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A Prospect for Pyrrolidine Iminosugars as Antidiabetic α-Glucosidase Inhibitors

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α-Glucosidase inhibitors are a class of oral antidiabetic agents that have been exploited for the effective management of type 2 diabetes and associated complications for about 20 years. These drugs significantly reduce the postprandial increase in glucose and plasma insulin levels in diabetic patients by inhibiting the activity of α-glucosidases involved in the digestion of carbohydrates. The enzyme inhibition reduces oligosaccharide hydrolysis and depresses intestinal glucose absorption. Currently three drugs (acarbose, miglitol, and voglibose) belonging to this category are in the market and have shown effective clinical use in spite of inducing gastrointestinal disturbance and some other side effects. However, α-glucosidase inhibitors reduce the cardiovascular harm and the risk of hypoglycaemia associated with other glucose-lowering drug types, demonstrating several comparative advantages over antidiabetics with other mechanism of action.[1]

Kato et al.[2] describe a new family of potent pyrrolidine α-glucosidase inhibitors with promising glucose-lowering activity. The first-in-class compound α-1-*C*-butyl-LAB is a potent inhibitor of intestinal α-glucosidase enzymes and displays an interesting selectivity and enzymatic profile addressing some of the undesired side effects of this class of antidiabetics. When tested in vivo in the carbohydrate-loading tests, α-1-*C*-butyl-LAB effectively reduces the rise of plasma glucose after food intake, with a dose about 10 times lower than that required for miglitol.

Antidiabetic α-glucosidase inhibitors share some common structural characteristics with a class of bioactive molecules that mimic the sugar structures (Figure 1). Generally, these are cyclic compounds containing a basic amine functionality with several hydroxyl substituents that have a tridimensional arrangement similar to the present in elemental carbohydrates. Sometimes, these structural similarities are translated to the carbohydrate functional roles, and numerous members of these families display interesting biological and enzymatic activities, especially as glycosidase inhibitors. In general, two main classes of carbohydrate mimetics are found: carbasugars, which contain a carbocycle scaffold,[3] and iminosugars,[4] having a saturated nitrogen heterocyclic ring where other heteroatom substituents and hydroxyl groups are attached (Figure 1). Both classes are represented among clinically relevant antidiabetic α-glucosidase inhibitors: acarbose and voglibose are carbasugars with α-amino substituents at the oxygen anomeric position, whereas miglitol is an *N*-alkyl derivative of deoxynojirimycin (DNJ), the prototypical iminosugar compound. Anomeric mimicry is directly achieved in carbasugars, where heteroatom substituents can be bonded to the carbocycle with identical stereochemistry of the parent sugar anomeric group. In contrast, the presence of an anomeric-like group is less common in iminosugar family because of instability of the *N*,*O*-acetal function. Usually these derivatives lack the presence of an anomeric substituent such as in DNJ, or alternatively, ring nitrogen alkylation is introduced as in miglitol. However, nitrogen substituents are not configurationally stable because of fast nitrogen inversion, and therefore, the structural correlation with the rigid anomeric substituent of the sugar is lost. A solution for this has been introduced in the 1-*C*-iminosugar family,[5] where an "anomeric" substituent is attached by a C−C bond to a position adjacent to the ring nitrogen (Figure 1). This is the approach used in the design of the α-1-*C*-alkyl-LAB family of compounds that has been synthesized in a straightforward sequence of reactions. The degree of structural similarity between hexoses and cyclohexane carbasugars or piperidine iminosugars is usually high, defining a related binding mode to proteins and enzymes. In contrast, the structural connection between the parent carbohydrate and pyrrolidine iminosugars is less evident, although these compouds give excellent enzymatic inhibitions and biological activities. The docking studies in the paper predict a different binding mode of piperidine iminosugars and α-1-*C*-butyl-LAB, a molecule with an L-configuration, opposite that present in the α-D-glucoside substrates (Figure 1). These structural features can explain the similar inhibitory potency on intestinal α-glucosidases of α-1-*C*-butyl-LAB and the related piperidine iminosugar α-1-*C*-butyl-DNJ but the better selectivity of the former over the other glycosidases tested. This illustrates that quite often a high degree of similarity of the inhibitors to the carbohydrate substrate is necessary but not sufficient to attain the enzymatic profile necessary for drug applications.

Regarding the antidiabetics directed to intestinal α-glucosidases, the inhibitors must be selective over other glycosyl enzymes and in particular to intracellular α-glucosidases. These include endoplasmic reticulum α-glucosidase I and II enzymes, involved in the maturation of protein glycosylation and acid α-lucosidase which operates in lysosomal carbohydrate degradation. Among marketed drugs, the selectivity for intestinal enzymes has been achieved by two different mechanisms. Acarbose and voglibose are poorly absorbed and remain localized in the digestive system until excreted. This confinement prevents its intracellular effects but originates some gastrointestinal complications due to the extensive inhibition of carbohydrate hydrolysis. In contrast, miglitol is fully absorbed, requiring a potent and selective inhibition of intestinal α-glucosidases to avoid systemic undesired side effects due to inhibition of other glycosidases. On the basis of

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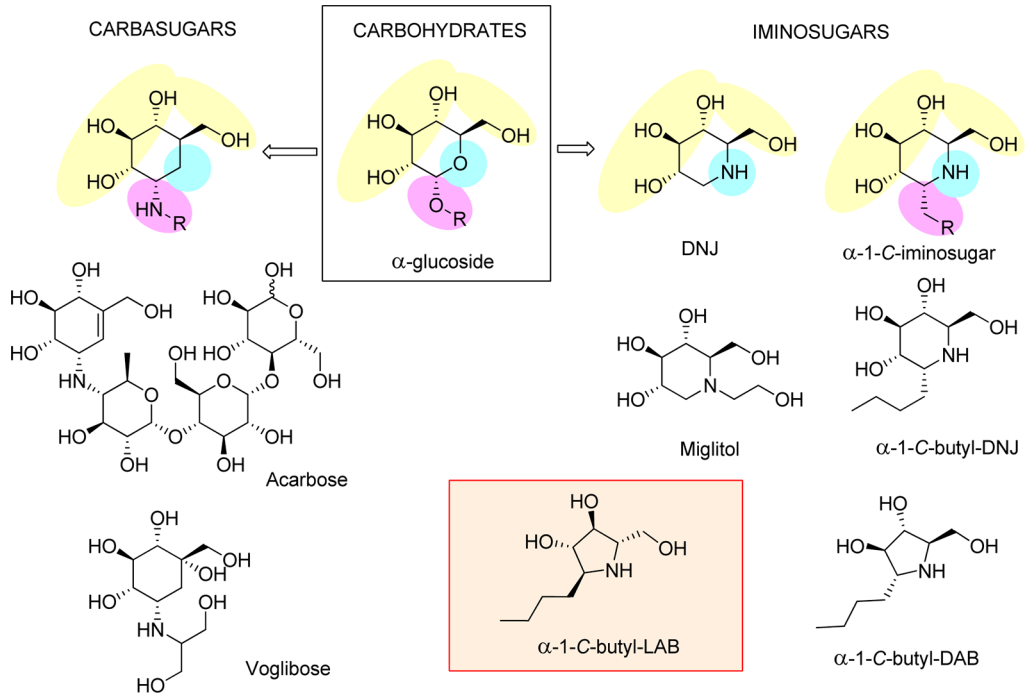

Figure 1. Sugar mimetics and antidiabetic α-glucosidase inhibitors.

some experimental evidence, α-1-*C*-butyl-LAB is proposed to be absorbed in the upper region of small intestine and to display a mechanism of action similar to miglitol, but this waits to be definitely confirmed. As shown in the paper of Kato et al.,[2] incubation of hepatocytes with 500 μM miglitol affects protein glycosylation by presumably affecting endoplasmic reticulum α-glucosidases, whereas α-1-C-butyl-LAB does not show any effects at the same concentration. However, it must be pointed out that these concentrations are much higher than those required for effective intestinal enzyme inhibition by these compounds, which have K_i values in the low micromolar to nanomolar range.

In summary, α-1-*C*-butyl-LAB characterizes a new structural class of α-glucosidase inhibitors showing potential for treating postprandial hyperglycemia that can be eventually developed in antidiabetic drugs. The results described in this article configure a promising profile for α-1-*C*-butyl-LAB, worthwhile for further studies in cellular and animal models to validate it as a lead candidate for clinical development.

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