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Abstracts

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BPC1

SYNTHESIS OF SUBPHTHALOCYANINES FOR FORMATION OF SUPRAMOLECULAR COMPLEXES WITH CUCURBITURIL

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Subphthalocyanines (SubPcs) are macrocyclic compounds formed by cyclotrimerization of phthalonitrile precursor with boron trihalide in high boiling solvent. They have non-planar cone-shaped conformation which reduces their aggregation. They can be used as dyes, in nonlinear optics or as photosensitizers in photodynamic therapy in cancer treatment.[1] We wanted to improve water solubility of SubPcs by preparing SubPcs with adamantane substituent on the periphery for supramolecular complexation with cucurbituril (CB). CBs are macromolecules composed of methylene bridged glycoluril monomers with hydrophobic cavity and hydrophilic portals where they can bind appropriate guest molecules.[2]

Two types of SubPc were synthetized, either with hydroxy- or aminoadamantane as peripheral substituents. After cyclotrimerization of 4-iodophthalonitrile, Sonogashira coupling was used to prepare final SubPcs. Both compounds were then titrated with CB[7] and their absorption and fluorescence spectra in water were recorded. Small change in both spectra were observed only in aminoadamantane substituted SubPc after addition of CB[7], which indicates that complexation of SubPc helps monomerization in water.

The study was supported by SVV 260 547 and Czech Science Foundation (20-09212S).

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SYNTHESIS OF LOW-SYMMETRY PHTHALOCYANINES VIA [3+1] INTERMOLECULAR CYCLIZATION REACTION

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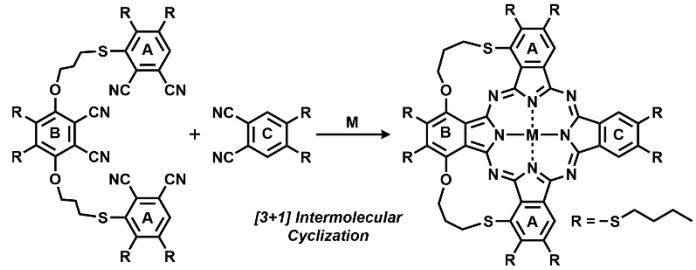
Phthalocyanines (Pc) are a class of π-conjugated heteroaromatic macrocycles, consisting of four isoindole rings linked together by nitrogen bridges. Upon introducing asymmetry, the molecular structure gets perturbated electronically allowing a fine-tuning of their physical properties. However, the chemistry of structurally modified low-symmetric phthalocyanine has received mediocre attention than regular Pc's with D_{4h} symmetry.[1]



Controlled formation of target Pc with a minimal amount of side products could be achieved by a [3 + 1] approach *i.e,* a base-promoted condensation of pre-linked trisphthalonitrile (ABA-trimer) and a free phthalonitrile (C) in the presence of a metal template (M).[2] We have successfully synthesised the subunit B of ABA-trimer with *n*-butylthio linkers at the *β*-position and propoxy linkers at the *α*-position. Correspondingly, the propoxy linkers at the *α*-position of subunit B are connected to the *α*-position of phthalonitrile A, via a sulphur atom constituting the targetted trimer. Moreover, the pre-connected ABA-trimer and free phthaonitrile C can be appropriately chosen to generate exotic phthalocyanine derivatives for varied applications.

This work was supported by EFSA-CDN project (reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by the European Union.

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COMPLEXATION METHOD AS A USEFUL TOOL IN SILICON(IV) TETRAPYRAZINOPORPHYRAZINES SYNTHESIS

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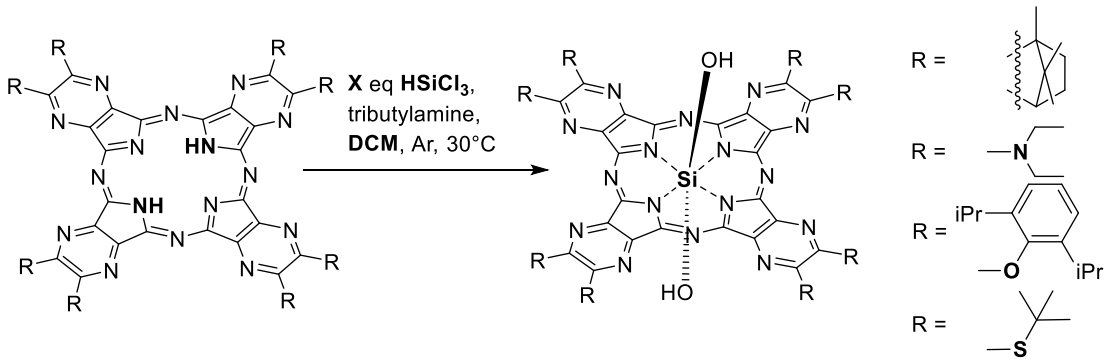
Phthalocyanine dyes are known to be succesfully used in medicinal fields due to their exaptional photophysical and photochemical propesties (*e.g.* singlet oxygen and fluorescence quantum yield production).[1] Their silicon complexes provide one additional adventious attribute represented by axial bonds priventing these flat molecules from aggregation; typical though undesirable phenomen.[2] So far their aza-analogues from family of tetrapyrazinoporphyrazines were not described in detail. Therefore, the aim of this study was to take closer look at the preparation of these derivatives focusing on the conditions of the complexation method of the synthesis and the influence of the peripheral substituent character on the reaction progress.



The study was supported by Charles University (PRIMUS/20/SCI/013; SVV 260 547) and Czech Science Foundation (21-14919J).

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BPC4

FUNCTIONALIZED GLASS SURFACE AS TEMPLATE FOR CERAMIDES ANCHORING

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Skin, the biggest organ in the human body, provides protection against excessive water loss and hampers the entrance of undesired substances.[1] Skin's outermost layer, the stratum corneum (SC), holds the principal skin barrier. Human SC consists of flattened dead cells known as corneocytes, that are embedded in a hydrophobic lipid matrix. Ceramides anchored on the corneocytes surface are forming the so-called "corneocyte lipid envelope" (CLE)[2]. Most research strategies to mimic the SC function, are considering only the lipidic matrix. In our attempt to create an SC alternative model which would incorporate CLE ''mimicking'' entities together with the lipidic matrix, we combine organic synthesis with chemical engineering. The project is divided into two synthetic parts. In the first route that we have already developed, the synthesis of ω-activated ceramide derivatives, which possess a protecting group on their polar head, is described. Thus, the second part consists of the glass surface modification for the selective tethering of the activated ceramides. This model will be further used for the investigation of the putative scaffolding role for the peculiar CLE structure in skin barrier function.

The study was supported by GAUK 262821 and GACR 22-20839K

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BPC5

SYNTHESIS OF MODIFIED CERAMIDE-COATED GOLD NANOPARTICLES TO STUDY SKIN BARRIER ARRANGEMENT

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Ceramides (Cer), essential lipids for skin barrier function, are one of the main components of the stratum corneum (SC) extracellular matrix where they make up around half of the lipids by weight. Apart from free lipids, Cer also covalently anchored to the surface of corneocytes forming a corneocyte lipid envelope, a structure required for the lamellar arrangement of free lipids in SC [1]. In this study, we synthesized a thiol-terminated Cer [2] attached to gold nanoparticles (GNPs) to simulate the corneocyte lipid envelope in SC. The resulting coated GNPs were purified and characterized by UV-visible spectroscopy, Zeta sizer, and Raman spectroscopy.

Modified Cer was prepared by an attachment of a 3-sulfanylpropionic acid linker to an ω-hydroxyl group followed by self-assembly with GNPs in different ratios in THF as solvent. Modified GNPs showed a high level of particle size uniformity, and the Cer attachment prevented an aggregation. The UV-Vis spectra showed a peak around 570 nm which is in good agreement with the size result and confirmed the attachment of Cer to GNPs. In the future, Cer-coated GNPs will be used in model lipid membranes as a scaffold for the orientation and arrangement of free lipids and to study the effect of GNPs on the lipid matrix nanostructure and permeability. The importance of this study is to shed more light on lipid organization in SC and to improve current models used for SC investigation.

The study was supported by GAUK (No. 348222).

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BPC6

METAL CATION FLUORESCENCE SENSORS BASED ON AXIAL AZA-CROWN LIGANDS

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Phthalocyanines and their analogues have interesting and highly applicative photophysical properties, whose switching is controlled by photo-induced electron transfer (PET)[1] and are investigated to be used in photodynamic therapy, fluorescence sensing, and as logic gates.[2]

This work aimed to prepare fluorescence sensors for alkali and alkaline earth metal cations by designing subphthalocyanines and their pyrazine analogues with sensitive axial aza-crown ligands (Fig. 1). Water solubility was achieved using nanoparticles as delivery systems.

The synthetic pathway included the multi-step synthesis of the axial ligands, and synthesis of macrocycles coordinating BCl, after which the metal ion-sensitive ligands were attached to the axial positions. The switching properties were studied by titration with various metal cations and their binding constants were determined. The selectivity and sensitivity towards metal cations, the influence of counter anion towards sensitivity, stability, stoichiometry of interaction and pH dependence in aqueous medium of the prepared macrocyclic sensors, were studied.

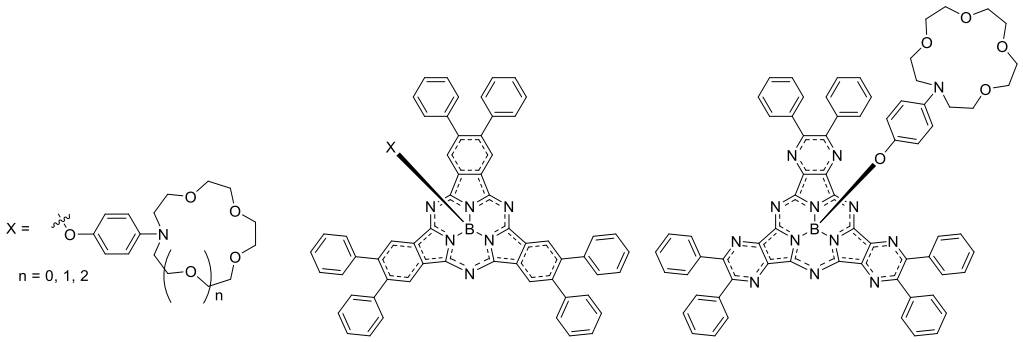

Fig. 1: Subphthalocyanines and subazaphthalocyanine prepared and studied in the project.

The study was supported by Czech Science Foundation (project No. 21-14919J) and Charles University (SVV 260 547).

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DIENE-TRANSMISSIVE DIELS-ALDER REACTIONS OF ELECTRON-POOR [3]DENDRALENES

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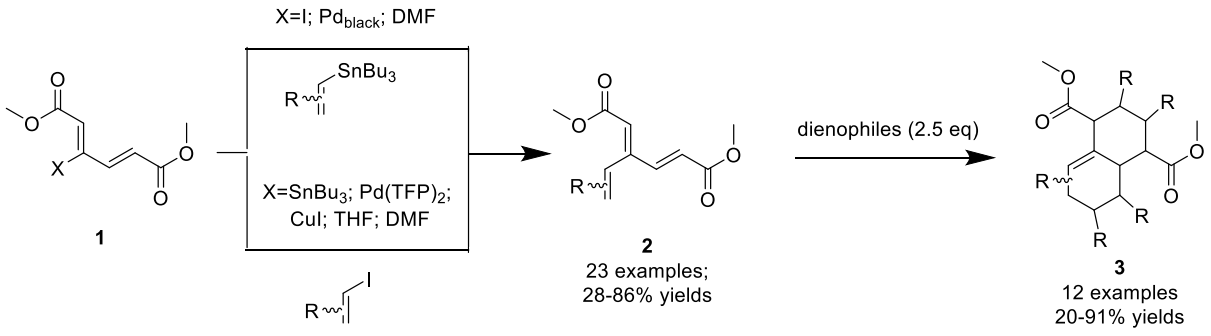
Dendralenes[1] are a group of cross-conjugated olefins, which have enjoyed renaissance over the past few years thanks to the work of Sherburn et al.[2] Unlike other conjugated olefins, dendralenes are not limited to a single Diels-Alder (DA) cycloaddition. Cross-conjugation allows dendralenes to undergo multiple DA reactions in diene-transmissive (DT) manner, where one cycloaddition furnishes a new conjugated diene subunit, which than can undergo another DA reaction. Thus, dendralenes can provide complex, polycyclic frameworks in one step. Our aim was to prepare a series of novel, electron-poor dendralenes (in contrast to generally electron-rich dendralenes, which are more common) and probe their reactivity in (DT)DA cycloadditions. The synthesis, was achieved in good yields with two variations of Stille coupling (Scheme 1)[3], providing us with a library of electronpoor [3]dendralenes **2**. Next, DTDAs, were accomplished with mostly high yields of DTDA products **3**. Unfortunately, our electron-poor dendralenes showed unusual selectivity for electron-poor dienophiles. This fact currently limits their further synthetic utilization. However, it is also an interesting example of atypical diene/dienophile pairing (poor-poor), which is in partial contrast with the general knowledge of DA reactions.

This project is supported by the EFSA-CDN project (Reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-funded by the European Union.

Scheme 1. General preparation and reactivity of dendralenes



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TOWARDS NATURAL PRODUCTS AND COMPLEX MOLECULES VIA HETEROCYCLIC DENDRALENES

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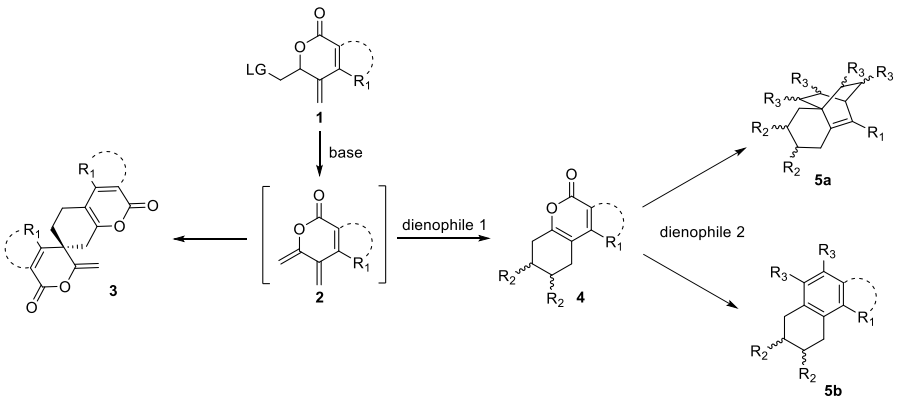
General structure of lactone **1**[1] (Scheme 1), binding an appropriate leaving group (e.g. iodide or mesylate), serves under basic conditions as a precursor of non-isolable and highly reactive exocyclic dienes or [3] and [4] dendralenes **2** (depending on side cyclic or acyclic chain R_1). Such intermediates act as substrates of diene-transmissive Diels-Alder cycloadditions. Depending on the presence of a dienophile in the reaction mixture, spirocyclic bislactone **3** or substituted lactone **4 (**sharing structural similarity with a number of biologically active natural products)[2,3] can be isolated. Formation of a new diene moiety in the molecule **4** allows another Diels-Alder cycloaddition to get a more complex structures **5a** or **5b**, depending on reaction conditions.

Scheme 1



The study was supported by Charles University (SVV reg. No. 260 547 and GAUK reg. No. 205007), "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/00169359) and Czech Science Foundation (reg. No. 22-19209S).

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GOLD(I) CATALYSIS & ORGANOCATALYSIS: DO THEY MATCH?

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Both gold catalysis and organocatalysis are useful tools for synthesis of various naturally occurring compounds. To date, only a few examples of combining these two methods have been described[1]. Based on our previous research[2] and the interest of the prof. Christmann group in organocatalytical reactions[3], new attempts were tried to merge gold(I) catalysis and organocatalysis to obtain optically pure heterocycles. The preliminary results of this new methodology will be discussed.

The study was supported by EFSA-CDN project (reg. No. CZ.02.1.01/0.0/0.0/16_019/0000841) co-founded by ERDF

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BPC10

[3]DENDRALENES AS ACCEPTORS FOR MICHAEL AND ANTI-MICHAEL ADDITIONS

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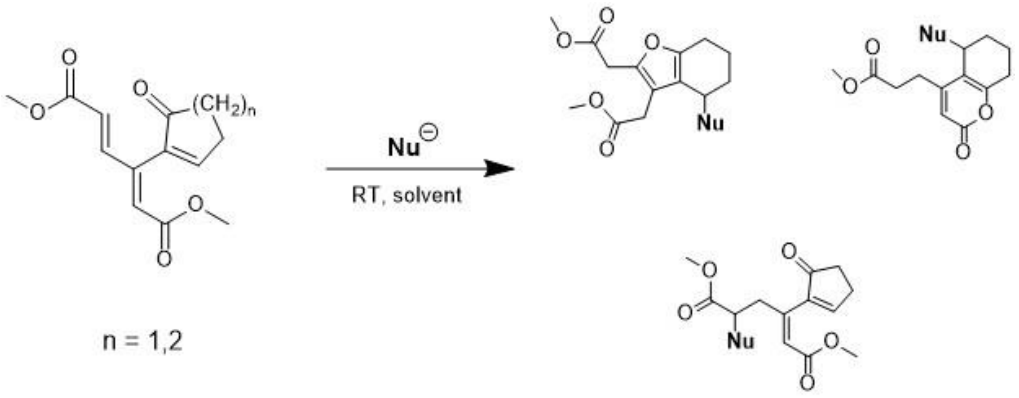
Dendralenes are acyclic cross-conjugated polyenes with an interesting, as yet unexamined reactivity and high potential for further synthetic applications.1 Our research group developed a novel synthesis of variously substituted electron-poor [3]dendralenes with a distinct dissonant character, and discovered an unexpected behaviour of these compounds upon nucleophilic attack. We assume that elimination of the dissonant nature was the driving force of these transformations. Based on the preliminary results, we further focused on different versions of Michael additions to dendralenic structures. In some cases, anti-Michael additions also occurred. Using mild conditions and different combinations of nucleophiles and dendralenes, we observed cyclizations and/or simple additions.



The study was supported by Charles University (SVV 260 547, GAUK 362421) and Czech Science Foundation (Project No. 22-19209S).

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PROGRESS IN TOTAL SYNTHESIS OF NOSTOTREBIN 6

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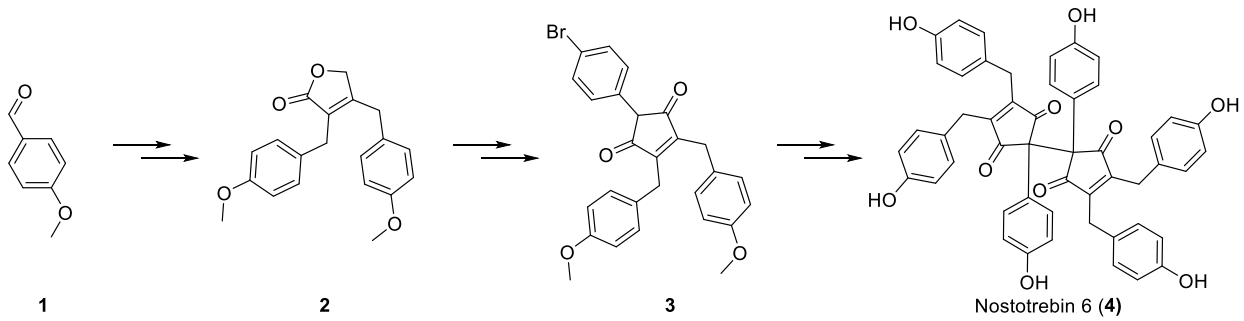
Nostotrebin 6 is a polyphenolic compound isolated from the cyanobacterial strain Nostoc sp. Its skeleton is composed of fully substituted 2,2'-bis(cyclopent-4-en-1,3-dione). It has various biological activities such as antimicrobial, antibacterial, and antifungal activity.1

The aim of this work is to develop and optimize the synthesis of nostotrebin 6 and its analogues, and later to test their biological activities. In the last years, our research group has been trying to synthesize nostotrebin 6, but previous procedures did not lead to desired results. Recently, we made progress in the synthesis of nostotrebin 6 as analogs with different functional groups were prepared. Therefore, we believe that in a few more steps the final compound of nostotrebin 6 could be synthetized.

Scheme 1. – preparation of nostotrebin 6



This work was supported by Charles University (SVV 260547, GAUK 332122) and Czech Science Foundation (Project No. 22-19209S).

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DESIGN, SYNTHESIS, AND PRELIMINARY RESULTS OF BIOLOGICAL EVALUATION OF NEW BORONIC ACIDS DERIVATIVES

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The presented compounds follow up the research of a previously studied series of hybrid compounds, that exerted high *in vitro* antimycobacterial activity. They were designed as hybrids combining pyrazinamide and *para*-aminosalicylic acid.[1] The current study is focused on the combination of pyrazinamide with 4-aminophenylboronic acid, a bioisostere of *para*-aminobenzoic acid, which is a crucial precursor in the folate pathway. Bioisosteric replacement of the carboxylic group with boronic acid could afford the ability of the compounds to form a reversible covalent bond toward a potential biological target.

The compounds were synthesized by condensation of 4-aminophenylboronic acid pinacol ester with variously substituted heteroaromatic acids that underwent the previous activation. The subsequent deprotection of boronic acid pinacol ester proceeded smoothly to afford novel compounds.[2]

The synthesized compounds were subjected to biological *in vitro* screening against a panel of clinically important fungi and bacteria, and Hep G2, and PC-3 cancer cell lines. Some of the compounds showed promising antiproliferative activity.

The study was supported by Charles University project SVV 260 547 (Czech Republic).

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NOVEL QUINAZOLONES AS POTENTIAL ANTI-STAPHYLOCOCCAL AGENTS

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Staphylococcs aureus (*SA*) is the leading cause of life-threatening infections.[1] One of the solutions to control *SA* infections is to develop novel agents preferably with novel mechanism of action that are effective against both drug-sensitive and drug-resistant strains. Quinazolone represents a very important scaffold for various biological interactions. Structure-activity-relationships of antistaphylococcal quinazolones (AQs) are already established in the literature, refer to Figure 1. Molecular targets for AQs include penicillin binding protein (PBP), DNA topoisomerase, and lactate dehydrogenase (LDH). In this work, we combined our long-term knowledge on antimicrobials and what is reported in the literature with the help of in silico docking in order to design novel, potentially active AQs targeting PBP 2a. Results of biologi-cal evaluations will be discussed during the presentation.

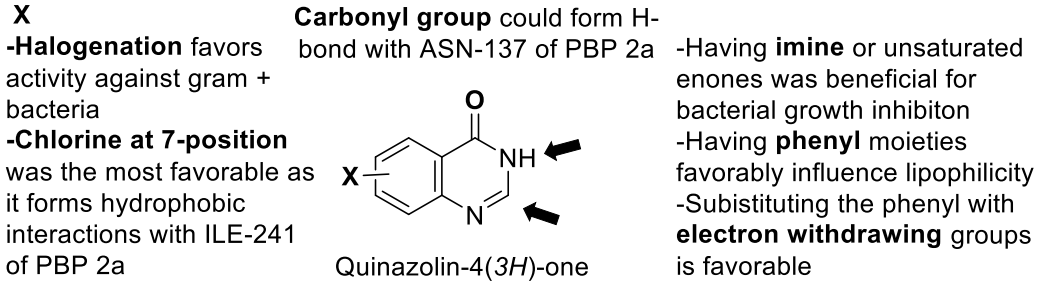

Figure 1. SAR of antistaphylococcal quinazolones based on literature search.

The study was supported by EFSA-CDN, grant number CZ.02.1.01/0.0/0.0/16_019/0000841, co-funded by ERDF; and by the Ministry of Health of the Czech Republic, grant nr. NU21-05-00482.

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BPC14

DYE-FUNCTIONALIZED PEPTIDE SYNTHESIS AND THEIR INTERACTIONS WITH BETA-AMYLOID PEPTIDE

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Alzheimer's disease is a neurodegenerative disease that leads to loss of neurons and synapses in the cerebral cortex. Among all neurodegenerative diseases, AD is the most prevalent, accounting for more than 60% cases of dementia[1]. It is a conformational disease where the misfolding of protein tau and amyloid beta leads to the emergence of neurofibrillary tangles and the build-up of plaques resulting in damage and death of neurons. Such brain changes are not visible instantly on patients behaviour, sometimes it takes up to 20 years to develop visible symptoms. To date, there are no available treatments to reverse AD progression, and only neuroprotective agents may slow down disease progression. After diagnosis usual life expectancy is estimated up to 10 years[2].

For better understanding of the process leading to the fibrillation we decided to design and synthesize four different short peptides linked to environment sensitive fluorescent dye that could give us an insight into the interaction with beta amyloid peptide.

The study was supported by the project "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935).

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BPC15

COMPARING DIFFERENT APPROACHES TO ERADICATE STAPHYLOCOCCAL BIOFILMS FORMED ON PIG SKIN MODEL

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The antibiotic tolerance of bacterial biofilms has reduced effectiveness of antibiotics commonly used against wound and skin infections caused by *Staphylococcus aureus* (SA). [1] Although the search for new antibiotic compounds continues, standardized ways to evaluate the efficacy of antimicrobial agent against skin biofilms are not available. While *in vitro* methods are common routine, *ex vivo* testing using excised animal skin as a substrate would provide more accurate protocols. [2] Sterilized samples of pig skin were exposed to SA culture and biofilms were form for 48 hrs. Different approaches of a treatment were then applied. Chlorhexidine, water, and antimicrobial cream were used to eradicate formed biofilms. Compounds were used as a liquid agent and on a cloth wipe. Pressure of the wiping and a time of exposure of each compound were monitored. Surviving cells were then recultivated and the cell count was compared with untreated control. Eradication of planktonic culture was more prominent compared to biofilm. Wiping was more effective comparing to exposure to liquid agent.

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PROTEOCHEMOMETRIC MODELLING OF SLC5 TRANSPORTERS

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Solute carrier transporters (SLC) are one of the largest superfamilies of membrane proteins facilitating the transport of organic and inorganic molecules. The impaired function of numerous SLCs has been linked to severe defects like diabetes mellitus (DM), or CNS disorders, making SLCs promising targets for new drugs. In the case of the SLC5 family, the SLC5A2 (sodium glucose cotransporter 2, SGLT-2) already proved a valuable target for the treatment of DM, with the gliflozins being widely used marketed drugs.

Quantitative structure-activity relationship (QSAR) modelling as well as machine learning are well-established tools in computational drug design. To overcome the usual QSAR pitfalls due to focusing solely on the ligands, proteochemometrics (PCM) was introduced combining information from both ligands and targets for deriving structure-activity models.[1]

We downloaded all ligands available in ChEMBL30 associated with twelve distinct human, rat, and mouse SLC5 transporters. Focusing only on IC_{50} and EC_{50} values led to a data set of 2314 datapoints, representing 1736 unique molecules and activities against 6 transporters. PCM modelling yielded models with cross-validation scores (Q^2) in the range of 0.71–0.80, depending on the algorithm and the descriptors used. Variable importance analysis revealed a set of amino acids contributing to transporter selectivity, some already confirmed by results from mutational analyses. The models can be used to predict the activity and selectivity of potential inhibitors, or effects of point mutations in the SLC5 family transporters.

The study was supported by the project "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935).

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SYNTHESIS OF FURAN DERIVATIVES, MICROSCALE THERMOPHORESIS, AND CRYSTALLOGRAPHIC STUDIES

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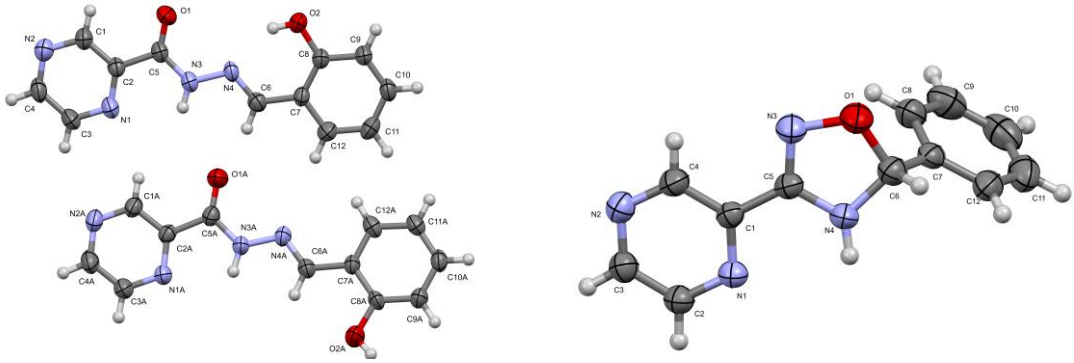
We present synthesis of substituted 5-(3-cyano-5-hydroxyphenyl)furan-2-esters using suzuki coupling reactions as an active molecules against mycobacterial tuberculosis (Mtb). Microscale thermophoresis (MST) analysis, a method to determine the K_d or EC_{50} of ligand-protein interactions of active small molecules on enzymes/proetins. Crystallographic studies of single crystals of small molecules on X-ray diffractometer to define the structural properties of small molecules in unit cell; methods of protein crystallisation techqniques such as hang drop-method.



The study was supported by the project "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935); Pallabothula, V. S. K. acknowledge the support by Charles University, project GA UK No. 349721 and project SVV 260 547.

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JOURNEY FROM ANTIMYCOBACTERIAL TO ANTISTAPHYLOCOCCAL ACTIVITIES – HOW TO APPROACH RATIONALLY, WHEN MECHANISM OF ACTION IS UNKNOWN

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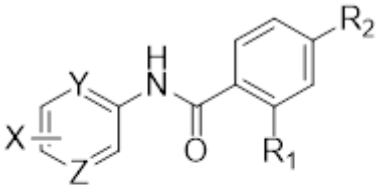
The development of new antibacterial agents evolves rapidly and simultaneously with the advancement of technologies. New antibacterial agents are needed because of the increase in drug resistance. We aim to widen the spectrum of antimycobacterial compounds usually prepared in our group and extend their activity to *Staphylococcus aureus*. The mechanism of action of the chosen compounds[1] (see the structure) is not known, which makes the goal even more challenging.



Y = C or N
Z = C or N
X = Cl
R_1, R_2 = H, OH, OAc

The first step was to synthesize various derivatives, determine those with the best antistaphylococcal activity and evaluate SAR. The series showed significant antimycobacterial activities (MIC = 3.91 μg/ml), but not so high antibacterial activities (MIC = 62.5 μg/ml). The second step is the determination of a specific molecular target by a biochemical approach called 'target fishing'[2] with use of biotin-labeling. After this determination, we can process results *in silico* and modify the design of the compound rationally.

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BPC19

DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF NEW ANTIMICROBIAL COMPOUNDS DERIVED FROM INHIBITORS OF ASPARTATE DECARBOXYLASE

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The aspartate decarboxylase PanD is a key enzyme of the pantothenate pathway, a process responsible for the biosynthesis of Coenzyme A, a cofactor essential for several metabolic processes (Krebs cycle, beta oxidation...). [1] PanD inhibition is linked with reduced bacterial growth and virulence. [1] Previous studies have identified pyrazinoic acid (POA, the active metabolite of first line antitubercular agent pyrazinamide) and its derivative 3-(1-naphthamido) pyrazine-2-carboxylic acid as competitive PanD inhibitors. [2] This work describes *in silico* studies of the interactions between 3-(1-naphthamido) pyrazine-2-carboxylic acid and mycobacterial PanD, the design, chemical synthesis and biological evaluation of more potent mycobacterial PanD inhibitors and explores the extention of PanD inhibition to different structures of bacterial PanDs.

The study was supported by the project of Specific Academic Research (SVV 260 547) and by the project National Institute of virology and bacteriology (Programme EXCELES, ID Project No. LX22NPO5103) - Funded by the European Union - Next Generation EU

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BPC20

SYNTHESIS OF PURINE DERIVATIVES WITH ANTIMYCOBACTERIAL ACTIVITY

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Tuberculosis (TB) is one of the top 10 causes of death worldwide from a single infectious agent. The World Health Organization estimated 10 million new cases and 1.2 million deaths from TB in 2020.[1] Some strains of mycobacteria causing TB show numerous resistances to first-line drugs (isoniazid /INH/ and rifampicin) and to second-line drugs (fluoroquinolones, amikacin, bedaquilin, etc.). The development of new anti-TB drugs with new mechanism of action is necessary to improve TB therapy and to fight against resistant TB as well. We identified compound K1297 with good anti-TB activity with minimum inhibitory concentration MIC_{99} = 4 μM against $H_{37}R_v$ strain (for comparison, MIC_{99} /INH/ = 0.5 μM). The main structural motif of this molecule is purine scaffold, which was modified and functionalized to elucidate the structure-activity relationships (SAR) and to identify derivatives with low toxicity and higher efficiency than the initial hit K1297. The effects of individual structural fragments on *in vitro* antimycobacterial activity, toxicity and selectivity of action have been evaluated. Finally, derivatives with optimized activity/toxicity ratio have been found and their pharmacokinetic profile and *in vivo* efficacy will be evaluated. In the cooperation with foreign collaborators, we have also determined the mechanism of action of these compounds using genome sequencing of the resistant mutants and metabolic radiolabelling experiments.

The study was supported by the project "Grant Schemes at CU" (reg. no. CZ.02.2.69/0.0/0.0/19_073/0016935)

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SYNTHESIS OF PYRIMIDINE DERIVATIVES WITH ANTITUBERCULAR ACTIVITY

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Tuberculosis (TB) is a transmissible infectious disease caused by the intracellular bacteria, *Mycobacterium tuberculosis* (MtB),[1] which is currently one of the top 10 leading causes of death in low and middle-income countries[2]. M. tuberculosis can quickly develop resistance against anti-TB regimens, and if not cured adequately, it can evolve into MDR-TB (multidrug resistant TB) and XDR-TB (extensive-drug resistant TB).[1]

We screened our in-house library of small molecules for their potential antimycobacterial properties identifying compound K1827 with excellent antimycobacterial in vitro activity against M. Kansasii (MIC99 = 0.25 μM) and moderate activity against M. tuberculosis H37Rv (MIC99 = 32 - 64 μM). This core scaffold of K1827 is pyrimidine that was functionalized to develop derivatives with higher activity against M. tuberculosis, better safety profile, and to determine the structure-activity relationships in the series. The effect of individual structural fragments on in vitro antimycobacterial activity, toxicity and selectivity of action have been evaluated and will be discussed within our contribution.

The study was supported and by the Grant Agency of Charles University (project No. 392822).

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SYNTHESIS OF RESVERATROL DERIVATIVES AS POTENTIAL INHIBITORS OF TOPOISOMERASE II BETA

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Anthracyclines (ANT) such as daunorubicin or doxorubicin are used as anti-cancer drugs. ANTs have a strong anti-tumor effect. Unfortunately, a limiting factor of ANT usage in clinical practice is their serious chromic cardiotoxicity. This side effect can lead to heart failure via irreversible damage of heart muscle cells. Only drug against this side effect used in therapy is dexrazoxane (DEX).[1]

Recent research or us and others showed that inhibition of topoisomerase II beta (TOP2B) in heart is the actual mechanism of action of DEX.[2] The aim of this work was to explore the cardioprotective potency of other and structurally distinct topoisomerase II inhibitor resveratrol (RES).[3] Resorcinol part in molecule of RES mimics one of piperazine-2,6-dione ring in DEX structure. Thus, derivatives of RES with preserved resorcinol part and with modified phenol part have been prepared. Furthermore, analogs of RES with amide bond instead of double bond were prepared. All the prepared substances are being evaluated for their TOP2B inhibitory activity and in vitro cardioprotective activity.

The study was supported by GAUK no. 361422

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CHEMICAL SHIFT PREDICTIONS IN INTRINSICALLY DISORDERED PROTEINS: MACHINE LEARNING AND QUANTUM CALCULATIONS

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Intrinsically disordered proteins (IDPs) compose nearly 32% of the human proteome and are involved in many biological processes and disorders. (1) IDPs are difficult to measure structurally, so ensemble conformations are used to assess them. Several prediction tools (neural network, ProCS-15, Sparta+, ShiftX) and quantum (DFT) simulations are used to generate these ensembles. DFT calculations were done using fragmentation as described in our previous works. (2) In this investigation, two IDPs (human tyrosine hydroxylase 1, hTH1 and MAP protein, MAP2C) were simulated with modifications (phosphorylation and artificial secondary structures) to understand the impact of phosphorylation. Several ensembles were generated with clustering algorithms and dimensional reduction of φ/ψ angles. Results show clustering algorithms based on RMSD are inadequate, while φ/ψ dimensional reduction shows improvement. Sparta+ and ShiftX had the best overall performance, while ProCS-15 and Quantum DFT performed best at interpreting phosphorylation. Prosecco provided the best agreement with experimental data, though it is severely limited in the output data. Ensemble generation is critical for studying IDP-related disorders, and current medications and treatments benefit from accurate MD simulations. *Research was financed by the Czech Science Foundation Grant 19-14886Y; Computational resources by the project "e-Infrastruktura CZ" (e-INFRA CZ ID:90140 and e-INFRA CZ LM2018140) supported by the Ministry of Education, Youth and Sports of the Czech Republic.*

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ENSEMBLE BASED CALCULATION OF NMR SPIN-SPIN COUPLINGS IN PROTEINS

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To gain a better understanding of protein functions at the molecular level, it is essential to understand their three-dimensional structure. Solution Nuclear Magnetic Resonance (NMR) spectroscopy is an ideal technique to probe protein dynamics and structure, and the in-silico prediction and modeling of NMR parameters, including spin-spin (J) couplings, has become an invaluable tool for creating structural ensembles to match experimental NMR observables. Calculations of J-couplings at the quantum mechanics level is hampered by the large system size as well as by the large number of conformations sampled by proteins over time.[1] To address this problem, this project aims to develop a protocol for the design of structural ensembles that lead to accurate and efficient calculations of J-couplings in proteins. For this purpose, we combine molecular dynamics simulations with the UMAP dimensional reduction and K-means clustering techniques as well as with protein fragmentation by the adjustable density matrix assembler and density functional methods. In order to validate our methodology, we use the structured proteins Gb3 and Ubiquitine along with an example of an intrinsically disordered protein fragment Tau(210-240). In our contribution, we will illustrate the performance of the computational approach by validating the computed J-couplings against experimental NMR data and estimates made using empirically parametrized Karplus equations.

This research is supported by the Charles University Grant Agency (GA UK). The computational resources necessary for this project are secured from MetaCentrum and supported by the Ministry of Education, Youth and Sports of the Czech Republic through the e-INFRA CZ(ID:90140).

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AGONIST AND ANTAGONIST AFFECT CONFORMATIONAL CHANGES IN THE TGR5 BINDING CAVITY

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The interaction between ligands and proteins can trigger conformational changes in the ligand binding domain (LBD) of the proteins. The publication of the cryo-electron microscopy structure of TGR5 provided an opportunity to find out the difference in LBD between TGR5 INT-777 (agonist) and Corydaline (antagonist)[1,2]. To address this issue, molecular docking, and molecular dynamic (MD) simulations were carried out. Both ligands form hydrogen bonds with Tyr240 which is crucial in TGR5 activation. Interestingly, the 50 ns MD simulation revealed that Corydaline's hydrogen bond with Tyr240 had been disrupted, pointing to a conformational shift in the TGR5 LBD. This alteration could be crucial information for understanding how ligand interactions affect the TGR5 LBD. In conclusion, an antagonist ligand induces conformational changes in the TGR5 LBD and this knowledge contributes to further study in the discovery of novel agonist and antagonist ligands.

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