Doctoral dissertation abstract

„Application of microwave technology in the development of a synthesis pathway for an innovative small-molecule MERTK inhibitor with high anticancer activity against acute lymphoblastic leukemia (ALL).”

The main goal of this doctoral thesis was to design and synthesize an appropriate library of chemical compounds and to select among them a potential small-molecule Mer kinase inhibitor inhibiting the development of acute lymphoblastic leukemia (ALL). An additional goal was also to use new technologies, such as a microwave and flow reactor for the synthesis of the mentioned class of molecules.

Generally speaking, leukemia is a disease of the hematopoietic system that involves the uncontrolled multiplication of cells present in the bone marrow and lymph nodes, which ultimately become cancer cells. One type of this cancer is acute lymphoblastic leukemia (ALL), which is the most common type of cancer occurring in children aged 2 to 5 years. It involves cancerous changes in lymphoid cells, which leads to the accumulation of immature B and T lymphoblasts in the bone marrow and blood and the displacement of healthy cells. Treatment of people, mainly children, suffering from this type of cancer most often involves the administration of chemotherapy, i.e. the use of chemical compounds that have a destructive effect on cancer cells. The final form of therapy is allogeneic transplant. This is a type of transplant in which the donor is a person related to the recipient or not. Acute lymphoblastic leukemia ALL is closely associated with receptor tyrosine kinases, namely with abnormal expression of Mer kinase. This kinase belongs to the TAM family of receptor tyrosine kinases, which also includes Tyro-3 and Axl kinases. These are enzymes responsible for the protein phosphorylation reaction, and their incorrect expression results in the pathogenesis of human cancers. Due to the fact that these kinases are very active in cancer cells, they have become an intriguing topic for research groups looking for new oncological drugs. Currently, existing small molecule inhibitors are characterized by multispecificity towards TAM family kinases, which is associated with low selectivity and significant toxicity. Therefore, molecules that have high anticancer activity against acute lymphoblastic leukemia, the ability to selectively inhibit the MerTK receptor, and do not have toxic side effects are still being sought. After a preliminary analysis of publicly available literature, selecting a reference compound (MRX2843) and using in silico bioinformatics methods, taking into account the properties of the molecules, a library of new structures was designed. The next step was to dock these compounds onto a MerTK kinase

crystal to visualize each structure in the active pocket of the receptor. On this basis, appropriate modifications were created at the sites of functional groups and examined for the relationship between the structure and biological activity of the compounds (SAR). As a result, a library of 120 molecules, which are pyrrolopyrimidine and pyrimidine derivatives, was obtained. Chemical synthesis was performed in the Laboratory of the Medicinal Chemistry Department, while ADMET tests were performed in the Physicochemical Analysis Laboratory and the Preclinical Research Department of Celon Pharma S.A. The obtained compounds were first tested on Mer kinase to determine their activity, as well as in terms of solubility in acidic and neutral media and stability on microsomes. From the entire library, three molecules were selected whose results of the above tests were most similar to the reference compound, and the synthesis process was optimized and scaled to obtain gram amounts of each molecule. Further physicochemical and stability tests, as well as tests on cells and animals, were carried out for the compounds prepared in this way in order to select the best lead compound ("*hit to lead*" process). The next stages, i.e. toxicological and then clinical tests, are underway. At the same time, during the research, optimization of all stages of the synthesis was carried out, which led to obtaining the reference compound MRX2843. For this purpose, the Discover 2.0 microwave reactor and the E-series Vapourtec Easy MedChem flow reactor were used. Both of these technologies allowed for a significant reduction in the duration of individual stages and the entire synthesis, which involves the intensification of processes and also has a positive impact on the ecological and economic evaluation.