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Stereoselective synthesis of 2-acetamido-1,2-dideoxynojirimycin (DNJNAc) and ureido-DNJNAc derivatives as new hexosaminidase inhibitors†

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2-Acetamido-1,2-dideoxyiminosugars are selective and potent inhibitors of hexosaminidases and therefore show high therapeutic potential for the treatment of various diseases, including several lysosomal storage disorders. A stereoselective synthesis of 2-acetamido-1,2-dideoxynojirimycin (DNJNAc), the iminosugar analog of *N*-acetylglucosamine, with a high overall yield is here described. This novel procedure further allowed accessing ureido-DNJNAc conjugates through derivatization of the endocyclic amine on a key pivotal intermediate. Remarkably, some of the ureido-DNJNAc representatives behaved as potent and selective inhibitors of β-hexosaminidases, including the human enzyme, being the first examples of neutral sp^2-iminosugar-type inhibitors reported for these enzymes. Moreover, the amphiphilic character of the new ureido-DNJNAc is expected to confer better drug-like properties.

Introduction

Since the isolation of nojirimycin in 1966, iminosugars—sugar analogs where the oxygen ring atom has been replaced by a nitrogen—have attracted an exponential interest as mimics of the transition state of the enzymatic hydrolysis of glycosidic substrates.[1,2] Their ability to act as inhibitors of a great diversity of carbohydrate processing enzymes, including glycosidases, glycosyl transferases, nucleoside-processing enzymes and glycogen phosphorylases, and the broad variety of biological and pathological processes in which carbohydrates are involved make iminosugars invaluable tools in glycobiology and promising candidates for the development of glycotherapies.[3–5] In fact, some iminosugars are already marketed drugs, such as miglitol (Glyset) and *N*-butyl-1-deoxynojirimycin (Zavesca), used for the treatment of type II diabetes mellitus and type 1 Gaucher disease respectively.[6]

Iminosugars reduced at C-1 and bearing an acetamido group at the position equivalent to C-2 in the parent monosaccharides, namely 2-acetamido-1,2-dideoxyiminosugars, have been the focus of considerable attention in recent years. Several representatives of acetamido iminosugars, for instance pochonicine (**1**),[7] siastatin B (**2**),[8] or nagstatin (**3**)[9,10] have been isolated from natural sources while derivatives from those and other compounds have been obtained by chemical synthesis.[11,12] Most of these representatives are piperidine derivatives, such as 2-acetamido-1,2-dideoxynojirimycin (DNJNAc, **4**)[13–16] and its *manno* (DMJNAc, **5**)[14,17] or *galacto* epimers (DGJNAc, **6**),[18,19] although acetamido iminosugars with five- (*e.g.* **7**)[20,21] or seven-membered ring skeletons (*e.g.* **8**)[22] have also been described (Fig. 1). Several of these compounds have proven to be highly selective inhibitors of hexosaminidases—the enzymes cleaving off amino sugar residues from oligosaccharides and glycoconjugates—with inhibition constant (K_i) values in the low micromolar to nanomolar range. This property makes them potentially useful in the treatment of several diseases involving abnormal levels of *O*-linked glucosamine (GlcNAc) in glycoproteins, including diabetes, Parkinson's, osteoarthritis, and some cancers.[23–27] Furthermore, at subinhibitory concentrations competitive inhibitors of the hexosaminidases are able to promote the correct folding of mutant disease-associated lysosomal enzymes, thus bearing promise for the development of pharmacological chaperone

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† Electronic supplementary information (ESI) available: Experimental procedures for the synthesis of 3-acetamido-1,3-dideoxyaltronojirimycin (**29**), and derivatives **32b–d** and **10b–d**. ^{1}H and ^{13}C spectra of all new compounds and selected Lineweaver–Burk plots of ureido-DNJNAc derivative **10c**. CCDC 1053544 and 1053545. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c5ob00507h