Iminosugars as glucosylceramide processing enzymes inhibitors: design, synthesis and evaluation

Liu, B.

5 Biphenyl-L-*ido* DNJ Derivatives as Dual GCS/GBA2 Inhibitors

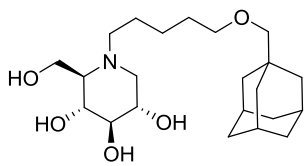
Introduction

N-alkyl-deoxynojiricin derivatives (*N*-alkyl iminosugars) are an important class of biologically active molecules that are applied both in fundamental glycobiology studies and in clinical settings.[1] *N*-alkyl-DNJ derivatives are potent inhibitors of the glucosylceramide metabolizing enzymes, glucosylceramide synthase (GCS) and neutral glucosylceramidase (GBA2) as well as intestinal glucosidases. Literature reports suggest that this dual activity make such *N*-modified DNJs promising leads for the development of type 2 diabetes. In these studies, it was also shown that *N*-alkyl derivatives of the C-5 epimer of DNJ, the L-*ido*-configured

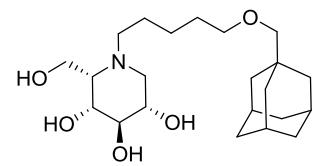
iminosugars are at least equally potent GCS and GBA2 inhibitors as their DNJ counterparts, but do not target intestinal glycosidases. Based on this comparative selectivity, L-*ido*-DNJ derivatives may be considered as starting point for the development of therapeutics for the treatment of lysosomal storage disorders, in particular those in which GCS (and possibly also GBA2) are involved, such as Gaucher disease.[2]

As is described in Chapter 4, GCS, the enzyme responsible for the biosynthesis of glucosylceramide, is targeted in substrate reduction therapy for Gaucher disease. Compensatory overexpression of GBA2 in the cytoplasm has however been associated with LSDs symptoms as well.[3] Therefore, dual GCS/GBA2 inhibitors that are otherwise clean with respect to other glycoprocessing enzymes are thought to be promising compounds for the development of new and more effective drugs for treatment of these LSDs. This in turn indicates that further perusal of diverse, *N*-alkyl-L-*ido*-DNJ derivatives is a worthy research objective.

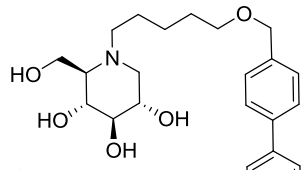
***Figure 1**: Various potent GCS and GBA2 inhibitors*



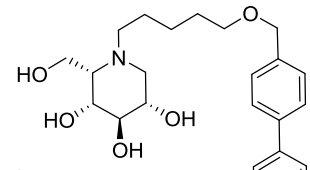
1 IC_{50} GCS 200 nM
IC_{50} GBA1 0.1 μM
IC_{50} GBA2 2 nM



2 IC_{50} GCS 100 nM
IC_{50} GBA1 30 μM
IC_{50} GBA2 1 nM



3 IC_{50} GCS 8 nM
IC_{50} GBA1 0.4 μM
IC_{50} GBA2 0.6 nM



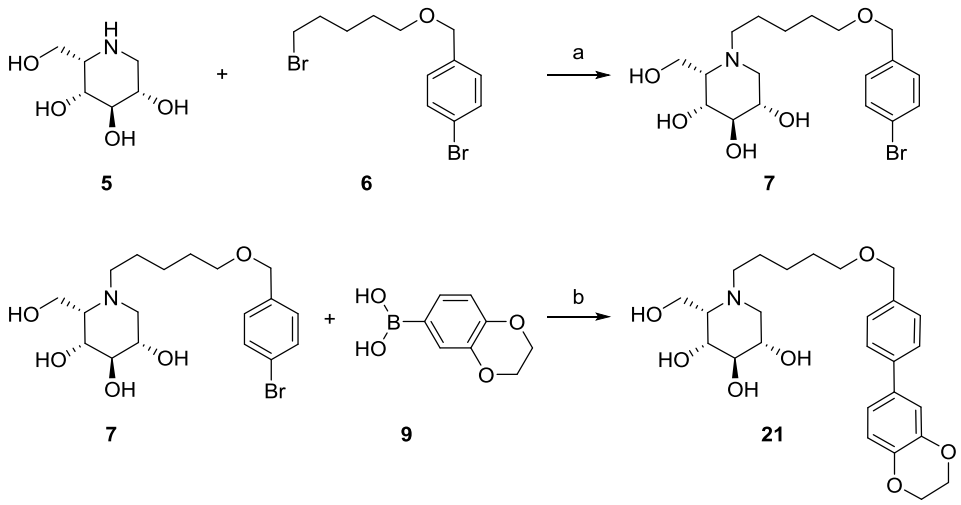
4 IC_{50} GCS 6 nM
IC_{50} GBA1 15 μM
IC_{50} GBA2 1 nM

From initial work on comparing the efficacy of DNJ and L-*ido*-DNJ derivatives as GCS/GBA2 inhibitors, *N*-AMP DNJ (MZ-21, **1**) and *N*-AMP L-*ido*-DNJ (MZ-31, **2**) emerged as the most effective compounds. Both are potent GCS/GBA2 inhibitors and, as outlined above, whereas compound **1** has a considerable number of other glycosidases as off-targets, compound **2** is much more selective. More recent studies on a series of *N*-alkyl and *N*-aryl derivatives revealed *N*-penyloxymethylbiaryl DNJ (**3**) and its L-ido-DNJ derivative (**4**) as more potent inhibitors that retain the selectivity profile of their parent compounds, **1** and **2**, respectively.[2] In these studies, the impact on altering the nature of the nitrogen substituent has been studied in depth on DNJ,

but less so on L-*ido*-DNJ, this while the latter class is considered more promising for the discovery of new LSD therapeutics.[2] For this reason, it was decided to expand the number and variety of *N*-substituted, L-idose configured iminosugars. The results on the design, synthesis and evaluation of a set of such compounds as GCS/GBA1/GBA2 inhibitors in comparison with relevant literature compounds, including their D-glucose configured counterparts, are presented in this Chapter.

Results and discussion

Scheme 1: *General approach to synthesize biphenyl substituted iminosugars*

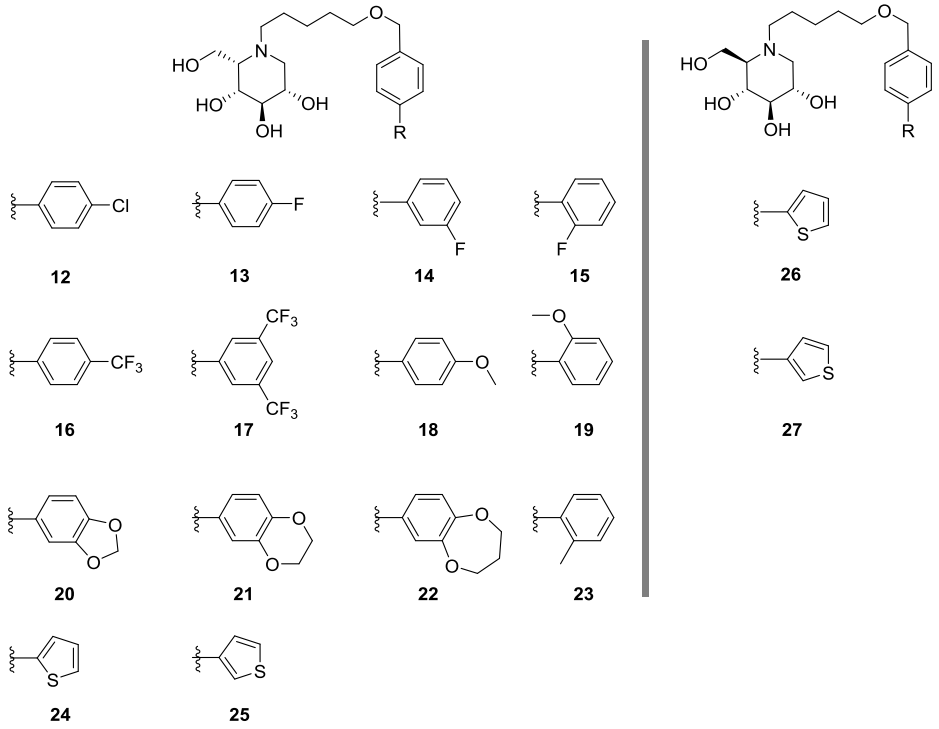


Reagents and conditions: [**a**] K_2CO_3, DMF, 80 °C, 46%; [**b**] $Pd(PPh_3)_4$, NaOMe, EtOH, 65 °C, 18 h, 11%.

The synthetic strategy employed to obtain functionalized biphenyl substituents is illustrated in Scheme 1 for the synthesis of protected catechol derivative **21**. Following this strategy, first a large batch of bromobenzyl-L-*ido*-DNJ derivative (such as the *para*-bromobenzyl derivative **7**) is made, which is then diversified into compound families using Suzuki cross-coupling methodology with a variety of commercially available phenylboronates as the cross-coupling counterpart. Thus, and following conditions as described in previous chapters,[4] L-*ido*-DNJ **5** is alkylated with bromide **6** to provide in acceptable yields and in a scalable fashion compound **7**. Treatment of bromide **7** with catechol **9**, a catalytic amount of $Pd(Ph_3)_4$ and sodium methoxide in ethanol provided after HPLC purification compound **21** in 11% yield. This yield is not impressive. Moreover, yields from the cross-coupling/purifications sequence involving different phenylboronates, yielding other library entries (see Figure 3 for their structure and in the experimental part for their synthesis) were sometimes, as low as 1%.

Nonwithstanding these yields, which were not optimized, sufficient quantities of material in excellent structural purity were obtained to perform enzyme inhibition assays, which was the primary objective of the research in this Chapter: are L-*ido*-DNJ derivatives more potent and selective than their D-*gluco*-counterparts in inhibiting GCS and GBA2 irrespective of the nature of the nitrogen substituent.

Figure 3: *Substituents for external phenyl ring modifications*



In order to obtain insight in what causes the low efficiency in the Suzuki reactions, HPLC traces were perused for potential side products that were formed during the reaction. From these studies it became apparent that compound **10** (Figure 4; when starting from DNJ) and **11** (from L-*ido*-DNJ), the dehalogenated starting materials, were formed as major products. Dehalogenation of the aryl halide is a known side reaction in Suzuki cross couplings and can be suppressed by the addition of tertiary amine bases such as trimethylamine.[5]

Figure 4: *Dehalogenated side products*

In case needed (for instance when larger quantities of a given iminosugar are required) optimization of the cross-coupling event including the addition of such amines may be considered. Alternative literature procedures for the optimization of this key step includes modulating the amount of potassium carbonate used and the temperature at which the reaction is executed.[6]

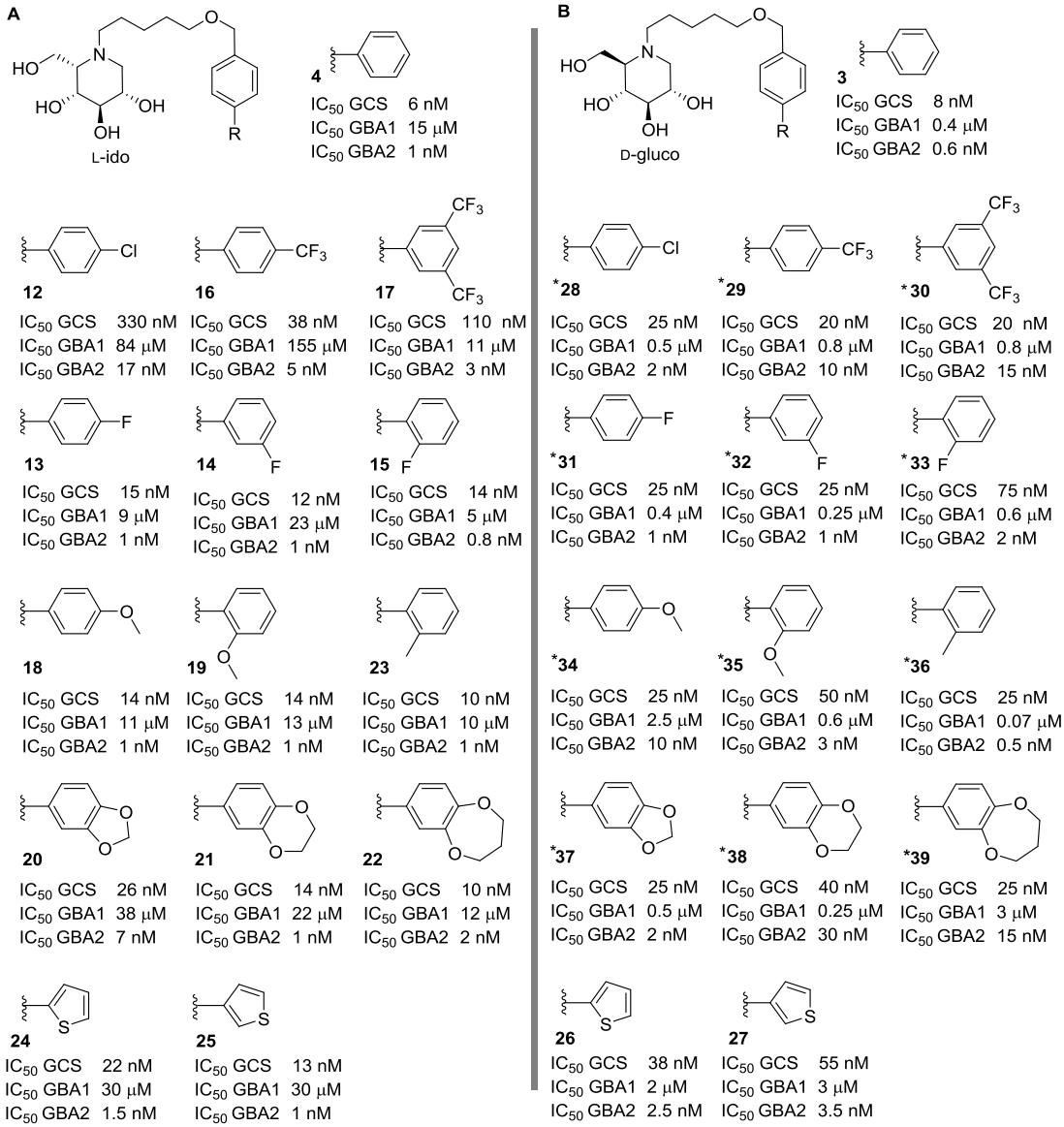
Inhibition activity

As discussed above, an established trend is that L-idose configured iminosugars are more potent GCS inhibitors than their D-glucose configured counterparts. As can be seen (Figure 5), this trend in general also holds up after evaluation of the newly synthesized DNJ derivatives. There are however some notable exceptions to this rule: compounds **12**, **16** and **17** are less potent GCS inhibitors than their corresponding DNJ derivatives (**28**, **29** and **30**). The differences in potency are however too small to draw any structure-activity relationship conclusions from this observation. It can be generally concluded that the compound series contain many nanomolar GCS inhibitors and therefore many compounds that may be of interest for further perusal as *in vivo* GCS inhibitors.

With the exception of **12** and **16** all compounds in the L-*ido* series inhibit GBA1 with IC_{50} values ranging from 5 to 40 μM. These compounds are therefore rather potent inhibitors of GBA1, however there is a considerable window between GCS and GBA1 (GCS: nanomolar, GBA1: micromolar). This window is much more pronounced than the one in the D-*gluco* series, containing many nanomolar inhibitors of GBA1 (an enzyme one does not wish to inhibit, neither in relation to type 2 diabetes nor in relation to LSDs). Finally, all compounds inhibit GBA2 in the nanomolar range (IC_{50} 0.8 – 17 nM), with *ortho*-F substituted **15** (IC_{50} = 0.8 nM) as the most potent compound of the series. Though less pronounced than seen for GCS, the L-*ido*-compounds do seem to outperform their D-*gluco* counterparts in inhibition potency towards GBA2. Returning to GCS inhibition potency, one striking observation is that *para*-fluoride **13** significantly more potent than *para*-chloride **12**. This observation is opposite from what is observed in the D-*gluco* series (compare **28** and **31**).

Besides the construction of new L-*ido*-DNJ derivatives bearing known (for DNJ) *N*-substituents the compounds synthesised in the framework of this Chapter also include a new functionality: thiophene derivatives **24**-**27** with the thiophene (appended through either of the two optional carbons) replacing the terminal phenyl ring in **3** and **4**. Following the trend L-*ido* congeners **24** and **25** are 2 to 3 times more potent GCS inhibitors than the corresponding DNJ compounds **26** and **27**, though overall GCS inhibitory potency has suffered from this phenyl-to-tiophene substitution.

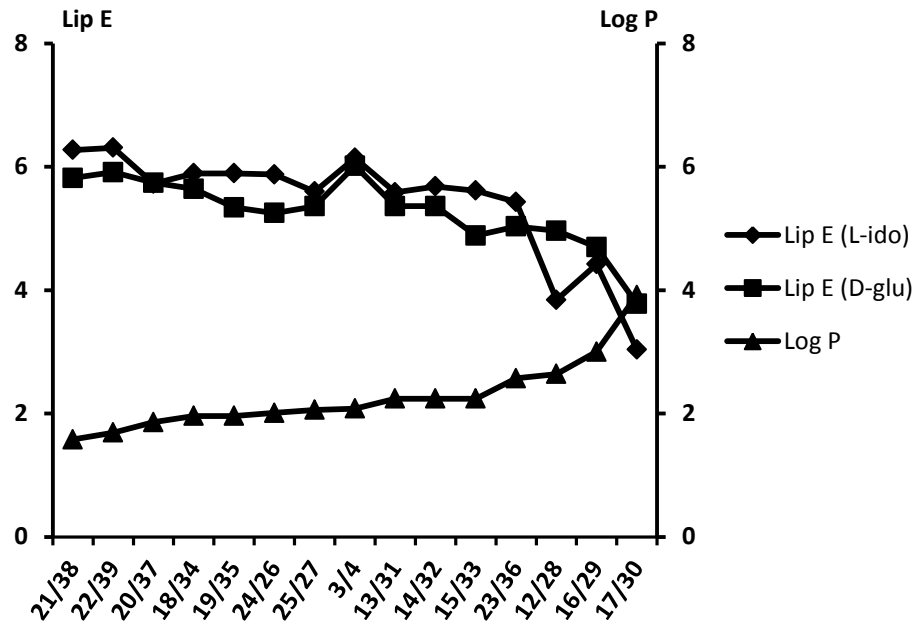
***Figure 5**: Structures and GCS, GBA1 and GBA2 IC_{50} values of the biphenyl analogue containing iminosugars*



*IC_{50} values of 29 – 40 are from the literature.[2]

Overall, the introduction of different substituents at the biphenyl external ring has not led to inhibitors with significantly improved or decreased activity against GCS, GBA1 and GBA2, compared to the lead structures. When looking at selectivity, however, *para*-CF_3 substituted compound **16** may be of interest, as it is the most selective GCS/GBA2 dual inhibitor when taking into account GBA1 as an undesired off-target.

***Figure 6**: Lipophilic ligand efficiency values (LipE) of D-gluco and L-ido series for GCS inhibition*



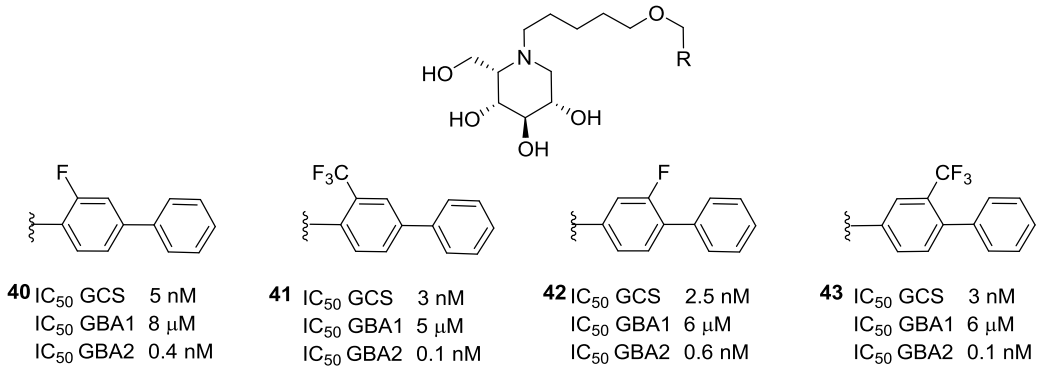
To obtain some more insight into the potential relevance of the here-presented inhibitors for potential future *in vivo* application, their lipophilic ligand efficiency (LipE) was calculated (Figure 6). LipE is defined as pIC_{50} - LogP, which is a composite parameter often referred to when correlating the potency of a molecule towards an isolated target (or gleaned from an *in vitro* assay) to its potential druglikeness.[7] A high LipE indicates the affinity of the inhibitor with the target enzyme tends to be driven by specific molecule-protein interaction, rather than a non-specific entropy-driven binding.[7] It can be observed from Figure 6 that the L-*ido* series exhibits better performance in this index when the LogP value is low, whereas the D-*glu* series has a higher LipE value when the logP value is higher (see: **12/28**, **16/29** and **17/30**). From all the iminosugars discussed in this Chapter, compounds **21** and **22** seem to perform better than lead structure **4** in this evaluation. It should however be realized that this evaluation is not very precise, as for instance chiral information is not included and furthermore that the lipophilicity data is generated *in silico*, rather than by experimentation.

Conclusion

In this Chapter, 14 new L-*ido*-DNJ derivatives were designed and synthesized, with as key step a Suzuki-Miyaura cross coupling event. The results in this Chapter complement literature studies, and while no spectacularly active and selective new inhibitors are identified, the list of

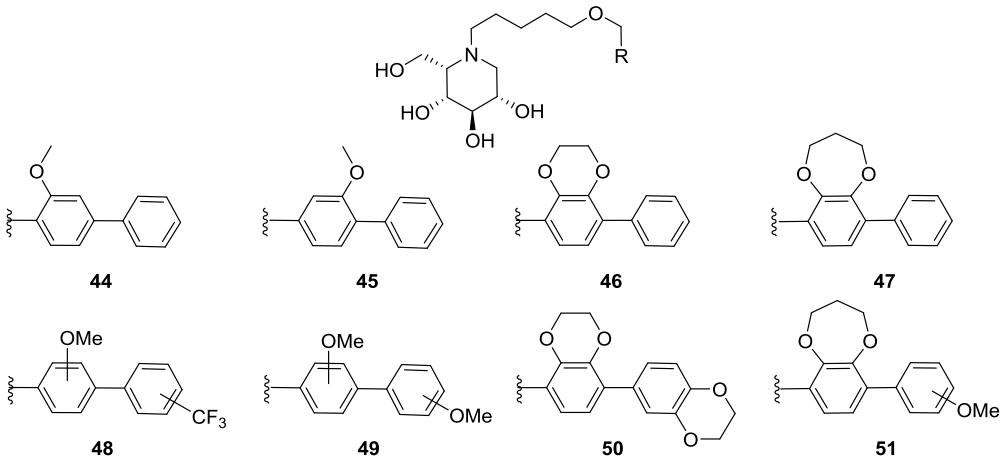
compounds with D-*gluco* and L-*ido* configuration and bearing a large number of different *N*-alkyl groups, alongside with GCS/GBA1/GBA2 inhibitory potencies obtained, now provide some hints as to what would make a *N*-substituted iminosugar a potent and/or selective GCS/GBA2 inhibitor. For instance, as can be concluded from the inhibitors presented here, alteration of the terminal phenyl ring in a biphenyl substituent does little for activity/selectivity (but is also not detrimental).

Figure 7: *Potent internal phenyl ring modified L-ido iminosugar derivatives*



This is in contrast to the literature report on related compounds, but in which focus has been more on modulating the internal phenyl ring of the biphenyl moiety. For instance, L-*ido*-DNJ derivatives **41** - **44** (Figure 7) turned out to be potent GCS/GBA2 inhibitors, more so than lead compound **4** as well as noniminosugar GCS inhibitors reported in the literature.[2] One future direction may be to take those inner-ring substituents for potency/selectivity, and equip these with the most optimal terminal rings in terms of logP values, leading to, for instance, analogues **49**–**52** in (Figure 8) as potentially interesting targets for the future.

Figure 8: *Low logP modified biphenyl L-ido iminosugars*



Experimental section

Enzyme inhibition assays: The potencies (IC_{50} values) of the *N*-alkyl-DNJ derivatives as GCS, GBA1 and GBA2 inhibitors were determined by exposing cells or enzyme preparations to an appropriated range of iminosugar concentrations.

GCS: IC_{50} values for GCS activity were measured using living cells with NBD-ceramide as substrate.[8] Briefly, cells were incubated with 50 nmol C6-NBD-ceramide (6-[*N*-methyl-*N*-(7-nitrobenz-2-oxa-1,3-diazol-4-yl)aminododecanoyl]sphingosine) in the presence of increasing compound concentrations. The cells were harvested after 2h followed by lipid extraction. The formed C6-NBD-glucosylceramide was quantified using a Molecular Dynamics Typhoon phosphor imaging device. IC_{50} values were determined from the titration curves. The experiment was performed twice.

GBA1: IC_{50} values for lysosomal GBA1 were measured using 4-methylumbeliferyl-β-D-glucoside as substrate.[9] Briefly, recombinant GBA1 was incubated with increasing compound concentrations for 30 min at 0 °C. Enzyme activity was determined with 3.7 mM 4-methylumbelliferyl-β-D-glucopyranoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.2, 0.1% Triton X-100 (v/v) and sodium taurocholate (0.2%, w/v). Assays were incubated at 37 °C for 30 min and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

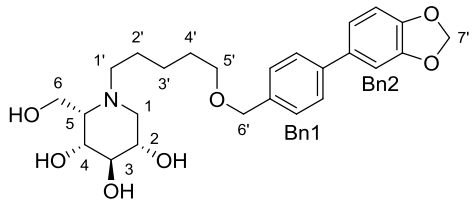
GBA2: IC_{50} values for the non-lysosomal glucocerebrosidase (GBA2) were measured with 4-methylumbeliferyl-β-D-glucoside as substrate.[8] GBA2-rich membrane suspensions were prepared from enzyme-overexpressing HEK cells by sonicating, and the suspension was pre-incubated for 30 min at 37 °C with conduritol-B-epoxide (1 mM, CBE, Sigma) to inhibit the lysosomal glucocerebrosidase (GBA1). The prepared GBA2-rich suspension was then incubated with increasing compound concentrations for another 30 min, and then incubated with 3.7 mM 4-methylumbeliferyl-β-D-glucoside in McIlvaine buffer (0.1 M citrate and 0.2 M phosphate buffer), pH 5.8. Assays were incubated at 37 °C for 1 hour and quenched by the addition of glycine/NaOH (0.2 mL, pH 10.6). The amount of liberated 4-methylumbeliferyl was determined with a PerkinElmer Life Sciences LS30 fluorimeter, excitation wavelength 366 nm, emission wavelength 445 nm. Assays were performed in triplicate.

General compound synthesis, purification and analysis methods: All solvents and reagents were obtained commercially and used as received unless stated otherwise. Reactions were executed at room temperature unless stated otherwise. Moisture sensitive reactions were performed under argon atmosphere. Water was removed from starting compounds by repetitive coevaporation with toluene. Solvents were removed by evaporation under reduced pressure. DCM, DMF, and THF were dried over activated 4Å molecular sieves for at least 12 hours before use. Compounds were visualized during TLC analyses by UV (254 nm), and with the following staining solutions: aqueous solution of $KMnO_4$ (5 g/L) and K_2CO_3 (25 g/L). Visualization of hemiacetals and glycosides was achieved by spraying with a solution of 20% H_2SO_4 in ethanol followed by charring at ≈ 200 °C. Column chromatography purification was performed on silica gel (40-63 μm). ^1H and ^{13}C-APT NMR spectra were recorded on a Bruker AV 400 (400/100 MHz), Bruker 600 (600/150 MHz) or Bruker 600 (850/215 MHz) spectrometer in $CDCl_3$, MeOD or D_2O. Chemical shifts are given in ppm (δ) relative to TMS as internal standard (^1H NMR in $CDCl_3$) or the signal of the deuterated solvent.[10] Coupling constants (*J*) are given in Hz. High resolution mass spectra were recorded by direct injection (2 μL of a 2 μM solution in water/acetonitrile/*tert*-butanol 1:1:1 v/v/v) on a mass spectrometer (Thermo

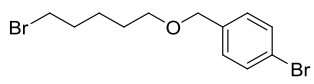
Finnigan LTQ Orbitrap) equipped with an electrospray ion source with resolution R = 60000 at m/z 400 (mass range m/z = 150-2000). IR spectra were recorded on a Shimadzu FTIR-8300 and are reported in cm^{-1}. Optical rotation were measured on an automatic polarimeter of sodium D-line, at λ = 589 nm. Size-exclusion purifications were performed on an ÄKTA-explorer, column size d = 26 mm, l = 60 mm, mobile phase NH_4HCO_3 (0.15 M) in H_2O, flow 1.5 mL/min. HPLC Purification were performed on a Prep LCMS, Gemini from Phenomenex B.V. (C-18, 110 Å, 5 µm, 19 x 150 mm column).

General procedure: Suzuki-Miyaura cross coupling: Solutions and stock solutions used were degassed with ultrasonic bath with an argon flow for at least 15 minutes. The reactions were carried out under argon protection. A stock solution of *N*-[5-(4-bromobenzyloxy)pentyl]-1-deoxynojirimycin (1.2 M) in ethanol, a stock solution of boronic acid (1.5 M) in ethanol and a stock solution of $Pd(PPh_3)_4$ (5%) in ethanol were made. NaOMe (0.180 gram, 3.3 mmol) was added to the reaction vails containing an argon atmosphere, followed by the additions of the stock solutions of *N*-[5-(4-bromobenzyloxy)pentyl]-1-deoxynojirimycin (1.2 M, 0.417 mL, 0.5 mmol), boronic acid (1.5 M, 0.500 mL, 0.75 mmol) and $Pd(PPh_3)_4$ (2 mol%, 0.40mL). The reaction mixture was stirred at 65 °C for 18 h. After HPLC analysis indicated the complete consumption of starting material, the reaction mixture was diluted with ethanol filtered over Cilite and the volatiles were evaporated. The residue was purified by HPLC purification. Yields vary from 1% - 11%.

***Figure 9**: Proton and carbon NMR numbering of iminosugars:*

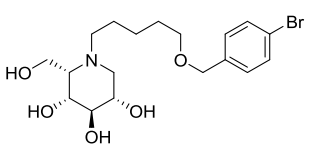


5-(4-Bromobenzyloxy)pentyl-1-bromide (6):



To a mixture of 5-(4-bromobenzyloxy)pentane-1-ol (4.00 g, 14.6 mmol) and triphenyl phosphine (5.80 g, 22.2 mmol) in DCM (150 mL) was added CBr_4 (7.35 g, 22.2 mmol) at 0 °C. The reaction mixture was stirred for 2 hours. After which TLC analysis showed the complete consumption of starting material, Celite was added and the volatiles were evaporated. The residue was purified with silica gel column (4:1 → 0:1, PE:toluene) to give **6** (3.20 g, 7.03 mmol, 50%) as yellow oil. R_F = 0.70 (toluene). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57 – 7.38 (m, 2H, H_{Ar} Bn), 7.24 – 7.11 (m, 2H, H_{Ar} Bn), 4.44 (s, 2H, H_2-6), 3.46 (t, *J* = 6.3 Hz, 2H, H_2-5), 3.40 (t, *J* = 6.8 Hz, 2H, H_2-1), 1.97 – 1.80 (m, 2H, H_2-2), 1.71 – 1.58 (m, 2H, H_2-4), 1.58 – 1.43 (m, 2H, H_2-3). ^{13}C NMR (100 MHz, $CDCl_3$) δ 137.6 (C_q Bn), 131.5 (CH_{Ar} Bn), 129.3 (CH_{Ar} Bn), 121.4 (C_q Bn), 72.2 (C-6), 70.2 (C-5), 33.9 (C-1), 32.6 (C-2), 29.0 (C-4), 25.0 (C-3). IR/cm^{-1}: 2935, 2856, 1487, 1356, 1093, 1010.

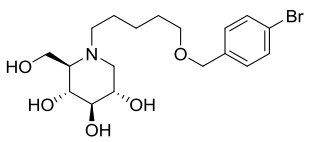
***N*-[5-(4-Bromobenzyloxy)-pentyl]-L-*ido*-1-deoxynojirimycin (7):**



To a mixture of **6** (7.57g, 22.73 mmol) and K_2CO_3 (4.27, 30.90 mmol) was added a solution of **5** (2.47g, 15.1 mmol) in DMF (75 mL). This was stirred overnight at 80 °C. After cooling to room temperature, the mixture was filtered and concentrated. The crude compound was purified with silica gel column (4:1 EtOAc: MeOH + 1% NH_4OH → 6:4:1 EtOH:H_2O:NH_4OH) to give **7** in 46% yield (3.22g, 7.70 mmol). ^{1}H NMR (400 MHz, MeOD) δ 7.47 (d, *J* = 8.1 Hz, 2H, H_{Ar} Bn), 7.25 (dd, *J* = 8.2, 3.5 Hz, 2H, H_{Ar} Bn),

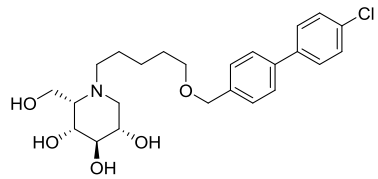
4.43 (s, 2H, H_2-6'), 3.84 (t, *J* = 5.3 Hz, 2H, H_2-6), 3.77 – 3.66 (m, 1H, H-4), 3.59 – 3.53 (m, 1H, H-2), 3.47 (t, *J* = 6.4 Hz, 2H, H_2-5'), 3.42 (t, *J* = 8.5 Hz, 1H, H-3), 3.09 – 3.05 (m, 1H, H-5), 2.83 (dd, *J* = 12.3, 4.8 Hz, 1H, H-1a), 2.80 – 2.73 (m, 1H, H-1'a), 2.71 – 2.65 (m, 1H, H-1'b), 2.61 (dd, *J* = 12.4, 9.7 Hz, 1H, H-1b), 1.80 – 1.47 (m, 4H, H_2-2', H_2-4'), 1.38 (p, *J* = 7.7 Hz, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 139.1 (C_q Bn), 132.4 (CH_{Ar} Bn), 130.5 (CH_{Ar} Bn), 122.2 (C_q Bn), 75.5 (C-3), 72.9 (C-6'), 72.6 (C-4), 71.4 (C-5'), 71.0 (C-2), 64.1 (C-5), 57.6 (C-6), 55.4 (C-1'), 52.8 (C-1), 30.5 (C-2'), 28.1 (C-4'), 24.9 (C-3'). $[\alpha]^{20}_D$ = 10.4 (c = 1.00, MeOH). IR/cm^{-1}: 3339, 1670, 1433, 1200, 1134, 1070. HRMS: found 418.12236, 420.12032 $[C_{18}H_{29}BrNO_5+H]^+$, calculated for $[C_{18}H_{29}BrNO_5+H]^+$ 418.12237, 420.12030.

N-[5-(4-Bromobenzyloxy)-pentyl]-1-deoxynojirimycin (8):



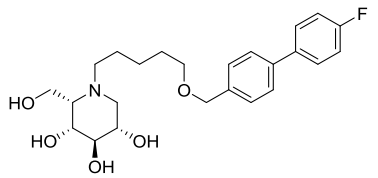
8 (3.57 g, 8.57 mmol) was synthesized from **6** (2.00 g, 12.8 mmol) and DNJ (5.16 g, 15.4 mmol) according to the procedure described for the preparation of compound **8** as a white solid with 67% yield. R_F = 0.45 (30% MeOH in EtOAc, 1% NH_4OH). ^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.47 (m, 2H, H_{Ar} Bn), 7.33 – 7.27 (m, 2H, H_{Ar} Bn), 4.50 (s, 2H, H_2-6'), 4.09 (dd, *J* = 12.3, 2.1 Hz, 1H, H-6a), 3.94 (dd, *J* = 12.5, 3.0 Hz, 1H, H-6b), 3.76 – 3.70 (m, 1H, H-2), 3.62 (t, *J* = 9.5 Hz, 1H, H-4), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.49 – 3.38 (m, 2H, H-1a, H-3), 3.31 – 3.25 (m, 1H, H-1'a), 3.23 – 3.14 (m, 1H, H-1'b), 3.02 (dd, *J* = 11.7, 5.2 Hz, 1H, H-5), 2.95 (t, *J* = 11.5 Hz, 1H, H-1b), 1.88 – 1.75 (m, 2H, H_2-2'), 1.73 – 1.69 (m, 2H, H_2-4'), 1.55 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 137.8 (C_q Bn), 131.1 (CH_{Ar} Bn), 129.3 (CH_{Ar} Bn), 120.9 (C_q Bn), 76.9 (C-3), 71.6 (C-6'), 69.8 (C-5'), 67.9 (C-4), 66.8 (C-2), 66.0 (C-5), 54.4 (C-6), 53.8 (C-1), 52.7 (C-1'), 28.8 (C-4'), 23.2 (C-3'), 22.8 (C-2'). $[\alpha]^{20}_D$ = -0.2 (c = 1.00, MeOH). IR/cm^{-1}: 3273, 1670, 1433, 1274, 1200, 1132, 1030, 1012. HRMS: found 418.12236, 420.12032 $[C_{18}H_{29}BrNO_5+H]^+$, calculated for $[C_{18}H_{29}BrNO_5+H]^+$ 418.12237, 420.12030.

N-[5-((4'-Chloro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (12):



12 (4.0 mg, 0.009 mmol, 2% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (600 MHz, MeOD) δ 7.65 – 7.57 (m, 4H, H_{Ar} Bn2), 7.44 (ddd, *J* = 8.2, 4.5, 2.2 Hz, 4H, H_{Ar} Bn1), 4.55 (s, 2H, H_2-6'), 4.07 – 3.88 (m, 4H, H-4, H_2-6, H-2), 3.84 (s, 1H, H-3), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.54 – 3.39 (m, 2H, H-5. H-1a), 3.35 – 3.23 (m, 3H, H-1b, H_2-1'), 1.98 – 1.66 (m, 4H, H_2-2', H_2-4'), 1.54 – 1.43 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 140.7, 139.4, 134.4, (C_q BiPh), 130.0, 129.5, 127.9 (C_{Ar} BiPh), 73.6 (C-6'), 72.3 (C-4), 71.0 (C-5'), 69.0 (C-2), 68.2 (C-3), 63.8 (C-5), 62.4 (C-6), 55.0 (C-1'), 54.2 (C-1), 30.2 (C-4'), 24.6 (C-3'), 24.1 (C-2'). $[\alpha]^{20}_D$ = +3.33 (c = 0.06, MeOH). IR/cm^{-1}: 3319, 2920, 2867, 1674, 1437, 1204, 1134, 1072. HRMS: found 450.20396 $[C_{24}H_{32}ClNO_5+H]^+$, calculated for $[C_{24}H_{32}ClNO_5+H]^+$ 450.20418.

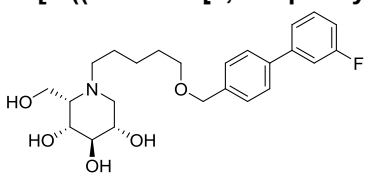
N-[5-((4'-Fluoro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (13):



13 (12.4 mg, 0.028 mmol, 6% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.72 – 7.53 (m, 4H, H_{Ar} Bn1), 7.46 – 7.37 (m, 2H, H_{Ar} Bn2), 7.23 – 7.06 (m, 2H, H_{Ar} Bn2), 4.54 (s, 2H, H_2-6'), 4.02 (s, 1H, H-4), 3.99 – 3.90 (m, 3H, H_2-6, H-2), 3.85 (t, *J* = 4.0 Hz, H-3), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.42 (m, 2H, H-5, H-1a), 3.35 – 3.30 (m, 3H, H-1b, H_2-1'), 1.96 – 1.81 (m, 1H, H-2'a), 1.73 – 1.69 (m, 3H, H-2'b, H_2-4'), 1.52 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 165.1, 162.7, 140.8, 138.9 (C_q BiPh), 129.8, 129.5, 127.9, 127.9, 116.6, 116.4, 116.4 (C_{Ar} BiPh), 73.6 (C-6), 72.3 (C-4), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.4 (C-6), 55.0 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +5.45 (c = 0.22, MeOH). IR/cm^{-1}: 3362, 2924, 1676,

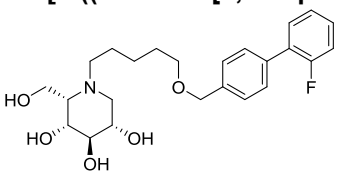
1439, 1205, 1134, 1074. HRMS: found 434.23353 $[C_{24}H_{32}FNO_5+H]^+$, calculated for $[C_{24}H_{32}FNO_5+H]^+$ 434.23373.

_N_-[5-((3'-Fluoro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (14):



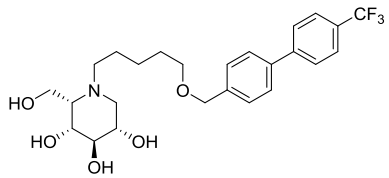
14 (7.8 mg, 0.017 mmol, 3% yield) was synthesized according the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 8.16 – 7.41 (m, 8H, H_{Ar} BiPh), 4.58 (s, 2H, H_2-6'), 4.04 (br s, 1H, H-4), 4.00 – 3.96 (m, 3H, H_2-6, H-2), 3.89 (d, *J* = 4.0 Hz, 1H, H-3), 3.59 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.56 – 3.46 (m, 2H, H-5, H-1a), 3.41 – 3.32 (m, 3H, H-1b, H_2-1'), 2.00 – 1.64 (m, 4H, H_2-2', H_2-4'), 1.55 – 1.51 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 163.5, 143.2, 138.3 (C_q BiPh), 130.3 – 113.0 (C_{Ar} BiPh), 72.1 (C-6'), 70.9 (C-4), 69.7 (C-5'), 67.6 (C-2), 66.6 (C-3), 62.4 (C-5), 60.0 (C-6), 53.7 (C-1'), 53.0 (C-1), 28.7 (C-4'), 23.2 (C-3'), 21.9 (C-2'). $[\alpha]^{20}_D$ = +6.00 (c = 0.10, MeOH). IR/cm^{-1}: 3362, 2924, 1676, 1437, 1204, 1134, 1074. HRMS: found 434.23349 $[C_{24}H_{32}FNO_5+H]^+$, calculated for $[C_{24}H_{32}FNO_5+H]^+$ 434.23373.

_N_-[5-((2'-Fluoro[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (15):



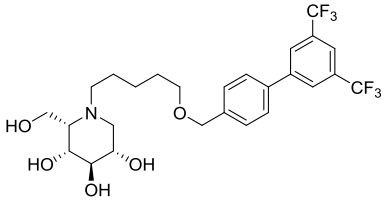
15 (9.1 mg, 0.021 mmol, 4% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.16 (m, 8H, H_{Ar} BiPh), 4.59 (s, 2H, H_2-6'), 4.04 (br s, 1H, H-4), 4.01 – 3.93 (m, 3H, H_2-6, H-2), 3.89 (t, *J* = 3.7 Hz, 1H, H-3), 3.60 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.57 – 3.45 (m, 2H, H-5, H-1a), 3.39 – 3.32 (m, 3H, H-1b, H_2-1'), 1.98 – 1.70 (m, 4H, H_2-2', H_2-4'), 1.56 – 1.52 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 162.3 – 131.8 (C_q BiPh), 130.4 – 116.9 (C_{Ar} BiPh), 73.6 (C-6'), 72.4 (C-4), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.2 (C-4'), 24.6 (C-3'), 23.3 (C-2'). $[\alpha]^{20}_D$ = +3.64 (c = 0.22, MeOH). IR/cm^{-1}: 3377, 2866, 2324, 1670, 1204, 1136, 1074. HRMS: found 434.23350 $[C_{24}H_{32}FNO_5+H]^+$, calculated for $[C_{24}H_{32}FNO_5+H]^+$ 434.23373.

_N_-[5-((4'-Trifluoromethyl[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (16):



16 (1.3 mg, 0.003 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (850 MHz, MeOD) δ 7.82 (d, *J* = 8.1 Hz, 2H, H_{Ar} BiPh), 7.74 (d, *J* = 8.2 Hz, 2H, H_{Ar} BiPh), 7.70 – 7.59 (m, 2H, H_{Ar} BiPh), 7.53 – 7.42 (m, 2H, H_{Ar} BiPh), 4.57 (s, 2H, H_2-6'), 4.10 – 3.63 (m, 5H, H-4, H_2-6, H-2, H-3), 3.57 (t, *J* = 6.3 Hz, 2H, H_2-5'), 3.49 – 3.38 (m, 2H, H-5, H-1a), 3.35 – 3.23 (m, 3H, H_2-1', H-1b), 2.02 – 1.56 (m, 2H, H_2-2'), 1.51 – 1.28 (m, 4H, H_2-4', H_2-3'). ^{13}C NMR (215 MHz, MeOD) δ 145.9 (C-7), 140.2, 130.3, 129.5 (C_q BiPh), 128.5 – 126.8 (C_{Ar} BiPh), 73.5(C-6'), 72.3(C-4), 71.2(C-5'), 69.0(C-2), 66.3(C-3), 63.9 (C-5), 55.1 (C-6), 52.9 (C-1'), 52.3 (C-1), 33.1 (C-4'), 30.3 (C-3'), 24.7 (C-2'). $[\alpha]^{20}_D$ = +20.00 (c = 0.01, MeOH). IR/cm^{-1}: 3402, 2930, 2349, 1683, 1506, 1203, 1130, 1070. HRMS: found 484.23023 $[C_{25}H_{32}F_3NO_5+H]^+$, calculated for $[C_{25}H_{32}F_3NO_5+H]^+$ 484.23053.

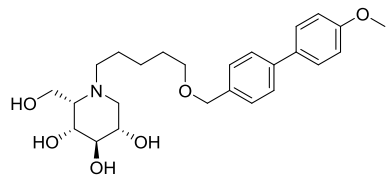
_N_-[5-((3',5'-Bis(trifluoromethyl)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-_ido_-1-deoxynojirimycin (17):



17 (24.5 mg, 0.04 mmol, 8.9% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 8.19 (d, *J* = 1.6 Hz, 2H, H_{Ar} BiPh), 7.95 (s, 1H, H_{Ar} BiPh), 7.77 – 7.70 (m, 2H, H-BiPh), 7.52 (d, *J* = 8.0 Hz, 2H, H-BiPh), 4.59 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 3.87 (t, *J* = 4.0 Hz, 1H, H-3), 3.58 (t, *J* = 6.2 Hz,

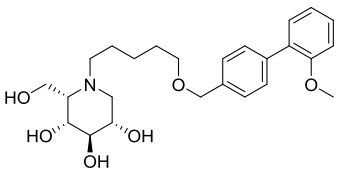
2H, H_2-5'), 3.53 – 3.47 (m, 2H, H-5, H-1a), 3.37 – 3.31 (m, 3H, H-1b, H_2-1'), 2.03 – 1.64 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 144.7, 141.0, 138.5, 133.5, 133.2 (C_q BiPh, CF_3), 129.7 – 121.8 (C_{Ar} BiPh), 73.4 (C-6'), 72.4 (C-4), 71.2 (C-5'), 69.0 (C-2), 68.0 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.2 (C-4'), 24.6 (C-3'), 23.3 (C-2'). $[\alpha]^{20}_D$ = +4.23 (c = 0.52, MeOH). IR/cm^{-1}: 3331, 2930, 2862, 1674, 1456, 1383, 1278, 1132, 1057. HRMS: found 552.21748 $[C_{26}H_{31}F_6NO_5+H]^+$, calculated for $[C_{26}H_{31}F_6NO_5+H]^+$ 552.21792.

N-[5-((4'-Methoxy[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (18):



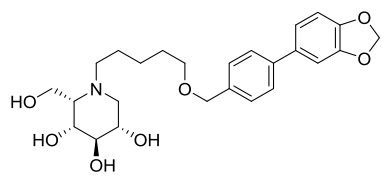
18 (4.6 mg, 0.01 mmol, 2% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.59 – 7.51 (m, 4H, H_{Ar} BiPh), 7.41 – 7.35 (m, 2H, H_{Ar} BiPh), 7.04 – 6.93 (m, 2H, H_{Ar} BiPh), 4.53 (s, 2H, H_2-6'), 4.01 (d, *J* = 3.0 Hz, 1H, H-4), 3.99 – 3.89 (m, 3H, H_2-6, H-2), 3.86 (d, *J* = 3.7 Hz, 1H, H-3), 3.83 (s, 3H, OMe), 3.56 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.54 – 3.43 (m, 2H, H-5, H-1a), 3.32 – 3.26 (m, 3H, H-1b, H_2-1'), 1.98 – 1.65 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.3 – 138.1 (C_q BiPh), 129.5, – 115.3 (C_{Ar} BiPh), 73.7 (C-6'), 72.4 (C-4), 70.9 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 55.7 (C-7'), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = -5.71 (c = 0.07, MeOH). IR/cm^{-1}: 3449, 2957, 2345, 2620, 1682, 1506, 1204, 1186, 1134. HRMS: found 446.25320 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

N-[5-((2'-Methoxy[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (19):



19 (11.6 mg, 0.026 mmol, 5% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.50 – 7.44 (m, 2H, H_{Ar} BiPh), 7.35 (d, *J* = 8.1 Hz, 2H, H_{Ar} BiPh), 7.34 – 6.94 (m, 4H, H_{Ar} BiPh), 4.53 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 3.98 – 3.93 (m, 3H, H_2-6, H-2), 3.86 (t, *J* = 3.8 Hz, 1H, H-3), 3.78 (s, 3H, OMe), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.54 – 3.44 (m, 2H, H-5, H-1a), 3.34 – 3.30 (m, 3H, H-1b, H_2-1'), 1.99 – 1.63 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 157.9, 139.6, 138.2 (C_q BiPh), 131.6 – 112.6 (C_{Ar} BiPh), 73.8 (C-6'), 72.3 (C-4), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 56.0 (C-7'), 55.0 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +3.33 (c = 0.24, MeOH). IR/cm^{-1}: 3323, 2943, 2857, 2311, 1674, 1487, 1202, 1134, 1074. HRMS: found 446.25351 $[C_{25}H_{35}NO_6+H]^+$, calculated for $[C_{25}H_{35}NO_6+H]^+$ 446.25371.

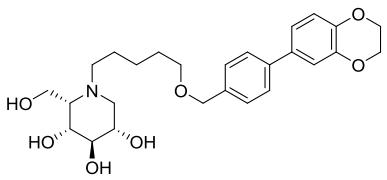
N-[5-((3',4'-*O*-Methylene-3',4'-bishydroxy)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (20):



20 (2.5 mg, 0.005 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.60 – 7.48 (m, 2H, H_{Ar} BiPh), 7.41 – 7.31 (m, 2H, H_{Ar} BiPh), 7.14 – 7.06 (m, 2H, H_{Ar} BiPh), 6.88 (d, *J* = 8.7 Hz, 1H, H_{Ar} BiPh), 5.98 (s, 2H, H_2-7'), 4.53 (s, 2H, H_2-6'), 4.03 – 4.01 (m, 1H, H-4), 3.98 – 3.90 (m, 3H, H_2-6, H-2), 3.86 (t, *J* = 3.8 Hz, 1H, H-3), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.44 (m, 2H, H-5, H-1a), 3.34 – 3.30 (m, 2H, H_2-1'), 2.02 – 1.74 (m, 1H, H-2'a), 1.74 – 1.65 (m, 3H, H-2'b, H_2-4'), 1.56 – 1.44 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 149.7, 141.7, 138.4, 136.4 (C_q BiPh), 129.4 – 102.5 (C_{Ar} BiPh), 102.5 (C-7'), 73.6 (C-6'), 72.3 (C-4), 70.9 (C-5'), 68.9 (C-2), 68.1 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = -6.67 (c = 0.06, MeOH). IR/cm^{-1}: 3400, 2918, 1674, 1506, 1202,

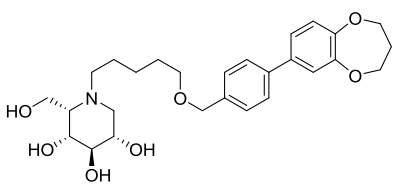
1184, 1070, 1040. HRMS: found 460.23277 $[C_{25}H_{33}NO_7+H]^+$, calculated for $[C_{25}H_{33}NO_7+H]^+$ 460.23298.

N-[5-((3',4'-*O*-Ethylene-3',4'-bishydroxy)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (21):



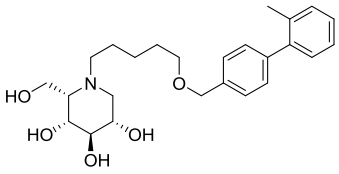
21 (26.4 mg, 0.06 mmol, 11% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.55 – 7.47 (m, 2H, H_{Ar} BiPh), 7.36 (d, *J* = 7.9 Hz, 2H, H_{Ar} BiPh), 7.08 (dd, *J* = 7.8, 1.6 Hz, 2H, H_{Ar} BiPh), 6.94 – 6.79 (m, 1H, H_{Ar} BiPh), 4.51 (s, 2H, H_2-6'), 4.26 (d, *J* = 1.3 Hz, 4H, H_2-7', H_2-8'), 4.02 (br s, 1H, H-4), 3.99 – 3.91 (m, 3H, H_2-6, H-2), 3.87 (t, *J* = 3.7 Hz, 1H, H-3), 3.54 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.51 – 3.41 (m, 2H, H-5, H-1a), 3.36 – 3.25 (m, 3H, H-1b, H_2-1'), 1.91 – 1.62 (m, 4H, H_2-2', H_2-4'), 1.50 – 1.46 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 145.2, 144.7, 141.3, 138.3, 135.4 (C_q BiPh), 129.4 – 116.5 (C_{Ar} BiPh), 73.7 (C-6'), 72.4 (C-4), 70.9 (C-5'), 68.9 (C-2), 68.0 (C-3), 65.7 (C-7', C-8'), 63.8 (C-5), 61.3 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +5.20 (c = 0.50, MeOH). IR/cm^{-1}: 3306, 2932, 2870, 1674, 1497, 1435, 1037, 1202, 1130, 1069. HRMS: found 474.24832 $[C_{26}H_{35}NO_7+H]^+$, calculated for $[C_{26}H_{35}NO_7+H]^+$ 474.24863.

N-[5-((3',4'-*O*-Propylene-3',4'-bishydroxy)[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (22):



22 (15.9 mg, 0.032 mmol, 6% yield) was synthesized according to Suzuki-Miyamura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.57 – 7.49 (m, 2H, H_{Ar} BiPh), 7.38 (d, *J* = 8.0 Hz, 2H, H_{Ar} BiPh), 7.25 – 7.12 (m, 2H, H_{Ar} BiPh), 7.01 (d, *J* = 8.2 Hz, 1H, H_{Ar} BiPh), 4.52 (s, 2H, H_2-6'), 4.19 (q, *J* = 5.3 Hz, 4H, H_2-7', H_2-9'), 4.05 – 3.84 (m, 5H, H-4, H_2-6 H-2, H-3), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.42 (m, 3H, H_2-5, H-1a), 3.36 – 3.29 (m, 3H, H-1b, H_2-1'), 2.18 (p, *J* = 5.5 Hz, 2H, H_2-8'), 1.95 – 1.80 (m, 1H, H-2'a), 1.79 – 1.62 (m, 3H, H-2'b, H_2-4'), 1.51 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 153.0 – 137.6 (C_q BiPh), 129.4 – 121.0 (C_{Ar} BiPh), 73.6 (C-6'), 72.3 (C-4), 72.0 (C-7', C-9'), 71.0 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 55.1 (C-1'), 54.4 (C-1), 33.3 (C-8'), 30.1 (C-4'), 24.6 (C-3'), 23.2 (C-2'). $[\alpha]^{20}_D$ = +3.13 (c = 0.32, MeOH). IR/cm^{-1}: 3381, 2872, 2324, 1684, 1522, 1310, 1204, 1134, 1065. HRMS: found 488.26396 $[C_{27}H_{37}NO_7+H]^+$, calculated for $[C_{27}H_{37}NO_7+H]^+$ 488.26428.

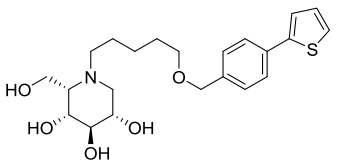
N-[5-((2'-Methyl[1,1'-biphenyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (23):



23 (20.4 mg, 0.05 mmol, 10% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.43 – 7.09 (m, 8H, H_{Ar} BiPh), 4.56 (s, 2H, H_2-6'), 4.03 (br s, 1H, H-4), 3.99 – 3.87 (m, 3H, H_2-6, H-2), 3.89 – 3.85 (m, 1H, H-3), 3.58 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.54 – 3.45 (m, 2H, H-5, H-1a), 3.40 – 3.29 (m, 3H, H-1b, H_2-1'), 2.23 (s, 3H, Me), 2.00 – 1.65 (m, 4H, H_2-2', H_2-4'), 1.53 – 1.49 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 142.9, 142.9, 138.4, 136.3 (C_q BiPh), 131.3 – 126.8 (C_{Ar} BiPh), 73.8 (C-6'), 72.3 (C-4), 71.1 (C-5'), 68.9 (C-2), 68.0 (C-3), 63.8 (C-5), 61.3 (C-6), 55.1 (C-1'), 54.4 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.3 (C-2'), 20.6 (C-7'). $[\alpha]^{20}_D$ = +6.25 (c = 0.45, MeOH). IR/cm^{-1}: 3318, 1670, 1437, 1277, 1204, 1074. HRMS: found 430.25863 $[C_{25}H_{35}NO_5+H]^+$, calculated for $[C_{25}H_{35}NO_5+H]^+$ 430.25880.

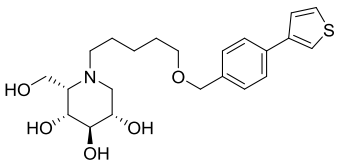
N-[5-((4-(Thiophen-2-yl)benzyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (24):

24 (2.2 mg, 0.005 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (850 MHz, MeOD) δ 7.66 – 7.58 (m, 2H, H_{Ar} BiPh), 7.40 –



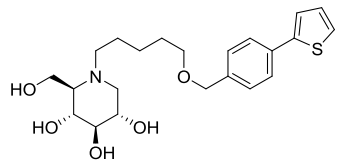
7.32 (m, 4H, H_{Ar} BiPh), 7.09 (dd, *J* = 5.1, 3.6 Hz, 1H, H_{Ar} BiPh), 4.52 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 4.00 – 3.92 (m, 3H, H_2-6, H-2), 3.86 (br s, 1H, H-3), 3.55 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.53 – 3.44 (m, 2H, H-5, H-1a), 3.39 – 3.32 (m, 3H, H-1b, H_2-1'), 1.92 – 1.73 (m, 2H, H_2-2'), 1.73 – 1.69 (m, 2H, H_2-4'), 1.52 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (215 MHz, MeOD) δ 145.1, 139.1, 135.3 (C_q BiPh), 129.5 – 124.3 (C_{Ar} BiPh), 73.6 (C-6'), 72.4 (C-4), 71.0 (C-5'), 69.0 (C-2), 68.1 (C-3), 63.8 (C-5), 61.4 (C-6), 55.1 (C-1'), 54.5 (C-1), 30.1 (C-4'), 24.6 (C-3'), 23.3 (C-2'). $[\alpha]^{20}_D$ = -3.57 (c = 0.056, MeOH). IR/cm^{-1}: 3366, 2924, 2326, 2872, 2326, 2207, 1684, 1506, 1202, 1134, 1101. HRMS: found 422.19949 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

N-[5-((4-(Thiophen-3-yl)benzyl]-4-yl)-methoxy)-pentyl]-L-*ido*-1-deoxynojirimycin (25):



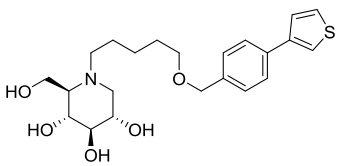
25 (10.0 mg, 0.024 mmol, 5% yield) was synthesized according to Suzuki coupling general procedure. ^{1}H NMR (400 MHz, MeOD) δ 7.69 – 7.59 (m, 3H, H_{Ar} BiPh), 7.48 – 7.44 (m, 2H, H_{Ar} BiPh), 7.37 (d, *J* = 8.0 Hz, 2H, H_{Ar} BiPh), 4.51 (s, 2H, H_2-6'), 4.02 (br s, 1H, H-4), 3.99 – 3.91 (m, 3H, H_2-6, H-2), 3.86 (t, *J* = 3.7 Hz, 1H, H-3), 3.55 (t, *J* = 6.1 Hz, 2H, H_2-5'), 3.53 – 3.41 (m, 2H, H-5, H-1a), 3.31 – 3.15 (m, 3H, H-1b, H_2-1'), 1.96 – 1.64 (m, 4H, H_2-2', H_2-4'), 1.51 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (100 MHz, MeOD) δ 141.8, 137.1, 135.3 (C_q BiPh), 128.1 – 119.9 (C_{Ar} BiPh), 72.3 (C-6'), 70.9 (C-4), 69.5 (C-5'), 67.5 (C-2), 66.6 (C-3), 62.4 (C-5), 60.0 (C-6), 53.6 (C-1'), 53.0 (C-1), 28.7 (C-4'), 23.2 (C-3'), 21.8 (C-2'). $[\alpha]^{20}_D$ = +9.00 (c = 0.20, MeOH). IR/cm^{-1}: 3319, 2926, 2862, 1674, 1427, 1201, 1134, 1072. HRMS: found 422.19946 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

N-[5-((4-(Thiophen-2-yl)benzyl]-4-yl)-methoxy)-pentyl]-1-deoxynojirimycin (26):



26 (1.8 mg, 0.004 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (600 MHz, MeOD) δ 7.55 – 7.44 (m, 2H, H_{Ar} BiPh), 7.39 – 7.17 (m, 5H, H_{Ar} BiPh), 4.47 (s, 2H, H_2-6'), 4.10 (d, *J* = 12.4 Hz, 1H, H-6a), 3.88 (dd, *J* = 12.5, 3.1 Hz, 1H, H-6b), 3.67 (ddd, *J* = 11.5, 9.2, 5.0 Hz, 1H. H-2), 3.59 (t, *J* = 9.8 Hz, 1H, H-4), 3.53 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.44 (dd, *J* = 12.0, 4.9 Hz, 1H, H-1a), 3.39 – 3.35 (m, 1H, H-1'a), 3.36 (t, *J* = 9.2 Hz, 1H, H-3), 3.22 – 3.14 (m, 1H, H-1'b), 3.02 (dd, *J* = 10.3, 2.9 Hz, 1H, H-5), 2.97 (t, *J* = 11.7 Hz, 1H, H-1b), 1.89 – 1.73 (m, 2H, H_2-2'), 1.72 – 1.66 (m, 2H, H_2-4'), 1.52 – 1.48 (m, 2H, H_2-3'). ^{13}C NMR (150 MHz, MeOD) δ 140.1, 139.2 (C_q BiPh), 132.5 – 122.3 (C_{Ar} BiPh), 78.2 (C-3), 73.1 (C-6'), 71.1 (C-5'), 68.8 (C-4), 67.8 (C-2), 67.4 (C-5), 54.9 (C-6), 54.8 (C-1), 54.3 (C-1'), 30.1 (C-4'), 24.5 (C-3'), 23.9 (C-2'). $[\alpha]^{20}_D$ = -4.00 (c = 0.20, MeOH). IR/cm^{-1}: 3402, 2943, 2868, 2324, 2241, 1683, 1205, 1134. HRMS: found 422.19961 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

N-[5-((4-(Thiophen-3-yl)benzyl]-4-yl)-methoxy)-pentyl]-1-deoxynojirimycin (27):



27 (2.5 mg, 0.006 mmol, 1% yield) was synthesized according to the Suzuki-Miyaura cross coupling general procedure. ^{1}H NMR (850 MHz, MeOD) δ 7.67 – 7.59 (m, 3H, H_{Ar} BiPh), 7.50 – 7.43 (m, 2H, H_{Ar} BiPh), 7.40 – 7.35 (m, 2H, H_{Ar} BiPh), 4.52 (s, 2H, H_2-6'), 4.10 (d, *J* = 12.4 Hz, 1H, H-6a), 3.88 (dd, *J* = 12.5, 3.2 Hz, 1H, H-6b), 3.66 (ddd, *J* = 11.3, 9.3, 4.9 Hz, 1H, H-2), 3.59 – 3.57 (m, 1H, H-4), 3.56 (t, *J* = 6.2 Hz, 2H, H_2-5'), 3.43 (dd, *J* = 12.1, 5.0 Hz, 1H, H-1a), 3.37 (dt, *J* = 12.8, 4.9 Hz, 1H, H-1'a), 3.35 (t, *J* = 9.3 Hz, 1H, H-3), 3.19 (td, *J* = 12.5, 5.0 Hz, 1H, H-1'b), 3.01 (dd, *J* = 10.4, 3.0 Hz, 1H, H-5), 2.97 (t, *J* = 11.7 Hz, 1H, H-1b), 1.86 – 1.73 (m, 2H, H_2-2'), 1.72 – 1.68 (m, 2H. H_2-4'), 1.55 – 1.47 (m, 2H, H_2-3'). ^{13}C NMR (215 MHz, MeOD) δ 143.2, 138.5 (C_q BiPh), 136.7

– 121.3 (C_{Ar} BiPh), 78.2 (C-3), 73.7 (C-6'), 70.9 (C-5'), 68.8 (C-4), 67.8 (C-2), 67.4 (C-5), 54.9 (C-6), 54.8 (C-1), 54.3 (C-1'), 30.1 (C-4'), 24.5 (C-3'), 23.9 (C-2'). $[\alpha]^{20}_D$ = -15.00 (c = 0.20, MeOH). IR/cm^{-1}: .3364, 2918, 2349, 1670, 1506, 1205, 1138. HRMS: found 422.19948 $[C_{22}H_{31}NO_5S+H]^+$, calculated for $[C_{22}H_{31}NO_5S+H]^+$ 422.19957.

References:

1. Platt, F. M.; Neises, G. R.; Dwek, R. A.; Butters, T. D. *N*-butyldeoxynojirimycin is a novel inhibitor of eglycolipid biosynthesis. *J. Biol. Chem.* **1994**, *269*, 8362-8365.
2. Ghisaidoobe, A. T.; van den Berg, R. J. B. H. N.; Butt, S. S.; Strijland, A.; Donker-Koopman, W. E.; Scheij, S.; van den Nieuwendijk, A. M. C. H.; Koomen, G. J.; van Loevezijn, A.; Leemhuis, M.; Wennekes, T.; van der Stelt, M.; van der Marel, G. A.; van Boeckel, C. A. A.; Aerts, J. M. F. G.; Overkleeft, H. S. Identification and development of biphenyl substituted iminosugars as improved dual glucosylceramide synthase/neutral glucosylceramidase inhibitors. *J. Med. Chem.* **2014**, *57*, 9096-9104.
3. Nietupski, J. B.; Pacheco, J. J.; Chuang, W. L.; Maratea, K.; Li, L. Y.; Foley, J.; Ashe, K. M.; Cooper, C. G. F.; Aerts, J. M. F. G.; Copeland, D. P.; Scheule, R. K.; Cheng, S. H.; Marshall, J. Iminosugar-based inhibitors of glucosylceramide synthase prolong survival but paradoxically increase brain glucosylceramide levels in Niemann-Pick C mice. *Mol. Genet. Metab.* **2012**, *105*, 621-628.
4. Wennekes, T.; van den Berg, R. J. B. H. N.; Donker, W.; van der Marel, G. A.; Donker, W.; van der Marel, G. A.; Strijland, A.; Aerts, J. M. F. G.; Overkleeft, H. S. Development of adamantan-1-yl-methoxy-functionalized 1-deoxynojirimycin derivatives as selective inhibitors of glucosylceramide metabolism in man. *J. Org. Chem.* **2007**, *72*, 1088-1097.
5. Ahmadi, Z.; McIndoe, J. S. A mechanistic investigation of hydrodehalogenation using ESI-MS. *Chem. Commun.* **2013**, *49*, 11488-11490.
6. Jedinak, L.; Zatopkova, R.; Zemankova, H.; Sustkova, A.; Cankar, P. The Suzuki Miyaura cross-coupling reaction of halogenated aminopyrazoles: method development, scope, and mechanism of dehalogenation side reaction. *J. Org. Chem.* **2017**, *82*, 157-169.
7. Shultz, M. D. Setting expectations in molecular optimizations: strengths and limitations of commonly used composite parameters. *Bioorg. Med. Chem. Lett.* **2013**, *23*, 5980-5991.
8. van Weely, S.; van Leeuwen, M. B.; Jansen, I. D. C.; Debruijn, M. A. C.; Brouwerkelder, E. M.; Schram, A. W.; Clarasamiranda, M.; Barranger, J. A.; Petersen, E. M.; Goldblatt, J.; Stotz, H.; Schwarzmann, G.; Sandhoff, K.; Svennerholm, L.; Erikson, A.; Tager, J. M.; Aerts, J. M. F. G. Clinical phenotype of gaucher disease in relation to properties of mutant glucocerebrosidase in cultured fibroblasts. *Biochim. Biophys. Acta* **1991**, *1096*, 301-311.
9. Overkleeft, H. S.; Renkema, G. H.; Neele, J.; Vianello, P.; Hung, I. O.; Strijland, A.; van der Burg, A. M.; Koomen, G. J.; Pandit, U. K.; Aerts, J. M. F. G. Generation of specific deoxynojirimycin-type inhibitors of the non-lysosomal glucosylceramidase. *J. Biol. Chem.* **1998**, *273*, 26522-26527.
10. Fulmer, G. R.; Miller, A. J. M.; Sherden, N. H.; Gottlieb, H. E.; Nudelman, A.; Stoltz, B. M.; Bercaw, J. E.; Goldberg, K. I. NMR chemical shifts of trace impurities: common laboratory solvents, organics, and gases in deuterated solvents relevant to the organometallic chemist. *Organometallics* **2010**, *29*, 2176-2179.