Thymol-derived 1,3,5-triazines, the non-indole and non-sulfone 5-HT_6 receptor ligands, as a starter in search for innovative treatment of memory- and mood disorders

Mass-scale diseases (so-called civilization/lifestyle diseases) are becoming huge problem of our society due to their increasing occurrence as well as lack of availability of effective therapy in many cases. Among them, the great place goes to central nervous system disorders such as depression, demention or Alzheimer's and Parkinson's diseases. These irregularities are caused by dysfunction of proteins which are responsible to signal transmission in the body, especially within brain. These proteins include serotonin receptors, which contains from seven main class (5-HT_1-5-HT_7). Among this protein family, serotonin receptor 5-HT_6 should be distinguished as one of the latest discovered serotonin group member and with remaining numerous challenges for scientists. The lines of evidence described its significant role in pathophysiological processes leading to above-mentioned civilization diseases. Worth mentioning that, none of the 5-HT_6R ligands (chemical compounds with high affinity to the receptor) is available on pharmaceutical market as therapeutic agent. Thus, search for novel chemicals with high affinity to 5-HT_6 receptor, and consequently with potential antidepressant, anxiolytic and procognitive activity is so important scientific approach.

Our previous studies led to identification totally new chemical class of compounds, triazines, which interact with serotonin 5-HT_6 receptor. This group is structurally original in comparison to predominant chemical families of indole and/or sulfone-compounds that have been under consideration for last 25 years. Performance of in-depth structure-activity relationship analysis enabled to indicate further directions of chemical modifications, which are likely to provide desired pharmacological properties. Hence, the aim of the project is design, synthesis and *in vitro*/*in vivo* pharmacological evaluation of thymol-triazine derivatives. As the first stage, molecular modeling techniques will be applied to design novel chemical combinations and initial, virtual assessment of their ability to bind with receptor and drugability. Subsequently, the selected compounds will be obtained within multistep organic synthesis. Among others, we planned synthesis of selenium-containing derivatives. These would be the first selenoligands of 5-HT_6 receptor in the word, what is particularly interesting due to confirmed neuroprotection role of this element and its potential for future therapy of neurodegenerative diseases. The compounds with the most promising *in vitro* properties will be tested with use of animal model to confirm their antidepressant, anxiolytic and procognitive activity and also to assess their pharmacokinetic profile (ADME – administration, distribution, metabolism and excretion).

The planned comprehensive studies will allow for selection of compound(s) with the most interesting activity and the highest safety profile. It will bring much closer to initiate the clinical studies. All the results from this project will extend actual knowledge about 5-HT_6 receptor ligands, their molecular mechanisms of action and, what is even more important, their significance in future therapies of increasingly occurring civilization diseases. We believe that our efforts will contribute in discovery of an innovative drug that will get pharmaceutical market, and thus will improve the life quality of people affected by dementia, Alzheimer's disease or depression.