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Investigation of acute toxicity of novel 3,7-dihydro-1H-purine-2,6-dione derivatives

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ABSTRACT

The past thirty years of investigation and development in pharmacophore design has produced revolutionary results. Ring structure give molecules their basic form, determine whether molecules are rigid or flexible, and keep substituents in their appropriate sites. In many biologically active structures, rings are directly involved in communications with cell receptors, either through heteroatoms forming hydrogen bonds with suitable protein residues or through hydrophobic interactions. The latter relays to many branches of bioinformatics like in-silico algorithms, biochemical assays, better pharmacokinetics/pharmacodynamics (PK/PD) models, ADME models, and wide variety of toxicology surveys.

KEW WORDS *xanthine, purine, synthesis, acute, toxicity.*

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INTRODUCTION

Nowadays, practical pharmacy lacks new drugs. Therefore, the development of new low-toxic and highly effective drugs for the prevention and treatment of various diseases is one of the priority tasks of modern pharmacy.

Ring systems in molecules form a keystone of organic chemistry and consequently also the drug discovery effort. Ring structure give molecules their basic form, determine whether molecules are rigid or flexible, and keep substituents in their appropriate sites. In numerous biologically active structures, rings are directly involved in interactions with cell receptors, either through heteroatoms forming hydrogen bonds with suitable protein residues or through hydrophobic interactions [1-5].

Interest in the chemistry of purine is because it plays a fundamental role in vital processes and is the structural basis of many drugs. All this indicates that the synthesis in the series of purine and its derivatives is of great interest in terms of the search for substances with biological activity that can be used in practical medicine.

The first stage of almost all investigations of the biological activity of the novel compounds is the study of acute toxicity, which significantly reduces the intensity of side effects in clinical use [6].

The purpose of toxicological studies of purine-2,6-dione derivatives was to identify the nature and severity of their harmful effects on the metabolism of experimental animals and assess their safety. The method is based on the proposal to use the test substances in doses, which are placed on a logarithmic scale with an interval of 0.1. Possible reliable results of LD50 and their errors have been calculated in advance.

MATERIALS AND METHODS

Acute toxicity studies were performed on white rats. We used 4 groups of animals with 2 observations in each with the additional use of one previous and next dose.

Water-soluble compounds were dissolved in 1.5 ml of purified water and administered using a syringe intraperitoneally. Water-insoluble compounds were stabilized with tween-80 and injected through a metal probe into the stomach. Observations were performed after 24 hours. The results of the study are shown in the tables below.

The research results (Table 2) were processed by modern statistical methods of analysis on a personal computer using a standard Microsoft Office software package (Microsoft Excel) and «STATISTICA® for Windows 6.0» [7-9].

RESULTS AND DISCUSSION

As a result of the experiment, acute toxicity for 20 new purine-2,6-dione derivatives was studied. It was found that all synthesized compounds (Table 1) have a characteristic dependence of the toxicity index according on the substituent in C8 position of the purine moiety.

Table 1

Physicochemical constants of purine-2,6-dione derivatives (1-20)

Compound	R
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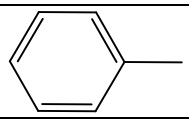
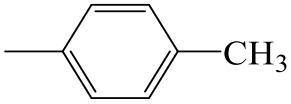
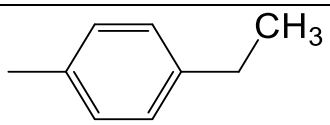
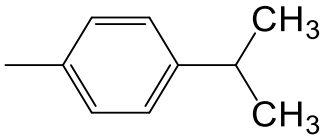
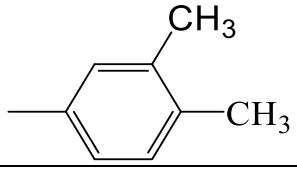
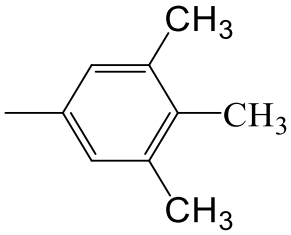
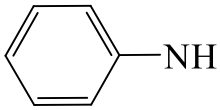
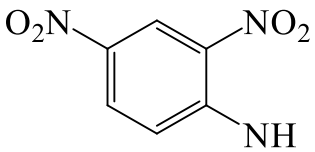
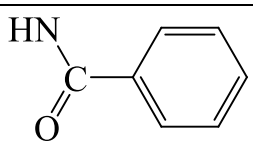
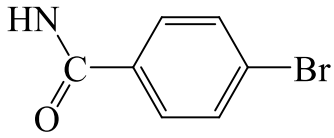
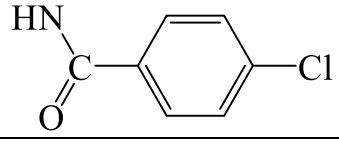
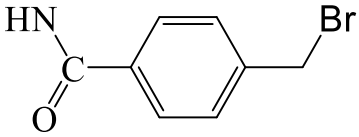
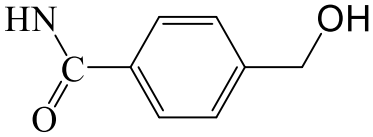
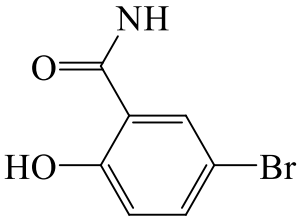
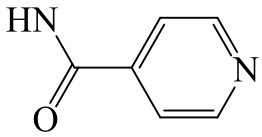
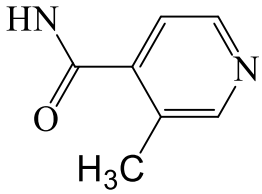
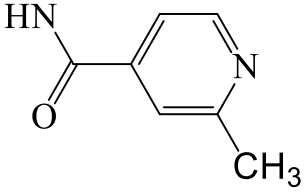
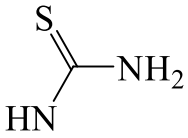
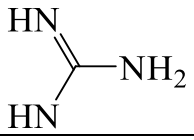
2	
3	
4	
5	
6	
7	
8	
9	
10	

Table 1 cont.d

11	
12	
13	
14	
15	
16	
17	
18	
19	
20	

According to the results of the study of acute toxicity it was found (Table 2) that the LD50 of this all compounds lies in the range from 536 to 1403 mg/kg. According to the Sidorov classification [10], they belong to class IV toxicity – low-toxic compounds. Analysis of the results of the study of acute toxicity among derivatives of 3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purine-8-carbaldehyde (1-20) revealed some patterns [11] between the structure and toxicological characteristics of the synthesized substances.
Thus, the incorporation of aromatic radicals into 8-(hydrazonomethyl)-3-methyl-3,7-dihydro-1H-purine-2,6-dione leads to increase of toxicity from 953 mg/kg to 536 mg/kg. But increasing number of methyl groups in the structure of aromatic substituent at the C8 (4-7) we slightly reduce LD50 of such compounds (Table 2). The highest toxicity amongst the C8-substituted benzene derivatives has compound (9), which contains a two nitro groups in the benzene ring – 804 mg/kg, and the lowest - 5-bromo-2-hydroxy-N'-((3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)methylene)benzohydrazide (15) (1403 mg/kg, Table 2).
Also, it was found that the replacement of the chlorine atom onto the bromine leads to the moderate decrease in toxicity values. However, the introduction of a hydroxyl group into the aromatic nucleus also leads to such results.
Incorporation of heteroaromatic fragments of carbonyl compounds in the structure of the initial compound leads to a decrease of the toxic properties of the obtained compounds (16-18).

Table 2

Acute toxicity of 3-methyl-8-((2-R-hydrazono)methyl)-3,7-dihydro-1H-purine-2,6-dione (1-20)

Comp. №	LD_{50}, mg/kg
1	953 (774-797)
2	536 (510-563)
3	752 (733-775)
4	687 (682-691)
5	778 (772-784)
6	870 (844-892)
7	905 (882-926)
8	1035 (1005-1064)
9	804 (792-815)
10	1116 (1100-1131)
11	1275 (1261-1289)
12	897 (890-904)
13	1212 (1206-1218)
14	1340 (1322-1357)
15	1403 (1387-1418)
16	792 (788-796)
17	818 (812-823)
18	829 (820-838)
19	1077 (1071-1083)
20	1035 (1029-1041)

CONCLUSION

The acute toxicity of 20 new 3,7-dihydro-1H-purine-2,6-dione derivatives was studied. The least toxic compound was found to be 5-bromo-2-hydroxy-N'-((3-methyl-2,6-dioxo-2,3,6,7-tetrahydro-1H-purin-8-yl)methylene)benzohydrazide (compound 15), which in the subsequent planning of synthetic strategies can be used as a lead compound for the construction of combinatorial libraries.

The obtained results can be used for further research not only by chemists, but also by pharmacologists. Our search for new low-toxic biologically active substances in a row of purine-2,6-dione continues.

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