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Recent Progress on Fucosyltransferase Inhibitors

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Abstract: Fucosyltransferases (FucTs) are enzymes that transfer L-fucose from GDP-fucose to a glycoside or a peptide. They have important roles in a variety of diseases including cancer and autoimmune disorders, viral and bacterial infections and inflammatory processes, and thus they represent important drug targets for the development of agents for the treatment of such disorders. This review highlights recent developments regarding carbohydrate mimics as inhibitors of FucTs. The most recent and relevant synthetic strategies are described.

Keywords: Fucosyltransferases, Carbohydrate mimics, Glycoconjugates, Piperidines, Pyrrolidines, *C*-Glycosides.

1. INTRODUCTION

Carbohydrates play important roles in living organisms. Their participation in energy metabolism and as constitutive elements in structural support matrices of plants, fungi and bacteria are well understood. In contrast, the knowledge about carbohydrates as part of glycoconjugates, which are key elements in inter- and intracellular communication (e.g. signaling, host-pathogen interaction, immunological recognition and molecular and cellular targeting) [1] is still very incomplete [2,3]. As a result, most of the detailed studies on a variety of diseases including viral and bacterial infections, cancer metastasis, autoimmune dysfunctions and inflammatory reactions involve multivalent enzyme-sugar interactions [4-7].

Numerous natural and synthetic carbohydrate derivatives with agonistic and antagonistic activities at carbohydrate receptors [8] or carbohydrate-processing enzymes have now been identified [9-11]. Among those enzymes glycosidases [12,13] and glycosyltransferases are of special importance due to their implication in a large number of biological processes [14-18]. Indeed, a large number of carbohydrate mimetics that act as glycosidase/glycosyltransferase inhibitors have also been discovered [19-23]. Although carbohydrate enzyme inhibitors can play important roles as modulators of disease processes, [24,25] they suffer from several limitations that restrict their development into drugs. Many carbohydrates are rapidly degraded by digestive, plasma and cellular glycosidases and frequently, bind to their targets with low affinities. For these reasons the major interest in carbohydrate mimicry has been directed towards glycosidase and glycosyltransferase inhibitors [19,26-31].

In particular, fucosyltransferases (FucTs) a family of enzymes that transfer L-fucose from GDP-fucose to an acceptor substrate (a glycoside or a peptide) are of a great interest [32-34]. According to the fucosylation site, FucTs are classified into α-1,2 (FUT1 and FUT2), α-1,3/4 (FUT3, FUT4, FUT5, FUT6, FUT7 and FUT9), α-1,6 (FUT8) and protein *O*- (POFUT1 and POFUT2) fucosyltransferases [32]. In eukaryotes the former three subgroups are found in the Golgi apparatus and transfer L-fucose to other glycosides. POFUTS represent a minor number of glycosyltransferases located in the endoplasmic reticulum and transfer L-fucose to peptides [35-36]. The intensive investigations focused on inhibition of FucTs are due to the implication of L-fucose transfer in several important pathologies [37-41]. Well-known examples are human FucT V that catalyzes fucosylation of the 3-hydroxyl group of *N*-Ac glucosamine in siallyllactosamine to form the antigen sialyl Lewis x (sLe(x)), [42] a target in cancer therapy and inflammatory processes and POFUT1, which is involved in the development of many tissues, including cell fate as well as in proliferation, apoptosis, differentiation and migration [43]. In the case of POFUT1 their inhibition could also be a strategy against a large number of diseases such as several types of T-cell leukemias [44,45] through attenuation of Notch signaling pathway [46,47].

In this review we will present major and representative recent achievements on the chemistry of carbohydrate mimics directed to the synthesis of FucTs inhibitors, [48] with special attention on the more active compounds. Among these compounds are *O*- and *C*-glycosides, carbacycles and nitrogen-containing heterocycles such as piperidines and

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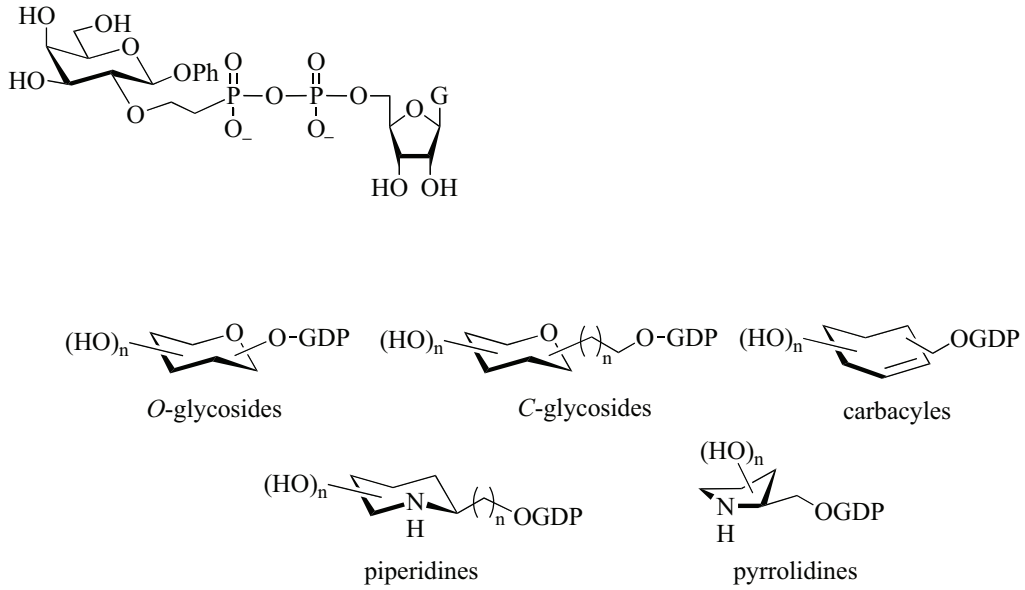


Fig. (1). Glycosyltransferase inhibitors.

pyrrolidines (Fig. **1**). The focus of all discussions will be on chemical methods, while biological activities will be mentioned where appropriate. For additional information on biological aspects of FucTs and fucosylation a number of excellent reviews have been published elsewhere [33,34, 49-51].

2. *O*-GLYCOSIDES

The first example of a mechanism-based fucosyltransferase inhibitor that utilizes both the acceptor and donor recognition potential of the enzyme active site is represented by compound **5**. This compound was able to inhibit α-(1,2)-fucosyltransferases with K_i = 4.4 μM exhibiting the characteristics of a classic bisubstrate analogue. Interestingly, derivative **4**, which lacks the GMP moiety was also found to be a competitive inhibitor with respect to the acceptor (K_i = 133 μM) and a mixer inhibitor with respect to GDP-fucose (K_i = 760 μM). Compounds **4** and **5** were prepared from a conveniently protected galactosyl bromide **1** as illustrated in (Scheme **1**) [52] After obtention of the phenyl glycoside **2** and incorporation of the side chain into C-2 of the galactose, deprotection of **3** afforded **4** in 58% yield. Compound **5** was obtained by incorporating the GDP moiety with GDP-morpholidate in the presence of tri-octylamine. The same authors reported inhibition of α-(1,2)-, α-(1,3)- and α-(1,4)-fucosyltransferases by deoxygenated substrates at C-4 position of the hexose moiety [53].

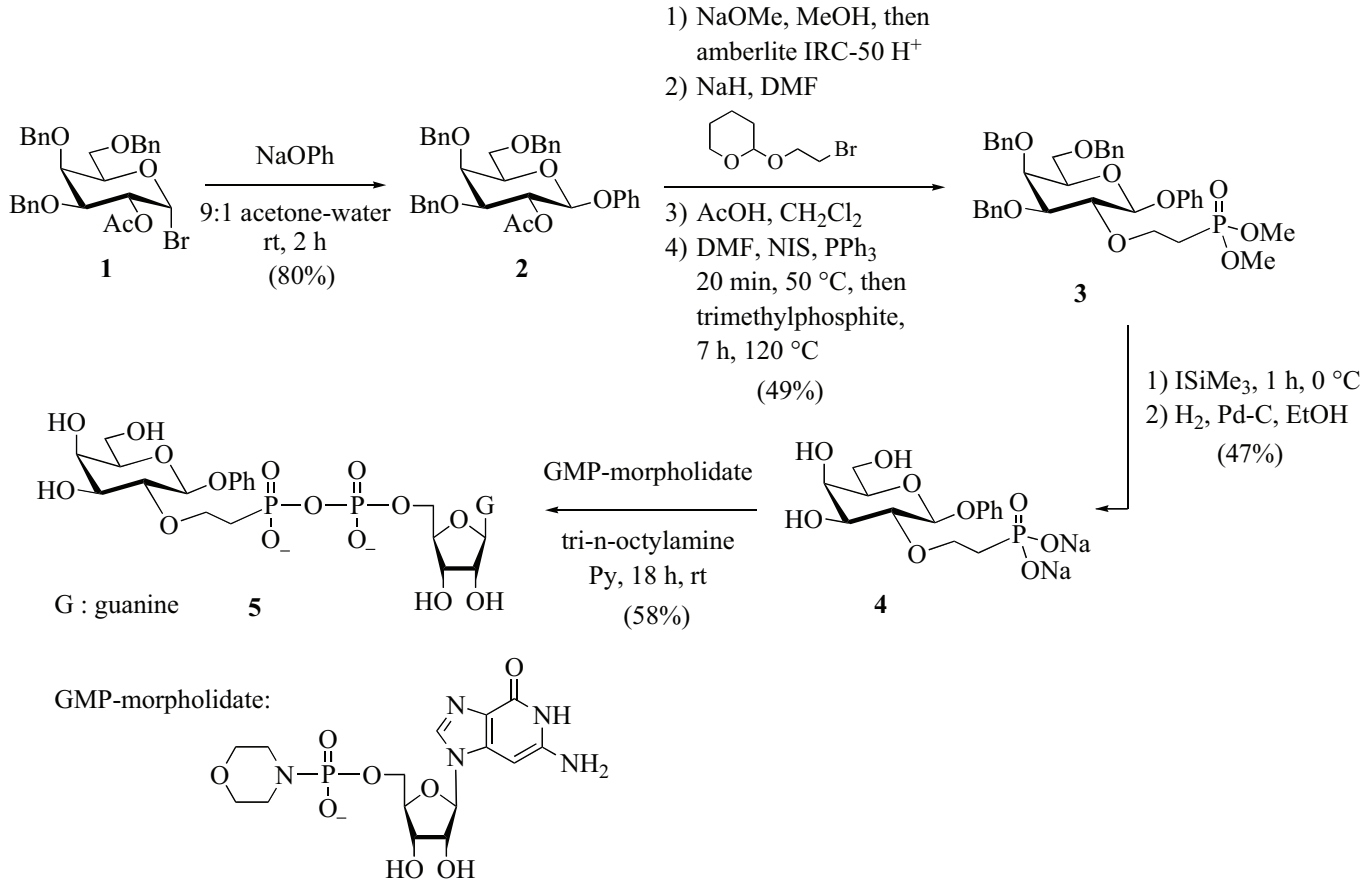
The trisubstrate analogue **10**, a potential inhibitor of α-(1,3)-fucosyltransferases has been prepared in 6 steps and 41.5% overall yield from protected 1-thio-β-L-fucopyranose **6**.[54] Key steps of the synthesis consisted of chemical fucosylation and incorporation of the GMP moiety (Scheme **2**).

Wong and co-workers reported a convenient procedure for preparing 2-deoxy-2-fluorosugar nucleotides *via* Selectfluor-mediated electrophilic fluorination of glycals. The obtained fluorinated sugar nucleotides have been used as probes for FucTs II, V, VI and VII [55]. The same authors reported the synthesis of *N*-acetyllactosamine derivatives **14** incorporating aromatic moieties at the anomeric center separated by a linker (Scheme **3**). These derivatives prepared through typical chemical *O*-glycosylation of trichloromacetimidate **13** with protected **12** revealed differential inhibition of sLe^X expression [56]. Indeed, enzyme kinetics experiments demonstrated that compounds **14** and, in particular those with naphthyl moieties are affinity inhibitors for FucT IV and VI. The corresponding methyl glycoside of compounds **14** (R=Me) in which the C-2' hydroxyl group of the galactose moiety was epimerized, showed to be a remarkably selective inhibitor for FucT VI [57]. Based on 3D-structure of sLe^x bisubstrate analogues formed by guanosine-5'-diphospho-L-galactose as a donor mimic and 2-hydroxyethyl-β-D-galactoside as an acceptor mimic were designed [58]. These analogues were moderate inhibitors of FucT VI suggesting that they bound to the donor site but not the acceptor binding site.

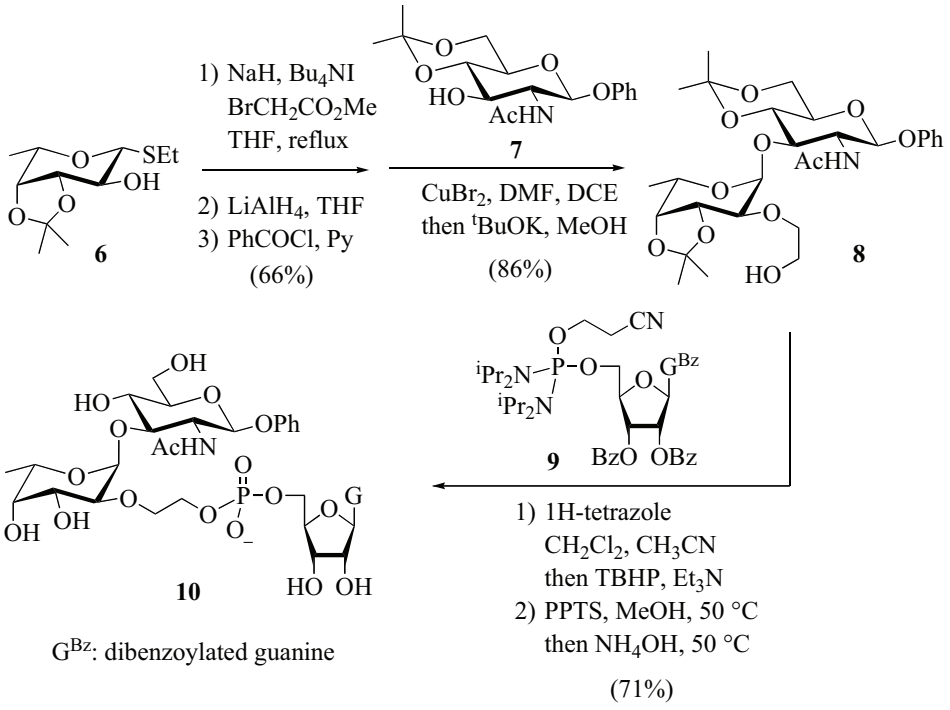
3. *C*-GLYCOSIDES

C-Fucopyranosyl analogues of GDP-L-fucose have been synthesized from tetra-*O*-acetyl-α-L-fucopyranose **15** through synthetic routes providing α- and β-*C*-fucosides with high selectivity (Scheme **4**) [59]. For the synthesis of **17** equatorial *C*-glycosylation took place in the cobalt catalyzed siloxymethylation of **15**, which took place in excellent stereoselectivity (>20:1). The homologation towards **20** was achieved by *C*-allylation catalyzed by trimethylsilyl triflate.

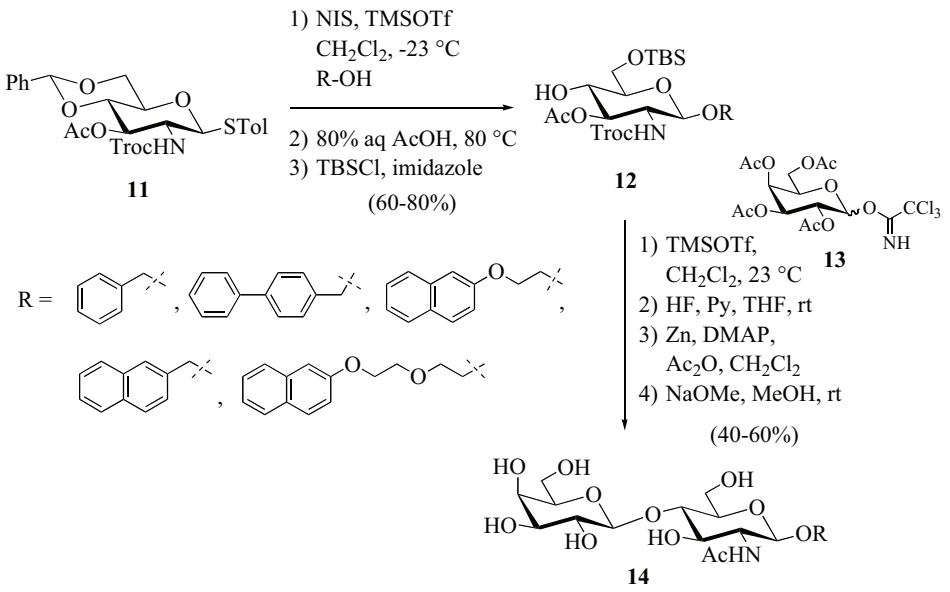
The trisubstrate analogue **25** has been prepared through NIS-mediated condensation of fucosyl donor **21** with protected glucopyranoside **22** as a key step. Further reduction of the azido function, elongation at the 1-amino group, deprotection and coupling with sugar **24** containing the heterocyclic base provided the target derivative **25** (Scheme **5**) [60].



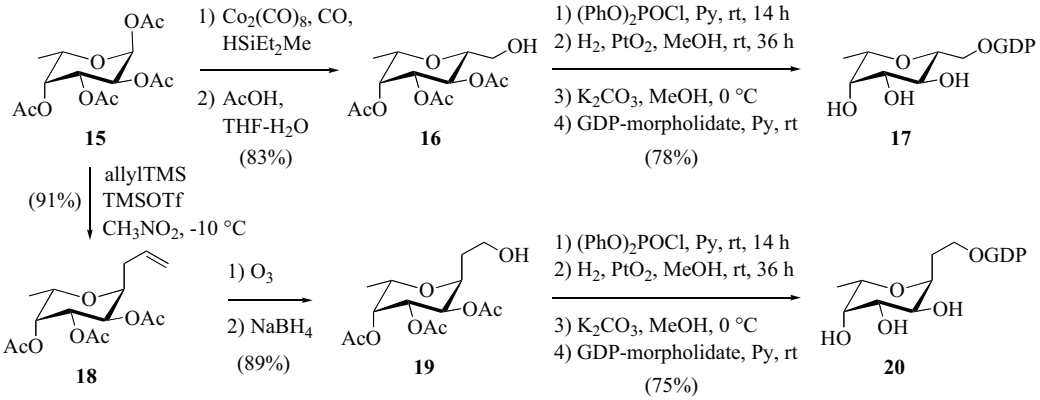
Scheme (1). Synthesis of an inhibitor of α-(1,2)-fucosyltransferases.



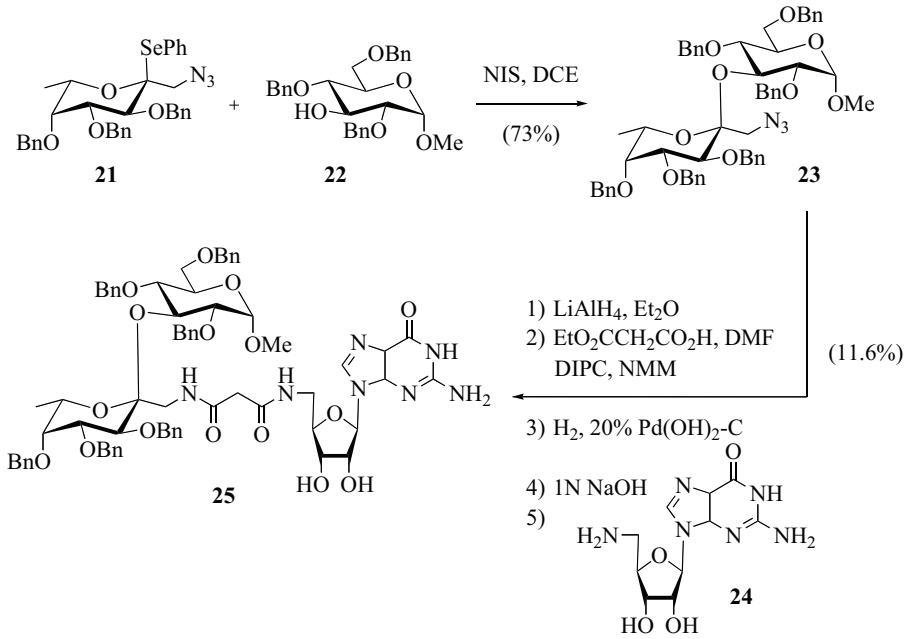
Scheme (2). Synthesis of an inhibitor of α-(1,3)-fucosyltransferases.



Scheme (3). Synthesis of *N*-acetyllactosamine derivatives.



Scheme (4). Synthesis of *C*-fucopyranosyl analogues.



Scheme (5). Synthesis of a trisubstrate analogue.

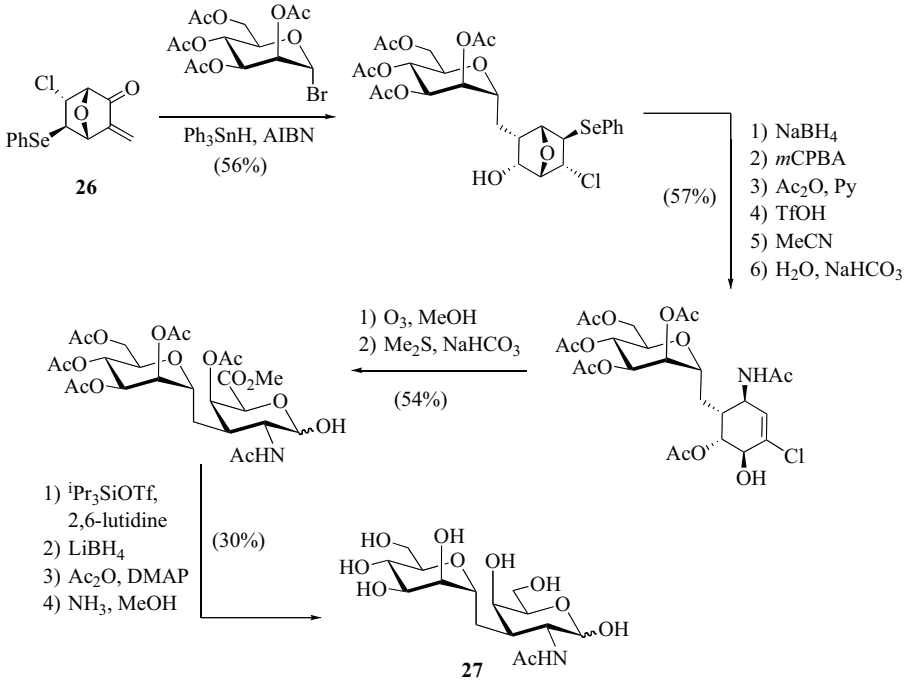
The neutral *C*-disaccharide **27** was prepared applying the Vogel's *naked sugars* strategy. After several steps, *C*-disaccharide **27** was obtained from enone **26**. Further transformations of **26** furnished the target compound **27** (Scheme **6**), which was revealed as good inhibitor of human FucT VI (K_i = 32 nM) [61].

A series of *C*-fucopyranosyl pyranosides have been prepared from the corresponding anomeric sulfoxides and tested as inhibitors of α-(1,6)-fucosyltransferases. Mechanical and dynamical molecular modeling was used to establish structure-activity-relationship results. The modest inhibitory activity found in most cases was explained on the basis of adoption of a $^4C_1$ conformation [62].

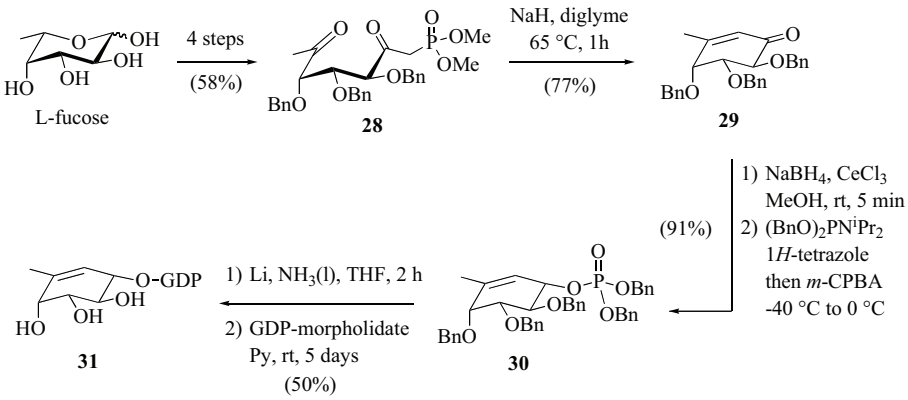
4. CARBACYCLES

The unsaturated carbocyclic analogue of GDP-fucose **31** has been prepared through an intramolecular Emmons-Horner-Wadsworth olefination of the corresponding 2,6-dioxophosphonate **28**, readily available from L-fucose in 4 steps and 58% yield. The formation of the endocyclic double bond took place with retention of stereogenic centers at C-2, C-3 and C-4. Chemo- and stereoselective reduction of the α,β-unsaturated inosose **29** was crucial for the obtention of **31** and it was obtained upon treatment with sodium borohydride in the presence of cerium trichloride (Scheme **7**) [63]. The complete reduction in two steps of intermediate **29** afforded a cyclohexane that allowed preparation of the corresponding saturated analogue of **31** (not represented in Scheme **7**). Both **31** and its saturated analogue exhibited a potent inhibitory activity against α-(1,3/4)-fucosyltransferases solubilized from colonia adenocarcinoma Colo205 cells.

The inhibitory activity of **31** and its saturated analogue has been investigated using ESI mass spectrometry. Compound **31** showed to be a competitive inhibitor with K_i = 67.1 μM similar to the Km value for GDP-fucose (50.4 μM) [64].



Scheme (6). Synthesis of a neutral *C*-disaccharide.



Scheme (7). Synthesis of unsaturated carbocyclic analogues of GDP-fucose from L-fucose.

A similar unsaturated carbocyclic analogue was prepared by Wong and co-workers starting from *p*-methoxyphenyl -D-mannopyranose **32** The corresponding GDP-fucose analogue **34** (Scheme **8**) showed inhibition constants K_i = 8 μM and K_i = 6 μM for FucT V and FucT VI, respectively.

5. PIPERIDINES

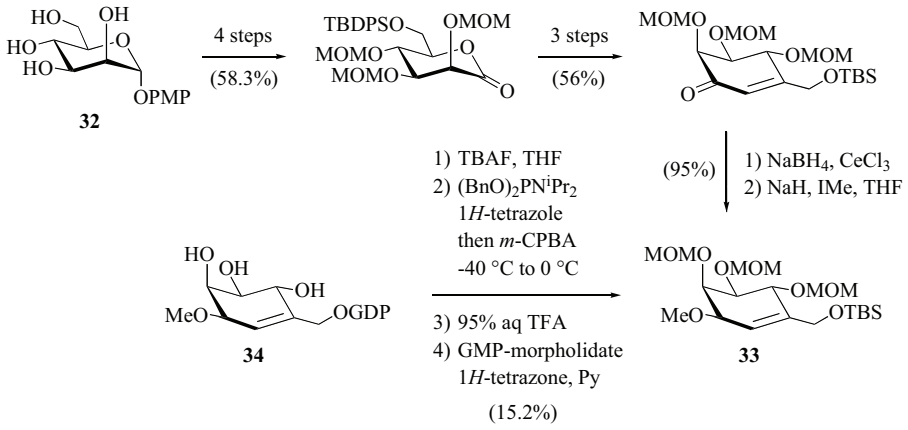
Azatrisaccharide **38**, containing a piperidine ring prepared by covalently linking the endocyclic nitrogen of -L-homofuconojirimycin **35** to the hydroxyl group at C-3 of protected *N*-Ac-lactosamine **37** (Scheme **9**) was found to be an effective inhibitor of FucT V in the presence of GDP [42]. The authors proposed a synergistic inhibition through the formation of a complex between GDP and **38** that mimics the transition state of the enzyme reaction. The iminocyclitol component of compound **38** can also be accessed through a chemoenzymatic strategy that allowed the synthesis of libraries of derivatives for the discovery of new selective fucosidase inhibitors [65]. Among these derivatives new compounds bearing *N*-Ac-lactosamine mimetics with an additional amino group has also been synthesized [66]. Azadisaccharides including those tethered by an aromatic ring also showed significant synergistic inhibition of FucT IV [67].

Six-membered GDP-iminocyclitols like **42** have been prepared chemoenzymatically by using fructose-diphosphate aldolase to obtain key intermediate aldol products such as **40** (Scheme **10**) [68]. Compound **42** showed inhibitory of FucT V and VI with K_i = 13 and 11 μM, respectively [69].

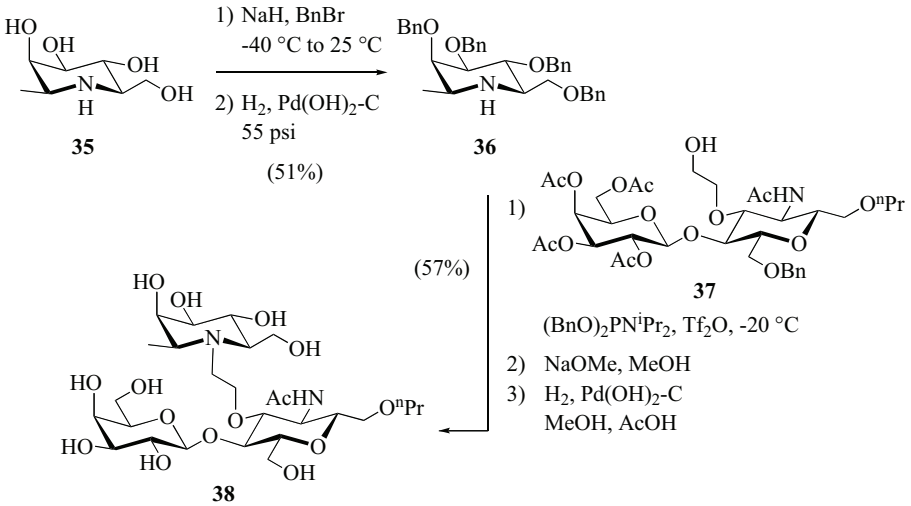
A rigid bicyclic analogue of α-L-fucose, prepared from protected L-gulonolactone was revealed as a moderate inhibitor of fucosyltransferases [70]. On the other hand, polyhydroxylated indolizidines showed to be good inhibitors of a α-(1,6)-fucosyltransferase from *Rhizobium sp* with a IC_{50} of $4.5 \cdot 10^{-5}$ M in the best case [71]. Those bicyclic compounds prepared through intramolecular conjugate addition of a γ-oxygenated-α,β-unsaturated sulphone [72].

6. PYRROLIDINES

In a similar way to the above mentioned piperidine-containing compounds, polyhydroxylated pyrrolidines showed synergistic inhibition of α-(1,3)-fucosyltransferases in the presence of GDP [73-74]. Those five-membered azasugars have been synthesized through a chemoenzymatic approach based on aldolase reactions [75] quite similar to that illustrated in (Scheme **10**). Incorporation of the five-membered nitrogen heterocycle to a GDP conjugate has been reported by using such chemoenzymatic approach (Scheme

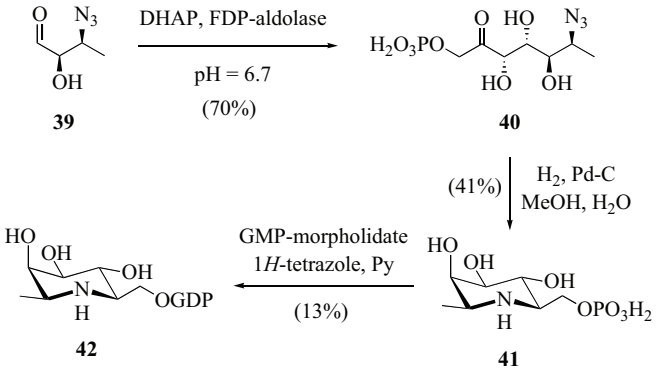


Scheme (8). Synthesis of unsaturated carbocyclic analogues of GDP-fucose from D-mannose.

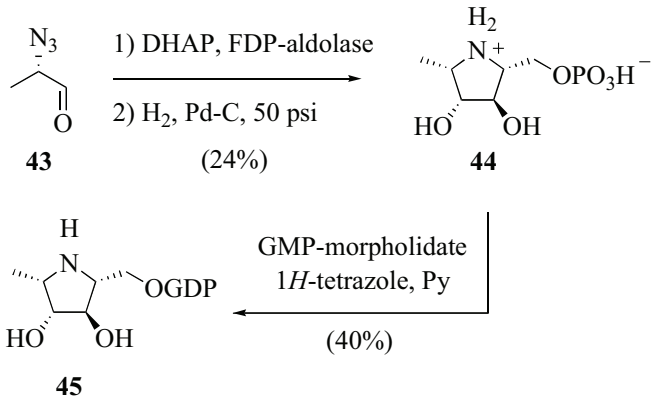


Scheme (9). Synthesis of azatrisaccharides.

11) [76]. Condensation of **43** with DHAP, catalyzed by FDP-aldolase afforded, after catalytic hydrogenation the phosphorylated iminocyclitol **44**. Incorporation of GMP moiety yielded inhibitor **45**. This compound showed to inhibit FucT IV in micromolar concentrations.



Scheme (10). Synthesis of six-membered GDP-iminocyclitols.



Scheme (11). Synthesis of polyhydroxylated pyrrolidines.

7. OTHER ANALOGUES

Several GDP-fucose mimics bearing different groups in the place of the fucose unit, other than carbohydrates or analogues like iminocyclitols have been described. As an example, GDP-hexanolamine **47** easily available through condensation of GMP-morpholidate and hexanol phosphate **46** (Scheme **12**) was found to be a competitive inhibitor of a recombinant α-(1,3)-fucosyltransferase [77].

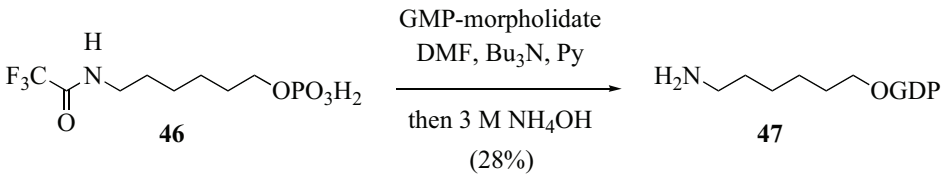
Wong and co-workers employed click-chemistry to design a potent and highly selective inhibitor of human α-(1,3)-fucosyltransferase [78]. By using triazole chemistry a library of compounds incorporating hydrophobic units linked to GDP through a triazole tether were prepared (Scheme **13**). A total of 85 compounds were prepared and after screening *in situ* compound **52** was selected. This compound showed potent inhibitory activities against several fucosyltransferases including FucT III (IC_{50} = 1.0 μM), FucT V (IC_{50} = 0.9 μM) and FucT VI (IC_{50} = 0.15 μM).

The use of monovalent carbohydrate microarrays allowed multiple screening directed to the high-throughput identification of fucosyltransferase inhibitors. By this method several compounds with nanomolar values of K_i were discovered [79]. Moreover, application of quantitative MALDI-TOF-based screening of compounds libraries constructed by way of triazole click-chemistry have recently allowed the discovery of compounds **53** and **54** as selective inhibitors for human recombinant α-(1,3)-fucosyltransferase (K_i = 293 nM) and α-(1,6)-fucosyltransferase (K_i = 13.8 μM), respectively [80].

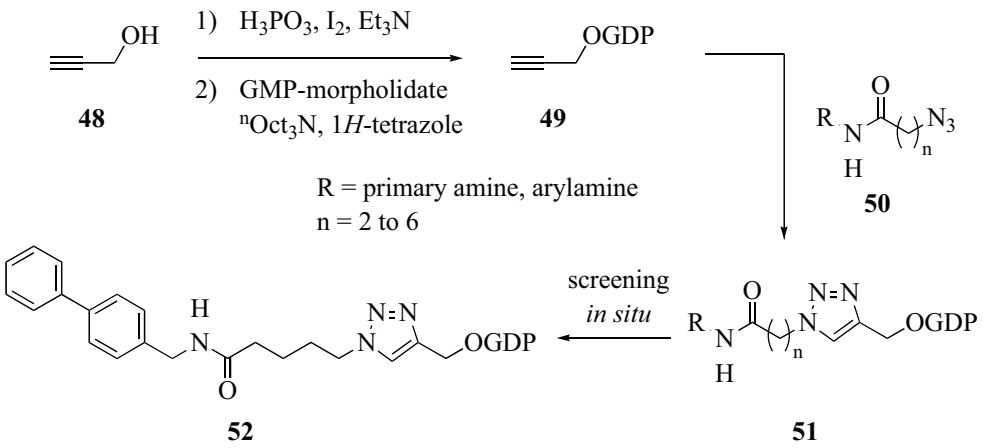
In addition to the various compounds discussed above, bearing a GDP unit, which demonstrate the necessity of interaction of such unit in the active site (in agreement to mechanistic studies), two types of completely different structures have been found in Nature to posses inhibitory activity against fucosyltransferases. That is the case of the octa- and nonaprenylhydroquinone sulfates **55** and **56** that have been isolated from the marine sponge *Sarcotragus sp*. Compounds **55** and **56** inhibited FucT VII with IC_{50} values of 3.9 and 2.4 μM, respectively [81]. Stachybotrydal **57** isolated from the fungus *Stachybotrytis cyclindrospora* exhibited a potent inhibitory activity against FucT V. Compound **57** is an uncompetitive inhibitor with respect to GDP-fucose and a non-competitive inhibitor with respect to *N*-Ac-lactosamine with Ki values of 10.7 and 9.7 μM, respectively [82].

8. CONCLUDING REMARKS

In summary, a variety of carbohydrates and structural analogues bearing a GDP unit in their structure should be considered as promising leads with inhibitory properties against FucTs. The presence of the GDP moiety seems to be crucial (with some exception) for achieving a good inhibitory activity, probably due to its direct interaction with hydrophobic residues located close to the active site of the enzyme. Interestingly, the presence of the fucose unit is not essential as demonstrated by the discovery of potent inhibitors through combinatorial chemistry techniques. On the other hand, potent inhibitors have been discovered with the common feature of incorporating a highly hydrophobic moiety, indicating the presence of a hydrophobic pocket close to the active site. Because of these reasons the preparation of particular complex structures designed with the aid of computational methods (docking) and structural analysis (X-ray and NMR) still remains a challenge and much effort will be needed in the future. Furthermore, there



Scheme (12). Synthesis of GDP-hexanolamine.



Scheme (13). Synthesis of inhibitors by using click-chemistry.

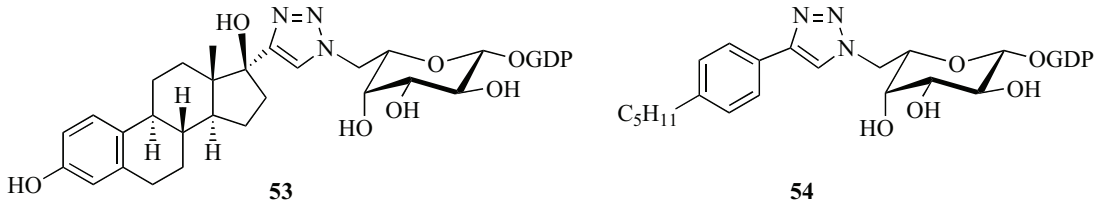


Fig. (2). Glycosyltransferase inhibitors prepared through click-chemistry.

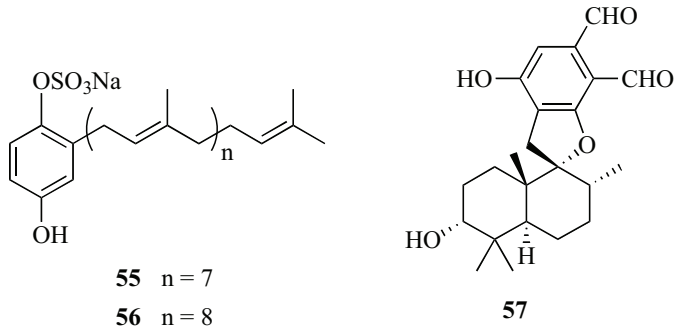


Fig. (3). Glycosyltransferases inhibitors withour GDP in their structure.

are currently no compounds in clinical trials so, the development of new carbohydrate mimics that improve the binding properties to the enzyme active site could spark the use of such compounds as drug candidates for the treatment of a variety of diseases.

CONFLICT OF INTEREST

The author(s) confirm that this article content has no conflicts of interest.

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ABBREVIATIONS

Ac	=	Acetyl
Bn	=	Benzyl
DCE	=	Dichloroethane
DHAP	=	Dihydroxyacetone phosphate
DMAP	=	4-(Dimethylamino)pyridine
DMF	=	Dimethylformamide
ESI	=	Electrospray ionization
FucT	=	Fucosyltransferase
FDP	=	Fructose diphosphate
GDP	=	Guanosine diphosphate
GMP	=	Guanosine monophosphate

NIS = *N*-iodosuccinimide

PPTS = Pyridinium *p*-toluensulfonate

Py = Pyridine

SLe^x = Sialyl Lewis x

SAR = Structure-activity relationship

TBHP = *tert*-butyl hydroperoxide

TBS = *tert*-butyldimethylsilyl

Tf = Trifluoromethanesulfonyl

TMS = Trimethylsilyl

REFERENCES

[1] Sears, P.; Wong, C. H. Intervention of carbohydrate recognition by proteins and nucleic acids. *Proc. Natl. Acad. Sci. U.S.A.,* **1996**, *93*, 12086-12093.

[2] Werz, D. B.; Seeberger, P. H. Carbohydrates as the next frontier in pharmaceutical research. *Chem. Eur. J.,* **2005**, *11*, 3194-3206.

[3] Atukorale, P. U.; Choi, S. S.; Aich, U.; Campbell, C. T.; Meledeo, M. A.; Yarema, K. J. Chemical biology of cell surface oligosaccharides. *Protein Targeting Small Mol.,* **2009**, 189-222.

[4] Kiessling, L. L.; Young, T.; Mortell, K. H. Multivalency in protein-carbohydrate recognition. *Glycoscience,* **2001**, *2*, 1817-1861.

[5] Lutzen, A.; Wittmann, V. Molecular basis of protein-carbohydrate interactions. *Highlights Bioorg. Chem.,* **2004**, 119-123.

[6] Walker-Nasir, E.; Kaleem, A.; Hoessli, D. C.; Khurshid, A.; Nasir ud, D. Galactose: a specifically recognized, terminal carbohydrate moiety in biological processes. *Curr. Org. Chem.,* **2008**, *12*, 940-956.

[7] Ghazarian, H.; Idoni, B.; Oppenheimer, S. B. A glycobiology review: Carbohydrates, lectins and implications in cancer therapeutics. *Acta Histochem.,* **2011**, *113*, 236-247.

[8] Mazik, M. Molecular recognition of carbohydrates by acyclic receptors employing noncovalent interactions. *Chem. Soc. Rev.,* **2009**, *38*, 935-956.

[9] Cipolla, L.; Araujo, A. C.; Bini, D.; Gabrielli, L.; Russo, L.; Shaikh, N. Discovery and design of carbohydrate-based therapeutics. *Expert Opin. Drug Discovery,* **2010**, *5*, 721-737.

[10] Lepenies, B.; Yin, J.; Seeberger, P. H. Applications of synthetic carbohydrates to chemical biology. *Curr. Opin. Chem. Biol.,* **2010**, *14*, 404-411.

[11] Galan, M. C.; Benito-Alifonso, D.; Watt, G. M. Carbohydrate chemistry in drug discovery. *Org. Biomol. Chem.,* **2011**, *9*, 3598-3610.

[12] Bojarova, P.; Kren, V. Glycosidases: a key to tailored carbohydrates. *Trends Biotechnol.,* **2009**, *27*, 199-209.

[13] Leonard, R.; Strasser, R.; Altmann, F. Plant glycosidases acting on protein-linked oligosaccharides. *Phytochemistry,* **2009**, *70*, 318-324.

[14] Furukawa, K.; Tsuchida, A.; Okajima, T.; Furukawa, K. Glycoconjugate glycosyltransferases. *Glycoconjugate J.,* **2009**, *26*, 987-998.

[15] Haerle, J.; Bechthold, A. The power of glycosyltransferases to generate bioactive natural compounds. *Methods Enzymol.,* **2009**, *458*, 309-333.

[16] Weadge, J. T.; Palcic, M. M. Chemistry of Glycosyltransferases *Wiley Encycl. Chem. Biol.,* **2009**, *2*, 198-210.

[17] Williams, G. J.; Thorson, J. S. Natural product glycosyltransferases: properties and applications. *Adv. Enzymol. Relat. Areas Mol. Biol.,* **2009**, *76*, 55-119.

[18] Wagner, G. K.; Pesnot, T. Glycosyltransferases and their assays. *ChemBioChem,* **2010**, *11*, 1939-1949.

[19] Khan, S. H.; Kushi, L. M. In *Glycoconjugates: Composition, structure and funtion*; Allen, H. J., Kisailus, E. C., Eds.; Marcel Dekker: New York, **1992**, p 361-378.

[20] Qian, X.; Palcic, M. M. Glycosyltransferase inhibitors. *Carbohydr. Chem. Biol.,* **2000**, *3*, 293-312.

[21] Compain, P.; Martin, O. R. Carbohydrate mimetics-based glycosyltransferase inhibitors. *Bioorg. Med. Chem.,* **2001**, *9*, 3077-3092.

[22] Compain, P.; Martin, O. R. Design, synthesis and biological evaluation of iminosugar-based glycosyltransferase inhibitors. *Curr. Top. Med. Chem.,* **2003**, *3*, 541-560.

[23] Kajimoto, T.; Node, M. Synthesis of glycosyltransferase inhibitors. *Synthesis,* **2009**, 3179-3210.

[24] Osborn Helen, M. I.; Evans Philip, G.; Gemmell, N.; Osborne Sadie, D. Carbohydrate-based therapeutics. *J. Pharm. Pharmacol.,* **2004**, *56*, 691-702.

[25] Ernst, B.; Magnani, J. L. From carbohydrate leads to glycomimetic drugs. *Nat. Rev. Drug Discovery,* **2009**, *8*, 661-677.

[26] Rempel, B. P.; Withers, S. G. Covalent inhibitors of glycosidases and their applications in biochemistry and biology. *Glycobiology,* **2008**, *18*, 570-586.

[27] Asano, N. Sugar-mimicking glycosidase inhibitors: bioactivity and application. *Cell. Mol. Life Sci.,* **2009**, *66*, 1479-1492.

[28] Cipolla, L.; La Ferla, B.; Airoldi, C.; Zona, C.; Orsato, A.; Shaikh, N.; Russo, L.; Nicotra, F. Carbohydrate mimetics and scaffolds: sweet spots in medicinal chemistry. *Future Med. Chem.,* **2010**, *2*, 587-599.

[29] Koester, D. C.; Holkenbrink, A.; Werz, D. B. Recent advances in the synthesis of carbohydrate mimetics. *Synthesis,* **2010**, 3217-3242.

[30] Roychoudhury, R.; Pohl, N. L. B. New structures, chemical functions, and inhibitors for glycosyltransferases. *Curr. Opin. Chem. Biol.,* **2010**, *14*, 168-173.

[31] Stocker, B. L.; Dangerfield, E. M.; Win-Mason, A. L.; Haslett, G. W.; Timmer, M. S. M. Recent Developments in the Synthesis of Pyrrolidine-Containing Iminosugars. *Eur. J. Org. Chem.,* **2010**, 1615-1637.

[32] Marques, E. T. A., Jr. Fucosyltransferases In *Carbohydrate in Chemistry and Biology*; Ernst, B., Hart, G. W., Sinay, P., Eds.; Wiley-VCH: Weinheim, **2000**, *3*, p 197-211.

[33] De Vries, T.; Knegtel, R. M. A.; Holmes, E. H.; Macher, B. A. Fucosyltransferases: structure/function studies. *Glycobiology,* **2001**, *11*, 119R-128R.

[34] Ma, B.; Simala-Grant, J. L.; Taylor, D. E. Fucosylation in prokaryotes and eukaryotes. *Glycobiology,* **2006**, *16*, 158R-184R.

[35] Luo, Y.; Koles, K.; Vorndam, W.; Haltiwanger, R. S.; Panin, V. M. Protein *O*-fucosyltransferase 2 adds O-fucose to thrombospondin type 1 repeats. *J. Biol. Chem.,* **2006**, *281*, 9393-9399.

[36] Luo, Y.; Nita-Lazar, A.; Haltiwanger, R. S. Two distinct pathways for O-fucosylation of epidermal growth factor-like or thrombospondin type 1 repeats. *J. Biol. Chem.,* **2006**, *281*, 9385-9392.

[37] Chandrasekaran, E. V.; Xue, J.; Piskorz, C.; Locke, R. D.; Toth, K.; Slocum, H. K.; Matta, K. L. Potential tumor markers for human gastric cancer: an elevation of glycan:sulfotransferases and a concomitant loss of α1,2-fucosyltransferase activities. *J. Cancer Res. Clin. Oncol.,* **2007**, *133*, 599-611.

[38] Moran, A. P. Relevance of fucosylation and Lewis antigen expression in the bacterial gastroduodenal pathogen Helicobacter pylori. *Carbohydr. Res.,* **2008**, *343*, 1952-1965.

[39] Guillon, P.; Ruvoen-Clouet, N.; Le Moullac-Vaidye, B.; Marchandeau, S.; Le Pendu, J. Association between expression of the H histo-blood group antigen, α1,2fucosyltransferases polymorphism of wild rabbits, and sensitivity to rabbit hemorrhagic disease virus. *Glycobiology,* **2009**, *19*, 21-28.

[40] McGovern, D. P. B.; Jones, M. R.; Taylor, K. D.; Marciante, K.; Yan, X.; Dubinsky, M.; Ippoliti, A.; Vasiliauskas, E.; Berel, D.; Derkowski, C.; Dutridge, D.; Fleshner, P.; Shih, D. Q.; Melmed, G.; Mengesha, E.; King, L.; Pressman, S.; Haritunians, T.; Guo, X.; Targan, S. R.; Rotter, J. I. Fucosyltransferase 2 (FUT2) non-secretor status is associated with Crohn's disease. *Hum. Mol. Genet.,* **2010**, *19*, 3468-3476.

[41] Fukuda, T.; Hashimoto, H.; Okayasu, N.; Kameyama, A.; Onogi, H.; Nakagawasai, O.; Nakazawa, T.; Kurosawa, T.; Hao, Y.; Isaji, T.; Tadano, T.; Narimatsu, H.; Taniguchi, N.; Gu, J. α-(1,6)-Fucosyltransferase-deficient Mice Exhibit Multiple Behavioral Abnormalities Associated with a Schizophrenia-like Phenotype: importance of the balance between the dopamine and serotonin systems. *J. Biol. Chem.,* **2011**, *286*, 18434-18443.

[42] Qiao, L.; Murray, B. W.; Shimazaki, M.; Schultz, J.; Wong, C.-H. Synergistic Inhibition of Human α-1,3-Fucosyltransferase V. *J. Am. Chem. Soc.,* **1996**, *118*, 7653-7662.

[43] Loriol, C.; Dupuy, F.; Rampal, R.; Dlugosz, M. A.; Haltiwanger, R. S.; Maftah, A.; Germot, A. Molecular evolution of protein O-fucosyltransferase genes and splice variants. *Glycobiology,* **2006**, *16*, 736-747.

[44] Jundt, F.; Schwarzer, R.; Dorken, B. Notch signaling in leukemias and lymphomas. *Curr. Mol. Med.,* **2008**, *8*, 51-59.

[45] Pancewicz, J.; Taylor, J. M.; Datta, A.; Baydoun, H. H.; Waldmann, T. A.; Hermine, O.; Nicot, C. Notch signaling contributes to proliferation and tumor formation of human T-cell leukemia virus type

1-associated adult T-cell leukemia. *Proc. Natl. Acad. Sci.,* **2010**, *107*, 16619-16624.

[46] Rampal, R.; Luther, K. B.; Haltiwanger, R. S. Notch signaling in normal and disease states: possible therapies related to glycosylation. *Curr. Mol. Med.,* **2007**, *7*, 427-445.

[47] Jafar-Nejad, H.; Leonardi, J.; Fernandez-Valdivia, R. Role of glycans and glycosyltransferases in the regulation of Notch signaling. *Glycobiology,* **2010**, *20*, 931-949.

[48] Van Der Marel, G. A.; Heskamp, B. M.; Veeneman, G. H.; Van Boeckel, C. A. A.; Van Boom, J. H. Design and synthesis of potential fucosyl transferase inhibitors. *Carbohydr. Mimics,* **1998**, 491-510.

[49] Schottelius, A. J.; Hamann, A.; Asadullah, K. Role of fucosyltransferases in leukocyte trafficking: major impact for cutaneous immunity. *Trends Immunol.,* **2003**, *24*, 101-104.

[50] Miyoshi, E.; Moriwaki, K.; Nakagawa, T. Biological function of fucosylation in cancer biology. *J. Biochem.,* **2008**, *143*, 725-729.

[51] Moriwaki, K.; Miyoshi, E. Roles of fucosylation in tumor immunology. *Trends Glycosci. Glycotechnol.,* **2010**, *22*, 239-246.

[52] Palcic, M. M.; Heerze, L. D.; Srivastava, O. P.; Hindsgaul, O. A bisubstrate analog inhibitor for α(1→2)-fucosyltransferase. *J. Biol. Chem.,* **1989**, *264*, 17174-17181.

[53] Hindsgaul, O.; Kaur, K. J.; Srivastava, G.; Blaszczyk-Thurin, M.; Crawley, S. C.; Heerze, L. D.; Palcic, M. M. Evaluation of deoxygenated oligosaccharide acceptor analogs as specific inhibitors of glycosyltransferases. *J. Biol. Chem.,* **1991**, *266*, 17858-17862.

[54] Heskamp, B. M.; van der Marel, G. A.; van Boom, J. H. Expeditious synthesis of a trisubstrate analog for α(1 → 3)fucosyltransferase. *J. Carbohydr. Chem.,* **1995**, *14*, 1265-1277.

[55] Burkart, M. D.; Vincent, S. P.; Duffels, A.; Murray, B. W.; Ley, S. V.; Wong, C. H. Chemo-enzymatic synthesis of fluorinated sugar nucleotide: useful mechanistic Probes for glycosyltransferases. *Bioorg. Med. Chem.,* **2000**, *8*, 1937-1946.

[56] Mong, T. K. K.; Lee, L. V.; Brown, J. R.; Esko, J. D.; Wong, C.-H. Synthesis of N-acetyllactosamine derivatives with variation in the aglycon moiety for the study of inhibition of sialyl Lewisx expression. *ChemBioChem,* **2003**, *4*, 835-840.

[57] Galan, M. C.; Venot, A. P.; Phillips, R. S.; Boons, G.-J. The design and synthesis of a selective inhibitor of fucosyltransferase VI. *Org. Biomol. Chem.,* **2004**, *2*, 1376-1380.

[58] Izumi, M.; Kaneko, S.; Yuasa, H.; Hashimoto, H. Synthesis of bisubstrate analogues targeting alpha-1,3-fucosyltransferase and their activities. *Org. Biomol. Chem.,* **2006**, *4*, 681-690.

[59] Luengo, J. I.; Gleason, J. G. Synthesis of C-fucopyranosyl analogs of GDP-L-fucose as inhibitors of fucosyltransferases. *Tetrahedron Lett.,* **1992**, *33*, 6911-6914.

[60] Heskamp, B. M.; Veeneman, G. H.; van der Marel, G. A.; van Boeckel, C. A. A.; van, B. J. H. Design and synthesis of a trisubstrate analog for α-(1,3)-fucosyltransferase: a potential inhibitor. *Tetrahedron,* **1995**, *51*, 8397-8406.

[61] Pasquarello, C.; Picasso, S.; Demange, R.; Malissard, M.; Berger, E. G.; Vogel, P. The C-Disaccharide α-C-(1,3)-Mannopyranoside of N-Acetylgalactosamine Is an Inhibitor of Glycohydrolases and of Human α-1,3-Fucosyltransferase VI. Its Epimer α-(1,3)-Mannopyranoside of N-Acetyltalosamine Is Not. *J. Org. Chem.,* **2000**, *65*, 4251-4260.

[62] Calderon, F.; Carpintero, M.; Garcia-Junceda, E.; Fernandez-Mayoralas, A.; Bastida, A. Structure/activity relationship of carba- and C-fucopyranosides as inhibitors of an α 1,6-fucosyltransferase by molecular modeling and kinetic studies. *Lett. Org. Chem.,* **2005**, *2*, 247-251.

[63] Cai, S.; Stroud, M. R.; Hakomori, S.; Toyokuni, T. Synthesis of carbocyclic analogs of guanosine 5'-(β-L-fucopyranosyl diphosphate) (GDP-fucose) as potential inhibitors of fucosyltransferases. *J. Org. Chem.,* **1992**, *57*, 6693-6696.

[64] Norris, A. J.; Whitelegge, J. P.; Strouse, M. J.; Faull, K. F.; Toyokuni, T. Inhibition kinetics of carba- and C-fucosyl analogues of GDP-fucose against fucosyltransferase V: implication for the reaction mechanism. *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 571-573.

[65] Wischnat, R.; Martin, R.; Takayama, S.; Wong, C. H. Chemoenzymatic synthesis of iminocyclitol derivatives: a useful library strategy for the development of selective fucosyltransfer enzymes inhibitors. *Bioorg. Med. Chem. Lett.,* **1998**, *8*, 3353-3358.

[66] Wischnat, R.; Martin, R.; Wong, C.-H. Synthesis of a New Class of N-Linked Lewis and LacNAc Analogs as Potential Inhibitors of Human Fucosyltransferases: A General Method for the Incorporation of an Iminocyclitol as a Transition-State Mimetic of the Donor Sugar to the Acceptor. *J. Org. Chem.,* **1998**, *63*, 8361-8365.

[67] Jefferies, I.; Bowen, B. R. Synthesis of inhibitors of α-1,3-fucosyltransferase. *Bioorg. Med. Chem. Lett.,* **1997**, *7*, 1171-1174.

[68] Mitchell, M. L.; Lee, L. V.; Wong, C.-H. Synthesis and evaluation of six-membered GDP-iminocyclitol. *Tetrahedron Lett.,* **2002**, *43*, 5691-5693.

[69] Mitchell Michael, L.; Tian, F.; Lee Lac, V.; Wong, C.-H. Synthesis and evaluation of transition-state analogue inhibitors of alpha-1,3-fucosyltransferase. *Angew. Chem. Int. Ed.,* **2002**, *41*, 3041-3044.

[70] Beacham, A. R.; Smelt, K. H.; Biggadike, K.; Britten, C. J.; Hackett, L.; Winchester, B. G.; Nash, R. J.; Griffiths, R. C.; Fleet, G. W. J. Inhibition of fucosyl transferase and fucosidase by a rigid bicyclic mimic of α-L-fucose. *Tetrahedron Lett.,* **1998**, *39*, 151-154.

[71] Bastida, A.; Fernandez-Mayoralas, A.; Arrayas, R. G.; Iradier, F.; Carretero, J. C.; Garcia-Junceda, E. Heterologous over-expression of α-1,6-fucosyltransferase from Rhizobium sp.: application to the synthesis of the trisaccharide β-D-GlcNAc(1,4)-[α-L-Fuc-(1,6)]-D-GlcNAc, study of the acceptor specificity and evaluation of polyhydroxylated indolizidines as inhibitors. *Chem. Eur. J.,* **2001**, *7*, 2390-2397.

[72] Carretero, J. C.; Arrayás, R. G. Stereoselective Synthesis of Polyhydroxylated Indolizidines from γ-Hydroxy α,β-Unsaturated Sulfones. *J. Org. Chem.,* **1998**, *63*, 2993-3005.

[73] Ichikawa, Y.; Lin, Y.-C.; Dumas, D. P.; Shen, G.-J.; Garcia-Junceda, E.; Williams, M. A.; Bayer, R.; Ketcham, C.; Walker, L. E.; Paulson, J. C.; Wong, C.-H. Chemical-Enzymatic Synthesis and Conformational Analysis of Sialyl Lewis x and Derivatives. *J. Am. Chem. Soc.,* **1992**, *114*, 9283-9298.

[74] Wong, C. H.; Dumas, D. P.; Ichikawa, Y.; Koseki, K.; Danishefsky, S. J.; Weston, B. W.; Lowe, J. B. Specificity, inhibition, and synthetic utility of a recombinant human α-1,3-fucosyltransferase. *J. Am. Chem. Soc.,* **1992**, *114*, 7321-7322.

[75] Wang, Y. F.; Dumas, D. P.; Wong, C. H. Chemoenzymic synthesis of five-membered aza sugars as inhibitors of fucosidase and fucosyltransferase: an issue regarding the stereochemistry discrimination at transition states. *Tetrahedron Lett.,* **1993**, *34*, 403-406.

[76] Schuster, M.; Blechert, S. Inhibition of fucosyltransferase V by a GDP-azasugar. *Bioorg. Med. Chem. Lett.,* **2001**, *11*, 1809-1811.

[77] Bamford, M.; Britten, C.; Draeger, E.; Gore, P.; Holmes, D. S. An improved method for the synthesis of GDP-hexanolamine derivatives, key reagents for the purification and characterization of carbohydrate-processing enzymes. *J. Carbohydr. Chem.,* **1996**, *15*, 727-737.

[78] Lee Lac, V.; Mitchell Michael, L.; Huang, S.-J.; Fokin Valery, V.; Sharpless, K. B.; Wong, C.-H. A potent and highly selective inhibitor of human alpha-1,3-fucosyltransferase via click chemistry. *J. Am. Chem. Soc.,* **2003**, *125*, 9588-9589.

[79] Bryan, M. C.; Lee, L. V.; Wong, C.-H. High-throughput identification of fucosyltransferase inhibitors using carbohydrate microarrays. *Bioorg. Med. Chem. Lett.,* **2004**, *14*, 3185-3188.

[80] Hosoguchi, K.; Maeda, T.; Furukawa, J.-i.; Shinohara, Y.; Hinou, H.; Sekiguchi, M.; Togame, H.; Takemoto, H.; Kondo, H.; Nishimura, S.-I. An Efficient Approach to the Discovery of Potent Inhibitors against Glycosyltransferases. *J. Med. Chem.,* **2010**, *53*, 5607-5619.

[81] Wakimoto, T.; Maruyama, A.; Matsunaga, S.; Fusetani, N.; Shinoda, K.; Murphy, P. T. Bioactive marine metabolites. 90. Octa- and nonaprenylhydroquinone sulfates, inhibitors of α-1,3-fucosyltransferase VII, from an Australian marine sponge Sarcotragus sp. *Bioorg. Med. Chem. Lett.,* **1999**, *9*, 727-730.

[82] Lin, T.-W.; Chang, W.-W.; Chen, C.-C.; Tsai, Y.-C. Stachybotrydial, a potent inhibitor of fucosyltransferase and sialyltransferase. *Biochem. Biophys. Res. Commun.,* **2005**, *331*, 953-957.

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