DEPARTMENT OF CHEMICAL DRUGS, FACULTY OF PHARMACY, MASARYK UNIVERSITY BRNO

CZECH PHARMACEUTICAL SOCIETY OF CZECH MEDICAL ASSOCIATION OF J. E. PURKYNĚ

50TH CONFERENCE SYNTHESIS AND ANALYSIS OF DRUGS

BOOK OF ABSTRACT

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Synthesis and Analysis of Drugs 2022

We are pleased to invite you to the 50th anniversary conference.

7TH - 9TH SEPTEMBER 2022

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50th Conference SYNTHESIS AND ANALYSIS OF DRUGS

The Book of Abstracts

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Editorial

Dear colleagues and friends,

the Organizing Committee is pleased to invite you to take part in the anniversary 50th conference SYNTHESIS AND ANALYSIS OF DRUGS (SAL 2022 Brno) that will take place in Brno (Czech Republic) in the period September 7-9, 2022.

Synthesis and Analysis of Drugs (Syntéza a analýza léčiv) is an annual conference with a long tradition, dating back to 1971. Every year, the conference facilitates knowledge transfer between top scientists from the fields of biochemistry, medicinal, organic, analytical chemistry, drug design, micro/macro biology, pharmacology, molecular biology, proteomics, docking and/or other related disciplines.

During the conference, participants have a unique opportunity to share knowledge, learn from and get inspired by the best researchers in the field. Conference offers lectures, workshops, poster sessions and rich social and networking programmes.

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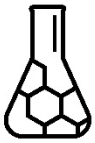

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VENUE

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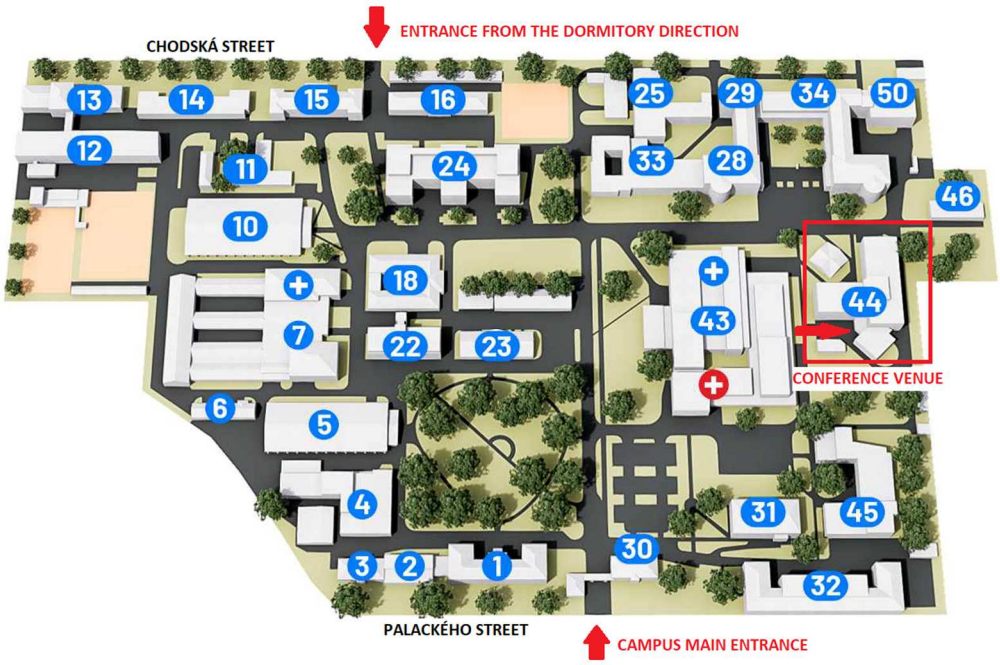

- **Registration, poster session & conference banquet:** building no. **44 (Faculty of Pharmacy I)** – lobby (022)
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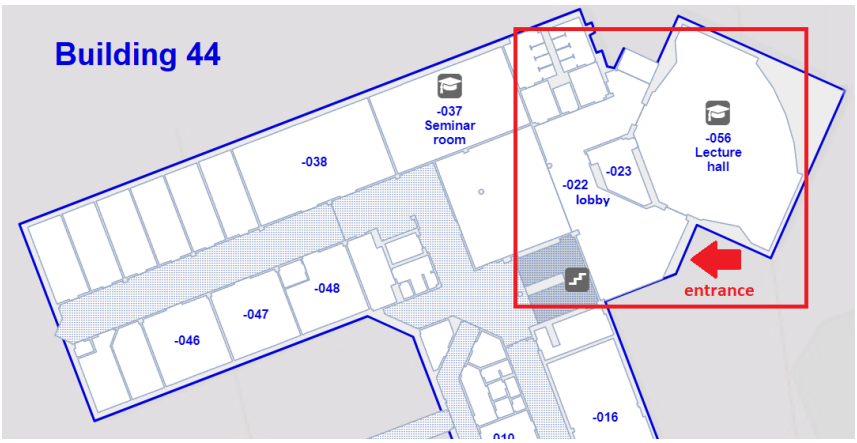

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CONFERENCE PROGRAMME

Wednesday, 7th September

arrival, registration of participants (12.00 - 17.00), poster set up time

14.30 - 14.45	**CONFERENCE OPENING**, practical information
	Block of lectures I. Chairs: Dr. Ross Jansen-Van Vuuren, assoc. prof. Oldřich Farsa
14.45 - 15.15	**PL04** SUSTAINABLE APPROACHES TO THE PREPARATION OF ISOTOPE-LABELLED PHARMACEUTICALS Jansen-Van Vuuren R. (University of Ljubljana, SI)
15.15 - 15.45	**PL06** ANTIMICROBIAL ACTIVITY OF RUTA CHALEPENSIS: A RESAZURIN ASSAY AND SCANNING ELECTRON MICROSCOPY-BASED APPROACH Sarker S. (Liverpool John Moores University, UK)
15.45 - 16.00	**L04** AROMATIC SCHIFF BASES AS AMINOPEPTIDASE N-INHIBITORS Farsa O. (Masaryk University Brno, CZ)
16.00 - 16.15	**L02** G-QUADRUPLEXES IN p53 CANCER BIOLOGY AND AS TARGETS OF DRUGS Brázdová M. (Masaryk University Brno, CZ)
16.15	**WELCOME DRINK**

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09.30 - 10.00	**L10** SYNTHESIS AND IN VITRO ANTIMICROBIAL ACTIVITY OF SOME HYBRID COMPOUNDS CONTAINING A PHENYLCARBAMIC ACID STRUCTURAL MOTIF Malík I. (Comenius University in Bratislava, SK)
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10.30 – 10.45	**L11** PRELIMINARY INVESTIGATION OF STRUCTURE–ACTIVITY RELATIONSHIPS FOR SEVERAL GROUPS OF JANUS KINASE INHIBITORS USING A CHEMOMETRIC PRINCIPAL COMPONENT ANALYSIS Nádaská D. (Comenius University in Bratislava, SK)
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PLENARY LECTURES

PL02

COMPUTATIONAL MODELING OF 3'-PHOSPHOADENOSINE 5'-PHOSPHOSULFATE SYNTHASE PAPSS

R. H. ETTRICH[1], B. MINOFAR[2], K. V. VENKATACHALAM[3]

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The sulfur nucleotide PAPS (3'-phosphoadenosine 5'-phosphosulfate) is the universal sulfuryl donor of the cell. In mammals 3'- phosphoadenosine 5'-phosphosulfate Synthase (PAPSS), using ATP, converts biochemically inert inorganic sulfate to the metabolically active PAPS. It is a bi-functional enzyme and catalyzes the formation of PAPS in two sequential steps [1] In the first step, inorganic sulfate reacts with ATP to form APS and pyrophosphate. The resulting phosphoric-sulfuric anhydride bond has high energy that is the chemical basis of sulfate activation. The second step is catalyzed by the kinase domain of PAPSS and involves the reaction of APS with ATP to form PAPS and ADP. The proper function of PAPSS is essential for normal physiology in the human being. As the ubiquitous sulfate donor in most biological systems, the product of the enzyme, PAPS, plays an essential role in ECM formation, embryonic development and biomolecule secretion. PAPSS has also been shown to be involved with the pathophysiology of a number of diseases and deficiency in human results in osteochondrodysplasias or defective cartilage and bone metabolism as evidenced in the clinical condition of the recessively inherited, spondyloepimetaphyseal dysplasia (SEMD). Using a combination of molecular docking, homology modeling, and molecular dynamics simulations in combination with experimental work we try to understand how the three dimensional structure of PAPSS determines the enzyme function, focusing on the roles of specific amino acid residues [2] /overall structures on the dynamics of the enzyme in aqueous solution and the related quaternary arrangements of the enzyme. Results are discussed that give a realistic picture of the enzyme activity.

References:

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PL04

SUSTAINABLE APPROACHES TO THE PREPARATION OF ISOTOPE-LABELLED PHARMACEUTICALS

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The preparation of isotope-labelled organic compounds, particularly deuterated compounds, has recently become a research area of significant interest for drug development [1, 2]. This surge in interest was partly triggered by the FDA approval of deutetrabenazine in 2017, the first for a deuterated pharmaceutical [3].

Two strategies are generally used for the synthesis of deuterium-labelled compounds: (i) a total-synthetic approach starting with commercially available deuterium-labelled precursors, and (ii) late-stage functionalization via hydrogen–deuterium (H-D) exchange. The latter approach can potentially produce deuterated compounds more rapidly and cost effectively [4]. H-D exchange is typically carried out using disposable iridium catalysts due to their regio- and stereo-selectivity, use of relatively mild reaction conditions, and treatment of a broad scope of substrates [5]. However, iridium is the ninth least abundant metal [6], and is currently experiencing a drastic price hike due to a surge in demand for its use in other applications such as the electrodes in fuel cells for electric cars. Thus, alternative approaches to iridium catalysis are being explored, and these will be expounded during my presentation, with a particular focus on embedding iridium within recyclable macromolecular architectures either as homogeneous or heterogeneous catalysts. I will also briefly introduce my research which centres on the development of recyclable dendrimer catalysts.

The research was supported by the European Union's Horizon 2020 research and innovation programme under the Marie Skłodowska-Curie grant agreement No 945380.

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PL05

DESIGN AND SYNTHESIS OF ASPARTYL(ASPARAGINYL)-BETA-HYDROXYLASE INHIBITORS FOR THE TREATMENT OF CANCER

M. OLSEN [1,2], P. IACOBAN [1]

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Aspartyl(Asparaginyl)-Beta-Hydroxylase (ASPH) is a 2-oxoglutarate (2OG) utilizing iron-dependent dioxygenase closely related to epigenetic enzymes such as KDM, TET1-3, and FTO [1]. ASPH catalyzes post-translational hydroxylation of critically positioned aspartic acids and asparagines in specific calcium-binding Epidermal Growth Factor (cbEGF) domains. Biologically, ASPH is involved in trophoblast invasion of the uterine wall and is expressed in the endoderm of developing embryos although expression in healthy adult tissue is extremely limited. Mutations in ASPH are linked with Traboulsi syndrome in humans [2]. Experimentally confirmed cbEGF substrates of ASPH include LDLR, C1R, JAGGED1, FX, and computationally predicted substrates include NOTCH1-4, JAGGED1&2, DLL1&4, DNER, DLK1&2 among others. A crystal structure of ASPH is available [3]. Hepatocellular carcinoma and pancreatic cancer are known to significantly over-express ASPH on the cell surface, conferring an aggressive, invasive phenotype. Other cancers such as mammary carcinoma may also over-express ASPH. ASPH has been demonstrated to aberrantly activate the NOTCH signaling pathway [4]. ASPH inhibitors have been rationally designed and synthesized, and demonstrate predicted activities in vitro, including suppression of migration, invasion, and NOTCH pathway related proteins [5]. In vivo proof-of-principle experiments demonstrate significant suppression of tumor growth of aggressive cancers including cholangiocarcinoma [6]. Current ASPH inhibitors are orally bioavailable, are not genotoxic, have no identified in vitro safety liabilities, and have not demonstrated intestinal toxicity unlike Gamma-secretase inhibitors. These compounds have demonstrated context dependent Notch pathway inhibition in vivo.

The study was supported by Midwestern University.

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PL06

ANTIMICROBIAL ACTIVITY OF *RUTA CHALEPENSIS*: A RESAZURIN ASSAY AND SCANNING ELECTRON MICROSCOPY-BASED APPROACH

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Iraq is surrounded by Turkey in the North, Saudi Arabia in the South, Iran in the East and Syria in the West. It has a rich diversity in its flora; there are *ca.* 360 medicinal plants from 270 genera and 98 families found in Iraq. However, about 3300 plant species belonging to 908 genera and 136 families grow in Iraq. Iraqi medicinal plants are the building blocks of Iraqi traditional medicinal heritage and practice, which still thrive in Iraq. Iraqi traditional medicine can be traced back to the Sumerian period (3000-1970 BCE) and then the Assyrian period (1970 to 589 BCE). Iraqi medicinal plants and their products have long been used for the treatment of various human diseases including infections.

As a part of our studies involving evidence-based phytotherapy, as well as plant-based drug discovery, which is the core research activity within the Centre for Natural Products Discovery at Liverpool John Moores University, different plant parts of *Ruta chalepensis* L., collected from Iraq, were studied for their antimicrobial activity, using a combination of the resazurin assay and scanning electron microscopy (SEM) to validate its traditional medicinal uses as an antimicrobial agent. Several antimicrobial compounds, predominantly coumarins and isoquinoline alkaloids, were isolated from *R. chalepensis* by preparative-reversed-phase-HPLC and the structures were elucidated by spectroscopic means. Some of these isolated compounds exhibited anti-MRSA activity against clinical isolates of methicillin-resistant *Staphylococcus aureus*.

PL07

NATURAL PRODUCTS FROM SEAGRASSES (ALISMATALES): CHEMICAL DIVERSITY, BIOACTIVITY, AND ECOLOGICAL FUNCTION

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Seagrasses are the only higher plants living in marine environments; they play a significant role in coastal ecosystems. Seagrasses inhabit the coastal shelfs of all continents except Antarctica and can grow in depths of up to 90 m. Because of their eminent ecological importance, many studies have been dedicated to seagrasses and their ecology. However, the phytochemistry has not been equally well investigated yet and many of the existing studies in chemical ecology are only investigating the chemistry at the level of compound classes, e.g. phenolics, and not at the level of chemically defined metabolites. Until the year 2016 (Zidorn, 2016), a total of 154 chemically defined natural products have been reported from the about 70 seagrass species known worldwide. Compounds reported include simple phenols derivatives (four compounds), phenylmethane derivatives (14 compounds), phenylethane derivatives (four compounds), phenylpropane derivatives including their esters and dimers (20 compounds), chalkones (four compounds), flavonoids including catechins (57 compounds), phenylheptanoids (four compounds), one monoterpene derivative, one sesquiterpene, diterpenoids (13 compounds), steroids (31 compounds), and one alkaloid. Recent studies from our group have been focused on apolar diarylheptanoids and the seasonal variation of natural products from *Zostera marina* from the Baltic Sea (Grauso et al., 2020; Li et al., 2019, 2021, 2022a, b).

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Grauso, L., Li, Y., Scarpato, S., Shulha, O., Rárová, L., Strnad, M., Teta, R., Mangoni, A., Zidorn, C., 2020. Structure and conformation of zosteraphenols, tetracyclic diarylheptanoids from the seagrass *Zostera marina*: an NMR and DFT study. Org. Lett. 22, 78-82. doi:10.1021/acs.orglett.9b03964

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LECTURES

L01

POLYMER PARTICLES AS CONTRAST AGENTS FOR PHOTOACOUSTIC TOMOGRAPHY

M. PAÚROVÁ[1], M. BABIČ[1*], I. ŠEDĚNKOVÁ[1], J. HROMÁDKOVÁ[1], P. MATOUŠ[2], P. KEŠA[2], P. JENDELOVÁ[3]

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Photoacoustic (PA) imaging detects an acoustic signal induced by light. This unique method provides simultaneously ultrasound anatomical information with high resolution along with a functional photoacoustic signal, which is created by transformation of a laser pulse to mechanical wave by some light absorbing chromophore. PA imaging shows great potential for various clinical procedures from diagnosis to therapy guidance, which arises from its ability to gather functional and molecular information in real-time regime with a high spatial resolution at clinically relevant depths together with the absence of ionizing beaming.

To maximize the contrast effect of the exogenous contrast agents (CA) in the living organism, the optical absorption of the CA should be optimally in the near-infrared (NIR) regions ~700 - 1100 nm and 1200 - 2000. We developed new heterogenous syntheses of polypyrrole (PPY) particles with PA contrast properties in NIR, which allow good control of size (10 nm step within the range 80-300 nm). Besides widely used linear water-soluble polymer stabilizers of the dispersion polymerizations, classical emulsifiers were also successfully employed in their synthesis, what broadens possibilities to employ less hydrophilic comonomers in the aqueous polymerization.

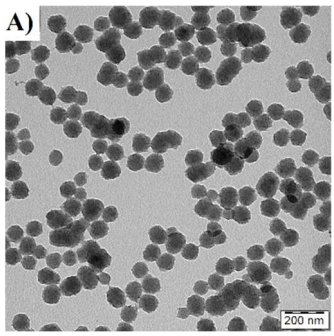

Figure: Transmission electron micrograph of polypyrrole particles prepared for photoacoustic imaging

This work was supported by the Ministry of Education, Youth and Sport of the Czech Republic [project no. LTAUSA18173 and Czech-BioImaging LM2018129].

L02

G-QUADRUPLEXES RECOGNITION BY P53 FAMILY AND MODULATION BY LIGANDS

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Putative G-quadruplexes (G4) motifs are frequently found in promoters, 5´UTRs and in the 3'UTRs. Recent evidence suggests G4s are involved in key genome functions such as transcription, translation, and epigenetic regulation. To date, different compounds have been developed that aim to target G4 structures (G4 ligands) and modulate or stabilize G4 structure formation. p63 and p73, members of the p53 family of transcription factors, can induce and repress transcription of an extensive network of common and unique genes by direct binding to a number of regulatory sites. We and others observed a strong correlation between DNA topology and transcription of p53 target genes. Also, we established p53 and G4 interactions [1]. G4 from c-myc promoter was strongly recognized by p53 and p53 binding lead to c-myc promoter repression in vivo. Furthermore, NMM stabilized G4 conformation of telomeric G4 was the G4 form of human telomere quadruplex favored by p53, suggesting conformational selectivity. Also, we have shown that R273H oncogenic mutant p53 frequently interacts with PQSs around transcription sites. Interaction of mutp53 with PQSs are presented as one of the mechanisms by which mutp53 actively promotes cancer. The main goal of our work is to prove G-quadruplexes as regulatory elements in p53 family biology. Several potential G-quadruplex forming regions in promoter, intronic or 5´UTR regions were selected based on our bioinformatics analysis. The project started with biophysical G4 structure analysis of potential G4 forming motifs derived from G-rich regulatory regions of selected p63 target genes (e.g. KRT14, BTG2, EGFR) and p73 target genes. G4 structure of these sequences was examined by CD spectroscopy. Analysis of NA binding properties of p63 isoforms was compared with p53. Different G4 ligands were used to probe protein-G4 interaction and target gene regulations in p53/p63/p73 biology.

The study was supported GAČR (grant No. 19-15168S).

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L03

THE EFFECT OF THE 'CATALYTIC TRIANGLE' ON THE LIPASE ACTIVITY

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Lipases in free or immobilized form belong to the most applicable catalysts pharmaceutical industry. The immobilization of lipases onto supports allows for obtaining higher catalytic activity. The intramolecular interactions between lipase, support, and substrate exist as a 'catalytic triangle'. Due to the evaluation of enzyme activity of lipase in a broad substrate spectrum, the optimal catalytic system can be gained [1-3]. The polyunsaturated (PUFAs) and monounsaturated (MUFAs) fatty acids, commonly named omega fatty acids, are characterized by multidirectional activity in human metabolism (e. g. cardioprotective, antiatherosclerotic, neuroprotective) [1-2]. Therefore, they were used as the substrates of fish and vegetable oils to evaluate lipase lipolytic activity [2]. The obtained results in our study showed high lipolytic activity of Amano lipase PS from Burkholderia cepacia (APS-BCL). Despite immobilized lipase activity decrease, compared with free form [1-2], the 'cut-off limit' to oils with a higher ω6/ω9 ratio (2.33 or higher), above that the lipolytic activity was higher, has been confirmed. The interactions mentioned above in the developed 'catalytic triangle' (diffusion of substrate info support, dispersion of lipase to substrate, lipase hyperactivation, the reaction medium, and the effect of immobilization) could influence lipase behavior. Therefore, it is suggested that an optimized catalytic system can be helpful in the future *in vitro* digestion of fats.

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L04

AROMATIC SCHIFF BASES AS AMINOPEPTIDASE N INHIBITORS

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Aminopeptidase N (APN) is a broad specificity zinc metallopeptidase involved in many physiological and pathological processes. Some of its inhibitors such as ubenimex or tosedostat were used as anticancer drugs. In the frame of this study, a series of thiosemicarbazones and semicarbazones derived from 2-, 3- or 4-(2-aminocetamido)acetophenones, where the amino group is a part of either dialkylamino group, or a saturated 5 – 7 membered nitrogenous heterocycle, which can be furtherly substituted, was prepared. Target compounds were isolated either as free bases, hydrochlorides, or perchlorates. The compounds were tested for inhibition activity against APN either by a standardized VIS-spectrophotometry method using a 96 well-plate reader or by an improved RP-HPLC procedure based on the method of Xiong et al.[1]. The activity results were processed into a QSAR study where the dependence of APN inhibition on lipophilicity expressed as log P and on electronic properties represented by the isoelectric point pI was demonstrated. Furthermore, five compounds with the best values of IC_{50} for APN (ranging between 13 – 23.5 μmol/l) underwent testing for inhibition of cell proliferation on the three different cell lines which differ one from each other in the level of APN expression [2 – 4]. All five compounds triggered a significant antiproliferative effect in the cell lines expressing APN, THP-1, and MCF-7, while in the cell line DU-145 with no APN expression, four of these five compounds did not affect proliferation at all. The remaining compound also inhibited DU-145 cells proliferation but less than in APN-positive THP-1 or MCF-7 lines. These results could suggest that the antiproliferative activity is linked with APN inhibition although other mechanisms can also participate in it.

The study was supported by MASARYK UNIVERSITY, grant numbers MUNI/IGA/0932/2021 and MUNI/A/1682/2020.

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L05

NOVEL 1,3,5-TRIAZINYL AMINOBENZENESULFONAMIDES AS POTENT ANTI-VRE AGENTS

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Carbonic anhydrases (CA, EC 4.2.1.1) are metalloenzymes catalysing the reversible hydration of CO_2, thereby affect the pH and affecting related physiological processes in various organisms [1].

In pathogenic bacteria, CAs play an important role in survival and growth [2]. Inhibition of bacterial CAs leads to growth retardation, growth defects and makes bacteria vulnerable to host defense mechanisms. Bacterial CAs are therefore a very promising target in the search for new antibiotics.

A series of 1,3,5-triazinyl aminobenzenesulfonamides substituted by aminoalcohol, aminostilbene, and aminochalcone structural motifs were synthesized as potential bacterial CAs inhibitors. The compounds were tested against vancomycin-resistant *Enterococcus faecalis* (VRE) isolates. A great number of the tested compounds exhibit a significant inhibitory activity against VRE.

To evaluate the selectivity of the compounds against bacterial CAs towards human CAs (hCA) the inhibitory activity of compounds against tumor-associated hCA IX and hCA XII, hCA VII isoenzyme present in the brain, and physiologically important hCA I and hCA II were determined. Tested compounds had only a negligible effect on physiologically important isoenzymes.

In conclusion, newly prepared compounds have a great potential as antibacterial agents with high activity and at the same time with high selectivity for bacterial CA in comparison with metabolically important hCA isoenzymes (e.g. hCA I, hCA II) found in the human body.

The study was supported by INGA MU (MUNI/A/1202/2020).

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L06

SYNTHETIC POLYMERS AS CARRIERS OF BIOLOGICALLY ACTIVE COMPOUNDS

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The use of nanomedicines consisting of polymer carriers as drug delivery systems is a promising strategy to reduce adverse effects and enhance the therapeutic efficacy of several disorders, namely, cancer. Polymer carriers can protect numerous bioactive compounds, improve their pharmacokinetic profile, and prolong their circulation time in the body. These compounds can be attached to the carrier via suitable biodegradable spacers responsive to various tumor-associated stimuli. Also, polymer-based nanomedicines are passively accumulated in solid tumors to a higher extent due to the “enhanced permeability and retention” (EPR) effect. Biologically active compounds can be released in the target tissue or cells after their specific target followed by their interaction with suitable receptors, thus improving their action.[1–3]

Synthetic polymer carriers based on *N*-(2-hydroxypropyl)methacrylamide (HPMA) copolymers are especially attractive for the construction of *in vivo* applicable nanomedicines since they are fully biocompatible, water-soluble, and lack any toxicity or immunogenicity. Their favorable pharmacokinetics enables a higher uptake in solid tumors or inflammation sites, therefore reducing dose-related adverse side effects on healthy organs, with an enhanced therapeutic outcome. The therapeutic specificity and potential of biocompatible nanomedicines can also be improved by attaching specific targeting moieties along the polymer backbone thus their selective interaction with overexpressed tumor cell receptors can trigger numerous biological activities, which makes them potential nanomedicines for anticancer therapy.

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L08

IMAGING OF ELEMENTS AND PROTEINS IN BIOLOGICAL TISSUES: MEDICAL AND PHARMACEUTICAL APPLICATIONS

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In the last decades, increased interest in imaging of elements/metals/proteins distribution, mainly in pharmaceutical, biomedicine research, or life science with direct application of research to specific problem/disease [1-3]. The main emphasis of this contribution is to demonstrate the unique method of laser ablation with inductively coupled plasma and mass spectrometry (LA-ICP-MS). It is a well-established method for multi-elemental analysis of elements at trace and ultra-trace. Nowadays, it is also starting to be used as a technique for the simultaneous specific determination of the protein of interest, which opens up the possibility of achieving the so-called multiplex analysis.

Proteins are imaged using an immunohistochemical method (binding nanoparticle-labeled antibodies to a specific protein) and LA-ICP-MS. The main advantages of utilizing LA-ICP-MS are the acquisition of comprehensive (Metallo)proteomic information about the tissue of a given disease (in this case, cancer or stroke) or low detection limits compared to other conventionally employed protein imaging techniques in combination with multiplex analysis of one sample.

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L09

A RAPID HPLC-ELSD METHOD FOR SEPARATION OF SUGARS AND SUGAR ALCOHOLS IN FRUITS OF CZECH *SORBUS* SPECIES

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Plants of the genus *Sorbus* are spread all over the world and their fruits are used in folk medicine, especially rowanberries are known for their diuretic effect and *S. domestica* fruits are traditionally consumed as an antidiabetic agent. However, the landscape of the Czech Republic provides a unique environment that enabled the creation of several endemic microspecies due to the ability of apomixis of *Sorbus* species. Unfortunately, these endemic species are overlooked and we know nothing about their phytochemical profile so far. Therefore, this is the first study dealing with Czech *Sorbus* species focused on the content of sugars and sugar alcohols. For this purpose, a rapid HPLC-ELSD method has been developed in order to simultaneous detection of sugars and sugar alcohols commonly occurring in various berries. All tested components have been completely separated within 12 min. Unsurprisingly, the analysis revealed the fruits of *Sorbus* species to be rich in glucose and sorbitol. However, based on the content of dominant sugars and based on the presence of minor ones, it can be pretty easily recognized which subgenera they belong to. Therefore, this separation method can be used for both analytical and chemophenetic purposes.

L10

SYNTHESIS AND *IN VITRO* ANTIMYCOBACTERIAL ACTIVITY OF HYBRID COMPOUNDS CONTAINING AN 2-/3-/4-ALKOXYPHENYLCARBAMIC ACID STRUCTURAL MOTIF

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The research focused on a synthesis, *in silico* evaluation and *in vitro* antimycobacterial screening of the molecules (**Ia** – **Vd**) consisting of an 2-/3-/4-alkoxyphenylcarbamoyloxy moiety (alkoxy = methoxy to butoxy), connecting 2-hydroxypropan-1,3-diyl chain and 4-[(substituted)phenyl-/pyrimi-din-2-yl]piperazin-1-yl privileged structure (Figure). The lipophilicity, polarity, molecular flexibility, saturation, druglikeness and pharmacokinetic descriptors for basic forms (**IaB** – **VdB**) of final derivatives (**Ia** – **Vd**) were predicted employing several online predictor tools and software packages. The molecules **Ia** – **Vd** were tested against *M. tuberculosis* CNCTC My 331/88 (identical with $H_{37}R_v$ and ATCC 2794), *M. kansasii* CNCTC My 235/80 (identical with ATCC 12478), *M. avium* CNCTC My 330/88 (identical with ATCC 25291) and *M. kansasii* 6509/96 clinical isolate, respectively, by standardized microdilution methods using isoniazid, rifampicin and ethambutol reference drugs [1 – 3]. The insight into structure–antimycobacterial activity relationships considering the *in silico* and estimated biological descriptors was provided as well.

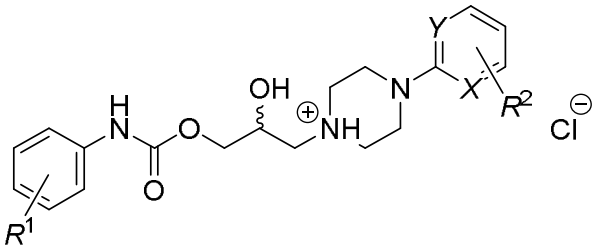

Figure Structure of synthesized 1-[3-(2-/3-/4-alkoxyphenylcarbamoyloxy)-2-hydroxypropyl]-4-[(substituted)phenyl/pyrimidin-2-yl]piperazin-1-ium chlorides (**Ia** – **Vd**; alkoxy = methoxy to butoxy), which were *in vitro* screened against the *M. tuberculosis* CNCTC My 331/88 (identical with $H_{37}R_v$ and ATCC 2794), *M. kansasii* CNCTC My 235/80 (identical with ATCC 12478), *M. avium* CNCTC My 330/88 (identical with ATCC 25291) and *M. kansasii* 6509/96 strain, respectively.

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L11

PRELIMINARY INVESTIGATION OF STRUCTURE–ACTIVITY RELATIONSHIPS FOR SEVERAL GROUPS OF JANUS KINASE INHIBITORS USING A CHEMOMETRIC PRINCIPAL COMPONENT ANALYSIS

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The research focused on structure–activity relationships (SAR) for several groups of Janus kinase isoenzyme (JAK1 – JAK3) inhibitors (n = 74) containing a **purinone**, **pyrazolopyrimidine** or **benzimid-azole** scaffold (Figure). The SAR analyses inspected possible connections between *in silico* descriptors of those derivatives and their ability to *in vitro* inhibit JAK1 – JAK3 [1] employing a Principal Component Analysis (PCA) tool for dimensionality reduction, data compression, feature extraction as well as data visualization. All JAK1 – JAK3 inhibitory activity constants (IC_{50} values) were adopted [2 – 4]. The calculated physicochemical descriptors were molecular weight (*MW*), number of carbon atoms in sp^3 hybridization (*csp3*), molecular volume (*MV*), molar refractivity (*MR*) or lipophilicity parameters (log *P* values predicted by several methods), among others, using several interactive online predictor tools as well as software packages. Positive correlation defined by a Pearson's correlation coefficient (r) was found between predicted lipophilicity (LOGP (SILICOS-IT) method) and JAK1 inhibitory activity of the ligands (r = 0.694); given conclusion mainly concerned the **purinone** derivatives (n = 29, r = 0.765). The *csp3* descriptor for **purinone** compounds inversely correlated with both JAK1 (r = -0.670) and JAK2 (r = -0.706) inhibitory efficiency. The current study hypothesized that analyzed molecules might inhibit both JAK1 and JAK2 in a similar manner.

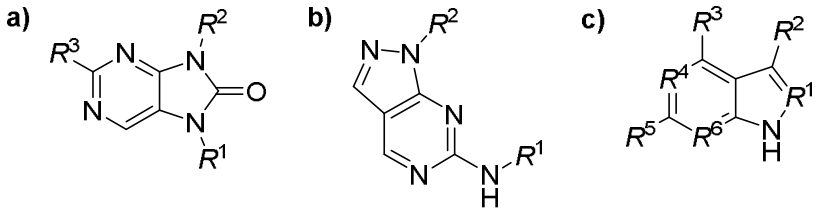

Figure General structure of Janus kinase inhibitors containing a variously substituted **a) purinone**, **b) pyrazolopyrimidine** or **c) benzimidazole** scaffold.

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L12

PHARMACOKINETIC PROFILING VIA DRIED BLOOD SPOT SAMPLING METHOD

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Pharmacokinetic (PK) profiles are still an inevitable part of preclinical safety studies. Generally, PK studies require the collection of a series of blood samples in sufficient volumes (usually about 200 µl). Typically, animal protocols limit the total blood draw between 10 and 15 % of the total blood volume allowed within a 2-week period. Further, animal models are subjected to ethical standards to be carefully monitored and principles of the 3Rs are required: replacement, reduction and refinement [1].

Blood microsampling can be defined as blood sample collection that is no more than 50 µl total volume. Blood microsampling techniques cover capillary blood or plasma microsampling, dried blood spots (DBS) and accurate volume dried blood sampling. The usage of DBS in preclinical PK studies enables serial sampling from a single animal which results in data quality improvement, significantly reduces the number of animals required and offers significant ethical and cost benefits supporting the overall objectives of 3Rs. Further, a recent scientific paper suggests a very good correlation of PK parameters obtained from whole blood in the form of DBS and plasma samples [2].

Our pilot PK study of clozapine (CLO) was conducted in a single Wistar albino rat. The study was approved by the local and national animal welfare committee (No. 58013/2017-MZE-17214). CLO was administrated subcutaneously in a single dose bolus (20 mg/kg) and blood samples were taken from a retroorbital plexus by a calibrated glass capillary and spotted onto the card (Whatman 903 Protein Saver Card). CLO concentrations were acquired by LC-MS method and corresponding PK parameters were calculated by Kinetica 4.4 software. The obtained pharmacokinetic parameters are in agreement with those reported previously [3].

The study was supported by the Grant Agency of Masaryk University, project MUNI/G/1464/2018 and MUNI/A/1440/2021.

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L13

PRENYLATED PHENOLICS AS PLEIOTROPIC BIOACTIVE SUBSTANCES

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Natural substances often have a pleiotropic effect and can affect several cellular processes in parallel. They can have parallel anti-inflammatory and antibacterial effects, together with the current antiviral effect. Their mechanism of action is complex. However, the problem of natural substances is often their limited solubility and consequently also problematic bioavailability [1]. Series of prenylated phenols were isolated from Paulowniaceae, Moraceae, and Euphorbiaceae plants [2-5]. As part of the lecture, we will introduce the isolation and identification of prenylated phenols with potential antiviral and anti-inflammatory effects, we will describe their bioactivity, their formulations to increase solubility, and will describe the possibilities of their further development. We described the effects of phenolics in vitro in cellular or biochemical systems on the production and release of inflammation-related cytokines; their effects on the inhibition of cyclooxygenases and lipoxygenases, and also some in vivo experiments confirming activity. At the end, an improvement of solubility by incorporating of tested substances into liposomes was presented.

The work was supported by Czech Science foundation, project no. 21-38204L Complexes of selected transition metals with plant-derived compounds with anti-NF-kappa B and pro-PPAR dual activities.

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L14

PERHALOACETALDEHYDES IN THE ENANTIOSELECTIVE ORGANOCATALYZED FRIDEL-CRAFTS ALKYLATION: REACTION CONDITIONS DEVELOPMENT

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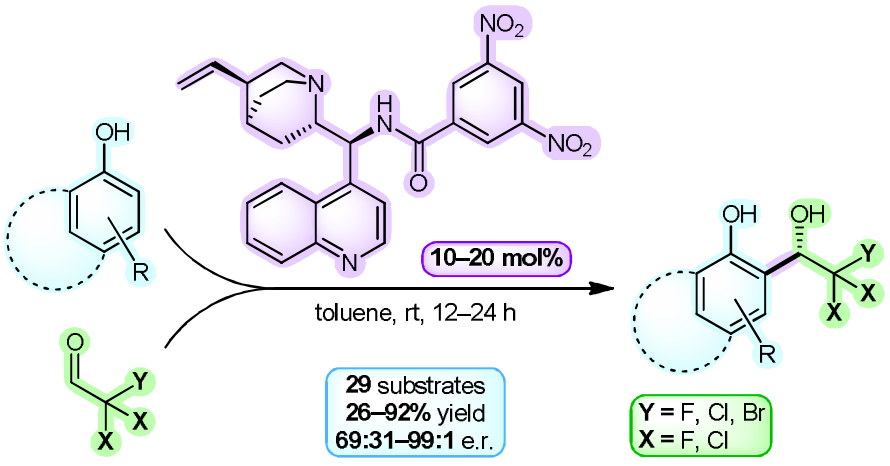
Trihaloacetaldehydes represent useful electrophiles in asymmetric processes that can grant access to many biologically active compounds containing CX_3 groups. One of the possibilities for obtaining aromatic trihaloethanols is the asymmetric organocatalyzed Friedel-Crafts reaction between phenol and trihaloacetaldehyde, which represents the subject of our current research. As such, we started with the extensive three-phase catalyst screening. Cinchona alkaloid-based amide derivatives showed the best enantioselectivity in the initial stage of catalyst testing. Improvement of the catalyst structure revealed 3,5-dinitrobenzamide of 9-amino*epi*cinchonidine as the lead catalytic molecule. Next, a series of optimizations were performed to establish the most suitable reaction conditions. Having the optimal parameters in hand, the reaction between electron-rich phenols and trihaloacetaldehydes or their hemiacetals conveniently provided enantioenriched adducts with good to excellent enantiomeric ratios (up to 99:1) within 12–24 h at 25 °C. The substrate scope included 29 derivatives containing $–CF_3$, $–CCl_3$, $–CF_2Cl$, and $–CF_2Br$ groups. Additionally, several stereoretentive downstream transformations of products were identified. This work constitutes the first organocatalyzed method for the synthesis of chiral non-racemic 2,2,2-trihalo-1-hydroxyalkylphenols [1].



The study was supported by the projects MUNI/A/1510/2020 and MUNI/A/1682/2020.

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L15

INTRODUCTION TO THERANOSTICS

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Drug delivery systems (DDS) are extensively studied and developing in commercial products to improve the efficacy and administration of active pharmaceutical compounds, such as low molecular drugs, recombinant proteins and enzymes, peptides, vaccines, antibodies, various contrast agents etc. There also some limitations for application of nanosystems for medical application. Nanotoxicity and interaction with immune system are the most important ones. From the pharmacological point of view e.g., first pass effect, instability in body fluids, intolerance and induction of immune unwanted and harmful response, fluctuations in plasma drug levels resulting in limited effectiveness, lack of selectivity, poor bioavailability, etc. To achieve the goal of targeted and selective delivery a plethora of controlled DDS have been developed.

The DDS become an indispensable tool also for development of commercial product for preclinical and clinical theranostics, combining both diagnostic and therapeutic properties to improve medical intervention in various disease. The diagnosis and treatment of cancer is in the first line of application of theranostics, but also brain diseases and inflammation are of great importance.

Some aspect of modern theranostics and imaging system will be presented and discussed.

L16

THE COMBINED TREATMENT OF METHOTREXATE WITH CARNOSIC ACID INFLUENCES HEPATIC mRNA EXPRESSION OF INFLAMMATORY AND ANTIOXIDANT GENES IN MODEL OF ADJUVANT ARTHRITIS IN RAT

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Rheumatoid arthritis (RA) is a chronic autoimmune inflammatory disease characterised by polyarthritis and systemic low-grade inflammation. The inflammation is accompanied also by oxidative stress and changes in levels of antioxidant enzymes, such as catalase (CAT), paraoxonase (PON-1), superoxide dismutase 1 (SOD-1) or heme oxygenase 1 (HO-1) [1]. A combination of standard therapy with natural compounds with anti-inflammatory or antioxidant activities may improve treatment effectivity, allow reduced dosing and thus decrease the side effects. The aim of our study was to test the therapeutic potential of carnosic acid (CA), the natural compound with anti-inflammatory and antioxidant activities [2], as a monotherapy or in combination with methotrexate (MTX) for the treatment of adjuvant arthritis (AA). AA, the pathology similar to RA, was in rats induced by intradermal administration of heat-inactivated *Mycobacterium butyricum* in incomplete Freund´s adjuvant. The expression of antioxidant and inflammatory genes was measured in the liver, after isolation of RNA and analysis by quantitative PCR. In our experimental settings, the mRNA expression of SOD-1 was unchanged under inflammatory conditions. Although in monotherapy, CA was not effective, combination treatment with MTX was in arthritic rats associated with a significant reduction of hind paw volume and arthritic score, and also with reduced gene expression of IL-1β, HO-1 and upregulated gene expression of CAT, PON-1. Since PON1 is also part of the HDL, its upregulation may improve HDL functionality and thus improve cardiovascular health in patients. These results suggest a promising therapeutic potential of CA in combination with MTX.

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L16

LIBERATION OF IBUPROFEN FROM POLYSACCHARIDE HYDROGELS

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In this comparative study, rheological and texture properties of 11 polysaccharide-based hydrogels were comprehensively investigated along with the *in vitro* release of model drug ibuprofen (IBU). At first, the rheological properties of the hydrogels as dependencies of shear stress on the shear rate were evaluated to recognize the type of flow. Based on viscosity values, three categories of hydrogels were selected, i.e., low-, medium- and high-viscous and two later categories were further studied for texture properties. In the second step, hardness, adhesiveness, and minimal retracting force, were evaluated by texture profile analysis.

Drug release kinetics were compared through the coefficient of determination expressed for the regression line of five kinetic models. The values indicated that the drug release of the hydrogels during *in vitro* diffusion studies follows mostly the Higuchi model, whereas drug release from CS hydrogels follows zero-order kinetic. Significant differences in IBU diffusion were statistically confirmed among the groups of the hydrogels composed of positively charged, neutral, or negatively charged polysaccharides. Here, differences in provided interactions (mainly attractive/repulsive Coulomb forces) of the ionic polymers with the formulated anionic drug played a key role in different IBU release profiles, as supported by statistical analysis (Student's t-test). The knowledge on provided interactions can be utilized when formulating one or more drugs with their different character and release kinetics.

The knowledge on rheological and texture properties as well as drug release kinetic profiles of individual polysaccharide hydrogels, as comprehensively presented in this work, can also be advantageously utilized in the creation of various hydrogel preparations with modified drug release profiles suitable for particular drug delivery purposes.

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POSTERS

P01

DETERMINATION OF THE CRITICAL MICELLAR CONCENTRATION OF HEPTACAINIUM CHLORIDE IN AQUEOUS AND ALCOHOL SOLUTIONS USING THE OPTICAL DENSITY METHOD

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Micelles are self-assembled aggregates that are formed, in many different structures, from surfactants and have a wide range of applications. The critical micellar concentration (CMC) is the concentration of surfactant in a bulk phase, above which aggregates of surfactant molecules start to form. The CMC is an important characteristic for surfactants.
The CMC value of heptacainium chloride [1] in aqueous medium at laboratory temperature was determined by measuring the optical density on a microtiter plate [2].
Subsequently, the CMC value of heptacainium chloride in solutions of monohydric alcohols - methanol, ethanol and propanol - in concentrations of 10%, 20%, 30% and 40% was determined by this method. In the case of all three monohydric alcohols, a gradual increase in CMC was observed, together with an increasing concentration of alcohol in the solutions, and when a certain point was reached, the CMC value began to decrease again.

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P02

SCHIFF BASES AS POTENTIAL INHIBITORS OF AMINOPEPTIDASE N AS ANTICANCER AGENTS

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Many Schiff bases appear to be important intermediates in a number of enzymatic reactions. The presence of the azomethine group, as well as their interesting physical and chemical properties, cause the widespread application of their metal complexes [1]. Synthesized groups of basic thiosemicarbazone and semicarbazone derivatives of acetophenone have these properties as well.

Aminopeptidase N (AP-N), or membrane alanyl aminopeptidase (m-AAP), is a neutral zinc-binding metallopeptidase that cleaves N-terminal residues from protein and peptides. This aminopeptidase turns out to be identical to the human cluster differentiation antigen CD13 expressed on the surface of myeloid progenitors and myeloid leukemia cells [2]. Potential inhibitors of AP-N may offer effective and broad-spectrum therapy.

Determination of AP-N inhibition by using a high-performance liquid chromatography has become the analytical method of choice. L-Leucine-*p*-nitroanilide was used as a substrate and its hydrolytic product, *p*-nitroaniline was monitored at 405 nm absorption wavelengths. The compounds with the best inhibitory activity on the APN enzyme underwent testing for inhibition of cell proliferation on the three different cell lines. A simple QSAR model describing the dependence between the inhibitory activity expressed as IC_{50} and the descriptors derived from the chemical structure was constructed.

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P03

SYNTHESIS OF BIOLOGICALLY ACTIVE HETEROCYCLES DERIVED FROM ISATIN

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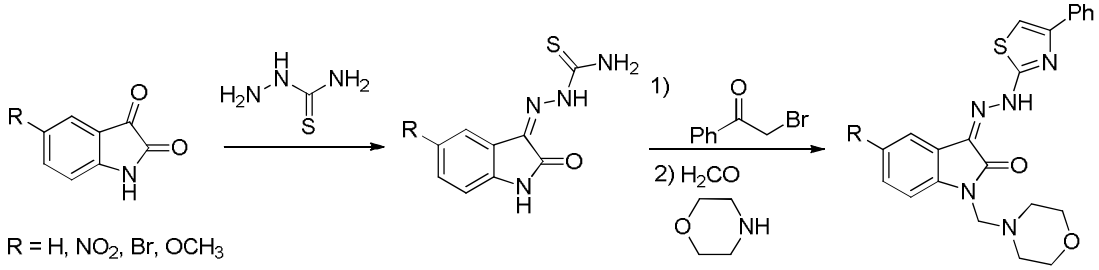
Isatin has been widely used in drug discovery. The ring is part of many naturally occurring compounds and is used to design compounds with diverse biological activities. Structurally, isatin is a fusion of six-membered benzene ring and five-membered ring containing nitrogen. The isatin derivatives possess several biological properties such as anticancer effect in different types of cancer [1], antibiotics and antidepressants [2], anxiogenic, sedative, anticonvulsant [3], antibacterial, antifungal and antidiabetic [4] etc.

Diabetes mellitus is a group of metabolic disorders of carbohydrate metabolism characterized by high blood glucose levels (hyperglycemia), resulting from defects in insulin secretion, insulin action, or both [5]. A set of four novel isatin-thiazole derivatives with potential antidiabetic activity [6] were synthesized by three-step synthesis from comercially available isatines. Final isatin-thiazole derived compounds were prepared in overall yield 48-66 %. The individual intermediates and the final products were confirmed by ^{1}H NMR and ^{13}C NMR spectroscopy.



R = H, NO_2, Br, OCH_3

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P04

DETERMINATION OF SUGAR PROFILE IN MILK AND SPECIAL INFANT'S FORMULAS BY HPLC

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Lactose is a disaccharide, typically called milk sugar, composed of galactose and glucose. This disaccharide is present in higher amount of milk carbohydrates content. For babies it is the most important saccharide, and it is cleaved by enzyme called lactase (hydrolase) to monosaccharides, which are utilized. The aim of this paper was primary to develop and apply a method for the determination and quantification of lactose, but in case that sample contents other sugars like glucose, galactose, sucrose and maltodextrins, we can determinate than and some quantify. In commercially available samples of whole cow´s milk and selected neonatal dairy nutrition was lactose determined and quantified. In case, that milk was treated by high temperature (UHT, ultra–high temperature; special types of milk), it could by present lactulose, a synthetic isomer of lactose.

HPLC (high performance liquid chromatography) in mode HILIC (hydrophilic interaction chromatography) could be nowadays quite often used in pharmacy. HILIC has some benefits like speed of analyses (typically high flow grade) and type of analytes (in our case carbohydrates, which cannot be determinate so easy by normal reversed phase chromatography). With a suitable combination of polar and non–polar components of the mobile phase, we can quickly separate carbohydrates. However, since carbohydrates do not contain any chromophore in their structure, a conventional UV–detector is unusable, and thus an evaporative light-scattering detector (ELSD) can be advantageously used. Stacionary phase used in HILIC mode is silica, which is in most cases modified with polar groups (hydroxy, amine, amide,…). Mobile phase is usually mixture of water (polar) and acetonitrile (nonpolar). The method was developed on a Dionex UltiMate 3000 HPLC kit (ThermoFisher Scientific, USA) with a HALO Penta–HILIC 4.6 x 150 mm column (AMT, USA) with a stationary phase of modified silica particles with a maximum size of 2.7 μm and an ELS detector Varian 380–LC (Varian, USA). Chromeleon and MS Excel software were used to evaluate the obtained data. After optimizing the conditions of the method, the temperature was determined to be 10 °C, the flow rate of the mobile phase 2 ml per minute and the use of a mixture of acetonitrile and 30 mmol/l ammonium formate buffer as mobile phase. Gradient elution was used. Detection conditions were determined at a nitrogen flow of 1 slm, a temperature of a nebulizer and an evaporator of 40 °C.

Under our optimized conditions, the method can determinate lactose in 12.60 min, lactose–lactulose resolution 1.70; repeatability (peak area) 2,73%; repeatability (lactose retention time) 2,26%; LOD 60,26 mg/ml and LOQ 109,01 mg/ml, recovery (method of externally standard addition) 96,7–107,1%.

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P05

APPLICATION OF THIN LAYER CHROMATOGRAPHY ANALYSIS FOR EVALUATION OF THE LIPOPHILICITY OF SELECTED ANTIANDROGEN DRUGS

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Lipophilicity is an important physicochemical parameter of a drug. It affects its activity and toxicity [1]. This value determines the bioavailability of the drug as well as its solubility in body fluids. Lipophilicity is a widely used parameter in the process of designing substances as candidates for new drugs. The most frequently used methods for determining lipophilicity parameters are reverse phase thin layer chromatography and high performance chromatography (RP-TLC, RP-HPLC). We also distinguish computational methods - computer programs [2]. The subjects of the research were drugs belonging to the group of antiandrogens such as abiraterone, bicalutamide, flutamide, nilutamide, leflunomide, teriflunomide and ailantoine. They are used in the treatment of prostate cancer and belong to different including a newer generations of antiandrogens. In this work, the usefulness of the TLC method and selected computational algorithms for the determination of the lipophilicity parameter of these drugs were assessed. In conducted lipophilicity studies, the following chromatographic plates were used as stationary phases: $RP2F_{254}$, $RP18F_{254}$ and $RP18WF_{254}$ and the mixture of ethanol-water, propanol-water, acetonitrile-water in various volume ratios as the mobile phases. Compounds were analyzed at λ = 254 nm. The chromatographic parameter of lipophilicity of the tested compounds was compared with the theoretical values estimated with the use of a computer programs. The obtained results indicate the usefulness of the TLC method for determining the experimental lipophilicity parameter of the tested compounds. It was stated that cluster analysis allowed to estimate the similarity between the compounds studied on the basis of obtained results of both, chromatographic and theoretical parameters of lipophilicity.

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P06

BIOLOGICALLY ACTIVE XANTHONES FROM *MACLURA POMIFERA*

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Xanthones are secondary metabolites occuring only in a few plant families and are known for their *in vitro* cytotoxic, antitumor and antimalarial activity [1].
Maclura pomifera is an interesting source of biologically active xanthones, often with side prenylated modification. Based on the literature data and our previous research [2, 3], ethanolic extract of maclura stem bark was prepared using maceration and ultrasonication; the liquid/liquid extraction followed. Column chromatography of ethyl acetate fraction led to the isolation of three xanthones - toxyloxanthone C, mesuaxanthone A and osajaxanthone. Isolated compounds were identified using HPLC, MS and 1D and 2D NMR experiments.
Subsequent semi-preparative HPLC chromatography of selected subfraction enabled isolation of another two xanthones, currently being identified.
Isolated compounds will be screened for biological activity, especially anti-inflammatory and antioxidant effect to broaden the spectrum of potential therapeutical applications of these xanthones. Based on further studies, they could find application in therapy of e.g. some skin diseases demanding the combination of dual biological activity. Moreover, our isolation of xanthones with different substituent modification can enable to better describe the structure-activity relationship.

The study was supported by Masaryk University (Specific research—support for student projects), grant number MUNI/A/1688/2020.

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P07

STUDY OF IBUPROFEN LIBERATION FROM HYDROGELS CONTAINING COMBINED GELLING AGENTS

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In pharmaceutical preparation, polysaccharide-based excipients are substances capable to influence and control the release of the drug and therefore its bioavailability. By their combination, it is possible to additionally modify and adjust the drug release. In this work, combinations of cationic hydrogels with neutral or anionic ones were performed to illustrate possibilities of providing modified ibuprofen (IBU) release profiles. Three combinations of polysaccharide hydrogels were studied for rheological and texture properties and ibuprofen diffusion: (i) cationic hydrogel with ionic (anionic) one, (ii) cationic hydrogel with ionizable (anionic) one, and (iii) cationic hydrogel with a neutral one. For this, 3% high molecular weight chitosan CS HMW was combined with 0.5% and 1% sodium salt of carboxymethylcellulose NaCMC (i), carboxymethylcellulose CMC (ii), and methylcellulose MC (iii). In this context, chitosan was presented as an effective modifier of diffusion profiles for negatively charged drugs formulated into combined polymeric systems, providing their prolonged release.

A combination of cationic hydrogel (CS) with the neutral one (MC) showed the slowest IBU release. It can be explained simply by an increased number of free functional groups of the polymers offering additional interactions/binding (mainly H–bonds) with IBU. On the other hand, a combination of cationic hydrogel (CS) with anionic ones (NaCMC and CMC) speeds up the IBU release. The IBU diffusion can be influenced by several mechanisms including ionic crosslink of the polymers via their oppositely charged groups, attraction of IBU via free (non-crosslinked) amino groups of CS, repulsion of IBU via free (non-crosslinked) carboxylate groups of NaCMC or CMC, and, obviously, binding via several electroneutral functional groups of NaCMC or CMC (mainly through H–bonds).

Hence, for future studies, when considering the formulation of a group of hydrophobic drugs possessing a negatively charged functional group (as model drug ibuprofen), CS can be advantageouslyutilized as a basis for designing new (e.g., combined polymer) systems for controlled drug release mainly prolonged or sustained.

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P08

ISOLATION AND IDENTIFICATION OF DITERPENES FROM *COLEUS FORSTERI* 'MARGINATUS' AND *PLECTRANTHUS CILIATUS*

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Coleus forsteri 'Marginatus' (Benth.) A.J.Paton and *Plectranthus ciliatus* E.Mey. are ornamental plants belonging to the Lamiaceae family [1]. Although only little information regarding their phytochemistry was published [2, 3, 4], many species of the medicinally important genus *Plectranthus s.l.* have been shown to produce phenolic compounds and terpenes. Within the group of terpenes, diterpenes have become the most studied subgroup because of their structural diversity and various biological activities such as antimicrobial, antiprotozoal, cardiotonic, gastroprotective, and cytotoxic activity [1, 4].

In our present work, we aimed to investigate the methanolic extracts of the aerial parts of *C. forsteri* 'Marginatus' and *P. ciliatus* which led to the isolation of four abietane and two kaurane diterpenes, respectively. Five of them have never been reported in these species. The substances were isolated using flash chromatography and RP-HPLC and their identification was carried out by high-resolution mass spectrometry, one-dimensional and two-dimensional nuclear magnetic resonance spectroscopy as well as circular dichroism spectroscopy.

The study was supported by Grant Agency of Masaryk University (grant number MUNI/A/1688/2020), the Centre for International Cooperation of Masaryk University (Exchange program ERASMUS+), and the NKFIH, Hungary (K-134704).

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P09

2-HYDROXYNAPHTHALENE-1-CARBOXAMIDES POSSESSING ANTIMYCOBACTERIAL ACTIVITY

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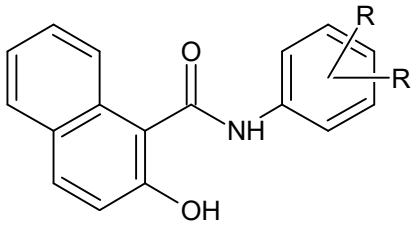
Despite of the approval of some new antituberculosis drugs in recent years (such as bedaquillin, delamanid, pretomanid), tuberculosis (TB) now ranks alongside human immunodeficiency virus as a leading death causing infectious disease worldwide. Based on the recent World Health Organization tuberculosis report, TB killed 1.5 million people in 2020 worldwide; 9.9 million people are estimated to have fallen ill with TB in 2020. Almost 70% of new TB cases was caused by rifampicin-resistant strains (4% in 2010). The rapid increase of resistance makes the discovery of new molecular scaffolds a priority to achieve effective control of the disease. [1]

The aim of recent work was to synthetize series of *N*-(phenyl)-2-hydroxynaphthalene-1-carboxamides with multiple substitution on phenyl ring (Fig. 1). 30 compounds with halogen, trifluoromethyl, methyl, methoxy and nitro substituted anilide ring were prepared according to well approved microwave-assisted synthetic method. [2] Structure of novel compounds was confirmed by ^{1}H and ^{13}C NMR, HRMS and IR spectroscopy. Primary *in vitro* screening of the synthesized compounds was performed against *Mycobacterium marinum*, *Mycobacterium kansasii* and *Mycobacterium smegmatis*. Several compounds showed antimycobacterial activity comparable to standards Pyrazinamide and Rifampicine.



R: -Me, -OMe, -F, -Cl, -Br, $-CF_3$, $-NO_2$

Figure 1 Substituted *N*-(phenyl-2-hydroxynaphthalene-1-carboxamides

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P10

INSIGHT INTO SYNTHESIS OF POLYHYDROXY 2-ARYLBENZOFURANS

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Benzofurans which possess prenyl or geranyl chains are naturally occurring compounds that are of pharmaceutical interest thanks to their broad spectrum of biologicalactivity. Mulberrofurans, geranylated polyhydroxy benzofurans, found in bark root of Morus sp. have been studied mainly for their antiphlogistic, antioxidative and cytotoxic effect [1, 2, 3].
Although these compounds are known for more than 40 years only a few of these compounds were synthesized [4, 5]. This work aims to prepare mulberrofuran Y, which could then be further analyzed and studied in various biological assays and hopefully used as a template for preparing more potential derivatives.
First attempts aimed to prepare substituted O-arylhydroxylamine which could be used as a key intermediate in process of preparing 2-arylbenzofuran skeleton, but this pathway led to no success [6]. Another unsuccessful trial was carried out using isovanillin as a starting compound, aiming to prepare polysubstituted 2-iodophenol as another key intermediate [7].
Aiming to prepare the same key intermediate, salicylaldehyde and methyl 4-iodosalicylate have been chosen as precursors in other synthetic pathways, which among other things, resulted in the synthesis of several novel compounds as well as the finding of unpredictable chemical behavior within synthetic pathways.

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P11

EFFECT OF LACTOBACILLI ON 5-FLUOROURACIL-INDUCED INTESTINAL MUCOSITIS *IN VITRO*

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5-Fluorouracil (5-FU) is commonly used for the treatment of various tumors and is the key drug in colorectal cancer treatment (CRC) [1]. Intestinal mucositis is the most frequent side effect of such therapy, significantly impacts on patient quality of life, delay in treatment cycle, therefore reduce the overall efficacy of the treatment [2]. Our aim was to study the effect of potential probiotic strain *Limosilactobacillus reuteri* E (LRE; isolated and identified by Bilková et al., 2011 [3]) on the 5-FU induced inflammation and its function in strengthen the intestinal barrier in the model of human cell line Caco-2 derived from colon adenocarcinoma.
Caco-2 cells were cultivated 21 days on permeable inserts under standard conditions (DMEM medium, penicillin and streptomycin 1%; 10 % FBS; 37°C; 5 % CO2). Differentiation of cells was verified by measurement of transepithelial electrical resistance and expression of genes coding tight junction proteins (CLDN1, CLDN2, OCLN) by qPCR. Caco-2 cells were pretreated with 5-FU (100 μM; 24 h) and treated with LRE ($1x10^8$ CFU/ml; 4 h). MTT test was used for research the effect of LRE on 5-FU induced cytotoxicity in Caco-2 cells. Effect of LRE on inflammation (IL-1β, IL-8, NFκβ, A20, PPARα) and integrity of cell barrier was studied by qPCR.
LRE increased viability ($p<0.05$) of Caco-2 cells after 5-FU pretreatment. Moreover, we observed significant increase in the expression of CLDN1 ($p<0.05$), OCLN ($p<0.01$), and IL-8 ($p<0.01$) in 5-FU + LRE treated cells *vs* control, while significant decrease was detected in the expression of NFKβ ($p<0.01$) and PPARα ($p<0.001$). The significant changes in expression of selected genes were also seen in the Caco-2 cells treated with 5-FU or LRE individually.
Our results indicate that LRE effects inflammation/intestinal mucositis induced by 5-FU *in vitro* and therefore clarification of its role in this process is going to be studied further.

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P12

STRUCTURAL HYBRIDS OF FLUOROQUINOLONS AND THEIR PROSPECTS AS NEW ANTIMICROBIAL MEDICINES

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Nowadays the creation of novel antimicrobials still belongs to challenging task despite the fact that medical scientists all over the world have contributed greatly to this issue. Moreover, new diseases that appear together with the problem of resistance of microorganisms create a vast area for united chemical and pharmacological research.

Therefore, our scientific team has been fruitfully working with fluoroquinolones and their hybridization based on docking studies with further investigation of the antibacterial activity of the obtained compounds. Our findings as well as the results of the other scientists [1-3] in this area prove that representatives of the second generation of fluoroquinolones can be modified in the C-3 or C-7 position with the creation of new biologically active molecules.

Through the course of our research ciprofloxacin and norfloxacin substituted with 1,2,3-triazole moiety at C-7 revealed moderate activity against *St. aureus* ATCC 25923, *E. coli* ATCC 25922, *B. subtilis* ATCC 6633, *P. aeruginosa* ATCC 27853, *C. albicans* NCTC 885-653. Furthermore, C-3 substituted arylsulfonyl derivatives were synthesized and their activity is under study now.

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P13

EFFICACY AND SAFETY OF THE ANTIDEPRESSANT VORTIOXETINE

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Introductions. Vortioxetine is an antidepressant that was approved by the FDA for the treatment of major depressive disorder. The **aim** of the work was to assess the efficacy and safety of vortioxetine in patients with depression.

Materials and methods. The analysis of scientific publications on the effectiveness and tolerability of vortioxetine was conducted in the scientific systems MEDLINE, Google Scholar, and ScienceDirect.

Results and discussion. The most common adverse effects reported with vortioxetine in the studies were nausea, vomiting, and constipation. Nausea frequency was dose-dependent, reaching 32% when taking vortioxetine at a dose of 20 mg / day [1]. Nausea was practically the only reason for early discontinuation of vortioxetine treatment.

Other important side effects of vortioxetine therapy are hypertensive crisis and increased suicidal risk. A case of acute vortioxetine poisoning with suicidal intent was registered [2].

The proportion of patients with sexual dysfunction was 1.7% in the Vortioxetine 5–10 mg group and 2.3% in the Vortioxetine 15–20 mg group [3].

Analysis of data from short-term studies showed that treatment with vortioxetine did not lead to any clinically significant changes in blood pressure and heart rate. At the same time, serotonergic transmission and modulation play a role in hemostasis. Therefore, it is recommended to use the drug with caution in patients with bleeding disorders.

Conclusions. Administration of vortioxetine in clinical trials in the dose range from 40 mg to 75 mg caused exacerbation of the following side effects: nausea, postural dizziness, diarrhea, abdominal discomfort, generalized pruritus, drowsiness, and facial flushing. Post-marketing experience mainly concerns overdose of vortioxetine up to 80 mg. The most common side effects are nausea and vomiting. Seizures and serotonin syndrome have been reported after taking doses several times higher than the therapeutic range.

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P14

DERIVATIVES OF PUTRESCINE AND SPERMIDINE FROM FLOWERS OF *AMORPHA FRUTICOSA* L., FABACEAE

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The aim of the assay was selection of the most potent compounds, responsible for anticholinesterase activity of methanolic extracts of *Amorpha fruticosa* L., Fabaceae.

Amorpha fruticosa L., Fabaceae is a shrub native to North America, which is known by several common names, false indigo bush, desert false indigo bush. It used to blue staining [1]

The ethyl acetate extract of flowers was subjected on silica gel column using chloroform: methanol to afford 26 fractions. Fractions AF_K_E_8 and AF_K_E_9 were selected for separation on semi-preparative HPLC. The six main compounds were obtained. For structure elucidation of compounds (1-6) were measured UV spectra, HRMS and NMR spectra.

After evaluating the results by spectral methods and comparing them with the literature, the substances were identified: compound (1) as mongolicin A (or N1- (E) -N6- (Z) -di-p-coumaroylputrescine). [4] Compound (2), as N1, N6- (E) -di-p-coumaroylputrescine.[5] Coumpound (3) was identified as safflospermidine B (or N1- (E) -N5, N10- (Z) -tri-p-coumaroylspermidine) [6. Compound (4) was identified as N1, N5-(Z)-N10-(E)-tri-p-coumaroylspermidin [7]. The yield of the compound (5) was only 0.56 mg, making it difficult to identify. However, based on the similarity of the UV spectra of the isolated substances, it is assumed that it is one of the isomers. Compound (6) was obtained in the largest amount and was determined from spectral data, it is „all trans“isomer - N1, N5, N10-(E)-tri-p-coumaroylspermidin.

This type of substances was isolated from flowers of *Amorpha fruticosa* for the first time. The anticholinesterase activity of the isolated substances will be measured.

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P15

BILE ACIDS – NATURAL BUILDING BLOCKS FOR POROUS COORDINATION SELF-ASSEMBLIES

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Bile acids are relatively rigid amphiphilic molecules naturally contained in bile, which are responsible for digestion and transport of lipids and lipid-soluble nutrients [1]. Inspired by their properties, behavior, and biological activity, we have decided to employ bile acids in design and preparation of ligands and their supramolecular coordination self-assemblies [2,3]. Unsymmetric and inherently chiral pyridyl ligands (L) were used for coordination with model palladium(II) nods forming various cationic complexes in a controlled fashion, *e.g.*, Pd_3L_6 (Fig. 1), Pd_6L_{12}, or even $Pd_{12}L_{16}$. These large concave complexes containing metals and numerous chiral centers can resemble enzymatic binding pockets or transmembrane channels. Some of the complexes can further self-organize upon external stimulus into nano- or microscopic particles (Fig. 1).

Figure 1. Self-assembly of bile acid-based coordination complexes Pd_3L_6 and their self-organization into microparticles [3].

Our work introduces sustainable natural products, bile acids, as main components of coordination ligands for preparation of large chiral coordination self-assemblies. This further leads to development of a new family of porous metal-organic materials with intriguing properties and applications.

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P16

MOLECULAR DOCKING OF 3 SERIES OF POTENTIAL CANCEROSTATICS TO CAS AND HDACS

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Histone deacetylase and Carbonic anhydrase are both zinc depended metalloenzymes involved in cancer progression. New inhibitors of these enzymes, especially isoenzymes CA IX, CA XII and HDAC 1, 2, 3 and 8 could act as small molecular cancerostatistics.[1,2] Series of 3 groups of potential inhibitors were docked to the carbonic anhydrase isoenzymes CA I, CA II, CA III, CA IV, CA VII, CA IX, CAXII, CA XII, CAXIV and isoenzymes of histone deacetylase HDAC 1, HDAC 2, HDAC 3, HDAC 4, HDAC 6, HDAC 7, HDAC 8. Series of the ligands consists of (2E)-3-phenylprop-2-enhydroxamates, (2E)-3-phenylprop-2-enthiols and (2E)-N-(2-aminophenyl)-3-phenylprop-2-enamides. Various substituted 2-hydroxy-N-phenylacetamides were attached to the phenyl in position 4. The docking was performed in the program Schrodinger Glide [3] with XP precision for all ligands. Ligands belonging to the hydroxamate group were docked to HDACs in monodentate and also bidentate binding modes. Whereas, the best docking scores for poses docked in isoenzymes HDAC 1,4,7 were achieved by the bidentate binding mode, the poses in complexes with isoenzymes HDAC 2,3,6 have higher docking score in monodentate binding mode. In general, it is very convenient if the imine nitrogens of the two closest histidines, HIS140 and HIS141 (Numbering according to HDAC 1 [PDB: 5ICN [4]]) are oriented to the hydrogens of the hydroxamate functional group. Poses of the ligands MO22, MO23, MO19, show the highest docking scores in complexes with isozymes HDAC 1, 2, 3 and 8.

The thiol derivatives were docked with constraints of coordination bond between zinc dication and sulphur of the thiol group. The average docking score of poses of the ligand SH03 for HDAC 1, 2, 3, 8 isoenzymes was -8,71. Although the docking scores of this ligand are slightly lower for CA isoenzymes (-7,43 for CA IX and -6,89 for CA XII) the molecule could be a significant target of interest for dual inhibitor design.

For the docking of the group of benzamide ligands the position of the functional group of the ligand from crystal structure HDAC2 with a benzamide [PDB: 5IWG [5]] was used as a core pattern for the pose comparison. The highest average docking score was obtained by the poses of molecule BA14 with value -7,92 for HDAC 1, 2, 3 and 8. The lower average docking score of benzamide derivatives could be explained by larger volume of the functional group.

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P17

SYNTHESIS AND BIOEVALUATION OF FLOURESCENT MOLECULAR PROBES FOR THE EARLY DETECTION AND PROGRESSION OF ALZHEIMER DISEASE

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Alzheimer disease (AD) is a chronic, irreversible, progressive neurodegenerative disease with the most common symptom dementia [1]. Currently, there are neither effective therapeutics nor easily accessible, non-invasive, reliable, and inexpensive diagnostic tools. Therefore, the development of a diagnostic method that allows widespread early AD detection and disease progression will be a defining moment that will lead to the identification of vulnerable but asymptomatic populations that may be more susceptible to existing therapeutics. Moreover, such a diagnostic method will certainly accelerate the development of improved AD therapeutic options [2].

The Košmrlj group is focused on the design and synthesis of fluorescent molecular probes for the *ex vivo* detection of AD-related proteins, such as amyloid β, tau protein, etc., in the blood of AD patients. The molecular probes consist of three crucial moieties: a) an electron donor group, b) an aromatic π-linker, and c) an electron-withdrawing group, which are essential for the fluorescent properties due to the push-pull electron effect. This diagnostic method is based on the differences of molecular probes' optical properties, as the absorption, emission, and excitation maxima are red-shifted in the presence of AD proteins compared to unbound probes. *In vitro* determination of the dissociation constants (K_d) of molecular probes to amyloid β and tau protein in buffer, as well as *ex vivo* staining of these proteins on *post-mortem* brain slices from patients with AD pathology, are currently under investigation. We expect that such a stepwise approach will lead to the design of a "smart molecular probe" that will allow detection of AD-related proteins in the blood of patients.

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P18

DETERMINATION OF DRUG-PROTEIN BINDING PARAMETERS BY CE-FA METHOD WITH CONDUCTIVITY AND UV-VIS DETECTION

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Plasma proteins increase a drug solubility and act as a transport system, however, the bound drug is not able to permeate through the membrane to tissues and provide its pharmacological activity. The strength of interaction affects the pharmacological profile of the drug. In this regard, it is important to know the binding parameters, such as binding constant (K_b) and stoichiometry of the interaction (n). Nowadays, there is an increasing emphasis on the development of sensitive and highly efficient laboratory methods that will help to understand and describe these interactions in the detail. In newly created methods, the emphasis is on low consumption of samples and chemicals, physiological conditions of studied interactions or in conditions close to physiological one, and finally, that neither of the interaction partners is immobilized or tagged, as this may lead to the binding parameters. One of the methods fulfilling these criteria is the capillary electrophoresis-frontal analysis (CE-FA) [1-3]. The aim of this study was to optimize a new approach that combines CE-FA method with contactless conductivity detection (C^4D) for studying of plasma protein-drug.

The model of salicylic acid (SA) and human serum albumin (HSA) was chosen as the interaction pair of drug and plasma protein. The binding parameters were calculated from experimental data by nonlinear regression analysis. The binding parameters of SA-HSA measured by CE-FA C^4D method were log K_b = 4.24 ± 0.05 and n = 3.23 ± 0.10. The obtained binding values correspond to results of the conventional CE-FA with ultraviolet-visible (UV-VIS) detection and the range reported in the literature too. Optimized CE-FA C^4D analysis lasted less than 5 minutes and the binding data were characterized by good repeatability, RSD = 1.09 % for log K_b and RSD = 3.04 % for n.

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P19

COMPARATIVE STUDY OF IBUPROFEN LIBERATION FROM CATIONIC AND ANIONIC POLYSACCHARIDE HYDROGELS

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Polysaccharide-based gelling agents are attractive in pharmacy due to their safety, biocompatibility, biodegradability, relatively easy method of preparation, and low price. Due to their variable physical-chemical properties, polysaccharides have potentialities to be used for designing new drug delivery systems for controlled drug release. In this work, rheologic and texture properties, and the drug release of model drug ibuprofen, were investigated in cationic (high molecular weight chitosan CS HMW, chitosan derived from crab shells CSc, and chitosan derived from shrimp shells CSs) and anionic (carboxymethylcellulose CMC, sodium salt of carboxymethylcellulose NaCMC, tragacanth TRG, carrageenan CRG, xanthan gum XTG) polysaccharide-based hydrogels.

Due to their favorable properties for topical applications (structural viscosity >10.0 N.S m^{-2}) 6% NaCMC, 8% and 10% CMC, 2%, 4% and 6% TRG, and 8% and 10% CRG, 4% and 6% TXG, 2% and 3% CSc, 2% and 3% CSs, 2% and 3% CS HMW were studied for texture properties and IBU release. The most promising tested IBU hydrogels for topical administration, considering the hardness and adhesiveness, were 6% NaCMC, 6% TRG, 4% and 6% XTG, 2% and 3% CSc, 3% CSs, and 2% and 3% CS HMW with hardness > 5 g, adhesiveness > 5 g.s. and minimal retracting force > 5 g. The amount of released IBU in 180 min increased in order: 3% CS HMW (15.5%), 3% CSs (16.9%), 3% CSc (17.0%), 2% CS HMW (20.9%), 2% CSc (20.1%), 2% CSs (21.0%), 10% CMC (51.2%), 10% CRG (55.5%), 8% CRG (56.6%), 8% CMC (56.8%), 6% TRG (58.2%), 6% XTG (58.3%), 6% NaCMC (61.8%), 4% XTG (62.4%), 4% TRG (63.4), and 2% TRG (64.5%). CS hydrogels showed sustained release following zero order kinetics. In general, a higher IBU diffusion was observed from anionic hydrogels in comparison with the neutral ones (probably due to the repulsive Coulomb forces between negatively charged groups in the ionic polymers and negatively charged (carboxylate) group of IBU). Although 2% TRG showed the fastest release of IBU, 4% hydrogel of XTG was chosen as optimal for topical dermal application because of its better adhesiveness, hardness, and viscosity, along with a still relatively fast release of IBU.

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P20

COMPARATIVE STUDY OF IBUPROFEN LIBERATION FROM CATIONIC AND NEUTRAL POLYSACCHARIDE HYDROGELS

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Polysaccharide-based gelling agents show a potential to be used for designing new drug delivery systems with controlled, prolonged, or sustained drug release. In this study, rheological and texture properties as well as the *in vitro* release of model drug ibuprofen of cationic (high molecular weight chitosan CS HMW, chitosan derived from crab shells CSc, and chitosan derived from shrimp shells CSs) and neutral hydrogels (methylcellulose MC, hydroxypropylmethylcellulose HPMC, hydroxyethylcellulose HEC) were investigated.

Based on values of structural viscosity, medium-viscous (10.0–50.0 N.S.m^{-2}), and high-viscous (>50.0 N.S.m^{-2}) hydrogels (including 6% MC, 2% HPMC, 4% and 6% HEC, 3% CSc, 2% and 3% CSs, 2% and 3% CS HMW) were further studied for texture properties. The texture profile analysis was used to investigate the effect of the concentration of the gelling substance, and the effect of IBU content on the mechanical properties of the resulting hydrogel. Hardness, adhesiveness, and minimal retracting force were evaluated and the most promising tested IBU-hydrogels for dermal application were: 2% HPMC, 6% HEC, 2% and 3% CSc, 3% CSs, and 2% and 3% CS HMW with hardness > 5 g, adhesiveness > 5 g.s and minimal retracting force > 5 g. The amount of released IBU after 180 min increased in order 3% CS HMW (15.5%), 3% CSs (16.9%), 3% CSc (17.0%), 2% CS HMW (20.9%), 2% CSc (20.1%), 2% CSs (21.0%), 4% MC (52.5%), 6% HEC (53.3%), 6% MC (54.3%), 2% HPMC (56.9%), and 4% HEC (57.0%). The drug release from CS hydrogels follows zero order kinetics and is sustained without initial burst release. The amount of released IBU after 330 min increased in order: 3% CSs (34.4%), 3% CS HMW (34.8%), 3% CSc (43.4%), 2% CSs (45.1%), 2% CSc (47.9%), and 2% CS HMW (51.3%).

Significant differences ($p < 0.01$) in IBU diffusion were statistically confirmed between the groups of the hydrogels composed of the positively charged polysaccharides and the neutral ones. This behavior can be explained via stabilization of CS-IBU associates by attractive Coulomb interactions, and, thus, a slower release of IBU from the CS hydrogels.

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SYNTHESIS AND BIOLOGICAL SCREENING OF PHENYLPIPERAZINE DERIVATIVES OF 3-SUBSTITUTED 1*H*-INDOLE-2-CARBOXYLIC ACIDS AND THEIR QUATERNARY SALTS

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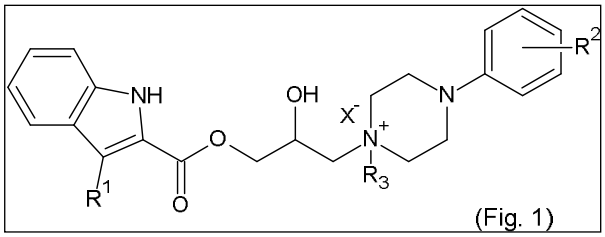
Aryloxyphenylpiperazinylpropanols are a wide group of synthetic compounds that have been prepared as potential drugs affecting the central nervous system, cardiovascular system and some also exhibit strong activity against various microorganisms [1].

A series of new 3-(4-arylpiperazin-1-yl)-2-hydroxypropylesters of 3-methyl- or 3-ethyl-1*H*-indole-2-carboxylic acids and their quaternary salts (Fig. 1) were synthesized by multistep reactions. In the first phase, 3-substituted 1*H*-indole-2-carboxylic acids were synthesized, 3-methyl derivatives by the methods we described previously [2] and 2-ethyl derivatives by a new different procedure. In the second phase the corresponding indole-2-carboxylic acids were converted to their potassium salts, which reacted with glycidyl tosylate to give oxirane intermediates. The oxirane ring was then opened by appropriate phenylpiperazine. In the third phase hydrochloride salts and quaternary ammonium salts (QUATs) were prepared from the final bases. The structure and purity of the prepared compounds were verified by the available methods of instrumental analysis (^{1}H-NMR, ^{13}C-NMR, FT-IR, TLC, HPLC).



(Fig. 1)

The hydrochloride salts and QUATs were tested for their acetylcholinesterase and butyrylcholinesterase inhibition activity by modified Ellman method. The QUATs were tested for antimicrobial activity against both Gram-negative and Gram-positive bacteria as well as anti-biofilm activity and anti-fungal activity. Finally, compounds displaying antimicrobial activity were tested for cytotoxicity against mammalian cell cultures.

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P22

ISOLATION AND IDENTIFICATION OF PHLOROTANNINS FROM BROWN ALGAE *ECKLONIA RADIATA* (C.Agardh) J.Agardh

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Ecklonia radiata (C.Agardh) J.Agardh (Lessoniaceae) is a small kelp found abundantly in the warm-temperate parts of South Africa, Australia, and New Zealand. Brown seaweeds, especially those of the *Ecklonia* genus, are known to be a rich source of phlorotannins [1]. Phlorotannins are polyphenolic compounds, which are formed through the polymerization of phloroglucinol (1,3,5-trihydroxybenze-ne) [2]. Studies over the past decades have shown that phlorotannins possess several bioactivities, including anti-herbivory, antioxidants, anti-inflammatory, antimicrobial, antiproliferative, antidiabetic, radioprotective, adipogenic, antiallergic, and antiviral, demonstrating promising potential in commercial applications in areas such as food, nutraceutical, and pharmaceutical applications [2,3].

The dried water-ethanolic extract of different parts of *E. radiata* was separated by liquid-liquid extraction into several portions. Ethyl acetate portion was subjected to further separation using column chromatography. Selected subfractions were subsequently separated using semi-preparative reversed-phase high-performance liquid chromatography. Identification of the isolated compounds was carried out using available spectral methods. Basic information about the structure was provided by ultraviolet and infrared spectroscopy. Exact mass and molecular formula were determined using high-resolution mass spectrometry. Structures of the isolated compounds were elucidated using one-dimensional and two-dimensional nuclear magnetic resonance spectroscopy.

The study was supported by the Czech Sciences Foundation (CSF Bilateral AT-CZ 21-38204L – Complexes of selected transition metals with plant-derived compounds with anti-NF-kappa B and pro-PPAR dual activities; K.Š.) and Masaryk University, Specific research – support for student projects (MUNI/ A/1688/2020). We thank Dr. Kannan R.R. Rengasamy (Faculty of Natural and Agricultural Sciences, North-West University, South Africa) for providing the plant material.

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P23

CHANGES IN BIOACTIVE COMPOUNDS CONTENT OF *CROCUS SATIVUS* STIGMA DURING PRE-SOWING CORMS TREATMENT

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The current report for the first time demonstrated the impact of treatment of *Crocus sativus* corms with plasma (CP, 3 and 5 min), vacuum (3 min), and electromagnetic field (EMF, 5 min) on amount of bioactive components in *Crocus sativus* stigma. Saffron spice is obtained from the dried stigmas of *Crocus* stigmas, which is a natural food coloring and medicinal raw material [1]. The influence of corms processing on emergence kinetics in field conditions, on growth and morphometric parameters of plants was determined; changes in antioxidant activity and total amount of phenolic compounds in leaves and stigma, changes in the number of leaf trichomes and changes in the amount of secondary metabolites in stigma. It was found that the maximum emergence (viability) in the field of control and treated corms was 100%. However, the longer (5 min) treatment with CP retarded emergence, while vacuum treatment increased emergence uniformity by 28%. The growth of plants in the CP5 and EMF groups was retarded as compared to the control. Treatment with all stressors significantly (42-74%) increased the number of lower leaf trichomes. CP3 significantly reduced the length and dry weight (43 and 60%, respectively) of flowers, and EMF treatment resulted in 27% longer flowers compared to controls. CP5 increased the antioxidant activity of leaves, the total content of phenolic compounds in leaves of the CP5 group was 44%, in EMF- 27% higher compared to controls. Treatment of corms with stressors caused significant changes in the amount of secondary metabolites in the pistils. The HPLC analysis was used to identify and quantify 26 compounds in the raw material, of which 23 compounds are crocetin (crocin) esters, as well as rutin, picrocrocin, and safranal. The main esters of crocetin were trans-4GG (about 40% of the total content), trans-3Gg, trans-2G, cis-4GG, trans-2-gg and cis-3Gg. The changes induced by vacuum treatment were smaller compared to those induced by CP and EMF. Treatment with CP reduced the amount of metabolites, meanwhile, EMF treatment resulted in a significant positive effect on the synthesis of secondary metabolites. We conclude that the treatment of corms with EMF has the potential to be applied for increasing the production of valuable saffron secondary metabolites.

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P24

ANTI-INFLAMMATORY POTENTIAL OF SELECTED PHENOLIC COMPOUNDS ISOLATED FROM *MORUS ALBA*

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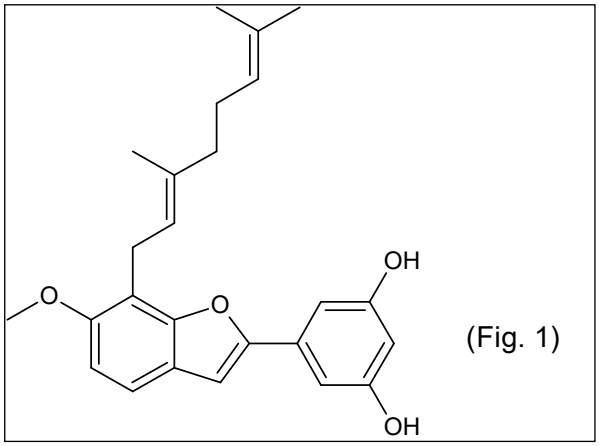
Morus alba L. (Moraceae), also known as white mulberry, is a medium-sized tree originally from China. It is mainly cultivated for silk farming; fruit production and its parts are ingredients in traditional Chinese medicine for the therapy of inflammation. *M. alba* has been a rich source of plant phenolics with various biological effects. Recently, a series of compounds were isolated: three geranylated 2-arylbenzofurans mulberrofuran A and B, and mulberroside C, two flavonoids kuwanon C and U, and a Diels-Alder adduct kuwanon H [1].

Regarding the traditional usage, we decided to experimentally verify the anti-inflammatory activity of the isolated compounds. Firstly, the effect of the compounds on viability of THP-1-XBlue™-MD2-CD14 cell line (Invivogen, CA, USA) was measured using WST-1 assay kit (Roche, Switzerland). Further, the inhibitory effect of the test compounds in non-toxic concentration (1 μM) after 24h incubation on the NF-κB cellular pathway was assessed using a QUANTI-Blue™ assay [2].



(Fig. 1)

Among the test compounds, the highest inhibitory effect was observed after incubation mulberrofuran B (Fig. 1) – the activity of NF-κB was decreased to 69 ± 17% ($p \leq 0.0001$), which is comparable to the effect of positive control, prednisolone. The anti-inflammatory effect of mulberrofuran B was described also by Čulenová et al., although in a different method – in vivo assay using carrageenan-induced paw edema [1].

The study was supported by Masaryk University, Specific research – support for student projects [grant number MUNI/A/1654/2020 – Testing of biological activity of selected natural substances in vitro].

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P25

TARGETING METALLOENZYMES WITH NEWLY DESIGNED INHIBITORS FOR POTENTIAL THERAPEUTIC INTERVENTION

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Almost half of all enzymes must cooperate with metal ions to function. Most metalloproteins play a crucial role in metabolically essential processes [1]. They also significantly impact the progression of various human diseases, including cancer, heart disease, and HIV/AIDS [2]. Due to this reason, they are an attractive medical target for the treatment of a wide range of human disorders.

In this work, we focused on zinc metalloproteins such as carbonic anhydrase (CA) and histone deacetylase (HDAC), which are cancer-related enzymes [3,4].

We designed structures for promising metalloenzyme inhibitors. The zinc-binding group was thiol, benzamide, hydroxamate, or other functional groups with good chelating properties. As a linker part of the designed structure, we used the *p*-Coumaric acid motif. Molecular docking was performed in the Schrodinger Glide program with XP precision for all molecules [5]. Only physiologically relevant human CA and HDAC isoforms were chosen for the docking. According to *in silico* results, we have synthesized compounds with considerable high docking scores, indicating their satisfying binding at the active site of selected metalloenzymes.

The study was supported by the project MUNI/IGA/1339/2021

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P26

SILVER(I) COMPOUNDS WITH BIOACTIVE MOLECULES AS CARRIERS FOR ANTIMICROBIAL AND CYTOTOXIC SILVER(I) ION

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We have been fighting the global pandemic caused by COVID-19 for the third year in a row, but the worrying fact is that other serious diseases and their treatment remain in the shadow of the pandemic. Antibiotic resistance is still a threat to public health during this pandemic, and the forecasts of the deaths caused by antimicrobial resistance infections are relatively pessimistic in the coming years. Thus, it is very important to continue to develop and improve the treatment of emerging infectious diseases and to face the growing number of resistant microbial pathogens. In addition, a research of the new anticancer drugs and other therapeutics should not be left behind.
The aim of our experimental study was the synthesis, solid-state characterization and *in vitro* biological evaluation of the new silver(I) coordination compounds with bioactive molecules such as amino acids and *N*-heterocyclic compounds. Some of the prepared compounds exhibit higher levels of biological activity than commercially used drugs, silver(I) sulfadiazine and cisplatin, and even selective inhibition of the growth of pathogenic and probiotic bacteria as well as cancer and healthy cells has been observed [1-3]. Based on the obtained results it is appropriate to consider carrying on other pharmacology studies in the future.

The study was supported by P. J. Šafárik University in Košice vvgs-2022-2123 and Slovak grant agency KEGA 006UPJŠ-4/2021.

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P27

CRITICAL MICELLE CONCENTRATION AND CYTOTOXICITY OF PHENYLCARBAMIDACID DERIVATES

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The critical micellar concentration (CMC) of base esters of various substituted phenylcarbamic acid (occupationally labeled 6a, 6b, 6c, 6d, 6e, 6i, 6j, 6k, and 6l) in the aqueous solution was determined using absorption spectroscopy in the UV/VIS spectrum area using pyrene as a probe in the environment. This dependence had a sigmoidal character, and the CMC was the center of the sigmoid (1, 2).

The cytotoxicity/inhibitory effect of the individual substances was determined using the MTT test on Hela cell line. Test substances 6a, 6b, 6c, 6d, and 6e showed significant cytotoxicity at 100 and 2500 µg/mL concentrations. Substances 6i, 6j, 6k, and 6l were more toxic than the previous substances; 5 µg/mL concentration showed medium cytotoxicity. No inhibitory activity was observed at the lower concentrations of tested substances. IC_{50} values were calculated using nonlinear regression analysis using GraphPad Prism 7. Substances 6a, 6b, 6c, 6d, and 6e had a lesser effect on inhibiting HeLa cell proliferation than substances 6i, 6j, 6k, and 6l. The CMC values for all study substances were more significant than their corresponding IC_{50} values. Depending on -logc (-logCMC and -logIC_{50}) on the number of carbon atoms (n) in the hydrophobic chain, the analytes' CMC is not responsible for inhibition because all the studied substances act in the monomer state.

KEYWORDS: Critical micelle concentration. Phenylcarbamates. Absorption spectroscopy. Cytotoxicity

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P28

THE EFFECT OF POORLY COMPRESSIBLE ASCORBIC ACID ON DILUTION POTENTIAL OF CO-PROCESSED EXCIPIENTS

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Direct compression is a common method consisting of compression dry powder blend of active pharmaceutical ingredient (API) and excipients to tablet. Appropriate choice of excipients and their optimal ratio can compensate for poor compressible and tabletable properties of API. An example of such a substance is ascorbic acid (AA) [1,2]. The ability of excipients to retain their tabletability even after dilution with another ingredient is called dilution potential [1,3].

The study aimed to find the dilution potential of six co-processed excipients (CPE) – Advantose® FS95, Cellactose® 80, CombiLac®, MicroceLac® 100, Pearlitol® Flash and StarLac®. From each CPE were prepared four batches containing 1 % of sodium stearyl fumarate and 0, 25, 50 or 75 % of AA. Tablets from each batch were compressed at five compaction forces (3, 4, 5, 6, 7 kN) and were evaluated on the pharmacopoeial requirement. The results of work potential (determined by Minchom and Armstrong), MA index and dilution capacity index (proposed by Habib et. al.) were calculated by determination of area under the curve of tensile strength versus compression pressure profile [3,4].

The obtained values of dilution potential of all CPE were over 70 weights % of AA. But none of the batches of tablets containing 75 % AA did not meet to require properties (friability and disintegration). The tablets which met these requirements were: Cellactose® 80 with 25 % AA compressed by forces 5–7 kN; CombiLac® with 25 % AA compressed by forces 4–7 kN, MicroceLac® 100 with 25 % AA compressed by forces 3–6 kN and MicroceLac® 100 with 50 % AA compressed by force 7 kN.

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P29

ISATIN HYDRAZONES-BIOLOGICALLY ACTIVE COUMPOUNDS

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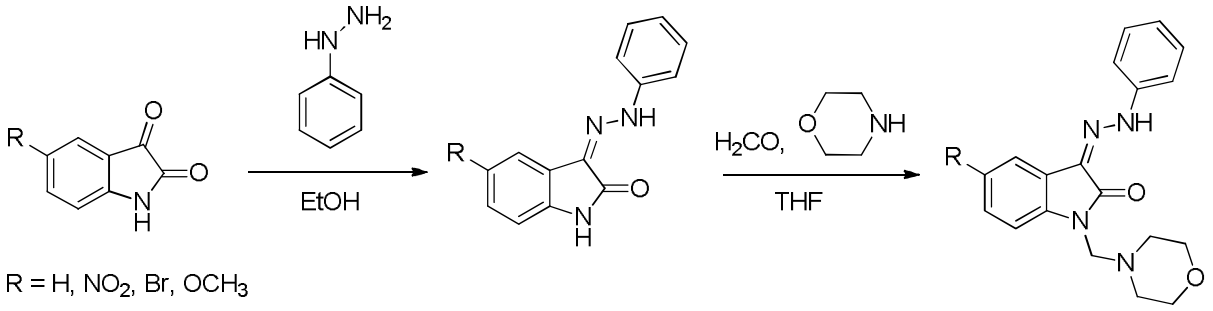
The research is focused on the synthesis, characterization and study of the biological properties of isatin hydrazones as suitable candidates for new drugs. Isatin and its derivatives belong to the organic compounds used in chemical practice. They are used primarily in areas such as medicinal chemistry (e.g. as antibiotics, antimalarials, etc.), in the field of nanotechnology, development of analytical reagents and dyes, and in the field of synthesis of heterocyclic compounds and stereoselective procedures. The high application potential of isatin and its derivatives, their occurrence and the occurrence of their metabolites in plants and in the human body have aroused the great interest of chemists, doctors and pharmacists in the study of their chemical reactivity. [1] The aim of the work was the synthesis of new, not yet described in the literature, derivatives of 3-(phenylhydrazono)isatin with a methylmorpholine substituent in the N-1 position. [2]



R = H, NO_2, Br, OCH_3

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P30

TEXTUROMETRIC ANALYSIS OF MUCOADHESIVE LYOPHILISATES CONTAINING GENTAMICIN

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Texture profile analysis (TPA), texturometry, is used to determine textural properties of food, packaging material, pharmaceutical and cosmetic products. Structural and physical properties are quantitatively tested: cohesion, resistance, hardness, elasticity, brittleness, breakability, elasticity, adhesion, compressibility, expandability, elongation, spreadability, chewability. The instrument intended for TPA, the texturometer, simulates the stress situations during the use or consumption of the tested sample. Testing takes place in one or more cycles, through pressure and tension.

The pilot study was focused on the formulation of lyophilisates that could serve as mucoadhesive dosage forms for the treatment of aphthae, containing gentamicin as an antibacterial agent. Gentamicin is an aminoglycoside broad-spectrum antibiotic, used in 0,5% w/w concentration. The initial aim of the study was to determine the mechanical and texturometric properties of individual lyophilizates and to evaluate their potential applicability when applied to the oral mucosa. Lyophilisates, prepared by freeze drying of hydrogels based on chitosan (high molecular weight) and semi-synthetic cellulose derivatives (hydroxypropylmethylcellulose, hydroxyethylcellulose) were evaluated texturometrically. For the evaluation, a texturometer interfaced with Stable Micro Systems' Exponent computer software was used.

Each type of lyophilizate was texturometrically measured and evaluated as having good mechanical strength. Not a single sample was disrupted due to mechanical stress during the measurement itself, it kept its integrity and completeness. The best results in strength were observed with 3% chitosan lyophilizate.

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MEDICINAL MUSCHROOMS *OPHIOCORDYCEPS SINENSIS* AND *CORDYCEPS MILITARIS*

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The main component of *Ophiocordyceps sinensis* and *Cordyceps militaris* extracts are polysaccharides. These natural biopolymers represent a large class of biologically active components and contribute to the total pharmacological activity and effect on health. They contain monosaccharides as rhamnose, ribose, arabinose, xylose, mannose, glucose, galactose, mannitol, fructose or sorbose. The exopolysaccharide fraction has a large number of pharmacological effects, two most important of them are immunomodulatory and antitumor effects. Among the polysaccharides belongs also mannoglucan showing weak cytotoxic activity against the SPC-I cancer line [1]. More than ten nucleosides and their related compounds including adenine, adenosine, inosine, cytidine, cytosine, guanine, uridine, thymidine, uracil, hypoxanthine and guanosine have been successively isolated from *Ophiocordyceps sinensis*. It contains many amino acids and polypeptides, with expected effect on cardiovascular system. They also have a sedative and hypnotic effect, with tryptophan as the most effective component among them.

Polysaccharides were extracted from four samples: sample no. 1 (grown on *Oryza sativa indica* substrate, *Ophiocordyceps sinensis* strain), sample no. 2 (grown on *Oryza sativa japonica* substrate, *Ophiocordyceps sinensis* strain), sample no. 3 (grown on *Oryza sativa indica* substrate, *Cordyceps militaris* strain), sample no. 4 (grown on *Oryza sativa japon*ica substrate, *Cordyceps militaris* strain). The stable 2,2-diphenyl-1-picrylhydrazyl radical has been used to determine the antioxidant activity. From the results for the samples no. 1 – 4 we can see the highest antioxidant activity of sample no. 3 (IC_{50} = 2.85 ±0.04 $mg.ml^{-1}$). Through NMR spectroscopy and according to the literature, we found out that the majority chemical compound in the deproteinized extracts was a hydrophilic polyglucan signed as CBHP.

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DETERMINATION OF FIREWEED ORGANIC ACID COMPOSITION

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The study of organic acid content is necessary to determine the dynamics of metabolism of plants that are promising for the treatment of diseases associated with metabolic disorders, inflammatory diseases, and others. *Chamaenerion angustifolium* (L.) Scop., commonly known in North America and Europe as “fireweed” or “rosebay willow-herb”, is a very widespread and variable species of the willowherb family (Onagraceae) [1]. Fireweed is a traditional food and medicinal plant in Europe. The current work included the study of organic acids of aerial part and rhizomes of *C. angustifolium* occurred in Ukraine and Poland by gas chromatography-mass spectrometry (GC–MS) method using a Shimadzu GC-MS-QP2010 equipped with an Rxi-5ms (Restek Corporation capillary column (30 m × 0.25 mm, 0.25 μm) with a liquid stationary phase (5% diphenyl and 95% polysiloxane) after derivatization with MTBSTFA reagent. The method was discarded early [2]. The study results confirm present 26 free carboxylic acids in raw plant material of *C. angustifolium*, among them 10 amino acids, 10 low chain organic acids, 3 phenolic acids, 1 heterocyclic acid, and 2 fatty acids. The low-molecular-weight organic acids were represented as mono-, di- and tricarboxylic acids. The number of monocarboxylic acids prevailed among other groups in fireweed raw materials and were represented by lactic acid, glycolic acid, hydracrylic acid, propanoic acid, glyceric acid. Among dicarboxylic acids, oxalic acid, succinic acid, fumaric acid, and malonic acid amid contained in the aerial part and rhizomes of *C. angustifolium*. 3-Hydroxybenzoic acid, shikimic acid, and caffeic acid were identified in fireweed raw materials among phenolic compounds. Major organic acids in the highest concentrations in the aerial parts of samples were glyceric acid (0.74±0.02 – 2.01±0.05 % of total organic acids amount) and citric acid (1.49±0.87 –3.87±1.32 % from total organic acids amount). The citric acid (3.19±1.07 – 5.09±1.33 % from total organic acids amount) also dominated in the underground parts. An aerial part of *C. angustifolium* is the more promising raw material for the development of medicines and dietary supplements according to organic acids content.

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SYNTHESIS OF NEW DERIVATIVES WITH ARYLOXYAMINOPROPANOL AND ARYLAMINOETHANOL FRAGMENT AND STUDY OF THEIR POTENTIAL BIOLOGICAL ACTIVITIES

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Aryloxyaminopropanols drugs are used as antiarrhythmics, antihypertensives, beta-blockers and are also characterized by a lipolytic effect [1]. Drugs with antagonistic effect on alpha- and beta- receptors also include derivatives with an arylaminoethanol fragment [2, 3]. The work deals with the synthesis of new aryloxyaminopropanol and arylaminoethanol derivatives with a carbamate functional group in the aromatic part of the molecule and a modified amino group, which is a part of piperidine. The wide possibility of substitution of the aromatic ring and substituents on the nitrogen can leads to the preparation of compounds with combined pharmacological properties. Aryloxyaminopropanol derivatives were prepared by a three step synthesis from *para*- and *meta*-substituted aminophenol. Arylaminoethanol carbamates were prepared by a four step synthesis from 1-(4-aminophenyl)ethan-1-one. Selected synthesized compounds were tested for anticholinesterase activity (inhibition of acetylcholinesterase and butyrylcholinesterase) and antimicrobial activity (*Escherichia coli*, *Staphylococcus aureus*). The tests showed that an aryloxyaminopropanol *meta*- derivative with an ethyl substituent on the carbamate functional group reduced acetylcholinesterase activity (28.1 ± 0.8 %) and butyrylcholinesterase activity (24.5 ± 2.8 %). Antimicrobial activity of *Escherichia coli* and *Staphylococcus aureus* strains showed, that all *meta*- substituted carbamate derivatives suppressed the growth of *Staphylococcus aureus* bacteria over *para*- substituted aryloxyaminopropanol derivatives. The highest ability to inhibit the growth of bacteria of the *Staphylococcus aureus* strain was observed in the *meta*- derivative with a methyl substituent on the carbamate functional group (128.5% RIZD).

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BIOAVAILABLE SILVER(I) AND ZINC(II) COMPLEXES AND THEIR BIOLOGICAL RESPONSE

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Pathogenic bacteria and viruses have endangered people every day. In conjunction with growing knowledge in the field of biology, medicine and pharmacy, numerous drugs have been developed, which are capable of inhibiting the growth of these microorganisms. However, since drug resistance is a ubiquitous phenomenon, new antimicrobials are still developed continuously. In addition to current antimicrobials that are isolated either from various strains of microorganisms or synthetically (semi-synthetically) prepared, metal ion-based antiseptics have also recently emerged as promising alternatives.

It is known that compounds based on Ag(I), Zn(II) and Cu(II) are the ones antimicrobially most active, but there are currently also tests with Ga(III), In(III), Ru(II) and others samples [1]. However, finding a suitable form of their application to organisms is a difficult process. One of the ideas is to combine biologically active metal ions with effective organic ligands like are N-heterocyclic carbenes, phosphines, peptides and carboxylic acids have so far been most frequently used [2].

The contribution will present the antimicrobial and anticancer effects of selected silver(I) and zinc(II) complexes prepared in our laboratory with a focus on the relationship between their structure and biological activity [3,4].

The study was supported by Slovak grant agency KEGA 006UPJŠ-4/2021.

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BENZYL AMIDES OF 4-METHYLTHIENOPYRIMIDINE AS NOVEL ANTIBACTERIALS

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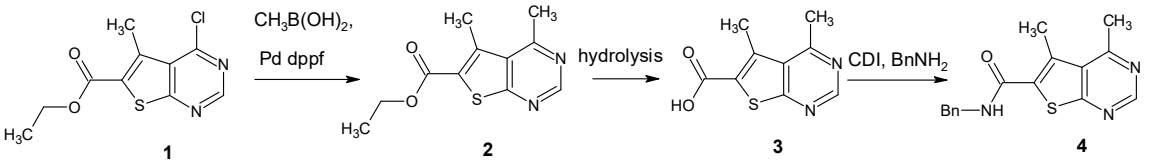
The recent studies show that thieno[2,3-d]pyrimidine core modified with amide functional group at 4, 5 or 6 of the core heterocyclic structure is a promising structure for antibacterial. Some recent studies confirmed their ability to be inhibitors of bacterial TrmD and as the result make them interesting compound for antibacterial activity screening [1].

In present research we focused our efforts on introduction of methyl group at position 4 of thieno[2,3-d]pyrimidine and carboxamide group at position 6. We used Suzuki coupling with of the corresponding chloride **1** to replace chlorine with 4-methyl substituent. Further the core acid **3** was obtained by hydrolysis of an ester **2**. Acid **3** showed good reactivity in peptide coupling regents' promoted reactions with amines (Scheme).

Scheme



The study of antibacterial activity for the synthesized amides **4** revealed high antimicrobial activity for the benzyl amides, which shoved growth inhibition of *Pseudomonas aeruginosa* ATCC 27853 strain.

The study was supported by the Ministry of Health Care of Ukraine at the expense of the State Budget in the framework # 2301020 "Scientific and scientific-technical activity in the field of health protection" on the topic "Synthesis and study of new thienopyrimidines for the detection of antimicrobial and related types of pharmacological activity" (State registration number: 0121U109472. Order of the Ministry of Health of Ukraine of November 17, 2020 № 2651). The authors acknowledge Enamine Ltd. for the measurement of ^{1}H, ^{13}C NMR and LC-MS spectra of the obtained substances. We are grateful to T.P. Osolodchenko (Mechnikov Institute of Microbiology and Immunology of the NAMS of Ukraine, Kharkiv, Ukraine) for her assistance in carrying out antimicrobial activity study.

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STUDY OF SURFACTANT PARTITIONING INTO MAMMALIAN AND BACTERIAL MODEL MEMBRANES.

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Due to alarming increase in the number of cases of antibiotic-resistant bacterial infections, it is necessary to study the mechanism of antimicrobial action. Solubilisation of bacterial membranes is the mechanism of antimicrobial effect of surfactants. The interaction of surfactant *N,N*-dimethyl-1-dodecanamine-*N*-oxide (DDAO) with mammalian and bacterial model membranes was studied using static light scattering and fluorescence spectroscopy. Unilamellar liposomes (ULLs), consisting of palmitoyloleoylphosphatidylcholine (POPC) with cholesterol (CHOL) were used for mimicking the lipid part of the mammalian cytoplasmic membrane. A mixture of palmitoyloleoylphosphatidyl-ethanolamine (POPE) and palmitoyloleoylphosphatidylglycerol (POPG) was used to mimic the inner membrane of *Escherichia coli*. The solubilisation is a complex process of liposome-mixed micelle transformation. The process is accompanied by decreasing particle sizes, which was observed nephelometrically on ULLs. Critical DDAO concentrations causing saturation of the bilayers (D_t^{SAT}), complete solubilisation (D_t^{SOL}), as well as DDAO concentration causing 50% decrease of the scattering intensity (D_t^{MID}) were calculated. The first phase of the solubilization process (membrane perturbation) was observed using fluorescence spectroscopy. Leakage of the fluorescent probe calcein, that was encapsulated inside the ULLs, through the pores in the bilayer created by DDAO, was detected by the increasing values of fluorescence intensity. Critical DDAO concentrations causing heavy (D_t^{PERT}) and full (D_t^{RLS}) release of the probe were calculated. All experiments were performed at various lipid concentrations. Using the dependences of all critical DDAO concentrations on the lipid concentration, we have calculated the partition coefficients of DDAO for both types of model membrane, as well as the effective ratios of the amount of DDAO integrated into the bilayer to the amount of lipid. Our data show that the partition coefficient of DDAO is higher when interacting with bacterial model membranes and the bacterial model membranes need more incorporated surfactant to undergo the solubilisation.

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AUTHOR INDEX

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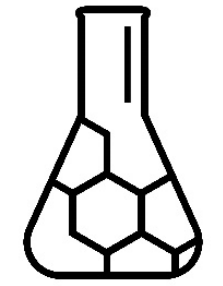

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