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Abstract

Structural and Biological Evaluation of Novel Multi-Target Compound with Potential Application in the Treatment of Schizophrenia †

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In the process of searching for novel compounds with antipsychotic properties, structure-based virtual screening was conducted [1]. Among found dopamine D_2 receptor antagonists, the compound D2AAK3 with 115 nM affinity for D_2 receptor was identified. It also shows nanomolar or low micromolar affinity for D_1, D_3, 5-HT_{1A}, 5-HT_{2A} and 5-HT_7 receptors, what makes it a good candidate for a multi-target drug. Interactions of D2AAK3 with its molecular targets at the molecular level were studied *in silico* by performing homology modeling, molecular docking and molecular dynamics. The main contact of D2AAK3 with all studied receptors is the electrostatic interaction between the proton attached to the nitrogen atom of the ligand and the conserved Asp(3.32), what is typical for orthosteric binding mode in aminergic GPCRs. Behavioral studies [2] performed for D2AAK3 revealed that it decreases amphetamine-induced hyperactivity measured as spontaneous locomotor activity in mice, improves memory consolidation after acute treatment in passive avoidance test and exhibits anxiogenic activity 30 minutes after acute treatment in mice in elevated plus maze (this effect was reversed 60 minutes after administration of D2AAK3). Further optimization of reported compound, toward obtaining molecule with properties resembling atypical antipsychotics, will be conducted.

References

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