The new strategy in structure-based pharmacophore model generation and its applications in virtual screening

Rafał Kurczab, Stefan Mordalski, Tomasz Kosciolek, Andrzej J. Bojarski

Department of Medicinal Chemistry, Institute of Pharmacology Polish Academy of Sciences, 12 Smętna Street, Kraków 31-343, Poland

The method of structure-based pharmacophore model generation based on docking of known ligands to a set of different receptor conformations, and further complexes analysis with structural interaction fingerprints (SIFts) [1], is presented. The set of over 700 known, and structurally diversified, 5-HT7R ligands was docked (Glide SP mode) to the six, previously developed [2], homology models of 5-HT7R. To analyze such large population of ligand-receptor complexes SIFt profile was calculated, pointing out crucial amino acids involved in interactions with ligands. At the same time, the docked ligand conformations were mapped to a set of pharmacophore features (HBA, PI, HYD, 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 hypotheses were created from the averaged cluster centroid points, but only ones matching amino acids indicated by SIFts analysis. All possible combinations of three-, four- and five-features pharmacophore models were tested on the external set containing 177 actives (not used in model training) and 1600 decoys (prepared using DUD methodology [3]) using Screen Library protocol from Discovery Studio 2.5. The performance of the obtained models was analyzed comparing actives recall, precision, accuracy, enrichment factor (EF), the Mathews correlation coefficient (MCC) and F-score. Acknowledgements The study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism. [1] Deng J, Leo KW, Sanchez T, Cui M, Neamati N, Briggs, JM, J. Med. Chem. 2005, 48, 1496-1505. [2] Kołaczkowski M, Nowak M, Pawłowski M, Bojarski AJ, J. Med. Chem. 2006, 49, 6732. [3] Huang N, Shoichet BK, Irwin JJ, J. Med. Chem., 2006, 49, 6789.