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Sylviane Picasso*

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Introduction

Glycoproteins have many important biological functions: receptors, carriers, structural proteins, enzymes, hormones, lectins, and antibodies. Inhibitors of glycosidases, key enzymes in glycoprotein processing, are thus important as potential antiviral, antiadhesive, antitumoral, antibacterial, antihyperglycemic, or immunostimulatory agents [1]. Thus, an intense interest in the chemistry, biochemistry and pharmacology of glycosidase inhibitors has grown during the last decade and has

*Correspondence: Dr. S. Picasso
Institut de chimie organique
Université de Lausanne
CH–1015 Lausanne

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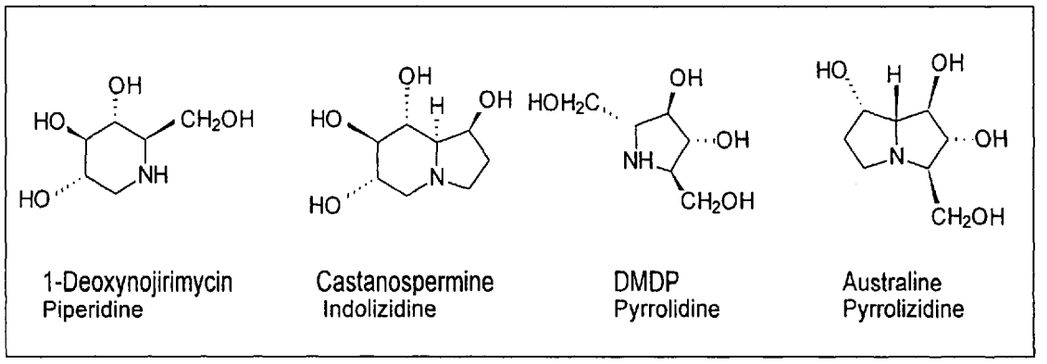

Fig. 1. *Some azasugar glycosidase inhibitors*

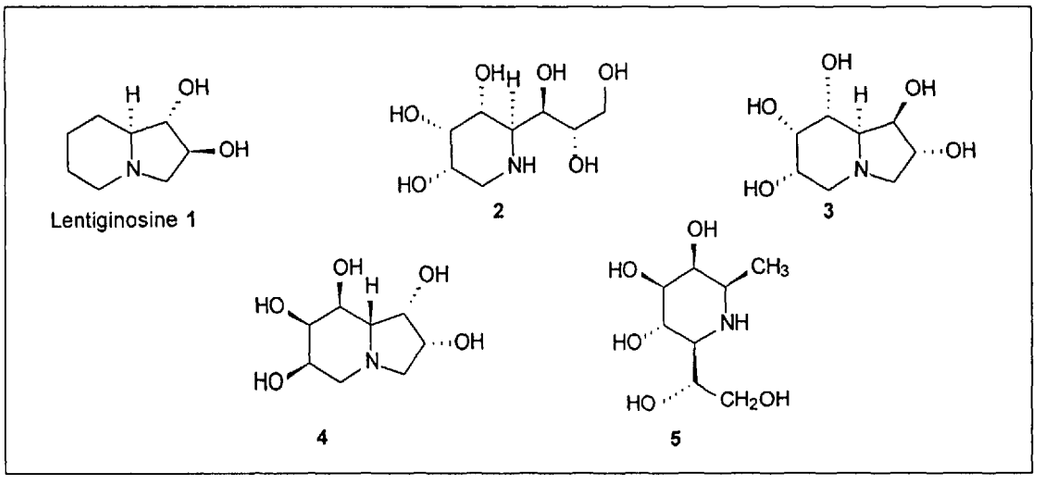

Fig. 2. *New azasugar glycosidase inhibitors*

led to a tremendous interest and demand for new compounds.

An important family of inhibitors are the azasugar compounds, analogues of monosaccharides in which the ring O-atom has been replaced by a N-atom. This renders the compound metabolically inert, but does not prevent its recognition by glycosidases due to mimicking of the furanosyl and pyranosyl moieties of the corresponding substrate. Azasugars include polyhydroxylated derivatives of piperidines, pyrrolidines, indolizidines, and pyrrolizidines (*Fig. 1*). Many have been isolated from plants and microorganisms and a number of synthetic analogues have been synthesized.

Activity of Some New Azasugars

Enzyme inhibition tests were performed on 24 commercial glycosidases with corresponding *p*-nitrophenyl glycoside substrates. IC_{50} values (concentration of inhibitor required for 50% inhibition of enzyme activity) and inhibition constants (*Ki*) were determined for some new azasugar compounds (*Fig. 2*).

Lentiginosine (**1**), a dihydroxylated indolizidine isolated from a natural source, is a powerful and specific inhibitor of amyloglucosidases (1,4-α-D-glucanglycohydrolases, EC 3.2.1.3) [2]. The absolute configuration of the alkaloid was determined on the basis of amyloglucosidases inhibition tests with both lentiginosine enantiomers synthesized in *Brandi*'s laboratory (University of Firenze). The enzymatic tests showed that the active enantiomer was the (+)-compound with a *Ki* = 2 μM. The absolute configuration of natural lentiginosine ((+)-**4**) was determined to be (1*S*,2*S*,8a*S*)-1,2-dihydroxyindolizidine [3]. Some compounds synthesized in our laboratory also displayed interesting glycosidase inhibition activity. The first 1,5-dideoxy-1,5-iminooctitols and the corresponding pentahydroxyindolizidines were prepared by *Chen* and *Vogel* [4]. The imino-octitol (**2**) and the pentahydroxyindolizidine (**3**) are better inhibitors of β-galactosidases than swainsonine (*Fig. 1*). The polyhydroxyindolizidine (**4**) is, like swainsonine, a powerful inhibitor of α-mannosidases from jack beans and almonds (*Ki* = 2 and 10 μM) but more specific than the natural alkaloid because it does not inhibit β-galactosidases [5]. A synthetic piperidine with the absolute configuration of β-D-*galacto*-hexopyranoside (**5**) was also submitted to the tests and this, surprisingly, showed complete inactivity against five β-galactosidases but it was a good competitive inhibitor of β-glucosidases (*Ki* =15 μM) from sweet almonds [6].

Conclusions and Perspectives

Our screening of potential glycosidase inhibitors is proceeding with many different molecules of both natural and synthetic origins, with samples from several laboratories. For the future, we are planing to enlarge the enzyme screening panel with recombinant mammalian glycosidases and glycosyltransferases.

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