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A new access to polyhydroxy piperidines of the azasugar class: synthesis and glycosidase inhibition studies

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A new synthetic strategy has been devised to access a variety of polyhydroxylated piperidines belonging to the azasugar class of glycosidase inhibitors. The key precursor (3a*R*, 7a*R*)-5-benzyl-2,2-dimethyl-7-methylenehexahydro[1,3]dioxo[4,5-*c*]pyridine is obtained by photoinduced electron transfer (PET) cyclization of the corresponding α-trimethylsilylmethylamine radical cation to the tethered acetylene functionality. The new molecules have been evaluated for inhibitory properties for certain β-glycosidases and have been found to be moderate to weak inhibitors of the enzymes under study.

Introduction

Polyhydroxy piperidines, also characterized as inhibitors of glycosidases, have found widespread interest,[1] especially, after being postulated as possible therapeutics in the treatment of a variety of carbohydrate mediated diseases.[2] These low-molecular weight entities, also termed as "azasugars", are suggested to bind to glycosidases by mimicking the shape and charge of the postulated oxo-carbenium ion intermediate for the glycosidic bond cleavage reaction.[3] Based on the studies on the relationship between structure and inhibitory activity in glycosidase inhibitors, the research groups of Bols,[4] Ichikawa[5] and Nishimura[6] have developed a new class of sugar mimic inhibitor having a nitrogen atom at the anomeric position. These designed azasugars have displayed high inhibitory potencies towards β-glycosidases, whose substrates they have mimicked. In particular, isofagomine[4a] (**1**, $R^1 = CH_2OH$, R^2 = H), isoglucuronofagomine[5d] (**2**, R^1 = COOH, R^2 = H), 5-hydroxy isofagomine[5c] (**3**, $R^1 = CH_2OH$, R^2 = OH), noeuromycin[4d] (**4**, $R^1 = CH_2OH$, R^2 = H), isogalactofagomine[5b] (**5**) and isofucofagomine[5a,4b] (**6**) have been found to be extremely potent and selective inhibitors of β-glycosidases (Chart 1).

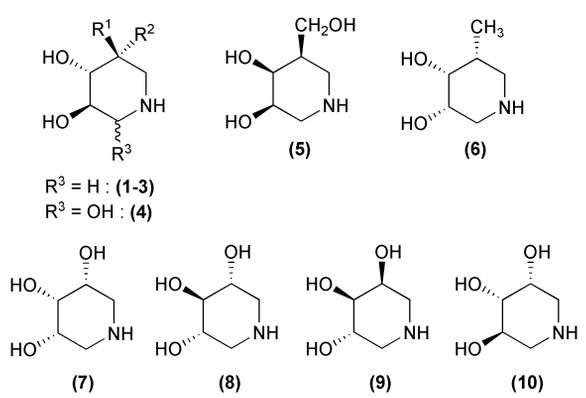

Chart 1 Azasugar type glycosidase inhibitors.

3,4,5-Trihydroxy piperidines (**7**–**10**), first synthesized by Ganem *et al*., are also shown to exhibit moderate to good glycosidase inhibitory activity.[7] These compounds (**7**–**9**) were subsequently, isolated from *Eupatorium Fortunei* TURZ by Kusano and co-workers[8] and were shown to be active components of the extracts of this plant which had been used traditionally in Chinese and Japanese folk medicine for a variety of disorders.

Although tremendous effort has been put into the development of synthetic routes towards these piperidines,[9,10] these deceptively simple looking molecules have not been easy to synthesize. Barring a few approaches, most of the groups rely upon carbohydrates as starting materials for the polyhydroxy framework. The construction of the aminomethylene moiety in the neighborhood of a stereocenter and the lack of suitably substituted carbohydrates make the approaches towards these molecules lengthy and rather tedious. In this context, other than the approaches of the groups of Ganem[9c] and Nishimura,[6d] a general and flexible synthetic route towards this class of inhibitors is unknown. As a part of our ongoing interest in the polyhydroxy piperidines, we envisioned an entity of type **11** (Chart 2) as a general representative synthon for an easy access to these classes of compounds.[11] This design was surmised keeping in mind the general substitution pattern of the azasugars of type **12**.

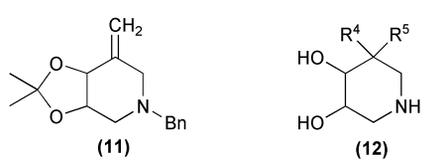

Chart 2

These substituted piperidines (**11**) were envisaged to be accessed utilizing our methodology developed for the synthesis of cyclic amines *via* the photoinduced electron transfer (PET) mediated cyclization of α-trimethylsilylmethylamine radical cation to a tethered acetylene functionality.[12] The acetonide moiety was chosen in order to lock the conformation for better diastereoselection during the functionalization of the exocyclic olefin. We report herein the full details[13] on the synthesis of a variety of the azasugars through the general route as depicted retrosynthetically in Scheme 1, as well as the evaluation of the glycosidase inhibitory properties of some of the new molecules.

Results and discussion

As a part of our broad research program aimed at the design, synthesis and evaluation of new glycosidase inhibitors of the azasugar class, we initially chose isofagomine (**1**) as our target. This compound was synthesized[11] (Scheme 2) by the hydroboration of the D-*threo* precursor **15** using 9-BBN followed by the removal of the protecting groups. The key precursor

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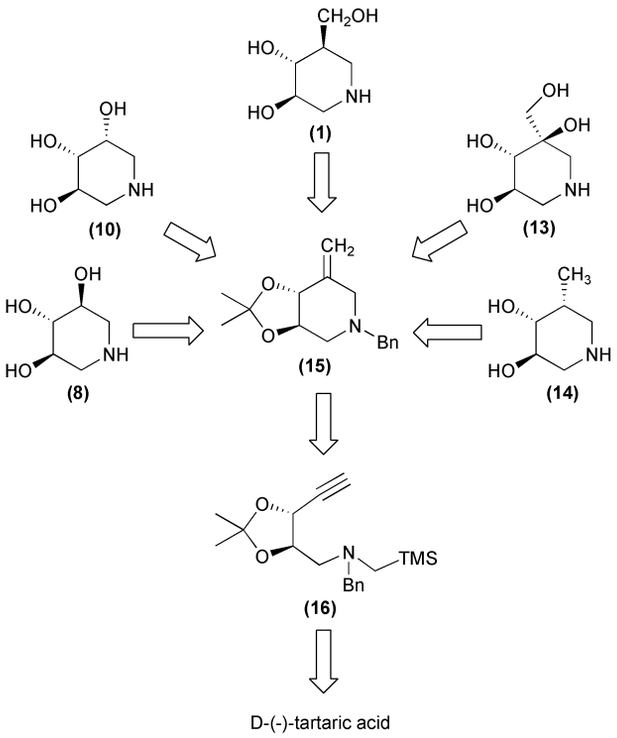
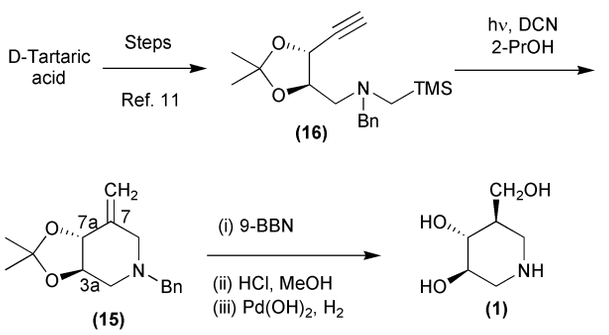


Scheme 1

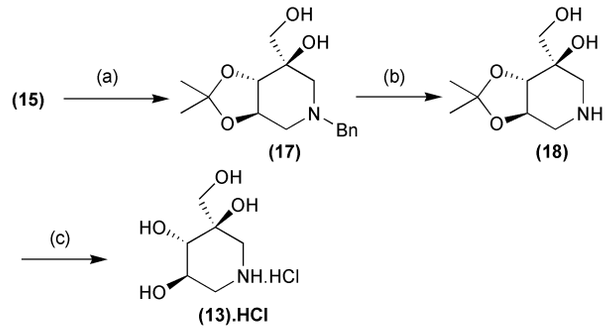


Scheme 2 Synthesis of isofagomine.

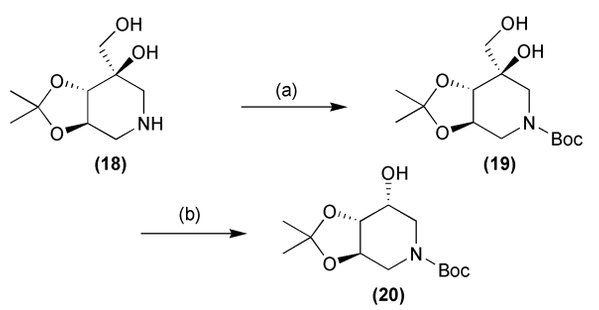
(3a*R*, 7a*R*)-5-benzyl-2,2-dimethyl-7-methylenehexahydro[1,3]-dioxo[4,5-*c*]pyridine (**15**) was obtained in 60% yield by the PET cyclization[12] of **16** which in turn was synthesised from (D)-tartaric acid by following simple synthetic steps.[11] Hydroboration of **15** took place selectively from the α-face, possibly due to the preferential low energy equatorial orientation of the bulky bicyclic boron in the four membered transition state. In a similar fashion (−)-isofagomine was also synthesized starting from the L-*threo* precursor (*ent*-**15**)

This success prompted us to go in for the further development of our strategy and we took up the preparation of 5-hydroxy-5-*epi*-isofagomine (**13**) (Scheme 3). Osmium tetroxide dihydroxylation of **15** afforded **17** as a single diastereomer. The stereochemistry of the product was adjudged by HETCOR and COSY experiments. Although, **13** could be obtained by a one-pot hydrogenation of **17** in acidic medium, we failed to purify it by any of the available means. Therefore, a two-step sequence, *N*-debenzylation followed by acetonide deprotection, was adopted to obtain **13** in a pure state.

Subsequently, it was visualized that the corresponding synthesis of piperidines **8**–**10** could also be achieved from the D- and L-*threo* precursors. Towards the planned synthesis of des(hydroxymethyl)-deoxymannojirimycin (**10**), the diol **17** was first subjected to *N*-debenzylation to obtain **18** and was reprotected as *N*-Boc derivative **19**. This deprotection–protection sequence was performed to avoid any possible complications during periodate oxidation. The periodate oxidation of **19** followed by the reduction of the corresponding ketone (Scheme 4), failed to give a good yield of the expected alcohol **20**. Therefore, we reverted back to **17** once again.

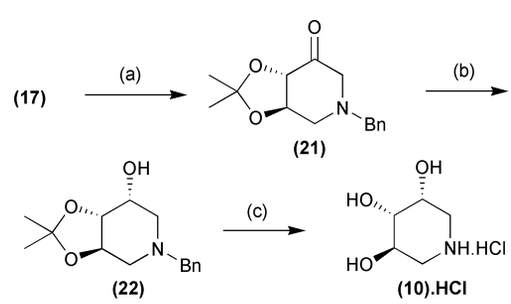


Scheme 3 *Reagents and conditions:* (a) OsO_4, NMO, pyridine, acetone–water (9 : 1), from 0 °C to rt, 24 h, 95%; (b) $Pd(OH)_2$, H_2, EtOH, 65 psi, 6 h, 90%; (c) HCl, MeOH, rt, 4 h, quant.



Scheme 4 *Reagents and conditions:* (a) $(Boc)_2O$, TEA, DCM, from 0 °C to rt, overnight, 80%; (b) (i) $NaIO_4$, EtOH–H_2O (4 : 1), rt, 30 min, 70%; (ii) $NaBH_4$, MeOH, rt, 36 h, then saturated NaCl, rt, 24 h, 25%.

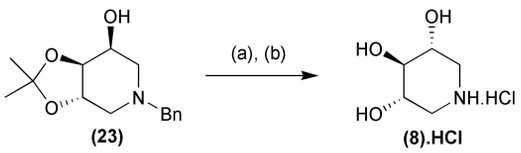
The diol **17** upon periodate oxidation afforded **21** (Scheme 5), which was quickly subjected to sodium borohydride reduction resulting in the formation of **22** in 85% yield. The diastereomeric ratio (9 : 1), was determined by the capillary GC analysis (Varian CP-Sil 5CB, 30 m, 0.25 mm i.d. column). These diastereomers were found to be non-separable at this stage. One pot *N*-debenzylation and acetonide removal afforded **10** as a hydrochloride salt. Purification of the crude **10** was carried out by column chromatography as a free base, which was reconverted back to its hydrochloride salt for spectral characterization. The stereochemistry of **10** was determined by COSY experiments. The optical rotation ($[\alpha]_D^{25} = -12$ (*c* 0.15, MeOH); lit[7] $[\alpha]_D^{25} = -16$ (*c* 0.9, MeOH)) and spectral characteristics for **10**·HCl were found to be in close agreement with those reported in literature.[7]



Scheme 5 *Reagents and conditions:* (a) $NaIO_4$, EtOH–H_2O (4 : 1), rt, 1 h, 80%; (b) $NaBH_4$, MeOH, rt, 40 h, then saturated NaCl, rt, 24 h, 85%; (c) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 36 h, quant; silica gel chromatography, 88%.

Next, we targeted the synthesis of *meso*-des(hydroxymethyl)-deoxynojirimycin (**8**). It was visualized that **8** could be accessed easily by inverting the stereochemistry of the free hydroxy group either in **22** or **23** (*ent*-**22**). Mitsunobu esterification[14] of

23 followed by the cleavage of the *p*-nitrobenzoate and acetonide deprotection as well as *N*-debenzylation afforded **8** as its hydrochloride salt (Scheme 6). Usual purification of the basified material by column chromatography afforded pure **8**. Spectral characteristics of **8**·HCl were found to be in excellent agreement with reported values.[7]

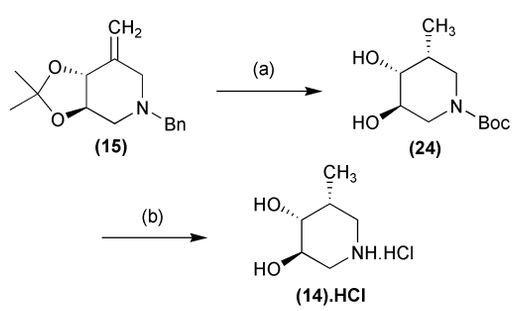


Scheme 6 *Reagents and conditions:* (a) (i) diisopropyl azodicarboxylate, PPh_3, *p*-nitrobenzoic acid, THF, rt, overnight; (ii) LiOH, MeOH, 60% over two steps; (b) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, rt, 20 h, quant; silica gel chromatography, 90%.

Further, we adopted a one-pot strategy for the synthesis of 5′-deoxy-5-*epi*-isofagomine (**14**) (Scheme 7).

This effort was prompted by the fact that the fucose analog **6** was found to be an extremely potent inhibitor of fucosidases.[5a,4b] Therefore, it was decided to evaluate **14**, the C-3 epimer of **6** and compare its activity with the dihydroxy analog **13**. The catalytic hydrogenation of **15**, *N*-debenzylation as well as acetonide removal afforded **14** in a 4 : 1 diastereomeric ratio (as determined by NMR). The free amines were not separable and therefore, were converted to the corresponding *N*-Boc derivatives. Careful column chromatography afforded the major diastereomer as a pure compound. The stereochemistry of the 5-methyl group was adjudged by the coupling constants for H_4, which was observed as a dd (J = 6.8, 4.0 Hz) at δ 3.63. The *N*-Boc moiety was cleaved to afford **14** as a hydrochloride salt.

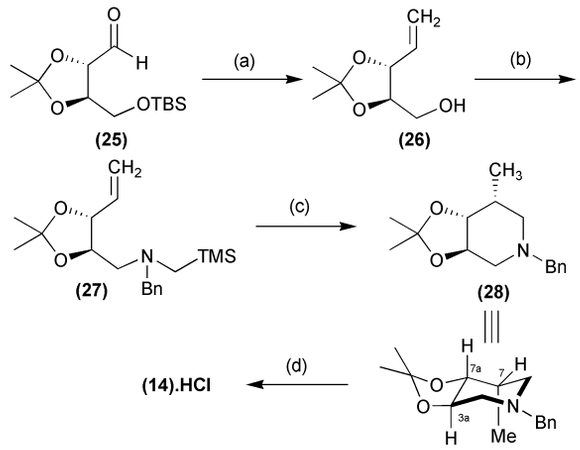
The moderate diastereoselectivity in the synthesis of **14**, encouraged us to improve upon it by attempting the direct PET cyclization of **27** (Scheme 8).



Scheme 7 *Reagents and conditions:* (a) (i) Pd/C, MeOH, HCl, H_2, 1 atm, rt, 12 h, 89%; (ii) $(Boc)_2O$, TEA, DCM, rt, 48 h, 75%; (b) HCl, MeOH, from 0 °C to rt, 4 h, quant.

Towards this end, the efforts began by deriving the alcohol **26** from D-tartaric acid. Wittig olefination of the aldehyde **25**,[15] followed by TBS removal afforded **26**, data for which is in accordance with that reported in literature for its enantiomer.[16] Nucleophilic displacement of the corresponding tosylate using $PhCH_2NHCH_2TMS$, afforded **27**. This amine, when irradiated under PET cyclization conditions, yielded **28** as almost a single diastereomer (>97% as determined by GC). The stereochemistry of the methyl group was ascertained by the coupling constants for H_{7a} (δ 3.24, ddd, J = 9.9, 4.0, 1.2 Hz). A small coupling constant of 4.0 Hz pointed to the axial–equatorial relationship of H_{7a} and H_7. The coupling constant of 1.2 Hz was attributed to long range coupling, probably with one of H_6 protons. The protecting groups were removed to afford **14**·HCl.

In a manner similar to that described earlier, utilizing the L-*threo* precursor, we prepared the corresponding enantiomeric azasugars, **29** (*ent*-**13**), **30** (*ent*-**14**) and des(hydroxymethyl)-deoxygalactonojirimycin (**9**) (Chart 3).



Scheme 8 *Reagents and conditions:* (a) (i) PPh_3, *n*-BuLi, THF, −15 °C to rt, 16 h, 60%; (ii) TBAF, THF, rt, 4 h, 90%; (b) (i) TsCl, pyridine, DCM, rt, 24 h, 95%; (ii) $PhCH_2NHCH_2TMS$, Cs_2CO_3, TBAI, CH_3CN, reflux, 72 h, 58%; (c) *hv*, DCN, 2-PrOH, 2 h, 55%; (d) $Pd(OH)_2$ on C, HCl, MeOH, H_2, 1 atm, 28 h, quant.

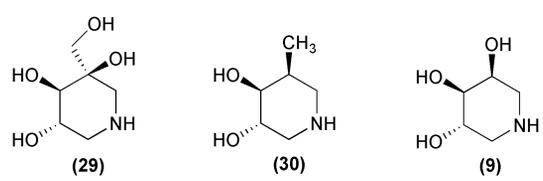


Chart 3 The azasugars obtained from L-*threo* precursor.

The new compounds were tested for inhibitory activities of β-glucosidase and β-mannosidase. The results of the study are summarized in Table 1. The compounds tested exhibited moderate to weak inhibition for the glycosidases under study. The dihydroxy compound **13** and the 5′-deoxy compound **14**, both derived from the D-*threo* precursor **15**, displayed moderate inhibition for β-glucosidase. Surprisingly **14**, which lacks the hydroxy group at the 5-position was found to be a better inhibitor than **13**. The iminosugar **14**, however, did not inhibit β-mannosidase. The corresponding enantiomers, derived from L-*threo* precursor, were found to be weak inhibitors of β-glucosidase. Substrate **29** inhibited β-mannosidase to some extent. We also tested the *N*-benzyl derivatives of the corresponding dihydroxy compounds but no general trend was observed for these compounds.

In conclusion, a new synthetic strategy to access polyhydroxy piperidines of the 1-*N*-iminosugar type has been generalized by synthesizing a variety of 1-*N*-iminosugars. It is quite obvious that this methodology can easily be extended to derive other azasugars in which the C-3 and C-4 hydroxy are *syn*, utilizing precursors of the D- and L-*erythro* type.

Experimental

General methods

All reagents were used as supplied. Unless otherwise mentioned, all reactions involving sensitive reagents and anhydrous solvents, were carried out under an argon atmosphere. The boiling point range of the petroleum ether referred to throughout the Experimental section was 60–80 °C. Melting points reported are uncorrected. ^1H and ^{13}C NMR spectra were run on Bruker AC 200 and DRX 500 instruments. GC-MS was performed on Shimadzu QP 5000 GC/MS coupled to Shimadzu 17A GC using a DB1 column. GC analysis was performed on a Varian CP 3800 GC using CP-Sil 5CB column. ESI (Electrospray Ionization) HRMS spectra were obtained on QSTAR PULSAR LC-MS/MS-TOF using an infusion method. Optical rotations were measured on a Jasco P1030 polarimeter in units of 10^{-1} deg cm^2 g^{-1}. The glycosidases and

Table 1 Enzyme inhibition studies

Glycosidase	*Ki*/μM					
	13	**14**	*N*-Bn-**13**	**29**	**30**	*N*-Bn-**29**
β-Glucosidase (37 °C, pH 6.0)	96	30	590	580	370	300
β-Mannosidase (25 °C, pH 4.0)	NT[a]	NI[b]	NT	290	NI	1500

[a] NT = not tested. [b] NI = no inhibition up to 2 mM.

the corresponding *p*-nitrophenyl β-D-glycosides were purchased from Sigma. The optical density measurements were carried out on a Varian CARY-50 BIO UV-VIS spectrophotometer.

For the synthesis of the D- and L-*threo* precursors (15 and *ent*-15 respectively) and the preparation of isofagomine, see ref. [11]

General procedure for the PET cyclization. A typical PET cyclization procedure involves irradiation of a solution containing the substrate (1 mmol) and a catalytic amount of 1,4-dicyanonaphthalene (DCN) (0.15–0.30 mmol) in 2-propanol (0.5 mL per mg of substrate), in an open vessel, using a 450 W Hanovia medium pressure mercury vapor lamp as the light source. The lamp is housed in a Pyrex water-jacketed immersion well so as to allow only the wavelengths greater than 280 nm to pass through. The reaction is monitored by TLC or GC and when the consumption of the starting material is found to be complete (>90%), the irradiation is discontinued. The solvent is removed under reduced pressure and the photolysate is purified by column chromatography.

(3a*R*,7*R*,7a*S*)-5-Benzyl-7-(hydroxymethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (17). To a solution of **15** (0.119 g, 0.46 mmol) in acetone–water (3 mL, 9 : 1) was added pyridine (40 μL, 0.46 mmol), followed by *N*-methylmorpholine-*N*-oxide (0.108 g, 0.92 mmol). The reaction mixture was cooled to 0 °C and to it was added a catalytic amount of osmium tetroxide (0.002 g). The reaction mixture was allowed to come to rt and was stirred for 24 h. It was passed through a short pad of Celite and the solvent evaporated off. The crude reaction mixture upon column chromatography (silica, pet. ether–ethyl acetate, 3 : 2) afforded the diol **17** as a colorless solid (0.128 g, 95%). Mp 150–152 °C; $[a]_D^{25}$ −21.6 (*c* = 1.4, MeOH); δ_H (500 MHz, $CDCl_3$) 7.40 (m, 5H, Ar), 4.25 (d, *J* 11.5 Hz, 1H, CH_2–OH), 3.85 (ddd, *J* 9.9, 9.7, 4.3 Hz, 1H, H_{3a}), 3.78 (d, *J* 11.5 Hz, 1H, CH_2–OH), 3.76 (d, *J* 13.8 Hz, 1H, N–CH_2–Ph), 3.71 (d, *J* 13.8 Hz, 1H, N–CH_2–Ph), 3.61 (d, *J* 9.7 Hz, 1H, H_{7a}), 3.30 (dd, *J* 9.7, 4.3 Hz, 1H, H_{4eq}), 2.92 (d, *J* 11.7 Hz, 1H, H_{6eq}), 2.31 (dd like t, *J* 10.1, 9.9 Hz, 1H, H_{4ax}), 2.21 (d, *J* 12.0 Hz, 1H, H_{6ax}), 1.50 (s, 6H, 2 × CH_3); δ_C (50 MHz, $CDCl_3$) 137.7, 128.6, 128.3, 127.3 (Ar), 110.7 (C_2, –C–), 86.2 (C_{7a}, CH), 73.6 (C_{3a}, CH), 71.5 (C_7, –C–), 65.0 (*C*H_2OH, CH_2), 61.5 (N–*C*H_2Ph, CH_2), 59.3 (C_6, CH_2), 54.5 (C_4, CH_2), 26.5 (2 × CH_3); *m*/*z* (%) 293 (M^+)(5), 235 (25), 134 (45), 120 (41), 91 (100).

(3a*R*,7*R*,7a*S*)-7-(Hydroxymethyl)-2,2-dimethylhexahydro[1,3]dioxolo[4,5-*c*]pyridin-7-ol (18). An ethanolic solution (2 mL) of the diol **17** (0.100 g, 0.34 mmol) was hydrogenated for 6 h in the presence of $Pd(OH)_2$ on charcoal (20%) (0.005 g) at 60 psi. The catalyst was filtered off and the solvent removed *in vacuo*. The crude reaction mixture was purified using column chromatography (silica, chloroform–methanol, 9 : 1) to afford pure **18** (0.063 g, 90%) as a colorless gum. $[a]_D^{25}$ −24.7 (*c* = 0.9, MeOH); δ_H (500 MHz, D_2O) 3.81 (d, *J* 12.1 Hz, 1H, CH_2OH), 3.79 (d, *J* 12.1 Hz, 1H, CH_2OH), 3.69 (ddd, *J* 10.0, 9.9, 4.4 Hz, 1H, H_{3a}), 3.62 (d, *J* 9.5 Hz, 1H, H_{7a}), 3.35 (dd, *J* 11.9, 4.0 Hz, 1H, H_{4eq}), 3.24 (d, *J* 13.9 Hz, 1H, H_{6eq}), 2.70 (dd like t, *J* 11.1, 10.3 Hz, 1H, H_{4ax}), 2.37 (d, *J* 13.9 Hz, 1H, H_{6ax}), 1.43 (s, 3H, CH_3), 1.42 (s, 3H, CH_3); δ_C (125 MHz, D_2O) 110.2 (C_2, –C–), 84.1 (C_{7a}, CH), 73.7 (C_7, –C–), 72.9 (C_{3a}, CH), 60.0 (*C*H_2OH), 49.6 (C_6, CH_2), 46.0 (C_4, CH_2), 25.4 (2 × CH_3); ESI HRMS found 204.1236, $C_9H_{18}NO_4$ requires 204.1236.

(3*R*,4*S*,5*R*)-3-(Hydroxymethyl)piperidine-3,4,5-triol, hydrochloride salt (13·HCl). To a solution of substrate **18** (0.025 g, 0.12 mmol) in distilled methanol (0.5 mL) was added conc. HCl (2 drops) and the reaction mixture was stirred at rt for approximately 4 h. The solvent was evaporated to dryness and the residue dissolved in water (1 mL) and lyophilized to afford **13**·HCl (0.024 g, ~100%) as an amorphous solid. $[a]_D^{25}$ +11.0 (*c* = 0.2, EtOH); δ_H (500 MHz, D_2O) 4.11 (m, 1H, H_3), 3.85 (d, *J* 4.4 Hz, 1H, H_4), 3.71 (d, *J* 12.0 Hz, 1H, CH_2OH), 3.64 (d, *J* 12.0 Hz, 1H, CH_2OH), 3.43 (d, *J* 13.6 Hz, 1H, H_{6eq}), 3.30 (m, 2H, H_2), 3.16 (d, *J* 13.6 Hz, 1H, H_{6ax}); δ_C (125 MHz, D_2O) 71.5 (C_5, –C–), 68.1 (C_3, CH), 66.6 (C_4, CH), 63.6 (*C*H_2OH, CH_2), 46.1 (C_2, CH_2), 45.2 (C_6, CH_2); ESI HRMS found 164.0916, $C_6H_{14}NO_4$ requires 164.0923.

(3a*R*,7a*S*)-5-Benzyl-2,2-dimethyltetrahydro[1,3]dioxolo-[4,5-*c*]pyridin-7(4*H*)-one (21). To a solution of **17** (0.100 g, 0.34 mmol) in ethanol–water (2 mL, 8 : 2), was added sodium periodate (0.090 g, 0.4 mmol) in three portions over a period of 15 min. The white suspension was stirred for an additional hour and filtered. The solvent was evaporated off and the white pasty mass was extracted into ethyl acetate (3 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent was removed under reduced pressure. Column chromatography (silica, pet. ether–ethyl acetate, 4 : 1) of the crude mixture afforded pure **21** (0.071 g, 80%) as a colorless liquid. δ_H (200 MHz, $CDCl_3$) 7.30 (m, 5H, Ar), 4.26 (dd, *J* 10.2, 1.5 Hz, 1H, H_{7a}), 3.90 (ddd, *J* 10.0, 9.8, 4.4 Hz, 1H, H_{3a}), 3.75 (m, 2H, N–CH_2Ph), 3.40 (dd, *J* 10.3, 4.4 Hz, 1H, H_{4eq}), 3.25 (d, *J* 14.2 Hz, 1H, H_6), 3.05 (d, *J* 14.2 Hz, 1H, H_6), 2.72 (dd like t, *J* 10.2, 9.8 Hz, 1H, H_{4ax}), 1.50 (s, 3H, CH_3), 1.49 (s, 3H, CH_3).

(3a*R*,7*R*,7a*R*)-5-Benzyl-2,2-dimethylhexahydro[1,3]dioxolo-[4,5-*c*]pyridin-7-ol (22). Sodium borohydride (0.009 g, 0.23 mmol) was added to a solution of **21** (0.050 g, 0.019 mmol) in methanol (0.5 mL). The resulting mixture was stirred for 48 h and then quenched by the adding a saturated solution of NaCl in excess. The resultant white suspension was stirred overnight and then extracted into ethyl acetate (4 × 3 mL). The combined organic extracts were dried over anhydrous Na_2SO_4 and the solvent evaporated off. The residue was purified using column chromatography (silica, pet. ether–ethyl acetate, 3 : 2) to afford **22** (0.043 g, 85%) as a colorless oil (9 : 1 mixture of diastereomers). $[a]_D^{25}$ −36.2 (*c* = 0.13, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.35 (m, 5H, Ar), 4.30 (m, 1H, H_7), 4.10 (ddd, *J* 10.3, 9.7, 4.4 Hz, 1H, H_{3a}), 3.87 (d, *J* 13.7 Hz, 1H, N–CH_2Ph), 3.79 (d, *J* 13.7 Hz, 1H, N–CH_2Ph), 3.45–3.30 (m, 2H, H7a, H_{4eq}), 3.20 (m, 1H, H_{6eq}), 2.80 (br s, 1H, O*H*), 2.40 (m, 2H, H_{4ax}, H_{6ax}), 1.50 (s, 3H, CH_3), 1.49 (s, 3H, CH_3); δ_C (125 MHz, $CDCl_3$) 137.2, 128.7, 128.1, 127.1 (Ar), 110.1 (C_2, –C–), 81.4 (C_7, CH), 70.6 (C_{7a}, CH), 65.7 (C_{3a}, CH), 61.5 (N–*C*H_2Ph), 56.5 (C_4, CH_2), 54.7 (C_6, CH_2), 26.5 (CH_3), 26.3 (CH_3); GC/MS: *m*/*z* (%) 263 (M^+)(<1%), 207 (3), 172 (7), 149 (20), 91 (100).

(3*R*,5*R*)-Piperidine-3,4,5-triol, hydrochloride salt (des-(hydroxymethyl)deoxy-mannojirimycin) (10·HCl). To a solution of **22** (0.030 g, 0.11 mmol) in distilled methanol (0.5 mL) was

added conc. HCl (2 drops), followed by $Pd(OH)_2$ on C (20%) (0.003 g) and the reaction mixture was hydrogenated at atmospheric pressure for approximately 16 h. After passing through a short pad of Celite, the solvent evaporated off to dryness to afford **10**·HCl (19 mg, ~100%). Pure **10** was obtained by column chromatography of the corresponding free base (silica, chloroform–2-propanol–aq. NH_3, 8.5 : 1.5 : 0.5). The combined fractions containing the compound were pooled together and concentrated. Water (2 mL) was added and the solution concentrated. The residue was dissolved in water (0.5 mL) and hydrochloric acid (1 mL, 6 M) was added. This solution was concentrated and the residue lyophilized from water to yield **10**·HCl (0.0167 g, 88%) as a white solid. $[\alpha]_D^{25}$ −12 (*c* = 0.15, MeOH); lit[7] $[\alpha]_D^{25}$ −16 (*c* = 0.9, MeOH); For des(hydroxymethyl)deoxygalactonojirimycin, **9**·HCl, $[\alpha]_D^{25}$ +18 (*c* = 0.14, MeOH); lit[7] $[\alpha]_D^{25}$ +16 (*c* = 0.5, MeOH); δ_H (500 MHz, D_2O) 4.20 (m, 1H, H_5), 4.06 (ddd, *J* 8.3, 7.8, 3.9 Hz, 1H, H_3), 3.75 (dd, *J* 7.6, 3.2 Hz, 1H, H_4), 3.37 (dd, *J* 13.2, 3.9 Hz, 1H, H_{2eq}), 3.26 (dd, *J* 12.9, 5.9 Hz, 1H, H_{6eq}), 3.18 (m, 1H, H_{6ax}), 2.92 (dd, *J* 12.7, 8.4 Hz, 1H, H_{2ax}); δ_C (125 MHz, D_2O) 70.7 (C_5, CH), 65.0 (C_4, CH), 64.6 (C_3, CH), 45.9 (C_2, CH_2), 45.4 (C_6, CH_2); ESI HRMS found 134.0813, $C_5H_{12}NO_3$ requires 134.0817.

(3*R*,5*S*)-Piperidine-3,4,5-triol, hydrochloride salt (des-(hydroxymethyl)deoxy-nojirimycin) (8·HCl). To a solution of **23** (0.090 g, 0.34 mmol) in dry THF (2 mL) was added triphenyl phosphine (0.099 g, 0.38 mmol) and *p*-nitrobenzoic acid (0.063 g, 0.38 mmol). The resulting reaction mixture was cooled to 0 °C and to it was added diisopropyl azodicarboxylate (81 μL, 0.41 mmol). The reaction mixture was allowed to warm to rt and was stirred overnight. This was followed by extraction into DCM (5 mL) with sodium bicarbonate washes (2 M, 3 × 3 mL). The organic layer, after drying over anhydrous Na_2SO_4, was concentrated under reduced pressure. This residue was dissolved in a minimum quantity of DCM and to it was added petroleum ether to precipitate out the phosphine oxide. The resulting slurry was loaded onto a column of silica gel and eluted. The combined fractions were concentrated *in vacuo* to afford the benzoate. This benzoate was dissolved in distilled methanol (2 mL) and to it was added lithium hydroxide (0.016 g, 0.68 mmol) and the reaction mixture was stirred at rt for about 6 h. Water (5 mL) was added, followed by ethyl acetate (6 mL) and the layers were separated. The organic layer was dried (anhydrous Na_2SO_4) and concentrated under reduced pressure to afford the alcohol (0.054 g, 60%).

This alcohol was dissolved in distilled methanol (1.5 mL) and conc. HCl (2 drops) was added and the resulting reaction mixture was hydrogenated at atmospheric pressure in the presence of $Pd(OH)_2$ on carbon (20%) (0.002 g), for about 7 h. The catalyst was filtered off and the filtrate evaporated to dryness to afford **8** as a hydrochloride salt (0.035 g, ~100%), which was further purified by column chromatography as a free base (silica, chloroform–2-propanol–aq. NH_3, 8.5 : 1.5 : 0.5). Utilizing exactly the same procedure as described for compound **10**, the triol **8** was reconverted back to its hydrochloride salt for spectral characterization (0.0315 g, 90%). $[\alpha]_D^{25}$ 0.0 (*c* = 0.2, MeOH); δ_H (500 MHz, D_2O) 3.72 (ddd, *J* 10.2, 8.4, 4.4 Hz, 2H, H_3, H_5), 3.46 (t, *J* 8.4 Hz, 1H, H_4), 3.40 (dd, *J* 12.7, 4.3 Hz, 2H, H_{2eq}, H_{6eq}), 2.86 (dd, *J* 12.7, 10.3 Hz, 2H, H_{2ax}, H_{6ax}); δ_C (125 MHz, D_2O) 74.3 (C_4, CH), 66.5 (C_3, C_5, 2 × CH), 45.9 (C_2, C_4, 2 × CH_2); ESI HRMS found 134.0822, $C_5H_{12}NO_3$ requires 134.0817.

***tert*-Butyl (3*R*,4*R*,5*R*)-3,4-dihydroxy-5-methylpiperidine-1-carboxylate (24).** To an ethanolic solution (1 mL) of **15** (0.040 g, 0.15 mmol), was added conc. HCl (50 μL) followed by Pd/C (10%) (0.005 g) and the mixture was hydrogenated at atmospheric pressure for over 12 h. The suspension was passed through a short pad of Celite and the mixture evaporated to dryness to afford the hydrochloride salt (0.023 g, 89%). NMR analysis of the crude mixture indicated it to be a mixture of diastereomers in a ratio of 4 : 1, which were non-separable. This salt was basified using conc. NH_4OH and the excess ammonia was evaporated off. This was dissolved in DCM (1 mL) and triethyl amine (0.1 mL, 0.7 mmol) was added and the resulting mixture was cooled to 0 °C. $(Boc)_2O$ (35 μL, 0.15 mmol) was added and the reaction mixture was stirred at rt for 48 h. The excess triethyl amine was removed at the pump and the crude mixture upon column chromatography (silica, pet. ether–ethyl acetate, 3 : 2) afforded pure **24** (0.030 g, 70 %) as a gummy mass. $[\alpha]_D^{25}$ +50 (*c* = 0.1, MeOH); δ_H (500 MHz, $CDCl_3$) 3.82 (dd, *J* 2.4, 1.0 Hz, 1H, H_{2eq}), 3.72 (ddd, *J* 10.8, 6.8, 4.0 Hz, 1H, H_3), 3.63 (dd, *J* 6.8, 4.0 Hz, 1H, H_4), 3.43 (dd, *J* 13.3, 6.7 Hz, 1H, H_{6eq}), 3.29 (dd, *J* 13.1, 2.8 Hz, 1H, H_{6ax}), 3.18 (dd, *J* 13.5, 6.7 Hz, 1H, H_{2ax}), 2.15 (m, 3H, 2H D_2O exchangeable, H_5, 2 × O*H*), 1.50 (s, 9H, ^{t}Bu), 0.98 (d, *J* 7.1 Hz, 3H, CH_3); δ_C (75 MHz, $CDCl_3$) 155.7 (C=O), 80.0 (O–$C(CH_3)_3$), 74.0 (C_4, CH), 68.4 (C_3, CH), 46.7 (C_4, C_6, 2 × CH_2), 32.5 (C_5, CH), 28.4 (^{t}Bu, 3 × CH_3), 12.1 (CH_3); GC/MS: *m*/*z* 231(M^+), 207, 186, 175, 158, 145, 57.

(3*R*,4*R*,5*R*)-5-Methylpiperidine-3,4-diol, hydrochloride salt (14·HCl). To a solution of **24** (0.032 g, 0.13 mmol) in distilled methanol (0.5 ml) was added conc. HCl (100 μL) at 0 °C. The reaction mixture was stirred at rt for about 4 h and the solvent evaporated to dryness. The residue was lyophilized from water (1 mL) to afford **14**·HCl (0.021 g, ~100%) as a colorless solid mass. $[\alpha]_D^{25}$ + 7.7 (*c* = 0.2, MeOH); δ_H (500 MHz, D_2O) 4.01 (m, 1H, H_3), 3.76 (m, 1H, H_4), 3.25 (dd, *J* 13.3, 1.7 Hz, 1H, H_{2eq}), 3.17 (dd, *J* 14.7, 1.2 Hz, 1H, H_{2ax}), 3.07 (dd, *J* 12.7, 4.3 Hz, 1H, H_{6eq}), 2.87 (dd like t, *J* 12.7, 12.4 Hz, 1H, H_{6ax}), 2.30 (m, 1H, H_5), 0.9 (d, *J* 7.1 Hz, 3H, CH_3); δ_C (125 MHz, D_2O) 68.2 (C_4, CH), 65.4 (C_3, CH), 43.9 (C_2, CH_2), 43.8 (C_6, CH_2), 27.3 (C_5, CH), 12.9 (CH_3); ESI HRMS found 132.1021, $C_6H_{14}NO_2$ requires 132.1025.

***N*-Benzyl-*N*-[(trimethylsilyl)methyl]-*N*-{[(4*R*,5*R*)-2,2-dimethyl-5-vinyl-1,3-dioxolan-4-yl]methyl}amine (27).** Pyridine (0.23 mL, 2.85 mmol) was added to a solution of **26** (0.300 g, 1.89 mmol) in dry DCM (3 mL) at 0 °C. To this was added *p*-toluene sulfonyl chloride (0.434 g, 2.28 mmol) in portions over a period of 30 min. The reaction mixture was stirred overnight at rt and worked up by extraction in DCM. The combined organic extracts were dried over anhydrous Na_2SO_4 and concentrated *in vacuo*. The residue upon column chromatography (silica, pet. ether–ethyl acetate, 19 : 1) afforded pure tosylate (0.562 g, 95%) as a colorless oil. $[\alpha]_D^{25}$ + 8.4 (*c* = 1.0, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.75 (d, *J* 8.3 Hz, 2H, Ar), 7.35 (d, *J* 8.3 Hz, 2H, Ar), 5.75 (m, 1H, C*H*=CH2), 5.25 (m, 2H, CH=C*H*2), 4.25–4.0 (m, 3H, H_4, H_5, one of CH_2OTs), 3.85 (m, 1H, CH_2-OTs), 2.45 (s, 3H, Ar–CH_3), 1.40 (s, 3H, CH_3), 1.35 (s, 3H, CH_3); δ_C (50 MHz, $CDCl_3$) 144.8 (Ar), 134.0 (*C*H=CH_2, CH), 132.3 (Ar), 129.7 (Ar), 127.7 (Ar), 119.5 (CH=*C*H_2, CH_2), 109.7 (C_2, –C–), 78.5 (C_4, CH), 77.7 (C_5, CH), 67.7 (*C*H_2–OTs), 26.7 (*gem* CH_3), 26.4 (*gem* CH_3), 21.4 (Ar–CH_3); GC/MS: *m*/*z* (%) 297 (M^+ − 15) (8), 155 (34), 98 (29), 83 (53), 43 (100).

A mixture of the tosylate (0.325 g, 1.041 mmol), $PhCH_2$-$NHCH_2TMS$ (0.402 g, 2.083 mmol), anhydrous cesium carbonate (1.696 g, 5.2 mmol), and tetra-*n*-butyl ammonium iodide (0.020 g) in dry CH_3CN (4 mL) was refluxed under an inert atmosphere for about 72 h. The reaction mixture was filtered and the solvent evaporated off. The crude residue upon column chromatography (silica, pet. ether–ethyl acetate, 98 : 1) afforded **27** (0.201 g, 58%) as a colorless oil. $[\alpha]_D^{25}$ +28.3 (*c* = 1.5, $CHCl_3$); δ_H (200 MHz, $CDCl_3$) 7.30 (m, 5H, Ar), 5.75 (m, 1H, C*H*=CH_2), 5.25 (m, 2H, CH=CH_2), 4.0 (m, 1H, H_4), 3.88 (m, 1H, H_5), 3.75 (d, *J* 13.7 Hz, 1H, N–CH_2Ph), 3.45 (d, *J* 13.7 Hz, 1H, N–CH_2Ph), 2.60 (dd, *J* 13.2, 4.1 Hz, 1H, CH_2–N–), 2.53 (dd, *J* 13.2, 5.9 Hz, 1H, CH_2–N–), 2.13 (d, *J* 14.6 Hz, 1H, N–CH_2TMS), 2.01 (d, *J* 14.6 Hz, 1H, N–CH_2TMS), 1.42 (s,

3H, CH_3), 1.38 (s, 3H, CH_3), 0.05 (s, 9H, 3 × CH_3, –$SiMe_3$); δ_C (50 MHz, $CDCl_3$) 139.6 (Ar), 135.4 (*C*H=CH_2, CH), 128.8 (Ar), 127.9 (Ar), 126.6 (Ar), 117.9 (CH=*C*H_2, CH_2), 108.7 (C_2, –C–), 80.9 (C_4, CH), 79.8 (C_5, CH), 62.6 (N–*C*H_2Ph, CH_2), 58.1 (–*C*H_2–N–, CH_2), 46.9 (–N–*C*H_2TMS), 27.0 (CH_3), 26.7 (CH_3), −1.35 (3 × CH_3); GC/MS: *m*/*z* (%) 333 (M+) (<1%), 260 (<1%), 206 (57), 134 (12), 91 (100), 73 (10).

(3a*R*,7*R*,7a*R*)-5-Benzyl-2,2,7-trimethylhexahydro[1,3]-dioxolo[4,5-*c*]pyridine (28). A solution containing **27** (0.200 g, 0.6 mmol) and 1,4-dicyanonaphthalene (DCN) (0.015 mg, 0.08 mmol) in 2-propanol (100 mL) was irradiated using a 450 W Hanovia medium pressure mercury vapor lamp as the light source. After about 2 h, when most of the starting material (>90%) had reacted, the irradiation was discontinued and the solvent was removed under reduced pressure. The crude photolysate was purified using column chromatography (silica, pet. ether–acetone, 99 : 1) to afford **28** (0.086 g, 55%) as a colorless oil. $[a]_D^{25}$ −8.0 (*c* = 0.2, $CHCl_3$); δ_H (500 MHz, $CDCl_3$) 7.30 (m, 5H, Ar), 3.65 (m, 2H, N–CH_2Ph), 3.59 (ddd, *J* 10.3, 8.7, 4.0 Hz, 1H, H_{3a}), 3.24 (ddd, *J* 9.9, 4.0, 1.2 Hz, 1H, H_{7a}), 2.97 (dd, *J* 10.6, 8.9 Hz, 1H, H_{4eq}), 2.87 (dd, *J* 11.7, 3.8 Hz, 1H, H_{6eq}), 2.18 (t, *J* 9.9 Hz, 1H, H_{4ax}), 2.0 (m, 1H, H_7), 1.82 (t, *J* 11.1 Hz, 1H, H_{6ax}), 1.46 (s, 3H, *gem* CH_3), 1.44 (s, 3H, *gem* CH_3), 1.0 (d, *J* 6.8 Hz, 3H, CH_3); δ_C (125 MHz, $CDCl_3$) 137.8, 128.7, 128.0, 126.9 (Ar), 109.7 (C_2, –C–), 85.3 (C_{3a}, CH), 76.3 (C_{7a}), 61.7 (N–*C*H_2Ph, CH_2), 58.8 (C_4, CH_2), 54.5 (C_6, CH_2), 33.7 (C_7, CH), 26.7 (*gem* CH_3), 26.5 (*gem* CH_3), 15.2 (CH_3); GC/MS *m*/*z* 261 (M^+), 246, 203, 134, 120, 91.

Preparation of 14·HCl from 28. To a solution of **28** (0.021 g, 0.077 mmol) in distilled MeOH (0.5 mL) was added conc. HCl (2 drops) and the reaction mixture was hydrogenated for 7 h at atmospheric pressure in the presence of $Pd(OH)_2$ on charcoal (20%) (0.001 g). The reaction mixture was passed through a short pad of Celite and the solvent was removed under reduced pressure to afford **14**·HCl (0.013 g, ~100%) as an amorphous solid.

General procedure for enzyme inhibition assay. The inhibitory potencies of the azasugars were determined spectrophotometrically, by carrying out the inhibition assay of the glycosidases in the presence of the azasugars utilizing the corresponding *p*-nitrophenyl glycosides as the substrates.

In the case of β-glucosidase, each assay was performed in a citrate buffer (100 mM, pH 6.0) with *p*-nitrophenyl β-D-glucoside as the substrate. Varying concentrations of the substrate and the iminosugar were employed. The reaction was initiated by the addition of 100 μL of appropriately diluted enzyme and the reaction mixture, which had a final volume of 1 mL, was incubated at 37 °C, for 10 min. Thereupon, it was quenched by the addition of 2 mL of 1 M Na_2CO_3 solution and the optical density of the resulting solution was read at 405 nm.

In the case of β-mannosidase, the assay was performed in an acetate buffer (100 mM, pH 4.0). The reaction was carried out at 25 °C for 20 min and then quenched by Na_2CO_3 solution. The K_i values were determined from the Lineweaver–Burke double reciprocal plots of 1/*v vs*. 1/[*S*]. K_i for competitive inhibition was determined using the formula:[10f] $K_i = [I]/\{(\text{Slope } (I)/\text{ Slope } (0)) - 1\}$.

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