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Abstracts

Section 3 - Bioorganic and Pharmaceutical Chemistry

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BPC1

PET-CONTROLLED SILICON PHTHALOCYANINES FOR PRECISION PHOTODYNAMIC THERAPY

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Conventional chemotherapeutic treatment of Cancer poses a threat to healthy cells, presenting the need for selective cell death. Although photodynamic therapy[1] of cancer is an efficient non-invasive therapy, an ideal photosensitizer (PS) is still on the lookout. Silicon phthalocyanines are macrocyclic tetramers with interesting photophysical properties and highly applicative singlet oxygen production capabilities which can be fine-tuned. Cathepsin B is a lysosomal cysteine protease that plays a pivotal role in tumour development and its overexpression is associated with tumour environments. Its dicarboxypeptidase activity makes it cleave a valine-citrulline labile bridge[2] at the C-terminus. In this work we develop an optimized photosensitizer for precision medicine, possessing desired water solubility, absorption in the biological window of tissues and high singlet oxygen production. It is modified further with ferrocene to make the PS a PET (photoinduced electron transfer)-controlled switch for in-cell activation.

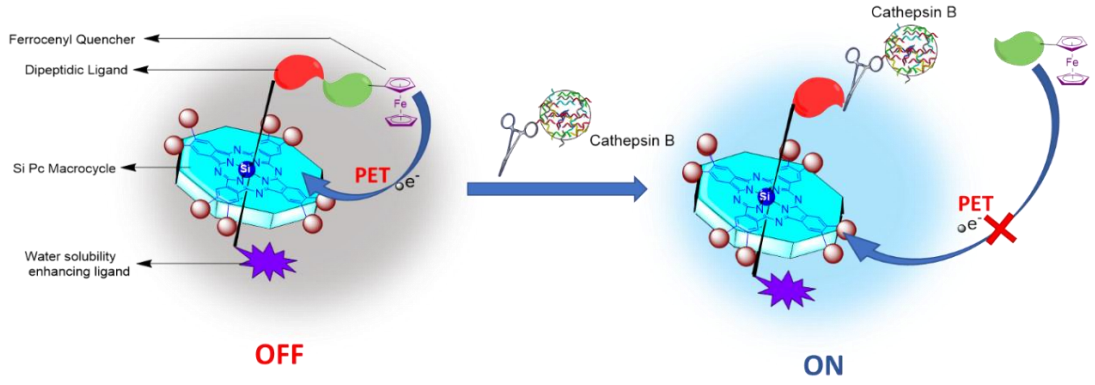

Fig 1: Schematic functioning of the antibody-drug conjugate with the cleavable Valine-Citrulline ligand.

The study was supported by ERC-CZ (Project LL2318), NETPHARM 101/92/4607-1-3 NETPH VZ1, and Charles University (SVV 260 666).

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BPC2

SELF-ASSEMBLY OF TETRAPYRAZINOPORHYRAZINES INTO J-AGGREGATES

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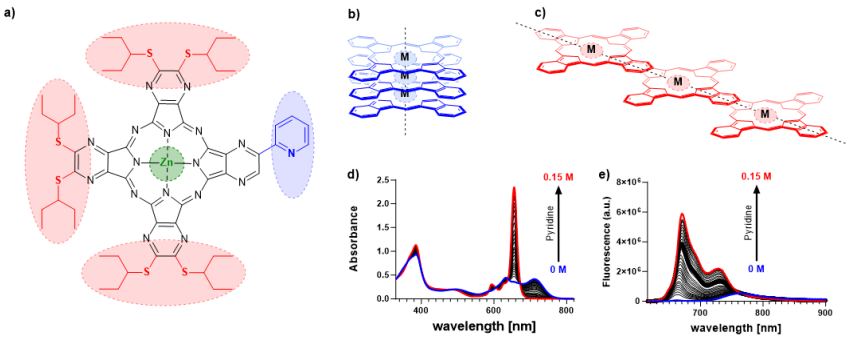
Phthalocyanines (Pcs) are synthetic macrocyclic dyes composed of four isoindoline units linked by azomethine bridges, structurally close to porphyrins. Their extended 18 π-conjugated system endows them with unique photophysical properties, making them valuable in various applications such as fluorescence sensors and photosensitizers in photodynamic therapy (PDT).[1] However, these properties are primarily associated with the monomeric form of Pcs. Aggregation of Pcs is usually undesirable, as the planar Pc core tends to aggregate through π-π stacking interactions. The most common H-type aggregates (Figure b) align molecules in a sandwich-like arrangement, leading to increased absorption at blue-shifted wavelengths and significantly reduced fluorescence emission. In contrast, J-aggregates (Figure c) result in red-shifted absorption bands and retain fluorescent properties.[2] In this study, we synthesized unsymmetrical Pc derivatives – tetrapyrazinoporphyrazines (Figure a) bearing one coordinating ligand (coordinating moiety, e.g., pyridyl) that formed slipped J-dimers upon coordination to the central cation of another Pc molecule in non-coordinating solvents (Figure d and e).



The study was supported by Charles University (GA UK 230723).

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BPC3

ENHANCEMENT OF AZAPHTHALOCYANINE FLUORESCENCE QUENCHING BY FORMATION OF SUPRAMOLECULAR COMPLEXES

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For development in the field of photosensitizers, it is desirable to study conventional and unconventional mechanisms of quenching to design new and improved analyte-activable fluorescence sensors and "smart" photosensitizers. It was reported that photoinduced electron transfer (PET) between a strong electron donor, such as ferrocene, and phthalocyanine acceptor leads to quenching.[1] In our project, we study the interactions of azaphthalocyanines with ferrocene-based quenchers. Azaphthalocyanines contain nitrogen atoms that increase their electron-deficient character compared to phthalocyanines, what makes them more susceptible to PET with electron donors. In this project, we tested quenching of fluorescence of an azaphthalocyanine derivative with a ferrocene-based quencher. The structure of both the azaphthalocyanine, and the quencher (Fig. 1) is designed to favor their interaction by additional supramolecular forces (charge-transfer complexes). The quenching was compared to the control systems lacking these key structural motives, and proved to be more efficient.

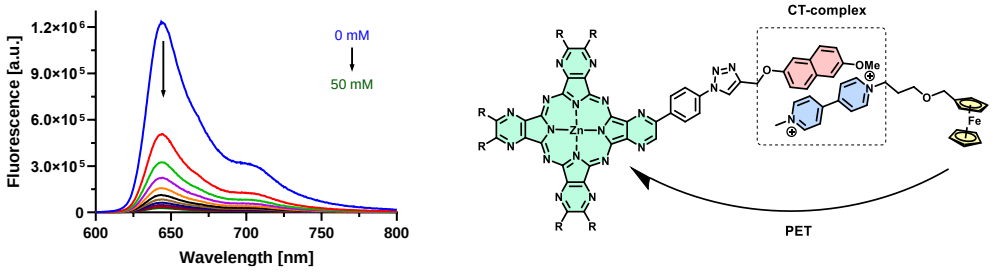

Fig. 1: Fluorescence spectra of the azaphthalocyanine derivative (5×10^{-6} M in acetonitrile) in solutions of quencher of different concentration, and structures of both components.

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

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BPC4

SYNTHESIS OF POLYPHENOLIC CYCLOPENTENEDIONES

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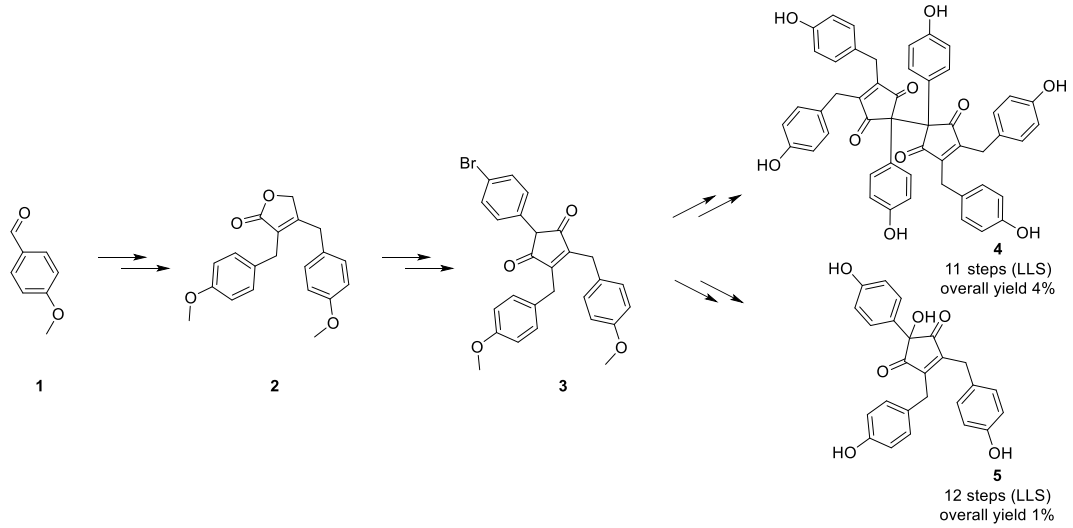
Nostotrebin 6 (Scheme 1; **4**) is a polyphenolic compound isolated from the cyanobacterial strain Nostoc sp. It has various biological activities, such as antimycobacterial and antibacterial.[1] We have established robust synthetical procedure starting from anisaldehyde (**1**), therefore, total syntheses of nostotrebin 6 and its monomeric derivative nostotrebinol 3 (**5**) were successfully achieved. Ongoing research includes the evaluation of biological properties of these compounds and their derivatives.

Scheme 1



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

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BPC5

PROGRESS IN TOTAL SYNTHESIS OF NOSTOLACTONE 4

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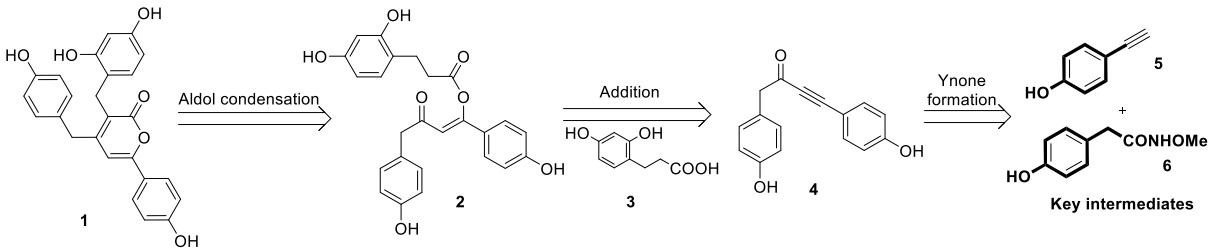
Nostolactone 4 (**1**) is a polyphenolic compound isolated from the cyanobacterial strain *Nostoc* sp. with biological activity against some Gram-positive bacteria.[1] Its skeleton is composed of 2,3,5-trisubstituted δ-lactone ring and it has not been synthesized yet. The aim of this work is to develop and optimize the synthesis of nostolactone 4 and its analogues and then to test their biological activities. One of the possible ways studied (Scheme 1) is based on the nucleophilic addition of propanoic acid **3** to the triple bond of ynone **4**, using gold catalyst. Aldol condensation of ester **2** would furnish the desired product nostolactone 4 (**1**). Various conditions for these reactions have been studied, such as type of gold catalyst for addition or bases used for aldol condensation. Other approaches of the total synthesis will be also discussed.

Scheme 1. – Retrosynthetic approach to synthesis of nostolactone 4



This work was supported by Charles University (SVV 260661, GAUK 149124) and Czech Science Foundation (Project No. 22-19209S).

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BPC6

SYNTHESIS AND REACTIVITY OF HYDROPHYLIC DENDRALENES AND PYRAN-2-ONES

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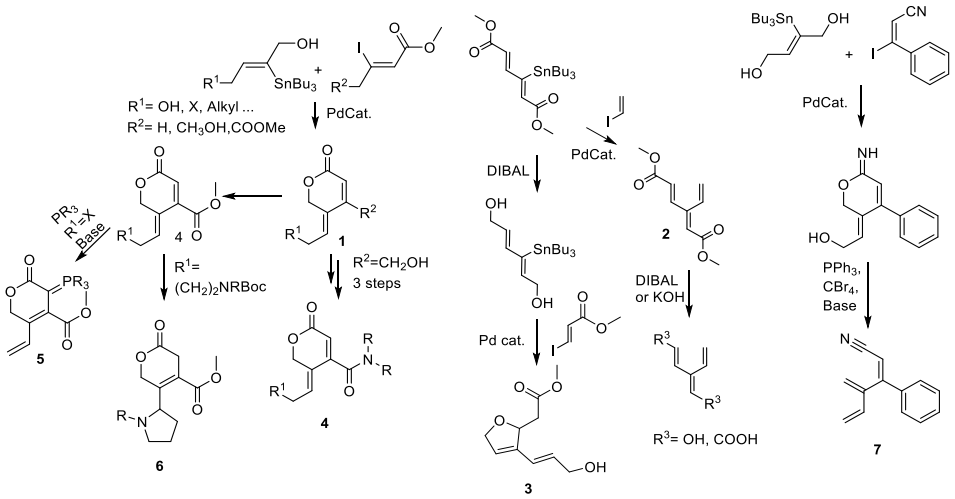
Utilizing Stille coupling, our group developed a method that leads to variously derived pyran-2-ones **1** and dendralenes **2**.[1] Our current goal is to use this method to get water-soluble, electron rich dendralenes **3**. These molecules can undergo Diels-Alder reaction in click-like fashion, so their hydrophilic derivatives could be used in conjugation chemistry. Next, we aim to synthesize hydrophilic pyran-2-ones and dendralenes containing dimethyl fumarate fragment **4**. Dimethylfumarate, is a naturally occurring compound produced by Fumaria officinalis with immunosuppressive properties. Recently some of its lactone enlocked analogues shown enhanced effects and tolerability by the organism.[2] Some of our lactones also show interesting behaviour with P and N nucleophiles **5**, **6** and **7**.



This work was supported by 2022–2024 This work was supported by Charles University (SVV 260661), Czech Science Foundation (Project No. 22-17868S) and The project New Technologies for Translational Research in Pharmaceutical Sciences /NETPHARM, project ID CZ.02.01.01/00/22_008/0004607, that is co-funded by the European Union.

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BPC7

CERAMIDE ANALOGS ON MICA – INTERACTIONS WITH SKIN LIPID MONOLAYERS

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Skin's outermost layer, the stratum corneum (SC), holds the principal skin barrier and consists of corneocyte dead cells embedded in the lipidic matrix. Corneocyte cells are decorated with covalently anchored ceramides on their surfaces, forming the corneocyte lipid envelope (CLE). During the last decade, attempts to explore the role of corneocyte lipid envelope were performed, considering only the lipidic matrix. In our approach we attempted to introduce the ´´anchoring template´´ of ceramides in our studies, combining organic chemistry with chemical engineering and surface chemistry. Initially, ω-hydroxyl ceramides were synthesized and activated through a high-yielding process to enhance the covalent coupling on the mica surface. The mica surface was modified in various ways obtaining an ultrathin covalently bonded amino-functionalized catechol film, alkylated and ceramide-enriched film. Isolated skin lipids were deposited as monolayers through a Langmuir-Blodgett (LB) technique on the CLE-mimicking entities. The synthetic models were further studied by transfer ratio analysis, by AFM, fluorescence microscopy, and Raman spectroscopy. Studies are ongoing for exploring the functional role of CLE-mimicking entities on the skin lipid orientation.

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BPC8

SYNTHESIS OF LOW-SYMMETRICAL SILICA-PHTHALOCYANINES WITH AXIAL MODIFICATION FOR PHOTODYNAMIC THERAPY

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Photodynamic therapy (PDT) is an effective form of cancer therapy involving a photochemical reaction with a photosensitizer (PS), light and molecular oxygen.[1] Phthalocyanines (Pcs) one of such PSs, are aromatic macrocycles having 18 π-electron and are comprised of four isoindole units linked together through their 1,3-positions by aza bridges, first characterized in detail by Linstead et al.[2] Pcs have maximal absorption in the phototherapeutic window i.e., 650-800nm, and can produce high singlet oxygen making them optimal PSs for PDT for cancer. The macrocyclic core can be modified to achieve better targeting, enhanced water solubility, and increased singlet oxygen production. Among all core-substituted Pcs, silicon phthalocyanines (SiPcs) have gained particular attention due to their good singlet oxygen production and the possibility of functionalizing with various axial ligands, preventing undesirable aggregation and allowing precise control over SiPcs properties.[3] Therefore, this project focuses on synthesizing low symmetrical SiPc as shown in Fig 1, bearing a functional group for attachment of targeting moiety. The axial ligands can be varied enabling the introduction of "switchable" axial ligands and those that improve water solubility.

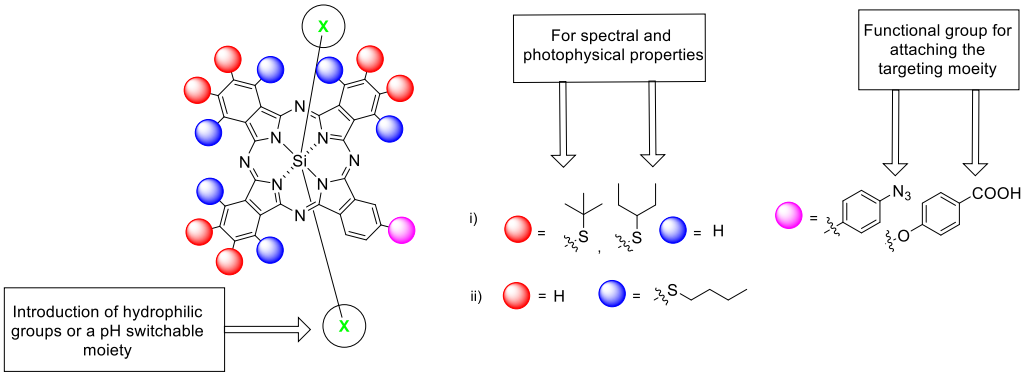

Fig. 1 Schematic representation of the target Low-symmetrical SiPc

This study was supported by ERC-CZ (Reg. No. LL2318).

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BPC9

VIRTUAL SCREENING FOR PROLYL-tRNA SYNTHETASE INHIBITORS

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The increasing number of cases of bacterial resistance emphasises the importance of the discovery of antimicrobial agents with a new mechanism of action. Prolyl-tRNA synthetase (ProRS), an enzyme belonging to the aminoacyl tRNA synthetase family, is present in all living organisms.[1] ProRS is crucial for protein synthesis by catalysing the covalent attachment of proline to its cognate tRNA and thus is considered a new promising antimicrobial target.[2]

In this study, we aim to discover novel structurally diverse potential prolyl-tRNA synthetase inhibitors with the use of High-Throughput Virtual Screening (HTVS). That contains *in silico* screening of compound library and other molecular modelling tools such as 3D pharmacophore model generation and subsequent pharmacophore screening, HTVS docking, high-precision docking, generation and evaluation of protein-ligand interaction fingerprints.

We identified 15 promising hits, which were evaluated for activity against multiple (myco)bacterial strains. Several compounds demonstrated activity against mycobacteria (*M. tuberculosis* H37Ra; MIC = 62.5 μg/mL) and bacteria (*Staphylococcus aureus* subsp. *aureus*; MIC = 125 μM).

The study was supported by Charles University (project GA UK No. 219823), SVV 260 666 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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BPC10

IMPROVING ANTIMYCOBACTERIAL ACTIVITY OF ASPARTATE DECARBOXYLASE INHIBITORS

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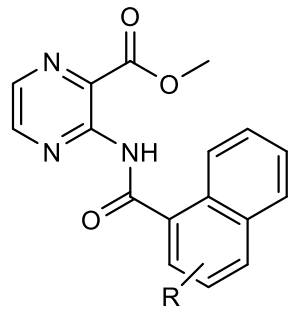
The aspartate decarboxylase (PanD) is a key enzyme of the pantothenate pathway, a process responsible for the biosynthesis of Coenzyme A, a cofactor essential for several metabolic processes (Krebs cycle, beta oxidation...). [1] PanD inhibition is linked with reduced bacterial growth and virulence. [1] 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 an approach combining *in silico* studies, chemical synthesis, and biological evaluations to identify structural derivatives of 3-(1-naphthamido)pyrazine-2-carboxylic acid with more potent antimycobacterial activity and potentially higher PanD inhibition.



The study was supported by the Grant Agency of Charles University with Project GA UK No. 230 623. The study was supported the project National Institute of virology and bacteriology (Programme EXCELES, ID Project No. LX22NPO5103) - Funded by the European Union - Next Generation EU. Additional support was provided by SVV 266 666.

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BPC11

DECIPHERING THE CHIRALITY OF METALLOCARBORANES

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In the quest for new potential drugs, metallocarboranes have gained a noteworthy interest. These boron-containing compounds are not only synthetically accessible and chemically stable but also exhibit favourable pharmacological properties, such as low cytotoxicity or efficient cell penetration.[1] In this project, we focused on two scientific questions connected to *C*-substituted cobalt-bis(dicarbollide) (COSAN): the facile identification of enantiomers and the exploration of chiral behavior on cyclodextrin columns.

The enantiomer identification followed the established methodology of comparing experimental electronic circular dichroism (ECD) spectra with theoretical Boltzmann-weighted DFT calculations, producing satisfactory agreement. This allowed, for the first time, the assignment of unknown samples from chiral chromatography to their likely configurations.

The chiral behaviour of COSANs was investigated by monitoring the binding events in the presence of native or permethylated β-cyclodextrin (βCD) using molecular dynamics. In total, 15 μs were simulated, allowing atomistic insight into the binding of *C*-substituted COSAN to βCD. The binding modes were analyzed and compared to the available NMR data, implying the correctness of the observations.

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.“ and by the research project 2200/04/2024-2026 as part of the "Competition for 2024-2026 Postdoctoral Job Positions at the University of Hradec Králové", at the Faculty of Science, University of Hradec Králové.

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BPC12

SYNTHESIS AND EVALUATION OF ANTIMICROBIAL ACTIVITY OF NEW ACETOPHENONE DERIVATES

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In designing new compounds, combining parent scaffolds with intrinsic biological activity into a single molecule is beneficial.[1] This study focuses on acetophenone derivatives and hydrazides, known for their broad biological activities, including antimycobacterial, antifungal, and antibacterial effects.[2] We selected 4'-cyclohexylacetophenone, 4'-piperidinoacetophenone, and 2- or 4-substituted benzohydrazides and pyridinecarbohydrazides as precursors for a new series of hydrazide-hydrazones. These compounds were satisfactorily prepared by reacting the ketones with the corresponding hydrazide in methanol, with the addition of glacial acetic acid (23-84 % yields). All prepared compounds were evaluated as values of minimum inhibitory concentration (MIC) against various bacteria including resistant strains (both G+ and G- strains; MIC >125 μM), fungi (MIC >125 μM), and mycobacteria (MIC from 0.195 $\mu g \cdot mL^{-1}$) by microdilution broth method. Furthermore, enzymatic inhibitory activity was assessed against cholinesterases, revealing IC_{50} values ranging from 10.16 μM for acetylcholinesterase and from 38.34 μM for butyrylcholinesterase. Cytotoxicity studies were also conducted to evaluate the safety profile of these compounds. This study highlights the potential of our newly synthesized hydrazide-hydrazones as promising candidates for further pharmacological development.

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. Supported by Ministry of Health of the Czech Republic, grant nr. NW24-05-00539.

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BPC13

SYNTHESIS OF NOVEL DEXRAZOXANE DERIVATIVE

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Daunorubicin, doxorubicin, and related compounds belong to the anthracycline (ANT) family. ANTs are widely used anti-cancer agents known for their potent efficacy against leukemias and solid tumors. However, their clinical application is significantly limited by severe cardiotoxicity, which can lead to heart failure due to irreversible damage to cardiomyocytes. Currently, dexrazoxane (DEX) is the only drug approved for managing ANT-induced cardiotoxicity.[1] Previous research has shown that the cardioprotective effect of DEX is achieved mainly through the catalytic inhibition of topoisomerase II beta (TOP2B), a key mechanism in reducing ANT-induced cardiotoxicity.[2] Unfortunately, the solubility of dexrazoxane in water is very low. The aim of this work is to prepare an analogue of DEX (figure 1) with additional hydroxymethyl group. The hydroxyl group can improve the solubility and can be used to prepare suitable prodrugs.

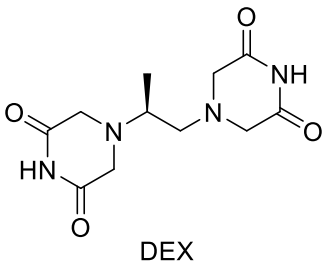

Figure 1: Structure of dexrazoxane

The study was supported by GAUK (reg. No. 361422).

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BPC14

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 2023, 10.8 million patients fell ill with TB. In that year, 1.25 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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SYNTHESIS OF MODIFIED CERAMIDE-COATED GOLD SURFACE TO STUDY SKIN BARRIER ARRANGEMENT

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Acylceramides are essential derivatives of ceramides (Cer) for skin barrier function in the stratum corneum (SC) extracellular matrix where they make up around 10% of Cer structures by weight. Apart from free lipids, acylceramides are also covalently anchored to the surface of corneocytes forming a corneocyte lipid envelope (CLE), a structure required for the proper arrangement of free lipids in SC.

The aim of this project was to investigate the process occurring when free skin barrier lipids are self-assembled on the Corneocyte Lipid Envelope. For this, thiol-terminated ceramide (HS-Cer) was first synthesized as a modified procedure from Opálka et al. [1] Then it was covalently attached to gold surfaces of Quartz Crystal sensors, representing a simple model for the CLE. The self-assembly process was investigated by Quartz Crystal Microbalance with Dissipation Monitoring (QCM-D) by introducing liposomes of skin barrier lipids extracted from the human skin (SC). [2] Preliminary results illustrate that the covalently attached lipid envelope influences the self-assembly process of the lipid matrix, compared to bare gold or hydrophilic surfaces that were used as controls.

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