Searching of novel leads for 5-HT7 receptor antagonists – selectivity hints from molecular modeling studies

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There are extensive data demonstrating that central serotonin receptors (5-HTR) are involved in many neurological and psychiatric diseases including anxiety, depression, obsessive compulsive disorder, migraine headaches, chronic pain conditions and schizophrenia. Among 13 different 5-HTR subtypes which belong to the GPCR class, the 5-HT7 is particularly a target for treating depression and is also suggested to be involved in antipsychotic drug action. Due to a high homology of transmembrane region of different 5-HTR subtypes (and several other aminergic GPCRs, too) obtaining of an active ligands with sufficient level of specificity or finding compounds with a desired multireceptoral profile, are common problems in medicinal chemistry. Fortunately, based on previous docking experiments of diverse groups of known antagonists to virtual 5 HT7R models, we found that specific interactions with residues of the TMHs 7 3 may be important for selectivity over the other receptors. To identify new lead structures the pilot set of compounds has been designed based on the above mentioned selectivity hints from molecular modeling studies, and structural features, present in several model ligands. For these structurally diversified compounds binding affinities for 5 HT7R and other therapeutically important: 5 HT1AR, 5-HT2AR, 5-HT6R as well as dopamine D2 receptors, were assessed. On the basis of obtained results which were additionally rationalized by docking experiments, two lead compounds with confirmed 5 HT7R antagonistic properties have been selected: one with purposeful selectivity, and the second with multireceptoral profile. Acknowledgments This study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism