PREDICTION OF GABAERGIC MECHANISM OF ACTION OF ACETAMIDE DERIVATIVE 6-(PYRIDINYL-2)-PYRIMIDINE-4-THIONE

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Introduction. Despite the successful development of various new anti-epileptic drugs within recent decades, all of them are characterized by a wide range of side effects, and the lion's share is occupied by CNS disorders, i.e. depression, anxiety states, and cognitive disorders. The spread of refractory epilepsy is also an important problem for today. The search for new anticonvulsants for the treatment of epilepsy with higher efficacy and better tolerability remains relevant.

Aim. The aim of the present study was to predict the affinity for GABAergic biotargets of the new anticonvulsant N-(3,4-dimethoxyphenyl)-2-((2-methyl-6-(pyridin-2-yl)pyrimidin-4-yl)thio)acetamide.

Materials and methods. The molecular docking studies were performed with AutoDock Vina and Auto-DockTools 1.5.6 programs. Protein Data Bank was used to select specific macromolecules, i.e.: GABAAR (PDB ID 4COF), GABAAT (PDB ID 10HW), hBCATc (PDB ID 2COI).

Results and discussion. Previously, efficiency N-(3,4-dimethoxyphenyl)-2-((2-methyl-6-(pyridin-2-yl)pyrimidin-4-yl)thio)acetamide using PTZ-induced seizures was established, which suggests that the mentioned compound may act as a GABA agonist or inhibit GABA aminotransferase. To predict the GABAergic mechanism of anticonvulsant activity, we determined N-(3,4-dimethoxyphenyl)-2-((2-methyl-6-(pyridin-2-yl)pyrimidin-4-yl)thio)acetamide interaction with the active sites of the type-A γ-aminobutyric acid receptor ($GABA_AR$), γ-aminobutyrate aminotransferase ($GABA_{AT}$) enzyme, and human cytosolic branched-chain aminotransferase (hBCATc). The reference drugs were, respectively, which enhances the inhibitory neurotransmission by allosterically modulating $GABA_A$ receptor-mediated Cl- currents; vigabatrin, which increases GABA intracellular concentration in human's brain by GABA aminotransferase irreversible inhibition; gabapentin, one which mechanisms for GABA concentration increasing is the influence on leucine transport and increase of glutamate decarboxylase activity.

In silico studies have shown the following results: scoring function value -7.3 kcal/mol was rather close to the reference drug's value – phenobarbital (-7.6 kcal/mol), which points to the possibility of anticonvulsant activity realization of the experimental ligand as $GABA_A$ receptor agonist; pyrimidine derivative with the active site $GABA_{AT}$ showed better affinity and a lower scoring function value of -7.8 kcal/mol compared to the native ligand, vigabatrin (-6.7 kcal/mol); at pyrimidine derivative interaction with hBCATc active site, high binding energy value was observed: -4.2 kcal/mol, while for the native ligand – gabapentin – it was -7.6 kcal/mol.

Conclusions. Thus, after analysing the degree of affinity, the conformational location of the ligand in the active sites of the biotargets and the interaction with amino acid residues, the possibility of anticonvulsant action through agonism to the GABAA receptor and through inhibition of the $GABA_A$ enzyme was confirmed.