



**HAL**  
open science

## Chemical synthesis of oligosaccharides and their application in new drug research

Zhimin Lv, Hongyu Liu, Huifang Hao, Faiz-Ur Rahman, Yongmin Zhang

► **To cite this version:**

Zhimin Lv, Hongyu Liu, Huifang Hao, Faiz-Ur Rahman, Yongmin Zhang. Chemical synthesis of oligosaccharides and their application in new drug research. *European Journal of Medicinal Chemistry*, 2023, 249, pp.115164. 10.1016/j.ejmech.2023.115164 . hal-03978291

**HAL Id: hal-03978291**

**<https://hal.science/hal-03978291>**

Submitted on 8 Feb 2023

**HAL** is a multi-disciplinary open access archive for the deposit and dissemination of scientific research documents, whether they are published or not. The documents may come from teaching and research institutions in France or abroad, or from public or private research centers.

L'archive ouverte pluridisciplinaire **HAL**, est destinée au dépôt et à la diffusion de documents scientifiques de niveau recherche, publiés ou non, émanant des établissements d'enseignement et de recherche français ou étrangers, des laboratoires publics ou privés.

# Chemical synthesis of oligosaccharides and their application in new drug research

Zhimin Lv <sup>a</sup>, Hongyu Liu <sup>a</sup>, Huifang Hao <sup>a</sup>, Faiz-Ur Rahman <sup>a</sup>, Yongmin Zhang <sup>a, b, c, \*</sup>

<sup>a</sup> Inner Mongolia University Research Center for Glycochemistry of Characteristic Medicinal Resources, School of Chemistry and Chemical Engineering, Inner Mongolia University, Hohhot, 010021, China.

<sup>b</sup> Sorbonne Université, CNRS, Institut Parisien de Chimie Moléculaire, UMR 8232, 4 Place Jussieu, 75005 Paris, France.

<sup>c</sup> Key Laboratory of Tropical Medicinal Resource Chemistry of Ministry of Education, College of Chemistry and Chemical Engineering, Hainan Normal University, Haikou, 571158, China.

## ABSTRACT

Oligosaccharides are the ubiquitous molecules of life. In order to translate human bioglycosylation into clinical applications, homogeneous samples of oligosaccharides and glycoconjugates can be obtained by chemical, enzymatic or other biological methods for systematic studies. However, the structural complexity and diversity of glycans and their conjugates present a major challenge for the synthesis of such molecules. This review summarizes the chemical synthesis methods of oligosaccharides, the application of oligosaccharides in the field of medicinal chemistry according to their related biological activities, and shows the great prospect of oligosaccharides in the field of pharmaceutical chemistry.

**Keywords:** Synthesis; Oligosaccharide; Glycosylation; Drug Research, Biological Activity.

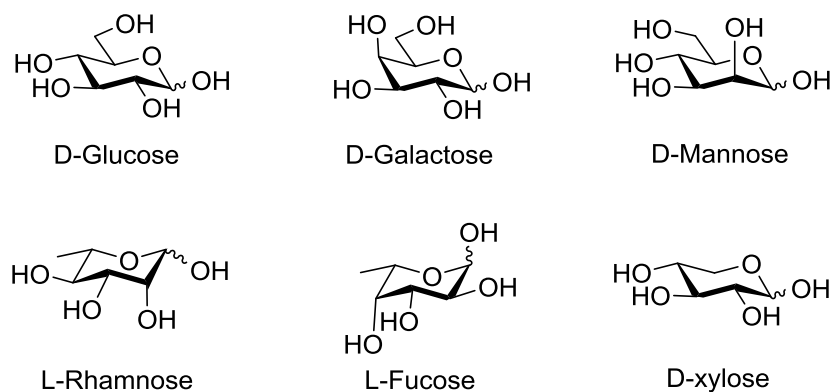
## Contents

1. Introduction .....	2
2. Strategy for chemical synthesis of oligosaccharides .....	4
2.1 Effect of Protective Groups on Glycosylation Reaction Without Catalyst.....	4
2.1.1 The effect of proximal ( C1, C2 ) protective groups on the glycosylation reaction.....	4
2.1.2 Effect of distal auxiliary groups on glycosylation reaction .....	7
2.2 Metal-catalyzed glycosylation reaction .....	8
2.3 Non-metal-catalyzed glycosylation reaction.....	14
2.4 One-pot glycosylation reaction.....	18
2.5 Solid-phase glycosylation reaction .....	21
3. Study on new drugs related to oligosaccharides .....	23
3.1 Anti-infective activity .....	24
3.1.1 Anti-bacterial activity .....	24

3.1.2 Anti-viral activity.....	36
3.1.3 Anti-parasitic activity .....	41
3.2 Anti-inflammatory activity .....	41
3.3 Antitumor activity.....	43
3.4 Hypoglycemic activity.....	49
3.5 Other activities.....	51
Conclusion .....	53
References .....	54

## 1. Introduction

According to the definition of the Joint Committee on Biochemical Nomenclature (IUPAC-IUBMB), natural carbohydrates consisting of 3-10 monosaccharide units in a linear or branched structure connected by  $\alpha$ - and/or  $\beta$ -glycosidic bonds are defined as oligosaccharides, whose constituent monosaccharides can be galactose, glucose, fructose, xylose, etc. (Fig. 1).<sup>[1-2]</sup> Oligosaccharides are found in large quantities in plants, animals and microorganisms (Fig. 2).<sup>[3-4]</sup> These natural sources provide sufficient raw materials for the extraction and isolation of oligosaccharides, offering ample possibilities for the preparation of different derivatives for specific applications.<sup>[5-7]</sup>



**Fig. 1.** Common monosaccharide structures in oligosaccharides.



**Fig. 2.** Source of oligosaccharides.

Oligosaccharides are structurally complex and, as biopolymers prevalent in life, are thought to play an important role in various biological systems and signal recognition processes.<sup>[7-9]</sup> These important roles of oligosaccharides have made it a focus of attention in the life sciences. In the human body, more than 300 genes are involved in the biosynthesis of glycans, which are linked to lipids and proteins, and different mechanisms control the expression of genes with different results, forming glycoconjugates with diversity, and analyzing these different results can be used as a diagnostic and therapeutic tool with great potential for new drug research.<sup>[10-11]</sup>

Oligosaccharides are used in a wide range of industrial markets, such as skin care, food, livestock and pharmaceutical industries, among others.<sup>[12-14]</sup> Oligosaccharides have the activities of anti-cancer, anti-bacterial, anti-inflammatory, anti-viral and enhancing human immune regulation. The synthesis of oligosaccharides is crucial in the field of medicine.<sup>[1]</sup> However, obtaining homogeneous samples during glycosylation is a challenge, and historically, chemical synthesis as an exploratory research

method to obtain homogeneous samples can cope with the preparation of homogeneous oligosaccharides.<sup>[8]</sup>

In recent years, there has been an increasing number of studies on the synthesis of oligosaccharides by chemical methods for novel drugs, and this review aims to collate the relevant contents.

## **2. Strategy for chemical synthesis of oligosaccharides**

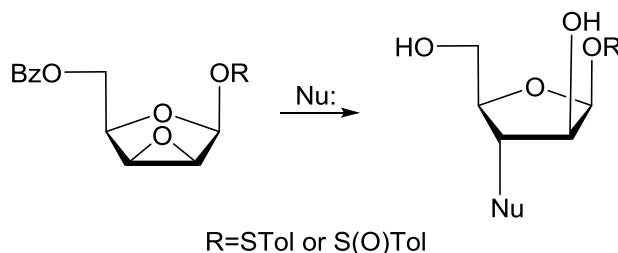
Although oligosaccharides can be obtained by purification and isolation of polysaccharides widely distributed in plants and animals by physicochemical means, it is a great challenge to obtain homogeneous oligosaccharide samples for further studies. In the field of chemical synthesis of oligosaccharides, although the synthetic analysis of products is more advantageous, there are still challenges in some aspects, such as stereoselectivity and regioselectivity during glycosidic bond formation. Most of these problems have been reported to be solved by chemical methods that can provide most structurally complex oligosaccharide products,<sup>[15-16]</sup> such as the synthesis of 92-mer arabinogalactan from mycobacteria.<sup>[17]</sup>

### **2.1 Effect of Protective Groups on Glycosylation Reaction Without Catalyst**

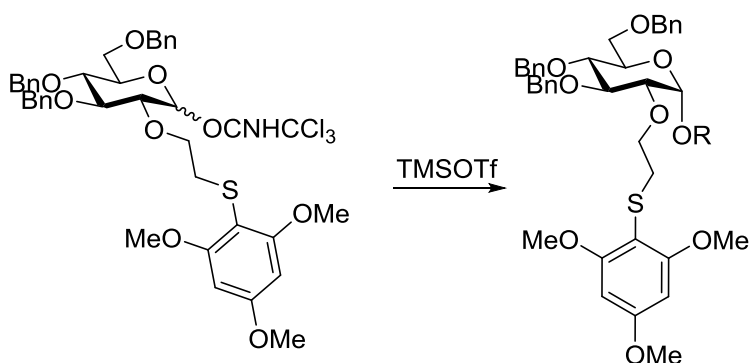
#### **2.1.1 The effect of proximal ( C1, C2 ) protective groups on the glycosylation reaction**

Stereoselective construction of glycosides has been the goal of scientists since the first report of glycosylation reactions of glycosyl donors in 1964. Depending on the mechanism, glycosylation can take place between the C-1 and C-2 substituents in a trans- or cis-selective manner.<sup>[18]</sup> Among numerous parameters (e.g., nucleophilicity of the receptor), the protecting group has the strongest influence on the stereochemistry of glycosylation.<sup>[8]</sup> The formation of 1,2-trans-glycosidic linkages can usually be sterically controlled using the involvement of the five-membered ring neighbor group participation of 2-O-acetyl-protected glycosyl donors.<sup>[19]</sup> H. Shi et al. used the Mitsunobu reaction to achieve 1,2-trans-glycosidic bonds of unprotected flavonoids and pyranose by one-step glycosylation under mild conditions with excellent yields. The high stereoselectivity and regioselectivity of this method easily enabled the conversion of unprotected flavonoids to the corresponding glycoside structures.<sup>[20]</sup> However, the synthesis of 1,2-cis-glycosides is quite difficult.<sup>[21]</sup> R. R. Gadikota et al. reported a way to generate highly stereoselective glycosidic alcohols by protecting C-2 and C-3 of

arabinose by generating epoxides to obtain 1,2-cis- $\beta$ -arabinofuranosides (Scheme 1).<sup>[22]</sup> G. P. Singh et al. reported a way to control the diastereoselectivity of glycosylation by introducing a highly electron-rich non-chiral aromatic thiol-2,4,6-trimethoxyphenylthio in the donor 2-O-ethyl ether, through six-ring neighboring group participation, using the stereocentric conformation of the auxiliary group to obtain high  $\alpha$ -selective 1,2-cis-configuration glycosides (Scheme 2).<sup>[19,23]</sup>

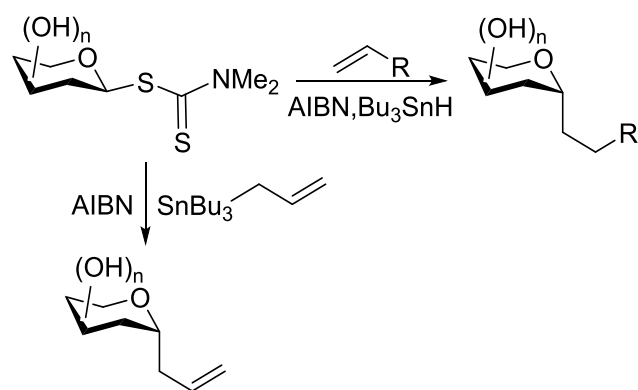


**Scheme 1.** Synthesis of 1,2-cis  $\beta$ -arabinofuranosides.

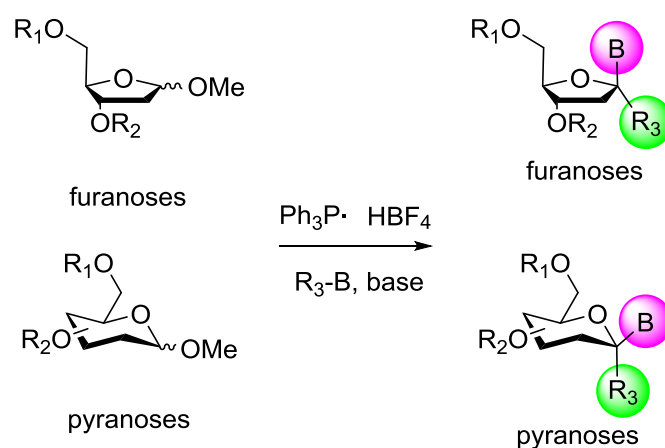


**Scheme 2.** Synthesis of 1,2-cis  $\alpha$ -glycosides.

The use of leaving groups can also affect the stereoselectivity of glycosylation.<sup>[24]</sup> So far, 1-thioglycoside is one of the most popular glycosylation donors.<sup>[25-26]</sup> G. Li et al. achieved the first unprotected/deprotected process of radical C-glycosylation by a one-step preparable glycosyl dithiocarbamate (GDTC). Giese-type reactions of unprotected GDTCs and radical allylation reactions were successfully carried out under mild reaction conditions to stereoselectively obtain the corresponding  $\alpha$ -C-glycosides (Scheme 3).<sup>[27]</sup> W. C. Zhao et al. used triphenylphosphine as the leaving group and 1,2-boronic acid salts to simultaneously introduce gem-C, B bonds at the anomeric stereocenters of furanose and pyranose (Scheme 4).<sup>[28]</sup>

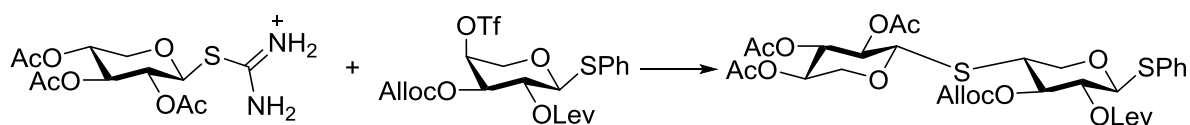


**Scheme 3.** Synthesis of  $\alpha$ -C-glycosides without protecting groups.

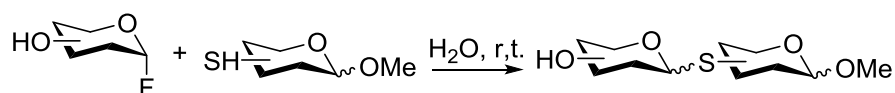


**Scheme 4.** Synthesis of gem-C, B glycosylation.

Thioglycosides are more resistant to enzymatic hydrolysis than their O-linked counterparts, thereby becoming attractive targets for carbohydrate-based therapeutic development. C. Romanò et al. introduced S-bonds in arabinoxylan oligosaccharides (AXs) by anomeric thiol S-alkylation of orthogonally protected L-arabinopyranoside triflate, which facilitates the introduction of branched chain L-arabinofuranoside in oligosaccharide synthesis (Scheme 5).<sup>[29]</sup> G. L. Zhang et al. achieved thioglycosidation in aqueous phase using readily prepared fluorosides as donors (Scheme 6). Notably, no sugar protection was required for this reaction.<sup>[30]</sup>



**Scheme 5.** Synthesis of S-linked disaccharide.

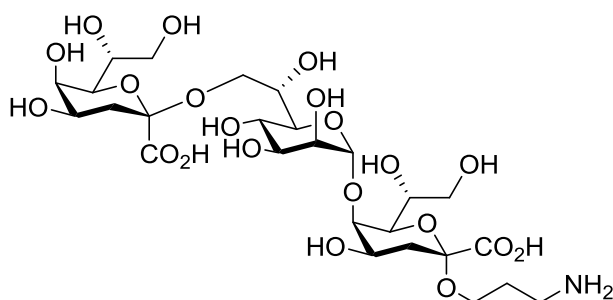


**Scheme 6.** Synthesis of glucosinolate bonds in aqueous phase.

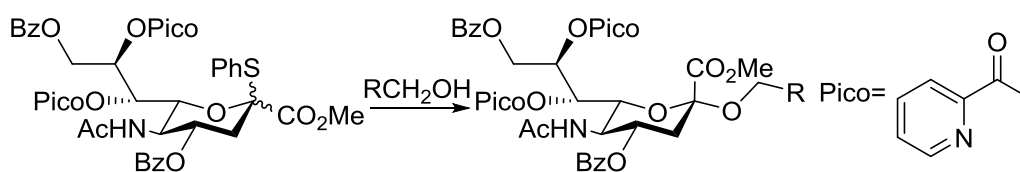
### 2.1.2 Effect of distal auxiliary groups on glycosylation reaction

On the other hand, auxiliary groups at distal positions (e.g., C-3, C-4, C-5, etc.) have an effect on stereoselectivity during glycosylation. The tuning effect of carboxylate ester groups at C5-position on the glycosylation stereoselectivity of Kdo (3-deoxy-D-mano-oct-2-ulosonic acid) thioglycoside donors was reported by W. Huang et al. . The Kdo thioglycosides of 5-O-benzoate or acetate groups were highly  $\alpha$ -selective in their glycosylation reactions with the acceptor; 5-O-Quin Kdo donors reacted with the primary hydroxy acceptor glycosylation to give  $\beta$ -glycosides, and when the acceptor was a secondary hydroxy, mainly  $\alpha$ -glycosides were obtained; in contrast, 5-O-4-nitropicoloyl Kdo donors reacted with the primary or tertiary hydroxy acceptor glycosylation reaction, mainly  $\alpha$ -glycosides are obtained, and when the acceptor is a seco-hydroxy, mainly  $\beta$ -glycosides are obtained. W. Huang et al. successfully prepared trisaccharides containing both  $\alpha$ - and  $\beta$ -glycosidic linkages by the above method (Fig. 3).<sup>[31]</sup> Y. F. Wu et al. reported that the glycosyl donor C6-linked 7,8-di-O-picolinyl group was used to direct the  $\alpha$ -configuration glycosylation of primary hydroxy glycosides and was successfully applied to the synthesis of ganglioside Hp-s1 by chemoselective glycosylation (Scheme 7).<sup>[32]</sup> X. Li et al. used two groups, N-phenyltrifluoroacetimidoyl (PTFAI) and 2-diphenylphosphinoyl-acetyl (DPPA), as leaving groups to achieve  $\alpha$ - and  $\beta$ -glycosylation of multiple glycosyl groups, respectively, with high stereoselectivity through remote guidance (Scheme 8). The imine group of PTFAI can remotely attack the allosteric position of the sugar, forming a relatively stable intermediate of the bridge ring and thus shielding the same side of the sugar ring, allowing the receptor to attack only from the other side to obtain a single  $\alpha$ -glycoside.<sup>[33]</sup> DPPA is an excellent hydrogen-bonded receptor with a phosphine oxygen functional group, which has the advantages of neutrality and less interference. It can tract the receptor to the ipsilateral side through intermolecular hydrogen bonding and then obtain a single  $\beta$ -glycoside from the ipsilateral attack on the heterocapsid of the sugar.<sup>[34]</sup>

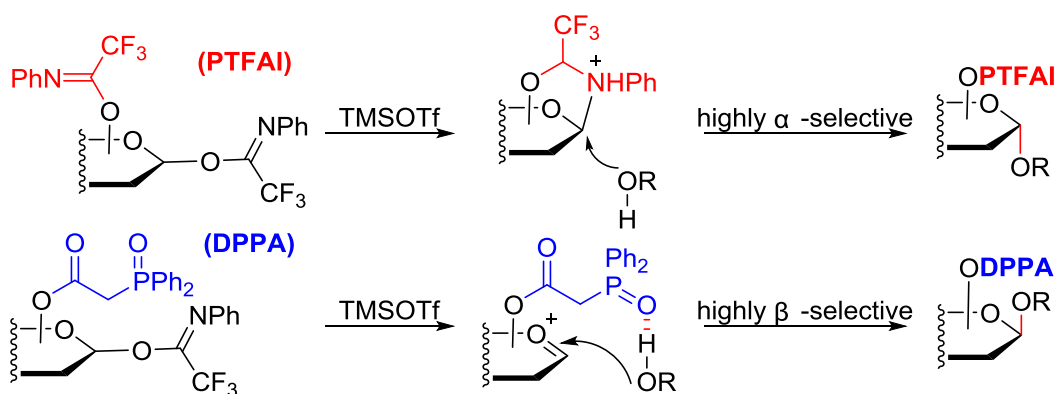




**Fig. 3.** Structure of  $\beta$ -Kdo-(2 $\rightarrow$ 7)- $\alpha$ -Hep-(1 $\rightarrow$ 5)- $\alpha$ -Kdo trisaccharide.



**Scheme 7.** 7,8-di-O-picoloyl sialyl donors control the generation of  $\alpha$ -configuration glycosidic bonds.

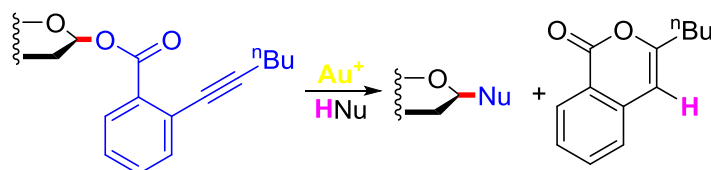


**Scheme 8.** PTFAI-mediated alpha glycosylation and DPPA-mediated beta glycosylation.

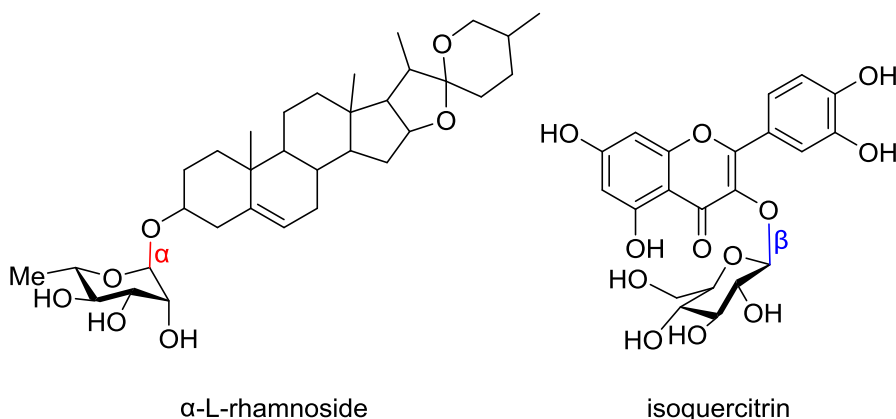
## 2.2 Metal-catalyzed glycosylation reaction

Gold catalysis has become a hot spot in organometallic chemistry. In recent years, metal-catalyzed glycosylation reactions have also been developed. B. Yu developed a new chemical approach to alkynophilic gold(I) catalysts using glycosyl *o*-alkynyl benzoates as donors under gold(I) catalysis with  $\text{Ph}_3\text{PAuNTf}_2$  and  $\text{Ph}_3\text{PAuOTf}$ , which can be widely applied to the synthesis of the majority of glycosidic bonds. The method has been successfully applied to the synthesis of a variety of complex glycans and glycoconjugates, such as nucleobases and flavonoids. Moreover, some sensitive glycosidic ligands, such as dammarane C20-ol, have been realized for the first time (Scheme 9).<sup>[35]</sup> On the basis of this method, B. Yu et al. firstly synthesized a cyclic starfish saponin with unique

structure.<sup>[36]</sup> In addition, J. Fu et al. successfully synthesized nucleoside antibiotics amicetin, plicacetin and cytosaminomycin using this method.<sup>[37]</sup> A glycosylation method for the stereoselective synthesis of glycosylphosphates using Au(I)-catalyzed glycosylation with phosphate as the acceptor was also reported by X. Zhang et al. The broad substrate compatibility and high  $\alpha$ -selectivity of the Au(I)-catalyzed glycosylation method were demonstrated.<sup>[38]</sup> Jiang Xuefeng's group achieved anti-toxic oxidative addition of transition metals through palladium-catalyzed allyl rearrangement, back attack on thiosulfate, and stereoselective thioglycosylation of uronic acid to obtain  $\alpha$ -thioglycosides, and can produce a variety of substituents. Now through the synthesis of stereospecific thioglucals, glycoconjugates diosgenyl  $\alpha$ -L-rhamnoside ( $\alpha$ -oxy-rhamnoside) and isoquercitrin ( $\beta$ -oxy-glucoside) have been successfully obtained, which is expected to be further studied in biological activity (Fig. 4).<sup>[39]</sup> Q. Wang et al. developed a palladium-catalyzed reaction between an enolose donor and an arylboronic acid in an open system using a base as an additive to construct an aryl oxygen glycosidic bond.<sup>[40]</sup>



**Scheme 9.** Gold(I)-catalyzed glycosylation with glycosyl O-alkynylbenzoates as donors.



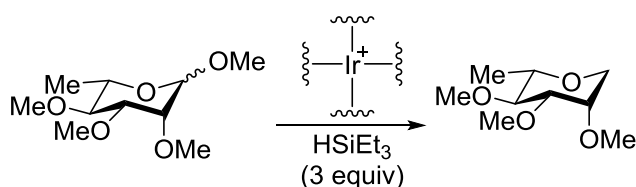
**Fig. 4.** Structure of  $\alpha$ -L-rhamnoside ( $\alpha$ -oxy-rhamnoside) and isoquercitrin ( $\beta$ -oxy-glucoside).

According to M. Kumar et al.,  $\text{Bi}(\text{OTf})_3$  can directly catalyze the synthesis of 2-deoxyglucoside from 'armed' and 'disarmed' glycols with high stereoselectivity. This method can be applied to the

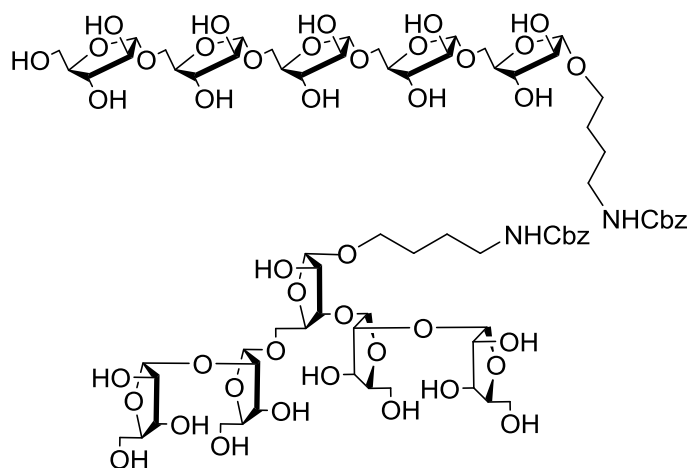
oligosaccharide synthesis of natural products and drugs and other 2-deoxyglycosylation reactions (Scheme 10).<sup>[41]</sup> C. A. H. Jones et al. developed an iridium-catalyzed hydrosilylation method for the selective demethylation of O-arylglycosides, a cationic bis(phospho)iridium complex catalyzed a variety of 2,3,4-tri-O-methylpyranose, providing a unique approach to 3-hydroxy or 3-acetyl 2,4-di-O-methylpyranose (Scheme 11).<sup>[42]</sup> Synthesis of linear and branched penta-arabinofuranosides using a silver-assisted gold-catalyzed glycosylation method was reported by Y. Sutar et al (Fig. 5).<sup>[43]</sup>



**Scheme 10.** Bi(OTf)<sub>3</sub>-catalyzed access to α-glycosidic bonds.



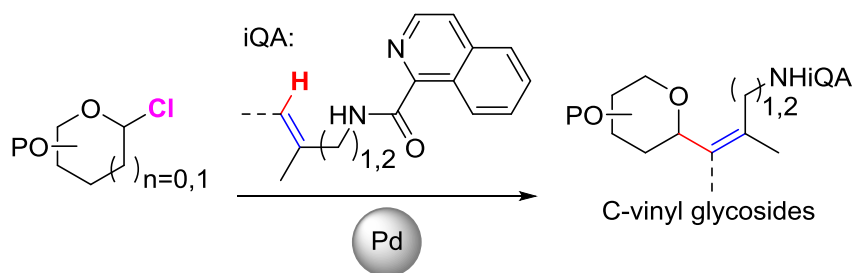
**Scheme 11.** Selective demethylation of O-aryl glycosides by iridium-catalyzed hydrosilylation.



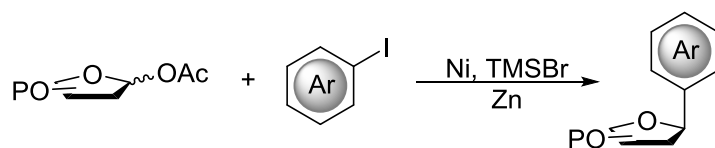
**Fig. 5.** Structure of linear and branched pentaarabinofuranosides in α-configuration.

Q. Sun et al. reported a new method for the synthesis of alkenyl carbon glycosides based on palladium-catalyzed guide-group regulation. Using readily available isoquinoline carboxylic acid (iQA) as auxiliary group and palladium compound as catalyst, almost a single α-glycoside product was obtained (Scheme 12), which provided a new method for the synthesis of alkenyl and alkyl

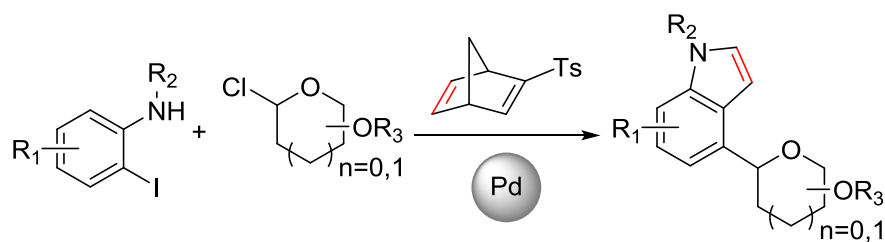
carbon glycosides.<sup>[44]</sup> Y. Li et al. used furanosyl acetate and (hetero) aryl iodide 2-bromo-4-iodoanisole as model substrates, nickel(II) acetylacetonate as catalyst, TMSBr as Lewis acid, Zn was used as a reducing agent to react in THF to obtain C-aryl nucleoside analogs through cross-coupling reaction (Scheme 13). This nickel-catalyzed method has mild reaction conditions, a wide substrate range, good  $\beta$ -selectivity, and high functional group compatibility. The unique chemoselectivity for aryl iodides enables efficient preparation of various C-aryl halide furanosides.<sup>[45]</sup> Y. An et al. reported a palladium-catalyzed C-H glycosylation and retro Diels–Alder tandem reaction via structurally modified norbornadienes (smNBDs). smNBDs are used to modulate the reactivity of aryl norbornadiene palladium rings (ANPs) with high chemoselectivity and regioselectivity to construct a series of highly functionalized C4-glycosyl indole reactions with C2 and C3 unsubstituted (Scheme 14). This method has a wide range of applications and can be used for the smooth reaction of halogenated six- and five-membered glycosides, as well as the reaction of N-alkyl (primary, secondary and tertiary) C4-glycosidic indoles.<sup>[46]</sup> The first ruthenium-based catalyzed highly stereo- and site-selective ortho- and meta-C-H glycosylation was reported by X. Y. Gou et al. using the substrate 2-phenylpyridine and the glycosyl chloride donor as a model,  $[\text{RuCl}_2(\text{p-cymene})]_2$  was used as a catalyst to obtain the ortho-/meta-glycosylation products by a key oxidative addition/reductive elimination or  $\sigma$ -activation strategy. This method can be used for the synthesis of a variety of C-aryl pyranosides and furanosides.<sup>[47]</sup> J. Wu. et al. used this method to also obtain the corresponding C-aryl glycosides via glycosyl bromide donors (Scheme 15).<sup>[48]</sup>



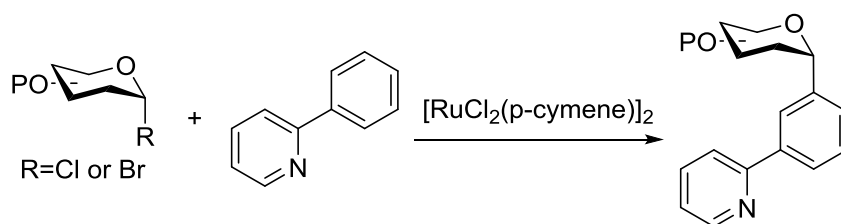
**Scheme 12.** Synthesis of C-vinyl glycosides.



**Scheme 13.** Synthesis of C-aryl nucleoside analogs.

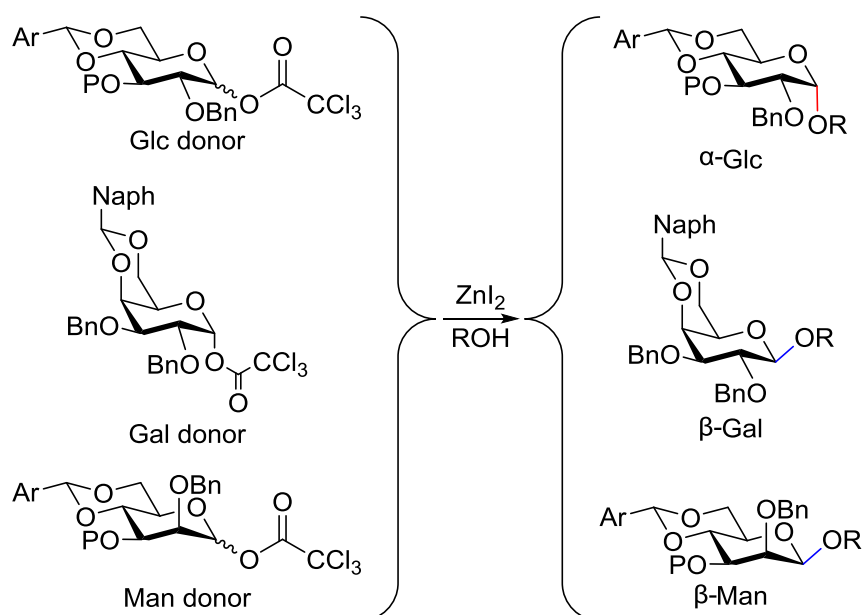


**Scheme 14.** Synthesis of C4-glycosidic indoles via palladium/structurally modified norbornadiene (smNBDs).

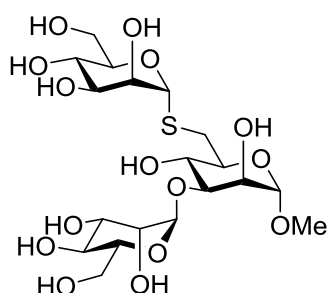


**Scheme 15.** Synthesis of C-aryl glycoside.

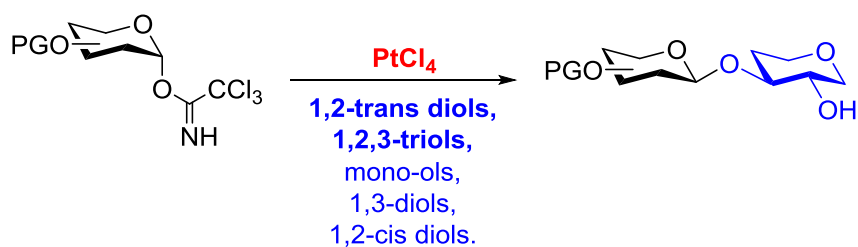
F. Ding group reports a ZnI<sub>2</sub>-catalyzed  $\alpha$ -glycosylation strategy in which ZnI<sub>2</sub> acts as a Lewis acid activator of the glycosyl donor leaving group and a targeted control agent of nucleophilic reagent attack for the highly stereospecific construction of  $\alpha$ -glucosides.<sup>[49]</sup> When mannose is used as a glycosyl donor,  $\beta$ -mannoside is obtained by the same reaction mechanism catalyzed by ZnI<sub>2</sub> because mannose is in the opposite direction of 2-C-O of glucose.<sup>[50]</sup> When galactose was used as the glycosyl donor, the 4-C-O orientation of galactose was opposite to that of glucose, resulting in a different conformation of the 4,6-O-naphthylidene protecting group of galactose and glucose. Therefore, under the catalysis of ZnI<sub>2</sub>, by the same reaction mechanism, the 6-C-O in the 4,6-O-naphthylidene protecting group will be coordinated with zinc ion to obtain  $\beta$ -galactoside due to the end-group isomerization effect of galactose (Scheme 16).<sup>[51]</sup> A method for the iterative synthesis of thioglycosides without protecting groups in aqueous phase was developed by P. Wen et al. It introduces sulfhydryl groups at different positions of sugar molecules, and utilizes Ca(II) in water at room temperature to promote the unprotected thioglycosylation reaction to obtain 1,2-trans thioglycosides with high chemical and stereoselectivity. And further applied to the synthesis of 3,6-branched mannose cores of N-linked glycans (Fig. 6).<sup>[52]</sup> T. Li et al. developed a new method for glycosidation via an "acid-base catalyzed" pathway using platinum (IV) chloride as a catalyst and O-glycosyl trichloroacetimide ester as a glycosyl donor (Scheme 21). This method can be applied to the highly stereoselective glycosylation of various glycosyl donors and glycosyl acceptors.<sup>[53]</sup>



**Scheme 16.** Synthesis of  $\alpha$ -Glc,  $\beta$ -Gal,  $\beta$ -Man glycosides.



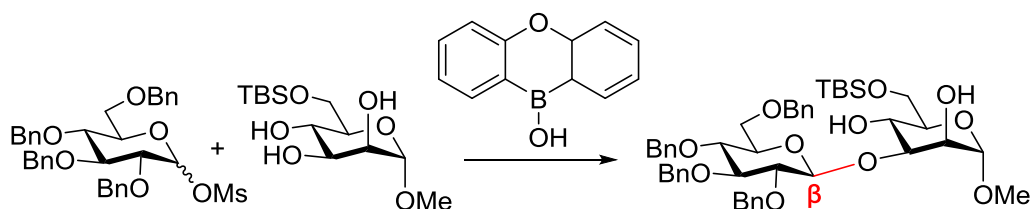
**Fig. 6.** Structure of S-trimannose.



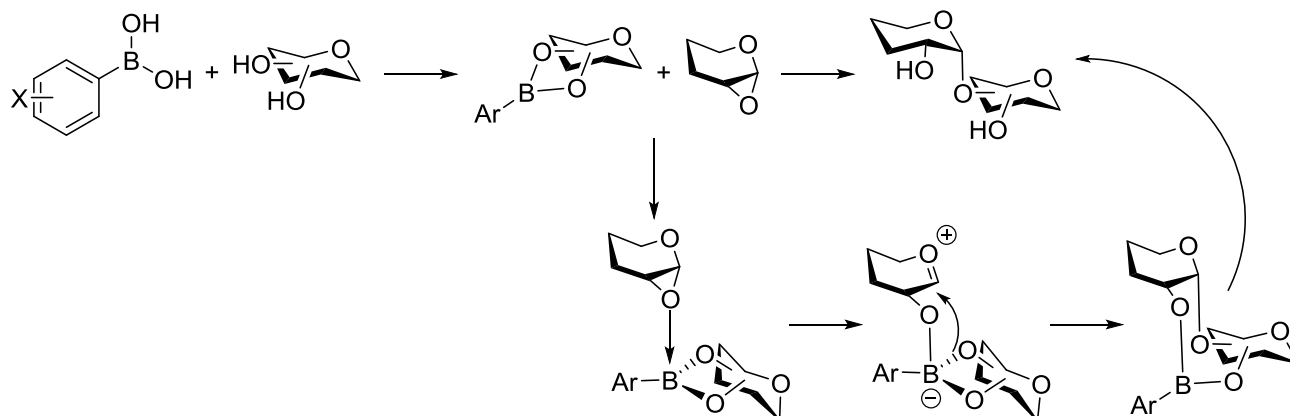
**Scheme 17.** Stereoselective glycosylation of O-glycosyltrichloroethylimine donors catalyzed by  $\text{PtCl}_4$ .

### 2.3 Non-metal-catalyzed glycosylation reaction

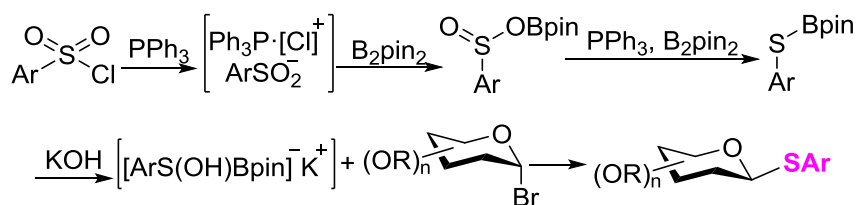
In addition to metal-catalyzed methods, there are also non-metal-catalyzed methods. K. A. D'Angelo et al. used diarylboronic acids as catalysts, glycosyl mesylate donors and partially protected pyranoside and furanoside acceptors for regioselective and stereoselective coupling, via an associative mechanism,  $\beta$ -glycosidic structures can be selectively obtained (Scheme 18).<sup>[54]</sup> D. Takahashi et al. reported a highly 1,2-cis-selective product glycosylation using organoboron reagents and 1,2-anhydroglycosyl donors to obtain highly 1,2-cis-selective product glycosylation by an intramolecular acid-base catalyzed  $S_N2$ -type reaction via hydrogen bond-mediated formation of a cyclic transition state, this method is also called hydrogen bond-mediated aglycon delivery (HAD), which is representative in the synthesis of biologically active natural products and complex oligosaccharides (Scheme 19).<sup>[55]</sup> S. Li et al. achieved boron-promoted thiosidylation by boron-promoted reductive deoxygenation coupling reaction using readily available bromosaccharides and sulfonyl chloride as raw materials (Scheme 20). This method has the advantages of mild conditions, wide range of substrates, good functional group compatibility and excellent stereoselectivity, while the corresponding thioglycoside products were obtained in excellent yields.<sup>[56]</sup>



**Scheme 18.** Boronic acid-catalyzed access to  $\beta$ -glycosidic bonds.

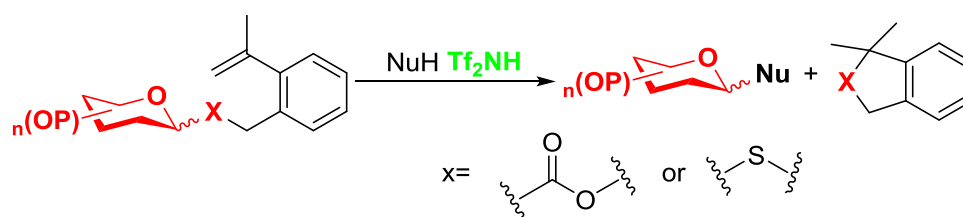


**Scheme 19.** Boronate-catalyzed formation of 1,2-cis-glycosidic bonds.



**Scheme 20.** Proposed mechanism.

Z. Qiao et al. established a novel acid ( $\text{Tf}_2\text{NH}$ )-catalyzed glycosylation of glycosyl 2-isopropenyl phenylacetate and 2-isopropenyl benzyl glucoside for complex oligosaccharides and glycoconjugates. The synthesis provides new synthetic means (Scheme 21).<sup>[57]</sup>

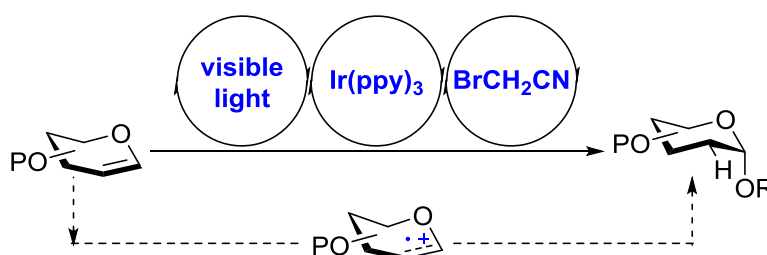


**Scheme 21.** Acid-catalyzed glycosylation of glycosyl 2-isopropenyl phenyl acetate and 2-isopropenyl benzyl glycosides.

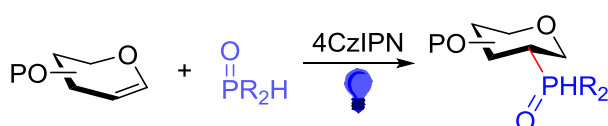
K. M. Liu et al. reported a fast photocatalytic glycosylation method that proceeds through a bromide-based hydrogen species and electron transfer process using  $\text{Ir}(\text{ppy})_3$  as a catalyst (Scheme 22). This method can be used for stereoselective iterative synthesis of 2-deoxyoligosaccharides.<sup>[58]</sup> Q. Li et al. exploited the catalytic effect of electron-rich bis(thiourea) on unprotected or minimally



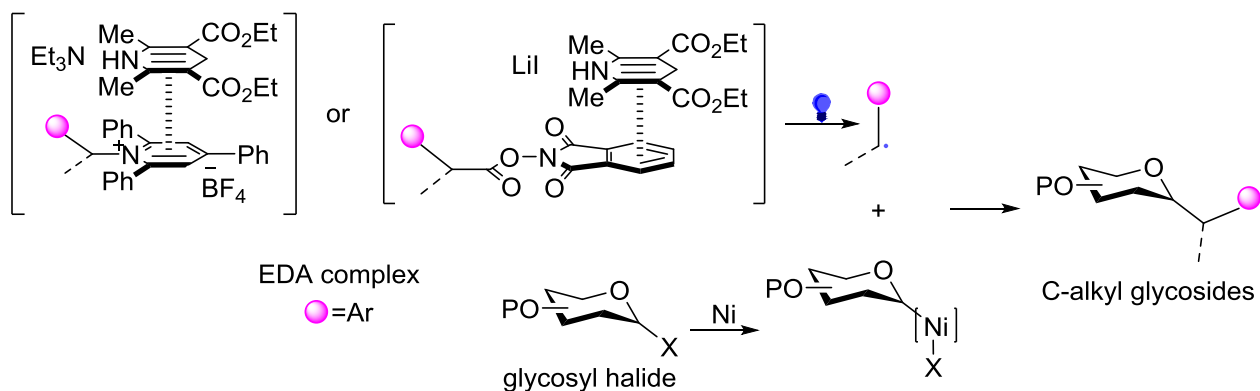
protected monosaccharides (disaccharides) to achieve high stereoselectivity and precise site-control of galactose and mannose glycosylation reactions by effectively exploiting non-covalent interactions.<sup>[59]</sup> H. Li et al. developed a light-mediated metal-free glycosylation method for the synthesis of C2-phosphonylated carbohydrates from glyoxal and diarylphosphine oxide using the photosensitizer 4CzIPN as the catalyst in order to avoid the use of excessive metal co-catalysts (Scheme 23).<sup>[60]</sup> Y. Wei et al. obtained NHPI esters (or pyridine salts) by photoinduced decarboxylation (or deamination) cross-coupling, and photoactive electron donor-acceptor (EDA) complexes by complexation with Hantzsch ester and LiI (or Et<sub>3</sub>N), which were used in the next C-alkyl glycosylation reaction by obtaining alkyl radicals under blue LED irradiation (Scheme 24).<sup>[61]</sup> Q. Wang et al. obtained photoactive electron donor-acceptor (EDA) complexes by combining cesium acetate (CsOAc) with Hantzsch ester; its association with 2-pyridyl glycosyl sulfone under blue LED irradiation gave glycosyl radicals (Scheme 25). The sugar radicals further react with coupling reagents of different substituents to give the corresponding C-alkenyl, C-heteroaryl, and S-aryl and S-alkyl glycosides etc. .<sup>[62]</sup> D. Xie et al. used EDA complexes formed by glycosyl sulfoxide, pyridine salts and hydrated fluoride ions to obtain glycosyl radicals under blue LED irradiation for the next step of C-glycoside reaction. This approach enabled the glycosylation modification of the vasodilator drug fasudil (Fig. 7).<sup>[63]</sup>



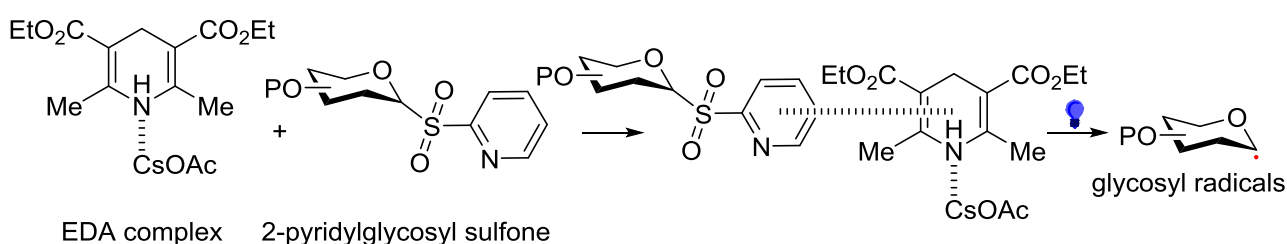
**Scheme 22.** Photoinitiated intermolecular hydroetherification of glycols with acceptors.



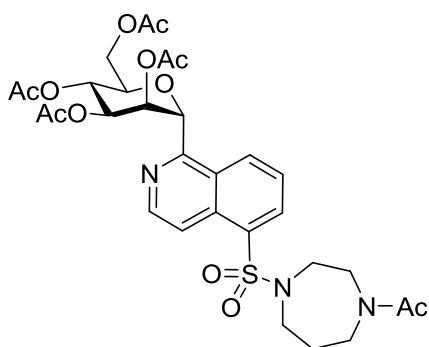
**Scheme 23.** Synthesis of 1,2-dideoxy-2-phosphonylated carbohydrates.



**Scheme 24.** Synthesis of C-alkyl glycosides with blue LED.

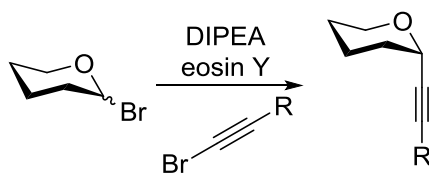


**Scheme 25.** Synthesis of glycosyl radicals with blue LED.

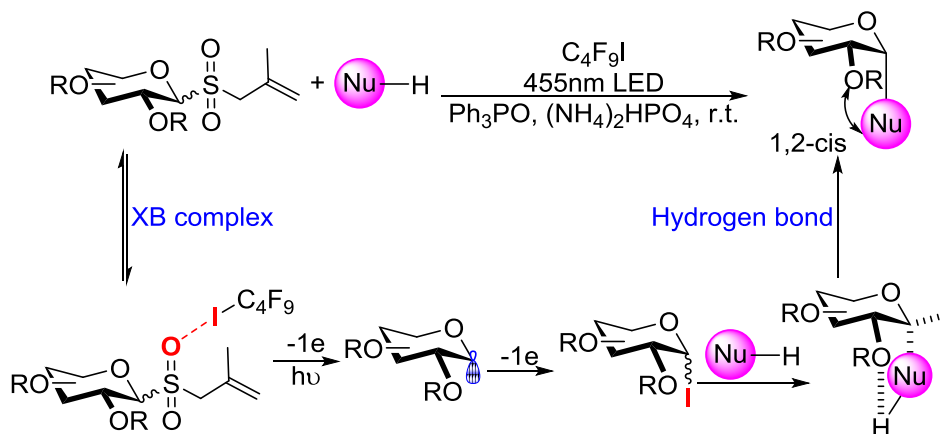


**Fig. 7.** Structure of glycosylation-modified fasudil.

L. Xia et al. obtained C-alkynyl glycosides by photooxidative (eosin Y) reductive catalysis (organic base N, N-diisopropylethylamine) coupling of alkynyl bromides and brominated glycosides, which is a versatile, convenient and highly  $\alpha$ -stereoselective method (Scheme 26).<sup>[64]</sup> C. Zhang et al. used allyl glycosyl sulfone (as a donor) to convert stable allyl glycosyl sulfone to electron-philic glycosyl iodide by glycosyl radicals using XB-assisted and light-promoted single electron transfer cascade activation (Scheme 27). Sterically convergent 1,2-cis-glycosides were obtained under mild conditions using in situ capture of nucleophilic reagents.<sup>[65]</sup>



**Scheme 26.** Synthesis of  $\alpha$ -C-alkynyl glycosides with alkyne bromide.

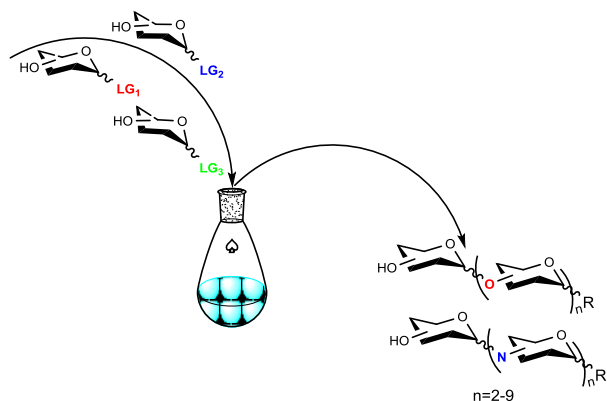


**Scheme 27.** XB-assisted radical activation of donors.

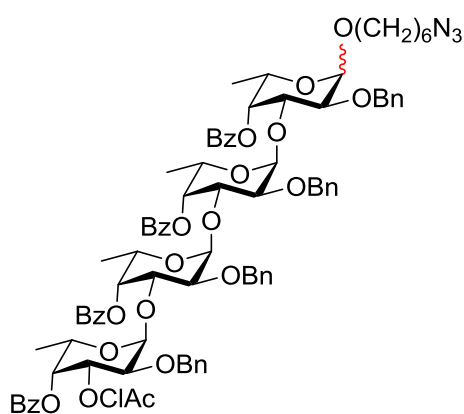
## 2.4 One-pot glycosylation reaction

Of course for the synthesis of oligosaccharides, one-pot glycosylation is an important approach, increasing the overall efficiency of the synthesis by minimizing steps and eliminating post-processing and purification procedures (Fig. 8).<sup>[66]</sup> Sequential chemoselective activation under orthogonal conditions takes advantage of the reactivity differences at different sites of the donor and acceptor.<sup>[67]</sup> R. Liu et al. successfully constructed a one-pot synthesis of trisaccharides under mild conditions using NIS/TMSOTf as a promoter and a tetranucleoside related to n-hexynyl benzoic acid glycoside as a donor. And it is applied to the synthesis of tetrafucosides related to type I fucoidan fragments using phthalic acid sugar group as the donor (Fig. 9).<sup>[68]</sup> Z. Zhang et al., developed a computer program using data from the determination of -STol glycoside donor reactivity and its correlation with the chemical shift of the acceptor anomeric proton, using a database of thioglycosides as glycosyl donors Opti Mer, one-pot assembly building blocks for oligosaccharides.<sup>[69]</sup> A more advanced Auto-CHO software was developed by C. W. Cheng et al. to accommodate more data processing and to support hierarchical one-pot synthesis using fragments as

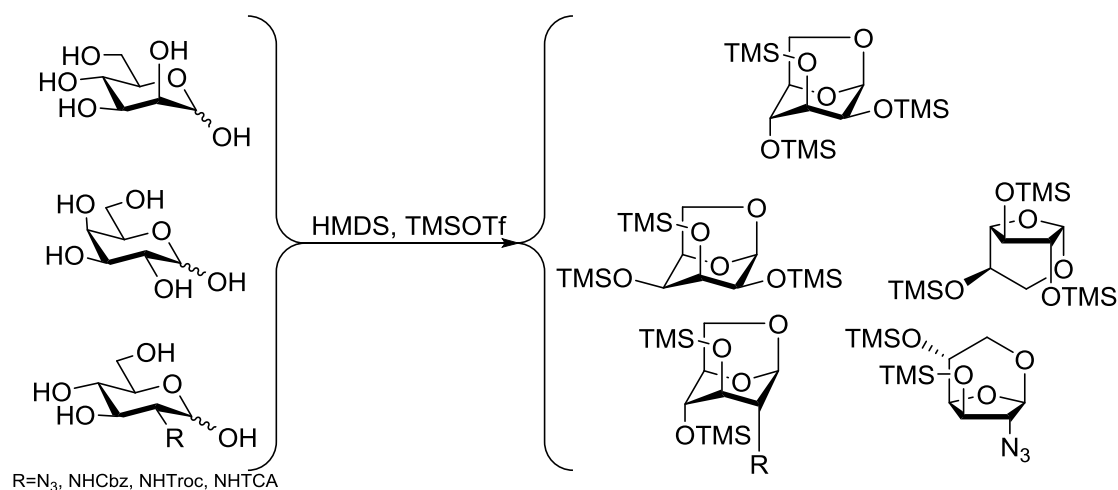
building blocks generated by one-pot synthesis. It provides a potential synthetic solution for complex glycans, such as the glycosylceramide Globo-H hexasaccharide that can be used in prostate cancer antigen vaccines.<sup>[70]</sup> Y. C. Ko et al. used a microwave-assisted one-pot method to generate per-O-trimethylsilylated monosaccharide intermediates in situ with trimethylsilyl trifluoromethanesulfonate or trimethylsilyl trifluoromethanesulfonate, respectively, under microwave irradiation. Treatment with methyl(4-methylphenylthio)silane and ZnI<sub>2</sub> provides 1,6-anhydrosugars or thioglucosides, which are further processed by regioselective protecting groups for many thioglucoside and disilylated derivatives. This approach opens up the possibility to generate appropriate protective building blocks arrays for oligosaccharide assembly in a short time with minimal purification stages (Scheme 28).<sup>[71]</sup>



**Fig. 8.** Schematic diagram of the one-pot method.

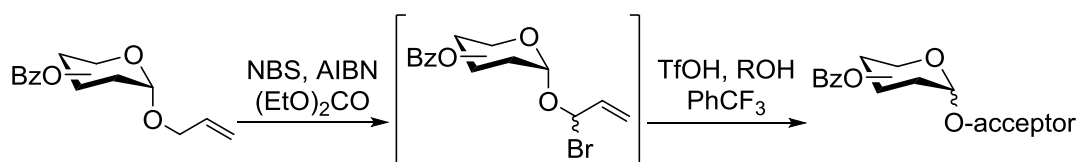


**Fig. 9.** Structure of tetrasaccharide backbone of type I fucoidan.

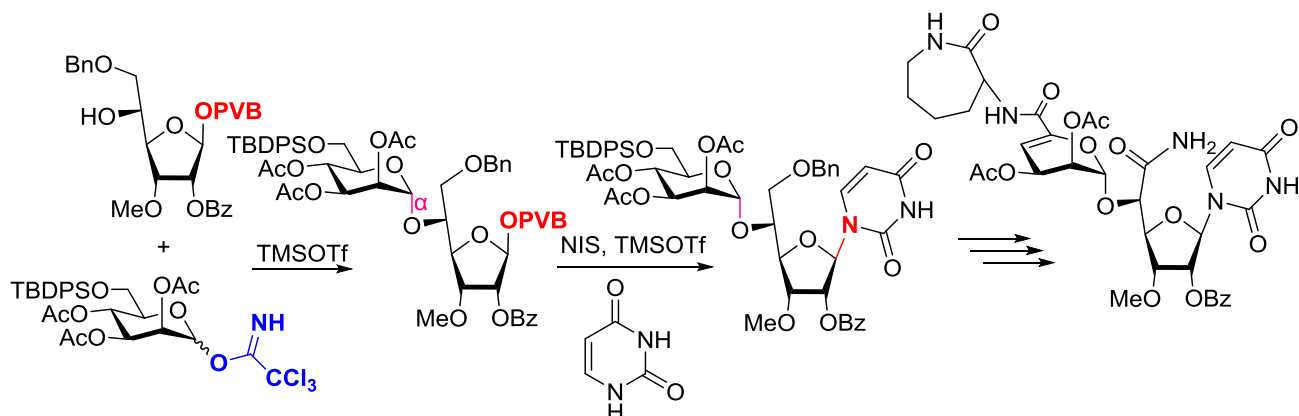


**Scheme 28.** Microwave-assisted one-pot synthesis of different 1,6-anhydrosugars.

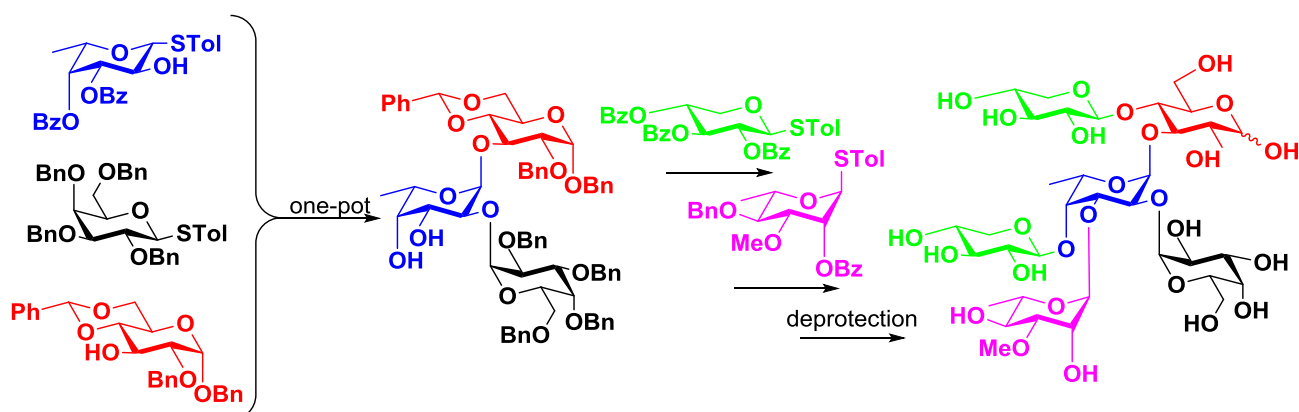
A. Das et al. reported an allyl halide-mediated glycosylation of allyl glycosides without carbon tetrachloride as a solvent, using silver trifluoromethanesulfonate as the promoter, in (EtO)<sub>2</sub>CO and PhCF<sub>3</sub> solution. A one-pot allylic halogenation and subsequent glycosylation method was developed. Xylose-pyranoside disaccharides and trisaccharides have been synthesized using this method (Scheme 29).<sup>[72]</sup> C. M. Carthy et al. took advantage of the higher nucleophilicity of anomeric sulfur in ethyl glucosinolate, using N-trifluoromethyl thiosaccharin and thioperoxide as promoters, by a one-pot oligosaccharide glycosylation method, to provide protocols for stereoselective synthesis of glycosylation.<sup>[73]</sup> H. He et al. reported a one-pot glycosylation strategy for glycan and nucleoside synthesis based on ortho-(1-phenylvinyl)benzyl (PVB) glycosides, it can be used to synthesize the anti-tuberculosis drug Capuramycin (Scheme 30).<sup>[74]</sup> Professor X. S. Ye's research group improved the regioselectivity and stereoselectivity of oligosaccharide assembly by changing the order of addition of sugar residues, and successfully synthesis of hexasaccharide attached to ATCV-1 (Acanthocystis turfacea Chlorella virus) by one-pot glycosylation reaction (Scheme 31).<sup>[75]</sup>



**Scheme 29.** Allyl halogenation and TfOH-promoted glycosylation take place in one-pot.



**Scheme 30.** Synthesis of capuramycin via the orthogonal one-pot glycosylation strategy based on PVB-glycosyl.



**Scheme 31.** Synthesis of hexasaccharide attached to ATCV-1 by one-pot glycosylation strategy.

## 2.5 Solid-phase glycosylation reaction

Solid-phase synthesis is another effective method to accelerate the preparation of oligosaccharides, not only the reaction process is automated, but the reaction does not require purification of the reaction intermediates. Automated glycan assembly (AGA) is mainly used for the synthesis of trans-glycosidic bonds, where C2 is involved in a protecting group to ensure stereoselective coupling.<sup>[76-77]</sup> Since the generation of the cis-configuration cannot rely on C-2 participation, H. S. Hahm et al. successfully obtained multiple cis-containing glycosides using monosaccharides containing distantly participating protecting groups (acetyl or benzoate) as AGA building blocks linked oligosaccharides.<sup>[78]</sup> The fully automated Glyconeer 2.1™ has been deployed in the laboratory (Fig. 10).<sup>[79]</sup> D. Budhadev et al. performed iterative solid-phase glycosylation on photolabile resins, followed by photochemical cleavage and glycan purification using simple flash column chromatography. Synthesis of complex heparan sulfate oligosaccharide precursors by automated

glycan assembly using disaccharide donor building blocks.<sup>[80]</sup> Other examples of automated methods such as: one-pot solution-phase oligosaccharide synthesis by Quest-210 (Takahashi), fluorine label-assisted synthesis (Pohl) based on automated liquid handlers and fluorine solid phase extraction (FSPE) techniques. HPLC-assisted oligosaccharide synthesis (Demchenko, Stine) and automated electrochemical synthesis (Nokami), among others, are also worth noting.<sup>[81]</sup> K. L. M. Hoang et al. reported a traceless photo-unstable linkage method for the preparation of carbohydrates with free reducing ends and the preparation of oligosaccharide fragments and linear as well as branched  $\beta$ -oligosaccharide assembled asymmetric biphasic N-glycans by AGA.<sup>[82]</sup> J. Jung et al. successfully synthesized bromoalkyl glycosides on a microreactor scale by Fischer glycosylation with improved yields via acidic catalysts.<sup>[83]</sup> Based on the principle of preactivated one-pot, multicomponent glycosylation reaction and continuous multiplying amplification synthesis, X. S. Ye's research group independently developed a new type of dual-mode solution-phase glycan automatic synthesizer (Fig. 11), the synthesis of oligosaccharides and polysaccharides with various complex structures has been realized, among which the molecular size of the synthetic polysaccharides has reached an astonishing 1080 sugar (1080-mer),<sup>[84]</sup> far surpassing the synthesis level of nucleic acids (up to 200-mer)<sup>[85]</sup> and proteins (up to 472-mer).<sup>[86]</sup> The synthesizer provides a platform for non-professionals to assemble target glycans, fills the gaps in the development of liquid phase sugar synthesizers at home and abroad, and is of landmark significance to sugar science and its application in the fields of medicine and materials.

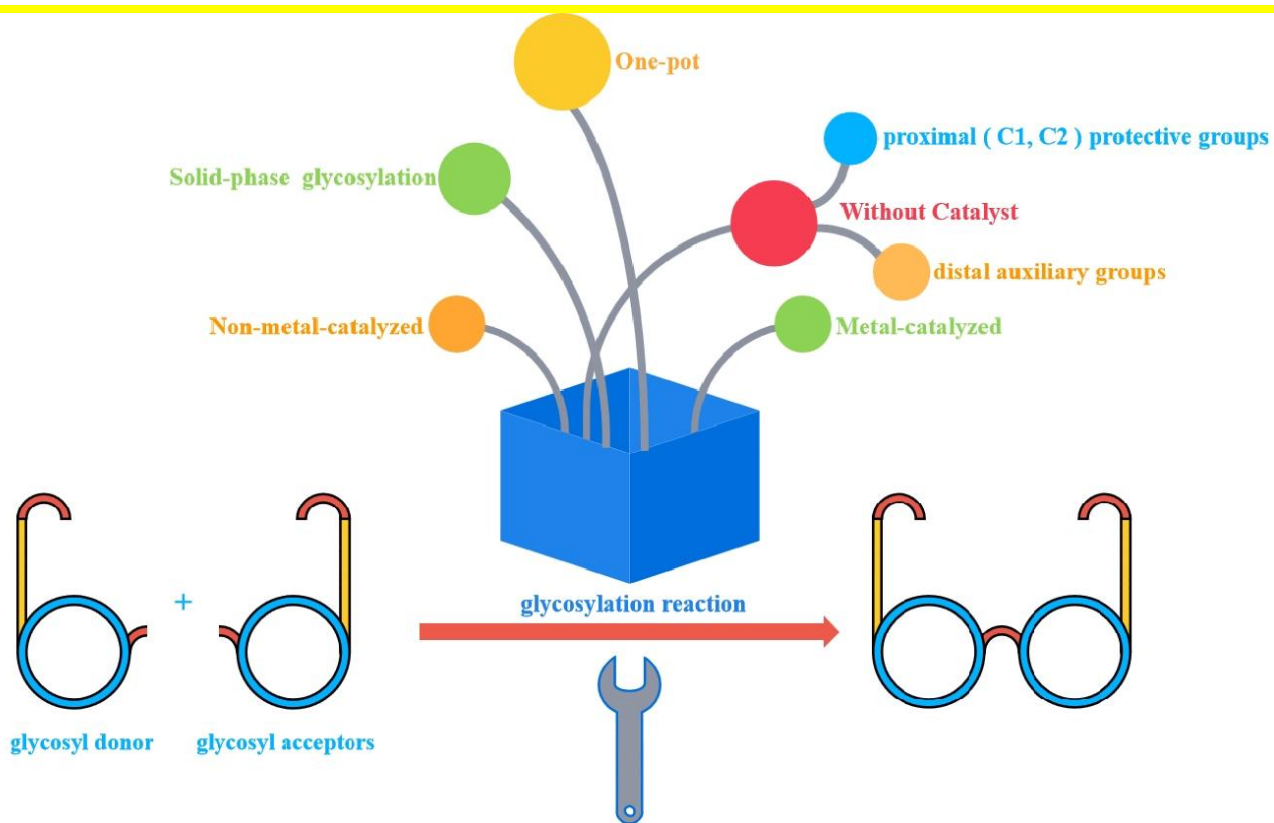


**Fig. 10.** Automation: Glyconeer 2.1™.



**Fig. 11.** Automation synthesizer.

The chemical synthesis method of glycosylation occupies an important position in the field of chemical synthesis of carbohydrate, and is crucial for the study of homogeneous glycosylation products (Fig. 12).



**Fig. 12.** Summary of chemical synthesis of oligosaccharides.

### 3. Study on new drugs related to oligosaccharides



The concept of carbohydrate drugs can be divided into broad and narrow sense. In the narrow sense, carbohydrate drugs refer to drugs containing sugar structures. In the broad sense, carbohydrate drugs can be extended to carbohydrate-based drugs, because carbohydrates can not only be used as drugs alone, it can also bind to and interact with many compounds such as proteins, fats, etc., and affect some physiological and pathological processes.<sup>[87]</sup>

Oligosaccharide drugs usually use six-membered ring pyranose, five-membered ring furanose, aza sugar and high-carbon sugar sialic acid as the structure as the backbone. It has applications in infectious diseases, tumor diseases, cardiovascular and cerebrovascular diseases, endocrine and metabolic diseases, respiratory system diseases, skin diseases, nervous system diseases and other fields.<sup>[88]</sup>

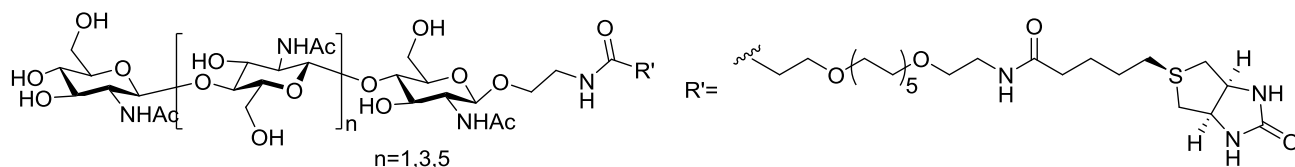
### **3.1 Anti-infective activity**

Anti-infective drugs, as drugs for the treatment of pathogenic infections, include two categories of antimicrobial drugs and anti-parasitic drugs. Antimicrobial drugs include antibiotics, synthetic antibacterials, anti-tuberculosis drugs, anti-leprosy drugs, and antiviral drugs. It has long been recognized that soluble carbohydrates can prevent microorganisms from binding and multiplying on the cell surface.<sup>[89]</sup> For example, human milk oligosaccharides are thought to prevent infection in nursing infants. The highly glycosylated mucins constitute another line of defense against pathogenic infection.<sup>[90]</sup> This understanding has led to the rapid development of carbohydrate drugs in the field of anti-infection.<sup>[89]</sup>

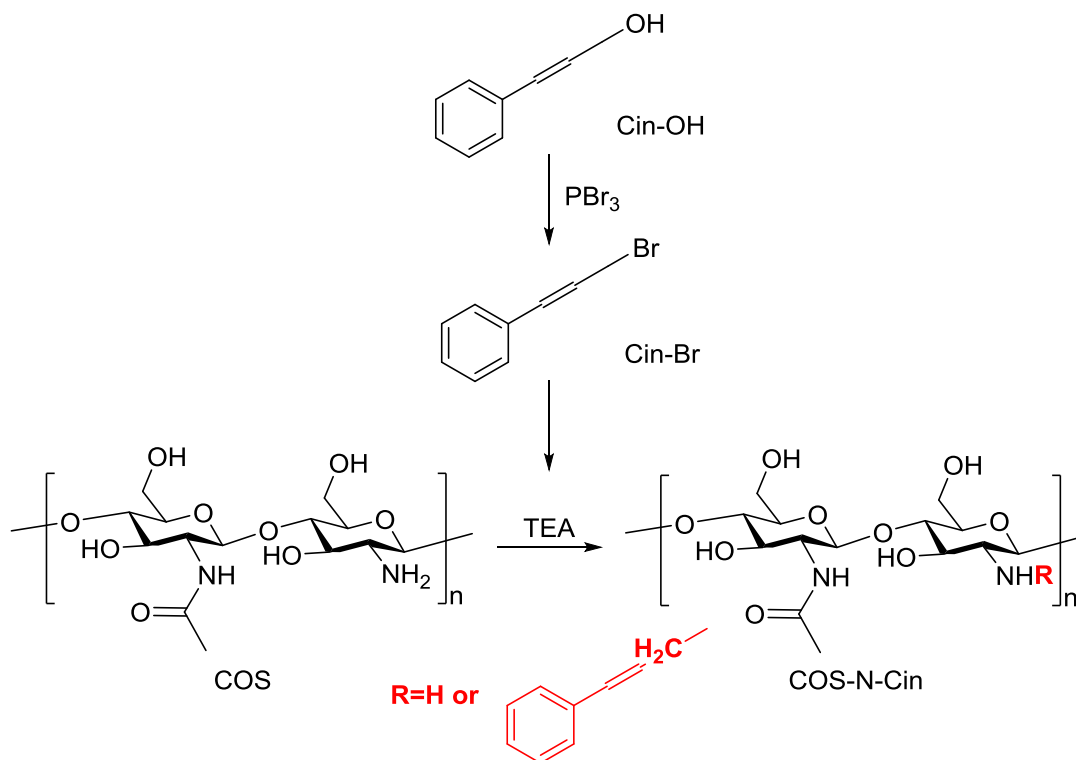
#### **3.1.1 Anti-bacterial activity**

Chitosan hydrolysates are water soluble with antibacterial activity.<sup>[91]</sup> Y. E. Tsvetkov et al. synthesized a series of  $\beta$ -(1 $\rightarrow$ 4)-linked N-acetyl-D-glucosamine oligomers as major components of the fungal cell outer wall (Fig. 13). And observed in vitro evaluation in RAW 264.7 cells. It has effective immune response and immune regulation, and no cell proliferation and cytotoxicity were observed after 48h, showing strong immune regulation activity. It is expected to serve as a potential antigen for in vitro diagnosis of candidiasis and monitoring of antifungal therapy.<sup>[92]</sup> Using triethylamine (TEA) to catalyze the substitution reaction of Cinnamyl Bromide (Cin-Br) with chitooligosaccharides, L. Yue et al. synthesized COS-N-Cin1-3 in one step ( the molar ratio of COS

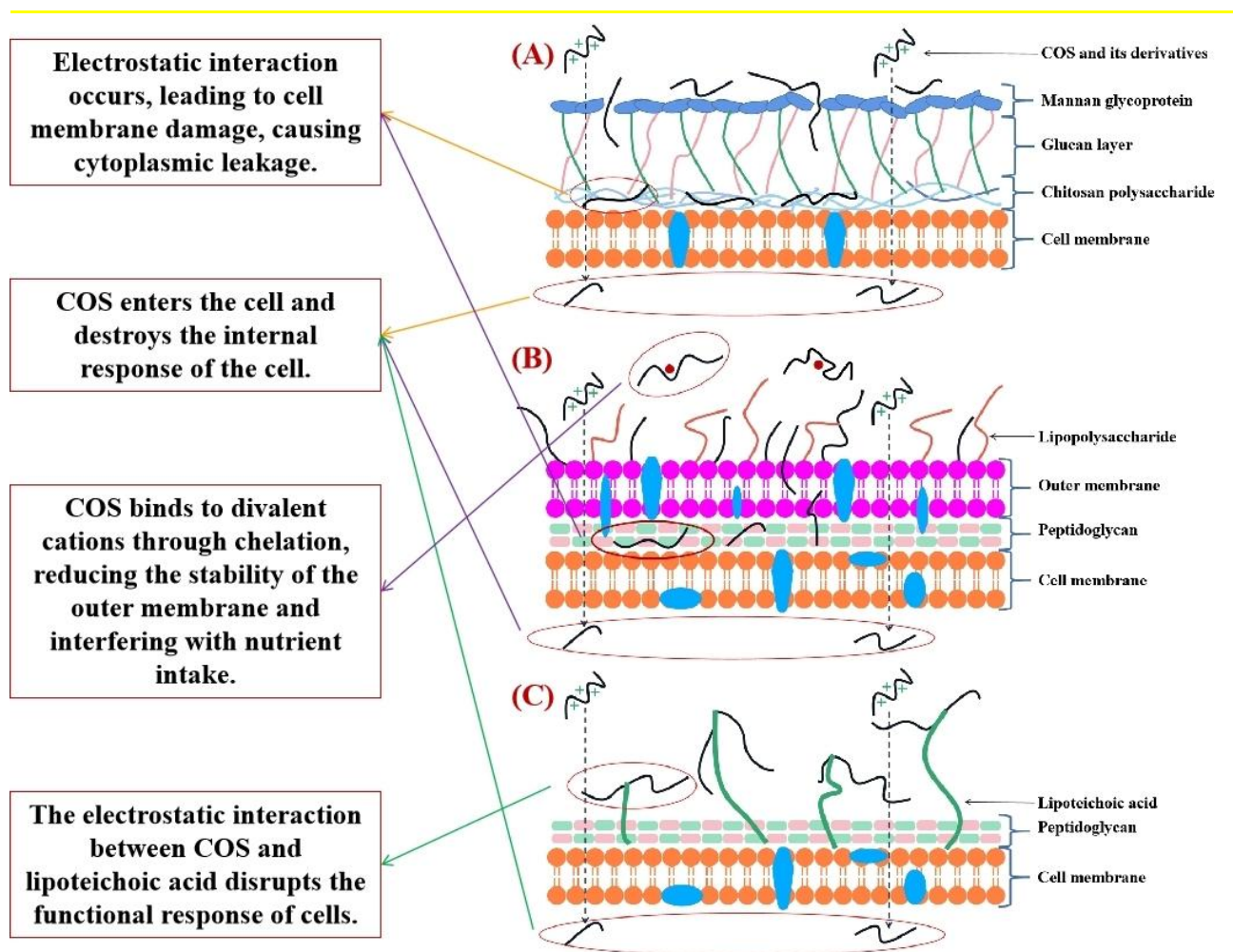
to Cin-Br was 1:1/1:2/1:3, respectively ). The antibacterial activity test showed that it had excellent antibacterial activity against *Escherichia coli* and *Staphylococcus aureus*, and the antibacterial activity was proportional to the degree of substitution of cinnamic acid (Scheme 32).<sup>[93]</sup>



**Fig. 13.** Structures of biotinylated chitooligosaccharide.



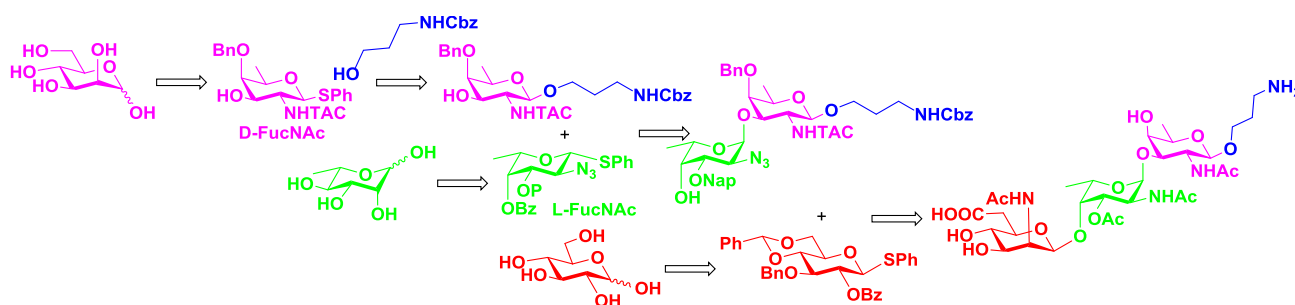
**Schemg 32.** Synthesis of oligosaccharide COS-N-Cin.



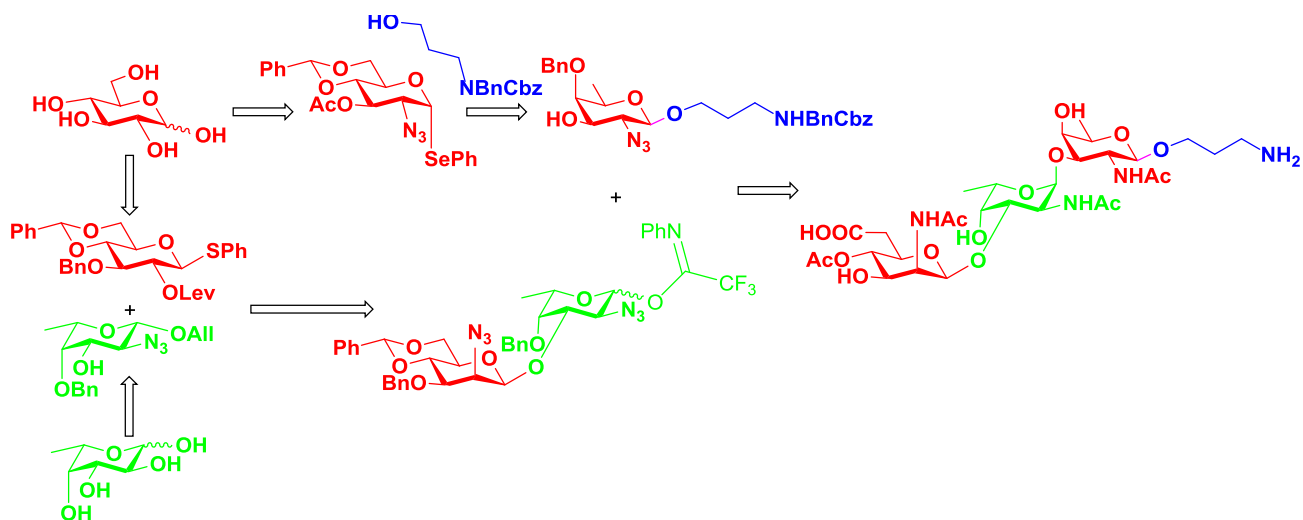
**Fig.14.** Mechanism of COS and its derivatives against (A)Fungi, (B)Gram-negative Bacteria, (C)Gram-positive bacteria.

Staphylococcus aureus is a Gram-positive bacterium that mainly infects skin, lungs and joints. Newborns and immunocompromised people are more likely to be infected.<sup>[94-96]</sup> Its antibiotic resistance seriously affects the safety of the global public health system.<sup>[97]</sup> Under environmental pressure and immune conditions of the host immune system, the capsular polysaccharide (CP) on the surface of S.aureus can provide protection, so CP is considered to be an effective target for the development of anti-infective agents.<sup>[98]</sup> Most strains of known serotype capsular polysaccharide express capsular polysaccharide type 5 (CP5) or 8 (CP8).<sup>[99]</sup> A. Behera et al. obtained D-FucNAc and L-FucNAc units from D-mannose and L-rhamnose, obtained disaccharide units by 1,2-cis linkage, protected the C3 position of L-FucNAc unit, and introduced D-glucoside glucosinolate donor at the C4 position to obtain CP5 trisaccharide repeating unit (Scheme 33) for the first time, providing a new synthetic method for the development of glycoconjugate vaccines.<sup>[100]</sup> After, M. Zhao et al.

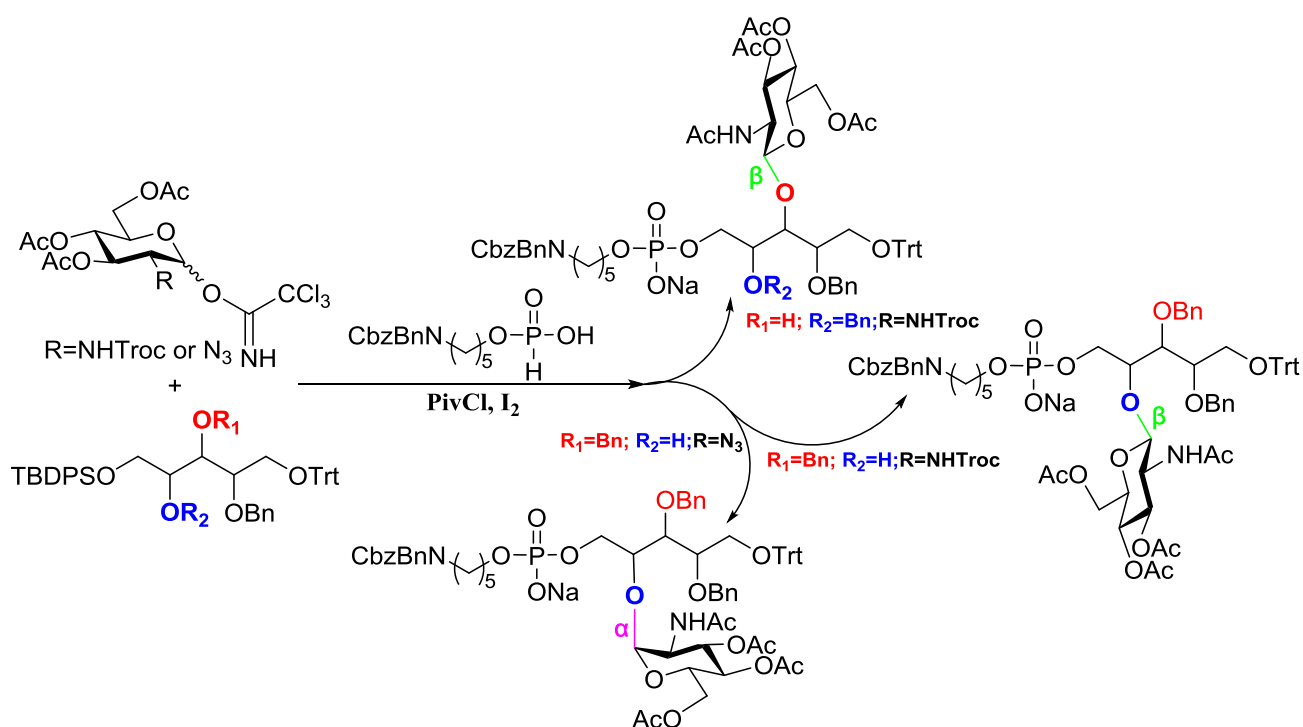
synthesized amino-terminated CP8 trisaccharide by chemical method using D-glucose and L-fucose as raw materials (Scheme 34). The conjugate of CP8 trisaccharide and CRM197 protein expressed strong immunoglobulin G (IgG) immune response in mice. Both the serum antibody and the prepared monoclonal antibody could recognize *S.aureus* strains, demonstrating the great potential of CP8 trisaccharide as an efficient antigen vaccine.<sup>[101]</sup> Wall teichoic acids (WTAs) composed of repeating ribitol phosphate (RboP) residues modified by D-alanine and N-acetyl-D-glucosamine (GlcNAc) are an important part of the cell wall of *S.aureus* and interact with the host immune system. Therefore, WTAs are also considered as potential targets for the development of glycoconjugate vaccines.<sup>[102]</sup> P. Shen et al. used D-ribose derivatives and H-phosphate linker as raw materials, using PivCl catalysis and iodine in situ reduction one-pot reaction to obtain WTAs main chain, and modified it by D-glucose derivatives through glycosylation reaction to obtain modified WTAs (Scheme 35). In vivo immunological studies, WTAs glycoconjugates induce a strong T cell-dependent immune response and induce high levels of specific IgG antibodies; in further immunological studies in vitro, the antibodies of WTAs glycoconjugates had significant phagocytic killing activity. It shows that WTAs glycoconjugates can be used as preventive vaccines and effective antigens.<sup>[103]</sup>



**Scheme 33.** Synthesis of CP5 trisaccharide repeating unit.



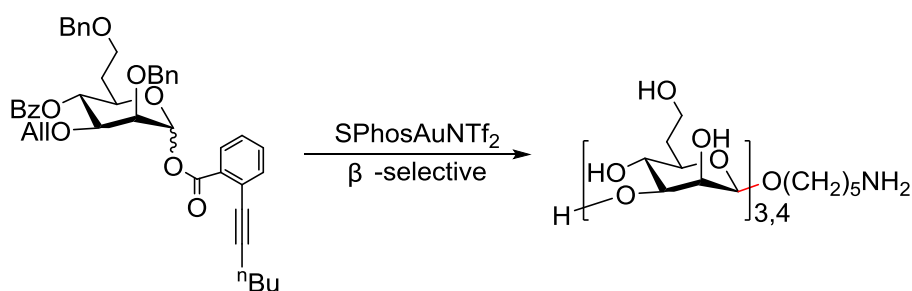
**Scheme 34.** Synthesis of CP8 trisaccharide repeating unit.



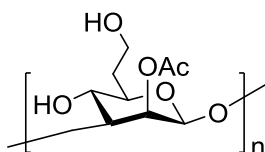
**Scheme 35.** Synthesis of WTAs glycoconjugates.

*Burkholderia pseudomallei* and *Burkholderia mallei* are highly infectious pathogens that cause serious illness in humans due to their high levels of resistance, diverse symptoms, difficulty in diagnosis, and high mortality.<sup>[104-105]</sup> Many glycoconjugate vaccines based on CPS have been clinically applied<sup>[106]</sup> (such as *Haemophilus influenzae* type b(Hib) glycoconjugate vaccine<sup>[107]</sup>), with

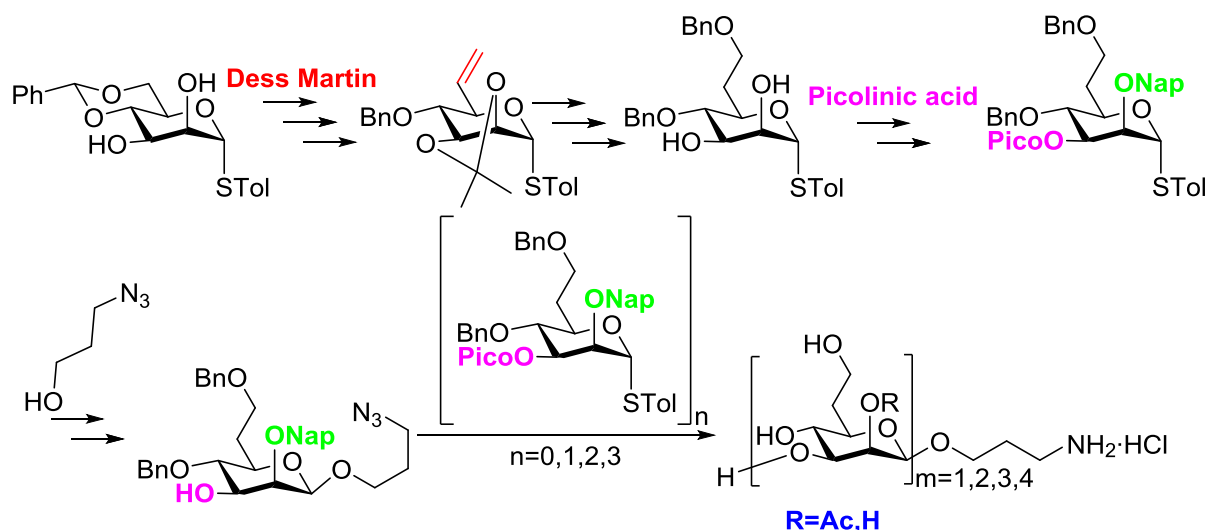
good tolerance and lifelong immunity. CPS-based *Burkholderia pseudomallei* and *Burkholderia mallei* glycoconjugate vaccines need to be developed. Y. Chen et al. used SPhosAuNTf<sub>2</sub> acts as a promoter for the stereoselective synthesis of 6-deoxy-D-manno-heptopyranosyl o-hexyl benzoate (Scheme 36) associated with the surface polysaccharides of *Burkholderia pseudomallei* and *Burkholderia mallei* (Fig. 15).<sup>[108-111]</sup> X. Y. Geng et al. added a carbon at the C-6 position of mannose through the Dess-Martin Oxidation reaction, and then introduced a hydroxyl group at the C-7 position through anti-Markovnikov hydroboration / oxidation ; next, the Pico group was introduced at the C-3 position and the hydrogen-bond-mediated aglycone delivery ( HAD ) strategy was used to stereoselectively synthesize 6-deoxy-D-mannoheptose and its β-(1→3) linked oligomer (Scheme 37). The preliminary in vivo immunological evaluation of these oligomers in mice confirmed their efficacy in triggering high titers of immunoglobulin G antibodies and strong T cell-dependent immune responses.<sup>[112]</sup> The triose conjugates were also found to elicit the strongest immune responses.<sup>[108]</sup>



**Scheme 36.** Stereoselective synthesis of 6-deoxy-D-manno-heptopyranose tri- and tetrasaccharides.

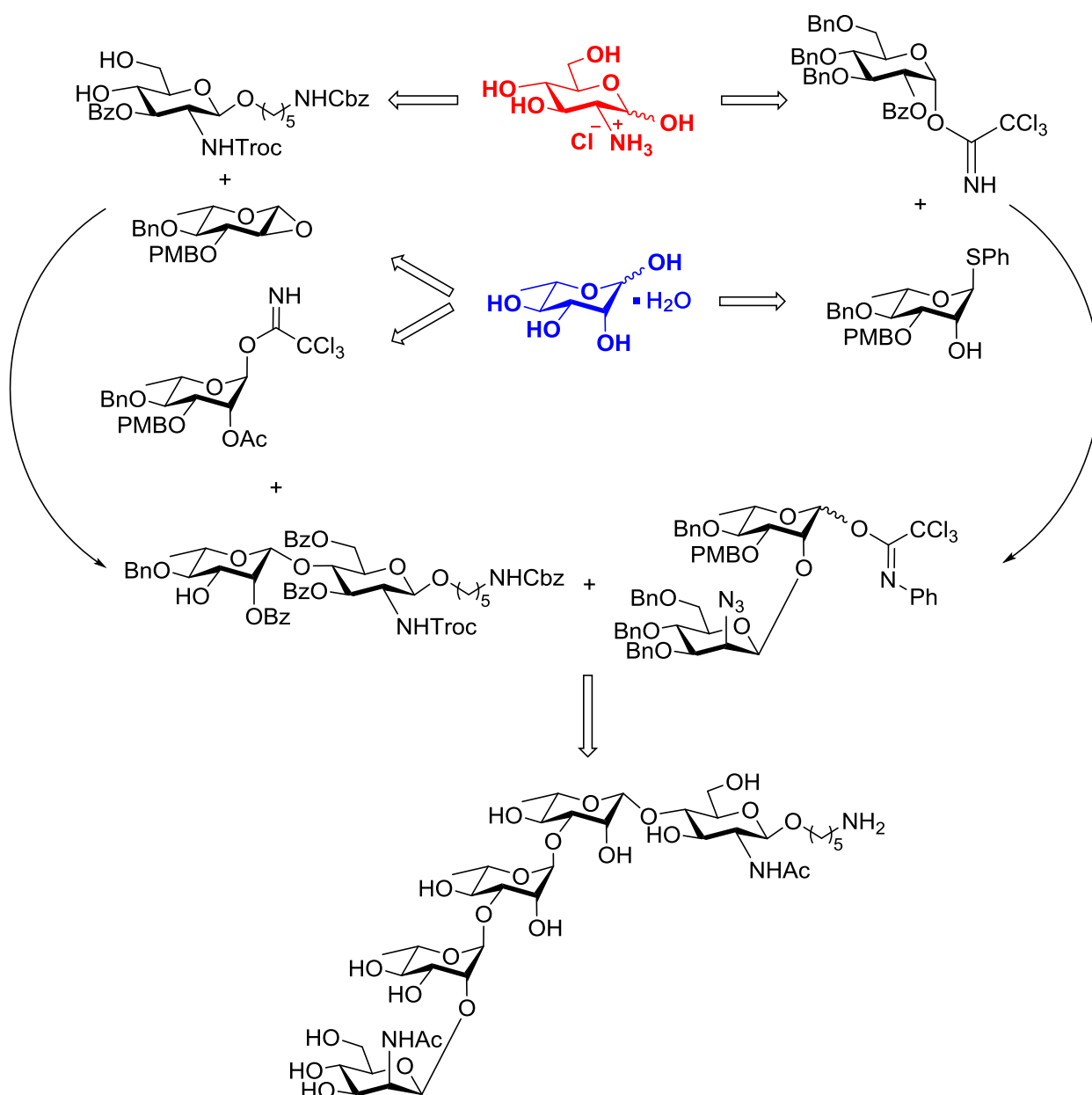


**Fig. 15.** Structures of surface polysaccharides of *B. pseudomallei*. and *B. mallei*. .

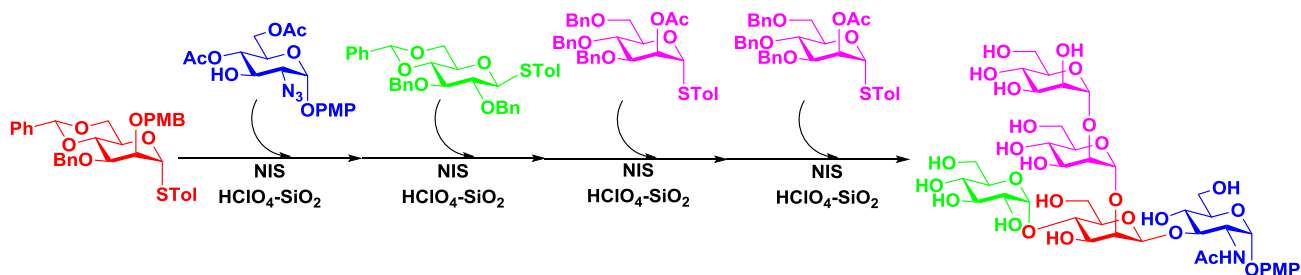


**Scheme 37.** Synthesis of 6-deoxy-D-mannoheptose and its  $\beta$ -(1 $\rightarrow$ 3) linked oligomer.

As a human intestinal symbiotic bacteria, *Escherichia coli* can cause diarrhea, urinary tract infection and even sepsis and other serious diseases due to its toxicity.<sup>[113]</sup> N. Nishi et al. firstly synthesized LPS pentasaccharide repeat unit from pathogenic *E. coli* O1 (Scheme 38) and its conjugate with BSA from L-rhamnose monohydrate and D-glucosamine hydrochloride. ELISA detection using semi-synthetic glycoconjugates and APEC O1 (zoonotic risk) immunized chicken serum showed great potential as vaccine development antigens.<sup>[114]</sup> M. Kundu et al. used a sequential glycosylation strategy, using D-mannosyl thioglycoside as a glycosyl donor, N-iodosuccinimide (NIS) and silica-loaded perchloric acid ( $\text{HClO}_4\text{-SiO}_2$ ) as accelerators, and successfully obtained the branched pentasaccharide repeat unit of o-antigen cell wall polysaccharide of *E. coli* O44:H18 (Scheme 39).<sup>[115]</sup> It provides a basis for further development of *E. coli* vaccine. S. K. Jana et al. used the same method to successfully synthesize the pentasaccharide repeating unit rich in 2-acetylamino sugars corresponding to the O-antigen polysaccharide of *Escherichia coli* (*E. coli*).<sup>[116]</sup>



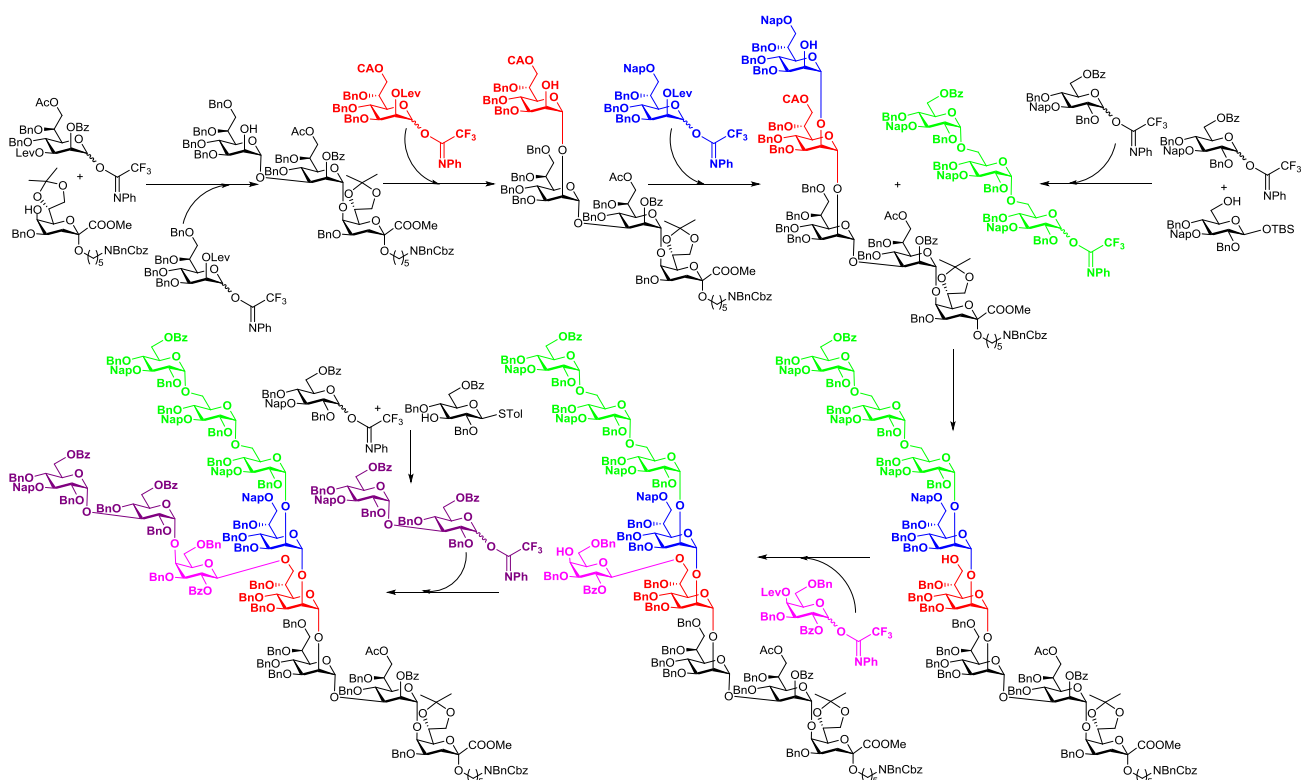
**Scheme 38.** Synthesis of the lipopolysaccharide mimetic pentasaccharide repeating unit of virulent *Escherichia coli* O1.



**Scheme 39.** Synthesis of the synthesized pentasaccharide repeating unit of the O-antigenic polysaccharide of *E. coli* O44:H18 strain.

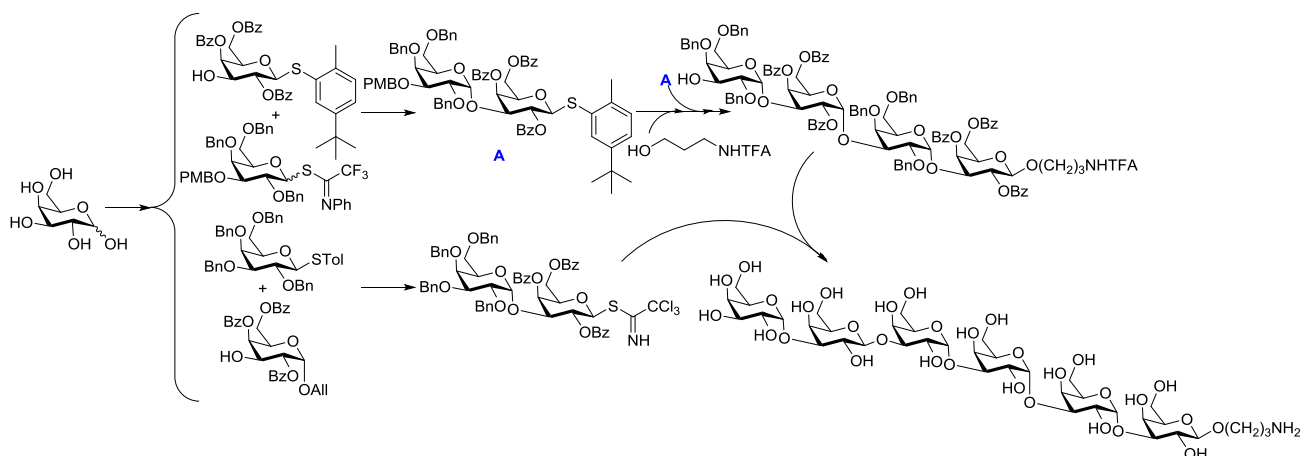


*Helicobacter pylori* is a microaerophilic gram-negative pathogen. Long-term infection of *Helicobacter pylori* can lead to diseases such as gastritis, peptic ulcer and duodenal ulcer, which may develop into gastric cancer.<sup>[117-120]</sup> The high resistance of traditional antibiotic therapy increases the risk of repeated infection in cured patients.<sup>[121]</sup> Therefore, a safe and effective new glycoconjugate *Helicobacter pylori* vaccine needs to be developed. The outer nucleus and O-antigen contained in lipopolysaccharide covering the surface of *Helicobacter pylori* are considered to be effective targets for glycoconjugate vaccines.<sup>[122-124]</sup> Professor J. Yin 's research group has made a series of important progress in the synthesis and activity of *Helicobacter pylori* glycan antigen, and has completed the chemical synthesis and antigenicity of *Helicobacter pylori* outer core octasaccharide,<sup>[125]</sup> O2 serotype O-antigen hexasaccharide,<sup>[126]</sup> O6 serotype O-antigen tridecasaccharide.<sup>[127]</sup> On this basis, the high steric hindrance core undecylose of *Helicobacter pylori* lipopolysaccharide was used as the target molecule to carry out chemical synthesis research. The core glycan structure of *Helicobacter pylori* lipopolysaccharide is relatively conserved, and the core structure of lipopolysaccharide of different serotypes is very similar, which can be used for the development of broad-spectrum glycoconjugate vaccines for various serotypes. The core undecylose is composed of an octasaccharide backbone  $\alpha$ -D-Glc-(1→3)- $\alpha$ -D-Glc-(1→4)- $\beta$ -D-Gal-(1→7)-[ $\alpha$ -D,D-Hep-(1→2)]- $\alpha$ -D, D-Hep-(1→2)- $\alpha$ -L, D-Hep-(1→3)- $\alpha$ -L, D-Hep[P/AEP]-(1→5)-Kdo and an  $\alpha$ -(1→6)-glucan trisaccharide branch.<sup>[128]</sup> Professor Yin Jian 's research group first synthesized several monosaccharide units including manno-heptose unit which is not easy to synthesize, and completed the synthesis of lipopolysaccharide core undecasaccharide of *Helicobacter pylori* by linear [2+(1+(3+(1+(1+3))))] synthesis strategy (Scheme 40). Glycan Microarrays technology was further used to analyze the antigenicity of glycans. It was found that  $\alpha$ -1,6-glucotriose had a strong binding effect with the serum of most *Helicobacter pylori* infected patients and was an important epitope of core undecasaccharide. The number and intensity of phosphorylated core trisaccharide binding to infected serum were significantly higher than those of phosphate-free core trisaccharide, indicating that the phosphate group is an important specific structure of the core undecasaccharide. This study provides an important theoretical basis for the development of *Helicobacter pylori* glycoconjugate vaccine.<sup>[129]</sup>

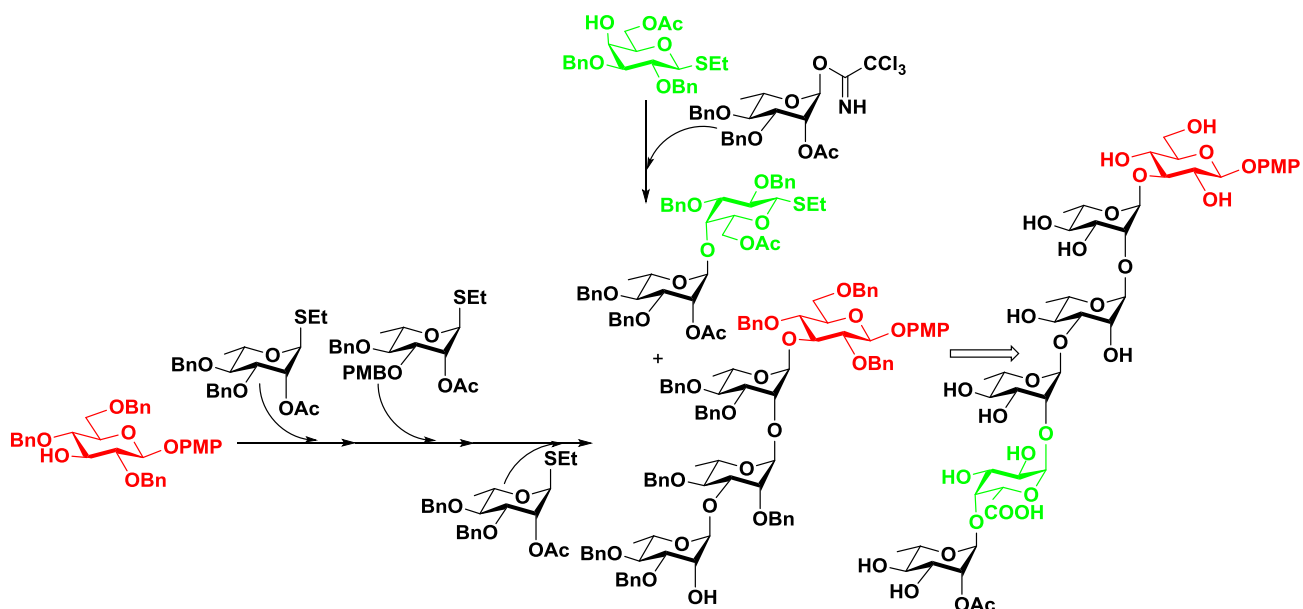


**Scheme 40.** Synthesis of lipopolysaccharide core undecasaccharide of *Helicobacter pylori* by linear [2+(1+(3+(1+(1+3))))] synthesis strategy.

The Gram-negative pathogen *Klebsiella pneumoniae* is one of the multidrug-resistant bacteria responsible for infections and epidemics.<sup>[130]</sup> D. A. Argunov et al. successfully synthesized the galactosyl-II O-specific chain hexasaccharide repeat unit of *Klebsiella pneumoniae* LPS using D-galactose as the starting material (Scheme 41), and its biotinylated derivatives were used as components of the glycoarray built up on the surface of streptavidin-coated microtiter plates, which could be effectively recognized in the screening of serum antibodies against *Klebsiella pneumoniae* O1. It has shown great potential in the development of vaccines and diagnostic kits.<sup>[131]</sup> P. Shit et al. synthesized tetrasaccharide acceptors from D-glucose and L-rhamnose, and disaccharide thioglycoside donors from D-galactose and L-rhamnose. The hexasaccharides were stereoselectively synthesized by [4+2] strategy using NIS and HClO<sub>4</sub>-SiO<sub>2</sub> as catalysts. The primary hydroxyl group was oxidized to carboxyl group by TEMPO and bis (acetoxy) iodobenzene (BAIB) to obtain capsular polysaccharide of *Klebsiella* serotype K-34 type hexasaccharide repeat unit (Scheme 42).<sup>[132]</sup>

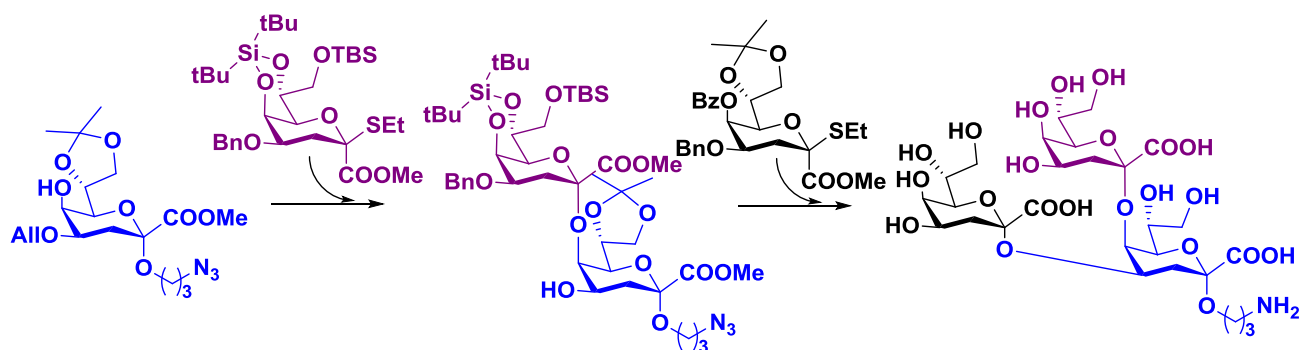


**Scheme 41.** Synthesis of galactosyl-II O-specific chain hexasaccharide repeat unit.



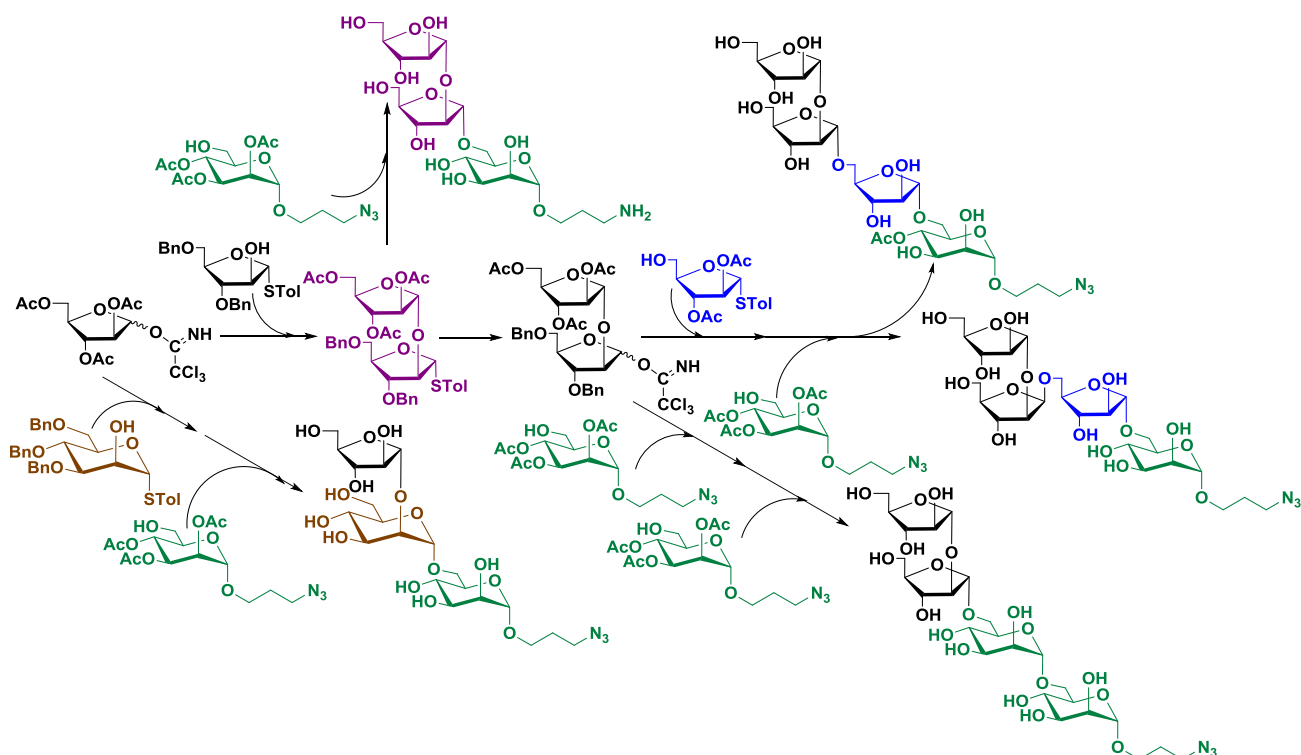
**Scheme 42.** Synthesis of K-34 type hexasaccharide repeat unit.

Acute pneumonia, meningitis, sepsis and other serious diseases can be caused by *Acinetobacter baumannii*.<sup>[133]</sup> X. Y. Zhou et al. synthesized for the first time four oligosaccharide fragments of the core within the LPS of *Acinetobacter baumannii* strain ATCC 17904 and evaluated them antigenically using sugar microarray technology, in which the 4,5-branched Kdo trisaccharide (Scheme 43) has strong binding ability to IgG antibody in infected serum, which can be used as a potential minimal epitope for the development of diagnostic tools and vaccines against *Acinetobacter baumannii*.<sup>[134]</sup>

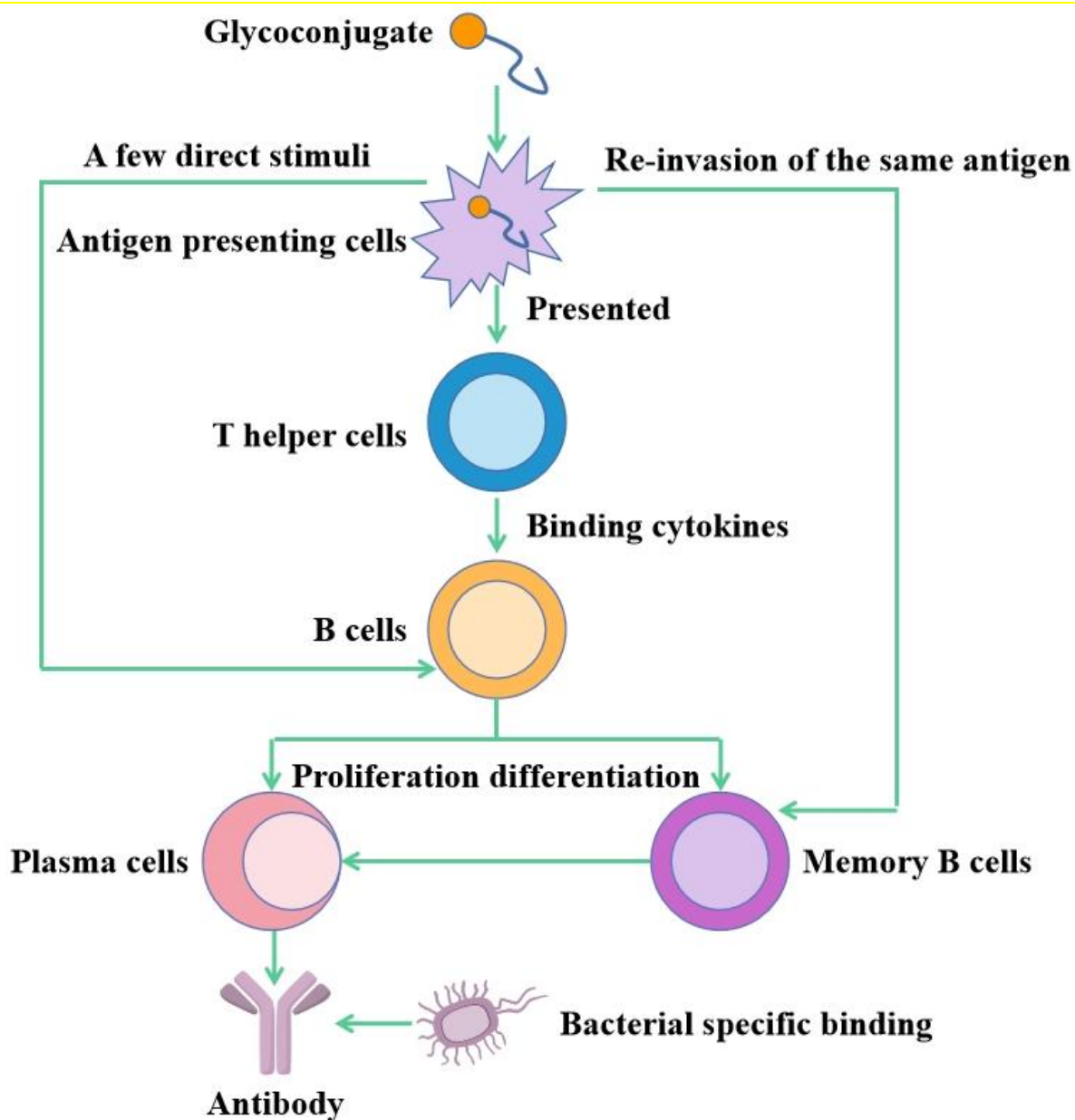


**Scheme 43.** Synthesis of 4,5-branched Kdo trisaccharide.

Tuberculosis (TB), which is one of the top ten causes of death globally due to mycobacterial infection,<sup>[135]</sup> and the alarming increase in clinical cases of drug-resistant tuberculosis (TB) have prompted the need for the rapid development of novel chemotherapeutic agents with novel mechanisms of action.<sup>[136-138]</sup> As the main component of mycobacterial cell walls, the polysaccharide lipoarabinomannan (LAM) has always attracted the interest of researchers.<sup>[139]</sup> Z. Li et al. synthesis of five LAM oligosaccharide compounds using D-arabinose and D-mannose as potential candidates for conjugate vaccines (Scheme 44).<sup>[140]</sup>



**Scheme 44.** Synthesis of five LAM oligosaccharides.



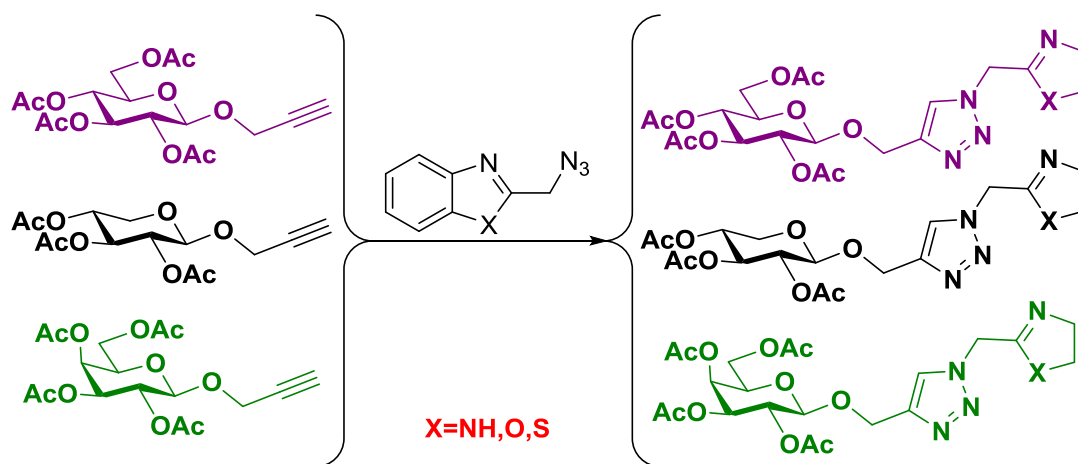
**Fig. 16.** Anti-bacterial mechanism of glycoconjugate vaccine.

### 3.1.2 Anti-viral activity

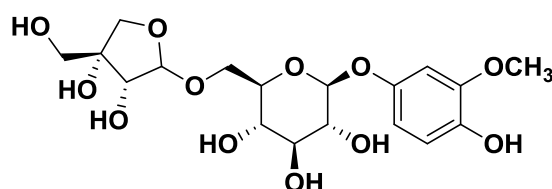
The long-term epidemic of coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has caused a health crisis worldwide.<sup>[141]</sup> COVID-19 can cause fever, fatigue, cough, shortness of breath, and severe pneumonia.<sup>[142]</sup> At present, Paxlovid has been authorized by FDA for emergency use,<sup>[143]</sup> but in vitro studies and clinical trials of effective therapies for SARS-CoV-2 infection are still ongoing.<sup>[144]</sup> Chitosan-derived is considered to have antiviral activity.<sup>[145]</sup> D. Jang et al. first proposed that chitoooligosaccharides could produce anti-SARS-CoV-2 virus activity in vitro.<sup>[146]</sup> H. Hamada et al. co-cultured

SARS-CoV-2 infected MRC5 lung cells with different concentrations of resveratrol oligosaccharides, and found that the inhibitory effect of resveratrol oligosaccharides on the death of infected cells exceeded that of resveratrol at the concentration of 0.1%, and could effectively inhibit SARS-CoV-2 infection at the concentration of 5%-10%, indicating that resveratrol oligosaccharides are effective anti-SARS-CoV-2 drugs.<sup>[147]</sup>

Influenza is an acute viral respiratory disease caused by respiratory tract infection with influenza virus ( RNA virus ), which is spread worldwide.<sup>[148]</sup> Influenza viruses are classified into three types, A, B and C according to their internal protein antigens. Type A (e.g. H1N1) is the most toxic to humans due to its extensive host range and causes millions of deaths worldwide.<sup>[149]</sup> Vaccination and specific antiviral drugs are two main strategies for influenza prevention and treatment.<sup>[150]</sup> The drug resistance caused by the excessive use of antiviral drugs and the continuous evolution of influenza viruses are urgent to develop new anti-influenza virus drugs.<sup>[151]</sup> The approved antiviral drugs include neuraminidase inhibitors (NAIs) (zanamivir), M2 ion channel blockers (amantadine), RNA polymerase inhibitors (favipiravir).<sup>[152-154]</sup> Neuraminidase glycoprotein ( NA ) is a glycoprotein on the surface of influenza virus. It is still a favorable target for the development of anti-influenza virus drugs.<sup>[155]</sup> O. Kutkat et al. using Cu( II)-catalyzed click chemistry, produced 1,2,3-triazole glycosides by the reaction of terminal alkynyl glycosides with azido groups (Scheme 45), which have high antiviral activity against wild-type and neuraminidase inhibitor-resistant strains of avian influenza H5N1 and human influenza H1N1 viruses in vitro and in mice.<sup>[156]</sup> S. M. Mohamed et al. isolated the oligosaccharide compound Canthoside C from *Gardenia latifolia* Aiton (Fig. 17), Rubiaceae and evaluated its activity against influenza A (H1N1) virus. Canthoside C has significant antiviral activity against H1N1, with a half inhibitory concentration of 10.93 $\mu$ g/mL, and has low cytotoxicity to host MDCK cells, CC50 value of 140.8 $\mu$ g/mL and a SI of 12.88, indicating its potential in anti-H1N1 virus.<sup>[157]</sup>

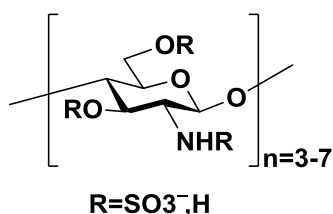


**Scheme 45.** Synthesis of 1,2,3-triazole glycosides.

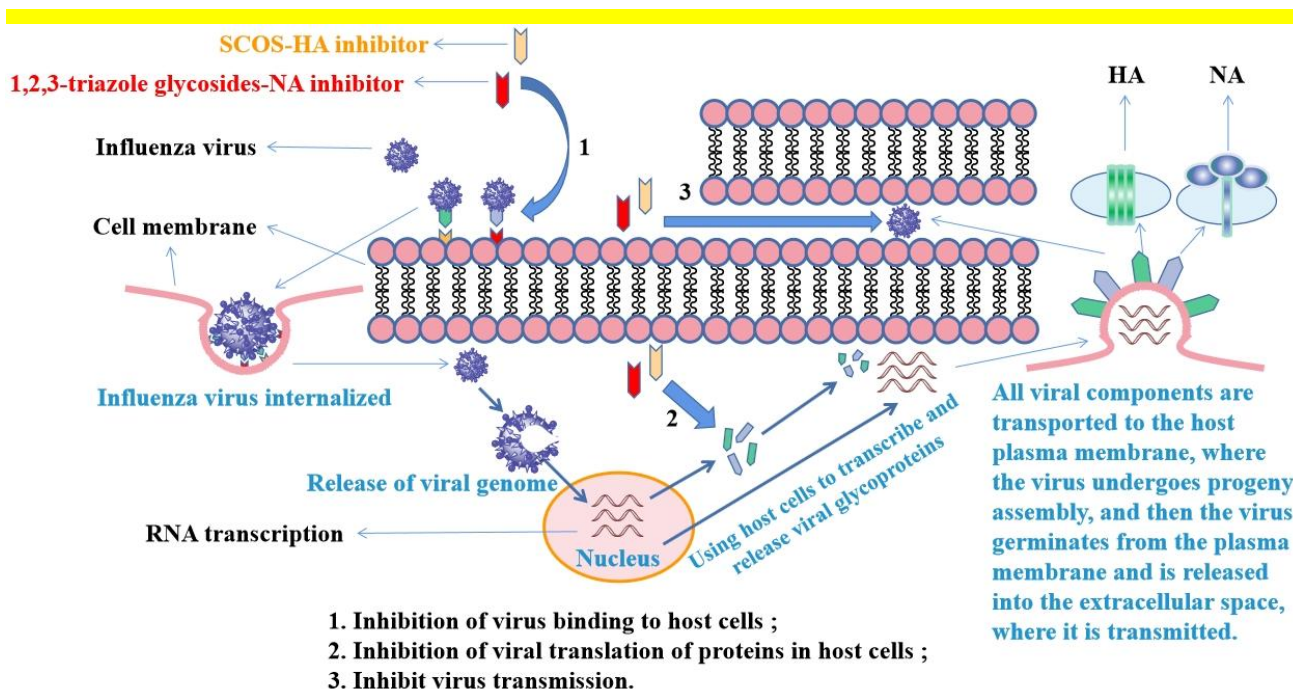


**Fig. 17.** Structure of Canthoside C.

The binding of glycoprotein hemagglutination of influenza A virus to Host membrane viral is one of the main processes of infection. Therefore, glycoprotein hemagglutinin (HA) is also a potential target for influenza drug research.<sup>[158]</sup> S. Wang et al. tested the antiviral activity of the synthesized sulfated chitosan oligosaccharides (SCOS) (Fig. 18) in vitro and in vivo, and showed good inhibitory effect on IAV infection. SCOS binds to HA protein and blocks the entry of IAV into the infection process by inhibiting IAV adsorption and subsequent membrane fusion.<sup>[159]</sup>



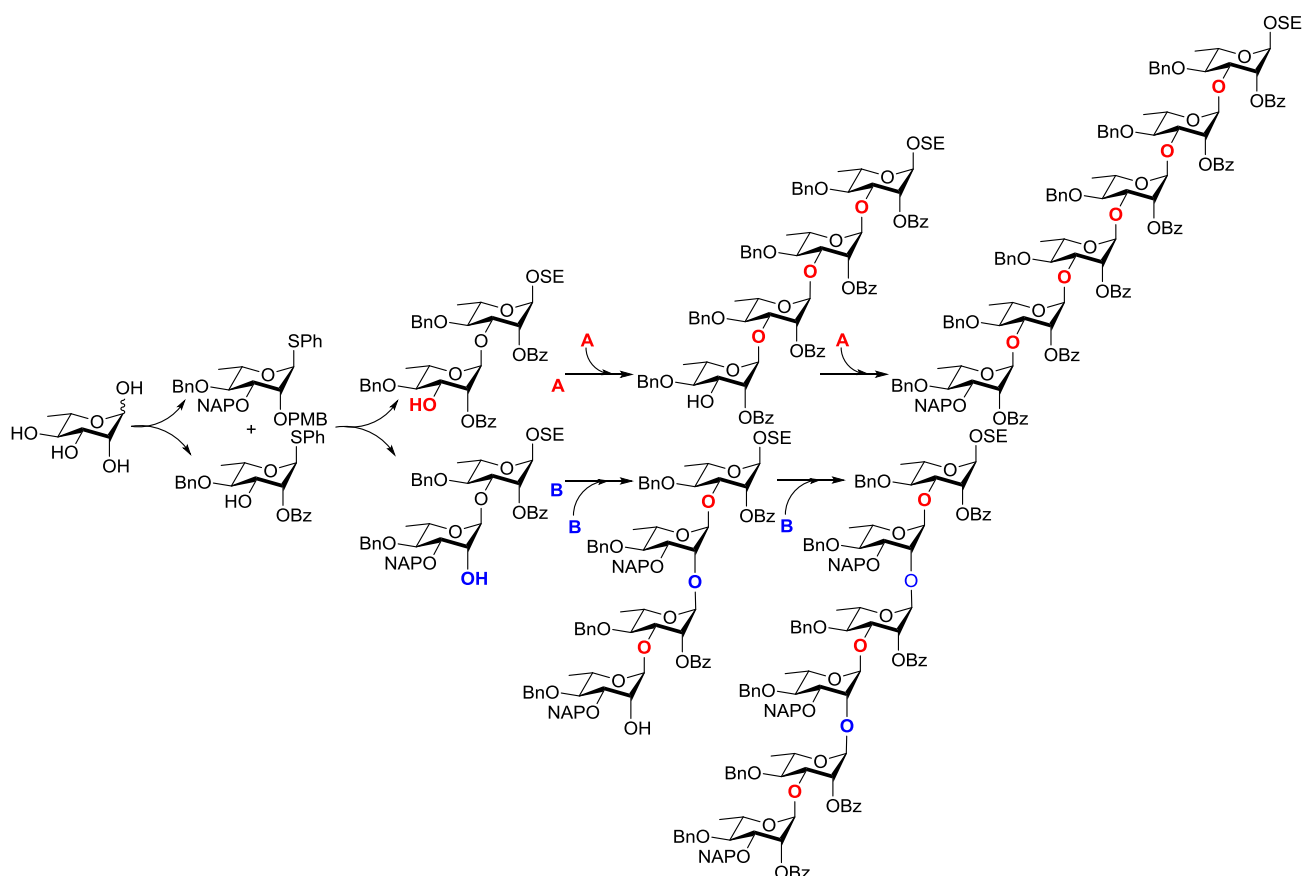
**Fig. 18.** Structure of SCOS.



**Fig. 19.** The anti-viral mechanism of 1,2,3-triazole glycosides and SCOS.<sup>[160]</sup>

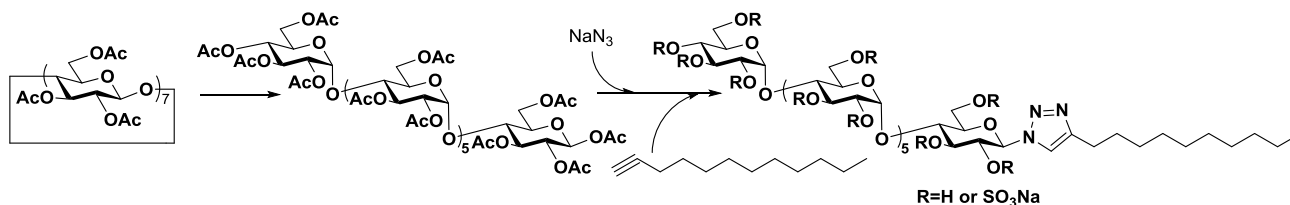
Herpes simplex virus type 2 ( HSV-2 ) is a large double-stranded DNA virus. As a popular human pathogen, it can establish a lifelong latency in the dorsal root ganglion by escaping the host 's innate immunity after initial infection.<sup>[161]</sup> The sulfated polysaccharide purified from *Monostroma nitidum* Wittrock contains a large amount of L-rhamnose and a small amount of D-glucose, mainly composed of 1,2-and 1,3-linked rhamnose residues, which is called rhamnan sulfate (RS). It exhibits strong antiviral activity by preventing the adsorption and penetration of HSV-2 virus on the surface of host cells.<sup>[162]</sup> H. Tanaka et al. successfully developed a concise synthesis of rhamnose hexasaccharides with alternating  $\alpha$ -(1 $\rightarrow$ 2)/(1 $\rightarrow$ 3)-bonds and repeating  $\alpha$ -(1 $\rightarrow$ 3)-bonds by using iterative  $\alpha$ -glycosylation of disaccharide structural units (Scheme 46), providing favorable conditions for their application in anti-HSV-2.<sup>[163]</sup>





**Scheme 46.** Synthesis of repeating  $\alpha$ -(1 $\rightarrow$ 3)-linkages and alternating  $\alpha$ -(1 $\rightarrow$ 2)/(1 $\rightarrow$ 3)-linkages hexasaccharides.

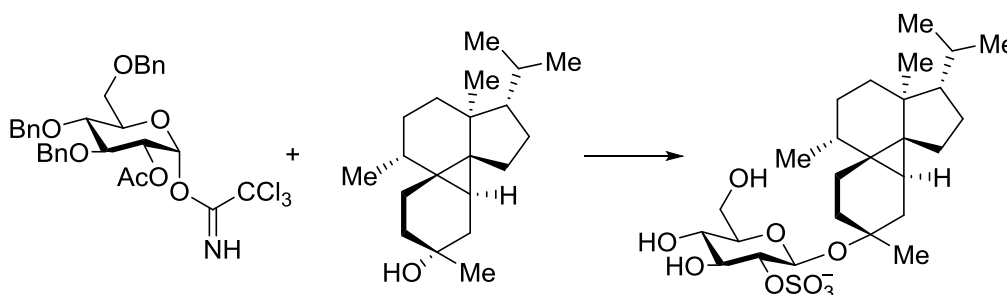
HIV ( human immunodeficiency virus ) is an RNA retrovirus with high genetic variability and rapid adaptation.<sup>[164]</sup> The gp120 is main envelope glycoprotein on HIV-1 virus particles and the binding protein for virus entry.<sup>[165]</sup> The glycan shield on gp120 is a vulnerable site for broad-spectrum neutralizing antibodies and has the effect of host HIV-1 adaptive immune response, which is a noteworthy target for anti-HIV-1 virus research.<sup>[166]</sup> Sulfated polymannuronate ( SPMG ) binds gp120 protein with high affinity to fight HIV-1 infection.<sup>[167]</sup> M. Bai et al. used  $\beta$ -cyclodextrin as raw material to synthesize sulfated alkyl heptasaccharides with long alkyl chains by click chemistry (Scheme 47). The long-chain alkyl groups pass through and are fixed in the lipid bilayer of HIV, and the negatively charged sulfated alkyl heptasaccharide part interacts with the positively charged amino acid through electrostatic interaction with HIV gp120 molecules, thereby achieving inhibition of HIV infection.<sup>[168]</sup>



**Scheme 47.** Synthesis sulfated alkyl heptasaccharides.

### 3.1.3 Anti-parasitic activity

In 2019, B. K. Chhetri et al. isolated for the first time two marine sulfated diterpene glycosides peyssonnosides from the red alga *Peyssonnelia* sp. It exhibits good antimalarial activity against hepatic stage *Plasmodium berghei*.<sup>[169]</sup> G. A. Chesnokov et al. succinctly and efficiently realized the first asymmetric total synthesis of (-)-peyssonnoside A (Scheme 48), which provides a reference for the antimalarial treatment of *Plasmodium berghei*.<sup>[170]</sup>

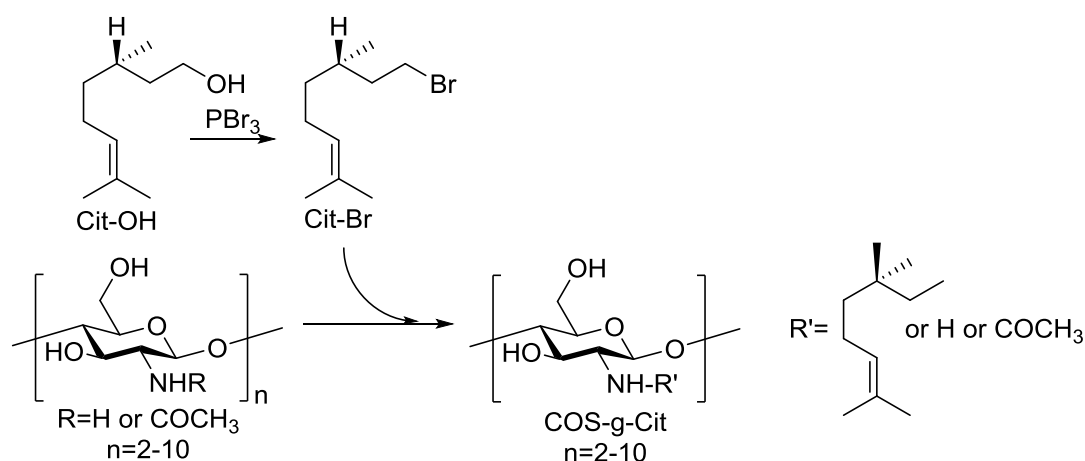


**Scheme 48.** Synthesis of peyssonnoside A.

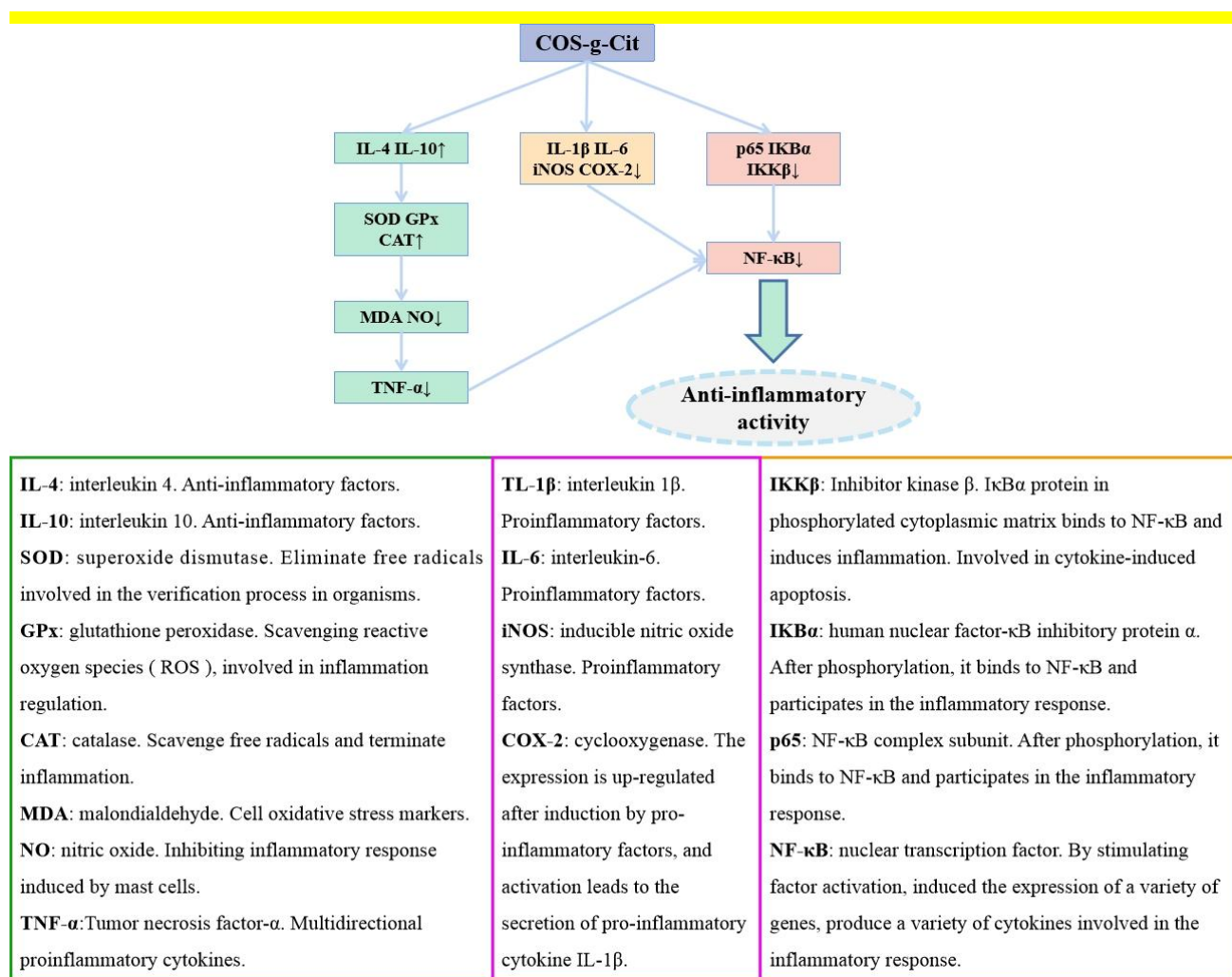
### 3.2 Anti-inflammatory activity

Inflammation is an innate immune response initiated by foreign antigens and injurious stimuli, and numerous studies have demonstrated that inflammation is accompanied by a broad range of diseases, such as diabetes<sup>[171-172]</sup>, cancer,<sup>[173-174]</sup> atherosclerosis,<sup>[175]</sup> asthma,<sup>[176]</sup> and Alzheimer's disease,<sup>[177-178]</sup> and these diseases can be ameliorate by enhancing anti-inflammatory response.<sup>[179-182]</sup>

S. Mao et al. obtained a chitosan oligosaccharide-grafted citronellol derivative (COS-g-Cit) (Scheme 49) by grafting citronellol (Cit) onto a chitosan oligosaccharide (COS) backbone with anti-inflammatory activity in vivo. Evaluations indicate that it has modulating anti-inflammatory activity to reduce foot edema.<sup>[183]</sup>



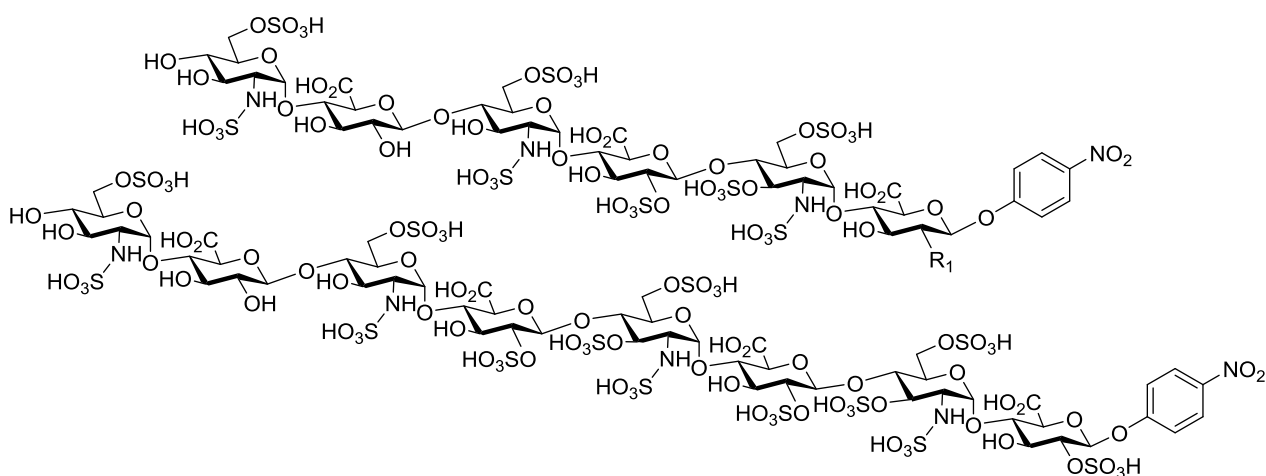
**Scheme 49.** Synthesis of COS-g-Cit.



**Fig. 20.** The anti-inflammatory mechanism of COS-g-Cit.<sup>[182]</sup>

Cerebral hemorrhage (ICH) occurs when cerebral blood vessels rupture, leading to inflammation and cell death.<sup>[184-185]</sup> T. W. Hung et al. tested a human milk oligosaccharide (2-Fucosyllactose (2FL))

with potent anti-apoptotic and anti-inflammatory effects by cell symbiosis to simulate ICH in vitro,<sup>[186-187]</sup> and the test data showed that it could neuroprotective effect on ICH by inhibiting neuroinflammation and ER stress.<sup>[188]</sup> J. Li et al. synthesized 3-O-heparan sulfate oligosaccharides by 2-O-sulfated glucuronic acid (GlcA2S) and 3-O-sulfated glucosamine (GlcNS3S), in vitro biological experiments were correlated with tau protein and Increased binding of HMGB-1, both proteins thought to be involved in inflammatory processes, which in turn are implicated in Alzheimer's disease pathogenic processes(Fig. 21).<sup>[189]</sup>



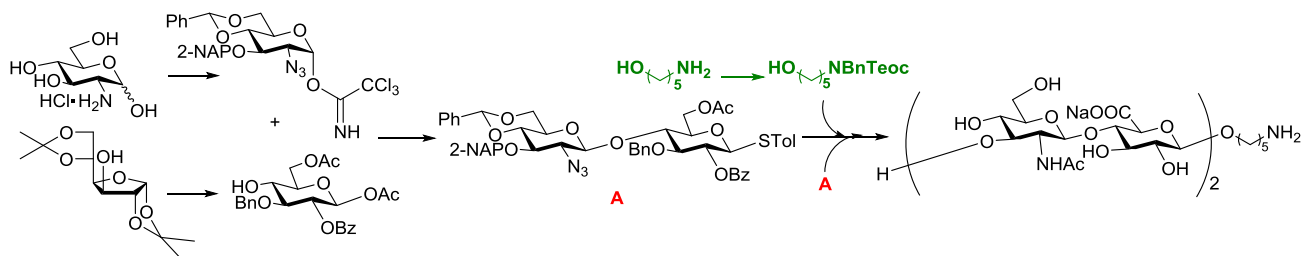
**Fig. 21.** Structures of hexasaccharides and octasaccharides containing a 3-O-sulfated glucosamine residue.

### 3.3 Antitumor activity

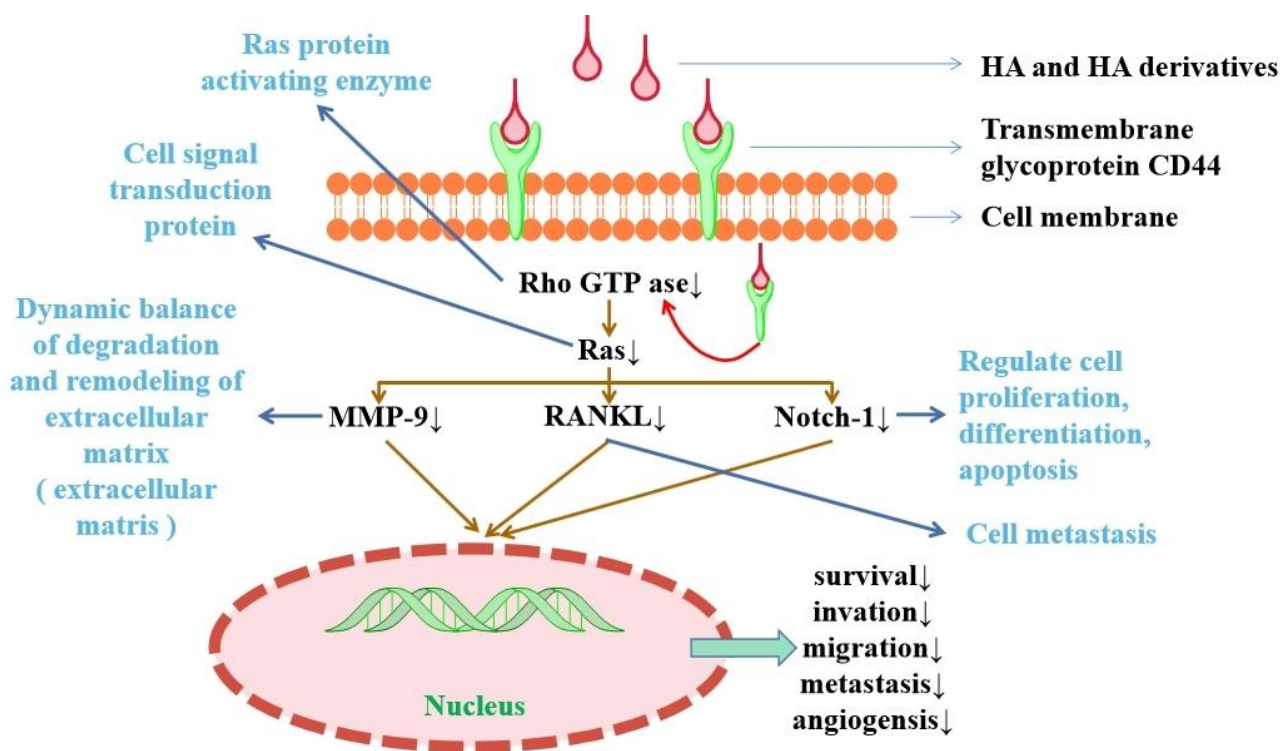
Cancer is the second leading cause of death worldwide responsible for about 10 million deaths per year.<sup>[190]</sup> Globally, nearly one-sixth of all deaths are caused by cancer.<sup>[191]</sup> At present, the methods of cancer treatment mainly include surgery, radiotherapy and chemotherapy. These treatments are very damaging to the patient, and the pain that the patient needs to endure during the treatment process may be greater than the tumor itself. Several oligosaccharide drugs that have been developed have brought hope for a more effective solution to this problem, including DNA synthesis inhibitors for tumor cells, and immune enhancers to enhance patient immunity.

Both the anionic linear non-sulfated glycosaminoglycan hyaluronic acid (HA) and the transmembrane glycoprotein CD44, which are ubiquitous in the extracellular matrix, have good biological activities.<sup>[192-198]</sup> The interaction between HA and CD44 can provide ideas for the research of new tumor drugs has been confirmed. C. J. Yeh et al. synthesized the hyaluronic acid HA repeat

fragment (GlcNAc-GlcA) tetrasaccharide through the  $S_N2$  reaction using a glucosamine donor and a glucoside acceptor, which was shown to be the shortest fragment bound to CD44 by ITC analysis(Scheme 50).<sup>[192]</sup>

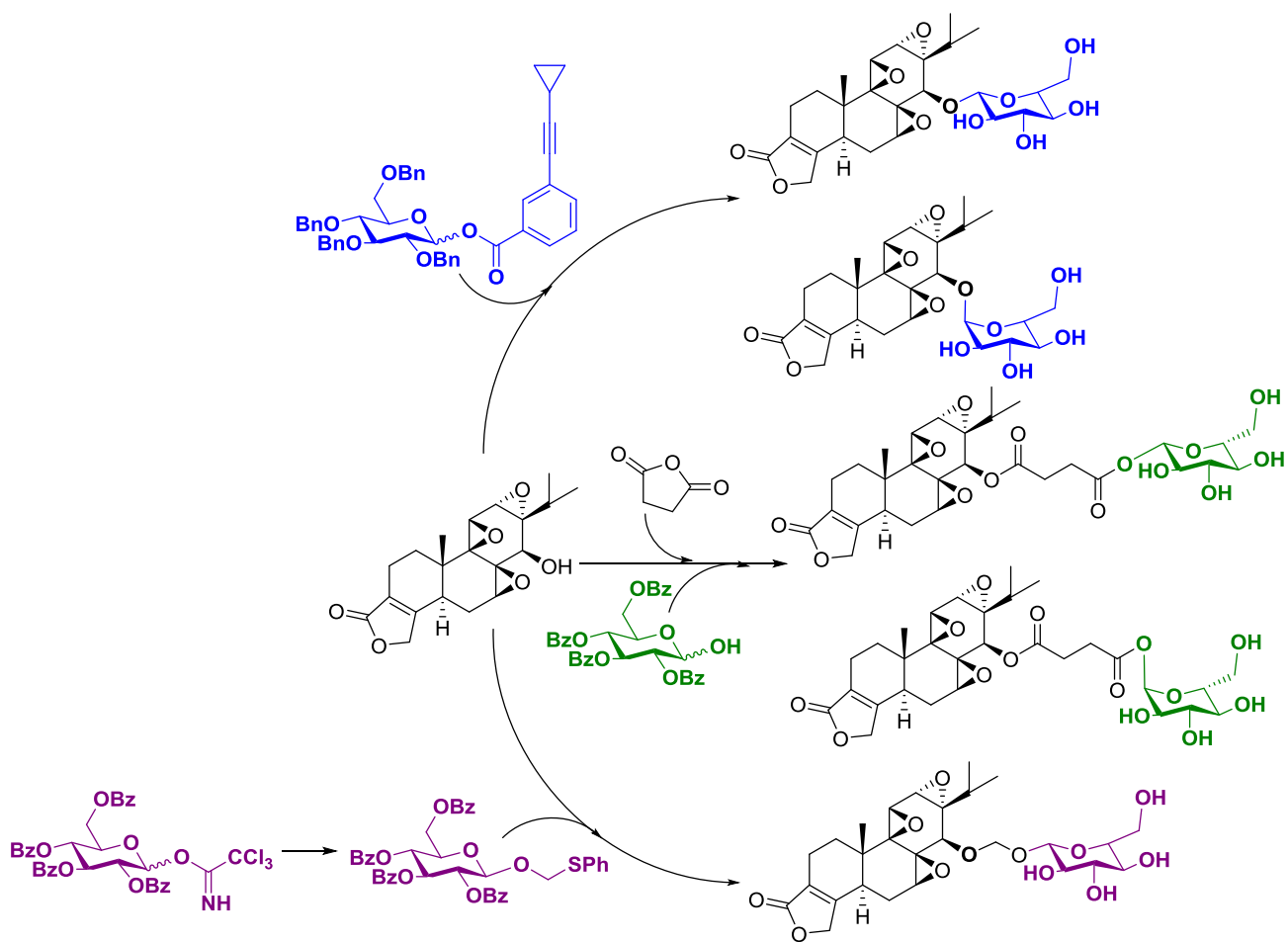


**Scheme 50.** Synthesis of the HA tetrasaccharide fragment.

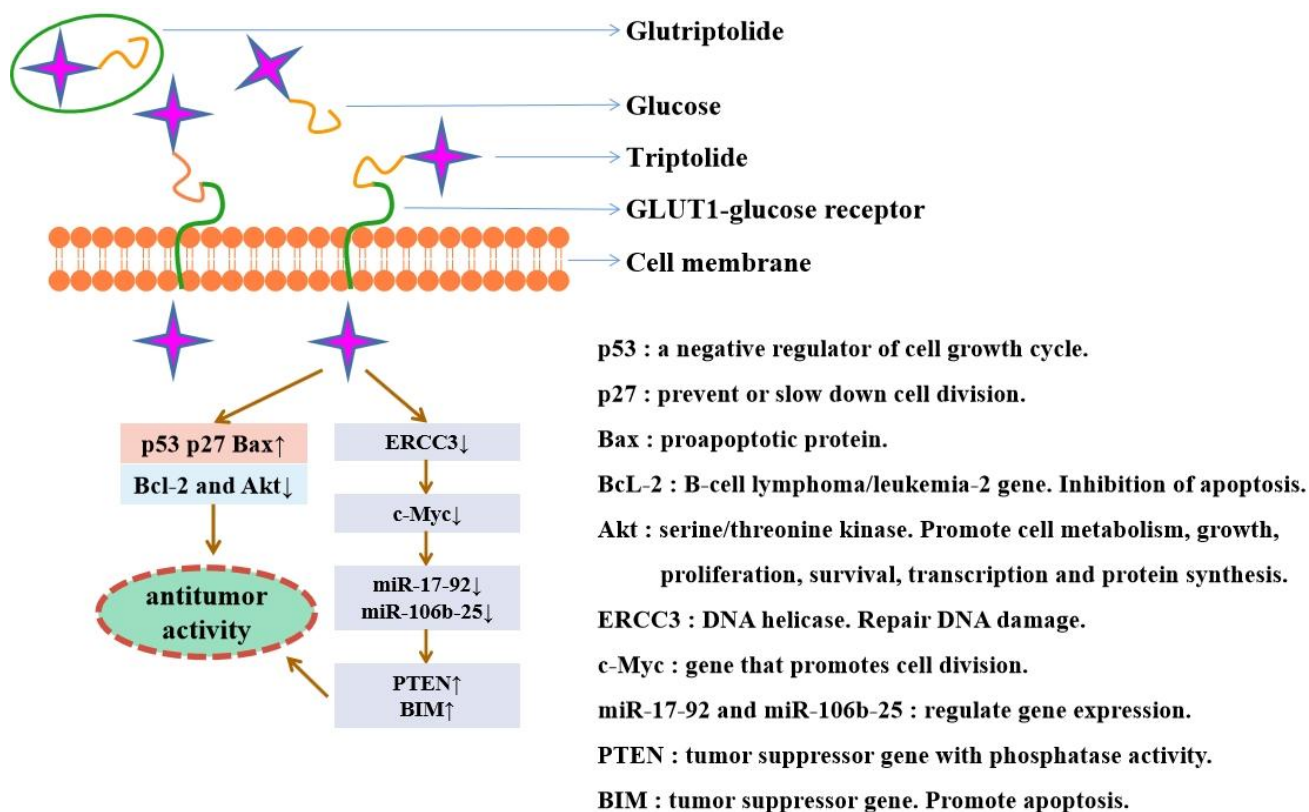


**Fig. 22.** The anti-tumor mechanism of HA-CD44 conjugate.<sup>[199]</sup>

Triptolide has strong antitumor activity and is difficult to develop due to its toxicity and low water solubility.<sup>[200-204]</sup> Q. L. He et al. synthesized glutriptolide, which can selectively target tumor cells overexpressing glucose transporters, by conjugation of triptolide and glucose. The cytotoxicity of Glutriptolide to tumor cells was significantly higher than that of normal cells, and the water solubility was higher than that of triptolide. And it shows remarkable tumor control in vivo, which is expected to provide a lead for the development of new anticancer drugs(Scheme 51).<sup>[205]</sup>

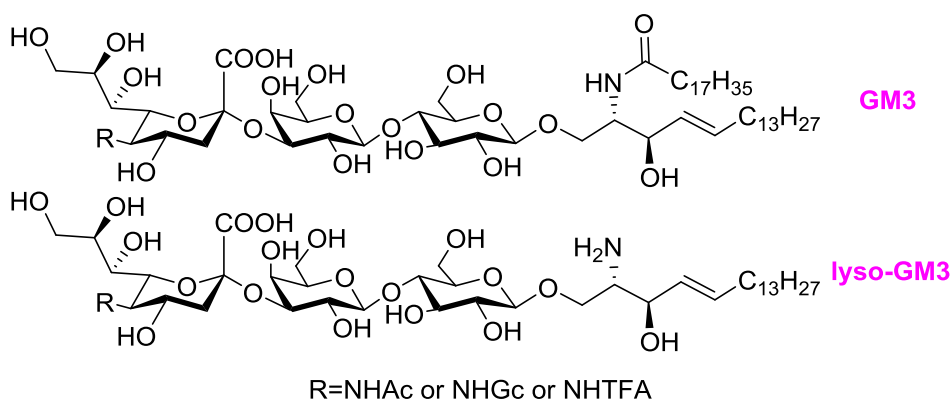


**Scheme 51.** Synthesis of glutriptolide.

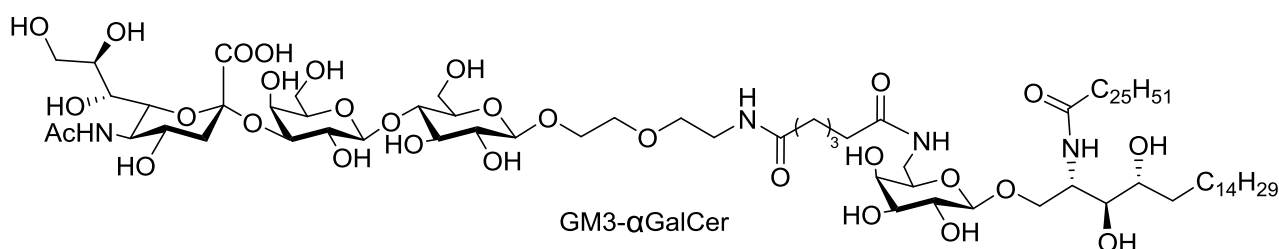


**Fig. 23.** The anti-tumor mechanism of glutriptide.<sup>[206]</sup>

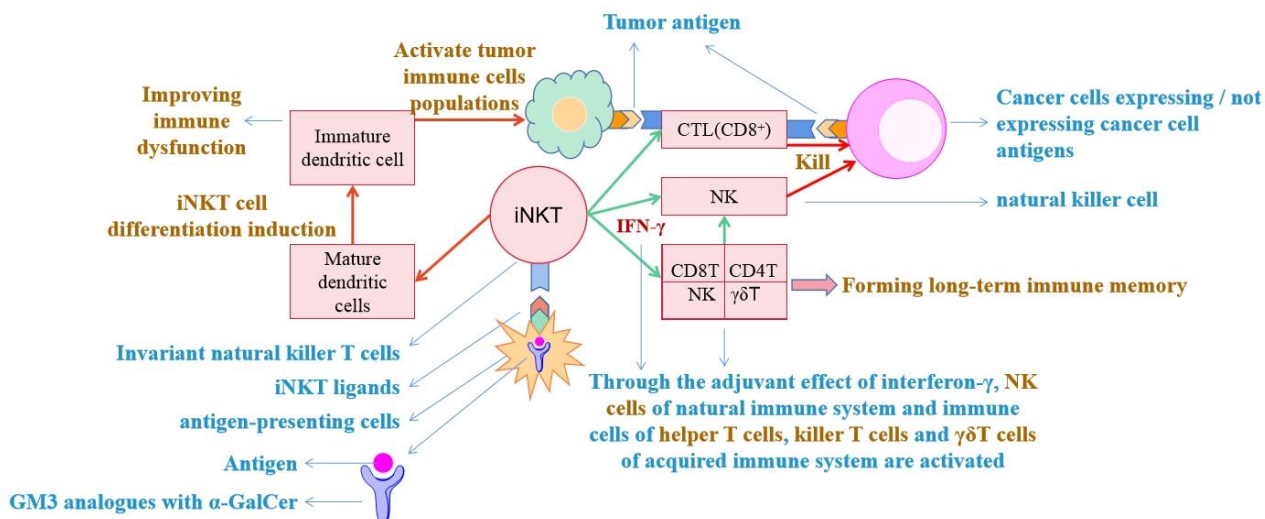
GM3 is a typical tumor-associated carbohydrate antigen and is considered an important target for cancer vaccine development, but its low immunogenicity limits its application.<sup>[207]</sup> Ganglioside GM3 is a GSLs that composed of a single terminal sialic acid, lactose and ceramide.<sup>[208]</sup> T. Li et al. synthesized ganglioside GM3 and Lyso-GM3 by chemoenzymatic method (Fig. 24). The anti-proliferative activity study showed that they can effectively inhibit the migration of melanoma B16-F10 cells, which provides value for the search for new anti-tumor therapeutic drugs 's reference.<sup>[209]</sup> X. G. Yin et al. obtained a vaccine candidate with strong antitumor activity by non-covalently binding GM3 to the cellular agonist  $\alpha$ -GalCer (Fig. 25).<sup>[207]</sup>



**Fig. 24.** Structure of GM3 and Lyso-GM3.



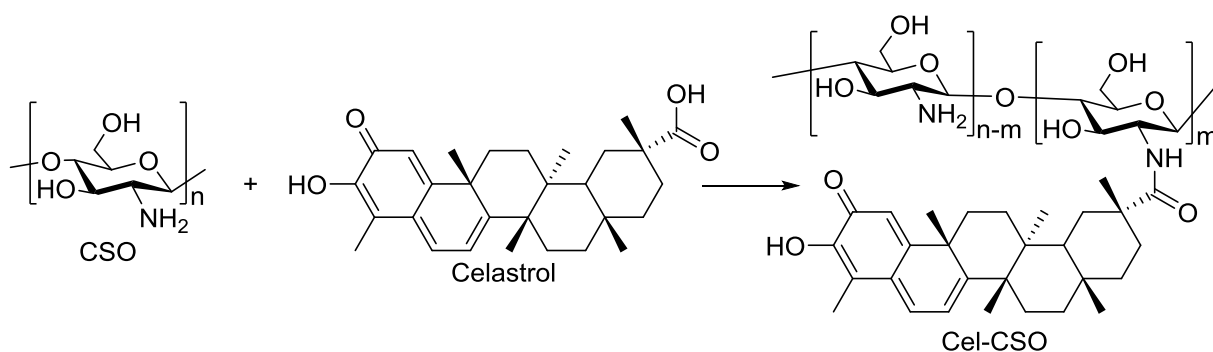
**Fig. 25.** Structure of GM3-αGalCer.



**Fig. 26.** Anticancer mechanism of GM3 analogues with  $\alpha$ -GalCer.<sup>[210]</sup>

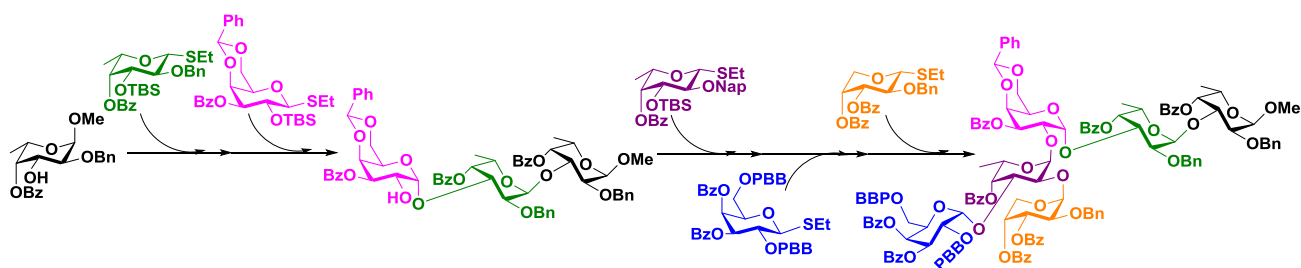
As a promising antitumor candidate, poor water solubility and cytotoxicity limit the application of Celastrol.<sup>[211-212]</sup> X. Zeng et al. synthesized Celastrol (Cel)-chitosan oligosaccharide (CSO) conjugate (Cel-CSO) (Scheme 52), which increased water solubility and decreased cytotoxicity, and showed significant expression in human pancreatic cancer cells (BxPC-3). It inhibits tumor growth, induces apoptosis and effectively inhibits tumor metastasis.<sup>[213]</sup>





**Scheme 52.** Synthesis of Cel-CSO.

Telomerase plays a crucial role in the course of human cancers.<sup>[214]</sup> Telomerase is overactivated in 90% of cancers to induce sustained cell proliferation,<sup>[215]</sup> making telomerase inhibition a potential target for cancer therapy.<sup>[216]</sup> Sulfated polysaccharides are ubiquitous in biological systems and possess anti-tumor activities.<sup>[217]</sup> Axinelloside A is a highly sulfated lipooligosaccharide was isolated from a marine sponge *Axinella infundibula*,<sup>[218]</sup> possessing excellent human telomerase inhibitory activity.<sup>[219]</sup> Axinelloside A consists of 1 cyanocrab inositol and 1 D-arabinose, 5 D-galactose, 5 L-fucose, linked by 1,2-cis/trans glycosidic bonds and modified by (R)-3-hydroxy-octadecanoic acid, 3 (E)-2-hexadecenoic acids, and 19 sulfates.<sup>[220]</sup> S. J. Li et al. successfully completed the synthesis of a highly branched hexasaccharide backbone at the non-reducing end of Axinelloside A (Scheme 53) by means of a linear synthesis strategy using chemical synthesis. Its use as a well-defined oligosaccharide can be used for the study of the structure-activity relationship between telomerase and this sulfate polysaccharide, providing a basis for further application to anticancer drug research.<sup>[221]</sup>



**Scheme 53.** Synthesis of hexasaccharide backbone at Axinelloside A.

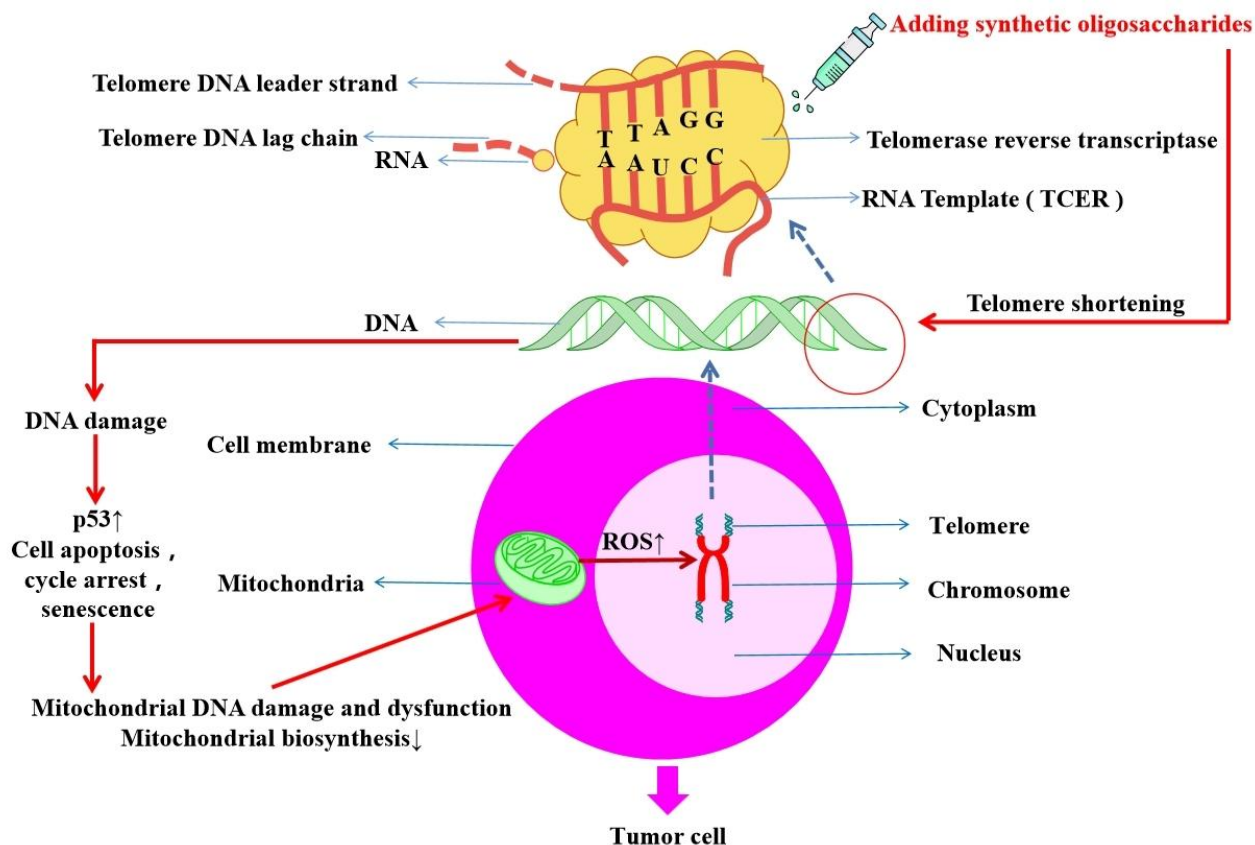
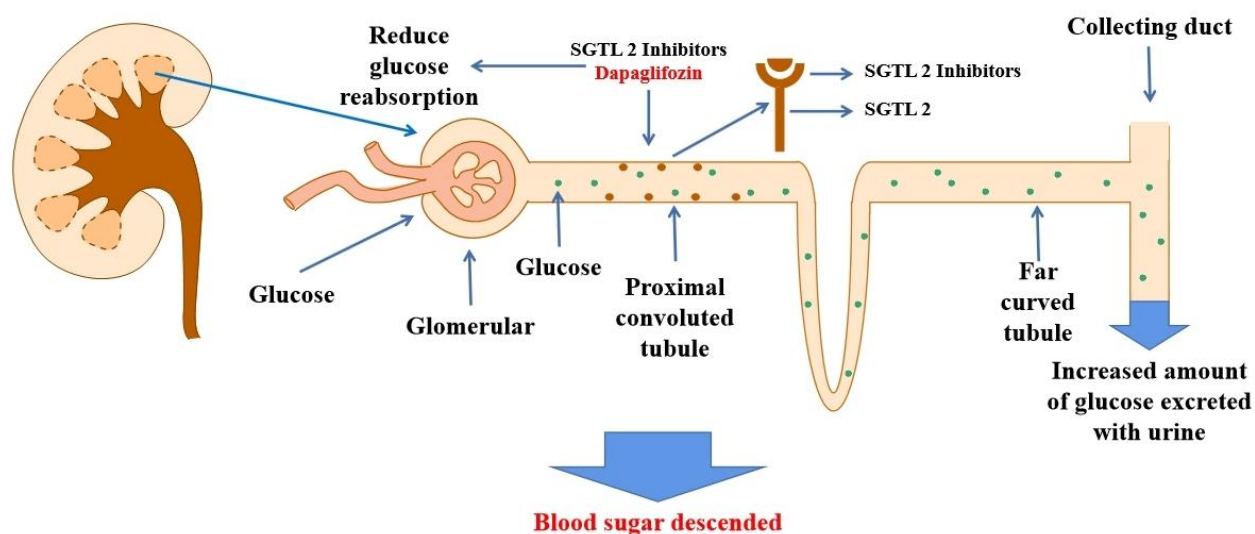


Fig. 27. Anti-tumor mechanism of telomerase inhibitor.<sup>[222]</sup>

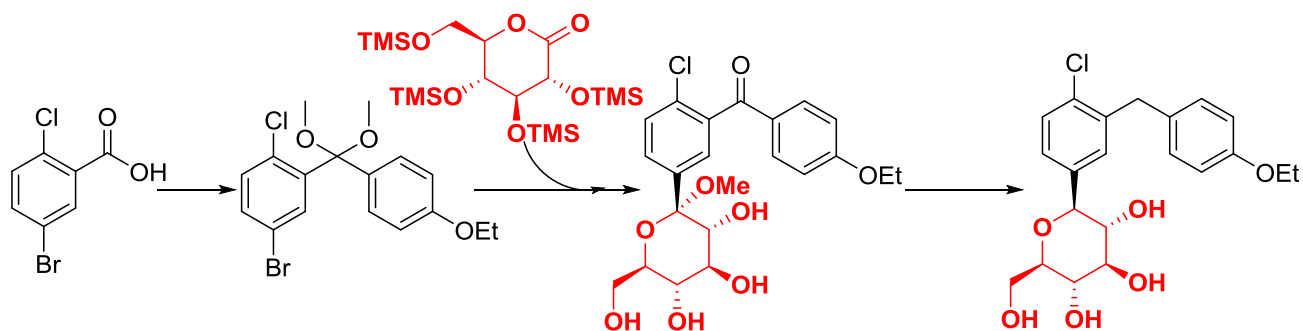
### 3.4 Hypoglycemic activity (antidiabetic)

The symptoms of higher blood glucose levels than normal due to defects in insulin secretion or ( and ) action and metabolic disorders of the three major nutrients<sup>[223]</sup> are called diabetes. Diabetes increases the risk of cardiovascular and cerebrovascular diseases while causing complications such as retinopathy, nephropathy and neuropathy.<sup>[224]</sup> Insulin replacement therapy for type 1 diabetes (T1D)<sup>[225]</sup> and sodium-glucose cotransporter 2 (SGLT2) inhibitor therapy for type 2 diabetes (T2D)<sup>[226]</sup> are two commonly used therapies, Type 2 diabetes is a common type.<sup>[227]</sup> Dapaglifozin (Forxiga®) is a C-glucoside drug approved by the European Union as a T2D therapeutic drug in 2014.<sup>[228-229]</sup> It is an efficient and reversible SGLT2 inhibitor, but its synthesis method has rarely been reported.<sup>[230-231]</sup> SGLT2 inhibitors reduce blood glucose levels by promoting glucose excretion, thereby inhibiting the repeated absorption of glucose (Fig. 28).<sup>[232]</sup>

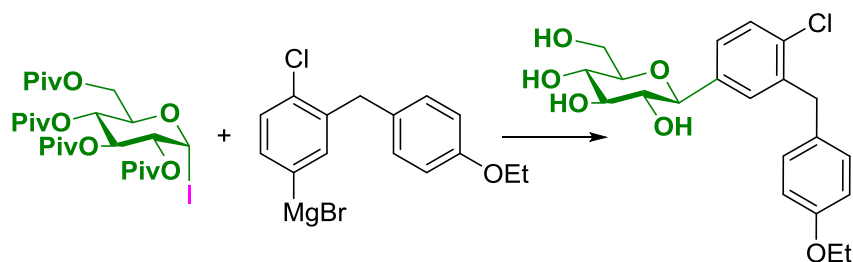


**Fig. 28.** The hypoglycemic mechanism of SGLT2 inhibitor Dapagliflozin.<sup>[233]</sup>

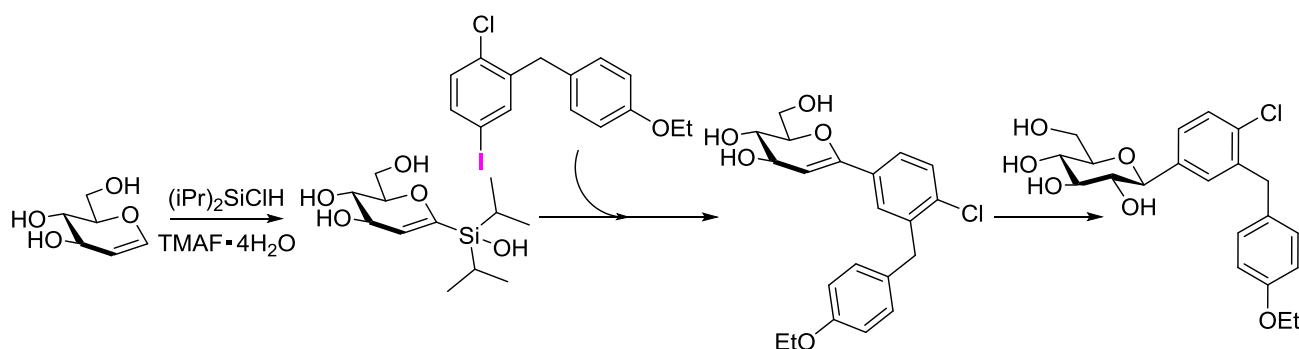
Using 5-bromo-2-chlorobenzoic acid and gluconolactone as starting materials, L. Hu et al. realized the green and simple synthesis of dapagliflozin in only 4 steps by one-pot method (Scheme 54).<sup>[234]</sup> V. V. Triantakonstanti et al. successfully synthesized dapagliflozin by selective synthesis of  $\beta$ -C-glycosides using  $\alpha$ -D-tetra-O-pivaloylglucosyl iodide as a glucosyl donor (Scheme 55).<sup>[235]</sup> Under mild conditions, K. Vaková et al. realized the Hiyama reaction of unprotected unprotected 1-diisopropylsilyl-D-glucal with iodo- or bromo- (hetero) arenes to synthesize (hetero) aryl C-glycosides under the catalysis of palladium (Scheme 56). On this basis, dapagliflozin was obtained by two-step method.<sup>[236]</sup> In the presence of copper chloride and DBU, R. Venkatesh et al. successfully synthesized the antidiabetic drug dapagliflozin analogues by the cross-coupling reaction of 1-thiosaccharose with aryl diazonium salts, followed by S-arylation to prepare S-aryl glucosinolates (Scheme 57).<sup>[237]</sup>



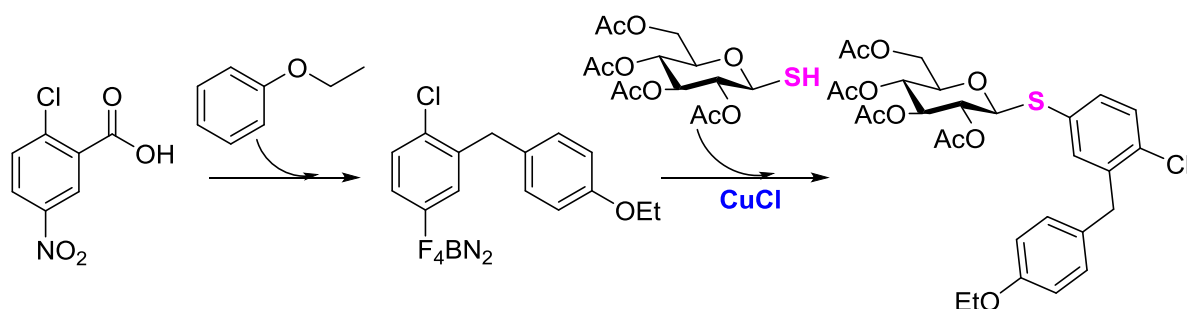
**Scheme 54.** synthesis of dapagliflozin.



**Scheme 55.** Synthesized dapagliflozin by selective synthesis of  $\beta$ -C-glucosides.



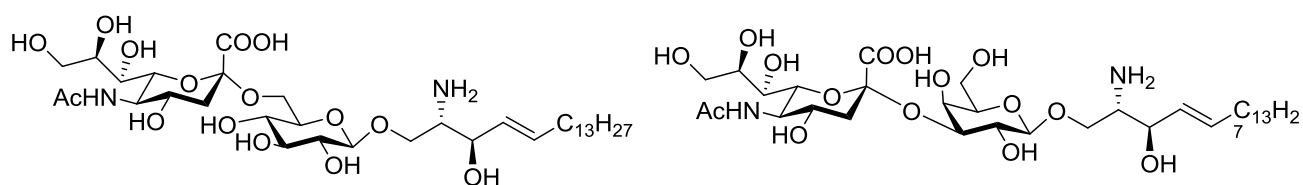
**Scheme 56.** Synthesized of dapagliflozin.



**Scheme 57.** Synthesized of S-aryl dapagliflozin analogues.

### 3.5 Other activities

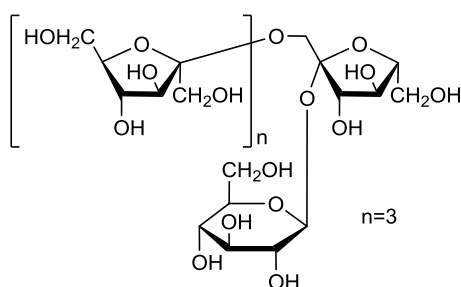
L. Zhang et al. used orthogonally protected trisaccharides as key building blocks to synthesize fucosylated chondroitin sulfate oligosaccharides through glycoside coupling, which selectively inhibited intrinsic tenase and exhibited potent anticoagulant activity, which can be developed anticoagulant or antithrombotic drugs.<sup>[238]</sup> C. Zheng et al. synthesized ganglioside GM3 analogs (Fig. 29) and used PC12 cells as a model to assess the effect of GM3 analogs on NGF-induced neurite outgrowth. Biological experiments have shown that GM3 analogs can induce neurite outgrowth, providing a valuable reference for potential nervous system therapy after injury.<sup>[208]</sup>



**Fig. 29.** Structures of two GM3 analogs.

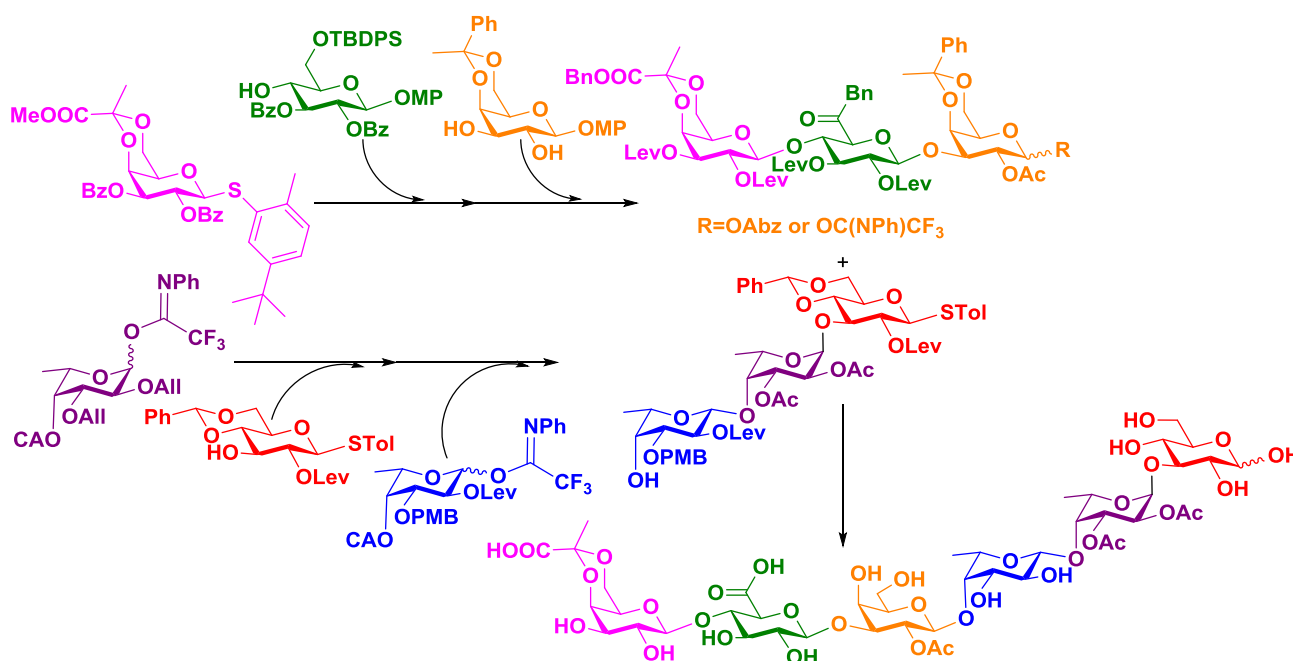
Obesity-related hypertension is a global medical challenge that greatly increases the risk of stroke, coronary heart disease and chronic renal failure. Its pathogenesis is mainly related to the kidneys and sympathetic nervous system. J. Peng et al. found that mice lacking the inhibitory immunoglobulin G (IgG) receptor Fc $\gamma$ RIIB were protected from high-fat diet (HFD)-induced obesity, which may cause blood pressure and other effects. Breaking the link between obesity and hypertension by supplementing the sialic acid precursor N-acetyl-mannosamine (ManNAC) could serve as a new way to prevent related diseases.<sup>[239]</sup>

Chitosan (COS) is a bioactive oligosaccharide with hepatoprotective effects.<sup>[240-241]</sup> P. Liu et al. used carbon tetrachloride (CCl<sub>4</sub>) to induce hepatic fibrosis in mice, which could be protected from hepatic fibrosis by oral administration of COS, and targeted hepatic macrophage polarization to regulate immune homeostasis to achieve hepatic fibrosis treatment, suggesting that COS may be an effective therapeutic measure for hepatic fibrosis.<sup>[242]</sup> Z. W. Zhang et al. revealed at the molecular level that *Morinda citrifolia* oligosaccharide (MOO) (Fig. 30) (pentasaccharide as the main active ingredient) can positively regulate the tryptophan  $\rightarrow$  5-hydroxytryptophan (5-HTP)  $\rightarrow$  5-hydroxytryptamine (5-HT) metabolic pathway in the intestinal flora (*Clostridium butyricum*, etc.). The enhanced level of tryptophan hydroxylase and the inhibition of 5-hydroxytryptophan decarboxylase activity in the intestinal flora. As a result, the level of 5-HTP increases and crosses the blood-brain barrier, using the metabolism of 5-HTP to increase the level of 5-HT in the brain, realizing the "intestine-brain" dialogue and achieving the purpose of antidepressant.<sup>[243]</sup>



**Fig. 30.** Structure of the main active component of MOO- the pentasaccharide.

Colonic acid (CA) is the main extracellular polysaccharide in *Enterobacteriaceae*,<sup>[244]</sup> and plays a crucial role in adaptation to the external environment.<sup>[245]</sup> CA has great potential in the food, cosmetic and healthcare industries.<sup>[246]</sup> Recent studies have found that CA has good anti-aging activity.<sup>[247-248]</sup> CA hexasaccharide repeating unit consists of D-galactose, L-fucose, D-glucose and D-galacturonic acid,<sup>[249]</sup> and is modified with three O-acetyl (Ac) and one pyruvate groups.<sup>[250]</sup> B. Yu's group was the first to use chemical methods to stereoselectively synthesize CA hexasaccharide (Scheme 58), providing the basis for further in-depth study of their biological activities.<sup>[251]</sup>



**Scheme 58.** Synthesis of CA hexasaccharide.

#### 4. Conclusion

Oligosaccharides are molecules that play an important role in life. The structures of oligosaccharides are complex and diverse. Obtaining homogeneous samples of oligosaccharides and glycoconjugates by chemical synthesis is the basis of oligosaccharide synthesis. Stereoselective construction of glycosidic bonds using C1 linking different types of leaving groups, C3-C6 and other linking distal auxiliary groups, construction of glycosidic bonds using metal/nonmetal catalysts, construction of more enzymatically resistant S-glycosides, automated glycan assembly method and the widely applied one-pot method have been widely used in the construction of 1,2-cis/trans glycosidic bonds. Homogeneous oligosaccharide molecules obtained by chemical synthesis methods and their glycoconjugates formed with proteins or lipids have promising biological activities in

anti-infective, anti-inflammatory, and antitumor fields. Using chemical methods to synthesize oligosaccharide molecules plays an important role in exploratory studies to understand biological glycosylation. At present, the stereoselective construction of different glycosidic bonds of oligosaccharides still has potential for development. There is still a huge space for the synthesis and development of existing oligosaccharide drugs. The structure-activity relationship of some oligosaccharide compounds in the field of medicinal chemistry still needs to be clarified.

## **Acknowledgements**

The authors acknowledge the “JUN-MA” High-level Talents Program of Inner Mongolia University (No. 21300-5195112, No. 21300-5205107), and the funding from the Science & Technology Department of Inner Mongolia Autonomous Region (No. 2021CG0029, No. 15000021T000000020229).

## **References**

- [1] C. Zhao, Y. Wu, X. Liu, B. Liu, H. Cao, H. Yu, S. D. Sarker, L. Nahar and J. Xiao, Functional properties, structural studies and chemo-enzymatic synthesis of oligosaccharides, *Trends in Food Science & Technology*, 66 (2017) 135-145.
- [2] S. I. Mussatto and I. M. Mancilha, Non-digestible oligosaccharides: A review, *Carbohydrate Polymers*, 68 (2007) 587-597.
- [3] A. Fallacara, E. Baldini, S. Manfredini and S. Vertuani, Hyaluronic acid in the third millennium, *Polymers*, 10 (2018) 701.
- [4] G. M. Miller and L. C. Hsieh-Wilson, Sugar-dependent modulation of neuronal development, regeneration, and plasticity by chondroitin sulfate proteoglycans, *Experimental Neurology*, 274 (2015) 115-125.
- [5] X. Zhai, C. Li, D. Ren, J. Wang, C. Ma and A. M. Abd El-Aty, The impact of chitooligosaccharides and their derivatives on the in vitro and in vivo antitumor activity: A comprehensive review, *Carbohydrate Polymers*, 266 (2021) 118132.
- [6] R. N. Tharanathan, Biodegradable films and composite coatings: past, present and future, *Trends in Food Science & Technology*, 14 (2003) 71-78.
- [7] L. Zhao, Z. Ma, J. Yin, G. Shi and Z. Ding, Biological strategies for oligo/polysaccharide synthesis: biocatalyst and microbial cell factory, *Carbohydrate Polymers*, 258 (2021) 117695.
- [8] L. Krasnova and C. H. Wong, Oligosaccharide synthesis and translational innovation, *Journal of the American Chemical Society*, 141(2019)3735-3754.
- [9] A. Varki, Biological roles of glycans, *Glycobiology*, 27 (2017) 3-49.

- [10] E. Rodriguez, S. T. T. Schettters and Y. van Kooyk, The tumour glyco-code as a novel immune checkpoint for immunotherapy, *Nature Reviews Immunology*, 18 (2018) 204-211.
- [11] J. Schmid, Recent insights in microbial exopolysaccharide biosynthesis and engineering strategies, *Current Opinion in Biotechnology*, 53 (2018) 130-136.
- [12] S. Patel and A. Goyal, Functional oligosaccharides: production, properties and applications, *World Journal of Microbiology and Biotechnology*, 27 (2011) 1119-1128.
- [13] T. Meyer, N. S. M. Miguel, D. E. R. Fernández and G. Ortiz, Biotechnological production of oligosaccharid-applications in the food industry, *Food Production and Industry*, 2 (2015) 25-78.
- [14] G. Singh, A. K. Verma and V. Kumar, Catalytic properties, functional attributes and industrial applications of beta-glucosidases, *3 Biotech*, 6 (2016) 3.
- [15] B. H. Li and X. S. Ye, Recent advances in glycan synthesis, *Current Opinion in Biotechnology*, 58 (2020) 20-27.
- [16] S. Wang, Y. Yang, Q. Zhu, G. Q. Lin and B. Yu, Chemical synthesis of polysaccharides, *Current Opinion in Biotechnology*, 69 (2022) 102154.
- [17] Y. Wu, D. C. Xiong, S. C. Chen, Y. S. Wang and X. S. Ye, Total synthesis of mycobacterial arabinogalactan containing 92 monosaccharide units, *Nature Communications*, 8 (2017) 14851.
- [18] P. O. Adero, H. Amarasekara, P. Wen, L. Bohe and D. Crich, The experimental evidence in support of glycosylation mechanisms at the S<sub>N</sub>1-S<sub>N</sub>2 interface, *Chemical Reviews*, 118 (2018) 8242-8284.
- [19] G. P. Singh, A. J. Watson and A. J. Fairbanks, Achiral 2-hydroxy protecting group for the stereocontrolled synthesis of 1,2-cis-alpha-glycosides by six-ring neighboring group participation, *Organic Letters*, 17 (2015) 4376-4379.
- [20] H. Shi, J. Yang, Y. Cheng, J. Yang, X. Lu and X. Ma, 1, 2-trans-stereoselective 7-O-glycosylation of flavonoids with unprotected pyranoses by Mitsunobu reaction, *Chemistry An Asian Journal*, 17 (2022) e202200120.
- [21] S. S. Nigudkar and A. V. Demchenko, Stereocontrolled 1,2-cis glycosylation as the driving force of progress in synthetic carbohydrate chemistry, *Chemical Science*, 6 (2015) 2687-2704.
- [22] R. R. Gadikota, C. S. Callam, T. Wagner, B. D. Fraino and T. L. Lowary, 2,3-anhydro sugars in glycoside bond synthesis. Highly stereoselective syntheses of oligosaccharides containing  $\alpha$ - and  $\beta$ -arabinofuranosyl linkages, *Journal of the American Chemical Society*, 125 (2003) 4155-4165.
- [23] J. H. Kim, H. Yang, G. J. Boons, Stereoselective glycosylation reactions with chiral auxiliaries, *Angewandte Chemie International Edition*, 28 (2005) 947-949.
- [24] G. Lian, X. Zhang and B. Yu, Thioglycosides in carbohydrate research, *Carbohydrate Research*, 403 (2015) 13-22.
- [25] J. D. Codee, R. E. Litjens, L. J. van den Bos, H. S. Overkleeft and G. A. van der Marel, Thioglycosides in sequential glycosylation strategies, *Chemical Society Reviews*, 34 (2005) 769-782.
- [26] X. Zhu and R. R. Schmidt, New principles for glycoside-bond formation, *Angewandte Chemie*



International Edition, 48 (2009) 1900-1934.

[27] G. Li, M. Noguchi, G. Arisaka, Y. Tanaka and S. Shoda, A protecting group-free approach for synthesizing C-glycosides through glycosyl dithiocarbamates, *Organic & Biomolecular Chemistry*, 19 (2021) 3134-3138.

[28] W. C. Zhao, R. P. Li, C. Ma, Q. Y. Liao, M. Wang and Z. T. He, Stereoselective gem-C, B-glycosylation via 1,2-boronate migration, *Journal of the American Chemical Society*, 144 (2022) 2460-2467.

[29] W. Huang, Y. Y. Zhou, X. L. Pan, X. Y. Zhou, J. C. Lei, D. M. Liu, Y. Chu and J. S. Yang, Stereodirecting effect of C5-carboxylate substituents on the glycosylation stereochemistry of 3-deoxy-d- manno-oct-2-ulosonic acid (Kdo) thioglycoside donors: stereoselective synthesis of alpha- and beta-Kdo glycosides, *Journal of the American Chemical Society*, 140 (2018) 3574-3582.

[30] Y. F. Wu and Y. F. Tsai, Assistance of the C-7,8-picoloyl moiety for directing the glycosyl acceptors into the alpha-orientation for the glycosylation of sialyl donors, *Organic Letters*, 19 (2017) 4171-4174.

[31] X. Liu, Y. Song, A. Liu, Y. Zhou, Q. Zhu, Y. Lin, H. Sun, K. Zhu, W. Liu, N. Ding, W. Xie, H. Sun, B. Yu, P. Xu and W. Li, More than a leaving group: N-Phenyltrifluoroacetimidate as a remote directing group for highly alpha-selective 1,2-cis glycosylation, *Angewandte Chemie International Edition*, (2022) e202201510.

[32] X. Liu, Y. Lin, Q. Sun, H. Sun, P. Xu, G. Li, Y. Song, W. Xie, H. Sun, B. Yu and W. Li, 2-Diphenylphosphinoyl-acetyl as a remote directing group for the highly stereoselective synthesis of beta-glycosides, *Chinese Journal of Chemistry*, 40 (2022) 443-452.

[33] C. Romano, H. Jiang, I. Boos and M. H. Clausen, S-glycosides: synthesis of S-linked arabinoxylan oligosaccharides, *Organic & Biomolecular Chemistry*, 18 (2020) 2696-2701.

[34] G. L. Zhang, M. R. Gadi, X. Cui, D. Liu, J. Zhang, V. Saikam, C. Gibbons, P. G. Wang and L. Li, Protecting-group-free S-glycosylation towards thioglycosides and thioglycopeptides in water, *Green Chemistry*, 23 (2021) 2907-2912.

[35] B. Yu, Gold(I)-catalyzed glycosylation with glycosyl O-alkynylbenzoates as donors, *Accounts of Chemical Research*, 51 (2018) 507-516.

[36] D. Zhu, M. Geng and B. Yu, Total synthesis of starfish cyclic steroid glycosides, *Angewandte Chemie International Edition*, 61 (2022) e202203239.

[37] J. Fu, P. Xu and B. Yu, Total synthesis of nucleoside antibiotics amicetin, plicacetin, and cytosaminomycin A-D, *Chinese Journal of Chemistry*, 39 (2021) 2679-2684.

[38] X. Zhang, Y. Yang, J. Ding, Y. Zhao, H. Zhang and Y. Zhu, Stereoselective gold(I)-catalyzed approach to the synthesis of complex alpha-glycosyl phosphosaccharides, *Nature Communications*, 13 (2022) 421.

[39] J. Li, M. Wang and X. Jiang, Diastereoselective synthesis of thioglycosides via Pd-catalyzed allylic rearrangement, *Organic Letters*, 23 (2021) 9053-9057.

[40] Q. Wang, M. Lai, H. Luo, K. Ren, J. Wang, N. Huang, Z. Deng, K. Zou and H. Yao,

Stereoselective O-glycosylation of glycals with arylboronic acids using air as the oxygen source, *Organic Letters*, 24 (2022) 1587-1592.

[41]M. Kumar, A. Gurawa, N. Kumar and S. Kashyap, Bismuth-catalyzed stereoselective 2-deoxyglycosylation of disarmed/armed glycal donors, *Organic Letters*, 24 (2022) 575-580.

[42]C. A. H. Jones and N. D. Schley, Selective demethylation of O-aryl glycosides by iridium-catalyzed hydrosilylation, *Chemical Communications*, 57 (2021) 5953-5956.

[43]Y. Sutar, M. Vangala and S. Hotha, Silver-assisted gold-catalyzed solid phase synthesis of linear and branched oligosaccharides, *Chemical Communications*, 58 (2022) 641-644.

[44]Q. Sun, H. Zhang, Q. Wang, T. Qiao, G. He and G. Chen, Stereoselective synthesis of C-vinyl glycosides via palladium-catalyzed C-H glycosylation of alkenes, *Angewandte Chemie International Edition*, 60 (2021) 19620-19625.

[45]Y. Li, Z. Wang, L. Li, X. Tian, F. Shao and C. Li, Chemoselective and diastereoselective synthesis of C-aryl nucleoside analogues by nickel-catalyzed cross-coupling of furanosyl acetates with aryl iodides, *Angewandte Chemie International Edition*, 61 (2022) e202110391.

[46]Y. An, B. S. Zhang, Y. N. Ding, Z. Zhang, X. Y. Gou, X. S. Li, X. Wang, Y. Li and Y. M. Liang, Palladium-catalyzed C-H glycosylation and retro Diels-Alder tandem reaction via structurally modified norbornadienes (smNBDs), *Chemical Science*, 12 (2021) 13144-13150.

[47]X. Y. Gou, Y. Li, W. Y. Shi, Y. Y. Luan, Y. N. Ding, Y. An, Y. C. Huang, B. S. Zhang, X. Y. Liu and Y. M. Liang, Ruthenium-catalyzed stereo- and site-selective ortho- and meta-C-H glycosylation and mechanistic studies, *Angewandte Chemie International Edition*, 61 (2022) e202205656.

[48]J. Wu, N. Kaplaneris, J. Pohlmann, T. Michiyuki, B. Yuan and L. Ackermann, Remote C-H glycosylation by ruthenium(II) catalysis: modular assembly of meta-C-aryl glycosides, *Angewandte Chemie International Edition*, 61 (2022) e202208620.

[49]S. Zhou, X. Zhong, A. Guo, Q. Xiao, J. Ao, W. Zhu, H. Cai, A. Ishiwata, Y. Ito, X. W. Liu and F. Ding, ZnI<sub>2</sub>-directed stereocontrolled alpha-glucosylation, *Organic Letters*, 23 (2021) 6841-6845.

[50]X. Zhong, S. Zhou, J. Ao, A. Guo, Q. Xiao, Y. Huang, W. Zhu, H. Cai, A. Ishiwata, Y. Ito, X. W. Liu and F. Ding, Zinc(II) iodide-directed beta-mannosylation: reaction selectivity, mode, and application, *The Journal of Organic Chemistry*, 86 (2021)16901-16915.

[51]S. Zhou, J. Ao, A. Guo, X. Zhao, N. Deng, G. Wang, Q. Yang, A. Ishiwata, X. W. Liu, Q. Li, H. Cai and F. Ding, ZnI<sub>2</sub>-mediated beta-galactosylation of C2-ether-type donor, *Organic Letters*, 24 (2022) 8025-8030.

[52]P. Wen, P. Jia, Q. Fan, B. J. McCarty and W. Tang, Streamlined iterative assembly of thio-oligosaccharides by aqueous S-glycosylation of diverse deoxythio sugars, *Chemistry and Sustainable Chemistry*, 15 (2022) e202102483.

[53]T. Li, T. Li, H. Zhuang, F. Wang, R. R. Schmidt and P. Peng, O-glycosyl trichloroacetimidates as glycosyl donors and platinum(IV) chloride as a dual catalyst permitting stereo- and regioselective glycosidations, *American Chemical Society Catalysis*, 11 (2021) 10279-10287.

[54]K. A. D'Angelo and M. S. Taylor, Borinic acid catalyzed stereo- and regioselective couplings of

- glycosyl methanesulfonates, *Journal of the American Chemical Society*, 138 (2016) 11058-11066.
- [55]D. Takahashi, M. Tanaka, N. Nishi and K. Toshima, Novel 1,2-cis-stereoselective glycosylations utilizing organoboron reagents and their application to natural products and complex oligosaccharide synthesis, *Carbohydrate Research*, 452 (2017) 64-77.
- [56]S. Li, Y. Wang, L. Zhong, S. Wang, Z. Liu, Y. Dai, Y. He and Z. Feng, Boron-promoted umpolung reaction of sulfonyl chlorides for the stereospecific synthesis of thioglycosides via reductive deoxygenation coupling reactions, *Organic Letters*, 24 (2022) 2463-2468.
- [57]Z. Qiao, P. Wang, J. Ni, D. Li, Y. Sun, T. Li and M. Li, Triflic imide-catalyzed glycosylation of disarmed glycosyl ortho-isopropenylphenylacetates and ortho-isopropenylbenzyl thioglycosides, *European Journal of Organic Chemistry*, 2 (2022) e202101367.
- [58]K. M. Liu, P. Y. Wang, Z. Y. Guo, D. C. Xiong, X. J. Qin, M. Liu, M. Liu, W. Y. Xue and X. S. Ye, Iterative synthesis of 2-deoxyoligosaccharides enabled by stereoselective visible-light-promoted glycosylation, *Angewandte Chemie International Edition*, 61 (2022) e202114726.
- [59]Q. Li, S. M. Levi, C. Wagen, A. E. Wendlandt and E. N. Jacobsen, Site-selective, stereocontrolled glycosylation of minimally protected sugars, *Nature*, 608 (2022) 74-79.
- [60]H. Li, K. C. Yu, J. K. Su, W. Ouyang, N. L. Fan and X. G. Hu, Photo-mediated synthesis of 1,2-dideoxy-2-phosphinylated carbohydrates from glycals: the reduction of glycosyl radicals to glycosyl anions, *Green Chemistry*, 24 (2022) 8280-8291.
- [61]Y. Wei, Q. Wang and M. J. Koh, A photoinduced, nickel-catalyzed reaction for the stereoselective assembly of C-linked glycosides and glycopeptides, *Angewandte Chemie International Edition*, (2022) e202214247.
- [62]Q. Wang, B. C. Lee, T. J. Tan, Y. Jiang, W. H. Ser and M. J. Koh, Visible light activation enables desulfonylative cross-coupling of glycosyl sulfones, *Nature Synthesis*, (2022).
- [63]D. Xie, Y. Wang, X. Zhang, Z. Fu and D. Niu, Alkyl/glycosyl sulfoxides as radical precursors and their use in the synthesis of pyridine derivatives, *Angewandte Chemie International Edition*, 61 (2022) e202204922.
- [64]L. Xia, M. Jin, Y. Jiao and S. Yu, Synthesis of C-alkynyl glycosides by photoredox-catalyzed reductive coupling of alkynyl bromides with glycosyl bromides, *Organic Letters*, 24 (2022) 364-368.
- [65]C. Zhang, H. Zuo, G. Y. Lee, Y. Zou, Q. D. Dang, K. N. Houk and D. Niu, Halogen-bond-assisted radical activation of glycosyl donors enables mild and stereoconvergent 1, 2-cis-glycosylation, *Nature Chemistry*, 14 (2022) 686-694.
- [66]S. S. Kulkarni, C. C. Wang, N. M. Sabbavarapu, A. R. Podilapu, P. H. Liao and S. C. Hung, "One-pot" protection, glycosylation, and protection-glycosylation strategies of carbohydrates, *Chemical Reviews*, 118 (2018) 8025-8104.
- [67]M. Panza, S. G. Pistorio, K. J. Stine and A. V. Demchenko, Automated chemical oligosaccharide synthesis: novel approach to traditional challenges, *Chemical Reviews*, 118 (2018) 8105-8150.
- [68]R. Liu, Q. Hua, Q. Lou, J. Wang, X. Li, Z. Ma and Y. Yang, NIS/TMSOTf-promoted glycosidation of glycosyl ortho-hexynylbenzoates for versatile synthesis of O-glycosides and

nucleosides, *The Journal of Organic Chemistry*, 86 (2021) 4763-4778.

[69]Z. Zhang, I. R. Ollmann, X. S. Ye, R. Wischnat, T. Baasov and C. H. Wong, Programmable one-pot oligosaccharide synthesis, *Journal of the American Chemical Society*, 121 (1999) 734-753.

[70]C. W. Cheng, Y. Zhou, W. H. Pan, S. Dey, C. Y. Wu, W. L. Hsu and C. H. Wong, Hierarchical and programmable one-pot synthesis of oligosaccharides, *Nature Communications*, 9 (2018) 5202.

[71]Y. C. Ko, C. F. Tsai, C. C. Wang, V. M. Dhurandhare, P. L. Hu, T. Y. Su, L. S. Lico, M. M. Zulueta and S. C. Hung, Microwave-assisted one-pot synthesis of 1,6-anhydrosugars and orthogonally protected thioglycosides, *Journal of the American Chemical Society*, 136 (2014) 14425-14431.

[72]A. Das and N. Jayaraman, Carbon tetrachloride-free allylic halogenation-mediated glycosylations of allyl glycosides, *Organic Biomolecular Chemistry*, 19 (2021) 9318-9325.

[73]C. Mc Carthy and X. Zhu, Chemoselective activation of ethyl vs. phenyl thioglycosides: one-pot synthesis of oligosaccharides, *Organic Biomolecular Chemistry*, 18 (2020) 9029-9034.

[74]H. He, L. Xu, R. Sun, Y. Zhang, Y. Huang, Z. Chen, P. Li, R. Yang and G. Xiao, An orthogonal and reactivity-based one-pot glycosylation strategy for both glycan and nucleoside synthesis: access to TMG-chitotriomycin, lipochitooligosaccharides and capuramycin, *Chemical Science*, 12 (2021) 5143-5151.

[75]Y. S. Wang, Y. Wu, D. C. Xiong and X. S. Ye, Total synthesis of a hyperbranched N-Linked hexasaccharide attached to ATCV-1 major capsid protein without precedent, *Chinese Journal of Chemistry*, 37 (2018) 42-48.

[76]A. P. Vargas, M. Delbianco and P. H. Seeberger, Automated glycan assembly as an enabling technology, *Current Opinion in Chemical Biology*, 46 (2018) 48-55.

[77]H. S. Hahm, M. Hurevich and P. H. Seeberger, Automated assembly of oligosaccharides containing multiple cis-glycosidic linkages, *Nature Communications*, 7 (2016) 12482.

[78]H. S. Hahm, M. K. Schlegel, M. Hurevich, S. Eller, F. Schuhmacher, J. Hofmann, K. Pagel and P. H. Seeberger, Automated glycan assembly using the Glycoconer 2.1 synthesizer, *Proceedings of the National Academy of Sciences of the United States of America*, 114 (2017) E3385-E3389.

[79]D. Grunhaus, A. Friedler and M. Hurevich, Automated synthesis of heavily phosphorylated peptides, *European Journal of Organic Chemistry*, 2021 (2021) 3737-3742.

[80]D. Budhadev, K. Saxby, J. Walton, G. Davies, P. C. Tyler, R. Schwörer and M. A. Fascione, Using automated glycan assembly (AGA) for the practical synthesis of heparan sulfate oligosaccharide precursors, *Organic Biomolecular Chemistry*, 17 (2019) 1817-1821.

[81]B. Ernst and J. L. Magnani, From carbohydrate leads to glycomimetic drugs, *Nature Reviews Drug Discovery*, 8 (2009) 661-677.

[82]K. L. M. Hoang, A. P. Vargas, Y. Zhu, Y. Yu, M. Loria, M. Delbianco and P. H. Seeberger, Traceless photolabile linker expedites the chemical synthesis of complex oligosaccharides by automated glycan assembly, *Journal of the American Chemical Society*, 141 (2019) 9079-9086.

[83]J. Jung, L. Kaiser, H. P. Deigner and M. S. Schmidt, Continuous synthesis of bromoalkyl

- glycosides by Fischer glycosylation in a microreactor, *Journal of Flow Chemistry*, 12 (2022) 9-15.
- [84] W. Yao, D. C. Xiong, Y. Yang, C. Geng, Z. Cong, F. Li, B. H. Li, X. Qin, L. N. Wang, W. Y. Xue, N. Yu, H. Zhang, X. Wu, M. Liu and X. S. Ye, Automated solution-phase multiplicative synthesis of complex glycans up to a 1,080-mer, *Nature Synthesis*, 1 (2022) 854-863.
- [85] R. A. Hughes and A. D. Ellington, Synthetic DNA synthesis and assembly: putting the synthetic in synthetic biology, *Cold Spring Harbor Perspectives in Biology*, 9 (2017).
- [86] H. Sun and A. Brik, The journey for the total chemical synthesis of a 53 kDa protein, *Accounts of Chemical Research*, 52 (2019) 3361-3371.
- [87] H. Jiang, X. Qin, Q. Wang, Q. Xu, J. Wang, Y. Wu, W. Chen, C. Wang, T. Zhang, D. Xing and R. Zhang, Application of carbohydrates in approved small molecule drugs: a review, *European Journal of Medicinal Chemistry*, 223 (2021) 113633.
- [88] G. Mulvey, P. I. Kitov, P. Marcato, D. R. Bundle and G. D. Armstrong, Glycan mimicry as a basis for novel anti-infective drugs, *Current Opinion in Drug Discovery & Development*, 83 (2001) 841-847.
- [89] W. Zhou, H. Jiang, L. Wang, X. Liang and X. Mao, Biotechnological production of 2'-fucosyllactose: a prevalent fucosylated human milk oligosaccharide, *American Chemical Society Synthetic Biology*, 10 (2021) 447-458.
- [90] Z. Pakulski, F. Poly, N. Dorabawila, P. Guerry and M. A. Monteiro, ChemInform abstract: 6-deoxyheptoses in nature, chemistry, and medicine, *Current Organic Chemistry*, 18 (2014) 1818-1845.
- [91] Y. J. Jeon, P. J. Park and S. K. Kim, Antimicrobial effect of chitooligosaccharides produced by bioreactor, *Carbohydrate Polymers*, 44 (2001) 71-76.
- [92] Y. E. Tsvetkov, E. Paulovicova, L. Paulovicova, P. Farkas and N. E. Nifantiev, Synthesis of biotin-tagged chitosan oligosaccharides and assessment of their immunomodulatory activity, *Frontiers in Chemistry*, 8 (2020) 554732.
- [93] L. Yue, M. Wang, I. M. Khan, S. Niazi, B. Wang, X. Ma, Z. Wang and W. Xia, Preparation and characterization of chitosan oligosaccharide derivatives containing cinnamyl moieties with enhanced antibacterial activities, *Food Science and Technology*, 147 (2021) 111663.
- [94] J. P. Yasomanee, S. Visansirikul, P. Pornsuriyasak, M. Thompson, S. A. Kolodziej and A. V. Demchenko, Synthesis of the repeating unit of capsular polysaccharide staphylococcus aureus type 5 to study chemical activation and conjugation of native CP5, *The Journal of Organic Chemistry*, 81 (2016) 5981-5987.
- [95] B. Hagen, J. H. M. van Dijk, Q. Zhang, H. S. Overkleeft, G. A. van der Marel and J. D. C. Codee, Synthesis of the Staphylococcus aureus strain M capsular polysaccharide repeating unit, *Organic Letters*, 19 (2017) 2514-2517.
- [96] Y. Toyama, K. Hisata, Y. Kasa, S. Nakano, M. Komatsu, T. Shimizu, Molecular epidemiology of methicillin-sensitive Staphylococcus aureus in the neonatal intensive care unit, *Journal of Hospital Infection*, 129 (2022) 75-81.

- [97] S. Visansirikul, S. A. Kolodziej and A. V. Demchenko, Synthesis of D-FucNAc-D-ManNAcA Disaccharides Based On the Capsular Polysaccharides Staphylococcus aureus Type 5 and 8, *The Journal of Organic Chemistry*, 84 (2019) 216-227.
- [98] N. Tien, C. Y. Ho, S. J. Lai, Y. C. Lin, C. S. Yang, Y. C. Wang, W. C. Huang, Y. Chen and J. J. Chang, Crystal structure of the capsular polysaccharide-synthesis enzyme CapG from Staphylococcus aureus, *Acta Crystallographica Section F-Structural Biology Communications*, 78 (2022) 378-385.
- [99] S. Visansirikul, S. A. Kolodziej and A. V. Demchenko, Staphylococcus aureus capsular polysaccharides: a structural and synthetic perspective, *Organic & Biomolecular Chemistry*, 18 (2020) 783-798.
- [100] A. Behera, D. Rai and S. S. Kulkarni, Total syntheses of conjugation-ready trisaccharide repeating units of pseudomonas aeruginosa O11 and staphylococcus aureus type 5 capsular polysaccharide for vaccine development, *Journal of the American Chemical Society*, 142 (2020) 456-467.
- [101] M. Zhao, C. Qin, L. Li, H. Xie, B. Ma, Z. Zhou, J. Yin and J. Hu, Conjugation of synthetic trisaccharide of Staphylococcus aureus type 8 capsular polysaccharide elicits antibodies recognizing intact bacterium, *Frontiers in Chemistry*, 8 (2020) 258.
- [102] S. Ali, A. Hendriks, R. van Dalen, T. Bruyning, N. Meeuwenoord, H. S. Overkleeft, D. V. Filippov, G. A. van der Marel, N. M. van Sorge and J. D. C. Codee, (Automated) Synthesis of well-defined Staphylococcus aureus wall teichoic acid fragments, *Chemistry - A European Journal*, 27 (2021) 10461-10469.
- [103] P. Shen, H. Lin, Y. Bao, H. Hong and Z. Wu, Synthesis and immunological study of a glycosylated wall teichoic acid-based vaccine against Staphylococcus aureus, *Chinese Chemical Letters*, (2022).
- [104] I. Khan, L. H. Wieler, F. Melzer, M. C. Elschner, G. Muhammad, S. Ali, L. D. Sprague, H. Neubauer and M. Saqib, Glanders in animals: a review on epidemiology, clinical presentation, diagnosis and countermeasures, *Transboundary and Emerging Diseases*, 60 (2013) 204-221.
- [105] E. M. Meumann, A. C. Cheng, L. Ward and B. J. Currie, Clinical features and epidemiology of melioidosis pneumonia: results from a 21-year study and review of the literature, *Clinical Infectious Diseases*, 54 (2012) 62-369.
- [106] C. Jones, Vaccines based on the cell surface carbohydrates of pathogenic bacteria, *Anais da Academia Brasileira de Ciências*, 77 (2005) 293-324.
- [107] R. D. Astronomo and D. R. Burton, Carbohydrate vaccines: developing sweet solutions to sticky situations? *Nature Reviews Drug Discovery*, 9 (2010) 308-324.
- [108] Y. Chen, Z. Wu, X. Li, Y. Hu and Y. Yang, Promoter-assisted stereoselective synthesis of the 6-deoxy-beta-d-manno-heptopyranose oligosaccharides, *Organic Letters*, 23 (2021) 3216-3220.
- [109] M. N. Burtnick, C. Heiss, R. A. Roberts, H. P. Schweizer, P. Azadi and P. J. Brett, Development of capsular polysaccharide-based glycoconjugates for immunization against

- melioidosis and glanders, *Frontiers in Cellular and Infection Microbiology*, 2 (2012) 108.
- [110] A. E. Scott, M. N. Burtnick, M. G. Stokes, A. O. Whelan, E. D. Williamson, T. P. Atkins, J. L. Prior and P. J. Brett, *Burkholderia pseudomallei* capsular polysaccharide conjugates provide protection against acute melioidosis, *Infection and Immunity*, 82 (2014) 3206-3213.
- [111] C. Maude, M. Kevin, R. Gokulakrishnan and G. Charles, Polysaccharides from *Burkholderia* species as targets for vaccine development, immunomodulation and chemical synthesis, *Natural Product Reports*, 35 (2018) 1251-1293.
- [112] X. Geng, G. Wang, Z. Guo and G. Gu, Synthesis of the oligosaccharides of *Burkholderia pseudomallei* and *B. mallei* capsular polysaccharide and preliminary immunological studies of their protein conjugates, *The Journal of Organic Chemistry*, 85 (2020) 2369-2384.
- [113] P. Shit and A. K. Misra, Synthesis of the pentasaccharide repeating unit corresponding to the capsular polysaccharide of *Escherichia coli* O20:K83:H26, *Tetrahedron*, 122 (2022) 132948.
- [114] N. Nishi, K. Seki, D. Takahashi and K. Toshima, Innenrücktitelbild: synthesis of a pentasaccharide repeating unit of lipopolysaccharide derived from virulent *E. coli* O1 and identification of a glycotope candidate of avian pathogenic *E. coli* O1, *Angewandte Chemie International Edition in English*, 60 (2021) 1789-1796.
- [115] M. Kundu, A. Guchait and A. K. Misra, Synthesis of the pentasaccharide repeating unit of the O-antigenic polysaccharide of enteroaggregative *Escherichia coli* O44:H18 strain, *Tetrahedron*, 91 (2021) 132245.
- [116] S. K. Jana, P. Shit and A. K. Misra, Straightforward synthesis of the pentasaccharide repeating unit of the O-antigenic polysaccharide from the enteropathogenic *Escherichia coli* O142, *Synthesis*, 54 (2022) A-F.
- [117] N. R. Salama, M. L. Hartung and A. Muller, Life in the human stomach: persistence strategies of the bacterial pathogen *Helicobacter pylori*, *Nature Reviews Microbiology*, 11 (2013) 385-399.
- [118] J. G. Kusters, A. H. van Vliet and E. J. Kuipers, Pathogenesis of *Helicobacter pylori* infection, *Clinical Microbiology Reviews*, 19 (2006) 449-490.
- [119] B. J. Marshall and H. M. Windsor, The relation of *Helicobacter pylori* to gastric adenocarcinoma and lymphoma: pathophysiology, epidemiology, screening, clinical presentation, treatment, and prevention, *The Medical Clinics of North America*, 89 (2005) 313-344.
- [120] C. Wang, Y. Yuan and R. H. Hunt, The association between *Helicobacter pylori* infection and early gastric cancer: a meta-analysis, *American Journal of Gastroenterology*, 102 (2007) 1789-1798.
- [121] G. Ayala, W. I. Escobedo-Hinojosa, C. F. de la Cruz-Herrera and I. Romero, Exploring alternative treatments for *Helicobacter pylori* infection, *World Journal of Gastroenterology*, 20 (2014) 1450-1469.
- [122] E. Altman, V. Chandan, B. A. Harrison, M. Schur, M. F. Goneau, J. Li and M. Gilbert, Chemoenzymatic synthesis of an alpha-1,6-glucan-based conjugate vaccine against *Helicobacter*

pylori, *Glycobiology*, 32 (2022) 691-700.

[123] D. Esmaeilli, A. M. Mobarez, A. H. Salmanian and A. Z. Hosseini, Bioactivity and immunological evaluation of LPS from different serotypes of *Helicobacter pylori*, *Iranian Journal of Microbiology* 5 (2013) 142-146.

[124] M. A. Monteiro, S. Britton, L. A. Applebee and S. Baqar, Synthesis and immunogenicity of a *Helicobacter pylori* lipopolysaccharide-based conjugate, *Vaccine*, 29 (2011) 3098-3102.

[125] X. Zou, C. Qin, C. L. Pereira, G. Tian, J. Hu, P. H. Seeberger and J. Yin, Synergistic glycosylation as key to the chemical synthesis of an outer core octasaccharide of *Helicobacter pylori*, *Chemistry - A European Journal*, 24 (2018) 2868-2872.

[126] G. Tian, C. Qin, Z. Liu, D. Shen, X. Zou, J. Fu, J. Hu, P. H. Seeberger and J. Yin, Total synthesis of the *Helicobacter pylori* serotype O2 O-antigen  $\alpha$ -(1 $\rightarrow$ 2)- and  $\alpha$ -(1 $\rightarrow$ 3)-linked oligoglucosides, *Chemical Communication*, 56 (2020) 344-347.

[127] G. Tian, J. Hu, C. Qin, L. Li, X. Zou, J. Cai, P. H. Seeberger and J. Yin, Chemical synthesis and immunological evaluation of *Helicobacter pylori* serotype O6 tridecasaccharide O-antigen containing a DD-heptoglycan, *Angewandte Chemie International Edition*, 59 (2020) 13362-13370.

[128] J. A. Ferreira, L. Silva, M. A. Monteiro and M. A. Coimbra, *Helicobacter pylori* cell-surface glycans structural features: role in gastric colonization, pathogenesis, and carbohydrate-based vaccines, *Carbohydrate Chemistry*, 37 (2012) 160-193.

[129] X. Zou, J. Hu, M. Zhao, C. Qin, Y. Zhu, G. Tian, J. Cai, P. H. Seeberger and J. Yin, Chemical synthesis of the highly sterically hindered core undecasaccharide of *Helicobacter pylori* lipopolysaccharide for antigenicity evaluation with human serum, *Journal of the American Chemical Society*, 144 (2022) 14535-14547.

[130] J. N. Pendleton, S. P. Gorman and B. F. Gilmore, Clinical relevance of the ESKAPE pathogens, *Expert Review of Anti-infective Therapy*, 11 (2013) 297-308.

[131] D. A. Argunov, A. S. Trostianetskaia, V. B. Krylov, E. A. Kurbatova and N. E. Nifantiev, Convergent synthesis of oligosaccharides structurally related to galactan I and galactan II of *Klebsiella pneumoniae* and their use in screening of antibody specificity, *European Journal of Organic Chemistry*, 26 (2019) 4226-4232.

[132] P. Shit, S. Sahaji and A. K. Misra, Convergent synthesis of the hexasaccharide repeating unit of the capsular polysaccharide of *Klebsiella* serotype K-34, *Tetrahedron*, 129 (2022) 133159.

[133] C. Fall, O. Sow, F. P. Ly, B. Diop, B. S. Ba and Y. Dieye, An extensively drug resistant *Acinetobacter baumannii* from soft tissue isolated in a hospital in senegal, *Case Reports in Clinical Medicine*, 11 (2022) 72-78.

[134] X. Y. Zhou, L. X. Li, Z. Zhang, S. C. Duan, Y. W. Huang, Y. Y. Luo, X. D. Mu, Z. W. Chen, Y. Qin, J. Hu, J. Yin and J. S. Yang, Chemical synthesis and antigenic evaluation of inner core oligosaccharides from *Acinetobacter baumannii* lipopolysaccharide, *Angewandte Chemie International Edition*, 61 (2022) e202204420.

[135] G. Kumar, R. Narayan and S. Kapoor, Chemical tools for illumination of tuberculosis



biology, virulence mechanisms and diagnosis, *Journal of Medicinal Chemistry*, 63 (2020) 15308-15332.

[136] S. Y. Zhao, N. Li, W. Y. Luo, N. N. Zhang, R. Y. Zhou, C. Y. Li and J. Wang, Retraction: chemical synthesis and antigenic activity of a phosphatidylinositol mannoside epitope from *Mycobacterium tuberculosis*, *Chemical Communications*, 57 (2021) 5985.

[137] M. Joe, D. Sun, H. Tana, G. C. Complete and J. E. Croudace, The 5-deoxy-5-methylthio-xylofuranose residue in mycobacterial lipoarabinomannan. absolute stereochemistry, linkage position, conformation, and immunomodulatory activity, *Journal of the American Chemical Society*, 128 (2006) 5059-5072.

[138] A. Hoelemann, B. L. Stocker and P. H. Seeberger, Synthesis of a core arabinomannan oligosaccharide of *Mycobacterium tuberculosis*, *Journal of Organic Chemistry*, 71 (2006) 8071-8088.

[139] A. Lee, S. W. Wu, M. S. Scherman, J. B. Torrelles, D. Chatterjee, M. R. Mcneil and K. H. Khoo, Sequencing of oligoarabinosyl units released from mycobacterial arabinogalactan by endogenous arabinanase: identification of distinctive and novel structural motifs, *Biochemistry*, 45 (2006) 15817-15828.

[140] Z. Li, C. Zheng, M. Terreni, T. Bavaro, M. Sollogoub and Y. Zhang, A concise synthesis of oligosaccharides derived from Lipoarabinomannan (LAM) with glycosyl donors having a nonparticipating group at C2, *European Journal of Organic Chemistry*, 14 (2020) 2033-2044.

[141] S. Chutipongtanate, A. L. Morrow and D. S. Newburg, Human milk oligosaccharides: potential applications in COVID-19, *Biomedicines*, 10 (2022).

[142] C. Huang, Y. Wang, X. Li, L. Ren, J. Zhao, Y. Hu, L. Zhang, G. Fan, J. Xu, X. Gu, Z. Cheng, T. Yu, J. Xia, Y. Wei, W. Wu, X. Xie, W. Yin, H. Li, M. Liu, Y. Xiao, H. Gao, L. Guo, J. Xie, G. Wang, R. Jiang, Z. Gao, Q. Jin, J. Wang and B. Cao, Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China, *Lancet*, 395 (2020) 497-506.

[143] D. V. Parums, Editorial: current status of oral antiviral drug treatments for SARS-CoV-2 infection in non-hospitalized patients, *Medical Science Monitor*, 28 (2022) 1-4.

[144] S. Drożdżal, J. Rosik, K. Lechowicz, F. Machaj, B. Szostak, J. Przybyciński, S. Lorzadeh, K. Kotfis, S. Ghavami and M. J. Łos, An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment, *Drug Resistance Updates*, 59 (2021) 100794.

[145] N. Jaber, M. Al-Remawi, F. Al-Akayleh, N. Al-Muhtaseb, I. S. I. Al-Adham and P. J. Collier, A review of the antiviral activity of chitosan, including patented applications and its potential use against COVID-19, *The Society for Applied Microbiology*, 132 (2022) 41-58.

[146] D. Jang, D. Lee, Y. C. Shin, J. S. Lee, J. Jung and S. Ryoo, Low molecular weight chitooligosaccharide inhibits infection of SARS-CoV-2 in vitro, *The Society for Applied Microbiology*, 00 (2022) 1-10.

[147] H. Hamada, H. Hamada, K. Shimoda, A. Kuboki, T. Iwaki, Y. Kiriake and K. Ishihara, Resveratrol oligosaccharides (gluco-oligosaccharides) effectively inhibit SARS-CoV-2 infection: glycoside (polysaccharide) approach for Treatment of COVID-19, 16 (2021) 1-3.

- [148] T. M. Uyeki, D. S. Hui, M. Zambon, D. E. Wentworth and A. S. Monto, *Influenza, The Lancet*, 400 (2022) 693-706.
- [149] C. C. Wang, S. S. Kulkarni, M. M. Zulueta and S. C. Hung, *Synthesis of hemagglutinin-binding trisaccharides*, *Advances in Experimental Medicine and Biology*, 705 (2011) 691-726.
- [150] K.L. Prachanronarong, A. S. Canale, P. Liu, M. Somasundaran, S. Hou, Y. P. Poh, T. Han, Q. Zhu, N. Renzette, K. B. Zeldovich, T. F. Kowalik, N. Kurt-Yilmaz, J. D. Jensen, D. N. A. Bolon, W. A. Marasco, R. W. Finberg, C. A. Schiffer and J. P. Wang, *Mutations in Influenza A Virus neuraminidase and hemagglutinin confer resistance against a broadly neutralizing hemagglutinin stem antibody*, *Journal of Virology*, 93 (2019).
- [151] E.M. Abdelwhab, J. Veits and T. C. Mettenleiter, *Biological fitness and natural selection of amantadine resistant variants of avian influenza H5N1 viruses*, *Virus Research*, 228 (2017) 109-113.
- [152] L.M. Alame, E. Massaad and H. Zaraket, *Peramivir: A novel intravenous neuraminidase inhibitor for treatment of acute influenza infections*, *Frontiers in Microbiology*, 7 (2016) 450.
- [153] K. Shiraki and T. Daikoku, *Favipiravir, an anti-influenza drug against life-threatening RNA virus infections*, *Pharmacology & Therapeutics*, 209 (2020) 107512.
- [154] R. M. Pielak and J. J. Chou, *Influenza M2 proton channels*, *Biochimica et Biophysica Acta*, 1808 (2011) 522-529.
- [155] L. Gubareva and T. Mohan, *Antivirals targeting the neuraminidase*, *Cold Spring Harbor Perspectives Medicine*, 12 (2022) a038455.
- [156] O. Kutkat, A. Kandeil, Y. Moatasim, Y. A. M. M. Elshaier, W. A. El-Sayed, S. T. Gaballah, A. El Taweel, M. N. Kamel, M. El Sayes, M. A. Ramadan, R. El-Shesheny, F. M. E. Abdel-Megeid, R. Webby, G. Kayali and M. A. Ali, *In vitro and in vivo antiviral studies of new heteroannulated 1,2,3-triazole glycosides targeting the neuraminidase of influenza A viruses*, *Pharmaceuticals*, 15 (2022) 351.
- [157] S. M. Mohamed, S. A. Ross and M. A. M. Ahmed, *Diverse glycosides from gardenia iatifolia with antiviral activity and chemosystematic significance*, *Revista Brasileira de Farmacognosia*, 32 (2022) 1038-1041.
- [158] A. Roy, S. Byrne, N. K. Sarangi, P. V. Murphy and T. E. Keyes, *A cell free biomembrane platform for multimodal study of influenza virus hemagglutinin and for evaluation of entry-inhibitors against hemagglutinin*, *Frontiers in Molecular Biosciences*, 9 (2022) 1017338.
- [159] S. Wang, Y. Luo, L. Huang, S. Wang, C. Hao, L. Sun, Y. Zhang, W. Wang and C. Li, *The inhibition effects and mechanisms of sulfated chitooligosaccharides on influenza A virus in vitro and in vivo*, *Carbohydrate Polymers*, 286 (2022) 119316.
- [160] Q. Zhang, T. Liang, K. S. Nandakumar and S. Liu, *Emerging and state of the art hemagglutinin-targeted influenza virus inhibitors*, *Expert Opinion on Pharmacotherapy*, 22 (2021) 715-728.
- [161] H. Hu, M. Fu, C. Li, B. Zhang, Y. Li, Q. Hu and M. Zhang, *Herpes simplex virus type 2*

inhibits TNF- $\alpha$ -induced NF- $\kappa$ B activation through viral protein ICP22-mediated interaction with p65, *Frontiers in Immunology*, 13 (2022) 983502.

[162] J. B. Lee, S. Koizumi, K. Hayashi and T. Hayashi, Structure of rhamnan sulfate from the green alga *Monostroma nitidum* and its anti-herpetic effect, *Carbohydrate Polymers*, 81 (2010) 572-577.

[163] H. Tanaka, Y. Hamaya, N. Nishiwaki and H. Ishida, A concise synthesis of rhamnan oligosaccharides with alternating  $\alpha$ -(1 $\rightarrow$ 2)/(1 $\rightarrow$ 3)-linkages and repeating  $\alpha$ -(1 $\rightarrow$ 3)-linkages by iterative  $\alpha$ -glycosylation using disaccharide building blocks, *Carbohydrate Research*, 455 (2018) 23-31.

[164] C. Saturnino, F. Grande, S. Aquaro, A. Caruso, D. Iacopetta, M. G. Bonomo, P. Longo, D. Schols and M. S. Sinicropi, Chloro-1,4-dimethyl-9H-carbazole derivatives displaying anti-HIV activity, *Molecules*, 23 (2018) 286.

[165] Y. J. Lee, I. J. Yeo, D. Y. Choi, J. Yun, D. J. Son, S. B. Han and J. T. Hong, Amyloidogenic, neuroinflammatory and memory dysfunction effects of HIV-1 gp120, *Archives of Pharmacal Research*, 44 (2021) 689-701.

[166] L. Sun, M. Ishihara, D. R. Middleton, M. Tiemeyer and F. Y. Avci, Metabolic labeling of HIV-1 envelope glycoprotein gp120 to elucidate the effect of gp120 glycosylation on antigen uptake, *The American Society for Biochemistry and Molecular Biology*, 293 (2018) 15178-15194.

[167] H. Liu, M. Geng, X. Xin, F. Li, Z. Zhang, J. Li and J. Ding, Multiple and multivalent interactions of novel anti-AIDS drug candidates, sulfated polymannuronate (SPMG)-derived oligosaccharides, with gp120 and their anti-HIV activities, *Glycobiology*, 15 (2005) 501-510.

[168] B. Mingxue, B. Chaolumen, D. Asai, H. Takemura, K. Miyazaki and T. Yoshida, Role of a long-chain alkyl group in sulfated alkyl oligosaccharides with high anti-HIV activity revealed by SPR and DLS, *Carbohydrate Polymers*, 245 (2020) 116518.

[169] B. K. Chhetri, S. Lavoie, A. M. Sweeney-Jones, N. Mojib and J. Kubanek, Peyssonosides A-B, unusual diterpene glycosides with a sterically encumbered cyclopropane motif: structure elucidation using an integrated spectroscopic and computational workflow, *The Journal of Organic Chemistry*, 84 (2019) 8531-8541.

[170] G. A. Chesnokov and K. Gademann, Concise total synthesis of Peyssonoside A, *Journal of the American Chemical Society*, 143 (2021) 14083-14088.

[171] A. S. Major, D. G. Harrison, What fans the fire: insights into mechanisms of inflammation in atherosclerosis and diabetes mellitus, *Circulation*, 124 (2011) 2809-2811.

[172] W. Xie, L. Du, Diabetes is an inflammatory disease: Evidence from traditional Chinese medicines, *Diabetes, Obesity and Metabolism*, 13 (2011) 289-301.

[173] S. I. Grivennikov, F. R. Greten and M. Karin, Immunity, inflammation, and cancer, *Cell*, 140 (2010) 883-899.

[174] J. K. Kundu and Y. J. Surh, Inflammation: gearing the journey to cancer, *Mutation Research/Fundamental and Molecular*, 659 (2008) 15-30.

- [175] P. Libby, Inflammation in atherosclerosis, *Nature*, 420 (2002) 868-874.
- [176] Jang, H. Jae, Soyoun, S, Jae, H. Jin, Jung, Kyungsook, Y. Ho, S. Woong and M. Chual, Anti-inflammatory activity of eudesmane-type sesquiterpenoids from *salvia plebeia*, *Journal of Natural Products*, 80 (2017) 2666-2676.
- [177] M. Y. Donath and S. E. Shoelson, Type 2 diabetes as an inflammatory disease, *Nature Reviews Immunology*, 11 (2011) 98-107.
- [178] O. N. Kokiko-Cochran and J. P. Godbout, The inflammatory continuum of traumatic brain injury and alzheimer's disease, *Frontiers in Immunology*, 9 (2018) 672.
- [179] J. M. Assini, E. E. Mulvihill, B. G. Sutherland, D. E. Telford, C. G. Sawyez, S. L. Felder, S. Chhoker, J. Y. Edwards, R. Gros and M. W. Huff, Naringenin prevents cholesterol-induced systemic inflammation, metabolic dysregulation, and atherosclerosis in *Ldlr* (-)/(-) mice, *Journal of Lipid Research*, 54 (2013) 711-724.
- [180] J. S. Fan, D. N. Liu, G. Huang, Z. Z. Xu, Y. Jia, H. G. Zhang, X. H. Li and F. T. He, *Panax notoginseng* saponins attenuate atherosclerosis via reciprocal regulation of lipid metabolism and inflammation by inducing liver X receptor alpha expression, *Journal of Ethnopharmacology*, 142 (2012) 732-738.
- [181] R. Klempfner, J. Leor, A. Tenenbaum, E. Z. Fisman and I. Goldenberg, Effects of a vildagliptin/metformin combination on markers of atherosclerosis, thrombosis, and inflammation in diabetic patients with coronary artery disease, *Cardiovascular Diabetology*, 60 (2012).
- [182] S. Bhaskar, K. S. Kumar, K. Krishnan and H. Antony, Quercetin alleviates hypercholesterolemic diet induced inflammation during progression and regression of atherosclerosis in rabbits, *Nutrition*, 29 (2013) 219-229.
- [183] S. Mao, B. Wang, L. Yue and W. Xia, Effects of citronellol grafted chitosan oligosaccharide derivatives on regulating anti-inflammatory activity, *Carbohydrate Polymers*, 262 (2021) 117972.
- [184] R. F. Keep, Y. Hua and G. Xi, Intracerebral haemorrhage: mechanisms of injury and therapeutic targets, *Lancet Neurology*, 11 (2012) 720-731.
- [185] K. N. Sheth and J. Rosand, Targeting the immune system in intracerebral hemorrhage, *Japan Automobile Manufacturers Association Neurology*, 71 (2014) 1083-1084.
- [186] C. Tschoe, C. D. Bushnell, P. W. Duncan, M. A. A. Miller and S. Q. Wolfe, Neuroinflammation after intracerebral hemorrhage and potential therapeutic targets, *Journal of Stroke*, 22 (2020) 29-46.
- [187] W. Jian, Preclinical and clinical research on inflammation after intracerebral hemorrhage, *Progress in Neurobiology*, 92 (2010) 463-477.
- [188] T. W. Hung, K. J. Wu, Y. S. Wang, E. K. Bae, Y. Song, J. Yoon and S. J. Yu, Human milk oligosaccharide 2'-fucosyllactose induces neuroprotection from intracerebral hemorrhage stroke, *International Journal of Molecular Sciences*, 22 (2021) 9881.
- [189] J. Li, G. Su, Y. Xu, K. Arnold, V. Pagadala, C. Wang and J. Liu, Synthesis of 3-O-sulfated heparan sulfate oligosaccharides using 3-O-sulfotransferase isoform 4, *American Chemical Society*

Chemical Biology, 16 (2021) 2026-2035.

- [190] S. Singh, D. Utreja and V. Kumar, Pyrrolo[2,1-f][1,2,4]triazine: a promising fused heterocycle to target kinases in cancer therapy, *Medicinal Chemistry Research*, 31 (2022) 1-25.
- [191] H. Sung, J. Ferlay, R. L. Siegel, M. Laversanne, I. Soerjomataram, A. Jemal and F. Bray, Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries, *Cancer Journal for Clinicians*, 71 (2021) 209-249.
- [192] C. J. Yeh, M. M. L. Zulueta, Y. K. Li and S. C. Hung, Synthesis of hyaluronic acid oligosaccharides with a GlcNAc-GlcA repeating pattern and their binding affinity with CD44, *Organic Biomolecular Chemistry*, 18 (2020) 5370-5387.
- [193] Z. Yaghoobi, A. Movassaghpour, M. Talebi, M. A. Shadbad, K. Hajiasgharzadeh, S. Pourvahdani and B. Baradaran, The role of CD44 in cancer chemoresistance: A concise review, *European Journal of Pharmacology*, 903 (2021) 174147.
- [194] J. X. Tan, X. Y. Wang, X. L. Su, H. Y. Li, Y. Shi, L. Wang and G. S. Ren, Upregulation of HYAL1 expression in breast cancer promoted tumor cell proliferation, migration, invasion and angiogenesis, *The Public Library of Science ONE*, 6 (2011) e22836.
- [195] C. G. Johnson, V. P. Stober, J. M. Cyphert-Daly, C. S. Trempus, G. P. Flake, V. Cali, I. Ahmad, R. J. Midura, M. A. Aronica, S. Matalon and S. Garantziotis, High molecular weight hyaluronan ameliorates allergic inflammation and airway hyperresponsiveness in the mouse, *American Journal of Physiology Lung Cellular & Molecular*, 315 (2018) L787-L798.
- [196] J. Dzwonek and G. M. Wilczynski, CD44: molecular interactions, signaling and functions in the nervous system, *Frontiers in Cellular Neuroscience*, 9 (2015) 175.
- [197] C. M. McKee, M. B. Penno, M. Cowman, M. D. Burdick, R. M. Strieter, C. Bao and P. W. Noble, Hyaluronan (HA) fragments induce chemokine gene expression in alveolar macrophages, *Journal of Clinical Investigation*, 98 (1996) 2403-2413.
- [198] O. L. Ortega and L. S. Argumedo, Myosin 1g contributes to CD44 adhesion protein and lipid rafts recycling and controls CD44 capping and cell migration in B lymphocytes, *Frontiers in Immunology*, 8 (2017) 1731.
- [199] L. T. Senbanjo and M. A. Chellaiah, CD44: a multifunctional cell surface adhesion receptor is a regulator of progression and metastasis of cancer cells, *Frontiers in Cell and Developmental Biology*, 5 (2017) 18.
- [200] S. Yang, J. Chen, G. Zhen, X. M. Xu and L. Zhang, Triptolide inhibits the growth and metastasis of solid tumors1, *Molecular Cancer Therapeutics*, 2 (2003) 65-72.
- [201] P. A. Phillips, V. Dudeja, J. A. Mccarroll, D. Borja-Cacho, R. K. Dawra, W. E. Grizzle, S. M. Vickers and A. K. Saluja, Triptolide induces pancreatic cancer cell death via inhibition of heat shock protein 70, *Cancer Research*, 67 (2007) 9407-9416.
- [202] X. Shi, Y. Jin, C. Cheng, H. Zhang, W. Zou, Q. Zheng, Z. Lu, Q. Chen, Y. Lai and J. Pan, Triptolide inhibits Bcr-Abl transcription and induces apoptosis in STI571-resistant chronic myelogenous leukemia cells harboring T315I mutation, *Clinical Cancer Research An Official Journal*

of the American Association for Cancer Research, 15 (2009) 1686-1697.

[203] B. J. Chen, Triptolide, a novel immunosuppressive and anti-inflammatory agent purified from a chinese herb tripterygium wilfordii hook F, *Leukemia & Lymphoma*, 42 (2001) 253-265.

[204] F. Du, Z. Liu, X. Li, J. Xing, Metabolic pathways leading to detoxification of triptolide, a major active component of the herbal medicine tripterygium wilfordii, *Journal of Applied Toxicology*, 34 (2014) 878-884.

[205] Q. L. He, I. Minn, Q. Wang, P. Xu, S. A. Head, E. Datan, B. Yu, M. G. Pomper and J. O. Liu, Targeted delivery and sustained antitumor activity of triptolide through glucose conjugation, *Angewandte Chemie International Edition*, 55 (2016) 12214-12218.

[206] S. G. Li, Q. W. Shi, L. Y. Yuan, L. P. Qin, Y. Wang, Y. Q. Miao, Z. Chen, C. Q. Ling and W. X. Qin, C-Myc-dependent repression of two oncogenic miRNA clusters contributes to triptolide-induced cell death in hepatocellular carcinoma cells, *Journal of Experimental & Clinical Cancer Research*, 37 (2018) 51.

[207] X. G. Yin, J. Lu, J. Wang, R. Y. Zhang and J. Guo, Synthesis and evaluation of liposomal anti-GM3 cancer vaccine candidates covalently and noncovalently adjuvanted by  $\alpha$ -GalCer, *Journal of Medicinal Chemistry*, 64 (2021) 1951-1965.

[208] C. Zheng, H. Qu, W. Liao, T. Bavaro, M. Terreni, M. Sollogoub, K. Ding and Y. Zhang, Chemoenzymatically synthesized GM3 analogues as potential therapeutic agents to recover nervous functionality after injury by inducing neurite outgrowth, *European Journal of Medicinal Chemistry*, 146 (2018) 613-620.

[209] T. Li, X. Wang, P. Dong, P. Yu, Y. Zhang and X. Meng, Chemoenzymatic synthesis and biological evaluation of ganglioside GM3 and lyso-GM3 as potential agents for cancer therapy, *Carbohydrate Research*, 509 (2021) 108431.

[210] Y. Zhang, R. Springfield, S. Chen, X. Li, X. Feng, R. Moshirian, R. Yang and W. Yuan, alpha-galCer and iNKT cell-based cancer immunotherapy: realizing the therapeutic potentials, *Frontiers in Immunology*, 10 (2019) 1126.

[211] X. Chen, X. Hu, J. Hu, Z. Qiu and G. Zheng, Celastrol-loaded galactosylated liposomes effectively inhibit AKT/c-met-triggered rapid hepatocarcinogenesis in mice. *Molecular Pharmaceutics*, 17 (2020) 738-747.

[212] W. Niu, J. Wang, Q. Wang and J. Shen, Celastrol loaded nanoparticles with ROS-response and ROS-inducer for the treatment of ovarian cancer, *Frontiers in Chemistry*, 8 (2020) 574614.

[213] X. Zeng, X. Zhu, Q. Tian, X. Tan, N. Sun, M. Yan, J. Zhao, X. Wu, R. Li, Z. Zhang and H. Zeng, Celastrol-conjugated chitosan oligosaccharide for the treatment of pancreatic cancer, *Drug Delivery*, 29 (2022) 89-98.

[214] P. M. Lansdorp, telomeres, telomerase and cancer, *Archives of Medical Research*, (2022).

[215] S. Sharma and S. Chowdhury, Emerging mechanisms of telomerase reactivation in cancer, *Trends in Cancer*, 8 (2022) 632-641.

[216] N. Maciejewska, M. Olszewski, J. Jurasz, M. Baginski, M. Stasevych, V. Zvorych, M. Folini

and N. Zaffaroni, Teloxantron inhibits the processivity of telomerase with preferential DNA damage on telomeres, *Cell Death and Disease*, 13 (2022) 1005.

[217] Ø. Arlov, D. Rüttsche, M. A. Korayem, E. Öztürk and M. Z. Wong, Engineered sulfated polysaccharides for biomedical applications, *Advanced Functional Materials*, 31 (2021) 2010732.

[218] J. Rodriguez and M. A. Walczak, Synthesis of asymmetrically substituted scyllo-inositol, *Tetrahedron Letters*, 57 (2016) 3281-3283.

[219] J. Guang, Z. A. Rumlow, L. M. Wiles, S. O'Neill and M. A. Walczak, Sulfated liposaccharides inspired by telomerase inhibitor axinelloside A, *Tetrahedron Letters*, 58 (2017) 4867-4871.

[220] K. Warabi, T. Hamada, Y. Nakao, S. Matsunaga, H. Hirota, R. W. M. V. Soest and N. Fusetani, Axinelloside A, an unprecedented highly sulfated lipopolysaccharide inhibiting telomerase, from the marine sponge, *Axinella infundibula*, *Journal of American Chemical Society*, 127 (2005) 13262-13270.

[221] S. J. Li, Q. Fang, Y. W. Huang, Y. Y. Luo, X. D. Mu, L. Li, X. C. Yin and J. S. Yang, Chemical synthesis of the nonreducing hexasaccharide fragment of Axinelloside A based on a stepwise glycosylation approach, *Organic Letters*, 24 (2022) 7088-7094.

[222] E. Mizukoshi and S. Kaneko, Telomerase-targeted cancer immunotherapy, *International Journal of Molecular Sciences*, 20 (2019) 1823.

[223] M. Kuwabara, K. Niwa, M. Ohno and I. Hisatome, High rate of calories from protein is associated with higher prevalence of hypertension, *Journal of Human Hypertension*, 33 (2019) 340-344.

[224] A. Adler, P. Bennett, S. Colagiuri Chair, E. Gregg, K. M. Venkat Narayan, M. Ines Schmidt, E. Sobngwi, N. Tajima, N. Tandon, N. Unwin, S. Wild, J. Yudkin, N. Levitt, V. Mohan, S. Montgomery, M. J. Nyirenda, J. Tuomilehto, S. Den Boon and S. Hocking, Reprint of: classification of diabetes mellitus, *Diabetes Research and Clinical Practice*, (2021) 108972.

[225] J. J. Chamberlain, K. Doyle-Delgado, L. Peterson and N. Skolnik, Diabetes technology: review of the 2019 American diabetes association standards of medical care in diabetes, *Annals of Internal Medicine*, 171 (2019) 415-420.

[226] J. Paik and H. A. Blair, Dapagliflozin: a review in type 1 diabetes, *Drugs*, 79 (2019) 1877-1884.

[227] P. N. Davis, U. A. Ndefo and A. Oliver, Dapagliflozin: a sodium glucose cotransporter 2 Inhibitor for the treatment of diabetes mellitus, *Journal of Pharmacy Practice*, 29 (2016) 165-171.

[228] X. J. Wang, L. Zhang, D. Byrne, L. Nummy, D. Weber, D. Krishnamurthy, N. Yee and C. H. Senanayake, Efficient synthesis of Empagliflozin, an inhibitor of SGLT-2, utilizing an AlCl<sub>3</sub>-promoted silane reduction of a beta-glycopyranoside, *Organic Letters*, 16 (2014) 4090-4093.

[229] F. Zhu, J. Rodriguez, T. Yang, I. Kevlishvili, E. Miller, D. Yi, S. O'Neill, M. J. Rourke, P. Liu and M. A. Walczak, Glycosyl cross-coupling of anomeric nucleophiles: scope, mechanism, and applications in the synthesis of aryl C-glycosides, *Journal of the American Chemical Society*, 139

(2017) 17908-17922.

- [230] S. Dhillon, Dapagliflozin: a review in type 2 diabetes, *Drugs*, 79 (2019) 1135-1146.
- [231] J. Yu, Y. Cao, H. Yu and J. Wang, A concise and efficient synthesis of dapagliflozin, *Organic Process Research & Development*, 23 (2019) 1458-1461.
- [232] R. Mukkamala, R. Kumar, S. K. Banerjee and I. S. Aidhen, Synthesis of benzyl C-analogues of dapagliflozin as potential SGLT2 Inhibitors, *European Journal of Organic Chemistry*, 2020 (2020) 1828-1839.
- [233] L. Xie and W. Xia, Characteristics and molecular mechanisms through which SGLT2 inhibitors improve metabolic diseases: a mechanism review, *Life Sciences*, 300 (2022) 120543.
- [234] L. Hu, P. Zou, W. Wei, X.-M. Yuan, X.-L. Qiu and S.-H. Gou, Facile and green synthesis of dapagliflozin, *Synthetic Communications*, 49 (2019) 3373-3379.
- [235] V. V. Triantakostanti, A. Toskas, N. S. Iordanidis, T. Andreou, T. V. Koftis and J. K. Gallos, Pivaloyl-protected glucosyl iodide as a glucosyl donor for the preparation of  $\beta$ -C-glucosides, *Tetrahedron Letters*, 61 (2020) 152173.
- [236] K. Vankova, M. Rahm, J. Choutka, R. Pohl and K. Parkan, Facile approach to C-glucosides by using a protecting-group-free Miyaura cross-coupling reaction: high-yielding dapagliflozin synthesis, *Chemistry - A European Journal*, 27 (2021) 10583-10588.
- [237] R. Venkatesh, V. Tiwari and J. Kandasamy, Copper(I)-catalyzed Sandmeyer-type S-arylation of 1-thiosugars with aryl diazonium salts under mild conditions, *Journal of Organic Chemistry*, 87 (2022) 11414-11432.
- [238] L. Zhang, P. Xu, B. Liu and B. Yu, Chemical synthesis of fucosylated chondroitin sulfate oligosaccharides, *The Journal of Organic Chemistry*, 85 (2020) 15908-15919.
- [239] J. Peng, W. Vongpatanasin, A. Sacharidou, D. Kifer and P. W. Shaul, Supplementation with the sialic acid precursor N-acetyl-D-mannosamine breaks the link between obesity and hypertension, *Circulation*, 140 (2019) 2005-2018.
- [240] A. S. Chen, T. Taguchi, K. Sakai, Y. Matahira, M. W. Wang and I. Miwa, Effect of chitobiose and chitotriose on carbon tetrachloride-induced acute hepatotoxicity in rats, *Biological and Pharmaceutical Bulletin*, 28 (2005) 1971-1973.
- [241] M. Senevirathne, C. B. Ahn and J. Y. Je, Hepatoprotective effect of chitoooligosaccharides against tert-butylhydroperoxide-induced damage in Chang liver cells, *Carbohydrate Polymers*, 83 (2011) 995-1000.
- [242] P. Liu, H. Li, J. Gong, Y. Geng, M. Jiang, H. Xu, Z. Xu and J. Shi, Chitoooligosaccharides alleviate hepatic fibrosis by regulating the polarization of M1 and M2 macrophages, *Food & Function*, 13 (2022) 753-768.
- [243] Z. W. Zhang, C. S. Gao, H. Zhang, J. Yang, Y. P. Wang, L. B. Pan, H. Yu, C. Y. He, H. B. Luo, Z. X. Zhao, X. B. Zhou, Y. L. Wang, J. Fu, P. Han, Y. H. Dong, G. Wang, S. Li, Y. Wang, J. D. Jiang and W. Zhong, *Morinda officinalis* oligosaccharides increase serotonin in the brain and ameliorate depression via promoting 5-hydroxytryptophan production in the gut microbiota, *Acta*



Pharmaceutica Sinica B, 12 (2022) 3298-3312.

[244] Y. Zhan, J. Qiao, S. Chen, X. Dong, Y. Wu, Z. Wang and X. Wang, Metabolic engineering for overproduction of colanic acid in *Escherichia coli* mutant with short lipopolysaccharide, *Journal of Agricultural and Food Chemistry*, 70 (2022) 8351-8364.

[245] C. Wang, H. Zhang, J. Wang, S. Chen, Z. Wang, L. Zhao, X. Wang, Colanic acid biosynthesis in *Escherichia coli* is dependent on lipopolysaccharide structure and glucose availability. *Microbiol Research*, 239 (2020) 126527.

[246] J. Qiao, Y. Zhan, X. Tan, Y. Liu, X. Hu and X. Wang, Colanic acid: biosynthetic overproduction by engineering *Escherichia coli* and physical property characterization, *Journal of Agricultural and Food Chemistry*, 69 (2021) 13881-13894.

[247] B. Han, P. Sivaramakrishnan, C. J. Lin, I. A. A. Neve, J. He, L. W. R. Tay, J. N. Sowa, A. Sizovs, G. Du, J. Wang, C. Herman and M. C. Wang, Microbial genetic composition tunes host longevity, *Cell*, 169 (2017) 1249-1262.

[248] L. A. Hartsough, M. Park, M. V. Kotlajich, J. T. Lazar, B. Han, C. J. Lin, E. Musteata, L. Gambill, M. C. Wang and J. J. Tabor, Optogenetic control of gut bacterial metabolism to promote longevity, *Elife*, 9 (2020) 56849.

[249] J. C. Sadler, R. C. Brewster, A. F. González, J. S. Nirikko, S. Varzandeh and S. Wallace, Overproduction of native and click-able colanic acid slime from engineered *Escherichia coli*. , *The Preprint Server for Biology*, (2022).

[250] G. Ren, Z. Wang, Y. Li, X. Q. Hu and X. Y. Wang, Effects of lipopolysaccharide core sugar deficiency on colanic Acid biosynthesis in *Escherichia coli*. , *Journal of Bacteriology*, 198 (2016) 1576-1584.

[251] X. Zhang, P. Xu and B. Yu, Chemical synthesis of a colanic acid hexasaccharide, *Organic Letters*, 24 (2022) 7779-7783.