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The Novel Approach in Structure-Based 3D Pharmacophore Model Generation. An Application to Searching for 5-HT$_6$R Selectivity Hypothesis.

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Herein, we present the new strategy in structure-based 3D pharmacophore model generation based on docking of known ligands, and further ligand-receptor complexes analysis using structural interaction fingerprints (SIFts) [1]. To explore the binding site hot-spot amino acids, the cross-docking (Glide SP mode) of the set of around 300 known (structurally diversified) 5-HT$_6$R ligands to a set of homology models was performed. The structure of actives were extracted from ChEMBL 14 database [2] using activity threshold Ki < 300 nM. Parallel, the docked ligand conformations were mapped to a set of pharmacophore features (HBA, HBD, PI, HYD and AR) creating a comprehensive map of spatial distribution of various pharmacophore points in the binding site. The pharmacophore features of the same kind were then clustered, taking distances between all pairs of centroids as a classification criterion. The final pharmacophore map was created from the averaged cluster centroid points, but only those matching crucial amino acids indicated by a parallel SIFts analysis of ligand-receptor complexes. Combinations of three-, four- and five-features were next used to generate a set of pharmacophore hypotheses (Screen Library Protocol, Discovery Studio 2.5).
They were next used to search the best combination of models, by optimization (maximization) of selectivity coefficient between some serotonin receptor subtypes, i.e. 5-HT$_6$/5-HT$_7$ and 5-HT$_6$/5-HT$_{1A}$. For this purpose, the set containing molecules with determined dual affinity values were extracted from ChEMBL 14 database and used to search and test the final pharmacophore combination. To assess the capabilities of proposed algorithm, the comparison between results obtained by optimized combination and existing ligand-based 5-HT$_6$R pharmacophore models [4] will be presented.

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