Concise syntheses of selective inhibitors against α-1,3-galactosyltransferase†

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Several iminosugar-based uridine diphosphate galactose (UDP-Gal) mimetics **1–4** including D- and L-epimers were designed and synthesized by concise routes, and these synthetic compounds were evaluated for the inhibition of α-1,3- and β-1,4-galactosyltransferases *in vitro*. The experimental data demonstrated that L-epimer **2** displayed the strongest inhibitory activity with moderate selectivity against α-1,3-galactosyltransferase.

Introduction

Oligosaccharides which are attached to proteins and lipids on cell surfaces play pivotal roles in many important molecular recognition processes such as bacterial and viral infections, immune response, cell growth, cell–cell adhesion in inflammation and metastasis, and many other intercellular communication and signal transductions.[1] Glycosyltransferases as the oligosaccharide-synthesizing enzymes have been actively studied.[2] Selective inhibitors against glycosyltransferases may lead to the discovery of new therapeutic agents. The synthetic inhibitors of glycosyltransferases known to date involve acceptor analogues,[3] donor sugar nucleotide analogues,[4,5] or transition-state analogues[6,7] including bisubstrate[8] and trisubstrate analogues.[9]

We have chosen α-1,3-galactosyltransferase (α1,3GalT) as the target enzyme because of its biochemical importance in xenotransplantation.[10] α1,3GalT catalyzes the transfer of galactose from UDP-galactose to an acceptor with the retention of the anomeric configuration of the galactose moiety transferred.[11,12] α1,3GalT is an enzyme expressed on the cell surface of most mammals including primates and New World monkeys, but not humans, apes, and Old World monkeys.[13] This enzyme leads to the Galα1,3Galβ1,4GlcNAc epitope, which can react with about 1% of circulating endogenous antibodies in species lacking this enzyme.[14] It will cause the hyperacute rejection response when pig organs are transplanted into human.[15] Although selective inhibitors against α1,3GalT are very important to xenotransplantation, only limited success has been achieved so far.[16] To search for better inhibitors, herein we report the syntheses of several iminosugar-based UDP-galactose mimetics **1–4** (Fig. 1).

Iminosugars were chosen as the galactose mimetics since they could mimic the transition state of the enzymatic reaction.[17] On the other hand, the *O*-sulfamoylamide group[18] was used as the surrogate of pyrophosphate in UDP-galactose because this structure is more stable under physiological conditions. To check the effect of configurations of iminosugars on inhibitory activities, compounds **1** (D-epimer) and **2** (L-epimer) were designed. Compound **3** was designed to examine whether an increase of the carbon atom number of the acyl group can improve the inhibitory ability.

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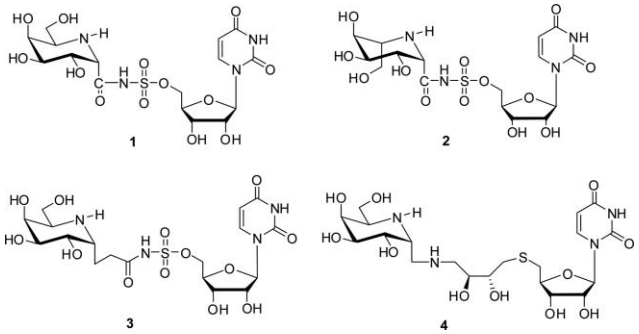
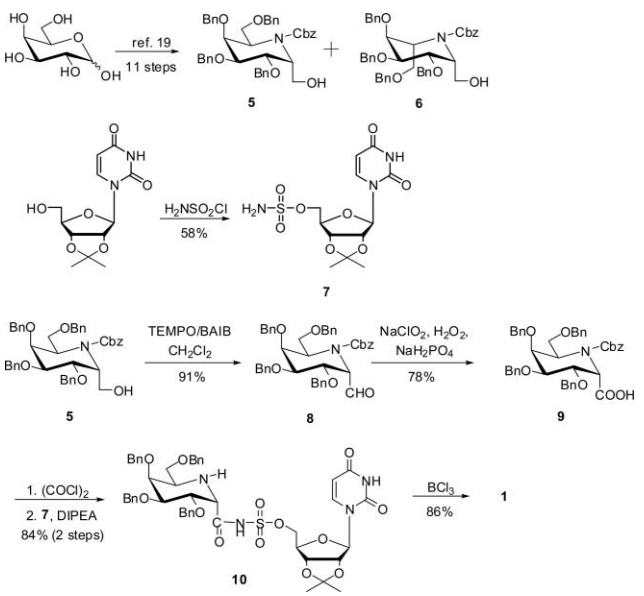


Fig. 1 The structures of designed target molecules **1–4**.

Compound **4** was designed because the vicinal diol moiety[16a] was proved to benefit inhibition against α1,3GalT.

Results and discussion

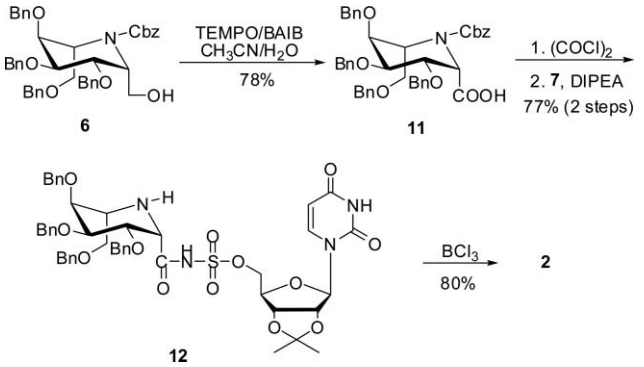
The preparation of UDP-galactose mimetic **1** is shown in Scheme 1. The key materials iminosugar derivatives **5** and **6** were obtained from D-galactose according to the procedure described previously.[19] Treatment of commercially available



Scheme 1 Synthesis of UDP-galactose mimetic **1**.

2′,3′-isopropylidene-uridine with sulfamoyl chloride (H_2NSO_2Cl) in dry pyridine gave the desired *O*-sulfamoylamide **7** in 58% yield.[20] The alcohol **5** was oxidized by 2,2,6,6-tetramethyl-1-piperidinyloxy (TEMPO) free radical/(diacetoxyiodo)benzene (BAIB) or pyridinium chlorochromate (PCC)[21] to provide aldehyde **8** in high yield, which was readily converted to the acid **9** in 78% isolated yield by treatment with $NaClO_2/NaH_2PO_4$ in the presence of 30% hydrogen peroxide.[19] Next, the key coupling reaction of **9** and **7** was carried out. Initially, when the coupling reagents (1*H*-benzotriazole-1-yl)-1,1,3,3-tetramethyluronium hexafluorophosphate(HBTU)/diisopropyl ethylamine (DIPEA) or *N*-hydroxysuccinimide (HOSu)/1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) were employed, no desired product was obtained. There was still no reaction when compound **9** was fully deprotected which was followed by the coupling with **7** under the above-mentioned conditions. Eventually, the acid **9** was reacted with $(COCl)_2$ to afford the carbonyl chloride intermediate, which was successfully converted to the coupling product **10** with the benzyloxycarbonyl group deprotected in satisfactory yield (84%) by the treatment with **7** in the presence of DIPEA. Full deprotection of compound **10** was one of the critical steps of the synthetic route. When the $NaBrO_3/NaS_2O_4$ system[22] was used to cleave the benzyl groups, no desired product was produced. Catalytic hydrogenolysis was also used to remove the benzyl groups, but the double bond in compound **10** was always reduced in spite of many efforts. Finally, this problem was successfully solved by using BCl_3 as the deprotection reagent.[23] All benzyl groups and the isopropylidene group were deprotected in one step and the target compound **1** was obtained in 86% isolated yield in the form of hydrochloride salt.

The preparation of mimetic **2** is displayed in Scheme 2. The alcohol **6** was oxidized by TEMPO/BAIB. It was found that different oxidation products were obtained by the use of different solvents. The alcohol **6** was able to be directly converted to the acid **11** in 78% isolated yield in acetonitrile–water mixed solvent, whereas only the aldehyde product was collected in 90% yield when dichloromethane was used as the solvent. Subsequently, similar to the preparation of **10**, the coupling reaction of **11** and **7** afforded compound **12** in 77% yield. Full deprotection of **12** by BCl_3 solution achieved the target molecule **2** in satisfactory yield. It should be noted that the control of reaction time was very important, a long reaction time makes the product decompose

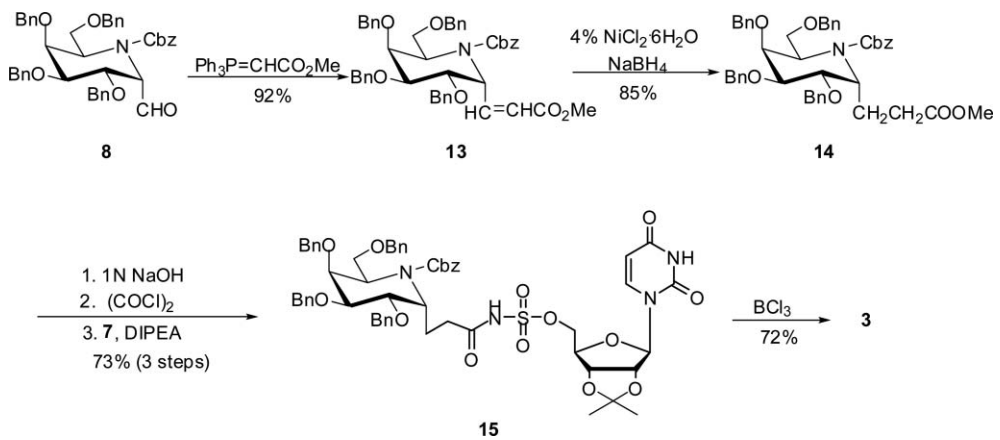


Scheme 2 Synthesis of UDP-galactose mimetic **2**.

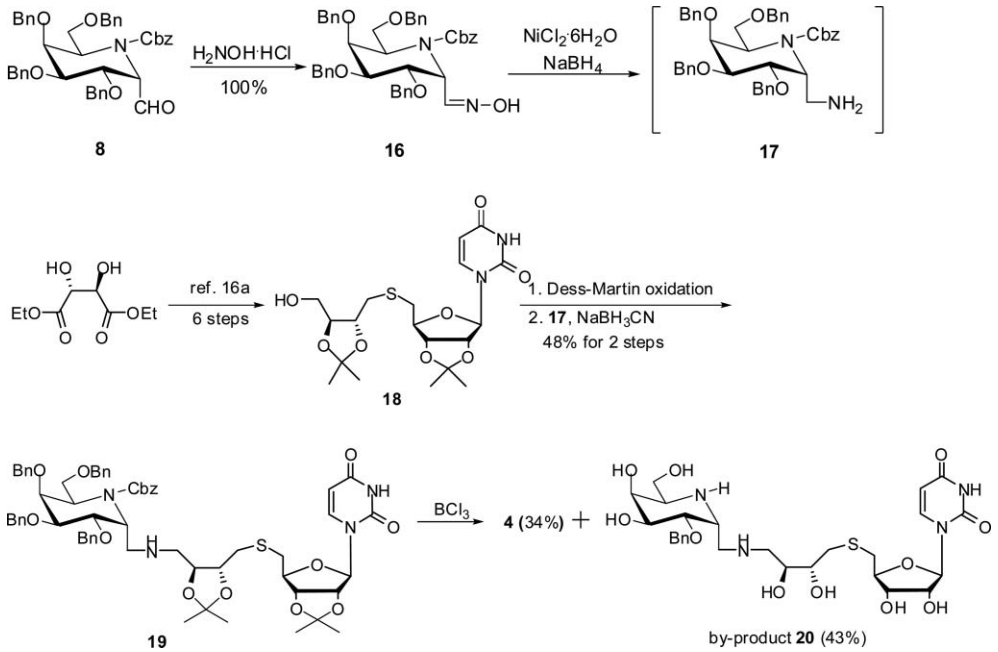
and a short reaction time leads to at least one benzyl group remaining.

The preparation of UDP-galactose mimetic **3** is shown in Scheme 3. Compound **8** underwent Wittig reaction with $(EtO)_2P(O)CH_2CO_2Et$[24] in the presence of NaH to provide the product, but the yield was not satisfactory (less than 70%). The decomposition of aldehyde **8** caused by NaH might be the major reason. Therefore, an alternative reagent $Ph_3P{=}CHCO_2Me$[25] was used for the reaction, in which the use of NaH was avoided, and compound **13** was afforded in excellent yield (92%) as a chromatographically inseparable mixture of *Z* and *E* isomers. The double bond in **13** was selectively reduced by 4% $NiCl_2{\cdot}6H_2O$ in the presence of $NaBH_4$, yielding the saturated ester **14**. By treatment of **14** with 1.0 M NaOH aqueous solution at 60 °C, the methyl ester **14** was saponified and the crude product was directly reacted with $(COCl)_2$ followed by the coupling with *O*-sulfamoylamide **7** in the presence of DIPEA, successfully providing compound **15** in good yield (73% for three steps). Global deprotection of **15** under the above-mentioned conditions afforded the target molecule **3**.

The synthesis of UDP-galactose mimetic **4** is exhibited in Scheme 4. The aldehyde **8** was readily converted to the oxime **16** in quantitative yield by treatment with hydroxylamine hydrochloride.[21] Reduction of **16** using $NiCl_2{\cdot}6H_2O/NaBH_4$ produced the amine **17** which was used for the next reaction. On the other hand, starting from commercially available L-tartaric acid diethyl ester, the uridine derivative **18** was synthesized *via* six steps according to the reported procedure.[16a] Using the Dess–Martin



Scheme 3 Synthesis of UDP-galactose mimetic**3**.



Scheme 4 Synthesis of UDP-galactose mimetic **4**.

reagent compound **18** was oxidized to the aldehyde, which was then coupled with the amine **17** by way of a reductive amination approach, providing **19** in moderate yield (48% for two steps). Deprotection of **19** using BCl_3 afforded the target compound **4** in 34% yield and the by-product **20** with one benzyl group intact in 43% yield. The structure of compound **20** was identified based on the analyses of the 1D- (^1H, ^{13}C) and 2D- (COSY, HSQC, HMBC) NMR spectra. Both increasing the amount of BCl_3 and prolonging the reaction time failed to improve the yield of the target compound **4**. Besides, when compound **20** was further treated with BCl_3 in the hope of getting **4**, there was no reaction and the material was fully recovered.

The synthetic compounds **1–4** and by-product **20** were evaluated *in vitro* for the inhibition of α-1,3-galactosyltransferase (α1,3GalT)[26,27] and β-1,4-galactosyltransferase (β1,4GalT)[28,29] by using radiolabeled UDP-Gal as the donor and *N*-acetyllactosamine (LacNAc) or *N*-acetyl-D-glucosamine(GlcNAc) as the acceptors (see Experimental section for details). The results are shown in Table 1. It was found that all the compounds showed some inhibitory activities and compound **2** displayed the strongest inhibitory ability (IC_{50} = 320 μM) (Fig. 2) among the five synthetic compounds. It seemed that compounds **1**, **2**, **4** and **20** showed moderate selectivity for inhibition. The experimental data showed that the addition of the uridine moiety improved the inhibition by comparing the inhibition of compound **2** (78% inhibition) with that of the fully-deprotected product of **11** (5.5% inhibition at 1.0 mM against α1,3GalT). Comparing the inhibition of D-epimer **1** (63.5% inhibition) with that of L-epimer **2** (78% inhibition), it was suggested that the configuration of the hydroxymethyl group has effects on the inhibition against α1,3GalT. Prolonging the carbon chain of the acyl group decreased the inhibitory activity based on the fact that compound **1** (63.5% inhibition at 1.0 mM against α1,3GalT) exhibited better inhibition than compound **3** (23.5% inhibition at 1.0 mM against α1,3GalT). Comparing the inhibition of compound **4** with that of **20**, it was clear that the existence of the benzyl group can improve the inhibitory activity against β1,4GalT, suggesting that the hydrophobic character may be important to the inhibition.

Table 1 Inhibition of the synthetic compounds against α-1,3- and β-1,4-galactosyltransferases

	α1,3GalT		β1,4GalT	
compound	concentration	inhibition	concentration	inhibition
1	1.0 mM	63.5%	1.0 mM	36%
	50 μM	NI	50 μM	NI
2	IC_{50} = 320 μM		1.0 mM	38%
			50 μM	18%
3	1.0 mM	23.5%	1.0 mM	16%
	50 μM	NI	50 μM	12%
4	1.0 mM	21%	1.0 mM	6%
	50 μM	NI	50 μM	NI
20	1.0 mM	25%	1.0 mM	28%
	50 μM	NI	50 μM	22%

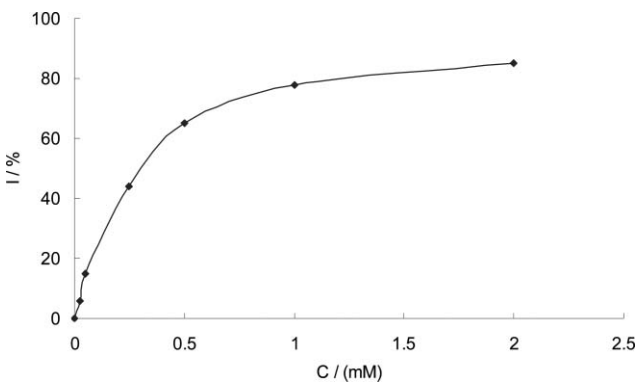


Fig. 2 Inhibition of α1,3GalT by compound **2**: I = inhibition, C = concentration of inhibitor.

Conclusion

In summary, we designed and synthesized four stable iminosugar-based UDP-Gal mimetics in high yields using concise synthetic routes. These compounds were evaluated *in vitro* for the inhibition of α-1,3- and β-1,4-galactosyltransferases. It was clear that the L-epimer **2** displayed the strongest inhibitory ability (IC_{50} = 320 μM) with moderate selectivity against α-1,3-galactosyltransferase. In addition, prolonging the carbon chain of the acyl group decreased the inhibitory activity. The experimental data also suggested that the hydrophobic character may be important to the inhibition activity against β-1,4-galactosyltransferase. The disclosed information may benefit the discovery of more potent and selective galactosyltransferase inhibitors.

Experimental

General

All chemicals were purchased and used without further purification. Tetrahydrofuran (THF) was distilled over sodium/benzophenone, methylene chloride (CH_2Cl_2) over calcium hydride. All reactions were carried out under an argon atmosphere with dry, freshly distilled solvents under anhydrous conditions, unless otherwise noted. Reactions were monitored with analytical TLC on silica gel 60-F_{254} precoated aluminium plates and visualized under UV (254 nm) and/or by staining with acidic ceric ammonium molybdate. Column chromatography was performed on silica gel (35–75 μm). NMR spectra were recorded on a Varian VXR-300M or Varian INOVA-500M spectrometer. Mass spectra were recorded using a PE SCLEX QSTAR spectrometer. Elemental analysis data were recorded on PE-2400C elemental analyzer. α-1,3-Galactosyltransferase recombinant from *E. coli* (0.15 U mL^{-1}) and β-1,4-galactosyltransferase I human (14.6 U g^{-1}), recombinant from *Saccharomyces cerevisiae*, were purchased from Sigma. Uridine 5′diphosphate galactose-[6-^{3}H] was purchased from American Radiolabeled Chemicals (specific activity: 20 Ci $mmol^{-1}$, concentration: 1 mCi mL^{-1}). OPTi-Fluor scintillation cocktail was purchased from Perkin Elmer. The scintillation counter used was the Packard Tri-Carb 2100 TR. Other reagents were from commercial sources.

2′,3′-*O*-Isopropylidene-5′-*O*-sulfamoyluridine (7). 2′,3′-*O*-Isopropylidene-uridine (570 mg, 2.0 mmol) was suspended in CH_2Cl_2 (20 mL) and dry pyridine (0.57 mL). Sulfamoyl chloride (463 mg, 4.0 mmol) was added to the stirred reaction mixture. After stirring for one day at 40 °C, the solvent was removed and the residue was purified by column chromatography on silica gel (CH_2Cl_2–methanol 80 : 1 to 60 : 1) to provide **7** (420 mg, 58%) as a white solid. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.20 (s, 3H), 1.49 (s, 3H), 4.15 (dd, J = 2.5, 11.5 Hz, 1H), 4.22–4.25 (m, 2H), 4.80 (dd, J = 3.5, 6.5 Hz, 1H), 5.06 (dd, J = 1.5, 6.5 Hz, 1H), 5.64 (dd, J = 2.0, 8.0 Hz, 1H), 5.82 (d, J = 2.0 Hz, 1H), 7.60 (s, 2H), 7.71 (d, J = 4.0 Hz, 1H), 11.44 (br.s, 1H). The ^{1}H NMR data were in good agreement with those reported.[20]

(2,3,4,6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)aldehyde (8). To a solution of**5** (307 mg, 0.45 mmol) in CH_2Cl_2 (20 mL) was added BAIB (260 mg, 0.81 mmol) and TEMPO (63 mg, 0.41 mmol). The reaction mixture was stirred for 36 h at 40 °C. The solvent was removed under reduced pressure, the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 18 : 1 to 15 : 1) to provide **8** (278 mg, 91%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.67 (br.s, 1H), 3.81–3.92 (m, 3H), 3.99 (t, J = 10.0 Hz, 1H), 4.09 (d, J = 3.0 Hz, 1H), 4.38–4.61 (m, 8H), 4.75–4.85 (m, 1H), 4.99 (d, J = 12.0 Hz, 1H), 5.17 (d, J = 12.0 Hz, 1H), 7.16–7.36 (m, 25H), 9.76 (s, 1H). The data were in good agreement with those reported.[19]

(2,3,4,6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)formic acid (9). To a solution of aldehyde **8** (68.0 mg, 0.10 mmol) in acetonitrile (1.5 mL), sodium dihydrogen phosphate in water (1.5 mL, 100 mg mL^{-1}), and 30% H_2O_2 (0.38 mL) was added dropwise a solution of sodium chlorite (3.0 mL, 130 mg mL^{-1}) in water. After stirring for 10 h at room temperature, the aqueous solution was extracted with ethyl acetate. The combined organic layers were dried (Na_2SO_4) and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 3 : 1 to 1 : 1) to yield **9** (54.2 mg, 78%) as a yellow oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.55 (dd, J = 8.0, 3.0 Hz, 1H), 3.80–4.06 (m, 4H), 4.12 (dd, J = 7.0, 4.5 Hz, 1H), 4.28–4.44 (m, 3H), 4.51 (d, J = 11.5 Hz, 1H), 4.57 (d, J = 11.5 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.63–4.70 (m, 2H), 4.78 (br., 1H), 4.84 (d, J = 12.0 Hz, 1H), 5.02 (d, J = 12.5 Hz, 1H), 7.11–7.24 (m, 25H). The ^{1}H NMR data were in good agreement with those reported.[19]

2′,3′-*O*-Isopropylidene-5′-*O*-(2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)formamidosulfamoyluridine (10). To a solution of **9** (93 mg, 0.13 mmol) in dry toluene (6.0 mL) was added $(COCl)_2$ (95 μL, 1.30 mmol). The reaction mixture was stirred for 10 h at 40 °C. The solvent was removed under reduced pressure, the residue was dissolved in CH_2Cl_2 (6.0 mL). To this solution, compound **7** (70 mg, 0.20 mmol) and DIPEA (46 μL, 0.26 mmol) were added. After stirring overnight at room temperature, the solvent was removed and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc/methanol 2 : 1 : 0.08 to 2 : 1 : 0.1) to provide **10** (102 mg, 84%) as a colorless oil. ^{1}H NMR (500 MHz, DMSO): δ 1.26 (s, 3H), 1.46 (s, 3H), 3.69–3.71 (m, 4H), 3.95–3.98 (m, 2H), 4.09 (dd, J = 5.0, 10.5 Hz, 1H), 4.14–4.17 (m, 2H), 4.21 (dd, J = 4.5, 9.0 Hz, 1H), 4.43 (d, J = 12.5 Hz, 1H), 4.50 (d, J = 12.5 Hz, 1H), 4.51 (d, J = 12.0 Hz, 1H), 4.52 (d, J = 11.5 Hz, 1H), 4.54 (d, J = 12.0 Hz, 1H), 4.58 (d, J = 12.0 Hz, 1H), 4.62 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 12.0 Hz, 1H), 4.76 (dd, J = 3.5, 6.0 Hz, 1H), 4.94 (dd, J = 2.5, 6.5 Hz, 1H), 5.61 (d, J = 8.0 Hz, 1H), 5.83 (d, J = 2.5 Hz, 1H), 7.24–7.37 (m, 20H), 7.77 (d, J = 8.0 Hz, 1H), 8.86 (br.s, 2H), 11.40 (br.s, 1H). ^{13}C NMR (125 MHz, DMSO): δ 25.14, 26.97, 54.14, 67.38, 70.74, 72.04, 72.30, 72.62, 80.73, 83.46, 84.16, 91.74, 101.93, 113.18, 127.27, 127.45, 127.65, 128.09, 128.17, 128.24, 128.30, 138.15, 142.42, 150.31, 163.19. HRMS (ESI, positive) Calcd for $C_{47}H_{53}N_4O_{13}S$ [(M + H)$^+$] 913.3324, found: 913.3328.

5′-*O*-(1,5-Dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)formamidosulfamoyluridine (1). To a solution of **10** (33 mg, 0.04 mmol) in dry CH_2Cl_2 (3.0 mL) was added BCl_3 in hexane (1 M solution, 0.48 mL, 0.48 mmol). The reaction mixture was stirred for 3 h at 0 °C, and then the solids formed were

dissolved by the addition of MeOH (1.0 mL) and water (1.0 mL). The solvent was removed and the residue was purified by flash column chromatography on C18-reverse phase silica gel (H_2O as eluent), providing **1** (17 mg, 86%) as a white solid in the form of hydrochloride salt. ^{1}H NMR (500 MHz, D_2O): δ 3.81–3.84 (m, 1H), 3.94–4.02 (m, 3H), 4.25–4.28 (m, 2H), 4.31–4.35 (m, 4H), 4.40 (dd, J = 1.5, 11.5 Hz, 1H), 4.48 (d, J = 11.5 Hz, 1H), 5.93–5.95 (m, 2H), 7.81 (dd, J = 1.5, 8.5 Hz, 1H). ^{13}C NMR (125 MHz, D_2O): δ 56.32, 58.00, 58.28, 65.40, 68.37, 69.31, 70.11, 70.50, 74.15, 82.24, 89.85, 103.20, 142.36, 152.37, 166.89, 172.70. HRMS (ESI, positive) Calcd for $C_{16}H_{25}N_4O_{13}S$ [(M + H)$^+$] 513.1133, found: 513.1138.

(2,3,4,6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-L-*galacto*-heptitolyl)formic acid (11). To a solution of **6** (82 mg, 0.12 mmol) in CH_3CN and H_2O (v/v 1 : 1, 20 mL) was added BAIB (98 mg, 0.30 mmol) and TEMPO (19 mg, 0.12 mmol). The reaction mixture was stirred for 24 h at room temperature. The solvent was removed under reduced pressure, and the residue was extracted with EtOAc (3 × 50 mL) and washed with brine (20 mL). The organic layers were combined, dried (Na_2SO_4), filtered, and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 6 : 1 to 3 : 1) to provide **11** (65 mg, 78%) as a yellow oil. ^{1}H NMR (500 Hz, $CDCl_3$) δ 3.54–3.55 (m, 1H), 3.86–3.87 (m, 1H), 3.99 (br.s, 1H), 4.36–4.52 (m, 10H), 4.72–4.80 (m, 2H), 5.10–5.21 (m, 2H), 7.26–7.32 (m, 25H). The ^{1}H NMR data were in good agreement with those reported previously.[19]

2′,3′-*O*-Isopropylidene-5′-*O*-(2,3,4,6-tetra-*O*-benzyl-1,5-dideoxy-1,5-imino-D-*glycero*-L-*galacto*-heptitolyl)formamidosulfamoyluridine (12). Compound **12** was prepared from **11** (20 mg, 0.03 mmol) as described in the preparation of **10**, providing **12** (20 mg, 77%) as a colorless oil.^{1}H NMR (500 MHz, d_6-DMSO): δ 1.26 (s, 3H), 1.46 (s, 3H), 3.70 (d, J = 4.5 Hz, 2H), 3.77 (br.s, 2H), 4.04 (br.s, 1H), 4.08 (dd, J = 5.5, 11.0 Hz, 1H), 4.15 (dd, J = 4.0, 10.5 Hz, 1H), 4.21 (dd, J = 4.0, 8.5 Hz, 1H), 4.31 (d, J = 11.5 Hz, 2H), 4.44 (d, J = 12.0 Hz, 1H), 4.48 (d, J = 12.5 Hz, 2H), 4.55 (d, J = 12.0 Hz, 2H), 4.61 (d, J = 11.5 Hz, 1H), 4.63 (d, J = 11.5 Hz, 1H), 4.67 (d, J = 11.5 Hz, 1H), 4.76 (dd, J = 3.5, 6.0 Hz, 1H), 4.95 (dd, J = 2.5, 6.0 Hz, 1H), 5.61 (dd, J = 1.5, 8.0 Hz, 1H), 5.83 (d, J = 2.5 Hz, 1H), 7.14–7.36 (m, 20H), 7.76 (d, J = 8.5 Hz, 1H), 8.67 (br.s, 2H), 11.40 (d, J = 1.5 Hz, 1H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 25.12, 26.95, 52.17, 58.08, 67.40, 70.33, 72.13, 72.29, 72.58, 80.75, 83.43, 84.15, 91.77, 101.89, 113.15, 127.52, 127.62, 127.79, 127.94, 128.02, 128.14, 128.19, 128.27, 137.86, 142.42, 150.29, 163.15. HRMS (ESI, positive) Calcd for $C_{47}H_{53}N_4O_{13}S$ [(M + H)$^+$] 913.3324, found: 913.3337.

5′*O*-(1,5-Dideoxy-1,5-imino-D-*glycero*-L-*galacto*-heptitolyl)formamidosulfamoyluridine (2). Compound **2** was prepared from **12** (32 mg, 0.04 mmol) as described in the preparation of **1**, providing light yellow solids. The crude product was purified by HPLC (95% water and 5% methanol as eluent), giving **2** (15 mg, 80%) as a white solid in the form of hydrochloride salt after lyophilization. ^{1}H NMR (500 MHz, D_2O): δ 3.18 (br.s, 1H), 3.86 (dd, J = 5.5, 12.0 Hz, 1H), 3.92 (br.s, 2H), 3.95 (dd, J = 2.5, 10.5 Hz, 1H), 4.06 (t, J = 3.5 Hz, 1H), 4.31–4.36 (m, 5H), 4.43 (d, J = 11.0 Hz, 1H), 5.94 (s, 1H), 5.96 (d, J = 4.0 Hz, 1H), 7.84 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, D_2O): δ 55.38, 59.37, 60.16, 64.72, 68.82, 70.21, 70.71, 70.94, 74.18, 82.48, 89.64, 103.23, 142.37, 152.48, 166.97. HRMS (ESI, positive) Calcd for $C_{16}H_{25}N_4O_{13}S$ [(M + H)$^+$] 513.1133, found: 513.1133.

(2,3,4,6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)methyl acrylate (13). To a solution of **8** (170 mg, 0.25 mmol) in dry THF (5.0 mL) was added $Ph_3P{=}CHCOOMe$ (165 mg, 0.50 mmol). The reaction mixture was stirred overnight at room temperature. The reaction was quenched by several drops of NH_4Cl aqueous solution, and the mixture was extracted with EtOAc (3 × 50 mL) and washed with aqueous $NaHCO_3$ (20 mL) and NaCl (20 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 15 : 1 to 13 : 1) to provide **13** (170 mg, 92%) as a colorless oil.^{1}H NMR (500 MHz, $CDCl_3$): δ 3.47 (dd, J = 3.0, 9.0 Hz, 1H), 3.73 (s, 3H), 3.80–3.88 (m, 1H), 4.00–4.07 (m, 3H), 4.19–4.57 (m, 4H), 4.59–4.65 (m, 1H), 4.68 (d, J = 11.5 Hz, 2H), 4.72 (d, J = 12.0 Hz, 2H), 4.78 (d, J = 11.5 Hz, 1H), 4.89 (br.s, 1H), 5.08 (d, J = 7.0 Hz, 1H), 5.20 (d, J = 2.0 Hz, 1H), 5.98–6.03 (m, 1H), 7.18–7.34 (m, 25H). MS-ESI: 742 [M + H$^+$]. Anal. Calcd for $C_{46}H_{47}NO_8$: C, 74.47; H, 6.39; N, 1.89. Found: C, 74.52; H, 6.35; N, 1.88%.

(2, 3, 4, 6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1, 5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)methyl propionate (14). To a solution of **13** (170 mg, 0.23 mmol) in dry CH_2Cl_2 (1.3 mL) and MeOH (8.0 mL) was added 4% solution of $NiCl_2{\cdot}6H_2O$ in MeOH (2.3 mL, 0.39 mmol) at 0 °C. After stirring for 20 min, a portion of $NaBH_4$ (35 mg, 0.92 mmol) was added. The reaction mixture was stirred for another 5 h at room temperature. The reaction was quenched by several drops of HOAc. The solvent was removed and the residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 18 : 1 to 16 : 1) to provide **14** (145 mg, 85%) as a yellow oil. ^{1}H NMR (400 MHz, d_6-DMSO, 70 °C): δ 1.97–2.00 (m, 2H), 2.24–2.27 (m, 2H), 3.52 (s, 3H), 3.63 (br.s, 1H), 3.73–3.82 (m, 2H), 3.91 (br.s, 2H), 4.01 (br.s, 1H), 4.36 (d, J = 12.0 Hz, 2H), 4.42 (d, J = 12.4 Hz, 1H), 4.47 (d, J = 12.0 Hz, 1H), 4.57 (d, J = 12.4 Hz, 1H), 4.61 (d, J = 12.0 Hz, 1H), 4.65 (d, J = 12.0 Hz, 2H), 4.69 (d, J = 8.3 Hz, 1H), 4.86 (d, J = 12.8 Hz, 1H), 5.01 (d, J = 12.4 Hz, 1H), 7.20–7.35 (m, 25H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 18.99, 30.19, 51.17, 53.85, 54.44, 66.48, 67.70, 71.67, 71.88, 71.95, 73.42, 74.29, 76.20, 79.68, 127.28, 127.36, 127.43, 127.69, 128.02, 128.17, 128.24, 129.12, 129.45, 134.54, 136.68, 138.26, 138.48, 138.87, 154.96, 157.00, 173.03. MS-ESI: 766 [M + Na$^+$]. Anal. Calcd for $C_{46}H_{49}NO_8$: C, 74.27; H, 6.64; N, 1.88. Found: C, 74.53; H, 6.87; N, 1.79%.

2′,3′-*O*-Isopropylidene-5′-*O*-(2,3,4,6-tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)-propionamidosulfamoyluridine (15). To a solution of **14** (55 mg, 0.07 mmol) in MeOH (2.0 mL) was added 1 M NaOH aqueous solution (0.28 mL, 0.28 mmol). After stirring for 5 h at 60 °C, a portion of cation exchange resin was added until the pH value was between 5 and 6. After the resin was filtered off, the solvent was removed and the residue was purified by short column chromatography on silica gel (petroleum ether/EtOAc 3 : 1 to 1 : 1) to provide the crude product (51 mg). The product was treated under the conditions as described in the preparation of **10**,

yielding **15** (58 mg, 73% for three steps) as a colorless oil. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.26 (s, 3H), 1.46 (s, 3H), 1.98 (br.s, 2H), 2.27–2.31 (m, 2H), 3.75–3.79 (m, 4H), 3.99–4.05 (m, 2H), 4.22–4.25 (m, 2H), 4.37 (dd, J = 7.0, 10.5 Hz, 3H), 4.47 (dd, J = 4.0, 10.5 Hz, 2H), 4.57 (br.s, 2H), 4.70 (br.s, 4H), 4.79 (dd, J = 4.0, 6.5 Hz, 1H), 5.06 (dd, J = 2.0, 6.5 Hz, 2H), 5.61 (dd, J = 2.5, 8.0 Hz, 1H), 5.80 (d, J = 2.0 Hz, 1H), 7.23–7.35 (m, 20H), 7.70 (d, J = 8.0 Hz, 1H), 11.44 (d, J = 2.0 Hz, 1H), 12.21 (br.s, 1H). ^{13}C NMR (125 MHz, d_6-DMSO): δ 25.01, 26.81, 32.07, 54.42, 71.59, 71.88, 72.02, 74.14, 80.72, 83.53, 84.22, 93.31, 101.81, 113.30, 127.30, 127.47, 127.79, 128.00, 128.13, 128.17, 128.21, 128.27, 138.86, 143.23, 150.29, 163.23, 171.02. HRMS (ESI, positive) Calcd for $C_{57}H_{66}N_5O_{15}S$ [$(M + NH_4)^+$] 1092.4271, found: 1092.4254.

5′-*O*-(1,5-Dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)-propionamidosulfamoyluridine (3). Compound **3** was prepared from **15** (39 mg, 0.04 mmol) as described in the preparation of **1**, providing light yellow solids. The crude product was purified by HPLC (70% water and 30% methanol as eluent), giving **3** (15 mg, 72%) as a white solid in the form of hydrochloride salt after lyophilization. ^{1}H NMR (500 MHz, D_2O): δ 1.91–1.99 (m, 1H), 2.15–2.22 (m, 1H), 2.53–2.67 (m, 2H), 3.60–3.63 (m, 1H), 3.70 (dd, J = 6.5, 11.5 Hz, 1H), 3.87 (dd, J = 3.5, 8.5 Hz, 1H), 3.91–3.97 (m, 2H), 4.11 (dd, J = 4.5, 8.5 Hz, 1H), 4.20 (t, J = 3.0 Hz, 1H), 4.29–4.34 (m, 2H), 4.36 (t, J = 4.5 Hz, 1H), 4.46 (dd, J = 3.5, 11.5 Hz, 1H), 4.53 (dd, J = 2.0, 11.5 Hz, 1H), 5.91 (d, J = 4.0 Hz, 1H), 5.93 (d, J = 8.0 Hz, 1H), 7.78 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, D_2O): δ 20.74, 34.16, 54.23, 56.61, 58.58, 66.28, 67.45, 69.62, 69.86, 71.09, 73.91, 81.62, 90.42, 103.14, 142.52, 152.31, 166.90, 175.97. HRMS (ESI, positive) Calcd for $C_{18}H_{29}N_4O_{13}S$ [$(M + H)^+$] 541.1446, found: 541.1452.

(2,3,4,6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)oxime (16). To a solution of **8** (275 mg, 0.40 mmol) in MeOH (8.0 mL) was added hydroxylamine hydrochloride (42 mg, 0.60 mmol) and $KHCO_3$ (60 mg, 0.60 mmol). The reaction mixture was stirred for 5 h at room temperature. The mixture was extracted with EtOAc (3 × 80 mL) and washed with $NaHCO_3$ aqueous solution (20 mL) and brine (20 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 6 : 1 to 5 : 1) to provide **16** (281 mg, 100%) as a colorless oil. The ^{1}H NMR data were in good agreement with those reported previously.[21]

(2,3,4,6-Tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)ethylamine (17). To a solution of **16** (280 mg, 0.40 mmol) in MeOH (8.0 mL) was added $NiCl_2 \cdot 6H_2O$ (485 mg, 2.0 mmol) and $NaBH_4$ (15 mg, 4.0 mmol). The reaction mixture was stirred for 5 h at room temperature. The reaction was quenched by several drops of HOAc. The mixture was extracted with EtOAc (3 × 80 mL) and washed with $NaHCO_3$ aqueous solution (20 mL) and brine (20 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by flash column chromatography on silica gel (petroleum ether/EtOAc 1.5 : 1 to 1 : 1.5 containing 1% $NH_3 \cdot H_2O$) to provide **17** (220 mg) as a yellow oil, which was unstable and directly used for the next reaction.

2″,3″-*O*-Isopropylidene-5″-*S*-((2,3,4,6-tetra-*O*-benzyl-*N*-benzyloxycarbonyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)ethylamine-4′,5′-*O*-isopropylidene-vicinal diolyl)uridine (19). To a solution of **18** (20 mg, 0.05 mmol) in CH_2Cl_2 (2.0 mL) was added Dess–Martin periodinane (30 mg, 0.08 mmol) at 0 °C. After stirring for 3 h, the mixture was extracted with EtOAc (3 × 40 mL) and washed with $NaHCO_3$ aqueous solution (10 mL) and brine (10 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. The crude product was dissolved in MeOH (2.0 mL), and a solution of compound **17** (32 mg, 0.05 mmol) in MeOH (2.0 mL) was added. Then a portion of HOAc was added dropwise until the pH value was between 5 and 6. After stirring for 1 h at room temperature, a portion of $NaBH_3CN$ (10.0 mg, 0.15 mmol) was added. The reaction mixture was stirred overnight at room temperature, and quenched with 1 N HCl aqueous solution (0.2 mL). The mixture was extracted with EtOAc (3 × 30 mL), washed with $NaHCO_3$ aqueous solution (10 mL) and brine (10 mL). The organic phases were combined, dried (Na_2SO_4), filtered and concentrated. The residue was purified by column chromatography on silica gel (petroleum ether/EtOAc 1 : 1 to 1 : 1.5) to provide **19** (24 mg, 48% for two steps) as a colorless oil. ^{1}H NMR (500 MHz, d_6-DMSO): δ 1.24 (s, 3H), 1.27 (s, 3H), 1.28 (s, 3H), 1.46 (s, 3H), 2.66–2.70 (m, 3H), 2.78–3.20 (m, 5H), 3.76–4.13 (m, 8H), 4.40–4.64 (m, 9H), 4.71 (dd, J = 4.0, 6.5 Hz, 1H), 4.91 (br.s, 1H), 5.02 (dd, J = 2.0, 6.5 Hz, 2H), 5.62 (d, J = 8.0 Hz, 1H), 5.75 (s, 1H), 5.78 (d, J = 2.0 Hz, 1H), 7.27–7.32 (m, 25H), 7.69 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, DMSO): δ 25.10, 26.90, 27.03, 27.07, 34.21, 34.42, 50.77, 54.88, 66.31, 71.86, 73.95, 78.73, 79.54, 82.83, 83.46, 85.74, 92.03, 101.89, 108.09, 113.26, 127.24, 127.30, 127.37, 127.66, 128.08, 128.14, 128.17, 128.24, 136.61, 138.21, 138.47, 138.60, 138.73, 142.80, 150.21, 163.16. HRMS (ESI, positive) Calcd for $C_{62}H_{73}N_4O_{15}S$ [$(M + H)^+$] 1113.4889, found: 1113.4902.

5′-*S*-((1,5-Dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)-ethylamine-vicinal diolyl)uridine (4) and 5′-*S*-((2-*O*-benzyl-1,5-dideoxy-1,5-imino-D-*glycero*-D-*galacto*-heptitolyl)ethylamine-vicinal diolyl)uridine (20). Compounds **4** and **20** were prepared from **19** (22 mg, 0.02 mmol) as described in the preparation of **1**, providing light yellow solids **4** (3.9 mg, 34%) and white solids **20** (5.7 mg, 43%) in the form of hydrochloride salt after lyophilization. For compound **4**: ^{1}H NMR (500 MHz, D_2O): δ 2.79 (dd, J = 8.0, 13.5 Hz, 1H), 2.86 (dd, J = 5.5, 13.5 Hz, 1H), 2.93–2.97 (m, 1H), 3.04–3.08 (m, 1H), 3.31–3.37 (m, 2H), 3.49–3.52 (m, 2H), 3.78–3.93 (m, 5H), 4.09–4.15 (m, 2H), 4.19–4.22 (m, 3H), 4.28 (dd, J = 5.0, 9.0 Hz, 1H), 4.41–4.43 (m, 1H), 5.86 (d, J = 4.5 Hz, 1H), 5.91 (d, J = 8.0 Hz, 1H), 7.74 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, D_2O): δ 34.59, 35.69, 44.90, 51.74, 57.10, 59.32, 65.60, 66.92, 67.02, 68.04, 69.88, 71.70, 72.66, 73.75, 83.37, 90.95, 103.17, 142.96, 152.28, 166.90. HRMS (ESI, positive) Calcd for $C_{20}H_{35}N_4O_{11}S$ [$(M + H)^+$] 539.2018, found: 539.2022. For compound **20**: ^{1}H NMR (500 MHz, D_2O): δ 2.76 (dd, J = 8.0, 14.0 Hz, 1H), 2.83 (dd, J = 5.5, 14.0 Hz, 1H), 2.93–2.97 (m, 1H), 3.04–3.07 (m, 1H), 3.13–3.16 (m, 3H), 3.35 (dd, J = 9.0, 13.5 Hz, 1H), 3.41 (dd, J = 5.0, 13.0 Hz, 1H), 3.70–3.79 (m, 4H), 3.84 (dd, J = 3.0, 10.0 Hz, 1H), 3.97 (dt, J = 2.5, 7.0 Hz, 1H), 4.02 (dd, J = 5.5, 9.5 Hz, 1H), 4.06–4.07 (m, 1H), 4.18–4.21 (m, 2H), 4.40 (t, J = 4.5 Hz, 1H), 4.68 (d, J = 11.5 Hz, 1H), 4.80 (d, J = 11.5 Hz, 1H), 5.85 (d, J = 4.5 Hz, 1H), 5.88 (d, J = 8.5 Hz, 1H), 7.42–7.49 (m, 5H), 7.72 (d, J = 8.0 Hz, 1H). ^{13}C NMR (125 MHz, D_2O): δ 34.61, 35.68, 44.75, 50.56, 54.87, 61.02, 68.21, 68.98, 69.96, 71.71, 72.66, 73.77, 74.43,

76.57, 83.45, 90.96, 103.15, 129.43, 129.55, 129.68, 137.89, 142.91, 152.20, 166.83. HRMS (ESI, positive) Calcd for $C_{27}H_{41}N_4O_{11}S$ [(M + H)$^+$] 629.2487, found: 629.2483.

Activity measurements of inhibitors against α-1,3-galactosyltransferase

The assays contained $MnCl_2$ (10 mM), α-1,3-galactosyltransferase (0.0004 U mL^{-1}), UDP-[6-^{3}H]-galactose (0.05 μM), UDP-galactose (49.5 μM), LacNAc (0.5 mM), inhibitor (0.025–2.0 mM), bovine serum albumin (1.0 mg mL^{-1}), MES buffer (50 mM, pH 6.0) in a total assay volume of 0.05 mL. Assays were performed at 37 °C for 30 min. Reactions were quenched by the addition of cold water (0.3 mL). The reaction mixtures were transferred onto a Dowex 1 × 8 column (1.0 mL). The column was washed with an additional 0.6 mL of water (2 × 0.3 mL). The flow-through and column washes were collected and added OPTi-Fluor scintillation cocktail (4.0 mL). A control experiment without enzyme and inhibitor was used to establish the background count. The IC_{50} was determined by plotting the ratio of inhibition *versus* concentration of inhibitor.

Activity measurements of inhibitors against β-1,4-galactosyltransferase

The assays contained $MnCl_2$ (10 mM), β-1,4-galactosyltransferase (0.004 U mL^{-1}), UDP-[6-^{3}H]-galactose (0.05 μM), UDP-galactose (49.5 μM), GlcNAc (0.5 mM), inhibitor (0.05–1.0 mM), bovine serum albumin (1.0 mg mL^{-1}), HEPES buffer (50 mM, pH 7.4) in a total assay volume of 0.05 mL. Reaction temperature, work up, *etc.* are the same as the above-described inhibitory assay for α-1,3-galactosyltransferase.

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