# A SELECTION OF PROJECTS FOLLOWING RUŽIČKA'S RESEARCH

The projects have been selected by Vladimir Mrša, Faculty of Food Technology and Biotechnology University of Zagreb, Member of the Croatian Academy of Engineering

*Nives Galić et al.*[1]

## Aromatic hydrazones: synthesis, structural analysis, biological activity and analytical application

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The main goal of the project is to develop new methods for metal ions determination as well as new extraction chromatographic materials for separations of some important radionuclides. The active components in such systems will be aromatic hydrazone derivatives. They will be synthesized by condensation reactions of hydrazide and differently substituted aldehydes or ketones. Since different tautomeric and isomeric forms of hydrazones can have diverse chelating properties, the detailed study of the corresponding equilibria is important for successful application of these compounds and will be performed within the project. Protonation properties and kinetics of hydrolysis of hydrazones in solvents containing water will be examined. For structural characterization of ligands in solution mass spectrometry, liquid chromatography, and different spectroscopic techniques (NMR, UV-Vis, fluorescence, IR and Raman spectroscopy) will be used. The computational studies will be carried out as well. The complexation reactions of hydrazones with selected metal ions and radionuclides will be investigated in solution. Whenever possible, complex stability constants will be determined and solid complexes will be isolated. Based on the results obtained, spectrophotometric and/or spectrofluorimetric methods for metal ions determination will be developed. The selectivity of the proposed methods will be further improved using extraction procedure. The influence of surfactants on the extraction systems will be explored. Furthermore, hydrazones abilities as extraction chromatographic resins towards selected radionuclides will be investigated. Prepared hydrazones and their complexes will be screened for biological activity on selected microbial species and fungi. Finally, the correlation of the hydrazones structures and their physico-chemical properties will be proposed, which is of great importance for successful applications of such compounds as bioactive agents or analytical reagents.

*Branka Zorc et al.*[1]

## Design, synthesis and evaluation of novel anticancer agents based on primaquine, vorinostat and sorafenib scaffolds

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The long-term goal of the proposed research is development of novel compounds with a potential for development to drug lead(s) and anticancer drug(s). The project will focus on rational design, synthesis and biological screening of novel derivatives of three marketed drugs: antimalarial primaquine and two antitumoral drugs vorinostat and sorafenib. The potential for discovery of new anticancer agents among antimalarials was first noted when commonly used antimalarials showed significant anticancer activity (7 of them have reached a clinical stage of development). We have focused our attention to primaquine, the antimalarial agent with quinoline moiety. In our several papers novel urea and semicarbazide primaquine derivatives with strong antiproliferative activity and/or high selectivity were reported. The highest selectivity against MCF-7 cells and practically no activity against other tested cancer cell lines showed hybrid of two primaquine ureas. Based on these results we intend to design, synthesize and evaluate novel primaquine hybrid compounds as potential anticancer agents. First objective is to design and prepare novel twin drugs based on primaquine and vorinostat scaffolds 3-6. These compounds will differ in length of aliphatic chain and/or functional groups: compounds 3 are esters, 4 are carboxylic acids and 6 hydroxamic acids like vorinostat itself. Reduction of compounds 4 would generate amines 7 and amides 8. Further on, we plan to prepare primaquine amides 9 with substituted cinnamic acid and sorafenib analogs 14 based on pyrazine structure, hoping that additional nitrogen atom would increase the binding interactions. To study how the amide part of the molecule affects the activity and physico-chemical properties of the new pyrazine analogs, the preparation of a number of amides is planned. All new compounds will be screened for cytostatic activity in vitro on several human cancer cell lines, inhibition of specific enzymes and antioxidative activity.

*Igor Jerković et al.*[1]

## Research of natural products and flavours: chemical fingerprinting and unlocking the potential

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The proposed project develops up-to date topic in the subject area, offers high-quality research of natural products (NPs) and flavours (FLs) and tends to impact the biodiversity, traceability and authentication issues of targeted samples (major EU concerns), as well as to unlock the potential (useful activities of the samples/NPs). Targeted samples are unexplored or insufficiently investigated honeys, honeydews, bee-products, wines, cheese, others. While characteristic NPs (secondary metabolites) already possess flavours, other flavour compounds can derive from precursors during processing, fermentation, dry-curing, heating, others (e.g. Maillard reactions, Strecker degradations, retro-aldol reactions, Amadori rearrangements, heterocyclizations, lipid oxidations and others). NPs/FLs isolation involves application of selective preparative procedures followed by the organic analysis applying modern chromatographic and spectroscopic techniques. Specific project goal is to determine reliable chemical fingerprints of targeted samples depending on biodiversity of natural sources in different regions. Varieties of acetate, shikimate, mevalonate and/or deoxyxylulose biosynthetic pathway derivatives are expected to be found. Among them, it can be possible to find specific or nonspecific chemical biomarkers characterizing certain sources. In addition, the obtained NPs or selected samples will be evaluated in order to unlock their potential, particularly antioxidant activity by different assays and corrosion inhibition potential with in-situ and ex-situ electrochemical/non-electrochemical techniques. Project work plan includes: 1) the samples selection and preliminary characterisation; 2) set-up of preparative/chromatographic/spectroscopic methods followed by elaboration of the obtained chemical fingerprints); 3) set-up of antioxidant/corrosion inhibition assays followed by unlocking the samples/NPs potential; 4) training of young researchers/cooperation.

*Krešimir Molčanov et al.*[1]

## Novel metal-organic systems based on the oxalate and quinoid ligands with tuned properties suitable for applications

[1] Institute Ruđer Bošković in Zagreb

The project targets at efficient and progressive design of novel and advanced functional materials based on metal-organic complexes. Combination of metal centres with polydentate organic ligands provide colossal, structurally-diverse, platforms possessing a variety of magnetic, electrical, thermal, optical and other properties. In the proposed project, two analogue bridging ligands, oxalate and substituted 2,5-dihydroxyquinonate (DHQ), will be used in the preparation of the coordination polymers of different dimensionality and topology. Their interactions with transition metal cations involve a variety of magnetic phenomena, which can be tuned by highly sensitive selection of structural fragments. The oxalate-based complexes will be studied not only as potential magnetic materials ordering at a certain temperature, but also as the single-source precursors for the preparation of technologically important mixed-metal oxides through the thermal decomposition process. This method of preparing oxides, as compared to conventional solid-state reactions, has several advantages: shorter thermal treatment at lower temperature, without repeating grinding procedures, and the products are more homogeneous. The DHQ complexes will be studied due to their potential for charge transfer, which may lead to materials with reversible magnetic transition. Also, promising class of the ligands are stable semiquinone radicals derived from variously substituted DHQs. So far, their complexes with transition metals are little-known and have not been exploited for design of functional materials. The interdisciplinary nature of the project requires a variety of methods to characterise these advanced materials: single-crystal and powder X-ray diffractions including X-ray charge density studies, thermal analyses (TG/DTA), IR, UV/Vis and EPR spectroscopies, etc. The results obtained will be used to correlate their structure and properties.

*Guest Editor's Notice:*

*I wish to bring to the readers' attention that Professor Ružička is known in the scientific and professional literature under the names Lavoslav and Leopold, respectively. Since the articles in this Bulletin are both in Croatian and English, we have decided to use the name Lavoslav Ružička in the Croatian texts, and the name Leopold Ružička is used in the English texts. We kindly ask you to take this explanation into account.*