PIPERAZINE DERIVATIVES AS ACTIVE HISTAMINE H_3 RECEPTOR LIGANDS – MOLECULAR MODELING, SYNTHESIS, PHARMACOLOGICAL EVALUATION

One of the initial stages in the search for new drugs, that should act through binding to a required receptor, is the design and synthesis of compounds of a specific structure highly affine to a particular biological target. Proteins belonging to G-protein coupled receptors (GPCR) superfamily are one of the most often explored therapeutic target in drug design and discovery process. Up to date, at least 40% of drugs available on pharmaceutical market are GPCR ligands. Significance of research on this target is still increasing.

Undoubtedly, one of the GPCR receptors – histamine H_3 receptor serves as an interesting research object. This relatively new biological target was discovered in the early eighties of the last century and its importance in the pathogenesis of central and peripheral nervous system diseases has not been fully explained yet. The first, and so far the only selective antagonist for histamine H_3 receptors – pitolisant (Wakix®), has been registered as a drug in March 2016 for the treatment of narcolepsy with or without cataplexy. Although, along other side effects, it displays a negative influence on cardio-vascular system, at patients with concomitant heart disease. Therefore, the search for other selective histamine H_3 receptor ligands, with safe pharmacokinetic profile, remains a big challenge for medicinal chemistry and could be crucial in treatment of central and peripheral nervous system disorders.

During many years of research on active histamine H_3 receptors ligands in Department of Technology and Biotechnology of Drugs (DTBD), an abstract description of molecular features that are necessary for molecular recognition of a ligand by a biological macromolecule, called the pharmacophore model for such compounds was developed. As a result of previous research of the proposed Project Manager, a novel series of ligands were synthesized, among which most active compounds with high affinity for human histamine H_3 receptors were emerged. All of these structures are characterised by innovatory for H_3R ligands chemical moiety that can be found in their so called 'basic part'. As a leading compound for further studies, KSK3 with promising *in vitro* as well as *in vivo* test results, was chosen.

The ultimate goal of this work is to obtain a series of novel, active and selective, histamine H_3 receptor ligands, whilst maintaining a favorable physicochemical properties and ADMET parameters. Moreover, the aim of the project is to characterize the pharmacological properties of obtained compounds.

The research will be performed in the group of piperazine derivatives and comprise the following steps:

1) *Ligand design,*
2) *Synthesis of designed compounds,*
3) *In vitro pharmacological studies.*

As a result of the project, selective compounds with high affinity to histamine H_3 receptors will be identified. This project also aims at creating the necessary structural requirements that distinguish obtained piperazine derivatives, in order to give the desired activity and selectivity. Scheduled tasks tend to select compounds ready for *in vivo* testing.

This project takes the challenge of modern pharmaceutical sciences, which is new drug development, starting from choosing of biological target and ending with selection of compound ready for *in vivo* experiments that further in the future might be submitted to clinical trials. Innovative approach, which is an integration of molecular modeling with chemical synthesis and pharmacological screening, will allow to obtain molecules with desired properties and deep protein – ligand interactions and structure – activity analysis.