Voglibose (Basen®, AO-128), One of the Most Important α-Glucosidase Inhibitors

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Abstract: The number of people with diabetes is expected to rise from the current estimated 150 million to 220 million in 2010 and 300 million in 2025, and 90% is Type 2 diabetes or non-insulin dependant diabetes mellitus (NIDDM). Voglibose, one of the most important α-glucosidase inhibitors, delays the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia and hyperinsulinemia, and is the aid in the treatment of diabetes. In this paper, properties and the preparation of voglibose are reviewed.

Keywords: Voglibose, Glucosidase inhibitor, Preparation, NIDDM.

INTRODUCTION

Currently there is a growing interest in diabetes, as the number of people with diabetes is expected to rise from the current estimated 150 million to 220 million in 2010 and 300 million in 2025 [1]. Of the two main forms of diabetes, Type 1 diabetes [2] is the most common chronic disease of children and is due to auto-immune-mediated destruction of pancreatic β-cell islets resulting in absolute insulin deficiency. It can be treated by supplying exogenous insulin. Type 2 diabetes or non-insulin dependant diabetes mellitus (NIDDM), which represents 90% of cases, is a multifactorial disease characterized by insulin resistance in peripheral tissues and/or abnormal insulin secretion from the pancreas and increasing blood glucose levels [3]. The NIDDM is taking an increasingly important place both in developed and developing countries and is associated with sedentary lifestyle and obesity [4]. Many complications such as retinitis, neuro- and nephropathies are associated with NIDDM, and lowering blood glucose may be an effective mechanism for preventing the development of diabetic complications [5].

At present, therapies for NIDDM are directed toward the reduction of hyperglycemia itself [6,7]. Thus, sulfonylureas and related insulin secretagogues [8] increase insulin release from pancreatic islets; the biguanide metformin [9] delays the absorption of dietary carbohydrates by inhibiting the glucose transporter found on the brush border of the epithelial lining of the intestine and so reduces hepatic glucose production. Thiazolidinediones [10], which are peroxisome proliferator-activated receptor-γ agonists, enhance insulin action. Insulin itself inhibits glucose production and increases glucose utilization [11].

D-Glucose and insulin levels of plasma are usually high in diabetes especially after food ingestion, and reducing intestinal carbohydrate absorption, such as monosaccharides, which are hydrolyzed by α-amylase and α-glucosidase, is one way to control disorders of carbohydrate metabolism. Therefore, α-glucosidase inhibitors are suggested to be valuable aids in the treatment of diabetes. They act by delaying the digestion and absorption of carbohydrates, thereby inhibiting postprandial hyperglycemia and hyperinsulinemia.

Since the middle 1970s, quite a few pseudooligosaccharides of microbial origin that exhibit an excellent inhibitory effect on intestinal α-glucosidase have been reported [12,19] and some of them, including voglibose and acarbose, have aroused medical interest in the treatment of metabolic diseases such as diabetes. In general, these microbial α-glucosidase inhibitors have valioline (1), valienamine (2) and validamine (3) as their key constituents, which were first found in validamycins. Therefore, the preparation of 1, 2 and 3 has been the hot research field [19,20].

Voglibose (code number: AO-128, trade name: Basen®) [21,22], (1S)-[1(OH),2,4,5/3]-5-[(2-hydroxy-1-(hydroxymethyl) ethyl) amino]-1-C-(hydroxymethyl)-1,2,3,4-cyclohexanetetrol, is an N-substituted derivative of valioline, which is a branched-chain aminocyclitol, or pseudo-aminosugar, and its N-substituted moiety is derived from glycerol. The structure of voglibose is represented in (Fig.1). Voglibose has attracted considerable interest due to its wide range of therapeutic and pharmacological properties, which include its excellent inhibitory activity against α-glucosidases and its action against hyperglycemia and various disorders caused by hyperglycemia. It has shown strong anti-obesity and anti-diabetic activities, as it is a new, potent glucosidase inhibitor and is a drug used for NIDDM in Japan, China and Korea. In an animal experiment, voglibose showed approximately 20- to 30-fold more potent inhibition of semipurified porcine small intestine disaccharides as compared with acarbose, a typical α-glucosidase inhibitor [23]. Voglibose significantly reduced postprandial blood glucose concentration in some animals and healthy volunteers [24,25]. Clinical trials in patients with diabetes mellitus also demonstrated that voglibose improves postprandial blood glucose levels. Treatment with voglibose resulted in a significant decline of triglyceride level and an elevation of high-density lipoprotein (HDL), cholesterol and apolipoprotein A-1 [26]. Comparing with acarbose in the clinical trials involving IDDM and NIDDM patients, which caused 58% of the subjects complaining of...
gastrointestinal symptoms, voglibose caused few adverse symptoms. Furthermore, there was a tendency for these side effects to decline over the course of voglibose treatment [26]. Therefore, voglibose is more effective and has fewer side effects than acarbose. The synthesis of voglibose has aroused considerable interest among researchers. In this review, the properties and preparation of voglibose are illustrated.

1. CHEMICAL STRUCTURES OF VOGLIBOSE AND RELATED PSEUDO-AMINOSUGARS

The structures of voglibose (AO-128) 1, valiolamine 2, valienamine 3, validamine 4, validoxylamine A 5, validamycin A 6, and acarbose 7, are shown in the (Fig. 1).

2. PHYSICO-CHEMICAL PROPERTIES VOGLIBOSE

Voglibose has the molecular formula C\textsubscript{10}H\textsubscript{21}NO\textsubscript{7} and molecular weight 267.28; its crystal, m.p. about 166\textdegree E, has no smell but sweet. It is easily soluble in water and acetic acid, but not easily soluble in methanol, and ethanol, and almost insoluble in ether. The \textsuperscript{1}H NMR of voglibose hydrochloride (D\textsubscript{2}O), \(\delta\): 1.94 (1H, dd, J=3.0, 16.2 Hz), 2.33 (1H, dd, J=2.1, 16.2 Hz), 3.60-3.70 (4H, m), 3.80-4.0 (7H, m). The \textsuperscript{1}H NMR of voglibose (D\textsubscript{2}O), \(\delta\) : 1.55 (1H, dd, J=2.1, 15.0 Hz), 2.10 (1H, dd, J=2.7, 15.0 Hz), 2.9 (1H, m), 3.40-3.55 (2H, m), 3.59 (2H, m), 3.64-3.80 (5H, m), 3.88 (1H, t, J=9.6 Hz).

3. \(\alpha\)-GLUCOSIDASE INHIBITORY ACTIVITIES OF VOGLIBOSE AND OTHER N-SUBSTITUTED VALIOLAMINE DERIVATIVES AND RELATED COMPOUNDS

Voglibose can inhibit the intestinal \(\alpha\)-glucosidases, which are responsible for the digestion of disaccharides such as maltose and sucrose, including maltase and sucrase. So, inhibitory properties of voglibose for the maltase and sucrase are significant for the treatment of NIDDM. The inhibitory effects of voglibose, together with other typical simple N-substituted valiolamine derivatives on the porcine maltase and sucrase [21,27,28], were compared to the effects of the corresponding N-substituted valienamine derivatives [29,30] and validamine derivatives [27,28]. The valiolamine derivatives were found to have higher inhibitory effects than the corresponding valienamine and validamine derivatives, as well as the parent valiolamine, and the presence and configuration of the hydroxyl group of the aralkyl unit of N-(\(\beta\)-hydroxyphenethyl)valiolamines also markedly influenced the inhibitory activities (Table 1). Stereochemistry of the hydroxyl group on the cyclohexyl unit of N-(\(\beta\)-hydroxyphenethyl)valiolamines also markedly influenced the enzymatic activities (Table 2). The hydroxy group of the N-[(1R, 2R)-2-hydroxycyclohexyl] isomer 15 showed a positive effect on enzymatic activities, while the hydroxyl group of the N-[(1S, 2S)-2-hydroxycyclohexyl] isomer 19 exhibited a negative effect on enzymatic activities in comparison with the non-substituted cyclohexyl derivative 17.

Fig. (1). Chemical structures of voglibose and related glucosidase inhibitors.
Table 1. Inhibitory Effects (IC₅₀ (µM)) of N-Substituted Valienamine, Validamine and Valiolamine Derivatives on Porcine Maltase and Sucrase

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<tr>
<th>N-substituted substances</th>
<th>Maltase</th>
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<th>N-substituted substances</th>
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With the introduction of a hydroxyl group into the proper position on the alkyl, the inhibitory activities tended to increase, especially against porcine maltase.

Replacement of the valienamine unit of acarviosin (25) [31,33] and its 6-hydroxy derivative 21, the key pseudo-disaccharides of naturally occurring oligosaccharide α-glucosidase inhibitors, with a valiolamine unit led to a remarkable rise in porcine maltase and sucrase inhibitory activities, particularly maltase inhibitory activity (16 and 23).

The $K_i$ values of N-[2-hydroxy-1-(hydroxymethyl)ethyl] derivatives of valiolamine [34, 35], valienamine and validamine for rat intestinal disaccharidases (maltase and sucrase) are shown in (Table 3). The $K_i$ values of voglibose for sucrase and maltase were about $10^6$ and $10^5$ times smaller than the $K_m$ values for sucrose and maltose. But, from the experiments, voglibose showed no α-amylase and β-D-glucosidase inhibitory activity in vitro. This strong inhibitory activity of voglibose against the disaccharidases could be explained by assuming that the hydroxyl group of the N-substituent unit (-CH(CH$_2$OH)$_2$) could assume a three-dimensional position that is very similar to that of the C-3 hydroxyl groups in the fructofuranoside portion of sucrose and the reducing glucose portion of maltose by rotation around the pseudo-glucosidic linkage bond (-C-NH-C-) between the valiolamine unit and the -CH(CH$_2$OH)$_2$ unit. In the NMR spectral data on voglibose, NOE was observed between the two protons; the C-1 proton of valiolamine and the α-proton of the N-substituent. This indicated that the geometry of voglibose is similar to that of maltose and its related compound in aqueous solution (Fig. 2) and the conformation is stabilized by the formation of an intramolecular hydrogen bond between the two hydroxyl groups in the -C(OH)-C-N-C-C(OH)- moiety.

Synthetically, especially for large-scale preparation, the N-[2-hydroxy-1-(hydroxymethyl)ethyl] derivatives are more attractive than the derivatives which have an asymmetric carbon in their N-substituted moieties and require a stereoresolution. With the ease of preparation and the safety of the possible metabolites of the N-substituted moiety in the living body, voglibose was selected by Takeda Pharmaceutical Company Limited for further biological evaluation over the other N-substituted valiolamine derivatives, which showed high α-glucosidase inhibitory activity, and have been the drugs for the treatment of NIDDM.

Fig. (2). Relative disposition of functional groups in voglibose (10, AO-128) and maltose
Table 2. Inhibitory Effects (IC$_{50}$ (µM)) of N-Substituted Valienamine, Validamine and Valiolamine Derivatives on Porcine Maltase and Sucrase

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Table 3. $K_i$ Values (µM) of Valienamine, Validamine and Valiolamine Derivatives for Rat Small Intestinal Disaccharidase

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<th>Sucrase</th>
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<tr>
<td>VD-R</td>
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<tr>
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<td>Soluble starch</td>
<td>Palatinose</td>
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<td>$K_m$(µM)</td>
<td>3.4 × 10$^{4}$</td>
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<td>9.5 × 10$^{3}$a</td>
<td>6.2 × 10$^{3}$</td>
<td>1.1 × 10$^{4}$</td>
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</table>

VE = Valienamine, VD = Validamine, VO = Valiolamine, R

a: g/ml
4. PREPARATION OF VOGLIBOSE

A. Synthesis of Voglibose from Valiolamine

Voglibose was first synthesized from valiolamine. Valiolamine, (1S)-1(OH), 2,4,5/1]-5-amino-1-hydroxymethyl-1,2,3,4-cyclohexanetetrol, was isolated from the fermentation broth[22]. Since the discovery of valiolamine, five total syntheses of valiolamine[20] have been reported with one starting from a Diels-Alder (furanacrylic acid) cycloadduct, one from D-glucose via a Ferrier rearrangement, the third one from 2, 3, 4, 6- tetra-O-benzyl-D-glucono-1, 5-lactone employing an aldol reaction as the key step, the fourth one from (-)-quinic acid via the approach in the facile synthesis, a novel acetyl migration and internal displacement reaction involving neighboring group participation, and the last one from validamine and valienamine via the stereoselective conversion.

In one method [36], valiolamine is oxidatively deaminated to produce valiolone 27 with oxidizing agents in alcohol at 50°C. Oxidizing agents, which are known to be effective in converting amines to imines, can be used. 3, 5-Di-t-butyl-1,2-benzoquinone (DBQ), nicotinic aldehyde in the presence of a base and benzothiazole-2-aldehyde were used as oxidizing agents. Then, hydrolysis preceded using oxalic acid and conditions for hydrolyzing an imine to a ketone at pH 5.0. After the achievement of valiolone, voglibose could be prepared by reacting valiolone with 2-amino-1, 3-propanediol (serinol) in the presence of a reducing agent, Na(CN)BH3, with or without an acid catalyst (e.g., acetic acid, HCl), according to the reaction (Scheme 1).

B. Synthesis from compound 28

A method [37] is described in (Scheme 1) about the synthesis of voglibose from compound 28, a hexenopyranoside derivative. The total yield was more than 65%.

C. Synthesis of Voglibose from Glucose

In a synthetic method [21], a bis(methylthio) group was chosen as the electron-withdrawing group. As shown in (Scheme 3), tetra-O-benzyl-D-glucono-1,5-lactone, which is readily available from D-glucose, was treated with bis(methylthio)methylithium to give the 1-C-[bis(methylthio)methyl]-D-glucopyranose derivative 35.

The direct oxidation of the D-gluco-2-heptulose derivative 35 to the D-xylo-2, 6-heptodiulose derivative 37...
was difficult, because the targeted C-6 hydroxyl group was masked by pyranose ring formation. Therefore, the D-gluco-2-heptulose derivative 35 was reduced with lithium aluminum hydride to yield the acyclic heptitol derivative 36. Although the heptitol derivative 51 was obtained as a mixture of two stereoisomers at the C-2 hydroxyl group in a ratio of approximately 14:1 (1R-isomer and 1S-isomer), the mixture was subjected to the next reaction without resolution of the two isomers, as this chiral center disappeared in the next oxidation reaction.

The oxidation of the unprotected hydroxyl groups of the heptose dithioacetal derivative 36 with dimethyl sulfoxide (DMSO), trifluoroacetic anhydride and triethylamine (Swern oxidation) gave the 2, 6-dioxo-heptose 1, 1-dithioacetal derivative 37. The 2, 6-dioxo-heptose derivative 37 was too labile to isolate as a pure compound; however, the partially purified compound showed reasonable spectral data.

The 2, 6-dioxo-heptose derivative 37 underwent intramolecular aldol condensation via the intermediate enolate anion 38 to give the desired α,α- bis(methylthio)inosose derivative 39 stereospecifically not only with sodium acetate in the presence of 18-crown-6 ether, but also with silica gel during the silica gel chromatography of the 2, 6-dioxo-heptose derivative 37.

Desulfurization of the α,α- bis(methylthio)inosose derivative 39 using hydrogen-saturated Raney nickel gave the desulfurized inosose derivative 40.

Finally, voglibose was synthesized with high stereoselectivity by direct reductive amination of the branched-chain inosose 40 with 2-amino-1, 3-propanediol to give 41 and then removal of the O-benzyl protecting group. The epimer of 1 was not found in the reaction mixture. The results can be explained by the fact that the attack by the reducing agent occurs on the less-hindered side of the intermediate Schiff’s base. The branched-chain inosose derivative 40 should be a useful synthon for the branched-chain cyclitol moiety of N-substituted valiolamine derivatives, especially when the synthon for the substituent moiety is advantageously available in the form of an amino compound.

D. Synthesis of Voglibose from 42

With (1S)-[1(OH), 2,4,4/1,3]-2,3,4-tri-O-benzyl-6,6- dichloro-5-oxo-1-C-[benzyloxymethyl]-1,2,3,4-cyclohexanetetrol 42 as the starting material [38], voglibose was successfully prepared (Scheme 4). 42 was first dechlorinated to obtain 40. Then there were two routes to prepare voglibose from 40. One was that 40 reacted with ammonium acetate to form 43, and then 43 reacted with dihydroxyacetone to obtain 41. The other was that 40 reacted directly with 2-amino-1,3-propanediol in the presence of reducing agents to form 41. Finally the protecting group was deleted to form 1.
5. PROSPECT OF VOGLIBOSE

α-Glucosidase inhibitors (AGI) are antihyperglycemic agents that, by blockade of oligosaccharide catabolism, delay (in small doses) or inhibit (in larger doses) carbohydrate digestion and absorption, and, thus inhibit/ maintain smooth and lower blood glucose levels after a meal. Current consensus supports their use as monotherapy or adjunct therapy for poorly controlled NIDDM. Among α-glucosidase inhibitors, which can be available in clinical use, such as acarbose (approved in 1999 by FDA), voglibose (in Japan, Korea) and miglitol (approved in 1999 by FDA), voglibose is the most effective one. They have the chemical structures similar to that of oligosaccharides derived from the digestion of starch. These structural configurations allow them to competitively and reversibly inhibit α-glucosidases. As a consequence of reductions in average postprandial glucose levels over time, AGI significantly reduce levels of glycated hemoglobin A1c (HbA1c) in patients with NIDDM.

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