NEW TYPE OF ANALOGS AND CONJUGATES OF FOLIC ACID WITH POTENTIAL THERAPEUTIC APPLICATION IN TREATMENT OF HORMONE-DEPENDENT CANCERS

The issue of breast cancers, due to their unidentified etiology, has attracted the attention of many doctors and scientists throughout the centuries. Despite extensive research and a variety of therapies, breast cancer still remains one of the main causes of women's death in highly developed countries. *National Cancer Institute* estimates that in 2021 only in the United States, more than 281 000 new cases will be diagnosed and 43 000 patients will die as a result of the disease. It is worth pointing out the fact that approximately 95% of cancer cases in their initial growth phase show a hormone-dependent nature. For this reason, biologically active hormones (including estrogens and androgens) play a crucial role in the growth and proliferation of tumor cells, and therefore new therapies should focus on the use of pharmaceuticals, which will effectively reduce the delivery of active hormones to cancer cells. One of the main hormone-dependent breast cancer treatment strategies is based on the application of biologically active compounds, which exhibit the ability to inhibit the activity of enzymes responsible for the synthesis of estrogens and androgens. In recent years, intensive research has been conducted to find new and effective STS inhibitors.Unfortunately, a large group of potential drugs (especially those based on steroid scaffolds), in addition to exhibiting the desired effect, were characterized by estrogenic properties, which were responsible for the increased proliferation of tumor cells. One of the approaches to eliminate this side effect is the development of inhibitors, which will contain a non-steroidal core in their structures and exactly this strategy will be used in our project. It is also worth mentioning that compounds with cytotoxic properties used in cancer treatment therapies often exhibit low specificity, which consequently results in high levels of systemic toxicity and several undesirable side effects. Many research groups engage the attempt to create a way of delivering a potential drug to cancer cells that will be characterized by the highest possible level of efficiency and selectivity. Due to the fact that folic acid (FA) is a molecule that rapidly proliferating cancer cells have a very high demand for FA may play an important significance in this process. Moreover, the FAup-take mechanism is a relevant issue and is based on several types of transport systems, of which specific folic acid receptors (FR) are prominent. FR (especially FRα) exhibits low levels of expression in normal, healthy cells, as opposed to the cancer cells, which demonstrate a very high level of FA requirement due to the rapidly dividing and growing process of these cells.

The aim of this research project is the synthesis of two series of compounds with potential therapeutic applications in the treatment of hormone-dependent cancer. Compounds of SERIES I will exhibit structural similarity to FA through the presents of glutamine acid residue in their structure, which is a very important unit of FA. The introduction of structural elements present in the FA structure into STS inhibitors may lead to compounds characterized by high inhibitory activity against STS as well as enhanced selectivity against cancer cells. Moreover, the aforementioned derivatives will have 1,2,3-triazole, coumarin, tyramine, flavone core in their structure, which exhibits geometrical similarity to natural, steroid substrates of STS. Furthermore, this project involves creating a large library of conjugates of folic acid and STS inhibitors (SERIES II). These compounds will be designed based on the results of biological studies for compounds of SERIES I The most promising derivatives will be selected and conjugated to FA molecule. Moreover, all compounds will contain sulfamate pharmacophore in their structure, whose effectiveness has already been proven in the course of our previous studies.

In conclusion, STS is a very attractive, new molecular target for the development of hormone-dependent cancer therapy, and therefore the synthesis of novel, effective, and selective STS inhibitors is a crucial challenge for modern medicinal chemistry. Considering also that FR expression steadily increases with tumor progression, it is hypothesized that the newly developed compounds will be effective in treating advanced tumor states and can be a basis of a highly effective targeted therapy.