действие новых алкилипроизводных 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-1,2,4-триазол-3-тиолов.

Материалы и методы. Установлено, что при переходе в ряду от бутильного до децильного, октильного, вентильного, пропиллю- га, октильного и гептильного углеводородных заместителей токсичность 3-бутилтиольного, а до 5-(2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол-3-тиолов 5-(фуран-2-ил)-4-амино-4H-1,2,4-триазол-3-тиола. Acute toxicity was conducted on white rats weighing 160–250 g, which were injected once intraperitoneally with the investigated substances. The rats were received from the nursery of the Pharmacology and Toxicology Institute of Ukraine Medical Sciences Academy. The animals were kept on a standard diet with natural light mode “day–night”.

Results and discussion. After the acute toxicity studies in a group of 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол-3-тиолов 5-(фуран-2-ил)-4-амино-4H-1,2,4-триазол-3-тиола. Acute toxicity was conducted on white rats weighing 160–250 g, which were injected once intraperitoneally with the investigated substances. The rats were received from the nursery of the Pharmacology and Toxicology Institute of Ukraine Medical Sciences Academy. The animals were kept on a standard diet with natural light mode “day–night”.

Conclusions. The investigated 3-alkylthiol 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол derivatives belong to the IV-V toxicity class. The toxicity of 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол alkyl derivatives varies depending on the hydrocarbon substitution, so the presence of 3-пропилтиоль заместителя in the С₂ atom at 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол leads to the toxicity increase. Introduction of 3-бутилтиол to the molecule of 5-(фуран-2-ил)-4-амино-4H-1,2,4-триазол, and the 3-пропилтиоль substituents in the 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол results the formation of lowest acute toxicity.

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Key words: Acute Toxicity, 1,2,4-triazoles, Activity, LD₅₀.

Острая токсичность алкилипроизводных 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-1,2,4-триазол-3-тиолов

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Цель работы – детально исследовать острую токсичность новых алкилипроизводных 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-1,2,4-триазол-3-тиолов.

Материалы и методы. В исследованиях использованы впервые синтезированные производные 5-(фуран-2-ил, 2-метилфуран-3-ил)-4-амино-4H-1,2,4-триазол-3-тиолов. Оценка острой токсичности была проведена на белых крысах массой 160–250 г, которым...
In this study we used first time synthesized 5-(furan-2-yl, 2-methylfuran-3-yl)-4-amino-4H-1,2,4-triazole-3-thione derivatives study which contain the remains of furan heterocyclic system and amino groups as typical substituents. The authors convincingly demonstrated that an active “symbiosis” of 1,2,4-triazole, furan and amino groups in one molecule have positive effect on the new compounds’ properties.

The first experience of domestic scientists is an evidence of absolute necessity and obvious perspective for further research of these derivatives. The bright example of a typical functional substituents successful combination in one molecule is a new domestic drug “Tryfuzol”, which is now widely used in veterinary practice. Previously was noted [1] that further testing of new 5-(furan-2-yl, 2-methylfuran-3-yl)-4-amino-1,2,4-triazole-3-thiol derivatives is important to have theoretical and practical significance.

The purpose of our work was the further exploration of the new 5-(furan-2-yl, 2-methylfuran-3-yl)-4-amino-1,2,4-triazole-3-thiol alkyl derivatives’ acute toxicity, setting some patterns of alkyl substituents influence by the Sulfur atom on acute toxicity.

Research materials and methods
In this study we used first time synthesized 5-(furan-2-yl, 2-methylfuran-3-yl)-4-amino-4H-1,2,4-triazole-3-thione derivatives (Table 1).

Acute toxicity assessment was conducted on white rats weighing 160–250 g, which were injected once intraperitoneally with the investigated substances. The rats were received from the nursery of the Pharmacology and Toxicology Institute of Ukraine Medical Sciences Academy. The animals were kept on a standard diet with natural light mode “day – night” [2,3].

The study was conducted on the basis of “Pharmacological agents preclinical safety evaluation rules (GLP)” [4,6].

In the acute toxicity study each investigated compound was taken in the four doses range, each dose was tested in 2 animals [5]. Follow-up term was 14 days, during which we studied the nature and duration of intoxication symptoms, death dates and the number of dead animals from each dose [6].

Results and their discussion
After the acute toxicity studies in a group of 5-(furan-2-yl, 2-methylfuran-3-yl)-4-amino-4H-1,2,4-triazole 3-alkyl derivatives it was found that among the all studied structures the most toxic was 2e, LD50 of which was 263 mg/kg, and the least toxic
compound was 2a, LD₅₀ of which was 1570 mg/kg, that belongs to the V toxicity class [3].

For a more in-depth acute toxicity analysis we compared the LD₅₀ test substances with the acute toxicity of well-known drugs. It is known that LD₅₀ of anticancer drug Anastrazol is ≈50 mg/kg [7], which exceeds the compound 2e by the toxicity in 5 times, dapiprazol’s LD₅₀ is in the range 1189–2100 mg/kg [7], which is comparable to the toxicity of the compounds 1b, 2a, 2c.

After comparing the acute toxicity of well-known antimycotic agent fluconazole with the index of LD₅₀ that most of compounds are less toxic than the comparison drug dapiprazol’s LD₅₀, which exceeds the compound 2e by the toxicity in 5 times, it is known that LD₅₀ to the V toxicity class [3].

Having analyzed the chemical structure of these 1,2,4-triazole derivatives, some dose–acute toxicity patterns were found (Table 2).

So the transition from the furan-2-yl substituent in the C₅ Carbon atom to the 2-methylfur-an-3-yl substituent in alkyl thio derivatives with the propyl (1a, 2a) and pentyl (1c, 2c) substituents results the toxicity decrease.

In the transition from furan-2-yl substituent at the C₅ Carbon atom to the 2-methylfur-an-3-yl substituent in alkyl thio derivatives with the butyl (1b, 2b), heptyl (1d, 2e), octyl (1e, 2f) and nonyl (1f, 2g) substituents shows the growth of acute toxicity.

It was found that the transition in a group from butyl to decyl, octyl, ventyl, propyl, nonyl and heptyl substituents in the molecule of 3-alkylthio 5-(furan-2-yl)-4-amino-4H-1,2,4-triazole is accompanied by the toxicity increasing.

Speaking about the 5-(2-methylfur-an-3-yl)-4-amino-4H-1,2,4-triazole 3-alkylthio derivatives we can find that this dependence is observed in a number from propyl, pentyl, nonil, butyl, heksyl, octyl and heptyl hydrocarbon chains.

Acknowledgments

1. The investigated 3-alkylthio 5-(furan-2-yl, 2-methylfur-an-3-yl)-4-amino-4H-1,2,4-triazole derivatives belong to the IV–V toxicity class and their LD₅₀ ranges from 263 mg/kg to 1570 mg/kg.

2. The toxicity of 5-(furan-2-yl, 2-methylfur-an-3-yl)-4-amino-4H-1,2,4-triazole alkyl derivatives varies depending on the hydrocarbon substituents, so the presence of 3-heptithiol substituent in the C₅ atom at 5-(furan-2-yl, 2-methylfur-an-3-yl)-4-amino-4H-1,2,4-triazole leads to the toxicity increase.

3. Introduction of 3-butylthiol to the molecule of 5-(furan-2-yl)-4-amino-4H-1,2,4-triazole, and the 3-propylthiol substituents in the 5-(2-methylfur-an-3-yl)-4-amino-4H-1,2,4-triazole results the formation of lowest acute toxicity (1131 mg/kg and 1570 mg/kg, respectively).

Conflicts of Interest: authors have no interest conflicts to declare.

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