Theses of doctoral (Ph.D.) dissertation

SYNTHESIS OF NOVEL GLUCOPYRANOSILIDENE-SPIRO-HETEROCYCLES AND *C*-GLUCOPYRANOSYL 1,2,4-TRIAZOLES

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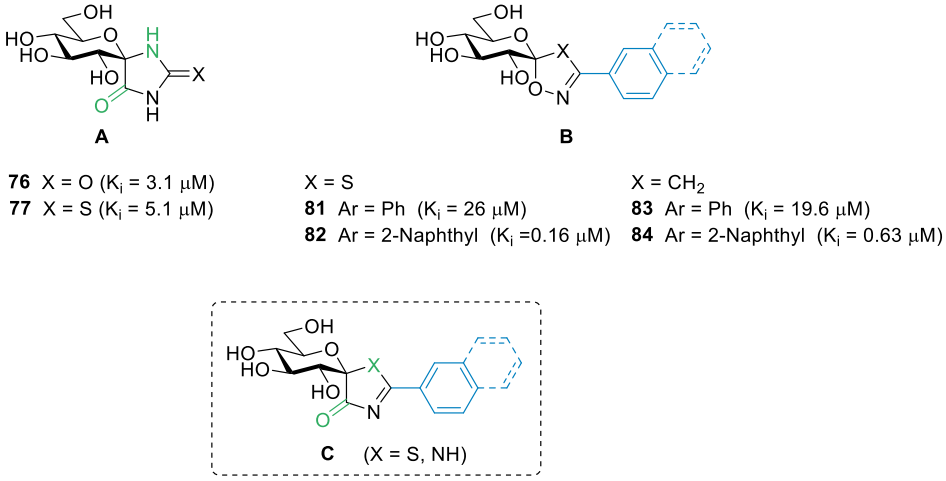
1. Introduction

According to reports of the WHO and IDF, the number of adults living with diabetes has more than doubled in the past two decades. At the moment, nearly half a billion people suffer from diabetes in the world and the rise of the prevalence of the disease is still expected in the upcoming years. In addition to the rapid spread, another worrisome feature is that diabetes is affecting the younger generation, not only young adults but also adolescents and children. The most common type of diabetes is type 2 diabetes mellitus (T2DM), which accounts for more than 90% of all cases of diabetes. To the best of our knowledge, it is not possible to cure T2DM, the doctors try to keep the blood glucose concentration within the normal range during the medicinal treatment with oral antihyperglycemic agents. However, the available medicines are often ineffective and possess many side effects, therefore, intensive research has been carried out to develop new therapeutic options. A new possible treatment may be to reduce the elevated hepatic glucose production, which can be achieved by the inhibition of glycogen phosphorylase (GP, the key enzyme of glycogenolysis).

In our research group the preparation of new glucose analogue glycogen phosphorylase inhibitors has been investigated for more than 20 years. Several types of compounds proved to be efficient inhibitors: *N*-acyl-*N*'-β-D-glucopyranosyl ureas, *C*-β-D-glucopyranosyl heterocycles, glucopyranosylidene-spiro-heterocycles. I joined this research field during my PhD work and my goal was the synthesis of five membered spiro-glucopyranosylidene-heterocycles and *C*-glucopyranosyl 1,2,4-triazoles.

Glucopyranosylidene-spiro-hydantoin (**A**, X = O) and thiohydantoin (**A**, X = S) were active against GP in the low micromolar concentration range (Scheme 1). According to the X-ray crystallography of the enzyme-inhibitor complexes, the importance of the H-bond donor β-NH groups, as well as the presence of the α-carbonyl groups was revealed. In the case of the 2-naphthyl substituted glucopyranosylidene-spiro-oxathiazoles (**B**, X = S) and isoxazolines (**B**, X = CH_2) the K_i values are lower by an order of magnitude. The large and properly oriented aromatic moieties of the molecules that form interactions with the β-channel of the enzyme were accounted for the strong binding of these compounds. Based on these structure–activity relationships, we envisaged the improvement of these molecules and the synthesis of new spirocycles that unify the properties of the best inhibitors. The target compounds (**C**) should have a rigid spirobicyclic scaffold in which the carbonyl group is oriented at the α-position and a large aromatic group must be present on the spirocycle. We planned to examine the role of

the X group, in the case when the heterocycle bears a H-bridge donor NH or non-hydrogen bond donor sulphur atom in this position.



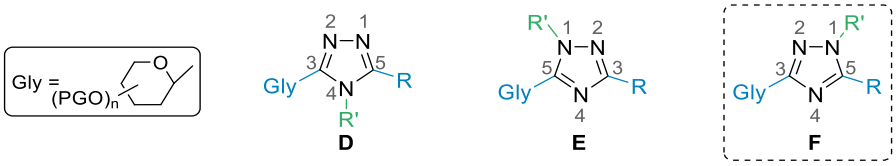
76 X = O (K_i = 3.1 μM)
77 X = S (K_i = 5.1 μM)

X = S
81 Ar = Ph (K_i = 26 μM)
82 Ar = 2-Naphthyl (K_i =0.16 μM)

X = CH_2
83 Ar = Ph (K_i = 19.6 μM)
84 Ar = 2-Naphthyl (K_i = 0.63 μM)

Scheme 1: Selected spirobicyclic inhibitors (**A**, **B**), their inhibition constants against rabbit muscle GP enzyme (RMGP*b*) and the target compounds (**C**)

The possible synthetic pathways for the preparation of *C*-glycopyranosyl 1,2,4-triazoles were studied earlier in our research group. As a continuation of our efforts in these syntheses, the preparation of trisubstituted 1,2,4-triazoles has been investigated. From the three possible isomeric structures (Scheme 2) the synthetic methods of 3-glycosyl-4,5-disubstituted-triazoles (**D**) and 5-glycosyl-1,3-disubstituted-triazoles (**E**) have already been elaborated. Consequently, we planned to prepare 3-β-D-glucopyranosyl-1,5-disubstituted-1,2,4-triazoles (**F**).



Scheme 2: Possible isomeric forms of trisubstituted *C*-glycopyranosyl 1,2,4-triazoles

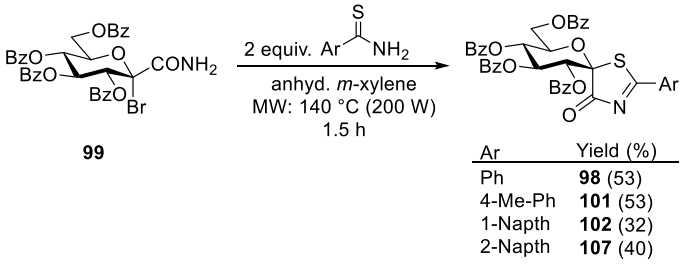
2. Methods

In the course of the synthetic work, macro-, semi-micro- and micro-scale methods of the 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, elemental analysis) 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. A new method was developed for the preparation of *O*-acyl protected (1'*R*)-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylthiazolin-4-ones. Novel alcohol and water addition products were discovered during the experiments towards to deprotection of the acyl protected spiro derivatives.

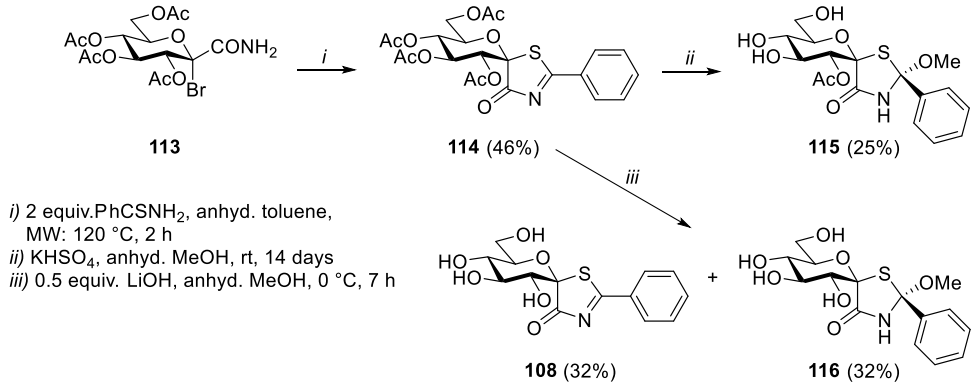
The reaction of *C*-(2,3,4,6-tetra-*O*-benzoyl-1-bromo-1-deoxy-β-D-glucopyranosyl) formamide (**99**) with aromatic thioamides by heating in inert solvents provided glucopyranosylidene-spiro-thiazolinone derivatives (Scheme 3, **98**, **101**, **102**, **107**). Optimization of reaction conditions were performed and shorter reaction time was achieved with the application of microwave-assisted heating instead of oil bath and the yields improved, too (e.g. the yield of thiazolinone **98** raised from 33 % to 53 %). The configuration of the anomeric centre was proven by the measurement of three bond coupling constant (in the case of thiazolinone **98** $^3J_{H2,CO}$ = 6.0 Hz).



Ar	Yield (%)
Ph	**98** (53)
4-Me-Ph	**101** (53)
1-Napth	**102** (32)
2-Napth	**107** (40)

Scheme 3: Synthesis of perbenzoylated 2-aryl-glucopyranosylidene-spiro-thiazolin-4-ones

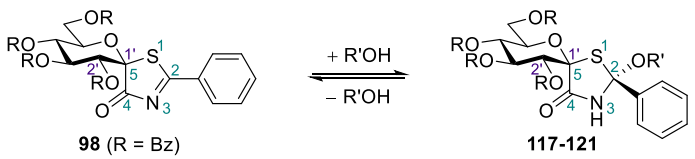
Attempts to remove the benzoyl protecting groups under a series of transesterification conditions or under basic hydrolysis conditions proved unsuccessful. After this, the use of the more readily removable *O*-acetyl protecting groups was envisaged. Experiments were carried out to facilitate the *O*-deacetylation of compound **114** and we could isolate products in two cases (Scheme 4). The use of $KHSO_4$ resulted in a moderate yield of **115** with the C-2' *O*-acetyl group remaining intact in the molecule and the addition of the solvent methanol molecule also occurred to the C=N bond of thiazolinone ring. Removal of the acetyl protecting groups with LiOH in methanolic solution provided the expected unprotected sugar (**108**) as a mixture with the methanol addition product (**116**).



Scheme 4: Preparation of (1'*R*)-2',3',4',6'-tetra-*O*-acetyl-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-phenylthiazolin-4-one and experiments towards its deprotection

The presence of MeOH addition products **115** and **116** in the deacetylation mixtures prompted us to investigate the reaction of **98** and **114** with MeOH and EtOH without any other additive (Table 1, entries 1-4). It turned out that both alcohols added to the thiazolinone moiety to furnish **117-120** as the major stereoisomers. These preponderant diastereomers were formed although the attack of the alcohol could have been expected from both sides of the planar thiazolinone ring. This observation may be explained by a steric hindrance of the C-2 centre by the 2'-OAc or 2'-OBz groups facilitating the addition reaction from the opposite side. This addition reaction proved to be reversible, since by heating **117** (at 80 °C) or **119** (at 60 °C) in toluene thiazolinones **98** and **114** were recovered, respectively. The addition of water was also tested with **114** (entry 5) and the formation of **121** was observed in a mixture with the starting compound.

Table 1: Addition of alcohols and water onto spiro-thiazolinones **98** and **114**



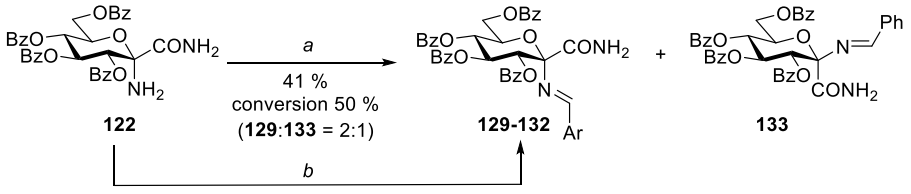
Entry	Starting compound	R' group	Product
1.	**98**	Me	**117**
2.		Et	**118**
3.	**114**	Me	**119**
4.		Et	**120**
5.		H	**121**[a]

[a]Partial addition (**114**:**121** ~ 1:0,4 in the case of toluene-water system; **114**:**121** ~ 1:0,7 in the case of dioxane-water system)

Since no NMR methods seemed suitable to determine the configuration of C-2 of the addition products **115**–**121**, ECD measurements and TDDFT-ECD calculations were performed. Sándor Balázs Király, Attila Mándi and Tibor Kurtán provided us help to carry out these studies This method was extended to compound **114** to determine the absolute configuration of C-1' spiro centre in order to confirm the previously obtained NMR results independently.

3.2. *C*-(1-Arylideneamino-2,3,4,6-tetra-*O*-benzoyl-1-deoxy-D-glucopyranosyl) formamides were prepared in both anomeric configurations and a novel ring-closure method was developed for the synthesis of (1'*R*)- and (1'*S*)-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylimidazoline-4-ones.

C-(1-Amino-2,3,4,6-tetra-*O*-benzoyl-1-deoxy-β-D-glucopyranosyl)formamide (**122**) was reacted with benzaldehyde in an acid catalyzed condensation reaction and the anomeric mixture of the corresponding Schiff bases were formed (**129**, **133**, Scheme 5 method *a*). We were not able to separate these compounds due to their identical chromatographic mobility so the transformation was performed by using an aminocatalytic method (Scheme 5 method *b*) to afford the expected *C*-(1-arylideneamino-2,3,4,6-tetra-*O*-benzoyl-1-deoxy-β-D-glucopyranosyl)formamides (**129**-**132**) in good yields.



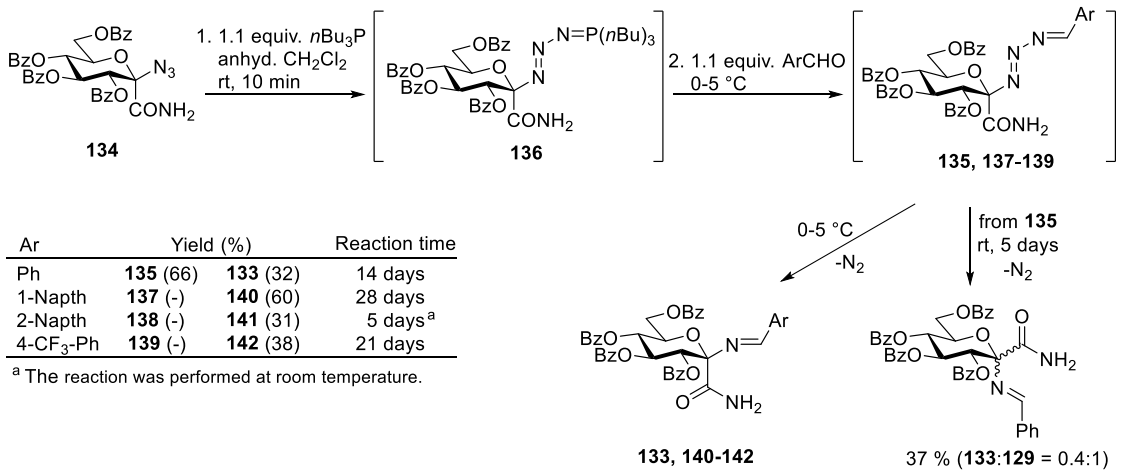
Ar	Yield (%)
Ph	**129** (86)
1-Napth	**130** (75)
2-Napth	**131** (58)
4-CF_3-Ph	**132** (68)

a: 8.8 equiv. PhCHO, cat. AcOH, anhyd. MeOH-$CHCl_3$, reflux, 2 days
b: 1.1 equiv. ArCHO, 10 mol% pyrrolidine, 4 Å MS, anhyd. CH_2Cl_2, rt

Scheme 5: Transformation of *C*-(1-amino-2,3,4,6-tetra-*O*-benzoyl-1-deoxy-β-D-glucopyranosyl)formamide into the corresponding arylideneamino derivatives

The epimeric compounds were prepared from *C*-(1-azido-2,3,4,6-tetra-*O*-benzoyl-1-deoxy-α-D-glucopyranosyl)formamide (**134**). In this case, the arylideneamino function was formed by an aza-Wittig reaction (Scheme 6). In the first step of the transformation, a phosphazide intermediate (**136**) was generated, since the loss of N_2 molecule did not occur spontaneously. Then, **136** was further reacted with aldehydes to result in the formation of triazene derivatives **135**, **137**-**139**. The release of nitrogen from these compounds afforded the Schiff bases as anomeric mixtures at room temperature. When the reaction mixtures were kept

at low temperatures (0-5 °C), the desired **133**, **140**-**142** compounds were isolated in pure anomeric state.



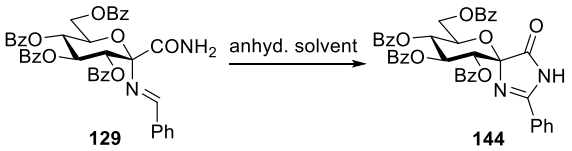
Ar	Yield (%)		Reaction time
Ph	**135** (66)	**133** (32)	14 days
1-Napth	**137** (-)	**140** (60)	28 days
2-Napth	**138** (-)	**141** (31)	5 days[a]
4-CF_3-Ph	**139** (-)	**142** (38)	21 days

[a] The reaction was performed at room temperature.

Scheme 6: Aza-Wittig reaction of *C*-(1-azido-2,3,4,6-tetra-*O*-benzoyl-1-deoxy-α-D-glucopyranosyl)formamide

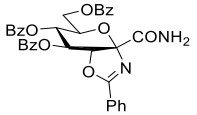
Several methods were tried to facilitate the intramolecular cyclization reaction of the imine **129** (Table 2). Heating and treatment with a Lewis acid resulted in the same unexpected oxazoline **143** in low yield. Decomposition was observed in basic medium. The preparation of the spiro-imidazolinone ring of **144** was achieved by the activation of the imine-type molecule with NBS. Upon addition of bases in order to neutralise the evolved HBr, the yields improved significantly (see Table 2, entries 5-7).

Table 2: Experiments towards the ring closure of *C*-(2,3,4,6-tetra-*O*-benzoyl-1-benzylideneamino-1-deoxy-β-D-glucopyranosyl)formamide



Entry	Reaction conditions	Observation
1.	DMF, 160 °C, MW, 30 min	**143** (24 %)
2.	*m*-xylene, reflux, 3 days	**143** (17 %)
3.	20 mol% $BF_3{\cdot}OEt_2$, CH_2Cl_2, rt, 3 days	**143** (25 %)
4.	pyridine, reflux, 2 days	Decomposition
5.	NBS (1.1 equiv.), CH_2Cl_2, rt, 2 days	**144** (41 %)
6.	NBS (1.1 equiv.), K_2CO_3, CH_2Cl_2, rt, 2 days	**144** (60 %)
7.	NBS, pyridine (1.1 equiv. – 1.1 equiv), CH_2Cl_2, rt, 2 days	**144** (71 %)

Observed side-product:

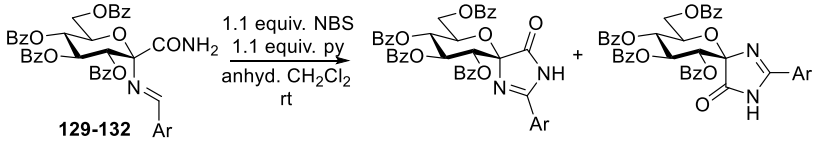


143

This procedure has not been known in the literature so far to produce similar rings. To understand the process of ring closure better, the reaction was followed by ^{1}H NMR measurements and a mechanism was proposed for the transformation. The formation of the bicyclic oxazoline **143** was studied from compounds **129**, **133** and **122**.

The imine-type molecules **129**-**133**, **140**-**142** were reacted with NBS and pyridine (1.1 equiv. – 1.1 equiv.) and spirocycles **144**-**151** were obtained in good yields (Scheme 7 and 8). We observed the formation of the epimeric spiro-heterocycles from the pure anomeric forms of the starting compounds, although only in small amounts. Imines **133**, **140**-**142** showed significant anomerization during the ring closure reactions at room temperature. In the case of Schiff base **133,** the reaction provided the expected imidazolinone **148** with 43 % yield and the epimer **144** with 32 % yield. Repeating the reaction at a lower temperature (0-5 °C) the anomerization was greatly reduced (68 % of **148** and 10 % of **144**, respectively). As the last step, the removal of the ester protecting groups by the Zemplén procedure provided compounds **152**-**159** in good yields. The separation of the products could be achieved with column chromatography in both steps.

The configuration of the anomeric carbon atoms of the protected compounds was confirmed by NMR measurements (**129**: $^3J_{H2,CO}$ = 2.3 Hz; **133**: $^3J_{H2,CO}$ = 5.4 Hz; **144**: $^3J_{H2,CO}$ = 2.8 Hz; **148**: $^3J_{H2,CO}$ = 5.5 Hz).

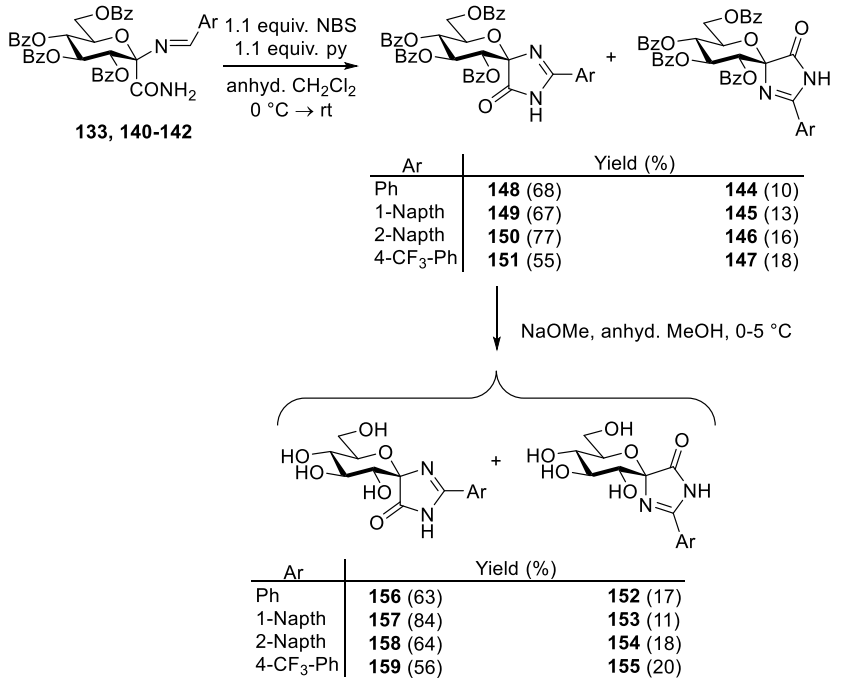


Ar	Yield (%)	
Ph	**144** (70)	**148** (10)
1-Napth	**145** (60)	**149** (9)
2-Napth	**146** (65)	**150** (16)
4-CF_3-Ph	**147** (63)	**151** (11)

NaOMe, anhyd. MeOH, rt

Ar	Yield (%)
Ph	**152** (91)
1-Napth	**153** (81)
2-Napth	**154** (79)
4-CF_3-Ph	**155** (51)

Scheme 7: Synthesis of (1'*R*)-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylimidazoline-4-ones



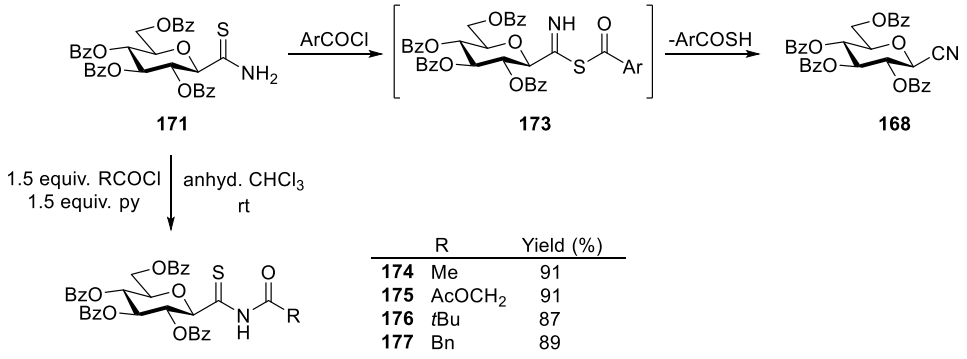
Ar	Yield (%)	
Ph	**148** (68)	**144** (10)
1-Napth	**149** (67)	**145** (13)
2-Napth	**150** (77)	**146** (16)
4-CF_3-Ph	**151** (55)	**147** (18)

Ar	Yield (%)	
Ph	**156** (63)	**152** (17)
1-Napth	**157** (84)	**153** (11)
2-Napth	**158** (64)	**154** (18)
4-CF_3-Ph	**159** (56)	**155** (20)

Scheme 8: Preparation of (1'*R*)-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylimidazoline-4-ones

3.3. A new method for the preparation of 3-β-D-glucopyranosyl-1,5-disubstituted-1,2,4-triazoles was elaborated and novel disubstituted 1,2,4-triazoles were synthesized.

Extensive studies have been carried out in our research group in order to prepare *C*-glycosyl 1,2,4-triazoles and my task was to synthesize 3-β-D-glucopyranosyl-1,5-disubstituted-1,2,4-triazoles. The *N*-acylation of *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl) thioformamide (**171**) was carried out smoothly with aliphatic acid chlorides to give **174**-**177** in excellent yields (Scheme 9). In stark contrast to these results, the attempts to acylate thioformamide **171** with aromatic acid chlorides provided glucosyl cyanide **168** as the major product. This phenomenon may be explained by the formation of an *S*-acylated derivative (**173**), which then underwent a spontaneous loss of thioacid and thus lead to the observed nitrile **168**.

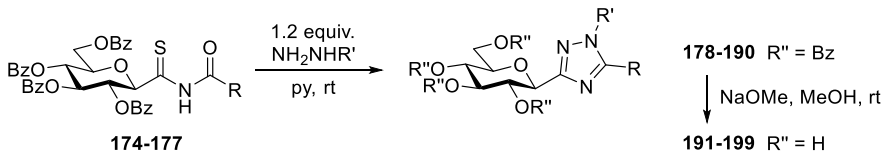


	R	Yield (%)
174	Me	91
175	$AcOCH_2$	91
176	*t*Bu	87
177	Bn	89

Scheme 9: Acylation reaction of *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)thioformamide

To facilitate the formation of 1,2,4-triazole rings, *N*-acyl-thioformamides **174**-**177** were reacted with hydrazine and substituted hydrazines in pyridine (Table 3). The corresponding *C*-glycopyranosyl 1,2,4-triazoles (**178**-**190**) were isolated in good yields and the removal of the benzoyl protecting groups by NaOMe in methanol gave unprotected triazoles **191**-**199**.

Table 3: Synthesis of 3-β-D-glucopyranosyl-1,5-disubstituted-1,2,4-triazoles



174-177

Entry	Starting compound	R	R'	Yield (%)	
				R" = Bz	R" = H
1.	**174**	CH_3	H	**178**[a] (55)	-
2.			Ph	**179** (67)	**191** (70)
3.			C_2H_4OH	**180** (70)	**192** (72)
4.			Ts	**181**[a] (63)	-
5.	**175**	$AcOCH_2$	H	**182**[a] (92)	-
6.			Ph	**183** (70)	**193** (84) R = CH_2OH
7.			C_2H_4OH	**184** (65) R = CH_2OH	**194** (62) R = CH_2OH
8.	**176**	*t*Bu	H	**185**[a] (79)	-
9.			Ph	**186** (66)	**195** (50)
10.			C_2H_4OH	**187** (65)	**196** (65)
11.	**177**	Bn	H	**188** (75)	**197** (45)
12.			Ph	**189** (71)	**198** (70)
13.			C_2H_4OH	**190** (90)	**199** (51)

[a] Earlier in our group the compound was prepared by the reaction of N^1-tosyl-*C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formamidrazone and the corresponding acid chloride.

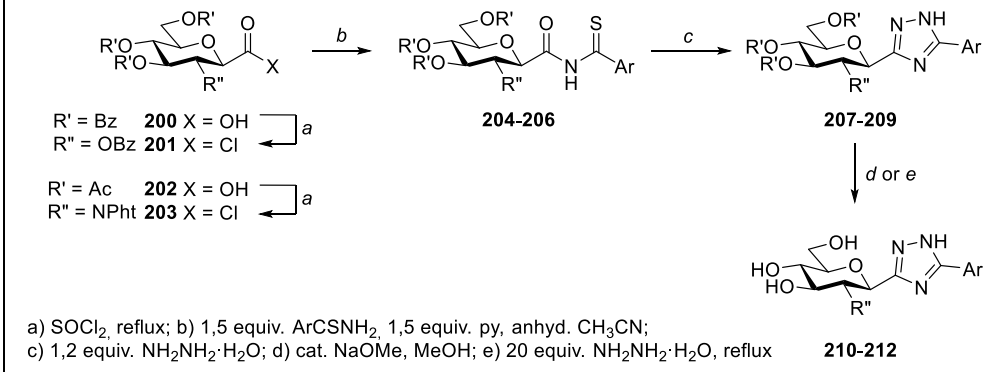
In the case of the substituted hydrazines the ring closure reactions proceeded in a regioselective manner because of the distinctively different reactivity of the C=O and C=S moieties in the *N*-acyl-thioamides. The structure of triazole **191** was confirmed by measurements of nuclear Overhauser effects (NOE, Scheme 10). The spectra demonstrated the vicinity of the methyl protons and Ph groups, which implies that structure **191a** is produced as the result of the reaction.

Scheme 10: The possible isomeric structures of 1,2,4-triazoles **191**

Unprecedented *C*-glycosyl-tri- and disubstituted-1,2,4-triazoles can be synthesized by the above described method. The only limitation of this synthetic pathway is that no aromatic substituent can be introduced in the 5-position of the triazole ring.

Based on a known synthetic method, novel disubstituted 1,2,4-triazoles were also synthesized (Table 4). The prepared molecules **210**-**212** are interesting with regard to the structure-activity relationships, however, they were not available by any of the earlier applied synthetic routes. The corresponding anhydro-aldonic acids **200**, **202** were transformed to acid chlorides **201**, **203** and then reacted with aromatic thioamides to give *N*-glucopyranosylcarbonyl-thiocarboxamides **204**-**206** in good yields. The desired 1,2,4-triazole rings were prepared by the treatment with hydrazine hydrate. The benzoyl protected **207** was isolated and the protecting groups were removed by NaOMe catalyzed transesterification to yield **210**. Triazoles **208**, **209** were deprotected after the ring closure reactions in a'one-pot' method with an excess of hydrazine and 5-aryl-3-(2′-amino-2′-deoxy-β-D-glucopyranosyl)-1,2,4-triazoles **211**, **212** were also isolated.

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



Entry	Product	Ar	R'	R"	Yield (%)
1.	**204**	1-Naphthyl	Bz	OBz	71
2.	**205**	Ph	Ac	NPht	82
3.	**206**	2-Naphthyl	Ac	NPht	74
4.	**207**	1-Naphthyl	Bz	OBz	70
5.	**208**	Ph	Ac	NPht	-
6.	**209**	2-Naphthyl	Ac	NPht	-
7.	**210***	1-Naphthyl	-	OH	90
8.	**211***	Ph	-	NH_2	40
9.	**212***	2-Naphthyl	-	NH_2	68

* Compound **210** was prepared by method *d*), compounds **211**, **212** were deprotected by method *e*).

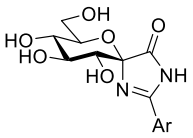
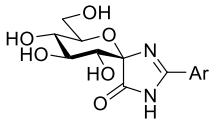
4. Enzyme kinetic studies and structure – activity relationships

The new compounds were tested against glycogen phosphorylase enzyme at the Department of Medical Chemistry of the University of Debrecen and at the Department of Biochemistry and Biotechnology of the University of Thessaly (Biopolis, 41500 Larissa, Greece). Rabbit muscle glycogen phosphorylase *a* and *b* forms (RMGP*a* and RMGP*b*) and the recombinant human liver GP*a* (HLGP*a*) were used for the enzyme kinetic measurements.

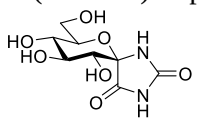
The glucopyranosyl-spiro-thiazolinones were not suitable for testing the inhibition against the enzyme. The unprotected thiazolinone derivative **108** was isolated only in a mixture with thiazolidinone **116** which was formed by methanol addition. Similar addition may occur with water during the enzymatic tests necessarily carried out under aqueous conditions, thereby thwarting the study of these compounds as enzyme inhibitors.

The inhibition constants of the spiro-imidazolinones are summarized in Table 5. The (1'*R*)-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylimidazolin-4-ones **152-155** proved to be weak inhibitors or showed no inhibition. The carbonyl group at the β-position is probably unfavourable in terms of the binding with the catalytic site and therefore the aromatic substituent does not fit to the β-channel in this orientation.

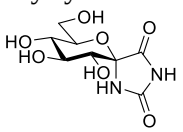
Table 5: Inhibition of 1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylimidazolin-4-ones

Structure			K_i (μM)		
	Ar		RMGP*b*	RMGP*a*	HLGP*a*
	Ph	**152**	135.5	34.17 ± 0.63	119.11 ± 6.15
	1-Naphthyl	**153**	no inhibition (625 μM)	653.78 ± 18.08	1173.67 ± 36.92
	2-Naphthyl	**154**	25 % (625 μM)	212.39 ± 15.94	370.79 ± 14.47
	4-CF_3-Ph	**155**	no inhibition (625 μM)	-	-
	Ph	**156**	8.97	4.45 ± 0.27	8.43 ± 0.41
	1-Naphthyl	**157**	12.98	6.64 ± 0.17	22.24 ± 0.90
	2-Naphthyl	**158**	2.14	1.13 ± 0.06	1.72± 0.07
	4-CF_3-Ph	**159**	no inhibition (625 μM)	-	-

Inhibition constants (RMGP*b*) of previously synthetised spiro-hidantoins:



76 K_i = 3.1 μM

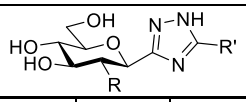


78 K_i = 105 μM

A similar phenomenon was also observed during the studies of the anomeric spiro-hydantoins **76**, **78**. The (1'*S*)-1',5'-anhydro-D-glucitol-spiro-[1',5]-2-arylimidazolin-4-ones **156-158** proved to be efficient inhibitors, although in contrast to our expectations they did not achieve outstanding inhibition. X-ray studies are not available yet, but it may be supposed that the imidazolinone ring may not be in the appropriate tautomeric form to establish hydrogen bond with the residue His377 of the enzyme.

The 3-β-D-glucopyranosyl-1,5-disubstituted-1,2,4-triazoles **191-199** were inactive (in 625 μM concentration). Compared to the disubstituted-1,2,4-triazoles tested earlier that showed good inhibition, the additional substituent negatively affected the binding. In this case the heterocycle is unable to form H-bond with the enzyme and the unsuitable orientation of the substituent may prevent the tight binding. The disubstituted-1,2,4-triazoles **210-212** showed inhibitions, although the results were not outstanding (Table 6). In comparison with the inhibition constants of the *C*-β-D-glucosaminyl 1,2,4-triazoles **211**, **212** with their glucopyranosyl counterparts (**67**, **68**) the latter ones are more potent inhibitors. X-ray crystallography revealed that the structural basis of this difference in potency lies in the strength of the hydrogen bond interactions formed by the group at the 2′-position of the glucopyranose moiety with protein residues of the active site (N-H···X hydrogen bonds are known to be weaker than O-H···X ones).

Table 6: Inhibition constants (RMGP*b*) of *C*-glucopyranosyl-1,2,4-triazoles

Structure			K_i (μM)		
					
Compound	R	R'	RMGP*b*	RMGP*a*	HLGP*a*
210	OH	1-Naphthyl	11.50 ± 0.23	3.38 ± 0.28	8.91 ± 0.44
211	NH_2	Ph	35.2 ± 2.6	30.2 ± 2.2	30.8 ± 1.2
212	NH_2	2-Naphthyl	4.8 ± 0.35	5.3 ± 0.4	7.6 ± 0.1
67*	OH	Ph	7	-	1.35
68*	OH	2-Naphthyl	0.41	-	0.172

*Previously prepared compounds.

5. Possible application of the results

In the course of my research, potential glycogen phosphorylase inhibitors were prepared. After further biological studies, the most efficient inhibitors may be applicable for the treatment of T2DM. In addition, they may also be useful for other diseases associated with glycogen metabolism (cardioprotective, antitumor activity). Recent research has shown that blood glucose levels can also be reduced by inhibition of type 2 sodium glucose cotransporter (SGLT2) in the kidney. Previously approved drugs are diarylmethane *C*-glycoside derivatives and the modification of these compounds may result in more potent SGLT2 inhibitors. The developed novel method for the preparation of 3-β-D-glucopyranosyl-1,5-disubstituted-1,2,4-triazoles could be a useful synthetic pathway to obtain new *C*-glycosides.

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Neptun ID: DMYXIS
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List of publications related to the dissertation

Foreign language scientific articles in international journals (4)

1. Kun, S., Begum, J., Kyriakis, E., Stamati, E. C. V., Barkas, T. A., Szennyes, E., Bokor, É., **Szabó, E. K.**, Stravodimos, G. A., Sipos, Á., Docsa, T., Gergely, P., Moffatt, C., Patraskaki, M. S., Kokolaki, M. C., Gkerdi, A., Skamnaki, V. T., Leonidas, D. D., Somsák, L., Hayes, J. M.: A multidisciplinary study of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazole derivatives as glycogen phosphorylase inhibitors: computation, synthesis, crystallography and kinetics reveal new potent inhibitors.
   Eur. J. Med. Chem. 147, 266-278, 2018. ISSN: 0223-5234.
   DOI: http://dx.doi.org/10.1016/j.ejmech.2018.01.095
   IF: 4.519 (2016)

2. **Szabó, E. K.**, Páhi, A., Somsák, L.: C-Glycosyl 1,2,4-triazoles: Synthesis of the 3-β-d-glucopyranosyl-1,5-disubstituted and 5-β-d-glucopyranosyl-1,3-disubstituted variants.
   Tetrahedron. 73 (27-28), 3810-3822, 2017. ISSN: 0040-4020.
   DOI: http://dx.doi.org/10.1016/j.tet.2017.05.014
   IF: 2.651 (2016)

3. **Szabó, E. K.**, Kun, S., Mándi, A., Kurtán, T., Somsák, L.: Glucopyranosylidene-Spiro-Thiazolinones: Synthetic Studies and Determination of Absolute Configuration by TDDFT-ECD Calculations.
   Molecules. 22 (10), 1760-1774, 2017. EISSN: 1420-3049.
   DOI: http://dx.doi.org/10.3390/molecules22101760
   IF: 2.861 (2016)

4. Bokor, É., Kyriakis, E., Solovou, T. G. A., Koppány, C., Kantsadi, A. L., **Szabó, E. K.**, Szakács, A., Stravodimos, G. A., Docsa, T., Skamnaki, V. T., Zographos, S. E., Gergely, P., Leonidas, D. D., Somsák, L.: Nanomolar Inhibitors of Glycogen Phosphorylase Based on β-d-Glucosaminyl Heterocycles: A Combined Synthetic, Enzyme Kinetic, and Protein Crystallography Study.
   J. Med. Chem. 60 (22), 9251-9262, 2017. ISSN: 0022-2623.
   DOI: http://dx.doi.org/10.1021/acs.jmedchem.7b01056
   IF: 6.259 (2016)

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List of other publications

Foreign language scientific articles in international journals (5)

5. Szőcs, B., Bokor, É., **Szabó, E. K.**, Kiss-Szikszai, A., Tóth, M., Somsák, L.: Synthesis of 5-aryl-3-C-glycosyl- and unsymmetrical 3,5-diaryl-1,2,4-triazoles from alkylidene-amidrazones.
RSC Advances. 5 (54), 43620-43629, 2015. ISSN: 2046-2069.
DOI: http://dx.doi.org/10.1039/C5RA05702G
IF: 3.289

6. Kuki, Á., Nagy, L., **Szabó, E. K.**, Antal, B., Zsuga, M., Kéki, S.: Activation Energies of Fragmentations of Disaccharides by Tandem Mass Spectrometry.
J. Am. Soc. Mass Spectrom. 25 (3), 439-443, 2014. ISSN: 1044-0305.
DOI: http://dx.doi.org/10.1007/s13361-013-0793-8
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7. Nagy, L., Kuki, Á., **Szabó, E. K.**, Sipos, A., Zsuga, M., Kéki, S.: Fragmentation study of noscapine derivatives under electrospray conditions.
Rapid Commun. Mass Spectrom. 28 (7), 822-828, 2014. ISSN: 0951-4198.
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8. Kuki, Á., **Szabó, E. K.**, Nagy, L., Zsuga, M., Kéki, S.: Rapid identification of disaccharides by tandem mass spectrometry.
J. Mass Spectrom. 48 (12), 1276-1280, 2013. ISSN: 1076-5174.
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9. Fazekas, E., **Szabó, E. K.**, Kandra, L., Gyémánt, G.: Unexpected mode of action of sweet potato β-amylase on maltooligomer substrates.
BBA-Proteins Proteomics. 1834 (10), 1976-1981, 2013. ISSN: 1570-9639.
DOI: http://dx.doi.org/10.1016/j.bbapap.2013.06.017
IF: 3.191

DEBRECENI EGYETEM Egyetemi és Nemzeti Könyvtár

Total IF of journals (all publications): 30,677
Total IF of journals (publications related to the dissertation): 16,29

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of Web of Science, Scopus and Journal Citation Report (Impact Factor) databases.

19 June, 2018

Conference participations

Oral presentations

1. M. Tóth, B. Szőcs, T. Kaszás, **K. E. Szabó**, T. Docsa, P. Gergely, L.Somsák
   Synthesis of C-(β-D-Glucopyranosyl) Heterocycles and 4-(β-D-Glucopyranosyl) Semicarbazones: Potent Glycogen Phosphorylase Inhibitors
   4th German-Hungarian Workshop, Synthesis, Isolation, and Biological Activity of Natural Products and Related Systems
   June 14-16, 2011, Debrecen, Hungary. Oral presentation, Book of Abstracts OP-7.

2. B. Szőcs, T. Kaszás, **K. E. Szabó**, M. Tóth, L. Somsák
   Glükózhoz kapcsolt acilhidrazon származékok heterociklizációja
   MTA Szénhidrát-, Nukleinsav- és Antibiotikum Munkabizottsága előadóülése Debrecen, 2012. máj. 31-jún. 1.

3. B. Szőcs, S. Kun, M. Tóth, **K. E. Szabó**, É. Bokor, 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 Munkabizottsága előadóülése
   Mátrafüred, 2013. máj. 22-24.

4. **K. E. Szabó**, A. Páhi, L. Somsák
   Synthesis of trisubstituted C-glucopyranosyl-1,2,4-triazoles
   MTA Szénhidrát-, Nukleinsav- és Antibiotikum Munkabizottsága előadóülése
   Mátraháza, 2015. máj. 27-29.

5. **K. E. Szabó**, A. Páhi, L. Somsák
   Triszubsztituált C-(β-D-Glükopiranozil)-1,2,4-triazolok szintézise
   Innováció a Természettudományban Doktorandusz Konferencia
   Szeged, 2015. szeptember 26.

6. **K. E. Szabó**, S. Kun, L. Somsák
   Experiments towards new glycopyranosilidene-spiro-heterocycles
   MTA Szénhidrát-, Nukleinsav- és Antibiotikum Munkabizottsága előadóülése
   Mátraháza, 2016. máj. 25-27.

7. **K. E. Szabó**, S. Kun, A. Mándi, T. Kurtán, L. Somsák
   Further results towards new glucopyranosylidene-spiro-heterocycles
   MTA Szénhidrát-, Nukleinsav- és Antibiotikum Munkabizottsága előadóülése Mátraháza, 2017. máj. 31-jún 1.

8. **K. E. Szabó**, S. Kun, L. Somsák
   Kísérletek új típusú glükopiranozilidén-spiro-heterociklusok előállítására
   MTA Heterociklusos és Elemorganikus Kémiai Munkabizottsági Ülés
   Balatonszemes, 2018. Június 6-8.

Posters

9. B. Szőcs, T. Kaszás, **K. E. Szabó**, M. Tóth, T. Docsa, P. Gergely, L. Somsák
   Synthesis of C-(β-D-Glucopyranosyl) Heterocycles and 4-(β-D-Glucopyranosyl) Semicarbazones
   4th European Conference on Chemistry for Life Sciences, Budapest, 2011. August 31-September 3.

10. **K. E. Szabó**, A. Páhi, L. Somsák
    Synthesis of 5-(β-D-glucopyranosyl)-1,3-disubstituted)- and 3-(β-D-glucopyranosyl)-1,5-disubstituted)-1,2,4-triazoles
    18th European Carbohydrate Symposium Moscow, Russia, 2015. August 2-6.

11. **K. E. Szabó**, A. Páhi, L. Somsák
    5-(β-D-glükopiranozil)-1,3-diszubsztituált- és 3-(β-D-glükopiranozil)-1,5-diszubsztituált-1,2,4-triazolok szintézise
    Magyar Kémikusok Egyesülete 2. Nemzeti Konferencia
    Hajdúszoboszló, 2015. augusztus 31- szeptember 2.

12. **K. E. Szabó**, A. Páhi, L. Somsák
    Preparation of trisubstituted C-(β-D-glucopyranosyl)-1,2,4-triazoles
    András Lipták Memorial Conference
    Debrecen, 2015. november 6-8.

13. S. Kun, **K. E. Szabó**, N. Kánya, N. Galó, A. Páhi, A. Mándi, T. Kurtán, L. Somsák
    Glucopyranosylidene-spirocycles with five and six membered heterorings: synthesis, CD studies and inhibition of glycogen phosphorylase
    19th European Carbohydrate Symposium, Barcelona, Spain, 2017. July 2-6.