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The study of the toxic properties of potential hepatoprotectors from new pyrimidine derivatives class.

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ABSTRACT

The basic toxic properties of the potential hepatic protectors of the pyrimidine derivatives class were studied on the basis of Daphnia culture experiments. These protectors are the new analogues of the domestic drug Xymedon. The doses of acute toxicity, the chronic toxicity and embryotoxicity values are determined. It was revealed that according to all the studied toxicometry parameters the 29-R compound has the least levels of toxicity.

Keywords: Hepatic protectors, pyrimidine derivatives, toxicity, Daphnia

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INTRODUCTION

Finding the ways to improve the environmental safety of chemicals developed for the use in various fields of human consumption, is one of the most important problems of our time. The pyrimidine bases are the part of the nucleic acids, and therefore, both natural pyrimidines and pyrimidine derivatives have diverse effects on the body. They constitute one of the largest groups of substances involved in medicine, agriculture and other fields of human activity. Their main properties are the low toxicity, theability to raise immune biological defenses, stimulate hemopoiesis, make anti-stress and adaptogenic influence, regulate the inflammatory and regenerative processes, as well as antitoxic, antioxidant and membrane stabilizing properties [1,2]. The pyrimidine derivatives contribute to the restoration of the liver functional activity and its morphological structure at acute and chronic poisoning with CCl4, trinitrotoluene and sodium selenite [3,4]. The antitoxic effect of pyrimidines is based on different mechanisms. If you are poisoned by some poisons (methanol, CCl4, some FOS) – it is an antioxidant mechanism. If you are poisoned by other poisons – it is the activity of microsomal liver enzymes stimulation and the enhancement of its detoxifying function [4].

The aim of this work is to study the toxic properties of four new potential hepatic protectors of pyrimidine derivatives class synthesized on the basis of Xymedon drug. The biological testing procedure of 30-D, 29-R, 29-W, 27-D compounds toxicity is performed in laboratory conditions of the IOFH named after A.E. Arbuzov KazSC RAS, on the Daphnia magna Straus crustacean culture [5]. The method is based on determining the Daphnia mortality at toxic substance influence present in the test aqueous medium compared to control culture in the samples which do not contain toxic substances. The acute toxic effects of individual chemical solutions on Daphnia were determined by their mortality over a certain period of exposure. In short-term experiments of the acute toxic effect determination the median lethal concentration of the substances was set causing the death of 50% or more of the test organisms (LK^{96}_{50},). The criterion for acute toxicity is the death of 50% or more Daphnia in 96 hours within the test water, provided that the death does not exceed 10% in the control experiment. The determination of each sample and dilution toxicity is performed in 3 parallel series. Three parallel series with the cultivation (biologizing) water are used for the control.

In chronic experiments the parameters of chronic toxicity and embryotoxicity of compounds in a single seeding of the parental generation (P) and the constant seeding of Daphnia in a number of generations (P-F1-F2-F3) were determined in terms of "survival" and "fertility". Chronic toxicity criterion is the death of 20% or more, and (or) the significant difference in fertility of survived test organisms number compared with the control group. The determination of each sample and dilution toxicity is performed in 5 parallel series. During the determination of the chronic toxic effect of compounds the statistical processing of the obtained data was performed using the Student's t-criterion.

The calculation of acute lethal toxicity indicator, which causes 50% of Daphnia mortality during 96 hours of exposure was carried out graphically. Table 1 shows the values of the acute lethal toxicity values of the test compounds used on daphnia. During the determination of the test compounds 30-D, 29-R, 29-W, 27-D acute lethal toxicity it was shown that the tested compounds by the influence degree on Daphnia magna Straus are classified as "practically nontoxic substances" (toxicity class V).

Table 1 - Values of the acute lethal toxicity of the test compounds (mg/l) tested on Daphnia

	Compounds			
	29-R	29-W	30-D	27-D
LK50 24h	730	355	480	212
LK50 48h	440	272	360	190
LK50 96h	360	153	310	118

29-W and 30-D compounds (1/5 of LC_{50}) in a single seed have increased mortality of Daphnia in the first two generations. In the next generations the survival index is restored to the control level. The survival at the concentrations of 1/10, 1/30 and 1/60 of the LC_{50} for 29-W, 29-R, 30-D compounds was maintained at a

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control level. 27-D (1/5 and 1/10 of LC_{50}) compound in a single seed conditions increases the Daphnia mortality in all generations. The survival at the concentrations of 1/30 and 1/60 for 27-D compound remained at the control level. Under the constant seeding of 29-W, 30-D (1/5 of the LC_{50}) and 27-D (1/5 and 1/10 of LC_{50}) compounds they also increase the Daphnia mortality. The chronic embryotoxical effect of test compounds is not observed in these concentrations (Table. 2).

Table 2 - Maximum values of ineffective concentration of the test compounds (mg/l)

Compounds	The survival rate in single addition	The survival rate in regular addition	The fecundity in single addition	The fecundity in regular addition
29-R	72	72	36	36
29-W	15,3	15,3	15,3	5,1
27-D	3,9	3,9	3,9	3,9
30-D	31	48	48	48

During the chronic toxicity study according to the fertility parameter the greatest inhibition of fertility is observed for 27-D compound in constant and single seeding conditions (Figure 1, Figure 2). The lowest embryotoxic properties are revealed for 29-R compound. These compounds stimulate the fertility increase during single and continuous seedings by 34% in comparison with the control group ($p < 0.05$).

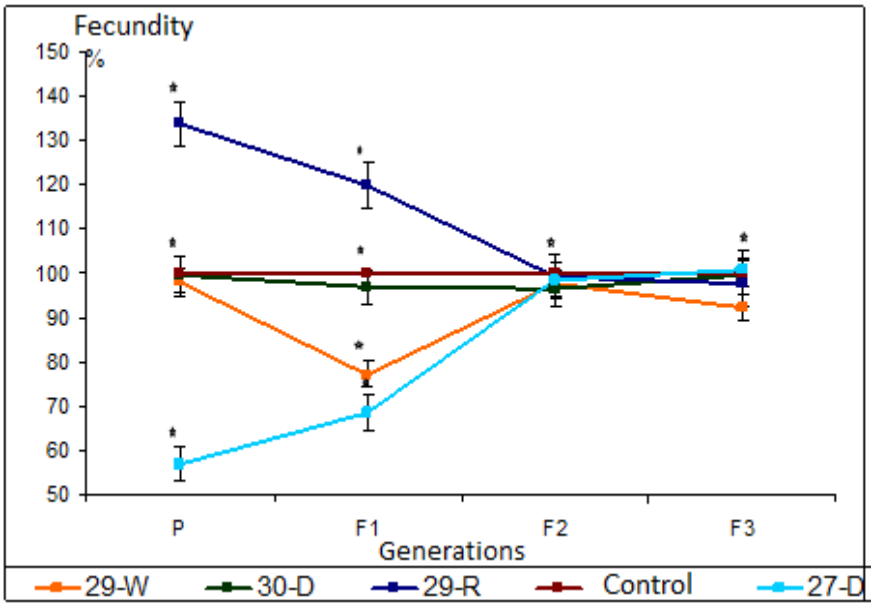

Figure 1: Daphnia fertility in a number of generations P-F1-F2-F3 on 21st day with a single seeding of 29-W, 30-D, 29-R, 27-D compounds at the concentrations of 1/10 LC_{50}

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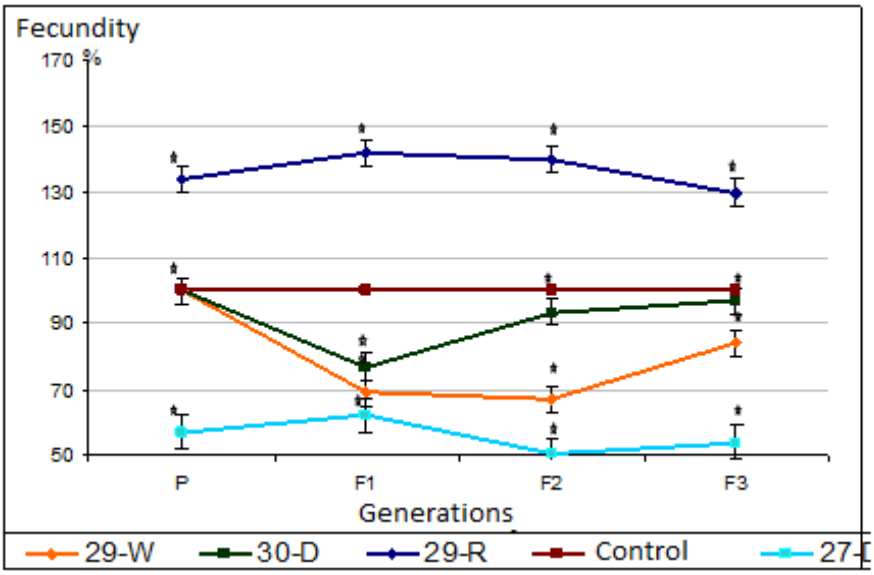

Figure 2: Daphnia fertility in a number of P-F1-F2-F3 generations on the 21st day of continuous operation of 29-W, 30-D, 29-R, 27-D compounds at the concentrations of 1/10 LC_{50}

Thus, the major toxic properties of four potential hepatic protectors of pyrimidine derivatives class were studied. These protectors are synthesized on the basis of Xymedon drug. All compounds are classified as "almost non-toxic" substances (toxicity class V). 29-R compound has the least toxic properties among all studied toxicometric parameters.

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REFERENCES

[1] Izmailov S.G., Izmailov G.A., Aver'yanov M.Y., Reznik V.S. Xymedon in clinical practice. - Nizhny Novgorod, 2001 - 188 pages.

[2] Bano T., Kumar N., Dudhe R. Organic and Medicinal Chemistry Letters, 2012.

[3] Study of hepatoprotective effects of xymedon/ Vyshtakalyuk A.B., Nazarov N.G., Zueva I.V., Lantsova A.V., Minnehanova O.A., Busygin D.V., Porphyriev A.G., Evtyugin V.G., Reznik V.S., Zobov V. V. // Bulletin of experimental biology and medicine. 2013 V. 155. № 5. Pages 595-598.

[4] Kamilov F.H., Lazareva D.N., Plechev V.V. Pyrimidines and their use in medicine. - Ufa, 1992 - 159 pages.

[5] Zobov V.V. Zobov V.V., Aslyamova A.A. A Practical Guide to biotesting chemicals on planktonic organisms: educational-methodical development. - Kazan State University, 2001 - 18 pages.