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Original article

Reprint

Relationship between the results of in silico and in vivo studies of hypoglycemic, hypolypidemic and hepatoprotective properties of a new 1,4-dihydropyridine derivative

Elena S. Ketova [1] ✉, Anna V. Miazina [2], Igor V. Bibik [1], Elena Yu. Bibik [1, 3], Sergey G. Krivokolysko [3, 4]

✉ ketova_elena@mail.ru

[1]Belgorod State National Research University, Belgorod, Russia
[2]V.I. Vernadsky Crimean Federal University, Simferopol, Russia
[3]St. Luke Lugansk State Medical University, Lugansk, Russia
[4]Dahl Lugansk State University, Lugansk, Russia

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Abstract:
Objective: to identify the relationship between the results of in silico and in vivo studies of hypoglycemic, hypolipidemic, and hepatoprotective properties expressed by a new 1,4-dihydropyridine derivative with the laboratory code AZ-383.
Material and Methods. Virtual biological screening of the AZ-383 compound was conducted using SwissTargetPrediction online tool. The identified biotargets were promising for pharmacological correction of multiple metabolic disorders, which was confirmed in an in vivo experiment conducted on male Wistar rats: the levels of glucose, total cholesterol, triglycerides, alanine aminotransferase, aspartate aminotransferase, and total bilirubin in the blood were examined; the microarchitecture of the rat liver was assessed after pharmacological correction (using the AZ-383 compound) of the modeled metabolic disorders.
Results. The presence of hypoglycemic, hypolipidemic and hepatoprotective properties in the compound AZ-383, along with its favorable effect on body weight, was revealed. The glucose level reached values of 7.9±0.4 mmol/L. The body weight of rats after the use of AZ-383 was 378±12 g. Under the influence of AZ-383, we observed an increase in the number of hepatocytes by 17.8%, a reduction in the size of hepatocytes by 7%, and a decrease in the area of the cytoplasm and nuclei of hepatocytes by 5.2% and 18.7%, respectively, vs. the control group of animals.
Conclusion. Our in vivo experimental study confirmed the presence of hypoglycemic, hypolipidemic and hepatoprotective properties in the AZ-383 compound, which corresponds to the biotargets determined in silico for this 1,4-dihydropyridine derivative.

Keywords: cyanothioacetamide derivatives, 1,4-dihydropyridine derivative, nutritional load, steroid-induced diabetes, pharmacological correction of metabolic disorders

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Introduction

At present, alimentary obesity, hyperglycemia, dyslipidemia, a cluster of interconnected factors that constitutes metabolic syndrome, and the accompanying hepatobiliary disease are becoming especially relevant health care issues [1-5]. This is caused by the increasing prevalence of these diseases, which can be associated with changes in a lifestyle, lack of physical activity, high-fat and high-calorie diet of contemporary people, as well as other important factors, such as drug-induced metabolic disorders and others [2, 4, 6-8]. Along with a reduction in the quality and duration of life in patients with metabolic disorders, it is worth considering the factor of increasing economic costs in health care associated with the treatment of obesity, type 2 diabetes mellitus (DM2), lipid metabolism disorders, and liver diseases [3].

Currently, many groups of pharmaceutical drugs affect human metabolism and are used for pharmacological correction of the specified nosologies [1, 2, 9]. Despite this, scientists continue to search for new drugs, as well as points of their application, in order to pursue a comprehensive approach to the treatment of metabolic syndrome. It should be noted that existing hypoglycemic and hypolipidemic drugs, along with agents for the treatment of obesity, trigger various adverse reactions and have a limited effect on the complex pathogenesis of diseases [1, 9]. In connection with the above, the search for (and preclinical study of) novel means of complex pharmacological correction of metabolic disorders, including alimentary obesity, hyperglycemia,

dyslipidemia and pathology of the hepatobiliary system, is very relevant.

Cyanothioacetamide is a multifunctional reagent that is actively used in synthetic organic chemistry [10]. Based on the scientific data of individual researchers, it can be concluded that heterocyclic derivatives of α-cyanothioacetamide are promising for the search for new medicines with hypoglycemic, hypolipidemic and hepatoprotective activity, as well as the ability to reduce body weight [11, 12]. Of particular interest are novel derivatives of α-cyanothioacetamide synthesized by us at the ChemEx Research Laboratory of Dahl Lugansk State University and then subjected to virtual biological screening to search for potential targets to predict their pharmacological activity.

Objective – to identify the relationship between the results of in silico and in vivo studies of hypoglycemic, hypolipidemic, and hepatoprotective properties expressed by a new 1,4-dihydropyridine derivative with the laboratory code AZ-383 (2-methyl-N-(2-methylphenyl)-4-(2-furyl)-5-cyano-6-({2-[(4-ethoxyphenyl)amino]-2-oxoethyl}thio)-1,4-dihydropyridine-3-carboxamide).

Materials and Methods

Virtual biological screening of compounds on the basis of new cyanothioacetamide derivatives synthesized at the ChemEx research laboratory of Dahl Luhansk State University was carried out using the SwissTargetPrediction online tool developed by scientists from the Swiss Institute of Bioinformatics.

For a number of new heterocyclic compounds, presumed biotargets that may be useful for pharmacological correction of disorders of carbohydrate and lipid metabolism, as well as in the spectrum of hepatoprotective activity, were identified in silico.

Based on the results of our study, taking into account the effect on certain biotargets, we selected a compound from among new 1,4-dihydropyridine derivatives with the laboratory code AZ-383, which presumably has hypoglycemic, hypolipidemic and hepatoprotective properties, along with a favorable effect on body weight. The structural formula of this compound is shown in *Figure 1*.

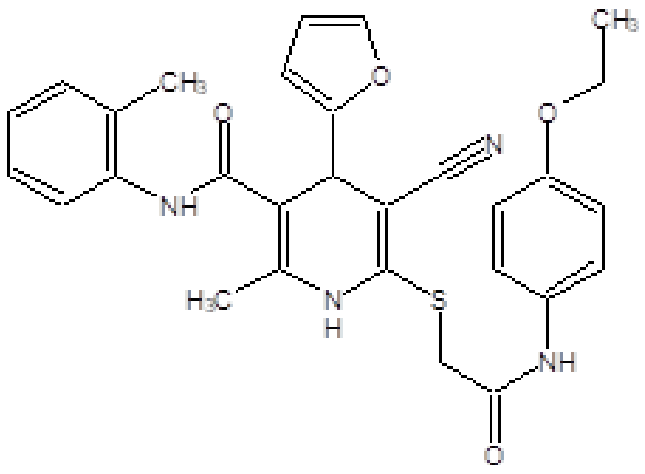

Figure 1. Chemical formula of the compound with laboratory code AZ-383

We conducted the experimental in vivo study in the Research Institute of Experimental Biology and Medicine at Voronezh State Medical University of the Russian Federation Ministry of Healthcare of the (RIEBM VSMU) on 40 mature male Wistar rats. The animals were randomly distributed among an intact group (n=8) and a control group (n=8). In addition to their daily diet, the animals received an excess amount of palm oil in the amount of 30 g/kg of their body weight during 8 weeks, followed by dexamethasone in the amount of 0.125 mg/kg of their body weight intraperitoneally for 13 days. All rats in the comparison and experimental groups were given a high-fat diet and subsequent glucocorticoid load to simulate metabolic disorders. The pharmacological correction period lasted 14 days. In the experimental group (n=8), the animals were administered the AZ-383 compound (1 mg/kg) intragastrically. The animals in comparison groups I (n=8) and II (n=8) received metformin in the amount of 300 mg/kg of animal body weight and 8 mg/kg of vildagliptin, respectively.

At all stages of the study, we selected sexually mature male Wistar rats without visual signs of disease and anatomical abnormalities, which had undergone the necessary quarantine and adaptation period at RIEBM VSMU.

All manipulations with laboratory animals were carried out in accordance with the Technical Standard of the Russian Federation (GOST) No. 33216-2014, Guidelines for the Maintenance and Care of Laboratory Animals. Rules for the Maintenance and Care of Laboratory Rodents and Rabbits; GOST 33215-2014, Guidelines for the Maintenance and Care of Laboratory Animals. Rules for the Equipment of Facilities and Organization of Procedures; and GOST 33044-2014, Principles of Good Laboratory Practice. The experimental design was approved at a meeting of the VSMU Ethics Committee.

In the course of the experiment, we weighed animals on a weekly basis. The obtained information on the dynamics of body weight was compared between the groups and subsequently analyzed.

Hypoglycemic, hypolipidemic and hepatoprotective properties were assessed when animals were withdrawn from the experiment. Blood glucose, total cholesterol (TC), and triglyceride (TG) levels were measured via the enzymatic colorimetric method (Vital Diagnostics, Russia). The following biomarkers for liver function were assessed: alanine aminotransferase (ALT) and aspartate aminotransferase (AST) by the kinetic method; and total bilirubin (TB) by the Jendrassik-Grof method.

After the rats were withdrawn from the experiment, liver micropreparations were subjected to standard sample preparation methods, 4-μm-thick sections were stained with eosin and Gill's hematoxylin, and then examined using a ZEISS Axio Imager.A2 microscope. The mean number of hepatocytes per field of view, mean size of hepatocytes, and nuclear-cytoplasmic ratio were assessed when examining at least 40 fields of view.

The obtained data were checked for normality of their distribution using the Shapiro-Wilk test. Since all data followed a normal distribution, they were processed using the methods of parametric statistics. The Student's t-test was employed to assess the statistical significance of differences between each experimental group and intact animals.

Results

The obtained data of virtual biological screening identified the following putative biotargets for the compound with the laboratory code AZ-383 from a series of 1,4-dihydropyridine derivatives: types 1 and 2 orexin receptors; bile acid receptors associated with G protein 1; glycogen synthase kinase 3 (GSK-3); nicotinamide phosphoribosyltransferase (NAMPT); adenosine receptors A1, A2a and A2b, which are of interest regarding the regulation of carbohydrate and lipid metabolism, and their ability to perform hepatoprotective activity.

Our in-silico results illustrate the prospects of compound AZ-383 regarding its favorable effect on body weight, its hypoglycemic, hypolipidemic and hepatoprotective activities, and regulation of metabolic disorders.

These findings are fully consistent with the results of our in vivo experiment.

Modeled metabolic disorders by successive nutritional and dexamethasone loads led to the development of alimentary obesity, hyperglycemia, dyslipidemia, increased content of liver blood markers, and disruption of the liver microarchitecture.

Long-term intake of excess palm oil in addition to the daily diet led to an increase in the body weight of Wistar rats all the way up to the development of class 1 and class 2 obesity. E.g., by the end of week 8 of observation, the body weight of animals consuming a high-fat diet was 20% higher than the body weight of rats in the intact group. Later on, weight reduction was observed under the effect of dexamethasone. However, the weight of control group rats still exceeded the weight of intact animals (386.8±12 g vs. 376.5±12 g). After the administration of glucocorticoids was stopped, we observed a gradual increase in body weight of animals.

The disorders modeled by nutritional and dexamethasone loads were reflected in the biochemical parameters of the blood in the form of changes in carbohydrate and lipid metabolism, as well as hepatotoxic effects. ALT and AST levels increased by 77% and 31%, respectively. The levels of TB, glucose, TC and TG increased by 118%, 45%, 54% and 171 vs. the intact group (*Table*).

When studying microscopic preparations of the rat liver in the control group using light microscopy, we detected pronounced structural transformations of the parenchyma in this detoxification organ. The liver tissue was an almost homogeneous mass; among the visualized hepatocytes, it was possible to distinguish areas of tissue detritus representing accumulations of glycogen and nuclear residues. In all samples, the phenomena of parenchymatous dysproteinosis, fatty degeneration and necrosis were recorded (*Figure 2*).

A comparative analysis of the obtained morphometric data showed that the nutritional and dexamethasone loads in the control group rats led to an increase of 6.7% in the mean number of hepatocytes in the field of view (43.68±0.98) vs. the intact group (40.92±1.04). Besides that, the simulated metabolic disorders led to an increase of 11.3% in the mean size of hepatocytes (90.79±0.48) relative to intact animals (81.59±0.59), and we also observed a change in the nuclear-cytoplasmic ratio, which increased by 30% (0.17±0.004) vs. the intact group (0.13±0.004).

Table. Blood biochemistry parameters in experimental animals of each group according to the experimental design, M±σ

Parameter	ALT, IU/L	AST, IU/L	TB, μmol/L	Glucose, mmol/L	TC, mmol/L	TG, mmol/L
Intact group	59.53±8.2	146.51±16.84	10.88±1.0	7.9±0.7	1.3±0.2	0.7±0.3
Control group	105.29±9.9*	192.65±9.0*	23.72±3.5*	11.44±1.1*	2.0±0.2*	1.9±0.4*
Comparison group I (metformin)	57.49±6.6	181.67±10.90*	10.70±1.1	7.3±0.5	1.6±0.2	0.9±0.2
Comparison group II (vildagliptin)	53.23±6.4	156.23±8.5	11.93±1.5	7.9±0.4	1.6±0.2	0.6±0.2
Experimental group (AZ-383)	56.78±6.6	155.87±14.53	11.92±0.7	7.9±0.4	1.4±0.1	0.7±0.2

*$p<0.05$ compared to intact group; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TB, total bilirubin; TC, total cholesterol; TG, triglycerides.

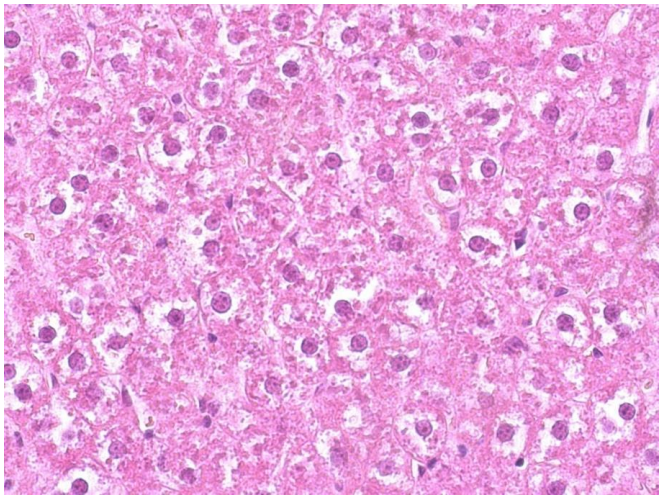

Figure 2. Liver of control rat (×400; Gill's hematoxylin and eosin staining)

In the experimental group of animals, the use of a new AZ-383 compound from a series of 1,4-dihydropyridine derivatives for pharmacological correction of simulated metabolic disorders has led to a more gradual and significantly less intense weight gain after the end of dexamethasone administration. E.g., the body weight of rats after intragastric administration of AZ-383 for 14 days was 378±12 g, while under the influence of metformin in the comparison group 1, it was 419±14 g and in the comparison group 2 under the influence of vildagliptin, it amounted to 416±13 g.

When analyzing the data presented in Table, it is obvious that the AZ-383 compound has hypoglycemic and hypolipidemic properties, along with the ability to restore liver markers after their increase during the period of modeling high-fat and dexamethasone loads. Also, AZ-383 exhibits a hypoglycemic activity equal in strength to vildagliptin. However, this compound has more pronounced hypolipidemic and hepatoprotective properties than metformin and vildagliptin, which is an important aspect of comprehensive correction of metabolic disorders, given the comorbidity inherent in patients.

In the rat liver parenchyma sections of the experimental group, where animals received the AZ-383 compound for pharmacological management, liver trabeculae are clearly visible, and the hepatocytes are polygonal in shape with a pronounced cytoplasmic membrane. Inside the cytoplasm, there is a large number of glycogen inclusions. The nuclei are round or oval in shape with one or two nucleoli closer to the center of the cells, with a well-stained nuclear membrane (*Figure 3*).

Under the effect of AZ-383, a statistically significant increase in the number of hepatocytes by 17.8% was noted relative to the control group of animals. Under the influence of metformin or vildagliptin, such increase amounted to 4.6% or 12%, respectively. The size of hepatocytes under the impact of metformin, vildagliptin, and the AZ-383 compound statistically significantly diminished by 4, 4, and 7%, respectively, relative to the control group of animals. The most significant decrease in the area of the cytoplasm and nuclei of hepatocytes was achieved when using the compound AZ-383. It amounted to 5.2% and 18.7%, respectively, vs. the liver parenchyma of rats in the control group. Pharmacological management using metformin has led to the nuclear-cytoplasmic ratio reduction by 11.8%. Administration of the compound with the laboratory code AZ-383 and vildagliptin was accompanied by a decrease in the nuclear-cytoplasmic ratio by 17.6% vs. control rats.

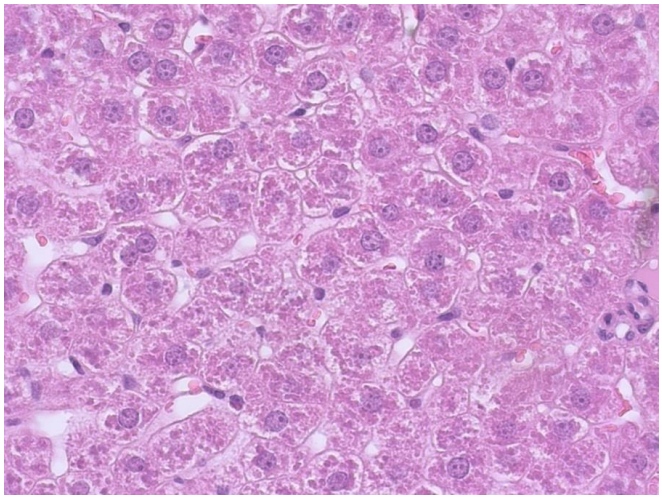

Figure 3. Rat liver from the experimental group that received a new derivative of cyanothioacetamide coded AZ-383 (×400; Gill's hematoxylin and eosin staining)

Discussion

The results of our study support the point of view expressed by many authors. Considering the biotargets of the AZ-383 compound identified in silico, we conclude that they are important links in the pathogenesis of metabolic disorders.

For instance, according to the researchers, orexin A is one of the regulators of eating behavior and energy balance [13]. This peptide implements its effects via types 1 and 2 orexin receptors of. The latter are involved in the regulation of carbohydrate metabolism and appetite. The level of expression of type 1 orexin receptor gene and the content of immunopositive orexin A in hypothalamic neurons is regulated depending on the duration of high-fat/high-calorie nutrition and the severity of metabolic disorders. This can be considered in terms of a compensatory response aimed at reducing the severity of lipid metabolism disorder and, consequently, carbohydrate metabolism disorder [13, 14]. Thus, the orexin system is an important target for the correction and prevention of obesity development, as well as the associated insulin resistance as one of the key components of the DM2 pathogenesis.

Biosynthesis of bile acids is one of the important pathways for cholesterol excretion. Bile acids regulate the expression of genes involved in the metabolism of primary bile acids, cholesterol and TG in hepatocytes and plasma [15]. In DM2 and concomitant insulin resistance of peripheral tissues, the function of bile acids is impaired, which leads to a reduction in their absorption and an increase in fatty infiltration of the liver, accumulation of TG and low-density lipoproteins. Therefore, disorders of carbohydrate and lipid metabolism are closely related to each other through the functioning of bile acids, as well as their receptors. Stimulation of bile acid receptors associated with G protein 1 triggers insulin production by pancreatic β-cells, helps reducing insulin resistance and body weight, and normalizes lipid metabolism in the blood by lowering TC levels [15].

We should also emphasize the role of such an important enzyme as GSK-3. One of its functions is the regulation of glycogen synthesis and glucose metabolism [16]. Inhibition of this enzyme results in an increase of glycogen synthesis and causes proliferation of pancreatic β-cells. Insulin inactivates GSK-3 by phosphorylation of specific serine residues. In addition, GSK-3 is an important protein that regulates neuronal function by participating in neurotransmitter metabolism, neurogenesis, and synaptic plasticity. GSK-3 has recently become the subject of research, as it is involved in a number of diseases, including DM2, obesity, Alzheimer's disease, inflammation, cancer and bipolar disorder [16].

The development of various diseases and conditions, such as obesity, insulin resistance and diabetes, atherosclerosis and arterial hypertension, is primarily triggered by low-grade systemic inflammation. Afterwards, endothelial dysfunction and dyslipidemia are formed, which support and enhance inflammation. NAMPT catalyzes stage I in the biosynthesis of nicotinamide adenine dinucleotide (NAD) from nicotinamide. Proinflammatory molecules affect NAD metabolism, thereby causing a sharp increase in the expression of the enzyme involved in limiting the synthesis of NAD from nicotinamide. Considering the effect on carbohydrate metabolism, it should be noted that NAMPT possesses antidiabetic activity. NAMPT is suppressed in

obesity due to an increase in the level of microRNA miR-34a, which leads to a reduction in the level of NAD+ and the activity of sirtuin 1. The latter is involved in the development of insulin resistance [17].

Adenosine receptors are broadly represented in the human body, performing various functions including control of the cardiovascular and central nervous systems, intraocular pressure, blood circulation, kidney function, and inflammatory response in the blood. Stimulation of adenosine receptors (A1, A2A, A2b) increases the level of antioxidant protection, promotes cytoprotective effect on various organs and tissues, including the liver, thereby triggering hepatoprotective properties [18, 19].

Our data obtained during the in vivo experiment match the results of virtual biological screening, illustrating the presence of likely hypoglycemic, hypolipidemic and hepatoprotective properties of AZ-383 and its positive effect on body weight.

Long-term consumption of palm oil in addition to the standard daily diet and subsequent intraperitoneal administration of dexamethasone has led to the development of metabolic disorders manifested by excess body weight, obesity, elevated blood glucose levels, increased blood content of liver markers (ALT, AST and TB), dyslipidemia, along with structural disorganization of liver tissue at the microscopic level. Simulated metabolic disorders caused an increase in both the number and size of hepatocytes. These changes are consistent with the data of multiple authors on the development of morphological changes in the liver, corresponding to hepatosis and diabetes. Pronounced disorders in the structure of this detoxifying organ with a simultaneous increase in the number and size of hepatocytes can be regarded as a compensatory response triggered by damaging exotoxic factors (nutritional load by excess palm oil and the introduction of glucocorticoids).

Pharmacological correction with the AZ-383 compound resulted in normalization of glycemia to the level recorded in intact animals. It is worth noting that hypoglycemic properties of the studied compound were as strong as of vildagliptin (a dipeptidyl peptidase-4 inhibitor). In our experiment, weight gain was observed in experimental Wistar rats after discontinuation of dexamethasone administration. However, the rates of body weight increase were different in the animals of the comparison groups and in the experimental group. E.g., intragastric administration of AZ-383 resulted in less intense weight gain, which was confirmed by a 10% difference between the body weight of rats in the experimental group and animals taking metformin or vildagliptin. This illustrates the favorable effect of AZ-383 on lipid metabolism, in particular, the weight of rats. Besides that, the levels of blood lipids (TC and TG) under the influence of the new compound were statistically lower than in animals of the comparison groups. Studying its effect on the liver as the main organ of detoxification, actively involved in lipid and carbohydrate metabolism, we would like to point out that this compound has pronounced hepatoprotective properties. Under its influence, a statistically significant reduction in the content of liver markers was noted, along with normalization of the liver microarchitecture, which was confirmed by an increase in the number of hepatocytes. We believe that this was caused by proliferative activity in response to the damaging effect of simulated nutritional and dexamethasone loads.

Comparing in silico data with in vivo data, we established that the hypoglycemic, hypolipidemic and hepatoprotective properties of AZ-383 compound, as well as its favorable effect on the body weight, are due to its influence on several biotargets involved in the pathogenesis of metabolic disorders. This highlights the potential for further study of new 1,4-dihydropyridine derivatives regarding their hepatoprotective properties and their tentative use for pharmacological correction of carbohydrate and lipid metabolism disorders.

Conclusion

We have established for the first time in silico the biotargets of a new 1,4-dihydropyridine derivative with the laboratory code AZ-383. These biotargets play a key role in the pathogenesis of carbohydrate and lipid disorders, and also have an effect on the liver as the main organ of detoxification involved in the development of metabolic disorders. In an in vivo experiment conducted on Wistar rats, we confirmed the hypoglycemic, hypolipidemic and hepatoprotective properties of the AZ-383 compound, along with its favorable effect on body weight. Our results suggested the need for further study of the new 1,4-dihydropyridine derivative with the code AZ-383, its role in pharmacological management of metabolic disorders, and its other potential useful properties.

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Conflict of interest: The authors declare no conflicts of interest.

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Authors:
Elena S. Ketova – PhD, Department of Pharmacology and Clinical Pharmacology, https://orcid.org/0000-0002-4595-8103;
Anna V. Miazina – PhD, Instructor, Department of Normal Anatomy, https://orcid.org/0000-0001-5736-2385;
Igor V. Bibik – PhD, Department of Pharmacology and Clinical Pharmacology, https://orcid.org/0000-0003-4053-1431;
Elena Yu. Bibik– DSc, Professor, Chair of the Department of Fundamental and Clinical Pharmacology, https://orcid.org/0000-0001-7470-608X;
Sergey G. Krivokolysko – DSc, Scientific Director of the ChemEx Research Laboratory, https://orcid.org/0000-0001-9879-9217.