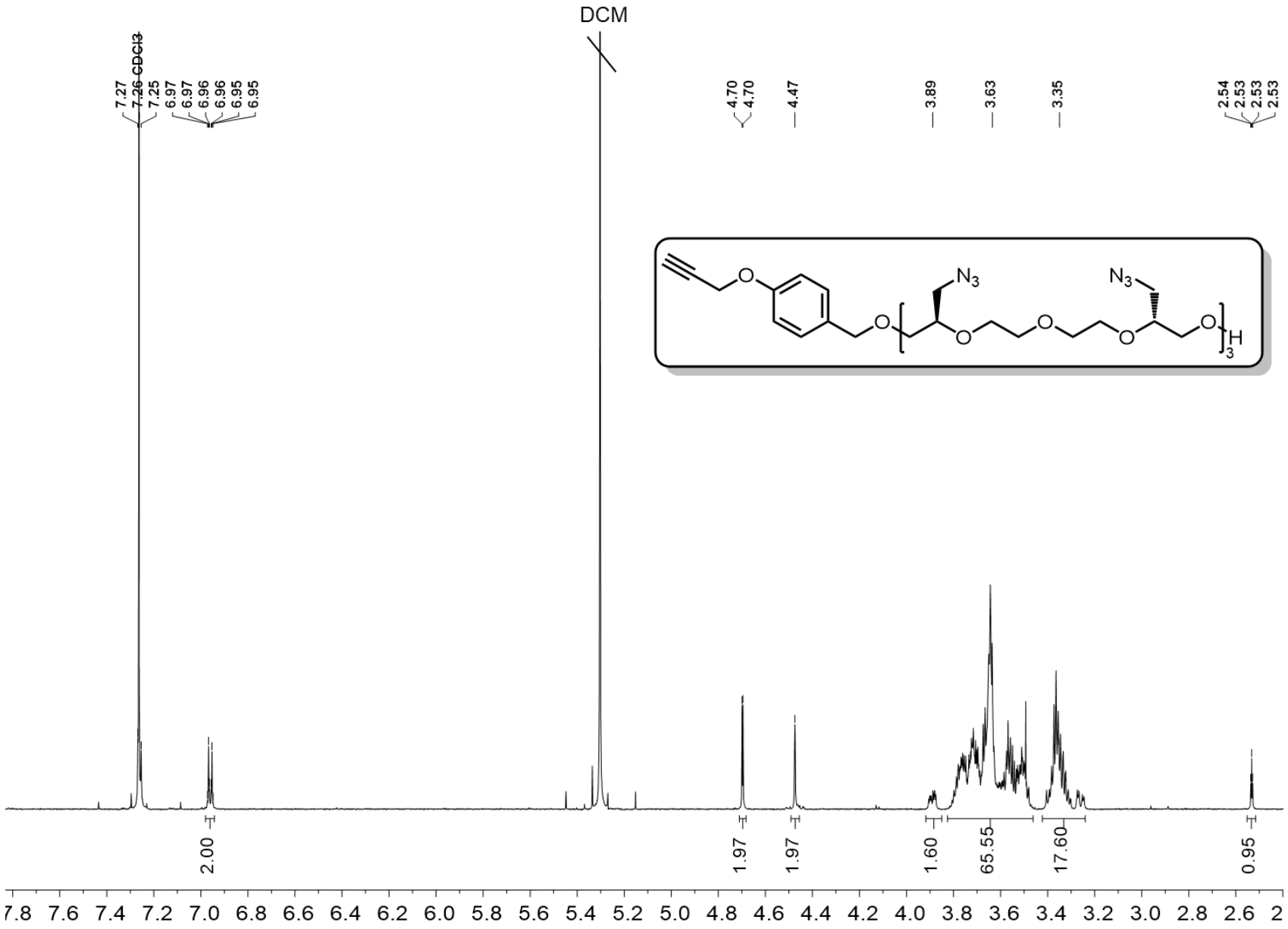
O
O
O
O
O
H
2
DCM
2.00
1.92
1.92
1.69
38.98
9.71
1.74
0.89
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4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2.54
2.53
2.53
2.53
N3
N3
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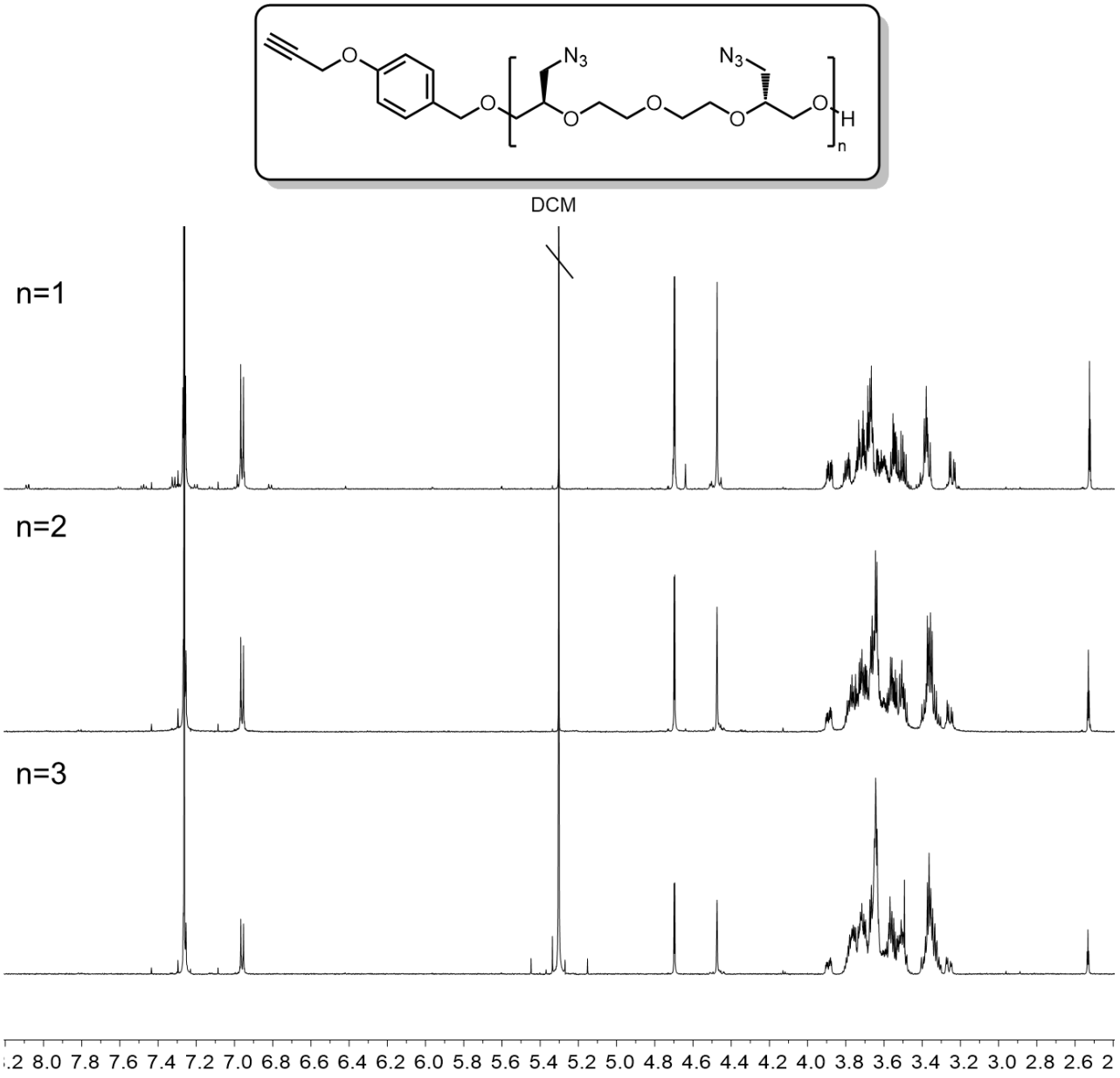
1.97
1.97
1.60
65.55
17.60
0.95
7.8 7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2


DCM
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n=2
n=3
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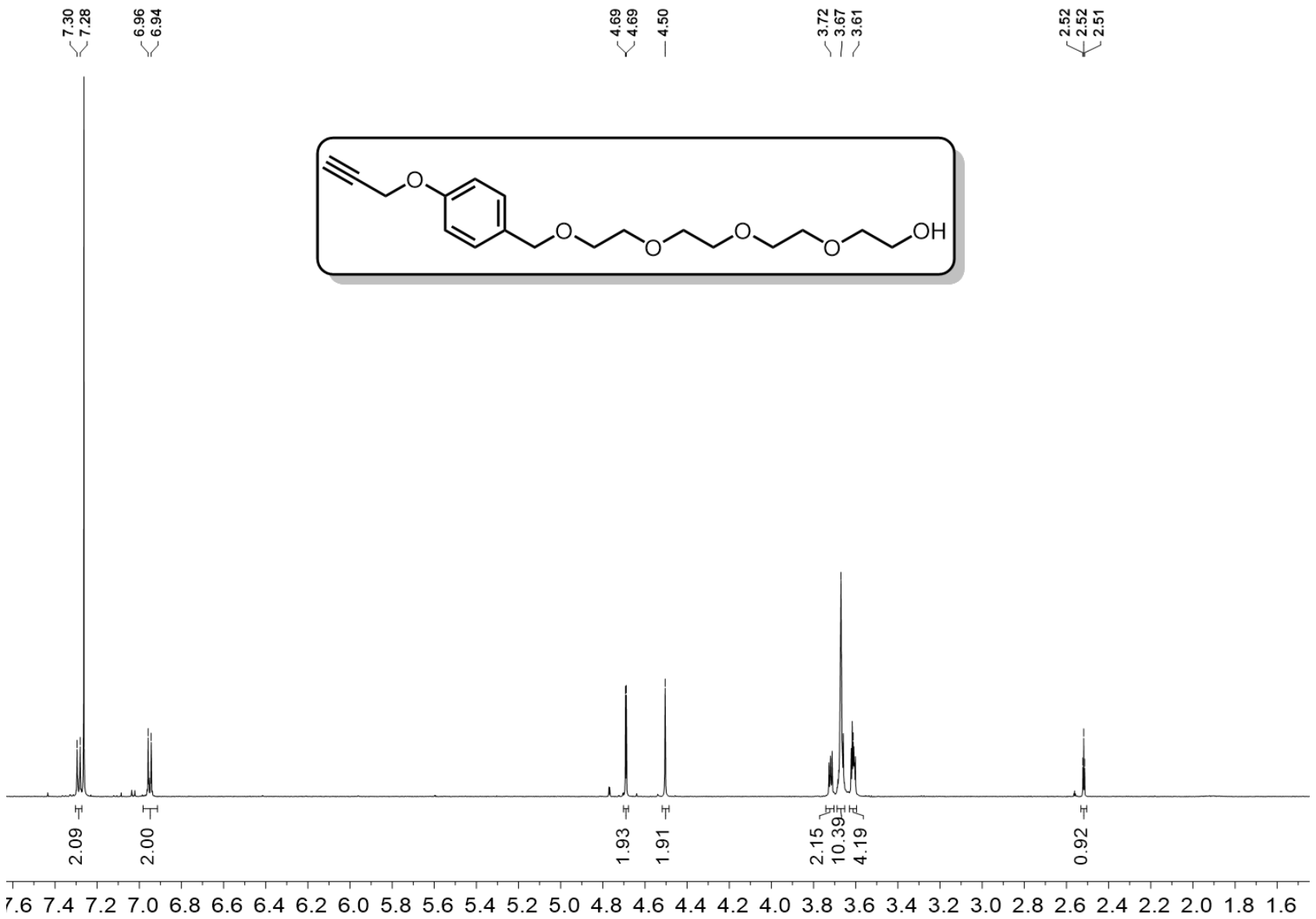
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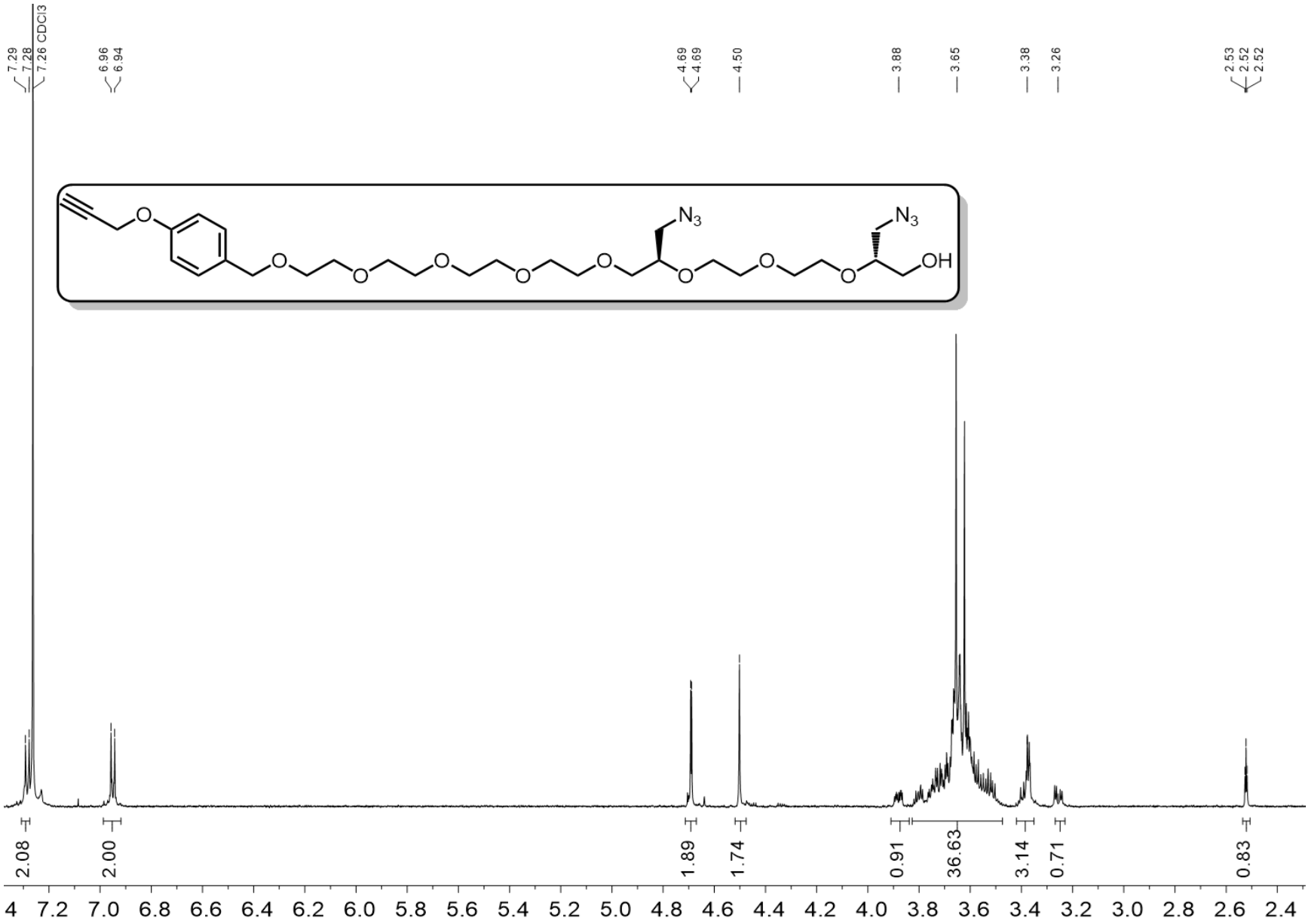
2.52
2.51
O
O
O
O
O
OH
2.09
2.00
1.93
1.91
2.15
10.39
4.19
0.92
7.6 7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4 2.2 2.0 1.8 1.6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7.28
7.26 CDCl3
6.96
6.94
4.69
4.69
4.50
3.88
3.65
3.38
3.26
2.53
2.52
2.52
N3
N3
OH
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1.74
0.91
36.63
3.14
0.71
0.83
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7.2
7.0
6.8
6.6
6.4
6.2
6.0
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5.6
5.4
5.2
5.0
4.8
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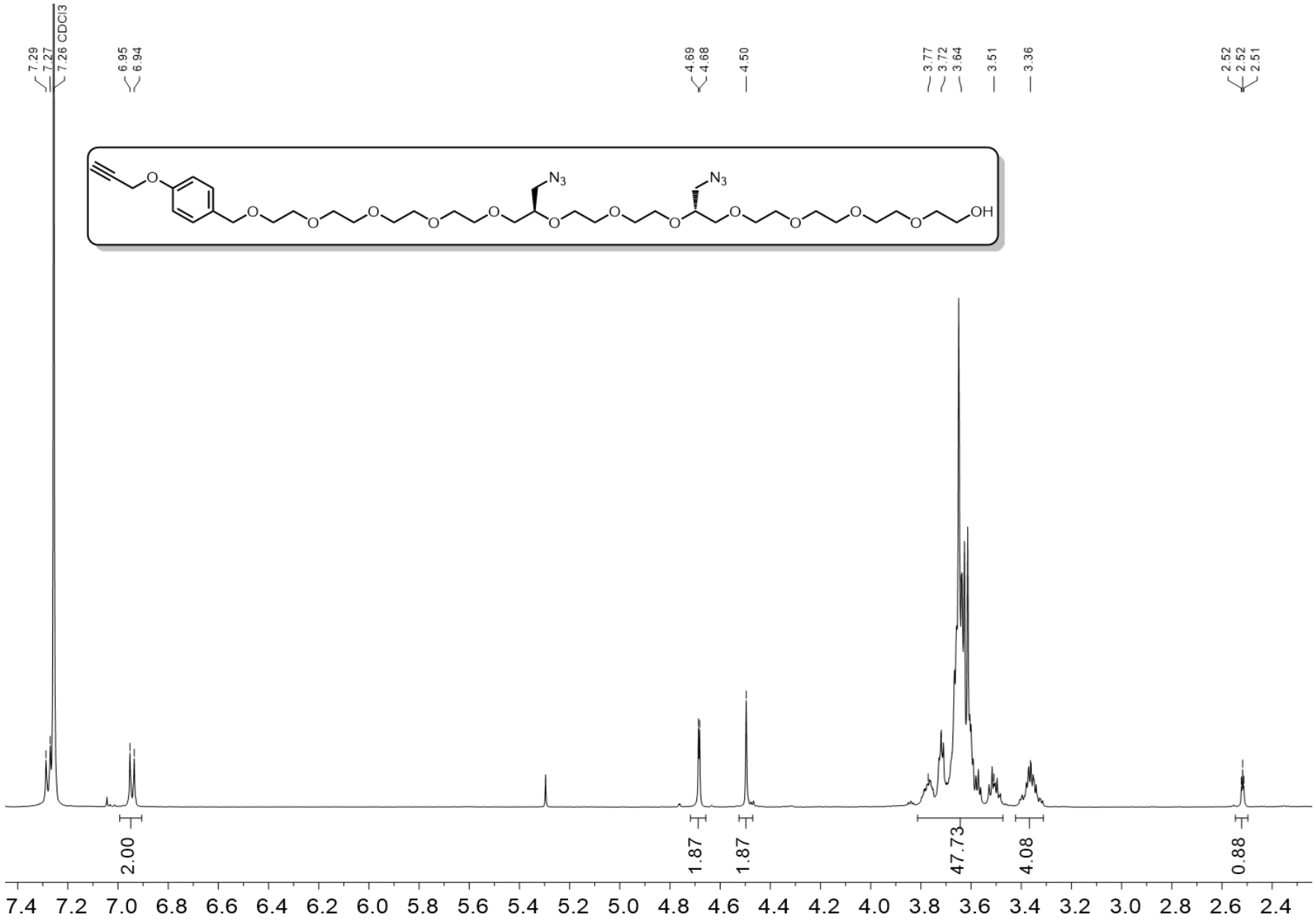
2.4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2.52
2.51
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1.87
47.73
4.08
0.88
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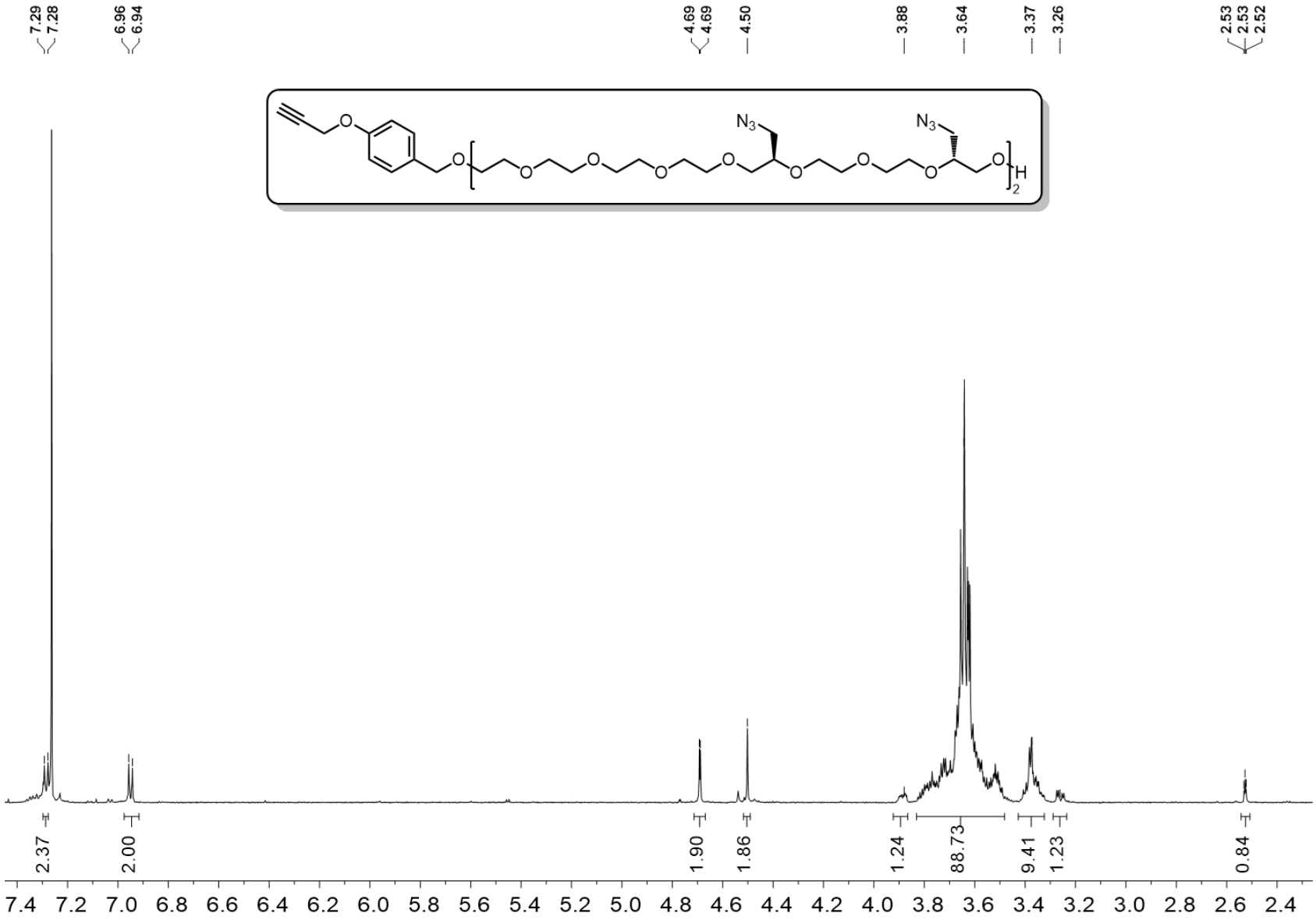
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6.94
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3.37
3.26
2.53
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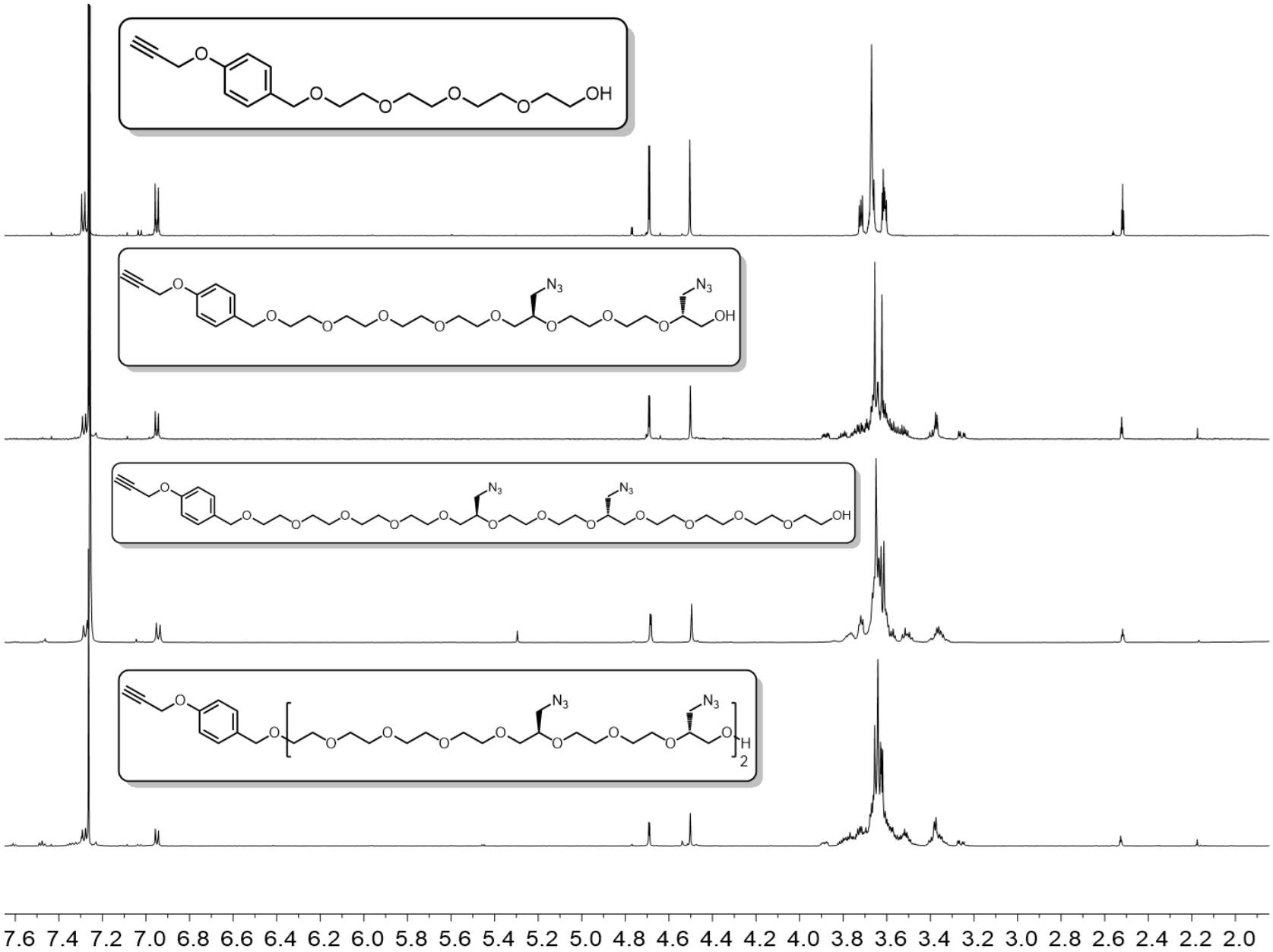
2.52
N3
N3
H
2
2.37
2.00
1.90
1.86
1.24
88.73
9.41
1.23
0.84
7.4 7.2 7.0 6.8 6.6 6.4 6.2 6.0 5.8 5.6 5.4 5.2 5.0 4.8 4.6 4.4 4.2 4.0 3.8 3.6 3.4 3.2 3.0 2.8 2.6 2.4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N3
OH
N3
N3
OH
N3
N3
H
2
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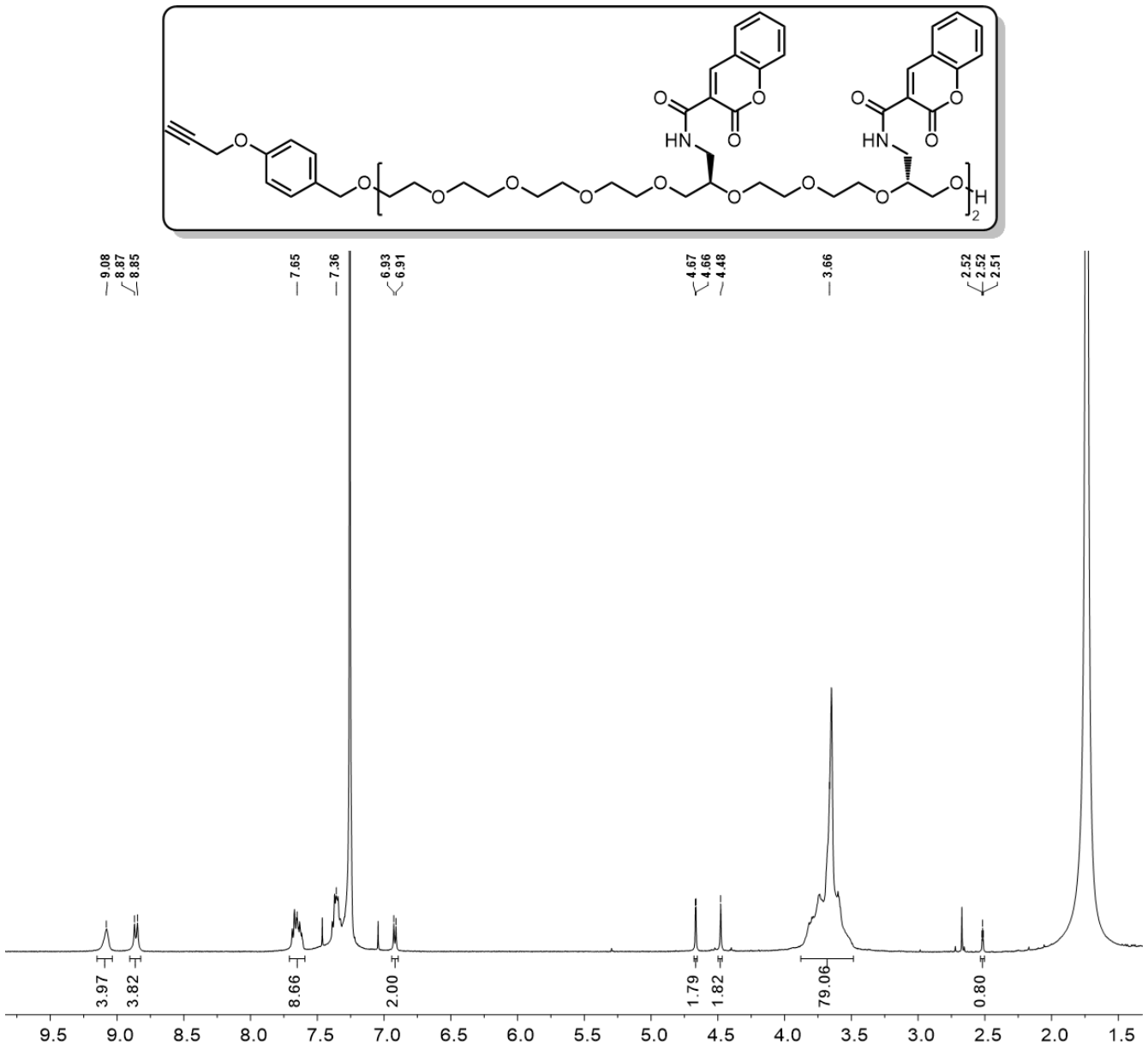
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2.52
2.51
3.97
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1.82
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0.80
9.5
9.0
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8.0
7.5
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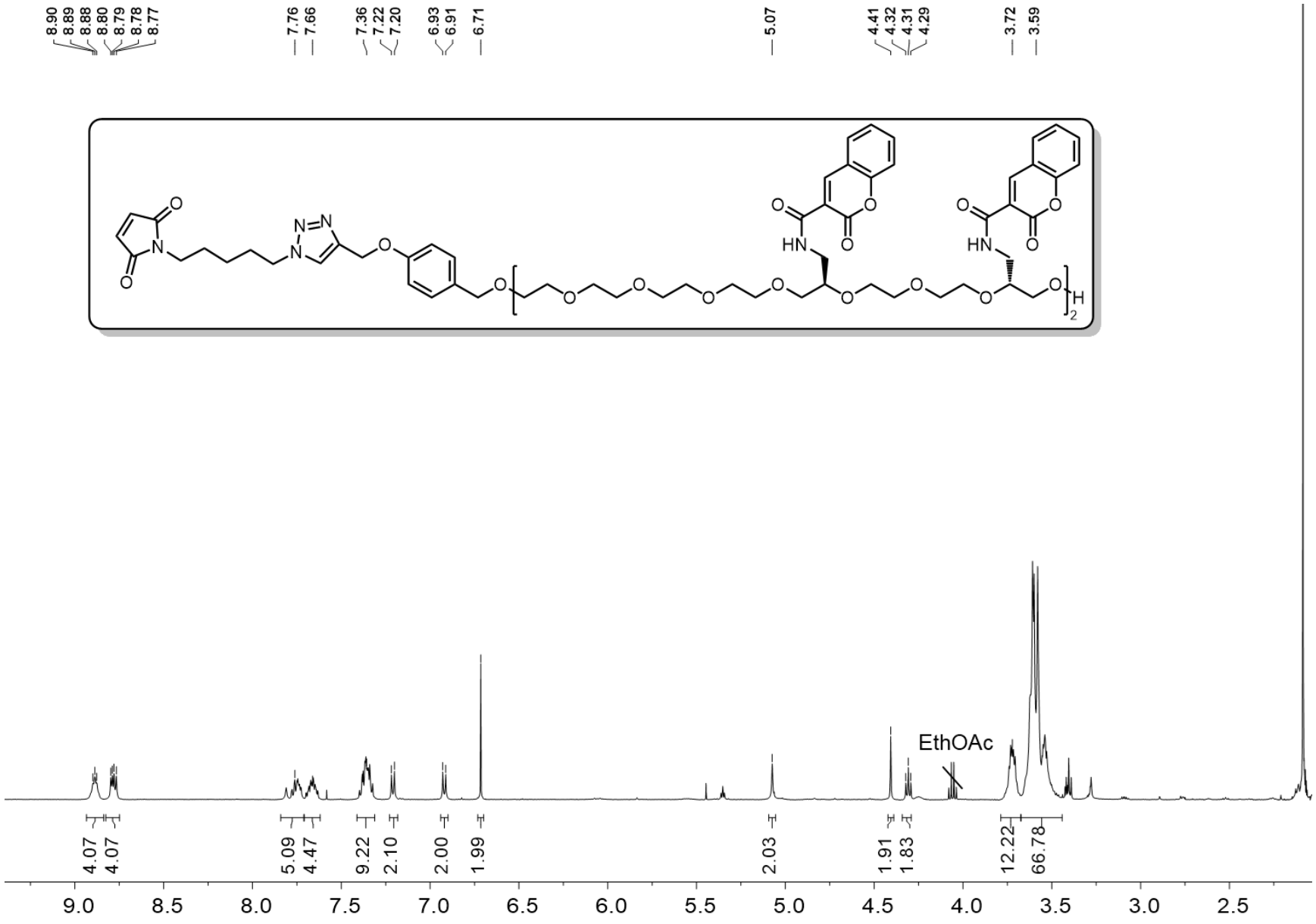
1.5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4.07
4.07
5.09
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1.99
2.03
1.91
1.83
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8.0
7.5
7.0
6.5
6.0
5.5
5.0
4.5
4.0
3.5
3.0
2.5

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