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Linear Combination of Pharmacophore Hypotheses as a New Tool in Search of New 5-HT$_{1A}$ Receptor Ligands.

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Matthews correlation coefficient (MCC) is a measure of the quality of binary classifications which is often used in evaluation of prediction models. The range of MCC is from -1 to 1, where value of 1 represents perfect prediction; 0 random, and -1 an inverse prediction. Here, MCC was used to discus efficiency of 5-HT1AR pharmacophore models and their linear combinations.
Generation of pharmacophore hypotheses was based on three different approaches of 5-HT1AR ligands clustering: (i) using 3D pharmacophore, (ii) MOLPRINT 2D fingerprints (as implemented in Canvas software [1]), or (iii) manually, based on a common core, containing two basic pharmacophore features. Next, for the obtained clusters (27, 36 and 28, respectively) representative compounds were selected (diversity-based selection tool, Canvas [1]), to be used for final models production (Phase, [2]). The best hypothesis for each cluster was then tested on different test sets, consisting of 200 active compounds (not used in pharmacophore development), 200 decoys (extracted from ChEMBL database [3]) and 200 assumed inactives (already used drugs lacking data for 5-HT1A receptor).
Statistics for all possible linear combinations of hypotheses were calculated by an in-house script. Finally, the best linear combination from each approach was validated on test set consisting of compounds extracted from an updated ChEMBL version (May 2011) which were not present in previously used release. The linear combination of pharmacophore models created on automatically clustered ligands by using MOLPRINT2D approach was the most efficient. Moreover, in all the cases efficiency of single hypotheses was much worse than their linear combinations. 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.

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[1] Canvas, version 1.4, Schrödinger, LLC, New York, NY, 2011.
[2] Phase, version 2.2, Schrödinger, LLC, New York, NY, 2011
[3] https://www.abi.ac.uk/chembl/