# Therapeutic Applications of Sugar-Mimicking Glycosidase Inhibitors

Naoki Asano[a]*, Atsushi Kato[b] and Alison A. Watson[c]

[a]*Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan*

[b]*Department of Hospital Pharmacy, Toyama Medical and Pharmaceutical University, Toyama 930-0194, Japan*

[c]*Molecular Nature Limited, Plas Gogerddan, Aberystwyth, Cardiganshire SY23 3EB, UK*

**Abstract**–Sugar-mimicking alkaloids inhibit the glycosidases involved in a wide range of important biological processes, principally owing to their structural resemblance to the sugar moiety of the natural substrate. The possibility of modifying and blocking these processes by using such inhibitors for therapeutic applications has attracted a lot of attention.

## 1. INTRODUCTION

Alkaloids mimicking the structures of sugars are now believed to be widespread in plants and microorganisms and inhibit glycosidases because of a structural resemblance to the sugar moiety of the natural substrate and the presence of the nitrogen atom mimicking the positive charge of the glycosyl cation intermediate in the enzyme-catalyzed glycoside hydrolysis. Glycosidases are involved in a wide range of important biological processes, such as intestinal digestion, post-translational processing of glycoproteins and the lysosomal catabolism of glycoconjugates [1]. The possibility of modifying or blocking these processes by using glycosidase-inhibiting sugar mimetics for cell biological and therapeutic applications has attracted a lot of attention, since some sugar-mimic alkaloids show potential antidiabetic [2], antiviral and anticancer effects [3]. Inhibitors are also being used to study the mechanism of action, topography of the active site and the purification of glycosidases [4].

## 2. α-GLUCOSIDASE INHIBITORS

### 2.1. Natural Occurrence

In 1966 nojirimycin (NJ) (**1**) was discovered as the first natural glucose mimic, with a nitrogen atom in place of the ring oxygen [5]. NJ was first described as an antibiotic produced by *Streptomyces roseochromogenes* R-468 and *S. lavendulae* SF-425, and was shown to be a potent inhibitor of α- and β-glucosidases from various sources [5, 6]. However, because this iminosugar with the hydroxyl group at C-1 is fairly unstable, it is usually stored as bisulfite adducts or it may be reduced by catalytic hydrogenation with a platinum catalyst or by $NaBH_4$ to 1-deoxynojirimycin (DNJ) (**2**). DNJ was first prepared by the reduction of NJ as described above but later it was isolated from the roots of mulberry trees and called molanoline [7]. DNJ is also produced by many strains in the genera *Bacillus* and *Streptomyces* [8-10]. The first naturally occurring *N*-methyl derivative of DNJ was isolated from the leaves and roots of *Morus* spp. (mulberry trees) and, furthermore, the genus *Morus* has been shown to co-produce many kinds of glycosides of DNJ such as 2-*O*-, 3-*O*-, 4-*O*-α-D-glucosides, 2-*O*-, 3-*O*-, 4-*O*-, 6-*O*-β-D-glucosides, and 2-*O*- and 6-*O*-α-D-galactosides [11, 12]. In 1988, α-homonojirimycin (α-HNJ) (**3**) was isolated from the neotropical liana *Omphalea diandra* [13]. This isolation was the first report of the naturally occurring C-1 branched DNJ derivative. However, before the isolation of the natural product, its 7-*O*-β-D-glucoside (MDL 25637) had been designed as a potential drug for the treatment of diabetes mellitus [14, 15]. Recently, α-HNJ and its 7-*O*-β-D-glucoside (MDL 25637) were also isolated from whole plants of *Aglaonema treubii* (Araceae) and the bulbs of *Hyacinthus orientalis* [16, 17].

In 1976, 2*R*,5*R*-dihydroxymethyl-3*R*,4*R*-dihydroxypyrrolidine (DMDP) (**4**) that mimics β-D-fructofuranose was found in the leaves of the legume *Derris elliptica* [18]. DMDP is being reported from many disparate species of plants and microorganisms, which would indicate that this is a common metabolite [19]. Removal of one hydroxymethyl group from DMDP gives 1,4-dideoxy-1,4-imino-D-arabinitol (D-AB1) (**5**), which was first found in the fruits of *Angylocalyx boutiqueanus* and this is similarly also now being reported from many disparate species of plants [19]. The polyhydroxypyrroline nectrisine (FR-900483) (**6**) was isolated as an immunomodulator from the culture broth of the fungus *Nectria lucida* [20, 21].

Castanospermine (**7**) was isolated in 1981 from the seeds of *Castanospermum australe* [22], and later from the dried pods of *Alexa leiopetala* [23]. Castanospermine may be regarded as a bicyclic derivative of DNJ, with an ethylene

*Address correspondence to this author at the Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3 Kanagawa-machi, Kanazawa 920-1181, Japan; Fax: +81 76 229 6196; E-mail: naoki22@po.incl.ne.jp

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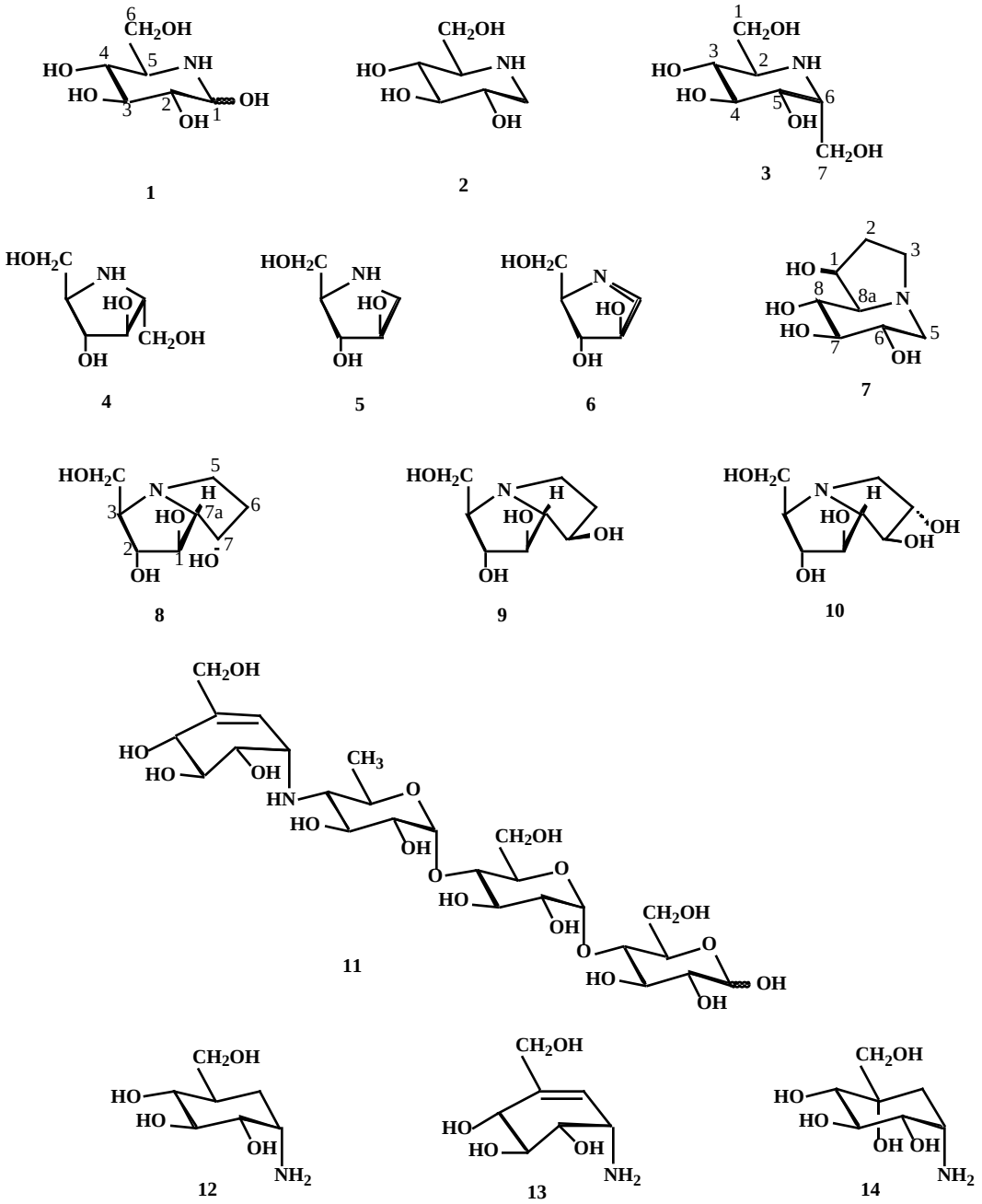


**Fig. (1)**. Structures of naturally occurring α-glucosidase inhibitors.

bridge between the hydroxymethyl group and the ring nitrogen. X-Ray crystallography showed that the chiral center of the six-membered ring of castanospermine corresponds to the *gluco* configuration [22]. In addition to indolizidine alkaloids, *C. australe* was reported to produce the polyhydroxylated pyrrolizidine alkaloids australine (**8**) [24] and 7-*epi*-australine (**9**) [25] as well. Although these both alkaloids recently have been enantioselectively synthesized [26, 27], the $^1$H-NMR spectrum of the synthetic 7-*epi*-australine did not match the data reported in the literature [25]. The published data of **9** have subsequently been shown to be those for australine (**8**). There is no doubt the structure of australine as determined by X-ray diffraction [24], but the NMR data in the literature have subsequently been shown to be those for 1-*epi*-australine [27]. This means that 7-*epi*-australine (**9**) has not yet been found as a natural product. Australine can be regarded as either a ring-contracted form of castanospermine or a derivative of DMDP with an ethylene bridge between the hydroxymethyl group and the ring nitrogen. Casuarine (**10**) and its 6-*O*-α-D-glucoside occur in the bark of *Casuarina equisetifolia* (Casuarinaceae) which has been prescribed in Western Samoa as a herbal treatment for breast cancer [28]. Both compounds were also isolated from the leaves of *Eugenia jambolana* (Myrtaceae) [29], which is a well known tree in India for the therapeutic value of its seeds, leaves and fruits against diabetes and bacterial infections.

Since the late 1960s the Bayer group had searched for inhibitors of intestinal sucrase for clinical development in the treatment of diabetes and found the pseudotetrasaccharide

acarbose (**11**) from the fermentation broth of the *Actinoplanes* strain SE 50 [30]. The characteristic core-structure for inhibition is composed of a trihydroxy(hydroxymethyl)cyclohexene moiety and a 4-amino-4,6-dideoxy-D-glucopyranose moiety, bonded by way of an imino linkage at the allylic position. A similar structural unit is found in the antibiotic validamycin [31]. Later, the carba-glucosylamines validamine (**12**), valienamine (**13**), and valiolamine (**14**), were isolated as α-glucosidase inhibitors from the culture broth of the validamycin-producing organism *Streptomyces hygroscopicus* var. *limoneus* [32].

## 2.2 Biological Activities and Therapeutic Application

The intestinal oligo- and disaccharidases are fixed components of the cell membrane of the brush border region of the wall of the small intestine. These enzymes digest dietary carbohydrate to monosaccharides which are absorbed through the intestinal wall. They include sucrase, maltase, isomaltase, lactase, trehalase and hetero-β-glucosidase. Inhibition of all or some of these activities by inhibitors could regulate the absorption of carbohydrate. Mulberry leaves have traditionally been used to cure "Xiao-ke" (diabetes) in Chinese medicine. The original isolation of DNJ was prompted by the knowledge that extracts of mulberry were able to suppress the rise in blood glucose that follows eating and the discovery of the inhibitory effect of DNJ on mammalian α-glucosidases opened the possibility of a therapeutic application for this compound. However, despite the excellent α-glucosidase inhibitory activity *in vitro*, its efficacy *in vivo* was only moderate [2]. Therefore, a large number of DNJ derivatives were prepared in the hope of increasing the *in vivo* activity. Thus, miglitol (BAY m 1099) (**15**), emiglitate (BAY o 1248) (**16**), MDL 25637 (**17**) and MDL 73945 (**18**) were selected as the most favorable inhibitors out of a large number of *in vitro* active agents. These derivatives have been reported to effectively reduce postprandial elevations of blood glucose and plasma insulin in animals in loading tests with starch and sucrose [15, 33-35]. The inhibitor dose which reduces the postprandial increase in blood glucose by 50% ($ED_{50}$) in sucrose loading tests in rats was calculated for miglitol and emiglitate as 0.24 mg and 0.16 mg/kg body weight, respectively [36]. Both compounds are also characterized by a long lasting effect*in vivo*. MDL 25637 and MDL 73945 appear to be more effective when administered 30-60 min before a sucrose load than when given simultaneously with sucrose [15, 34]. The long lasting effect of MDL 73945 has been reported to be caused by quasi-irreversible binding to α-glucosidases [34]. Acarbose (**11**) is a potent inhibitor of pig intestinal sucrase with an $IC_{50}$ value of 0.5 μM and this was also effective in carbohydrate loading tests in rats and healthy volunteers, reducing postprandial blood glucose and increasing insulin secretion [36]. Acarbose was introduced onto the market (GLUCOBAY$^{TM}$) in 1990 for the treatment of diabetes. Valiolamine (**14**) is a potent inhibitor of pig intestinal maltase and sucrase, with $IC_{50}$ values of 2.2 and 0.049 μM, respectively. Horii and co-workers synthesized numerous *N*-substituted valiolamine derivatives in order to enhance its α-glucosidase inhibitory activity *in vitro*. The very simple derivative AO-128 (genetic name voglibose (**19**)) was obtained by reductive amination of valiolamine with dihydroxyacetone [37]. Its $IC_{50}$ values towards maltase and sucrase were 0.015 and 0.0046 μM, respectively. Voglibose is also now on the market (BASEN$^{TM}$).

The lumen of the endoplasmic reticulum (ER) provides a highly specialized compartment for the folding and oligomeric assembly of secretory proteins, plasma membrane proteins, and proteins destined for the various organelles of the vacuolar system. Their conformational maturation is a complex process determined not only by the amino acid sequence but also by post- and co-translational modifications, by the intralumenal milieu, and by a variety of chaperones and folding enzymes [38, 39]. The ER possesses efficient quality control mechanisms to ensure that transport is limited to properly folded and assembled proteins [40]. As shown in Fig. (**3**), *N*-linked oligosaccharide chains are co-translationally added to proteins in the ER lumen as $Glc_3Man_9GlcNAc_2$ precursors. The outer and two inner glucoses are trimmed by ER α-glucosidases I (GLCase I) and II (GLCase II), respectively. Incorrectly folded glycoproteins are recognized by the

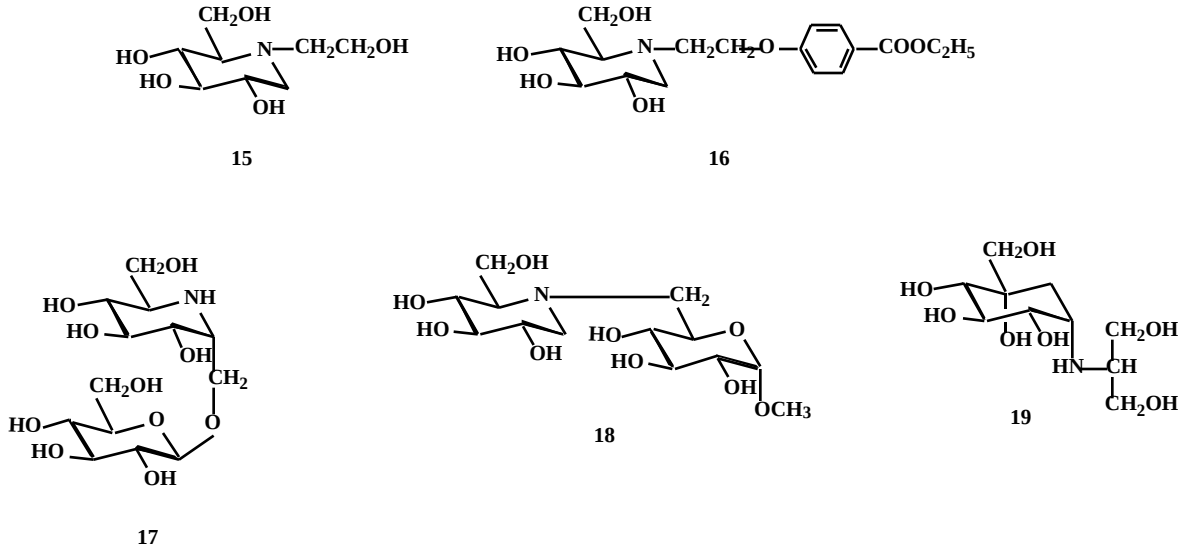



**Fig. (2)**. Structures of chemically synthesized antidiabetic agents.

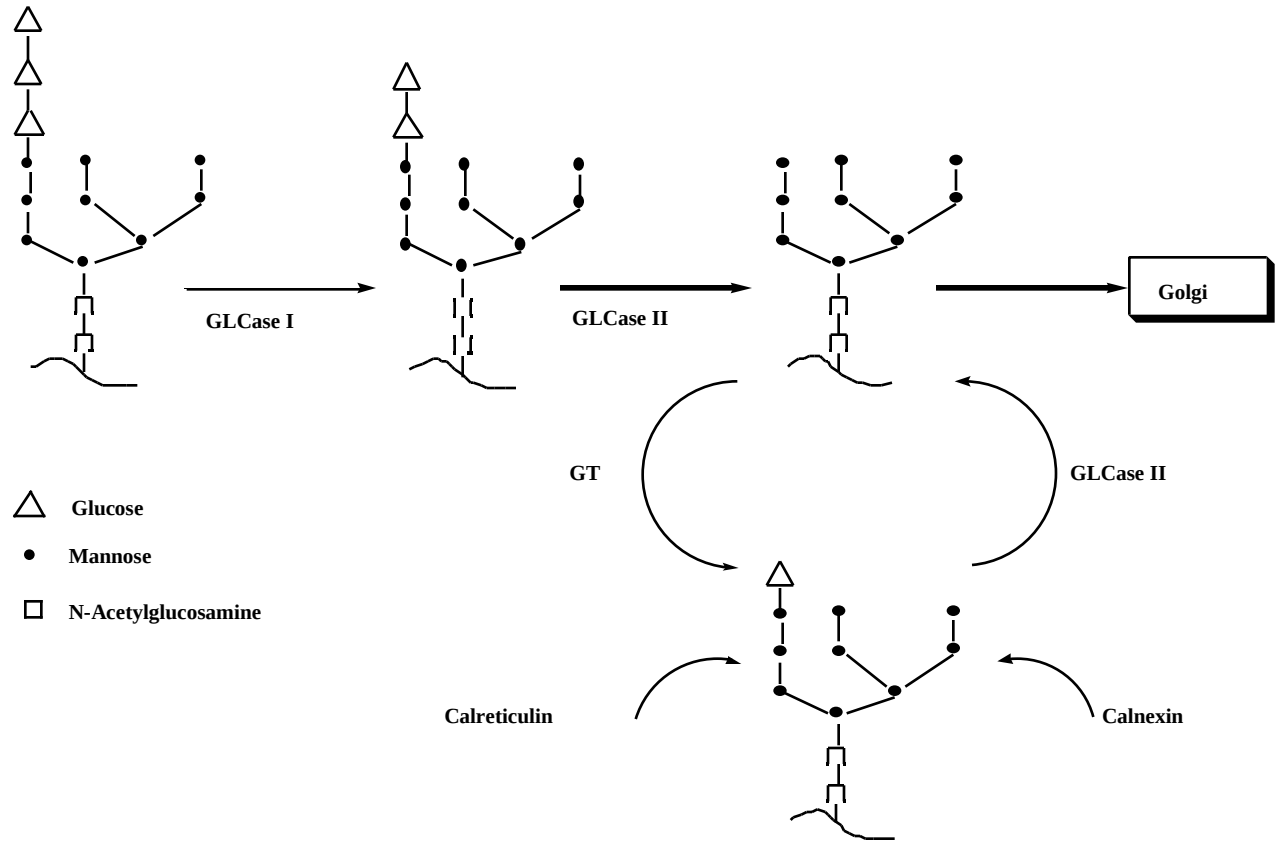



**Fig. (3)**. Processing of the N-linked oligosaccharide chains and binding to the chaperones calnexin and calreticulin in the ER lumen. GLCase I = α-glucosidase I. GLCase II = α-glucosidase II. GT = UDP-glucose:glycoprotein glucosyltransferase.

enzyme UDP-Glucose:glycoprotein glucosyltransferase (GT) which re-attaches a single glucose to the *N*-linked oligosaccharide chain [41]. Monoglucosylated glycans are then recognized by the lectin-like ER chaperones, calnexin (CNX) and calreticulin (CRT) which promote correct folding by inhibiting aggregation and preventing premature oxidation and oligomerization. The re-attached glucose is then removed by GLCase II. Depending on the folded state of the glycoprotein, it will then either continue down the maturation pathway in the Golgi apparatus or will enter a reglucosylation/deglucosylation cycle until it is fully folded and can exit the ER. Inhibitors of ER α-glucosidases which prevent glycoprotein binding to CNX and CRT are known to cause delays in the folding and intracellular transport of glycoproteins [42].

The oligosaccharide chains of the *N*-linked glycoproteins are believed to confer biological specificity at the cell surface where they may be involved in cell-cell adhesion, differentiation, recognition, regulation, modulation of protein receptors, and so on. Thus, it is not surprising that there is such great interest in compounds that can prevent the glycosylation of *N*-linked glycoproteins or cause alterations in the structure of the carbohydrate chains. Certain sugar mimetics have been effective and valuable tools to study how alterations in oligosaccharide structure affect the function of specific *N*-linked glycoproteins, and whether such alterations in turn affect cell function. Although DNJ (**2**), α-HNJ (**3**) and castanospermine (**7**) inhibit processing GLCases I and II, DNJ and α-HNJ inhibit GLCase II more strongly, whereas castanospermine has a greater affect on GLCase I [43, 44]. *N*-Alkylation of DNJ and α-HNJ induces a shift in specific inhibition of purified glucosidases from GLCase II to GLCase I [43- 45]. Castanospermine has been found to be more effective against GLCase I than DNJ [43].

α-Glucosidase inhibitors, such as DNJ, *N*-butyl-DNJ (Bu-DNJ) and castanospermine, are potent inhibitors of HIV replication and HIV-mediated syncytium formation *in vitro* [46, 47]. All sugar mimetics showing anti-HIV activity have the common property that they are potent inhibitors of processing GLCase I. It is presumed, although not proven, that the anti-HIV activity results from the inhibition of processing GLCase I, since there is a good correlation between the potency of inhibition of this enzyme and viral control [48-50]. Treatment of HIV-1 infected cells with an inhibitor such as Bu-DNJ causes an inhibition of syncytium formation and a reduction in release of infectious virus [51]. This reduction is not caused by a decrease in the numbers of virus particles produced, but rather the particles have been structurally modified so that they are unable to infect new cells. It has been reported that a major mechanism of action of Bu-DNJ as an inhibitor of HIV replication is the impairment of viral entry at the level of post-CD4 binding, due to an effect on viral envelope components [51]. Furthermore, analysis of gp120 by a panel of conformation-dependent antibodies revealed structural changes within the V1/V2 loop region of the glycoprotein [52]. However,

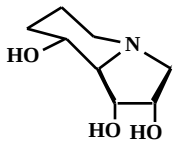
problems in achieving the therapeutic serum concentrations of Bu-DNJ needed to inhibit GLCase I sufficiently in humans may limit the practical use of this drug as an anti-HIV agent [53].

In contrast to the HIV envelope glycoproteins, which contain about 30 glycosylation sites, the hepatitis B virus envelope proteins contain only one or two glycosylation sites. In this virus, correct glycosylation appears to be necessary for the processes involved in transport of the virus out of the cell and *in vitro* treatment of hepatitis B virus with Bu-DNJ results in a high proportion of virus particles being retained inside the cell [54]. Furthermore, this may imply that correct processing by GLCases I and II is required for proper binding to CNX/CRT in the ER [53].

## 3. α-MANNOSIDASE INHIBITORS

### 3.1. Natural Occurrence

In 1979 the toxicity to livestock of the legume *Swainsona canescens* in Australia led to the isolation of the toxic principle swainsonine (**20**) [55] which motivated research on sugar mimetics with a nitrogen in the ring and their applications. Swainsonine is also present in locoweeds (*Astragalus* and *Oxytropis* species), which cause the disorder "locoism" in the western United States [56]. *C. australe* produces 6-*epi*-castanospermine (**21**), together with castanospermine (**7**) [57]. 6-*Epi*-castanospermine has the *manno* configuration in the piperidine ring and is a good inhibitor of human neutral α-mannosidase [58]. 1-Deoxymannojirimycin (DMJ) (**22**) was first isolated from the seeds of the legume *Lonchocarpus sericeus*, a native of the West Indies and tropical America [59] and later isolated from the neotropical liana, *Omphalea diandra* (Euphorbiaceae) [13], and the legume *Angylocalyx pynaertii* growing in tropical African forests [60]. In addition, DMJ was isolated from the culture broth of *Streptomyces lavendulae* GC-148

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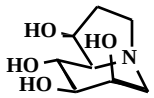


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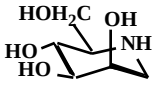


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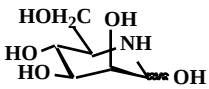


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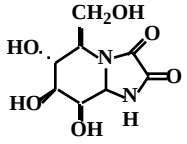


**24**

**Fig. (4)**. Structures of naturally occurring α-mannosidase inhibitors.

[61], which also produces high yields of DNJ (**2**) [10]. *Streptomyces subrutilus* ATCC 27467 similarly produces both DNJ and DMJ in its culture broth, and mannojirimycin (MJ) (**23**) has been suggested as an intermediate in the biosynthesis of DMJ [62]. In this organism, it has been postulated that epimerization of MJ can occur at C-2 to give NJ (**1**) which is then dehydrated and reduced to DNJ. *Agrobacterium* sp. strain 19-1 has been shown to be able to epimerize DNJ to DMJ [63]. A new inhibitor of Golgi α-mannosidase I, kifunensine (**23**), was initially isolated as a weak inhibitor of jack bean α-mannosidase ($IC_{50}$ = 100 μM) from the culture broth of the actinomycete, *Kitasatosporia kifunense* 9482 [64-66]. Kifunensine can be regarded as the cyclic oxamide of 1-amino-deoxymannojirimycin and its structure is quite different from those of other α-mannosidase inhibitors, although it could still be classified as a sugar mimetic with a nitrogen in the ring.

### 3.2. Biological Activities and Therapeutic Applications

The indolizidine alkaloid swainsonine (**20**) is a potent inhibitor of lysosomal α-mannosidase and prolonged ingestion of swainsonine by animals leads to a neurological disorder that is a phenocopy of the genetically induced lysosomal storage disease mannosidosis [67, 68]. Mannosidosis is characterized by accumulation in cells, and excretion in the urine, of mannose-rich oligosaccharides resulting from a deficiency of lysosomal α-mannosidase. Swainsonine is a lysosomotropic compound and it accumulates rapidly in the lysosomes of normal human fibroblasts in culture giving rise to inhibition of intracellular lysosomal α-mannosidase [69], and it is assumed that this is its mode of action *in vivo*.

Swainsonine (**20**) is the first compound that was found to inhibit glycoprotein processing. Swainsonine was shown to be a potent inhibitor ($IC_{50}$ = 0.2 μM) of rat liver Golgi α-mannosidase II, but was without effect on Golgi α-mannosidase I [70]. When swainsonine is placed in the culture medium of various animal cells, it causes the formation of hybrid types of oligosaccharides having an oligomannosyl core [$Man_5(GlcNAc)_2$] characteristic of neutral oligosaccharides, and a (or several) NeuNAc-Gal-GlcNAc sequence(s) characteristic of complex chains (Fig. (**5**) ). Swainsonine has been used in a number of studies in order to determine whether changes in the structure of the *N*-linked oligosaccharides affect glycoprotein function. In most cases, it has little effect on the glycoprotein in question, which may indicate that a partial complex chain is sufficient for activity, and that protein conformation is not altered [71]. On the other hand, DMJ is a fairly potent inhibitor of rat liver Golgi α-mannosidase I, with an $IC_{50}$ value of 1 μM, but not Golgi α-mannosidase II or ER α-mannosidase [72]. In intact cells, DMJ blocked the synthesis of complex types of *N*-linked oligosaccharides and caused the accumulation of glycoprotein having $Man_{7-9}(GlcNAc)_2$ structures, with predominant $Man_9(GlcNAc)_2$ oligosaccharides [73]. Kifunensine (**24**) proved to be an effective inhibitor of plant α-mannosidase I ($IC_{50}$ = 0.02 μM) but had no activity against plant α-mannosidase II [74]. When kifunensine was added to the culture medium of mammalian cells at concentrations of 1 μg/ml or higher, it caused a complete

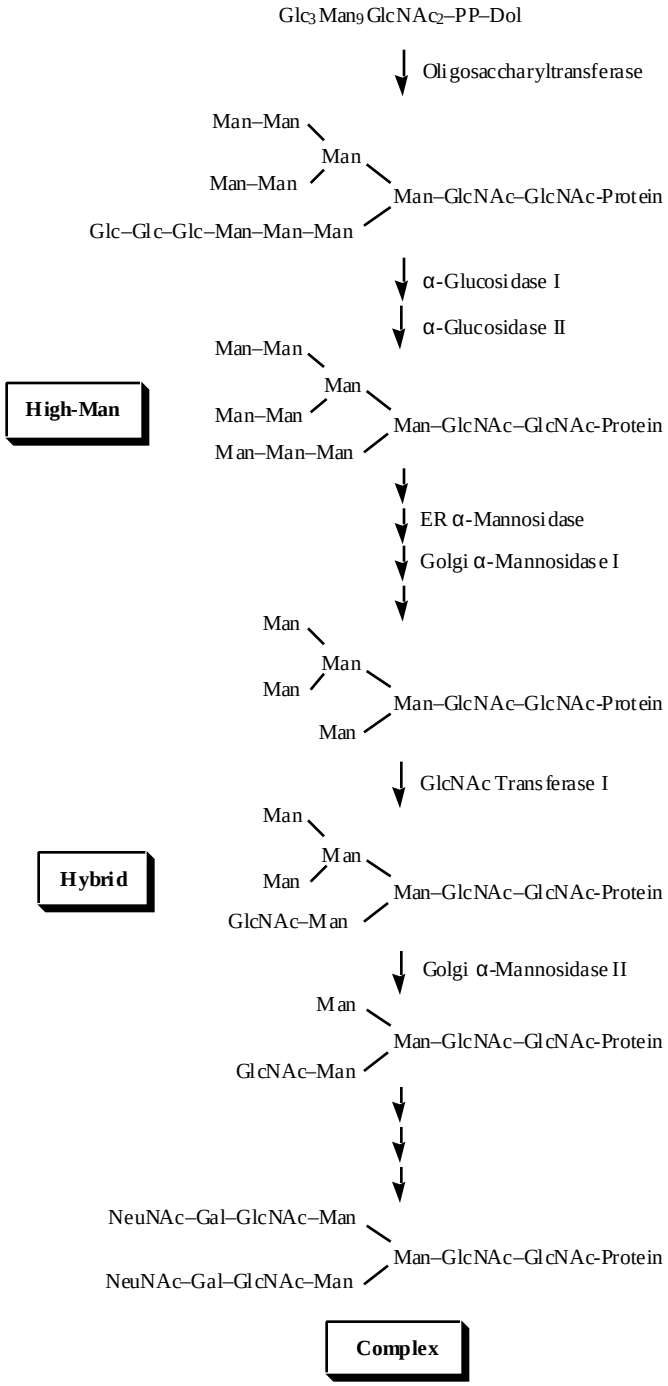


**Fig. (5)**. Reactions involved in the processing of the oligosaccharide chains of the *N*-linked glycoproteins. Glc = glucose, Man = mannose, Gal = galactose, NeuNAc = *N*-acetylneuraminic acid (sialic acid), GlcNAc = *N*-acetylglucosamine.

shift in the *N*-linked oligosaccharide chains produced from complex structures to $Man_9(GlcNAc)_2$ structures [74].

Although a number of the sugar-mimicking alkaloids have been reported to show anticancer activity, research has concentrated on developing swainsonine (**20**) as a candidate for the management of human malignancies. Swainsonine has a complex mode of action in the whole animal. It inhibits the growth of tumour cells and prevents the dissemination of malignant cells from the primary tumour to secondary sites (a process known as metastasis). However, swainsonine also has a direct stimulatory effect on the immune system.

There is considerable evidence that swainsonine enhances the natural antitumour defences of the body [75, 76]. In animal models, it was observed that the reduction in metastasis of tumour cells induced by swainsonine administration continued for a number of days after the drug was withdrawn [77]. It was discovered that this results from the ability of swainsonine to activate immune effector cells such as natural killer cells (which are peripheral blood

lymphocytes), T-lymphocytes and macrophages [78, 79]. These phagocytic cells have diverse functions that include antigen presentation, cytokine production (e.g. interleukins), immune surveillance and cytocidal activity against tumour cells. However, many of the properties of these cells are apparent only after they have been activated [79]. Swainsonine stimulates proliferation of spleen cells, thereby increasing the numbers of natural killer cells. It also increases lymphocyte sensitivity to interleukin-2 (IL-2) and other cytokines [80, 81]. Studies showed that the extent of activation by swainsonine of peritoneal macrophages to cytotoxicity against tumour cells was comparable to that obtained with known macrophage-activating agents such as interferon and bacterial lipopolysaccharide. It was associated with increased secretion of interleukin-1 (IL-1) by the macrophages, induction of protein kinase C activity and enhanced secretion of the major histocompatibilty antigen on the cell surfaces [82]. Swainsonine can also induce tumouricidal activity in resident tissue-specific macrophages of both the lung and spleen [79], with activation being both time- and dose-dependent. This is relevant to the clinical management of metastatic diseases since visceral organs are common sites for metastasis formation. The review by Watson et al. [83] has covered recent advances in clinical trials of swainsonine for malignancies.

## 4. α-GALACTOSIDASE INHIBITORS

### 4.1. Natural Occurrence

In 1988, the β-galactosidase inhibitor galactostatin (**25**) was isolated as its bisulfite adduct from *Streptomyces lydicus* PA-5726 [84], and its 1-deoxy derivative, 1-deoxygalactonojirimycin (DGJ) (**26**), was prepared by the catalytic reduction of galactostatin [85]. However, before the preparation of DGJ from galactostatin, it had been chemically synthesized as a powerful inhibitor of coffee bean α-galactosidase, with a $K_i$ value of 1.6 nM [86]. The first α-1-*C*-hydroxymethyl derivative of DGJ, α-homogalactonojirimycin (α-HGJ) (**27**), was synthesized from 2,3,4,6-tetra-*O*-benzyl-D-galactose [87], and the first naturally occurring β-1-*C*-butyl derivative (**28**) of DGJ has recently been isolated from *Adenophora* sp. (Campanulaceae) [88].

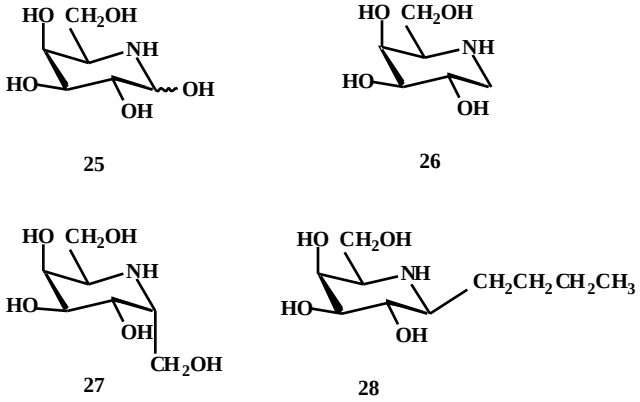


**Fig. (6)**. Structures of α-galactosidase inhibitors.

### 4.2. Biological Activities and Therapeutic Applications

Fabry disease is a disorder of glycosphingolipid (GSL) metabolism caused by deficiency of human lysosomal α-galactosidase A (α-Gal A), resulting in renal failure along with premature myocardial infarction and strokes [89]. No effective treatment of this disorder is available at present. Fan et al. [90] recently demonstrated that DGJ (**26**), which also inhibits α-Gal A in a competitive manner, effectively enhanced the mutant enzyme activity in lymphoblasts established from Fabry patients with R301Q or Q279E mutations. Furthermore, oral administration of DGJ to transgenic mice expressing a human mutant α-Gal A (R301Q) substantially elevated the enzyme activity in major organs. It was proposed that a functional compound that is able to facilitate the correct folding of a mutant protein may serve as a specific chemical chaperone for the mutant protein to promote the smooth escape from the ER quality control system [90]. In order to establish the concept of using competitive inhibitors as specific chemical chaperones, a number of naturally occurring and chemically synthesized DGJ derivatives were tested for intracellular enhancement of a mutant α-Gal A activity in Fabry lymphoblasts. α-HGJ (**27**) and β-1-*C*-butyl-DGJ (**28**) also significantly increased enzyme activity in R301Q lymphoblasts and the effectiveness of intracellular enhancement paralleled the *in vitro* inhibitory activity, indicating that a potent inhibitor serves as an effective enhancer [91]. This strategy may be extensively applicable to other lysosomal storage diseases.

## 5. CONCLUDING REMARKS AND FUTURE PROSPECTS

Since glycosidases are involved in a wide range of metabolism and turnover, glycosidase inhibitors could have many kinds of beneficial effects as therapeutic agents, e.g., as antihyperglycemic agents, as inhibitors of tumor metastasis and viral replications, or as drugs to prevent obesity. It is now known that a number of human diseases are due to specific point mutations in proteines which influence their trafficking and lead to retaining of proteins in the ER [92,93]. In many cases these mutations are not so severe as to totally destroy the biological activity of the particular gene product, rather, the mutations often result in only subtle folding abnormalities [94]. Recently, a class of compounds called chemical chaperones has been shown to increase the transport of mutant proteines out of the ER and to decrease the portion of mutant proteins targeted to intracellular degradation [90, 91, 95, 96]. Chemical chaperones may prove to be effective in correcting the protein folding abnormalities underlying a number of human genetic disorders.

Recent studies have demonstrated that ER class I α1,2-mannosidase plays a key role in the degradation of misfolded glycoproteins [42, 97-99], and that the trimming of a single mannose in the middle branch of $Man_9GlcNAc_2$ (Figs. 3 and 5) creates a signal that targets misfolded glycoproteins for translocation out of the ER and degradation by the proteasome [93, 100]. Very recently, it has been found that the inhibitors of ER class I α1,2-mannosidase such as kifunensine (**23**) and DMJ (**22**) suppress ER-associated

degradation of misfolded glycoproteins [99, 101-103]. These α-mannosidase inhibitors as well as chemical chaperones may be excellent candidates for a new molecular therapy of human genetic disorders.

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