Theses of doctoral (PhD) dissertation

SYNTHESIS OF NOVEL *C*-GLYCOSYL HETEROCYCLES

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1. Introduction

Diabetes is a serious disease affecting more and more people worldwide. It is characterized by chronically elevated blood glucose levels (hyperglycemia) which is a consequence of impared insulin secretion and/or insulin resistance. Treatment of type 2 diabetes mellitus (T2DM) representing more than 90 % of diabetic cases includes administration of oral antihyperglycemic agents such as insulin sensitizers, insulin secretagogues, α-glucosidase and sodium dependent glucose cotransporter 2 inhibitors. As the currently applied antidiabetic drugs are not devoid of adverse effects new therapeutic possibilities are continuously searched for both in academic and industrial circles.

One of these approaches aims at lowering elevated hepatic glucose output typical of T2DM by inhibition of glycogen phosphorylase, a key regulatory enzyme of glucose production in the liver.

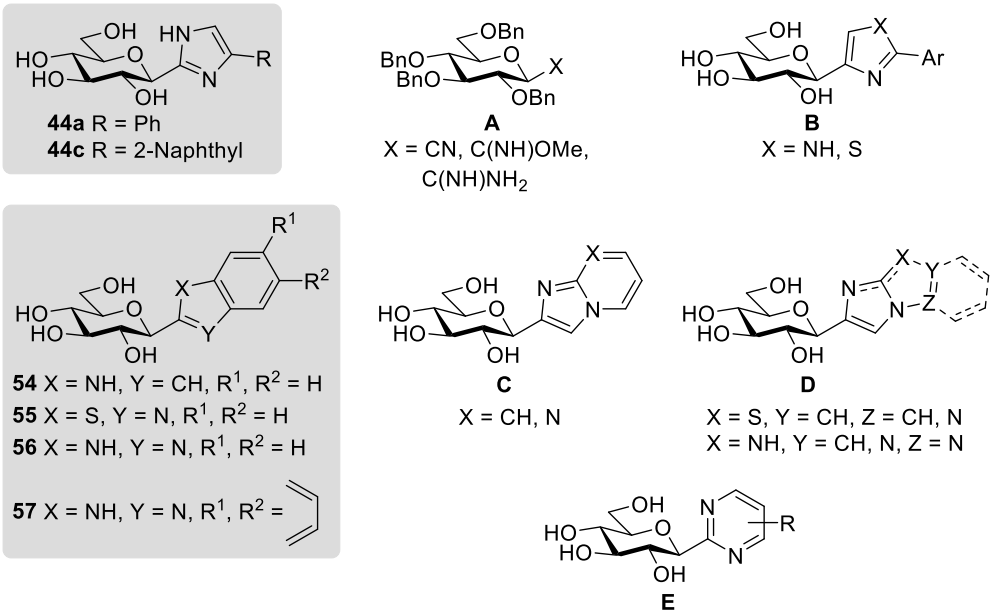
A great majority of GP inhibitors are glucose derivatives that bind primarily at the active site of the enzyme. Several *C*- and *N*-glucopyranosyl azoles displaying inhibitory potency in the low micro- and nanomolar ranges were developed in our research group by nonclassical bioisosteric replacement of the amide moiety of *N*-acyl-(β-D-glucopyranosyl)amines (Glc_p-NH-CO-R). Among them 2-(β-D-glucopyranosyl)imidazoles (**44a,c**,* Scheme 1) are the most potent glucose analogue inhibitors known to date.

The methods elaborated in our laboratory allow to synthesize imidazoles **44a,c** in low overall yields due to the lability of perbenzoylated carbohydrate precursors used under basic reaction conditions. To overcome this issue the synthesis of perbenzylated 2,6-anhydro-aldonic acid derivatives (β-D-glucopyranosyl cyanide, -formimidate and -formamidine) was envisaged (compounds **A**, Scheme 1).

To extend the structure-activity relationship studies preparation of further 4(5)-aryl-2-(β-D-glucopyranosyl)imidazoles and new *C*-(β-D-glucopyranosyl)azoles (molecules **B**) was planned.

To broaden the scope of condensed heterocyclic glucose derivatives possessing GP inhibitory activity (**54**-**57**, Scheme 1) the synthesis of new *C*-glycosylated imidazo-fused heterocycles (structures **C**, **D**) was envisaged.

*Compound numbers given in the doctoral dissertation are used in the theses.



Scheme 1. Target compounds

The synthesis of practically unknown 2-(β-D-glucopyranosyl)pyrimidines (compounds **E**) was also envisioned by Pinner type cyclocondensations of perbenzylated *C*-(β-D-glucopyranosyl)formamidine and 1,3-dielectrophiles.

2. Methods

In the course of 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.

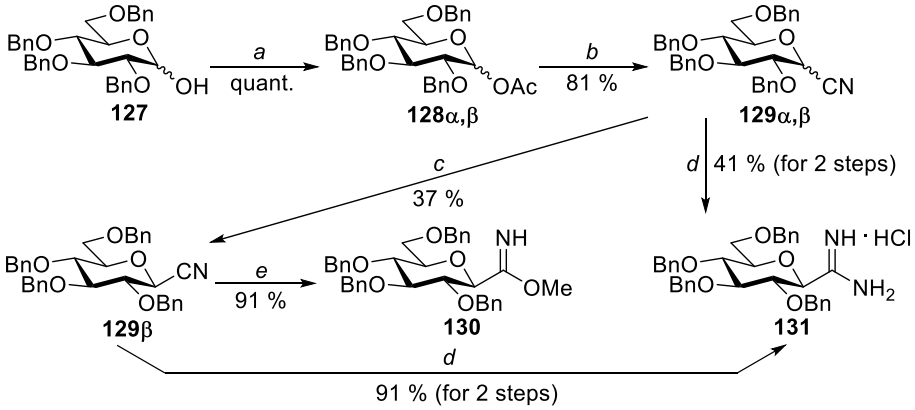
3. Results

3.1. Synthesis of carbohydrate precursors for the preparation of *C*-glucopyranosyl heterocycles

*Methods for the gram-scale synthesis of 2,3,4,6-tetra-*O*-benzyl-β-D-glucopyranosyl-cyanide (**129β**), methyl 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptonimidate (**130**), 2,6-anhydro-3,4,5,7-tetra-*O*-benzyl-D-glycero-D-gulo-heptonimidamide (**131**) and 3,7-anhydro-4,5,6,8-tetra-*O*-benzoyl-1-bromo-1-deoxy-D-glycero-D-gulo-2-octulose (**138**) were elaborated.*

3.1.1. Synthesis of per-*O*-benzylated 2,6-anhydro-aldonic acid derivatives

Perbenzylated glucopyranosyl cyanides (**129α,β**) were obtained from 1-*O*-acetyl-2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (**128α,β**) and TMSCN in the presence of a Lewis acid according to a modified literature procedure (Scheme 2). The pure **129β** cyanide was isolated from the reaction mixture by crystallization. Methyl formimidate (**130**) was synthesized starting from **129β** using sodium methoxide. Both **129β** and **129α,β** were transformed into formamidine hydrochloride **131** in two steps without the isolation of **130**.



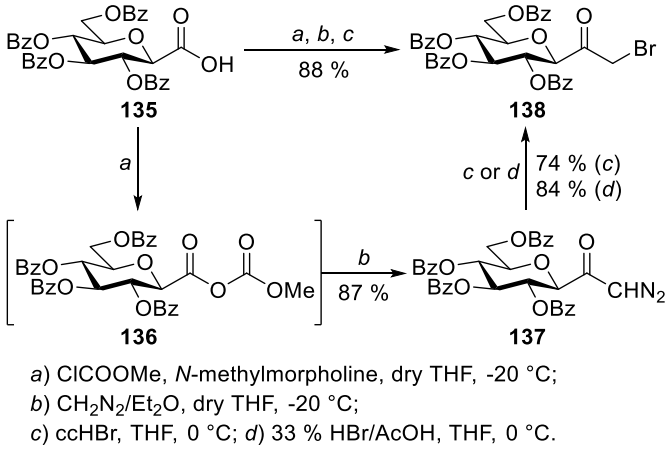
a) Ac_2O, dry pyridine, rt; *b*) TMSCN, $BF_3{\cdot}Et_2O$, dry MeCN, rt;
c) crystallization from EtOH; *d*) 1. NaOMe/MeOH, dry $CHCl_3$, rt, 2. NH_4Cl, rt;
e) NaOMe/MeOH, rt.

Scheme 2. Synthesis of per-*O*-benzylated 2,6-anhydro-aldonic acid derivatives

3.1.2. Synthesis of 3,7-anhydro-4,5,6,8-tetra-*O*-benzoyl-1-bromo-1-deoxy-D-*glycero*-D-*gulo*-2-octulose

2,3,4,6-Tetra-*O*-benzoyl-β-D-glucopyranosyl diazomethyl ketone (**137**, Scheme 3) was prepared from *C*-(2,3,4,6-tetra-*O*-benzoyl-β-D-glucopyranosyl)formic acid (**135**) via mixed anhydride **136** in two steps. Compound **137** was transformed into bromomethyl

β-D-glucopyranosyl ketone (**138**) with concentrated hydrogen bromide solutions. A three step *one-pot* procedure was elaborated for the synthesis of **138** starting from **135** as described above.



a) ClCOOMe, *N*-methylmorpholine, dry THF, -20 °C;
b) CH_2N_2/Et_2O, dry THF, -20 °C;
c) ccHBr, THF, 0 °C; *d*) 33 % HBr/AcOH, THF, 0 °C.

Scheme 3. Synthesis of 3,7-anhydro-4,5,6,8-tetra-*O*-benzoyl-1-bromo-1-deoxy-D-*glicero*-D-*gulo*-2-octulose

3.2. Synthesis of novel *C*-glucopyranosyl azoles

*An improved method for the synthesis of 4(5)-aryl-2-(β-D-glucopyranosyl)imidazoles (**44**) was elaborated. Methods for the syntheses of 2-aryl-4(5)-(β-D-glucopyranosyl)imidazoles (**140**), 2-aryl-4-(β-D-glucopyranosyl)thiazoles (**142**) and novel* C*-glycosylated imidazo-fused heterocycles (**145**, **146**, **149**, **150**, **152**, **157**) were developed.*

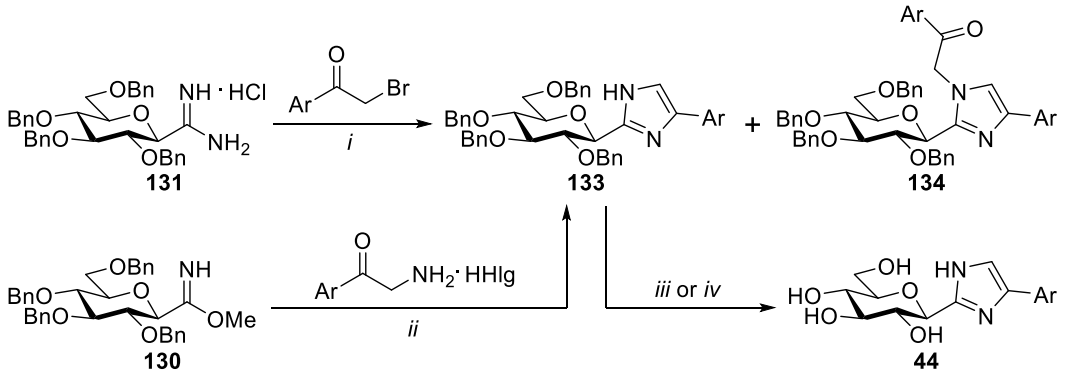
3.2.1. Synthesis of 4(5)-aryl-2-(β-D-glucopyranosyl)imidazoles

The per-*O*-benzylated 4(5)-aryl-2-(β-D-glucopyranosyl)imidazoles (**133a-d**) were synthesized from **131** and α-bromoketones under basic conditions in moderate to good yields (Table 1). Cyclocondensation of **130** and α-aminoketones to get **133a,c** proved to be less effective as compared to the previous method in terms of yields. Debenzylation of **133a-d** to obtain deprotected imidazoles (**44a-e**) was carried out by catalytic hydrogenation (**133a,d)** or applying $BF_3{\cdot}Et_2O$ in the presence of EtSH as benzyl cation scavenger (**133b-d**).

3.2.2. Synthesis of 2-aryl-4(5)-(β-D-glucopyranosyl)imidazoles

α-Bromoketone **138** was condensed with aromatic carboxamidines in the presence of potassium carbonate to get 2-aryl-4(5)-(3',4',6'-tri-*O*-benzoyl-β-D-glucopyranosyl)imidazoles (**139a,c**, Scheme 4) which were deprotected to **140a,c** by the Zemplén method.

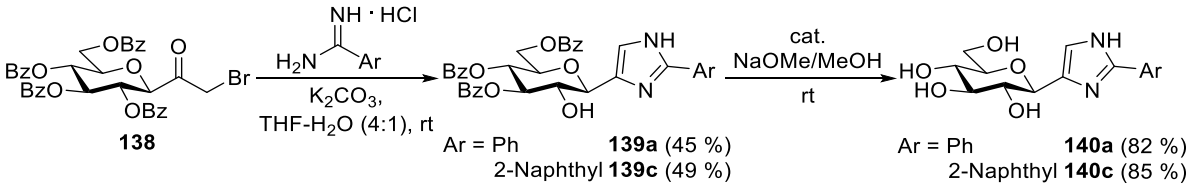
Table 1. Synthesis of 4(5)-aryl-2-(β-D-glucopyranosyl)imidazoles



i) K_2CO_3, THF-H_2O (4:1), rt; *ii*) dry pyridine, rt;
iii) $Pd(OH)_2/C$, H_2, 1 drop of ccHCl, EtOAc-EtOH (1:1), rt; *iv*) $BF_3 \cdot Et_2O$, EtSH, DKM, rt.

	Ar	Reaction conditions and yields (%)				
			133	**134**		**44**
a	Ph	*i*	72	7	*iii*	89
		ii	33	–		
b	1-Naphthyl	*i*	45	–[a]	*iv*	59
c	2-Naphthyl	*i*	69	8	*iii*	–[b]
		ii	47	–	*iv*	82
d	4-NO_2-Ph	*i*	36	–[a]	*iv*	45
e	4-NH_2-Ph	–	–	–	*iii* (from **133d**)	66

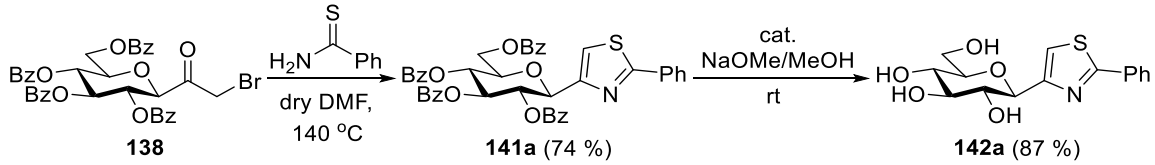
[a]traces; [b]inseparable mixture of **44c** and tetraline derivatives.



Scheme 4. Synthesis of 2-aryl-4(5)-(β-D-glucopyranosyl)imidazoles

3.2.3. Synthesis of 4-(β-D-glucopyranosyl)-2-phenylthiazole

4-(β-D-Glucopyranosyl)-2-phenylthiazole **142a** was obtained by Hantzsch cyclocondensation of **138** and thiobenzamide followed by Zemplén deacylation of the formed **141a** (Scheme 5).



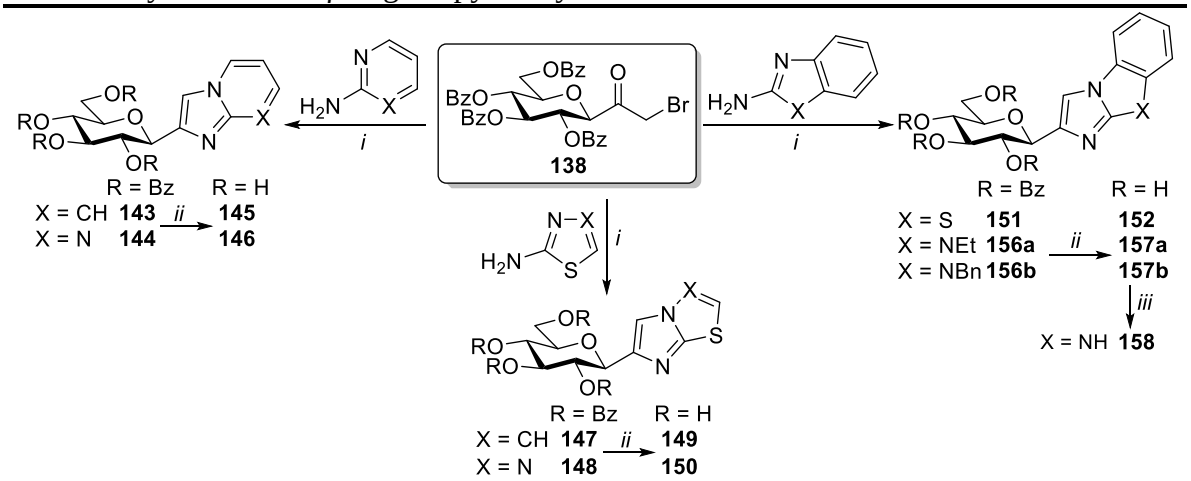
Scheme 5. Synthesis of 4-(β-D-glucopyranosyl)-2-phenylthiazole

3.2.4. Synthesis of *C*-β-D-glucopyranosyl derivatives of some imidazo-fused heterocycles

Condensed heterocyclic glucose derivatives were obtained from **138** and 2-amino-N-heterocycles by cyclocondensation in refluxing 1,4-dioxane (Table 2): imidazo[1,2-*a*]pyridine (**143**), imidazo[1,2-*a*]pyrimidine (**144**), imidazo[2,1-*b*]thiazole (**147**), imidazo[2,1-*b*][1,3,4]thiadiazole (**148**) and benzo[*d*]imidazo[2,1-*b*]thiazole (**151**). Deprotection was carried out using a catalytic amount of sodium methoxide in dry methanol to get **145**, **146**, **149**, **150** and **152**.

Trials to condense **138** with NH containing amino-azoles such as 5-amino-1*H*-tetrazole, 3-amino-1*H*-1,2,4-triazole and 2-aminobenzimidazole were unsuccessful. Ring closure of **138** with 2-aminobenzimidazole was achieved after protection of its endocyclic nitrogen atom to get benzo[*d*]imidazo[1,2-*a*]imidazoles (**156a,b**). Deprotected derivatives (**157a,b**, **158**) were obtained by the Zemplén method and catalytic hydrogenation.

Table 2. Synthesis of *C*-β-D-glucopyranosyl derivatives of some fused azoles



Reaction conditions	Product (yield)
i) dry 1,4-dioxane, reflux	**143** (48 %), **144** (48 %), **147** (66 %), **148** (40 %), **151** (58 %), **156a** (42 %), **156b** (37 %).
ii) cat. NaOMe/MeOH, rt	**145** (79 %), **146** (76 %), **149** (93 %), **150** (49 %), **152** (85 %), **157a** (83 %), **157b** (72 %).
iii) H_2, $Pd(OH)_2$/C, dry EtOH, reflux	**158** (73 %)

3.3. Synthesis of 2-(glycopyranosyl)pyrimidines

*General methods for the synthesis of unknown 2-(glycopyranosyl)pyrimidines were elaborated. Per-*O*-benzylated and deprotected* C*-(β-*D*-glucopyranosyl)formamidines (**131**, **159**) and 1,3-dielectrophiles (1,3-diketones, 3-ketoesters, dimethyl malonate, substituted methylene malonic acid derivatives, trimethylsilyl ynones and vinamidinium salts) were reacted by Pinner type reactions to give 2-(β-*D*-glucopyranosyl)pirimidines (**160**, **162**, **163**, **164**, **165**, **166**, **168**, **169**, **171**, **174**, **177**). A three step* one-pot *procedure was developed for the synthesis of 2-(glycopyranosyl)pyrimidines (**164**, **187-190**) starting from glycosyl cyanides (**132**, **183-186**).*

3.3.1. Synthesis of 2-(β-D-glucopyranosyl)pyrimidines from *C*-(β-D-glucopyranosyl)-formamidines

3.3.1.1. Synthesis of 4,6-disubstituted-2-(β-D-glucopyranosyl)pyrimidines

4,6-Disubstituted-2-(β-D-glucopyranosyl)pyrimidines **160a-d**, **162a-d** were synthesized from amidines **131**, **159** and β-chloro-α,β-unsaturated ketones prepared from the corresponding diketones by chlorination (Table 3, entry 1). For the deprotection of **160a-d** by catalytic hydrogenation elevated temperature was necessary which was attributed to catalyst poisoning by the pyrimidine ring (Table 3, entry 8).

3.3.1.2. Synthesis of 2-(β-D-glucopyranosyl)pyrimidine-4(3*H*)-ones

2-(β-D-Glucopyranosyl)pyrimidine-4(3*H*)-ones **163a-d**, **164a-d** were prepared from amidines **131**, **159** and 3-ketoesters under basic reaction conditions (Table 3, entry 2). The reaction of dimethyl malonate and amidines **131**, **159** resulted in 6-hydroxypyrimidines **165** and **166**, respectively (entry 3). Debenzylation of **163a,d** and **165** was achieved by catalytic hydrogenation at reflux temperature (entry 8).

3.3.1.3. Synthesis of 2-(β-D-glucopyranosyl)pyrimidines from methylene malonic acid derivatives

Variously substituted 2-(β-D-glucopyranosyl)pyrimidines **168a-f**, **169a-f** were obtained from amidines **131**, **159** and ethoxymethylene malonic acid derivatives, 2-benzylidenemalononitrile or ethyl 2-cyano-3-phenylacrylate in the presence of sodium methoxide in methanol (Table 3, entry 4). Debenzylation of 2-(β-D-glucopyranosyl)pyrimidin-5-carbonitriles **168a,c,e,f** failed even at elevated temperature presumably due to the complexation of cyanide group with palladium to result in loss of catalyst activity. Ethyl 2-(β-D-glucopyranosyl)pyrimidin-5-carboxylates **168b,d** were deprotected by catalytic

hydrogenation in the presence of a drop of concentrated hydrochloric acid at room temperature to get **169b,d** (entry 9).

2-(β-D-Glucopyranosyl)-6-oxo-1,6-dihidropyrimidin-5-carboxylates **171a,b** were obtained in two steps from **131** (Table 3, entry 5). Debenzylation of **171a,b** gave glucosyl pyrimidine derivatives **172a,b** (entry 8).

3.3.1.4. Synthesis of 2-(β-D-glucopyranosyl)-4-substituted-pyrimidines

Per-*O*-benzylated 2-(β-D-glucopyranosyl)-4-substituted-pyrimidines (**174a-d**) were prepared from **131** and trimethylsilyl ynones under basic conditions (Table 3, entry 6). Removal of benzyl protecting groups was achieved using a Lewis acid to get **175a-c** (entry 10).

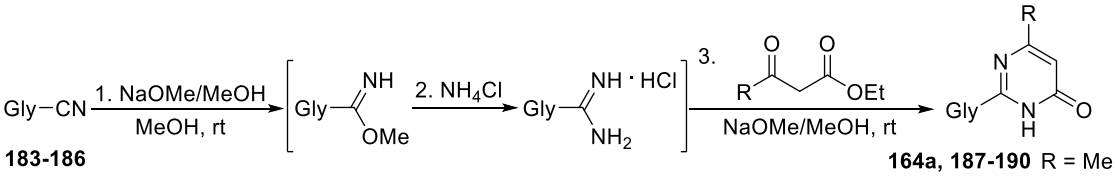
3.3.1.5. Synthesis of 2-(β-D-glucopyranosyl)pyrimidines from vinamidinium salts

Ring clousure of **131** and vinamidinium salts in the presence of sodium methoxide resulted in 2-(β-D-glucopyranosyl)pyrimidines (**177a-d**, Table 3, entry 7).

3.3.2. *One-pot* procedure for the synthesis of 2-glycopyranosylpyrimidines

The per-*O*-acylated glycosyl cyanides **132**, **183-186** were transformed into methyl *C*-glycopyranosyl-formimidates, then reacted with ammonium chloride and in the final step with 3-ketoesters. The pyrimidines **164a,d** and **187-190** were isolated in moderate to high yields (Table 4).

Table 4. Synthesis of 6-methyl-2-glycopyranosylpyrimidine-4(3*H*)-ones



183-186

164a, 187-190 R = Me

164d R = Ph

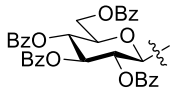
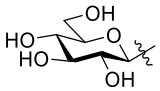
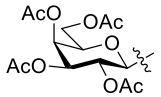
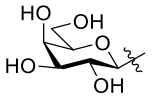
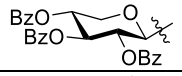
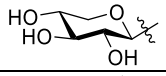
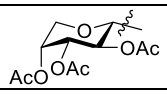
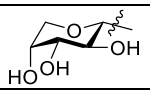
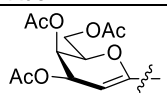
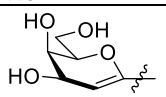
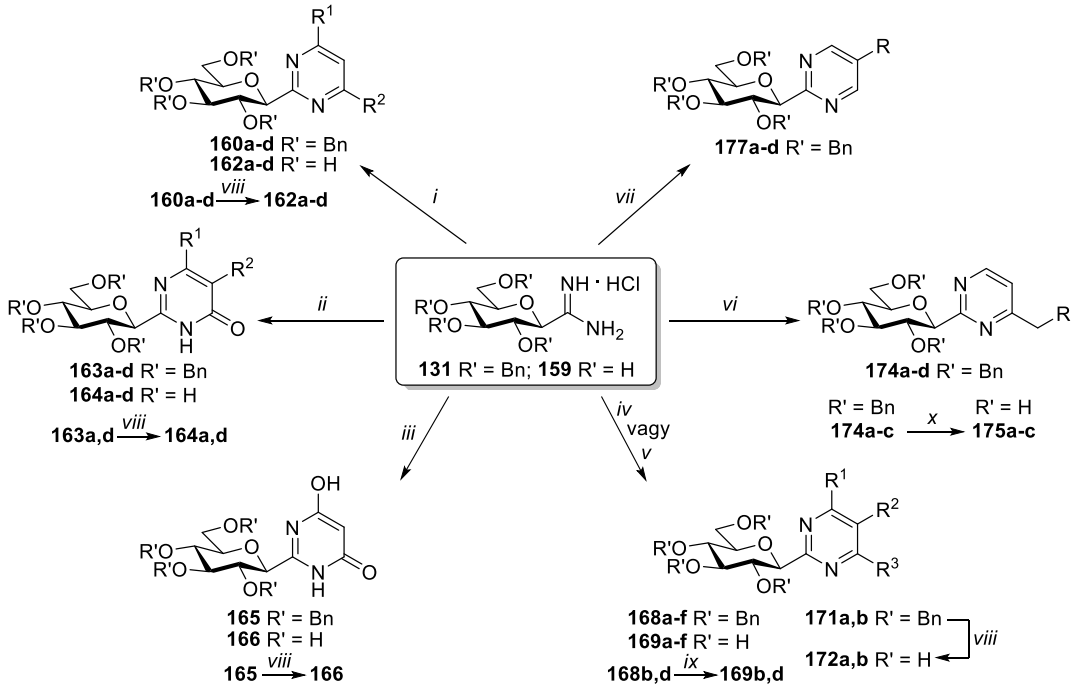
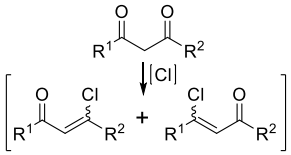
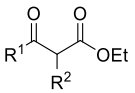
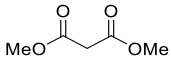
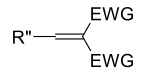
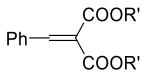
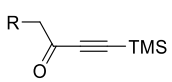
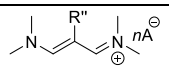
Gly				Yield (%)
Starting material		Product		
132		**164a**		43
		164d		25
183		**187**		70
184		**188**		27
185		**189**		43
186		**190**		94

Table 3. Synthesis of 2-(β-D-glucopyranosyl)pyrimidines by Pinner reaction



Entry		Reagent and conditions		Product (yield) from **131**	Product (yield) from **159**
1	*i*		K_2CO_3, 4 Å mol. sives, dry DMF, 0 °C, then rt	**160a-d** (65-74 %)	**162a-d** (62-75 %)
				R^1 = CH_3, CF_3; R^2 = Ph, CH_3	
2	*ii*		NaOMe/MeOH, dry MeOH, rt	**163a-d** (43-87 %)	**164a-d** (59-88 %)
				R^1 = CH_3, CH_2Cl, Ph; R^2 = H, Cl	
3	*iii*		NaOMe/MeOH, dry MeOH, rt	**165** (82 %)	**166** (71 %)
4	*iv*	 R" = EtO, Ph; EWG = COOEt, CN	NaOMe/MeOH, dry MeOH, 0 °C	**168a-f** (30-78 %)	**169a-f** (20-85 %)
				R^1 = H, Ph; R^2 = COOEt, CN; R^3 = NH_2, OH	
5	*v*	 R' = Me, Et	1. NaOR'/R'OH, dry R'OH, rt; 2. DDQ, R'OH, rt	**171a,b** (48-53 %, for 2 st.) R^1 = Ph; R^2 = COOMe, COOEt; R^3 = OH	–
6	*vi*		Na_2CO_3, MeCN, cat. H_2O, reflux	**174a-d** (45-67 %) R = Ph, *p*-OMe-Ph, 2-Naphthyl, Cl	–
7	*vii*	 R" = H, Cl, Br, CH=NMe_2^+; *n* = 1, 2; A^- = PF_6^-, ClO_4^-	NaOMe/MeOH, dry MeOH, rt	**177a-d** (60-97 %) R = H, Cl, Br, CHO	–
8	*viii*	H_2, $Pd(OH)_2$/C, EtOAc-EtOH, reflux		**160a-d** → **162a-d** (19-92 %) **163a,d** → **164a,d** (62-77 %) **165** → **166** (47 %) **171a,b** → **172a,b** (58-70 %)	
9	*ix*	H_2, $Pd(OH)_2$/C, EtOAc-EtOH, ccHCl, rt		**168b,d** → **169b,d** (51-67 %)	
10	*x*	BCl_3, dry CH_2Cl_2, -78 °C		**175a-c** (49-75 %)	

3.4. Study of glycoenzyme inhibition

Inhibitory potency of the synthesized compounds was tested in the frame of cooperations. Low micromolar glycogen phosphorylase inhibitors were found among the C*-glucopyranosyl azoles and some of the 2-(glucopyranosyl)pyrimidines proved to be submillimolar inhibitors of glycosidases.*

3.4.1. Rabbit muscle glycogen phosphorylase *b* (RMGP*b*) inhibiton

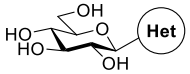
Enzyme kinetic assays of new azoles **44b,d,e**, **140a-c**, **142a,c**, **145**, **146**, **149**, **150**, **152**, **157a**, **158** were performed at the Department of Medical Chemistry of the University of Debrecen (Table 5).

The most potent inhibitor of rabbit muscle glycogen phosphorylase *b* (RMGP*b*) was found to be 4(5)-(*p*-aminophenyl)-2-(β-D-glucopyranosyl)imidazole (**44e**) with a K_i value of 0.41 μM. 4(5)-Aryl-2-(β-D-glucopyranosyl)imidazoles **44b**,**d**, 2-aryl-4(5)-(β-D-glucopyranosyl)-imidazoles **140a,c** and 2-(β-D-glucopyranosyl)-4-(2-naphthyl)thiazole **142c** proved to be low micromolar RMGP*b* inhibitors.

While 4-phenylthiazole **43a** and 2-phenylthiazole **142a** showed similar inhibition, the 4-(β-D-glucopyranosyl)-2-(2-naphthyl)-thiazole **142c** displayed, somewhat surprisingly, one order of magnitude stronger binding than its 4-(2-naphthyl)-substituted isomer **43c**.

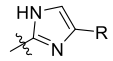
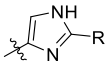
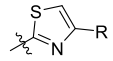
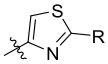
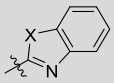
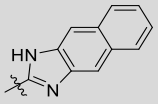
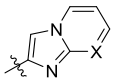
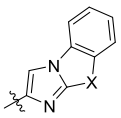
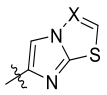
Unlike the previously prepared condensed heterocyclic glucose derivatives **55-57** *C*-glycosylated fused azoles **145**, **146**, **149**, **150**, **152**, **157a**, **158** exhibited very weak or no inhibition against the enzyme at 625 μM concentration (Table 5). This may be attributed to the loss of hydrogen bond capacity of the new heterocycles. Comparing the inhibitions one can conclude that changing the position of nitrogen atoms in the imidazole ring is detrimental to the inhibition.

2-(β-D-Glucopyranosyl)pirimidines **162a-d**, **164a-d**, **166**, **169a-f** did not display GP inhibition at 625 μM.



C-glucopyranosyl heterocycle

Table 5. Inhibitory potency of *C*-(β-D-glucopyranosyl)-heterocycles* against RMGP*b* (K_i, [μM])

Het		R	K_i	Het		R	K_i
44 	**a**	Ph	0.28	**140** 	**a**	Ph	37
	b	1-Naphthyl	1.5		**b**	1-Naphthyl	93
	c	2-Naphthyl	0.031		**c**	2-Naphthyl	5.4
	d	4-NO_2-Ph	1.14				
	e	4-NH_2-Ph	0.41				
43 	**a**	Ph	310	**142** 	**a**	Ph	326
	c	2-Naphthyl	158		**c**	2-Naphthyl	23
Het		X	K_i	Het		X	K_i
	**55**	S	76 229		**57**	–	2.1
	56	NH	8.6 11				
	**145**	CH	28 %[a]		**152**	S	n. i.[b]
	146	N	25 %[a]		**157a**	NEt	n. i.[b]
					158	NH	n. i.[b]
	**149**	CH	15 %[a]				
	150	N	10 %[a]				

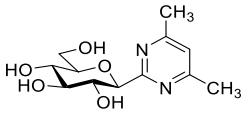
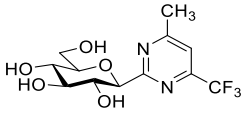
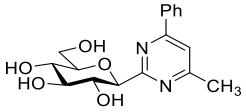
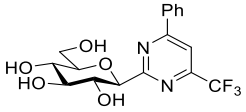
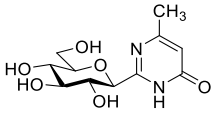
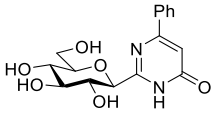
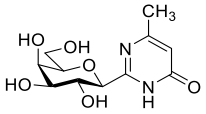
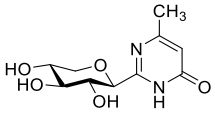
*Cells highlited in grey indicate previously synthesized compounds.
[a]at 625 μM inhibitor concentration; [b]n. i. – no inhibition at 625 μM.

3.4.2. Glycosidase inhibition

Inhibitory potency of 2-glycosylpyrimidines against some glycosidase enzymes were tested at the Department of Inorganic and Analytical Chemistry of the University of Debrecen.

2-Glycosylpyrimidines **162a-d**, **164a,d**, **187** and **188** showed weak or no inhibition against α-glucosidase and β-galactosidase enzymes (Table 6). The most effective derivatives, i.e. 2-(β-D-glucopyranosyl)-6-trifluoromethyl-4-phenylpyrimidine (**162d**) and 2-(β-D-glucopyranosyl)-6-phenylpyrimidin-4(3*H*)-one (**164d**) displayed submillimolar activity.

Table 6. Inhibitory potency of 2-(β-D-glucopyranosyl)pyrimidines against glycosidases

	Compound	Inhibition (concentration, [mM])	
		α-Glucosidase[a]	β-Galactosidase[b]
162a		33 % (3.1)	45 % (3.1)
162b		30 % (1.6)	20 % (1.6)
162c		90 % (5.7)	56 % (5.7)
162d		54 % (6.8)	IC_{50} = 0.34 mM
164a		27 % (2.1)	n. i.[c] (2.1)
164d		IC_{50} = 0.70 mM	56 % (3.2)
187		10 % (1.3)	n. i.[c] (1.3)
188		14 % (0.8)	n. i.[c] (0.8)

[a]yeast; [b]bovine liver; [c]n. i. – no inhibition.

4. Possible applications of the results

In the course of my research numerous *C*-glycosyl heterocycles were synthesized. Inhibitory potencies of *C*-(β-D-glucopyranosyl)azoles and 2-(β-D-glucopyranosyl)pyrimidines against rabbit muscle glycogen phosphorylase *b* and glycosidase enzymes were determined. After further biological studies the most efficient compounds may find application in the treatment of type 2 diabetes mellitus (T2DM) or other diseases connected to glycogen breakdown such as ischemia or tumor growth. On the other hand, glycosidase inhibitors may be utilized in treatments of lysosomal and several neurological disorders related to the malfunction of glycosidase enzymes.

C-Glycosyl arenes possessing di(het)arylmethane type aglycons are used for the treatment of T2DM as sodium dependent glucose cotransporter 2 inhibitors (SGLT-2). The synthesized 4-arylmethyl-2-(β-D-glucopyranosyl)pyrimidines contain this characteristic feature, therefore the method for their synthesis may be used in the future for the development of novel SGLT-2 inhibitors.

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MTMT ID: 10055024

List of publications related to the dissertation

Foreign language international book chapters (1)

1. **Szennyes, E.**, Bokor, É., Kiss-Szikszai, A., Somsák, L., Pascal, Y.: Preparation of 2,6-anhydro-3,4,5,7-tetra-O-benzyl-D-glycero-D-gulo-heptonimidamide.
In: Carbohydrate Chemistry: Proven Synthetic Methods / Christian Vogel, Paul Murphy, CRC Press-Taylor & Francis Group, Boca Raton, 323-332, 2017, (Volume 4) ISBN: 9781498726917

Foreign language scientific articles in international journals (3)

2. **Szennyes, E.**, Bokor, É., Docsa, T., Sipos, Á., Somsák, L.: Synthesis of C-β-D-glucopyranosyl derivatives of some fused azoles for the inhibition of glycogen phosphorylase.
Carbohydr. Res. 472, 33-41, 2019. ISSN: 0008-6215.
DOI: http://dx.doi.org/10.1016/j.carres.2018.11.003
IF: 2.074 (2017)

3. **Szennyes, E.**, Bokor, É., Langer, P., Gyémánt, G., Docsa, T., Sipos, Á., Somsák, L.: The first general synthesis of 2-C-(β-D-glycopyranosyl)pyrimidines and their evaluation as inhibitors of some glycoenzymes.
New J. Chem. 42 (21), 17439-17446, 2018. ISSN: 1144-0546.
DOI: http://dx.doi.org/10.1039/C8NJ04035D
IF: 3.201 (2017)

4. **Szennyes, E.**, Bokor, É., Batta, G., Docsa, T., Gergely, P., Somsák, L.: Improved preparation of 4(5)-aryl-2-(β-D-glucopyranosyl)-imidazoles, the most efficient glucose analogue inhibitors of glycogen phosphorylase.
RSC Adv. 6 (97), 94787-94794, 2016. EISSN: 2046-2069.
DOI: http://dx.doi.org/10.1039/C6RA21839C
IF: 3.108

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List of other publications

Foreign language scientific articles in international journals (2)

5. 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: 4.816 (2017)

6. Bokor, É., **Szennyes, E.**, Csupász, T., Tóth, N., Docsa, T., Gergely, P., Somsák, L.: C-(2-Deoxy-D-arabino-hex-1-enopyranosyl)-oxadiazoles: synthesis of possible isomers and their evaluation as glycogen phosphorylase inhibitors.
Carbohydr. Res. 412, 71-79, 2015. ISSN: 0008-6215.
DOI: http://dx.doi.org/10.1016/j.carres.2015.04.016
IF: 1.817

Total IF of journals (all publications): 15,016
Total IF of journals (publications related to the dissertation): 8,383

The Candidate's publication data submitted to the iDEa Tudóstér have been validated by DEENK on the basis of the Journal Citation Report (Impact Factor) database.

28 February, 2019

Conference participations

Oral presentations

1. É. Bokor, Cs. Koppány, T. Csupász, **E. Szennyes**, L. Somsák
   Modifications of the sugar moiety of C*-glucopyranosyl-heterocycles: first synthetic steps towards new inhibitors of glycogen phosphorylase*
   MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése
   Mátraháza, 2014. május 21-23.

2. **E. Szennyes**, É. Bokor, L. Somsák
   Synthesis of 2-β-D-glucopyranosyl pyrimidines
   MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése
   Mátraháza, 2015. május 27-29.

3. S. Kun, J. Begum, **E. Szennyes,** K. E. Szabó, É. Bokor, L. Juhász, T. Docsa, P. Gergely, J. M. Hayes, L. Somsák
   A new series of C*-glucopyranosyl-1,2,4-triazoles as glycogen phosphorylase inhibitors*
   MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése
   Mátraháza, 2015. május 27-29.

4. L. Somsák, S. Kun, J. Begum, **E. Szennyes**, É. Bokor, L. Juhász, T. Docsa, P. Gergely, J. M. Hayes
   Virtual screening synthesis and enzymatic evaluation of 3-(β-D-glucopyranosyl)-5-substituted-1,2,4-triazoles for the inhibition of glycogen phosphorylase
   18th European Carbohydrate Symposium, Moscow, Russia, August 2-6, 2015.

5. Kun S., Begum J., **Szennyes E.**, Bokor É., Juhász L., Docsa T., Gergely P., Hayes J. M., Somsák L.
   3-(β-D-Glükopiranozil)-5-szubsztituált-1,2,4-triazolok virtuális szűrése, szintézise és glikogén foszforiláz gátló hatásának vizsgálata
   MKE 2. Nemzeti Konferencia, Hajdúszoboszló, 2015. aug. 31.-szept. 2., Sz-O-11, p. 64.

6. **Szennyes E.**, Bokor É., Somsák L.
   2-β-D-Glükopiranozil-pirimidinek szintézise
   Innováció a Természettudományban - Doktorandusz konferencia
   Szeged, 2015. szeptember 26.

7. **E. Szennyes**, É. Bokor, L. Somsák
   New transformations of O*-perbenzylated glucopyranosyl formamidine*
   MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése
   Mátraháza, 2016. május 25-27.

8. **E. Szennyes**, É. Bokor, L. Somsák
Synthesis of new C*-glucopyranosyl azoles for the inhibition of glycogen phosphorylase*
MTA Szénhidrát, Nukleinsav és Antibiotikum Munkabizottság előadóülése
Mátraháza, 2017. május 31.-június 2.

9. É. Bokor, **E. Szennyes**, L. Somsák
*First syntheses of 2-*C*-glucopyranosyl pyrimidines*
29th International Carbohydrate Symposium, Lisboa, Portugal, August 14-19, 2018.

Posters

1. É. Bokor, **E. Szennyes**, T. Csupász, T. Docsa, P. Gergely, L. Somsák
*Synthesis of 1-*C*-hetaryl-glucals for the inhibition of glycogen phosphorylase*
20th International Conference on Organic Synthesis, Budapest, Hungary, June 29 – July 4, 2014. P-108.

2. E. Szennyes, É. Bokor, L. Somsák
Synthesis of C*-(β-D-glucopyranosyl)formamidine and its transformation into 2-(β-D-glucopyranosyl)-pyrimidines*
18th European Carbohydrate Symposium, Moscow, Russia, August 2-6, 2015. P-13.

3. **E. Szennyes**, É. Bokor, L. Somsák
C*-(β-D-Glükopiranozil)formamidin szintézise és átalakítása 2-(β-D-glükopiranozil)-pirimidinekké*
MKE 2. Nemzeti Konferencia, Hajdúszoboszló, 2015. aug. 31. – szept. 2., Sz-P-24, p. 192.

4. S. Kun, J. Begum, **E. Szennyes**, É. Bokor, L. Juhász, T. Docsa, P. Gergely, J. M. Hayes, L. Somsák
A new series of C*-(β-D-glucopyranosyl)-1,2,4-triazoles for the inhibition of glycogen phosphorylase: virtual screening, synthesis and in vitro evaluation*
Debrecen Colloquium on Carbohydrates 2015; András Lipták Memorial Conference, Debrecen, Hungary, November 6-8, 2015. P-19. Book of abstracts p. 64.

5. **E. Szennyes**, É. Bokor, L. Somsák
Preparattion of 2-(β-D-glucopyranosyl)-pyrimidines
Debrecen Colloquium on Carbohydrates 2015; András Lipták Memorial Conference, Debrecen, Hungary, November 6-8, 2015. P-29. Book of abstracts p. 74.

6. S. Kun, **E. Szennyes**, É. Bokor, Á. Sipos, T. Docsa, P. Gergely, L. Somsák
Újabb C*- és* N*-glükopiranozil azolok szintézise és glikogén foszforiláz gátló hatásuk*
MKE Vegyészkonferencia, Hajdúszoboszló, 2017. jún. 19-21. P-28, p. 68.

7. S. Kun, **E. Szennyes**, É. Bokor, Á. Sipos, T. Docsa, P. Gergely, L. Somsák
New representatives of C- *and* N-*glucosyl azoles: syntheses and glycogen phosphorylase inhibition*
19th European Carbohydrate Symposium, Barcelona, Spain, July 2-6, 2017. P 360. Abstract book p. 627.

8. **E. Szennyes**, É. Bokor, T. Docsa, Á. Sipos, L. Somsák
C-*Glucosyl derivatives of some imidazo-fused heterocycles: syntheses and glycogen phosphorylase inhibition*
29th International Carbohydrate Symposium, Lisboa, Portugal, August 14-19, 2018. P-MD-12, Abstract book p. 577.