Synthesis of *C*-glycosyl heterocycles for glycogen phosphorylase inhibition

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Closing report

Aims of this research project

The inhibition of glycogen phosphorylase (GP, the key enzyme of the glycogen metabolism) is a current investigational concept in the therapeutic intervention of type two diabetes because of having the potential to diminish blood sugar levels by the suppression of hepatic glucose production.[1] For this purpose, several inhibitor classes of various molecular scaffolds have been developed[2, 3] involving a great number of glucose derivatives which bind to the catalytic site of the enzyme.[4, 5]

At the beginning of this project, it was known that some *C*-(β-D-glucopyranosyl)-imidazoles and -1,2,4-triazoles displayed nanomolar inhibitory activity towards RMGP*b* (rabbit muscle glycogen phosphorylase *b*).[6]

Considering the above molecules as lead structures, the aims of this research project have been the design and syntheses of further *C*-glycosyl heterocycles for the inhibition of glycogen phosphorylase to extend structure-activity relationships. These studies involved novel or improved preparations of the leads, and construction of additional five- and six-membered heterorings attached to the C-1 carbon of the glucose part. The planned syntheses included the use of known anhydro-aldonic acid derivatives as starting materials (e.g. glycosyl cyanides, -formamides, -formimidates and -formamidines) obtained by known or newly elaborated methods, and also the formation of additional related precursors. Another part of this research was directed to the investigation of the variability of the glucose unit in the highly active *C*-glucosyl heterocyclic compounds by a) removal or b) changing the substituents of the glucose moiety and c) by introduction of a double bond at the 1,2-positions of the glucopyranose ring.

Beside the synthetic work, studies of the inhibitory and binding properties of the prepared compounds as well as molecular dockings to help prediction of promising structures have been implemented in the frames of national and international collaborations.

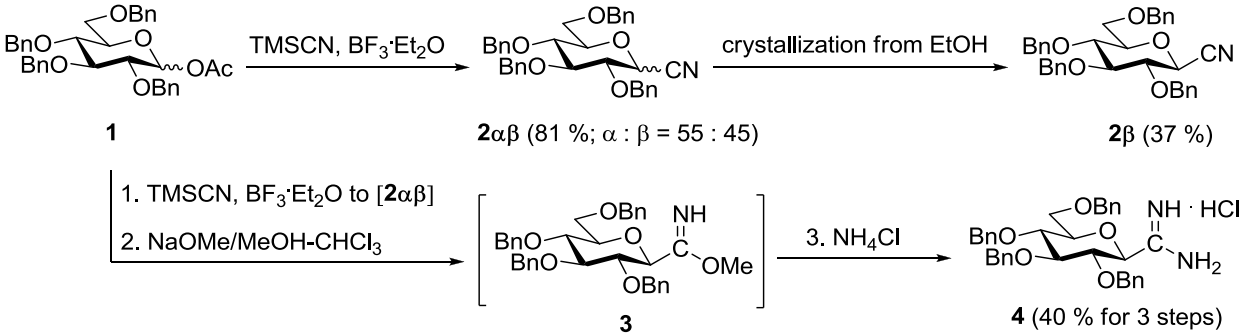
Results of this research project

1. Investigations into the syntheses of glycosyl cyanides and their transformations into further precursors

For a new synthesis of per-*O*-acylated β-D-glucopyranosyl cyanide the reaction of methyl 2,3,4,6-tetra-*O*-acetyl-α-D-glucopyranoside with TMSCN was investigated in the presence of $AuBr_3$[7] as well as pyridinium salts[8] (*sym*-collidine, 2,2'-dipyridyl), however, these experiments were unsuccessful.

To get per-*O*-benzylated β-D-glucopyranosyl cyanide we turned to a literature method. In this procedure $BF_3{\cdot}Et_2O$ promoted substitution of 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose with TMSCN furnished an anomeric mixture of the glucosyl cyanide, from which separation of the pure β-cyanide was performed by preparative thin layer chromatography followed by crystallization from EtOAc.[9]

For a large scale synthesis of the above glucosyl cyanide (Scheme 1, **2β**) some modifications of the original protocol had to be made: contrary to the literature, EtOH proved suitable for the crystallization of **2β** after column chromatographic purification of the mixture **2αβ**. In addition, the conversion of **1** into **2αβ** was the starting point of the preparation of per-*O*-benzylated β-D-glucopyranosyl-formamidine **4**, as well (Scheme 1). This compound was obtained in a consecutive reaction sequence **1**→[**2αβ**→**3**]→**4** (in which the **2*α*** cyanide remained intact) without the need of purification of the intermediates. This method has been submitted to a book series compiling controlled protocols for carbohydrate syntheses; currently the checking procedure is in progress.[10]



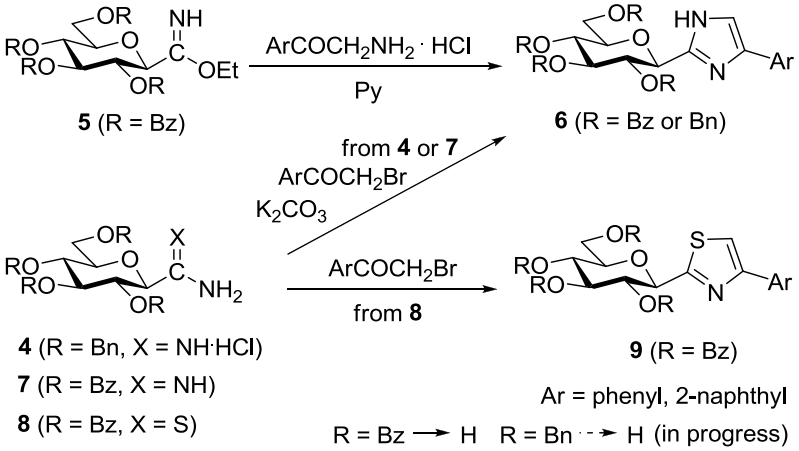
Scheme 1: Gram-scale synthesis of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl cyanide and -formamidine

For the conversion of the above and other glycosyl cyanides into the corresponding *C*-glycosyl formamides (which were also important starting materials for the construction of the planned heterocycles) a new Ru-complex catalyzed chemoselective hydration was worked out.[11]

2. Syntheses of *C*-(β-D-glucopyranosyl)-heterocycles

2.1. New syntheses of *C*-(β-D-glucopyranosyl)-imidazoles and studies on the preparation of related compounds

Our earlier synthetic procedure for the formation of 4(5)-aryl-2-(β-D-glucopyranosyl)-imidazoles was based on the ring closure of *O*-benzoyl protected *C*-(β-D-glucopyranosyl)-formamidine with α-bromoketones (Scheme 2, **7**→**6** R = Bz),[6] however, this reaction furnished the heterocycles only in low yields (10-29 %). In order to find a high-yielding method further synthetic possibilities were investigated.



Scheme 2: Preparation of *C*-(β-D-glucopyranosyl)-imidazoles and -thiazoles

Cyclocondensation of per-*O*-benzoylated ethyl *C*-(β-D-glucopyranosyl)formimidate[12] (**5**) with hydrochlorides of α-aminoketones resulted in the desired heterocycles in moderate yields (42-45 %), while the use of other reagents e.g. *N*-tosylated, *N*-*tert*-butoxycarbonylated α-aminoketones or modifications of the reaction conditions were not successful. On the other hand, other transformations of imidate **5** were also attempted (reagents e.g. oxalyl chloride, glycine ethyl ester, ethylene diamine), however these experiments gave none of the planned heterocycles (imidazolin(di)one, imidazoline).

To improve the yield of the amidine-based synthesis the application of the base stable *O*-perbenzylated amidine **4** was also examined. This protecting group change proved to be effective providing the imidazole derivatives in satisfactory yields (60-70 %). In this case the final deprotection steps to get the test compounds are still in progress.

Beside the synthesis of imidazoles the preparation of the analogous thiazole derivatives was also accomplished (route **8**→**9**) for structure-activity relationship studies.

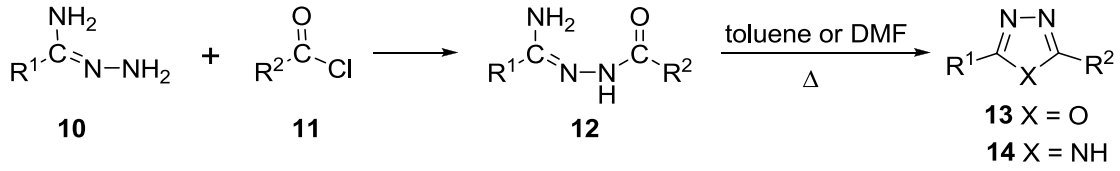
The first preparation of the imidazoles (**7**→**6**) and the synthesis of thiazoles **9** with their enzyme kinetic data for RMGP*b* was summarized in a short communication.[13] Another paper containing the improved synthesis of the imidazoles along with human enzyme kinetic evaluation (HLGPa), and X-ray analyses together with computational predictions (for explanations see section 4.) is in preparation.[14]

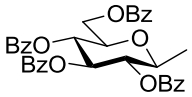
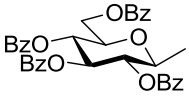
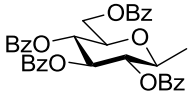
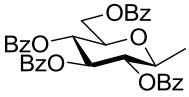
2.2. Extended studies on the preparation of *C*-(β-D-glucopyranosyl)-1,2,4-triazoles and synthesis of new representatives

Several synthetic ways were studied for the preparation of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles.[15-18] Among them the cyclisation of *N*-acyl-amidrazone type *C*-(β-D-glucopyranosyl)formamidrazones and -formic acid hydrazides gave bifurcated results: depending on the position of the sugar and the aromatic part the ring closure led to the formation of the target 1,2,4-triazoles or undesired 1,3,4-oxadiazoles.[6]

Further investigations were performed to elucidate this bifurcation of the ring-closures (Table 1). By the reaction of carboxamidrazones (**10**) with acid chlorides (**11**) each possible variant of the N^1-acyl-amidrazones (**12**) was prepared and subjected to thermic cyclisation (Table 1). To make a complex analysis theoretical calculations were also carried out in collaboration with the István Komáromi group. The quantum chemical calculations on simple model compounds confirmed our synthetic observations indicating that the substitution pattern of the N^1-acyl-amidrazones can strongly influence the direction of the ring closing reaction.[16]

Table 1: Syntheses and ring closures of N^1-acyl-amidrazone derivatives



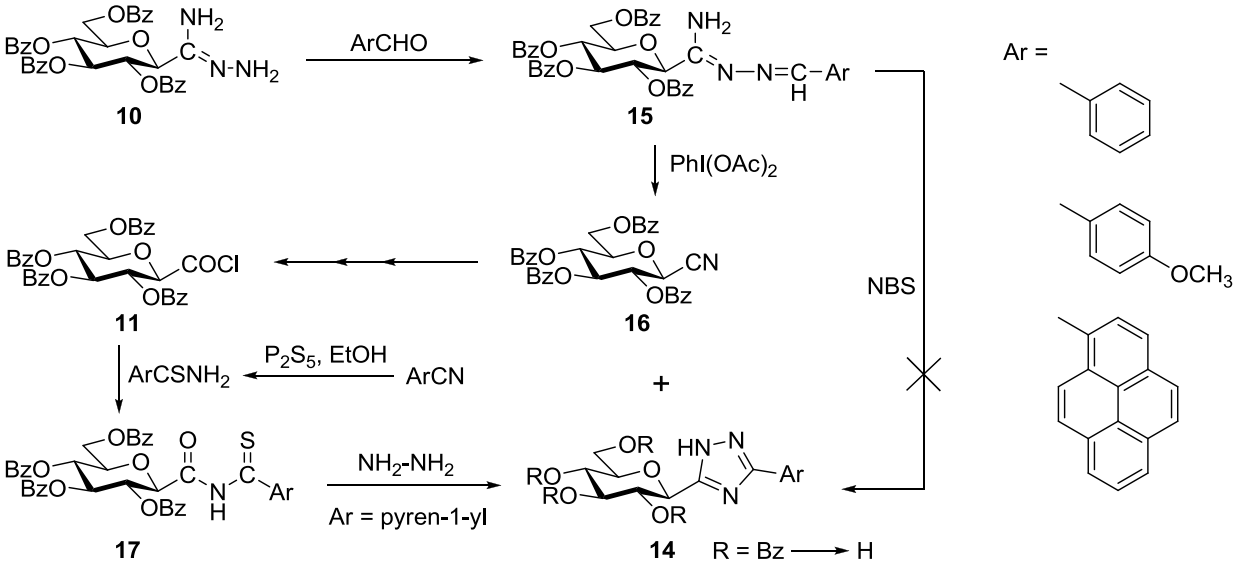
Entry	Starting material of the ring-closing step (**12**)		Isolated (%) or detected* product	
	R^1	R^2	**13**	**14**
1.		Ph	68-71	-
2.	Ph		-	85-90
3.			Traces*	73-76
4.	Ph	Ph	-	70-97

In order to find new efficient representatives of 5-aryl-3-(β-D-glucopyranosyl)-1,2,4-triazoles virtual screening and docking calculations were carried out by the Joseph M. Hayes group focusing on the aryl substituents of these heterocycles. Based on the computational predictions for 150 compounds the pyren-1-yl substituted derivative proved to be one of the most promising ones. Since the structural and the chemical features of this aromatic moiety show high resemblance to those of the 1-naphthyl group, and because of the failure of

preparation of the 1-naphthyl substituted 1,2,4-triazole derivative in each previous way, new synthetic possibilities were tried to obtain these target compounds.

To this end, a recent, novel method for the preparation of 3-(β-D-glycopyranosyl)-5-substituted-1,2,4-triazoles, namely the oxidative ring closure of N^1-(β-D-glycopyranosylmethylidene)-arenecarboxamidrazones[18] was applied to the formally reversed N^1-arylidene-*C*-(β-D-glucopyranosyl)formamidrazones (Scheme 3, **15**) obtained from amidrazone **10**. However, on attempted cyclisations by NBS or PIDA, the expected triazoles were not formed in respectable yields due to other side reactions (NBS resulted in complex mixtures, while PIDA gave cyanide **16** as the main product).[18]

Meanwhile, a useful synthetic route was elaborated for the preparation of the 1-naphthyl substituted 1,2,4-triazole in our laboratory. This method, including the acylation of an aromatic thioamide with *C*-glucopyranosyl formyl chloride **11** followed by ring closure of the resulting intermediate **17** with hydrazine, was successfully employed for the formation of the pyrene-1-yl substituted triazole derivative **14** (Scheme 3). A paper that contains the synthetic details of these compounds and further seven forecasted derivatives as well as the computational and enzyme kinetic results is in preparation.[19]



Scheme 3: New investigated routes towards *C*-(β-D-glucopyranosyl)-1,2,4-triazoles

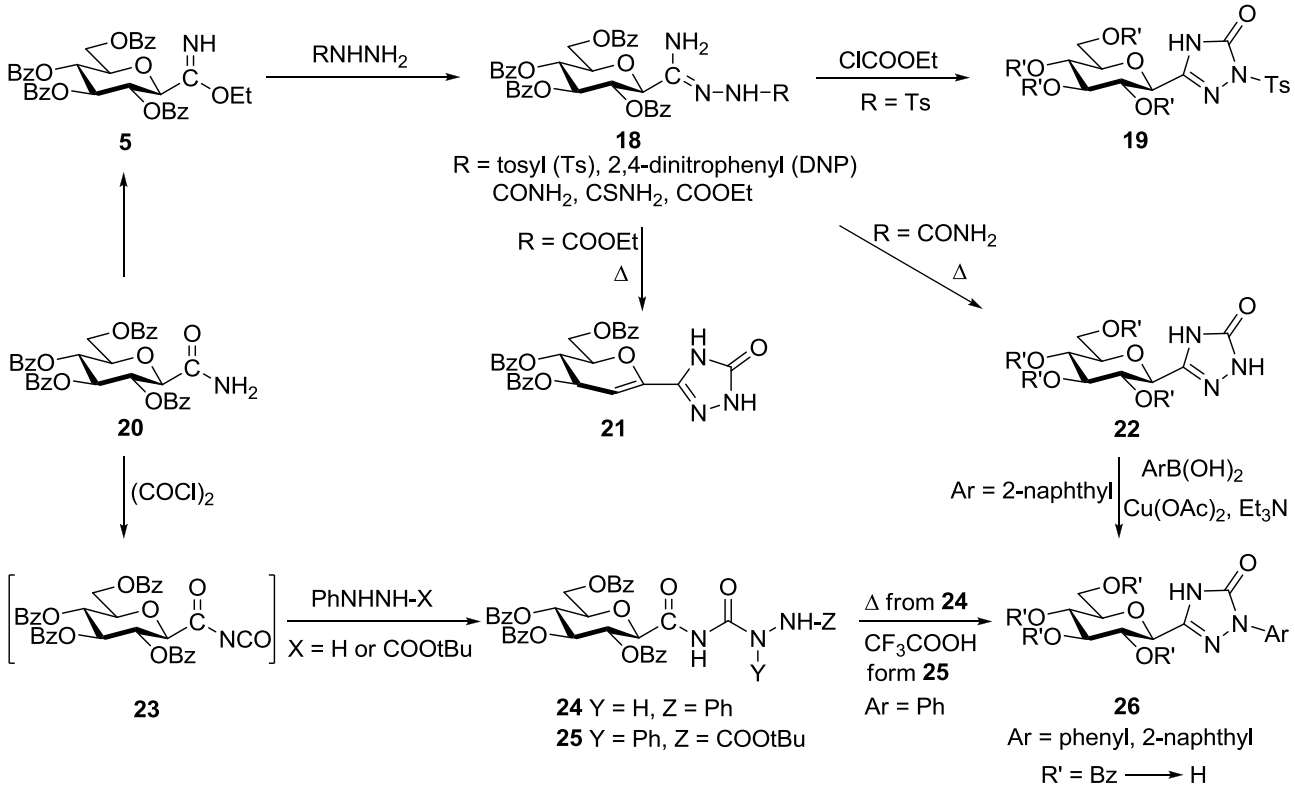
2.3. Synthesis of *C*-(β-D-glucopyranosyl)-1,2,4-triazol-5-ones

In view of the efficiency of the *C*-glucosyl-1,2,4-triazoles, preparation of their 1,2,4-triazolone analogues was also carried out (Scheme 4).

For the construction of these heterocycles we first investigated the cyclisation of N^1-substituted-*C*-(β-D-glucopyranosyl)formamidrazones **18**, which were obtained in the reaction of per-*O*-benzoylated *C*-(β-D-glucopyranosyl)formimidate[12] (**5**) with the corresponding hydrazine reagents. Among subsequent ring closures acylation of the N^1-tosyl-formamidrazone[16] with ethylchloroformate (**18**→**19**) and intramolecular ring closure of the N^1-carbamoyl-formamidrazone (**18**→**22**) gave the desired triazolones. In other cases, either

formation of unexpected products (e.g. **18** (R = COOEt) → **21**) or no reaction (e.g. failure of cyclisation of compound **18** (R = 2,4-dinitrophenyl) with ethylchloroformate) was observed.

Next, for the synthesis of 1-aryl-1*H*-1,2,4-triazole-5(4*H*)-ones two synthetic ways were worked out: a) on route **20→23→24/25→26** the treatment of *in situ* prepared glucopyranosylcarbonyl-isocyanate with phenylhydrazine derivatives followed by intramolecular ring closure of the resulting N^4-glucopyranosylcarbonyl-semicarbazides furnished the phenyl substituted triazolone derivative, and b) copper(II)-catalyzed *N*-arylation of the unsubstituted triazolone **22** with naphthalene-2-boronic acid gave the 1-(2-naphthyl)-triazolone **26**. A manuscript about the synthesis and enzyme kinetic evaluation of these compounds was submitted to Carbohydrate Research (minor revision according to the referees' suggestions is in progress).[20]



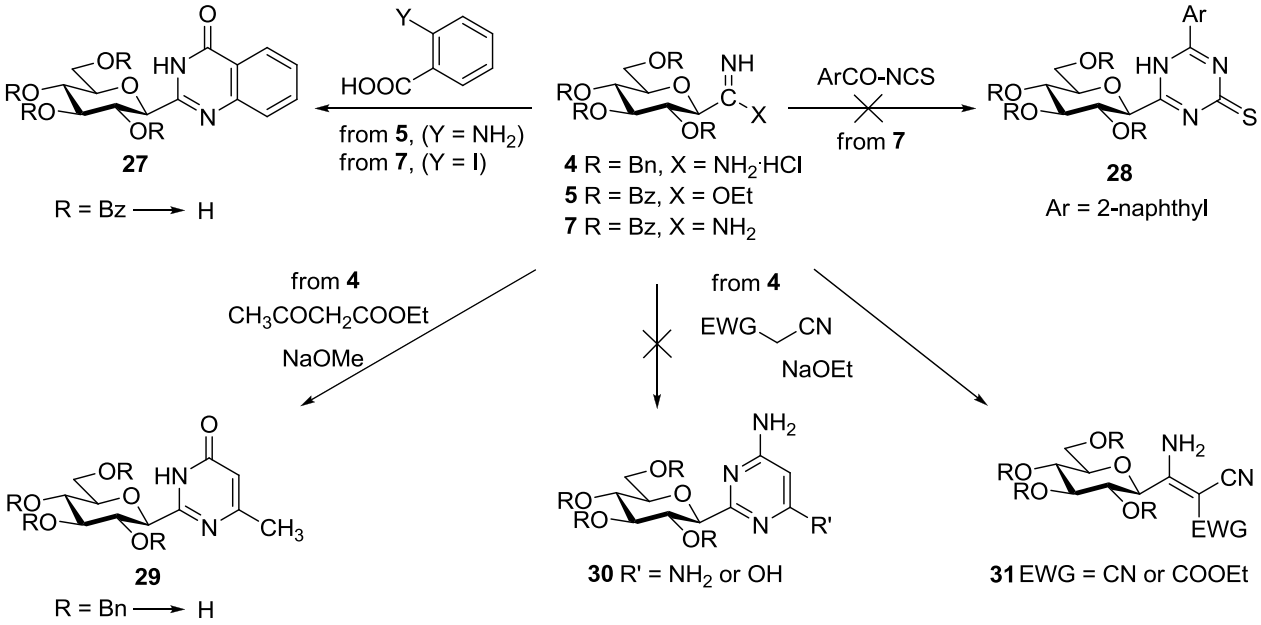
Scheme 4: Preparation of *C*-glucosyl-1,2,4-triazol-5-ones

2.4. Experiments for the syntheses of 6-membered *C*-(β-D-glucopyranosyl)-heterocycles

The use of *C*-(β-D-glucopyranosyl)-formimidate and -formamidines was investigated for the syntheses of six-membered heterocycles (Scheme 5).

To get benzocondensed heterorings from imidate[12] **5** experiments with e.g. 1,8-diaminonaphthalene (to perymidine), 2-amino-benzylamine (to 3,4-dihydroquinazoline) and 2-amino-benzoic acid (to quinazolin-4-one) were carried out, among them the latter cyclisation **5→27** proved to be effective. The cyclocondensation of amidine **7** with 2-naphthoyl isothiocyanate was also attempted, however the expected triazine derivative **28** could not be obtained.

In order to construct *C*-glucosylated analogues of effective nucleoside-based inhibitors of GP[21] the reactions of glucosyl-formamidines with β-dicarbonyl compounds were examined. On treatment of *O*-perbenzoylated glucosyl-amidine[16] **7** with ethyl acetoacetate or diethyl malonate no reactions were observed under neutral conditions, while the use of organic or inorganic bases brought about decomposition. Because of these failures we turned to the application of the less base sensitive amidine **4**. In route **4→29** the 2-glucosyl-6-methylpyrimidin-4(3H)-one was produced, while the planned route towards compounds **30** failed, because unexpected condensations of **4** with the active methylene group of the malonic acid derivatives took place (**4→31)**.



Scheme 5: Studies on the synthesis of 6-membered *C*-(β-D-glucopyranosyl)-heterocycles

3. Syntheses of new *C*-glycosyl-imidazoles, -1,2,4-triazoles and -oxadiazoles

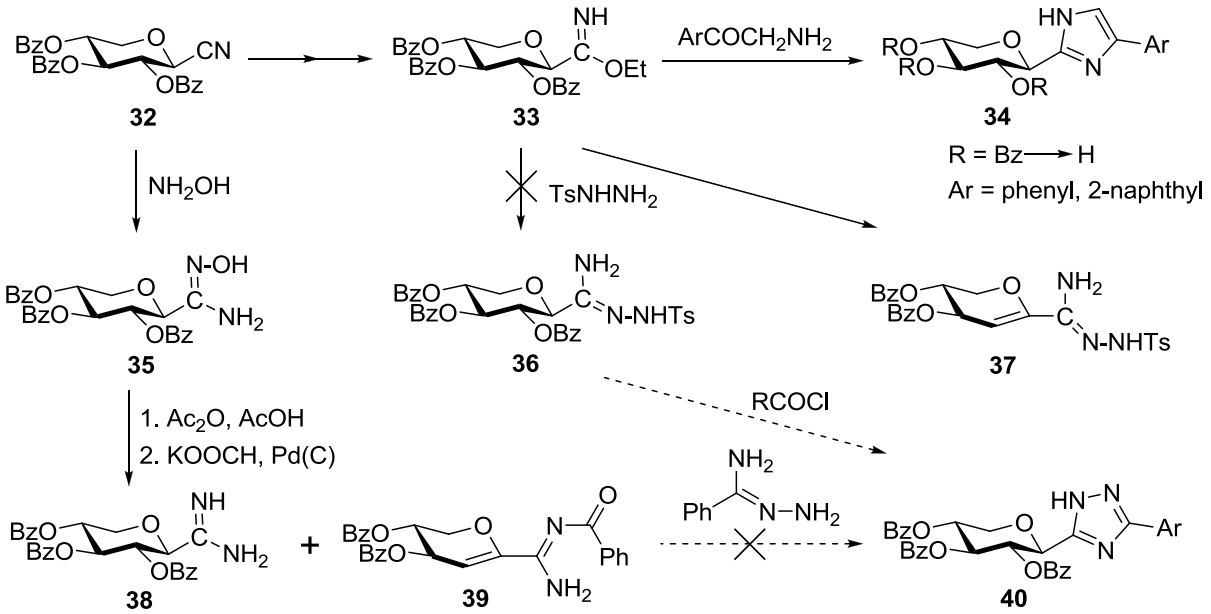
3.1. Investigations into the preparation of *C*-(β-D-xylopyranosyl)-imidazoles and -1,2,4-triazoles

To extend the structure-activity relationships of GP inhibitors the synthesis of xylopyranosyl analogues of the best glucose based compounds i. e. the corresponding imidazole and 1,2,4-triazole derivatives was envisaged (Scheme 6).

For the synthesis of *C*-(β-D-xylopyranosyl)-imidazoles **34** cyclisation of per-*O*-benzoylated ethyl *C*-(β-D-xylopyranosyl)formimidate[22] (**32**) with the corresponding α-amino-ketones was carried out resulting in the target heterocycles in low yields.

The formation of the *C*-(β-D-xylopyranosyl)-1,2,4-triazoles **40** was envisaged by starting from the corresponding *O*-perbenzoylated β-D-xylopyranosyl-cyanide[23] **32** via N^1-tosyl-formamidrazone **36** (route **32→33→36→40**) or formamidine **38** (route **32→35→38→40**). However, neither attempted preparation of amidrazone **36** from imidate[22] **33** nor reduction of the *O*-acetylated derivative of amidoxime **35** to amidine **38** were successful because of

concomitant β-elimination processes (**33→37** and **35→39**). Parallel to these experiments the synthesis of these heterocycles was achieved from *C*-(β-D-xylopyranosyl)-tetrazole in our laboratory, therefore, and due to the above failures the construction of the 1,2,4-triazole ring via amidrazone type intermediates was discontinued.[22]



Scheme 6: Experiments for the synthesis of *C*-(β-D-xylopyranosyl)-imidazoles and -1,2,4-triazoles

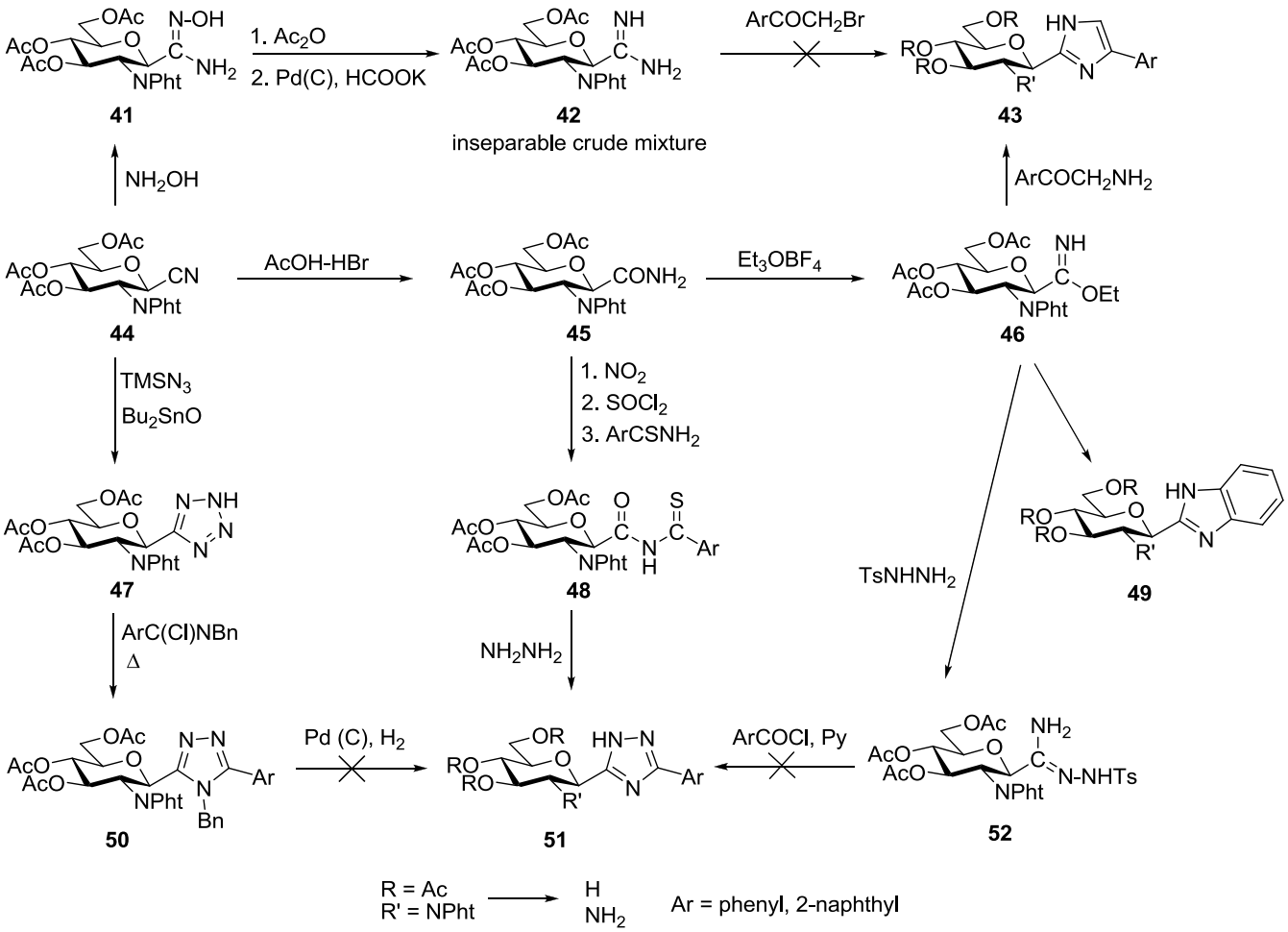
3.2. Synthesis of *C*-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-imidazoles and -1,2,4-triazoles

For the alteration of the glucose part of the best *C*-glucosyl-heterocycles an isosteric replacement of the hydroxyl group in position 2 by an amino group was also studied.

For the syntheses of *C*-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-imidazoles routes **44→41→42→43** and **44→45→46→43** were examined (Scheme 7). The transformation of cyanide[24] **44** into amidoxime **41** was smoothly accomplished, hovewer, its transfer hydrogenation resulted in the expected amidine **42** along with a high amount of inseparable by-products. On the other route the conversion of amide[25] **45** into imidate **46** and subsequent cyclocondensation with α-amino-ketones provided the imidazole derivatives **43** in moderate yields. In addition, the benzimidazole derivative **49** was also prepared by using **46**.

The formation of 1,2,4-triazole derivatives was tried in three routes (Scheme 7). The ring-closing reaction of tosyl-amidrazone **52** obtained from imidate **46** led to a multicomponent reaction mixture from which the desired heterocycle **51** could not be isolated. By cycloaddition of the cyanide **44** with $TMSN_3$, tetrazole **47** was produced which was then treated with imidoyl-chlorides to afford the 5-aryl-4-benzyl-1,2,4-triazoles **50**. However, attempted cleaveage of the *N*-benzyl group (**50→51**) either from the *O*-acyl-protected or from the deacylated compounds failed. Finally, formamide **45** was transformed into **48** in a three-

step procedure and subsequent treatment with hydrazine furnished the heterocycles **51**. This synthetic work is ready for publication and along with the enzymatic results (see below in section 4.) will be reported soon.[26]



Scheme 7: Preparation of *C*-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-imidazoles and -1,2,4-triazoles

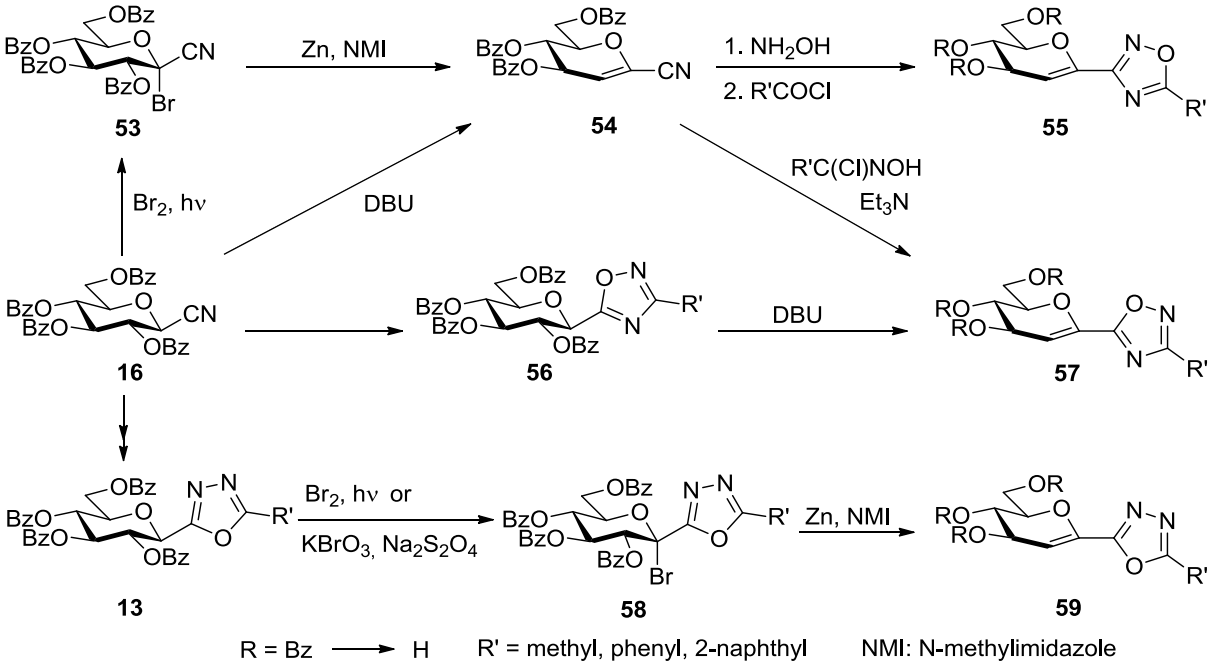
3.3. Synthesis of 1-*C*-hetaryl-glucals and -2'-acyloxy-glucals

The conformation of the sugar part of D-glucal derived compounds (half chair) is very similar to that of the glycosylium ion like intermediate of the GP-catalyzed reaction.[27] Therefore, it was assumed that heterocycles attached to the C-1 atom of D-glucal or 2-deoxy-D-glucal can bind to the active centre of the enzyme.

The preparation of 1-*C*-hetaryl-glucals and -2-hydroxy-glucals was investigated in two main routes: a) by the formation of a suitable glucal-based anhydro-aldonic acid precursor followed by construction of the heterocycle in the final stage or b) introduction of the 1,2-double bond into a pre-formed *C*-β-D-glucopyranosyl heterocycle.

By applying the above mentioned synthetic strategies each constitutional variant of *C*-(2'-deoxy-D-*arabino*-hex-1'-enopyranosyl)-oxadiazoles was easily obtained (Scheme 8). The 5-aryl-substituted 1,2,4-oxadiazoles were prepared in route **16→(53)→54→55** via the

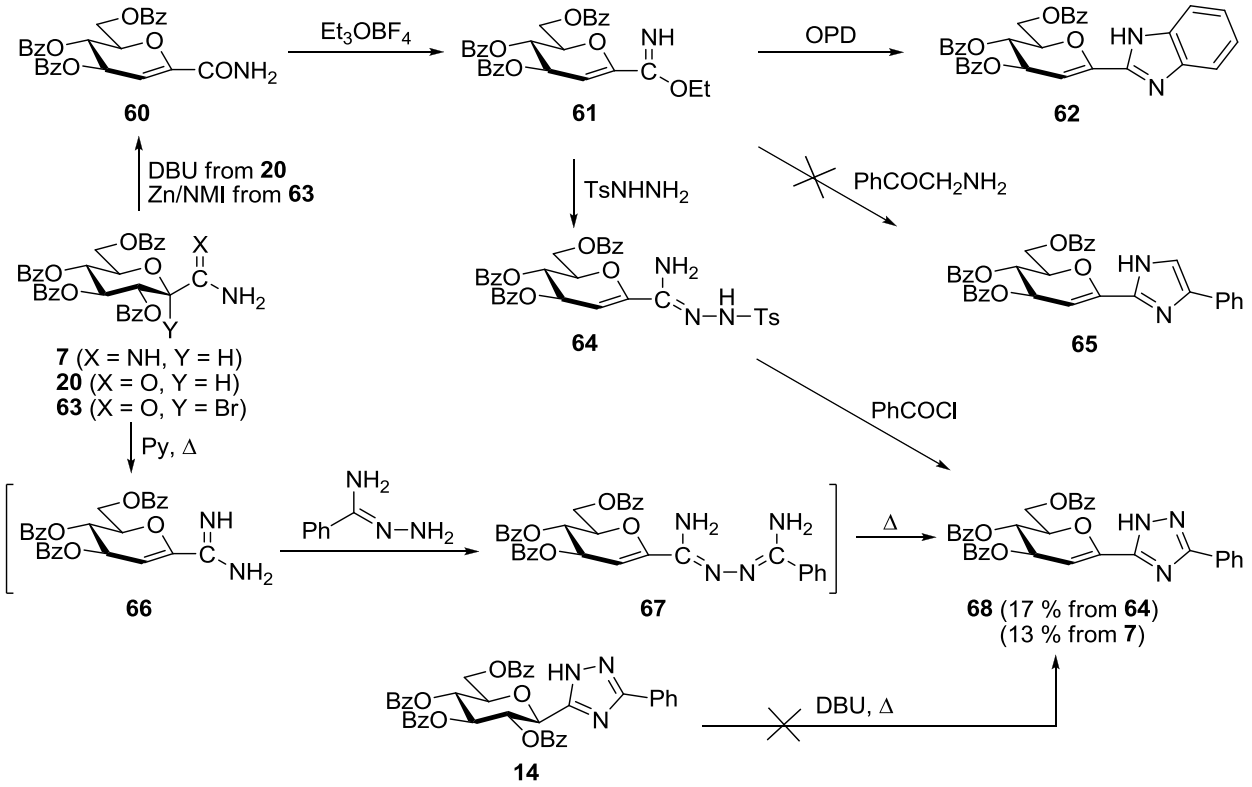
corresponding cyano-glucal **54**. For the formation of the reversed 3-aryl-1,2,4-oxadiazoles both transformation of the cyano-glucal **54** and base-induced elimination of benzoic acid from the corresponding glucopyranosyl-oxadiazoles **56** were succesfully employed. The 1,3,4-oxadiazoles were achieved in route **16→13→58→59** by using the Zn-mediated reductive elimination of the brominated compound **58** as the key step of this procedure.[28]



Scheme 8: Synheses of *C*-(2'-deoxy-D-arabino-hex-1'-enopyranosyl)-oxadiazoles

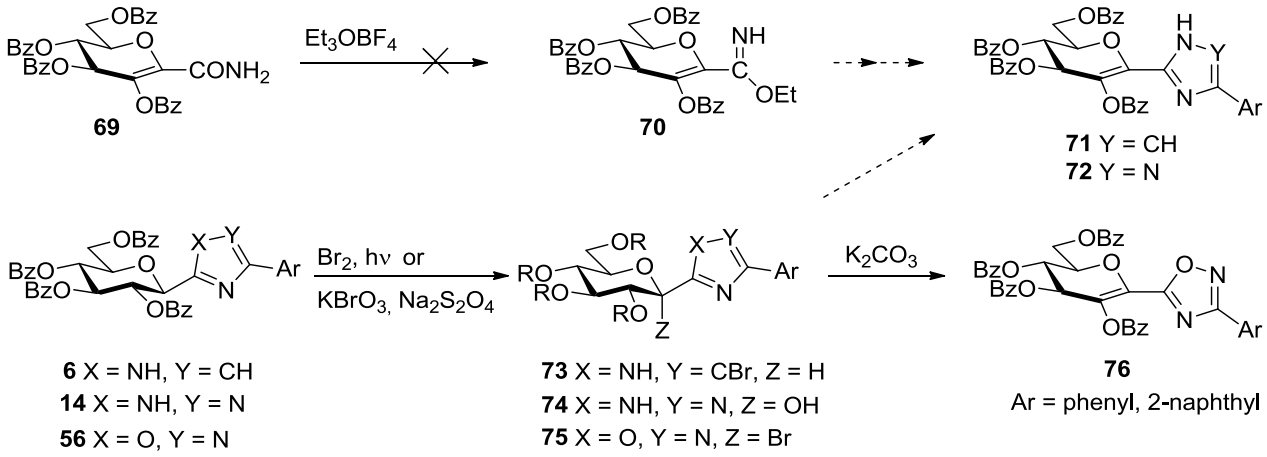
For the construction of imidazole as well as 1,2,4-triazole rings attached to the C-1 atom of the glucal the use of precursors similar to those applied in the glycopyranosyl series was planned.

Treatment of imidate **61** (Scheme 9) obtained in route **20(63)→60→61** with 1,2-diaminobenzene gave the benzimidazole derivative **62**, while its reaction with phenacylamine to get imidazole **65** resulted in decomposition products. For the synthesis of the phenyl substituted 1,2,4-triazole **68** ring-closing reaction of the N^1-tosyl-amidrazone **64** gave the target compound **68** in low yield. Synthesis of the same heterocycle was tried in route **7→66→67→68** which proved a low-yielding method, as well. On the other hand, preparation of **68** was also attempted form the corresponding *O*-perbenzoylated glucopyranosyl-1,2,4-triazole **14**, however no reaction was observed. To get the above heterocycles **62** and **68** in sufficient amounts for the final debenzoylation step the reaction sequences will have to be repeated.



Scheme 9: Investigations on the preparation of *C*-(2'-deoxy-D-arabino-hex-1'-enopyranosyl)-imidazoles and -1,2,4-triazoles

The imidazole- and 1,2,4-triazole-containing 2'-benzoyloxy-glucals **71** and **72**, respectively, could not be achieved (Scheme 10,), because none of the above type precursors could be prepared in the applied synthetic routes. Attempted conversion of the corresponding amide[29] **69** into imidate **70** resulted in a complex reaction mixture, while the radical bromination of the corresponding glucopyranosyl heterocycles (**6**, **14**) afforded unwanted products (**73**, **74**) instead of the expected α-bromo compounds (Z = Br).



Scheme 10: Investigations on the preparation of *C*-(D-arabino-hex-1'-enopyranosyl)-heterocycles

Contrarily, the latter strategy was easily carried out for the preparation of the 1,2,4-oxadiazole derivatives **76**. After bromination at the C-1 centre of compounds[30] **56** K_2CO_3-mediated HBr elimination yielded the 1,2-unsaturated derivatives **76**. Since these molecules decomposed under Zemplén conditions, further experiments will be necessary to get the unprotected test compounds.

4. Enzymatic studies

The inhibitory potency of the final deprotected compounds was assayed against rabbit muscle glycogen phosphorylase *b* (RMGP*b*) in cooperation with the Pál Gergely group in the Department of Medical Chemistry of the University of Debrecen.

These data showed (Table 2) that the replacement of the imidazole and 1,2,4-triazole rings by analogous heterocycles such as thiazoles[13] and triazol-5-ones,[20] respectively, resulted in significant impairment of the inhibitory activities (see the comparable pairs in entries 1 and 2, and 6 and 7, respectively). Furthermore, the quinazolin-4-one (entry 9) as the first tested six-membered *C*-glucopyranosyl-heterocycle displayed no inhibition.

The introduction of the pyrene-1-yl substituent of the 1,2,4-triazole moiety (entry 6) decreased the solubility of the molecule thereby making the kinetic measurement impossible. Among other substituents predicted by Joseph M. Hayes and co-workers (School of Physical Sciences & Computing, Division of Chemistry, University of Central Lancashire, United Kingdom) some other aryl groups proved beneficial providing new micromolar inhibitors of RMGP*b*.[19]

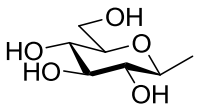
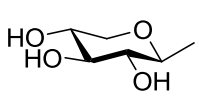
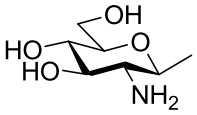
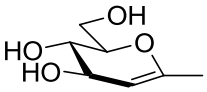
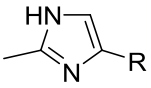
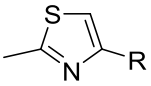
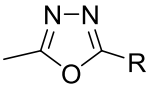
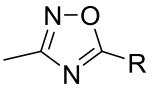
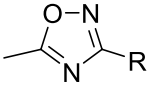
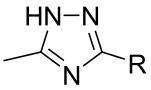
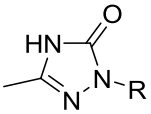
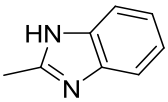
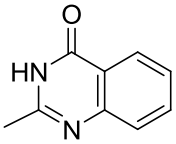
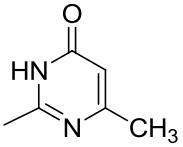
The alterations of the sugar part of the glucose-based heterocycles were detrimental for the inhibition resulting in either inactive or less efficient molecules (entries 1, 3-5, 6, 8). However, in case of the glucosamine-based imidazoles, the aglycon part, especially with the 2-naphthyl substituent, could significantly compensate the modification of the sugar unit (entry 1), rendering the above molecule to a nanomolar inhibitor of GP.[26]

As part of a collaboration with Demetres D. Leonidas and co-workers (Department of Biochemistry and Biotechnology, University of Thessaly, Larissa, Greece) kinetic measurements with human liver enzyme and X-ray crystallographic analysis of the best compounds such as *C*-(β-D-glucopyranosyl)-imidazoles, -1,2,4-triazoles and *C*-(2'-amino-2'-deoxy-β-D-glucopyranosyl)-imidazoles were also carried out. According to the *in vitro* enzyme kinetic results these compounds are equipotent inhibitors of each investigated isoenzyme (RMGP*b*, RMGP*a*, HLGP*a*). The protein crystallographic studies on the binding peculiarites of these heterocycles revealed that the NH-group of the heteroaromatic rings forms a direct H-bond with the main chain carbonyl group of the His377 amino acid residue, which plays a key role for the strong binding at the active site of RMGP*b*.[14, 26, 31]

In the frame of a cooperation with the Igor Tvaroska group (Institute of Chemistry, Slovak Academy of Sciences, Bratislava, Slovakia) molecular dockings for a set of azole-type *C*-glucopyranosyl heterocycles were also performed, and these calculations confirmed the superior effectiveness of the 2-naphthyl-imidazole derivative, as well.[14]

In vivo studies by using some of the most efficient inhibitors are in progress in the Department of Medical Chemistry of the University of Debrecen.

Table 2: Inhibitory effect (K_i/IC_{50}* [μM]) of *C*-glycosyl heterocycles against rabbit muscle glycogen phosphorylase *b* (RMGP*b*)

Entry	Het	R	Gly–C Het: Gly 			
1.		Phenyl	[a]0.28[6]	800	1.74	-
		2-Naphthyl	[a]0.031[6]	Insoluble	0.19	-
2.		Phenyl	310[13]	-	-	-
		2-Naphthyl	158[13]	-	-	-
3.		Methyl	212,[32] 145[33]	-	-	[b]NI[28]
		Phenyl	10 % at 625 μM[30]	-	-	[b]NI[28]
		2-Naphthyl	10 % at 625 μM[30]	-	-	[b]NI[28]
4.		Phenyl	10 % at 625 μM[34]	-	-	[b]NI[28]
		2-Naphthyl	38[34]	-	-	[b]NI[28]
5.		Phenyl	64[30]	-	-	[b]NI[28]
		2-Naphthyl	12 (2.4)[30]	-	-	[b]NI[28]
6.		Phenyl	[a]7[6]	[b,c]NI[22]	[d]EP	-
		2-Naphthyl	[a]0.41[6]	[c]491[22]	[d]EP	-
		Pyren-1-yl	Insoluble	-	-	-
7.		H	[b]NI[20]	-	-	-
		Phenyl	191[20]	-	-	-
		2-Naphthyl	80[20]	-	-	-
		Tosyl	[b]NI[20]	-	-	-
8.		-	11,[32] 9[33]	[b]NI[22]	150*	-
9.		-	[b]NI	-	-	-
10.		-	[d]EP	-	-	-

The cells showing the compounds related to this research project are highlighted in grey
[a]Lead compounds of this study
[b]NI: no inhibition at 625 μM
[c]Because of our synthetic difficulties these compounds were prepared in an independent way.
[d]Enzyme kinetic measurements are in progress

Publications

Related to the scientific results of this work 10 papers have been published (marked in bold in the reference list) mostly in international journals (refs. 11, 13, 15-18, 22, 28), among them a manuscript is subject of requested minor revision before final acceptance for publication (ref. 20), and an overview about the antidiabetic research topics based on sugar derived compounds was also published in a Hungarian journal (ref. 35).[35] Two of the papers received publication prizes (refs. 15 and 16). In addition, further 4 papers, including our synthetic results, and computational, human enzyme kinetic and X-ray crystallographic studies of our international collaborators, are in preparation (refs. 14, 19, 26, 31, underlined). Another description about an elaborated synthetic method has been submitted to a book series compiling controlled protocols for carbohydrate syntheses (ref. 10, underlined). In the course of this research project 12 oral lectures and 15 posters were presented in domestic and international conferences.

Diploma theses related to this research project:
Széles, Zsolt: *C-Glikopiranozil-1,2,4-triazol(ti)onok, mint lehetséges glikogén foszforiláz inhibitorok előállítása* (BSc diploma thesis, 2012)
Koppány, Csenge Dóra: *Új C-(β-D-glikopiranozil)-azolok előállításának vizsgálata a glikogén foszforiláz enzim gátlására* (MSc diploma thesis, 2014)
Csupász, Tibor: *1-C-Hetaril-glükál származékok prekurzorainak szintézise és átalakítási lehetőségeik vizsgálata* (BSc diploma thesis, 2014)
Szakács, Andrea: *2-(β-D-Glikopiranozil)-4(5)-(2-naftil)-imidazolok előállítása a glikogén foszforiláz enzim gátlására* (BSc diploma thesis, 2014)
Tóth, Nóra: *Anomer centrumon módosított C-glükozil-oxadiazolok szintézisének vizsgálata a glikogén foszforiláz enzim gátlására* (BSc diploma thesis, 2015)

Possible utilization of the results of this research

This research project resulted in some efficient glycogen phosphorylase inhibitors. After further biological and pharmacological assays and drug development processes these compounds may have therapeutical application in the medication of type two diabetes.

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