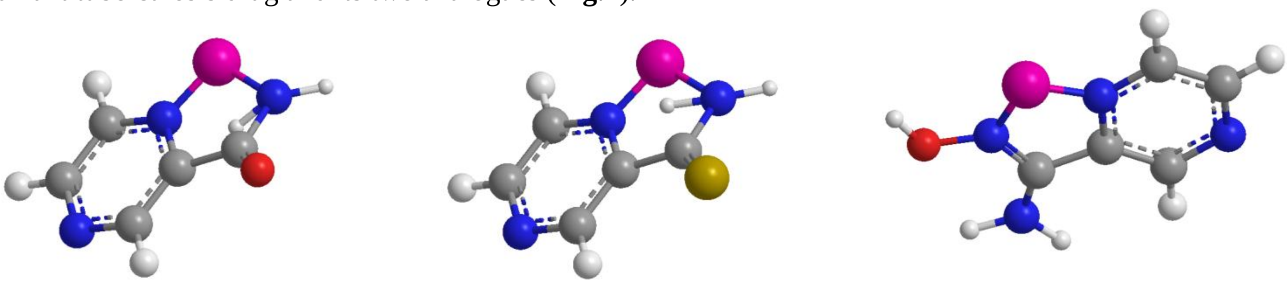
“Coordination chemistry of pyrazine-2-carboxamide and its analogues towards trivalent Ir and Os ions: design, synthesis, characterization and biological activity”

Treatment of infectious diseases still remains an essential and challenging problem because of various factors like emerging infections and the increasing number of multidrug resistant microbial pathogens. There is a real need to discover new compounds (for example complexes) which perform antimicrobial activity. These complexes are possibly acting upon mechanisms which are different from those of well-known classes of antimicrobial agents to which many clinical relevant pathogens are now resistant. Present medicinal inorganic chemistry remains a promising field with many challenges. The potential of expansion of chemical diversity of new structural and active compounds of high therapeutic impact is unquestionable.

Metal complexes applied in biological assay have several requirements in terms of their structure, which determine their activity. Firstly, coordination compounds should have a high thermodynamic stability to deliver the metal to the active site. Secondly, the presence of bidentate ligand in complex structures caused increasing inhibition of pathogens in the regard to monodentate one (chelate effect). The total charge of the complexes plays an important role. Generally, the antimicrobial efficiency decreases in the order of cationic > neutral > anionic complex. The nature of counterion is another factor that can influence the activity of compounds. In the case of ionic complexes, the chloride or chlorate(VII) ions are preferred. The molecular weight of the metal complex is also essential. The coordination compounds of low molecular weight with neutral charge and good water solubility may slip through biological membranes by passive diffusion. The pharmacological activity of metal complexes is highly dependent on the nature of the metal ions and the donor sequence of the ligand because different ligand exhibit different biological properties. The ligands containing S, N and N, O donor atoms are important owing to their significant antifungal, antibacterial and anticancer activities. Furthermore, a type of chelating ligands does not only have an influence on the biological properties but also has impact on the stability of the formed complex. Various biological aspects of the metal complexes based drugs depend on the ease of cleaving the bond between the metal ion and the ligand. As a consequence, it is essential to understand these interactions in biological systems.

The activity of each compound is a function of the oxidation state of the metal center and the nature of coordinated ligands. These features are decisive not only for how the drug interacts with the disease target but also for the biological transformations that occur on its route. By manipulating these features of activity, it is possible to achieve, on the one hand, maximum biological activity, and on the other hand - minimizing the general toxicity of the drugs. Application of Ir(III) and Os(III) complexes as biological agents exhibited specific pharmacological effect as a result of their unique physicochemical properties: the rate of ligand exchange kinetics (similar to Pt(II) complexes) and the possibility of its control by coordinating ligands with appropriate features. The range of accessible oxidation states (+II, +III) under physiological conditions allows to control their redox potential.

The present project involves synthesis, physicochemical and microbiological properties and application of new, previously not described in literature, d-block metal ion complexes of pyrazine-2-carboxamide (*PZA*) – an antituberculosis drug and its two analogues (**Fig.1**).



a) **b)** **c)**

Fig.1. A binding mode of selected pyrazine derivatives to metal ion (Ir(III)/Os(III)): a) pyrazine-2-carboxamide (*PZA*), b) pyrazine-2-thiocarboxamide (*PTCA*), c) pyrazine-2-amidoxime (*PAOX*)

Experimental study combines three research areas: chemistry (synthesis and physicochemical studies), pharmaceutical microbiology (antimicrobial activity assay) and biotechnology (cytotoxicity studies) which indicates interdisciplinary character of the proposed subject. The part of the new research and innovation is exploring the antimicrobial potential of ligands and Ir(III)/Os(III) complexes towards planktonic pathogens. The main purpose of this project is to determine physicochemical parameters of Ir(III) and Os(III) complexes which imply their biological activity. The implementation of the project is based on the determination of the influence of the coordination center on complexing properties of selected chelate ligands. One of the tasks of the proposed project is the answer to the question of how to change the physicochemical, acid-base, electrochemical properties, stability and biological activity of analogues complexes within the period (Os → Ir).