Five-membered iminocyclitol α-glucosidase inhibitors: Synthetic, biological screening and in silico studies


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The design and synthesis of a small library of pyrrolidine iminocyclitols with a structural similarity to 1,4-dideoxy-1,4-imino-o-arabitol (DAB-1) is reported. This library was specifically designed to gain a better insight into the mechanism of inhibition of glycosidases by polyhydroxylated pyrrolidines or iminocyclitols. Pyrrolidine-3,4-diol 15a and pyrrolidine-3,4-diol diacetate 15b had emerged as the most potent α-glucosidase inhibitors in the series. Docking studies performed with an homology model of α-glucosidase disclosed binding poses for compounds 15a, 15b, 16a, and 16a' occupying the same region as the NH group of the terminal ring of acarbose and suggest a closer and stronger binding of compound 15a and 15b with the enzyme active site residues. Our studies indicate that 2 or 5-hydroxyl substituents appear to be vital for high inhibitory activity.

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1. Introduction

The iminocyclitols—polyhydroxylated pyrrolidines and piperidines—are a family of important pharmacologically active compounds that are both potent glycosidase and glycosyltransferase inhibitors due to their mimicry of the transition state of the enzymatic reaction, including serendipitous electrostatic binding interactions. For this reason, they have been selected as therapeutic agents in several areas such as cancer, viral infections (particularly influenza) and diabetes, etc. For example, deoxinojirimicin (DNJ) is an inhibitor of endoplasmic reticulum α-glucosidases, and 1,4-dideoxy-1,4-imino-o-arabitol (DAB-1) is a potent inhibitor of α-glucosidase. Calveras et al. showed that a library of α-glucosidase inhibitors in the series. Docking studies performed with an homology model of α-glucosidase disclosed binding poses for compounds 15a, 15b, 16a, and 16a' occupying the same region as the NH group of the terminal ring of acarbose and suggest a closer and stronger binding of compound 15a and 15b with the enzyme active site residues. Our studies indicate that 2 or 5-hydroxyl substituents appear to be vital for high inhibitory activity.