Doctoral Dissertation Abstract

„Application of Microwave and FLOW chemistry technologies in development of innovative small-molecule inhibitor as high antitumor activity against acute myeloid leukemia (AML)"

The aim of this study was to develop and optimize the synthesis of inhibitors of FTL3 kinase responsible for the development of acute myeloid leukemia AML. In the literature part, I present a description of the malignant cancer disease AML and methods of its treatment. For this purpose, intensive chemotherapy and bone marrow transplantation are most often used. Mutations in the FLT3 kinase, which belongs to the family of class III receptor tyrosine kinases (RTK III), contribute mainly to the development of acute myeloid leukemia as well as other cancer diseases. It regulates a number of processes responsible for proliferation, i.e. cell multiplication, differentiation, adhesion, mobility, metabolism and programmed cell death (apoptosis). Moreover, FLT3 kinase oversees the proper development of stem cells and the immune system. Internal tandem duplication and point mutations are the main types of abnormalities in FLT3 kinase function. Destruction during chemotherapy, which includes both disease cells and effects, as well as side effects and toxicity of this therapy that may occur as a result of targeted treatments. These preparations are nothing more than inhibitors that must have therapeutic activity, exclude toxicity, but above all, access to cancer cells while releasing access to resources. Currently, many FLT3 kinase inhibitors have been developed and have qualified for clinical trials. Due to patent rights related to the synthesis of inhibitors, in this work I did not present the reactions leading to their preparation. The limited clinical effectiveness of the FLT3 kinase inhibitors developed so far, as well as the multidrug resistance that often appears during treatment and the body's often short-term response to the treatment, inspired me to undertake work related to with the development of an innovative, small-molecule FLT3 inhibitor with high oral bioavailability, low toxicity and a favorable pharmacokinetic profile. Additionally, the developed inhibitor should be safe and highly effective in the treatment of people with acute myeloid leukemia.

In the development of a new biologically active molecule, I first used in silico bioinformatics methods, mainly the KNIME program. Thanks to it, I created a virtual library of compounds containing 700 structures. Molecular docking, in turn, provided me with information on how to match potential inhibitors to the receptor. Moreover, these methods

helped me choose modifications that improved both the activity and properties of the molecule. After a detailed analysis of the data obtained from docking, I synthesized 110 compounds for further research. The molecules which I synthesize are primarily pyrimidine derivatives such as and pyrrolopyrimidine, because, according to the data available in the literature, pyrimidine is one of the most important structural elements of many medicinal preparations. These compounds also belong to the family of heterocyclic compounds containing in their structure an element structurally similar to the purine ring. For all molecules, their activity towards FLT3 kinase and selected reference compounds was determined: UNC2025 and MRX-2843. Chemical stability and stability on mouse and human microsomes were also determined. Physicochemical parameters and solubility in solutions with pH 4.5 and 7.4 were determined. Analyzes were also carried out to determine the permeability of new molecules through biological membranes. Derivatives with the best possible selectivity for FLT3 kinase were then tested on cell models such as: KASUMI-1, NOMO-1 and MOLM-13. These are human acute myeloid leukemia cell lines. Among the compounds I synthesized, chose two leading structures. These compounds were selected based on structural similarity to reference compounds. Moreover, the IC50 values of the selected compounds were close to the IC50 values of the reference compounds. Moreover, this choice was dictated by an in vitro study, which showed much better effectiveness of compounds that have a C1-C4 system with one unsaturated bond in their structure. These molecules also have much better solubility and bioavailability. Additionally, these compounds were subjected to toxicological tests in order to determine their maximum tolerable dose. One of the selected lead compounds shows great potential for being a "medicine" and qualifying for clinical trials in the future.

In this work, I also described the process of optimizing the synthesis path of one from selected reference compounds. I performed the optimization work mainly using flow technology (FLOW), which has been dynamically developing in recent years. I also optimized some stages using a microwave reactor.