Affinity prediction of perspective anticonvulsant API to human adenosine receptors

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Introduction. Influence on purinergic system through modulation of adenosine receptors can be one of the promising directions of API anticonvulsant activity realization. Pharmacological model that implements the mentioned direction is caffeine-induced seizures. To predict pharmacological activity on the given model in an *in vivo* experiment of a new API of epimidine – 1-(4-methoxyphenyl)-5-[2-[(4-(4-methoxyphenyl)piperazin-1-yl]-2-oxo-ethyl]pyrazolo[3,4-d]pyrimidin-4-one – the docking into the binding site of a highly selective inhibitor of human adenosine receptors A_2A type – 4-(2-[7-amino-2-(2-furyl)-[1,2,4]triazole[2,3-a][1,3,5]triazin-5-ylaminoethyl)phenol (ZM24135) – was suggested [1, 2].

Materials and methods. AutoDock Vina software was used for molecular docking. The macromolecule was downloaded from Protein Data Bank [3]: A_2A – PDB ID 3EML. BIOVIADraw 2017R2 software was used to construct the structures, as well as Chem3D software – to optimize them. The macromolecule preparation and results visualization were carried out by Discovery Studio Visualizer 2017/R2. Grid box size and its centers coordinates were determined according to the native ligands: x = -9.06, y = -7.14, z = 55.86; wherein the size of x =12, y = 10, and z = 16.

Results and discussion. Epimidine binding energy was -7.9 kkal/mol, which is almost comparable to the affinity of the native reference ligand ZM241385 (-8.5 kkal/mol). The detailing of the amino acid interaction demonstrated the possibility of formation of 10 strong hydrophobic interactions with all epimidine molecule fragments and peptide residues only of the active site: two stacking interactions between the pyrazolopyrimidine ring and the phenylalanine phenyl radical (Phe168), as well as two bonds with isoleucine (Ile274) and leucine (Leu249) methyl fragments; 4-methoxyphenyl in the first position reacts with SMe methionine (Met177) and methyl leucine (Leu85, 249); piperazine fragment – with phenyl 4-hydroxytyrosine (Tyr271), and methoxyphenyl from the other end of the molecule reacts with alkyl (Leu267). Hydrogen bonds are possible with the amino- and carboxamide groups of asparagine residues (Asn253*, 181). Analyzing the docking results under conformation with the native ligand, it's worth stating that epimidine is able to enter completely into the hydrophobic pocket of the active site and occupy a position identical to the native ligand: the final fragments of both ligands are overlapping, and the main pharmacophores – epimidine pyrazolopyrimidine ring and triazolotriazine ZM241385 – are also located in the same area and are overlapping by the rings.

Conclusions. According to the docking results for 1-(4-methoxyphenyl)-5-[2-[(4-(4-methoxyphenyl)piperazin-1-yl]-2-oxo-ethyl] pyrazolo [3,4-d] pyrimidin-4-one, high affinity level to A_2A inhibitor site was predicted, as well as its probable caffeine antagonism, which substantiates the feasibility of its study in an *in vivo* experiment on a model of caffeine-induced seizures.

References

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