DESCRIPTION FOR THE GENERAL PUBLIC

The objective of the project

Designing compounds with a multifunctional mechanism of action is one of the strategies of searching for new biologically active substances with potential application in the therapy of diseases with complex etiology. The development of a multifunctional drug involves obtaining a compound that acts simultaneously on several biological targets resulting in a wider spectrum of activity and a greater pharmacological effectiveness. The aim of this project is to design and obtain several series of new compounds demonstrating at the same time features of channel antagonists associated with transient potential receptors (TRP), TRPA1 subtype, and PDEs, especially isozymes 1, 3, 4, and 7. Taking into account that both TRPA1 channels and PDEs play an important role in the pathogenesis of chronic pain (neuropathic pain) and chronic respiratory diseases (e.g. chronic obstructive pulmonary disease, COPD), compounds of this type may be a new beneficial therapeutic option in the treatment of these diseases. The new therapeutic approach will be verified by assessing the biological activity of the obtained compounds both in vitro and in vivo. TRPA1 channel blocking and inhibition of selected PDEs by new compounds as well as their anti-inflammatory, antioxidant, and anti-fibrotic properties will be evaluated in several in vitro tests. This will allow for the selection of the most interesting compounds for pharmacokinetic and then in vivo pharmacological studies to determine their analgesic and anti-inflammatory activity in animal models of pain, as well as their effectiveness in an animal model of COPD.

Description of the research to be carried out

Research in the field of medicinal chemistry at the first stage concentrates on the design of chemical structures that promise the assumed direction of pharmacological action. In this project, for this purpose the computer-aided drug design was used, which based on the analysis of the binding site and ligand-receptor interactions with the use of among others pharmacophore models will allow to indicate essential structural features for the designed multifunctional molecules. The designed compounds will then be synthesized in multisteps procedure and their structures will be confirmed using spectral methods, including advanced nuclear magnetic resonance (NMR) and mass spectrometry (MS) techniques. In the next step, the compounds will be tested in preliminary screening tests in vitro, based on appropriately prepared cells with a high expression of human TRPA1 channels and recombinant human PDEs, which will allow for the selection of potent multifunctional TRPA1 antagonists and PDEs inhibitors. The most active compounds will undergo further in vitro studies using cellular assays to assess their anti-inflammatory, antioxidant, and anti-fibrotic activities. The most promising compounds selected on the basis of the in vitro study results, after examining their toxicity in vitro and pharmacokinetic properties in vivo will be tested in selected animal models of pain, including neuropathic pain, and chronic respiratory diseases (model of COPD).

Present reasons for choosing the research topic

Chronic diseases, such as neuropathic pain or chronic respiratory diseases are a significant, growing health, social, and economic problem. They lower the quality of patient’s life, impede professional functioning, and in the case of e.g. COPD may lead to premature death. The mechanism of these diseases is complex and not fully understood and their current pharmacotherapy is not entirely effective. Hence the search for new drugs to treat the above-mentioned diseases is in line with the current research directions. At the same time, the paradigm "one disease, one gene, one molecular target, one drug" loses importance in diseases of complex etiology, as the effectiveness of treatment of such diseases is associated with the simultaneous impact on several biological targets. The designed studies may allow to obtain innovative compounds demonstrating the multifunctional activity, i.e. blocking of TRPA1 channels and inhibition of several PDEs, with more beneficial pharmacological properties resulting from additive or synergistic effects on several biological targets. Compounds with such a unique profile of action may constitute scientifically original, new "pharmacological tools" that will allow for the better understanding of interactions with the studied biological targets in both molecular and pharmacological aspects.