SUMMARY

Cancer is now one of the leading causes of death worldwide, and the incidence of cancer is steadily rising. Despite significant advances in anticancer therapies, uncontrolled growth, metastasis and drug resistance of cancer cells is an important problem limiting the effectiveness of treatment. In this regard, the research on new anticancer drugs with high activity and low toxicity is an important task for medicinal chemistry. An effective way to search for new active compounds is to modify the structures of currently used drugs to improve their activity and reduce toxicity.

In anticancer drug design, an important issue is to find molecular targets against which these compounds will act. Recently, neutrophil elastase has been shown to be an important target for compounds directed against cancer cells. It is a neutrophil serine protease whose increased activity has been associated with the pathomechanism of breast, lung, prostate and colon cancer growth and progression. Elastase inhibitors have also been shown to exhibit antiproliferative activity in a number of cancer models.

The research presented in this doctoral thesis focused on modifying the structure of the well-known anticancer drug - thalidomide, to obtain new compounds, previously unknown in the literature, that exhibit the highest possible anticancer and elastase inhibitory activity.

Using as pharmacophores the rings of phthalimide, thiazole and azetidine-2,4-dione system, 5 series of new thalidomide derivatives were designed. Efficient methods of synthesis, separation and purification of the newly designed compounds were presented and their structures were confirmed using spectroscopic methods. The next step was to evaluate the antiproliferative activity of the obtained derivatives against 7 cancer cell lines and to test their toxicity against 2 healthy cell lines. The inhibitory activity of porcine pancreatic elastase and human neutrophil elastase was tested and the mechanism of inhibition was determined. For selected derivatives, the ability to inhibit EGFR tyrosine kinase, activate caspase 3/7 and affect the processes of apoptosis, necrosis and the cell cycle were also investigated. In addition, the chemical stability of the newly designed compounds was determined. The final stage of the study was molecular docking, which allowed to find out the mechanism of interaction of the new thalidomide derivatives with the elastase structure.

As a result of the conducted research, a total of 29 new thalidomide derivatives, previously unknown in the literature, were obtained. Most of the new compounds were characterized by high antiproliferative activity with simultaneous low toxicity to healthy cells. The newly designed compounds proved to be good elastase inhibitors, and the most active of them were

active in the nanomolar range. The performed research identified a lead structure for new thalidomide derivatives with high anticancer and elastase inhibitory activities, which could be used as potential drugs in cancer therapy in the future.

Keywords: elastase, thalidomide derivatives, cancer, molecular docking, thiazole