8th Central European Conference "Chemistry towards Biology"

28th August – 1st September 2016

Hotel Myslivna, Brno, Czech Republic

http://sites.google.com/site/ctb2016brno

University of Veterinary and Pharmaceutical Sciences Brno

Faculty of Pharmacy

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FACULTAS PHARMACEUTICA BRUNENSIS

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Dear Colleagues,

It is our pleasure to extend a very warm welcome to the honourable scientists and young researchers participating in the 8th Central European Conference "Chemistry towards Biology" here in Brno, Czech Republic.

This series of conferences has attracted many leading scientists. This conference is a platform for promoting cooperation between scientists sharing scientific interests in chemical biology and biological chemistry.

The 8th Central European Conference "Chemistry towards Biology" addresses the following research topics:

Drug design, research and development
Chemistry of natural compounds
Carbohydrate chemistry
Molecular biology
Biochemistry
Biomaterials
Structure, function and interactions of proteins
Engineered enzymes
Nucleic acids chemistry
Pharmacology and ADME
Drug formulations and drug delivery systems

The aim of the 8th Central European Conference "Chemistry towards Biology" is to develop a platform for scientific contacts between researchers dealing with biomedical sciences from the European and other countries and to support cooperation between scientists in this field.

We are most grateful to all the scientists who have travelled from all corners of the world to the “heart of Europe” – the Czech Republic – to participate in this scientific symposium. We hope that you will find your participation in the 8th Central European Conference "Chemistry towards Biology" intellectually stimulating and socially enjoyable.

Best regards,

Josef Jampílek
Chairman of Local Steering Committee
CTB 2016 Brno

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CONFERENCE PROGRAMME

SUNDAY, AUGUST 28th 2016

arrival, accommodation, registration of participants (12.00–14.00)

14.00 **OPENING SESSION**

Chairmen: *András Perczel, Jaroslav Koča*

Plenary Lectures:

14.30–15.15 **PL-01, Weissig V. (USA):** From dequalinium to mitochondrial nanocarriers

15.15–16.00 **PL-02, Koča J. (Czech Republic):** Structural bioinformatics – towards revealing biologically relevant information hidden in databases

16.00–16.45 **PL-03, Kozlowski H. (Poland):** Specific roles of histidyl and cysteinyl residues in the metal ion binding sites in peptides and proteins

Chairmen: *Volkmar Weissig, Henryk Kozlowski*

Lectures:

16.45–17.15 **O-01, Kolesinska B. (Poland):** Epitope mapping of selected human proteins – potential triggers of rheumatoid arthritis

17.15-17.30 **O-02, Dall'Acqua S. (Italy):** Natural deep eutectic solvents for the extraction of phytochemicals

17.30–17.50 **O-03, Oberer M. (Austria):** Of yeast, bacteria and men: Structure-function studies of monoacylglycerol lipases reveal evolutionary conserved cap architectures and regulatory functions in ethanol metabolism

17.50–18.05 **O-04, Penke B. (Hungary):** The role of metal ions in Alzheimer's disease

18.05–18.20 **O-05, Adámik M. (Czech Republic):** p53 interactions with DNA quadruplexes

18.30 **WELCOME RECEPTION**

MONDAY, AUGUST 29th 2016

registration (8.00–11.00), poster set up time (8.00–17.00)

Chairmen: *Ricardo D. Enriz, Jarosław Polański*

Plenary lectures:

8.30–9.15 **PL-04, Polański J. (Poland):** Big data problem in drug design and structure-property studies

9.15–10.00 **PL-05, Enriz R. D. (Argentina):** Simulating ligand-receptor interactions. The challenge to understand a dynamic process by using static techniques

Lectures:

10.00–10.30 **O-06, Tassano E. (Austria):** Asymmetric biocatalytic Cannizzaro-type reaction: A sustainable route to chiral profens and profenols

10.30–10.45 **O-07, De Zorzi R. (Italy):** Structure and stereochemistry of self-assembling heterochiral tripeptides

10.45–11.00 **COFFEE BREAK**

Chairmen: *Mark Olsen, Vladimír Sklenář*

Plenary lectures:

11.00–11.45 **PL-06, Sklenář V. (Czech Republic):** Disentangling puzzles – atomic resolution studies of intrinsically disordered proteins

11.45–12.15 **PL-07, Olsen M. (USA):** Aspartyl(asparaginyl)-beta-hydroxylase inhibitors for the treatment of hepatocellular carcinoma

Lectures:

12.15–12.30 **O-08, Rizzo R. (Italy):** Hydrophobic segments in the exopolysaccharide extracted from *Burkholderia multivorans* biofilms

12.30–12.45 **O-09, Bogár F. (Hungary):** The Collins's rule and the Hofmeister effect as revealed by a simple molecular dynamics model

12.45–13.00 **O-10, Bąk A. (Poland):** Ligand and structure-based probability-quided pharmacophore mapping in multidimensional QSAR studies

13.00–14.00 **LUNCH**

Chairmen: *Renata Riva, Michael Gütschow*

Plenary lectures:

14.00–14.45 **PL-08, Gütschow M. (Germany):** Limiting the number of possible pocket occupations by introducing symmetry into ligands: Development of protease inhibitors

14.45–15.30 **PL-09, Riva R. (Italy):** New strategies for the synthesis of high added value fine chemicals combining multicomponent reactions with biocatalysis or organocatalysis

Lectures:

15.30–16.00 **O-11, Krzek M. (Netherlands):** Synthesis of a novel flavin cofactor analogue, N6-(butyl-2-en-4-amine)-FAD for enzyme immobilization

16.00–16.15 **O-12, Goldschmidt-Góz V. (Hungary):** New synthetic approaches to pyranoid β-sugar amino acids

16.15–16.30 **O-13, Kovács A. (Hungary):** Synthesis methods of peptide-luciferin conjugates

16.30–16.45 **O-14, Otevřel J. (Czech Republic):** Development of biphenyl-based bis(thiourea) organocatalysts for asymmetric Henry reaction

16.45–17.00 **O-15, Mándity I. (Hungary):** Continuous flow solid phase synthesis of peptides and foldamers with exceptionally low amino acid consumption

17.00–17.20 **O-16, Pavkov-Keller T. (Austria):** Regioselective *para*-carboxylation of phenols by a prFMN-dependent decarboxylase

17.20 **POSTER SESSION (with COFFEE BREAK)**

TUESDAY, AUGUST 30th 2016

registration (8.00–11.00)

Chairmen: *Janez Košmrlj, Hong-Jie Zhang*

Plenary lectures:

8.30–9.00 **PL-10, Zhang H.-J. (Hong Kong):** Discovery of bioactive lead compounds from thousands of plant extracts through bioassay-guided separation

9.00–9.45 **PL-11, Košmrlj J. (Slovenia):** Chemical and biological utility of pyridine-appended click triazole derivatives

Lectures:

9.45–10.15 **O-17, Batta G. (Hungary):** Antifungal disulfide miniproteins: Stress induced unfolding and dynamic structures

10.15–10.30 **O-18, Gjorgjieva M. (Slovenia):** Discovery of benzothiazole based Hsp90 inhibitors with antiviral activity

10.30–10.50 **COFFEE BREAK**

Chairmen: *Aidan Coffey, Gyula Batta*

Plenary lectures:

10.50–11.20 **PL-12, Coffey A. (Ireland):** Characterization and applications of a cysteine-histidine-dependent amidohydrolase/peptidase enzyme targeting MRSA

Lectures:

11.20–11.35 **O-19, Peron G. (Italy):** Exploring the cranberry activity against uropathogenic *E. coli* by metabolomics: A pilot study

11.35–11.50 **O-20, Hošek J. (Czech Republic):** Anti-inflammatory potential of prenylated flavonoids from *Paulownia tomentosa*

11.50–12.05 **O-21, Lehoczki G. (Hungary):** Anti-amylase and antifungal effect of common herbs and spices

12.05–12.25 **O-22, Pazourek J. (Czech Republic):** Invasion of *Pectinatella magnifica* in fresh water resources of the Czech Republic

12.30–13.30 **LUNCH**

13.40 **DEPARTURE from Hotel Myslivna**

15.00–17.30 **EXCURSIONS – BREWERY ČERNÁ HORA**

18.00–22.00 **CONFERENCE DINNER – SLADOVNA, ČERNÁ HORA**

WEDNESDAY, AUGUST 31st 2016

registration (8.00–11.00), poster set up time (8.30–16.00)

Chairmen: *Marc Diederich, Glen J. Smith*

Plenary lectures:

9.00–9.45 **PL-13, Smith G.J. (USA):** The US FDA generic drug review process: Present and future challenges

9.45–10.15 **PL-14, Diederich M. (Korea):** Natural compound-regulated crosstalk between cell death modalities as a pharmacological target

Lectures:

10.15–10.45 **O-23, Rijnders T. (Netherlands):** European Lead Factory – Collective intelligence boosting drug discovery

10.45–11.00 **COFFEE BREAK**

Chairmen: *Zbygniew Kamiński, Danijel Kikelj*

Plenary lectures:

11.00–11.45 **PL-15, Kikelj D. (Slovenia):** Discovery of inhibitors of DNA gyrase B and topoisomerase IV inspired by marine alkaloid oroidin

Lectures:

11.45–12.15 **O-24, Kamiński Z. (Poland):** Predictable enantioselective coupling reagents for synthesis of peptides from racemic substrates

12.15–12.45 **O-25, El-Shahawy A. (Egypt):** DFT-Anti-cancer effect of anionic ibuprofen drug in the human body

12.45–13.00 **O-26, Paragi G. (Hungary):** Cooperativity in halogen bonds: A molecular orbital theory based explanation.

13.00–14.00 **LUNCH**

Chairmen: *Pavel Matějka, Stephen Hanessian*

Plenary lectures:

14.00–14.45 **PL-16, Hanessian S. (Canada):** The enterprise of drug discovery from an academic perspective: A personal odyssey

14.45–15.30 **PL-17, Matějka P. (Czech Republic):** From vibrational spectroscopy to nanoscopy of skin systems with nanoparticles

Lectures:

15.30–15.45 **O-27, Musiał W. (Poland):** Synthesis and formulation of thermosensitive drug carrier for controlled delivery of naproxen

15.45–16.00 **O-28, Kecskeméti Á. (Hungary):** The application of non-covalently immobilized trypsin in a poly(dimethylsiloxane) microfluidic device for rapid protein digestion

16.00–16.15 **O-29, Chyba J. (Czech Republic):** Encapsulation of potential platinum drugs with macrocyclic carriers

16.15–16.30 **O-30, Kyzioł A. (Poland):** Silver, gold and copper nanocomposites based on chitosan

16.30–16.45 **O-31, Stopková L. (Slovakia):** Solubilization of valsartan in the presence of tetradecyltrimethylammonium bromide

16.45–17.00 **O-32, Stupák I. (Czech Republic):** Introduction to project Golem and biorelevant dissolutions

17.00–17.15 **O-33, Burek M. (Poland):** Trehalose-functionalized thermoresponsive glycomicrogels as scaffolds for 3D cell culture

17.15–17.30 **O-34, Salahiddin A. (Uzbekistan):** Antiulcer activity of a new derivative of glycyrrhizic acid

17.30 **POSTER SESSION (with COFFEE BREAK)**

THURSDAY, SEPTEMBER 1st 2016

Chairmen: *Atanas G. Atanasov, Robert Musioł*

Plenary lectures:

8.30–9.00 **PL-18, Musioł R. (Poland):** Antifungal styrylquinolines as efflux pumps inhibitors

9.00–9.45 **PL-19, Atanasov A.G. (Austria):** Bioactive natural compounds targeting vascular functionality

Lectures:

9.45–10.30 **O-35, Šmejkal K. (Czech Republic):** Anti-inflammatory potential of prenylated phenolics

10.30–10.45 **O-36, Vochyánová Z. (Czech Republic):** Prenylated flavonoids and experimentally induced bowel inflammation

Plenary closing lecture:

10.45–11.30 **PL-20, Perczel A. (Hungary):** Amyloid fibril formation in details: The dead end street of protein folding?

11.30 **CONFERENCE CLOSURE**

11.45–13.00 **COFFEE BREAK, DEPARTURE**

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O-02	Faggian, M.; Sut, S.; Baldan, V.; Peron, G.; **Dall'Acqua, S.**	Natural deep eutectic solvents for the extraction of phytochemicals
O-03	Aschauer, P.; Heier, Ch.; Rengachari, S.; Taschler, U.; Lichtenegger, J.; Gruber, K.; Breinbauer, R.; Birner-Grünberger, R.; Zimmermann, R.; **Oberer, M**.	Of yeast, bacteria and men: Structure-function studies of monoacylglycerol lipases reveal evolutionary conserved cap architectures and regulatory functions in ethanol metabolism
O-04	**Penke, B.**; Datki, Z.; Fülöp, F.	The role of metal ions in Alzheimer's disease
O-05	**Adámik, M.**; Krejčí, A.; Renčiuk, D.; Petr, M.; Bažantová, P.; Helma, R.; Polášková, A.; Bábková, Z.; Kejnovská, I.; Navrátilová, L.; Vorlíčková, M.; Brázdová, M.	p53 interactions with dna quadruplexes
O-06	**Tassano, E.**; Tripp, A.; Hall, M.; Faber, K.	Asymmetric biocatalytic Cannizzaro-type reaction: A sustainable route to chiral profens and profenols
O-07	**De Zorzi, R.**; Garcia Fernandez, A.M.; Igleasias, D.; Destefanis, L.; Marchesan, S.	Structure and stereochemistry of self-assembling heterochiral tripeptides
O-08	Distefano, M.; Cescutti, P.; **Rizzo, R.**	Hydrophobic segments in the exopolysaccharide extracted from *Burkholderia multivorans* biofilms
O-09	Násztor, Z; Dér, A.; **Bogár, F.**	The Collins's rule and the Hofmeister effect as revealed by a simple molecular dynamics model
O-10	**Bąk, A.**; Kozik, V.; Jampílek, J.	Ligand and structure-based probability-quided pharmacophore mapping in multidimensional QSAR studies
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O-12	**Goldschmidt Gőz, V.**; Pintér, I.; Farkas, V.; Perczel, A.	New synthetic approaches to pyranoid β-sugaramino-acids
O-13	**Kovács, A.K.**; Hegyes, P; Szebeni, G.J.; Puskás, L.G.; Tóth. G.K.	Synthesis methods of peptide-6-amino-D-luciferin conjugates for detection of protease activity
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O-15	**Mándity, I.M.**; Fülöp, F.	Continuous flow solid phase synthesis of peptides and foldamers with exceptionally low amino acid consumption
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O-20	**Hošek, J.**; Hanáková, Z.; Dall'Acqua, S.; Schuster, D.; Polanský, O.; Šmejkal, K.	Anti-inflammatory potential of prenylated flavonoids from *Paulownia tomentosa*
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O-24	**Kamiński, Z.J.**; Kasperowicz-Frankowska, K.; Kolesińska, B.	Predictable enantioselective coupling reagents for synthesis of peptides from racemic substrates
O-25	**El-Shahawy, A.**; Qusti, S.; Ezzat, G.; Gashlan, H.; Emara, H.	DFT-Anti-cancer effect of anionic ibuprofen drug in the human body
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O-28	**Kecskeméti, A.**; Bako, J.; Csarnovics, I.; Gaspar, A.	The application of non-covalently immobilized trypsin in a poly(dimethylsiloxane) microfluidic device for rapid protein digestion

O-29	**Chyba, J.**; Wawrocka, K.; Marek, R.	Encapsulation of potential platinum drugs with macrocyclic carriers
O-30	**Kyzioł, A.**; Regiel-Futyra, A.; Sebastian, V.; Hueso, J.L.; Irusta, S.; Arruebo, M.; Stochel, G.	Silver, gold and copper nanocomposites based on chitosan
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O-33	**Burek, M.**; Waśkiewicz, S.; Lalik, A.; Student, S.; Wandzik, I.	Trehalose-functionalized thermoresponsive glycomicrogels as scaffolds for 3D cell culture
O-34	Mirzaahmedova, K.T.; **Salahiddin, A.**	Antiulcer activity of a new derivative of glycyrrhizic acid
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O-36	**Vochyánová, Z.**; Rotrekl, D.; Smékal, V.; Hošek, J.	Prenylated flavonoids and experimentally induced bowel inflammation

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P-04	**Bąk, A.**; Kozik, V.; Dybał, P.	Molecular lipophilicity profile in drug discovery
P-05	**Bakalova, A.**; Cherneva, E.; Konstantinov, S.	Cytotoxic activity and theoretical investigation of new mixed ammine/amine platinum complexes with 3'-amino-5-metyl-5-phenylhydantoin
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P-25	**Hřibová, P.**; Vysloužilová, P.; Navrátilová, A.; Pokorná, M.; Kadlecová, D.	Inhibition of lipoxygenase by natural compounds
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P-63	**Prvulović, D.**; Malenčić, D.; Ljubojević, M.; Barać, G.; Ognjanov, V.	Effect of extraction solvent on the antioxidant activity of sweet cherry stalks
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P-72	**Szánti-Pintér, E.**; Maksó, L.; Wouters, J.; Herman, B. E.; Szécsi, M.; Skoda-Földes, R.	Synthesis and $C_{17,20}$-lyase inhibition of 16α-amino-pregnanes

P-73	Szkudlarek, A.; Maciążek-Jurczyk, M.; Pawełczak, B.; **Chudzik, M.**; Sułkowska, A.	The effect of temperature on binding tolbutamide to glycated serum albumin
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P-75	**Taricska, N.**; Perczel, A.; Bokor, M.; Tompa, K.	Under freezing point liquid water surrounding globular and disordered proteins
P-76	**Tassano, E.**; Tripp, A.; Hall, M.; Faber. K.	Asymmetric biocatalytic Cannizzyaro-type reaction: A sustainable route to chiral profens and profenols
P-77	**Tyliszczak, B.**	Biopolymer hydrogel containing metallic nanoparticles for biomedical application
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P-81	**Vaculíková, E.**; Pisárčik, M.; Černíková, A.; Peikertová, P.; Dědková, K.; Plachá, D.; Jampílek, J.	Preparation of glibenclamide nanoparticles for solubility enhancement
P-82	**Valenta, T.**; Lapčíková, B.; Lapčík, L.	Thermal properties of food hydrocolloids
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P-84	**Vinklárková, L.**; Masteiková, R.; Foltýnová, G.; Bernatoniene, J.	Matrix film wound dressing with local anesthetic
P-85	**Virant, M.**; Gazvoda, M.; Pevec, A.; Košmrlj, J.	A novel mesoionic palladium(II) complex efficiently catalyses Sonogashira reaction under green reaction conditions
P-86	**Żamojć, K.**; Zdrowowicz, M.; Jacewicz, D.; Chmurzyński, L.	Dihydroxycoumarins as highly selective fluorescent probes for the fast detection of 4-amino-TEMPO
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P-88	**Padrtová, T.;** Marvanová, P.; Odehnalová, K.; Humpa, O.; Mokrý, P.	Quaternary ammonium derivatives – synthesis and evaluation of physico-chemical properties

PLENARY LECTURES

PL-01

FROM DEQUALINIUM TO MITOCHONDRIAL NANOCARRIERS

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1,1'–Decamethylene bis (4-aminoquinaldiniumchloride), a cationic bolaamphiphile referred to as dequalinium (DQA) has been used for over 50 years as an antimicrobial agent in mouthwashes, lozenges, ointments and paints. The exclusive localization of DQA inside mitochondria was experimentally demonstrated 30 years ago [1] while mechanistic aspects of its mitochondriotropism have been discussed more recently [2]. DQA possesses a wide variety of pharmacological activities as summarized in [3]: K^+ channels, F1-ATPase, calmodulin, proteinase K and mitochondrial DNA all have been reported as potential molecular targets. In the mid1990's, during the search for a then putative DNA gyrase-like topoisomerase activity associated with apicoplast DNA in *P. falciparum* [4], a large number of compounds known to interfere with DNA metabolism [5] have been screened and one of them was DQA. By pure chance it was found that under certain experimental conditions DQA is able to self-assemble into liposome-like vesicles named at the time of that discovery DQAsomes (DeQAlinium-based lipoSOMES) [6]. The strong affinity of DQA for mitochondria combined with its ability to form nano-sized cationic vesicles have led to the proposal of using DQAsomes as the very first potential mitochondria-targeted DNA delivery system [7], the proof-of-concept for which was provided 10 years later with the very first report of a successful functional transgene expression in mammalian mitochondria [8]. In parallel to developing them as a mitochondrial transfection vector, DQAsomes have effectively been exploited *in vitro* and *in vivo* as mitochondria-specific nanocarrier for improving the mitochondria-based proapoptotic activity of small molecules, summarized in [9]. Nowadays, DQAsomes are considered as the prototype of all mitochondria-targeted pharmaceutical nanocarriers [10]. Here, applications for mitochondria-specific drug and DNA delivery systems will be described, the current state-of-the-art of mitochondrial drug targeting technology will be reviewed and its future perspective will be discussed.

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PL-02

STRUCTURAL BIOINFORMATICS – TOWARDS REVEALING BIOLOGICALLY RELEVANT INFORMATION HIDDEN IN DATABASES

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Structural bioinformatics is a part of bioinformatics (see, for example [1-2]), which is dealing with the analysis and prediction of the three-dimensional structure of biological macromolecules. It is closely related to computational chemistry and computational biology. As the production of new 3D structural data is fascinating, one needs qualitatively new approaches to extract structurally and (consequently) biologically relevant information from such a huge amount of data. Such an information can then be used in search for biologically active compounds including drugs.

A part of our research focus is oriented in this direction. We have developed a collection of software tools that contribute to 3D data analysis and consequent implications. Among these are PatternQuery [3] for quick definition and extraction of biomacromolecular fragments, SiteBinder [4] for fast and accurate comparison of these fragments, MotiveValidator [5] and ValidatorDB [6] for validation of ligands and non-standard residues. In order to step forward towards biology, one needs to characterize the above extracted and validated data subsets. For these purposes, we offer AtomicChargeCalculator [7] for fast calculation of partial atomic charges on small molecules, biomacromolecules and their complexes. We also offer MOLE [8], a software tool for detection and characterization of channels and pores in biomacromolecules. All the software tools are accessible from the link http://ncbr.muni.cz/WebChemistry. The majority of software is available also through PDBe, Protein Structure Database in Europe, and through PDBsum: a Web-based database of summaries and analyses of all PDB structures. Both platforms are operated by EMBL EBI, European Bioinformatics Institute in Hinxton, UK.

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PL-03

SPECIFIC ROLES OF HISTIDYL AND CYSTEINYL RESIDUES IN THE METAL ION BINDING SITES IN PEPTIDES AND PROTEINS

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Metal ions are crucial for the survival and well-being of all known living organisms. They are necessary for proper cell metabolism, effective immune functioning, and healthy reproduction. Their role and homeostasis in living organisms varies, and the deficiency of the particular metal causes clinical symptoms.

The interactions of Cu^{2+}, Ni^{2+}, Zn^{2+} and other metal ions with peculiar regions of proteins, containing sequences rich in the consecutive repeats of single amino acids are very interesting from the chemical point of view. Normally, Cys and His residues exist in protein sequences with relatively low frequency (<2.5%), but in some cases these amino acids may be highly enriched in certain proteins (e.g. poly-histidine regions in synthetic poly-histidine tags, snake venoms or transcription factors and poly-cysteine repeats in bacterial chaperones or proteins involved in neurodegenerative processes) to fulfill a unique function with the biological or medical consequences [1].

Experimental evidence showed that unique properties of the histidine-tag sequences may be extremely important for the biological behavior of many peptides and proteins, which contain motifs of this type. Histidine is not only an excellent metal binder, but it can also be versatile amino acid that influences protein conformation and enzymatic activity [2-5].

The typical role of poly-Cys proteins is the maintenance of metal ion (Zn^{2+} or Cu^{+}) homeostasis and the detoxification of toxic metal ions (*e.g.* Cd^{2+} or Ni^{2+}) [6]. Studies of peptides containing different number of CXXC motifs have shown examples of the sequences that are remarkably efficient in Zn^{2+}, Cd^{2+} and Ni^{2+} ion binding [7]. Studies on mutants of the poly-Cys sequence of the loop domain of HypA, a protein responsible for the homeostasis of Ni^{2+} in *Helicobacter pylori*, showed the role of these residues in the structure and the stability of Zn^{2+}, Cd^{2+} complexes with Cys-rich domains in the proteins [8].

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PL-04

BIG DATA PROBLEM IN DRUG DESIGN AND STRUCTURE-PROPERTY STUDIES

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Chemistry attempts to find the rules that control the behavior of chemical compounds. Preferably for the universal laws, this refers to a whole population of molecules and/or substances, e.g., conservation energy law. On the other hand, classical QSAR (QSPR) used to describe a small series of congeneric compounds. With the enlargement of chemical space we could have modified the questions asked. For example, we got interested if a general rule exists that differentiates drugs from non-drugs, which molecular descriptors decide this or what does drug-likeness mean. At the same time the availability of computers resulted in the explosion of information. Accordingly, we realized that data became big recently. There are many definitions of big data but generally what decides a difference between the conventional and big datasets are *volume*, *velocity* and *variety*, where volume refers to a massive size of datasets; velocity to the rate of the information increase and variety to the diverse data forms here. Alternatively, big data is sometimes defined by high information complexity where traditional methods fail when used for processing. How should big data be gathered and managed? What questions to ask in order to address and answer real problems, in particular in drug design?

During the lecture we will address the question of the data type that we can encounter as big records in drug design. Let us define the data simply as the collection of information formed by records. This can grow big both by an increase of the number of objects, by the increase of the number of variable entries describing individual object or by the increase of both the objects and observables. We can further observe that there are several basic big data type, i.e., properties measured for factual chemical space (FCS) substances, properties predicted for FCS or virtual chemical space (VCS) substances or descriptors calculated for FCS or VCS molecules. We will discuss here the precise definitions of CS, properties and descriptors [1].

In particular, we will discuss the main problems of big data vs. traditional QSAR analyses, i.e., data availability for various molecular populations in chemical space, statistical verification of the models, etc. For example, despite common belief, measured properties are rare in chemical space [1]. What are the differences between the traditional QSAR and molecular statistics in the context of the model descriptive, predictive or prescriptive ability. In particular, we will illustrate the problem by a case study attempted to answer the question: **how much does a molecule cost?** The relationship between the structure and a property of a chemical compound is an essential concept in chemistry guiding drug design. Actually, however, we need economic considerations to fully understand the fate of drugs on the market. We have recently reported for the first time quantitative structure-economy relationships (QSER) for a large dataset of a commercial building block library of over 2.2 million chemicals, i.e., molecular statistics that shows that on average what we are paying for is a quantity of matter. Synthetic availability scores and selected atom counts also matters here. [2]

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PL-05

SIMULATING LIGAND-RECEPTOR INTERACTIONS. THE CHALLENGE TO UNDERSTAND A DYNAMIC PROCESS USING STATIC TECHNIQUES

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The affinity of a ligand (L) by its biological receptor (R) will depend primarily on their ability to form the L-R complex. The formation of such a complex is a dynamic process in which are involved many intermolecular interactions that stabilize and destabilize the formation of this L-R complex. For many years, medicinal chemists have been kept sleepless trying to make a correct evaluation of the L-R complex formation, and this difficulty continues unsolved until nowadays. This is understandable since an accurate description of this process would allow the design and development of new more specific and more effective drugs, which are principal goals of medicinal chemistry.

The simulation of this essentially dynamic process with current molecular modeling techniques face a tradeoff: i) perform these simulations using dynamic techniques which evaluate quite poorly the intermolecular interactions, or ii) use techniques of quantum mechanics which are much more accurate to evaluate these interactions, but they only can assess a static process.

We report here a comparative study based on the results obtained in eight different biological systems of interest in medicinal chemistry: dopaminergic receptors (D1 and D2); beta-secretase (BACE-1), dihydrofolate reductase (DHFR), sphingosine kinase 1 (SPHK1), acetylcholinesterase (AChE), proto-oncogene serine/threonine kinase (B-RAF) and DNA gyrase-subunit B (GyrB)). Our results indicate that an acceptable or poor performance of the simulations depend on various factors. The size of the active site (space and depth), the number and type of interactions involved in the formation of the L-R complex, the structural variability of the ligands under study and the role of the surrounding interactions. In this presentation the scope and limitations of using different molecular modeling techniques (static, dynamic and combined approaches) to study the formation of L-R complexes are discussed.

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PL-06

DISENTANGLING PUZZLES – ATOMIC RESOLUTION STUDIES OF INTRINSICALLY DISORDERED PROTEINS

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Among of all available techniques of modern structural biology NMR represents the ultimate tool for studies of unstructured or partially disordered proteins at the atomic resolution. In principle, intrinsically disordered proteins can be studied using a standard set of triple-resonance NMR experiments applied to ^{13}C, ^{15}N-labelled samples. However, combination of the structural disorder with a high incidence of sequential repeats often results in spectra with severely overlapped peaks, impossible to decipher by the traditional approach. The lecture will review recent methodology developed in our lab to significantly shorten time needed for thorough description of unstructured or partially disordered proteins. To facilitate the atomic resolution studies, we have designed a suite of high-dimensional (4D-5D) NMR experiments, which combines ^{13}C-direct detection, non-uniform sampling, and non-standard data processing procedures to substantially enhance the attainable resolution. The power of the developed methodology is documented on studies and disorder characterization of 20 kDa delta subunit of RNA polymerase unique for gram-positive bacteria, 12.8kDa intrinsically disordered WIPs protein having a high content of proline residues (26%) in the sequence, and 49.2 kDa microtubule-associated protein 2c.

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PL-07

ASPARTYL(ASPARAGINYL)-BETA-HYDROXYLASE INHIBITORS FOR THE TREATMENT OF HEPATOCELLULAR CARCINOMA

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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 [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. 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 also over-express ASPH. ASPH has been demonstrated to aberrantly activate the NOTCH signaling pathway [2], and cleaved ASPH is capable of suppressing NK cell activity [3]. ASPH inhibitors have been rationally designed and synthesized, and demonstrate predicted activities *in vitro* [4], including suppression of migration, invasion, and activation of NOTCH pathway related proteins. *In vivo* proof-of-principle experiments demonstrate significant suppression of tumor growth at 1mg/kg [5]. 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.

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PL-08

LIMITING THE NUMBER OF POSSIBLE POCKET OCCUPATIONS BY INTRODUCING SYMMETRY INTO LIGANDS: DEVELOPMENT OF PROTEASE INHIBITORS

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Benzamidine and benzguanidine moieties have been successfully utilized as arginine mimetics for the assembly of peptidomimetic inhibitors for trypsin-like serine proteases. Herein, an approach for the development of inhibitors for matriptase-2 and related trypsin-like serine protease is reported. The type II transmembrane protease matriptase-2 was identified to be a key regulator of iron homeostasis since mutations in the corresponding *TMPRSS6* gene have been shown to cause iron refractory iron deficiency anemia [1]. Matriptase-2 suppresses hepcidin and thereby increases plasma iron levels via BMP/SMAD signaling, by cleaving the BMP co-receptor hemojuvelin [2]. Hence, matriptase-2 becomes an attractive target for the treatment of iron-related disorders, *e.g.* hemochromatosis and β-thalassemia [3].

In the course of the study, symmetry was introduced in bi- and tribasic compounds to reduce conformational space in docking calculations and to simplify binding mode selection by limiting the number of possible pocket occupations. Asymmetric bisbenzamidines were used as starting points for a multistage and structure-guided optimization. A series of protease inhibitors with either two or three benzamidine substructures was synthesized and evaluated lading to potent symmetric inhibitors of five serine proteases, including matriptase-2. This study underlines the relevance of ligand symmetry for chemical biology [4].

Synthetic routes to phosphono bisbenzguanidines as irreversible dipeptidomimetic matriptase-2 inhibitors have been developed. In addition to a phosphonate warhead, these dipeptides possess two benzguanidine moieties to provide affinity for matriptase-2 by binding to the S1 and S3/S4 subpockets, respectively. This binding mode was strongly supported by covalent docking analysis. Inactivators were obtained as mixtures of two diastereomers and separated into the single epimers. A compound with (*S*)-configuration at the N-terminal amino acid and (*R*)-configuration at the phosphonate carbon was the most potent matriptase-2 inactivator with a k_{inac}/K_i value of 2790 $M^{-1}s^{-1}$ and abolished the activity of membrane-bound matriptase-2 on the surface of intact cells. Based on the chemotype of phosphono *bis*-benzguanidines, the design and synthesis of a fluorescent probe by insertion of a coumarin label was accomplished. The *in-gel* fluorescence detection of matriptase-2 was demonstrated by applying this dipeptidomimetic inactivator as the first activity-based probe for this enzyme [5].

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PL-09

NEW STRATEGIES FOR THE SYNTHESIS OF HIGH ADDED VALUE FINE CHEMICALS COMBINING MULTICOMPONENT REACTIONS WITH BIOCATALYSIS OR ORGANOCATALYSIS

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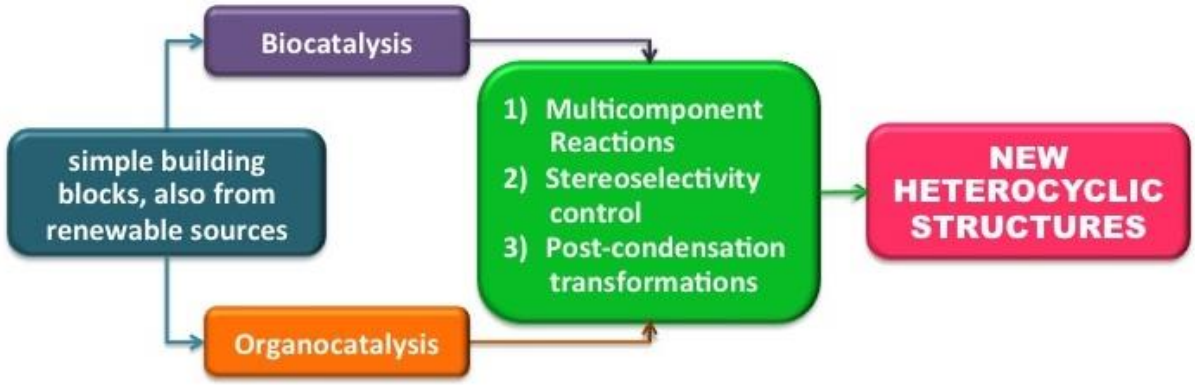
A main interest of our group is to devise new strategies for the synthesis of new fine chemicals using also renewable sources, by combination of biocatalysis or organocatalysis with multicomponent reactions (MCR), especially those based on isocyanides such as the Passerini and the Ugi reactions. Towards this goal, biocatalytically or organocatalytically produced chiral building blocks are used as inputs for diastereoselective MCRs to give highly decorated structures [1].



MCRs, if coupled with appropriate post-condensation transformations, represent a powerful methodology for a fast assembly of complex structures characterized by cyclic or acyclic skeletons as well. This strategy can be used for example to prepare new heterocyclic scaffolds for possible applications as drugs, following a diversity oriented approach [2 .
On overview of the most recent results within this topic will be presented.

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PL-10

DISCOVERY OF BIOACTIVE LEAD COMPOUNDS FROM THOUSANDS OF PLANT EXTRACTS THROUGH BIOASSAY-GUIDED SEPARATION

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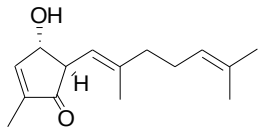
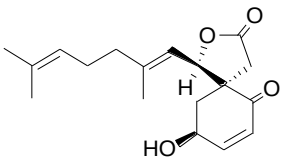
It is our goal to discover and develop new chemical entity (NCE) drugs and herbal medicines from natural resources [1-4]. For decades, our medicinal plant research program has evaluated the anticancer, antiviral (including HIV, bird flu and Ebola), antimalarial, antifungi and antibacteria (including TB) activities of several thousands of terrestrial plant and microbial samples, especially the extracts derived from the plants in Lingnan. Lingnan is a region that covers several Southern provinces of China as well as the northern area of Vietnam. The sub-tropical zone area is rich in plant biodiversity, providng an excellent source for discovery of novel and bioactive compounds. Our screening program has determined that many of the Lingnan plant extracts displayed biological activities. Further phytochemical and biological studies of some of these plant leads led to the identification of a number of potent antimicrobial and anticancer compounds. For example, we have discovered novel anti-HIV compounds with IC_{50} values in the range of 15-40 nM, and new anticancer compounds active against multiple cancer cell lines with low IC_{50} values. The anti-HIV compounds also displayed potent inhibitory activity against drug-resistant HIV-1 isolates of both nucleotide analogue and non-nucleotide analogue. Some of the anticancer compounds have been investigated for their *in vivo* efficacy in xenograft mouse models.



An anti-HIV agent



An anticancer agent

The work described in this paper was collaborative efforts within multi-disciplinary cooperative programs supported by grants from the Research Grants Council of the Hong Kong Special Administrative Region, China (Project No. HKBU 262912 and HKBU12103014), HKBU Interdisciplinary Research Matching Scheme (RC-IRMS/12-13/03), the Health and Medical Research Fund (12132161) of the Food and Health Bureau, Hong Kong SAR, Faculty Research Grant, Hong Kong Baptist University (FRG2/14-15/047), and NIH Grants 3U01TW001015-10S1 and 2U01TW001015-11A1 (administered by the Fogarty International Center as part of an International Cooperative Biodiversity Groups program, through funds from NIH, NSF, and Foreign Agricultural Service of the USDA.

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PL-11

CHEMICAL AND BIOLOGICAL UTILITY OF PYRIDINE-APPENDED CLICK TRIAZOLE DERIVATIVES

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Although 1,2,3-triazole has been known for more than a century,[1] commenced from the discovery of the copper-catalysed cycloaddition between organic azide and terminal acetylene (Click reaction),[2] the number of applications of this heterocycle has increased dramatically.[3] With no doubt, “there is more function to the 1,2,3-triazole unit than first meets the eye.”[4]

We have been interested in 1,4-disubstituted 1,2,3-triazoles tethered to pyridine as well as pyrimidine, and pyrazine rings.[5] These molecules have been studied as versatile coordination ability ligands for platinum, palladium, copper, ruthenium, rhodium, silver, gold, mercury, and others, enabling supramolecular associations.[6]

We have developed a highly selective and efficient protocol to transform pyridine functionalized 1,4-disubstituted 1,2,3-triazoles into the corresponding 1,4-disubstituted-3-methyl-1,2,3-triazolium salts,[7] which found application in organometallic chemistry as precursors for 1,2,3-triazol-5-ylidene ligands, an interesting class of chelating pyridyl-mesoionic carbene ligands.[8] Their complexes with transition metal ions have been investigated as homogeneous catalysts in organic chemistry. Remarkably, a palladium complex of pyridine-appended 1,2,3-triazolylidene catalysed the copper-, amine-, phosphine-, and additive-free aerobic Sonogashira alkynylation of (hetero)aryl bromides in water as the only reaction solvent.[9]

Pyridine-appended 1,2,3-triazoles, their 1,2,3-triazolium salts, and 1,2,3-triazolylidene-metal complexes show interesting biological activities. For example, we have demonstrated that 1,2,3-triazolium salts possess high anticancer activity against several different tumour cell lines, as well as carboplatin and cisplatin-resistant sublines. The cytotoxicity was cell type dependent and significantly higher against tumour cells than normal cells.[10]

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PL-12

CHARACTERIZATION AND APPLICATIONS OF A CYSTEINE-HISTIDINE-DEPENDENT AMIDOHYDROLASE/PEPTIDASE ENZYME TARGETING MRSA

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Staphylococcus aureus is a major cause of infection in humans and animals causing a wide variety of conditions from local inflammations to fatal sepsis. The bacterium is commonly multi-drug resistant and thus many front-line antibiotics have been rendered practically useless for treating human infections. We sequenced the genome of anti-staphylococcal phage K, which has a broad host range among staphylococci. We then cloned the gene for the phage endolysin. This enzyme, named LysK, was found to have a modular organisation with three domains, a cysteine/histidine-dependent amido hydrolase peptidase (CHAPk), an amidase, and thirdly a cell-wall binding domain. The latter facilitates attachment of the enzyme to the bacterial cell wall, while former two domains catalyse the degradation of the peptidoglycan, mediating rapid bacterial cell death. Deletion analysis of the enzyme showed that full lytic activity against live antibiotic-resistant staphylococci was retained when the endolysin was truncated to its CHAPk (peptidase) domain. *In silico* elucidation of the three-dimensional structure of the peptidase domain indicated a net positive charge on the molecule. This property is fortuitous as it facilitates attraction to the negatively charged cell wall of staphylococci, a charge resulting from the presence of teichoic acid moities. The positive charge is not always associated with endolysins targetting staphylococci. The enzyme was purified by ion-exchange chromatography and characterized in detail including elucidation of its 3-D structure [1]. Addition of the enzyme to a turbid bacterial MRSA culture resulted in elimination of turbidity. The peptidase was used in in-vivo studies in mouse models where it successfully eliminated MRSA colonization without adverse effects on the animals; and furthermore, ex-vivo studies confirmed a low immunogenicity [2].

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PL-13

THE USFDA GENERIC DRUG REVIEW PROCESS: PRESENT AND FUTURE CHALLENGES

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Generic drugs marketed in the United States of America must first be assessed and approved by the United States Food and Drug Administration (US FDA). The review process for the approval of an Abbreviated New Drug Application has undergone significant changes in recent years, particularly for the chemistry, manufacturing and controls (CMC) sections of the application. Passage of the Generic Drug User Fee Amendment of 2012 (GDUFA), the adoption of Quality by Design (QbD) principles, the formation of the Office of Pharmaceutical Quality (OPQ) and the beginnings of adoption of formal Lifecycle management principles have all had and will continue to influence the review process. An overview of these changes and the impact they have on the approval of Abbreviated New Drug Applications (ANDA) will be discussed.

PL-14

NATURAL COMPOUND-REGULATED CROSSTALK BETWEEN CELL DEATH MODALITIES AS A PHARMACOLOGICAL TARGET

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Cell death plays an essential role in the development of organs, homeostasis, and cancer. Apoptosis and programmed necrosis are two major types of cell death, characterized by different cell morphology and pathways. Accumulating evidence shows autophagy as a new alternative target to treat tumor resistance. Besides its well-known pro-survival role, autophagy can be a physiological cell death process linking apoptosis and programmed necrosis cell death pathways, by various molecular mediators.

Here, we summarize the effects of pharmacologically active compounds as modulators of different types of cancer cell death depending on the cellular context. Indeed, current findings show that both natural and synthetic compounds regulate the interplay between apoptosis, autophagy and necroptosis stimulating common molecular mediators and sharing common organelles. In response to specific stimuli, the same death signal can cause cells to switch from one cell death modality to another depending on the cellular setting.

The discovery of important interconnections between the different cell death mediators and signaling pathways, regulated by pharmacologically active compounds, presents novel opportunities for the targeted treatment of cancer. The aim of this review is to highlight the potential role of these compounds for context-specific anticancer therapy.

PL-15

DISCOVERY OF INHIBITORS OF DNA GYRASE B AND TOPOISOMERASE IV INSPIRED BY MARINE ALKALOID OROIDIN

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Bacterial DNA gyrase and topoisomerase IV (topoIV) are heterotetrameric proteins consisting of two GyrA or ParC subunits involved in DNA transit, and two GyrB or ParE subunits containing the ATPase domains, respectively. They are well-known and validated targets in the discovery of antibacterial drugs but inhibitors of their ATP-binding subunits GyrB and ParE, have so far not reached the clinical use. Growing resistance against the fluoroquinolones that target the GyrA/ParC subunits, limits their therapeutic potential and requests the search for novel inhibitors targeting the GyrB/ParE ATP-binding sites. Several recent publications and patent applications on bacterial DNA gyrase and topoIV inhibitors emphasize the attractiveness of these two enzymes for antibacterial drug discovery [1].

Recently, we have found that the 4,5-dibromo-1*H*-pyrrole-2-carboxamide moiety, present in *Agelas oroides* marine sponge alkaloid oroidin, is important or binding to the hydrophobic pocket of the *Escherichia coli* GyrB ATP-binding site [2]. Structure-based optimization of initial low micromolar hits based on the 4,5,6,7-tetrahydrobenzo[1,2-*d*]thiazole scaffold resulted in a series of low nanomolar *E. coli* and submicromolar *Staphylococcus aureus* DNA gyrase inhibitors possessing also micromolar inhibitory activity against *E. coli* and *S. aureus* topoIV. These compounds also displayed modest antibacterial activity against Gram positive *S. aureus* and *Enterococcus faecalis*, while they were found to be efflux pump substrates in *E. coli*, which most likely leads to their inactivity against Gram negative bacterial strains [2]. Replacement of the 4,5,6,7-tetrahydrobenzo[1,2-*d*]thiazole core by the benzothiazole scaffold [3] resulted in almost equipotent *E. coli* DNA gyrase inhibitors some of which possessed balanced dual DNA gyrase/topoIV inhibitory activities. High resolution co-crystal structure of the *E. coli* GyrB in complex with a benzothiazole inhibitor gave insight into its interactions within the ATP-binding site and provided basis for further structure-based optimization.

Starting from the 4,5,6,7-tetrahydrobenzo[1,2-*d*]thiazole series of *E. coli* DNA gyrase inhibitors, a new structural class of *N*-phenylpyrrolamides was designed and, through several optimisation cycles, led to low nanomolar *E. coli* DNA gyrase inhibitors. The binding mode of this structural class to the ATP-binding site of *E. coli* GyrB was revealed by a high-resolution crystal structure of the enzyme in complex with a *N*-phenyl-4,5-dibromopyrrolamide-based inhibitor [4,5].

Potent inhibition, observed antibacterial activity and available structural information highlight these structural classes of DNA gyrase and topoIV inhibitors as promising starting points for structure-based design of inhibitors with improved antibacterial activity.

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PL-16

“THE ENTERPRISE OF DRUG DISCOVERY FROM AN ACADEMIC PERSPECTIVE: A PERSONAL ODYSSEY”

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Monumental achievements in drug development within the pharmaceutical industry worldwide have benefitted humankind with improving our quality of life and providing life-saving medicines over decades of dedicated work. Academic research has also been instrumental in making fundamental contributions at the interface between the chemical, physical and biological sciences, and especially in the training of future scientists who eventually contribute to the invention of new medicines. Indeed some of the most important insights into our understanding of basic chemical and biological processes at the molecular level continue to come from academic groups.

The lecture will cover various aspects of our research projects in the area of structure-based organic synthesis toward novel drug prototypes emphasizing a biology-inspired, chemistry driven approach and highlighting examples of highly successful collaborative projects with a plethora of research groups in various pharmaceutical companies without compromising the sanctity of basic research principles and the noble objective of coworker training in an academic setting.

PL-17

FROM VIBRATIONAL SPECTROSCOPY TO NANOSCOPY OF SKIN SYSTEMS WITH NANOPARTICLES

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Vibrational spectroscopy, consisting of infrared absorption/reflection spectroscopy and Raman spectroscopy, represents a powerful molecular spectroscopic tool for chemical characterization of different materials from elemental ones to complex biological systems. However, especially in the case of biological samples both (1) the high chemical sensitivity including the ability of trace amount detection and (2) spatially resolved information are essential to elucidate the complexity of systems and the dynamics of biological processes.

Firstly, the surface-enhanced vibrational spectroscopic (SEVS) techniques based on either surface-enhanced Raman scattering or surface-enhanced infrared absorption can be used for detection and/or identification of low amount of organic/biologically important compounds. The plasmonic metal nanoparticles and/or nanostructures are used to spectroscopic signal enhancement. However, the interaction of metallic nanoparticles with the components of biological systems can affect their native properties. Furthermore, the healing (basically antibacterial and anti-inflammatory) effects of silver and/or gold nanoparticles (AgNPs/AuNPs) are already known. The vibrational spectroscopic studies of skin systems shows that AgNPs/AuNPs influence the permeation properties of outer skin layers and affects the penetration of various organic substances, for example B vitamins or peptides. The effects of quantities and types of NPs on skin penetration characteristics are evident evaluating the data by multivariate chemometric algorithms, e.g. principal component analysis, partial least square regression and soft independent modelling of class analogy.

Secondly, classical vibrational micro-spectroscopy is limited from the point of view of spatial resolution by the diffraction limit. That means, that confocal Raman micro-spectroscopy can go down below 1-μm lateral resolution with visible laser excitation, while the mid infrared micro-spectroscopy is limited at the level of ten μm. Hence, the classical vibrational micro-spectroscopy cannot provide detailed information on nanostructures or even individual molecules. The study of nanostructures at molecular or even atomic resolution is accessible using scanning probe microscopic (SPM) techniques. Nowadays, we can combine the spatial resolution of SPM technique with the chemical/molecular specificity of vibrational spectroscopy using the advanced techniques of tip-enhanced Raman spectroscopy (TERS) and scanning near-field infrared microscopy (SNIM). TERS combines SPM with Raman spectroscopy and enables both outstanding detection sensitivity down to single-molecule level and high spatial resolution down to sub-nanometers. In the case of SNIM, the source of irradiation is a tunable infrared laser, adjusted to a specific wavenumber for an imaging/mapping experiment. The laser beam is focused to a space under the tip and coupled with tip oscillations. SNIM measurement reveals the chemical nano-scaled imaging information about the sample based on “distribution” of absorption and radiation phase shifts at the selected wavenumber for the molecules which absorb the radiation at this wavenumber and are located under the tip. Both TERS and SNIM are studied to be applied for model systems of skin constituents, mainly for the samples related to *stratum corneum* and various topically applied molecular and nano- systems.

Financial support from the specific university research (MSMT No 20-SVV/2016) and the University of Chemistry and Technology Prague is gratefully acknowledged.

PL-18

ANTIFUNGAL STYRYLQUINOLINES AS EFFLUX PUMPS INHIBITORS

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Candida albicans is fungal opportunistic pathogen. Although, most commonly it causes superficial, though often persistent oral or vaginal candidiasis, in patients with immunodeficiency infection can result in life-threatening systemic candidiasis. Additionally, *C. albicans* is shown to gain resistance to commonly used antifungals, such as azoles. One of the main mechanism of resistance is overexpression and activity of ABC (*ATP-binding cassettes*) transporters, Cdr1p and Cdr2p, which actively export xenobiotics out of the cell.

In this study we present styrylquinolines (SQLs) as new antifungal agents. SQLs have interestingly vide spectrum of activity covering antimicrobial and antiproliferative potency [1-3]. Preliminary screening showed inhibition of the *C. albicans* growth by those compounds and their synergistic activity with fluconazole. Δ*CDR1* mutant was more sensitive to tested compounds. This result may indicate that styrylquinolines are substrate for Cdr1p pump which we confirmed using the rhodamine 6G assay. Additionally using GFP-tagged Cdr1p we showed that styrylquinolines induce expression of this transporter. After 4 hours of incubation with the compounds we observed partial delocation of GFP fluorescence from plasma membrane to the cytoplasm. The similar effect was observed after incubation with amphotericin B and filipin, both compounds that bind to ergosterol and destabilize the cell membrane.

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PL-19

BIOACTIVE NATURAL COMPOUNDS TARGETING VASCULAR FUNCTIONALITY

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Vascular disturbances such as atherosclerosis are underling cause of cardiovascular disease, the number one cause of death in the world. Therefore, identification of bioactive compounds with beneficial action in this context is highly relevant. Natural products encompass diverse chemical scaffolds, and are evolutionary optimized to serve diverse relevant biological functions. Therefore, natural products are an especially relevant source for discovery of novel pharmacologically active therapeutics. High number of plant-derived natural products targeting diverse proteins with pathophysiological relevance, as well as diverse cellular processes involved in the pathogenesis of atherosclerosis, has been recently identified by our research group. In detail will be discussed the discovery and mechanistic characterization of natural products able to prevent atherosclerotic plaque cholesterol deposition by enhancing the macrophage cholesterol efflux, a process that counteracts the transformation of macrophages into cholesterol-enriched foam cells which play a significant role in the development of this vascular pathology.

Supported by the Austrian Science Fund (FWF) project P25971-B23 ("Improved cholesterol efflux by natural products"), and by the Vienna Anniversary Foundation for Higher Education (Hochschuljubiläumsstiftung der Stadt Wien) project H-297332/2014 ("Metabolomics-assisted dissection of molecular mechanisms underlying the action of natural products increasing macrophage cholesterol efflux").

PL-20

AMYLOID FIBRIL FORMATION IN DETAILS: THE DEAD END STREET OF PROTEIN FOLDING?

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Out of the ~100 000 proteins of a eukaryotic cell ~70% are built up from domains and modules of autonomous 3D-fold. Several known diseases are related to protein domain misfolding proceeded amyloidogenesis, where globular proteins misfold and thus misassemble making insoluble and toxic olig- and polymeric cross-β-sheet fibrils, called as amyloids. They have been found to be a result of the formation of amyloid aggregates that are practically independent of the original primary sequence of the protein. Consequently, the driving force of the transformation from original to disordered amyloid fold is expected to lie in the protein backbone, which is common to all proteins. However, the exact explanation for the existence of such a "dead-end" structure is still unknown. Using systematic first principle calculations on carefully selected but large enough systems modelling the protein backbone we show that the β-pleated sheet structure, the building block of amyloid fibres, is the thermodynamically most stable supramolecular arrangement of all the possible peptide dimers and oligomers both in vacuum and in aqueous environments. Even in a crystalline state (periodical, tight peptide attachment), the β-pleated sheet assembly remains the most stable superstructure. This lecture provides a quantum-level explanation for why proteins can take the amyloid state, when local structural preferences jeopardize the functional native global fold and why it is a β-pleated sheet-like structure they prefer.

LECTURES

O-01

EPITOPE MAPPING OF SELECTED HUMAN PROTEINS – POTENTIAL TRIGGERS OF RHEUMATOID ARTHRITIS

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Rheumatoid arthritis is the most common rheumatic diseases. Aspects that affect disease development are genetic, environmental and pathogenic [1]. The persistent survival of *H. pylori* in humans is possible because of an overall downregulation of the immune's system due to molecular mimicry [2]. This phenomena is defined as shared amino acid sequences between microbial antigens and host proteins which can result in immune response against both the host proteins and microbial antigens. Taking into account that *H. pylori* urease has been suggested as dominant antigen detected in infected patients and phenomena of molecular mimicry we were looking for human proteins with motifs similar to *H. pylori* urease fragment recognized by antibodies against this protein. We focused our attention on two human proteins: NEDD4L and LAF-4 which contain fragments with high homology to *H. pylori* urease. NEDD4L (Neural precursor cell expressed developmentally downregulated gene 4-like) is an ubiquitin ligase which found in brain, lung, heart, and kidneys, and synoviocyte. NEDD4L protein modulates gene transcription of metalloproteinase (MMP) 1 and 13. MMP-1 and MMP-13 can degrade type II collagen in cartilage, thereby contributing to the development of rheumatoid arthritis [3]. In addition, the protein contributes to the formation of pannus, which forms a barrier between the cartilage and synovial fluid, thus blocking the access of nutrients necessary for proper functioning cartilage. At the same time it produces osteoclast activating factors damaging cartilage and structure of the epiphysis.

Protein LAF-4 (lymphoid nuclear protein related to AF4) has been involved in autoimmune diseases, namely rheumatoid arthritis, psoriatic arthritis, and juvenile idiopathic arthritis and was also found expressed in 20% of mammary tumor cells [4]

To select immunologically active fragments, the epitope mapping of NEDD4L protein has been performed using polyclonal antibodies against urease. Then, the selected most active epitopes were treated with sera of RA patients. It has been found significantly stronger reactions for RA patients in comparison with healthy blood donors.

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O-02

NATURAL DEEP EUTECTIC SOLVENTS FOR THE EXTRACTION OF PHYTOCHEMICALS

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Natural Deep eutectic solvents (NADES) are mixtures of small natural compounds having a melting point significantly lower than that of either individual component. Such solvents have gained much attention from the scientific community in the green chemistry area being considered useful to replace common organic solvents. Main advantage of NADES towards solvents are low toxicity and volatility and high solvent power[1,2]. NADES are obtained by the complexation of an hydrogen acceptor and a hydrogen-bond donor and can be formed using aminoacids ,sugars, organic acids and small compounds like urea, choline etc [1,2] Thus NADES due to their "green" nature can be considered as future solvents being especially useful for the plant extraction. In this paper we report our experience in the preparation of NADES using sugars, aminoacid and organic acids. Prepared mixtures were used for extraction of phytoconstituents from vegetal matrix such as *Valeriana officinalis*, *Echinacea pallida*, *Melissa officinalsi, Commiphora myrrha, Boswellia serrata* and *Passiflora incarnata*. Extracted phytoconstituents were analyzed by different techniques namely HPLC-DAD, HPLC-MS and GC-MS and the extraction yields were compared with solvent showing the ability of some NADES to extract the bioactive compounds in the same amount or better than aqueous ethanol mixtures. In order to study the possibility to use NADES as administration vehicle a proline, glutamic acid NADES was used to solubilize rutin (quercetin-3-O α-L-rhamnopyranosyl-(1→6))-β-D-glucopyranose). The pharmacokinetic of rutin dispersed in water (20 mg/mL) and in proline glutamic acid NADES (20 mg/mL) was studied in mice. Plasmatic levels of rutin were measured by HPLC-MS/MS method showing increased plasmatic peak for NADES treated animals and showing a longer period of rutin permanence in plasma.

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O-03

OF YEAST, BACTERIA AND MEN: STRUCTURE-FUNCTION STUDIES OF MONOACYLGLYCEROL LIPASES REVEAL EVOLUTIONARY CONSERVED CAP ARCHITECTURES AND REGULATORY FUNCTIONS IN ETHANOL METABOLISM

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Many essential cellular processes are conserved between mammals and the yeast, one of the simplest eukaryotic organisms. Therefore, *Saccharomyces cerevisiae* is frequently used to study basic molecular processes conserved throughout all kingdoms of life. The enzyme monoacylglycerol lipase (MGL) has been known for its eponymous ability to hydrolyze monoacylglycerols (MGs) and thus plays important roles in energy homeostasis. Human MGL also plays an important part in mediating endocannabinoid-based signaling rendering it an important pharmacological target. In bacteria, MGLs are thought to have a role in detoxification processes because short chain MGs are highly toxic to these organisms. Despite the longstanding research efforts invested in this enzyme class, structural data were scarce until 2010 when first structures of human MGL (hMGL) were published. Very recently, our group determined the 3D structure of a MGL from a bacterial species and just now determined the structure of MGL from yeast *S. cerevisiae* (Yju3p). These data provide the basis for an in-depth structure-function analysis of these different MGLs: They adopt an α/β-hydrolase fold core which is covered by a cap region. The cap regions of MGLs differ in length, amino acid sequence and secondary structure, yet still adopt a strikingly similar overall architecture. The hydrolytic reaction is catalyzed by a catalytic triad which resides within the core domain. Using protein crystallography, we could take snapshots of these lipases undergoing conformational changes between open and closed conformations in absence and presence of ligands. Based on the structural conservation of the cap, we tested biochemically largely uncharacterized proteins from the PDB and could experimentally pinpoint a previously unknown MGL hydrolase activity. Structure analysis also enabled correlation between size and shape of substrate binding cavities and substrate specificities. Yeast MGL was found to exhibit highest activity in the hydrolysis of mono-unsaturated MGs with 16 and 18 carbon atoms which correlates nicely with the most common fatty acid species in *S. cerevisiae* . As a very novel result, we could show that yeast MGL contributes more than 90% of cellular fatty acid ethyl ester (FAEE) hydrolase activity and that loss of yeast MGL leads to accumulation of FAEE. FAEE are formed upon reaction of fatty acids with alcohols, exhibit very intense flavors and are responsible for characteristic flavors of fruit, beer, liquor and other food. A small proportion of the alcohol consumed by humans can be converted into FAEE during non-oxidative degradation and it is believed that these products contribute to the toxicity of alcohol. So far, very little our knowledge on enzymes degrading FAEE in mammals has been rather scarce. Our studies showed that heterologous expression of mammalian MGL in yju3Δ mutants restored cellular FAEE hydrolase activity. Thus we demonstrate that the newly discovered FAEE-hydrolyzing function of MGL has been conserved during evolution.

O-04

THE ROLE OF METAL IONS IN ALZHEIMER'S DISEASE

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Dysregulation of the proteostasis network leads to protein supersaturation and the formation of amyloid state. This state is associated with protein misfolding, formation of toxic oligomers in the brain, dysfunction of neurons and synapses. In Alzheimer's disease (AD) β-amyloid (Aβ) may initiate the disease by interacting with cellular proteins and subcellular organelles. Most of the proteins interacting with Aβ occupy central positions in the cellular protein network (e.g. chromatin organization, transcription, translation, quality control, energy metabolism).

Heavy metal ions (e.g. Zn^{2+} and Cu^{2+}) play important role in amyloid formation simply by changing the structure (conformation) and charge of proteins. Complexation of heavy metal ions represents one of the AD-drug treatment strategies.

Metal protein-attenuating compounds disrupt the interaction between metals and the Aβ peptide in the brain. Clioquinol and PBT2 (metal ionophores) have been used as AD drug candidates. These compounds prevented metal-mediated Aβ accumulation in tg mice by translocating Zn^{2+} and Cu^{2+} ions into the cell and thus reducing extracellular ion levels. Unfortunately, these drug candidates could not prevent the progression of AD in human clinical studies (Phase II).

The use of metal ion chelators is another possibility for the regulation of Zn^{2+} and Cu^{2+} ion concentration in the brain. Zn^{2+} chelators such as captopril and perindopril are angiotensin converting enzyme (ACE) inhibitors and have been used for the treatment of high blood pressure. A meta-analysis of drug side-effects showed that perindopril treatment decreased the rate of dementia in old patients. We tried to analyze the mechanism of the neuroprotective effect of perindopril both *in vitro* and *in vivo*.

The results of our experiments proved the neuroprotective effect of perindopril in the APPxPS1 transgenic AD mouse model. In humans high blood pressure represents a severe risk factor of AD. Perindopril might perform its neuroprotective activity in humans as an anti-hypertensive drug. However, perindopril protected also young normotensive AD mice from Aβ-accumulation and learning/memory disturbances. This fact represents an indirect proof for the direct action of perindopril on Zn^{2+}-redistribution and restoring metal homeostasis in AD brain.

O-05

p53 INTERACTIONS WITH DNA QUADRUPLEXES

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G-rich DNA segments containing at least four G-blocks formed by two or more consecutive guanines can adopt non-B DNA structures known as G-quadruplexes. These structures are formed by several of so-called guanine tetrads, each composed of four guanines stabilized by Hoogsteen hydrogen bonds into a planar rectangular shape. These tetrads stack over each other to form the quadruplex, which is further stabilized by monovalent cations, coordinating the guanine oxygens (O6) in the central channel of the quadruplex. The formation of particular quadruplex type (strand arrangement, guanine conformations, loops) depends on the primary DNA sequence and conditions pre- and post- folding.

The tumor suppressor protein p53 is a key factor in genome stability and one of the most studied of DNA binding proteins. This is the first study on the interaction of wild-type p53 with guanine quadruplexes formed by the human telomere sequence. Using electromobility shift assay and ELISA, we show that p53 binding to telomeric G-quadruplexes increases with number of telomeric repeats. Further, p53 strongly favors G-quadruplexes folded in potassium over those formed in sodium, indicating the telomeric G-quadruplex conformational selectivity of p53. The presence of the quadruplex-stabilizing ligand, N-methyl mesoporphyrin IX (NMM), increases p53 recognition of G-quadruplexes in potassium. Using deletion mutants and selective p53 core domain oxidation, both p53 DNA binding domains are shown to be crucial for telomeric G-quadruplex recognition.

This work was supported by the Czech Science Foundation (13-36108S to M.B. and 14-33947P to D.R.) and by the ASCR (RVO68081707) and IGA VFU Brno 316/2016/FaF.

O-06

ASYMMETRIC BIOCATALYTIC CANNIZZARO-TYPE REACTION: A SUSTAINABLE ROUTE TO CHIRAL PROFENS AND PROFENOLS

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Among the various disproportionation processes in the field of organic chemistry, the Cannizzaro reaction stands out for its attractiveness: employing an aldehyde as starting material, it leads to equimolar amounts of the corresponding alcohol and carboxylic acid. Typically catalyzed by a strong base, this reaction is however limited to non-enolizable aldehydes [1]. The biocatalytic variant of the Cannizzaro reaction, on the other hand, accepts enolizable aldehydes, including α-substituted compounds. A single alcohol dehydrogenase (ADH) catalyzes concurrently the oxidation and the reduction reactions, requiring only aqueous buffer and catalytic amount of nicotinamide cofactor as hydrogen shuttle [2].

Both the exquisite stereoselectivity of the enzyme and the spontaneous racemization of the starting aldehyde are key features in the biocatalytic reaction, allowing a parallel dynamic asymmetric process to take place and providing two enantioenriched products (in up to 99% *ee*) in a redox neutral fashion (Figure 1).

Herein we present recent data of this ongoing project, aiming at expanding the synthetic applicability of the system to pharmaceutical targets, including profen derivatives. The influence of various parameters, such as enzyme concentration and nicotinamide (reduced and/or oxidized) amount, on conversion, product ratio and *ee* value of products was investigated. Additionally, the use of Design of Experiments shed light on unexpected parameter interactions and system shortcomings.

Eventually, the substrate acceptance was investigated and the influence of the electronic properties of different substituents on reactivity was studied.

Overall, a promising application for the sustainable production of optically pure profens derivatives, such as ibuprofen or naproxen, is envisaged.

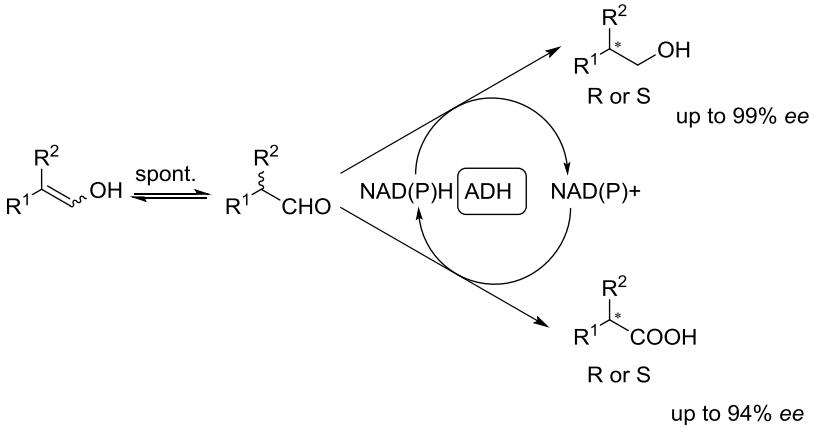

Figure 1. Biocatalytic disproportionation of enolizable aldehydes using alcohol dehydrogenase

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O-07

STRUCTURE AND STEREOCHEMISTRY OF SELF-ASSEMBLING HETEROCHIRAL TRIPEPTIDES

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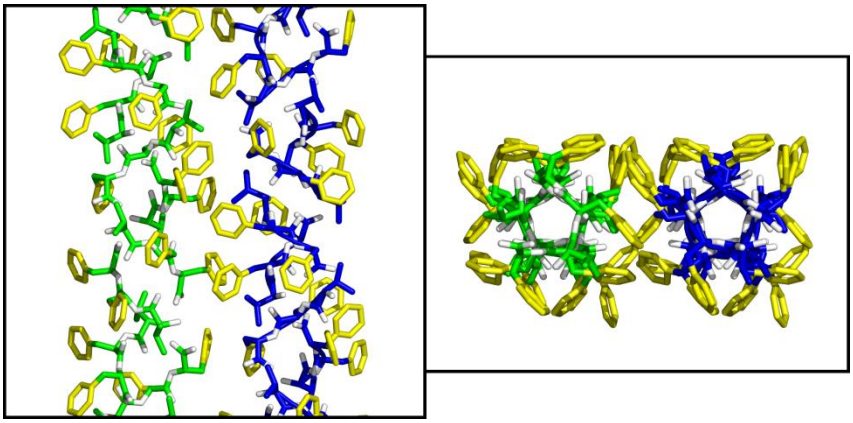
In recent years, considerable effort has been spent in researching innovative materials that can be easily and reversibly produced by self-assembly of simple building blocks. Small molecules able to generate hydrogels at a macroscopic level have been studied for their applications to biology and medicine. Among the different systems considered, short peptides appear to be particularly interesting for their compatibility with biological systems, together with a relatively easy and low-cost synthesis. The group of Marchesan introduced a new strategy for the design of hydrogel-forming peptides, consisting in the appropriate positioning of amino acids of different stereochemistry along a tripeptide sequence [1-3]. In particular, they characterized and demonstrated the rheological properties of Val-Phe-Phe stereoisomers [4]. While wildly investigated at a macroscopic level, the lack of information about the structural arrangement of the building blocks leading to the formation of the hydrogel has limited our ability to design new materials and to control their properties. Here we present a structural investigation of heterochiral tripeptides with different stereoisomery and we elucidate the differences induced by the chirality change on the supramolecular structures formed by the stereoisomers. The comparison between the supramolecular structures of hydrogel-forming and non-hydrogel-forming peptides helps our understanding of hydrogel molecular basis. A strong network of hydrogen bonds seems to play a key role in the organization of the peptides in the crystals, but the macroscopic behaviour is most likely associated with the different conformations of the backbone and the resulting orientation of the phenyl groups (Figure).



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O-08

HYDROPHOBIC SEGMENTS IN THE EXOPOLYSACCHARIDE EXTRACTED FROM *BURKHOLDERIA MULTIVORANS* BIOFILMS

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Burkholderia multivorans can infect cystic fibrosis (CF) patients, sometimes with lethal outcome. Most of the clinical strains produce exopolysaccharides (EPOLs), which are important components of the biofilm matrix. Biofilms of *B. multivorans* reference strain C1576, produced on two media (Müller-Hinton and Yeast extract-Mannitol), were investigated for their EPOLs content and structure. When cultured on Müller-Hinton agar in biofilm forming mode, a novel EPOL (named EPOL-C1576) was extracted from *B. multivorans* biofilm matrix and structural studies revealed the following repeating unit [1]:

$$[3\text{-}\alpha\text{-D-Man}p\text{-}(1\rightarrow2)\text{-}\alpha\text{-D-Man}p\text{-}(1\rightarrow2)\text{-}\alpha\text{-D-Rha}p\text{-}(1\rightarrow3)\text{-}\alpha\text{-D-Rha}p\text{-}(1\rightarrow]_n$$
$$\begin{matrix}3\\ \text{OMe}\ (50\%)\end{matrix}$$

The presence of 6-deoxy sugars suggests hydrophobic domains along the macromolecular chain. Such hydrophobic character is enhanced by substitution of some alcoholic functions with *O*-methyl groups. The co-presence of hydrophilic and hydrophobic chain segments might favour interactions of the EPOLs with other macromolecules, probably essential for the formation and maintenance of the biofilm matrix architecture.

With the aim of searching for hydrophobic domains, the EPOL-C1576 was investigated by fluorescence spectroscopy in the presence of hydrophobic probes (ANS and TNS), already tested for the interaction with cyclodextrin cavities [2]. The experiments showed an increase of probe's fluorescence intensity in the presence of the EPOL-C1576, but not with dextran, thus demonstrating the actual interaction between probes aromatic moieties and the EPOL-C1576. NMR spectra obtained on the mixtures EPOL/ANS and EPOL/TNS showed a marked enlargement of aromatic resonance peaks related to the decrease of dynamics on the probe molecules, thus further confirming the molecular interactions.

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O-09

THE COLLINS'S RULE AND THE HOFMEISTER EFFECT AS REVEALED BY A SIMPLE MOLECULAR DYNAMICS MODEL

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The presence of Hofmeister active ions in the solution of proteins influences their stability. In addition to the direct interaction, this influence manifests through the local alterations of the interfacial water structure induced by the anions and cations present at this region. In our earlier work it was pointed out that the influence of Hofmeister active sodium salts on the stability of the Trp-cage miniprotein can be modelled qualitatively using non-polarizable force-fields [1,2]. Using the fluctuations of the solvent accessible surface area, the ion-induced alterations of the surface tension were also calculated [1].

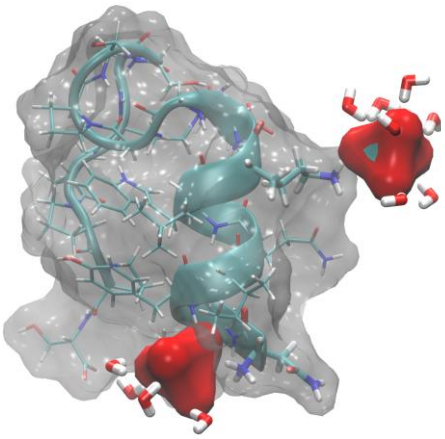

Fig. 1 Partially desolvated ClO_4^- ions at the surface of trp-cage miniprotein.

In the present molecular dynamics (MD) study we focus on the pair forming properties of the chaotropic ClO_4^- and kosmotropic F^- ions with the charged side chains of Trp-cage miniprotein. The simulations were performed on our test system in pure water, and in water with the selected Hofmeister salts, each of 1 M final concentration. The Amber ff99SB-ILDN force field and the TIP3P water model were used in our GROMACS MD simulations. For the Na^+, F^- ions the parametrization of Joung *et al.* [3], for the ClO_4^- ion parameters of Baaden *et al.* [4] were applied. We point out using the distribution of minimal anion-peptide distances that the kosmotropic F^- ion rarely form pairs with the positively charged chaotropic groups of the miniprotein, while the chaotropic ClO_4^- ion prefers pairing with them. This accords with the recently published empirical rules of Collins et al.[5] (law of matching water affinities). Finally, we also investigated how the solvation structure of the ions and the miniprotein changes during this interaction. It is revealed that in the present non-polarizable model, the strongly bound hydration shells of F^- ions highly overlap with the first water shell of the protein, increasing its immobility further. The chaothopic ClO_4^- ions lose a large part of their hydration shell during their interaction with the protein (see Fig. 1). This can be observed not only at the charged groups but also at some concavities of the miniprotein surface containing atoms with positive partial charge. The extent of these effects is compared for constrained and unconstrained protein structures, as well.

Acknowledgement: This research was supported by the Hungarian Scientific Research Fund (OTKA K 101821 and OTKA K 101825).

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O-10

LIGAND AND STRUCTURE-BASED PROBABILITY-QUIDED PHARMACOPHORE MAPPING IN MULTIDIMENSIONAL QSAR STUDIES

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The rational production of the desired compound pharmacological profile is enormously challenging issue that still lacks a general approach. The computer–assisted drug design (CADD) is regarded as the art of specifying molecules of potential therapeutic values working as preliminary stage namely 'pre-synthesis' or 'intuitive roadmap' on the path towards *the production of properties*. The elementary idea underlying the CADD for the robust identification of hit→lead→drug candidate is the comprehensive projection of the compound topology and/or topography into the chemical property space. A variety of the CADD methodologies, in particular multidimensional quantitative structure–activity ligand-based (RI) and structure-based (RD) relationships (mD–QSAR) procedures employ implicitly or explicitly the similarity principle where *compounds with similar structure are expected to have similar biological activity.*

A number of modern drugs are not available to the patients due to their poor aqueous solubility and permeability. Generally, modification/optimization of poor permeability through membranes can be solved by selection of appropriate excipients to function as transporters (surfactants or pharmaceutical complexing agents, permeability enhancers) being components of a dosage form. These excipients that increase absorption of drugs to blood circulation are known as intestinal absorption promoters in oral drug formulations and transdermal penetration enhancers in transdermal therapeutic systems. Cholic acid is one of the most important human bile acids. Bile acid derivatives/analogues are an important class of compounds with a range of pharmacological activities. Bile acids could be easily modified by derivatisation of the functional groups on the steroid nucleus and were studied also as transdermal penetration enhancers.

It is of interest to compare the impact of the coding molecular systems on the efficiency of structure–activity performance using 3D (CoMFA and CoMSA) and 4D (standard and neural formalism) methods on the ensemble of drug absorption promoters. Additionally, we concentrated on systematic model space inspection with splitting data collection into training/test subsets to monitor statistical estimators performance in the effort for mapping of the probabilistic pharmacophore geometry using stochastic model validation (SMV) approach. The automated variable reduction with IVE–PLS procedure represents a sieve for detecting only those descriptors, which have prescribed the greatest individual weighting to the observed cholic acids analogue activity. A 'pseudo–consensus' 4D–QSAR methodology was used to extract an 'avarage' 3D–pharmacophore by exploration of a various data subpopulations which embodies the quantity for quality argument to indicate the relevant contributing factors of the cholic acid absorption activity.

Additionally, a comparative structure-affinity study of anthraquinone dyes adsorption on cellulose fibre was performed using receptor-dependent (RD) 4D-QSAR methods based on grid and neural (SOM) methodology coupled with IVE-PLS procedure. The RD 4D-QSAR methodology together with IVE-PLS procedure provides a robust and predictive modeling technique, which facilitates detailed specification of the molecular motifs significantly contributing to the fiber-dye affinity.

O-11

SYNTHESIS OF A NOVEL FLAVIN COFACTOR ANALOGUE. N6-(BUTYL-2-EN-4-AMINE)-FAD FOR ENZYME IMMOBILIZATION

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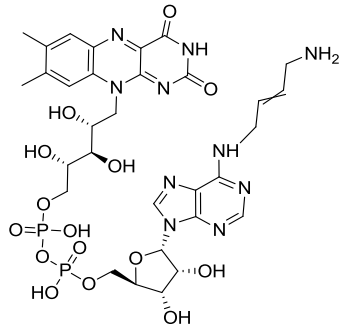
Flavin-containing enzymes can be used in various biotechnological applications, including biosensors, biofuels and bio(electro)reactors. Effective enzyme immobilization is often essential for such advanced applications. Most flavoenzymes contain a dissociable FAD cofactor. Intriguingly, the adenine part of the flavin cofactor is often close to the protein surface [1]. We have recently developed carrier material that contains covalently coupled FAD in which the flavin cofactor is attached to the adenine moiety via an aliphatic spacer. Using this FAD-decorated carrier, we could reconstitute apo flavoenzymes. By this approach we obtained tightly immobilized, stable and active flavoenzymes that can be used for biocatalysis [2].



Methods for the preparation of FAD derivatized with an aliphatic spacer attached to the adenine part have been described in literature but involve long and laborious procedures, with very poor efficiency [1]. At the moment, synthesis by qualified suppliers is extremely costly. This work presents a new, synthetic pathway for obtaining a novel FAD derivative (see figure). The N6-(butyl-2-en-4-amine)-FAD was obtained at 75 % purity with yield of 40 % starting from FAD.

Structural formula of the synthesized novel flavin cofactor analogue, N6-(butyl-2-en-4-amine)-FAD

The final structure of the novel FAD analogue was confirmed and characterized using spectroscopic methods (NMR, UV-Vis, MS) and cyclic voltamperometry. The FAD analogue contains an aliphatic linker with a terminal primary amine. This makes it a suitable FAD analogue for cofactor-mediated flavoenzyme immobilization.

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O-12

NEW SYNTHETIC APPROACHES TO PYRANOID β-SUGARAMINOACIDS

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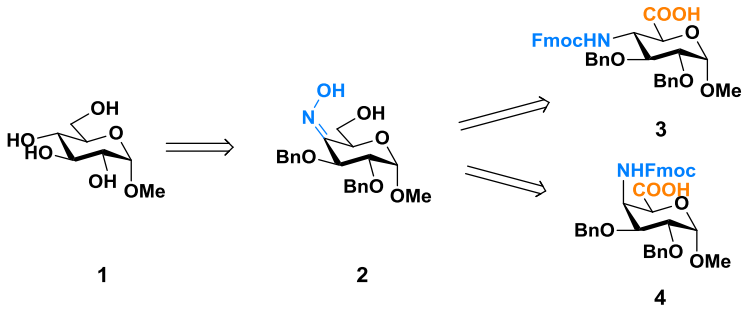
β-Sugar amino acids (β-SAA) both of furanoid and pyranoid ring are interesting and useful building blocks in foldamer syntheses [1]. Although D-glucosamino-1-carboxylic acid was used to form tetra- and hexapeptide foldamers [2] any analogous application of related 4-amino-4-deoxy-pyranuronic acids is not known so far. 4-Amino-4-deoxy-α-D-glucopyranuronic acid (H-GlcAPU(Me)-OH) [3] and its C-4 epimer 4-amino-4-deoxy-α-D-galactopyranuronic acid (H-GalAPU(Me)-OH) [4] are appropriate components of homo- or heterooligopeptides. Their derivatives were earlier described, however, the synthetic procedure is long, expensive and not reasonable. Therefore, we developed a new, shorter pathway for the synthesis of protected derivatives (**3**, **4**) which produces both epimer from a common oxime (**2**) intermediate (Scheme 1). Further advantage of this method is found in the simpler working up and in the reproducibility in larger scale.



Scheme 1. The new pathway

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O-13

SYNTHESIS METHODS OF PEPTIDE-6-AMINO-D-LUCIFERIN CONJUGATES FOR DETECTION OF PROTEASE ACTIVITY

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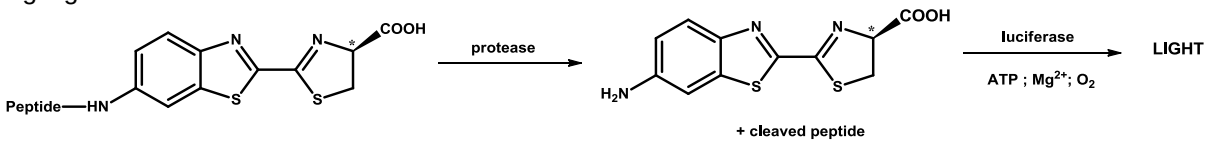
Amino-luciferin (aLuc) is a firefly luciferin with its 6-position hydroxyl group substituted with an amino group. This modification allows amino-luciferin to form amide bonds with a peptide, while retaining the transport and bioluminescent properties of luciferin, resulting in a good substrate for different important proteases, which can be used for the determination of the enzymatic activity in different therapeutically highlighted cases.



The synthesis of peptide-aLuc conjugate precursors has been published and some of them – alongside peptide-aLuc itself - are commercially available. [2] However, due to the difficulties with their synthesis and the resulted side products, the application of these conjugates is very limited. Our aim was to develop a simple, economical way for the synthesis of peptide-aLuc conjugates.

We developed three distinct methods: one with solid phase Fmoc strategy, one with fragment condensation strategy and one with solid phase Boc strategy.

With the solid phase Fmoc strategy there is a high risk for dehydrogenation and racemisation, due to the basic conditions.

In order to avoid these problems, we worked out a fragment condensation strategy. Although this way it is possible to synthetize the desired conjugates, the method has certain limitations: when attaching longer peptides, solubility problems will occur. This made us use solid phase peptide synthesis with Boc strategy.

First we had to prepare a Boc-protected amino-luciferin, a completely new substance which has not been published yet. Then this substance was attached to resin, and at the moment we are working on building the peptide chain, which will be followed by cleaving the resulting peptide-luciferin conjugate from the resin.

If we manage to carry out the synthesis with this Boc method, it will be a breakthrough in the synthesis of peptide-6-amino-D-luciferin conjugates, as it will make the synthesis of any substrate possible.

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O-14

DEVELOPMENT OF BIPHENYL-BASED BIS(THIOUREA) ORGANOCATALYSTS FOR ASYMMETRIC HENRY REACTION

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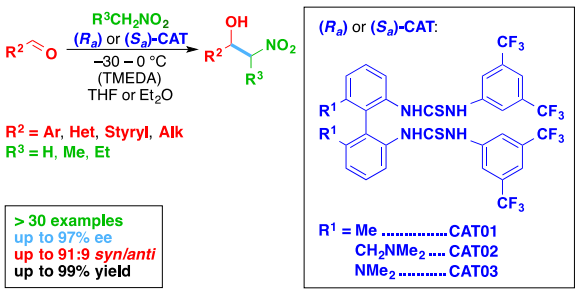
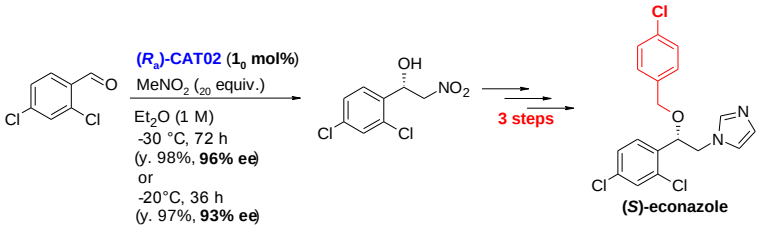
Henry reaction is a powerful C–C bond forming reaction providing a source of enantioenriched nitroaldols, which are ubiquitously used as building blocks for pharmaceuticals and agrochemicals. In the organocatalyzed asymmetric Henry reaction, the homogeneous chiral thiourea catalysts proved their excellent effectiveness and selectivity [1-4]. However, the currently known chiral thiourea organocatalysts for the enantioselective nitroaldol reaction of aromatic aldehydes are associated with limited possibilities of further functionalization of their structure, expensive resolution agents or carcinogenic synthetic precursors, difficult low-yield syntheses involving precious transition-metal complexes and chromatographic purification, cumbersome isolation of the final nitroaldol products from the reaction mixture and none or low (predominantly *anti*) diastereoselectivities.

In our current work, we focused on a simplification of the chiral backbone of the catalysts to the "bare minimum" and present the novel C_2-symmetric bis(thiourea) organocatalysts based on axially chiral biphenyls. Catalysts were prepared via high-yield and scalable syntheses avoiding transition-metal complexes, protecting groups and chromatography using inexpensive resolution agents. Modification of a chiral biphenyl backbone allowed us to incorporate the tertiary amine functionalities to the structure of the catalysts that eliminates the need of auxiliary base during the reaction. All synthesized catalysts were fully structurally elucidated and prepared in both enantiopure forms. Organocatalysts were tested in the asymmetric Henry reaction of mainly aromatic and heteroaromatic aldehydes with linear nitroalkanes. Under optimized reaction conditions the excellent chemical yields, very good to excellent enantioselectivities and remarkable *syn*-selectivities were observed, especially for the electron-deficient aromatic and heteroaromatic substrates. Although it was not our primary intent, we also performed some kinetic and spectroscopic experiments to complete the mechanistic picture of the reaction. Finally, the developed synthetic strategy was applied in the catalytic enantioselective synthesis of (*S*)-econazole.





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O-15

CONTINUOUS FLOW SOLID PHASE SYNTHESIS OF PEPTIDES AND FOLDAMERS WITH EXCEPTIONALLY LOW AMINO ACID CONSUMPTION

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The importance of synthesis of peptides and foldamers is warranted by the need for peptide-based medicines, the roles of peptides and foldamers in drug discovery, etc. Since its introduction by Merrifield, peptide synthesis was performed almost exclusively on solid supports. It has been applied for the synthesis of foldamers as well. [1] The solid-phase peptide synthesis (SPPS) technique has subsequently been progressively developed. However, still a general property of these methodologies are the high number of amino acid equivalents required for total coupling. [2]
Continuous-flow (CF) approaches have recently gained in significance among synthetic techniques. [3] We show here that the number of amino acid equivalents used for SPPS can be lowered drastically to around 1.5 equivalents through the application of a CF technique and by complete reaction parameter optimization.

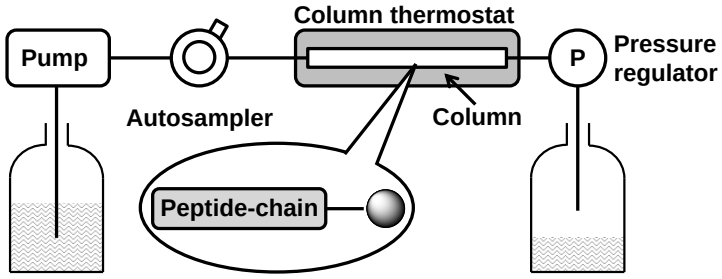

Figure 1. Schematic representation of the constructed CF reactor

Under the optimized conditions the couplings of all 20 proteinogenic amino acids with 1.5 amino acid equivalents proceeded with excellent conversions. To demonstrate the efficiency of the CF-SPPS methodology, known difficult sequences were synthetized in automated way. The purities of the resulting crude peptides were comparable with literature result, but the CF-SPPS methodology requires much less amino acid and solvent. As further evidence of the effectiveness, β-peptide foldamers with alicyclic side-chains, were synthetized in excellent yields. Nonetheless the direct synthesis of N-methylated peptides was carried out by the utilization of Fmoc-protected N-methylated amino acids too. Predominantly, the fast synthesis of protected sequences was carried out too. Importantly, exotic and expensive artificial amino acids were incorporated into sequences by an automated way through the use of exceptionally low numbers of amino acid equivalents at low costs. [4]

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O-16

REGIOSELECTIVE *para*-CARBOXYLATION OF PHENOLS BY A prFMN-DEPENDENT DECARBOXYLASE

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In recent years various concepts of enzyme catalyzed carboxylation processes, in particular for electron-rich (hetero)aromatic compounds have been developed as attractive 'green' alternatives to chemical methods [1]. A biocatalytic toolbox for the regioselective *ortho*- and β-carboxylation of phenols and hydroxystyrenes, respectively, was established by running decarboxylases in the reverse carboxylation direction at the expense of bicarbonate as CO_2 source [2].

In order to expand the bio-carboxylation concept towards the regio-complementary *para*-carboxylation of phenols, a search for appropriate biocatalysts was initiated. It was found that *para*-benzoic acid decarboxylases — in contrast to phenylphosphate carboxylases — were able to catalyze the desired reaction without ATP-depending substrate activation.

In order to gain more insight into the so far unknown catalytic mechanism [3], we elucidated the crystal structure of 3,4-dihydroxybenzoic acid decarboxylase from *Enterobacter cloacae* (3,4-DHBD). Intensive mutagenesis study, analytical and activity measurements, surprisingly showed that 3,4-DHBD depends on a recently discovered, novel, prenylated FMN (prFMN) as cofactor, which is provided by the prenyltransferase UbiX from *E. coli* [4]. Although the exact role of prFMN in catalysis is not yet clear, it may assist in appropriately orienting the substrate via π-π-stacking.

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O-17

ANTIFUNGAL DISULFIDE MINIPROTEINS: STRESS INDUCED UNFOLDING AND DYNAMIC STRUCTURES

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The antifungal disulfide protein PAF [1] was shown to be a three-state folder upon temperature changes in between the -8^{o}C ... +71^{o}C range [2]. A detailed analysis of cold & heat "denaturing" experiments yielded the thermodynamic parameters of unfolding, and suggested that a considerable amount of NMR invisible conformers may persist in aqueos buffer even at the highest stability temperature. ^{15}N NMR relaxation dynamics reports on a rock-hard protein on the ps-ns timescale and the absence of exchange. However, molecular dynamics calculations combined with chemical shift data support the presence of a few conformational clusters and Chemical Exchange Saturation Transfer (CEST-NMR) provided evidence on sparsely populated (0.15%) conformer in slow exchange with the major, visible conformer.

Interestingly, chemical "denaturation" was efficient with dimethyl-sulfoxide, however induced two-state unfolding of PAF and a PAF^{D19S} variant. New members (PAFB and NFAP) of this protein family have been prepared and their solution structure and dynamics exhibited similarities with PAF.

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O-18

DISCOVERY OF BENZOTHIAZOLE BASED Hsp90 INHIBITORS WITH ANTIVIRAL ACTIVITY

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Influenza viruses are one of the main cause of respiratory infections in the humans and influenza remains one of the biggest global concerns since it causes significant mortality, morbidity and economic loss [1]. In a larger screening project against different types of viruses, several benzothiazole based compounds, originally designed by us as gyrase B inhibitors, were found to possess promising activity against different types of influenza viruses. Since, on one side, Hsp90 chaperone plays an important function as a host protein in the viral replication and, on the other side, DNA gyrase and Hsp90 both are ATPases from the group of GHKL (**G**yrase, **H**sp90, Histidine **K**inase, Mut**L**) enzymes that have similar ATP-binding sites [2], our benzothiazole compounds active against influenza A and influenza B viruses, were assayed for binding to Hsp90 to test a hypothesis that their antiviral activity could be due to their inhibition of Hsp90 chaperone. In a microscale thermophoresis assay 11 of our compounds showed good binding to Hsp90 with K_d in the range of 0.26-51 μM. The benzothiazole based compounds described as a gyrase B and topoisomerase IV inhibitors with activity against influenza viruses A and B, which bind to Hsp90 and are not toxic against different cell cultures, are a promising starting point for design of compounds with dual action, combining antibacterial and antiviral activity in the same molecule.

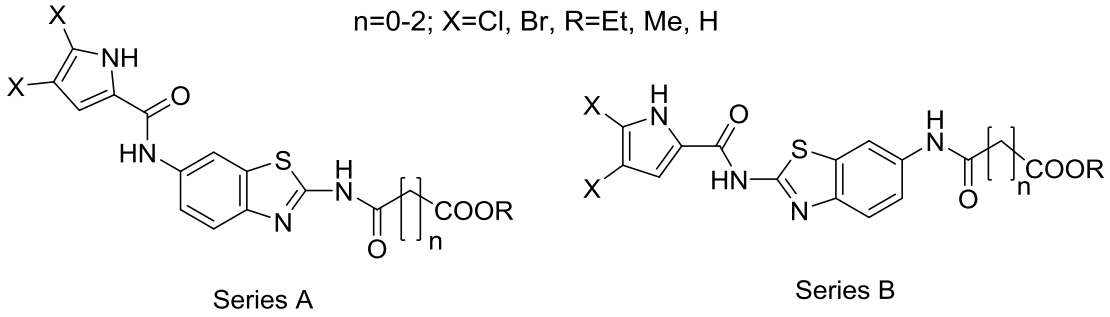

Figure 1. Chemical structures of benzothiazole compounds used in this study; Compounds from series B showed antiviral activities against virus influenza.

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O-19

EXPLORING THE CRANBERRY ACTIVITY AGAINST UROPHATOGENIC *E. COLI* BY METABOLOMICS: A PILOT STUDY

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American cranberry (*Vaccinium macrocarpon*) is frequently used for the prevention and treatment of non-complicated urinary tract infections (UTI)[1-3], due to its antiadhesive properties against uropathogenic bacteria such as *Escherichia Coli*. Nowadays, cranberry is employed for the production of food supplements and is sold worldwide. During the last years, many studies focused on cranberry activity against uropathogenic bacteria, showing that cranberry could effectively inhibit bacterial adhesion to the urinary mucosal epithelium. Un-adhered bacteria could be flushed away with urine, preventing the colonization of the urinary tract[3]. Moreover, many other studies attributed anti-adhesive activity of cranberry to oligomeric A-type procyanidins (OPAC-A), being responsible for the cranberry effects on UTI[2-3]. Many *in vitro* experiments on cranberry and on isolated A-type procyanidins showed that they effectively exhibit antiadhesive activity against bacteria, up to concentrations in the order of μg/mL[1]. Nevertheless, doubts about the *in vivo* activity of OPAC-A still persist, due to their poor bioavailability and rapid intestinal metabolism. Recently, some authors proposed that in *vivo* antiadhesive activity of cranberry could be due to OPAC-A metabolites, as phenols and benzoic, phenylacetic and phenylpropionic acids[4], or to the synergy of all cranberry components and/or its metabolites rather than just PACs[5].

In the study here presented, we evaluated the antiadhesive activity of human urines collected after the consumption of 360 mg of dry cranberry extract (standardized at 30% of PAC-A) against uropathogenic *Escherichia coli* and we related the observed activity to specific treatment biomarkers, detected in urine samples using an untargeted metabolomic approach and multivariate analysis methods. 6 healthy adult volunteers (2 males and 4 females) took orally the cranberry extract and they collected urinary output at 2, 4, 6, 8 and 24 hours after cranberry consumption. Urines were also collected 24 hours prior to cranberry consumption (control) and immediately after extract intake (T_0). Urine samples were analysed using an UPLC-QTOF-based metabolomic approach and specific HPLC-MS/MS methods were employed for the determination of urinary concentration of intact PAC-A and related intestinal metabolites. The results showed that PAC-A bioavailability was very low and only small amounts of intact dimeric PAC-A were excreted in the urines. Microbiological assays showed a significant antiadhesive activity of urines collected at 6-8 hours after cranberry consumption, and the activity was related to the presence of PAC-A intestinal metabolites, such as valeric acid and valerolactones derivatives. The data here presented allow to hypothesize novel mechanisms of action of cranberry against uropathogenic bacteria, highlighting also the possible role of PACs metabolites.

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O-20

ANTI-INFLAMMATORY POTENTIAL OF PRENYLATED FLAVONOIDS FROM *PAULOWNIA TOMENTOSA*

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Chromatographic separation of an ethanolic extract from *Paulownia tomentosa* fruits lead to the isolation of twenty-three C6-prenylated flavanones. The anti-inflammatory potential of these compounds was evaluated by several different methods. Flavonoid substances were assayed for their ability to inhibit cyclooxigenase COX-1 and COX-2, and lipoxigenase 5-LOX. Some of the substances tested showed promising ability to inhibit COX-2 comparable with ibuprofen used as a positive control. Promising activity against 5-LOX was also noticed. The ability of tested compounds to interact with above mentioned enzymes was supported by docking studies revealing the possible incorporation of substances into the active sites of these enzymes. The ability of flavonoids to decrease the production of the pro-inflammatory cytokine TNF-α in THP-1 cells after bacterial lipopolysaccharide (LPS) stimulation was evaluated in a primary *in vitro* screening test. Structure-activity relationships of these derivatives were also studied and the correlation of TNF-α inhibitory activity with their lipophilicity was investigated. Five compounds were tested for their ability to inhibit activation of NF-κB, which controls the expression of TNF-α, through the blocking of IκB degradation. Furthermore, one of the active substances diplacone was analyzed *in vitro* to obtain the proteomic overview of its effect on inflammation in LPS treated THP-1 macrophages, which proved its previously observed anti-inflammatory activity and revealed the mechanism of its effect more.

O-21

ANTI-AMYLASE AND ANTIFUNGAL EFFECT OF COMMON HERBS AND SPICES

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Diabetes is one of the most common metabolic diseases in the world and the prevalence is steadily increasing [1]. Herbs and spices have been expansively used in folk medicine for decades according to ancient empirical knowledge. The most frequent use of medicinal plants is water infusion. In this *in vitro* study, we attempt to scientifically prove the efficiency of the water extract of 60 common herbs and spices against α-amylase and *Candida albicans*.

A familiar way to decrease blood sugar level is the inhibition of carbohydrate digesting enzymes. Our research group developed a new ITC-based method to determine enzyme activity using an human salivary amylase (HSA)-starch model system [2]. Applying this method, the inhibition effect of extracts on alpha-amylase was ascertained in a wide concentration range (0.1 - 20 $mgmL^{-1}$). A number of publications are available about plant-derived α-glycosidase and α-amylase inhibitors, using different calorimetric assays. Using our new single injection method, the disadvantages of colorimetric techniques could be eliminated, hence this measurement based on the sensitive detection of heat changes. Among the investigated spice extracts cinnamon and allspice showed the lowest IC_{50} values, 0.6 and 0.8 $mgmL^{-1}$, respectively. Some herbs also have verified anti-amylase effect. Notable reduction of HSA activity was observed in presence of the leaf extracts of raspberry, blackberry and strawberry, where IC_{50} values were 1.1, 1.2 and 1.2 $mgmL^{-1}$, respectively.

A rarely mentioned result of diabetes is oral *Candida* infection due to long standing hyperglycaemia caused impaired salivary gland function [3]. Antifungal property of the extracts were tested against ATCC10231 *C. albicans* reference strain in a wide concentration range (0.5 – 10 $mgmL^{-1}$) according to the CLSI standard M27-A3 protocol [4]. Seven extracts showed notable antifungal activity (MIC_{50}<10 μgmL^{-1}), namely clove, allspice, leave of strawberry, raspberry, blueberry, blackberry and willowherb. These extracts were selected for further analysis, where their activities were determined by micro- and macrodilution against *C. albicans* clinical isolates. Based on both micro- and macrodilution experiments, clove resulted in the most effective antifungal activity. Therefore, time-kill experiments were carried out against the two *C. albicans* clinical isolates and reference strain. According to time-kill results, the clove extract had fungistatic effect at ≥5 $mgmL^{-1}$. *C. albicans* may produce biofilm both on the biotic and abiotic surfaces providing a reduced susceptibility against antifungal agents. Antibiofilm activity of all seven extracts was remarkable against biofilms produced by *C. albicans* clinical isolates and reference strain. Compounds responsible for any biological activity have been indentified using mass spectrometry.

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O-22

INVASION OF *PECTINATELLA MAGNIFICA* IN FRESH WATER RESOURCES OF THE CZECH REPUBLIC

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Pectinatella magnifica (Leidy, 1851) is an invasive fresh water animal that lives in colonies. A colony (a gelatinous blob) can be up to several feet in diameter large and under favourable conditions it exhibits an extreme growth rate.

A native area of the animal is east part of the Mississippi River, from Ontario to Florida, where it was observed already in 19th century. Since then *Pectinatella magnifica* (PM) has been spreading to Korea, India, Japan, Turkey, France and Germany. Recently other European countries around rivers of Elbe, Oder, Danube, Rhine and Vltava have confirmed invasion of PM, including freshwater reservoirs in South Bohemia (Czech Republic).

While freshwater bryozoans (being filter feeders) often improve water quality, large PM colonies can clog water intake and irrigation pipes creating economic and engineering challenges. Our project (Czech Science Foundation, GAČR P503/12/0337) is focused onto biology and chemistry of PM. We monitor the organism occurrence in selected South Bohemia ponds and sandpits during the last years, collecting information about physical properties of surrounding water, and sampling the colonies for various analyses (classification, maps of secondary metabolites, toxicity tests). The final goal of our study is to assess toxicity risks related to fresh water resources invaded by PM, and to understand the process of invasion, which can enable to control it.

O-23

EUROPEAN LEAD FACTORY – COLLECTIVE INTELLIGENCE BOOSTING DRUG DISCOVERY

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The IMI - European Lead Factory is the first pharmaceutical and life sciences partnership of its kind, combining open innovation, crowdsourcing and several established pharmaceutical companies. Two years after the start, the first scientific results can be evaluated and some case studies of screening and triaging as well as learning points can be shared.

Targets from public partners are screened at the top-modern, industry-standard European Screening Centre (ESC) against the Joint European Compound Library (JECL). Seven large pharmaceutical companies have joined forces and contributed proprietary compounds to the core. A recent study reports the character of these compounds and the complementarities of the 7 library contributions. Since January 2015, the screening set is further complemented with novel compounds synthesised by ELF.

ELF has been designed to create unrivalled opportunities for the discovery of new drug lead molecules. Through the European Lead Factory, academics and SMEs have access to an 'industry-like' discovery platform at no upfront cost, as all resources are covered by funding by the IMI. Scientists with innovative drug targets or ideas of novel chemical library designs are welcome to participate in the EU Lead Factory.

O-24

PREDICTABLE ENANTIOSELECTIVE COUPLING REAGENTS FOR SYNTHESIS OF PEPTIDES FROM RACEMIC SUBSTRATES

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The predictive coupling reagents were obtained from the classic peptide-bond-forming agent by attachment of the chiral component in such a way, that it departs after activation of carboxylic group [1]. Until recently the synthetic value of this concept has been confirmed in the case of reagents obtained by treatment of achiral 1,3,5-triazine derivatives with optically active tertiary amines. The chiral *N*-triazinylammonium salts formed as reactive intermediates, after selection of the enantiomer at the activation stage and departure of the chiral component, forms achiral “superactive” [2] triazine esters, exactly the same as participating in coupling mediated by classic, achiral triazine reagents. Coupling experiments confirm that synthetic results like configuration, optical purity of the product, reaction conditions and the efficiency of coupling are exactly predictable on the basis of a single experiment carried on with a model carboxylic substrate. Syntheses involving triazine reagents and alkaloids (brucine, strychnine, quinine) as chiral components yielded peptides with up to 99% enantiomeric purity from racemic *N*-protected amino acids, with expected configuration, under coupling conditions typical for native achiral triazine coupling reagents [3].

Herein we presents an access to the non-toxic chiral components necessary for synthesis of predictive enantioselective coupling reagents available in both enantiomeric forms. These are obtained by transformation of proline, readily available in D and L form, into both enantiomers of chiral tertiary amine components. The most interesting results were obtained using bicyclic derivatives prepared from diphenylprolinol. Reagent derived form (*S*)-(-)-diphenylprolinol selectively activated and incorporated into peptides D enantiomers with 80-98% ee when racemic *N*-protected aminoacid derivative was used. Reagent prepared from (*R*)-(+)–diphenylprolinol selectively activated L enantiomer amino acid of racemic substrate with 80-99% ee.

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O-25

DFT-ANTI-CANCER EFFECT OF ANIONIC IBUPROFEN DRUG IN THE HUMAN BODY

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After administration of Ibuprofen (IBF) drug in the human being, it passes through the full stomach after meal and the pH lies between 4-5 in. Therefore the ionization energy, Ip, of Ibuprofen drug molecule by DFT method, 6.6837 eV, decreases drastically on arriving to the small intestine at which the pH value lies between 8-9 and the value of the ionization potential is equal to 0.9015 eV. Therefore the IBF anions exist side by side with its molecular forms to be a wise electron donor in the small intestine. In the same way, the electron affinity of Ibuprofen drug in the stomach is equal to 0.8879 eV which decreases in the small intestine to be -1.4392 eV. This means that Ibuprofen drug hasn't the ability to receive an electron from the nucleic acid bases in contact with the cell nucleus even in the anionic or molecular form.. From comparison point of view with respect to the nucleic acid bases it has been found the following values of the electronic total energy, TE, ionization energy, Ip and electron affinity, Ea, in the following table.

DFT parameters of nucleic acid bases (N.A.B.) and ibuprofen drug.

Compound	TE au	Ip eV	Ea eV
Adenine	-467.17488	6.4061	+1.2672
Guanine	-542.37704	6.1879	+1.2828
Cytosine	-394.82291	6.5819	+1.4768
Uracil	-414.70313	7.3316	+1.8626
Ibuprofen in the Stomach	-656.54088	6.6837	+0.8879
Ibuprofen in the small intestine	-655.99444	0.9015	-1.4392

On assumption that the cancer is the electron deficiency in the cell nucleus and Since the pH value in the human blood equals to 7.5, therefore the IBF drug exists in the anionic and molecular forms in the blood compensating the electron deficiency in the cell nucleus to cure the colon cancer, prostate cancer, breast cancer and lung cancer.

O-26

COOPERATIVITY IN HALOGEN BONDS: A MOLECULAR ORBITAL THEORY BASED EXPLANATION

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We present here a detailed analysis of the nature of halogen bonds, how they resemble and also how they differ from the better understood hydrogen bonds.[1] An accurate physical model of the halogen bond follows from quantitative Kohn–Sham molecular orbital (MO) theory, energy decomposition analyses (EDA) and Voronoi deformation density (VDD) analyses of the charge distribution. It appears that the halogen bond arises not only from classical electrostatic attraction but also receives substantial stabilization from HOMO–LUMO interactions just as in the case of hydrogen bonds.

In this presentation, we focus in particular on the resonance-assisted hydrogen and halogen bonding mechanism (RAHB and RAXB) in special structures like guanine quadruplex analogues or halogen bonded linear chains. Similar to RAHB, the RAXB arise not only from classical electrostatic interaction but also receive substantial strengthening from donor–acceptor interactions within the σ-electron system. There is also a small stabilization by π-electron delocalization. Our analyses prove that the observed cooperativity in N-halo-guanine quartets and natural guanine quartets both originate from the charge separation that occurs with donor–acceptor orbital interactions in the σ-electron system.[3]

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O-27

SYNTHESIS AND FORMULATION OF THERMOSENSITIVE DRUG CARRIER FOR CONTROLLED DELIVERY OF NAPROXEN

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Nanospheres and microspheres are developed very intensively, and there is a tremendous progress in technology of this polymeric structures. Controlled drug delivery systems attract attention for many years, due to the presumed reduction of dosing frequency, and the decreased level of side effects [1]. Poly-N-isopropyl acrylamide (pNIPA) is a representative of substances sensitive to environmental temperature changes [2]. Volume phase transition temperature (VPTT) of pNIPA is ca. 32 ° C - 34 °C, and is in the range of known superficial human body temperature [3]. It is possible to affect the value of VPTT by copolymerization of hydrophobic monomers with NIPA or by controlling the molecular weight of the polymer [4].

The aim of the study was to investigate the effect of pNIPA co-polymers on the release of non-steroidal antiinflammatory drug: naproxen sodium (NS), from hydrogels based on hydroxypropyl methylocellulose, at standard human body temperature, and at elevated temperature.

pNIPA co-polymers P1-P4 were synthesized using the surfactant free precipitation polymerization (SFPP), without specific co-monomer (P1), with hydrophilic co-monomer (P2, P4), and with lipophilic co-monomer (P3), in specialized reactor. Cationic initiator was used in this study. Synthesized systems were purified by equilibrium dialysis, and freeze-dried in Steris Lyovac GT2 device. The hydrodynamic diameters of the obtained polymeric particles were measured by dynamic light scattering (DLS) using Zeta Sizer Nano Malvern Instruments, at a wavelength of 678 nm. Hydrogel formulations F1-F4 of 4% naproxen sodium were prepared ex tempore, with addition of the synthesized polymers, respectively: P1-P4, and 0.5% of hydroxypropylmethylcellulose (HPMC). The release kinetics of NS from hydrogel was assessed in a device dedicated for evaluation of transdermal therapeutic systems, according to pharmacopoeial standards.

The course of the polymerization reaction was confirmed in NMR evaluations. NS release at 22 °C for all formulations F1-F4 was similar, also in comparison to the control formulation. However, after increase of the temperature up to 42 °C, there was a clearly more rapid release of the NS. In formulations F1-F3 released amounts of NS were similar, and were higher compared to the control formulation with HPMC. The calculated kinetics fitted to the mathematical model of Higuchi. These model is used in many cases, and describes the process of dissolution, especially when the drug substance is released from the polymer matrix [5]. Modification of the release process via addition of NIPA derivative may be also VPTT dependent.

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O-28

THE APPLICATION OF NON-COVALENTLY IMMOBILIZED TRYPSIN IN A POLY(DIMETHYLSILOXANE) MICROFLUIDIC DEVICE FOR RAPID PROTEIN DIGESTION

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We described an immobilized enzymatic microfluidic device (MD) capable of rapid and efficient proteolysis. The MD was made of poly(dimethylsiloxane) (PDMS), a supreme adsorbent of proteins, which enables non-specific trypsin adsorption on the channel walls of the MD. Trypsin activity on the PDMS surface was investigated with subsequent peptide mapping of bovine serum albumin. The digestions of the BSA samples provided reproducible peptide maps (RSD% values for migration times were less than 1%). The immobilized trypsin MD was capable of rapid digestion of different proteins (hemoglobin, myoglobin, lysozyme and BSA) in a wide size range (15-70 kDa) with a contact time less than 1 min. The number of the separated peaks correlated well with the expected number of peptides formed in the complete tryptic digestion of the proteins. Trypsin retained its activity for 2 hours, within this period the MD can be used for digestion multiple times. The simplicity of the channel pattern, the immobilization procedure and the easily regeneratable or disposable feature make this MD to one of the simplest but efficient enzymatic microreactors.

O-29

ENCAPSULATION OF POTENTIAL PLATINUM DRUGS WITH MACROCYCLIC CARRIERS

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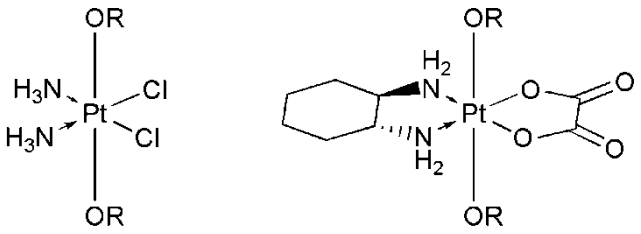
Cisplatin, carboplatin, and oxaliplatin are approved metallodrugs for anticancer treatment, however, their clinical applications are accompanied by undesirable effects (e.g., nausea, hair loss, inflammation) originating in side reactions of platinum drugs during their transport to cancer tissue. To overcome such drawbacks, new kinetically more inert Pt(IV) complexes, which can release a biologically active Pt(II) form after entering a cancer cell, have been designed and prepared[1]. For further improvement of the platinum-drug delivery, a coupling of Pt complexes with various carriers has been examined[2].

Herein we focus on the supramolecular inclusion complexes, composed of a potential platinum drug encapsulated in a biocompatible macrocyclic cavitand via the axial leaving ligands. These leaving ligands were installed in axial positions of cisplatin and oxaliplatin, resulting in a formation of the octahedral Pt(IV) complexes. The compounds were characterized primarily by ^{1}H, ^{13}C, and ^{195}Pt NMR spectroscopy as well as IR, Raman, and ESI-MS techniques. The encapsulation of potential Pt-based drugs with macrocyclic carriers will be presented and discussed.



OR - axial ligand

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O-30

SILVER, GOLD AND COPPER NANOCOMPOSITES BASED ON CHITOSAN

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Metal nanoparticles have attracted considerable attention in many fields such as catalysis, optoelectronics, photovoltaic technology, information storage, environmental technology, engineering, biosensors development, medicine, *etc.* [1,2]. Moreover, the need for low-cost, scalable, and dispersion-processable nanomaterials is a leading motivation for extensive research in the field of nanocrystal synthesis. The use of silver, gold and copper nanoparticles is nowadays a cause of intensive research due to excellent properties of these metals (*e.g.* good thermal and electrical conductivity, which might be used in electronics, or optical properties, which might be exploited in catalysis, diagnostics, sensing, and therapeutic applications). In particular, since multidrug-resistant microorganisms are a major problem for current medicine, nanoscale materials bring new possibilities in the development of effective antimicrobial agents. Extensive studies on silver, gold and copper nanoparticles as potent antibacterial agents with reduced cyto- and genotoxicity toward mammalian cells have been nowadays carried out.

Chitosan, a biocompatible carbohydrate polymer, has been used as a reducing and stabilizing agent in a green synthesis of metal NPs [3,4]. Herein, the synthesis of materials based on Ag, Au, Cu NPs and chitosan with the careful analysis in terms of physicochemical properties and biological activity will be presented. Detailed procedures of optimization of chitosan based metal nanocomposites will be showed. Materials with high antibacterial activity and simultaneously low cytotoxicity will be pointed out. Correlation between chitosan properties and Ag, Au and Cu NPs characteristics will be discussed.

In detail, the chemical structure, size, and morphology of metal NPs in the chitosan matrix have been studied by scanning electron microscopy (SEM), scanning transmission electron microscopy with energy-dispersive X-ray analysis (STEM-EDX) and powder X-ray diffraction (XRD). The surface oxidation state of the metallic nanoparticles and elemental analysis by depth profiling have also been evaluated by X-ray photoelectron spectroscopy (XPS). FTIR measurements were carried out to identify possible interactions between metal nanoparticles and chitosan molecules. Antibacterial activity was evaluated according to the European Norm ASTM E2180-07 for polymeric materials, against selected, resistant Gram-positive and negative bacterial strains (*Staphylococcus aureus* and *Pseudomonas aeruginosa*, respectively). In view of the potential biomedical application, the cytotoxicity of the selected nanocomposites was evaluated using two human cell lines: A549 (human lung adenocarcinoma epithelial cell line) and HaCaT (an immortal human keratinocyte).

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O-31

SOLUBILIZATION OF VALSARTAN IN THE PRESENCE OF TETRADECYLTRIMETHYLAMMONIUM BROMIDE

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An important role of micelles that has particular meaning in pharmacy is their ability to enhance the solubility of water insoluble molecules by a process known as solubilization [1]. Micellar solubilization can improve the system of poorly soluble drugs increasing their bioavailability, and they can be used as a model system for biomembrane [2]. In this work there was investigated the interaction of valsartan (VAL), an angiotensin II receptors antagonist, with cationic surfactant tetradecyltrimethylammonium bromide (TTAB). The effect of TTAB micelles on the solubilization of VAL was carried out using UV spectrophotometry at physiological conditions pH 7.4. The results showed that the solubilization of VAL in micellar media solutions was higher compared to its solubility in water. The highest solubilization of VAL was investigated at concentration TTAB 2.7 % w/v. Also the parameters of solubilization as χ, K_M and ΔG^0_S for VAL showed the solubility increase with growing concentration of TTAB in solutions.

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O-32

INTRODUCTION OF GOLEM V2, A NEW MODEL FOR BIORELEVANT DISSOLUTION STUDIES

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Generic drug products represent a dominant portion of the pharmaceutical market. This results in a considerable interest in the topics of generic formulation development and bioequivalence studies. In this respect, our team focuses on innovative *in vitro* dissolution studies employing a dynamic biorelevant dissolution instrument – Golem; developed for physiologically relevant simulation of drug dissolution process occurring in human stomach and small intestine [1,2]. Recently, we have introduced new improvements to the instrumental design of Golem, developed in the course of our continuous research. Here, we present the modifications incorporated in Golem v2 and the initial optimization assays. The *in vitro* performance of new compartment design and peristaltics simulation was assessed using an immediate release drug formulation and compared with USP 2 dissolution.

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O-33

TREHALOSE-FUNCTIONALIZED THERMORESPONSIVE GLYCOMICROGELS AS SCAFFOLDS FOR 3D CELL CULTURE

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Standard two-dimensional (2D) monolayer cell culture has evolved to a mainstay in the research of both molecular mechanisms of tumor progression and anticancer drugs discovery because of its ease, convenience, and high cell viability. However, 2D cell culture systems lack the mechanical and chemical features of three-dimensional (3D) microenvironment in native tumor tissue, which play key roles in cancer cell signaling and metastatic potential, leading to the loss of tissue-specific architecture, mechanical and biochemical cues, as well as cell–cell and cell–matrix communications. To bridge the gap between *in vitro* 2D cell culture and *in vivo* systems, 3D *in vitro* culture methods has been developed. Among many proposed biomaterials, hydrogel scaffolds are especially attractive, as they could provide biomimetic microenvironments because of their similarity to extracellular matrix. Moreover, since the enormous versatility of hydrogel materials it is possible to design tailored scaffolds with predefined mechanical properties, as well as with desired biofunctionality.

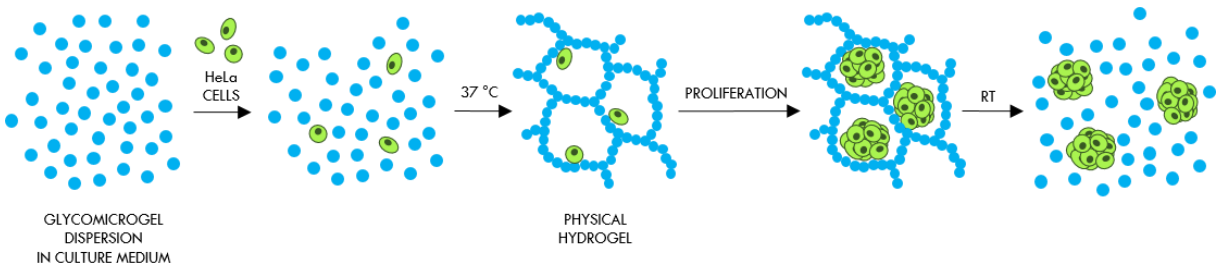

Fig. 1. Schematic of generation and separation of 3D cell structures using glycomicrogels

Herein, we present reversibly thermogelable scaffolds for 3D culture of HeLa cervical cancer cells based on trehalose-functionalized thermoresponsive glycomicrogels. At ambient temperature they form stable dispersion, but gel upon heating to physiological temperature forming macroscopic hydrogels, which liquefy again when cooled back. These thermo-driven gelling behavior allows for facile and non-invasive cell encapsulation within scaffold and harvesting of generated multicellular structures after culture without enzymatic treatment (Fig. 1.).

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O-34

ANTIULCER ACTIVITY OF A NEW DERIVATIVE OF GLYCYRRHIZIC ACID

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The search for new sources of highly active drugs based on local raw materials is an urgent task of modern science. It is known that licorice root is widely used in various sectors of the economy, the main component of it is glycyrrhizic acid. The presence of anti-inflammatory activity, low toxicity and lack serious side effects make new synthetic derivative of glycyrrhizic acid promising for medicine compounds.

The purpose of the study. To study the antiulcer activity glycerinate on an experimental model of neurogenic ulcers caused by 24-hour immobilization of animals and to identify the mechanism of antiulcer activity.

Materials and methods. Experimental model of neurogenic ulcers caused by 24-hour immobilization of animals were performed in rats. In the experimental groups daily for a week to stress, was orally given glycerinate at a dose of 100 mg/kg in the control group in the corresponding the volume of distilled water. The effect of the drug was compared with Cimetidine, which was administered in the dose of 400 mg/kg. After 24 hours all animals were macroscopically deceptional and watched the gastric mucosa and evaluated the effect of antiulcer drugs. Studied the effect of glycitrinate on the secretory function of the stomach and gastric acidity in rats. The drug was administered orally during the week, 20 min after the last injection, the pylorus was pervasively under ether anesthesia. Then after 2-3 hours the animals are sacrificed and measured the volume of gastric juice was titrated with 0.1 N NaOH solution until pink staining. In the blood serum of rats was determined by the activity of the enzyme superoxide dismutase (SOD) and catalase.

The results of the study. The experiments showed that in the control group of rats the average number of ulcers 5.66±0.54, and the average total area of the ulcers of 6.33±0.54 mm^2. Under the influence of the drug glycitrinat the average number of ulcers and average total area of the ulcers was reduced by 2.33±0.18 and 2.0±0.18 (58% and 68%). Under the influence of Cimetidine, the average number of ulcers and average total area was decreased by 4.66±0.36 and 3.33±0.54 (18% and 48%), respectively, compared with the control group. To understand the mechanism of antiulcer action studied the effect of glycitrinat on the secretory function of the stomach and gastric acidity in rats. The results of the experiments showed that in the control group of rats volume of gastric juice made up 2.05 ml, pH = 1.33, total acidity 0.5 ml, titratable unit was 100 TU. Under the influence of the drug volume of gastric juice was reduced to 39%, pH 3.25, total acidity -0.37, titratable unit -74 TU. The development of ulcerative process proceeded on the background of reducing the activity of antioxidant enzymes superoxid dismutas [of 1.07(1.0±1.14)] and catalas [1.41(0.94±1.88)]. Glycitrinat increased the activity of catalas compared with control 3.3-times [4.76(1.96±7.6)], superoxid dismutas [1.24(1.14±1.34)]. Thus, under the action of the drug the pH shifted to the alkaline side 1.4-times, reduced total acidity by 26%.

O-35

POTENTIAL THERAPEUTIC APLICATIONS OF PRENYLATED PHENOLS

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The flavonoids are plant pigments containing benzopyrane substituted with a phenyl ring at position 2 or 3. Their aglycones can be lipophilic; their lipophilicity can be further enhanced by methylating the hydroxyl groups, or by prenylation or geranylation at different positions on the skeleton. The prenyl or geranyl moiety may be modified in different ways and enhances the interaction with organism.

Different chromatographic methods were used for isolation of series of prenylated phenols. Experimental *in vitro* and *in vivo* studies have revealed many biological and pharmacological activities of flavonoids. We worked with prenylated compounds from *Morus alba* and *Paulownia tomentosa*.

Inflammation is a multiple and complex response by the body to infection or injury. Prenylated compounds show pleiotropic effects and can modulate a broad spectrum of inflammatory regulatory nodes. Their anti-phlogistic action combines many particular effects: it can be mediated by several pathways: *via* anti-oxidant and pro-oxidant effects, by interacting directly with pro-inflammatory proteins, and by interacting with signal pathways and inhibiting the expression of inflammation-related genes. *In vivo* tests have confirmed all of the effects of flavonoids previously observed in *in vitro* experiments. The antibacterial effect of prenylated substances was confirmed, some synergy with standard antibiotics was observed against MRSA.

Prenylated phenols are good candidates for further research to discovered new therapeutics for treatment of diseases connected with bacterial infection and inflammatory disorders.

O-36

PRENYLATED FLAVONOIDS AND EXPERIMENTALLY INDUCED BOWEL INFLAMMATION

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Many *in vitro* and *in vivo* studies have shown the ability of flavonoids to act as anti-inflammatory agents. A group of prenylated flavonoids combines the anti-inflammatory and anti-oxidant properties of flavonoids with enhanced lipophilicity of the structure caused by presence of prenyl chain. Such as modification can enhance their bioactivity and make prenylated flavonoids suitable for treatment of chronic inflammatory disorders such as inflammatory bowel disease (IBD). The aim of this work was to evaluate the best candidates from previous *in vitro* screening in animal models of inflammation.

Two models of chemically induced bowel inflammation were established. Geranylated flavanones diplacone and mimulone were evaluated in dextran sodium sulfate-induced colitis, prenylated flavone cudraflavone B in 2,4,6-trinitrobenzensulfonic acid-induced model of intestinal inflammation. The activity of disease was monitored, the colonic tissue was evaluated macroscopically, histologically, and by performing immunodetection and zymography to determine levels and activities of antioxidant enzymes, and proteins associated with inflammation and tissue destruction. Furthermore, the effect of diplacone and cudraflavone B on contractility of isolated mice ileal segments was evaluated.

All of compounds tested exerted therapeutic effectivity similar or greater than that of sulfasalazine. Diplacone and mimulone reduced the disease activity index, the expression of cyclooxygenase-2, and the activity of matrix metalloproteinase 2. Cudraflavone B reduced the macroscopic and microscopic damage scores, the activity of matrix metalloproteinases 2 and 9, and the level of transforming growth factor β1; however high dose of cudraflavone B was not effective as confirmed by macroscopic and histological evaluation. In *ex vivo* study cudraflavone B inhibited the contractility of isolated ileum in dose-dependent manner.

The multiple mechanisms of action of tested prenylated flavonoids suggest their potential for IBD treatment and for preventing their possible complication such as cramps, fibrosis or cancer. However, further studies are necessary to confirm their therapeutic value because of possible non-effectivity or even toxicity at higher doses.

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POSTER PRESENTATIONS

P-01

SYNTHESIS OF TRIFLUORMETHYLATED PIPERIDINE AND AZEPANE DERIVATIVES

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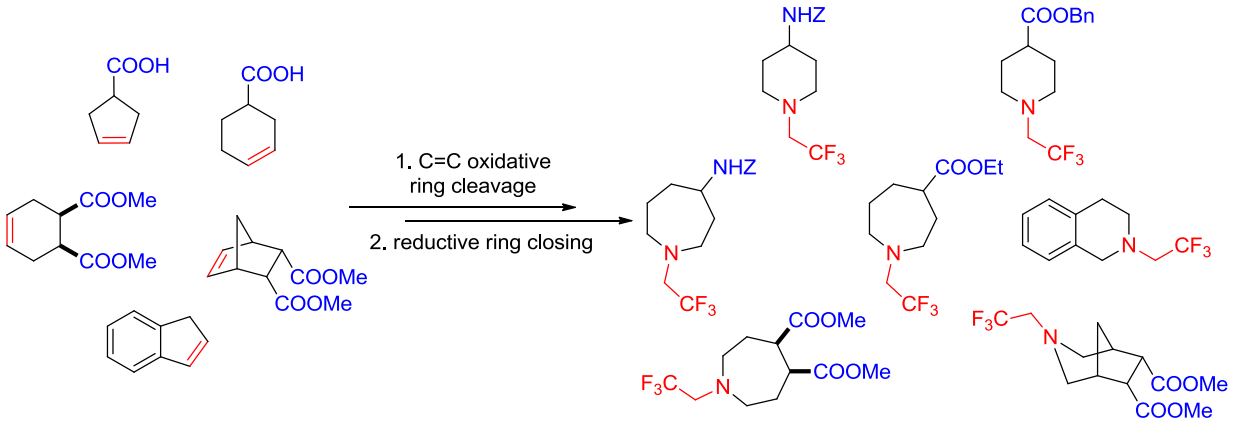
Fluorinated organic compounds have gained increasing attention in biochemistry and pharmacology over the past decade because of their interesting biological potential [1]. The replacement of one or more atoms by fluorine in biomolecules can generate changes in their physical, chemical and biological properties [2]. Fluorinated biomolecules, containing β-fluorinated or β-trifluorinated amine unit are of considerable importance in medicinal chemistry. Some biologically active molecules with trifluoroethylamine element are known for example as nootropic agents or cholesterol lowering drugs [1]. Our aim was to develop a novel, convenient and efficient procedure for the access of substituted, trifluoromethyl group containing six or seven membered *N*-heterocyclic derivatives. The synthesis of new trifluromethyl containing piperidin or azepane derivatives started from substituted cycloalkenes and the key steps of the synthetic route are the C=C double bond oxidative ring cleavage and the reductive ring closure by reductive amination of the diformyl intermediates using 2,2,2-trifluorethylamine hydrochloride.



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P-02

NEW NANOCATALYSTS IN SELECTIVE PREPARATION OF CYCLIC ACETALS

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A new, efficient method for the selective preparation of cyclic acetals is being investigated. It involves the usage of specially prepared nano-metalic catalysts in the condensation reaction of polydiols with various aldehydes or ketones. The Cyclic acetals are widely used in organic chemistry [1][2]. They are used in the perfume industry, as fragrances and flavors additives in the food industry and also in the household chemicals [2]. the acetals functional group occur in a structures of pharmaceuticals and natural substances. As a monomers for polymeric nanomaterials they can be used in tissue engineering and drug deliveries [3]. It can be also used as a fuel additives for biodiesel to improve its properties [2]. The glycerol proved to be the best substrate among the tested polydiols. The glycerin is a by-product a number of technological processes due the fact as a substrate with great potential it has a low cost and offers a numerously eventual combinations. The catalysts were obtained by depositing a nanometer size metals grains on the low-dispersion size silica, which was made by the sol-gel process. According to the concept of the green chemistry this method is not require the solvents and it is carried out under mild conditions (55 °C) in a short time (less than three hours). This is a one-step reaction, and ultimately does not generate waste.

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P-03

FLUORESCENT PROPERTIES AND BIOLOGICAL ACTIVITY OF HYDROXYNAPHTHALENE CARBOXANILIDE DERIVATIVES

Z. BÁBKOVÁ[1], A. KREJČÍ[1], A. POLÁŠKOVÁ[2], R. HELMA[2], M. ADÁMIK[2], J. KOS[3], T. GONĚC[3], J. JAMPÍLEK[4], M. BRÁZDOVÁ[1]

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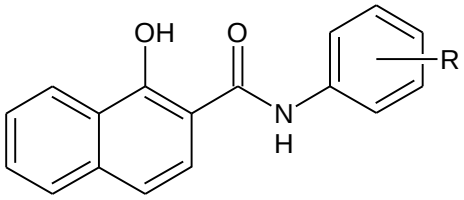
Hydroxynaphthalene carboxanilide derivatives are mostly investigated for their antifungal, antibacterial and antimycobacterial activity. Multidrug-resistant bacterial or mycobacterial strains are a worldwide problem. Primary *in vitro* screening of investigated compounds against different *Mycobacterium* strains was performed. Toxicity against the human monocytic leukemia THP-1 cell line was determined. The presence of an amide group is characteristic for various antimycobacterial drugs and number of herbicides acting as photosynthesis inhibitors [1]. Delocalized π-electron systems, may exhibit optical properties that may be utilized for potential applications e.g. fluorescent dyes [2].

Investigated derivatives, which have antimycobacterial activity were tested in this study from biophysical point of view. Basic absorption and fluorescence properties, including determination of the fluorescence quantum yield, Stokes shift and the molar absorption coefficient, were characterized for the studied derivatives especially for their possible use in cell biology. The cytotoxicity of these compounds was investigated in colorectal carcinoma cell line and association with *TP53* status was also determined. High values of fluorescence quantum yield of 1-hydroxy-*N*-phenylnaphthalene-2-carboxamide derivatives allowed their use in confocal microscopy for monitoring the penetration of compounds into the cells.



Scheme 1: Structure of the 1-hydroxy-*N*-phenylnaphthalene-2-carboxamide derivatives (where -R represents different substituent) for which the basic absorption and fluorescence properties were characterized.

This work was supported by IMA VFU Brno 2015-FaF-11, IGA VFU Brno 316/2016/FaF, IGA VFU Brno 37/2014/FaF, IGA VFU Brno 67/2014/FaF and 13-36108S (GACR).

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P-04

MOLECULAR LIPOPHILICITY PROFILE IN DRUG DISCOVERY

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Lipophilicity is generally regarded as a first-rate physicochemical parameter increasingly relevant in specification both the pharmacokinetic (ADMET) and pharmacodynamic aspects of drug-receptor/enzyme interactions which often correlates well with the bioactivity of chemicals. Its quantitative descriptor (logP), considerably used in the early stages of drug development, indicates the ratio of neutral solute concentrations in the organic (apolar) and aqueous (polar) phase of a two-component (n-octanol/water) mixture under equilibrium conditions. Unfortunately, the experimental procedures for the partition coefficient estimation are basically time- and/or material-consuming and require a high purity of the solute; therefore the alternative lipophilicity descriptors have been provided using mainly *in-silico* predictive models e.g., Hansch's π constant derived for chemical constituents as an additive property. On the other, it is possible that some methods for theoretical calculation of lipophilicity might be more or less suitable for specific series of compound analyzed, thus a variety of approaches should be employed and subsequently compared with the empirical data.

In theoretical calculations the 'one-dimensional' representation of lipophilicity which mimics the overall molecular property can be decomposed into fragments (atom or larger functional groups) represented by particular components whose values estimate the individual lipophilic contribution of each group (sometimes augmented with the structural correction factors) to yield the logP assessment according to the following formula:

$$\log P = \sum_i f_i$$

However, the routine application of various logP predictors requires a continuous evaluation of their credibility by comparison with empirical data taken as a reference. Partition coefficient can be measured experimentally using at least several procedures ranging from 'shake-flask' technique to popular thin-layer (TLC) or high-performance liquid (HPLC) chromatographic methods. The determination of the partition coefficient by direct measurement using the 'shake-flask' faces issues such as poor reproducibility; therefore the advantageous application of non-polar stationary phase and polar mobile phase in so called reverse phase TLC (RP-TLC) or *vice versa* in normal phase TLC is an attractive and reliable alternative to troublesome procedures.

Apart from the purely structural design and synthesis, the additional objectives of our investigation was the experimental determination of the lipophilic profiles of the amides offspring and subsequent critical assessment of the relationship between the retention parameters and the corresponding numerical values. The experimental logP values were related with the corresponding calculated values and physicochemical properties using MATLAB programming environment.

The chromatographic data were determined for the investigated set of the amides derivatives by RP-TLC method and related with theoretical partition coefficient calculated by means of *in-silico* procedures. Statistically, significant correlation was found between experimental R_{MO} values and the quantitative descriptor of lipophilicity (logP) specified by OSIRIS and Sybyl predictors. The impact of the calculated physicochemical and structural descriptors on the retention parameters was elucidated by variable elimination procedure IVE-PLS, indicating the involvement of various factors on hydrophobic forces.

P-05

CYTOTOXIC ACTIVITY AND THEORETICAL INVESTIGATION OF NEW MIXED AMMINE/AMINE PLATINUM COMPLEXES WITH 3'-AMINO-5-METYL-5-PHENYLHYDANTOIN

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Some mixed ammine/amine Pt(II) complexes have been synthesized and investigated for anticancer activity against various human solid tumor cell lines [1]. Mixed ammine/amine Pt(IV) complexes with equatorial chloro and axial carboxylato or hydroxo ligands also demonstrate cytotoxic activity against cisplatin resistant cells *in vitro*. Octahedral Pt(IV) complexes act as prodrugs of their Pt(II) counterparts and represent an important role of recent metal-based anticancer research.

Two new Pt(II) and Pt(IV) complexes with 3'-amino-5-metyl-5-phenylhydantoin as carrier ligand were synthesized. The complexes were studied by melting points, elemental analysis, IR, Raman and NMR spectral analysis. On the basis of the spectral characteristic the following molecular formulas were proposed – *cis*-[PtL(NH_3)Cl_2] and *cis,cis,trans*-[PtL(NH_3)Cl_2($OH)_2$]. The structures were confirmed by DFT calculations. Experimental and theoretical vibrational analysis of the metal-free ligand and its Pt(II) and Pt(IV) complexes have been studied and the results showed that a good coincidence was observed. Some basic parameters as dipole moments, bond lengths, angles and energy of the compounds were calculated. Different conformers of the new platinum complexes were studied and the most energetically stable conformers for both complexes were proposed.

All compounds were tested for cytotoxic activity *in vitro* on panel of human tumor cell lines. The results showed that the new platinum complexes exerted concentration dependent antiproliferative activity.

The investigation is supported by the Medical Science Council at the Medical University – Sofia within the Grant № 51/2016.

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P-06

SYNTHESIS OF NUCLEOSIDE-ESTRONE BIOCONJUGATES APPLYING COPPER CATALYZED ALKINE AZIDE CLICK REACTION

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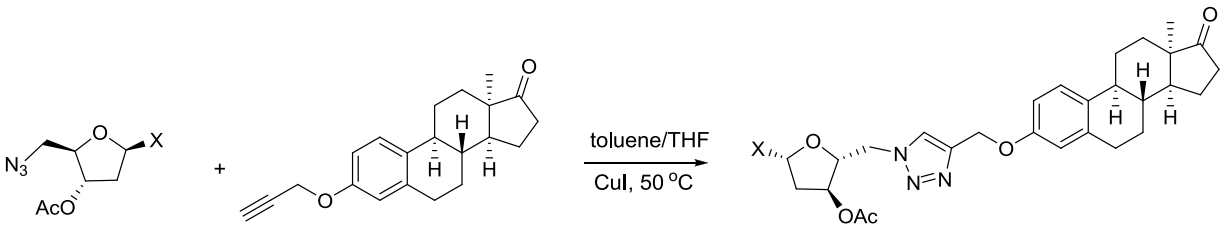
The major drawback of the currently applied anticancer therapies is the low selectivity causing side-effects on non-targeted cells. A selective enrichment of the therapeutics in the targeted cells can decrease both the effective dose and the side-effects. As the enhanced proliferation of cancer cells requires an increased amount of nucleotide building blocks, the uptake of nucleosides is significantly higher in cancer cells compared to the healthy ones [1-2].

This prompted us to consider the chemical synthesis of nucleoside conjugates of a 13α-estrone derivative having already anticancer properties [3]. The copper catalized alkyne azide click reaction [4] was chosen for the conjugation, which requires the preliminary introduction of an alkyne and an azide functions to the building blocks of the conjugate.

The chemical synthesis of the 5'-azido-nucleosides and the click coupling reactions with the alkyne modified 13α-estrone were investigated and optimized (Scheme 1.).



X = nucleobase: 6-*N*-benzoyladenine
4-*N*-benzoylcytosine
thymine

Scheme 1. Synthesis of nucleoside conjugates of 13α-estrone

The structures of the new conjugates were confirmed by ^{1}H, ^{13}C NMR and MS analyses.

The biological evaluation of the synthesized bioconjugates is in progress.

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P-07

MULTI-EXPERIMENTAL CHARACTERIZATION OF SELECTED MEDICAL PLANTS GROWING IN CZECH REPUBLIC

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Growing attention has recently been focused on the improvement of human health via the consumption of food or food supplements rich in antioxidants, dietary intake of which plays important role in protection of the human organism against oxidative damage. Connection between the antioxidant activity of naturally occurring compounds present in diet and prevention of certain diseases, e. g. coronary heart diseases or cancer is well documented [1, 2]. Medical plants are potent natural source of antioxidants; the most abundant are phenolic compounds, comprising flavonoids, phenolic acids, tannins, chalcones, coumarins or stilbens. The presence of non-flavonoid antioxidants such as ascorbic acid, α-tocopherol, glutathione, carotenoids and some metals (e.g. Cu, Fe, Mn, Zn and Se) has also been proved [3].

In the current study, the impact of post-production conditions on antioxidant status, content of selected polyphenols, colour and concentration of selected metals was evaluated in the group of 10 most popular medical plants conventionally produced in the Czech Republic. UV-VIS-NIR, EPR, HPLC and ICP-OES were employed for these purposes. The entire dataset of obtained experimental characteristics was processed also by multivariate statistical methods, e.g. by factor analysis (Fig.1), which shows strong correlations among individual parameters, particularly for polyphenolic compounds (rutin, caffeic acid, myricetin) TPC, TFC and antioxidant activity express as TEAC. From these results follows, that parameters as RS, colour characteristic L*, a*, TEAC and content of Na - as non-correlating – could be effectively used for differentiation of plants extracts according chosen technological, production and post-production criteria.

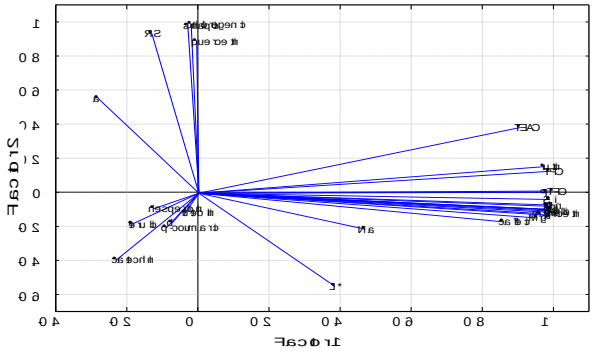

Fig. 1: Differentiation of medical plants extracts parameters using factor analysis with Varimax rotation

This work is a partial study of the research project "Improvement of nutritional and sensorial parameters of fruity and vegetable drinks via an inert gases application - ITMS 26220220175" implementation, supported by the Research & Development Operational Programme funded by the European Regional Development Fund.

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P-08

EXOPOLYSACCHARIDE PRODUCED BY A *KLEBSIELLA PNEUMONIAE* CLINICAL ISOLATE IN BIOFILMS AND FLOCS. PRIMARY STRUCTURE AND INTERACTION WITH ANTIMICROBIAL PEPTIDES

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The genus *Klebsiella* comprises opportunistic pathogens which cause bacteremia, pneumonia and urinary tract infections in humans. Although these microorganisms do form biofilms, little is known about the polysaccharides present in their matrix. *K. pneumoniae* strain Kp113 was isolated from a patient with urinary tract infection. Kp113 was grown as biofilm on cellulose membranes deposited on agar plates, in order to recover enough matrix for polysaccharide extraction and its structural determination. Established chemical derivatization methods followed by GC-MS, and NMR spectroscopy, lead to the definition of the repeating unit structure of the polysaccharide produced by Kp113 (Kp113 Epol) which is identical to that of *Klebsiella* capsular polysaccharide K24:

$$[2)\text{-}[\text{D-Manp}(\beta1\text{-}4)]\text{-D-GlcpA-}(\alpha1\text{-}3)\text{-D-Manp-}(\alpha1\text{-}2)\text{-D-Manp-}(\alpha1\text{-}3)\text{-D-Glcp-}(\beta1\text{-}]_n.$$

Kp113 was also grown in liquid medium, where it formed flocs. NMR analysis of the polysaccharide extracted from flocs revealed an identical chemistry, thus suggesting a structural role in the biofilm matrix for the Kp113 Epol. The protective effect of the polysaccharide towards bovine cathelicidin antimicrobial peptides BMAP-27 and Bac7(1-35), which have distinct modes of action, and towards colistin was assessed. Interaction of the polysaccharide with BMAP-27 was demonstrated by circular dichroism spectroscopy, thus explaining the protective function. The present investigation shows that the polysaccharide produced by Kp113 is not only part of the biofilm architecture but it also possesses specific biological functions.

P-09

INFLUENCE OF SELECTED ALAPTIDE ANALOGUES ON PENETRATION OF THEOPHYLLINE

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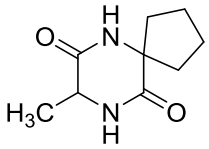
Skin has about 1.7 m^2, and it is the largest organ of the human body. There have been many attempts to use skin for administration of drugs. Drugs can be administered on the skin in the form of ointments, creams, gels as well as transdermal patches (patches are commonly used for reduction of pain, application of contraceptives, etc.). There are many possibilities to improve the transdermal penetration of active pharmaceutical substances: physical, chemical and technology approaches. One of the chemical approaches is to use accelerators of penetration/permeation – transdermal enhancers. Alaptide was chosen to modify the transdermal penetration of drugs in pharmaceutical formulations suitable for transdermal administration of drugs. Alaptide, 8-methyl-6,9-diaza-spiro[4.5]decane-7,10-dione (see Figure 1), is a cyclic dipeptide, and its structure is capable to interact with components of the skin. Alaptide was synthesized in 1980s in Prague by Kasafírek *et al.* It showed a significant therapeutic effect in various therapeutic areas, particularly in stimulation of cells growth and proliferation, and a very low acute toxicity in rats and mice [1,2]. Alaptide proved to have excellent enhancement effect, thus other alaptide analogues were prepared and tested [3,4].



8-methyl-6,9-diazaspiro[4.5]decane-7,10-dione

alaptide

The present research concerns the investigation of the modification effect of two alaptide analogues – alaptide analogue I and alaptide analogue II – on the permeation of the model drug theophylline (donor compound) through full-thickness pig ear skin from propylene glycol/water (PG/water, 1:1) and physiological buffer (pH 7.4) donor vehicles using static vertical Franz diffusion cells.

This study was supported by IGA VFU Brno 302/2015/FaF and by the Technology Agency of the Czech Republic TA04010065.

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P-10

ANTITRYPANOSOMAL ACTIVITY OF *TITHONIA DIVERSIFOLIA*

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The African Trypanosomiases, also commonly called African sleeping sickness in humans (HAT) and "Nagana" in domestic livestock, are fatal neglected diseases that occur in 36 sub-Saharan African countries. The disease progresses through two stages and is caused by two subspecies of the parasite *T. brucei*: *T. b. gambiense* (West Africa; *Tbg*) and *T. b. rhodesiense* (East Africa; Tbr). *T. brucei* is also pathogenic to wild and domestic animals causing "Nagana", a disease that has a significant impact on socioeconomic development in many parts of rural Africa. Current treatments are considered unsatisfactory due to treatment failures and high toxicity. Therefore, there is a great need of new and cost-effective drugs to treat the disease, especially at later stages when the parasites infect the brain. Drug discovery efforts are nowadays directed towards natural products and medicinal plants represent a validated source for discovery of new lead compounds and standardized herbal medicines against trypanosomiases [1].

Tithonia diversifolia (Hemsl.) A.Gray, well-known as Mexican sunflower, is a bushy perennial weed commonly found on the fields, wasteland and road sides of tropical areas in South America, Asia and Africa. The plant belongs to the Asteraceae family and used as traditional medicine for the treatment of various diseases, including malaria [2]. The phytochemical analyses of *T. diversifolia* indicate1d the presence of bioactive substances such as alkaloids, saponins, glycosides, flavonoid, tannins, terpenoid and phenols in the methanolic extract [3]. The leaves methanolic extract showed a quite remarkable inhibitory activity against *Trypanosoma brucei brucei* TC221. For this reason, a chromatographic separation of total methanolic extract has been performed, obtaining 17 fractions. The phytochemical composition of crude extract and purified fractions were investigated using HPLC-ESI-MS/MS and 1D and 2D NMR spectra. The isolated fractions have been selected as valid candidates for investigation as potential inhibitors of *T. brucei*. The results of this study will be discussed.

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P-11

NANOSTRUCTURED MATERIALS FOR CONTROLLED DRUG DELIVERY

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Synthetic or natural (bio)polymers are extensively explored for drug delivery and other medical applications. Polymeric materials with porous structure and high water contents are advantageous because of their tuneable mechanical and biochemical properties [1-3]. The amount and kinetic of the active agent release from the porous structure hydrogel can be adjust by the application of filler materials. Due to their lamellar structure, surface charge and biocompatible behaviours, clays and layer double hydroxides are widely used in biomedical applications [4,5]. The hydrophobization (functionalization) of initial lamellae with different surfactant molecules allows the immobilization of poorly water soluble molecules into the layers. Different drug molecules (*Kynurenic acid as* antiexcitotoxic and anticonvulsant agent and *Mytomycin* as chemotherapeutic agent) were encapsulated in layered structure inorganic drug carrier systems (positively charged layered double hydroxide /LDH/) and in biocompatible and biodegradable Ca- alginate beads. The synthetized composite were investigated by IR, XRD and thermoanalytical methods. The active agent molecules were successfully intercalated into the interlayers. According to the results the amount and kinetic of the released drug were highly adjustable by the synthesis conditions.

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P-12

DIHALODEAZAGUANINES: DEVELOPING SMART LIGANDS FOR NUCLEIC ACID QUADRUPLEXES

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Repetitive guanine-rich nucleic acid sequences can assemble into four-stranded structures called guanine (G) quadruplexes.[1] These structures play a crucial role in maintaining the genome stability and cell live cycle. The small molecule ligands affecting the topology and stability of G-quadruplexes become objects of intensive research due to their potential applications in medicine as anticancer agents.[2] Vast majority of ligands that bind selectively to telomeric G-quadruplex employ π-π stacking interactions with guanine bases as well as electrostatic interactions between positively charged ligand and negatively charged phosphate groups of nucleic acids. Therefore, the rational design of new G-quadruplex ligands typically builds-up on the positively charged aromatic compounds. Recently, it has been demonstrated that the guanine-based ligands with porphyrin core can be used as markers of G-quadruplex assemblies in the cell tissues.[3] Herein we explore the model systems of the 3-deazaguanine-based ligands[4] by methods of density-functional theory. We calculate the energy of formation for modified guanine tetrads as well as those for the modified tetrads stacked on the top of natural guanine tetrads. We decompose interaction energy to the contributions of hydrogen bonding, stacking, and ion coordination and the twist-rise potential energy scan is performed to find the individual local minima. The energy decomposition analysis shows the impact of various substituents (F, Cl, Br, I, Me, NMe_2) on individual energy terms. The studied systems are demonstrated to be a promising candidates for quadruplex ligands mainly due to the enhanced stacking interactions compared to natural guanine.[5]

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P-13

BIODEGRADATION OF VOCs MIXTURE IN THE COMPACT TRICKLE BED BIOREACTOR (CTBB)

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Volatile Organic Compounds (VOCs) and odors substances represent a significant part of hazards indoors as well as outdoors pollution. VOCs consist of chemicals, which are easily evaporated into the air. This class of compounds is composed of isoprenoids, alkanes, alkenes, aromatics, carbonyls, alcohols, esters, ethers, organic acids and others. VOCs in the Earth atmosphere originate from natural and anthropogenic sources and/or may be formed as (sub)products of the transformations of other VOCs. Some VOCs may be detrimental to human health in the long – term exposure and provoke serious illnesses, for example, sore throats, feelings of tiredness and dizziness, asthma, immune and reproductive system problems, mutagenic or carcinogenic effects. From an environmental point of view, VOCs lead to increased amount of ozone at troposphere thereby contribute to photochemical smog and the greenhouse effect as well [1-3].

Emission of VOC is facing increasingly stringent environmental regulations on account of VOCs contribution to present or future hazard to human health and undesirable environmental effects. In consequence, polluting industries have been made to implement an effective air pollution treatment processes. The VOC's biotreatment carried out in the Compact Trickle Bed Bioreactor (CTBB) based on Know How of Ekoinwentyka has become an attractive alternative for many physical and physicochemical methods of air purification. The main advantages include low pressure and low temperature of the biodegradation process, friendliness to human beings and surrounding environment, lack of secondary waste and low operating costs [4].

The aim of this work was biopurification of air stream from VOCs mixture using a compact trickle bed bioreactors (CTBB) operating with continuous bed fid with a mineral salt solution. The primary object of the investigation was searching for the optimal operational conditions in terms of air pollutant concentration and nutrients addition for a best purification efficiency. The experimental results of the biodegradation the VOCs mixture will be used to provide a theoretical model of the process.

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P-14

SONOGASHIRA REACTION CATALYZED BY A NOVEL Pd-NHC COMPLEX PROCEEDS THROUGH AN UNPRECENDENTED MECHANISM

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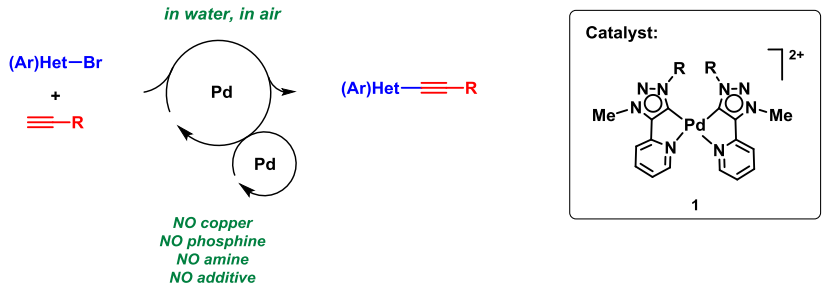
The Sonogashira reaction has witnessed a tremendous success in both academia and industry, being used as the key step in the synthesis of many natural products, bio-active compounds and pharmaceuticals. [1] In spite of this, protocols that operate in the absence of copper, allowing the presence of air and employing water as the only reaction solvent are scarce, and no such example has previously been reported for Pd-NHCs as catalysts (NHC = *N*-heterocyclic carbenes). [2]
Appropriate tuning of the stability and activity of the palladium complexes is essential in designing better catalysts, leading to improved reaction conditions. In this context, we have developed a novel type of NHC palladium(II) catalyst, bis(pyridyl-functionalized 1,2,3-triazol-5-ylidene)-palladium(II) complex, $[Pd(Py\text{-}tzNHC)2]^{2+}$ **1**. [3] We found that complex **1** efficiently catalyzed the copper-, amine-, phosphine-, and additive-free aerobic Sonogashira alkynylation of (hetero)aryl bromides in water as the only reaction solvent. To get an insight into the mechanism of this process, the cross-coupling reactions with **1** were monitored by high-resolution electrospray ionization mass spectrometry (ESI-HRMS). Based on the identified palladium species the reaction mechanism was proposed to proceed along two connected Pd-cycles with homogeneous *bis*-carbene Pd^0 and Pd^{II} species.



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P-15

MONOMER AND DIMER STATE OF AMYLOID BETA PEPTIDE: A MOLECULAR DYNAMICS STUDY

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The pathogenesis of Alzheimer's disease (AD) includes many factors [1]. The accumulation of amyloid-beta (Aβ) plaques in the central nervous system is one of the most widely known sign of the evaluation of the disease. In the last decade it was pointed out that the plaques are not the most toxic form of the Aβ peptide [2]; small oligomers are considered as more crucial players in the toxicity of the peptide. Taking into account the flexibility of small complexes, the traditional experimental methods of structural biology (NMR, X-ray) have failed to provide proper 3D structures of the monomers or the oligomers of the Aβ1−42 peptide. Therefore, here we present a molecular dynamical investigation to better understand the conformational space of Aβ monomers and dimers.

In the present work 250 ns long replica exchange molecular dynamical (REMD) running with 48 replicas were performed in explicit water under physiological circumstances. From the MD running the last 150 ns part of the trajectory were considered to sample the conformational space. Secondary structural search did not find any significant structural element, which is in accordance with the intrinsically disorder character of the monomer or dimer peptide. However, further examinations like hydrogen bond analysis, residue contact map, radius of gyration calculation or clusterizations point out certain interactions, which can help us in the identification of new target points for further investigations.

This work was supported by the Hungarian Brain Research Program - Grant No. KTIA_13_NAP-A-III/7.

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P-16

THE INFLUENCE OF INITIATOR ON THE PROPERTIES OF THERMOSENSITIVE DRUG CARRIERS

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Stimuli –sensitive polymers are a class of "intelligent" materials that are able to react to environmental changes. These polymers are very interesting because of possible biomedical applications such as drug delivery [1], targeted therapy [2], tissue engineering [3]. Thermoresponsive N-isopropyl acrylamide (NIPAM) gained huge attention of researches, and is intensively studied due to sharp and reversible phase transition at 32^{o}C, (lower critical solution temperature, LCST), which good correspond to the physiological temperature. Nanometer size of sensitive polymers is additional desirable feature in drug delivery systems because of the small size particles which facilities may access various regions in the body and pass through capillaries.

The aim of the work was to evaluate the influence of concentration of anionic initiator-potassium persulfate (KPS) on physicochemical properties and behavior of synthesized polymers of NIPAM.

Polymeric nanoparticles (P-1, P-05, P-01, P-005, P-001) were prepared by free radical precipitation polymerization without an emulsifier (surfactant free precipitation polymerization, SFPP). In all studied systems we used the same amount of monomer and increasing amounts of KPS. The polymerization was carried out at 70°C for 6 hours under a nitrogen atmosphere. The course of each reaction was monitored by measuring the conductivity.

The composition and morphology of products were confirmed by ATR FT-IR measurements. Hydrodynamic diameter and zeta potential were measured in aqueous dispersions of the synthesized polymers by DLS method (λ = 678 nm).

Comparisons of FTIR spectra of polymers P-1, P-05, P-01, P-005, P-001 with spectrum of NIPAM proves that the vinyl bond was saturated. Main characteristic peak for the monomer assigned for C=C stretching vibrations at 1620 cm^{-1} [4], disappeared after synthesis of the polymer. Measured at 18°C values of hydrodynamic diameter are ca. 20, 22, 50, 63, 530 nm respectively for P-1, P-05, P-01, P-005, P-001. The values of zeta potential in all cases are negative in the range -2,5 to -12,9 mV at the 18°C. The effects of temperature on hydrodynamic diameter and potential zeta were analyzed in the range 18-42°C for all the synthesized polymers. Significant changes on the temperature trends appears in the same range of temperature for both hydrodynamic and potential zeta measurements. These occurrence may enable determination of the LCST via electrokinetic measurements.

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P-17

MODIFICATION OF THE HUMAN SOLUBLE EPOXIDE HYDROLASE ACTIVE SITE ACCESSIBILITY BY ENGINEERING OF ITS ENTRANCE TUNNEL

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The aim of this study was to identify gates and anchoring residues in human soluble epoxide hydrolase (hsEH) as well as to introduce rational changes in entrance of the tunnel which can modify the accessibility of the enzyme active site.

Epoxide hydrolases are enzymes which play important role in metabolism of drugs and xenobiotics. They catalyse the conversion of epoxides to corresponding diols by adding the water. [1] This reaction increases the products solubility in water. Catalytic triad of hsEH is buried inside protein structure. Tunnels provide the passage of molecules to and from the active site of the enzyme. Residues which build pathways of transported molecules and can control the accessibility of the tunnels are known as gates. [2] Anchoring residues are able to stabilize the open/closed conformation of gates. These specific properties of gates and anchoring residues can regulate enzymes specificity, selectivity and rate-determining step of catalysis.

In this study *in silico* methods of molecular modelling were applied. The Amber14 package was used to run and analyse 50 ns classical molecular dynamics simulation of human soluble epoxide hydrolase enzyme structure (PDB ID: 4JNC). [3] Caver 3.02 software was used for tunnels detection. [4] Gating and anchoring residues identification was performed based on analysis of amino acids conformational changes. The results of this study allowed to identify residue Phe497 as a gate, which modify throughput one of the identified tunnels providing access to the active site and His524 building active site as an anchoring residue. Proposed rational mutants were constructed using FoldX, based on the results from *in silico* study and analysis of the amino acids conservativity at the gate position. MD simulations and Caver 3.02 were used for variants analysis. The preliminary results show that variant Phe497Pro causes invariably opening of the tunnel, which throughput was controlled by the gate in wild-type enzyme structure. Furthermore, the Phe497Arg mutation causes significant changes in tunnels network, because of repulsion between introduced Arg497 and His524 working as anchoring residue.

The work is supported by a grant SONATA-BIS 2013/10/E/NZ1/00649 financed by the National Science Centre Poland (www.ncn.gov.pl)

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P-18

SYNTHESIS AND ANTIMICROBIAL EVALUATION OF ALKYL 1-[(2-SUBSTITUTED PHENYL)CARBAMOYL]NAPHTHALENE-2-YL CARBAMATES

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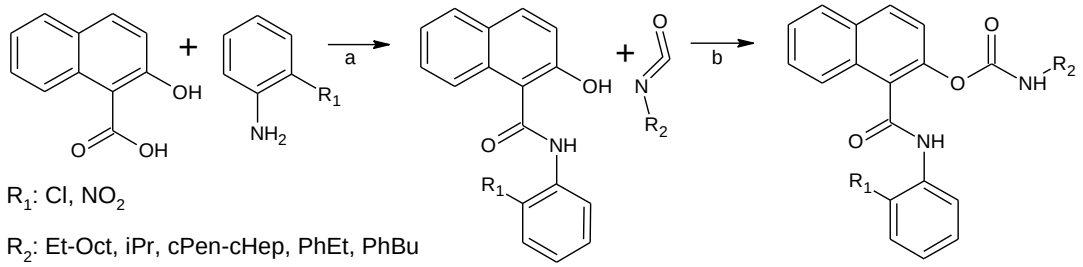
Alkyl 1-[(2-substituted phenyl)carbamoyl]naphthalen-2-yl carbamates, synthesized in the present work, can be considered as cyclic analogues of salicylanilides. Pattern compounds of these carbamates – *N*-(2-chlorophenyl)-2-hydroxynaphthalene-1-carboxamide and *N*-(2-nitrophenyl)-2-hydroxynaphtha-lene-1-carboxamide showed antimycobacterial or antibacterial activity at insignificant cytotoxicity on human cells in previous screening [1]; therefore the aim of this contribution was preparation of various alkyl, cycloalkyl and arylalkyl carbamates and investigation of their antimicrobial activity.

All the studied compounds were prepared according to Scheme 1. Appropriate anilide (1.0 mmol) and triethylamine (1.1 mmol) were suspended in dry acetonitrile (10 mL). The solution of the appropriate alkyl isocyanate (1.2 mmol) in acetonitrile (5 mL) was added in four portions within 2 h, and the reacting mixture was stirred for 24 h at ambient temperature. The solvent was evaporated under reduced pressure; the solid residue was washed with methanol and dichlormethan to give pure product.

Primary *in vitro* screening of the synthesized compounds was performed against *Staphylococcus aureus*, two methicillin-resistant *S. aureus* strains, *Mycobacterium marinum* and *M. kansasii.* 1-[(2-chlorophenyl)carbamoyl]naphthalen-2-yl ethylcarbamate and 1-[(2-nitrophenyl)-carbamoyl]naphthalen -2-yl ethylcarbamate showed antistaphylococcal (MICs = 42 μM against MRSA) and antimycobacterial (MICs = 21 μM) activity against the tested strains comparable with or higher than that of the standards ampicillin and isoniazid, respectively. In case of bulkier carbamate tails (R > propyl/isopropyl), the activity was similar (MICs ca. 70 μM). Screening of the cytotoxicity of both most effective compounds was performed using THP-1 cells, and no significant lethal effect was observed (LD_{50} >30 μM).



R_1: Cl, NO_2

R_2: Et-Oct, iPr, cPen-cHep, PhEt, PhBu

Scheme 1. a) PCl_3; MW; chlorobenzene b) TEA; ACN

This study was supported by IGA VFU Brno 320/2015/FaF, 311/2016/FaF and 328/2016/FaF. The HPLC/HRMS system forms a part of the National Infrastructure CzeCOS (LM2015061); Michal Oravec was supported by the National Sustainability Program (NPU I; Grant No. LO1415 POLYMAT)

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P-19

BIORELEVANT DISSOLUTION OF CANDESARTAN CILEXETIL

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During drug development it is essential to investigate factors which influence drug absorption, especially for oral solid dosage forms. The prediction of the limiting factors can be facilitated by *in vitro* tests [1]. To establish a reliable *in vitro* investigation it is important that the artificial environments simulate the biological conditions as closely as possible. *In vitro* dissolution tests should mimic the drug performance in the human gastrointestinal tract. However, the level of simulation *in vitro* conditions is depended on the used medium [2].

Dissolution media were initially intended for quality control purposes, water was frequently used as a dissolution medium. Only later approach brought the development of a new medium that could reflect conditions in the stomach or small intestine. Simulated Gastric Fluid (SGF) and Simulated Intestinal Fluid (SIF) were the first proposals. These traditional media do not contain any surfactants. Therefore, Dressman et al. [3] and Galia et al. [4] proposed addition of synthetic surfactants – TritonX® 100 and sodium lauryl sulfate (SLS). Really biorelevant medium is Fasted State Simulated Gastric Fluids (FaSSGF) proposed by Vertzoni in 2005. The medium contains the natural surfactants taurocholate and lecithin. Other biorelevant media - Fasted State Simulated Intestinal Fluids (FaSSIF), Fed State Simulated Gastric Fluids (FeSSGF) and Fed State Simulated Intestinal Fluids (FeSSIF) - or its updates were proposed by Jantratid et al. in 2008 [5].

Seven media were chosen to model fasted and fed state conditions in the stomach and small intestine before and after meal intake. These are SGF, SGF_{SLS}, FaSSGF, FeSSGF, SIF, FaSSIF and FeSSIF. The following volumes were used to approximate the volumes available in the proximal GIT: fasted state stomach/ small intestine 500 ml and fed state stomach/ small intestine 900 ml. Although volumes in GIT can be lower (fasted state) or higher (fed state), the limiting fact was the minimum and maximum volume of a dissolution apparatus. We used the standard USP paddle apparatus. As case example of lipophilic drug was chosen candesartan cilexetil (Figure 1). Candesartan cilexetil is practically insoluble in water (less than 0.05 μg/ml). Very low solubility across the physiological pH range resulted in an incomplete absorption and it is a reason for the low bioavailability of candesartan cilexetil (about of 15%) [6]. Candesartan cilexetil solubility in particular media was estimated. Substantial differences in dissolution profiles of candesartan cilexetil were observed between compendial and biorelevant media.

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P-20

METAL COMPLEXES AS ENZYME INHIBITORS

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Numerous metal complexes exhibit enzyme inhibitory properties. Their mechanism of enzyme inhibition often differs significantly from the typical, purely organic inhibitors, thus providing an additional insight into the catalytic mechanism of the particular enzyme as well as possibilities for development of novel inhibitors with unique properties [1]. The activity of certain enzymes was brought into connection with pathogenesis of various medical conditions, e.g. urease in *Helicobacter pylori*, leading to increased demand for development of new inhibitors.

As a part of our research, we were investigating the inhibitory properties of various metal complexes, in particular towards urease and protein tyrosine phosphatase [2,3]. The ligands used in the synthesis of complexes were mostly of aminopolycarboxylate or Schiff base type. Some of the complexes showed promising inhibitory activities and are likely candidates for further investigation. Also, we are interested in elucidating the specific inhibitory mechanism of metal complexes and in establishing the dependence of the activity on the kind of metal ion and on the structure of the ligands.

This work was supported by the Slovak Research and Development Agency under the contract No. APVV-0516-12.

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P-21

H/D ISOTOPIC RECOGNITION MECHANISM IN HYDROGEN-BONDED CRYSTALS OF SELECTED NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

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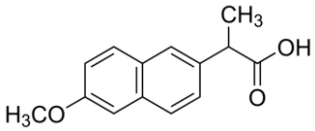
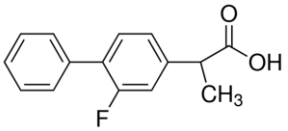
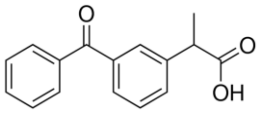
Nonsteroidal anti-inflammatory drugs (NSAIDs) are widely used for their anti-inflammatory, analgesic, antipyretic and anti-coagulating activity. NSAIDs can also be used to prevent colorectal cancer and may protect against the development of Alzheimer's disease as well [1-4]. Most NSAIDs inhibit the activity of enzymes called cyclooxygenase-1 (COX-1) and cyclooxygenase-2 (COX-2), and thereby, the production of a class of compounds in the body known as prostaglandins [1-4]. The deuterium substitution effect on polarized infrared spectra of selected arylpropionic acid derivatives: naproxen (NPS), flurbiprofen (FLB) and ketoprofen (KPF), is presented.



(NPS) naproxen



(FLB) flurbiprofen



(KPF) ketoprofen

Polarized infrared spectra have been measured for monocrystals of selected NSAIDs at 293K and 77K. The studied systems, FLB and KPF, contain molecular dimers in their lattices, whereas NPS have chain hydrogen bond aggregates. Analysis of the results mainly concerned H/D isotopic and temperature effects, observed in the spectra of the hydrogen and deuterium bond at the frequency ranges of the $\nu_{X\text{-}H}$ and the $\nu_{X\text{-}D}$ bands, respectively.

The differences in the fine structure patterns of the $\nu_{X\text{-}H}$ and $\nu_{X\text{-}D}$ bands, temperature and H/D isotopic effects in crystals of selected NSAIDs suggested that the spectral properties in IR remain in a close relation with the electronic structure of the individual molecular systems. IR spectra of the deuterium-substituted compounds show that the H/D isotopic dilution process did not change the fine structure patterns and the spectral effects observed in NSAIDs crystal spectra. This phenomenon is attributed to the H/D isotopic self-organization process depending on a non-random distribution of protons and deuterons in the hydrogen bridges in the NSAIDs crystal lattices [5]. Thus the dynamical cooperative interactions in hydrogen bonding of selected NSAIDs exist and diversify these systems. In NPS identical hydrogen isotope atoms, occupy domains in each individual hydrogen bond chain. In FLB and KPF cycles identical hydrogen isotope atoms exist in whole hydrogen bond systems.

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P-22

SOLUTION STRUCTURE AND DYNAMICS OF THE NEW ANTIFUNGAL PROTEIN PAFB VARIANTS

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Our research group is interested in the structure/dynamics/function aspects of small, basic antifungal proteins, that are rich in lysines and cysteins. A new member of this family is PAFB (produced by *Penicillium chrysogenum*) was shown to form three disulfide bridges, leading to greek-key supersecondary, and β-barrel solution structure similarly to PAF [1-2]. According to ESI-MS and NMR spectroscopy, three PAFB variants were detected. These variants differ in their lenght (56, 57 or 58 residues). We determined the structure of sfPAFB (short form, 56 aa) using NMR methods. ^{15}N NMR relaxation data yielded ps-ns timescale dynamics and showed that sfPAFB is as rigid as PAF. The full PAFB (58 aa) sequence is identical with pgAFP [3], whos experimental structure is not known yet. In summary, though the sequence similarity between sfPAFB and PAF is less than 40%, their solution structure and dynamics are very similar. This fact may have implications for understanding their biological activity.

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P-23

SYNTHESIS OF 1,3,5-TRIAZINE DERIVATIVES CARRYING 4-(AMINOMETHYL)BENZENE-/ 4-(2-AMINOETHYL)BENZENE-1-SULFONAMIDE AND AMINOALCOHOL STRUCTURAL MOTIVES USING GREEN CHEMISTRY METHODS

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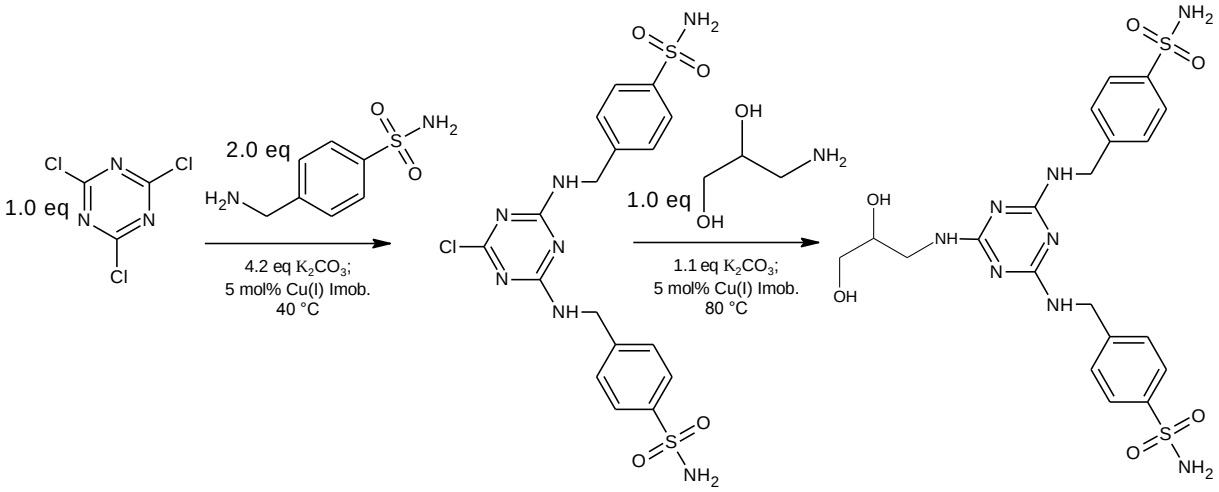
As the target of our interest we chose a 1,3,5-triazine derivatives with potencial antitumor activity against isozyme carboanhydrase hCAIX (associated with tumor growth).

For the prediction of the biological activity of these derivatives we used a forwarded Artificial Neuronal Networks.

Target structural motifs are introduced to the s-triazine skeletone by one through an aliphatic primary or secondary amino group by the substitution of chlorine atoms in the commercially available cyanuric chloride (2,4,6-trichloro-1,3,5-triazine). We found that substitution of the chlorine atoms of cyanuric chloride can be carried out as C-N coupling catalyzed by Cu(I) supported on weakly acidic macropourous cation exchanger resine of polyacrylate type via the oxidative addition - heterolytic addition - reductive elimination processes. We found reaction conditions for a one-pot synthetic process that is carried out under temperature controll in DMF as a solvent and supported Cu(I) cations as catalyst is used. We achieved higher yields with shorter reaction times in comparison with similar usual syntheses. These optimized synthetic procedures may be applied in the preparation of the various s-triazine derivatives with slight variations with respect to the chemistry of the individual nucleophilic reagents.



P-24

PHOTOCHEMICALLY INDUCED *SYN-ANTI* ISOMERIZATION OF QUINAZOLINONE-DERIVED SCHIFF'S BASES: EPR, NMR AND DFT ANALYSIS

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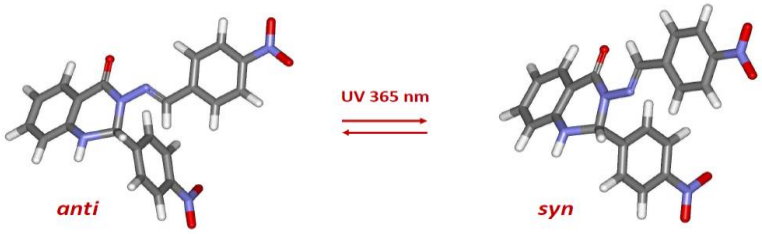
Photochemical properties of organic molecules are subject of a number of studies due to their potential applications in both macroscopic and microscopic scales. Among various photochemically active molecules, Schiff's bases are widely studied as they are involved in important biological processes. Here we present detailed analysis of isomerization process of two new photochemically active quinazolin-4-one-derived Schiff's bases. The analysis was performed using various spectroscopic and theoretical methods including EPR, NMR, UV-VIS as well as DFT calculations. UV irradiation led to isomerization around the N-N bond in the -C(=O)-N-N=C-(H) array of atoms with a formation of the *syn* isomer:



This process could be monitored by NMR spectroscopy where the signals arising from the newly formed *syn* isomer were detected in ^{1}H NMR spectra at 600 MHz. UV-VIS spectra showed significant effects on the absorption bands depending on the type and the position of the substituent in investigated Schiff's bases. EPR spectroscopy confirmed generation of the reactive intermediates resulting from the interaction of activated molecular oxygen with solvent molecules. The activation of molecular oxygen is caused by electron transfer from the excited states of molecules to molecular oxygen forming reactive oxygen species. DFT calculations pointed out on conjugation of the nitrogen lone pairs increasing the bond order in investigated isomers. Further details describing the structure and properties of the studied Schiff's bases will be discussed.

P-25

INHIBITION OF LIPOXYGENASE BY NATURAL COMPOUNDS

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Several compounds mostly with flavonoid structure have been isolated in the Department of Natural Drugs and tested for their anti-inflammatory potential. Lipoxygenase (LOX) ELISA inhibition assay (kit purchased from Enzo) for detection of LTB_4 was used to evaluate the inhibitory activity of selected compounds against LOX isolated from human neutrophils. Colorimetric screening assay kit with a potato lipoxygenase purchased from Cayman Chemical was also used to screen the compounds for their inhibitory potential.

A series of tomentodiplacones and mimulones did not show any inhibition against potato LOX. Mangostanin and its derivatives only expressed low inhibitory activity against LOX. Diplacone as well as cudraflavone B were shown to possess anti-inflammatory effect [1,2] but it has not been tested for LOX inhibition specifically. In the ELISA assay, cudraflavone B did not exhibit a concentration dependent activity as expected; the result it gave was a significant inhibitory activity, but the lower the concentration the higher the activity. Kuwanon S seems to be a promising compound since its inhibitory activity was comparable to the standard zileuton. Diplacone was tested using both assays and showed a significant inhibitory potential.

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P-26

ALKYL [(AMINOHYDROXYPROPYL)PHENYL]CARBAMATES AND THEIR PRECURSORS: SYNTHESIS AND CHARACTERIZATION

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Structural motives of arylalkylamines are common in molecules of antiarrhythmic drugs. Effect on an activity, selectivity and side-effect incidence, have modifications of amino-substituents, especially tertiary amines, and form and length of alkyl chain. [1]

The synthesis of new arylaminopropanole derivatives and their precursors is the aim of this study. A potential antiarrhythmic [1, 2] or ACHE-inhibitory effects are expected.

We focused on simple arylaminopropanole alkylcarbamates with different substituents on tertiary amine. The synthesis is based on Mannich reaction – alkylester of 4-acetylphenylecarbamoic acid reacts with paraformaldehyde and respective secondary amine. Obtained precursors (ketones) and target structures (alcohols) were isolated as stable salts with proper acids and characterized using ^{1}H-NMR, ^{13}C-NMR, IR spectroscopy and other methods.

Preliminary results of biological activity will be presented, further examination and biological characterization is expected.

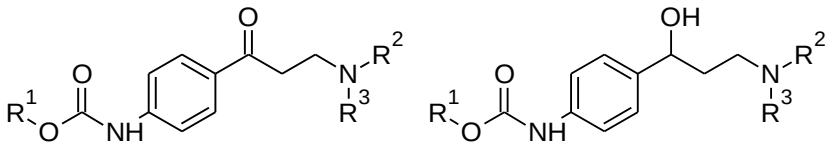

Fig. 1: Structures of prepared compounds and their precursors.
R^1 = alkyl C_1 to C_4; R^2 = ethyl or butyl; R^3 = methyl or ethyl;

Acknowledgement: IGA VFU 330/2016/FaF

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P-27

UTILIZATION OF GRAPE POMACE FOR LACTIC ACID PRODUCTION

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Residues remains after grape processing are called grape pomace. It includes pulp, seeds, skin and stems. The wine industry produces large quantities of pomace. It offers large potential of uses. Typically, it is composted or processed into animal feed. Also it could be used for extraction of grape seed oil and polyphenols. These applications have one disadvantage because of limited markets that can absorb only a small portion of the waste generated. Conversion of grape pomace into other valuable products promise different options. [1]

One of these valuable products could be lactic acid. It is organic acid usually used in food and pharmaceutical industries. Nowadays it has great potential as monomer for producing the biodegradable plastics. Polylactic acid (PLA) is suitable alternative to traditional plastics. Its large-scale application is limited by high price of lactic acid production. High price of production could be reduced by optimization of fermentation and searching of cheaper raw materials. [2]

We tried to use grape pomace as raw material for lactic acid production. For fermentation we used three different species of lactic acid bacteria and one thermotolerant bacteria. Traditional lactic acid producers have optimal temperatures of growing and fermenting about 30 to 40˚C. There could be disadvantage because of the sterilization of media before the fermentation. Accordingly, we tried to ferment with thermotolerant *Bacillus coagulans*. This bacteria can grow and ferment at temperatures from 50 to 60 ˚C. The other advantages are simple nutrition requirement and production of high optical pure L-lactic acid. [2]

In experiment we used 100 mL of 15% (w/v) grape pomace and water suspension. It was hydrolysed by two stage hydrolysis. First we used physico-chemical hydrolysis by 2% HCl and 121°C for 15 minutes. After this we used enzymatic hydrolysis by successive adding of cellulase complex (Novozymes, NS50013) and β-glucosidase (Novozymes, NS 50010). We chose conditions applicable for both enzymes and we optimised the hydrolysis. The following step was fermentation by selected species of bacteria.

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P-28

STRUCTURAL CHANGES OF SERUM ALBUMIN INDUCED BY THE AGEING PROCESS. SPECTROSCOPIC STUDIES

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Pathological conditions in the organism e.g. renal or hepatic diseases, cataract, dysfunction of coronary artery, diabetes mellitus and also intensive workout induce the structural modification of serum albumin called molecular ageing or isomerization N-A [1]. Understanding the mechanism of alkaline ageing of serum albumin tertiary structure allows for determination of an effective therapy and also contributes to the detection of the factors that slow down the ageing process.

In the present work the spectroscopic characteristics of alkaline ageing process were performed. We compared A(aged) with N(non-modified) form of human (HSA) and bovine (BSA) serum albumin using the method of second derivative of absorption and fluorescence spectra. We also determined changes of the content α-helix, β-sheet and rotation degree of aged human (AHSA) and bovine (ABSA) serum albumin using circular dichroic technique.

We proved that the ageing process causes structural changes - the greatest were observed around tryptophanyl and tyrosyl residues and the smaller in the phenyloalanine environment in HSA and BSA. For ABSA the increase of polarity within tryptophanyl residue surroundings was greater than for AHSA. Process of albumin ageing affects also the binding affinity of ligands to specific sites located in subdomain IIA and IIIA.

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P-29

MOLECULAR BACKGROUND OF GEL AND/OR CRYSTAL FORMATION OF PROTECTED GLUCOSAMINE DERIVATIVES

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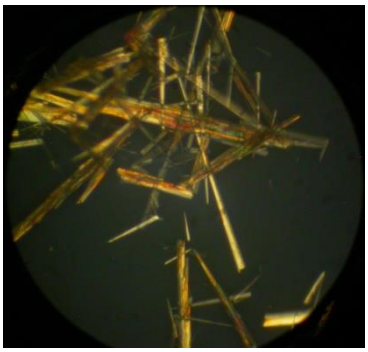
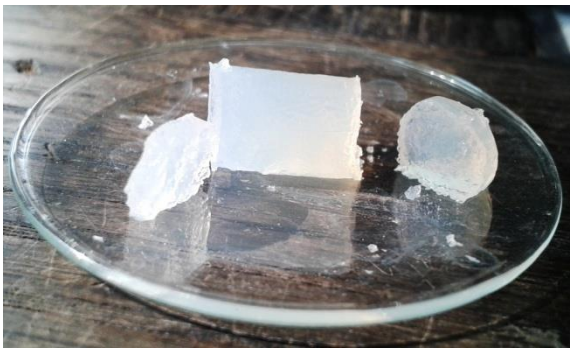
A variety of intra- and intermolecular interactions (*e.g*. H-bond, VdW, π↔ion) determine the structural properties of biomolecules in the lattice, particularly true for carbohydrates. Handful examples are where carbohydrates, typically containing free OH group(s) form hydrogels [1-3]. However, the molecular background of these crystal or hydrogel formations is yet unspecified, though used for various purposes, such as drug delivery, artificial joints [4-6]. Here we present the hydrogel formation of fully protected α- and β-anomers of 2-amino-2-deoxy-glucopyranose, where the NH protecting group is the well known 9-fluorenylmethoxy-carbonylamino (Fmoc) of peptide chemistry.
While the most stable conformer / isomer of the β-anomer is “curved” and stabilized by intermolecular interactions, the lowest energy form of the α-anomer has extended-like structure and presents multiple intermolecular interaction. Both molecular packing and interactions were determined by X-ray diffraction and NMR measurements completed by DFT calculations. Serious attempts were made to rational the molecular background of conformer selection and thus, hydrogel or crystal formation.





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P-30

THE REACTION BETWEEN 1,4-BENZOQUINONES AND SULFITE ION

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Benzoquinones are photosensitive substances in aqueous solutions forming hydroxyl-quinones and hydroquinones in their photoreaction. Halobenzoquinones are known as a group of emerging disinfection byproducts in drinking water and swimming pool waters. Halide displacement may be performed by UV irradiation or ozonization [1-2]. Transformation of halobenzoquinones to less pollutant substances is possible using sodium-sulfite reducing agent [3]. However, sodium sulfite can play several different roles in these systems: it can be a reducing agent/ a buffer/ a weak base depending on the active form we use or a reactant of the ketone-bisulfite addition reaction [4]. The stoichiometry and kinetics of the reactions between 1,4-benzoquinones and sulfite ion was investigated in details, both by experimental and by quantum chemistry methods.

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P-31

OPTIMALIZATION OF HRM-PCR METHOD FOR IDENTIFICATION LACTIC ACID BACTERIA FROM COMPLEX SAMPLES

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Molecular based differentiation of various bacterial species is important mainly in diagnostic, epidemiological and food quality control studies, particularly where phenotype makes the identification of bacteria difficult. Molecular methods based on the amplification of 16S ribosomal RNA gene analysis are more rapid, reliable, and reproducible and have greater sensitivity [1,2]. High resolution melting (HRM) curve analysis is a simple, low-cost, closed tube method for amplicon discrimination and easy integration with real-time polymerase chain reaction (HRM –PCR) [1,3].

In this contribution we report rapid species identification of lactic acid bacteria using HRM-PCR in complex food samples. Three different DNA isolation methods were used in this work: phenol extraction [4], separation using magnetic particles and commercial kit. Three sets of primers targeted hypervariable region (V1-F - V1-R , V3-F - V3-R , V6-F - V6-R) were tested for amplification of the 16S rRNA gene [3]. Presented method was optimized on 6 Reference collection of 6 strains (*L. bulgaricus* CCM 7190^T, *L. casei* CCM 7088^T, *Streptococcus thermophilus* CCM 4757, *L. plantarum* CCM 7039^T, *L. acidophilus* CCDM LA 10, *L. rhamnosus* CCM 1825^T) was used for identification of lactic acid bacteria in food supplements Lactomax and Lactobacily forte. Real time PCR and HRM profiles generated reproducible results which allow species recognition in real samples. However, further research with larger strains collectionist is required to validate the sensitivity and robustness of this method.

The financial support of internal grant FCH-S-15-2827 is gratefully acknowledged.

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P-32

RING-SUBSTITUTED 6-HYDROXYNAPHTHALENE-2-CARBOXANILIDES AS POTENTIAL HERBICIDAL AGENTS

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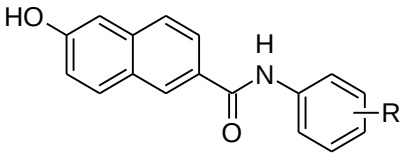
In this study, a series of twenty-six ring-substituted 6-hydroxynaphthalene-2-carboxanilides (Figure 1) was prepared and characterized. Inhibition of photosynthetic electron transport (PET) in spinach chloroplasts has been investigated. The PET inhibiting activity of the studied compounds depends on compound lipophilicity, on the position of substituents on the anilide moiety as well as on electron-accepting and electron-donating properties of these substituents. The most active PET inhibitors are *m*-substituted derivatives; the lowest activity is shown by *o*-substituted ones. The most potent PET inhibitor is 6-hydroxy-*N*-(3-trifluoromethylphenyl)naphthalene-2-carboxamide (IC_{50} = 10.8 μmol/L). The study of chlorophyll *a* fluorescence in the suspension of spinach chloroplasts in the presence of the studied compounds confirms their site of action in PS II, and it can be assumed that the inhibitory site of action of the studied compounds is situated on the acceptor side of PS II at Q_B site.



R = Cl, F, Br, CH_3, OCH_3, CF_3, NO_2

Figure 1

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SYNTHESIS METHODS OF PEPTIDE-6-AMINO-D-LUCIFERIN CONJUGATES FOR DETECTION OF PROTEASE ACTIVITY

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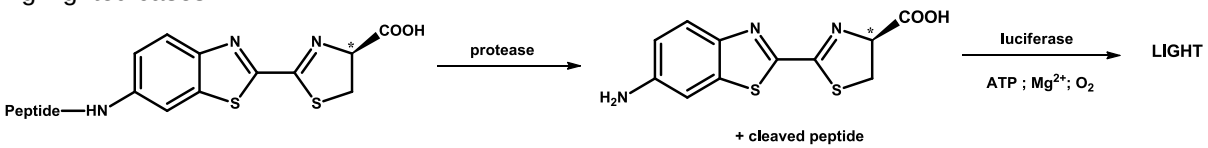
Amino-luciferin (aLuc) is a firefly luciferin with its 6-position hydroxyl group substituted with an amino group. This modification allows amino-luciferin to form amide bonds with a peptide, while retaining the transport and bioluminescent properties of luciferin, resulting in a good substrate for different important proteases, which can be used for the determination of the enzymatic activity in different therapeutically highlighted cases.



The synthesis of peptide-aLuc conjugate precursors has been published and some of them – alongside peptide-aLuc itself - are commercially available. [2] However, due to the difficulties with their synthesis and the resulted side products, the application of these conjugates is very limited. Our aim was to develop a simple, economical way for the synthesis of peptide-aLuc conjugates.

We developed three distinct methods: one with solid phase Fmoc strategy, one with fragment condensation strategy and one with solid phase Boc strategy.

With the solid phase Fmoc strategy there is a high risk for dehydrogenation and racemisation, due to the basic conditions.

In order to avoid these problems, we worked out a fragment condensation strategy. Although this way it is possible to synthetize the desired conjugates, the method has certain limitations: when attaching longer peptides, solubility problems will occur. This made us use solid phase peptide synthesis with Boc strategy.

First we had to prepare a Boc-protected amino-luciferin, a completely new substance which has not been published yet. Then this substance was attached to resin, and at the moment we are working on building the peptide chain, which will be followed by cleaving the resulting peptide-luciferin conjugate from the resin.

If we manage to carry out the synthesis with this Boc method, it will be a breakthrough in the synthesis of peptide-6-amino-D-luciferin conjugates, as it will make the synthesis of any substrate possible.

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P-34

SYNTHESIS OF NOVEL CARBAMATES AND THIOSEMICARBAZONES AS POTENTIAL ANTICANCERS

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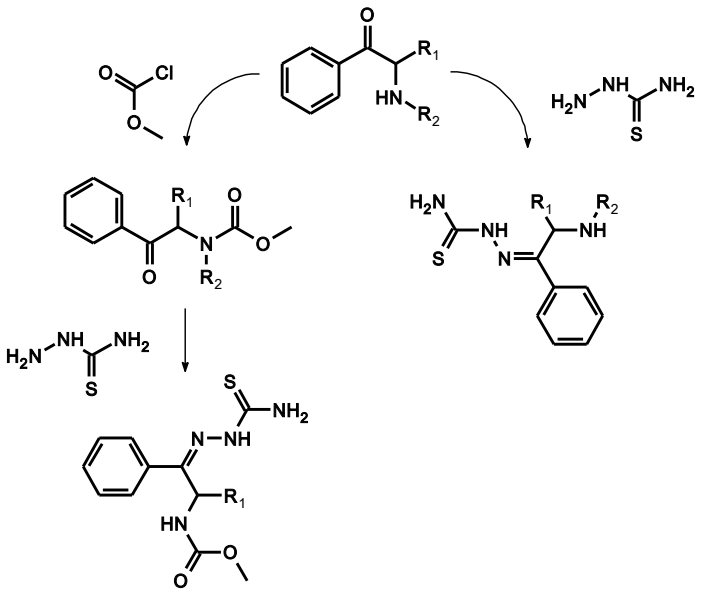
Carbamate and thiosemicarbazone moieties are one of the privileged structural arrangements, widely deployed within pharmaceutical and crop protection industries. Their broad scope of utility, especially as anticancers or antimicrobial drugs, rendered them as an object of great interest for many years. Thus, their area of utility was broadly explored, and recent 20 years of research has proven that junction of carbamate or thiosemicarbazone moieties with aromatic ketones and phenylethylamines yield a series of structures that display a wide scope of bioactivity. Our research objective is a synthesis of carbamates and thiosemicarbazones based on the 1-phenyl-2-amine-1-ketone moieties as shown on scheme below.



Scheme 1. Synthesis of carbamates and thiosemicarbazones

Such a structure has its origins in the nature. Extensive studies displayed [ref], that functionalization of naturally occurring products by means of diverse substituents would lead to novel compounds with diverse bioactivity profile. An example of such approach is the lead structure of natural chrysanthemic acid, a molecular fragment used as a skeleton of many novel insecticides. Additionally derivatives of cathinone, substance derived from Khat plant, are convenient starting materials in synthesis of tetrahydroisochinolines. Cathinones itself have a good synthetic availability.

P-35

CHEMICAL FUNCTIONALIZATION OF GRAPHENE OXIDE

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Modifications of grafide oxide can be performed in two ways, namely covalent and noncovalent. In the case of covalent functionalization a GO surface is modified by the formation of chemical bonding while in the noncovalent mode van der Waals forces, hydrogen bonding, and p–p stacking interactions[1-2]. It is noteworthy that covalent modification seems to be a more useful since prepared by the noncovalent method are more unstable. Covalent modification allows obtaining compounds of desired properties which are more stable and can be used many times.

Synthesis of GO-IDA is based on the nucleophilic substitution of IDA (iminodiacetic acid) to graphene oxide nanoparticles. In the first step, IDA was transformed into IDA methyl ester hydrochloride in order to protect the C-terminal of the amino acid [3]. The obtained product, activated in situ, was used for the formation of amido binding between IDA and GO.

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P-36

THE INFLUENCE OF HYDROXYNAPHTHALENE CARBOXANILIDE DERIVATIVES TO ENZYMATIC ACTIVITY OF DNA TOPOISOMERASES

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Infectious diseases caused by antimicrobial drug resistance represent worldwide threat, therefore further research and development of new compounds with possible antimicrobial potential is required. A number of biologically active compounds including hydroxynaphthalene carboxanilide derivatives contain an amide group with hydrophobic residue in its close vicinity. The amide functional group is able to interact with various enzymes and by means of these target sites affect the biological response. Also its properties can be easily modified by diverse substitutions, thus the presence of amide group is characteristic for many antibacterial, antimycobacterial and antiparasitic agents [1,2].

Bacterial topoisomerases are enzymes essential for control of the topological state of DNA during pivotal cellular processes such as replication or transcription which makes them suitable targets in development of new antibacterial as well as anticancer drugs [3]. The effects of hydroxynaphthalene carboxanilide derivatives were tested using enzyme DNA topoisomerase I (*E. coli*) which catalyzes relaxation of negatively supercoiled DNA and DNA gyrase (*E. coli*) which on the contrary introduces negative supercoiling.

About 35 compounds showing antimicrobial activity were investigated as a potential inhibitors of bacterial enzymes DNA topoisomerase I and DNA gyrase by employment of electrophoretic methods based on analysing alterations in DNA supercoiling. In accordance with obtained results, minimal inhibition concentration IC_{50} was determined. For the most effective compounds including NM22, NM31, NM33 a NM57 the IC_{50} value ranged between 10-30 μM using enzyme DNA topoisomerase I. In general, better inhibition induced by tested compounds was achieved in case of topoisomerase I relative to DNA gyrase.

This study was supported by project IGA VFU Brno 37/2014/FaF, 67/2014/FaF, IMA VFU Brno 2015-FaF-11 and by IGA VFU Brno 316/2016/FaF.

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P-37

SYNTHESIS OF A NOVEL FLAVIN COFACTOR ANALOGUE. N6-(BUTYL-2-EN-4-AMINE)-FAD FOR ENZYME IMMOBILIZATION

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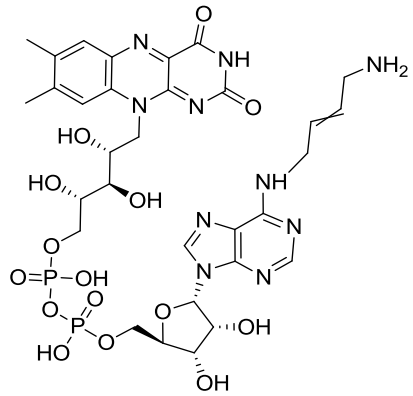
Flavin-containing enzymes can be used in various biotechnological applications, including biosensors, biofuels and bio(electro)reactors. Effective enzyme immobilization is often essential for such advanced applications. Most flavoenzymes contain a dissociable FAD cofactor. Intriguingly, the adenine part of the flavin cofactor is often close to the protein surface [1]. We have recently developed carrier material that contains covalently coupled FAD in which the flavin cofactor is attached to the adenine moiety via an aliphatic spacer. Using this FAD-decorated carrier, we could reconstitute apo flavoenzymes. By this approach we obtained tightly immobilized, stable and active flavoenzymes that can be used for biocatalysis [2].



Methods for the preparation of FAD derivatized with an aliphatic spacer attached to the adenine part have been described in literature but involve long and laborious procedures, with very poor efficiency [1]. At the moment, synthesis by qualified suppliers is extremely costly. This work presents a new, synthetic pathway for obtaining a novel FAD derivative (see figure). The N6-(butyl-2-en-4-amine)-FAD was obtained at 75 % purity with yield of 40 % yield starting from FAD.

Structural formula of the synthesized novel flavin cofactor analogue, N6-(butyl-2-en-4-amine)-FAD

The final structure of the novel FAD analogue was confirmed and characterized using spectroscopic methods (NMR, UV-Vis, MS) and cyclic voltamperometry. The FAD analogue contains an aliphatic linker with a terminal primary amine. This makes it a suitable FAD analogue for cofactor-mediated flavoenzyme immobilization.

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P-38

NOVEL HALOGENATED PYRAZINE-BASED CHALCONES AS POTENTIAL ANTIMICROBIAL DRUGS

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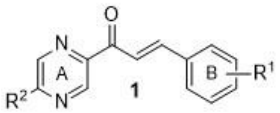
Chalcones are naturally occurring compounds. They are intermediates in flavonoids biosyntesis, but they occurr in plants as final secondary metabolites as well. Chalcones are chemically 1,3-diphenylprop-2-en-1-ones. They exert a wide range of bio-activities, e. g. antioxidant, anti-inflammatory, anticancer, anti-infective etc. [1]

Our research group has been focused on their pyrazine analogues, several series have been synthesized and tested on *in vitro* antifungal and antimycobacterial activity. The highest potency was exhibited by derivatives with electron withdrawing groups (EWG) in positions 2 and 4 of the ring B. [2–4] As halogens also have electron withdrawing properties, novel halogenated derivatives were prepared (**1**).



a) R^1 = 2-F, R^2 = H, *tert*-butyl, propyl
b) R^1 = 4-F, R^2 = H, *tert*-butyl
c) R^1 = 2-Br, R^2 = H, *tert*-butyl, isobutyl,butyl, propyl, isopropyl
d) R^1 = 4-Br, R^2 = H, *tert*-butyl, isobutyl, butyl, propyl, isopropyl, pentyl
e) R^1 = 2-Cl, R^2 = H, *tert*-butyl
f) R^1 = 4-Cl, R^2 = H, *tert*-butyl, isobutyl, butyl, propyl, isopropyl, pentyl

All compounds were submitted for antifungal and antibacterial evaluation. In antifungal assay against eight strains of selected fungi, growth inhibition of *Candida glabrata* and *Trichophyton interdigitale* was shown by non-alkylated derivatives with 2-bromo or 2-chloro substitution. In the panel of selected bacteria, both 2-chloro derivatives showed the most potent inhibitory effect on *Staphylococcus* spp. In addition, all products were also screened for their antimycobacterial activity against *Mycobacterium tuberculosis* H37Rv, *M. kansasii* My 235/80, *M. avium* 152/80 and *M. smegmatis* CCM 4622. Some of the compounds examined, inhibited growth of *M. kansasii* and *M. smegmatis* with MICs comparable with those of isoniazid.

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P-39

THE EFFECT OF NATURAL ANTIOXIDANTS AS A POLYLACTIDE PROTECTIVE AGENTS AGAINST AGEING

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The stabilizers determine the polymer lifetime. All of the polymers undergo degradation when exposed to an environment factors. The preparation of polymeric materials for technological applications requires a good understanding of the possible mechanisms that determine the oxidation processes in the materials [1].

There are several major groups of stabilizers. The division is determined by the types of environmental factors against which the material should be protected [2]. One of the most important groups of stabilizers are antioxidants. The polymer industry used synthetic antioxidants but it seems that more interest is directed towards natural substances with anti-aging properties. Natural antioxidants may be a novel, environmentally friendly alternative to the aromatic amines frequently used in polymers [1].

Phenolic compounds are significant and very large group of compounds with antioxidant properties. They are commonly found in plants. Depending on the criteria are divided into different classes. Due to structure of basic carbon skeleton are distinguished: phenolic acids, flavonoids, stilbenes and lignans [3,4].

Flavonoids are consist of two benzene rings (A and B), which are connected by oxygen containing pyrene ring (C) (Fig. 1) [5].

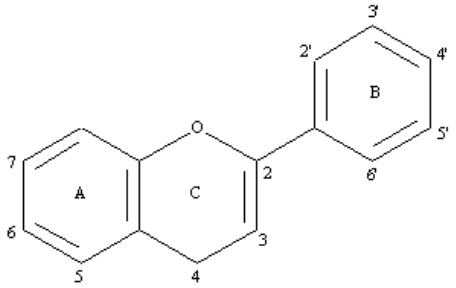

Fig. 1. Structure and determination of carbon in the basic skeleton flavone [3].

Flavonoids have a high reduction in oxidation. Thus, it should protect polymeric materials from the negative influence of environmental factors and can be used as ecological anti-ageing substances.

The antioxidant activity of polyphenols was determined by ABTS, DPPH, FRAP and CUPRAC assays. The second step of the research was the application of natural antioxidants for polyesters composites (such as polylactide) to protect against UV, termooxidation ageing and weathering.

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P-40

KINETIC INVESTIGATION OF HUMAN SALIVARY α-AMYLASE USING MICROCALORIMETRY

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The environmental or genetic factors caused metabolic diseases become more common, but among them the incidence of diabetes is significant. The better understanding of the action of carbohydrate modifying enzymes could reveal new targets, which contribute to the development of new effective therapies.

Isothermal titration calorimetry (ITC) is an increasingly used technique to investigate the molecular interactions but it is also appropriate for enzyme kinetic measurements.

In this pilot study an ITC-based method was developed to determine the reaction rate of salivary α-amylase catalysed hydrolysis reactions using free- and chromophore containing maltoheptaose and $GalG_2CNP$ as substrates. In the course of the measurement the heat change was followed as a function of reaction time, where the difference between the baseline and the minimum point of the curve were considered as the reaction rate [1]. Plotting these values as a function of substrate concentration, a saturation curve was obtained, which was used to determine the main enzyme kinetic parameters (K_M, V_{max}). According to our results, there are no significant differences in K_M values at the free and 2-chloro-4-nitrophenol chromophore group containing maltoheptaose (1.24 and 0.64 mM, respectively), in spite of the high number of aromatic residues near the active site of HSA. The results of our ITC-based measurements are correlated well with data obtained with spectrophotometry.

ITC was also used to characterize two known inhibitors, acarbose and glucopyranosylidene-spiro-thiohydantoin [2]. Based on the rate values the kinetic constants (IC_{50}, K_i) and inhibition types were determined on the classical and a recent published way [3]. All the curve fittings were performed by Grafit® program. IC_{50} values and the determined types of inhibition were in good agreement with the information found in literature.

This work is a preliminary study which forms the part of an investigation including more enzymes and inhibitors. The optimized methods are well applicable, thus it can serve as a good basis to our further examinations and can be a real alternative to photometric methods.

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P-41

SERUM ALBUMIN OXIDATIVE MODIFICATION IN THE PRESENCE OF FATTY ACIDS

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Human serum albumin (HSA) is a multi-functional component of blood plasma. HSA is responsible for binding of drugs and xenobiotics. It is sensitive to the toxic effects of oxidative stress, which causes a lot of albumin modifications. Reactive oxygen species (ROS) result in oxidation of serum albumin, which causes a number of structural changes in the spatial structure, may influence the binding and cause significant drug interactions.

The aim of the study was to evaluate the effect of oxidation on the structure of albumin, both in the presence and absence of fatty acids, using absorption and fluorescence spectroscopy. Changes of albumin conformation were examined by comparison of modified (oHSA) and nonmodified human serum albumin (HSA) absorption spectra, emission spectra and their second derivatives, red-edge shift (REES) and synchronic spectroscopy. Modification of free thiol group in the Cys residues in HSA was quantitatively determined by the use of Ellman's reagent. Studies of absorption spectra indicated that changes in the value of absorbance associated with spectral changes in the region of 200 to 250 nm involve structural alterations in peptide backbone conformation. Synchronic fluorescence spectroscopy technique confirmed changes of position of tryptophanyl and tyrosyl residues fluorescent band caused by chloramine T (CT). Moreover analysis of REES effect allowed to observe structural changes by CT in the region of the hydrophobic pocket containing the tryptophanyl residue.

This work was supported by grants KNW-2-008/N/5/N, KNW-2-O15/N/6/K and KNW-1-034/K/6/0 from Medical University of Silesia, Katowice, Poland. Calculations have been carried out using resources provided by Wroclaw Centre for Networking and Supercomputing (http://wcss.pl), grant No. 382.

P-42

DESIGN, SYNTHESIS AND BIOLOGICAL EVALUATION OF NEW SALICYLAMIDE DERIVATES AS ANTI-CANCER AGENT

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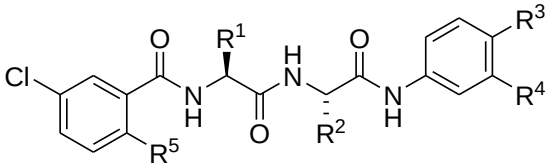
Cancer is one of the potentially fatal disease, which is characterised by uncontrolled division of group of cells leading to metastasis and invasion to adjacent tissue. Although many chemotherapeutic agents are in clinical use, synthesis new anticancer agents with less side effect and increased selectivity is still ongoing area of interest in medicinal chemistry. In drug discovery, several beneficial properties have been attributed to substituted salicylamide derivatives possessing diverse therapeutic activities such as antimicrobial,[1] antifungal,[2] or antimitotic and antiplaque agents.[3] Recently, our group successfully introduced substituted 2-hydroxy-*N*-(arylalkyl)benzamides (diamide) with interesting antiproliferative properties.[4]

In the course of our ongoing search for the new bioactive salicylamides molecules with significant antiproliferative activities, we design, synthesized and characterized a novel triamide derivates containing functionalized salicylic moiety and neutral optically pure amino acids (L-Leu and L-Phe) eventually dipeptide (see Fig. 1. for general structure). The diamide resp. triamides moieties were evaluated for their cytotoxicity against K562 and MCF7 cell line, whose IC50 values reached the single digits micromolar range.



R^1, R^2 = Amino acids, R^3 = Halogens,
R^4 = H, Halogens, R^5 = O-Benzyl, OH

Fig. 1 General structure of triamide

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P-43

IRON CHELATORS IN PHOTODYNAMIC THERAPY

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Photodynamic therapy (PDT) is a promising and developing approach in the treatment of cancer. The basis of photodynamic therapy is combined action of a photosensitizer, light and molecular oxygen within malignant tissue. Under these conditions, administration of the photosensitizer (PS) to the tumor and local exposure to light of a specific wavelength can lead to a series of photochemical reactions and consequently the generation of singlet oxygen and reactive oxygen species (ROS) [1]. Accumulation of ROS may cause induction of protein damage, DNA disruption, lipids peroxidation and consequently - triggering of apoptosis. Currently, the combination therapy is growing approach to increase the overall therapeutic efficacy of PDT. The basis of the combination therapy is the combination of two or more drugs, that can exert preferably additive or synergistic effects [2]. In our group, the promising results were obtained when novel thiosemicarbazones derivatives (TSC) were used in combination with 5-aminolevulinic acid (ALA) which is precursor in ALA-PDT treatment [3].
Recently we focused deeper on the interactions of novel highly active thiosemicarbazones with known PS - chlorine and temoporfin (Foscan) in combined PDT. We performed an *in vitro* assay of cell viability on human colon cancer cell lines (HCT116 +/+) to examine the dark- and photo-toxicity effects of the drugs (TSC and PS) alone and in combination, respectively. Accumulation sites for those drugs were evaluated in co-localization experiments on confocal scanning microscopy. In addition, we measured the production of singlet oxygen, change of expression of SOD and CAT as well as lipids peroxidation by TSC, PS and combination thereof as major factors leading to the apoptosis induction.

The reported studies are financial supported by the Polish National Center for Science (NCN, grant no 2014/13/D/NZ7/00322).

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P-44

STRUCTURE – ANTIMICROBIAL PROPERTIES EVALUATION OF PHENYLCARBAMIC ACID DERIVATIVES CONTAINING *N*-ARYLPIPERAZINE SCAFFOLD

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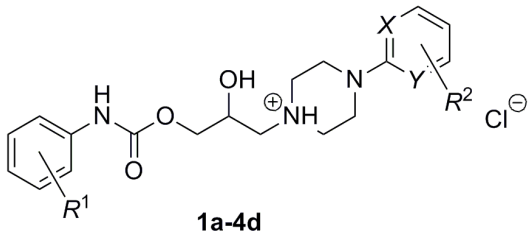
Antimicrobials, particularly antibiotics (ATBs), have been a mainstay of modern medicine for the last eight decades. On contrary, number of infections caused by multidrug-resistant bacteria is increasing globally, and the spectre of untreatable infections is becoming a reality. At least some clinical isolates of many pathogenic bacterial strains – *Mycobacterium tuberculosis, Neisseria gonorrhoeae, Enterococcus faecium, Staphylococcus aureus,* methicillin-resistant *S. aureus*, *Klebsiella pneumoniae, Acinetobacter baumannii, Pseudomonas aeruginosa,* carbapenem-resistant *Enterobacteriaceae*, and some species of *Salmonella* and *Shigella* – are now resistant to most ATBs. In other words, multidrug-resistant bacteria and yeasts currently remain one of major sources of global morbidity and mortality, especially among patients with underlying immune suppression [1-3]. Following given, current research has been focused on structure–antimicrobial properties investigation of phenylcarbamic acid derivatives which salt forming fragment has been formed by privileged *N*-arylpiperazine moiety. The spectrum of *in vitro* tested strains of microorganisms has been covered by *Staphylococcus aureus* ATCC 29213, methicillin-resistant *S. aureus* 63718, *Escherichia coli* ATCC 25922, *Enterococcus faecalis* ATCC 29212, *Candida albicans* CCM 8261, *C. parapsilosis* CCM 8260 and *C. crusei* CCM 8271, respectively. Possible impact of (i) electronic and steric properties of the substituents attached to lipophilic (the substituent R^1) and salt forming fragment (R^2), (ii) (hetero)aromatic system presence, (iii) lipohydrophilic features of the molecules **1a**-**4d** on their antimicrobial efficiency has been discussed.



1a-4d

R^1 = 2-/3-/4-OCH_3, 2-/3-/4-OC_2H_5
X, *Y* = CH, N
R^2 = 2-CH_3, 3-CF_3, 4-F

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P-45

SYNTHESIS AND DETERMINATION OF PHYSICOCHEMICAL PROPERTIES OF NEW ARYLCARBONYLOXYAMINOPROPANOL DERIVATIVES CONTAINING N-PHENYLPIPERAZINE MOIETY

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This contribution is focused on the synthesis and determination of the physico-chemical properties of new derivatives of arylcarbonyloxyaminopropanoles with substituted 1-phenylpiperazine moiety in the basic part of the molecule, that were designed as soft drugs in accordance with the concept proposed by N. Bodor [1]. The pharmacokinetics in the human body and the bioavailability of the drugs are described by various physico-chemical properties, e.g. ionization constant (pK_a), distribution coefficient (log D) or lipophilicity (log P) [2].

The studied compounds, 3-(4-arylpiperazin-1-yl)-2-hydroxypropyl 4-alkoxyethoxybenzoates, were prepared as hydrochloride salts by 6-step synthesis and their structure and purity were verified by available methods of instrumental analysis (1H FT-NMR, 13C FT-NMR, FT-IR, TLC, HPLC). The lipophilicity index (log k) was determined by means of RP-HPLC and ionizability (pK_a) was determined by means of CZE. The experimentally determined values have been compared with the values calculated by different prediction programmes. The final products have not been described in literature so far and are expected to have β-adrenolytic, α-adrenolytic and ultrashort effect as the drugs with similar structural features act in scientific investigation or in clinical practice [3-6]. The compounds will be tested for their biological activity.

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GOLD NANOPARTICLES AND THEIR CONJUGATES – NEW METHODS OF BEATING CANCER

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Gold nanoparticles (GNPs) are attractive and promising biocompatible materials due to their special physical and chemical properties [1]. There is more and more research where GNPs are used in the medical imaging or in the cancer therapy [1,2]. GNPs are currently being explored as contrast agents for anti-cancer PTT (photothermal therapy) because their absorption cross sections and photostabilities are far superior to traditional molecules used in PTT [1].

Although GNPs can act alone as a drug, nowadays the most interesting and promising approach to the usage of GNPs is their conjugation with many types of drugs or biomarkers [1]. One of such biomolecule can be antibody, which can help to supply the drug directly to the tumour. GNPs can be also conjugated with imaging agents or even nucleic acid sequences. Since early 2000's many examples of chemically [3] and biologically [4] functionalized GNPs have been described in the literature; however, these conjugates are very often instable. Although GNPs are rather stable in period of many months, modified nanoparticles – conjugates GNPs to drug, dye or antibody are often instable in a long period, particularly in the presence of high salts and proteins, which is the essence of human body [2].

Thiosemicarbazones (TSCs) are an interesting class of ligands that show a diverse range of biological activity such as anti-cancer, anti-fungal and even anti-viral effects. Among them di-2-pyridylketone 4,4-dimethyl-3-thiosemicarbazone (Dp44mT) is one of the most promising TSC. Many papers have shown its high anti-cancer activity proved by *in vitro* and *in vivo* examinations [5-6]. Dp44mT was shown to overcome multidrug resistant, which is a major obstacle in cancer treatment [5].

Our team have been developing nanotechniques, the usage and production of nanomaterials for many years. Furthermore, we synthesise various compounds (also TSCs) which have anticancer activity and can be developed into novel anticancer treatment. Therefore, it is not surprising that we decided to combine these two paths of our studies.

Our purpose is to obtain stable GNPs with diameter less than 50 nm because these GNPs have the most appropriate physical and biological properties [1]. We want to determine size, shape, dispersity and stability of the obtained GNPs. The next step will be coupling nanoparticles with our potential drugs. These bioconjugates will be examined in the *in vivo* biological studies.

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HOFMEISTER-ACTIVE SALT INDUCED CHANGES IN THE FIRST SOLVATION SHELL OF THE TC5B MINIPROTEIN

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The tc5b miniprotein has been used on the course of both theoretical and experimental investigations, so far. This molecule is known for its well-defined secondary and tertiary structure, providing an ideal model system of globular proteins. Beside the stable spatial structure of the tc5b miniprotein there are structure-stabilizing factors present, such as the set of hydrophobic interactions formed within its hydrophobic core, or the salt bridge formed between the Asp9 and Arg16 residues. These interactions are likely to be influenced by the contact interactions of Hofmeister-active ions. Our previous investigations [1] demonstrated that kosmotropic fluoride and chaotropic perchlorate ions have dissimilar properties at the tc5b miniprotein-solvent interface in accordance with experimental findings. The accumulation of Hofmeister-active ions turned out to have a surface-exposed charge driven nature, which was detected by using radial distribution functions. Furthermore, the investigated salts induced opposing changes regarding the average reorientation time of water molecules located in this interfacial region. In this present theoretical framework we focus on a more detailed mapping of these solvation characteristics in terms of protein-ion and "near-surface" water-water interactions.
The molecular dynamics (MD) simulations were carried out by the using the GROMACS program package. For the evaluation a 50 ns long NPT dynamics was done, with 2 fs integration time steps, the coordinates were saved in every 50^{th} step. The investigated system contained one tc5b molecule solvated by TIP3P water molecules in a cubic simulation box. Aside to the neat water case NaF and $NaClO_4$ salts were also added in 1 M final concentration in the other two considered systems.
The aforementioned radial distribution functions do not provide information about the features of the protein-ion interaction. Addressing this is issue was done by the calculation of distance distribution of the closest ions. By applying this descriptor the types of possible interactions could be classified: direct protein-ion and one- or two water shell intermediated ones. Major differences were identified between chaotropic and kosmotropic ions in terms of protein-ion interaction types: the former ones have increased propensity for direct interaction, while the latter ones mainly tend to preserve their first- or even second solvation shell. This feature can be analysed for the whole surface and for selected residues, as well. Calculations regarding residues participating in important structure-stabilizing interactions show different characteristics of protein-ion interactions. Furthermore, "near surface" water properties were also modified due to the addition of Hofmeister-active salts in terms of local water O atom density. Moreover, in the first solvation shell of the tc5b miniprotein both the average water number and the average HB number formed between water molecules are changed.

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FREE ENERGY PROFILE AND FLUCTUATIONS AT THE PROTEIN-WATER INTERFACE

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The complexity of the Hofmeister effect motivated the development of many theoretical treatments, one of them is the interfacial tension concept (ITC) introduced by Dér and co-workers [1]. The ITC was successfully applied to a variety of systems, describing both kosmotropic salting out and chaotropic salting in effects and was useful in interpreting the Hofmeister effects (HE) on protein conformation. In this concept the salt-induced changes in the features of the protein-solvent interface are assumed to play a central role. These changes are influencing the solvation free-energy profile of the protein and have a direct link to the conformational fluctuations.

In this present work we address the ITC theory by a molecular dynamics (MD) simulation approach using the tc5b miniprotein as a model system. In our investigations, the Amber ff99SB-ILDN force field and the TIP3P water model were used in three 600 ns long replica exchange molecular dynamics (REMD) simulations carried out with the Gromacs simulation package. The model system contained a single tc5b molecule and approximately 2200 water molecules in a cubic box, while NaF and $NaClO_4$ salts were added to the solution in 1 M final concentration in the other considered cases. The REMD simulation ran on 32 different temperatures ranging between 300 K and 450 K, exchange attempts were made in every 2000^{th} step. Data for evaluation was collected from the last 400 ns long part of the simulation.

In a previous paper [2] by using ITC an effective surface tension change arising from Hofmeister-active salt addition was calculated, besides alterations of the protein-solvent interface was described. However, this interfacial region could be further investigated with respect to free energy profiles and fluctuations of ion number and side chains. One of the main assumptions of ITC for the description of Hofmeister effects on protein conformations is the existence of a U-shaped free-energy landscape. The results of free energy calculations both in the presence and absence of ions are proved to be in line with the main assumptions of this theory. On the other hand, pronounced local differences were found for the “near-surface” ion properties, in accordance with their position in the Hofmeister series. The kosmotropic and chaotropic ions show different propensity for accumulation to the interfacial region and have contrary fluctuation features. Average side chain heavy atom root men square fluctuations (RMSF) are also modified by the presence of ions. Moreover, close correlation was identified between the average side-chain RMSF and local ion gathering features.

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PRENYLATED FLAVONOIDS – RELATIONSHIP BETWEEN STRUCTURE AND ANTIMICROBIAL ACTIVITY

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Different structurally modified prenylated/geranylated flavonoids were isolated at the Department of Natural Drugs UVPS Brno from fruit of *Paulownia tomentosa* and root bark of *Morus alba* and tested for the antibacterial activity against clinical isolates of methicillin resistant *Staphylococcus aureus* (MRSA). According to results obtained we tried to assume basic relationships between antibacterial activity and structure modifications of flavonoids.

A hydroxylation at the C-5, C-7 and C-4´ position is determinant for the anti-MRSA activity of flavanones. The 3´-methoxy-4´-hydroxyphenyl ring B and 3´-methoxy or 3´, 5´-dimethoxy substitution probably increases antibacterial activity due to the planar structure of molecule. Contrary to this presumption; compounds had no significant anti-MRSA activity when their geranyl is modified. We suppose that the substitution of geranyl side chain with carbonyl, hydroxyl and methoxyl decreases the activity. The cyclization between C-6 geranyl and C-7 hydroxyl group also diminishes the activity. Hydroxylation at the C-3 of flavonol has probably beneficial effect on the activity. MIC value could be also influenced by length of side chain and number of prenyl groups. It is supposed that geranyl substitution increases lipophilicity of the flavonoid substance and thereby penetration to the cell membranes. Structure disposing of C-6 unmodified geranyl and hydroxylation at C-5 and C-7 is not able to inhibit the bacteria growth if lacking the B-ring. C-4´ position should be modified with hydroxy- or methoxy-group without considerable changes in the antibacterial activity.

In connection with these findings, prenylated/geranylated flavonoids would be helpful to propose therapeutic strategy for the treatment of bacterial infections and also in a design and a synthesis of different antibacterial agents.

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IN VITRO COMBINATORY ANTIMICROBIAL EFFECT OF JUGLON WITH OXACILLIN, TETRACYCLINE AND CIPROFLOXACIN AGAINST *STAPHYLOCOCCUS AUREUS*

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Juglon (5-hydroxy-1,4-naphthoquinone), naturally distributed among *Juglans* species, has been reported to have antimicrobial activity against a wide range of microorganisms. In this study, juglon was examined for its combinatory antimicrobial effect with oxacillin, tetracycline and ciprofloxacin against strains of *Staphylococcus aureus*, including its methicillin-resistant strain. Minimum inhibitory concentrations were determined through the broth microdilution method. The combinatory effect was evaluated according to the sum of fractional inhibitory concentration (ΣFIC) indices. Synergy was obtained for combination with oxacillin and tetracycline against two strains of *Staphylococcus aureus* (ΣFIC range 0.1–0.5), including its methicillin-resistant strain.

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STEREOCHEMICAL DISCRIMINATION IN THE SYNTHESIS OF β-PEPTIDE OLIGOMERS: ORIGIN OF HOMOCHIRALITY

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Foldamers are artificial self-organizing system, of which adopt well-defined three-dimensional structures. [1] The most prominent representatives of these oligomers are the β-peptides. The rules concerning the fine-tuning of the secondary structures of β-peptides are well known and it has been stated, that the β-peptides can construct helical, strand or turn structures. Importantly, the helices are more stable than those of natural α-peptidic helical structures. Moreover, helices of β-peptides mimic the overall geometry of the natural α-peptides. We wanted to investigate (*i*) whether this strong propensity for secondary structure (helix, strand) formation can be exploited in the stereochemically discriminated synthesis of β-peptides, as it is in the reference case of α-helical structure, [2] and (ii) we wanted to gain some insights into the origin of biological homochirality.

For this purpose, we synthetized homooligomers 1-4 (Figure 1), in a continuous-flow solid phase peptide synthesizer (CF-SPPS) using the Fmoc technique. The chain-length of the oligomers varied between 3-6 units. On these homooligomers the coupling of racemic Boc protected amino acids in a solvent system consisting of CH_2Cl_2/DMF in the presence or absence of H_2O; was performed and the diastereoselecitvity of the coupling reaction was investigated by means of HPLC-MS.

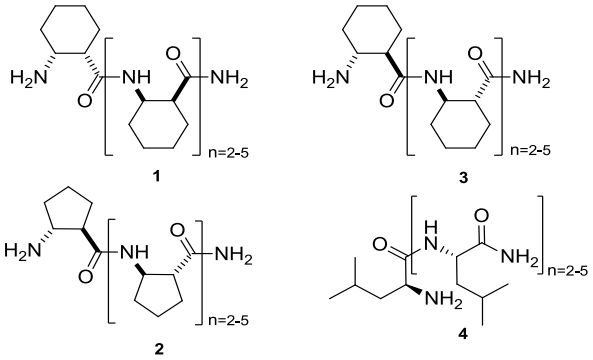

Figure 1. The investigated model compounds

The preliminary results show, that there is a strong propensity for homochiral homooligomer formation. Furthermore, we found that the diastereoselecivity of the synthesis increases in the presence of water which can be explaining due to the water induced self-association of peptides. [3] Noteworthy, the diastereoselecivity was chain-length dependent.

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PROPERTIES OF POLYLACTIDE COMPOSITES STABILIZED WITH NATURAL ANTIOXIDANTS

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1. Introduction

Nowadays, polymer materials are common, use of many areas. Unfortunately, short life time of these products generates a large amount of onerous waste. Maybe biodegradable polymers are the solution. Which are environmentally friendly and harmless to health. Biopolymers have advantageous properties, but require stabilization. During processing, storage and using polymer materials may to happen many process in their structures, for example this are degradation, depolymerysation, destruction, cross-linking. Factors bring on this reactions are lighting, high temperature, shear stress, chemical substances, oxidation. The addition of stabilizers can prevent or inhibit ageing in polymers. This solution allow to extend using lifetime and preserve satisfactory properties of polymer materials. These materials should be biodegradable in its entirety [1-2].

2. Experimental

We have explored influence of curcumin, chalcone and hesperidin - natural antioxidants on the properties of polylactide (PLA) and polyhydroxyalkanoate (PHA) composites Sample preparation was carried out by using a laboratory mixing mill but in the second method was used solvent-impregnation process. The *UV aging, weathering, thermooxidation* behavior of PLA and PHA samples was tested. Oxidation of the polymer matrix was evaluated by UV-visible, FTIR spectroscopy and DSC. Selected composites was subjected to biodegradation process, change colours and contact angle tests. Stabilization against ageing has been estimated by studying the morphology changes of the exposed surfaces by UV -Vis spectroscopy. The surface energy and chemical changes have been assessed by using FTIR and contact angle measurement. Results show that curcumin provides rewarding results in stabilizing against oxidation processes.

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DESIGN AND DRUG-LIKE PROPERTIES OF NEW 5-METHOXYSALICYLALDEHYDE BASED HYDRAZONES WITH ANTI-BREAST CANCER ACTIVITY

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Hydrazones derived by condensation of salicylaldehyde and different acid hydrazides possess high antiproliferative activities [1-3]. Various derivatives of salicylaldehyde have been used in order to discover new bioactive compounds with high antitumor activity and minimal toxicity [4-7]. The inserting of the methoxy group in the molecule of salicylaldehyde strongly influences the biological activity of the hydrazones.

Novel benzoylhydrazones were designed and synthesized by condensation of 5-methoxysalicylaldehyde and benzhydrazides with different substituents at the 4^{th} position. The structures of the new derivatives were confirmed by elemental, IR, ^{1}H-NMR and ^{13}C-NMR spectroscopy. The molecular properties of the compounds, important for drug pharmacokinetics and biodisposition in the human body, were assessed with the Lipinski's rule of five. *In silico* evaluation of the value of logP and the remaining parameters of drug similarity, as well as the topological polar surface area and absorption percentage, were used only as a first step in the study. The investigated 5-methoxy-derivative hydrazones were further tested for *in vitro* cytotoxicity on three leukemic and two breast cancer human cell lines using the MTT-dye redcution assay. The bioassay demonstrated that the compounds exhibited concentration-dependent antiproliferative activity at low micromolar concentrations against the investigated human cell lines. The solid tumor-derived cell lines were generally more sensitive to the effects of the hydrazones with IC_{50} values ranging 0.91 μmol/l - 12.07 μmol/l. The results confirm that all compounds are more potent than the standard drug melphalan and have appropriate properties as potential drug candidates.

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PHYSICOCHEMICAL PROFILING OF NEW 2-HYDROXYPROPYL-4´-ALKOXYBENZOATE DERIVATIVES

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Antagonists of β-adrenergic receptors are widely used in therapy of many cardiovascular indications because of their positive effects on cardiovascular system. Moreover, newly synthesized compounds have also other beneficial effects such as vasodilatory activity or ultrashort effect that predetermine them to improve haemodynamic and metabolic profile, preventing atherosclerosis complication or ischaemia-reperfusion injury and using in urgent cases [1].

The physicochemical parameters such as lipophilicity (log*P*), distribution coefficient (log*D*) and dissociation constant (pK_a) of a pharmaceutical substance belong to crucial properties used to estimate the absorption, distribution, metabolism, and excretion (ADME) of compounds in biological systems [2]. Ionization constant characterizes the charge state of an analyte at particular pH of its environment. Partition coefficient and apparent partition coefficient refer to chemical equilibrium of partitioning of all charge-state forms of analyte between two immiscible liquids.

In the present work log k_w^{app}, a lipophilicity index, and pK_a of 18 newly synthesized 2-hydroxypropyl-4´-alkoxybenzoate derivatives, with potential α and β-adrenolytic properties are determined. In the case of log k_w^{app} determination, isocratic retention factors were measured by RP-HPLC method at pH 7.4 and extrapolated to zero organic phase concentration. The pK_a values were determined from dependence of effective mobility of the analyte measured by means of capillary electrophoresis (CE) on pH of the background electrolyte using non-linear regression analysis.

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FTO INHIBITORS AS POTENTIAL THERAPEUTIC AGENTS FOR ALZHEIMER'S DISEASE

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Genetic variation in FTO has been linked with Alzheimer's Disease (AD) in human studies [1], and patients with variant FTO are also associated with decreased brain volume [2]. FTO is a highly expressed 2-oxoglutarate utilizing enzyme in the brain involved in the demethylation of RNA N6-methyladenosine (m6A) residues [3]. Novel FTO inhibitors were designed and synthesized [4]. Neuroblastoma cells were cultured and treated with vehicle or a novel FTO inhibitor. Following vehicle or drug treatment, mRNA was isolated, degraded, and A,G,C,T and m6A were quantified by HPLC. Neuroblastoma cells were also cultured and treated with vehicle or FTO inhibitor, total mRNA was isolated, labeled with Cy5, and analyzed by microarray and by Digital Gene Expression. Numerous microRNAs were either up-regulated or down-regulated by the novel FTO inhibitor. Analysis of modulated mRNA includes protein folding chaperones, energy associated mitochondrial proteins, and SNORDs. In conclusion, FTO variation has been identified as a risk factor for AD. A novel blood-brain barrier penetrating FTO inhibitor has demonstrated the ability to increase cellular m6A residues, and subsequent modulation of microRNA. The pattern of microRNA modulation suggests that mitochondrial transport may be altered in treated cells relative to control. Future studies investigating the modulation of microRNA in CNS cell types may be useful in evaluating the potential of a FTO inhibitor in CNS disease states, including AD.

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2-SUBSTITUTED-1,3-THIAZOLIDIN-4-ONES AS POTENTIAL ANTIFUNGAL DRUGS

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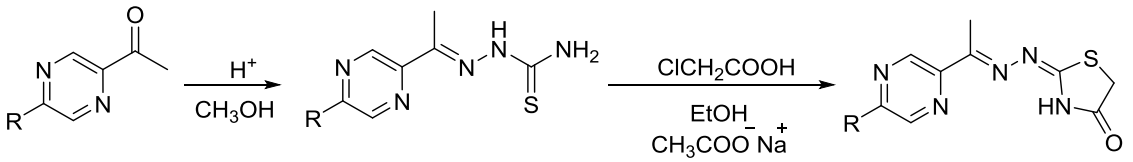
Thiazolidin-4-ones belong to privileged structures in designing and synthesis of novel drugs. Their properties and biological effects were described in several excellent reviews [1-4]. As a part of our continuing efforts to study compound comprising both pyrazine and thiazole moiety [5], a series of 2-{[1-(5-alkylpyrazin-2-yl)ethyliden]hydrazono}thiazolidin-4-ones was prepared (Scheme 1).



R = H, propyl, isopropyl, butyl, isobutyl, pentyl, hexyl, benzyl, 4-methoxybenzyl

Scheme 1

Antifungal activity of the compounds was evaluated against eight fungal organisms by the modified microdilution broth CSLI standards. The organisms examined included *Candida albicans* ATCC 44859 *Candida tropicalis* 156, *Candida krusei* E 28, *Candida glabrata* 20/I, *Trichosporon asahii* 1188, A*spergillus fumigatus* 231, *Lichtheimia corymbifera* (formerly *Absidia corymbifera*) 272, and *Trichophyton interdigitale* (formerly *T. mentagrophytes*) 445. Most compounds exhibited very good *in vitro* antifungal activity (MIC range = 3.9–125 μmol/l). Their potency against most fungal strains (except *C. albicans*) was much better than that of fluconazole, and in some cases better than potency of voriconazole.

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PROTOPORPHYRIN IX AFFINITY TO HUMAN SERUM ALBUMIN

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Ligands are bound preferentially with carrier proteins in blood, mainly with human serum albumin (HSA). The binding of medicines to HSA determines their biological effects and adverse reactions. The derivative of heme, protoporphyrin (Pp) IX, is a hydrophobic photosensitizer widely used in the photodynamic diagnosis (PDD) and photodynamic therapy (PDT) of various malignant disorders. The goal of present studies was to investigate the mechanism of Pp IX binding to HSA macromolecule. The formation of complex between Pp IX and HSA has been studied by molecular docking and confirmed with absorption and fluorescence spectroscopy. Computational experiment was performed using the $PLANTS_{PLP}$ docking algorithm implemented in the CLC Drug Discovery Workbench software (version 2.5). Docking results were graphically elaborated using the Accelrys Discovery Studio visualizer (version 4.1) [1]. The conformation of Pp IX molecule was energy-minimized using the Austin Model 1 (AM1) semi-empirical method. The X-ray structure of HSA required for docking simulation were downloaded from the Protein Data Bank (1AO6.pdb) [2].

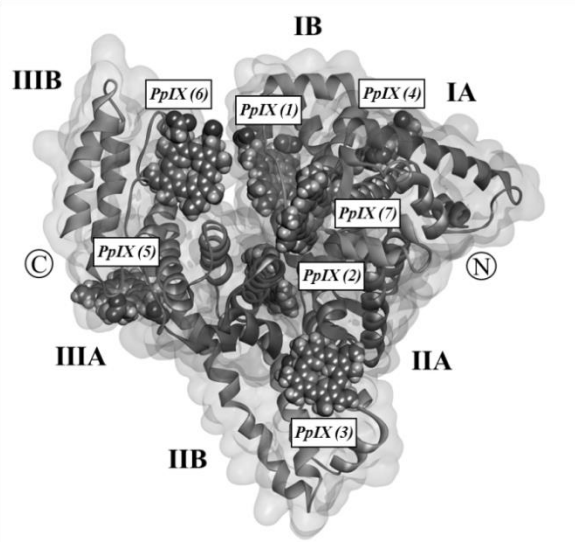

Figure 1. The macromolecule of HSA complexed with Pp IX molecules. Each subdomain of HSA is marked according to the model proposed by Carter and Ho [3].

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PREPARATION AND CHARACTERIZATION OF LIPOSOMES AS THERAPEUTIC DELIVERY SYSTEMS

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For more than thirty years, extensive research has been performed on new techniques for obtaining liposomes and on their application in targeted delivery of drugs and other substances to specific tissues in the body. Liposomal vesicles, although they themselves do not possess medicinal properties, can be used to transfer substances, which can significantly improve the condition of the body or preserve life. Liposomes incorporating drugs are mainly used in the treatment of cancerous tumors, diabetes, rheumatic diseases, enzymopathy, disorders associated with metal accumulation, and the like [1-3]. Understanding the interactions which occur between nanomaterials and biomolecules is one of the most important issues in nanotechnology. Determining the properties of nanoparticles obtained through the use of novel methods and defining the scope of their application as drug carriers has important practical significance. Nanoparticles containing methotrexate and cytarabine obtained by a modified reverse-phase evaporation method (mREV) were studied using differential scanning calorimetry (DSC), Fourier transform infrared spectroscopy (FT-IR) and nuclear magnetic resonance (NMR). These techniques have proven to be a very powerful tool in studying the structure and dynamics of phospholipid bilayers.

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SESQUITERPENE DERIVATIVES AND PHENOLIC CONSTITUENTS FROM *ARTEMISIA ALBA* TURRA GROWING IN NORTH-EAST ITALY

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Artemisia alba Turra is an Euri-Mediterranean plant belonging to the Asteraceae family and used in Veneto (North-East Italy) as traditional medicine for the treatment of various diseases. *Artemisia* have been used all over the world in the treatment of various diseases such as malaria, fever, hepatitis, helminthiasis, cardiac and digestive problems, neurodegenerative disorders, cancer, inflammation and infections by fungi, bacteria and viruses [3]. The phytochemical knowledge, is limited but this specie is known for the production of unusual sesquiterpene[1,2]. In the present paper the phytochemical composition of a tincture obtained from the aerial parts of *A. alba* growing in Veneto is presented. Extensive chromatographic separations lead to the isolation of four new sesquiterpene derivatives whose structures were elucidated by 1D and 2D NMR experiments and MS spectrometry. New compounds are 5-methyl-3-[1-(5-methyl-6-oxabicyclo[3.1.0]hex-2-yl)ethyl]-4-oxohexanoic acid (1), 1-[3-(1-hydroxy-2-methylpropyl)-2-methyl-3-(propan-2-yl)oxiran-2-yl]-3-methylbutan-2-one (2), 3-hydroxy-3-methyl-5-(3-methyl-4-oxocyclopent-2-en-1-yl)hexanoic acid (3), 5,5-dimethyl-2-(1-((5S)-5-methyl-5-vinyltetrahydrofuran-2-yl)ethyl)-2,5-dihydrofuran-2-ol (4). Furthermore, the flavonoid composition and volatile constituents of the tincture of *A. alba* were studied by HPLC-MS^n, and GC-MS, respectively showing the presence of quercetin, isorhamnetin and kaempferol glucosides in the polar fraction while 32 volatile components were identified in the tincture, mainly monoterpenoids and sesquiterpenoids.

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SYNTHESIS OF PRENYLATED STILBENOIDS WITH POTENTIAL ANTI-INFLAMMATORY ACTIVITY

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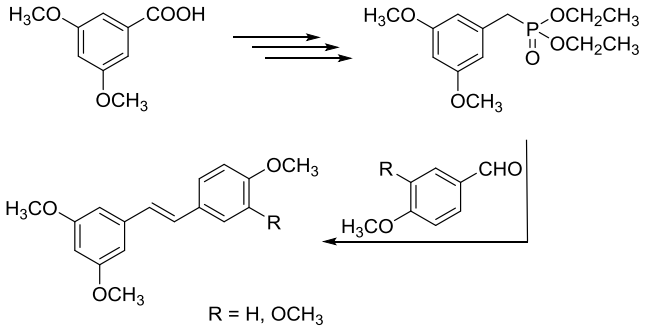
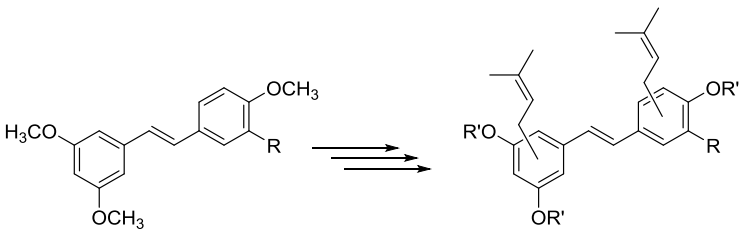
Stilbenoids are a class of plant phenolic compounds with the general scaffold of stilbene. They contain two hydroxylated aromatic rings connected with ethylene bridge [1]. They are distributed in higher plants in the form of monomers, oligomers or as glycosides [2]. A large number of stilbenoids have been investigated for their diverse biological activities including antitumor, antimicrobial, cardio protective properties, antiplatelet aggregation, antioxidant and anti-inflammatory effects. Prenylated stilbenoids exhibit plant pathogen defense properties and pharmacological activities with potential benefits to human health. Increased lipophilicity of prenylated stilbenoids due to the isoprenyl group attached to the stilbene skeleton could offer additional health advantages to these compounds which are often associated with better penetration through cell membranes. An increase in lipophilicity often correlates positively with increased biological activity within different groups of compounds of similar structure [3]. The noticeable *in vitro* anti-inflammatory activity of prenylated 2-arylbenzofurans has been validated recently [4]. Therefore, we have focused our attention on the synthesis of selected prenylated stilbenoids with potential anti-inflammatory activity.



R = H, OCH_3

The multistep synthesis of protected stilbene intermediates included selective reduction of carboxylic function with Red-Al, chlorination and subsequent Michaelis-Arbuzov reaction followed by the base catalysed Horner-Wadsworth-Emmons reaction with the picked methoxybenzaldehydes. Several reaction conditions have been tested for prenylation of protected stilbene intermediates. The total and selective deprotection of hydroxy groups has been carried out in various conditions. Prepared compounds will be tested *in vitro* for their anti-inflammatory activity.



R = H, OCH_3 R = H, OR' R' = H, CH_3

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INFLUENCE OF p53 CONFORMATION ON RESPONSE TO CYTOTOXIC TREATMENT IN GLIOBLASTOMA AND COLON CELL LINES

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TP53 is mutated in more than 50% of tumor cases and glioblastoma multiforme (GBM) is the most common primary brain tumor in adults and characterized by rapid growth, invasion and resistance to chemo-/radiotherapy. p53 is a tumor suppressor that reacts to DNA damage or oxidative stress by transactivation of target genes involved in cell cycle arrest, DNA repair and apoptosis. Expression of mutant p53 proteins is associated with increased cancer resistance to chemo- and radiotherapy and tumor progression. Intriguingly, the status of p53 may have a great importance on the composition of treatment strategy. In previous studies it was found that zinc treatment induced the transition of mutant p53 protein (R175H) into a functional conformation. Restoration of wtp53 function induces growth arrest or apoptosis depending on the cell lines [1-3].

Protein p53 often occurs in tumor cells in much higher concentrations than in healthy cells. This is mainly due to mutations in *TP53* gene, which result in destabilization of protein conformation and consequently partial devaluation of innate p53 decay mechanisms. The accumulation of mutant p53 is then reflected in dysregulation of genes promoting proliferation, survival and resistance to cytostatics [3,4] sometimes posing obstacles to conventional therapy.

Utilizing several glioblastoma and colon cancer cell lines, zinc ion, chemical agent restoring p53 conformation [4,5] and commonly used cytostatic drugs we investigated the combinatorial effect on p53 and its target genes at both protein and mRNA levels. Combining therapies seems to be a viable strategy to circumvent drug resistance.

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INTRACELLULAR AND EXTRACELLULAR RETINOID-LIKE ACTIVITY OF WIDESPREAD CYANOBACTERIAL SPECIES

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Cyanobacteria are common and potentially harmful inhabitants of freshwater worldwide. They are producers of various types of bioactive compounds, which are toxic and they may cause animal death, embryotoxicity, teratogenicity and adversely affect human health. Recent studies indicate that some phytoplankton species can produce retinoid-like compounds that could contribute to some of these effects. Retinoids comprise a family of polyisoprenoid lipids which include vitamin A and its natural and synthetic analogues. These substances act by binding to retinoic acid receptors (RAR), and regulate proliferation, differentiation, apoptosis, cytokine production, gut mucosal immunity and malignant transformation of cells. The aim of our work was to evaluate the variability in production of retinoid-like compounds, which could be released into the environment, by selected widespread cyanobacterial species. We tested *in vitro* potential of extracts and exudates from laboratory-cultured species to induce responses mediated through retinoid acid receptor (RAR) using transgenic murine embryonic carcinoma cell line, which contains reporter luciferase gene under the control of retinoic acid-responsive element. The detailed investigations focused on commonly occurring cyanobacterial species with tendency to form massive water blooms, one coccal (*Microcystis aeruginosa*) and four filamentous cyanobacteria (*Aphanizomenon gracile, Limnothrix redekeii, Cylindrospermopsis raciborskii and Planktothrix agardhii)*. We analysed 18 extracts and exudates of the five different cyanobacteria. We found activation of retinoid receptor after exposure to intracellular samples from all studied cyanobacterial species. The cyanobacterial exudates of all species except of *P.agardhii* also contained retinoid-like activity reaching up to over 6 µg/l in case of one cultivation of *L.redekeii*. We have recalculated total produced retinoid-like activity using extract and exudate data for each tested cyanobacterial species. The total retinoid-like activity of the five selected species ranged from 0.1 to several µg ATRA/g dry weight. The production of retinoid-like compounds was recalculated to biomass dry weight as well as to cell density. This enables to estimate the production in environmental biomasses characterized by cell density and thus assessment of risks of the produced retinoid-like compounds.

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EFFECT OF EXTRACTION SOLVENTS ON THE ANTIOXIDANT ACTIVITY OF SWEET CHERRY STALKS

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Cherry stalks (stems) have been used in alternative medicine in different parts of the world. Herbal teas made of sour or sweet cherry stalks are used as mild diuretic remedy and decoction to relief of renal stones, edema and hypertension[1]. It has been known that stalks posses high content of different phenolic compounds and strong antioxidant activity [2,3].

In this study the antioxidant and antiradical properties of stalks of six different sweet cherry (*Prunus avium* L.) cultivars (Burlat, Germendorf, New Star, Peter, sandor and Summit) extracted with four different solvents (70% acetone, 70% ethanol, 70% methanol and water) were determined. Antioxidant capacity of extracts of sweet cherry stalks were measured by five different assays (1,2-diphenyl-2-picryl-hydrazyl (DPPH) assay, ferric-reducing antioxidant power (FRAP) assay, 2,2'-azinobis-(3-ethylbenzothiazoline-6-sulphonic acid (ABTS) assay, total antioxidant activity (TAA) by phosphomolybedenum complex formation method and nitroblue tetrazolium (NBT)-superoxide dismutase (SOD) mimetic assay (NBT test). Another significant goal of this study was to determine total polyphenolic and total flavonoid content in extracts of sweet cherry stalks.

Differencies in the structure of phenolic compounds determine their solubility in solvents of different polarity. Therefore type of extraction solvent may have a significant impact on andtioxidant capacity and the yield of extraction polyphenols from plant material [4]. The highest contents of phenolic compounds and antioxidant activities were found in 70% acetone extracts, followed 70% methanol and 70% ethanol extracts. Among the investigated sweet cherry stalks, Sandor and Burlat cultivars contained the highest amounts of total polyphenolics and flavonoids. Total polyphenolics in stalks ranged from 38.25 (Sandor, acetone extract) to 10.57 (New Star, aqueous extract) mg gallic acid equivalents/g dry weight. The examined cultivars posses a high antioxidant capacity, and all measured phenolic groups were highly correlated with performed antioxidant assays. The genotype influence the extent of antioxidant and antiradical activity in sweet cherry stalks. Data on phenolic compounds investigated in this study, as well as the antioxidant activity of extracts of sweet cherry stalks cultivars could be valuable to the pharmaceutical and food industries for selection of cultivars rich in bioactive compounds and could be also valuable for producers in order to increase the biological value of the commercial products.

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SYNTHESIS AND SPECTROSCOPIC CHARACTERIZATION OF THIOSEMICARBAZONES BASED ON 4-(4-CYANOPHENYL)PIPERAZINE-1-CARBOTHIOHYDRAZIDE

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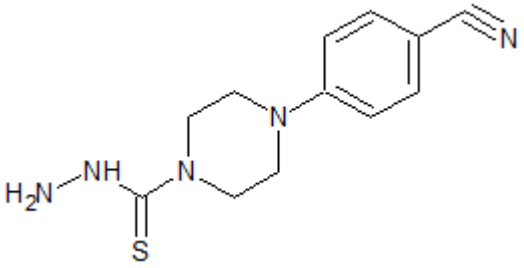
Thiosemicarbazones (TSC) and thiosemicarbazides are an important class of sulfur and nitrogen donor ligands, especially for transition metal ions. The presence of multiple donor atoms within the same chelator multiplying coordination modes and affects the properties of ligand and complexes.
This kind of compounds exhibits a wide range of medical applications, which include antitumor, antibacterial and antifungal activities. Some of them could be used as antitubercular drug and for the treatment of malaria [1-3].
Corresponding all of the biological properties of thiosemicarbazones, it is important to be able to synthesize new series of TSC which shows biological activities without any side effects [4].
During our work, 4-(4-cyanophenyl)piperazine-1-thiocarbohydrazide was prepared using a reflux method (2 h under reflux in ethanol) and eight thiosemicarbazones were synthesized using a microwave – assisted methodology, all of them are novel compounds.
For the preparing thiosemicarbazones we used obtained thiosemicarbazide and eight aldehydes. The reaction mixtures were irradiated in a scientific microwave reactor at 83˚C for 20 minutes at 50 W. As the environment of the reaction we used 5 ml of ethanol, and the two drops of acetic acid as a catalyst. This method permit to obtain products in high-purity and satisfactory yields after a short time. The structures of received thiosemicarbazides and thiosemicarbazones were fully characterized by Liquid Chromatography - Mass Spectrometry, ^{1}H- and ^{13}C-NMR spectroscopy and the purity were confirmed by using TLC and HPLC technique. TSC were characterized also by HMQC and COSY spectroscopic method.



4-(4-CYANOPHENYL)PIPERAZINE-1-CARBOTHIOHYDRAZIDE

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β-CAROTENE EFFECT ON REPRODUCTION AND ITS ANTI-CANCER EFFECT

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During the last two decades, it was shown that some specific nutrients play an important role in growth, reproduction and immunity. Among of these nutrients, BC (β-carotene) is required not only for maintaining vitality of the tissues in the reproductive tract but also for keeping the body in good health in general. Also there is a possible role of β-carotene as protective nutrient against cancer has been reported. As well other studies reported that β-carotene protects against lung cancer and probably against stomach cancer and it may also be protective against cancers of ovary, cervix, breast and other cancers except the cancers of colon or rectum. Feed of sheep is mainly poor in vitamin A, simply because of deficient BC in roughages, cereal stubble wheat straw, stored alfalfa hay and barely grain. Although green forages are the major source of carotenoids including β-carotene (BC), but they are not available throughout the year. This means that BC should be taken from exogenous sources in order to cover the deficiency of vitamin A from one side and to fill the tissue vitamin A reserves from the other side. Therefore, the aim of this study was to investigate the long-term effect of BC on LBW, age at puberty, number and percentage of estrus coming post-puberty, types of estrous cycle following puberty and P4 and E2 profiles at puberty and pre-and post- puberty in Farafra ewe lambs. The study contained 48 ewe lambs with mean body weight 13.25 ± 0.43 kg and divided into two equal groups (24 per each), the first group was injected i.m. with arachis oil (peanut oil) and considered control for the other treated group because it can be metabolized easily in the body, the second group was injected i.m. 0.1 mg/kg by BC loaded on arachis oil 2 times a week for 4 months starting from weaning period to age at puberty. Beside detection of estrus by a ram, P4 value was taken as a marker in determining age at puberty. Olive oil can not be used for long time because of its destruction of the tissues. All ewe lambs were fed maintenance ration and housed in semi-open pens under Upper-Egypt environment conditions, El-Minia Governorate. P4 Blood samples (10 ml/animal) were withdrawn from 6 animals per each group (control and treatment) by jugular vein puncture into tubes without anticoagulant.After clotting blood samples were centrifuged at 3,000×g for 10 min to separate the sera, which was stored at −20°C until P4 and E2 assay. Both BC and vit. A were assayed by colorimetric method.

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SYNTHESIS AND ANTI-INFECTIVE EVALUATION OF PHENYLCARBAMOYLPYRAZINE-2-CARBOXYLIC ACID DERIVATIVES

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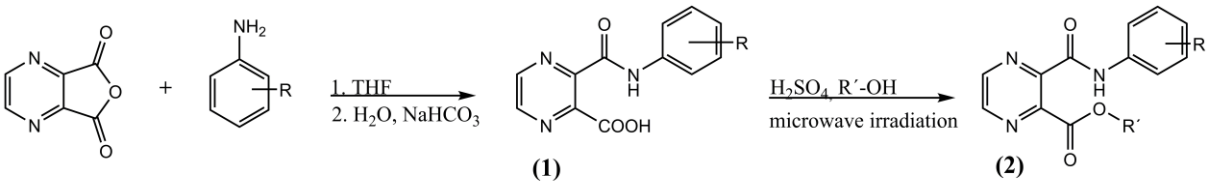
Tuberculosis still represents a major public health issue all over the world. According to Global Tuberculosis Report 2015 there were 9.6 million new TB cases and 1.5 million TB deaths in 2014. Globally in 2014, the percentage of new TB cases that have multidrug-resistant TB (MDR-TB) was 3.3% and 12% of the 9.6 million people who developed TB worldwide were HIV-positive. [1] Pyrazine ring was chosen as a basic part for drug design because of its presence in many clinically used substances, especially in pyrazinamide (PZA) – first-line antituberculotic drug. PZA has a multi-target effect, its active form pyrazinoic acid (POA) causes acidification of cytoplasm [2], inhibits trans-translation [3] and aspartate decarboxylase [4]. 5-ChloroPZA and esters of POA inhibit fatty acid synthase I [5].



R - H; 2,5-diCH_3; 4-CH_2CH_3; 2,4-diOCH_3; 2-OH; 4-NO_2; 4-$N(CH_3)_2$; 2,4-diF; 3,4-diCl; 4-Br; 3-CF_3; 4-CF_3; 2-CH_3, 5-F; 5-CH_3, 2-Cl; 2-OH, 5-NO_2; 2-OH, 5-Cl

R´- methyl, propyl

Series of substituted 3-(phenylcarbamoyl)pyrazine-2-carboxylic acids and their methyl esters were synthesized. The starting compound 2,3-pyrazinedicarboxylic acid anhydride reacted with substituted aniline to obtain compound with amide and carboxylic moiety (**1**). In the following step the carboxylic group was esterificated by methanol (**2**). Microwave irradiation was used to form ester. Prepared compounds were characterized with analytical data and tested *in vitro* for their antimycobacterial (*M. tuberculosis* H37Rv, *M. avium*, *M. kansasii* and *M. smegmatis*), antibacterial and antifungal activity. Three phenylcarbamoyl acids with 4-Br, 2-OH and 4-$N(CH_3)_2$ substitution exerted moderate antimycobacterial activity with MIC = 50 μg/mL against *M. tuberculosis*. The following esterification with methanol did not lead to more active compounds. Any prepared compound was not active against tested bacterial and fungal strains. Esters with longer alkyl chain will be prepared.

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STUDIES ON BONE-DERIVED HYDROXYAPATITE

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In recent years, the development composite materials with expected biological, physicochemical and mechanical properties have been the subject of a very intensive research. This domain of science is one of the fastest growing in the scientific world. It is confirmed by increasing expenditures on this type of research, as well as the increasing number of research teams. Elaboration of technology basis for new biomaterials' manufacturing will allow their practical implementation and adaptation to changing market needs. One of the key components in the developed composite material will be natural origin hydroxyapatite obtained from bone products [1-4]. We developed a novel method of obtaining hydroxyapatite for biomedical applications, which is characterized by reduced cost of material obtaining in comparison to traditional methods, and which allows to obtain a material with expected parameters.

In this study pork bones from the cutting and boning of the meat were used. After pre-treatment and of bones form residual soft tissues, the resultant bone pulp was boiled with the addition of deionized water and 80% lactic acid (AR) and then fractionated. In the hydrolysis process the concentration of lactic acid addition was tested. The resulting slurry was undergone high temperature thermal treatment in a stationary oven with different temperature and time of calcination depending on sample.

Obtained materials were initially characterized using different instrumental methods, e.g. Fourier transform infrared (FTIR) spectroscopy, X-ray diffraction (XRD), scanning electron microscopy (SEM) and inductively coupled plasma optical emission spectrometry (ICP-OES).

The success of further more detailed studies of the obtained materials based on hydroxyapatite have a chance of becoming the basis for the development of new implantation and dental materials with high chance of commercialization.

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P-68

SYNTHESIS AND STUDY OF BIOLOGICAL ACTIVITY OF HYDROXYNAPHTHALENE CARBOXANILIDE DERIVATES

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Salicylanilides represents compounds with a wide range of pharmacological activities [1-5]. Hydroxynaphthalene carboxanilide derivatives are mostly investigated for their antibacterial/antifungal [3-8] and antimycobacterial [3-5, 8-9] activity. Recently, it was shown that substituent position on the anilide is important for their biological activity [10]. Meta- and para-position to one of these substituents is necessary for already described biological effects. In the group of substituents we can place for example methoxy, nitro, methyl, chloro or any other function group [10]. In our study, we focused on determining cytotoxicity of these derivatives on human cancer cell lines with different p53 status. Antiproliferative activity of the synthesized compounds was tested by the MTS assay against the human colon adenocarcinoma cell lines with normal expression of p53 protein (Hct116 p53+/+) and mutants with disabled TP53 gene (Hct116 p53-/-). Moreover we have tested their activity against nontumor human fibroblast to determine their selectivity.

Several *N*-substituted hydroxybenzamides analogues were found to have markedly greater antiproliferative activity than doxorubicin. Salicylanilides derivatives inhibit the proliferation of tumor cells and thus can be used as anticancer drugs. Our analyses contribute to the study of the biological activity of hydroxynaphthalene carboxanilide derivatives as new potential chemotherapeutic agents.

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P-69

MICELLIZATION BEHAVIOR OF HOMOLOGOUS OF MORPHOLINOETHYL ESTERS 2-ALKOXYSUBSTITUENTED OF PHENYLCARBAMIC ACID

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Micellization behavior of selected alkyloxy homologs of local anesthetic *N*-[2-(2-alkyloxyphenyl-carbamoyloxy)-ethyl]morpholium chloride with n = 2, 4, 5, 6, 7, 8 and 9 carbons in alkyloxy substituent have been studied by absorption spectroscopy in the UV/VIS spectral region with the use of a pyrene probe. In the homologous series of the studied amphiphilic compounds, critical micellar concentration (*cmc*) was observed to be depend exponentially on the number of carbon atoms n in the hydrophobic chain: $\ln(cmc) = 0.707 - 0.967\,n$. The free Gibbs energy necessary for the transfer of the methylene group of the alkoxy chain from the water phase into the inner part of the micelle at the temperature of 25 °C and pH ≈ 4.5 – 5.0 is (-0.967 ± 0.226)RT.

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INTRODUCTION OF GOLEM V2, A NEW MODEL FOR BIORELEVANT DISSOLUTION STUDIES

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Generic drug products represent a dominant portion of the pharmaceutical market. This results in a considerable interest in the topics of generic formulation development and bioequivalence studies. In this respect, our team focuses on innovative *in vitro* dissolution studies employing a dynamic biorelevant dissolution instrument – Golem; developed for physiologically relevant simulation of drug dissolution process occurring in human stomach and small intestine [1,2]. Recently, we have introduced new improvements to the instrumental design of Golem, developed in the course of our continuous research. Here, we present the modifications incorporated in Golem v2 and the initial optimization assays. The *in vitro* performance of new compartment design and peristaltics simulation was assessed using an immediate release drug formulation and compared with USP 2 dissolution.

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PROTON INDUCED INTARMOLECULAR INHIBITION

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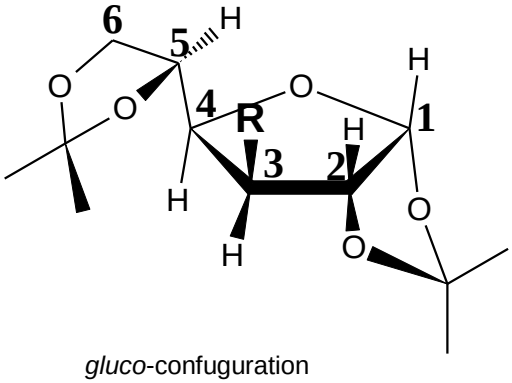
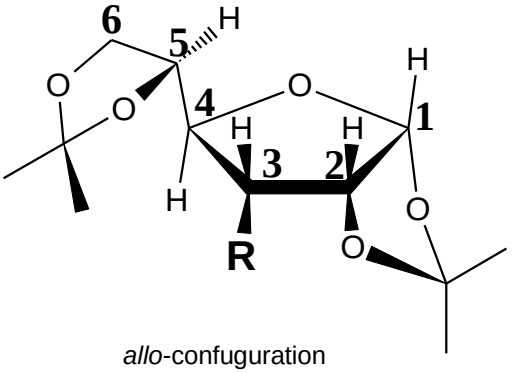
Isopropylidene group as selective protection group is common used in organic synthesis. In the case of glucofuranose the acidic cleavage (hydrolysis) of the 5,6-O-isopropylidene group is reported in the literature with various reagents.3-O-substituated 1,2:5,6-Di-O-isopropylidene glucofuranose was investigated to see if the substituent in this position 3 may be catalyse of the hydrolosis one or the other isopropylidene group [1-3].

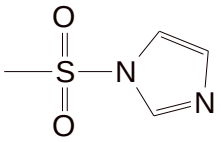
It was found that 3-O substituated by imidazole sulfonil group the substituent didn't catalyze but inhibited the 5,6-O-izopropylidene group. The same invest was also carried out on the allo configuration wich also produced comparable results.



gluco-confuguration



allo-confuguration

R: 

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SYNTHESIS AND $C_{17,20}$-LYASE INHIBITION OF 16α-AMINO-PREGNANES

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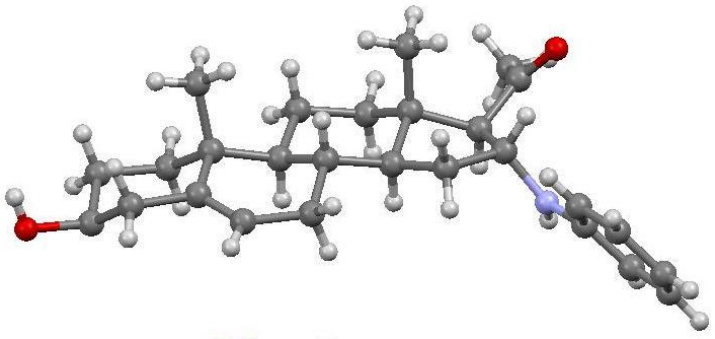
17α-Hydroxylase-$C_{17,20}$-lyase ($P450_{17α}$) is a key regulator in the androgen biosynthesis. Inhibitors of this enzyme have potential application for the treatment of androgen-dependent diseases. Earlier studies support that pregnenolone derivatives with *N*-heterocyclic ring at C-17 are effective inhibitors of $P450_{17α}$. [1] To the best of our knowledge, no $P450_{17α}$ inhibition studies have been reported with 16-substituted *N*-heterocyclic derivatives.

In this work 16α-amino-substituted pregnanes were synthesized *via* aza-Michael addition in a basic ionic liquid and their biological activity was evaluated.

Basic ionic liquids are environmentally friendly alternatives of organic solvents due to their low melting point, good chemical stability and high solubility of organic and inorganic compounds. They can play the role of reaction medium and catalyst too, replacing traditional base catalysts. Diazabicyclo-[5.4.0]-undec-7-ene derived ionic liquids were found to be efficient catalysts of aza-Michael addition. [2]

Aza-Michael addition of 16-dehydropregnenolone was studied in the presence of [DBU][Ac] as catalyst and solvent. The reaction was carried out with different primary and secondary amines as *N*-nucleophiles. The products were obtained in moderate to good yields and were characterized by ^{1}H and ^{13}C-NMR, MS, IR and in one case by X-ray crystallography. The ionic liquid was found to be an efficient catalyst and it was reused five times efficiently. The products were investigated against the $C_{17,20}$-lyase activity of the $P450_{17α}$ *in vitro* and displayed moderate inhibitory effect.



Scheme 1. X-ray structure of 16α-(*N*-phenyl-amino)-3β-hidroxy-pregn-5-ene-20-one

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THE EFFECT OF TEMPERATURE ON BINDING TOLBUTAMIDE TO GLYCATED SERUM ALBUMIN

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Human serum albumin binds with exogenous substances including drugs. Drugs associated with the protein does not have a therapeutic effect. The temperature may affect the binding between ligands and albumin and affect the stability of the complex. The study was based on bovine serum albumin (BSA) and BSA glycated by the *Maillard method* (gBSA). It was tested how the glycation of BSA changes the binding of tolbutamide. The effect of temperature on the binding process was also studied. Measurements were carried out at temperatures 36^0C, 37^0C, 38^0C, 39^0C, 40^0C and 41^0C using a spectrophotometric technique. The formation of Advanced Glycation End-products (AGEs) in glycated gBSA was proved. Quenching of BSA fluorescence by tolbutamide was estimated. The analysis of the emission fluorescence BSA proved the formation of the complexes between BSA and TB and between TB and gBSA. A stronger quenching of unmodified albumin by TB is compared with the glycosylated one and shows negative effect of glycation on the binding of tolbutamide to albumin. Tryptophan and tyrosyl residues take part in the integration between TB and both BSA and gBSA. The shape of Stern-Volmer curves shows that two types of fluorophores are exited in both BSA-TB and TB-gBSA complexes. The analysis of the binding constants K_a tolbutamide to the unmodified and glycated albumin, determined from the Klotz equation, confirmed the effect of temperature on the binding TB to macromolecule. The increase of temperature above the physiological temperature leads to the weakening of binding between drug and albumin. The increase of temperature may lead to the increase of the concentration of free drug fraction in the plasma. On the basis of thermodynamic parameters it has shown that binding of tolbutamide to BSA and gBSA is a spontaneous process. During pharmacotherapy of diabetes with tolbutamide, people should pay attention on the temperature of the body. Fever causes weakening of drug binding to albumin, which may contribute to the tolbutamide side effects including hypoglycemia, allergic reactions or cholestatic jaundice. In that cases, it seems to be necessary to reduce the dose of the drug.

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RP-HPLC DETERMINATION OF SELECTED DYES IN PHARMACEUTICALS

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In addition to the active ingredient, various additives are used in the manufacture of pharmaceuticals and drugs. This group of compounds includes dyes. A colour additive or food colourant is any dye, pigment, or other substance that imparts colour to food, drink or any non-food applications including pharmaceuticals. Moreover, a colour additive is also any chemical compound that reacts with another substance and causes formation of a colour [1,2]. The pharmaceutical industry employs various inorganic and, especially, organic dyes. These are pigments of natural origin or synthetic chemical compounds. However, most of the dyes obtained from natural sources are unstable and can easily undergo degradation during the processing of pharmaceutical products. Therefore, dyes of synthetic origin are widely used, not only because of their stability, but also given the low cost of production when compared to natural dyes [3]. The contents of these dyes must be controlled because their presence with some kinds of drugs in human body can cause an allergic reaction. The aim of the current work was the identification and determination of food dyes (Quinoline Yellow E 104, Sunset Yellow E110, Ponceau 4R E124, Tartrazine E102 and Carmine E120) by a reversed-phase HPLC with isocratic elution in set of vitamins samples from different producers. The dyes were analyzed within 10 min using column with stationary phase C 18 (250 mm x 4.6 mm, 5 µm) at 40°C, with isocratic elution and the mobile phase contained acetonitrile and mixture of CH_3COONa:CH_3OH (85:15, v/v) in the ratio of 10:90 (v/v) for yellow-coloured capsules and 20:80 (v/v) for red-coloured capsules, respectively. The diode-array detector was used to monitor the dyes between 190 and 800 nm. It was established that the analyzed samples contain synthetic dyes in the concentration range from 79.5 ± 0.01 µg/capsule of Ponceau 4R, E 124 to 524 ± 0.01 µg/capsule of Tartrazine, E 102. The obtained results were compared with existing Acceptable Daily Intakes (ADIs) for individual dyes.

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P-75

UNDER FREEZING POINT LIQUID WATER SURROUNDING GLOBULAR AND DISORDERED PROTEINS

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There are a few techniques only applicable for measuring biomolecule's and protein's conformation bellow 0°C. Among these wide line NMR spectroscopy is a powerful one: by investigating the hydration properties under freezing point of a protein, it's conformational properties can be back "calculated". In this low temperature region (-80°C<T <0°C) water molecules surrounding globular or disordered proteins show differences in term of mobility [1].

Up to now, information on very few number and quite different proteins are available only. The present technique was applied to measure small miniproteins (20-25 amino acids) of great similarity standing for folded, unfolded and acid induced denatured states [2-4]. Results enforce that wide line NMR spectroscopy in conjunction with MD simulation can indeed be used to decipher important folding information otherwise unreachable.

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ASYMMETRIC BIOCATALYTIC CANNIZZARO-TYPE REACTION: A SUSTAINABLE ROUTE TO CHIRAL PROFENS AND PROFENOLS

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Among the various disproportionation processes in the field of organic chemistry, the Cannizzaro reaction stands out for its attractiveness: employing an aldehyde as starting material, it leads to equimolar amounts of the corresponding alcohol and carboxylic acid. Typically catalyzed by a strong base, this reaction is however limited to non-enolizable aldehydes [1]. The biocatalytic variant of the Cannizzaro reaction, on the other hand, accepts enolizable aldehydes, including α-substituted compounds. A single alcohol dehydrogenase (ADH) catalyzes concurrently the oxidation and the reduction reactions, requiring only aqueous buffer and catalytic amount of nicotinamide cofactor as hydrogen shuttle [2].

Both the exquisite stereoselectivity of the enzyme and the spontaneous racemization of the starting aldehyde are key features in the biocatalytic reaction, allowing a parallel dynamic asymmetric process to take place and providing two enantioenriched products (in up to 99% *ee*) in a redox neutral fashion (Figure 1).

Herein we present recent data of this ongoing project, aiming at expanding the synthetic applicability of the system to pharmaceutical targets, including profen derivatives. The influence of various parameters, such as enzyme concentration and nicotinamide (reduced and/or oxidized) amount, on conversion, product ratio and *ee* value of products was investigated. Additionally, the use of Design of Experiments shed light on unexpected parameter interactions and system shortcomings.

Eventually, the substrate acceptance was investigated and the influence of the electronic properties of different substituents on reactivity was studied.

Overall, a promising application for the sustainable production of optically pure profens derivatives, such as ibuprofen or naproxen, is envisaged.

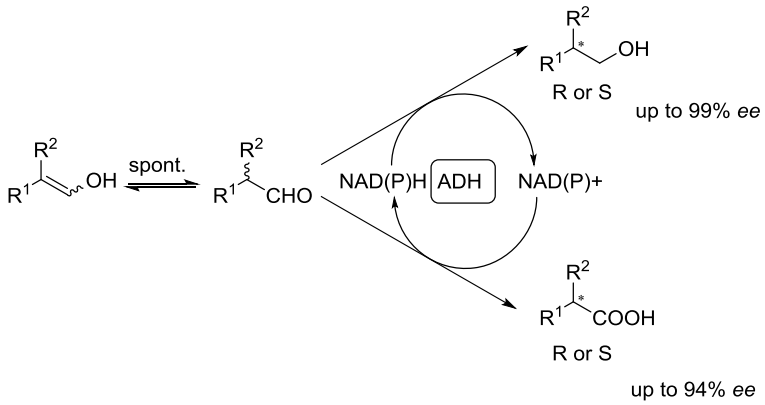

Figure 1. Biocatalytic disproportionation of enolizable aldehydes using alcohol dehydrogenase

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P-77

BIOPOLYMER HYDROGEL CONTAINING METALLIC NANOPARTICLES FOR BIOMEDICAL APPLICATION

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Hydrogels belong to materials commonly used in medicine, pharmacy, and tissue engineering. Due to its specific features, they are generally used at production of innovative bandaging materials. The aim of the thesis was evaluation of the impact of the modification of the hydrogel matrix with xanthan gum on the properties and structure of polymer superabsorbents.
During the research studies, there were carried out syntheses of the hydrogels (acryl-chitosan matrix) having different percentage content of the xanthan gum. The range of the research included measurement of the absorption abilities of collected samples. It was stated that the synthesized hydrogels are swelling both in distilled water and physiological salt. Due to the above feature they can be used in bandage materials, allowing to absorb the effusion from the wound and keep it wet what speeds up the process of healing. There were also carried out an incubative studies of the synthesized samples in the distilled water, Ringer solution and artificial saliva. The pH value of the researched solutions did not show large differences between hydrogel samples of different percentage content of the xanthan gun. Moreover, there was no violent changes of pH, it testifies about the compatibility of collected material with a particular environment. During the research studies, there was determined the biological activity of hydrogels. The studies showed that collected gels have this feature. For the purpose of more detailed analysis of the biological activity of materials, there need to be carried further studies e.g. on the cell lines. There was also carried analysis of the polymer matrix structure of collected hydrogels and samples after incubation using spectroscopy in infra-red with Fourier transformation (FT-IR).

The research (work) was supported by grant C-4/439/2016/DS

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P-78

COMPARISON OF HYDROGELS BASED ON COMMERCIAL CHITOSAN AND BEETOSAN® CONTAINING NANOSILVER

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Chitosan – a well-known polysaccharide sourced mainly from external skeletons of shellfish – represents an alternative material to the preparation of polymer hydrogels. Due to its properties i.e. non-toxicity, biodegradability and biocompatibility such polymers can be applied for biomedical purposes [1]. However, alternative sources of chitosan constitute insects including honeybees. Material obtained from exoskeletons of naturally died honeybees is called Beetosan®. Procedure for its preparation requires several steps necessary to remove from the body of the mentioned insects other undesirable substances [2]. It is worth noting that proposed technology of obtaining Beetosan® is beneficial to the environment since it uses a material collected as a waste for the synthesis of polymers with a large range of potential applications. In the presented research two series of hydrogels have been synthesized. During first of them chitosan was used as a polymer matrix and in the other case hydrogels were obtained on the basis of Beetosan®. Futhermore, in each case silver nanoparticles (AgNPs) were introduced into a hydrogel. These nanoparticles are well-known for their antibacterial activity [3]. Due to this characteristic AgNPs constitute a component of modern wound dressings [4].

Hydrogels containing silver nanoparticles and based on chitosan of different origin have been presented in the research. Mentioned materials have been synthesized using UV radiation. It is worth noting that selected method used for obtaining described polymers – i.e. photopolymerization - simultaneously causes their sterilization. The scope of the study included comparison of the properties of synthesized materials. What is more, chemical structure and sorption capacity of both kind of attained polymers have been determined. Furthermore, impact of the type of matrix comprising a hydrogel and a presence of additives in the form of silver nanoparticles within the matrix on the physic-chemical properties of attained materials have been defined. Suggested polymers have been designed for biomedical applications therefore conducted studies aimed at determining their properties and usefulness in these areas.

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THE IMPACT OF THE PRESENCE OF MAGNETIC NANOPARTICLES IN THE POLYMER MATRIX ON THE PROPERTIES OF HYDROGELS BASED ON A6ACA

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Recently, acryloyl-6-aminocaproic acid (also known as A6ACA) becomes a very interesting chemical compound useful in the synthesis of polymer materials. Its popularity stems from the fact that it has unique properties. Due to its chemical structure and the different behavior depending on the pH value of the environment in which it is placed mentioned compound can be applied in the preparation of self-healing hydrogels. Two separate fragments of such material after immersing in a solution having a pH ≤ 3 are characterized by an ability to form hydrogen bonding between particular functional groups and connect in an uniform, compact structure. The opposite behavior is observed in a solution of pH > 9, wherein the described materials separate from one another [1,2].

In the presented research hydrogels based on A6ACA have been obtained by means of UV radiation. Furthermore, these materials have been modified by introducing magnetic nanoparticles into the polymer matrix. Nanoparticles constituting the additive to the synthesized hydrogels are widely applied in medicine. Great interest is aroused particularly by the use of them in antitumor therapy. Hyperthermia, in which described nanoparticles are used, causes destruction of cells affected by tumor. This is caused by the high temperature generated by the magnetic field. It is worth noting that magnetic nanoparticles are also applied as drug carriers, contrast agents in magnetic resonance imaging (MRI) and in tissue repair [3].

The scope of this work included the synthesis of hydrogel materials with / without the addition of magnetic nanoparticles and characterization of the properties of the attained polymers. Furthermore, an important aspect of the research was to determine the impact of the presence of magnetic nanoparticles in the hydrogel matrix on its properties. Incubation studies and tests aimed at determining a sorption capacity of obtained materials have been carried out. First of the mentioned involve immersing the sample of synthesized material for a certain period of time in simulated body fluids. Such study is conducted in order to determine whether the hydrogel become degraded in the fluid of a composition similar to the fluids present in the human body.

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P-80

NUCLEOTIDE-STABILIZED Au AND Au/Ag NANOCLUSTERS FOR BIOSENSOR APPLICATIONS

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The noble metal nanoparticles (NPs) (mainly the gold and silver) can be used in many different ways. They have large specific area, therefore they are excellent catalysts. They have unique shape-, size- and material quality-dependent optical properties (plasmon resonance or fluorescence), so it is possible to develop NPs-based biosensors. In recent years, the biocompatible preparation route of nanosized noble metals is in focus of extensive research. In this case the gold/biomolecule hybrid nanostructures are synthesized by using one biomolecule. This molecule has parallel both reducing and stabilizing role as well. Different nanostructures (NPs or nanoclusters/NCs) can be synthesized depending on the molar ratio of gold precursor and the ligand. Small ligand excess results the formation of plasmonic NPs with diameter larger than 2 nm. In contrast, at high biomolecule excess sub-nanometer sized clusters are formed (d<2nm). The ultra-small Au and Au/Ag alloy NCs show unique physical and chemical properties such as well-defined molecular structure, discrete electronic transitions and characteristic photoluminescence. If the gold NCs consist of only a few-atoms (blue-emitting NCs) the presence of the emission peak depends on the number of metal atoms in the clusters. Furthermore, if the size of the NCs reaches the few nm (red-emitting NCs) both the oxidation state of the surface metal atoms (for example Au^0 or Au^I state) and the surface ligand effect influence the wavelength of the emission maximum. The luminescent few nanometer Au NPs (the size more than 2 nm) show plasmonic feature, because the collective oscillation of the free electron is occurred. It has to mention that, the plasmonic Au NPs can show characteristic short-time fluorescence, which is depend on the surface roughness or the grain size effect.

In our work different nucleotide have been used to synthesize fluorescent Au and Au/Ag alloy NCs. We investigated the effect of several factors on the final products: nucleotide chemical properties, bioligand/precursor ration, pH etc. The plasmonic NPs and the fluorescent NCs were analysed by numerous technique. The optical features were determined by UV-Vis spectrophotometry and fluorescence spectroscopy. The morphology and the size of the nano-object were characterized by HRTEM and DLS measurements. Various structural analysis were performed by using FT-IR, XRD and MS techniques and the oxidation state of cluster's core metal atoms was analysed by XPS. The Au and Au/Ag alloy NCs are promising nanomaterials for metal ions and inorganic anions detection due their excellent photostability and low toxicity. We have investigated the effect of several cations (K^+, Mg^{2+}, Cu^{2+}…) and anions (HPO_4^-, Br^-, SO_4^-…) for the fluorescence quenching. The quenching constants (K_{SV}) and various thermodynamic parameters (ΔG, ΔH, ΔS) were determined by Stern-Volmer fitting of the fluorescence data.

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P-81

PREPARATION OF GLIBENCLAMIDE NANOPARTICLES FOR SOLUBILITY ENHANCEMENT

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Glibenclamide (GBCD) is an antidiabetic drug from the sulfonylurea group. GBCD is an insulin sensitizer that stimulates insulin release from pancreatic β-cells. GBCD and its metabolites are excreted in the bile and urine contrary to elimination of other sulfonylureas that are excreted mainly in the urine. The half-life of the unchanged drug is about 1.4-1.8 hours, and the half-life of metabolites is 10 hours. The effect of GBCD lasts from 12 to 24 hours. Dosing must be adjusted in patients with renal impairment due to the risk of GBCD metabolites accumulation. GBCD is contraindicated in patients with glomerular filtration under 60 mL/min [1-3]. Hypoglycaemia is a main side effect of GBCD [4]. GBCD belongs to Class II of the Biopharmaceutical Classification System; drugs of the mentioned class are characterized by poor water solubility but sufficient permeability. Thus, preparation of nanoparticles (NPs) should allow administering of lower doses with higher efficacy.

GBCD NPs were prepared by the precipitation technique [5]. A solution of GBCD in acetone (100mg/10mL) was slowly dropped to the aqueous solution of carboxymethyl dextrane sodium salt (1mg/10mL), and the final mixture was stirred for 15 minutes, after which the mixture was transferred to an ultrasonic bath, where it was mixed again for 20 minutes for homogenization of the sample. Finally, the solvent was evaporated. The sample was characterized by dynamic light scattering (11.0±0.2 nm), scanning electron microscopy and Fourier transform mid-infrared spectroscopy. Then the solubility of bulk and nanoparticle GBCD was investigated.

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P-82

THERMAL PROPERTIES OF FOOD HYDROCOLLOIDS

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In previous years, thermal properties of some hydrocolloids have been intensively studied. In particular, the gelatinization process of starch regarding its structure and conformational changes was described in detail [1,2,3]. However, little is known about the gelatinization properties of several other hydrocolloids, notably about the properties of their pure powder samples.

The aim of this study was to clarify the thermal properties of selected polysaccharides, which are used as food hydrocolloids. Their powder samples were investigated by thermogravimetric analysis (TGA) and differential thermal analysis (DTA). For most samples, the peak gelatinization temperature (T_p) was about 70 ˚C and the gelatinization enthalpy (ΔH_{gel}) between 120 and 180 $J.g^{-1}$, except dextrin (81.7 °C, 104 $J.g^{-1}$). The moisture content of the polysaccharides was in the range of approx. 8.0-12.0 %, except dextrin again (only 6.3 %). The values determined for dextrin can be related to the specific structure of this polysaccharide; dextrin's low-molecular structure consisting of short chains seems to reduce its water-binding capacity.

No peak of gelatinization temperature and no gelatinization enthalpy were determined for CMC refined (Blanose) because the sample did not contain any reactive water. On the other hand, the potato starch (Solamyl) had relatively high water content (12.2 %) and its peak gelatinization temperature was relatively low (69.4 °C).

The largest value of gelatinization enthalpy was determined for alginic acid Na salt: 182.6 $J.g^{-1}$. This fact corresponds to the large value of weight loss, respectively moisture content (12.2 %), and a peak of gelatinization temperature (74.2 ˚C). These results could confirm the specific properties of alginic acid Na salt, which is extensively used as a gelling agent (e.g., in manufacture of jams, puddings, jellies and aspics).

The study proved that water molecules have a function of plasticizing agents of polymeric molecules, i.e., the moisture promoted the beginning of the gelatinization process. The results of this research also confirmed the ability of hydrocolloids to bind moisture in varying degrees depending on their structure which is of decisive importance for their thermal characteristics and using in food products.

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P-83

BINDING STUDIES OF CRISPR/CAS9 GUIDE RNAS WITH *IN VITRO* ASSAYS

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Genome editing, thanks to the CRISPR (Clustered Regularly Interspaced Palindromic Repeats) system, is one of the most faster developing field of molecular biology.[1] It generally employ CRISPR associated nuclease 9 (Cas9) protein which uses small RNA molecules, the gRNAs, by exploring complementary sequences to guide Cas9 to its specific genomic target where it makes a double strand DNA brake.[2] The affinity of the gRNA/Cas9 interactions are crucial step in this process.

Here we developed an *in vitro* method for testing the binding of the Cas9-gRNA complex to its DNA target which are based on shielding the recognition site of a restriction enzyme by nuclease inactive Cas9 (dCas9). The assay includes (i) a plasmid DNA substrate harbouring a Cas9 target site (*A*) overlapping with a recognition site of a restriction enzyme, (ii) an gRNA targeting the *A* site and (iii) dCas9. After incubation of these components, the plasmid is digested with the restriction enzyme, and the resulted DNA fragments are analyzed with electrophoresis.

We also propose a method for testing the association of a given gRNA to the Cas9 protein by a competition assay based on above approach. By pre-incubating dCas9 with a *B* gRNA that does not target the *A* site, dCas9 is charged with *B* gRNA that effectively blocks the binding of *A* gRNA, as assessed by restriction digestion. This approach might allow for assessing the affinity of a given *B* gRNA to the Cas9 protein.

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MATRIX FILM WOUND DRESSING WITH LOCAL ANESTHETIC

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Pain is a major issue for patients with acute and chronic wounds. Effective assessment and management of wound pain could facilitate an improvement in healing rates and overall quality of life. Wound-related pain can be temporary (acute) or persistent (chronic) [1]. Acute wound pain can be exacerbated whenever the wound is handled or manipulated: during dressing removal, wound cleansing or debridement (removing of necrotic tissues). Pain during wound dressing changes or debridement can be substantially reduced using local anesthetics such as lidocaine, tetracaine or prilocaine, which can be injected into the tissue in and around the wound [2] or applied topically as a solution, gel, or cream [3,4]. Application of topical anesthetics is significantly less painful than infiltration, and was found to have similar efficacy [2]. Wound dressing containing local anesthetic should be useful in acute pain management because it is more comfortable for application than liquid or semisolid preparation and enables accurate dosing. Therefore, the aim of the work was to prepare and evaluate matrix film wound dressing with lidocaine.

The partially substituted sodium carboxymethylcellulose (NaCMC) in the form of non-woven textile was used as film-forming material, macrogol 300 and glycerine served as plastifiers. The polymer dispersion was composed of 1% (w/w) NaCMC and 2% plastifier in purified water. Films were prepared using sequential solvent casting method. The acidification both of polymer dispersion and film after drying resulted in formation of insoluble polymer matrix consisted of acidic form of CMC, which owed to improvement of mechanical properties of film after wetting. Lidocaine (5 mg/cm^2) was incorporated as the last layer of the film. Prepared films were evaluated visually and using microscope. Alterations of surface pH, swelling and mechanical properties as well as *in vitro* drug release were measured.

Prepared films were homogenous and translucent with smooth surface. Observation of microscopic appearance confirmed that partially substituted CMC maintained fibrous nature. Values of surface pH were below 5; that is surface of the films was acidic, which is positive property for wound dressing. Films exhibited a mild degree of swelling, while maintaining their excellent structural integrity and mechanical properties. Drug content uniformity was within ±15%. Evaluation of *in vitro* drug release demonstrated that prepared films should have rapid onset of action – more than 80% of lidocaine were released during the first 15 min., and during the first hour was released all content of the drug.

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A NOVEL MESOIONIC PALLADIUM(II) COMPLEX EFFICIENTLY CATALYSES SONOGASHIRA REACTION UNDER GREEN REACTION CONDITIONS

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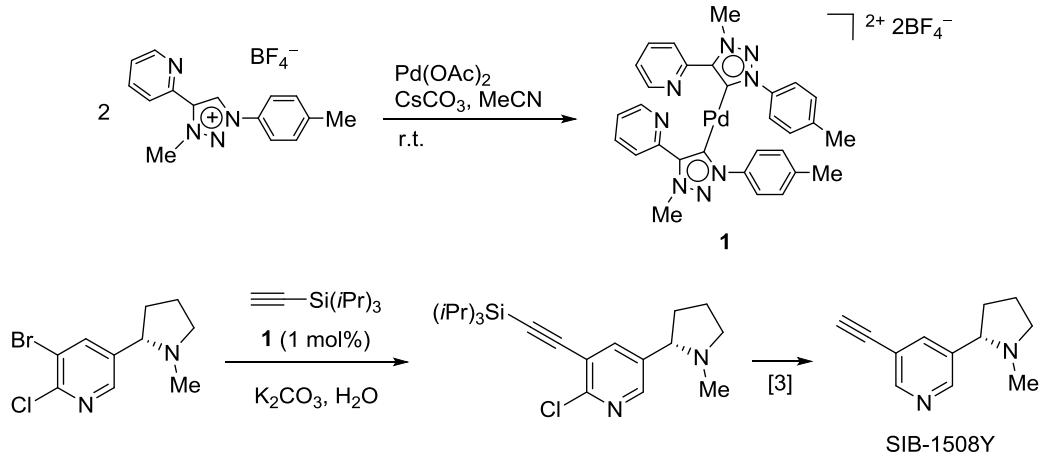
N-Heterocyclic carbenes (NHCs) have become one of the most important ligands in transition-metal catalysis. The success of normal NHCs is greatly attributed to their superior σ-donating capabilities as compared to phosphines, which is even greater in abnormal NHC counterparts. Employed as ligands in palladium complexes, NHCs contributed greatly to the stabilization and activation of precatalysts. Interesting examples of abnormal NHCs are based on the mesoionic 1,2,3-triazol-5-ylidene structure (*tz*NHC). [1]

We aimed at developing palladium catalysts with improved stability and catalytic efficiency that are based on pyridine-substituted 1,2,3-triazol-5-ylidene (Py-*tz*NHC). A simple laboratory procedure at ambient reaction conditions allowed the coordination of Py-*tz*NHC to palladium(II) to form organometallic compound $[Pd(Py\text{-}tzNHC)_2]^{2+}$ (**1**). The structure of **1** was determined by NMR spectroscopy, high resolution mass spectrometry and X-ray diffraction analysis. [2]

Complex **1** was evaluated as a (pre)catalyst for the Sonogashira reaction in water as the only solvent under aerobic conditions in the absence of copper, amines, phosphines and other additives. The robustness of the (pre)catalyst **1** was demonstrated on a broad scope of (hetero)arly bromides and acetylenes that were cross-coupled into the corresponding products in high yields. The applicability of **1** was demonstrated in the synthesis of an intermediate in the preparation route of SIB-1508Y (Altinicline), a potential drug for treating neurodegenerative diseases. [2,3]



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P-86

DIHYDROXYCOUMARINS AS HIGHLY SELECTIVE FLUORESCENT PROBES FOR THE FAST DETECTION OF 4-AMINO-TEMPO

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TEMPO (2,2,6,6-tetramethylpiperidine-1-oxyl) and its derivatives are stable membrane permeable nitroxide radicals, which effectively protect cells and tissues from damages due to the presence of oxidative and nitrosative stress conditions. It has been proven, for instance, that 4-hydroxy-TEMPO interacts with nitrogen dioxide (one of the compounds responsible for an oxidative stress) and decreases its concentration in cells even 500 times [1,2]. Profluorescent nitroxides have been reported previously as probes for a detection of free radicals as well as damages mediated by these species [3,4]. On the other hand there is no literature data on fluorescent sensors (which display the fluorescence enhancement) used for the detection of nitroxides. We report herein dihydroxycoumarins as highly selective fluorescent probes for the fast detection for TEMPO derivative, 4-amino-TEMPO.
A series of 25 coumarin derivatives has been studied with the use of different analytical techniques as fluorescent sensors for a 4-amino-TEMPO radical. The UV absorption and fluorescence emission spectra of these coumarins were recorded in aqueous solution at the temperature of 25 °C in the absence of 4-amino-TEMPO and in the presence of the increasing amounts of that radical. In case of strictly physical interactions – the fluorescence quenching – the mechanism of quenching and Stern-Volmer quenching constants were determined. Only in case of some dihydroxy-substituted coumarins the fluorescence intensity under the action of 4-amino-TEMPO increased significantly. We state that the unique fluorescence enhancement attributes to the formation of each coumarin dimer. The dimers were determined with the use of HPLC coupled with mass spectrometry. As dihydroxycoumarins were found to interact with 4-amino-TEMPO selectively, they may be applied in measurements of that TEMPO derivative concentration. Additionally, limits of detection (LOD) and quantitation (LOQ) of 4-amino-TEMPO with the use of dihydroxycoumarins were determined.

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MODIFIED NUCLEOSIDES – EVALUATION OF THEIR CYTOTOXICITY AND PROPENSITY TO BE INCORPORATED INTO GENOMIC DNA

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Nucleoside analogs seem to be potential, non-toxic candidates for effective sensitizers of DNA damage induced by ionizing radiation [1]. Structural modifications of nucleosides should rely on the introduction of suitable substituents to nucleobases that increase nucleosides' sensitivity to degradation induced by solvated electrons to which native DNA is negligibly reactive. The halogen derivatives of nucleobases are the most widely studied group of sensitizing compounds. Our theoretical and experimental studies have shown that also the thiocyanate derivative of 2'-deoxyuridine might be an effective radiosensitizer, with a similar or even greater than bromonucleosides sensitivity [2,3].

In the current project, the cytotoxicity and degree of incorporation of bromodeoxynucleosides (5-bromo-2'-deoxyuridine, 5-bromo-2'-deoxycytidine, 8-bromo-2'-deoxyguanosine, 8-bromo-2'-deoxyadenosine) and 5-thiocyanato-2'-deoxyuridine into genomic DNA were evaluated. The cytotoxicity was estimated using the MCF-7 human breast cancer cell line (by the MTT assay. The assay was performed for the studied nucleoside analogs at concentrations spanning a range of 10^{-9} to 10^{-4} M. Obtained results showed no significant cytotoxic response (cells viability >80%), even for compounds used at 10^{-5} M concentration.

Incorporation of the substituted nucleosides into the MCF-7 cells was performed using two methods: (i) via the modified nucleosides and (ii) through the substituted nucleobases (the latter method exploits the reserve pathway of nucleotide biosynthesis, where the attachment of phosphoribosyl pyrophosphate to the nucleobase takes place without the participation of a kinase). The labeling level was assessed with the use of enzymatic digestion of the DNA isolated from the cells followed by the HPLC analysis of nucleoside mixture.

Our study demonstrates that out of the five tested nucleobase derivatives only 5-bromo-2'-deoxyuridine is extensively incorporated into genomic DNA.

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QUATERNARY AMMONIUM DERIVATIVES – SYNTHESIS AND EVALUATION OF PHYSICO-CHEMICAL PROPERTIES

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The aim of the project was the synthesis and structural analysis of a number of new arylcarbonyloxyaminopropanol derivatives with potential β-adrenolytic and antiarrhythmic activity with ultrashort action and their conversion to quaternary ammonium derivatives. In the first part of the synthesis, the preparation of tertiary amines was carried out according to the Tengler et al [1]. In the second part, it was focused on the conversion of tertiary amines to the quaternary ammonium salts. There was the N-alkylation of tertiary amine with appropriate alkyljodide. The reaction carried out in a microwave reactor with the using of solvent. Within the present project, a series of new compounds of type quaternary ammonium derivatives of arylcarbonyloxyaminopropanols have been prepared. It was managed to optimizing the individual steps of the synthesis. The pharmacokinetics in the human body and the bioavailability of the drugs are described by various physico-chemical properties, e.g. ionization constant (pKa), distribution coefficient (log D) or lipophilicity (log P) [2]. The structure of all final compounds was confirmed, and the purity was verified by available methods of instrumental analysis (NMR, IR, HPLC). The synthetised compounds will be tested for their biological activity.

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