Carbohydrate Research ■■ (2016) ■■–■■

Contents lists available at ScienceDirect

Carbohydrate Research

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

Note

Voglibose-inspired synthesis of new potent α-glucosidase inhibitors *N*-1,3-dihydroxypropylaminocyclitols

Wisuttaya Worawalai, Pornthep Sompornpisut, Sumrit Wacharasindhu, Preecha Phuwapraisirisan *

Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand

ARTICLE INFO

Article history:
Received 9 January 2016
Received in revised form 8 April 2016
Accepted 9 April 2016
Available online

Keywords:
Diabetes mellitus
Glucosidase
Voglibose
Cyclitol
Serinol
Quercitol

ABSTRACT

Voglibose, an *N*-1,3-dihydroxypropylaminocyclitol, has widely been used as an effective α-glucosidase inhibitor for diabetes therapy. Several attempts have been made to synthesize closely related analogues through the coupling of various aminocyclitols and propane-1,3-diol; however, most of them showed weaker or no inhibition. In this communication, we synthesized a pair of new *N*-1,3-dihydroxypropylaminocyclitols (**10** and **11**) using (+)-*proto*-quercitol (**1**) as a cyclitol core structure. The newly synthesized compounds revealed potent rat intestinal α-glucosidases, particularly against maltase, with IC_{50} values at submicromolar. Subsequent study on mechanisms underlying the inhibition of **11** indicated the competitive manner towards maltase and sucrase. The potent inhibition of these compounds was elaborated by docking study, in which their binding profiles towards key amino acid residues in the active site were similar to that of voglibose. Therefore, introduction of propane-1,3-diol moiety to suitable cyclohexane core structure such as aminoquercitol would be a potential approach to discover a new series of effective α-glucosidase inhibitors.

Effective control of hyperglycaemia is a critical approach for diabetes and its complication therapy. The high blood glucose level can be attenuated by inhibiting α-glucosidase, the enzyme catalyzing hydrolysis of oligosaccharide to glucose. To date, there have been three α-glucosidase inhibitors, namely acarbose, miglitol and voglibose, currently approved for hyperglycaemia control; of which voglibose is the newest and most effective. The outstanding efficacy of voglibose can be rationalized by its synergistic effects when applied together with different antidiabetic drugs. Plasma glucose control was improved in 65% of patients who exhibited a poor response to sulphonylurea while no major adverse effects were observed.[1] In comparison with acarbose (100 mg), voglibose at much lower dosage (0.2 mg) significantly decreased postprandial insulin and glucose levels with less gastrointestinal side effect.[2] In addition, voglibose has been used to improve glycaemic control by suppressing glycated haemoglobin (HbA1c) level at lower dose (0.6 mg) than miglitol (150 mg).[3] More interestingly, voglibose also showed hypoinsulinaemic and hypolipidaemic effects through improvement of insulin sensitivity.[4]

Since the launch of voglibose by Takeda Pharmaceutical Company in 1994, several attempts to synthesize voglibose-related analogues have been made. Noticeably, most derivatives were prepared from reductive amination of 2-amino-1,3-propanediol (commonly known as serinol) and polyhydroxycycloalkanones with larger ring size (Fig. 1). Le Merrer's group synthesized cycloheptane-aminocyclitol and a series of cyclooctane analogues,[5–10] in the hope that the flexibility of the larger ring and new spatial distribution of hydroxyl groups would enhance the inhibitory effect. However, most of them showed weaker or no inhibition against α-glucosidases. Although the critical role of serinol moiety in enzyme binding is not yet well understood, the cyclohexane-C1-aminocyclitols possessing this moiety are likely to reveal inhibition nearly equipotent to that of voglibose. The observed tendency is possibly associated with the fact that the cyclohexane-C1-aminocyclitols core structure is capable of mimicking the transition state of the enzyme-substrate complex while the serinol group on the nitrogen atom enhances tight binding with the active site. With this assumption in mind, we have the idea to introduce quercitol as the cyclohexane-cyclitol core structure of choice to synthesize new *N*-1,3-dihydroxypropylaminocyclitols. We hope that the lack of C1-residue ($-CH_2OH$) in the quercitol structure will not alter its inherent binding affinity to the active site of the enzyme.

Quercitol is a natural cyclitol possessing five contiguous hydroxyl groups in which (+)-*proto*-quercitol (**1**) is the most naturally abundant and widely applied in organic synthesis. The versatility of this building block has been demonstrated by a diverse series of quercitol-derived analogues.[11–13] Noticeably, functional group modification of (+)-*proto*-quercitol mostly afforded products with

* Corresponding author. Department of Chemistry, Faculty of Science, Chulalongkorn University, Bangkok 10330, Thailand. Tel.: +662 2187624; fax: +662 2187598.
E-mail address: preecha.p@chula.ac.th (P. Phuwapraisirisan).

http://dx.doi.org/10.1016/j.carres.2016.04.014
0008-6215/

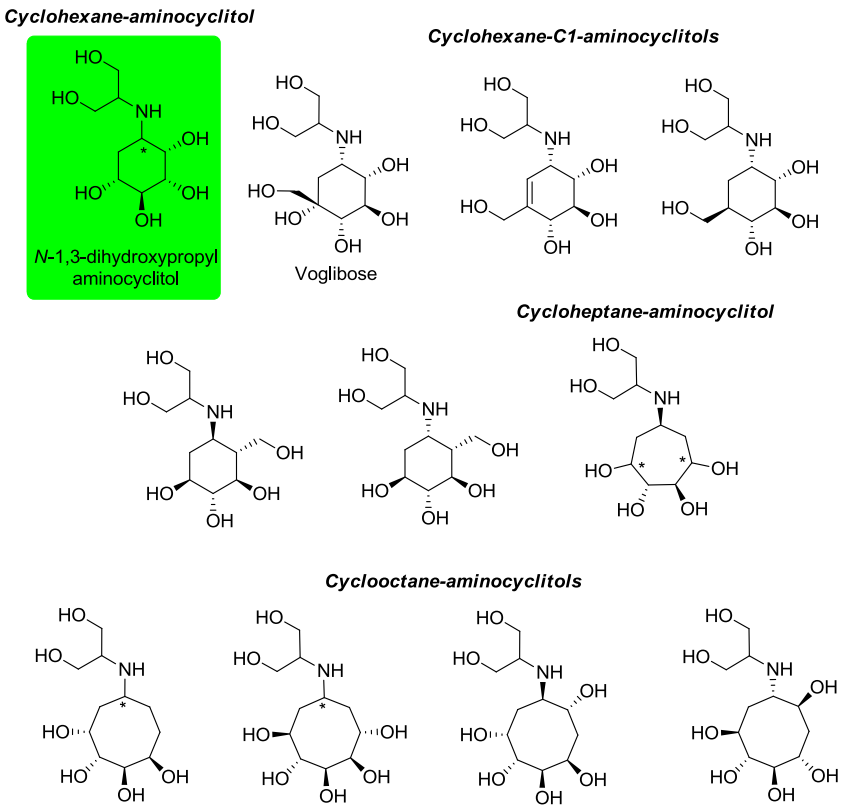
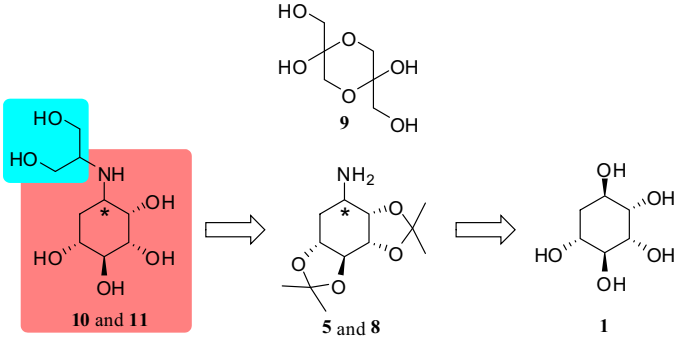


Fig. 1. Structures of *N*-1,3-dihydroxypropylaminocyclitols.

enhanced inhibition, therefore suggesting the good fit of the quercitol core structure to the active site of an enzyme. In this communication, we plan to synthesize new α-glucosidase inhibitors having (+)-*proto*-quercitol as the cyclitol core structure modified with serinol moiety. Furthermore, the inhibitory mechanism and computational study of the targeted compounds are herein described.

We designed the synthesis of the targeted *N*-1,3-dihydroxypropylaminocyclitols (**10** and **11**) through the reductive amination of aminoquercitol bisacetonides (**5** and **8**) and 1,3-dihydroxyacetone dimer (**9**) as shown in Scheme 1. The aminoquercitol bisacetonides **5** and **8** were prepared from naturally available (+)-*proto*-quercitol (**1**) using our protocol (Scheme 2) as previously described.[11] Initially, the hydroxy groups in **1** were protected by the reaction with $Me_2C(OMe)_2$ in the presence of *p*-TsOH, thus yielding bisacetonide **2** as a single product in 75% yield. The conversion of the remaining hydroxy moiety into the amino group in **2** was accomplished in three steps. Mesylation of **2** with $MeSO_2Cl$ generated the mesylate **3**. Nucleophilic substitution of the mesylate with azide occurred with inversion to yield **4**. Finally, reduction of the azide group using $LiAlH_4$ produced the desired aminoquercitol bisacetonide **5**.



Scheme 1. Retrosynthesis of *N*-1,3-dihydroxypropylaminocyclitols (**10** and **11**).

With **5** in hand, we next planned to synthesize aminoquercitol bisacetonide **8** (Scheme 3), with the C-1 configuration of C-1 opposite to that of **5**. Starting from **2**, Albright–Goldman oxidation using Ac_2O/DMSO[14] afforded the corresponding ketone **6**. Subsequent reduction of the ketone furnished the hydroxybisacetonide **7** as a single product with excellent yield (93%). The expected aminoquercitol bisacetonide **8** was obtained using the same methodology applied for **2**.

Finally, the desired *N*-1,3-dihydroxypropylaminocyclitol **10** was synthesized by reductive amination between aminoquercitol bisacetonide **5** and 1,3-dihydroxyacetone dimer (**9**) in the presence of $NaBH_3CN$/AcOH (Scheme 4). In similar fashion, *N*-1,3-dihydroxypropylaminocyclitol **11** was also prepared from aminoquercitol bisacetonide **8** and 1,3-dihydroxyacetone dimer (**9**) using the above method.

The two *N*-1,3-dihydroxypropylaminocyclitols (**10** and **11**) were assessed as inhibitors of α-glucosidases from two different sources: baker's yeast and rat intestine. Both compounds were strong inhibitors of maltase (0.57–0.90 μM) and sucrase (1.7–2.1 μM) whereas the inhibition against yeast α-glucosidase was not observed. These results were similar to those observed for antidiabetic drugs voglibose. Noticeably, the opposite configuration at C-1 of **10** and **11** did not significantly alter enzyme inhibition. Conversely, the related analogues possessing larger cycloalkane rings (cycloheptane and cyclooctane; Table 1) revealed no inhibitory effect against α-glucosidase. The observed results preliminarily suggested that the six-membered aminocyclitol core structure is more pivotal than the larger and more flexible cycloheptane- and cyclooctane-cyclitols as earlier postulated by Le Merrer.[5–10] This observation suggests that

Please cite this article in press as: Wisuttaya Worawalai, Pornthep Sompornpisut, Sumrit Wacharasindhu, Preecha Phuwapraisirisan, Voglibose-inspired synthesis of new potent α-glucosidase inhibitors *N*-1,3-dihydroxypropylaminocyclitols, Carbohydrate Research (2016), doi: 10.1016/j.carres.2016.04.014