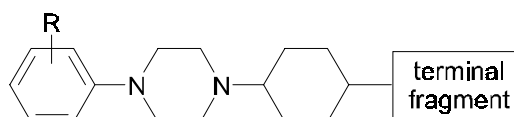# The Modeling of the 5-HT$_{1A}$ Receptor, Based on an Interaction with Arylpiperazine Derivatives with Restricted Conformational Flexibility

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Complex arylpiperazine derivatives constitute one of the most important classes of serotonin 5-HT$_{1A}$ receptor ligands, being a valuable source of potential therapeutic agents in the treatment of psychiatric disorders. Of the several published models of the serotonin 5-HT$_{1A}$ receptor, only two explored arylpiperazine interaction mode.[1] Computationally derived models of ligand-receptor complexes remain ambiguous, mainly due to the flexibility of the investigated ligands.

Recently, a set of novel, rigid arylpiperazine derivatives was synthesized, in which a flexible aliphatic chain connecting the arylpiperazine fragment with the second terminal pharmacophoric group was replaced with a cyclohexane ring.[2] The present study describes the application of those highly

R = H, 2-OMe, 3-Cl, 3-CF$_3$

active arylpiperazine derivatives for the optimization of the 5-HT$_{1A}$ receptor model. Our approach is based on the assumption that the rigidity of a compound encodes significant information about the binding site geometry.

Homology modeling methods (MODELLER v6) were used to construct a rat 5-HT$_{1A}$ receptor model, with recently published X-ray structure of bovine rhodopsin as a template. 400 various models were produced in a single MODELLER run. The most appropriate model was chosen, on the basis of a series of docking experiments (AUTODOCK3) with several rigid and flexible arylpiperazine derivatives with high affinity for the 5-HT$_{1A}$ receptor. The following criteria were used:

- the interaction between aspartic acid in the third transmembrane helix and a basic nitrogen atom of piperazine (i.e., the distance between carboxy group of Asp116 and N4);
- the energy of ligand-receptor interactions, as assessed by AUTODOCK;
- the correlation between experimental and computationally evaluated K_i values in the training set of ligands.

Subsequently, the selected model was optimized via force field energy minimization and molecular dynamics simulation with backbone atoms restrained.

An experiment in which a larger portion of our library of arylpiperazine derivatives is docked to the receptor model is presently performed, to show the usefulness of this modeling approach.

(1) M. L. Lopez-Rodriguez, D. Ayala, B. Benhamu, M. J. Morcillo, A. Viso, *Curr. Med. Chem.*, **2002**, *9*, 413.
(2) M. H. Paluchowska, M. J. Mokrosz, A. Bojarski, A. Wesołowska, J. Borycz, S. Charakchieva-Minol, E. Chojnacka-Wójcik, *J. Med. Chem.*, **1999**, *42*, 4952.