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Abstracts

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BPC1

HOW TO NOT KILL MOSQUITO: CYSTEINE-TARGETED INSECTICIDES

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Acetylcholinesterase cysteine-targeted insecticides against malaria vector *Anopheles gambia* and other mosquitos have already been introduced. We have applied the olefin metathesis for the preparation of cysteine-targeted insecticides in high yields. The prepared compounds with
either a succinimide or maleimide moiety were evaluated on *Anopheles gambiae* and human acetylcholinesterase with relatively high irreversible inhibition of both enzymes but poor selectivity. The concept of cysteine binding was not proved by several methods, and poor stability was observed of the chosen most potent/selective compounds in a water/buffer environment. Thus, our findings do not support the proposed concept of cysteine-targeted selective insecticides for the prepared series of succinimide or maleimide compounds.

The study was supported by Ministry of Health of the Czech Republic (no. NV16-34390A), University of Hradec Kralove (no. SV2115-2018, no. VT2019-2021 and postdoctoral job positions at UHK), and University of Defence (Faculty of Military Health Sciences, Long-term development plan and SV/FVZ2019/01).

CYCLIZATION REACTIONS MEDIATED BY TRANSITION METALS

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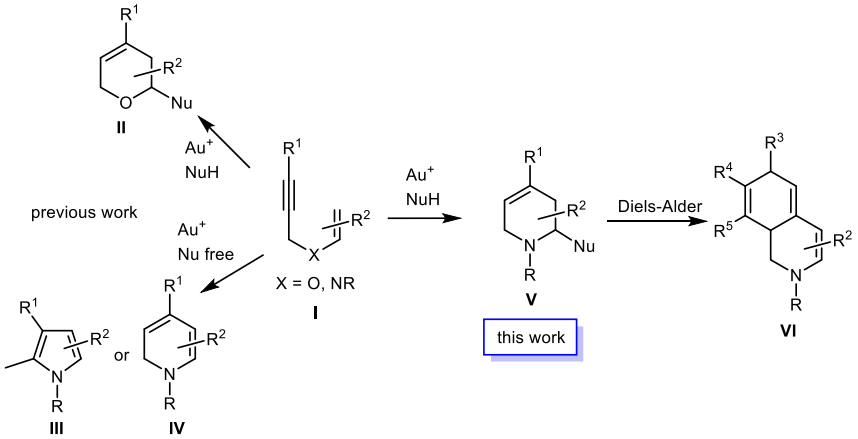
Synthesis of various types of heterocycles is possible from enyne precursors using cationic gold(I) species as catalysts. Our previous research on the cyclisation of propargyl vinyl ethers to dihydropyrans **II**[1] as well as chemoselective cyclizations of *β*-propargylamino acrylic esters to dihydropyridines **IV**[2] was extended to include nucleophile-assisted reactions.

The optimized synthetic protocol was applied to the preparation of a library of substituted tetrahydropyridines **V**. Their further transformations via i.e. cycloadditions gave highly substituted isoquinoline derivatives **VI**.



Scheme 1: Gold(I)-Catalyzed Synthesis of Piperidine Aminals

The study was supported by Charles University (GAUK 262416 and 1590119 and SVV 260 401) and Czech Science Foundation (Project No. 18-17868S).

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SYNTHESIS AND REACTIVITY OF ELECTRONICALLY TUNED [3]DENDRALENES

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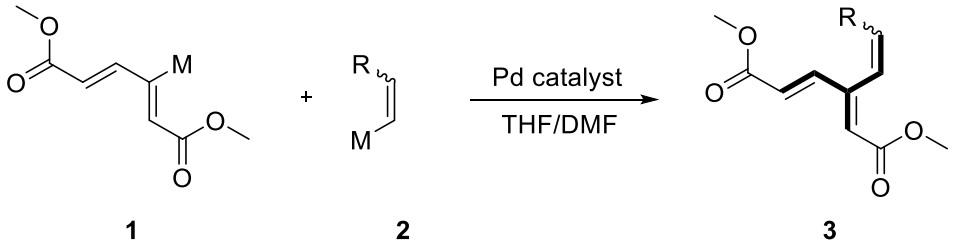
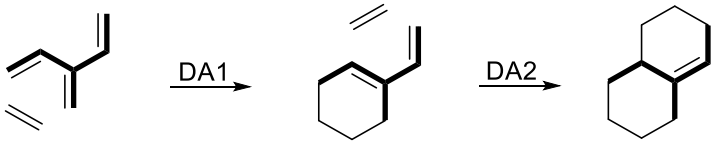
Dendralenes are acyclic cross-conjugated polyenes with an interesting, as yet unexamined reactivity and high potential for further synthesis.[1] We have focused on the synthesis of variously substituted electron poor [3]dendralenes containing electron withdrawing groups (e.g. carboxylic group), or a combination of electron withdrawing and donating groups. Synthesis is based on readily available *Z*-metallodienes **1**, which are subjected to Migita-Stille coupling[2] yielding the intended final products **3** (Scheme 1). Syntheses and possible applications of new compounds in domino Diels-Alder sequences (Scheme 2) will be discussed.



1 **2** **3**

Scheme 1: Migita-Stille coupling



Scheme 2: Diels-Alder reactions

The study was supported by Charles University (SVV 260 401, GAUK 1348119) and Czech Science Foundation (Project No. 18-17868S).

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UNUSUAL 1,3-IZOMERIZATION: PREPARATION OF POLYSUBSTITUTED PYRAN-2-ONES

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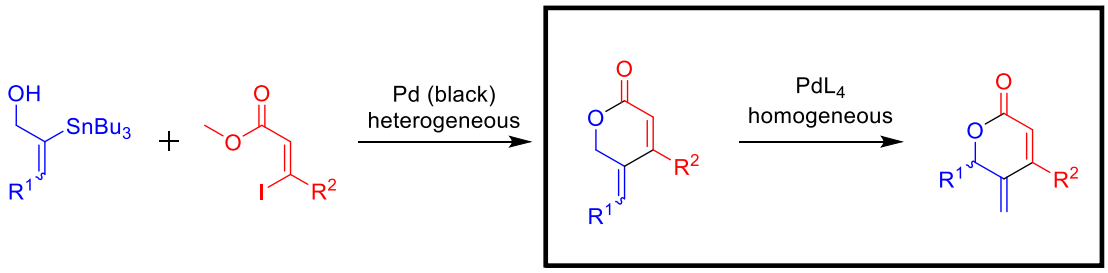
Originally discovered as minor by-products of our previous studies to the synthesis of disubstituted pyranones 1 (Scheme 1)1, we developed preparation of isomeric trisubstituted derivatives 22 into proper synthetic protocol. Having optimized the reaction conditions, we were able to prepare a broad library of compounds in high yields using mild conditions. In addition, our synthetic protocol showed high tolerance of functional groups. Screening of chiral ligands was also performed to probe the possibility of enantiocontrol over the newly introduced chiral centre.

We also performed quantum chemistry calculations in order to gain more insight into the mechanism of this transformation, which is seemingly unfavourable.



Scheme 1 General structures

The study was supported by Grant Agency of Charles University (project No. 1054216), Czech Science Foundation (project No. 18 17868S) and Faculty of Pharmacy in Hradec Kralove (SVV-260-401).

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PREPARATION, HPLC PURIFICATION, AND EVALUATION OF MODIFIED OLIGODEOXYNUCLEOTIDE PROBES

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Melting temperature difference between complementary and mismatched duplex has crucial role for discrimination of point mutations. Several oligodeoxynucleotide probes (ODNs) conjugated with melting temperature modifiers (acridine derivatives, modified Hoechst 33258) were prepared using copper-free click chemistry.[1] 13 and 18 bases long ODNs, containing one or two aza-dibenzocyclooctyne, were used. Modified ODNs were purified by zetadex gel filtration columns and HPLC. For HPLC purification PhenylHexyl column, triethylammonium acetate buffer (TEAA), and ACN in various ratios were used.[2] All samples were analysed using isocratic elution. Minor changes in ratio of TEAA and ACN were needed for optimization of elution times and resolution. Isocratic elution was used also for semipreparative HPLC. Two peaks were observed on all chromatograms (Figure 1). They were identified as constitutional isomers, and were taken together as one fraction. HPLC purified ODNs were tested for ability to increase melting temperature (Figure 2).

The study was supported by Technology Agency of the Czech Republic (060/860681) and The Charles University

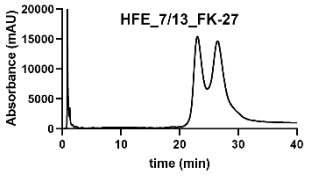

Figure 1 Chromatogram of probe modified by FK-27

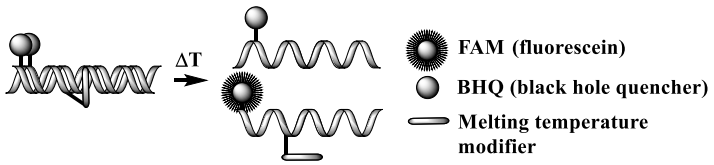

Figure 2 Scheme of hybridization study

Grant Agency (994218)

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BPC6

SYNTHESIS OF 1-AMINOADAMANTANE SUBSTITUTED PHTHALOCYANINES AND STUDYING THEIR SUPRAMOLECULAR COMPLEXES WITH CUCURBITURIL

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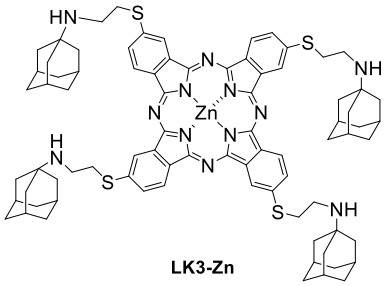
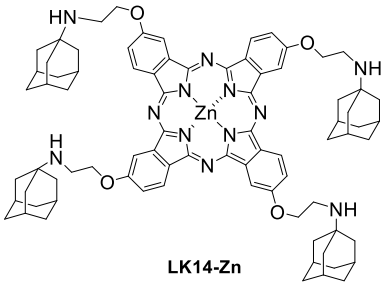
Phthalocyanines (Pc) are macrocyclic compounds with central metal cation. They can be used for example as dyes, pigments, catalysts or as photosensitizers in photodynamic therapy in cancer treatment. One big limitation of Pc is their poor solubility and aggregation in water. Cucurbiturils (CB) are pumpkin shape macromolecules composed of various number of glycoluril monomers.[1] They can bind guest molecules into their cavities. We used one of the strongest reported interaction between CB[7] and 1-aminoadamantane.[2] By creating a supramolecular complex of Pc and CB we should be able to improve solubility and aggregation of Pc in water. Three phthalonitrile precursors were prepared and after cyclotetramerization reactions two Pcs **LK3-Zn** and **LK14-Zn** with four peripherally 1-aminoadamantane substituents were synthesized. Photophysical properties of **LK3-Zn** were measured and were compared to its cucurbituril complex. Biological tests on HeLa cells showed ten times higher photodynamic activity of Pc-CB complex compared to Pc without CB.



LK3-Zn



LK14-Zn

The study was supported by SVV 260 401 and Grant Agency of Charles University (1606119).

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BPC7

ANIONIC AND CATIONIC PHTHALOCYANINES FOR PHOTODY-NAMIC THERAPY AND THEIR INTERACTION WITH BOVINE SERUM ALBUMIN

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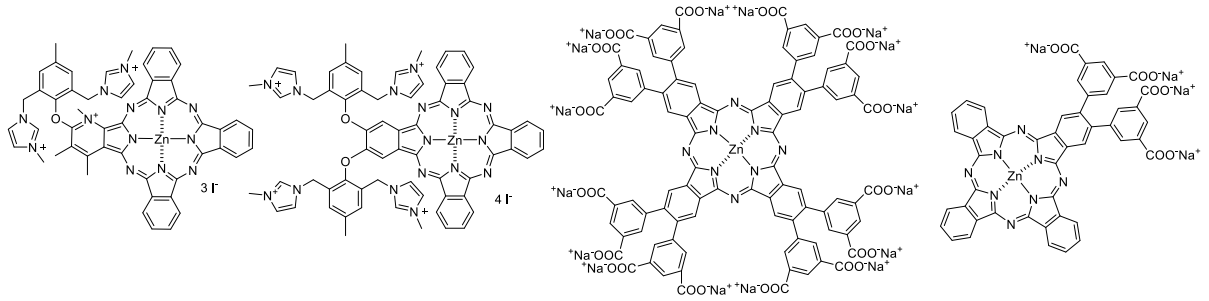
Phthalocyanines (Pcs) and their aza-analogues are macrocyclic compounds with interesting photophysical properties (strong absorption in area over 600 nm and strong singlet oxygen production) highly suitable for the use in photodynamic therapy of cancer. The aim of this work was synthesis and study of interaction of symmetrical and unsymmetrical anionic and cationic Pcs with bovine serum albumin and effect of this interaction on their photodynamic activity. Symmetrical Pcs were obtained by cyclotetramerization reaction (initiator magnesium butoxide) of one precursor while unsymmetrical Pcs were prepared by statistical condensation of phthalonitrile with 4,5-disubstituted phthalonitrile. Magnesium complexes were converted to metal-free ligands and then to zinc complexes. Basic hydrolysis of ester bonds was the last step of the synthesis of anionic Pcs. Quaternization of basic nitrogens was the last step of the synthesis of cationic Pcs. Pcs were tested on photodynamic activity in vitro on HeLa cells with different results in serum-free medium (SFM) and serum-containing medium (SCM). Effect of binding to serum proteins was studied as change in absorption and fluorescence spectra of Pcs after addition of bovine serum albumin. Obtained results corresponded well with change in photodynamic activity of these compounds in SFM and SCM.



The work was supported by Czech Science Foundation, grant. No. 19-14758Y and SVV 260 401

BPC8

SYNTHETIC AND BIOLOGICAL STUDY ON RHODANINE DERIVATIVES AND THEIR OXYGEN ISOSTERES

KUČEROVÁ-CHLUPÁČOVÁ, M.,[1] KONEČNÁ, K.,[2] NOVOTNÁ, S.,[2] DIEPOLTOVÁ, A.,[2] DUŠKOVÁ, A.,[1] JANĎOUREK, O.,[2] KUNEŠ, J.,[3] DOLEŽAL, M.[1]

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Rhodanine derivatives have shown interesting biological activities. In the series of (*Z*)-5-arylmethylidenerhodanines, inhibition of *Staphylococcus* spp. was detected in the past.[1] Recently, selected compounds were re-tested on collection strains and evaluated in advanced studies, e.g. bacteriocid/bacteriostatic effect and checkerboard with some standard antibiotics.

Despite the rhodanine scaffold (2-thioxothiazolidin-4-one) being included in the PAINS filter (pan assay interference compounds)[2], it can serve in drug design for scaffold hopping approach[3,4]. Oxygen isosteres of some (*Z*)-5-arylmethylidenerhodanines were prepared, tested on antimicrobial activity, including antimycobacterial and compared with rhodanines.

The study was supported by Progres Q42 and SVV 260 401 (both from Charles University, Czech Republic).

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BPC9

THE WAY FROM THE SYNTHESIS TO POTENTIAL CLINICAL TRIALS - FOCUSED ON CANDIDATE ANTIBACTERIAL DRUGS, CHALCONES

KONEČNÁ, K.,[1] KUČEROVÁ-CHLUPÁČOVÁ, M.,[2] DIEPOLTOVÁ, A.,[1] TREJTNAR, F.,[3] JANĎOUREK, O.,[1] VOXOVÁ, B.,[1] DOLEŽAL, M.,[2]

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Chalcones and their derivates represent a group of compounds with a wide range of biological activities.[1] According to this fact, these compounds can be rightfully included in the group of a privileged structures in medicinal chemistry and they represent promising starting points for new drug design.

In our study, we have focused on the investigation of the antimicrobial activity of newly designed and synthesized chalcone derivates. The total number of twelve compounds has been subjected to evaluation of antimicrobial potential. Based on results from the basic methodical approach for the antimicrobial activity testing, two of these compounds were selected for advanced preclinical study.

In an advanced study, the antibacterial activity was confirmed by using bacterial strains, clinical isolates that fully represent the epidemiological situation in medical practice. Further, the investigation of *in vitro* (HepG2 cell line) and *in vivo* toxicity (acute and subacute toxicity testing, the invertebrate model *Galleria mellonella*)[2] was done. In view of previous satisfactory results, the *in vitro* interactions (checkerboard studies)[3] of candidate tested compounds with selected antibiotics commonly used in medical practice were further investigated in order to identify a "partner drug" for synergic interaction.

The study was supported by Progres Q42 and SVV 260 401 (both from Charles University, Czech Republic).

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BPC10

DESIGN AND SYNTHESIS OF CASEIN KINASE II (CK2)/ HISTONE DEACETYLASES (HDAC) DUAL INHIBITIORS

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The aim of this study is to design and synthesize dual inhibitors combining the pharmacophores of the protein kinase CK2 and Histone Deacetylase (HDAC), see Figure below. CK2 is a ubiquitous serine/threonine protein kinase, whose upregulation is linked to tumor progression.[1] On the other hand, HDACs are a class of epigenetic enzymes responsible for gene silencing. Altered expression and mutations of genes that encode HDACs is linked to tumor development.[2] Synthetic procedures to obtain final compounds will be discussed in details during the presentation.

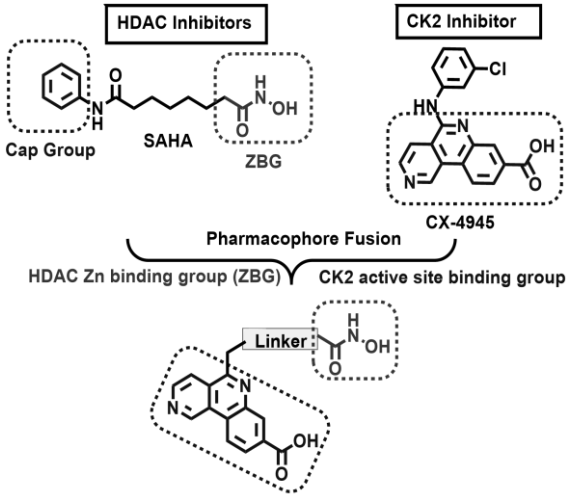

Figure: Design rational of title compounds.

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DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF POSITIONAL DERIVATIVES OF A SERIES OF N-(PYRAZIN-2-YL)CARBOXAMIDES

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Tuberculosis, a disease caused by Mycobacterium Tuberculosis, is leading cause of death worldwide[1] among infectious diseases and major threat to public health. Tuberculosis can effectively be treated with first-line anti-TB drugs however, due to rising antimicrobial resistance new approach to eradicate the disease is needed. A series of new N-(pyrazin-2-yl)carboxamides as potential antimycobacterial and antibacterial agent is presented. Derivatives to be presented are compounds based on positional derivatives of picolinic acid linked to pyrazine derivatives (pyrazin-2-amine, 6-chloropyrazin-2-amine, propyl 5-aminopyrazine-2-carboxylate), 4-amino-2-hydroxybenzoic acid or 4-aminobenzoic acid by amidic bond. Compounds were tested for biological activity against selected strains of *Mycobacterium* (*M. tuberculosis* H37Rv, *M. tuberculosis* H37Ra, *M. kansasii*, *M. avium*, *M. smegmatis*, *M. aurum)*. The minimum inhibitory concentration (MIC) for tested mycobacterial strains was determined for all tested compounds beside isoniazid, ciprofloxacin and rifampicin as a reference standard drug. Results of the biological testing and structure activity relationships are discussed in the presentation.

The study was supported by the Ministry of Education, Youth and Sports of the Czech Republic (SVV 260 401) and by Grant Agency of Charles University (project C-C3/1572317).

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BPC12

SYNTHESIS OF FREE OMEGA-HYDROXY CERAMIDES AND THEIR BEHAVIOUR IN THE STRATUM CORNEUM MODEL LIPID MEMBRANES

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Omega hydroxy ceramides (O-Cer) belong to a subclass of Cer with ultralong ω-hydroxylated *N*-acyl chains. In extracellular spaces of human *stratum corneum* (SC), they are present in the free form or linked to the surface of corneocytes via their free hydroxy group and form the corneocyte lipid envelope (CLE). The main aim of this project was to prepare 3 subclasses of O-Cer (Cer OS, OP and OdS) using an improved synthetic strategy and study their behaviour after their addition into model lipid membranes.

Complete synthesis of O-Cer has not yet been reported. We modified previously published procedure, where we focused on possible improvements of the synthesis of 32- hydroxydotriacontanoic acid, the backbone of O-Cer. The previously used Wittig reaction was changed for other olefinations, *e.g*. Julia and Julia-Kocienski reactions, which led to a significant improvement in the reaction yield.

Synthesized O-Cer were added into model lipid membranes consisting of a mixture of Cer, free fatty acids, cholesterol and cholesteryl sulfate mimicking the composition of SC. Membrane organization showed that an addition of O-Cer does not change the arrangement in the long periodicity phase (~12.3 nm), essential for the proper barrier function. Complete replacement of acylCer with O-Cer led to a formation of a new phase with shorter repeat distance (~10.7 nm). Permeability of the model membranes did not change significantly after an addition of O-Cer, however the complete replacement of acylCer with O-Cer increased permeability. In conclusion, the addition of O-Cer to the membrane did not improve the barrier properties and after a complete replacement of acylCer with O-Cer, the barrier was even more perturbed.

The study was supported by the Czech Science Foundation (19-09135J) and by Charles University (GAUK 1194119).

SYNTHESIS OF NOVEL 2,3-DISUBSTITUTED PYRAZINES AS POTENTIAL ANTIMICROBIALS

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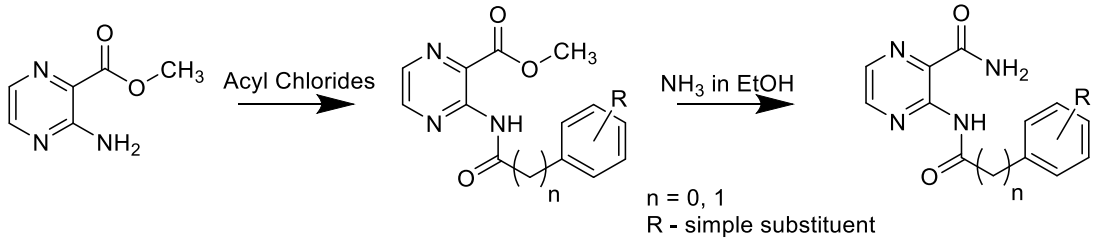
This research project is focused on synthesis of novel 3-substituted derivatives of pyrazinamide. The synthesis involves acylation of amino group of 3-aminopyrazine-2-carboxylate with acyl chlorides (benzoyl chlorides or phenylacetyl chlorides), followed by ammonolysis by ammonia in dry ethanol (Scheme 1).



Scheme 1. Synthesis of final compounds

The compounds will be assessed for *in vitro* antimicrobial activity against several mycobacterial strains (*Mycobacterium tuberculosis* H37Ra and H37Rv, *M. avium, M. kansasii, M. smegmatis, M. aurum*) and bacterial and fungal strains of clinical importance.

As an off-spin to this project, the compounds will also be studied as potential inhibitors of (human) prolyl-tRNA synthetase. This is rationalized by their structural similarity to confirmed inhibitors reported in literature[1].

The study was supported by the Ministry of Education, Youth and Sports of the Czech Republic (SVV 260 401) and by CELSA—Project title: Structure-based design of new antitubercular medicines—KU Leuven (Arthur Van Aerschot)—Charles University in Prague (Martin Doležal).

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BPC14

N-PYRAZINOYL SUBSTITUTED AMINO ACIDS AS POTENTIAL ANTIMYCOBACTERIAL AGENTS – SYNTHESIS AND BIOLOGICAL EVALUATION OF ENANTIOMERS

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Tuberculosis is an infectious disease caused by *Mycobacterium tuberculosis* (Mtb), each year causing millions of deaths. We present synthesis and biological evaluation of new potential antimycobacterial compounds containing fragment of the first-line antitubercular drug pyrazinamide (PZA), coupled with methyl or ethyl esters of selected amino acids (Fig. 1). The antimicrobial activity was evaluated on a variety of mycobacterial strains including *Mycobacterium tuberculosis* (Mtb) H37Ra and bacterial and fungal strains of clinical importance *e.g. Staphylococcus aureus* or *Aspergillus flavus*. Emphasis was made on comparison of activities of individual enantiomers.

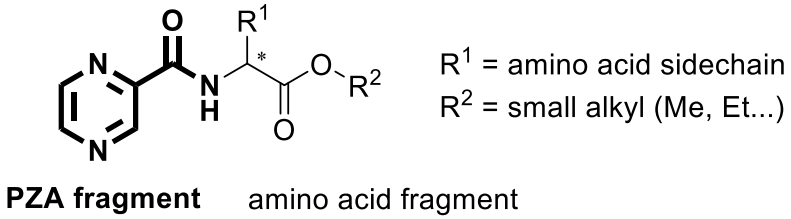

Fig. 1 General structure of the synthesized compounds

Overall, high activity against Mtb was seen in derivatives containing more lipophilic L-amino acids. The most active derivative contained phenylglycine moiety (MIC <1.98 μg/ml, <7.3 μM). Compounds possessed low cytotoxicity in HepG2 cell line (IC_{50} >500 μM) and good selectivity towards Mtb (SI >40). No significant activity was detected against tested bacterial and fungal strains. To our best knowledge, this is the first study comparing the activities of D- and L-amino acid derivatives of pyrazinamide as potential antimycobacterial compounds.

The study was supported by the Ministry of Education, Youth and Sports of the Czech Republic (SVV 260 401).

BPC15

SYNTHESIS OF SILICON COMPLEXES OF TETRAPYRAZINOPORPHYRAZINES

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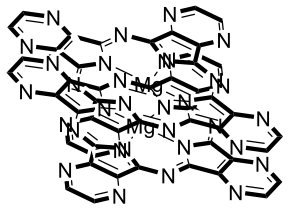
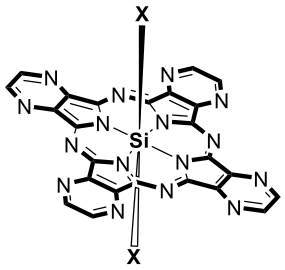
Azaphthalocyanines such as tetrapyrazinoporphyrazines are widely examined compounds. Due to their large system of conjugated double bonds, they posses interesting photophysical and photochemical properties. They find use in many medicinal fields as photodynamic therapy, monitoring RT-PCR or diagnostic imaging. As their structure is planar, strong π-π interactions between macrocycles cause aggregation of molecules.[1] This is an undesirable property of all azaphthalocyanine derivatives, because they loose their photoactivity in this state. One approach to suppress aggregation presents an introduction of suitable metal cation into the macrocyclic core. Silicon cation has been used mainly in phthalocyanine chemistry for this intention yet.[2] Its binding capacity exceeds coordinating bonds in the macrocycle core and provides spear axiall bonds, which can bear bulky substituents creating sufficient inhibition of the aggregation proccess. In this project we focus on different ways of silicon tetrapyrazinoporphyrazine synthesis.





The study was supported by Charles University (reg. No. SVV 260401).

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(*E*)-2-(2-ISONICOTINOYLHYDRAZINEYLIDENE)PROPANOIC ACID DERIVATIVES AS PROMISING ANTIMYCOBACTERIAL SUBSTANCES

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(*E*)-2-(2-Isonicotinoyl)hydrazonopropanoic acid has been presented and tested as an antimycobacterial agent by Kryukova et al.[1] in the Soviet Union in the 1970s. A basic set of antibacterial tests has been described. Since then, derivatives of this compound have been presented only randomly. We are introducing a new comprehensive series in which we have been working on adjusting this structural motif (Fig. 1).

We are focused primarily on modifications of free carboxyl group by various amines or phenols to yield functional derivatives (amides and esters) *via* EDC coupling catalysed by 1-hydroxybenzotriazole or 4-(dimethylamino)pyridine.

The prepared compounds were tested against *Mycobacterium tuberculosis* and some atypical strains of mycobacteria (*M. avium, M. kansasii*) with significantly lower MIC values (sometimes up to 64 times lower) compared to the parent drug isoniazid (INH) used as a synthetic precursor. The derivatives don't show cytotoxicity to mammalian cells (assays were performed on HepG2 and MonoMac6 cells) and exhibit a much greater ability to inhibit growth of the mycobacterial cells in comparison to the INH.

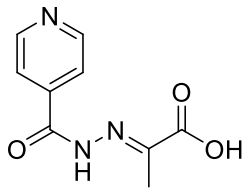

Figure 3 *– (E)-2-(2-Isonicotinoylhydrazineylidene)propanoic acid*

The study was supported by the Czech Science Foundation (reg. No. 17-27514Y) and Charles University (SVV 260 401).

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N-METHYLHYDRAZINE-1-CARBOXAMIDES AS POTENTIAL CHOLINESTERASES INHIBITORS

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Due to the increasing number of cases, Alzheimer's disease is a neurodegenerative disease that represents a serious threat to mankind. The impairment that this disease causes to one's health, urge for the research of new potential drugs for the treatment of this illness. Nowadays, the therapy of Alzheimer's disease is focused primarily on the use of acetylcholinesterase (AChE) inhibitors and dual AChE-butyrylcholinesterase (BuChE) inhibitors.[1] Based on this fact, derivatives of *N*-methyl-hydrazine-1-carboxamide (Fig. 1) have been designed within this goal. The ability of the different derivatives to inhibit both AChE and BuChE was evaluated using modified Ellman's method.[2] AChE was inhibited with IC_{50} values within the range of 44-73 μM, whereas BuChE was inhibited with IC_{50} within the range of 170-514 μM. The most active compound for AChE inhibition was 2-(4-chlorobenzoyl)-*N*-methylhydrazine-1-carboxamide (IC_{50} = 44.08 μM) (Fig. 2). More derivatives will be tested in order to determine the structure-activity relationship.

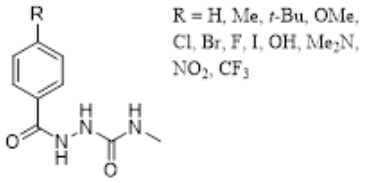

Fig. 1 *N*-Methylhydrazine-1-carboxamides

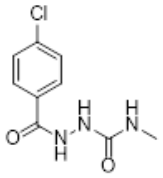

Fig. 2 The most active AChE inhibitor

The study was supported by the Czech Science Foundation projects No. 17-27514Y and 20-*19638Y*.

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