RECENT TRENDS IN THE SYNTHESIS AND BIOLOGICAL APPLICATIONS OF TRIAZOLE FUSED CARBOHYDRATE GLYCOCONJUGATES TOWARDS DRUG DISCOVERY

Abstract

The synthesis and biological applications of triazole-containing glycomimetics is discussed. Carbohydrate heteroanalogue skeleton ranging from four membered to seven membered fused with 1,2,3-triazole moieties in their structure, are covered. The various types of glycoconjugates targeted here include iminosugar, thiosugar, and carbasugar-triazole conjugates, which have recently emerged as molecular targets of biological importance.

Keywords: Glycomimetics, azide-alkynecycloaddition, glycoconjugate, TriazolylglycoconjugatesGlycosyltri -azoles, imino-osugars, thio-sugars, carba-sugars, glycosidase inhibitor

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I. INTRODUCTION

The triazole nucleus is one of the most important and well-known heterocycles, a common and essential feature in many natural products and pharmaceuticals. Triazoles have attracted much attention over the past few decades due to their presence in many bioactive compounds. Triazole nuclei exist as core structural components in many drug categories such as Parkinson's disease, antidiabetics, anti-obesity drugs, immunomodulatory drugs, etc. The broad and potent activity of triazoles and their derivatives has established them as pharmacologically important scaffolds. The basic heterocycles present in various drugs are 1,2,3-triazole and 1,2,4-triazole. These heterocycles are stable to metabolic degradation and their incorporation into molecules can improve solubility and bioavailability, further underscoring their interest as pharmacophoric entities[1]. Much research has been done on triazoles and their derivatives, demonstrating the pharmacological importance of this heterocyclic core.[2] The combination of triazoles with other biologically active moieties gives resulting molecules a larger biological profile. Examples of these compounds include bicyclic or polycyclic derivatives with triazole units and other heteroaromatic nuclei such as imidazole,[3] indole, benzothiophene,[4] pyrazolopyrimidine,[5] benzothiazole[6] or quinoline,[6b] other aromatic systems including benzodiazepine scaffolds,[7] chalcones,[8] and non-aromatic cyclic motifs, namely homoserine lactones,[9] β-lactams,[10] or oxetanes.[11] Therefore, much research has been conducted with significant advances in the development of synthetic routes to triazole-containing molecules.[12]

Various examples of triazolylglycoconjugates have been shown to possess a variety of biological effects such as antimicrobial, antitumor or anti-inflammatory properties.[13] Carbohydrates are involved in cell adhesion and other cellular recognition processes that are crucial for the development of bacterial and viral infections and inflammation,[14] tumor angiogenesis and metastasis.[15] The interference of normal cell recognition by a sugar-like molecule known as glycomimetics that mimics the bioactive function of a carbohydrate is a potential therapeutic strategy for a variety of diseases. In addition, a sugar mimetic has a tendency to inhibit enzymes acting on carbohydrates, namely glycosidases and glycosyltransferases. These enzymes are responsible for carbohydrate processing and expression, functions that are altered in some diseases such as diabetes or rheumatoid arthritis, and for the biosynthesis of disease-associated carbohydrates. Therefore, glycomimetics have emerged as molecular scaffolds of therapeutic interest. This class of compounds includes the iminosugars,[17] the thiosugars,[18] and the carbasugars,[19] which have demonstrated a broad biological profile, motivating research into efficient synthetic methods for their synthesis.[19,20] With advances in synthetic approaches to small molecules, the Carbohydrate mimics and the construction of triazolyl systems, particularly fueled by the development of the click chemistry version of the Huisgen cycloaddition,[21] significant research has been carried out over the last decade, focusing in particular on hybrid molecules in which triazolyl systems are conjugated to glycomimetic structures . Such molecules have shown promising bioactive effects by combining the ability of both cyclic scaffolds to confer bioactivity. This chapter aims to cover the synthetic strategies and biological properties of triazole-containing glycomimetics, namely triazole derivatives with iminosugar, thiosugar, and carbasugar backbones.

II. TRIAZOLE FUSED SUGARS

Triazolylglycoconjugates include molecules possessing a triazole ring attached to a sugar backbone at anomeric (i.e., glycosyltriazoles) or at other positions of sugars, conjugates in which these structural fragments are not directly linked, and compounds in which the triazole ring serves as a linking moiety between saccharidic systems, namely triazole-linked pseudo-oligosaccharides, or between a sugar moiety and another motif. Other glycoconjugates containing triazole rings include triazole-containing analogs of sugar amino acids, glycopeptides, as well as larger molecules that mimic complex multi-branched oligosaccharides such as triazole-containing glycoclusters and glycodendrimers. These types of compounds have been extensively reviewed in a number of reviews.[13,22] However, before turning to triazole-containing carbohydrate heteroanalogs, it is worth briefly commenting on the syntheses and biological profile of the conjugates constructed on normal sugar backbones.

N-Glycosyltriazoles are typically synthesized by reacting glycosyl azides with terminal alkynes. The versatility and frictionless conditions of the CuI-catalyzed azide-alkyne cycloaddition (CuAAC) process, which tolerates both *O*-protected and deprotected glycosyl azides and allows for regiochemical, anomeric, and configurational control, has enabled its application to the synthesis of a variety of glycosyltriazoles with a variety of biological activities, some relevant structures of which are highlighted here (Figure 1).

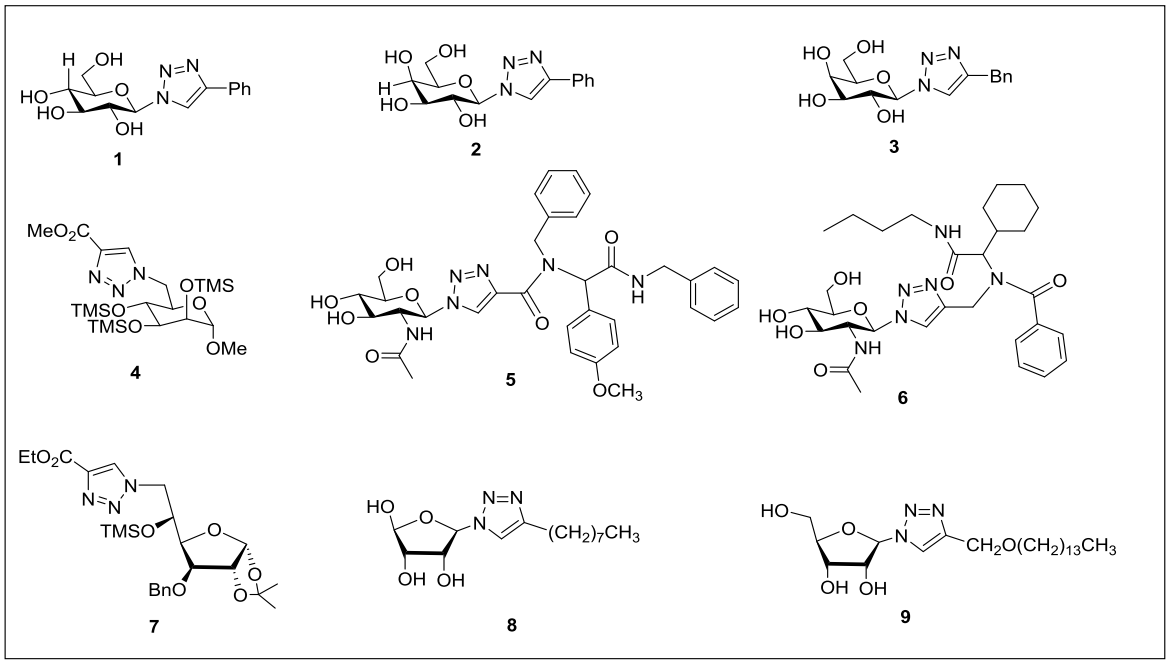
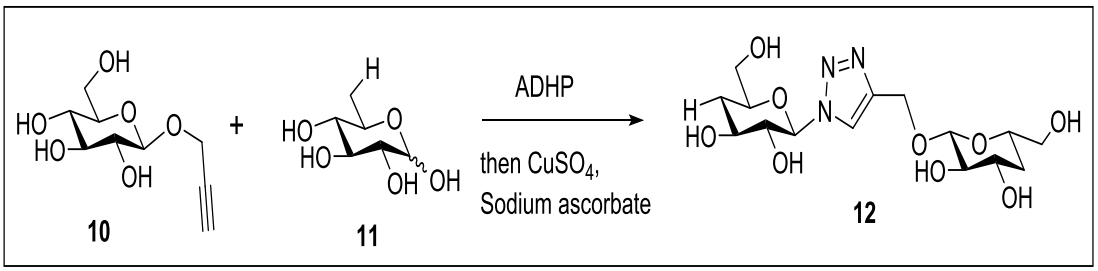


Figure 1: Glycosyl triazoles possessing biological properties.

1-Glycosyl-4-phenyltriazoles (**1**, **2**), prepared by copper iodide-catalyzed cycloaddition of peracetylated glycosyl azides with phenylacetylene and subsequent deacetylation, showed glycosidase inhibitory activity, particularly against Escherichia coli galactosidase (ECG) and bovine liver galactosidase (BLG).[23] The most prominent Compound was the 1-β-D-glucosyltriazole which showed BLG inhibition with a *Ki* of 1.6 ± 0.4mM. A library of 1-galactosyl-4-substituted triazole derivatives and related compounds possessing

the triazole moiety at C-6 of methylgalactoside was screened for their ability to target the trans-sialidase of Trypanosoma cruzi (TcTS), the causative agent of chagas disease. , which is involved in invasion of mammalian host cells.[24] Some compounds showed moderate inhibitory activity of TcTS at concentrations as low as 0.51 mM, among which the 1-galactosyl-4-benzyltriazole derivative (**3)** was the most active with 37 % inhibition was. In vitro evaluation of the trypanicidal activity of the sugar triazole library against the trypomastigote form of T. cruzi Y strain revealed that some compounds were active in the low 100 micromolar range. Similarly, 1,3-dipolar cycloadditions (click reaction) to generate 1,4-triazole derivatives (**4)** and (**7)** are also achieved by regioselective azidotrimethylsilylation of carbohydrates.[25]Ribosyltriazoles synthesized via microwave-assisted cycloadditions between arabinosylazide and terminal alkynes supported by copper iodide on silica gel,were evaluated for their in vitro cytostatic activity.[26] The triazole derivative with a 4-octyl chain **(8)** was the most potent drug of the series, the Antiproliferative activities against murine leukemia cells (L1210) and human T-lymphocyte cells (Molt4/C8 and CEM) with IC_{50} values ranging from 44 to 56 M. Compound (**8)** with hydrophobic chains of different lengths was tested using Mycobacterium bovis BCG as a model for M tuberculosis tested for antimycobacterial activity.[27] Most triazole derivatives showed mild to moderate effects on mycobacterial cell growth. The most active compound was the glycoconjugate with a tetradecyl side chain (**9**) with a minimum inhibitory concentration (MIC) value of 31 g/ml. Triazole derivatives of *N*-acetylglucosamine also showed antibacterial effects.[28] In particular, compound (**5)** inhibited the growth of Bacillus cereus with an MIC of 39 g/mL and compound (**6)** showed an MIC of 45 g/mL for B. subtilis. These activities have been linked to the ability of such compounds to inhibit *N*-acetylglucosaminidases, enzymes important in the remodeling and recycling of peptidoglycans in bacterial cell walls.

Triazole moieties have been used as linkers for the assembly of saccharide fragments, resulting in disaccharide and oligosaccharide systems. These glycoconjugates can be prepared by cycloaddition reactions between sugar azides and sugar alkynes. Some useful one-pot procedures that allow direct access to triazole-bound molecules have been developed.



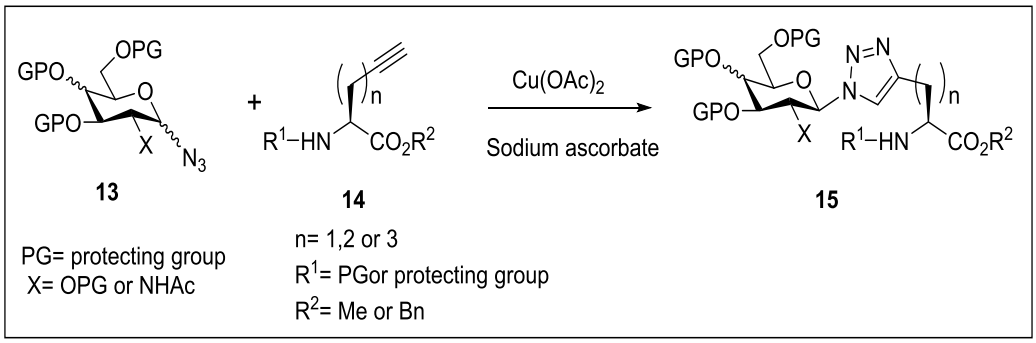
Scheme 1: One-pot synthesis of triazole-linked di- and oligosaccharides from deprotected sugars.

In one of them, propargylic mono- and disaccharide derivatives (Scheme 1,**10**) were treated with free and deprotected sugars **(11)** in the presence of 2-Azido-1,3-dimethylimidazolinium hexafluorophosphate (ADHP), which enabled in situ formation of a glycosyl azide, and copper sulfate/sodium ascorbate for the click cycloaddition process.[29b]

The reactions proceeded stereoselectively with the formation of only β-anomers (Scheme 1,**12**).

Triazole-linked *C*-disaccharides belong to another type of disaccharide analog. Their synthesis was successfully performed via a click cycloaddition method performed in an ionic liquid medium involving a benzyl-protected ethynyl-*C*-glycosyl derivative and 6-azido sugars.

Triazoles have also been exploited as linking moieties between glycosyl segments and amino acids to access glycosyl amino acid and glycopeptide mimetics. Such glycoconjugates can exhibit biological properties such as *N*- or *O*-glycosyl amino acids and *N*- or *O*-linked glycopeptides, with the advantage of being chemically and metabolically more stable than their *N*- or *O*-linked acid or dipeptide counterparts (**15**) have been demonstrated by [3+2] cycloaddition between glycosyl azides(**13)** and acetylenic amino acids (Scheme 2,**14**).[31] On the other hand, the coupling of glycosylalkynes with azide-containing amino acids is reported to afford *C*-glycosyl analogues (compounds types **16** and **17,** Figure 2).[31 ,32]



Scheme 2: Access of triazole-linked glycopeptides and glycosyl amino acids by click chemistry

Other triazole-containing glycopeptide mimics include the fucose-derived glycopeptide bistriazoles(**18)** and (**19)**, which were designed as potential selectin antagonists and whose scaffolds are based on the structure of the tetrasaccharidesialylLewis^X (sLe^X).[33] Adhesion of sLe^X to two selectins (E and P), regulates leukocyte shedding, attachment and their extravasation in inflammation, which can become a pathogenic process if excessive. Therefore, the inhibition of the sLe^X-selectin interaction by potential selectin ligands was pursued. However, studies of molecular modeling and STD NMR experiments indicated a modest ability of conjugates (**18)**and (**19)** to bind to a fucose-specific lectin.

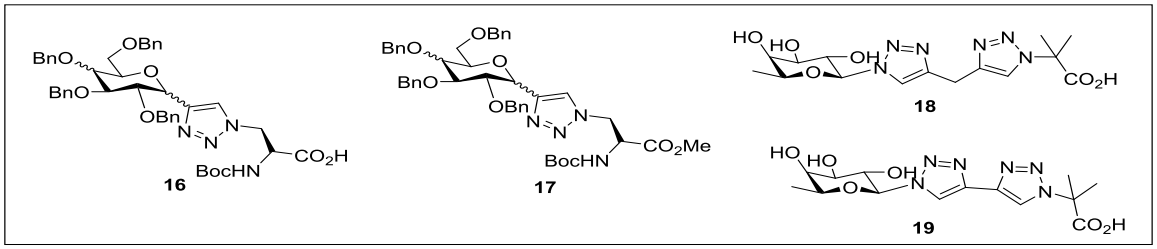
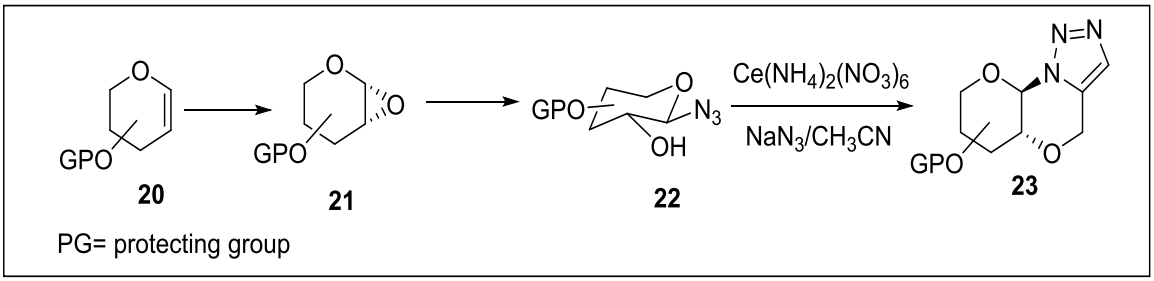


Figure 2: Triazole-containing glycoamino acid/glycopeptide mimetics.

III. TRIAZOLE-CONTAINING SUGAR-DERIVED MORPHOLINE

Several methodologies has been reported in the literature for the synthesis of morpholine derived triazole moieties. The synthesis of 1,2,3-triazoles is easily carried out by using the well-known "click chemistry" whereby an acetylene and an azide moiety are condensed under a modified procedure[34]. NaN_3, Ceric ammonium nitrate and water found to be useful reagent in the synthesis of sugar-derived 1-azido 2-alcohol derivative (22) from 1,2-anhydrous sugars (21). They (21) were further converted to morpholine linked 1,2,3-triazoles (23) which have shown good inhibition activity against few glycosidases. For example, compound (23) is a selective R-glucosidase inhibitor and exhibited fairly good activity in the micromolar range.[35]



Scheme 3: Synthesis of Morpholine linked triazole.

Triazole fused glycomimetics

In the next part, attention will be given to triazole moeity embedded on carbohydrate heteroanalog backbones, in which the sugar endocyclic oxygen atom has been replaced by nitrogen sulfur (thio sugars), (imino sugars), or carbon (carba sugars or cyclitols). The following discussion will focus on synthetic procedures of triazole derivatives that has been highlighted for their biological applications.

Triazole fused imino sugars: Iminosugars are broadly defined as sugar analogues in which the endocyclic hemiacetal oxygen atom has been replaced with nitrogen, i.e. polyhydroxylated alkaloids. They are widespread in plants and have been isolated from fermentation broths of various bacterial strains. Compounds of this class are often biologically active, generally inhibiting glycosidases by virtue of their structural and electronic resemblance to the transition states of glycoside hydrolysis.[36,37]While most iminosugars act as transition state mimics, and therefore in a competitive manner, there are examples of iminosugars that interfere with carbohydrate processing enzymes in a non-competitive fashion.[38] Glycosidases are involved in a huge number of biological processes, including those associated with a number of diseases and disorders, and inhibitors of these enzymes constitute viable therapeutic targets for the treatment of various medical conditions.[39] The dense stereochemical complexity coupled with the potential medical applications of iminosugar inhibitors makes them challenging and rewarding synthetic targets.[40,41] This thesis is primarily concerned with iminosugar synthesis from carbohydrate starting materials.

1. **Natural occurrence and significance of iminosugars:** There are five main categories into which iminosugar natural products fall: the monocyclic five- membered pyrrolidines

and six-membered piperidines; and the bicyclic pyrrolizidines, indolizidines and nortropanes (Figure 3).[42] Interest in the field of iminosugars was sparked with the isolation of the piperidine 5-deoxy-5-amino-D-glucopyranose, or nojirimycin [NJ] (**29)**, from a Streptomyces culture in the mid sixties.[43] It was not until 1973 that iminosugars were first reported from plant sources with the isolation of fagomine [FG] (**30)**,[44] which is the 1,2-dideoxy analogue of NJ (**29)**. Shortly afterwards came the isolation of 1-deoxy-NJ [DNJ] (**31)** from mulberry trees,[45] which had already been synthesised a decade earlier with the discovery of NJ (**29)**,[46] and it as later isolated from bacterial culture.[47] The pyrrolidine 2,5-dideoxy-2,5-imino-D-mannitol [DMDP] (**32)** was also first isolated around this time,[48] and has since been found in a very wide range of plant sources.[42] FG (**30)**, DNJ (**31)** and DMDP (**32)**, so called iminocyclitols, all lack the hemiaminal function of NJs, which greatly increases their stability. As a result, much of the focus in the synthetic field is associated with these iminocyclitols, this thesis being no exception. Following these early discoveries, the array of known naturally occurring iminosugars, especially from plant sources, has exploded.

The first isolated indolizidines were swainsonine (**36)**[49] and castanospermine (**35)**[50] from Australian legumes Swainsonacanescens and Castanospermum australe around 1980, which had been known to be toxic to livestock for some time. The first pyrrolizidines appeared towards the end of the decade in the form of alexine (**33)**[51] and australine (**34)**[52] from Alexa leiopetala and C. australe, along with the first polyhydroxylated nortropanes, the calystegines,[53] from Calystegiasepium. When specifically screened for, iminosugars can often be found in common plants in which their existence was hitherto not considered. Many potatoes are particularly rich sources of nortropane iminosugars,[54] which survive cooking, including the various processes in the manufacture of crisps, and are consumed regularly by an enormous proportion of the world's population. Many traditional herbal medicines contain relatively high levels of iminosugars and it has been suggested that it may be these nitrogen heterocycles that confer the health benefits associated with the plant extracts,[55,56] Mulberry leaves, which are a rich source of the glucosidase inhibitor DNJ (**31)**, are used in traditional Chinese medicine to treat type II diabetes.[42] The N-hydroxyethyl DNJ derivative miglitol is a liscenced drug that serves the same purpose. Some animals have been found to store iminosugars; the pupae of the Swallowtail moth Urania fulgens feed on iminosugar rich plants and store the alkaloids into maturity, even the eggs laid by the adult moths contain iminosugars.[57] The precise reason for the accumulation of iminosugars in animals is not certain, but a plausible explanation is a defence mechanism associated with the toxicity of some iminosugars, or even simply reducing the nutritional value of an insect through inhibition of the predator's digestive enzymes. The Death's- head hawk-moth (Acherontiaatropus) stores calystegines, including calysegines A_3 (**37)** and B_2 (**38)**, gained from the potatoes that nourished its pupa,[54] and bees accumulate iminosugars from iminosugar-containing nectars; some African varieties of honey show relatively high levels of iminosugars and may have health benefits associated with them.[58] The UK's common bluebell Hyacinthoides non-scripta is a rich source of iminosugars and grows in woodland traditionally fenced off for the protection of livestock, to which it is toxic.[59] On the other hand, it has been observed that badgers are quite partial to the common bluebell, and given the antibacterial properties of some iminosugars this could be interpreted as self-medicating behaviour in an animal renowned as a carrier of tuberculosis, particularly in the south-west of England – though this would be quite a leap of deduction.

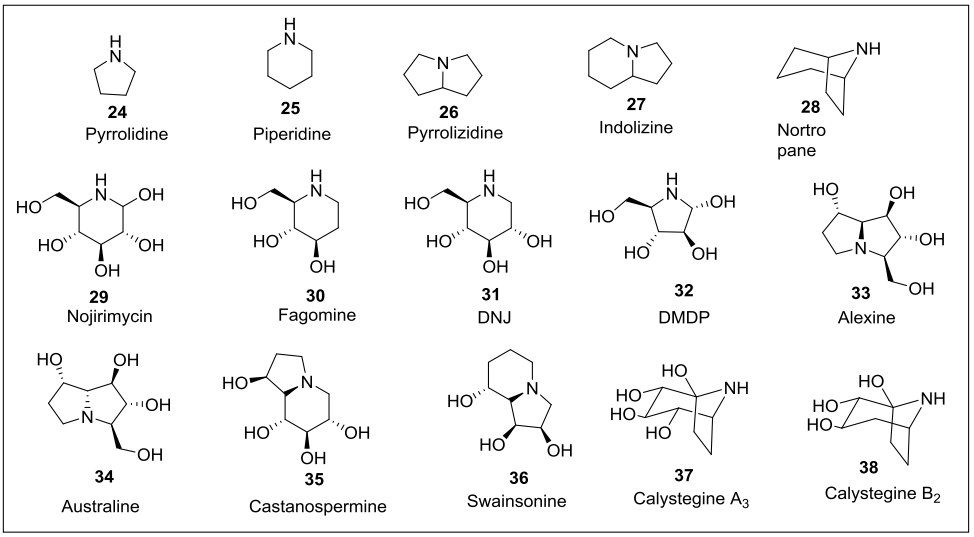
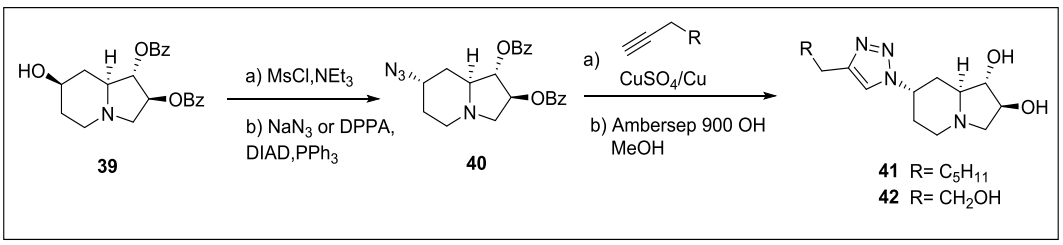


Figure 3: Generic iminosugar scaffolds and examples of naturally occurring iminosugars

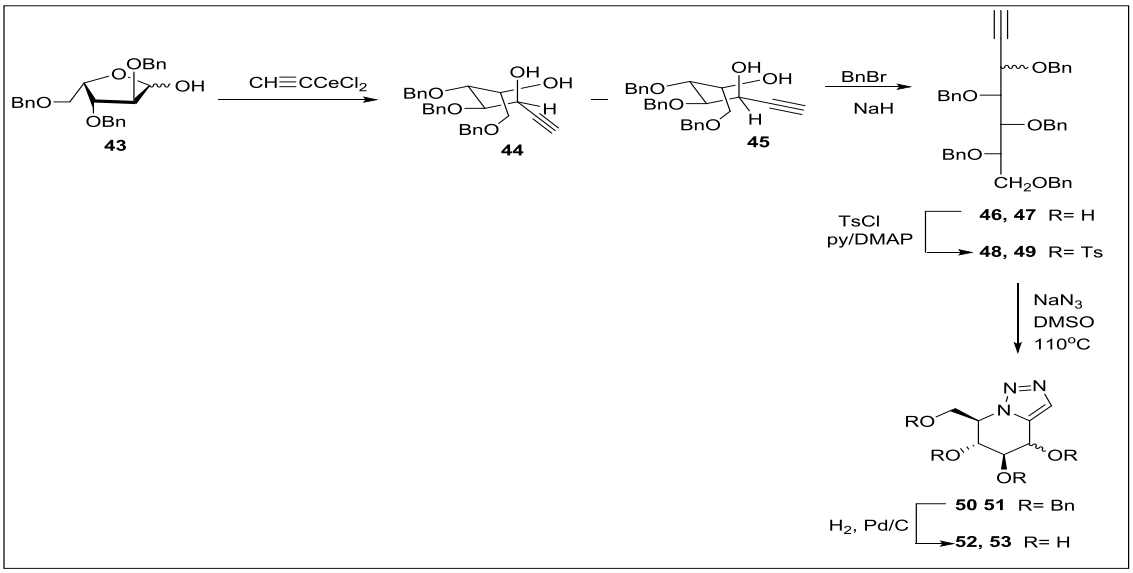
2. **Synthesis of triazole linked iminosugars:** Molecules in which a triazole moiety is *C*-linked to 2-deoxyiminosugars based on hydroxylated piperidine or azepane systems at the endocyclic nitrogen were synthesized by the cycloaddition reaction of N-propargyliminosugars and alkyl azides.[60] Bicyclic deoxyiminosugar-triazole conjugates composed of polyhydroxylated indolizidine structures attached to C-7 linked to a triazole moiety (**41**–**42**,Scheme 4) were synthesized based on the structure of (+)-lentiginosine, which is a selective inhibitor of amyloglucosidases.[61] Hence the indolizidinol (**39)** was obtained via mesylation and further nucleophilic exchange into the corresponding 7-azido derivative (**40)** with sodium azide or directly under Mitsunobu conditions using diphenylphosphorylazide (DPPA), diisopropylazodicarboxylate (DIAD), and triphenylphosphine. 1,3-Dipolar cycloaddition of (**40)** with 1-octyne or 3-butyn-1-ol in the presence of in situ generated Cu(I) followed by hydrolysis of the benzoate groups gave the desired triazole derivatives (**41)** and (**42)** in 80 % and 45 % overall yield, respectively. These molecules showed moderate inhibitory activities on amyloglucosidase (16-26%) and -glucosidase (17%-67%) at 1 mM.



Scheme 4: Synthesisoftriazole-containingindolizidines

Fused triazole iminosugar hybrids were designed and synthesized as potential glycosidase inhibitors, designed to mimic the transition state of natural substrates in enzyme catalysis. Various conjugates based on a triazole fused structure have been reported that involve a sp^2 anomeric carbon such that it might adopt a closed and flattened

half-chair conformation that might be very similar to the oxocarbenium ion. The earliest reported synthesis of compounds of this type involved 5–7 steps starting from tri-O-benzyl-L-xylofuranose **(43**,Scheme 5).[62] It was converted into heptitols (**44)** and **45** in 86% yield by treatment with ethynylcerium(III) dichloride.



Scheme 5: Early synthesis of triazole-fused iminosugars

Alternatively, a larger-scale synthesis of (**44–45)** was performed in three steps, involving oxidation of (**27)** to the aldonolactone, followed by addition of (trimethylsilyl)ethynyllithium, and subsequent reduction of the resulting hemiacetals with sodium borohydride. Regioselective benzylation of (**44–45)** afforded (**46–47)**, which after tosylation and further treatment of the resulting tosylates(**48–49)** with sodium azide in DMSO at 110°C directly afforded the triazole derivatives (**50–51)**via intramolecular cycloaddition of the intermediate azidoalkynes. Debenzylation of (**50-51)** provided the target compounds (**52-53)**. Evaluation of the glycosidase inhibitory activity of (**52)** and (**53)** revealed low activity against all enzymes tested. Compound (**52)**, which has a gluco configuration, showed the best activity with an IC_{50} of 2mM for the glucosidase from Caldocellunsaccharolyticum, while the natural substrate had a KM of 1.5mM. These results suggest that the presence of a lone pair-providing heteroatom directly linked to the pseudoanomeric carbon in the triazole system, which can potentially be protonated, is essential for binding to the enzyme.

The effect that the replacement of the OH-2 in (**52)** with an amino group and with an *N*-acetylamino group would have on the glycosidase inhibitory ability of this type of fused derivatives was then investigated (Scheme 5).[63] Thus improved bioactivity was derived from the glucosamine related triazoles **54** and **55** are shown. At optimal pH, (**54**) showed a lower IC_{50} value (0.9 mM) against *C. saccharolyticum* than the corresponding alcohol counterpart (**52)** (IC_{50} = 2 mM), while the *N*-acetyl derivative (**55**) has a much better enzyme inhibitor profile than the previous ones derivatives and has been shown to inhibit bovine kidney *N*-acetylglucosaminidase with an IC_{50} of 8 mM.

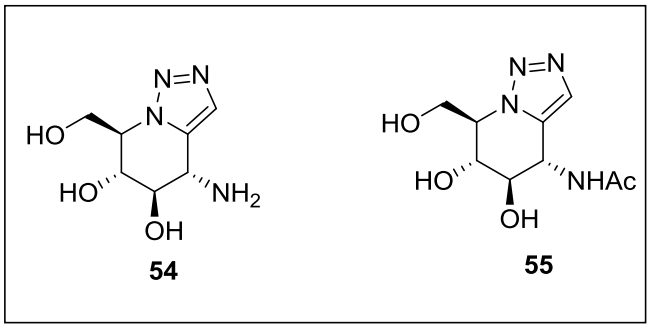
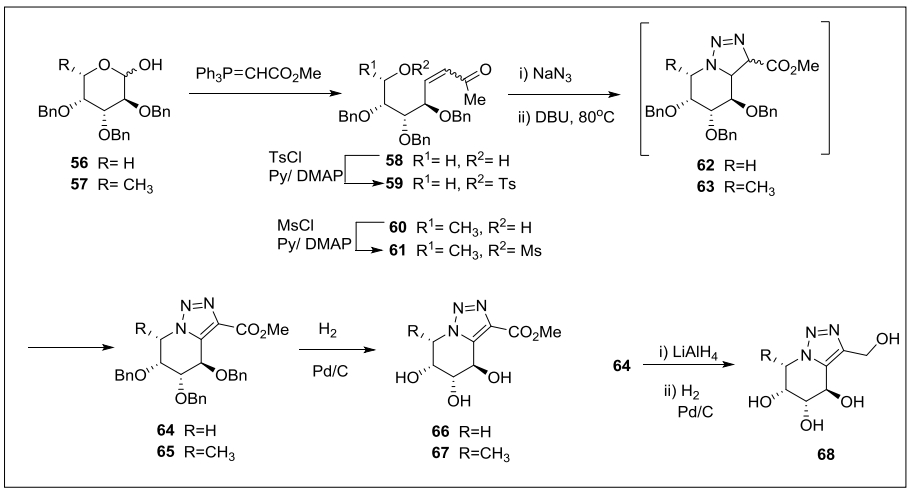


Figure 4: Glucosamine-relatedtriazole-fusediminosugars

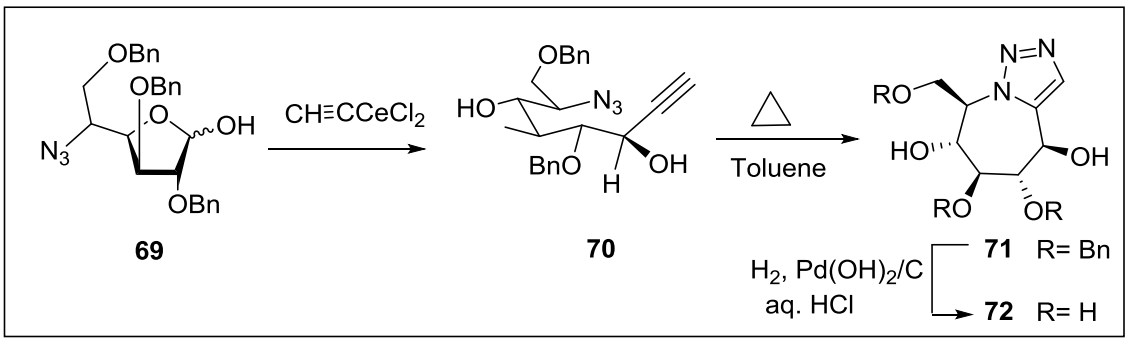
In another work, fused triazole bicyclic carboxylic acids comprising hydroxylated piperidine systems with D-gluco and D-galacto configurations were synthesized as potential anionic mimetics of carbohydrates and their glycosidase inhibitory potential was investigated.[64] Although none of the compounds showed significant glycosidase inhibition , The D-gluco-configured triazole carboxylic acid showed an inhibitory effect on glycogen phosphorylase b (GPb), a therapeutic target for type 2 diabetes, with a *Ki* value of 7.4 mM.

Triazole-fused iminosugars with D-arabino and L-fuco configurations could be synthesized in 8 steps from D-arabinose and L-fucose.[65] The key transformation was achieved by an efficient one-pot p The effect that the replacement of the OH-2 in (**52**) with an amino group and with an *N*-acetylamino group would have on the glycosidase inhibitory ability of this type of fused derivatives was then investigated (Scheme 5).[63] Thus improved bioactivity was derived from the glucosamine related triazoles (**54**) and (**55**) are shown. At optimal pH, 54 showed a lower IC_{50} value (0.9 mM) against *C. saccharolyticum* than the corresponding alcohol counterpart (**52**) (IC_{50} = 2 mM), while the *N*-acetyl derivative (**55**) has a much better enzyme inhibitor profile than the previous ones derivatives and has been shown to inhibit bovine kidney -*N*-acetylglucosaminidase with an IC_{50} of 8 mM. involving azide introduction and intramolecular addition to an unsaturated carbonyl functionality and oxidation (Scheme 6). Thus, the conveniently accessible 2,3,4-tri-*O*-benzyl derivatives of D-arabinose and L-fucose **(56,57)** were converted into stereoisomeric mixtures ofunsaturated esters (**58)**and (**59)** by a Wittig reaction (**58)** and mesylation of (**59)** gave the corresponding sulfonate esters (**60)**and (**61)** respectively. Subsequent treatment of (**59)** and (**60)** with sodium azide followed by *in situ* addition of 1,8-diazabicyclo-[5.4.1]-undec-7-ene -DBU, generated the triazoles (**64)** and (**65)** through spontaneous oxidation of the intermediate triazoline derivatives (**62, 63)** in an overall yield of 30 %. The scope of this transformation has been extended to an allylic alcohol analogue containing an azide functionality, which upon oxidation develops through intramolecular cycloaddition of the corresponding α,β-unsaturated aldehyde intermediate to the bicyclic triazole derivative. Debenzylation of (**64,65)** gave the deprotected triazole conjugates (**66,67**) while (**64)** also underwent reduction of the ester functionality followed by hydrogenation to give (**68).**



Scheme 6: Synthesisoftriazole-fusediminosugarsviaaone-potsubstitution–cyclization–oxidation procedure

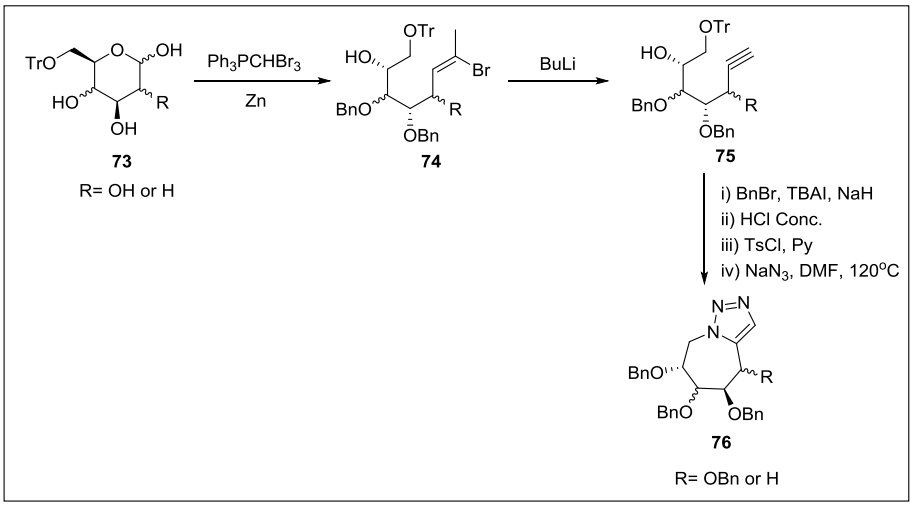
Bicyclic fused triazoles, which embody higher homologues of hydroxylated iminosugars, namely polyhydroxylated azepanes, as the core structure have also been reported. These triazole conjugates can be prepared in a few steps by intramolecular 1,3-dipolar cycloaddition of azide-containing glycoinitols. The azepanic counterpart of compound (**52)**(Scheme 5) was prepared in three steps in 72 % overall yield from 5-azido-5-deoxy-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene. D-glucofuranose **(69,** Scheme 7).[66]Ethylation of (**69)**stereoselectively afforded the octinitol(**70)**, which evolved to the triazole-fused azepane(**71**) upon heating in toluene. Final deprotection provided the target compound (**72).**



Scheme7: Synthesis of a triazole-fused azepane

A variety of fused triazole azepanes were accessed from tritylated aldoses (compounds type **73**, Scheme 8) by a methodology different from that previously reported in the early step of chain elongation at the anomeric center. Thus, the introduction of the terminal alkyne functionality was accomplished by a two-step procedure that avoided the formation of a new stereocenter at the sugar core.[67] The hemiacetal underwent Wittig-type olefination to afford a dibromoolefin**(74)**, which upon treatment with butyllithium, gave the glyco-ynitol**(75).** A sequence of benzylation, detritylation, tosylation, and a one-pot azide substitution/thermal cyclization procedure afforded the target fused triazoles **(76).**

This strategy has been successfully applied to the synthesis of bicyclic triazole derivatives in which the azepane backbone includes a 2-deoxy-D-gluco, D-gluco, D-manno, and D-galacto configuration.



Scheme 8: Synthesis of a triazole-fused azepanes comprising 2-deoxy-D-gluco,D-gluco,D-manno and-galacto configuration.

Triazoles fused to hydroxylated pyrrolidines were designed to behave like conformationally restricted iminosugars in the search for more specific glycosidase inhibitors. Few reports on the synthesis of pyrrolidotriazoles have been published.[68] A recent study on triazole-containing analogues of iminosugar-type pyrrolizidine alkaloids, including L-ribo**(77),**L-xylo**(88),**L-arabino **(79),** and L-lyxo**(80)** configuration (Fig. 5).[68c] Their synthesis required 8 steps from glycal-derived δ-hydroxy-α,β-unsaturated aldehydes and involved a one-pot thermal tandem azidation/intramolecular cycloaddition procedure of the azidoacetylene intermediates. These molecules were subjected to glycosidase inhibition assays using a panel of eleven enzymes. All compounds showed selective, potent and specific inhibition of α-glucosidase from rice and from *Aspergillus niger* with $K_i$values ranging between 11.48 and 40 μM. The conformational restriction of these compounds due to their fused and planar structure has been suggested as a key factor for the one observed high degree of enzyme inhibition selectivity.

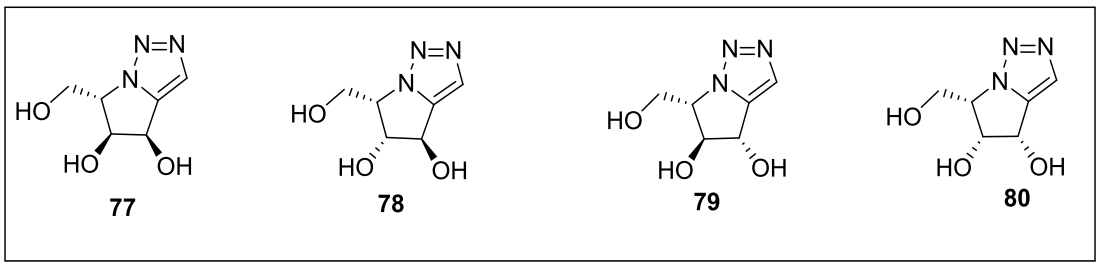


Figure 5: Triazole-fused pyrrolidine imino sugars possessing selective glycosidase inhibitory activitytowardsα-glucosidasefrom riceand from *Aspergillus niger*.

Triazole fused thiosugars: The replacement of the ring oxygen in carbohydrates by its closely related neighbor in the periodic table, sulfur, leads to remarkable changes in physicochemical and biological properties due to the electronic difference between the sulfur and oxygen atoms. The sulfur atom is less electronegative and more polarizable, which modifies the reactivity of the thiosugars relative to their naturally oxygenated counterparts. Therefore, thiosugars play an important role as glycomimetics and have been reported as potent inhibitors of glycosidases as well as other therapeutic targets relevant to various diseases such as diabetes, Gaucher disease, cancer, cystic fibrosis, HIV infection or tuberculosis, with the advantage of being less susceptible for hydrolysis and metabolic attack, resulting in improved bioavailability. [69] The first examples of thiosugars were reported in the early 1960s with the synthesis of 5-thio-L-idopyranose (81, Figure 6) and 5-thio-D-xylopyranose.[70] Since the isolation of 5-thio-D-mannose (82) from the sea sponge Clathriapyramida in 1987,[71] notable examples were given by nature, such as salacinol (83) and kotalanol (84), which were isolated from an antidiabetic Ayurvedic drug Salacia reticulate WIGHT and proved to be potent inhibitors for intestinal α-glycosidases such as sucrose, maltase and isomaltase.[72]

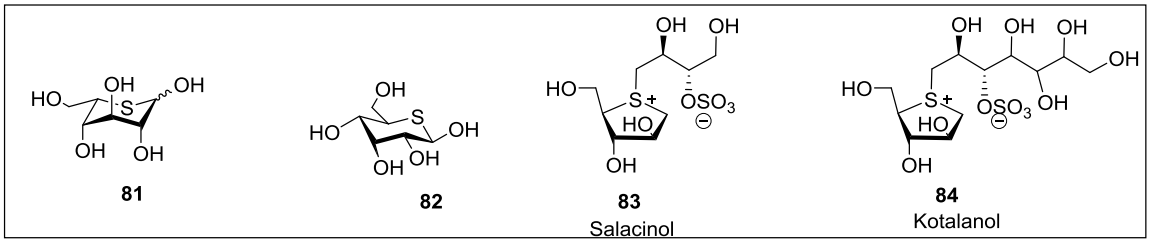
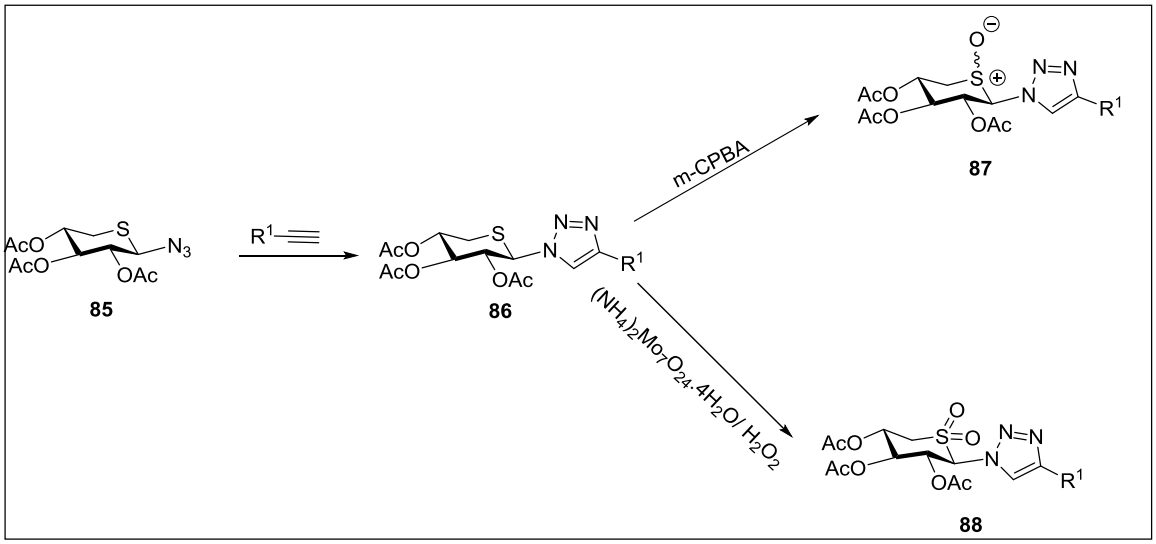


Figure 6: Synthetic and natural thiosugars.

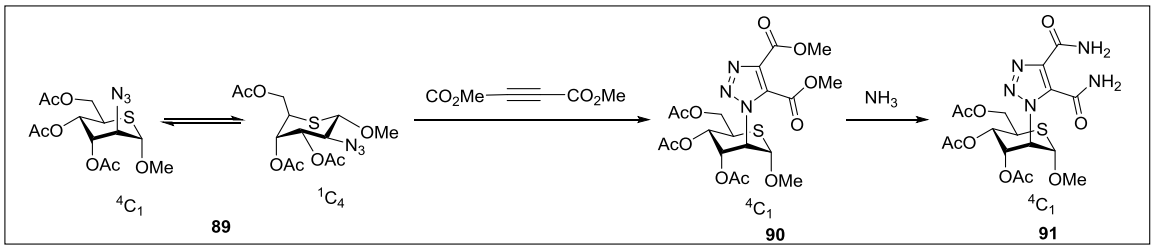
Therefore, the interest in expanding the scope of thiosugars has led to the development of suitable synthetic methods for highly functionalized thiosugarglycomimetics. Recent examples include the new access to 5-thio-D-galactopyranose from diacetone galactofuranose, (**73)** the enzymatic and organocatalyzed asymmetric aldolization reactions to thiofur

Recently, 5-thioxylopyranosyl-1,2,3-triazoles **(86,** Scheme 9) were synthesized through the CuAAC methodology using 5-thioxylopyranosyl azides with a variety of acetylenes and further controlled oxidation of the endocyclic sulfur, leading to the synthesis of corresponding sulfoxides and sulfones **(87, 88)**. These compounds have been evaluated as glycogen phosphorylase inhibitors; nevertheless, they showed weak inhibition compared to the oxo-glucopyranosyl analogues, most likely due to the lack of the hydroxymethyl group.[75]



Scheme 9: CuAAC for the synthesis of 5-thioxylopyranosyl 1,2,3-triazoles and controlled oxidationtowardsulfoxides and sulfones

Following the idea that triazole building blocks might confer extracellular viability and anticancer properties, the first report of thiosugars with a 1,2,3-triazole motif arose from the cycloaddition of 2-azidoaltroside (**89**, Scheme 10) with dimethyl acetylenedicarboxylate to form intermediate **(90)** which was further converted into the desired 4,5-dicarboxamide derivative **(91).**[76] Possibly due to the repulsion between the triazole substituent at C-2 and the methoxyl group at C-1, the triazole Derivatives 90 and 91 take adopts the $^4C_1$ conformation, in contrast to the starting azide(**89)**, in which both the $^4C_1$ and $^1C_4$ forms are in equilibrium. Therefore, the triazole isothionucleoside introduces significant steric differences that can lead to favorable biological properties, nevertheless no further activity assays for this derivative have been reported.



Scheme 10: Synthesis of 1,2,3-triazoloisothionucleosides from 2-azido-altroside

Triazole fused carbasugars: Highly functionalized cyclohexanes or cyclopentanes that resemble carbohydrate structure and mimic their biological activity have been termed pseudosugars, carbasugars, or cyclitols. Due to the correct orientation of the ring substituents, these molecules can inhibit important biological targets, although they lack the sugar endo-oxygen atom, which is replaced by a non-hydrolyzable methylene, resulting in analogs that are more stable towards endogenous degrading enzymes than at any typical one carbohydrate reaction.[69] This similarity along with the idea of promising improvements in pharmacological properties led to the synthesis of pseudosugars such as 5a-carba-α-D-talopyranose**(92,** Figure

7) and 5a-carba-α-D-galactopyranose**(93)** in 1966 ,[77] showed antibiotic activity, but a few years later 5a-carba-α-D-galactopyranose was isolated from a natural source of *Streptomyces sp* fermentation.[78] Therefore, extensive efforts have been devoted to the synthesis and identification of new carbasugars with therapeutic interest and one of the recent most popular examples is oseltamivir **(94),** the neuramidase inhibitor introduced as Tamiflu to treat influenza virus synthesized from natural carbasugars shikimic acid **(95)** or quinic acid **(96).**[79]

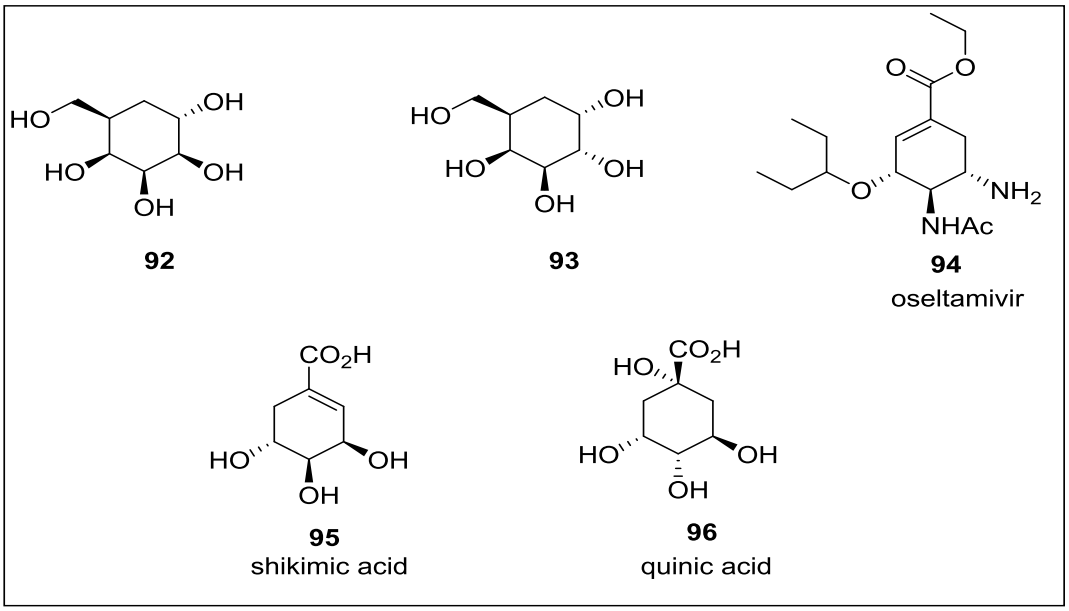


Figure 7: Natural and synthetic carbasugars.

Ribavirin (**97**, Fig. 8) is a 1,2,4-triazolylnucleoside that was discovered in the early 1970's in a campaign by the ICN Pharmaceuticals Nucleic Acid Research Institute to provide new nucleosides that would be effective as antiviral agents. Remarkably, ribavirin is clinically effective against unrelated viruses from three different families, such as chronic hepatitis C virus (HCV), Lassa fever virus and respiratory syncytial virus (RSV), which have very different RNA viruses with virtually no sequence homology.[80,81] These properties have made ribavirin a drug of significant research interest and have also expanded research efforts on its carba-sugar analogues. For the synthesis of carbaribavirine**(98)** and 5-norcarbaribavirine **(99),** the 1,2,4-triazole moiety was achieved by hydrazine coupling with ethylcarbethoxyformimidate followed by ring closure. However, no significant antiviral activity was observed for these analogues.[82,83] 2,3-didehydroxycarbocyl-ribavirin was obtained by a Pd(0)-catalyzed coupling between the heterocyclic base and the cyclopentenyl derivative.[84]To access 1,2,3-triazolyl derivatives of ribavirin, the synthetic strategy is based on the reaction of carbasugar azides with various acetylenes. Carbocyclic and phosphonocarbocyclic analogues **(100, 101)** have been envisaged against HCV; however, no significant activity was observed. However, when screened using other viruses, these compounds are found to be moderate HIV-1 inhibitors with IC_{50} values of 43.8 and 37 μM, respectively[85]

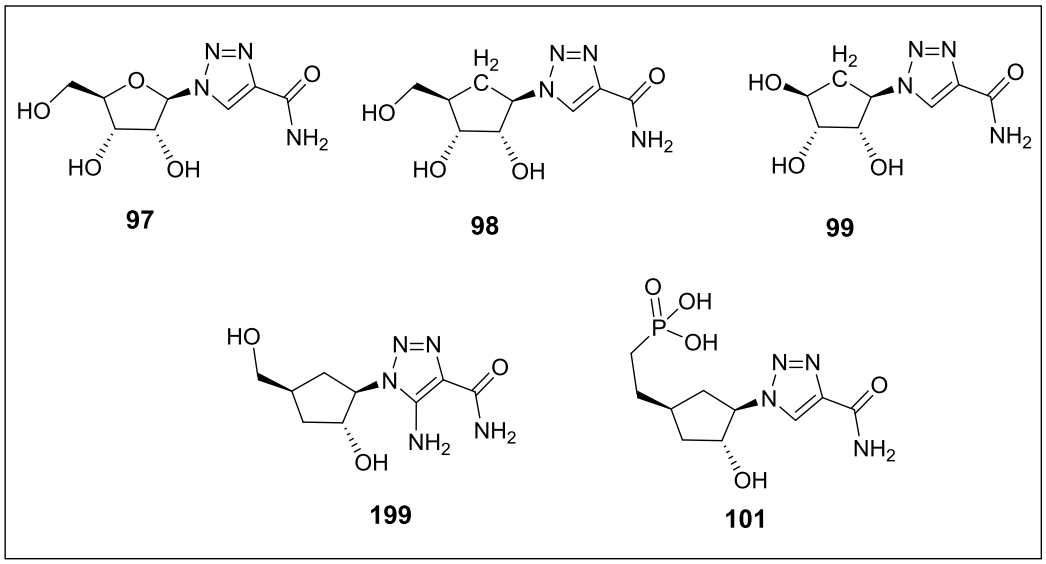
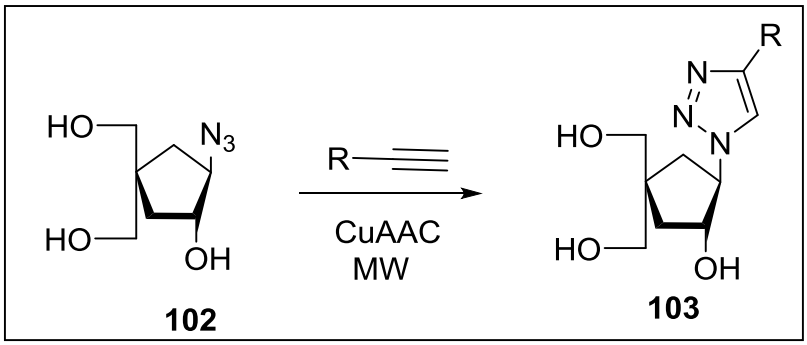


Figure 8: Ribavirin and its carbasugar analogs

A methodological study was performed to evaluate the copper-catalyzed azide–alkyne cycloaddition (CuAAC) process for the rapid conversion of the azido carbocycle (**102)** into the desired carbanucleosides(**103)** and microwave irradiation with Cu(0)/$CuSO_4$ was found to be the most efficient system for this reaction.[86,87] However, none of the compounds synthesized inhibited the production of vaccinia virus (Lister strain) or vaccinia virus (Brighton strains) in Vero cells as intended by the authors.1,2,3-Triazolyl iodocarba nucleosides and 2,3-Didehydrocarba nucleosides have been evaluated as antiviral agents. The synthesis was based on an iodoazidecarba-sugar as an intermediate to a library of compounds, however only one of the synthesized compounds showed moderate activity against varicella zoster virus kinase positive strain (EC_{50} 4.5 μg).[88]



Scheme 11: CuAAC methodology under microwave irradiation

Recently, Corey lactone was used as a starting material for the additional decoration of the cyclopentane ring of carbasugar nucleosides, leading to the promising structures (**105)** and (**106)** (Fig. 9), which have not previously been investigated for their biological properties.[89]

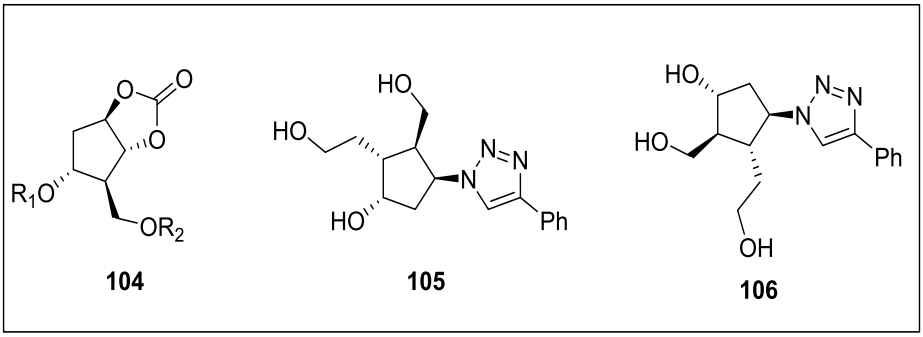


Figure 9: Corey lactone and its 1,2,3-triazole derivatives.

In order to obtain synthetic analogues of neplanocin A (NPA, **107**, Figure 10), a carbocyclic nucleoside isolated from *Ampullariellaregularis,* as potential antiviral agents, use of the ring-closing metathesis method led to the synthesis of the carbasugar 108 towards the access to 1,2,4 - and 1,2,3-triazoles using either Mitsunobu or CuAAC approaches, respectively. While the 1,2,4-triazole carbocyclic nucleoside (**109)** showed only moderate activity against severe acute respiratory syndrome coronavirus (SARSCoV, EC_{50} 21 μM) when tested against a panel of viruses, the corresponding 1,2, 3-Triazole (**110)** moderate activities against SARSCoV (EC_{50} 47 μM) and cowpox virus (EC_{50} 39 μM), but strong activity against vaccinia virus (EC_{50} 0.4 μM). These results indicate the importance of the triazolyl moiety for activity/selectivity.[90]

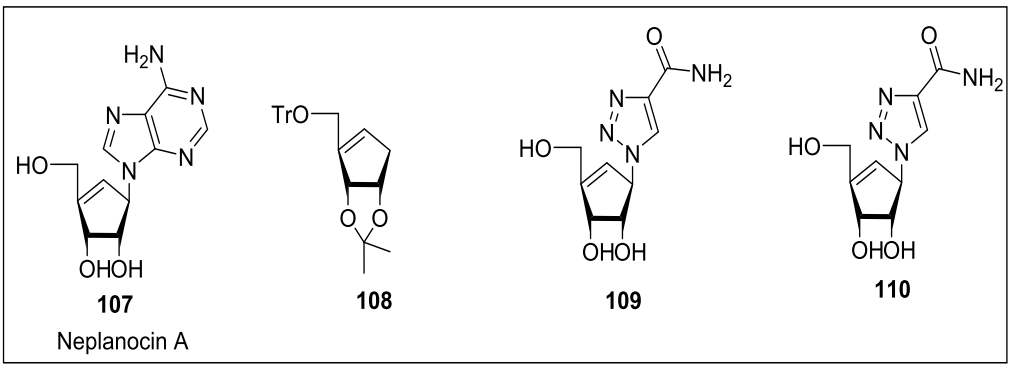


Figure 10: NeplanocinA and its carbasugar precursor and analogs.

Hygromycin A (**111**, Figure 11) is a natural antibiotic that also exhibits immunosuppressive activity and was first isolated from *Streptomyces hygroscopicus* with well-defined pharmacophoric moieties including cyclitol, cynnamoyl, and furanose. Based on the finding that the furanose counterpart was not mandatory for activity, a diversity-oriented design of azidocyclitols and alkynes was envisaged to explore and tune the activity of related dimer structures **(112).** However, the compounds synthesized showed promising antifungal activity but lacked the immunosuppressive effects described for hygromycin A.[91]

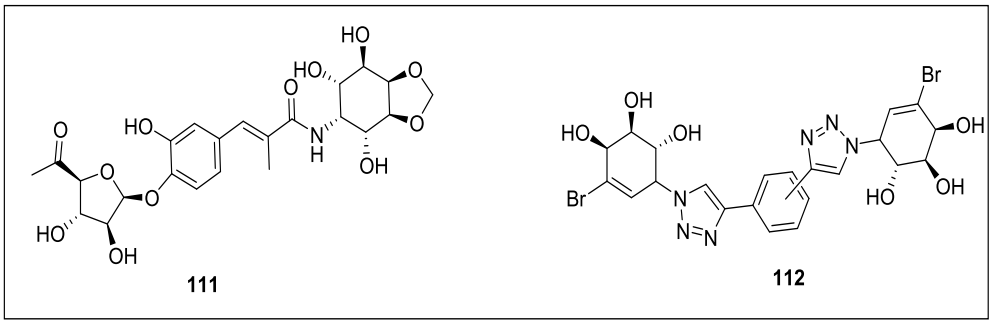


Figure 11: Hygromycin A(111)and its related triazole linked dimeric structures(112).

N-substituted aminocyclitols were envisioned as potential glucocerebrosidase (GCase) chaperones with pharmacological interest in Gaucher disease, so a small library of 1,2,3-triazole derivatives with alkyl spacers of different lengths (**113**, Figure 12) was designed and was synthesized. Shorter spacers (n = 1) between the alkyltriazolyl system and the aminocyclitol core led to the most active GCase inhibitors with $K_i$in the nM range, revealing a determining effect of the position of the triazole ring on activity.[92]

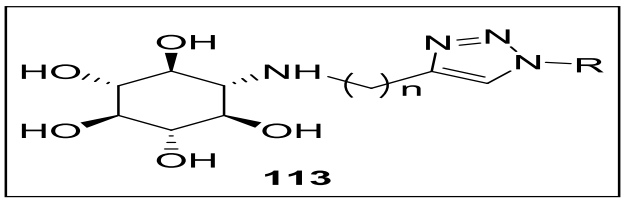
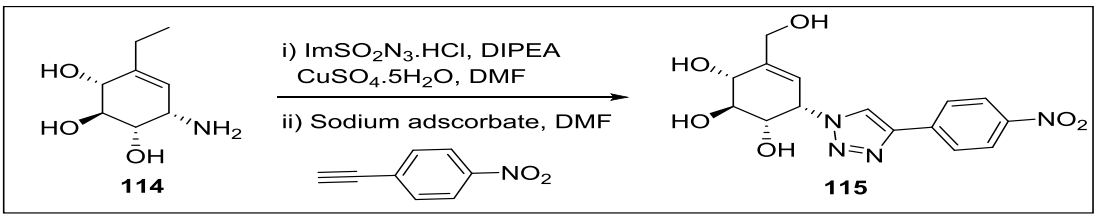


Figure12: *N*-substituted aminocyclitols with GCase inhibitors

Recently, the synthesis of a C_7-*N*-aminocyclitol-derivatized 1,2,3-triazole library was accomplished by an elegant one-pot diazotransfer followed by CuAAC using imidazole-1-sulfonylazide hydrochloride as an efficient and storage-stable diazotransfer reagent (exemplified in Scheme 9 shown). Valienamine (**114**), validamine, and valiolamine were used as starting materials to provide the desired triazoles (such as **115**) in 72–89 % yields, demonstrating a broad scope for using this method to synthesize glycomimetics.[93]



Scheme 12. One-potsynthesis of triazolylaminocyclitols

IV. CONCLUSIONS

Triazoles are one of the most important heterocyclic system that have gain much attention in the past few decades owing to their presence in many bioactive molecules. They are recognized as emerging molecules in the field of medicinal chemistry and have motivated

the design and synthesis of molecules in which the triazole is core nucleus combined with other heteroanalogue of high bioprofile. Molecules containing triazole units are known to display a wide variety of biological relevance. Carbohydrates are amongst those molecular frameworks and triazole have proven their healing potential. Next to carbohydrates, their mimetics heteroanalogs, specifically imino sugars, carba sugars and thio-sugars, came out to be appealing scaffolds of pharmacological interest and innovative triazole conjugates containing those moieties have attracted large interest as targets. Efficient synthetic procedures for the development of those varieties of molecules, wherein the triazole unit can be related or fused to the sugar moiety or it can also act as connecting unit to every other fragment, had been developed by utilizing the azido-alkyne cycloaddition methodology. Triazole-glycomimetics conjugates proved to be important for inducing conformational constrain and permitting selectivity of glycosidase inhibition. Studies conducted till date shows that the combination of triazoles and glycomimetics structures holds promise in drug discovery, especially for the development of more potent and selective glycosidase inhibitors for therapeutics applications and antiviral compounds.

V. ABBREVIATIONS AND ACRONYMS

Ac	Acetyl
ADHP	2 -Azido-1,3-dimethylimidazolinium hexafluorophosphate
allo-DNJ	1-Deoxyallonojirimycin, 1,5-dideoxy-1,5-imino-D-allitol
altro-DNJ	1-Deoxyaltronojirimycin, 1,5-dideoxy-1,5-imino-D-altritol
aq	Aqueous
BCG	Bacillus Calmette-Guerin
Boc	*tert*-Butoxycarbonyl
Bu	n-Butyl
Bn	Benzyl
BLG	bovine liver galactosidase
CAN	Ceric ammonium nitrate
CH_3CN	Acetonitrile
Cbz	Benzyloxycarbonyl
CuAAC	CuI-catalyzed azide-alkyne cycloaddition
$Cu(OAc)_2$	Copper acetate
$CuSO_4$	Copper sulphate
Cy	Cyclohexyl
d.r.	Diastereomeric ratio
DCM	Dichloromethane
DGDP	2,5-Dideoxy-2,5-imino-D-glucitol
DGJ	1-Deoxygalactonojirimycin, 1,5-dideoxy-1,5-imino-D-galactitol
DIAD	Diisopropyl azodicarboxylate
DMDP	2,5-Dideoxy-2,5-imino-D-mannitol
DMF	Dimethylformamide
DMJ	1-Deoxymannonojirimycin, 1,5-dideoxy-1,5-imino-D-mannitol
DMSO	Dimethylsulfoxide
DNJ	1-Deoxnojirimycin, 1,5-dideoxy-1,5-imino-D-glucitol
DPPA	diphenylphosphoryl azide
ECG	Escherichia coli galactosidase
Et	Ethyl
FG	Fagomine, 1,2-dideoxynojirimycin, 1,5-imino-1,2,5-trideoxy-D-*arabino*-hexitol

GCase	glucocerebrosidase
GPb	glycogen phosphorylase b
h	Hours
HIV	Human immunodeficiency virus
HCV	hepatitis C virus
IC_{50}	Half maximal inhibitory concentration
IPA	Isopropanol
K_i	Inhibition constant
LAB	1,4-Dideoxy-1,4-imino-L-arabinitol
m.p.	Melting point
Me	Methyl
mCPBA	Meta perchloro benzoic acid
min	Minutes
MIC	minimum inhibitory concentration
mM	mili molar
n-Bu	n-Butyl
NaN_3	Sodium azide
NH_3	Ammonia
NJ	Nojirimycin, 5-amino-5-deoxy-D-glucopyranose
NPA	neplanocin A
Ph	Phenyl
Py	Pyridine
R_f	Retention factor
RSV	respiratory syncytial virus
RT	Room temperature
sLe^X	tetrasaccharide sialyl $Lewis^X$
SARSCoV	severe acute respiratory syndrome coronavirus
TBAF	Tetra-*N*-butylammonium fluoride
TBDPS	*tert*-Butyldiphenylsilyl
TBS	*tert*-Butyldimethylsilyl
^tBu	*tert*-Butyl
TcTS	Trypanosoma cruzi
TEA	Triethylamine
Tf	Trifluoromethanesulfonyl
TFA	Trifluoroacetic acid
THF	Tetrahydrofuran
Tosylate	*p*-Toluenesulfonate
Triflate	Trifluoromethanesulfonate
Ts	*p*-Toluenesulfonyl

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