SHORT THESIS FOR THE DEGREE OF DOCTOR OF PHILOSOPHY (PHD)

Synthesis of multivalent glycomimetics, carbohydrate-containing chimeras and antibiotics with potential biological relevance

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The PhD Defense takes place on **12th of July**, **2022** at **13:00**.

If you wish to participate, please indicate via email to le.thai.son@pharm.unideb.hu until 12:00 noon, 11th of July, 2022. Late registration is not possible due to technical reasons.

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List of abbreviations

ABR = antibiotic resistance

ABS= antibiotics

MALDI-ToF MS = Matrix-Assisted Laser Desorption and Ionization - Time of Flight Mass Spectrometry

NMR = nuclear magnetic resonance spectroscopy

TLC = thin layer chromatography

CuAAC=copper-catalyzed azide-alkyne cycloaddition

MIC= minimum inhibitory concentration

HIA = hemagglutination inhibition assay

SPA = surface plasmon resonance

DIPEA= *N*,*N*-diisopropylethylamine

DPAP= 2,2-dimethoxy-2-phenylacetophenone

AFL: *Aspergillus fumigatus lectin*

RSL: *Ralstonia solanacearum* lectin

AAL: *Aleuria aurantia lectin*

AOL: *Aspergillus oryzae lectin*

PA-IIL: *Pseudomonas aeruginosa lectin B*

BC2L-C: *Burkholderia cenocepacia lectin C*

PA-IL: *Pseudomonas aeruginosa lectin A*

MAP= 4-methoxyacetophenone

TFA= trifluoroacetic acid

1. Introduction

Antibiotic resistance (ABR) is an alarming multifaceted problem, and it is predicted to be one of the greatest threats to human health in the next few decades, which requires immediate action to tackle before it is too late. Since the first introduction in the late 1940s, antibiotics (ABS) effectively treated serious infections and saved millions of lives, but resistance was quickly developed and recognized shortly thereafter. In 2004, more than 70% of pathogenic bacteria were estimated to be resistant to at least one type of antibiotic. Should this problem remain unsolved, it would cause more than 10 million deaths by 2050. This rising issue poses both a clinical threat and an economical burden on patients and the health care system. It is obvious that resistance can occur spontaneously through mutation, but exposure to antibiotics hastens this process further. This particularly happens in hospital settings where obvious relationships between the use of antibiotics and the appearance of multiresistant strains can be detected. ABS will eradicate drug-sensitive bacteria but leave resistant strains behind, and these resistant ones will continue to grow and reproduce as a result of natural selection. Resistant genes then can be inherited from relatives or can be acquired from nonrelatives. As a consequence, the more antibiotics are used, the more serious the resistance is. Especially when the first and then second-line of antibiotic treatments are unavailable or ineffective, patients have to resort to using drugs that are more expensive and more toxic. In the light of this global problem, we aimed to tackle ABR through three approaches during my doctoral research including building multivalent glycomimetics, developing chimeric antibiotics, and modifying mutilin-type antibiotics.

2. Literature review

2.1 Importance of carbohydrate-specific proteins: Lectins

Lectins have long been molecules of interest in the field of glycobiology, as they can be found in most organisms and have a wide range of applications in biology and medicine. They are involved in a number of physiological processes including cell-cell interactions, cell transport, biosignaling, immunological response, and toxicity. Particularly, lectins are of special importance in cellular recognition. Pathogens are well-known to use these proteins to specifically distinguish and attach to the host's glycoconjugates. Bacterial adhesion and colonization are the most important steps in pathogenesis, as to trigger infection the pathogens need to stick to the host surface strong enough. From this aspect, blocking the pathogen attachment is an important tactic to prevent or treat infections, since unattached organisms are

easily eliminated by host cleansing mechanism or host defence system. Using saccharides to inhibit bacterial/viral lectins is the most feasible method and has been supported with plenty of *in vitro* evidence. But the major drawback of antiadhesion therapy is that blocking only one type of adhesin is not sufficient to prevent colonization and symptomatic infection, since most pathogens possess more than one type of adhesin. These problems could be overcome by linking monovalent ligands to a structured scaffold, for instance polymer, dendrimer, or fullerene to create a multivalent carbohydrate inhibitor. With this multivalency strategy, such inhibitors can be used at much lower concentration (within micromolar or even nanomolar scale) with higher binding affinity and avidity. The effectiveness of adhesion inhibition suggests that it has the potential to improve or even replace antibiotic treatments, as it does not result in the development of resistance, and the viability of pathogens is not affected since these antiadhesion agents do not kill or interrupt the growth of bacteria. Hence, antiadhesion therapy is a noteworthy, novel strategy that can be used in the fight against microbial resistance along with developing new antibiotics.

2.2 Synthetic goals

2.2.1 Synthesis of multivalent glycomimetics

The first part of synthetic work mainly focused on developing antiadhesive therapy by synthesizing a wide panel of carbohydrate-based ligands for bacterial lectins. In particular, L-fucopyranoside and D-galactopyranoside were chosen as monosaccharide units. The purpose of this synthesis is to study the effect of structural alterations on lectin binding ability.

The next step is to build multivalent glycocluster compounds from monosaccharides with the most suitable configuration, which are α-L-fucopyranoside and β-D-galactopyranoside. The purpose is to find out the appropriate scaffold, linker, and multivalent structure as well as to find out the best universal inhibitors for carbohydrate-specific lectins.

2.2.2 Invention of novel chimeric antibiotics

The second part of my research is to invent new ABS to fight against the bacterial resistance crisis by synthesizing novel chimeric antibiotics, which are built upon the most suitable multivalent glycoclusters and ABS. The chimeric ABS are expected to detach bacteria from host cells, reduce bacterial infection, inhibit bacterial biofilm formation, and thus may enhance the effect of conjugated ABS. The other advantage of chimeric molecules over conventional ABS is that upon binding to the carbohydrate moieties of the molecules, the conjugated antibiotic is delivered directly to the binding bacteria and exerts antibacterial

activity in a targeted therapy manner. This approach not only reduces the antibiotic side effects on the host but also increases the antibiotic concentration available to bacteria, thus improving antibacterial efficacy.

2.1 Structural modification of pleuromutilin and lefamulin

The third part of my research concentrated on structural modification of pleuromutilin and lefamulin antibiotics at terminal alkene C19-20 by thio-ene click reaction. The goal of this synthesis is to create a series of new mutilin analogues in order to discover the better derivatives compared to parent mutilin as well as to find out new binding mode at this position. New compounds will be tested against a wide range of bacteria and studied for structure-activity relationship.

3. Methods

Optical rotations were measured at room temperature with a Perkin-Elmer 241 automatic polarimeter. TLC analysis was performed on Kieselgel 60 F_{254} (Merck) silica gel plates with visualization by immersing in a sulfuric acid solution (5% in EtOH) followed by heating. Column chromatography was performed on silica gel 60 (Merck 0.063–0.200 mm), flash column chromatography was performed on silica gel 60 (Merck 0.040–0.063 mm). Gel filtration was performed on Sephadex G-25, using methanol or water as the eluent. Organic solutions were dried over $MgSO_4$ and concentrated under vacuum. The ^{1}H (400 and 500 MHz) and ^{13}C NMR (100.28, 125.76 MHz) spectra were recorded with Bruker DRX-400 and Bruker Avance II 500 spectrometers. Chemical shifts are referenced to Me_4Si or DSS (0.00 ppm for ^{1}H) and to solvent signals ($CDCl_3$: 77.00 ppm, CD_3OD: 49.15 ppm, DMSO-d_6: 39.51 ppm for ^{13}C). MS (MALDI-TOF) analysis was carried out in positive reflectron mode with a BIFLEX III mass spectrometer (Bruker, Germany) with delayed-ion extraction. The matrix solution was a saturated solution of 2,4,6-trihydroxy-acetophenone (THAP) in MeCN. ESI-QTOF MS measurements were carried out on a maXis II UHR ESI-QTOF MS instrument (Bruker), in positive ionization mode. The following parameters were applied for the electrospray ion source: capillary voltage: 3.6 kV; end plate offset: 500 V; nebulizer pressure: 0.5 bar; dry gas temperature: 200 °C and dry gas flow rate: 4.0 L/min. Constant background correction was applied for each spectrum; the background was recorded before each sample by injecting the blank sample matrix (solvent). Na-formate calibrant was injected after each sample, which enabled internal calibration during data evaluation. Mass spectra were recorded

by OTOF Control version 4.1 (build: 3.5, Bruker) and processed by Compass DataAnalysis version 4.4 (build: 200.55.2969).

4. Results

4.1 Synthesis of L-fucose and D-galactose containing glycoclusters as potential ligands of lectins

CuAAC click reaction was used as a main synthetic method to conjugate linker into monosaccharide and monosaccharide into different scaffolds. First, L-fucopyranoside was alkylated by Fischer-type glycosylations using sulfamic acid and propargyl alcohol, with an α:β anomer ratio of approximately 3:1, to give propargyl α-L-fucopyranoside. This product was coupled with a short monoazido-monotosyl-ethylene glycol linker via CuAAC reaction; the tosyl leaving group was then converted into the azido functional group. The overall 2-step reaction gave a triazole-bearing sugar product in good yield. Propargyl α-L-fucopyranoside was also coupled with a long diazido-tetraethylene glycol linker using the same reaction method to produce mono- and divalent products in lower yield.

Secondly, 1-thio analogue was also prepared from per-*O*-acetylated-L-fucopyranoside. This thio-analogue is more stable than *O*-analogue as it is more resistant to degrading enzymes. 2,3,4-tri-*O*-acetyl-α-L-fucosyl bromide was reacted with thiourea, followed by reduction to produce 2,3,4-tri-*O*-acetyl-1-*S*-β-L-fucose in good yield. This product was then subjected to *O*-deacetylation by Zemplén deprotection to give the desired compound 1-*S*-β-L-fucose, or oxidized by H_2O_2 and then deprotected to give 1,1´-disulfide, both reactions underwent in good yield.

An alkylated derivative was also produced from 2,3,4-tri-*O*-acetyl-1-*S*-β-L-fucopyranoside by using propargyl bromide and DIPEA to give propargyl 2,3,4-tri-*O*-acetyl-1-*S*-β-L-fucopyranoside in good yield. This product was then subjected to deacetylation to produce propargyl 1-thio-β-L-fucopyranoside, which was later coupled with a long diazido-tetraethylene glycol linker through a CuAAC reaction to give a triazole-bearing 1-*S*-β-L-fucose with a flexible side chain.

Furthermore, 2-acetoxy-3,4-di-*O*-acetyl-L-fucal was allowed to react with 2-mercaptoethanol using thiol-ene radical addition with an added amount of DPAP catalyst to give an additive product of α configuration in moderate yield, which was then deacetylated to produce 2-hydroxyethyl-1-*S*-α-L-fucopyranoside in good yield. These mono- and divalent compounds were suitable for testing their interactions with fucose-specific lectins and discovering structure-binding relationships.

In order to build multivalent glycoclusters, we started from per-*O*-acetylated-D-galactopyranoside and propargyl α-L-fucopyranoside. Propargyl α-L-fucopyranoside was protected by acetylation. Per-*O*-acetylated-D-galactopyranoside was alkylated using boron

trifluoride diethyl etherate and propargyl alcohol to produce propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside in good yield. These two propargyl monosaccharides are suitable for coupling into azido-containing scaffolds via CuAAC click reaction.

Methyl gallate and pentaerythritol structures were favoured as tri- and tetravalent scaffolds, respectively. Each of these two scaffolds was decorated with azido-containing tetraethylene or ethylene glycol chains. As a result, four scaffolds with various side chains were produced and later coupled with propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside to produce four β-D-galactose-containing glycoclusters in moderate to excellent yield. *N*-(*t*-butyloxycarbonyl)-tris-(hydroxymethyl)-aminomethane was also chosen as a trivalent structure. First, it was alkylated using propargyl bromide in the presence of KOH; the propargylated product was then coupled with monotosyl-monoazido-tetraethylene glycol linker via CuAAC reaction in high yield. Tosyl group was later converted into azido functional group by nucleophilic substitution reaction to give azido-containing trivalent scaffold in good yield. This scaffold again via CuAAC reaction was coupled with propargyl 2,3,4-tri-*O*-acetyl-α-L-fucopyranoside- and propargyl 2,3,4,6-tetra-*O*-acetyl-β-D-galactopyranoside to produce two trivalent compounds in high and moderate yield, respectively. Finally, all the desired non-protected glycoclusters were obtained with high yield by the Zemplén-deacetylation method.

All the synthesized monovalent, divalent, and multivalent compounds were examined for biological investigations. The MICs value were determined and inhibitory potency was evaluated based on the results from HIA and/or SPR methods. As a result, we have found some potential lead structures for anti-adhesion therapy.

4.2 Synthesis of carbohydrate-antibiotic chimeras

In an attempt to synthesize novel antibiotics, we came up with the concept of ”chimeric” antibiotics by conjugating the multivalent glycocluster with conventional antibiotics. Azido-containing trivalent glycoclusters were able to couple with propargyl-containing antibiotics through CuAAC click reaction in just one step. In order to prepare *N*-propargyl derivatives of fluoroquinolone antibiotic, the secondary -*N*H group of ciprofloxacin and moxifloxacin was alkylated by propargyl bromide or monopropargyl-monobromo-tetraethylene glycol in the presence of sodium bicarbonate. As a result, four propargyl fluoroquinolones were produced in moderate to high yield.

The *Boc* protecting group of both α-L-fucose- and β-D-galactose-containing-*N*H-Boc-tris glycoclusters previously synthesized was then removed in a solution of TFA/DCM 1:1 to generate a primary amine -*N*H_2 functional group, which was then converted into azido moiety

in an amine-azide transfer reaction to give two azido-containing trivalent glycoclusters in good yield. These two new scaffolds bearing azido group were coupled with propargyl-containing antibiotics via CuAAC click reaction to produce novel chimeric antibiotic molecules with a 1,4-disubstituted-1,2,3-triazole linker. The acetyl protecting group from sugar moieties was then removed by Zemplén deacetylation to give the final desired chimeric products in high yield. All the newly synthesized chimeric antibiotics were tested for antibacterial activity as well as hemagglutination inhibition property.

4.3 Semisynthetic modification of pleuromutilin and lefamilin

In addition to the synthesis of chimeric ABS, we also performed pleuromutilin and lefamulin structural modification by using thiol-ene radical addition reaction with the help of DPAP catalyst to conjugate thiols to C19-20 terminal alkene in order to find out more potent antibacterial candidates from these two antibiotics. We proposed that photoinitiated thiol-ene radical addition would be an efficient strategy to couple a wide range of thiol-compounds to this reactive double bond.

New pleuromutilin derivatives were synthesized directly from pleuromutilin with various thiols in moderate to excellent yield including sugar moieties, lipophilic side chains, sodium ethyl sulfonate (mesna), benzylmercaptan, thioacetic acid, protected cysteines, hydroxyethylmercaptan, 2-thio-*N*-acetylneuraminic acid. Interestingly, the internal ester bond at C-21 position was conserved under KOH condition during the deprotection process. In general, a reaction carried out at low temperature (-40°C or -80°C) with 2-3 irradiation cycles would give a better overall yield. In case of thioacetic acid, the combination of MAP and DPAP reagents is necessary, which acted as photosensitizer and photoinitiator, respectively. Because lefamulin contains -NH_2 basic group in its structure, which could interfere with thiol reactant by abstracting a hydrogen atom from it and thus preventing the formation of thiyl radical, the addition of TFA to neutralize this basic group is necessary. All synthesized compounds were tested for antibacterial activity and studied for structure-activity relationship.

5. Summary

During my doctoral research, I have proposed three approaches to cope with bacterial infection and resistance issues through 1) antiadhesion therapy, 2) synthesis of novel chimeric antibiotics, and 3) structural modification of mutilin antibiotics.

Firstly, a wide panel of L-fucose analogues were synthesized to find out the best candidates as well as to study the relationship between structure and lectin binding activity. CuAAC click reaction was employed as the main tool to conjugate short and long linkers into monosaccharides. Moreover, this method is apposite to creating multivalent glycomimetic compounds. Tri- and tetravalent glycoclusters containing L-fuco or D-galactose units were successfully synthesized by conjugating ethylene glycol and tetraethylene glycol into methyl gallate, pentaerythritol, and *N*H-Boc-Tris scaffolds. All the synthesized multivalent glycoclusters showed very high lectin binding activity compared to standard monosaccharide L-fucose or D-galactose. Particularly, the fucose-containing trivalent glycocluster displayed strong inhibitory activity against fucose-specific lectins of bacterial origin *PA-IIL*, *BC2L-C*, *RSL* or fungal origin *AFL*, *AAL*, and *AOL*. Likewise, D-galactose-containing tri- and tetravalent glycoclusters exhibited a very strong inhibitory effect on galactose-specific lectin PA-IL. Importantly, these multivalent structures could exert their effect on micromolar concentration. In my synthetic work, I have found universal ligands for bacterial lectins, and these sugar-containing multivalent compounds are potential candidates for antiadhesion therapy, especially against bacterial lectin PA-IL and PA-IIL.

Secondly, I have synthesized L-fucose- or D-galactose-containing chimeric antibiotics. Fluoroquinolones with different alkylated side chains were conjugated intro trivalent scaffold through CuAAC click reaction. The reaction yield of compounds with short side chains is higher than that of compounds with longer side chains. Although the antibacterial activity of these chimeric compounds was weaker than the effect of their fluoroquinolone parents, they could however target the Gram-positive bacteria infection and reduce Gram-negative bacteria binding, especially for cystic fibrosis patients who are usually infected by both *Staphylococcus aureus* and *Pseudomonas aeruginosa* bacteria. This type of new molecules and their results boded well for the future application of chimeric antibiotics. Deciphering from the *in vitro* results and chemical structure, a cleavable bond between glycocluster and fluoroquinolone is necessary in order to efficiently deliver antibiotic unit into a bacterial cell.

Lastly, different derivatives of pleuromutilin and lefamulin were synthesized by thiol-ene radical addition reaction by conjugating these antibiotics with a wide range of carbohydrate-thiol compounds, butyl-, octyl-, dodecyl-mercaptan, sodium ethyl sulfonate

(mesna), benzylmercaptan, thioacetic acid, *N*-Ac-cysteine, *N*-Fmoc-cysteine, hydroxyethylmercaptan, and 2-thio-*N*-Ac-neuraminic acid. From the above-synthesized derivatives, three thioether compounds with a terminal negative charge exhibited a good antibacterial result including hydroxyethyl, *N*-Ac-cysteine, and *N*-Ac-neuraminic acid. These three thiols were radically conjugated to lefamulin but the opposite outcome was observed. Two derivatives were inactive, and only one compound with hydroxyethyl conjugate showed a weak antibacterial effect. From this point of view, we might come to conclusion that pleuromutilin and lefamulin have different binding modes, hence with the same conjugated moiety, they could exhibit distinct effect. Nonetheless, structural modification at terminal alkene position is a very promising tactic as many potential thiols or reactive agents are still unexplored.

New scientific results:

- Anti-adhesion therapy: 6 multivalent glycoclusters (4 fucoclusters and 2 galactoseclusters) were synthesized with greatly enhanced lectin inhibitory activity. I have found universal candidates for bacterial/fungal lectin.
- Chimeric strategy: 6 chimeric antibiotics were synthesized with potential anti-adhesive property and a slight antimicrobial effect. This type of compound has the potential to detach and kill pathogens with a wide-spectrum effect.
- Structural modification: 17 mutilin derivatives were synthesized, and I have found several analogues with improved antibacterial effect.

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7. List of scientific publications

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Registry number: DEENK/535/2021.PL
Subject: PhD Publication List

Candidate: Son Le Thai
Doctoral School: Doctoral School of Pharmacy

List of publications related to the dissertation

1. **Le Thai, S.**, Páll, D., Rőth, E., Tran, T., Debreczeni, N., Bege, M., Bereczki, I., Ostorházi, E., Milánkovits, M., Herczegh, P., Borbás, A., Csávás, M.: The Very First Modification of Pleuromutilin and Lefamulin by Photoinitiated Radical Addition Reactions: synthesis and Antibacterial Studies.
   Pharmaceutics. 13 (12), 1-21, 2021.
   DOI: http://dx.doi.org/10.3390/pharmaceutics13122028
   IF: 6.321 (2020)
2. **Le Thai, S.**, Malinovská, L., Vaskova, M., Mező, E., Kelemen, V., Borbás, A., Hodek, P., Wimmerová, M., Csávás, M.: Investigation of the Binding Affinity of a Broad Array of l-Fucosides with Six Fucose-Specific Lectins of Bacterial and Fungal Origin.
   Molecules. 24 (12), 1-17, 2019.
   DOI: http://dx.doi.org/10.3390/molecules24122262
   IF: 3.267
3. Malinovská, L., **Le Thai, S.**, Herczeg, M., Vaskova, M., Houser, J., Fujdiarová, E., Komárek, J., Hodek, P., Borbás, A., Wimmerová, M., Csávás, M.: Synthesis of [beta]-D-galactopyranoside-Presenting Glycoclusters, Investigation of Their Interactions with Pseudomonas aeruginosa Lectin A (PA-IL) and Evaluation of Their Anti-Adhesion Potential.
   Biomolecules. 9 (11), 1-22, 2019.
   DOI: http://dx.doi.org/10.3390/biom9110686
   IF: 4.082

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List of other publications

4. Szűcs, Z., Kelemen, V., **Le Thai, S.**, Csávás, M., Rőth, E., Batta, G., Stevaert, A., Vanderlinden, E., Naesens, L., Herczegh, P., Borbás, A.: Structure-activity relationship studies of lipophilic teicoplanin pseudoaglycon derivatives as new anti-influenza virus agents.
Eur. J. Med. Chem. 157, 1017-1030, 2018.
DOI: http://dx.doi.org/10.1016/j.ejmech.2018.08.058
IF: 4.833

Total IF of journals (all publications): 18,503
Total IF of journals (publications related to the dissertation): 13,67

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.

17 December, 2021

DEBRECENI EGYETEM
Egyetemi és Nemzeti Könyvtár

8. List of scientific lectures and posters

1. **CARBOHYDRATE-BASED POTENTIAL ANTIMICROBIAL DRUGS AND GLYCOPEPTIDES WITH OLD AND NEW THERAPEUTIC GOALS**
   M. Csávás, L. Malinovská, G. Jančaříková, **Son Thai Le**, Zs. Szűcs, P. Herczegh, M. Wimmerová, A. Borbás
   Joint Meeting of Medicinal Chemistry, Prága, 2019

2. **SYNTHESIS OF ANTIBACTERIAL MULTIVALENT CARBOHYDRATE-ANTIBIOTIC CHIMERAS WITH POTENTIAL AFFINITY TO BACTERIAL LECTINS**
   Son Le Thai, Anikó Borbás, Magdolna Csávás
   International Workshop on Chemistry and Chemical Biology of Carbohydrates, Nucleic Acids and Antibiotics, Mátrafüred, 2019

3. **CARBOHYDRATE-ANTIBIOTIC CHIMERAS WITH POTENTIAL ANTIMICROBIAL EFFECTS**
   Son Thai Le, M. Csávás
   Research and Development for Therapeutical Purposes Conference, Debrecen, 2019

4. **MULTIVALENS SZÉNHIDRÁTOK SZINTÉZISE ÉS LEKTINEKKEL VALÓ KÖLCSÖNHATÁSÁNAK VIZSGÁLATA**
   Csávás Magdolna, Lenka Malinovská, Gita Jancariková, **Son Thai Le**, Herczeg Mihály, E. Kövér Katalin, Michaela Wimmerová, Borbás Anikó
   International Chemical Conference, Sovata, 2019

5. **SYNTHESIS OF CARBOHYDRATE-ANTIBIOTIC CHIMERA: COUPLING OF AN ALPHA-L-FUCOSIDE CONTAINING MULTIVALENT GLYCOCLUSTERS WITH FLUOROQUINOLONE ANTIBIOTICS**
   Son Thai Le, Gyula Batta, Anikó Borbás, Magdolna Csávás
   Chemistry towards Biology, Budapest, 2018

6. **SYNTHESIS OF AN ALPHA-L-FUCOSIDES PRESENTING CHIMERIC GLYCOCLUSTER**
   Son Thai Le, Gyula Batta, Anikó Borbás, Magdolna Csávás
   Annual meeting of the Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences, Mátrafüred, 2018

7. **STRUCTURE-ACTIVITY RELATIONSHIP STUDIES OF LIPOPHILIC TEICOPLANIN PSEUDOAGLYCON DERIVATIVES AS NEW ANTI-INFLUENZA VIRUS AGENTS**
   Zsolt Szűcs, Viktor Kelemen, **Son Thai Le**, Magdolna Csávás, Erzsébet Rőth, Gyula Batta, Evelien Vanderlinden, Anikó Borbás, Lieve Naesens, Pál Herczegh
   Annual meeting of the Working Committee for Carbohydrates, Nucleic Acids and Antibiotics of the Hungarian Academy of Sciences, Mátraháza, 2017