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„Synteza i badania aktywności biologicznej pochodnych związków naturalnych - salinomycyny i kolchicyny”

Streszczenie w języku angielskim

Facing continuously growing number of cancer cases and insufficient effectiveness of the currently used anti-cancer therapies, it is necessary to search for new compounds showing anti-cancer activity. Since chemical modification of natural compounds is still one of the most effective methods of searching for new drugs, I chose two compounds of natural origin - salinomycin and colchicine, as the objects of my research.

Salinomycin is a natural ionophore antibiotic with a broad spectrum of biological activity, isolated from *Streptomyces albus*. Colchicine, on the other hand, is a pseudoalkaloid with an anti-inflammatory and antimitotic effect, which can be found in autumn crocus (*Colchicum autumnale*).

The results of my research have been presented in a series of 6 scientific articles, which constitute the basis of my doctoral dissertation entitled "*Synthesis and biological activity of derivatives of natural compounds- salinomycin and colchicine*". Modifications of the salinomycin molecule included reductive amination, selective oxidation of the C20 hydroxyl group, inversion of the absolute configuration of the C20 carbon atom, as well as esterification, amidation and acylation reactions. Modifications of colchicine, on the other hand, included selective demethylation of methoxy groups at C1 and C10 positions, acylation, hydrolysis, reductive amination and rearrangement of the tropolone ring under the influence of UV radiation. As a result of the performed syntheses, I obtained 49 new derivatives of salinomycin and 48 new derivatives of colchicine.

The structure and purity of the derivatives obtained were determined using nuclear magnetic resonance spectroscopy (^{1}H NMR, ^{13}C NMR, 2D NMR), crystallographic analysis, mass spectrometry (ESI-MS), infrared spectroscopy (FT-IR), and elemental analysis (EA).

All obtained compounds were tested for anti-cancer activity in cooperation with scientists from Polish and foreign research centers. The cytotoxicity of the salinomycin derivatives was determined against the primary acute lymphoblastic leukemia (ALL-5), human breast adenocarcinoma (MDA-MB-231), primary colon cancer (SW480), metastatic colon cancer (SW620), metastatic prostate cancer (PC3), human cell lines breast

mesenchymal cells with stem cell properties (HMLER $CD24^{low}$ / $CD44^{high}$), an isogenic non-stem cell epithelial line of breast cells (HMLER $CD24^{high}$ / $CD44^{low}$), and against a panel of 60 human tumor cell lines (NCI-60). On the other hand, the obtained colchicine derivatives have been tested against the following cancer cell lines: human lung adenoma (A549), human breast adenoma (MCF-7), human colorectal adenoma (LoVo) and drug-resistant human colorectal adenoma (LoVo / DX) line. In addition, selectivity and resistance indexes were also determined for all tested compounds. This allowed us to determine the correlation between the structure of the new derivatives and their biological activity (*SAR*).

The obtained results have proven the right choice of the research objects - natural compounds with high anti-cancer potential. Their modifications allowed me to show that a well-planned synthesis of salinomycin and colchicine analogs can lead to new and more active derivatives, proving that the power of nature can be improved.