Serotonin 5-HT7 G-protein coupled receptor: New Target for chronic pain, learning and memory. Homology Modeling, docking and molecular dynamics simulations study

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Serotonin 5-HT_7 G-protein coupled receptor (GPCR) is proposed as novel pharmacotherapy for chronic pain (neuropathy) and learning and memory. Because the crystal structure of 5-HT_7 is not available, the 5-HT_{1B}–based 5-HT_7 homology model was built, optimized in a lipid POPC membrane and equilibrated in molecular dynamics simulations. To study drug-receptor interactions at the 5-HT_7 GPCR, for drug design purposes, we have carried out docking, molecular dynamics, and experimental binding affinity and mutagenesis studies. Ligands in this study are *(2S)* and *(2R)* enantiomers of novel compounds 2'-X-5PAT; where X = F, Cl, and 5PAT=5-phenyl-2-dimethylaminotetrahydronaphtalene. We found stereoselectivity in 5-HT7 binding favoring the *(2S)* enantiomers. When docked at 5-HT7, significant differences were found in *(2S)* and *(2R)* enantiomers conformations and specific interactions at the orthosteric pocket. The 2'-X substituent did not play a significant role in binding, however, greater stereoselectivity was found for un-substituted 5PAT. Molecular modeling findings and experimental studies were analyzed to delineate the molecular determinants of ligand–receptor interactions at $5HT_7$ receptor for drug design purposes.

Keywords: serotonin 5-HT_7; GPCR homology modeling; Docking; Molecular Dynamics; stereoselectivity, Ligand Binding Affinity; Drug Design