BOOK OF ABSTRACTS

NEW TRENDS IN CHEMISTRY

Trends in chemistry, research and education at Faculty of Science of P.J. Šafárik University in Košice

November 9, 2018, Faculty of Natural Science, Pavol Jozef Šafárik University in Košice, Slovakia

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New trends in chemistry, research and education at Faculty of Science of P. J. Šafárik University in Košice 2018

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Complexes of Macrocyclic Ligands for Special Magnetic Resonance Imaging Applications

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Among medical imaging methods, Magnetic Resonance Imaging (MRI) has a prominent position as it does not utilize ionizing radiation. The method is used world-wide and is commonly used for imaging of mainly soft tissues. In a substantial number of examinations, contrast agents (CAs) are administered to improve resolution and sensitivity of the method. The clinically approved CAs are exclusively based on complexes of highly paramagnetic metal ions (mostly trivalent gadolinium) with polydentate ligands as DTPA or DOTA or their derivatives. However, these approved CAs do not exhibit optimal efficiency as their molecular parameters are far away from the values which theory predicts to be optimal [1]. The most important parameters governing efficiency of the CAs (so called relaxivity r_1; r_1 is enhancement of water protons T_1 relaxation time in the presence of 1 mM concentration of a contrast agent) are tuneable through ligand design. They are a number of directly coordinated water molecules in the complex (q), a residence time of the metal-bound water molecule (τ_M) and overall tumbling of the CAs (τ_R). Over the years, the optimization of properties of the complex has led to a substantial understanding of chemistry of the MRI CAs [2]. However, novel systems are still far away from the optimum.

Nowadays, a general drop down in relaxivity with increasing strength of magnetic field used in new scanners somewhat changes strategy of CAs' development. Today, tissue-specific agents and compounds enabling "hot-spot" imaging are of the main interest. With this respect, heteroatom-MRI is rapidly developing, especially with use of ^{19}F-containing probes. The main reason lies in the fact, that ^{19}F has similar gyromagnetic ratio as ^{1}H and, therefore, standard ^{1}H scanners can be used for ^{19}F MRI after only minor hardware optimization. Moreover, fluorine has no natural abundance in the human's body and, therefore, it enables *e.g.* cellular tracking (after appropriate labelling of cells before transplantation) due to zero background. However, ^{19}F nuclei bound in organic molecules have generally long relaxation time, which prolongs a time needed for an image acquisition. Therefore, complexes of paramagnetic metal ions with fluorine-containing ligands are of a high interest, as the presence of the paramagnetic centre influences (fasten) signal relaxation and thus enable fast repetition of data acquisition.

Besides heteroatomic imaging, some special measurement techniques employing "standard" ^{1}H nuclei were also introduced. Among them, pulse sequences employing saturation transfer through chemical exchange of hydrogen atoms between CA molecule and bulk water (so-called CEST effect, Chemical Exchange Saturation Transfer) started to be widely studied and used. In this field, paramagnetic complexes offer enlargement of chemical shift scale of their ^{1}H NMR signals, which simplifies measurements and, therefore, it makes such paramagnetic CEST agents (paraCEST agents) very attractive.

In the contribution, some recent results achieved by Group of Bioinorganic and Coordination Chemistry of Faculty of Science, Charles University, in field of development of new CAs for MRI will be presented.

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New Trends in Chemistry from the Point of View of an Old Chemist

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Following topics will be presented in this lecture.

1. Structure, preparation and applications of Metal-Organic Frameworks (MOF). Special attention will be paid on the applications of MOF as catalysts as well as gas storage materials. Application of MOF at xenon recovery will be mentioned.
2. Structure, preparation and applications of Molecular-Organic Frameworks. Comparison of KOF and MOF.
3. Nanocatalysts and magnetical nanocatalysts. Examples of their preparation as well as applications in organic synthesis will be given.
4. New, non-traditional solvents in synthesis.
   - 4.1. Water as non-traditional solvents in organic synthesis. Reactions in water and on water, reactions in nanomicelles.
   - 4.2. Ionic liquid (IL)s and Deep Eutectic Solvents (DES). Description, method of preparations will be presented. Special attention will be given to their industrial applications as well as their usage in organic as well as inorganic reactions and biochemistry. Examples of their applications at different extraction processes will be given.
5. Switchable solvents.
6. Fluorous solvents and fluorous chemistry. Phase vanishing method. Application of perfluorinated solvents as blood substitutes will be mentioned.

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Toward Synthesis of Dodeca-cavitane, Sugar-based Analogue of Dodecahedrane Possessing a Cavity for Hydrogen Bonding

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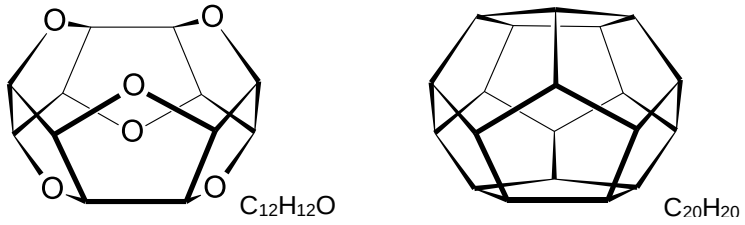
1,4:3,6-Dianhydro-D-mannitol contains two *cis*-fused tetrahydrofuran five-membered rings with their dihedral angle of approximately 116°, decorated with two free *endo*-oriented hydroxyl groups. A formal triple intramolecular extension of this structural motif results in a unique, convex-cylindrical structure composed of six fused antiparallel tetrahydrofuran rings (Fig. 1 (1)). This hexa-anhydro C_{12}-cyclitol, or simply dodeca-cavitane, containing twelve symmetry-equivalent C-H units, can be formally derived also from dodecahedrane (Fig. 1 (2)) [1], *viz*. by a formal removal of two antipodal carbon atoms and simultaneous replacement of their six naked neghbouring carbon atoms by the oxygen atoms.



1 **2**

Figure 1 Structural formulae of dodeca-cavitane (**1**) and dodecahedrane (**2**)

The molecular modelling studies revealed, among others, that the distance between proton placed into this $C_{12}H_{12}O_6$ double crown ether cavity and its oxygen atoms is 2.088 Å. Sequential and block approaches undertaken towards the synthesis of this novel compound will be presented too.

Acknowledgements

This work was supported by the grant agency VEGA, project 2/0024/16.

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Health Risk Assessment from the Gajdovka Mineral Spring Water in Košice

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Mineral water from the source of Gajdovka in Košice is very popular among the inhabitants. It is characterized by its sulphan odour and also by the presence of arsenic which comes into the water by the hydrolytic decomposition of sulfide iron minerals containing arsenic. The concentration of this potentially toxic element in water is variable. The work is focused on the analysis of basic chemical and microbiological indicators of mineral water quality in the period of the years 2013 to 2015. It focuses in particular on monitoring the total arsenic concentration which was determined at regular weekly intervals during the year of 2014. The results of the total arsenic concentration for 51 samples which were evaluated in 2014, ranged from 0.047 to 0.110 mg dm^{-3} with a mean of 0.063 mg dm^{-3} [1]. This value, as well as the average concentrations in 11 individual months, exceeds the defined limit value for As(III) content. Assuming that As(III) accounts for 80 to 90 % of total arsenic [2], the limit value was exceeded in seven months. Exceeding of other chemical and microbiological indicators has not been established. Based on the analysis results, an estimation of the health risk from the consumption of mineral water was made. The estimation of the cancer growth risk in lifetime exposure was calculated, as well as an estimation of the maximum daily intake of arsenic when consuming different amounts of mineral water. When consuming Gajdovka mineral water, consumers should follow the instructions and recommendations of the state authorities that are published at the mineral water collection site.

Acknowledgements

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Nanosafety: Research, Development, Commercialisation and Ethical Aspects

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The research is focused on study of unknown thermodynamic, redox and corrosion properties of metallic nanoparticles (NPs) using electrochemical techniques, quartz crystal microbalance technique, FIB microscopy with aim to develop new kind of sensor for determination of stability and life-time of any metallic nanoobjects. Thermodynamic aspects are mainly joint with redox properties, corrosion behavior of metallic nanoobjects in environmental and biomedical applications but are still complicated to monitor due to the lacks of experimental techniques and weak theoretical basis. Nanobjects differ in reactivity compared to bulk material, especially where is no information about Pourbaix diagramme for metals in nanoscale which say about their noblessness. Together with the fact, that surface of exposed metallic nanoobjects in various applications could be modified lead to different interaction with environment and to enormous changes in their original characteristics and their life-time suitable for specific application.

Experimental measurements were compared with the results coming from quantum chemical calculations to explain mechanism of changed reactivity of NPs after surface treatment in environment of interest. Assessment of safe use of NPs vs. potential hazard will be set-up in database as support for EU legislation. Development of technique based on traditional electrochemical methods hyphenated with non-electrochemical methods and with support of quantum chemical calculations in strong interdisciplinary nanotechnology area can lead to series of new results which have been not explained in complex form until nowadays. Research contributes on preventing step in helping scientists and decision makers to add more safety issue in nanotechnology sector together with opening question on ethical aspects.

Acknowledgements

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The Study of Protein Nanomechanics Employing Optical Force Meter

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When looking at protein structures at atomic resolution, it is often tempting to use macroscopic mechanical analogies to describe their function as molecular machines. However, such analogies are often misleading because boundaries between independently stable subdomains cannot often be determined precisely, owing to the high cooperativity between the individual structural parts. Single-molecule optical force meter has emerged as a tool to study protein conformational space and identify hinges, breaking points, as well as mechanically stable subdomains [1]. My research includes the study of most prominent examples of protein machines undergoing large conformational changes: adenylate kinase (AdK) [2] and the Hsp70 chaperone DnaK [3-5].

Subnanometer enzyme mechanics

AdK catalyzes the reversible conversion of ATP and AMP to two ADPs and thereby plays an important role in the energy balance in the cell. Adk consists of three domains. The ATP- and AMP-lid are responsible for binding of substrates, and the CORE domain governs the overall stability of the enzyme. During its catalytic cycle, AdK undergoes a large conformational change and the ATP- and AMP-lid close over the CORE domain, thereby reducing unproductive active site fluctuations and minimizing non-productive hydrolysis. We used subnanometre single-molecule optical force meter to measure the substrate-dependent forces that drive AdK into a closed conformation. In the presence of the bisubstrate inhibitor diadenosine pentaphosphate (AP5A), closing and opening of both lids is cooperative and tightly coupled to inhibitor binding. Surprisingly, binding of the substrates ADP and ATP exhibits a much smaller energetic drive towards the fully closed state. Instead, we observe a new functionally important states with both lids half closed. Our results, combining experiment and molecular dynamics simulations, give detailed mechanical insights into how an enzyme can cope with the seemingly contradictory requirements of rapid substrate exchange and tight closing, to ensure efficient catalysis.

Hsp70 chaperone nanomechanics

Hsp70 is a protein nanometer-sized molecular machine operating similar to a macroscopic engine: combustion of fuel (ATP in the case of Hsp70) triggers a mechanical motion for its function. However, in contrast to macroscopic engines, protein molecular machines face additional limitations imposed by thermal fluctuations and by the low intrinsic stability of the individual components of such machine. Using single-molecule force spectroscopy, we drive the passive machine through its mechanical states allowing us to detect its relevant hinges and moving parts [3]. Applying this approach to the substrate binding domain (SBD) of Hsp70, we identified mechanical subunits and hinges of the SBD. Interestingly, these parts are also involved in an ATP-fueled biological conformational change of Hsp70. In summary, single-molecule manipulation gives insight into the basic operating principles of nanoscale molecular machines.

Acknowledgments

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Innovation of Content, Form and Methodology of Inorganic Laboratory Practice with Direct Cooperation of Company DUSLO, a. s., Production Operation Strážske Like Potential Employer of Inorganic Chemistry Field Leavers

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Human society has changed more than ever before over the last fifty years. Our lifestyle and labour market have changed and employers' requirements to young school leavers (their potential employees) also have been changed. Workers in the 21st century must have the skills to process information, including reader literacy, mathematical literacy and problem-solving skills. Today, the school is only one of the places where students learn.

In this context, the role of dialogue between schools and employers is increasingly recognized. These time requirements should also be addressed to educational institutions in chemical professions. The subjects of practical education in the area of natural education are crucial for the readiness and applicability of graduates in the labor market. Based on these requirements, in cooperation with employers, we innovate practical lessons at bachelor level in all study fields, inorganic chemistry, analytical chemistry, physical chemistry and biochemistry, focusing on the requirements of practice.

Within the content and methodological innovations, diagnostic procedures used in company DUSLO, a. s., production operation Strážske (titrations – potentiometric, complexometric (CaO, MgO determination, calcite analysis) will be established into Inorganic laboratory practice. Moreover spectroscopic methods (for Fe content determination in calcite, in condensate, for NO_3^- and NH_4^+ content determination in the effluents which are produced in the production of calcium nitrate and nitric acid.

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Innovation of Content, Form and Methodology of Physical Chemistry Laboratory Practice with Direct Cooperation of Institute of Forensic Science in Košice like Potential Employer of Physical Chemistry Field Leavers

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Progress and innovation in technology over the past 20 years have changed the human society and our life. Consequently, employers' requirements to young school leavers (their potential employees) also have been changed. Recently, the school leavers should possess a general knowledge of skills with good working attitude. A good Chemistry degree opens the door to an extensive choice of careers, hovewer school-leavers lack essential workplace skills. Today, the school curriculum should be more responsive to the needs of employers. If school leavers have good communication skills, this would give a strong credential advantage for them in the view of employers.

Based on these requirements, in cooperation with employers, we innovate practical lessons at bachelor level in physical chemistry focusing on thevaluable skills that employers look for. The aim of the innovation process is to involve potential industrial employers into the teaching process and the preparation of students for the labour market.

Within the content and methodological innovations, analytical and expertise procedures used in Institute of Forensic Science in Košice (ion mobility. spectrometry, chemographic and microscopic analysis) will be established into Physical chemistry laboratory practice.

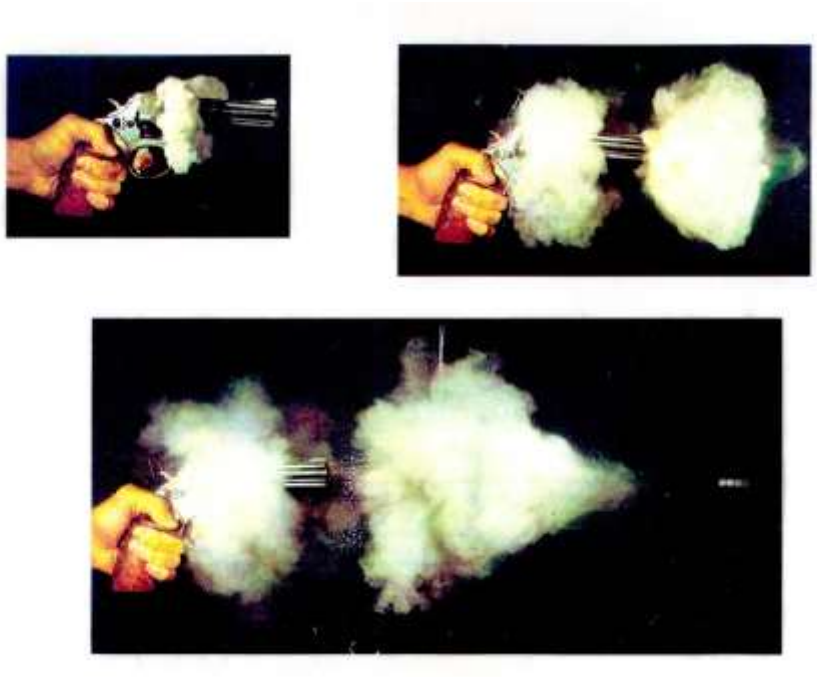

Figure 1 The formation of gunshot residues after shooting from firearm

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Application of the Optical Probe in Analytical Chemistry

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Results and discussion

Recent achievements in using of the optical probes in analytical chemistry will be presented and discussed [1-3].

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Alternative Function of Cytochrome c

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Cytochrome c (cyt c) is a well-known hemeprotein located on the external side of the inner mitochondrial membrane. The main function of cyt c is to shuttle electrons in mitochondrial respiratory chain between Complex III and Complex IV [1].

Recently, it has been found out that cyt c plays important role in the activation of a programmed cell death cascade [2], can function as a cardiolipin-specific oxygenase that chemically oxidizes cardiolipin, and is an active player in regulation of oxidative stress by removal of H_2O_2. All the above alternative functions of cyt c depends on its peroxidase-like activity [3]. However, the peroxidase-like activity of cyt c in its native and non-native hexacoordinated conformational states is still puzzling since in order to the H_2O_2 to be consumed it needs to interact with the heme iron [4]. While some authors proposed that cyt c peroxidase-like activity has to be activated by H_2O_2-induced covalent modifications [5], several other reports clearly demonstrated that an increased peroxidase-like activity of cyt c induced by point mutation [6] or as the result of interaction with cardiolipin containing vesicles [7] was not accompanied by significant conformational change of cyt c and its heme region of remains in the native-like state. The apparent absence of conformational change suggests that the increased peroxidase-like activity is intermediated by transiently populated pentacoordinated state of the heme iron likely due to increased dynamics of the heme region as a result of reversible unfolding of the least stable foldons of cyt c. This suggestion was supported by demonstration of the binding of small ligands, such as cyanide [8] to the heme iron. In our recent work we show that peroxidase-like activity, measured by guaiacol oxidation and the ferrous oxidation in xylenol orange methods, correlates with the accessibility of the heme iron, which was assessed from the association rate constant of cyanide binding to cyt c.

Our results suggest that dynamics equilibrium among the denaturant-induced non-native coordination states of cyt c, very likely due to reversible unfolding of the least stable foldons, is pre-requisite for enhanced peroxidase-like activity of cyt c in its compact state. Dynamics replacement of the native sixth coordination bond of methionine-80 by other ligands such as lysines (72, 73, and 79) and partially also by histidines (26 and 33) provides an efficient way how to increase peroxidase-like activity of cyt c without significant conformational change at physiological conditions.

Acknowledgements

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Metal-Organic Frameworks: History, Design and Applications

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Metal−organic frameworks (MOFs) have emerged as an extensive class of crystalline materials with ultrahigh porosity and enormous internal surface areas, extending beyond 10 000 m^2g^{-1}. These properties, together with the extraordinary degree of variability for both the organic and inorganic components of their structures, make MOFs of interest for potential applications in gas storage and separations, catalysis, ion exchange, drug delivery and biomedical imaging (Fig. 1). Since the 1990s, after the discovery of MOF-5, this area of chemistry has experienced an almost unparalleled growth, as evidenced by not only the sheer number of research papers published but also the ever-expanding scope of the research.

One of the hallmarks of MOFs is their topologically diverse and aesthetically pleasing structures, many of which are derived from minerals in nature. Designing a target structure with specific properties and functions represents an eternal aspiration for materials scientists. The combination of the two components of a MOF, the metal ion or cluster and the organic linker, provides endless possibilities. The sum of the physical properties of the inorganic and organic components and the possible synergistic play between the two provide intriguing properties for a MOF. In our design strategy we have prepared and characterized several novel MOFs using the combination of tetrahedral tetracarboxylic acids and planar tricarboxylic acids in combination with different transition/nontransition metals. Materials were tested as gas adsorbents for nitrogen, hydrogen, methane and carbon dioxide, as heterogeneous catalysts in Knoevenagel condensation of active methylene compounds with different bulky aldehydes, as an effective ion exchangers and in addition as supports for controlled drug delivery.

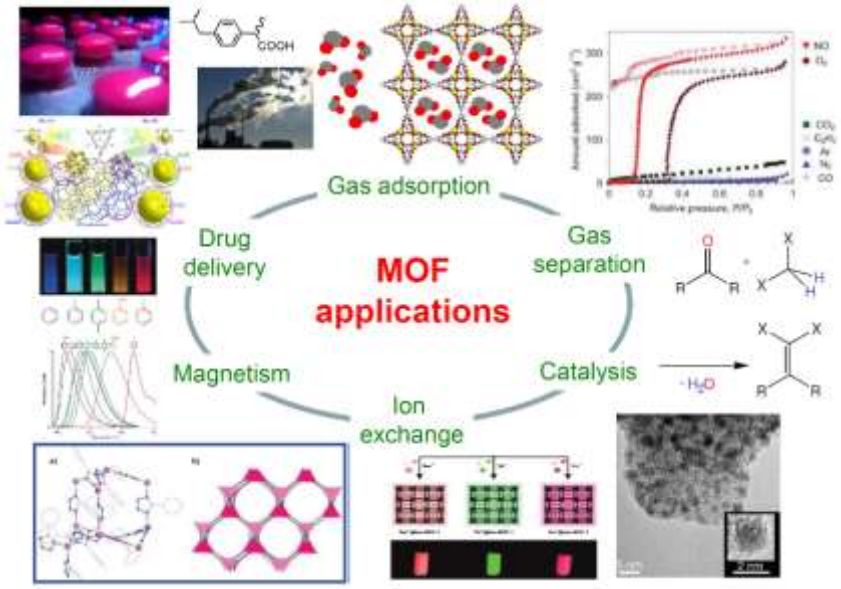

Figure 1 Different areas of MOF applications

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Hydrophobicity Enhancement of Metal–Polymer Hybrid Layers

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We have prepared new nickel-polymer nanohybrid layers by electrochemical deposition and spin-coating. Polymer layer was spin-coated [1] on to previously electrodeposited layer of certain hydrophobicity. We have used high density polyethylene solution a source of polymer. To examine influence of polymer layer to the final hydrophobicity we have prepared two types of hybrid layers. The first one was prepared using of 120 μL of polymer solution, the second one using 60 μL of polymer solution. The aim of the work was to characterize the hydrophobicity of metal-polymer hybrids. Hydrophobicity was quantified as surface energy calculated using Owens-Wendt method presented elsewhere [2, 3]. Surface polarity was calculated as the ratio of polar and dispersive component of surface tension. It was shown that presence of polymer layer increases surface hydrophobicity. In case of polymer layer of 60 μL was observed change in surface energy of 1.22 mJm^{-2} and in case of polymer layer of 120 μL was observed surface energy change of 4.0 mJm^{-2}. Even though the hybrid prepared using 60 μL of polymer solution did not have the lowest surface energy we consider this structured polymer the most hydrophobic due to highest value of water and diiodomethane contact angle and the highest surface polarity. This study provides the comparison of hydrophobicity enhancement caused by presence of thin polymer layer spin-coated directly on to prepared metal surface as it is stated in our previous publication [4].

Acknowledgements

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Therapeutic Drug Monitoring of Piperacillin-Tazobactam

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Piperacillin-tazobactam is a beta-lactam/beta-lactamase combination antimicrobial therapy with broad-spectrum activity against both Gram-negative and Gram-positive bacteria. Piperacillin-tazobactam is preferentially prescribed in hospital or critical care settings for the treatment of moderate to severe infection [1].

Piperacillin (Fig. 1) is a semisynthetic ureidopenicillin with high antibacterial activity. However, the usage of piperacillin was restricted due to the increased occurrence of beta-lactamase-producing bacteria [2].

Tazobactam (Fig. 2) is a synthetic Penicillanic acid sulfone. It works as a betalactamase inhibitor and protects piperacillin from destruction by betalactamase enzyme [2].

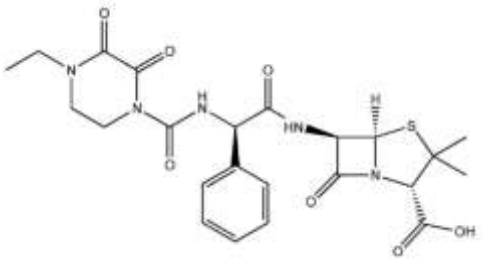

Figure 1 Piperacillin

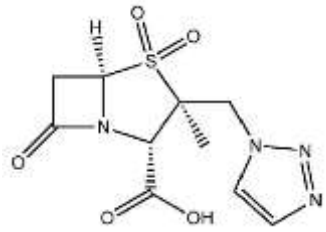

Figure 2 Tazobactam

Antimicrobial therapy is usually based on standard dosing protocols. However, numerous studies point out that heterogenous patient populations with growing complexity have pharmacokinetics that are subject to substantial inter-individual variation. Accordingly, traditional antibiotic dosing strategies are becoming increasingly problematic, as the pharmacokinetic/pharmacodynamic (PK/PD) target that is required for effective treatment of severe infections may not be reached [3]. The therapeutic drug monitoring (TDM) provides an advanced option for therapy optimization, especially by seriously ill intensive care patients. For the time-dependent killing kinetics of these drugs, the effectiveness depends crucially on the fact that the concentration of the antibiotic over long stretches of the dose interval is above the MIC (minimal inhibitory concentration) of the responsible pathogen [4].

Various analytical methods for multi-analyte antibiotic TDM have been published in the past. Among these, several high-performance liquid chromatography (HPLC) procedures were combine with UV-detection. These methods, however usually have rather long run times, low detection capabilities and they are not very selective. Especially in the case of seriously ill patients with intensive care is an increased risk of interference with co-medications and endogenous substances. Liquid chromatography coupled to tandem mass spectrometric (LC-MS/MS) detection is a very powerful tool and has many advantages, such as enhanced specificity and the ability to simultaneously measure multiple analytes in highly complex biological matrices [5].

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Polysaccharide Derivatives in Chromatographic Separation of some Drug Enantiomers

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Polysaccharide-based chiral stationary phases can resolve a wide range of racemic compounds including many chiral pharmaceuticals.

In general, the native amylose and cellulose are weak chiral selectors and therefore only their chemical derivatives are applied in practice. At present, the best known are tris-benzoate and tris-phenylcarbamate derivatives of amylose and cellulose which can be coated or immobilized on a silica gel support.

In this work, an immobilized amylose-based chiral stationary phase was used for the enantioselective LC separation of selected drugs. The effects of the mobile phase composition and other experimental variables on the enantioresolution were investigated.

Acknowledgements

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Applications of Dispersive Liquid-Liquid Microextraction in the Analysis of Estrogens

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Estrogens are important human hormones responsible for the function of female gonadal system and numerous biological actions within the organism in both males and females. The interest in the determination of estrogens has grown since they have been linked to many adverse effect on human health and living organisms. Low concentrations (ng L^{-1}) of estrogens can be found not only in biological matrices but also in environmental and food samples. Despite the high sensitivity and selectivity provided by current analytical methods employed in the analysis of estrogens, it is still very difficult to directly use them for their determination due to very low concentrations of estrogens in often very complex character of analysed samples. The use of extraction method prior to the analysis itself, therefore, still remains mandatory in order to preconcentrate the analyte and to reduce the matrix effect.

Recent research activities in modern analytical chemistry are oriented towards the development of environmentally-friendly, efficient, economical, and miniaturized extraction procedures that adapt the principles of conventional sample techniques such as liquid-liquid extraction and solid-phase extraction. One of the latest microextraction approaches termed dispersive liquid-liquid microextraction (DLLME) was introduced in 2006 by Rezaee et al. [1]. This extraction technique is based on the distribution of the analyte within ternary system consisting of the aqueous phase and the mixture of suitable extraction and dispersive solvents. DLLME has become a very popular method owing to its accessibility, rapidity and applicability to various types of matrices.
This work provides an overview of DLLME applications to the determination of estrogens in different types of matrices [2, 3].

Acknowledgements

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Application of LED Induced Fluorescence Spectroscopy for Determination of Photoluminescence Quantum Yields of some Fluorescence Dyes

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In the last few decades, luminescence techniques have become one of the most popular and sensitive analytical and detection tools. In the most cases the source of this fluorescence signal can be some organic dyes, metal-ion complexes, quantum dots, fluorophore-doped or fluorophore-labeled particles. A key parameter for fluorophores comparison is the photoluminescence quantum yield, which is direct measure the efficiency of the conversion of absorbed light into emitted light [1]. The quantum yields the series of 12 organic dyes were determined and compared by the relative method. For the determination the QY of the sample dye we measure the fluorescence spectrum and compare its integrated intensity of with reference fluorescence dye with a known QY under the constant experimental conditions [2]. For prevention the inner filter effects (self-quenching) when the emitted light is absorbed by the same solution of the dye we prepared and measured the solutions of this dyes with smaller than 0.1 absorbance units at λ_{MAX} when after this action these effects may be negligible. As the QY standard we chose the diluted solution of Rhodamine 6G which is considered as one of the well-established photoluminescence QY standard. As the excitation light source was used the 100 W white LED diode with constant spectral radiant flux whose emission spectrum partially overlaps each of the excitation spectrums of studied dyes. We studied these dyes: Rhodamine 6G; Rhodamine B; Fluorescein; Acridine orange G; Cresyl Violet; Pyronine B; 1,1',3,3,3',3'-Hexamethyl-2,2'-diindocarbocyanine chloride (Cy3); 1,1',3,3,3',3'-Hexamethyl-2,2'-diindodicarbocyanine iodide (Cy5); 3,3'-Diethyloxadicarbocyanine iodide (DODC); Astrazon Gelb; Astrazon Brilliant Red 4G and Basacryl Red. The absorption spectrums were recorded by Ocean Optics USB4000 UV-VIS spectrometer and the fluorescence emission spectrums were recorded simultaneously by Ocean Optics Flame spectrometer all in quartz flow fluorescence cuvette.

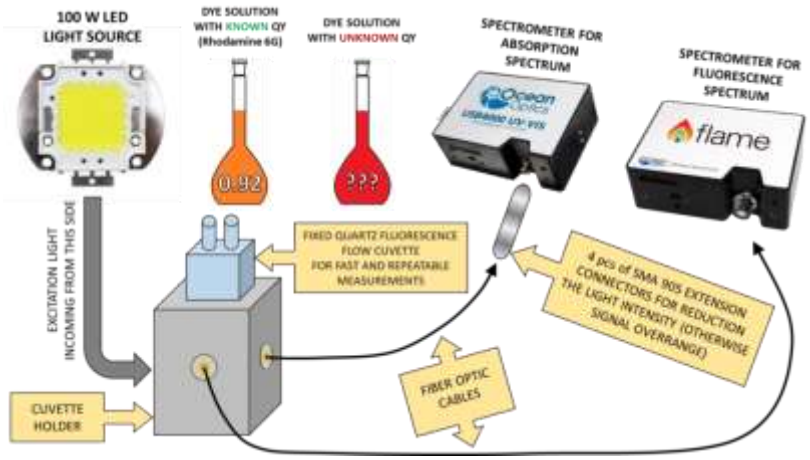

Figure 1 Schematic illustration of used system

Acknowledgements

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Organic Solvent's Influence on Adsorption Spectra of Complex Compound Pd(II) with 3-Nitro-(1(5-Benthiltiazol-2-il)Azo-Naphtalen-2-ol

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Development of the new analytical methods for the determination of Pd in environmental samples was caused by the use of this element in cars fitted with exhaust catalysts. Thiazolylazo dyes represent synthetic reagents which are widely used in analytical chemistry within spectrophotometry. These dyes have attracted much attention as the largest group of organic analytical reagents used in spectrophotometric analysis owing to the high sensitivity and selectivity. New analytical reagent 3-nitro-(1(5-benthiltiazol-2-il)azo-naphtalen-2-ol (nitro-BnTAN, Fig. 1) react with Pd(II) ions in wide range of pH. Adsorption spectra of nitro-BnTAN have maximum at 496 nm in alcohol solution. Adsorption spectra of complex compound nitro-BnTAN with Pd(II) ions have maximum at 684 nm. The acidity of the environment changes the maximum's height of the compound, the highest value is observed at pH = 1.0. Reaction goes without heating. Complex compound is not dissolved in aqua solution that is why it was extracted to organic solvent.

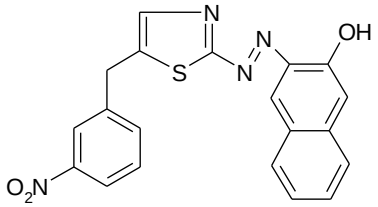

Figure 1 Structural formula of 3-nitro-(1(5-benthiltiazol-2-il)azo-naphtalen-2-ol

Table 1 Spectra's maximums and molar attenuation coefficient of the reagent and compound in different organic solvents

Solvent	reagent		compound		Solvent	reagent		compound	
	λ, nm	$\varepsilon\times10^{-3}$	λ, nm	$\varepsilon\times10^{-3}$		λ, nm	$\varepsilon\times10^{-3}$	λ, nm	$\varepsilon\times10^{-3}$
Cyclohexane	480	3,3*	-	-	Dichlormethan	481	6,9*	-	-
Acetylacetone	482	10,7	680	11,2	Chloroform	480	6,5*	-	-
1-decanol	485	7,3	680	4,1	n- butylacetat	483	7,7	680	3,8
Isobutyl acetate	482	7,4	679	5,7	Triethylamine	547	6,5	567	6,2
Tetrachlormethan	481	6,9	-	-	n-amylacetat	483	7, 8	680	6,4
Methyl-isobutylketon	482	7,8	680	10,4	n-propylalkohol	480	10,4	679	7,8
1-octanol	484	7,7	680	5,6	Toluen	480	3,5	684	7,7
n-heptane	484	4,0*	-	-	n-butylalkohol	483	5,1	678	3,1*
Tributyl phosphate	483	5,8	679	11,7	n-amylalkohol	483	8,3	679	4,9
n-hexane	481	3,9*	-	-	xylen	482	8,3*	685	5,6

- extraction does not pass; *extraction is not full; ε molar attenuation coefficient, l/(mol×cm)

We studied more than 20 organic solvents and we can conclude that:

1. Saturated hydrocarbons (n-heptane, n-hexane) don't extract the complex compound.
2. Spectra of chlorinated derivatives of saturated hydrocarbons (1,2-dichloroethane, Dichlormethan, Chloroform) blurred due to water and sodium sulfate
3. Extraction with the lower alcohols (n-butylalkohol) is not complete
4. The best extraction is observed with ketones (Acetylacetone, Methyl-isobutylketon)

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HPLC Analysis of Preservatives in Cough Syrup

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Preservatives are added to pharmaceutical formulations to ensure that they do not carry pathogenic microorganisms and to eliminate the growth of microbes. The safety of pharmaceutical products should be considered in the presence of preservatives. The acceptable daily intake (ADI) represents amount of daily consumption of substance without any risk even for a lifetime. According to ADI, the maximum permitted limit for food additives is based on mg/kg of body weight [1]. The most commonly used preservatives in pharma liquid products such as syrups are benzoate, sorbate, benzoic acid and sorbic acid. It is therefore necessary for pharmaceutical product manufacturers to develop methods to screen drugs for these compounds. The determination of these substances in pharmaceuticals is important in quality control, especially considering the numerous reports of allergic reactions caused by preservatives [2]. High performance liquid chromatography on reverse phase (RP-HPLC) ranks among the most important analytical techniques in the field of pharmaceutical analysis thanks to its robustness and the ability to separate and qualitatively and quantitatively analyse the compounds presented in various samples. The ongoing progress in the development of novel stationary phases and detection techniques allows rapid analysis and to get comprehensive characterization of the analytes presented in the complex samples even at very low concentrations. The aim of the research work was to perform the optimization of chromatographic conditions for determination of sorbic acid used as a preservative in cough syrup for kids. Sorbic acid is an antimicrobial agent frequently used in liquid solutions in different pharmaceutical formulations.

Methods

Chromatografic analysis was performed using a Dionex UltiMate 3000RS system (Thermo Fisher Scientific, Germany) equipped with quaternary pump, degasser, automated injector, column oven, diode array detector (DAD) and programmable Chromeleon Chromatography Data System, Version 7.2. Chromatographic separation was achieved on the chromatographic column Polaris C18-A (250×4.6 mm; 5 μm) (Varian, USA). The mobile phase consisted of the mixture of acetate buffer solution (pH 4.48) and acetonitrile (60:40, v/v). By using isocratic elution, the preservative was successfully analysed within 10 minutes. The column temperature was set at 45°C, the flow rate was set at 1.0 mL/min and the injection volume was set at 10 μL. The detection wavelength was set at 259 nm.

Results

Several tests were performed for optimizing the components of mobile phase to achieve good chromatographic peak shape and resolution. Good separation of the target compound and short run time were obtained by using a mobile phase system of acetate buffer solution (pH 4.48) and acetonitrile (60:40, v/v). Under the chosen chromatographic conditions, sorbic acid showed a retention time of 4.07 min. Quantification was achieved with UV detection at 259 nm based on peak area. The equation of linear regression obtained for the six concentration levels, each one injected three times, was $y=1.4233x+8.6425$. The regression coefficient R^2 was 0.9976, indicating good linearity. From the analytical curve, the linearity of the method was evaluated, demonstrating a linear interval in the range of 25 to 152 μg/mL.

Acknowledgements

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Preparation of MOFs Using Bulky Tetrahedral Linkers

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Porous metal-organic frameworks (MOFs) represent a class of crystalline micro-/mesoporous materials constructed by assembly of metal cations or their clusters as connectors, and usually anionic organic ligands as linkers [1]. The final structure and dimensionality of MOFs depends on several factors, such as molar ratio of reactants, composition and the ratio of the mixture of solvents, choice of organic linker and inorganic salt, pH value, reaction temperature etc. [2]. One of the most important properties of porous MOFs is their high specific surface area, which may lead to applications in the fields of gas storage and separation, achiral and chiral catalysis, drug delivery, sensor technology, polymerization reactions in the channels [3].
The synthesis of MOFs can be considered as "construction game", because the final architecture depends on the building blocks and their compatibilities. Depending on the synthetic conditions is possible to prepare compounds with different composition and topology. The reaction conditions influenced the molecular geometry and connectivity of the selected ligand. Our design strategy was to synthesize different bulky tetrahedral carboxylic acids for final metal-organic frameworks preparation. We have successfully prepared four derivates of methanetetracarboxylic acid with extended arms, namely:

- 4,4′,4′′,4′′′-(1E,1′E,1′′E,1′′′E)-(4,4′,4′′,4′′′-methanetetrayltetrakis(benzene-4,1-diyl)tetrakis(azan-1-yl-1-ylidene))tetrakis(methan-1-yl-1-yliden)tetrabenzoic acid (H_4MIB)
- 4,4′,4′′,4′′′-(1E,1′E,1′′E,1′′′E)-(4,4′,4′′,4′′′-methanetetrayltetrakis(benzene-4,1-diyl)tetrakis(azan-1-yl-1-ylidene))tetrakis(methan-1-yl-1-yliden)tetrabenzoic acid (H_4MAB)
- 4',4'',4''',4''''-methanetetrayltetrabiphenyl-4-carboxylic acid (H_4MTBC)
- 4,4′,4′′,4′′′-(1E,1′E,1′′E,1′′′E)-(4,4′,4′′,4′′′-methanetetrayltetrakis(benzene-4,1-diyl)tetrakis(aza))tetrakis(methan-1-yl-1-yliden)tetrabenzoic (H_4MTFAB)

Four novel tetrahedral carboxylic acids were prepared and characterized by the methods of infrared spectroscopy (IR) and nuclear magnetic resonance (NMR). Synthesized bulky acids will be used in the preparation of MOFs, which will be further test as adsorbents for carbon dioxide and hydrogen storage.

Acknowledgements

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Lithium Exchanged Cationic MOFs for Hydrogen Storage

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Over the last two decades, metal–organic frameworks (MOFs) have received great attention and the number of reported compounds is still growing, which is mainly due to their amazing structures and various pore topologies, accessible cages and their potential applications in different fields, such as gas storage, separation, ion-exchange and catalysis [1]. Among these, ion-exchange processes are considered as the post-synthetic parturient technique as it can achieve dominant applications [2]. There are two primary types of ion-exchange processes (anionic and cationic) and each type may use naturally occurring and synthetic materials.

The aim of our work, was to synthesize lithium exchanged metal-organic frameworks for hydrogen storage. In our design strategy, we have prepared three porous cationic MOFs with compositions $\{(DMA)[Mg(FOR)_3]\}_n$, $\{(DMA)[Co(TAD)]\}_n$ and $\{(DMA)[Zn(BTC)]\cdot DMF\}_n$ which contain dimethylammonium ions (DMA) in their structures for stabilization of the frameworks. Polymeric skeletons are build form carboxylic linkers with different sizes, from the simplest formate (FOR) through 1,2,3-triazole-4,5-dicarboxylate (TAD) and the largest linker, benzene-1,3,5-tricarboxylate (BTC). In the synthesized samples, DMA ions were exchanged by lithium ions (Fig. 1). It is known, that lithium ions have high affinity to hydrogen molecules and therefore these ions were selected for ion exchange process. Prepared materials were characterized by several physicochemical methods and in the future plans, they will be tested as adsorbents for hydrogen storage.

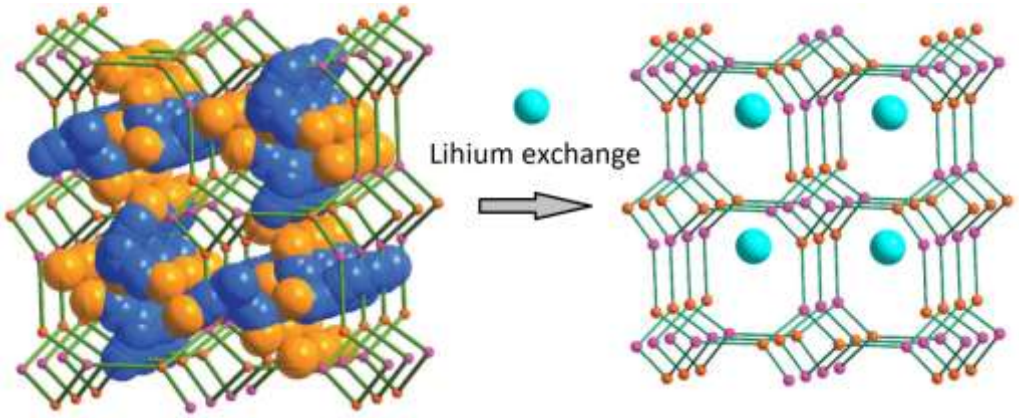

Figure 1 Lithium exchange process in compound $\{(DMA)[Co(TAD)]\}_n$ (DMA = dimethylammonium cation; TAD = 1,2,3-triazole-4,5-dicarboxylate)

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Stimuli-responsive Mesoporous Silica Nanoparticles for Drug Delivery Applications

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Mesoporous silica nanoparticles (MSNs) offer a biocompatible multifunctional platform with intrinsically high surface area and porosity that able to deliver drugs such as chemotherapeutic agents, antibiotics, anti-inflammatory molecules. One of their main advantages is their ability to be used for both hydrophilic active agents and poorly water soluble drugs by increasing their solubility. MSNs readily accommodate stimulus-responsive functionalization to enable on-command release of drug cargo in response to a variety of stimuli, including light, pH, temperature, magnetic field [1].

In this work, we present two different types of stimuli-responsive controlled drug delivery systems (DDSs). The first one is a light-activated DDS consisting of mesoporous silica with surface modified by p-coumaric acid derivative as photo-switchable ligands. It was studied for delivery of naproxen that is non-steroidal anti-inflammatory drug. For this purpose, MCM-41 mesoporous silica was post-synthetically modified by derivative of p-coumaric acid which undergoes a reversible photo-dimerization under UV irradiation and creates the "valves" on the surface of silica allowing targeted opening/closing of the pores. After a complete materials characterization, the drug release was studied and differences were observed after irradiation of material by UV light with λ=365 nm (closed pore configuration) and UV light with λ = 254 nm (opened pore configuration) [2].

The second one is a pH-responsive DDS consisting in cyclodextrin (CD)-capped MSNs. The pH-responsive nanovalves are composed of an amine-based stalk attached to silica nanoparticles that can bind beta-cyclodextrin units non-covalently through supramolecular interactions. When the pH is decreased from its initial value (pH=7.4), the amine derivatives become protonated resulting a binding affinity to the cyclodextrin that is drastically decreased. The cyclodextrin caps are thus dispersed around from the stalks and pores are un-blocked. An antineoplastic agent for the treatment of gastrointestinal cancers, 5-fluorouracil was employed as the cargo model.

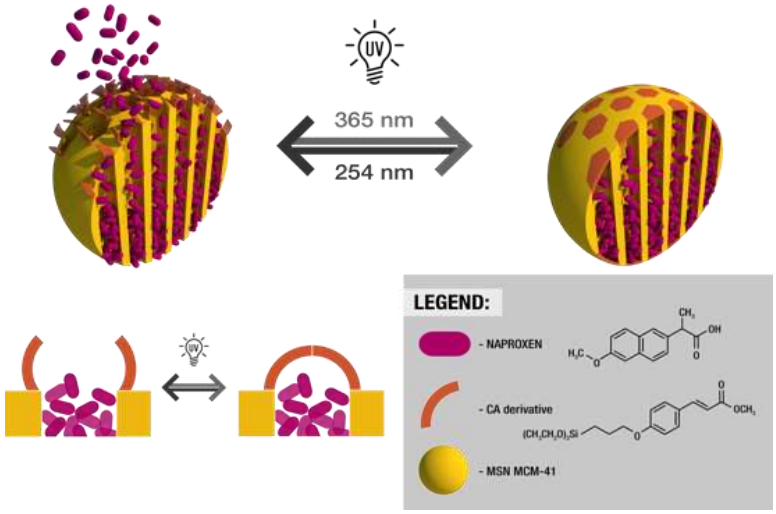

Figure1 Schematic representation of UV light - activated drug delivery system

Acknowledgements

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Aryl-Substituted Spiroacridines with Promising DNA-Binding Properties

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DNA is the pharmacological target of many of the drugs that are currently in clinical use or in advanced clinical trials. Targeting DNA to regulate cell functions by modulating transcription (gene expression and protein synthesis) or by interfering with replication (a major step in cell growth and division) seems logical, intuitively appealing and conceptually straightforward. Small ligand molecules bind to DNA and artificially alter and/or inhibit the functioning of DNA [1].

The study of interaction of drug with DNA is very exciting and significant not only in understanding the mechanism of interaction, but also for the design of new drugs. However, mechanism of interactions between drug molecules and DNA is still relatively little known. It is necessary to introduce more simple methods for investigating the mechanism of interaction [2].

Toward this goal a series of 1-[(*E*)-(R-methylidene)amino]-5-oxo-1,5-dihydro-10'*H*-spiro[acridine-9',2-pyrrole]-4-carbonitriles was synthesized. These compounds have been characterized by NMR, infrared spectroscopy, single-crystal X-ray structure analysis and elemental analysis. Moreover, the DNA-binding properties of these spiroacridines were investigated by electronic absorption, and fluorescence spectroscopy. The observed trend in hypochromism of Uv-vis absorption bands, reflects strong DNA-binding properties of drugs. Additionally, competitive binding studies with ethidium bromide (EB) have revealed through the quenching of DNA-EB fluorescence. The ability of the drugs to displace EB from the EB-DNA system suggesting intercalation as a possible mode of their interaction with calf thymus DNA (CT-DNA). All tested compounds exhibit good binding propensity to CT-DNA. From linear Stern-Volmer plot the K_{SV} binding constants were established in the range from 9.76×10^4 M^{-1} to $2{,}75\times10^5$ M^{-1}. Our results provide useful information about small ligand-DNA interactions, which are valuable for the rational drug design.

Acknowledgements

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Innovation of Biochemical Laboratory Practice in Cooperation with the Institute of Forensic Science of Slovak Republic Police Corps: When Biomolecules Can Help Reveal a Crime

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The general need for highly qualified and "ready to use" graduates led us to innovate the content of practical exercises, so that the students could gain knowledge and skills for independent professional work. From the areas where the specific chemical procedures are used routinely, we can mention criminological laboratories. Their main objective is to provide police with strong physical evidence tying suspects to crime scenes. One of the many branches that participate on this process is dactyloscopy. It relies on the analysis and classification of patterns in fingerprints even if the fingerprints are not very often visible by naked eye. Anyway, latent fingerprints can be made visible by various physical, chemical and physico-chemical methods.

In the field of biochemistry, the students will have the opportunity to visualize dactyloscopic traces. These contain, among other things, remains of biomolecules such as amino acids and lipids (contained in sweat) as a result of direct contact between a skin and a solid surface. They will learn how to make fingerprints as well as pushbacks of the palm visible professionally. To achieve this, they will apply methods that are routinely used in the Institute of Forensic Science of Slovak Republic Police Corps, Section of Dactyloscopy.

In the framework of this approach, new practical tasks will be introduced as a part of biochemistry practical classes with the aim to practice chemical and physico-chemical methods using ninhydrin as an agent that chemically reacts with amino acids contained in sweat and iodine vapors that adhere on the sticky sweat residuals. We hope that the skills acquired during this laboratory practicals would help our students to understand how scientific principles could be used by professionals. Last but not least, the acquired experiences might facilitate the students to get better position in the labor market.

Acknowledgements

This work was supported by the Ministry of Education, Science, Research and Sport of the Slovak Republic under the grant KEGA 008UPJŠ-4/2018.

Identification of G-Quadruplex Motif in Sequences of HIV Regions by Application of Characteristic Induced CD Signal of Complex G-Quadruplex-Thiazole Orange

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G-Quadruplexes (G4), noncanonical nucleic acid structures, act as silencers in the promoter regions of human genes; putative G-quadruplex forming sequences are also present in promoters of other mammals, yeasts, and prokaryotes. Mutations disrupting G4 formation enhanced HIV promoter activity in cells, whereas treatment with a G4 ligand impaired promoter activity and displayed antiviral effects. This findings disclose the possibility of inhibiting the HIV-1 LTR promoter by G4-interacting small molecules [1]. Beyond its use as model target for the identification of a structure specific synthetic ligand, probably that the stable HIV-G4 conjugate assembled might be exploited to isolate and identify G4-specific protein binders thereby providing new insights into viral regulation pathways. The formation of distinct viral G4 structures has been associated to distinct functional consequences in latency, virulence, or mutation rates [2].

More than 9 thousand genomic sequences of HIV isolates have been sequenced and analyzed. We have analyzed a series of DNA sequences with the potential to form G4 structures. Several such sequences were found in various coding and noncoding HIV virus domains, including the U3 LTR, tat, rev, env, and vpx regions [3]. These domains are not necessarily located only in regulating LTRs, but also in other gene coding regions. G-rich domains were also located in the minus-strand of many HIV-1 isolates, the sequence of which is highly homological with the well-known sequence forming the interlocked and extremely stable HIV integrase aptamer [4]. The sequences derived from original isolates were analyzed using standard spectral and electrophoretic methods. In addition, a new strategy developed in our laboratory where the unique characteristic spectral profile of G4-Thiazole Orange (TO) complexes of induced circular dichroism (ICD) was applied [3]. The ICD of any such complexes shows the positive ICD signals at ~495 and ~510 nm and the negative ICD signals at ~475 nm at certain condition. TO stabilizes G4 structures, it may also induce topological conversion of antiparallel to parallel form and facilitates G4 multimerization. The ICD signatures can be used to determine whether specific unknown sequences form G4 motifs [5].

Targeting the G4 or peptide domains corresponding to the G-rich coding sequence in HIV offers researchers attractive therapeutic targets which would be of particular use in the development of novel antiviral therapies. The analysis of G-rich regions can provide researchers with a path to find specific targets which could be of interest for specific types of virus [3].

Acknowledgements

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Spectral Changes and Stabilization of Curcumin Solubilized in Aqueous Environment by Hydrotropic Compound Disodium Cromoglicate

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Low aqueous solubility of chemical substances – potential drugs presents barrier for their full therapeutic utilization. It is referred, that about 40% of marketed drugs do not meet optimal solubility profile [1; 2]. Among drugs administrated *via* oral route, 37% are classified as poorly water-soluble [3].

Hydrotropes can be used for solubilisation enhancement of hydrophobic compounds [4]. Advantages of hydrotropy in the field of pharmaceutical solubilisation techniques are presented as follows: the solvent character is independent of pH, has high selectivity and does not require emulsification [5].

Disodium cromoglicate (DSCG) is an antiallergic drug used in clinical practice since 1970s [6]. This long application in humans proved cromolyn to be non-toxic and effective agent in humans. Moreover, it has interesting physicochemical properties - is able to form lyotropic liquid crystals and act as hydrotrope [7; 8].

We studied by spectroscopic methods efficacy of hydrotropic solubilisation and stabilization of curcumin – controversial lipophilic unstable compound, which struggles on its way to reach full employment in clinical practice, therefore represents a precious agent for development of novel techniques aiming to improve bioavailability of poorly water soluble drugs [9].

DSCG is able to increase absorbance as well as stability of curcumin in acidic and neutral pH.

Acknowledgements

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DNA Binding Properties and Antiproliferative Activity of Biscoumarin Derivatives Based on 7-Hydroxycoumarin

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Coumarins attract so much attention for their broad pharmacological properties. In recent years, the O-substituted analogues of 7-hydroxycoumarin and biscoumarin have attracted intense interest due to their anticancer effects [1]. A recent study revealed that coumarin interacts with DNA through groove binding mode [2]**.**

In this study, we examined the molecular interaction between calf thymus DNA (ctDNA) and new synthetized biscoumarin derivatives based on 7-hydroxycoumarin (Fig. 1), using UV-vis absorption, fluorescence spectroscopy and circular dichroism (CD) techniques. The binding constant, K_{sv} was obtained by fluorescence quenching that showed a static mechanism. The values of K_{sv} were in range of $10^2 – 10^3$ M^{-1}. The thermodynamic parameters were calculated from the fluorescence data measured at three different temperatures, and showed that the binding of **BC1-4** to the ctDNA was driven mainly by Van der Waal´s forces and hydrogen. The negative values of ΔG confirm that the binding process is enthalpy driven and spontaneous. In DNA melting experiment the change in melting temperature ctDNA in presence **BC1-5** was very small and was in range of 0.88 - 3.37 °C. The result of other experiments such as iodide inducted quenching and CD spectral analysis indicated that binding affinity between **BC1-5** and ctDNA is the non-intercalative groove binding mode.

The antiproliferative activity of **BC1-5** in A549 lung adenocarcinoma cell line was assessed using different techniques, such as MTT assay, quantification of cell number, viability and cell cycle distribution analysis. MTT assay indicated that the most significant decrease in metabolic activity of A549 cells was observed 48 h after action of **BC4** and **BC5**. IC_{50} values were evaluated as 57.37×10^{-6} M for **BC4** and 34.89×10^{-6} M for **BC5**. All of tested derivatives displayed significant decreased proliferative activity of cancer cells without affecting their viability. This suppression of proliferation by compound **BC3-5** was accompanied with accumulation of A549 cells in G0/G1 phase.

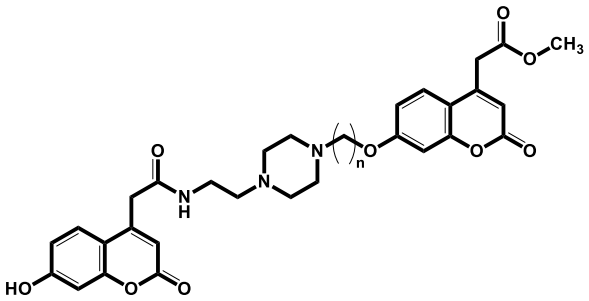

Figure 1 Structure of the biscoumarin derivatives (**BC1-5**, n = 3 – 4, 6 – 8)

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3,6-Diamino-9-Substituted Acridines and Their Interactions with Poly(rA): Anticancer and Gene Expression Regulatory Potential of the Anthracene Related Dyes

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The interaction of acridine derivatives with DNA plays an essential role in their biological activity. Acridine and its derivatives are interesting heterocyclic, aromatic, organic compounds, many of which exhibit several biological effects, including promising anticancer and cytotoxic properties. They represent an important class of drugs, capable of intercalation into DNA and inhibition of topoisomerase or telomerase enzymes. They are also used as antibacterial, antiprotozoal and antimalarial agents, biological fluorescent probes or in the treatment of HIV and Alzheimer´s disease. Last studies suggest that trisubstituted acridine derivatives exhibit strong anti-tumor effect, which involves several parallel mechanisms like telomere uncapping, direct or indirect telomerase inhibition with the characteristic induction of senescence and apoptosis. Currently the subject of various synthetic methods is preparation of target acridine skeletons or modifications of even naturally occurring compounds that exhibit promising anticancer activities. Since we know, that various serious human diseases (HIV, hepatitis C, AIDS, etc.) are caused by RNA viruses, designing of new RNA binding compounds seems to be more than necessary. All eukaryotic mRNAs possess the unique structural region, represented by 200-250 bases long polyriboadenylic acid [poly(rA)] at the 3´-end. Polyadenylation of primary transcripts is an important determining factor in maturation, initiation of translation and stability, and is catalysed by the enzyme poly(A) polymerase (PAP). Poly(rA) therefore plays an essential role in gene expression. It has been found, that human PAP is significantly overexpressed in human cancer cells and represents a tumour-specific target [1-6].

For the purpose of finding new, potent, anti-tumour agents capable of selectively interact with poly(rA), new 3,6-diamino-9-substituted acridine derivatives were synthetized [7]. Their biochemical and biophysical properties were tested using spectroscopic techniques (UV-Vis absorption and fluorescence spectroscopy, circular dichroism and thermodynamic studies). Interactions were investigated using single and double stranded poly(rA) at pH 7.1 respectively 4.5. The obtained results can serve as an inspiration for the design and development of new acridine based molecules specifically targeted to poly(rA) structures.

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Design, Synthesis and Anticancer Activity of Trifluoromethylphenylamino Analogs of 1-methoxyspirobrassinol Methyl Ether

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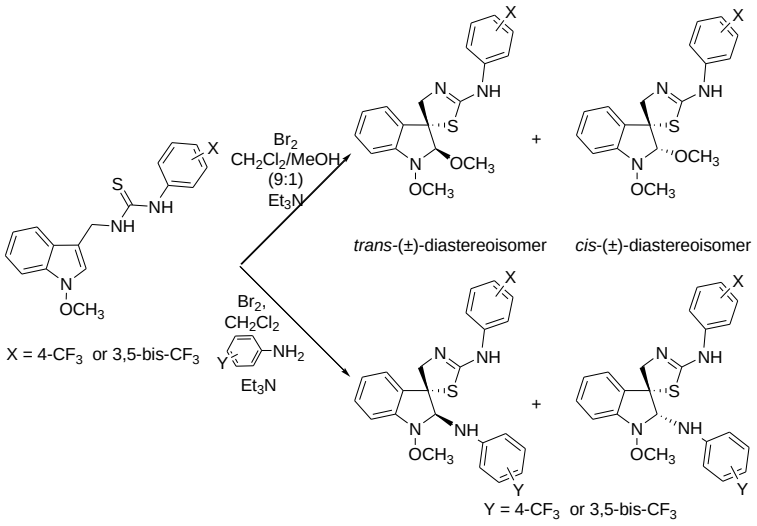
Organofluorines are a group of fluorinated substances with broad application as pharmaceuticals, agrochemicals and polymers [1]. We designed and synthesized a series of new biologically active trifluoromethyl containing indole derivatives. Target 2´-aminoanalogs and 2,2´-diaminoanalogs of 1-methoxyspirobrassinol methyl ether bearing (4-trifluoromethylphenylamino) or 3,5-bis(trifluoromethyl)phenylamino moiety were prepared by spirocyclization methodology. The present spirocyclization protocol simply utilizes thioureas as starting compounds, bromine as cyclizating agent and methanol, 4-(trifluoromethyl)aniline or 3,5-bis(trifluoromethyl)aniline as nucleophiles. The newly synthesized indole analogs display higher potency of antiproliferative effect against eight human leukemia and solid tumor cell lines than their parental natural phytoalexin. The most potent antiproliferative agents were 2,2´-diaminoanalogs possessing two 3,5-bis(trifluoromethyl)phenylamino groups, which displayed higher potency than cisplatin against screened cancer cell lines, but at the same time lower cytotoxicity than cisplatin on non-malignant murine fibroblasts NIH 3T3.



Scheme 1 Synthesis of 2´-aminoanalogs and 2,2´-diaminoanalogs of 1-methoxyspirobrassinol methyl ether

Acknowledgements

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Synthesis and Biological Activity of FTY720 Analogues with the Integrated Azobenzene Switch

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FTY720 is a structurally simplified version of myriocin (ISP-I) [1]. Its *in vivo* phosphorylated form is analogous to S1P and has the ability to interact with four out of five S1P receptors, thus regulating biological processes such as cell proliferation and migration, as well as the cellular growth and migration [2]. Introduction of a photosensitive switch into its structure might possibly endow the molecule with ability to turn on/off its activity.

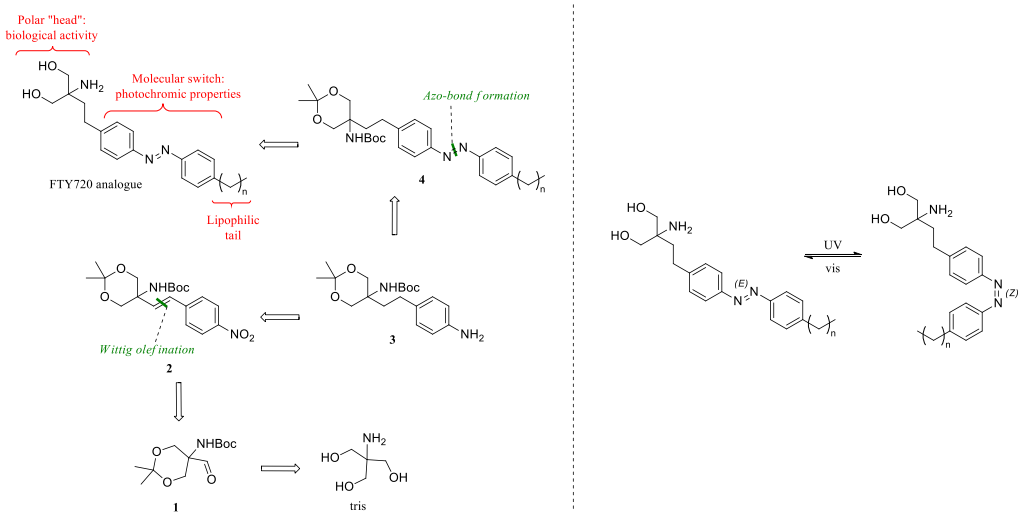

Figure 1 Retrosynthesis of FTY720 analogues and isomerisation upon UV/vis irradiation

Synthesis and results

The synthesis comprises three major modifications; firstly, transformation of tris into aldehyde **1** [3], secondly, Wittig olefination of **1** with an ylide of a suitable triphenylphosphonium salt [3] and subsequent catalytic hydrogenation of the product **2**, and at last, azo-bond formation via Mill's reaction along with the final deprotecion.

After the successful synthesis of FTY720 analogues, standard photoisomerisation and thermal relaxation experiments were performed and finally the target molecules were assayed against six malignant cell-lines (MDA, Caco, Hela, MCF, Jurkat, HCT, A549) both in a dark adapted *trans*-form and less stable *cis*-form. The results showed a moderate cytotoxic activity with only marginal differences between the two forms, which can be ascribed to the fast thermal relaxation of the *cis*-state.

Acknowledgements

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Stereoselective Synthesis of the Precursor of (7*S*)-(6)-deoxylactacystin

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In 1991 Omura isolated from bacteria of the genus *Streptomyces*, new natural compound (+)-lactacystin [1]. Next year in 1992 Corey and Reichard realized first total synthetis of (+)-lactacystin [2]. (+)-Lactacystin is selective inhibitor of 20S proteasome and is biologically active against ischemia, asthma and arthritis [3].

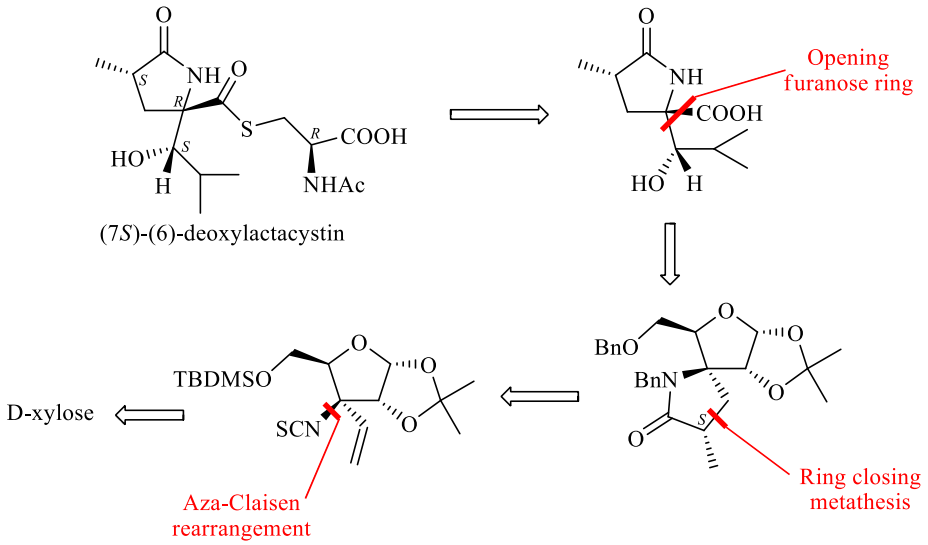

Figure 1 Retrosynthesis of (7*S*)-(6)-deoxylactacystin

We present synthesis of the precursor of (7*S*)-(6)-deoxylactacystin starting from D-xylose. Firstly isothiocyanate was prepared using aza-Claisen rearrangement [4]. Our first key step is ring closing metathesis to synthetise five member lactam ring. The second key step is opening of furanose ring and transform other functional groups.

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Stereoselective Approach to C-8a Branched-chain Polyhydroxylated Indolizidine Alkaloids

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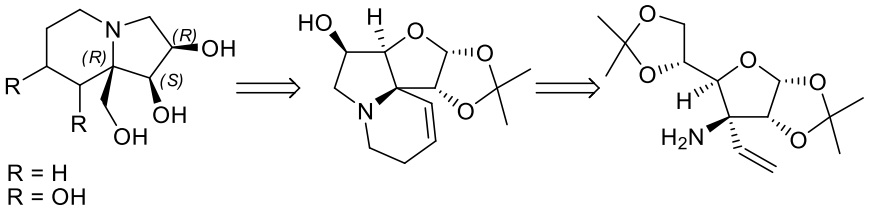
Polyhydroxylated indolizidines as glycosidases inhibitors posses interesting target compounds for organic synthesis. Members of this group originally isolated from natural sources mimic structure of saccharides [1]. Inhibition activity dramatically depends on number and position of hydroxyl groups and configuration of stereogenic centers, but prediction of inhibition activity is not so clear [2]. Synthesis of new derivatives is therefore essential for understanding of mechanism and activity.



Scheme 1 Retrosynthetic analysis of target compounds

According to our previous work [3] we present here synthetic approach to novel unnatural polyhydroxylated indolizidine alkaloids bearing a hydroxymethyl substituent on C-8a position starting from chiral glucose-derived amine. Products will be tested on biological activity towards various glycosidases.

Acknowledgements

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Stereoselective Synthesis of Sphingoid Bases with Incorporated Molecular Switches

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Sphingosine **1** and its biosynthetic precursor dihydrosphingosine **2** are naturally occurring compounds possessing an interesting biological activity [1]. A synthesis of a sphingoid base with an integrated azobenzene switch offers a promising way of creating a photobiological compound whose potential bioactivity could be modulated through irradiation with light of a proper wavelength [2,3].

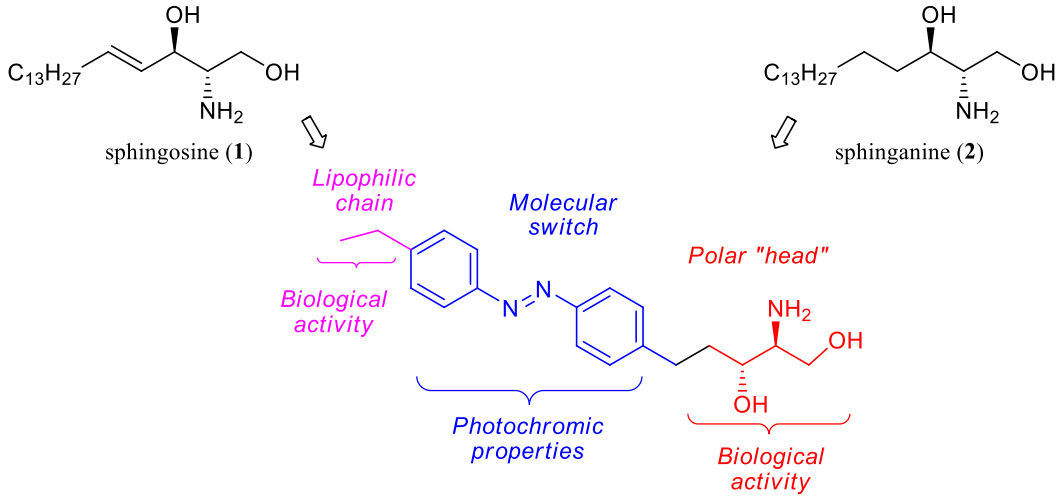

Figure 1 Sphingoid base with an integrated azobenzene switch

We present stereoselective synthesis of sphingoid base analogue with azobenzene switch, where a polar portion of the sphingoid base uses a chiral D-isoascorbic acid as the starting material [4]. Subsequently the azobenzene moiety is built into the molecule via Wittig olefination reaction. The synthesis is followed by the study of the photochromic properties and the biological activity of both *trans* and *cis* form of the sphingoid base against cancer cell-lines.

Acknowledgements

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Hydroxylated Octahydroindoles-Synthesis and Biological Activity

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A number of polyhydroxylated alkaloids, for example castanospermine [1] are well known for their biological acitivity as glycosidase inhibitors. Together with the group of carbasugars bearing various substitued amino moiety [2] are potential candidates for β-galactosidase and β-glucosidase inhibition.

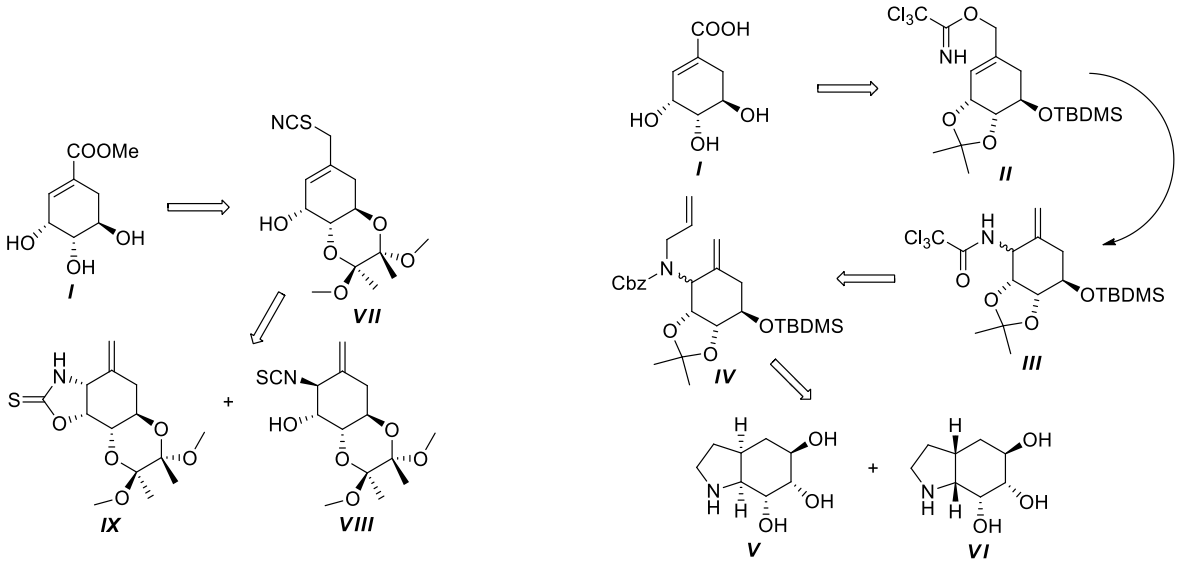

Figure 1 Retrosynthesis of ***V*** and ***VI*** utilising Overman and aza-Claisen rearrangement

As a continuation of our effort to prepare novel polyhydroxylated iminosugars we carried out a stereoconvergent synthesis of compounds ***V*** and ***VI*** using rearrangement of allylic trichloroacetimidate ***II*** and allylic thiocyanate ***VII***. Antiproliferative effect of final compounds and some intermediates was tested on eight tumor cell lines, as well as inhibition activity of compound ***V*** on three glycosidases, all with promising results.

Acknowledgements

The present work was supported by the Grant Agency (No. 1/0047/18) of the Ministry of Education, Slovak Republic. It was also supported by the Slovak Research and Development Agency (SRDA Grant No. APVV-14-0883), Slovakia and by the project MediPark Košice: 26220220185 supported by Operational Programme Research and Development (OPVaV-2012/2.2/08-RO, contract No. OPVaV/12/2013).

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Cholinesterase Inhibition Properties, Kinetic Study, Molecular Docking and Permeability Assay for BBB of Tacrine-Coumarin and Tacrine-7-chloroquinoline Hybrids with Thiourea Linkers

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The design of new heterodimeric dual binding site acetylcholinesterase inhibitors constitutes the main goal-directed to the development of new anticholinesterase agents with the expanded pharmacological profile. In this study, we described the design, synthesis, and evaluation of series tacrine-coumarin and tacrine-quinoline compounds which were found to show potential inhibition of ChEs and penetration of the blood-brain barrier.

All compounds were tested for their inhibitory activity on human AChE/BChE. The Ellman´s method [1] was used to determine inhibition kinetics and IC_{50} values. In order to predict passive blood brain penetration of novel compounds, modification of the parallel artificial membrane permeation assay has been used. Docking studies were performed in order to predict the binding modes of new hybrids with *h*AChE/ *h*BChE respectively.

Tacrine-quinoline hybrids **7a** exhibited the highest activity towards *h*BChE (IC_{50} = 0.97 μmol) and **7d** towards *h*AChE (IC_{50} = 0.32 μmol). Kinetic and molecular modelling studies revealed that **7d** was a mixed-type AChE inhibitor (*K*i = 1.69 μmol) and **7a** was a mixed-type BChE inhibitor (*K*i = 1.09 μmol). Moreover, hybrid **5d** and **7c** could penetrate the CNS.

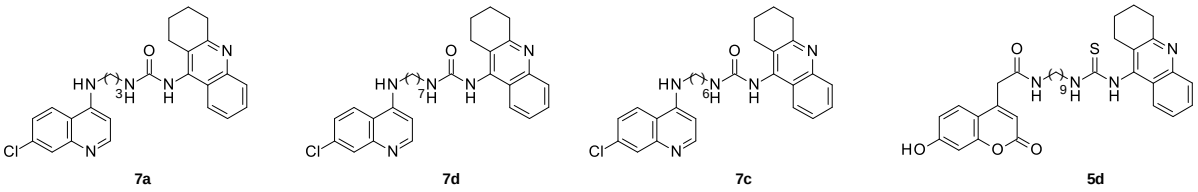

Figure 1 Chemical structures of the most active tacrine-coumarin and tacrine-quinoline hybrids.

Acknowledgements

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Acridine – a Biologically Active Scaffold

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Acridine and other derivatives of this class are very familiar as DNA intercalators [1]. Proflavine (**1**) is a small molecule that intercalates into DNA and, thereby, acts as an anticancer agent. The equilibrium constant for the binding reaction with DNA was calculated to be 1,60 ± 0,04 x 10^5 M^{-1} at T = 298,15 K [1]. The binding of proflavine (**1**) to DNA was favored by both negative enthalpy and positive entropy contributions to the Gibbs energy [1]. Proflavine (**1**) is also able to interact with human telomeric G–quadruplex DNA and tRNAphe [2,3]. All these intercalation capability makes proflavine (**1**), 3,6–diaminoacridine, and its derivatives interesting target of medicinal chemistry. We have synthetised a new antiproliferative active compound **3** as an inprovement of our former result **2** [4]. In silico screening has been invoved to define a new molecular design of the targed compound **3**.

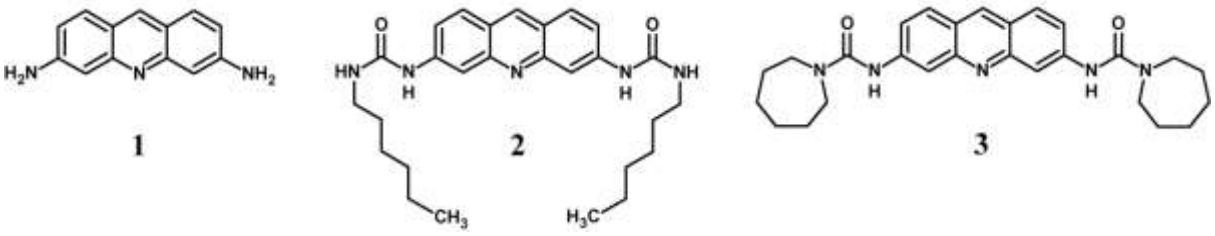

Figure 1 The structure of proflavine (**1**) and the related ureas **2** and **3**

Acknowledgements

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New Thioureas Containing the Carbohydrate Fragment as the Potential Organocatalysts in the Synthesis of Biologically Active Substances

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Carbohydrates and their derivatives are very suitable for use in organocatalyzed reactions [1]. A large number of available isomers allows for the synthesis of organocatalysts with different configurations at different stereogenic centers. Thioureas are derivatives that achieve good results in the organocatalysis of different types of reactions.The modification of the thiourea sacharide fragment can control the formation of isomers in the catalysed reactions.

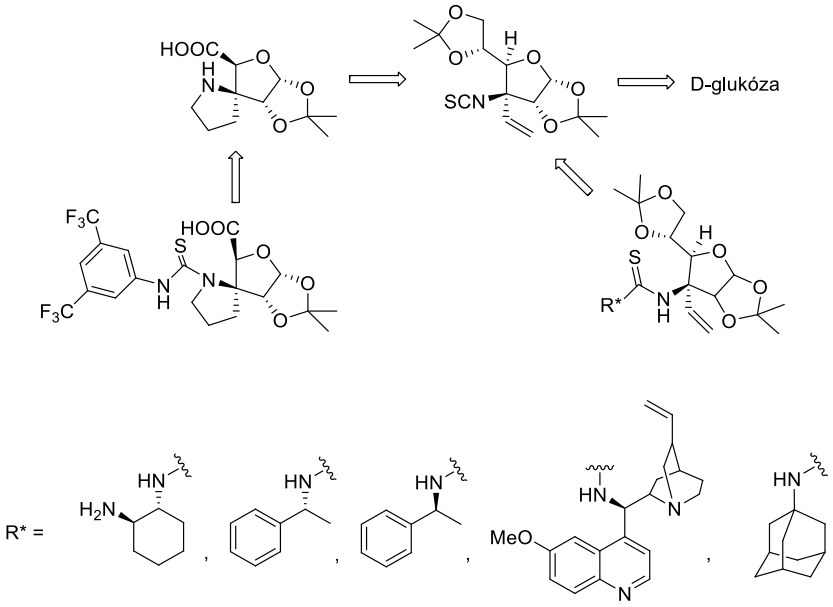

Figure 1 Retrosynthetic strategy of preparation new thioureas

Our synthetic strategy of novel thioureas containing carbohydrate skeleton come out from comercially avaliable D-glucose. Series of transformations using [3,3] -sigmatropic rearrangement we modified the structure to isothiocyanate [2], which served as an advances precursor in the next synthesis [3]. A novel thiourea was prepared with a bis (3,5- (trifluoromethyl) phenyl fragment or with fragment containing various chiral amines. The organocatalytic activity of all the prepared derivatives was tested in various types of reactions such as Henry reactions and Michael additions.

Acknowledgements

The present work was supported by the Grant Agency (No. 1/0047/18) of the Ministry of Education, Slovak Republic. It was also supported by the Slovak Research and Development Agency (SRDA Grant No. APVV-14-0883), Slovakia and by the project MediPark Košice: 26220220185 supported by Operational Programme Research and Development (OPVaV-2012/2.2/08-RO, contract No. OPVaV/12/2013).

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The Stereoselective Synthesis of Sphingoid Bases Bearing Quaternary Stereocenter

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Sphingolipids (SLs) represent a family of the natural occuring compounds with a wide range of biological activities. They have an essencial structural role in the plasma membrane of eukaryotic cells and in modulation of signal transduction [1]. The common structural fragment of complex SLs are sphingoid bases – long chain aminoalcohols varying in lenght of the hydrocarbon chain, number, position and streochemistry of double bonds and hydroxyl groups [2]. Herein we present our synthetic route towards two new sphingoid bases **1** and **2** with quartenary stereocenter, analogues of serin palmitoyl transferase inhibitors, with potencial antiproliferative and antimikrobial activity.

Synthesis

As shown in Figure 1, the lipophilic hydrocarbon chain of our target diastereoisomeric sphingoid bases **1** and **2** will be constructed through OCM reaction of precursors **3** and **4** with the corresponding vinyl moiety. New quaternary asymmetric centres of synthons **3** and **4** will be incorporated via the [3,3]-heterosigmatropic rearrangements of allylic substrates, thiocyanate (*E*)-**5** and imidate (*E*)-**6**. They will be prepared from dimethyl L-tartrate **7** using synthetic operations such as an application of the protecting groups, oxidation, HWE olefination and reduction. A benefit of the presented synthetic approach is the possibility of construction of analogues **1** and **2** with various length of the hydrocarbon chain due to Grubbs' cross metathesis chemistry.

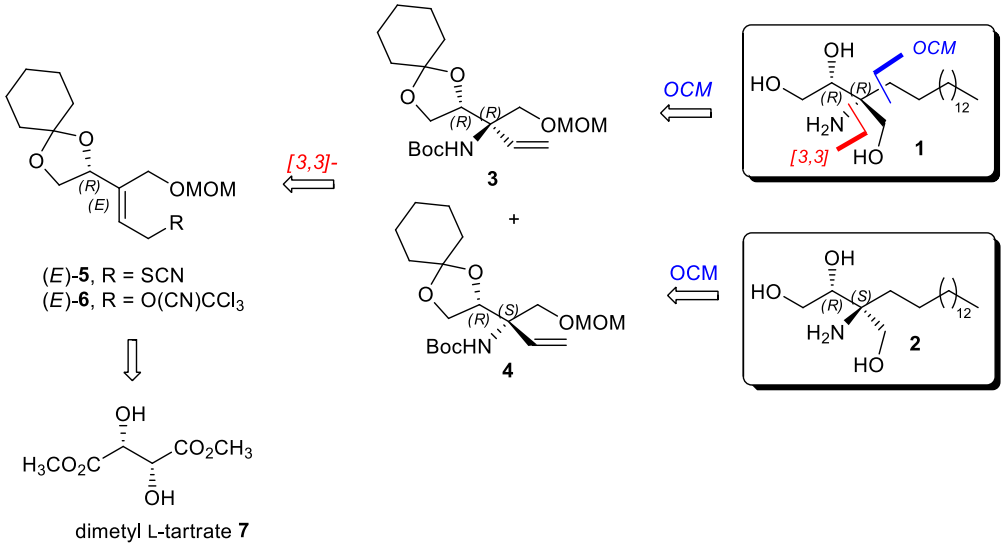

Figure 1 Retrosynthetic route towards **1** and **2**

Acknowledgements

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Synthesis and Potential Anticancer Activities of a Series of Acridine Based Chalcones

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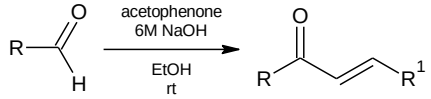
Cancer is the second leading cause of mortality in the world. Despite great effort in developing anticancer drugs in the past decades, the synthesis and testing of novel anticancer agents is still a challenge for chemists and biologists [1,2]. Before, we evaluated the ability of 3 new acridine containing chalcones to supress cancer cell proliferation and to induce cancer cell death. Our results indicate that antiproliferative effect of these compounds is associated with G2/M cell cycle arrest, induction of the mitochondrial pathway of apoptosis as well as modulation of selected signalling pathways [3].

Here, we synthesize novel derivatives of chalcones by introducing acridin-9(4)-yl moiety (Scheme 1). The methoxy substituents on the phenyl ring were simultaneously altered to investigate their contribution to the biological activity. Additionally, introduction of halogen (F or Br) on the phenyl ring were investigated to their contribution to biological activity, too. We investigated chalcones for their inhibitory effects and selectivity towards 7 human cancer cell lines and a non-malignant cell line 3T3. Among the acridin-9-yl chalcones, compound **2c** was most active and exhibited the most potent antiproliferative activity against HCT-116 cells and cytotoxicity of **2c** against non-cancer cells (3T3) was low with IC_{50} more than 10-times higher. Compounds with acridin-4-yl moiety **4a–4c,e** were found to be the most potent. Compounds **4b** and **4c** demonstrated the strongest cytotoxic activity against HCT-116 cells with 4.5 times lower (**4b**) or no toxicity (**4c**) against non-cancer 3T3 cells (Table 1). By comparing the cytotoxicity potential of all tested compounds, the following conclusions were drawn: (i) introducing acridine-4-yl fragment led to enhanced cytotoxicity; (ii) the presence of methoxy groups is essential; (iii) the presence of halogen reduced the activity markedly. The outcome of this study may be useful for the further modifications and investigation of acridine-chalcones due to their antiproliferative potential.



1: R = acridin-9-yl
3: R = acridin-4-yl

2a-g
4a-g

$R^{1:}$ (**a)** Ph, (**b)** 4-MeOPh, (**c)** 2,6-diCH_3OPh, (**d)** 2,4,6-triMeOPh, (**e)** 3,4,5-triMeOPh, (**f)** 4-FPh, (**g)** 4-BrPh

Scheme 1 Synthesis of substituted (2*E*)-3-(acridin-9(4)-yl)-1-phenylprop-2-en-1-ones **2a–g**, **4a–g**

Table 1 Selected IC_{50} ($\mu mol.L^{-1}$) ± SD of tested compounds in different cell lines after 72 h incubation

Cmpd	Cell line							
	A-549	**HCT-116**	**HeLa**	**MCF-7**	**MDA-MB-231**	**Jurkat**	**Caco-2**	**3T3**
2c	10.67± 4.2	4.13±0.35	24.43 ± 3.7	16.38±6.2	10.88±1.9	8.0±1.5	25.0±4.2	46.87±3.3
4a	> 100	6.23±0.88	32.0±1.23	33.5±3.35	33.1±2.34	6.24±0.88	28.31±1.23	25.33±5.23
4b	35.56±3.28	5.28±1.01	22.64±3.67	29.45±2.58	> 100	6.23±1.26	35.21±8.55	23.83±8.51
4c	>100	5.88±0.87	70.55±7.23	>100	> 100	35.34±8.56	45.81±12.33	>100
4e	35.26±6.45	10.34±1.67	25.12±9.23	45.23±5.23	6.6±1.23	8.23±1.65	> 100	35.34±7.85

Acknowledgements

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Total Synthesis of D-*erythro*-sphingosine Isomeric Analogues

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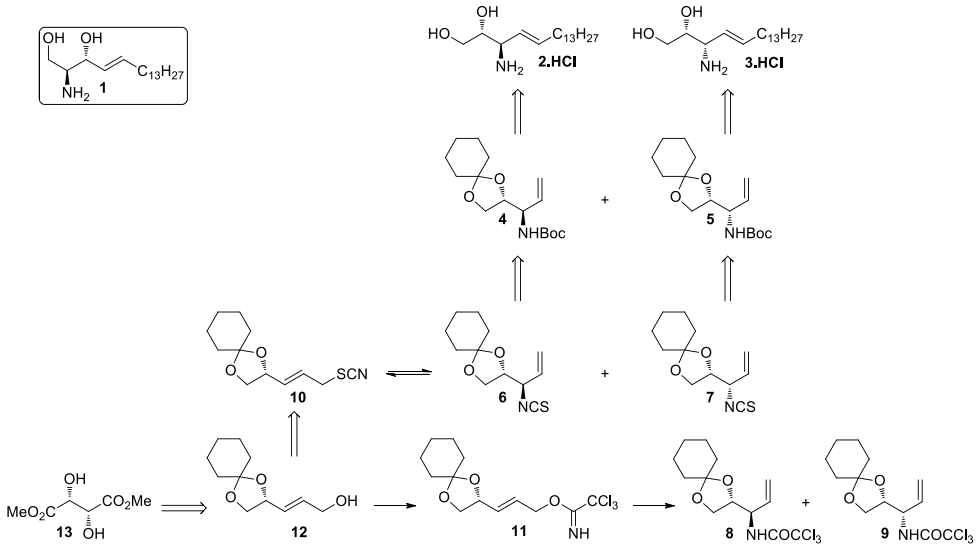
D-*erythro*-Sphingosine **1** is the most common long-chain aliphatic 2-amino-1,3-diol moiety of various sphingolipids. It displays the potent inhibitory activity against protein kinase C and constitutes a metabolic switch between the proapoptotic ceramide and the proliferative and angiogenic sphingosine-1-phosphate [1,2,3].

Synthesis

Recently, a new synthetic strategy toward D-*erythro*-sphingosine isomeric analogues **2**, **3** was developed in our laboratory [4]. The (*E*)-allylic alcohol **12** was prepared in six reaction steps from the commercially available dimethyl L-tartrate **13** (48% overall yield). The new C-N bond was incorporated into molecule using [3,3]-sigmatropic rearrangements of the appropriate allylic substrates, thiocyanate **10** and imidate **11**. However, we were not able to separate the obtained mixture of diastereomeric amides **8**, **9**, at the moment we decided to forward our synthesis with the chromatographically separable isothiocyanates **6** and **7**. The major rearranged product **6** was transformed to the *N*-Boc protected derivative **4** over two reaction steps. Finally, the desired product, isomeric D-*erythro*-sphingosine **2.HCl** was prepared from **4** *via* elongation its aliphatic chain using Grubbs' cross metathesis chemistry followed by acid hydrolysis. Analogously, the minor diastereomer **7** can be converted into **3.HCl** *via* synthon **5**.



Scheme 1 Our synthetic plan toward D-*erythro*-sphingosine isomeric analogues **2** and **3**

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Electrospun Carbon Microfibers as a Cathode Material for Li-S Batteries

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The researchers pay an intensive attention to the devices able to produce and store energy. Li-S batteries play a significant role in a development of rechargeable batteries. They are attractive adept due to their high theoretical capacity of sulfur (1672 mAh g-1), abundance and non-toxicity of sulfur and low cost of sulfur. Li-S battery belongs to the conversion type of battery; it means new chemical compounds during electrochemical reactions are formed [1, 2]. However, the batteries show some problems to be overcome. First, sulfur forms various products (Li2Sx, x = 1-8) during discharging. These products, called polysulfides, show poor ionic and electronic conductivity. The next problem is related to the volume variation of the sulfur cathode. Sulfur can change its volume of about 79%, what can cause the losing the electrical contacts with the conductive substrate or the current collector. The drastic volume variation of the electrodes can lead to serious safety problems [1, 3, 4]. Nowadays, electrospinning is a very popular technique. It is a fiber production method which uses electric force to draw charged threads of polymer solutions or polymer melts up to fiber diameters in the order of some hundred micro or nanometers [5]. This kind of carbon fibres should be able to accumulate sulfur inside the pores to control the volume increase and avoid the polysulfides to get into the electrolyte.

In our work, we are focusing on composite material based on sulfur and electrospun carbon microfibers to eliminate above-mentioned scientific problems of Li-S batteries.

Acknowledgements

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Non-enzymatic Electrochemical Sensors for Glucose Detection

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Glucose sensors represent an active part of electrochemical sensors research and they constitute the 85 % of biosensors industry. In general, glucose sensors are divided into two parts, enzymatic and non-enzymatic sensors. Enzymatic sensors are based on glucose oxidation by enzyme, for example glucose oxidase. Although, the enzymatic sensors are widely used in clinical practice, they establish some disadvantages. The glucose oxidase is affected by temperature, humidity, toxic chemicals, pH. Moreover, the instability and the denaturation of enzyme significantly influence the forming process, storage, and the electrode usage [1]. To overcome these drawbacks, non-enzymatic sensors attract increasingly attention. Non-enzymatic sensors are based on direct oxidation of glucose on the electrode surface without using of enzymatic component. Gold catalysis has been the subject of recent intense research and much effort has been devoted to the development of novel nanostructured gold substrates with various morphologies to exploit the innovative nanoscale chemical effects [2].

To reach ideal properties of glucose sensor, the gold microelectrodes were used. The microelectrodes were modified by electrodeposited gold nanostructures. The amount of electrodeposition cycles was studied with aim to achieve preferably electroanalytical properties. Gold microelectrodes were studied by scanning electron microscopy, atomic force microscopy, confocal microscopy and electrochemical methods such as cyclic voltammetry, chronoamperometry, electrochemical impedance spectroscopy were used. The modified microelectrode displays the linear range from 0.5 to 50 mM, limit of detection 351 μM and sensitivity 1.133 μA/mM.

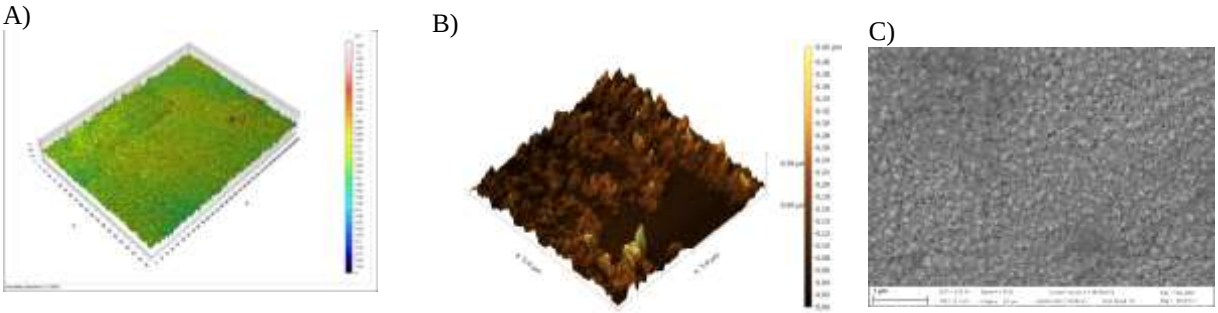

Figure 1 Modified gold microelectrodes by 5 cycles of deposition, image by A) confocal microscopy, B) atomic force microscopy, C) scanning electron microscopy

Acknowledgements

This work was supported by the projects VEGA 1/0074/17 of the Slovak Scientific Grant Agency, APVV-16-0029 of the Slovak Research and Development Agency, VVGS-PF-2018-794 and VVGS-PF-2018-795 of Pavol Jozef Šafárik University in Košice.

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Electrochemical Determination of Insulin on Nanomodified Pencil Graphite Electrode

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Insulin is a polypeptide hormone consists of 51 amino acids arranged in A and B chain connected with two disulfide bridges. Different methods, which can be divided into two main groups: immune (radio immunoassay, enzyme immunoassay, luminescent immunoassay) and non-immune (high performance liquid chromatography, capillary electrophoresis) methods, are currently used for insulin determination. The main disadvantages of these methods are insufficient sensitivity, high price and time-consuming analysis [1]. Usage of electrochemical methods for insulin determination could overcome mentioned drawbacks. Electrochemical methods dispose of high sensitivity, wide linear range and low detection limit [2].

This work deals with electrochemical determination of insulin on pencil graphite electrodes (PGEs), which are cheap carbon based electrodes with strictly define surface area and small size. PGEs were modified using multi walled nanotubes and electrodeposited NiO nanoparticles to increase active surface area and improve the catalytic activity. Also, chitosan as a polymer membrane was used to stabilize nanoparticles on the electrode surface during electrochemical measurements. Surface of NiONPs/chitosan-MWCNTs/PGEs was characterized with TEM, STEM and SEM with EDX analysis. Active surface area of bare (0.33 mm^2) and NiONPs/chitosan-MWCNTs/PGEs (1.33 mm^2) was calculated via Cottrell and Randles-Ševčik equation using cyclic voltammetry and chronoamperometry methods. Cyclic voltammetry method was also used for calculating of detection limit (260 nm), sensitivity (0.64 μA/μM) and linear range (0.05 μM-5 μM) of NiONPs/chitosan-MWCNTs/PGE. Correlation coefficient (0.99) was determined using chronoamperometry method.

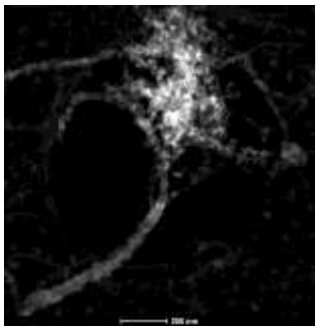
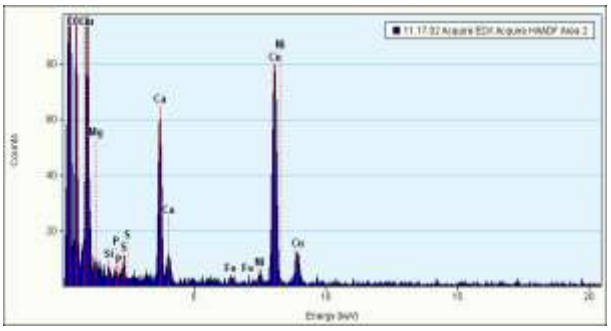
A)  B) 

Figure 1 STEM image of NiONPs/chitosan-MWCNTs/PGE (A) with EDX analysis (B)

Acknowledgements

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Study of the Positive Electrodes with Additives PPy and PEG in Lithium-Sulfur Batteries

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One of the most promising concepts of the new generation of batteries are lithium-sulfur batteries. These batteries provide high theoretical energy density, for use in electric vehicles and large stationary energy storage systems as well as in electric aircrafts. There is a wide scale of practical use of lithium-sulfur batteries due to very high theoretical capacity of sulfur – 1675 mAh/g, which in combination with the potential around 2.1 V against lithium means, that its gravimetric energy density reaches about 3000 Wh/kg [1]. Lithium-sulfur batteries have many advantages, for example high theoretical capacity and energy density, low cost or environmental compatibility. Before releasing these batteries into the real world, it is necessary to solve a number of problems, such as poor cyclability and life-time stability of sulfur cathode. During the discharge process, polysulfides are created. Higher polysulfides (S_8^{2-}, S_6^{2-}, S_4^{2-}) are dissolved in the electrolyte during the cycling which leads to a very steep drop of the capacity. This process is also known as the "shuttle effect". Another disadvantage is low conductivity of material because of non-conductivity of sulfur. Material during cycling volumetrically expands which leads to approximately 80 % increase of volume [1], 0.

In this work we prepared cathode with combination of 60 wt % sulfur, 20 wt % Super P and 20 wt % was a mixture of PPy-PEG (97 wt % PPy and 3 wt % PEG). The mixture was dried at 150 °C for two hours and then one hour at 300 °C. Dried mixture was dissolved in N-methyl-2-pyrrolidone (NMP) and the slurry was stirred for 24 hours. After then the slurry was deposited on Al foil by a coating bar. The foil was dried at 55 °C for two hours. Electrodes were cut out with hand cutter with the diameter of 18 mm and they were dried again for half an hour at 55 °C. Electrodes were inserted into the electrochemical test cell (El-Cell®). The whole assembly was done in Ar-filled glove box. Metal lithium was used as a counter electrode and also as a reference electrode. The electrolyte was 0.7 M LiTFSI dissolved in a solvent mixture of DME and DOL (2:1) with 0.25 M $LiNO_3$ as an additive. The electrolyte was impregnated into glass fiber-based separator. Galvanostatic cycling was used to analyse cathode electrodes during charging and discharging. Potential window was set at 1 to 3 V. Capacity calculated in the first discharge cycle was 1300 mAh/g, which is almost as theoretical capacity of sulfur.

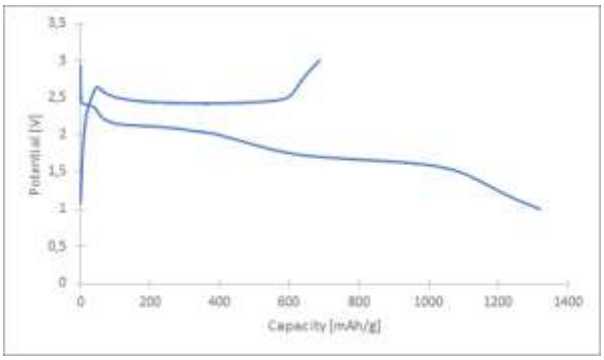

Figure 1 First charge and discharge cycle of sulfur electrode with additives PPy and PEG

Acknowledgements

This work was created with the support of the project NATO Peace and Security Project grant 985148.

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Properties of the Metallic Sintered Fe-Cu Biomaterials

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The development of biomaterials consists of three generations. An inert biomaterials at the first generation, bioactive materials and biodegradable materials at the second generation, and finally the materials stimulating cells to produce special response within the molecular level at the third generation [1].
Copper (Cu) is not only an essential trace element required for human body health, but also well known for its antibacterial and antifungal effects [2]. Proper addition of Cu in biomaterials represents a novel approach to improving of these materials. The materials of interest were investigated from three points of view. We were focused on the mechanical properties of sintered alloys, corrosion behaviour and electrochemical impedance spectroscopy (EIS) measurements. The samples prepared from mixtures of iron and copper powders or from copper-coated iron powders, produced by a cementation process, were studied. For this purpose different copper contents were used (3, 8 or 12 wt %). After sintering process, microgradient structures were observed.

The addition of copper to iron powder results in improved mechanical properties of the sintered products. The distribution of microhardness values on the sample surface was examined and the effective Young's modulus was determined. Its elastic modulus varied with different Cu content. Values about 150 GPa are almost the same as that of sintered iron (154 GPa). The lower values were measured only for a sample with 8 wt % Cu [3]. The corrosion characteristics and EIS measurements were observed in contact with Hank's solution by electrochemical methods. From the polarisation measurements it was found, that presence of Cu in the iron material leads to a rate corrosion control. EIS has been used to characterize the physical structure of the superficial layers. For the interpretation of impedance data, equivalent circuit models were selected considering the correlation of experimental data with the theoretical fit.

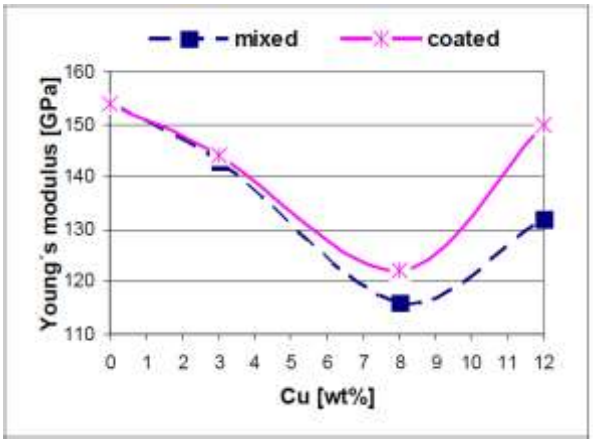

Figure 1 Young´s modulus of the Fe-Cu samples

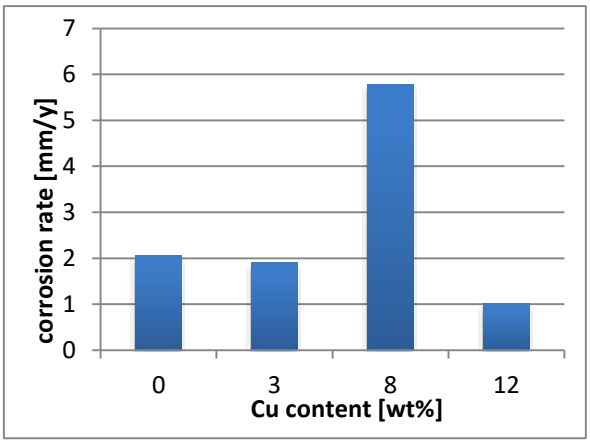

Figure 2 Corrosion rates Fe-Cu samples

Acknowledgement

This work was supported by the Slovak Grant Agency VEGA under project VEGA 1/0074/17, VEGA 2/0100/15 and by the project APVV-16-0029.

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Decomposition of Methane Over Carbon Microfibers Modified by Ni, Co, Cu Catalysts to Produce Hydrogen

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H_2-O_2 fuel cells are environmentally friendly and highly efficient devices that produce electricity and heat by electrochemical oxidation of hydrogen. However, current hydrogen production processes, such as methane, light naphtha and methane reforming, produce a huge amount of carbon dioxide. In addition, hydrogen, which is synthesized by these methods after purification, contains a large amount of CO that acts on proton-exchange-membrane as catalytic poison. Under these circumstances, the direct production of hydrogen by the pyrolysis decomposition of methane is the most ideal alternative. The synthesis of hydrogen by thermal decomposition of methane does not produce any CO, so it can be supplied directly to the fuel cell. In the pyrolysis process alone without the use of a catalyst, the maximum yield is a couple of decimal places. Catalyst application significantly increases the yield of hydrogen [1,2].

Carbon microfibers fortified with Co, Ni and Cu as a catalyst in the pyrolysis conversion of methane to hydrogen were selected. The aim was comparing the efficiency of these three catalysts and calculate kinetic parameters. Kinetic parameters were calculated based on the Demitcheli kinetic model. The pyrolysis efficiency was studied by the Py-GC method. The experiment was carried out at a constant pressure of 300 kPa and the temperature range was from 700 to 800 ° C. The highest conversion rate was achieved using carbon microfibers doped with cobalt in a hydrogen reduction atmosphere - 54.2%. This value corresponded to the lowest value of the carbon deposition rate and was also the most stable.

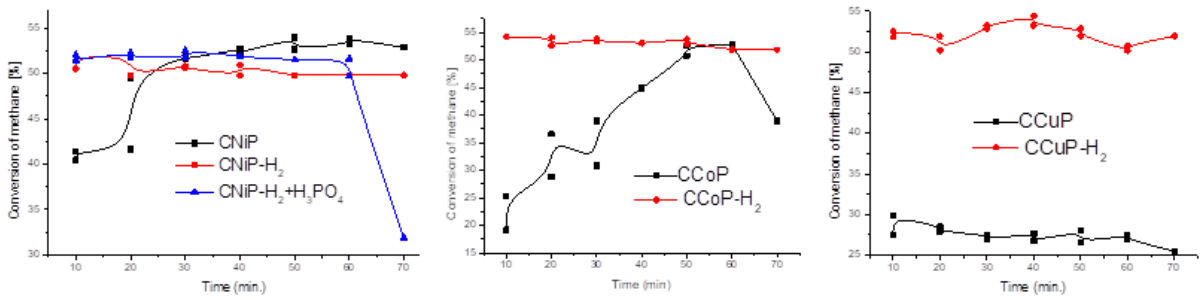

Figure 1 Comparison of catalysts sintered only under an inert argon atmosphere and catalysts sintered in the Ar atmosphere as well as reducing hydrogen

Acknowledgements

This research has been financially supported by grant MŠ SR VEGA 1/0074/17, APVV-16-0029.

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Catalytic Pyrolysis Conversion of Cellulose to Specific Chemical Compounds

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Lignocellulosic biomass is a promising feedstock that can be simultaneously converted into syngas, biofuels, and renewable resources of solid fuels, and it is the most potential new energy to replace fossil resources. Therefore, obtaining high-quality liquid fuel and high value-added chemicals from biomass has received widespread attention [1]. Cellulose, as one of the major constituents of biomass with 47% contribution, is a rich source of chemicals and fuels and its pyrolysis behaviour significantly influenced the thermochemical conversion of the whole biomass. Pyrolysis is a method whereby liquid mixture of organic compounds - bio-oil can be formed at moderate temperatures. Bio-oil is considered as substitute for petroleum and with appropriative treatment can be used as fuel for diesel engines or as source of hydrogen. However, high levels of oxygen in the bio-oil composition result in non-volatility, corrosiveness or thermal instability of liquid product. With the addition of a catalyst the composition of the bio-oil can be enhanced.

For the pyrolysis of cellulose to bio-oil nanostructured ZnO as a mild catalyst has been chosen with the addition of copper to the structure to improve the catalytic properties. The pyrolytic degradation of cellulose over ZnO/Cu doped nanocatalysts has been studied over the temperature range 400–800 °C with kinetic parameters evaluation. The results showed that with ZnO/2% Cu and ZnO/7% Cu, which had been heat-treated at 1000 °C, the yields significantly increased at 600 and 700 °C and the main components were aldehydes. In contrast, ZnO/Cu nanocatalysts prepared at 200 °C mostly generated ketones. The increasing amount of copper increased or decreased the content of some components at specific temperatures. The results demonstrated that ZnO/Cu nanocatalysts with different proportions of copper prepared and heat-treated at different temperatures affected the composition of the bio-oil.

Acknowledgements

This research has been financially supported by Grant MŠ SR VEGA 1/0074/17, APVV-16-0029.

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Haemocompatibility of Open Cell Iron Biomaterials Coated with PEI

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Bioresorbable cellular iron materials could be an alternative to permanent orthopaedic implants in the treatment of bone defects [1]. They have ability to degrade directly in the human body therefore second surgery for removal of permanent implant is unnecessary. These materials must exhibit excellent biocompatibility [2]. Neither iron scaffold nor its corrosion products may cause damage to the surrounding tissue. This work deals with the development of iron-based materials prepared by powder metallurgy and modification of their surface by polymeric (polyethylenimine, PEI) coating in different concentrations in order to enhance biocompatibility.

Haemocompatibility of the material was examined. Platelet adhesion, haemolysis and blood clotting were studied using sheep blood. Platelet adhesion was studied by scanning electron microscopy (Fig. 1). Haemolysis was determined by optical density ratio and blood clotting by measuring the weight of formed blood clot on the surface of the sample. All samples with polymeric coating were haemocompatibile with the values of optical density at comparable level. Weigth of blood clot formed on the surface of pure iron was highest in compare to that of coated samples. All materials exhibited good haemocompatibility and can be considered as a potential biodegradable implant.

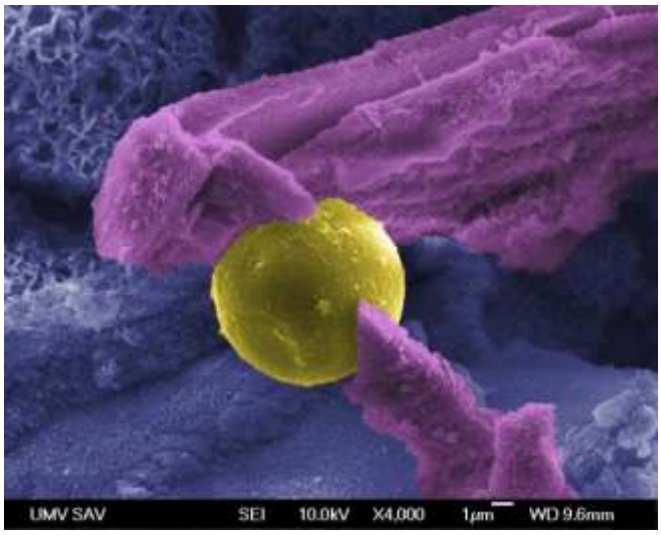

Figure 1 Detail of the blood platelet on the surface of pure iron sample

Acknowledgements

This work was supported by the projects APVV-16-0029 of the Slovak Research and Development Agency and VEGA 1/0074/17 of the Slovak Scientific Grant Agency.

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Electrochemically Deposited Silver Dendritic Substrate for SERS Cancer Diagnostics from Human Blood Plasma

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Surface-enhanced Raman spectroscopy (SERS) of human blood plasma on an electrochemically prepared silver surface has been studied as a label-free, and non-invasive diagnostic test for colorectal cancer. ITO glass substrates were modified with 0.01 M silver nitrate using the pulsed double-potentiostatic method. The prepared silver substrates were tested with Rhodamine 6G as a model analyte and the surface with the highest signal enhancement was selected. This silver dendritic surface was used as a diagnostic substrate for SERS measurements of human blood plasma. A group of oncological patients with declared colorectal carcinoma (n = 15) and the control group of healthy volunteers (n = 15) were compared. The biomolecular changes in chemical composition in the cancer samples were detected by statistical processing of the resulting SERS spectra. 94 % specificity and 100 % sensitivity was achieved for the analysis by the ratio of the SERS peak intensity at 725 cm^{-1} for adenine to the peak intensity at 638 cm^{-1} for tyrosine and 100 % specificity and sensitivity by using principal component analysis (PCA).

This new method of SERS diagnostics of colorectal cancer, which does not require the nanoparticle preparation, mixing and incubation of plasma with a colloidal solution as in conventional tests, is a rapid, inexpensive method, which could be introduced as a primary diagnostic test.

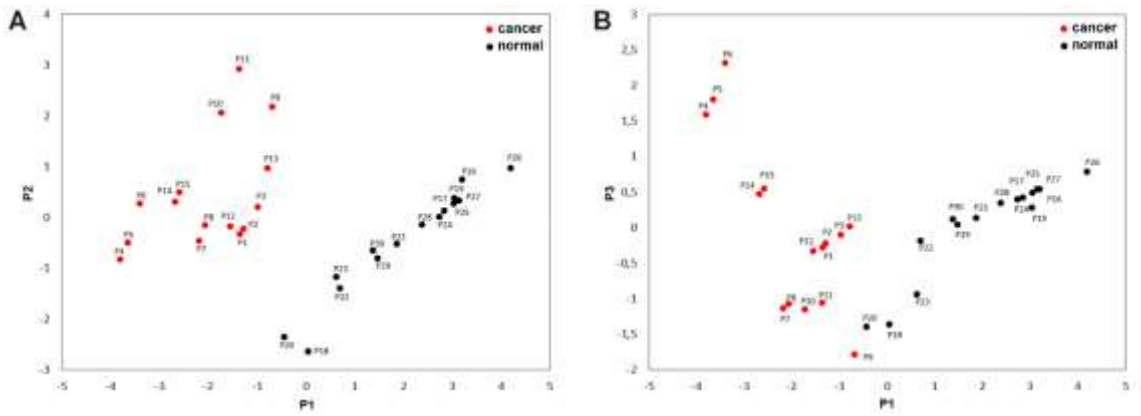

Figure 1 (A) Plots of the PC1 versus the PC2 for normal group (black points) and cancer group (red points). The two groups were separated with 100 % sensitivity and specificity. (B) Plot of the PC1 versus PC3 for normal group (black points) and cancer group (red points). The two groups were separated with 94 % sensitivity and 100% specificity

Acknowledgements

This research has been financially supported by grant VEGA 1/0074/17 of the Slovak Scientific Grant Agency and APVV-16-0029 of the Slovak Research and Development Agency. Clinical research was approved by the Ethics committee of Louis Pasteur University Hospital in Kosice.

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Plasmonic Substrates Prepared by Colloidal Litography

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Nowadays, the demands on speed, accuracy and detection limits of analytical methods are increasing. These conditions are met by surface enhanced Raman spectroscopy, which uses the effect of enhancement the analytical signal on nanostructured surfaces or nanoparticles. The amplification of the analytical signal significantly depends on the morphology and chemical composition of the surface. By modulating surface morphology, it is possible to vary the position of the absorption peak within the UV-IR range.

A suitable method for preparing nanostructured plasmonic surfaces is colloidal lithography in combination with electrochemical deposition. Surface morphology depends on the diameter of the nanospheres used as well as the time of electrochemical deposition. Surfaces so prepared are called nanocavities films having a high homogeneity in the range of several tens of millimeters to centimeters.

The most used metals for the preparation of plasmonic surfaces are silver and gold. The disadvantage of electrochemical deposition of silver is the formation of dendritic structures, which greatly reduces the surface homogeneity and thus the reproducibility of the measurements. On the other hand, gold can be electrochemically deposited as a smooth film, but it is incomparably more expensive than silver, which greatly increases the cost of such surfaces. It is convenient to use a combination of metals such as nickel and silver. Such a combination of nickel nanocavities with silver nanoparticles has proved to be a suitable combination due to its inexpensive preparation, cost, and major excellent results in the application of plasmon surfaces in the surface of enhanced Raman spectroscopy.

We prepared the Ni/Ag substrates with different normalized thickness of Ni and Ag layers. The most appropriate thickness was set to t ~ 0.5, which was confirmed with FDTD theoretical results. The higher enhancement of Raman signal was obtained from nanocavities film using 500 nm colloidal mask. Electrochemically deposited amount of Ag nanoparticles on Ni nanocavities substrate was tested, finally [1].

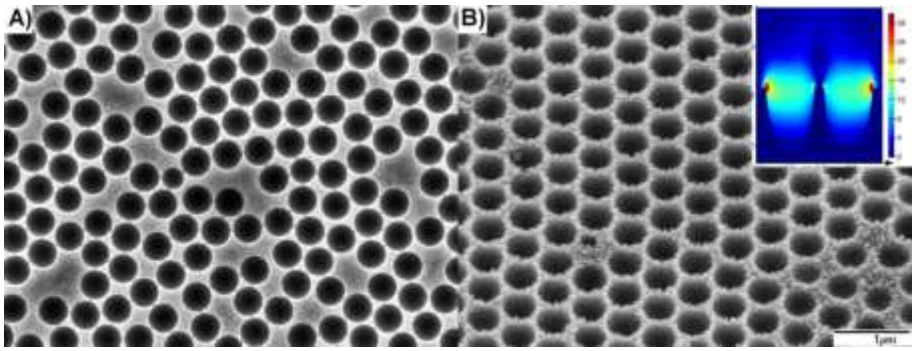

Figure 1 SEM images of A) Ni and B) Ni/Ag nanocavities with 500 nm in diameter. The inset shows the FDTD simulation of E field intensity distribution on Ni / Ag nanocavities film

Acknowledgements

This research has been financially supported by grant VEGA 1/0074/17 of the Slovak Scientific Grant Agency and APVV-16-0029 of the Slovak Research and Development.

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Computer-Based Teaching of the Topic Factors Affecting the Rate of Chemical Reactions

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The application of digital technologies to students' experimental work responds to the requirements of 21st century education. The realization of experiments using measuring systems (such as Vernier, Coach, Pasco) is effective in understanding the nature of many natural phenomena and processes [1]. Therefore, the method in which this approach is implemented in teaching Natural Sciences is also important.

At the Department of Didactics of Chemistry, in the framework of the National project IT Academy – Education for the 21st Century, we have prepared 10 methodologies (i.e. methodological sheets for teachers and worksheets for students) for the implementation of computer-based experiments (CBE) to teaching the topic *Chemical Reactions, Chemical Equations* at the grammar schools. The methodologies were implemented in the preparation of future chemistry teachers at the Master's degree in the subjects *Special Experimental Practice I* and *Activating Methods of Chemistry Teaching.* Implementation took place in the academic years 2016 – 2018 and is still ongoing. Students performed CBE on topics such as *Energy Changes in Chemical Reactions, Effects of Different Factors on Decomposition of Hydrogen Peroxide, Acid-Base Titration with Thermometric and Potentiometric Indication of Equivalence Point, and Determination of the Concentration of Acetic Acid in Vinegar.* The analysis of students' opinions and attitudes to CBE showed that students were interested the CBE, especially acknowledged the clarity of the observed phenomena, the speed of data acquisition and the possibility of their immediate processing. The use of CBE in teaching shifts chemistry as a subject among subjects with more popularity and greater interest. CBE help to develop cognitive skills such as critical thinking, communication or collaboration, and the abilities of scientific work, such as the ability to predict, the ability to measure, the ability to interpret data, or the ability to make conclusions and generalizations.

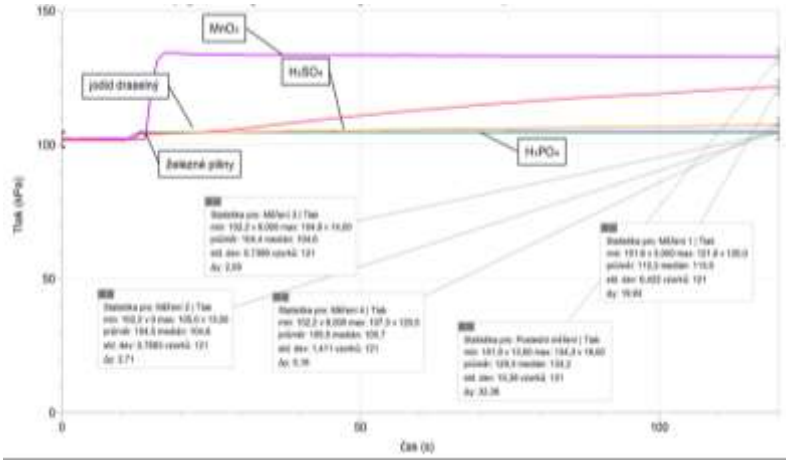

Figure 1 An example of a graph – The effect of different catalysts on the decomposition of hydrogen peroxide

Acknowledgements

This work was supported by the Project VEGA No. 1/0265/17 Formative Assessment in Natural Sciences, Mathematics and Computer Science and National project IT Academy – Education for the 21st Century No. 312011F057, which is supported by the European Social Fund and the European Regional Development Fund in the framework of the Operational Programme Human Resources.

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LIST OF POSTERS
Sessions 1 – 6

Analytical Chemistry

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Inorganic Chemistry

P2 E. Beňová, Virginie Hornebecq, Miroslav Almáši, Vladimír Zeleňák, David Bege-Lefranc: Stimuli-responsive Mesoporous Silica Nanoparticles for Drug Delivery Applications

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