Synthesis, Biological Evaluation and Docking Studies of Casuarine Analogues: Effects of Structural Modifications at Ring B on Inhibitory Activity Towards Glucoamylase


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We report the total synthesis of a series of pyrrolizidine analogues of casuarine (1) and their 6-O-$\alpha$-glucoside derivatives. The synthetic strategy is based on a totally regio- and stereoselective 1,3-dipolar cycloaddition of suitably substituted alkenes and a carbohydrate-based nitrone. We also report the evaluation of the biological activity of casuarine and its derivatives towards a wide range of glycosidases and a molecular modeling study focused on glucoamylase (GA) in which the binding modes of the newly synthesized compounds within the enzyme cavity are investigated. The results highlight the prominent structural features of casuarine and its derivatives that make them selective glucoamylase inhibitors.

Introduction

Iminosugars are very attractive carbohydrate mimics in which the endocyclic oxygen atom is replaced by the more basic, trivalent nitrogen atom.[1] In their protonated form, iminosugars resemble the transition state or intermediate generated during the hydrolysis reaction catalysed by glycosidases, key hydrolytic enzymes involved in many physiological functions. Since the discovery of the inhibitory properties of iminoalditols towards glycosidases, they have received increasing attention as diagnostic compounds as well as tools for the investigation of the structures, functions and catalytic mechanisms of carbohydrate-processing enzymes.[2–3] Furthermore, given the important role of glycosidases and glycosyltransferases in controlling the structures and functions of carbohydrates at the cell surface, competitive inhibitors of these classes of enzymes are potential anti-diabetes, anti-viral and anti-cancer agents.[1,2] Recently, interesting immunosuppressive activities have been discovered for this class of compounds.[4] In the past 40 years, more than 100 polyhydroxylated alkaloids have been isolated from plants and microorganisms[5] with structures that include polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes. For instance, the piperidine alkaloid 1-deoxynojirimycin (DNJ, Scheme 1), prepared first by Paulsen et al. in 1967[6a] and then isolated from a species of *Moris* (Moraceae),[6b] was found to strongly inhibit $\alpha$-glucosidases.[5a] $N$-Alkylated derivatives of DNJ have found applications as anti-diabetic drugs (i.e., Miglitol, Glyset) or anti-HIV agents (Glycovir, SC 49483).[2a] The indolizidine alkaloid (+)-lentiginosine (Scheme 1) was isolated in 1990 from the leaves of *Astragalus lentiginosus* and was found to inhibit amyloglucosidases.[7] Its non-natural enantiomer (–)-lentiginosine was recently discovered to possess proapoptotic activity towards tumoral cells.[8] Castanospermine (Scheme 1), isolated in 1981 from the seeds, leaves and barks of *Castanospermum austral* and in 1988 from the seeds, leaves and barks of *Alexa sp.*, and its ester and salt derivatives are able to inhibit tumour growth and metastasis.[9]

Casuarine (1, Scheme 2) and its 6-O-$\alpha$-glucoside, casuarine-6-O-$\alpha$-glucopyranoside (2, Scheme 2), have been isolated from the bark of *Casuarina equisetifolia* L. (Casuarinaceae) and from the leaves of *Eugenia jambolana* Lam. (Myrtaceae).[10] We recently reported that casuarine (1) is able to inhibit a human maltase-glucoamylase (MGAM,