Supporting Information

Epimers switch galectin-9 domain selectivity: 3*N*-Aryl galactosides bind the C-terminal and gulosides bind the N-terminal

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General methods

All reactions were carried out in oven-dried glassware. All solvents and reagents were mainly purchased from Sigma-Aldrich or Fluka and were used without further purification or synthesized via literature protocol. TLC analysis was performed on pre-coated Merck silica gel 60 F_{254} plates using UV light and charring solution (10 mL conc. H_2SO_4/ 90 mL EtOH). Flash column chromatography was done on SiO_2 purchased from Aldrich (technical grade, 60 Å pore size, 230-400 mesh, 40-63 μm). All NMR spectra were recorded with Bruker DRX 400 MHz spectrometer (400 MHz for ^{1}H, 100 MHz for ^{13}C, 376 MHz for ^{19}F, ESI) at ambient temperature using $CDCl_3$, CD_3OD as solvents. Chemical shifts are given in ppm relative to the residual solvent peak (^{1}H NMR: $CDCl_3$ δ 7.26; CD_3OD δ 3.31; ^{13}C NMR: $CDCl_3$ δ 77.16; CD_3OD δ 49.00) with multiplicity (b = broad, s = singlet, d = doublet, t = triplet, q = quartet, quin = quintet, hept = heptet, m = multiplet, app = apparent), coupling constants (in Hz) and integration. High resolution mass analyses were obtained using Micromass Q-TOF mass spectrometer. Analytical data is given if the compound is novel or not fully characterized in the literature. Purity analysis was performed using UPLC/MS with UV/VIS detection on a Waters Acquity UPLC + Waters XEVO-G2 system using a Waters Acquity CSH C18, 1.7 um, 2.1 x100 mm column. Samples were run using a gradient with water (0.1% formic acid) and acetonitrile using a flow rate of 0.50 mL/min and a column temperature 60°C. Gradient parameters: 0-0.7min: 40% acetonitrile, 0.7-10.0 min: 40-99% acetonitrile, 10.0-11.0 min 99% acetonitrile, 11.0-11.1 min 99-40% acetonitrile, 11.1-13 min 40% acetonitrile, 3 or 6 μL injection, detection 190-300 nm. MS parameters: Cap voltage 3.0 kV, Cone voltage 40 kV, Ext 4, Source temp 120°C, Desolvation temp 500°C, cone gas 50, desolvation gas 800, Centroid resolution mode, m/z interval 50-1200, Lockspray. Calibration: Leu-Enkephalin m/z 556.2771, 0.25 s every 30 s, average 3. All final compounds were purified using preparative HPLC on an Agilent 1260 Infinity system with a SymmetryPrep C18 5 μM 19x100 mm column using a gradient (water with 0.1% formic acid and acetonitrile); 0-20 minutes 10-100% acetonitrile, 20-23 minutes 100% acetonitrile. Monitoring and collection based on UV/VIS absorbance at 210 and 254 nm. All tested compounds were >95% pure according to analytical HPLC analysis. Fluorescense polarization experiments were performed[1,2] as reported with detailed conditions for each galectin as described earlier.[3,4]

Methyl 3-azido-3-deoxy-β-D-gulopyranoside 11

To the solution of **9**[5] (1.8g, 3.94 mmol) in DMF (20 mL) was added sodium azide (1.03 g, 15.77 mmol) and the reaction was heated at 60 °C for 8 h. The DMF was evaporated, the residue diluted with DCM (50 mL), and washed with water. The organic phase was dried over Na_2SO_4, filtered and concentrated. Flash chromatography (Heptane: EtOAc 2:1) of the residue gave **10** (1.05 g, 76%) as white solid. The crude azide **12** (1g, 2.86 mmol) was dissolved in 90% AcOH (20 mL) and heated at 90^{0}C for 4 h. The was co-evaporated with toluene (3×10 mL) and the residue was dissolved in MeOH and freshly prepared methanolic sodium methoxide was added until pH 10. The solution was stirred at room temperature for 1h and then neutralized with DOWEX 50W H^+ resin. The mixture was filtered through a cotton plug and the solvents were evaporated under reduced pressure. Flash chromatography (DCM:MeOH 9:1) of the residue gave **11** (452 mg, 72%). $[\alpha]_D^{25}$ -23.8 (c 0.7, CH_3OH. ^{1}H NMR (CD_3OD, 400 MHz): 4.45 (d, 1H, *J* 8 Hz), 3.93 (t, 1H, *J* 4 Hz), 3.83 (dd, 1H, *J* 4 Hz, *J* 4 Hz), 3.75 (d, 1H, *J* 4 Hz), 3.71-3.68 (m, 3H), 3.52 (s, 3H). ^{13}C NMR (CD_3OD: 100 MHz): 103.4, 75.0, 69.7, 69.3, 66.8, 62.2, 57.1. HRMS calcd for $C_7H_{13}N_3O_5+NH_4^+$ $(M+NH_4)^+$: 237.1193, found: 237.1199.

Methyl 3-amino-3-deoxy-β-D-gulopyranoside 12

To the solution of azide **11** (490 mg, 2.53 mmol) in MeOH was added 5% Pd/C (305 mg) The mixture was stirred under H_2 at atmospheric pressure at rt for 1 h. The Pd/C was removed by

filtration through Celite® and the filtrate was concentrated in vacuo to remove the MeOH. The residue was given wash with DCM (2×15 mL) and dried under vacuo to give the amine **12** (324 mg, 75%). $[\alpha]_D^{25}$ -3.7 (c 0.8, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 4.52 (d, 1H, *J* 7.2 Hz), 3.95 (m, 1H), 3.78-3.69 (m, 4H), 3.61 (dd, 1H, *J* 7.2 Hz, *J* 14 Hz). ^{13}C NMR (CD_3OD: 103.1, 75.1, 69.1, 62.8, 58.3, 57.0, 56.0, 18.4. HRMS calcd. for $C_7H_{15}NO_5+H^+$ $(M+H)^+$: 194.1023, found: 194.1028.

General procedure for *N*-arylation of the amines 12, 23, and 33

To a solution of the amine (**12**, **23**, or **33**, 1eq) in acetonitrile, the aryl triflate (0.98 eq) was added followed by CsF (2eq). The reaction mixture was stirred at room temperature for 8 h. Then the solvent was evaporated and the residue dissolved in EtOAc (10 mL), washed with brine (2×10 mL), dried over Na_2SO_4, filtered, and concentrated.

Methyl 3-deoxy-3-phenylamino-β-D-gulopyranoside 14

Compound **12** (50 mg, 0.258 mmol) was arylated with **13a** (62 μL, 0.254 mmol) in presence of CsF (78 mg, 0.516 mmol) following general procedure. The crude was initially purified by flash chromatography (DCM:MeOH 15:1) and further purified by preparative HPLC to afford **14** (41.8 mg, 60%) as a colorless oil. $[\alpha]_D^{25}$ -5.8 (c 0.7, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.12 (t, 1H, J 8Hz, 6.72 (d, 2H, J 8 Hz), 6.65 (t, 1H, J 8 Hz), 4.60 (d, 1H, J 8 Hz), 3.94-3.88 (m, 3H), 3.76-3.69 (m, 3H), 3.56 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 149.6, 130.1, 118.6, 114.4, 103.4, 75.2, 68.3, 68.2, 62.8, 59.4. HRMS calcd for $C_{13}H_{19}NO_5+H^+$ $(M+H)^+$: 270.1341, found: 270.1338.

Methyl 3-deoxy-3-(4-methoxyphenylamino)-β-D-gulopyranoside 15 and methyl 3-deoxy-3-(3-methoxy-phenylamino)-β-D-gulopyranoside 16

Compound **12** (50 mg, 0.258 mmol) was arylated with **13b** (71 μL, 0.254 mmol) in presence of CsF (78 mg, 0.516 mmol) following general procedure. The crude material was purified by flash column (DCM:MeOH 15:1) to give **15** and **16** (50 mg, 65%) as a mixture (3:1) as a colorless oil, which was separated and purified by preparative HPLC.

Data for compound **16**: $[\alpha]_D^{25}$ -4.9 (c 0.6, CH_3OH) ^1H NMR (CD_3OD, 400 MHz): 6.76 (m, 2H), 6.70 (m, 2H), 6.58 (d, *J* 8.0 Hz), 3.94-3.87 (m, 3H), 3.77-3.65 (m, 3H), 3.71 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 162.3, 153.9, 142.6, 116.0, 115.8, 103.4, 75.2, 68.3(2), 62.9, 60.3, 56.9, 56.1. HRMS calcd for $C_{14}H_{21}NO_6+H^+$ $(M+H)^+$: 300.1447, found: 300.1445. Data for compound **17**: $[\alpha]_D^{25}$ -6.1 (c 0.5, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.02 (t, 1H, *J* 8.0 Hz), 6.32 (m, 1H), 6.24 (m, 1H), 4.60 (d, 1H, *J* 8.0 Hz), 3.94-3.88 (m, 3H), 3.78-3.66 (m, 3H), 3.74 (s, 3H), 3.56 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 162.3, 150.9, 130.8, 107.3, 104.0, 103.3, 100.4, 75.2, 62.8, 59.3, 56.9, 55.5. HRMS calcd for $C_{14}H_{21}NO_6+H^+$ $(M+H)^+$: 300.1447, found: 300.1443.

Methyl 3-deoxy-3-(4-methyl-phenylamino)-β-D-gulopyranoside 17 and methyl 3-deoxy-3-(3-methyl-phenylamino)-β-D-gulopyranoside 18

Compound **12** (50 mg, 0.258 mmol) was arylated with **13c** (66 μL, 0.254 mmol) in presence of CsF (78 mg, 0.516 mmol) following general procedure. The crude material was purified by flash column (DCM:MeOH 15:1) to give **17** and **18** (1:1, 44.7 mg, 61%) as a colorless oil, which was separated and purified by preparative HPLC. Data for compound **17**: $[\alpha]_D^{25}$ -9.1 (c 0.6, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 6.50 (d, 2H, *J* 8Hz), 6.64 (d, 2H, *J* 8Hz), 4.58 (d, 1H, *J* 8Hz), 3.94-3.88 (m, 3H), 3.76-3.66 (m, 3H), 3.56 (s, 3H), 2.19 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 147.2, 130.6, 127.9, 114.7, 103.4, 75.2, 68.3, 62.9, 59.7, 56.9, 20.5. HRMS calcd for $C_{14}H_{21}NO_5+H^+$ $(M+H)^+$: 284.1498, found: 284.1497. Data for compound **18**: $[\alpha]_D^{25}$ -8.6 (c 0.5, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.00 (t, 1H, *J* 8 Hz), 6.57-6.48 (m, 3H), 4.59 (d,

1H, *J* 8 Hz), 3.94-3.88 (m, 3H), 3.77-3.66 (m, 3H), 3.56 (s, 3H), 2.34 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 149.6, 139.8, 130.0, 119.5, 115.1, 111.7, 103.3, 75.2, 68.3, 68.3, 62.9, 59.4, 56.9, 21.7. HRMS calcd for $C_{14}H_{21}NO_5$+H^+ $(M+H)^+$: 284.1498, found: 284.1497.

Methyl 3-deoxy-3-(3,4-dimethylphenylamino)-β-D-gulopyranoside 19

Compound **12** (50 mg, 0.258 mmol) was arylated with **13d** (67μL, 0.254 mmol) in presence of CsF (78 mg, 0.516 mmol) following general procedure. The crude was initially purified by flash chromatography (DCM: MeOH 15:1) and re-purified by preparative HPLC to afford **20** (44.6 mg, 58%) as a colorless oil. $[\alpha]_D^{25}$ -13.2 (c 0.7, CH_3OH). ^{1}H NMR (CD_3OD, 400 MHz): 6.88 (d, 1H , *J* 8.0 Hz), 6.56 (d, 1H, J 2.4 Hz), 6.47 (dd, 1H , *J* 2.4 Hz, *J* 8.0 Hz), 4.58 (d, 1H, *J* 8.0 Hz), 3.94-3.88 (m, 3H), 3.77-3.66 (m, 3H), 3.56 (s, 3H), 2.18 (s, 3H), 2.12 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 164.9, 147.5, 147.5, 138.0, 131.1, 126.6, 116.3, 112.2, 103.4, 75.2, 68.3, 62.9, 59.7, 56.9, 20.1, 18.8. HRMS calcd for $C_{15}H_{23}NO_5$+H^+ $(M+H)^+$: 298.1654 found: 298.1657.

Methyl 3-(3-chlorophenylamino)-3-deoxy-β-D-gulopyranoside 20

Compound **12** (50 mg, 0.258 mmol) was arylated with **13e** (70 μL, 0.254 mmol) in presence of CsF (78 mg, 0.516 mmol) following general procedure. The crude was initially purified by flash chromatography (DCM: MeOH 15:1) and re-purified by preparative HPLC to afford **20** (41.8 mg, 60%) as a colorless oil. $[\alpha]_D^{25}$ -20.1 (c 0.8, CH_3OH) ^{1}H NMR (CD_3OD, 400 MHz): 7.06 (t, 1H, *J* 8.0 Hz), 6.74 (t, 1H, *J* 2.4 Hz), 6.66-6.59 (m, 2H), 4.60 (d, 1H, *J* 8.0 Hz), 3.95-3.83 (m, 3H), 3.76-3.67 (m, 3H), 3.57 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 151.0, 135.9, 131.2, 117.9, 113.6, 112.7, 103.3, 75.2, 68.2, 68.0, 62.7, 59.2, 56.9. HRMS calcd for $C_{13}H_{18}NO_5Cl$+H^+ $(M+H)^+$: 304.0952, found: 304.0949.

Methyl 3-deoxy-3-(3,4-difluorophenylamino)-β-D-gulopyranoside 21

Compound **12** (50 mg, 0.258 mmol) was arylated with **13f** (71 μL, 0.254 mmol) in presence of CsF (78 mg, 0.516 mmol) following general procedure. The crude was initially purified by flash chromatography (DCM: MeOH 15:1) and re-purified by preparative HPLC to afford **21** (41.8 mg, 60%) as a colorless oil. $[\alpha]_D^{25}$ -16.8 (c 0.7, CH_3OH) ^{1}H NMR (CD_3OD, 400 MHz): 6.97 (m , 1H), 6.61 (m, 1H), 6.46 (m, 1H), 4.58 (d, 1H, *J* 8 Hz), 3.93-3.87 (m, 2H), 3.81 (m, 1H), 3.76-3.65 (m, 3H), 3.56 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 165.5, 153.3 (d, *J* 13.3 Hz), 150.9 (d, *J* 13.2 Hz), 147.1 (d, *J* 7.3 Hz), 145.2 (d, *J* 12.5 Hz), 142.9 (d, *J* 12.9 Hz), ^{19}F (CD_3OD, 376 MHz) -140.5 (d, *J* 22.6), -156.3 (d, *J* 22.6). HRMS calcd for $C_{13}H_{17}NO_5F_2$+H^+ $(M+H)^+$: 306.1155, found: 306.1155.

3,4-Dichlorophenyl 3-azido-3-deoxy-1-thio-α-D-galactopyranoside 23

The acetyl protected azide **22**[6] (844 mg, 1.72 mmol) was dissolved in methanolic solution of NaOMe (15 mL, 1M). After 1h, TLC confirmed the complete conversion to the product and the reaction was neutralized using DOWEX 50W H^+ resin. The mixture was filtered through a cotton plug to remove the resin and the solvents were evaporated under reduced pressure and purified in flash chromatography (DCM:MeOH 15:1) to afford compound **23** (620 mg, 99%**).** $[\alpha]_D^{25}$ +7.4 (c 1.1, CH_3OH). ^{1}H NMR (CD_3OD, 400 MHz): 7.72 (d, 1H, *J* 2 Hz), 7.47 (dd, 1H, *J* 2 Hz, *J* 8.4 Hz), 7.42 (d, 1H, *J* 8.4 Hz), 5.67 (d, 1H, *J* 5.6 Hz), 4.38 (dd, 1H, *J* 5.6 Hz, *J* 10.8 Hz), 4.25 (t, 1H, *J* 5.6 Hz), 4.04 (d, 1H, *J* 2 Hz), 3.72-3.62 (m, 2H), 3.48 (dd, 1H, *J* 2.8 Hz, *J* 10.8 Hz). ^{13}C NMR (CD_3OD, 100 MHz): 136.5, 134.5, 133.5, 132.7, 132.2, 131.7, 91.1, 73.5, 69.6, 68.2, 64.5, 62.2. HRMS calcd $C_{12}H_{13}Cl_2N_3O_4S$ -$H^+$$(M-H)^+$: 363.9926, found: 363.9923.

3,4-Dichlorophenyl 3-amino-3-deoxy-1-thio-α-D-galactopyranoside 24

To the solution of azide **23** (610 mg, 1.67 mmol) in MeOH (20 mL) was added 5% Pd/C (204 mg) The mixture was stirred under H_2 atmosphere at rt for 1h. The Pd/C was removed by filtration through Celite®, the filtrate was concentrated, washed with DCM (3×10 mL), and dried under vacuo to give the amine **24** in (385 mg, 68%). $[\alpha]_D^{25}$ +5.1 (c 1.5, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.72 (d, 1H, *J* 2 Hz), 7.47-7.41 (m, 2H), 5.63 (d, 1H, *J* 5.2 Hz), 4.26 (t, 1H, *J* 5.6 Hz), 4.00 (dd, 1H, *J* 5.6 Hz, *J* 10.8 Hz), 3.92 (d, 1H, *J* 2 Hz), 3.73-3.63 (m, 2H), 2.81 (dd, 1H, *J* 3.2 Hz, *J* 10.8 Hz). ^{13}C NMR (CD_3OD, 100 MHz): 137.0, 134.3, 133.5, 132.6, 132.0, 131.6, 91.3, 74.0, 70.4, 69.6, 62.4, 54.6. HRMS calcd for $C_{12}H_{15}Cl_2NO_4S+H^+$ $(M+H)^+$: 340.0177, found: 340.0179.

3,4-Dichlorophenyl 3-deoxy-3-(3-methoxyphenylamino)-1-thio-α-D-galactopyranoside 25 and 3,4-dichlorophenyl 3-deoxy-3-(4-methoxyphenylamino)-1-thio-α-D-galactopyranoside 26

Compound **25** (135 mg, 0.398 mmol) was arylated with **13b** (102 μL, 0.39 mmol) in presence of CsF (121 mg, 0.796 mmol) following general procedure. The crude material was purified by flash column (DCM:MeOH 20:1) to give **25** and **26** (90.4 mg, 0.203 mmol, 44%) as a mixture which then was purified by preparative HPLC (as 3:1 meta to para) as a colorless oil. Data for compound **25**: $[\alpha]_D^{25}$ +19.5 (c 0.7, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.77 (d, 1H, *J* 2.0 Hz), 7.51 (dd, 1H, *J* 2.0 Hz, *J* 8.0 Hz), 7.45 (d, 1H, *J* 8.0 Hz), 7.03 (t, 1H, *J* 8.0 Hz), 6.36-6.32 (m, 2H), 6.25 (m, 1H), 5.71 (d, *J* 5.2 Hz), 4.34 (t, 1H, *J* 6.4 Hz), 4.23 (dd, 1H, *J* 5.2 Hz, *J* 10.8 Hz), 4.06 (d, 1H, *J* 1.6 Hz), 3.74 (s, 3H), 3.73-3.64 (m, 2H), 3.58 (dd, 1H, *J* 2.8 Hz, *J* 10.8 Hz). ^{13}C NMR (CD_3OD, 100 MHz): 162.3, 150.6, 137.0, 134.4, 133.5, 132.7, 132.1, 131.7, 130.8, 108.0, 104.0, 101.2, 91.6, 74.0, 68.9, 67.9, 62.6, 57.8, 55.5. HRMS calcd for $C_{19}H_{21}Cl_2NO_5S+H^+$ $(M+H)^+$: 446.0596, found: 446.0596. Data for compound **26**: $[\alpha]_D^{25}$ +18.9 (c 0.6, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.77 (d, 1H, *J* 2.0 Hz), 7.51 (dd, 1H, *J* 2.0 Hz, *J* 8.0 Hz), 7.44 (d, 1H, *J* 8.0 Hz), 6.79-6.74 (m, 4H), 5.71 (d, 1H, *J* 13.2 Hz), 4.32 (t, 1H, 6.0 Hz), 4.21 (dd, *J* 5.2 Hz, *J* 10.8 Hz), 4.01 (d, 1H, *J* 2.0 Hz), 3.72 (s, 3H), 3.69-3.66 (m, 2H), 3.46 (dd, *J* 2.8 Hz, *J* 10.8 Hz). ^{13}C NMR (CD_3OD, 100 MHz): 154.2, 137.0, 134.2, 132.7, 131.7, 117.4, 115.8, 91.5, 74.0, 68.9, 67.5, 62.6, 59.3, 56.2. HRMS calcd for $C_{19}H_{21}Cl_2NO_5S+H^+$ $(M+H)^+$: 446.0596, found: 446.0594.

3,4-Dichlorophenyl 3-deoxy-3-(3,4-dimethylphenylamino)-1-thio-α-D-galactopyranoside 27

Compound **24** (103 mg, 0.304 mmol) was arylated with **13d** (79 μL, 0.298 mmol) in presence of CsF (92.3 mg, 0.608 mmol) following general procedure. Then the crude was initially purified by flash chromatography (DCM: MeOH 20:1) and re-purified by preparative HPLC to afford **29** (76.7 mg, 57%) as a colorless oil. $[\alpha]_D^{25}$ +27.3 (c 0.9, CH_3OH).^1H NMR (CD_3OD, 400 MHz): 7.77 (d, 1H, *J* 2.0 Hz), 7.51 (dd, 1H, *J* 2.0 Hz, *J* 8 Hz), 7.44 (d, 1H, *J* 8.0 Hz), 6.90 (d, 1H, *J* 8.0 Hz), 6.59 (s, 1H), 6.51 (d, 1H, *J* 8.0 Hz), 5.71 (d, 1H, *J* 5.2 Hz), 4.33 (t, 1H, *J* 6.0 Hz), 4.21 (m, 1H), 4.02 (s, 1H), 3.72-3.63 (m, 2H), 3.54 (d, 1H, 8.8 Hz), 2.18 (s, 3H), 2.14 (s, 3H). ^{13}C NMR (CD_3OD, 100 MHz): 138.0, 137.0, 134.4, 133.5, 132.7, 132.1, 131.6, 131.1, 127.0, 117.5, 113.3, 91.6, 74.0, 68.9, 67.7, 62.6, 58.4, 20.1, 18.8. HRMS calcd for $C_{20}H_{23}NO_4SCl_2+H^+$ $(M+H)^+$: 444.0803, found: 444.0807.

3,4-Dichlorophenyl 3-(3-chlorophenylamino)-3-deoxy-1-thio-α-D-galactoyranoside 28

Compound **24** (68 mg, 0.2 mmol) was arylated with **13e** (48 μL, 0.196 mmol) in presence of CsF (60.8 mg, 0.4 mmol) following general procedure. Then the crude was initially purified by flash chromatography (DCM: MeOH 20:1) and re-purified by preparative HPLC to afford **28** (54.9 mg, 61%) as a colorless oil. $[\alpha]_D^{25}$ +25.9 (c 0.7, CH_3OH). ^1H NMR (CD_3OD, 400 MHz): 7.78 (d, 1H, *J* 2 Hz), 7.52 (dd, 1H, *J* 2.0 Hz, *J* 8.0 Hz), 7.46 (d, 1H, *J* 8.0 Hz), 7.06 (t, 1H, *J* 8

Hz), 6.74 (t, 1H, *J* 2.0 Hz), 6.65 (dd, 1H, *J* 2 Hz, *J* 8.0 Hz), 6.60 (m, 1H), 5.71 (d, 1H, *J* 5.2 Hz), 4.37 (t, 1H, *J* 6.0 Hz), 4.24 (dd, 1H, *J* 5.2 Hz, *J* 10.8 Hz), 4.04 (d, 1H, *J* 1.6 Hz), 3.73-3.64 (m, 2H), 3.58 (dd, 1H, *J* 2.8 Hz, *J* 10.8 Hz). ^{13}C NMR (CD_3OD, 100 MHz): 150.8, 136.9, 135.9, 134.5, 132.7, 131.7, 17.8, 114.3, 113.0, 91.6, 73.9, 69.0, 67.9, 62.5, 57.4. HRMS calcd for $C_{18}H_{18}NO_4SCl_3$+H^+ $(M+H)^+$: 450.0100, found: 450.0103.

3,4-Dichlorophenyl 4,6-*O*-benzylidene-1-thio-α-D-galactopyranoside 30

To solution of **29**[4] (2.5 g, 7.33 mmol) in acetonitrile (30 mL) was added benzaldehyde dimethyl acetal (4.6 mL, 18.3 mmol) and catalytic amount of camphor sulfonic acid. The reaction mixture was stirred at room temperature for 4 h. Solvent was evaporated and the residue purified by flash chromatography (Heptane:Ethyl acetate:1:2) to give compound **30** (2.18 g, 68%). $[\alpha]_D^{25}$ +37.2 (c 1.6, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.61 (d, 1H, *J* 1.6 Hz), 7.51-7.49 (m, 2H), 7.40-7.37 (m 3H), 7.36 (s, 1H), 7.32 (dd, 1H, *J* 1.6 Hz, *J* 6.4 Hz), 5.86 (d, 1H, 4 Hz), 5.60 (s, 1H), 4.37-4.34 (m, 2H), 4.28 (dd, 1H , *J* 1.2 Hz, *J* 10 Hz), 4.18 (bs, 1H), 4.15 (dd, 1H, *J* 1.2 Hz, *J* 10 Hz), 3.81 (dd, 1H, *J* 2.8 Hz, *J* 8 Hz). ^{13}C NMR (CD_3Cl, 100 MHz): 137.3, 134.6, 132.0, 130.8, 129.8, 129.6, 128.5, 126.4, 101.6, 89.3, 75.5, 70.8, 69.6, 69.4, 64.3. HRMS calcd for $C_{19}H_{18}SO_5Cl_2$ +H^+ $(M+H)^+$: 429.0330, found: 429.0332.

3,4-Dichlorophenyl 2-*O*-acetyl-3-*O*-(1,1,1-trifluoromethanesulfonyl)-4,6-*O*-benzylidene-1-thio-α-D-galactopyranoside 31

To a solution of **30** (2 g, 4.66 mmol) in dry DCM (20 mL) at 0^{o}C was added pyridine (1.7 mL, 18.7 mmol) and then triflic anhydride (0.78 mL, 4.66 mmol). The reaction was stirred for 30 min, then warmed to room temperature, acetic anhydride (0.5 mL, 5.12 mmol) was added, and the reaction was stirred at room temperature for another 1 h. The reaction was quenched by 1N HCl (25 mL) solution and then washed with sat'd aqueous NaCl (2×20 mL). The organic layer was dried over anhydrous Na_2SO_4, filtered and evaporated to afford of **31** (67%, 1.8 g). The crude **31** was used for the next step without further purification.

3,4-Dichlorophenyl 2-*O*-acetyl-3-azido-3-deoxy-4,6-*O*-benzylidene-1-thio-α-D-gulopyranoside 32

To a solution of **31** (1.8 g, 3.12 mmol) in DMF (25 mL) was added sodium azide (0.8 g, 12.48 mmol) and the mixture was heated at 65 ^{0}C for 12 h. DMF was evaporated and the residue was dissolved in DCM (50 mL) and washed with water (2×25 mL). The organic phase was dried with Na_2SO_4 and concentrated. The residue was purified by flash chromatography (Heptane: EtOAc: 2:1) to afford **33** (1.12 g, 76%) as a white solid. $[\alpha]_D^{25}$ -40.4 (c 1.9, $CHCl_3$). ^{1}H NMR ($CDCl_3$, 400 MHz): 7.58 (d, 1H, *J* 2 Hz), 7.52-7.49 (m, 2H), 7.40-7.33 (m, 4H), 7.30 (dd, 1H, *J* 2 Hz, *J* 8 Hz), 5.94 (d, 1H, *J* 5.6 Hz), 5.58 (s, 1H), 5.56 (dd, 1H, J 3.6 Hz, J 6 Hz), 4.31 (dd, 1H, *J* 1.2 Hz, *J* 13.2), 4.17-4.10 (m, 4H), 2.17 (s, 3H). ^{13}C NMR (CD_3Cl, 100 MHz: 169.5, 137.1, 136.9, 133.0, 131.5, 131.3, 129.4, 129.3, 126.6, 128.4, 126.2, 101.4, 85.4, 74.9, 69.4, 68.7, 60.2, 59.1, 20.8. HRMS calcd for $C_{21}H_{19}N_3O_5SCl_2$+H^+ $(M+H)^+$: 496.0500, found: 496.0501.

3,4-Dichlorophenyl 3-azido-3-deoxy-1-thio-α-D-gulopyranoside 33

The azide **32** (1.1g, 2.22 mmol) was dissolved in 90% aqueous AcOH (20 mL) and heated at 90 ^{0}C for 4 h. Then the acetic acid and water were evaporated, the residue was dissolved in methanolic solution of NaOMe (15 mL, 1M) was added until pH 10, and the mixture was stirred at room temperature for 1h. The reaction was neutralized using DOWEX 50W H^+ resin, filtered through a cotton plug to remove the resin, the solvents were evaporated under reduced pressure, and the residue purified by flash chromatography (DCM:MeOH 15:1) to afford compound **33** (490 mg, 61%). $[\alpha]_D^{25}$ -23.6 (c 1.4, CH_3OH). ^{1}H NMR (CD_3OD, 400 MHz): 7.74 (d, 1H, *J* 2

Hz), 7.49 (dd, 1H, *J* 2 Hz, *J* 8 Hz), 7.43 (d, 1H, *J* 8 Hz), 5.49 (d, 1H, 5.2 Hz), 4.50 (dd, 1H, *J* 3.6 Hz, *J* 2 HZ), 4.26 (m, 1H), 4.87 (t, 1H, J 3.6 Hz), 3.84 (dd, 1H, *J* 1.6 Hz, *J* 4.4 Hz), 3.71 (d, 2H, *J* 6 Hz). ^{13}C NMR (CD3OD, 100 MHz): 136.5, 134.4, 133.40, 132.7, 132.1, 131.6, 91.1, 73.4, 69.5, 68.2, 64.4, 62.1. HRMS calcd $C_{12}H_{13}Cl_2N_3O_4S$ $+H^+(M+H)^+$: 366.0082, found: 366.0079.

3,4-Dichlorophenyl 3-amino-3-deoxy-1-thio-α-D-gulopyranoside 34

To a solution of **33** (100 mg, 0.27 mmol) in dry THF (10 mL) was added $LiAlH_4$ (19 mg, 0.54 mmol) under N_2 atmosphere, the reaction mixture was stirred at room temperature for 30 min, and quenched with MeOH. The excess $LiAlH_4$ was removed by filtration through Celite®, the solvent was evaporated, and the residue was purified by column chromatography (DCM: MeOH 1:1) to give **34** (40 mg, 44%). $[\alpha]_D^{25}$ -17.6 (c 0.6, CH_3OH). ^{1}H NMR (CD_3OD, 400 MHz): 7.76 (d, 1H, *J* 2.4 Hz), 7.48 (dd, 1H, *J* 2 Hz, *J* 8.4 Hz, *J* 2.0 Hz), 7.42 (d, 1H, *J* 8.4 Hz), 5.55 (d, 1H, *J* 4.4 Hz), 4.34-4.28 (m, 2H), 3.89 (dd, 1H *J* 5.6 Hz, *J* 3.2 Hz), 3.83 (dd, 1H, *J* 11.6 Hz, *J* 6.8 Hz) , 3.79 (dd, 1H, *J* 4.8 Hz, *J* 11.6 Hz), 3.20 (t, 1H, *J* 4.8 Hz). ^{13}C NMR (CD3OD, 100 MHz): 138.5. 133.5, 133.3, 131.7, 131.60, 131.58, 88.9, 72.7, 70.2, 68.6, 61.3, 55.9. HRMS calcd for $C_{12}H_{15}Cl_2NO_4S+H^+$ $(M+H)^+$: 340.0177, found: 340.0179.

3,4-Dichlorophenyl 3-deoxy-3-(3-methoxy-phenylamino)-1-thio-α-D-gulopyranoside 35 and 3,4-dichlorophenyl 3-deoxy-3-(4-methoxyphenylamino)-1-thio-α-D-gulopyranoside 36

The gulo amine **34** (30 mg, 0.088 mmol) was arylated with **13b** (23 μL, 0.0.86 mmol) in presence of CsF (27 mg, 0.516 mmol) following general procedure. The crude material was purified by flash column (DCM:MeOH 20:1) to give **35** and **36** (8.9 mg, 25%, 3:1 ratio) as a colorless oil. The mixture of **35** and **36** was purified and separated by preparative HPLC. Data for **35**: ^{1}H NMR (CD_3OD, 400 MHz): 7.81 (d, 1H, *J* 2 Hz), 7.54 (dd, 1H, *J* 2 Hz, *J* 8.4 Hz), 7.46 (d, 1H, *J* 8.4 Hz), 7.06-7.02 (m, 1H), 6.37-6.34 (m, 1H), 6.33 (t, 1H, *J* 2.0 Hz), 6.29-6.26 (m, 1H), 5.59 (d, 1H, *J* 5.2 Hz), 4.50 (t, 1H, *J* 4.8 Hz), 4.41-4.38 (m, 1H), 3.98 (dd, 1H, *J* 4.8 Hz, *J* 2.4 Hz), 3.75 (dd, 2H, *J* 6.4 Hz, *J* 2.4 Hz), 3.75 (s, 3H), 3.69 (t, 1H, *J* 4.0 Hz). ^{13}C NMR (CD_3OD, 100 MHz): 162.3, 150.6, 138.4, 133.5, 132.2, 132.0, 131.6, 130.9, 107.7, 104.4, 100.8, 90.6, 71.4, 68.8, 66.9, 62.2, 58.9, 55.5. HRMS calcd for $C_{19}H_{21}Cl_2NO_5S+H^+$ $(M+H)^+$: 446.0596, found: 446.0593. Data for **36**: ^{1}H NMR (CD_3OD, 400 MHz): 7.78 (d, 1H, *J* 2.0 Hz), 7.52 (dd, 1H, *J* 8.4 Hz, *J* 2.0 Hz), 7.44 (d, 1H, *J* 8.4 Hz), 6.80-6.73 (m, 4H), 5.56 (d, 1H, *J* 4.8 Hz), 4.49 (t, 1H, *J* 4.8 Hz), 4.43-4.39 (m, 1H), 3.96 (dd, 1H, *J* 4.4 Hz, *J* 2.4 Hz), 3.77-3.72 (m, 5H), 3.60 (t, 1H, *J* 4.0 Hz). ^{13}C NMR (CD_3OD, 125 MHz): 154.2, 143.1, 138.7, 133.9, 132.5, 132.2, 131.9, 131.6, 116.7, 115.8, 90.7, 71.3, 68.8, 66.8, 62.2, 60.0, 56.1. HRMS calcd for $C_{19}H_{21}Cl_2NO_5S+H^+$ $(M+H)^+$: 446.0596, found: 446.0594.

Molecular dynamics simulations

All computations were performed with Schrödinger software suite 2018-3. The crystal structures of PDB 3WLU of galectin-9N in complex with selenolactose and PDB 3NV3 of galectin-9C in complex with a biantennary oligosaccharide were prepared for molecular dynamics simulation using the Protein Preparation Wizard. Compounds **6** and **18** were positioned with the galactose ring in an orientation identical to that of the galactoside ring of selenolactose and the biantennary oligosaccharide in the crystal structures 3WLU and 3NV3, respectively. MD simulations were performed using Desmond with default settings except for the duration, which was 120 ns. The carbohydrate O4 atom and all beta sheet backbone atoms were subjected to light position restraint with a force contestant of 1 kcal mol-1 Å-2.

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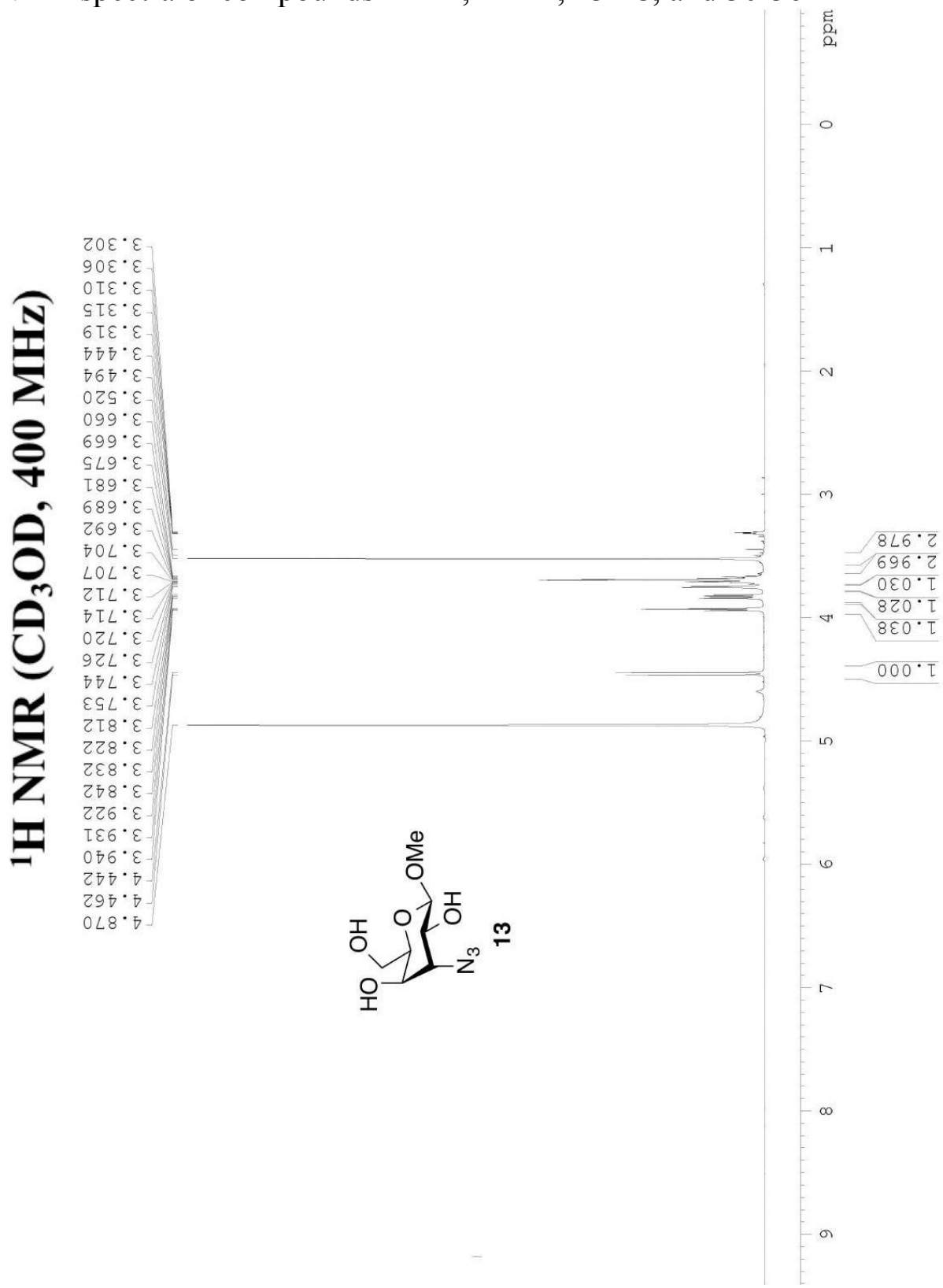
NMR spectra of compounds **11**-**12**, **14**-**21**, **23**-**28**, and **30**-**36**



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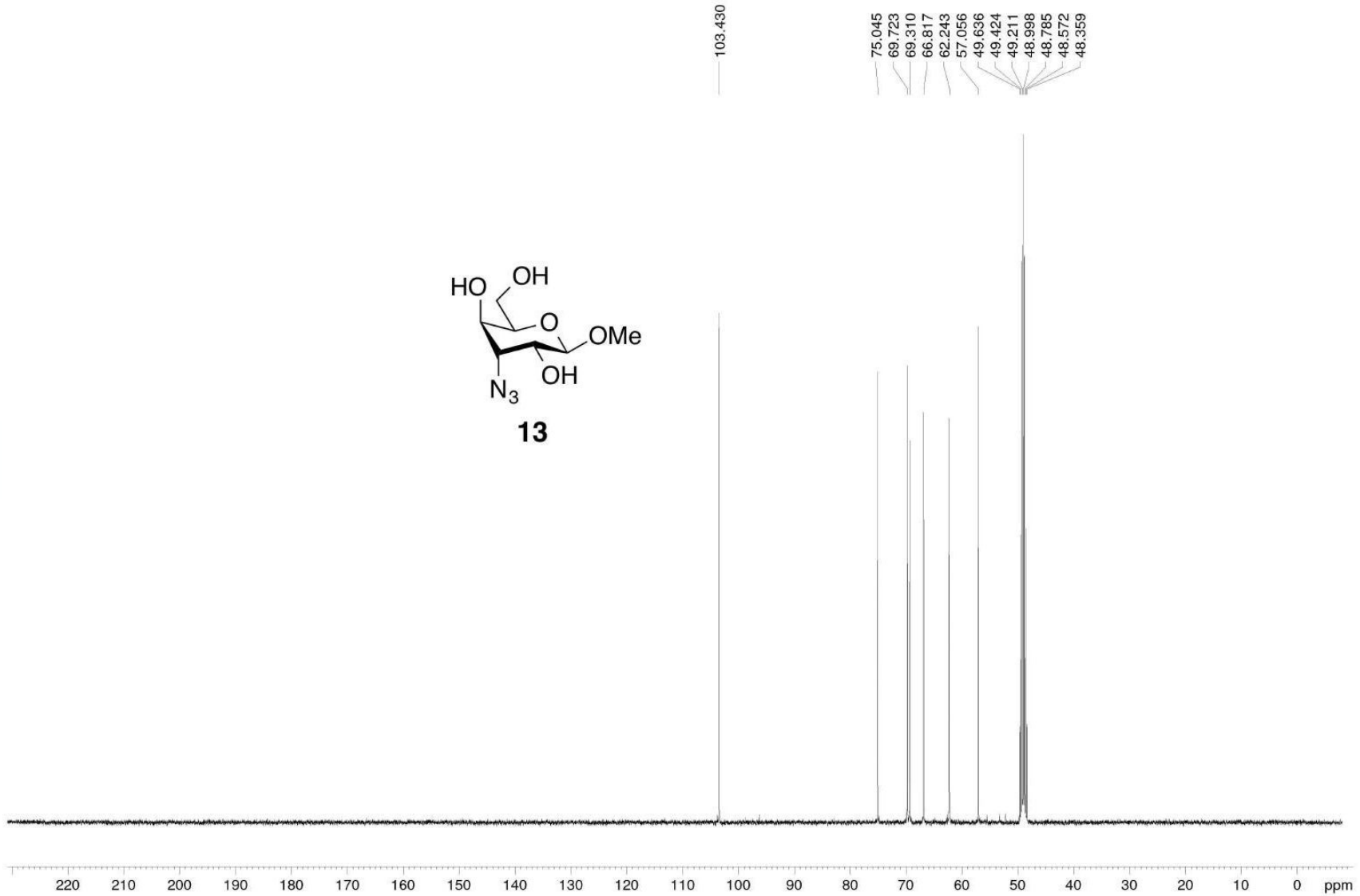
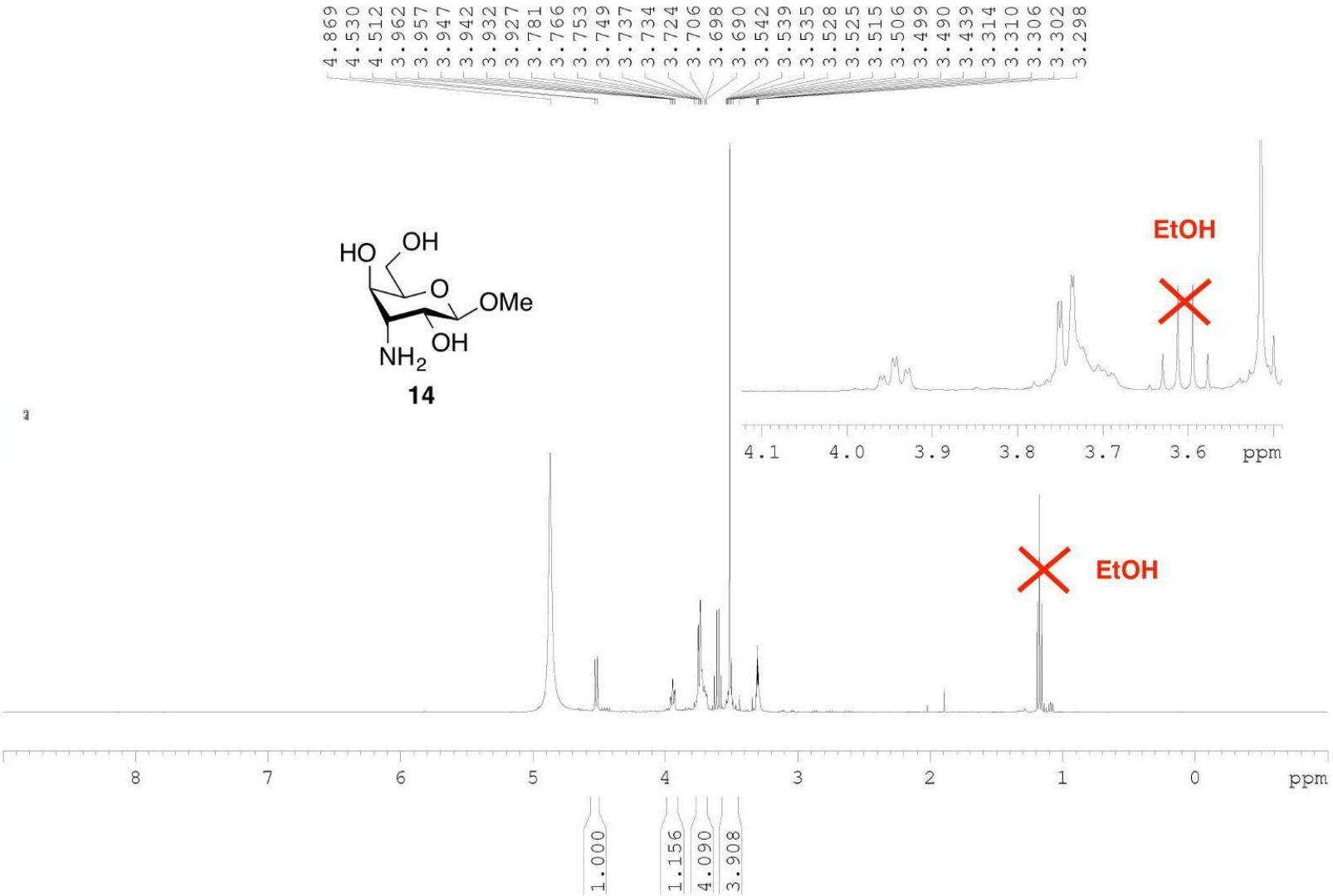
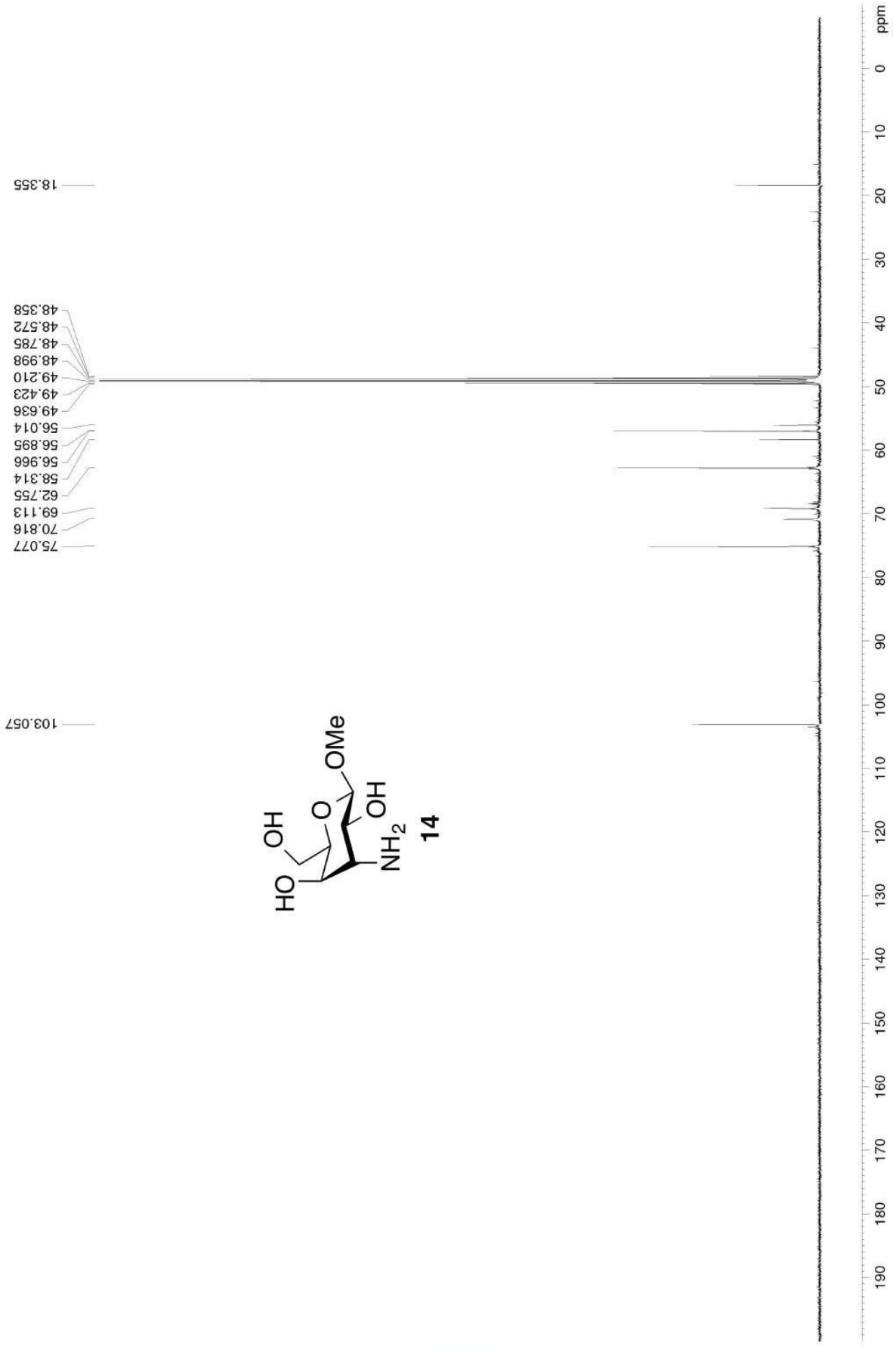


^{1}H NMR (CD_3OD, 400 MHz)

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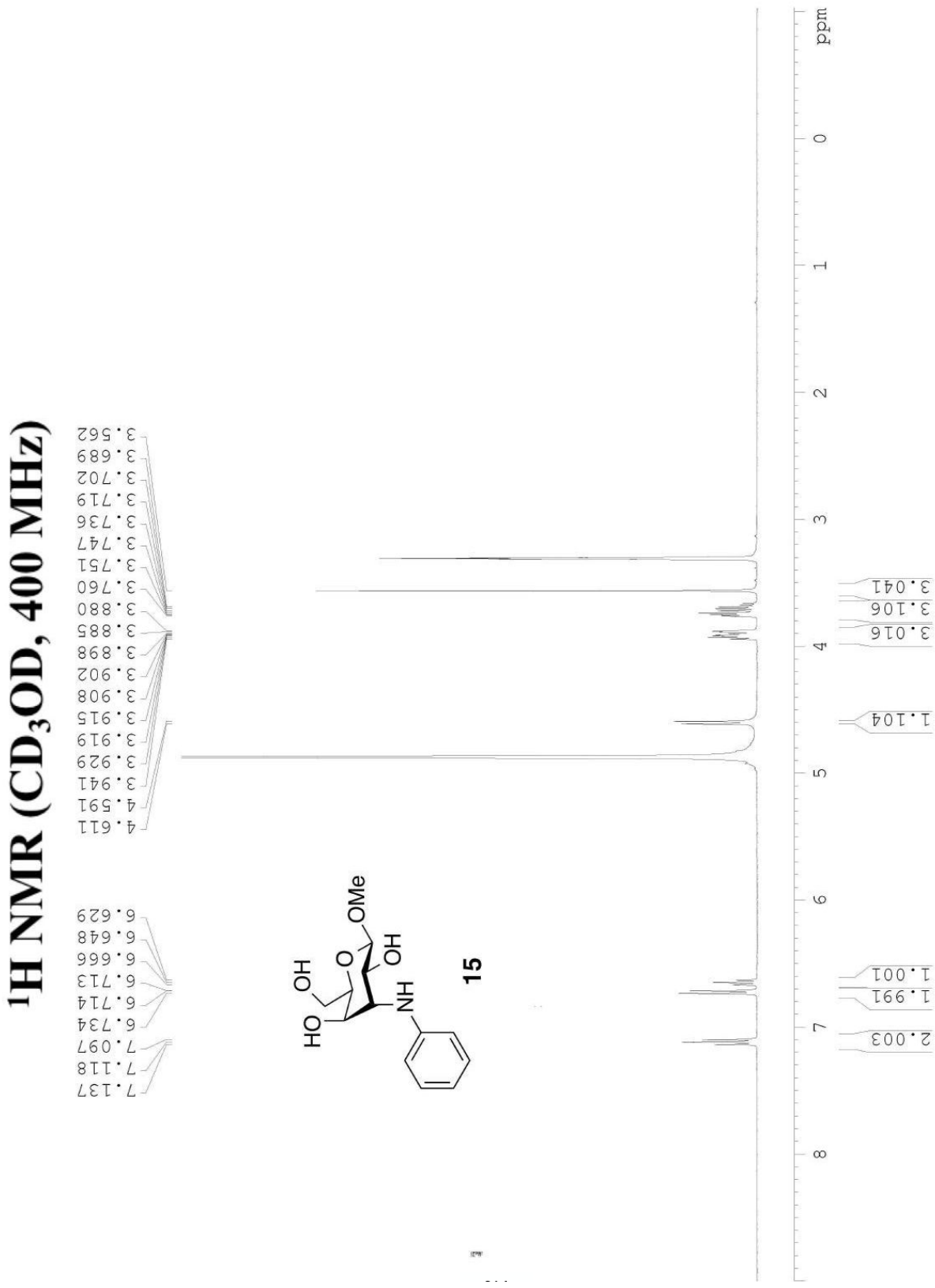
48.358
48.572
48.785
48.998
49.210
49.423
49.636
56.014
56.895
56.966
58.314
62.755
69.113
70.816
75.077
103.057
OMe
OH
O
OH
HO
NH2
14
ppm


1H NMR (CD3OD, 400 MHz)
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7.118
7.097
6.734
6.714
6.713
6.666
6.648
6.629
4.611
4.591
3.941
3.929
3.919
3.915
3.908
3.902
3.898
3.885
3.880
3.760
3.751
3.747
3.736
3.719
3.702
3.689
3.562
OMe
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OH
HO
NH
15
ppm
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1
2
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4
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6
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8
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1.001
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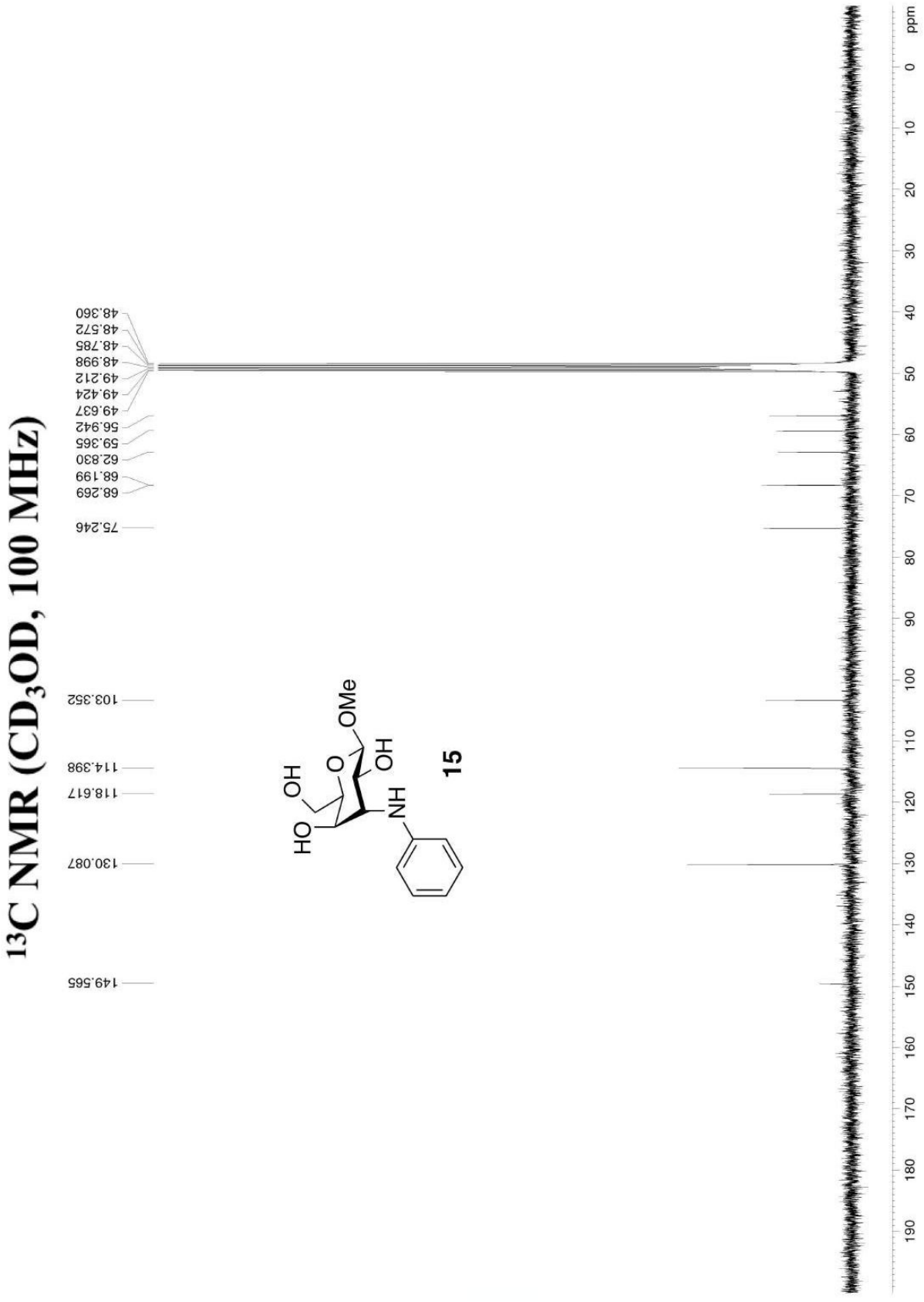
3.016
3.106
3.041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48.785
48.998
49.212
49.424
49.637
56.942
59.365
62.830
68.199
68.269
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103.352
114.398
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149.565
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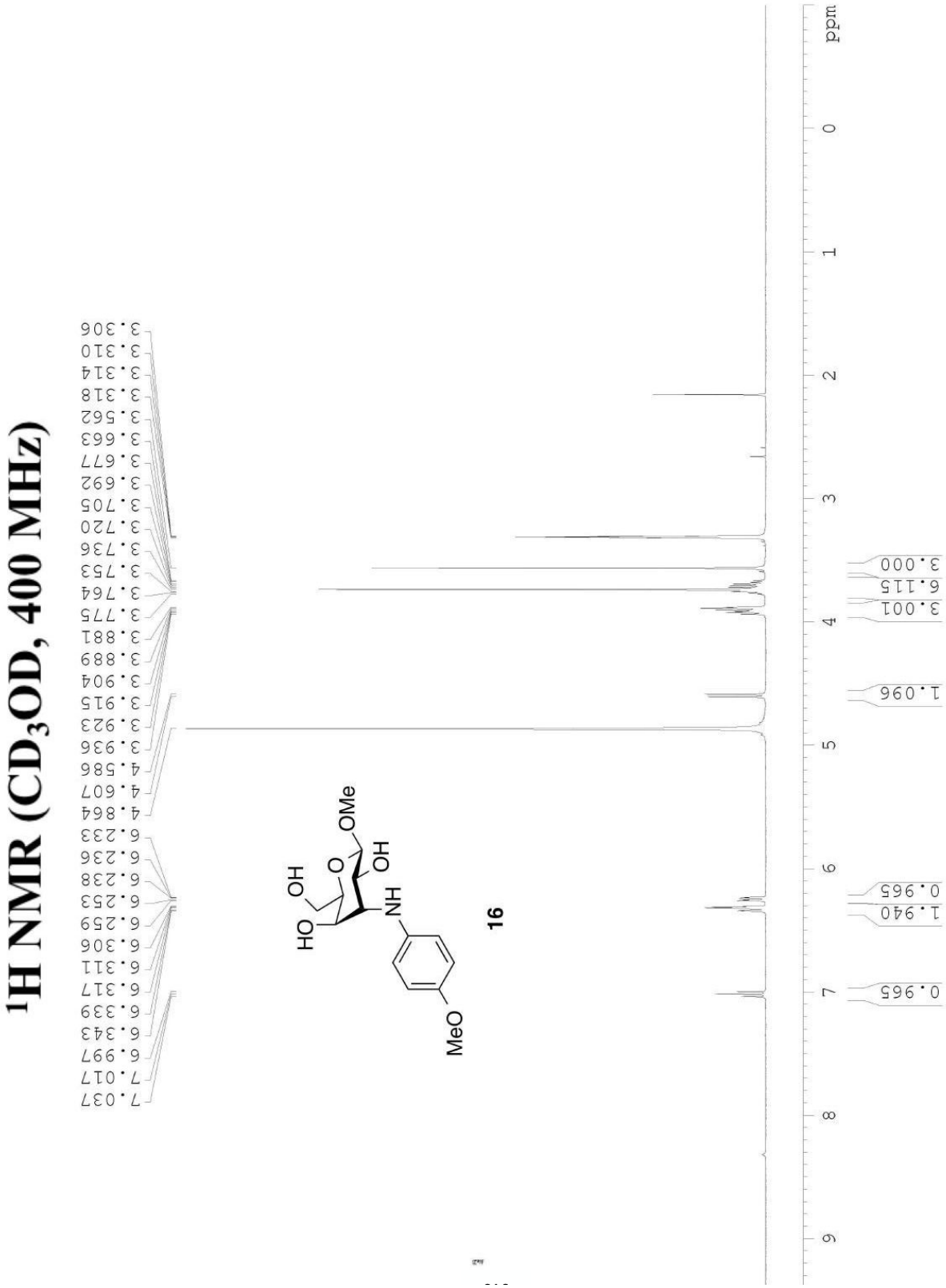
OH
HO
NH
15
ppm


1H NMR (CD3OD, 400 MHz)
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O
OH
HO
NH
MeO
ppm
0
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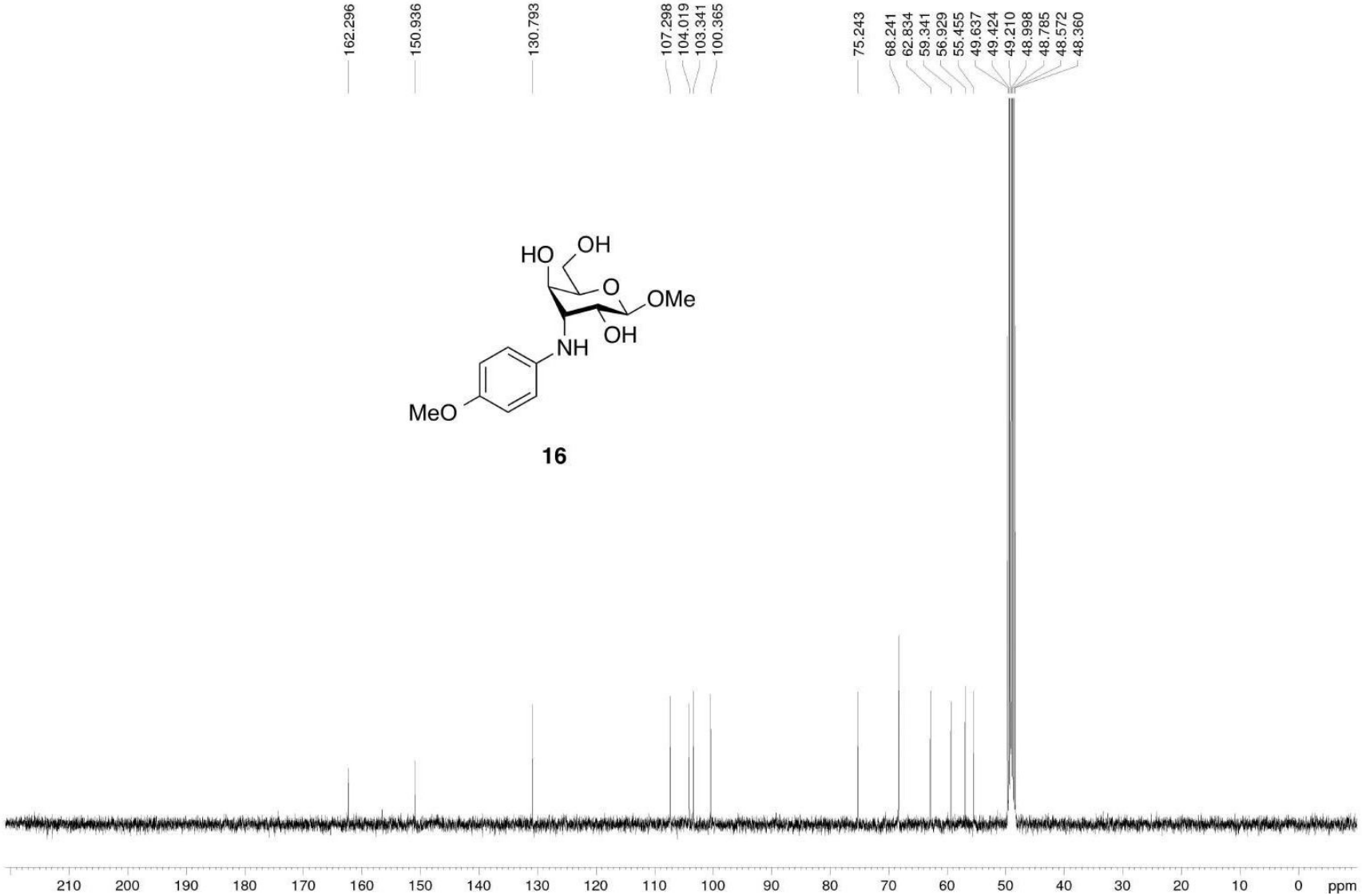
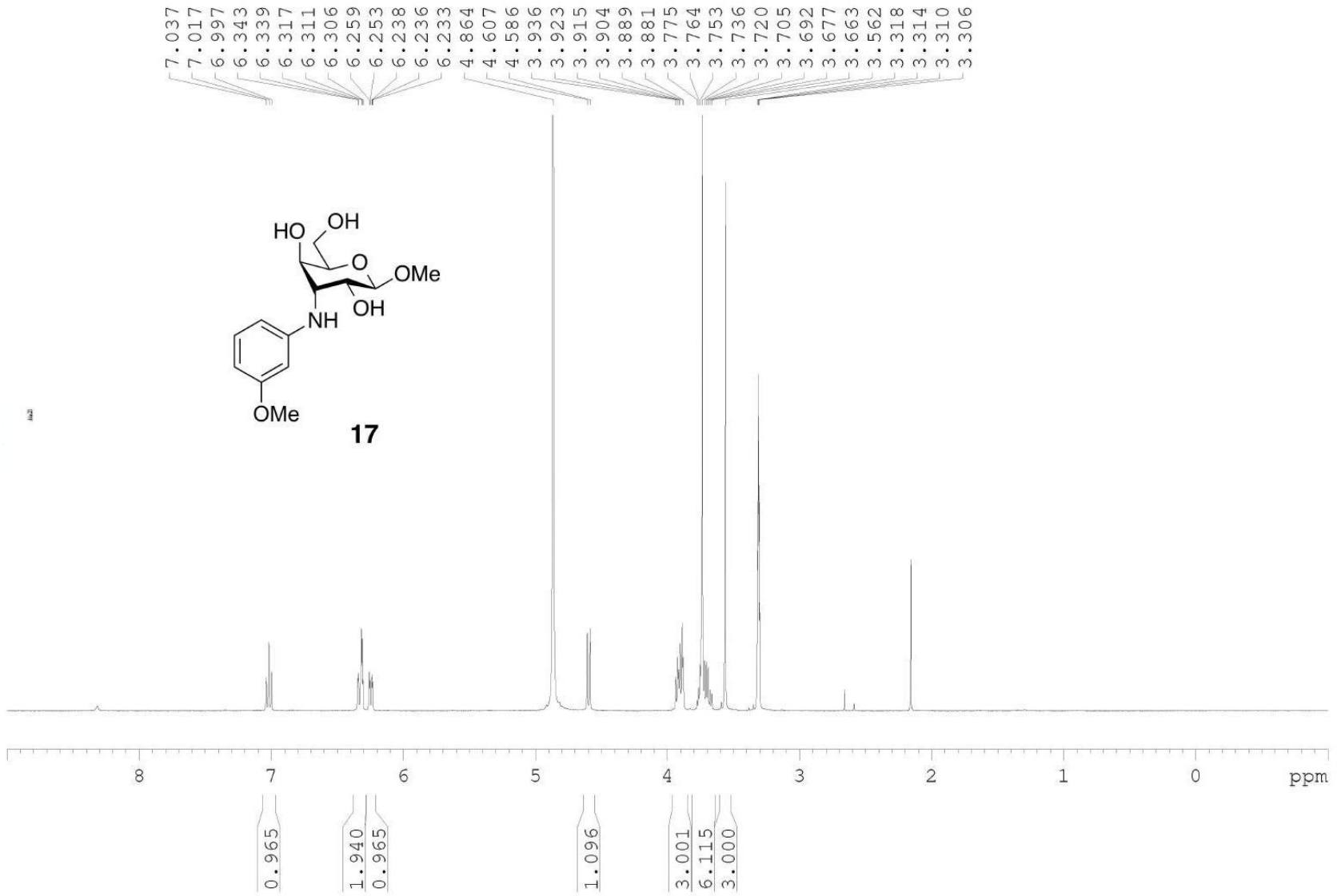
2
3
4
5
6
7
8
9
3.001
6.115
3.000
1.096
1.940
0.965
0.965
7.037
7.017
6.997
6.343
6.339
6.317
6.311
6.306
6.259
6.253
6.238
6.236
6.233
4.864
4.607
4.586
3.936
3.923
3.915
3.904
3.889
3.881
3.775
3.764
3.753
3.736
3.720
3.705
3.692
3.677
3.663
3.562
3.318
3.314
3.310
3.306

^{13}C NMR (CD_3OD, 100 MHz)



16

^{1}H NMR (CD_3OD, 400 MHz)



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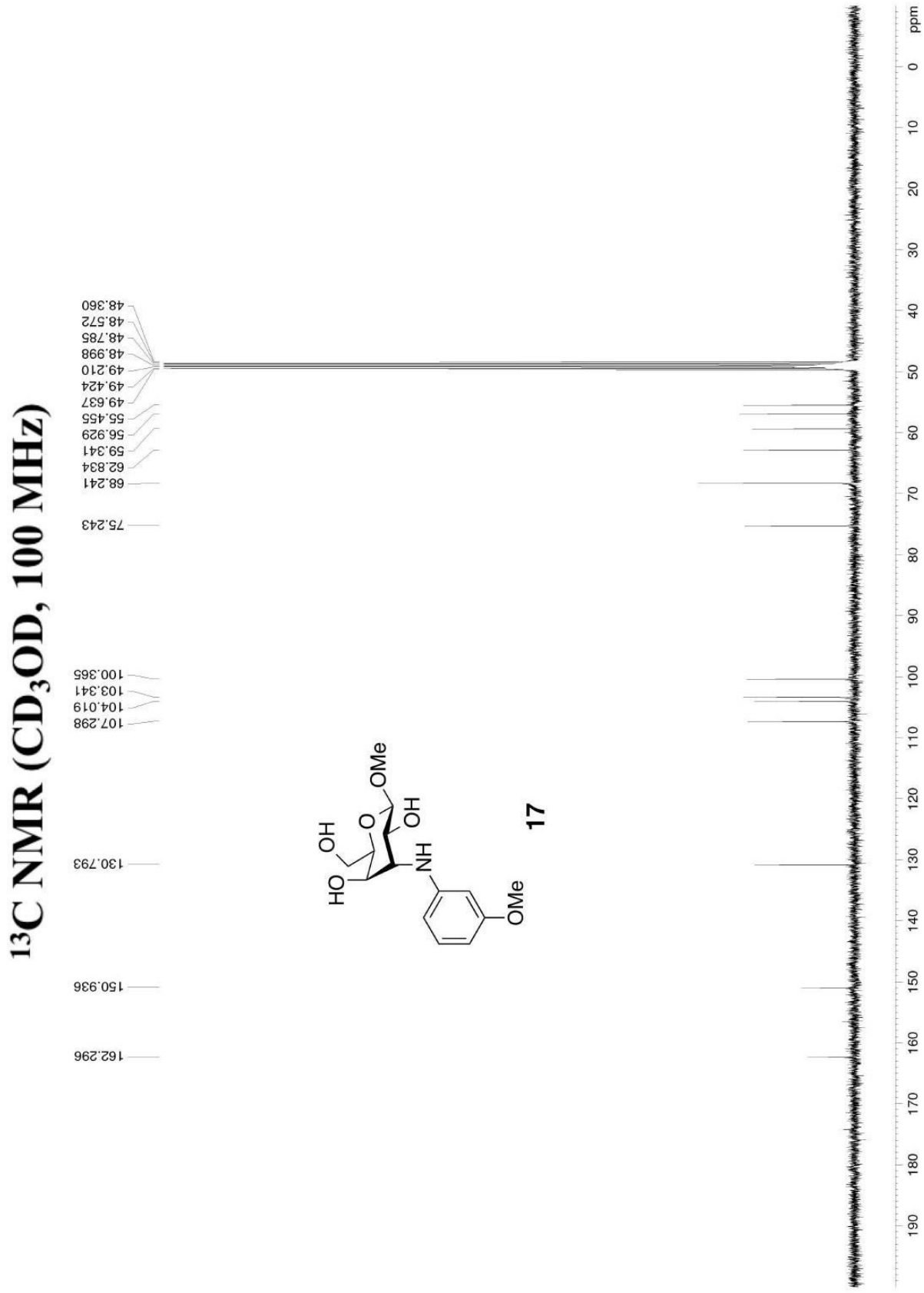
13C NMR (CD3OD, 100 MHz)
48.360
48.572
48.785
48.998
49.210
49.424
49.637
55.455
56.929
59.341
62.834
68.241
75.243
100.365
103.341
104.019
107.298
130.793
150.936
162.296
OMe
OH
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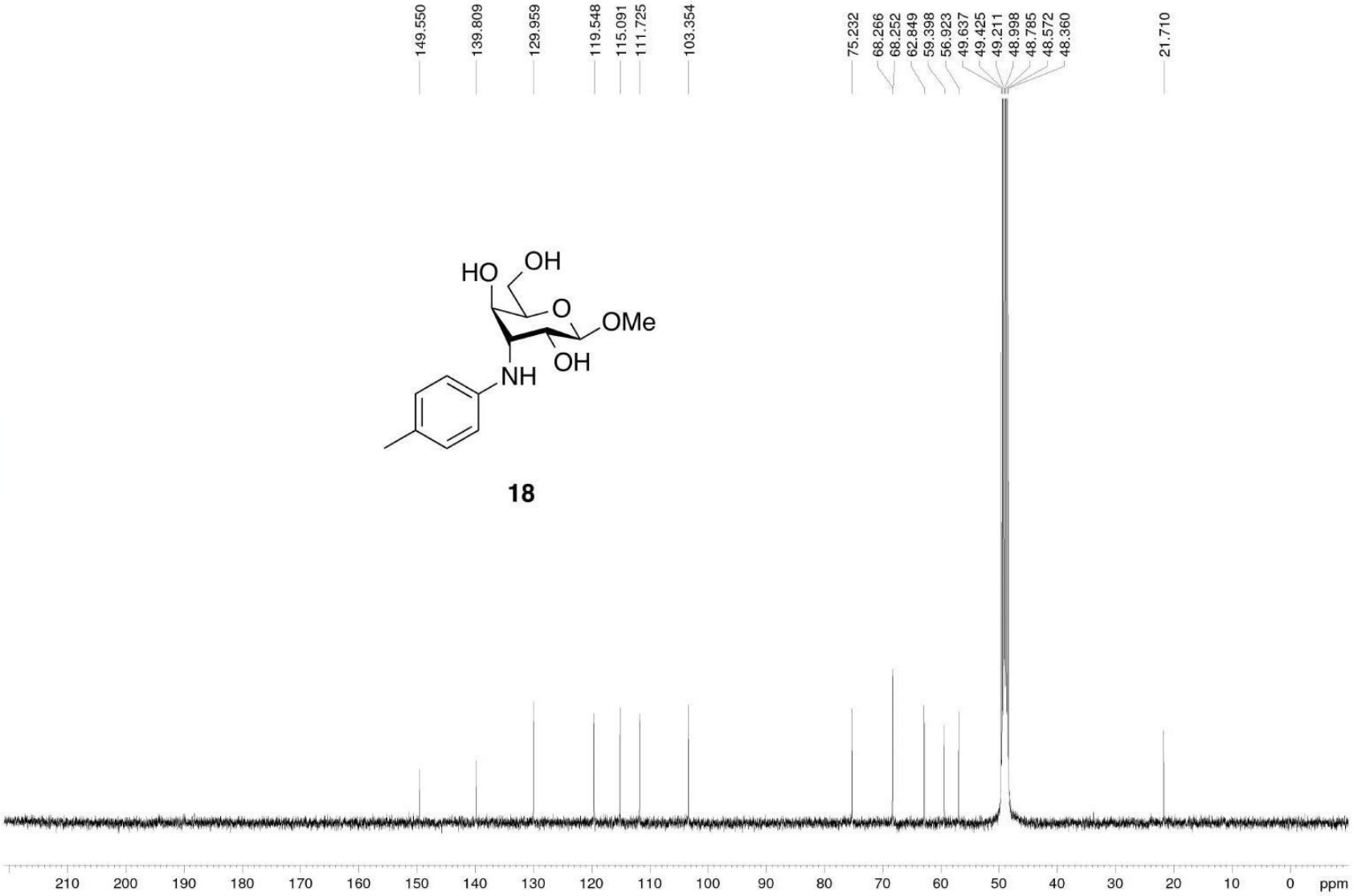
OH
NH
HO
OMe
17
ppm

^{1}H NMR (CD_3OD, 400 MHz)

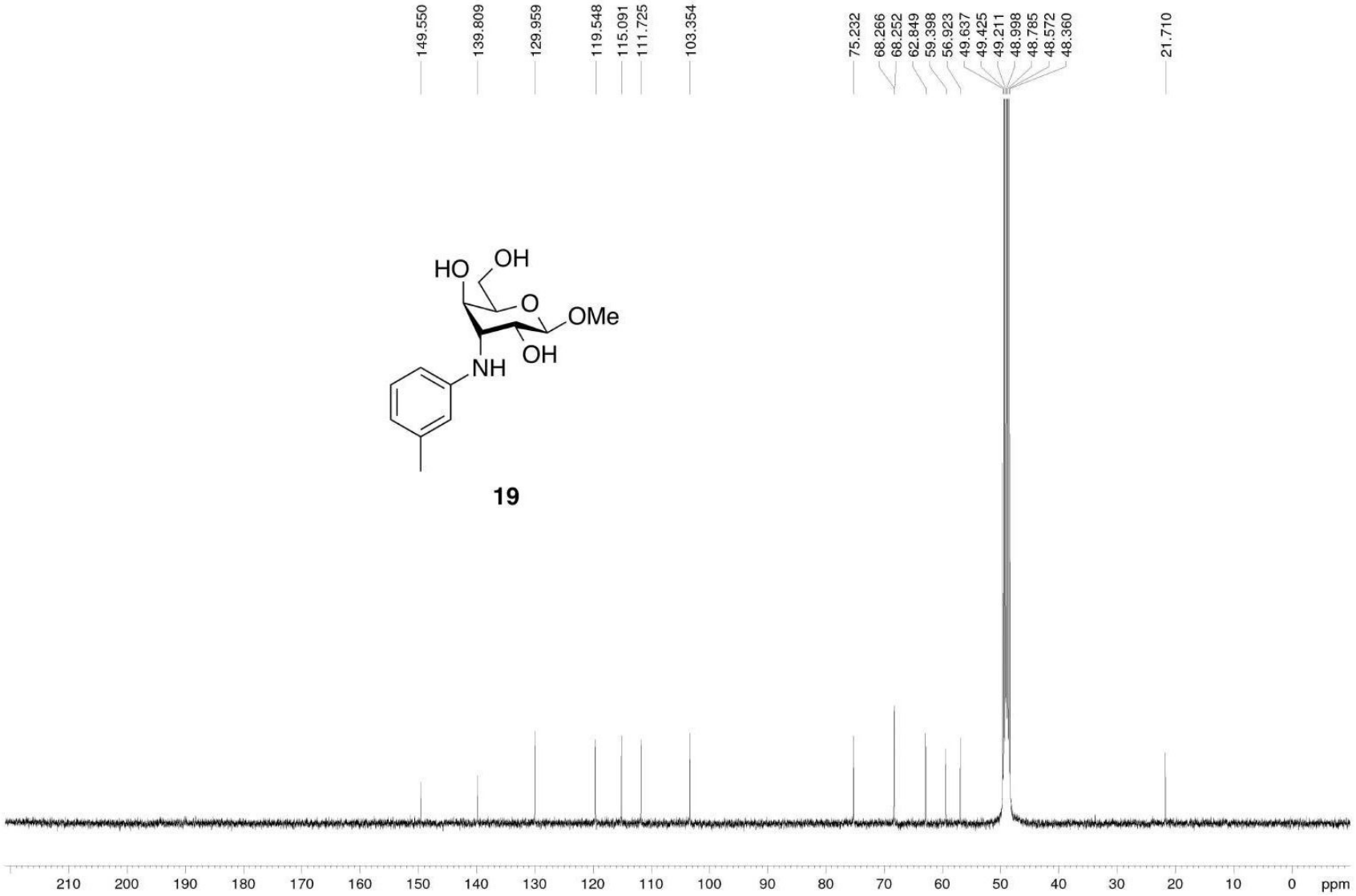
^{13}C NMR (CD_3OD, 100 MHz)



18

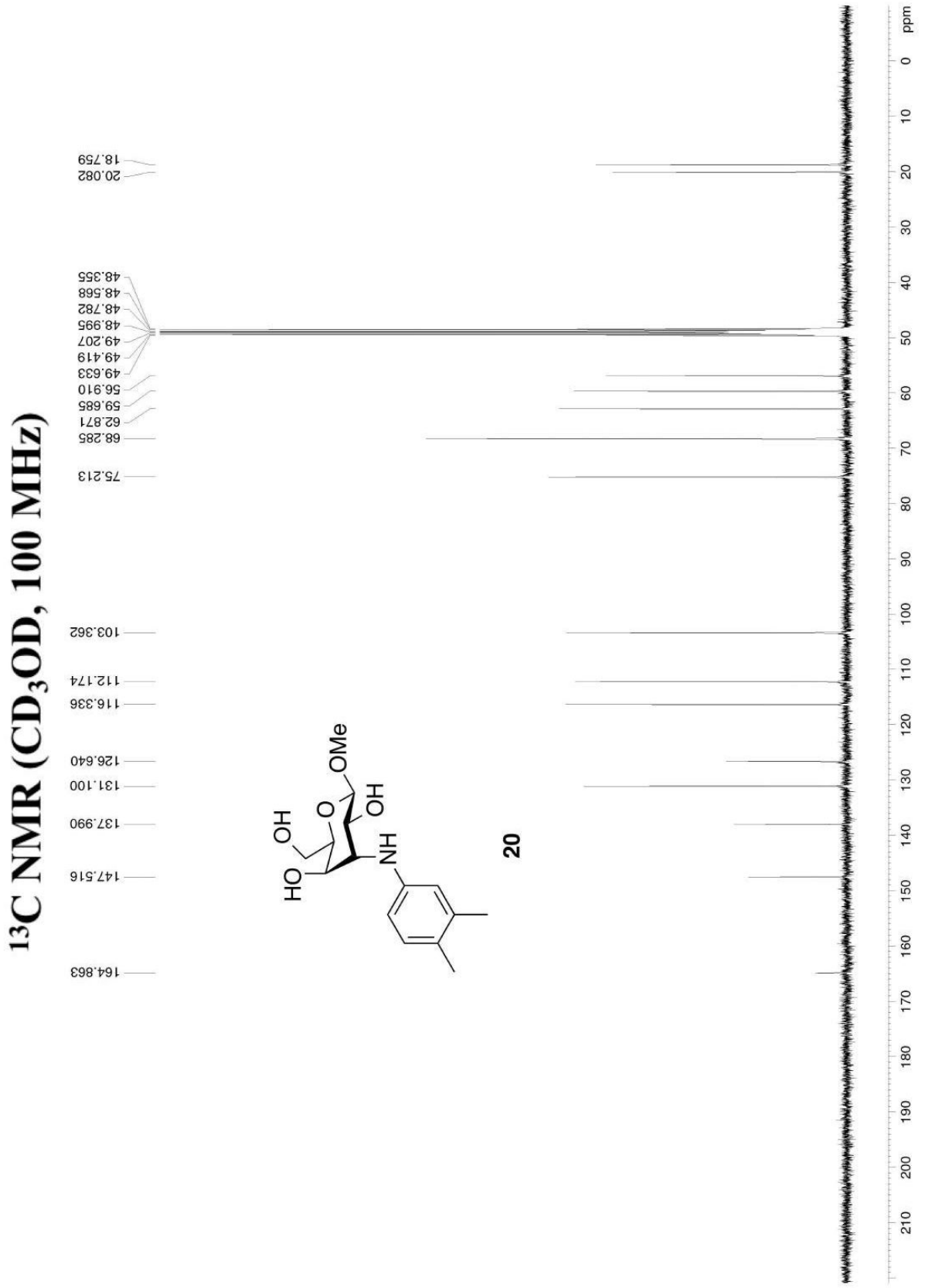
^{1}H NMR (CD_3OD, 400 MHz)

^{13}C NMR (CD_3OD, 100 MHz)



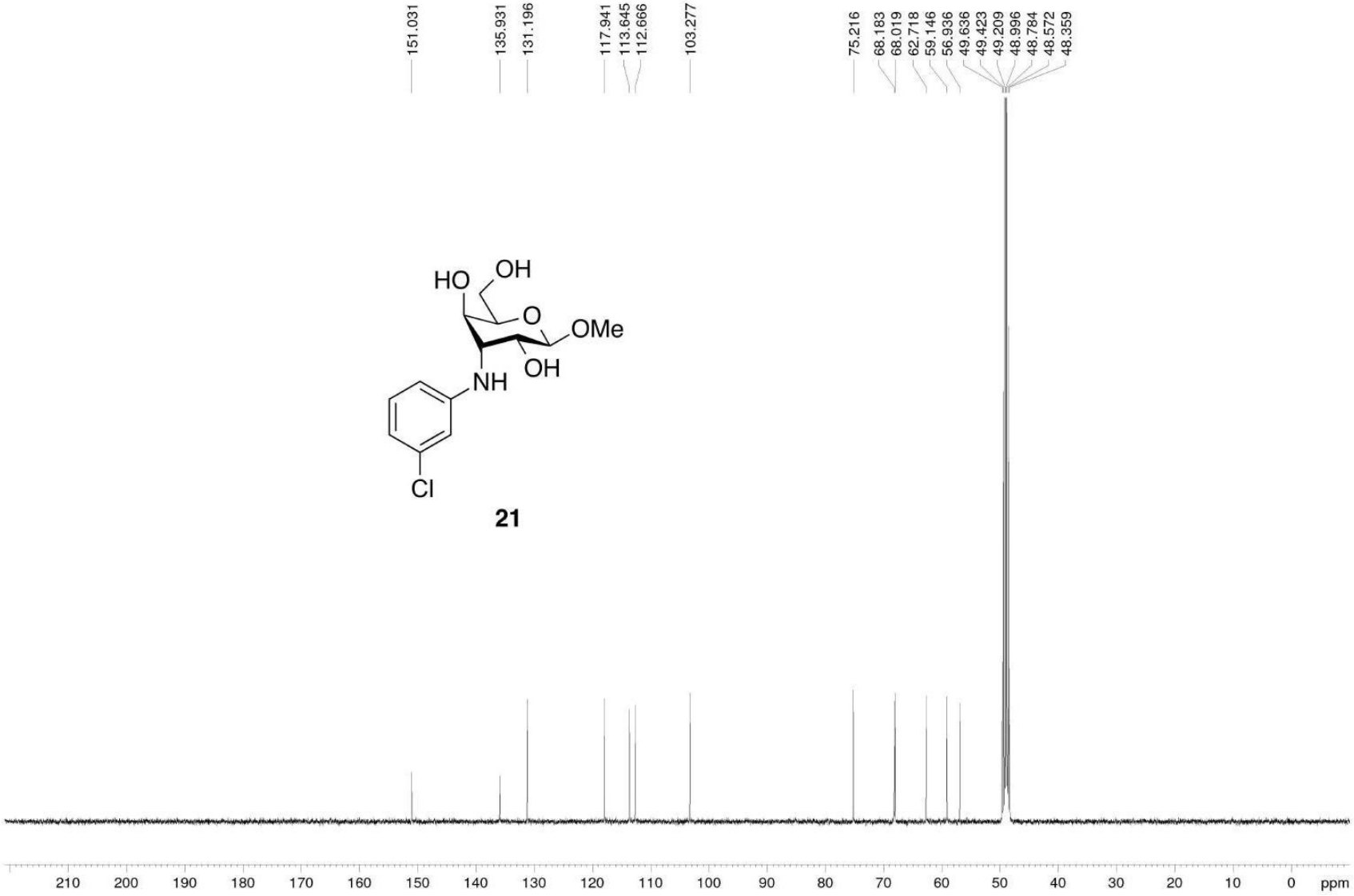
19

^{1}H NMR (CD_3OD, 400 MHz)

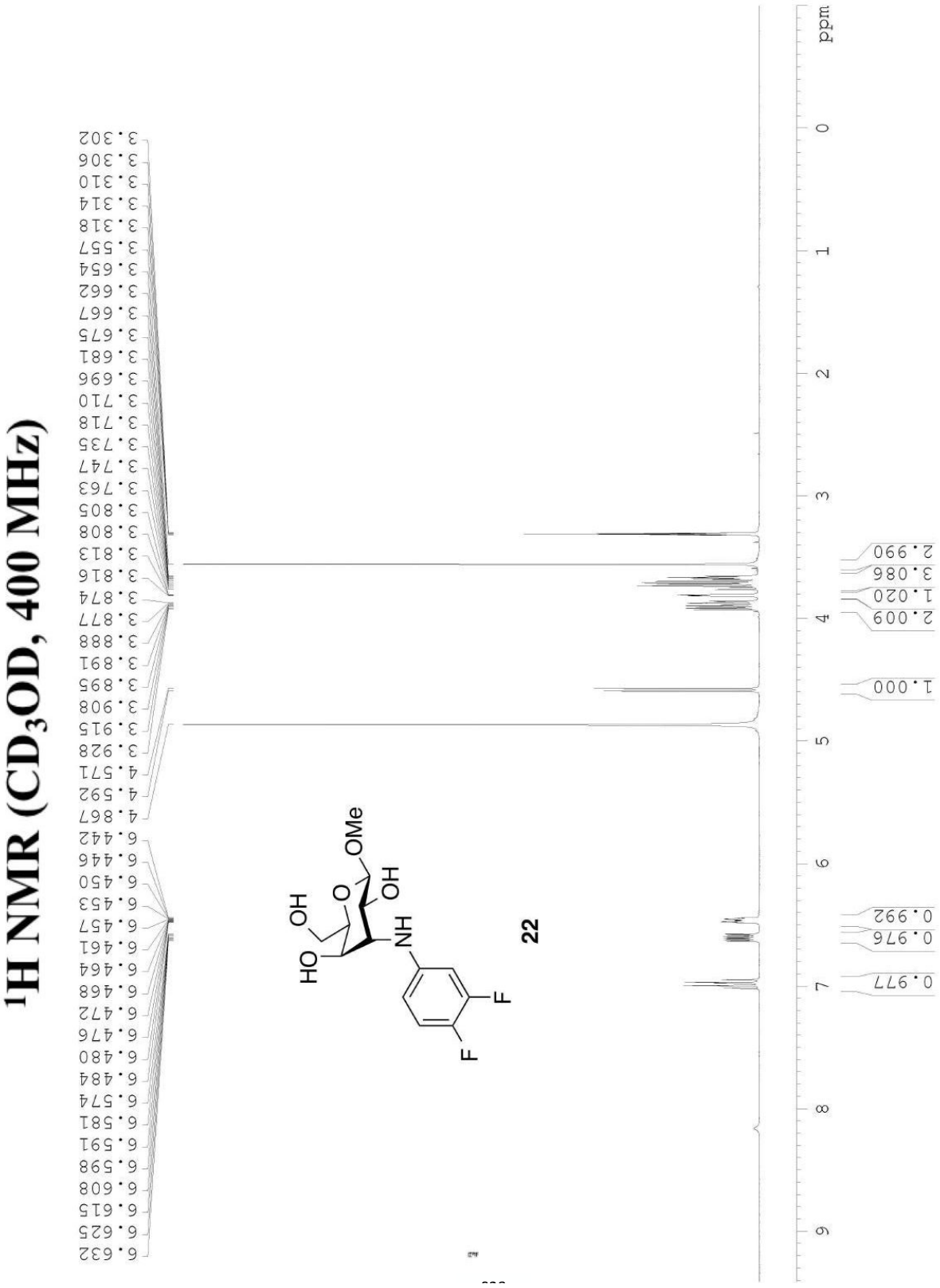

^{13}C NMR (CD_3OD, 100 MHz)
18.759
20.082
48.355
48.568
48.782
48.995
49.207
49.419
49.633
56.910
59.685
62.871
68.285
75.213
103.362
112.174
116.336
126.640
131.100
137.990
147.516
164.863
OMe
OH
O
OH
HO
NH
20
ppm

^{1}H NMR (CD_3OD, 400 MHz)

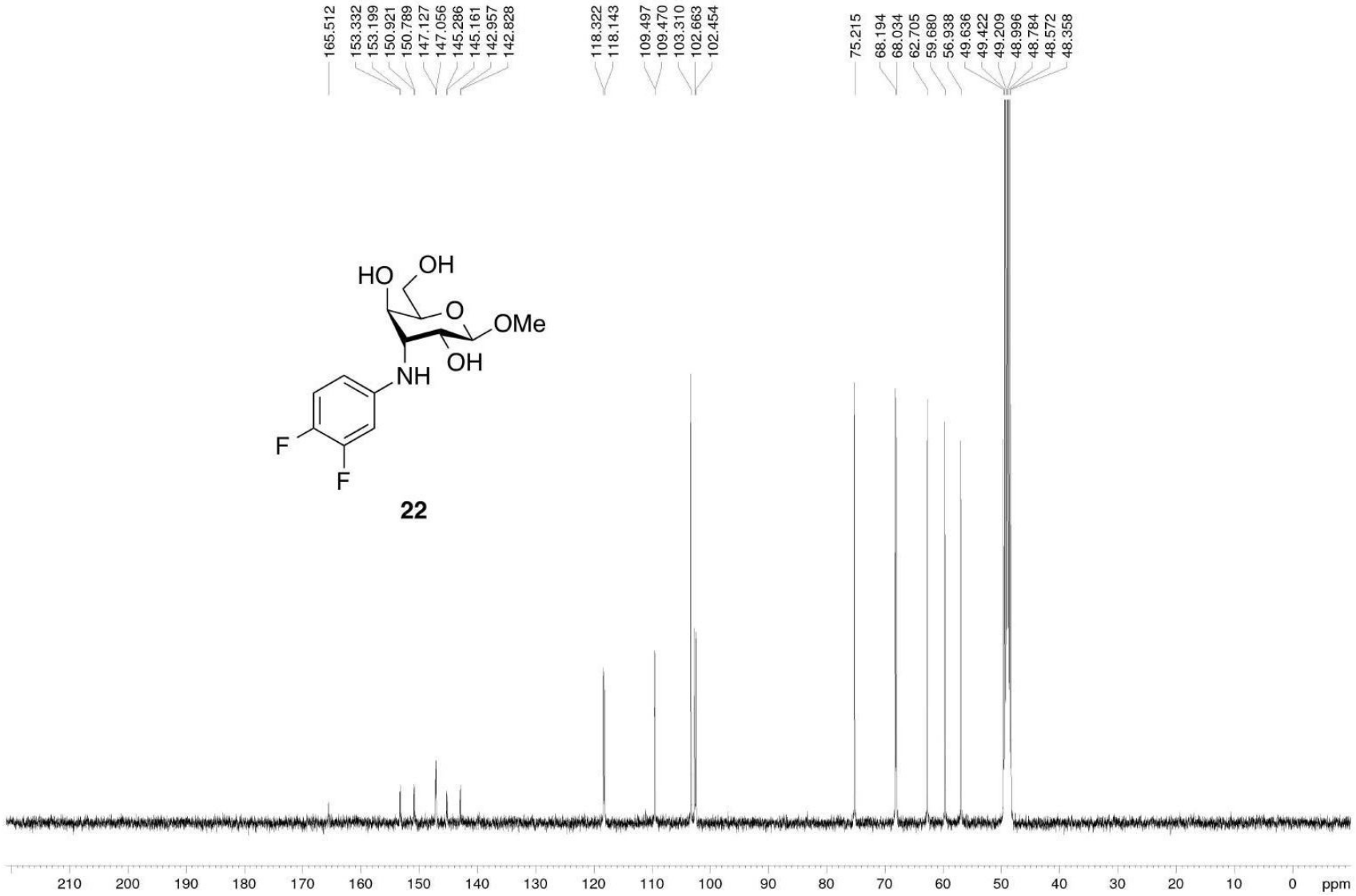
^{13}C NMR (CD_3OD, 100 MHz)



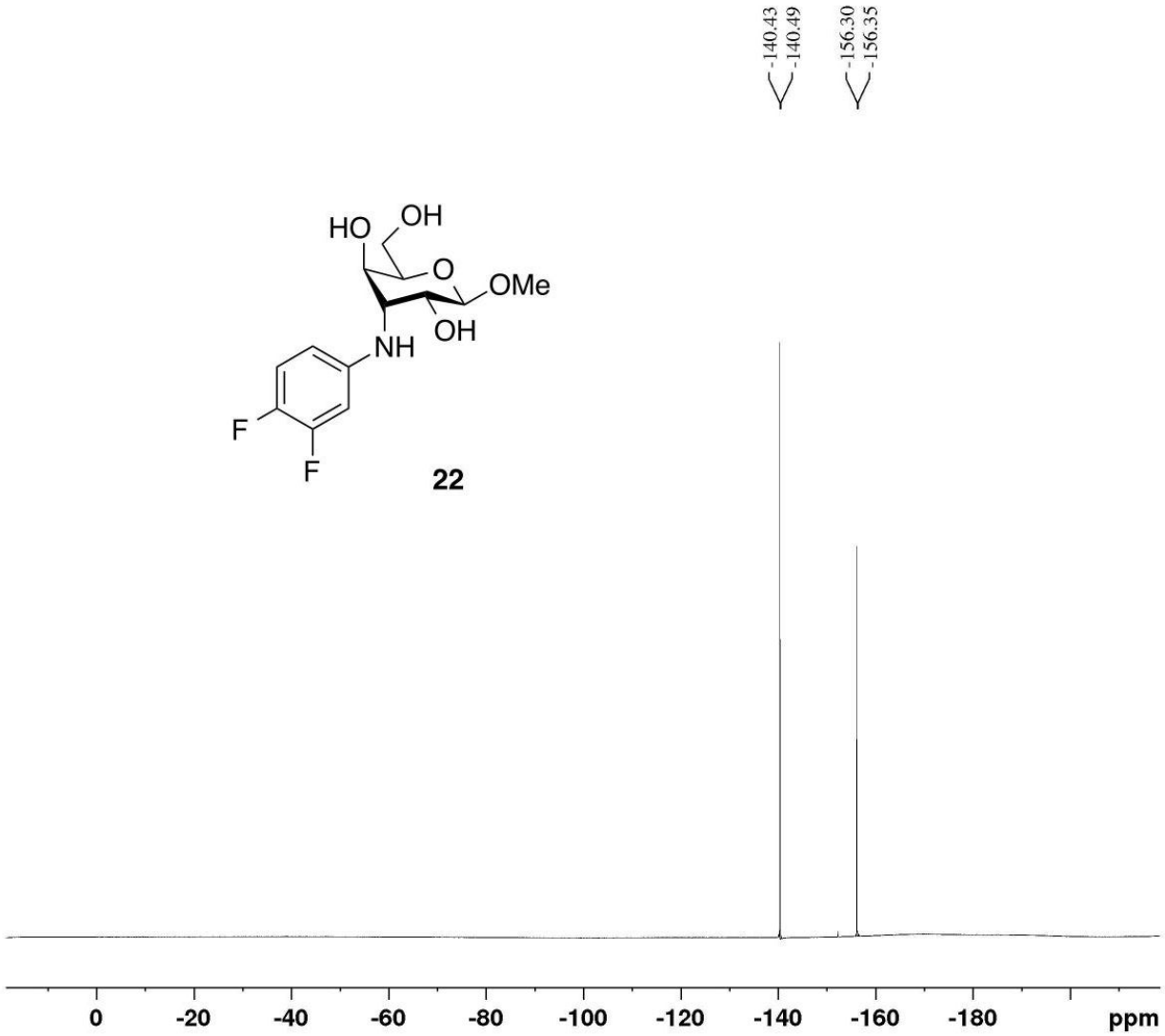
^{1}H NMR (CD_3OD, 400 MHz)



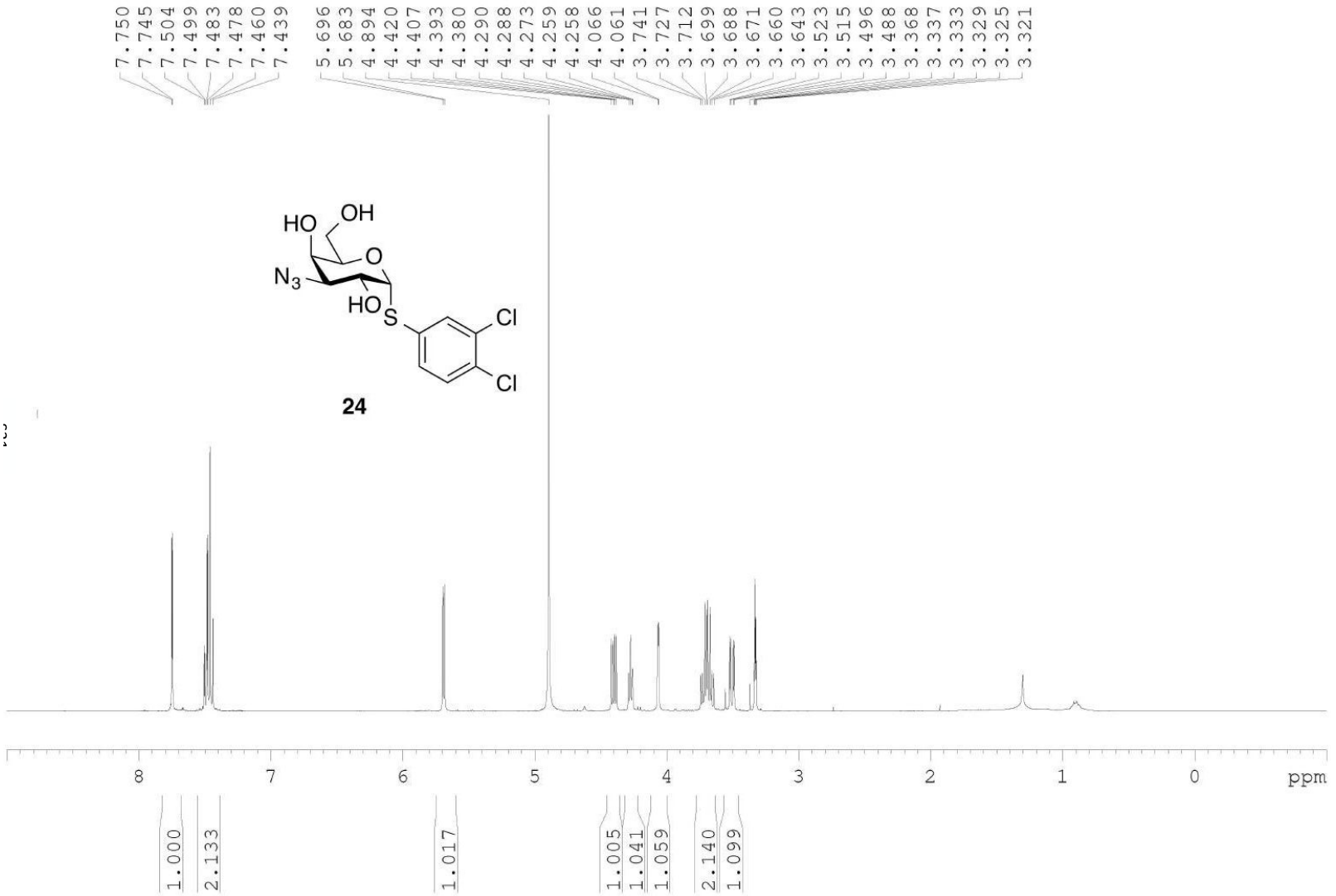
^{13}C NMR (CD_3OD, 100 MHz)



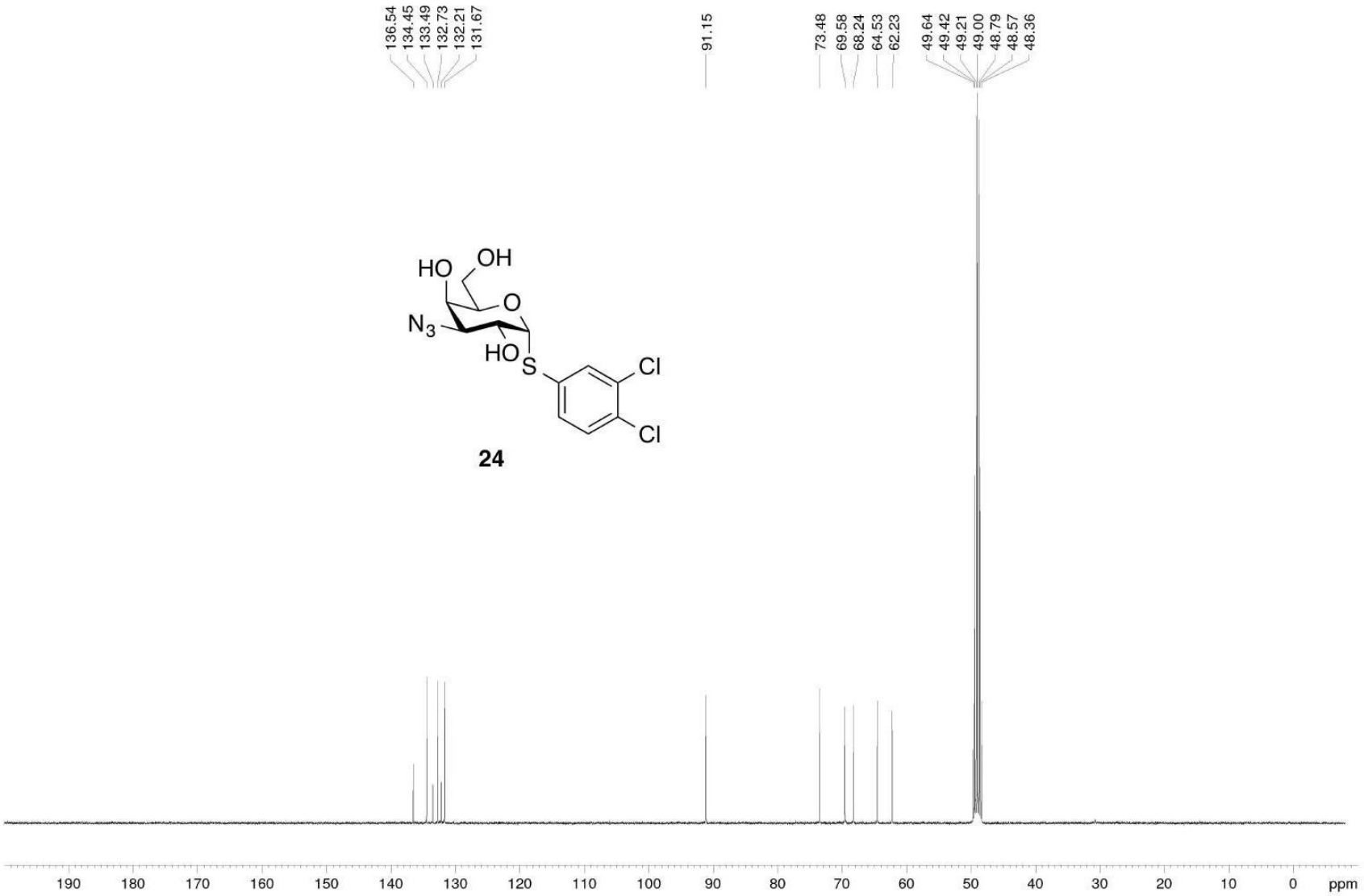
^{19}F NMR (CD_3OD, 376 MHz)



^{1}H NMR (CD_3OD, 400 MHz)



^{13}C NMR (CD_3OD, 100 MHz)



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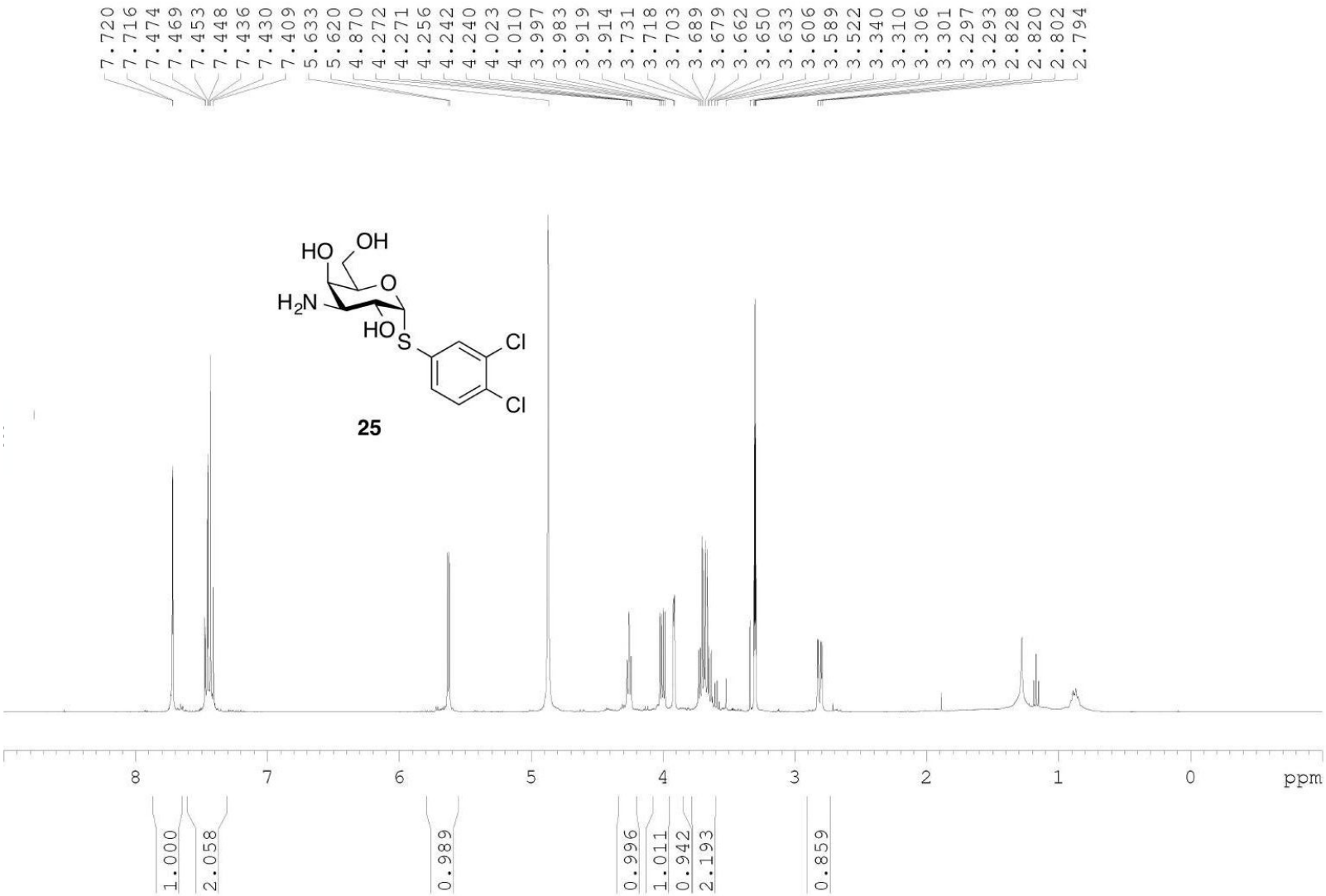
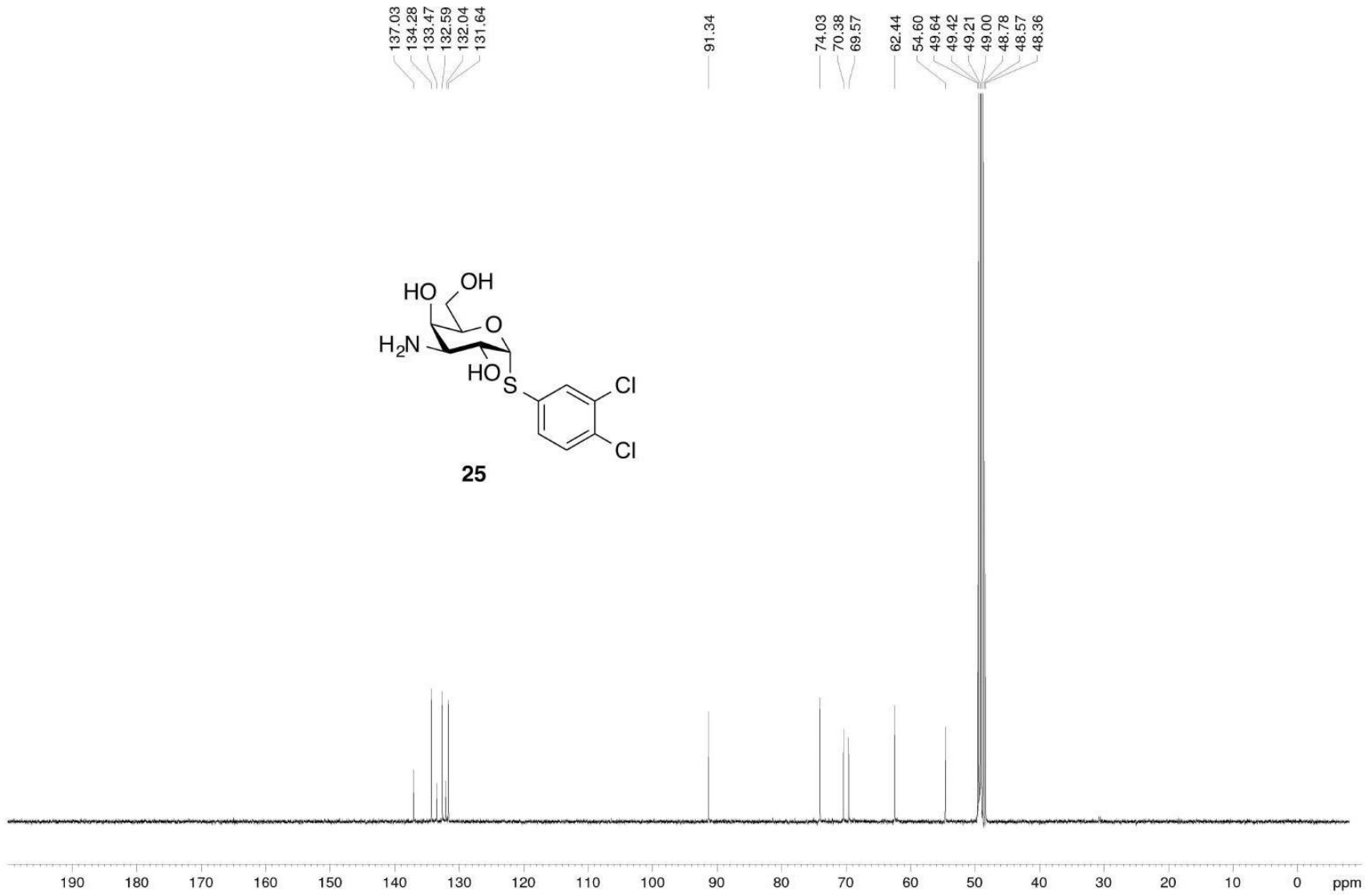


^{13}C NMR (CD_3OD, 100 MHz)



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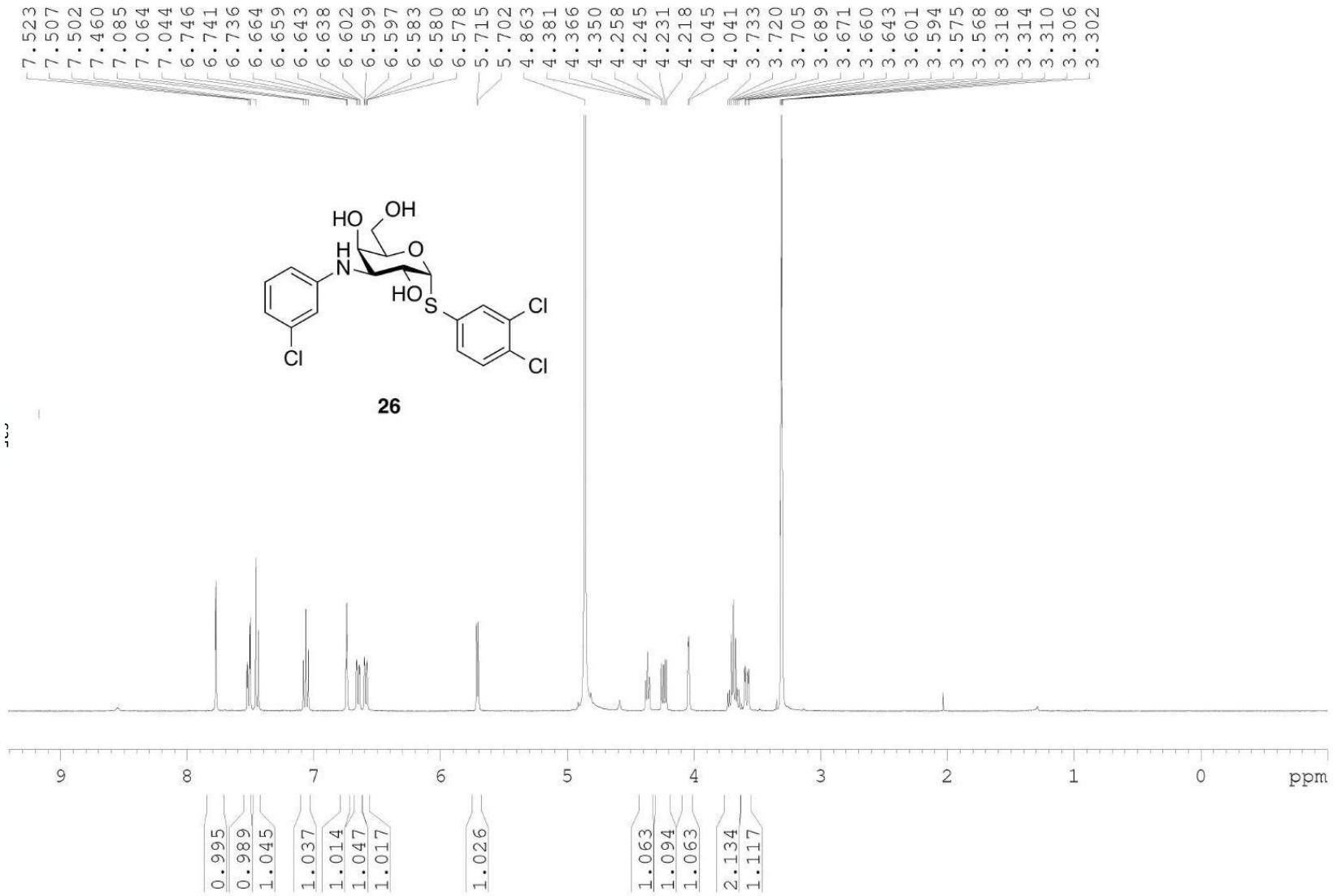
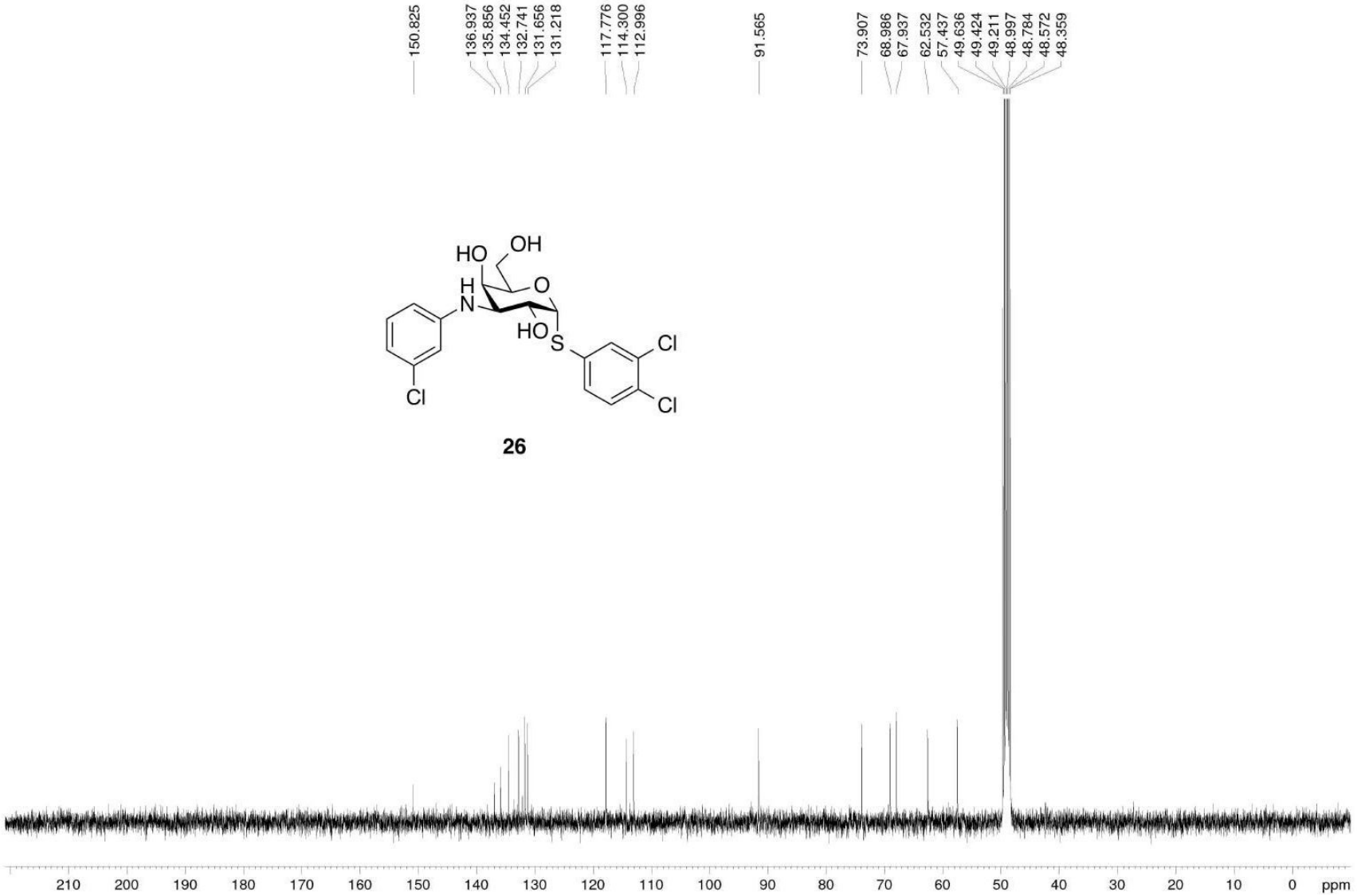


26

^{13}C NMR (CD_3OD, 100 MHz)



26

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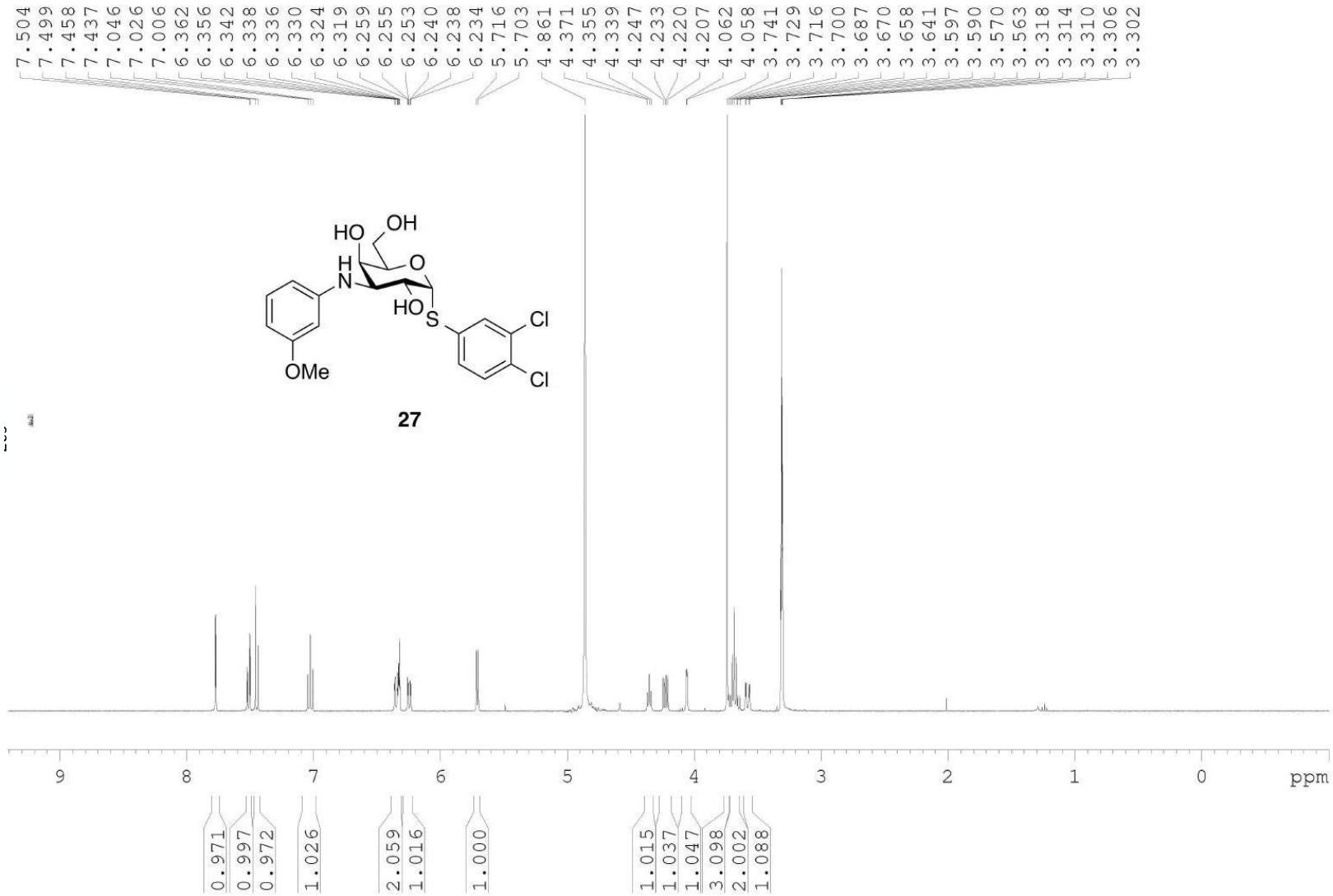

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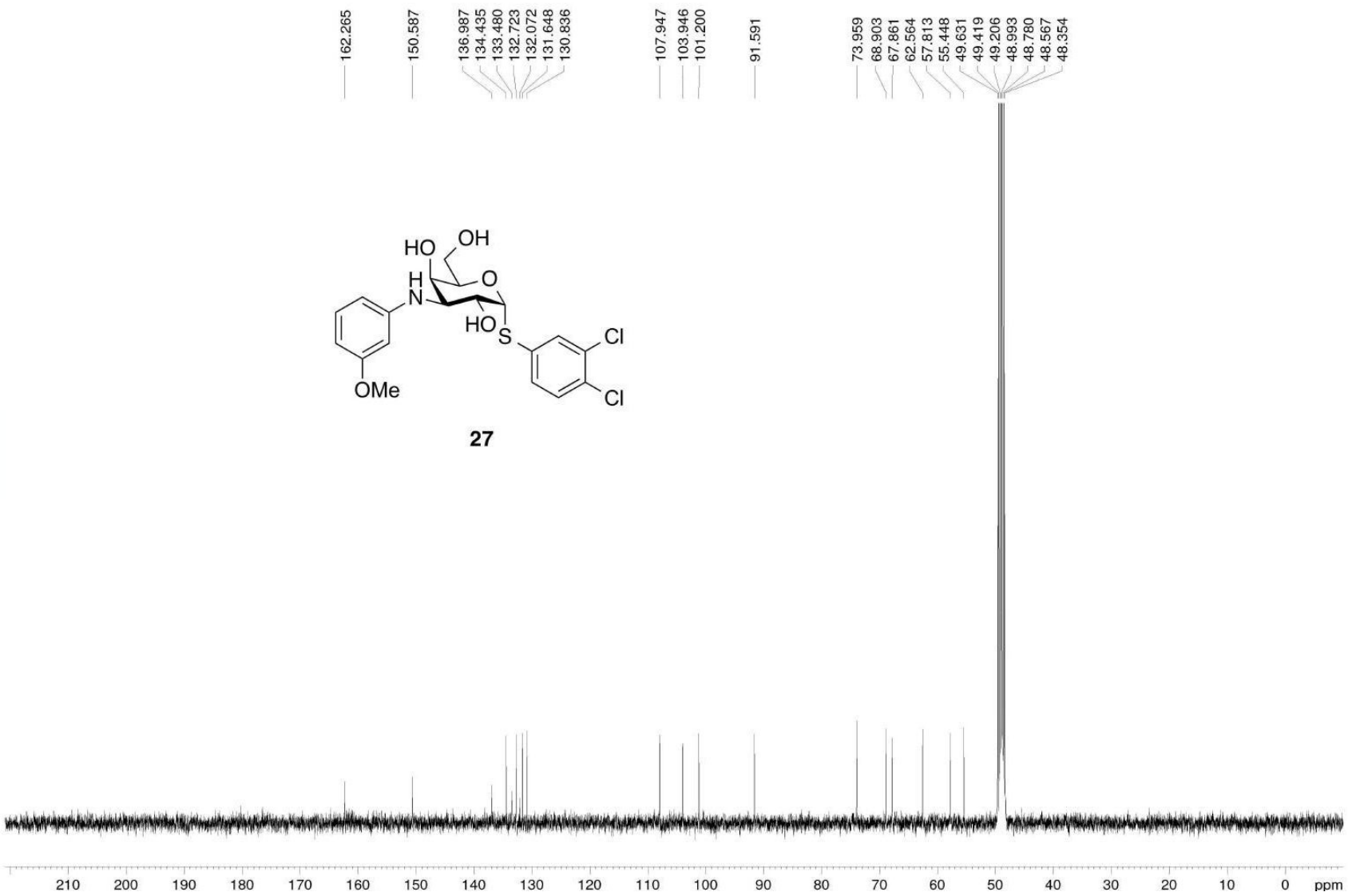
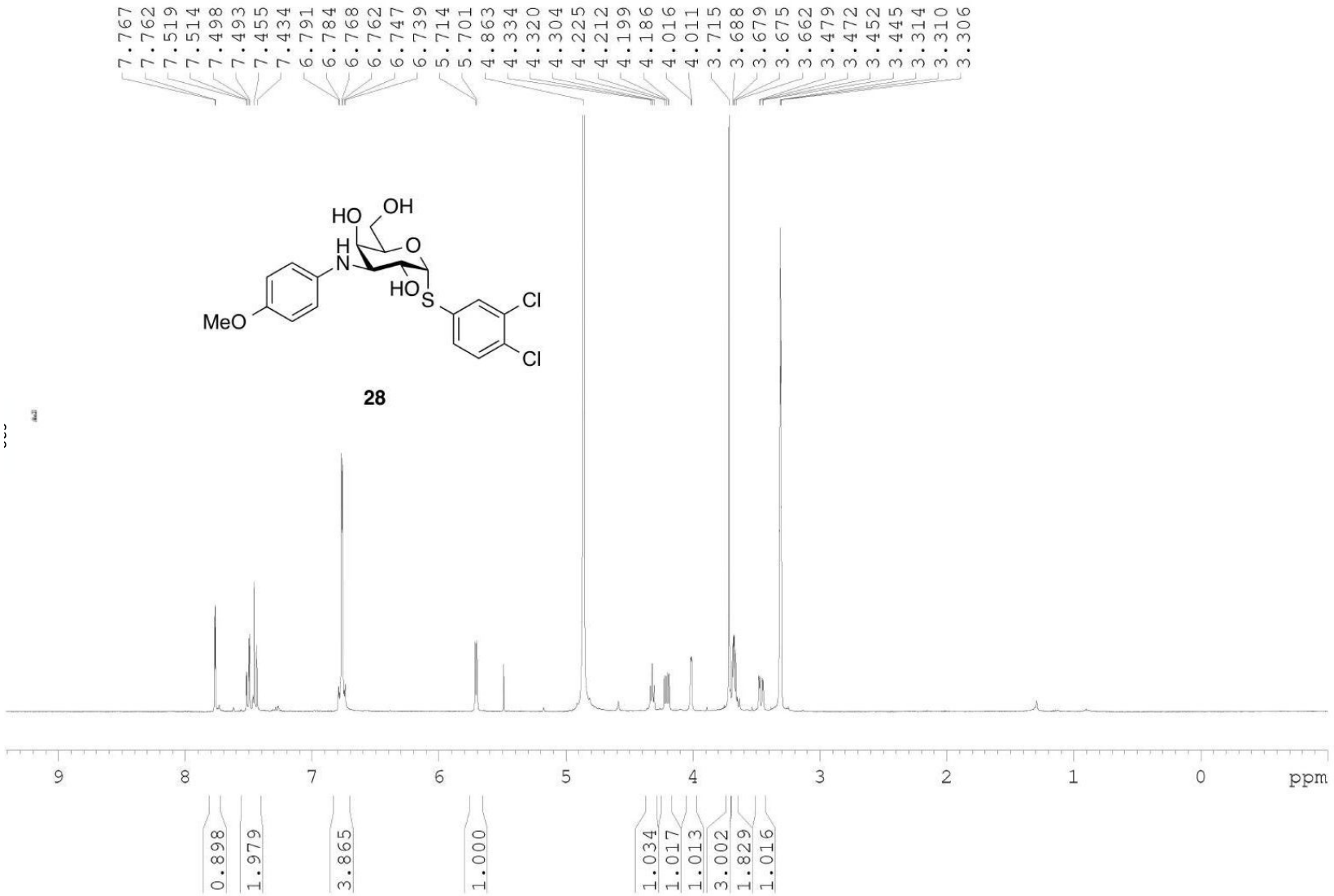
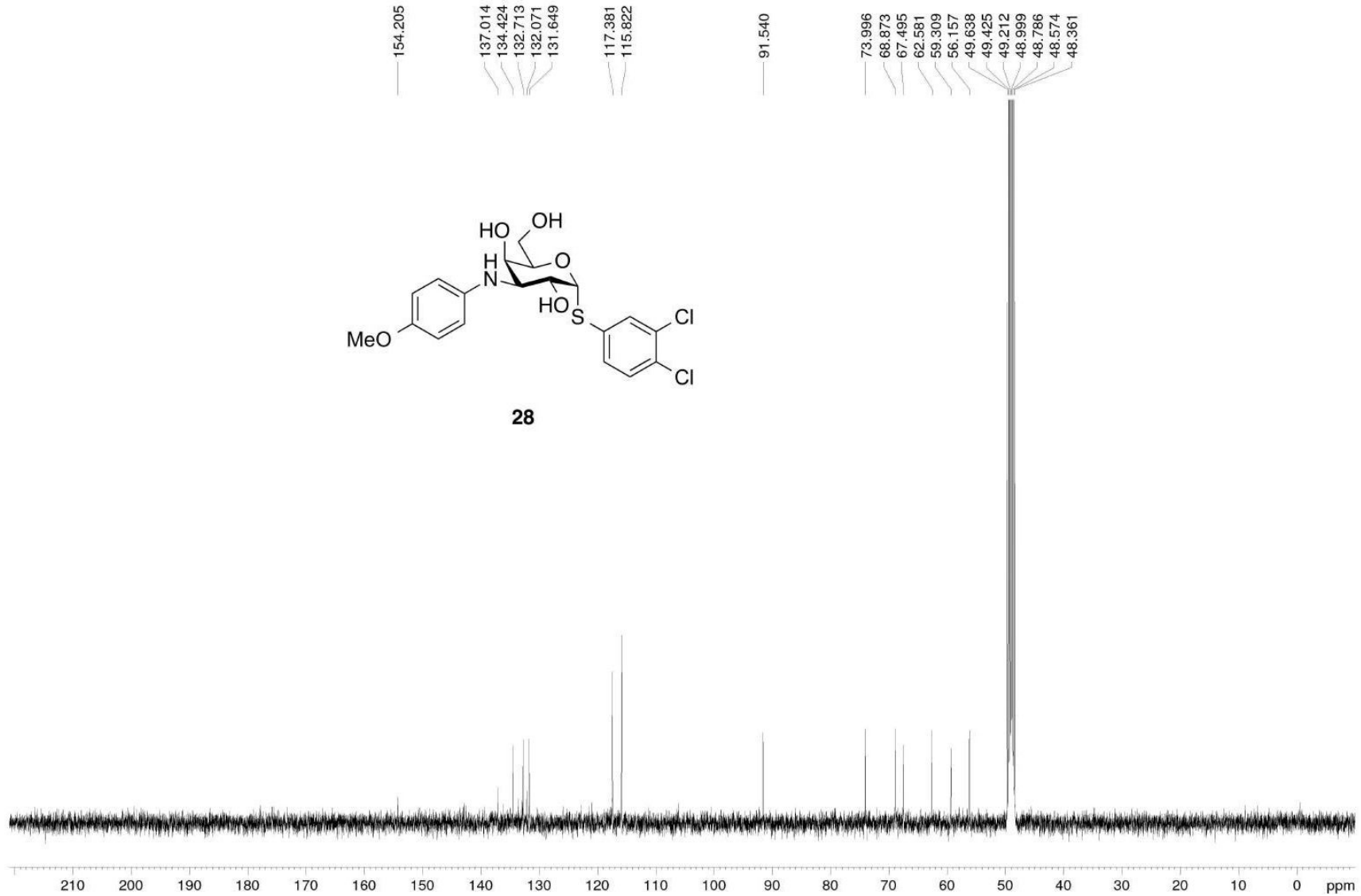


27

^{1}H NMR (CD_3OD, 400 MHz)



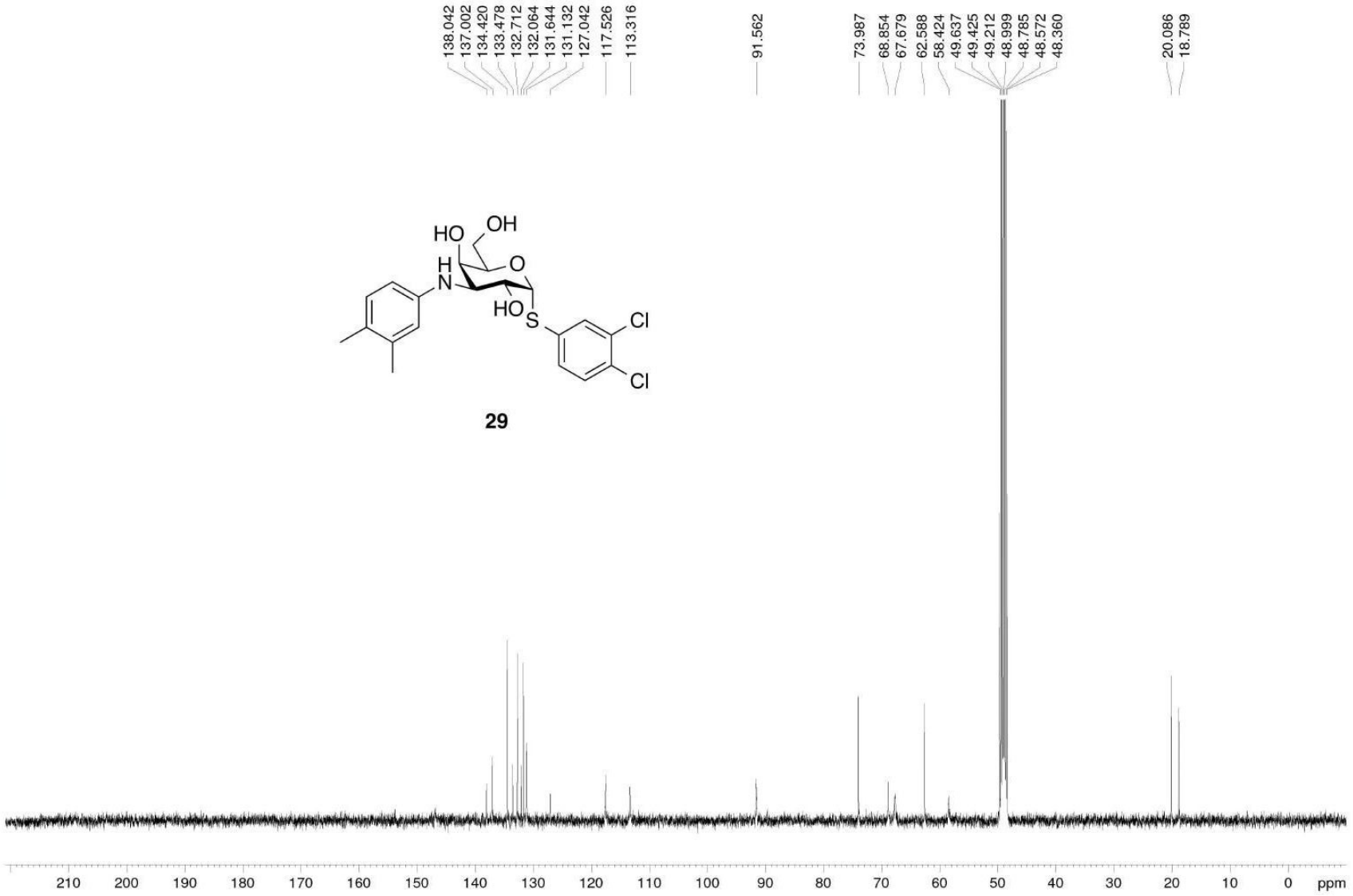
^{13}C NMR (CD_3OD, 100 MHz)



28

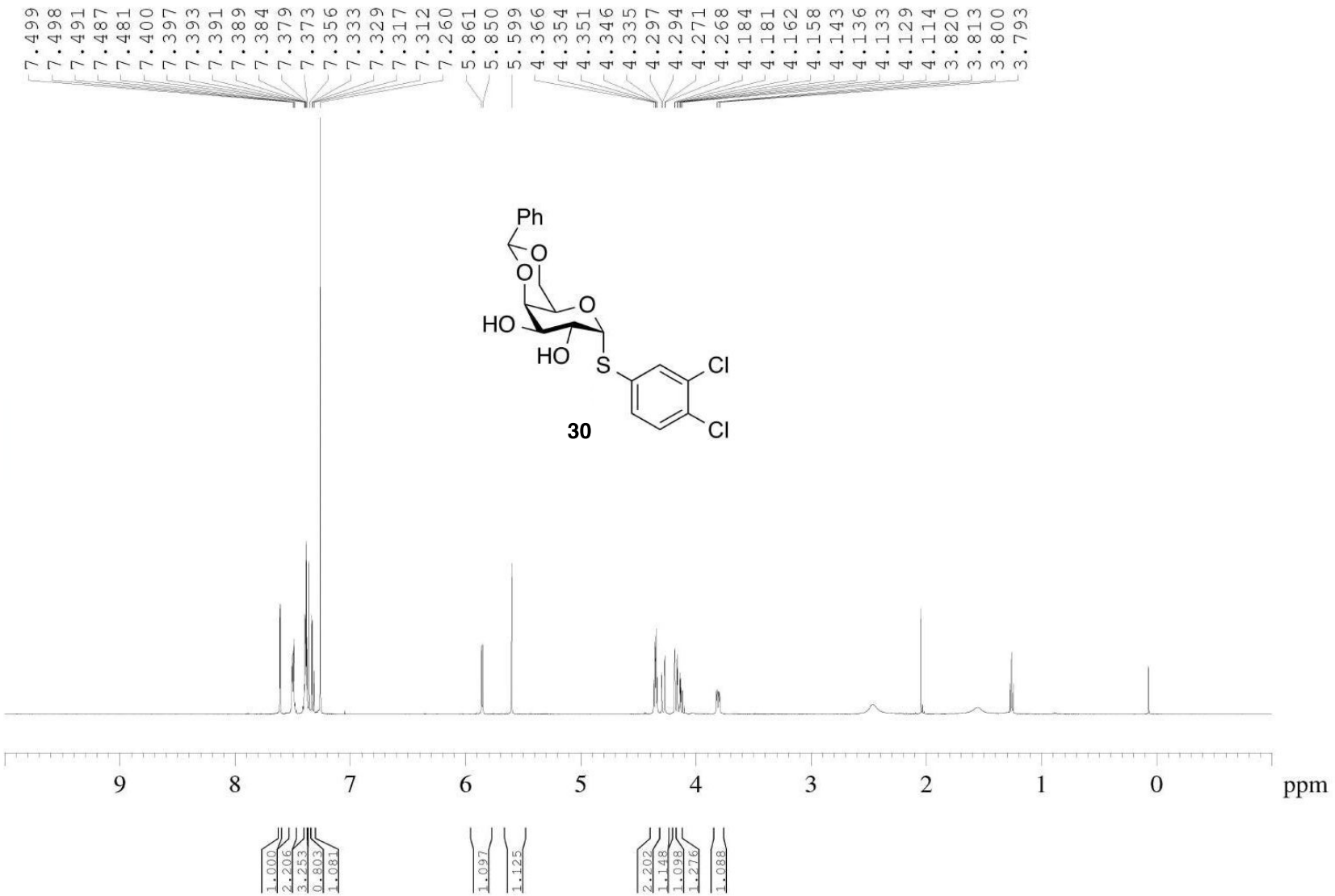
^{1}H NMR (CD_3OD, 400 MHz)

^{13}C NMR (CD_3OD, 100 MHz)

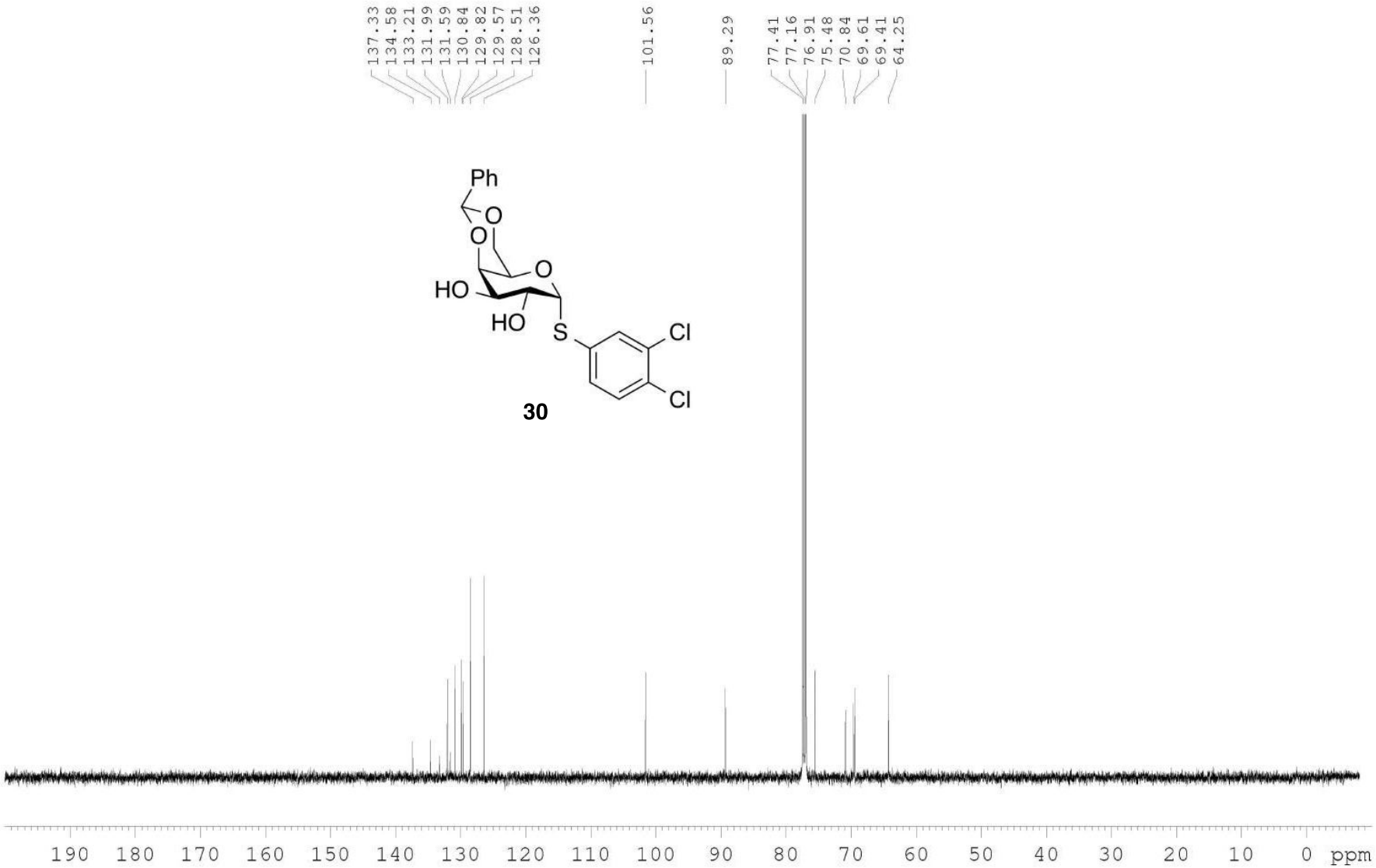


29

^{1}H NMR ($CDCl_3$, 400 MHz)

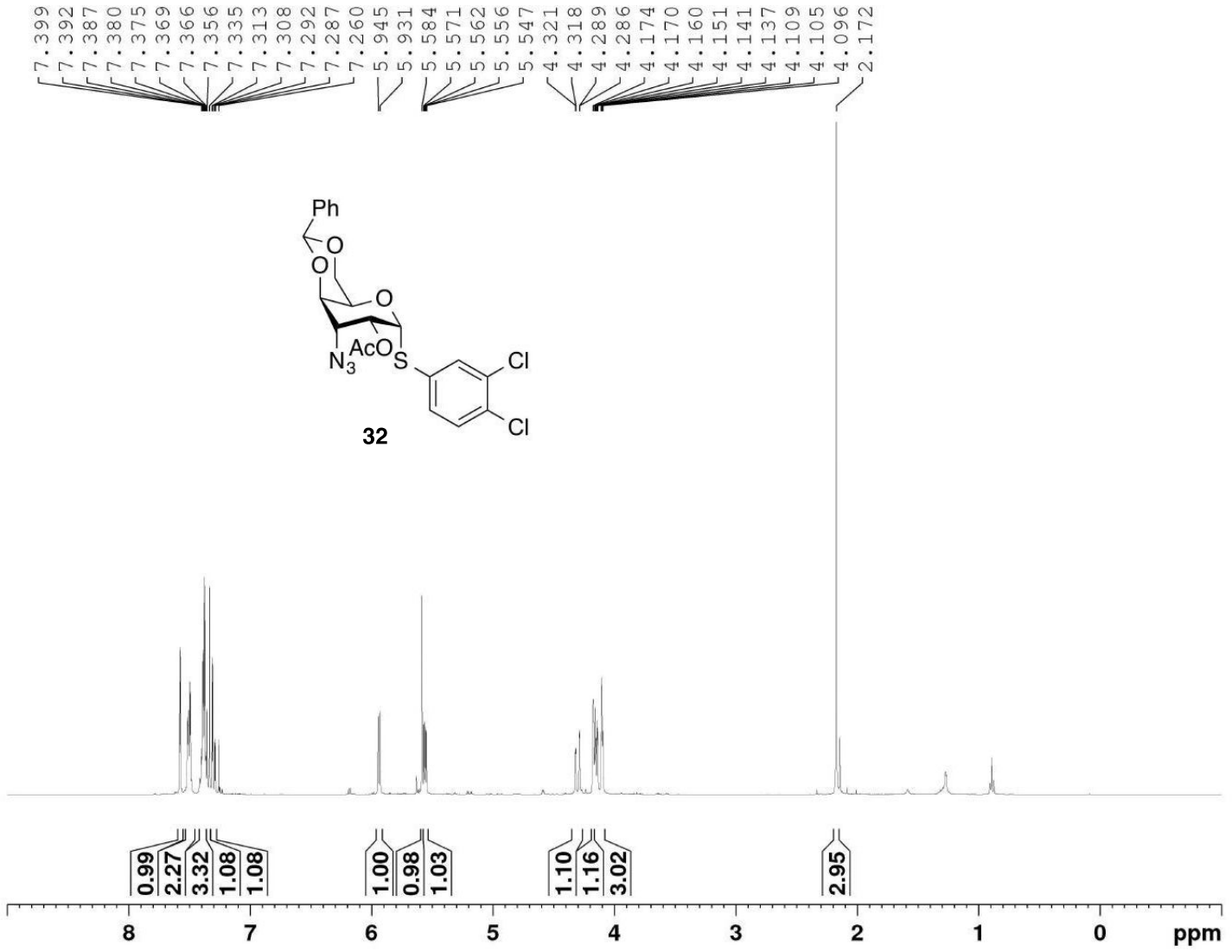


^{13}C NMR ($CDCl_3$, 100 MHz)



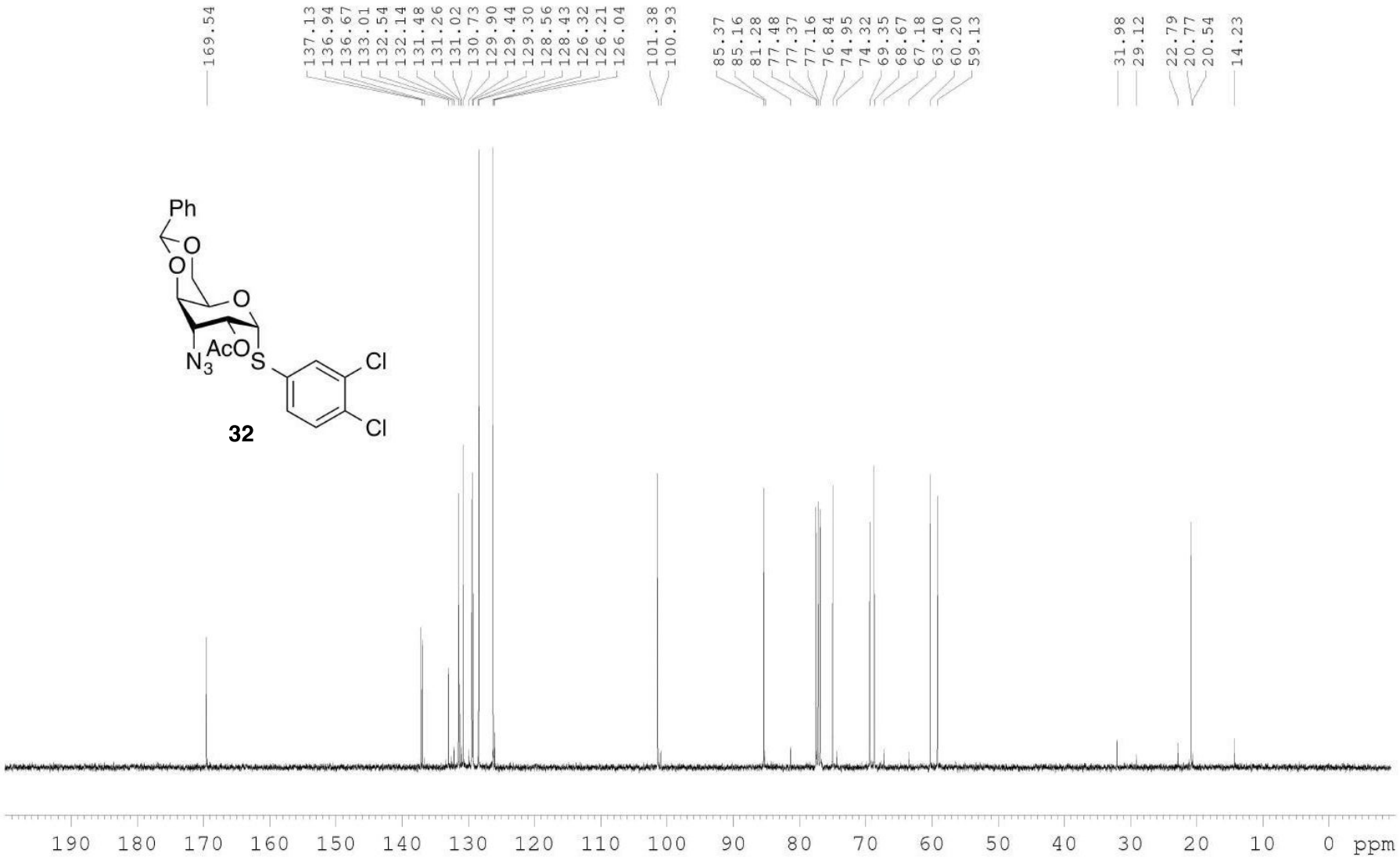
30

^{1}H NMR ($CDCl_3$, 400 MHz)

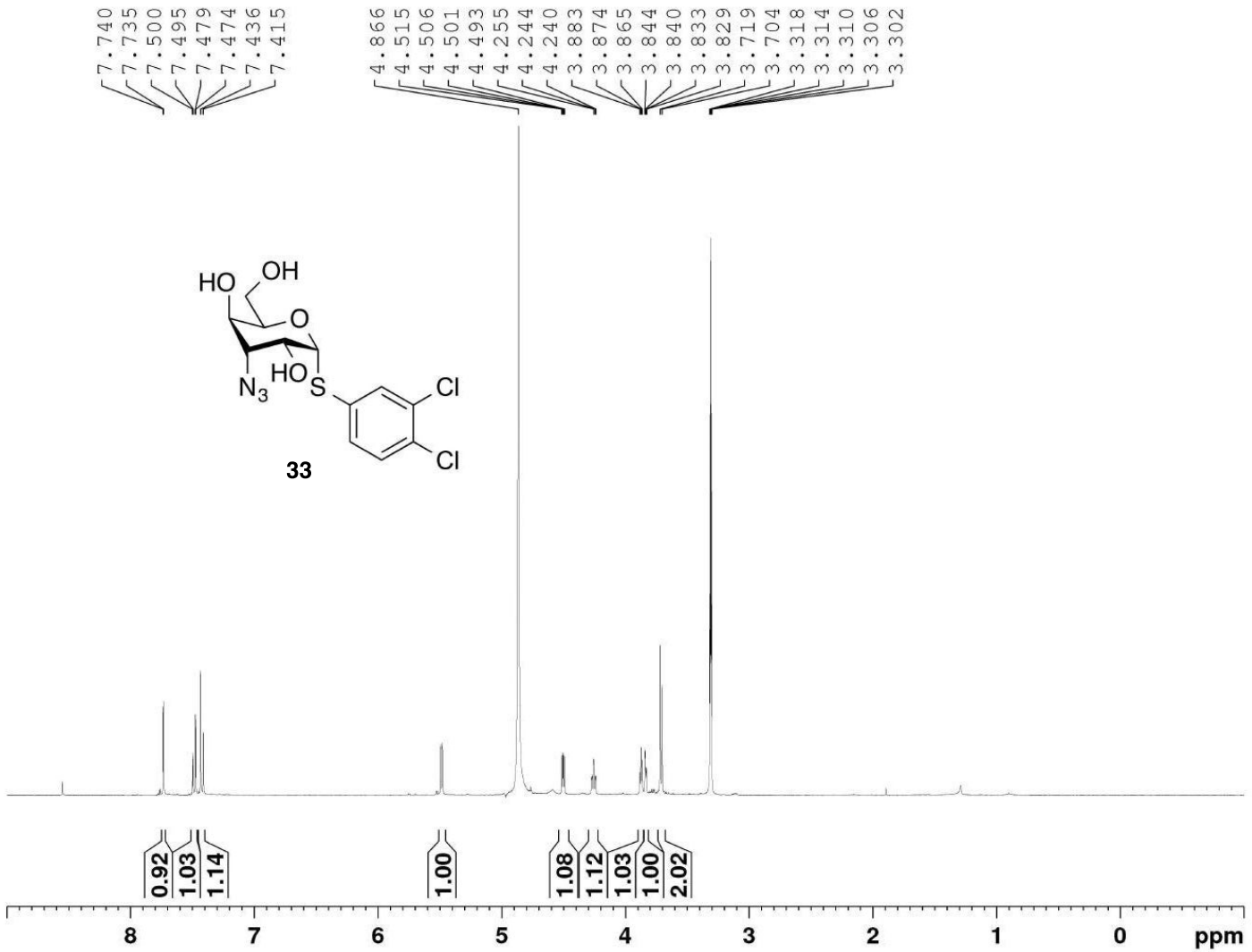


32

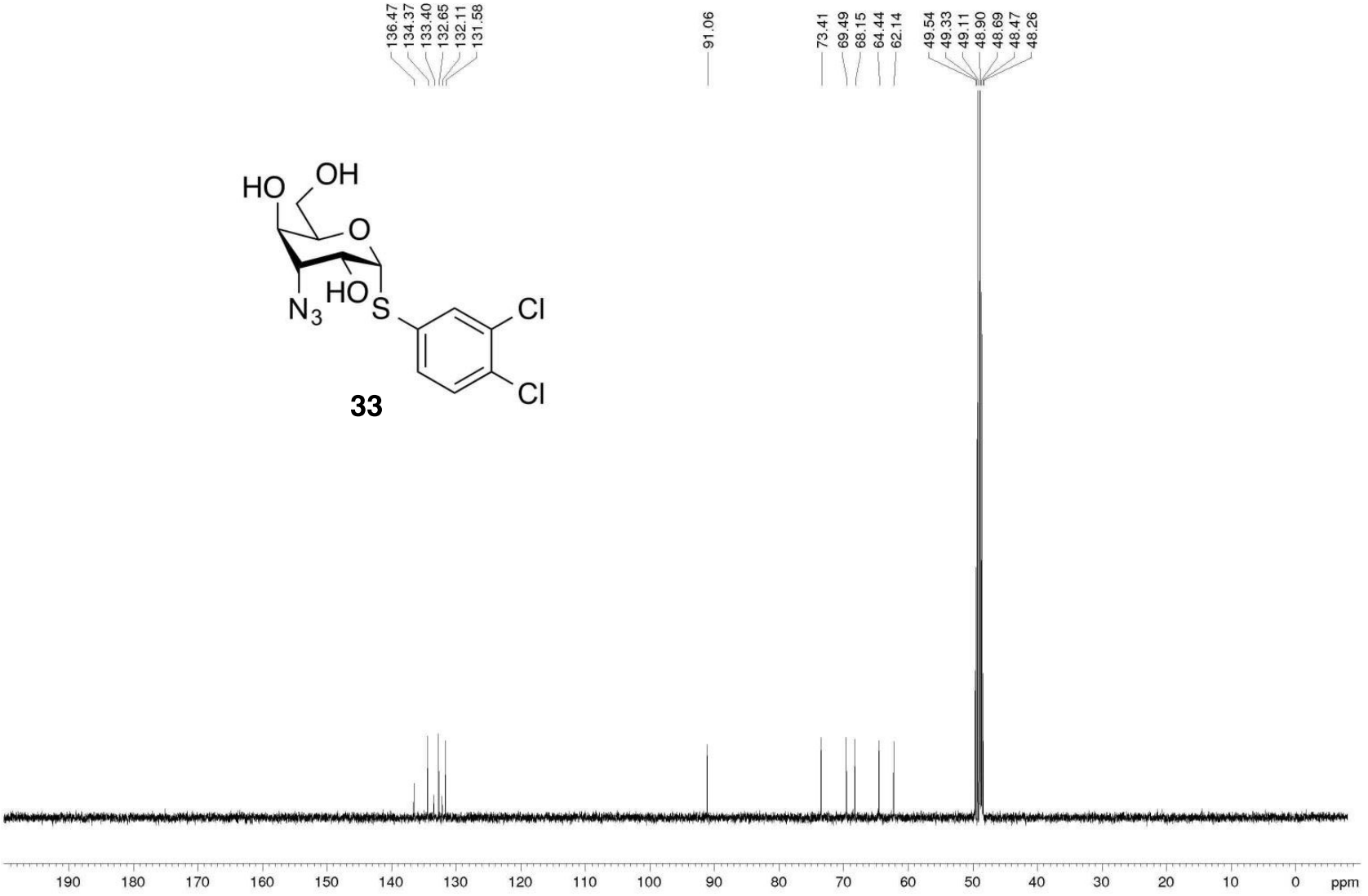
^{13}C NMR ($CDCl_3$, 100 MHz)



^{1}H NMR (CD_3OD, 400 MHz)



^{13}C NMR (CD_3OD, 100 MHz)



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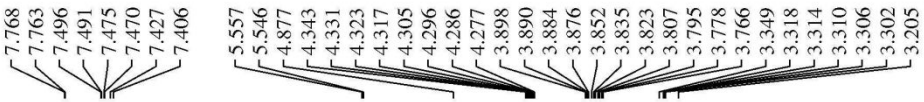
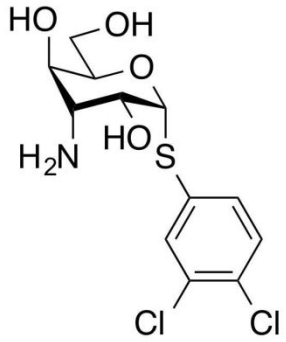
^{1}H NMR, $CDCl_3$, 400 MHz





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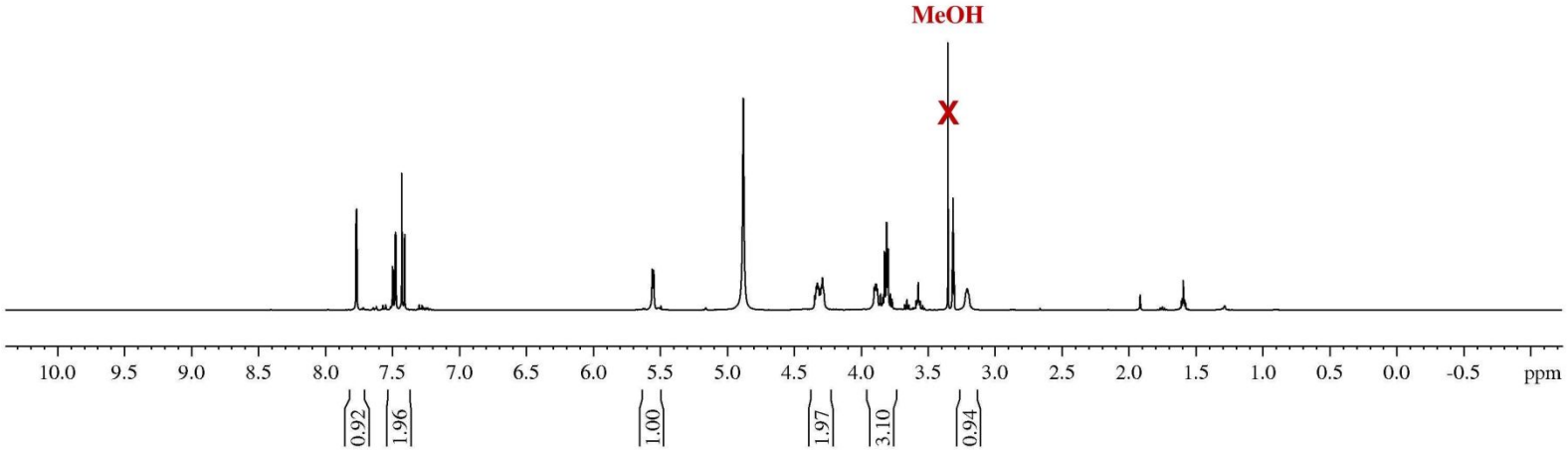
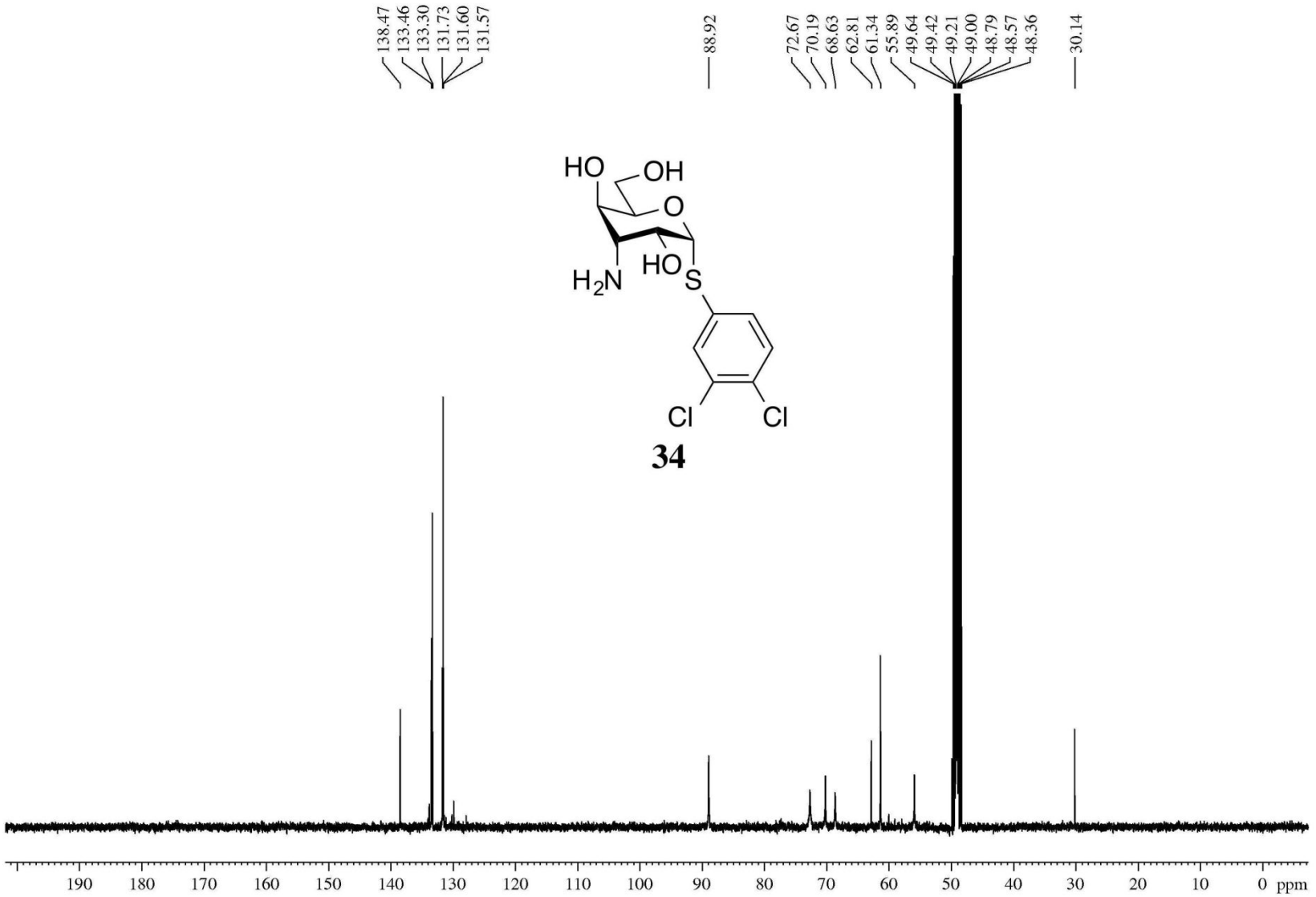
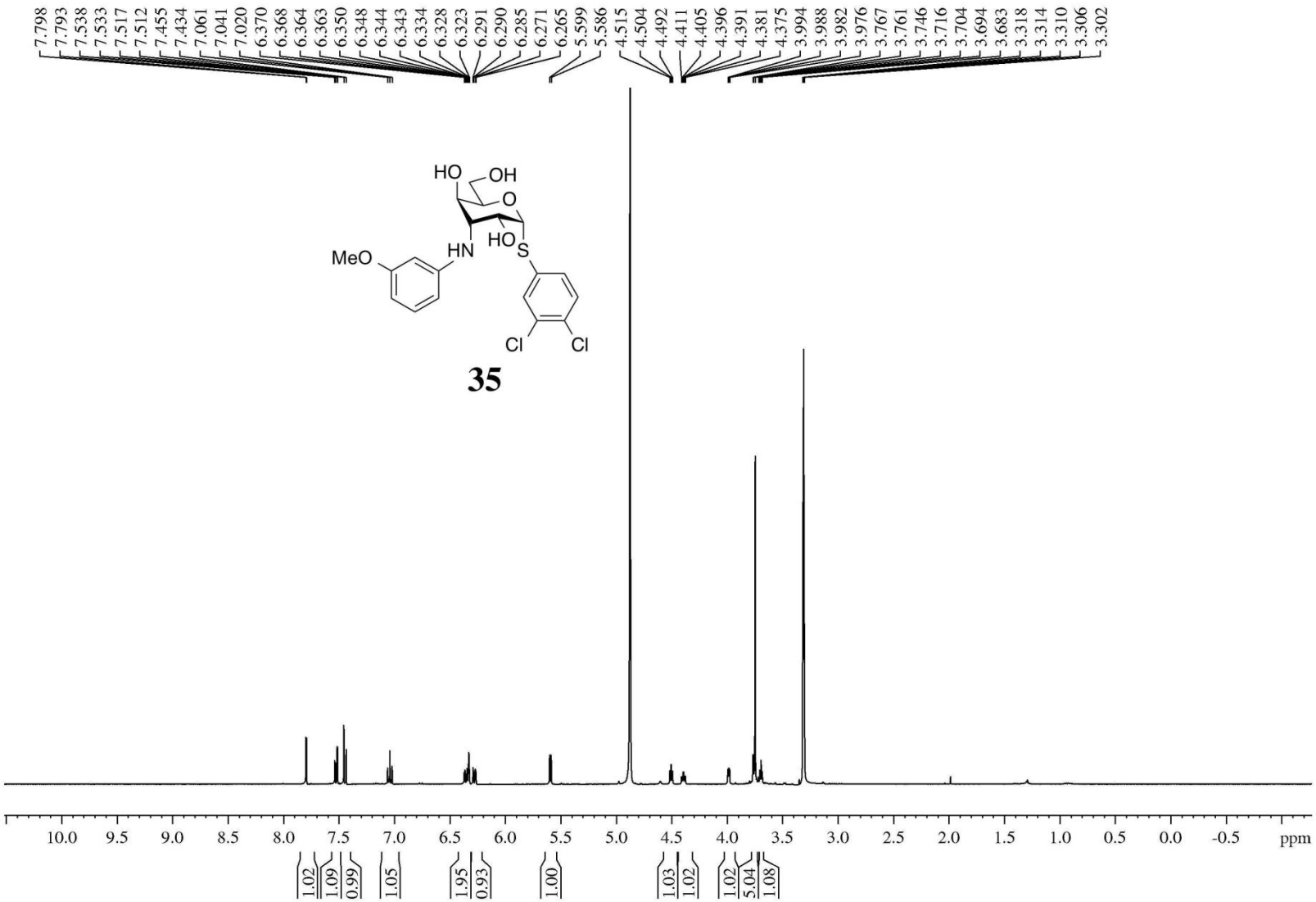


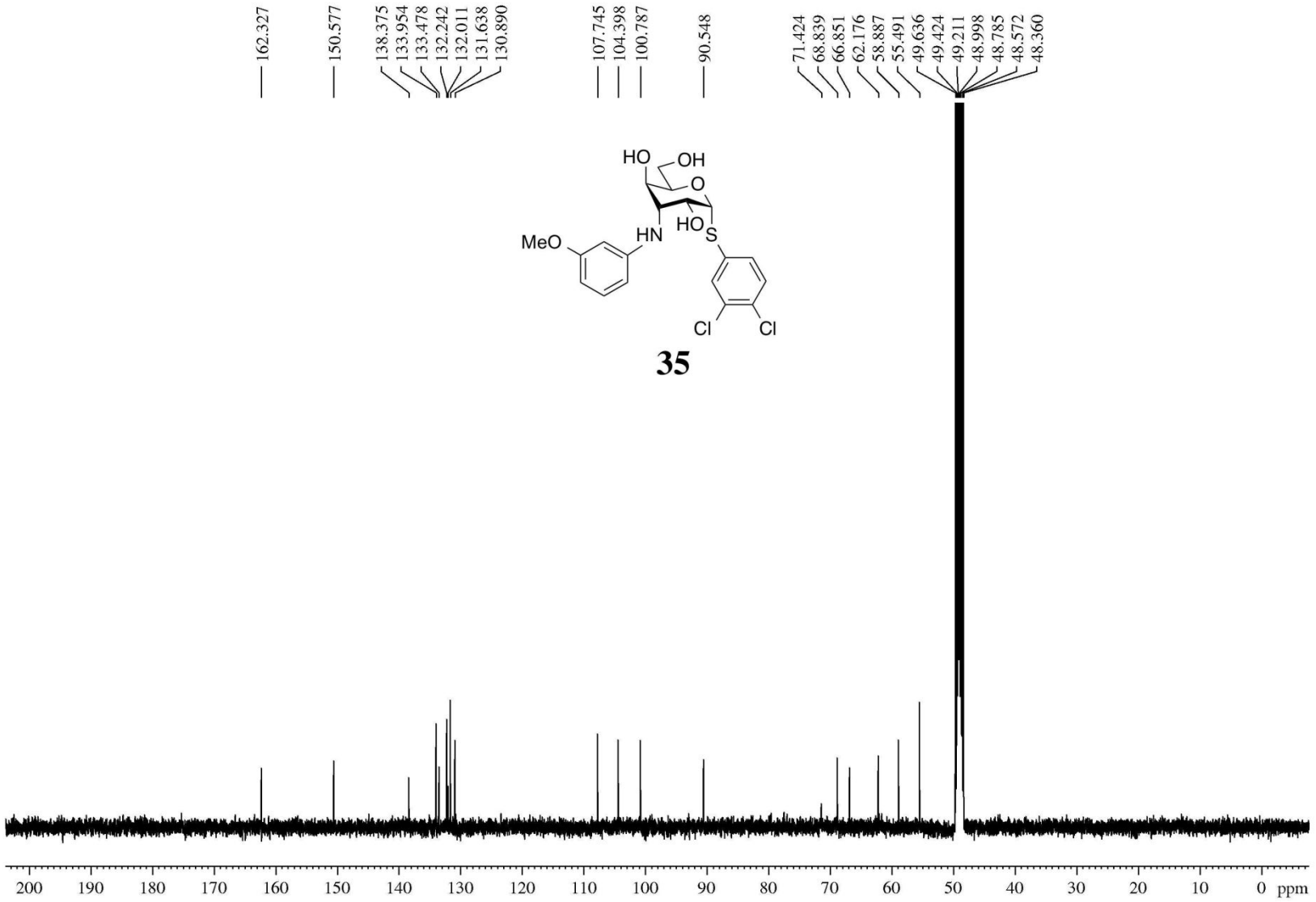
^{13}C NMR, $CDCl_3$, 100 MHz



^{1}H NMR, CD_3OD, 400 MHz



^{13}C NMR, CD_3OD, 100 MHz



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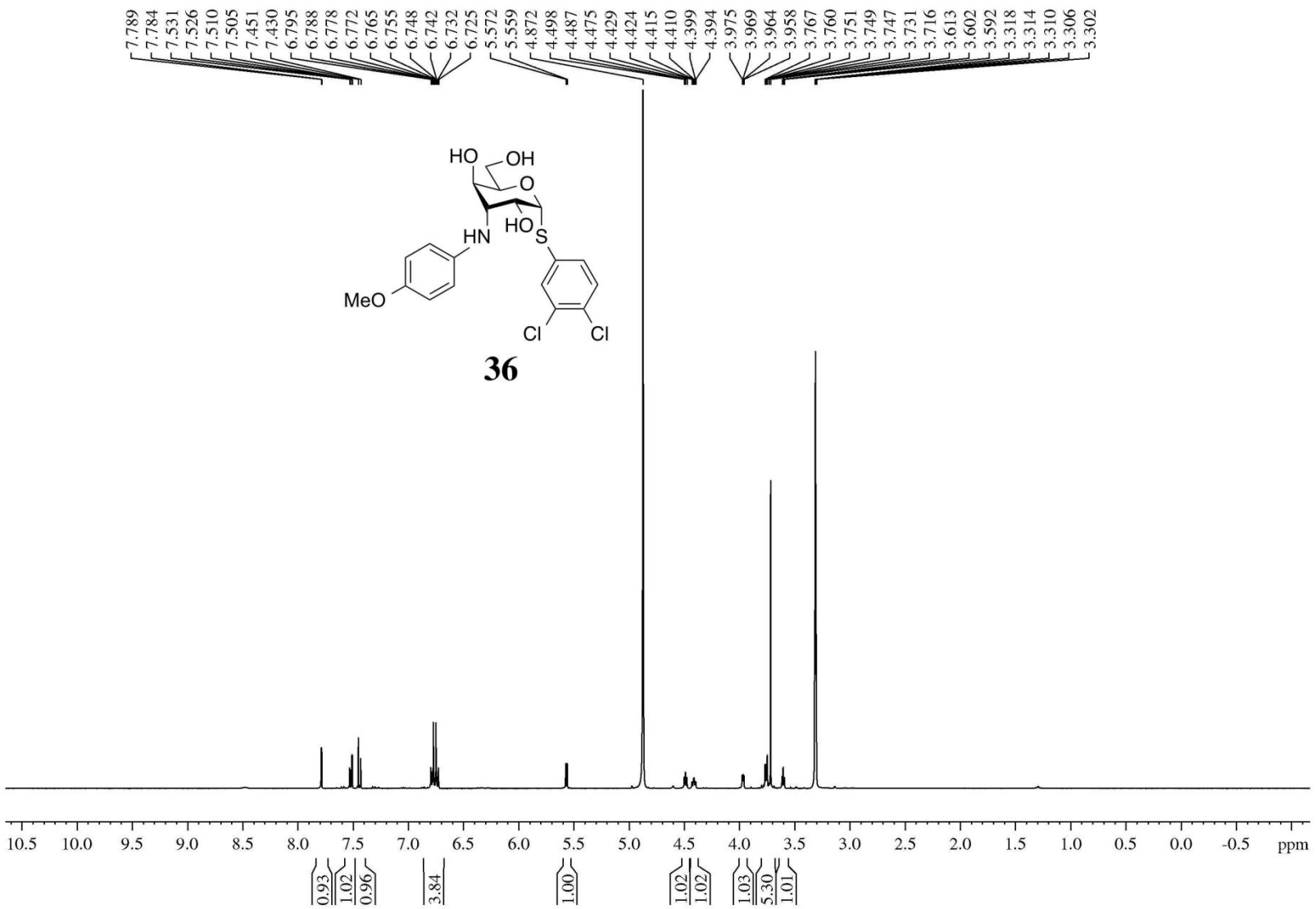
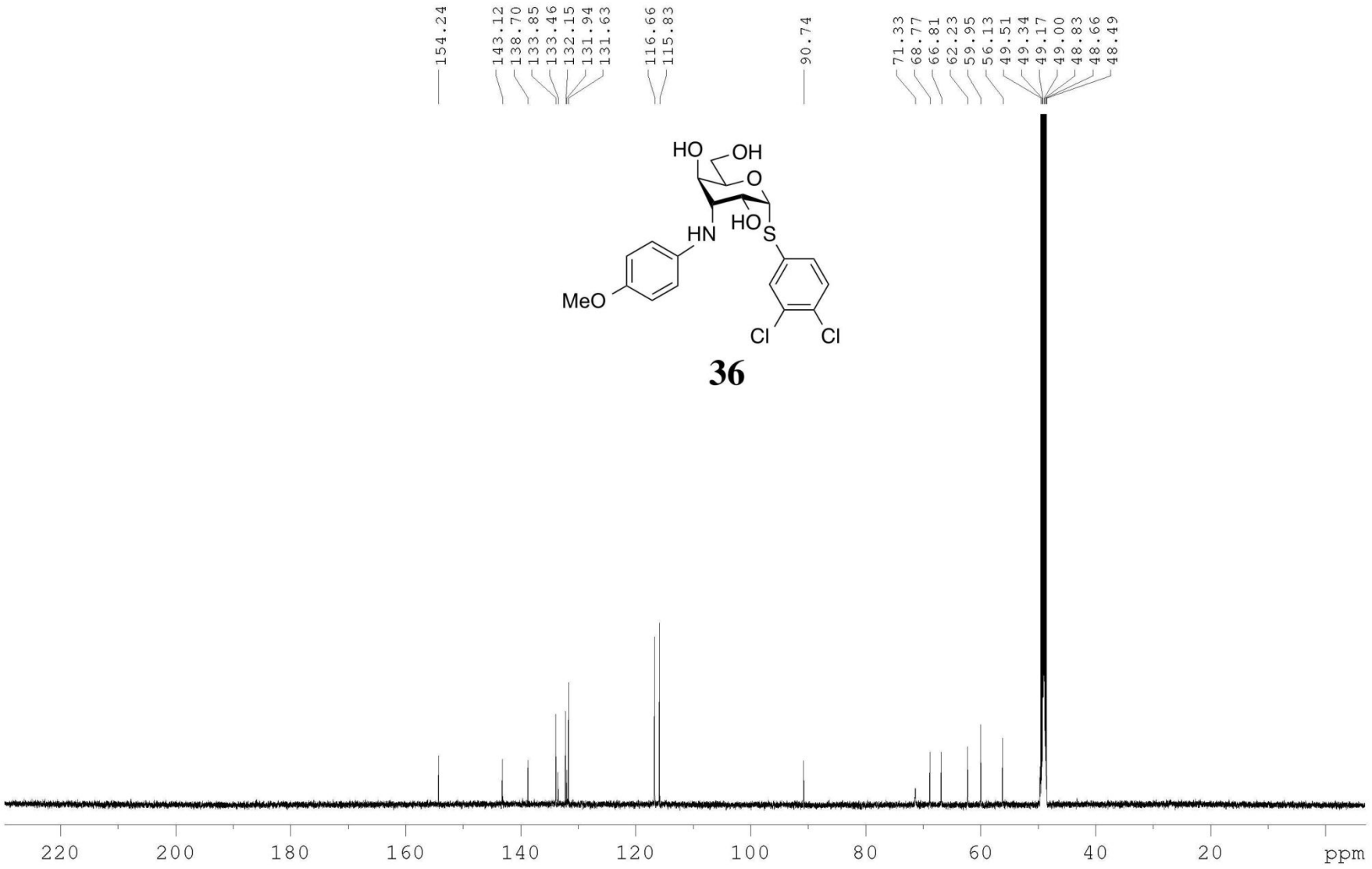
^{1}H NMR, CD_3OD, 400 MHz



^{13}C NMR, CD_3OD, 125 MHz



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