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Research Article

Effect of some compounds from the series of derivatives of cyanothioacetamide with analgesic activity on liver function parameters of rats with chronic administration of paracetamol against the background of alcohol load

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Abstract

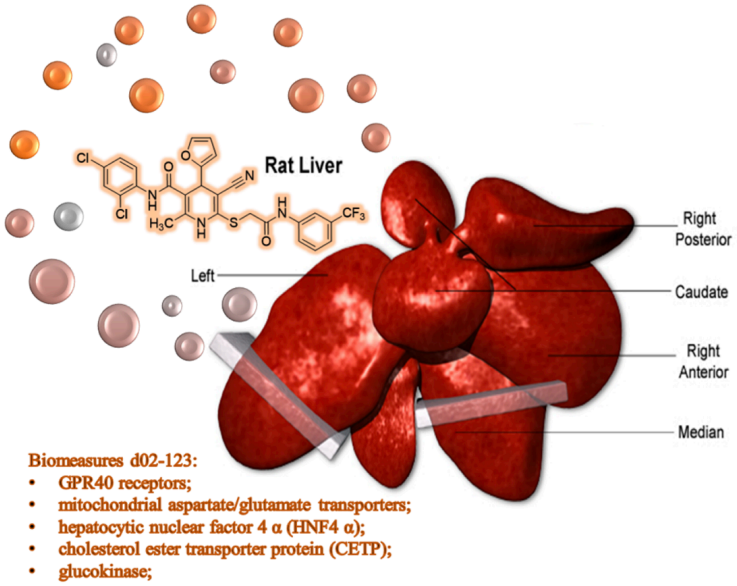
Introduction: Derivatives of 1,4-dihydropyridines from a series of α-cyanothioacetamide derivatives are a potentially promising class of compounds with analgesic activity.

Materials and methods: The experiment was carried out on 64 white male rats weighing 220-250 g. The rats were divided into 8 groups: intact, control, comparison (thiotriazoline 50 mg/kg) and 5 experimental groups (derivatives of 1.4-dihydropyridine and thiadiazine 5 mg/kg). Acute paracetamol-alcohol liver damage was modeled after two weeks of taking 1 mL of 40^0 ethanol and paracetamol at a dose of 500 mg/kg.

Results: The total bilirubin level in the control group, compared to that in the intact, increased by 2.88 times, direct bilirubin – by 37.8%, ALT – by 38.85%, AST – by 51.54%, and alkaline phosphatase – by 163%. In the reference group, compared to the intact, the ALT level increased by 44.76%, AST – by 18.11%, alkaline phosphatase – by 19.4%, and AST reduced by 22.06%. In the Mar-014 group, direct bilirubin reduced by 42.7%. In the CV-150 compound group, total bilirubin reduced by 51.6%, AST – by 18.64%, and alkaline phosphatase – by 272.4%. In the TD-0331 group, the AST index increased by 35.7%, whereas alkaline phosphatase decreased by 43.1%. In the CV-131compound group, when compared with the control group, total bilirubin reduced by 75.3%, direct bilirubin – by 10.1%, and AST – by 12%. In the d02-123 group, no indicators exceeded the values of rats in the intact group.

Conclusion: The most pronounced hepatoprotective properties were shown by the compound with the code d02-123.

Graphical abstract



Keywords

hepatotoxicity, hepatoprotectors, non-steroidal anti-inflammatory drugs, paracetamol-alcoholic liver damage, cyanothioacetamide derivatives

Introduction

According to WHO experts, 90% of all diseases are associated with pain. The vast majority of modern painkillers with proven efficacy have a wide range of side effects, contraindications and drug interactions, which makes their practical use a very difficult task. In modern society, a significant problem in clinical medicine is the problem of polypragmasy, the consequences of which affect the health of many patients (Antonenko 2013; Koroleva 2015; Meldekhanov et al. 2019). In addition, the need for effective management of pain syndrome, both acute and chronic, taking into account combat operations and disability of the civilian population and military personnel, is extremely urgent (Zimmerman and Vologzhanina 2018). NSAIDs are one of the most popular groups of drugs due to their unique combination of anti-inflammatory, antipyretic and analgesic actions. Side effects of NSAIDs, including serious ones, are quite often noted due to their widespread and often uncontrolled use in various pathological conditions. According to WHO data, about 20% of the world's population regularly use drugs of this group (Balukova et al. 2018). In general, drugs are responsible for up to 40% of all cases of hepatitis and up to 25% of fulminant hepatic failure. In contrast to the lungs and kidneys, which suffer equally from the toxic effects of drugs administered intravenously and orally, drug-induced liver damage occurs more often during enteral administration, which is associated with the peculiarities of blood supply to the liver and metabolism of drugs in it (Zholobova et al. 2009). NSAIDs are toxic not only to the mucosa of the digestive tube, but also to the liver. An illustration of the social significance of the problem of adverse effects of NSAIDs on the liver is the inclusion of acute liver failure due to NSAID intake in the very limited list of indications for liver transplantation. The problem of hepatotoxic effect of some NSAIDs is so acute that in a number of countries

these drugs are not legally allowed for use, for example, the NSAID nimesulide is currently banned for use in Spain, Finland, Israel, India, and Sri Lanka. In the USA, UK, Canada and Australia, the drug is not authorised for registration. Analgin is banned for use in 70 countries worldwide. Paracetamol causes dose-dependent necrosis of hepatocytes in the liver and is among the top three in the ranking of drugs used for deliberate suicidal withdrawal (Shukevich et al. 2020).

Chronic alcohol abuse contributes to the development of hepatotoxic reactions when drugs are administered at lower doses and also increases the severity of drug-induced liver damage caused, for example, by the use of paracetamol, isoniazid or nicotinamide (Marshalko et al. 2018; Bibik et al. 2021). One potentially promising class of compounds with analgesic activity are derivatives of 1,4-dihydropyridines from a series of α-cyanothioacetamide derivatives (Bibik et al. 2017a, 2017b). Cyanothioacetamide-based ring systems are useful in the development of drugs due to their easy availability and polyfunctionality, as well as the presence of several nucleo- and electrophilic centres (Diachenko et al. 2018). Pyridine and dihydropyridine are part of vitamins, coenzymes, alkaloids, antibiotics, and other compounds. Pyridine and dihydropyridine frameworks in drugs are considered important structural components because they influence their pharmacological properties. For example, the pyridine component can improve biochemical activity as it helps to increase the rate of chemical reactions. In addition, it stabilizes drugs, increases their permeability through the membranes and facilitates the binding of new compounds to blood proteins (Bibik et al. 2017a, 2017b).

More than eight thousands original derivatives of α-cyanothioacetamide have been synthesized in the specialized scientific chemical laboratory 'ChemEx' of Vladimir Dahl Lugansk State University, and targeted synthesis in this direction continues now (Dotsenko et al. 2019).

Cyanothioacetamide is an accessible reagent that has proved to be an indispensable building block in the preparation of a wide range of sulfur- and nitrogen-containing heterocyclic compounds. First of all, cyanothioacetamide is used in the synthesis of important intermediates of fine organic synthesis – 2-mercapto (2-thioxo) nicotinonitriles and related 3-cyanopyridine-2-thiolates. They are actively used in further heterocyclisations into thieno[2,3-b]pyridine derivatives, thiazolo[3,2-a]pyridine, isothiazolo[5,4-b]pyridine (Gouda et al. 2018; Khot et al. 2021), pyrido[2,1-b][1,3,5]thiadiazine and a number of other heterocyclic structures (Ahmed et al. 2019; Yang et al. 2020).

According to the results of our studies and works of foreign authors, it is known that 1.4-dihydropyridin-3-carbonitriles show hepatoprotective properties; pyrido-1,3,5-thiadiazines have antiviral effect against Powassan virus and tick-borne encephalitis virus, and also have analgetic effect, anti-inflammatory and adaptogenic effect in paracetamol-alcoholic hepatitis and chronic osteomyelitis. It is also known that hexahydroquinoline derivatives are active against HIV (Khan et al. 2016; Daina et al. 2019).

The first stage of the search for the most effective compounds in terms of analgesic properties and safety was the *in silico* study. The design of further studies included various classical pharmacological tests and allowed us to select the leading compounds, the analgesic properties of which exceed those of the reference drug metamizole sodium by dozens of times. In our earlier experimental studies, we found pronounced analgesic properties of some cyanothioacetamide derivatives and their low acute oral toxicity (Khot et al. 2021). Thus, earlier experiments in the orofascial-trigeminal pain test showed that a single intragastric injection of a pyridine derivative under the code Mag-014 at a dose of 5 mg/kg has a 9.8 times stronger analgesic effect than sodium metamisole (Gouda et al. 2018). We found that the derivative of 1,4-dihydropyridine, when administered at the same dose, is able to increase the time of stay of animals of the experimental group on the surface of the heated metal plate in comparison with that in rats receiving sodium metamisole by 3 times (Gouda et al. 2018).

Materials and Methods

Animals

The experiment was carried out in the laboratory of the Department of Fundamental and Clinical Pharmacology of St. Luke Lugansk State Medical University of the Ministry of Health of the Russian Federation in autumn-winter period on 64 white mongrel male rats weighing 220-250 g obtained from the vivarium of St. Luke Lugansk State Medical

University of the Ministry of Health of the Russian Federation.

All rats were kept in plastic cages under natural light conditions at a temperature of 22-24ºC and relative humidity of 40-50%.

The studies were approved by the Bioethics Commission of St. Luke Lugansk State Medical University, minutes №6 of November 1, 2021.

All manipulations with laboratory animals were carried out in accordance with the principles of bioethics, the good laboratory practices (GLP), the requirements of the Federal Law of the Russian Federation N 4979-1 of May 14,1993 'On Veterinary Medicine' (as amended on July 2, 2021), Directive 2010/63/EU of the European Parliament and Council of the European Union 'On the Protection of Animals Used for Scientific Purposes', GOST 33216-2014 'Guidelines for the Maintenance and Care of Laboratory Animals. Rules for Keeping and Care of Laboratory Rodents and Rabbits', GOST 33215-2014 'Guidelines for Keeping and Care of Laboratory Animals. Rules for Equipment of Premises and Organisation of Procedures', GOST 33044-2014 "Principles of Good Laboratory Practice".

The studies were carried out in autumn to exclude the influence of seasonal rhythms on the animals. Daily observation of behaviour and general condition of animals was carried out. All studies were performed in accordance with the methodological recommendations for preclinical studies of drugs (Habriev 2005; Mironov et al. 2012).

At all stages, sexually mature male rats without external signs of diseases and anatomical abnormalities were selected for the studies.

Animals whose weight differed by more than 50 g, as well as female animalsб were not included in the experiment.

Animals with aggressive behaviour and injured animals were excluded from the experiment.

Randomisation was carried out using the envelope method.

Study design

The experiment was based on the model proposed by Revyakin A.O. and co-authors in 2014. In this model, acute combined paracetamol-alcoholic liver damage developed in animals after two weeks of enteral administration of 1 ml of 40° ethanol and paracetamol at a dose of 500 mg/kg once a day. For further pharmacological correction, new compounds from a series of cyanothioacetamide derivatives as well as reference drugs were used. The effect of new derivatives of 1,4-dihydropyridine and thiodiazine with laboratory codes **Mar-014, do2-123, CV-150, CV-131, TD-0331** was evaluated for their analgesic and hepatoprotective activity, as well as their influence on the structural and functional organisation of the liver.

Rats were distributed randomly into 8 groups of 8 animals each: intact (rats without pathology), control (animals with combined paracetamol-alcoholic liver damage), comparison (received thiotriazolin at a dose of 50 mg/kg via gastric tube daily from the fourth to the fourteenth day of modelling acute liver injury) and 5 experimental groups (which received samples of investigated derivatives of 1.4-dihydropyridine and thiadiazine **Mar-014, d02-123, CV-150, CV-131, TD-0331** at a dose of 5 mg/kg). Continuous monitoring of the animals was carried out. Position, behaviour, feed and water consumption, and coat condition were recorded. On the fifteenth day, slaughter was performed, and blood was collected from the femoral vein. The levels of total bilirubin, direct bilirubin, ALT, AST and alkaline phosphatase were determined using standard methods on an automatic analyser for biochemical and immunoturbidimetric analysis 'VitaLine 200' (Russian Federation) and a set of reagents produced by 'Vital' (Russian Federation).

The studied compound

Samples of new cyanothioacetamide derivatives were pre-selected according to the results of virtual bioscreening 'Swiss Target Prediction'. The structure in the form of chemical formulae of the studied substances is given below in Fig. 1.

Statistical analysis

For medical research, the level of reliability (confidence level) $p = 0.95$ and $p = 0.98$ were accepted. The number of repetitions of measurements n in the series of experiments, depending on $p = 0.95$ (significance level $\alpha = 0.05$) and acceptable error $\varepsilon = \pm 3\sigma$, was taken as 3, and for $p = 0.98$ $n = 4$.

The required sample size according to the calculations of the online calculator (https://medstatistic.ru/calculators/calcsize.html) for studies with an accuracy of 0.3 at $p = 0.95$ and confidence coefficient $t = 2.0$ is at least 44, and at least 70 at $p = 0.98$ and confidence coefficient $t = 2.2$.

Estimation of excluded data values and smoothing of data series were performed on the

basis of confidence intervals, the size of which for experimental groups was determined depending on the values of a_{sr}, σ and sample size.

Statistical processing of the obtained experimental results was carried out according to the known methods of mathematical statistics characterising quantitative variability. When processing the experimental data, the arithmetic mean (a_{sr}) value was determined. Determination of reliability of differences of the compared variants was made on the basis of Student's t-criterion (on the basis of online resource https://medstatistic.ru/calculators/averagestudent.html) with the critical value of Student's t-criterion equal to 2.101 and significance level $p<0.05$ (Table 1).

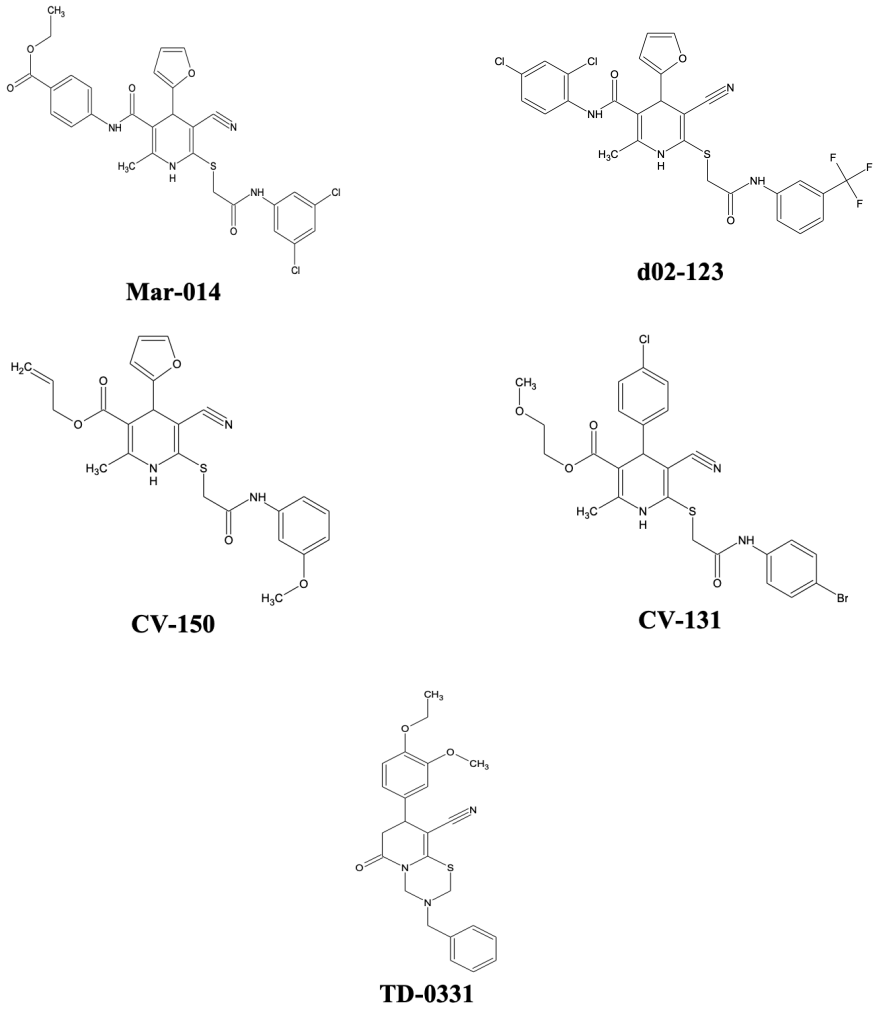


Figure 1. Structure of the molecules of the studied new original derivatives of cyanothioacetamide.

Table 1. Reliability analysis in relation to the control group based on Student's distribution (test of equality of mean values)

Groups	Indicators				
	Total bilirubin	Direct bilirubin	ALAT	AsAT	Alkaline phosphatase
Group 3 (CV-131)	5.1	0.9	5	2.19	11.6
Group 4 (Mar-014)	9.96	7.02	5.2	6.42	11.5
Group 5 (CV-150)	7.32	1.11	-0.04	3.2	13.96
Group 6 (TD-0331)	10.73	4.49	3.37	2.76	18.8
Group 7 (d02-123)	9.78	5.53	2.8	11.83	11.4
Group 8 (thiotriazoline)	8.3	4.5	-0.85	5.42	10.24

Results

While monitoring the behavioural activity of control group rats receiving paracetamol and 40° ethanol, the animals were observed to be aggressive towards one another: they tried to fight, and two rats had their tails damaged. The rats consumed less food. In the experimental groups with pharmacocorrection by thiadiazine and 1,4 dihydropyridine derivatives, the behaviour of rats was normal: they moved calmly around the cage, their appetite and desire to consume water did not differ from those of rats of the intact group. The data of biochemical investigations according to the design of the experiment are given in Table 2.

Table 2. Blood biochemical parameters of rats with chronic paracetamol-alcoholic hepatitis against the background of pharmacocorrection with new dihydropyridine and thiadiazine derivatives

Groups	Indicators				
	Total bilirubin	**Direct bilirubin**	**ALAT**	**AsAT**	**Alkaline phosphatase**
Group 1 (intact)	a = 1.21; σ^2 = 0.08; σ = 0.23; V = 67.3%; â = 2.47.	a = 1.71; σ^2 = 0.28; σ = 0.53; V = 30.76%; â = 0.43;	a = 40.7; σ^2 = 134.3; σ = 11.9; V = 28.47%; â = 7.93;	a = 180.93; σ^2 = 948.56; σ = 30.8; V = 17.02%; â = 20.09;	a = 96.9; σ^2 = 674.36; σ = 87.6; V = 44.49%; â = 62.31;
Group 2 (control)	a = 3.49; σ^2 = 4.72; σ = 2.17; V = 62.33%; â = 1.85;	a = 2.75; σ^2 = 6.06; σ = 2.46; V = 89.6%; â = 2.02;	a = 56.51; σ^2 = 602.77; σ = 24.55; V = 43.44%; â = 17.19;	a = 274.19; σ^2 = 10250.5; σ = 101.24; V = 36.93%; â = 81.66;	a = 254.81; σ^2 = 16565.89; σ = 128.71; V = 50.51%; â = 98.59;
Group 3 (**CV-131**)	a = 1.99; σ^2 = 3.91; σ = 1.98; V = 99.35%; â = 1.65;	a = 2.47; σ^2 = 3.67; σ = 1.92; V = 77.64%; â = 1.47;	a = 42.93; σ^2 = 132.36; σ = 11.50; V = 26.8%; â = 9.13;	a = 241.42; σ^2 = 12172.24; σ = 110.33; V = 45.7%; â = 90.89;	a = 101.51; σ^2 = 837.17; σ = 28.93; V = 28.5%; â = 19.69;
Group 4 (**Mar-014**)	a = 1.22; σ^2 = 0.52; σ = 0.72; V = 58.76%; â = 0.54;	a = 0.98; σ^2 = 0.25; σ = 0.50; V = 51.06%; â = 0.41;	a = 41.46; σ^2 = 236.05; σ = 15.36; V = 37.06%; â = 12.72;	a = 203.56; σ^2 = 1848.64; σ = 43.0; V = 21.12%; â = 27.13;	a = 90.99; σ^2 = 3835.60; σ = 61.93; V = 68.07%; â = 51.39;
Group 5 (**CV-150**)	a = 1.69; σ^2 = 1.34; σ = 1.16; V = 68.54%; â = 0.83;	a = 2.43; σ^2 = 2.22; σ = 1.49; V = 61.22%; â = 1.09;	a = 56.64; σ^2 = 625.48; σ = 25.01; V = 37.53%; â = 17.89;	a = 223.08; σ^2 = 14944.62; σ = 122.25; V = 54.8%; â = 93.70;	a = 68.42; σ^2 = 1266.68; σ = 35.59; V = 52.02%; â = 2.97;
Group 6 (**TD-0331**)	a = 1.13; σ^2 = 0.17; σ = 0.34; V = 30.23%; â = 0.26;	a = 1.57; σ^2 = 0.79; σ = 0.89; V = 56.77%; â = 0.75;	a = 47.67; σ^2 = 81.07; σ = 9.01; V = 18.89%; â = 6.57;	a = 245.63; σ^2 = 495.79; σ = 22.27; V = 9.06%; â = 15.92;	a = 55.08; σ^2 = 1749.90; σ = 41.83; V = 75.94%; â = 33.42;
Group 7 (**d02-123**)	a = 1.27; σ^2 = 0.46; σ = 0.68; V = 53.57%; â = 0.53;	a = 1.24; σ^2 = 134; σ = 1.16; V = 93.5%; â = 1.03;	a = 48.92; σ^2 = 129.78; σ = 11.40; V = 23.29%; â = 8.89;	a = 153.62; σ^2 = 1990.51; σ = 44.62; V = 29.04%; â = 33.92;	a = 95.8; σ^2 = 2812.41; σ = 53.03; V = 55.36%; â = 43.0;
Group 8 (thiotriazoline)	a = 1.58; σ^2 = 0.26; σ = 0.80; V = 51.27%; â = 0.43;	a = 1.51 σ^2 = 104; σ = 1.19; V = 73,8%; â = 1.07;	a = 58.92; σ^2 = 140.77; σ = 14.04; V = 43.94%; â = 4.92;	a = 213.69; σ^2 = 124.51; σ = 46.86; V = 59.04%; â = 32.92;	a = 115.7; σ^2 =1082.40; σ = 43.37; V = 50.64%; â = 55.0;

***Note*:** a – arithmetic mean; σ2 – dispersion; σ – standard deviation; V – coefficient of variation; â – mean linear deviation.

The index of total bilirubin in biochemical blood analysis of rats of the control group increased by 65.3% in comparison with the indices in the intact group. Direct bilirubin in them increased by 37.8%. ALT activity increased by 38.85%, AST – by 51.54%, and alkaline phosphatase – by 163% compared to the values in intact animals. This indicates the intensity of the pathological process and damage of hepatocytes.

In animals of the reference group, receiving thiotriazolin, comparing with the corresponding indicators determined by us in rats of the control group, the level of direct bilirubin was 45% lower, ALT activity had no significant differences, and AST activity was 22.06% lower. If we compare it with the corresponding indices determined by us in rats of the intact group, ALT exceeded by 44.76%, AST – by 18.11% of normal values, and alkaline phosphatase increased by 19.4%.

As can be seen from Table 2, in the experimental group with the code **Mag-014** rats that had received new derivatives of 1.4-dihydropyridine for 11 days, the indices of total bilirubin, aminotransferases and alkaline phosphatase had no significant differences with the intact group. The index of direct bilirubin was reduced by 42.7%. In the **TD-0331** group, the indices of total and direct bilirubin, as well as ALT have values close to normal, corresponding to the rats of the intact group. AST index increased by 35.7% and alkaline phosphatase index decreased by 43.1%.

Administration according to the experiment design of partially hydrogenated pyridine with laboratory code **CV-131** also showed its protective ability with respect to this organ. In comparison with the values of the control group, total bilirubin was 75.3% lower, direct bilirubin – 10.1% lower, and AST activity – 12% lower, while the values of alkaline phosphatase activity and ALT were within normal values.

Comparing the values of hepatic samples in the blood of rats receiving the derivative with code **CV-150**, there was a decrease in total bilirubin by 51.6% and in direct bilirubin – by 11.6%, AST activity decreased by 18.64% and alkaline phosphatase activity – by 272.4% compared to that of rats in the group without pharmacocorrection.

Application of cyanothioacetamide derivative with laboratory code **d02-123**, which had previously showed high anti-inflammatory and analgesic activity in experiments on white rats, promoted normalization of the investigated liver samples. The indices of total direct bilirubin, aminotransferases and alkaline phosphatase did not exceed normal values in comparison with those in the intact group.

Discussion

The results obtained during the experimental study indicate a pronounced cytolysis of hepatocytes under chronic exposure to paracetamol and alcohol. At the same time, the growth of alkaline phosphatase activity registered in rats of the control group indicates the presence of cholestasis and atrophic changes in the liver.

The effectiveness of pharmacological hepatoprotective action of new samples of 1,4-dihydropyridine and thiadiazine is substantiated by the levelling of adverse effect of hepatoxic poisons used in combination, leading to normalisation of indices of the investigated hepatic samples in biochemical blood analysis of laboratory animals.

In the studies we carried out over the last 5 years, it was shown that cyanothioacetamide derivatives are of great relevance and promise in terms of analgesic, anti-inflammatory, hypoglycaemic, hypolipidemic, as well as hepatoprotective and immunotropic properties.

Our in silico studies allowed us to identify putative biotargets for the leader compound with the code name d02-123 (5-cyano-N-(2,4-dichlorophenyl)-4-(2-furyl)-2-methyl-6-[(2-oxo-2-{[3(trifluoromethyl)phenyl]amino}ethyl)thio]-1,4-dihydropyridine-3-carboxamide).Among the most significant are GPR40 G protein-coupled receptors, mitochondrial aspartate/glutamate transporters, hepatocyte nuclear factor 4α (HNF4α), cholesterol ester transfer protein (CETP) and glucokinase.

The predicted effects of compound **d02-123** on GPR40 G-protein coupled receptors, hepatocyte nuclear factor 4α (HNF4α), cholesterol ester transfer protein (CETP), and glucokinase are associated with positive effects on carbohydrate and lipid metabolism, hypoglycaemic and hypolipidaemic properties.

In addition, the presumed affinity of d02-123 for Janus kinases, mast cell chymase, cyclooxygenase-2, δ- and κ-opioid receptors, as well as cannabinoid CB1 and prostanoid EP1 receptors, was revealed, which accounts for the possible analgesic and anti-inflammatory properties of the compound.

Conclusion

Thus, the most pronounced hepatoprotective properties according to the results of the conducted studies on the model of paracetamol-alcoholic liver damage were shown by the compound – derivative of 1.4-dihydropyridine with laboratory code **d02-123** ((5-cyano-N-(2,4-dichlorophenyl)-4-(2-furyl)-2-methyl-6-[(2-oxo-2-{[3-(trifluoromethyl)phenyl]amino}ethyl)thio-1,4-dihydropyridine-3-carboxamide)), daily administration of which at a dose of 2.5 mg/kg helped to prevent changes in liver test parameters in the biochemical blood analysis of animals. The obtained data illustrate the necessity of further study of new cyanothioacetamide derivatives with regard to their effect on metabolic processes.

Additional information

Conflict of interest

The authors declare that there is no conflict of interest.

Ethical statement

The studies were approved by the Bioethics Commission of St. Luke Lugansk State Medical University, minutes №6 of November 1, 2021.

Funding

The study was performed at St. Luke Luhansk State Medical University of the Ministry of Health of the Russian Federation. The work was carried out with the financial support of research work within the framework of the state assignment of the Ministry of Education and Science of the Russian Federation on the topic: 'New Heterocyclic Derivatives of Methylenactive Nitriles, Thioamides and Selenamides: Synthesis, Properties and Biological Activity' (code 'FREE-2023-0002'), and also with the financial support of research work within the framework of the state assignment of the Ministry of Health of the Russian Federation on the topic 'Search for New Highly Effective and Safe Medicines Among Previously Unknown Heterocyclic Cyanothioacetamide Derivatives of Domestic Production' (code 'ZUNP-2024-0002').

Data availability

All of the data that support the findings of this study are available in the main text.

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