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ВСЕУКРАЇНСЬКОЇ НАУКОВО- ПРАКТИЧНОЇ КОНФЕРЕНЦІЇ З МІЖНАРОДНОЮ УЧАСТЮ

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Materials and methods: traditionally, toxicity levels are experimentally determined in laboratory animals. Considering contemporary possibilities and ethical standards, we analyzed a series of compounds and selected a model for studying acute toxicity using the Kerber method in the modification of A.O. Loyt and M.F. Savchekov.

Experimental Design: 6 groups were formed, one serving as a control, each consisting of 6 rats. White non-linear rats were weighed and marked. The investigational compound's aqueous solution was administered intraperitoneally to the animals on an empty stomach.

The experiments were conducted on 55 adult white non-linear male rats with a weight range of 220-260 g. The rats were sourced from the breeding facility affiliated with the Institute of Pharmacology and Toxicology of the Academy of Medical Sciences of Ukraine. The animals were maintained on a standard diet and subjected to a natural light regimen simulating "day and night."

Peripheral Analgesic Mechanism Study: for the study of peripheral analgesic effects, a classical screening model of "acetic acid-induced writhing" was employed. Intraperitoneal administration of a 0.6% acetic acid solution promotes the general activation of the nociceptive system and local release of histamine, serotonin and prostaglandins, leading to the development of abdominal muscle contractions, known as "writhing," accompanied by stretching of the hind limbs and arching of the spine.

Results: according to the acute toxicity study, the investigated compounds fall into the IV-V toxicity class (practically non-toxic).

It was observed that the reference drug, metamizole sodium, exhibited a potential difference of 6.60 ± 1.03 V in the two measurements, corresponding to an analgesic activity of 94.12% compared to the control. 4 test compounds demonstrated a substantial decrease in pain sensation in animals subjected to electric current.

The research results indicate that derivatives of 4-R, 5-pyridine-1,2,4-triazole-3-thiols represent a promising class for the ongoing exploration of substances with potential analgesic properties.

Conclusion: Our findings indicate the presence of analgesic activity in a series of 1,2,4-triazole derivatives, laying the groundwork for further in-depth and specific exploration of the most active substances.

SYNTHESIS AND PROPERTIES OF 4-(4-CHLOROPHENYL)-5-(PYRROL-2-YL)-1,2,4-TRIAZOLE-3-THIOL DERIVATIVES

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Introduction. A long-term study of 1,2,4-triazole derivatives has revealed the great chemical and pharmacological potential of these compounds, which makes them promising for the development of new medicines. Particular attention is paid to the possibility of combining this cycle with heterocyclic synthons of a different structure at the early stages of the formation of the starting compound. This approach greatly simplifies chemical transformations and helps to obtain the desired product, which may have the potential to become a biologically active substance in the future.

The aim of our research work has been the synthesis of 4-(4-chlorophenyl)-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol derivatives to obtain compounds with potential biological activity.

In the course of the research, initially, the synthesis of 2,2,2-trichloro-(1-pyrrol-2-yl)ethanone was carried out by the interaction of pyrrole with trichloroacetyl chloride. Further, pyrrole-2-carbohydrazide was obtained by hydrazinolysis of the starting material. This product has been used in the reaction with 4-chlorophenylisothiocyanate, which has been synthesized before. The resulting *N*-(4-chlorophenyl)-2-(pyrrole-2-carbonyl)hydrazine-1-carbothioamide was subjected to

intramolecular heterocyclization in the next step. The synthesized 4-(4-chlorophenyl)-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol has been used in alkylation reactions with halogenated alkanes.

The structure of the obtained compounds has been confirmed by elemental analysis, IR spectrophotometry and ^{1}H NMR spectroscopy, as well as by chromatography-mass spectrometry with additional confirmation of individuality. The next stage of research involved the use of computer chemistry methods. For this purpose, the SwissADME web resource and molecular docking were used. For docking studies, the model lanosterol-14α-demethylase was used, which was downloaded from the Protein Database. All experiments at the stage of docking studies were performed using a package of programs such as AutoDock 4.2.6, Open Babel 3.1.1, MGL Tools-1.5.6, and BIOVIA. The results obtained and their discussion confirm that most of the studied compounds meet the required standards in terms of physicochemical properties, lipophilicity, pharmacokinetic characteristics and bioavailability.

According to the results of SwissADME analysis, it was found that the synthesized compounds met the required criteria in terms of molar mass, molecular refraction and topological plane of the polar surface. It was also found that in a number of the synthesized compounds, derivatives with the number of Carbon atoms in the alkyl substituent not exceeding six possess the required lipophilicity. Most of the synthesized compounds successfully overcome Lipinski, Ghose, Veber, Egan and Muegge filters. The probability of gastrointestinal absorption for most of the synthesized compounds is high. At the same time, the chance of crossing the blood-brain barrier is low for the obtained substances. The range of values of the molecular permeability index through the skin suggests a satisfactory possibility of realizing this property. According to the results of the prediction, the risk of multiple drug resistance to the synthesized compounds is low.

The graphical representation of the molecular docking results confirms that the studied ligands can form stable complexes with the active sites of model enzymes. In particular, the complexes with lanosterol-14α-demethylase look particularly convincing.

The minimum energy of affinity of the synthesized compounds for lanosterol 14α-demethylase is expectedly high, although none of them exceeds fluconazole in this respect. The nature of the amino acid residues involved in the formation of bonds with fluconazole and the studied compounds in most cases was identical. However, in terms of the number of bonds formed, a number of the synthesized compounds are superior to fluconazole. The active role here is played by the *S*-alkyl substituent of the 1,2,4-trizole cycle, with which most hydrophobic interactions are formed.

Conclusions.Thus, the optimal conditions for the synthesis of *S*-alkyl derivatives of 4-(4-chlorophenyl)-5-(pyrrol-2-yl)-1,2,4-triazole-3-thiol were determined, and the prospects for further research in this area, in particular in the context of their antifungal activity, were demonstrated.