O-16

In Silico Studies in Directed Synthesis of Potential Anticonvulsants

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Work is devoted to targeted search for potential anticonvulsants, taking into account the specificity of different methods of computer prediction and relationship between them. We have carried out the construction of 50 groups substances derivatives 1,2,3(1,2,4) triazoles, 1,3,4-oxa(thia)diazoles. Molecular design of new compounds was performed according to the algorithm, which included successive stages. Based on research *in silico* (virtual pharmacological screening, PASS-computer program, testing for compliance with the concept of "drug-likeness", molecular docking to biotargets) eleven groups of compounds derivatives of five-membered di(three)azaheterocycle was selected for further screening as perspective anticonvulsants. We have identified possible mechanisms of anticonvulsant action and proposed experimental models for pharmacological studies of anticonvulsant activity. In order to determine the potential anticonvulsant activity of 1,2,3(1,2,4)triazole, 1,3,4-oxa(thia)diazole we investigated the mechanisms of action that involve the interaction of the ligand NMDA-, $GAMK_a$- or glutamate receptors and GABA-AT ligand-enzyme. GABA-ergic mode of action for 8 groups of derivatives and glutamatergic mode of action for 3 groups of derivatives five-membered di(three)azaheterocycle was predicted.

The correctness of the algorithm propoused have been proved experimentally by purposeful synthesis of predefined groups of new derivatives of five-membered di(three) aza-heterocycles and pharmacological research in comparison with known anticonvulsant drugs. Pharmacological studies of new derivatives on manifestation of their anticonvulsant activity have been conducted on different animal convulsive models according to the predicted mechanism of action. It should be noted that result of docking research coincided with the results of PASS prediction for eight groups of compounds. Proof of effectiveness of the proposed methodological approach to targeted synthesis of potential anticonvulsants agents was the discovery of new anticonvulsants derivatives 5-methyl(amino)-1,2,3-triazoles(1*H*), [1,2,4]-triazolo[1,5-a]pyrimidine, 1,3,4-oxadiazoles and 1,3,4-thiadiazole with a significant level anticonvulsive action exceeding the activity of referens drug [1]. We have determined the dependence anticonvulsive activity in these groups of compounds from modifying the structure (SAR analysis).

[1] Perekhoda L.O. The progress of recent years in a search of potential anticonvulsants among the derivatives of aza-heterocycles // Annals of Mechnikov Institute– 2015, № 3, – P. 37-45