Theses of doctoral (Ph.D.) dissertation

SYNTHESIS OF *C*-GLYCOSYL HETEROCYCLES FOR INHIBITION OF GLYCOGEN PHOSPHORYLASE

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1. Introduction

Type two *diabetes mellitus* is a severe metabolic disease of carbohydrate metabolism with economic and social consequences. Since there is no cure for this disease, the primary goal of the treatment is to keep the blood sugar concentration at a desirable level. A new possible treatment is the suppression of hepatic glucose output by the inhibition of glycogen phosphorylase, the main regulatory enzyme of glycogen degradation.

N-Acyl-β-D-glucopyranosylamines (**1**) and *N*-acyl-*N'*-β-D-glucopyranosyl ureas (**2**) are efficient competitive inhibitors of GP (Table 1). X-ray crystallographic studies showed that a direct hydrogen bond exists between the amide NH of *N*-acyl-β-D-glucopyranosylamines and the enzyme, and plays a significant role in the strong binding. This hydrogen bridge is missing in the case of *N*-acyl-*N'*-β-D-glucopyranosyl ureas, the good inhibition is the result of the more extensive favourable interactions of the aglycone and the β-channel.

Former studies pointed out that replacing the NHCO moiety of *N*-acyl-β-D-glucopyranosylamines with non-classical bioisosteric heterocycles (**3-7**) resulted in chemically more stable molecules, which were similarly efficient in terms of inhibition.

Table 1: Glucose analogue inhibitors of GP (RMGP*b*, K_i [μM])

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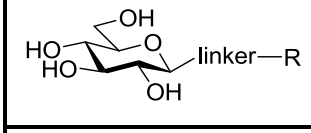
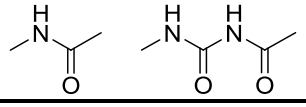
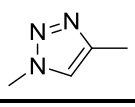
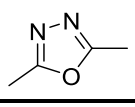
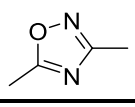
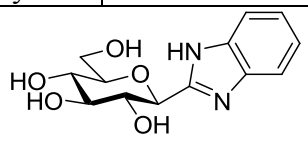
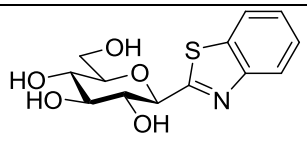
					
R	**1**	**2**	**3**	**4**	**5**
a CH_3	32	305	-	145	-
b Phenyl	81	4.6	151	-	64
d 2-Naphthyl	10	0.35	16	-	2.4

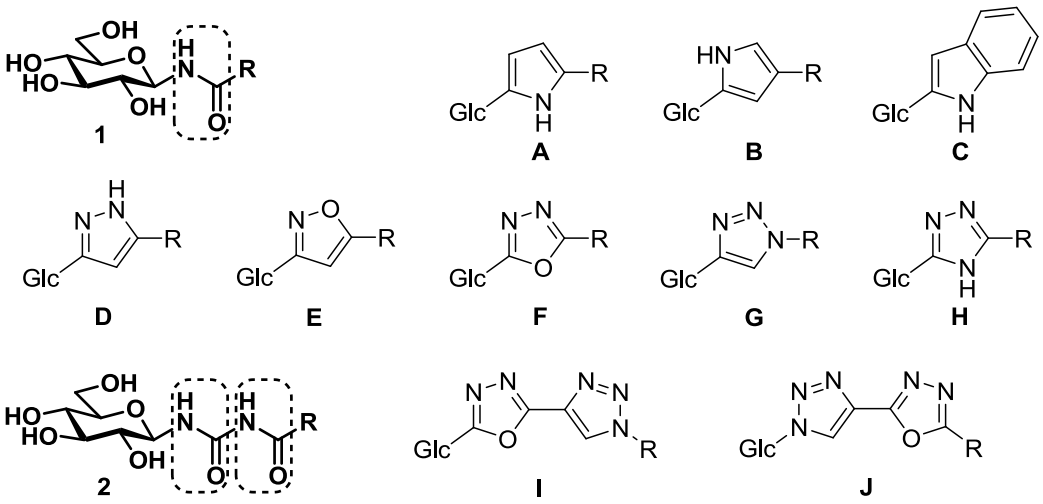


6 K_i = 9 μM



7 K_i = 76 μM

The aim of our research was the preparation of azole type *C*-glycosyl heterocycles (Scheme 1) representing a formal replacement of the NHCO moiety of *N*-acyl-β-D-glucopyranosylamines (**1**) with pyrrole (**A**, **B**), indole (**C**), pyrazole (**D**), isoxazole (**E**), 1,3,4-oxadiazole (**F**), 1,2,3-triazole (**G**) and 1,2,4-triazole (**H**), as well as the double replacement of NHCO units in *N*-acyl-*N*'-β-D-glucopyranosyl ureas (**2**) with 1,3,4-oxadiazole and 1,2,3-triazole (**I**, **J**).



Scheme 1: Inhibitor design

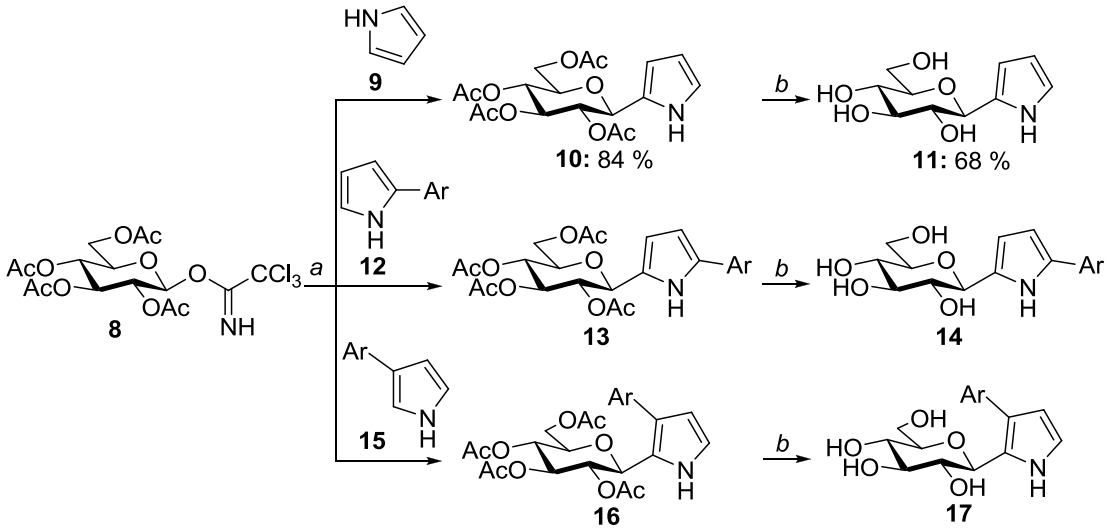
2. Methods

In the course of the synthetic work, macro, semimicro and micro methods of modern preparative organic chemistry were applied. Reactions were monitored by thin-layer chromatography. Products of the reactions were purified by column chromatography and/or crystallization. New compounds were characterized by their physical properties (melting point, optical rotation) and their structures were elucidated by one or two-dimensional ^{1}H and ^{13}C NMR methods as well as mass spectrometry.

3. Results

3.1. Synthesis of 2-(β-D-glucopyranosyl)-pyrroles

Pyrrole (**9**) and 2- and 3-aryl-pyrroles (**12**, **15**), synthesised by literature methods, were *C*-glycosylated with trichloroacetimidate **8** to give 2-(2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl)-pyrroles **10**, **13**, and **16**, respectively (Scheme 2). From 3-aryl-pyrroles **15** the sterically crowded 2-glucosyl-3-aryl pyrroles **16** were formed instead of the expected 4-aryl-2-glucosyl-pyrroles. Acetyl protecting groups were cleaved by the Zemplén method to yield **11**, **14**, and **17**.



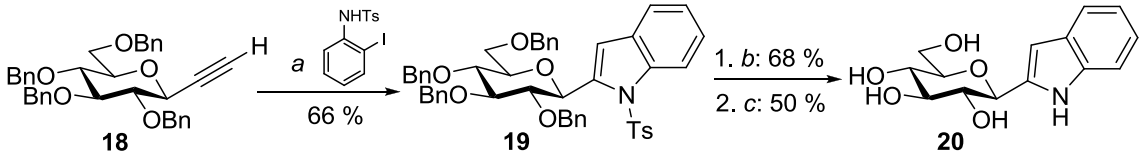
	Yields (%)			
Ar	**13**	**14**	**16**	**17**
a Ph	57	80	44	78
b 2-Naphthyl	51	58	69	70

a: $BF_3{\cdot}Et_2O$, abs. CH_2Cl_2, -50 °C, 4Å MS
b: NaOMe, abs. MeOH

Scheme 2: Synthesis of 2-(β-D-glucopyranosyl)-pyrroles

3.2. Synthesis of 2-(β-D-glucopyranosyl)-1*H*-indole

The Pd-catalyzed cross-coupling of ethyne **18** with *N*-tosyl-2-iodoaniline followed by a ring closure furnished the protected indole derivative **19** (Scheme 3). Removal of the tosyl and benzyl groups resulted in 2-β-D-glucopyranosyl-indole **20**.

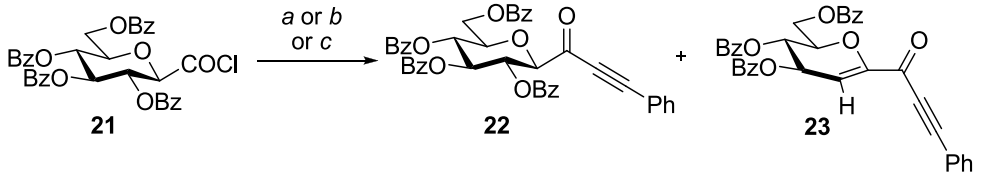


a: $Pd(PPh_3)_4$, CuI, PPh_3, Et_3N, 75 °C; *b*: 1. TBAF, THF, reflux; *c*: 10 bar H_2, Pd(C), abs. EtOAc

Scheme 3: Synthesis of 2-(β-D-glucopyranosyl)-indole

3.3. Synthesis of 3-(β-D-glucopyranosyl)-5-phenyl-1*H*-pyrazole and 3-(β-D-glucopyranosyl)-5-phenyl-isoxazole

These target compounds were synthesised from ethynyl-ketone **22** as a common starting material. Under the widely used basic conditions (*a*) for the synthesis of ethynyl-ketones, acid-chloride **21** gave glycal **23**. To avoid the elimination, base free conditions and flash chromatography were utilized (*c*) to get the desired product **22** in medium yield.

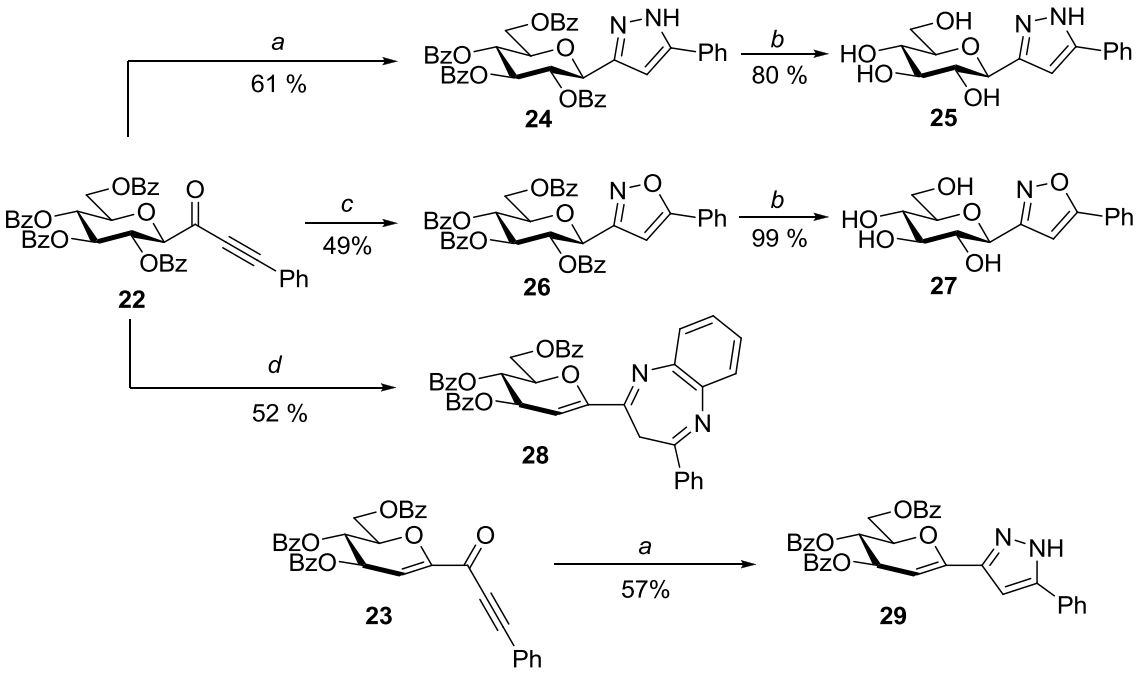


	Reaction conditions	Yields (%)	
		22	**23**
a	PhCCH, $PdCl_2(PPh_3)_2$, CuI, TEA, abs. THF, Ar, r.t.	-	9
b	$PhCCSnBu_3$, $Pd(PPh_3)_4$, abs. toluene, 50°C, Ar, column chromatography	-	31
c	$PhCCSnBu_3$, $Pd(PPh_3)_4$, abs. toluene, 50°C, Ar, flash chromatography	50	traces

Scheme 4: Synthesis of phenylethynyl-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-ketone

Transformations of **22** and **23** with binucleophiles gave pyrazoles **24** and **29**, isoxazole **26** and benzodiazepine **28** (Scheme 5). Protecting groups of **24** and **26** were removed by NaOMe catalyzed transesterification to yield **25** and **27**.[1]

[1] Compound **27** was obtained from a batch of **26** synthesized independently in our research group.

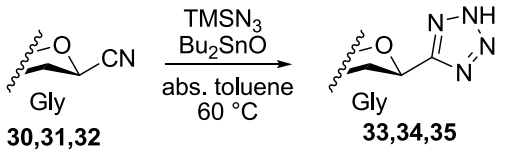


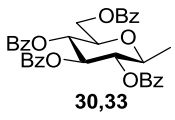
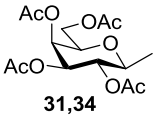
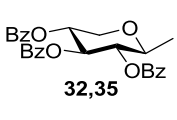
a: $NH_2NH_2 \cdot AcOH$, abs. pyridine, r.t.; *b*: NaOMe, MeOH
c: $NH_2OH \cdot HCl$, abs. EtOH, reflux; *d*: *o*-phenylenediamine, MeOH, AcOH, reflux

Scheme 5: Synthesis of heterocycles from phenylethynyl-ketones

3.5. Synthesis of 2-(β-D-glucopyranosyl)-2-substituted-1,3,4-oxadiazoles

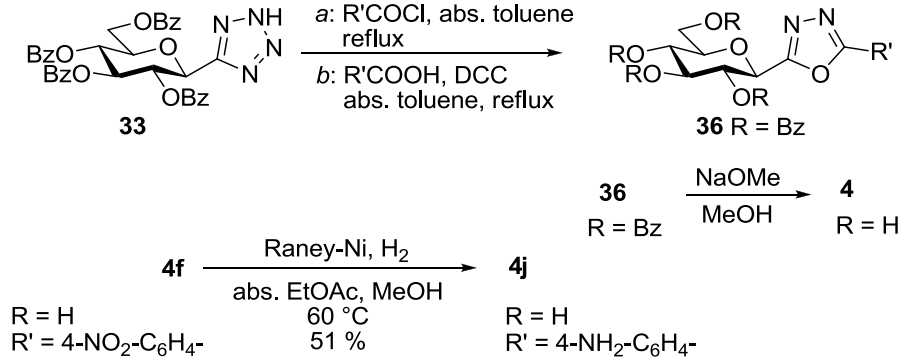
To avoid chromatographic purification in larger scale preparations new reaction conditions were applied for the formation of tetrazoles from anhydro-aldonitriles (Scheme 6). Cyanides **30-32** were converted to tetrazoles with azidotrimethylsilane and dibutyltin oxide. The method proved scalable and per-*O*-acylated β-D-gluco-, galacto- and xylopyranosyl-tetrazoles **33-35** could be isolated by crystallization.



Gly	 30,33	 31,34	 32,35
Products (yields)	**33** (95 %)	**34** (93 %)	**35** (91 %)

Scheme 6: Synthesis of 5-(β-D-glucopyranosyl)-tetrazoles

Acylation and ring transformation of tetrazole **33** yielded 1,3,4-oxadiazoles **36** (Scheme 7). Acylation was carried out by using acid-chlorides (*a*) or DCC activated carboxylic acids (*b*), both methods proved efficient. Removal of the ester protecting groups by the Zemplén procedure gave **4b,d,e,f,i**. Reduction of the 4-nitrophenyl derivative **4f** yielded 4-aminophenyl-1,3,4-oxadiazole **4j**.

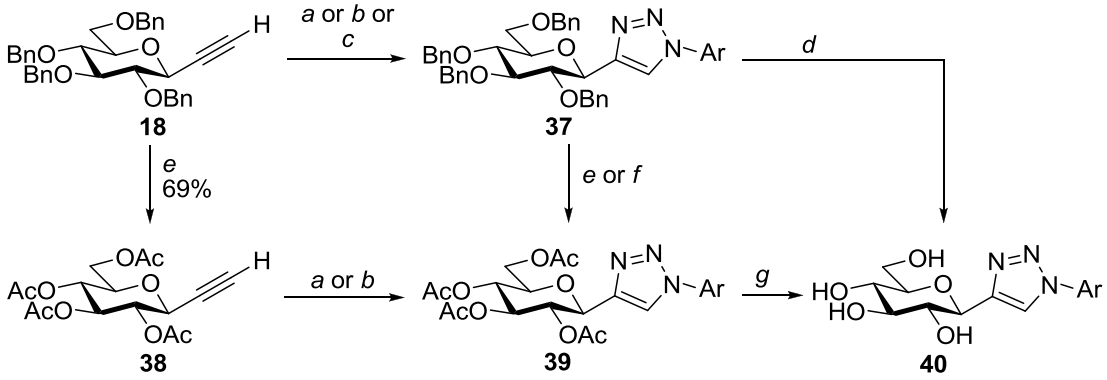


Products **(36)**	R'	Method	Yields (%)	Products **(4)**	R'	Yields (%)
b	C_6H_5	*b*	56	**b**	C_6H_5	91
d	4-MeO-C_6H_4	*a*	40	**d**	4-MeO-C_6H_4	65
e	4-CH_3-C_6H_4	*a*	70	**e**	4-CH_3-C_6H_4	67
f	4-NO_2-C_6H_4	*a*	63	**f**	4-NO_2-C_6H_4	76
g	4-AcO-C_6H_4	*b*	41	**i**	4-HO-C_6H_4	45
h	-C≡CH	*b*	59	**-**	-	-

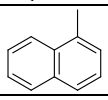
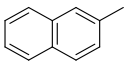
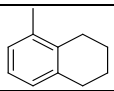
Scheme 7: Synthesis of 2-(β-D-glucopyranosyl)-5-substituted-1,3,4-oxadiazoles

3.5. Synthesis of 1-aryl-4-(β-D-glucopyranosyl)-1,2,3-triazoles

Copper(I) catalyzed 1,3-dipolar cycloadditions of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-ethyne (**18**) with aromatic azides (*a*, *b*, *c*) gave 1-aryl-4-(2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl)-1,2,3-triazoles **37 (**Scheme 8). The benzyl groups of **37a** were cleaved by catalytic hydrogenolysis (*d*) to yield **40a**. Formation of a tetraline derivative was observed during the deprotection of **37b**. The mixture of products was acylated and separated to yield **39b** and **39d** (*f*). To avoid this side reaction **39b** and **39c** were synthesized by a protecting group change from **37c** (*e*) or by a cycloaddition from 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-ethyne (**38**) (*a*, *b*). Acetyl groups of **39b,c** were removed by the Zemplén method (*g*) to give **40b,c**.



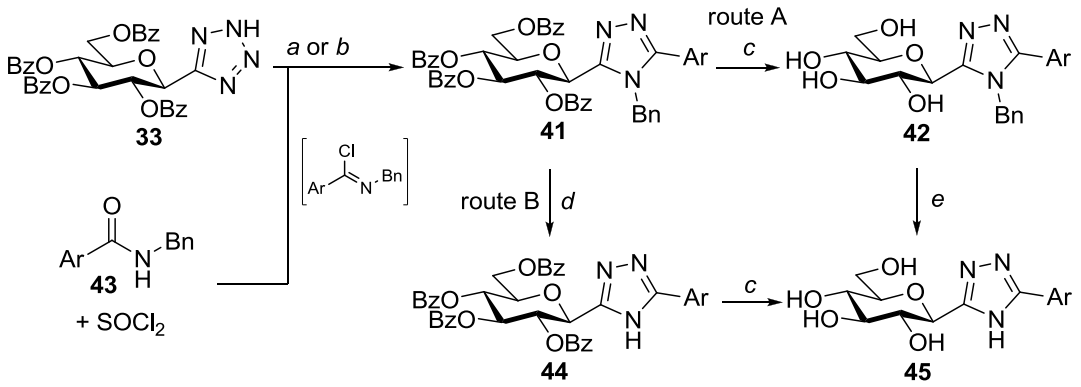
a) ArN_3, $CuO(CO)C_3H_7(PPh_3)_2$, abs. CH_2Cl_2, r.t.
b) 1. Ar-$B(OH)_2$, NaN_3, $CuSO_4 \cdot 5H_2O$, MeOH, r.t.;
2. **18** or **38**, L-ascorbic acid, CH_2Cl_2 : H_2O = 1 : 1, 50 °C
c) 1. Ar-$B(OH)_2$, NaN_3, $CuSO_4 \cdot 5H_2O$, MeOH, r.t.; 2. **18**, $CuO(CO)C_3H_7(PPh_3)_2$, abs. CH_2Cl_2, r.t.
d) H_2, Pd(C), abs. EtOH, EtOAc
e) TMSOTf, Ac_2O, -40 °C
f) 1. H_2, Pd(C), abs. EtOAc, MeOH; 2. Ac_2O, pyridine
g) NaOMe, MeOH, r.t.

Ar	Reaction conditions and yields (%)					
	37		**39**		**40**	
a 	*a*	78 (from **18**)	-		*d*	92 (from **37a**)
b 	*a*	85 (from **18**)	*f* *a*	29 (from **37b**) 91 (from **38**)	*g*	94 (from **39b**
c 	*b* *c*	79 (from **18**) 71 (from **18**)	*e* *b*	68 (from **37c**) 80 (from **38**)	*g*	96 (from **39c**)
d 	-	-	*f*	3 (from **37b**)	-	-

Scheme 8: Synthesis of 1-aryl-4-(β-D-glucopyranosyl)-1,2,3-triazoles

3.6. Synthesis of 5-aril-3-(β-D-glucopyranosyl)-1,2,4-triazoles

N-Benzyl-arenecarboxamides **43** were treated with thionyl chloride to yield the corresponding imidoyl chlorides whose reaction with tetrazole **33** (*a* or *b*) resulted in the formation of 4-benzyl-5-aryl-3-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1,2,4-triazoles **41** (Scheme 9). The benzoyl groups were removed according to the Zemplén procedure (*c*), the benzyl groups were cleaved by catalytic hydrogenolysis (*d*, *e*). The removal of the protecting groups of **41a** was carried out in both orders (routes „A" and „B"). Deacylation followed by benzyl cleavage (route „A") provided higher yields, so later on this sequence was followed for the synthesis of 1,2,4-triazoles **45**.



a: abs. toluene, reflux; *b*: abs. *m*-xylene, reflux; *c*: NaOMe, abs. MeOH
d: H_2, Pd(C), abs. EtOAc; *e*: H_2, Pd(C), abs. MeOH

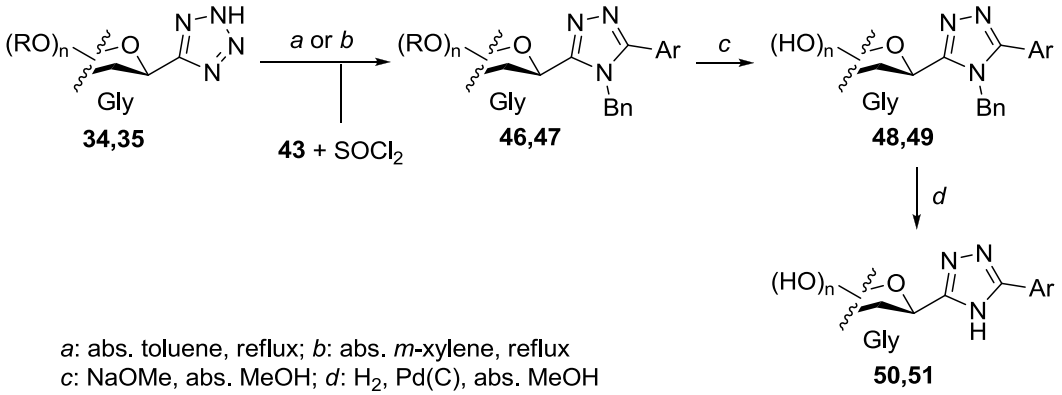
	Ar	Yields (%)			
		41	**42**	**44**	**45**
a	C_6H_5	69 (*a*)	73	75	85 (from **42a**) 62 (from **44a**)
b	4-CH_3-C_6H_4	49 (*b*)	94	-	90
c	4-$(CH_3)_3C$-C_6H_4	61 (*b*)	98	-	79
d	4-CF_3-C_6H_4	88 (*a*)	61	-	77
e	4-NO_2-C_6H_4	38 (*a*)	91	-	-
f	4-NH_2-C_6H_4	-	-	-	82 (from **41e**)
g	3,4,5-$(CH_3O)_3$-C_6H_2	65 (*b*)	91	-	92
h	4-COOBn-C_6H_4	69 (*b*)	-	-	-
i	4-COOH-C_6H_4	-	-	75 (from **40h**)	86 (from **44i**)
j	2-Naphthyl	52 (*a*)	85	-	70

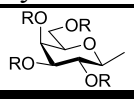
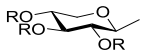
Scheme 9: Synthesis of 5-aryl-3-(β-D-glucopyranosyl)-1,2,4-triazoles

Applying the same reaction conditions, 3-phenyl-5-β-D-galactopyranosyl-1,2,4-triazole (**50a**) and several 3-aryl-5-β-D-xylopyranosyl-1,2,4-triazoles **51** were prepared from the corresponding tetrazoles **34** and **35** (Scheme 10).

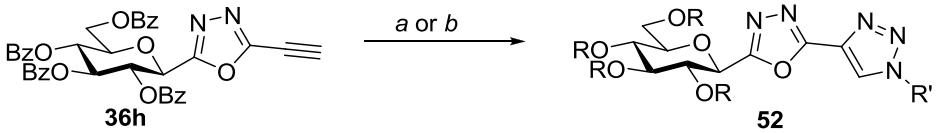
3.7. Synthesis of 2-(β-D-glucopyranosyl)-5-(1-substituted-1,2,3-triazol-4-yl)-1,3,4-oxadiazoles

In the copper(I) catalysed cycloaddition of aromatic azides and ethynyl-oxadiazole **36h,** (1,2,3-triazol-4-yl)-1,3,4-oxadiazoles (**52**) were prepared (Scheme 11). Azides were prepared and isolated previously (*a*) or generated from boronic acids (*b*) and used in the cycloaddition without isolation. These two methods were similarly efficient for the synthesis of **52a**. Removal of the ester protecting groups by the Zemplén procedure gave **53**



Starting material				Yields (%)			
				46		**48**	**50**
Gly			Ar	R			
34 R = Ac		**a**	C_6H_5	Ac	65	78	81
				47		**49**	**51**
				R			
35 R = Bz		**a**	C_6H_5	Bz	68	91	91
		c	4-$(CH_3)_3C$-C_6H_4		42	63	77
		e	4-NO_2-C_6H_4		52	68	-
		f	4-NH_2-C_6H_4		-	-	79 (from **48e**)
		j	2-Naphthyl		52	76	90

Scheme 10: Synthesis of 3-aryl-5-β-D-galacto- and -xylopyranosyl-1,2,4-triazoles



a: R'-N_3, $CuSO_4 \cdot 5H_2O$, L-ascorbic acid
CH_2Cl_2 : H_2O = 1 : 1, 50 °C
b: 1. R'-$B(OH)_2$, NaN_3, $CuSO_4 \cdot 5H_2O$, MeOH, r.t.;
2. **36h,** L-ascorbic acid, CH_2Cl_2 : H_2O = 1 : 1, 50 °C

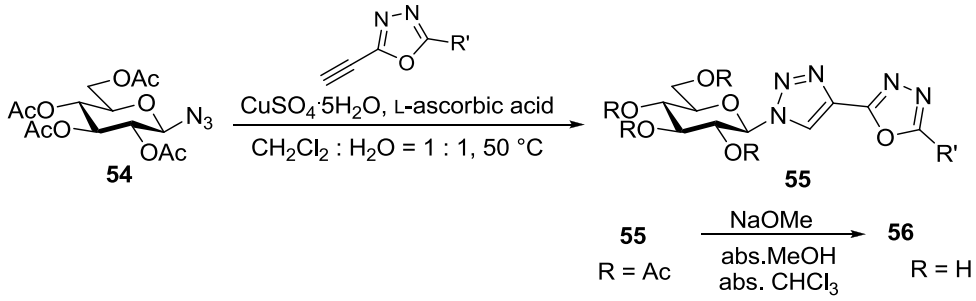
52 (R = Bz) —NaOMe, abs.MeOH, abs. $CHCl_3$→ **53** (R = H)

Products **(52)**	R	R'	Method	Yields (%)	Products **(53)**	R	R'	Yields (%)
a	Bz	Ph	*a*	73	**a**	H	Ph	85
			b	68				
b	Bz	1-Naphthyl	*a*	82	**b**	H	1-Naphthyl	91
c	Bz	2-Naphthyl	*b*	77	**c**	H	2-Naphthyl	79
d	Bz	Ac_4-β-D-Glc_p	*a*	91	**e**	H	β-D-Glc_p	93

Scheme 11: Synthesis of 2-(β-D-glucopyranosyl)-5-[1-(substituted)-1,2,3-triazol-4-yl]-1,3,4-oxadiazoles

3.8. Synthesis of 2-aryl-5-[1-(β-D-glucopyranosyl)-1,2,3-triazol-4-yl]-1,3,4-oxadiazoles

Reaction of 2,3,4,6-tetra-*O*-acetyl-β-D-glucopyranosyl-azide (**54**) and 2-aryl-5-ethynyl-1,3,4-oxadiazoles in the presence of $CuSO_4$ and L-ascorbic acid yielded (1,2,3-triazol-4-yl)-1,3,4-oxadiazoles **55** (Scheme 12). Acetyl groups of **55** were removed to give unprotected **56**.

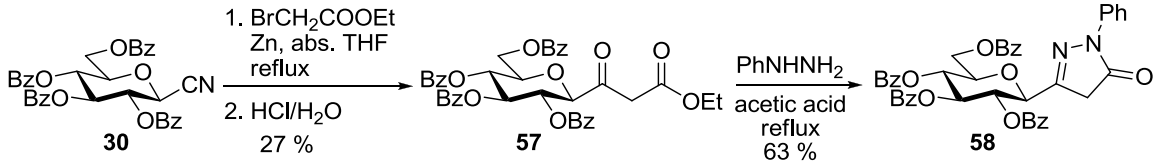


Products (**55**)	R	R'	Yields (%)	Products (**56**)	R	R'	Yields (%)
a	Ac	Ph	87	**a**	H	Ph	99
b	Ac	1-Naphthyl	77	**b**	H	1-Naphthyl	98
c	Ac	2-Naphthyl	74	**c**	H	2-Naphthyl	98

Scheme 12: Synthesis of 2-(aryl)-5-[1-(β-D-glucopyranosyl)-1,2,3-triazol-4-yl]-1,3,4-oxadiazoles

3.8. Synthesis of 1-phenyl-3-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1*H*-pyrazol-5(4H)-one

Reaction of cyanide **30** with ethyl bromoacetate in the presence of zinc dust followed by an acidic hydrolysis furnished β-ketoester **57**. Treatment of **57** with phenylhydrazine yielded pyrazolone **58** which decomposed during the benzoyl deprotection.

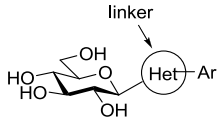
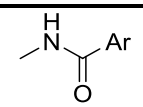
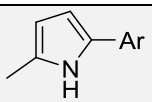
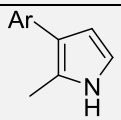
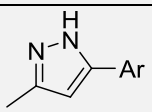
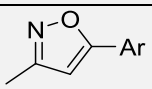
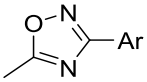
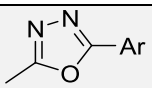
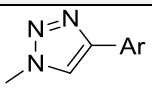
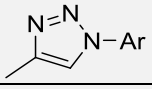
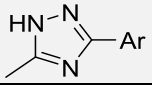
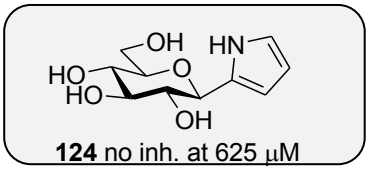
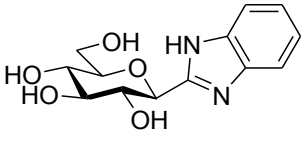


Scheme 13: Synthesis of 1-phenyl-3-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)-1*H*-pyrazol-5(4H)-one

4. Structure-activity relationships

The synthesized derivatives were evaluated as inhibitors of rabbit muscle glycogen phosphorylase *b* (RMGP*b*) at the Department of Medical Chemistry of the University of Debrecen.

Table 2: Comparison of the inhibition by the synthesized compounds[2] and known inhibitors (RMGP*b*, K_i [μM])

	Ar			
Linker	Ph		2-Naphthyl	
	**1b**	81	**1c**	4
	**14a**	IC_{50} = 700 μM	**14b**	no inh. at 625 μM
	**17a**	no inh. at 625 μM	**17b**	no inh. at 625 μM
	**25**	400 IC_{50} = 850 μM	-	-
	**27**	no inh. at 650 μM	-	-
	**5b**	64	**5c**	2,4
	**4b**	10 % at 625 μM	**4c**	10 % at 625 μM
	**3b**	151	**3c**	16
	**40b**	no inh. at 625 μM	**40c**	no inh. at 625 μM
	**45a**	7	**45j**	0.41
 **124** no inh. at 625 μM		 **38** K_i = 9 μM		

[2] The cells showing the new compounds are highlighted in grey.

The 2,3-disubstituted pyrroles **17a,b** were inactive. This was probably the result of the substitution pattern of the heterocycle which caused unsuitable orientation of the aglycone at the active center. From the 2,5-disubstituted pyrroles **14a,b** the phenyl derivative showed weak inhibition.

The isoxazole **27** was inactive against glycogen phosphorylase, the pyrazole **25** displayed weak binding.

Surprisingly the aryl substituted 1,3,4-oxadiazoles **4b-f,i,j** did not show any meaningful inhibition. X-Ray studies of RMGP*b*-methyl 1,3,4-oxadiazole **4a** complex indicated that the methyl group did not point to the direction of the β-channel. This orientation seems unfavourable for the bulky aryl-1,3,4-oxadiazoles, thus these compounds can't bint to the active site.

According to the kinetic results 1-aryl-4-β-D-glucopyranosyl-1,2,3-triazoles **40** proved inactive against GP, it is surprising in the light of good inhibition effect of isomeric 4-aryl-1-β-D-glucopyranosyl-1,2,3-triazoles **3**.

The 1,2,4-triazoles **45** were outstandingly efficient GP inhibitors, however their activity was highly affected by the aryl substituent. The 2-naphthyl **45j** (K_i = 0.41 μM) and the 4-aminophenyl **45f** (K_i = 0.67 μM) derivatives were inhibitors in the submicromolar range, but the 4-*t*Bu-phenyl **45c** and the 4-carboxyphenyl **45i** derivatives proved entirely inactive.

The xylosyl-1,2,4-triazoles **51** showed no or very weak inhibition. This points to the fact that the presence of the CH_2OH group in the pyranose ring is essential, an aglycone with high affinity towards the β-channel is not enough for strong binding.

The acyl-urea analogue 2-(1,2,3-triazol-4-yl)-1,3,4-oxadiazoles **53** and **56** proved practically inefficient. The double replacement of NHCONHCO moieties by 1,3,4-oxadiazole and 1,2,3-triazole caused the complete loss of inhibition compared to the parent compounds.

5. Possible application of the results

In the course of my research potential glycogen phosphorylase inhibitors of *C*-glycosyl heterocyclic structure were prepared. The enzyme kinetic parameters of the synthesized compounds were determined against rabbit muscle glycogen phosphorylase *b*. After further biological studies the most efficient inhibitors may be applicable for the treatment of type two *diabetes mellitus* as well as other diseases connected to disorders of glycogen metabolism (e. g. myocardial and cerebral ischemias or tumourous growth).

Documented scientific results

Scientific articles published in peer reviewed international journals

Papers related to the theses

1. M. Tóth, **S. Kun**, É. Bokor, M. Benltifa, G. Tallec, S. Vidal, T. Docsa, P. Gergely, L. Somsák, J.-P. Praly
   Synthesis and structure–activity relationships of *C*-glycosylated oxadiazoles as inhibitors of glycogen phosphorylase
   Bioorg. Med.Chem., **2009**, *17*, 4773–4785.
   IF: 2.903 Independent citation: 15

2. Somsák L., Bokor É., Czifrák K., Kónya B., **Kun S.**, Tóth M.
   A glikogén foszforiláz glükózanalóg gátlószerei, mint potenciális antidiabetikumok (Glucose analogue inhibitors of glycogen phosphorylase as potential antidiabetic agents)
   Magy. Kém. Folyóirat, **2010**, *116*, 19-30.
   IF: - Independent citation: 1

3. **S. Kun**, G. Z. Nagy, L. Czecze, M. Tóth, A. N. V. Nienh, T. Docsa, P. Gergely, M.-D. Charavgi, P. V. Skourti, E. D. Chrysina, T. Patonay, L. Somsák
   Synthesis of variously coupled conjugates of D-glucose, 1,3,4-oxadiazole, and 1,2,3-triazole for inhibition of glycogen phosphorylase
   Carbohydr. Res., **2011***, 346,* 1427-1438.
   IF: 2.044 Independent citation: 3

4. Somsák L., Bokor É., Tóth M., Juhász L., Czifrák K., Kónya B., **Kun S.,** Páhi A., Szőcs B., Varga G., Kóder L.-né, Nagy K.-né, Gergely P., Docsa T.
   Glikogén foszforiláz inhibitorok
   PCT/HU 2012/000116 international patent application.

5. **S. Kun**, É. Bokor, G. Varga, B. Szőcs, A. Páhi, K. Czifrák, M. Tóth, L. Juhász, T. Docsa, P. Gergely, L. Somsák
   New synthesis of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles, nanomolar inhibitors of glycogen phosphorylase
   Eur. J. Med. Chem., submitted.

Other publications

1. M. Tóth, **S. Kun,** L. Somsák, D. Goyard
   Preparation of exo-Glycals from 2,6-Anhydro-aldose-tosylhydrazones
   Carbohydrate Chemistry: Proven Synthetic Methods, CRC Press, Boca Raton, 2012, Vol.1. pp. 367-375. (ISBN: 978-1-4398-6689-4)

Conference participations

Oral presentations

1. É. Bokor, **S. Kun**, L. Somsák
   Heterocyclic derivatives of D-glucose for glycogen phosphorylase inhibition
   MTA Szénhidrátkémiai Munkabizottsága éves előadóülése, Mátrafüred, 2007. május 23.-25.

2. É. Bokor, **S. Kun**, M. Tóth, T. Docsa, P. Gergely, N. G. Oikonomakos, L. Somsák
   Nitrogen-heterocyclic derivatives of D-glucose as inhibitors of glycogen phosphorylase
   Third German-Hungarian Workshop: Synthesis, Isolation, and Biological Activity of Natural Products, Paderborn 15.-17. May 2008.

3. É. Bokor, **S. Kun**, M. Tóth, L. Czecze, L. Somsák
   New heterocyclic derivatives of D-glucose as inhibitors of glycogen phosphorylase
   MTA Szénhidrátkémiai Munkabizottsága éves előadóülése, Mátrafüred, 2008. május 29.-30.

4. É. Bokor, **S. Kun**, M. Tóth, T. Docsa, P. Gergely, N. G. Oikonomakos, L. Somsák.
   C- And *N*-glucopyranosyl heterocycles as inhibitors of glycogen phosphorylase
   4th Central European Conference: Chemistry towards Biology, Dobogókő, Hungary, Sep 8-11, 2008, Book of Abstracts, p. 69.

5. **S. Kun**, É. Bokor, M. Tóth, L. Somsák
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6. É. Bokor, **S. Kun**, M. Tóth, T. Docsa, P. Gergely, L. Somsák
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   Eurocarb 15, July 19-24, 2009, Vienna, Austria. OC 119. Book of Abstracts p. 167.

7. Somsák L., Bokor É., Czifrák K., Kónya B., **Kun S.**, Páhi A., Szőcs B., Tóth M., Vidal S., Praly J.-P.
   Heterociklusos glükózszármazékok, mint potenciális antidiabetikumok
   MTA Kém. Tud. Oszt., Heterociklusos Kémiai Munkabizottsága előadóülése, Balatonszemes, 2010. május 19-21.

8. **S. Kun**, É. Bokor, L. Somsák
   C-Glycosyl azole derivatives for glycogen phosphorylase inhibition
   MTA Szénhidrátkémiai Munkabizottsága éves előadóülése, Mátrafüred, 2010. május. 27.-28.

9. Tóth M., Czecze L., Juhász L., **Kun S.**, Kónya B., Polyák M., Docsa T., Gergely P., Somsák L.
   N- és *C*-glükopiranozil heterociklusok, mint potenciális glikogén foszforiláz inhibítorok
   MKE 1. Nemzeti Konferencia, Sopron, 2011. május 22-25.

10. B. Szőcs, **S. Kun**, É. Bokor, M. Tóth, K. E. Szabó, K. Czifrák, L. Juhász, G. Varga, A. Páhi, T. Docsa, P. Gergely, L. Somsák:
    Synthesis of 3-glucopyranosyl-5-substituted-1,2,4-triazoles and their evaluation as glycogen phosphorylase inhibitors
    MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése Mátrafüred, 2013. május 22-24.

11. **Kun S.**, Bokor É., Szőcs B., Tóth M., Czifrák K., Juhász L., Varga G., Páhi A., Docsa T., Gergely P., Somsák L.
    3-(β-D-Glükopiranozil)-5-szubsztituált-1,2,4-triazolok, a glikogén foszforiláz enzim új nanomólos inhibitorai
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Posters

12. Bokor É., **Kun S.**, Tóth M., Czecze L., Somsák L.
    2-(β-D-Glükopiranozil)-1,3,4-oxadiazol származékok, mint glikogén foszforiláz inhibítorok előállítása
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13. **S. Kun**, L. Somsák
    Synthesis of *C*-glucosyl pyrroles for inhibition of glycogen phosphorylase
    16th European Carbohydrate Symposium, Sorrento, Italy, 2011. July 3-7.

14. **S. Kun**, L. Somsák, T. Docsa, P. Gergely
    Synthesis and evaluation of 2-β-D-glucopyranosyl-4- and -5-aryl pyrroles for inhibition of glycogen phosphorylase
    4th German-Hungarian Workshop, Synthesis, Isolation and Biological Activity of Natural Products and Related Systems, Debrecen, 2011, June 14-16.

15. **S. Kun**, L. Somsák, T. Docsa, P. Gergely
    Synthesis of 2-β-D-glucopyranosyl-4-and-5-aryl pyrroles
    4th European Conference on Chemistry for Life Sciences, Budapest, 2011. August 31 – September 3.

16. É. Bokor, **S. Kun**, B. Szőcs, M. Tóth, K. Czifrák, L. Juhász, A. Páhi, M. Polyák, T. Docsa, P. Gergely, L. Somsák
    3-(β-D-Glucopyranosyl)-5-substituted-1,2,4-triazoles as new nanomolar inhibitors of glycogen phosphorylase
    5th European Conference on Chemistry for Life Sciences, Barcelona, Spain, June 10-12, 2013. PO21, Book of abstracts p. 94.