Extensive pharmacophore modeling studies on 5-HT1A receptor ligands – single hypothesis vs. linear combinations

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Out of over 6 000 of 5-HT1AR ligands stored in ChEMBL database (version of August 2010) [1], these with Ki < 100 nM (3616 compounds) were extracted, and clustered by three different approaches: (i) using 3D pharmacophore, (ii) MOLPRINT 2D fingerprints (as implemented in Canvas software [2]), or (iii) manually, based on a common core, containing two basic pharmacophore features (protonated nitrogen, and aromatic system), e.g. indolylalkylamines, aminotetralines, arylpiperazines, ergolines, etc. Next, for the obtained clusters (27, 36 and 28, respectively) representative compounds were selected (diversity-based selection tool, Canvas [2]), to be used for generating of pharmacophore models (Phase, [3]). The best hypothesis for each cluster (i.e. with maximal number of features, the highest number of matched representative compounds, and the highest value of selectivity score) was then tested on different test sets, consisting of 200 active compounds (not used in pharmacophore development), 200 decoys (extracted from ChEMBL database) and 200 assumed inactives (already used drugs lacking data for 5-HT1A receptor). Models from different approaches were characterized by Matthews correlation coefficient (MCC), which is a measure of the quality of binary classifications. Finally, MCC for all possible linear combinations of hypotheses were calculated by an in-house script. The efficiency of single hypotheses, in comparison to their linear combinations, and relation between quality of pharmacophore models and methodology of clusters generation are discussed. The created pharmacophore models will be used in further studies in multistep virtual screening in order to search for new compounds acting on 5-HT1A receptor. Acknowledgments This study was partly supported by a grant PNRF-103-AI-1/07 from Norway through the Norwegian Financial Mechanism [1] https://www.abi.ac.uk/chembl/ [2] Canvas, version 1.4, Schrödinger, LLC, New York, NY, 2011. [3] Phase, version 2.2, Schrödinger, LLC, New York, NY, 2011