

Serotonin receptors are a type of protein located in the brain and other parts of Central Nervous System (CNS), whose task is to provide signals to ensure the proper functioning of the body. Serotonin 5-HT₆ receptors are the most recently discovered subtypes of serotonin receptors whose function is affected by the feelings and behavior in humans and mammals, including recognition, mood, feeling of anxiety or weight gain.

Much smaller than the protein chemical compounds with special construction, called ligands are capable of selectively regulation of corresponding proteins functions, including the 5-HT₆ receptor. The receptor can be activated through interactions with a ligand known as agonist or blocked by antagonist.

Conducted clinical and preclinical studies involving animals and humans have confirmed the effectiveness of 5-HT₆ receptor ligands for the treatment of diseases and abnormalities which, due to the increasing number of cases in modern society are called lifestyle diseases. Examples include Alzheimer's disease, anxiety, depression, schizophrenia and obesity. The number of therapeutically effective 5HT₆ ligands is insufficient and none of them has yet gotten to the market. Therefore a search for new ligands in a new group of chemical compounds is a major challenge for today's pharmaceutical sciences.

Faced with this challenge, the project involves a search of such ligands in a new group of compounds called triazines, in which several representatives exhibiting significant interaction with the 5-HT₆ receptor in vitro have been found. The search for novel ligands will be carried out in a rational manner by means of computer tools. Virtual design of various chemical compounds and modelling the interaction with the virtual structure of the 5-HT₆ receptor will enable the selection of only those structures that can interact with (bind to) receptor.

In this group of structures, a computer analysis of the drug-like properties such as stability, distribution and ability to cross biological barriers in order to reach the brain will be also carried out. In addition, the potential toxic effects will be assessed. In this way, from out of thousands of possible combinations of chemical fragments containing the triazine moiety, several selected structures with the estimated best properties, will then be obtained by chemical synthesis.

Pure synthesized connections will be tested in vitro using tritium-labeled ligands in order to assess their effects (affinity) for receptor 5-HT₆ and other receptors (serotonin, adrenergic, and dopamine) which are also found in the CNS and may compete in the interaction with the ligand.

Preliminary affinity studies and selectivity for competitive receptor will choose a group of several ligands potently and selectively acting on the 5-HT₆ receptor, which in a further step will be examined in in vivo tests on animals. These studies will include evaluation of the effect of compounds on cognition, depression, and anxiolytic. For the most potent compounds, metabolic tests assessing the impact on eating habits, will be conducted as useful in treating obesity.

Selected after in vivo tests active structures will be good starting points for broader pharmacological studies. The proposed design work will bring, therefore, an important contribution to the search for effective therapies in the fight against modern civilization diseases such as dementia, depression and obesity.