New transformations of monosaccharide derivatives at and around the anomeric centre

Closing report

Project N^{o} 109450 (2013-2018)

The project, as formulated in the proposal, had a dual general goal:

i) systematic study of new, with the investigated sugar derivatives mostly unprecedented reactions to get novel multifunctionalized derivatives of monosaccharides or to simplify synthetic availability of known structures, and

ii) based also on the results of the previous point, design and synthesis of new inhibitors for glycoenzymes which may be relevant for disease.

The targeted glycoenzymes were

a) glycogen phosphorylase (GP), relevant especially in antidiabetic research but also for cerebral and myocardial ischemias, cardiovascular disorders, and tumors;

b) *O*-GlcNAcase (OGA) and hexosaminidases, whose disregulation is among others linked to cardiovascular disorders, type 2 diabetes, erectile disfunction, retinopathy and Alzheimer's disease.

In the research plan three aims were formulated, and this report is constructed to follow those objectives. Among the results those that have already been published will be described in a concise manner with reference to the publication, while those awaiting for publication will be presented in details.

Aim 1. *Synthetic uses of and glycoenzyme inhibition by hydrazones of monosaccharides*

Cross couplings of *O*-peracylated 2,6-anhydro-aldose tosylhydrazones with alcohols, phenols, and carboxylic acids were studied under thermic or photolytic conditions in the presence of K_3PO_4 or LiOtBu. The reactions failed with EtOH, BnOH or *t*BuOH, however, $(CF_3)_2CHOH$, electron poor phenols and carboxylic acids including monosaccharide derived ones gave the corresponding *C*-β-D-glycopyranosylmethyl ethers and esters, respectively.[1]

Cross couplings of *O*-peracylated 2,6-anhydro-aldose tosylhydrazones with aliphatic, (hetero)aromatic and sugar derived thiols were studied under thermic conditions in the presence of K_3PO_4. The reactions with aliphatic thiols gave the corresponding *C*-β-D-glycopyranosylmethyl sulfides in 20-50 % yields, while 50-80 % yields were achieved with thiophenols.[2]

In the above transformations a relationship between the acidity of the coupling reagent and the yields of the products could be recognized that was explained by mechanistic considerations in the papers.

Palladium-catalyzed cross-couplings of *O*-peracylated and *O*-permethylated 2,6-anhydro-aldose tosylhydrazones with aryl bromides were studied under thermic conditions in the presence of LiOtBu and phosphine ligands. The reactions gave the corresponding aryl substituted *exo*-glycals as mixtures of diastereomers in 11-75% yields. The double bond of some of these *exo*-glycals was saturated to give good yields of benzylic *C*-glycosyl derivatives.[3]

Palladium-catalyzed cross-couplings of *O*-peracylated 2,6-anhydro-aldose tosylhydrazones with benzyl bromides were studied under thermic conditions in the presence of LiOtBu. The reactions gave the corresponding *C*-glycopyranosyl styrenes in up to 59 % yields. A detailed analysis of the reaction mixtures to identify all by-products allowed to suggest a mechanistic scheme which explains the moderate-medium yields of the target compounds.[4]

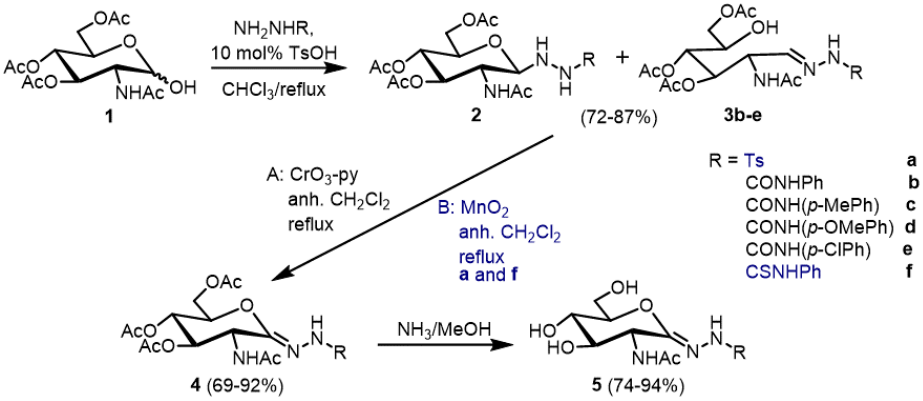
In the following areas several experiments have been carried out, however, these have not yet reached a conclusive and publishable level, therefore, their study will be continued in a forthcoming approved project (FK 128766).

Cross-coupling reactions of anhydro-aldose tosylhydrazones or their Li-salts with phenylboronic acids were also studied. In these experiments generally multicomponent product mixtures were formed whose separation did not allow the isolation of each component in pure form. Structural elucidation of the obtained products by 2D NMR and MS revealed the formation of the expected coupled *C*-glycosyl derivative together with its ring-opened tautomer.

O-Peracetylated and *O*-perbenzylated D-gluconolactone tosylhydrazones were obtained from the free sugar in four or five steps, respectively, and the latter was transformed into its Na-salt by NaOEt in EtOH. Experiments to couple these derivatives with phenylboronic acid neither with *in situ* deprotonation nor by using the pre-formed salt gave the expected products under thermic conditions.

Experiments to couple anhydro-aldose-tosylhydrazones with benzoxazole in the presence of a Cu(I)butyrate type catalyst, and metal-free couplings with aliphatic and aromatic primary and secondary amines resulted in decomposition products only. A search for other catalysts and reaction conditions is in progress. Metal-free coupling of β-D-gluco configured anhydro-aldose-tosylhydrazone with phenyl tetrazole resulted in the corresponding 5-phenyl 2-(β-D-glucopyranosyl)methyl-2H-tetrazole in good yield.

2-Acetamido-2-deoxy-D-glucono-1,5-lactone (thio)semicarbazone and tosylhydrazone derivatives were synthesized in order to create potential inhibitors against clinically important glycosidases, namely *N*-acetyl-β-glucosaminidase (β-Hexosaminidase, EC 3.2.1.52) and protein *O*-linked β-*N*-acetyl-glucosaminidase (*O*-GlcNAcase, OGA, EC 3.2.1.169). These enzymes are able to release *N*-acetyl-glucosamine from glycosaminoglycans, and also from intracellular proteins covalently modified by a single *N*-acetyl-glucosaminyl group, respectively. Our synthetic procedure is outlined in Scheme 1.



Scheme 1. Synthesis of lactone-hydrazone type inhibitors

Thus, 2-acetamido-tri-*O*-acetyl-2-deoxy-D-glucose (**1**) was converted to mixtures of glycosyl hydrazine **2** and its open-chain tautomer **3** derivatives which were oxidized to the protected lactone hydrazones **4**. Standard protective group removal furnished the target compounds **5** which were subjected to enzyme kinetic evaluations.

Due to the significance and emerging activity in the field of OGA inhibition, we have decided to acquire knowledge in expressing and handling of this enzyme. The gene, which encoded the full length human OGA enzyme was carried by a pET28 vector construct kindly provided by Professor D. Vocadlo (Simon Fraser University, Burnaby, Canada). With this plasmid construct we were able to develop a heterologous expression and isolation strategy to obtain soluble, stable and active wild type enzyme for inhibition studies. This study also revealed important environmental factors that greatly affected hOGA stability.

N-Acetylhexosaminidase (EC 3.2.1.52) is a lysosomal enzyme and expressed in several tissues, mostly in a mixture of two isoenzymes: *N*-acetylhexosaminidase A (HexA) and *N*-acetylhexosaminidase B (HexB). Both isoforms appear in plasma and in synovial fluid and become elevated in inflammatory processes. In our inhibitory studies, we have applied the commercially available bovine kidney lysosomal *N*-acetylhexosaminidase, which contains a mixture of HexA and HexB. The substitution of human

N-acetylhexosaminidase isomforms into the bovine kidney enzymes in these investigations is based on the fact that the bovine HexA and HexB share very high sequence similarity with the corresponding human enzymes (93% and 70%, respectively).

With the above enzymes, by using Michaelis-Menten kinetics, the inhibition for the synthesized compounds was characterized in the presence of a chromophore substrate (4-nitrophenyl-*N*-acetyl-β-D-glucosaminide: pNP-GlcNAc) for the less potent, and a fluorescent substrate (4-methylumbelliferyl-*N*-acetyl-β-D-glucosaminide: 4-Mu-GlcNAc) for the tight binding inhibitors. Each compound bound to hOGA and to *N*-acetylhexosaminidase in a competitive manner. Binding constants (K_i) of the inhibitors were established by the Dixon method. For the increasingly tight binding inhibitors, K_i was also defined by using Morrison's quadratic equation. The obtained inhibition constants of 70-270 nM and 170-400 nM for hOGA and Hex, respectively, are shown in Chart 1.

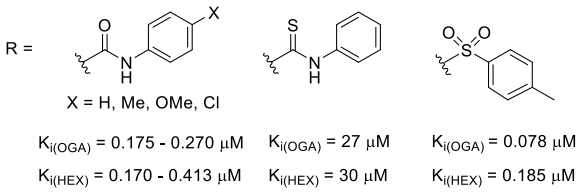


Chart 1. Inhibition of hOGA and Hex enzymes
(R refers to the side chain of compounds **5** in Scheme 1)

The tightest binding was observed in case of the tosylhydrazone derivative to hOGA. Surprisingly, the 4-phenylthiosemicarbazone derivative exhibited two magnitude lower binding affinity (K_i = 30 μM) to both enzymes. Among the synthetized inhibitors, the tosylhydrazone and the 1-chloro-4-phenylsemicarbazone derivatives have a two-fold preference for hOGA. These derivatives represent a new class of inhibitors of hOGA which are simpler to synthesize than other known inhibitors. A paper is in preparation to disclose these results.

Aim 2. *Synthesis of glycosylidene-spiro-heterocycles for glycogen phosphorylase inhibition.*

Within the framework of this research glycopyranosylidene-spiro-heterocycles were synthesized with ten different heterocycles for biological studies.

Glucopyranosylidene- and xylopyranosylidene-spiro-isoxazolines and xylopyranosylidene-spiro-oxathiazoles were prepared according to previously developed methods. Xylose derivatives were not effective GP inhibitors.[5] *In vitro*, *ex vivo* and *in vivo* studies of glucose derived spiro-isoxazolines showed promising antihyperglycaemic effect by diminishing hepatic glucose output in diabetic rats by ~30% that may be relevant for therapeutic use.[6]

An *in vivo* investigation of the already known glucopyranosylidene-spiro-thiohydantoin (TH) in diabetic rats demonstrated the blood glucose lowering effect of TH and the whole body insulin sensitivity was also restored for the treated animals.[7]

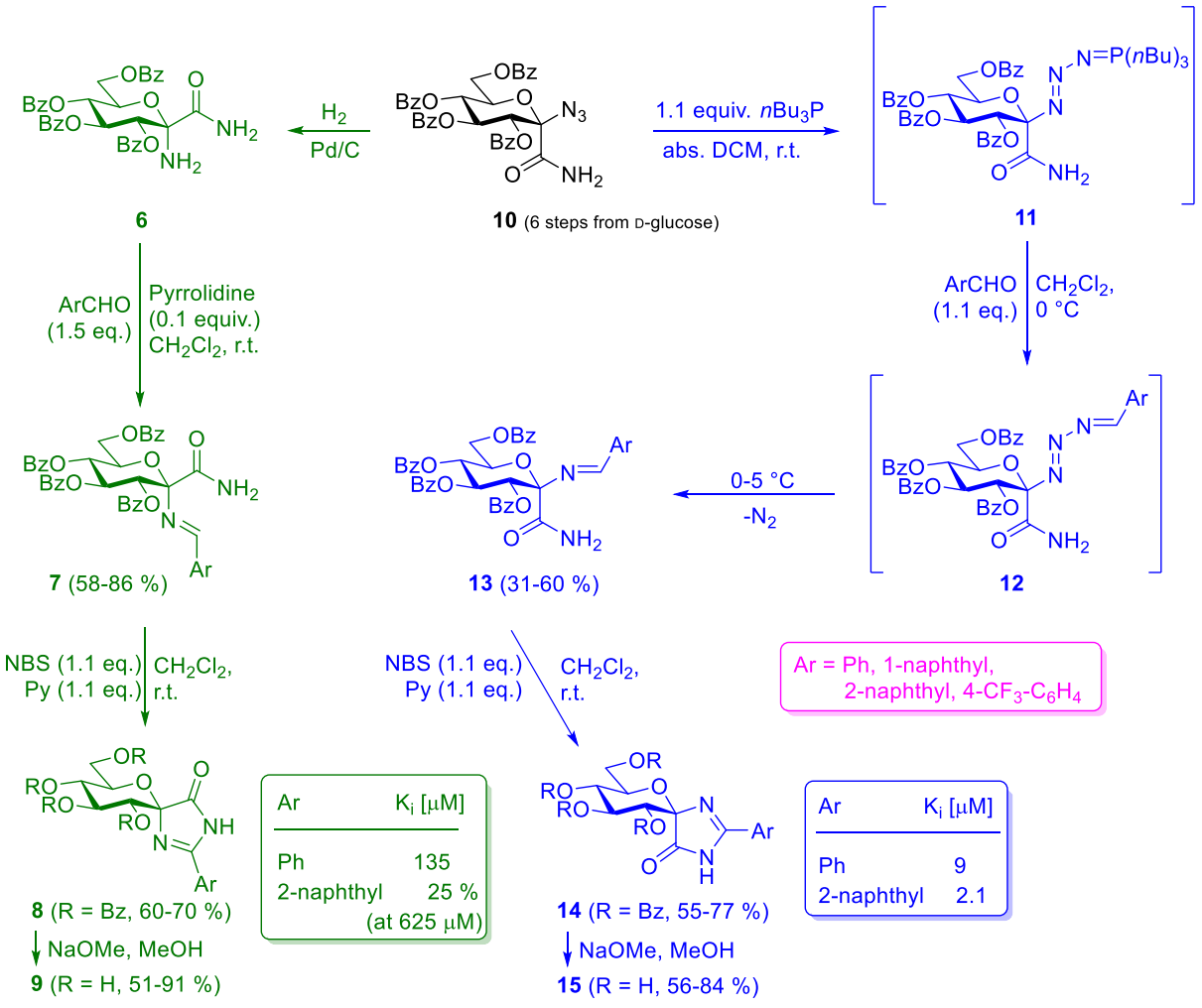
Reaction of ketones with (ulopyranosyl bromide)onamide and ulopyranosonamide derivatives yielded glucopyranosylidene-spiro-iminodioxolanes and oxazolidinones, respectively. The deprotected spiro-oxazolidinones had no GP inhibitory effect.[8]

Spiro-iminothiazolidinone was synthesized from (ulopyranosyl bromide)onamide or onic acid methyl ester and thiourea, then a library was prepared by further acylation, sulfonylation and alkylation of the heterocycle. Binding mode of some low micromolar GP inhibitors from this series was established by X-ray crystallography.[9]

New spirocycles (namely thiazolinones, and imidazolinones) were designed to unify structural properties of spiro-hydantoins and isoxazoles in the hope to get more efficient GP inhibitors. *O*-Benzoyl and *O*-acetyl protected glucopyranosylidene-spiro-thiazolinones were prepared from the corresponding

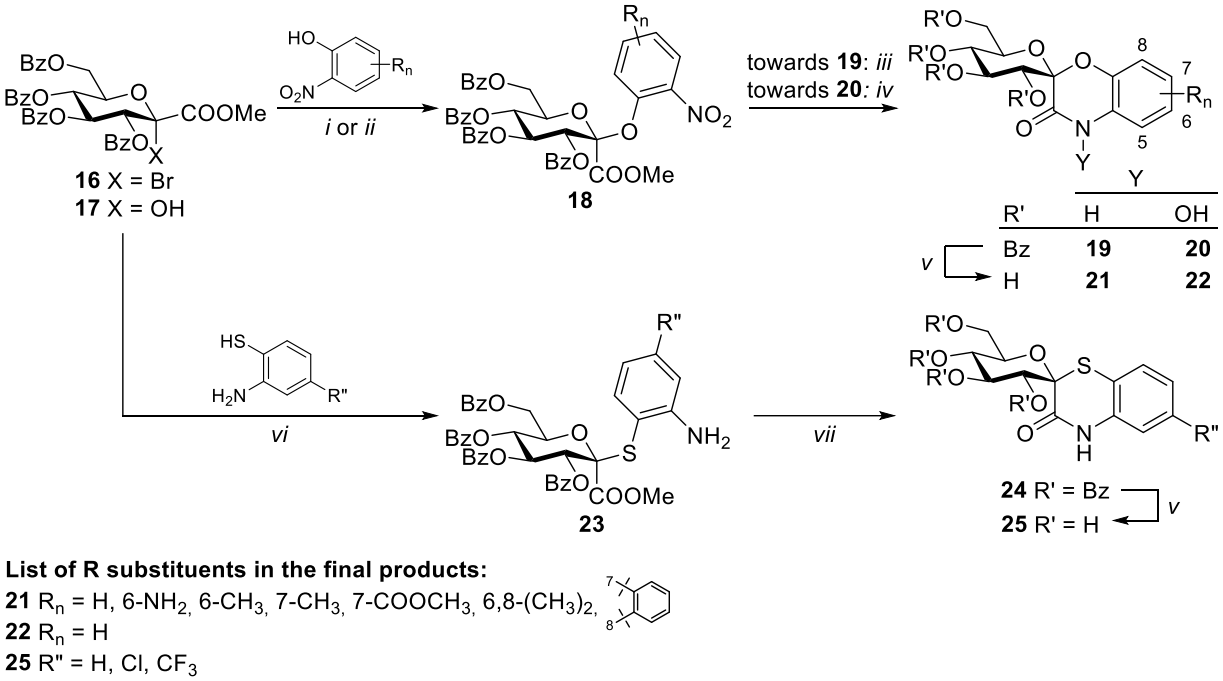
(gluculopyranosyl bromide)onamides and thiobenzamides. During unsuccessful attempts on the removal of the protecting groups alcohol addition products were observed and addition of water could also be verified. CD spectroscopy, supported by TDDFT-ECD calculations was utilized to identify the structure of these byproducts. The water addition prevented these molecules from being studied as GP inhibitors.[10]

For the synthesis of glucopyranosylidene-spiro-imidazolinones several cyclocondensations were attempted from (ulopyranosyl bromide)onic acid derivatives (amides, esters, imidates), without success. Finally, from 2-deoxy-2-azido-ulopyranosonamide **10**, the target compounds could be made with both spiro epimeric configurations (Scheme 2). Thus, **10** was reduced to **6** which on reaction with aldehydes gave Schiff bases **7**. The epimeric compounds **13** were obtained from **10** under Staudinger conditions: the anomalous adduct **11** reacted with aldehydes to give intermediates **12** which furnished the expected imines **13** at low temperature. Ring closure of neither **7** nor **13** was successful under basic or acidic conditions, therefore, a new, oxidative cyclization was developed by using NBS in the presence of pyridine to give the spirocycles **8** and **14**, respectively. Standard deprotection gave the test compounds **9** and **15** which were assayed against rabbit muscle GPb. The measured inhibition constants are shown in Scheme 2 for the most efficient derivatives. It can be concluded that these compounds have not proven better inhibitors over other known spirocyclic compounds, especially spiro-isoxazolines with submicromolar inhibition constants. The reasons for this are not yet clear, nevertheless, the ongoing X-ray crystallographic investigation of the corresponding enzyme-inhibitor complexes will hopefully give an explanation for this finding. The work will be published together with the structural biology studies.



Scheme 2. Syntheses of glucopyranosylidene-spiro-imidazolinones

Spiro-oxa- and -thiazinones were synthesized as outlined in Scheme 3. 2-Nitrophenyl glycosides **18** were prepared from (gluculopyranosyl bromide)onic acid methyl ester **16** by silver salt promoted transformations or from methyl ulopyranosonate **17** by Mitsunobu reaction. Complete reduction of the nitro group resulted in spontaneous lactamization to give spiro benzo[b][1,4]oxazinones **19**, while partial reduction gave the corresponding cyclic hydroxamic acid derivative **20** which is a structural analogue of a natural benzoxazinoid, called DIBOA-Glc. The analogous benzo[b][1,4]thiazinones (**24**) were also obtained by a similar reactions sequence via (2-aminophenylthio)glycosides **23**. Standard deprotections gave the test compounds **21**, **22**, and **25**. GP inhibition of the lactams **21**, **25** and the allelophatic effect of the hydroxamic acid **22** was tested but none of the compounds showed any significant activity. A paper to report these results is in preparation.



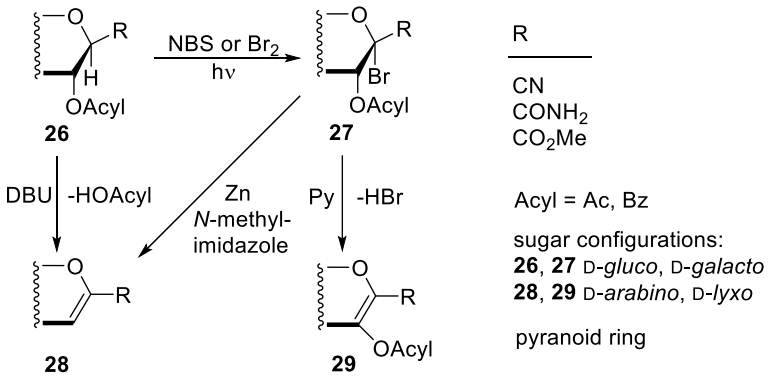
List of R substituents in the final products:
21 R_n = H, 6-NH_2, 6-CH_3, 7-CH_3, 7-$COOCH_3$, 6,8-$(CH_3)_2$,
22 R_n = H
25 R" = H, Cl, CF_3

Reagents, conditions and yields: i) **16**, AgOTf, Et_3N, 4 Å MS, anh. CH_2Cl_2, rt (60-93 %); *ii)* **17**, DEAD, PPh_3, anh. THF, rt (76-87 %); *iii)* H_2, Pd(C) anh. EtOAc, rt (28-82 %); *iv)* H_2, Pd(C), pyridine, rt (57 %); *v)* cat. NaOMe, anh. MeOH, $CHCl_3$, rt (32-94 %); *vi)* K_2CO_3, anh. acetone, rt (48-77 %); *vii)* anh. *m*-xylene, reflux (73-80 %).

Scheme 3. Syntheses of glucopyranosylidene-spiro-oxa- and thiazinones

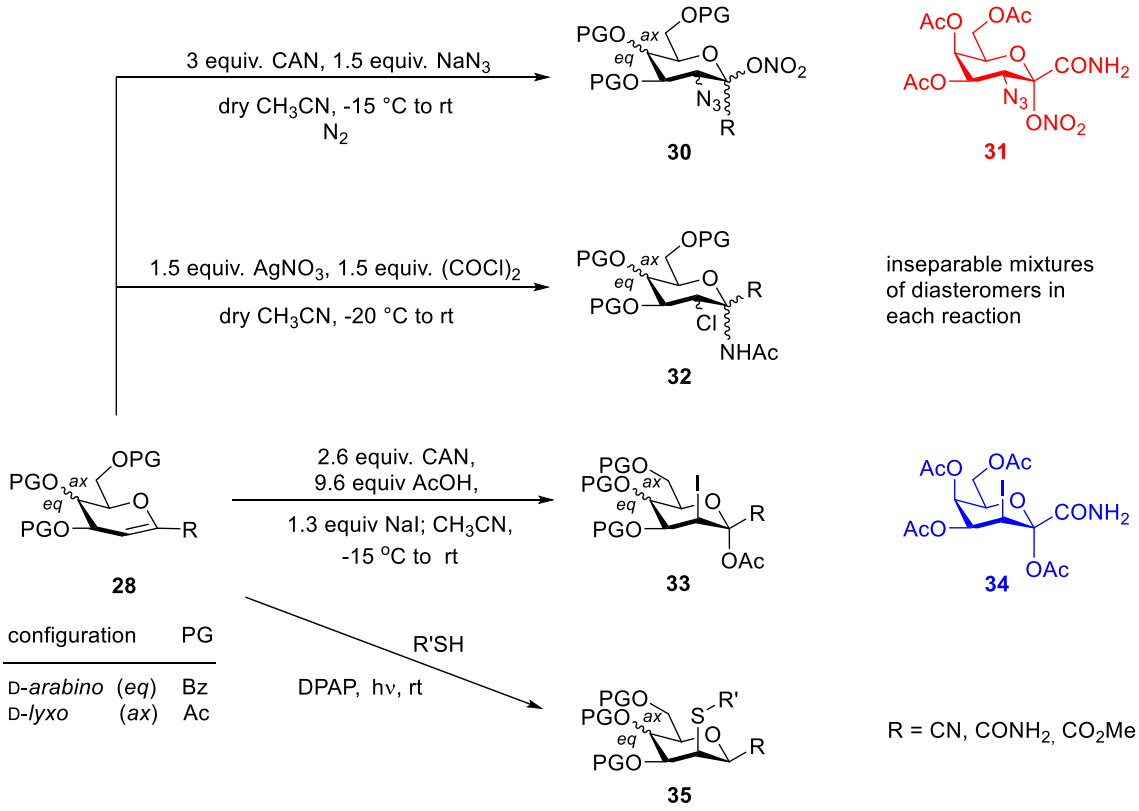
Aim 3. *Study of reactions of 1-C-substituted glycal derivatives*

1-C-Substituted glycals **28** were synthesized (Scheme 4) from anhydro-aldonic acid derivatives **26** either by direct elimination of an acid from the 1,2-positions or, more advantegously, in a two-step sequence of bromination of **26**[11] to **27** followed by a reductive elimination to give the expected product in higher yield and excellent purity.[12] Base induced elimination of HBr from **27** furnished the 1-C-substituted-2-hydroxy glycals **29** in their *O*-peracylated form.[12]



Scheme 4. Syntheses of 1-C-substituted pyranoid glycals

Azidonitration of cyano- and methoxycarbonyl substituted glycals **28** (R = CN, CO_2Me) gave inseparable mixtures of the diastereomeric products **30** in low to moderate yields (Scheme 5). The reaction of the amide substituted galactal (**28**, D-*lyxo* configuration, R = $CONH_2$) provided one major isomer of the corresponding azidonitrated derivative **31** in 66% yield. Structural elucidation of **31** was possible by high level NMR methods and CD measurements supported by TDDFT calculations.



Scheme 5. Transformations of 1-C-substituted pyranoid glycals

Chloroamidation was investigated with each compound **28** to show that the reaction took place, however, the crude products obtained in 40-80 % yields contained diastereomeric mixtures of **32** whose separation was not successful. Thus, the synthetic utility of these transformations seemed not promising, therefore, these studies were discontinued.

The iodoacetoxylation of glycals **28** was also studied and the reaction conditions were selected by the reactions of the D-*lyxo* configured **28**. With the classical NIS/AcOH reagent no reaction could be observed in 4 days. CAN/NaI/AcOH gave the expected **33** in one day in 33 % yield, while Me_3SI/PIDA/AcOH proved to be the best furnishing **33** (*ax*, R = $CONH_2$) in 61 % yield (for **33** (*eq*, R = $CONH_2$) 60 % was isolated). Under these conditions from the reamining glycals **28** the CN-substituted derivatives remained intact, while the COOMe-substituted ones gave the expexted **33** in 68-71 % yields. The structure of these molecules was identified by sophisticated NMR measurements and X-ray crystallography in the case of **34**.

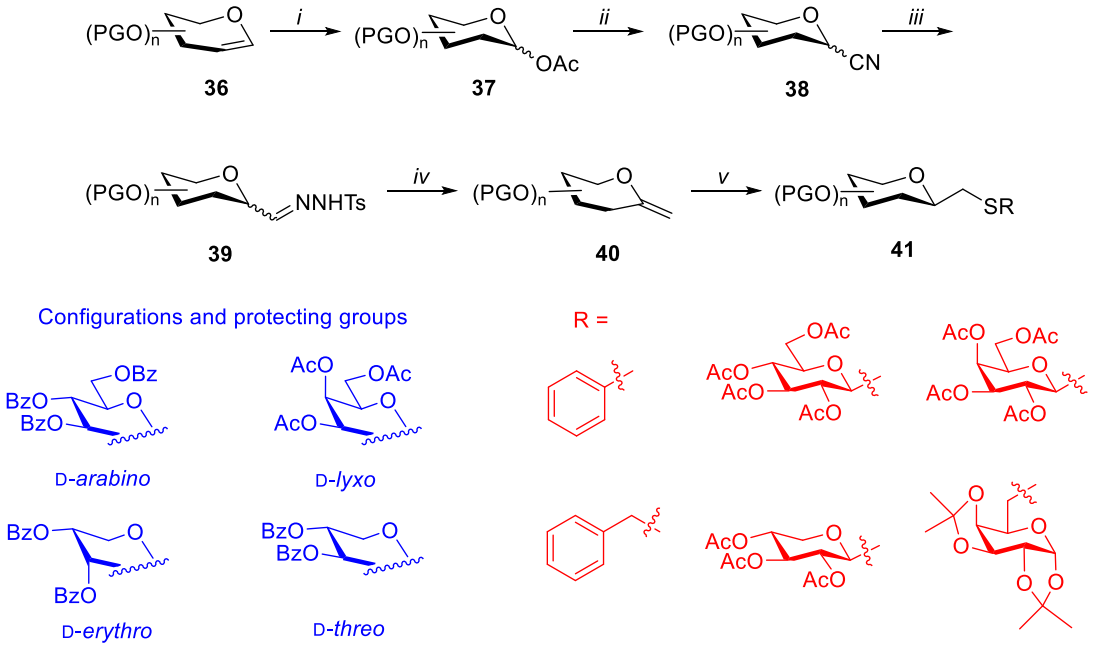
Publications to report the azidonitration and iodiacetoxylation reactions are in preparation.

Free-radical hydrothiolation of glycals **28** of D-*arabino* and D-*lyxo* configurations with a range of mostly sugar derived thiols was also studied. In all cases, the thiol-ene coupling reactions took place with full regio- and stereoselectivities whereby the thiol attacked axially on the C-2 centre of the substrates and the closing hydrogen abstraction took place from the α-side to give the unique thiodisaccharides **35**. The yield of the addition product strongly depended on the electron-withdrawing effect of the 1-C substituent (range of yields: 1-CN < 1-COOMe < 1-$CONH_2$), and this reflected the same reactivity tendency as observed above. Furthermore, neither the orientation of 4-*O*-substituent nor the nature of the *O*-acyl protecting group (acetyl vs. benzoyl) affected the stereochemical outcome of the hydrothiolation. LCMS studies of the reaction mixtures revealed the structure of most of the by-products, thus making it possible to suggest a detailed mechanism of the transformation.[13] Under similar conditions the 1-C-substituted-2-hydroxy glycals **29** proved unreactive.

The thiol-ene couplings were extended to *O*-peracylated *exo*-glycals of D-*gluco*, D-*galacto* and D-*xylo* configurations as well. These reactions gave the corresponding β-D-glycosylmethylthio derivatives in high yields with exclusive regio- and very high stereoselectivity, including disaccharide mimicks with Gly-CH_2-S-Gly scaffolds.[14, 15]

This method was utilized for the synthesis of otherwise not easily available mimetics of 2-deoxy-β-D-glycopyranosides. To this end 2-deoxy-*exo*-glycals **40** with D-*arabino*, D-*lyxo*, D-*erythro*, and D-*threo* configuration were synthesized by applying our previous method. The necessary 2-deoxy-glycopyranosyl cyanides **38** were obtained from the respective glycals **36** via 2-deoxy-glycopyranosyl acetates **37**. Cyanides **38** were formed as anomeric mixtures which were separated in most cases, and the compounds were fully characterized since all but one were unknown in the literature. These mixtures of **38** were transformed into tosylhydrazones **39** which were used without purification, and gave the expected *exo*-glycals **40** under Bamford-Stevens conditions. The photoinitiated thiol-ene additions of these derivatives with a range of mostly sugar-derived thiols resulted in the corresponding 2-deoxy-glycosylmethyl sulfides **41** having the CH_2-S-R moiety in equatorial position. The paper reporting this series of transformations is in preparation.

α-S-Linked maltooligomers were prepared by consecutive photoinitiated thiol-ene coupling reactions of 2-acetoxy-glucals and 4-thioglucose derivatives. The necessary glucals and thiols were obtained from the same starting material, thereby eliminating the need for complex protecting group strategies. Here also, the thiol-ene addition reactions proved to be completely regio- and stereoselective providing the expected 4-thiomaltooligosaccharides up to the pentasaccharide level.[16] The method represents a simple alternative to the known syntheses of similar products. The obtained α-S-linked maltooligomers serve as precursors for the synthesis of cyclodextrin mimetics containing S-interglycosidic bonds.



Reagents and conditions: i) AcOH/Ac_2O, cat. 30% HBr/AcOH, dry CH_2Cl_2; *ii)* 4 equiv. TMSCN, cat. $BF_3 \cdot OEt_2$, dry CH_3NO_2, r.t.; *iii)* 1.1 equiv. $TsNHNH_2$, 8.4 equiv. NaH_2PO_2, Raney-Ni, Py-AcOH-H_2O/r.t.; *iv)* 5 equiv. K_3PO_4, dry 1,4-dioxane, reflux; *v)* RSH, DPAP, toluene, hν, r.t.

Scheme 6. Syntheses of 2-deoxy-D-glycosylmethyl sulfide type glycomimetics

Other results

Computationally motivated synthesis of *N*-(β-D-glucopyranosyl)-1,2,4-triazolecarboxamides was carried out to reveal new low micromolar inhibitors of GP. The compounds showed promising ADME properties without any toxicity. The paper came on the cover of MedChemComm.[17]

Some precursors obtained in trials towards anomeric spirocycles were also suitable for cyclizations to get *C*-glycopyranosyl heterocycles, and along this we have elaborated a highly variable general method to get trisubstituted *C*-glycosyl 1,2,4-triazoles.[18] These compounds were also tested for GP inhibition, but had no activity.

A method was worked out to get carotenoid-monosaccharide conjugates by using CuAAC between carotenoid pentynoates and protected or unprotected glycopyranosyl azides.[19]

It was proven that GP inhibitors activated the pathway of insulin secretion, indicated by enhanced glycolysis, mitochondrial oxidation and calcium signalling, and increased the size of islets of Langerhans in the pancreas and improved glucose-induced insulin release in mice. These findings have revealed a new target tissue for GP inhibitors and suggest that these drugs should be repurposed to preserve or even ameliorate β-cell function.[20]

A highly cited review article was published on the synthesis and antidiabetic utility of C-glycopyranosyl arenes and hetarenes.[21]

Most of the results of this project were included in a popular educational survey of research on glycomimetics at the Department of Organic Chemistry of the University of Debrecen.[22]

Besides the publications in the reference list 6 other papers are in preparation as indicated in the relevant parts of this report. The realization of the project resulted in 3 PhD dissertations, 4 MSc and 6 BSc theses. The published papers have already received 61 independent citations.

References

1. Kaszás, T.; Tóth, M.; Kun, S.; Somsák, L. Coupling of anhydro-aldose tosylhydrazones with hydroxy compounds and carboxylic acids: a new route for the synthesis of C-β-D-glycopyranosylmethyl ethers and esters. *RSC Adv.* **2017,** 7, 10454-10462.
2. Kaszás, T.; Tóth, M.; Somsák, L. A new synthesis of C-β-D-glycopyranosylmethyl sulfides by metal-free coupling of anhydro-aldose tosylhydrazones with thiols. *New. J. Chem.* **2017,** 41, 13871-13880.
3. Kaszás, T.; Ivanov, A.; Tóth, M.; Ehlers, P.; Langer, P.; Somsák, L. Pd-catalyzed coupling reactions of anhydro-aldose tosylhydrazones with aryl bromides to produce substituted exo-glycals. *Carbohydr. Res.* **2018,** 466, 30-38.
4. Kaszás, T.; Tóth, M.; Langer, P.; Somsák, L. *C*-Glycosyl styrene type compounds by Pd-catalyzed cross-coupling reactions of anhydro-aldose tosylhydrazones with benzyl bromides. *Adv. Synth. Catal.* **2018**, Doi: 10.1002/adsc.201801059.
5. Somsák, L.; Bokor, É.; Czibere, B.; Czifrák, K.; Koppány, C.; Kulcsár, L.; Kun, S.; Szilágyi, E.; Tóth, M.; Docsa, T.; Gergely, P. Synthesis of C-Xylopyranosyl- and Xylopyranosylidene-Spiro-Heterocycles for Inhibition of Glycogen Phosphorylase. *Carbohydr. Res.* **2014,** 399, 38-48.
6. Goyard, D.; Kónya, B.; Chajistamatiou, A. S.; Chrysina, E. D.; Leroy, J.; Balzarin, S.; Tournier, M.; Tousch, D.; Petit, P.; Duret, C.; Maurel, P.; Somsák, L.; Docsa, T.; Gergely, P.; Praly, J.-P.; Azay-Milhau, J.; Vidal, S. Glucose-derived spiro-isoxazolines are anti-hyperglycemic agents against type 2 diabetes through glycogen phosphorylase inhibition. *Eur. J. Med. Chem.* **2016,** 108, 444-454.
7. Docsa, T.; Marics, B.; Németh, J.; Hüse, C.; Somsák, L.; Gergely, P.; Peitl, B. Insulin sensitivity is modified by a glycogen phosphorylase inhibitor: glucopyranosylidene-spiro-thiohydantoin in streptozotocin-induced diabetic rats. *Curr. Top. Med. Chem.* **2015,** 15, 2390-2394.
8. Páhi, A.; Czifrák, K.; Kövér, K. E.; Somsák, L. Anomeric Spirocycles by Solvent Incorporation: Reactions of *O*-Peracylated (Glyculopyranose and Glyculopyranosyl Bromide)onamide Derivatives with Ketones. *Carbohydr. Res.* **2015,** 403, 192-201.
9. Czifrák, K.; Páhi, A.; Deák, S.; Kiss-Szikszai, A.; Kövér, K. E.; Docsa, T.; Gergely, P.; Alexacou, K.-M.; Papakonstantinou, M.; Leonidas, D. D.; Zographos, S. E.; Chrysina, E. D.; Somsák, L. Glucopyranosylidene-spiro-iminothiazolidinone, a New Bicyclic Ring System: Synthesis, Derivatization, and Evaluation for Inhibition of Glycogen Phosphorylase by Enzyme Kinetic and Crystallographic Methods. *Bioorg. Med. Chem.* **2014,** 22, 4028-4041.
10. 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* **2017,** 22, 1760/1-1760/15.
11. Nagy, V.; Czifrák, K.; Juhász, L.; Somsák, L.; Apelt, O. Preparation of glycosyl bromides of α-D-*gluco*-hept-2-ulopyranosonic acid derivatives. In *Carbohydrate Chemistry: Proven Synthetic Methods*, Vogel, C.; Murphy, P. V., Eds. CRC Press: Boca Raton, 2017; Vol. 4, pp 71-78.
12. Kun, S.; Deák, S.; Czifrák, K.; Juhász, L.; Somsák, L.; Apelt, O. Preparation of 2,6-anhydro-hept-2-enonic acid derivatives and their 3-deoxy counterparts. In *Carbohydrate Chemistry: Proven Synthetic Methods*, Vogel, C.; Murphy, P. V., Eds. CRC Press: Boca Raton, 2017; Vol. 4, pp 79-90.
13. Lázár, L.; Juhász, L.; Batta, G.; Borbás, A.; Somsák, L. Unprecedented β-manno type thiodisaccharides with a C-glycosylic function by photoinitiated hydrothiolation of 1-C-substituted glycals. *New. J. Chem.* **2017,** 41, 1284-1292.
14. Lázár, L.; Csávás, M.; Tóth, M.; Somsák, L.; Borbás, A. Thio-click approach to the synthesis of stable glycomimetics. *Chem. Pap.* **2015,** 69, 889-895.
15. József, J.; Juhász, L.; Illyés, T. Z.; Csávás, M.; Borbás, A.; Somsák, L. Photoinitiated hydrothiolation of pyranoid *exo*-glycals: the D-*galacto* and D-*xylo* cases. *Carbohydr. Res.* **2015,** 413, 63-69.
16. Lázár, L.; Borbás, A.; Somsák, L. Synthesis of thiomaltooligosaccharides by a thio-click approach. *Carbohydr. Res.* **2018,** 470, 8-12.

17. Begum, J.; Varga, G.; Docsa, T.; Gergely, P.; Hayes, J. M.; Juhász, L.; Somsák, L. Computationally motivated synthesis and enzyme kinetic evaluation of *N*-(β-D-glucopyranosyl)-1,2,4-triazolecarboxamides as glycogen phosphorylase inhibitors *Med. Chem. Comm.* **2015,** 6, 80-89.
18. 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* **2017,** 73, 3810-3822.
19. Agócs, A.; Bokor, É.; Takátsy, A.; Loránd, T.; Deli, J.; Somsák, L.; Nagy, V. Synthesis of Carotenoid-Monosaccharide Conjugates via Azide–Alkyne Click-reaction. *Tetrahedron* **2017,** 73, 519-526.
20. Nagy, L.; Márton, J.; Vida, A.; Kis, G.; Bokor, É.; Kun, S.; Gönczi, M.; Docsa, T.; Tóth, A.; Antal, M.; Gergely, P.; Csóka, B.; Pacher, P.; Somsák, L.; Bai, P. Glycogen phosphorylase inhibition improves β-cell function. *Brit. J. Pharmacol.* **2018,** 175, 301-319.
21. Bokor, É.; Kun, S.; Goyard, D.; Tóth, M.; Praly, J.-P.; Vidal, S.; Somsák, L. C-Glycopyranosyl Arenes and Hetarenes: Synthetic Methods and Bioactivity Focused on Antidiabetic Potential. *Chem. Rev.* **2017,** 117, 1687-1764.
22. Somsák, L. Glikomimetikumok kutatása a Debreceni Egyetem Szerves Kémiai Tanszékén. *Magy. Kém. Lapja* **2018**, accepted for publication.