Glycosylation Pathways as Drug Targets for Cancer: Glycosidase Inhibitors

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Abstract: The combined and ordered sequential action of glycosidases and glycosyltransferases in mammalian cell compartments leads to the addition of defined glycans to proteins and lipids. Altered glycosylation patterns, neoexpression, underexpression or overexpression of glycans are a hallmark of cancer. These changes are either found in the core or the terminal structures of the carbohydrates of glycoproteins. Affected proteins can be either cellular, cell-surface or secreted proteins, and glycosylation modifications frequently result in a modified expression, metabolism, functions, properties, stability and/or cellular localization of glycoproteins in cancer cells, resulting in part in their uncontrolled growth and aggressive behavior. Therefore glycosylation pathways, and the glycosidases and glycosyltransferases of these pathways, represent potential innovative modalities for drug development in cancer therapies which are just beginning to be explored. This review proposes to summarize the published information for glycosidases and their inhibitors in cancer.

Key Words: Cancer, glycosidases, inhibitors, mannosidase, glucosidase.

INTRODUCTION

The functions and expression of proteins are regulated at several levels: gene transcription, proper folding, cell trafficking, compartmentalization and secretion, and activation or inhibition. The roles of gene transcription, activation and inhibition have been largely studied. In the biosynthesis of proteins, the post-translational glycosylation patterns of proteins in the various cellular compartments will determine not only the function, structure, physical and biochemical properties, but also the fate of a protein, such as retention in a determined cell compartment, secretion, degradation, insertion in the cell membranes, interactions with other molecules, binding to a membrane receptors. Oligosaccharides are linked to proteins *via* the δ-amino group of asparagines (Asn) (*N*-linked glycosides) or through an α-linkage to the side-chain of the hydroxyl group of serine (Ser) or threonine (Thr) (*O*-linked glycosides) [1]. Post-translational modifications are performed by families of glycosidases [2,3] and glycosyltransferases [4,5] acting in very tightly controlled and regulated sequential fashion. Cycles of carbohydrate hydrolysis and addition ensure the proper oligosaccharide structure, which will determine the fate and cell localization of the protein to which a particular oligosaccharide is added. Glycosyltransferases transfer monosaccharides from activated nucleotide sugars, as donors, to an hydroxyl groups of an appropriate carbohydrate, as acceptor, and these enzymes exhibit remarkable regio- and stereoselectivity, while glycosidases are less restrictive on the fine structure of their substrates. The biosynthesis of the *N*-linked oligosaccharide chain (Fig. **1**) involves two distinct pathway [review in 6].

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First the assembly of the oligosaccharide chain is initiated in the endoplasmic reticulum (ER). N-Acetyl-glucosamine (GlcNAc), mannose (Man) and glucose (Glc) ($Glc_3Man_9(GlcNAc)_2$-) are sequentially added to a lipid carrier, dolichyl pyrophosphate, and transferred to an asparagine (Asn-X-Ser/Thr) on the nascent protein in the process of synthesis on the ribosomes. At that stage all glycoproteins will bear the same carbohydrate structure. This carbohydrate-assembled structure serves as quality control sensors for protein folding, secretion or degradation in the ER.

Then a second phase of ordered trimming of selected monosaccharides by glycosidases and addition of others by glycosyltransferases begins in the ER and continues in the Golgi apparatus (Fig. **1**), which is pre-determined, protein-selective and cell-specific, but does not request a template as is necessary for the synthesis of DNA, RNA and proteins. The first processing enzyme, α-glucosidase I, removes the outermost α1,3-Glc, then α-glucosidase II removes the two α1,2-Glc to produce a $Man_9(GlcNAc)_2$-protein. Then α-mannosidase I removes a single α1,2-Man, and the nascent glycoprotein is transported to the cis Golgi, where α-mannosidase I can remove other Man to produce a $Man_5(GlcNAc)_2$-protein. Other mannosidase activities may be involved here. In the medial Golgi, a GlcNAc transferase I adds a GlcNAc group from UDP-GlcNAc to the α1,3-Man branch. This addition is a signal for α-mannosidase II to remove the α1,3-Man and α1,6-Man to form $GlcNAcMan_3(GlcNAc)_2$-protein. Other mannosidases, homologue to α-mannosidase II, may provide alternate pathways [7]. This is an important step since other GlcNAc, galactose, fucose, sialic acid can then be added by a variety of glycosyltransferase in the trans Golgi. Alternate pathways mediated by endomannosidases [8] can bypass a block of the ER glucosidases by hydrolyzing high mannose oligosaccharides producing a $Man_8(GlcNAc)_2$ -protein.

In the ER, the number and location of glycans added to glycoproteins instruct cells about the folding states of and

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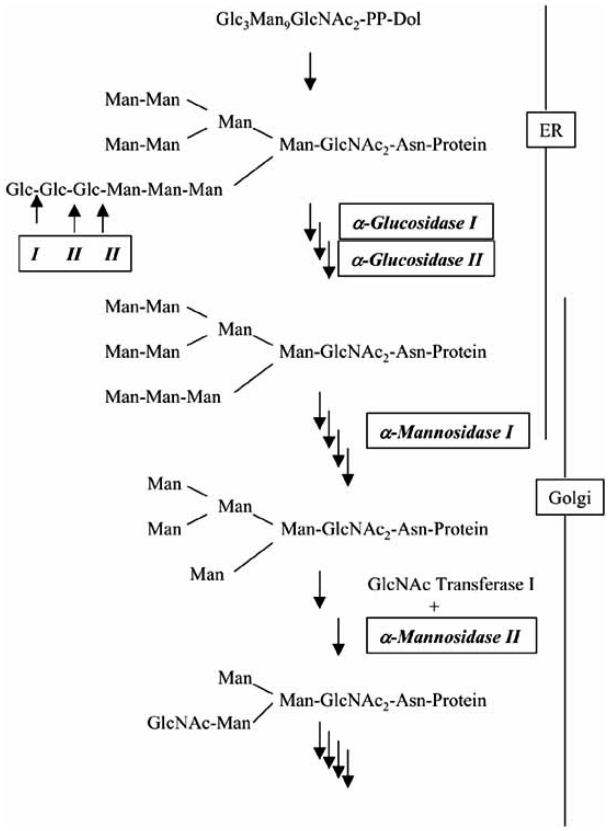


Fig. (1). Glycosidases of the cellular glycosylation pathways.

their consequences for the nascent proteins (for a more detailed discussion of these early cellular processes of the quality control system in the biosynthesis of proteins, which is out of the scope of the present mini-review, readers can see excellent reviews by others [6, and references herein]). Thus one important consequence of inhibiting the early steps of protein glycosylation will be to affect the quality control system of proteins in the ER, like the action of ER glucosidases and the binding of the lectin-like chaperones calnexin/calreticulin on mono-glucosylated nascent glycoproteins [6,9], and inhibitors of the enzymes involved in these early glycosylation processes (as expected with statins, tunicamycin or castanospermine) may interfere with a large number of down-stream targets, whereas inhibitors for the latter phases of protein glycosylation (such as mannosidase inhibitors like swainsonine) may be more selective for defined target proteins. Following secretion, out of the ER into the cytoplasm or out of the cell, modification of the carbohydrate moiety of a glycoprotein will also determine its half-life and interactions with other proteins [10], either cell membrane-bound, extracellular matrix-bound or soluble, and important biological processes such as cell adhesion/de-adhesion, migration [11,12].

Therefore, depending on the global and local protein conformation and the availability of the glycosylation-processing enzymes for the particular cell type, protein glycosylation is protein-specific, site-specific, and tissue/cell-specific. Oligosaccharides structures are highly heterogeneous and a single protein may exist as a complex collection of glycoproteins, which differ only in the amount or structure of attached carbohydrate moieties, dependent on the biological activation and/or differentiation state of the cells. Targeting protein glycosylation in cancer treatment, either immunotherapy, the development of inhibitors for carbohydrate-processing enzymes or of mimics of glycans involved in adhesion of cancer cells, is becoming a therapeutic option [reviews in 13-17]. In this mini-review we will consider only *N*-linked oligosaccharides and glycosidases, and the synthetic inhibitors developed for these enzymes which have been evaluated in cancer. However, modification of the expression of various glycosyltransferases [18] and defects in the *O*-linked glycosylation pathways of mucins [19,20] and carbohydrate antigens [11] have also been shown to determine human cancer progression.

GLYCOSIDASES IN CANCER

Glycosylation as an additional level of regulation has been documented for human diseases, including cancer, and it has been realized that glycans expressed by diseased cells are either displayed at different levels, or with different structures than in normal cells. Glycans regulate tumor proliferation, differentiation, invasion, metastasis, immune surveillance and angiogenesis. Altered glycosylation results in alterations in the expression of cell surface oligosaccharides, or altered protein folding and stabilization of tertiary structure, resulting in defects in glycoprotein recognition and elimination by the cell quality control mechanisms [21,22]. Therefore, glycosides and carbohydrate-dependent cellular pathways are important for the diagnosis, prognosis and progression of cancer, as well as representing potential new targets for therapeutic approaches [reviews in 23-28]. Unlike proteins and nucleic acids, glycosylation pathways as drug targets have remained relatively little studied until very recently. However, in view of the importance of carbohydrates in fundamental cellular processes, therapeutic strategies will necessitate that drugs either are selective for defined cells, or are able to modulate rather than ablate defined glycosylation pathways.

Thus, changes in glycosylation pattern of glycoproteins is a common feature of human cancers, which influences tumor behavior, metastasis and immune surveillance [9,29]. Changes in protein glycosylation can also be used in histological evaluation of cancer tissues, such as the use of lectins or the determination of mucins expression [30-32] to ascertain tumor staging and grading. Sugar receptors are also potential targeting molecules, such as the hyaluronic acid (HA) receptor CD44 on tumor cells or immune cells [30,33]. Several secreted, cell-surface and intracellular glycoproteins have been shown to bear aberrant glycosylation in cancer, which non-exclusively include the insulin-receptors and major histocompatibility systems [9,34,35], cadherins [36], protease expression, activation and secretion [37,38] such as the protease prostate-specific antigen (PSA) [39]. Thus inhibitors of specific enzymes of the tumor cell glycosylation pathways may prove useful to control cancer progression, at different levels of regulation. For example, statins depress the synthesis of dolichyl pyrophosphate, and induce growth arrest of melanoma cells, mediated by defect in the expression of underglycosylated insulin-receptor at the surface [40]. Tunicamycin (TM), a naturally occurring antibiotic, blocks this

first step of the biosynthesis of *N*-linked oligosaccharide. TM significantly enhanced the sensitivity to cisplatin of head and neck carcinoma cells *in vitro*, and *in vivo*, the administration of TM in combination with cisplatin inhibited local tumor growth and increased apoptosis of cisplatin-resistant tumor cells as compared to cisplatin alone [41].

In summary, the post-translational glycosylation of a protein is a complex process, subjected to multiple control steps, and whose outcome is important for the bio-availability of a protein. Therefore due to the cell specificity of the organization of glycosylation pathways, the selectivity and specificity of these modifications, the final structure and carbohydrate composition of a glycoprotein is dependent on the cell type, and on its state of cell activation and/or differentiation [42], in particular cancer cells compared to the non-tumoral cells. A defect in glycosylation may result in misfolding of a nascent protein, ubiquitination and destruction by the cytoplasmic proteasome system or in the lysosomal compartment, in an accelerated secretion of a protein, or on the contrary in the retention or an increased reuptake from the cell extracellular space *via* the endosome/lysosome pathway. All of these mechanisms would result in a modified metabolism of a protein, which may be either detrimental or beneficial to the organism, depending on the context. Small oligosaccharide and glycosidase inhibitors and their analogues have demonstrated efficacy in inhibiting several experimental and human cancers, uncluding glioblastoma and melanoma growth [17,43-48]. High levels of glycosidases [49], mostly active at the C-1 position of the sugar backbone, have been found in thyroid, gastric and colon carcinoma [2,3,11,17,50-61], which have been hypothesized to be linked to defective maturation in the Golgi network of lysosomal α-glycosidase in colon cancer cells [52]. Acid lysosomal glycosidases, including α-sialidase, β-galactosidase, α- and β-mannosidases, and/or cytosolic glycosidases are involved in protein catabolism, and the carbohydrate structure of their protein substrates may be an important factor in the half-lives of cellular glycoproteins [62]. Increased expression of catabolic glycosidases has been demonstrated in cancer [63]. Increased acidic β-galactosidase activity has been linked to drug-induced senescence of tumor cells [64], whereas high expression of β-glucosidase and β-galactosidase activities in cancer cells can also be useful to activate less-toxic geldamycin-carbohydrate conjugates to active geldamycin in target tumor cells [65]. In the present review, we will outline the information which has been obtained using glycosidase inhibitors in experimental approaches to treat cancers.

GLYCOSIDASE INHIBITORS

Carbohydrate properties can evoke new concepts in therapy, however, unlike proteins and nucleic acids they have remained relatively underutilized until now as a target for therapeutic agents. The catalytic mechanism of glycosidases has been determined [66,67], and may be either of the retaining or inverting type (Fig. **2**).

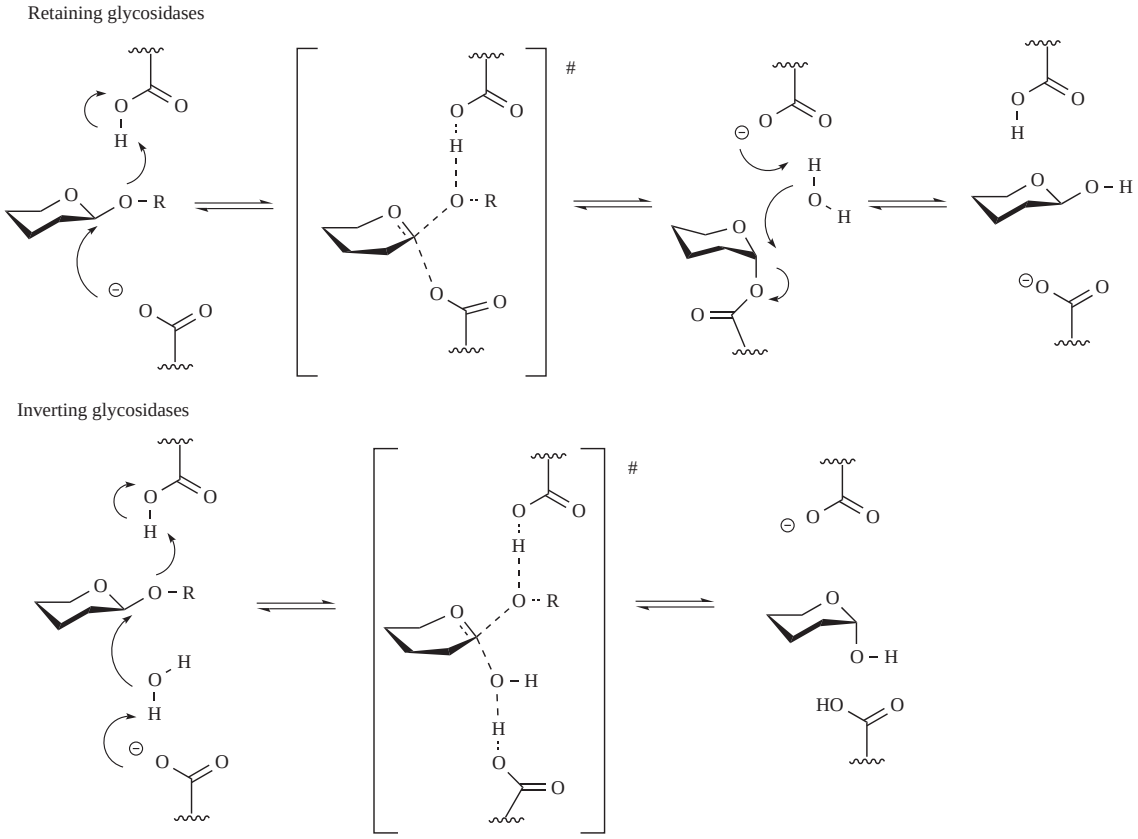


Fig. (2). Mechanism of enzymatic hydrolysis of glycosides by retaining and inverting glycosidases (# : reaction intermediate).

The enormous structural variability of oligosaccharides defined by the sequence of sugar units, the anomeric α or β-configuration and the positions of inter-residue linkages may provide opportunities for the development of banks of molecules with different properties [15-17,44]. Advances in understanding the role of glycosidases in various diseases have resulted in the development of new molecules or new analogues of known molecules [43,68-75]. Therefore, inhibitors of the α-glucosidases and α-mannosidases involved in the trimming reactions in cells have been either isolated from natural sources or chemically synthesized.

Naturally occurring sugar mimics are classified into five structural classes: polyhydroxylated piperidines, pyrrolidines, indolizidines, pyrrolizidines and nortropanes. A large number of compounds belonging to these classes inhibit miscellaneous glycosidases but only few of them demonstrated properties suggesting therapeutic potential. Alkaloids mimicking the structures of monosaccharides are widespread in plants and microorganisms and these sugars mimics, where the ring oxygen has been replaced by nitrogen, bind specifically to the active sites of glycosidases like the corresponding natural substrates [review in 17]. Apart from the natural alkaloids, studies are underway in several groups to develop inhibitors of glycosidases which may be useful therapeutic agents [17,68,76,77]. Some modified glycosides are in clinical use or under clinical trials for cancer, such as Streptozotocin, a derivative of glucosamine. However, the unselective inhibition of several glycosidases achieved by these natural derivatives may result in side-effects since deficit in lysosomal glycosidases involved in protein catabolism causes lysosomal storage diseases.

In applications other than cancer, glycosidase inhibitors (Fig. **3**) have already found some promising applications, including in agriculture, or human diseases such as type II diabetes or as antiviral agents [16,78,79,80].

In the field of cancer, α-mannosidases and α-glucosidases are the most promising potential targets for the development of inhibitors of cellular glycosidases. The first chemically synthesized of these inhibitors were swainsonine (SW), an inhibitor of α-mannosidase II, then castanospermine (CST) an inhibitor of α-glucosidases I and II.

α-Glucosidase Inhibitors

The removal of the outer α1-2-glucose is achieved by glucosidase I, and the two remaining α1-3-glucose residues by glucosidase II. The monoglucosylated structure resulting from the removal of the outer two glucoses, or following reglucosylation, allows the monoglucosylated protein to interact with the quality control chaperones calnexin and calreticulin. Recently, the putative active site of α-glucosidases has been modeled as a guide to the design of inhibitors [81]. Castanospermine (CST) (Fig. **4**), which is a potent inhibitor of α-glucosidase I, was tested for its potency to inhibit the ability of metastatic cells to cause platelet aggregation, a frequent, necessary, but not sufficient, step in the metastatic process [82]. T24-H-ras-transformed 10T1/2 fibroblasts, displaying increasing metastatic potential to the lungs when injected into the tail vein of syngeneic mice, were grown in the presence of CST (50 μM), and a significant reduction in their ability to aggregate platelets was observed, correlated with the ability of CST to inhibit tumor lung colonization by the treated cells.

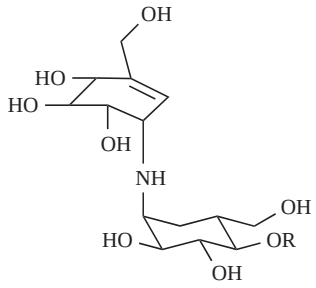
CST and N-methyldeoxynojirimycin (N-MDNJ) (Fig. **4**) an inhibitor of α-glucosidases I and II, were also studied for their ability to reduce angiogenesis [83]. *In vivo*, in nude mice injected either with the murine tumor cells EHS-BAM or with the human prostate tumor cell line Tsu-pr1, CST (50 mg/mouse/day for two weeks) was able to reduce tumor growth by about 50%. This treatment also resulted in a 70-80% decrease in blood vessel infiltration of tumors. Moreover, in endothelial cell grown *in vitro*, CST and N-MDNJ prevented capillary-like structure formation. The ability of endothelial cells to adhere to extracellular matrix proteins was retained, but CST- or N-MDNJ-treated cells exhibited increased cell aggregation and reduced cell migration, preventing their alignment and organization to form tubular structures. These results suggest that CST and N-MDNJ increased cell-cell adhesion by glycoside-dependent interactions resulting in the blockage of the reorganization of cells into capillary-like networks. Analogues of the natural ester sintenin (Fig. **4**) displaying moderate inhibitory activity toward α-glucosidase also exhibited significant cytotoxicity toward human tumor cell lines from hepatocellular, nasopharyngeal, lung, prostate and cervical (adeno)carcinoma [84].

α-Mannosidase Inhibitors

Mannosidases play a key role in the processing of glycoproteins, and thus are of pharmacological interest as targets for the development of anticancer therapies. α(1,2)Mannosidases I are inverting enzymes. Jack bean, lysosomal and Golgi α-mannosidases II contain identical sequences at their active sites, and hydrolyse α(1,2), α(1,3) and α(1,6) linkages. They are retaining enzymes, releasing α-D-mannose. The alkaloids swainsonine (SW) and deoxymannojirimycin (DMJ) are potent inhibitors of α-mannosidases II with arylmannoside as substrates (Fig. **5**). Determination of the structure of Golgi α-mannosidase II, in the presence or absence of SW or DMJ, demonstrated the presence of a zinc ion at the active site, and a putative GlcNAc binding pocket [57]. Swaisonine mimicks the transition-state binding of the substrate [60].

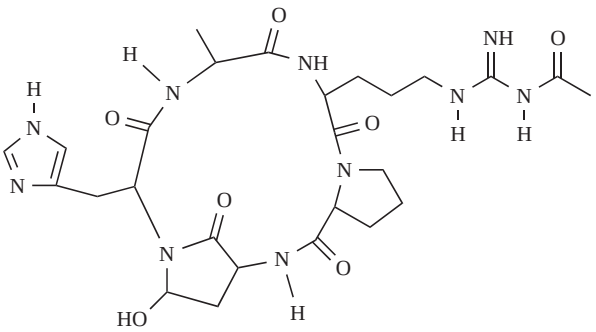
The effect of SW on different human cancer cell lines was evaluated. Treatment of human hepatoma cells with SW resulted in an accelerated secretion of hybrid forms of the glycoproteins transferrin, ceruloplasmin, α2-macroglobulin and α1-antitrypsin, whereas the secretion of non-glycoproteins was not affected [85]. The transport of these hybrid glycoproteins through the Golgi apparatus was faster than the transport of normal glycoproteins. In *in vivo* experiments [86] in mice injected with the B16-F10 murine melanoma cell line, melanoma cells incubated with SW prior to injection displayed a dose-dependent inhibition of lung colonization. Nevertheless the tumorigenic properties of B16-F10 cells were not affected by SW. In experimental murine cancer models, administration of SW in drinking water, before or after surgical excision of the primary tumor, inhibited by 95 and 88% the formation of spontaneous metastases to the

Insecticides and pesticides



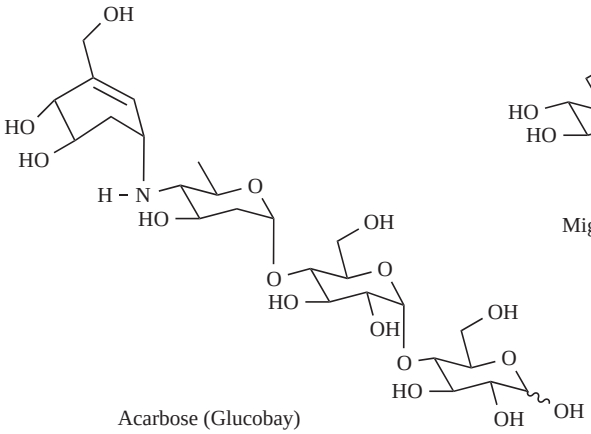
Validamycin A
R = β-D-glucopyranosyl

trehalase inhibitor

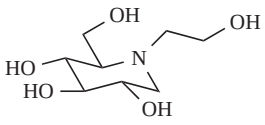


Argadin
Lucilia cuprina chitinase inhibitor
IC_{50} = 150 nM, 37°C

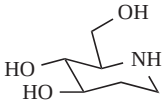
Treatment of type II diabetes



Acarbose (Glucobay)
pig intestinal sucrase, IC_{50} = 0.5 μM

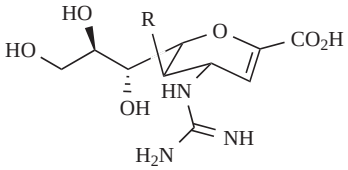


Miglitol (Glyset)

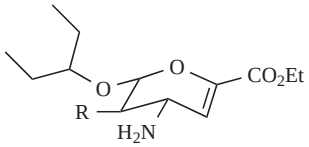


Isofagomine
hepatic glycogen phosphorylase, IC_{50} = 0.7μM

Antiviral agents



Zanamivir, R = $NHCOCH_3$
Influenza A, B NA inhibitor (IC_{50} < 1nM)



R = $NHCOCH_3$, Oseltamivir
Influenza NA inhibitor (IC_{50} = 1 nM)

Fig. (3). Glycosidase inhibitors with efficacy in applications other than cancer.

liver and the lungs of the highly invasive M5076 murine reticulosarcoma or B16-F10 murine melanoma cells [17,87]. SW also enhanced the immune effector functions and decreased the toxicity of several anticancer agents [47]. Phase I clinical trials of patients with advanced malignancies demonstrated that some patients showed a significant decrease of tumor mass when given SW [48]. The major side-effects observed with intraveineous or oral administrations were pulmonary edema and neurological symptoms only for the oral study.

Ester analogs of SW were prepared in order to increase the bioavailability of the drug [88]. 2-Aryloxy and 2-alkyloxy analogs of SW were relatively poor inhibitors of α-mannosidases from jack bean and from the lysosomes of MDAY-D2 tumor cells. Nevertheless, the 2-*p*-nitrobenzoy-

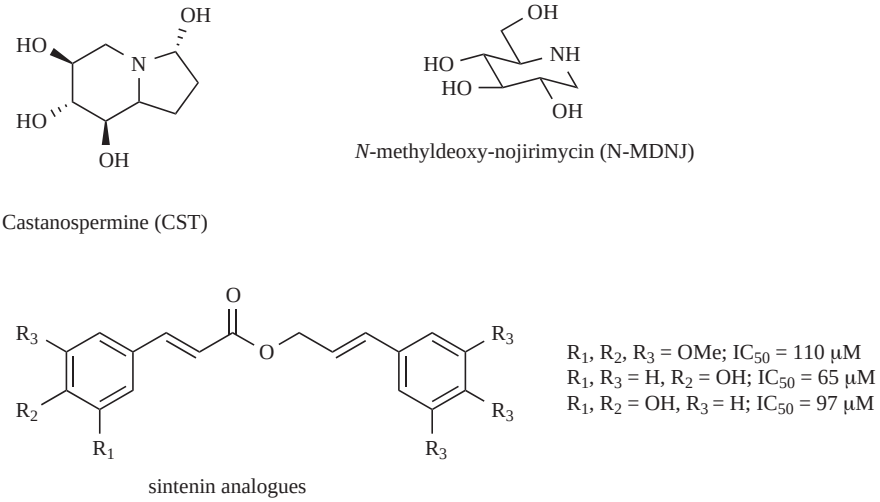


Fig. (4). α-glucosidase inhibitors as anti-cancer agents.

loxy-, 2-octanoyloxy- and 2-butanoyloxy-derivatives had protective effects comparable to SW against the toxic effects of the lectin L-PHA in MDAY-D2 cells, suggesting that cellular esterases may convert these analogs into SW inside cells. *In vivo*, among the various carbonoyloxy analogues of SW, the 2-octanoyloxy derivative induced the highest rate of survival of mice 28 days after injection of SW analogues-treated cancer cells, similar to the rate obtained with SW.

In vitro SW increased the adhesion of bladder cancer cells to laminin, collagen IV and fibronectin, associated to decreased migratory ability [86], but did not directly inhibit

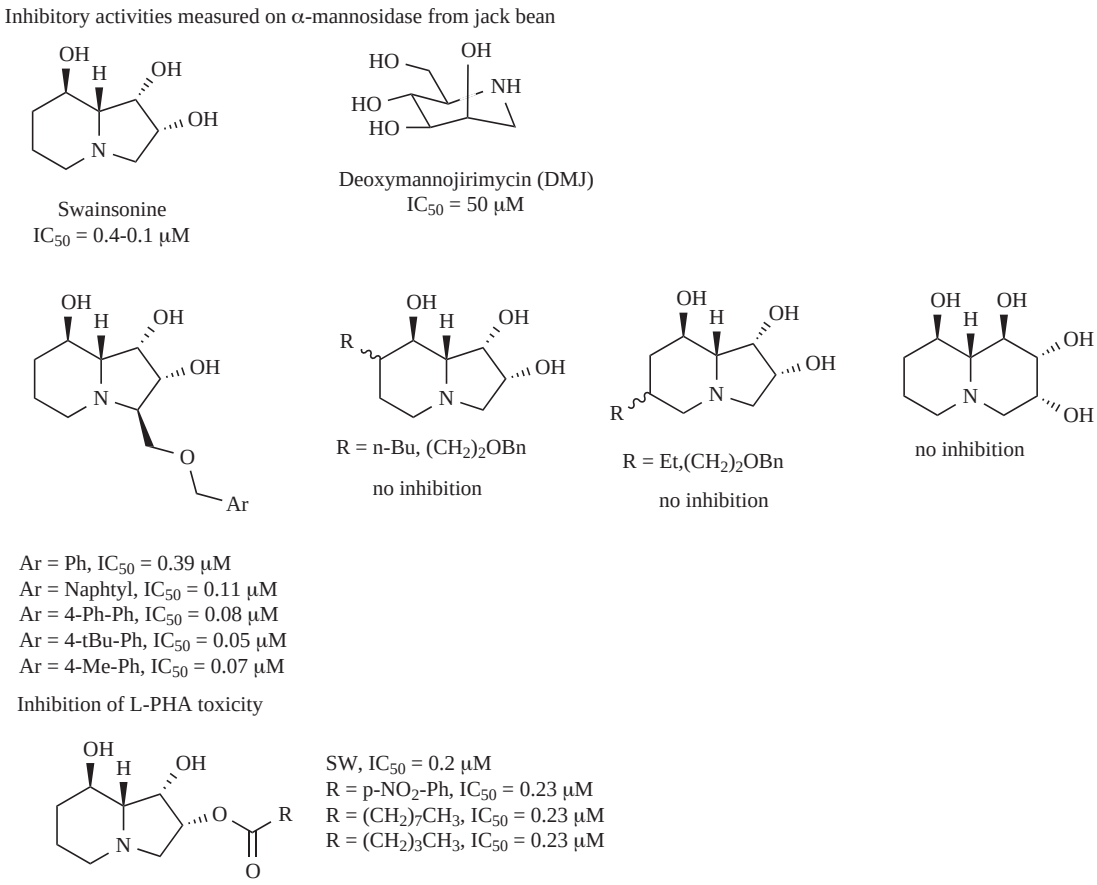


Fig. (5). Deoxymannojirimycin and Swainsonine and its analogues as potential anti-cancer agents.

tumor cell growth [review in 17], which we postulated to be due to a poor cell uptake and transport across membranes [43]. Therefore, to improve the cell penetration of α-mannosidase inhibitors, the introduction of various substituents on SW was attempted by several groups. The introduction of aryl hydroxymethyl groups at C(3) position enhanced inhibition [90,91], while substitution at C(6) and C(7) dramatically decreased the inhibition of α-mannosidase from jack bean [92]. Ring-expanded analogues of SW were also poorer inhibitors of α-mannosidase than the parent molecule [93]. Moreover all these derivatives did not show significant effects in cancer cells. We showed that simpler analogs of SW consisting of functionalized pyrrolidines (Fig. **6**) are potent, selective and competitive inhibitors of α-mannosidase from jack bean with K_i values ranging from 2.3 to 0.7 μM for the best congeners. Lipophilic groups such as ester and amide moieties were introduced to allow penetration into cancer cells. In particular, the 4-bromobenzoate derivative displayed promising growth inhibition of glioblastoma and melanoma cells, tumors associated with poor prognosis and multiresistance toward conventional chemotherapeutic treatments. As postulated for the lipophilic derivatives of SW, the ester moiety promoted internalization of the drug by the tumoral cells and cellular esterases were postulated to convert this prodrug into the active inhibitor.

CONCLUSIONS

Inhibitors of selected glycosidases have a potential therapeutic interest in human cancer, and other diseases, as summarized in Table **1**. The information obtained until now indicates that the target glycosidases are of ubiquitous expression in normal cell as well as in tumor cell glycosylation processes. The differences may reside in the expression levels, or the cell localization of these enzymes. Mutations and/or alternate variants have been demonstrated for human glycosyltransferases, resulting in defective enzymatic activity or defective cell organelle location of these enzymes, and ultimately in severe physiological deficits. It is not known, to the best of our information, whether such defects in glycosidases can exist in human cancer, or if they result in embryonic lethality.

Our results using functionalized pyrrolidines [43], and results from others using swainsonine [86-93], suggest that the target of α-mannosidase inhibitors in cancer and normal cells are intracellular. Therefore the design of inhibitors must take this information into consideration to achieve the development of efficient, and cell-permeable (pro)drugs. The wide functions of these enzymes in normal physiological processes will also require that targeting of the inhibitors to defined target cells, and defined organelles in these target cells, may be achieved, in order to limit wide-spread cytotoxicity and side-effects. Therefore, for the next generation of glycosidase inhibitors it will be necessary:

- to better define the exact enzymes and potential enzyme variants involved, and their cellular location,
- to prepare and evaluate in relevant models, cell permeable, cell selective and organelle-selective inhibitors for the targeted glycosidases

in order to achieve cancer selectivity combined with limited side-effects in chemotherapies with these inhibitors.

ABBREVIATIONS

Asn	=	Asparagine
CST	=	Castanospermine
DMJ	=	Deoxymannojirimycin
DNJ	=	Deoxynojirimycin
ER	=	Endoplasmic reticulum
Glc	=	Glucose
GlcNAc	=	N-Acetyl-glucosamine
Man	=	Mannose

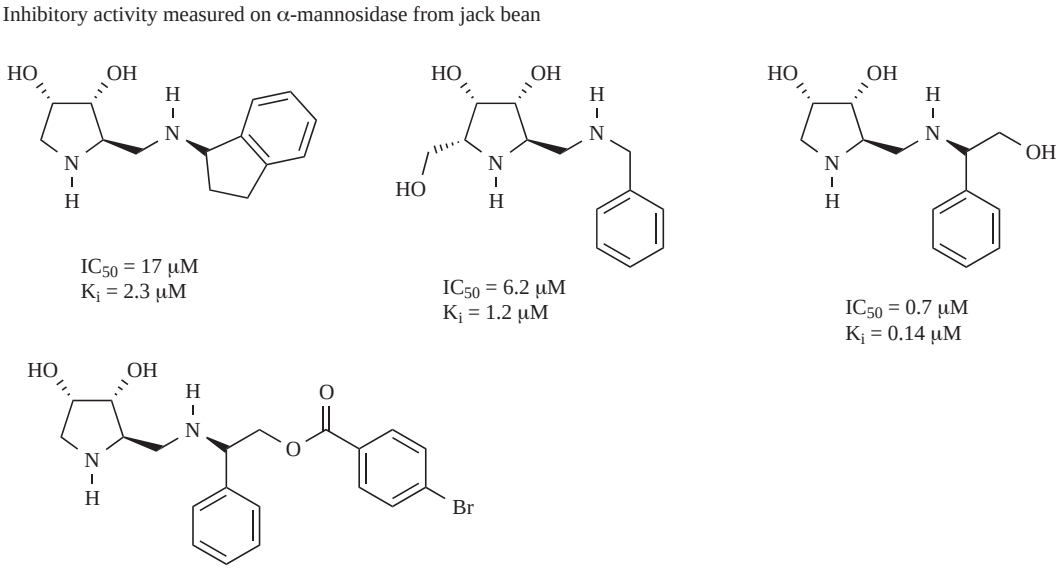


Fig. (6). Pyrrolidine derivatives as growth inhibitors of human cancer cells.

Table 1. Glycosidase Inhibitors as Potential Anti-Cancer Agents (A) and as Drugs for Other Diseases (B)

Compound References	Targeted glycosidase	Type of cancer	*In vitro* / *In vivo*	Results
A				
CST [82,83]	α-glucosidase I	lung prostate	*in vivo* *in vivo*	Inhibition of platelets aggregation and tumor lung colonization Reduction of tumor growth, decrease of blood vessel infiltration
N-MDNJ [83]	α-glucosidase I and II	endothelial cells	*in vitro*	Increased cell aggregation and reduced cell migration
Sintenin analogues [84]	α-glucosidase I and II	hepatocellular, naso-pharyngeal, Lung, prostate, cervical carcinoma cells	*in vitro*	Inhibiton of cellular growth
SW [17,47,48,85,85,87,89]	Golgi α-mannosidase II	melanoma, reticulocarci-noma bladder cells advanced tumors	*in vivo* *in vitro* *phase I*	Inhibition of lung colonization, inhibi-tion of metastases formation after excision of the primary tumor Increased adhesion of tumor cells to laminin, collagen IV and fibronectin, decreased migratory ability Reduction of tumor mass
2-carbonoyl SW [88]	Poor inhibition of α-mannosidases	melanoma	*in vivo*	Increased rate of survival 28 days after injection of treated cancer cells
Pyrrolidine derivatives [43]	α-mannosidase II	Glioblastoma, melanoma	*in vitro*	Inhibition of cellular growth
TM [41]	Inhibition of the first step of N-oligosaccharide biosyn-thesis	Squamous cell carci-noma of head and neck Cis-platin resistant mouse model	*in vitro* *in vivo*	Increased sensitivity of carcinoma cells to cis-platin Inhibition of local tumor growth by administration of TM and cis-platin
Streptozotocin (STZ)	Reduction of β-glycosidase activities in kidney	Carcinoid tumors Pancreatic tumor	Clinical use Clincal use	In combination with 5-fluorouracil, increased median survival to 64 weeks In combination with 5-fluorouracil and mitomycin, increased median survival to 10 months
B				
Acarbose (Glucobay)	Digestive α-glucosidase	Type II diabetes	Commercial drug	Reduction of blood glucose elevation
Miglitol (Glyset)	Intestinal α-glucosidase	Type II diabetes	Commercial drug	Reduction of blood glucose elevation, increase of insulin level, fewer gastro-intestinal side effects
Zanamivir (Relenza)	Neuraminidase	Influenza	Commercial Drug	Antiviral-agent against A and B influ-enzae, low oral bioavailibility
Oseltamicir (Tamiflu)	Neuraminidase	Influenza	Commercial Drug	Antiviral-agent against A and B influ-enzae, improved oral bioavailibility

NB-DNJ = N-butyldeoxynojirimycin

N-MDNJ = N-methyldeoxynojirimycin

Ser = Serine

STC = Streptozotocin

SW = Swainsonine

Thr = Threonine

TM = Tunicamycin

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