Conference paper

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New syntheses towards *C*-glycosyl type glycomimetics

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Abstract: Glycomimetics are compounds that resemble carbohydrate molecules in their chemical structure and/or biological effect. A large variety of compounds can be designed and synthesized to get glycomimetics, however, *C*-glycosyl derivatives represent one of the most frequently studied subgroup. In the present survey syntheses of a range of five- and six membered *C*-glycopyranosyl heterocycles, anhydro-aldimine type compounds, *exo*-glycals, *C*-glycosyl styrenes, carbon-sulfur bonded oligosaccharide mimics are described. Some of the *C*-glycopyranosyl azoles, namely 1,2,4-triazoles and imidazoles belong to the most efficient glucose analog inhibitors of glycogen phosphorylase known to date. Biological studies revealed the therapeutical potential of such inhibitors. Other synthetic derivatives offer versatile possibilities to get further glycomimetics.

Keywords: anhydro-aldimines; *C*-glycosyl compounds; cross couplings; *exo*-glycals; glycogen phosphorylase; glycomimetics; ICS-29; inhibitors; thiol-ene additions; tosylhydrazones.

Introduction

Carbohydrates (saccharides, glycans) are, in the strictest sense, around us and inside us. These compounds make about 2/3 of the yearly renewing biomass; they are among the main ingredients of our everyday meals either as digestible and nutritious materials or indigestible dietary fibers indispensable for maintaining our health; they are components of each living cell, building blocks of the most important biomolecules, and participants of forming complex cell organelles; are present in every living organism as skeletal or feed stuffs; play a role in all fundamental biological processes from the fertilization via the formation of tissue structure and the development of immune response to the apoptosis; they serve as general signaling molecules to present a cell's nature, age and status in cell- and tissue specific recognition events; they are essential components of several, in the clinical practice routinely applied medicines and vaccines; are lead structures for drug development; they offer solutions to material science problems, as well as power generation and industrial production based on renewable feedstocks [1].

The universal role of carbohydrates and their derivatives in the vast majority of biological phenomena has become a scientific commonplace in the recent 2–3 decades [2, 3]. The glycans are present in every cell and on the cell surface, and their roles are indispensable in each known life form. A present focus of glycoscience is to understand the biological roles of natural glycans and glycoconjugates (glycoproteins and glycolipids), to map the corresponding saccharide-protein interactions, to decipher the sugar code, the third language of biology and, as an outcome, to apply this knowledge in biomedical fields and drug design [4, 5].

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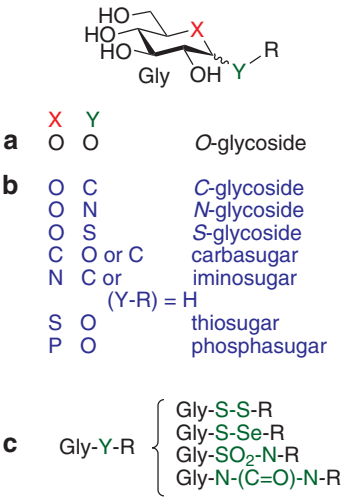


Fig. 1: Glycomimetics. (a) The glycosidic bond in a natural glycan; (b) Some types of glycomimetics; (c) Examples for the replacement of the glycosidic oxygen by multiple atomic linkers.

From the above considerations several goals and tasks can be deduced for the synthetic carbohydrate chemistry. One of these is the quest of powerful methods needed to assemble saccharides of limited availability from natural sources. Due to the complexity of such molecules and the difficulties of chemical synthesis (originating e.g. from the necessity of complicated protecting group strategies [6], from the changing ring size, the stereoselective formation of the glycosidic bond [7]), the preparation of glycosides still represents a serious challenge [8, 9]. A further obstacle of biological studies and applications is represented by the sensitivity of the glycosidic bond (Fig. 1a) towards acidic and enzymatic hydrolysis. The unfavorable pharmacokinetic properties also pull back the utility of natural glycans as drugs.

Another task for carbohydrate chemistry is to eliminate the drawbacks connected to the structural peculiarities and synthetic difficulties of glycosides by providing glycomimetics, i.e. compounds resembling the structure and/or the biological properties of natural glycans [10]. Some carbohydrate-based glycomimetics are exemplified in Fig. 1b, while Fig. 1c illustrates more complex glycomimetic molecules. Such compounds may have the advantage of simpler syntheses, resistance toward hydrolysis and metabolic processes, can offer a wide range of derivatization possibilities, and can, therefore, be utilized as glycobiological tools and leads in drug design.

An outstanding group of glycomimetics modulates, most frequently inhibits the action of glycoenzymes, such as glycosyl transferases and glycoside hydrolases. Glycomimetic compounds and glycoenzyme inhibitors are already in use in the clinical practice in several indications, e.g. against blood coagulation, osteoarthritis, epilepsy, Gaucher and Niemann-Pick diseases, influenza, diabetes [11]. A most recent breakthrough is the introduction of gliflozins for the treatment of type 2 diabetes mellitus. These compounds of *C*-glycosyl arene type structures are inhibitors of renal sodium-dependent glucose cotransporter 2 (SGLT2), thereby eliciting benign glycosuria to diminish blood sugar levels [12–14].

In our work we are dealing with the design and synthesis of glycoenzyme inhibitors (of which those of glycogen phosphorylase will be highlighted here) as well as the elaboration of new synthetic methodologies to obtain *C*-glycosyl compounds.

Glucose analog inhibitors of glycogen phosphorylase

Glycogen phosphorylase (GP) can be found in the liver, muscles and brain in slightly different isoforms [15]. The liver isoform is the rate determining enzyme for the degradation of the storage polysaccharide glycogen, and this isoenzyme has a direct influence on blood sugar levels. Thus, inhibition of liver GP may result

in a decrease of serum glucose levels, and this enzyme has become a validated target in the search of new therapeutic possibilities of type 2 diabetes [16–19].

The mode of operation and the structure of GP are well known from biochemical and crystallographic studies, and seven binding sites have been identified so far [20]. Among these the catalytic site is the most intensively studied by glucose derived inhibitors [12, 21–24]. Besides the antidiabetic potential of glycogen phosphorylase inhibitors [19, 25, 26] such compounds have the potential for utilization against cardiac arrhythmias and other cardiovascular disorders [27, 28], cardiac and cerebral ischemias [29, 30], and tumorous growths [31–36].

The best glucose analog inhibitors of GP displaying submicromolar inhibition constants (K_i) can be found among glucopyranosylidene-spiro-heterocycles, *N*-acyl-*N*′-β-D-glucopyranosyl ureas, and *C*-glucopyranosyl heterocycles [13, 23]. Here, the most recent results on the latter type of GPIs are summarized.

Design and syntheses of *C*-glucopyranosyl azoles as glycogen phosphorylase inhibitors

Among the first low micromolar GPIs were the *N*-acetyl-β-D-glucopyranosylamine [37] (Fig. 2a, R = CH_3, K_i = 32 μM) and its 2-naphthoyl counterpart [38] (Fig. 2a). Later the corresponding ureas (Fig. 2b) and their *N*-acyl derivatives (Fig. 2c) were also synthesized and the *N*-(β-D-glucopyranosyl)-*N*′-(2-naphthoyl) urea (Fig. 2c) was found to be the first submicromolar GPI [23]. These compounds were the basis for bioisosteric replacements [39–42] during which the amide units highlighted in Fig. 2 were substituted by five-membered heterocycles leading to a range of *C*- and *N*-glucopyranosyl compounds. Compounds were made for each type shown in Fig. 2 (heterocycles: pyrrole [43], pyrazole [44], imidazole [43–47], isoxazole [44, 48], thiazole [44], 1,2,3- [47–52] and 1,2,4-triazoles [53–62], 1,2,4- [63] and 1,3,4-oxadiazoles [51, 64–67], 1,3,4-thiadiazole [65], tetrazoles [47, 51, 64]), however, only the syntheses of *C*-glucopyranosyl 1,2,4-triazoles and imidazoles, essentially unknown before, are described here.

A few trisubstituted *C*-glucopyranosyl 1,2,4-triazoles were reported in the literature [68, 69], however, these proved irreproducible in our laboratory. For the synthesis of the necessary 5-β-D-glucopyranosyl-3-substituted-1,2,4-triazoles several methods were elaborated (Scheme 1, preparation of the starting compounds was described in the original papers and is not detailed here). Among cyclocondensation routes

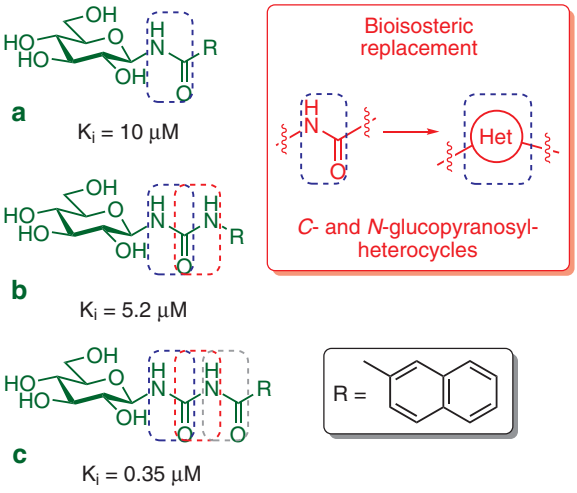
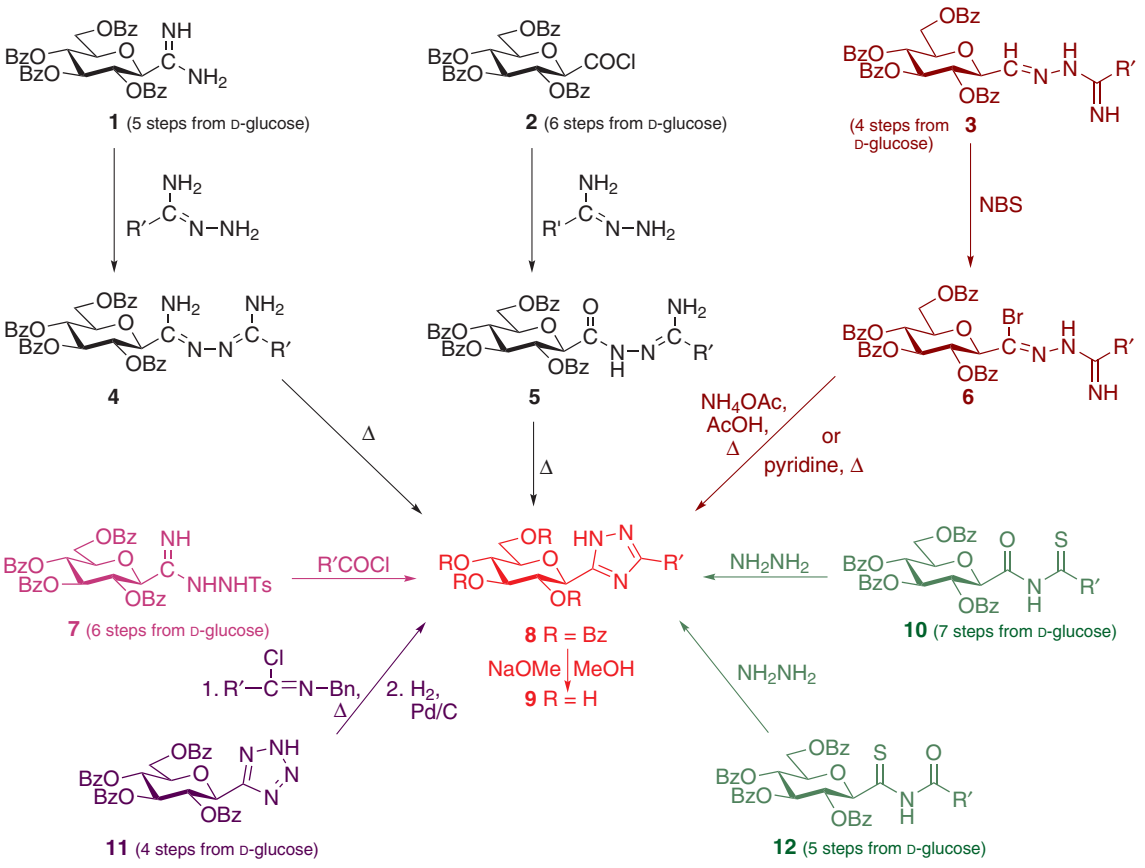


Fig. 2: Some inhibitors of glycogen phosphorylase [K_i against rabbit muscle GPb (RMGPb)]. *N*-Acyl-β-D-glucopyranosylamine (a), *N*-substituted-*N*′-β-D-glucopyranosyl urea (b) and *N*-acyl-*N*′-β-D-glucopyranosyl urea (c) type inhibitors as the basic compounds for bioisosteric replacements.

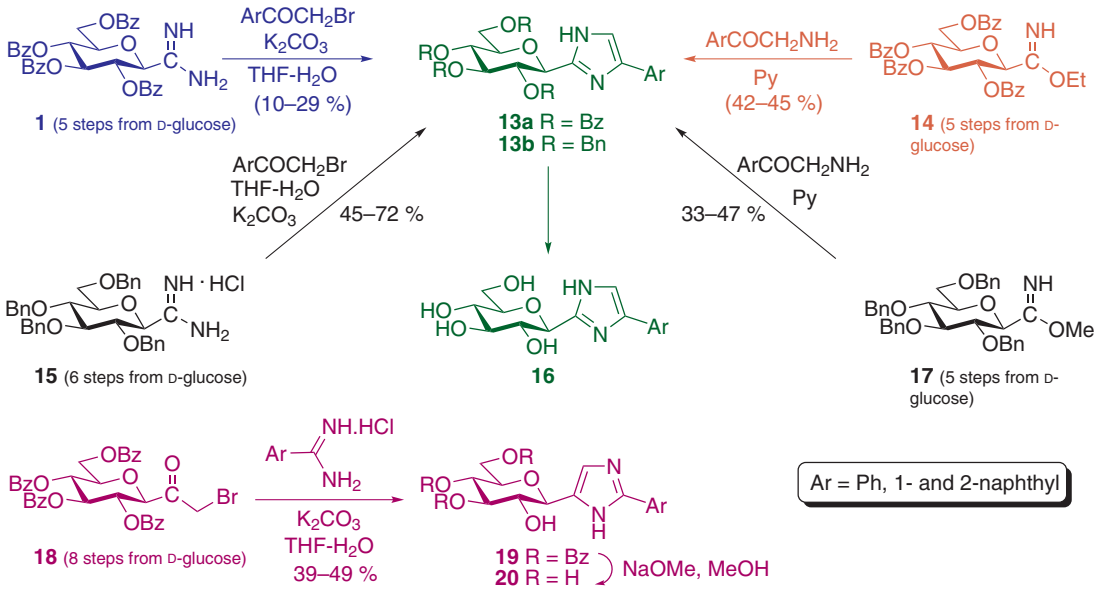


Scheme 1: Key-reactions of the syntheses of *C*-glucopyranosyl 1,2,4-triazoles.

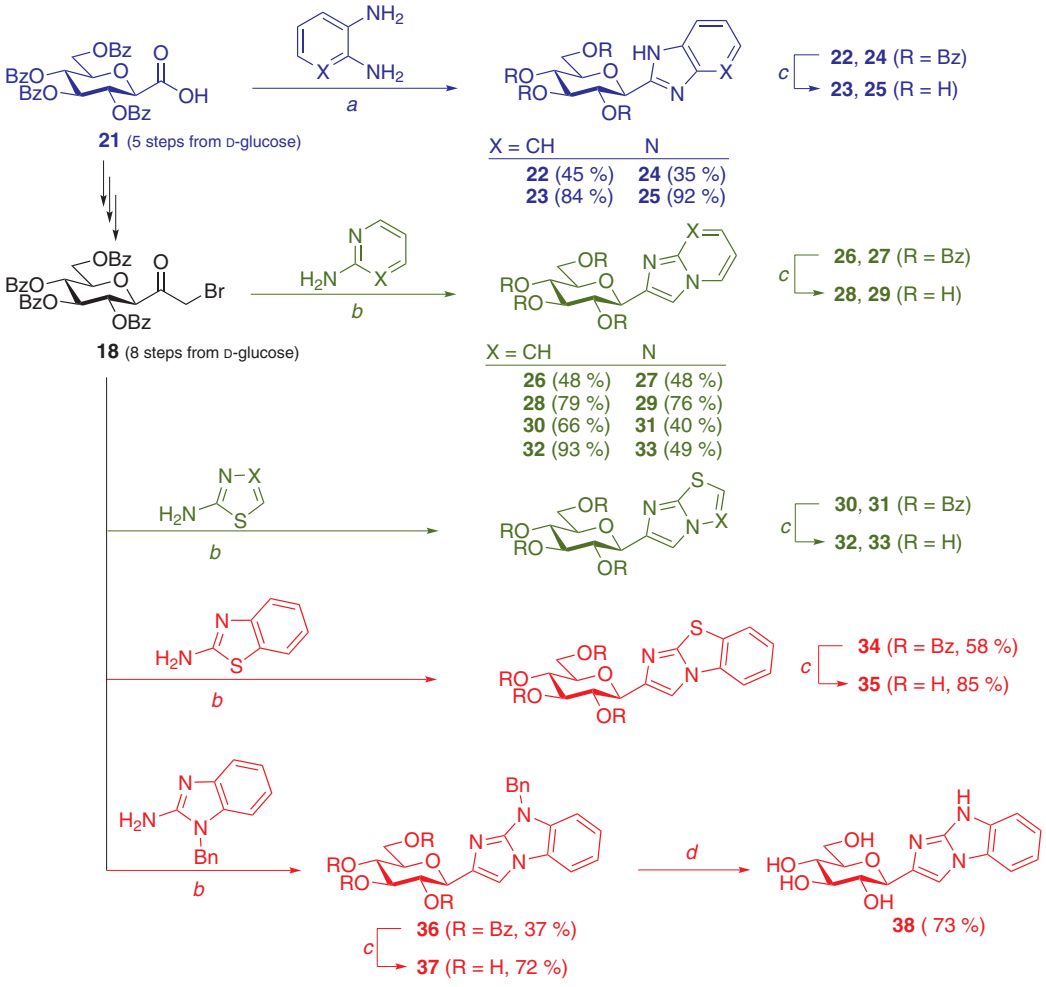
reactions of amidine **1** or acid chloride **2** with amidrazones gave intermediates **4** and **5**, respectively, which on heating gave the expected 1,2,4-triazoles **8** [54]; transformations of tosylamidrazone **7** by acid chlorides [53], or reactions of *N*-acyl thioamides **10** and **12** with hydrazine [59] also led to **8**. A further procedure, representing a new synthesis for 1,2,4-triazoles in general, was based on the bromination of imidoylhydrazones **3** to give the surprisingly stable derivatives **6** which were cyclized to **8** under basic conditions [57]. Finally, ring transformations of tetrazole **11** by imidoyl chlorides also gave, via *N*-benzylated 1,2,4-triazole intermediates, the protected triazoles **8** [55] which were debenzoylated under Zemplén conditions to the test compounds **9**. Taking into account the availability of the necessary carbohydrate precursors and reagents routes **3→6→8** and **11→8** are the most advantageous. It is worth noting that the transformations of precursors **10–12** facilitate the syntheses of all regioisomers of trisubstituted *C*-glucopyranosyl 1,2,4-triazoles, too [59].

A single representative of *C*-glycopyranosyl imidazoles, 2-β-D-glucopyranosyl-imidazole [70] was known at the outset of our studies. The necessary 2-glycosyl-4(5)-substituted-imidazoles **13a** were first prepared by the cyclocondensation of amidine **1** and α-bromoketones [44] (Scheme 2). The yields of **13a** were improved by reactions of imidate **14** with α-aminoketones [43]. The *O*-perbenzylated **13b** were obtained in similar yields from imidate **17** while the best results were achieved from amidine **15** [46]. The regioisomeric imidazole **19** was made from glucose derived α-bromoketone **18** [71]. Standard deprotection protocols led then to the test compounds **16** and **20**.

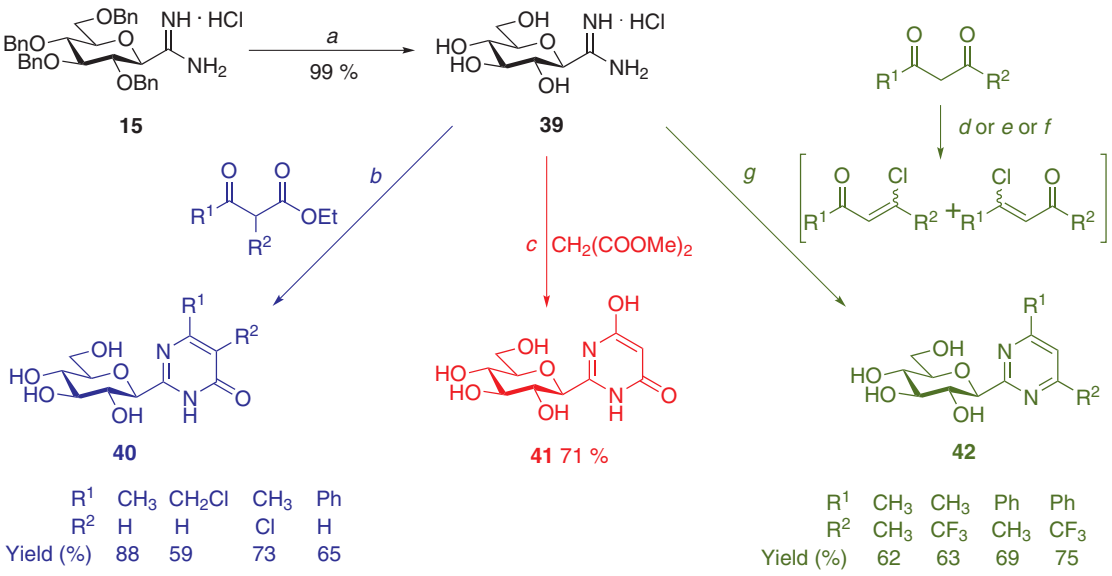
A series of fused *C*-glucopyranosyl imidazole type compounds was also synthesized (Scheme 3). Anhydroaldonic acid **21** was condensed with 1,2-diaminobenzene or 2,3-diaminopyridine in the presence of $P(OPh)_3$ to give **22** and **24**, respectively [45, 72]. Reactions of α-bromoketone **18** with various amino-heterocycles resulted in the corresponding annelated derivatives **26**, **27**, **30**, **31**, and **34**. The *O*-benzoyl protecting groups were removed by the Zemplén protocol to give **23**, **25**, **28**, **29**, **32**, **33**, and **35**, respectively. Transformation of **18** with



Scheme 2: Syntheses of *C*-glucopyranosyl imidazoles.



Scheme 3: Syntheses of fused *C*-glucopyranosyl imidazole type compounds. Conditions: (a) $P(OPh)_3$, dry pyridine, reflux; (b) dry 1,4-dioxane, reflux; (c) ~1 M NaOMe in MeOH, rt; (d) H_2, $Pd(OH)_2/C$, dry EtOH, reflux.



Scheme 4: Syntheses of 2-*C*-β-D-glucopyranosyl pyrimidines from *C*-β-D-glucopyranosyl formamidines. Conditions: (a) H_2, $Pd(OH)_2/C$, dry EtOAc-EtOH (1:2), 1 drop of cc. HCl, rt; (b) β-ketoester (2 equiv.), 1 M NaOMe in dry MeOH (3 equiv.), dry MeOH, rt; (c) dimethyl malonate (10 equiv.), 1 M solution of NaOMe in dry MeOH (10 equiv.), dry MeOH, rt; (d) PCl_5 (1 equiv.), dry Et_2O, rt; (e) $(COCl)_2$ (1.2 equiv.), DMF (1.3 equiv.), dry CH_2Cl_2, 0 °C to rt; (f) $SOCl_2$ (3 equiv.), dry $CHCl_3$, cat. DMF, reflux; (g) K_2CO_3 (4 equiv.), α,β-unsaturated chloroketone (1.2 equiv.), 4 Å mol. sieves, dry DMF, 0 °C to rt.

2-amino-benzimidazole was only feasible by the derivative benzyl-protected on the ring nitrogen to give **36** which was first debenzoylated to **37** then debenzylated to **38** [72].

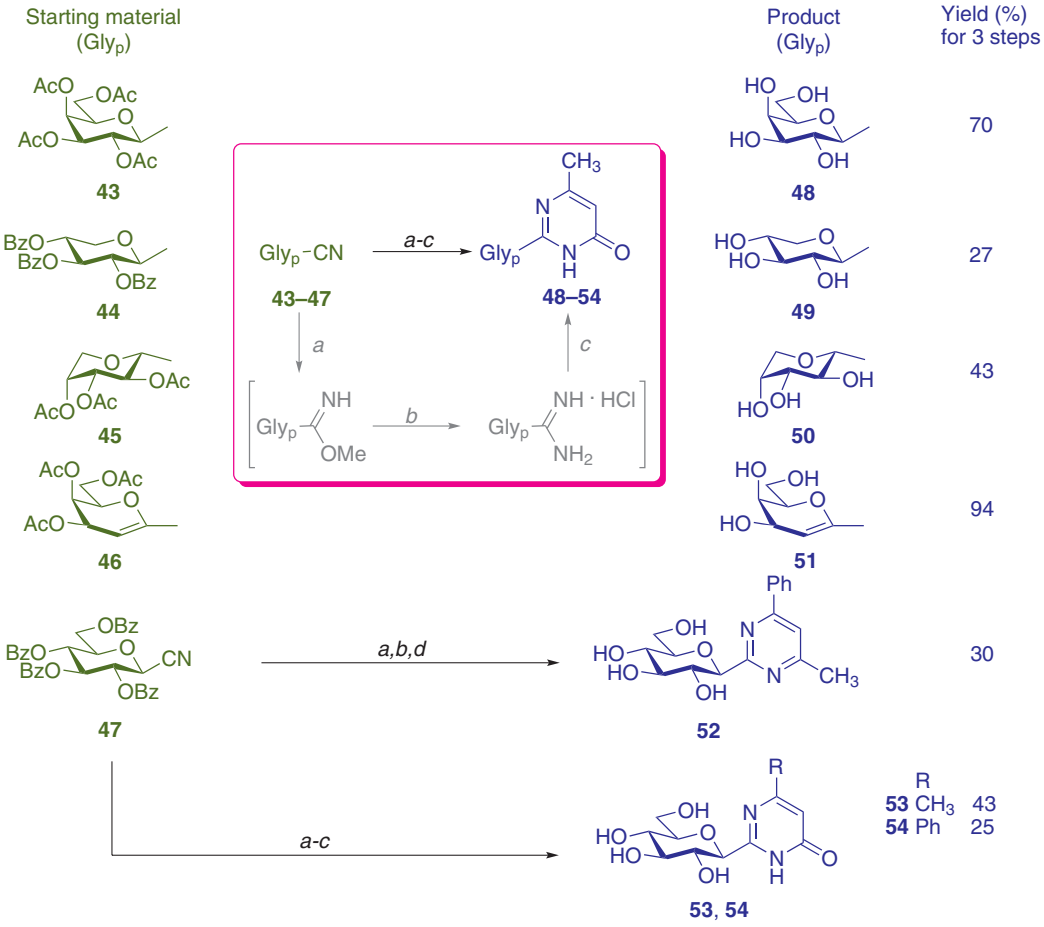
Syntheses of *C*-glycopyranosyl pyrimidines

The large scale availability of amidine **15** [46, 73] facilitated the first general syntheses of 2-*C*-β-D-glucopyranosyl pyrimidines which were practically unknown before (only sporadic mentions could be found about similar compounds [74–76]). Although the cyclocondensation of **15** with various 1,3-dicarbonyl compounds could be carried out, the removal of the *O*-benzyl protective groups in the products was problematic in several cases. Therefore, debenzylation of **15** was performed in the usual way to give **39** (Scheme 4) which was then reacted under basic conditions with β-ketoesters, dimethyl malonate, and α,β-unsaturated β-chloroketones obtained from β-diketones to furnish *C*-glucopyranosyl pyrimidines **40**, **41**, and **42**, respectively, in good yields [77].

Since the amidine precursor glycosyl cyanides, such as compounds **43–47** in Scheme 5, are more easily accessible in *O*-peracylated forms, a one-pot procedure was also elaborated to get 2-*C*-β-D-glycopyranosyl pyrimidines from these starting materials [77]. Thus, a glycosyl cyanide **43–47** was treated with NaOMe followed by NH_4Cl and a β-dicarbonyl reagent in a continuous operation to give pyrimidines **48–54** in 25–94 % yields over three steps.

Inhibition of glycogen phosphorylase

The *C*-β-D-glucopyranosyl heterocycles were assayed against rabbit muscle GPb, the prototype [15] of glycogen phosphorylases. The inhibition data for the azole derivatives are collected in Table 1 together with those



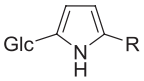
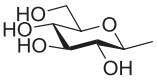
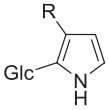
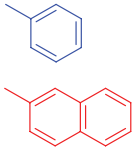
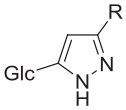
Scheme 5: One-pot–three-step syntheses of 2-*C*-β-D-glucopyranosyl pyrimidines from *O*-peracylated D-glycopyranosyl cyanides. Conditions: (a) 1 M NaOMe in dry MeOH (20 mol%), dry MeOH, dry $CHCl_3$, rt; (b) NH_4Cl (1.2 equiv.), dry MeOH; (c) $RCOCH_2COOEt$ (2 equiv.), 1 M NaOMe in dry MeOH (3 equiv.), dry MeOH, rt (R = CH_3 toward **48–51** and **53**, R = Ph toward **54**); (d) K_2CO_3 (4 equiv.), α,β-unsaturated β-chloroketone (1.2 equiv.) freshly prepared from 1-phenylbutane-1,3-dione, 4 Å molecular sieves, dry DMF, 0 °C to rt.

of some *N*-β-D-glucopyranosyl compounds. The structure-activity relationships cannot be analyzed in details here, but it can be highlighted that the most efficient inhibitors are imidazole **V** and 1,2,4-triazole **X** with R = 2-naphthyl substituents (the former is the best known glucose derived GPI). It is noteworthy that both types of heterocycles can form H-bonds with the enzyme main chain carbonyl of His377 next to the catalytic site as revealed by X-ray crystallography of the enzyme-inhibitor complexes [43, 61, 62]. In each type of the investigated compounds the 2-naphthyl-substituted derivatives proved better inhibitors in comparison to the phenyl-substituted ones. This can be attributed to more extensive van der Waals interactions of the former in the so-called β-channel of the enzyme [60]. The constitution of the heterocycle linking the glucose moiety and the aromatic group as well as the *C*- or *N*-glycosidic linkage mode have a decisive effect on the inhibition as exemplified by comparisons of **V–VII**, **XI–XII** or **XIII–XV**.

The 2-*C*-β-D-glucopyranosyl pyrimidines were non-inhibitory at the maximal studied concentration of 625 μM [77]. This is in sharp contrast with the potency of several *N*-β-D-glucopyranosyl derivatives of pyrimidine type nucleobases to show low micromolar [78, 79] or even nanomolar inhibition [80]. Why and how the *C*- or *N*-glycosyl structure of the inhibitors affect the binding still remains to be understood.

Some of the 2-*C*-β-D-glucopyranosyl pyrimidines had weak inhibition against glycosidase enzymes [77].

Table 1: Inhibition of rabbit muscle glycogen phosphorylase b (RMGPb) by *C*- and *N*-β-D-glucopyranosyl azoles (K_i [μM]).

	n.i.[a] n.i.[a]				
I			Glc = 		
	n.i.[a] n.i.[a]				
II			R = 		
	400				
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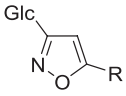	n.i.[a]		n.i. = no inhibition		
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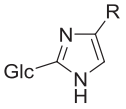
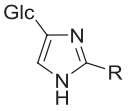
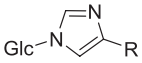
	0.28 0.031		37 5.4		n.i.[a]
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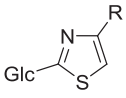
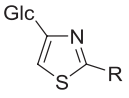
	310 158		326 23		
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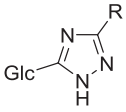
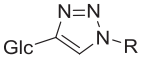
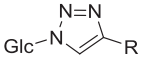
	7 0.41		n.i.[a] n.i.[a]		151 16
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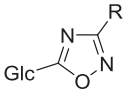
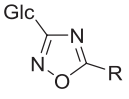
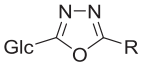
	64 2.4		10 %[a] 38		10 %[a] 10 %[a]
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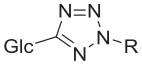
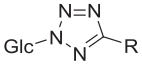
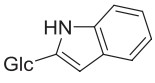
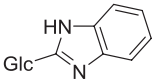
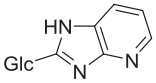
	n.i.[a]		n.i.[a]		327
XVI		**XVII**		**XVIII**	
	625 (IC_{50})		8.6		21
XIX		**XX**		**XXI**	

[a]Measured at 625 μM the maximal concentration tested.

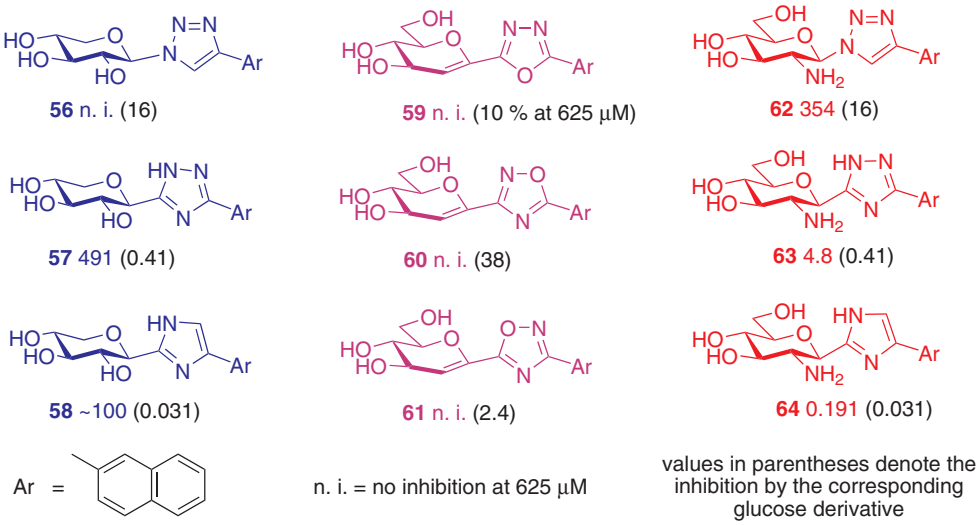


Fig. 3: Inhibition of RMGPb by compounds with modified glucose units (K_i [μM]).

Inhibition of RMGPb by compounds modified in the glucose unit

In some series of inhibitors the effects of modifications of the glucose moiety were also studied (Fig. 3). The simplest change is to cut off the hydroxymethyl side chain i.e. the synthesis and investigation of xylose derivatives. This alteration resulted in inactive compounds among xylopyranosylidene-spiro-heterocycles (not shown) [81, 82] and for *N*-xylosyl-1,2,3-triazoles **56** [82, 83]. In the cases of 1,2,4-triazoles **57** and imidazoles **58**, which aglycons gave the best inhibitors with an attached glucose unit, a weakening of three orders of magnitude could be observed [82]. Introduction of a double bond into the glucopyranose ring as in **59–61**, to make the compounds somewhat similar to the glycosyliumion-like transition state of the catalyzed reaction, resulted in inefficient derivatives [84]. However, the exchange of the 2-OH to the isosteric NH_2 group gave highly active compounds **62–64**, nevertheless, these lagged behind the parent glucose derivatives by factors of ~22, ~12 and ~6, respectively [85]. These compounds represent the first strongly binding GPIs with modified glucose moieties that can be advantageous from the point of view of selectivity in applications.

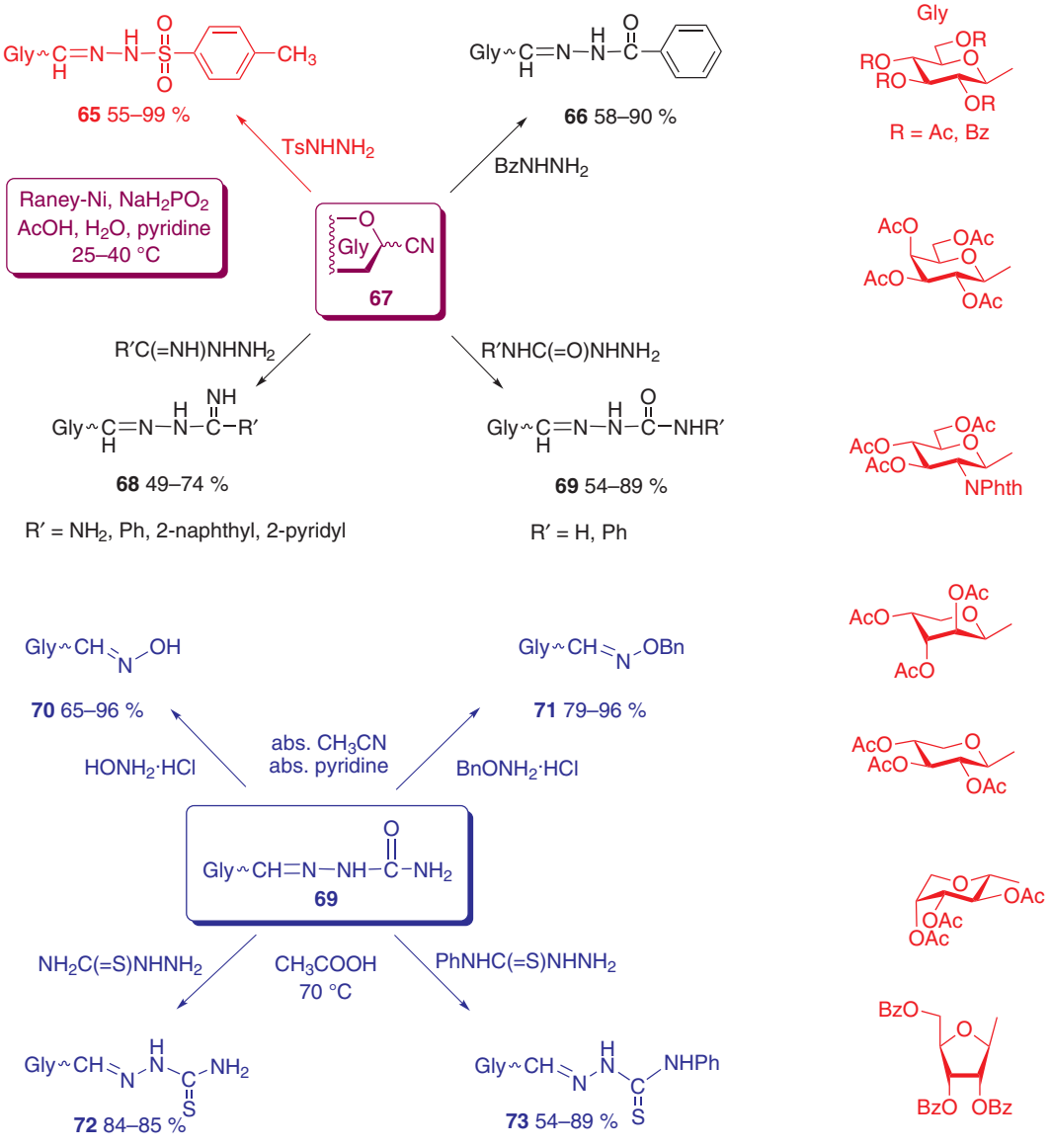
Biological investigations with glucose derived GPIs

Although biological studies with *C*-glycosyl compounds have not yet been available, other glucose derived GPIs had shown promising effects indicating that probably similar efficiencies might be expected with the *C*-glycosyl derivatives, too. In Zucker diabetic rats, administration of glucopyranosylidene-spiro-thiohydantoin diminished blood sugar levels and also decreased the GPa level in the liver [86]. In addition, it increased plasma insulin levels and restored the whole body insulin sensitivity in streptozotocin induced diabetic rats [87]. The spiro-thiohydantoin and some *N*-acyl-*N*′-β-D-glucopyranosyl ureas improved glucose tolerance in mice under normoglycaemic and diabetic conditions [88]. An *N*-acyl-*N*′-β-D-glucopyranosyl urea increased the size of pancreatic Langerhans islets in mice, and improved the glucose-induced insulin secretion, thereby, GPIs may be suitable to preserve or even ameliorate β-cell function in diabetic states [89]. A single dose of a glucopyranosylidene-spiro-isoxazoline significantly lowered the hepatic glucose production (~30 %) which may be relevant for therapeutic applications [90].

Syntheses of other glycomimetics and their precursors

In this section we summarize new synthetic methods for *C*-glycosyl compounds which can be diversely transformed towards glycomimetics.

Generally applicable reactions were elaborated for the conversion of readily available glycosyl cyanides **67** to various *C*-glycosyl imine type compounds (Scheme 6). Under reductive conditions in the presence of Raney-Ni, NaH_2PO_2, and an added acylhydrazine type reagent tosylhydrazones **65** [91–94], acylhydrazones **66** [95], imidoylhydrazones **68** [57], semicarbazones and carbamoylhydrazones **69** [95] could be prepared in good to excellent yields. With hydroxylamine and its derivatives this reaction was not feasible, however, transimination of semicarbazones **69** resulted in oximes **70** and **71**. Thiosemicarbazones **72** and **73** were prepared similarly from **69** since the direct route from **67** was not possible due to catalyst poisoning by the sulfur containing thiosemicarbazide reagents.



Scheme 6: Preparation of anhydro-aldimine derivatives.

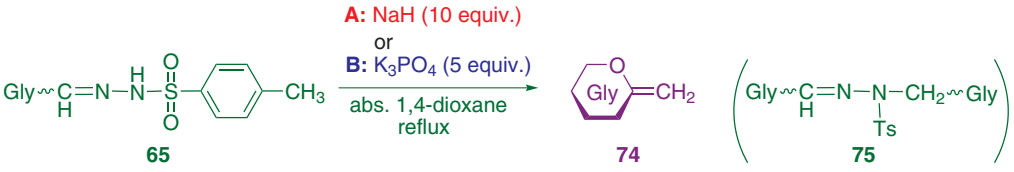
Numerous synthetic applications of the above derivatives include oxidative ring closure of **66** and **69** to *C*-glycosyl-1,3,4-oxadiazoles [65–67], transformations of **68** to 1,2,4-triazoles [57], conversion of **73** to 1,3,4-thiadiazoles [65]; oximes **70** as nitrile-oxide precursors are starting compounds for 1,3-dipolar cycloadditions [96–98].

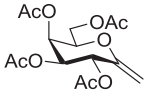
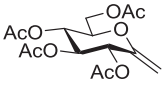
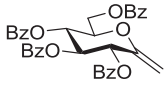
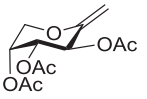
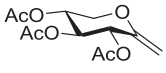
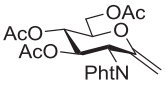
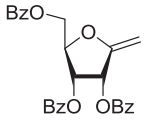
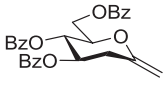
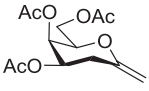
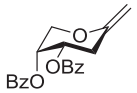
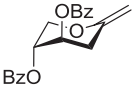
Next, versatile transformations of tosylhydrazones **65** are presented in details. The well known Bamford-Stevens reaction of tosylhydrazones leads to alkenes in the presence of bases either under thermic or photochemical activation. During the transformation the deprotonated hydrazone loses a sulfinate ion and nitrogen to give a carbene which, in the absence of any other reaction partner, furnishes an alkene by an insertion into the neighboring C–H bond. This reaction was applied for a new, variable synthesis of *exo*-glycals **74** [92, 93, 99] (Table 2). In the presence of a sufficiently large excess of a base the carbene insertion into the NH bond of **65** to give **75** becomes subordinate and the *exo*-glycals **74** can be isolated in good yields.

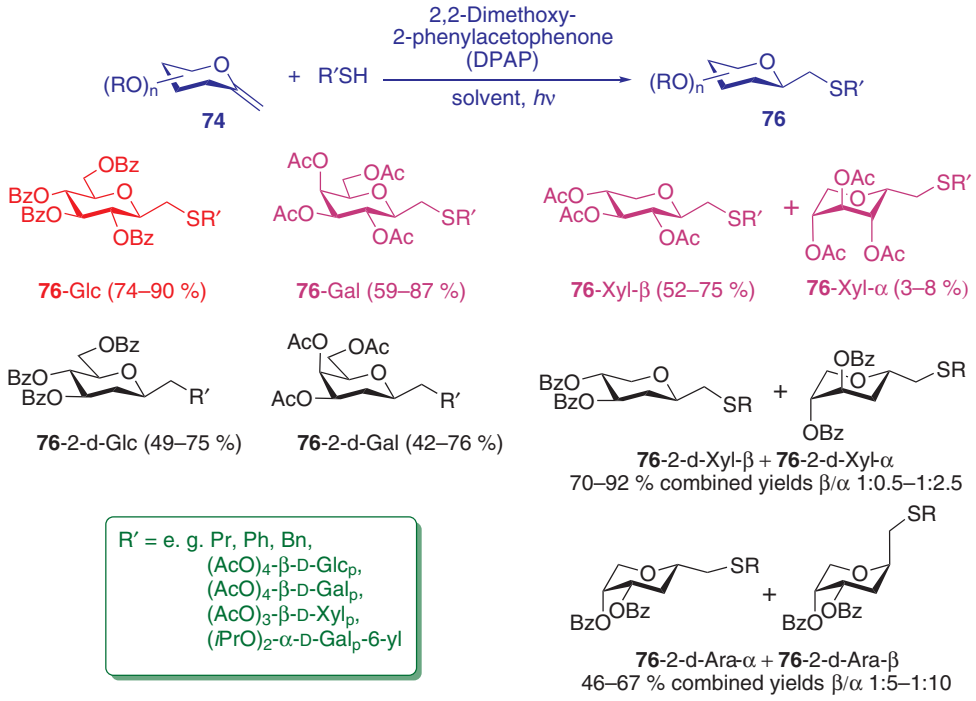
Exo-glycals **74** proved to be excellent substrates for the preparation of glycosylmethyl sulfide type glycomimetics as well as C-S bonded disaccharide mimetics (Scheme 7). To this end, in collaboration with Anikó Borbás' group, photoinitiated thiol-ene addition reactions were applied to give the target compounds **76** in mostly very good yields [100–103]. These additions were fully regio- and stereoselective (only the conformationally more labile D-*xylo*, 2-deoxy-D-*xylo* and 2-deoxy-D-*arabino* derivatives yielded more or less amounts of both anomers). Base induced and acid catalyzed additions of thiols to *exo*-glycals leading to thioglycoside type products were discussed in Ref. [103].

The thiol-ene reactions were applied to 1-C-substituted glycals, e.g. **77** [104] (Scheme 8). Additions of thiols proceeded with exclusive regio- and stereoselectivity in these cases, as well, furnishing the D-*talo* configured adducts **78** from **77** of D-*lyxo* configuration. The yields for compounds **78** diminished depending on the 1-C-substituents $CONH_2 > CO_2Me > CN$. Since the thiyl radicals are electrophilic, this observation can be

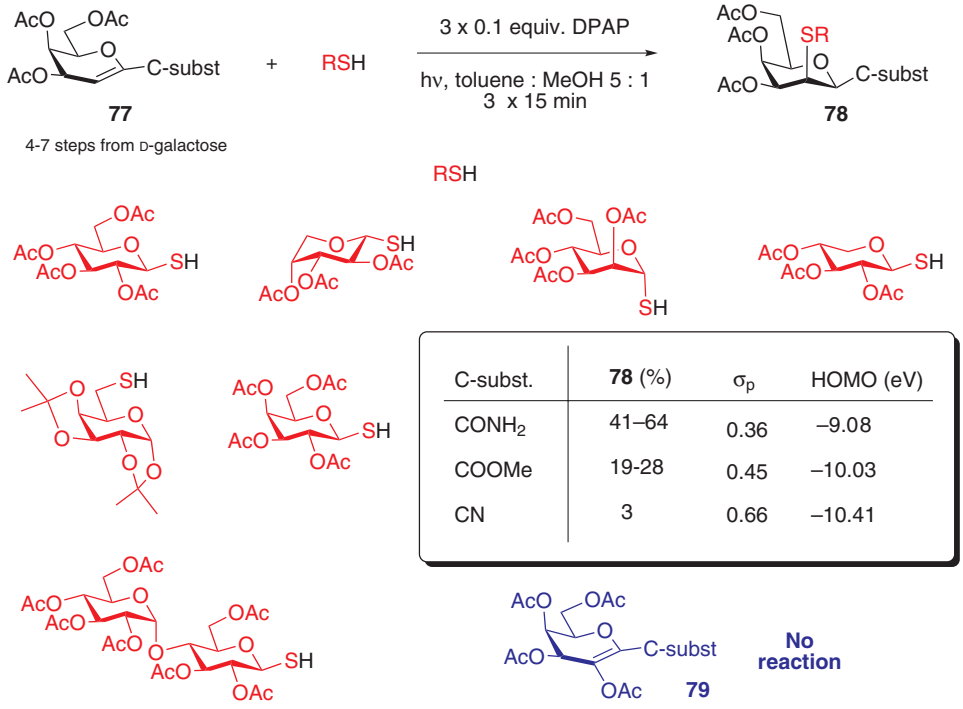
Table 2: Synthesis of *exo*-glycals from anhydro-aldose tosylhydrazones **65** [92, 93, 99].



Gly = CH_2					
Isolated yield (%)	**74**	**A:** 82	**A:** 39 + 22 % of **75**	**A:** 72	**A:** 86 (2 eq NaH)
Gly = CH_2					
Isolated yield (%)	**74**	**A:** 99 (4 eq NaH) [82]	**A:** 74	**A:** 50 (2 eq NaH)	
Gly = CH_2					
Isolated yield (%)	**74**	**B:** 52 [100]	**B:** 59 [100]	**B:** 76 [100]	**B:** 40 [100]



Scheme 7: Photoinitiated thiol-ene couplings of *exo*-glycals.

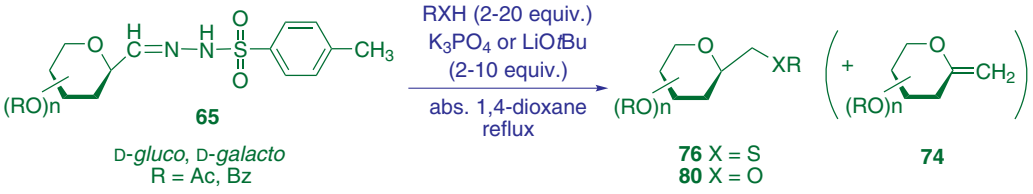


Scheme 8: Photoinitiated thiol-ene additions with 1-C-substituted D-galactals.

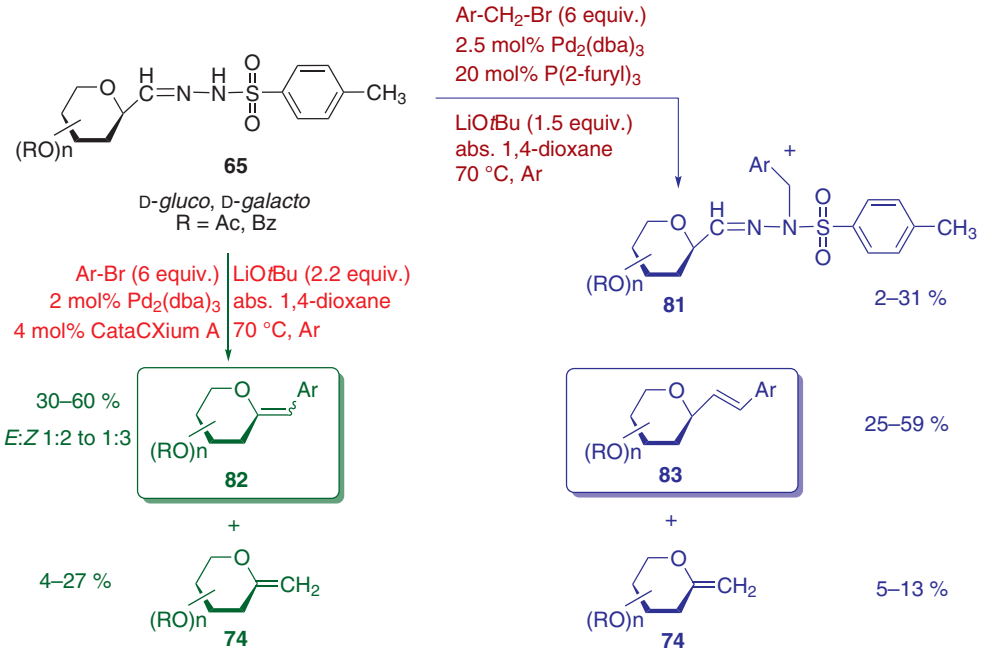
well correlated with the Hammett σ_p values characterizing the electron withdrawing ability of the substituents as well as the calculated HOMO energy levels of the double bonds. Extension of the thiol-ene additions to 1-C-substituted-2-acetoxy-galactals **79** remained unsuccessful.

In the presence of RXH reagents and bases, tosylhydrazones **65** undergo coupling reactions to produce Gly-CH_2-X-R type compounds as summarized in Table 3. In such reactions the intramolecular formation of *exo*-glycals **74** is competing with the intermolecular coupling, therefore, **74** can always be isolated from the reaction mixtures. Aliphatic alcohols except hexafluoro-isopropanol gave no coupled product **80** (Entries 1 and 2). With phenols **80** were formed in moderate yields (Entry 3). In the reactions with carboxylic acids the yields of **80** increased to give the best results with sugar derived acids (Entries 4–6) [105]. The glycosylmethyl sulfides **76** were obtained in moderate and good yields with aliphatic thiols and thiophenols, respectively (Entries 7 and 8) [106]. The observed yields and the acidity of the reagents may be correlated: there is no

Table 3: Couplings of anhydro-aldose tosylhydrazones **65** with hydroxy compounds, carboxylic acids and thiols.



Entry	R	XH	Product	Isolated yield (%)	pK_a (RXH)
1	Aliphatic	OH	**80**	–	17–14
2	$(CF_3)_2CH$-	OH	**80**	35	9.3
3	Aromatic	OH	**80**	25–39	10–7
4	Aliphatic	COOH	**80**	28–58	5–4
5	Aromatic	COOH	**80**	36–43	4–2.5
6	Sugar	COOH	**80**	48–66	
7	Aliphatic	SH	**76**	21–51	11–9
8	Aromatic	SH	**76**	53–77	7–5



Scheme 9: Syntheses of substituted *exo*-glycals and ω-(*C*-glycopyranosyl)-styrenes by Pd-catalyzed cross couplings of anhydro-aldose tosylhydrazones.

reaction if the pK_a is >11, moderate yields can be achieved in the 11–9 range, while with more acidic compounds the coupling can be rather efficient. It is to be noted, that the two routes applied for the preparation of glycosylmethyl sulfides **76** proved complementary: with aliphatic thiols the two-step transformations (thiol addition to *exo*-glycals **74** formed from tosylhydrazones **65**), while with thiophenols the direct couplings with tosylhydrazones **65** were more efficient in terms of overall yields [106].

Carbenes to be formed from tosylhydrazones are able to coordinate to metal centers e.g. in Pd-complexes. Rearrangements of such carbene complexes and subsequent reductive elimination may lead to various products depending on other compounds present in the coordination sphere of the metal. Thus, the reactions of **65** with aryl bromides in the presence of $Pd_2(dba)_3$ resulted in aryl-substituted *exo*-glycals **82** [107], while with benzyl bromides *C*-glycopyranosyl styrenes **83** were formed [108] (Scheme 9). In these transformations several pathways are open both for the deprotonated tosylhydrazone and the carbene intermediate and, as a consequence, the formation of **81** by a nucleophilic substitution of the tosylhydrazone on the benzyl bromide as well as that of *exo*-glycals **74** due to intramolecular insertion can be observed and the by-products can be isolated. In the light of these parallel reactions the yields for **82** and **83** are satisfactory and these reactions are competitive alternatives of other synthetic methods.

Conclusion

The summarized works demonstrate the versatile transformations based on glycosyl cyanides and other precursors derived from them to lead to a wealth of glycomimetic compounds. Thus, various *C*-glycosyl heterocycles and other *C*-glycosyl derivatives like anhydro-aldimine type compounds, *exo*-glycals, C–S bonded oligosaccharide mimetics can be obtained by the elaborated synthetic methods. Some representatives of the *C*-glycosyl heterocycles, notably 1,2,4-triazoles and imidazoles are the most efficient, nanomolar, glucose analog inhibitors of glycogen phosphorylase known to date. Biological studies conducted with these and other inhibitors demonstrated that beside the expected decrease of blood sugar levels other remarkable effects were also induced that may have potential for therapeutic applications.

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