DESCRIPTION FOR THE GENERAL PUBLIC

The 5-hydroxytryptamine receptors (5-HTR) are a kind of protein located in the brain and other parts of central nervous system (CNS). The 5-HT_6R is a "youngest" serotonin receptors group, discovered by three separate teams of scientists in 1993. Their action is reflected in the behavior of humans and other mammals, that is the perception, mood swings, anxiety and weight gain. Tests on humans and animals in the form of clinical and preclinical provide high performance 5-HT_6R in the treatment of lifestyle diseases such as Parkinson's disease, obesity and mental illness. In this study is planned to examine 8 chemical compounds that can become potential drugs due to its effect on the 5-HT_6 receptor. Planned studies include identifying "druglikeness" (ADME-Tox) parameters for the compounds, which determine the fate of the compound in the body after administration, also the absorption, distribution, metabolism, excretion and potential toxicity.

In the first stages of the development of new drugs, ADME-Tox parameters are often tested using *in vitro* methods to save time by high-throughput screening, which is also associated with the reduction in costs. Alternative methods are aimed in principle "3R" of W. Russell and R. Burch to reduce the number of animals (Reduction), to replace them (Replacement), to improve methods (Refinement). The development of those areas affected by the letter of the law, that is the EU Directive on " the protection of animals used for scientific purposes".
For this project the following *in vitro* methods based on cell cultures, artificial biological membranes and enzyme assays have been chosen, that reflect *in* vivo conditions in the human body. Absorption and permeability of the compounds will be determined by PAMPA assay. This method involves the use of the artificial membranes imitating biological membranes.
Considering the next aspect will be the affinity of the tested substances to the transport protein-P-glycoprotein which is responsible for the drug absorption in the intestine. The compounds inhibition ability will be determined by using enzyme assays. In the next part of project, the affinity for plasma proteins and metabolic stability of compounds will be estimated. Those parameters are needed to evaluate the distribution and elimination of the potential drug from the human body. During this project it is planned also a series of studies related to the safety profile, including at the identifying of potential drug-drug interaction, on the toxic effects on human cells, including liver cells, the toxic effects on the heart beat and the estimation of the mutagenicity of the examined compounds.

The proposed experiments can make therefore, an important contribution to the search for effective therapies in the fight against modern lifestyle diseases such as depression, dementia or obesity. They will also provide the knowledge to select from the promising from the medical point of view group of compounds the best drug candidates. Above all, the realization of this project will allow the development of tools in the search for new therapeutic agents in the form of high-speed and high-performance tests *in vitro*. The results will be published in the international journals, promoted at national and international conferences and will be included in the planned PhD thesis.