Allosteric and allosteric-orthosteric bitopic ligands of histamine receptor H4 as a way to increase selectivity and biased properties of potential anti-inflammatory and anti-cancer drugs

The histamine H4 receptor (H4R) (Fig. 1), a member of the G-protein coupled receptors (GPCR) family, is an increasingly attractive drug target. It plays a key role in many cellular pathways, and many H4R ligands are studied for the treatment of several inflammatory, allergic and autoimmune disorders, as well as for the analgesic activity, however, this does not translate into treatment. The approved for clinical use compounds comprise histamine H1-receptor (H1R) antagonists, which are used to control allergic inflammation, H2R antagonists, which therapeutically decrease gastric acid release, and an antagonist of H3R, which is indicated to treat narcolepsy. H4R ligands are still being tested pre-clinically and in clinical trials of inflammatory diseases, including rheumatoid arthritis, asthma, dermatitis, and psoriasis. Recently, various HR ligands, including H1R antagonists, H2R antagonists, and H4R agonists have been used to study their effects also on tumor progression in many different cancer types.

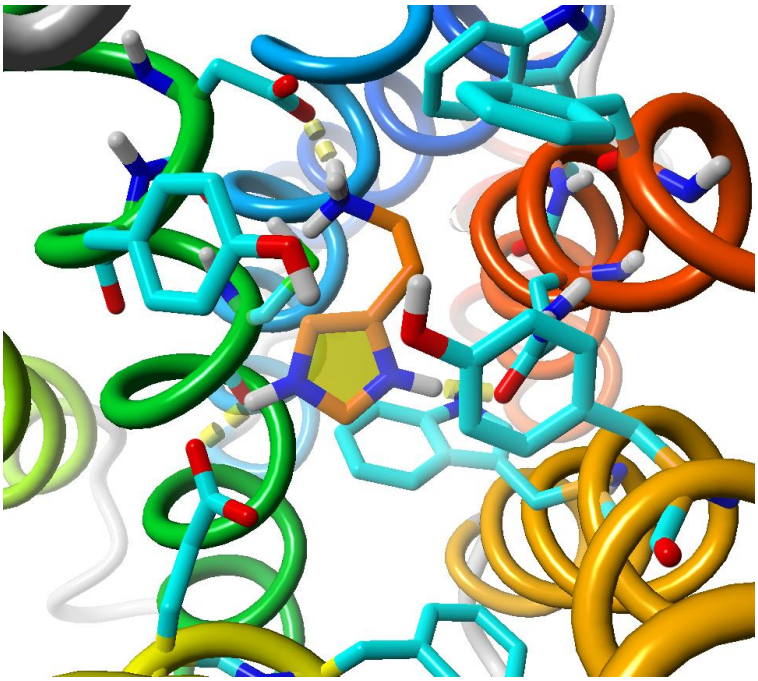

Fig. 1. Histamine docked to the orthosteric site of modeled H4 receptor. The transmembrane helices are colored from blue (TM1) to red (TM7). Histamine is doubly protonated and its carbon atoms are colored in orange.

Since GPCRs pass the activation signal via both G protein and arrestin it is very important to link particular pathway with specific cell response. In the project we propose to explore different areas in H4R structure to find out their suitability to obtain biased signaling i.e. blocking or activating specific signaling paths. The allosteric as well as allosteric-orthosteric bitopic ligands are proposed to study for obtaining increased affinity and selectivity toward H4R. The allosteric-orthosteric coupling will be also investigated to elucidate how the preferential signaling is achieved. By exploring different binding sites, allosteric and orthosteric, it would be possible to discover how they influence the signal transduction. The Project is interdisciplinary, involving three institutions, and it will be pursued by the specialists from different fields of the life, natural, and computational sciences including pharmacy, biology, organic chemistry, analytical chemistry, as well as statistics and computer simulations.