Streszczenie rozprawy doktorskiej w języku angielskim

The aim of this doctoral dissertation was the synthesis as well as spectroscopic and spectrometric analysis of derivatives of natural origin compounds – ivermectin and monensin. Additionally, the obtained analogs were examined for their anticancer and/or antiparasitic activity against various human cancer cell lines and model species of pathogenic parasites (*in vitro* assays), which allowed for the determination of the correlation between the structure of these compounds and their biological activity.

The research conducted within the framework of this doctoral dissertation is a response to the most important challenges faced by modern science and medicine, as identified by the World Health Organization (WHO). According to WHO projections, the number of new cancer cases will increase dynamically in the coming years, reaching around 30 million cases by 2040.

The development of drug-resistant forms of parasites may, in the future, significantly hinder the treatment of diseases such as malaria – the most deadly parasitic disease in the world – as well as African sleeping sickness, which belongs to the group of so-called neglected tropical diseases. In light of these reports, it is crucial to search for new drug candidates, particularly for combating the aforementioned diseases.

I selected ivermectin and monensin as the subjects of my research – naturally occurring compounds that exhibit a broad spectrum of biological properties. Their use in medicine and/or veterinary science is due to their exceptionally high antiparasitic activity. Furthermore, both compounds have been shown to be highly effective in destroying cancer cells, involving various mechanisms of action. Rational modification of the structure of these compounds could lead to analogs with better therapeutic potential (higher biological activity and selectivity) than the parent compounds.

This doctoral dissertation consists of a series of seven scientific publications (**I**–**VII**) and a commentary on these works. In the research on ivermectin, I focused on the chemical modification of the C13 position, which connects the aglycone fragment of the molecule with the sugar component. As a result of multi-step syntheses, I obtained a series of C13-*epi*-amides of ivermectin and its bioconjugates with other biologically active compounds. Additionally, I discovered a new, previously unknown rearrangement reaction of the

hexahydrobenzofuran system of ivermectin, which led to the synthesis of a series of its doubly modified analogs.

In the experimental work on the chemical modification of monensin, I focused on modifying it at the C1 and C26 positions. As a result, I obtained bioconjugates of monensin with the trifenyphosphonium cation, i.e., hybrids targeting the mitochondria of cancer cells. The development of synthesis methods for the C26-azide and C26-amino derivatives of monensin opened entirely new synthetic possibilities, leading to the C26-*N*-acylated analogs and macrocyclic products.

The analysis of biological activity allowed for the identification of highly bioactive analogs, which greatly surpassed the parent compounds in terms of effectiveness. Examples include the non-rearranged and rearranged 2-chloroacetyl amides of ivermectin which demonstrated approximately 230 times higher *in vitro* activity against parasites causing African sleeping sickness compared to unmodified ivermectin. On the other hand, the conjugate of this drug with artesunate effectively inhibited the proliferation of cancer cells used in the tests and exhibited a lack of cytotoxicity towards the reference cell line. Additionally, the *O*-phenyl urethane of monensin proved to be about 8 times more active against malaria-causing parasites than the parent compound, achieving an IC_{50} value lower than 1 nM.

The research I conducted demonstrated that chemical modification of the structures of ivermectin and monensin is a promising approach for the discovery of new bioactive compounds with high anticancer and antiparasitic potential. Many of the studies carried out, such as the evaluation of the anticancer properties of ivermectin derivatives, the development of its rearrangement reaction, or the synthesis of C26-azido and C26-amino derivatives of monensin, were conducted for the first time. This serves as a kind of “signpost” that not only can guide scientists toward new research directions, but also proves that chemical modifications of known natural compounds can still be a source of promising research outcomes, unexpected discoveries, and inspiration.