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Iminosugars: from botanical curiosities to licensed drugs

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Special edition of Tetrahedron: Asymmetry in honour of Professor George Fleet's 65th birthday

ABSTRACT

George Fleet was a pioneer in establishing the structures of naturally occurring iminosugars and in developing novel methods for the chemical synthesis of iminosugars and related compounds. Iminosugars can inhibit or moderate the activity of a wide range of enzymes that act on carbohydrates and can probably affect the function of other carbohydrate-recognising proteins. These effects can be exploited for therapeutic purposes by using iminosugars to modify the glycosylation of eukaryotic cells, the metabolism of carbohydrates and glycoconjugates, the carbohydrate-dependent properties of glycoproteins such as folding and transport and the carbohydrate-mediated interaction of host cells with infective agents. The synthetic derivative of DNJ, *N*-hydroxyethyl DNJ, which inhibits intestinal disaccharidases and delays postprandial hyperglycemia, was approved for use in type 2 diabetes in 1996. Initially iminosugars were found to disrupt the lysosomal catabolism of glycoconjugates by inhibition of lysosomal glycosidases thereby causing chemically induced phenocopies of genetic lysosomal storage diseases. Paradoxically iminosugars are now being tested as potential therapeutic agents for human lysosomal storage diseases by exploiting some of their other properties. *N*-Butyl-DNJ, which inhibits the first step in the biosynthesis of many glycosphingolipids, is licensed for substrate reduction therapy for non-neuronopathic Gaucher's and Niemann-Pick C diseases. 1-Deoxygalactonojirimycin can act as a molecular chaperone for mutant alpha-galactosidases in patients with Fabry disease. Several other compounds are being evaluated in pre-clinical studies or early clinical trials for lysosomal storage and other diseases.

Contents

1. Historical Introduction

In 1980 Peter Dorling (Murdoch University, Western Australia), who had recently discovered and characterised swainsonine **1** (Fig. 1),[1] visited London to hold discussions about the isolation of novel plant alkaloids with Linda Fellows at the Jodrell Laboratory of the Royal Botanic Gardens at Kew. Linda's team, which included Robert Nash at that time, had isolated several novel plant alkaloids that inhibited glycosidases of plant and insect origin and had many potential industrial and medical applications.[2] A crucial aspect of the work at Kew was rigorous structural

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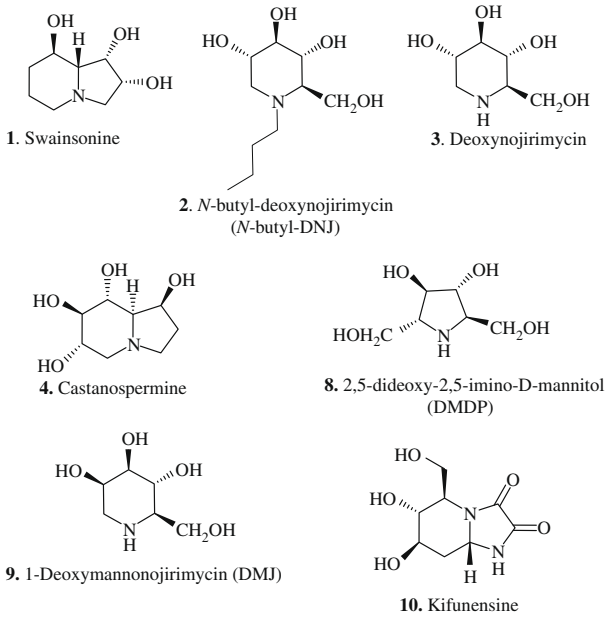


Figure 1. Structures of iminosugars.

analysis of the novel alkaloids by physicochemical techniques and chemical synthesis, which was carried out in conjunction with George Fleet in Oxford. Peter Dorling also visited Bryan Winchester at Queen Elizabeth College (QEC, University of London) in Kensington to discuss the mechanism of inhibition of mammalian alpha-mannosidases by swainsonine. The QEC group was studying the structure, function and mechanism of action of mammalian glycosidases, in the context of diseases in children and animals resulting from genetic defects in these enzymes. Peter realised that the groups had complementary interests and expertise and introduced Bryan to Linda and George. This was the beginning of a very productive, enjoyable and long-standing collaboration amongst the three groups to investigate the biological properties of natural and synthetic iminosugars. It is ironical that it was an antipodean visitor who brought together the two London laboratories, which were only a few miles apart!

During the 1980s the network of three original laboratories grew up to include academic groups in many countries including Denmark, France, Japan, New Zealand, UK (particularly the Glycobiology Institute in Oxford) and USA. The inhibition of glycosidases by many synthetic and natural piperidines, pyrrolidines, indolizidines, pyrrolizidines, calystegines and related compounds, for example, lactams was investigated. The results provided insight into the mechanism of action, specificity and structural requirements for inhibition of different glycosidases.[3–5] In turn this stimulated the synthesis of modified iminosugars, which could mimic the transition state of specific enzyme-substrate complexes or target sub-cellular sites. Many of the novel synthetic routes originated in George Fleet's laboratory.[6] An inspired suggestion from Linda Fellows was that alkylation of the ring nitrogen would enhance the uptake of iminosugars into mammalian cells.[7] This moment of inspiration about the development of *N*-butyl DNJ **2** (Fig. 1) as an anti-HIV drug apparently occurred in a pub at Kew Green according to a television documentary! Alkylation was also found to modify the specificity of inhibition in vitro.[8] In fact, almost every possible iminosugar or derivative has been synthesised chemically, including epimers, deoxy-derivatives, ring N-substituted compounds, C1 substituents, C-glycosides, fusion products with aromatic rings and glycosides as inhibitors for disaccharidases, endoglycosidases and glycosyltransferases.[9] The QEC laboratory, which moved to the UCL Institute of Child Health at Great Ormond Street Hospital in 1988, also tested, in confidence, several hundred synthetic compounds produced by pharmaceutical companies for their ability to inhibit human glycosidases. Not all these compounds were iminosugars.

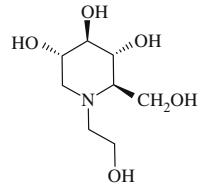
Research in the three original laboratories produced some significant papers, including several important reviews, which summarised current knowledge and included speculation on future applications and developments.[10–12] Not only did this research lay the foundation for the subsequent exciting development of therapeutic drugs but it also provided an excellent training for many young and talented scientists by exposing them to different disciplines. Several of them are authors of contributions in this issue. The multidisciplinary nature of the research was illustrated wonderfully by a conference held in Logan, Utah, USA in 1987, 'Swainsonine and Related Glycosidase Inhibitors'.[13] It brought together, biochemists, cell biologists, chemists, oncologists, plant toxicologists, veterinary pathologists and a few cowboys! Swainsonine had just been shown to be the cause of locoweed poisoning of livestock in the West.[14] All of us who attended this meeting, (including, Peter Dorling, Linda Fellows, George Fleet, Robert Nash and Bryan Winchester) agree to this date that it was one of the most stimulating and worthwhile meetings that we have ever attended. This was despite the arcane licensing laws of Utah State, which were circumvented with some ingenuity by the Australian contingent!

2. Potential therapeutic and industrial applications of iminosugars[9,15,16]

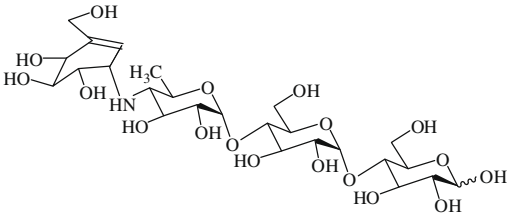
Iminosugars can inhibit or moderate the activity of a wide range of enzymes that act on carbohydrates and can probably affect the function of other carbohydrate-recognising proteins. These effects can be exploited to modify the glycosylation of eukaryotic cells, the metabolism of carbohydrates and glycoconjugates, the carbohydrate-dependent properties of glycoproteins such as folding and transport and the carbohydrate-mediated interaction of host cells with infective agents. This is a very active area of research both in academia and industry. Therefore I will concentrate on those applications, which are either in clinical practice and/or have evolved from work carried out by George Fleet or groups with which he has collaborated.

2.1. Intestinal glycosidases, obesity, diabetes and glycogenolysis

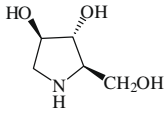
Glycosidases were the first therapeutic targets for iminosugars. Several natural alpha-glucosidase inhibitors, for example, DNJ **3** and castanospermine **4** can inhibit intestinal disaccharidases and delay postprandial hyperglycemia, making them potential antidiabetic and obesity drugs (Fig. 1). The synthetic derivative of DNJ, *N*-hydroxyethyl DNJ or Miglitol **5**, is approved for use in type 2 diabetes (Fig. 2). It decreases moderately postprandial blood glucose, insulin and glycated haemoglobin levels but causes considerable gastrointestinal discomfort due to undigested polysasccharides.[17] The pseudotetrasaccharide acarbose **6**, which is not absorbed appreciably, has a similar action. Acarbose is also useful for the differential assay of blood alpha-glucosidases for the diagnosis of the lysosomal storage disorder, Pompe's disease.[18] The blood glucose level can also be regulated by controlling glycogenolysis. The pyrrolidine, 1,4-dideoxy-1,4-imino D-arabinitol or DAB-1 **7** is another potential drug for type 2 diabetes because it can decrease glucagon-induced and spontaneous hyperglycemia by inhibition of hepatic glycogen phosphorylase probably by allosteric inhibition of phosphorylase A.[19] Miglitol also inhibits glycogenolysis.[20]



5. Miglitol (Bayer) *N*-hydroxyethylDNJ



6. Acarbose (Bayer) pseudotetrasaccharide



7. 1,4,-dideoxy-D-arabinitol (DAB-1)

Figure 2. Antidiabetic (type II) agents.

The effects of several other iminosugars on glycogenolysis have been studied in vitro.[21]

2.2. Glycoprotein processing

Iminosugars (Fig. 1) can inhibit specific processing glycosidases in the endoplasmic reticulum and Golgi apparatus (Fig. 3) and can alter the cellular repertoire of N-linked glycans on glycoproteins. Inhibition of an early enzymic step in processing can block the formation of a precursor for a particular type of mature glycan and can divert the processing to an alternative pathway. This has been exploited extensively to investigate the function of the glycosylation of specific glycoproteins and to alter cellular glycosylation for therapeutic purposes such as modulation of the immune response,[15] cancer therapy[22] and anti-viral activity.[23,24] Less progress has been made in developing inhibitors for processing glycosyltransferases. However, second generation 1-C derivatives of iminosugars, including glycosides, should provide the structural features for inhibiting these enzymes and glycosidases more specifically.

2.3. Other anti-infective drugs (Fig. 4)

Specific inhibition of an enzyme, which is expressed in an infecting organism but not in the host, is an ideal drug target. Such an enzyme is the elongating α-D-mannosylphosphate transferase of the *Leishmania* parasite. This enzyme is involved in the synthesis of the cell surface phosphoglycans that are essential for the survival and infectivity of the parasite and is not expressed in mammalian hosts. Novel iminosugars (1-oxabicyclic β-lactams) **11** have been synthesised based on the transition state of the enzyme and have been shown to be potent inhibitors of the enzyme.[25] This could be the basis of a new type of anti-Leishmania drug. George Fleet adopted a similar strategy to synthesise iminosugar drugs for combating other infectious microorganisms such as the mycobacteria that cause leprosy and tuberculosis. Pyrrolidine analogues of D-galactofuranose[26] and L-galactofuranose[27] **12**–**15** can inhibit *Mycobacterium* galactan biosynthesis. The Oxford group also synthesised a peptidomimetic of UDP-Galf incorporating a galactofuranose analogue.[28] Attempts to find iminosugars with antifungal activity have been less successful. Although some C-2 substituted polyhydroxypyrrolidines do inhibit chitin synthase activity in vitro they do not have any antifungal activity towards several pathogenic fungi.[29] The piperidine derivative, Siastatin B **16**, which can be isolated from *Streptomyces*, inhibits mammalian, viral and bacterial neuraminidases and its 3-epimer is a particularly good inhibitor of influenza virus neuraminidase.[30]

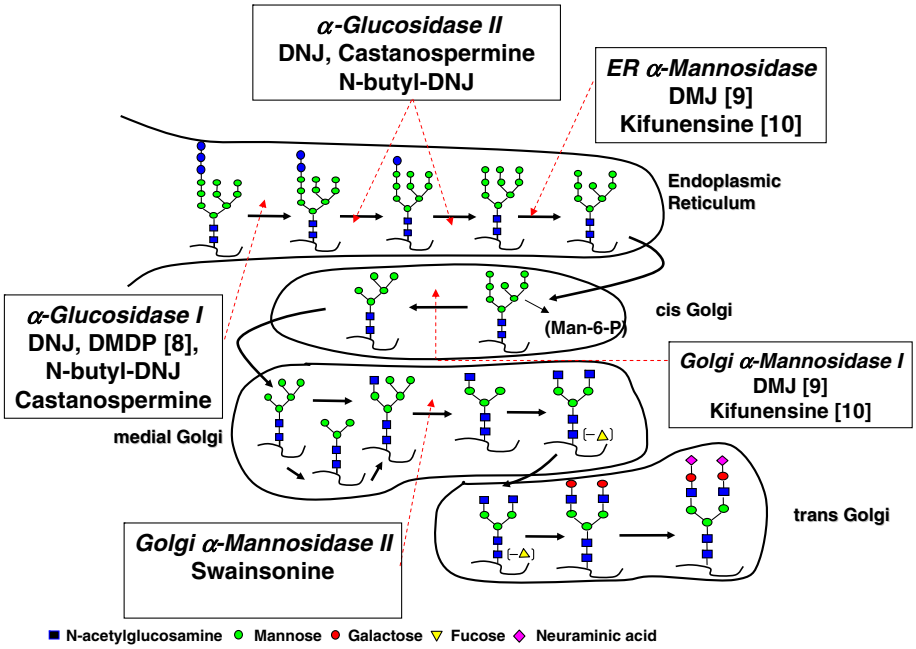
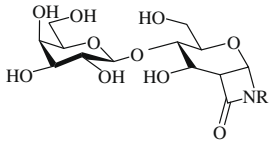
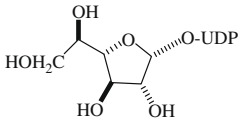


Figure 3. Inhibition of processing glycosidases.

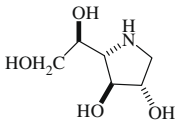
11. 1-oxabicyclic β-lactams

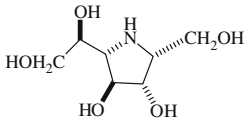


12-15. Pyrrolidine inhibitors of *Mycobacterium* galactan biosynthesis

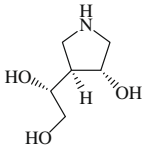


UDP-Galf

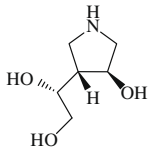




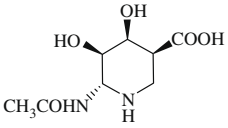
12,13 imino-D-galactofuranose analogues



14, L-galacto configuration

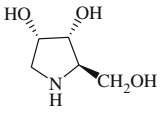


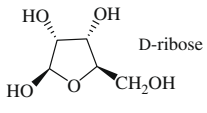
15. Diastereoisomerof 14



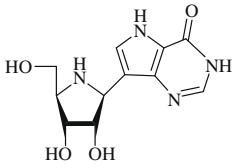
16. Siastatin B

Figure 4. Anti-infective drugs.





17. 1,4-dideoxy-1,4-imino-D-ribitol (DRB)



18. Immucillin H

Figure 5. Inhibitors of DNA polymerase and purine nucleoside phosphorylase.

2.4. DNA and purine and pyrimidine metabolism (Fig. 5)

As RNA and DNA contain ribose and deoxy-ribose, respectively, pyrrolidine iminosugars are potential inhibitors of steps in the biosynthesis, degradation or salvage of these nucleic acids. Of the eight pyrrolidine iminosugars tested, only 1,4-dideoxy-1,4-imino-D-ribitol (DRB) **17** was found to selectively inhibit eukaryotic but not prokaryotic DNA polymerase. In addition it did not inhibit HIV-reverse transcriptase, T7 RNA polymerase or bovine deoxyribonuclease.[31] The *N*-ribosyltransferases are another important therapeutic target because phosphoribosyltransferases are involved in both the *de novo* and salvage synthetic pathways for nucleotides, the nucleoside phosphorylases catalyse the formation of free bases from nucleosides and DNA glycosylases participate in DNA repair. The inhibition of specific *N*-ribosyltransferases could be useful in the treatment of disorders where nucleotide metabolism is involved in the pathogenesis. A deficiency of human purine nucleoside phosphorylase (PNP) causes a specific immunodeficiency in which activated T-lymphocytes undergo apoptosis. Therefore a drug-induced deficiency of PNP could be effective in treating diseases in which T-cell activation plays a role in the pathology, such as T-cell leukemias, some autoimmune diseases, and transplant rejection. Imino-C-nucleoside analogues that mimic the transition state of the catalytic mechanism are potent inhibitors of *N*-ribosyltransferases.[32] The iminoribitol-C-nucleoside, Immucillin-H **18**, which is a potent inhibitor of PNP in the presence of 2′-deoxyguanosine, has been tested in a phase I clinical trial against T-cell leukemia.[33] More potent and specific immucillins are being synthesised.[34] Immucillins also inhibit PNP from the malaria parasite *Plasmodium falciparium*, which depends upon the purine salvage pathway for synthesis of RNA and DNA. The parasite is killed by purine starvation when it is cultured in human erythrocytes in the presence of immucillins, indicating their potential as antimalarial drugs.[35]

2.5. Lysosomal storage diseases[12,15,36,37]

Ingestion of iminosugars was originally considered to cause a lysosomal storage disease by inhibition of lysosomal hydrolases in situ, for example, in swainsona toxicosis[1] or locoweed poisoning.[14] This phenomenon was used to provide evidence for the feasibility of enzyme replacement therapy by showing that the lysosomal storage induced in cells by swainsonine was reversed when the inhibitor was removed and endogenous activity restored.[38] Paradoxically, iminosugars are now being exploited in several ways to develop novel therapies for the lysosomal storage diseases.

2.6. Preparation of human recombinant therapeutic enzymes with modified glycosylation

Recombinant human lysosomal enzymes produced in mammalian cells for enzyme replacement therapy contain a mixture of N-linked glycans, including complex, hybrid and at least one high-mannose with the mannose-6-phosphate motif for delivery of the enzyme to the lysosome by the mannose-6-phosphate receptor system. Enzyme replacement therapy for Gaucher's disease, the most common lysosomal disease, does not utilise the mannose-6-phosphate receptor system but targets the enzyme to the mannose-receptor on macrophages. Accordingly recombinant beta-glucocerebrosidase is processed chemically (and expensively) after production to expose mannose-residues on its N-linked glycans. A research proposal from our collaboration in the 1980s to the Science and Engineering Research Council to develop a technology for the production of recombinant proteins with defined patterns of

glycosylation using specific iminosugar inhibitors in the culture medium to control the processing pathway (Fig. 3) was rejected as 'unsound science'. Today a major biotechnology company is producing recombinant β-glucocerebrosidase with high-mannose chains by including an iminosugar in the fermentor culture medium!

2.7. Substrate reduction therapy (SRT) for the lysosomal glycosphingolipidoses[36,37]

The first evidence that iminosugars could affect the metabolism of glycosphingolipids came from treating normal fibroblasts in culture with castanospermine **3**, a powerful inhibitor of alpha-and beta-glucosidases.[39] The appearance of two additional major glycosphingolipids in the treated cells, which were not present in untreated normal cells or in cells from a patient with Gaucher's disease, suggested that glycosphingolipid biosynthesis had been disturbed or that the castanospermine was inhibiting an unknown enzyme in the catabolic pathway. Subsequently, Frances Platt, Terry Butters and Raymond Dwek of the Glycobiology Institute in Oxford showed that another alpha-glucosidase inhibitor *N*-butyl-DNJ **2**, which had been developed as an anti-HIV drug,[7] inhibited ceramide glucosyl-transferase, the first step in the biosynthesis of most glycosphingolipids.[40] Significantly, the inhibition occurred at much lower concentrations than required for the inhibition of the processing alpha-glucosidase and was competitive with respect to ceramide and non-competitive with respect to UDP-glucose, indicating that *N*-butyl DNJ was acting as a mimic of ceramide. *N*-butyl-DNJ slowed down the rate of synthesis of glycosphingolipids in cells in culture and in normal mice without detriment and when it was fed to a mouse model of Tay–Sachs disease, there was no further accumulation of glycosphingolipids.[41] This suggested that *N*-butyl-DNJ could be a generic drug for decreasing the rate of synthesis of all glycosphingolipids for which glucosylceramide is the precursor and, in consequence, decreasing the rate of accumulation of these glycosphingolipids in the glycosphingolipidoses in which their catabolism is impaired (Fig. 6). Further if a patient had sufficient residual ceramide glucosyltransferase activity to cope with the decreased supply of substrate, further storage could be prevented and the accumulated material may even be dispersed. This is the basis of substrate reduction therapy (SRT). On the basis of an encouraging clinical trial,[42] *N*-butyl-DNJ **2** (also known as OGT 918, Zavesca or Miglustat) has been licensed in Europe (2002) and USA (2003) for treatment of non-neuronopathic Gaucher disease type 1, in which there is some residual ceramide glucosyltransferase activity. Its use in routine clinical practice has been reviewed recently.[43,44] *N*-Butyl-DNJ **2** did not have any appreciable effect on the neurological manifestations of neuronopathic Gaucher disease type 3 but may have had positive effects on the systemic disease in these patients.[45] Clinical trials of SRT with *N*-butyl-DNJ for other glycosphingolipidoses, Fabry, late onset Tay-Sachs and juvenile and late-onset Sandhoff diseases did not show clinical benefit and have been abandoned. Several other compounds including some iminosugars are being evaluated in preclinical trials.[37]

There is secondary accumulation of G_{M2}- and G_{M3}-gangliosides in neurons in another lipid disorder, Niemann-Pick disease type C (NPC).[46] *N*-butyl-DNJ (Miglustat) decreased the accumulation of these gangliosides in mice and cats with NPC and reversed the lipid-trafficking defect in blood lymphocytes in a human NPC patient.[47] On the basis of these results a trial of substrate deprivation using Miglustat was carried out in NPC patients and an improvement in certain neurological parameters was observed.[48] This is the first treatment for NPC to show benefit. The galactose analogue of *N*-butyl-DNJ, *N*-butyl-deoxygalactonojirimycin **19** (see Fig. 8) is a more selective inhibitor of ceramide glucosyltransferase because it does not inhibit ceramide galactosyltransferase, lysosomal glycogen catabolism, sucrase or maltase

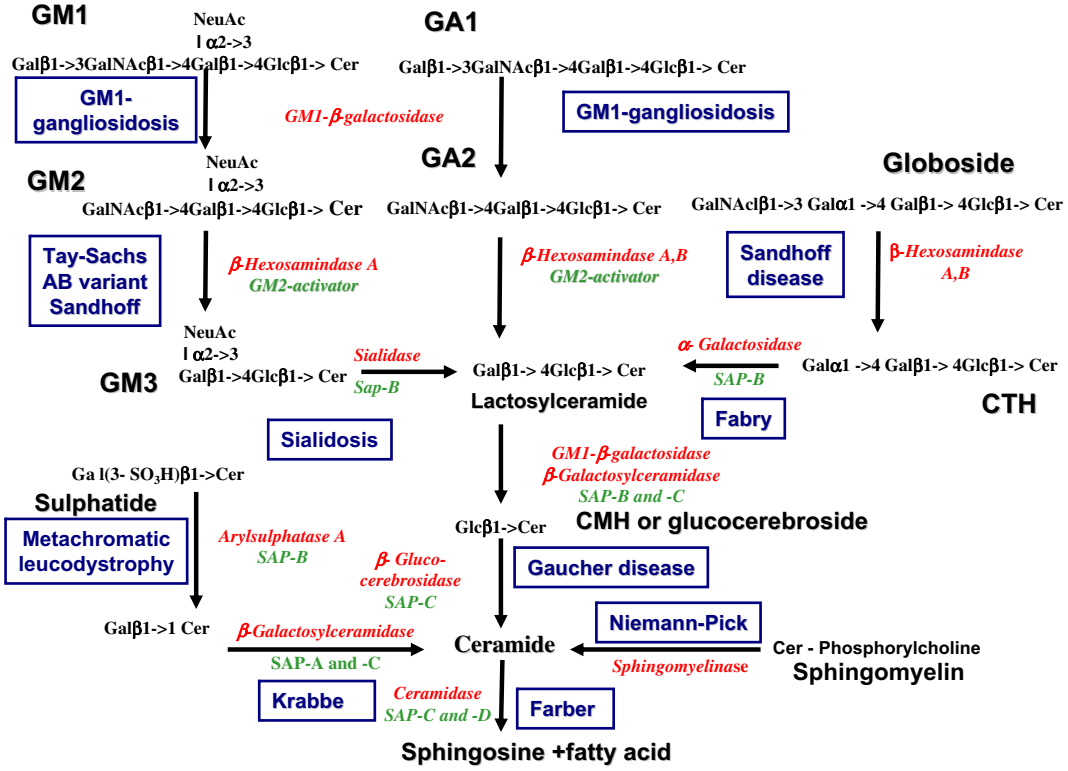


Figure 6. Lysosomal catabolism of glycosphingolipids.

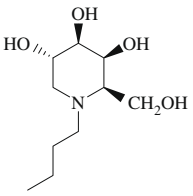
but it does inhibit lactase[49] Interestingly, these compounds may have potential as male contraceptives in some species because male mice become reversibly sterile after oral administration of *N*-butyl-DNJ or *N*-butyl-DGJ[50] but *N*-butyl-DNJ did not have any effect on spermatogenesis in normal men.[51]

2.8. Chaperone-mediated therapy (CMT)

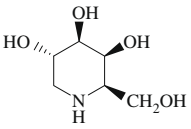
It had been common knowledge amongst enzymologists for many years that the addition of simple sugars, for example, sucrose or glucose protected glycosidases during their extraction from tissues and that imino- and amino-sugars were excellent ligands for affinity chromatographic media for the purification of glycosidases.[10,52] It had also been observed that sometimes iminosugars could activate rather than inhibit glycosidases in assays in vitro, suggesting in all cases that the tight binding of the iminosugars to the active sites of glycosidases stabilised them. However it was not until 1999 that Fan and co-workers put forward the concept of active site-specific chaperone-mediated therapy for lysosomal storage diseases using iminosugars to prevent misfolding and premature degradation of mutant enzymes in the endoplasmic reticulum (Fig. 7).[53] They showed that sub-inhibitory concentrations of the potent alpha-galactosidase inhibitor, deoxygalactonojirimycin (DGJ) **20** (see Fig. 8) increased the residual activity in lymphoblasts from patients with Fabry disease with two different missense mutations by seven- to eightfold over 5 days, whereas higher concentrations decreased the activity. The increase in activity was due to accelerated transport to the lysosome and a higher concentration of mature enzyme and not due to an increase in mRNA.[54] Comparison of a series of derivatives of DGJ indicated a correlation between potency as an inhibitor and effectiveness as a chaperone.[55] Oral administration of DGJ to mice expressing alpha-galactosidase with a missense mutation resulted in increased alpha-galactosidase activity in some tissues.[56] Even infusions of galactose, the product of the enzymic reaction and a weak inhibitor of the enzyme, led to clinical improvement in a Fabry patient with residual alpha-galactosidase activity.[57] A phase 1 clinical trial of DGJ (Amigal) in healthy volunteers was started by a company (Amicus) in 2004 and a phase 2/3 clinical trial in 26 Fabry patients was carried out in 2005-7. The preliminary results are encouraging. DGJ and *N*-butyl DGJ **19** also act as chaperones for mutant beta-galactosidases.[58] A phase 2 clinical trial is in progress for Pompe's disease using DNJ **3**. As iminosugars and their derivatives are usually water soluble and inert, can be taken orally and can cross the blood–brain barrier, they are attractive drugs for attempting to treat lysosomal storage diseases, especially any CNS involvement. Several iminosugars and derivatives are being tested as chaperones for Gaucher's disease[59,60] and G_{M2}-gangliosidosis.[61] Interestingly it has been suggested that preincubation of recombinant beta-glucocerebrosidase with a chaperone such as isofagomine **21** before infusion may improve the effectiveness of ERT for Gaucher's disease by stabilising the enzyme.[62]

3. Conclusions

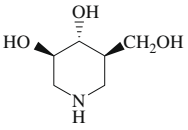
Iminosugars and their derivatives have a wide therapeutic potential but most compounds do not act exclusively on a single target enzyme or protein. This is illustrated by the diverse activities of *N*-butyl-DNJ as an anti-viral agent, male contraceptive,



19. *N*-butyldeoxygalactonojirimycin *N*-butyl DGJ



20. Deoxygalactonojirimycin DGJ
(Migalastat/Amigal)



21. Isofagomine

Figure 8. Iminosugars for chaperone-mediated therapy.

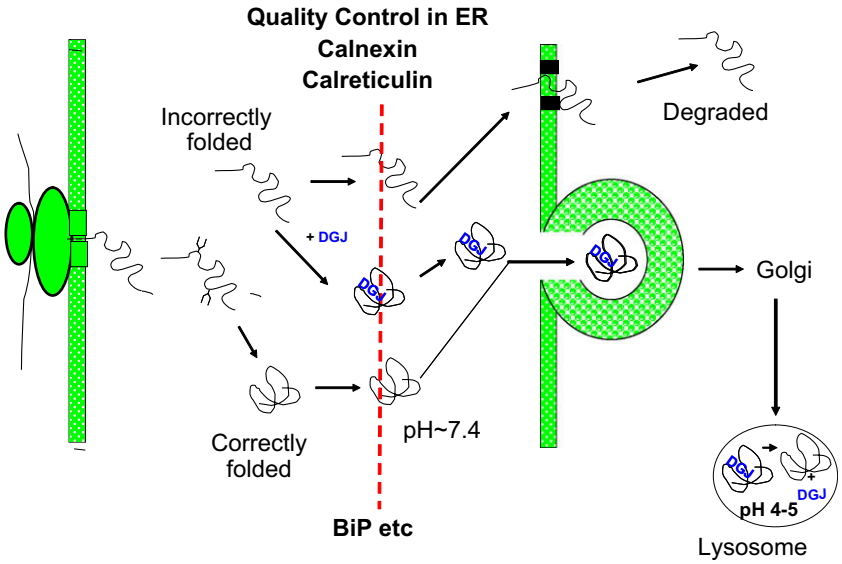


Figure 7. Active site-specific chaperone-mediated therapy (CMT).

inducer of glycogen storage, chaperone and inhibitor of glycolipid synthesis. Its specificity of action will be determined by its concentration at sub-cellular sites in different cells, which will in turn depend on its pK_a, hydrophobicity and substitutions. Great effort is being made to synthesise or isolate more selective compounds for targeting specific tissues, cells and sub-cellular compartments. Iminosugars lend themselves to use in combination with other drugs because of their metabolic inertness and low toxicity. Other applications for iminosugars will undoubtedly emerge because only a small proportion of the enzymes and proteins involved in the recognition and transformation of carbohydrates has been targeted to date.

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