SYNTHESIS OF NEW 2,5-DISUBSTITUTED DERIVATIVES OF 1,3,4-THIADIAZOLE, CONTAINING 1,2,4-TRIAZOLE FRAGMENT

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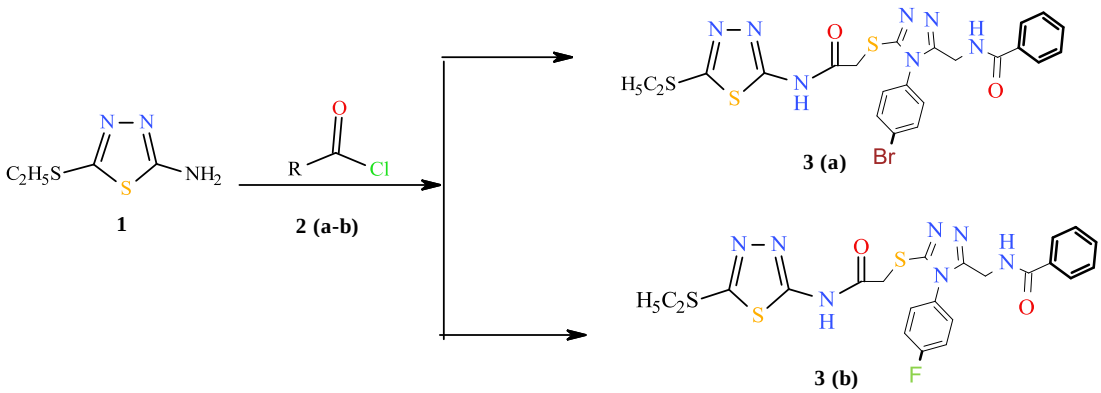
Introduction. The development and synthesis of molecules that are important as therapeutic agents for humans remain one of the main challenges of organic and medicinal chemistry. Synthesis of nitrogen- and sulfur-containing heterocyclic systems is of increasing interest, given that a large arsenal of compounds having antibacterial, antiviral, antitumor, antihypertensive and anticonvulsant activity have been obtained based on them. Thus, the search for biologically active substances based on 1,3,4-thiadiazole is an important area of pharmaceutical research.

Aim. Synthesis of new 2,5-disubstituted derivatives of 1,3,4-thiadiazole containing a 1,2,4-triazole moiety, establishing structure, studying physicochemical properties and testing the compounds obtained for compliance with the Lipinski Rule of Five.

Materials and methods. All solvents and reagents (Aldrich and Acros company) were used without additional purification. The melting points of the obtained substances were determined on the Kofler block. Nitrogen content was determined by the Dumas method. ^{1}H NMR spectra were recorded on a 400 MHz Varian Gemini instrument; tetramethylsilane was used as an internal standard. Testing molecules for compliance with the Lipinski Rule of Five was performed using Molinspiration cheminformatics and Chembiofinder.

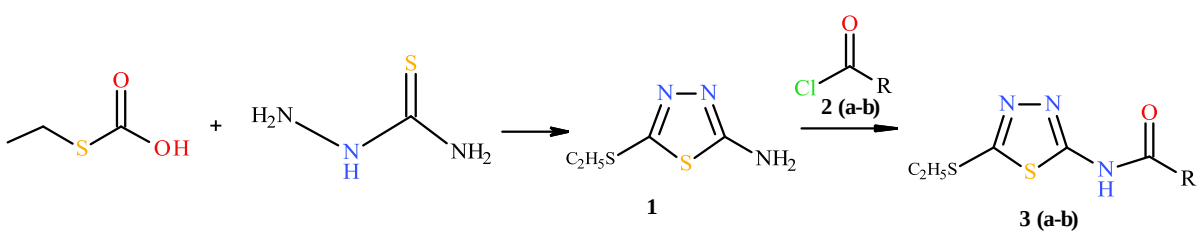
Results and discussions. Synthesis of the target 2,5-disubstituted 1,3,4-thiadiazoles 3 (a-b) was performed by acylation of 2-amino-5-ethylsulfanyl-1,3,4-thiadiazole 1 by the hydrochlorides of the hetero-substituted acids 2 (a-b) in two ways. The reaction mixture was heated to 85 ° C in anhydrous pyridine for 30 minutes (method A). (Scheme 1).

Scheme 1



In order to increase the yields of the target products, synthesis was performed by method B, namely by cyclization of thiosemicarbazide with the corresponding acids in the presence of *concentrated sulfuric acid* at 70єC for 3 hours. The obtained intermediates, without additional purification, were acylated by the amino group of the hydrochlorides of heterosubstituted acids in anhydrous pyridine for 30 minutes (Scheme 2)

Scheme 2



Synthesized derivatives 3 (a-b) are white crystalline substances with clear melting points soluble in ethanol, DMF, DMSO, propanol-2, insoluble in water.

The structure of the synthesized substances was confirmed by the complex use of modern physicochemical methods of analysis: ^{1}H-NMR spectroscopy and elemental analysis.

According to the results of testing the correspondence of the obtained compounds to Lipinski Rule it is found that with the set of physicochemical properties (molecular weight, lipophilicity ratio, the number of donors and acceptors of hydrogen bonds and the presence of nitro groups) they meet the requirements set for new substances at the stage of testing their pharmacological activity.

Conclusions. Synthesis of new 2,5-disubstituted derivatives of 1,3,4-thiadiazole containing 1,2,4-triazole moiety has been made. It was found that the yields of the target products were higher by method B, namely: by cyclization of thiosemicarbazide with the corresponding acids in the presence of concentrated sulfuric acid. The structure of the synthesized substances was confirmed by physical and chemical methods: ^{1}H-NMR spectroscopy and elemental analysis. In the aggregate of the physicochemical properties, the synthesized derivatives meet the requirements set for new substances at the stage of testing their pharmacological activity.