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MODERN CHEMISTRY OF MEDICINES

Матеріали
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М78 **Modern** chemistry of medicines: матеріали Міжнародної Internet-конференції «Modern chemistry of medicines» (18 травня 2023 р., м. Харків) – Електрон. дані. – Х. : НФаУ, 2023. – 284 с. – Назва з тит. екрана.

Збірник містить матеріали Міжнародної Internet-конференції «Modern chemistry of medicines» (18 травня 2023 р., м. Харків) присвячені висвітленню сучасних тенденцій створення оригінальних АФІ синтетичного та рослинного походження, фармацевтичної розробки, забезпечення якості лікарських засобів.

Для широкого кола наукових та практичних фахівців у галузі фармації та медицини, магістрантів, аспірантів, докторантів, співробітників фармацевтичних підприємств, викладачів закладів вищої освіти.

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SYNTHESIS AND PROPERTIES OF 5-METHYL-4-(4-METHYLPHENYL)-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES

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Introduction. The creation of new organic compounds for the purpose of their further introduction into the practice of various branches of the national economy is one of the urgent directions of the development of pharmacy. Heterocyclic systems are mostly the primary source of the creation of such compounds. And here the special attention of researchers is focused on significant opportunities in the production of biologically active compounds, which will ultimately allow to obtain the desired medicinal product. It is possible to increase the prospects of the mentioned work thanks to the combination of pharmacophores of different nature within one molecule. This opportunity is provided by the structure of 1,2,4-triazole, which in the process of its formation provides wide opportunities in combination with a wide variety of substituents. Thus, it is possible to obtain a target product of chemical transformation with a set of required properties.

The aim of the work was to conduct a set of studies aimed at identifying compounds with a pharmacological profile in a number of 5-methyl-4-(4-methylphenyl)-1,2,4-triazole-3-thiol derivatives.

Materials and methods. Carbon (IV) sulfide, ammonia and 4-methylaniline were used as the starting structure for the formation of the 4-(4-methylphenyl)-5-methyl-1,2,4-triazole-3-thiol molecule. The interaction of these substances led to the formation of 4-methylphenylisothiocyanate. At the same time, the interaction of the ethyl ester of ethanoic acid with hydrazine hydrate in an ethanol environment made it possible to synthesize hydrazide of ethanoic acid. Synthesized acetic acid hydrazide takes part in the interaction reaction with 4-methylphenylisothiocyanate to form 2-acetyl-*N*-(4-methylphenyl)hydrazinocarbothioamide.

The obtained hydrazinocarbothioamide in an alkaline medium was subjected to alkaline intramolecular heterocyclization with the formation of a 5-methyl-4-(4-methylphenyl)-1,2,4-triazole-3-thiol.

The next stage was carried out in an ethanol environment and involved interaction with haloalkanes.

To confirm the structure of all synthesized compounds, proton nuclear magnetic resonance (^{1}H NMR) and infrared (IR) spectra were recorded, and elemental analysis was also performed. The individual character of the obtained substances and the degree of their purity were confirmed using the data of chromato-mass spectra.

Melting points were determined in open capillaries using "Stanford Research Systems Melting Point Apparatus 100" (SRS, USA). Analysis of the percentage content of elements (C, H, N, S) was performed using the "Elementar vario EL cube" analyzer (Elementar Analysensysteme, Germany). IR spectroscopy (spectral range 4000 – 400 cm^{-1}) was performed on the basis of the Bruker ALPHA FT-IR spectrometer using the ALPHA-T module (Bruker optics, Germany). ^{1}H NMR spectra

were recorded on a Varian-Mercury 400 spectrometer using tetramethylsilane as an internal standard in DMSO-d_6 solution. Chromatograph "Agilent 1260 Infinity HPLC" with spectrometer "Agilent 6120" made it possible to obtain chromato-mass spectra (ionization method - electrospray (ESI)).

The implementation of *in silico* studies involved the following algorithm:

1) working with the ligand: forming structural formulas of compounds using the MarvinSketch 6.3.0 program and saving them in mol format; preparation of the 3D structure of compounds - molecular modeling (Hyper Chem 8 program using the MM+ molecular mechanics method and the semi-empirical quantum mechanical method PM3 with the maximum number of cycles and the Polak-Ribiere algorithm and saving in PDB file format); conversion of PDB- to PDBQT-files using the software product AutoDockTools-1.5.6;

2) working with the enzyme: elimination of water molecules and ligand from the file using the Discovery Studio 4.0 software package and saving the enzyme in PDB format; converting enzyme from PDB to PDBQT file using AutoDockTools-1.5.6;

3) molecular docking: using the "Vina" program; creation of visual objects using the Discovery Studio 4.0 software tool.

Results and their discussion. ^{1}H NMR spectra of the synthesized compounds contain signals of protons of aromatic fragments, which are fixed in the form of doublets of doublets and multiplets (aryl derivatives). The analysis of ^{1}H NMR spectra also demonstrates that the signals of protons of S-alkyl fragments are observed in the strong part of the field in the region of 3.27-0.84 ppm. For example, singlet signals of methyl protons of the S-CH_3 fragment are present at 1.86 ppm. Protons of the S-C_2H_5 group form a triplet at 1.35 ppm and a quadruple at 3.12 ppm. The gradual transition from the S-CH_3 to the S-$(CH_2)_9$-CH_3 fragment leads to a slight chemical shift of the proton signals of the CH_3 group to the region of stronger fields (from 2.63 to 0.84 ppm). Multiplet signals of protons of $(CH_2)_n$-fragments are also recorded in the high-field part of the spectrum (1.76-1.21 ppm) and are difficult to differentiate. The specified spectral features are determined by the electron-donating properties of the alkyl substituent and the positive inductive effect, which increases with the elongation of the alkyl substituent.

According to the results of molecular docking, it was established that there is a certain similarity in the nature of the amino acid residues involved in the location of the synthesized ligands and fluconazole in the active center of the enzyme. To quantify the ability of lanosterol-14α-demethylase to bind the studied ligands in the form of synthesized substances, the value of the free energy of interaction of the specified enzyme with model compounds was calculated.

Conclusions. Optimal conditions for the synthesis of 4-(4-methylphenyl)-5-methyl-1,2,4-triazole-3-thiol and its S-alkyl derivatives were established, which made it possible to obtain chemical transformation products with high yields.

Using the method of molecular docking of the synthesized compounds to the active site of lanosterol 14α-demethylase, the feasibility of further screening of antifungal activity for the studied ligands was substantiated.