

DESCRIPTION FOR GENERAL PUBLIC

State the objective of the project

Scientific research conducted at the Department of Medicinal Chemistry of the Faculty of Pharmacy (Jagiellonian University Medical College) focuses on the search for new biologically active substances acting on the central nervous system (CNS). The objective of this project is to obtain a library of new designed multiple ligands (DMLs) with phosphodiesterase type 10A (PDE10A) inhibitory activity and diversified functional selectivity towards serotonin 5-HT_{1A}/5-HT₇ and dopamine D₂ receptor, which may **exert beneficial effect on the improvement of cognitive function in the course of depression, anxiety and/or schizophrenia.**

The research to be carried out

Along with the design and synthesis of potentially biologically active chemical compounds, fundamental research is being carried out with the objective of improving the process of searching for new drugs. This process employs computer-aided structure design of new ligands (biologically active molecules) and the design of new computer models of interactions between receptors and ligands as well as the improvement of existing ones. The objective of the research related to pharmaceutical chemistry is as follows: at the first stage to design a molecule which promises proper direction of pharmacological activity and at the second stage to synthesize the designed, potentially biologically active compounds intended for initial screening tests. This screening constitutes stage three and is conducted with the use of *in vitro* methods, based on cell cultures or tissue fragments containing, for example, adequately prepared receptors. New, active chemical compounds selected as a result of such research undergo *in vivo* tests (i.e., tests on living organisms) on laboratory animals. The results of such tests make it possible to determine the profile of the pharmacological activity of the new substances and therefore assess their scientific usefulness.

Present reasons for choosing the research topic

With the decline in fertility and mortality rates accompanied by an improvement in child survival and increased life expectancy, a significant feature of demographic change is the progressive increase in the number of elderly persons. Increasing life span and poor health care add to the degree of disability among the elderly and compound the problems of care giving. A popular proverb "age is a heavy burden" captures the essence of the matter. The inevitable changes of aging can be both humbling and surprising. Skin wrinkles, hair fades, bodies chill, and muscle mass wanes. In addition, the brain shrinks, working memory goes on strike, and mental speed slows. But while many people do experience mild and gradual memory loss after age 40, severe and rapid memory loss is definitely not a part of normal aging. Dementia is a collection of symptoms including memory loss, personality change, and impaired intellectual functions resulting from disease or trauma to the brain. These changes are not part of normal aging and are severe enough to impact daily living, independence, and relationships. People who are depressed may have trouble concentrating. They may even suffer occasional memory lapses, which can make their mood worse. Depression in older adults and the elderly is often linked to physical illness, which can increase the risk for depression. Chronic pain and physical disability can understandably get you down. Symptoms of depression can also occur as part of medical problems such as dementia or as a side effect of prescription drugs.

The activity of each drug usually results from the interaction of its molecule with an appropriate "spot" within the body, called the receptor. This problem of is translated as "*lock-and-key*", and here, the receptor can be thought of as the "lock" and the ligand can be thought of as a "key". Multiple drug design may be described as construction of a key which fits a variety of definitely chosen locks. Molecular docking may be defined as an optimization problem, which would describe the "best-fit" orientation of a novel compound binds to a particular protein of interest. By binding to receptors, drugs stimulate or inhibit the relevant biochemical reactions in the cells of living organisms. These result in processes that may be used in disorders of tissue and organ function, leading to the "repair" of incorrectly functioning cells or systems.

In this project, it was decided to obtain a presumed therapeutically relevant effect, the structure of biologically active substances which combine elements to become "keys" for the receptors and the enzyme. In the scientific literature, this strategy is called designed multiple ligands (DMLs). **The pioneering nature of the project is reflected in the identification and validation of new combinations of existing biological targets for treating cognitive function in the course of depression, anxiety and/or schizophrenia.** Moreover, the proposed research will allow for a better understanding of mechanisms of receptors action, and this **may contribute to the development of new therapeutic options** for such problem as cognitive impairment, which are of great social importance.