INTERACTION OF SUBSTITUTED 5-AMINOPYRAZOLES WITH β-DICARBONIL COMPOUNDS

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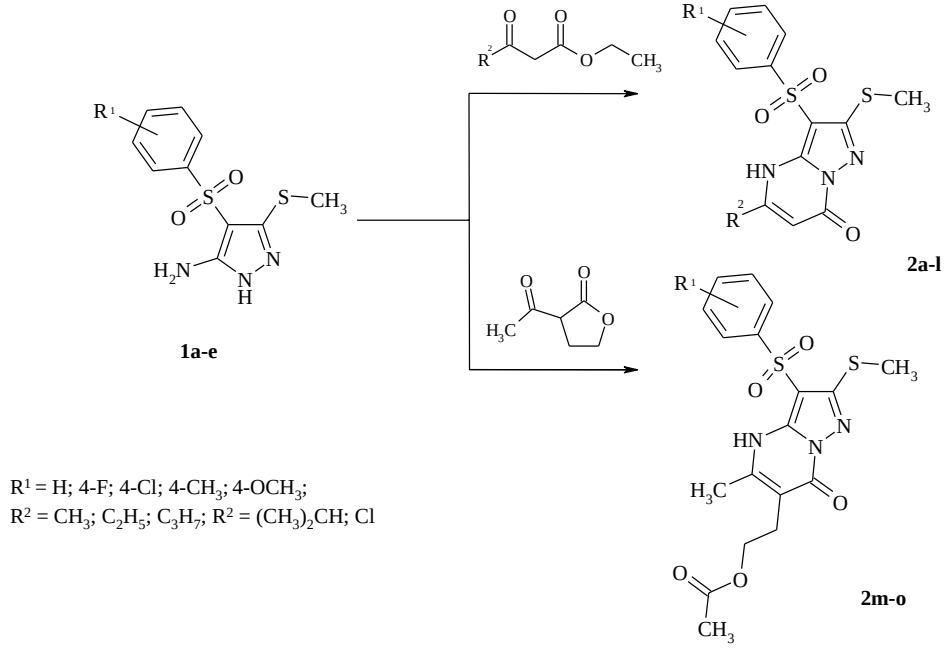
Introduction. In this paper we described the interaction of 5-amino-4-arylsulfonyl-3-methylthiopyrazoles with β-dicarbonyl compounds, which leads to the formation polycyclic systems of pyrazolo[1,5-*a*]pyrimidines for targeted synthesis of the novel pharmaceutical agents.

Aim. Synthesis of new substances in the series 5-amino-4-arylsulfonyl-3-methylthiopyrazoles.

Materials and methods. Methods of organic synthesis, physical and physical-chemical methods of analysis of organic compounds were used.

Results and discussion. Reaction 5-amino-4-arylsulfonyl-3-methylthiopyrazoles **1a-e** with some substituted acetyl acetates was carried out in acetic acid media with high yields and short time. As a result of the developed synthetic procedure 2-methylthio-3-arylsulfonylpyrazolo[1,5-*a*]pyrimidin-7(*4H*)-ones **2a-l** was obtained, which was confirmed by the results of TLS, LCMS and by data of ^{1}H NMR spectroscopy.

The reaction with acetylbutyrolactone occurs through opening of the tetrahydrofuran ring to form the corresponding *O*-acetyl derivatives **2m-o**.



R^1 = H; 4-F; 4-Cl; 4-CH_3; 4-OCH_3;
R^2 = CH_3; C_2H_5; C_3H_7; R^2 = $(CH_3)_2CH$; Cl

Conclusions. The obtained polysubstituted pyrazolo[1,5-*a*]pyrimidin-7(*4H*)-ones are promising enough for the further biological research.

DOCKING STUDIES AND ANTICONVULSANT ACTIVITY OF N-(5-ETHYL-[1,3,4]THIADIAZOLE-2-YL)-NITROBENZAMIDE

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Introduction. Diseases of the nervous system, which are accompanied by convulsions, are one of the most common and difficult to cure, and the known medicines for their treatment contribute to addiction. In this regard, scientists are actively searching for safe and effective biologically active substances with

anticonvulsant activity. N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide was synthesized at the department of medical chemistry of the *National* University of *Pharmacy*.

Aim. Investigation of anticonvulsant activity of N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide, conducting docking research concerning GABA and GABA-AT receptors, setting the correspondence of the investigated substance to the Lipinski rule.

Materials and methods. The experimental convulsive syndrome was modeled with subcutaneous injection of corazole (pentylenetetrazole of «Sigma» company, USA) at a dose of 80 mg/kg on white mice. Corazole was injected in 30 minutes after peroral injection of N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide at a dose of 50 mg/kg. The comparison group animals received intragastrically a classic anticonvulsant – sodium valproate (syrup "Depakine", Sanofi-Aventis, France) in a conventionally effective dose of 200 mg/kg. In order to estimate «in silico» affinity to GABA and GABA-AT receptors, software package Autodock 4.2.6. was used. Preparation of ligands for receptor-oriented flexible docking was carried out with the help of programs Vega ZZ and MGL Tools 1.5.6. The active center of the GABA receptor (PDB code 1GNU) and the GABA-AT receptor (GABA aminotransferase) (PDB code 1OHW) was used as the target for docking. Visual analysis of the complexes of the investigated molecule with the active site was carried out in the program Discovery Studio Visualizer 4.0.

Results and discussions. The results of a pharmacological study showed that Depakine in a dose of 200 mg/kg prolonged the latent period of convulsions, reduced the lethality of animals. N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide prevented the death of animals at a lower dose (50 mg/kg). At a dose of 50 mg/kg, the investigated substance reduced the duration of the convulsive seizure by two times compared with the control, that led to a further increase in the death of mice by 1.5 times.

The conducted docking studies showed that the interaction of the studied molecule with the active target-site of 1GNU and 1OHW is analogous to known ligands that exhibit anticonvulsant activity. The results of flexible molecular docking have obtained the values of the scoring function. For the complex of the investigated molecule with the GABA receptor (PDB code 1GNU) the values of the scoring function of phenobarbital (-4.75), carbamazepine (-5.37), valproic acid (-3.81), lamotrigine (-5.25), N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide (-5.72). For the complex of the investigated molecule with the GABA-AT receptor (PDB code 1OHW) the values of the scoring function of phenobarbital (-7.8), carbamazepine (-8.47), valproic acid (-5.29), lamotrigine (-7.91), N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide (-8.29.). Low values of the scoring function in the case of interaction of the investigated molecule with the active target-site 1GNU are most likely explained by the hydrophobicity of the fragment of the ligand. In the middle of the active site, hydrophobic interactions are formed, and hydrogen bonds with a hydrophilic environment are formed externally.

The studied substance was tested according to the Lipinski rule: no more than 5 hydrogen-bond donors (1), no more than 10 hydrogen-bond acceptors (7), molecular mass less than 500 (280.31), distribution coefficient (logP<5).

Conclusions.

The results of the pharmacological study have showed that N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide exhibits anticonvulsant effect at the level of the comparison preparation at a lower dosage. The values of the scoring function of the reference preparations and N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide indicate the thermodynamic probability and the energy susceptibility of the formation of complexes between the investigated molecule and the specified receptor and may be an argument for the benefit of the GABAergic mechanism of action of the investigated substance. According to the Lipinski rule N-(5-ethyl-[1,3,4]thiadiazole-2-yl)-nitrobenzamide is a relatively small and moderately lipophilic molecule, that is important for the pharmacokinetics of it in the human body.