SUPPORTING INFORMATION

# Diaminocyclopentane-Derived *O*-GlcNAcase Inhibitors for Combating Tau Hyperphosphorylation in Alzheimer´s Disease

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**Contents:**

## 1. General experimental procedures

Optical rotations were measured at 20 °C on a Perkin Elmer 341 polarimeter at 589 nm with a path length of 10 cm. NMR spectra were recorded on a Bruker Ultrashield spectrometer at 300.36 MHz ($^{1}$H) and 75.53 MHz ($^{13}$C), respectively. $CDCl_3$ was employed for protected compounds and $CD_3OD$ as well as $D_2O$ for unprotected inhibitors. Chemical shifts are listed in $\delta$ employing residual, non-deuterated solvent or residual $H_2O$ ($CD_3OD$) as the internal standard.[1] $CDCl_3$: 7.26 ppm ($^{1}$H), 77.16 ppm ($^{13}$C); $CD_3OD$: 4.87 ppm ($^{1}$H), 49.0 ppm ($^{13}$C); $D_2O$: 4.79 ppm ($^{1}$H). Signals were unambiguously assigned by COSY (correlation spectroscopy) and HSQC (heteronuclear single-quantum correlation spectroscopy) analysis. The signals of the aromatic groups are located in the expected regions and are not listed explicitly. MALDI-TOF was performed on a Micromass TofSpec 2E Time-of-Flight mass spectrometer. All reactions were monitored by thin-layer chromatography (TLC) performed on pre-coated aluminium plates silica gel 60 $F_{254}$ and detected with UV light (254 nm). For staining, a solution of vanillin (9 g) in a mixture of $H_2O$/EtOH/$H_2SO_4$ (950 mL-750 mL-120 mL) or ceric ammonium molybdate ($(NH_4)_6Mo_7O_{24}\cdot 4\ H_2O$ (100 g)/$Ce(SO_4)_2\cdot 4\ H_2O$ (8 g) in 10% $H_2SO_4$ (1 L)) were employed, followed by heating on a hotplate.

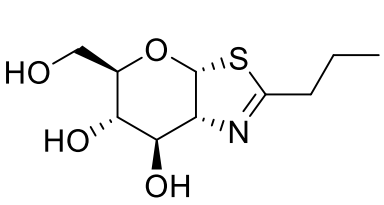
**General procedure A:** Reduction of “azido-isoxazolidines”
To a suspension (5%) of zinc (10 eq) and $NH_4Cl$ (4 eq) in THF-MeOH-$H_2O$ (3:1:1) the respective azide was added at 60 °C.[2] The mixture was heated up to reflux until the complete disappearance of the starting material was observed (30 min, cyclohexane-EtOAc 3:1). The suspension was allowed to reach ambient temperature and the solids were removed by filtration. The filtrate was washed twice with $CH_2Cl_2$ and the collected organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to furnish crude amine.

**General procedure B:** Hydrogenolysis of isoxazolidines
A 10% solution of the respective isoxazolidine in MeOH-THF (1:1) was adjusted to pH 1 (2 M HCl). Pearlman’s catalyst (20% $Pd(OH)_2$/C) was added and the suspension was stirred under an atmosphere of $H_2$ at ambient pressure. After the complete conversion was observed (2 h, $CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1), the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*.

**General procedure C:** Reductive amination of free aminocyclopentanes
A solution of the respective amine in MeOH (10%) was subsequently treated with AcOH, the respective aldehyde (1.3-1.5 eq), and $NaBH_3CN$ (1.5 eq). After the complete disappearance of the starting material was observed (15 min, $CHCl_3$-MeOH 3:1 + 1 vol% $NH_4OH$ (25%)) the solvent was removed under reduced pressure.

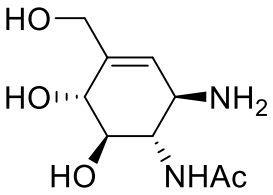
**General procedure D:** Reduction of azido groups
To a methanolic solution (10%) of the respective azide $CHCl_3$ (0.5 mL) and Pearlman’s catalyst (20% $Pd(OH)_2$/C) were added. The suspension was stirred, under an atmosphere of $H_2$ at ambient pressure, until complete reduction was observed (30 min, $CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1). The catalyst was filtered off and the solvents were removed *in vacuo*.

**General procedure E:** *N*-Dansylation
A solution of the respective amine was dissolved in MeOH (10%) and the solution was treated with $Na_2CO_3$ (2 eq) and dansyl chloride (1.1 eq). After the complete conversion (10 min, $CHCl_3$-MeOH 3:1 + 1 vol% $NH_4OH$ (25%)) the suspension was concentrated under reduced pressure.



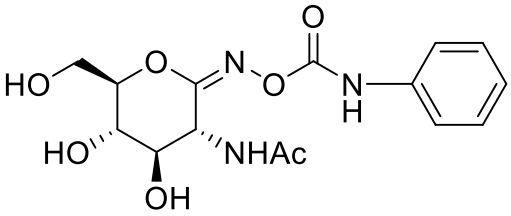
**1**

$K_i$ = 340 µM (GH20)
$K_i$ = 0.23 µM (GH84)
Selectivity = 1,500



**5**

$K_i$ = 34 µM (GH20)
$K_i$ = 6.2 µM (GH84)
Selectivity = 5.5



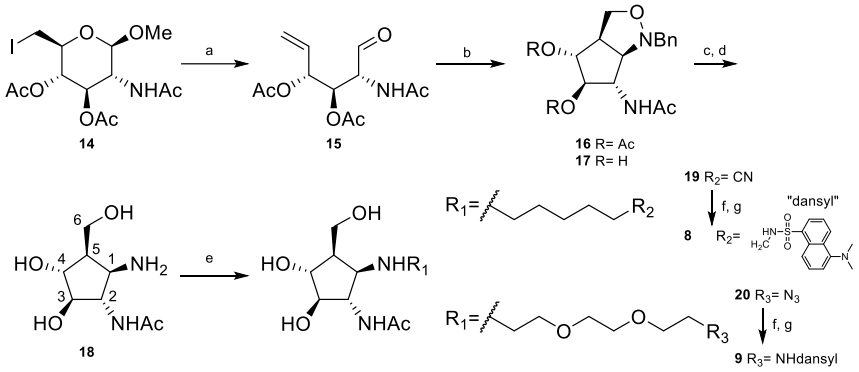
**7**

$K_i$ = 36 nM (GH20)
$K_i$ = 46 nM (GH84)
Selectivity = 0.8

**Scheme S1.** Known inhibitors of OGA with medium to low inhibitory activity and low selectivity: NButGT (**1**),[16] 2-acetamido-β-valienamine (**5**),[17] PUGNAc (**7**);[16] their respective $K_i$-values for human GH20 HexB and for GH84 OGA, and selectivities [$K_i$(HexB)/$K_i$(OGA)].

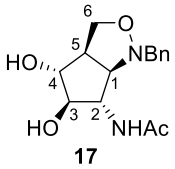
## 2. Synthetic procedures

Compounds **8**-**13** were prepared by adaption of procedures already reported previously.[3] Known 6-deoxyiodo sugar[4] **14** was reductively opened by treatment with zinc dust under slightly acidic conditions providing aldehyde **15**. Taking advantage of a (2+3)-cycloaddition reaction initially reported by the groups of Vasella[5] and Jäger, [6] reaction of aldehyde **15** with *N*-benzylhydroxylamine furnished exclusively *N*-benzylisoxazolidine **16**. Subsequent partial deprotection under Zemplen conditions[7] yielded diol **17** in 53% yield over three steps. Hydrogenolysis of compound **17** in presence of Pd/C and elevated pressure (4 bar) furnished amine **18** in high yield. Chemoselective *N*-alkylation with the respective bromo or tosyloxy alkane[8] directly followed by catalytic hydrogenation in the presence of Pd/C under an atmosphere of $H_2$ at ambient pressure gave amines **19** and **20** in 37% and 40% yield, respectively. N-dansylation of amines **19** and **20** under standard conditions gave inhibitors **8** and **9** in fair yield. (Scheme S2).




**Scheme S2.** Synthesis of inhibitors **8** and **9**. a: Zn, $NH_4Cl$, MeOH; b: BnNHOH•HCl, pyridine, MeOH; c: NaOMe, MeOH, 51% (3 steps); d: $H_2$, 20% $Pd(OH)_2$/C, THF-MeOH (1:1), HCl, 84%; e: respective alkyl bromide/tosylate, $NaHCO_3$, DMF, 70°C; f: $H_2$, 20% $Pd(OH)_2$/C, MeOH, 37% (**19**), 40% (**20**), 2 steps each), g: dansyl chloride, $Na_2CO_3$, MeOH, 63% (**8**), 55% (**9**). Alternative nomenclature derived from the nomenclature for carbohydrates is given as "(*name*)" for the respective compounds.

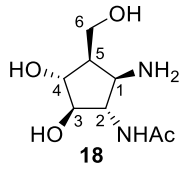
### *N*-((3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-Benzyl-4,5-dihydroxyhexahydro-1*H*-cyclopenta(*c*)isoxazol-6-yl) acetamide (17)




To a stirred suspension of zinc (8.23 g, 126 mmol) and $NH_4Cl$ (6.74 g, 126 mmol) in methanol (150 mL), known 6-deoxyiodo sugar **14**[4] (4.50 g, 10.5 mmol) was added and the mixture was further stirred until completed consumption of the starting material (1 h, cyclohexane-EtOAc 1:2). The solids were removed by filtration and the solvent was concentrated under reduced pressure. The remaining syrup was dissolved in $CH_2Cl_2$ and the organic layer was washed twice with brine, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The obtained aldehyde **15** was dissolved in methanol (50 mL) and subsequently treated with pyridine (3.69 mL, 46.6 mmol) and BnNHOH·HCl (1.84 g, 11.5 mmol). After complete conversion into intermediate **16** was observed (12 h, cyclohexane-EtOAc 1:2) a catalytic amount of 1 M NaOMe solution in MeOH was added dropwise. When complete deprotection was observed ($CH_2Cl_2$-MeOH 6:1) the reaction solution was neutralized with Amberlite® IR-120. The ion exchange resin was filtered off and the solvents were removed under reduced pressure. The remaining syrup was purified by silica gel chromatography ($CH_2Cl_2$-MeOH 10:1) to yield isoxazolidine **17** (1.57 g, 5.37 mmol, 51% over 3 steps) as a colorless solid. Treatment of isoxazolidine (32 mg, 0.109 mmol) with

methanolic HCl gave hydrochloride **17**·HCl as colorless crystals which could be employed for X-Ray structure determination. $m_p$ = 134 °C (decomposition). $[\alpha]_D^{20}$: +21.1 (c = 1.0, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 7.41-7.22 (m, 5 H, aromatic), 4.09 (dd, 1 H, $J_{5,6a}$ = $J_{6a,6b}$ 7.2 Hz, H-6a), 3.94 (d, 1 H, *J* 12.8 Hz, N-C<u>H</u>$_2$-Ph), 3.84 (d, 1 H, *J* 12.8 Hz, N-C<u>H</u>$_2$-Ph), 3.85-3.81 (m, 1 H, H-6b), 3.76 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 7.6 Hz, H-2), 3.70 (dd, 2 H, $J_{3,4}$ 8.0 Hz, H-3), 3.43 (dd, 1 H, $J_{1,5}$ 8.0 Hz, H-1), 2.86 (ddd, 1 H, $J_{5,6b}$ 2.2 Hz, H-5), 1.82 (s, 3 H, NH-CO-C<u>H</u>$_3$). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 173.3 (NH-<u>C</u>O-CH$_3$), 138.3 (*ipso*), 130.3, 129.3, 128.4 (aromatic), 80.7 (C-4), 80.2 (C-3), 71.0 (C-6), 70.2 (C-1), 60.5 (N-<u>C</u>H$_2$-Ph), 59.7 (C-2), 51.7 (C-5), 22.9 (NH-CO-<u>C</u>H$_3$). MS (MALDI): Calculated for ($C_{15}H_{20}N_2O_4Na$): *m/z* [M+Na]$^+$ 315.1321; found [M+Na]$^+$ 315.1322.

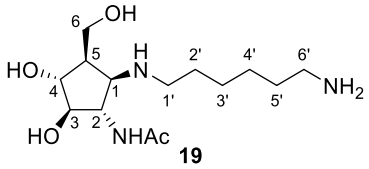
### *N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)acetamide "(2-Acetamido-1-amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (18)



**18**

A methanolic solution (20 mL) of isoxazolidine **17** (1.54 g, 5.27 mmol) was stirred with Pd/C (10%) under an atmosphere of $H_2$ (4 bar). After completed conversion (12 h, $CHCl_3$-MeOH-$NH_4OH$ 8:4:1), the catalyst was filtered off and the filtrate was concentrated under reduced pressure. The residue was chromatographed ($CHCl_3$-MeOH-$NH_4OH$ 8:4:1; silica gel) to yield **18** (904 mg, 4.43 mmol, 84%) as a white solid. Amine **18** (10 mg) was dissolved in MeOH and the pH was adjusted to 1 (12 M HCl). Removal of the solvents under reduced pressure furnished **18**·HCl. $[\alpha]_D^{20}$: +18.0 (c = 1.0, MeOH, free base); free base: $^1$H-NMR (300 MHz, $D_2O$) δ = 3.88-3.65 (m, 5 H, H-2, H-3, H-4, H-6), 3.24 (dd, 1 H, $J_{1,2}$ = $J_{1,5}$ 9.1 Hz, H-5), 2.13-1.98 (m, 4 H, H-5, NH-CO-C<u>H</u>$_3$). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 174.8 (NH-<u>C</u>O-CH$_3$), 78.7, 75.5 (C-3, C-4), 60.5 (C-2), 59.2 (C-6), 52.8 (C-1), 46.0 (C-5), 22.1 (NH-CO-<u>C</u>H$_3$). hydrochloride: $^1$H-NMR (300 MHz, $D_2O$) δ = 4.07 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.9 Hz, H-2), 3.97-3.88 (m, 2 H, H-3, H-4), 3.88 (dd, 2 H, $J_{5,6a}$ 4.7 Hz, $J_{6a,6b}$ 8.3 Hz, H-6), 3.76 (dd, 1 H, $J_{1,5}$ 8.6 Hz, H-1), 2.41-2.28 (m, 1 H, H-5), 2.05 (s, 3 H, NH-CO-C<u>H</u>$_3$). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 175.5 (NH-<u>C</u>O-CH$_3$), 76.9, 73.9 (C-3, C-4), 58.0 (C-6), 56.7 (C-2), 53.2 (C-1), 42.9 (C-5), 21.8 (NH-CO-<u>C</u>H$_3$). MS (MALDI): Calculated for ($C_8H_{16}N_2O_4Na$): *m/z* [M+Na]$^+$ 227.1008; found [M+Na]$^+$ 227.1007.

### *N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((6-Aminohexyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl) acetamide "(2-Acetamido-1-(6-aminohexyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (19)

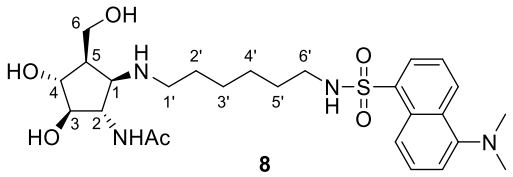


**19**

To a stirred solution of amine **18** (125 mg, 0.612 mmol) in DMF (5 mL), $NaHCO_3$ (154 mg, 1.84 mmol), and ω-bromohexanoic nitrile (105 µL, 0.796 mmol) were added. The reaction mixture was heated to 70°C until complete consumption of the starting material was observed (24 h, $CHCl_3$-MeOH 3:1 + 1 vol% $NH_4OH$). The solvents were removed under reduced pressure and the remaining syrup was quickly passed through a pad of silica gel ($CHCl_3$-MeOH 8:1 + 1 vol% $NH_4OH$). The obtained crude nitrile was dissolved in 5 mL of MeOH and was stirred with catalytic amounts of Raney-Ni under an atmosphere of $H_2$ at ambient temperature. After the full conversion of the starting material (10 min, $CHCl_3$-MeOH-$NH_4OH$ 8:4:1) the catalyst was removed and the filtrate was concentrated under reduced pressure. Chromatographic purification ($CHCl_3$-MeOH-$NH_4OH$ 8:4:1; silica gel) gave amine **19** (69.2 mg, 0.228 mmol, 37% over 2 steps) as a colorless oil. $[\alpha]_D^{20}$: +24.6 (c = 1.1, MeOH); $^1$H-NMR (300 MHz, $D_2O$) δ = 3.86 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.5 Hz, H-2), 3.82-3.75 (m, 3 H, H-4, H-6), 3.70 (dd, 1 H, $J_{3,4}$ 8.0 Hz, H-3), 3.16

(dd, 1 H, $J_{1,5}$ 8.5 Hz, H-1), 2.69-2.41 (m, 4 H, H-1′, H-6′), 2.25-2.12 (m, 1 H, H-5), 2.00 (s, 3 H, NH-CO-C$\underline{H}_3$), 1.52-1.23 (m, 8 H, H-2', H-3', H-4', H-5'). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 173.9 (NH-$\underline{C}$O-CH$_3$), 79.8 (C-3), 75.3 (C-4), 59.5 (C-6), 59.0 (C-2), 58.6 (C-1), 47.0 (C-1'), 45.5 (C-5), 40.3 (C-6'), 30.5, 28.3, 26.1, 25.7 (C-2', C-3', C-4', C-5'), 22.2 (NH-CO-$\underline{C}$H$_3$). MS (MALDI): Calculated for ($C_{14}H_{29}N_3O_4H$): *m/z* $[M+H]^+$ 304.2236; found $[M+H]^+$ 304.2236.

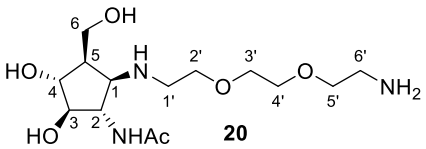
**_N_-((1_S_,2_R_,3_R_,4_R_,5_R_)-2-((6-((5-(Dimethylamino)naphthalene)-1-sulfonamido)hexyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)acetamide "(2-Acetamido-1-(6-dansylaminohexyl) amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (8)**



**8**

A solution of amine **19** (47.0 mg, 155 µmol) in methanol (2 mL) was treated with $Na_2CO_3$ (32.8 mg, 310 µmol) and dansyl chloride (46.0 mg, 170 µmol). After the completed conversion of the starting material (15 min, $CH_2Cl_2$-MeOH 6:1), the solvent was removed under reduced pressure. Purification on silica gel ($CH_2Cl_2$-MeOH 10:1) provided dansylated amine **8** (52.6 mg, 98.0 µmol, 63%) as a yellow syrup. $[\alpha]_D^{20}$: +9.3 (c = 0.98, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 8.55 (d, 1 H, *J* 8.5 Hz, dansyl), 8.35 (d, 1 H, *J* 8.6 Hz, dansyl), 8.18 (d, 1 H, *J* 7.3 Hz, dansyl), 7.58 (dd, 1 H, *J* 8.5 Hz, *J* 7.3 Hz, dansyl), 7.57 (dd, 1 H, *J* 8.6 Hz, *J* 7.5 Hz, dansyl), 7.27 (d, 1 H, *J* 7.5 Hz, dansyl), 3.94 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.3 Hz, H-2), 3.87 (dd, 1 H, $J_{5,6a}$ 4.0 Hz, $J_{6a,6b}$ 11.3 Hz, H-6a), 3.86 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 7.8 Hz, H-4), 3.84 (dd, 1 H, $J_{5,6b}$ 5.5 Hz, H-6b), 3.74 (dd, 1 H, $J_{3,4}$ 8.0 Hz, H-3), 3.41 (dd, 1 H, $J_{1,5}$ 9.3 Hz, H-1), 2.94-2.77 (m, 10 H, H-1′, H-6′, dansyl), 2.18 (dddd, 1 H, H-5), 2.00 (s, 3 H, NH-CO-C$\underline{H}_3$), 1.52-1.10 (m, 8 H, H-2', H-3', H-4', H-5'). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 174.6 (NH-$\underline{C}$O-CH$_3$), 153.2, 137.3, 131.2, 131.1, 131.0, 130.1, 129.1, 124.3, 120.6, 116.4 (dansyl), 80.1 (C-3), 75.9 (C-4), 63.0 (C-1), 2 × 59.8 (C-2, C-6), 48.8 (C-1'), 46.1 (C-5), 45.8 (dansyl), 43.7 (C-6'), 30.4, 28.3, 2 × 27.0 (C-2', C-3', C-4', C-5', C-6') 22.6 (NH-CO-$\underline{C}$H$_3$). MS (MALDI): Calculated for ($C_{26}H_{40}N_4O_6SNa$): *m/z* $[M+Na]^+$ 559.2567; found $[M+Na]^+$ 559.2565.

**_N_-((1_S_,2_R_,3_R_,4_R_,5_R_)-2-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxy methyl)cyclopentyl)acetamide "(2-Acetamido-1-(2-(2-(2-aminoethoxy)ethoxy)ethyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (20)**

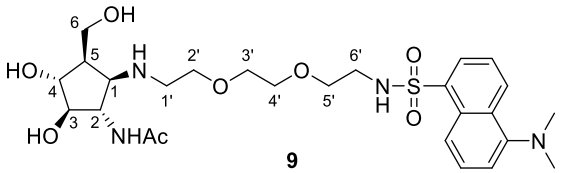


**20**

A suspension of amine **18** (138 mg, 0.676 mmol), $NaHCO_3$ (170 mg, 2.03 mmol) and 2-(2-(2-azidoethoxy)ethoxy)ethyl 4-tosylate[8b] (312 mg, 0.946 mmol) in DMF (5 mL) was stirred at 70°C. After complete alkylation (48 h, $CHCl_3$-MeOH 3:1 + 1 vol% $NH_4OH$), the solvents were removed under reduced pressure. The resulting syrup was quickly passed through a pad of silica gel ($CHCl_3$-MeOH 8:1 + 1 vol% $NH_4OH$). The obtained crude azide was dissolved in EtOH-$H_2O$ (3:1, 4 mL) and zinc dust (133 mg, 2.03 mmol) and $NH_4Cl$ (109 mg, 2.03 mmol) were added. The solution was heated to reflux. After the full conversion of the starting material (1 h, $CHCl_3$-MeOH-$NH_4OH$ 8:4:1), $NH_4OH$ (1 mL) was added and the solids were filtered off. The solvents were removed under reduced pressure and the remaining syrup was purified by silica gel chromatography ($CHCl_3$-MeOH-$NH_4OH$ 8:4:1) to yield amine **20** (98.4 mg, 0.272 mmol, 40% over 2 steps) as a colorless oil. Amine **20** (10 mg) was dissolved in MeOH and the pH was adjusted to 1 (12 M HCl). Removal of the solvents under reduced pressure furnished **20**·HCl. $[\alpha]_D^{20}$: +15.8 (c = 1.0, MeOH, hydrochloride); hydrochloride: $^1$H-NMR (300 MHz, $D_2O$) δ = 4.19 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.4 Hz, H-2), 4.00 (dd, 1 H, $J_{5,6a}$ 4.0 Hz, $J_{6a,6b}$ 12.2 Hz, H-6a), 3.96-3.69 (m, 12 H, H-1, H-3, H-4, H-6b, H-2′,

H-3′, H-4′, H-5′), 3.41-3.28 (m, 2 H, H-1'), 3.21 (t, 2 H, *J* 5.2 Hz, H-6'), 2.48-2.36 (m, 1 H, H-5), 2.05 (s, 3 H, NH-CO-C$\underline{H}_3$). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 174.9 (NH-$\underline{C}$O-$CH_3$), 77.7 (C-3), 73.4 (C-4), 69.8, 69.6, 66.4, 65.4 (C-2', C-3', C-4', C-5'), 60.2 (C-1), 57.8 (C-6), 56.1 (C-2), 46.6 (C-1'), 43.0 (C-5), 39.1 (C-6'), 22.0 (NH-CO-$\underline{C}H_3$). MS (MALDI): Calculated for ($C_{14}H_{29}N_3O_9Na$): *m/z* $[M+Na]^+$ 358.1954; found $[M+Na]^+$ 358.1955.

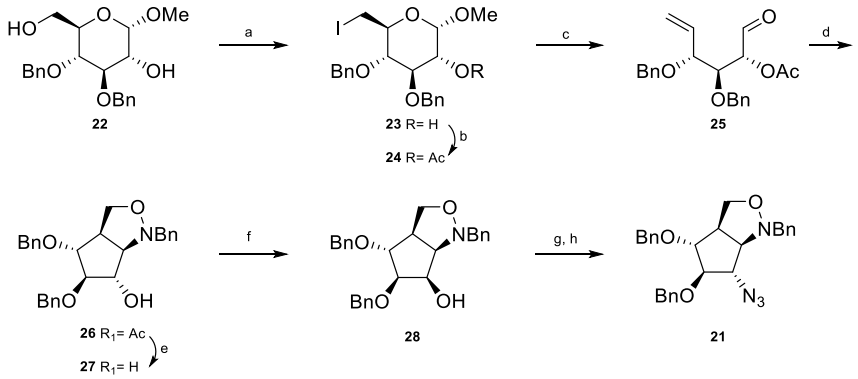
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(Dimethylamino)naphthalene)-1-sulfonamido)ethoxy)ethoxy) ethyl) amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl) acetamide "(2-Acetamido-1-(2-(2-(2-dansylaminoethoxy)ethoxy)ethyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (9)**




**9**

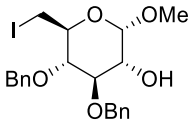
A solution of amine **20** (66.1 mg, 197 µmol) in methanol (3 mL) was treated with $Na_2CO_3$ (41.8 mg, 394 µmol) and dansyl chloride (58.5 mg, 217 µmol). After complete conversion of the starting material (15 min, $CH_2Cl_2$-MeOH 6:1) the solvent was removed under reduced pressure. Purification on silica gel ($CH_2Cl_2$-MeOH 10:1) provided *N*-dansyl **9** (57.5 mg, 101 µmol, 55%) as a yellow syrup. $[\alpha]_D^{20}$: +9.8 (c = 1.3, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 8.55 (d, 1 H, *J* 8.5 Hz, dansyl), 8.34 (d, 1 H, *J* 8.6 Hz, dansyl), 8.20 (d, 1 H, *J* 7.3 Hz, dansyl), 7.59 (dd, 1 H, *J* 8.5 Hz, *J* 7.3 Hz, dansyl), 7.57 (dd, 1 H, *J* 8.6 Hz, *J* 7.6 Hz, dansyl), 7.26 (d, 1 H, *J* 7.6 Hz, dansyl), 4.02 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.1 Hz, H-2), 3.91 (dd, 2 H, $J_{5,6a}$ 3.8 Hz, $J_{6a,6b}$ 10.6 Hz, H-6), 3.89 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 8.2 Hz, H-4), 3.88 (dd, 2 H, $J_{5,6b}$ 4.7 Hz, H-6b), 3.80 (dd, 1 H, H-3), 3.70-3.23 (m, 11 H, H-1, H-1', H-2', H-3', H-4' H-5'), 3.04 (t, 2 H, *J* 5.2 Hz, H-6′), 2.86 (s, 6 H, dansyl), 2.36-2.22 (m, 1 H, H-5), 2.00 (s, 3 H, NH-CO-C$\underline{H}_3$). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 174.4 (NH-$\underline{C}$O-$CH_3$), 153.2, 137.2, 131.2, 131.2, 131.0, 130.0, 129.1, 124.3, 120.6, 116.4 (dansyl), 80.5 (C-3), 76.6 (C-4), 71.2, 71.1, 70.6, 69.3 (C-2', C-3', C-4', C-5'), 62.6 (C-1), 60.5 (C-6), 60.4 (C-2), 49.0 (C-1'), 46.7 (C-5), 43.8 (C-6'), 22.7 (NH-CO-$\underline{C}H_3$). MS (MALDI): Calculated for ($C_{26}H_{40}N_4O_8SNa$): *m/z* $[M+Na]^+$ 591.2465; found $[M+Na]^+$ 591.2463.

Selective Garegg deoxy-iodination[9] of the primary hydroxyl function in compound **22** provided 6-deoxyiodo sugar **23** in 92% yield. *O*-Acetylation of **23** under standard conditions gave acetate **24**. Reduction of compound **24** with zinc under slightly acidic conditions furnished aldehyde **25**, which was subsequently cyclised by reaction with *N*-benzylhydroxylamine to provide exclusively desired diastereomer **26** in 85% yield over two steps. Removal of the acetyl group employing sodium methoxide in methanol resulted in alcohol **27**, which, in turn, was isomerized following a standard oxidation/reduction sequence to obtain alcohol **28** in high yield. Conversion of alcohol **28** to the corresponding triflates, directly followed by $S_N2$ reaction with sodium azide resulted in azide **21** in 81% yield over two steps (Scheme S3). This served as substrate for the following acylation reactions.



**Scheme S3.** Synthesis of compound **21**. a: $PPh_3$, imidazole, $I_2$, toluene, 70 °C, 92%; b: $Ac_2O$, $Et_3N$, $CH_2Cl_2$, 4-DMAP (cat.), 93%; c: Zn, $NH_4Cl$, MeOH/THF (1:1); d: BnNHOH·HCl, pyridine, MeOH-THF (3:1), 85% (2 steps); e: NaOMe, MeOH-THF (3:1), 95%; f: oxalyl chloride, DMSO, $(i\text{-}Pr)_2NEt$, $CH_2Cl_2$, - 70 °C; then $NaBH_4$, MeOH, - 20 °C, 84% (2 steps); g: $Tf_2O$, pyridine, $CH_2Cl_2$; 0 °C; h: $NaN_3$, DMF, 81% (2 steps).

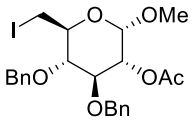
**Methyl 6-deoxy-6-iodo-3,4-*O*-dibenzyl-α-D-glucopyranoside (23)**




**23**

A solution of known[10] diol **22** (2.97 g, 7.93 mmol) in toluene (60 mL) was heated to 70 °C and $PPh_3$ (2.70 g, 10.3 mmol), imidazole (1.62 g, 23.8 mmol), and $I_2$ (2.42 g, 9.52 mmol) were added sequentially. After complete consumption of the starting material (30 min, cyclohexane-EtOAc 1:1), additional $I_2$ (0.40 g, 1.6 mmol) was added. The reaction mixture was stirred for another 10 min and allowed to reach ambient temperature. The solution was washed with saturated aqueous $Na_2S_2O_3$, dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. Purification of the remaining syrup on silica gel (cyclohexane-EtOAc 8:1) yielded iodosugar **23** (3.54 g, 7.31 mmol, 92%) as a colorless solid. $[\alpha]_D^{20}$: +84.7 (c = 1.0, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.42-7.24 (m, 10 H, aromatic), 4.95 (d, 1 H, *J* 11.0 Hz, O-C$\underline{H}_2$-Ph), 4.94 (d, 1 H, *J* 11.0 Hz, O-C$\underline{H}_2$-Ph), 4.84 (d, 1 H, *J* 11.0 Hz, O-C$\underline{H}_2$-Ph,), 4.78 (d, 1 H, $J_{1,2}$ 3.6 Hz, H-1), 4.71 (d, 1 H, *J* 11.0 Hz, O-C$\underline{H}_2$-Ph), 3.80 (dd, 1 H, $J_{2,3} = J_{3,4}$ 8.8 Hz, H-3), 3.71 (ddd, 1 H, $J_{2,OH}$ 8.3 Hz, H-2), 3.52 (dd, 1 H, $J_{5,6a}$ 2.8 Hz, $J_{6a,6b}$ 10.4 Hz,H-6a), 3.47 (s, 3 H, O-C$\underline{H}_3$), 3.46 (ddd, 1 H, H-5), 3.35 (dd, 1 H, $J_{4,5}$ 8.8 Hz, H-4), 3.34 (dd, 1 H, $J_{5,6b}$ 6.4 Hz, H-6b) 2.15 (d, 1 H, OH). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 138.5, 138.1 (ipso), 128.7, 128.6, 128.1, 128.0, 128.0 (aromatic), 99.5 (C-1), 83.0 (C-3), 81.3 (C-4), 75.6, 75.4 (2 × O-C$\underline{H}_2$-Ph), 73.3 (C-2), 69.8 (C-5), 55.7 (O-C$\underline{H}_3$), 7.5 (C-6). MS (MALDI): Calculated for ($C_{21}H_{25}IO_5Na$): *m/z* $[M+Na]^+$ 507.0645; found $[M+Na]^+$ 507.0646.

**Methyl 2-*O*-acetyl-6-deoxy-6-iodo-3,4-*O*-dibenzyl-α-D-glucopyranoside (24)**

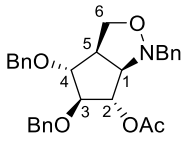



**24**

To an ice-cooled solution of alcohol **23** (2.56 g, 5.29 mmol) in $CH_2Cl_2$ (30 mL), $Et_3N$ (2.20 mL, 15.9 mmol), $Ac_2O$ (0.749 mL, 7.93 mmol) and a catalytic amount 4-dimethylaminopyridine were added. After consumption of the starting material (1 h, cyclohexane-EtOAc 2:1), MeOH (10 mL) was added and the solution was stirred for 15 min. The reaction mixture was consecutively washed with HCl (2 M) and saturated aqueous $NaHCO_3$ solution, the organic layer was dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. The remaining syrup was purified on silica gel (cyclohexane-EtOAc 10:1) to furnish iodosugar **24** (2.58 g, 4.90 mmol, 93%) as a colorless solid. $[\alpha]_D^{20}$: +88.9 (c= 0.93, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.40-7.23 (m, 10 H, aromatic), 4.95-4.84 (m, 1 H, H-2), 4.92 (d, 1 H, *J* 11.0 Hz, O-C$\underline{H}_2$-Ph), 4.81 (d, 1 H, *J* 11.4 Hz, O-C$\underline{H}_2$-Ph), 4.79 (d, 1 H, $J_{1,2}$ 3.9 Hz, H-1), 4.76 (d, 1 H, *J* 11.4 Hz, O-C$\underline{H}_2$-Ph,), 4.71 (d, 1 H, *J* 11.0 Hz, O-C$\underline{H}_2$-Ph), 4.05 (dd, 1 H, $J_{2,3} = J_{3,4}$ 8.9 Hz, H-3), 3.54-3.40 (m, 6 H, H-4, H-5, H-6a, O-C$\underline{H}_3$), 3.32 (dd, 1 H, $J_{5,6a}$ 6.3 Hz, $J_{6a,6b}$ 11.1 Hz,H-6b), 2.05 (s, 3 H, O-CO-C$\underline{H}_3$).$^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 170.4 (O-C$\underline{O}$-$CH_3$), 138.4, 138.0 (*ipso*), 128.7, 128.6, 128.1, 128.1, 127.9, 127.7 (aromatic), 97.2 (C-1), 81.7 (C-3), 80.0 (C-4), 75.7, 75.6 (2x O-C$\underline{H}_2$-Ph), 73.6 (C-2), 69.6 (C-5),

55.7 (O-$\underline{C}H_3$), 21.0 (O-CO-$\underline{C}H_3$), 7.1 (C-6). MS (MALDI): Calculated for ($C_{23}H_{27}O_6INa$): *m/z* [M+Na]$^+$ 549.0750 ; found [M+Na]$^+$ 549.0750.

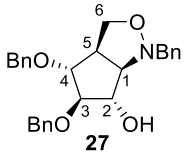
**(3a*R*,4*R*,5*S*,6*S*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-yl acetate (26)**




**26**

To a suspension of zinc (2.91 g, 44.5 mmol) and $NH_4Cl$ (0.476 g, 8.89 mmol) in MeOH/THF (1:1, 50 mL), 6-deoxyiodo sugar **24** (2.34 g, 4.45 mmol) was added. After completed conversion (20 min, cyclohexane-EtOAc 2:1), the solids were removed by filtration through a pad of celite. The solvents were removed under reduced pressure and the remaining syrup was dissolved in $CH_2Cl_2$ and washed with $H_2O$. The organic layer was dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure to obtain aldehyde **25**. Crude compound **25** was dissolved in MeOH and treated with pyridine (0.703 mL, 8.89 mmol) and *N*-benzylhydroxylamine hydrochloride (0.851 g, 5.33 mmol). After consumption of the starting material (2 h, cyclohexane-EtOAc 2:1) the reaction mixture was concentrated under reduced pressure and the residue was chromatographically purified (cyclohexane-EtOAc 2:1) to obtain isoxazolidine **26** (1.78 g, 3.76 mmol, 85% over 2 steps) as a white solid. $[\alpha]_D^{20}$: +24.9 (c = 1.2, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.42-7.20 (m, 15 H, aromatic), 5.23 (dd, 1 H, $J_{1,2}$ 5.7 Hz, $J_{2,3}$ 7.7 Hz, H-2), 4.76 (s, 2 H, O-C$\underline{H}_2$-Ph), 4.65 (d, 1 H, *J* 11.8 Hz, O-C$\underline{H}_2$-Ph), 4.56 (d, 1 H, *J* 11.8 Hz, O-C$\underline{H}_2$-Ph), 4.04 (dd, 1 H, $J_{5,6a}$ = $J_{6a,6b}$ 8.9 Hz, H-6a), 4.00-3.86 (m, 2 H, H-3, H-4), 3.93 (d, 1 H, *J* 13.1 Hz, O-C$\underline{H}_2$-Ph), 3.83 (d, 1 H, *J* 13.1 Hz, O-C$\underline{H}_2$-Ph), 3.68 (dd, 1 H, $J_{5,6b}$ 3.4 Hz, H-6b), 3.39 (dd, 1 H, $J_{1,5}$ 9.6 Hz, H-1), 3.02 (ddd, 1 H, $J_{4,5}$ 6.9 Hz, H-5), 1.91 (s, 3 H, O-CO-C$\underline{H}_3$). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 169.8 (O-$\underline{C}$O-CH$_3$), 138.4, 138.1, 137.0 (ipso), 129.1, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 127.5 (aromatic), 86.3 (C-3), 85.5 (C-4), 78.3 (C-2), 72.5, 72.4 (2 × O-$\underline{C}H_2$-Ph), 70.6 (C-6), 70.5 (C-1), 59.9 (N-$\underline{C}H_2$-Ph), 49.8 (C-5), 21.1 (O-CO-$\underline{C}H_3$). MS (MALDI): Calculated for ($C_{29}H_{31}NO_5H$): *m/z* [M+Na]$^+$ 474.2281; found [M+Na]$^+$ 474.2281.

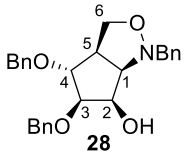
**(3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-ol (27)**




**27**

To a solution of isoxazolidine **26** (1.78 mg, 3.76 mmol) in MeOH/THF (3:1, 20 mL) a catalytic amount NaOMe (1 M, MeOH) was added. After completed saponification (10 min, cyclohexane-EtOAc 2:1), the solvents were removed under reduced pressure and the remaining syrup was quickly passed through a pad of silica gel (cyclohexane-EtOAc 2:1) to provide alcohol **27** (1.54 g, 3.57 mmol, 95%) as a colorless solid. $[\alpha]_D^{20}$: +25.2 (c = 0.99, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.42-7.23 (m, 15 H, aromatic), 4.82 (d, 1 H, *J* 12.2 Hz, O-C$\underline{H}_2$-Ph), 4.77 (d, 1 H, *J* 12.2 Hz, O-C$\underline{H}_2$-Ph), 4.62 (d, 1 H, *J* 11.8 Hz, O-C$\underline{H}_2$-Ph), 4.56 (d, 1 H, *J* 11.8 Hz, O-C$\underline{H}_2$-Ph), 4.09 (dd, 1H, $J_{5,6a}$ = $J_{6a,6b}$ 8.7 Hz, H-6a), 4.01 (d, 1 H, *J* 13.0 Hz, N-C$\underline{H}_2$-Ph), 3.96-3.72 (m, 3 H, H-2, H-3, H-4), 3.71 (d, 1 H, *J* 13.0 Hz, N-C$\underline{H}_2$-Ph), 3.62 (dd, 1 H, $J_{5,6b}$ 3.9 Hz, H-6b), 3.41 (dd, 1 H, $J_{1,2}$ = $J_{1,5}$ 6.2 Hz, H-1), 3.04-2.91 (m, 1 H, H-5), 2.48 (bs, 1 H, OH). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 138.7, 138.0, 136.7 (*ipso*), 129.2, 128.6, 128.5, 128.0, 127.9, 127.8, 127.8, 127.7 (aromatic), 87.1, 86.2 (C-3, C-4), 77.4 (C-2), 72.7, 72.3 (2 × O-$\underline{C}H_2$-Ph), 72.2 (C-1), 70.7 (C-6), 59.8 (N-$\underline{C}H_2$-Ph), 48.7 (C-5). MS (MALDI): Calculated for ($C_{27}H_{29}O_4NNa$): *m/z* [M+H]$^+$ 454.1994; found [M+H]$^+$ 454.1994.

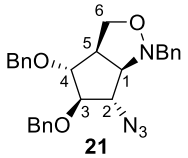
**(3a*R*,4*R*,5*R*,6*R*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-ol (28)**



**28**

A solution of oxalyl chloride (0.860 mL, 10.0 mmol) in $CH_2Cl_2$ (50 mL) was treated with DMSO (0.854 mL, 12.0 mmol) at -60 °C and stirred for 15 minutes. A 50% solution of alcohol **27** (1.73 g, 4.01 mmol) in $CH_2Cl_2$ was added to the reaction mixture. After an additional 20 min, $(i\text{-Pr})_2NEt$ (3.41 mL, 20.0 mmol) was added and the mixture was allowed to reach -20 °C. When completed oxidation to the corresponding ketone was observed (30 min, cyclohexane-EtOAc 2:1), MeOH (20 mL), and $NaBH_4$ (0.455 g, 12.3 mmol) were added at -20 °C. After complete reduction (10 min, cyclohexane-EtOAc 2:1), the suspension was allowed to reach ambient temperature. The reaction mixture was consecutively washed with HCl (2 M) and saturated aqueous $NaHCO_3$. The combined organic layers were dried ($Na_2SO_4$), filtered, and concentrated under reduced pressure. Column purification of the residue (cyclohexane-EtOAc 8:1) gave epimer **28** (1.46 g, 3.38 mmol, 84% over 2 steps) as a colorless solid. $[\alpha]_D^{20}$: +21.3 (c = 0.91, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.43-7.24 (m, 15 H, aromatic), 4.80 (d, 1 H, *J* 11.8 Hz, O-C$\underline{H}_2$-Ph), 4.76 (d, 1 H, *J* 12.2 Hz, O-C$\underline{H}_2$-Ph), 4.64 (d, 1 H, *J* 12.2 Hz, O-C$\underline{H}_2$-Ph), 4.57 (d, 1 H, *J* 11.8 Hz, O-C$\underline{H}_2$-Ph), 4.17 (d, 1 H, *J* 12.7 Hz, N-C$\underline{H}_2$-Ph), 4.06 (dd, 1 H, $J_{3,4}$ 7.9 Hz, $J_{2,3}$ 4.7 Hz, H-3), 4.04 (dd, 1 H, $J_{5,6a} = J_{6a,6b}$ 8.6 Hz, H-6a), 3.91 (dd, 1H, $J_{1,2}$ 5.4 Hz, H-2), 3.86 (d, 1 H, *J* 12.7 Hz, N-C$\underline{H}_2$-Ph), 3.67 (dd, 1 H, $J_{5,6b}$ 4.3 Hz, H-6b), 3.57 (bs, 1 H, OH), 3.01-2.90 (m, 1 H, H-5). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 138.4, 138.3, 136.3 (ipso), 129.1, 128.7, 128.6, 128.4, 127.9, 127.8, 127.7 (aromatic), 85.1 (C-3), 85.7 (C-4), 72.9, 72.0 (2 × O-C$\underline{H}_2$-Ph), 70.5 (C-6), 68.6 (C-2), 67.1 (C-1), 60.9 (N-C$\underline{H}_2$-Ph), 51.2 (C-5). MS (MALDI): Calculated for ($C_{27}H_{29}O_4NNa$): *m/z* $[M+H]^+$ 454.1994; found $[M+H]^+$ 454.1994.

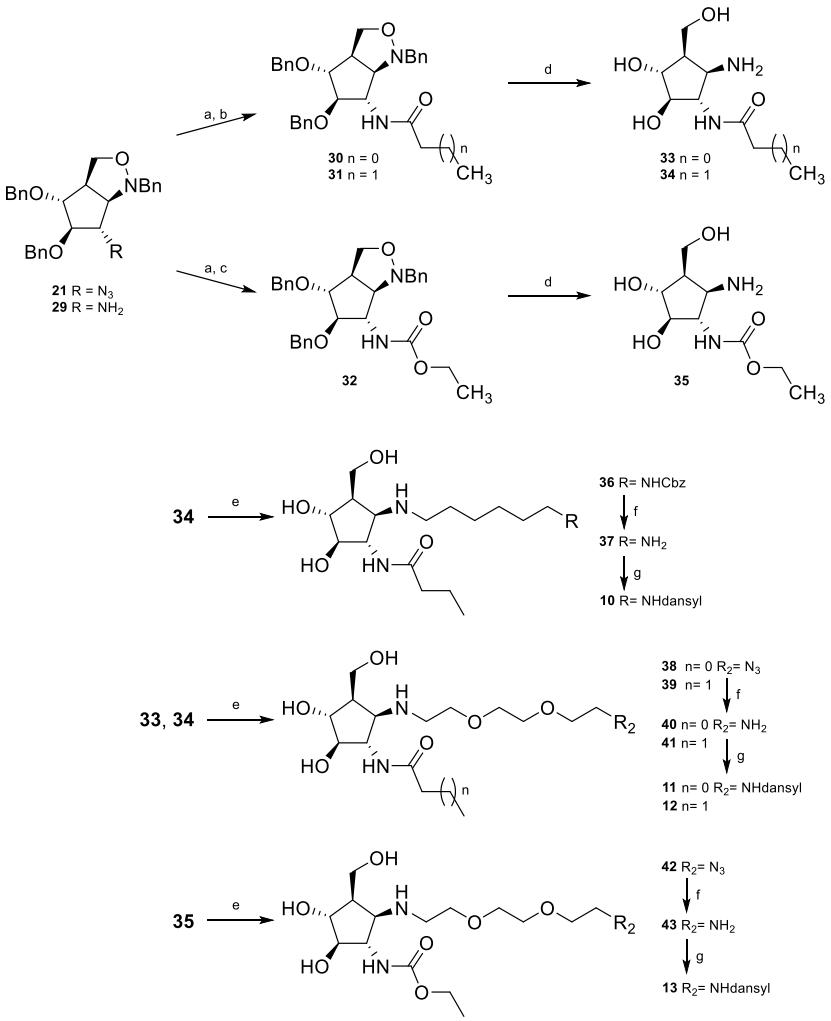
**(3a*R*,4*R*,5*R*,6*S*,6a*R*)-6-Azido-1-benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*) isoxazole (21)**



**21**

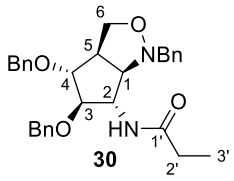
An ice-cooled solution of isoxazolidine **28** (1.46 g, 3.38 mmol) in $CH_2Cl_2$ (30 mL) was treated with pyridine (0.819 mL, 10.1 mmol) and $Tf_2O$ (0.683 mL, 4.06 mmol). After the completed reaction (10 min, cyclohexane-EtOAc 2:1), the reaction mixture was washed with saturated aqueous $NaHCO_3$, dried ($Na_2SO_4$) and the solvents were removed under reduced pressure at ambient temperature. The crude triflate was dissolved in DMF (20 mL) and $NaN_3$ (0.880 g, 13.5 mmol) was added. The suspension was stirred until complete conversion was observed (1 h, cyclohexane-EtOAc 3:1). Solids were filtered off and the filtrate was concentrated under reduced pressure. The remaining syrup was purified by silica gel chromatography (cyclohexane-EtOAc 10:1) to provide azide **21** (1.25 g, 2.74 mmol, 81% over 2 steps) as a colorless solid. $[\alpha]_D^{20}$: +4.8 (c = 0.91, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ= 7.41-7.24 (m, 15 H, aromatic), 4.78 (s, 2 H, O-C$\underline{H}_2$-Ph), 4.61 (d, 1 H, *J* 11.7 Hz, O-C$\underline{H}_2$-Ph), 4.56 (d, 1 H, *J* 11.7 Hz, O-C$\underline{H}_2$-Ph), 4.09 (dd, 1 H, $J_{5,6a} = J_{6a,6b}$ 8.4 Hz, H-6a), 3.98 (d, 1 H, *J* 12.9 Hz, N-C$\underline{H}_2$-Ph), 3.80-3.66 (m, 3 H, H-2, H-3), 3.69 (d, 1 H, *J* 12.9 Hz, N-C$\underline{H}_2$-Ph), 3.63 (dd, 1 H, $J_{5,6b}$ 2.3 Hz, H-6b), 3.47-3.38 (m, 1 H, H-1), 2.98-2.87 (m, 1 H, H-5). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 138.1, 137.8, 136.4 (*ipso*), 129.2, 128.7, 128.7, 128.6, 128.2, 128.0, 127.9, 127.9 (aromatic), 87.0 (C-4), 85.7 (C-3), 73.1, 72.5 (2 × O-C$\underline{H}_2$-Ph), 70.6 (C-6), 70.0 (C-1), 66.8 (C-2), 59.5 (N-C$\underline{H}_2$-Ph), 48.9 (C-5). MS (MALDI): Calculated for ($C_{27}H_{28}N_4O_3H$): *m/z* $[M+H]^+$ 457.2240; found $[M+H]^+$ 457.2240.

Reduction of azido intermediate **21** with zinc and sodium iodide in refluxing DMF-$H_2O$[11] or by treatment zinc in the presence of ammonium chloride[12] furnished the corresponding amine **29**, which was directly used for the respective acylation reaction. Reduction of azide **21**, followed by treatment with the respective acyl chloride resulted in corresponding amides **30** and **31**, N-Acylation with the respective chloroformate gave carbamate **32** in good yields. Catalytical hydrogenation in the presence of Pd/C of isoxazolidines **30-31** provided the corresponding polyols **33**-**35** in excellent yields. Introduction of the spacer arm via conventional alkylation reaction by treatment with the respective bromo alkane turned out unsuccessful. Thus, N-alkylation was achieved with a reductive amination under standard conditions with $NaBH_3CN$. To this end, polyols **33**-**34** were treated with the respective aldehyde (6-(*N*-benzyloxycarbonylamino)hexanal,[13] 2-(2-(2-azidoethoxy)ethoxy) acetaldehyde) to furnish amines **36**, **38**, **39**, **42** in 53-78% yield. Removal of the Cbz-group in compound **36** and reduction of the terminal azide in compounds **38**, **39**, **42** provided amines **37**, **40**, **41**, **43**, which were subsequently *N*-dansylated to give inhibitors **10-13** in 53-60%. (Scheme S4)




**Scheme S4.** Synthesis of inhibitors **10**-**13**. a: Zn, NaI, DMF/$H_2O$ (3:1), 120 °C or Zn, $NH_4Cl$, THF/MeOH/$H_2O$ (3:1:1), 60 °C; b: ClCO-R, $Et_3N$, $CH_2Cl_2$, 0 °C, 84% (**30**), 73% (**31**), 2 steps each; c: ethyl chloroformate, $Et_3N$, $CH_2Cl_2$, 0 °C, 74% (2 steps); d: $H_2$, 20% $Pd(OH)_2$/C, THF-MeOH (1:1), HCl, 95% (**33**), 93% (**34**), 96% (**35**); e: respective aldehyde, $NaBH_3CN$, AcOH, MeOH, 53% (**36**), 78% (**38**), 79% (**39**), 78% (**42**); f: $H_2$, 20% $Pd(OH)_2$/C, $CHCl_3$, MeOH, 94% (**40**), 93% (**41**), 97% (43); f: dansyl chloride, $Na_2CO_3$, MeOH, 49% (**10**, 2 steps), 53% (**11**), 58% (**12**), 60% (**13**).

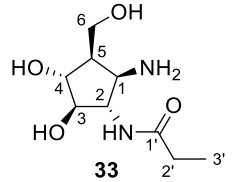
**_N_-((3a_R_,4_R_,5_R_,6_S_,6a_R_)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1_H_-cyclopenta[_c_]isoxazol-6-yl)propionamide (30)**



**30**

Azide **21** (573 mg, 1.26 mmol) was reduced by treatment with zinc (821 mg, 12.6 mmol) and $NH_4Cl$ (269 mg, 5.02 mmol), employing general procedure A. To a solution of crude amine **29** in $CH_2Cl_2$, $Et_3N$ (0.783 mL, 3.77 mmol) and propionyl chloride (0.164 mL, 1.88 mmol) were added at 0°C. The reaction mixture was allowed to stir overnight. The solution was treated with MeOH, stirred for 15 min and then concentrated under reduced pressure. Purification of the remaining oil was purified by silica gel chromatography (cyclohexane-EtOAc 10:1) furnished amide **30** as a colorless solid (513 mg, 1.05 mmol, 84% over 2 steps). $[\alpha]_D^{20}$: +25.9 (c = 0.99, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.42-7.22 (m, 15 H, aromatic), 5.47 (d, 1 H, *J* 7.5 Hz, NH), 4.73 (d, 1 H, *J* 11.7 Hz, O-C$\underline{H}_2$-Ph), 4.68 (d, 1 H, *J* 11.7 Hz, O-C$\underline{H}_2$-Ph), 4.62 (dd, 1 H, *J* 12.5 Hz, O-C$\underline{H}_2$-Ph), 4.58 (d, 1 H, *J* 12.5 Hz, O-C$\underline{H}_2$-Ph), 4.34 (dd, 1H, $J_{2,3}$ = $J_{3,4}$ 7.5 Hz, H-3), 4.11 (dd, 1H, $J_{5,6a}$ = $J_{6a,6b}$ 8.3 Hz, H-6a), 3.98 (d, 1 H, *J* 13.0 Hz, N-C$\underline{H}_2$-Ph), 3.81 (dd, 1H, $J_{4,5}$ 4.9 Hz, H-4), 3.80 (dd, 1H, $J_{1,2}$ 9.7 Hz, $J_{1,5}$ 6.2 Hz, H-1), 3.79 (d, 1 H, *J* 13.0 Hz, N-C$\underline{H}_2$-Ph), 3.74 (dd, 1H, H-2), 3.73 (dd, 1H, $J_{5,6b}$ 3.9 Hz, $J_{6a,6b}$ 8.3 Hz, H-6b), 3.07 (dddd, 1H, H-5), 1.98 (q, 2H, *J* 7.5 Hz, H-2′), 1.02 (t, 3H, *J* 7.5 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 173.7 (C-1′), 138.7, 138.1, 136.9 (*ipso*), 129.3, 128.6, 128.5, 128.0, 127.9, 127.8, 127.7, 127.5 (aromatic), 87.0 (C-4), 84.5 (C-3), 72.5, 72.1 (2 × O-C$\underline{H}_2$-Ph), 70.6 (C-6), 69.9 (C-1), 60.1 (N-C$\underline{H}_2$-Ph), 58.6 (C-2), 50.0 (C-5), 29.9 (C-2′), 9.6 (C-3′). MS (MALDI): Calculated for ($C_{30}H_{34}N_2O_4H$): *m/z* $[M+H]^+$ 487.2597; found $[M+H]^+$ 487.2597.

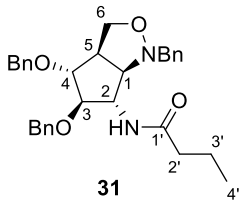
**_N_-((1S,2R,3R,4R,5R)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)propanoylamide "(1-Amino-2-deoxy-2-propanoylamino-"β-D-_gluco_-like"-cyclopentane)" (33)**



**33**

Following general procedure B, isoxazolidine **30** (486 mg, 0.999 mmol) was treated with $Pd(OH)_2$/C and stirred under an atmosphere of $H_2$. The remaining syrup was quickly passed through a pad of silica gel ($CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1) to provide amine **33** as a colorless solid (208 mg, 0.953 mmol, 95%). Amine **33** (10 mg) was dissolved in MeOH and the pH was adjusted to 1 (12 M HCl). Removal of the solvents under reduced pressure provided **33**·HCl. $[\alpha]_D^{20}$: + 27.9 (c = 1.0, MeOH,); free base: $^1$H-NMR (300 MHz, $D_2O$) δ = 3.91 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 9.2 Hz, H-2), 3.90-3.82 (m, 3 H, H-3, H-6), 3,80 (dd, 1H, $J_{3,4}$ = $J_{4,5}$ 8.5 Hz, H-4), 3.49 (dd, 1 H, $J_{1,5}$ 9.2 Hz, H-1), 2.32 (q, 2 H, *J* 7.6 Hz, H-2′), 2.25-2.14 (m, 1 H, H-5), 1.12 (t, 3 H, *J* 7.6 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ= 179.0 (C-1′), 78.0 (C-3), 74.8 (C-4), 58.8 (C-2), 58.7 (C-6), 53.0 (C-1), 44.6 (C-5), 29.1 (C-2′), 9.3 (C-3′). hydrochloride: $^1$H-NMR (300 MHz, $D_2O$) δ = 4.05 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.8 Hz, H-2), 3,92 (dd, 1 H, $J_{3,4}$ 8.0 Hz, H-3), 3.94-3.80 (m, 3 H, H-4, H-6), 3.75 (dd, 1 H, $J_{1,5}$ 9.8 Hz, H-1), 2.39-2.24 (m, 3 H, H-5, H-2′), 1.10 (t, 3 H, *J* 7.6 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 179.3 (C-1′), 77.0 (C-4), 73.9 (C-3), 58.0 (C-6), 56.7 (C-2), 53.3 (C-1), 42.8 (C-5), 28.8 (C-2′), 9.2 (C-3′). MS (MALDI): Calculated for ($C_9H_{18}N_2O_4H$): *m/z* $[M+H]^+$ 219.1345; found $[M+H]^+$ 219.1356.

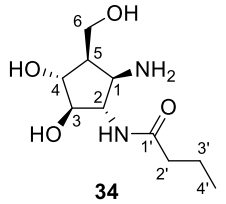
**_N_-((3a_R_,4_R_,5_R_,6_S_,6a_R_)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1_H_-cyclopenta(_c_)isoxazol-6-yl)butyramide (31)**




**31**

To a suspension of zinc (424 mg, 6.48 mmol) and NaI (583 mg, 3.89 mmol) in DMF-$H_2O$ (10:1, 5 mL),[8] azide **21** (296 mg, 0.648 mmol) was added. The mixture was heated to reflux until completed conversion was observed (30 min, cyclohexane-EtOAc 3:1). The suspension was allowed to reach ambient temperature and the solids were removed by filtration. The filtrate was washed twice with EtOAc and the collected organic layers were dried ($Na_2SO_4$) and concentrated under reduced pressure to furnish amine **29**. Crude amine **29** was dissolved in $CH_2Cl_2$ (10 mL) and treated with $Et_3N$ (0.270 mL, 1.95 mmol) and butyryl chloride (0.101 mL, 0.973 mmol) at 0°C. The reaction mixture was stirred for two hours and was subsequently quenched with MeOH. The solvents were removed under reduced pressure and the remaining syrup was purified on silica gel (cyclohexane-EtOAc 10:1) to yield corresponding amide **31** (238 mg, 0.475 mmol, 73% over 2 steps) as a colorless solid. $[\alpha]_D^{20}$: +19.9 (c = 0.67, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 7.40-7.19 (m, 15 H, aromatic), 5.50 (d, 1 H, $J_{2,NH}$ 7.3 Hz, NH), 4.71 (d, 1 H, *J* 12.6 Hz, O-C$\underline{H}_2$-Ph), 4.67 (d, 1 H, *J* 12.6 Hz, O-C$\underline{H}_2$-Ph), 4.59 (d, 1 H, *J* 11.6 Hz, O-C$\underline{H}_2$-Ph), 4.55 (d, 1 H, *J* 11.6 Hz, O-C$\underline{H}_2$-Ph), 4.32 (dd, 1 H, $J_{2,3}$ = $J_{3,4}$ 7.4 Hz, H-3), 4.09 (dd, 1H, $J_{5,6a}$ = $J_{6a,6b}$ 8.3 Hz, H-6a), 3.94 (d, 1 H, *J* 13.1 Hz, N-C$\underline{H}_2$-Ph), 3.82 (d, 1 H, *J* 13.1 Hz, N-C$\underline{H}_2$-Ph), 3.82-3.66 (m, 4 H, H-1, H-2, H-4, H-6b), 3.12-2.99 (m, 1 H, H-5), 1.93 (t, 2 H, *J* 7.2 Hz, H-2′), 1.57-1.43 (m, 2 H, H-3′), 0.88 (t, 3 H, *J* 7.3 Hz, H-4′). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 172.9 (C-1′), 138.7, 138.1, 137.1 (*ipso*), 129.2, 128.6, 128.4, 128.0, 127.9, 127.8, 127.7, 127.5 (aromatic), 87.0 (C-3), 84.6 (C-4), 72.4, 72.1 (2 × O-C$\underline{H}_2$-Ph), 70.5 (C-6), 70.2 (C-1), 60.2 (N-C$\underline{H}_2$-Ph), 58.4 (C-2), 50.0 (C-5), 38.9 (C-2′), 19.0 (C-3′), 13.9 (C-4′). MS (MALDI): Calculated for ($C_{31}H_{36}N_2O_4H$): *m/z* $[M+H]^+$ 501.2753; found $[M+H]^+$ 501.2753.

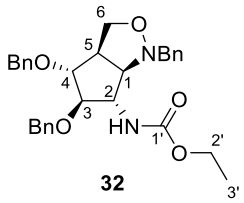
**_N_-((1_S_,2_R_,3_R_,4_R_,5_R_)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)butyramide "(1-Amino-2-butanoylamino-2-deoxy-"β-D-_gluco_-like"-cyclopentane)" (34)**




**34**

Following general procedure B, isoxazolidine **31** (486 mg, 0.999 mmol) was treated with $Pd(OH)_2$/C-$H_2$. The remaining syrup was quickly passed through a pad of silica gel ($CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1) to provide amine **34** as a colorless solid (98.1 mg, 0.422 mmol, 93%). Amine **34** was dissolved in MeOH and the pH was adjusted to 1 (12 M HCl). Removal of the solvents under reduced pressure gave **34**·HCl. $[\alpha]_D^{20}$: +17.2 (c = 1.2, MeOH, hydrochloride); hydrochloride:$^1$H-NMR (300 MHz, $D_2O$) δ = 4.04 (dd, 2 H, $J_{1,2}$ = $J_{2,3}$ 8.6 Hz, H-2), 3.91 (dd, 2 H, $J_{6a,6b}$ 8.0 Hz, H-6), 3.96-3.87 (m, 2 H, H-3, H-4), 3.77 (dd, 1 H, $J_{1,5}$ 8.6 Hz, H-1), 2.37 (ddd, 1 H, H-5), 2.29 (t, 2 H, *J* 7.4 Hz, H-2′), 1.69-1.55 (m, 2 H, H-3′), 0.92 (t, 3 H, *J* 7.4 Hz, H-4′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 178.6 (C-1′), 77.0, 73.9 (C-3, C-4), 57.9 (C-6), 56.8 (C-2), 53.6 (C-1), 42.9 (C-5), 37.5 (C-2′), 18.8 (C-3′), 12.9 (C-4′). MS (MALDI): Calculated for ($C_{10}H_{20}N_2O_4Na$): *m/z* $[M+Na]^+$ 255.1321; found $[M+Na]^+$ 255.1319.

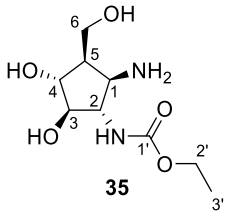
**Ethyl ((3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl)carbamate (32)**




**32**

Azide **21** (585 mg, 1.28 mmol) was treated with zinc (838 mg, 12.8 mmol) and $NH_4Cl$ (274 mg, 5.31 mmol) following general procedure A. A solution of crude amine **29** was dissolved in $CH_2Cl_2$ (10 mL) and treated with $Et_3N$ (0.533 mL, 3.84 mmol) and ethyl chloroformate (0.183 mL, 1.92 mmol) at 0 °C. The reaction mixture was stirred for two hours and was subsequently quenched with $H_2O$. After 20 min the organic layer was separated and the aqueous layer was washed with $CH_2Cl_2$. The combined organic layers were dried ($Na_2SO_4$), filtered, and evaporated *in vacuo*. The residue was purified employing silica gel chromatography (cyclohexane-EtOAc 10:1) to furnish corresponding carbamate **32** as a colorless solid (475 mg, 0.945 mmol, 74% over 2 steps). $[\alpha]_D^{20}$: +22.9 (c = 0.92, $CHCl_3$); $^1$H-NMR (300 MHz, $CDCl_3$) δ = 4.83-4.75 (m, 1 H, NH), 4.72 (s, 2 H, O-C$\underline{H}_2$-Ph), 4.61 (d, 1 H, *J* 11.9 Hz, O-C$\underline{H}_2$-Ph), 4.56 (d, 1 H, *J* 11.9 Hz, O-C$\underline{H}_2$-Ph), 4.34 (bs, 1 H, H-3), 4.07 (dd, 1 H, $J_{5,6a}$ = $J_{6a,6b}$ 8.6 Hz, H-6a), 4.01 (t, 2 H, H-2′), 3.97 (d, 1 H, *J* 13.0 Hz, N-C$\underline{H}_2$-Ph), 3.79 (d, 1 H, *J* 13.0 Hz, N-C$\underline{H}_2$-Ph), 3.79 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 6.4 Hz, H-4), 3.68 (dd, 1 H, $J_{5,6b}$ 3.8 Hz, H-6b), 3.73-3.50 (m, 2 H, H-1, H-2), 3.05-2.90 (m, 1 H, H-5), 1.20 (t, 3 H, *J* 7.1 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $CDCl_3$) δ = 155.7 (C-1′), 138.6, 138.1, 137.0 (*ipso*), 129.1, 128.6, 128.4, 128.0, 127.8, 127.8, 127.7, 127.5 (aromatic), 86.8 (C-4), 84.4 (C-3), 72.5, 72.2 (2 × O-$\underline{C}H_2$-Ph), 70.6 (C-6), 69.7 (C-1), 60.8 (C-2′), 59.9 (N-$\underline{C}H_2$-Ph), 59.1 (C-2), 49.5 (C-5), 14.7 (C-3′). MS (MALDI): Calculated for ($C_{30}H_{34}N_2O_5H$): *m/z* $[M+H]^+$ 503.2546; found $[M+H]^+$ 503.2548.

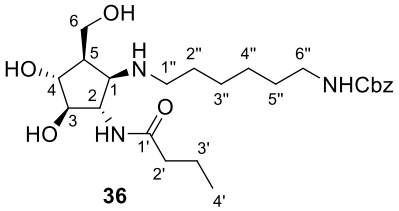
**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)carbamate "(1-Amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane)" (35)**




**35**

Isoxazolidine **32** (445 mg, 0.885 mmol) was dissolved in EtOH-THF (1:1) and the pH was adjusted to 1 (2 M HCl). Pearlman's catalyst (20% $Pd(OH)_2$/C) was added and the solution was stirred under an atmosphere of $H_2$ at ambient pressure. After the complete conversion (6 h, $CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1), the reaction mixture was filtered and the solvents were removed under reduced pressure. Silica gel filtration of the residue ($CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1) afforded amine **35** as a colorless solid (198 mg, 0.845 mmol, 96%). Amine **35** (10 mg) was dissolved in EtOH and the pH was adjusted to 1 (12 M HCl). Removal of the solvents under reduced pressure provided **35**·HCl. $[\alpha]_D^{20}$: +20.1 (c = 1.0, MeOH, hydrochloride); free base: $^1$H-NMR (300 MHz, $D_2O$) δ = 4.20-4.06 (m, 2 H, H-2′), 3.94-3.78 (m, 5 H, H-2, H-3, H-4, H-6), 3.7 (dd, 1 H, $J_{1,2}$ = $J_{1,5}$ 9.4 Hz, H-1), 2.37-2.24 (m, 1 H, H-5), 1.24 (t, 3 H, *J* 7.2 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 158.1 (C-1′), 77.1 (C-3), 74.0 (C-4), 62.2 (C-2′), 58.2 (C-6), 58.1 (C-2), 52.9 (C-1), 42.9 (C-5), 13.8 (C-3′). hydrochloride: $^1$H-NMR (300 MHz, $D_2O$) δ = 4.21-4.07 (m, 2 H, H-2′), 3.96-3.78 (m, 5 H, H-2, H-3, H-4, H-6), 3.77 (dd, 1 H, $J_{1,2}$ 8.8 Hz, $J_{1,5}$ 9.6 Hz, H-1), 2.39-2.26 (m, 1H, H-5), 1.24 (t, 3 H, *J* 7.1 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 158.8 (C-1′), 77.0 (C-3), 73.9 (C-4), 62.3 (C-2′), 58.2 (C-6), 57.9 (C-2), 53.0 (C-1), 42.7 (C-5), 13.8 (C-3′). MS (MALDI): Calculated for ($C_9H_{18}N_2O_5H$): *m/z* $[M+H]^+$ 235.1294; found $[M+H]^+$ 235.1290.

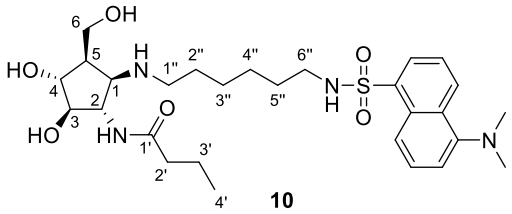
**Benzyl (6-(((1*R*,2*S*,3*R*,4*R*,5*R*)-2-butyramido-3,4-dihydroxy-5-(hydroxymethyl)cyclopentyl)amino) hexyl) carbamate "(2-Butanoylamino-1-(6-carbobenzyloxyaminohexyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (36)**



**36**

A solution of amine **34** (42.1 mg, 181 µmol) in methanol (2 mL) was treated with AcOH (50 µL), benzyl (6-oxohexyl)carbamate[13] (58.7 mg, 236 µmol) and $NaBH_3CN$ (17.1 mg, 272 µmol). After the complete conversion (30 min, $CHCl_3$-MeOH 3:1 + 1 vol% $NH_4OH$), the suspension was concentrated under reduced pressure. The residue was purified by silica gel chromatography ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$) to give carbamate **36** (44.7 mg, 96.0 µmol, 53%) as a colorless oil. $[\alpha]_D^{20}$: +17.6 (c = 0.97, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 7.40-7.24 (m, 5 H, aromatic), 5.06 (s, 2 H, NH-CO-O-C$\underline{H}_2$-Ph), 3.89 (dd, 2 H, $J_{1,2}$ = $J_{2,3}$ 8.4 Hz, H-2), 3.87-3.73 (m, 2 H, H-3, H-4), 3.82 (dd, 2 H, $J_{6a,6b}$ 11.6 Hz, H-6), 3.69 (dd, 1 H, $J_{3,4}$ 8.2 Hz, H-4), 3.16 (dd, 1 H, $J_{1,5}$ 8.4 Hz, H-1), 3.10 (t, 2 H, H-6″), 2.79-2.56 (m, 2 H, H-1″), 2.21 (t, 2 H, *J* 7.3 Hz, H-2′), 2.07 (ddd, 1 H, H-5), 1.73-1.22 (m, 10 H, H-3′, H-2″, H-3″, H-4″, H-5″), 0.95 (t, 3 H, *J* 7.3 Hz, H-4′).$^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 176.8 (C-1′), 158.9 (NH-$\underline{C}$O-O-$CH_2$-Ph), 138.5 (*ipso*), 129.4, 128.9, 128.7 (aromatic), 80.9 (C-3), 76.9 (C-4), 67.3 (NH-CO-O-$\underline{C}H_2$-Ph), 62.9 (C-1), 61.1 (C-6), 60.9 (C-2), 49.7 (C-1″), 47.2 (C-5), 41.7 (C-6″), 39.0 (C-2′), 30.8, 30.4, 27.8, 27.6, (C-2′, C-2″, C-3″, C-4″, C-5″, C-6″), 20.3 (C-3′), 14.0 (C-4′). MS (MALDI): Calculated for ($C_{24}H_{39}N_3O_6$H): *m/z* $[M+H]^+$ 466.2917; found $[M+H]^+$ 466.2914.

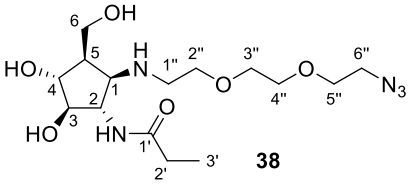
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((6-((5-(Dimethylamino)naphthalene)-1-sulfonamido)hexyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)butyramide "(2-Butanoylamino-1-(6-dansylamino hexyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (10)**



**10**

To a solution of carbamate **36** (44.0 mg, 94.5 µmol) in methanol (2 mL), 10% Pd/C was added and the reaction mixture was stirred under an atmosphere of $H_2$ at ambient pressure. After completed deprotection was observed (30 min, $CHCl_3$-MeOH-$NH_4OH$ 8:4:1), the catalyst was removed by filtration and the filtrate was concentrated under reduced pressure to yield crude amine **37**. This was dissolved in methanol (2 mL) and the solution was treated with $Et_3N$ (26.3 µL, 189 µmol) and dansyl chloride (28.0 mg, 104 µmol). After completed reaction (10 min, $CHCl_3$-MeOH 3:1 + 1 vol% $NH_4OH$ ), the solvents were removed *in vacuo* and the residue was purified on silica gel ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$) to give inhibitor **10** (26.3 mg, 46.6 µmol, 49% over 2 steps) as a yellow oil. $[\alpha]_D^{20}$: +15.3 (c = 0.97, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 8.55 (d, 1 H, *J* 8.5 Hz, dansyl), 8.36 (d, 1 H, *J* 8.6 Hz, dansyl), 8.18 (d, 1 H, *J* 7.2 Hz, dansyl), 7.58 (dd, 1 H, *J* 8.5 Hz, *J* 7.2 Hz, dansyl), 7.57 (dd, 1 H, *J* 8.6 Hz, *J* 7.5 Hz, dansyl), 7.27 (d, 1 H, *J* 7.5 Hz, dansyl), 3.84 (dd, 2 H, $J_{1,2}$ = $J_{2,3}$ 8.3 Hz, H-2), 3.84-3.69 (m, 3 H, H-4, H-6), 3.66 (dd, 1 H, $J_{3,4}$ 8.3 Hz, H-3), 3.06 (dd, 1H, $J_{3,4}$ 8.5 Hz, H-4), 2.88 (s, 6 H, dansyl), 2.83 (t, 2 H, H-6″), 2.63-2.39 (m, 2 H, H-1″), 2.19 (t, 2 H, *J* 7.2 Hz, H-2′), 2.04 (ddd, 1 H, H-5), 1.70-1.01 (m, 10 H, H-3′, H-2″, H-3″, H-4″, H-5″), 0.93 (t, 3 H, *J* 7.3 Hz, H-4′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 176.7 (C-1′), 153.2, 137.3, 131.2, 131.1, 131.0, 130.1, 129.0, 124.3, 120.6, 116.4 (dansyl), 81.1 (C-3), 77.1 (C-4), 62.9 (C-1), 61.3 (C-6), 61.1 (C-2), 49.8 (C-1″), 47.4 (C-5), 45.8 (dansyl), 43.7 (C-6″), 39.1 (C-2′), 30.5, 30.4, 27.6, 27.3, (C-2″, C-3″, C-4″, C-5″), 20.4 (C-3′), 14.0 (C-4′). MS (MALDI): Calculated for ($C_{28}H_{44}N_4O_6$SH): *m/z* $[M+H]^+$ 565.3060; found $[M+H]^+$ 565.3059.

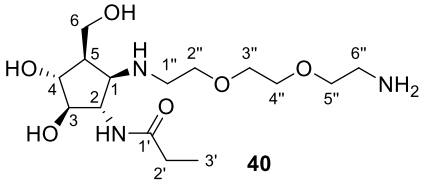
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)propanoylamide "(1-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (38)**



**38**

Reaction of amine **33** (193 mg, 0.884 mmol) with AcOH (100 µL), 2-(2-(2-azidoethoxy)ethoxy) acetaldehyde[14] (230 mg, 1.33 mmol) and $NaBH_3CN$ (83.4 mg, 1.33 mmol) following general procedure C resulted in crude azide **38**. Residue was purified using silica gel chromatography ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$ (25%)) to obtain azide **38** as a colorless oil (258 mg, 0.687 mmol, 78%). $[\alpha]_D^{20}$: +24.7 (c = 1.0, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 3.88 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.5 Hz, H-2), 3.81 (dd, 2 H, $J_{5,6a}$ = $J_{5,6b}$ 4.2 Hz, $J_{6a,6b}$ 11.1 Hz, H-6), 3.80 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 8.1 Hz, H-4), 3.72-3.54 (m, 9 H, H-3, H-2″, H-3″, H-4″, H-5″), 3.38 (t, 2 H, *J* 4.7 Hz, H-6″), 3.12 (dd, 1 H, $J_{1,5}$ 8.5, H-1), 2.94-2.70 (m, 2 H, H-1″), 2.25 (q, 2 H, *J* 7.6 Hz, H-2′), 2.09 (dddd, 1 H, H-5), 1.15 (t, 3 H, *J* 7.6 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 177.5 (C-1′), 81.5 (C-3), 77.4 (C-4), 71.6, 71.5, 71.3, 71.2 (C-2″, C-3″, C-4″, C-5″), 62.3 (C-1), 61.4 (C-2), 61.3 (C-6), 51.8 (C-6″), 49.2 (C-1″), 47.8 (C-5), 30.3 (C-2′), 10.4 (C-3′). MS (MALDI): Calculated for ($C_{15}H_{29}N_5O_6H$): *m/z* $[M+H]^+$ 376.2196; found $[M+H]^+$ 376.2198.

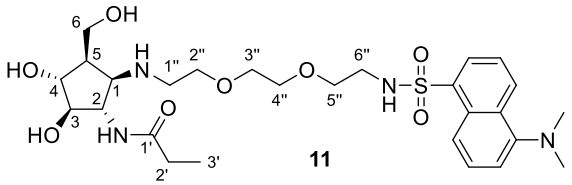
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl) cyclopentyl)propanoylamide "(1-(2-(2-(2-Aminoethoxy)ethoxy)ethyl) amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (40)**



**40**

Azide **38** (231 mg, 0.615 mmol) was reduced according to general procedure D. The residual oil was quickly passed through a pad of silica gel ($CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1) to yield amine **40** as a colorless solid (203 mg, 0.615 mmol, 94%). $[\alpha]_D^{20}$: +19.4 (c = 0.98, MeOH); $^1$H-NMR (300 MHz, $D_2O$) δ = 4.13 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.2 Hz, H-2), 3.96 (dd, 1 H, $J_{5,6a}$ 4.3 Hz, $J_{6a,6b}$ 12.1 Hz, H-6a), 3.92-3.80 (m, 3 H, H-3, H-4, H-6b), 3.80-3.69 (m, 8 H, H-2″, H-3″, H-4″, H-5″), 3.67 (dd, 1 H, $J_{1,5}$ 9.2 Hz, H-1), 3.29-3.12 (m, 4 H, H-1″, H-6″), 2.45-2.31 (m, 1 H, H-5), 2.32 (q, 2 H, *J* 7.6 Hz, H-2′), 1.12 (t, 3 H, *J* 7.6 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 178.5 (C-1′), 78.2, 73.8 (C-3, C-4), 69.7, 69.6, 66.4, 66.3 (C-2″, C-3″, C-4″, C-5″), 59.8 (C-1), 58.2 (C-6), 56.7 (C-2), 46.4 (C-1″), 43.6 (C-5), 39.1 (C-6″), 29.1 (C-2′), 9.3 (C-3′). MS (MALDI): Calculated for ($C_{15}H_{31}N_3O_6H$): *m/z* $[M+H]^+$ 350.2291; found $[M+H]^+$ 350.2292.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(Dimethylamino)naphthalene)-1-sulfonamido)ethoxy)ethoxy) ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)propanoylamide "(1-(2-(2-(2-Dansyl aminoethoxy)ethoxy)ethyl)amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (11)**

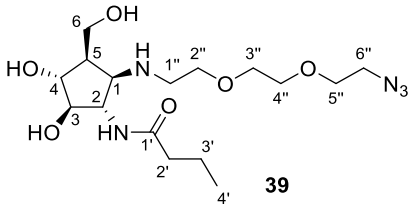


**11**

*N*-Dansylation of amine **40** (181 mg, 0.518 mmol) was done by treatment with $Na_2CO_3$ (110 mg, 1.04 mmol) and dansyl chloride (154 mg, 0.570 mmol) following general procedure E. Purification with silica gel chromatography ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$ (25%)) afforded inhibitor **11** as yellow oil (160 mg, 0.275 mmol, 53%). $[\alpha]_D^{20}$: +16.7(c = 0.93, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 8.56 (d, 1 H, *J*

8.5 Hz, dansyl), 8.37 (d, 1 H, *J* 8.6 Hz, dansyl), 8.22 (d, 1 H, *J* 7.2 Hz, dansyl), 7.60 (dd, 1 H, *J* 8.5 Hz, *J* 7.2 Hz, dansyl), 7.58 (dd, 1 H, *J* 8.6 Hz, *J* 7.5 Hz, dansyl), 7.28 (d, 1 H, *J* 7.5 Hz, dansyl), 3.88 (dd, 1 H, $J_{1,2} = J_{2,3}$ 8.2 Hz, H-2), 3.81 (dd, 2 H, $J_{5,6a}$ 6.4 Hz, $J_{6a,6b}$ 11.3 Hz, H-6a), 3.80 (dd, 1 H, $J_{3,4} = J_{4,5}$ 7.8 Hz, H-4), 3.77 (dd, 1 H, $J_{5,6b}$ 4.2 Hz, H-6b), 3.68 (dd, 1 H, H-3), 3.52-3.25 (m, 8 H, H-2″, H-3″, H-4″, H-5″), 3.10 (dd, 1 H, $J_{1,5}$ 9.1 Hz, H-1), 3.06 (t, 2 H, *J* 5.3 Hz, H-6″), 2.93-2.62 (s, 8 H, H-1″, dansyl), 2.24 (t, 2 H, *J* 7.7 Hz, H-2′), 2.09 (dddd, 1 H, H-5), 1.13 (t, 3 H, *J* 7.6 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 177.5 (C-1′), 153.2, 137.4, 131.2, 131.1, 131.0, 130.0, 129.1, 124.3, 120.7, 116.4 (dansyl), 81.4 (C-3), 77.4 (C-4), 71.2, 71.1, 71.1, 70.6, (C-2″, C-3″, C-4″, C-5″), 62.4 (C-1), 61.5 (C-6), 61.3 (C-2), 49.1 (C-1″), 47.8 (C-5), 45.8 (dansyl), 43.8 (C-6″), 30.3 (C-2′), 10.4(C-3′). MS (MALDI): Calculated for ($C_{27}H_{42}N_4O_8SH$): *m/z* $[M+H]^+$ 583.2802; found $[M+H]^+$ 583.2807.

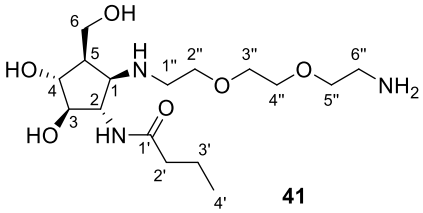
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)butyramide "(1-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino-2-butanoylamino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (39)**




**39**

Amine **34** (106 mg, 0.430 mmol) was treated with AcOH (60 µL), 2-(2-(2-azidoethoxy)ethoxy) acetaldehyde (96.9 mg, 0.559 mmol) and $NaBH_3CN$ (40.6 mg, 0.646 mmol), following general procedure C. The residual oil was purified using silica gel chromatography ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$ (25%)) to yield azide **39** as colourless oil (140 mg, 0.359 mmol, 79%). $[\alpha]_D^{20}$: +20.1 (c = 0.90, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 3.88 (dd, 1 H, $J_{1,2} = J_{2,3}$ 8.2 Hz, H-2), 3.80 (dd, 1 H, $J_{3,4} = J_{4,5}$ 7.5 Hz, H-4), 3.79 (dd, 1 H, $J_{5,6a}$ 4.3 Hz, $J_{6a,6b}$ 11.1 Hz, H-6a), 3.78 (dd, 1 H, $J_{5,6a}$ 4.1 Hz, H-6b), 3.70-3.54 (m, 9 H, H-3, H-2″, H-3″, H-4″, H-5″), 3.37 (t, 2 H, *J* 4.8 Hz, H-6″), 3.11 (dd, 1 H, $J_{1,5}$ 8.5, H-1), 2.94-2.69 (m, 2 H, H-1″), 2.21 (t, 2 H, *J* 7.4 Hz, H-2′), 2.08 (dddd, 1 H, H-5), 1.73-1.58 (m, 2 H, H-3′), 0.97 (t, 3 H, *J* 7.4 Hz, H-4′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 176.6 (C-1′), 81.5 (C-3), 77.4 (C-4), 71.5, 71.5, 71.3, 71.2 (C-2″, C-3″, C-4″, C-5″), 62.4 (C-1), 61.4 (C-6), 61.2 (C-2), 51.8 (C-6″), 49.3 (C-1″), 47.8 (C-5), 39.2 (C-2′), 20.4 (C-3′), 14.0 (C-4′). MS (MALDI): Calculated for ($C_{16}H_{31}N_5O_6H$): *m/z* $[M+H]^+$ 390.2353; found $[M+H]^+$ 390.2354.

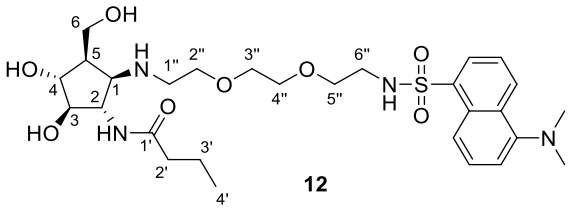
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)butyramide "(1-(2-(2-(2-Aminoethoxy)ethoxy))ethyl)amino-2-butanoylamino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (41)**




**41**

Azide **39** (113 mg, 0.290 mmol) was treated according to general procedure D. The remaining oil was quickly passed through a pad of silica gel ($CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1) to afford amine **41** as a colorless solid (98.2 mg, 0.270 mmol, 93%). $[\alpha]_D^{20}$: +14.4 (c = 1.0, MeOH); $^1$H-NMR (300 MHz, $D_2O$) δ= 4.06 (dd, 1 H, $J_{1,2} = J_{2,3}$ 8.1 Hz, H-2), 3.99-3.67 (m, 12 H, H-3, H-4, H-6, H-2″, H-3″, H-4″, H-5″), 3.45 (dd, 1 H, $J_{1,5}$ 9.3 Hz, H-1), 3.28 (t, 2 H, *J* 5.0 Hz, H-6″), 3.13-2.89 (m, 2 H, H-1″), 2.43-2.27 (m, 3 H, H-5, H-2′), 1.76-1.60 (m, 2 H, H-3′), 0.98 (t, 3 H, *J* 7.4 Hz, H-4′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ = 177.2 (C-1′), 79.1 (C-3), 74.7 (C-4), 69.6, 69.5, 68.2, 66.4 (C-2″, C-3″, C-4″, C-5″), 59.4 (C-1), 59.0 (C-6), 58.1 (C-2), 46.4 (C-1″), 44.7 (C-5), 39.2 (C-6″), 37.8 (C-2′), 18.9 (C-3′), 12.9 (C-4′). MS (MALDI): Calculated for ($C_{16}H_{33}N_3O_6H$): *m/z* $[M+H]^+$ 364.2448; found $[M+H]^+$ 364.2448.

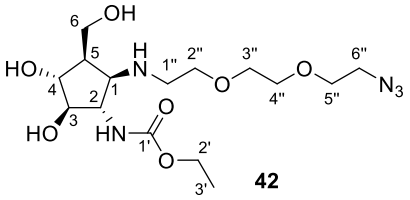
***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethoxy)ethoxy) ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)butyramide "(2-Butanoyl amino-1-(2-(2-(2-dansylaminoethoxy)ethoxy)ethyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (12)**



**12**

Amine **41** (83.2 mg, 0.229 mmol) was N-dansylated according to general procedure E. Chromatographic purification of the residue ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$ (25%)) afforded inhibitor **12** as yellow oil (79.8 mg, 0.134 mmol, 58%). $[\alpha]_D^{20}$: +14.0 (c = 1.1, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 8.56 (d, 1 H, *J* 8.5 Hz, dansyl), 8.36 (d, 1 H, *J* 8.6 Hz, dansyl), 8.21 (d, 1 H, *J* 7.3 Hz, dansyl), 7.60 (dd, 1 H, *J* 8.5 Hz, *J* 7.3 Hz, dansyl), 7.58 (dd, 1 H, *J* 8.6 Hz, *J* 7.6 Hz, dansyl), 7.28 (d, 1 H, *J* 7.6 Hz, dansyl), 3.88 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.1 Hz, H-2), 3.80 (dd, 2 H, $J_{5,6a}$ 4.6 Hz, $J_{6a,6b}$ 11.0 Hz, H-6a), 3.79 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 8.1 Hz, H-4), 3.78 (dd, 1 H, $J_{5,6b}$ 4.9 Hz, H-6b), 3.68 (dd, 1 H, H-3), 3.53-3.25 (m, 8 H, H-2″, H-3″, H-4″, H-5″), 3.09 (dd, 1 H, $J_{1,5}$ 9.1 Hz, H-1), 3.06 (t, 2 H, *J* 5.3 Hz, H-6″), 2.88 (s, 6 H, dansyl), 2.89-2.63 (m, 2 H, H-1″), 2.20 (t, 2 H, *J* 7.3 Hz, H-2′), 2.08 (dddd, 1 H, H-5), 1.71-1.55 (m, 2 H, H-3′), 0.94 (t, 3 H, *J* 7.4 Hz, H-4′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 176.6 (C-1′), 153.2, 137.4, 131.2, 131.1, 131.0, 130.0, 129.1, 124.3, 120.7, 116.4 (dansyl), 81.5 (C-3), 77.4 (C-4), 71.2, 71.1, 71.1, 70.6, (C-2″, C-3″, C-4″, C-5″), 62.5 (C-1), 61.5 (C-6), 61.2 (C-2), 49.2 (C-1″), 47.8 (C-5), 45.8 (dansyl), 43.8 (C-6″), 39.1 (C-2′), 20.3 (C-3′), 14.1 (C-4′). MS (MALDI): Calculated for ($C_{28}H_{44}N_4O_8SH$): *m/z* $[M+H]^+$ 597.2958; found $[M+H]^+$ 597.2958.

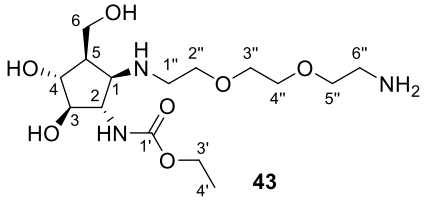
**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-azidoethoxy)ethoxy)ethyl)mino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)carbamate "(1-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane)" (42)**



**42**

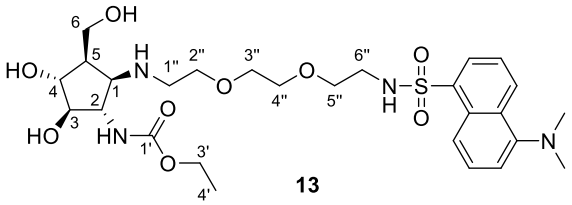
A solution of amine **35** (182 mg, 0.777 mmol) in MeOH was subsequently treated with AcOH (100 µL), 2-(2-(2-azidoethoxy)ethoxy)acetaldehyde (202 mg, 1.17 mmol) and $NaBH_3CN$ (73.2 mg, 1.17 mmol) following general procedure C. Silica gel chromatography of the remaining oil ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$ (25%)) yielded azide **42** as acolorless oil (238 mg, 0.608 mmol, 78%). $[\alpha]_D^{20}$: +17.3 (c = 0.92, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 4.18-4.03 (m, 2 H, H-2′), 3.85 (dd, 1 H, $J_{5,6a}$ 5.5 Hz, $J_{6a,6b}$ 10.2 Hz, H-6a), 3.78 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 7.9 Hz, H-4), 3.77 (dd, 1 H, $J_{5,6b}$ 4.9 Hz, H-6b), 3.73-3.53 (m, 10 H, H-2, H-3, H-2″, H-3″, H-4″, H-5″), 3.38 (t, 2 H, *J* 4.9 Hz, H-6″), 3.12 (dd, 1 H, $J_{1,2}$ = $J_{1,5}$ 8.5 Hz, H-1), 2.96-2.72 (m, 2 H, H-1″), 2.06 (dddd, 1 H, H-5), 1.25 (t, 3 H, *J* 7.0 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 159.2 (C-1′), 81.3 (C-3), 77.2 (C-4), 71.5, 71.5, 71.2, 71.2 (C-2″, C-3″, C-4″, C-5″), 62.7 (C-2), 62.0 (C-1), 61.8 (C-2′), 61.5 (C-6), 51.8 (C-6″), 49.2 (C-1″), 47.6 (C-5), 15.0 (C-3′). MS (MALDI): Calculated for ($C_{15}H_{29}N_5O_7H$): *m/z* $[M+H]^+$ 392.2145; found $[M+H]^+$ 392.2144.

**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-aminoethoxy)ethoxy)ethyl)mino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)carbamate "(1-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane) (43)**




An ethanolic solution of azide **42** (228 mg, 0.269 mmol) was adjusted to pH 1 (2 M HCl). Pearlman's catalyst (20% $Pd(OH)_2$/C) was added and the solution was stirred under an atmosphere of $H_2$ at atmospheric pressure. After the complete conversion (30 min, $CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1), the catalyst was removed by filtration and the filtrate was evaporated *in vacuo*. The residue was quickly passed through a pad of silica gel ($CHCl_3$-MeOH-$NH_4OH$ (25%) 8:4:1) to provide amine **43** as a colorless solid (206 mg, 0.564 mmol, 97%). $[\alpha]_D^{20}$: +13.9 (c = 0.96, MeOH); $^1$H-NMR (300 MHz, $D_2O$) δ= 4.25-4.08 (m, 2 H, H-2′), 4.00 (dd, 1 H, $J_{5,6a}$ 4.2 Hz, $J_{6a,6b}$ 12.1 Hz, H-6a), 3.97 (dd, 1 H, $J_{1,2}$ = $J_{2,3}$ 8.1 Hz, H-2), 3.92-3.71 (m, 12 H, H-1, H-3, H-4, H-2″, H-3″, H-4″, H-5″), 3.46-3.30 (m, 2 H, H-1″), 3.23 (t, 2 H, *J* 5.0 Hz, H-6″), 2.48-2.36 (m, 1 H, H-5), 1.25 (t, 3 H, *J* 7.1 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $D_2O$) δ= 158.3 (C-1′), 78.0 (C-3), 73.4 (C-4), 69.8, 69.6, 66.5, 65.5 (C-2″, C-3″, C-4″, C-5″), 62.3 (C-2′), 59.6 (C-1), 58.1 (C-6), 57.5 (C-2), 46.4 (C-1″), 43.1 (C-5), 39.1 (C-6″), 13.8 (C-3′). MS (MALDI): Calculated for ($C_{15}H_{31}N_3O_7H$): *m/z* $(M+H)^+$ 366.2240; found $(M+H)^+$ 366.2239.

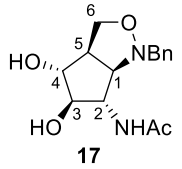
**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethoxy) ethoxy) ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)carbamate "(1-(2-(2-(2-Dansyl aminoethoxy)ethoxy)ethyl)amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane)" (13)**




Amine **43** (189 mg, 0.517 mmol was treated with $Na_2CO_3$ (110 mg, 1.03 mmol) and dansyl chloride (153 mg, 0.569 mmol) according to general procedure E. The residue was chromatographed ($CHCl_3$-MeOH 14:1 + 1 vol% $NH_4OH$ (25%)) to obtain inhibitor **13** as a yellow oil (185 mg, 0.309 mmol, 60%). $[\alpha]_D^{20}$: +11.7 (c = 0.95, MeOH); $^1$H-NMR (300 MHz, $CD_3OD$) δ = 8.56 (d, 1 H, *J* 8.5 Hz, dansyl), 8.37 (d, 1 H, *J* 8.7 Hz, dansyl), 8.21 (d, 1 H, *J* 7.2 Hz, dansyl), 7.60 (dd, 1 H, *J* 8.5 Hz, *J* 7.2 Hz, dansyl), 7.58 (dd, 1 H, *J* 8.7 Hz, *J* 7.3 Hz, dansyl), 7.28 (d, 1 H, *J* 7.3 Hz, dansyl), 4.15-4.01 (m, 2 H, H-2′), 3.82 (dd, 1H, $J_{5,6a}$ 4.5 Hz, $J_{6a,6b}$ 11.3 Hz, H-6a), 3.77 (dd, 1 H, $J_{3,4}$ = $J_{4,5}$ 8.0 Hz, H-4), 3.76 (dd, 2 H, $J_{5,6b}$ 4.1 Hz, H-6b), 3.66 (dd, 1 H, $J_{2,3}$ 8.0 Hz, H-3), 3.58 (dd, 1 H, $J_{1,2}$ 8.5 Hz, H-2),3.50-3.27 (m, 8 H, H-2″, H-3″, H-4″, H-5″), 3.09 (dd, 1 H, $J_{1,5}$ 9.4 Hz, H-1), 3.06 (t, 2 H, *J* 5.5 Hz, H-6″), 2.93-2.69 (m, 8 H, H-1", dansyl), 2.06 (dddd, 1 H, H-5), 1.22 (t, 3 H, *J* 7.1 Hz, H-3′). $^{13}$C NMR (75.5 MHz, $CD_3OD$) δ = 159.2 (C-1′), 153.2, 137.4, 131.2, 131.1, 131.0, 130.0, 129.1, 124.3, 120.7, 116.4, 81.3 (C-3), 77.2 (C-4), 71.1, 71.1, 70.6, 70.6 (C-2″, C-3″, C-4″, C-5″), 62.7 (C-2), 62.1 (C-1), 61.8 (C-2′), 61.5 (C-6), 49.1 (C-1″), 47.5 (C-5), 45.8 (dansyl), 43.8 (C-6″), 15.0 (C-3′). MS (MALDI): Calculated for ($C_{27}H_{42}N_4O_9SH$): *m/z* $[M+H]^+$ 599.2751; found $[M+H]^+$ 599.2752.

## 3. NMR and HRMS spectra of the new compounds

### *N*-((3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-Benzyl-4,5-dihydroxyhexahydro-1*H*-cyclopenta(*c*)isoxazol-6-yl) acetamide (17)




**17**

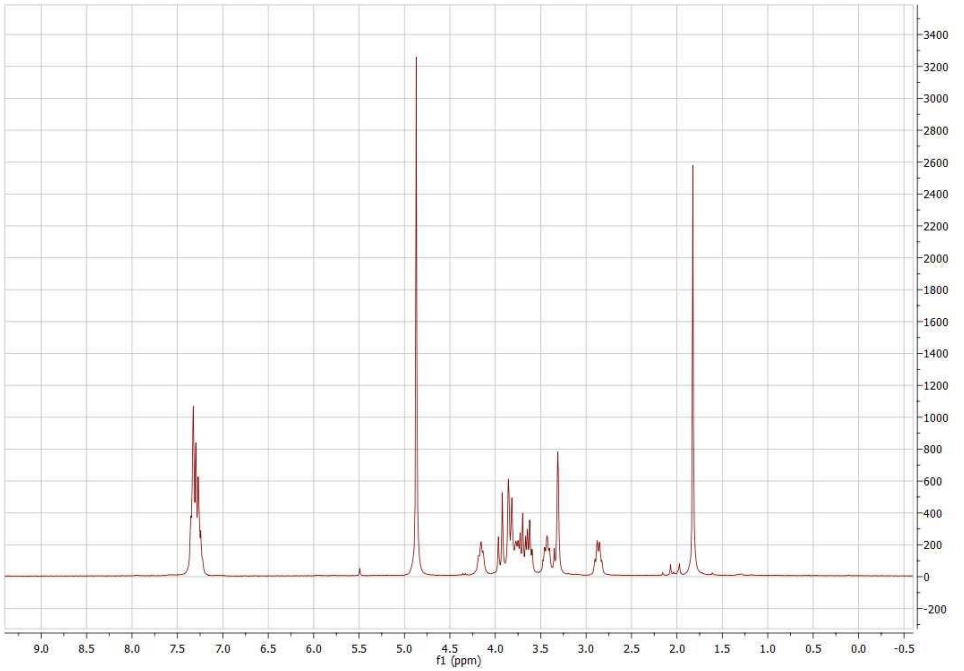



**Figure S1A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **17**.

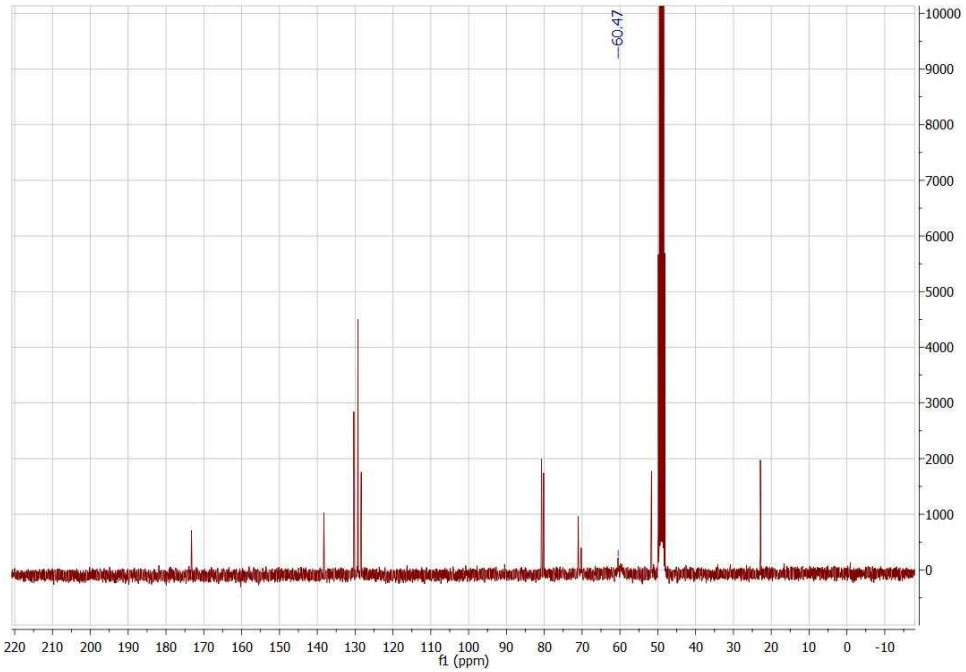



**Figure S1B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **17**.

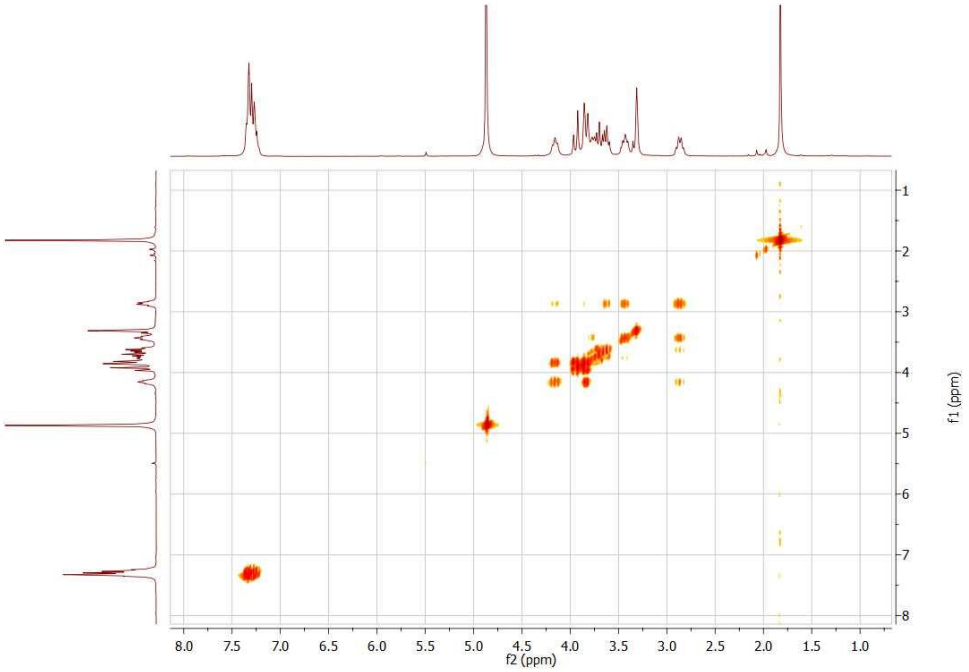



**Figure S1C. COSY** ($CD_3OD$) of compound **17**.

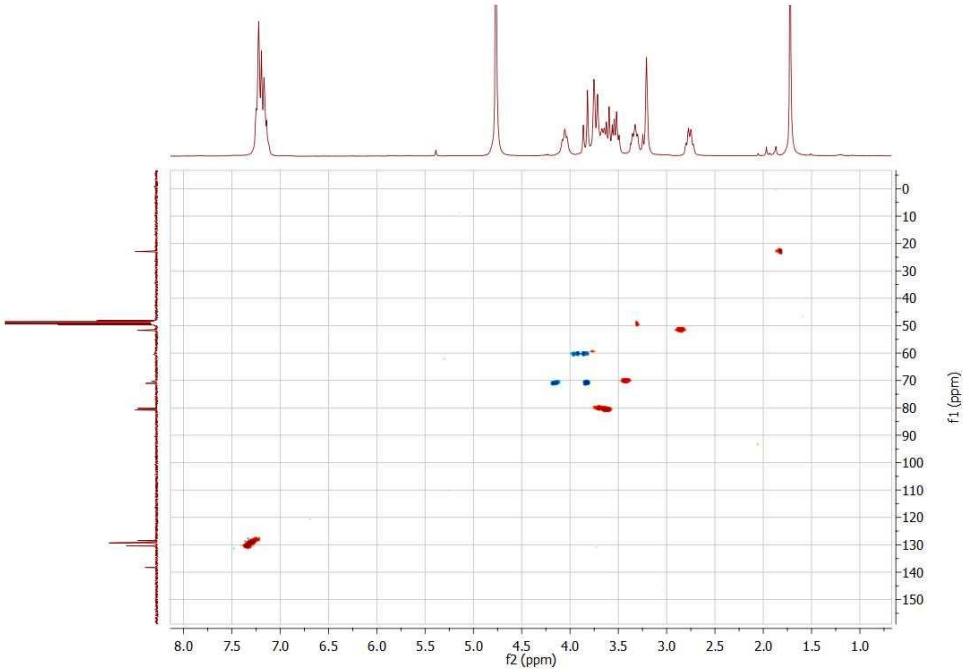



**Figure S1D. HSQC** ($CD_3OD$) of compound **17**.

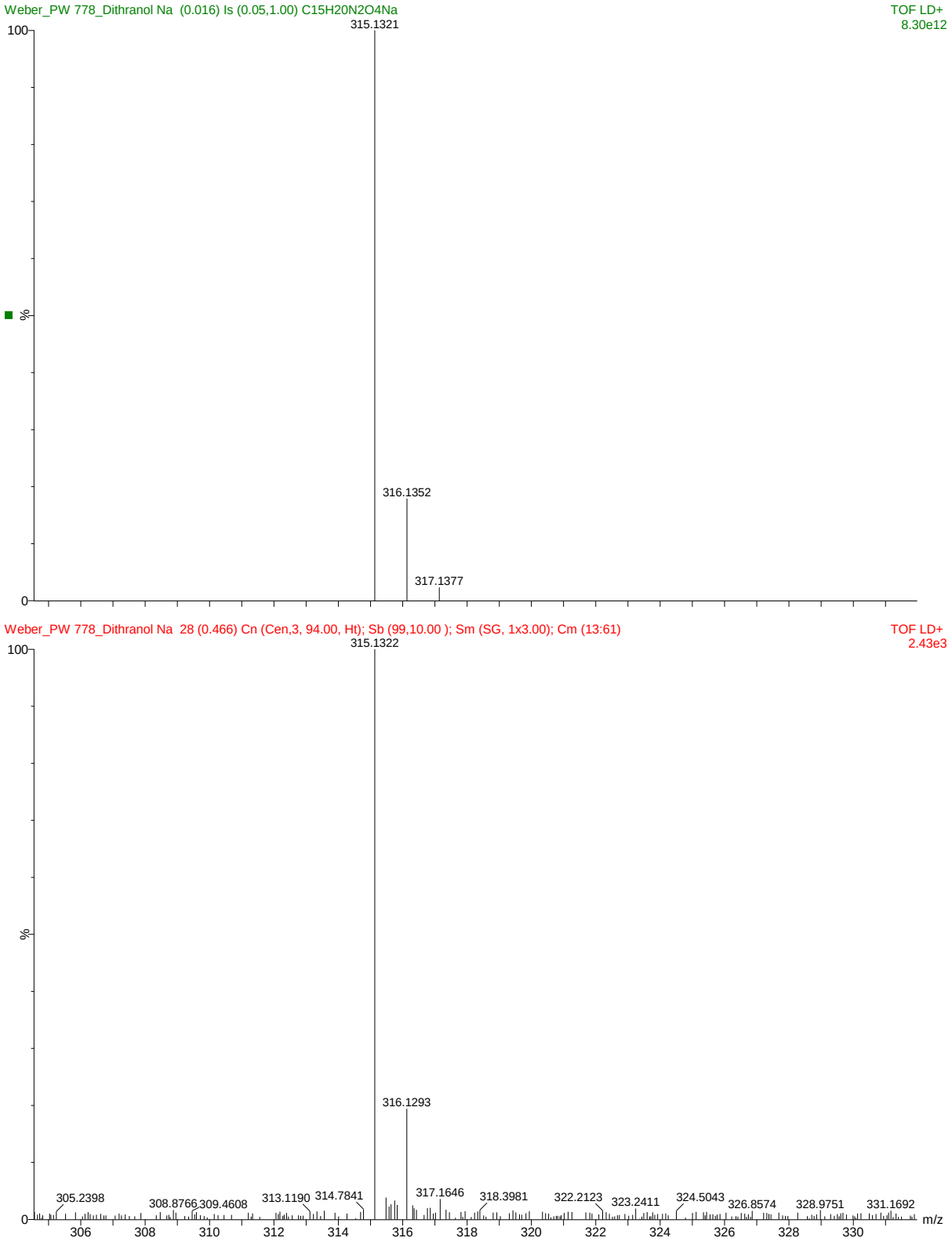
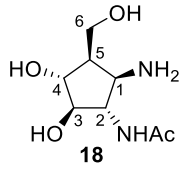



**Figure S1E. HRMS** of compound **17**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)acetamide "(2-Acetamido-1-amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (18)**




**18**

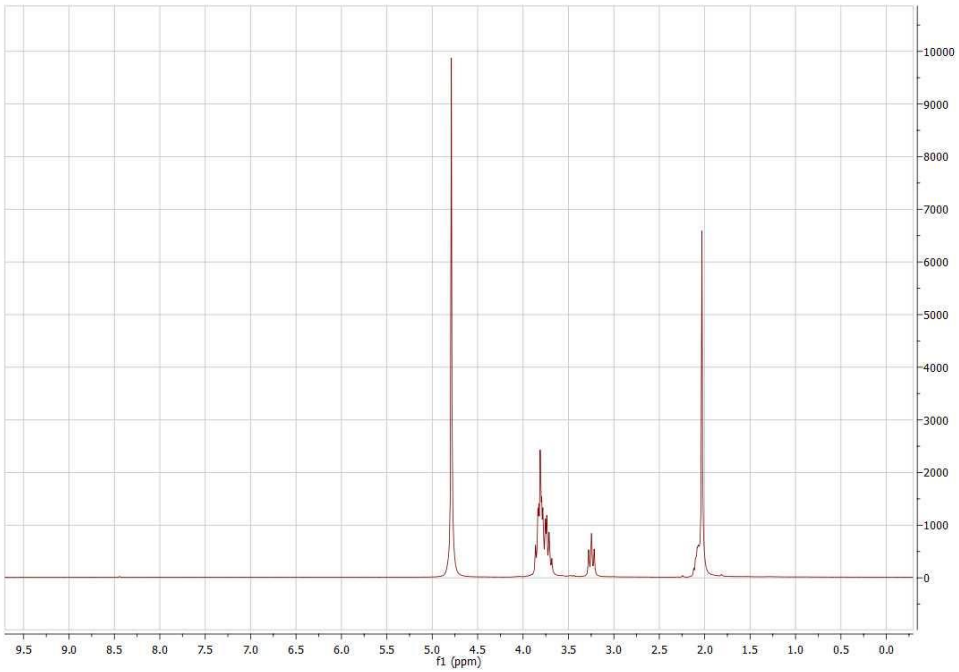



**Figure S2A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **18**, free base.

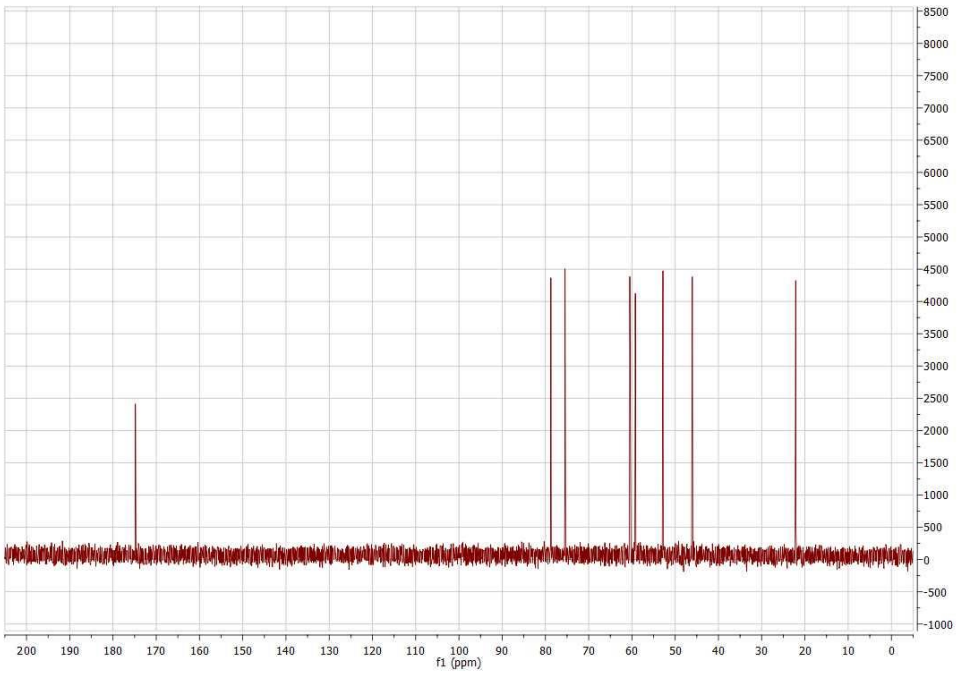



**Figure S2B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **18**, free base.

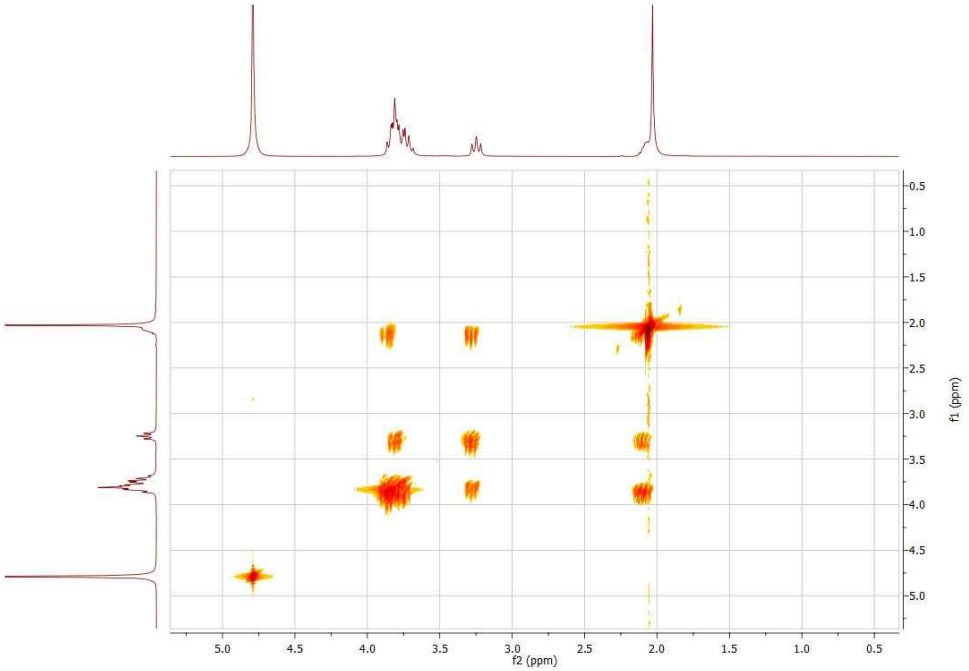



**Figure S2C. COSY** ($D_2O$) of compound **18**, free base.

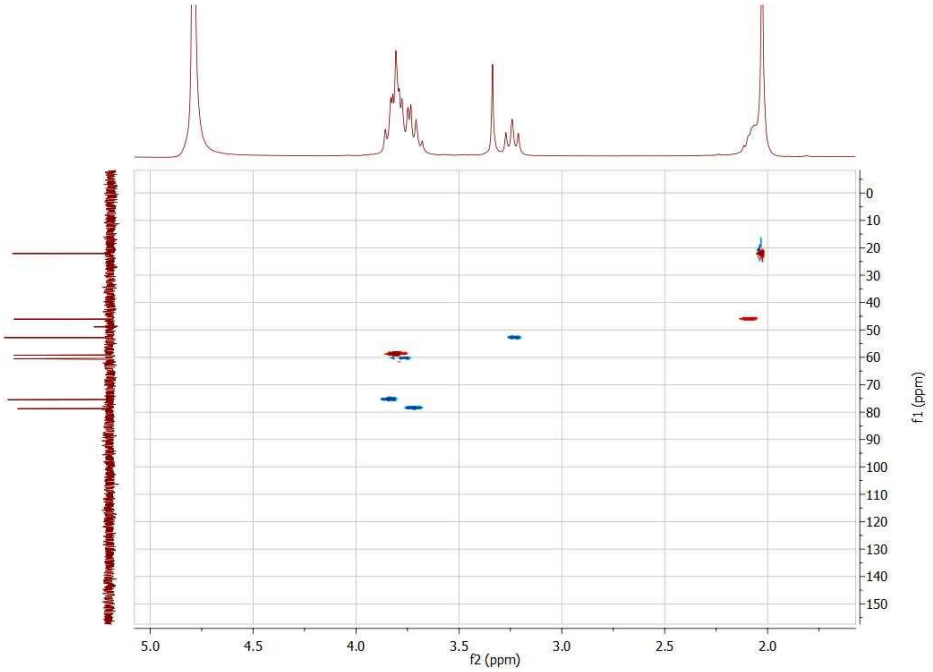



**Figure S2D. HSQC** ($D_2O$) of compound **18**, free base.

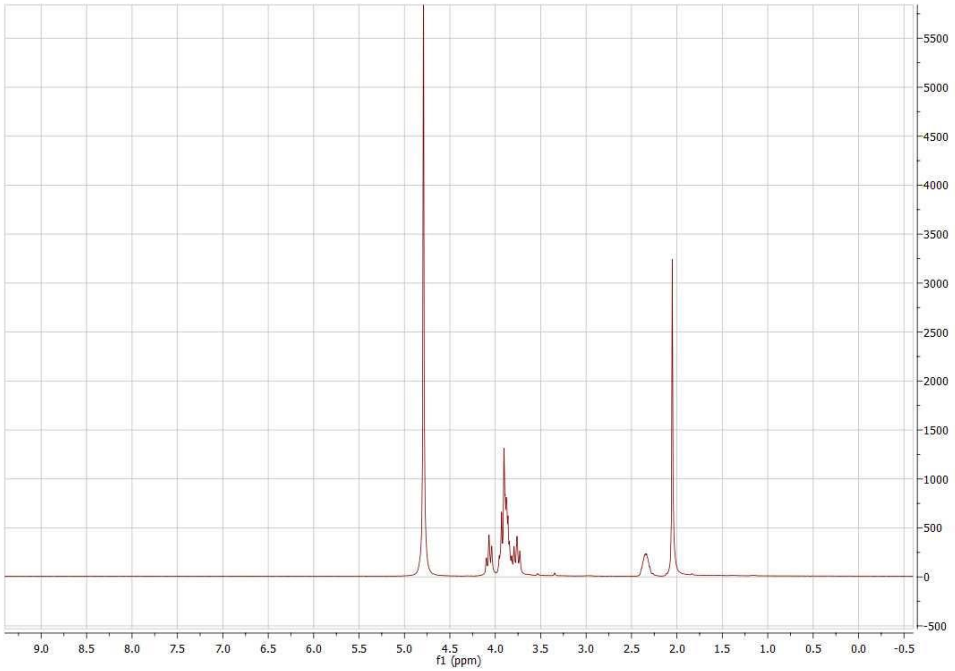



**Figure S2E. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **18**, hydrochloride.

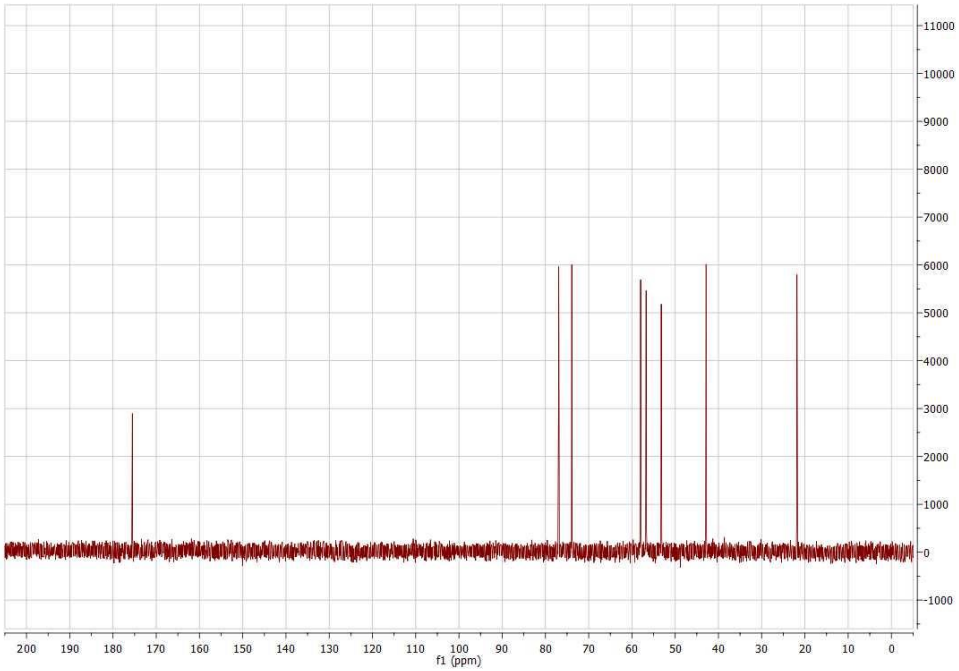



**Figure S2F. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **18**, hydrochloride.

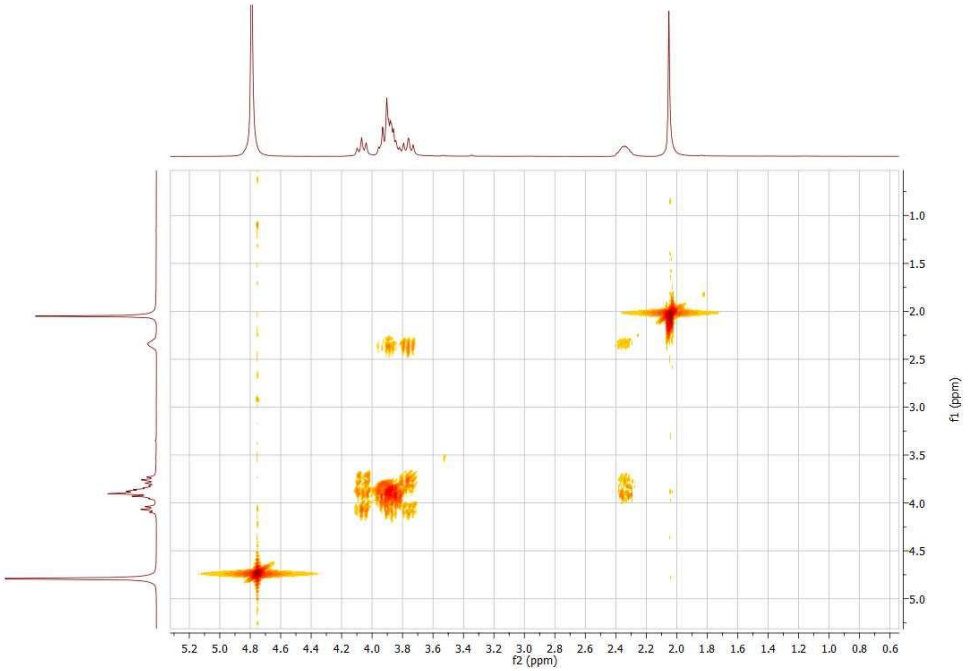



**Figure S2G. COSY** ($D_2O$) of compound **18**, hydrochloride.

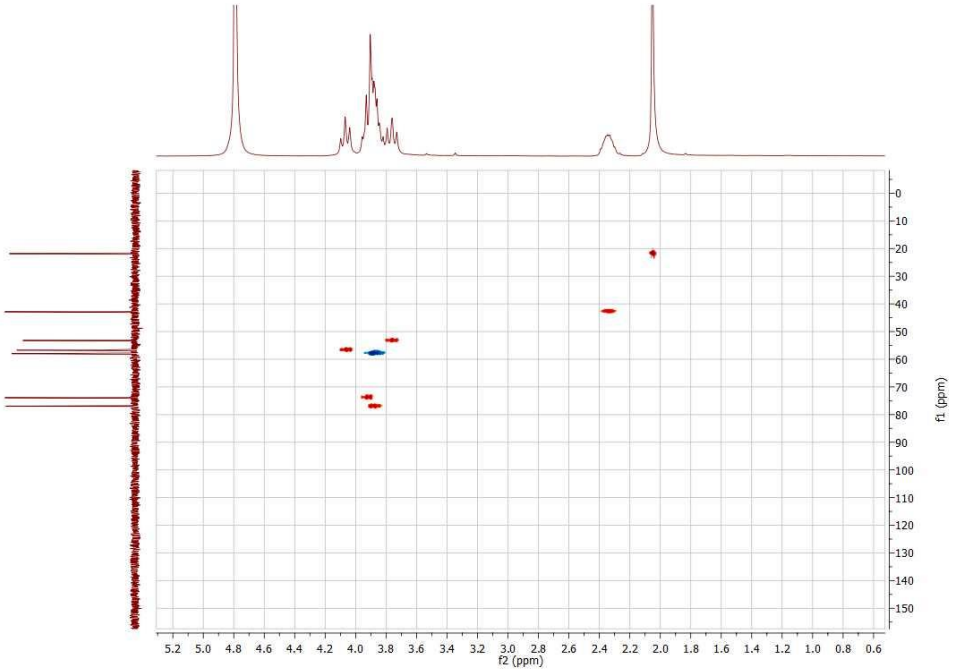



**Figure S2H. HSQC** ($D_2O$) of compound **18**, hydrochloride.

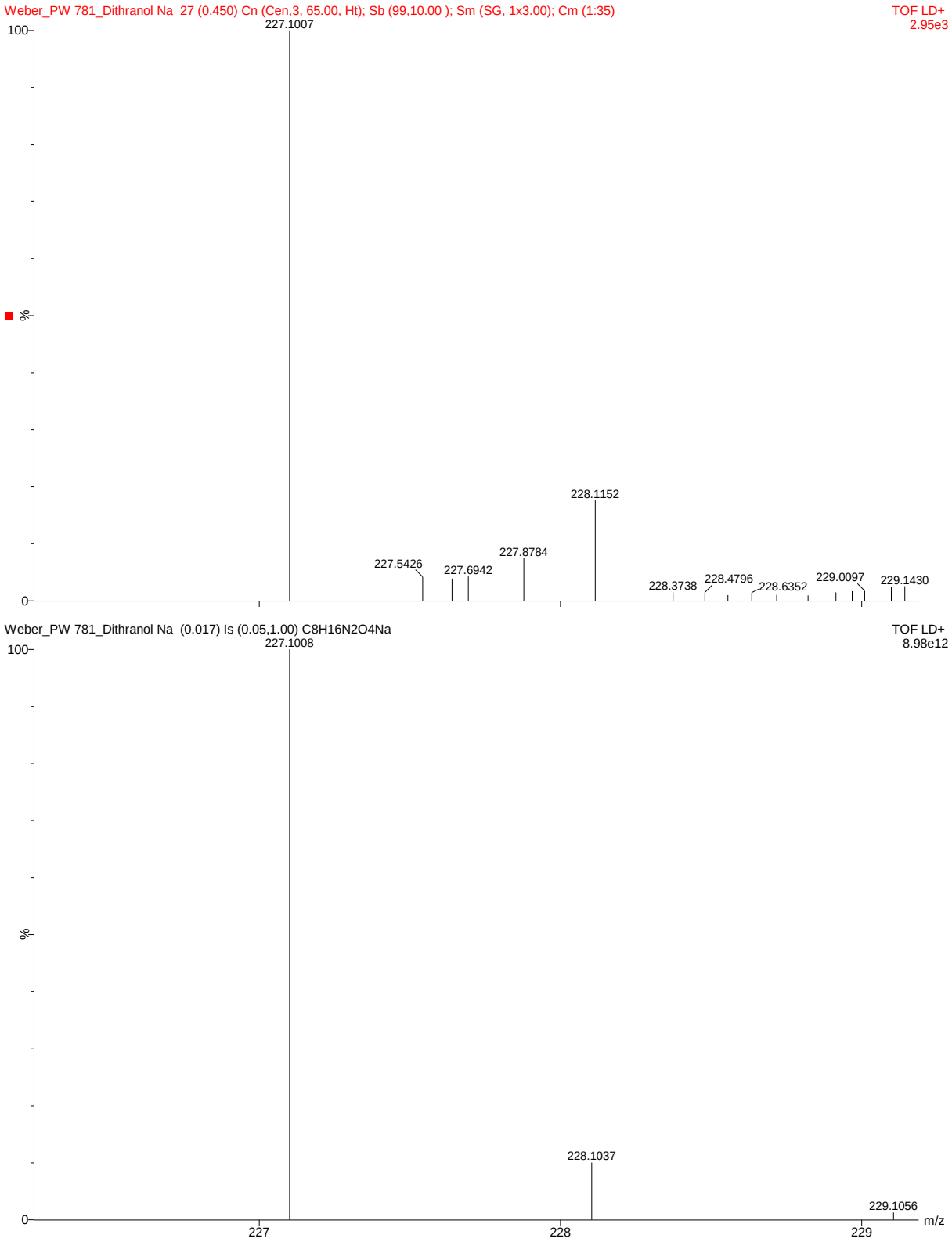
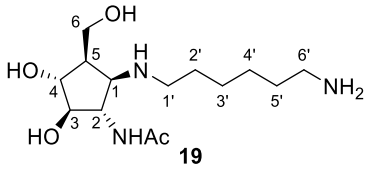



**Figure S2l. HRMS** of compound **18**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((6-Aminohexyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl) acetamide "(2-Acetamido-1-(6-aminohexyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (19)**




**19**

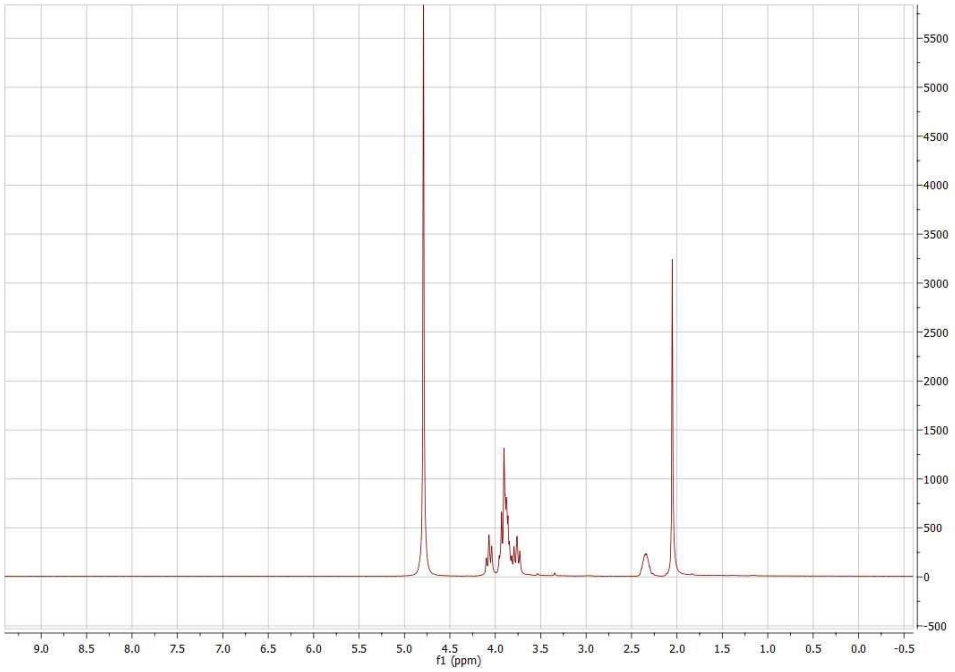



**Figure S3A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **19**.

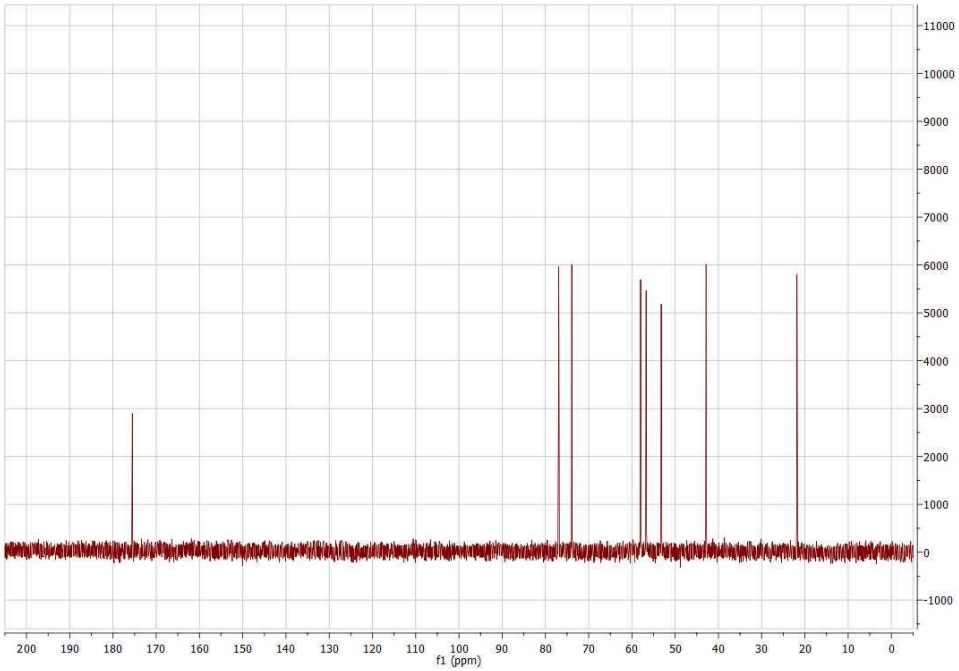



**Figure S3B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **19**.

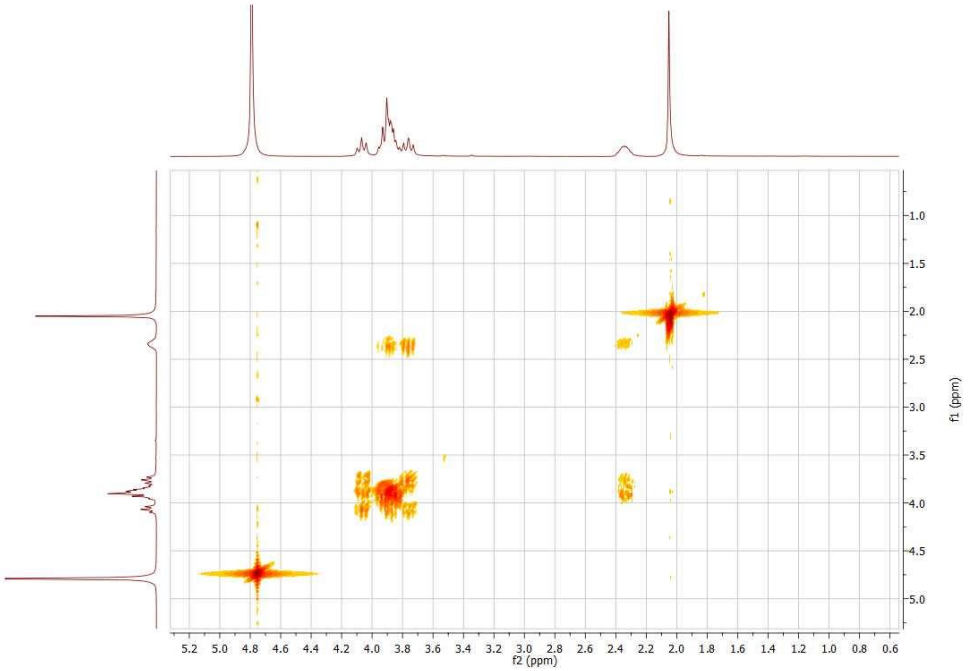



**Figure S3C. COSY** ($D_2O$) of compound **19**.

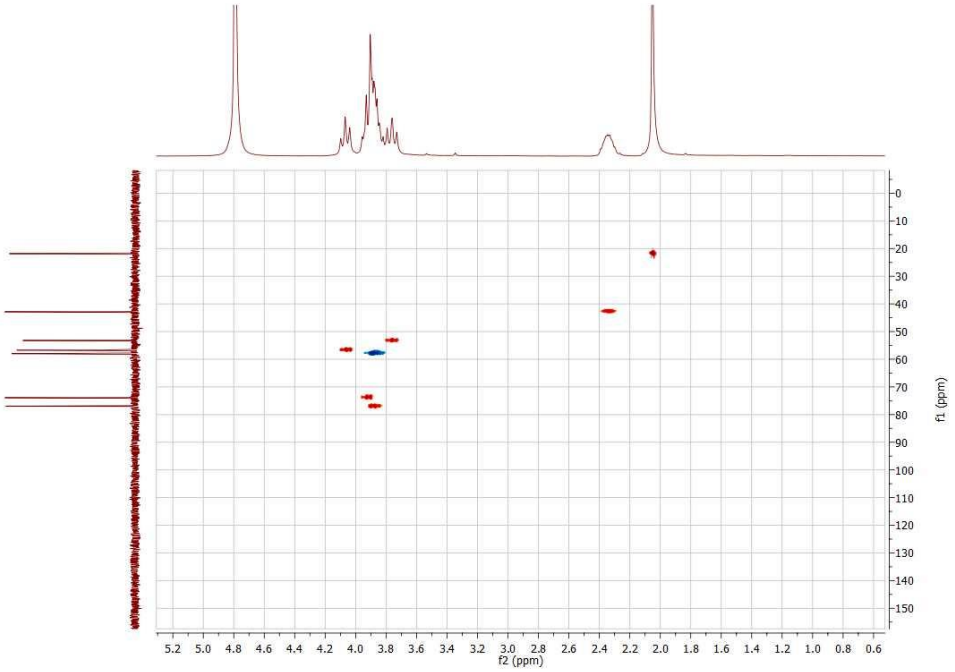



**Figure S3D. HSQC** ($D_2O$) of compound **19**.

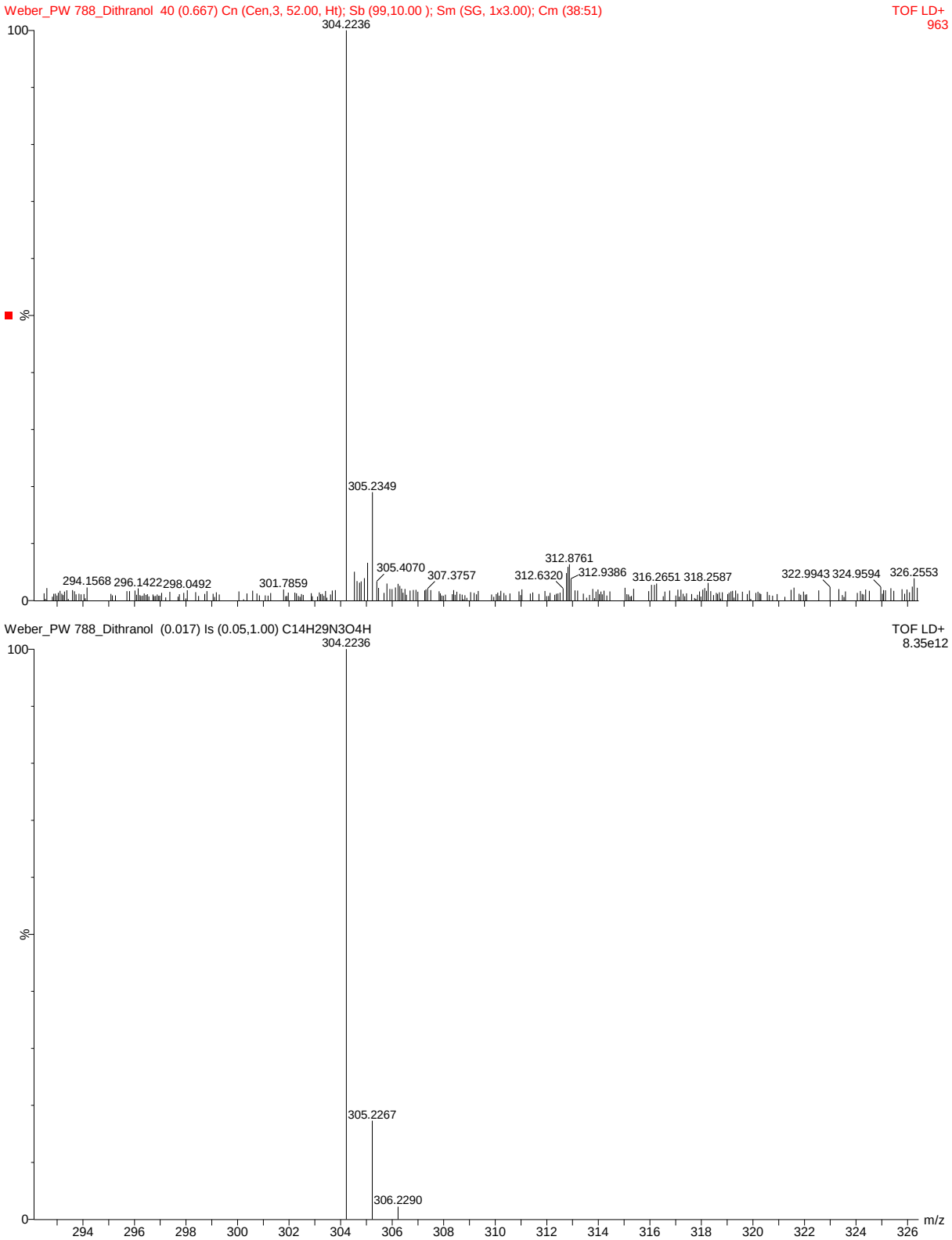
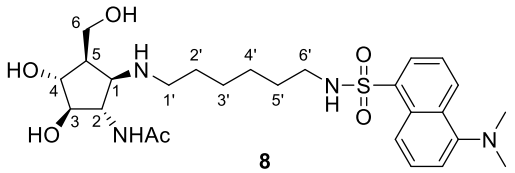



**Figure S3E. HRMS** of compound **19**.

**_N_-((1_S_,2_R_,3_R_,4_R_,5_R_)-2-((6-((5-(Dimethylamino)naphthalene)-1-sulfonamido)hexyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)acetamide**
**"(2-Acetamido-1-(6-dansylaminohexyl) amino-2-deoxy-"β-D-_gluco_-like"-cyclopentane)" (8)**




**8**

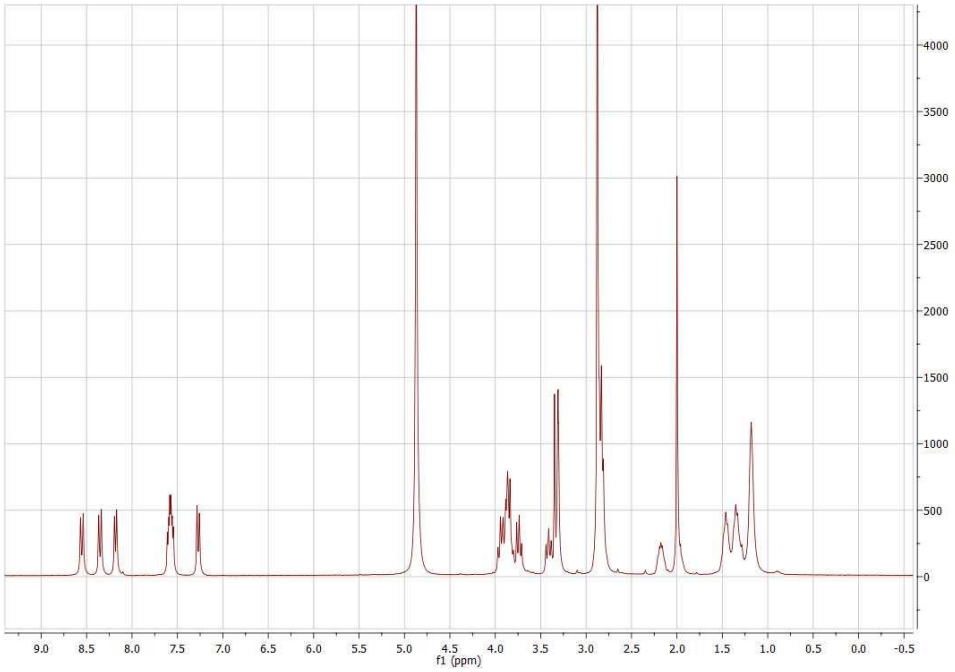



**Figure S4A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **8**.

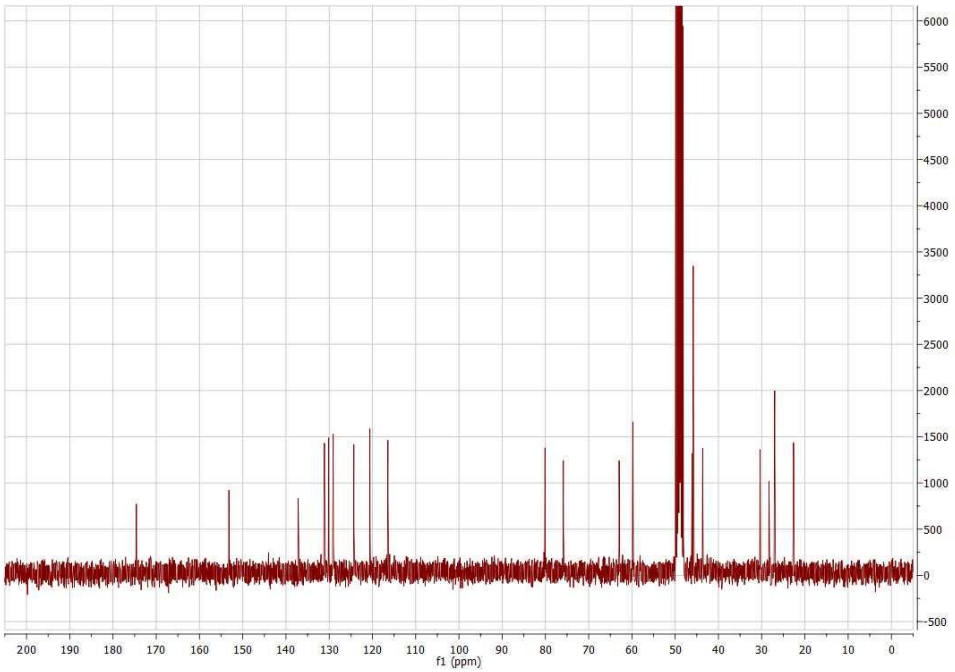



**Figure S4B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **8**.

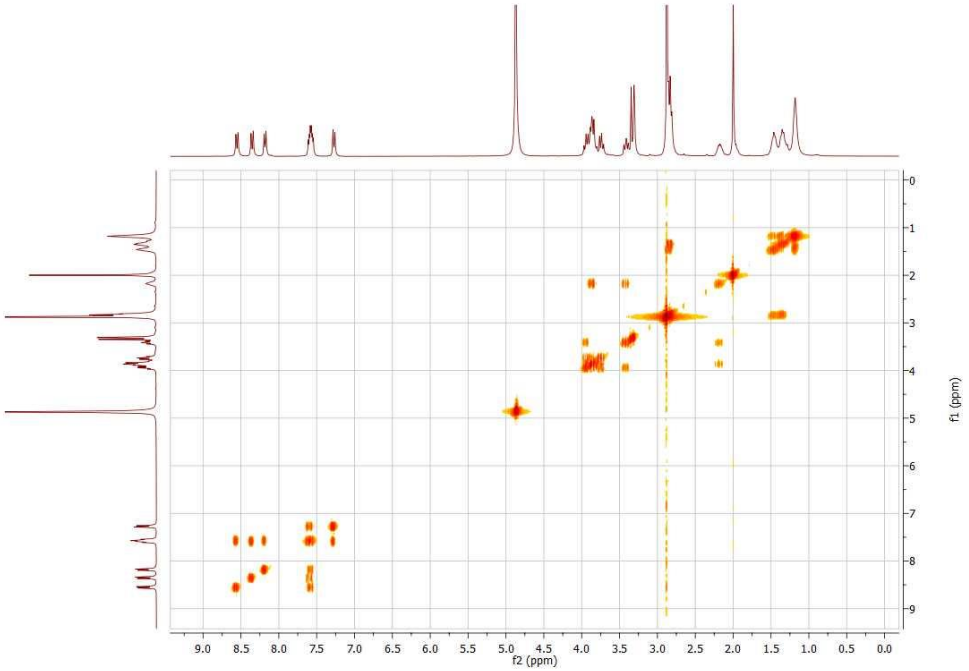



**Figure S4C. COSY** ($CD_3OD$) of compound **8**.

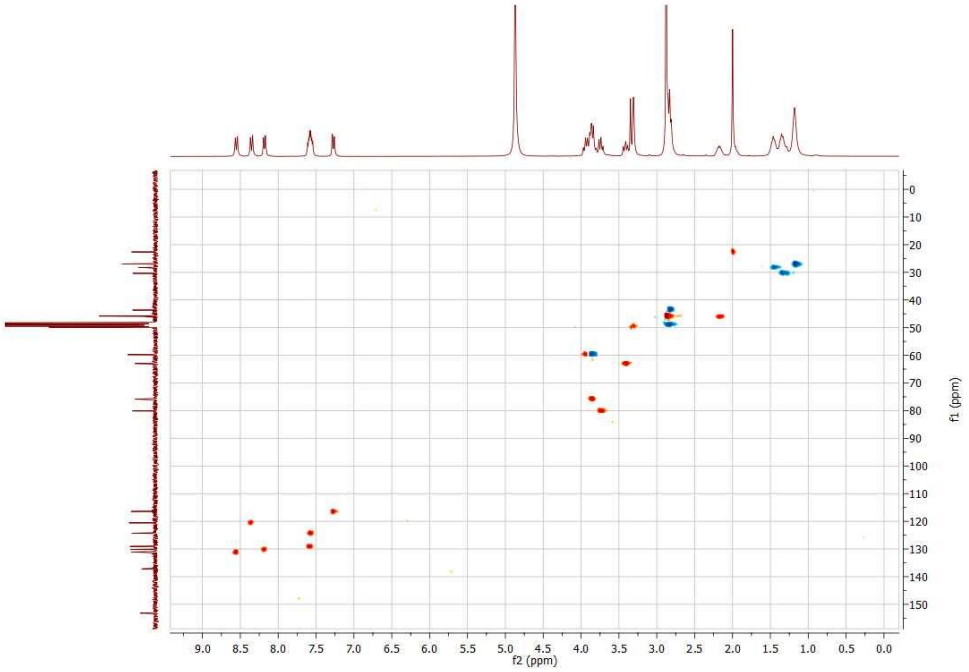



**Figure S4D. HSQC** ($CD_3OD$) of compound **8**.

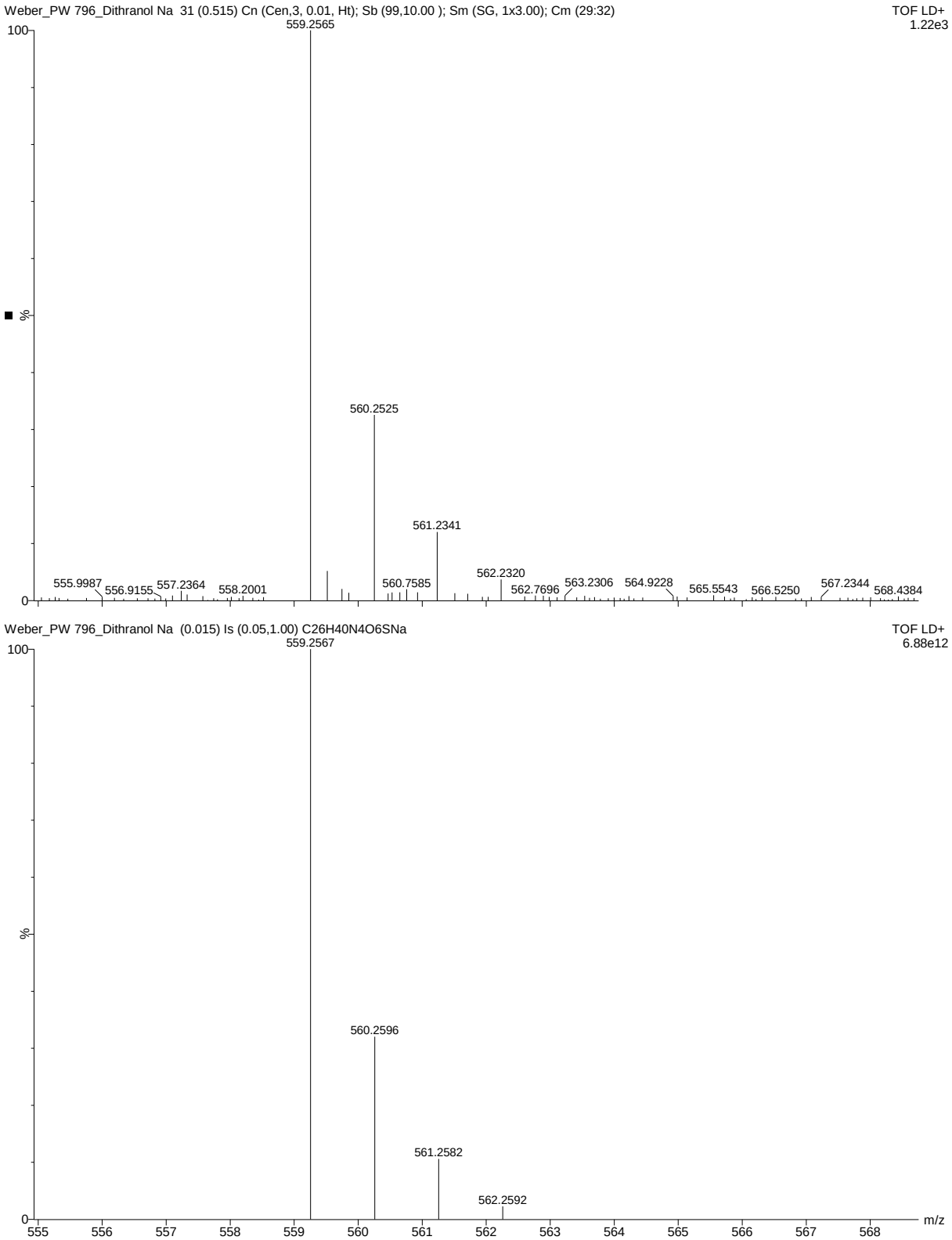
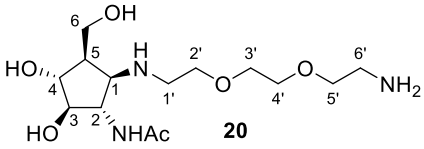



**Figure S4E. HRMS** of compound **8**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxy methyl)cyclopentyl)acetamide "(2-Acetamido-1-(2-(2-(2-aminoethoxy)ethoxy)ethyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (20)**




**20**

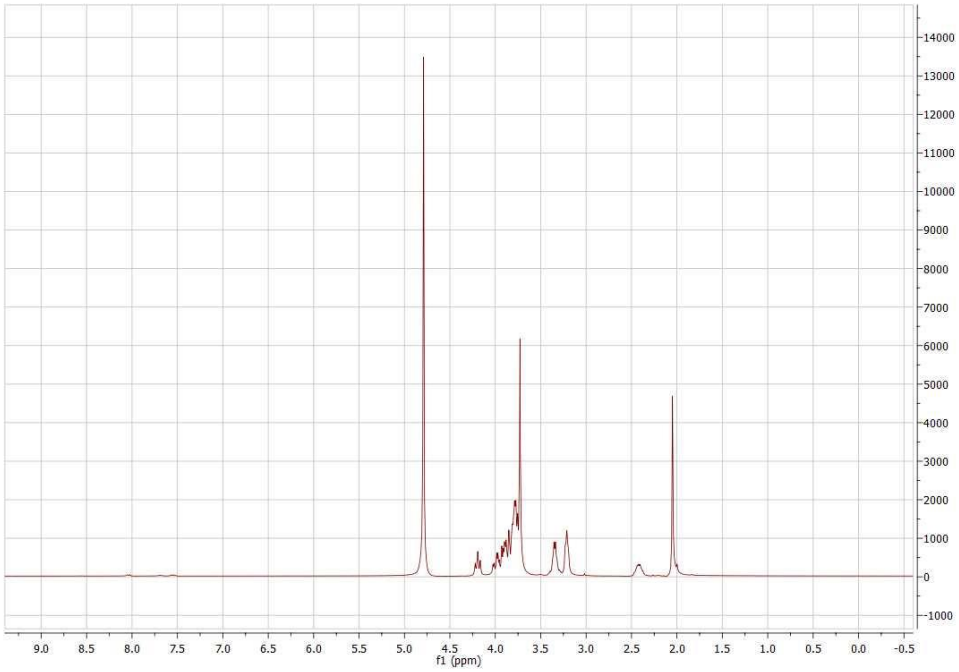



**Figure S5A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **20**.

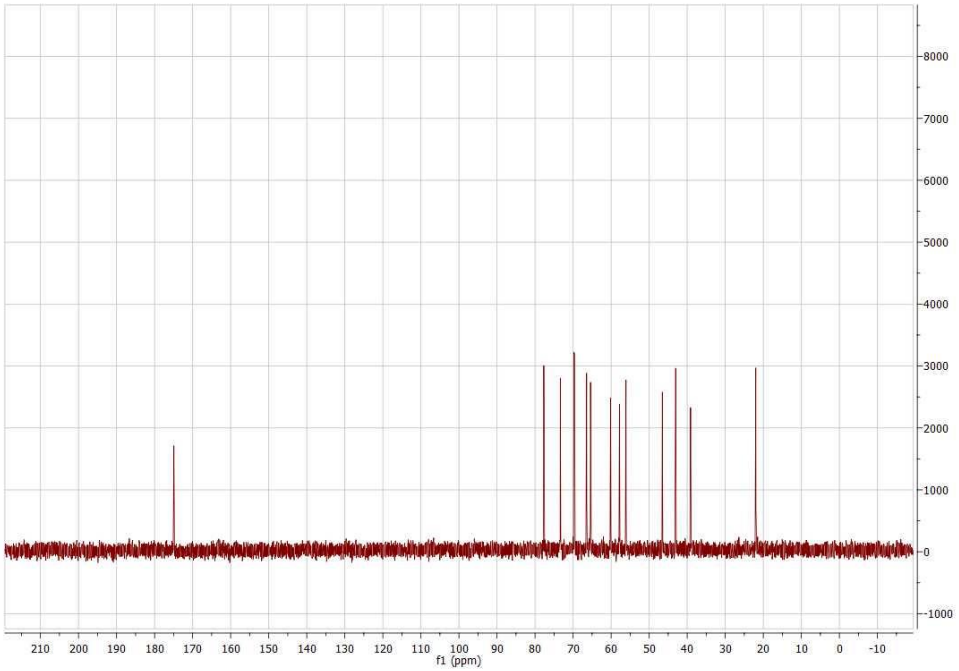



**Figure S5B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **20**.

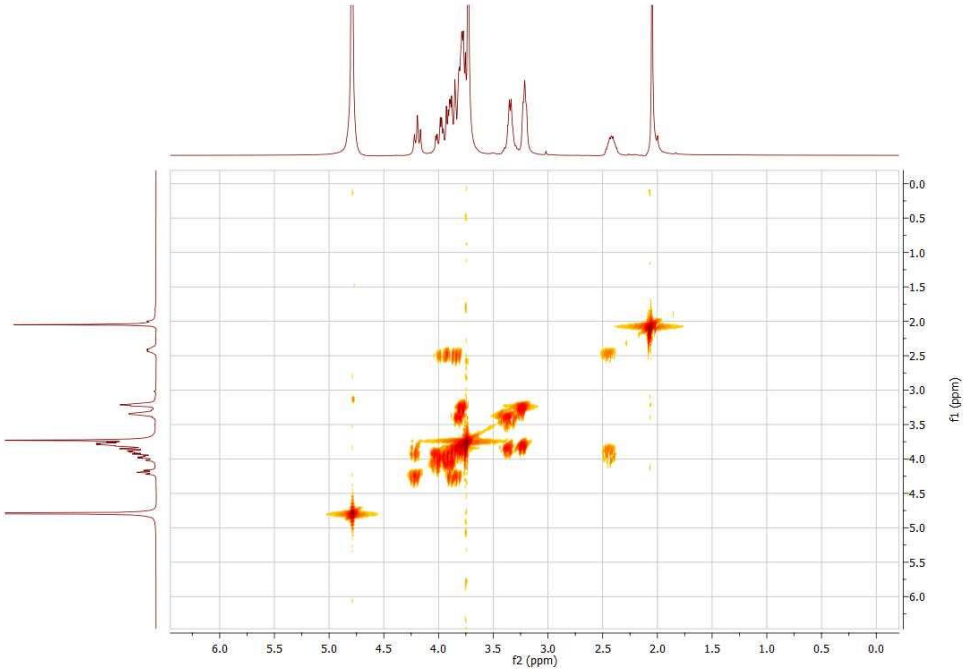



**Figure S5C. COSY** ($D_2O$) of compound **20**.

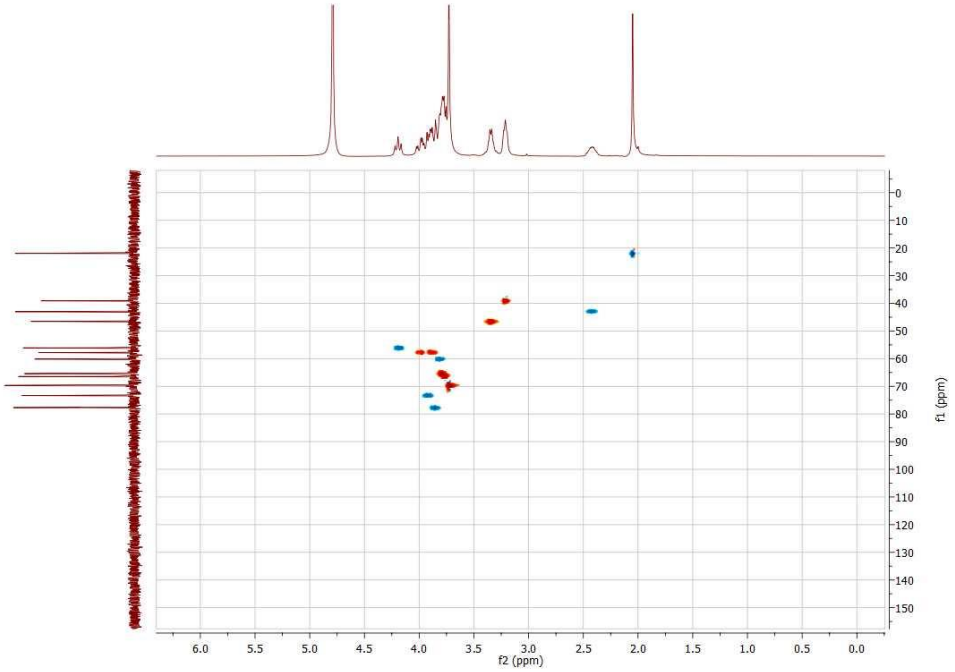



**Figure S5D. HSQC** ($D_2O$) of compound **20**.

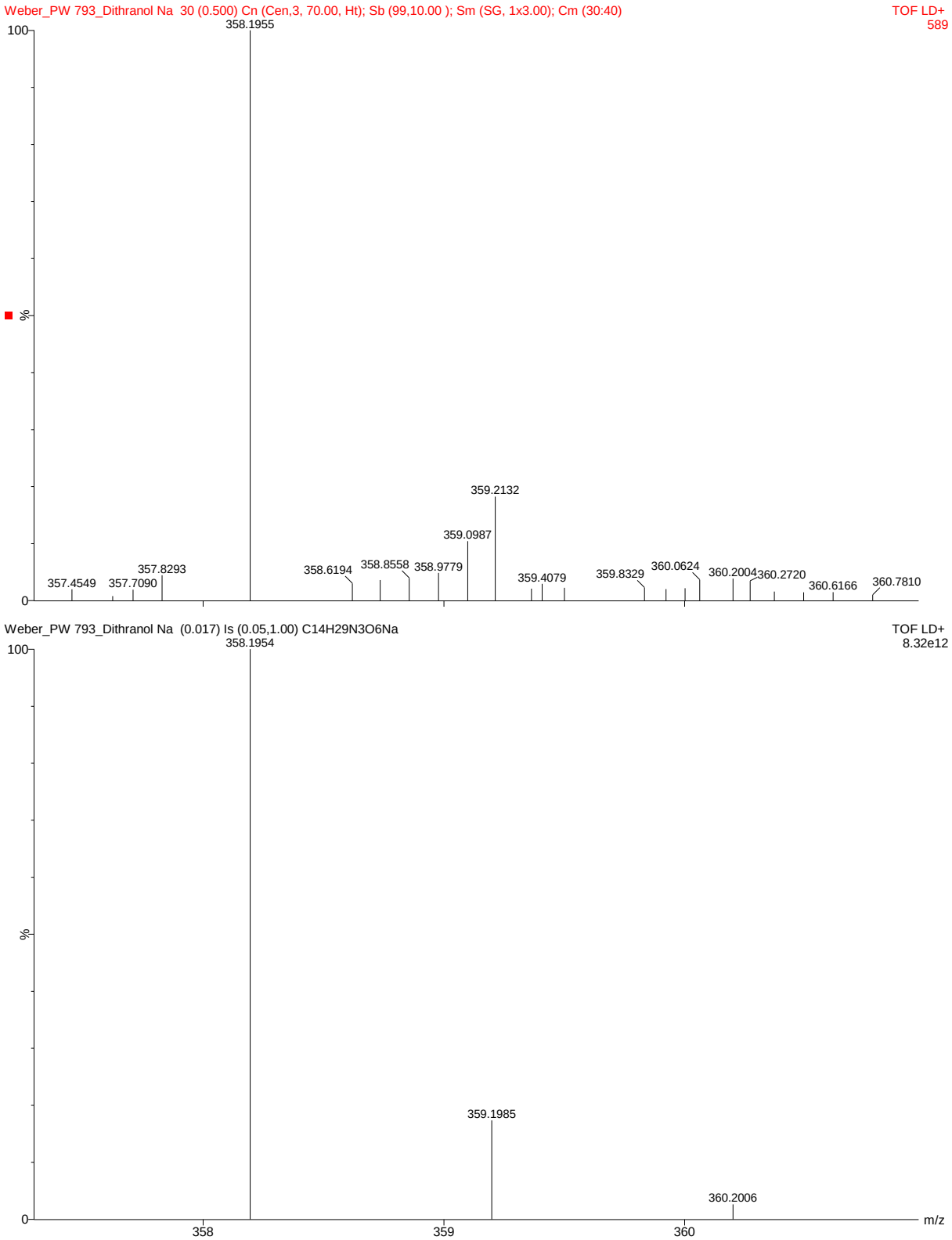
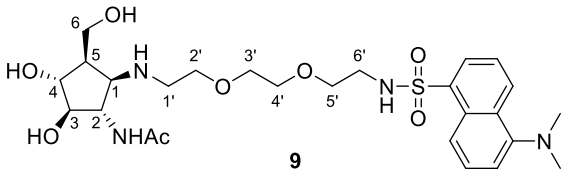



**Figure S5E. HRMS** of compound **20**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(Dimethylamino)naphthalene)-1-sulfonamido)ethoxy)ethoxy) ethyl) amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl) acetamide "(2-Acetamido-1-(2-(2-(2-dansylaminoethoxy)ethoxy)ethyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (9)**




**9**

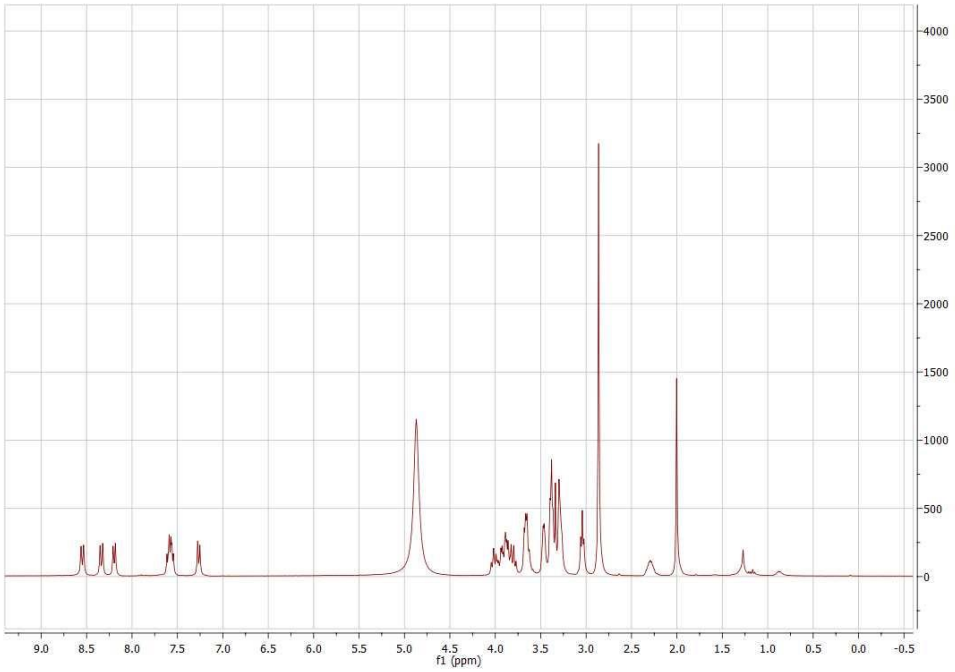



**Figure S6A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **9**.

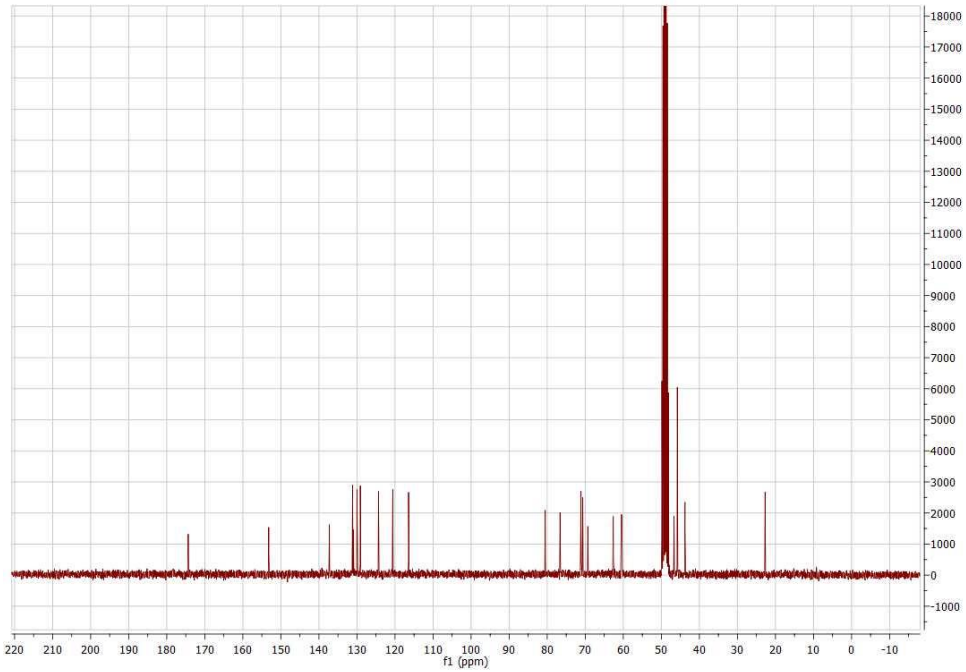



**Figure S6B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **9**.

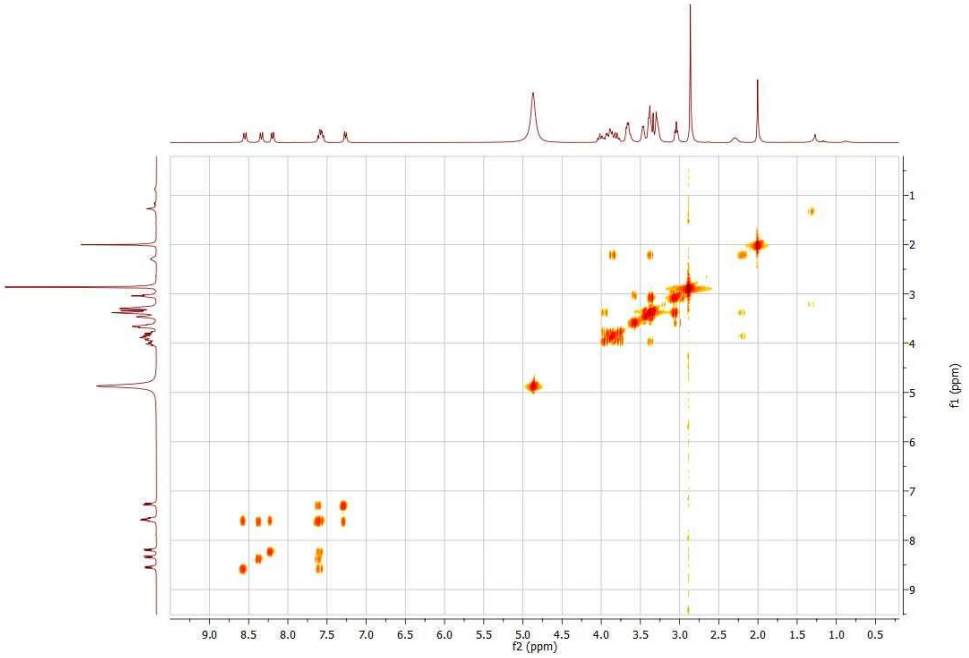



**Figure S6C. COSY** ($CD_3OD$) of compound **9**.

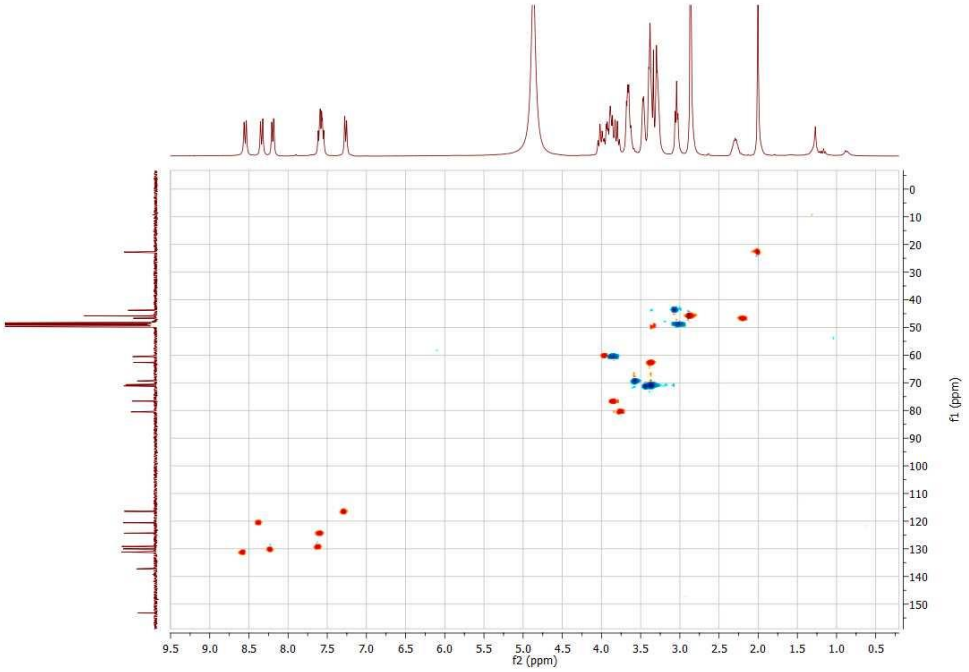



**Figure S6D. HSQC** ($CD_3OD$) of compound **9**.

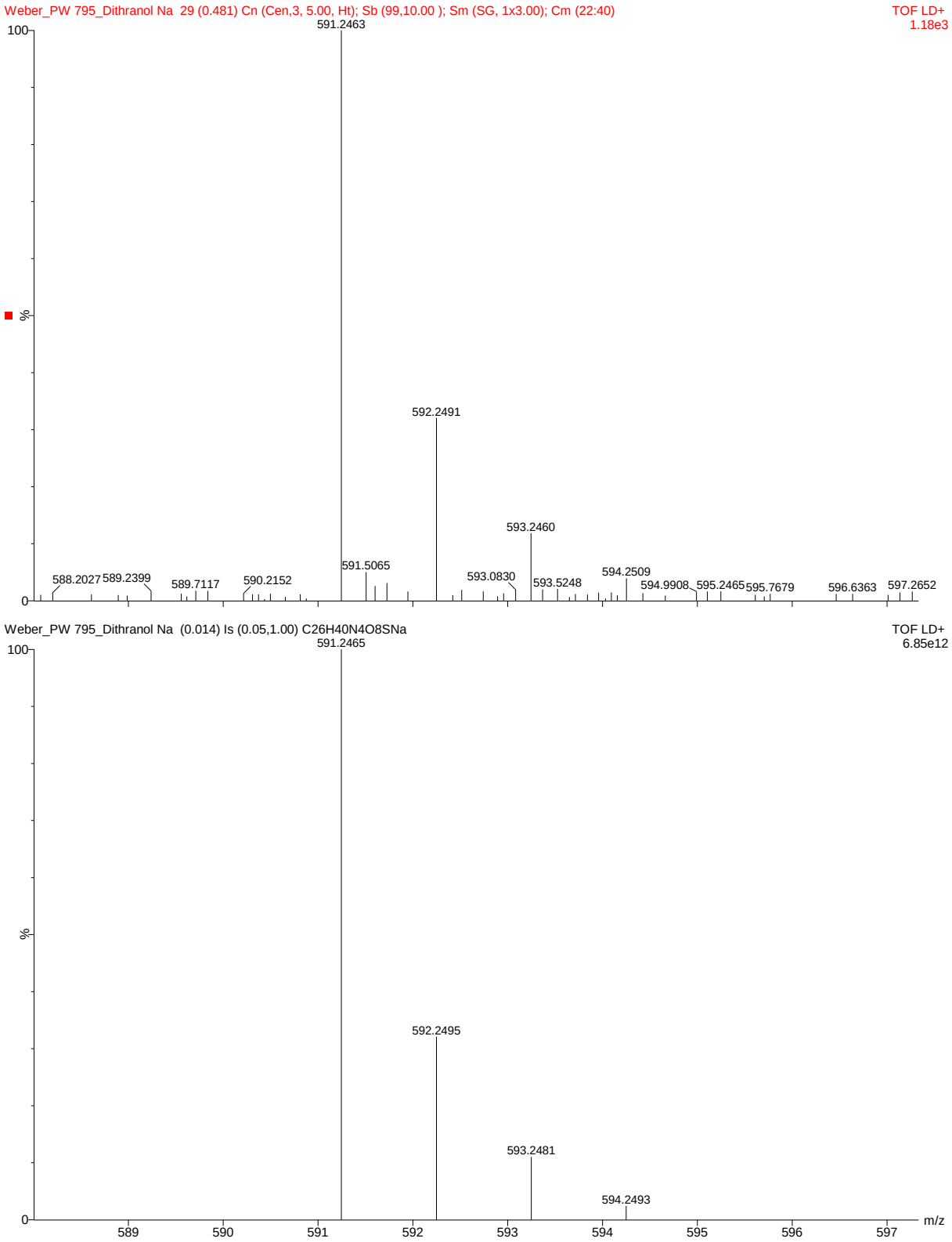
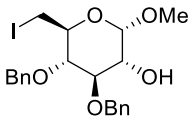



**Figure S6E. HRMS** of compound **9**.

**Methyl 6-deoxy-6-iodo-3,4-*O*-dibenzyl-α-D-glucopyranoside (23)**




**23**

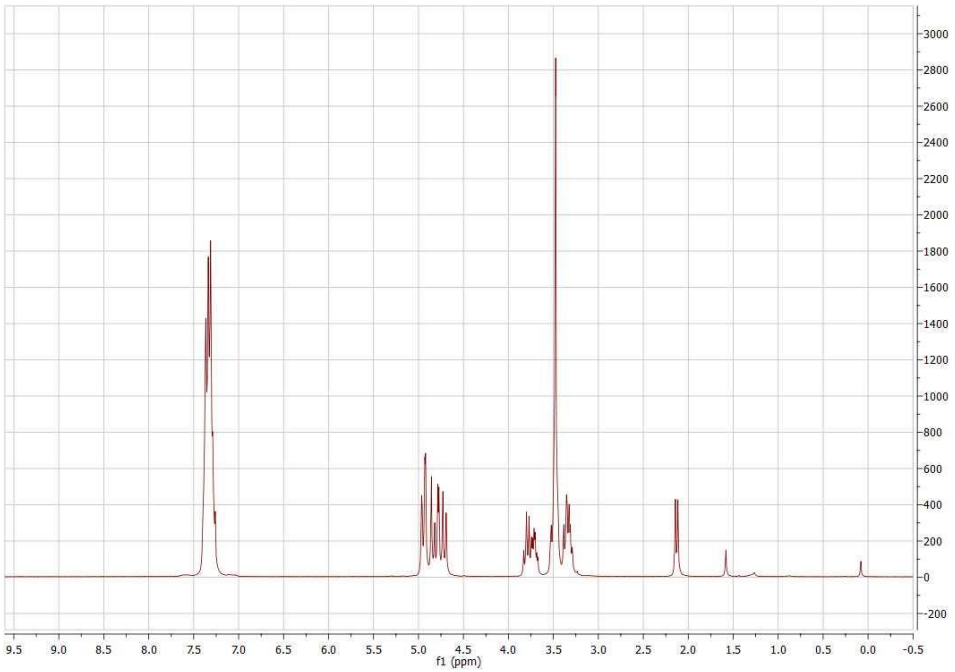



**Figure S7A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **23**.

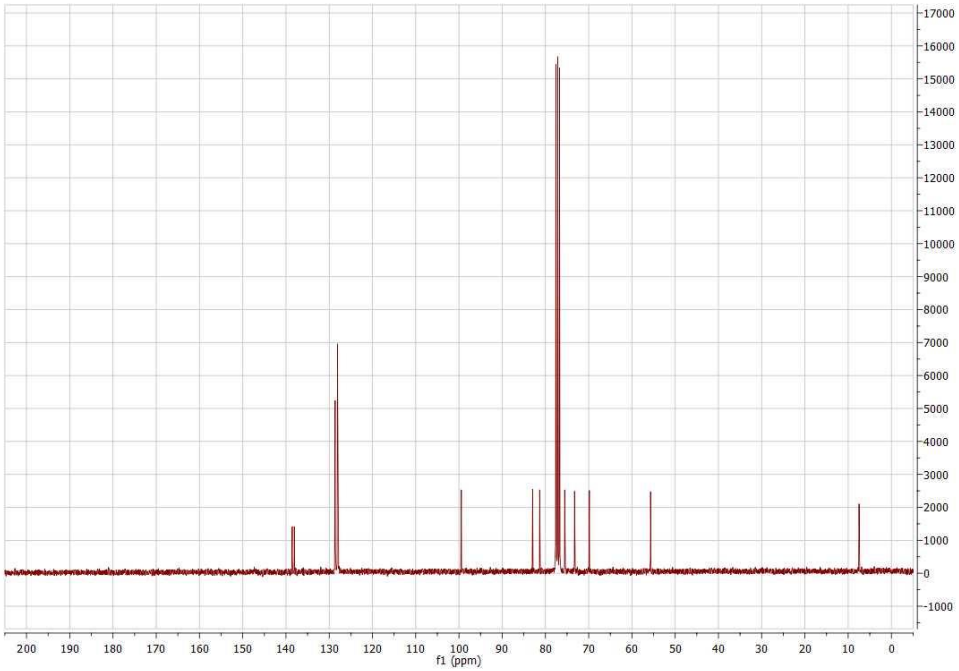



**Figure S7B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **23**.

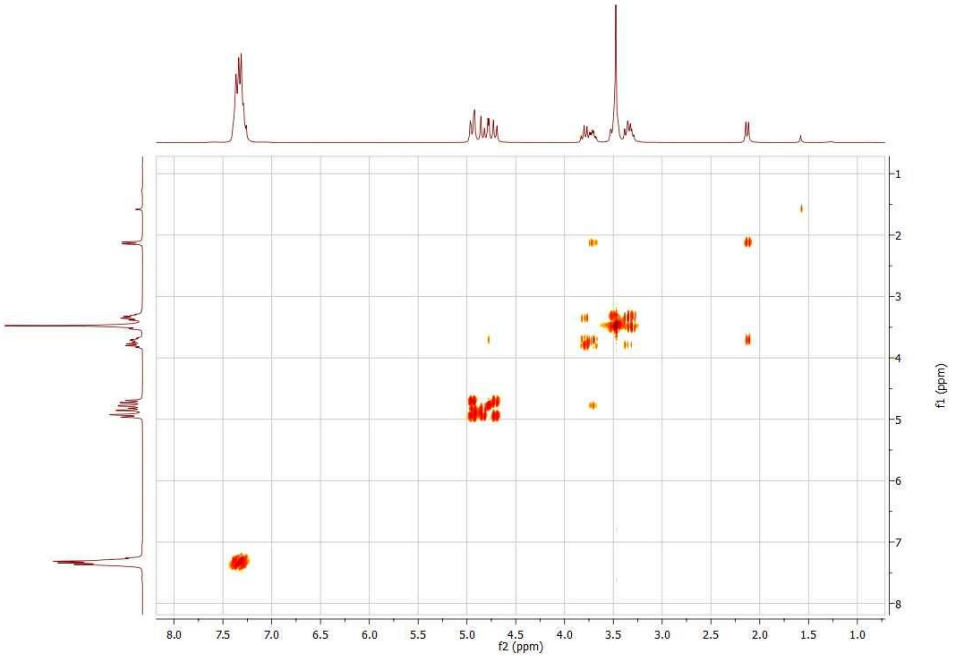



**Figure S7C. COSY** ($CDCl_3$) of compound **23**.

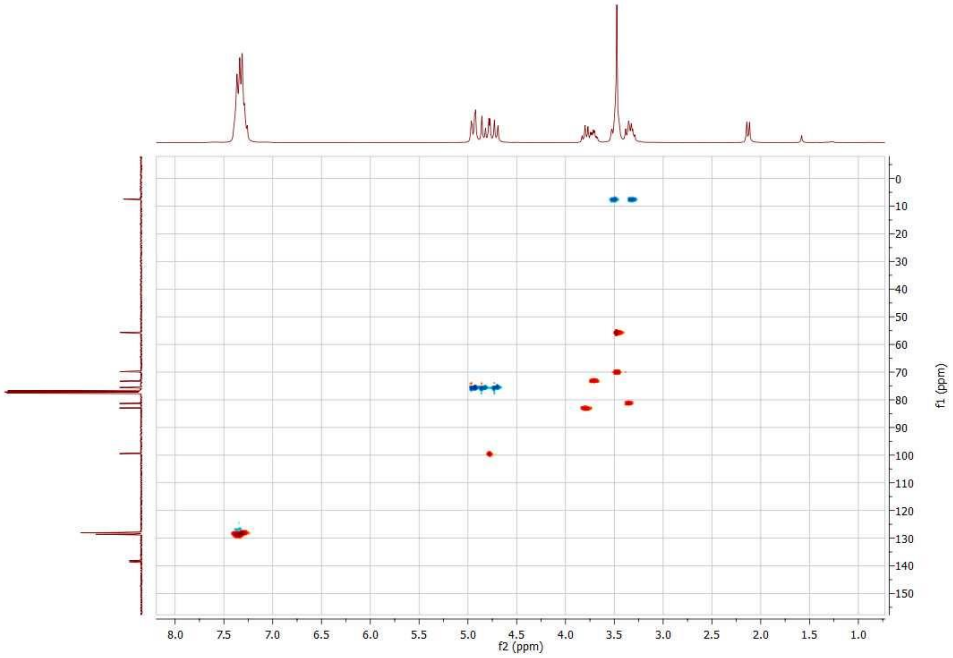



**Figure S7D. HSQC** ($CDCl_3$) of compound **23**.

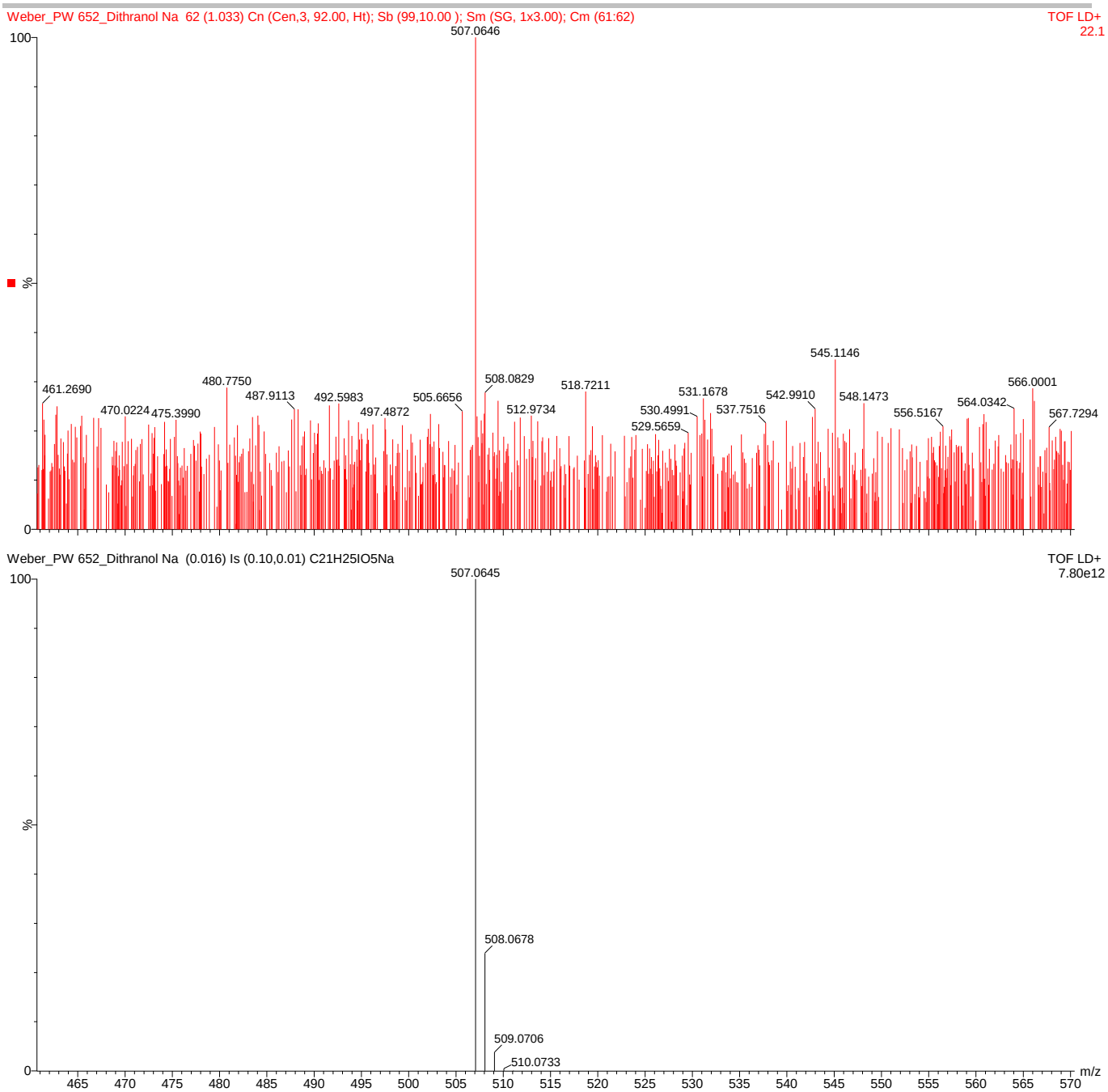
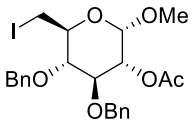



**Figure S7E. HRMS** of compound **23**.

**Methyl 2-*O*-acetyl-6-deoxy-6-iodo-3,4-*O*-dibenzyl-α-D-glucopyranoside (24)**




**24**

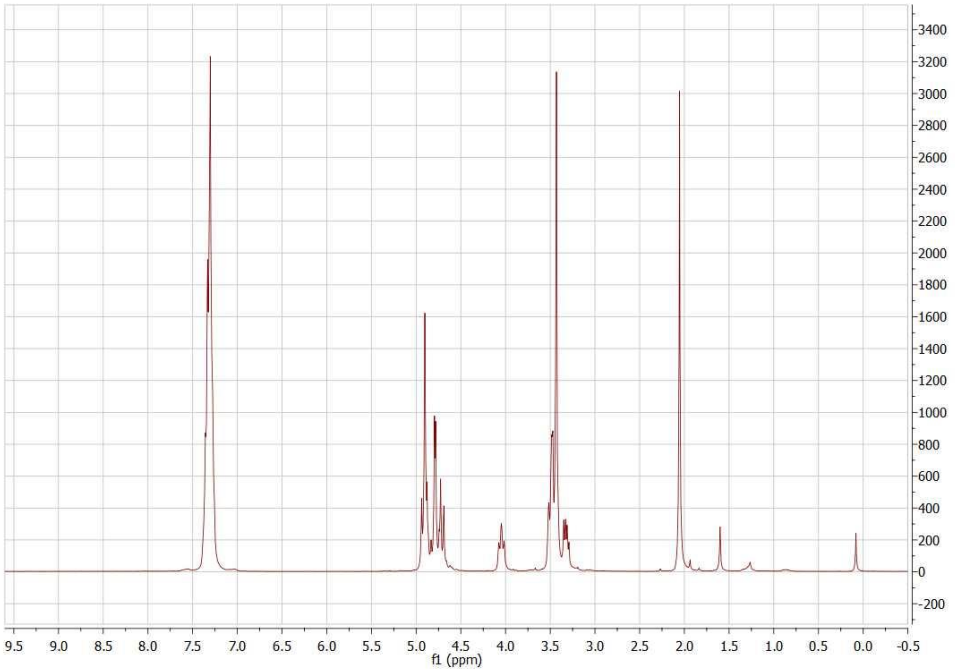



**Figure S8A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **24**.

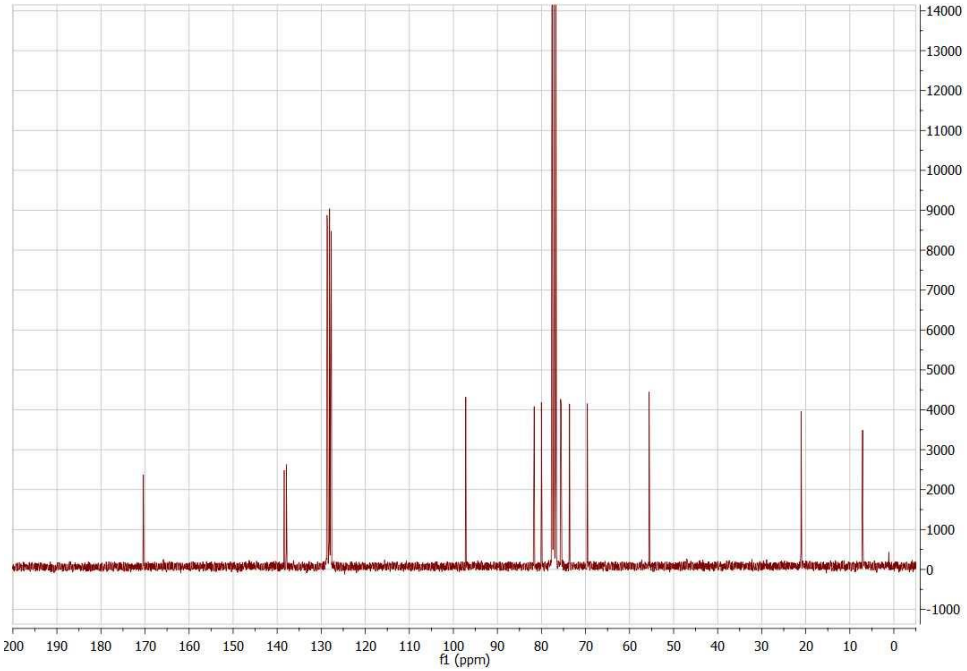



**Figure S8B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **24**.

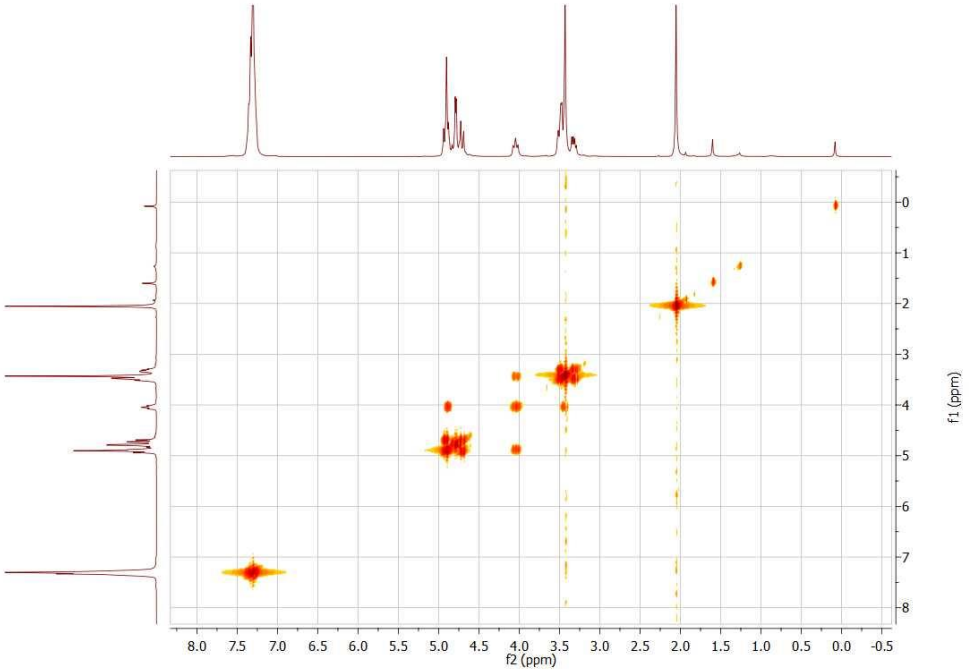



**Figure S8C. COSY** ($CDCl_3$) of compound **24**.

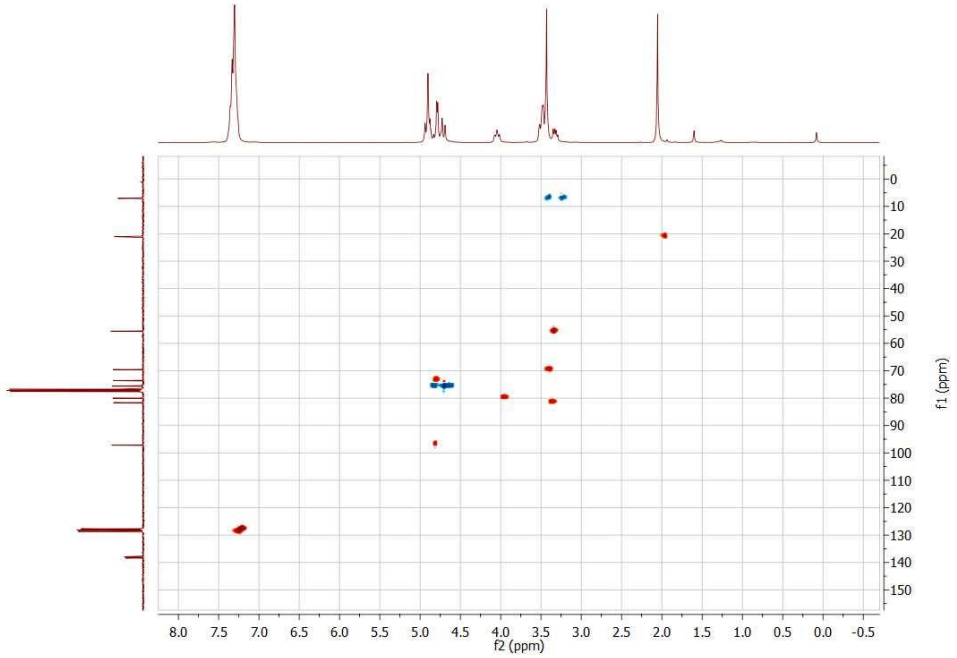



**Figure S8D. HSQC** ($CDCl_3$) of compound **24**.

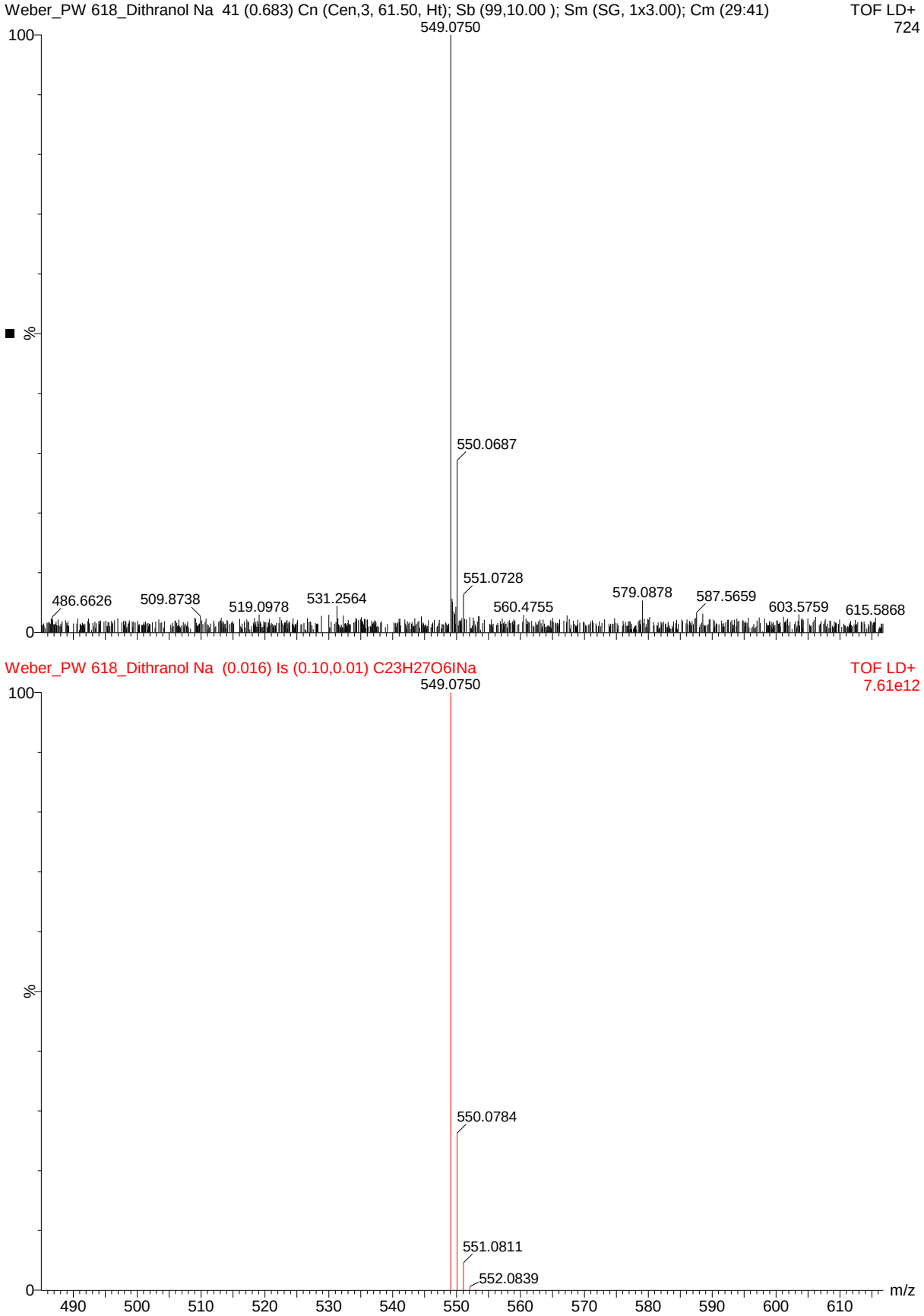
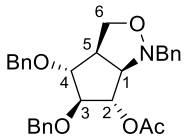



**Figure S8E. HRMS** of compound **24**.

**(3a*R*,4*R*,5*S*,6*S*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-yl acetate (26)**




**26**

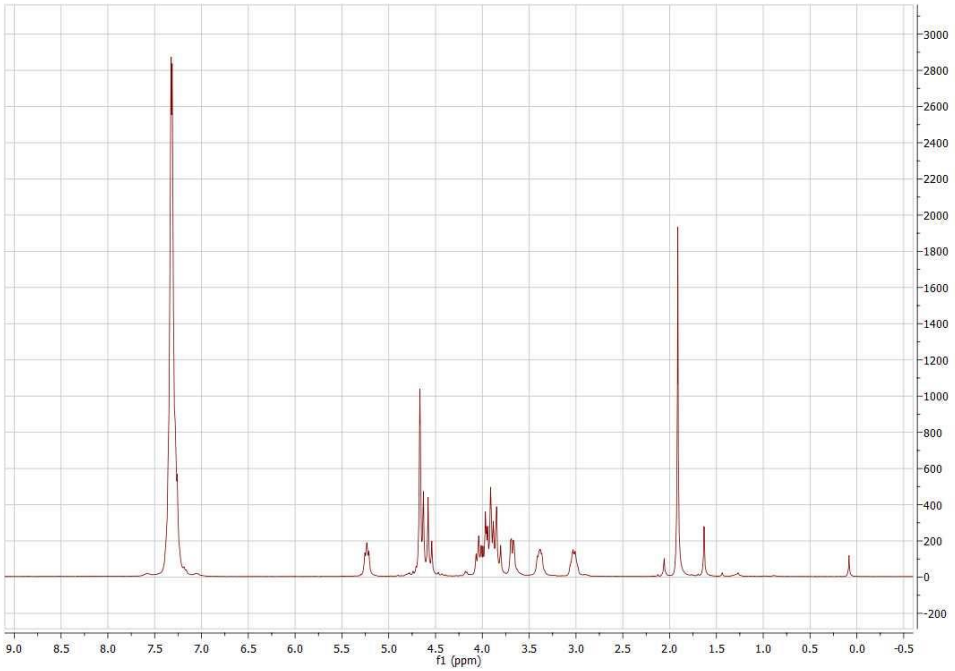



**Figure S9A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **26**.

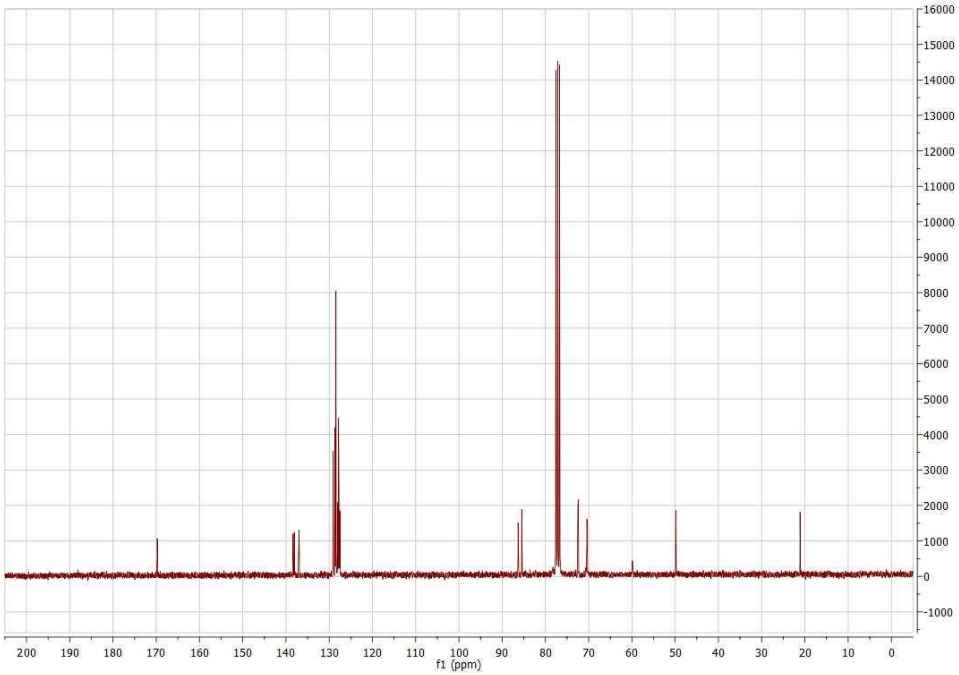



**Figure S9B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **26**.

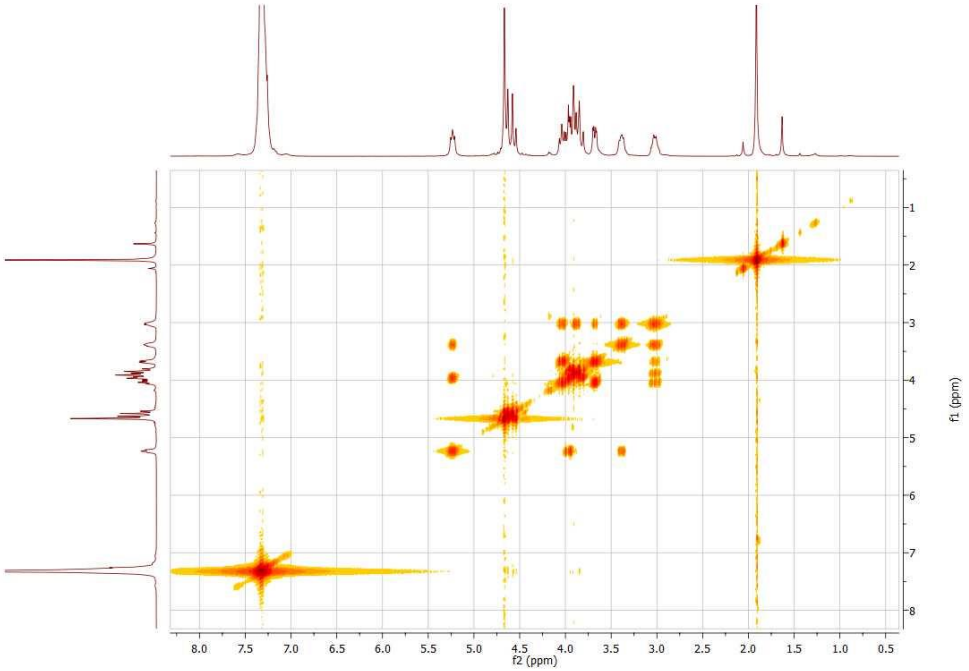



**Figure S9C. COSY** ($CDCl_3$) of compound **26**.

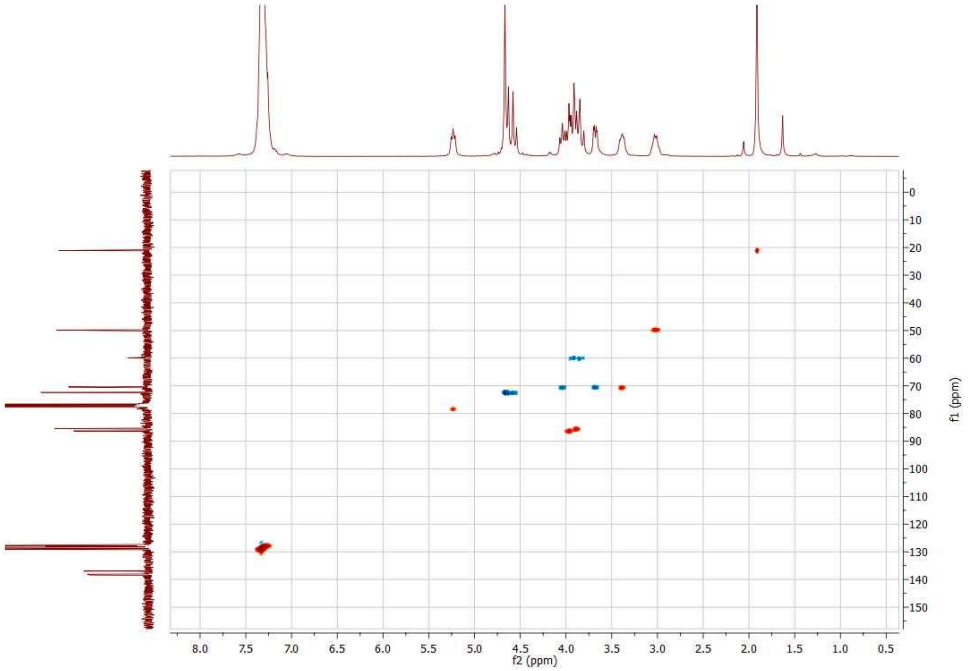



**Figure S9D. HSQC** ($CDCl_3$) of compound **26**.

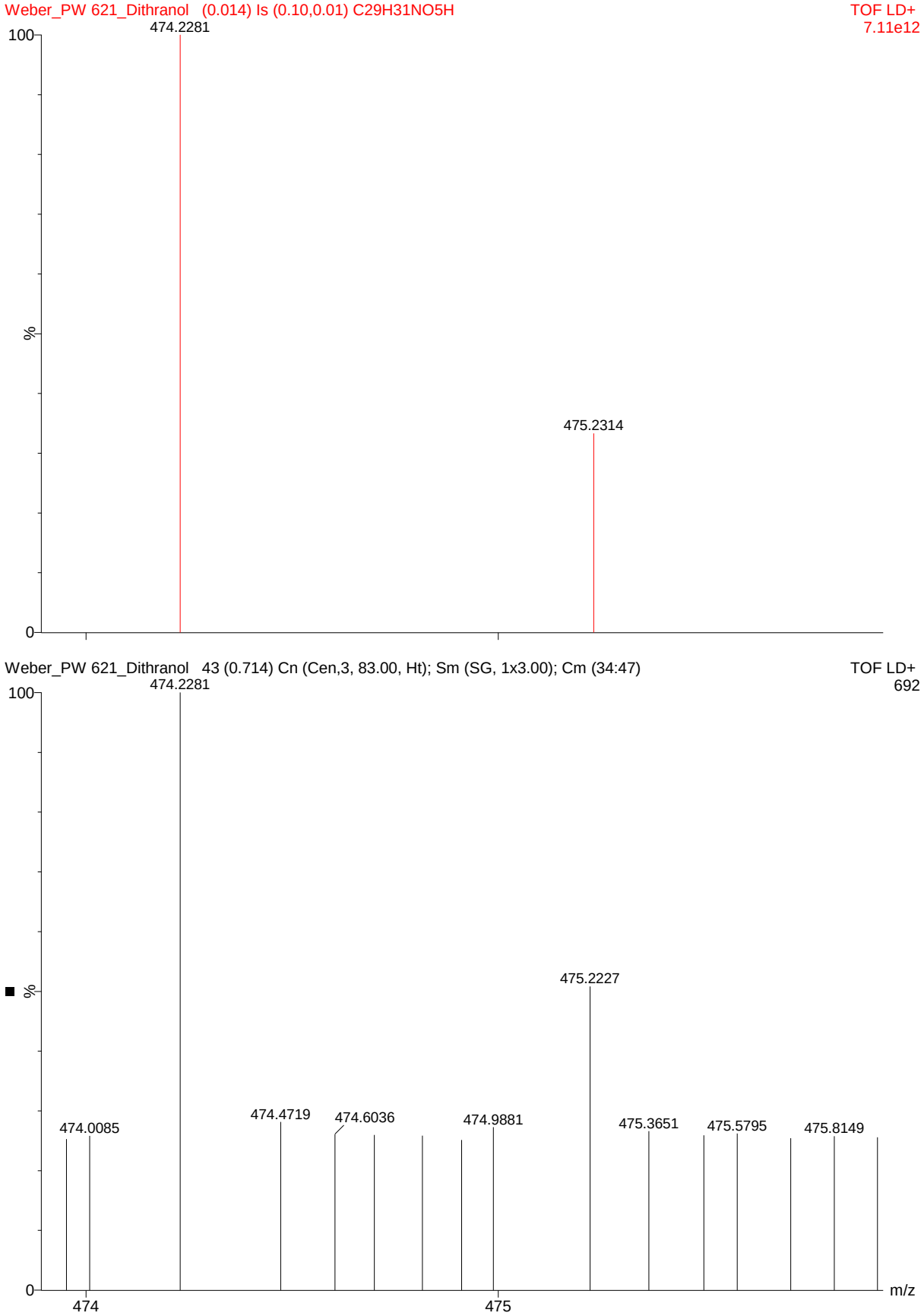
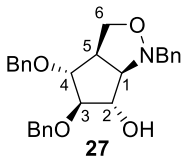



**Figure S9E. HRMS** of compound **26**.

**(3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-ol (27)**




**27**

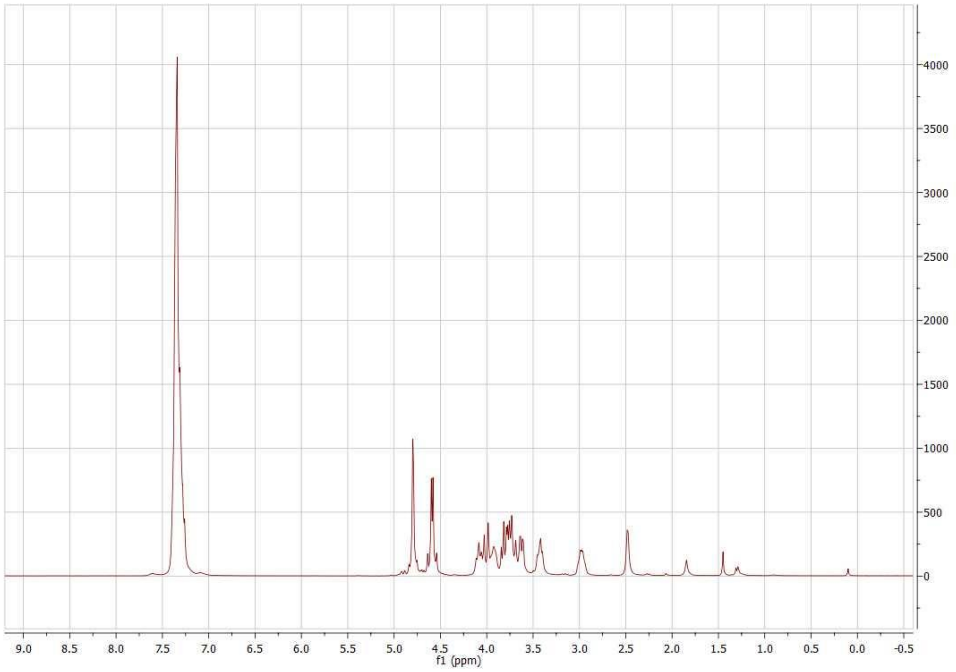



**Figure S10A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **27**.

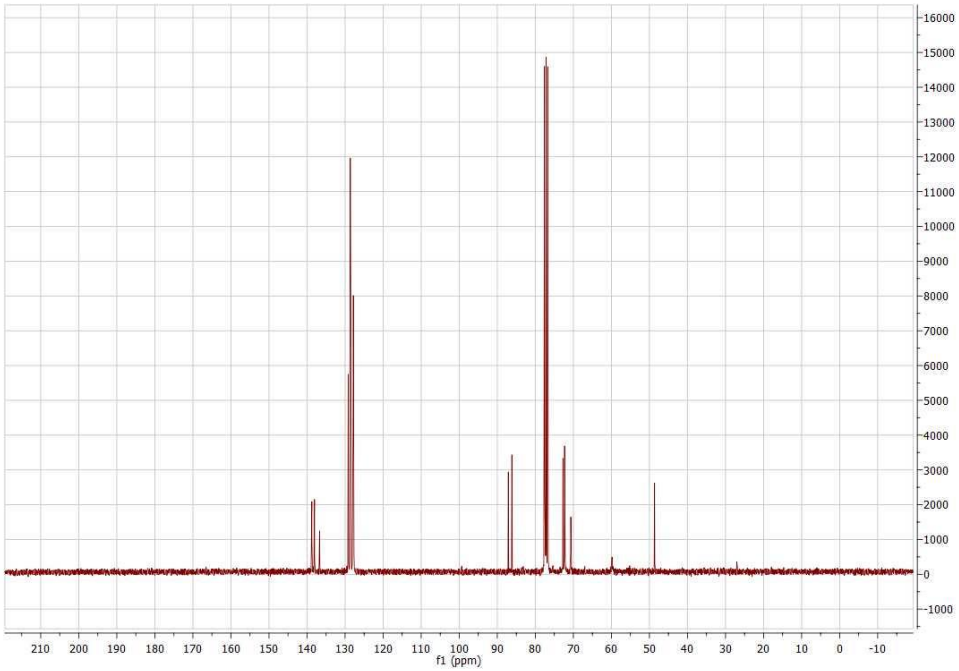



**Figure S10B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **27**.

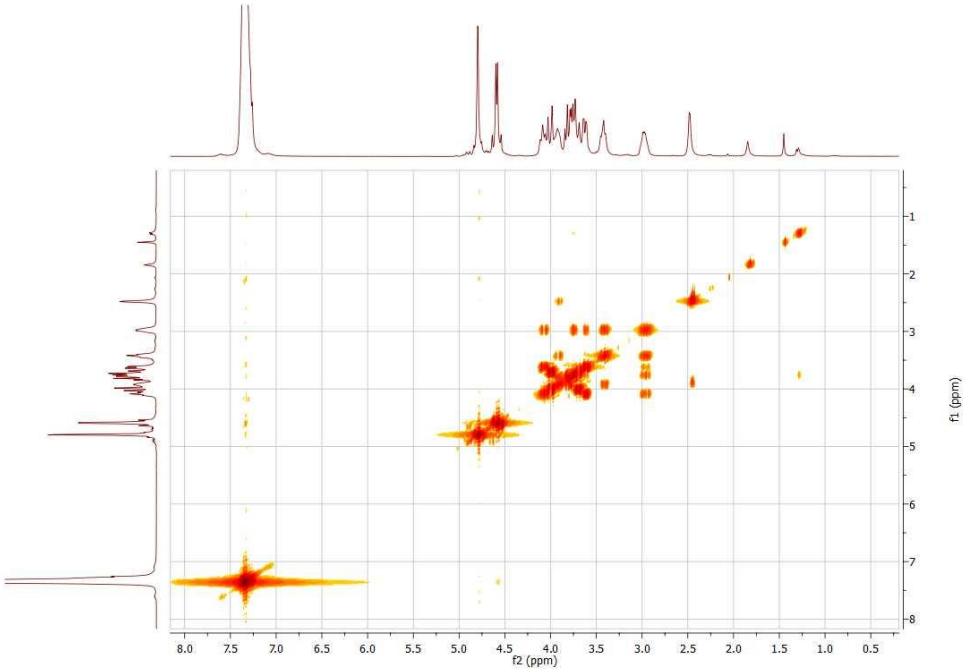



**Figure S10C. COSY** ($CDCl_3$) of compound **27**.

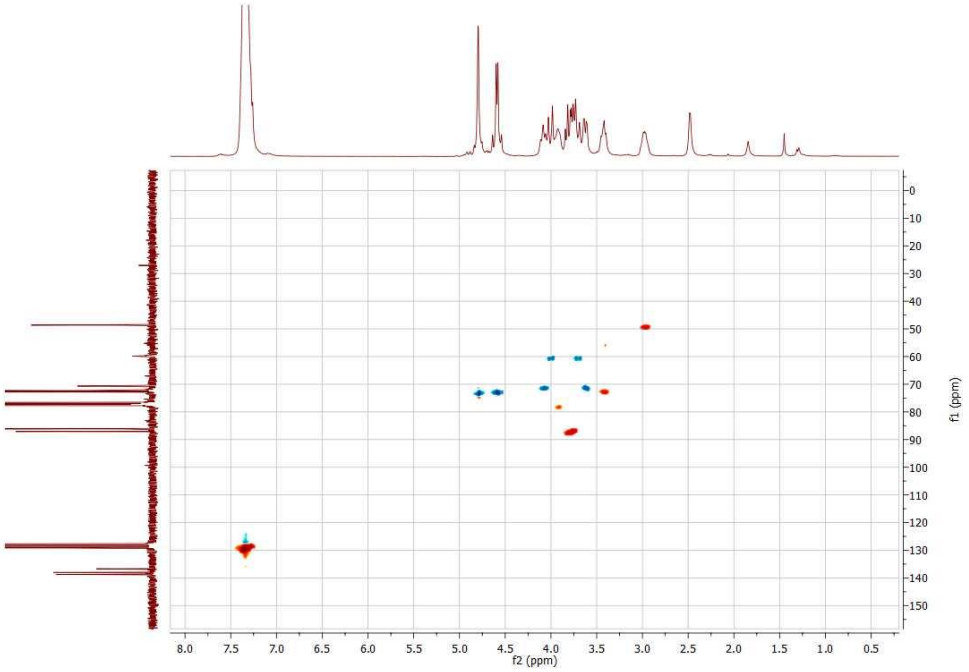



**Figure S10D. HSQC** ($CDCl_3$) of compound **27**.

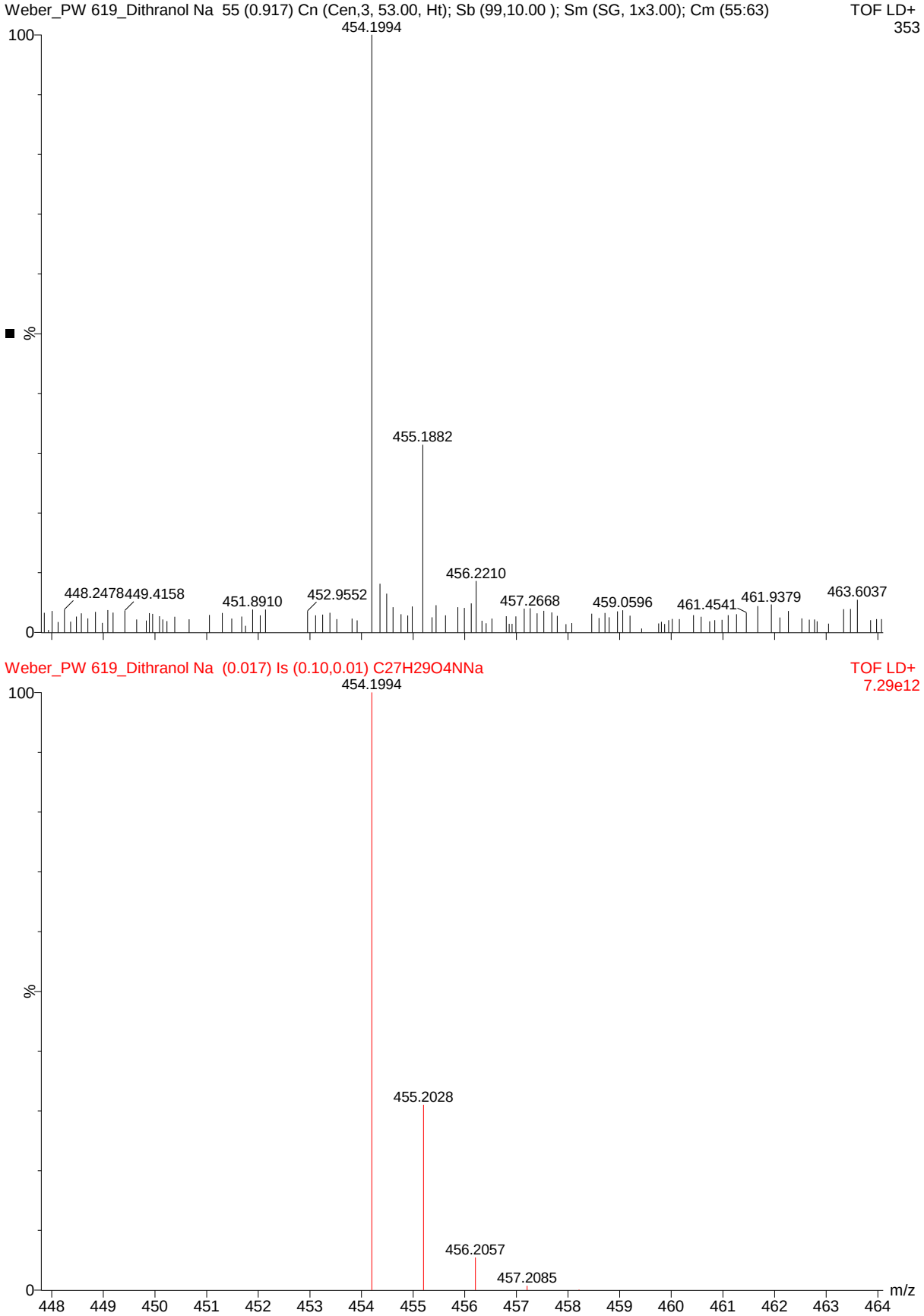
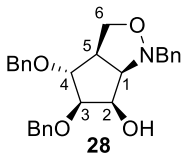



**Figure S10E. HRMS** of compound **27**.

**(3a*R*,4*R*,5*R*,6*R*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-ol (28)**




**28**

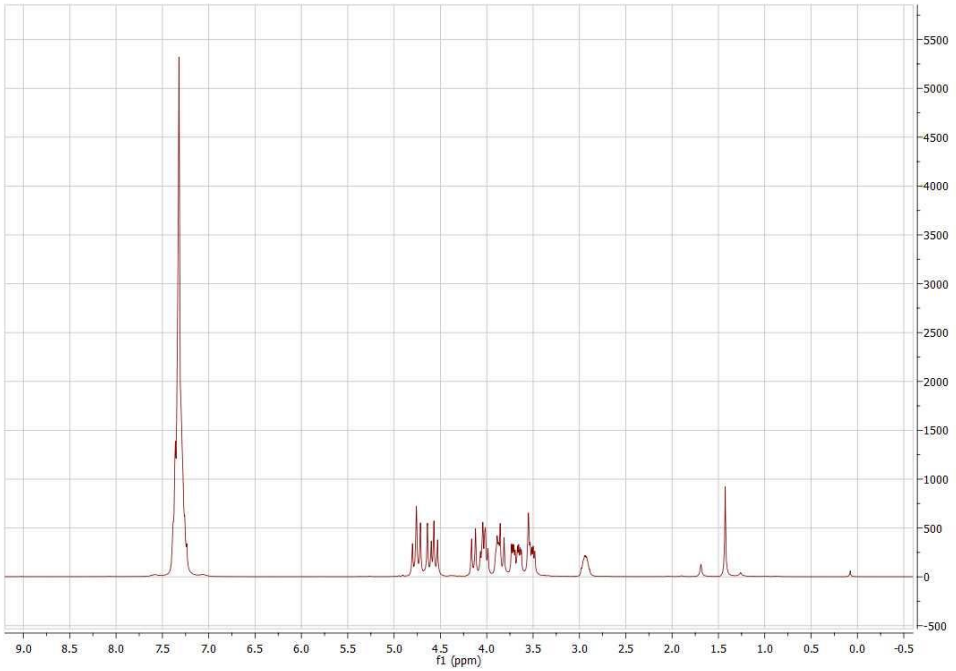



**Figure S11A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **28**.

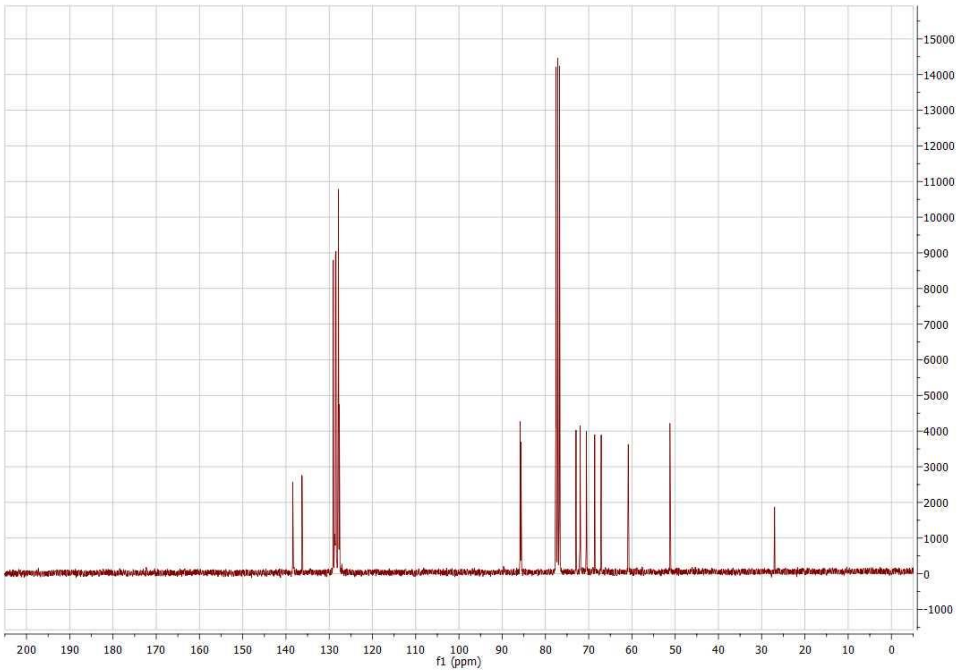



**Figure S11B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **28**.

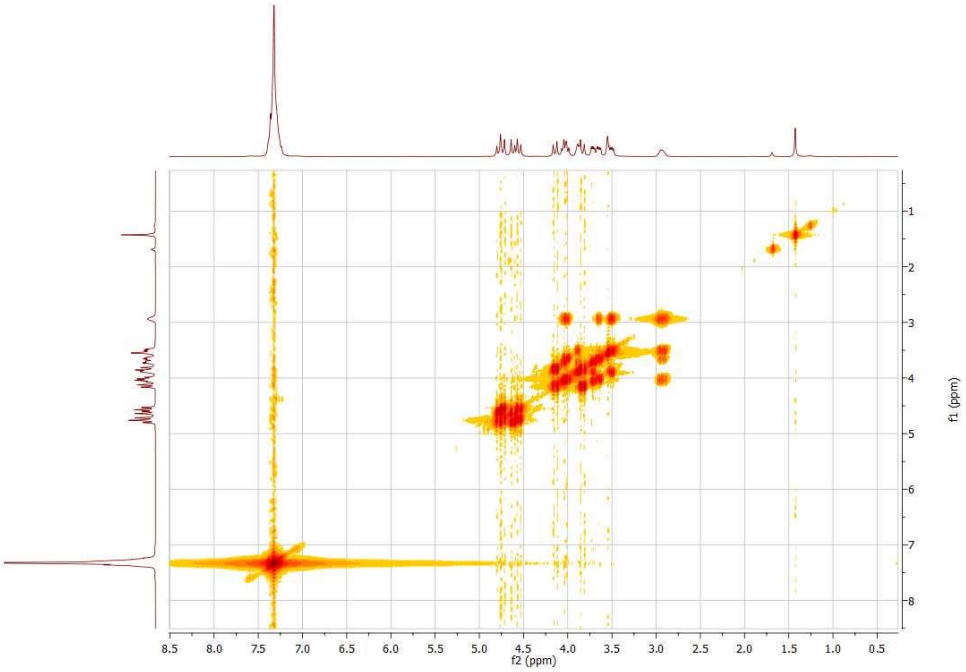



**Figure S11C. COSY** ($CDCl_3$) of compound **28**.

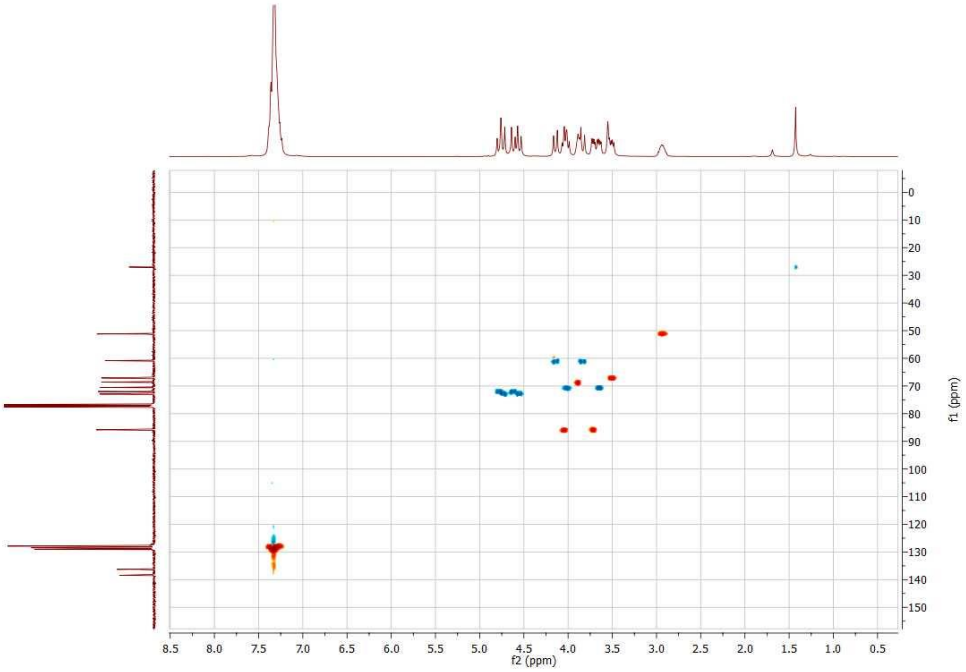



**Figure S11D. HSQC** ($CDCl_3$) of compound **28**.

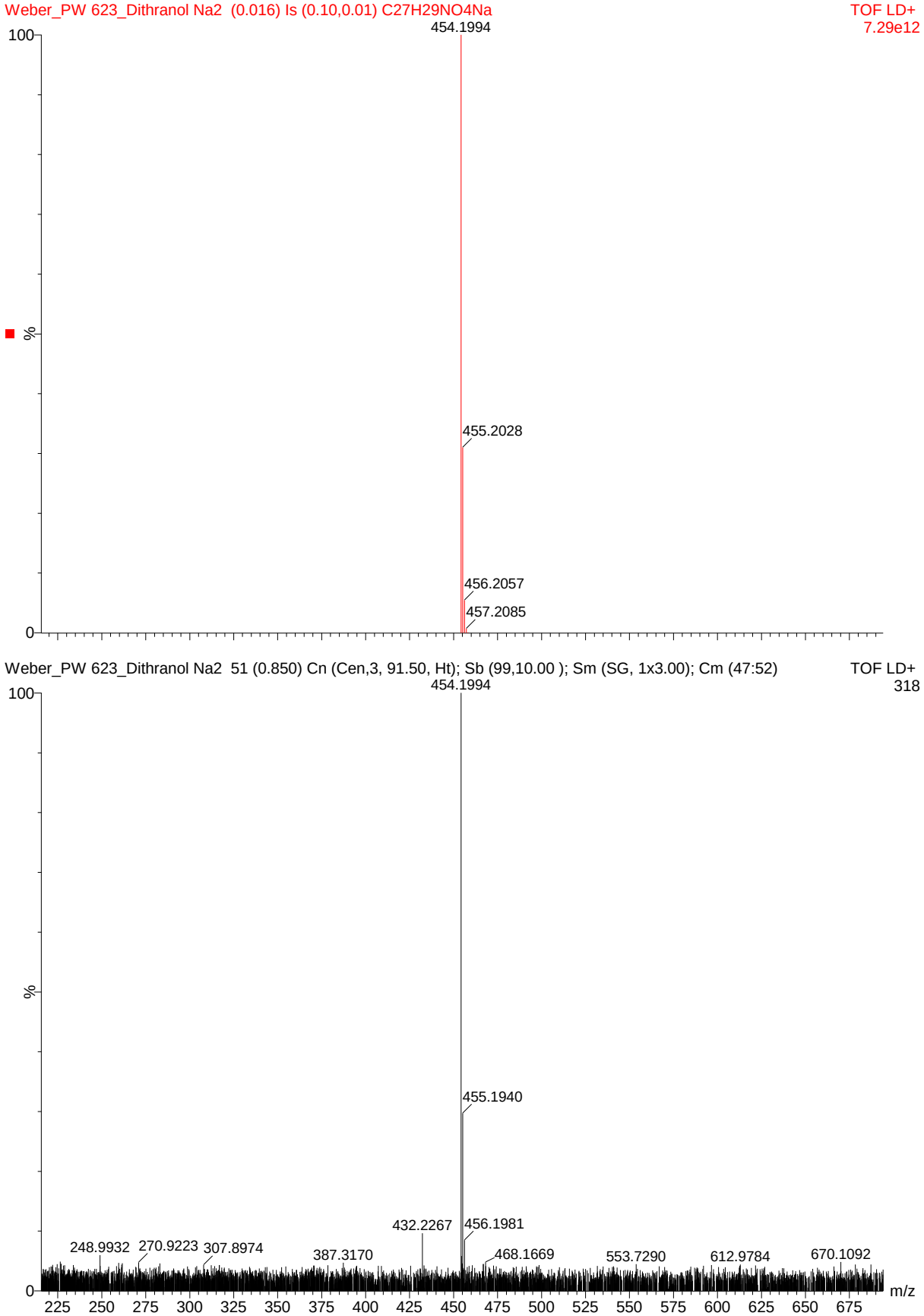
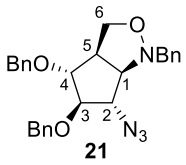



**Figure S11E. HRMS** of compound **28**.

**(3a*R*,4*R*,5*R*,6*S*,6a*R*)-6-Azido-1-benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*) isoxazole (21)**




**21**

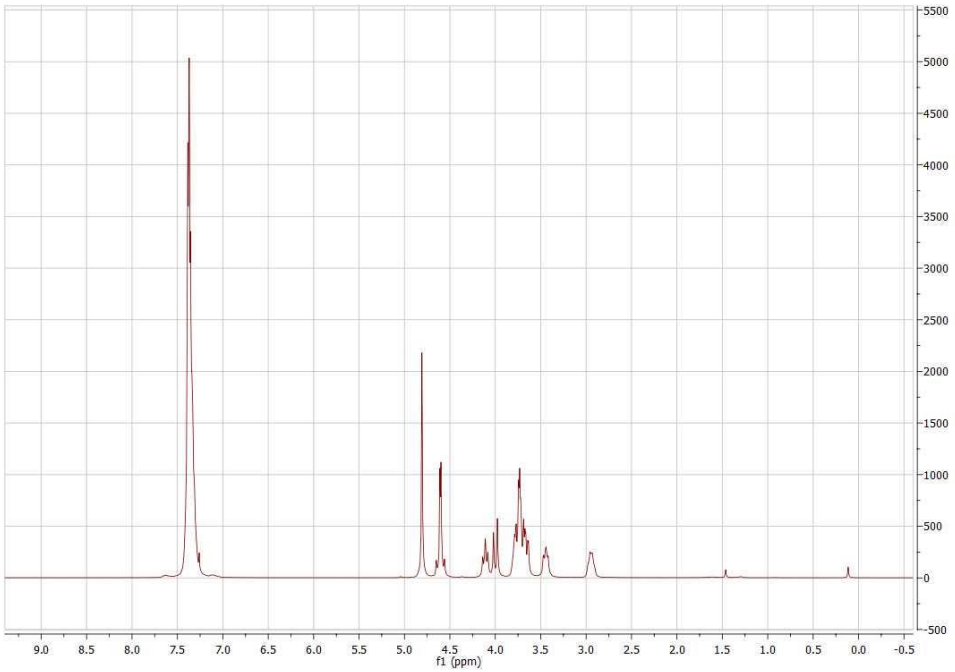



**Figure S12A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **21**.

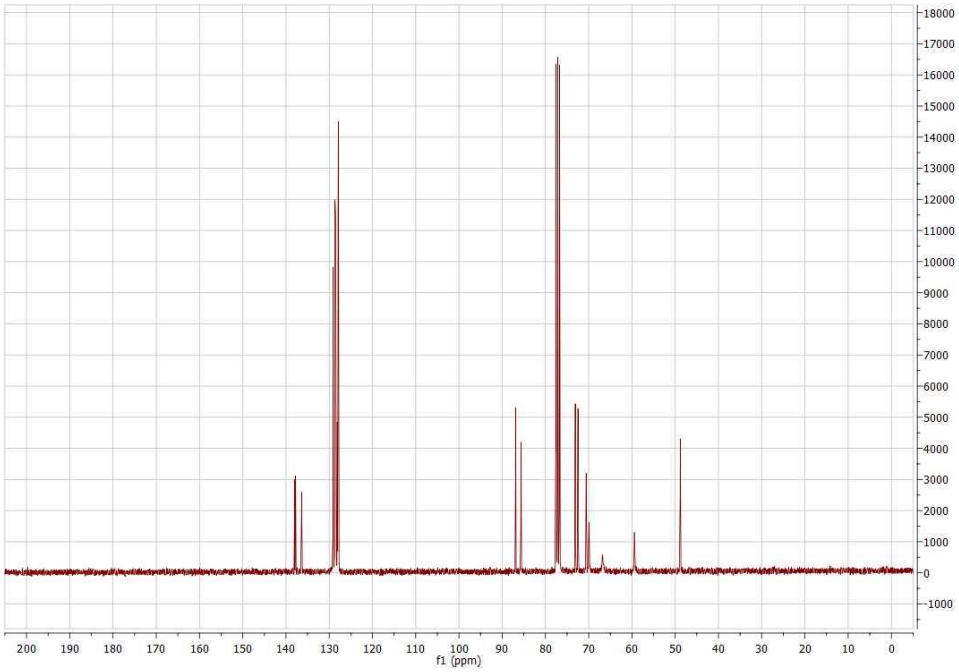



**Figure S12B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **21**.

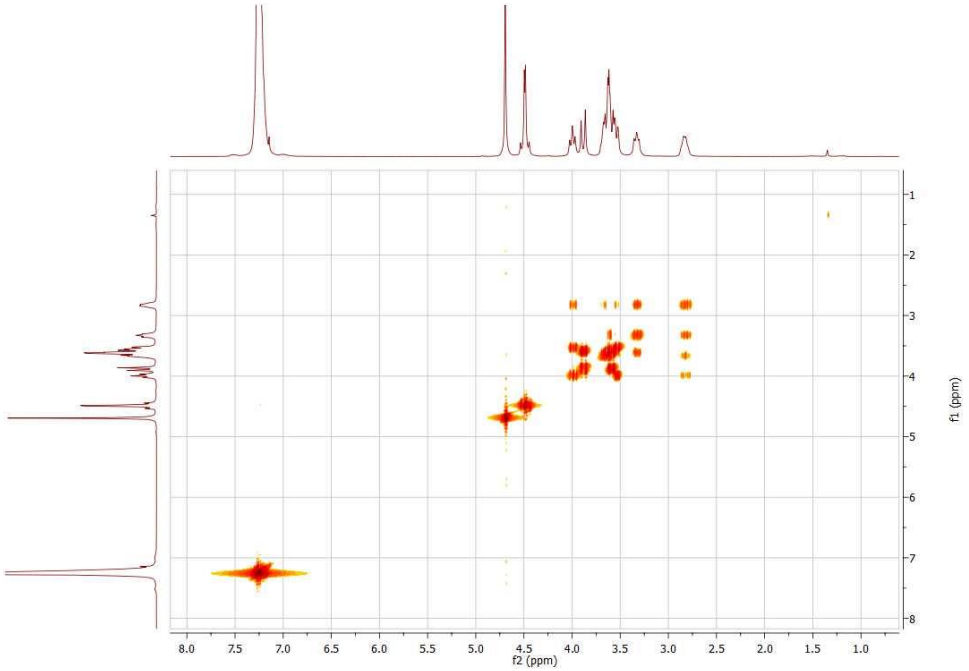



**Figure S12C. COSY** ($CDCl_3$) of compound **21**.

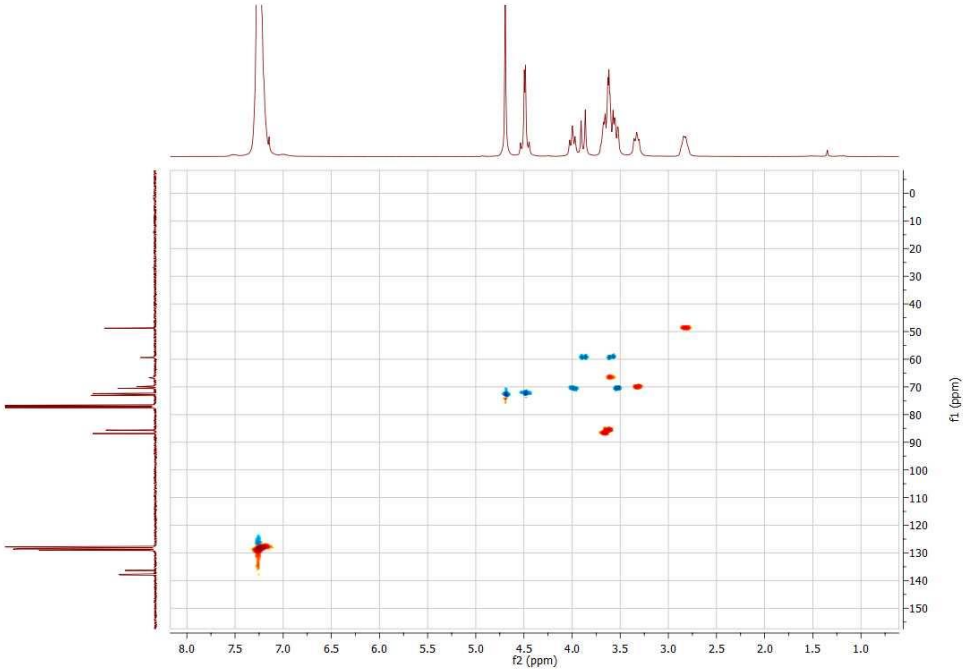



**Figure S12D. HSQC** ($CDCl_3$) of compound **21**.

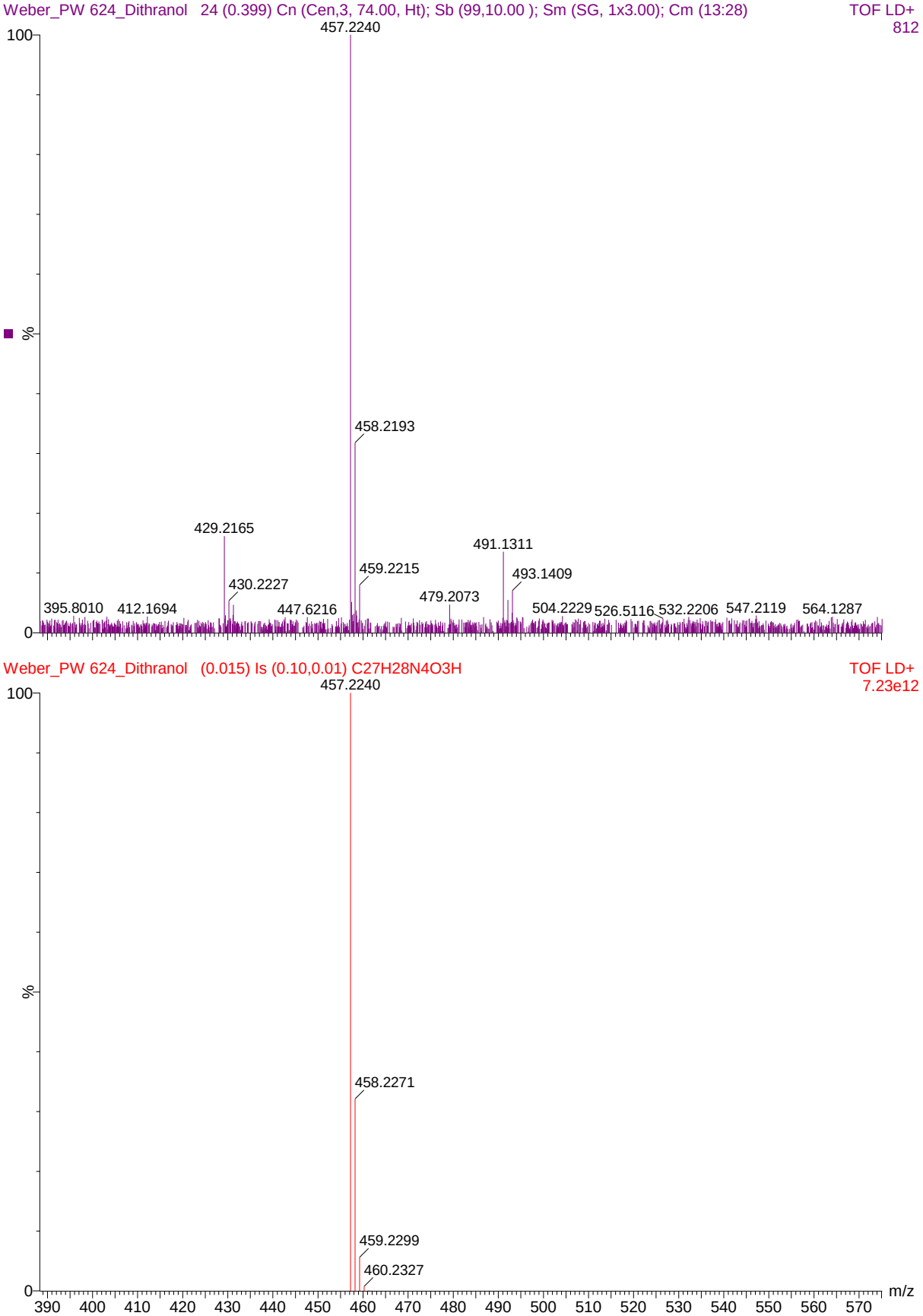
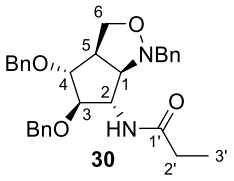



**Figure S12E. HRMS** of compound **21**.

***N*-((3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl)propionamide (30)**




**30**

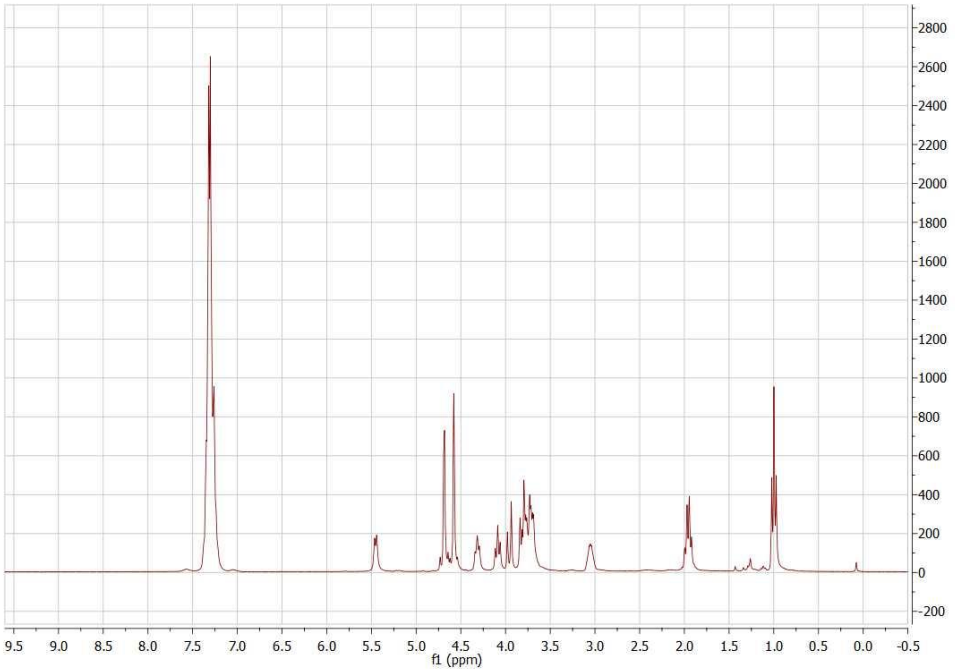



**Figure S13A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **30**.

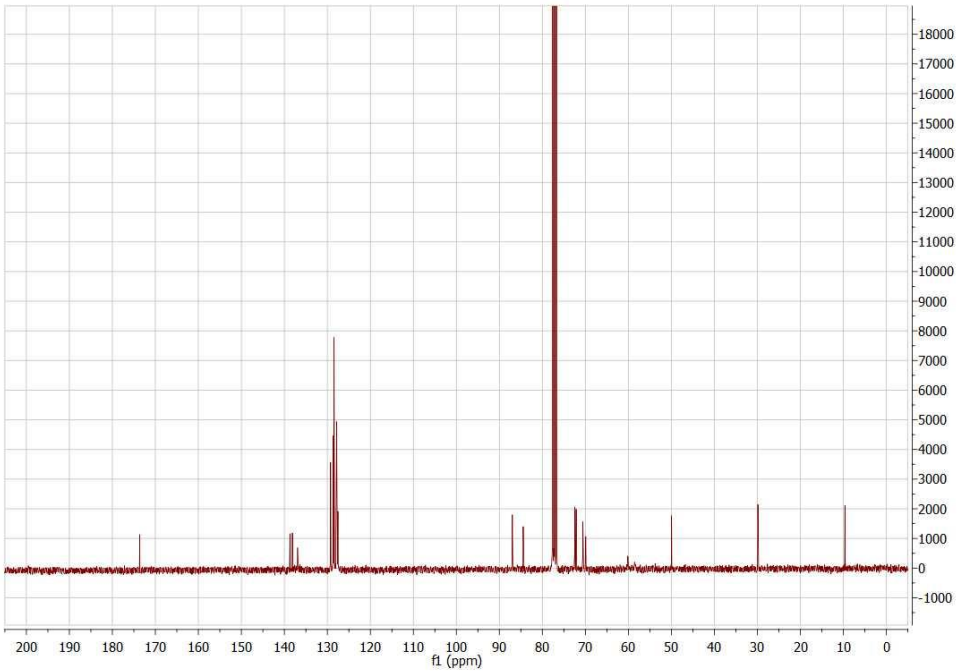



**Figure S13B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **30**.

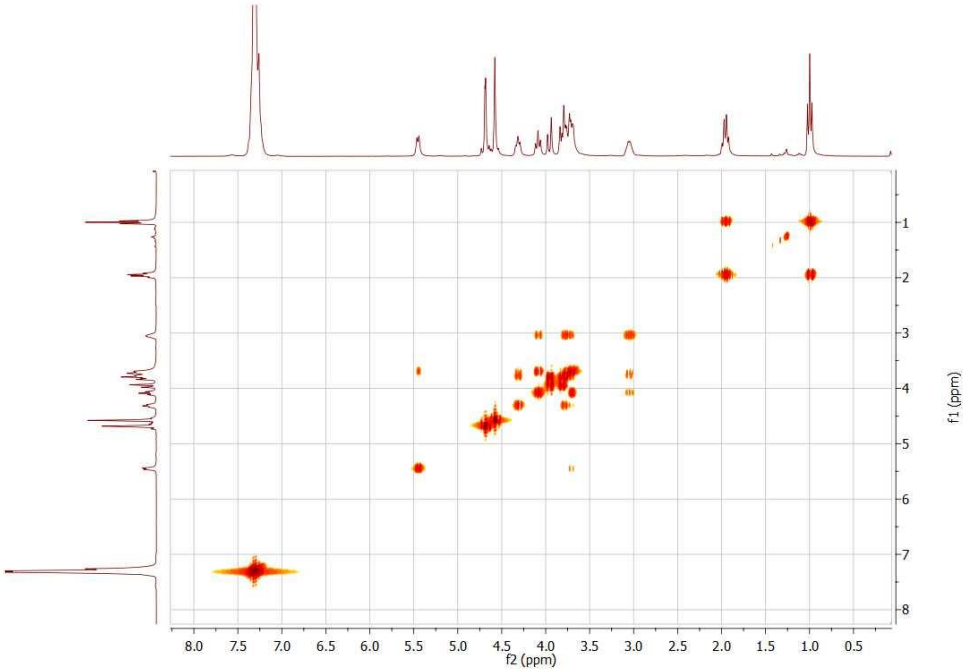



**Figure S13C. COSY** ($CDCl_3$) of compound **30**.

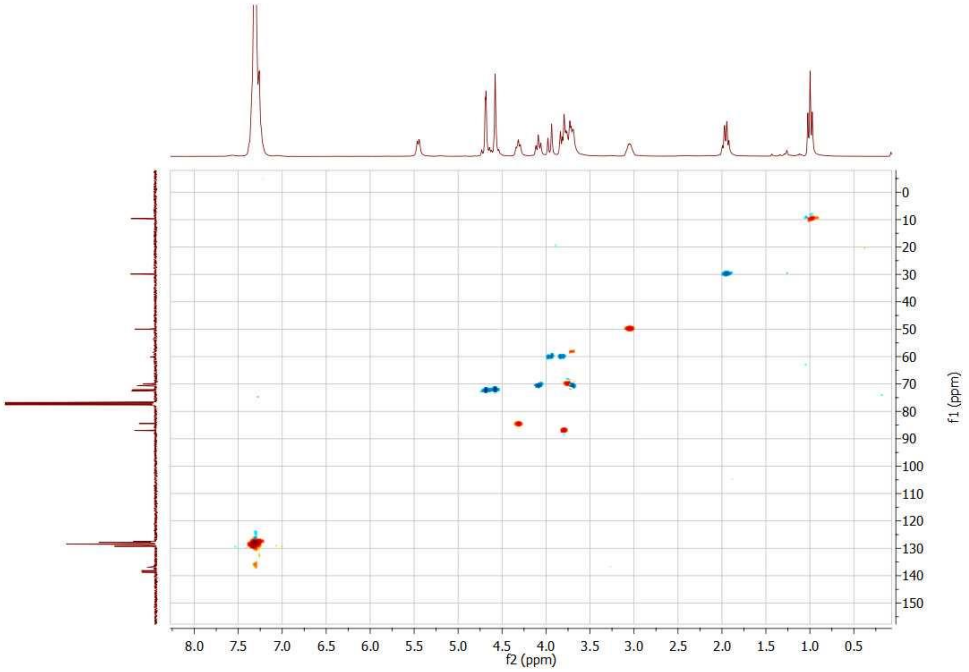



**Figure S13D. HSQC** ($CDCl_3$) of compound **30**.

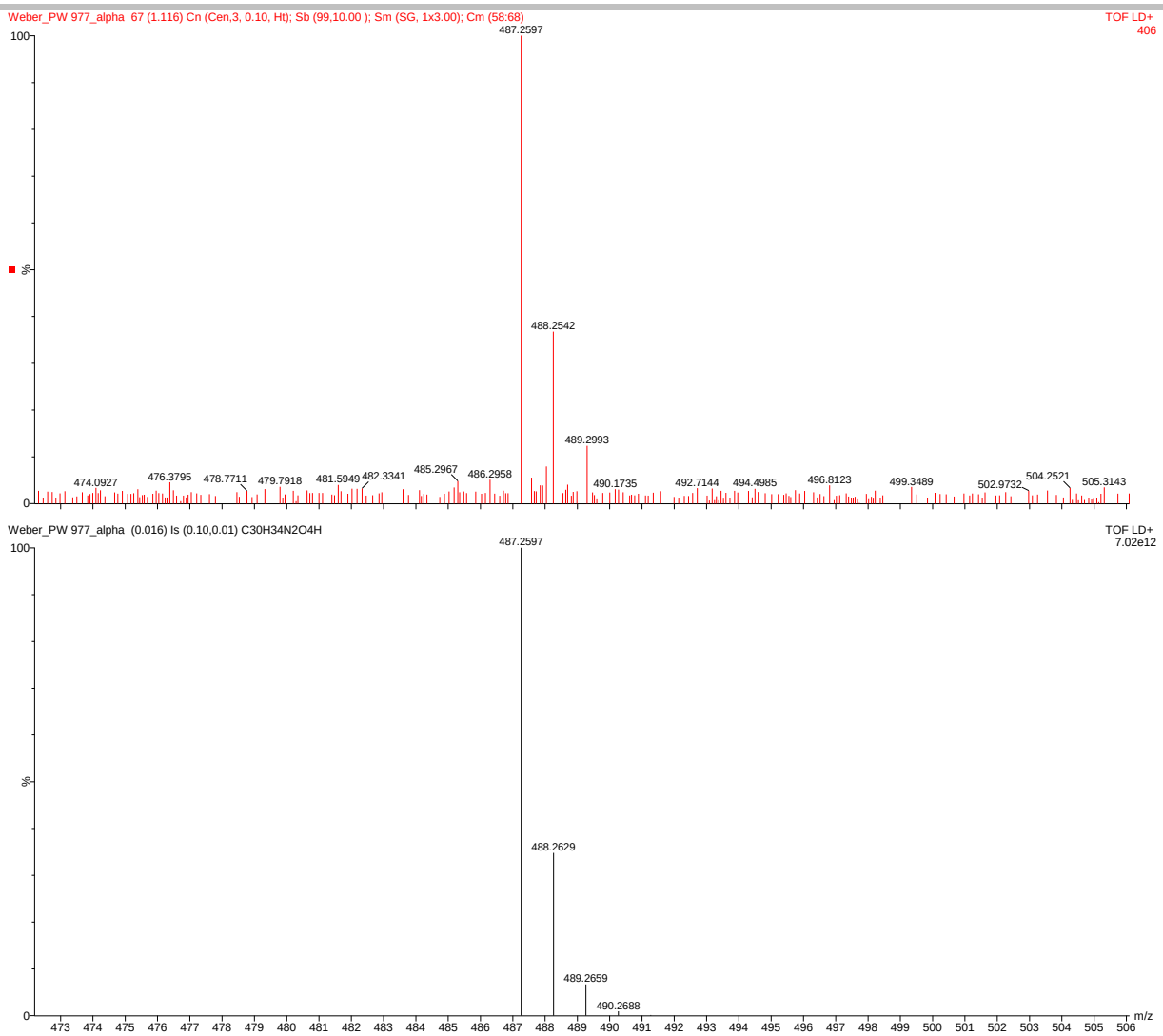
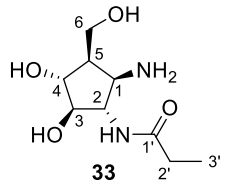



**Figure S13E. HRMS** of compound **30**.

***N*-((1S,2R,3R,4R,5R)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)propanoylamide "(1-Amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (33)**




**33**

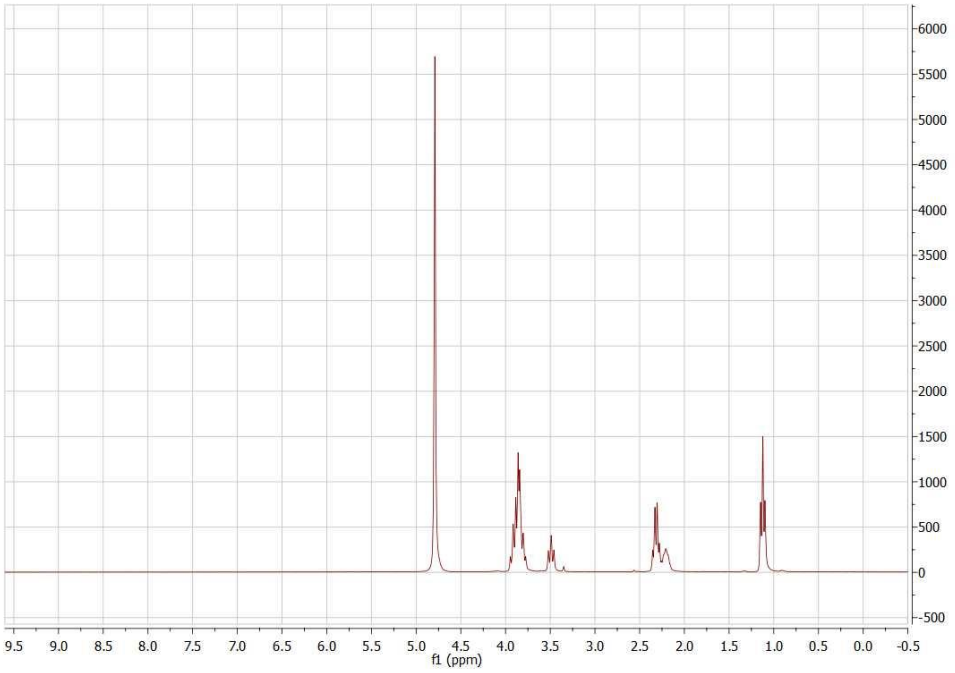



**Figure S14A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **33**, free base.

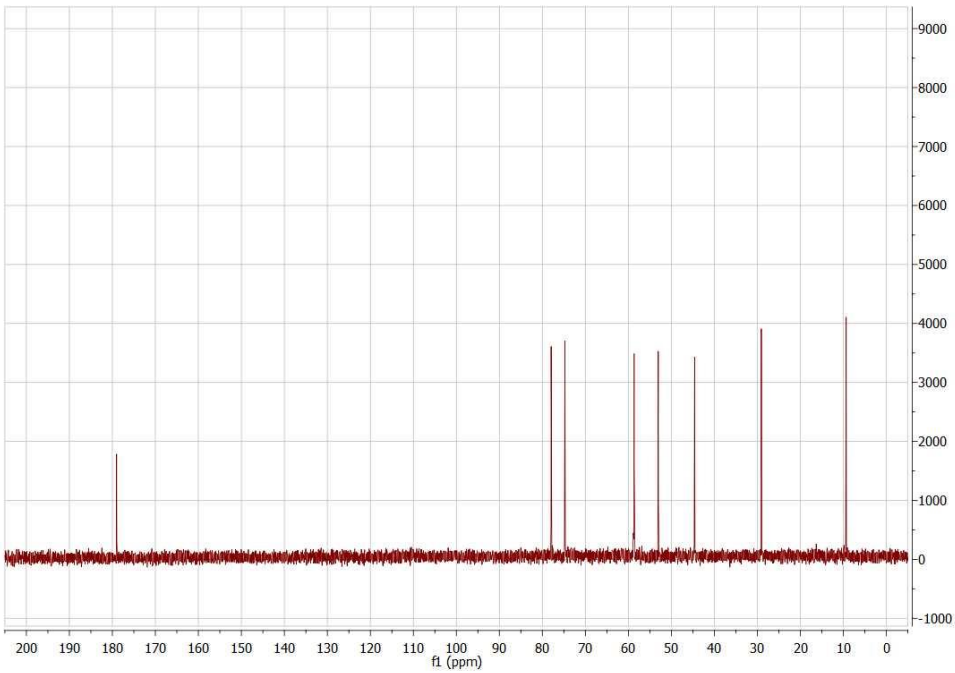



**Figure S14B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **33**, free base.

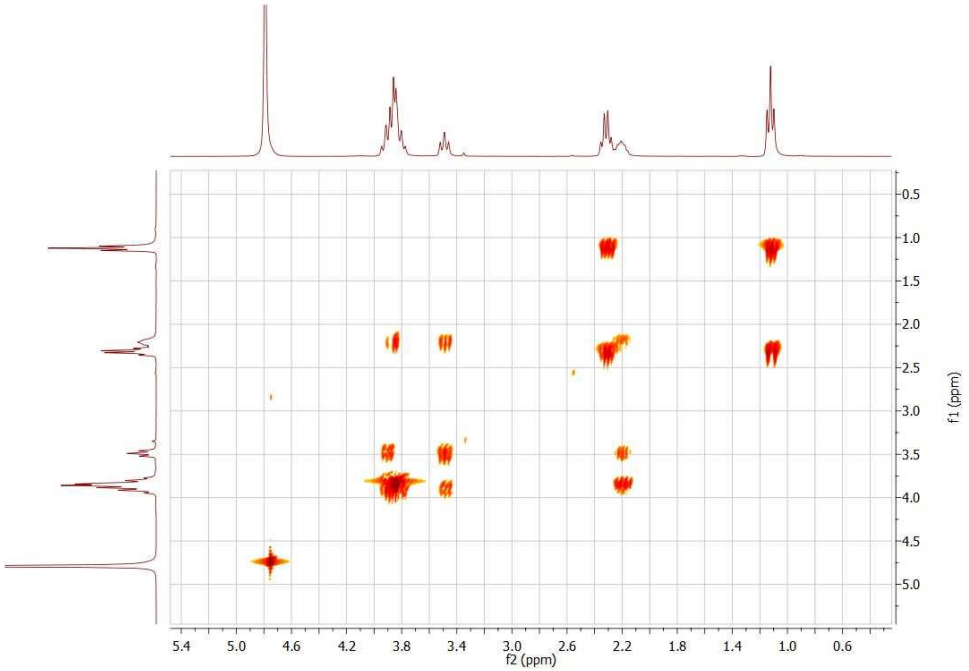



**Figure S14C. COSY** ($D_2O$) of compound **33**, free base.

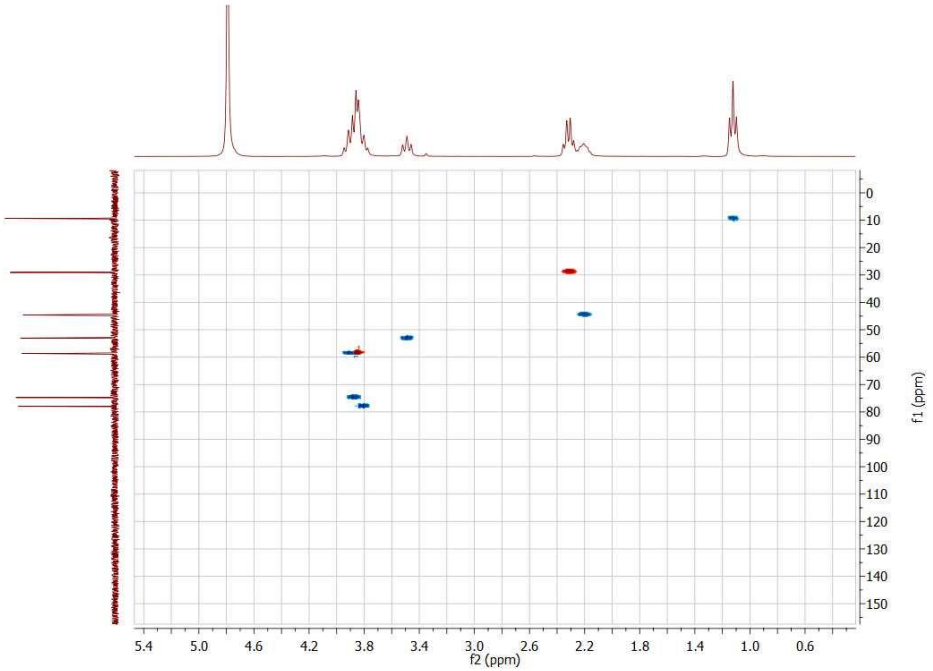



**Figure S14D. HSQC** ($D_2O$) of compound **33**, free base.

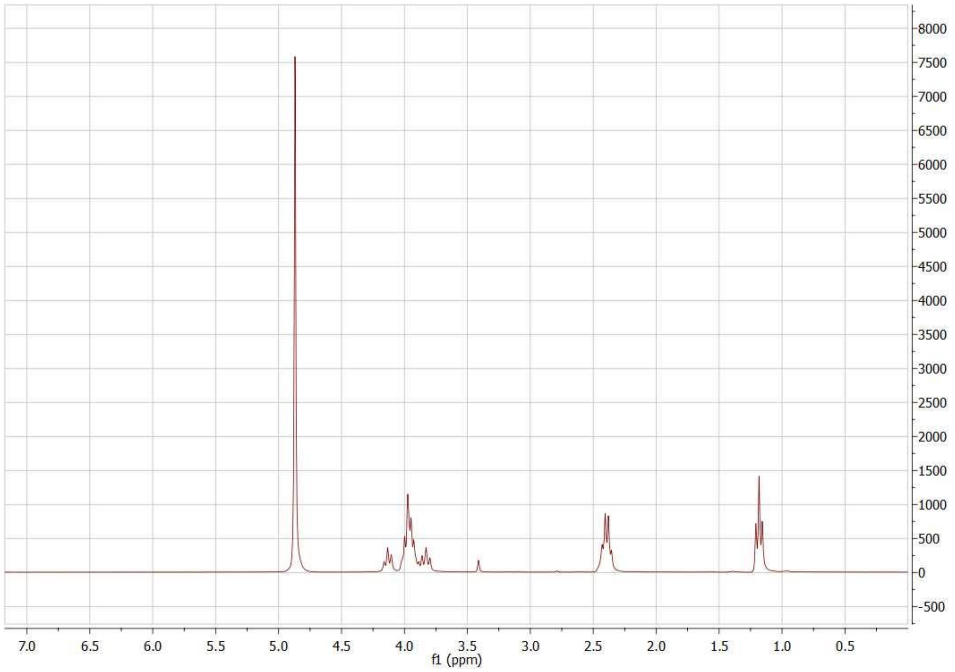



**Figure S14E. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **33**, hydrochloride.

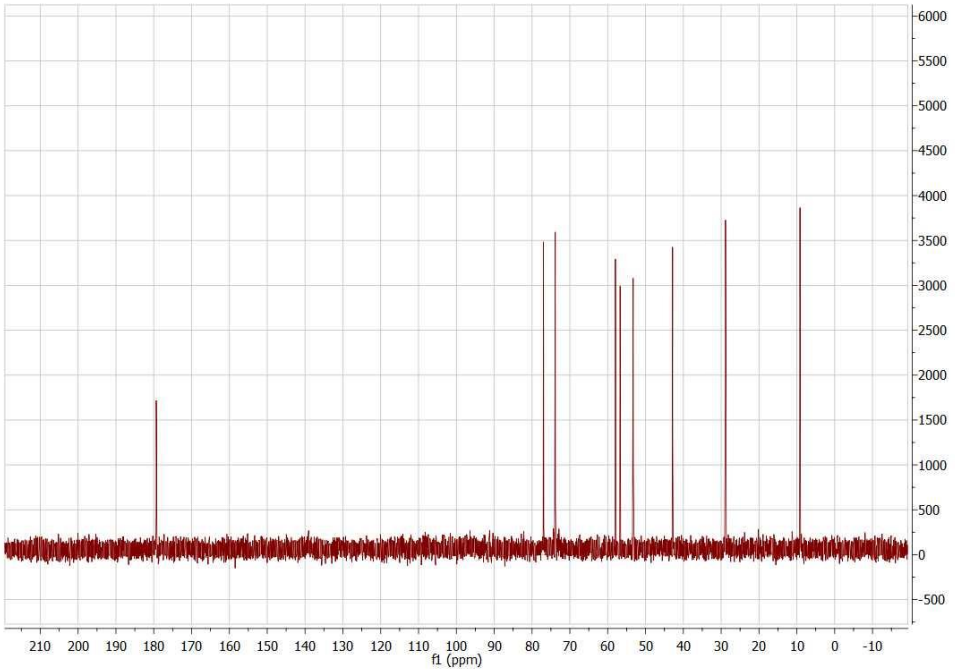



**Figure S14F. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **33**, hydrochloride.

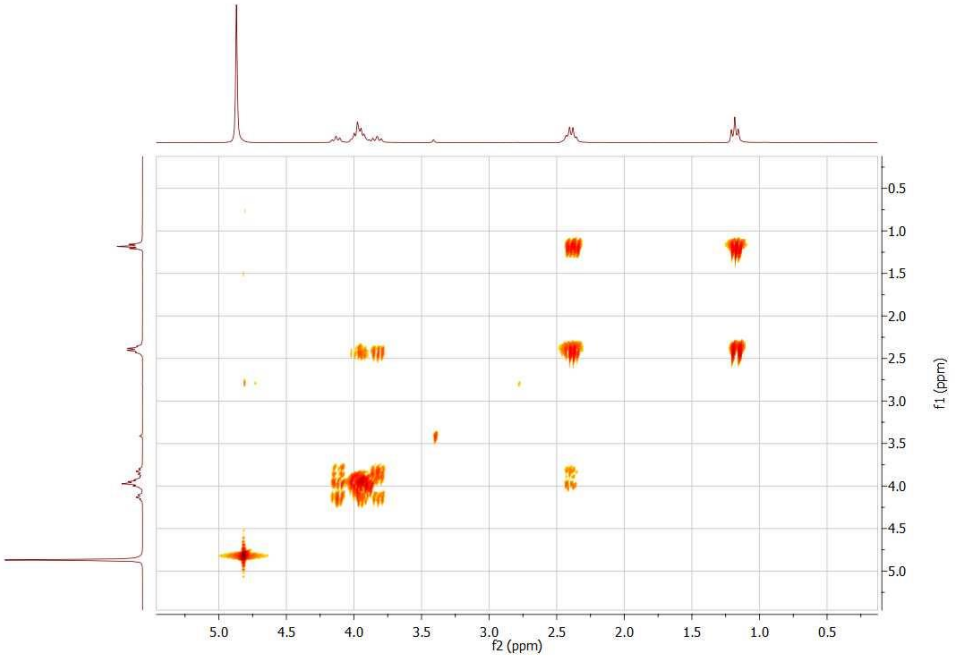



**Figure S14G. COSY** ($D_2O$) of compound **33**, hydrochloride.

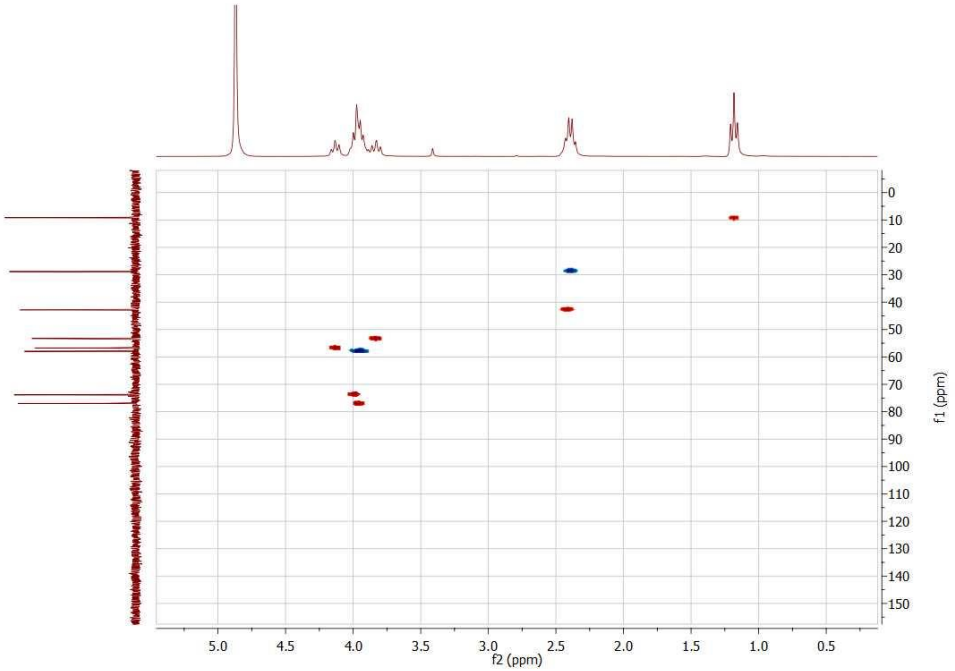



**Figure S14H. HSQC** ($D_2O$) of compound **33**, hydrochloride.

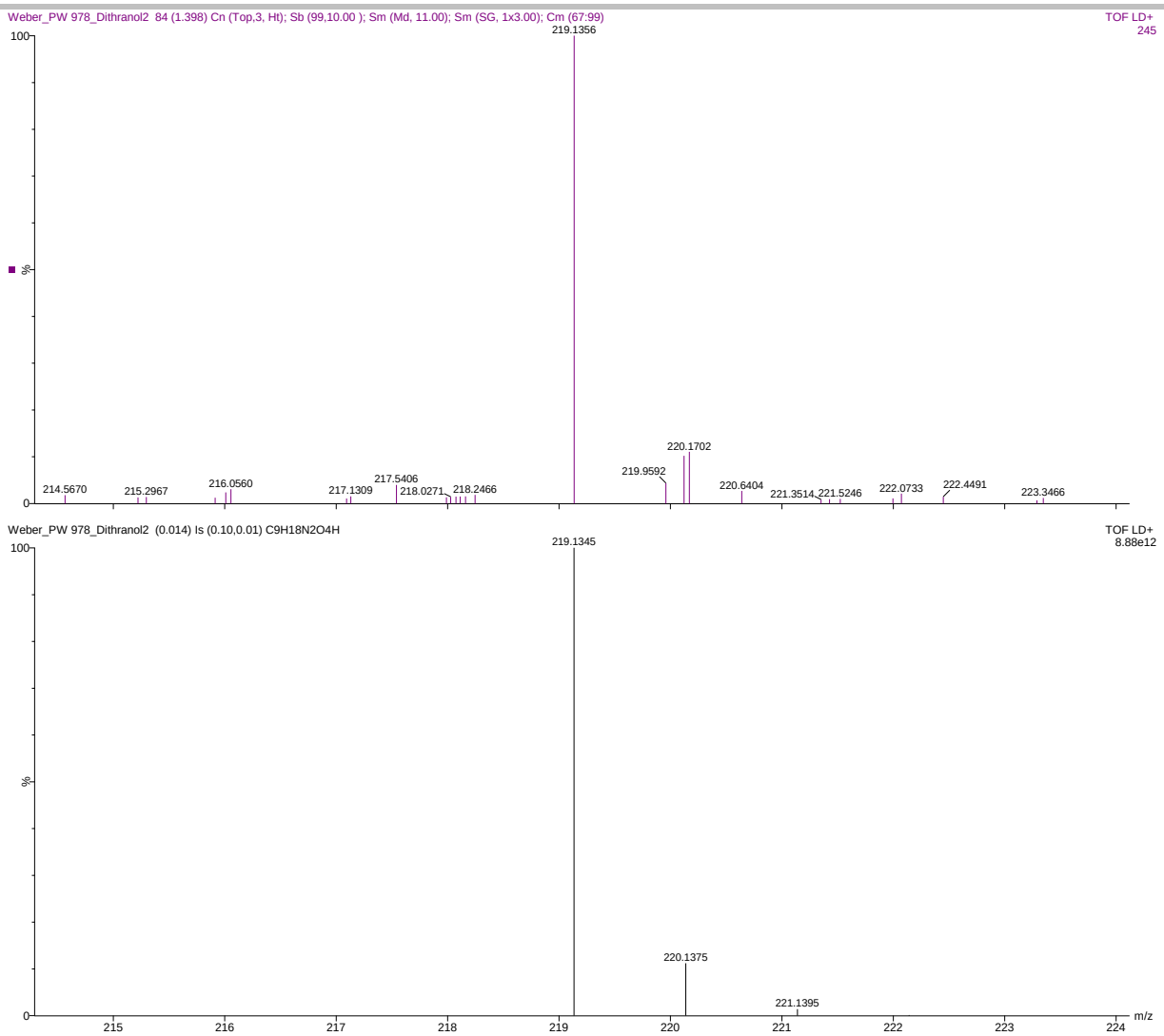
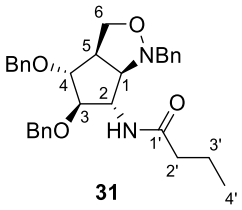



**Figure S14l. HRMS** of compound **33**.

***N*-((3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-Benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta(*c*)isoxazol-6-yl)butyramide (31)**




**31**

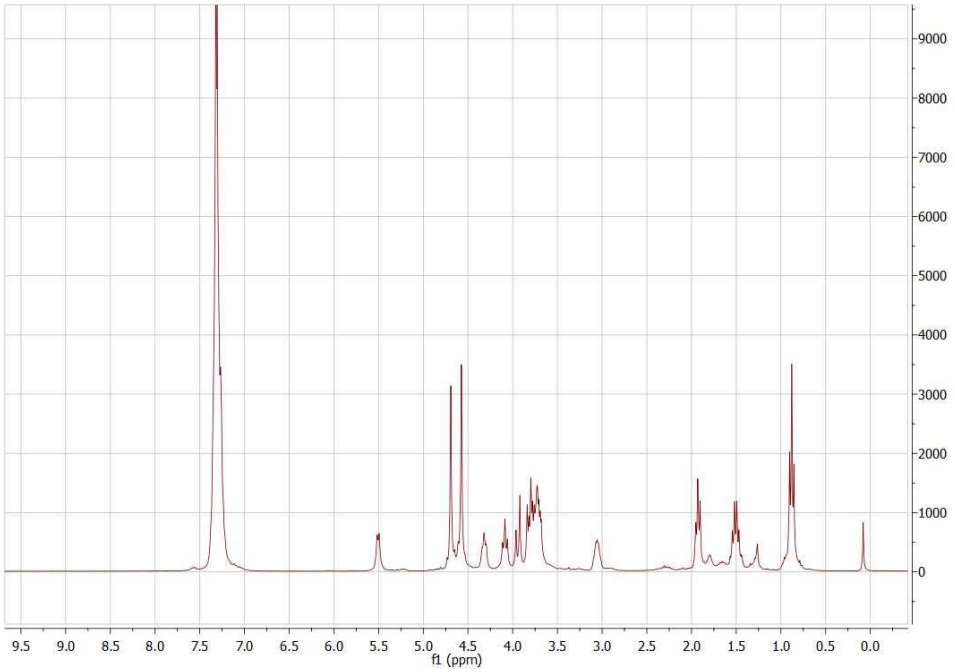



**Figure S15A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **31**.

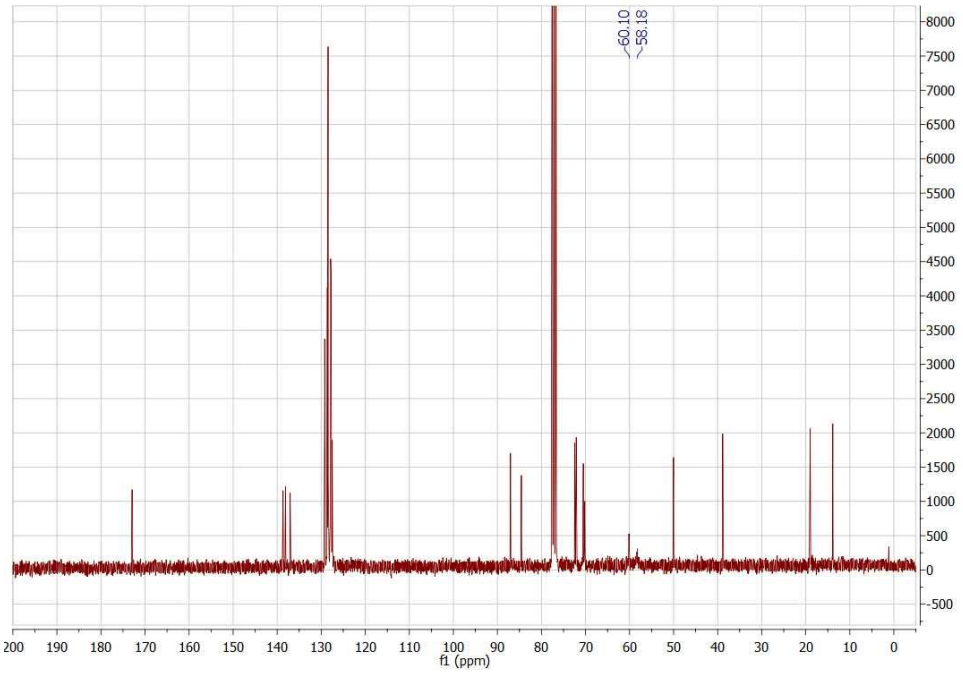



**Figure S15B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **31**.

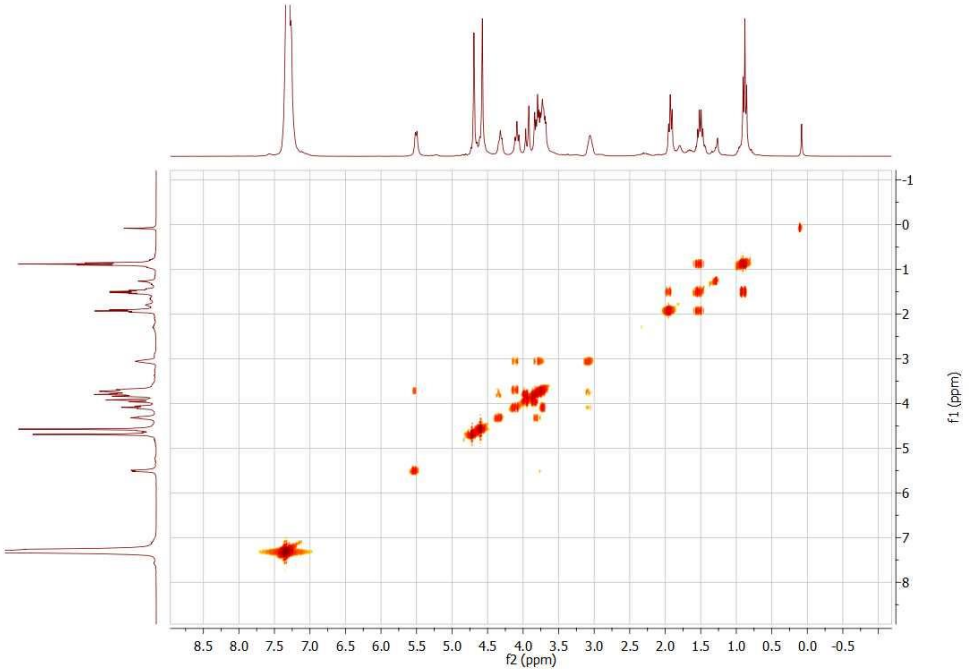



**Figure S15C. COSY** ($CDCl_3$) of compound **31**.

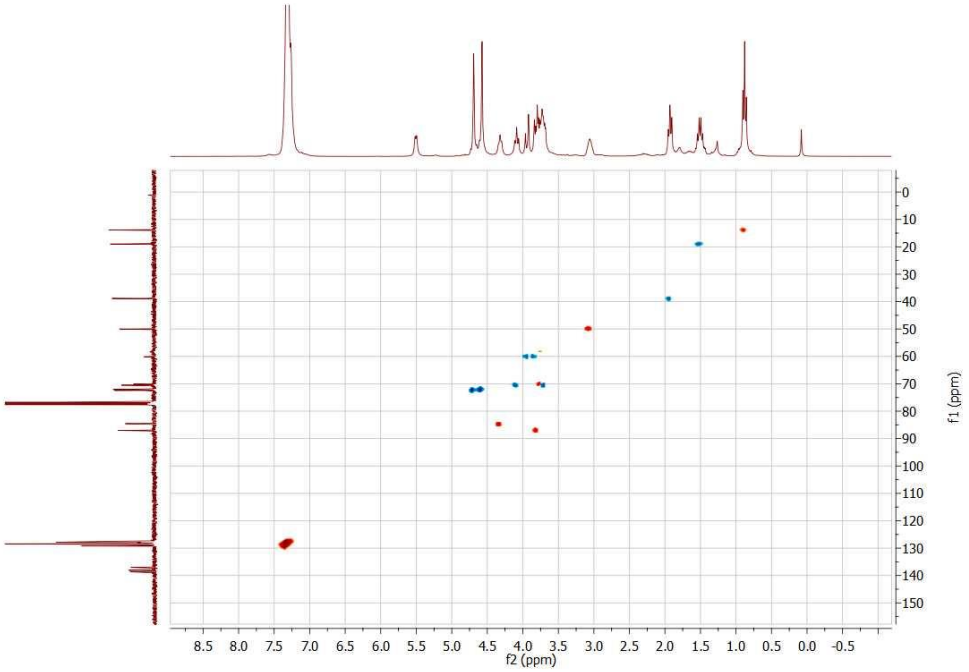



**Figure S15D. HSQC** ($CDCl_3$) of compound **31**.

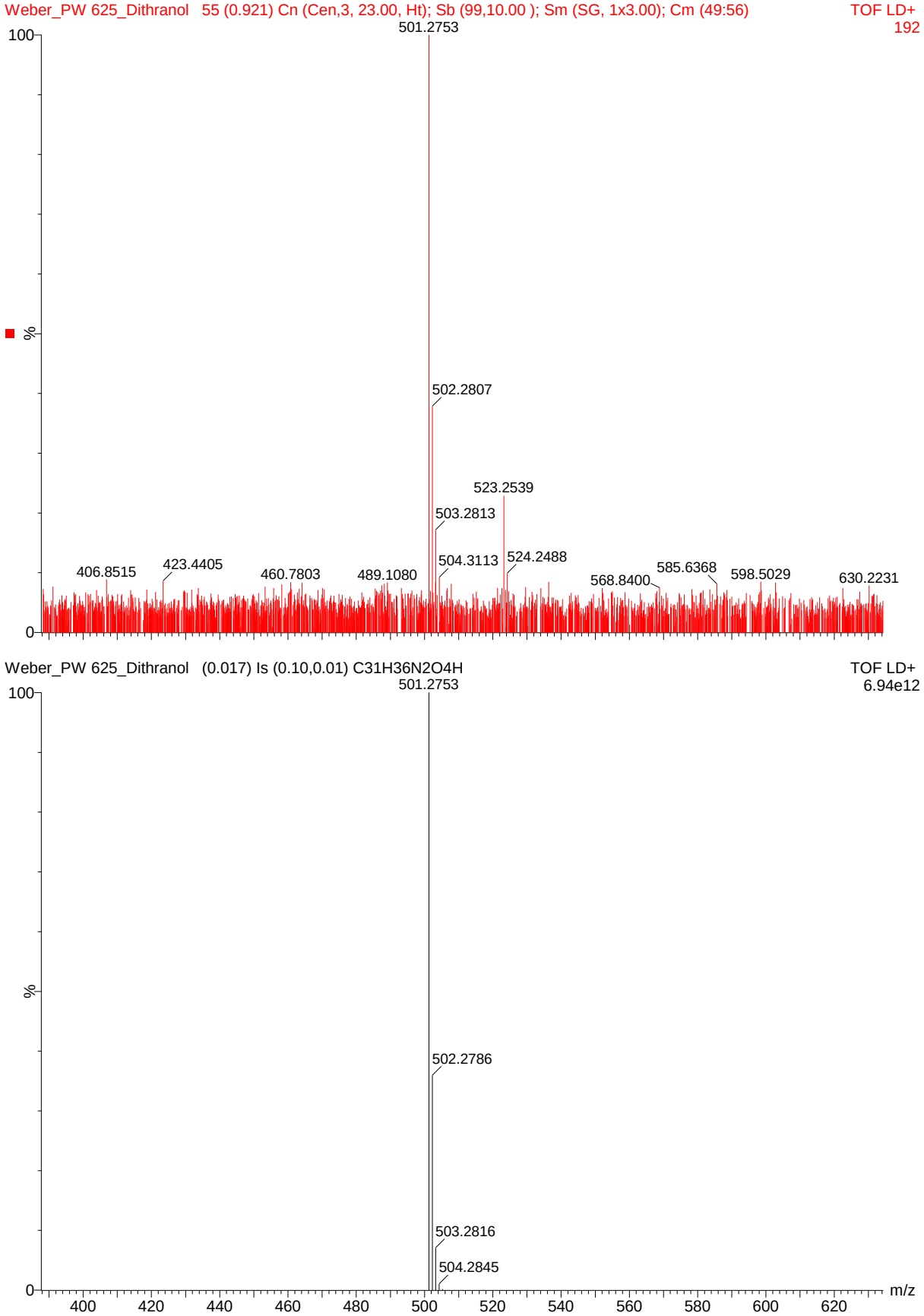
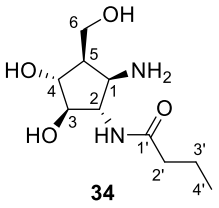



**Figure S15E. HRMS** of compound **31**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-Amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)butyramide "(1-Amino-2-butanoylamino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (34)**




**34**

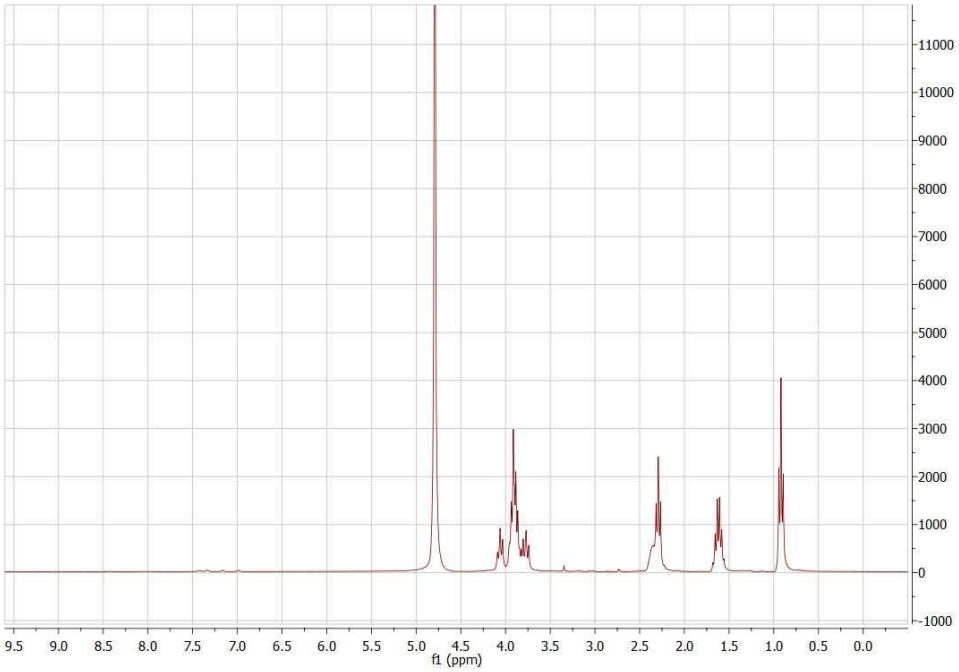



**Figure S16A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **34**, hydrochloride.

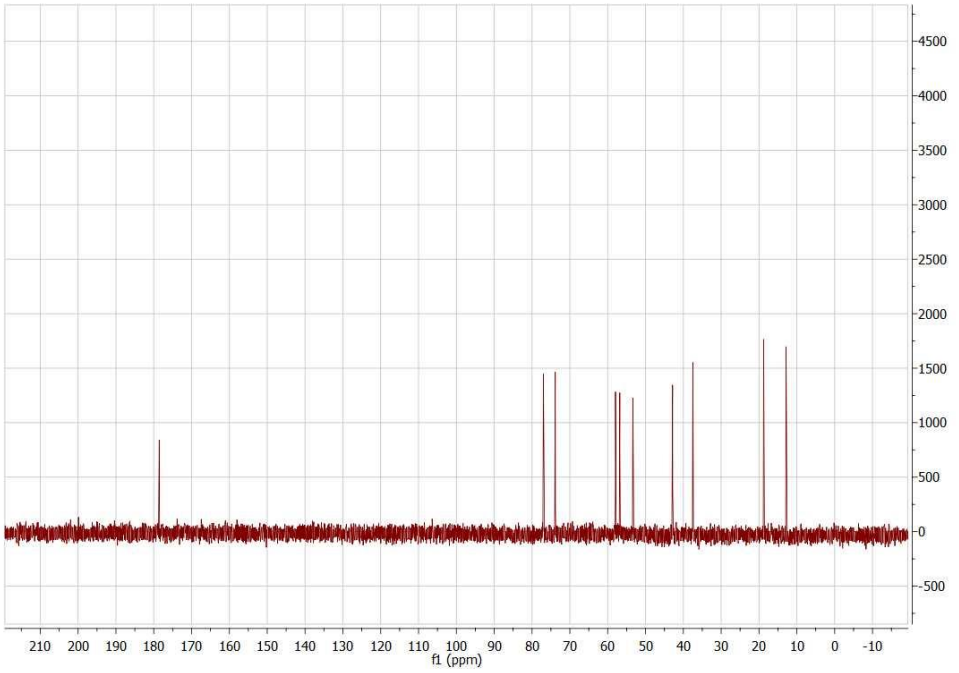



**Figure S16B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **34**, hydrochloride.

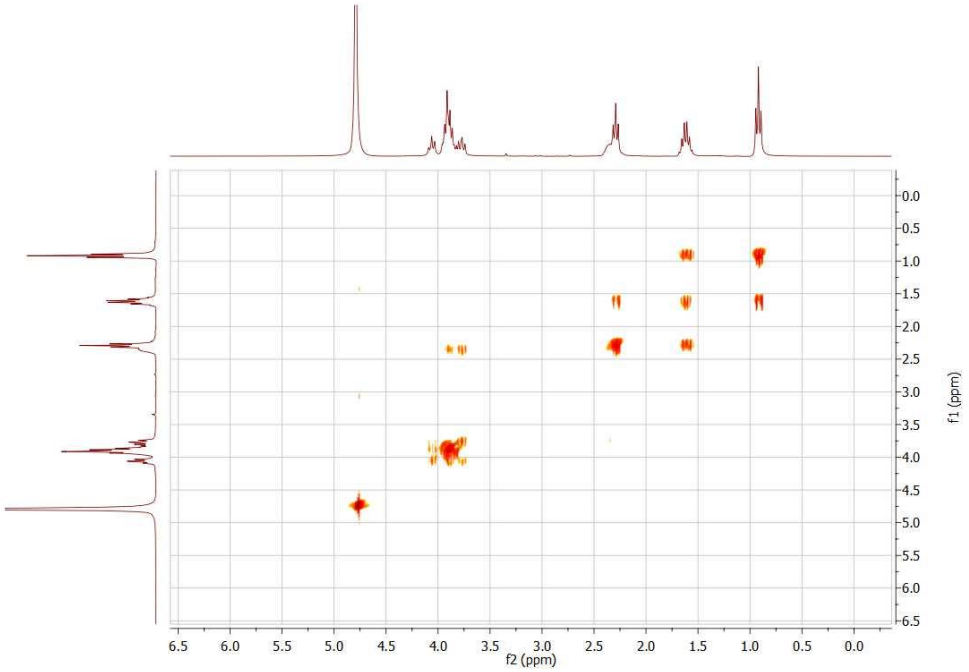



**Figure S16C. COSY** ($D_2O$) of compound **34**, hydrochloride.

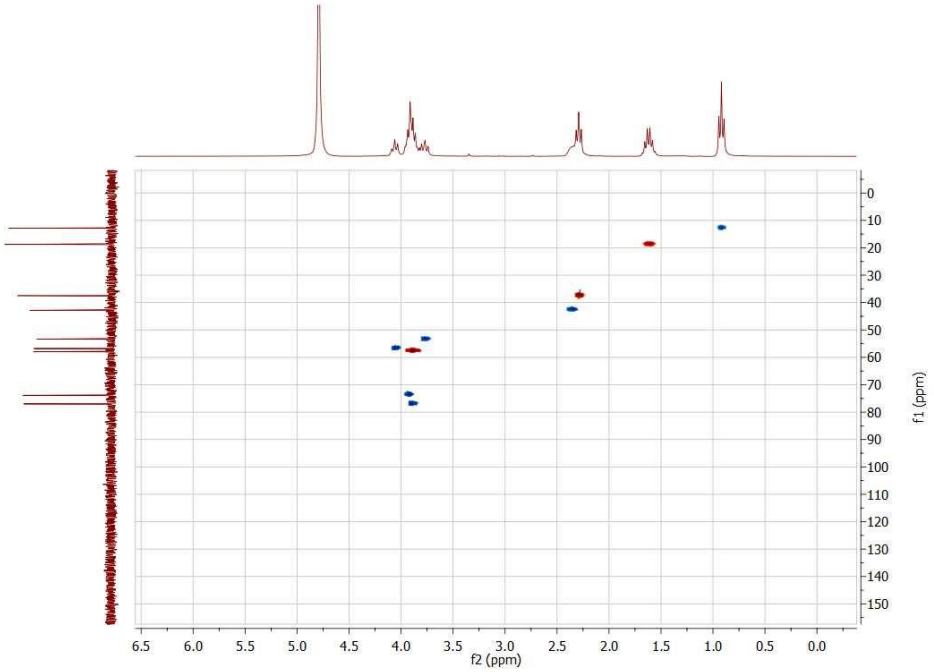



**Figure S16D. HSQC** ($D_2O$) of compound **34**, hydrochloride.

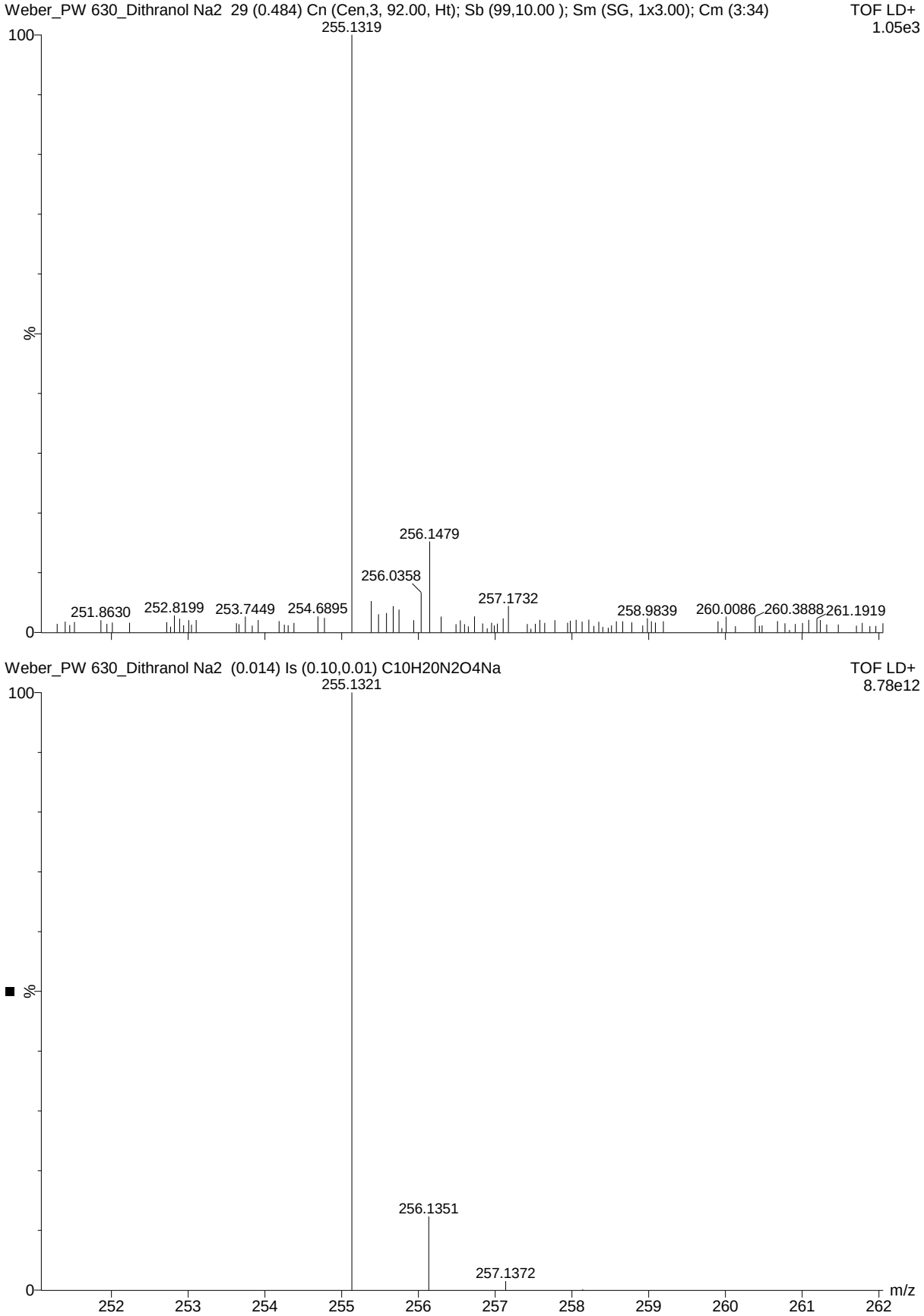
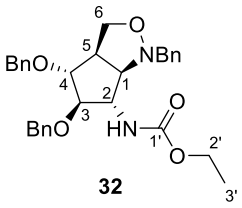



**Figure S16E. HRMS** of compound **34**.

**Ethyl ((3a*R*,4*R*,5*R*,6*S*,6a*R*)-1-benzyl-4,5-bis(benzyloxy)hexahydro-1*H*-cyclopenta[*c*]isoxazol-6-yl)carbamate (32)**




**32**

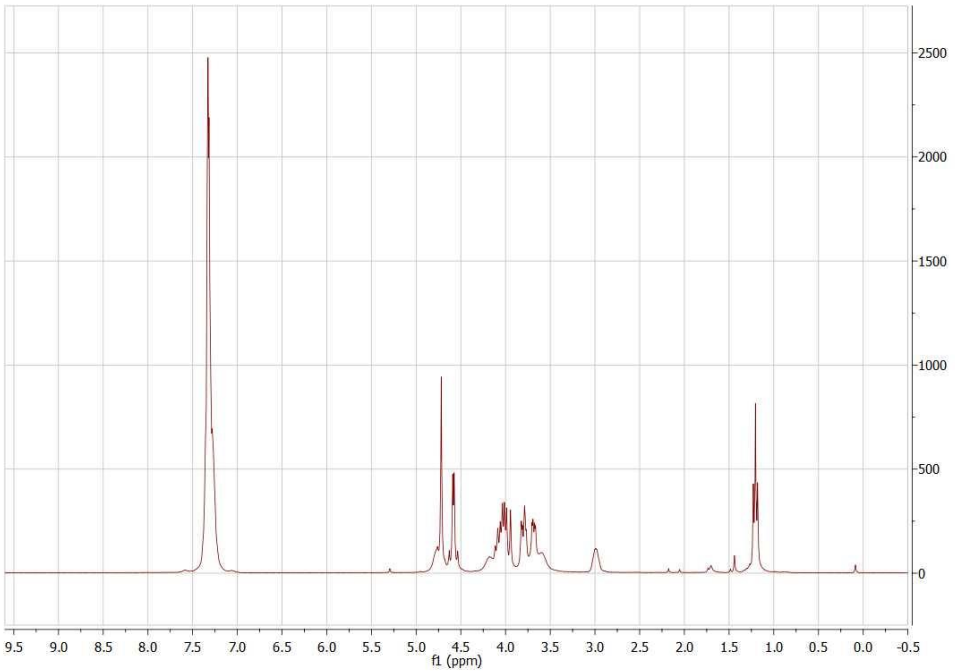



**Figure S17A. $^{1}$H NMR** (300 MHz, $CDCl_3$) of compound **32**.

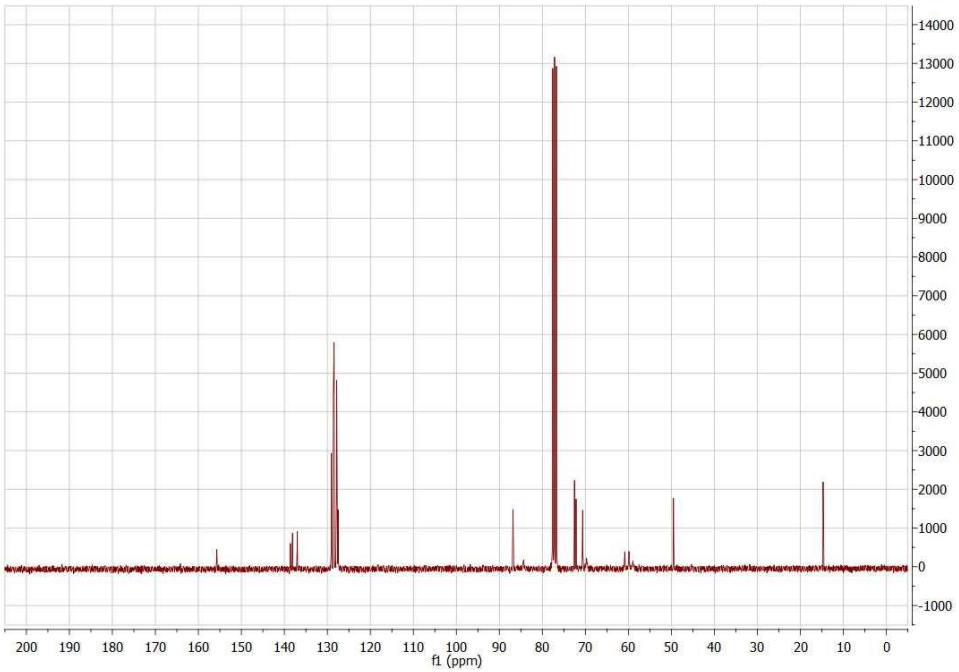



**Figure S17B. $^{13}$C NMR** (75.5 MHz, $CDCl_3$) of compound **32**.

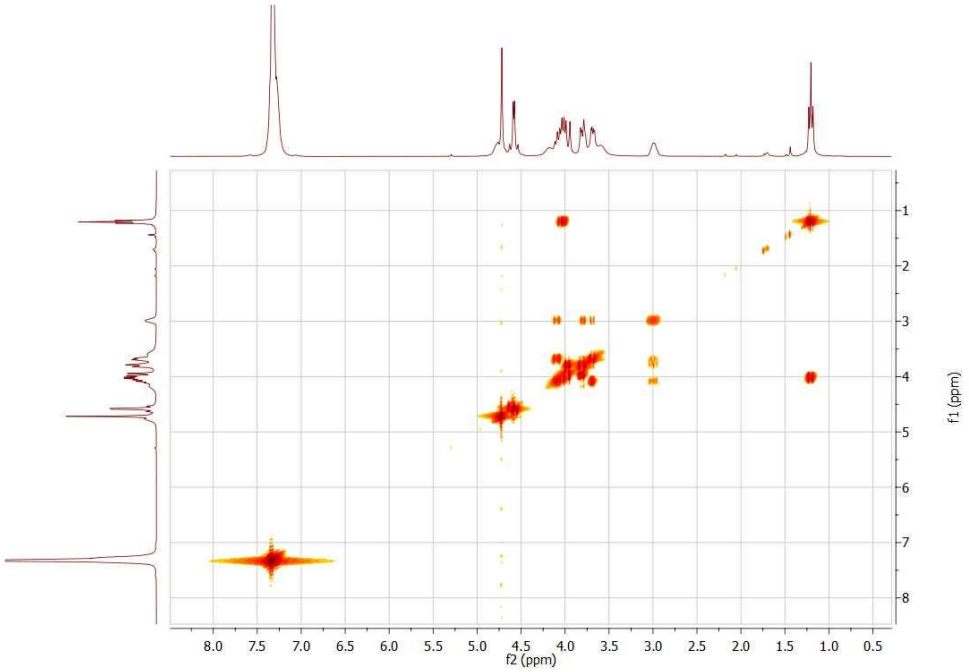



**Figure S17C. COSY** ($CDCl_3$) of compound **32**.

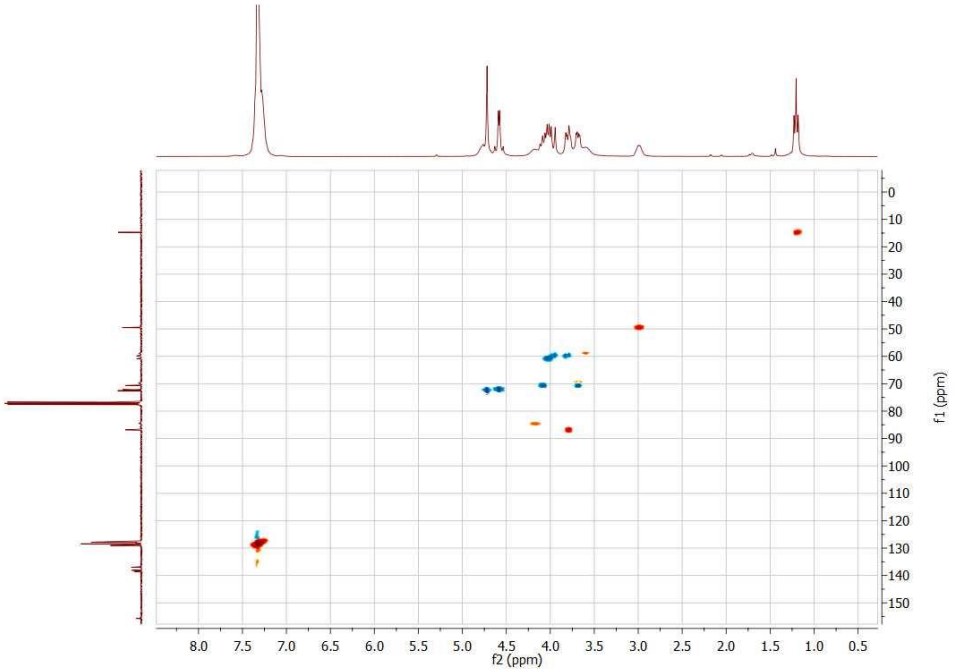



**Figure S17D. HSQC** ($CDCl_3$) of compound **32**.

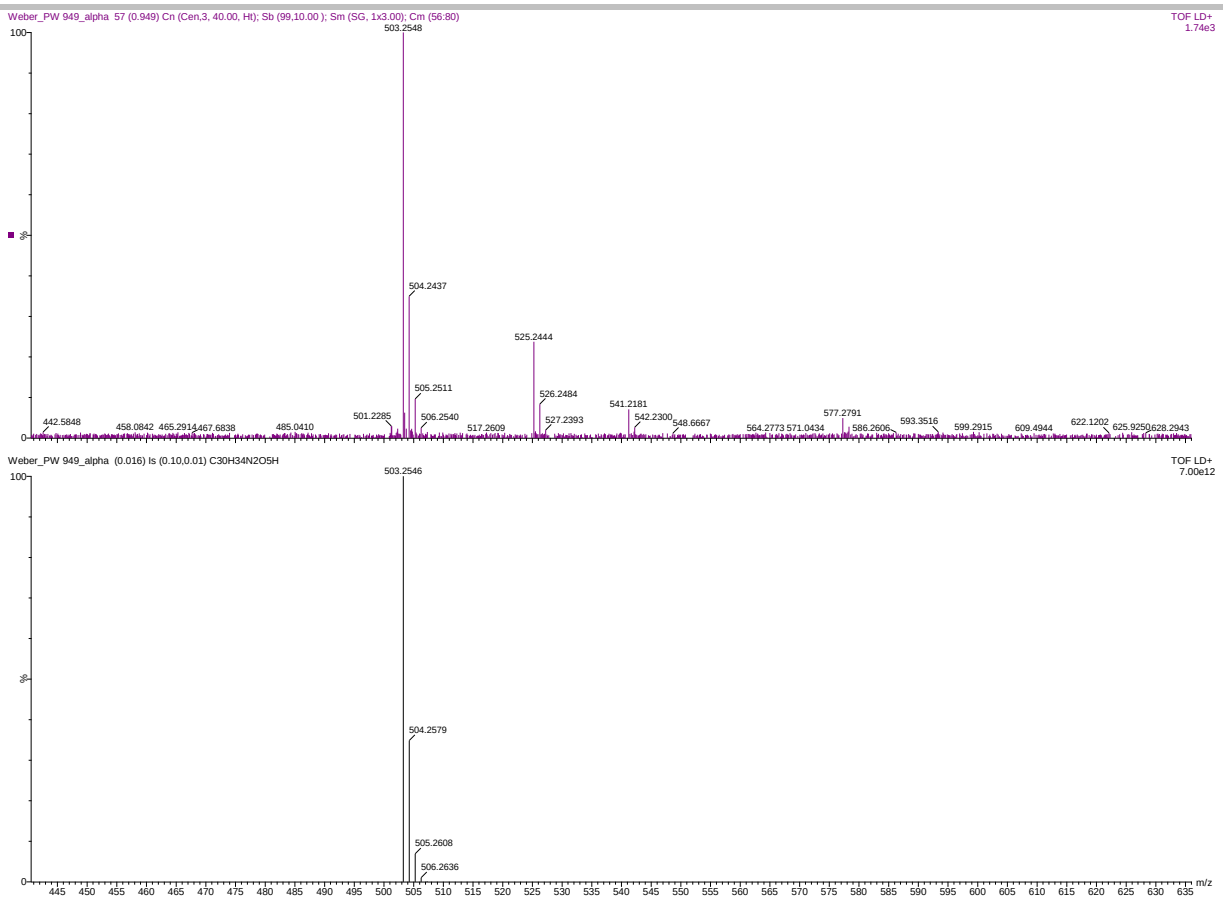
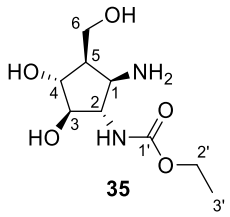



**Figure S17E. HRMS** of compound **32**.

**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-amino-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)carbamate "(1-Amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane)" (35)**




**35**

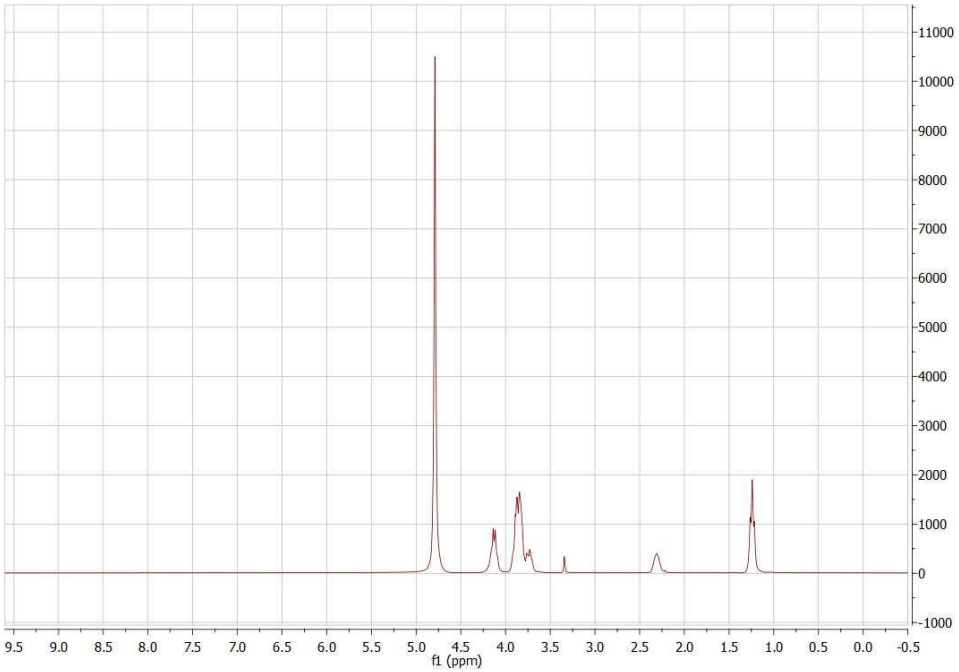



**Figure S18A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **35**, free base.

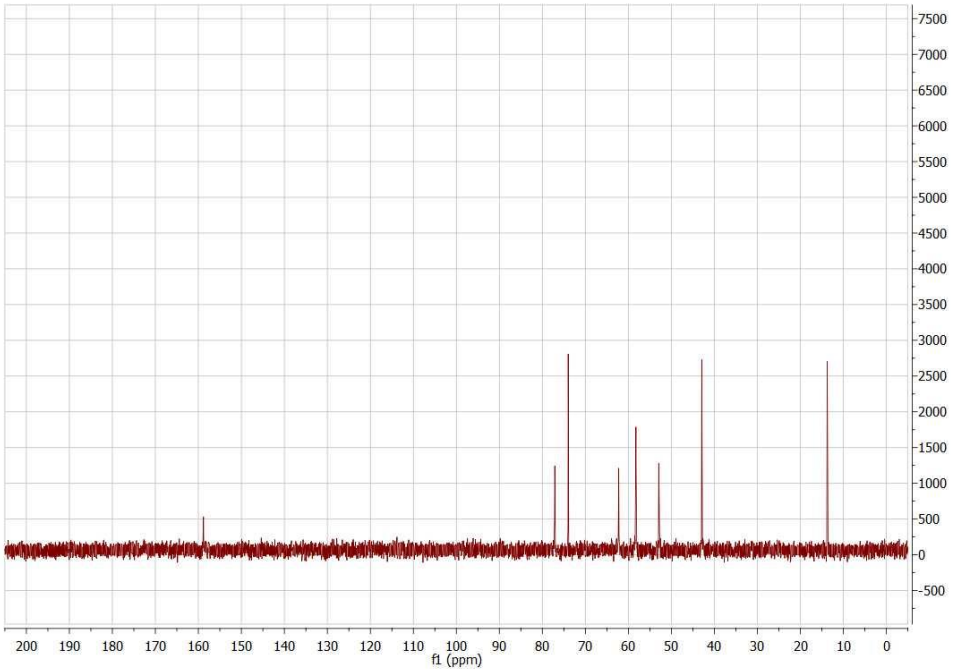



**Figure S18B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **35**, free base.

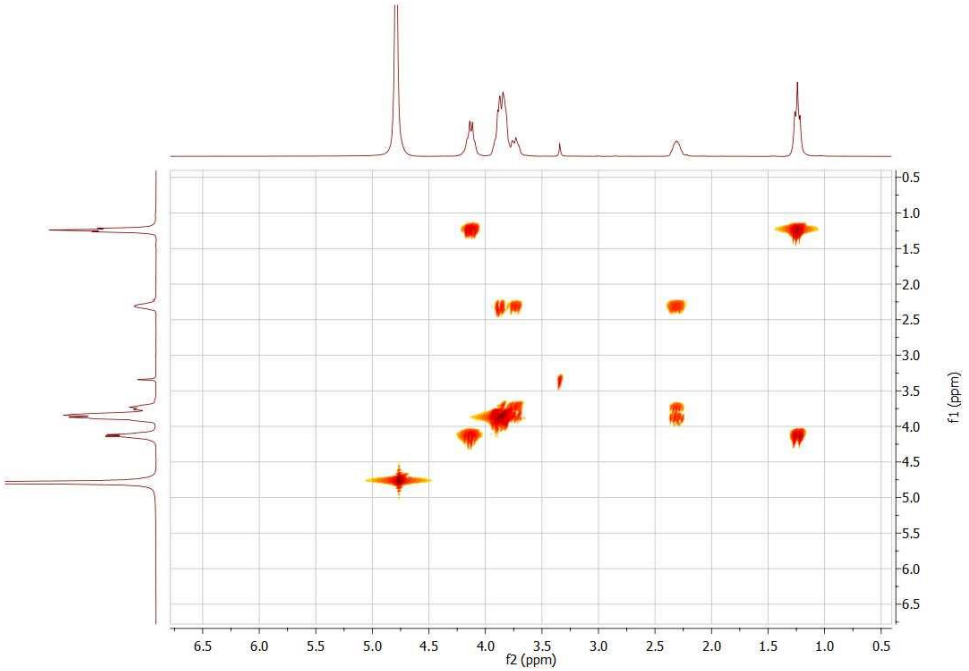



**Figure S18C. COSY** ($D_2O$) of compound **35**, free base.

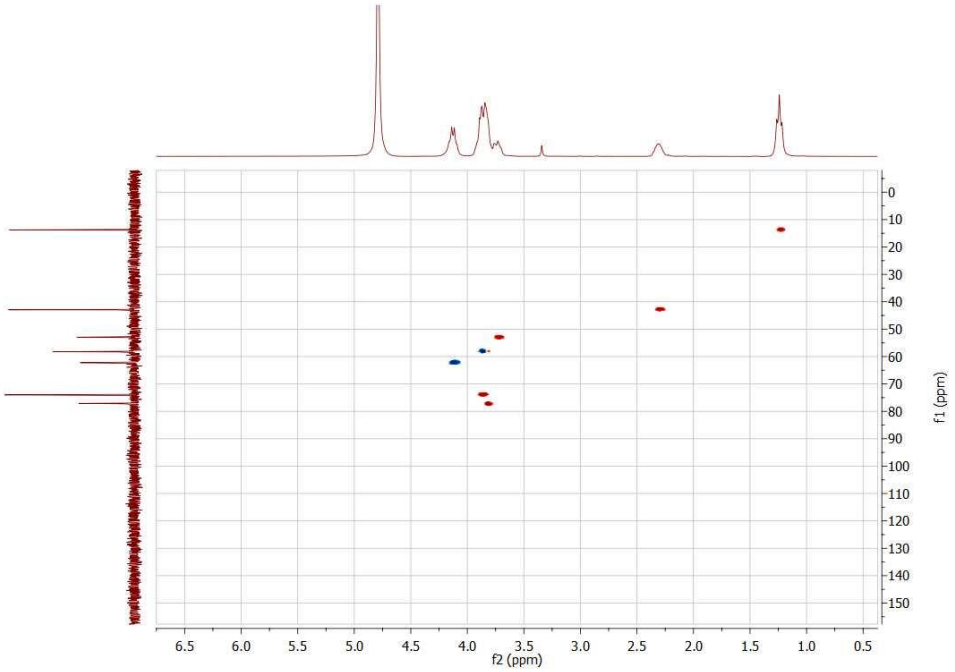



**Figure S18D. HSQC** ($D_2O$) of compound **35**, free base.

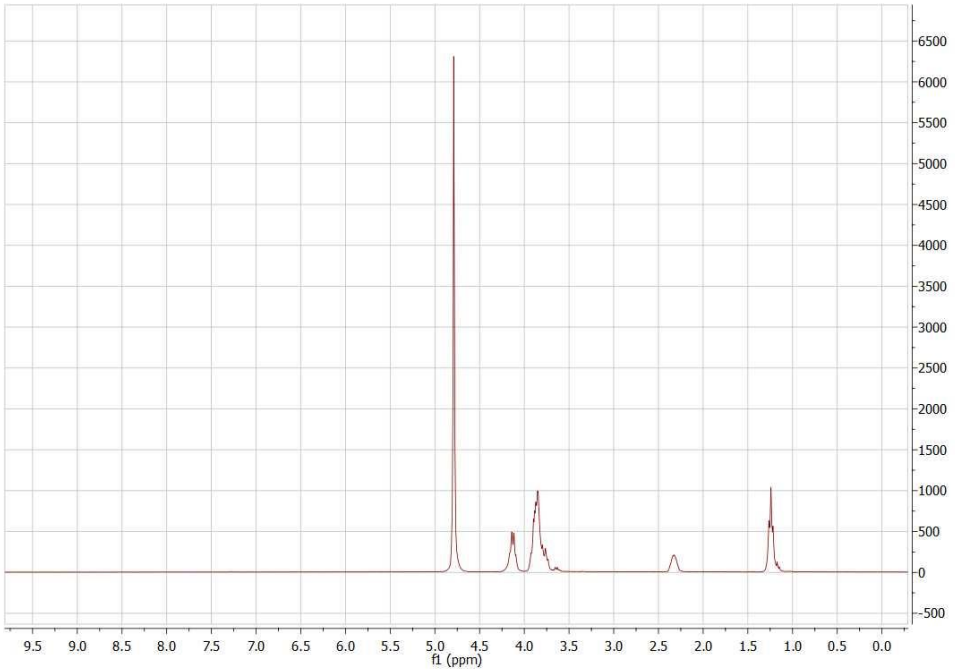



**Figure S18E. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **35**, hydrochloride.

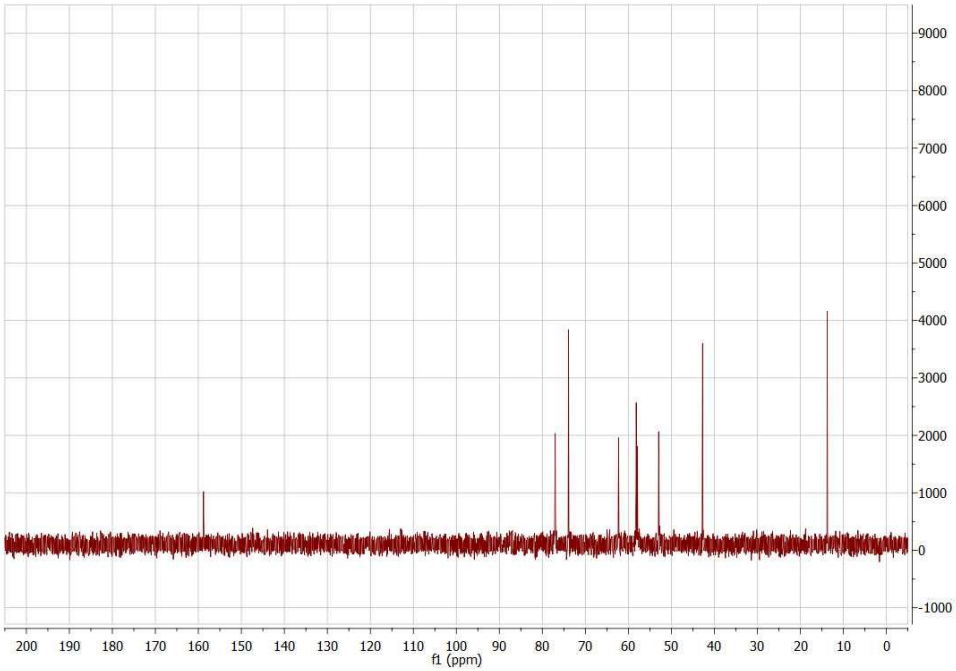



**Figure S18F. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **35**, hydrochloride.

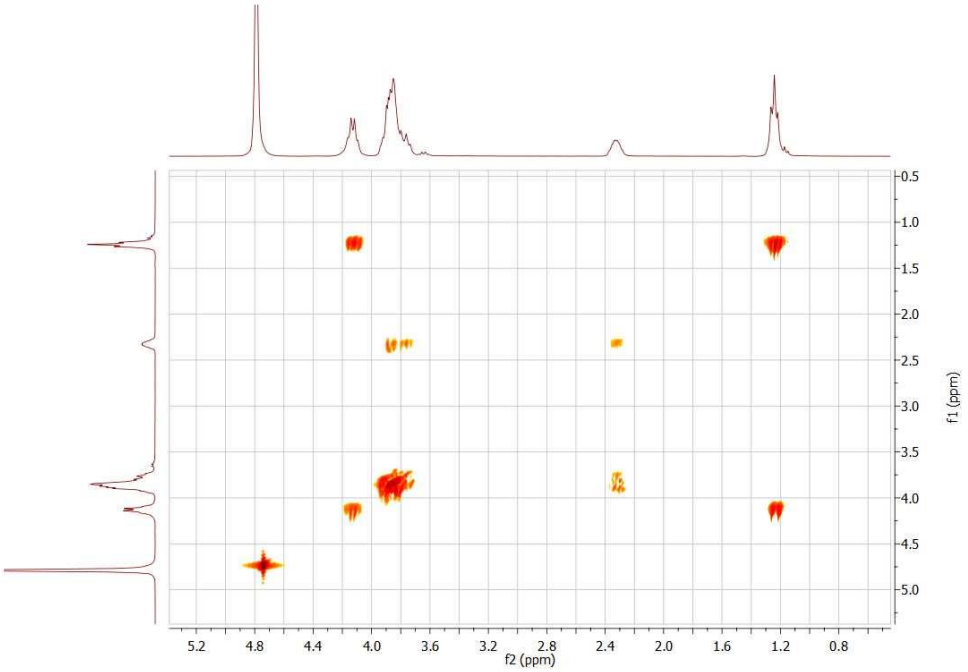



**Figure S18G. COSY** ($D_2O$) of compound **35**, hydrochloride.

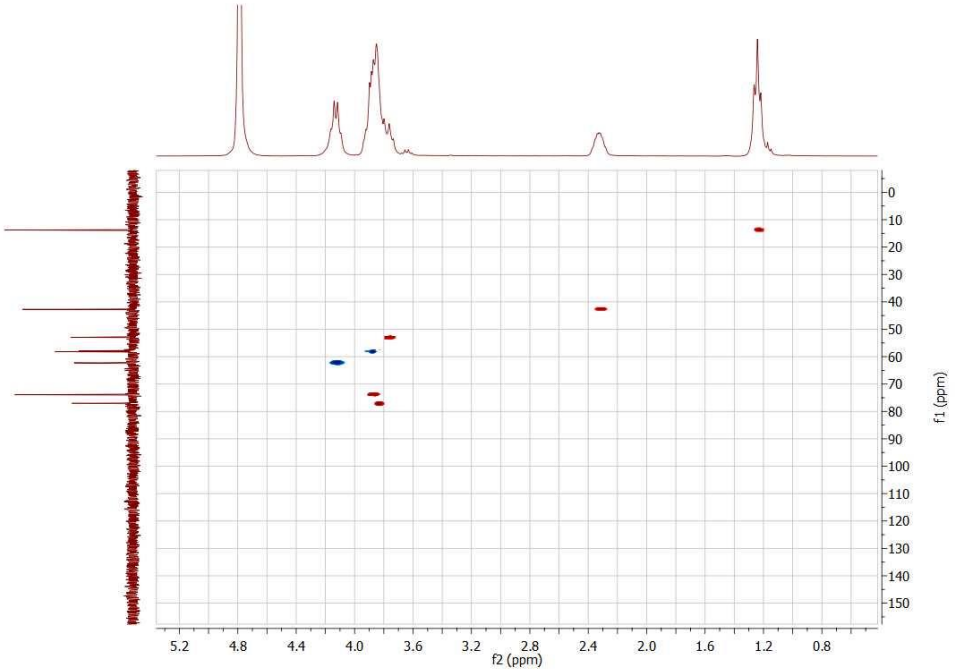



**Figure S18H. HSQC** ($D_2O$) of compound **35**, hydrochloride.

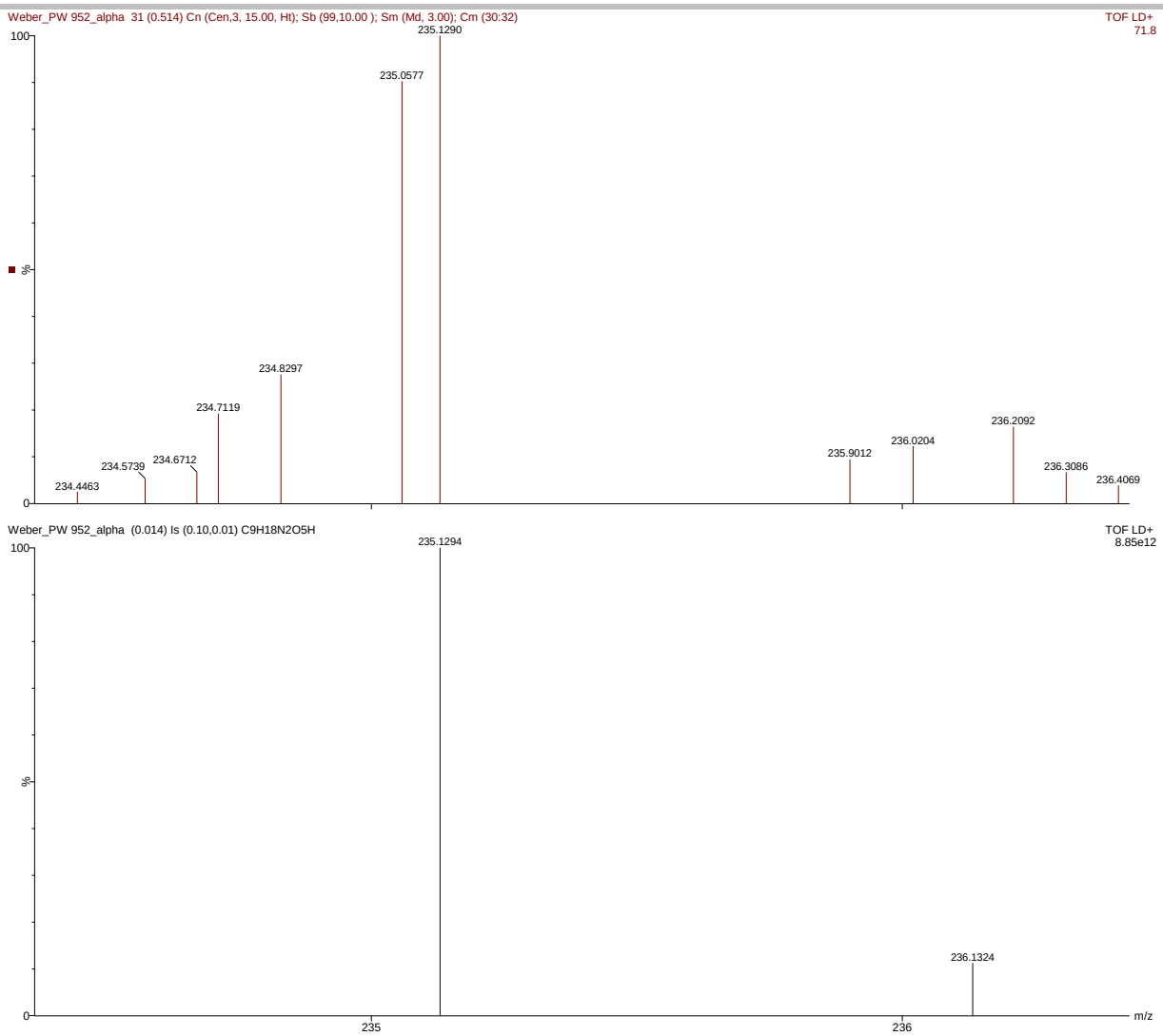
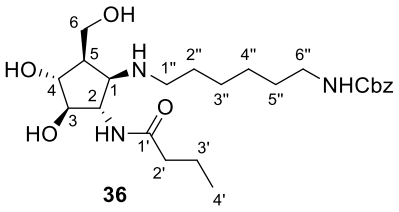



**Figure S18l. HRMS** of compound **35**.

**Benzyl (6-(((1*R*,2*S*,3*R*,4*R*,5*R*)-2-butyramido-3,4-dihydroxy-5-(hydroxymethyl)cyclopentyl)amino) hexyl) carbamate "(2-Butanoylamino-1-(6-carbobenzyloxyaminohexyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (36)**




**36**

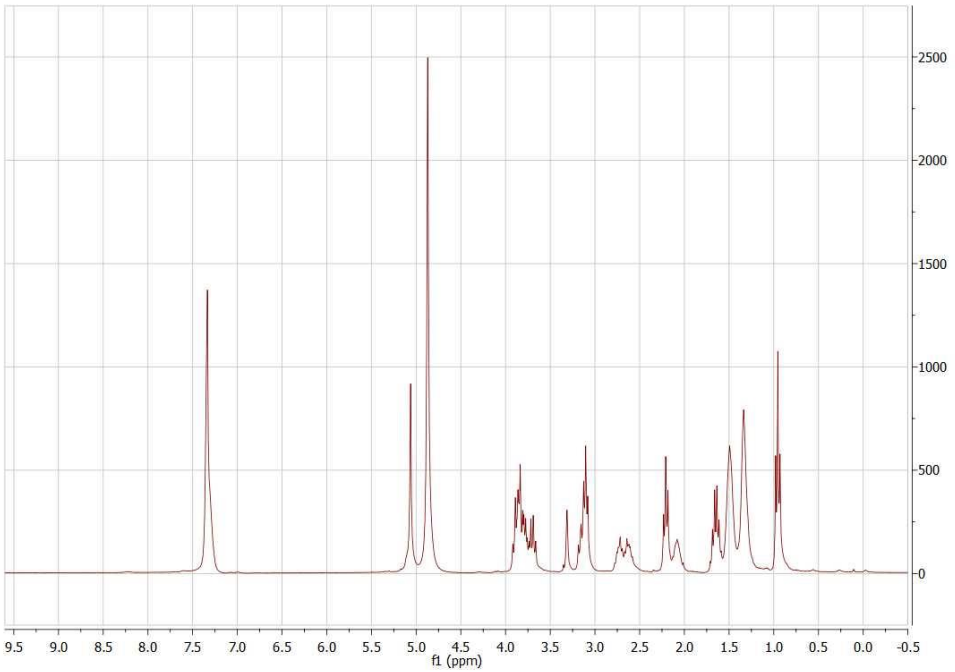



**Figure S19A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **36**.

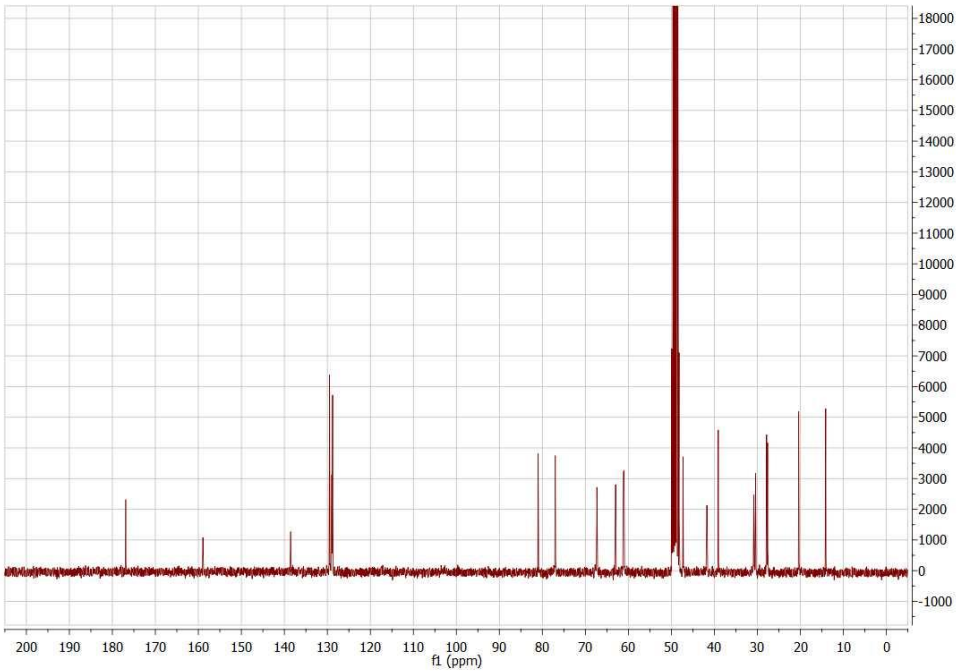



**Figure S19B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **36**.

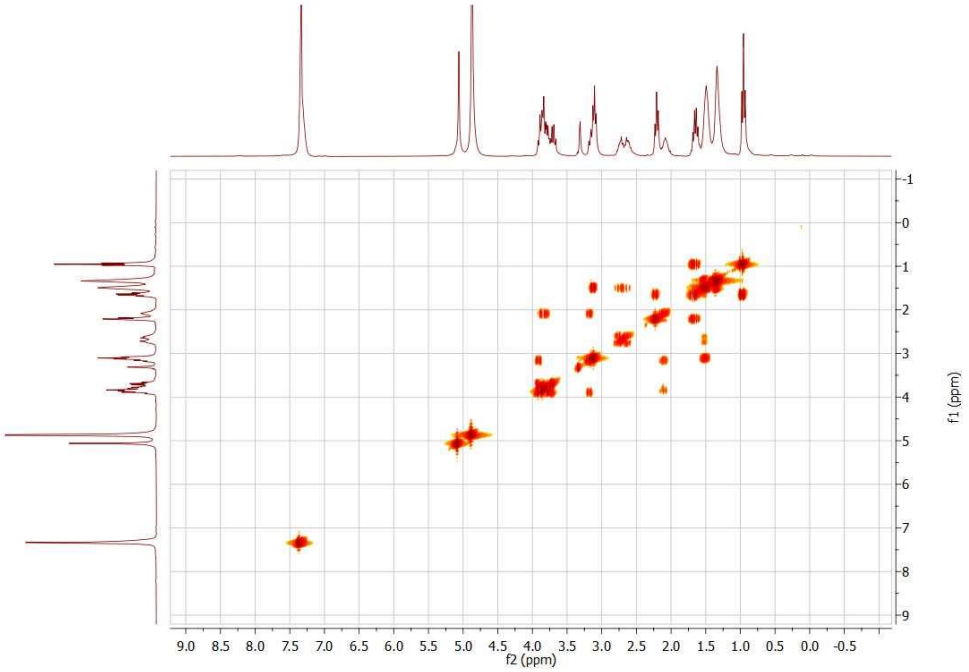



**Figure S19C. COSY** ($CD_3OD$) of compound **36**.

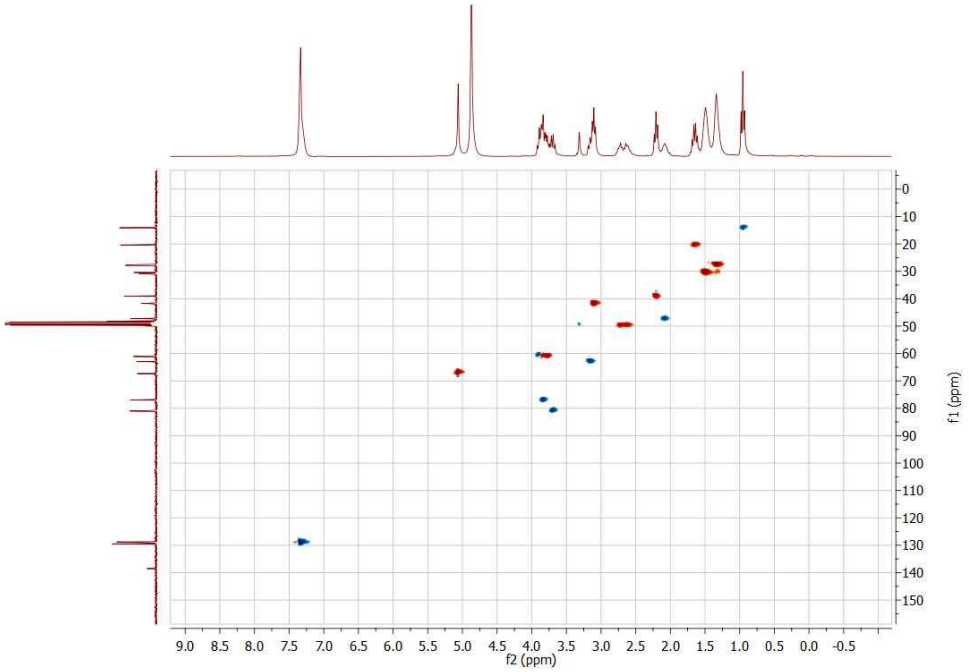



**Figure S19D. HSQC** ($CD_3OD$) of compound **36**.

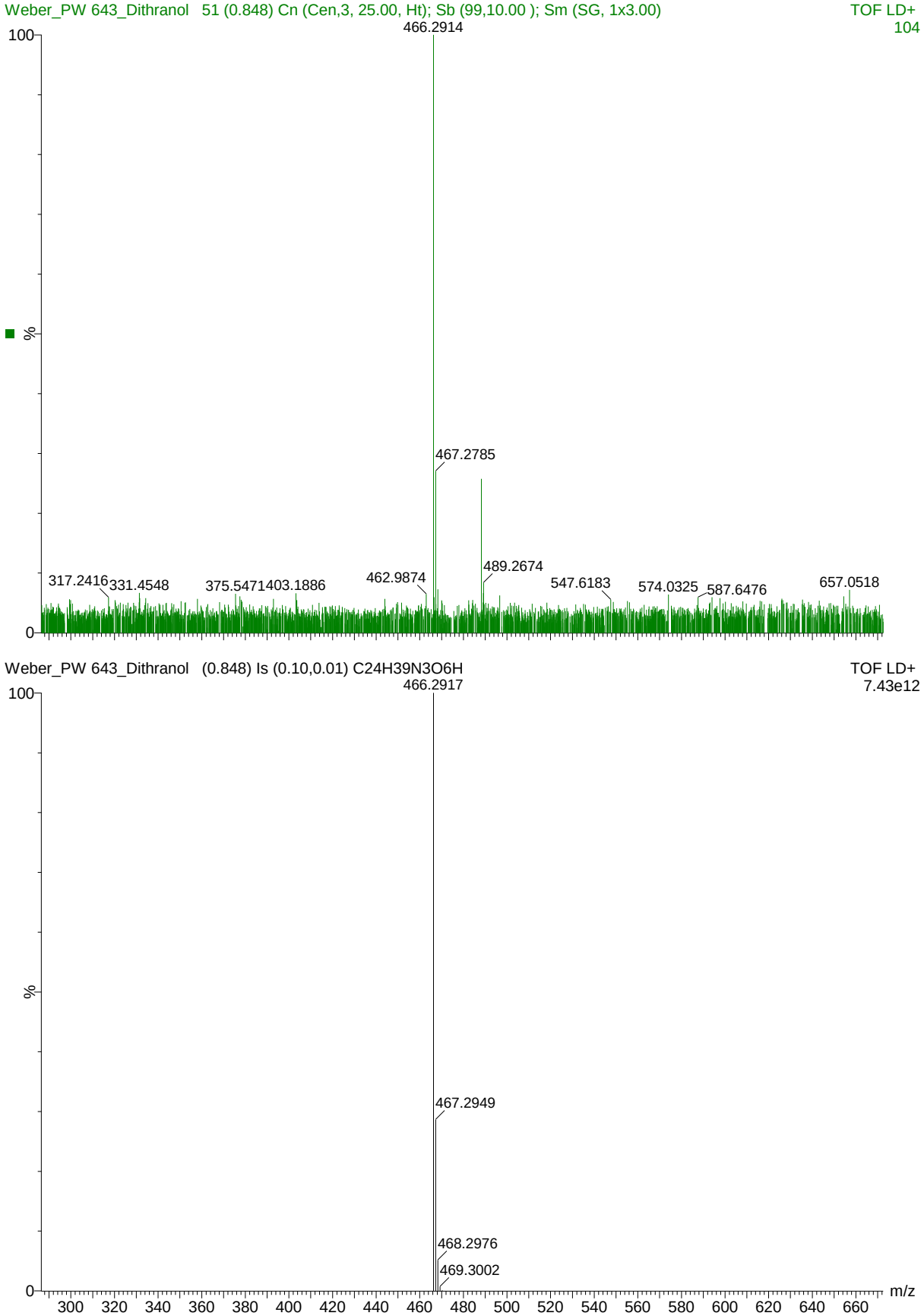
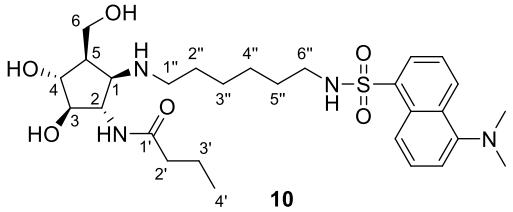



**Figure S19E. HRMS** of compound **36**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((6-((5-(Dimethylamino)naphthalene)-1-sulfonamido)hexyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)butyramide "(2-Butanoylamino-1-(6-dansylamino hexyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (10)**



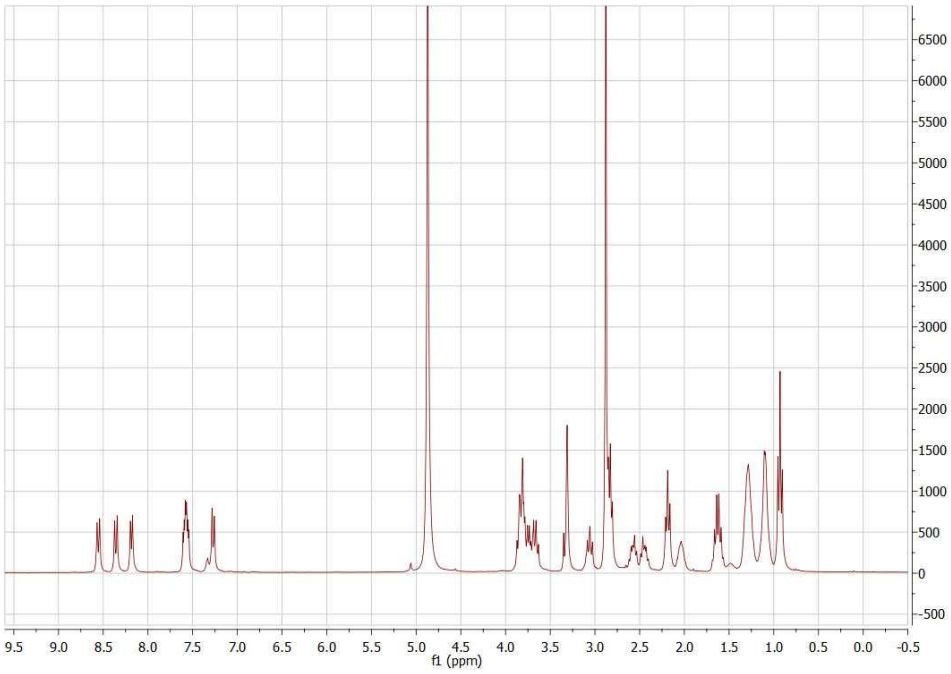




**Figure S20A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **10**.

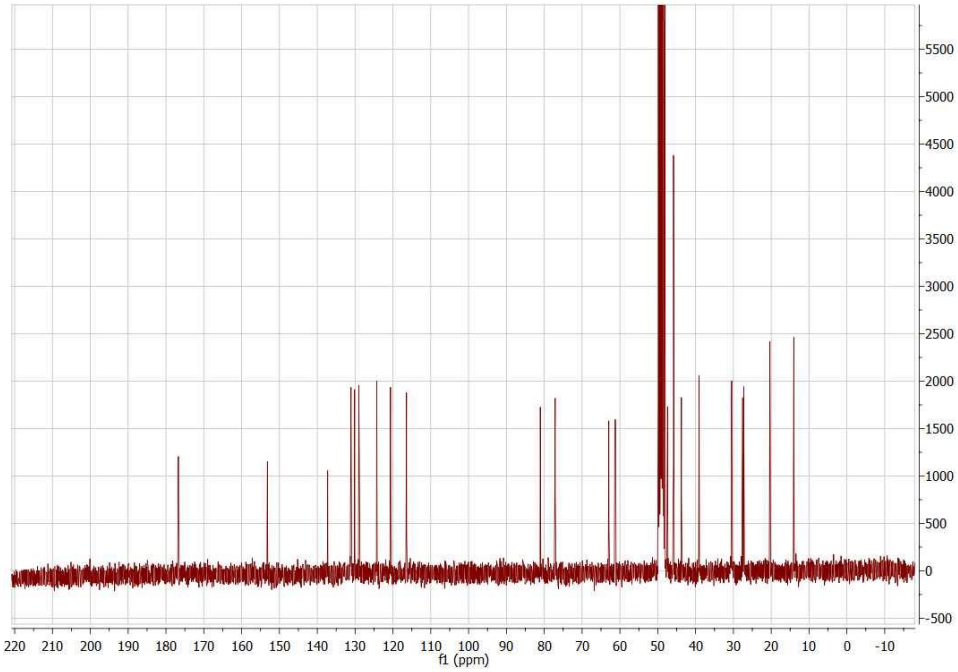



**Figure S20B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **10**.

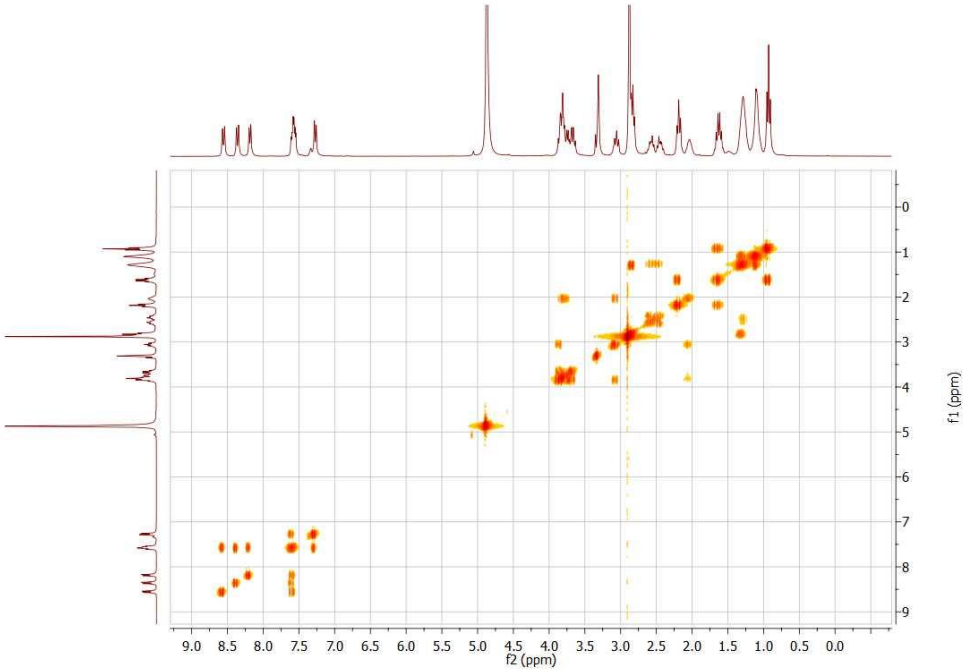



**Figure S20C. COSY** ($CD_3OD$) of compound **10**.

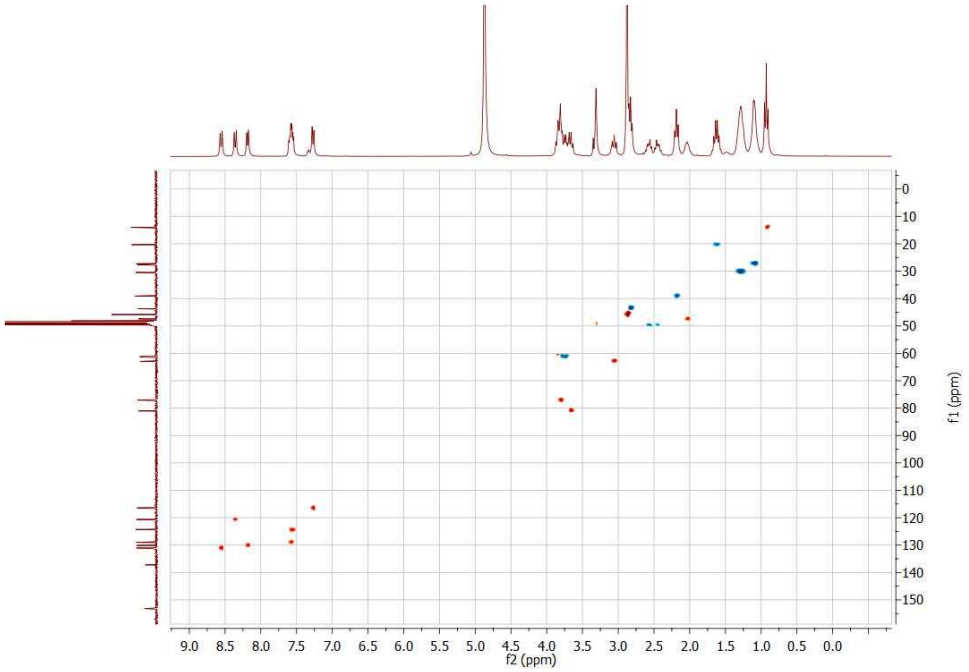



**Figure S20D. HSQC** ($CD_3OD$) of compound **10**.

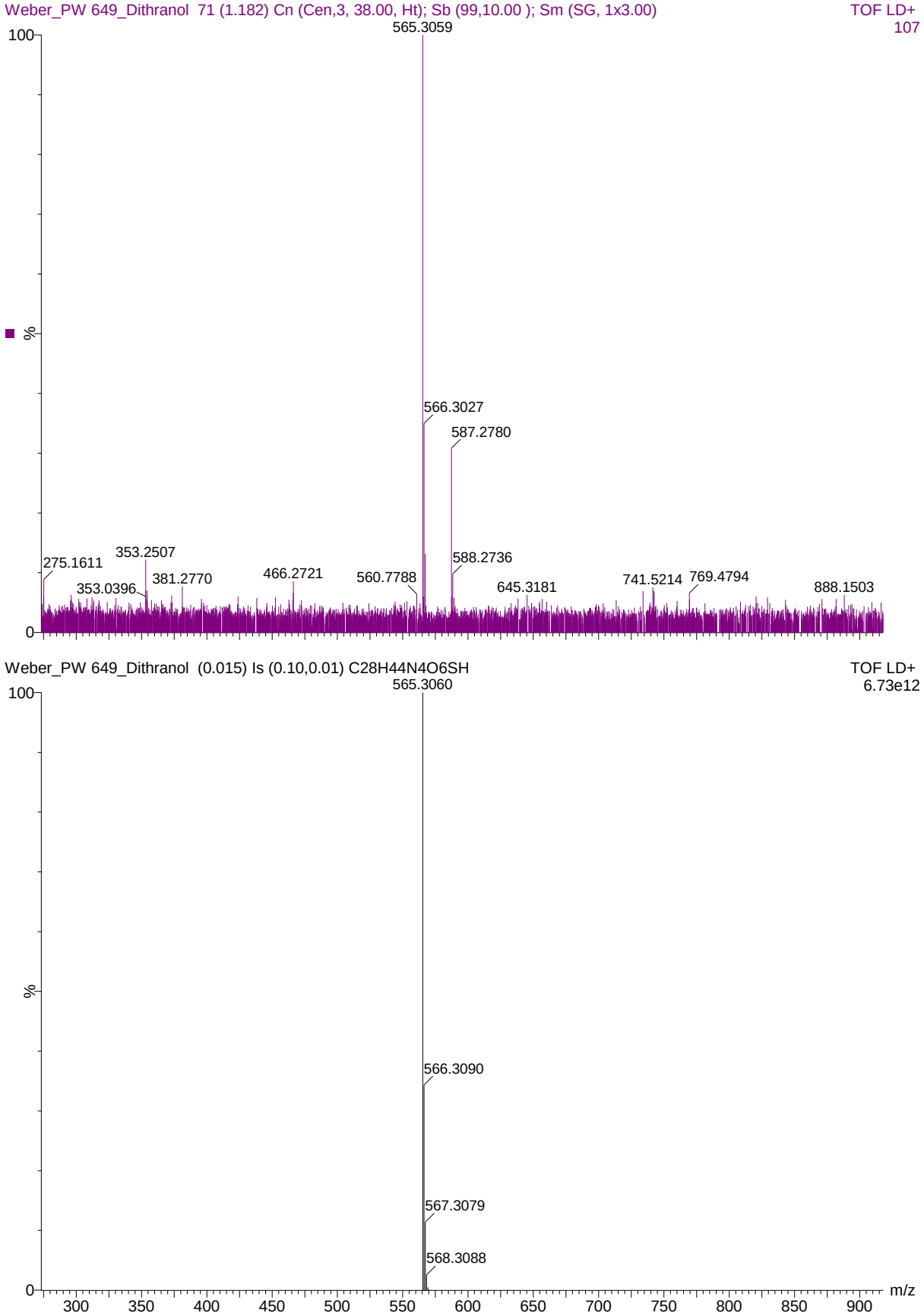
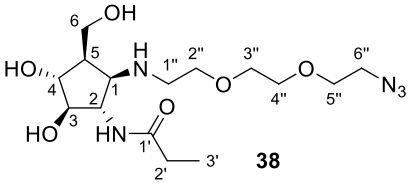



**Figure S20E. HRMS** of compound **10**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)propanoylamide "(1-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (38)**



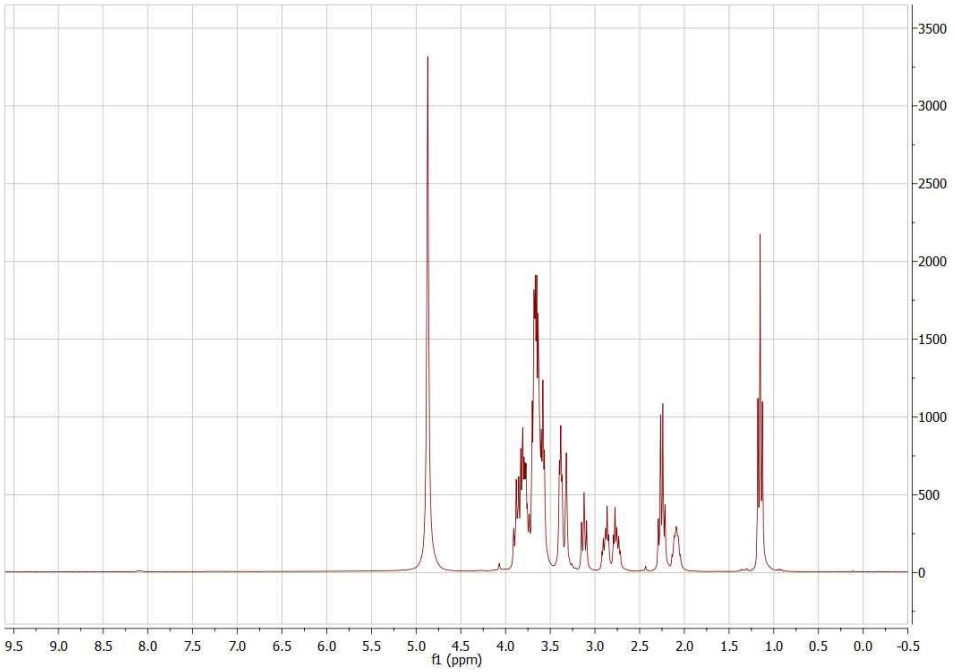




**Figure S21A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **38**.

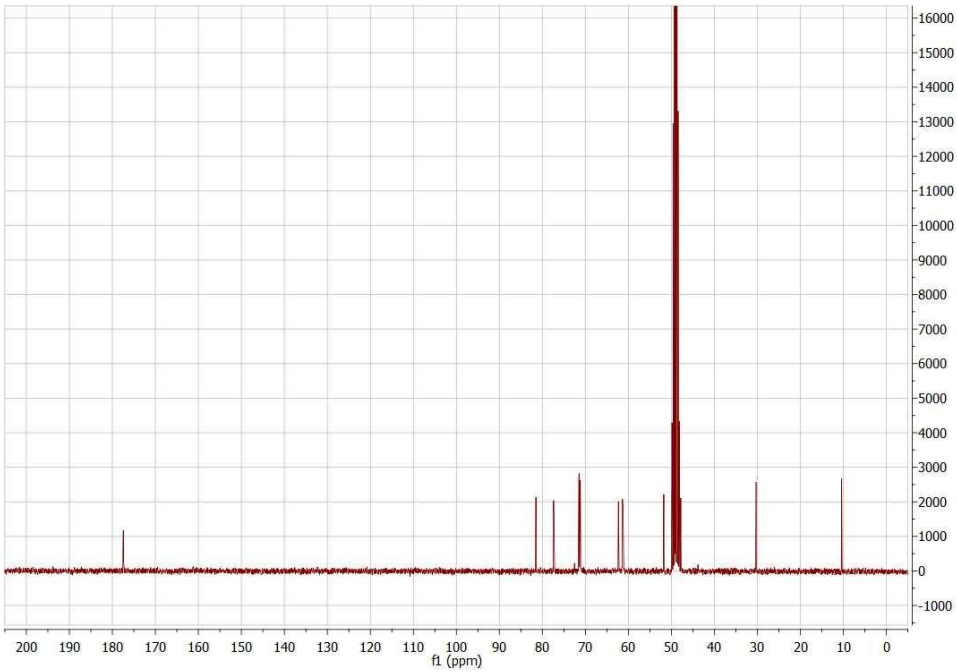



**Figure S21B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **38**.

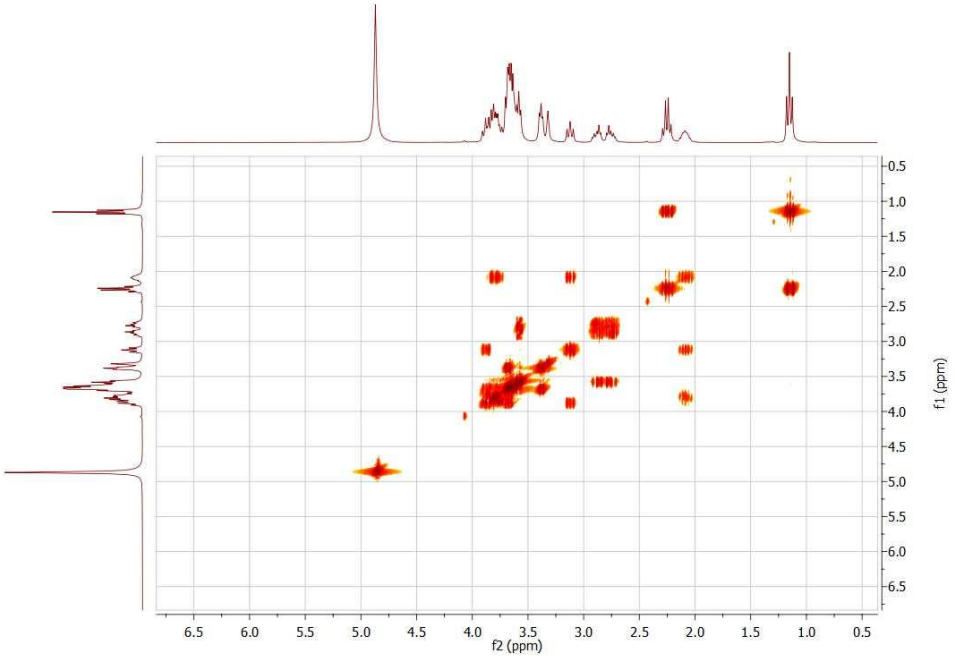



**Figure S21C. COSY** ($CD_3OD$) of compound **38**.

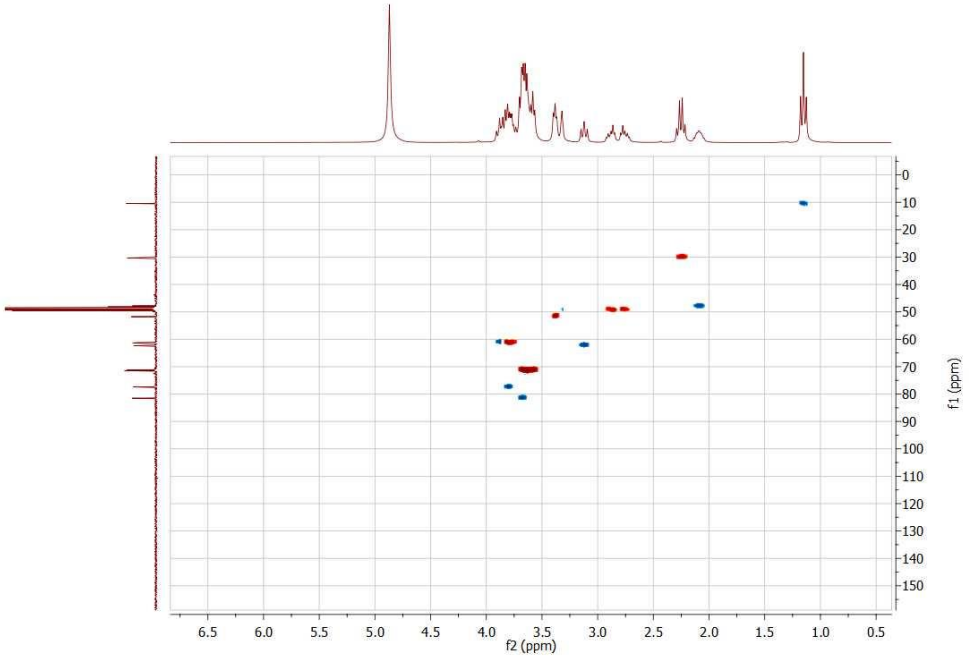



**Figure S21D. HSQC** ($CD_3OD$) of compound **38**.

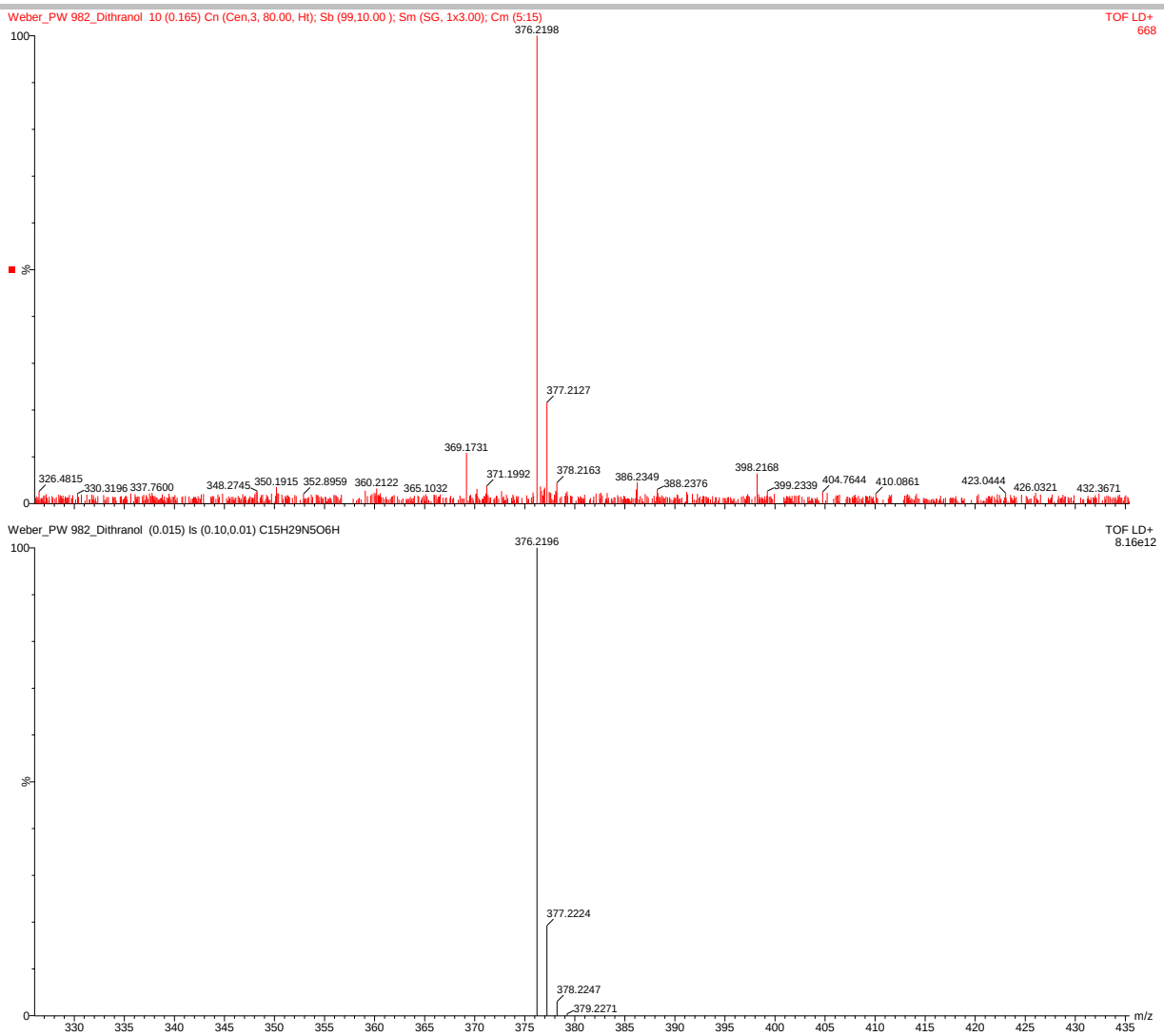
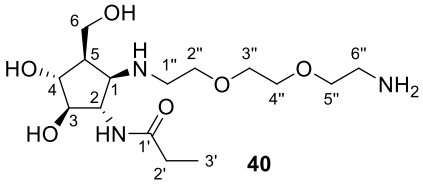



**Figure S21E. HRMS** of compound **38**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl) cyclopentyl)propanoylamide "(1-(2-(2-(2-Aminoethoxy)ethoxy)ethyl) amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (40)**



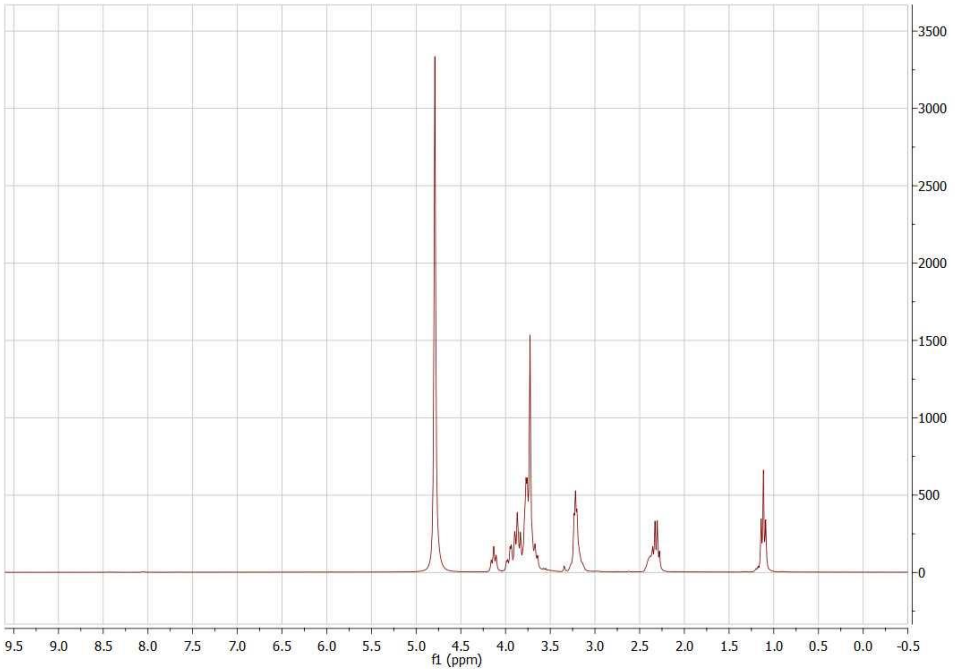




**Figure S22A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **40**.

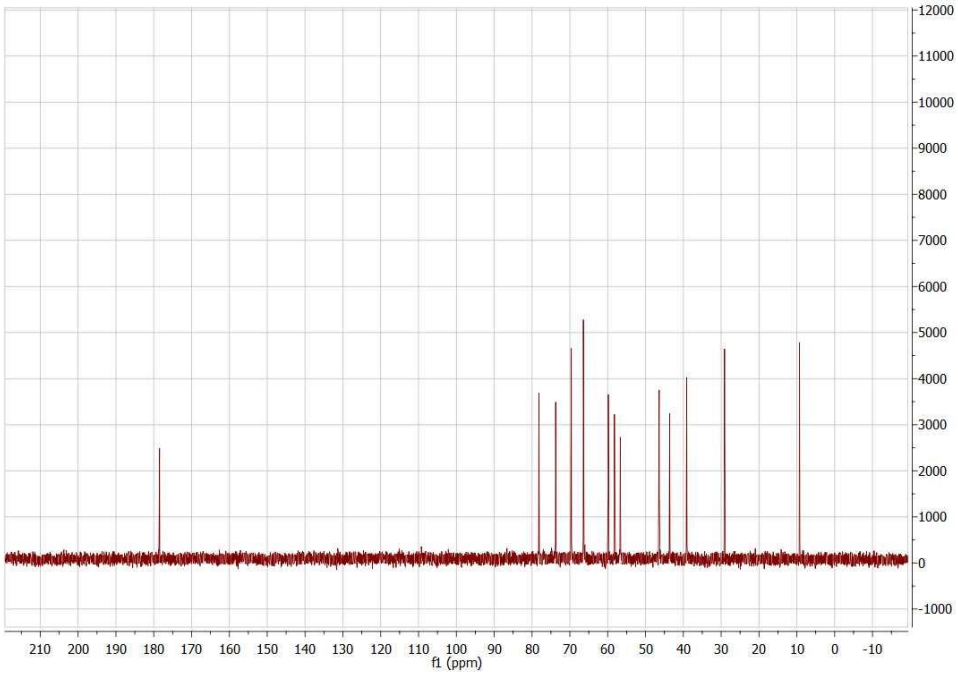



**Figure S22B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **40**.

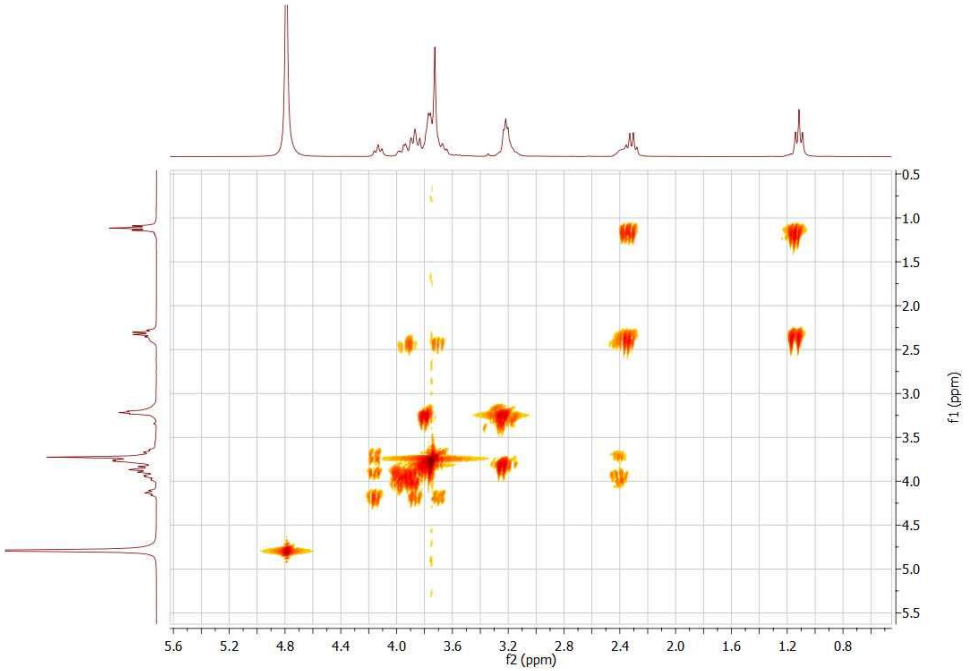



**Figure S22C. COSY** ($D_2O$) of compound **40**.

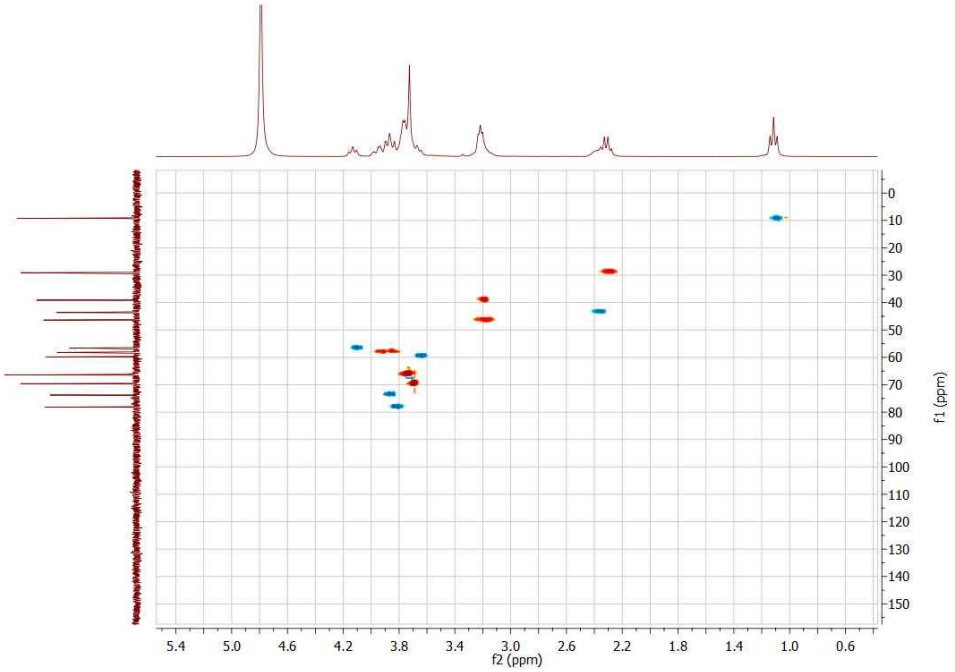



**Figure S22D. HSQC** ($D_2O$) of compound **40**.

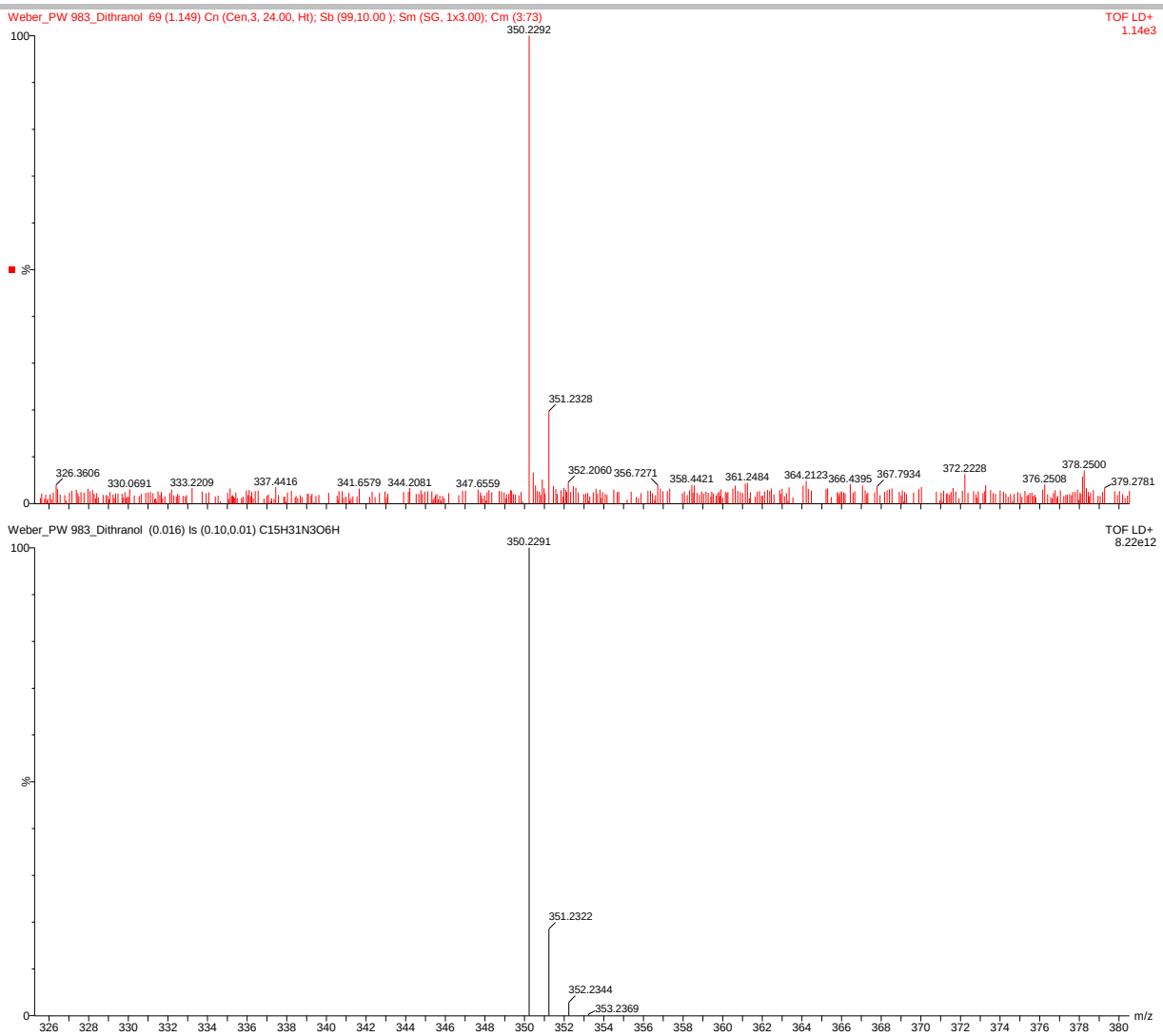
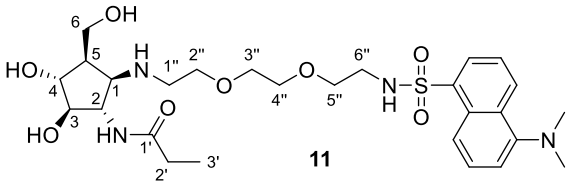



**Figure S22E. HRMS** of compound **40**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(Dimethylamino)naphthalene)-1-sulfonamido)ethoxy)ethoxy) ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)propanoylamide "(1-(2-(2-(2-Dansyl aminoethoxy)ethoxy)ethyl)amino-2-deoxy-2-propanoylamino-"β-D-*gluco*-like"-cyclopentane)" (11)**



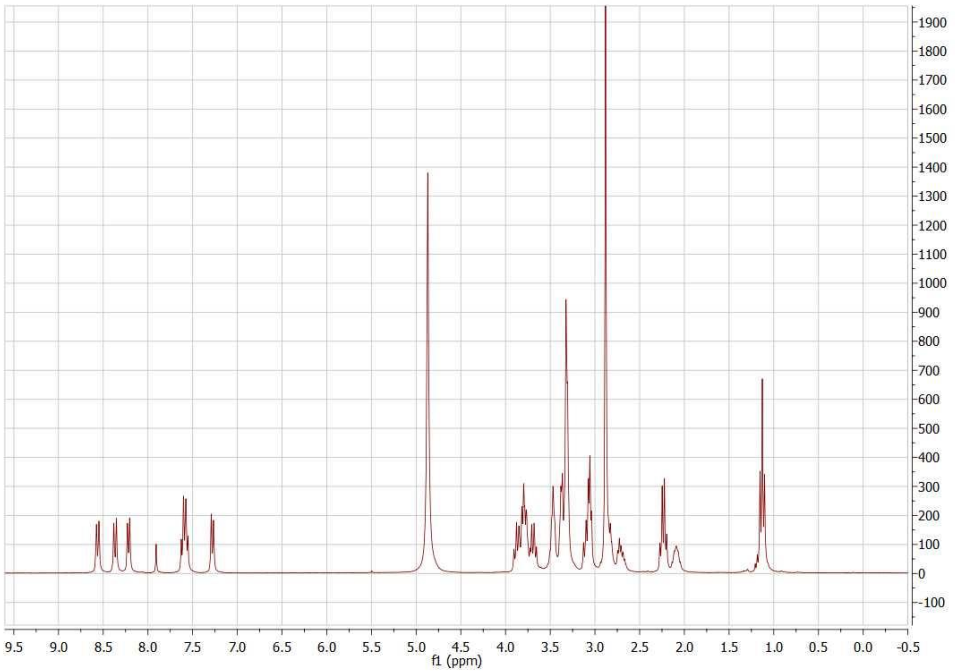




**Figure S23A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **11**.

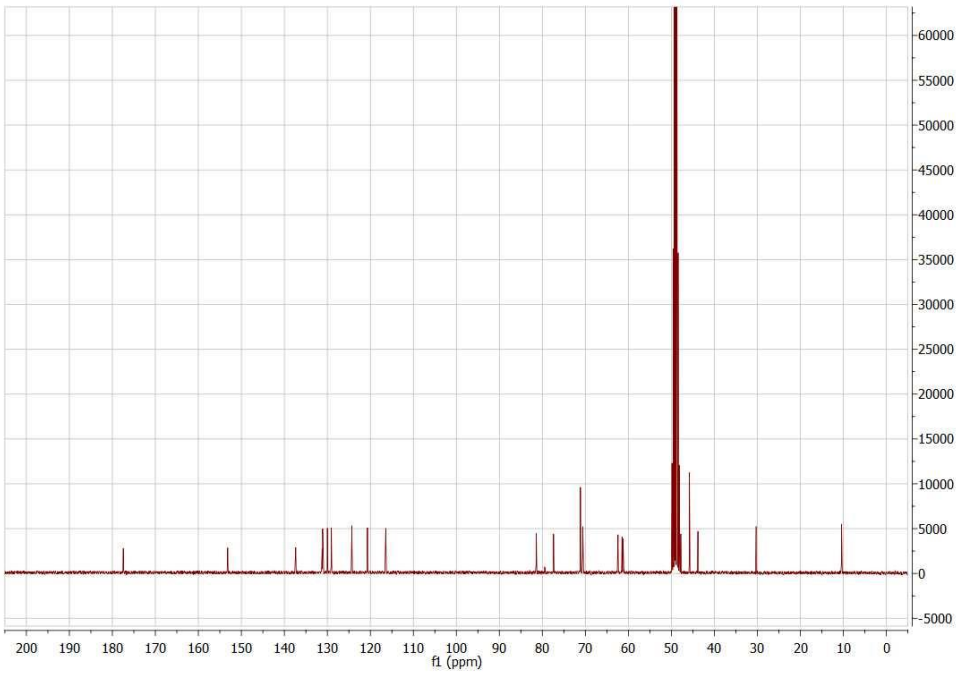



**Figure S23B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **11**.

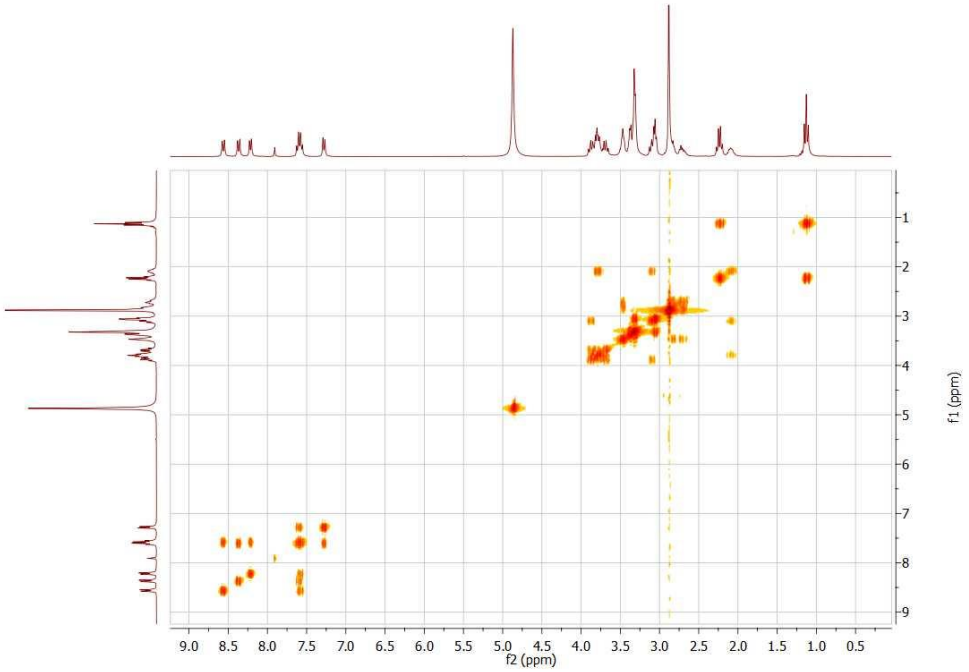



**Figure S23C. COSY** ($CD_3OD$) of compound **11**.

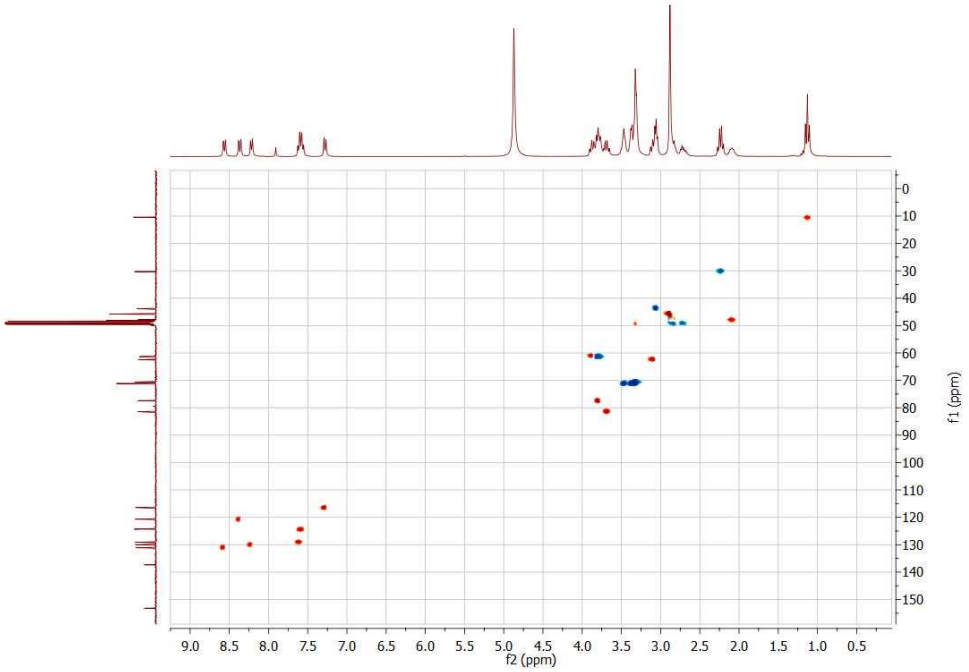



**Figure S23D. HSQC** ($CD_3OD$) of compound **11**.

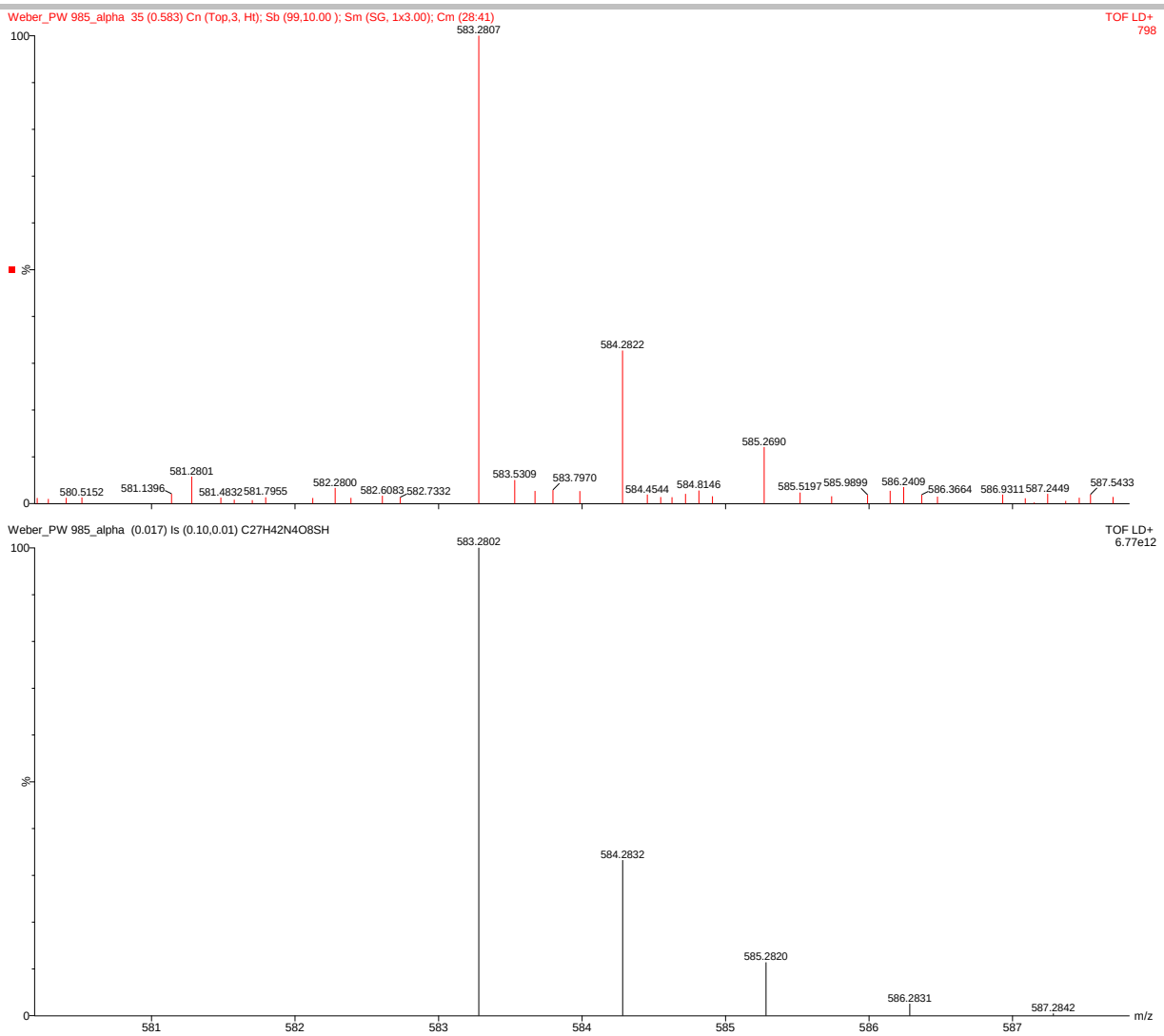
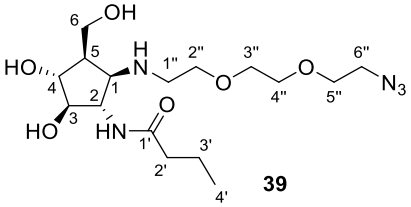



**Figure S23E. HRMS** of compound **11**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)butyramide "(1-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino-2-butanoylamino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (39)**




**39**

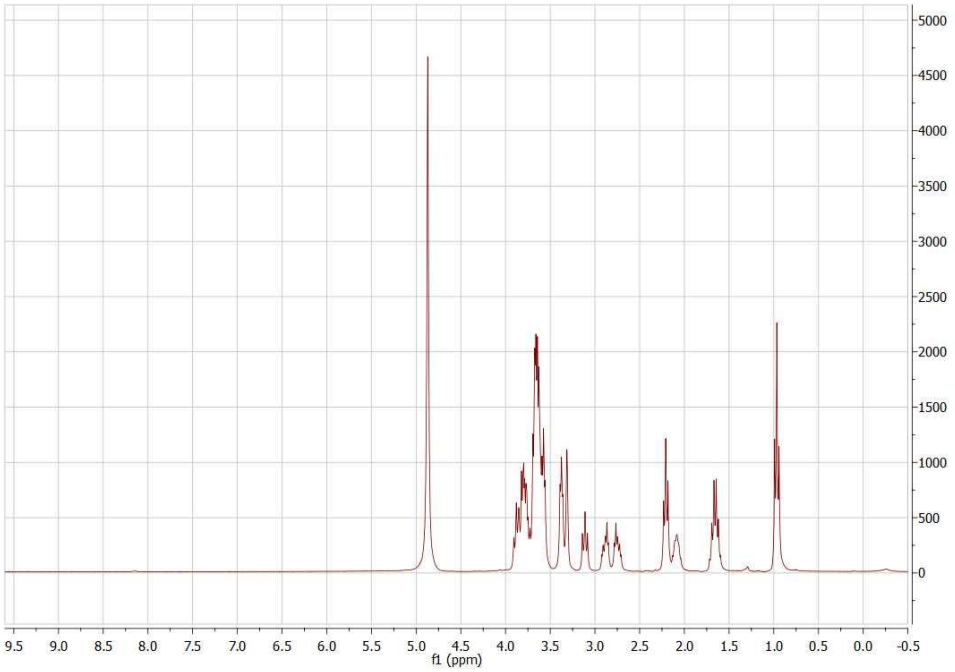



**Figure S24A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **39**.

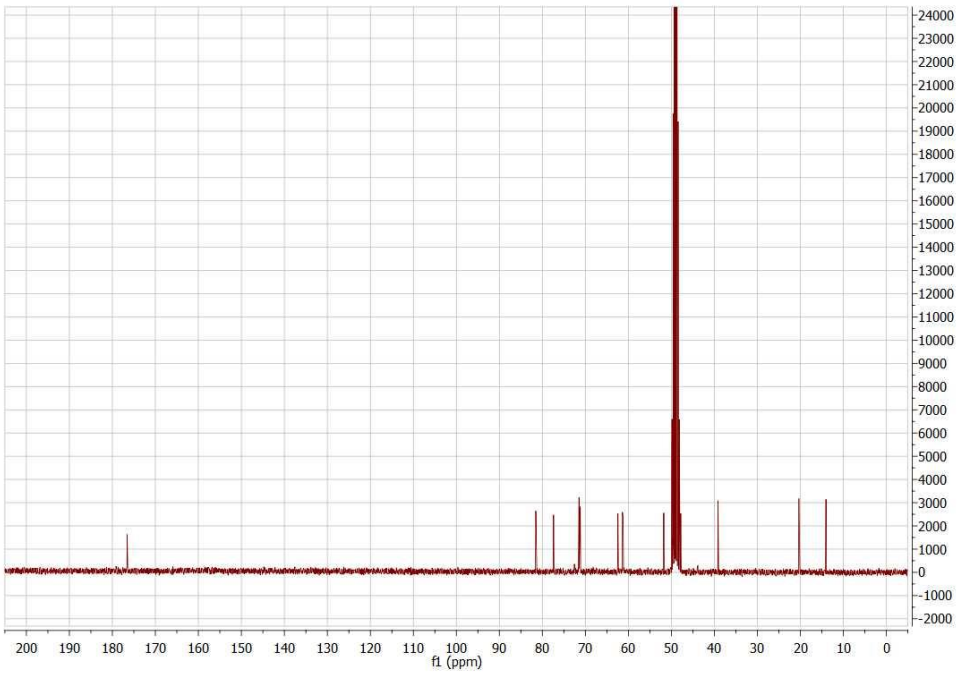



**Figure S24B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **39**.

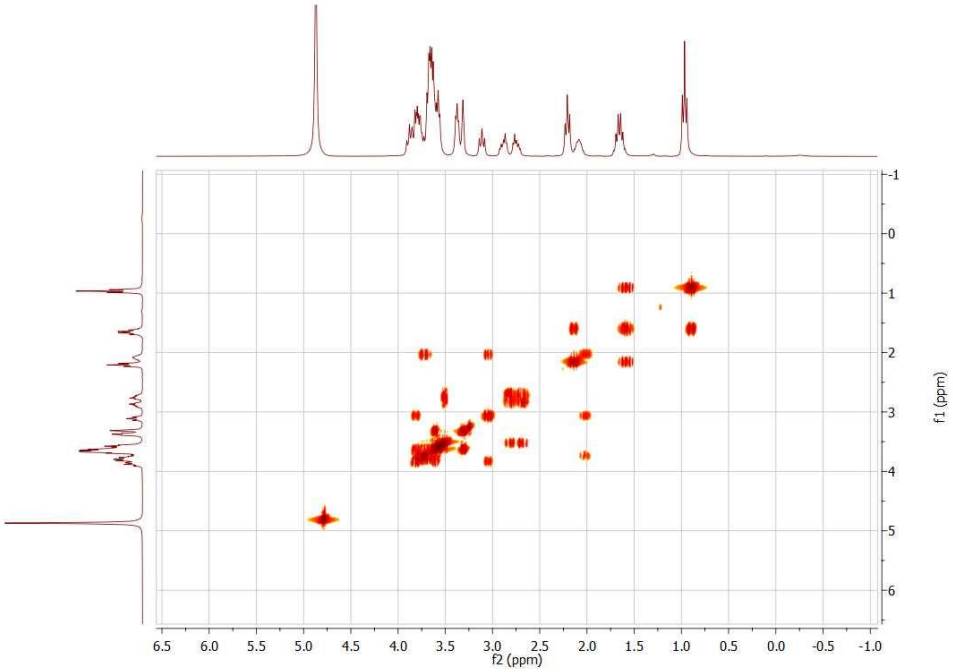



**Figure S24C. COSY** ($CD_3OD$) of compound **39**.

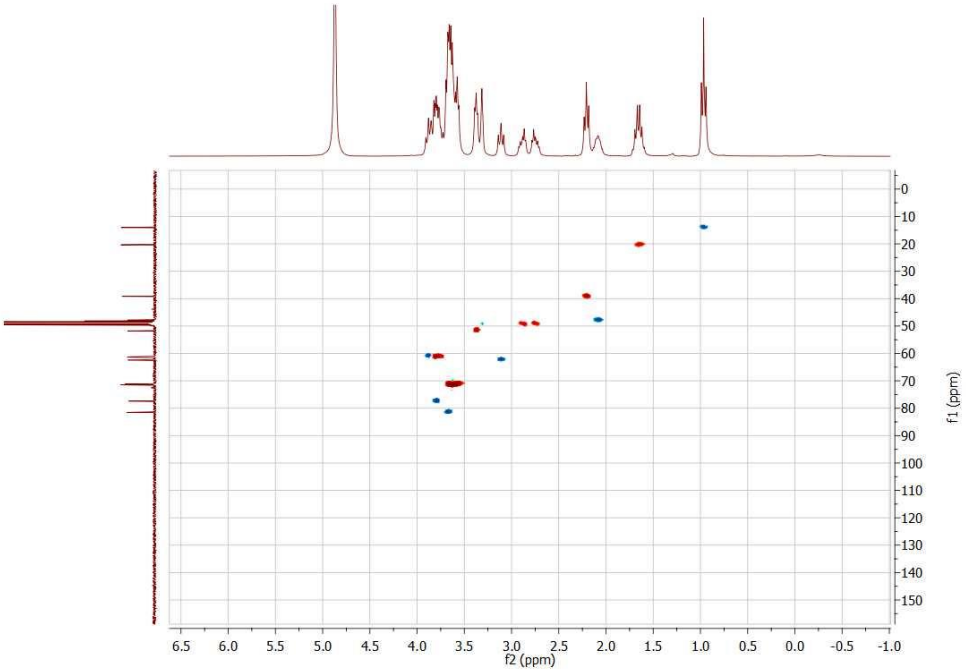



**Figure S24D. HSQC** ($CD_3OD$) of compound **39**.

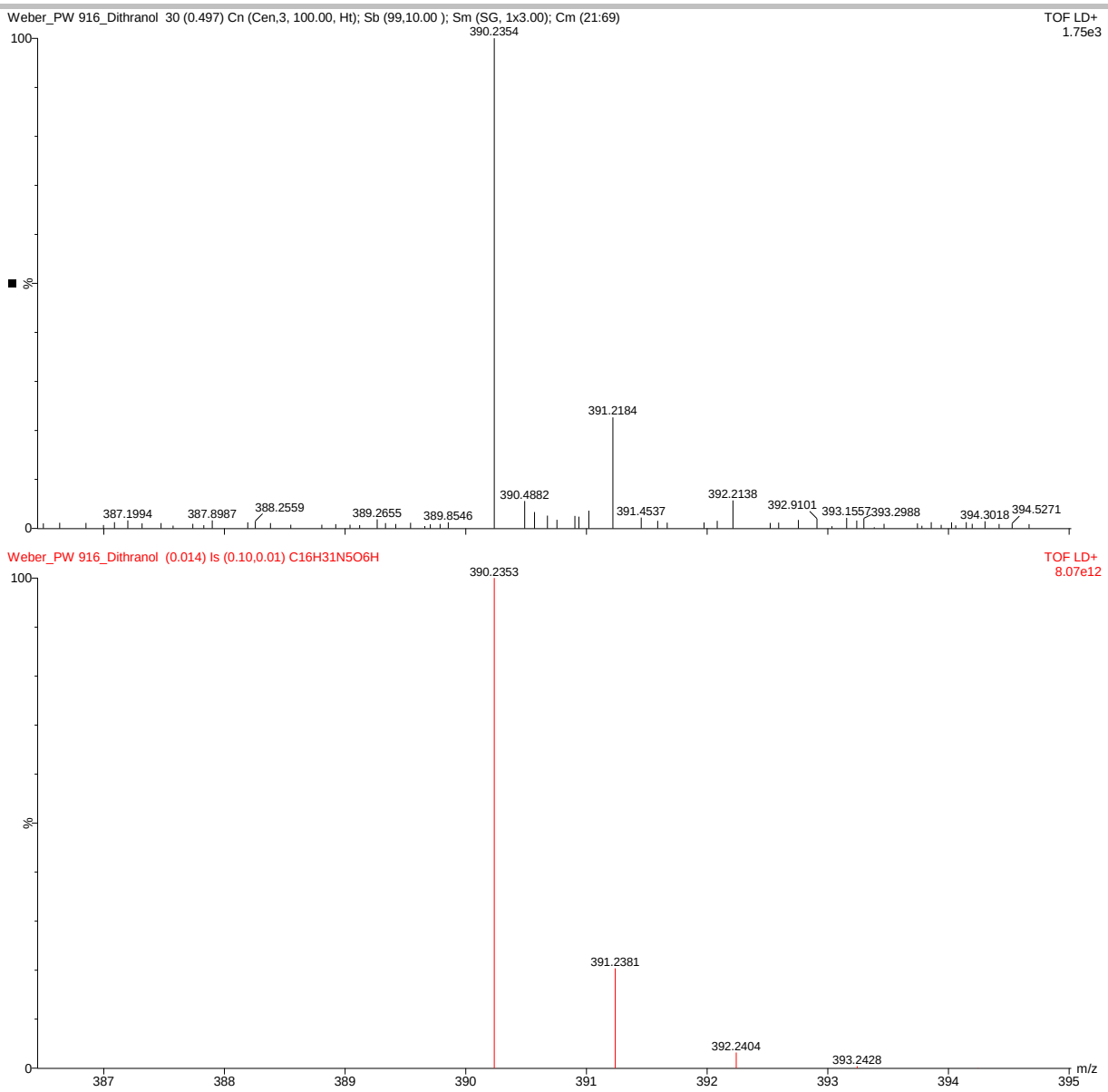
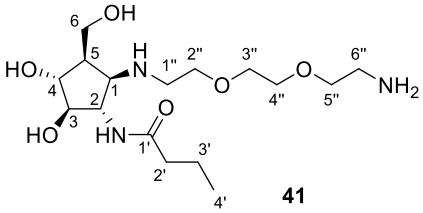



**Figure S24E. HRMS** of compound **39**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)butyramide "(1-(2-(2-(2-Aminoethoxy)ethoxy))ethyl)amino-2-butanoylamino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (41)**



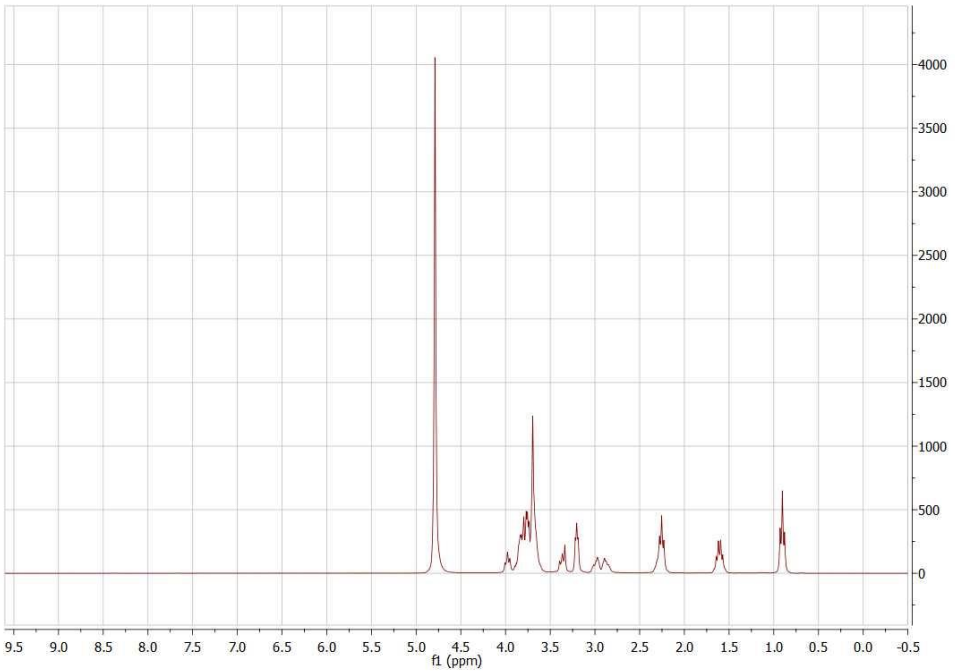




**Figure S25A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **41**.

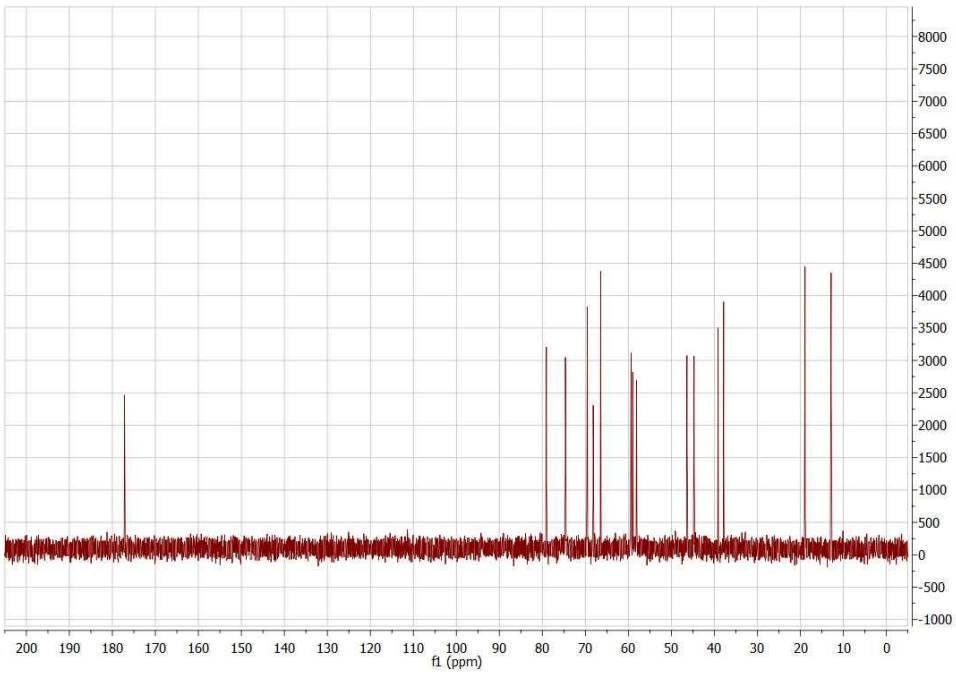



**Figure S25B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **41**.

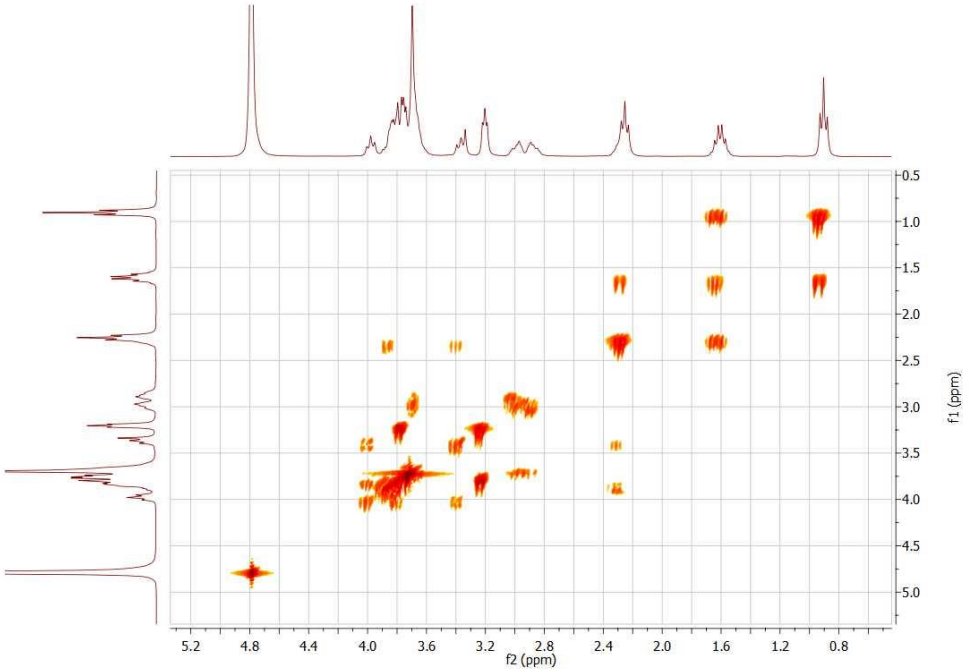



**Figure S25C. COSY** ($D_2O$) of compound **41**.

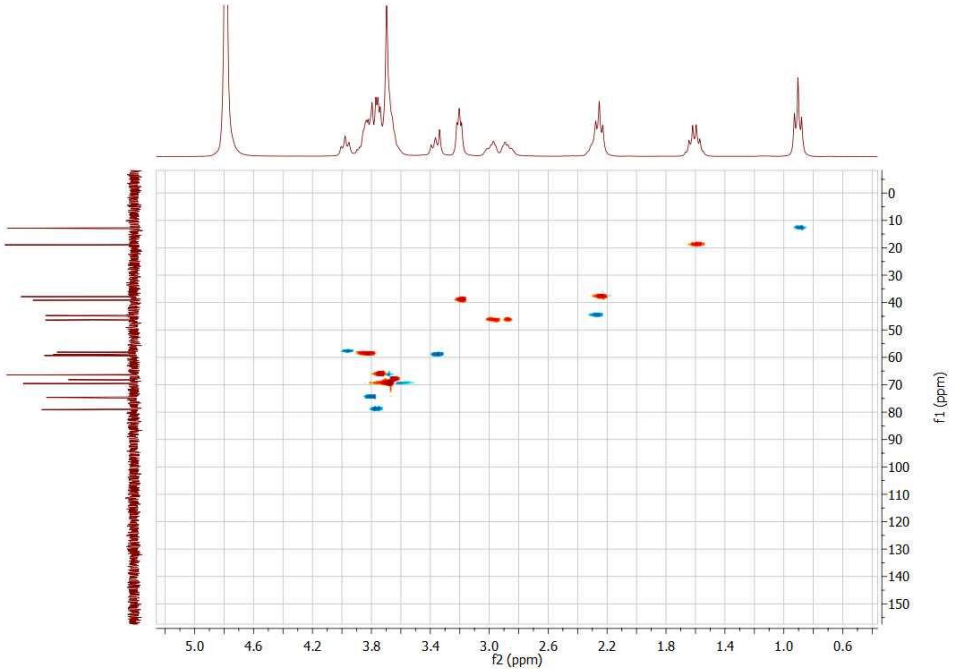



**Figure S25D. HSQC** ($D_2O$) of compound **41**.

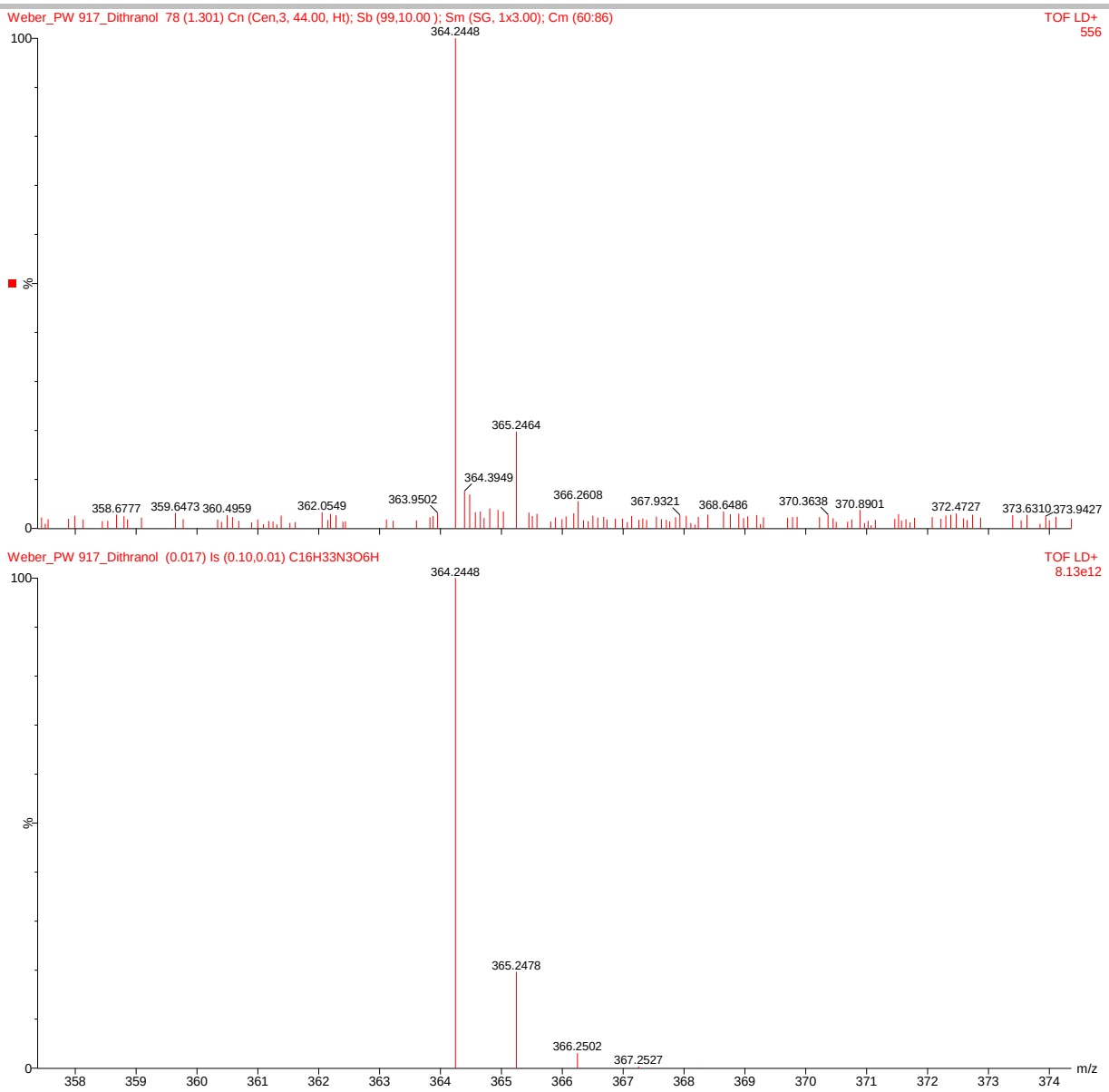
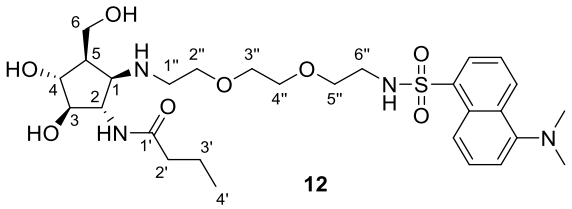



**Figure S25E. HRMS** of compound **41**.

***N*-((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethoxy)ethoxy) ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)butyramide "(2-Butanoyl amino-1-(2-(2-(2-dansylaminoethoxy)ethoxy)ethyl)amino-2-deoxy-"β-D-*gluco*-like"-cyclopentane)" (12)**



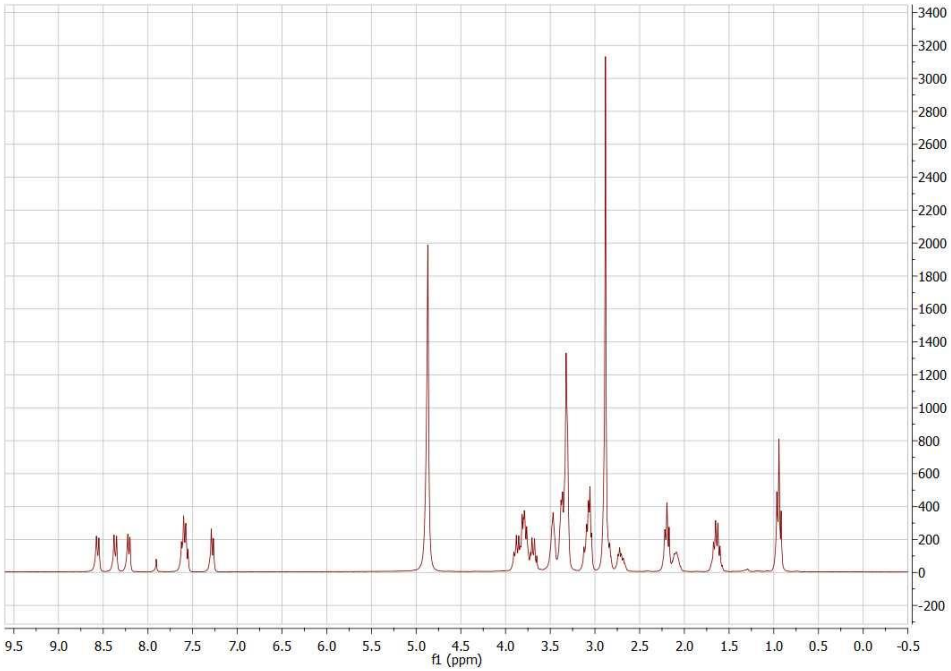




**Figure S26A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **12**.

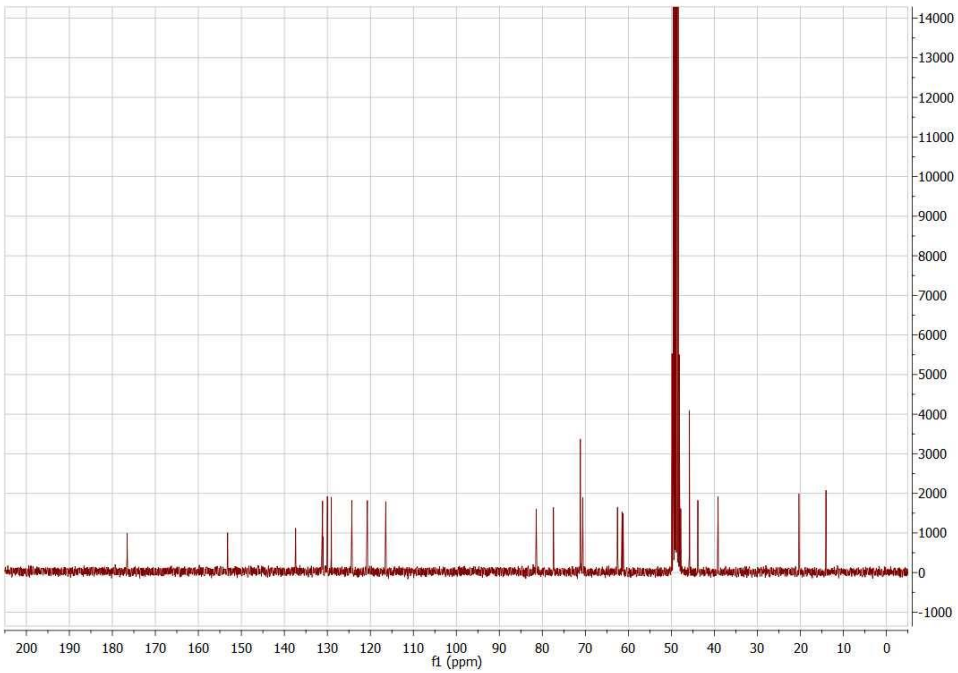



**Figure S26B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **12**.

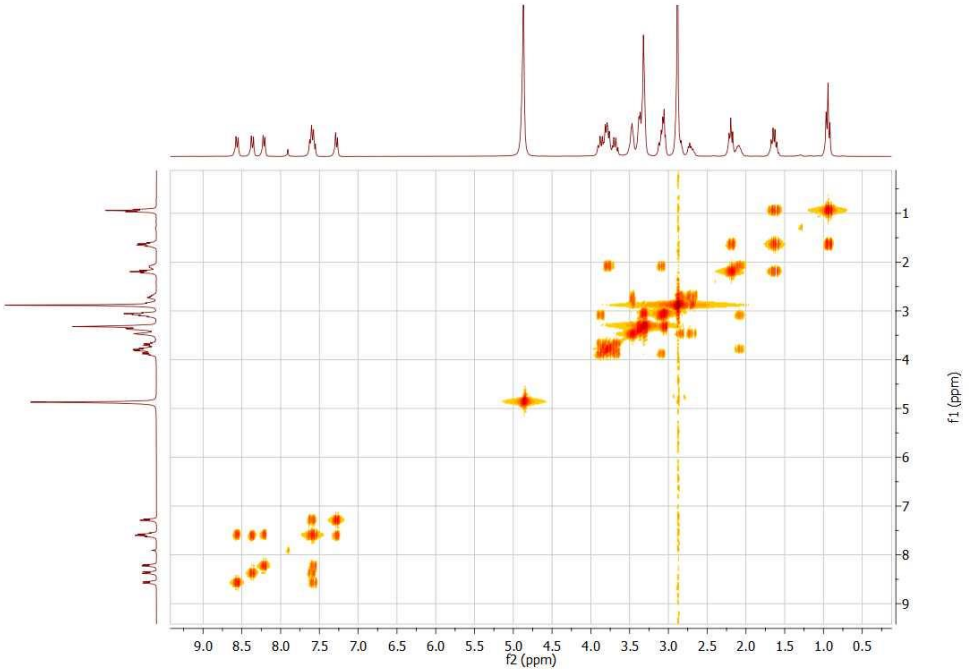



**Figure S26C. COSY** ($CD_3OD$) of compound **12**.

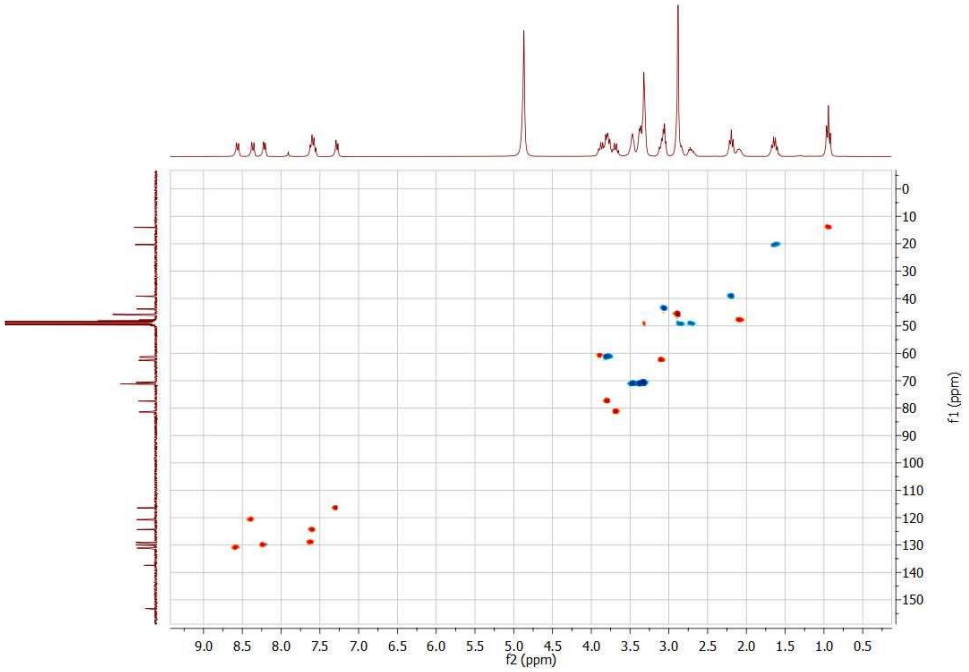



**Figure S26D. HSQC** ($CD_3OD$) of compound **12**.

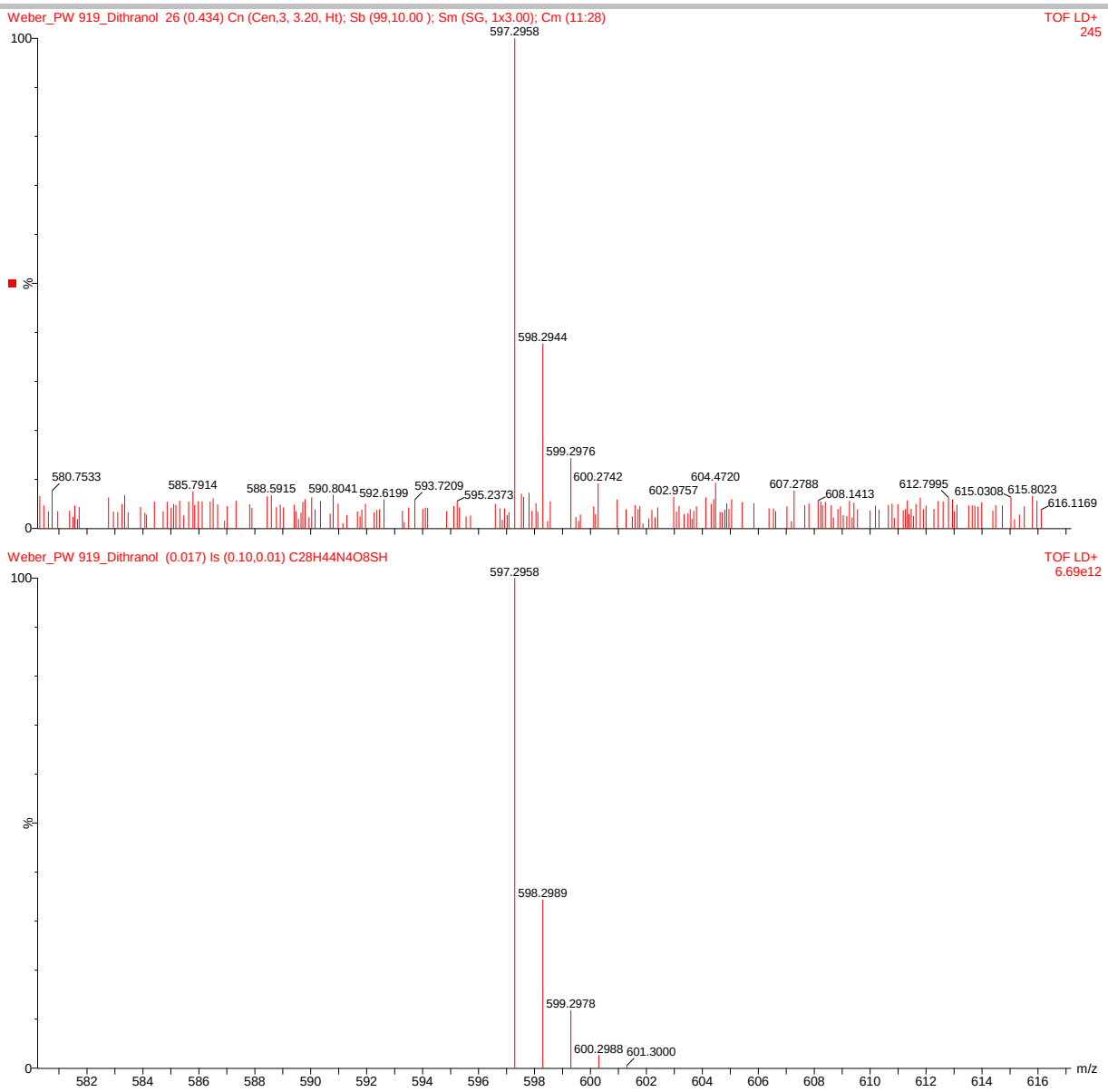
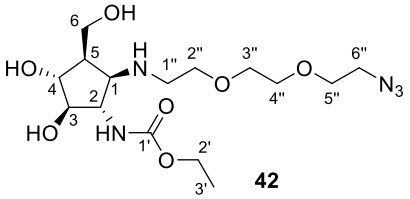



**Figure S26E. HRMS** of compound **12**.

**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-azidoethoxy)ethoxy)ethyl)mino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)carbamate "(1-(2-(2-(2-Azidoethoxy)ethoxy)ethyl)amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane)" (42)**




**42**

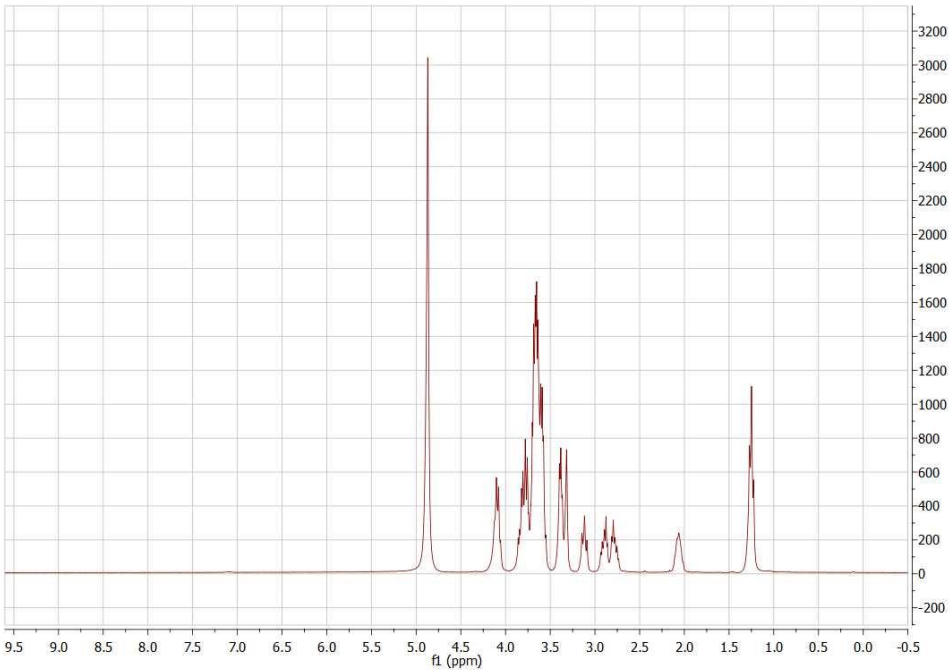



**Figure S27A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **42**.

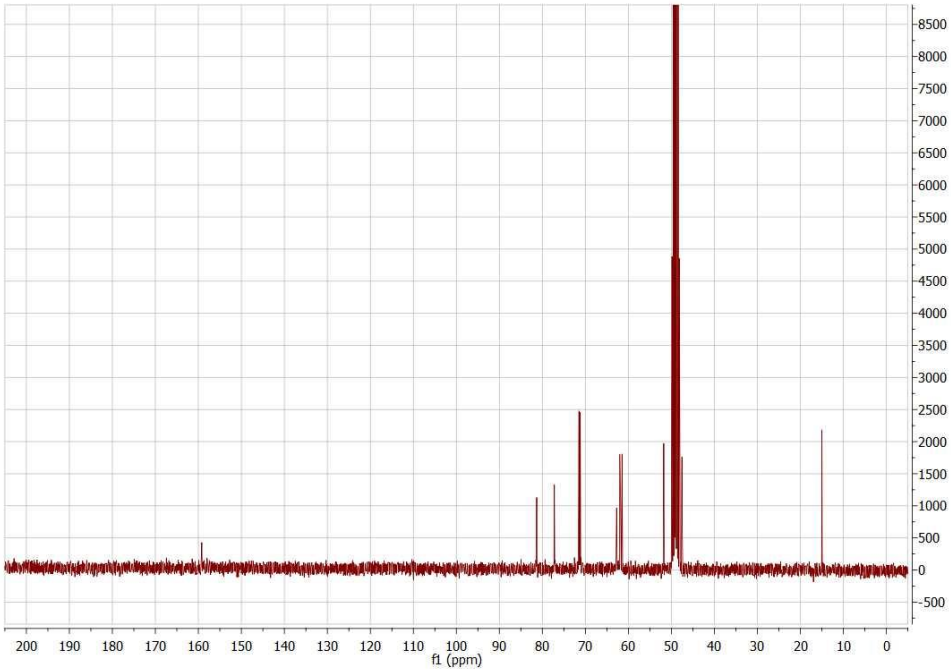



**Figure S27B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **42**.

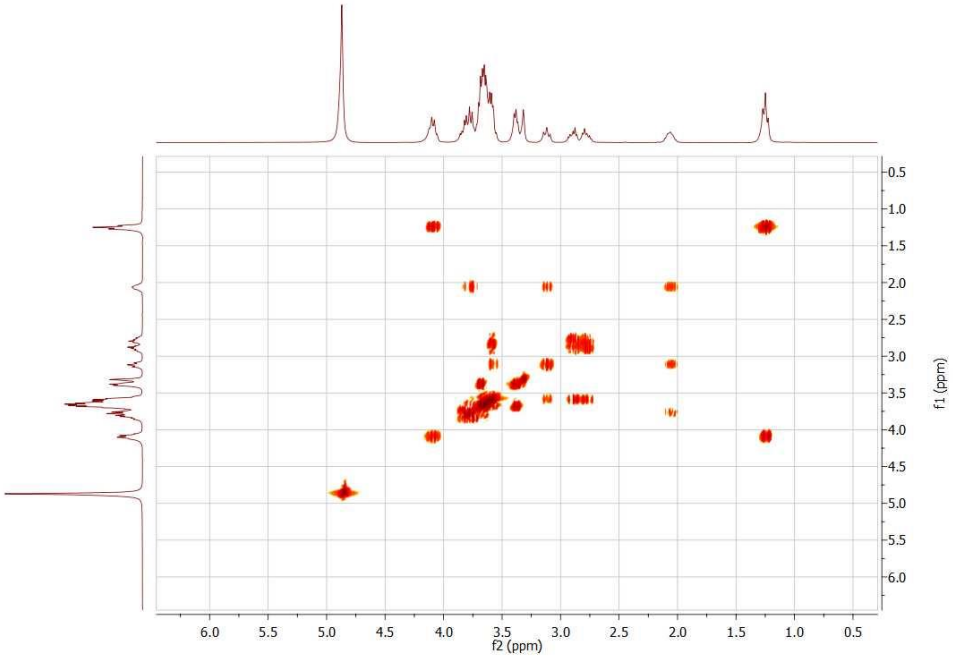



**Figure S27C. COSY** ($CD_3OD$) of compound **42**.

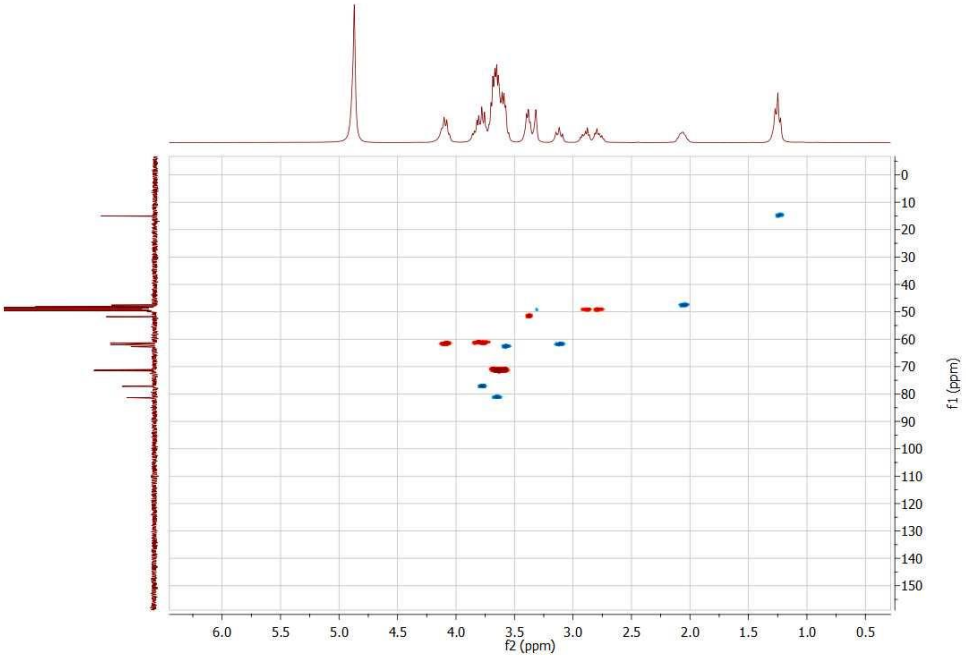



**Figure S27D. HSQC** ($CD_3OD$) of compound **42**.

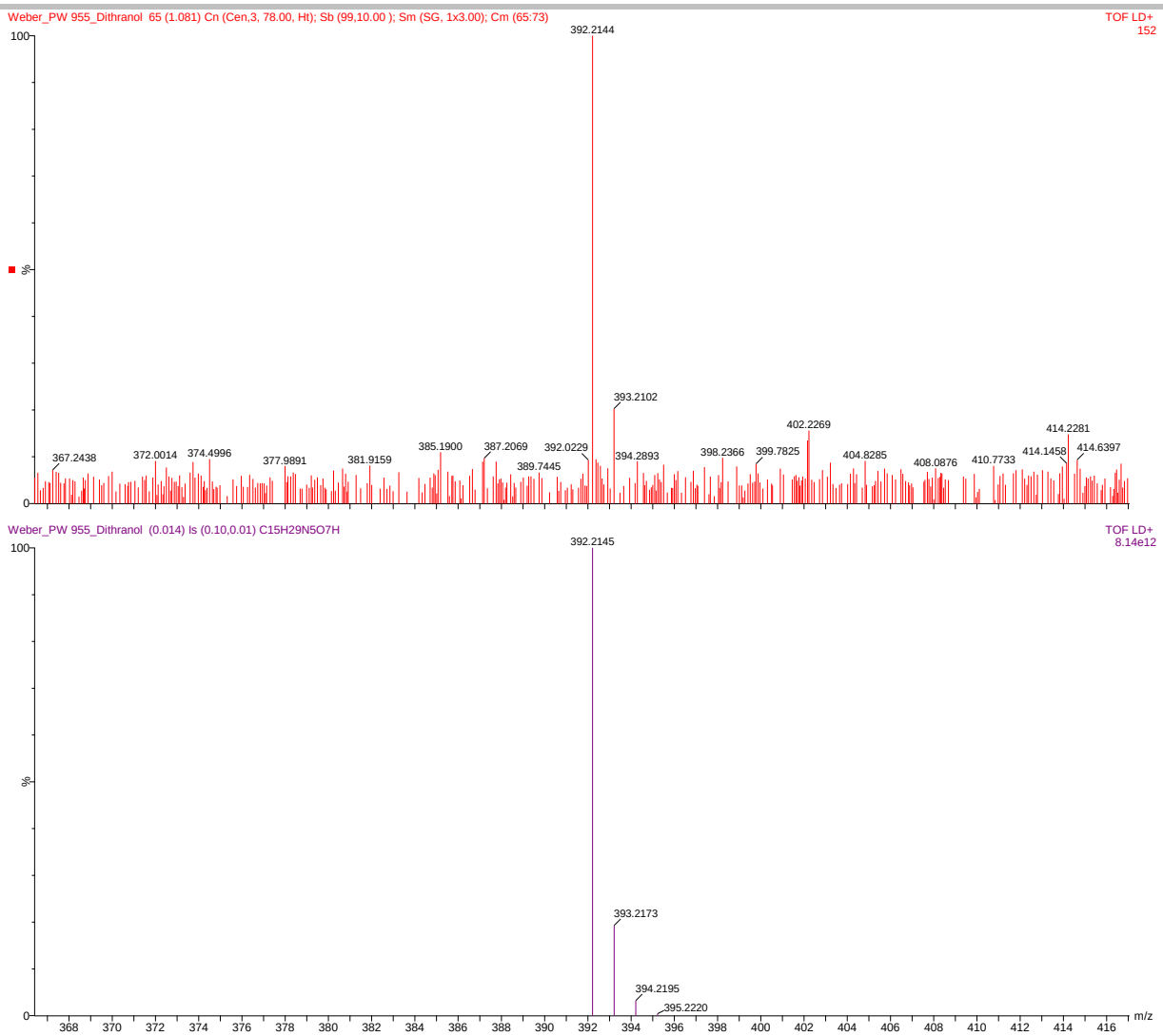
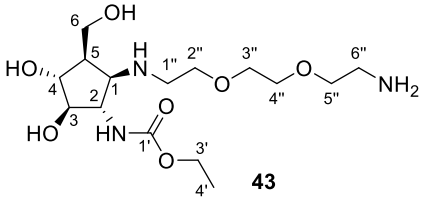



**Figure S27E. HRMS** of compound **42**.

**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-aminoethoxy)ethoxy)ethyl)mino)-4,5-dihydroxy-3-(hydroxyl methyl)cyclopentyl)carbamate "(1-((2-(2-(2-Aminoethoxy)ethoxy)ethyl)amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane) (43)**



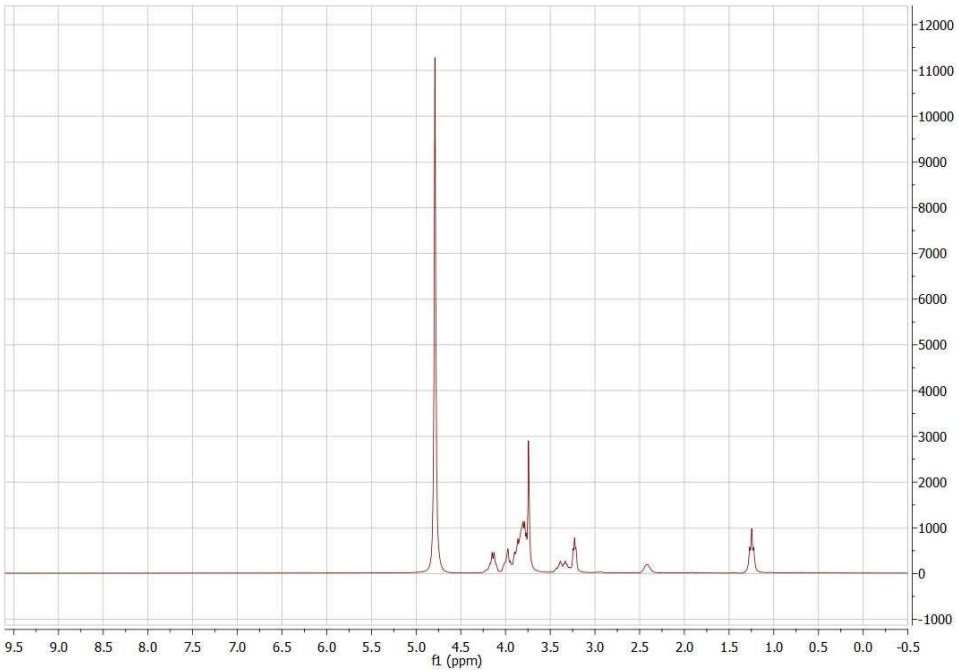




**Figure S28A. $^{1}$H NMR** (300 MHz, $D_2O$) of compound **43**.

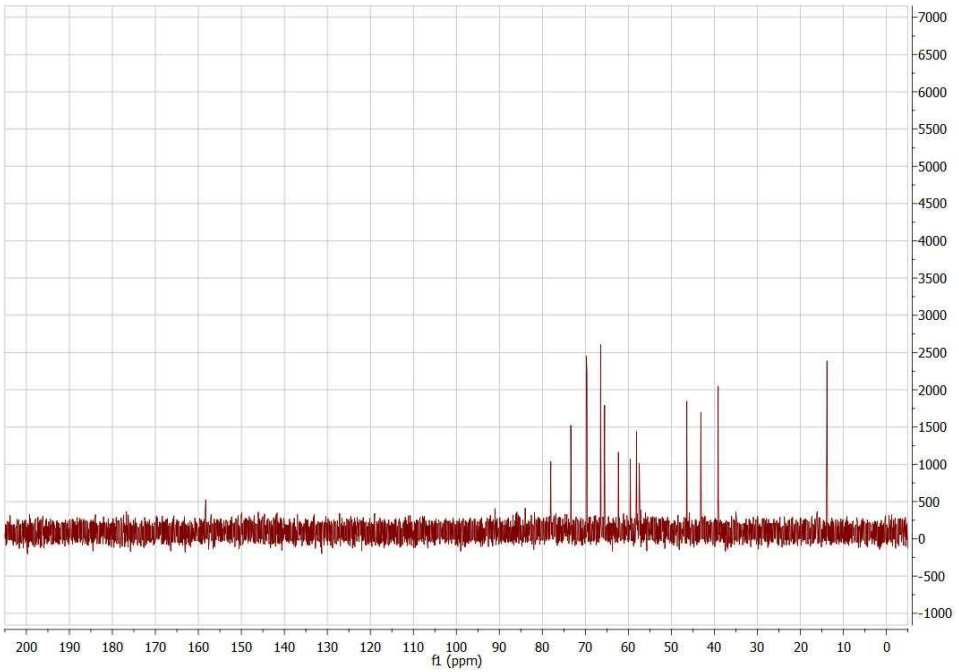



**Figure S28B. $^{13}$C NMR** (75.5 MHz, $D_2O$) of compound **43**.

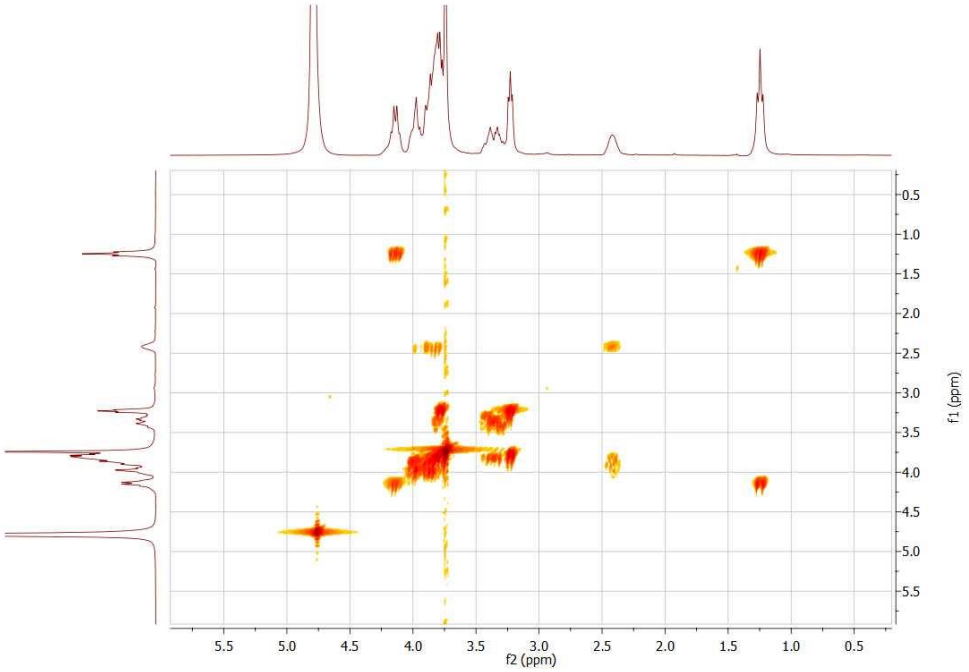



**Figure S28C. COSY** ($D_2O$) of compound **43**.

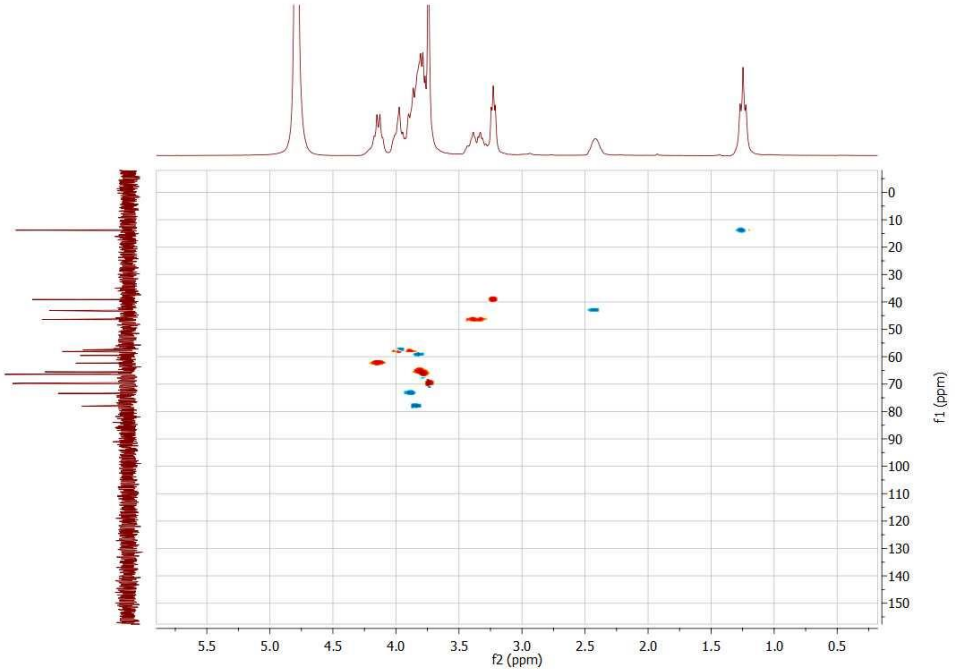



**Figure S28D. HSQC** ($D_2O$) of compound **43**.

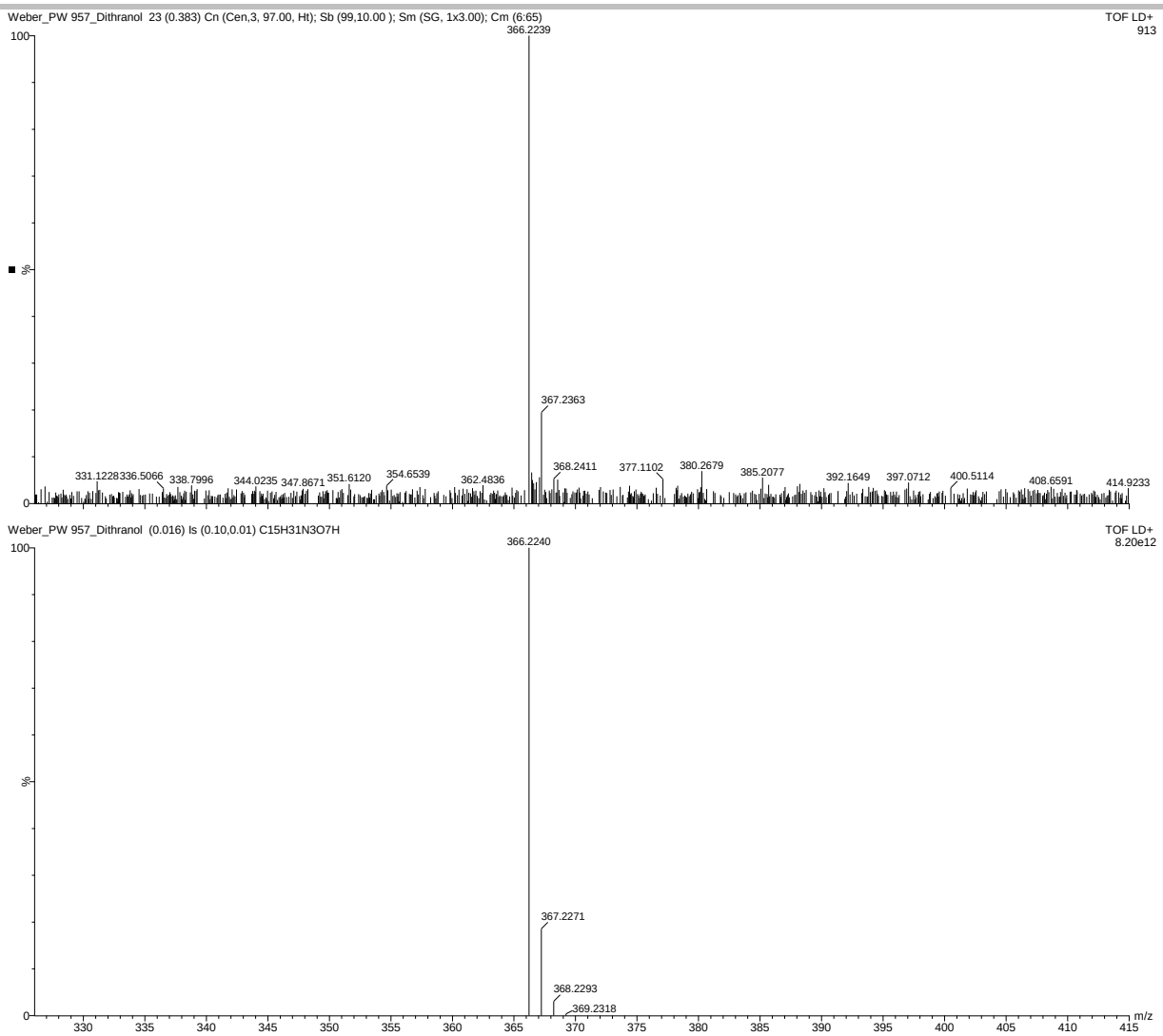
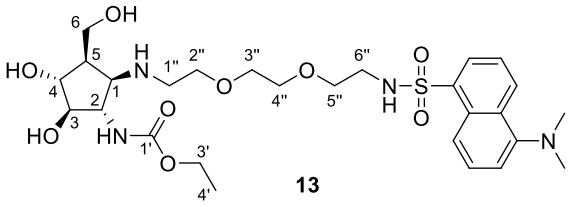



**Figure S28E. HRMS** of compound **43**.

**Ethyl ((1*S*,2*R*,3*R*,4*R*,5*R*)-2-((2-(2-(2-((5-(dimethylamino)naphthalene)-1-sulfonamido)ethoxy) ethoxy) ethyl)amino)-4,5-dihydroxy-3-(hydroxymethyl)cyclopentyl)carbamate "(1-(2-(2-(2-Dansyl aminoethoxy)ethoxy)ethyl)amino-2-deoxy-2-((ethyloxycarbonyl)amino)-"β-D-*gluco*-like"-cyclopentane)" (13)**



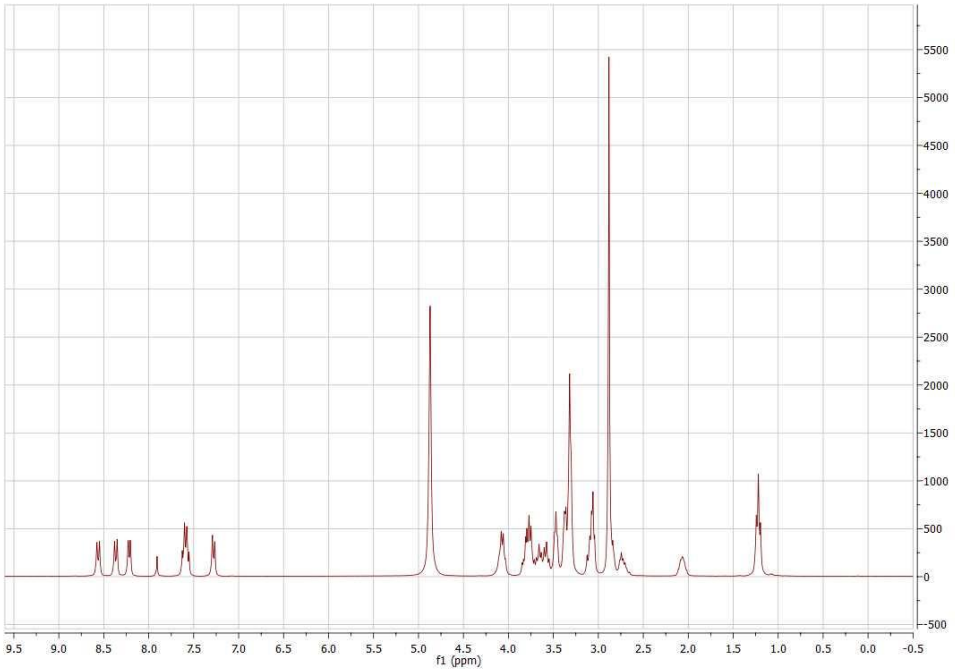




**Figure S29A. $^{1}$H NMR** (300 MHz, $CD_3OD$) of compound **13**.

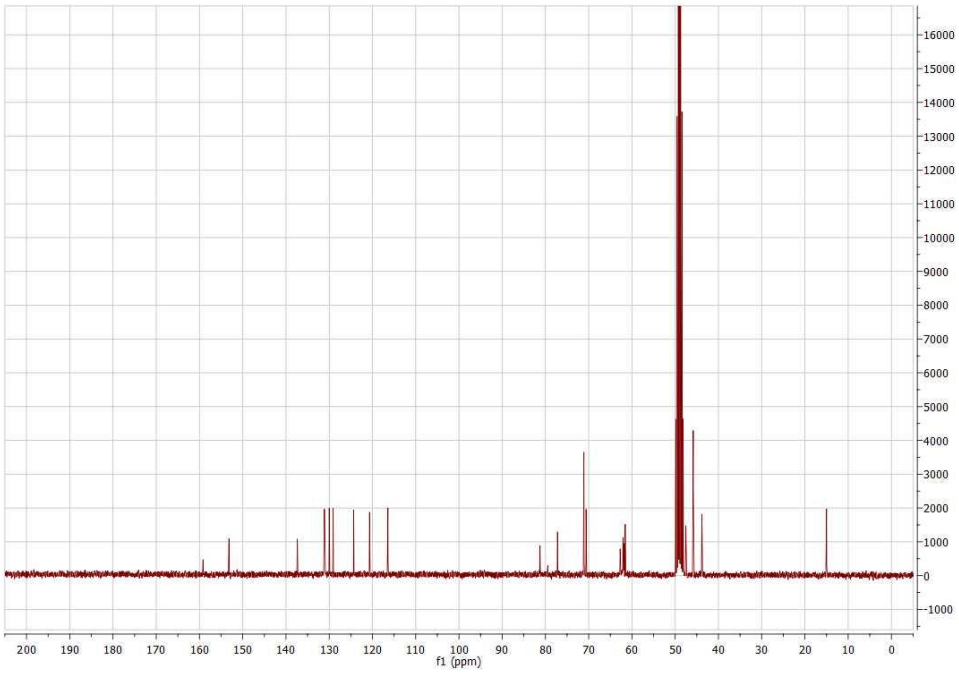



**Figure S29B. $^{13}$C NMR** (75.5 MHz, $CD_3OD$) of compound **13**.

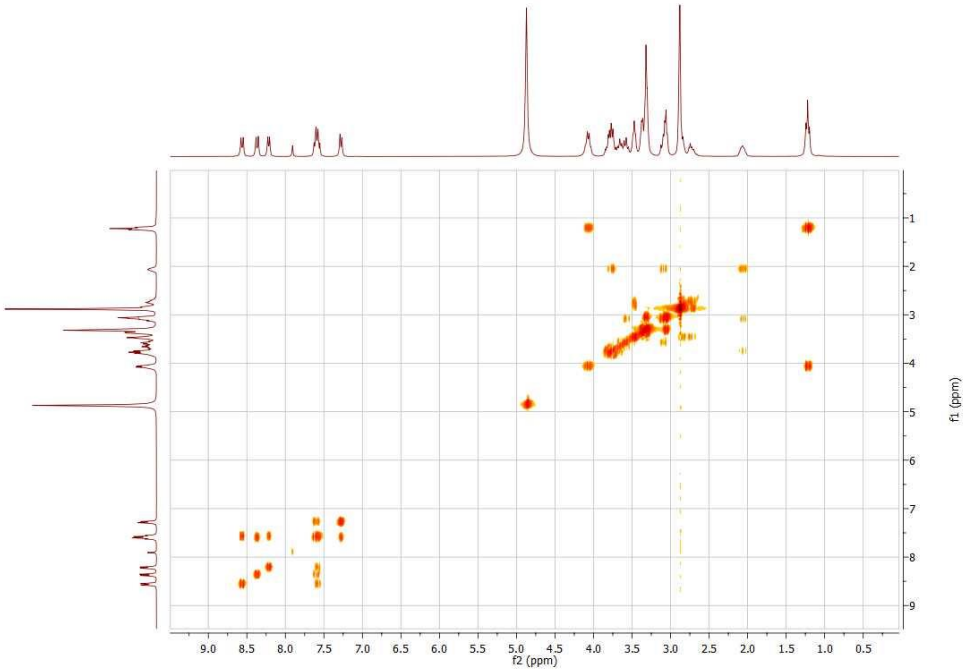



**Figure S29C. COSY** ($CD_3OD$) of compound **13**.

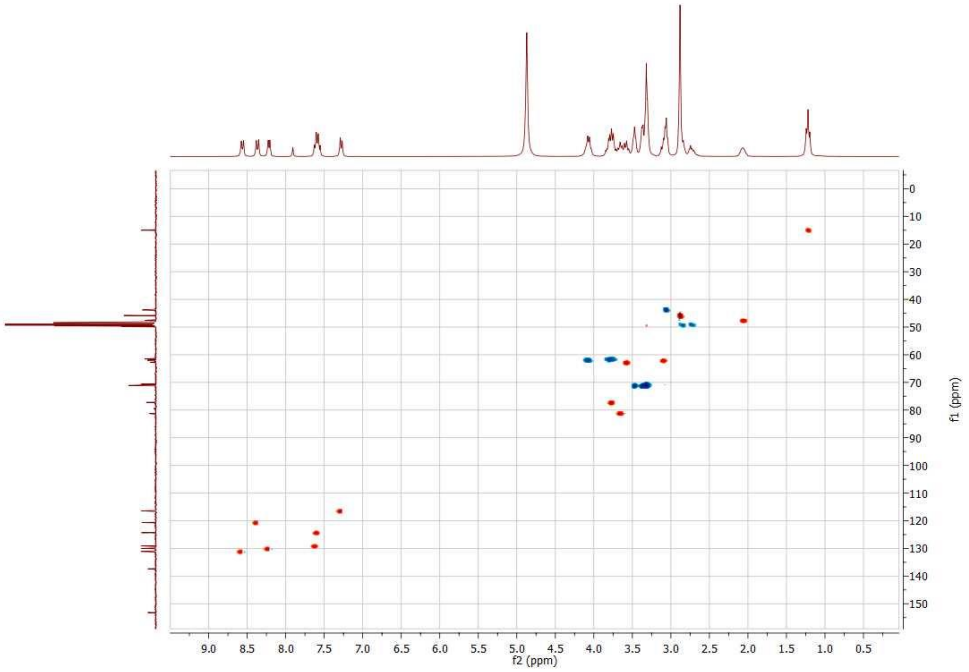



**Figure S29D. HSQC** ($CD_3OD$) of compound **13**.

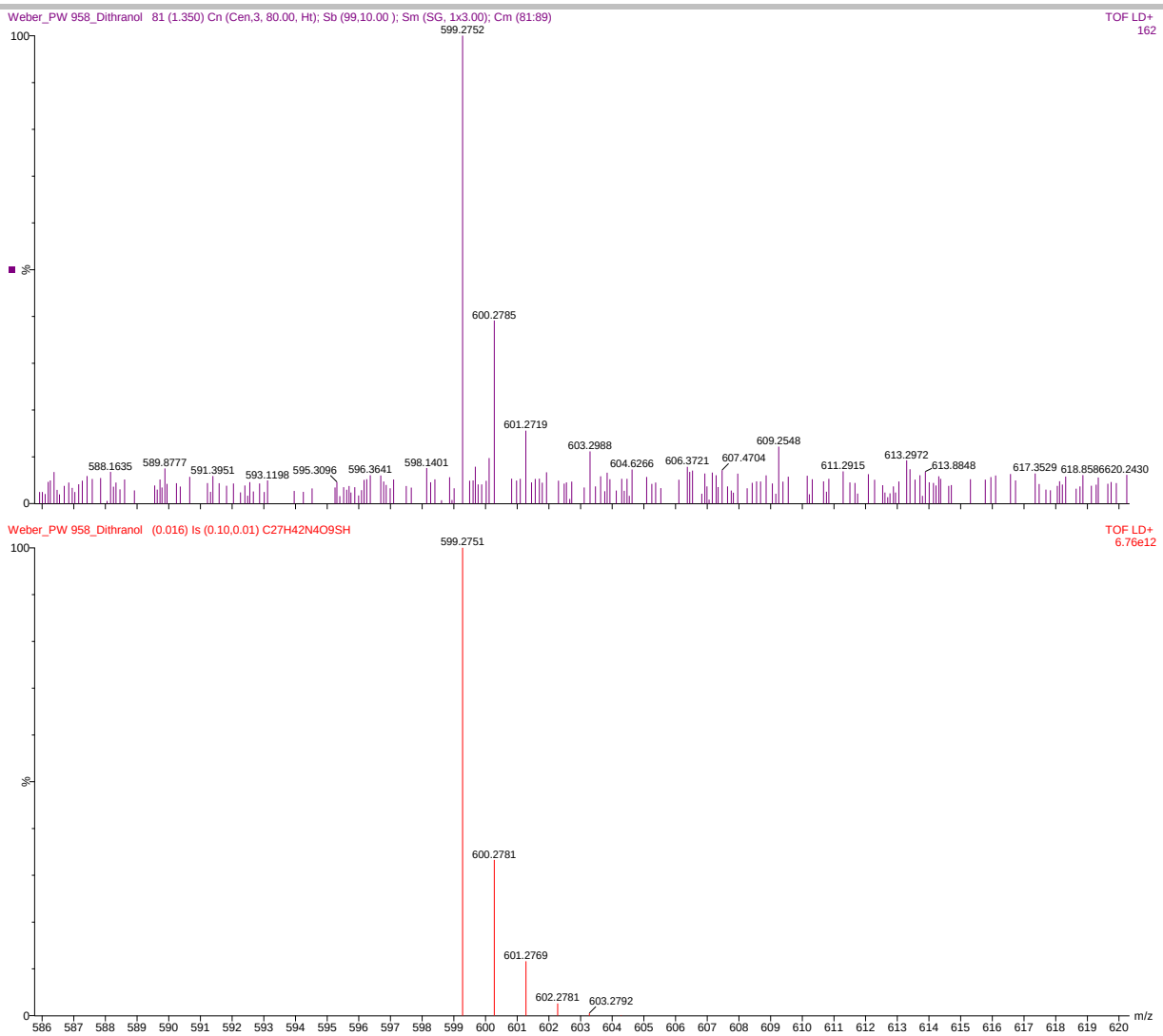


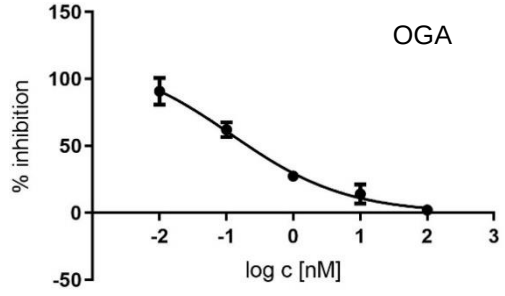

**Figure S29E. HRMS** of compound **13**.

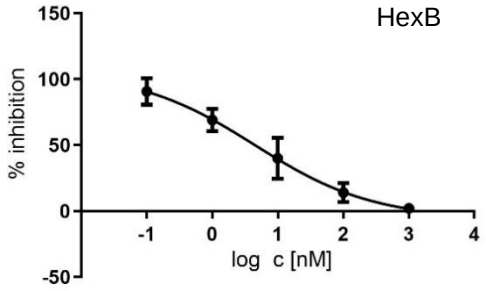
## 4. Production of OGA and HexB

The gene of human OGA containing a $His_6$-tag was kindly provided by Prof. D. Vocadlo (SFU, Burnaby, Canada). OGA was expressed intracellularly in *Escherichia coli* BL21 (DE3) pLysS strain under the induction by 0.5 mM IPTG (isopropyl-β-D-thiogalactoside, Merck, DE). After 16 hours of cultivation at 25 °C, the cells were harvested by centrifugation and lysed in a freshly prepared lysis buffer for 45 min at 37 °C (250 µL Triton X-100, 200 µL 1 M $MgCl_2$, 2.5 mL 1M NaCl, 50 µg lysozyme, 500 µL PMSF (phenylmethanesulfonyl fluoride, Merck, DE); all dissolved in binding buffer (20 mM $Na_2HPO_4$, 0.5 M NaCl, 20 mM imidazole, pH 7.4) to a total volume of 50 mL). The cells were then disrupted by sonication (6 × 1 min) followed by centrifugation to remove the cell debris. The collected supernatant was diluted 1:2 by the binding buffer and loaded onto an equilibrated 5 mL HisTrap column (GE Healthcare, US) connected to the Äkta Purifier protein chromatography system (GE Healthcare, US). The proteins bound to the column were eluted by the gradient (10 mL) of the elution buffer (20 mM $Na_2HPO_4$, 0.5 M NaCl, 500 mM imidazole, pH 7.4) and the fractions containing OGA were pooled, 5× diluted with 100 mM Tris/HCl + 100 mM NaCl buffer pH 7.4 and concentrated using Amicon Ultra Centrifugal Filters (Merck, DE) to remove the abundant imidazole.
Human HexB was expressed extracellularly in the methylotrophic yeast *Pichia pastoris* KM71H and isolated from its culture media by cation-exchange chromatography as described previously.[15] Both OGA and HexB were stored at 4 °C for several months without any significant loss of activity.

## 5. Kinetic assays

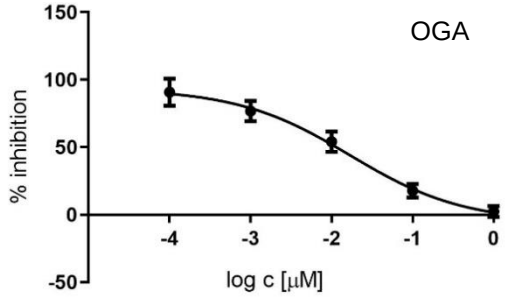
The β-*N*-acetylglucosaminidase activity was measured in a discontinuous spectrophotometric assay using *p*-nitrophenyl 2-acetamido-2-deoxy-β-D-glucopyranoside (*p*NP-β-GlcNAc) as a substrate (2 mM starting concentration). The reaction mixture was incubated in 50 mM citrate/ phosphate buffer (pH 5.0 for HexB; pH 7.0 for OGA) for 10 min at 35 °C and 1000 rpm. Then, the reaction (50 µL) was stopped by 1 mL of 0.1 M $Na_2CO_3$ and the concentration of the released *p*-nitrophenolate was determined spectrophotometrically (420 nm). One unit of enzymatic activity corresponds to the amount of enzyme releasing 1 µmol of *p*-nitrophenol per minute under the above conditions.
Kinetic and inhibition parameters ($IC_{50}$ and $K_i$) of human OGA and HexB were measured spectrophotometrically in a discontinuous assay using Tecan Sunrise plate reader (Tecan, AT). From the reaction mixtures (total volume 300 µL; incubation at 35 °C and 1000 rpm), which contained enzyme, *p*NP-β-GlcNAc as substrate (0.1–2 mM), inhibitors at various concentrations, and 50 mM citrate/phosphate buffer (pH 5.0 for HexB; pH 7.0 for OGA), 50 µL samples were taken in minute intervals into microplate wells containing 150 µL of 0.1 M $Na_2CO_3$ and the resulting absorbance at 420 nm was measured. In the assay for the $IC_{50}$ determination, the concentration of the substrate *p*NP-β-GlcNAc was fixed at the concentration corresponding to $K_M$ at the above conditions (0.3 mM for HexB; 0.6 mM for OGA). The inhibition parameters ($IC_{50}$ and $K_i$) were calculated using GraphPad Prism (GraphPad, UK); all data were acquired in triplicates.

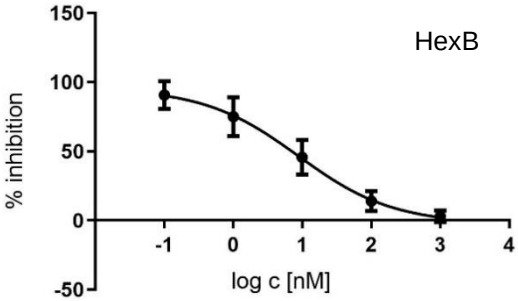



**Compound 8:** $IC_{50}$ = 126 ± 15.7 nM

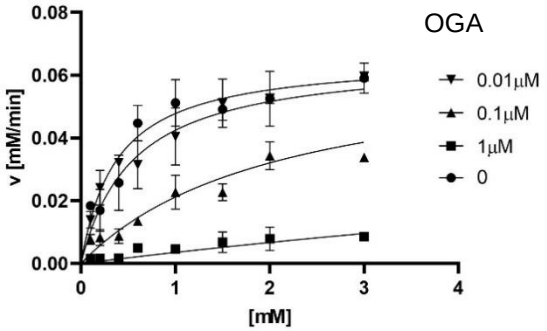
$IC_{50}$ = 4,480 ± 721 nM

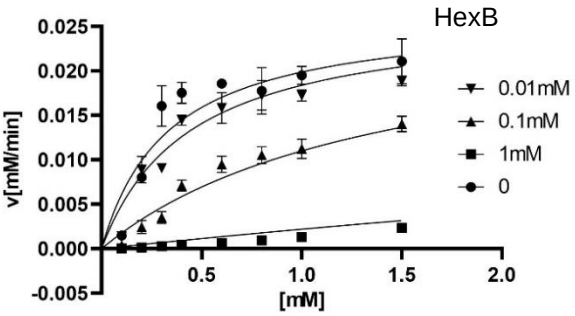



**Compound 44:** $IC_{50}$ = 17 ± 6.8 nM

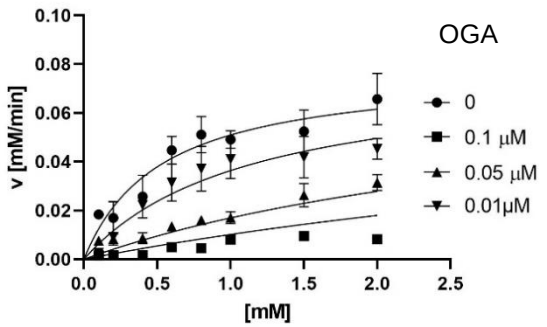
$IC_{50}$ = 8.8 ± 2.6 nM

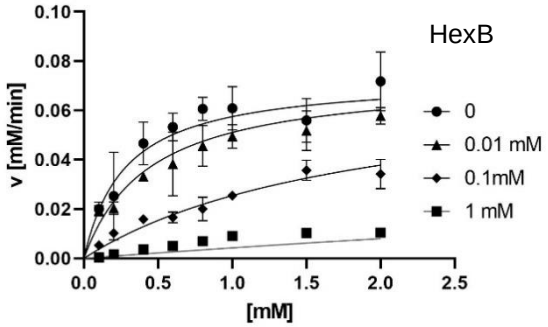



**Compound 9:** $K_i$ = 21.8 ± 3.9 nM

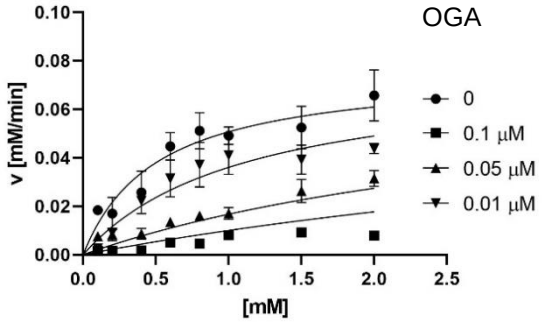
$K_i$ = 310,000 ± 4,386 nM

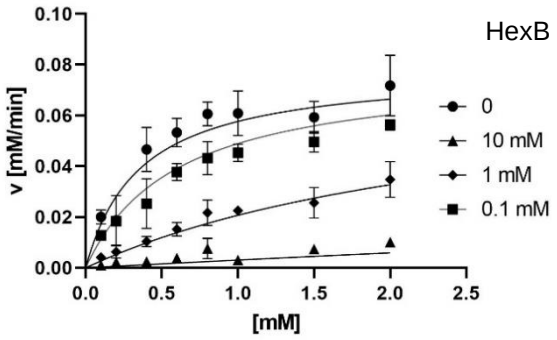



**Compound 10:** $K_i$ = 8.6 ± 1.3 nM

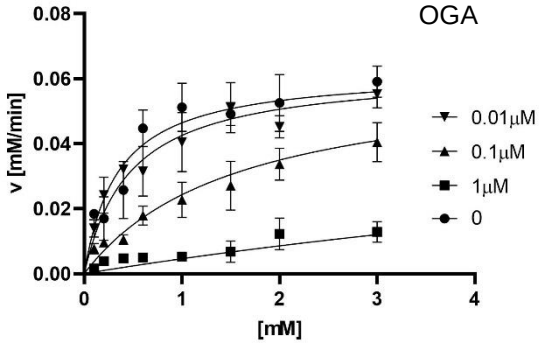
$K_i$ =17,270 ± 1,232 nM

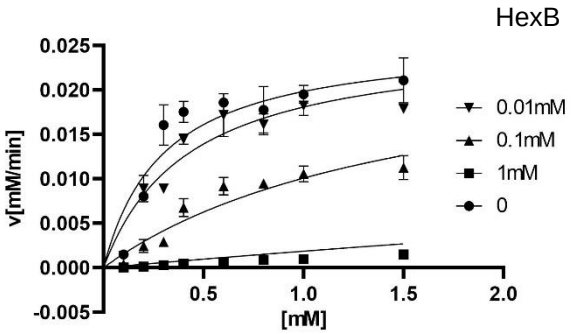



**Compound 11:** $K_i$ = 8.3 ± 0.8 nM

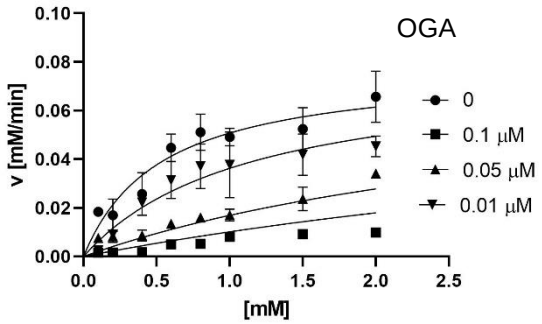
$K_i$ = 148,000 ± 10,600 nM

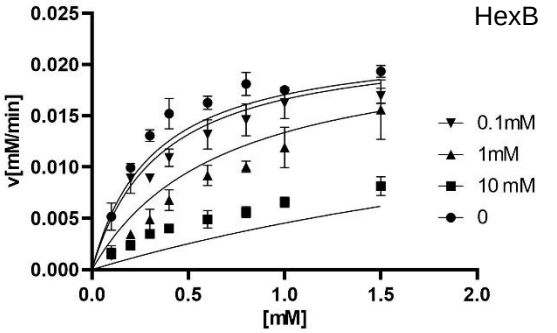



**Compound 12:** $K_i$= 28.1 ±1.1 nM

$K_i$= 23,900 ± 1,900 nM




**Compound 13:** $K_i$= 8.7 ± 1.6 nM

$K_i$= 797,600 ± 20,600 nM

**Figure S30.** Graphs of inhibition assays of compounds **8**-**13** and **44** with human OGA and HexB enzymes.

## 6. Cytotoxicity assays

*HepG2 and Balb/3T3 cell cultures*

Human hepatocyte carcinoma HepG2 cells (ECACC, Salisbury, UK) and mouse fibroblasts Balb/3T3 clone A31 (ATCC, Manassas, VA, US) were cultured at 37 °C in a humidified atmosphere containing 5% $CO_2$. The culture medium for HepG2 cells consisted of Dulbecco's modified Eagle's medium (DMEM; Sigma-Aldrich, St. Louis, MO, USA) supplemented with 1% (v/v) non-essential amino acids, 100 U/mL penicillin, 100 µg/mL streptomycin (Invitrogen, Carlsbad, CA, US) and 10% (v/v) fetal bovine serum (FBS; HyClone Laboratories, South Logan, UT, US). The culture medium for Balb/3T3 cells consisted of DMEM supplemented with 100 U/mL penicillin, 100 µg/mL streptomycin, 5% (v/v) FBS and 5% (v/v) newborn calf serum (Invitrogen). The cells were regularly sub-cultured before the confluence.

*Cell viability assay*

Both HepG2 and Balb/3T3 cells were seeded in the complete culture medium into a 96-well plate at $2 \times 10^4$ cells/0.2 mL/well. After overnight stabilization, the cells were treated in serum-free medium with 0.1% (v/v) DMSO (control), 1 µM sanguinarine or 1.5% (v/v) Triton X-100 (positive controls), or with 1.56–100 µM tested compounds **9** and **13** in 0.1% (v/v) DMSO. After 24 h of treatment, cell viability was determined by an MTT reduction assay. The cells were washed with phosphate-buffered saline and incubated for 2 h at 37 °C in a serum-free medium containing 0.5 mg/mL 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT; Sigma). The medium was then removed and the cells containing formazan produced by active mitochondria were solubilized in DMSO/25% (w/w) $NH_4OH$ (99:1; v/v). The absorbance at 540 nm was measured in a Tecan Infinite M200 Pro spectrophotometric plate reader (Tecan, AT) and used for calculating relative cell viability, where cells treated with DMSO alone represented 100% viability and cells treated with Triton X-100 represented 0% viability.

*Statistical analysis*

Results were expressed as means ± SD of three experiments. The differences in mean values were analyzed by Student´s *t*-test. A *p* value equal to or less than 0.05 was considered statistically significant.

**Results**

After 24 h of exposure, compound **9** at concentrations between 1.56 and 100 µM caused only small changes in the viability of human hepatoma HepG2 cells. As shown by the MTT assay, the viability of HepG2 cells reached 82–98%. Under the same conditions, compound **9** increased the viability of mouse fibroblasts Balb/3T3 in a dose-dependent manner. At the concentration of 100 µM, the viability of Balb/3T3 cells reached 138%. We conclude that compound **9** does not show a significant cytotoxic effect. At the same experimental conditions, the cell treatment with compound **13** had no cytotoxic effect on Balb/3T3 cells. The viability of HepG2 cells was weakly decreased by compound **13**, but the average viability ($n$ = 3) did not decrease under 85%.

Under the same conditions, 1 µM sanguinarine (a cytotoxic alkaloid used as a positive control) decreased the viability of Balb/3T3 and HepG2 cells to 20% and 41%, respectively (data not shown).

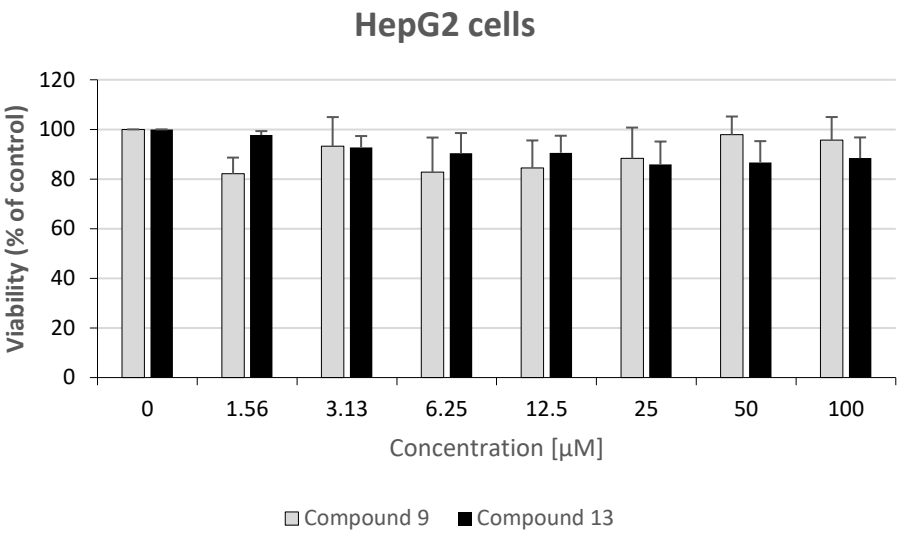



**Figure S31A.** Cytotoxicity assay with HepG2 cell line and compounds **9** and **13**.

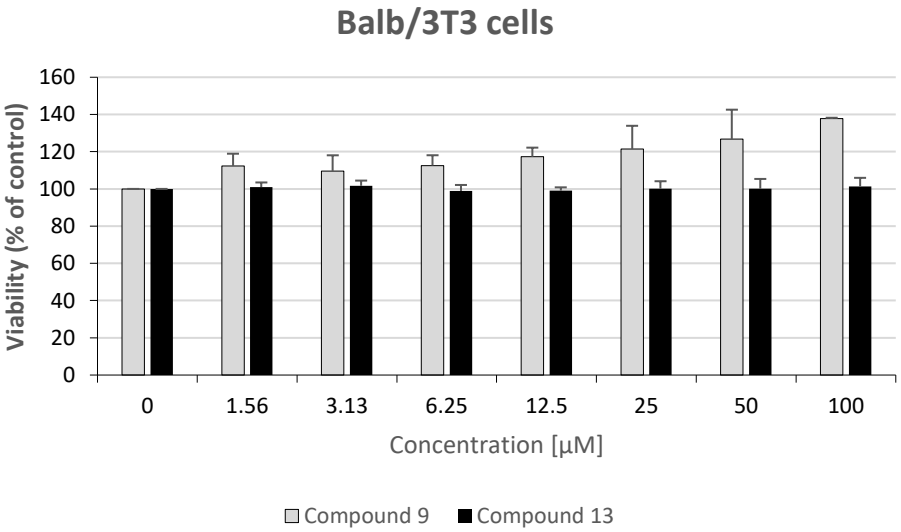



**Figure S31B.** Cytotoxicity assay with Balb/3T3 cell line and compounds **9** and **13**.

## 7. Experiments with murine neural cells

All experiments on animals and cells described in this work received approval of the Internal Review Board of the Ethical Committee of the School of Medicine, University of Zagreb, HR: 380-59-10106-17-100/27 received on 26.01.2017.

To quantify changes in the levels of glycosylation, we used neuronal astrocyte cultures obtained obtained from mouse neural stem cells. Neural stem cells were isolated from the telencephalic wall of 14-days-old mice embryos, and then grown in suspension in the proliferation medium composed of DMEM-F12+GlutaMAX (Gibco, ThermoFisher Scientific, Inc., Waltham, MA, USA), 1% Pen/Strep (Gibco), 5 mM Hepes (Sigma-Aldrich, St. Louis, MO, USA), supplemented with 1% N2 (Gibco), 2% B27 (Gibco) and growth factors comprising 20 ng/mL EGF, 10 ng/mL FGF-basic. As cells multiplied, they formed neurospheres, which were then dissociated when reaching 150-200 μm in diameter. For the experiment, cells of passage 4 (P4) were seeded for differentiation on poly-D-lysine (50 μg/mL, Sigma) and laminin (10 μg/mL, Sigma-Aldrich, St. Louis, MO, USA) coated wells in medium for differentiation (the same as proliferation medium but without growth factors, with addition of 1% heat-inactivated FBS (Gibco) and 2% of B27 plus (Gibco) instead of B27). After 4 days of growth in differentiation medium, the medium was replaced by Neurobasal medium (Gibco). Neurobasal medium was exchanged for a fresh one every 3 days. On day 10 of differentiation, when cells were differentiated and were expressing markers of mature neurons (MAP22, β3-tubulin), and astrocytes (GFAP), they were treated with inhibitor **13** (0.1 nM, 100 nM), and thiamet-G (100 nM) for 12 h.

After 12 h of treatment, proteins were extracted from treated cell cultures using RIPA lysis buffer and concentration was measured using Bradford reagent. 20 μg of proteins were loaded into each well. They were separated on 12% stain-free polyacryamide gel and transferred onto a PVDF membrane. Membranes were blocked with 5% low-fat milk for 1 h at room temperature and incubated with anti-*O*-linked *N*-acetylglucosamine antibody (1:1000, mouse IgG; abcam 2739) at 4 °C overnight. After washing steps were done, membranes were incubated with horseradish peroxidase-conjugated anti-mouse IgG (1: 150 000, abcam, ab6728) for 60 min followed by detection of immunolabeled bands using Supersignal West Femto Maximum Substrate (ThermoFisher). Chemiluminescent signals were detected using Bio-Rad ChemiDoc MP imager (Bio-Rad Laboratories, USA). Blots were quantified and normalized to the total protein amount using Image Lab 6.0.1 (Bio-Rad Laboratories, USA).

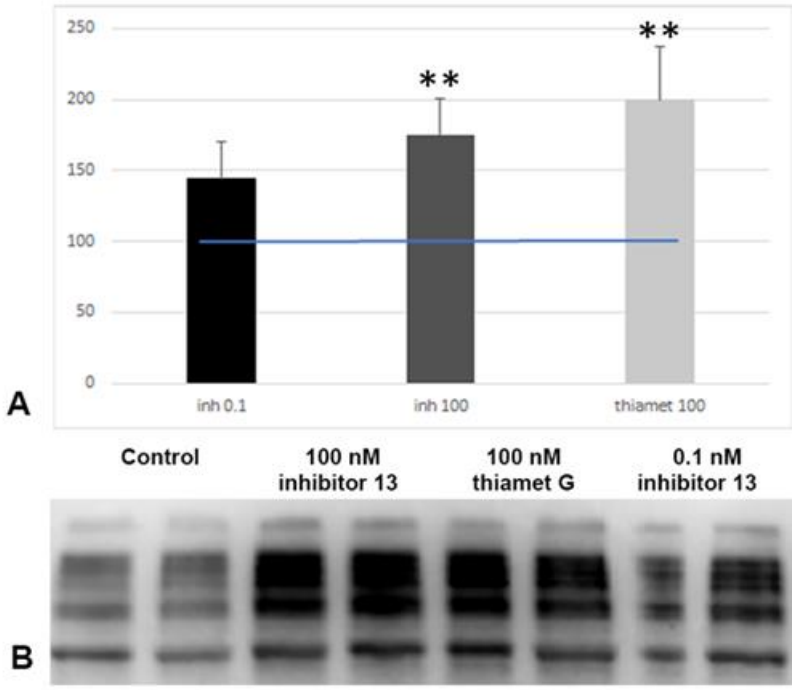
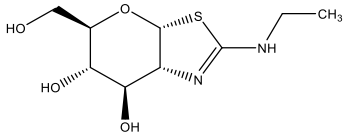
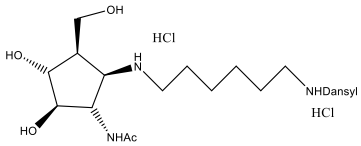
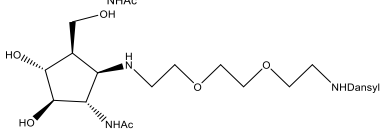
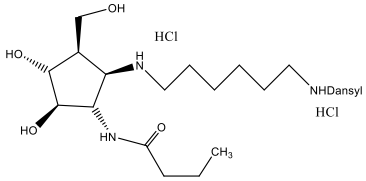
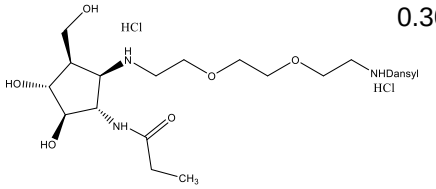
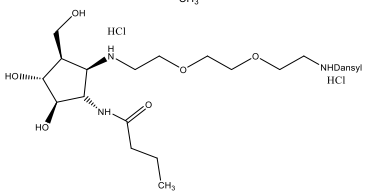
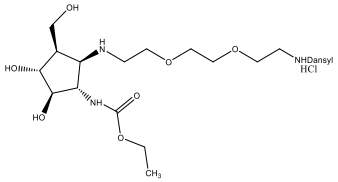



**Figure S32. A.** Increase in *O*-GlcNAcylation in mouse neuronal-astrocyte cultures. Inhibitor **13** (inh; 0.1 nM or 100 nM) increased protein *O*-GlcNAcylation to 1.44-fold or to 1.75-fold, respectively, compared with non-treated control cells. For comparison, 100 nM Thiamet-G increased protein *O*-GlcNAcylation to 2-fold compared with non-treated control cells. This increase was statistically significant ($P < 0.01$) for both inhibitors. **B.** Representative western blot visualizing levels of *O*-GlcNAcylation.

## 8. Calculated ADME and BBB parameters

Table S1. Theoretical ADME and BBB parameters of the OGA inhibiors calculated by ACD/Percepta 14.52.0 software

| Comp. | Structure | LogP | p*K*a acid | p*K*a base | Fraction ubound plasma[a] | LogPS [b] | LogBB [c] | Log (PS*fu)[d] |
|---|---|---|---|---|---|---|---|---|
| Thiamet-G |  | -0.57 | 13.17 | 3.8 | 0.57 | -3.5 | -.21 | -3.5 |
| **8** |  | 1.03 | 11.02 | 9.45 | 0.15 | -4.5 | -0.60 | -4.7 |
| **9** |  | -0.12 | 10.02 | 7.69 | 0.15 | -4.8 | -0.76 | -4.9 |
| **10** |  | 1.81 | 11.02 | 9.49 | 0.12 | -4.1 | -0.45 | -4.6 |
| **11** |  | 0.30 | 10.02 | 7.74 | 0.14 | -4.6 | -0.75 | -4.7 |
| **12** |  | 0.45 | 10.02 | 7.74 | 0.12 | -4.5 | -0.78 | -4.6 |
| **13** |  | 0.78 | 10.02 | 7.69 | 0.14 | -4.4 | 0.68 | 4.6 |

[a] Unbound fraction in plasma

[b] Rate of brain penetration

[c] Extent of brain penetration

[d] Brain/plasma equilibration rate

http://perceptahelp.acdlabs.com/help_v2020/index.php/BBB_Permeability

## 9. Molecular modelling

Docking of inhibitor 13 to human OGA was performed in the crystal structure of 5m7t with PugNAc inhibitor [18]. The structure of the inhibitor was built and minimized in YASARA [19]. Part of the disordered loop (residues 674-675) above the active site was completed using YASARA. Other inhibitors co-crystallized with hOGA were also used for docking validation - Thiamet G (5m7s [18]) and the pyrrolidine derivative VU347 (5m7u [18]). Docking was performed using Glide flexible docking (Schrödinger software [20]).

The calculated XP binding values [21] are listed in Table S2. For compound **13**, alternative possible orientations of the dansyl group were identified (with low scores), while the cyclopentane group is similarly placed in the active site (Figure S34).

Binding score of both poses of dansyl inhibitors are lower than those of known compounds (Table S2). The cyclopentane moiety forms hydrogen bonds with residues D285, N313, G67, N380, D174 and hydrophobic interactions with Y219. Another active part of the molecule, mainly involved in the stabilization of the dansyl group, is the sulfonamido group. It forms hydrogen bonds with Y69 in pose 1 and with R682 in pose 2. The dansyl group in pose 1 is stabilized by hydrophobic interactions with F625, T626. In pose 2, the dansyl moiety is stabilized by hydrophobic interactions with S649, S652 and W679 and by pi-pi stacking with W679. It is important to note that W679 belongs to a disordered loop and has a different structure in crystallized complexes with different compounds (namely pdf 5m7t and 5m7u).

Table S2. Binding Glide XP scores of inhibitors:

| Inhibitor/pdb source | Binding score [kJ/mol] |
|---|---|
| Thiamet G/5m7s | -26.97 |
| PugNAc/5m7t | -29.2 |
| Pyrrolidine derivative VV347/5m7u | -33.82 |
| Compound **13**, pose1 | -40.74 |
| Compound **13**, pose 2 | -35.57 |

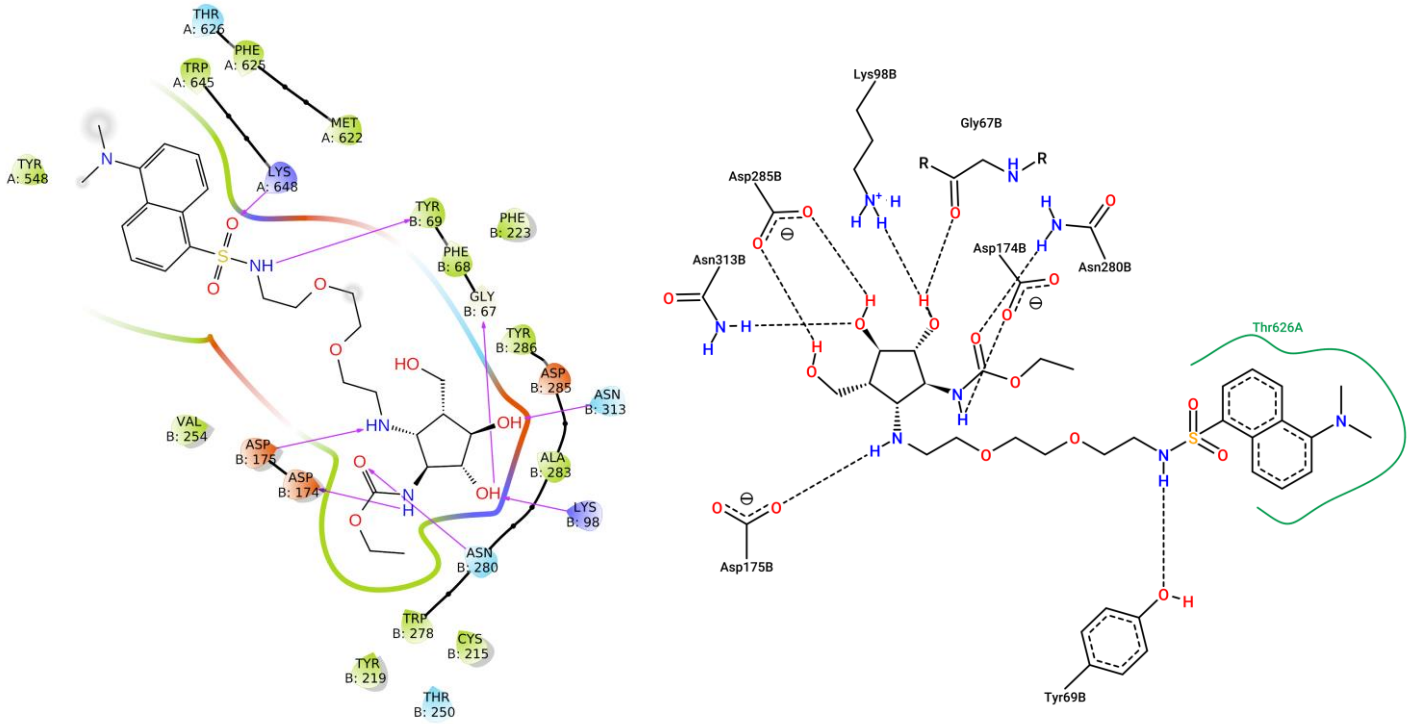



**Figure S33.** Interaction diagram for pose 1 of compound **13**. Amino acid residues within 3 Å from docked inhibitors are shown. Catalytical AA – ASP175 and ASP 174. Right - hydrophobic interaction is schematically shown by green lines and interaction residues are labeled by green color.

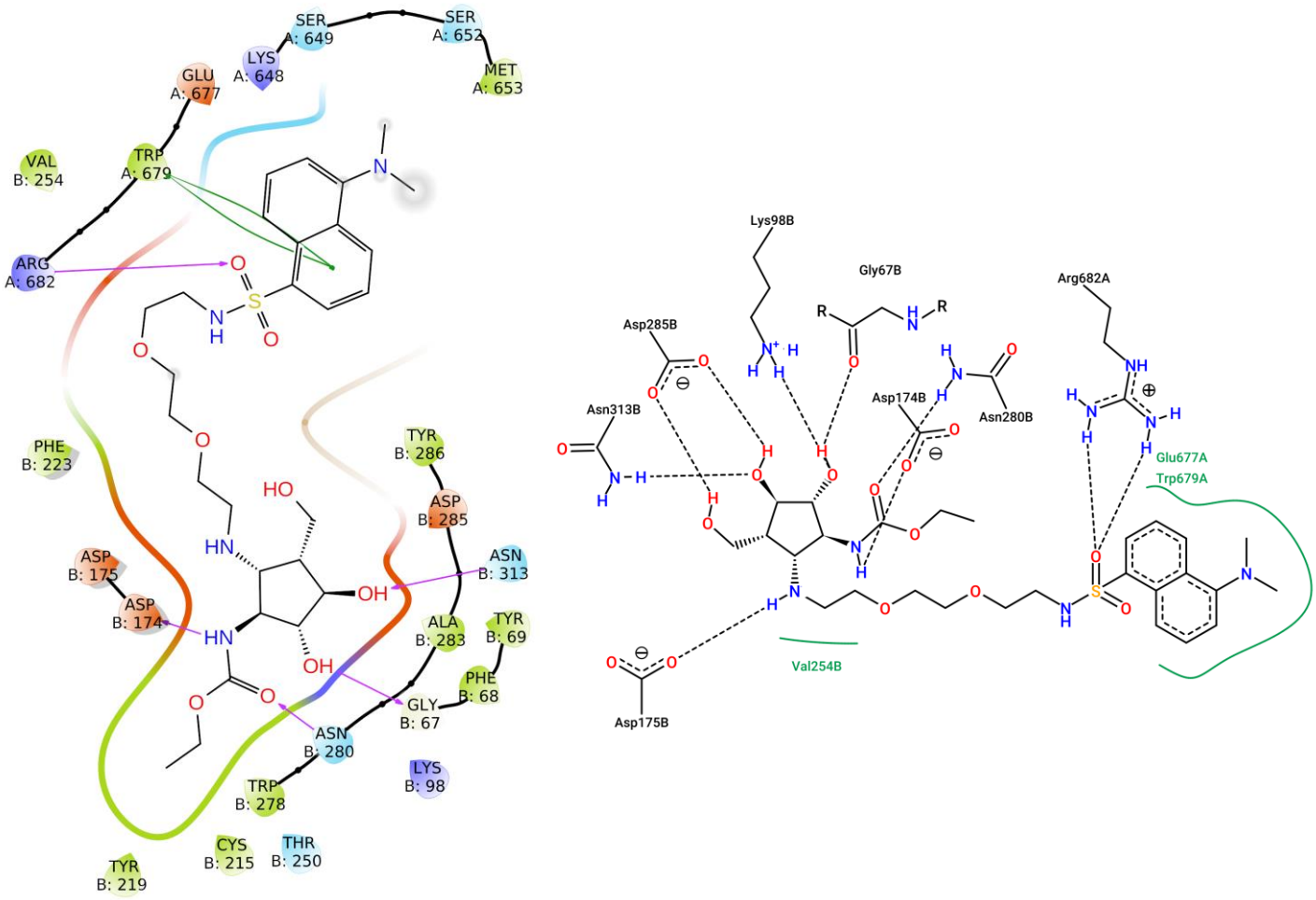



**Figure S34** Interaction diagram for pose 2 of compound **13**. Amino acid residues within 3 Å from docked inhibitors are shown. Right - hydrophobic interaction is schematically shown by green lines and interaction residues are labeled by green color. This pose 2 clearly demonstrates π-π interaction of dansyl with Trp679 and a larger substrate pocket closed by Tyr219, which is typical for OGA and that differentiates this enzyme from HexB. The size of this pocket and the length of the acylamido-substituent are instrumental for inhibitor selectivity.

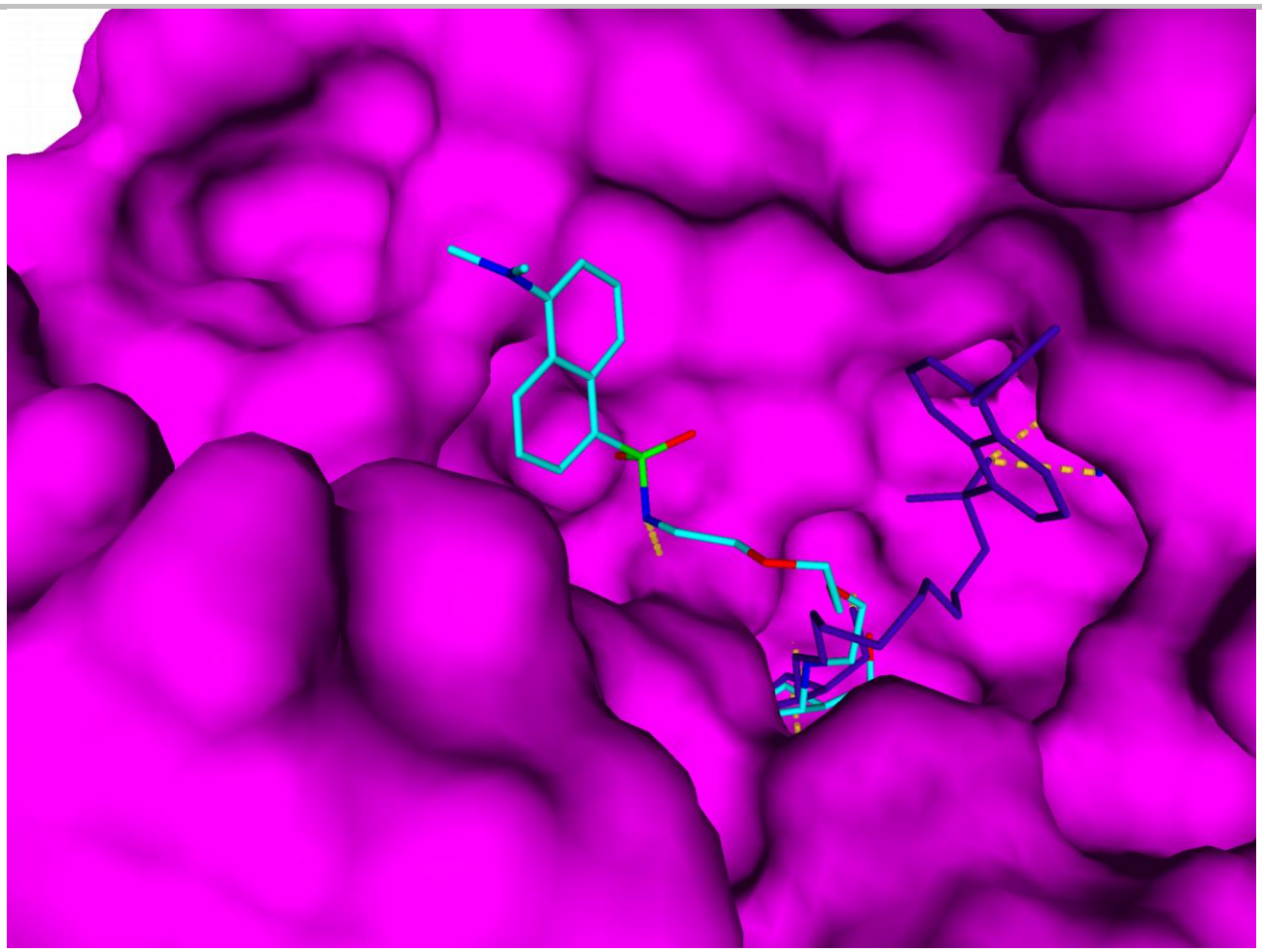


**Figure S35.** Position of the alternative docked poses in the active site. Pose 1 is colored by element colors, pose2 (alternative) – by dark violet. Protein is represented by surface (magenta). Hydrogens are hidden, hydrogen bonds are yellow dotted lines.

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