

Development of novel anti - depressants

Dr. Reena Gollapudy, Dr. Sudhir Kulkarni

Customer type

A leading pharmaceutical company

Software modules

BioPredicta

VLife Engine

Background:

Serotonin receptors regulate several neurological signals and are involved in neuronal diseases like depression. Serotonin receptors form a family and belong to family of GPCR receptors. The inhibition of 5HT1A receptor is expected to accumulate serotonin in the presynaptic region thereby reducing the depression.

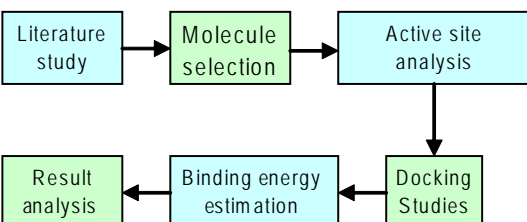
Design challenge:

Since 5HT1A is a membrane bound receptor its crystal structure is not available. The 5HT1A has seven trans membrane helices joined by loop regions. Using bovine rhodopsin as template (only template available at the time of study), homology model of 5HT1A was required to be developed. The known drugs and antagonists that bind to 5HT1A required to be studied to verify generated model.

Project work:

The mandate of work given by the customer was to prioritize set of ligands for synthesis based on feasibility of their interactions with 5HT1A active site. The homology model of 5HT1A was built using BioPredicta module of VLifeMDS. The longer loops were searched in PDB database for similarity and were attached to trans membrane helices. The model structure was energy minimized.

The active site of 5HT1A was analyzed for its electrostatics and hydrophobicity requirements. The size and shape of the active site limits conformations of the antagonists. The known antagonists of 5HT1A were energy optimized and conformers were generated. These conformers were docked in to the active site of 5HT1A.



Application

Ligand screening

Techniques

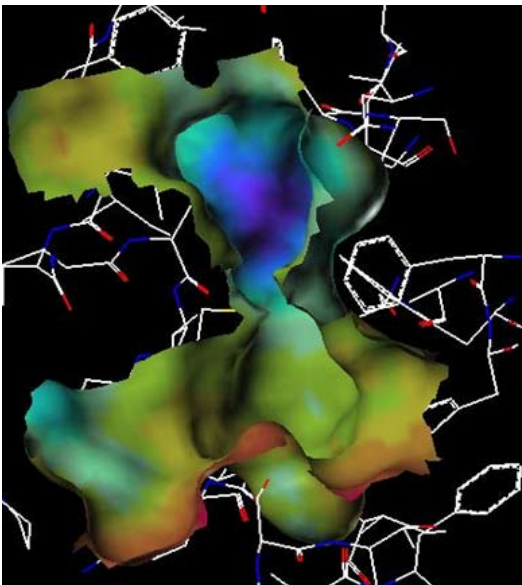
Active site analysis

Protein - ligand docking

Binding energy analysis



5HT1A homology model



Active site of 5HT1A

Result analysis:

The homology model showed RMSD of back bone of 0.8 Å with respect to template implying significance of the model. The important active site residues that are involved in interactions with known antagonists are Asp116, Tyr195, Ser199, Phe361, Phe362 and Tyr390. The presence of arylpiperazine ring as well as phenyl ring is essential requirement of the 5HT1A active site.

Based on the binding energies the trend for known antagonists was established and was further utilized to estimate activities of customer ligands. The priority list of ligands with improved binding to 5HT1A was provided to the customer.