Short thesis for the degree of Doctor of Philosophy (PhD)

Study of the reactivity of 1-C-substituted glycal derivatives: halogen addition and Ferrier rearrangement

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1. Introduction and objectives

Carbohydrates are one of the most common organic compounds which have key role in nature. Besides their primary functions as energy sources and structural components they have various biological functions in living organisms. Carbohydrates can be found in all living cells and on cell surfaces, therefore they play an important role in most of the physiological and pathological processes.

Carbohydrate derivatives containing a double bond are one of the most diverse derivatives in use and in chemical and biological properties. Recently, their reactivity, chemical and biological properties are widely studied. Reactions of glycals having an electron withdrawing substituent attached to the anomeric centre are less explored, so studying the reactivity of these derivatives can result in the preparation of synthetically useful compounds.

Based on the above our aim was studying the reactivity of 1-C-substituted glycals that can be synthesized from D-glucose and D-galactose.

We planned to examine the addition reactions of 1-C-substituted gylcals with halogens as simple electrophiles under ionic and radical conditions and transformations of the synthesized dihalogeno derivatives with nucleophiles under the conditions of nucleophilic substitution, elimination, or glycosylation reactions.

2,3-unsaturated glycosides can be synthesized under the conditions of Ferrier rearrangement. Previously described transformations prompted us to investigate the reactivity of 1-C-substituted glycals under the circumstances of Ferrier rearrangement with various nucleophiles in the presence of Brønsted and Lewis acids. We also planned to optimize the reaction conditions and study the effect of the used conditions to the regio- and stereoselectivity.

2. Methods

During our work methods of preparative organic chemistry, separation techniques and spectroscopy were applied. The progress of the reactions was monitored by thin-layer chromatography (TLC). Products of the reactions were purified by column chromatography or crystallization and the purity was checked by TLC. The structural

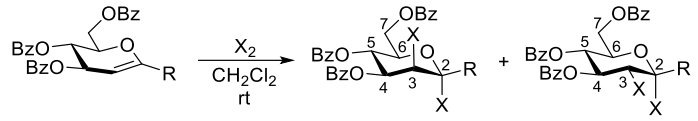
elucidation of the products was based on NMR, MS and IR measurements and the pure compounds were characterized by their optical rotations.

3. New results of the dissertation

3.1. Halogen addition reactions of 1-C-substituted glycals

We studied the addition of halogens to 1-C-substituted glycals **113-118** under ionic and radical conditions in dichloromethane (DCM) at room temperature (Table 1-2).

Table 1. Addition of halogens to 1-C-substituted glycals having D-*arabino* configuration



113-115 **172a-174a** **172b-174b**

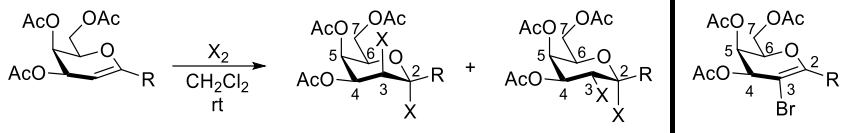
Glycal	R	X	Reaction time [h] (Other conditions)	Product (Yield [%])	Product ratio[a]
113	CN	Br	24	**172a** (64)[b]	
			3 (hν)	**172a** (97)[c]	
114	$CONH_2$	Br	4	**173a** + **173b** (89)[b,d]	**173a** : **173b** = 87 : 13
			0.5 (hν)	**173a** (97)[c]	
115	COOMe	Br	12	**174a** (79)[b]	
			1,5 (hν)	**174a** (98)[c]	

[a] Based on the ^{1}H NMR spectrum of the product mixture. [b] Isolated yield.
[c] Crude product. [d] Inseparable mixture.

O-Perbenzoylated D-*arabino* configured glycals **113-115** gave the corresponding dibromo compounds in good yield (64 – 89 %). Glycals **113** and **115** yielded the 2,3-*trans*-diaxial dibromo compounds **172a** and **174a**, respectively, as sole products, while glycal **114** furnished an inseparable mixture of the 2,3-*trans* diaxial **173a** and the 2-axial-3-equatorial **173b** dibromo derivatives in a ratio of 87 : 13 (Table 1).

The bromine addition of *O*-peracetylated D-*lyxo* configured substituted glycals **117** and **118** led to inseparable mixtures of products **177a** + **177b** (ratio 71 : 29) and **179a** + **179b** (ratio 96 : 4), respectively (Table 2).

Table 2. Addition of halogens to 1-C-substituted glycals having D-*lyxo* configuration



116-118 **175a-180a** **175b-180b** **181**

Glycal	R	X	Reaction time [h] (Other conditions)	Product (Yield [%])	Product ratio[a]
116	CN	Br	16	**175a** + **175b** + **181** (68)[b,d]	**175a** : **175b** : **181** 22 : 60 : 18
			2 (hν)	**175b** (95)[c]	
		Cl	36	**176a** + **176b** (66)[b,d]	**176a** : **176b** 44 : 56
117	$CONH_2$	Br	1	**177a** + **177b** (77)[b,d]	**177a** : **177b** 71 : 29
			0.25 (hν)	**177a** + **177b** (99)[c,d]	**177a** : **177b** 80 : 20
		Cl	0.5	**178a** + **178b** (66)[b,d]	**178a** : **178b** 5 : 95
118	COOMe	Br	3	**179a** + **179b** (88)[b,d]	**179a** : **179b** 96 : 4
			0.5 (hν)	**179a** + **179b** (98)[c,d]	**179a** : **179b** 93 : 7
		Cl	2	**180a** + **180b** (71)[b,d]	**180a** : **180b** 7 : 93

[a] Based on the ^{1}H NMR spectrum of the product mixture. [b] Isolated yield.
[c] Crude product. [d] Inseparable mixture.

Starting from the cyano substituted glycal **116** the formation of a mixture of three products **175a** + **175b** + **181** in a ratio of 22 : 60 : 18 was observed.

Based on these observations we revealed that that under the ionic conditions the 2,3-*trans*-diaxial dibromo compounds were the main products of the addition excepted the nitrile derivative **116**, whose reaction showed increased selectivity towards the 2-axial-3-equatorial stereoisomer.

Under radical conditions, using irradiation with UV light (254 nm) we observed the increasing of the reaction rate significantly by a factor of 4 – 8 (Table 1-2). Under radical conditions the stereoselectivity did not changed in case of glycals **113-116** but increasing of the selectivity was observed.

Chlorine addition reactions of D-*lyxo* configured glycals **116-118** were performed at room temperature with saturated solution of chlorine in DCM (Table 2). The reactions

yielded the inseparable mixture of dichloro derivatives **176a** + **176b** (ratio 44 : 56), **178a** + **178b** (ratio 5 : 95) and **180a** + **180b** (ratio 7 : 93), respectively. In case of a cyano substituent a slight while in case of a carbamoyl and a methoxycarbonyl substituents an exclusive selectivity for the formation of 2-axial-3-equatorial isomers were observed.

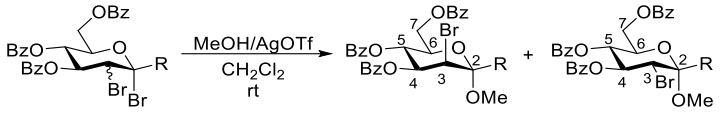
The structure elucidation of the products was based on 1D and 2D NMR and MS measurements. Mass spectra of the products showed the presence of two halogen atoms in the products. In the case of dihalogenated compounds **172-180** the $^{5}C_{2}$(D) conformation of the sugar rings and the configuration of the C-3 centre were clearly deduced from the $^{3}J_{H\text{-}H}$ coupling constants. The configuration of the anomeric centre was determined by the effect of the halogen in axial position to the chemical shifts of the H-4 and H-6 atoms, respectively. In the dihalogeno derivatives the presence of the halogen atom in axial position on the anomeric centre resulted in downfield shifts of the H-4 and H-6 protons compared to the corresponding non-halogenated compounds. For the 2-bromoglycal **181** the mass spectrum showed one bromine atom in the molecule. Small vicinal couplings of the ring protons and two quaternary carbon signals of the double bond indicated the presence of a fully substituted double bond and a half chair type ring which corresponds to the structure of **181**.

The stereochemical outcomes of these reactions were interpreted based on theoretical considerations. We revealed that the stereoselectivity of the addition reactions depends not only on the electron-withdrawing property of the 1-C substituents but also on their stabilizing effects on the intermediate cations/radicals. The product distribution is also influenced by the relative stability of the intermediates, the conformation of the carbohydrate ring and the protecting groups of the molecules.

3.2. Use of dibromo derivatives in glycosylation reactions and the study of their reactivity under the conditions of nucleophilic substitution and elimination reactions

We investigated the glycosylation reactions of dibromides **172-174** with MeOH in the presence of AgOTf as a promoter (Table 3).

Table 3. Glycosylation of methanol with dibromo adducts **172-174**



172-174 **182a-184a** **183b**

Starting compound	R	Product (Yield [%])
172a (Br-3 axial)	CN	**182a** (75)
173a + **173b** (87 : 13/Br-3 ax : eq)	$CONH_2$	**183a** + **183b** (84, Br-3 ax : eq = 87 : 13[a])[b]
174a (Br-3 axial)	COOMe	**184a** (76)

[a] Based on the ^1H NMR spectrum of the product mixture. [b] Not fully separable mixture. Pure **183b** could be obtained in 8 % yield.

The reactions gave the desired methyl glycosides in good yield. In the case of **172a** and **174a** glycosides **182a** and **184a** were formed as sole products, respectively. When **173a** + **173b** mixture was reacted, the formation of **183a** + **183b** mixture was observed in the same ratio as of the starting materials.

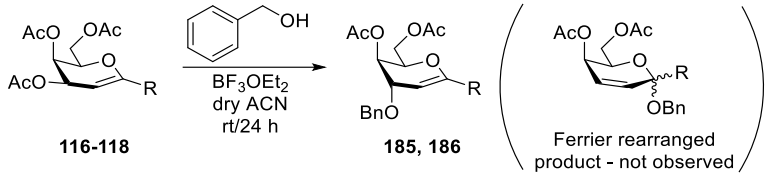
Structural elucidation of the products was carried out analogous to the dihalogeno derivatives. The α(D) configuration of glycosides **182-184** was determined by measurements of nuclear Overhauser effect (NOE) between the OMe, H-4 and H-6 protons.

Several other nucleophilic substitution and elimination reactions of **174a** were studied, but in all cases only the formation of glycal **115** was observed.

3.3. Reactions of 1-C-substituted glycals with nucleophiles under the conditions of Ferrier rearrangement

Reactions of 1-C-substituted glycals **116-118** were studied with equimolar amount of BnOH, in the presence of BF_3OEt_2 in dry acetonitrile (ACN) as solvent (Table 4).

Table 4. Reactions of 1-C-substituted glycals with BnOH[a]



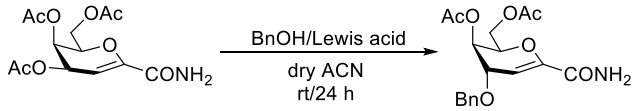
Starting compound	R	Conversion[b] (%)	Product	Corrected yield[c,d] (%)
116	CN	No reaction		
117	$CONH_2$	58	**185**	36
118	COOMe	65	**186**	12

[a]Reaction conditions: Glycal (100 mg, 1 eq.), BnOH (1 eq.), BF_3OEt_2 (1 eq.) in 2.5 mL of dry ACN under N_2 atmosphere at room temperature for 24 h. [b]Unreacted starting material was collected by column chromatography. [c]Yield was corrected with the conversion. [d]Isolated yield.

The reactions of the D-*lyxo* configured 1-carbamoyl **117** and 1-methoxycarbonyl **118** glycals led to the allyl substituted **185** and **186** glycals in low yield instead of the formation of the desired 2,3-unsaturated *O*-glycosides. In case of 1-cyano glycal **116** no reaction was observed.

The 1-carbamoyl substituted glycal **117** was reacted with benzyl alcohol in the presence of various Lewis acids (Table 5). The highest conversion can be reached using TMSOTf but because of the formation of a large amount side products, the reaction gave the desired product **185** in a low yield. Using $AlCl_3$, BCl_3 and BBr_3 gave similar result, while with promoters such as CF_3COOH, $ZnCl_2$, $InCl_3$, $Cu(OTf)_2$, AgOTf, $Sc(OTf)_3$, $Y(OTf)_3$, $Pd(TFA)_2$ and $Pd_2(dba)_3$/XPhos/TEA no transformation was detected.

Table 5. Reaction of glycal **117** with BnOH in the presence of various Lewis acids[a]



117 185

	Lewis sav	Konverzió[b] (%)	Korrigált hozam[c,d] (%)[a]
1	TMSOTf	87	19
2	$AlCl_3$	26	2
3	BCl_3	32	3
4	BBr_3	70	6
5	$TiCl_4$	33	53
6	$FeCl_3$	34	36
7	I_2	55	42
8	BF_3OEt_2	58	36

[a]Reaction conditions: Glycal (100 mg, 1 eq.), BnOH (1 eq.), BF_3OEt_2 (1 eq.) in 2.5 mL of dry ACN under N_2 atmosphere at room temperature for 24 h. [b]Unreacted starting material was collected by column chromatography. [c]Yield was corrected with the conversion. [d]Isolated yield.

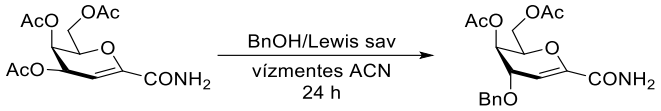
In case of BF_3OEt_2, $TiCl_4$, I_2 and $FeCl_3$ promoters the products can be isolated in similar yields.

Using I_2 and $TiCl_4$ further optimization reactions were carried out to study the effects of the reaction temperature and the amount of the nucleophile (Table 6).

In the presence of iodine, increasing the amount of the benzyl alcohol resulted in the decrease of the corrected yield. Using 10 equivalents of BnOH a complex mixture was obtained.

The reaction temperature has a significant effect on the yield. Increasing the temperature led to the decrease of the corrected yield but decreasing the temperature to or below 0 °C no reaction took place.

Table 6. The effect of the amount of BnOH and the applied temperature[a]



117 185

	Lewis acid	Amount of BnOH	T (°C)	Conversion[b] (%)	Corrected yield[c,d] (%)[a]
1	I_2	1 eq.	rt	55	42
2		2 eq.	rt	73	34
3		5 eq.	rt	88	18
4		10 eq.	rt	Complex mixture	
5		1 eq.	50 °C	Complex mixture	
6		1 eq.	reflux	Complex mixture	
7	$TiCl_4$	1 eq.	-20 °C	No reaction	
8		1 eq.	0 °C	No reaction	
9		1 eq.	rt	33	53
10		1 eq.	50 °C	53	43
11		1 eq.	reflux	60	32

[a]Reaction conditions: Glycal (100 mg, 1 eq.), BnOH (1 eq.), BF_3OEt_2 (1 eq.) in 2.5 mL of dry ACN under N_2 atmosphere at room temperature for 24 h. [b]Unreacted starting material was collected by column chromatography. [c]Yield was corrected with the conversion. [d]Isolated yield.

Some other glycals and nucleophiles were applied in the reactions in whose 1 equivalent of Lewis acid and 1 equivalent of nucleophile were used (Table 7).

Reactions of D-*lyxo* configured glycal **118** with allyl and propargyl alcohol gave low yield the corresponding 4-*O*-allyl **187** and 4-*O*-propargyl **188** substituted glycals.

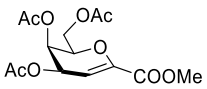
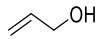
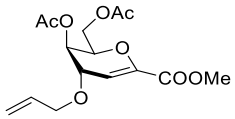
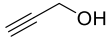
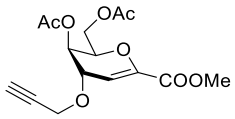
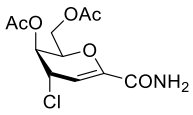
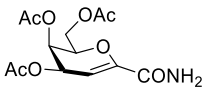
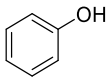
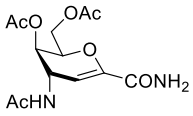
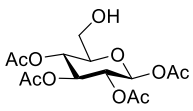
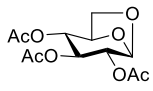
In the reaction of D-*lyxo* configured glycal **117** and phenol using $TiCl_4$ promoter the 4-chloro substituted **189** and using BF_3OEt_2 promoter the 4-acetamido substituted **190** glycals were formed as sole products, respectively. The reaction with NaN_3 resulted the 4-azido substituted glycal **199** derivative in moderate yield.

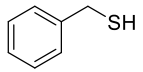
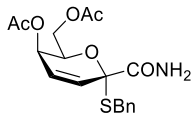
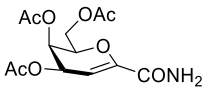
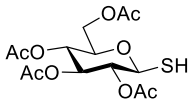
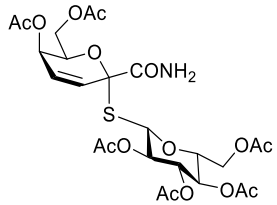
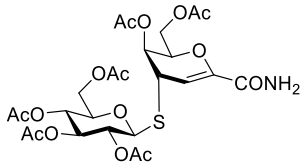
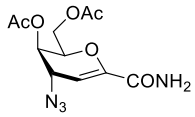
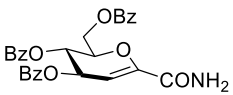
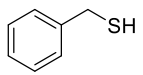
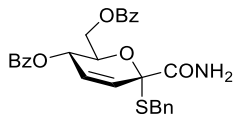
When glycal **117** was reacted with 1,2,3,4-tetra-*O*-acetyl-β-D-glucopyranose (**193**) only the formation of a 1,6-anhydro-glucose by-product **194** was observed.

In contrary to the previous experimental observations, in the reaction of D-*lyxo* configured 1-carbamoyl **117** and D-*arabino* configured 1-carbamoyl **114** glycals with benzyl thiol as a nucleophile the corresponding 2,3-unsaturated *S*-glycosides **195** and **200** were formed by Ferrier rearrangement.

The reaction of D-*lyxo* configured 1-cabamoyl glycal **117** with 2,3,4,6-tetra-*O*-acetyl-1-thio-β-D-glucose (**196**) yielded both the 3-substituted glycal **198** and the 2,3-unsaturated *S*-glycoside **197**, respectively.

Table 7. Transformations of 1-C-szubstituted glycals with nucleophiles

	Glycal	Nucleophile	Lewis acid	Product	Conversion (%)	Corrected yield (%)
1	 **118**		BF_3OEt_2	 **187**	71	24
2			BF_3OEt_2	 **188**	79	23
3			$TiCl_4$	 **189**	46	71
4	 **117**		BF_3OEt_2	 **190**	70	64
5		 **193**	$TiCl_4$ BF_3OEt_2	 **194**	0	65 63

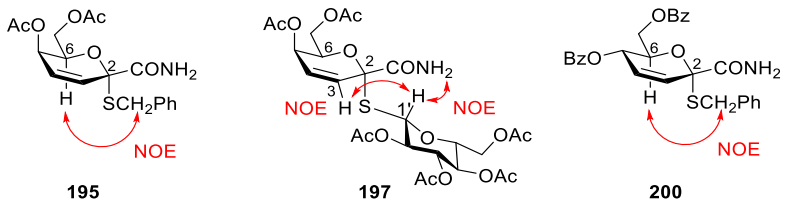
6			$TiCl_4$	 **195**	57	29
7	 **117**	 **196**	BF_3OEt_2	 **197**	70	29
8				 **198**		40
9		NaN_3	BF_3OEt_2	 **199**	63	45
10	 **114**		$TiCl_4$	 **200**	59	42

By the structural elucidation of the products several methods were applied. The structure of compound **190** was determined unequivocal by X-ray crystallography.

Mass spectrum of **189** clearly showed the presence of one chlorine atom in the molecule.

Chemical shifts of the C-2 atoms (δ (C-2) = 145.6 – 147.9 ppm) in products **185**-**190** and **198**-**199** indicated that instead of the desired 3,4-unsaturated glycosides the corresponding 4-substituted glycals were formed in the reactions. The configuration of the C-4 in compounds **185**-**189** and **198**-**199** was concluded from the comparisons with spectral data of these compounds and **190** with known configuration. Chemical shifts of the sugar ring protons are in a narrow range indicating the same configuration for C-4.

Chemical shifts of the C-2 atoms (δ (C-2) = 87.8 – 88.0 ppm) and the presence of two olefinic CH signal in products **195**, **197** and **200** clearly showed that these compounds are 3,4-unsaturated glycosides.



Scheme 1. Structure elucidation of *S*-glycosides

The α(D) configuration of glycosides **195** and **200** followed from measurements of nuclear Overhauser effects (NOE) showing proximity of the SCH_2- group with the H-6 protons of the sugar ring. In case of the compound **197** α(D) configuration was proven by the NOE effect between H-3 – H-1' and H-1' – $CONH_2$ protons.

4. Possible application of the results

During our work halogen addition reactions of 1-C-substituted glycals and the possible transformations of the formed dihalogeno derivatives were studied. Besides that, the reactivity of 1-C-substituted glycals with various nucleophiles in the presence of Lewis acids, under the conditions of Ferrier rearrangement was examined. The synthesized compounds may be starting materials in the synthesis of carbohydrate derivatives with a more complex structure which are possibly biologically active.

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List of publications related to the dissertation

Foreign language scientific articles in international journals (2)

1. **Homolya, L.**, Antal, D., Nagy, M., Juhász-Tóth, É., Tóth, M., Bényei, A., Somsák, L., Juhász, L.: Reactions of 1-C-acceptor-substituted glycals with nucleophiles under acid promoted (Ferrier-rearrangement) conditions.
   Carbohydr. Res. 519, 1-10, 2022. ISSN: 0008-6215.
   DOI: http://dx.doi.org/10.1016/j.carres.2022.108582
   IF: 2.975 (2021)

2. **Homolya, L.**, Juhász, L., Somsák, L.: Halogen addition to some 1-C-substituted pyranoid glycals.
   Carbohydr. Res. 504, 1-11, 2021. ISSN: 0008-6215.
   DOI: http://dx.doi.org/10.1016/j.carres.2021.108292
   IF: 2.975

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List of other publications

Foreign language scientific articles in international journals (1)

3. Voronova, K., **Homolya, L.**, Udvardy, A., Bényei, A., Joó, F.: Pd-Tetrahydrosalan-Type Complexes as Catalysts for Sonogashira Couplings in Water: Efficient Greening of the Procedure. *ChemSusChem.* 7 (8), 2230-2239, 2014. ISSN: 1864-5631.
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In: 47. Komplexkémiai Kollokvium : Az MKE Komplexkémiai Szakcsoportjának és az MTA Koordinációs Kémiai Munkabizottságának a rendezvénye, 2013. május 29-31., Mátraháza, [Magyar Kémikusok Egyesülete], [Budapest], E14, 2013.

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A PhD értekezés anyagához kapcsolódó előadások, poszterek

Előadások:

1. **Homolya Levente**, Somsák László, Juhász László; 1-C szubsztituált glikálok reakciója O- és S-nukleofilekkel – Ferrier átrendeződés vagy allil szubsztitúció; MTA Szénhidrát, Nukleinsav és Antibiotikumkémiai Munkabizottság 2021. évi ülés és szakmai előadónap; 2021. június 14., hétfő; online meeting
2. Juhászné Tóth Éva, **Homolya Levente**, Balogh Máté, Malecz Ádám Szilárd, Somsák László, Vágvölgyiné Tóth Marietta, Juhász László; 1-C szubsztituált 2-jódglikálok szintézise és Suzuki keresztkapcsolási reakcióik vizsgálata; MTA Szénhidrát, Nukleinsav és Antibiotikumkémiai Munkabizottság 2021. évi ülés és szakmai előadónap; 2021. június 14., hétfő; online meeting

Egyéb előadások, poszterek

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2. Voronova, K.; Bunda, Sz.; **Homolya, L.**; Joó, F.; Pd-szalán katalizátorok alkalmazása vizes közegű keresztkapcsolást reakciókban. 47. Komplexkémiai Kollokvium, Mátraháza, 2013. máj. 29-31.
3. **Homolya, L.**; Bunda, Sz.; Voronova, K., Joó, F.; Pd-szalán komplexek alkalmazása keresztkapcsolási reakciókban. MKE 2. Nemzeti Konferencia, Hajdúszoboszló, 2015. aug. 31 - szept. 2.
4. **Homolya, L.**; Mathomes, R.; Sipos, Á.; Docsa, T.; Juhász, L.; Hayes, J. M.; Somsák, L.; Computer aided design and synthesis of new glycogen phosphorilase inhibitors, International Workshop on Chemistry and Chemical Biology of Carbohydrates, Nucleic Acids and Antibiotics, Mátrafüred, Hungary, 2019. május 22-24.

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5. **Homolya L.**; Mathomes R.; Juhász L.; Hayes, J. M.; Somsák L.; *N*-(β-D-glükopiranozil)-azolkarboxamidok, mint potenciális GP inhibitorok előállítása. MKE Vegyészkonferencia, Eger, Magyarország, 2019. június 24-26.