Reg. No: 2015/18/M/NZ7/00377; Principal Investigator: mgr Sabina Marta Podlewska

The aim of the Project is to find structurally new compounds possessing the ability to modulate the activity of the serotonin receptor 5-HT_7, with the simultaneous optimization of the compounds' metabolic stability with the use of computational protocol based on the application of machine learning methods.

Serotonin receptors 5-HT_7 are mainly localized in the central nervous system, but they can be also found e.g., in stomach, intestines, heart, kidneys, as well as vascular smooth muscle. Compounds modulating activity of this receptor are very important in terms of the therapy of disorders that are crucial from the social point of view, such as depression, cognitive disorders, anxiety and Alzheimer disease. On the other hand, the activity alone is not sufficient for a compound to constitute a drug – it is necessary for the compound to possess also the proper physicochemical and pharmacokinetic properties, lack of toxicity and proper metabolic stability.

A lot of factors, such as the rapid growth of the computational power of computers, the rapid growth of knowledge on the human biology and important innovations that have been introduced in the field of experimental studies have revolutionized the process of new drugs development. Nowadays, it is no longer based on accident and serendipity, but the development of new drugs is a result of a long-lasting and systematic process of the search for new bioactive substances. On the other hand, the range of possibilities offered by the informatics industry allows the shortening and reducing the costs of this process by application of various computational tools. Nowadays, they are used in every stage of the new drugs design process, for the search of new compounds with activity towards the selected receptors, for optimization of physicochemical properties of compounds, for elimination of toxicity or improvement of metabolic stability, for performing statistical analyses from various stages of the research and even later, after introduction of the drug to the market, they help in monitoring and analysis of the drug side effects.

The increase in the amount of data, very helpful on one side, sometimes also constitutes a limitation for the computational methods due to insufficient computational power of computers. Therefore, there is a need to replace the computationally expensive tasks with those for which the requirements for computational resources are not so high. Incredible popularity in the field of computer-aided drug design are getting machine learning methods. They are part of artificial intelligence approaches and enable relatively fast analysis of huge amount of data.

In the presented Project, machine learning methods will be used for both activity towards 5-HT_7R and metabolic stability evaluation of compounds. The constructed tools will be used for the assessment of libraries of commercially available compounds, as well as for the evaluation of compounds generated in a virtual way on the basis of already known compounds active towards serotonin receptor 5-HT_7 (ligands). The predictive models will be constructed both only on the basis of already known 5-HT_7 R ligands (activity evaluation) and compounds with experimentally verified metabolic stability in the case of the assessment of this property (*ligand-based* approach), and also on the basis of a scheme of interaction of compounds with the confirmed activity with the 5-HT_7R and the selected cytochrome P450 subtypes, the enzymes responsible for the biotransformation of drugs in the organism, respectively (*structure-based* approach). The compounds indicated by computational tools as the most active and stable will be purchased, an in the case of the experimental confirmation of their preferential activity and stability, a series of their derivatives will also be synthesized.

The Project will be carried out in cooperation with the Faculty of Pharmacy University of Bari, the institution highly experienced both in the conduction of research oriented at finding new compounds active towards 5-HT_7R, as well as carrying out studies on compounds' metabolic stability.

Finding of new core structures for 5-HT_7R ligands with the good metabolic stability can eventually contribute to the development of new drugs acting within the central nervous system, enabling the therapy of the disorders greatly influencing the proper functioning of the society.