

HOMOLOGY MODELLING AND BINDING SITE MAPPING OF THE HUMAN HISTAMINE H1 RECEPTOR

Róbert Kiss^a, Zoltán Kovári^{a,b}, and György M. Keserű^{a,b}

^a Department of Computer Assisted Drug Discovery, Gedeon Richter Ltd., H-1475, Budapest 10, P.O. Box 27, Hungary

^b Department of Chemical Information Technologies, Budapest University of Technology and Economics, H-1111, Budapest, Szt. Gellért tér 4.

Three dimensional model of the human histamine H1 receptor was developed by homology modelling using the high resolution structure of bovine rhodopsin as template. Genetic algorithm based docking calculations were used to identify the role of several amino acids having an effect on agonist or antagonist binding. A reasonable theory for receptor activation mechanism of histamine, based on mutational data is presented. Binding mode analysis of four H1 antagonists (mepyramine, desloratadine, loratadine and acrivastine) allowed us to rationalise their binding affinity. Binding site mapping resulted in seven new potential aromatic interaction points (Tyr 108, Phe 184, Phe 190, Phe 199, Phe 424, Trp 428, Tyr 431), that took part in forming the lipophilic pocket of the antagonist binding cavity.

