Short thesis for the degree of doctor of philosophy (PhD)

Synthesis of potentially anticoagulant heparin analogue oligosaccharides

by Fruzsina Demeter

Supervisor: Dr. Mihály Herczeg

UNIVERSITY OF DEBRECEN

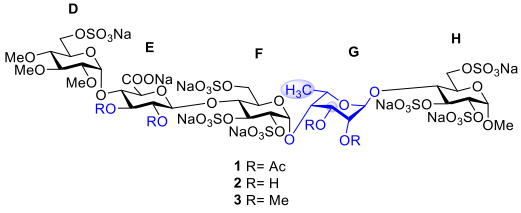
Doctoral School of Chemistry

Debrecen, 2021.

1. Introduction

It has long been known that heparin-analogue oligosaccharides contain L-iduronic acid and D-glucuronic acid units, in which the conformational flexibility of L-iduronic acid is essential for the formation of the biologically active structure and the conformation of the idose unit is greatly influenced by the degree of sulfation of the sugar units attached. Previously, several methods have been developed for the synthesis of these types of oligosaccharides, but the greatest challenge in each case is the efficient preparation of the L-idose or L-iduronic acid building block. Although a number of research has been carried out on the synthesis of L-idose, an efficient method has still not been developed for the synthesis of orthogonally protected L-idosyl donors that can be used directly to perform glycosylation reactions. Based on this, we set a dual goal during my doctoral work.

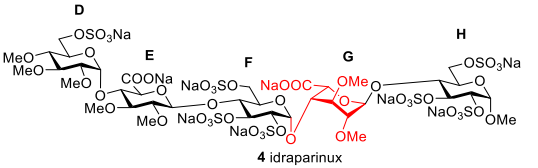
1. On the one hand we attempted to replace the L-iduronic acid unit by a simpler building block. We assumed that the skew boat conformation required for biological activity may also be provided by 6-deoxy-L-talopyranoside, which differs from L-idose in the configuration of the C-3 carbon atom and in the absence of the 6-OH. For this purpose, we planned to synthesize idraparinux analogue pentasaccharides in which the L-iduronic acid unit is substituted by the more easily producible 6-deoxy-L-talopyranoside. (**1-3, Scheme 1.**).



Scheme 1.: The structure of the planned 6-deoxy-L-talopyranoside-containing pentasaccharides

2. In parallel with the oligosaccharide syntheses, further developing the C-5 epimerization synthesis strategy (hydroboration/oxidation

reaction combination) previously described for *O*-glycosides, we planned to develop and optimize an efficient reaction pathway, starting from D-glucose, to produce L-idosyl thioglycosyl donors which may be suitable for the synthesis of oligosaccharides. The prepared donor molecules were then utilized in the synthesis of heparin-related oligosaccharides including idraparinux (**4**).



Scheme 2.: The structure of the idraparinux

2. Applied methods

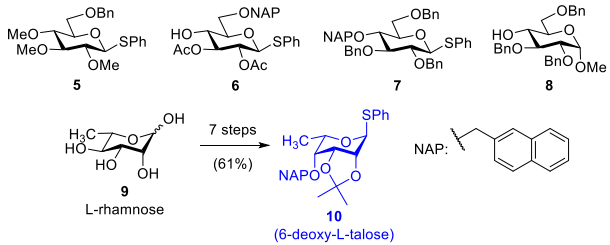
The macro-, semi-micro, and micro-methods of the modern preparative organic chemistry were used in the synthetic work. The purity of the substances, the ratio of products were controlled and the reactions were monitored by thin-layer chromatography. Purification of the crude products and separation of the isomers were carried out either by crystallization, or by column chromatography. The characterization and the structural elucidation of the compounds were carried out by elemental analysis, melting point- and optical rotation determination, and by one and two-dimensional (^{1}H-^{1}H-COSY, ^{13}C-^{1}H-HSQC, TOCSY, ROESY) NMR spectroscopy and MALDI/ESI-TOF mass spectrometric methods, respectively.

3. New scientific results of the dissertation

3.1. Synthesis of the 6-deoxy-L-talopyranose-containing idraparinux analogue pentasaccharides

3.1.1. The applied synthesis strategy

- To the synthesis of the planned pentasaccharides, the monosaccharide building blocks applied in previous research (**5-8, Scheme 3.**) and the 6-deoxy-L-talopyranoside donor (**10**) were used.
- The unit **G** (**10**), starting from L-rhamnose, could be synthesized in 7 steps with a total yield of 61%, which was really much simpler and have better yield than the preparation of the L-idose unit. (Using the method previously applied in the Department, the L-idose glycosyl donor was prepared in 9 steps in a total yield of 15%.)



Scheme 3.: Structure of the monosaccharide building blocks used for the preparation of the protected pentasaccharide

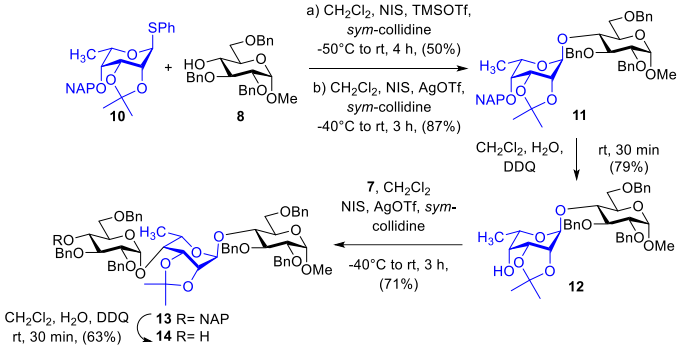
- During the synthesis benzyl ethers were used as permanent, acetyl, isopropylidene acetal and (2-naphtyl)methyl-ether protecting groups were applied as temporary protecting groups.
- The hydroxyls which are sulfated in the final products were protected as benzyl ethers.
- Acetyl protecting groups were used at positions where C-2 participant groups were required for the selective formation of 1,2-*trans*-interglycosidic bonds.
- Since monosaccharide uronic acid donors have previously been found to be of limited use in glycosylation reactions due to their reduced

reactivity, the carboxyl function at the unit **E** was formed at the pentasaccharide level.

- During the synthesis of the planned compounds, we followed the [2+3] block synthesis strategy already successfully used in our Research Group.
- To this end, the protected trisaccharide **FGH** was built up by two different pathways from the monosaccharides (**7**, **8**, **10**) shown in **Scheme 3**.

*3.1.2. Synthesis of the trisaccharide **FGH** I.*

First, compound **13** (**Scheme 4.**) was prepared by performing the L-rhamnose → L-talose conversion at the monosaccharide level and the isopropylidene-containing 6-deoxy-L-talopyranoside derivative **10** was coupled with the monosaccharide acceptor **8**.



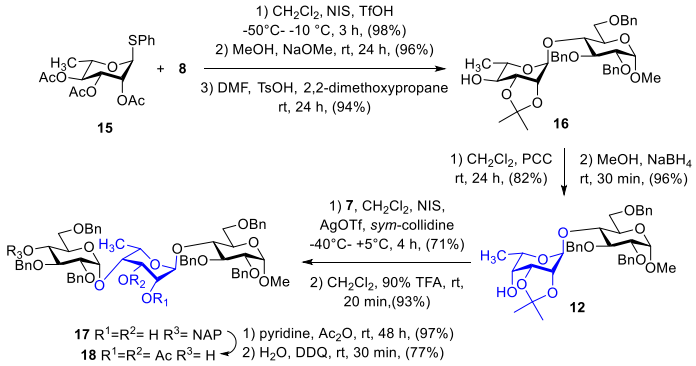
Scheme 4.: Synthesis of the trisaccharide acceptor **FGH** I.

During the reaction, despite the fact that the donor molecule (**10**) contained a non-participating acetal protecting group at the C-2 position, compound **11** was obtained in excellent yield and complete stereoselectivity, then it was transformed into an acceptor by oxidative removal of the 4-*O*-NAP ether group. Next, glycosylation of disaccharide **12** with monosaccharide **7** was performed, resulting in the protected trisaccharide **13** with excellent yield and stereoselectivity, which was

converted into an acceptor (**14**) in one step. This synthesis route required 20 steps starting from L-rhamnose, methyl α-D-glucopyranoside and D-glucose resulting in compound **13** in 7.1% overall yield.

*3.1.3. Synthesis of the trisaccharide **FGH** II.*

To improve the yield and shorten the synthesis, trisaccharide **13** was also prepared by a route using the phenyl-1-thio-α-L-rhamnopyranoside derivative (**15**) as a talose precursor building block and the C-4 epimerization (oxidation/stereoselective reduction) was performed at the disaccharide level (**Scheme 5.**). In this reaction pathway, the protected trisaccharide (**13**) was prepared in 18 steps in 11% overall yield using the building blocks already mentioned. The protected trisaccharide was then converted in 3 steps to an acceptor containing acetyl groups on unit **G** (**18**).

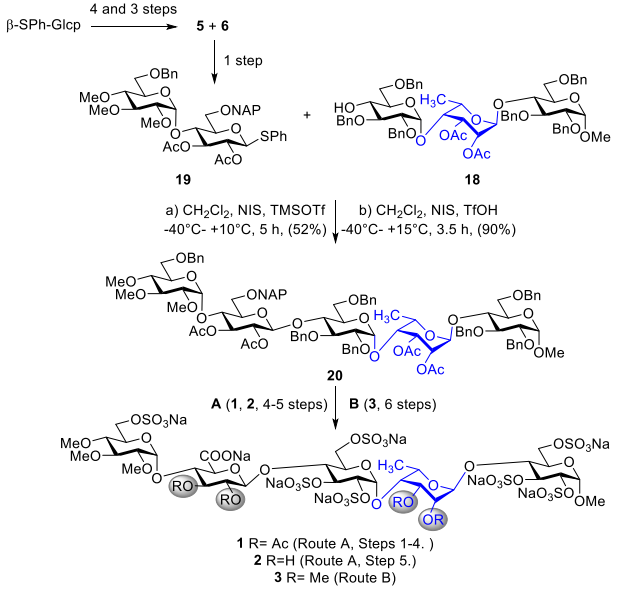


Scheme 5.: Synthesis of the trisaccharide acceptor **FGH** II.

3.1.4. Synthesis and transformations of the protected pentasaccharide

In the followings we performed the glycosylation reaction of **FGH** acceptor **18** with disaccharide donor **19**, which had been previously synthesized and successfully used in our research group (**Scheme 6.**). During the reaction, the protected pentasaccharide (**20**) formed in excellent yield and full stereoselectivity, and was then successfully converted into the three 6-deoxy-L-talopyranoside-containing

pentasaccharide derivatives (**1-3**) by formation of the final groups (methyl, carboxyl, sulfate ester). (Overall yields of final products: **1**: 33 steps, 0,9 %; **2**: 34 steps, 0,7 %; **3**: 35 steps, 0,8%).



Route A: 1) CH_2Cl_2, H_2O, DDQ, rt, 45 min, (65%), 2) CH_2Cl_2, H_2O, TEMPO, BAIB, rt, 48 h, (65%), 3) 96% EtOH, H_2/Pd-C, rt, 24 h, (94%), 4) DMF, SO_3·Et_3N, 50°C,48 h, 5) (77%), MeOH, 3M NaOH, 0 °C-rt, 24 h, (78%)

Route B: 1) MeOH, NaOMe, rt, 24 h, (88%), 2) DMF, MeI, NaH, 0°C- rt, 24 h, (81%), 3) CH_2Cl_2, H_2O, DDQ, rt, 40 min, (65%), 4) CH_2Cl_2, H_2O, TEMPO, BAIB, rt, 48 h, (78%), 5) 96% EtOH, H_2/Pd-C, rt, 24 h, (86%), 6) DMF, SO_3·Et_3N, 50°C,48 h, (92%)

Scheme 6.: Synthesis and transformations of the 6-deoxy-L-talopyranoside-containing pentasaccharides

3.1.5. Biological and NMR studies

By performing the factor Xa inhibition studies of the synthesized pentasaccharides (**1-3**), it was found that the modifications led to a complete loss of the anticoagulant effect. This is probably explained by the lack of a carboxyl group essential for binding at the unit **G** and by the fact that the bioactive ^2S_O conformer, according to NMR studies, is present in a smaller population in the conformational equilibrium of $^1C_4$, ^2S_O and $^4C_1$.

3.2. New synthesis of L-idosyl thioglycosyl donors

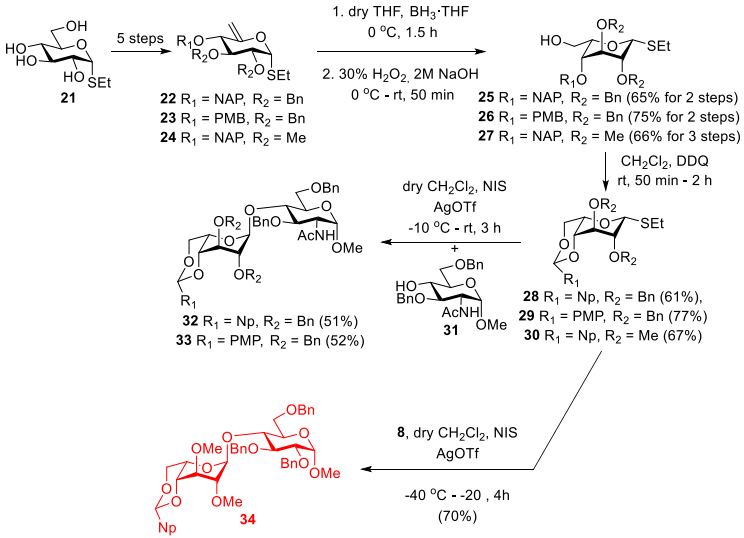
- Within these studies, the previously described synthesis method for *O*-glycosides was extended to thioglucoside derivatives.
- The key step of this method is the diastereoselective hydroboration/oxidation of hex-5-enopyranosides formed from properly protected carbohydrate derivatives.
- For the epimerization reactions, the 5,6-unsaturated compounds were prepared by the elimination reaction of the corresponding 6-deoxy-6-iodine derivatives.

3.2.1. Compatibility studies of the thio aglycone

Although it was known from previous results that the α-anomeric configuration is essential for the high L-*ido* selectivity, initial compatibility investigations were studied on β-thioglucosides which can be more easily synthesized than α-isomers. During the reactions, using different protecting group strategies, we found that in all cases the hydroboration and oxidation occurred with high efficiency, the oxidation conditions successfully applied for *O*-glycosides proved to be suitable for the tested thioglucoside derivatives, as the sulfur atom is not or very small extent oxidized. As expected, the D-*gluco* epimers formed as the main products.

3.2.2 Synthesis of L-idose starting from α-D-thioglucosides

In the followings, reactions of α-thioglucosides were studied. To this end, the hydroboration and oxidation reactions of exomethylene derivatives (**Scheme 7.**, **22**, **23**, **24**) protected with ether groups (Bn, PMB, NAP, Me) in different positions were investigated. Carrying out the three-step (elimination-hydroboration-oxidation) C-5 epimerization of these compounds, the products with L-*ido* configuration (**25**, **26**, **27**) were obtained in good yields, which have an anomeric group that can be activated and can be used as glycosyl donors after further conversion. Compounds **25**, **26** and **27** were synthesized in 11 steps starting from D-glucose in 16%, 15% and 28% overall yields, respectively.



Scheme 7.: New synthesis and glycosylation reactions of orthogonally protected L-idose thioglucoside donors – selection

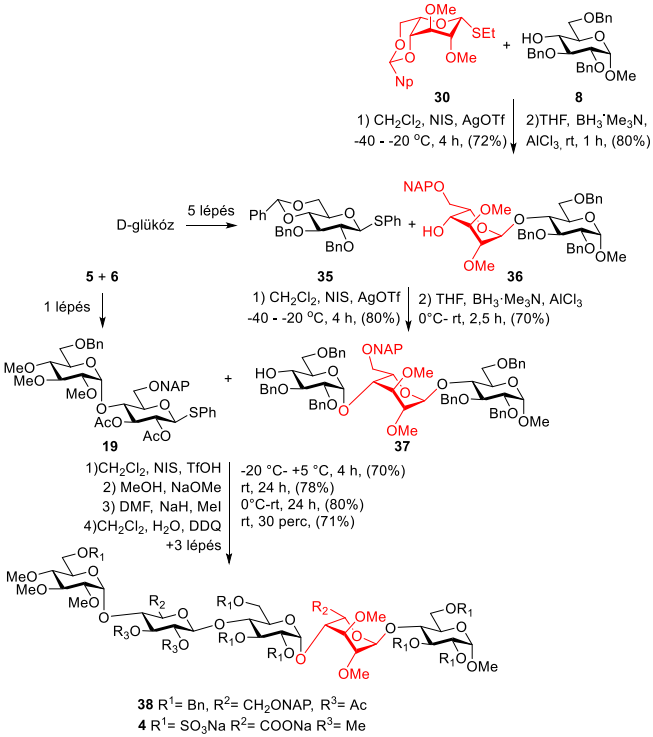
3.2.2. Glycosylation test reactions

In order to investigate the applicability of the synthesized L-idose derivatives, glycosylation test reactions were also performed. To this end, the prepared compounds could be converted into donors in one step in an oxidative acetal ring closure reaction (**28**, **29**, **30**, **Scheme 7.**). Using the obtained L-idosyl thioglycosyl donors, coupling reactions were performed in which protected heparin analogue disaccharides were prepared in good yields and stereoselectivity (**32**, **33**, **34**). Based on the reactions performed, the thioglycoside derivatives prepared can be said to be suitable for the synthesis of heparin analogue oligosaccharides.

3.3 New synthesis of idraparinux

Finally, in order to demonstrate the efficacy of the new L-idose synthesis method, we used the thioidoside donor **30** for the synthesis of the heparin analogue pentasaccharide with the best anticoagulant activity,

idraparinux, in a shorter and more efficient route than before (**Scheme 8.**, **4**).



Scheme 8.:: The shortest synthesis of idraparinux with the use of new α-selective L-idose thioglycosyl donor

The key steps of the new synthesis included the synthesis of 4,6-acetal-containing L-idose donor (**30**) and its use in the preparation of disaccharide **GH** (**36**). The exomethylene derivative (**24**) required for the preparation of the L-idose donor was synthesized from D-glucose in 10 steps and subsequent hydroboration followed by oxidation afforded the L-*ido* epimer (**27**) in good yield, which was converted into donor (**30**) by an oxidative ring closure reaction. Using compound **30** in the glycosylation step, the disaccharide **GH** containing an α-interglycosidic bond was formed in good yield and with complete stereoselectivity due

to the directing effect of the 4,6-acetal ring (**34**). Next, we successfully synthesized the trisaccharide acceptor **FGH** (**37**) and then the protected pentasaccharide (**38**) by block synthesis of trisaccharide **37** and disaccharide donor **DE** (**19**) [2 + 3] as before (**Scheme 8.**). The protected pentasaccharide (**38**) was finally converted into the final product (**4**) in 6 steps. Applying this method, idraparinux was synthesized in 0.15% yield starting from D-glucose and methyl α-D-glucopyranoside in 38 steps with 23 steps for the longest linear route. It is important to mention that during the synthesis of disaccharide **GH** and the L-idose donor, many intermediates were formed in crystalline form. With the successful synthesis of disaccharides and idraparinux, we have demonstrated that idosyl donors containing a 4,6-acetal ring can be used to perform 1,2-*trans*-α-selective glycosylation reactions in the lack of the C2-participating group, which may open new routes for even more diverse protecting group strategies for the synthesis of heparinoid oligosaccharides.

4. Possible application of the results

- During my PhD research, on the one hand, we have developed new methods for the preparation of heparin-analogue oligosaccharides.
- On the other hand, we have elaborated a new synthetic route for the preparation of L-idose thioglycoside donors that can be used directly for the synthesis of oligosaccharides and glycoconjugates.
- In addition, this method can be extended to the preparation of other hexoses and is generally applicable to the synthesis of rare L-hexoses.
- Furthermore, by biological and NMR studies of the carbohydrate derivatives produced, we were able to better understand the nature of the interaction of proteins related to our research (e.g., antithrombin) with carbohydrates.
- In addition, the methods developed during the synthesis of our compounds greatly contribute to the development of carbohydrate

chemical synthesis methods (glycosylation reactions, protecting group manipulations, synthesis of L-hexoses).

5. List of Publications

5.1 Közlemények az értekezés témájában/ Publications in the subject of the Ph.D. thesis

1. M. Herczeg, **F. Demeter**, T. Balogh, V. Kelemen, A. Borbás: Rapid Synthesis of L-Idosyl Glycosyl Donors from α-Thioglucosides for the Preparation of Heparin Disaccharides, *Eur. J. Org. Chem.* **2018**, 25, 3312-3316., **IF: 3.029**
2. **F. Demeter**, T. Gyöngyösi, Zs. Bereczky, K. E. Kövér, M. Herczeg and A. Borbás, Replacement of the L-iduronic acid unit of the anticoagulant pentasaccharide idraparinux by a 6-deoxy-L-talopyranose – Synthesis and conformational analysis, *Sci. Rep.*, 2018, 8, (1), 13736., **IF: 4.011**
3. **F. Demeter**, F. Veres, M. Herczeg and A. Borbás, Short synthesis of idraparinux by applying a 2-*O*-methyl-4,6-*O*-arylmethylene thioidoside as a 1,2-trans α-selective glycosyl donor, *Eur. J. Org. Chem.*, 2018, 48, 6901-6912. **IF: 3.029**
4. **F. Demeter**, A. Borbás, M. Herczeg, Synthesis of an orthogonally protected L-idose derivative using hydroboration/oxidation, Carbohydrate Chemistry, Proven Synthetic Methods, Paul Kosma, Tanja M. Wrodnigg and Arnold Stütz, ISBN: 9780815367888, CRC Press, 2021, Volume 5, Chapter 29, 233-240. **IF: 0.000**

5.2 Közlemények egyéb témában/ Publications in other subject

1. M. Herczeg, **F. Demeter**, E, Mező, M. Pap, A. Borbás: Simultaneous Application of Arylmethylene Acetal and Butane Diacetal Groups for Protection of Hexopyranosides: Synthesis and Chemoselective Ring-Opening Reactions, *Eur. J. Org. Chem.*, **2015**, *26*, 5730-5741., **IF: 3.068**
2. T.-K. Fu, S.-K. Ng, Y.-E. Chen, Y.-C. Lee, **F. Demeter**, M. Herczeg, A. Borbás, C.-H. Chiu, C.-Y. Lan, C.-L. Chen, M. D.-T. Chang, Rhamnose Binding Protein as an Anti-Bacterial Agent-Targeting

Biofilm of *Pseudomonas aeruginosa*, *Mar. Drugs*, **2019,** *17*, 355, 1-19., **IF: 4.073**

3. **F. Demeter**, T. Balogh, T.-K. Fu, M. D.-T. Chang, Y.-C. Lee, A. Borbás, M. Herczeg, Preparation of α-L-rhamnobiosides by open and conventional glycosylations for studies of the rHPL lectin, *Synlett*, **2019**, *30*, (19), 2185-2192., **IF: 2.006**
4. **F. Demeter**, M. D.-T. Chang, Y.-C. Lee, A. Borbás, M. Herczeg, An efficient synthesis of the pentasaccharide repeating unit of *Pseudomonas aeruginosa* Psl exopolysaccharide, *Synlett*, **2020**, *31*, (05), 469-474., **IF: 2.006**
5. **F. Demeter**, M. D.-T. Chang, Y.-C. Lee, T.-K. Fu, M. Herczeg, A. Borbás, Synthesis of α-1,2- and α-1,3-linked di-rhamnolipids for biological studies, *Carbohydr. Res.* **2020**, *496*, 108102., **IF: 1.841**
6. E. Lisztes, E. Mező, **F. Demeter**, L. Horváth, Sz. Bősze, B. I. Tóth, A. Borbás, M. Herczeg, Synthesis and cell growth inhibitory activity of six non-glycosaminoglycan-type heparin-analogue trisaccharides, *ChemMedChem*, **2021**, DOI: 10.1002/cmdc.202000917., **IF: 3.124**

5.3 Előadások és poszterek/Lectures and Posters

5.3.1. Konferencia előadások az értekezés témájában/ Lectures in the subject of the Ph.D. thesis

1. **F. Demeter**, A. Borbás, M. Herczeg, Synthesis of 6-deoxy-L-talopyranoside-containing analogues of the anticoagulant pentasaccharide idraparinux, *Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences, Mátraháza,* ***May 31– June 02, 2017.***
2. Herczeg M., **Demeter F**., Balogh T., Borbás A: Hatékony szintézismódszer kidolgozása ortogonálisan védett L-idóz donor előállítására, *Gyógyszerkémiai és gyógyszertechnológiai Szimpózium '17, Szeged,* ***2017. szeptember 11-12.***

3. **F. Demeter**, T. Balogh, V. Kelemen, M. Herczeg, A. Borbás: Rapid Synthesis of L-Idosyl Glycosyl Donors from Thioglucosides for the Preparation of Heparin Disaccharides, *Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences, Mátrafüred, May 23 – May 25, 2018.*
4. M. Herczeg, **F. Demeter**, F. Veres, A. Borbás: Application of the new idose synthesis: the preparation of Idraparinux, *Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences, Mátrafüred, May 23 – May 25, 2018.*

5.3.2. Poszterek az értekezés témájában/ Posters in the subject of the Ph.D. thesis

1. M. Herczeg, **F. Demeter**, A. Borbás: Synthesis of 6-deoxy-L-talopyranoside-containing analogues of the anticoagulant pentasaccharide idraparinux, *14th Bratislava Symposium on Saccharides „Glycochemistry for biology and medicine", Smolenice Castel, Slovakia, June 25 – 30, 2017. (page 78)*
2. **F. Demeter**, T. Gyöngyösi, K. Kövér, A. Borbás, M. Herczeg: Synthesis of 6-deoxy-L-talopyranoside-containing idraparinux-analogue pentasaccharide, *19th European Carbohydrate Symposium „Eurocarb", Barcelona, Spain, July 2 – 6, 2017. (page 657)*
3. **F. Demeter**, T. Balogh, M. Herczeg and Anikó Borbás: A new and efficient synthesis of orthogonally protected L-idose/L-iduronic acid glycosyl donors from D-glucose, *25th International Symposium: Synthesis in Organic Chemistry, Oxford, United Kingdom, July 17 – 20, 2017. (page P03)*
4. M. Herczeg, **F. Demeter**, A. Borbás: Synthesis of 6-deoxy-L-talopyranoside-containing analogues of the anticoagulant pentasaccharide idraparinux, *7th BBBB International Conference on Pharnaceutical Sciences, Balatonfüred, Hungary, 5 – 7 October, 2017. (page 164)*

5. **F. Demeter**, T. Balogh, F. Veres, V. Kelemen, A. Borbás and M. Herczeg, An efficient synthesis of orthogonally protected L-idosyl glycosyl donors from thioglucosides for the preparation of heparin oligosaccharides, *Chemistry towards Biology "Biomolecules as potential drugs", Budapest, Hungary, 24-27 September, 2018. (page 99)*

6. Veres Fanni, **Demeter Fruzsina**, Korponai Dóra, Borbás Anikó, Herczeg Mihály, Ortogonálisan védett L-idóz tioglikozidok hatékony szintézise, *MKE Vegyészkonferencia, Eger, 2019. június 24.-26.*

5.3.3. Konferencia előadások egyéb témában/ Lectures in other subject

1. **Demeter F.**, Herczeg M., Borbás A.: Kemoszelektív gyűrűnyitási reakciók vizsgálata kétféle dioxán típusú acetál védőcsoportot tartalmazó glüko- és galaktopiranozid származékokon, *Debreceni Egyetem Természettudományi és Technológiai Kar, 2014. évi Tavaszi Tudományos Diákköri Konferencia, 2014. május 16.*

2. **Demeter F.**: Csináltam egy anyagot! *Kutatók Éjszakája, Világító antibiotikumok, édes-savanyú oligoszacharidok, molekuláris kimérák – Felfedező gyógyszerkutatás a Debreceni Egyetem Gyógyszerészi Kémia Tanszékén c. program, Programfüzet, 2014. szeptember 26.*, 17.

3. **Demeter F.**, Mező E., Pap M., Herczeg M., Borbás A.: Kemoszelektív gyűrűnyitási reakciók vizsgálata kétféle dioxán-acetál védőcsoportot tartalmazó monoszacharidokon, *XXXVII. Kémiai Előadói napok, Program és előadás-összefoglalók, 2014. november 3-5.*, 219-223. (ISBN: 978-963-9970-53-3)

4. **Demeter F.**, Herczeg M., Borbás A.: Kemoszelektív gyűrűnyitási reakciók vizsgálata kétféle dioxán acetált tartalmazó glikozidokon, *Debreceni Egyetem Természettudományi és Technológiai Kar, 2014. évi Őszi Tudományos Diákköri Konferencia, 2014. november 28.*

5. M. Herczeg, E. Mező, **F. Demeter**, R. Pataki, A. Borbás: Simultaneous application of 1,3- and 1,4-dioxane acetal groups for protection of hexopyranosides. Synthesis and chemoselective ring opening reactions,

Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences, Mátraháza, May 21–23, 2014.

6. E. Mező, M. Herczeg, **F. Demeter**, A. Borbás: Simultaneous application of 1,3- and 1,4-dioxane acetal groups for protection of hexopyranosides. Synthesis and chemoselective ring opening reactions, *Symposium on Synthetic Carbohydrate Chemistry, Department of Pharmaceutical Chemistry, Faculty of Pharmacy, University of Debrecen, Debrecen, 2014. July 22.*

7. **Demeter F.**, Herczeg M., Borbás A., Kemoszelektív gyűrűnyitási reakciók vizsgálata kétféle dioxán acetált tartalmazó glikozidokon, *XXXII. Tudományos Diákköri Konferencia, Kémiai és Vegyipari Szekció, Veszprém, Pannon Egyetem, Mérnöki Kar, Kivonatok, 2015. április 9-11*, 241. (ISBN: 978-963-396-070-7)

8. **F. Demeter**, A. Borbás, M. Herczeg: An efficient synthesis of the pentasaccharide repeating unit of *Pseudomonas Aeruginosa* Psl exopolysaccharide for lectin-binding studies, *International Workshop on Chemistry and Chemical Biology of Carbohydrates, Nucleic Acids and Antibiotics, Mátrafüred, Hungary, 22-24 May, 2019.*

5.3.4. Poszterek egyéb témában/ Posters in other subject

1. E. Mező, M. Herczeg, **F. Demeter**, R. Pataki, A. Borbás: Simultaneous application of two different dioxane-acetal groups for protection of hexopyranosides, *13th Bratislava Symposium on Saccharides „Recent Advances in Glycomics", Smolenice, Slovakia, 2014. June 22-26.* (Page 103; ISBN: 978-80-971665-0-2, ISSN 1339-7036)

2. **F. Demeter**, M. Herczeg, A. Borbás: Synthesis of sulfonic acid-containing maltooligomers with potential antitumor and antimetastatic activity, *Debrecen Colloquium on Carbohydrates 2015, András Lipták Memorial Conference, Debrecen, Hungary, 6-8. November, 2015*. (page 53.)

3. **Demeter Fruzsina**, Borbás Anikó, Herczeg Mihály: A *Pseudomonas aeruginosa* Psl exopoliszacharid pentaszacharid részének hatékony szintézise az rHPL lektin biofilmképzés-gátló hatásának vizsgálatához, *MKE Vegyészkonferencia, Eger, 2019. június 24.-26.*
4. **Fruzsina Demeter**, Anikó Borbás, **Mihály Herczeg**, An efficient synthesis of the pentasaccharide repeating unit of *Pseudomonas aeruginosa* Psl exopolysaccharide for lectin-binding studies, *Eurocarb XX., Leiden, The Netherlands, June 30. - July 4., 2019.*

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Registry number: DEENK/112/2021.PL
Subject: PhD Publication List

Candidate: Fruzsina Demeter
Doctoral School: Doctoral School of Chemistry
MTMT ID: 10064786

List of publications related to the dissertation

Foreign language scientific articles in international journals (3)

1. Herczeg, M., **Demeter, F.**, Balogh, T., Kelemen, V., Borbás, A.: Rapid Synthesis of l-Idosyl Glycosyl Donors from α-Thioglucosides for the Preparation of Heparin Disaccharides. *Eur. J. Org. Chem. 2018* (25), 3312-3316, 2018. ISSN: 1434-193X.
   DOI: http://dx.doi.org/10.1002/ejoc.201800425
   IF: 3.029

2. **Demeter, F.**, Gyöngyösi, T., Bereczky, Z., Kövér, K. E., Herczeg, M., Borbás, A.: Replacement of the L-iduronic acid unit of the anticoagulant pentasaccharide idraparinux by a 6-deoxy-L-talopyranose: synthesis and conformational analysis.
   Sci Rep. 8 (1), 1-10, 2018. EISSN: 2045-2322.
   DOI: http://dx.doi.org/10.1038/s41598-018-31854-z
   IF: 4.011

3. **Demeter, F.**, Veres, F., Herczeg, M., Borbás, A.: Short Synthesis of Idraparinux by Applying a 2-O-Methyl-4,6-O-arylmethylene Thioidoside as a 1,2-trans-α-Selective Glycosyl Donor.
   Eur. J. Org. Chem. 48, 6901-6912, 2018. ISSN: 1434-193X.
   DOI: http://dx.doi.org/10.1002/ejoc.201801349
   IF: 3.029

DEBRECENI EGYETEM * Egyetemi és Nemzeti Könyvtár *

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

List of other publications

Foreign language scientific articles in international journals (6)

4. Lisztes, E., Mező, E., **Demeter, F.**, Horváth, L., Bősze, S., Tóth, I. B., Borbás, A., Herczeg, M.: Synthesis and cell growth inhibitory activity of six non-glycosaminoglycan-type heparin-analogue trisaccharides.
   ChemMedChem. [Epub ahead of print], 2021. ISSN: 1860-7179.
   DOI: http://dx.doi.org/10.1002/cmdc.202000917
   IF: 3.124 (2019)

5. **Demeter, F.**, Dah-Tsyr Chang, M., Lee, Y. C., Fu, T. K., Herczeg, M., Borbás, A.: Synthesis of α-1,2- and α-1,3-linked di-rhamnolipids for biological studies.
   Carbohydr. Res. 496, 1-17, 2020. ISSN: 0008-6215.
   DOI: http://dx.doi.org/10.1016/j.carres.2020.108102
   IF: 1.841 (2019)

6. **Demeter, F.**, Chang, M. D. T., Lee, Y. C., Borbás, A., Herczeg, M.: An Efficient Synthesis of the Pentasaccharide Repeating Unit of Pseudomonas aeruginosa Psl Exopolysaccharide.
   Synlett. 31 (05), 469-474, 2019. ISSN: 0936-5214.
   DOI: http://dx.doi.org/10.1055/s-0039-1690747
   IF: 2.006

7. **Demeter, F.**, Balogh, T., Fu, T. K., Chang, M. D. T., Lee, Y. C., Borbás, A., Herczeg, M.: Preparation of α-l-Rhamnobiosides by Open and Conventional Glycosylations for Studies of the rHPL Lectin.
   Synlett. 30 (19), 2185-2192, 2019. ISSN: 0936-5214.
   DOI: http://dx.doi.org/10.1055/s-0039-1690710
   IF: 2.006

8. Fu, T. K., Ng, S. K., Chen, Y. E., Lee, Y. C., **Demeter, F.**, Herczeg, M., Borbás, A., Chiu, C. H., Lan, C. Y., Chen, C. L., Dah-Tsyr Chang, M.: Rhamnose Binding Protein as an Anti-Bacterial Agent-Targeting Biofilm of Pseudomonas aeruginosa.
   Mar. Drugs. 17 (6), 1-19, 2019. ISSN: 1660-3397.
   DOI: http://dx.doi.org/10.3390/md17060355
   IF: 4.073

9. Herczeg, M., **Demeter, F.**, Mező, E., Pap, M., Borbás, A.: Simultaneous Application of Arylmethylene Acetal and Butane Diacetal Groups for Protection of Hexopyranosides: Synthesis and Chemoselective Ring-Opening Reactions.
   Eur. J. Org. Chem. 2015 (26), 5730-5741, 2015. ISSN: 1434-193X.
   DOI: http://dx.doi.org/10.1002/ejoc.201500732
   IF: 3.068

DEBRECENI EGYETEM Egyetemi és Nemzeti Könyvtár

UNIVERSITY of DEBRECEN

UNIVERSITY AND NATIONAL LIBRARY
UNIVERSITY OF DEBRECEN
H-4002 Egyetem tér 1, Debrecen
Phone: +3652/410-443, email: publikaciok@lib.unideb.hu

Foreign language abstracts (1)

10. **Demeter, F.**, Herczeg, M., Borbás, A.: Synthesis of sulfonic acid-containing maltooligomers with potential antitumor and antimetastatic activity.
In: Debrecen colloquium on carbohydrates 2015 András Lipták Memorial Conference : Program and abstracts. Ed.: Csávás Magdolna, Debreceni Egyetem, Debrecen, 53, 2015.
ISBN: 9789634738848

Total IF of journals (all publications): 26,187
Total IF of journals (publications related to the dissertation): 10,069

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.

25 March, 2021

DEBRECENI EGYETEM Egyetemi és Nemzeti Könyvtár