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Abstract of PhD thesis entitled: Evaluation of biological properties of nickel(II), cobalt(II), and copper(II) complexes with imidazole derivatives

Metal complexes, as synthesis products in pharmaceutical chemistry, are currently potential therapeutic compounds. The acquisition of antibiotic resistance by microorganisms or the effective elimination of cancerous cells necessitates the constant search of chemical compounds with specific biological activities. The hope for solving this problem are transition metals complexes, including complexes with imidazole derivatives, which show anticancer, anti-inflammatory, antibacterial, and antifungal properties. These studies require multithreaded and interdisciplinary analyzes aimed at determining their effectiveness as potential therapeutics.

The aim of the dissertation is to evaluate the biophysical, cytotoxic, and antimicrobial properties of new transition metal complexes: nickel(II), cobalt(II), and copper(II) with imidazole derivatives, i.e. 1-allylimidazole (1-allim) and 4-imidazoleacetic acid anion (iaa) ($[Ni(iaa)_2(H_2O)_2]\cdot H_2O$, $[Ni(1\text{-allim})_6](NO_3)_2$ $[Co(iaa)_2(H_2O)_2]\cdot H_2O$, $[Co(1\text{-allim})_6](NO_3)_2$, $[Cu(iaa)_2(H_2O)]$, and $[Cu(1\text{-allim})_4(NO_3)_2]$). Studies that use the method based on annexin (V) and propidium iodide and the MTT test showed that of all the six complexes tested in the study only the $[Ni(1\text{-allim})_6](NO_3)_2$ and $[Cu(1\text{-allim})_4(NO_3)_2]$ complexes have a selective cytotoxicity at a lower concentration against A549 tumor cells compared to normal BEAS-2B cells. On the basis of the circular dichroism method and spectroscopic methods, it has been shown that these complexes can affect protein activity without changing its structure. The $[Ni(iaa)_2(H_2O)_2]\cdot H_2O$, $[Ni(1\text{-allim})_6](NO_3)_2$ $[Co(iaa)_2(H_2O)_2]\cdot H_2O$, $[Co(1\text{-allim})_6]$ $(NO_3)_2$, $[Cu(iaa)_2(H_2O)]$, and $[Cu(1\text{-allim})_4(NO_3)_2]$ complexes inhibit the activity of recombinant phage endolysin, whereas only $Cu(1\text{-allim})_4(NO_3)_2]$ inhibited the activity of lysozyme. All studied complexes do not affect the structure of proteins: BSA, lysozyme and endolysin. In turn, based on the newly used PCR-HRM method, it was found that the studied complexes do not interact with DNA except $[Co(iaa)_2(H_2O)_2]\cdot H_2O$. In addition, the ability to penetrate into the cell is an important element in assessing the cytotoxicity of metal complexes. Research using the laser interferometry method, which was first applied to this type of studies, confirmed that all analyzed metals in the form of complexes with imidazole derivatives, i.e. an imidazole acetic acid anion or 1-allylimidazole, diffuse more effectively through the monolayer of CHO-K1 cells than their salts. The analysis of the tests using microbiological

techniques showed that the $[Ni(iaa)_2(H_2O)_2]\cdot H_2O$, $[Ni(1\text{-allim})_6](NO_3)_2$, $[Co(1\text{-allim})_6](NO_3)_2$ complexes, in contrast to Cu(II) complexes, have antifungal properties at a level similar to metal salts in non-cytotoxic concentrations relative to eukaryotic cells A549 and BEAS-2B. The $[Co(iaa)_2(H_2O)_2]\cdot H_2O$ complex has higher antifungal activity than $CoCl_2$ against *C. albicans* strains. The analyzed metal complexes do not show antibacterial properties against *E. coli, P. aeruginosa* and *S. aureus* in non-cytotoxic concentrations relative to eukaryotic cells A549 and BEAS-2B. Moreover, in this work a novel application of the PCR-HRM method was used to assess DNA damage and the laser interferometry technique dedicated to the analysis of the evolution of the concentration layer and the diffusion parameters of chemical compounds through the monolayer of eukaryotic cells.

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