Despite efforts continuously undertaken in the field of medicinal chemistry, with special interest observed in the development of innovative drugs targeted towards the most abundant and the most lethal diseases, pharmacotherapy of some conditions remains a sizable challenge. A prime example of that is breast cancer, which is the leading cause of disease-related deaths among women. Other examples include Alzheimer's disease, as well as other types of dementias, which belong to neurodegenerative diseases and were recognized by the World Health Organization as one of the ten most common causes of death in the world. High mortality is the terminal result, but it should not be forgotten that the course of the mentioned diseases for the patients is associated with a significant deterioration in the quality and comfort of life. Some important problems to overcome include the negative side effects of drugs taken, the problem with delivering the drug directly to the designated and desired location due to the insufficient permeability through biological membranes, as well as the high cost of innovative therapies.

For these reasons, intensive research on alternative molecular targets for new drugs continues, driven by the purpose of stopping the progression or even eliminating the underlying cause of the diseases. Often, these goals are to be achieved by sophisticated measures such as altering the metabolic pathways involved in the development of diseases, and one of the leading molecular targets is an enzyme called protein tyrosine phosphatase 1B (PTP1B). The latest studies prove that its excessive activity is involved in numerous detrimental processes, such as accelerated progression of breast cancers of various subtypes and an increased risk of metastases. In addition, this enzyme is also involved in intensification of the amyloid β plaque deposition in the brain, which could be observed in people diagnosed with Alzheimer's disease. At the same time, inhibition of PTP1B provides a protective effect for neurons along with a noticeable improvement in cognitive functions. Therefore, inhibition of this enzyme seems to be a promising therapeutic strategy in the treatment of breast cancer and various neurodegenerative diseases.

Consequently, the main goal of the project is to design a library of selective PTP1B inhibitors based on the conjugates of aryl difluoromethylenephosphonic acid and thiazole, and to synthesize and experimentally determine the properties of these molecules. As part of the project, the biological activity of the obtained compounds will be evaluated in terms of the effects on PTP1B enzyme. Their effectiveness will also be tested using cell lines representative of various subtypes of breast cancers and a model cell line of neurodegenerative diseases, including Alzheimer's disease. Effect of the obtained compounds on healthy cell lines will also be examined to assess toxicity. Additionally, theoretical simulations will be carried out to assess the mechanisms of action of the drugs, as well as to characterize the relationship between structures of the compounds and their activity.

The thiazole structure was chosen as an essential common element on which the structures of all synthesized small-molecule substances will be based. This choice is determined by several factors. First of all, small-molecule drugs, due to their low mass, are preferred when it comes to permeability through biological membranes, which significantly increases their bioavailability. In addition, thiazole derivatives are known for their low toxicity to non-cancer cells, and the thiazole structure has found its application as a component of several drugs already used in current therapeutic standards. The high polarity of the PTP1B active site is a significant factor, which is often an obstacle in drug design, because in order to match the enzyme, the designed drug should be endowed with a constant charge, which at the same time limits its permeability through biological membranes. Including thiazole moiety within the compound allows to minimize this inconvenience due to the delocalized electric charge of this polar heterocyclic structure.

Results of the presented project should significantly increase the state of knowledge regarding the design of inhibitors for an attractive molecular target, which is PTP1B. Moreover, due to the increasing incidence of breast cancer and neurodegenerative diseases, the priority is to facilitate the research on the development of innovative drugs effective in the treatment of the above-mentioned diseases. The presented project, by providing an essential foundation of basic research, may be a factor that contributes in the future to improving the quality of life and comfort of the disease-affected patients.