Novel ligands of the histamine H4 receptor
as potential anti-allergic and anti-inflammatory drugs

The histamine H4 receptor (H4R), belonging to the family of G protein-coupled receptors (GPCR), is an increasingly attractive therapeutic target. It plays an important role in many cell pathways, and new H4R ligands are being studied for the treatment of inflammation, allergic diseases and autoimmune disorders. Activation of H4R influences cytokine production, mast cell activation and eosinophil chemotaxis. The importance of this receptor has also been demonstrated in models of inflammatory processes: peritonitis, respiratory tract inflammation, colitis, osteoarthritis, and rheumatoid arthritis. Recent studies also suggest that H4R acts as a modulator in cancer, neuropathic pain, vestibular disorders and type 2 diabetes, but its role is still not fully understood.

In our research, models of human histamine H2, H3 and H4 receptors were constructed. For this purpose, our own server GPCRM (https://gpcrm.biomodellab.eu/) and the Schrodinger software package were used. In both cases, alternative receptor models were obtained (Fig. 1a). Although the main aim of the research was to find H4R antagonists, in order to find selective compounds they were also tested for binding to orthosteric sites in other histamine receptors. The structures of histamine receptors, in particular H4R, obtained by homology modeling, have been validated by docking known antagonists of these receptors (Fig. 1b), docked with other inactive compounds. This method, called ROC (Receiver Operating Characteristic), allows selection of the appropriate receptor structures for an extensive search for new ligands (Fig. 1c). In order to find the proper compounds which can bind to the orthosteric sites of these receptors, the High-Throughput Virtual Screening procedure was used. Before starting the search procedure for the ZINC Lead-Like database, all ligands from this database were prepared, taking into account their various protonation states and asymmetric centers, obtaining over 20 million compounds including their tautomers, isomers and stereoisomers.

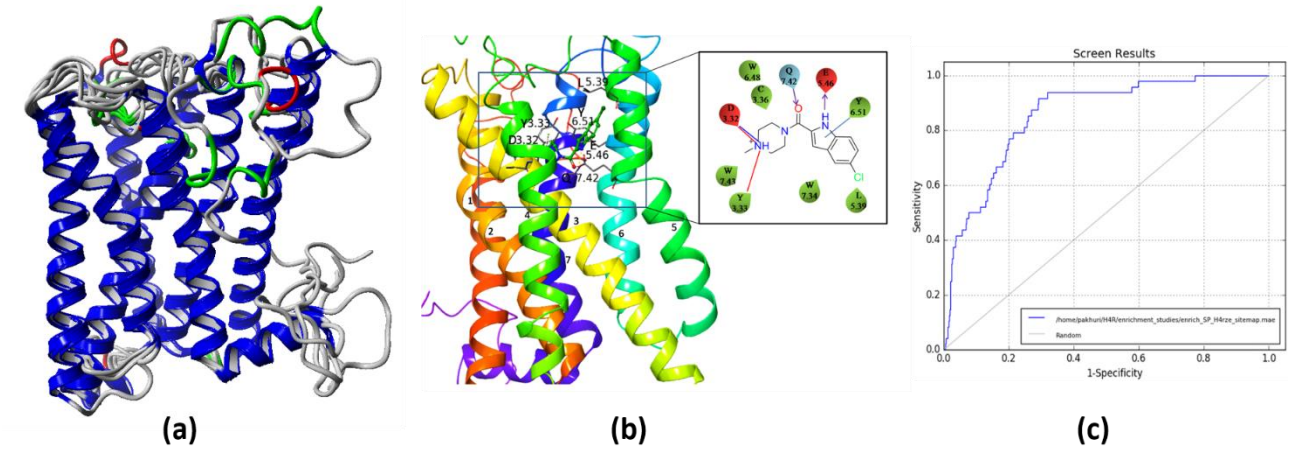

Figure 1. Obtaining the structure of the H4 receptor. (a) Alternative H4 receptor models obtained from different template structures. (b) H4 receptor model with docked selective antagonist JNJ7777120. (c) Receiver Operating Characteristic (ROC) plot for the best H4 receptor model showing the sensitivity and specificity of ligand recognition.

The 50 most active compounds, selective for H4R, were selected for further research stages, and in particular to optimize the structure of these compounds for their easier synthesis, while maintaining their binding properties and selectivity. Biological studies confirmed the activity of some of the selected compounds in functional cellular tests. At the same time, the affinity of these compounds for H4R was lower than for the reference compound JNJ7777120, which is the basis for their further optimization.

The H4 receptor is the latest discovered histamine receptor. The H4 receptor has been shown to play an important role in immune and inflammatory responses, and thus is important in the pathophysiology of diseases such as asthma, enteritis, allergic gastrointestinal disease, arthritis, atopic dermatitis and other chronic inflammatory diseases, as well as in the development of certain cancers. Therefore, new, active and selective H4R ligands can significantly improve the prognosis in these diseases, especially in the treatment of atopic dermatitis, where current antihistamines are ineffective.