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

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ABSTRACT

The design and synthesis of a small library of pyrrolidine iminocyclitol inhibitors with a structural similarity to 1,4-dideoxy-1,4-imino-D-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.

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.[1,2] 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) **1** is an inhibitor of endoplasmic reticulum α-glucosidases I,[3] and 1,4-dideoxy-1,4-imino-D-arabinitol (DAB-1) **2** and 2,5-dideoxy-2,5-imino-D-mannitol (DMDP) **3**[5] are powerful inhibitors of α-glucosidases[4] (Fig. 1). The synthesis of more potent novel analogues of these compounds is an important goal in medicinal chemistry, not only for targeting human disease, but also as tools to probe the mechanism of glucosidase function. In most cases, these molecules function as pure enantiomers.

It has been previously pointed out that structure–activity relationships for iminocyclitol glycosidase inhibitors are difficult to elucidate, making rational inhibitor design a difficult task.[1] It is also known that five-membered iminocyclitols can give rise to higher inhibition than their six-membered counterparts and subtle selectivities may be observed for five- over six-membered systems, thus making logical design based upon structural analogy difficult.[6] For this reason many types of five-membered iminocyclitols have been synthesized and screened. An examination of the literature showed that a number of diverse structural types have been screened for α-glucosidase inhibition. This includes those developed by Davis, for example, **4**[6] (Fig. 1) obtained from 3-pyrroline and tartaric acid, and showed no significant inhibition (3–13% at the 1 mM level). The five-membered iminocyclitol amide derivatives **5** developed by Wong's group showed inhibition with a K_i value of 53 nM[7] (which was better than that exhibited by the parent structure **6**) and the 2-alkylated analogues of type **7** (Fig. 1) were also shown by Wong[1b] to be weak α-glucosidase inhibitors (3–54% inhibition at 200 μM). Davis has also shown that a library of *N*-acyl(aroyl)-2-carboxyamide substituted pyrrolidine iminocyclitols of type **8**, showed little or no inhibition at 100 μM.[8] Wong has prepared and tested pyrrolidine iminocyclitols of type **9** with side-chains in both the 2 and the 5 positions,[9] in which some were very potent inhibitors. Calveras et al.[10] showed that a library of iminocyclitols of type **10** inhibited this enzyme at 1.6–4.2 nM level. In most cases the presence of a hydroxymethyl appendage seems to give significant inhibition, whereas when substituted by an alkyl group, as in **4** and **7** (Fig. 1), the inhibition is weaker or even absent, indicating that this substituent must be relevant to approximate the structures of the natural α-glucosidase sugar substrate.[6] This point has been echoed by Wong[9] and indeed, this hypothesis has been supported somewhat by the work of both Bols[11] and Lundt,[12] who prepared the 2,5-non-substituted pyrrolidine iminocyclitols **11**, **12** and **13**, with the hydroxymethyl appendage transposed to

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