Back to (non)-Basics: Recent Developments in Neutral and Charge-Balanced Glycosidase Inhibitors

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Abstract: Certain glycosidase inhibitors possess potent antiviral, antitumour and antidiabetic properties. Glyconic acid lactones, the earliest glycosidase inhibitors identified, have planar anomeric carbons that mimic the transition state of glycoside hydrolysis. Other classes include lactams, glycals, epoxides, halides and sulfonium ions, the latter based on the natural product salacinol from an antidiabetic herb.

Keywords: Glycosidase inhibitors, glucosidase, mannosidase, galactosidase, sialidase, salacinol, cyclophellitol.

1. INTRODUCTION

Hydrolysis of carbohydrate linkages is a fundamental chemical and biochemical reaction that is accelerated by an acid catalyst evoking an electron-deficient transition state as shown in Fig. (**1**). Oligosaccharides are remarkably robust at pH>7 [1] and nature uses a large family of enzymes, known collectively as glycosidases, to catalyse their consumption by providing both a proton source and nucleophile around the anomeric center [2]. Glycosidase inhibitors are important medicinal agents [3-5] due to their well-documented roles in lethal viral infections such as HIV [6-9], tumour growth and metastases [10, 11], glucose homeostasis [12, 13], and more recently, osteoarthritis [14]. Although lactones were the first class of glycosidase inhibitor discovered, alkaloid carbohydrate mimetics such as those in Fig. (**2**) have dominated research in this arena since the discovery of deoxynojirimycin (DNJ) in 1966 [15].

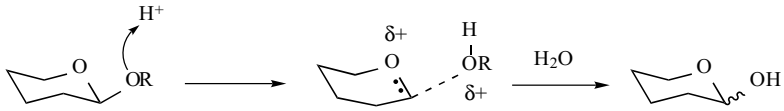

Fig. (1). Acid-catalyzed glycoside hydrolysis.

In addition to the many useful biological effects of DNJ, the *N*-hydroxyethyl analog of this compound is currently marketed as the antidiabetic drug Miglitol [16], while the *N*-butyl derivative shows promising activity against Tay-Sachs [17] and Gaucher's diseases [18]. The epimeric compound deoxymannojirimycin inhibits glycoprotein processing by blocking mannosidases (IA/B and II) requisite to the biosynthesis of complex oligosaccharides [19]. The discovery of many related alkaloid natural products, such as acarbose, castanospermine, and swainsonine, soon followed the isolation and characterization of DNJ. Acarbose possesses antidiabetic properties due to its ability to inhibit intestinal digestive enzymes such as α-amylase and is sold commercially for this purpose [20]. This natural oligosaccharide is being used to treat diabetes in both pediatric [21] and elderly patients [22]. Castanospermine's inhibition of glycoprotein processing enzymes (glucosidase I) accounts for its effectiveness against HIV progression [7] and tumour angiogenesis [11]. Swainsonine's ability to inhibit tumour metastasis is linked to its effectiveness at blocking the glycoprotein-trimming enzyme mannosidase II [10]. 1-Iminosugars such as isofagomine [23] are an emerging class of selective β-glycosidase inhibitors [24]. Work on the isolation and synthesis of a variety of iminosugars has continued to grow over the past two decades [25-27]. Paralleling most current pharmaceutical drug pursuits, combinatorial libraries of these compounds have been developed in attempts to rapidly identify potent and specific inhibitors [28-32].

Alkaloids are attractive inhibitors due to potential electrostatic interactions with one of two conserved catalytic carboxylates in the active site of glycosidases. The low nitrogen inversion barrier may better allow the adoption of distorted ring structures involved in glycoside hydrolysis. However, due to undesirable side effects associated with many alkaloids, glycosidase inhibitors that lack a basic nitrogen have been sought. Many metabolically stable mono- and di-saccharides have been synthesized by replacing the endo- or exo-anomeric oxygens with carbon or sulfur—Fig. (**3**). The syntheses of carbasugars [33, 34] including cyclitols [35-37], *C*-glycosides [38-40], thiasugars [41-44], and *S*-glycosides [45-48] have been reviewed extensively and will not be covered here. The primary focus of this review is on the diverse structural types other than alkaloids and synthetic iminosugars that inhibit common exoglycosidases, although related enzymes will be highlighted as well. Many neutral or charge-balanced systems (e.g.-lactams, sulfonium

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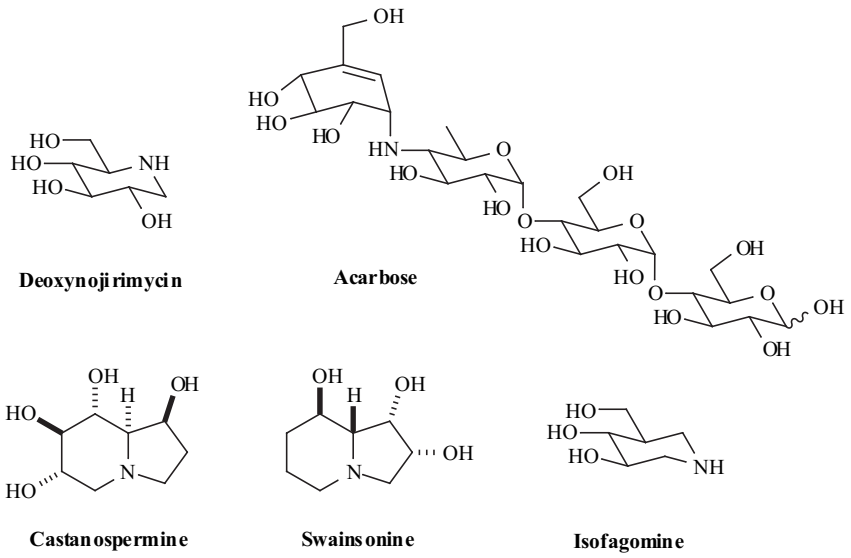


Fig. (2). Representative glycosidase inhibitors.

sulfates) have shown potent glycosidase inhibition and offer alternative pharmacological profiles to iminosugars.

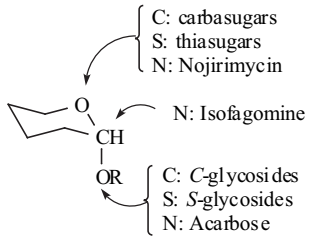


Fig. (3). Common points of hexose substitution found in glycosidase inhibitors and stable monosaccharide mimics.

2. TRANSITION STATE MIMICS

2.1 Carbonyl Derivatives and Related Compounds

The field of glycosidase inhibitors has come full circle since the discovery by Ezaki in 1940 [49] and Horikoshi in 1942 [50] of simple, neutral carbohydrate lactones as potent glycosidase inhibitors. In 1952, Levvy showed that inhibition of β-glucuronidase by certain sugars was actually due to trace amounts of sugar acid lactones present in these carbohydrates [51]. In the following decade, the use of lactones as β-glucuronidase inhibitors was shown by Carr to have significant antitumour effects in mice [52]. The sp^2 hybridization of the anomeric carbon can be considered a mimic of the distorted transition state structure formed in the enzyme active site. Gluconic acid lactone has been described to behave as such when inhibiting almond β-glucosidase, where an initial loose complex is formed before transformation to a more tightly bound species, presumably a glycosyl-enzyme intermediate [2]. This mimicry of the transition state can potentially outweigh benefits of electrostatic interaction possible with an analogous amine (i.e. reduction of the carbonyl group in a lactam). For example, a glucuronate-based lactam performs better than the corresponding amine at inhibiting β-glucuronidase [53].

Nishimura has recently reported the synthesis and glycosidase inhibition testing of the eight possible D-glyconic-δ-lactam stereoisomers [54]. The ketolactam **1** and hydrated ketolactone **2** were reported in 2001 as novel glucosidase inhibitors identified from deliberately complex reaction mixtures used to synthesize a range of related compounds [30]. Lactams where the nitrogen replaces the anomeric carbon are also potent glycosidase inhibitors. In these cases, the carbonyl oxygen can potentially participate as a more effective hydrogen bond acceptor than the 2-OH group or can act as a hydrogen bond donor in the tautaumeric form [55]. The lactam derivative of isogalactofagomine prepared by Bols and coworkers is a low nanomolar inhibitor [56] comparable to the corresponding amine [57]. Dihydropyridazinones developed by Vasella have an amide in the same position as Bols' lactam and these have proven to be effective inhibitors of jack bean α-mannosidase [58]. In 1999, an exocyclic amide derivative of DNJ was developed based on isotope edited NMR data that implicated aromatic residues in α-glucosidase that might interact favourably with the π-system of the amide bond [59].

An amide-type nitrogen is capable of forming stablized aminoketal structures that are less stable when the nitrogen is sp^3 hybridized—nojirimycin, for example, exists as an anomeric mixture in aqueous solution. García-Fernandez has incorporated this design feature in the cleverly constructed compound **3**, a urethane derivative of castanospermine [60]. The strengthened contribution to the anomeric effect from an sp^2 hybridized nitrogen anchors the α-configuration of the hydroxyl group and this dramatically increases selectivity between α- and β-glucosidases relative to the natural product (K_i = 2.2 μM versus yeast α-glucosidase, no inhibition of almond β-glucosidase) [61]. Disaccharide mimics using this design feature have also been created, but these are far less selective [62]. The natural product kifunensine seen in Fig. (**4**) is structurally similar (in that carbonyl groups on the nitrogens stabilize an otherwise labile anomeric arrangement) and is an immunomodulator that can inhibit α-mannosidase [63].

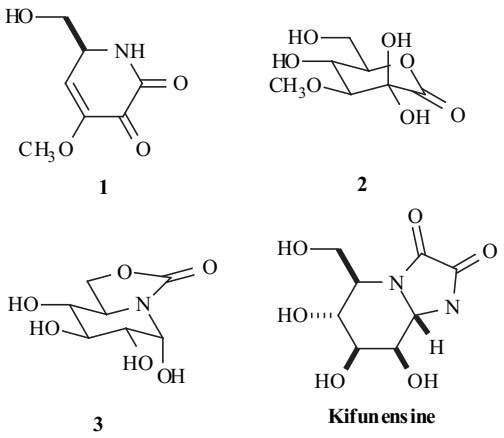


Fig. (4). Lactone and lactam-based inhibitors.

While a large number of glycosidases use a double displacement mechanism to bring about hydrolysis with overall retention of configuration, another class of these enzymes can carry out direct inversion during hydrolysis in a single step—Fig. (**5**). The active site is occupied by a water molecule that lies directly atop the anomeric carbon poised for direct displacement. In this case, tetrahedral anomeric structures offer the potential for selective inhibitors of this class. Drueckhammer has shown that phosphonamidate **4** offers modest inhibition of the inverting enzymes trehalase and glucoamylase, but this activity is encouraging considering these enzymes normally recognize disaccharide substrates [64].

2.2 Glycals

Compounds bearing a carbon-carbon double bond involving the anomeric carbon comprise a class of carbohydryates known as glycals and offer an alternative motif with sp^2 hybridization. These compounds are a misnomer based on Fischer's initial deduction that these were a new type of carbohydrate aldehyde [65], and indeed, the anomeric center of a glycal has the oxidation state of an aldehyde and undergoes some of the same reactions. The half-chair form of dihydropyran again emulates the transition-state of glycoside hydrolysis—Fig. (**1**). D-Galactal (**5**) actually serves as a pseudosubstrate for *E. coli* β-galactosidase since protonation at C-2 by the catalytic acid generates an oxonium-like intermediate that is trapped by the catalytic nucleophile [66, 67]. Hydrolysis of this intermediate then occurs as with other glycosyl-enzyme species generated from conventional substrates to release a 2-deoxy reducing sugar [2]. A series of C-1 substituted galactals has been developed by Kiss and Somsák into potent inhibitors of this enzyme [68]. Withers has shown that 2-acetamido-D-glucal also undergoes enzyme-catalyzed hydration in the presence of β-*N*-acetylhexosaminidases and is a low micromolar inhibitor of these enzymes [69]. The Michael acceptor 1-nitro-D-glucal acts as a time-dependent, irreversible inactivator of β-glucosidase by covalent modification but only at relatively high concentrations [70].

The most notable success in this area has involved the development of sialidase inhibitors as anti-influenza drugs [71]. Once the influenza virus has infected a cell, the newly synthesized viral progeny contain a sialidase (neuraminidase) that allows them to escape to invade other cells, and inhibitors of this enzyme stop the cycle of infection at this stage. From the X-ray crystal structure of sialic acid bound to a sialidase and known inhibitor **6** [72], Zanamivir (Relenza^{TM}) **7** was developed into a selective, potent inhibitor of the viral enzyme through rational drug design [73], and oligomers of this structural type are even more

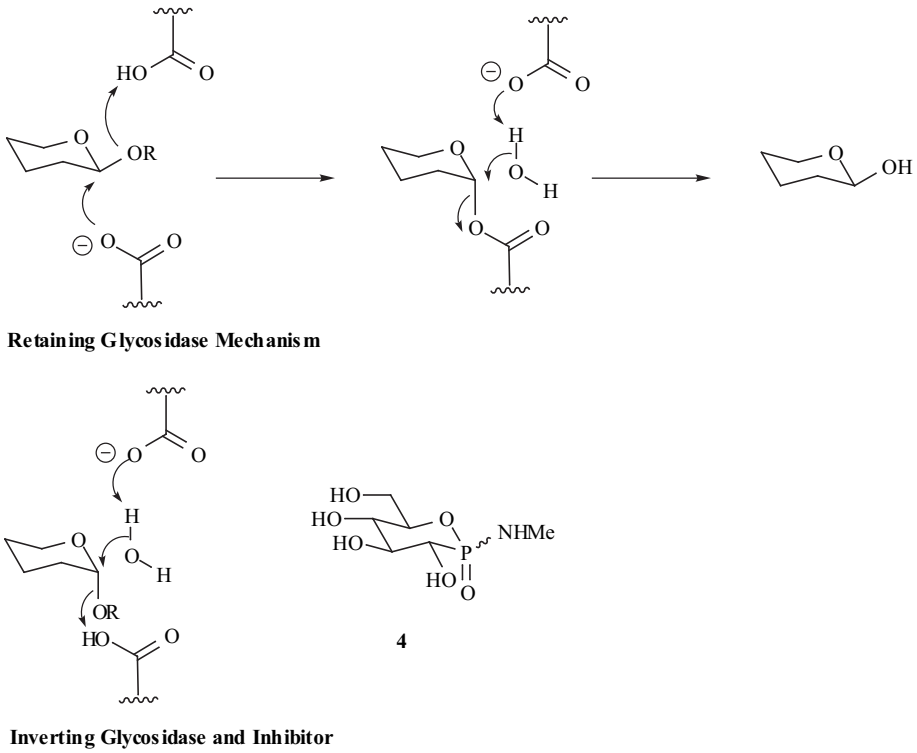


Fig. (5). Two classes of glycosidase mechanisms.

active [74]. Replacement of the glycerol side chain with hydrophobic groups, as in Oseltamivir (Tamiflu^{TM})[75] and **8** [76], has led to the further discovery of a number of active analogs [77, 78]. In related work, Schmidt has utilized the glycal framework to develop a series of sialyltransferase inhibitors [79].

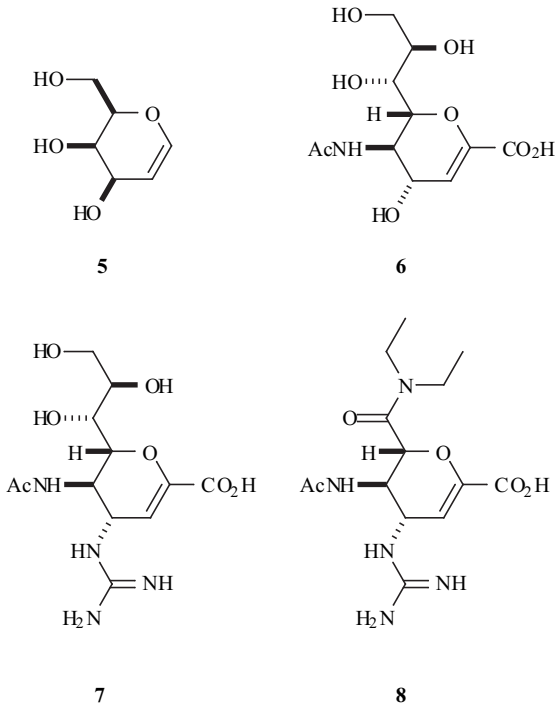


Fig. (6). Glycal inhibitors of glycosidases.

3. REACTIVE ELECTROPHILES

3.1 Epoxides

Electrophiles are not only useful irreversible enzyme inhibitors, but are important probes of active site structure [80]. Epoxides can act as mechanism-based inhibitors of glycosidases when they are positioned correctly in the active site [81]. The combined electron-withdrawing effect of multiple hydroxyl groups in close proximity to an epoxide renders this species less susceptible to acid-catalyzed hydrolysis and allows the oxirane to remain inert until bound by the enzyme. Once inside the confines of the active site, nucleophilic ring opening by a catalytic carboxylate is accelerated by protonation of the oxirane oxygen by the opposing catalytic acid. The need for both, differentially-protonated carboxylates for efficient ring opening is supported by *ab initio* calculations [82].

Legler first showed that conduritol B epoxide, Fig. (**7**), was an irreversible inactivator of β-glucosidase in 1966, the same year that DNJ was discovered [83]. This pseudo-symmetric compound can also inactivate α-glucosidase, but attack of the carboxylate occurs at the opposite oxirane carbon [2]. The epimer conduritol C epoxide resembles galactose in structure and serves as an inhibitor of β-galactosidase [84]. The natural product β-glucosidase inhibitor cyclophellitol was discovered in 1990 [85, 86], prompting a flurry of synthetic efforts in this area due to its activity against HIV [87, 88].

Epoxide aglycones can serve as selective inactivators of endoglycosidases when attached to the appropriate oligosaccharide substrate while simple epoxides themselves do not react with these enzymes even at elevated concentrations. Sharon and co-workers demonstrated this with epoxides extended from oligosaccharides of *N*-acetyl-D-glucosamine (e.g. **9**) for the inactivation of lysozyme [89]. Legler and Bause created the same type of inhibitor for cellulases using oligomers of β-(1→4)-linked glucose residues [90]. Despite the flexible nature of the linker in these types of compounds, the stereochemistry of the epoxide is important for specific glycosidase inhibtion in certain cases [91]. This method continues to be useful in mapping the large oligosaccharide binding sites surrounding the active sites of endoglycosidases [92-94]. Aziridines can also covalently modify a glycosidase active site in the same manner as epoxides as was originally established by Ganem [95] and Withers [96].

3.2 Halides

Halides are another obvious choice for alkylative enzyme inhibition and have been used in this capacity against

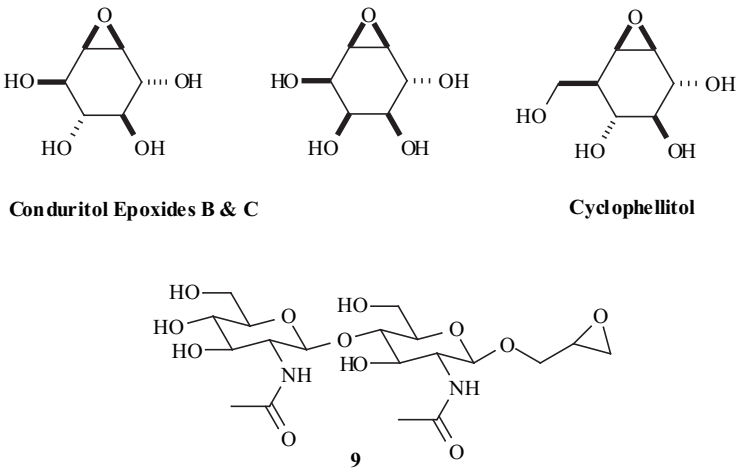
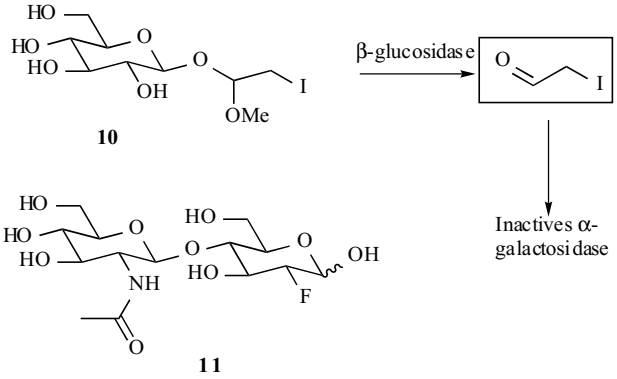


Fig. (7). Epoxide glycosidase inactivators.

glycosidases for a number of years. Bromoconduritol was used by Legler to inactivate β-glucosidase irreversibly in the same manner as conduritol epoxides [97]. As with the epoxides that target endoglycosidases, halides can be incorportated into the aglycone portion of the glycoconjugate to inactivate these enzymes. *N*-(Bromoacetyl) glycopyranosylamines are useful covalent modifiers of glycosidases [98, 99] due to the increased electrophilicity of α-keto halides, and bromoketone *C*-glycosides are effective inactivators of β-glucanases [100]. Ebrahim and co-workers have developed compounds such as **10** that can be considered a source of 2-haloaldehydes upon glycosidase cleavage [101]. They demonstrated that α-galactosidase can be inhibited by the iodoacetaldehyde that is released upon cleavage of **10** by a glucosidase as shown in Fig. (**8**).



10 **11**

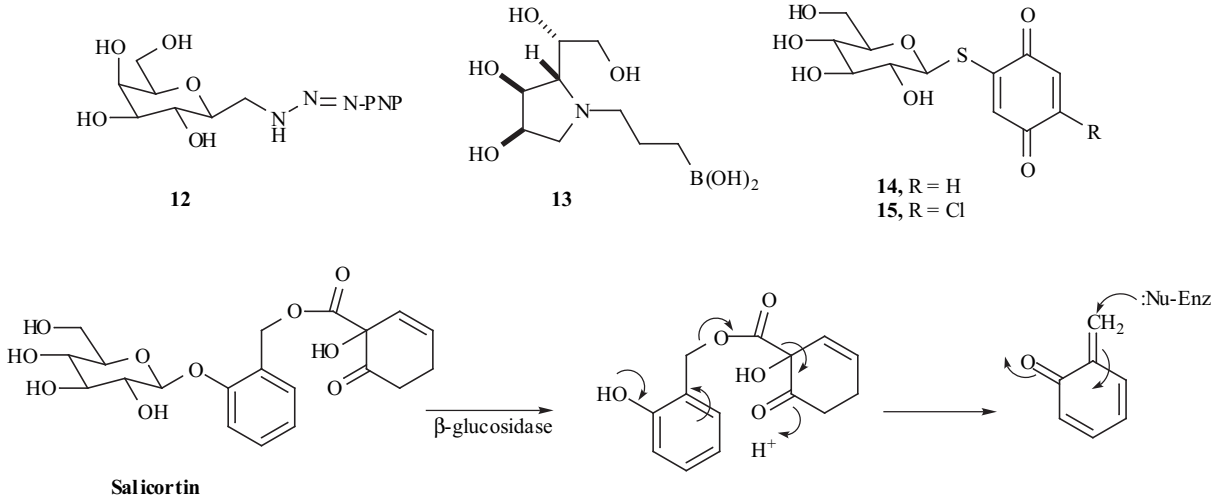
Fig. (8). Halosugars used in glycosidase inactivation.

The Withers group has used glycosyl fluorides extensively in the identification of active site nucleophiles for a variety of carbohydrate processing enzymes [102]. 2-Deoxy-2-fluorosaccharides form glycosyl-enzyme intermediates that have extended lifetimes relative to natural substrates allowing their discrete identification by mass spectrometry [103]. The fluorodisaccharide **11** has allowed detection of the elusive covalent intermediate involved in lysozyme cleavage of β-(1→4)-linked *N*-acetyl-D-glucosamine oligomers [104]. By synthesizing hexose-type difluorides where the second fluorine is in the 2- or 5-position, the stability of the glycosyl-enzyme intermediate can be increased due to the electron withdrawing effects of the second fluoride [105-107]. 2-Deoxy-2-fluoroglycopyranosyl fluorides are chemoprotective agents that inhibit the cytotoxicity of ricin in various cell lines [108]. Radioactive ^{18}F analogs of 2,6-difluorides have been synthesized as imaging probes for glucocerebrosidase [109]. Hartman and Coward have developed 5-fluorogalactosyl phosphates as inhibitors of galactosyltransferases [110].

3.3 Other Electrophiles

As they are for other proteins, diazonium ions and isothiocyanates [111] are useful affinity labels for glycosidases. In 1976, Sinnott and Smith reported inactivation of *E. coli* β-galactosidase using the galactosyl *p*-nitrophenyltriazine **12** [112] that decomposes to form a reactive diazonium ion then alkylates an active site methionine. Interestingly, a closely related anomeric diazoketone derivative of galactopyranose inactivates β-galactosidase from *A. oryzae* but not from *E. coli* [113]. Johnson and Houston have shown that boronic acid-tethered iminosugar mimics of galactose (**13**) are selective inhibitors of β-galactosidase (presumably through Lewis acid-base interaction with the same methionine that is alkylated by **12**) [114]. The boron is also capable of forming a charge-balanced Lewis acid-base complex with the nitrogen of the inhibitor thus protecting the amine from certain biochemical reactions.

Quinone derivatives can alkylate glycosidases causing irreversible inhibition; for example, the thiosugars **14** and **15** are inactivators of *A. faecalis* β-1,4-glucosidase with second-order rate constants [115]. The natural product salicortin is a suicide substrate of this enzyme and has been shown to react through a quinone methide intermediate [116]. Because this reactive species is formed when the compound is bound to the enzyme, it is a highly selective inactivator—Fig. (**9**). Natural product discoveries continue to provide a diverse array of pharmaceutical leads for glycosidase inhibitors, while others (cyclophellitol, salacinol) confirm the functional group choices already demonstrated in synthetic inhibitors.



12 **13** **14,** R = H **15,** R = Cl

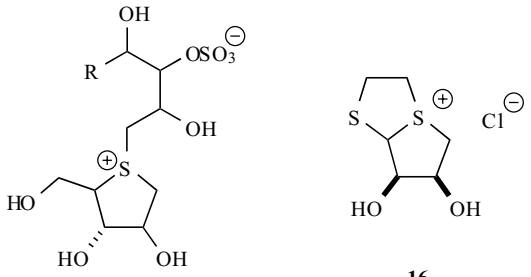
Salicortin

Fig. (9). Inactivators and inhibitors of β-galactosidase and β-glucosidase.

4. RECENT NATURAL PRODUCT LEADS

4.1 Salacinol and Derivatives

Inhabitants of India and Sri Lanka have long used extracts from *Salacia reticulata* to treat diabetes, but it was not until 1997 that the structure of a unique constituent salacinol, Fig. (**10**), was reported and demonstrated to inhibit α-glucosidase [117]. The related natural product kotalanol has the same core structure and is also charge balanced by virtue of an *O*-sulfate at C-3' [118]. The sulfonium ion in these compounds is a ground state mimic of the electron deficient transition state of glycoside hydrolysis. Unlike ammonium species formed by protonation of iminosugars such as DNJ, the charge of salacinol is permanent. In fact, replacement of the sulfur in salacinol with nitrogen to create a quaternary ammonium salt reduces its glycosidase inhibition activity markedly [119, 120]. Sulfonium ions were first demonstrated to inhibit glycosidases by Grierson using the synthetic compound **16**, a mannosidase inhibitor [121], and Pinto has reported the synthesis of the sulfonium analog of castanospermine [122]. The 7-thia-3a-thioniaperhydropentalene (**16**) is more potent than deoxymannojirimycin as an inhibitor of lysosomal mannosidases and more selective than swainsonine versus these enzymes.



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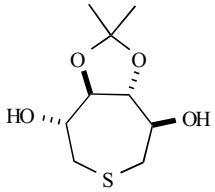

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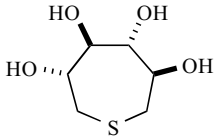

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Fig. (10). Sulfur heterocycle glycosidase inhibitors.

Much effort has been directed toward the total synthesis of salacinol and its derivatives in the past five years [123]. Yuasa and coworkers achieved the first total synthesis in 2000 [124] and another synthesis has been reported since [125]. Replacing the sulfur with selenium provides a compound with improved activity versus glucoamylase, but not α-amylase [126]. It is likely that sulfonium carbohydrate mimics will be developed for a wide range of glycosidases. The sulfonium motif has been utilized in the production of a fucosidase inhibitor that was shown to be 700 times more potent than the analogous uncharged sulfide [127]. Neutral, ring-expanded sulfides have, however, been shown to inhibit glucosidases. Intriguingly, the acetonide derivative **17** is a better inhibitor of α-glucosidase than the unprotected tetrahydroxy thiepane **18** [128]. It will be interesting to see how the inhibition profiles of sulfonium derivatives of these two compounds compare to the neutral sulfides.

4.2 Protein and Cyclic Peptide Inhibitors

Many plants synthesize their own proteinaceous inhibitors of glycosidases to protect themselves from pathogens. In 1971, Albersheim and Anderson first identified proteins in several plant cell walls that inhibited polygalacturonases of pathogenic origin [129]. The following decade, an endogenous α-amylase inhibitor was discovered in the kernels of barley [130]. Study of the interactions between these proteins and the enzymes they inhibit can offer guidance for creating alternative inhibitors. The crystal structure of a natural protein inhibitor from *Phaseolus vulgaris* in complex with human pancreatic α-amylase has been solved and a crucial arginine residue in the inhibitor has been identified [131]. Structural information from the interaction between xylanase-inhibiting protein XIP-I and xylanases from two different *Aspergillus* species has recently been obtained to decipher a 300-fold difference in binding affinity between these isozymes [132].

Natural cyclopentapeptide inhibitors of chitinase have been cocrystallized with the enzyme revealing how this natural product replaces the oligosaccharide substrate [133]. Simple cyclic dipeptides have also been identified as glycosidase inhibitors and since these compounds form six-memebered rings, they are related to the lactam inhibitors discussed in the first category of this review [134, 135]. Some of these carbohydrate-type lactams, such as mannonic-δ-lactam, have been shown to arise from microbial oxidation of the nojirimycin-type structure and are thus metabolites of natural inhibitors [136]. Cyclic peptide glycosidase inhibitors have also been identified from phage-displayed peptide libraries—cyclic KCHFEECLAY was discovered as a competitive inhibitor of α-glucosidase and glucoamylase using this method [137].

Catalytic antibodies with glycosidase-type activity have been developed by both Masamune [138] and Schultz [139]. These antibodies are generated using a hapten that captures the electrostatic and conformational biases of the transition state of glycoside bond cleavage. The latter example employed a DNJ derivative to create novel antibody-based glycosidases that accelerated anomeric bond hydrolysis of *p*-nitrophenyl β-D-glucopyranoside by five orders of magnitude over the acetic acid-catalyzed reaction. More importantly, these antibodies discriminate between stereochemical differences at the anomeric center as well as other positions on the monosaccharide [139]. Based on the conservation of active site carboxylates in glycosidases, it is not surprising that Asp/Glu residues have been identified as the acid catalysts in these antibodies. Understanding what ground state features can elicit a glycosidase-like antibody and probing the amino acids responsible for this activity will further aid the development of glycosidase inhibitors.

4.3 Aromatic and Conjugated Systems

Carbohydrate processing enzymes, including glycosidases, and carbohydrate binding proteins such as

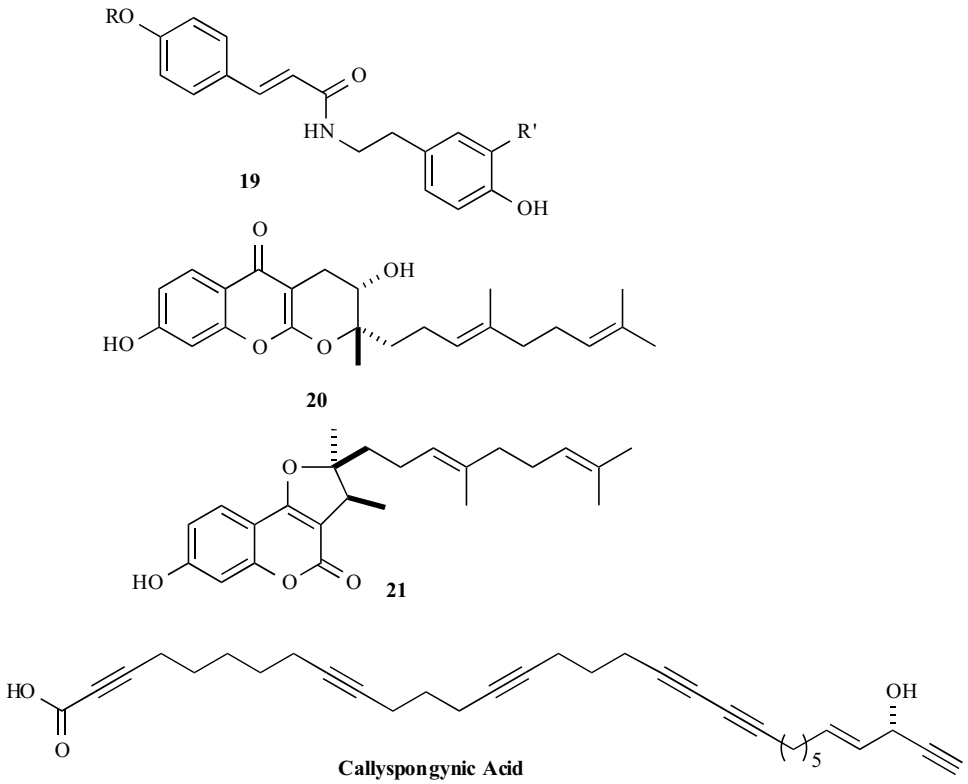

Fig. (11). Natural product glycosidase inhibitors.

lectins often contain aromatic amino acids in their binding sites to complement hydrophobic surface area on the substrate. The relative amount of hydrophobic surface area generally decreases with increasing oligosaccharide length (monosaccharide>disaccharide>trisaccharide), but simple monosaccarides can contain more surface area that is hydrophobic than is hydrophilic [140]. A number of aromatic compounds can inhibit glycosidases; for example, 3',4',7-trihydroxyisoflavone is an inhibitor of β-galactosidase, *N-p*-coumaroyltyramine (**19**, R=R'=H) can inhibit α-glucosidase, and related natural products of this type have recently been isolated from *Cuscuta reflexa*, Fig. (**11**) [141]. Methyl gallate and the flavone baicalein from *Scutellaria baicalensis* are also α-glucosidase inhibitors with activity against human intestinal sucrase [142]. The soy isoflavone genistein is a remarkably potent, non-competitive inhibitor of α-glucosidase (K_i = 57 nM) [143]. Several sesquiterpanoids found in a Mongolian plant medicine (e.g. **20** and **21**) have been reported by Choudhary and Atta-ur-Rahman to possess α-glucosidase inhibitory properties [144]. Finally, the marine sponge secondary metabolite callyspongynic acid is the latest in a series of polyacetylenic carboxylic acids that have activity versus α-glucosidase [145].

5. FUTURE DIRECTIONS

Glycosidase Inhibition without Carbohydrate-type Structures

It is apparent from the variety of natural products that are capable glycosidase inhibitors that close mimicry of monosaccharide structure is unnecessary for tight binding to exoglycosidase active sites. Hashimoto and co-workers have recently developed phthalimide-based inhibitors of α-glucosidase more potent than DNJ, Fig (**12**) [146]. Structure-activity relationships have revealed the importance of hydrophobic substituents on the nitrogen and the benefit of electron-withdrawing groups on the aromatic ring. The aromatic dye suramin inhibits heparanase (an endo-β-glucuronidase) from metastatic melanoma [147], and the stable 2,2-diphenyl-1-picrylhydrazyl free radical was recently found to be an α-glucosidase inhibitor [148]. Abbott has developed charge-balanced influenza sialidase inhibitors, A-192558 (**22**) [149] and A-315675 (**23**) [150], which retain only a faint resemblance to the natural substrate. None of

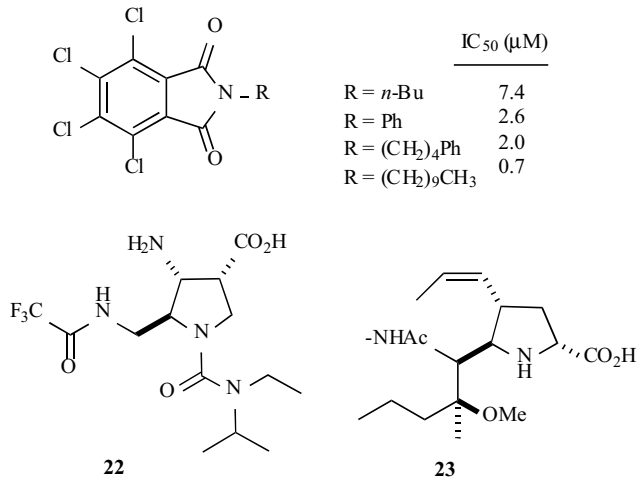

Fig. (12). New generations of glucosidase and sialidase inhibitors.

these compounds contain a free hydroxyl group, the insignia of carbohydrates. Indeed, with the generally low affinities of proteins for monosaccharide ligands, opportunities for development of non-carbohydrate based glycosidase inhibitors seem to be a potentially rich and currently under-cultivated field.

6 CONCLUSIONS

As work on lactam, epoxide and halide derivatives has seen a resurgence in recent times, the field of glycosidase inhibitors has returned to its roots—the seminal work of Ezaki, Levvy, Legler and many others in the mid-1900's. It is interesting to note that epoxide and sulfonium ion inhibitors were developed in synthetic systems well before they were discovered to occur naturally. Natural product research has uncovered some unusual structures that bear little similarity to most synthetic compounds that have been developed so far. The success of alkaloid-type amino- and iminosugars as the most important class of glycosidase inhibitors is obvious and research into these systems continues to expand. However, the discoveries of salacinol and phthalimide-based glucosidase inhibitors offer new paradigms for expanding research. The medicinal chemist can take advantage of the confluence of structural information regarding both inhibitors and glycosidases to push these boundaries further beyond the scope of simple monosaccharide mimics. It is anticipated that the next generation of glycosidase inhibitors used in medicine will look quite different to those of today [151].

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