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Synthesis of new *N*-substituted aminoquercitols from naturally available (+)-*proto*-quercitol and their α-glucosidase inhibitory activity

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General

All moisture-sensitive reactions were carried out under a nitrogen atmosphere. All solvents were distilled prior to use. Mass spectra were measured by ESI-MS and High Resolution (HR)-ESI-MS were obtained from a micrOTOF Bruker mass spectrometer. ^{1}H and ^{13}C NMR spectra were recorded ($CDCl_3$, D_2O, and CD_3OD as solvent) at 400 and 100 MHz, respectively, on a Varian Mercury^{+} 400 NMR and a Bruker (Avance) 400 NMR spectrometer using tetramethylsilane (TMS) as an internal standard. Chemical shifts are reported in ppm downfield from TMS. Optical rotations were measured on a Perkin-Elmer 341 polarimeter using a cell with 2 mL capacity and a 10 cm path length. Analytical thin layer chromatography (TLC) was performed on pre-coated Merck silica gel 60 F_{254} plates (0.25 mm thick layer) and visualized by potassium permanganate as the detecting agent. Column chromatography were performed using Merck silica gel 60 (70-230 mesh), Sephadex LH-20, and Dowex 50W-X8 (H^+). Sucrose, maltose, baker's yeast α-glucosidase, rat intestinal acetone powder, and *p*-nitrophenyl-α-D-glucopyranoside were purchased from Sigma-Aldrich (St. Louis, MO, USA). Glucose assay kit was purchased from Human Gesellschaft für Biochemica und Diagnostica mbH (Germany). Acarbose was obtained from Bayer (Germany).

General procedure for synthesis of *N*-acyl-aminoquercitols 4-7

To a stirred solution of aminocyclitol **2** or **3** (0.14 mmol) in CH_2Cl_2 (1.4 mL) was added DMAP (trace amount) and TEA (1.09 mmol). After the clear solution obtained, anhydride compounds (0.41 mmol) were added slowly, and the mixture was stirred at room temperature for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was treated with trifluoroacetic acid (0.74 mmol) in THF (2 mL) and stirred at room temperature for 4 h. The reaction mixture was evaporated to dryness, redissolved in EtOAc, and extracted with H_2O (3 × 10 mL). The combined aqueous layers were loaded onto Diaion HP-20 column and washed with H_2O followed by MeOH. Fractions eluted with H_2O were lyophilized to afford *N*-acyl aminoquercitols.

***N*-((1*S*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)acetamide (4).** White solid (74%). ^{1}H NMR (D_2O, 400 MHz) δ 3.91 (br s, 1H, H-2), 3.80 (br d, J = 12.0 Hz, 1H, H-1), 3.42-3.50 (m, 3H, H-3,4,5), 1.93 (s, 3H, -CH_3), 1.82 (m, 1H, H-6), 1.66 (q, J = 12.0 Hz, 1H, H-6); ^{13}C NMR (D_2O + one drop acetone-d_6, 100 MHz) δ 173.3, 74.2, 72.2, 70.8, 69.9, 47.0, 31.4, 21.8; HRMS *m/z* 228.0841 $[M+Na]^+$ (calcd for $C_8H_{15}NO_5Na$, 228.0848).

***N*-((1*S*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)butyramide (5).** White solid (63%). ^{1}H NMR (D_2O, 400 MHz) δ 3.89 (m, 1H, H-2), 3.77 (m, 1H, H-1), 3.41-3.45 (m, 3H, H-3,4,5), 2.13 (t, J = 7.2 Hz, 2H, -OC$\underline{CH_2}$-), 1.79 (m, 1H, H-6), 1.63 (q, J = 12.0 Hz, 1H, H-6), 1.48 (m, 2H, -CH_2-), 0.78 (t, J = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (D_2O, 100 MHz) δ 176.4, 74.2, 72.4, 71.0, 70.0, 46.9, 37.6, 31.6, 19.0, 12.8; HRMS *m/z* 256.1159 $[M+Na]^+$ (calcd for $C_{10}H_{19}NO_5Na$, 256.1161).

***N*-((1*S*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)hexanamide (6).** White solid (52%). ^{1}H NMR (D_2O, 400 MHz) δ 3.77 (br s, 1H, H-2), 3.68 (br d, J = 12.4 Hz, 1H, H-1), 3.29-3.34 (m, 3H, H-3,4,5), 2.05 (t, J = 7.2 Hz, 2H, -OC$\underline{CH_2}$-), 1.68 (m, 1H, H-6), 1.53 (q, J = 12.0 Hz, 1H, H-6), 1.38 (m, 2H, -CH_2-), 1.08 (br s, 4H, -$(CH_2)_2$-), 0.66 (t, J = 6.0 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.2, 74.6, 73.1, 71.2, 70.3, 46.9, 35.5, 32.1, 31.0, 25.2, 22.0, 12.8; HRMS *m/z* 262.1652 $[M+H]^+$ (calcd for $C_{12}H_{24}NO_5$, 262.1654).

***N*-((1*S*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)decanamide (7).** White solid (58%). $[\alpha]_D^{20}$ = -20.8 (*c* 0.23, CH_3OH); ^{1}H NMR (CD_3OD, 400 MHz) δ 3.77 (br s, 1H, H-2), 3.73 (m, 1H, H-1), 3.41 (dd, J = 9.6, 9.2 Hz, 1H, H-4), 3.31 (m, 1H, H-5), 3.23 (m, 1H, H-3), 2.10 (t, J = 7.6 Hz, 2H, -OC$\underline{CH_2}$-), 1.66-1.73 (m, 2H, H-6), 1.48-1.52 (m, 2H, -CH_2-), 1.20 (br s, 12H, -$(CH_2)_6$-), 0.80 (t, J = 6.4 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.7, 76.1, 74.6, 72.6, 71.8, 48.4, 37.0, 33.6, 33.1, 30.6, 30.5, 30.4, 30.3, 27.0, 23.7, 14.4; HRMS *m/z* 318.2286 $[M+H]^+$ (calcd for $C_{16}H_{32}NO_5$, 318.2280).

General procedure for synthesis of *N*-acyl-aminoquercitols 8-13

To a stirred solution of aminocyclitol **2** or **3** (0.14 mmol) in CH_2Cl_2 (1.4 mL) was added DMAP (trace amount) and TEA (1.09 mmol). After the clear solution obtained, anhydride compounds (0.41 mmol) were added slowly, and the mixture was stirred at room temperature for 3 h. The reaction mixture was extracted with CH_2Cl_2 (3×10 mL), washed with brine, dried over anhydrous Na_2SO_4, filtered and concentrated under reduced pressure. The crude product was treated with 1.25 M methanolic HCl (0.7 mL) and stirred at room temperature for 4 h. The reaction mixture was evaporated under reduced pressure to give *N*-acyl aminoquercitols.

***N*-((1*S*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)dodecanamide (8).** White solid (45%). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.77 (br s, 1H, H-2), 3.74 (m, 1H, H-1), 3.41 (dd, J = 9.2, 9.2 Hz, 1H, H-4), 3.32 (m, 1H, H-5), 3.24 (m, 1H, H-3), 2.11 (t, J = 7.6 Hz, 2H, -OC$\underline{CH_2}$-), 1.67-1.74 (m, 2H, H-6), 1.49-1.52 (m, 2H, -CH_2-), 1.20 (br s, 16H, -$(CH_2)_8$-), 0.81 (t, J = 6.0 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 175.7, 76.1, 74.6, 72.6, 71.8, 48.4, 37.0, 33.6, 33.1, 30.7, 30.6, 30.5, 30.4, 30.3, 27.0, 23.7, 14.4; HRMS *m/z* 368.2408 $[M+Na]^+$ (calcd for $C_{18}H_{35}NO_5Na$, 368.2413).

***N*-((1*R*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)acetamide (9).** Pale yellow oil (quantitative yield). ^{1}H NMR (D_2O, 400 MHz) δ 3.82 (br s, 1H, H-1), 3.67 (br s, 1H, H-2), 3.48 (br s, 1H, H-5), 3.38 (br s, 2H, H-3,4), 1.74 (s, 3H, -CH_3), 1.64 (m, 2H, H-6); ^{13}C NMR (D_2O, 100 MHz) δ 174.0, 73.8, 71.3, 70.7, 69.2, 48.5, 30.9, 22.0; HRMS *m/z* 206.1024 $[M+H]^+$ (calcd for $C_8H_{16}NO_5$, 206.1028).

***N*-((1*R*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)butyramide (10).** Yellow solid (52%). ^{1}H NMR (D_2O, 400 MHz) δ 3.89 (m, 1H, H-1), 3.72 (br s, 1H, H-1), 3.52 (m, 1H, H-5), 3.43 (m, 2H, H-3,4), 2.02 (t, J = 7.2 Hz, 2H, -OC$\underline{CH_2}$-), 1.70 (m, 2H, H-6), 1.34-1.43 (m, 2H, -CH_2-), 0.68 (t, J = 7.6 Hz, 3H, -CH_3); ^{13}C NMR ((D_2O, 100 MHz) δ 177.0, 73.7, 71.3, 70.6, 69.2, 48.4, 37.4, 30.8, 19.2, 12.6; HRMS *m/z* 234.1333 $[M+H]^+$ (calcd for $C_{10}H_{20}NO_5$, 234.1341).

***N*-((1*R*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)hexanamide (11).** Yellow oil (quantitative yield). ^{1}H NMR (D_2O, 400 MHz) δ 3.87 (br d, J = 3.6 Hz, 1H, H-1), 3.71 (br s, 1H, H-2), 3.51 (m, 1H, H-5), 3.41 (br d, J = 5.2 Hz, 2H, H-3,4), 2.03 (t, J = 7.2 Hz, 2H, -OC$\underline{CH_2}$-), 1.68-1.71 (m, 2H, H-6), 1.33-1.40 (m, 2H, -CH_2-), 1.02-1.12 (m, 4H, -$(CH_2)_2$-), 0.64 (t, J = 6.8 Hz, 3H, -CH_3); ^{13}C NMR (D_2O + one drop of acetone-d_6, 100 MHz) δ 177.0, 73.6, 71.1, 70.5, 69.0, 48.2, 35.3, 30.7, 30.3, 25.0, 21.5, 13.1; HRMS *m/z* 262.1650 $[M+H]^+$ (calcd for $C_{12}H_{24}NO_5$, 262.1654).

***N*-((1*R*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)decanamide (12).** White solid (83%). ^{1}H NMR (CD_3OD, 400 MHz) δ 4.04 (m, 1H, H-1), 3.71 (m, 1H, H-2), 3.55-3.61 (m, 2H, H-4,5), 3.49 (m, 1H, H-3), 2.11 (t, J = 7.2 Hz, 2H, -OC$\underline{CH_2}$-), 1.85 (m, 1H, H-6), 1.68 (m, 1H, H-6), 1.50 (br s, 2H, -CH_2-), 1.20 (br s, 12H, -$(CH_2)_6$-), 0.80 (t, J = 6.8 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 174.9, 73.5, 72.4, 71.0, 69.6, 47.6, 36.5, 31.7, 31.6, 29.2, 29.1, 29.0, 28.9, 25.7, 22.3, 13.0; HRMS *m/z* 318.2271 $[M+H]^+$ (calcd for $C_{16}H_{32}NO_5$, 318.2280).

***N*-((1*R*,2*S*,3*S*,4*S*,5*R*)-2,3,4,5-tetrahydroxycyclohexyl)dodecanamide (13).** White solid(quantitative yield). ^{1}H NMR (CD_3OD, 400 MHz) δ 4.03 (m, 1H, H-1), 3.71 (m, 1H, H-2), 3.55-3.61 (m, 2H, H-4,5), 3.49 (m, 1H, H-3), 2.11 (t, J = 6.8 Hz, 2H, -OC$\underline{CH_2}$-), 1.83 (m, 1H, H-6), 1.69 (m, 1H, H-6), 1.50 (br s, 2H, -CH_2-), 1.19 (br s, 16H, -$(CH_2)_8$-), 0.80 (t, J = 6.4 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 176.4, 74.9, 73.9, 72.5, 71.2, 48.4, 37.0, 33.2, 33.1, 30.7, 30.7, 30.6, 30.5, 30.4, 30.3, 27.1, 23.7, 14.4; HRMS *m/z* 368.2403 $[M+Na]^+$ (calcd for $C_{18}H_{35}NNaO_5$, 368.2413).

General procedure for reductive amination of aminocyclitols 2-3

Using AcOH

To a solution of aminocyclitols **2** or **3** (0.12 mmol) in methanol (1.1 mL) under an atmosphere of N_2 were treated with sodium cyanoborohydride (0.22 mmol), acetic acid (8 µL) and corresponding aldehyde (0.11 mmol). After stirring at room temperature for 2 days, the reaction mixture was evaporated to dryness, quenched with water and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was purified by flash chromatography or sephadex LH-20 column chromatography.

Using Ti(O^iPr)$_4$

To a solution of aminocyclitols **2** or **3** (0.16 mmol) in methanol (1.6 mL) under an atmosphere of N_2 were treated with corresponding aldehyde (0.19 mmol), titanium isopropoxide (0.20 mmol) and sodium cyanoborohydride (0.40 mmol). After stirring at 0 ºC for 1 day, the reaction mixture was evaporated to dryness, quenched with water and extracted with EtOAc (3×10 mL). The combined organic layers were washed with brine, dried over anhydrous Na_2SO_4 and concentrated under reduced pressure to afford crude product, which was purified by flash chromatography or sephadex LH-20 column chromatography.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-ethylcyclohexylamine (14). White solid (29%), (5% MeOH-EtOAc for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.37 (dd, J = 6.0, 4.4 Hz, 1H), 4.08 (dd, J = 8.8, 4.8 Hz, 1H), 3.47 (dd, J = 10.4, 8.8 Hz, 1H), 3.22 (m, 1H), 3.04 (m, 1H), 2.72 (q, J = 7.2 Hz, 2H), 2.33 (m, 1H), 1.50 (m, 1H), 1.47 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.10 (t, J = 7.2 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.0, 109.4, 82.4, 76.6, 75.1, 74.4, 54.7, 41.0, 30.5, 28.6, 26.9, 26.9, 26.2, 14.8.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-butylcyclohexylamine (15). White solid (34%), (100% EtOAc for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.36 (dd, J = 5.2, 4.4 Hz, 1H), 4.07 (dd, J = 8.4, 4.8 Hz, 1H), 3.49 (dd, J = 10.4, 8.8 Hz, 1H), 3.23 (m, 1H), 2.97 (m, 1H), 2.62-2.66 (m, 2H), 2.30 (m, 1H), 1.50 (m, 1H), 1.47 (s, 3H), 1.41-1.45 (m, 4H), 1.36 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 0.86 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.9, 108.4, 81.4, 75.6, 74.3, 73.4, 54.2, 45.8, 31.1, 29.8, 27.6, 25.9, 25.9, 25.2, 19.4, 12.9.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-hexylcyclohexylamine (16). Colorless oil (51%), (100% EtOAc for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.38 (dd, J =5.6, 4.4 Hz, 1H), 4.08 (dd, J = 8.4, 4.8 Hz, 1H), 3.47 (dd, J = 10.0, 8.4 Hz, 1H), 3.22 (m, 1H), 3.08 (m, 1H), 2.67 (t, J = 7.2 Hz, 2H), 2.33 (m, 1H), 1.54 (m, 1H), 1.46-1.51 (m, 2H), 1.46 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.23 (br s, 6H), 0.82 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.0, 109.5, 82.3, 76.5, 74.7, 74.2, 54.5, 46.5, 31.5, 30.1, 29.1, 28.5, 26.9, 26.9, 26.8, 26.2, 22.5, 14.0.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-decylcyclohexylamine (17). Pale yellow oil (60%), (80% EtOAc-hexane for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.34 (dd, J = 4.4, 4.4 Hz, 1H), 4.06 (dd, J = 8.4, 4.4 Hz, 1H), 3.49 (dd, J = 8.4, 8.4 Hz, 1H), 3.23 (m, 1H), 2.93 (m, 1H), 2.58-2.61 (m, 2H), 2.28 (m, 1H), 1.46 (s, 3H), 1.42-1.45 (m, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.30 (s, 3H), 1.19 (br s, 14H), 0.81 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.8, 109.2, 82.4, 75.6, 75.5, 74.5, 55.2, 47.2, 31.9, 31.0, 30.2, 29.6, 29.6, 29.5, 29.3, 28.6, 27.3, 26.9, 26.9, 26.2, 22.7, 14.1.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-dodecylcyclohexylamine (18). Pale yellow oil (50%), (80% EtOAc-hexane for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.36 (br s, 1H), 4.07 (m, 1H), 3.48 (dd, J = 8.8, 8.8 Hz, 1H), 3.23 (m, 1H), 2.98 (m, 1H), 2.63 (t, J = 7.6 Hz, 2H), 2.31 (m, 1H), 1.52-1.55 (m, 3H), 1.47 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.31 (s, 3H), 1.19 (br s, 18H), 0.81 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.0, 108.4, 81.4, 75.6, 74.3, 73.4, 54.1, 46.1, 30.9, 29.7, 28.9, 28.6, 28.6, 28.6, 28.5, 28.4, 28.3, 27.6, 26.3, 25.9, 25.9, 25.2, 21.7, 13.1.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-butylcyclohexylamine (19). Pale yellow oil (14%), (100% EtOAc for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24 (dd, J = 7.6, 6.8 Hz, 1H), 4.07 (dd, J = 8.0, 7.2 Hz, 1H), 3.65-3.68 (m, 2H), 3.02 (dt, J = 8.0, 7.6 Hz, 1H), 2.59 (m, 1H), 2.47 (m, 1H), 1.93 (m, 1H), 1.84 (m, 1H), 1.43 (s, 3H), 1.38-1.40 (m, 2H), 1.36 (s, 3H), 1.35 (s, 3H), 1.26-1.32 (m, 2H), 1.28 (s, 3H), 0.85 (t, J = 7.6 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.6, 109.9, 80.5, 78.8, 76.2, 72.6, 55.9, 47.3, 32.1, 30.2, 27.8, 27.1, 27.0, 25.2, 20.4, 13.9.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-hexylcyclohexylamine (20). Colorless oil (54%), (80% EtOAc-hexane for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24 (dd, J = 6.8, 6.8 Hz, 1H), 4.07 (dd, J = 7.2, 7.2 Hz, 1H), 3.65-3.70 (m, 2H), 3.02 (q, J = 7.2 Hz, 1H), 2.59 (m, 1H), 2.46 (m, 1H), 1.81-1.97 (m, 4H), 1.43 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.18-1.22 (m, 6H), 0.82 (t, J = 6.4 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.6, 109.9, 80.5, 78.7, 76.2, 72.6, 55.8, 47.6, 31.7, 30.2, 29.9, 27.8, 27.2, 27.0, 26.9, 25.2, 22.6, 14.0.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-decylcyclohexylamine (21). Colorless oil (67%), (80% EtOAc-hexane for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24 (dd, J = 8.0, 6.8 Hz, 1H), 4.07 (dd, J = 8.0, 6.8 Hz, 1H), 3.66-3.67 (m, 2H), 3.02 (ddd, J = 8.0, 7.6, 6.8 Hz, 1H), 2.58 (m, 1H), 2.47 (m, 1H), 1.94 (br s, 1H), 1.85 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.19 (br s, 16H), 0.81 (t, J = 6.8 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.6, 109.9, 80.4, 78.7, 76.2, 72.6, 55.8, 47.6, 31.9, 30.2, 29.9, 29.6, 29.5, 29.4, 29.3, 27.8, 27.2, 27.1, 27.0, 25.2, 22.7, 14.1.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*-dodecylcyclohexylamine (22). Colorless oil (32%), (80% EtOAc-hexane for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.24 (dd, J = 8.0, 5.6 Hz, 1H), 4.08 (dd, J = 8.0, 7.2 Hz, 1H), 3.67 (br d, J = 4.8 Hz, 2H), 3.01 (ddd, J = 8.0, 8.0, 7.2 Hz, 1H), 2.60 (m, 1H), 2.47 (m, 1H), 1.93 (m, 1H), 1.86 (m, 1H), 1.42 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.28 (s, 3H), 1.19 (br s, 20H), 0.81 (t, J = 8.0 Hz, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.6, 109.9, 80.5, 78.7, 76.2, 72.6, 55.8, 47.6, 31.9, 30.2, 29.9, 29.6, 29.6, 29.6, 29.6, 29.5, 29.3, 27.8, 27.2, 27.1, 27.0, 25.2, 22.7, 14.1.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*,*N*-diethylcyclohexylamine (23). Colorless oil (48%), (100% EtOAc for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.30 (dd, J = 4.4, 4.4 Hz, 1H), 4.03 (dd, J = 8.8, 4.4 Hz, 1H), 3.47 (dd, J = 9.6, 8.8 Hz, 1H), 3.24 (ddd, J = 11.6, 9.6, 3.2 Hz, 1H), 2.92 (dt, J = 12.0, 4.0 Hz, 1H), 2.69-2.77 (m, 2H), 2.52-2.60 (m, 2H), 2.11 (ddd, J = 11.6, 4.0, 4.0 Hz, 1H), 1.74 (m, 1H), 1.47 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.29 (s, 3H), 0.98 (t, J = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.8, 109.7, 82.5, 77.3, 76.7, 75.3, 57.4, 45.1, 28.9, 27.0, 26.9, 26.4, 26.3, 13.5.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*,*N*-dibutylcyclohexylamine (24). Yellow oil (51%), (1:4:5 MeOH-CH_2Cl_2-hexane for sephadex LH-20 column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (br s, 1H), 3.99 (dd, *J* = 8.8, 4.8 Hz, 1H), 3.46 (dd, *J* = 10.0, 8.8 Hz, 1H), 3.22 (m, 1H), 2.89 (br d, *J* = 10.8 Hz, 1H), 2.59-2.66 (m, 2H), 2.41-2.44 (m, 2H), 2.07 (br d, *J* = 10.8 Hz, 1H), 1.74 (ddd, *J* = 12.4, 12.4, 11.6 Hz, 1H), 1.45 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.19-1.26 (m, 8H), 0.84 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 109.8, 108.6, 81.6, 76.6, 75.6, 74.3, 56.7, 50.7, 29.9, 27.9, 25.9, 25.9, 25.1, 24.7, 19.4, 13.1.

(1*S*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*,*N*-dihexylcyclohexylamine (25). Pale yellow oil (38%), (0.5:2.5:7 MeOH-CH_2Cl_2-hexane for sephadex LH-20 column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (br s, 1H), 4.00 (dd, *J* = 8.0, 4.8 Hz, 1H), 3.46 (dd, *J* = 9.2, 9.2 Hz, 1H), 3.23 (m, 1H), 2.88 (br d, *J* = 11.2 Hz, 1H), 2.57-2.64 (m, 2H), 2.36-2.44 (m, 2H), 2.08 (br d, *J* = 11.6 Hz, 1H), 1.73 (m, 1H), 1.46 (s, 3H), 1.36 (s, 3H), 1.34 (s, 3H), 1.28 (s, 3H), 1.20 (br s, 16H), 0.82 (t, *J* = 6.8 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 110.8, 109.6, 82.6, 77.6, 76.6, 75.4, 57.8, 52.1, 31.8, 28.9, 28.7, 27.0, 26.9, 26.9, 26.1, 25.8, 22.7, 14.1.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*,*N*-diethylcyclohexylamine (26). Colorless oil (45%), (1:7:2 MeOH-CH_2Cl_2-hexane for sephadex LH-20 column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.29 (dd, *J* = 10.0, 7.2 Hz, 1H), 4.18 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.63 (dd, *J* = 10.4, 8.4 Hz, 1H), 3.54 (dt, *J* = 10.4, 7.2 Hz, 1H), 3.25 (ddd, *J* = 10.0, 8.8, 7.2 Hz, 1H), 2.45-2.60 (m, 4H), 1.99 (m, 1H), 1.75 (m, 1H), 1.44 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.02 (t, *J* = 5.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 112.1, 109.5, 80.4, 76.5, 76.1, 73.5, 57.7, 44.5, 27.4, 27.2, 27.1, 26.2, 24.5, 14.0.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*,*N*-dibutylcyclohexylamine (27). White solid (57%), (80% EtOAc-hexane for flash column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.27 (dd, *J* = 9.6, 8.4 Hz, 1H), 4.17 (dd, *J* = 8.4, 7.2 Hz, 1H), 3.63 (dd, *J* = 10.8, 7.2 Hz, 1H), 3.54 (dd, *J* = 10.8, 8.0 Hz, 1H), 3.19 (ddd, *J* = 9.6, 9.2, 8.4 Hz, 1H), 2.44-2.51 (m, 2H), 2.33-2.40 (m, 2H), 1.94 (m, 1H), 1.74 (m, 1H), 1.43 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.18-1.24 (m, 8H), 0.84 (t, *J* = 7.2 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 111.0, 108.4, 79.4, 75.4, 75.1, 72.5, 56.8, 49.9, 30.1, 26.4, 26.2, 26.1, 25.4, 23.7, 19.5, 13.1.

(1*R*,2*S*,3*S*,4*S*,5*R*)-(2,3:4,5-di-*O*-isopropylidene)-*N*,*N*-dihexylcyclohexylamine (28). Pale yellow oil (91%), (1:4:5 MeOH-CH_2Cl_2-hexane for sephadex LH-20 column). ^{1}H NMR ($CDCl_3$, 400 MHz) δ 4.26 (dd, *J* = 10.0, 8.4 Hz, 1H), 4.16 (dd, *J* = 8.4, 7.6 Hz, 1H), 3.63 (dd, *J* = 10.0, 7.6 Hz, 1H), 3.54 (dd, *J* = 10.8, 7.6 Hz, 1H), 3.19 (dd, *J* = 16.0, 10.0 Hz, 1H), 2.42-2.49 (m, 2H), 2.32-2.39 (m, 2H), 1.93 (m, 1H), 1.73 (m, 1H), 1.43 (s, 3H), 1.37 (s, 3H), 1.35 (s, 3H), 1.26 (s, 3H), 1.21-1.24 (br s, 16H), 0.81 (t, *J* = 7.6 Hz, 6H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 112.0, 109.4, 80.4, 76.5, 76.2, 73.5, 57.9, 56.3, 31.8, 28.9, 27.4, 27.2, 27.1, 27.1, 26.4, 24.6, 22.7, 14.1.

General procedure for deprotection of compounds 14-28

For the synthesis of *N*-alkyl-aminocyclitols 29-31, 34-35, and 38-43

To a solution of the protected *N*-alkyl aminoquercitols (0.05 mmol) in 1.25 M methanolic HCl (1 mL) were stirred at room temperature for 4 h. The reaction mixture was evaporated to dryness, redissolved in H_2O, loaded onto Dowex 50W-X8 (H^+) column and eluted with H_2O followed by 50% NH_3-H_2O. Fractions eluted with 50% NH_3-H_2O were evaporated to give the *N*-alkyl aminoquercitols.

For the synthesis of *N*-alkyl-aminocyclitols 32-33 and 36-37

To a solution of the protected *N*-alkyl aminoquercitols (0.08 mmol) in 1.25 M methanolic HCl (1 mL) were stirred at room temperature for 4 h. The reaction mixture was evaporated to dryness, redissolved in H_2O and extracted with EtOAc (3×10 mL). The combined aqueous layers were neutralized with 1 M $NaHCO_3$ and further extracted with EtOAc. The combined organic layers were evaporated under reduced pressure to afford the *N*-alkyl aminoquercitols.

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-ethylamino-cyclohexane-2,3,4,5-tetraol (29). Yellow oil (80%). ^{1}H NMR (D_2O, 400 MHz) δ 3.96 (br s, 1H, H-2), 3.33-3.35 (m, 2H, H-4,5), 3.25 (m, 1H, H-3), 2.90 (br d, *J* = 12.4 Hz, 1H, H-1), 2.68-2.75 (m, 2H, -HN<u>CH_2</u>-), 1.88 (m, 1H, H-6), 1.48 (m, 1H, H-6), 0.99 (t, *J* = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (D_2O, 100 MHz) δ 74.1, 72.3, 69.6, 68.5, 53.4, 40.1, 30.5, 11.9; HRMS *m/z* 192.1239 $[M+H]^+$ (calcd for $C_8H_{18}NO_4$, 192.1236).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-butylamino-cyclohexane-2,3,4,5-tetraol (30). Pale yellow oil (quantitative yield). ^{1}H NMR (D_2O, 400 MHz) δ 4.04 (br s, 1H, H-2), 3.44-3.46 (m, 2H, H-4,5), 3.36 (m, 1H, H-3), 2.49-2.68 (m, 3H, H-1, -HN<u>CH_2</u>-), 1.92 (br d, *J* = 12.4 Hz, 1H, H-6), 1.35-1.45 (m, 3H, H-6, -CH_2-), 1.21-1.28 (m, 2H, -<u>CH_2</u>CH_3), 0.83 (t, *J* = 7.6 Hz, 3H, -CH_3); ^{13}C NMR (D_2O, 100 MHz) δ 74.5, 72.9, 70.2, 69.6, 53.1, 45.1, 32.1, 30.7, 19.8, 13.2; HRMS *m/z* 220.1548 $[M+H]^+$ (calcd for $C_{10}H_{22}NO_4$, 220.1549).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-hexylamino-cyclohexane-2,3,4,5-tetraol (31). Pale yellow solid (59%). ^{1}H NMR (D_2O, 400 MHz) δ 3.94 (br s, 1H, H-2), 3.32-3.34 (m, 2H, H-4,5), 3.24 (m, 1H, H-3), 2.73 (d, J = 11.6 Hz, 1H, H-1), 2.50-2.59 (m, 2H, -HN$\underline{CH_2}$-), 1.85 (m, 1H, H-6), 1.34-1.41 (m, 3H, H-6, -CH_2-), 1.10 (br s, 6H, -$(CH_2)_3$-), 0.67 (br s, 3H, -CH_3); ^{13}C NMR (D_2O, 100 MHz) δ 74.3, 72.6, 69.9, 69.0, 53.5, 45.4, 31.2, 30.8, 27.5, 26.0, 21.9, 13.3; HRMS *m/z* 248.1854 $[M+H]^+$ (calcd for $C_{12}H_{26}NO_4$, 248.1862).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-decylamino-cyclohexane-2,3,4,5-tetraol (32). White solid (quantitative yield). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.91 (br s, 1H, H-2), 3.41 (dd, J = 9.2, 9.2 Hz, 1H, H-4), 3.27 (m, 1H, H-5), 3.16 (m, 1H, H-3), 2.44-2.57 (m, 3H, H-1, -HN$\underline{CH_2}$-), 1.81 (m, 1H, H-6), 1.40-1.52 (m, 3H, H-6, -CH_2-), 1.20 (br s, 14H, -$(CH_2)_7$-), 0.80 (t, J = 6.4 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 76.4, 75.1, 72.1, 70.9, 55.6, 47.4, 34.3, 33.1, 30.8, 30.7, 30.7, 30.6, 30.4, 28.5, 23.7, 14.4; HRMS *m/z* 304.2489 $[M+H]^+$ (calcd for $C_{16}H_{34}NO_4$, 304.2488).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-dodecylamino-cyclohexane-2,3,4,5-tetraol (33). White solid (75%). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.91 (br s, 1H, H-2), 3.41 (dd, J = 9.2, 9.2 Hz, 1H, H-4), 3.27 (m, 1H, H-5), 3.16 (dd, J = 9.6, 2.4 Hz, 1H, H-3), 2.43-2.58 (m, 3H, H-1, -HN$\underline{CH_2}$-), 1.82 (m, 1H, H-6), 1.40-1.49 (m, 3H, H-6, -CH_2-), 1.19 (br s, 18H, -$(CH_2)_9$-), 0.80 (t, J = 6.0 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 76.3, 75.1, 72.1, 70.9, 55.6, 47.4, 34.2, 33.1, 30.8, 30.7, 30.7, 30.7, 30.7, 30.6, 30.5, 28.5, 23.7, 14.4; HRMS *m/z* 332.2804 $[M+H]^+$ (calcd for $C_{18}H_{38}NO_4$, 332.2801).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-butylamino-cyclohexane-2,3,4,5-tetraol (34). Pale yellow oil (97%). ^{1}H NMR (D_2O, 400 MHz) δ 3.78 (br s, 1H, H-2), 3.51-3.63 (m, 3H, H-3,4,5), 2.98 (br d, J = 4.4 Hz, 1H, H-1), 2.55-2.63 (m, 2H, - HN$\underline{CH_2}$-), 1.76 (br s, 2H, H-6), 1.32-1.36 (m, 2H, -CH_2-), 1.13-1.18 (m, 2H, -$\underline{CH_2}CH_3$), 0.72 (t, J = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (D_2O, 100 MHz) δ 73.4, 71.8, 70.2, 69.1, 55.4, 46.2, 30.1, 29.7, 19.7, 13.1; HRMS *m/z* 220.1545 $[M+H]^+$ (calcd for $C_{10}H_{22}NO_4$, 220.1549).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-hexylamino-cyclohexane-2,3,4,5-tetraol (35). White solid (85%). $[\alpha]_D^{20}$ = +31.6 (*c* 0.31, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 3.79 (m, 1H, H-2), 3.52-3.65 (m, 3H, H-3,4,5), 3.01 (br d, J = 4.8 Hz, 1H, H-1), 2.57-2.65 (m, 2H, -HN$\underline{CH_2}$-), 1.75-1.81 (m, 2H, H-6), 1.37 (br s, 2H, -CH_2-), 1.12 (br s, 6H, -$(CH_2)_3$-), 0.68 (br t, J = 6.8 Hz, 3H, -CH_3); ^{13}C NMR (D_2O, 100 MHz) δ 73.1, 71.7, 70.0, 68.9, 55.3, 46.4, 30.7, 29.9, 27.3, 25.9, 21.9, 13.3; HRMS *m/z* 248.1858 $[M+H]^+$ (calcd for $C_{12}H_{26}NO_4$, 248.1862).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-decylamino-cyclohexane-2,3,4,5-tetraol (36). White solid (88%). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.62-3.72 (m, 4H, H-2,3,4,5), 2.90 (br d, J = 4.4 Hz, 1H, H-1), 2.60 (m, 1H, -HN$\underline{CH_2}$-), 2.48 (m, 1H, -HN$\underline{CH_2}$-), 1.83 (m, 1H, H-6), 1.70 (m, 1H, H-6), 1.41-1.44 (m, 2H, -CH_2-), 1.20 (br s, 14H, -$(CH_2)_7$-), 0.80 (t, J = 7.2 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 74.9, 74.2, 72.6, 71.2, 56.6, 48.4, 33.0, 32.6, 30.7, 30.7, 30.6, 30.5, 30.4, 28.4, 23.7, 14.4; HRMS *m/z* 304.2476 $[M+H]^+$ (calcd for $C_{16}H_{34}NO_4$, 304.2488).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-dodecylamino-cyclohexane-2,3,4,5-tetraol (37). White solid (52%). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.60-3.69 (m, 4H, H-2,3,4,5), 2.88 (br d, J = 3.2 Hz, 1H, H-1), 2.58 (m, 1H, -HN$\underline{CH_2}$-), 2.46 (m, 1H, -HN$\underline{CH_2}$-), 1.81 (m, 1H, H-6), 1.69 (m, 1H, H-6), 1.40-1.43 (m, 2H, -CH_2-), 1.19 (br s, 18H, -$(CH_2)_9$-), 0.80 (t, J = 6.0 Hz, 3H, -CH_3); ^{13}C NMR (CD_3OD, 100 MHz) δ 74.9, 74.2, 72.7, 71.2, 56.5, 48.5, 33.1, 32.7, 30.8, 30.7, 30.7, 30.7, 30.6, 30.6, 30.5, 28.5, 23.7, 14.4; HRMS *m/z* 332.2799 $[M+H]^+$ (calcd for $C_{18}H_{38}NO_4$, 332.2801).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-diethylamino-cyclohexane-2,3,4,5-tetraol (38). Colorless oil (quantitative yield). ^{1}H NMR (D_2O, 400 MHz) δ 4.12 (br s, 1H, H-2), 3.38 (br d, J = 7.2 Hz, 2H, H-3,5), 3.25 (br d, J = 7.2 Hz, 1H, H-4), 3.09 (br d, J = 12.4 Hz, 1H, H-1), 2.99 (br d, J = 6.4 Hz, 4H, -HN($\underline{CH_2}$)$_2$-), 1.98 (br d, J = 10.0 Hz, 1H, H-6), 1.68 (m, 1H, H-6), 1.03 (t, J = 6.4 Hz, 6H, -$(CH_3)_2$); ^{13}C NMR (D_2O, 100 MHz) δ 73.9, 72.3, 69.7, 68.2, 57.1, 44.1, 28.6, 8.9; HRMS *m/z* 220.1550 $[M+H]^+$ (calcd for $C_{10}H_{22}NO_4$, 220.1549).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-dibutylamino-cyclohexane-2,3,4,5-tetraol (39). Pale yellow solid (96%). ^{1}H NMR (D_2O, 400 MHz) δ 4.13 (br s, 1H, H-2), 3.33-3.38 (m, 2H, H-3,5), 3.23-3.27 (m, 2H, H-1,4), 3.01-3.05 (m, 4H, -HN($\underline{CH_2}$)$_2$-), 2.03 (br d, J = 12 Hz, 1H, H-6), 1.69 (m, 1H, H-6), 1.44-1.48 (m, 4H, -$(CH_2)_2$-), 1.15-1.20 (m, 4H, -$(\underline{CH_2})_2CH_3$), 0.73 (t, J = 6.8 Hz, 6H, -$(CH_3)_2$); ^{13}C NMR (D_2O, 100 MHz) δ 73.4, 71.9, 69.1, 67.4, 58.5, 49.9, 28.2, 24.9, 19.2, 12.6; HRMS *m/z* 276.2169 $[M+H]^+$ (calcd for $C_{14}H_{30}NO_4$, 276.2175).

(1*S*,2*S*,3*S*,4*S*,5*R*)-1-dihexylamino-cyclohexane-2,3,4,5-tetraol (40). White powder (49%). ^{1}H NMR (CD_3OD, 400 MHz) δ 4.02 (br s, 1H, H-2), 3.43 (dd, J = 9.2, 9.2 Hz, 1H, H-4), 3.30 (m, 1H, H-5), 3.16 (dd, J = 9.6, 2.0 Hz, 1H, H-3), 2.74 (br s, 5H, H-1, -HN($\underline{CH_2}$)$_2$-), 1.76-1.84 (m, 2H, H-6), 1.43 (br s, 4H, -$(CH_2)_2$-), 1.23 (br s, 12H, -$(CH_2)_6$-), 0.82 (t, J = 6.4 Hz, 6H, -$(CH_3)_2$); ^{13}C NMR (CD_3OD, 100 MHz) δ 76.2, 74.9, 72.2, 71.2, 59.3, 52.1, 32.8, 31.0, 28.0, 27.4, 23.7, 14.4; HRMS *m/z* 332.2796 $[M+H]^+$ (calcd for $C_{18}H_{38}NO_4$, 332.2801).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-diethylamino-cyclohexane-2,3,4,5-tetraol (41). Colorless oil (quantitative yield). $[\alpha]_D^{20}$ = +42.5 (*c* 0.25, H_2O); ^{1}H NMR (D_2O, 400 MHz) δ 3.94 (br s, 1H, H-2), 3.58 (br s, 2H, H-3,5), 3.51 (m, 1H, H-4), 2.87 (br d, *J* = 3.6 Hz, 1H, H-1), 2.50-2.65 (m, 4H, -HN($\underline{CH_2}$)$_2$-), 1.79 (m, 1H, H-6), 1.67 (m, 1H, H-6), 0.86 (t, *J* = 7.2 Hz, 6H, -(CH_3)$_2$); ^{13}C NMR (D_2O, 100 MHz) δ 73.5, 72.1, 69.5, 68.8, 57.3, 43.4, 27.6, 9.6; HRMS *m/z* 220.1552 $[M+H]^+$ (calcd for $C_{10}H_{22}NO_4$, 220.1549).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-dibutylamino-cyclohexane-2,3,4,5-tetraol (42). Pale yellow oil (50%). ^{1}H NMR (CD_3OD, 400 MHz) δ 3.86 (br s, 1H, H-2), 3.70-3.77 (m, 3H, H-3,4,5), 3.03 (br s, 1H, H-1), 2.54-2.57 (m, 2H, -HN$\underline{CH_2}$-), 2.39-2.42 (m, 2H, -HN$\underline{CH_2}$-), 1.72-1.75 (m, 2H, H-6), 1.36-1.40 (m, 4H, -(CH_2)$_2$-), 1.19-1.28 (m, 4H, -($\underline{CH_2}$)$_2$$CH_3$), 0.85 (t, *J* = 6.8 Hz, 6H, -(CH_3)$_2$); ^{13}C NMR (CD_3OD, 100 MHz) δ 74.5, 73.2, 72.3, 69.7, 57.3, 51.1, 31.2, 27.9, 21.6, 14.4; HRMS *m/z* 276.2169 $[M+H]^+$ (calcd for $C_{14}H_{30}NO_4$, 276.2175).

(1*R*,2*S*,3*S*,4*S*,5*R*)-1-dihexylamino-cyclohexane-2,3,4,5-tetraol (43). Pale yellow oil (46%). ^{1}H NMR (D_2O, 400 MHz) δ 3.91-3.97 (m, 3H, H-2,3,5), 3.84 (br s, 1H, H-4), 3.70 (m, 1H, H-1), 3.08-3.16 (m, 2H, -HN$\underline{CH_2}$-), 2.89 (br s, 2H, -HN$\underline{CH_2}$-), 1.80-1.94 (m, 2H, H-6), 1.51-1.62 (m, 4H, -(CH_2)$_2$-), 1.13 (br s, 12H, -(CH_2)$_6$-), 0.68 (t, *J* = 6.4 Hz, 6H, -(CH_3)$_2$); ^{13}C NMR (D_2O, 100 MHz) δ 73.3, 70.5, 69.2, 65.6, 56.9, 51.2, 30.4, 25.6, 25.1, 24.4, 21.7, 13.2; HRMS *m/z* 332.2799 $[M+H]^+$ (calcd for $C_{18}H_{38}NO_4$, 332.2801).

α-Glucosidase inhibitory activities

Baker's yeast α-glucosidase inhibitory activity

The α-glucosidase inhibition assay was performed according to the slightly modified method of Wacharasindhu *et al*.[1] The α-glucosidase (0.1 U/mL) and substrate (1 mM *p*-nitrophenyl-α-D-glucopyranoside) were dissolved in 0.1 M phosphate buffer, pH 6.9. 10 μL of synthesized compounds (1 mg/mL in DMSO) was pre-incubated with 40 μL of α-glucosidase at 37 ºC for 10 min. A 50 μL substrate solution was then added to the reaction mixture and incubated at 37 ºC for 20 min, and terminated by adding 100 μL of 1 M Na_2CO_3. Enzymatic activity was quantified by measuring the absorbance at 405 nm (Bio-Rad microplate reader model 3550 UV). The percentage inhibition was calculated by $[(A_0-A_1)/A_0] \times 100$, where A_0 is the absorbance without the sample, and A_1 is the absorbance with the sample. The IC_{50} value was determined from a plot of percentage inhibition versus sample concentration. Acarbose® was used as standard control and the experiment was performed in duplicate.

Rat intestinal α-glucosidase inhibitory activity

Rat intestinal α-glucosidase inhibitory activity was determined according to our previous report.[2] The crude enzyme solution prepared from rat intestinal acetone powder was used as a source of maltase and sucrase. Rat intestinal acetone powder (1 g) was homogenized in 30 mL of 0.9%NaCl solution. After centrifugation (12,000*g* × 30 min), the aliquot was subjected to assay. A 10 μL of synthesized compounds (1 mg/mL in DMSO) was added with 30 μL of the 0.1 M phosphate buffer (pH 6.9), 20 μL of the substrate solution (maltose: 10 mM; sucrose: 100 mM) in 0.1 M phosphate buffer, 80 μL of glucose assay kit, and 20 μL of the crude enzyme solution. The reaction mixture was then incubated at 37 ºC for 10 min (for maltose) and 40 min (for sucrose). Enzymatic activity was quantified by measuring the absorbance at 500 nm (Bio-Red microplate reader model 3550 UV). The percentage inhibition was calculated by $[(A_0-A_1)/A_0] \times 100$, where A_0 is the absorbance without the sample, and A_1 is the absorbance with the sample. The IC_{50} value was determined from a plot of percentage inhibition versus sample concentration. Acarbose® was used as standard control and the experiment was performed in duplicate.

Measurement of kinetic constant[2]

For kinetic analyses of maltase by the active compounds, enzyme and active compounds were incubated with increasing concentration of maltose (2-20 mM). The type of inhibition was determined by Lineweaver-Burk plot. For calculation of K_i value, slope from a Lineweaver-Burk plot were replotted vs. [I] which gave the secondary plot.

References

1) S. Wacharasindhu, W. Worawalai, W. Rungprom, P. Phuwapraisirisan, *Tetrahedron Lett.*, 2009, **50**, 2189-2192.
2) A. Wikul, T. Damsud, K. Kataoka, P. Phuwapraisirisan, *Bioorg. Med. Chem. Lett*. (accepted)

Electronic Supplementary Material (ESI) for Medicinal Chemistry Communications

NMR spectra of synthesized compounds

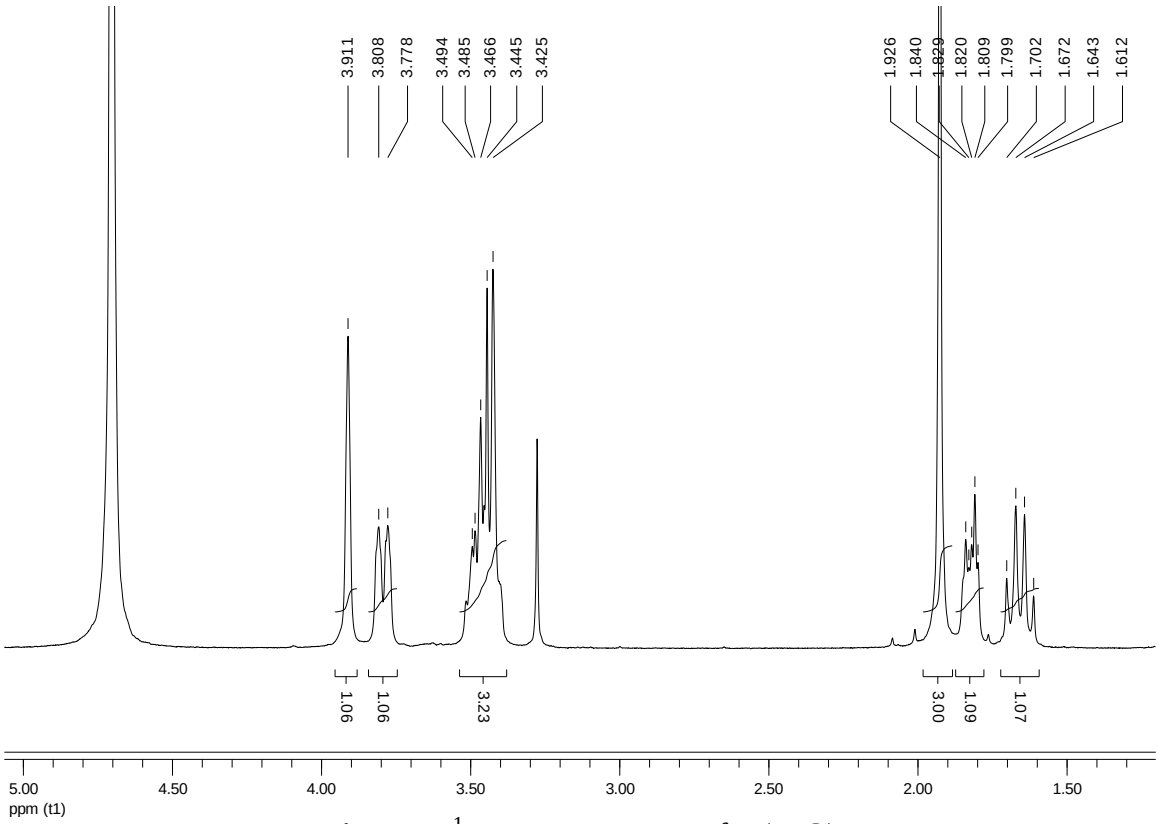

Figure 1. ^{1}H NMR spectrum of **4** (D_2O)

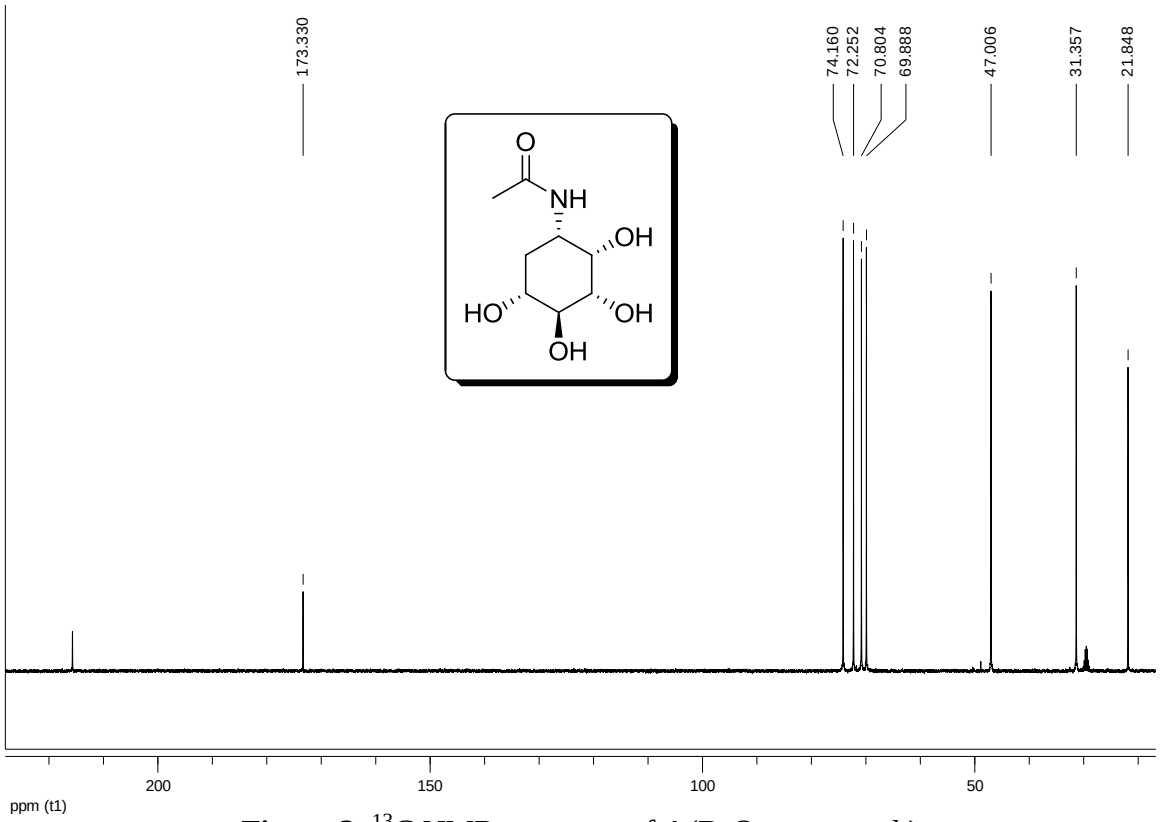

Figure 2. ^{13}C NMR spectrum of **4** (D_2O+acetone-d_6)

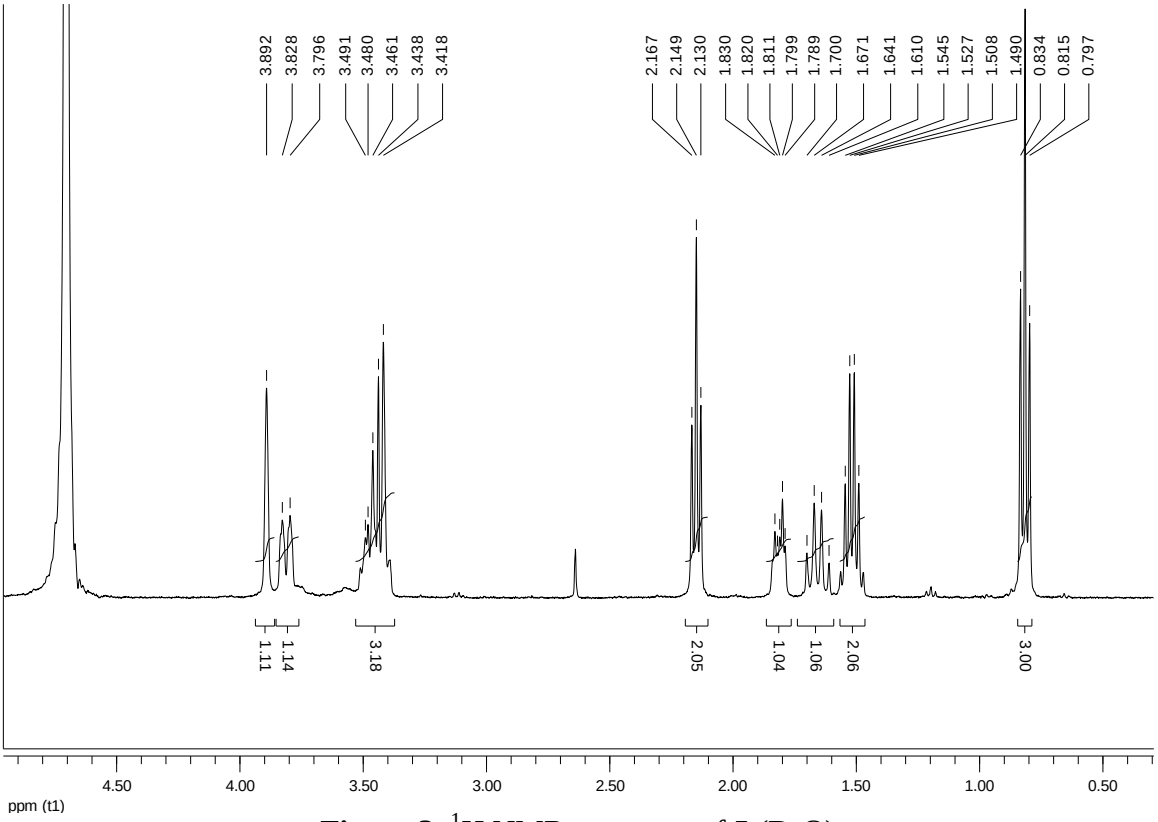

Figure 3. ^{1}H NMR spectrum of **5** (D_2O)

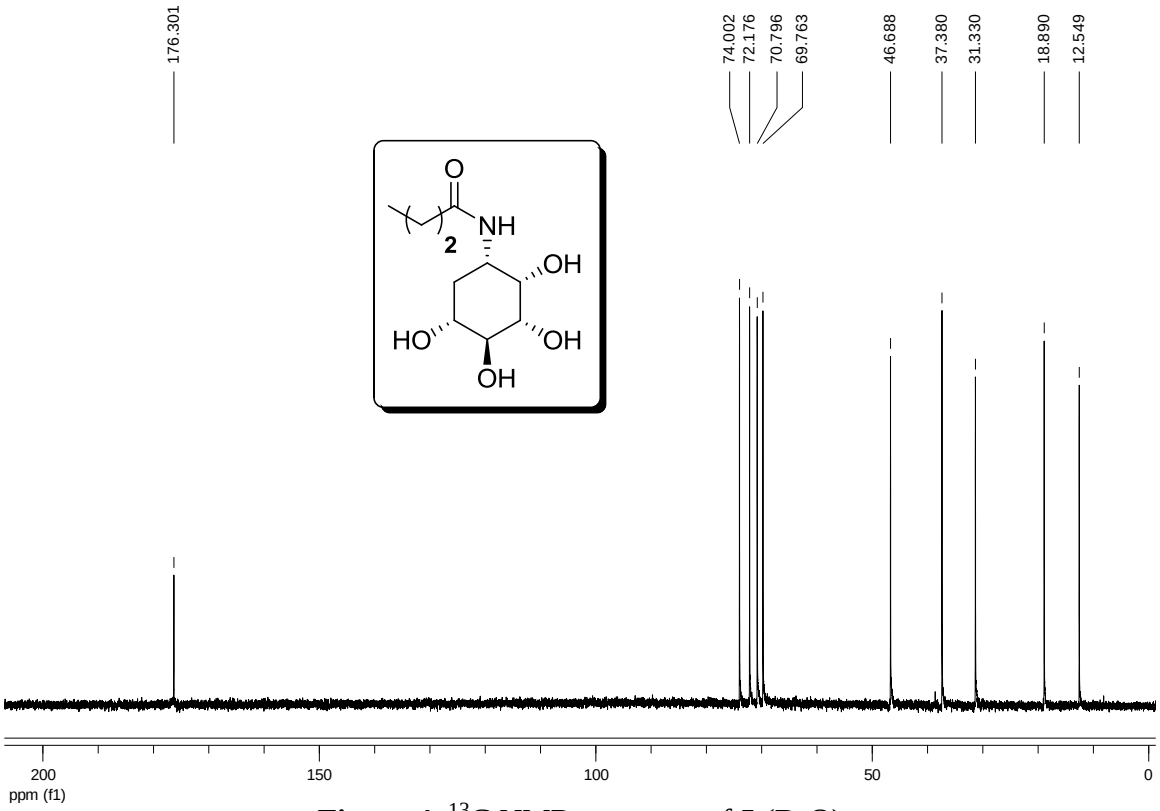

Figure 4. ^{13}C NMR spectrum of **5** (D_2O)

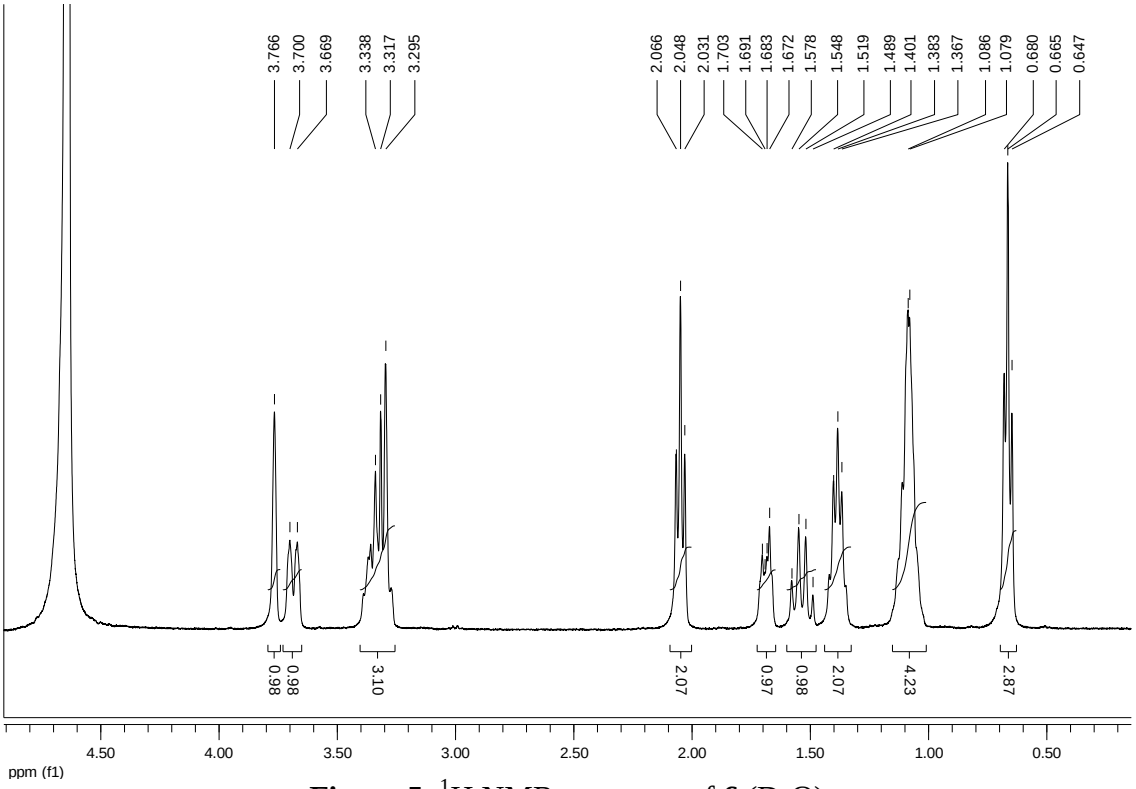

Figure 5. ^{1}H NMR spectrum of **6** (D_2O)

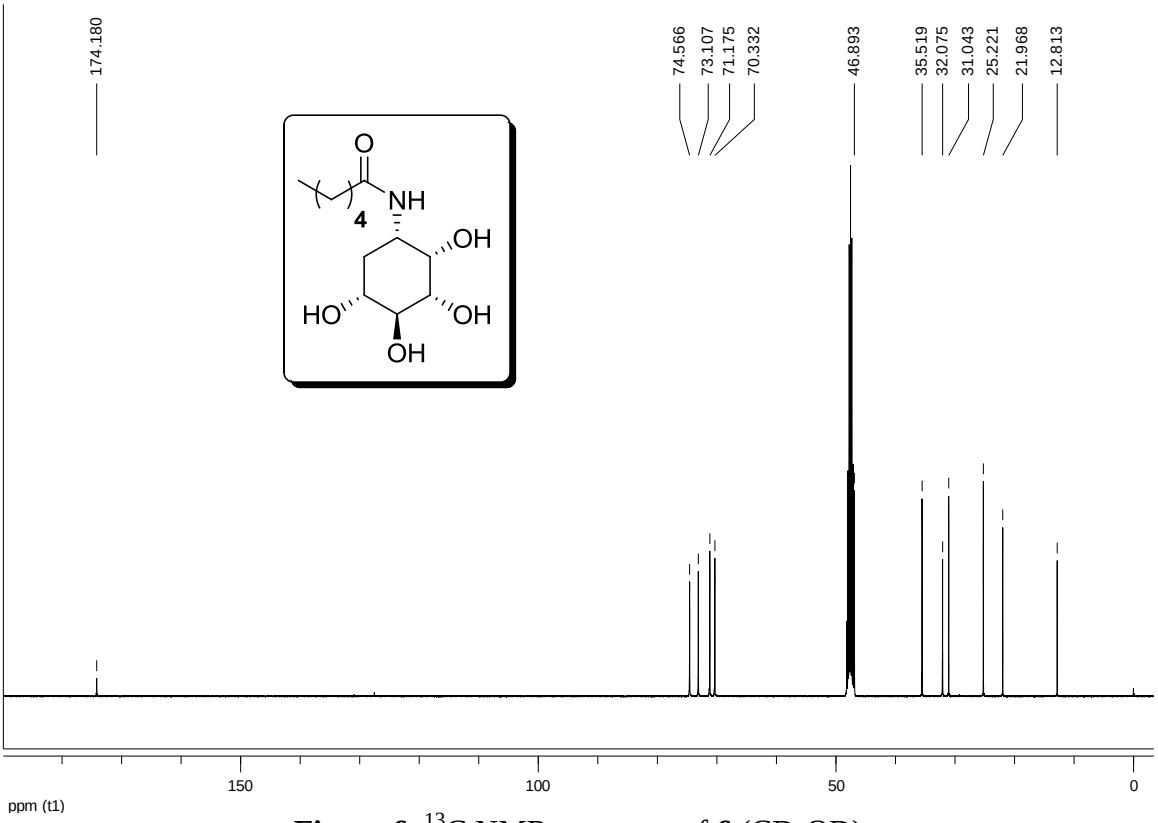

Figure 6. ^{13}C NMR spectrum of **6** (CD_3OD)

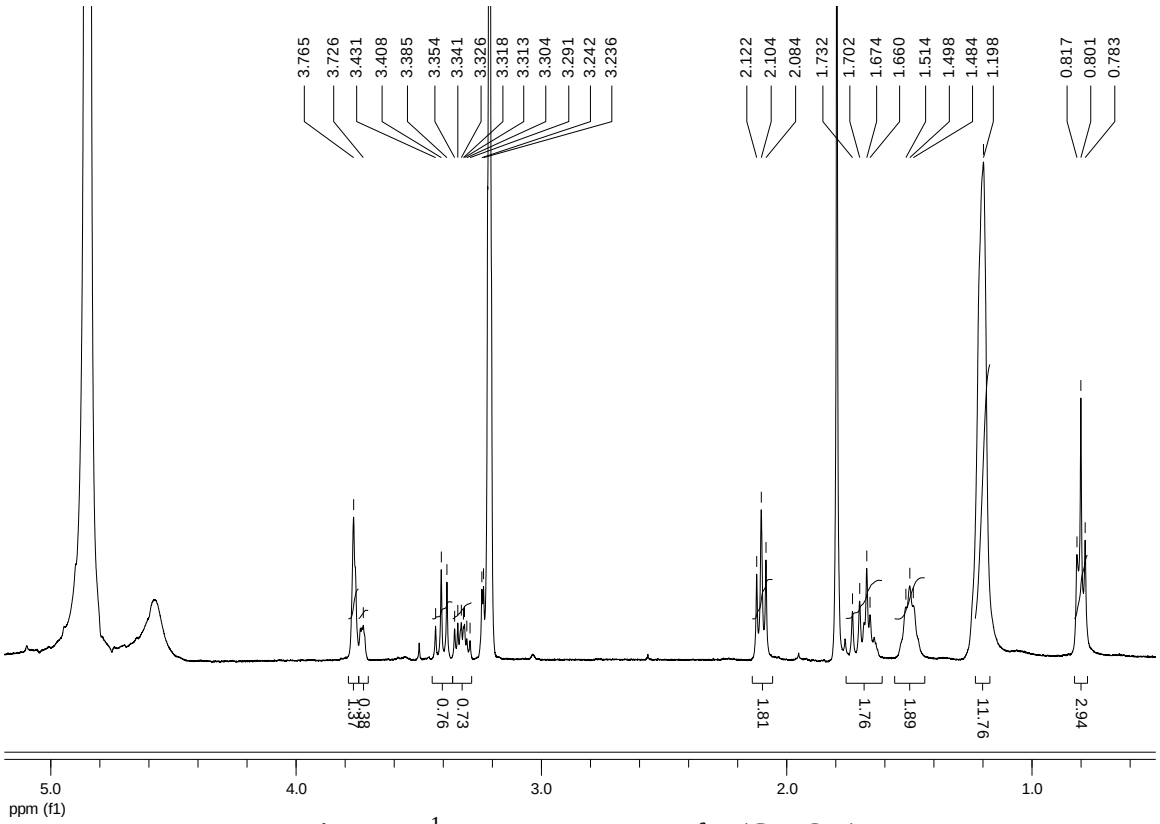

Figure 7. ^{1}H NMR spectrum of **7** (CD_3OD)

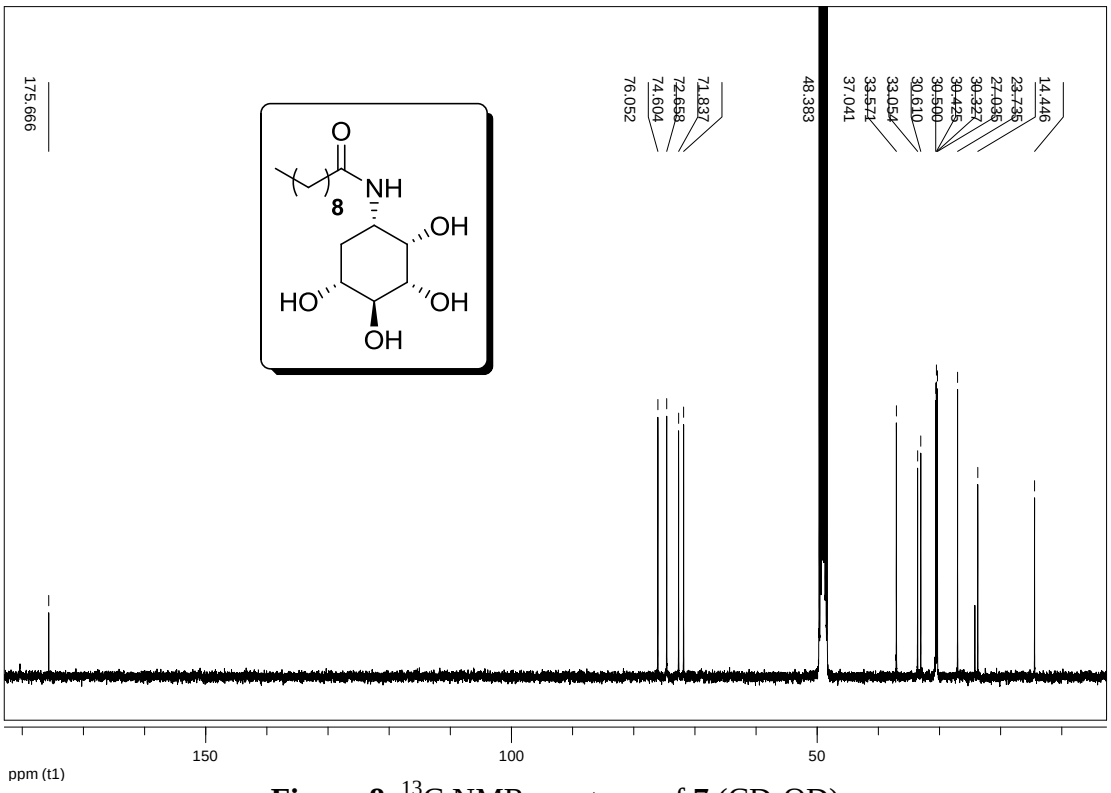

Figure 8. ^{13}C NMR spectrum of **7** (CD_3OD)

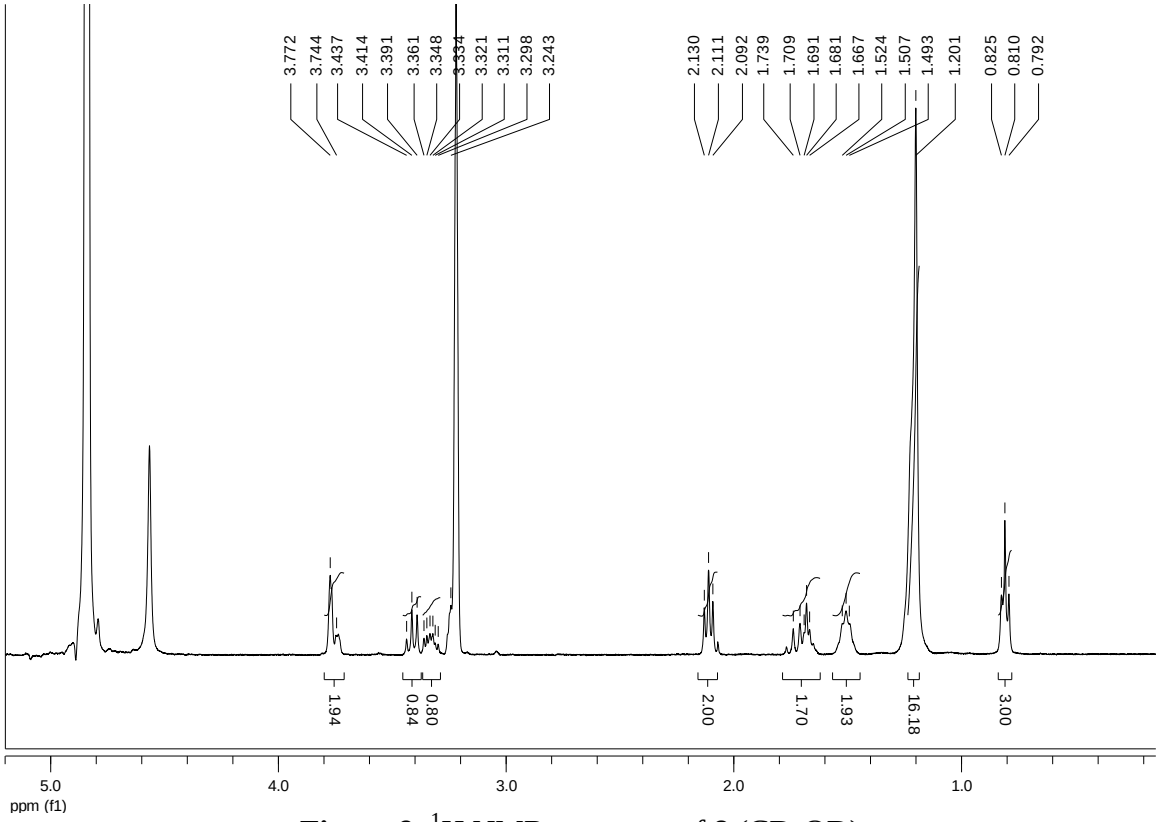

Figure 9. ^{1}H NMR spectrum of **8** (CD_3OD)

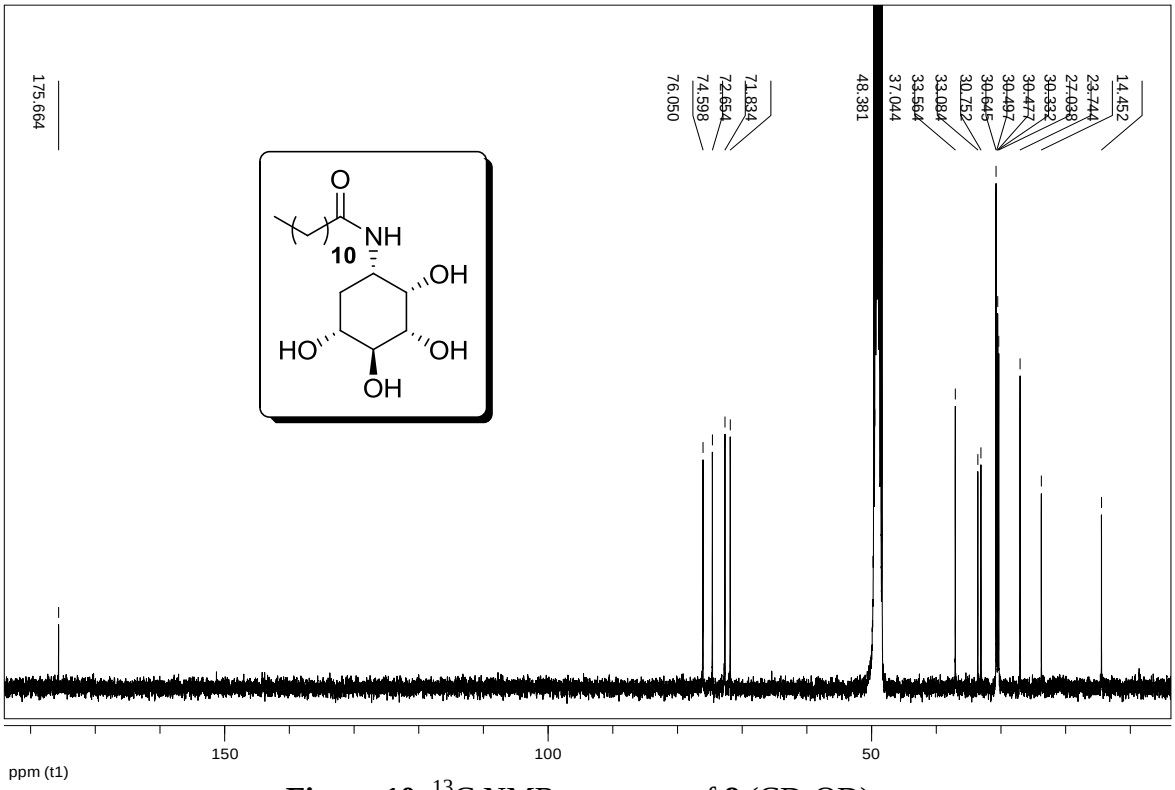

Figure 10. ^{13}C NMR spectrum of **8** (CD_3OD)

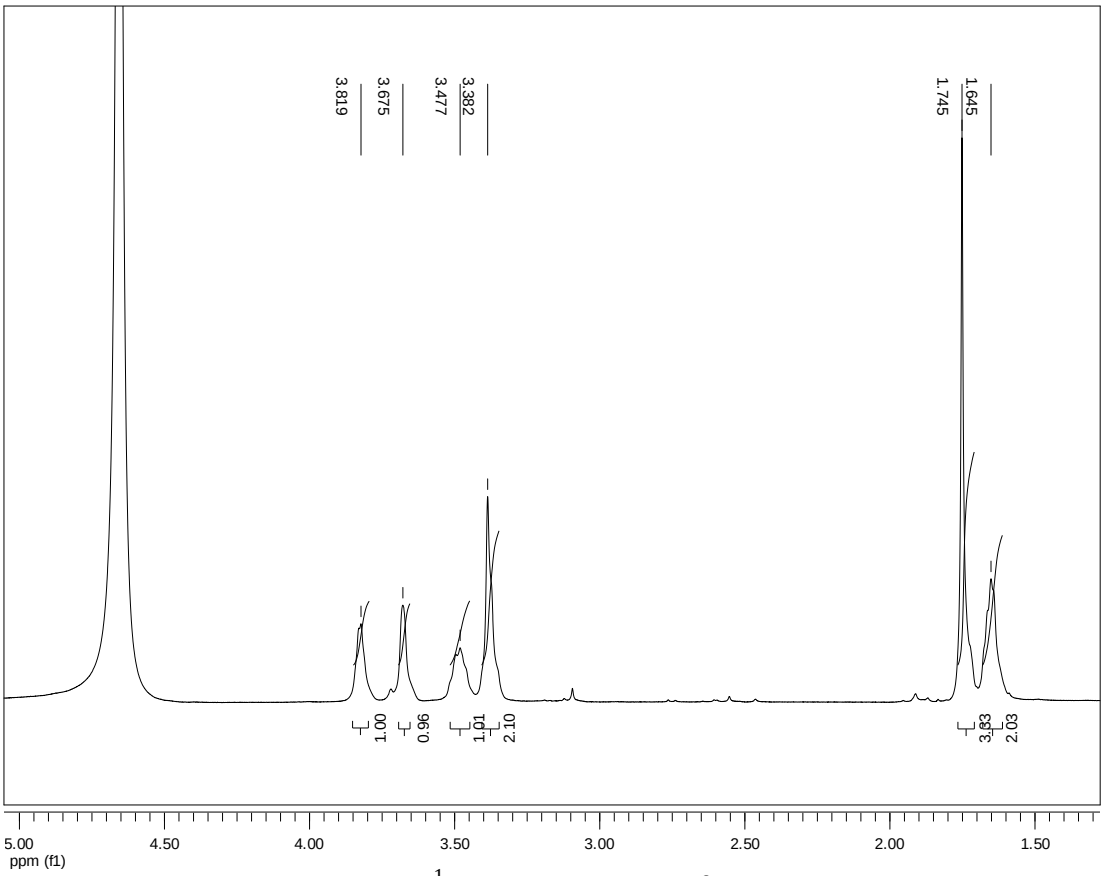

Figure 11. ^{1}H NMR spectrum of **9** (D_2O)

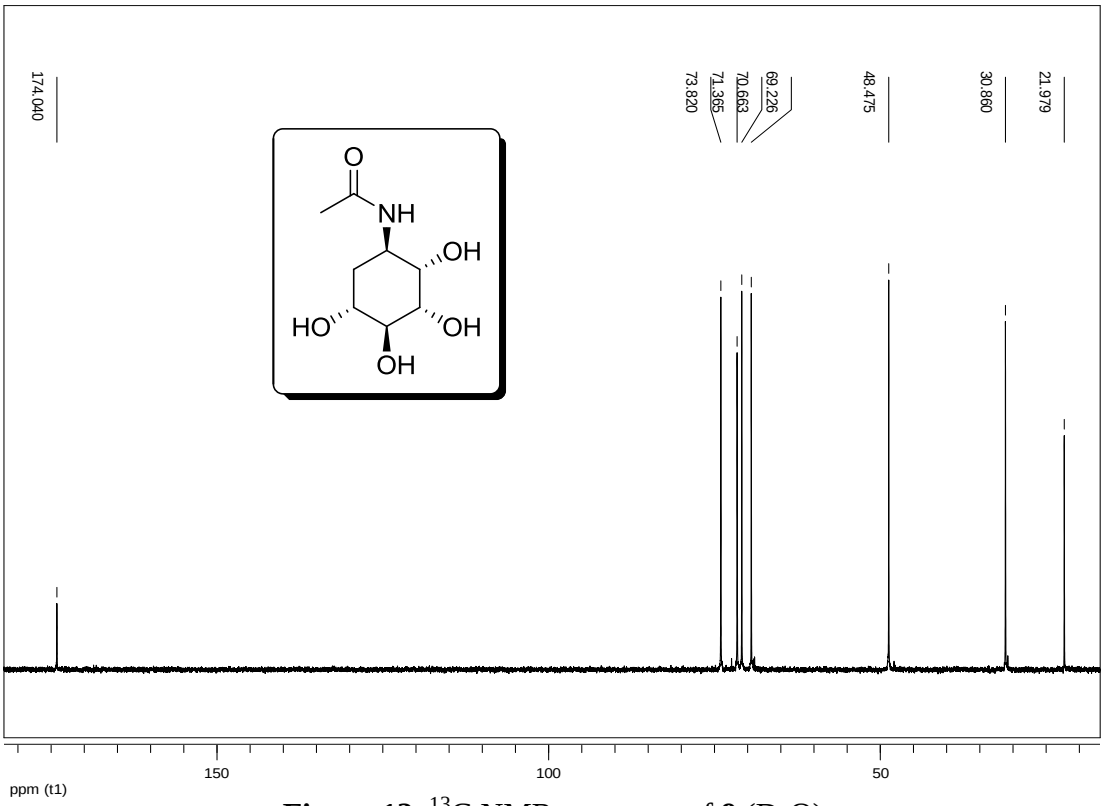

Figure 12. ^{13}C NMR spectrum of **9** (D_2O)

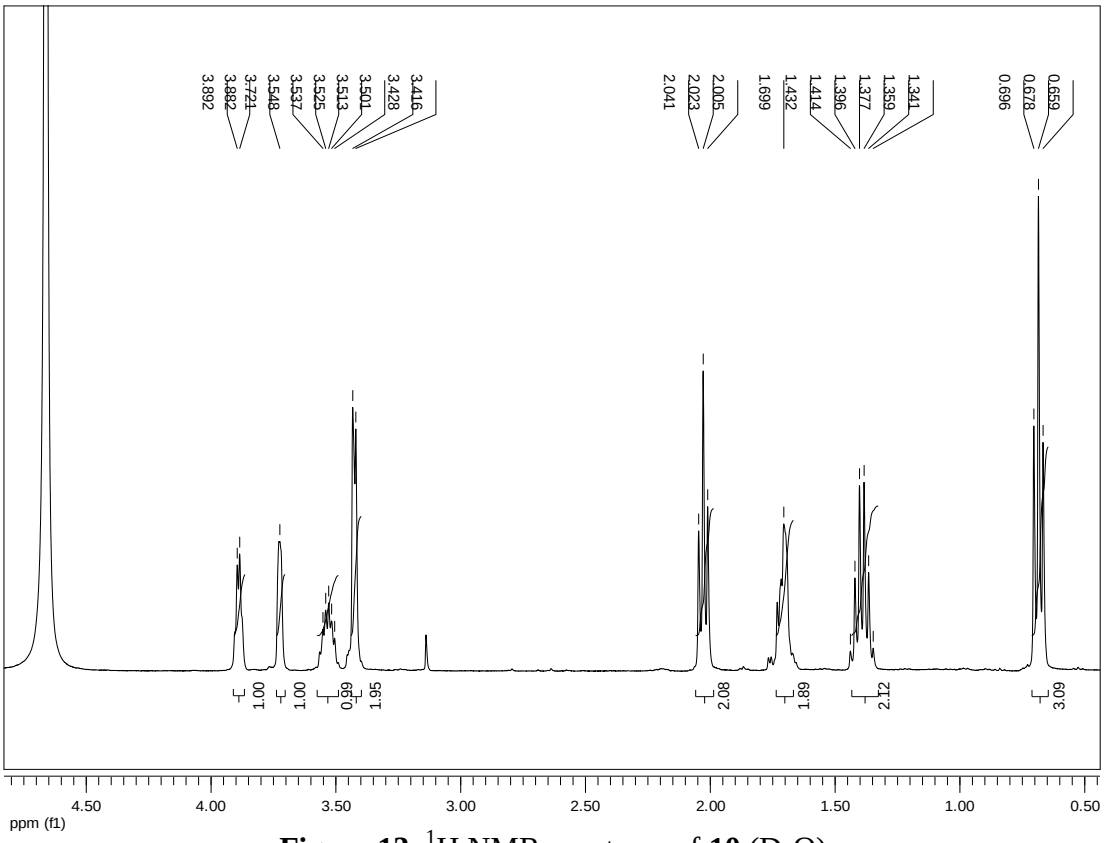

Figure 13. ^{1}H NMR spectrum of **10** (D_2O)

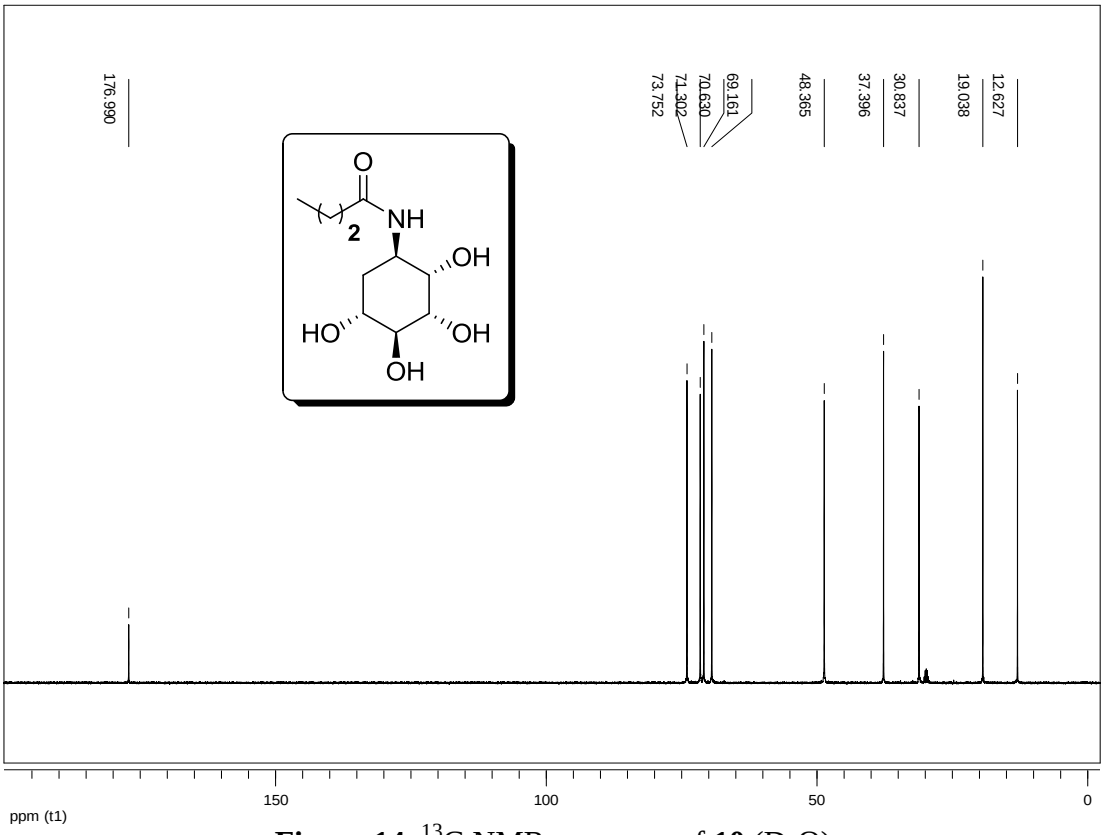

Figure 14. ^{13}C NMR spectrum of **10** (D_2O)

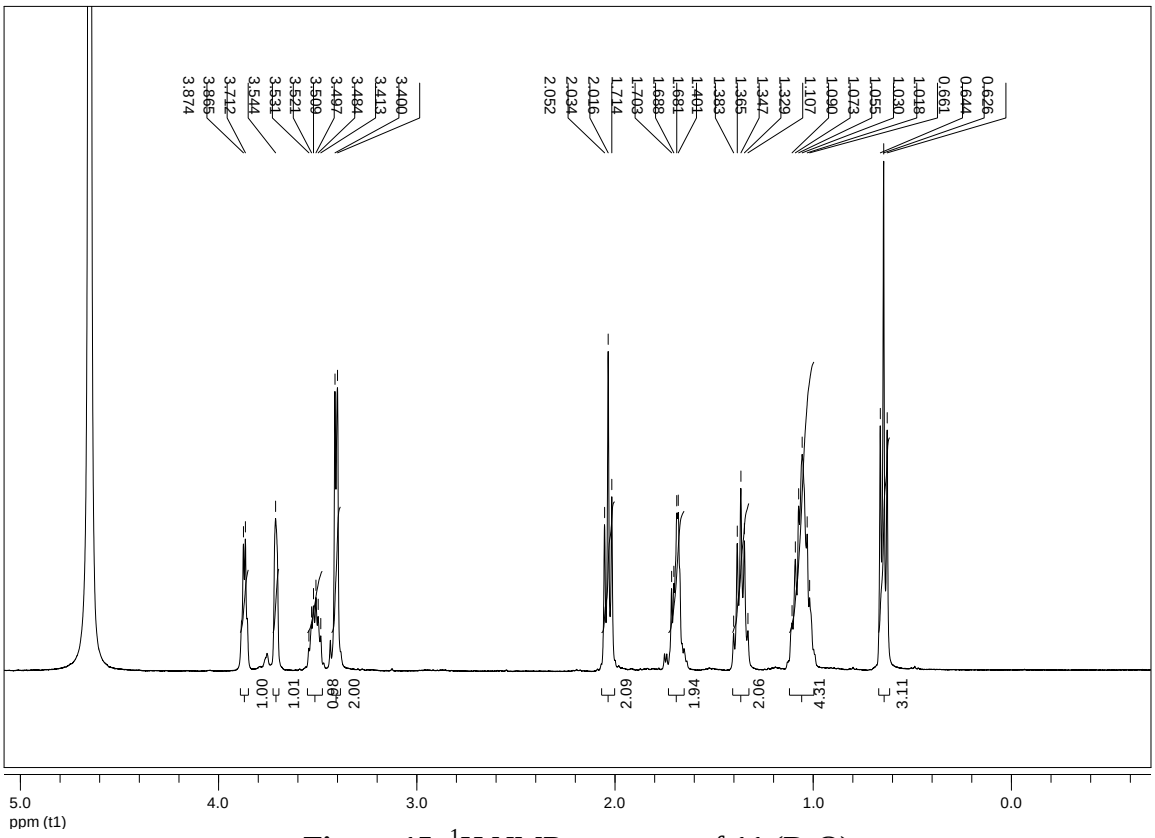

Figure 15. ^{1}H NMR spectrum of **11** (D_2O)

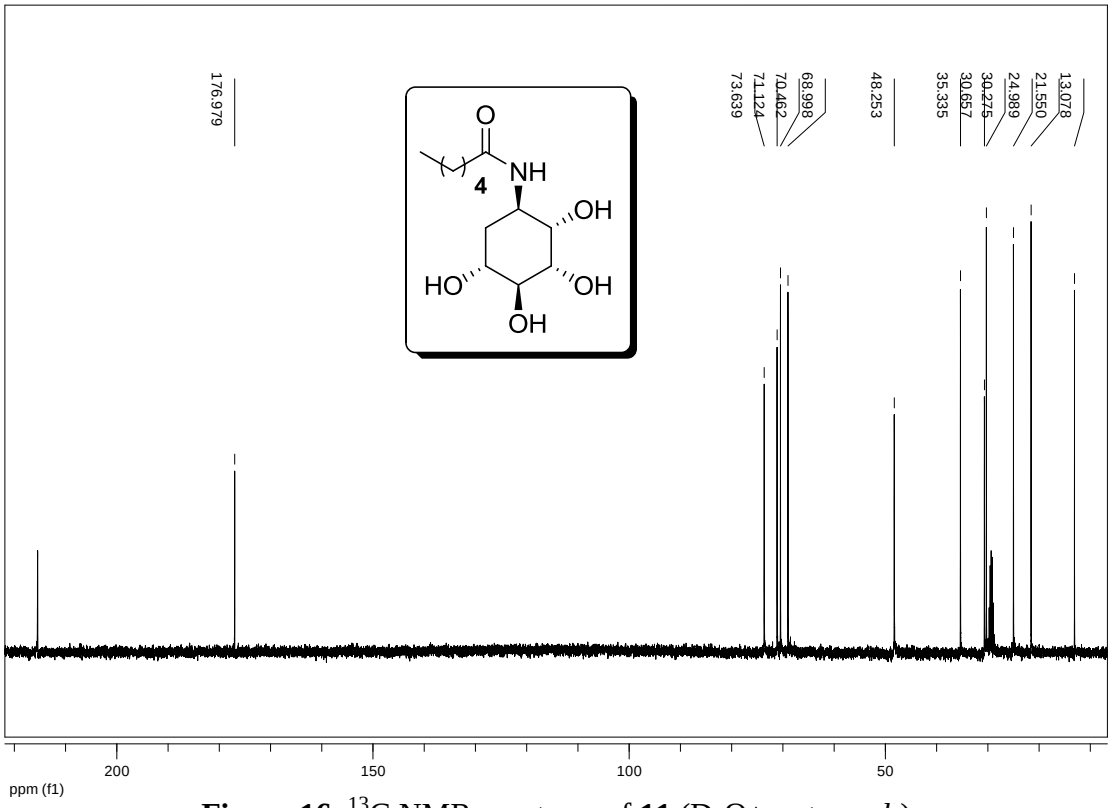

Figure 16. ^{13}C NMR spectrum of **11** (D_2O+acetone-d_6)

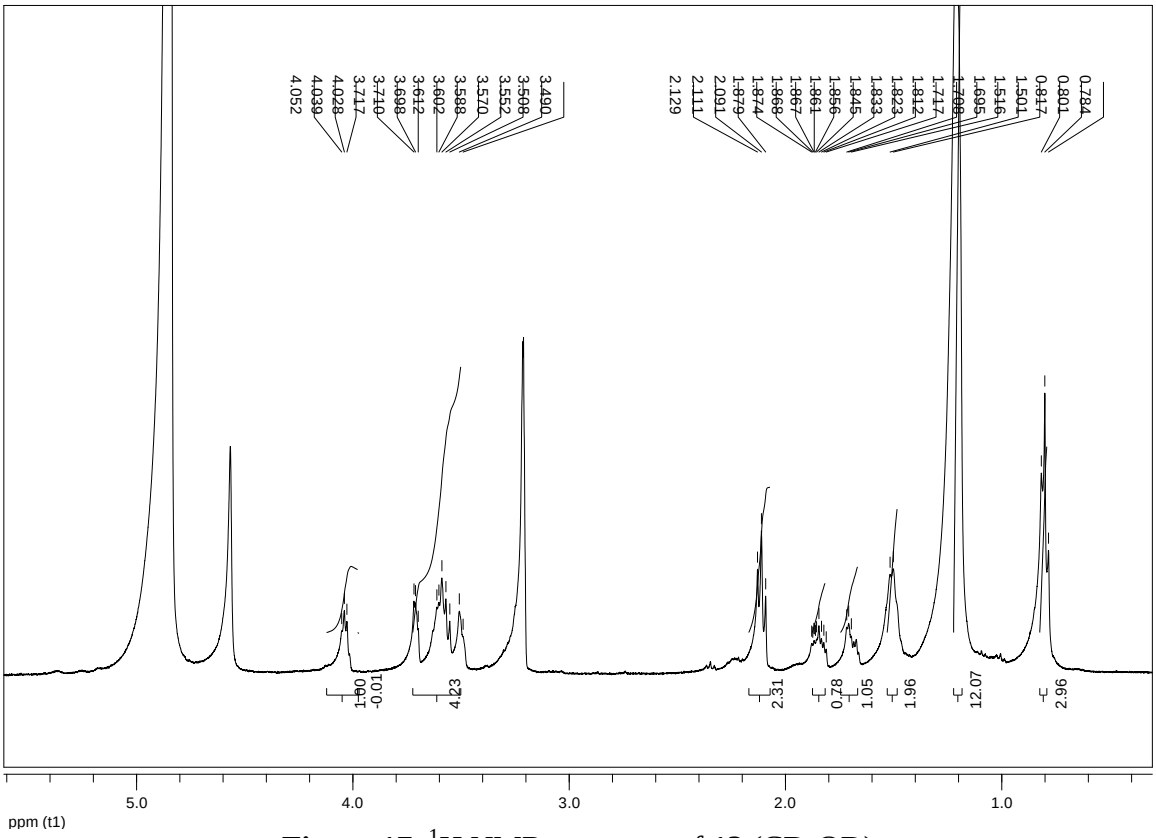

Figure 17. ^{1}H NMR spectrum of **12** (CD_3OD)

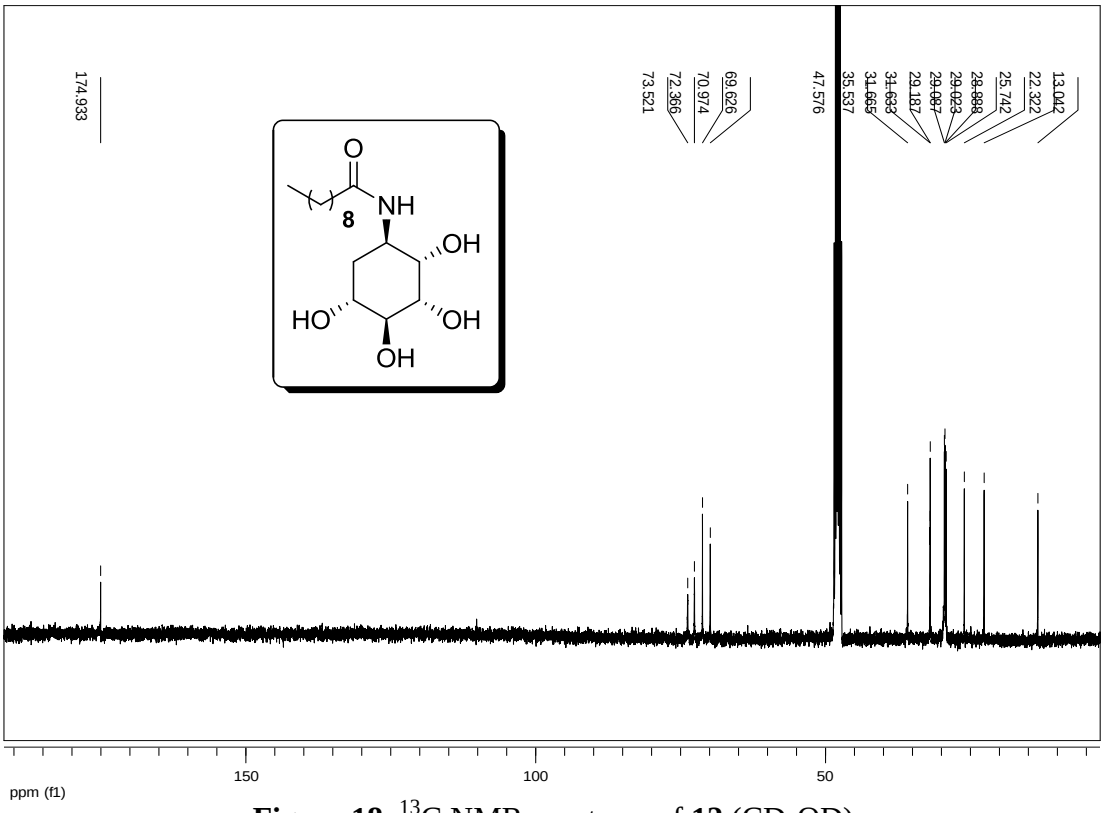

Figure 18. ^{13}C NMR spectrum of **12** (CD_3OD)

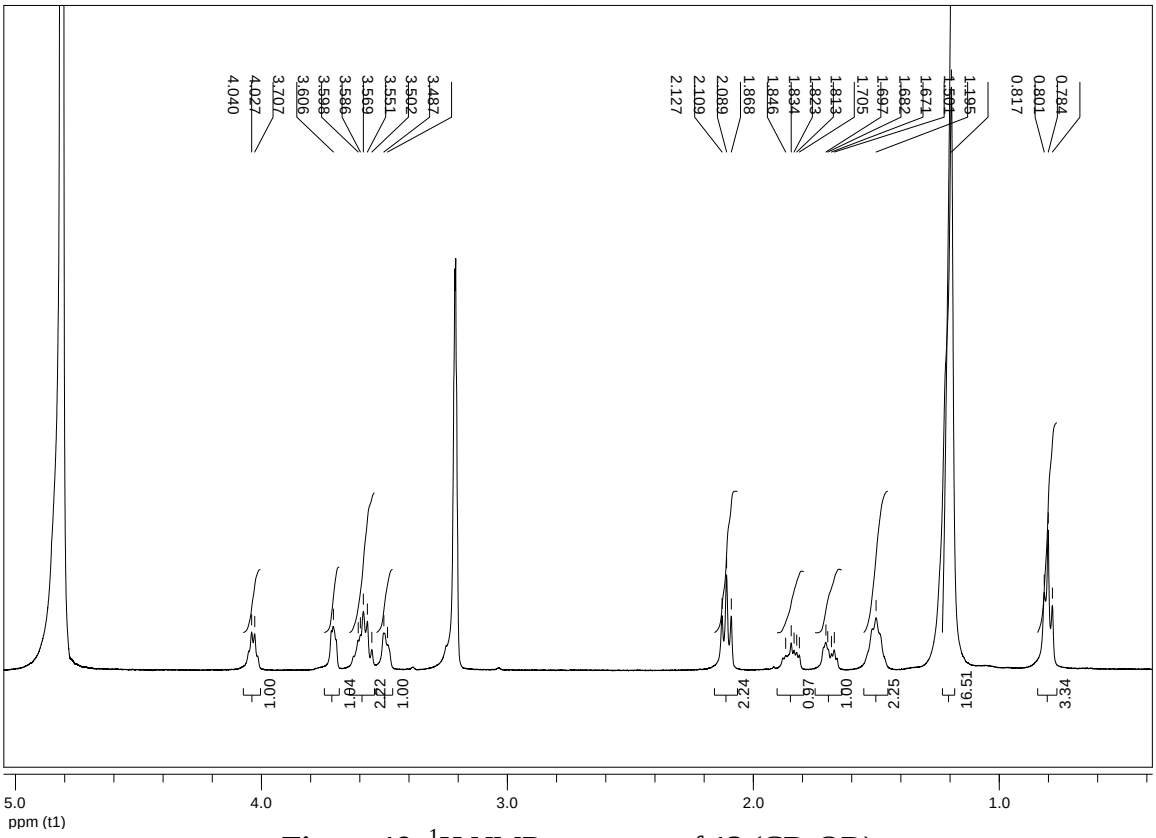

Figure 19. ^{1}H NMR spectrum of **13** (CD_3OD)

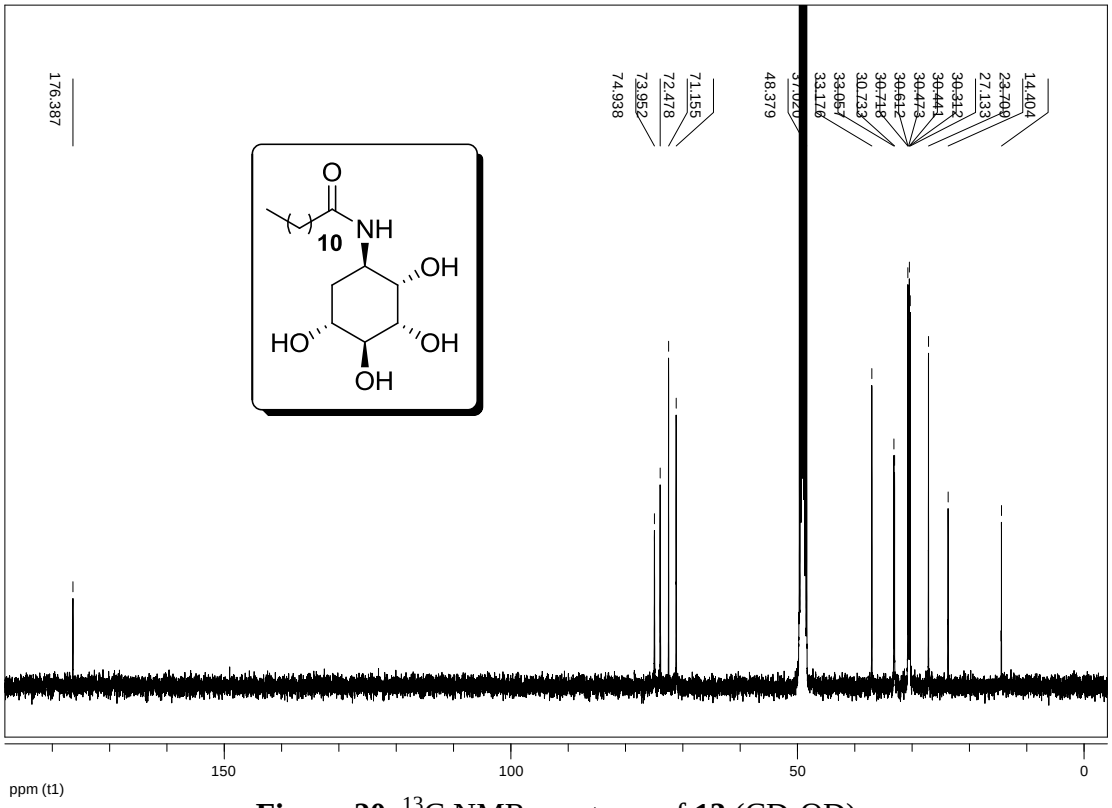

Figure 20. ^{13}C NMR spectrum of **13** (CD_3OD)

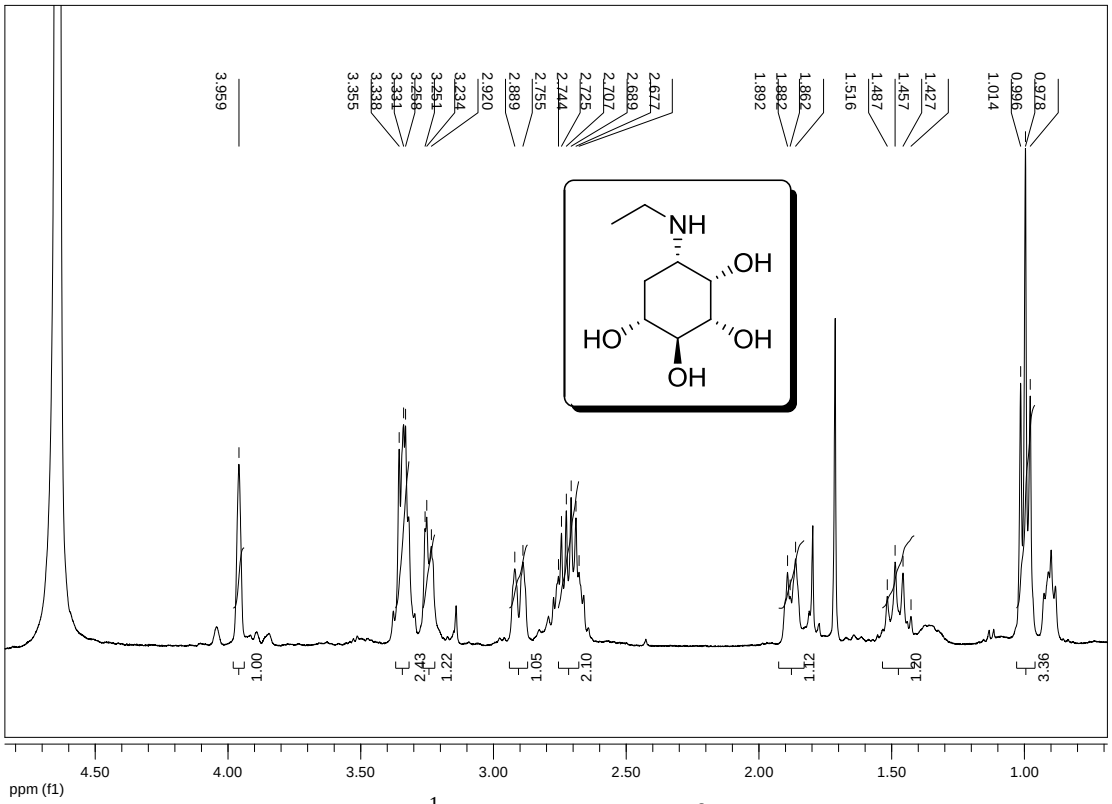

Figure 21. ^{1}H NMR spectrum of **29** (D_2O)

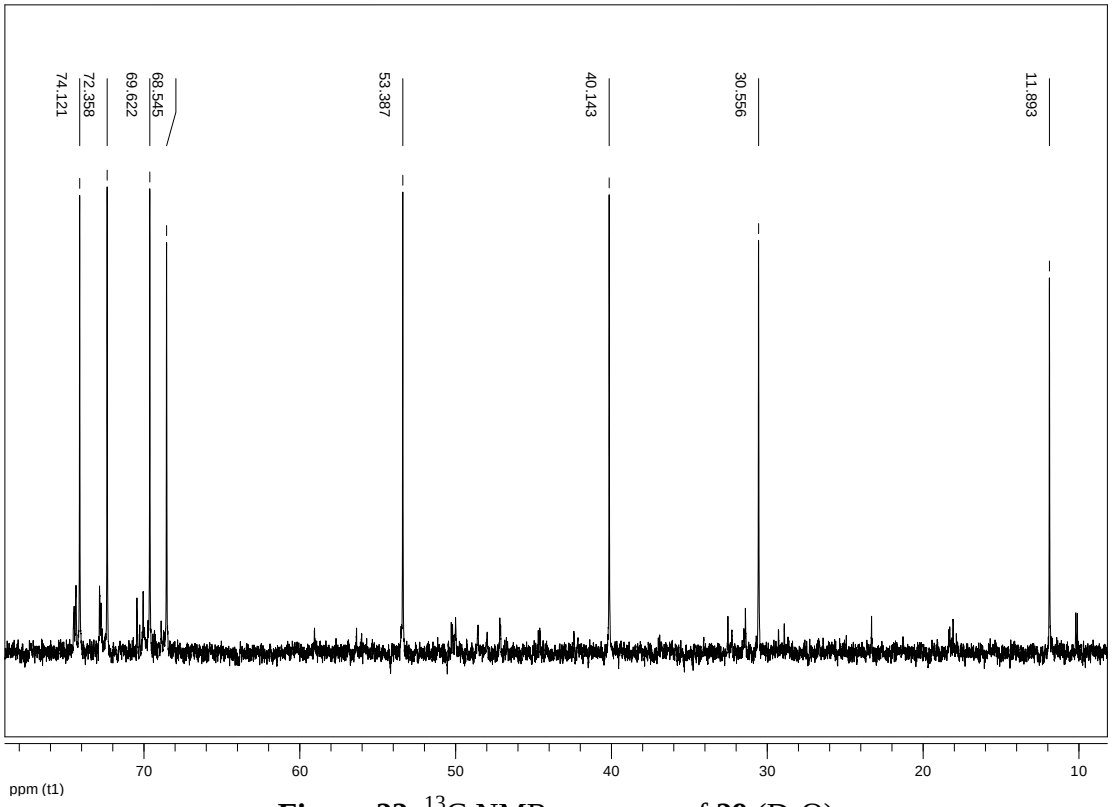

Figure 22. ^{13}C NMR spectrum of **29** (D_2O)

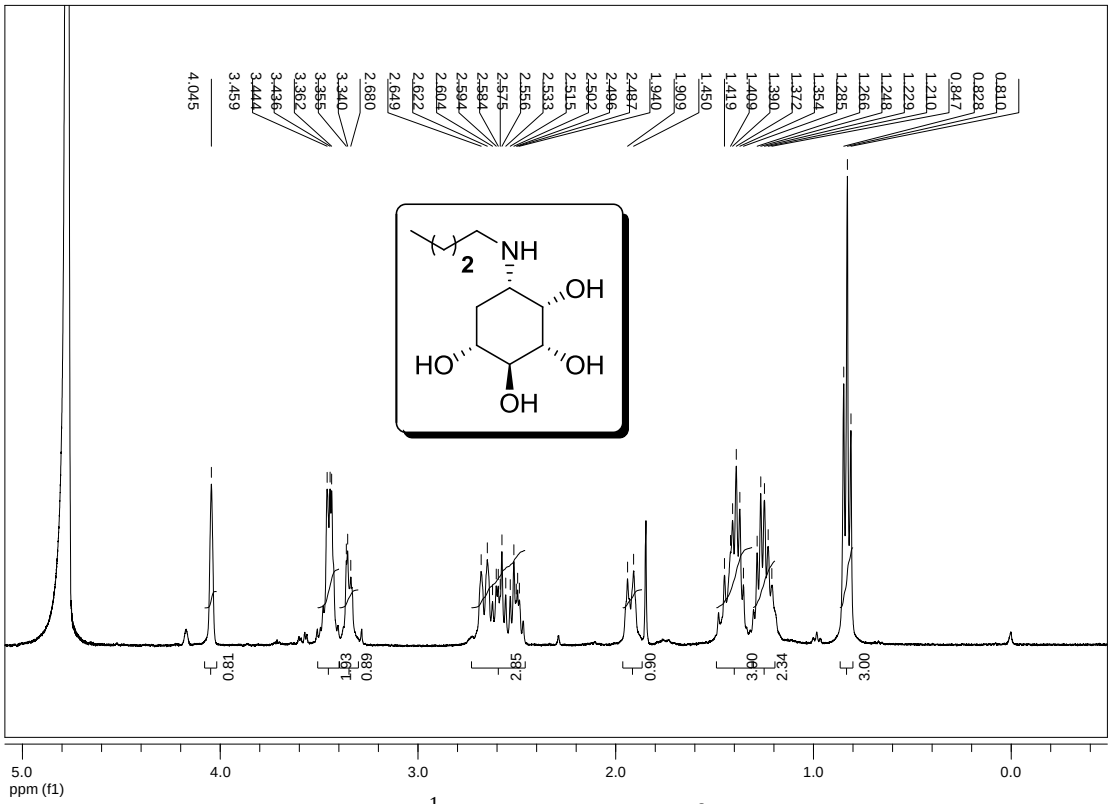

Figure 23. ^{1}H NMR spectrum of **30** (D_2O)

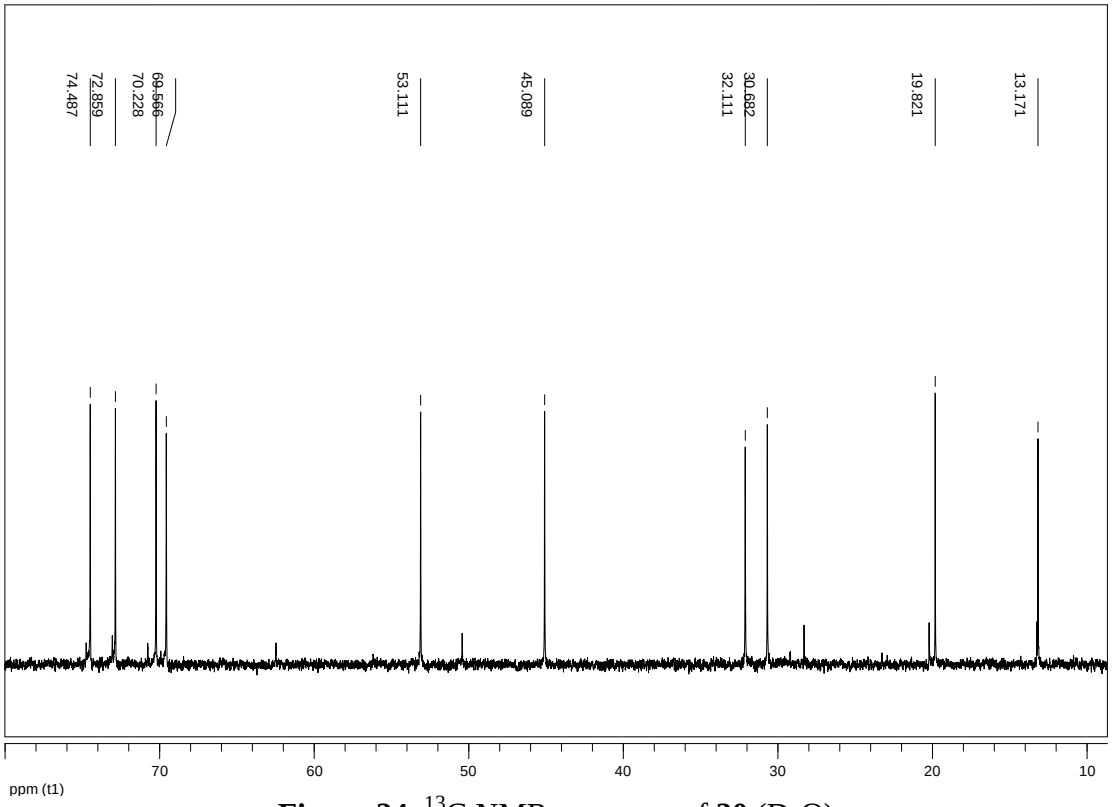

Figure 24. ^{13}C NMR spectrum of **30** (D_2O)

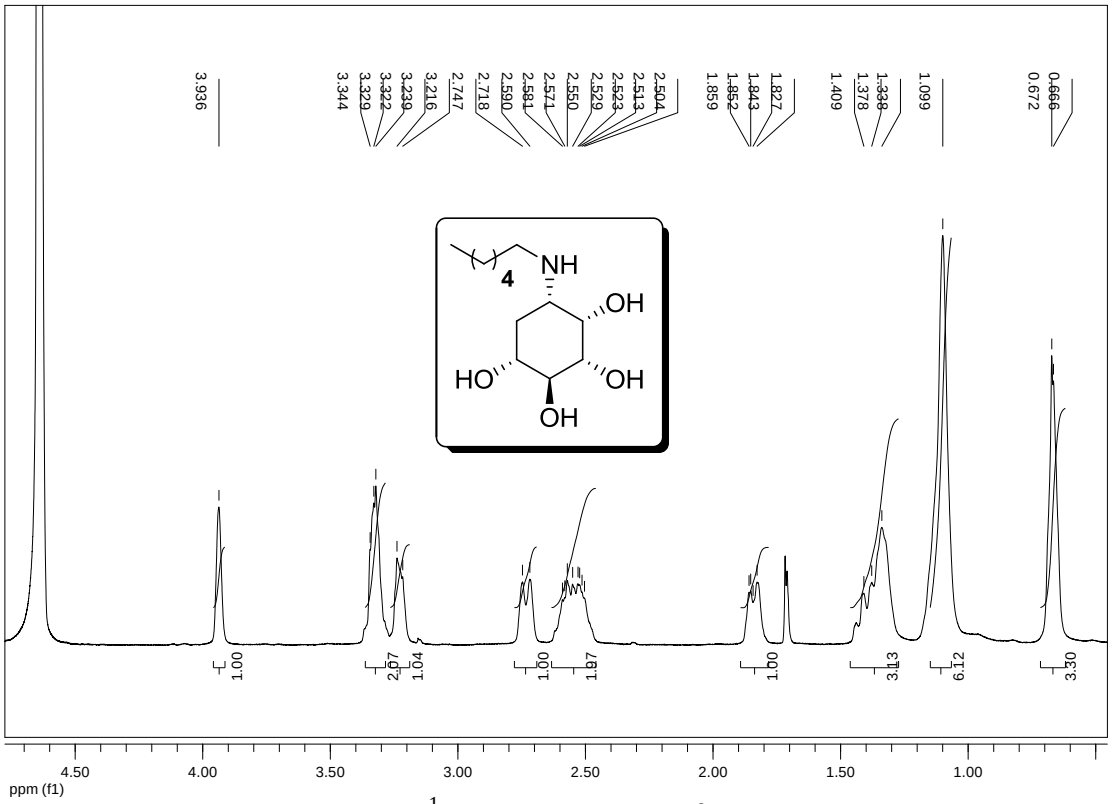

Figure 25. ^{1}H NMR spectrum of **31** (D_2O)

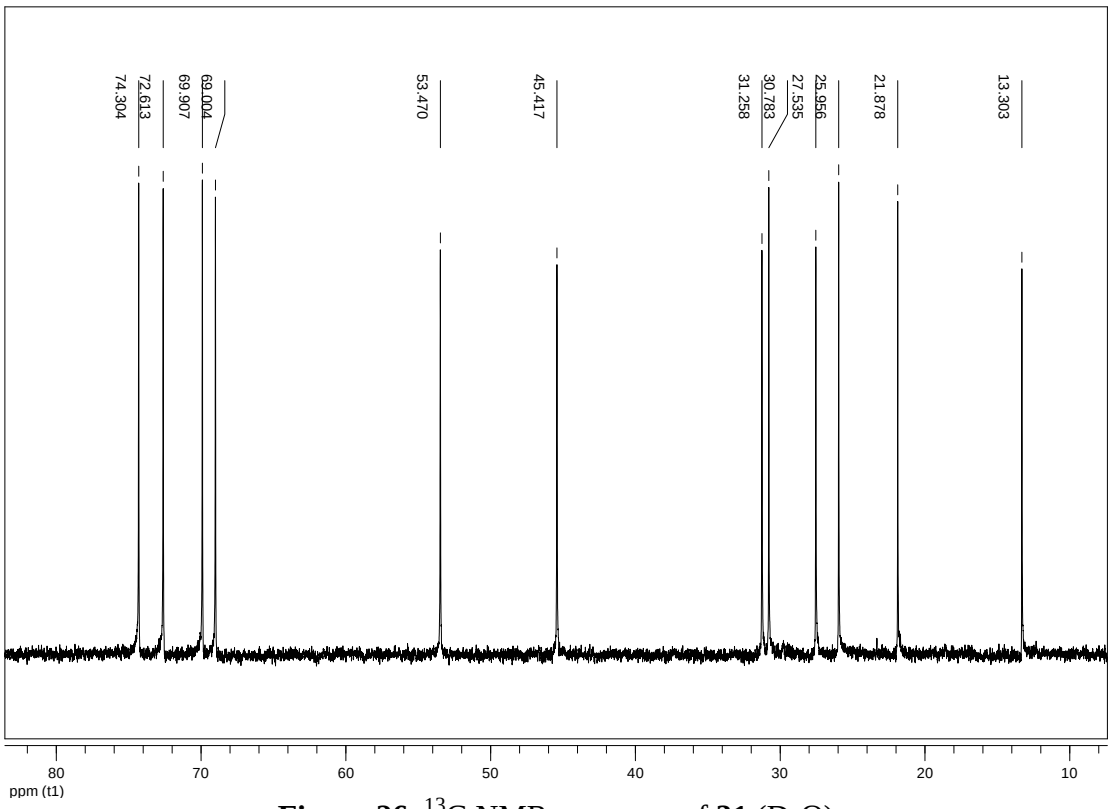

Figure 26. ^{13}C NMR spectrum of **31** (D_2O)

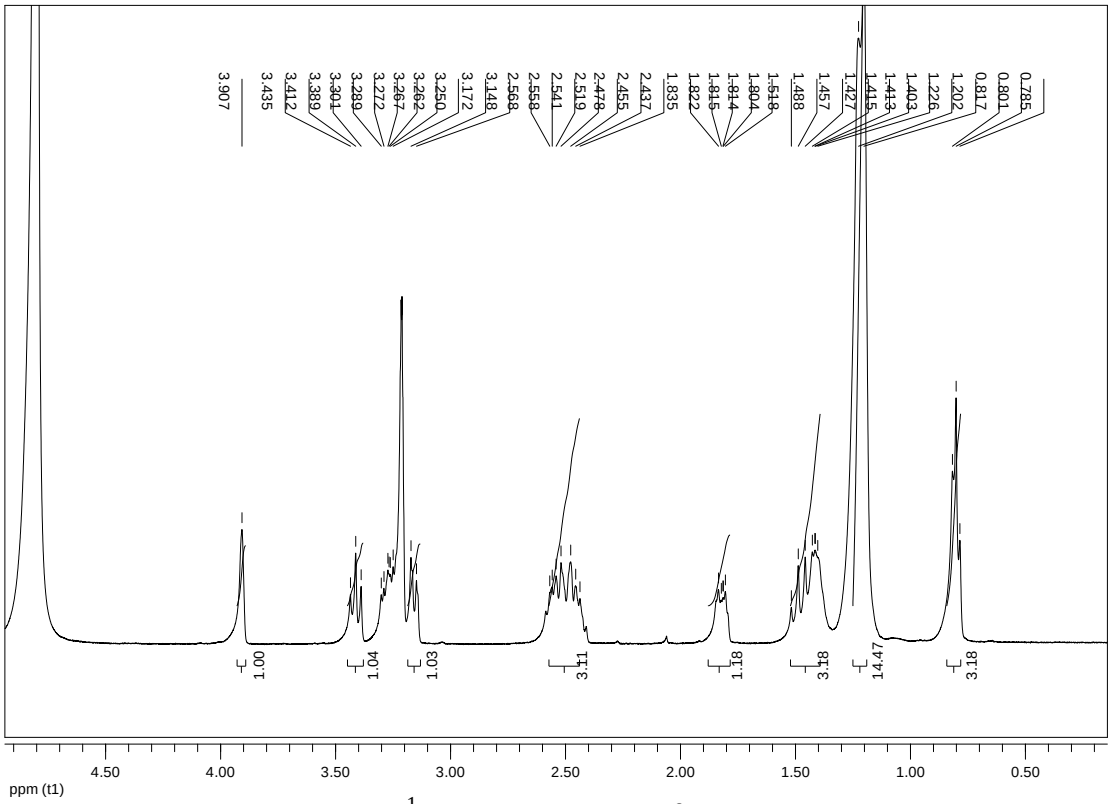

Figure 27. ^{1}H NMR spectrum of **32** (CD_3OD)

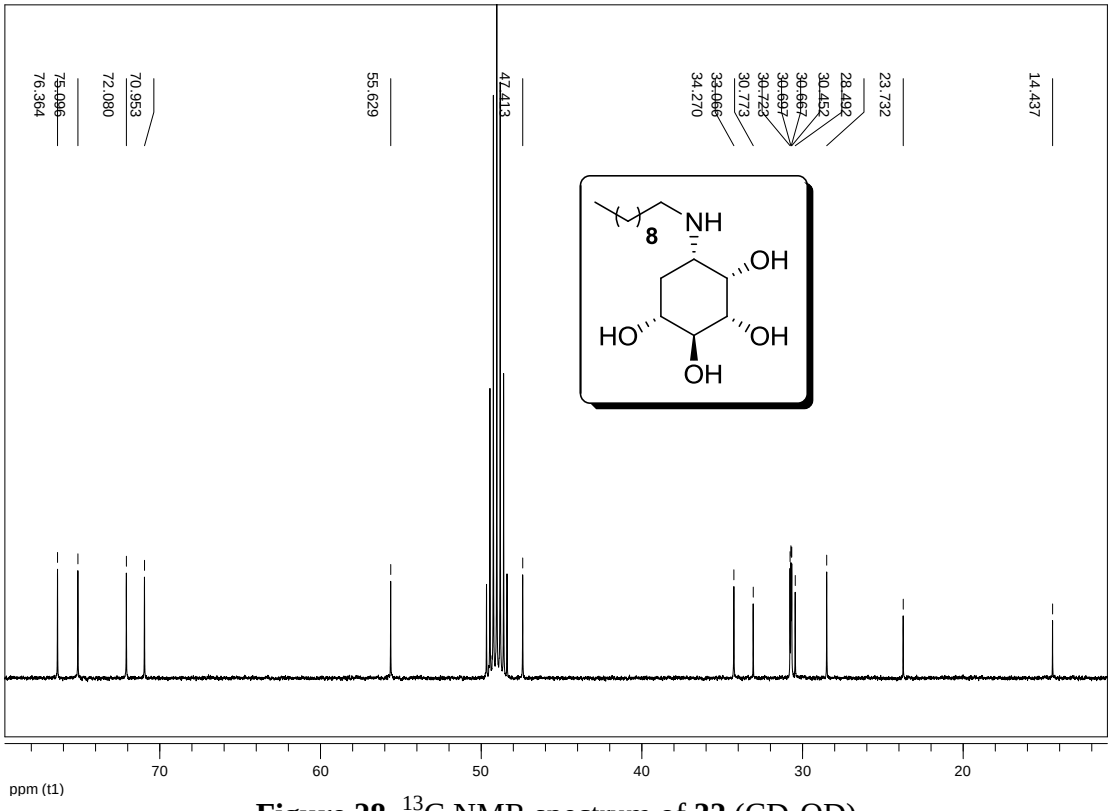

Figure 28. ^{13}C NMR spectrum of **32** (CD_3OD)

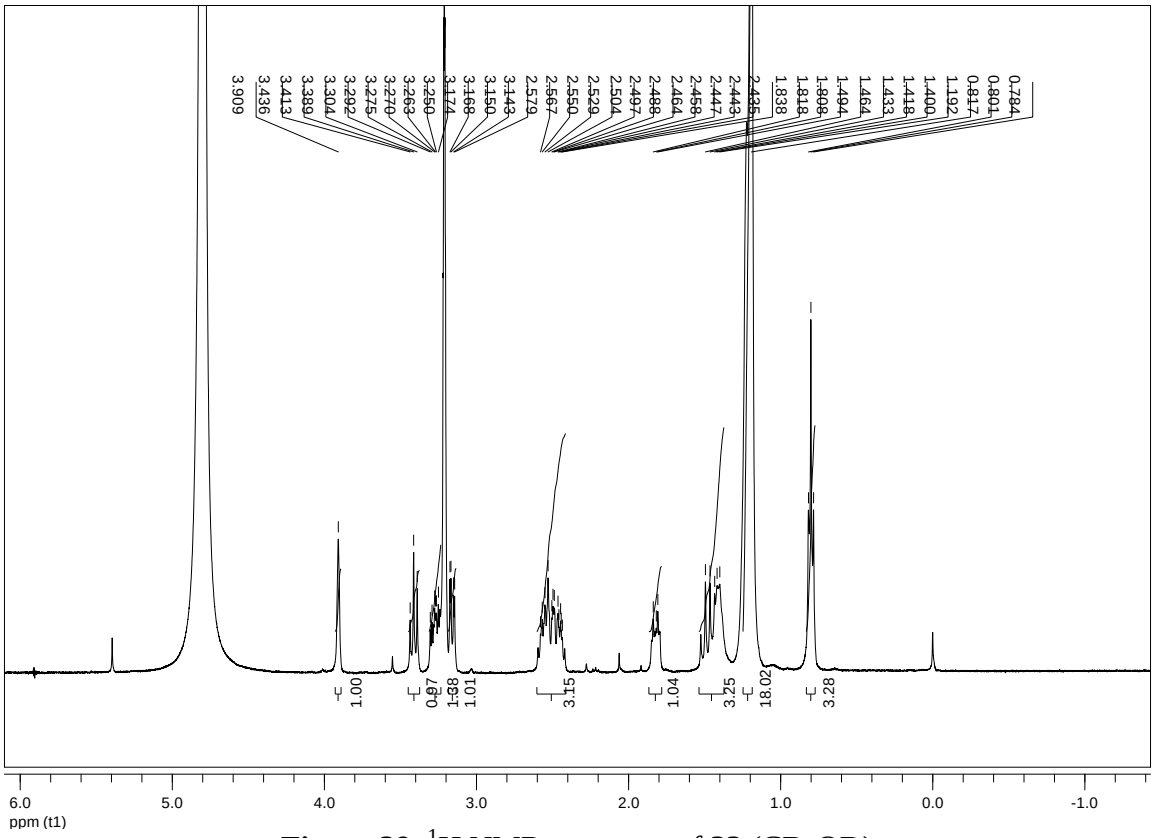

Figure 29. ^{1}H NMR spectrum of **33** (CD_3OD)

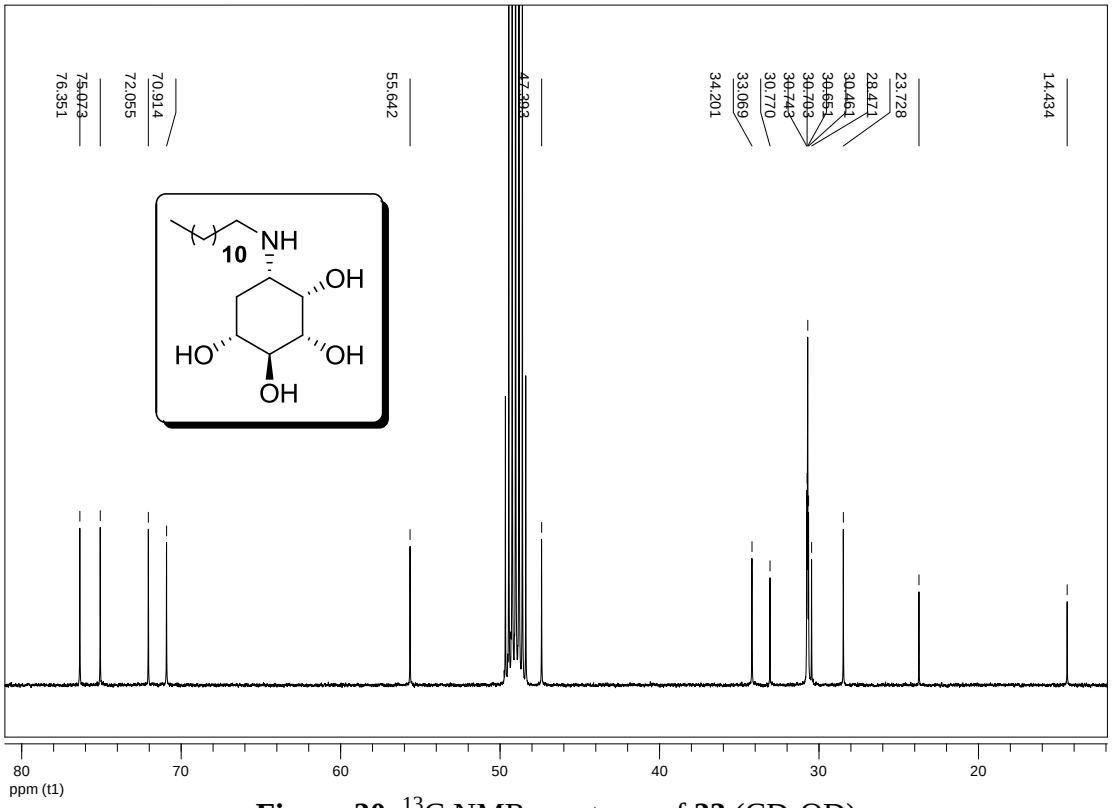

Figure 30. ^{13}C NMR spectrum of **33** (CD_3OD)

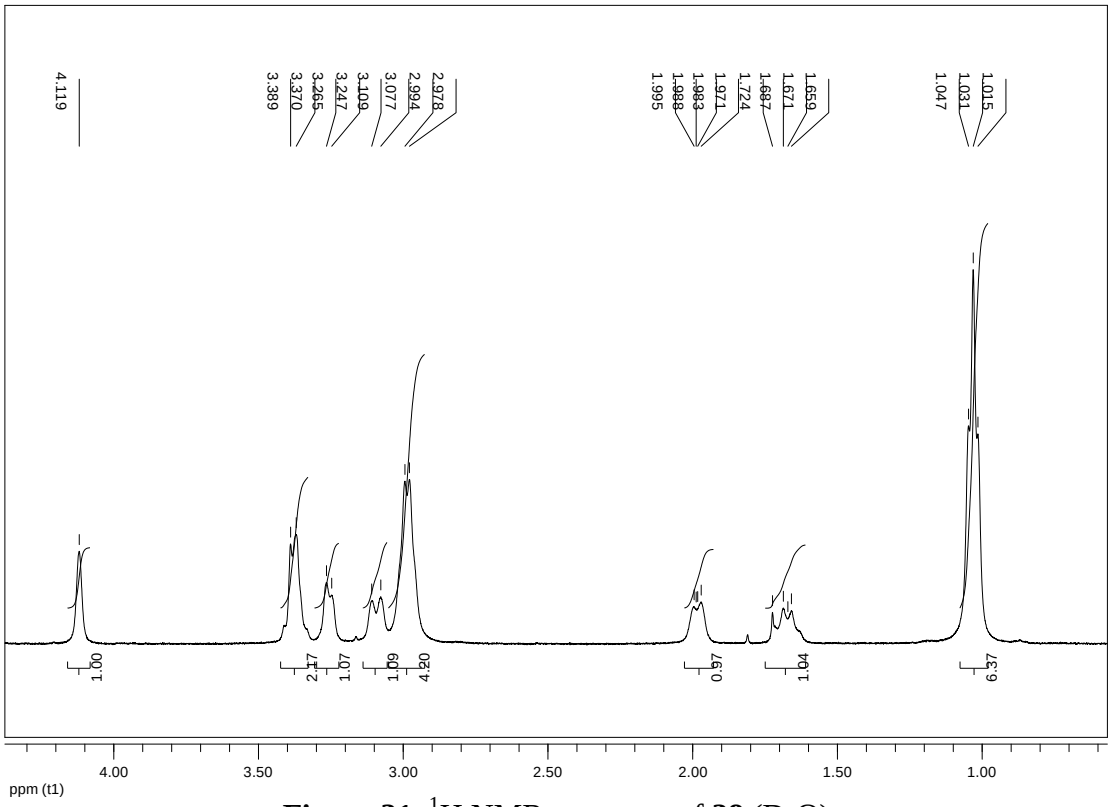

Figure 31. ^{1}H NMR spectrum of **38** (D_2O)

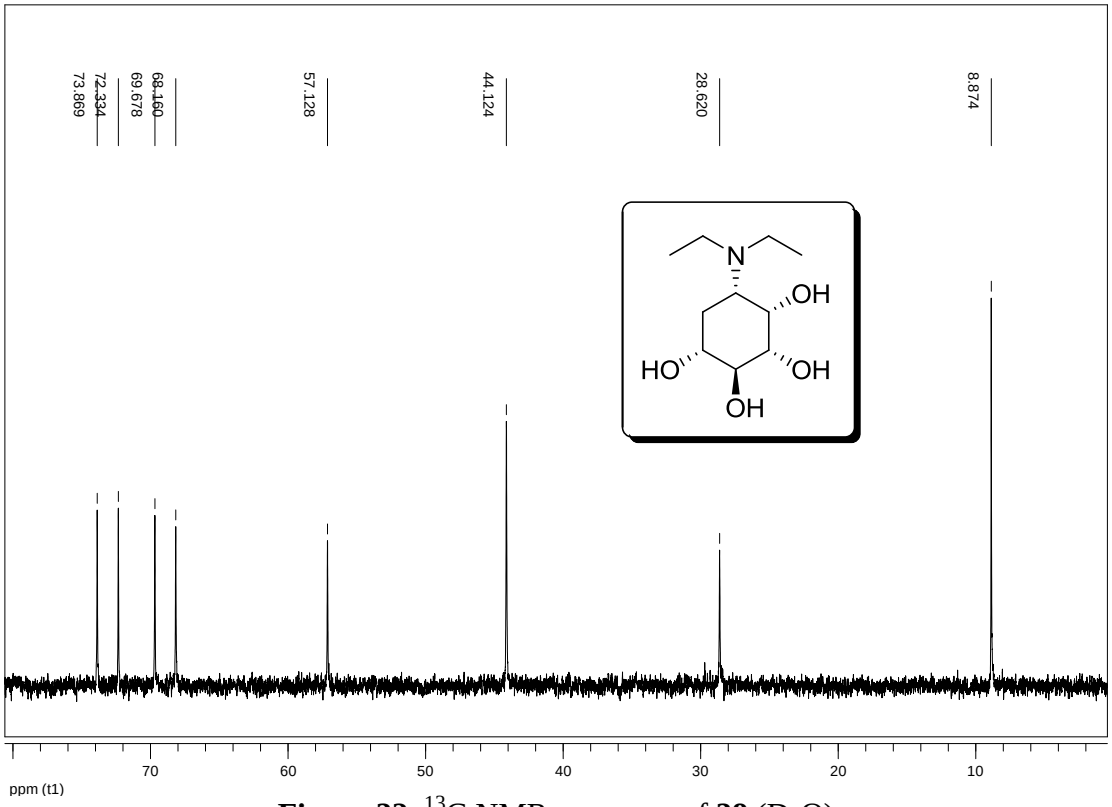

Figure 32. ^{13}C NMR spectrum of **38** (D_2O)

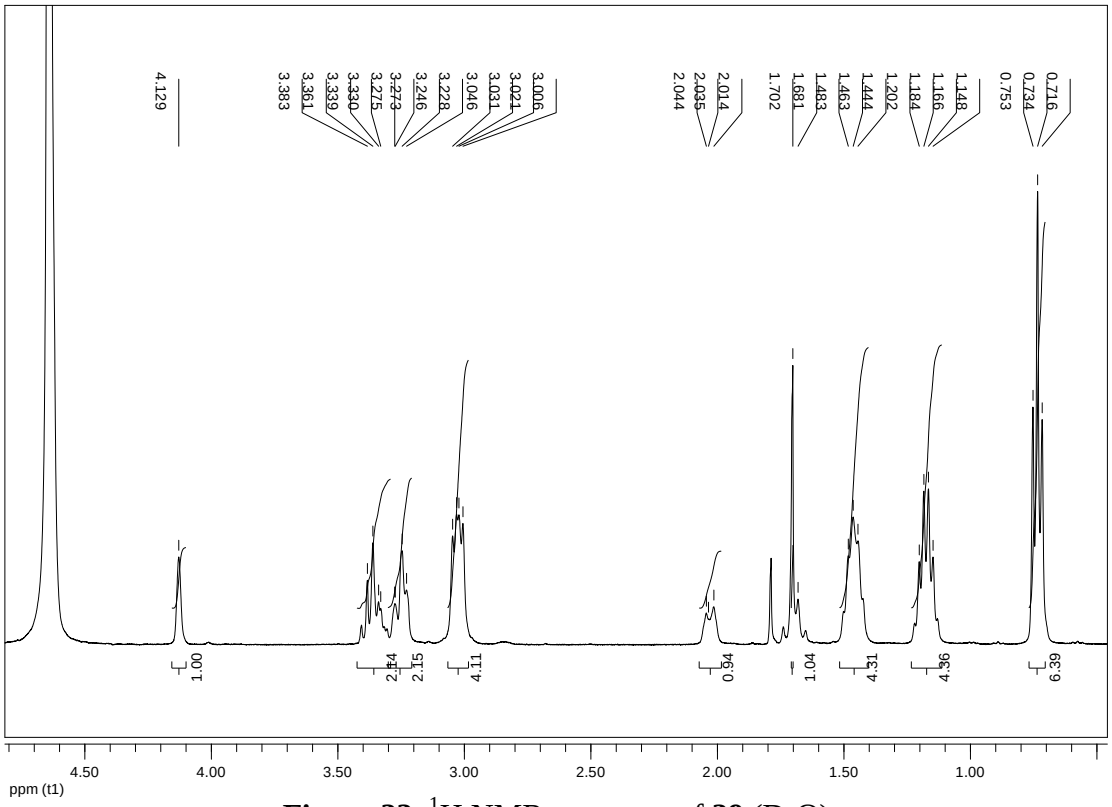

Figure 33. ^{1}H NMR spectrum of **39** (D_2O)

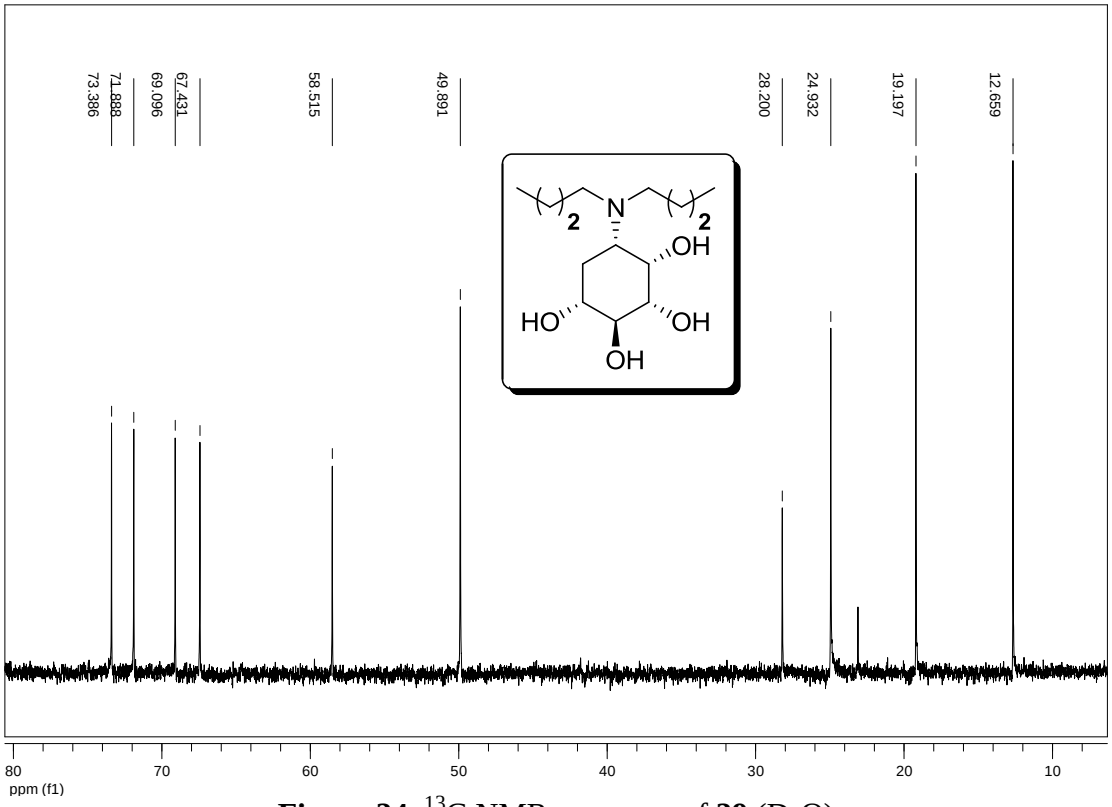

Figure 34. ^{13}C NMR spectrum of **39** (D_2O)

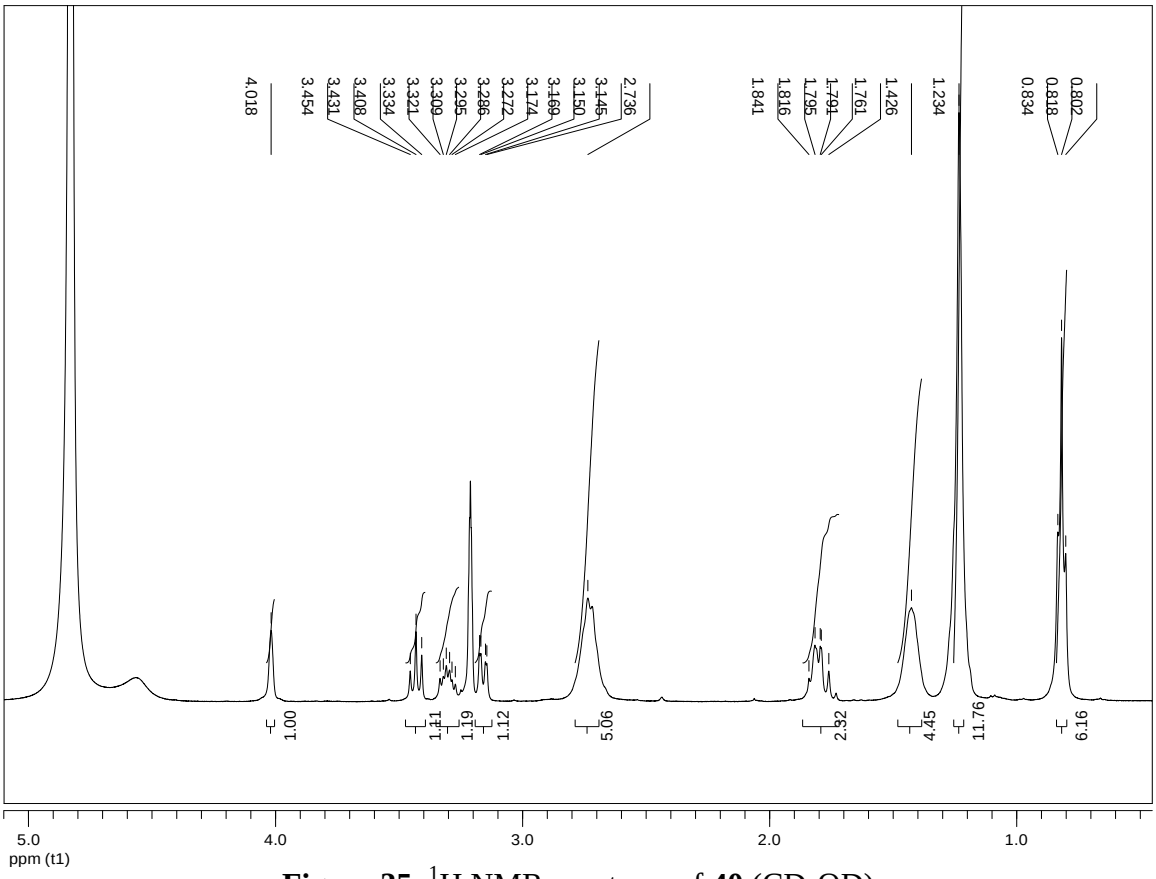

Figure 35. ^{1}H NMR spectrum of **40** (CD_3OD)

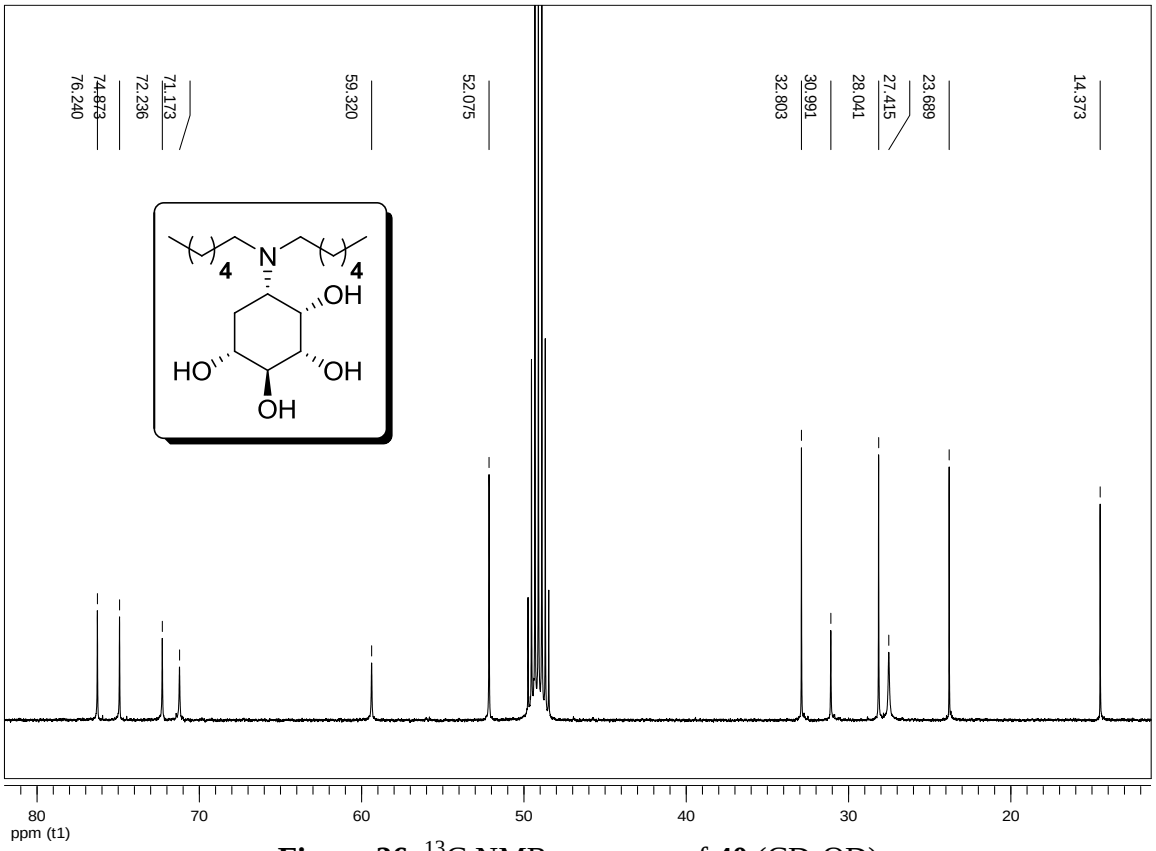

Figure 36. ^{13}C NMR spectrum of **40** (CD_3OD)

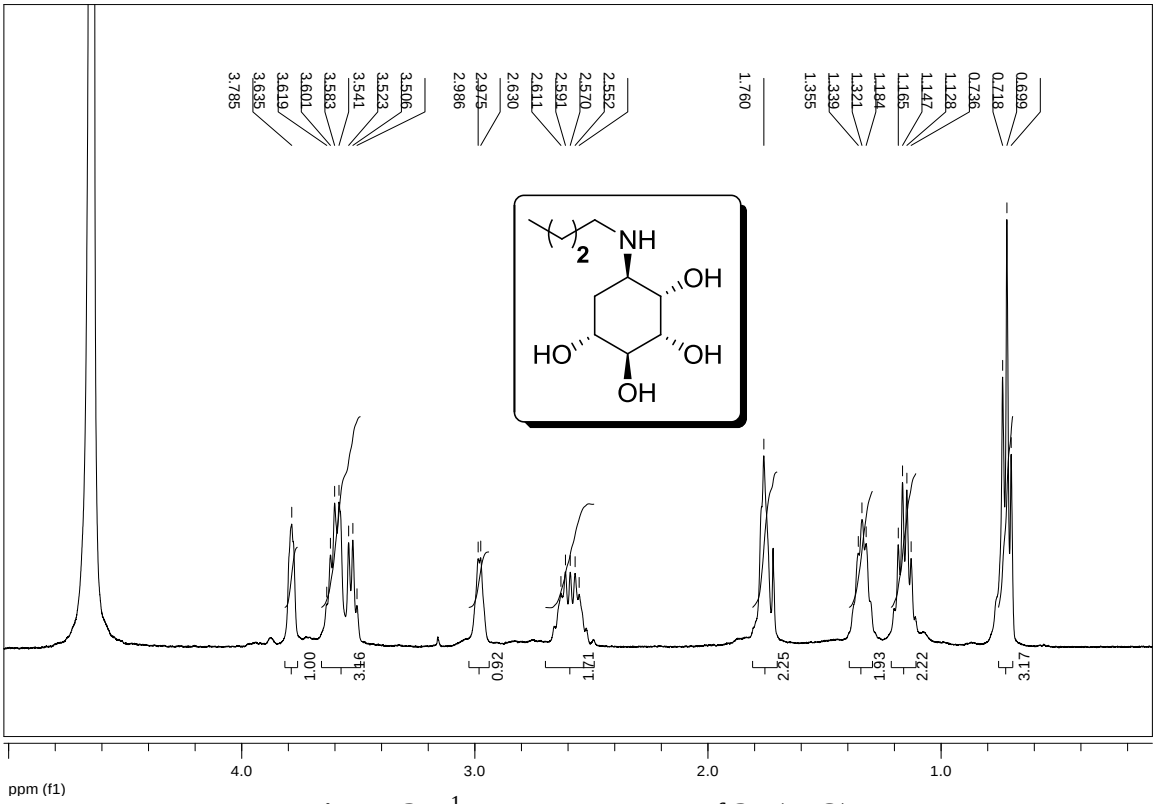

Figure 37. ^{1}H NMR spectrum of **34** (D_2O)

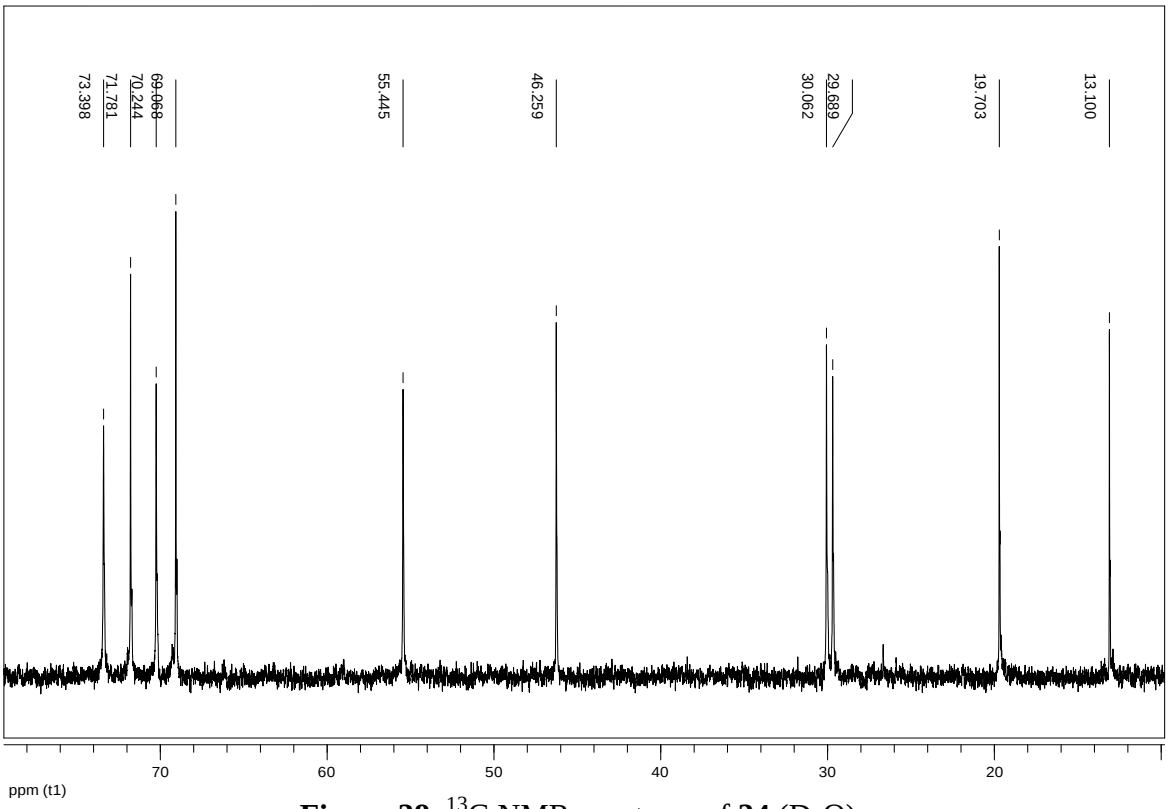

Figure 38. ^{13}C NMR spectrum of **34** (D_2O)

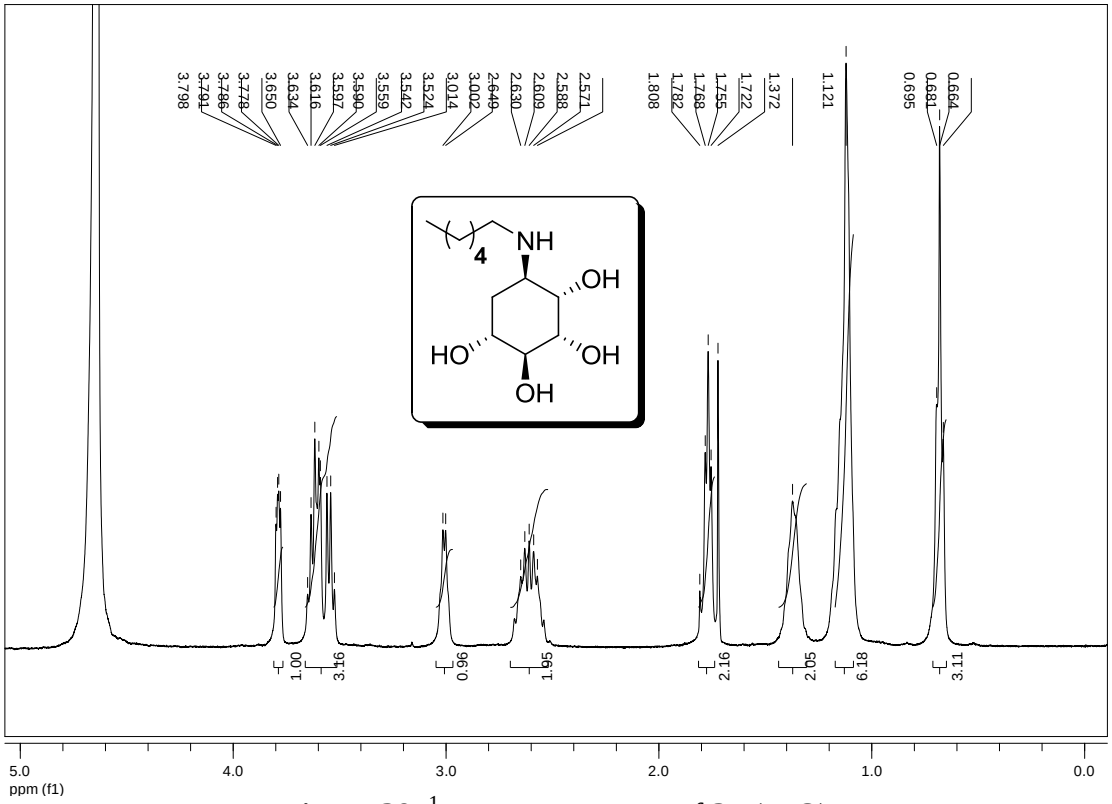

Figure 39. ^{1}H NMR spectrum of **35** (D_2O)

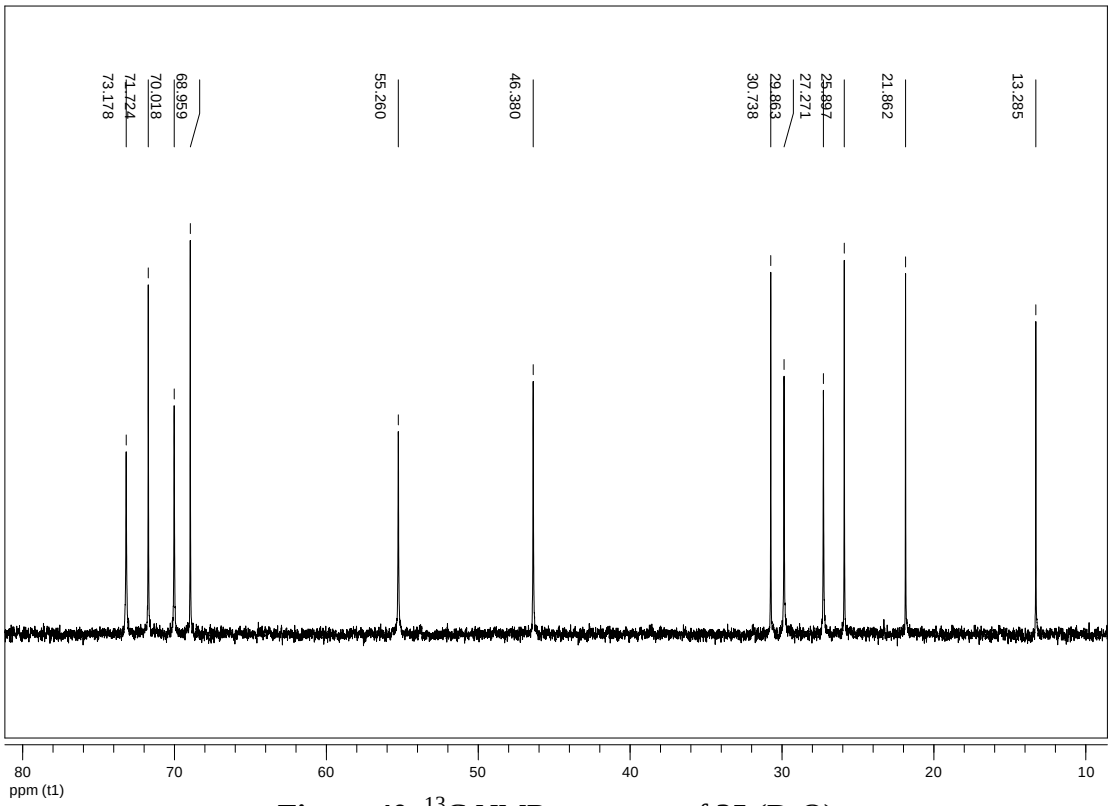

Figure 40. ^{13}C NMR spectrum of **35** (D_2O)

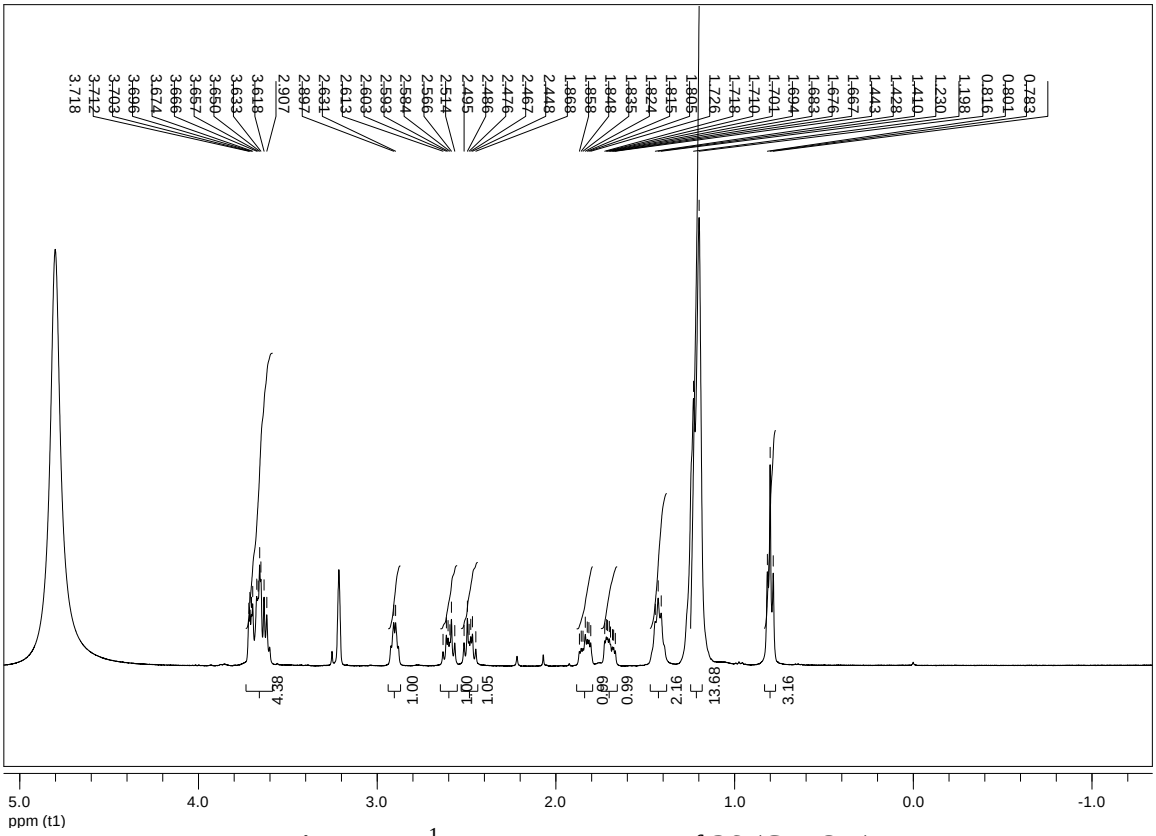

Figure 41. ^{1}H NMR spectrum of **36** (CD_3OD)

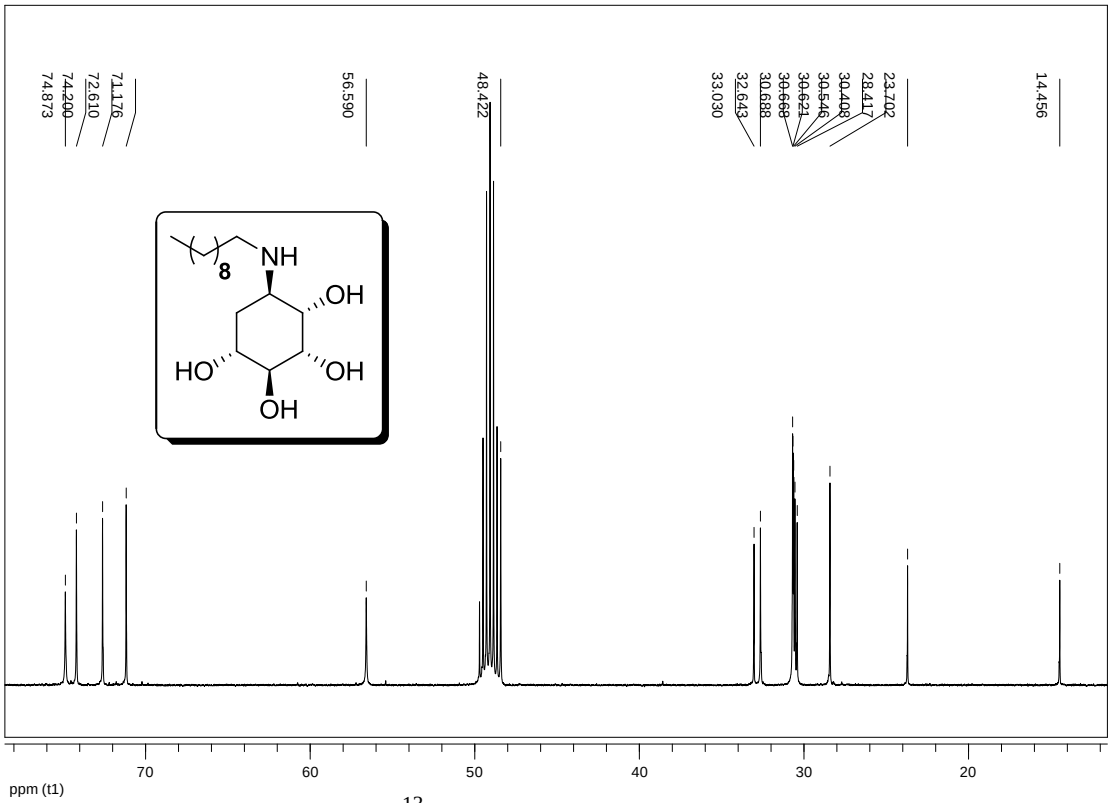

Figure 42. ^{13}C NMR spectrum of **36** (CD_3OD)

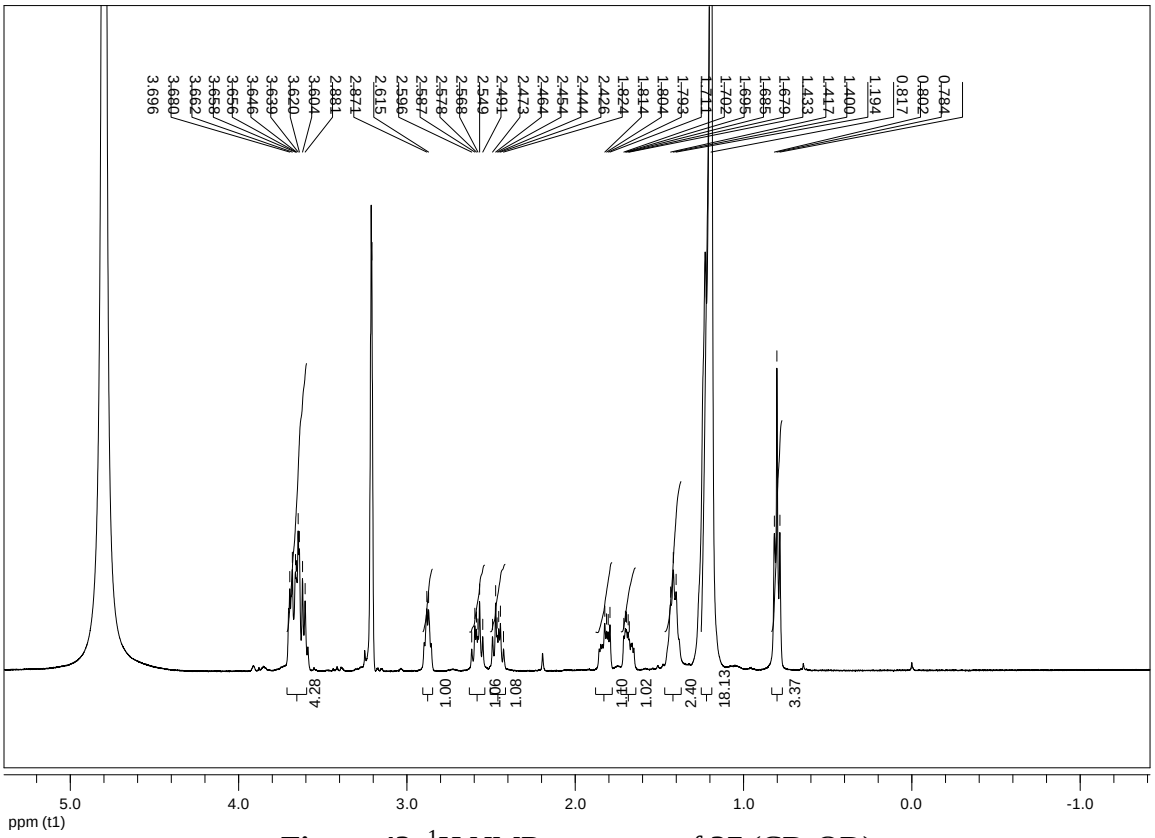

Figure 43. ^{1}H NMR spectrum of **37** (CD_3OD)

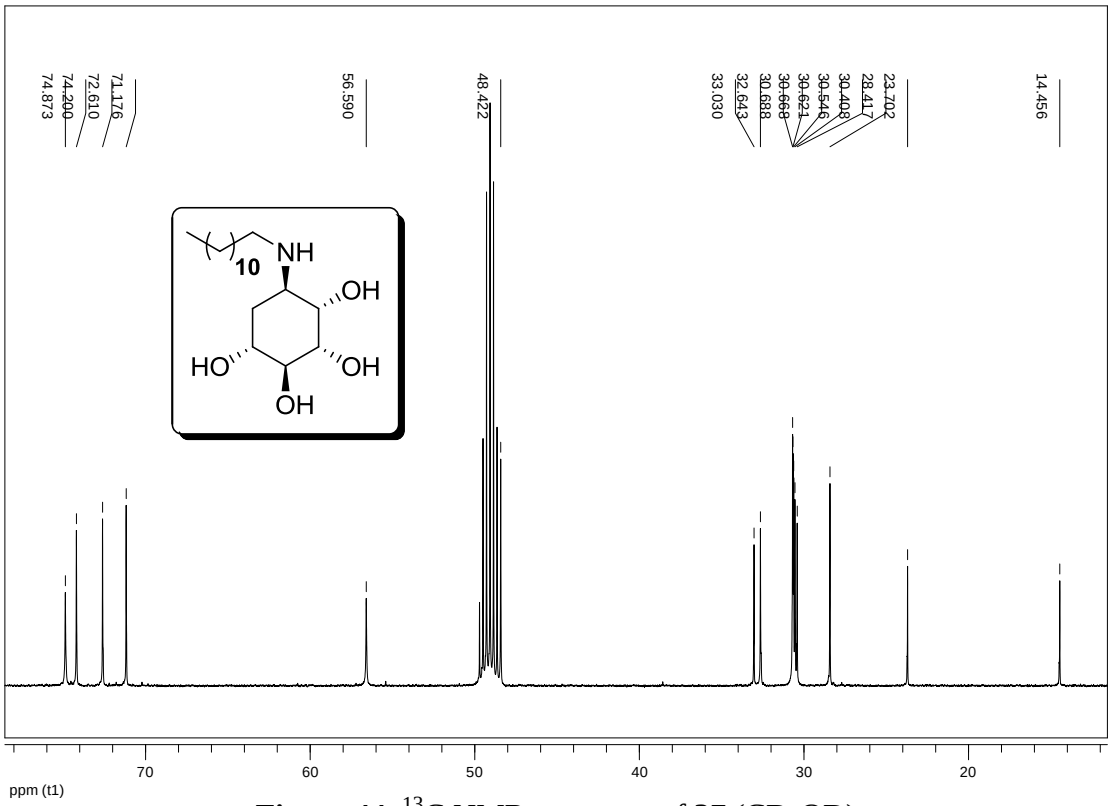

Figure 44. ^{13}C NMR spectrum of **37** (CD_3OD)

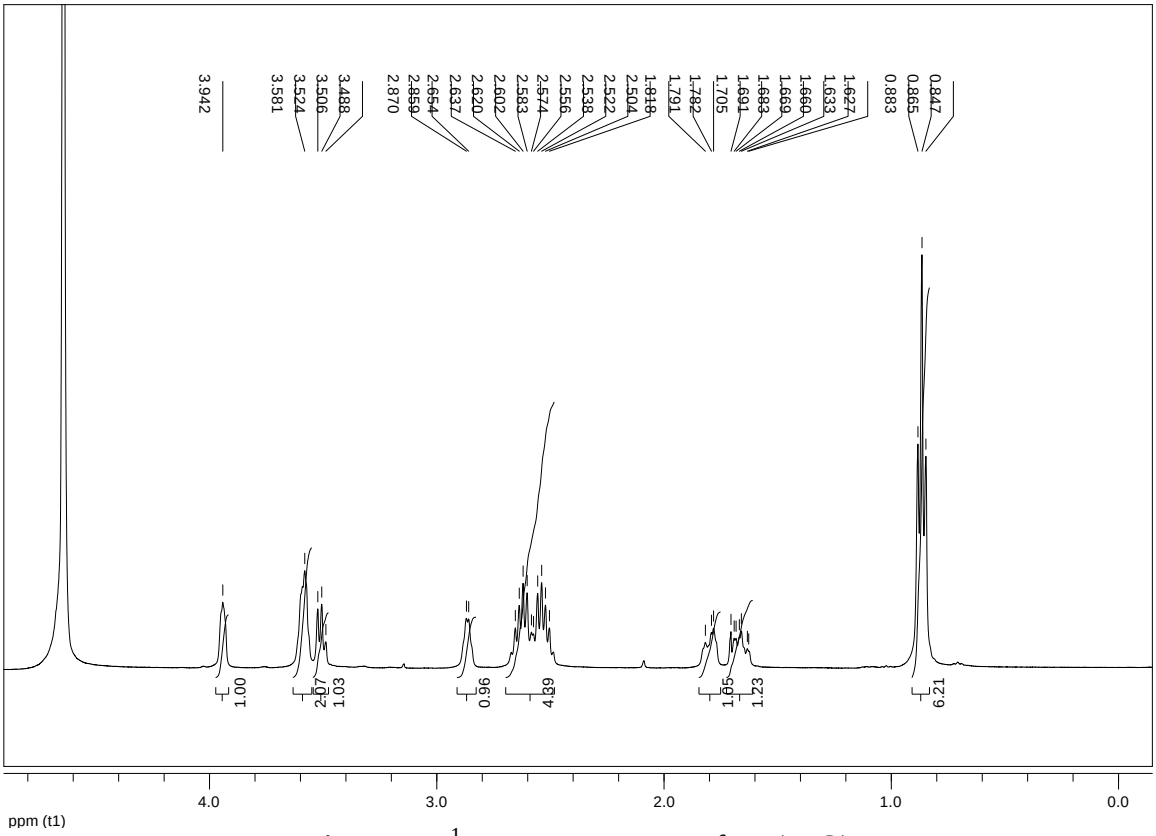

Figure 45. ^{1}H NMR spectrum of **41** (D_2O)

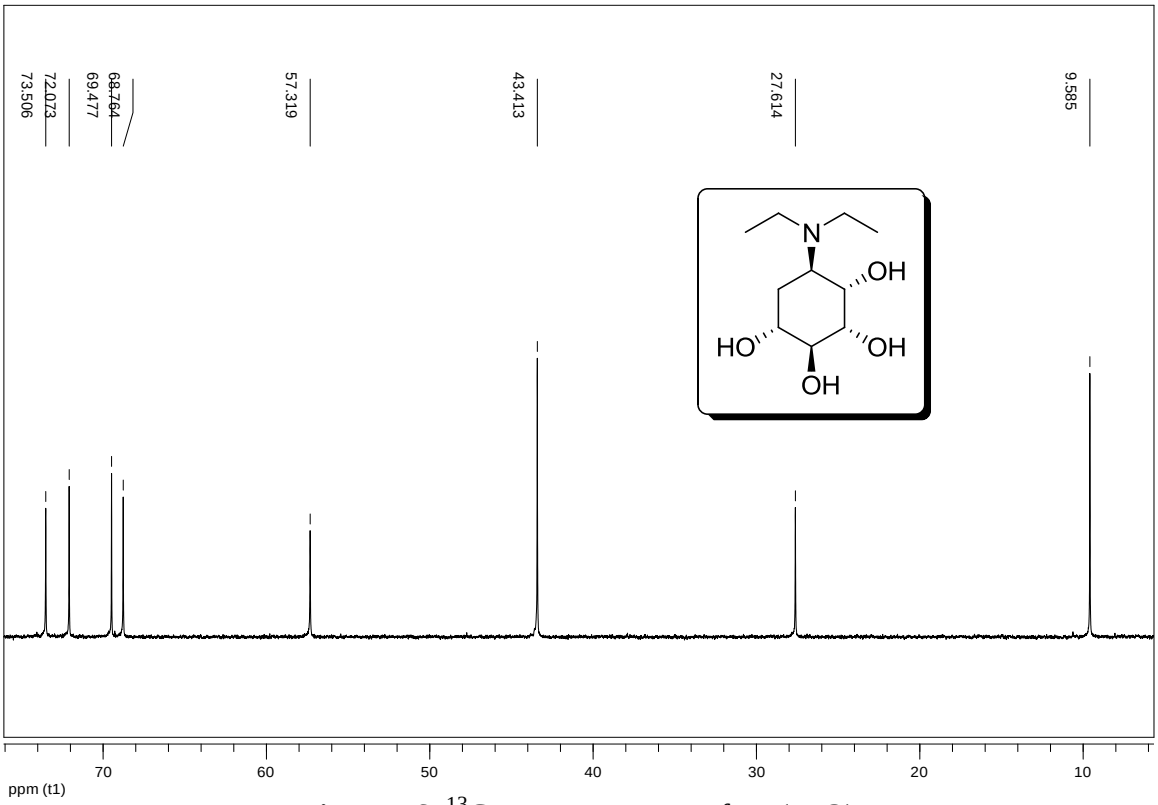

Figure 46. ^{13}C NMR spectrum of **41** (D_2O)

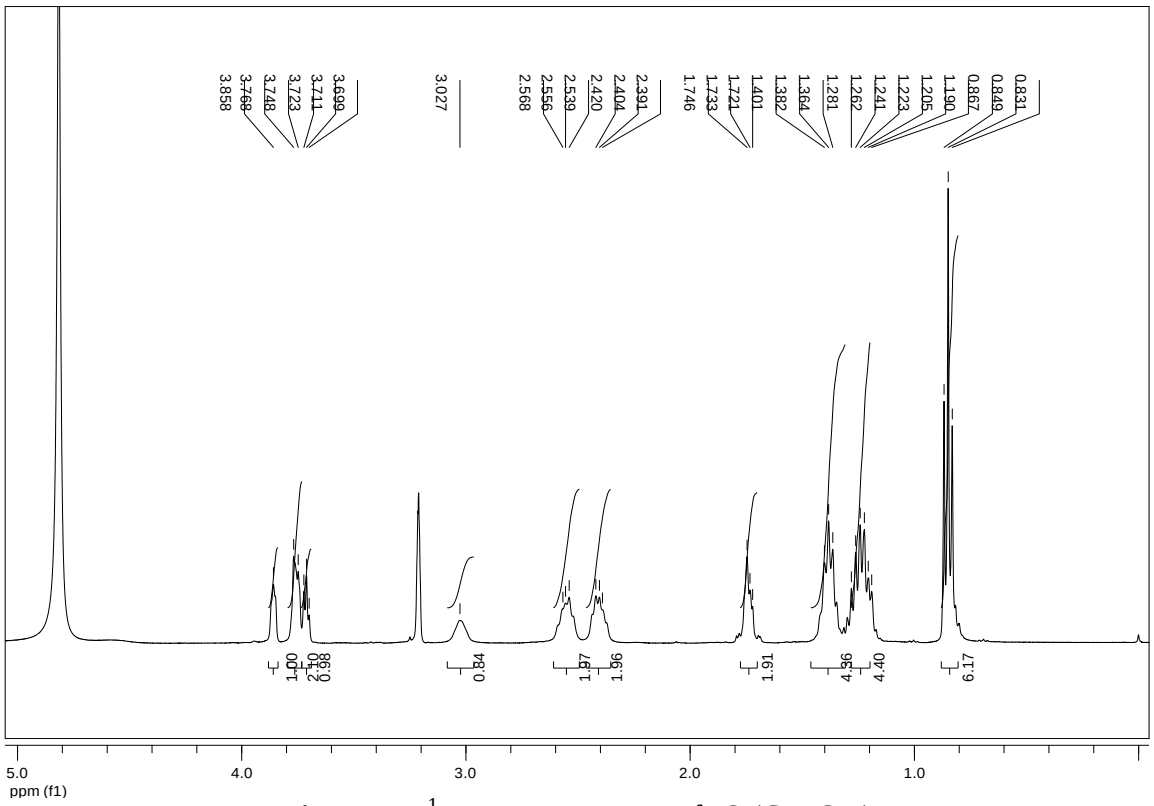

Figure 47. ^{1}H NMR spectrum of **42** (CD_3OD)

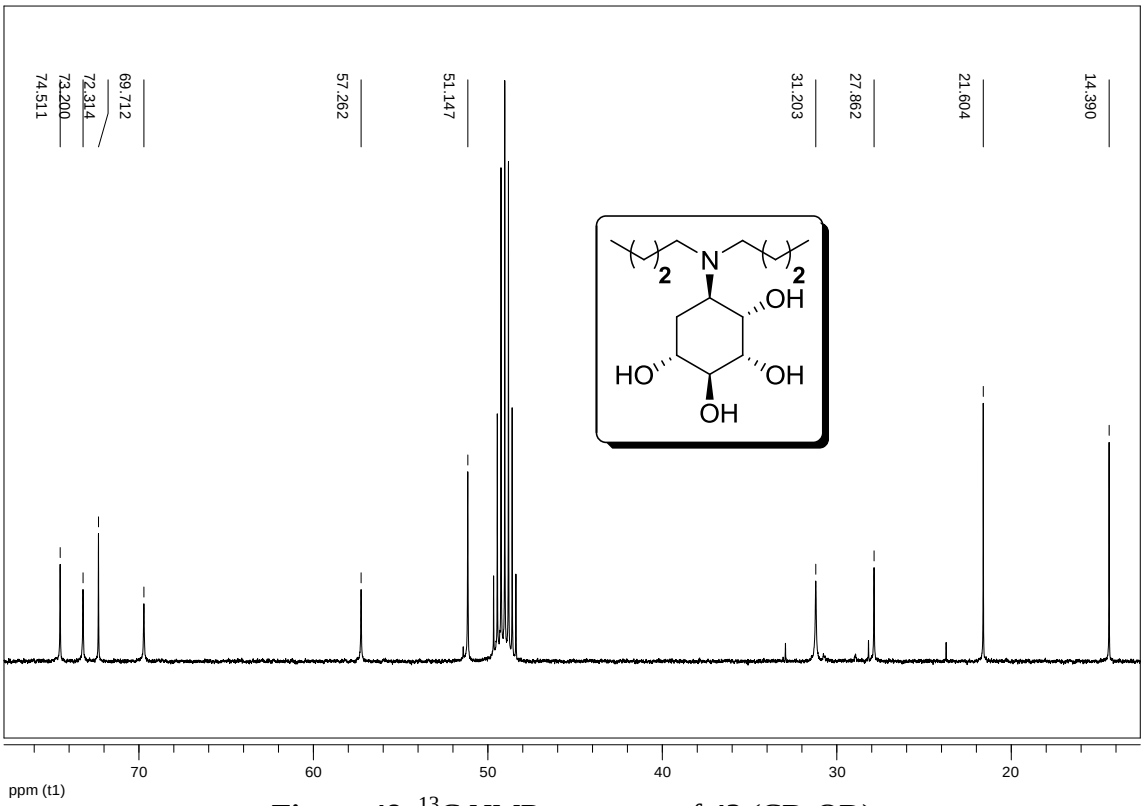

Figure 48. ^{13}C NMR spectrum of **42** (CD_3OD)

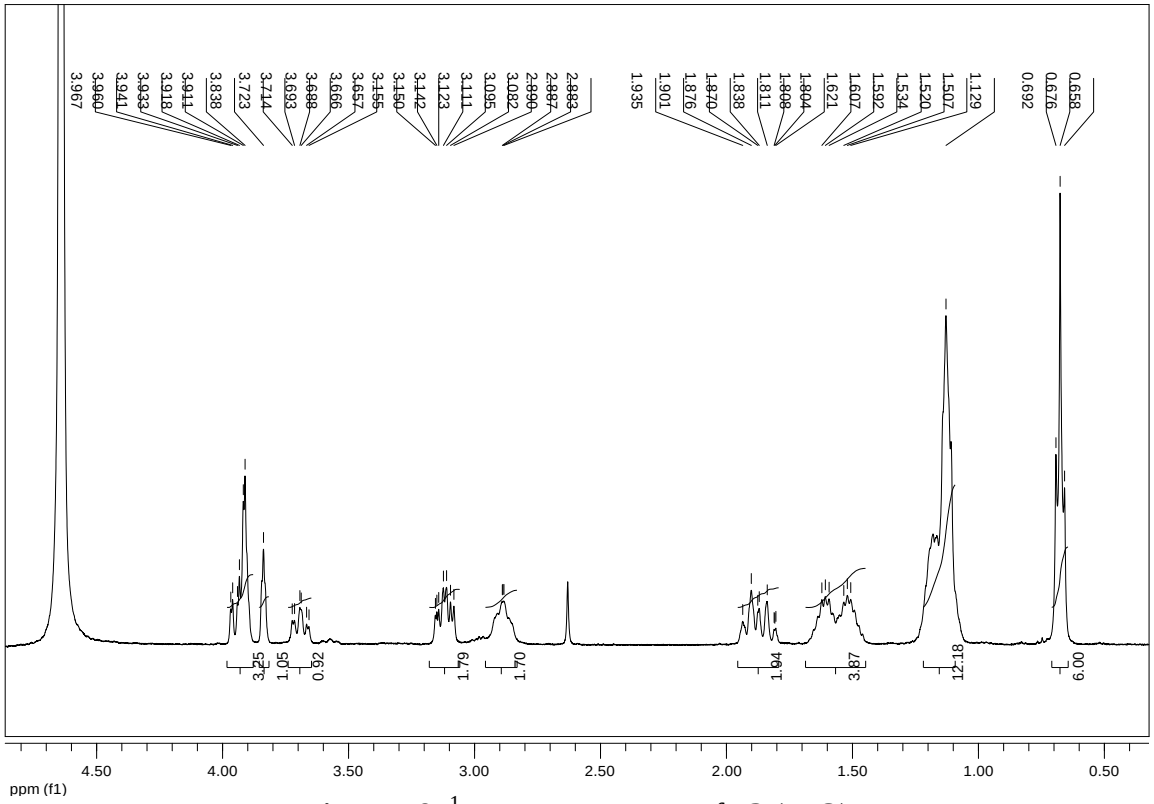

Figure 49. ^{1}H NMR spectrum of **43** (D_2O)

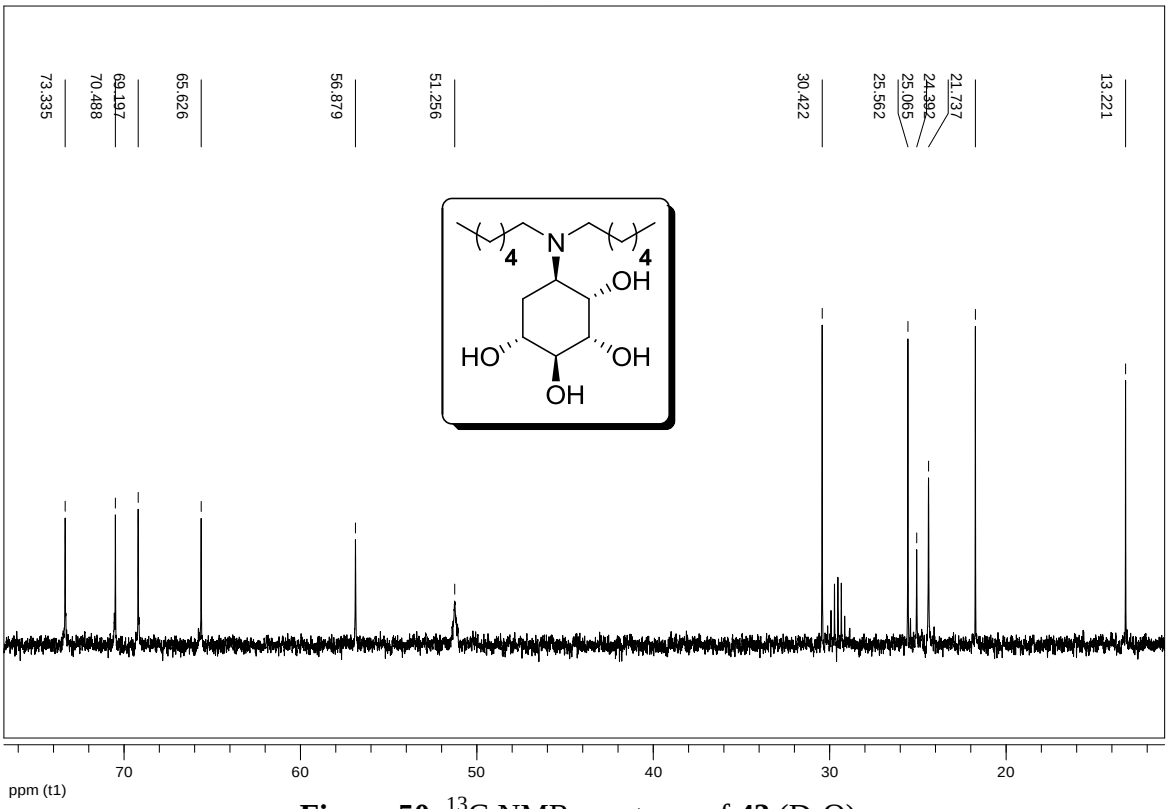

Figure 50. ^{13}C NMR spectrum of **43** (D_2O)