МІНІСТЕРСТВО ОХОРОНИ ЗДОРОВ'Я УКРАЇНИ
ЗАПОРІЗЬКИЙ ДЕРЖАВНИЙ МЕДИКО-ФАРМАЦЕВТИЧНИЙ УНІВЕРСИТЕТ

МАТЕРІАЛИ

ВСЕУКРАЇНСЬКОЇ НАУКОВО- ПРАКТИЧНОЇ КОНФЕРЕНЦІЇ З МІЖНАРОДНОЮ УЧАСТЮ

«ЗАПОРІЗЬКИЙ ФАРМАЦЕВТИЧНИЙ ФОРУМ - 2023»

23-24 листопада 2023 року

Запоріжжя – 2023

SYNTHESIS, TRANSFORMATION AND BIOLOGICAL PROPERTIES OF S-DERIVATIVES OF 4-AMINO-5-(5-R-PYRAZOL-3-YL)-1,2,4-TRIAZOLE-3-THIOL

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1,2,4-triazole derivatives have shown potential in the treatment of a wide range of diseases, including cancer, bacterial infections, and neurological disorders. The development of new derivatives with improved pharmacokinetic and pharmacodynamic properties can lead to the emergence of more effective and safer drugs. Continuation of research in this direction is a very important and urgent task for scientists from all over the world in the field of pharmacy and medicinal chemistry.

The main goal of the work is to study the potential of 1,2,4-triazole derivatives as a source of new drug candidates with improved safety and efficacy profiles. The research is aimed at the synthesis and characterization of a number of S-derivatives of 4-amino-5-(5-R-pyrazol-3-yl)-1,2,4-triazol-3-thiol, as well as at the evaluation of their physicochemical properties and biological functions.

Materials and methods. The synthesis involved several stages. The initial stage was the interaction of substituted acetophenones, as well as acetone with diethyl oxalate in the medium of methanol in the presence of sodium methylate. The formed substituted ethyl 2,4-dioxopentanoates were cyclized in propan-2-ol with the addition of a double excess of hydrazine hydrate. Further addition of hydrazine hydrate led to the formation of 5-substituted pyrazole hydrazides. The next stage included the interaction of the corresponding hydrazides with carbon disulfide and subsequent cyclization in the hydrazide hydrate environment and final acidification with ethanoic acid to a neutral environment, which made it possible to obtain the original thiols as a result.

Subsequently, the reaction of heating 3-(3-methyl-1H-pyrazol-5-yl)-5-(alkylthio)-1,2,4-triazol-4-amines with an excess of triethoxymethane during boiling was studied, as a result, 9-methyl-3-(alkylthio)pyrazolo[1,5-d][1,2,4]triazolo[3,4-f][1,2,4]triazines.

And for 3-(ethylthio)-5-(3-methyl-1H-pyrazol-5-yl)-4H-1,2,4-triazol-4-amine, the interaction reaction with potassium ethyl xanthate in a propane-2 medium was investigated -ol with intensive mixing and alkylation with haloalkanes without prior isolation resulted in 3-(ethylthio)-9-methyl-6-(alkylthio)pyrazolo[1,5-d][1,2,4]triazolo[3,4 -f][1,2,4]triazines.

3-(5-(4-Methoxyphenyl)pyrazol-3-yl)-6-R-[1,2,4]triazolo[3,4-b][1,3,4]thiadiazoles were obtained by interaction of the corresponding thiol with the equivalent of an aromatic carboxylic acid in a phosphorus oxochloride medium. The structure and individuality of the compounds were confirmed by a package of modern physicochemical methods (^{1}H NMR, IR spectroscopy, chromatography-mass spectrometry).

With the help of virtual prescreening studies, we carried out molecular docking in order to identify substances with potential biological activity. As a result, it was possible to select compounds that showed an energy of interaction with the active center of the corresponding model enzyme close to that of the comparison drugs. On the basis of the obtained results, biological studies on analgesic, antioxidant, antimicrobial and antifungal effects were carried out for compounds that demonstrated significant indicators of activity.

The results. As a result of biological tests, 2 compounds with the highest indicators of antioxidant, analgesic, antimicrobial and antifungal activity were selected. It was established that with the lengthening of the alkyl chain, the antifungal activity increases, the presence of carboxyl and phenolic fragments has a positive effect on the indicator of antioxidant and analgesic activity.

Conclusions. During the work, 72 new, previously undescribed compounds were synthesized. The pre-screening studies allowed to select 2 most promising compounds for more in-depth biological analysis.