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The novel approach in structure-based 3D pharmacophore model generation and its evaluation on 5-HT$_6$R homology models

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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]. The docking poses 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 features of the same kind were then clustered, taking distances between all pairs of centroids as a classification criterion. The final pharmacophore hypotheses were 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 pharmacophore hypotheses were next generated (Discovery Studio 2.5) and used to search the best combination, optimized for a given performance parameter.

The external set containing 170 actives (not used in the model training) and 1530 decoys (prepared using DUD methodology [2]) were used to assess the obtained models' combinations. The existing ligand-based 5-HT$_6$R pharmacophore models [1] were used to evaluate the capabilities of the proposed approach.

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