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# Abstracts

*Section 5 - Bioorganic and Pharmaceutical Chemistry*

# QUO VADIS, ORGANOCATALYSIS?

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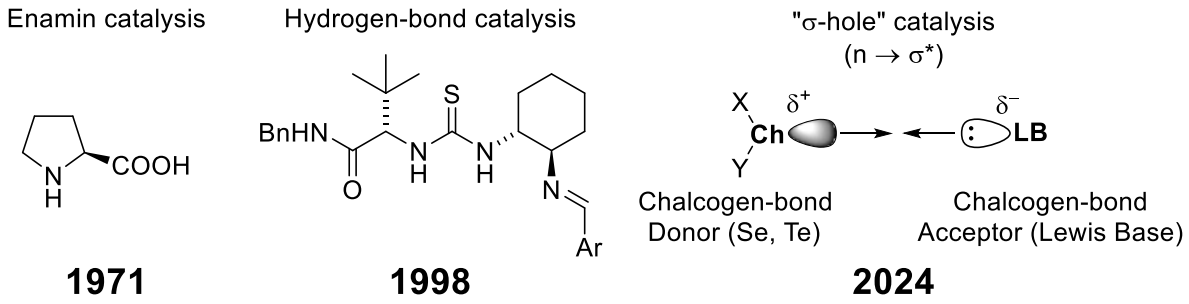
In the last century, metal catalysis dominated the field of synthetic chemistry but the general demand for more user-, and environmentally friendly, air/moister stable, and easily available catalysts ignited an interest in **no-metal-containing** catalytic systems.[1] The small-organic-molecule-based catalysts i.e. ***organocatalysts*** provide an advantage in the ability to **selectively control reaction events** and exhibit good functional group tolerance altogether with low sensitivity towards air and moister in comparison to their metallic colleagues.

The interactions between substrate and organocatalyst may have a **covalent** as well as a **non-covalent character** and often intertwine each other. The phenomenon of non-covalent catalysis has undoubtedly been dominated by hydrogen bonding. However, less explored **sigma-hole-based interactions** such as halogen bond or **chalcogen bond** broaden the working area for synthetic chemists and especially for our research team.

Organocatalysis passed an impressive journey but has left unexplored turns behind. Its journey and highlighted turns shall be discussed in the frame of this talk.

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**BPC1**

# PYRAZINAMIDE AND 1,2,3-TRIAZOLE: A PROMISING RELATIONSHIP

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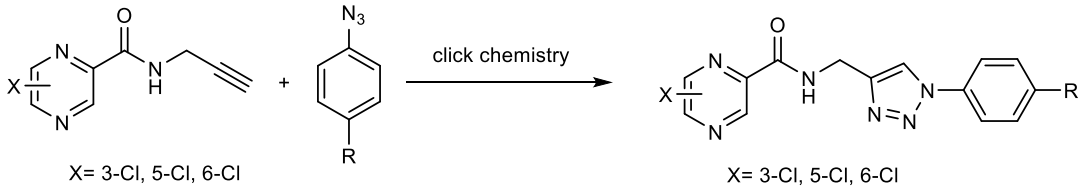
Pyrazinamide, a key antituberculotic agent, has been part of the 1st line treatment regimen of tuberculosis ever since its introduction in 1950.[1] Although tuberculosis can be treated, the course is lengthy (up to 6 months) and often complicated by antibacterial resistance.[1] To discover more potent antituberculotics, this work explores the combination of pyrazinamide with 1,2,3-triazole, a linker thoroughly reported in literature as part of the structure of many antimycobacterial agents.[2] The backbone of the synthesis of 1,2,3-triazole containing derivatives is so called "click chemistry" – a reaction combining two molecular building blocks as easily as a key inserted in its lock.[3] The specific click reaction consists of combining starting materials containing terminal alkynes with beforehand synthetized aromatic azides.[3] The reaction is catalysed by Cu(I), obtained by exposing a source of Cu (II) to a reducing agent, and results in dipolar cyclo addition of azides onto said alkynes.3 This reaction has high yields, an easy workup, straightforward purification, and obtained compounds present interesting antimycobacterial activity (*M.Tb.* H37Ra MIC =15,625 μg.mL$^{-1}$, *M.Tb.* H37Rv MIC = 6,25 μg.mL$^{-1}$, if R= 4-OH and X= 5-Cl).




*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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**BPC2**

# THE EFFECT OF ACYLCERAMIDES IMMOBILIZED ON GOLD NANOPARTICLES ON SKIN BARRIER LIPID ARRANGEMENT

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Acylceramides are vital representatives of ceramides (Cer) in human stratum corneum (SC) extracellular matrix, where they help maintaining the skin barrier function. Beyond their presence as free lipids, acylceramides are also covalently anchored to the surface of corneocytes forming a corneocyte lipid envelope, a structure presumably required for the proper arrangement of free lipids in SC[1], however the exact role of this envelope remains unclear.

The aim of this project was to shed more light on lipid organization in SC, in particular, to synthesize thiol terminated Cer derivatives[2] and to attach them to gold nanoparticles (GNPs), mimicking the structure and architecture of the corneocyte lipid envelope in the SC. The synthesis of modified Cer involved the attachment of a 3-mercaptopropionic acid linker to the ω-hydroxyl group of a Cer precursor, followed by self-assembly with GNPs.

The resulting coated GNPs were characterized using UV-visible spectroscopy, Raman spectroscopy, X-ray diffraction, $^{1}$H-NMR and dynamic light scattering. The UV-Vis spectra showed an increasing trend in the intensity of peak around 570 nm which is characteristic for the arrangement of a Cer polar part around GNPs.

Modified GNPs showed a high level of particle size uniformity, and the Cer attachment prevented an aggregation. In the future, Cer-coated GNPs will be used in model lipid films 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 study was supported by GAUK (No. 348222).*

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**BPC3**

# MONTANINE-TYPE DERIVATIVES: POTENTIAL ADJUVANTS IN ANTI-STAPHYLOCOCCAL THERAPY

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A loss of control over antibiotic-resistant pathogens has become a global issue reflected in complicated treatment, health costs and high mortality[1]. It may be time to look back at herbal remedies that have been used for their antimicrobial effects by different cultures for centuries[2]. In our project, a collection of semi-synthetically achieved montanine-type derivatives of alkaloids from *Amaryllidaceae* family was subjected to the antibacterial screening. 2 representants revealed encouraging activity against collection strains and clinical isolates predominantly from the *Staphylococci* genus (7.8-62.5 μM) and low *in vitro* and *in vivo* toxicity. With such premise, we hypothesize that our derivatives can be used as adjuvant molecules to commercial antibacterial drugs and potentially restore, conserve, or synergize with them, lower their efficient concentration, and prevent the spread of resistance. Therefore, a derivative with more favorable properties was employed in subsequent synergy study to explore its mutual effect in combination with 6 antibiotics with different mechanism of action. In all 6 combinations, no antagonistic effect was registered. With 4 antibiotics, our candidate acted synergically. To conclude, based on the observed antibacterial and biological attributes, our derivative can be considered a valid adjuvant molecule to support selected antibiotics.

*The study was supported by SVV Project No. 260 663 and by Ministry of Health of the Czech Republic, grant nr. NU21-05-00482.*

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**BPC4**

# ENSEMBLE BASED CALCULATION OF NMR SPIN-SPIN COUPLINGS IN PROTEIN

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To acquire a better understanding of how proteins work at the molecular level, it is crucial to understand their structural characteristics. Various techniques have been developed to achieve this, such as computer-based methods for calculating and predicting NMR measurements including the he spin-spin coupling constants(SSCCs). Multi-scale calculations combining molecular dynamics simulations with DFT calculations have become particularly feasible upon the emergence of fragmentation techniques and many successful studies for structured proteins appeared since then. On the contrary, examples of applications for IDPs remain virtually non-existent due to prohibitive computational demands caused by the use of extensive sequential structural ensembles. To alleviate the problem, we pursue the design of smaller size ensembles through the dimensionality reduction of the IDP conformational landscape and clustering of similar conformations. In our contribution, we will show the performance of the workflow employing the t-SNE and hierarchical clustering for the structured proteins GB3 and Ubiquitine and compare it to the disordered protein fragment Tau(210-240). Ensembles will be validated by comparing predicted SSCCs using Karplus equations and NMR data.

*This research is supported by the Charles University Grant Agency (GA UK).*

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**BPC5**

# DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF PYRAZINAMIDE DERIVATIVES AND THEIR STRUCTURE ACTIVE RELATIONSHIP

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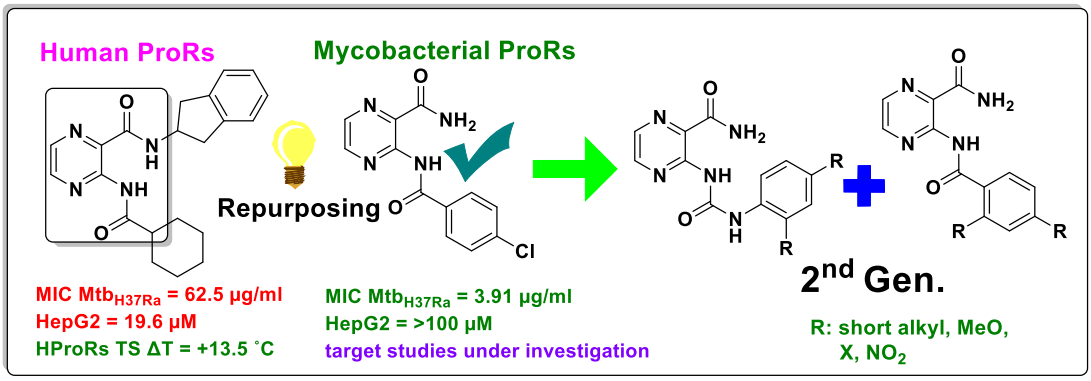
Our research focuses on mainly on synthesis of novel antimycobacterial derivatives using a highly specific target-oriented approach. Initially we have synthesised and published novel antimycobacterial derivatives of 3-amidopyrazine-2-carboxamide; potentially targeting mycobacterial prolyl t-RNA synthetase (mtProRs).[1] For this study, we started with structural modification of a human proly-tRNA synthetase (hProRS) inhibitor [2] to produce 1st generation of antimycobacterial compounds. Antimycobacterial evaluation MIC ranging from 1.92 to 15.625 µg/mL with minimal to no cytotoxicity for HepG2 ($IC_{50}$ > 100 µM).[1] From these results, we have developed an extended series with urea linking scaffold and another series of disubstituted amidic bridge derivatives. However, the urea derived compounds have huge limitations due to structural configuration for the activities, on the contrary the disubstituted amidic derivatives were active and their results were promising. As a complimentary study, we have produced cyclic derivatives of pyrazine-oxazinone derivatives and biologically evaluated.




*The study was supported by Charles University, project GA UK No. 349721 and project SVV 260 666.*

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**BPC6**

# AN AZAPHTHALOCYANINE DERIVATIVE FOR TERNARY COMPLEXES FACILITATED BY CUCURBIT[8]URIL

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Cucurbit[*n*]urils, CB[*n*], are widely used water soluble macrocyclic hosts. They can bind various types of guests (metallocene derivatives, adamantane derivatives, pyridinium derivatives); however, their prototypical guests are endowed with ammonium substituents.[1,2] Interestingly, the size of CB[8] cavity allows binding of two identical or different guests at the same time, resulting in formation of binary (1:2) or ternary (1:1:1) complexes, respectively. For a successful formation of a ternary complex, an electron deficient and an electron rich arene are required.[3] A very common electron deficient compound used for this purpose is a viologen cation. In our case, viologen is attached to an azaphthalocyanine (AzaPc). AzaPcs are used as photosensitizers for photodynamic therapy or as fluorescence sensors. By formation of ternary complexes, we plan to study possibilities of influencing their photophysical properties, such as quenching their fluorescence by photoinduced electron transfer (PET).[4] In our studies the PET donors (such as ferrocene) are covalently bound to an electron rich CB[8] guest based on the structure of 2,6-naphthalenediol. In this lecture, the synthesis of our target compounds and photophysical measurements will be discussed.

*The study was supported by Charles University Grant Agency (reg. No. 170223).*

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**BPC7**

# SELECTIVE BUTYRYLCHOLINESTERASE INHIBITORS STRUCTURALLY INSPIRED BY CARLTONINE-TYPE ALKALOIDS - DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION

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Butyrylcholinesterase (BChE) plays a pivotal role in the pathophysiology and progression of Alzheimer's disease (AD), a devastating neurodegenerative condition affecting millions worldwide.[1] In advanced stages of AD, acetylcholinesterase levels decrease by over 90%, while BChE levels rise to 165% of the normal level, suggesting a compensatory role.[2] In our efforts to develop novel drug candidates for AD, we focused on natural template structures, particularly Amaryllidaceae alkaloids carltonine A and B, known for their high human BChE (*h*BChE) selectivity. This study involves the design, synthesis, and *in vitro* evaluation of compounds exhibiting *h*BChE inhibitory potential, ranging from micromolar to low nanomolar scales. Compounds with inhibition below 100 nM underwent theoretical validation of central nervous system penetration using the BBB score algorithm and confirmed through *in vitro* PAMPA-assay. Safety profiles were assessed in human neuroblastoma and hepatocellular carcinoma cell lines. Notably, compounds **87** (*h*BChE $IC_{50}$ = 3.8 ± 0.2 nM) and **88** (*h*BChE $IC_{50}$ = 5.7 ± 1.5 nM) emerged as top-level BChE inhibitors. A crystallographic study was conducted to elucidate the binding mode of the most potent inhibitor **87**, revealing crucial interactions between **87** and the active site of *h*BChE.

*The study was supported by Charles University SVV 260 662.*

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**BPC8**

# *N*-BENZYLPIPERIDINE-BASED SCHIFF BASES ARE CHOLINESTERASE INHIBITORS – DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION

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The chemical structure of donepezil, a clinically used acetylcholinesterase (AChE) inhibitor for Alzheimer's disease (AD) treatment, includes an *N*-benzylpiperidine component (*N*-BP) that is important for its interaction with the peripheral anionic site within the AChE pocket.[1]

With the urgent need for more effective therapies for AD a novel series of Schiff base compounds also containing the *N*-BP component were designed, synthetized, and evaluated for their *in vitro* cholinesterase inhibitory activity against AChE and butyrylcholinesterase (BuChE) using Ellman's spectrophotometric method to determine their $IC_{50}$ values. Additionally, their antimicrobial properties were also evaluated. Encouraged by promising results in terms of cholinesterase inhibition, another series of Schiff bases were synthesized. The modification concerned for example the usage of isomeric amines or the reduction of selected Schiff bases to corresponding amines.

In this work, the overall design of this series, as well as the synthetic process and the results of the biological evaluation will be discussed.

*The study was supported 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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# COMPUTATIONAL INVESTIGATIONS OF HALOGEN BONDING OF CHLOROPYRAZINE DERIVATIVES

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The interest in weaker non-covalent interactions has been growing. Recently, halogen bonds (XBs) have become highly captivating for medicinal chemists as the XB formation has been described for several marketed drugs, e.g., diclofenac.[1]

This project focuses on XBs potentially formed by halopyrazine derivatives as important molecular fragments within antimicrobial research. Using quantum mechanics calculations, we investigated the parameters (energy, area, directionality) of σ-holes on chloropyrazines and related pyridines substituted with medicinally relevant electron-withdrawing substituents. The energy of the XB interaction with a fragment mimicking protein backbone (*N*-methylacetamide) was calculated at CCSD(T)/CBS with counterpoise correction mitigating the basis set superposition error.

Our results suggest that adding one nitrogen (pyrazines compared to pyridines) has a discernable effect on the size of the σ-hole and the strength of the halogen bond. The strongest XB interaction was observed for the 5-chloropyrazineamide derivative and reached $\Delta E$ = -2.91 kcal/mol. These findings might guide future pyrazine-based drug design efforts.

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**BPC10**

# SYNTHESIS AND DYNAMICS OF DEUTERIUM-LABELLED ACYLCERAMIDES

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Acylceramides are essential part of human skin barrier, their presence is necessary for formation of long periodicity lamellar phase and corneocyte lipid envelope which are responsible for correct barrier function of skin. However, there is still little known about the dynamics of these molecules in skin. One of the methods to study molecular dynamics is solid state NMR analysis, which requires specific labeling in molecule.

In this project we synthesized acylceramides with deuteration in their ultralong chain. Synthesis started with perdeuterated γ-butyrolactone and 1,12-dibromododecane which were modified and connected via a Wittig reaction providing 16C deuterated fragment. After modifications, this fragment underwent second Wittig reaction with 16C nondeuterated molecule, providing 32-carbon long chain with deuteration in frontal or rear part. This precursor was then esterified with linoleic acid and connected with sphingosine to form final molecules of acylceramides. Whole synthesis was performed in seventeen steps with yield of 2 % for deuteration in the rear half of the ultralong chain and in twelve steps with yield of 0,5 % for the front half. These modified acylceramides were studied with other skin lipids using lipid models. These models showed different molecular dynamics of the ultralong chain based on deuterium labeling: rear half of chain is more mobile (27 % of crystalline phase) compared to front part (53 % of crystalline phase). These findings allowed us to propose a new model of skin lipid arrangement.

*The study was supported by the Czech Science Foundation (22-20839K) and project "Grant Schemes at CU" (CZ.02.2.69/0.0/0.0/19_073/0016935).*

**BPC11**

# INSIGHTS INTO THE VASODILATORY MECHANISM OF FLAVONOID METABOLITE 4-METHYLCATECHOL VIA KV VOLTAGE CHANNEL BY REVERSE MOLECULAR DOCKING APPROACH

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4-methylcatechol (4-MC) is one of the flavonoid metabolites, polyphenolic compounds contained in foods such as vegetables, fruits, tea, red wine, and chocolate. 4-MC is formed by the gut microbiota and circulated in sufficient concentrations in the systemic and showed vasodilatory effects associated with protective effects on the cardiovascular system. This study aims to reveal insights into the mechanism of action of 4-MC with a reverse molecular docking approach supported by *ex-vivo* experiments. Of the 9 target proteins, reverse molecular docking confirmed that 4-MC docked to voltage-gated $K^+$ channel isoform 7.4 ($K_V$7.4) active site via hydrogen bond and hydrophobic interactions. Notably, 4-MC interacted with the essential residues for $K_V$7.4 activation: Trp242 and Phe246. In *Ex-vivo* experiments on Kv7 isoforms, 4-MC still showed vasodilatory effects despite the administration of a selective inhibitor of Kv7, linopirdine. In summary, our findings suggest that 4-MC exerts vasodilation by opening Kv channels with the involvement of $K_V$7.4.

*The study was supported by GAUK 136120, SVV 260 663 and SVV 260 666*

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# THROUGH VIRTUAL SCREENING TOWARDS NOVEL PROLYL-TRNA SYNTHETASE INHIBITORS

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In recent years, the increasing emergence of antimicrobial resistance has evoked the need to develop antimicrobials with mechanisms of action different from those of the currently used drugs. Prolyl-tRNA synthetase (ProRS) is a promising antimicrobial target which belongs to the group of aminoacyl-tRNA synthetases (aaRSs), enzymes that play a key role in protein synthesis by mediating the ligation of amino acids to their corresponding tRNAs.[1] The aaRSs are part of both eukaryotes and prokaryotes, but their significant evolutionary divergence provides the possibility to develop selective inhibitors.[2]

We aim to discover novel and structurally diverse prolyl-tRNA synthetase inhibitors with the use of High-Throughput Virtual Screening (HTVS). Our workflow contained *in silico* screening of a public compound library based on pharmacophore searching, HTVS docking, high-precision docking, and analysis of protein-ligand interaction fingerprints. Obtained *in silico* hits will be evaluated for antimycobacterial and antibacterial activity and assessed for their potential to interact with ProRSs from various microbial species of clinical importance.

*The study was supported by Charles University (project GA UK No. 219823; SVV 260 666). "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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**BPC13**

# SYNTHESIS AND STUDY OF PHTHALOCYANINE ANALOGUES FORMING J-DIMERS

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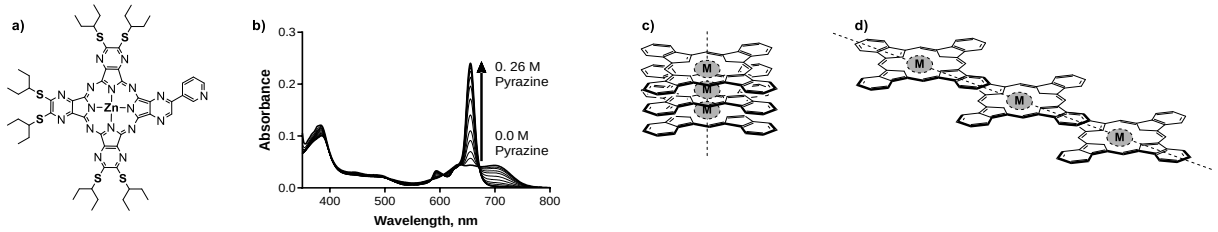
Phthalocyanines (Pcs) are synthetic macrocyclic dyes formed by four isoindoline units connected by azomethine bridges structurally close to porphyrins. Due to their extended 18 π-conjugated system, they show unique photophysical properties, and they have been largely investigated in various fields, such as fluorescence sensors or photosensitizers in photodynamic therapy (PDT).[1] However, these properties are related mostly to the monomeric form of the Pcs only. Aggregation of the Pcs is usually an unfavorable phenomenon. The planar Pc core tends to aggregate due to π-π stacking interactions. The most common H-type aggregates (Figure 1c) align molecules into a sandwich-like arrangement, resulting in increased absorption at blue-shifted wavelengths and strongly decreased fluorescence emission. However, J-aggregates (Figure 1d) give rise to red-shifted absorption bands and retain fluorescent properties. In this work, we synthesized unsymmetrical Pc derivatives containing one ligand (coordinating moiety, e.g., pyridyl) that formed slipped J-dimers upon coordination to the central cation of the second Pc molecule in non-coordinating solvents.




*The study was supported by Charles University (GA UK 230723 and SVV 260 666).*

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# SEMISYNTHETIC BERBERINE DERIVATIVES AS POTENTIAL ANTI-MYCOBACTERIAL AGENTS

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Tuberculosis is a widespread infectious illness attributed to *Mycobacterium tuberculosis*. The rising occurrence of drug-resistance or multidrug-resistant strains underscores the demand for novel antituberculosis agents featuring innovative chemical frameworks to address this ailment.[1]

Nature's bioactive molecules offer potent chemical scaffolds, but their non-drug-like traits and unfavorable selectivity pose limitations. To address this, chemical modifications and semi-synthesis are commonly applied. Notably, 18.9 % of FDA-approved drugs (n=1881) over 40 years were semi-synthetic derivatives of natural molecules.[2] Berberine, a natural alkaloid with notable bioactivities, faces clinical limitations due to its unfavorable pharmacokinetics. Derivatives, modified at various positions of the scaffold have shown significant improved activity against various *Mycobacterium* strains, including potent effects against resistant strains, suggesting potential for anti-tuberculosis drug development.[1,3]

In the perspective designed study, berberine derivatives will be presented as potential framework for development of new antimycobacterial agents, achieved preliminary results will be presented and further planned procedures will be discussed.

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**BPC15**

# WHEREVER YOU GO, I FOLLOW – APTAMER LINKED SWITCHABLE BODIPY FOR TARGETED PDT

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The conventional chemotherapeutic treatment of Cancer poses a threat to healthy cells, presenting the need for selective cell death. BODIPY are molecules with interesting photo physical properties and highly applicative singlet oxygen[1] production. Their structure can be modified by making them PET controlled switches for in-cancer activatable PDT therapy. Nucleoline being an over-expressed multifunctional protein that influences carcinogenesis and helps in the metastasis and survival of cancer cells works as an excellent antigen target to bind the photo-activatable drug. In this work, we convert non-specific nuclei acid damaging molecules into targeted weapons to bring about cell death using click chemistry with DBCO forming the triazole linker between Nucleoline and BODIPY units.

The design of the BODIPY included investigations to optimise singlet oxygen production by iodination, shift the absorption maximum to the red region by extension of the conjugation by Knovenagael condensation and finally making them photo switchable by the introduction of amines that quench the dye molecules in their OFF state. Photophysical experiments were done in both solution and on cells to test their functioning.

*The study was supported by SVV 260 666.*

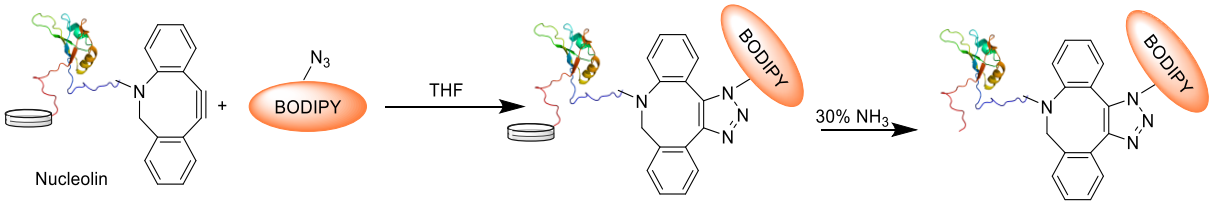


Fig 1: The attachment of BODIPY to aptamer, followed by cleavage from solid support and deprotection using $NH_3$.

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# SYNTHESIS OF PYRIMIDINE DERIVATIVES WITH ANTIMYCOBACTERIAL ACTIVITY

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Tuberculosis (TB) is a transmissible infectious disease caused by the intracellular pathogen, *Mycobacterium tuberculosis* (*Mtb*).[1] During 2021, 10.6 million patients fell ill with TB, 450 thousand of them were infected with drug-resistant *Mtb* strain. In that year, 1.6 million deaths caused by TB were recorded. *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 (extensively-drug resistant TB).[1] Therefore, there is a critical need to develop new chemotherapeutic agents with new mechanisms of action. [2]

We screened our in-house library of small molecules for their potential antimycobacterial properties identifying compounds K1827 with excellent antimycobacterial *in vitro* activity against *M. kansasii* ($MIC_{99}$ = 0.25 μM) and moderate activity against *M. tuberculosis* H37Rv (($MIC_{99}$ = 32 – 64 μM). The pyrimidine scaffold of K1827 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, and selectivity of action have been evaluated and will be discussed within our contribution.

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

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# CHALCOGEN-BONDING CATALYSIS WITH CHIRAL TELLURONIUM DICATIONS

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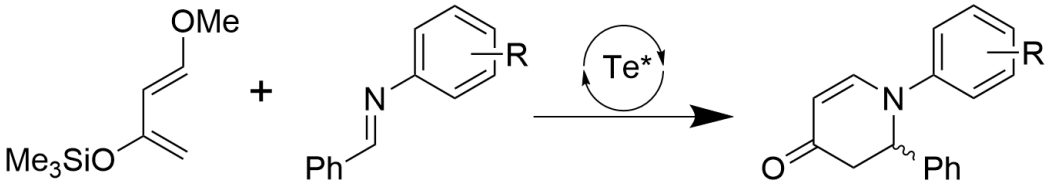
Chalcogen bonding is an attractive interaction between an electrophilic region (σ-hole) of a chalcogen atom and a Lewis base.[1] The most potent chalcogen bond donors are tellurium compounds, as tellurium is the most polarizable and least electronegative among chalcogens. Potential application of chalcogen bonding include anion transport[2] and Lewis acid catalysis.[3] Although it has been demonstrated that chalcogen bonding catalysis facilitates many chemical transformations, there is still no example of an enantioselective catalyst. Hereby we present a series of chiral telluronium catalysts. Study of their catalytic properties is underway (Scheme 1).




Scheme 1. Aza-Diels-Alder reaction catalyzed with a telluronium dication catalyst.

*The study was supported by PRIMUS Research Programme (PRIMUS/22/SCI/015) and Czech Science Foundation (22-25222I)*

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**BPC18**

# SYNTHESIS AND IMMOBILIZATION OF MODIFIED ULTRA-LONG CHAIN CERAMIDES ON FUNCTIONALIZED SURFACES FOR THE INVESTIGATION OF THEIR SCAFFOLDING ROLE IN THE SKIN LIPID BARRIER

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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, 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 that 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 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 and mica 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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# DESIGN, SYNTHESIS, AND BIOLOGICAL EVALUATION OF BORONIC ACIDS

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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. 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.

The synthesized compounds were subjected to biological *in vitro* screening against a panel of clinically important fungi and bacteria, and Hep G2, PC3, and LAPC4 cancer cell lines. Some of the compounds showed promising antiproliferative activity.

*The study was supported by Charles University project SVV 260 666 (Czech Republic).*

# TOWARDS TO NEW EFFECTIVE ATP MIMICKING INHIBITOR BASED ON 3-ACYLAMINO-2-PYRAZINECARBOXAMIDE

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The work is based on previous research on human prolyl-tRNA synthetase (ProRS) inhibitors. The key starting point for this research was the discovery of the binding position of 3-amino2-pyrazinecarboxamide in the ATP-binding site.[1] The pyrazine scaffold can perform same interactions as adenine core in the structure of ATP. Further research suggested possible inhibitors of mycobacterial ProRS with *para*-halogensubstituted 3-(Benzoylamino)-2-pyrazinecarboxamide. *Para*-halogen substitution enables new interaction (halogen bond) and is beneficial for penetration through the mycobacterial wall.[2]

This part of the research is focused on obtaining a ligand with a better binding affinity by introducing a ribose mimicking fragment in the scaffold. This change should bring the similarity between the intended inhibitor and ATP even greater. The best obtained scaffold with best binding affinity can be than modified specifically for targeted enzyme.

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