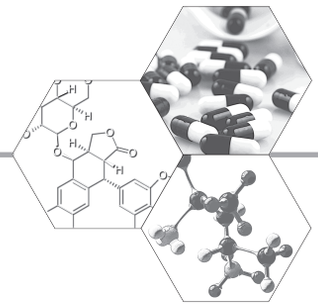

Iminosugars as therapeutic agents: recent advances and promising trends

For the purpose of this article, iminosugars are polyhydroxylated secondary and tertiary amines in which the molecules resemble monosaccharide sugars in which the ring oxygen is replaced by the nitrogen. The bicyclic structures may biologically resemble disaccharides. Very few iminosugars have been available up to now for evaluation of their pharmaceutical applications. The early compounds were discovered and selected for study due to glycosidase inhibition, which is now known to not be necessary for pharmacological activity and may cause off-target effects. Glyset® and Zavesca®, derived from the glucosidase-inhibiting natural product 1-deoxynojirimycin, are the first two examples of iminosugar drugs. Since the discovery of this first generation, many new natural products have been identified with a wide range of biological activities but few are widely available. Among the biological properties of these compounds are good oral bioavailability and very specific immune modulatory and chaperoning activity. Although the natural products from plants and microorganisms can have good specificity, modifications of the template natural products have been very successful recently in producing bioactive compounds with good profiles. The field of iminosugars continues to open up exciting new opportunities for therapeutic agent discovery and offers many new tools for precisely modifying carbohydrate structures and modulating glycosidase activity *in vivo*. Current efforts are directed towards a greater range of structures and a wider range of biochemical targets.

The **iminosugars** are a widespread group of plant and microbial compounds that have been attracting interest due to their ability to interact with human glycosidases, other proteins and sugar receptors. In their simplest form they resemble furanose and pyranose monosaccharides with a nitrogen replacing the oxygen in the ring **(Figure 1)**. For the purpose of this article iminosugars are considered to be polyhydroxylated secondary and tertiary amines in which the molecules resemble monosaccharide sugars in which the ring oxygen is replaced by the nitrogen. There are five ring structures fitting this classification that are most common in nature: pyrrolidine, piperidine, pyrrolizidine, indolizidine and *nor*-tropane **(Figure 2)**. These compounds have been given several names in the past in the literature, including aza-sugars, **glycosidase inhibitors** and sugar analogues, and the variety and distribution of natural compounds have been reviewed [1–3]. There are now approximately 200 reported as natural products [4,5]. However, very few have been widely available for drug discovery and most research has concentrated on the first compounds discovered, that is, **1-deoxynojirimycin** (DNJ), castanospermine, swainsonine, fagomine, 1,4-dideoxy-1,4-imino-D-arabinitol (DAB) and derivatives/variants of these compounds. The initial pharmaceutical interest in these compounds was related to their properties as glycosidase inhibitors and this also guided their isolation and early synthesis [6]. In the last 10 years it has become clear that they do not need to be glycosidase inhibitors for biological effects and can for example act as immune modulators and **chaperones** of misfolded proteins without inhibiting glycosidases [7,8,101,102]. It is probably the case that plants and microorganisms benefit from the protection from digestion by having compounds with broad activity; these compounds can form the basis of synthetic strategies to produce more selective molecules. It is intriguing that many natural iminosugar compounds isolated now also do not seem to be glycosidase inhibitors.

The productivity of the drug-discovery process has declined significantly over recent decades, with the number of new chemical entities entering the clinic declining in contrast to ever increasing costs [9]. There is a need, and opportunity, to bring to the table less conventional approaches to the discovery and development of new small-molecule actives. With perhaps 10^{65} conceivable organic molecules with a molecular weight under 500, efficiently mapping chemical space onto biological space represents a major challenge to the discovery of

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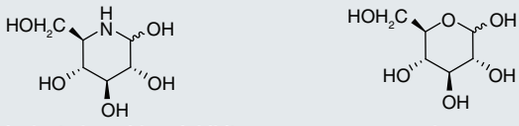

Figure 1. Basic structure of iminosugars.

Key Terms

Iminosugars: Mono- and di-saccharide mimetics including monocyclic and bicyclic molecules.

Glycosidase inhibitors: Iminosugars with the endocyclic nitrogen can inhibit glycosidases by acting as mimics of the transition state molecules.

1-deoxynojirimycin: One of the first glucosidase analogues discovered in plants and bacteria.

Chaperones: Iminosugars can improve the folding and function of proteins by binding to them.

new drug leads [10]. Considering that nature has had millennia to evolve small molecules for biological effect, where better than natural products to search for so-called 'privileged' bioactive templates [11–13]. There has been a long-standing reticence of mainstream pharmaceuticals to engage with carbohydrate-like hits and leads, which are often deemed to be too polar for delivery and bioavailability purposes. Glycobiology has had a reputation for being technically difficult but it offers great potential in pharmaceutical development since glycosylation is crucial to how the human body functions. There are a diverse range of structures displayed by carbohydrates and these provide a substantial opportunity for the identification of new targets and the development of new therapies. New carbohydrate receptors are being discovered and their functions are often unknown as yet. The discovery that iminosugars with no glycosidase inhibition can nonetheless have prophylactic and therapeutic effects opens up many exciting new areas for their utilisation. They will also be important tools for studying carbohydrate biology. In essence, the iminosugars represent a privileged scaffold and the timing is perfect because of an increased understanding of the structures and functions of carbohydrates. The challenge is to tune this bioactive template for specific therapeutic applications.

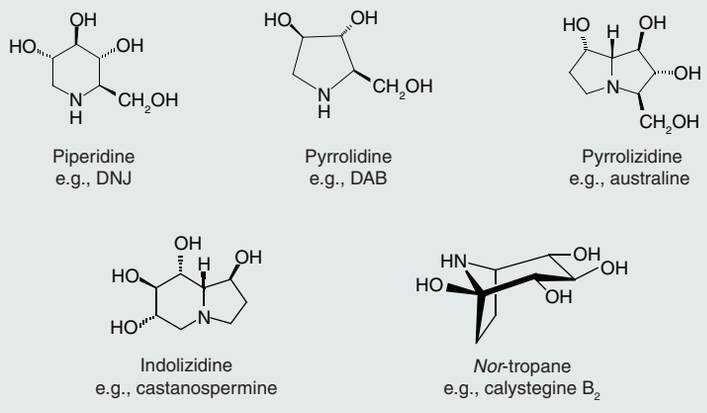

Figure 2. Most common natural structural classes of the iminosugars.

New generation iminosugars with enhanced efficacy & specificity

Iminosugars display a wide range of biomedically relevant activities: antiviral properties (against HIV-1, herpes simplex virus, bovine viral diarrhea virus [BVDV] and hepatitis C virus [HCV]) [5,14], antidiabetic properties (Miglitol, Glyset has been in the clinic for some time) [15,16], for use in lysosomal storage disorders, such as Gaucher's and Niemann–Pick type C disease (*N*-butyl-DNJ, miglustat, marketed as Zavesca®) [17,18] and immune modulation and anticancer activity [3,12]. Due to the great importance of carbohydrates in mammalian biochemistry and disease progression, it is clear that iminosugars have potential as small-molecule therapeutics in a wide range of disease areas in addition to their current successes. However, the lack of specificity of the agents that have been tested in the clinic so far, and the difficulties involved in isolating new iminosugars, mean that new approaches are required to exploit their potential. The identification of novel natural iminosugars and the synthesis of new active structures have been slow up to now even with the exciting therapeutic effects seen with DNJ, castanospermine and the other early iminosugar swainsonine. There are a number of reasons for the slow development including their high water solubility and the lack of a chromophore, thus increasing the technical challenges of working with these compounds. In plants and microbes, iminosugars are also masked by high concentrations of sugars and amino acids. A great step forward has been made recently with the realization that glycosidase inhibition is not necessarily required for their therapeutic activity [19,101,102]. Many of the iminosugars isolated or synthesized and disregarded due to lack of glycosidase inhibition, therefore, now deserve further evaluation. However, lack of glycosidase inhibition may also reflect the limited range of assays readily available and used; for example, one of the more interesting iminosugars isolated recently, steviamine **(Figure 3)** [20], is very specific in inhibiting an α-*N*-acetylgalactosaminidase that is rarely assayed but has important roles in the body [21].

History of natural iminosugars as therapeutic agents

The first natural iminosugar, nojirimycin, was discovered in Japan in 1966 as a novel antibiotic

from a *Streptomyces* isolate [22]. The closely related compound, DNJ, was originally synthesized by removing the anomeric hydroxyl by Inouye and co-workers in 1968 [23], but was later also isolated from mulberry in 1976 by Yagi *et al.* studying the antidiabetic activity of the plant. DNJ was found to be a potent inhibitor of the enzyme family of α- and β-glucosidases [24].

Medicinal chemistry was employed to the DNJ sugar template to produce *N*-hydroxyethyl-DNJ (Miglitol) **(FIGURE 4)**, which was successfully developed as an antidiabetic (Glyset®) by Bayer and was the first iminosugar drug to reach the market [15,16,25]. Since 1996, it has been approved for non-insulin-dependent diabetes mellitus, where it reduces the rate of complex carbohydrate digestion, thereby controlling the absorption of glucose after meals and preventing hyperglycaemia.

1-deoxynojirimycin was also adapted by Oxford University and Oxford Glycosciences, to enhance cell uptake, to produce *N*-butyl-DNJ (Zavesca) **(FIGURE 4)**, which is used for the treatment of type I Gaucher's disease and Niemann–Pick type C disease, lysosomal storage disorders. Gaucher's disease is caused by a deficiency in glucocerebrosidase and Niemann–Pick type C disease is due to a deficiency in metabolism of cholesterol and other lipids. There was no prior treatment for Niemann–Pick type C disease and prior to Zavesca patient management was restricted to symptom relief. Zavesca functions by inhibiting the enzyme glucosylceramide synthase involved in the glucosylation of many sphingolipids. This decreases the excessive cellular storage of glycolipids in neural tissue. Despite its efficacy, Zavesca has also been associated with side effects, which has had an impact on the product's development [3–5,26].

N-butyl-DNJ was also found to be effective at inhibiting HIV infectivity *in vitro* by blocking viral envelope glycoprotein trimming. This means that the viral particles produced in the presence of the iminosugar are non-infectious as the conformation of their envelope protein has been altered and they can no longer bind to their respective cell receptor. *N*-butyl-DNJ was evaluated by Searle-Monsanto in a Phase II clinical trial and although antiviral effects were observed, there were side-effect issues again – this time a high prevalence of gastrointestinal tract complications, attributable to the nonspecific activity of the drug. In addition, high serum levels of the drug were required for efficacy [27].

Castanospermine, isolated from the

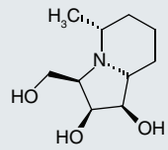

Figure 3. Steviamine.

Australian tree *Castanospermum australe*, was developed by Merrell Dow who, in order to increase its cell uptake, modified the sugar by the addition of a butanoyl group to form the prodrug known as Celgosivir (6-*O*-butanoyl-castanospermine) [14,27]. Celgosivir was shown to have anti-HIV activity and was evaluated in a Phase II clinical trial. However, similarly to *N*-butyl-DNJ, the clinical development was problematic, due to the compound's toxicity profile and competition from other less toxic anti-HIV drugs.

Celgosivir was also shown to have antiviral activity against other viruses including CMV, influenza and the HCV surrogate BVDV *in vitro* [3,14]. Despite advances in antiviral therapeutics, HCV infection continues to be a major worldwide health concern. In the search for newer agents with novel mechanisms of action, such as compounds that target virus-specific enzymes, inhibition of α-glucosidase I is considered an attractive anti-HCV strategy since this enzyme is involved in the biosynthesis of glycoproteins that, when expressed on the viral surface, are essential for virus–host interactions. Castanospermine is an α-glucosidase I inhibitor with marked antiviral activity against a number of viruses. Unfortunately, the agent also inhibits intestinal sucrases and causes osmotic diarrhea. In contrast, celgosivir, the 6-*O*-butanoyl derivative of castanospermine, is a relatively inactive inhibitor of intestinal sucrases and appears to be nontoxic to the GI tract. It possesses antiviral activity that is 30-fold greater than the parent compound, its active metabolite. Celgosivir has displayed potent antiviral activity *in vitro* and *in vivo* against several viruses, including HIV-1,

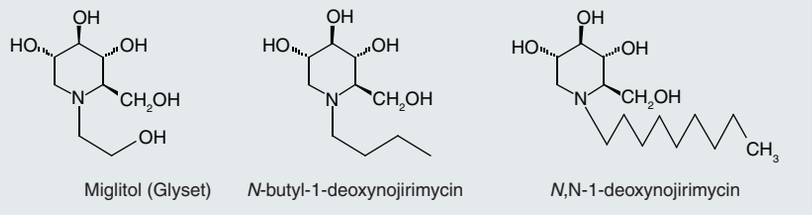

Figure 4. Derivatives of deoxynojirimycin.

Key Term

Casuarine: Nontoxic pyrrolizidine alkaloid that primes protective and therapeutic type-1 immune responses.

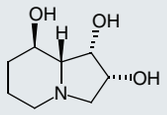

Figure 5. Swainsonine.

herpes simplex virus, BVDV and HCV, and the agent was chosen for further development as a treatment for HCV infection. The antiviral efficacy and safety of celgosivir were demonstrated in clinical trials in HIV-1-infected patients [14].

N-Nonyl-deoxynojirimycin has an additional antiviral mode of action against HCV by inhibiting formation of the p7 ion channel. HCV p7 is capable of forming cation selective ion channels in planar lipid bilayers. *In vitro*, HCV p7 ion channel activity can be inhibited by a range of compounds including *N*-Nonyl-deoxynojirimycin [28]. *N*-(*n*-Nonyl)-1-deoxygalactonojirimycin (DGJ) can also reduce the amount of HBV DNA produced in culture and has been under consideration for development as a human therapeutic. DGJ does not appear to inhibit HBV DNA polymerase activity or envelope antigen production [29].

Swainsonine has been isolated from both plants and microorganisms **(Figure 5)** [3]. It is a potent inhibitor of α-mannosidases and inhibits α-mannosidase II activity in the *N*-glycan biosynthesis pathway, blocking production of complex-type oligosaccharides. Swainsonine has been of great use in the study of *N*-glycan functions, with many important results published since its discovery. The anti-tumor activity of swainsonine has also been previously examined. Swainsonine exhibits not only cytotoxicity, but inhibits cancer cell metastasis, decreases the toxicity of chemotherapeutic drugs and works as immunomodulator. Despite its side-effects (mainly vacuolation caused by inhibition of lysosomal mannosidases), clinical studies on patients have shown that swainsonine is of some benefit as a chemotherapeutic drug, suggesting that it might have further applications in this field [3,30].

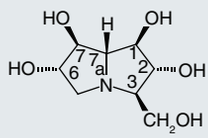

Figure 6. Casuarine.

The pyrrolidine iminosugar DAB, isolated initially from the African legume species *Angylocalyx braunii*, is an inhibitor of glycogen phosphorylase but is probably not an ideal therapeutic agent itself due to potent inhibition of α-glucosidases [31,32]. DAB was shown to be nearly completely orally available in rats and dogs and it can reduce glucagon-induced and spontaneous hyperglycaemia. Inhibition of hepatic glycogen phosphorylase may benefit glycaemic control in patients with Type 2 diabetes. It is of interest that iminosugars have recently started to arouse wider interest as potential antidiabetic and weight control agents through activities not related to inhibition of glucosidases [33].

Some of the first-generation imino sugars have been shown to be potent agonists of the human glucose sensor, sodium/glucose cotransporter type 3 (hSGLT3) [34]. Potent hSGLT3 activation was shown by the iminosugars (DNJ), *N*-hydroxylethyl-DNJ (miglitol), *N*-butyl-DNJ, *N*-ethyl-DNJ and DNJ-1-sulfonic acid, with $K_{0.5}$ values of 0.5 to 9 μM. DGJ activated hSGLT3 with a $K_{0.5}$ value of 11 mM, a 3000-fold less potent interaction than was observed for DNJ (4 μM).

A new generation of iminosugar therapeutic agents

Iminosugars have an excellent drug profile; they are small and simple in structure, stable and the few studied so far are orally available. Of those studied *in vivo* they are not metabolized or incorporated and are excreted unchanged primarily in urine. There is no doubt that many of the natural iminosugars will eventually find therapeutic applications once they are evaluated in suitable assays. **Casuarine** is a good example. It is a pentahydroxylated pyrrolizidine alkaloid with the unusual hydroxymethyl moiety at C-3 of the pyrrolizidine iminosugars **(Figure 6)**. It was first found as the major alkaloid of *Casuarina equisetifolia* bark in 1994 [35,36]. It is a good glucosidase inhibitor but subsequently was also found to be able to prime the immune system for an increased type-1 immune response, increasing levels of cytokines such as IL-2, IL-12, and IFN-γ, and it has potent activity in the B16/F10 melanoma in mice given a single oral dose of 100 μg/ml. What was particularly interesting was that glucosidase inhibition was not necessary for the immunological activity [101,103].

In addition to the possibilities of increasing or

correcting a deficient immune response to cancer cells using immune modulators such as casuarine, the iminosugars can be selective competitive and noncompetitive inhibitors of carbohydrate manipulation enzymes, such as glycosidases, which are involved in tumor cell invasion and migration [37]. Such enzymes are also responsible for the attachment of oligosaccharides to the cell surface of tumor cells, displayed as glycoproteins, glycolipids, and proteoglycans, which play an important role in malignant phenotype and tumor growth. Furthermore, cancer cells show an extremely active lysosomal system, which is reflected by enhancement of glycoprotein turnover. Iminosugars interact with glycosyl hydrolases responsible for this kind of action in cancer cells and thus introduce a new compound class into the research field of finding new anticancer activities. The specificity of enzyme inhibition that is becoming apparent with natural and synthetic variants makes it likely that the exciting activities of compounds such as swainsonine can be utilized without the off-target activities.

Pharmacological chaperones act on misfolded, unstable mutant proteins that exhibit residual biological activity. First suggested by Fan *et al.* in 1999 [38], the ability of iminosugars to act as pharmacological chaperones is opening up new therapeutic possibilities [39]. The compounds can bind to the catalytic sites of the deficient enzymes or other misfolded proteins and lead to improved trafficking in the endoplasmic reticulum, resulting in improved function. Fabry disease is an X-linked lysosomal storage disorder caused by mutations in the gene encoding α-galactosidase A (α-Gal A), with consequent accumulation of its major glycosphingolipid substrate, globotriaosylceramide. Over 500 Fabry mutations have been reported; approximately 60% are mis-sense. The iminosugar DGJ (migalastat hydrochloride, Amigal®) is a pharmacological chaperone that selectively binds α-Gal A, increasing physical stability, lysosomal trafficking, and cellular activity [40]. Importantly, the chaperoning activity of DGJ is observed at concentrations that do not inhibit the α-Gal A enzyme or other galactosidases. DGJ sometimes occurs alongside DNJ in plants and is found as various C-1 derivatives in the Chinese medicinal plant *Adenophora triphylla* (Campanulaceae), for example, β-1-*C*-butyl-DGJ and β-1-*C*-butenyl-1-DGJ **(FIGURE 7)** [41]. *N*-butyl-DNJ also acts as a pharmacological chaperone for the deficient lysosomal α-glucosidase causing Pompe's disease [42].

Other pharmacological chaperones have been designed based on natural iminosugar templates. An example is isofagomine (Plicera®) for treatment of Gaucher's disease **(FIGURE 8)**. The natural product fagomine occurs in mulberry (*Morus* species) alongside DNJ, is a weak inhibitor of glucosidases, and potentiates insulin release [3]. Isofagomine binds selectively to N370S glucocerebrosidase (deficient in Gaucher's disease) and increases activity threefold [43]. One potential problem with isofagomine is that it also inhibits glycogen phosphorylase.

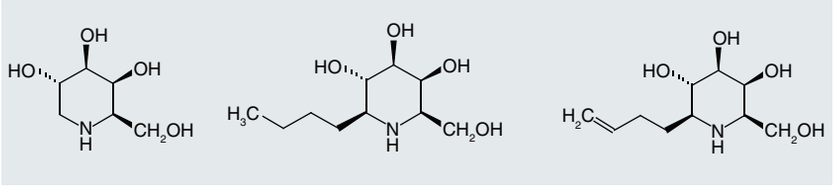

Figure 7. DGJ, β-1-*C*-butyl-DGJ and β-1-*C*-butenyl-1-DGJ.
DGJ: (*n*-Nonyl)-1-deoxygalactonojirimycin.

The competitive glucosidase inhibitor DAB and the noncompetitive glucosidase inhibitor enantiomer LAB [44] have been used as templates to produce inhibitors of β-*N*-acetylglucosaminidases [45]. 2-acetamido-1,4-imino-1,2,4-trideoxy-L-arabinitol (LABNAc) was synthesized along with the *N*-benzyl and *N*-butyl analogues and they were found to be potent inhibitors **(FIGURE 9)**. The enantiomers DABNAc **(FIGURE 9)** and *N*-Bn-DABNAc were also synthesized. The L-iminosugar LABNAc and its derivatives were found to be potent noncompetitive inhibitors of some β-*N*-acetylhexosaminidases, while the D-iminosugar DABNAc and its derivatives were found to be weaker competitive inhibitors. These results support the previous studies postulating that D-iminosugar mimics inhibit D-glycohydrolases competitively, and that their corresponding and usually un-natural L-enantiomers show noncompetitive inhibition of these enzymes [46,47]. Molecular modeling studies confirmed that the spatial organization in enantiomeric inhibitors leads to a different overlay with the monosaccharide substrate [33]. *N*-acetylhexosaminidases are of considerable importance in mammals and are

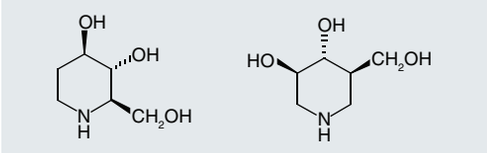

Figure 8. Fagomine and isofagomine.

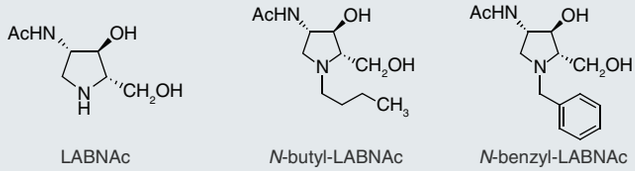

Figure 9. 2-acetamido-1,4-imino-1,2,4-trideoxy-L-arabinitol and its derivatives.

involved in various significant biological processes. In humans, deficiencies of these enzymes in the lysosome, resulting from inherited genetic defects, cause the glycolipid storage disorders Tay–Sachs and Sandhoff diseases. One promising therapy for these diseases involves the use of β-*N*-acetylhexosaminidase inhibitors as chemical chaperones to enhance the enzyme activity above subcritical levels. Initial cell-based studies suggest that *N*-Bn-LABNAc can act as a chaperone to enhance the deficient enzyme's activity to levels that may cause a positive pharmacological effect. LABNAc, *N*-Bn-LABNAc and *N*-Bu-LABNAc are potent and selective inhibitors of β-*N*-acetylhexosaminidase and, as such, may be useful as therapeutic agents for treating adult Tay–Sachs and Sandhoff diseases [45].

While iminosugar pharmacological chaperones that bind to catalytic sites hold potential as a treatment of disorders arising from aberrant protein folding, including in particular lysosomal storage diseases, there are now indications that some iminosugars can have chaperoning activity via binding to other sites on these enzymes. These compounds could have the advantage of being free of concerns over possible inhibition of nontarget glycosidase enzymes [102]. IsoDAB and isoLAB (isomers of DAB and LAB) have been synthesized **(Figure 10)** [19]. IsoDAB was a potent and specific inhibitor of a number of α-glucosidases. In contrast, isoLAB showed no significant inhibition of any glycosidase. DAB is a good inhibitor of glycogen phosphorylase [32] and a moderate inhibitor of glycoprotein processing glucosidases [3]; neither isoDAB or isoLAB showed any inhibition of these enzymes.

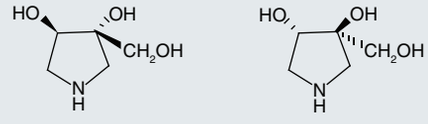

Figure 10. IsoDAB and isoLAB.

The combination of potency and specificity of isoDAB as an α-glucosidase inhibitor may provide a useful agent in the study of diabetes. The cystic fibrosis (CF) transmembrane conductance regulator (CFTR) is a protein involved in the transport of chloride ions across cell membranes which is mutated in cystic fibrosis. *N*-butyl-DNJ partially rescues the defective F508del-CFTR function in CF-KM4 cells and, thus, may have potential for the chemotherapeutic treatment of CF [48]; calnexin may be a therapeutic target for miglustat in CF. Although isoLAB showed no significant inhibition of any glycosidase, in preliminary experiments isoLAB also rescued CFTR function and thus is likely to be of value in the investigation of CF. This may be another example of an iminosugar that apparently acts as a chaperone but is not a glycosidase inhibitor.

Gem-diamine 1-*N*-iminosugars, are a new class of iminosugars which have a nitrogen atom in place of the anomeric carbon [49]. Natural gem-diamine 1-*N*-iminosugars, siastatin B and their analogues (A-72363 A-1, A72363 A-2 and A-72363 C), were isolated from *Streptomyces* cultures. Various 1-*N*-iminosugars have been synthesized from glyconolactones as a chiral source in a totally stereospecific manner and/or by the convergent strategy from siastatin B. The protonated form of 1-*N*-iminosugar mimics the charge at the anomeric position in the transition state of enzymatic glycosidic hydrolysis, resulting in a strong and specific inhibition of glycosidases and glycosyltransferases.

Future perspective

The increased knowledge of carbohydrate biochemistry and improved analytical and biological technology will mean that this field of drug discovery will now move fast. Despite very limited access to them to date, iminosugars have shown great potential in their ability to interact with varied mammalian biochemical processes involving carbohydrates without showing toxic effects and with high oral availability. With many more natural products now available and more synthetic molecules, it is clear that exciting new applications will open up due to their varied biological properties. Iminosugars can show great stereoselectivity in biological activity. Such selectivity is due to the chemical and biological diversity in terms of structural information of small sugars. The amazing biological diversity in such small molecules displays a remarkable economy in structural information in nature, completely surpassing in molecular weight

terms anything achieved by amino acids. The problems with broad glycosidase activity of the early molecules such as DNJ are largely due to the screening and isolation method employed for their discovery and with the realization that glycosidase activity is not necessary the field of iminosugars is not now so limited by trying to reduce off-target glycosidase effects.

Immucilin H (forodesine) **(FIGURE 11)** and DADMe-immucilin H for T-cell cancer and B-cell leukemia and psoriasis and autoimmunity, respectively [50,51], combine purine nucleotides with simple pyrrolidine iminosugars to form transition state inhibitors of purine nucleoside phosphorylases and show that iminosugars may have broad applications by replacing sugars in other drugs and thereby altering properties, including inhibiting deglycosylation.

Most plants producing iminosugars contain very complex mixtures of related compounds but with diverse and often very specific activities. To realize the potential of iminosugars from plants and microorganisms, the individual compounds need to be isolated and identified for bioassays. These molecules can then be modified by synthesis and semi-synthesis as has been very successful so far [52].

It is becoming clear that iminosugars are common components of plants and some have been reported from bacteria and fungi [3]. It is probable that many more microorganisms produce them than are currently documented. At the same time, one of the most surprising facts about herbal medicines is that we still do not know the active components of most of them or how exactly how they work even if there is good clinical data. The same is true of most fruit and vegetables, as the main nutrients are known but many health-promoting properties seem to be due to unidentified components. Great importance is given to different plant components at different times as knowledge increases; anti-oxidants, for example, have aroused great interest, but there is almost no clinical evidence supporting their health benefits by anti-oxidant activity. What seems increasingly likely is that the poor knowledge of the water-soluble components of herbal products and foods has meant that the bioactive iminosugars have been missed and may entirely explain the therapeutic and protective effects of many herbs. Given that most herbs were traditionally prepared in water, it seems increasingly probable that the elusive active components are in the water-soluble fractions that were largely ignored because they were difficult to analyze. Very few commercial herbal products are prepared in water and water-soluble components are rarely identified. It is also true that drug-discovery programs using plants have typically used solvents such as methanol, chloroform or hexane for extraction. In the case of microbial fermentations, the high concentrations of water-soluble media components often make it difficult to isolate water-soluble secondary metabolites. Mining the water-soluble fractions of plants and microbial broths for compounds such as iminosugars could therefore be very productive.

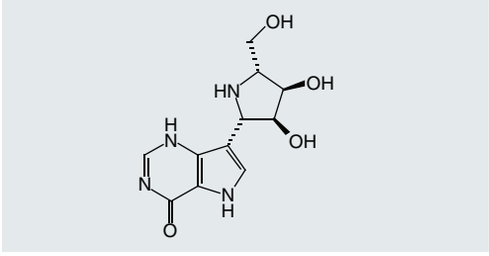

Figure 11. Forodesine.

Carbohydrates are of great importance in mammalian biochemistry. They help to determine the 3D structure of proteins, which is inherently linked to their function and efficacy. Iminosugars can act by modifying carbohydrate processing, as chaperones to produce otherwise defective glycoproteins, by inhibiting glycosidases elevated by tumor cells, controlling cancer cell glycosylation, by specifically altering viral and bacterial cell walls (reducing infectivity, the number of glycoforms and altering immune responses) and by binding to carbohydrate receptors. Due to their several mechanisms of action, there is great flexibility in the class.

It seems likely that plants produce iminosugars to protect their carbohydrate products produced via photosynthesis. Microorganisms probably produce them to reduce competition from other microorganisms by inhibiting their glycosidases. The glycosidase inhibitors may also help to regulate endogenous glycosidase activity. However, many of the natural products isolated in recent years are not inhibitors of any glycosidase tested as yet. This suggests that these compounds can have other functions and this is perhaps supported by the discovery of chaperoning activity and the ability of some agents to modulate the immune response of mammals [9]. Iminosugars may have widespread regulatory roles and it could be that some functions have been conserved by most organisms but only some plants and microorganisms accumulate them.

Executive summary

- The field of iminosugars continues to open up exciting new opportunities for therapeutic agent discovery.
- Iminosugars do not need to be glycosidase inhibitors for pharmacological activity.
- Lack of glycosidase inhibition removes many off-target activities.
- Iminosugars have wide applications from immune modulation to antiviral, diabetes and cystic fibrosis therapy.
- Iminosugars can chaperone misfolded proteins without being enzyme inhibitors.
- Synthesis can improve on the natural product templates.
- Current efforts are directed towards a greater range of structures and a wider range of biochemical targets.
- Iminosugars may be the elusive active components of many herbal products and functional foods.

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- ▪▪ of considerable interest

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