The mankind was searching for therapeutic agents from the beginning of their history, long before the onset of the so-called the scientific age. Several thousand years ago, people were looking for ways to treat various ailments and diseases by eating fruits and leaves of plants, chewing roots and bark or using animal and mineral products. However, the search for new drugs in the past centuries was largely a random activity. Nowadays it is clear that the drugs therapeutic effects result from their interaction with the macromolecules in the human organism, in particular with proteins: receptors and enzymes. This fact enables rational drug design in such a way that a drug fits a protein like a key fits a lock. One of contemporary approaches to elaborate new drugs is to find additional therapeutic application for already existing drugs so using a known key to open additional locks.

The aim of the project is to decipher the molecular mechanism of action of the novel compound displaying a broad spectrum of beneficial activity on the central nervous system and elaboration of its more potent analogs. This compound was first designed as a pharmacological tool to study the pathomechanism of schizophrenia. Preliminary results revealed its antipsychotic, anxiolytic and procognitive activity in respective animal models. In addition, this compound increases proliferation of hippocampus cells (the part of the brain involved i.a. in memory processes) *in vitro* and *in vivo*. Thus, the compound, apart from its application in schizophrenia studies, may be a useful pharmacological tool to study neurodegeneration and neuroprotection processes in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. The compound under investigation is a multi-target agent, i.e. a potential drug-key which fits a number of locks. In our project we will identify the proteins-locks responsible for the beneficial properties of the compounds and we will use computer-assisted methods to design tailor-made compounds interacting with these proteins-locks. The design of new derivatives will be aimed to maximize their interactions with the proteins responsible for increased proliferation of the hippocampus neurons. Secondly, it will be crucial to deprive them of activity to proteins important in schizophrenia (in particular they must be devoid of dopamine $D_2$ receptor antagonism). The designed compounds will be synthesized in a laboratory and tested using chemical and biological methods. We will determine their 3D structure using X-ray methods and investigate their biological activity using cell and animal models.

It should be emphasized that application of computer-assisted drug design techniques is a key part of the project. Application of these methods allows to limit a number of necessary experiments and thus costs, chemicals use, animal studies number, time and human effort. The idea of application of these methods to design new bioactive substances can be explained in the following way: both a drug and its molecular target (eg. protein) consist of atoms which can be represented by Cartesian coordinates in the same way as the tops of the prism. This makes it possible to use computer software for fitting a drug to a protein. In our project we will modify our compounds to fit them to a number of proteins (targets) and simultaneously not to make them fitting to other proteins (off-targets).

The justification of the topic of the project is first of all alarming epidemiologic data concerning neurodegenerative diseases. Neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease are an increasing medical, economic and social problem in countries where the life expectancy has increased, so also in Poland. The increasing prevalence of these diseases results i.a. from the population aging and increasing pace of life. Parkinson's disease affects 1% of the population over the age of 70. In turn, Alzheimer's disease affects about 1.5% of the population at the age of 65-70 and as much as 30% of the population over the age of 80. In spite of the progress in medicine, currently available drugs cannot stop the disease progression but only slow it down. Moreover, our promising preliminary studies results constitute an additional motivation to study neurodegeneration and neuroprotection processes in neurodegenerative diseases. We were able to identify an active compound and to indicate multiple proteins which could underlie its beneficial activity. The availability of this data considerably increases the project chances of success, i.e. clarification of the molecular mechanism of this substance activity and elaboration of its optimized analogs.

The project is expected to broaden the knowledge about the molecular mechanisms of neurodegeneration and neuroprotection processes in neurodegenerative diseases such as Alzheimer's disease and Parkinson's disease. We aim to determine the set of molecular targets responsible for favorable therapeutic activity of our compound. Moreover, more potent derivatives of the compounds will be obtained which will display expected activity in cell and animal models. New substances elaborated under the framework of the project can be applied as pharmacological tools to study the proteins involved in their activity and the pathomechanism of the neurodegenerative diseases.