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New non-basic ligands of serotonin receptor 5-HT_6 as a result of virtual screening based on machine-learning methods

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Virtual screening is one of the most popular techniques in computer-aided drug design with machine learning methods as representatives of the group of extensively explored methodologies in this field.[1] In the study, a variation of Support Vector Machines – a Sequential Minimal Optimization algorithm[2] was applied in the search of new 5-HT_6R ligands in the ChemBridge and ChemDiv databases. Three different fingerprints were used for molecules representation and consensus prediction was taken as the final answer. Selected compounds indicated as active were purchased and their affinity towards four serotonin receptors (5-HT_6, 5-HT_{1A}, 5-HT_{2A}, 5-HT_7) was examined in *in vitro* experiments. Two structurally new compounds were found to be characterized by a significant 5-HT_6R activity (119 and 670 nM).

The compounds do not possess positive ionisable group in their structure, therefore they belong to the group of atypical non-basic 5-HT_6R ligands. Although several reports have proven that the presence of a basic nitrogen atom enabling formation of the interaction of its protonated form and D3.32 is not indispensable for 5-HT_6R anchoring,[3] the fraction of non-basic compounds within known 5-HT_6R ligands is low (about 7%) and the majority of 5-HT_6R ligands keep fitting the standard pharmacophore model, which requires the possession of the positive ionisable group.[4]

One of the hits was selective over the remaining serotonin receptors, whereas for the other, the affinity for the 5-HT_{2A}R subtype was also marked. Docking and molecular dynamic simulation experiments proved that the obtained hits fit well in the 5-HT_6R binding cavity interacting with the amino acid residues reported as important for 5-HT_6R activity. Moreover, *in silico* evaluation of ADMET properties indicated their drug-like character.[5]

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