Thiosugars: reactivity, methodology and applications

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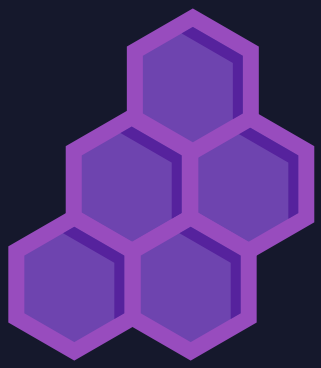
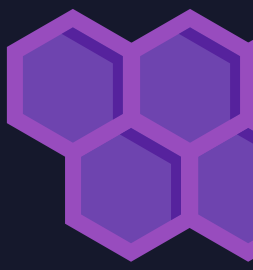
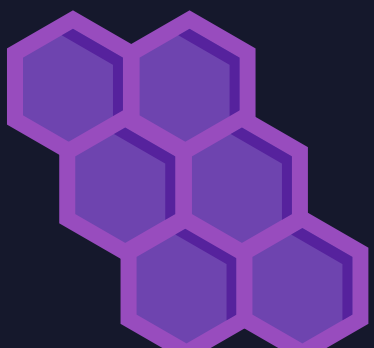
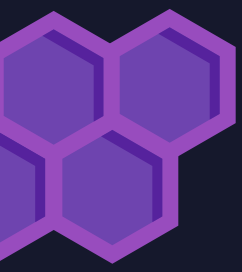
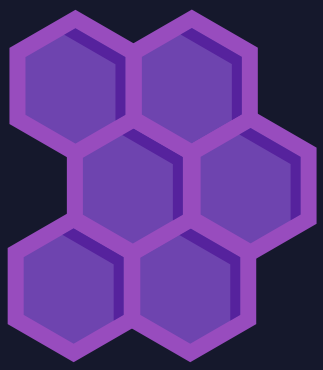



CHAPTER 1




INTRODUCTION




1.1 General carbohydrate chemistry

Carbohydrates are the most abundant and diverse class of biomolecules, found in all kingdoms of life. Carbohydrates can be found as mono-, oligo- and polysaccharides, as well as covalently linked to other molecules to form glycoproteins and glycolipids. Besides, DNA and RNA are polynucleotide chains having a backbone made of alternating (deoxy)ribose residues provided with a nucleobase and phosphate groups. Furthermore, mucins are essential macromolecules produced by your epithelial tissues, which are heavily glycosylated proteins (Figure 1). Traditionally, carbohydrates were simply thought of as source of energy (e.g. glycogen and starch, Figure 1) or as structural components of cell walls (e.g. cellulose for plants or chitin for arthropods, Figure 1). More important for contemporary glycoscience, carbohydrates are involved in countless different biological processes such as cellular adhesion, migration, development, disease progression, pathogen detection, and immune response.

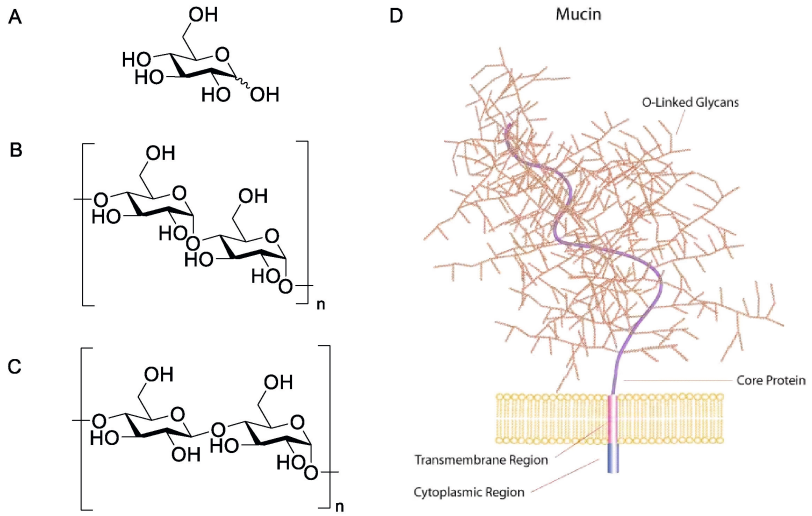


Figure 1. A) Glucose. B) (1→4)-α-D-glucose, or starch. C) (1→4)-β-D-glucose, or cellulose. D) Mucin, an example of a glycoconjugate.

The high structural diversity of carbohydrates and their involvement in the plethora of physiological and pathophysiological events has led to a search for carbohydrate-based drugs, vaccines and diagnostic tools. As an illustration, a few selected examples of carbohydrate-containing drugs are presented in Figure 2. Aminoglycoside antibiotics are an important class of antibiotic therapy. The first discovered member of this class is streptomycin, a pseudo-trisaccharide isolated from *Streptomyces griseus*, that is used to treat a number of different infections, such as tuberculosis. Due to antibiotic resistance, both natural and

semi-synthetic aminoglycoside antibiotics are presently explored. Various antitumor drugs contain carbohydrates, such as the group of anthracyclines. One of the most widely used anti-cancer medicine in the western world is Doxorubicin, isolated from *Streptomyces peucetius*. Notwithstanding their therapeutic value, side effects and multidrug resistance have stimulated the development of (semi)synthetic derivatives to acquire anthracyclines with an improved efficacy.[1–3]

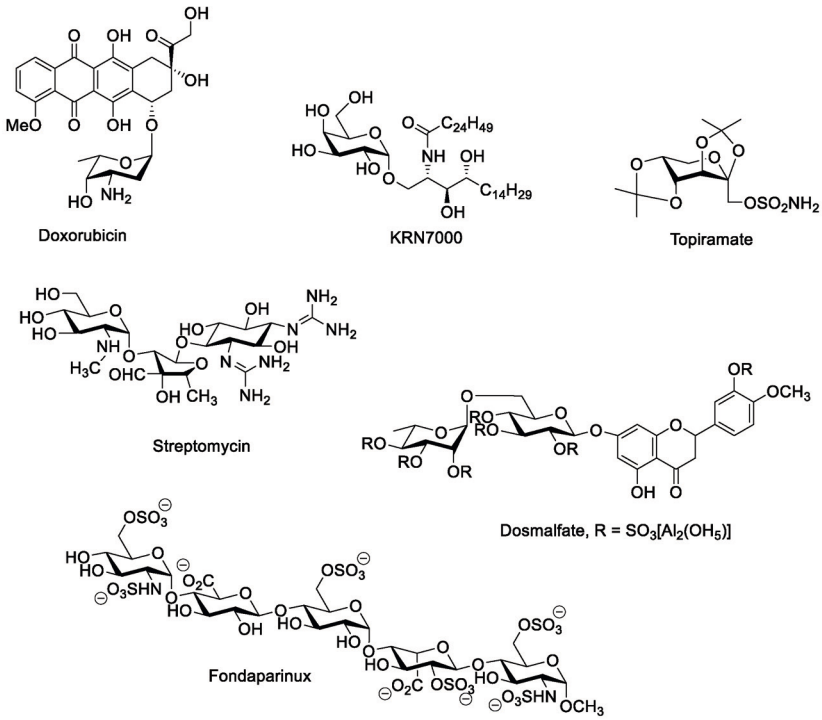


Figure 2. A selection of carbohydrate containing drugs.

Agelasphins are α-linked galactosyl ceramides and were isolated from *Agelas mauritianus*. These galactosyl ceramides were found to act as stimulants of human leukocytes, as they were able to activate invariant NKT immune cells. This leads to the production of different cytokines modulating a TH1/TH2 immune response balance, which is important in autoimmune diseases and cancer. This discovery guided the synthesis and evaluation of α-GalCer (KRN7000) and analogues thereof. Other examples of carbohydrate-based drugs are Topiramate, which is used for the treatment of epilepsy, Dosmalfate, a medicine against gastric ulceration, and Fondaparinux, an antithrombin drug, the structure of which is a mimetic of a pentasaccharide, that is found in heparin. An active field in glycoscience is the development of glycoconjugate vaccines. Cell-surface polysaccharides and glycoconjugates from pathogens may act as

antigens, but polysaccharides are poorly immunogenic as stand-alone entities and need to be conjugated to carrier proteins to elicit a robust immune response with immunological memory. Several vaccines in use today have incorporated naturally derived glycans. Chemically prepared conjugates have the potential to improve these vaccines, in particular for carbohydrates that are present in heterogenic mixtures and that cannot be isolated in sufficient amounts and purity. An example of a semi synthetic conjugate vaccine is the *Haemophilus influenzae* type b vaccine, which was developed in Cuba in 2004. This vaccine comprises of a synthetic capsular polysaccharide antigen from Hib, conjugated to tetanus toxoid (Figure 3). A similar approach is employed to find synthetic glycoconjugate vaccines to combat the pathogenic bacteria *Staphylococcus aureus* and *Streptococcus pneumonia*. The finding that many cancers can be characterized by 'tumor associated carbohydrate antigens' has stimulated a lot of research to the development of carbohydrate-based cancer vaccines.[4–7]

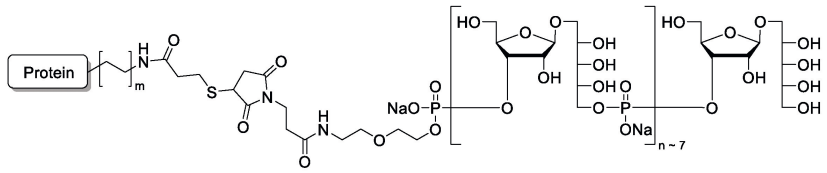


Figure 3. Vaccine for *Haemophilus influenzae* type b (Hib)

1.2 Glycomimetics

The most prominent structural element of carbohydrates is the glycosidic linkage. In glycobiology the assembly and processing of polysaccharides, glycoproteins and glycolipids is governed by two classes of enzymes; the glycosidases that cleave glycans, and the glycosyltransferases that introduce that introduce glycosidic linkages in a stereospecific manner. Glycosidic bonds are acetals (or ketals for ketoses), that can be cleaved under acidic conditions. The chemical and enzymatic stability of glycosidic bonds can be improved by the application of structural mimics (or glycomimetics) of functional glycans. Other issues in the design of these glycomimetics can be the enhancement of the bioavailability and the improvement of the affinity and selectivity toward the target. Intensively pursued glycomimetics are C-glycosides, N-glycosides and S-glycosides, in which the exocylic oxygen atom is replaced by a carbon, nitrogen or sulfur atom, respectively. [8,9]

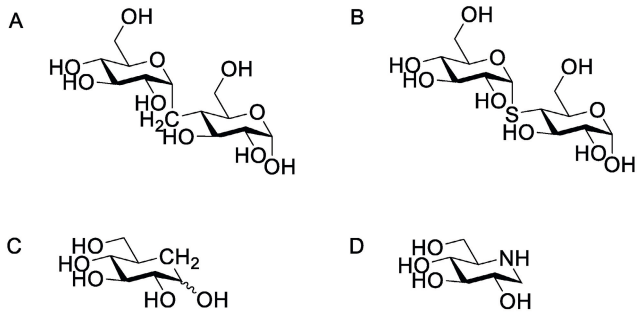


Figure 4. A) C-glycoside B) S-glycoside/thio-glycoside. C) Carbasugar D) iminosugar/azasugar

Various naturally occurring C-glycosides show biological properties, such as the antifungal agent Papulacandin A. Synthetic C-glycoside analogues, such as Dapagliflozin and Canagliflozin, function as SGLT2 inhibitors against type II diabetes. Another example of a synthetic C-analogues is KRN7000, which is used as immunostimulant. S-glycosides or thioglycosides, in which the anomeric O is replaced by a S, confer chemical and enzymatic stability while the biological activity with respect to the corresponding O glycosides is usually maintained. The synthetic procedures of S-linked oligosaccharides have been developed, as well as procedures for S-liked glycoconjugates for glycolipids and glycoproteins. S-glycosides and S-glycoconjugates have proven to be glycosidase inhibitors, antibacterial agents and antitumor drugs. Further application has shown that these glycans can be used as ligands for the purification of proteins using affinity chromatography. The group of Bundle reported the synthesis and immunological evaluation of two vaccines candidates, comprising S-linked trisaccharides based on an epitope derived from *Candida albicans*, conjugated to BSA (Figure 5).[10] The S-glycoside TD139 is an inhibitor of Galectin-3, a β-galactoside-binding lectin with a key role in the pathogenesis of idiopathic pulmonary fibrosis (Figure 5).[11,12]

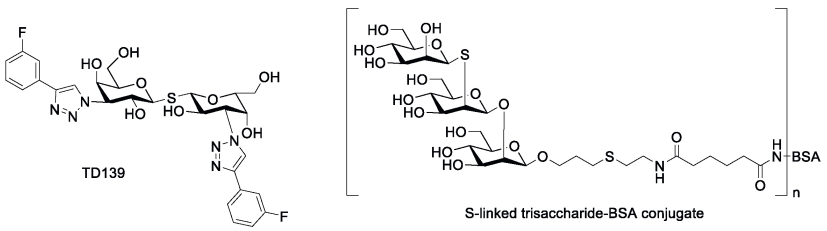


Figure 5. TD139 and S-linked trisaccharide-BSA conjugate

The endocyclic oxygen of both pyranose and furanose monosaccharides can also be replaced by a carbon, nitrogen or sulfur atom to give carbasugars, iminosugars and thiosugars respectively. The carba- and thio-glycomimetics

exhibit an increase in enzymatic stability. A well-known example of a synthetic carbasugar is Oseltamivir phosphate (Tamiflu, Figure 6), which inhibits the influenza viral neuraminidase and is used to treat infections by the influenza virus. The carbasugar Voglibose (Glustat, Figure 6) is an α-glucosidase inhibitor that is used as anti-diabetic drugs. Cyclophellitol is a carbasugar isolated from the mushroom *Phellinus sp.*, a potent mechanism-based inhibitor of retaining β-glucosidases. Inspired by cyclophellitol, the group of Overkleeft designed and synthesized a variety carbasugars, provided with an electrophilic trap, such as an epoxide or aziridine. This library of carbasugars were evaluated as mechanism-based covalent inhibitors and/or as activity-based probes.[13]

Iminosugars, which can also be considered as polyhydroxylated alkaloids, are widely and successfully explored as non-covalent inhibitors of glycosidases and glycosyltransferases. Miglitol (Glyset, Figure 6), an α-glucosidase inhibitor, is used for the treatment of type-2 diabetes.[14] Additionally, iminosugars have proven to be chaperones, which prevent cellular degradation of improperly folded glycosidases by conformational stabilisation. Miglustat (Figure 6) is used clinically to treat the lysosomal storage disorders Gaucher and Niemann-Pick type C. Iminosugars are also actively investigated as potential drugs for the treatment of viral infections, cancer, cystic fibrosis and other lysosomal storage diseases.

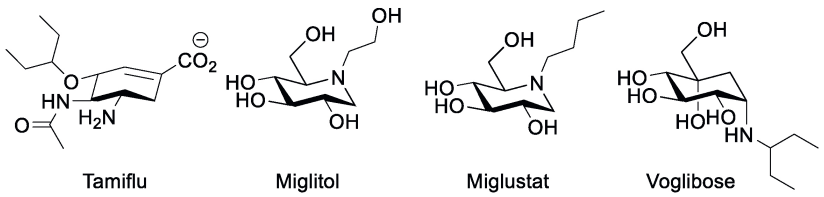


Figure 6. Synthetic glycomimetic drugs

The search for fully synthetic glycoconjugate vaccines is nicely illustrated by the development of vaccines against *Neisseria meningitidis*. This bacterium is one of the most significant causative agents of meningitidis in humans and has six clinically relevant serogroups. Various carbohydrate-based vaccines have been licensed to date and several others are in different phases of clinical trials. Synthetic glycoconjugate vaccines with well-defined carbohydrate epitopes incorporated are currently being explored. The capsular polysaccharide of *N. meningitidis* serogroup A (MenA) consists of (1→6)-2-acetamido-2-deoxy-α-D-mannopyranosyl phosphate repeating units, which are *O*-acetylated at position C3 or C4. This antigen is intrinsically unstable and has therefore been a target for the development of biologically active glycomimetics. Two types of MenA oligosaccharide mimics have been synthesized, conjugated to the protein

CRM197 and evaluated on their immunological properties (Figure 7). In the first mimetic the anomeric oxygen is replaced by a methylene group resulting in C-phosphonates, while in the second the ring oxygen is replaced by a methylene group to give the corresponding carba-mannosamine analogues. The latter conjugates could induce antibodies capable of recognizing the native MenA polysaccharide, but their immunogenicity proved to be unsatisfactory without acetylation of position C3 or C4. The immunogenicity was improved by randomly acetylating the carbaMenA octamer, displayed by antibody production reaching the same level as the benchmark MenA polysaccharide.[1,3,7,9,15–19]

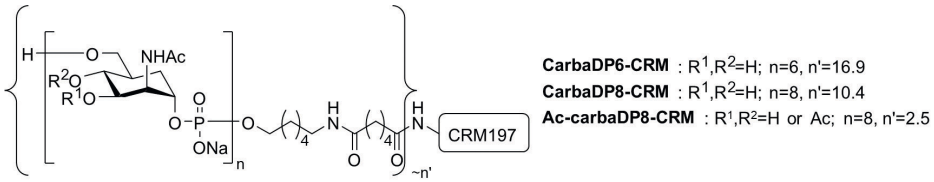
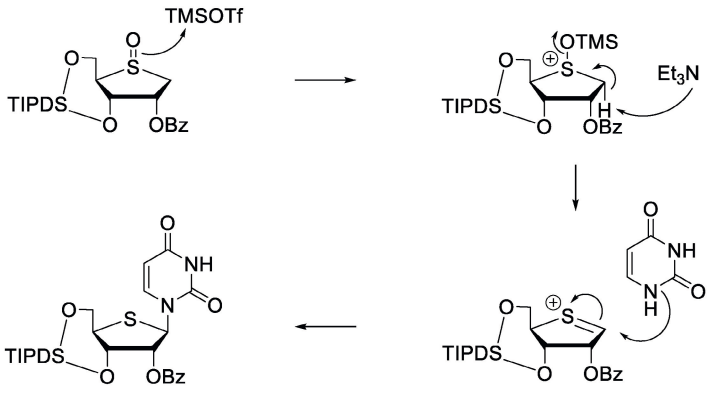


Figure 7. Carbasugar containing vaccine for meningococcus

1.2.1 Thiosugars

This Thesis focusses on thiosugars (also termed thiasugars), glycomimetics in which the endocyclic oxygen of the acetal moiety is substituted for a sulfur atom. The pentoses, D-ribose and D-deoxyribose in their furanose form, are constituents of RNA and DNA, respectively and the potential to function as therapeutics to combat cancers and diseases of bacterial or viral origin has led to an overwhelming effort to design, synthesize and evaluate modified (deoxy)nucleosides. In this framework a lot of research has been devoted to 4-thionucleosides, including usual (deoxy)nucleosides and nucleosides with other pentose configurations, resulting in the development of novel 4-thionucleosides, possessing anticancer, antibacterial and antiviral activities.[20–25] Several synthetic approaches to 4-thionucleosides have been published and the most efficient route with the Pummerer rearrangement as key step was independently devised by the groups of Matsuda and O'Neil (Scheme 1).[11,26,27]



Scheme 1. Pummerer rearrangement used for installing nucleobases

Among the biologically active 4-thionucleosides is for example 4-ethynyl-4-thio-deoxyguanosine (Figure 8), a very potent nucleoside reverse transcriptase inhibitor (NRTI). This 4-thionucleoside exhibits a higher potency and lower toxicity than its oxo-counterpart, displayed by a 20-fold increase in its selectivity index.[20] Another example is represented by cyclic ADP-4-thioribose, a stabilized analogue of the second messenger cyclic ADP-Ribose (Figure 8).[28] 4-Thionucleosides are also being considered for antisense oligonucleotide therapeutics and siRNA-based therapeutics. Yoshimura *et al.* describes the synthesis and properties of locked and bridged 4-thio nucleotides, which provides resistance to nucleases (Figure 8).[29]

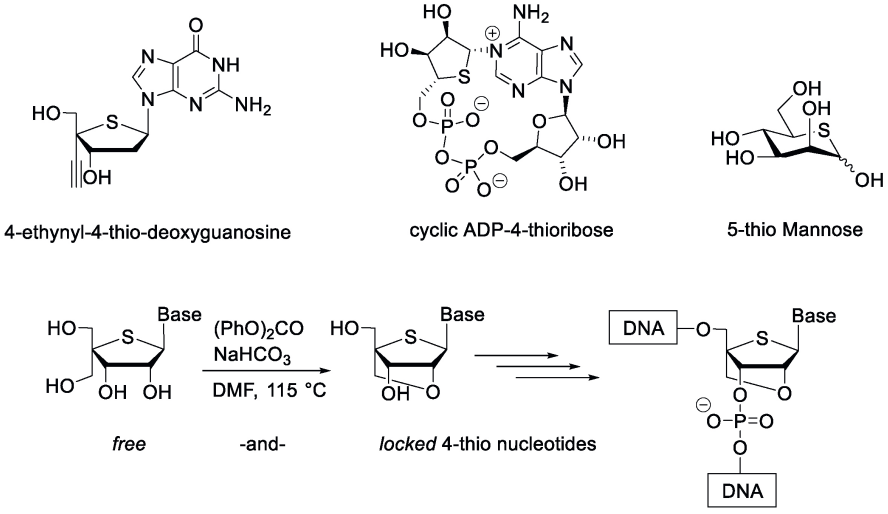


Figure 8. Thiosugar analogues

The only naturally occurring thiosugar hexose is 5-thio mannopyranose, which has been extracted from the marine sponge *Clathria pyramida* (Figure 8). Other differently configured 5-thio glycosides have been prepared by various synthetic routes, as was reviewed by Schmidt and Pachamuthu.[11] Evaluation of their inhibitory activity on glycosidases showed that 5-thio-L-fucose and 5-thio-D-glucose are able to inhibit α-fucosidases and α-glucosidases respectively, a finding that was explained by a hydrophobic interaction of the ring sulfur and the enzyme pocket. The increased (enzymatic) stability of 5-thiosugars is illustrated by the use of UDP-5-thio-GlcNAc as an inhibitor of HBP (hexosamine biosynthesis pathway) and OGT (O-GlcNAc transferase), as reported by the group of Vocadlo.[30] Palcic and co-workers synthesized GDP-5-thiosugars and demonstrated their use as glycosyl donor substrates for α-(1,2)-mannosyltransferase and α-(1,3)-fucosyltransferase.[31,32] The 5-thio analogues were accepted by the enzymes but transfer of the 5-thiosugars was significantly slower than their natural 5-*O* counterparts.

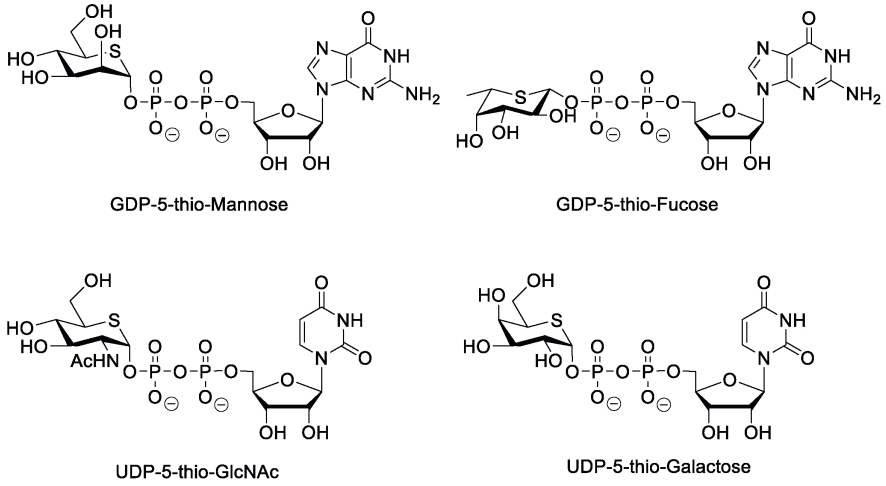


Figure 9. Thio analogies of common sugar nucleotides

Another class of thiosugars is represented by the 1,4-thioanhydrosugars, Salacinol (Figure 10) and Kotalanol that have been isolated from the plant *Salacia reticulata*, and which display inhibitory activity against intestinal α-glucosidases. Interestingly, the plant *Salacia reticula* has been used in traditional Ayurvedic medicine for centuries. Later it was discovered that more members of the genus Salacia contain similar sulfonium thiosugars, such as Neosalacinol, Salaprionol and Ponkoranol. These sulfonium thiosugars present a novel class of natural α-glucosidase inhibitors.[33–37] The inhibitory capacity of these compounds is based on the sulfonium ion structure which mimics an oxocarbenium ion, that occurs as an intermediate in the enzymatic hydrolysis of oligosaccharides.

Significant research has been devoted to the synthesis and biological evaluation of this class of compounds and various synthetic analogues with diverse alkylation patterns of the sulfonium side chain have been generated. Some of these have shown increased inhibition of α-glucosidases.[37] In the search for inhibitors of the galactofuranosyl transferase GlfT2, the sulfonium ion motif has been used to mimic the transition state of the galactofuranose transfer reaction.[38] The albomycins, isolated from several species of Streptomycetes contain a 6'-amino-4'-thioheptose nucleoside and an iron-chelating tri-δ-*N*-hydroxy-L-ornithine peptide siderophore that are connected via a serine residue (Figure 10). Albomycins exhibit potent inhibitory activities against a number of bacteria, including multi-drug resistant strains. Whereas the siderophore functions as targeting device, the thiocytosine moiety is an inhibitor of bacterial seryl-tRNA synthetase. Recently the first total synthesis of three natural albomycins was reported, this is considered as a solid base for developing bioactive analogues.[39]

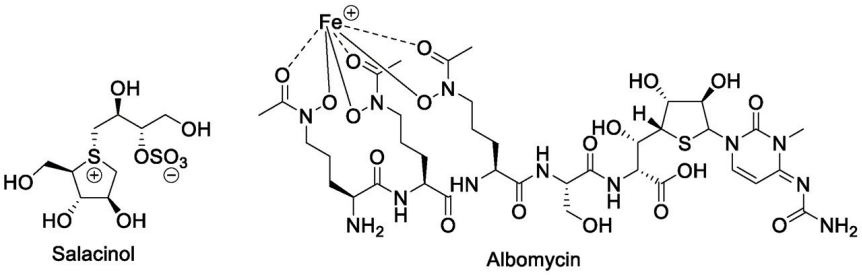


Figure 10. Naturally occurring thiosugars with therapeutic properties

At this stage it is relevant to pay attention to oligosaccharides with 5-thio-pyranosyl linkages, as sulfur is the closest chalcogen to oxygen, allowing for similar stereoelectronic interactions to natural substrates. In addition, the sulfur atom is regularly used as a mimic of the natural O-atom. While carbasugars generally offer optimal resistance to cleavage of the glycosidic bond, the methylene group is significantly larger than the single O-atom. When comparing thiosugar oligomers to thioglycosides, it is worth noting that the bond length of the exocyclic sulfur of a thioglycoside can be significantly longer than the natural oligosaccharide (see Figure 11).[40] Also, other authors noted good agreement of the three-dimensional structure of oligosaccharides with 5-thio-pyranosyl linkages with that of their corresponding oxygen counterparts.[41]

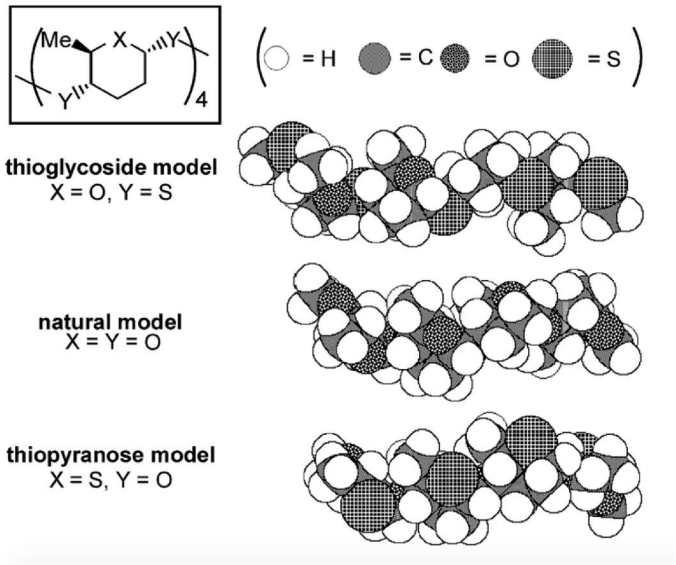
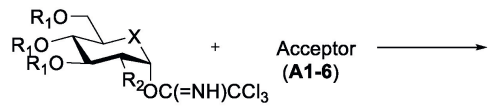


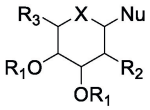
Figure 11. Comparison of a 'natural' oligosaccharide model with models of analogues containing thioglycosides and thiopyranoses.[40]

Several different methodologies have been reported for the synthesis of differently configured thiosugars[11] and the glycosylating properties of some of these have been investigated. Based on the presumption that the removal of benzyl protective groups in thioglucose derivatives can be problematic, peracetylated thioglucose donors have been investigated. Notwithstanding the neighbouring group participation that acetyl groups normally show in the formation of trans *O*-glycosidic bonds with standard 5-oxy-pyranosyl donors, anomeric mixtures, in which the α-anomer prevails were obtained when the peracetylated thioglucose donors were used. Using a *O*-benzyl protected glucosyl trichloroacetimidate donor (**5**, table 1) and TESOTf as activator the yield of the coupling reactions with different acceptors was improved up to 80% with a high α-stereoselectivity (>98:2). Further studies showed that (*p*-methoxybenzyl) MPM protected 5-thioglucopyranosyl trichloroacetimidates (**6**) with TESOTf as activator resulted in α -stereoselective glycosylations and deprotection of the MPM ethers proceeded smoothly with DDQ. Several α-linked disaccharides with one 5-thioglucopyranose but also an isomaltotetraoside mimic composed of 5-thioglucopyranose residues was prepared. Interestingly, both benzoyl and pivaloyl protected 5-thioglucopyranosyl trichloroacetimidate donors (**3** and **4**) with BF_3OEt_2 as activator and C6-OH glucopyranosyl as acceptors (**A1**) proceeded in β-stereoselective manner.[42] The peracetylated 5-thio-D-galactopyranose trichloroacetimidate donor (**10**) proved to be α-selective in the TMSOTf mediated condensation with phytosphingosine derivatives (**A4**) at −40 °C to give KRN7000 analogues in reasonable yields.[43]

A 5-thio-L-fucose-containing analogue of trisaccharide H-type II blood group determinant was obtained via a synthetic route, the final glycosylation of which entailed the α -selective and regioselective condensation of a disaccharide diol (**A5**) with peracetylated 5-thiofucosyl trichloroacetimidate in the presence of $BF_3 \cdot OEt_2$ at -20 °C, yielding the protected precursor of the target blood group determinant. Unexpectedly, the use of the per-O-acetyl-5-thiomannosyl trichloroacetimidate donor (**12**) proved to be unproductive and led to an unidentified mixture of products. The corresponding perbenzylated donor (**13**) was more effective and resulted in complete α-stereoselective couplings in satisfactory yield.[44,45] The glycosylating properties of three 5-thioglucosamine trichloroacetimidate donors which contain an acetamido (**7**), an azido (**8**) or a phthalimido (**9**) group at the 2-position, with the remaining hydroxyl functions acetylated, were investigated. Using the reactive secondary hydroxyl of 1,6-anhydro-2-azido-2-deoxy-D-glucopyranose **A3** as acceptor and $BF_3 \cdot OEt_2$ as activator, the 2-acetamido donor gave only the α -configured disaccharide together with the oxazoline derivative that is obtained as the only product with a similar glycosylation using the ring oxygen counterpart. Similar glycosylation with the 2-azido donor resulted in the main formation of the α -disaccharide together with a small amount of the b-disaccharide. Furthermore, the activator proved to be of importance as the use of TMSOTf predominantly gave the glycosylacetamide. In contrast the $BF_3 \cdot OEt_2$ mediated coupling with the 2-phthalimido donor led to the isolation of only the β-disaccharide, a result which is commonly seen with the ring oxygen counterparts.

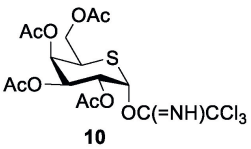
Table 1. Glycosylation reactions with 5-thio pyranosides. (* Yield over multiple steps, including glycosylation)





R_3=CH_2OPG. CH_3

1. X=O, R_1=Ac, R_2=OAc
2. X=S, R_1=Ac, R_2=OAc
3. X=S, R_1=Bz, R_2=OBz
4. X=S, R_1=Piv, R_2=OPiv
5. X=S, R_1=Bn, R_2=OBn
6. X=S, R_1=MPM, R_2=OMPM
7. X=S, R_1=Ac, R_2=NHAc
8. X=S, R_1=Ac, R_2=N_3
9. X=S, R_1=Ac, R_2=NPht



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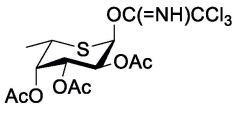

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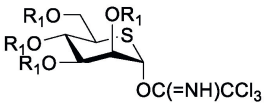
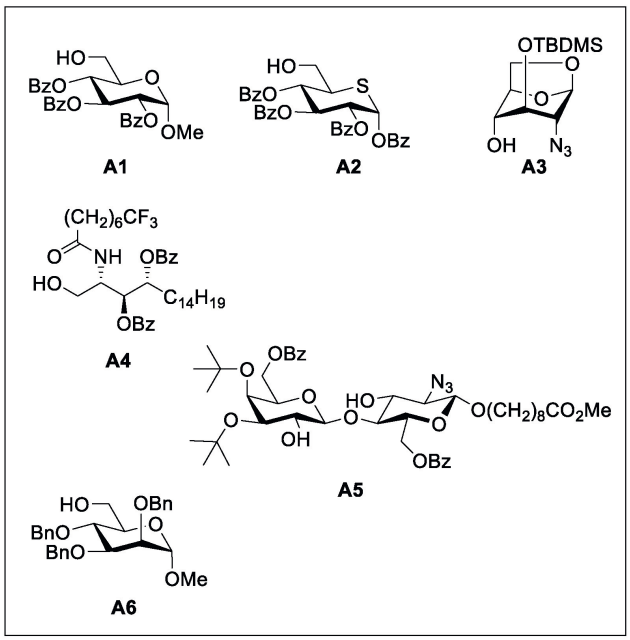


12. R_1=Ac
13. R_1=Bn



No.	Donor	Acceptor	Activator	Yield	Selectivity (α:β)
1	**1**	**A1**	$BF_3{\cdot}OEt_2$	76%	<5:95
2	**2**	**A1**	$BF_3{\cdot}OEt_2$	19%	30:70
3	**2**	**A2**	TESOTf	10%	>95:5
4	**3**	**A1**	$BF_3{\cdot}OEt_2$	77%	17:83
5	**3**	**A2**	$BF_3{\cdot}OEt_2$	62%	<5:95
6	**3**	**A1**	TESOTf	38%	84:16
7	**3**	**A1**	TMSOTf	11%	>95:5
8	**3**	**A1**	TfOH	33%	89:11
9	**4**	**A1**	$BF_3{\cdot}OEt_2$	69%	<5:95
10	**5**	**A2**	TESOTf	81%	>95:5
11	**6**	**A2**	TESOTf	94%	>95:5

Table 1. Continued

No.	Donor	Acceptor	Activator	Yield	Selectivity (α:β)
12	**6**	**A1**	TESOTf	82%	88:12
13	**7**	**A3**	$BF_3{\cdot}OEt_2$	45%	>95:5
14	**8**	**A3**	$BF_3{\cdot}OEt_2$	75%	86:14
15	**9**	**A3**	$BF_3{\cdot}OEt_2$	62%	<5:95
16	**10**	**A4**	TMSOTf	54-64%	>95:5
17	**11**	**A5**	$BF_3{\cdot}OEt_2$	24%*	>95:5
18	**12**	**A6**	$BF_3{\cdot}OEt_2$	mixture	-
19	**13**	**A6**	$BF_3{\cdot}OEt_2$	26%*	>95:5

A lot of attention has been devoted to elucidate the mechanism of glycosylation reactions involving standard glycosides, and many studies have been directed at the detection and characterisation of productive intermediates. Comparable studies to probe the glycosylating properties of 5-thiopyranosides, are largely lacking. Based on the results described above it can be concluded that glycosylation of 5-thio glycosyl donors proceed with a striking preference for the formation of axial glycosidic linkages, with neighboring group participation by 2-acyl groups falling short. The exact reason for this striking stereoselectivity remains unknown, although it has been argued that 5-thiosugars exhibit an increased anomeric effect,[46] which promotes the formation of axial glycosidic linkages. A notable difference between 5-thio and 5-oxo sugars is that 5-thiopyranosides adopt a more puckered conformation due to the longer C–S bonds and a smaller C–S–C angle in comparison with their 5-oxo counterparts. Hydrolysis studies have indicated that alkyl 5-thiopyranosides exhibit a larger anomeric effect and the endocyclic sulfur seems to stabilize the carbenium ion better than the oxygen atom. However, the barrier for the formation of a thiacarbenium ion has been estimated to be higher than the formation of the corresponding oxocarbenium ion.[46–50]

To obtain a better understanding of glycosylation reactions in general and those of 4-thiofuranosides and 5-thiopyranosides in particular, it is worthwhile to study glycosylating properties of 4-thiofuranosides and 5-thiopyranosides in more detail. The products of these glycosylation reactions may lead to molecules with valuable biological properties, as exemplified by the use of thiosugars as inhibitors of various glycosidases, substrates and inhibitors of glycosyltransferases, and as probes for lectins and constituents of vaccines, as outlined above.

1.3 Aim and outline of this thesis

The work described in this Thesis has studied various aspects of thiosugar chemistry. In **Chapter 2** the synthesis of all 4-thio pentofuranosides, that of ribose, arabinose, xylose and lyxose configurations, is described. These 4-thio pentofuranosides were transformed into donors and applied in glycosylation reactions that typically follow an S_N1 trajectory to determine the stereochemical outcome of the glycosylation reactions. This outcome has been related to the structure of the thiacarbenium ions involved, which are also probed using DFT-based computational studies.

Chapter 3 deals with the synthesis of 4-thionicotinamide riboside, carba-nicotinamide riboside and benzamide riboside. Next, their subsequent enzymatic conversion into 4-thio-NAD^+, carba-NAD^+ and benzamide adenine dinucleotide (BAD), respectively, is discussed. The inhibitory potential of these NAD^+ analogues for *Legionella pneumophila* Phosphoribosyl Ubiquitylating Enzyme SdeC was investigated.

The histone H2B is known to undergo ADP-ribosylation as a post-translational modification. In **Chapter 4** the synthesis of α-4-thio-ribosylated serine is discussed. The crucial glycosidic linkage between the 4-thio ribose donor and the serine acceptor was achieved using a gold(I)-catalyzed glycosylation. Using solid-phase peptide synthesis the α-4-thio-ribosylated serine building block was incorporated in a H2B peptide, and the subsequent addition of ADP resulted in a relevant ADP-4-thio-ribosylated peptide.

The synthesis and corresponding glycosylation properties of all four diastereomeric thio-pentapyranose donors is described in **Chapter 5**. In line with the study of Chapter 2, the 4-thiopyranosyl donors were glycosylated in S_N1-type glycosylations and the obtained experimental results were related to the structure of thiacarbenium ions, that were computationally studied using a DFT-based computational approach.

Chapter 6 has been devoted to the design and synthesis of cyclophellitol-derived endoglycosidase inhibitors, aimed at inhibiting heparanase. To achieve this, protected 5-thio glucose and 5-thio GlcNAc donors were synthesized and used in combination with cyclophellitol and decorated cyclohexene acceptors.

Finally, in **Chapter 7**, the achieved results are summarized and discussed, and future prospects are shared.

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