Design and Preparation of New Ligands Interacting with the Histamine H4 Receptor

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Chapter 1

AIM AND OUTLINE OF THE THESIS

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Aim of the thesis

Shortly after the discovery of the fourth histamine receptor, abbreviated as H_4R, the search for potent and selective ligands was initiated.[1-5] Such ligands are essential to investigate the pharmacological properties of the newly discovered receptor. Expression profiles can provide a first hint as to the role of the receptor. E.g. the expression of the H_4R on various cells of the immune system would suggest a role in inflammation and immunity.[6-9] However, the relative importance can only be assessed with selective agonists and antagonists that will enable appropriately designed *in vitro* and *in vivo* studies.

The design of such ligands is facilitated by the detailed knowledge of the essential receptor-ligand interactions as well as the concomitant shape requirements for the ligand. The structure of the H_4R has not been solved to date. However, it belongs to the class of G-Protein coupled receptors (GPCR) for which structural information on related receptors is available.[10-12] The field of GPCRs has evolved rapidly and for advancing the field, Brian Kobilka and Robert Lefkowitz were rewarded with the 2012 Nobel Prize of Chemistry. The quality of a homology model not only depends on the availability of structural information on homologous receptors[10-12] but also on the availability of selective and chemically diverse ligands.

It is clear that the availability of potent selective H_4R ligands that can be used in pharmacological and computational studies is a key factor to be able to advance the field of H_4R research. We therefore set out to design and prepare new H_4R ligands:

I. that posses improved physicochemical and DMPK properties in rodents to enable *in vivo* studies.

II. To generate a chemically diverse set of H_4R ligands to facilitate the design of a comprehensive overview of key structural features of H_4-ligands and their receptor.

Outline of thesis

This thesis explores the chemical diversity of new H_4R ligands. In **chapter 2** the status of the H_4R field is described at the time the work was initiated and an overview of the existing compound classes is provided. C**hapter 3** discusses the SAR of several new indolecarboxamides. The data enable the definition of a predictive QSAR model that allowed the identification of several compounds with an activity comparable to the current standard JNJ-7777120. Some of the new analogs are not only excellently soluble, but display, in addition, a significantly increased half-life in mouse liver microsomes. Moreover, the current studies also provide valuable information on the receptor ligand interactions between the indolecarboxamides and the H_4R protein. **Chapter 4** focuses on the elucidation of the binding mode of 2-aminopyrimidine ligands in the histamine H_4R. By combining SAR, protein–ligand modeling studies, and quantum mechanical calculations, we provide new insight into the molecular determinants of H_4R–ligand binding and propose ligand binding conformations and orientations in the H_4R binding pocket. In **chapter 5** we designed and synthesized 4-(4-methylpiperazin-1-yl)-6-phenyl-2-vinylpyrimidine (VUF14480) as a covalent binder which interact with $C98^{3.36}$ in TM3. The covalent interaction of VUF14480 with $C98^{3.36}$ confirmed our previously proposed 2-aminopyrimidine binding pose. In **chapter 6** we set out to investigate whether mild basic 2-aminopyrimidines in combination with the appropriate linker can serve as a replacement for the methylpiperazine moiety known to be essential in several compound classes. Not only have we discovered highly potent compounds, the correct methylpiperazine replacement results in compounds with improved metabolic properties. Combining the derived SAR with homology modelling leads to new detailed insights in the molecular aspects of ligand-H_4R binding in general, and specifically to the binding mode of the described bispyrimidines. **Chapter 7** is dedicated to the search for a new H_4R ligand series to increase the diversity of compounds in the low-risk physicochemical property area (low ClogP, one basic center with a medium pK_a). A new promising series, the triazoloquinoxalines, which has a good H_4R affinity with pK_i values up to 7.5, in combination with an acceptable metabolic stability, solubility and lipophilicity are identified. The SAR generated for this type of compounds allows the establishment of a reliable binding model in the H_4R.

Finally, in **chapter 8** an overview of the properties of selected compounds, their relative binding relationship, as well as an outlook of future H_4 research is provided.

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