TRIAZOLE-CONTAINING CARBOHYDRATE MIMETICS: SYNTHESIS AND BIOLOGICAL APPLICATIONS

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Abstract. *The synthesis and biological properties of triazole-containing glycomimetics, namely molecules comprising carbohydrate heteroanalog frameworks and triazole moieties in their structure, are covered. The different kinds of compounds focused herein encompass imino sugar-, thio sugar- and carba sugar-triazole conjugates, which have recently emerged as molecular targets of biological relevance.*

Contents

1. Introduction

Triazoles are among the heterocyclic systems that have attracted much attention in the last two decades owing to their presence in many bioactive compounds. Molecules embodying triazole units were shown to display a wide variety of biological properties, such as antitumor, anti-inflammatory, antiviral or antimicrobial, and thus potential for therapeutic applications.[1] The ability of triazole rings to interplay with biomolecular targets arise from their high dipole moment and from their aptitude for strong hydrogen bond interactions. This latter aspect together with its electronic structure makes the triazole motif a recognized bioisostere of the amide functionality.[2] These heterocycles are stable toward metabolic degradation and their incorporation in molecules may improve solubility and bioavailability which further supports their interest as pharmacophoric units.[1] Therefore, much research with significant progress has been made on the development of synthetic routes towards triazole-containing molecules.[3] The combination of triazoles with other moieties that are recognized as bioactive provides hybrid molecules with increased biological profile. Examples of these compounds include bicyclic or polycyclic derivatives bearing triazole units and other heteroaromatic nuclei, such as imidazole,[4] pyrazolopyrimidine,[5] indole, benzothiophene,[6] benzothiazole,[7] or

quinoline,[7b] other aromatic-containing systems, including chalcones,[8] benzodiazepine frameworks,[9] and non-aromatic cyclic motifs, namely homoserine lactones,[10] β-lactams[11] or oxetanes.[12] Among the triazolyl conjugates that have gained relevance as synthetic targets of biological interest are those comprising carbohydrate moieties. Numerous examples of triazolyl glycoconjugates were shown to possess a variety of biological effects such as antimicrobial, antitumor or anti-inflamatory properties.[13] Carbohydrates are involved in cellular adhesion and other cellular recognition events which are crucial for the development of bacterial and viral infections, inflammation,[14] tumor angiogenesis and methastesis.[15] Interfering with normal cell recognition using a sugar-like molecule known as glycomimetic, which mimics the bioactive function of a carbohydrate, is a potential therapeutic strategy towards a variety of diseases. Moreover, a sugar mimetic has the propensity to inhibit carbohydrate-acting enzymes, 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. Hence glycomimetics have emerged as molecular scaffolds of therapeutic interest.[16] Included in this class of compounds are the imino sugars,[17] the thio sugars[18] and the carba sugars,[19] which have demonstrated a wide biological profile thus motivating research on efficient synthetic methodologies towards their synthesis.[19,20] With the advances made on the synthetic approaches to small molecules mimicking carbohydrates and on the construction of triazolyl systems, particularly driven by the development of the click chemistry version of the Huisgen cycloaddition,[21] significant research work dealing with hybrid molecules in which triazolyl systems are conjugated with glycomimetic structures has been made, particularly in the last ten years. Such molecules have demonstrated promising bioactive effects, combining the ability of both of the cyclic frameworks to confer bioactivity. This review aims to cover the synthetic strategies and biological properties of triazole-containing glycomimetics, namely triazole derivatives comprising imino sugar, thio sugar and carba sugar backbones. Glycoconjugate mimetics embodying triazole moieties such as glycopeptide mimetics, triazole pseudo nucleosides or triazole glyco clusters/glyco dendrimers will not be exhaustively focused herein. Nevertheless, these molecules will be mentioned in a brief survey on triazole glycoconjugates, which will be given in the first section of this manuscript.

2. Triazole-containing sugars

Triazolyl glycoconjugates comprise molecules possessing a triazole moiety linked to a carbohydrate backbone at the anomeric (*i.e.* glycosyl triazoles) or at non-anomeric positions, conjugates in which these structural fragments are not directly connected and compounds in which the triazole ring serves as a connecting unit between saccharidic systems, namely triazole-linked pseudo oligosaccharides, or between a sugar unit and another motif. Other glycoconjugates incorporating triazole rings include triazole-containing analogs of sugar aminoacids, glycopeptides as well as larger molecules mimicking complex multi-branched oligosaccharides, such as triazole-containing glycoclusters and glycodendrimers. These types of compounds have been covered thoroughly in some reviews.[13,22] Nevertheless, before addressing triazole-containing carbohydrate heteroanalogs, it is useful to comment briefly on the syntheses and biological profile of the conjugates constructed on normal sugar frameworks.

N-Glycosyltriazoles are typically synthesized by reaction of glycosyl azides with terminal alkynes. The versatility and the smooth conditions of the Cu^{I}-catalyzed azide -alkyne cycloaddition (CuAAC) procedure, which tolerates both *O*-protected and deprotected glycosyl azides and allows regiochemical, anomer and configurational control, has enabled its application towards the synthesis of a variety of glycosyl triazoles exhibiting a variety of biological activities, from which some relevant structures are highlighted herein (Figure 1).

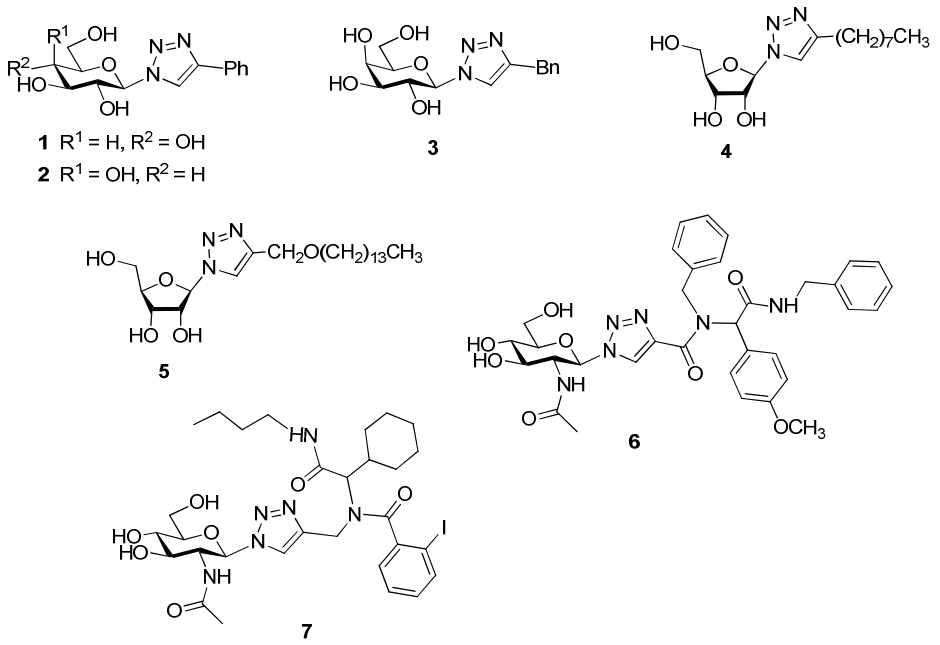


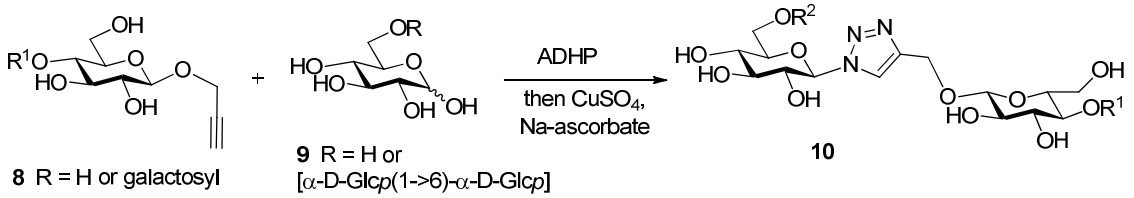
Figure 1. Glycosyl triazoles possessing biological properties.

1-Glycosyl-4-phenyl triazoles **1**-**2**, which were prepared by copper iodide-catalysed cycloaddition of peracetylated glycosyl azides with phenylacetylene followed by deacetylation, were shown to display glycosidase inhibitory activity, namely towards *Escherichia coli* galactosidase (ECG) and bovine liver galactosidase (BLG).[23] The most significant compound was the 1-β-D-glucosyl triazole, which showed a BLG inhibition with a K_i value of of 1.6 ± 0.4 mM. A library of 1-galactosyl-4-substituted triazole derivatives and related compounds possessing the triazole moiety at C-6 of methyl galactoside, were studied for their ability to inhibit the trans-sialidase from *Trypanosoma cruzi* (TcTS), the agent of Chagas' disease, which is involved in mammalian host-cell invasion.[24] Some compounds showed moderate inhibitory activity of TcTS at 0.5–1 mM concentrations, among which the most active one was the 1-galactosyl-4-benzyl triazole derivative **3** with 37% inhibition. The *in vitro* evaluation of the trypanocidal activity of the sugar triazole library against the trypomastigote form of *T. cruzi* Y strain revealed some compounds active in the low 100s micromolar range.

Ribosyl triazoles, synthesized *via* microwave-assisted cycloadditions between arabinosyl azide and terminal alkynes mediated by copper iodide supported on silica gel, were evaluated for their *in vitro* cytostatic activity.[25] The triazole derivative possessing a 4-octyl chain (**4**) was the most active compound of the series, displaying 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 μM. In another research, arabinosyl derivatives, which are analogs of compound **4**, possessing hydrophobic chains of different lengths

were tested for antimycobacterial efficacy using *Mycobacterium bovis* BCG as a model for *M. tuberculosis*.[26] Most of the triazole derivatives showed low to moderate effects on mycobacterial cell growth. The most active compound was the glycoconjugate comprising a tetradecyl side chain (**5**) with a minimum inhibitory concentration (MIC) value of 31 μg/mL. Triazole derivatives of *N*-acetylglucosamine were also shown to exhibit antibacterial effects.[27] In particular, compound **6** inhibited the growth of *Bacillus cereus* with an MIC value of 39 μg/mL and compound **7** displayed a MIC value of 45 μg/mL for *B. subtilis*. These activities were associated with the ability of such compounds to inhibit *N*-acetylglucosaminidases, enzymes that are important for bacterial cell wall peptidoglycan remodeling and recycling.

Triazole moieties have been used as linkers for the assembly of saccharidic fragments leading to disaccharide and oligosaccharide systems. These glycoconjugates can be prepared through cycloaddition reactions between sugar azides and sugar alkynes. Some useful one-pot procedures, allowing a direct access of the triazole-tethered molecules, have been developed.[28] In one of them, propargyl mono- and disaccharide derivatives (compounds-type **8**, Scheme 1) were reacted with free and deprotected sugars (compounds-type **9**) in the presence of 2-azido-1,3-dimethylimidazolinium hexafluorophosphate (ADHP), which allowed the *in situ* formation of a glycosyl azide, and copper sulphate/sodium ascorbate for the "click" cycloaddition process.[28b] The reactions proceeded stereoselectively, with the formation of only β-anomers (compounds type **10**).



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

Triazole-linked *C*-disaccharides belong to another type of disaccharide analogs. Their synthesis was successfully accomplished via a "click" cycloaddition procedure performed in ionic liquid medium involving a benzyl-protected ethynyl-C-glycosyl derivative and 6-azido sugars.[29]

Triazole-linked oligosaccharides have been synthesized to act as glycomimetics,[30] some of them possessing high structural complexity and displaying biological activities (Figure 2).Selected examples of such molecules include triazole-linked 1,6-oligomannosides of type **11**, which were designed to mimic the α-1,6-linked oligomannoside core present in some glycophospholipids of the cell wall of *Mycobacterium tuberculosis* (Mtb) and hence behave as potential inhibitors of α-1,6-mannosyltransferases, whose activity is required for the biosynthesis of the Mtb cell envelope.[30d] Various oligomers were prepared and among them the hexamer (**11,** n = 4) showed the highest inhibitory activity (IC_{50} = 0.14 mM) towards α-1,6-mannosyltransferases.

Other type of triazole-linked mannooligomer, the "dendritic" molecule **12**, was designed as potential mimic of the high-mannose oligosaccharide Man_8, which is a central framework of *N*-glycans, glycoconjugates that are present at the surface of many pathogenic microorganisms.[30e] The synthesis of **12** and studies regarding its affinity towards the mannose-specific lectin concanavalin A (Con A) were carried out. The rationale behind the structure of this glycoconjugate was based on the idea that the

mannosyltriazole fragments could behave as surrogate of the α-D-Man(1→2)α-D-Man motifs of Man_8. A concomitant multi "click" cycloaddition strategy involving α-D-mannopyranosyl azide and the appropriate tri-*O*-alkynyl disaccharide led to **12**. The compound proved to be a strong ligand for Con A, exhibiting an IC_{50} value of 12 μM, which is only 2.5-fold higher than that of the natural Man_8.

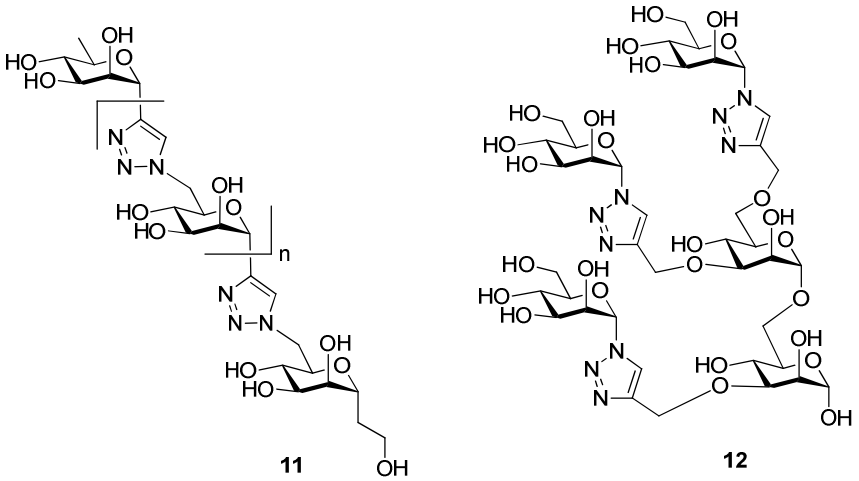
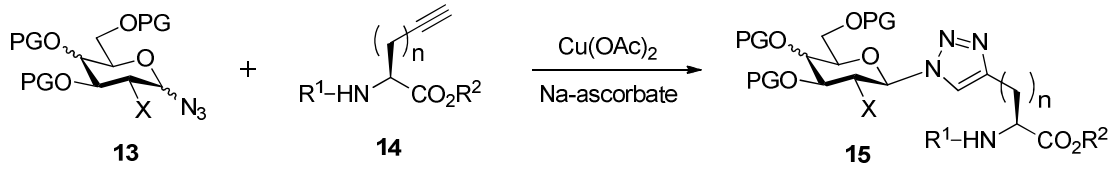


Figure 2. Triazole-linked oligosaccharides as mimics of oligosaccharides.

Triazoles have also been exploited as connecting moieties between glycosyl segments and amino-acids towards the access of mimetics of glycosyl amino acids and glycopeptides. Such glycoconjugates may exhibit biological properties as *N*- or *O*-glycosyl amino acids and N- or O-linked glycopeptides do, with the advantage of being chemically and metabolically more stable than their N- or O-linked counterparts.

Triazole-linked glycosyl amino acids or dipeptides (**15)** were synthesized by [3+2] cycloaddition between glycosyl azides **13** and acetylenic amino acids **14** (Scheme 2).[31] On the other hand, the coupling of glycosyl alkynes with azide-containing amino acids is reported to furnish *C*-glycosyl analogs (compounds type **16**, Figure 3).[31,32]



Scheme 2. Synthesis of triazole-linked glycosyl amino acids and glycopeptides by azide-alkyne 1,3-dipolar cycloaddition.

Other reported triazole-containing glycopeptide mimetics include fucose-derived glycopeptide bis-triazoles **17** and **18**, which were designed as potential selectin antagonists, possessing frameworks based on the structure of the tetrasaccharide sialyl $Lewis^X$ (sLe^X).[33] The adesion of sLe^X to two selectins (E and P), regulates leukocyte rolling, tethering and their extravasion in inflammation, which can become a pathogenic process when it becomes excessive. Hence, inhibition of sLe^X-selectin interaction by means of potential selectin ligands, was pursued. However, studies of molecular modeling and STD NMR experiments suggested a modest ability of the conjugates **17** and **18** to bind to a fucose-specific lectin.

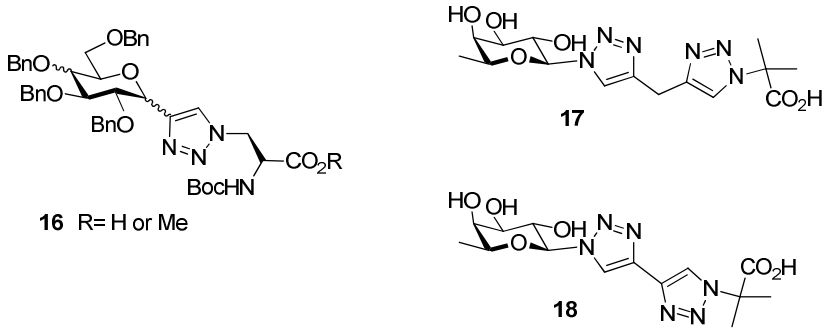


Figure 3. Triazole-containing glycoamino acid/glycopeptide mimetics.

3. Triazole-containing glycomimetics

In the next sections emphasis will be given to triazole derivatives constructed on carbohydrate heteroanalog backbones, frameworks in which the sugar endocyclic oxygen atom has been replaced by nitrogen (imino sugars), sulfur (thio sugars) or carbon (carba sugars or cyclitols). The following discussion will address the synthetic methodologies towards these glyco-related conjugates and highlight their biological potential.

3.1. Triazole-containing imino sugars

Imino sugars constitute one of the most interesting types of carbohydrate mimetics. Their ability to be protonated at physiological pH, make them potential mimics, in terms of charge and shape, of oxocarbenium ions, which are the transition state species during glycosidase catalysis. It is not therefore surprising that the therapeutic/biological potential of imino sugars arise mostly from their ability to inhibit glycosidases, whose activity play a role in a variety of diseases.[16a,34] Among the significant examples of this inhibitors are the naturally occurring nojirimycin (**19**),1-deoxynojirimycin (**20**, DNJ),[34]and synthetic derivatives of the latter which become clinically relevant molecules, such as the *N*-hydroxyethyl analogue (**21**), known as Miglitol,[35] which is a drug used for the treatment of diabetes type 2 and the *N*-butyl derivative (NB-DNJ, **22**) which has been launched for the treatment of Gaucher's disease, a rare lysosomal disorder (Figure 4).[36]

In the last fifteen years considerable advances have been made on the synthetic strategies towards imino sugars, which allowed increasing their structural variety, while new biological applications of this class of glycomimetics were found.[37]

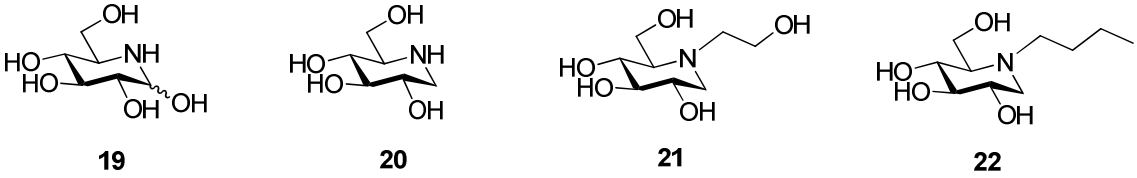
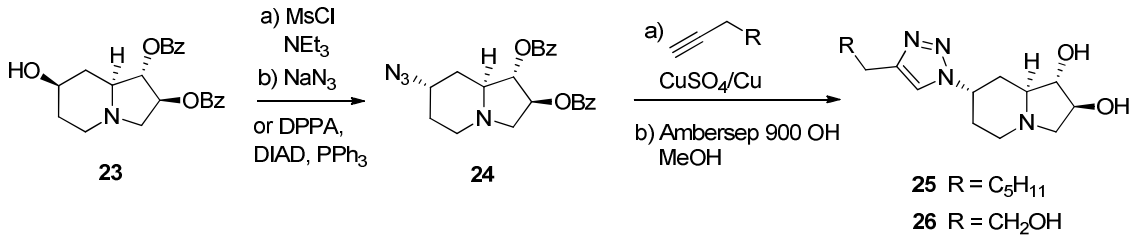


Figure 4. Imino sugars of biological/clinical relevance.

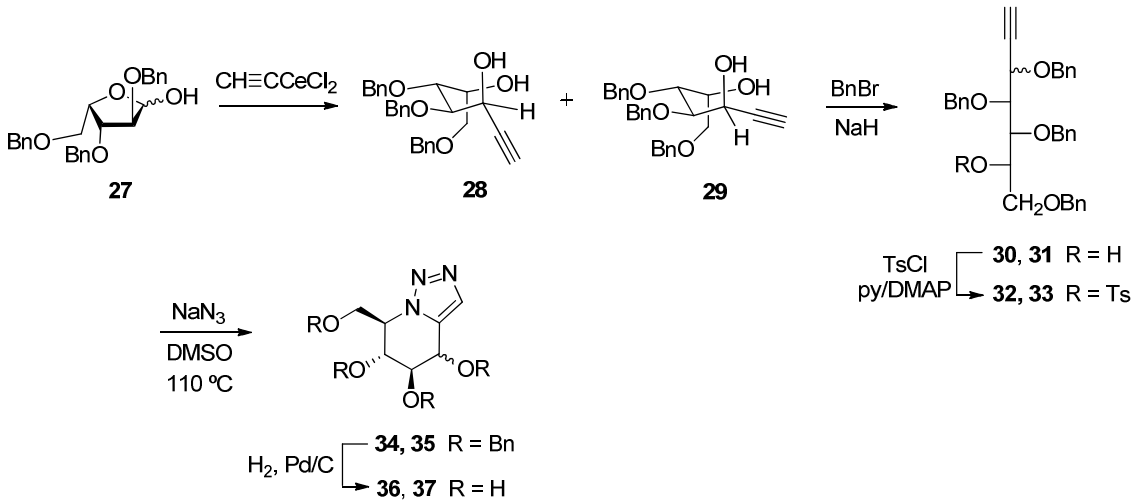
Triazole-imino sugar conjugates are among the innovative types of hybrid compounds having an imino sugar core that have been reported, in the search for new bioactive substances. Molecules in which a triazole moiety is *C*-linked to 2-deoxy imino sugars based on hydroxylated piperidine or azepane systems, at the endocyclic nitrogen, were synthesized *via* cycloaddition reaction of *N*-propargyl imino sugars and alkyl azides.[38] Bicyclic deoxy imino sugar-triazole conjugates consisting of polyhydroxylated indolizidine

structures connected to a triazole unit at C-7 (**25**-**26**, Scheme 3) were synthesized based on the structure of (+)-lentiginosine, which is a selective inhibitor of amyloglucosidases.[39] Hence, the indolizidinol **23** was converted into the corresponding 7-azido derivative **24** *via* mesylation and further nucleophilic replacement with sodium azide or, directly, under Mitsunobu conditions, using diphenylphosphoryl azide (DPPA), diisopropylazodicarboxylate (DIAD), and triphenylphosphine. 1,3-Dipolar cycloaddition of **24** with 1-octyne or 3-butyn-1-ol in the presence of *in-situ* generated Cu(I) and subsequent hydrolysis of the benzoate groups gave the target triazole derivatives **25** and **26** in 80% and 45% overall yield, respectively. These molecules showed moderate inhibitory activities at 1 mM on amyloglucosidase (16-26%) and β-glucosidase (17%-67%).



Scheme 3. Synthesis of triazole-containing indolizidines.

Fused triazole-imino sugar hybrids have been designed and synthesized as potential glycosidase inhibitors planned to mimic the transition state of the natural substrates in the enzyme catalysis. Various conjugates based on a triazole-fused structure, comprising a sp^2-anomeric carbon so that it could adopt a locked and flattened half-chair conformation that might closely resemble the oxocarbenium ion, have been reported. The earliest reported synthesis of compounds of this type comprised 5-7 steps starting from tri-*O*-benzyl-L-xylofuranose (**27**, Scheme 4).[40] It was converted to heptitols **28** and **29** in 86% yield by treatment of ethynylcerium(III) dichloride.

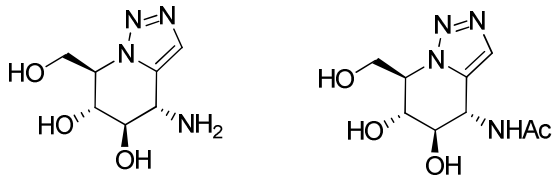


Scheme 4. Early synthesis of triazole-fused iminosugars.

Alternatively, a larger scale synthesis of **28**-**29** was accomplished in three steps involving the oxidation of **27** to the aldonolactone followed by addition of (trimethylsilyl)ethynyl-lithium and subsequent reduction of the resulting hemiacetals with sodium borohydride. Regioselective benzylation of **28**-**29** gave **30**-**31**, which upon tosylation and further treatment of the resulting tosylates **32**-**33** with sodium azide in DMSO at

110 ºC furnished directly the triazole derivatives **34-35**, *via* intramolecular cycloaddition of the intermediate azidoalkynes. Debenzylation of **34-35** provided the target compounds **36**-**37**. The evaluation of the glycosidase inhibitory effect of **36** and **37** revealed low activity towards all the enzymes tested. Compound **36**, possessing *gluco* configuration showed the best activity with an IC_{50} value of 2 mM for the β-glucosidase from *Caldocellun saccharolyticurn* while the natural substrate presented a K_M value of 1.5 mM. These results suggest that the presence of a lone-pair donating heteroatom directly linked to the pseudo anomeric carbon in the triazole system, which may be able to be protonated, is essential for the binding to the enzyme.

It was afterwards studied the effect that the replacement of the OH-2 in **36** by an amino group and by a *N*-acetylamino group would have on the glycosidase inhibitory ability of this type of fused derivatives (Figure 5).[41] Thus, improved bioactivites were displayed by the glucosamine-related triazoles **38** and **39**. At optimal pH, **38** showed a lower IC_{50} value (0.9 mM) towards *C. saccharolyticurn* than the corresponding alcohol counterpart **36** (IC_{50} = 2 mM), while the *N*-acetyl derivative **39** has a much better enzyme inhibitory profile than the previous derivatives and was shown to inhibit β-*N*-acetylglucosaminidase from bovine kidney with a IC_{50} value of 8 μM.



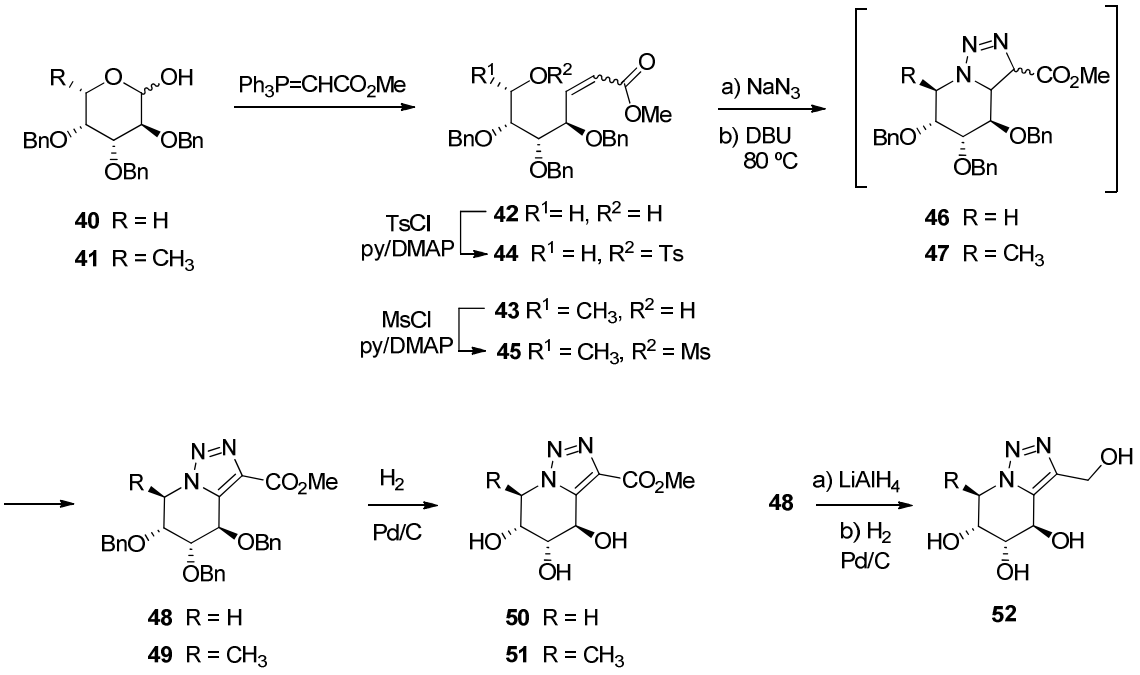
38 **39**

Figure 5. Glucosamine-related triazole-fused iminosugars.

In another research, fused bicyclic triazole-carboxylic acids comprising hydroxylated piperidine systems of D-*gluco* and D-*galacto* configuration were synthesized as potential anionic mimetics of carbohydrates and their glycosidase inhibitory potential was investigated.[42] Although none of the compounds showed significant glycosidase inhibition, the D-*gluco*-configured triazole carboxylic acid exhibited inhibition effect on glycogen phosphorylase b (GPb), a therapeutic target for diabetes type 2, with a K_i value of 7.4 mM.

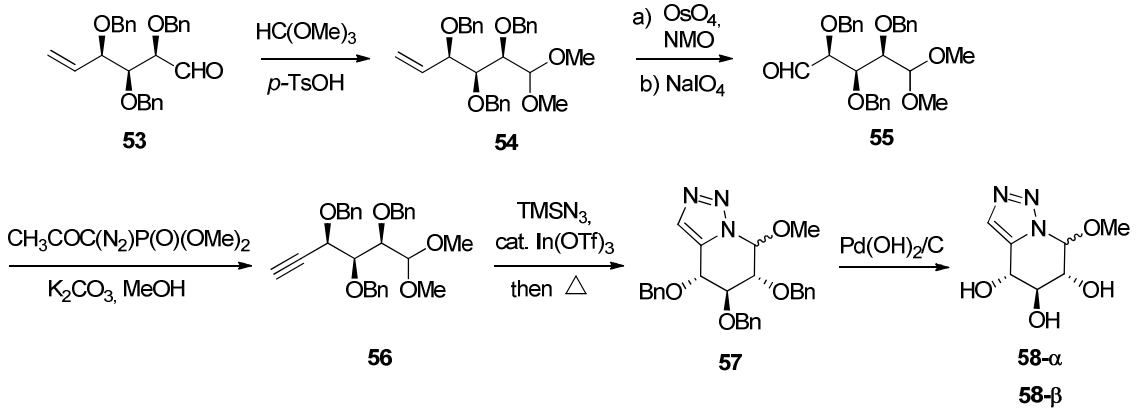
Triazole-fused imino sugars possessing D-*arabino* and L-*fuco* configuration could be synthesized in 8 steps from D-arabinose and L-fucose.[43] The key transformation was accomplished by an efficient one-pot procedure involving azide introduction, intramolecular addition to a α,β-unsaturated carbonyl functionality and oxidation (Scheme 5). Thus, the easily prepared 2,3,4-tri-*O*-benzyl-derivatives of D-arabinose and L-fucose (**40**, **41**) were converted by a Wittig-type reaction into stereoisomeric mixtures of α,β-unsaturated esters **42** and **43**. Further tosylation or **42** and mesylation of **43** afforded the corresponding sulfonate esters **44** and **45**, respectively. Subsequent treatment of **44** and of **45** with sodium azide, which was followed by *in situ* addition of 1,8-diazabicyclo-[5.4.1]-undec-7-ene DBU generated triazoles **48** and **49** via spontaneous oxidation of the intermediate triazoline derivatives **46**, **47** in overall yield of 30%. The scope of this transformation was broaden to an allylic alcohol analogous containing an azide functionality which, upon oxidation, evolved towards the bicyclic triazole derivative through intramolecular cycloaddition of the

corresponding α,β-unsaturated aldehyde intermediate. Debenzylation of **48**, **49** gave the deprotected triazole conjugates **50**, **51** while **48** was also subjected to reduction of the ester functionality followed by hydrogenation, affording **52**.



Scheme 5. Synthesis of triazole-fused iminosugars via a one-pot substitution–cyclization–oxidation procedure.

The synthesis of another type of bicyclic triazoles in which the triazole unit is fused to the piperidine-type imino sugar moiety at C-5, N and the anomeric position comprises a methoxyl group, *i.e.* methyl-*O*-glycosides of triazole-fused imino sugars, has been accomplished (Scheme 6).[44]

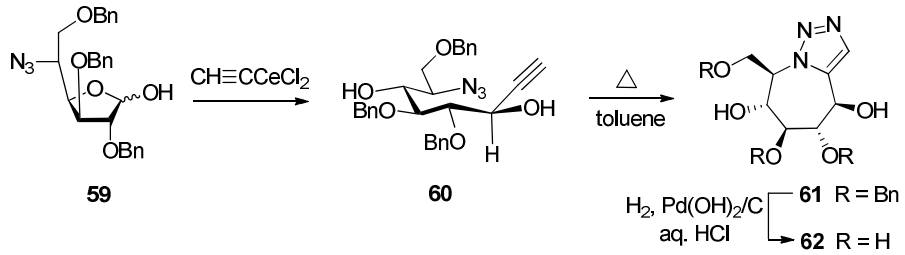


Scheme 6. Synthesis of methyl-*O*-glycoside derivatives of triazole-fused piperidine iminosugars.

For the access to the *xylo*-configured bicyclic analog of **36**, 2,3,4-tri-*O*-benzyl-5,6-dideoxy-D-xylo-hex-5-enose (**53**) was converted into the dimethoxyhex-5-yne derivative **56**. Protection of the aldehyde functionality of **53** to the corresponding dimethylacetal **54** was followed by osmylation and subsequent oxidative cleavage to give aldehyde **55**. The homologation of **55** using dimethyl-1-diazo-2-oxopropylphosphonate/methanol/potassium carbonate furnished **56**, which upon treatment with trimethylsilyl azide and heating led directly to the cycloadduct **57** in 82% yield as anomeric mixture. After

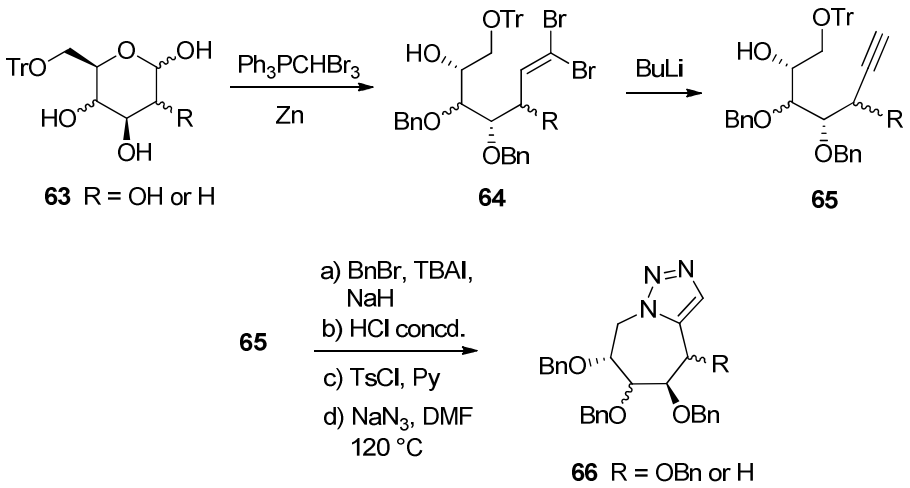
chromatographic separation, each anomer was subjected to hydrogenolysis to yield the corresponding deprotected derivatives **58-α**, **58-β**. This methodology was applied starting from other chiral building blocks related to **53**, enabling the access to a variety of bicyclic triazoles which differ on the configuration of the imino sugar backbone.

Bicyclic-fused triazoles embodying higher homologs of hydroxylated imino sugars, namely polyhydroxylated azepanes, as core structure have been also reported. These triazole conjugates may be prepared in few steps through intramolecular 1,3-dipolar cycloaddition of azide-containing *glyco*-initols. The azepane-containing counterpart of compound **36** (Scheme 4) was prepared in three steps in 72% overall yield from 5-azido-5-deoxy-3,6-di-*O*-benzyl-1,2-*O*-isopropylidene-α-D-glucofuranose (**59**, Scheme 7).[45] Ethynylation of **59** gave stereoselectively the octynitol **60** which upon heating in toluene evolved towards the triazole-fused azepane **61**. Final deprotection furnished the target compound **62**.



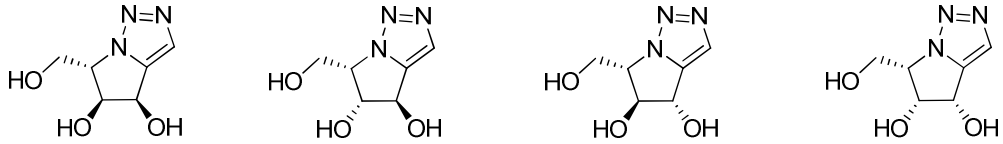
Scheme 7. Synthesis of a triazole-fused azepane.

A variety of triazole fused-azepanes were accessed from tritylated aldoses (compounds type **63**, Scheme 8) by a methodology that differed from the previously reported ones at the early step of chain elongation at the anomeric center. Thus, the introduction of the terminal alkyne function was accomplished by a two-step method which avoided creating a new stereocenter at the sugar core.[46] The hemiacetal was subjected to Wittig-type olefination to afford a dibromo olefin (**64**) which, upon treatment with buthyllithium, gave the *glyco*-ynitol (**65**). A sequence of benzylation, detritylation, tosylation and a one-pot procedure consisting on substitution with azide/thermal cyclization procedure furnished the target fused triazoles (**66**). This stategy was successfully applied to the synthesis of bicyclic triazole derivatives in which the azepane framework comprises 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 D-*galacto* configuration.

Triazoles annelated to hydroxylated pyrrolidines have been designed to behave as conformationally constrained imino sugars in the search for more specific glycosidase inhibitors. Few reports towards the synthesis of pyrrolidotriazoles have been published.[47] A recent research conducted to triazole-containing analogs of imino sugar-type pyrrolizidine alkaloids comprising L-*ribo* (**67**), L-*xylo* (**68**), L-*arabino* (**69**) and L-*lyxo* (**70**) configuration (Fig 6).[47c] Their synthesis required 8 steps from glycal-derived δ-hydroxy α,β-unsaturated aldehydes and involved a one-pot protocol for thermal tandem azidation/intramolecular cycloaddition of the azido acetylene intermediates. These molecules were subjected to glycosidase inhibition assays using a panel of eleven enzymes. All the 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 arising from their fused and planar structure was suggested as a key factor for the observed high degree of enzyme inhibition selectivity.

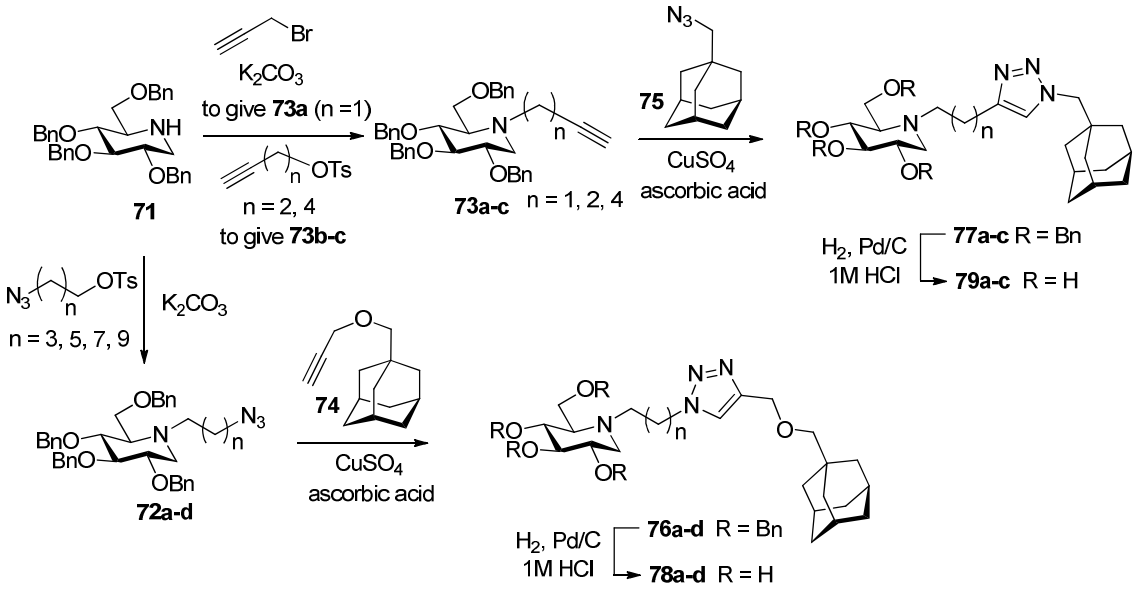


67 **68** **69** **70**

Figure 6. Triazole-fused pyrrolidine imino sugars possessing selective glycosidase inhibitory activity towards α-glucosidase from rice and from *Aspergillus niger*.

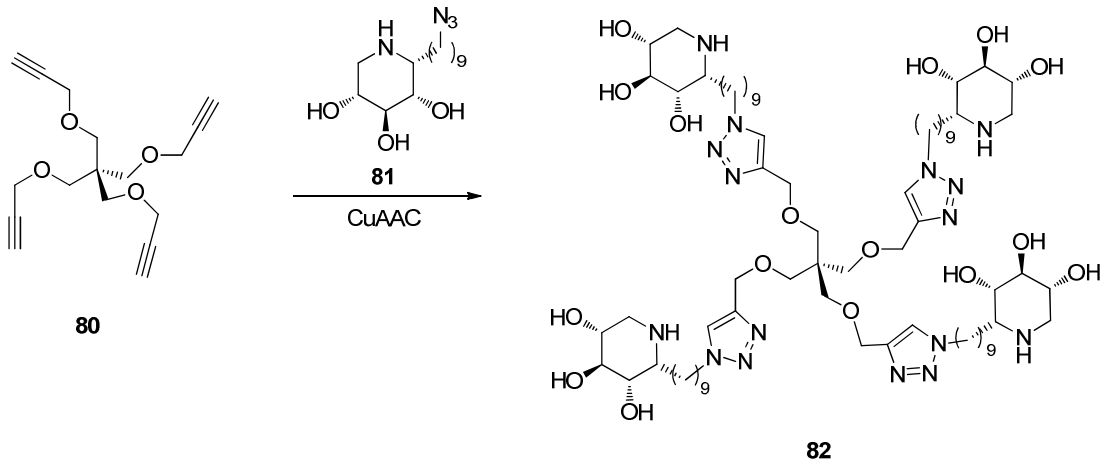
Triazole moieties have been used to connect imino sugar moieties to unnatural patterns leading to neoglycoconjugates of biological interest. Based on the structure and therapeutic profile of *N*-butyl deoxynojirimycin (NB-DNJ, **22**, Figure 4), the synthesis of various *N*-substituted deoxynojirimycin (DNJ) derivatives, in which the DNJ core is coupled to a hydrophobic motif through a triazole system and bearing an alkyl chain spacer, have been exploited for further bioactivity evaluation. Such triazole-containing iminosugar conjugates showed their potential application as therapeutic agents for Gaucher's disease.[48]

DNJ-triazole-adamantane conjugates were synthesized starting from*O*-benzylated DNJ (**71**, Scheme 9).[48a] *N*-alkylation of **71** with alkyl tosylates bearing an azido functionality or with propargyl bromide or alkynyl tosylates gave the corresponding azidoalkyl (**72**) or alkynyl DNJ derivatives **73**. Further "click" cycloaddition reaction of **72** with (propargyloxy)methyl adamantine (**74**) and of **73** with azidomethyl adamantine (**75**), gave triazole-linked DNJ-adamantane conjugates **76** and **77**, respectively, which were subsequently debenzylated by hydrogenation. All the compounds were assayed as glycosidase inhibitors and all of them displayed good inhibition towards α-glucosidases (from rice, rat intestinal maltase, rat intestinal sucrase) with some of them presenting IC_{50} values in the same order of magnitude or even lower than those of DNJ (**20**, Figure 4) or miglitol (**21**, Figure 4). The inhibitory activity was shown to improve with the hydrophobicity of the compounds, *i.e.* with the increase of the length of the compound's aliphatic spacer. Compounds' activities on the cellular enzymes relevant to the treatment of Gaucher's disease were also promising. In particular, compounds **78c** (n = 7) and **78d** (n = 9) were 20 times fold more potent on ceramide glucosyltransferase in cells than NB-DNJ (**22**, Figure 4). The latter enzyme plays a key role in the biosynthesis of glucosylceramide, which, in Gaucher's disease patients, accumulates in the lysosome. In a further research the glycoconjugates **78** and **79** and a *galacto*-configured analog of **78a** were shown to possess antiviral activity against bovine viral diarrhea virus, a surrogate model for the hepatitis C virus.[48c]



Scheme 9. Synthesis of triazole-linked DNJ-adamantane conjugates as potential therapeutic agents for Gaucher's disease.

Recently, the concept of multivalence was applied toward the construction of iminosugar clusters based on cyclodextrin cores for pharmacological chaperone development to Gaucher's disease treatment. The construction was based on a CuAAC approach for the attachment of different *N*-alkyl DNJ azides and *C*-alkyl-iminoxylitols to propargyl-β-cyclodextrin and simpler propargyl ethers in order to evaluate the multivalence effect as well as ligands, scaffolds, and alkyl spacer lengths effects (Scheme 10).[49,50] Significant multivalent effects in glucocerebrosidase (GCase) inhibition have been observed, but importantly it was shown that the compounds that display the best affinity for GCase are not necessarily the best chaperones, being the best chaperone obtained with the tetravalent DNJ **82** that led to a 3.3-fold GCase activity increase when assayed in Gaucher fibroblasts.



Scheme 10. Synthesis of triazole-linked multivalent *N*-alkyl DNJ conjugates as therapeutic chaperones for Gaucher's disease.

N-Butyl deoxynojirimycin (NB-DNJ, **22**, Figure 4) is a clinical candidate for the treatment of cystic fibrosis as it has the ability to correct a mutation in the gene for the cystic fibrosis transmembrane

conductance regulator (CFTR), which is responsible for the disease. Hence, the same multivalence concept was applied and, remarkably, a *N*-alkyl DNJ trivalent analogue was found to be up to 225-fold more potent than NB- DNJ, proving the great potential of multivalent approaches for the treatment of a number of protein folding disorders.[51]

3.2. Triazole-containing thio sugars

Replacement of the ring oxygen in carbohydrates by its close related neighbour in the periodic table, sulphur, leads to remarkable changes on physico-chemical and biological properties due to the electronic difference between the sulphur and oxygen atoms. The sulphur atom is less electronegative and more polarizable, which modify the reactivity of the thiosugars relatively their natural oxygenated counterparts. Thus, thiosugars play an important role as glycomimetics and have been reported as potent inhibitors for glycosidases as well for other therapeutic targets with relevance for several diseases such as diabetes, Gaucher's disease, cancer, cystic fibrosis, HIV infection or tuberculosis, with the advantage of being less susceptible to hydrolysis and metabolic attack, leading to improved bioavailability.[18b,c,52] The first examples of thio sugars were reported in the early 60's, with the synthesis of 5-thio-L-idopyranose (**83**, Figure 7) and 5-thio-D-xylopyranose.[53] Since the isolation of 5-thio-D-mannose (**84**) from the marine sponge *Clathria pyramida* in 1987,[54] remarkable examples have been given by Nature, such as Salacinol (**85**) and Kotalanol (**86**) isolated from an antidiabetic Ayurvedic traditional medicine *Salacia reticulate* WIGHT that proved to be potent inhibitors for intestinal α-glycosidases as sucrose, maltase and isomaltase.[55]

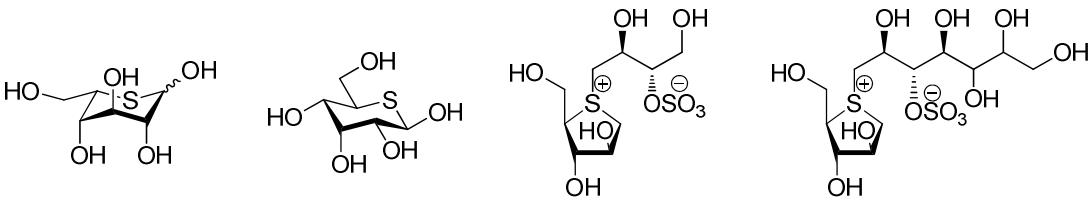
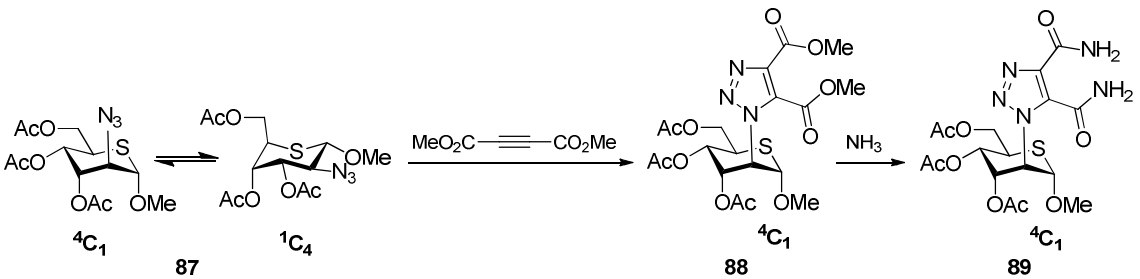


Figure 7. Synthetic and natural thio sugars.

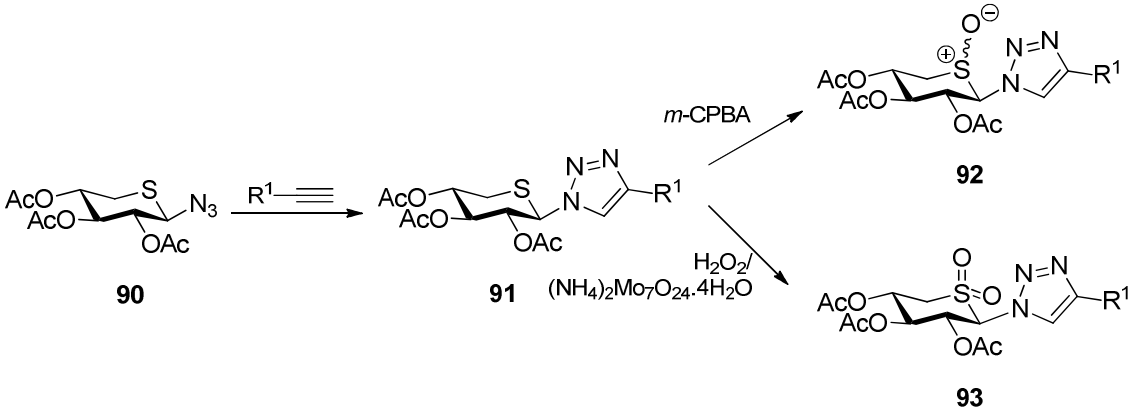
Hence, the interest on expanding the scope of thiosugars has led to the development of appropriate synthetic methodologies toward highly functionalized thiosugar glycomimetic. Recent examples are the new approach to 5-thio-D-galactopyranose from diacetone galactofuranose,[56] the enzymatic and organocatalyzed asymmetric aldolization reactions towards thiofuranoses and thiopyranoses,[57] or the synthesis of 5-thiosugar-fused butenolides and a 5-thiohex-1-enopyran-3-ulose from 3-uloses.[20d]

Following the idea that triazole building block may confer extra cell viability and anticancer properties, the first report on thio sugars containing a 1,2,3-triazole motif arised from the cycloaddition of 2-azido-altroside (**87**, Scheme 11) with dimethyl acetylene dicarboxylate to afford intermediate (**88**) that was further transformed in the desired 4,5-dicarboxamide derivative (**89**).[58] Possibly due to the repulsion between the triazole substituent at C-2' and the methoxyl group at C-1', the triazole derivatives **88** and **89** adopt the $^4C_1$ conformation unlike the starting azide **87**, in which, both $^4C_1$ and $^1C_4$ forms exist in equilibrium. Hence, the triazole isothionucleoside leads to significant steric differences that may result in favourable biological properties, nevertheless no further activity assays were reported for this derivative.



Scheme 11. Synthesis of 1,2,3-triazolo isothionucleosides from 2-azido-altroside.

More recently, 5-thioxylopyranosyl 1,2,3-triazoles (**91**, Scheme 12) were synthesized via CuAAC methodology using 5-thioxylopyranosyl azides with a variety of acetylenes, and further controlled oxidation of the endocyclic sulphur which led to the synthesis of the corresponding sulfoxides and sulfones (**92**, **93**). These compounds were evaluated as glycogen phosphorylase inhibitors; nevertheless they presented weak inhibition when compared to the oxo-glucopyranosyl analogues, most likely due to the lack of the hydroxymethyl group.[59]



Scheme 12. CuAAC for the synthesis of 5-thioxylopyranosyl 1,2,3-triazoles and controlled oxidation toward sulfoxides and sulfones.

3.3. Triazole-containing carba sugars

Highly functionalized cyclohexanes or cyclopentanes that resemble carbohydrate structure and mimic its biological activity have been named as pseudo sugars, carba sugars or cyclitols. Due to the correct orientation of the ring substituents, these molecules can inhibit important biological targets, even though they lack the sugar endo-oxygen atom that is replaced by a non-hydrolysable methylene, leading to analogs more stable toward endogenous degradative enzymes as these do not take part in any typical carbohydrate reaction.[19b,20c,52] This resemblance together with the idea of promising improvements on pharmacological properties led to the synthesis of pseudosugars such as 5a-carba-α-D-talopyranose (**94**, Figure 8) and 5a-carba-α-D-galactopyranose (**95**) in 1966,[60] displaying antibiotic activity, but few years later 5a-carba-α-D-galactopyranose was isolated from natural source of *Streptomyces* sp fermentation.[61] Hence, extensive efforts have been made to the synthesis and identification of new carbasugars with therapeutic interest and one of the recent most popular examples is oseltamivir (**96**), the neuramidase inhibitor launched as Tamiflu for treating influenza virus, that can be synthesized from natural carbasugars shikimic acid (**97**) or quinic acid (**98**).[62]

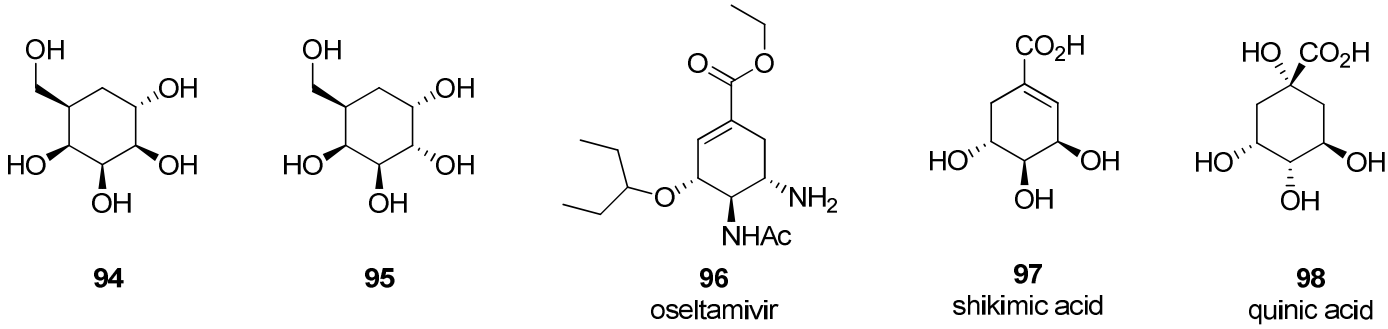


Figure 8. Natural and synthetic carba sugars.

Ribavirin (**99**, Figure 9) is a 1,2,4-triazolyl nucleoside discovered in the early 70's from a campaign of ICN Pharmaceuticals' Nucleic Acid Research Institute to afford new nucleosides which would have efficacy as antiviral agents. Remarkably, ribavirin is clinically effective against unrelated viruses from three diverse families, as chronic hepatitis C virus (HCV), Lassa fever virus, and respiratory syncytial virus (RSV) that are very different RNA viruses with virtually no sequence homology.[63,64] These characteristics have made ribavirin a drug of substantial research interest and also stretch research efforts on its carba sugar analogs.

For the synthesis of carbaribavirin (**100**) and 5-norcarbaribavirin (**101**), the 1,2,4-triazole moiety was achieved by hydrazine coupling with ethyl carboethoxyformimidate followed by ring closure. However, no significant antiviral activity was observed for these analogs.[65,66] 2',3'-Didehydroxycarbocylic ribavirin was achieved by a Pd(0)-catalysed coupling between the heterocyclic base and the cyclopentenyl derivative.[67]

In order to access 1,2,3-triazolyl derivatives of ribavirin, the synthetic strategy is based on the reaction of carba sugar azides with diverse acetylenes. Carbocyclic and phosphonocarbocyclic analogues (**102**,**103**) were envisaged against HCV; nevertheless no significant activity was observed. However in a screening using another viruses, these compounds turn out to be moderate HIV-1 inhibitors with IC_{50} of 43.8 and 37 μM, respectively.[68]

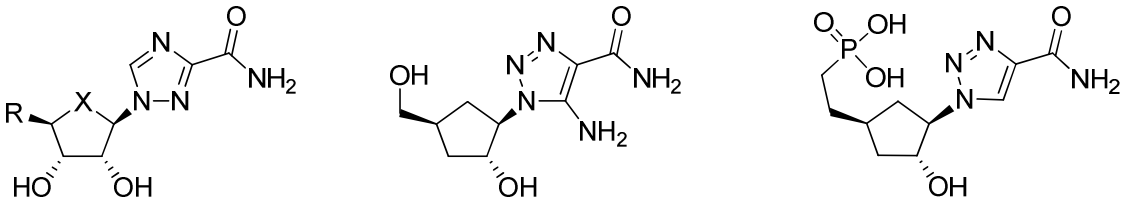
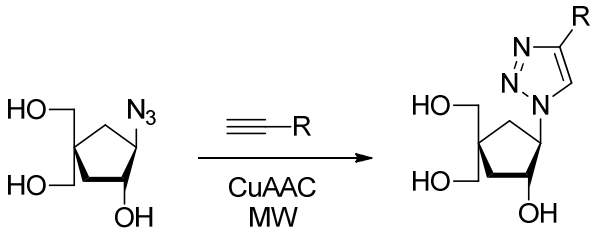


Figure 9. Ribavirin and its carba sugar analogs.

A methodology study was performed to evaluate the copper-catalyzed azide-alkyne cycloaddition procedure (CuAAC) toward the rapid conversion of azido-carbocycle **103** into the desired carbanucleosides **104**, and Cu(0)/$CuSO_4$ under microwave irradiation was showed to be the most efficient system for this reaction.[69,70] However, none of the synthesized compounds inhibited production of vaccinia virus (Lister strain) or cowpox virus (Brighton strains) in vero cells as it was envisaged by the authors.

1,2,3-Triazolyl iodocarba nucleosides and 2,3-didehydrocarba nucleosides were evaluated as antiviral agents. The synthesis was based on an iodoazide carba sugar as intermediate toward a library of compounds,

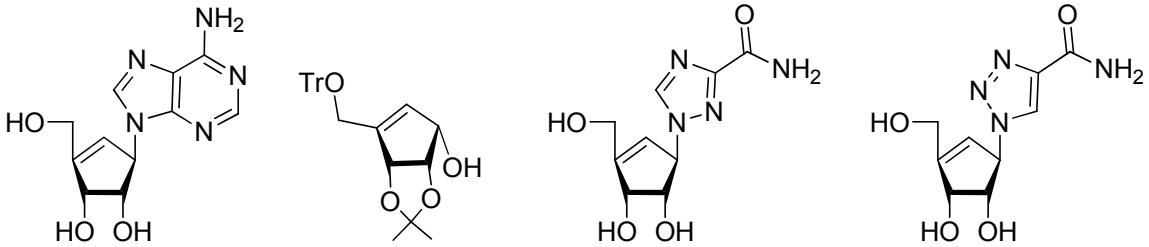
nevertheless when assayed against a panoply of viruses, only one of the compounds synthesized displayed moderate activity against varicella-zoster virus kinase positive strain (EC_{50} 4.5 μg).[71]



103 **104**

Scheme 13. CuAAC methodology under microwave irradiation.

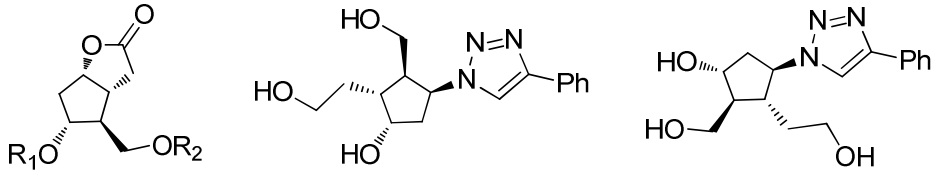
In order to afford synthetic analogs of Neplanocin A (NPA, **105**, Figure 10), a carbocyclic nucleoside isolated from *Ampullariella regularis*, as potential antivirals, the use of the ring-closing metathesis methodology led to the synthesis of the carba sugar **106** toward the access of 1,2,4- and 1,2,3-triazoles either using Mitsunobu or CuAAC approaches, respectively. While the 1,2,4-triazole carbocyclic nucleoside **107** displayed only moderate activity against Severe Acute Respiratory Syndrome Coronavirus (SARSCoV, EC_{50} 21 μM) when tested against a group of virus, the correspondent 1,2,3- triazole **108** showed moderate activies against SARSCoV (EC_{50} 47 μM) and cowpox virus (EC_{50} 39 μM), but potent activity against vaccinia virus (EC_{50} 0.4 μM). These results are indicative of the importance of the triazolyl unit for activity/selectivity.[72]



105 Neplanocin A **106** **107** **108**

Figure 10. Neplanocin A and its carba sugar precursor and analogs.

Recently, Corey lactone was used as starting material for extra decoration of the cyclopentane ring of carbasugar nucleosides leading to promising structures **110** and **111** (Fig 11), which were not evaluated for their biological properties so far.[73]



109 **110** **111**

Figure 11. Corey lactone and its 1,2,3-triazole derivatives.

For further extension of the 1,2,3-triazolyl derivatives, [1,2,3]-triazolo-[4,5-c]-pyridin-4-one analogues were also synthesized, however with no improvement on biological activities when compared with the triazole counterparts.[74]

Hygromycin A (**112,** Figure 12) is a natural antibiotic that also exhibits immunosuppressant activity, first isolated from *Streptomyces hygroscopicus* with well-defined pharmacophoric units including cyclitol, cynnamoyl and furanose. Due to the finding that the furanose counterpart was not mandatory for activity, a construction of azidocyclitols and alkynes in a diversity-oriented fashion was envisaged to explore and tune the activity of related dimer structures (**113**). However, the synthesized compounds showed promising antifungal activity but lacked the immunosuppressant action described for hygromycin A.[75]

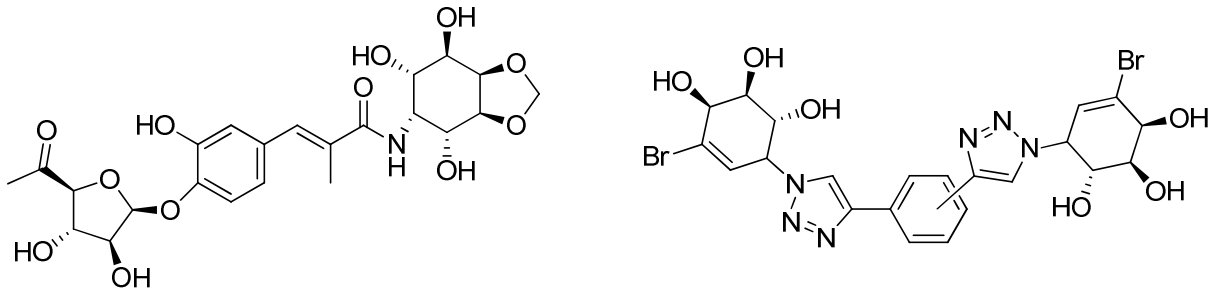


Figure12. Hygromycin A (**112**) and its related triazole linked dimeric structures (**113**).

N-Substituted aminocyclitols were envisaged as potential glucocerebrosidase (GCase) chaperones with pharmacological interest for Gaucher's disease so that a small library on 1,2,3-triazole derivatives with alkyl spacers of different lengths (**114**, Figure 13) was designed and synthesized. Shorter spacer (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 determinant effect of the location of the triazole ring on the activity.[76]

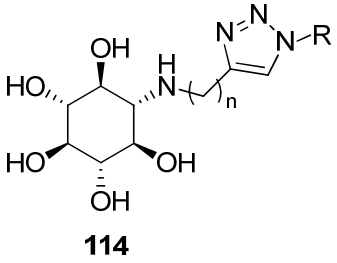
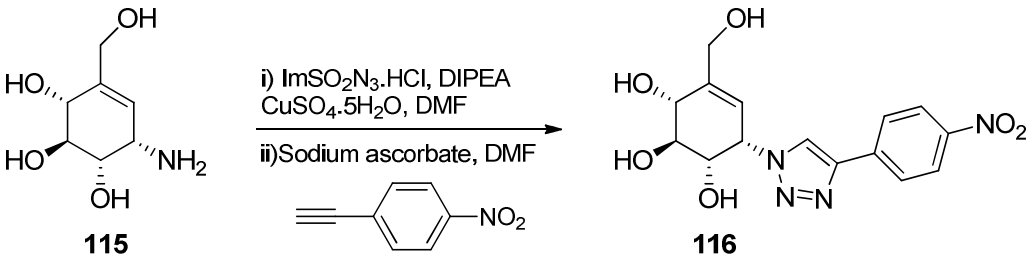


Figure 13. N-substituted aminocyclitols with GCase inhibitors.



Scheme 14. One-pot synthesis of triazolylaminocyclitols.

Recently, the synthesis of a of C_7 *N*-aminocyclitol-derivatised 1,2,3-triazole library was performed by an elegant one-pot diazo transfer followed by CuAAC using imidazole-1-sulfonyl azide hydrochloride as efficient and shelf-stable diazo transfer reagent (exemplified in Scheme 14). Valienamine (**115**), validamine

and valiolamine were used as starting materials to afford the desired triazoles (such as **116**) in yields from 72 to 89%, proving a wide scope for the use of this methodology toward the synthesis of glycomimetics.[77]

4. Conclusions

Triazoles are structural entities that are related to a wide variety of biological properties and hence the development of molecules comprising this system is highly encouraging in the search for new bioactive compounds. The growing importance of hybrid molecules in the field of medicinal chemistry has motivated the design and synthesis of molecules in which triazole nucleous are combined with other motifs of recognized bioprofile. Carbohydrates are among these molecular frameworks and triazole glycoconjugates have shown their therapeutic potential. Next to carbohydrates, their mimetic heteroanalogs, namely imino sugars, thio sugars and carba sugars, turned out to be attractive scaffolds of pharmacological interest and innovative triazole conjugates containing these moieties have recently attracted much attention as targets. Efficient synthetic approaches towards these types of molecules, in which the triazole unit may be linked or fused to the glycomimetic template or it serves as a connecting unit to another fragment, have been developed, mostly starting from carbohydrate derivatives and making use of the azido-alkyne cycloaddition methodology. Multi-valent glycomimetic-based structures could also be accessed through multiconjugation *via* triazole motifs. Triazole-glycomimetic conjugates exhibited in some cases enhanced biological properties in comparision with their parent monocyclic derivatives and the triazole unit proved to be essential for inducing conformational constrain and allowing selectivity of glycosidase inhibition.

The research conducted so far make evident that combining triazole systems to glycomimetic structures is a promising approach in drug discovery which may be particularly exploited for the development of more potent and selective glycosidase inhibitors for therapeutic applications and antiviral compounds.

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References

1. For reviews on the biological/therapeutic potential of triazole derivatives, see: (a) Pibiri, I.; Buscemi, S. *Curr. Bioact. Compd.* **2010**, *6*, 208-242. (b) Agalave, S. G.; Maujan, S. R.; Pore, V. S. *Chem. Asian J.* **2011**, *6*, 2696-2718. (c) Shalini, K.; Kumar, N.; Drabu, S.; Sharma, P. K.; *Beilstein J. Org. Chem.* **2011**, *7*, 668-677.
2. (a) Hou, J.; Liu, X.; Shen, J.; Zhao, G.; Wang, P. G. *Expert Opin. Drug Discov.* **2012**, *7*, 489-501. (b) Valverde, I. E.; Bauman, A.; Kluba, C. A.; Vomstein, S.; Walter, M. A.; Mindt, T. L. *Angew. Chem. Int. Ed.***2013**, *52*, 8957-8960.
3. (a) Holm, S. C.; Straub, B. F. *Org. Prep. Proc. Int.* **2011**, *43*, 319-347. (b) Lauria, A.; De Lisi, R.; Mingoia, F.; Terenzi, A.; Martorana, A.; Barone, G.; Almerico, A. M. *Eur. J. Org. Chem.* **2014**, 3289-3306.

4. (a) Su, Z.; Peng, L.; Worthington, R. J.; Melander, C. *ChemMedChem***2011**, *6*, 2243-2251. (b) Beena; Kumar, N.; Rohilla, R. K.; Roy, N.; Rawat, D. S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 1396-1398.
5. Kumar, A.; Ahmad, I.; Chhikara, B.S.; Tiwari, R.; Mandal, D.; Parang, K. *Bioorg. Med. Chem. Letters* **2011**, *21*, 1342-1346.
6. Minvielle, M. J.; Bunders, C. A.; Melander, C. *Med. Chem. Commun.* **2013**, *4*, 916-919.
7. (a) Mir, F.; Shafi, S.; Zaman, M.S.; Kalia, N. P.; Rajput, V. S.; Mulakayala, C.; Mulakayala, N.; Khan, I. A.; Alam, M.S. *Eur. J. Med.Chem.* **2014**, *76*, 274-283. (b) Patel, R. V.; Park, S. W. *Eur. J. Med. Chem.* **2014**, *71*, 24-30.
8. Guantai, E. M.; Ncokazi, K.; Egan, T. J.; Gut, J.; Rosenthal, P. J.; Smith, P.J.; Chibale, K. *Bioorg. Med. Chem.* **2010**, *18*, 8243-8256.
9. Donald, J. R.; Martin, S. F. *Org. Lett.*, **2011**, *13*, 852-855.
10. Stacy, D. M.; Le Quement, S. T.; Hansen, C. L.; Clausen, J. W.; Tolker-Nielsen, T.; Brummond, J. W.; Givskov, M.; Nielsen, T. E.; Blackwell, H. E. *Org. Biomol. Chem.* **2013**, 11, 938-954.
11. Raj, R.; Singh, P.; Haberkern, N. T.; Faucher, R. M.; Patel, N.; Land, K. M.; Kumar, V. *Eur. J. Med. Chem.* **2013**, 63, 897-906.
12. Lucas, S. D.; Fischer, H.; Alker, A.; Rauter, A. P.; Wessel, H. P. *J. Carbohydr. Chem.* **2011**, *30*, 498-548.
13. Tripathi, R. P.; Dwivedi, P.; Sharma, A.; Kushwaha, D.; Tiwari, V. K. Triazolyl Glycoconjugates in Medicinal Chemistry. In *Click Chemistry in Glycoscience: New Developments and Strategies*; Z. J. Witczak, R. Bielski, Eds.; John Wiley & Sons, Inc., **2013**, Hoboken, NJ, USA.
14. (a) Brandley, B. K.; Schnaar, R. L. *J. Leukoc. Biol.* **1986**, *40*, 97-111. (b) Brandley, B. K. *Semin. Cell Biol.* **1991**, *2*, 281-287. (c) Schnaar, R. L. *Arch. Biochem. Biophys.* **2004**, *426*, 163-172; (d) Sharon, N. *Biochim. Biophys Acta*. **2006**, *1760*, 527-537.
15. Kannagi, R.; Izawa, M.; Koike, T.; Miyazaki, K.; Kimura, N. *Cancer Sci.* **2004**, *95*, 377-384.
16. For reviews, see: (a) Asano, N. *Cell Mol. Life Sci.* **2009**, *66*, 1479-1492; (b) Magnani, J. L.; Ernst, B. *Discov. Med.* **2009**, *8*(43), 247-52.; (c) Ernst, B.; Magnani, J. L. *Nat. Rev. Drug Discov*. **2009**, *8*, 661-677.
17. *Iminosugars: From Synthesis to Therapeutic Applications*; Compain, P.; Martin, O. R. Eds.; Wiley-VCH: Weinheim, **2007**. (b) Asano, N. Azaglycomimetics: Natural Occurrence, Biological Activity, and Application, in *Glycoscience, Chemistry and Chemical Biology*, Fraser-Reid, B.O.; Tatsuta, K.; Thiem, J. Eds.; Springer Verlag, **2008,** Berlin, Heidelberg, New York, 1887-1911.
18. (a) Witczak, Z. J. *Curr. Med. Chem.* **1999**, *6*, 165-78.. (b) Z. J. Witczak, J. M. Culhane, *Appl. Microbiol. Biotechnol.* **2005**, *69*, 237-244; (c) Steiner, A.; Stütz, A.; Wrodnigg, T. Sulfur-Containing Glycomimetics. In *Glycoscience, Chemistry and Chemical Biology*, Fraser-Reid, B.O.; Tatsuta, K.; Thiem, J. Eds.; Springer Verlag, **2008**, Berlin, Heidelberg, New York, 1999-2020.
19. (a) Rassu, G.; Auzzas, L.; Pinna, L.; Battistini, L.; Curti, C. *Stud. Nat. Prod. Chem.* **2003**, *29*(J), 449-520. (b) Arjona, O.; Gomez, A. M.; Lopez, J. C.; Plumet, J. *Chem. Rev.* **2007**, *107*, 1919-2036.
20. (a) Xavier, N. M.; Rauter, A. P. *Curr. Top. Med. Chem.* **2014***, 14*, 1235–1243. (b) Lahiri, R.; Ansari, A. A.; Vankar, Y. D.; *Chem Soc Rev.* **2013**, *42*, 5102-18. (c) Kobayashi, Y. Carbasugars: Synthesis and Function. In *Glycoscience, Chemistry and Chemical Biology*, B. O. Fraser-Reid, K. Tatsuta, J. Thiem, Eds.; Springer Verlag, **2008**, Berlin, Heidelberg, New York, 1915-1997. (d) Robina, I.; Vogel, P.; Witczak, Z. J. *Curr. Org. Chem.* **2001**, *5*, 1177-1214; (e) Xavier, N. M.; Madeira, P. J. A.; Florêncio, M. H.; Rauter, A. P. *Eur. J. Org. Chem.* **2009**, *2009*, 4983-4991.
21. (a) Rostovtsev, V. V.; Green, L. G.; Fokin, V. V.; Sharpless, K. B. *Angew. Chem., Int. Ed.* **2002**, *41*, 2596-2599. (b) Tornøe, C. W.; Christensen, C.; Meldal, M. *J. Org. Chem.* **2002**, *67*, 3057-3064. (c) Sokolovaab, N. V.; Nenajdenko, V. G. *RSC Adv.* **2013**, *3*, 16212-16242.

22. (a) Kushwaha, D.; Dwivedi, P.; Kuanar, S. K.; Tiwari, V. K. *Curr. Org. Synth.* **2013**, *10*, 90-135. (b) Santoyo-González, F.; Hernández-Mateo, F. *Top. Heterocycl. Chem.* **2007**, *7*, 133-177.
23. Rossi, L. L.; Basu, A.; *Bioorg. Med. Chem. Lett.* **2005**, *15*, 3596-3599.
24. Carvalho, I.; Andrade, P.; Campo, V. L.; Guedes, P. M.; Sesti-Costa, R; Silva, J. S.; Schenkman, S.; Dedola, S.; Hill, L.; Rejzek, M.; Nepogodiev, S. A.; Field, R. A. *Bioorg. Med. Chem.* **2010**, *18*, 2412-2427.
25. El Akri, K.; Bougrin, K.; Balzarini, J.; Faraj, A.; Benhida, R. *Bioorg. Med. Chem. Lett.* **2007**, *17*, 6656-6659.
26. Wilkinson, B. L.; Long, H.; Sim, E.; Fairbanks, A. J. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6265-6267.
27. Kuhn, H.; Gutelius, D.; Black, E.; Nadolny, C.; Basu, A.; Reid, C. *Med. Chem. Commun.* **2014**, *5*, 1213-1217.
28. (a) Chittaboina, S.; Xie, F.; Wang, Q. *Tetrahedron Lett.* **2005**, *46*, 2331-2336. (b) Lim, D.; Brimble, M. A.; Kowalczyk, R.; Watson, A. J. A.; Fairbanks, A. J. *Angew. Chem. Int. Ed.* **2014**, *53*, 11907-11911.
29. Marra, A.; Vecchi, A.; Chiappe, C.; Melai, B.; Dondoni, A. *J. Org. Chem.* **2008**, *73*, 2458-2461.
30. Périon, R.; Ferrières, V.; García-Moreno, M. I.; Ortiz Mellet, C.; Duval, R.; García Fernández, J. M.; Plusquellec, D. *Tetrahedron* **2005**, *61*, 9118-9128. (b) Cheshev, P.; Marra, A.; Dondoni, A. *Org. Biomol. Chem.* **2006**, *4*, 3225-3227. (c) Nepogodiev, S. A.; Dedola, S.; Marmuse, L.; de Oliveira, M. T.; Field, R. A. *Carbohydr. Res.* **2007**, *342*, 529-540. (d) Conte, M. L.; Marra, A.; Chambery, A.; Gurcha, S. S.; Besra, G. S.; Dondoni, A. *J. Org. Chem.* **2010**, *75*, 6326-6336. (e) Cendret, V.; François-Heude, M.; Méndez-Ardoy, A.; Moreau, V.; García Fernández, J. M.; Djedaïni-Pilard, F. *Chem. Commun.* **2012**, *48*, 3733-3735.
31. Kuijpers, B. H. M.; Groothuys, S.; Keereweer, A. R.; Quaedflieg, P. J. L. M.; Blaauw, R.H.; van Delft, F. L.; Rutjes, F. P. J. T. *Org. Lett.* **2004**, *6*, 3123-3126.
32. Dondoni, A.; Giovannini, P. P.; Massi, A. *Org. Lett.* **2004**, *6*, 2929-2932.
33. Azcune, I.; Balentová, E.; Sagartzazu-Aizpurua, M.; Ignacio Santos, J.; Miranda, J. I.; Fratila, R. M.; Aizpurua, J. M. *Eur. J. Org. Chem.* **2013**, 2434-2444.
34. *Iminosugars as Glycosidase Inhibitors*, Nojirimycin and Beyond. A. E. Stütz Ed.; Wiley-VCH: Weinheim, **1999**.
35. Scott, L. J.; Spencer, C. M. *Drugs* **2000**, *59*, 521-549.
36. McCormack, P. L.; Goa, K. L. *Drugs* **2003**, *63*, 2427-2434.
37. For reviews, see: (a) R. J. Nash, A. Kato, C.-Y. Yu, G. W. J. Fleet, *Future Med. Chem.* **2011**, *3*(12), 1513-1521. (b) Horne, G.;. Wilson, F. X.; Tinsley, J.; Williams, D. H.; Storer, R. *Drug Discov. Today* **2011**, *16*(3-4), 107-118. (c) Horne, G.; Wilson, F. X. *Prog. Med. Chem.* **2011**, *50*, 135-176; (d) Xavier, N. M.; Rauter, A. P. *Curr. Top. Med. Chem.* **2014**, *14*, 1235-1243.
38. Wilkinson, B. L.; Bornaghi, L. F.; Lopez, M.; Healy, P. C.; Poulsen, S.-A.; Houston, T. A. *Aust. J. Chem.* **2010**, *63*, 821-829.
39. Cordero, F. M.; Bonanno, P.; Chioccioli, M.; Gratteri, P.; Robina, I.; Moreno Vargas, A. J.; Brandi, A. *Tetrahedron* **2011**, *67*, 9555-9564.
40. Heightman, T. D.; Locatelli, M.; Vasella, A. *Helv. Chim. Acta* **1996**, *76*, 2190-2200.
41. (a) Panday, N.; Meyyappan, M; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 513-538. (b) Panday, N.; Vasella, A. *Helv. Chim. Acta* **2000**, *83*, 1205-1208.
42. Krtille, T. M.; Fuente, C.; Pickering, L.; Aplin, R. T.; Tsitsanou, K. E.; Zographos, S. E.; Oikonomakos, N. G.; Nash, R. J.; Griffiths R. C.; Fleet, G. W. J. *Tetrahedron: Asymm.* **1997**, *8*, 3807-3820.
43. Flessner, T.; Wong, C.-H.; *Tetrahedron Lett.* **2000**, *41*, 7805-7808.

44. Yanai, H.; Obara S.; Taguchi, T. *Org. Biomol. Chem.* **2008**, *6*, 2679-2685.
45. Tetzuka, K.; Compain, P.; Martin, O. R. *Synlett* **2000**, *12*, 1837-1839.
46. Dolhem, F.; Al Tahli, F.; Lièvre, C.; Demailly, G. *Eur. J. Org. Chem.* **2005**, 5019-5023.
47. Liu, Z.; Byun, H.; Bittman, R. *J. Org. Chem.* **2011**, *76*, 8588-8598. (b) Kumar, I.; Mir, N. A.; Rode, C. V.; Wakhloo, B. P. *Tetrahedron: Asymm.* **2012**, *23*, 225-229. (c) Arora, I.; Kashyap, V. Kr.; Singh, A. K.; Dasgupta, A.; Kumar, B.; Shaw, A.K. *Org. Biomol. Chem.* **2014**, *12*, 6855-68.
48. (a) Ardes-Guisot, N.; Alonzi, D. S.; Reinkensmeier, G.; Butters, T. D.; Norez, C.; Becq, F.; Shimada, Y.; Nakagawa, S.; Kato, A.; Blériot, Y.; Sollogoub, M.; Vauzeille, B. *Org. Biomol. Chem.* **2011**, *9*, 5373-5388. (b) Diot, J. D.; Garcia Moreno, I.; Twigg, G.; Ortiz Mellet, C.; Haupt, K.; Butters, T. D.; Kovensky, J.; Gouin, S. G. *J. Org. Chem.* **2011**, *76*, 7757-7768. (c) Howe, J. D.; Smith N.; Lee, M. J.; Ardes-Guisot, N.; Vauzeilles, B.; Désiré, J.; Baron, A.; Blériot, Y.; Sollogoub, M.; Alonzi, D. S.; Butters, T. D. *Bioorg. Med Chem.* **2013**, *21*, 4831-4838.
49. Joosten, A.; Decroocq, C.; de Sousa, J.; Schneider, J. P.; Etamé, E.; Bodlenner, A.; Butters, T. D.; Compain, P. *ChemBioChem* **2014**, *15*, 309-319.
50. Decroocq, C.; Rodríguez-Lucena, D.; Ikeda, K.; Asano, N.; Compain, P. *ChemBioChem* **2012**, *13*, 661-664.
51. Compain, P.; Decroocq, C.; Joosten, A.; de Sousa, J.; Rodríguez-Lucena, D.; Butters, T. D.; Bertrand, J.; Clément, R.; Boinot, C.; Becq, F.; Norez, C. *ChemBioChem* **2013**, *14*, 2050-2058.
52. Brás, N. F.; Cerqueira, N. M.; Ramos, M. J.; Fernandes, P. A. *Expert Opin. Ther. Pat.* **2014**, *24*, 857-874.
53. Adley, T. J.; Owen, L. N. *Proc. Chem. Soc.* **1961**, 418.
54. Capon, R. J.; MacLeod, J. K. *J. Chem. Soc., Chem. Commun.* **1987**, 1200-1201.
55. Yoshikawa, M.; Murakami, T.; Yashiro, K.; Matsuda, H. *Chem. Pharm. Bull*. **1998**, *46*, 1339-1340.
56. Wang, Y.; Du, Y. *J. Carbohydr. Chem.* **2013**, *32*, 240-248.
57. Fanton, J.; Camps, F.; Castillo, J. A.; Guérard-Hélaine, C.; Lemaire, M.; Charmantray, F.; Hecquet, L. *Eur. J. Org. Chem.* **2012**, 203-210.
58. Al-Masoudi, N. A.; Al-Soud, Y. A.; Schuppler, T. *J. Carbohydr. Chem*. **2005**, *24*, 237-250.
59. Goyard, D.; Baron, M.; Skourti, P. V.; Chajistamatiou, A. S.; Docsa, T.; Gergely, P.; Chrysina, E. D.; Praly, J.-P.; Vidal, S. *Carbohydr. Res.* **2012**, *364*, 28-40.
60. McCasland, G. E.; Furuta, S.; Durham, L. J. *J. Org. Chem.* **1966**, *31*, 1516-1521.
61. Miller, T. W.; Arison, B. H.; Albers-Schonberg, G *Biotechnol. Bioeng.* **1973**, *15*, 1075-1080.
62. Federspiel, M.; Fischer, R.; Hennig, M.; Mair, H. J.; Oberhauser, T.; Rimmler, G.; Albiez, T.; Bruhin, J.; Estermann, H.; Gandert, C.; Gockel, V.; Gotzo, S.; Hoffmann, U.; Huber, G.; Janatsch, G.; Lauper, S.; Rockel-Stabler, O.; Trussardi, R.; Zwahlen, A. G. *Org. Process Res. Dev*. **1999**, *3*, 266-274.
63. Sidwell, R. W.; Robins, R. K.; Hillyard, I. W. *Pharmacol. Ther.* **1979**, *6*, 123-146.
64. Crotty, S.; Cameron, C.; Andino, R. *J. Mol. Med.* **2002**, *80*, 86-95.
65. Kuang, R.; Ganguly, A. K.; Chan, T.-M.; Pramanik, B. N.; Blythin, D. J.; McPhail, A. T.; Saksena, A. K. *Tetrahedron Lett.* **2000**, *41*, 9575-9579.
66. Tuncbilek, M.; Schneller, S. W. *Nucleos. Nucleot. Nucleic Acids* **2003**, *22*, 1995-2001.
67. An, GI.; Rhee, H. *Nucleos. Nucleot. Nucleic Acids* **2003**, *22*, 437-451.
68. Saito, Y.; Escuret, V.; Durantel, D.; Zoulim, F.; Schinazi, R. F.; Agrofoglio, L. A. *Bioorg. Med. Chem.* **2003**, *11*, 3633-3639.
69. Broggi, J.; Joubert, N.; Aucagne, V.; Zevaco, T.; Berteina-Raboin, S.; Nolan, S. P.; Agrofoglio, L. A. *Nucleos. Nucleot. Nucleic Acids* **2007**, *26*, 779-783.
70. Broggi, J.; Joubert, N.; Díez-González, S.; Berteina-Raboin, S.; Zevaco, T.; Nolan, S. P.; Agrofoglio, L. A. *Tetrahedron* **2009**, *65*, 1162-1170.

71. Pérez-Castro, I.; Caamano, O.; Fernández, F.; García, M. D.; López, C.; Clercq, E. D. *Org. Biomol. Chem.* **2007**, *5*, 3805-3813.
72. Cho, J. H.; Bernard, D. L.; Sidwell, R. W.; Kern, E. R.; Chu, C. K. *J. Med. Chem.* **2006**, *49*, 1140-1148.
73. González-González, C. A.; Fuentes-Benítez, A.; Cuevas-Yáñez, E.; Corona-Becerril, D.; González-Romero, C.; González-Calderón, D. *Tetrahedron Lett.* **2013**, *54*, 2726-2728.
74. Joubert, N.; Schinazi, R. F.; Agrofoglio, L. A. *Tetrahedron* **2005**, *61*, 11744-11750.
75. Carrau, G.; Drewes, C. C.; Shimada, A. L. B.; Bertucci, A.; Farsky, S. H. P.; Stefani, H. A.; Gonzalez, D. *Bioorg. Med. Chem.* **2013**, *21*, 4225-4232.
76. Díaz, L.; Bujons, J.; Casas, J.; Llebaria, A.; Delgado, A. *J. Med. Chem.* **2010**, 53, 5248-5255.
77. Ji, L.; Zhou, G. Q.; Qian, C.; Chen, X. Z. *Eur. J. Org. Chem.* **2014**, *2014*, 3622-3636.