Carbohydrate Research 408 (2015) 25–32

Contents lists available at ScienceDirect

Carbohydrate Research

journal homepage: www.elsevier.com/locate/carres

Synthesis, conformational study, glycosidase inhibitory activity and molecular docking studies of dihydroxylated 4- and 5-amino-iminosugars

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ARTICLE INFO

Article history:
Received 29 December 2014
Received in revised form
3 March 2015
Accepted 4 March 2015
Available online 12 March 2015

Keywords:
Iminosugar
Amino piperidine
Glycosidase inhibitor
Chiron approach
Reductive amino-cyclization
Molecular docking

ABSTRACT

An efficient methodology for the synthesis of new amino iminosugars **6a**, **7a** and **8**, starting from D-glucose, is reported. The conformational study using ^{1}H NMR data showed that the amino iminosugar **6a** exists in the $^{2}C_{5}$ while; the **7a** and **8** exist in the $^{5}C_{2}$ conformation. The inhibition activities with different glycosidases showed that **6a** and **7a** are poor glycosidase inhibitors. However, amino iminosugar **8** showed selective inhibition against the β-galactosidase (IC_{50}=43 μM, Ki=153 μM). These results are substantiated by the molecular docking studies.

1. Introduction

Polyhydroxylated cyclic compounds with the nitrogen atom in the ring, commonly called iminosugars, are the most notable carbohydrate mimetics, which comprises the low molecular weight heterocyclic molecules such as azitidines, pyrrolidines, piperidines, azepanes and bi-cyclic (nitrogen atom at the ring fusion) pyrrolizidines, indolizidines and quinolizidines *etc.*[1–7] This class of molecules are valuable for the basic understanding of glycobiology due to their action as inhibitors of glycosidases in the biological processes such as digestion, endoplasm reticulum associated degradations and lysosomal catabolism of glycoconjugates.[8–11] As a result, iminosugars are investigated as promising candidates for the treatment of carbohydrate disorder mediated diseases such as diabetes, obesity, cancer and viral infections.[12,13] For example, piperidine iminosugars namely N-hydroxyethyl-1-deoxynojirimycin (trade name Miglitol) and N-butyl-1-deoxynojirimycin (trade name Zavesca) are being used for the treatment of type-II diabetes and Gaucher diseases, respectively.[14] In the search for promising glycosidase inhibitors, modification of natural and unnatural iminosugars with the variation of stereochemistry and replacement of hydroxyl substituent with hydroxyalkyl,[15–22] aminoalkyl,[23,24] amine,[25–31] halogen[32–34] alkyl groups[35–39] and study of their structure–activity relationship is the established protocol in synthetic carbohydrate chemistry. Amongst these, mono- and bi-cyclic iminosugars in which hydroxyl group is substituted with amino group-amino iminosugars are known to be selective glycosidase inhibitors.[40,41] For example, Pandey et al. reported the synthesis of amino iminosugar **1** (Fig. 1) that showed good α-glucosidase inhibitory activity.[42] Bols et al. reported the synthesis of amino dihydroxypiperidine **2**-an amino analog of isofagomine, which showed selective inhibition activity against the β-glycosidase.[43] Fleet. et al. reported the *C*-2 amino analog of 1-deoxy nojirimycin **3a** (R=H) that showed a potent anticancer activity with 50% inhibition at 6 μM with Ki 0.9 μM and also showed a selective inhibition of β-N-acetylaminoglucosaminidase.[44] Tropak et al. and Wong. et al. reported a series of potent amino-piperidine compounds **3a**–**c** for Tay-Sachs and Sandhoff diseases.[45,46] In addition,

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http://dx.doi.org/10.1016/j.carres.2015.03.004
0008-6215/

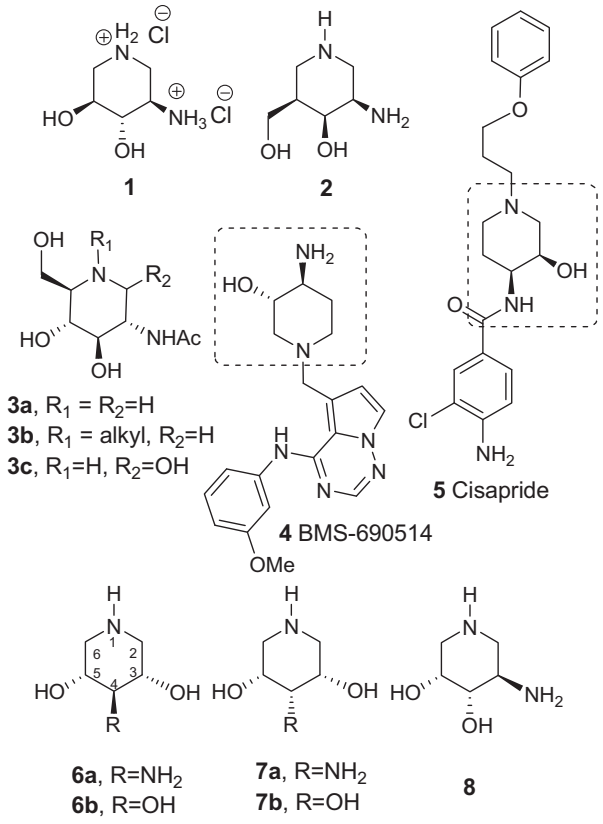


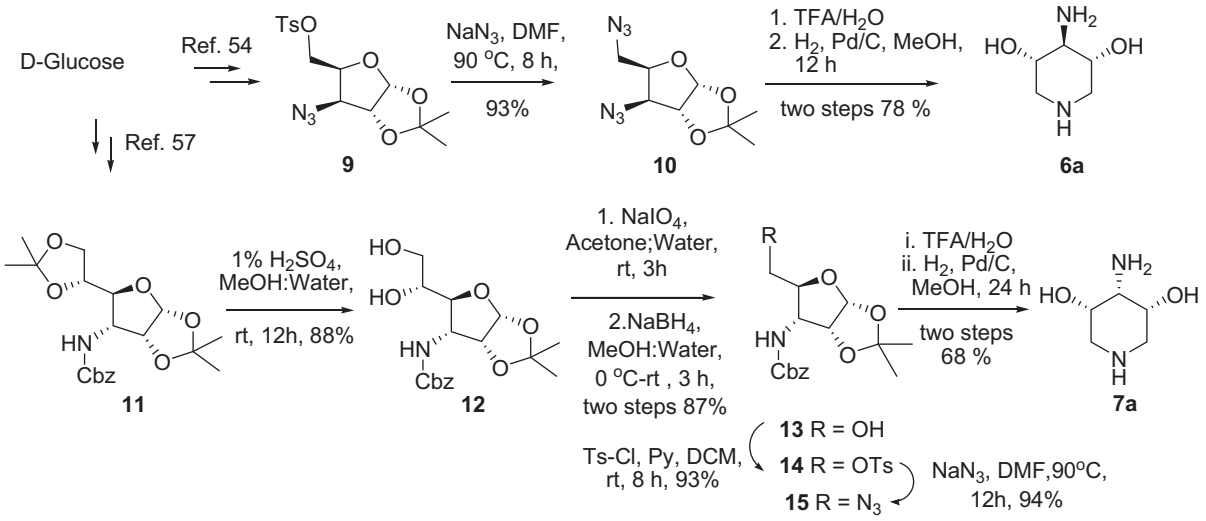
Fig. 1. Natural and synthesized iminosugars.

synthesis and glycosidase inhibitory activity of iminosugars (piperidine triols) **6b** and **7b**.[53] The structure–activity relationship (SAR) activity study presented here that the substitution of C4–OH in **6b** and **7b** with the amino group having same configuration diminishes the glycosidase inhibitory activity. While, substitution of the C3–OH in **7b** with the amino group having inverted orientation led to the potent selective inhibition against the β-Galactosidase. Our results are depicted herein.

2. Results and discussion

As shown in Scheme 1, D-glucose was converted to a 3-azido-3-deoxy-5-O-*p*-toluenesulphonyl-α-D-xylofuranose **9** using reported method.[54] Treatment of **9** with NaN_3 in DMF at 90 °C afforded a diazido-compound **10** in 93% yield.[55,56] Hydrolysis of 1,2-acetonide group in **10** using TFA/H_2O provided hemiacetal that was directly subjected for reductive amino-cyclization using 10% Pd/C, H_2, (80 psi) in methanol to afford amino-iminosugar **6a** in 78% (in two steps).

In order to synthesize amino iminosugar **7a**, D-glucose was converted to the 1,2:5,6-di-O-isopropylidene-3-deoxy-3-benzyloxycarbonylamino-α-D-allofuranose **11** using the reported method (Scheme 1).[57] Selective deprotection of 5,6-acetonide functionality with 1% H_2SO_4 afforded diol **12** in 88% yield.[58] Diol **12** on treatment with sodium metaperiodate in acetone–water followed by reduction with sodium borohydride in methanol–-water afforded a primary alcohol **13** in 87% yield (two steps).[59] The primary hydroxyl group of **13** was converted to a tosyl derivative **14** (TsCl, Py)[59] and then to a *C*-5 azido compound **15** (NaN_3, DMF) in 87% yield. Hydrolysis of the 1,2-acetonide group in **15** using TFA/H_2O followed by reductive amino-cyclization (10% Pd/C, H_2, 80 psi) afforded an amino iminosugar **7a** in 68% yield (two steps).



Scheme 1. Syntheses of amino iminosugars **6a**, **7a**.

the amino iminosugar framework is sometimes also part of drug candidates, such as, BMS-690514 **4** (developed for the treatment of non-small cell lung cancer) and Cisapride **5** (a potent gastric prokinetic agent with reduced dopamine D_2 receptor antagonist activity).[47,48] As a part of our continuous efforts in the area of iminosugars,[49–52] we now report a modest approach, in gram scale, for the synthesis of new amino iminosugars **6a**, **7a** and **8** from D-glucose and study of their glycosidase inhibitory activity along with correlation using molecular docking. Earlier we have reported the

For the synthesis of amino iminosugar **8**, D-glucose was transformed to 6-O-tosyl derivative **16** as per reported method (Scheme 2).[60] Intermolecular S_N2 displacement of a 6-O-tosyl group in **16** with NaN_3 in DMF at 90 °C afforded an azido-alcohol **17** in 92% yield.[61,62] The secondary *C*-5 hydroxy functionality in **17** was protected as benzyl ether using benzyl bromide and sodium hydride to get compound **18** in 93% yield. Hydrolysis of 1,2-acetonide group in **18** with TFA/H_2O provided hemiacetal that was directly subjected for the oxidative cleavage using $NaIO_4/H_2O$ to afford