Abstract of the doctoral dissertation in English

Salinomycin is a naturally occurring compound produced by the bacterium *Streptomyces albus*. It belongs to the group of ionophore antibiotics, which are capable of transporting metal cations across cell membranes. Salinomycin has been widely used in veterinary medicine as a coccidiostat due to its strong antiparasitic properties. Moreover, over the past two decades, its therapeutic potential against cancer cells, including cancer stem cells, has been repeatedly confirmed.

The subject of the doctoral dissertation titled *"Synthesis, structural analysis, and biological activity evaluation of salinomycin derivatives"* was the chemical modification of ionophore antibiotic, the examination of the ionophoretic properties of the obtained derivatives, and the assessment of their biological activity.

The dissertation includes three publications that describe the decomposition reaction of the salinomycin molecule under acidic conditions and the synthesis of its conjugates with phosphonium cations, obtained by modifying the molecule at positions C1 and C20. To determine and confirm the structures of the synthesized derivatives, a range of analytical techniques were conducted, including electrospray ionization mass spectrometry (ESI-MS), high-resolution mass spectrometry (HR-MS), infrared spectroscopy (FT-IR), elemental analysis (EA), X-ray diffraction (XRD), and nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR, ^{31}P NMR, 2D NMR).

Research in medicinal chemistry is interdisciplinary; therefore, the crystallographic analysis of the salinomycin degradation product was conducted in collaboration with Prof. Jan Janczak from the Institute of Low Temperature and Structure Research of the Polish Academy of Sciences in Wrocław.

In collaboration with Prof. Yuri N. Antonenko from the Moscow State University, studies were carried out on the ionophoretic properties of the obtained conjugates, examining their effect on artificial and natural biological membranes, as well as their ability to translocate through lipid bilayers.

The anticancer activity of the conjugates obtained in Publication III was thoroughly investigated by the research team of Prof. Marta Struga from the Medical University of Warsaw. *In vitro* tests were conducted using five human cancer cell lines: colorectal adenocarcinoma (SW480), metastatic colorectal adenocarcinoma (SW620), prostate cancer (PC3), breast cancer

(MDA-MB-231), and non-small cell lung cancer (A549). To assess the cytotoxicity of the obtained compounds, two normal cell lines were used: human keratinocytes (HaCaT) and Chinese hamster lung fibroblasts (V79). Additionally, the effect of selected derivatives on cancer cell mitochondria, mitochondrial membrane potential, and their influence on the cell cycle, apoptosis induction, and reactive oxygen species production were investigated.

The biological studies also included an analysis of the antibacterial properties of the obtained conjugates. The compounds were tested against Gram-positive bacteria (*Staphylococcus epidermidis* and *Staphylococcus aureus*) and Gram-negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*).

At the final stage of biological research on salinomycin and its derivatives, their effect on cellular respiration and their ability to transport cations were tested using the black lipid membrane technique. These studies were conducted in collaboration with Prof. Piotr Bednarczyk from the Warsaw University of Life Sciences.

The conducted biological studies demonstrated that the cytotoxicity of most derivatives was several times higher compared to unmodified salinomycin as well as the reference drug (doxorubicin). It was proven that the presence of a triphenylphosphonium cation in the antibiotic molecule affects mitochondrial functionality and the rate of membrane penetration. Furthermore, selected derivatives exhibited the ability to induce apoptosis in cancer cells.

The results presented in this dissertation confirmed that conjugation of bioactive molecules leads to promising outcomes and represents a valuable approach in the search for new and more effective anticancer compounds.