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Carbohydrate Mimetics-Based Glycosyltransferase Inhibitors

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Abstract—The search for carbohydrate mimetics-based glycosyltransferase inhibitors is a dynamic field that emerged 10 years ago. This review presents a description of the different types of glycosyltransferase inhibitors containing a carbohydrate mimetic (primarily an iminosugar, a carbasugar or a *C*-glycoside) and data on their biological activity whenever such data are available. The purpose of this account is to foster a synergy between the two expanding research areas of glycomimetics and glycosyltransferases.

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Introduction

The spectacular development of carbohydrate mimetics, prompted primarily by their properties as glycosidase inhibitors, has led to a wide variety of novel structures, the most significant ones belonging to the families of iminosugars and carbasugars.[1] In parallel, major progress in glycobiology has provided evidence for the importance of oligosaccharides and glycoconjugates, the considerable structural diversity of which is used by Nature for encoding biological information in a number of fundamental processes such as intercellular recognition, metastasis and immune response.[2,3] Consequently, the biosynthesis of polysaccharides and glycoconjugates mediated by glycosyltransferases has attracted increasing interest.[4–6]

Glycosyltransferases are divided in two groups: the enzymes of the Leloir[7] pathway which are responsible for the synthesis of most glycoproteins and other glycoconjugates in mammalian systems and those of non-Leloir pathways which typically utilize glycosyl phosphates or sucrose as activated donors.[8] This review will focus on the enzymes of the first group which catalyze the transfer of a sugar moiety from an activated nucleotide sugar to the hydroxyl group of an acceptor which may be a growing oligosaccharide, a lipid or a protein (Fig. 1).[9] Depending on the glycosyltransferase, this process may occur with inversion or retention of the anomeric configuration.[10]

As little information is yet available on the 3-D-structure of glycosyl transferases,[11] it is likely that much of the knowledge on the glycosyl transfer at the molecular level will be gained in the coming years from studies using substrate analogues and inhibitors. Different strategies have been used in order to identify potent inhibitors of glycosyltransferases.[12] The most important ones are the design of acceptor analogues, of donor analogues (i.e., unreactive sugar nucleotide),[13] and of transition state mimetics including bisubstrate or trisubstrate analogues. Nevertheless, rational design of glycosyltransferase inhibitors still remains a difficult task due to intrinsic features of glycosyltransferases: complex four-partner transition state (sugar donor, acceptor, metal, nucleotide), weak binding of the enzyme with their natural substrates (usual K_m values are in the mM range) and few structural data. Moreover, many aspects of the catalytic mechanisms of glycosyltransferases are still unknown.[11b,14]

Despite an increasing number of potential inhibitors, only a few of them have exhibited significant activity. From these studies, a new generation of inhibitors based on carbohydrate mimetics has recently emerged. Compounds of this family are structurally altered analogues of carbohydrates designed to simulate the shape and most functionalities of the natural substrates in the ground state or in the transition state, with the goal of modulating their biological activities.[15] The most common structural modification is the replacement of the endocyclic and/or the glycosidic oxygen atom by a heteroatom or by a carbon atom. In the case of inhibitors of glycosyltransferases, carbohydrate mimetics are often used to imitate the transition state of the enzymatic reaction, rather than the ground state, promising a better inhibition than the natural carbohydrate substrate. The field of carbohydrate mimetics is thus well positioned to provide a rich source of inspiration for the design of novel types of glycosyltransferase inhibitors.

The goal of this review is to stimulate further research in this area by providing a description of the different types of inhibitors containing a carbohydrate mimetic that have been reported since the early 1990's, and data on their biological activity whenever such data are available.

Iminosugar Derivatives and Analogues

Owing to their remarkable biological activities, iminosugars form certainly the most attractive class of carbohydrate mimetics reported so far. Since Paulsen's[16] pioneering work on sugars with nitrogen instead of the ring oxygen and the discovery of such a natural product,[17] numerous iminosugars have been synthesized or discovered opening a dynamic research area. As potent glycosidase inhibitors, iminosugars promise a new generation of carbohydrate based therapeutics for the control of various diseases including diabetes, cancer and viral infections.[18] The ability of iminosugars to become protonated in biological medium and to form a cation which can interact strongly with an anionic group (carboxylate) at the enzyme active site explains their high affinity for glycosidases.[19] In the case of piperidinols, the spatial arrangement of the hydroxyl groups resembles closely that of the natural substrates in their ground conformation, whereas in the case of pyrrolidinols the flattened structure of the five-membered ring is believed to mimic the half chair structure of the glycosyl cation involved as an intermediate (or a transition state) in the enzymatic mechanism. Consequently, pyrrolidinols are usually more potent but less selective than piperidinols as glycosidase inhibitors.[18a]

Less than 10 years ago, pyrrolidinols, piperidinols and also morpholine or simple pyrrolidine derivatives have been used to design potential glycosyltransferase inhibitors. Since glycosyltransferase reactions are thought to proceed through transition states similar to those of glycosidase reactions,[11b,f,14] iminosugars have become a very important source of new substrate analogues for the study of glycosyltransferases.

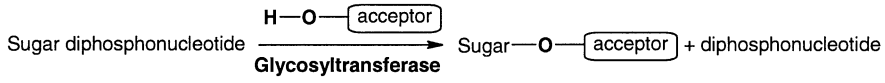


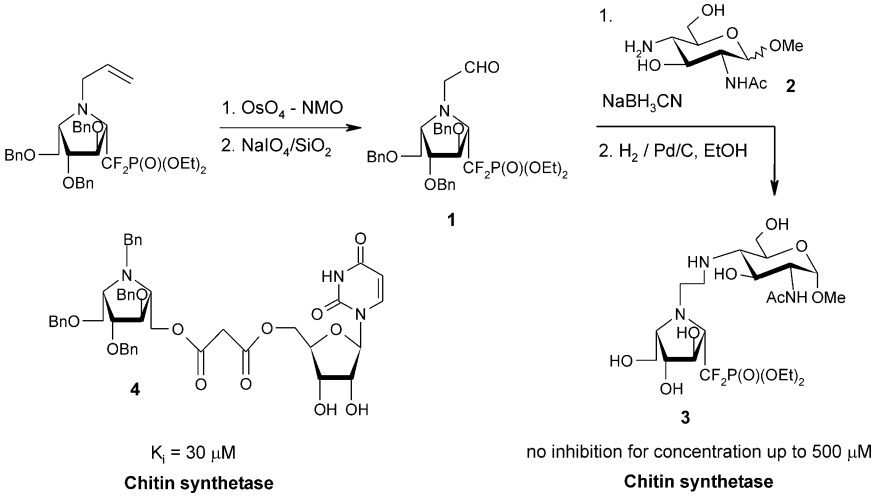
Figure 1. Glycosyltransferase-catalyzed glycosylation using sugar nucleotides as glycosyl donor.

Pyrrolidinols

Chitin synthetase inhibitors. Recently, Guillerm et al. have followed two different strategies in order to find novel inhibitors of chitin synthetase, an enzyme which catalyses polymerization of *N*-acetyl-D-glucosamine starting from UDP-GlcNAc. Such compounds are of interest also as potential antifungal agents. The authors have designed the bisubstrate analogue **3** which contains a pyrrolidine-type iminosugar to mimic the half chair conformation of the glycosyl cation in the postulated transition state and an amino GlcNAc derivative to mimic the acceptor partner.[20] The key step of the synthesis is the coupling of the diamino sugar **2** with the aldehyde **1** by way of a reductive amination using $NaBH_3CN$ (Scheme 1). Inhibition studies have shown that the bisubstrate analogue **3** did not inhibit chitin synthetase activity for concentration up to 500 μM. In a second approach,[21] Guillerm et al. have designed the sugar nucleotide analogue **4** in which both the sugar and the pyrophosphate group are modified. For stability reasons, the benzyl protective groups were not removed. The analogue **4** exhibited modest but encouraging activity against chitin synthetase ($K_i = 30$ μM) compared to that of the natural product Nikkomycin Z, used as reference ($K_i = 0.6$ μM).

β-1,4-Galactosyltransferase inhibitors. One of the most studied glycosyltransferase, the galactosyltransferase from bovine milk catalyses the transfer of galactose from UDP-galactose to the 4-OH of *N*-acetyl-glucosamine residues. Other galactosyltransferases of particular biological interest are involved in the biosynthesis of many cell surface oligosaccharide structures such as blood group antigens and sialyl Lewis x, a ligand for E-selectin involved in tumor development and inflammatory process.[22] As potent transition state-like inhibitors of various glycosidases,[23] four simple dehydro pyrrolidinol derivatives **5**–**6** were screened using electrospray mass spectrometry. Not surprisingly, these compounds were found to be weak inhibitors of β-1,4-galactosyltransferase (Fig. 2).[24] In another study of the same group,[25] five-membered iminoalditols **7**–**8** with a pseudo *galacto*-configuration showed some inhibitory activity except **7a** and the designed transition state analogue **8c**. Compound **8a** was as potent an inhibitor as UDP and the inhibition versus UDP-Gal was shown to be uncompetitive.

In a search for pyrophosphate mimics, Wong et al. investigated malonic and tartaric moieties as replacement of the pyrophosphate using pyrrolidinols with potent galactosidase inhibitory activity as the donor



Scheme 1. Synthesis and evaluation of chitin synthetase inhibitors.[20,21]

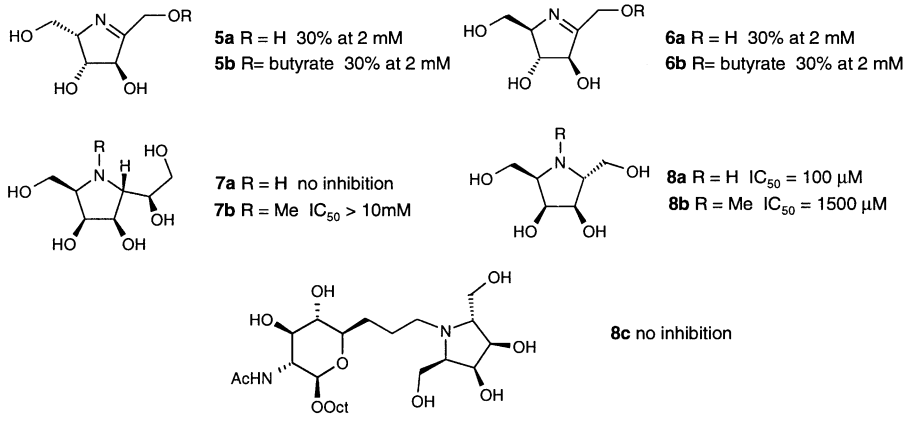


Figure 2. Evaluation of pyrrolidinols as β-1,4-galactosyltransferase inhibitors (% inhibition or IC_{50} value).[24,25]

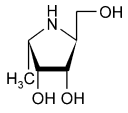
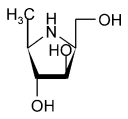
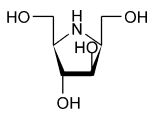
component.[26] Among the four compounds tested, only **12** with the pseudo *galacto* configuration showed some inhibition with a K_i of about 1 mM (Fig. 3). Interestingly, the analogue **11** containing a galactopyranose moiety exhibited no inhibition, which underlines the fact that the pyrrolidine may somehow compensate for the weakness of the malonic diester as a pyrophosphate substitute.

***α*-1,3-Fucosyltransferase inhibitors.** Human α-1,3-fucosyltransferase V (FucT V) catalyses the transfer of the L-fucose moiety from GDP-fucose to the 3-OH group of *N*-acetylglucosamine in sialyllactosamine to produce sialyl Lewis x (Fig. 4). Inhibitors of α-1,3-fucosyltransferase may provide a useful therapy for controlling inflammatory processes such as arthritis or for fighting tumor growth.[27]

The potential of simple pyrrolidinols as α-1,3-fucosyltransferase V inhibitors has been studied by Wong et al. (Table 1). The five-membered ring iminosugar analogue of fucose **14a** and its epimer **14b** have been efficiently prepared from the azido-aldehydes **13a** and **13b** following a chemo-enzymatic synthesis.[28] For example, reaction of the aldehyde **13a** with dihydroxyacetone 3-phosphate (DHAP) catalyzed by fuculose 1-phosphate aldolase afforded the expected pyrrolidinol **14a**, after removal of the phosphate group and reductive amination (Scheme 2).

The iminosugars **14a**,**b** and **15**, which are competitive inhibitors of α-L-fucosidase (K_i in the μM range), were found to be weak inhibitors of α-1,3-fucosyltransferase V (IC_{50} = 34–80 mM).[28–30]

Table 1. Inhibition of human α-1,3-fucosyltransferase V[28–30]

Inhibitors	% of inhibition α-1,3 FucT
 **14a**	50% at 80 mM
 **14b**	50% at 34 mM (K_i = 19 mM)
 **15**	50% at 52 mM
14a + 0.05 mM GDP	90% at 34 mM
14b + 0.05 mM GDP	80% at 80 mM

Very interestingly, the two pyrrolidinols **14a** and **14b** showed a strong synergistic inhibition of the fucosyltransferase in the presence of GDP. At the IC_{50} concentration and with 0.05 mM of GDP, more than 80% of the enzyme activity was inhibited (Table 1). According to the authors, this observation indicates that GDP and the iminosugar may form a complex in the active site which mimics the transition state of the fucosyltransfer reaction as depicted in Figure 5.[31a]

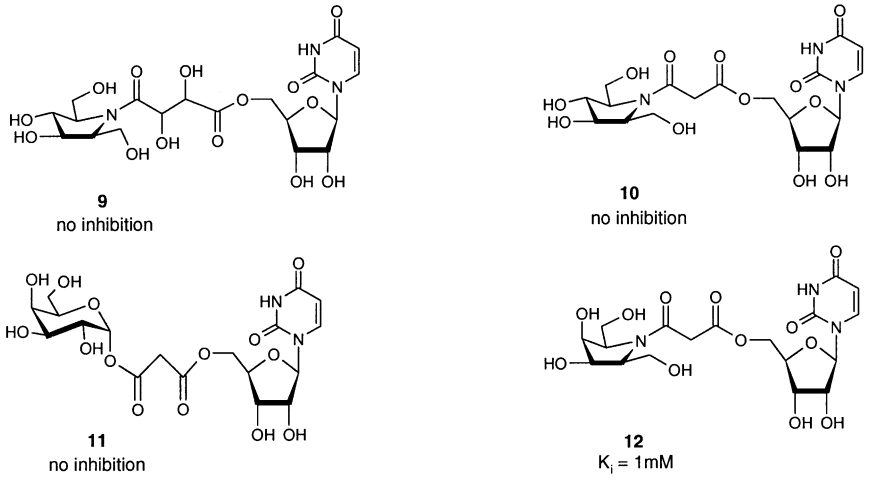


Figure 3. Evaluation of potential β-1,4-galactosyltransferase inhibitors.[26]

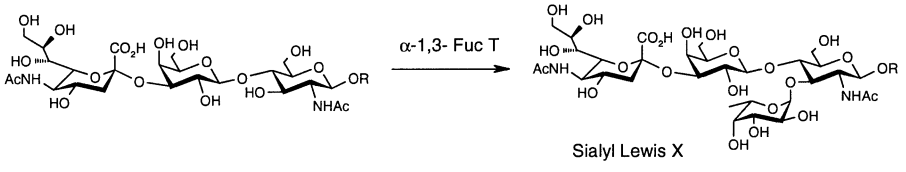
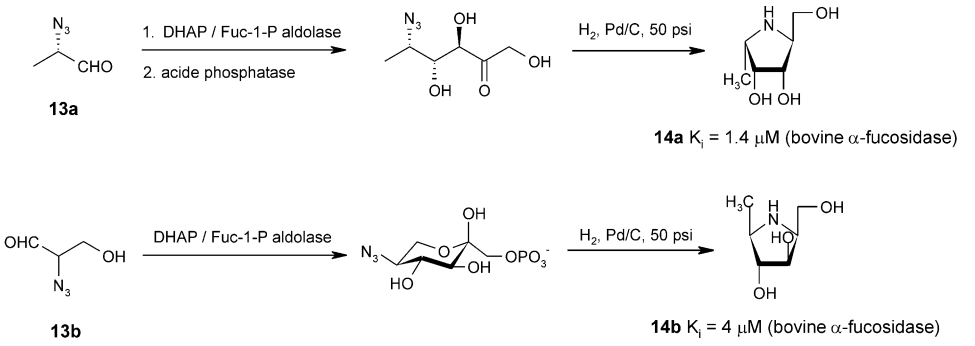


Figure 4. Fucosylation of sialyllactosamine.



Scheme 2. Synthesis of pyrrolidinols **14a** and **14b**.[28]

Ceramide glucosyltransferase inhibitors. Ceramide glucosyltransferase uses UDP-glucose as its donor substrate and normal fatty acid (NFA) ceramide as the glucose acceptor in vivo and 2-hydroxy fatty acid (HFA) ceramide in vitro (Fig. 6). As this enzyme plays an important role in the biosynthesis of glycosphingolipids, the search and discovery of selective inhibitors is of great interest and for example could constitute significant progress toward the treatment of Gaucher disease, one of the most common glycosphingolipid (GSL) storage disorder.[32]

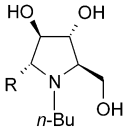
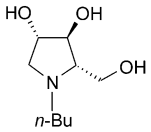
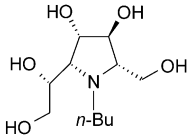
Very recently, Butters et al. have examined the relationships between structural features of various iminosugars and α-glucosidase and ceramide glucosyltransferase inhibitory activity in order to increase the selectivity of their designed inhibitors toward the transferase.[33] The authors assume that the cyclic constitution and the conformation of the *N*-alkylated iminosugars mimic the ceramide acceptor substrate rather than the transfered sugar unit on the basis of the fact that inhibition of ceramide glucosyltransferase by *N*-butyl-1-deoxynojirimycin is competitive for ceramide ($K_i = 7.4\,\mu M$) and non-competitive for UDP-glucose. All the five-membered ring iminosugars tested displayed promising inhibition activity in vitro but only **16a** was found to be active in cultured tissue cells with an activity comparable to *N*-butyl-1-deoxynojirimycin and a better selectivity toward α-glucosidase (Table 2). Results obtained with piperidinols are shown in the following section.

Piperidinols

Ceramide glucosyltransferase inhibitors. Among the numerous piperidinols tested, *N*-butyl-1-deoxynojirimycin **18d** and particularly *N*-butyl-1-deoxygalactonojirimycin **19a** exhibited the best selectivity towards ceramide glucosyltransferase in the cultured tissue cells assay (Table 3).[33,34] *N*-Butyl-1-deoxynojirimycin has been engaged very recently in a clinical trial as a potential therapy for the Gaucher disease. The first promising results have shown clear improvement in organ volume and haematological variables which warranted further exploration of *N*-alkyl iminosugars.[32]

α-1,3-Fucosyltransferase inhibitors. A great diversity of piperidinol-based structures have been investigated as potential inhibitors of the α-1,3-fucosyltransferase (Table 4). Among these compounds, bisubstrate analogues are the best inhibitors.[29,31,35] It is noteworthy that compound **25**,[35] the best inhibitor reported, make use of two carbohydrate mimics: an iminosugar for the fucose moiety and a phenol as a simple mimic of GlcNAc which appears to be better than GlcNAc itself; compound

Table 2. Inhibition of ceramide glucosyltransferase[33]

Inhibitors	Ceramide glucosyltransferase %inhibition (in vitro at 200 μM)	Ceramide glucosyltransferase %inhibition (in tissue culture at 0.5 mM)
		
16a R=CH_2OH	86	93–100
16b R=H	21	No inhibition
16c R=CH_3	11	No inhibition
 **17a**	25	No inhibition
 **17b**	6	No inhibition

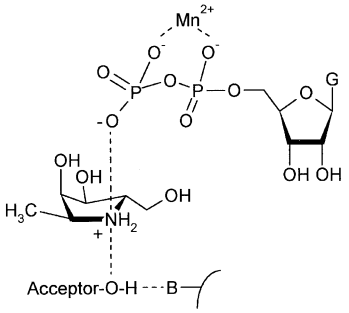


Figure 5. Model for the synergistic inhibition of α-1,3-fucT V proposed by Wong et al.[31a]

25 is indeed a stronger inhibitor than the trisaccharide derivative **28**.[31a] Although the iminosugar containing acceptor analogue **29a** is an inhibitor, the close 5-thiosugar analogue **29b** is a good substrate with a relative velocity of 51% compare to lactosamine (entry 7,8). As

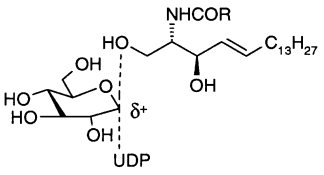
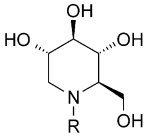
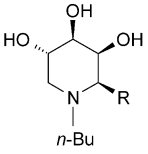
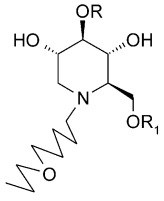
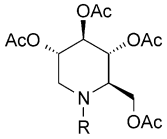
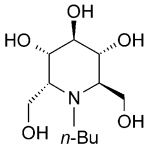
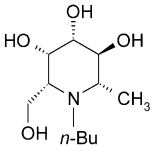
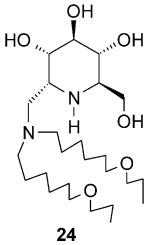


Figure 6. Model for the transition state of the ceramide glucosyltransferase reaction.

in the case of the two pyrrolidinols **14a** and **14b** (Table 1), a strong synergistic effect in the presence of GDP has also been observed (entry 2, 6, 12).

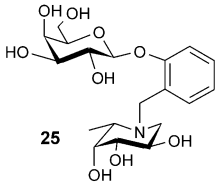
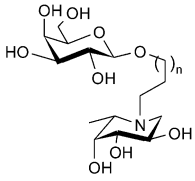
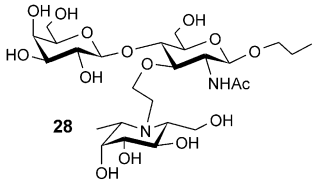
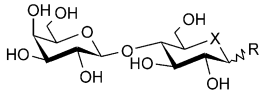
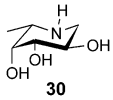
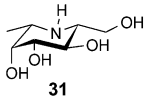
α-1,3-Galactosyltransferase inhibitors. α-1,3-Galactosyltransferase is responsible for the transfer of an α-galactose unit to the O-3′ of LacNAc; the design of inhibitors of this transfer is important in relation to problems of xenotransplant rejection caused by the recipient's anti-Gal antibody reaction to the donor's α-Gal epitope (3′-

Table 3. Inhibition of ceramide glucosyltransferase[33]

Inhibitors	Ceramide glucosyltransferase %inhibition (in vitro at 200 μM)	Ceramide glucosyltransferase %inhibition (in tissue culture at 0.5 mM
 **18a** R = –$(CH_2)_6O(CH_2)_2CH_3$	97	100
18b R = –$(CH_2)_8CH_3$	96	93 (at 0.01 mM)
18c R = –$(CH_2)_6O(CH_2CH_2O)_2CH_3$	93	87
18d R = *n*-Butyl	87	93–100
18e R = benzyl	73	93
18f R = –$(CH_2CH_2O)_3CH_3$	20	43
18g R = H	No inhibition	No inhibition
 **19a** R = –CH_2OH	71	93–100
19b R = –CH_3	No inhibition	No inhibition
 **20a** R = H R_1 = –$C(O)(CH_2)_2CH_3$	25	No inhibition
20b R = Me R_1 = H	No inhibition	27
 **21** R = –$(CH_2)_5O(CH_2)_2CH_3$	18	72
 **22**  **23**	No inhibition	No inhibition
 **24**	3	No inhibition

O-α-galactosylated LacNAc).[36] Very recently, Ichikawa et al. have reported the synthesis of the 1-*N*-iminosugar-based UDP-galactose analogue **35**, which was found to be a potent and selective inhibitor of the α-1,3-galactosyltransferase but not of the β-1,4-galactosyltransferase (Fig. 7).[37] Azasugars **32**–**35** have been designed to inhibit the enzyme activity by forming a strongly associated complex in the active site via favorable electrostatic

Table 4. Inhibition of α-1,3-fucosyltransferases

Entry	Inhibitors	α-Fucosyltransferase IC_{50} (mM)	References
1[a]	 **25**	0.081	35
2[a]	**25** + 2 μM GDP	0.05	35
3[a]	 **26** $n=1$	>0.5	35
4[a]	**27** $n=2$	0.233	35
5[b]	 **28**	5.7	31a
6[b]	**28** + 30 μM GDP	0.031	31a
7[c]	 **29a** X=NH, R=H	8	29
8[d]	**29b** X=S, R=OH	—[d]	29
9[a]	 **30**	3.5	35
10[b]	**30**	73.1	31a
11[b]	 **31**	71.5	31a
12[b]	**31** + 30 μM GDP	1.54	31a

[a]α-1,3-Fucosyltransferase IV with 8.5 μM of GDP-fucose.
[b]α-1,3-Fucosyltransferase V with 25 μM of GDP-fucose.
[c]α-1,3-Fucosyltransferase V with 100 μM of GDP-fucose.
[d]Substrate of α-1,3-fucosyltransferase V (K_m = 12 mM).

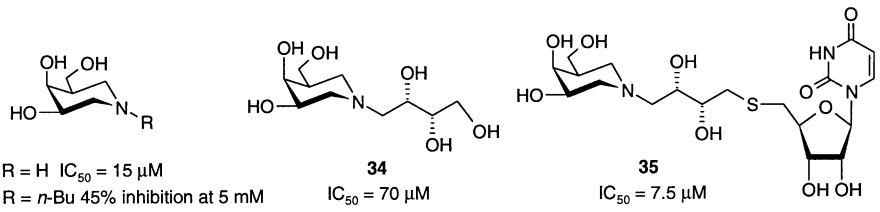


Figure 7. Inhibition of α-1,3-galactosyltransferase.[24,37]

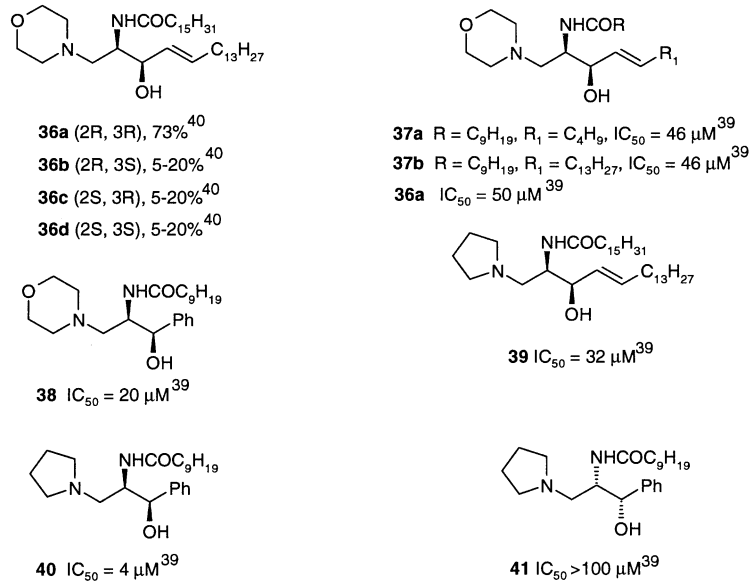


Figure 8. Inhibition of ceramide glucosyltransferase (% inhibition at 5 μM or IC_{50} value).[39,40]

interaction (hydrogen-bonded ion pair) in a manner similar to inhibitors of retaining glycosidases.[18a] It is noteworthy that 1-deoxygalactonojirimycin showed no inhibition toward the α-1,3-galactosyltransferase nor toward the β-1,4-galactosyltransferase.[24] These results indicate clearly that the position of the imino-group is crucial for the recognition of the piperidinols by the enzyme.

Surprisingly, analysis of the inhibition kinetic data indicated that neither **35** nor **32** showed a competitive mode of inhibition against UDP-Gal even though **35** is a UDP-Gal analogue. The authors suggested that **35** and **32** may interact not only with the free enzyme but also with the enzyme substrate complex.[37]

Morpholino- and pyrrolidinosphingolipid derivatives

In 1987, Inokuci and Radin[38] have shown that D-*threo*-1-phenyl-2-decanoylamino-3-morpholino-1-propanol (PDMP) **38** was an active competitive inhibitor of ceramide glucosyltransferase. This finding prompted investigations on a number of morpholino-, piperidino-, and pyrrolidino-derivatives of sphingosine and ceramide.[39,40] Among the different compounds tested, strongest inhibitions were found for stereoisomers having the unnatural (*R*,*R*)-configuration of D-*threo*-sphingosine (Figs 6 and 8). In addition, the pyrrolidino derivatives were slightly more potent than the morpholino derivatives (comparison between **36a** and **39** and between **38** and **40**).

Miscellaneous inhibitors

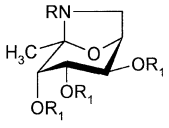
Fleet et al. have recently described the synthesis of a rigid bicyclic mimic of α-L-fucose **42a** which was found to be a selective and strong inhibitor of human liver and human placenta α-fucosidases ($K_i = 6$ and 68 μM, respectively) but a weak inhibitor of human α-1,3-fucosyltransferase ($IC_{50} = 35$ mM) (Fig. 9).[41] No enhancement of inhibition was observed with the *N*-alkylated analogues **42b** and **42c**.

In 1975, Berliner et al. reported the synthesis of a spin-labeled analogue of UDP-galactose, UDP-4-*O*-(2,2,6,6-tetramethyl-4-piperidinyl-1-oxy), which was found to be a competitive inhibitor of β-1,4-galactosyltransferase with a K_i of 380 μM.[42]

An interesting novel pyrrolidinol-peptidonucleoside analogue of UDP-Gal*f* has been designed recently by Fleet et al. for the study of *Escherichia coli* UDP-Gal mutase, an enzyme involve in the biosynthesis of mycobacterial cell wall.[43] Model compounds[44] or precursors of potential iminosugar-based inhibitors of glycosyltransferases have also been reported in the literature.[45]

Carbasugars and Analogues

Carbasugars[46,47] are analogues of furanoses or pyranoses in which the ring oxygen is replaced by a methylene group (branched-chain cyclitols). This class of carbohydrate mimetics, named 'pseudo-sugars' in the pioneering article of McCasland et al.,[48] are attractive because of their chemical stability as well as their interesting biological properties mainly as antibiotic[47] and as glycosidase inhibitors. For example, acarbose[49] and



42a R = R_1 = H IC_{50} = 35 mM
42b R = Bn, R_1 = H no inhibition
42c R = C_4H_9, R_1 = H no inhibition
42d R = Ac, R_1 = H no inhibition

Figure 9. Inhibition of human α-1,3-fucosyl transferase.[41]

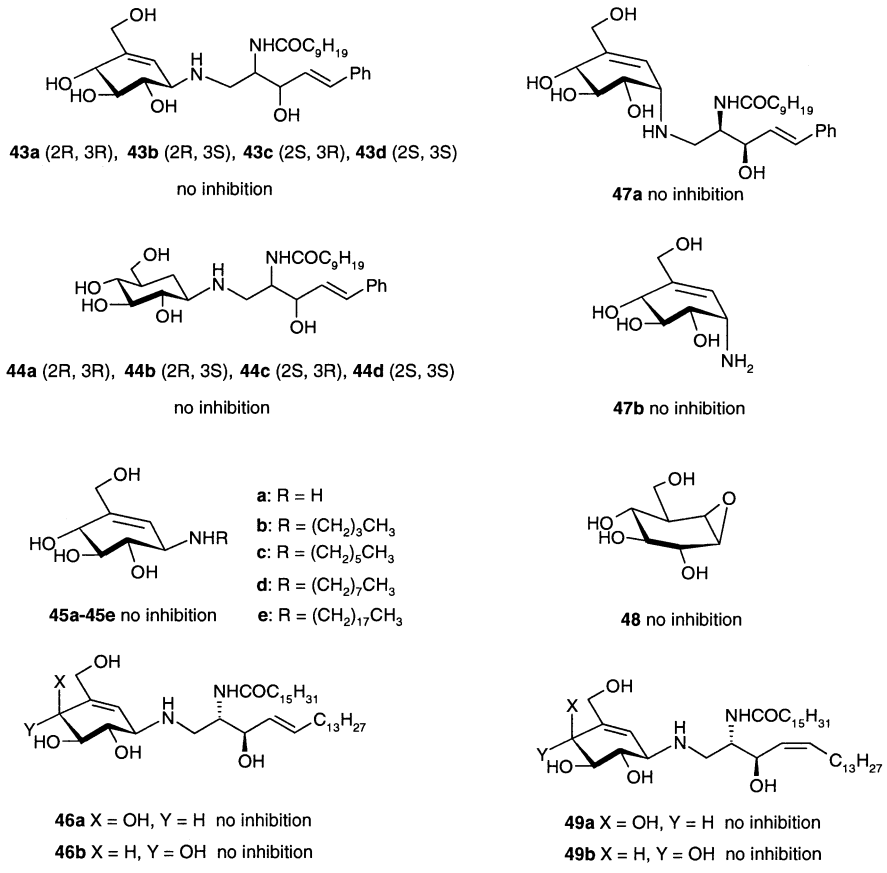


Figure 10. Biological evaluation of 5a-carba-glucosylceramide analogues as ceramide glucosyltransferase inhibitors.[51–53]

voglibose[50] are now clinically useful therapeutic agents to control diabetes.

Design of ceramide glucosyltransferase inhibitors

All 5a-carbasugar analogues of glucosylceramide (**43**–**49**) presented in Figure 10 were found to have no inhibition effect against ceramide glucosyltransferase.[51–53] Interestingly, all the compounds tested are potent inhibitors of β-glucocerebrosidase ($IC_{50} = 0.03–20\ \mu M$) except **47a**–**b** and **45a**.

Carbasugar nucleotide analogues

Sialyltransferase inhibitors. Sialic acid-containing glycoconjugate epitopes play a pivotal role in numerous important biological processes, such as inflammation and cell adhesion.[54] Therefore, efficient inhibitors of sialyltransferase might become, like sialidase inhibitors, prominent biochemical tools to elucidate the function of sialyl residues of glycoconjugates in biological systems. Consequently, they might also prove to be useful as antimetastasic, immunosuppressive or antiinflammatory agents. The various sialyltransferases use cytidine monophosphate *N*-acetylneuraminic acid (CMP-Neu5Ac) as the donor substrate (Fig. 11).

In 1980, Korytnyk et al. have prepared two simple carbasugars analogues of CMP-Neu5Ac **50a**–**b** (Fig. 12).[55] Those compounds were found to be weak inhibitors of sialyltransferases (between 2 and 28% of inhibition at 1.25 mM for ectosialyltransferase of L1210 cells and of human serum sialyltransferase).

Very recently, Schmidt et al. have reported several types of CMP-Neu5Ac analogues, some of which were potent

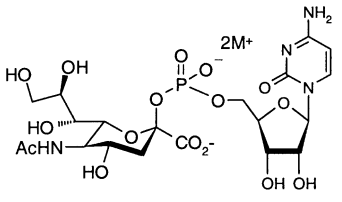


Figure 11. Cytidine monophosphate sialic acid.

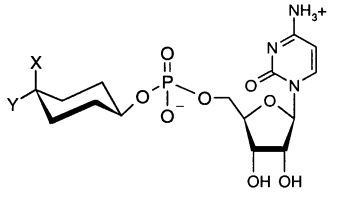
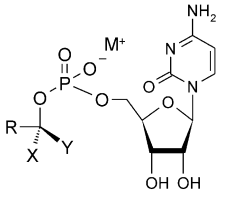
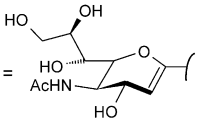
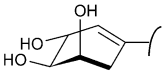
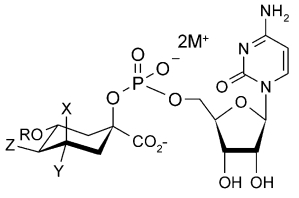
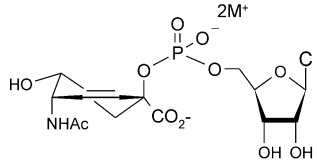
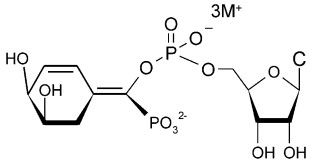
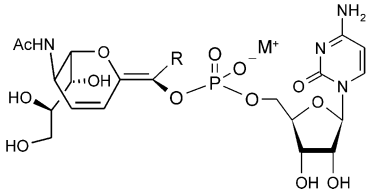


Figure 12. Evaluation of **50a**–**b** as inhibitors of sialyltransferases.[55]

sialyltransferase inhibitors (Table 5).[56,57] Donor analogues **52** showed generally comparable affinity to α-(2,6)-sialyltransferase as the natural substrate ($K_m = 46\ \mu M$).[57] As regards the design of transition state analogues, it appears that the neuraminyl residue can be replaced by a simple aryl or hetaryl moiety, to give potent inhibitors incorporating a flat pyranosyl ring mimic. For example, compounds **51f** and **51e** exhibited an activity comparable to that of **51i**. Replacement of the carboxylate group by a phosphonate group improved notably the binding affinity (**51a**–**b** compared to **51e**–**f**) (Table 5). The most potent inhibitor **55b**, with an inhibition constant $K_i = 40\ nM$ (1000-fold higher affinity than the natural substrate) combines a flattened neuraminyl residue and a phosphonate group as carboxylate surrogate. This remarkable transition state analogue paves the way for further studies devoted to the biological role of sialic acid containing glycoconjugates.

Fucosyltransferase inhibitors. The first example of a carbocyclic analogue of a nucleoside diphosphosugar has been described by Toyokuni et al. (Fig. 13).[58]

Table 5. Biological evaluation of sialyltransferase inhibitors[56,57]

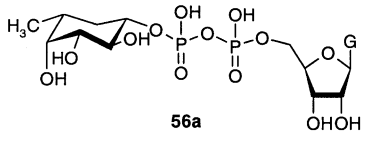
Inhibitors	Rat liver α(2-6)-sialyltransferase K_i (μM)
	
51a R = Ph, X = H, Y = CO_2Na	10
51b R = Ph, X = CO_2Na, Y = H	7
51c R = Bn, X = H, Y = CO_2Na	15
51d R = Bn, X = CO_2Na, Y = H	23
51e R = Ph, X = H, Y = —P(O)(OH)(ONa) **51f** R = Ph, X = –P(O)(OH)(ONa), Y = H	0.35–0.20
51g R = 2-furyl, X = H, Y = –P(O)(OH)(ONa) **51h** R = 2-furyl, X = –P(O)(OH)(ONa), Y = H	1–0.28
51i R =  X = –P(O)(OH)(ONa), Y = H	0.35
51j X = –P(O)(OH)(ONa), Y = H	1.60
51k R =  X = H, Y = –P(O)(OH)(ONa)	0.27
	
52a R = Y = H, X = Z = OH	44
52b R = X = H, Y = NHAc, Z = OH	84
52c R = X = H, Y = NH_3^+, Z = OH	1400
52d R = X = H, Y = NH_3^+, Z = NHAc	200
52e R = $(CH_2)_2OH$, X = Z = OH, Y = H	20
53 	15
54 	10
	
55a R = H	6
55b R = –P(O)(O)(ONa)	0.04

Preliminary inhibition assays have shown that carbasugar analogues of GDP-fucose **56** exhibit potent inhibitory activity toward α-(1→3,4)-fucosyltransferase, the activity being stronger than that of GDP.

Galactosyltransferase inhibitors. The carbasugar analogue of UDP-galactose **57** was found to be a competitive inhibitor of β-(1,4)-galactosyltransferase from bovine milk with a K_i value (58 μM) similar to the K_m value for UDP-galactose (25 μM) (Fig. 14).[59]

From these results and the preceding ones, the ring oxygen of the galactose or fucose moiety does not seem to be essential for recognition of the sugar nucleotide by the enzyme.

Glucuronosyltransferase inhibitors. Glucuronosyltransferases involved in the biotransformation of endogenous (steroid hormones and bilirubin) and exogenous toxic compounds transfer the glucuronic acid residue from UDP-glucuronic acid (UDP-GlcA) to various acceptors such as 4-nitrophenol or testosterone. The discovery of potent inhibitors active in vivo could be useful in obtaining a better insight into the role of glucuronidation in the biotransformation of drugs.[60] In 1990, van Boom et al. have designed transition-state analogues of the glucuronyl transfer based on GlcA mimetics in which the glucuronyl moiety was replaced by an aromatic group.[61] Selected inhibitors are presented in Table 6. Further kinetic studies with microsomal UDP-GlcA transferases have shown that **58b** was a competitive inhibitor with respect to both UDP-GlcA and 4-nitrophenol (K_i = 0.3 mM in both cases). The same results were obtained with compound **59c** (K_i = 0.1 mM in both cases). These aryl diphosphonucleotides did not exhibit very strong activities; the addition of a carboxylate group to the aromatic moiety may have contributed to increase significantly the activity of these compounds as glucuronosyltransferase inhibitors.



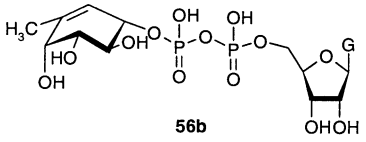


Figure 13. Carbasugar analogues of GDP-fucose.[58]

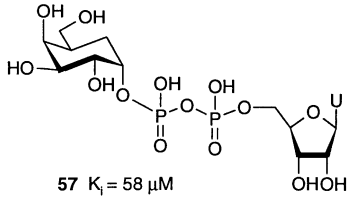
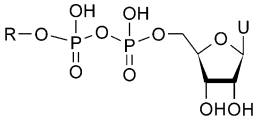
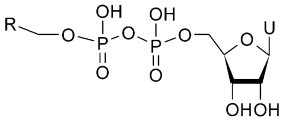
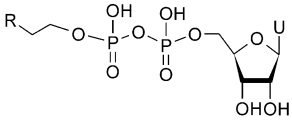
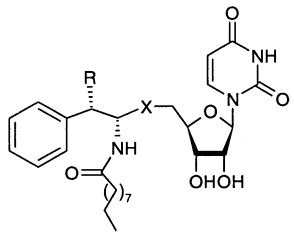


Figure 14. Carbasugar analogue of UDP-galactose **57**.[59]

In 1995, Radominska et al. described a new class of glucuronosyltransferase inhibitors in which the glucuronyl moiety was replaced by a *N*-acylated phenylalaninol group and the diphosphate bond by a carbonylaminosulfonyl linker. Selected inhibitors are presented in Figure 15.[62] Molecular modeling experiments showed that the best inhibitor found, compound **60c**, superimposed closely with the phenyl and the uridine parts of the transition state structure built according to an S_N2 transfer mechanism for the glucuronidation reaction as postulated by Noort et al.[61a]

Table 6. Inhibitory effects of aryl-diphosphonucleotides on the glucuronidation of 4-nitrophenol (assays performed with 0.5 mM of the acceptor substrate 4-nitrophenol and 0.8 mM of the inhibitor)[61]

Inhibitors (at 0.8 mM)	% inhibition
UDP	9
	
58a R = 4-chlorophenyl	11
58b R = 4-bromophenyl	79
58c R = 4-iodophenyl	50
58d R = 4-isopropylphenyl	61
58e R = 4-*t*-butylphenyl	71
58f R = 2-chlorophenyl	60
58g R = 2-bromophenyl	85
58h R = 2,5-dichlorophenyl	85
58i R = 2,6-dimethoxyphenyl	71
	
58j R = 3-methyl-2-nitrophenyl	32
	
59a R = 4-bromophenyl	23
59b R = 4-nitrophenyl	14
59c R = 1-naphtyl	81
59d R = 2-naphtyl	15



60a R=OH, X= -CH_2O-CO-NH-SO_2-O-, IC_{50} = 188 μM
60b R=H, X= -CH_2O-CO-NH-SO_2-O-, IC_{50} = 182 μM
60c R=H, X= -CH_2O-CO-CH_2-SO_2-O-, IC_{50} = 39 μM

Figure 15. Selected inhibitors of human UDP-glucuronosyltransferase UGT*6 (effects are measured with 4-methylumbelliferone as substrate).[62]

C-Glycosides

Since the early 1970's,[63] *C*-glycosides have been the subject of considerable interest in carbohydrate and bioorganic chemistry.[64] In the field of glycosyltransferase inhibitors, *C*-glycosides began to be used 10 years ago for the design of stable analogues of sugar nucleotides which can fit the requirement of the enzyme active site without undergoing enzymatic cleavage. Another interest of *C*-glycosides is the possibility of modifying the aglycon part in order to prepare bisubstrate analogues or pyrophosphate mimics.

***C*-Glycosidic sugar nucleotide analogues.** The various *C*-glycosidic sugar nucleotide analogues that have been reported are listed in Figure 16 (**61**–**64**).[65–69] Unfortunately, to the best of our knowledge, little information is available concerning their biological activity. Schmidt et al. have combined a glycal structure, to mime the hypothetic transition state, with a non cleavable C–C bond to the pseudo anomeric center.[69] The analogue **64** thus designed was found to be a good inhibitor of β-galactosyltransferase from bovine milk with an inhibition constant comparable to that of the carbasugar analogue **57** (Fig. 14). The corresponding monophosphonate of **64** exhibited a weaker binding affinity ($K_i = 1430\ \mu M$).[69]

Different types of *C*-glycosidic sugar nucleotide analogues containing a pyrophosphate mimic have also been designed (Fig. 17).[70,71] Preliminary biological studies using permeabilized cells have shown that UDP-glucose analogues **65a**–**d** had a distinct inhibiting effect on glycolipid biosynthesis.[70]

Transition state analogues

Glucuronosyltransferase inhibitors. Two different transition state analogues have been prepared by van Boom et al. (Fig. 18) as potential inhibitors of the glucuronosyltransferases.[72,73] Preliminary biological studies have shown that the two diastereomers of bisubstrate analogue **67** exert different inhibition patterns for several glucuronosyltransferases, the most pronounced activity being for UGT2B15, the isoenzyme that plays an important role in steroid glucuronidation.[72]

The design of the transition state analogue **68** was based on two points:[73] replacement of the UDP moiety by a more stable phosphonomethylene function and incorporation of the triphenylethyl moiety that is found in some inhibitors of glucuronosyltransferases.[61,74] Preliminary biological investigations indicated that **68** inhibits 4-methylumbelliferone and bilirubin glucuronidation in vitro (78 and 41% inhibition, respectively, **68** being in a 20-fold excess with respect to UDP-GlcA).[73]

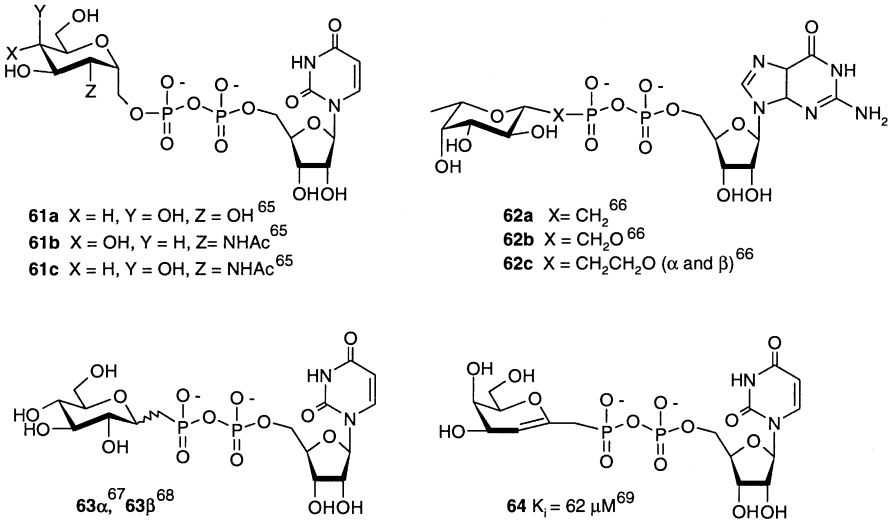


Figure 16. *C*-Glycosidic sugar nucleotide analogues.[65–69]

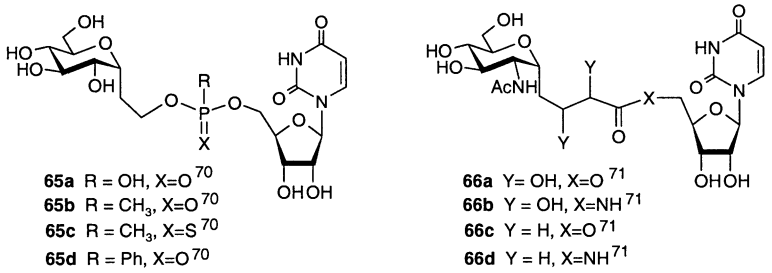


Figure 17. *C*-Glycosidic sugar nucleotide analogues based on pyrophosphate mimics.[70,71]

Fucosyltransferase inhibitors. To obtain an efficient inhibitor of α-1,3-fucosyltransferase, van Boom et al. have designed the bisubstrate analogue **69** incorporating the acceptor moiety, Glc (instead of GlcNAc), and a malonodiamido bridge instead of the pyrophosphate linkage between the guanosine and L-fucose.[75] The non-charged amide bonds were used to facilitate membrane transport (Fig. 19). Disappointingly, biological assays revealed that compound **69** exhibit no inhibitory effect on α-1,3-fucosyltransferase VI.[75b]

Very recently, Vogel et al. have synthesized two *C*-disaccharides **70a–b** by applying the 'naked sugar' strategy (Fig. 19).[76] Compound **70a** inhibits several glycosidases (for example α-L-fucosidase from human placenta with $K_i = 28\ \mu M$) and human α-1,3-fucosyltransferase VI with $K_i = 120\ \mu M$ whereas its epimer **70b** does not. Compound **70a**, which is the first *C*-disaccharide to have glycosyltransferase inhibitory activity, displayed a mixed inhibition pattern with respect to both the donor GDP-fucose and the acceptor substrate LacNAc ($K_i = 123$ and $128\ \mu M$, respectively). The authors made the hypothesis that **70a** mimics the α-L-Fuc-(1,3)-D-GlcNAc portion of the Lewis X trisaccharide (D-mannose replacing the L-fucose residue and D-GalNAc, the D-GlcNAc moiety). It is noteworthy that **70a** is a selective acceptor-based inhibitor which has no effect on human α-2,6-sialyltransferase and β-1,4-galactosyltransferase from human milk. Given the low affinity of α-1,3-fucosyltransferase VI for its natural substrate ($K_m = 32\ mM$), **70a** represents the first member of a promising new class of simple and selective inhibitors.

Conclusion

The search for carbohydrate mimetics-based glycosyltransferase inhibitors is a young and dynamic field that emerged 10 years ago. Despite the hundred or so compounds that have been evaluated on various glycosyltransferases, it is still difficult to draw general conclusions on structure–activity relationships because of the wide structural diversity of the (potential) inhibitors reported. Some features may be formulated.

First, the glycomimetics-based inhibitors tested are mainly iminosugars and carbasugars and to the best of our knowledge, no example of 5-thiopyranoses or 4-thiofuranoses have been reported.[77,78] It is noteworthy that the disaccharide **29b** containing a 5-thiosugar unit was found to be a good substrate for α-1,3-fucosyltransferase, whereas its close iminosugar analogue **29a** was an inhibitor with a IC_{50} of 8 mM (Table 4, entry 7, 8). Thus, it appears that the O→S substitution is a structural change that should be pursued in this area. As regards *C*-glycoside analogues, very few biological evaluations have been reported so far and it is therefore difficult to assess the significance of this family of mimetics.

Secondly, simple monocyclic iminosugars are weak inhibitors, generally in the mM range, except when they are used as mimic of the acceptor ceramide in the ceramide glucosylation reaction (Tables 2 and 3) and except for the very recently described pyrrolidinol **8a** (Fig. 2). In the presence of a selected nucleotide diphosphate, iminosugars exhibit strong synergistic inhibition by mimicry of the transition state.

Finally, in relation to ceramide glycosyltransferases, acceptor analogues with a morpholino or pyrrolidino moiety (Fig. 8) were found to be better inhibitors than iminosugars analogues, while carbasugars transition state analogues exhibit no inhibition at all (Fig. 10).

Very recently, decisive breakthroughs were achieved with the preparation of 1-azasugars **32** and **35**, first members of a simple class of potent and selective inhi-

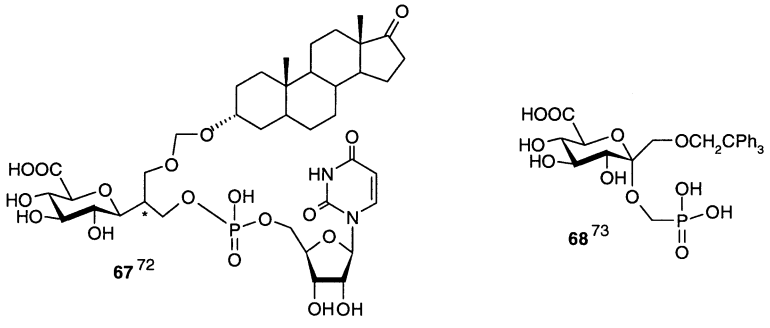


Figure 18. Potential glucuronosyltransferase inhibitors.[72,73]

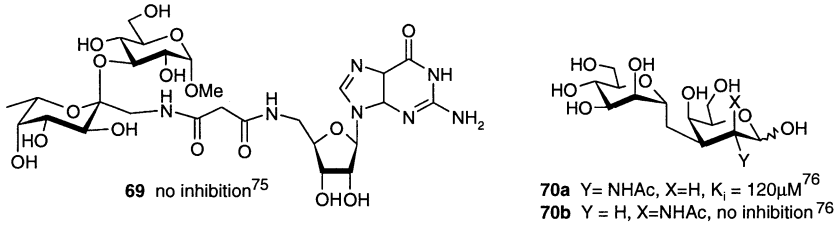


Figure 19. Designed analogues for the inhibition of α-1,3-fucosyltransferases VI.[75,76]

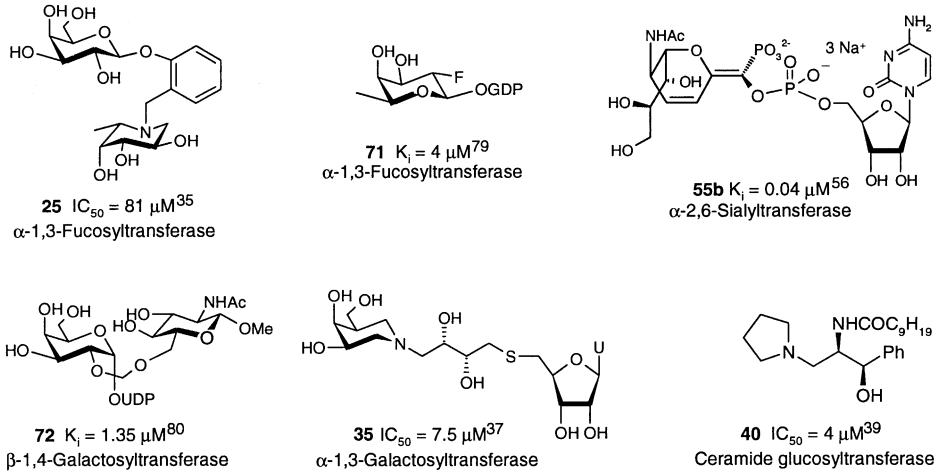


Figure 20. Selected inhibitors of some glycosyltransferases.[35,37,39,56,79,80]

bitors of α-glycosyltransferases (Fig. 7) and with the first report of an inhibitor in the nM range (Table 5, compound **55b**). Among the best designed inhibitors of glycosyltransferases known, carbohydrate mimetics are well indeed positioned (Fig. 20).

Needless to say, many challenging problems remain to be solved in the search for carbohydrate therapeutics based on glycosyltransferase inhibitors, including the understanding of the catalytic mechanism of these enzymes, the mapping of their active sites and the finding of stable and potent inhibitors in vivo. Given the results summarized in this review and the wide diversity of structure that may be designed, the creative research area of glycomimetics has a high potential for new discoveries in the field of carbohydrate therapeutics.

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Further reading

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Biographies

Professor Olivier Martin is a native from Switzerland. After studies in Chemistry and Chemical Engineering at the Federal Institute of Technology in Lausanne, he completed a Ph.D. degree at the University of Geneva (Laboratory of Prof. J.M.J. Tronchet). He received additional training in carbohydrate chemistry in the Laboratory of Prof. W.A. Szarek at Queen's University (Kingston Canada), then moved in 1984 to the State University of New York at Binghamton where he was appointed Assistant Professor. He was promoted to Associate Professor with tenure in 1989, then to Full Professor in 1993. In 1997, an opportunity arose to join the Institute of Organic and Analytical Chemistry, a CNRS research laboratory associated to the University of Orléans (France). He is now Professor of Chemistry at the University of Orléans and a member of this Research Institute. Professor Martin's research interests include synthetic and bioorganic aspects of carbohydrate chemistry, with a particular emphasis on the design and synthesis of carbohydrate mimetics as probes for the study of carbohydrate-processing enzymes.

Dr. Philippe Compain was born in 1970 near Paris, France. He received his Engineer degree in chemistry at the Ecole Supérieure de Chimie Industrielle de Lyon (now CPE). In 1997, he obtained his PhD in the laboratory of Professor J. Goré at the University of Lyon working on new synthetic methodologies, 1,2-chirality transfer and synthesis of spiropiperidine alkaloids. After a postdoctoral stay at the University of Montreal with Professor S. Hanessian on hetero Diels–Alder reactions, he was appointed *Chargé de Recherche* (researcher) at CNRS in the group of Professor O. R. Martin at the Institute of Organic and Analytical Chemistry (Orléans). His research interests include synthetic methodologies and asymmetric synthesis of biologically active heterocycles focusing on the design of new iminosugar-based glycosidase and glycosyltransferase inhibitors. In 1998, he received for his PhD the Dina Surdin Prize (French Chemical Society, organic chemistry division).