PHARMACOLOGY AND PHARMACY

STUDY OF ANTI-INFLAMMATORY AND ANTINOCICEPTIVE PROPERTIES OF NEW DERIVATIVES OF CONDENSED 3-AMINOTHIENO[2,3-b]PYRIDINES AND 1,4-DIHYDROPYRIDINES

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ABSTRACT

Background. *α-cyanothioacetamide derivatives are promising targets for the search for effective and safe antinociceptive agents with antipyretic and antiexudative activity.*

The aim. *To conduct in vivo experimental study of anti-inflammatory and analgesic effects of new thienopyridines and 1,4-dihydropyridines derivatives.*

Materials and methods. *The synthesized cyanothioacetamide derivatives were subjected to virtual bioscreening using Swiss Target Prediction online service. 140 laboratory rats were randomly distributed into intact and control (dextran edema) groups, reference groups (acetylsalicylic acid and nimesulide) and ten experimental groups for the investigated derivatives of thieno[2,3-b]pyridine and 1,4-dihydropyridine. The anti-inflammatory activity of the compounds at a dose of 5 mg/kg was evaluated by modeling acute dextran edema of rat paw. Determination of analgesic activity was carried out in the hotplate analgesic assay on 130 rats in comparison with sodium metamizole.*

Results. *1,4-dihydropyridines AZ331 and AZ420, as well as thienopyridine derivative AZ023 were determined to have strong anti-inflammatory activity (2.5 times more effective than nimesulide and 2.2 times more effective than acetylsalicylic acid). Compounds AZ023, AZ331 and AZ383 showed pronounced analgesic activity. The time of stay on the heated plate for rats of experimental groups that were fed with AZ331 and AZ383 for prophylactic purpose was respectively 9.56 and 9.93 times more than the same index in the reference group. The animals receiving AZ023 were characterized by an increase in the latent reaction time up to 241.2 seconds, which is 14.53 times higher than that in the rats received sodium metamizole.*

Conclusion. *New thienopyridine and 1,4-dihydropyridine derivatives with high anti-inflammatory and analgesic activity were synthesized and studied; they were recognized as promising targets for further preclinical studies.*

Key words: *condensed thienopyridines, 1,4-dihydropyridines, antiexudative properties, analgesic activity, anti-inflammatory properties, dextran edema*

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ИССЛЕДОВАНИЕ ПРОТИВОВОСПАЛИТЕЛЬНЫХ И АНТИНОЦИЦЕПТИВНЫХ СВОЙСТВ НОВЫХ ПРОИЗВОДНЫХ КОНДЕНСИРОВАННЫХ 3-АМИНОТИЕНО[2,3-b]ПИРИДИНОВ И 1,4-ДИГИДРОПИРИДИНОВ

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РЕЗЮМЕ

Обоснование. *Перспективными объектами для поиска эффективных и безопасных антиноцицептивных средств с жаропонижающей и антиэкссудативной активностью являются производные α-цианотиоацетамида. Цель исследования. Изучение противовоспалительной и болеутоляющей активности новых производных тиенопиридина и 1,4-дигидропиридина в эксперименте in vivo.*

Методы. *Синтезированные производные цианотиоацетамида подвергались виртуальному биоскринингу с использованием программного сервиса Swiss Target Prediction. 140 лабораторных крыс рандомно распределялись на интактную и контрольную («декстрановый отёк») группы, референтные группы (ацетилсалициловая кислота и нимесулид) и на десять опытных групп по исследуемым производным тиено[2,3-b]пиридина и 1,4-дигидропиридина. Противовоспалительная активность соединений в дозе 5 мг/кг оценивалась при моделировании острого «декстранового отёка» лапы крыс. Определение анальгетической активности проводилось в тесте горячей пластины на 130 крысах в сравнении с метамизолом натрия.*

Результаты. *Установлено, что 1,4-дигидропиридины AZ331 и AZ420, а также производное тиенопиридина AZ023 обладают отчётливо выраженной противовоспалительной активностью (в 2,5 раза эффективнее нимесулида и в 2,2 раза – ацетилсалициловой кислоты).*

Отчётливо выраженную анальгетическую активность проявили соединения AZ023, AZ331 и AZ383. Время пребывания на разогретой пластине крыс экспериментальных групп, получавших с профилактической целью AZ331 и AZ383 соответственно в 9,56 и 9,93 раза больше аналогичного показателя в референтной группе. Животные, получавшие AZ023, характеризовались увеличением латентного времени реакции до 241,2 секунды, что выше такового в 14,53 раза у крыс, которым вводили метамизол натрия.

Заключение. *Синтезированы и исследованы новые производные тиенопиридина и 1,4-дигидропиридина с установленной высокой противовоспалительной и болеутоляющей активностью, перспективные для дальнейших доклинических исследований.*

Ключевые слова: *конденсированные тиенопиридины, 1,4-дигидропиридины, антиэкссудативные свойства, анальгетическая активность, противовоспалительные свойства, декстрановый отёк*

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OBJECTIVES

The problem of the effectiveness and safety of the use of non-steroidal anti-inflammatory drugs (NSAIDs) in clinical practice is very relevant today. Statistical studies of the last decade indicate that on all continents more than 30 million people take NSAIDs constantly to eliminate the manifestations of pain, fever and inflammatory syndromes. About 300 million patients use this group of medicines periodically. Moreover, up to 200 million people of them purchase drugs without a prescription [1–3].

According to the results of the analysis of almost 4,000 spontaneous reports received by Federal Service for Surveillance in Healthcare of Russia (Roszdravnadzor) for the period 2008–2017, to record information about adverse reactions that occurred when using NSAIDs, it is reported that the most common reactions were registered to acetylsalicylic acid, diclofenac, ibuprofen and ketorolac. Disorders of the immune system, skin, subcutaneous tissues and digestive tract were predominant in the list of 6,500 reports. Such reactions to angioedema, urticaria (hives), erosive gastritis, skin rash and increased blood pressure are also characterized by a high frequency [4]. It is important to note that not in all patients the use of NSAIDs is accompanied by the desired relief of pain and elimination of signs of swelling of inflammatory genesis in diseases of various etiologies [5].

The low safety profile of NSAIDs and antipyretic analgesics common in clinical practice, as well as an extensive list of contraindications to their use, emphasize the importance of a targeted search for new highly effective and safe medicines. In this regard, the search for newly synthesized effective and safe painkillers and anti-inflammatory medicine currently remains relevant [6–9].

In the last decade, new organic compounds from a number of cyanothioacetamide derivatives have been of particular interest to scientists of chemical, biological, pharmaceutical and medical profiles, since cyanothioacetamide is an easily accessible and multifunctional reagent with several nucleophilic and electrophilic centers. Cyanothioacetamide easily reacts by condensation and cyclization with a wide range of reagents. This circumstance causes a significant variety of possible products of such reactions – sulfur- and nitrogen-containing heterocyclic compounds, which in many cases are structural fragments of natural molecules; a large number of biologically active compounds have been found among them [10–12].

Some α-cyanothioacetamide derivatives are promising targets for the search for effective and safe antinociceptive agents with antipyretic and antiexudative activity [13–18].

An important feature of cyanothioacetamide derivatives is the results of a study of their acute oral toxicity *in vivo*, indicating their low toxicity (toxicity classes 4–5) [19].

At the preparatory stage, before designing an experiment to determine samples of heterocyclic compounds, the most interesting in terms of their ability to bind to probable biotargets for the pharmacocorrection of pain, inflammatory or febrile syndromes, a virtual bioscreening of 340 new cyanothioacetamide derivatives synthesized by us in the ChemEx Research Laboratory of Lugansk State University named after Vladimir Dahl was carried out. At the same time, the following information resources were used: Online SMILES Translator and Structure File Generator of the U.S. National Cancer Institute, OPSIN: Open Parser for Systematic IUPAC nomenclature of the University of Cambridge, Center for Molecular Informatics [20, 21].

As a result, ten samples of new heterocyclic compounds containing 3-aminothieno[2,3-b]pyridine and 1,4-dihydropyridine fragments were selected, potentially capable of interacting with receptors and enzymes involved in the functioning of the antinociceptive system. These are samples with laboratory codes: AZ023, AZ169, AZ213, AZ257, AZ331, AZ420, AZ383, AZ729, AU04271 and AU04288. The structure and chemical formulas of these heterocyclic compounds are shown in Figure 1.

According to the results of virtual bioscreening, the biotargets for these samples are arachidonate-5-lipoxygenase, cyclooxygenase-2, phospholipase *A2*, phosphodiesterase, prostanoid, somatostatin, adenosine and cannabinoid receptors. Having planned a series of pharmacological studies in the in *vivo* experiments to study their analgesic and anti-inflammatory effects, the test of «dextran edema» of rat paw was selected among the recommended various classical pharmacological tests.

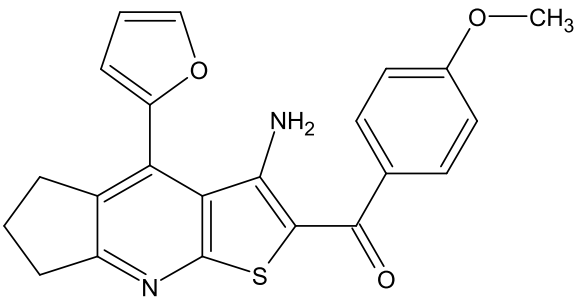
THE AIM OF THE STUDY

The study of anti-inflammatory and antinociceptive properties in *in vivo* experiments of new derivatives of 3-aminothieno[2,3-b]pyridine and 1,4-dihydropyridine in an experiment.

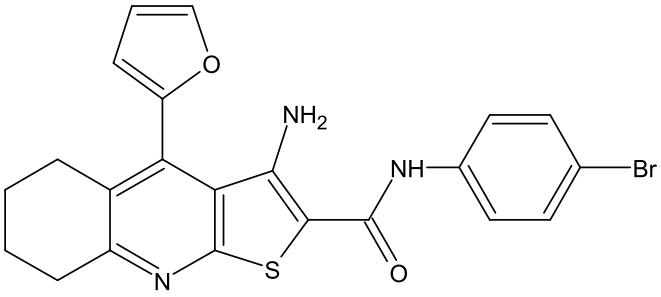
METHODS

The experiment was carried out on 140 white mongrel male rats weighing 250–280 g, obtained from the vivarium of the Lugansk State Medical University named after St. Luke in the autumn-winter period in the laboratory of the Department of Fundamental and Clinical Pharmacology. Laboratory animals were randomly (using the "envelope" method) divided into groups consisting of 10 rats.

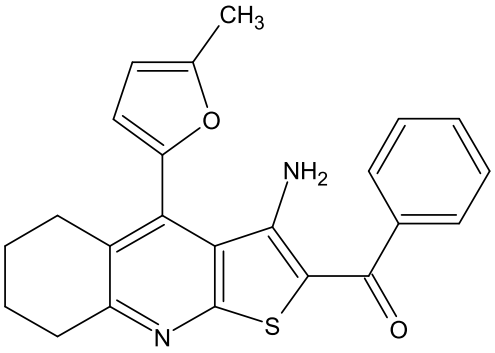
The animals were divided into intact, control (rats injected with 2 ml of 0.9 % sodium chloride solution intragastrically before the modelling process), two reference groups (receiving acetylsalicylic acid from Uralbiopharm OJSC at a dose of 50 mg/kg and nimesulide from Berezovsky Pharmaceutical Plant CJSC at a dose of 5 mg/kg) and 10 experimental groups according to the number of new derivatives of condensed



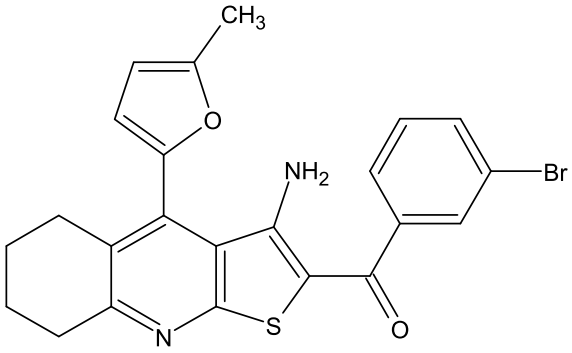
AU04288
[3-amino-4-(2-furyl)-6,7-dihydro-5*H*-cyclopenta[*b*]thieno[3,2-*e*]pyridin-2-yl](4-methoxyphenyl)methanone



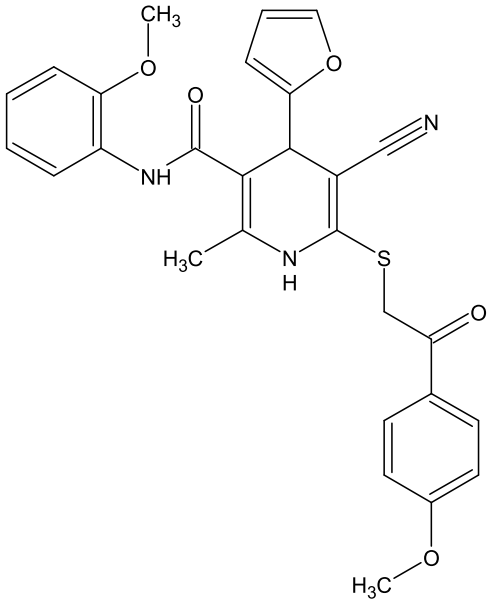
AU04272
3-amino-*N*-(4-bromophenyl)-4-(2-furyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinoline-2-carboxamide



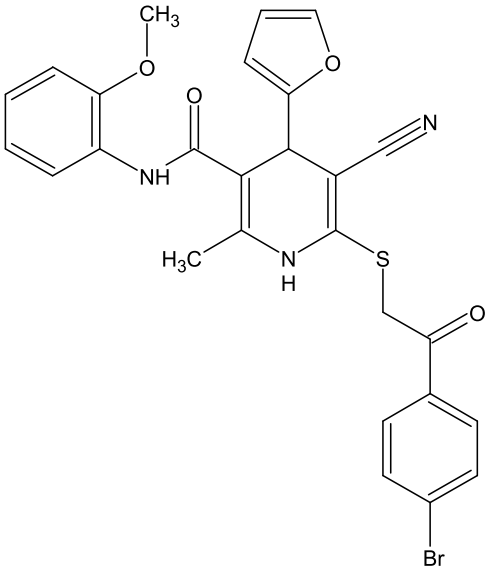
AZ023
[3-amino-4-(5-methyl-2-furyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-2-yl](phenyl)methanone



AZ729
[3-amino-4-(5-methyl-2-furyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-2-yl](3-bromophenyl)methanone

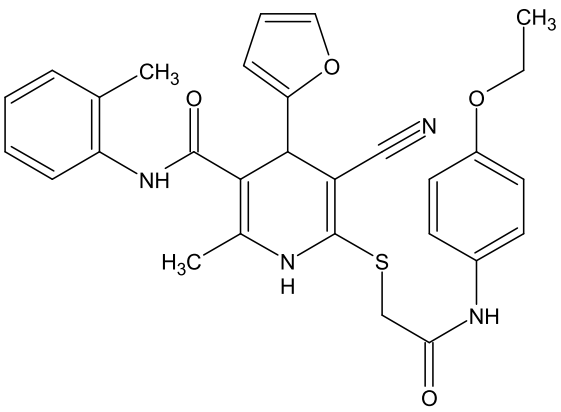


AZ331
5-cyano-4-(2-furyl)-*N*-(2-methoxyphenyl)-6-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-2-methyl-1,4-dihydropyridine-3-carboxamide

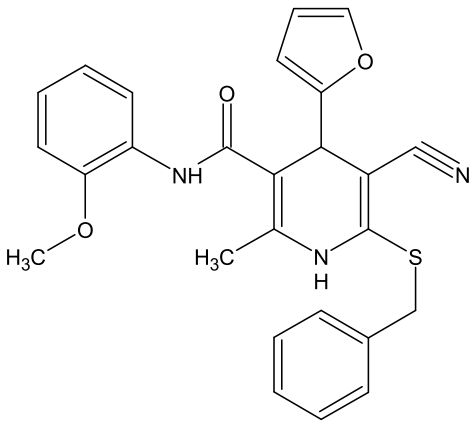


AZ257
6-{[2-(4-bromophenyl)-2-oxoethyl]thio}-5-cyano-4-(2-furyl)-*N*-(2-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxamide

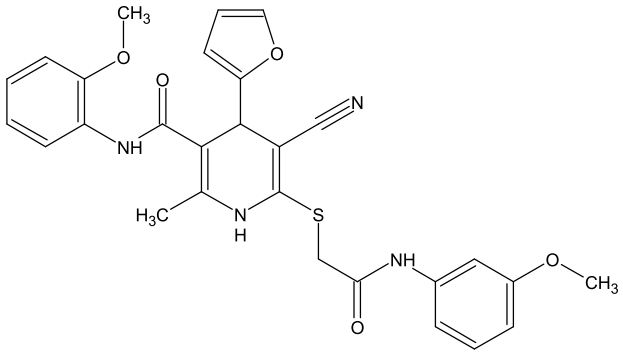
FIG. 1.
Structural formulas and names according to the IUPAC nomenclature for the studied 3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridines



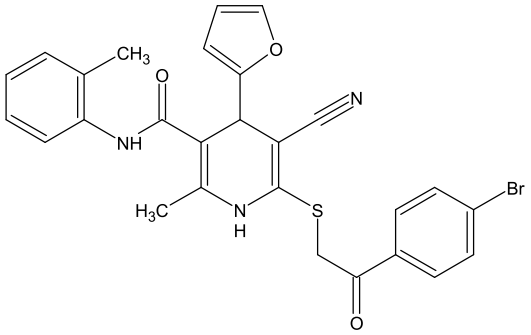
AZ383
5-cyano-6-({2-[(4-ethoxyphenyl)amino]-2-oxoethyl}thio)-4-(2-furyl)-2-methyl-*N*-(2-methylphenyl)-1,4-dihydropyridine-3-carboxamide



AZ169
6-(benzylthio)-5-cyano-4-(2-furyl)-*N*-(2-methoxyphenyl)-2-methyl-1,4-dihydropyridine-3-carboxamide



AZ420
5-cyano-4-(2-furyl)-*N*-(2-methoxyphenyl)-6-({2-[(3-methoxyphenyl)amino]-2-oxoethyl}thio)-2-methyl-1,4-dihydropyridine-3-carboxamide



AZ213
6-{[2-(4-bromophenyl)-2-oxoethyl]thio}-5-cyano-4-(2-furyl)-2-methyl-*N*-(2-methylphenyl)-1,4-dihydropyridine-3-carboxamide

FIG. 1. (contined)
Structural formulas and names according to the IUPAC nomenclature for the studied 3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridines

3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridine being studied. Rats with standard signs of inflammation formed during the modelling process were included in the experiment.

The anti-inflammatory properties of the new heterocyclic compounds synthesized by us were evaluated using modeling acute "dextran edema", formed after subplantar administration of a 6 % dextran solution with a volume of 0.1 ml into the right hind paw (Fig. 2, 3). The studied compounds were administered through a gastric tube at a dose of 5 mg/kg 1.5 hours before the induction of edema.

Registration and quantitative measurement of the swelling of the injected extremity in animals of all experimental groups were carried out oncometrically by changing the circumference of the right hind extremity 1 and 3 hours after the induction of inflammation, according to the method of A.F. Leshchinsky and the guidelines for preclinical studies [22, 23]. The data were compared with similar values of the symmetrical limb and with indicators in rats of the intact group. The animals of all groups were monitored for two weeks.

In parallel, an experiment was carried out on other 130 white mongrel male rats weighing 250–280 g, which were similarly divided into intact, control (rats injected with 2 ml of 0.9 % sodium chloride solution intragastrically before modeling the test), reference (animals receiving sodium metamizole intragastrically at 7 mg/kg) and 10 experimental groups (according to the number of samples of cyanothioacetamide derivatives). The studied compounds with laboratory codes AZ023, AZ169, AZ213, AZ257, AZ331, AZ420, AZ383, AZ729, AU04271, AU04288

FIG. 2.
Modeling dextran edema of the paw

FIG. 3.
Swelling of the right limb of the rat of control group an hour after subplantar administration of dextran solution

were administered intragastrically at a dose of 5 mg/kg 1.5 hours before the study.

Analgesic activity was determined in the hotplate analgesic assay based on behavioral reactions controlled by supraspinal structures in response to pain irritation. The animals were placed on a metal plate heated up to aprox. 52 °C (50–55 °C) and surrounded by a cylinder. We recorded the time from the moment we placed the animal on a hot surface to the appearance of a behavioral response to nociceptive stimulation in the form of jumps, jerks and licking of the hind legs. A statistically significant increase in the latent reaction period after administration of a biologically active compound was considered a criterion for the analgesic effect.

The studies were conducted in accordance with the Order of the Ministry of Health of the Russian Federation dated April 1, 2016 No. 199n "On approval of the rules of good laboratory practice". Throughout the entire research period, the animals were monitored with free access to water and food, which corresponds to GOST 33044-2014 "Principles of good laboratory practice" (approved by Order of the Federal Agency for Technical Regulation and Metrology No. 1700-st, dated November 20, 2014).

The study was approved by the Commission on Bioethics of the Lugansk State Medical University named after St. Luke (Protocol No. 6 dated November 1, 2021).

Statistical processing of the obtained data was carried out on the basis of [24], according to well-known formulas and methods of mathematical statistics characterizing quantitative variability. When processing experimental data, the following were determined: the arithmetic mean of the circumference of the extremity *a*; the variance of values s^2 around the arithmetic mean; the standard deviation s; the standard error of the arithmetic mean *m*. The uniformity of the experimental data obtained was estimated by the coefficient of variation *V*.

The statistical significance of the differences between the samples and the comparison preparations was determined using the Student's t-test with a critical value of the Student's t-test equal to 2,101, the level of statistical significance $\alpha = 0.05$ and the number of degrees of freedom $f = 18$ in the online calculator "Calculation of the Student's t-test when comparing averages"[1].

STUDY RESULTS

During statistical processing of data obtained in the reference (comparison drugs) and experimental (new condensed derivatives of thienopyridine and 1,4-dihydropyridine) groups, the values of the difference in circumference of the limbs were calculated 1 and 3 hours after the induction of inflammation. They are shown in Tables 1 and 2.

It should be noted that in the conditions of the conducted experiments, the value of the indicator p is inverse, i. e. the larger the p, the smaller the differences in the circumference of the limb when exposed to the test samples; therefore, a sample with a higher p value is more effective.

When comparing the circumference of the paws of animals of the intact group, the sizes of the right and left hind limbs differed slightly (based on the data presented in Tables 1 and 2). Subplantar injection of a 6 % dextran solution to laboratory rats of the control group contributed to the appearance of pronounced edema. At the same time, 1 hour after injection of dextran solution, the circumference of the right hind paw exceeded the corresponding value of the symmetrical left paw by 43.5 % (Table 1). Three hours after the reproduction of the inflammatory reaction to "dextran edema" in the modelling, the circumference of the right paw of the control group rats was 43.9 %

[1] https://medstatistic.ru/calculators/averagestudent.html

TABLE 1

STATISTICAL CHARACTERISTICS OF CHANGES IN THE CIRCUMFERENCE OF THE LIMBS OF RATS AFTER THE FORMATION OF DEXTRAN EDEMA 1 HOUR AFTER INDUCING INFLAMMATION

Groups of animals	Circumference of the limb (a), mm		Difference (δ)	
	left	right	mm	%
Intact	$a = 24,3$; $s^2 = 0,90$; $s = 0,95$; $m = 0,32$; $V = 3,9$ %	$a = 25,1$; $s^2 = 0,98$; $s = 0,99$; $m = 0,33$; $V = 3,9$ %	0.80	3.30
Control	$a = 24,6$; $s^2 = 0,71$; $s = 0,84$; $m = 0,24$; $V = 3,4$ %	$a = 35,3$; $s^2 = 25,8$; $s = 5,08$; $m = 1,69$; $V = 14,4$ %	10.7	43.5
	1. Student's test $t = 6.27$. The differences are statistically significant ($p = 0.000008$). 2. Student's test $t = 5.92$. The differences are statistically significant ($p = 0.000017$).			
	Comparison drugs			
Acetylsalicylic acid	$a = 27,6$; $s^2 = 0,63$; $s = 0,25$; $m = 0,08$; $V = 9,1$ %	$a = 34,5$; $s^2 = 1,29$; $s = 0,36$; $m = 0,12$; $V = 10,4$ %	6.90	25.0
	1. Student's test $t = 47.8$. The differences are statistically significant ($p < 0.00001$). 2. Student's test $t = 26.8$. The differences are statistically significant ($p < 0.00001$).			
Nimesulide	$a = 25,5$; $s^2 = 0,25$; $s = 0,16$; $m = 0.05$; $V = 6.3$ %	$a = 33,4$; $s^2 = 0,26$; $s = 0,16$; $m = 0,05$; $V = 4,8$ %	7.90	31.0
	1. Student's test $t = 111.7$. The differences are statistically significant ($p < 0.00001$). 2. Student's test $t = 24.9$. The differences are statistically significant ($p < 0.00001$).			
	New studied derivatives of condensed 3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridine			
AZ383	$a = 27,8$; $s^2 = 12,40$; $s = 3,52$; $m = 1,17$; $V = 12,7$ %	$a = 32,0$; $s^2 = 10,20$; $s = 3,20$; $m = 1,07$; $V = 10,0$ %	4.20	15.1
	1. Student's test $t = 2.65$. The differences are statistically significant ($p = 0.016875$). 2. Student's test $t = 6.16$. The differences are statistically significant ($p = 0.00001$).			
AZ023	$a = 25,9$; $s^2 = 2,54$; $s = 1,60$; $m = 0,53$; $V = 6,20$ %	$a = 28,9$; $s^2 = 4,10$; $s = 2,02$; $m = 0,67$; $V = 7,0$ %	3.00	11.6
	1. Student's test $t = 3.51$. The differences are statistically significant ($p = 0.002675$). 2. Student's test $t = 5.09$. The differences are statistically significant ($p = 0.000091$).			

TABLE 1 (*continued*)

AZ420	$a = 28,3$; $s^2 = 6,45$; $s = 2,54$; $m = 0,85$; $V = 9,0$ %	$a = 31,6$; $s^2 = 5,38$; $s = 2,32$; $m = 0,77$; $V = 7,3$ %	3.30	11.7
	1. Student's test $t = 2.88$. The differences are statistically significant ($p = 0.010453$). 2. Student's test $t = 7.76$. The differences are statistically significant ($p = 0.000001$).			
AZ257	$a = 29,3$; $s^2 = 6,90$; $s = 2,63$; $m = 0,88$; $V = 9,0$ %	$a = 34,3$; $s^2 = 5,34$; $s = 2,31$; $m = 0,77$; $V = 6,7$ %	5.00	17.1
	1. Student's test $t = 4.28$. The differences are statistically significant ($p = 0.000511$). 2. Student's test $t = 11.0$. The differences are statistically significant ($p < 0.00001$).			
AZ213	$a = 31,3$; $s^2 = 16,0$; $s = 4,00$; $m = 1,33$; $V = 12,8$ %	$a = 38,5$; $s^2 = 6,94$; $s = 2,63$; $m = 0,88$; $V = 6,8$ %	7.20	23.0
	1. Student's test $t = 4.51$. The differences are statistically significant ($p = 0.000306$). 2. Student's test $t = 14.26$. The differences are statistically significant ($p < 0.00001$).			
AZ331	$a = 28,8$; $s^2 = 4,18$; $s = 2,04$; $m = 0,68$; $V = 7,1$ %	$a = 32,9$; $s^2 = 2,77$; $s = 1,66$; $m = 0,55$; $V = 5,1$ %	4.10	14.2
	1. Student's test $t = 4.69$. The differences are statistically significant ($p = 0.000212$). 2. Student's test $t = 12.16$. The differences are statistically significant ($p < 0.00001$).			
AZ729	$a = 27,7$; $s^2 = 5,79$; $s = 2,40$; $m = 0,80$; $V = 8,7$ %	$a = 34,4$; $s^2 = 5,82$; $s = 2,41$; $m = 0,80$; $V = 7,0$ %	6.70	24.2
	1. Student's test $t = 5.92$. The differences are statistically significant ($p = 0.000017$). 2. Student's test $t = 10.75$. The differences are statistically significant ($p < 0.00001$).			
AZ169	$a = 26,5$; $s^2 = 4,72$; $s = 2,17$; $m = 0,72$; $V = 8,2$ %	$a = 32,4$; $s^2 = 16,0$; $s = 4,00$; $m = 1,33$; $V = 12,4$ %	5.90	22.3
	1. Student's test $t = 3.90$. The differences are statistically significant ($p = 0.001149$). 2. Student's test $t = 5.33$. The differences are statistically significant ($p = 0.000056$).			
AU04271	$a = 28,4$; $s^2 = 4,26$; $s = 2,06$; $m = 0,69$; V = 7,3 %	$a = 37,4$; $s^2 = 5,60$; $s = 2,36$; $m = 0,79$; $V = 6,3$ %	9.00	31.7
	1. Student's test $t = 8.58$. The differences are statistically significant ($p < 0.00001$). 2. Student's test $t = 14.37$. The differences are statistically significant ($p < 0.00001$).			
AU04288	$a = 25,1$; $s^2 = 0,98$; $s = 0,99$; $m = 0,33$; $V = 3,9$%	$a = 32,3$; $s^2 = 18,7$; $s = 4,32$; $m = 1,44$; $V = 13,4$ %	7.20	28.7
	1. Student's test $t = 4.86$. The differences are statistically significant ($p = 0.000143$). 2. Student's test $t = 4.87$. The differences are statistically significant ($p = 0.000143$).			

Note. 1 – in comparison with the indicators of the symmetrical limb; 2 – in comparison with the indicators in the intact group.

TABLE 2

STATISTICAL CHARACTERISTICS OF CHANGES IN THE CIRCUMFERENCE OF THE EXTREMITIES OF RATS AFTER THE FORMATION OF DEXTRAN EDEMA 3 HOURS AFTER INDUCING INFLAMMATION

Groups of animals	Circumference of the limb (*a*), mm		Difference (δ)	
	left	right	mm	%
Intact	$a = 24,3$; $s^2 = 0,90$; $s = 0,95$; $m = 0,32$; $V = 3,9$ %	$a = 25,1$; $s^2 = 0,98$; $s = 0,99$; $m = 0,33$; $V = 3,9$ %	0.80	3.30
Control	$a = 24,6$; $s^2 = 0,71$; $s = 0,84$; $m = 0,28$; $V = 3,4$ %	$a = 35,4$; $s^2 = 30,7$; $s = 5,54$; $m = 1,85$; $V = 15,6$ %	10.8	43.9
	1. Student's test $t = 5.77$. The differences are statistically significant ($p = 0.000023$). 2. Student's test $t = 5.48$. The differences are statistically significant ($p = 0.000041$).			
	Comparison drugs			
Acetylsalicylic acid	$a = 27,6$; $s^2 = 0,63$; $s = 0,25$; $m = 0,083$; $V = 9,1$ %	$a = 30,9$; $s^2 = 0,26$; $s = 0,16$; $m = 0,05$; $V = 5,3$ %	3.30	12.0
	1. Student's test $t = 34.1$. The differences are statistically significant ($p < 0.00001$). 2. Student's test $t = 17.38$. The differences are statistically significant ($p < 0.00001$).			
Nimesulide	$a = 25,5$; $s^2 = 0,25$; $s = 0,16$; $m = 0,053$; $V = 6,3$ %	$a = 30,9$; $s^2 = 0,16$; $s = 0,12$; $m = 0,04$; $V = 4,0$ %	5.40	21.2
	1. Student's test $t = 81.3$. The differences are statistically significant ($p < 0.00001$). 2. Student's test $t = 17.45$. The differences are statistically significant ($p < 0.00001$).			
	New studied derivatives of condensed 3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridine			
AZ383	$a = 27,8$; $s^2 = 12,4$; $s = 3,52$; $m = 1,17$; $V = 12,7$ %	$a = 30,9$; $s^2 = 6,99$; $s = 2,64$; $m = 0,88$; $V = 8,6$ %	3.10	11.2
	1. Student's test $t = 2.12$. The differences are statistically significant ($p = 0.049262$). 2. Student's test $t = 6.17$. The differences are statistically significant ($p = 0.000010$).			
AZ023	$a = 25,9$; $s^2 = 2,54$; $s = 1,59$; $m = 0,53$; $V = 6,16$ %	$a = 27,8$; $s^2 = 2,40$; $s = 1,55$; $m = 0,52$; $V = 5,6$ %	1.90	7.30
	1. Student's test $t = 2.56$. The differences are statistically significant ($p = 0.020332$). 2. Student's test $t = 4.38$. The differences are statistically significant ($p = 0.000405$).			

TABLE 2 (*continued*)

AZ420	$a = 28,3$; $s^2 = 6,45$; $s = 2,54$; $m = 0,85$; $V = 9,0$ %	$a = 31,1$; $s^2 = 2,10$; $s = 1,44$; $m = 0,48$; $V = 4,7$ %	2.80	9.90
	1. Student's test $t = 2.87$. The differences are statistically significant ($p = 0.010653$). 2. Student's test $t = 10.3$. The differences are statistically significant ($p < 0.00001$).			
AZ331	$a = 28,8$; $s^2 = 4,18$; $s = 2,04$; $m = 0,68$; $V = 7,1$ %	$a = 30,8$; $s^2 = 0,84$; $s = 0,91$; $m = 0,30$; $V = 3,0$ %	2.00	6.90
	1. Student's test $t = 2.69$. The differences are statistically significant ($p = 0.015465$). 2. Student's test $t = 12.78$. The differences are statistically significant ($p < 0.00001$).			
AZ257	$a = 29,3$; $s^2 = 6,90$; $s = 2,62$; $m = 0,87$; $V = 9,0$ %	$a = 34,7$; $s^2 = 8,90$; $s = 2,98$; $m = 0,99$; $V = 8,6$ %	5.40	18.4
	1. Student's test $t = 4.10$. The differences are statistically significant ($p = 0.000751$). 2. Student's test $t = 9.20$. The differences are statistically significant ($p < 0.00001$).			
AZ213	$a = 31,3$; $s^2 = 16,0$; $s = 4,0$; $m = 1,33$; $V = 12,8$ %	$a = 36,9$; $s^2 = 15,9$; $s = 3,98$; $m = 1,33$; $V = 10,8$ %	5.60	17.9
	1. Student's test $t = 2.98$. The differences are statistically significant ($p = 0.008454$). 2. Student's test $t = 8.61$. The differences are statistically significant ($p < 0.00001$).			
AZ169	$a = 26,5$; $s^2 = 4,72$; $s = 2,17$; $m = 0,72$; $V = 8,2$ %	$a = 30,2$; $s^2 = 7,51$; $s = 2,74$; $m = 0,91$; $V = 9,1$ %	3.70	14.0
	1. Student's test $t = 3.19$. The differences are statistically significant ($p = 0.005378$). 2. Student's test $t = 5.27$. The differences are statistically significant ($p = 0.000063$).			
AZ729	$a = 27,7$; $s^2 = 5,79$; $s = 2,40$; $m = 0,80$; $V = 8,7$ %	$a = 34,5$; $s^2 = 2,72$; $s = 1,65$; $m = 0,55$; $V = 4,8$ %	7.30	24.5
	1. Student's test $t = 7.00$. The differences are statistically significant ($p = 0.000002$). 2. Student's test $t = 16.06$. The differences are statistically significant ($p < 0.00001$).			
AU04271	$a = 29,4$; $s^2 = 13,38$; $s = 3,7$; $m = 1,23$; $V = 12,4$ %	$a = 38,1$; $s^2 = 4,54$; $s = 2,13$; $m = 0,71$; $V = 5,6$ %	8.70	29.6
	1. Student's test $t = 6.13$. The differences are statistically significant ($p = 0.000011$). 2. Student's test $t = 16.6$. The differences are statistically significant ($p < 0.00001$).			
AU04288	$a = 25,1$; $s^2 = 0,98$; $s = 0,99$; $m = 0,33$; $V = 4,0$ %	$a = 33,5$; $s^2 = 20,50$; $s = 4,5$; $m = 1,5$; $V = 13,5$ %	8.40	33.5
	1. Student's test $t = 5.47$. The differences are statistically significant ($p = 0.000042$). 2. Student's test $t = 5.47$. The differences are statistically significant ($p = 0.000042$).			

Note. 1 – in comparison with the indicators of the symmetrical limb; 2 – in comparison with the indicators in the intact group.

bigger than the same value of the left one. In other words, by this time of observation, pronounced edema, redness, soreness and dysfunction of the distal part of the free hind limb were registered (Fig. 3).

Non-steroidal anti-inflammatory drugs used as referents in comparison groups showed the expected anti-inflammatory activity in experiments.

Thus, preliminary (90 minutes before modeling an acute inflammatory reaction) intragastric administration of acetylsalicylic acid to rats of the corresponding group contributed to the formation of a less pronounced edema of the injected right paw (the difference in the circumference of the right and left limbs was 25 % at an early stage of observation).

It is important to note the following: 3 hours after administration of dextran solution in rats of the reference group treated with acetylsalicylic acid, the difference in the circumference of the hind paws is halved, amounting to almost 12 %. This highlights the fact that antiexudative activity increases over time.

Nimesulide, administered intragastrally to rats of the second reference group, has moderate antiedemic properties. So, 1 hour after modeling the inflammatory reaction, the difference in the circumference of the injected and non-injected limbs was 31 %. After another 2 hours, the signs of swelling decrease significantly, and the difference in the circumference of the paws of animals in this group is 21.2 % (Table 2).

When comparing the indicators of anti-inflammatory activity of new synthesized derivatives of thienopyridine and 1,4-dihydropyridine, it was found that derivatives of condensed 3-aminothieno[2,3-b]pyridines with laboratory codes AU04271 and AU04288 demonstrate anti-inflammatory properties almost identical to nimesulide at an early stage of the experiment.

Antiedemic activity similar to acetylsalicylic acid under the conditions of this pharmacological test is shown by three new studied heterocyclic compounds of 1,4-dihydrothiopyridine derivatives with codes AZ729, AZ213 and AZ169, administered intragastrally for prophylactic purposes. The difference between the circumference of the right and left hind limbs of the rats of these experimental groups 1 hour after modeling dextran edema was 24.2, 23.0 and 22.3 %, respectively.

The remaining 5 out of 10 new studied derivatives of condensed 3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridine are able to reduce the development of dextran edema more effectively than classical NSAIDs used by us as reference drugs in the early stages of follow-up.

Thus, the difference between the circumference of the injected right and non-injected left paws of rats of experimental groups receiving derivatives of 1,4-dihydropyridian with laboratory codes AZ257 and AZ383 through a gastric tube, 1 hour after the modelling of an acute inflammatory reaction, is at the level of 17.1 % and 15.1 %, respectively. This is almost 2 times less than after the use of nimesulide.

As shown in Table 1, the following three samples have significantly more pronounced anti-inflammatory properties according to the experimental results: derivatives of 1,4-dihydropyridine with the codes AZ331 and AZ420 and a condensed derivative of thienopyridine with the code AZ023. The difference in the circumference of the distal limbs of the animals of these experimental groups at the one-hour term of the experiment is 14.2, 11.7 and 11.6 %, respectively. This is more than 2.5 times less than the indicator registered in the comparison group after the administration of nimesulide, and 2.2 times less than the indicator registered after the use of acetylsalicylic acid. At the same time, when walking around the cage, the rats of these experimental groups showed no signs of severe pain that was present in rats of the control group without pharmacocorrection.

Observation in the dynamics of the experiment showed (Table 2) that 3 hours after administration of dextran solution, 7 out of 10 studied heterocyclic compounds have anti-inflammatory properties in the spectrum of their pharmacodynamic effects, which exceed those of nimesulide. The most pronounced ability to prevent the development of edema in this experimental test was shown by samples of new heterocyclic compounds with laboratory codes AZ331, AZ420 and AZ023. By this time of observation, the circumference difference between the injected and non-injected limbs ranges from 9.9 to 6.9 %.

The results of an experiment conducted on a pharmacological model to study antinociceptive properties showed that the average value of time on the surface of a heated plate in animals of the control group without pharmacocorrection was 8.6 seconds The use of sodium metamizole led to an increase in the latent reaction period by almost 2 times – up to 16.6 seconds In animals of the experimental groups, under the conditions of the experiment, it was recorded that the studied samples with laboratory codes AZ169, AU04271, AU04288 did not show antinociceptive activity, since the time on the surface of a heated plate before characteristic jumping and licking of paws ranged from 5.3 to 9.0 seconds in rats of these groups.

Moderate analgesic activity exceeding one and a half or more times that of the comparison drug metamizole sodium was detected by new heterocyclic compounds with laboratory codes AZ257, AZ729 and AZ213 in this test.

According to the results of the conducted studies, the new biologically active compound with the code AZ420 increases the latent reaction time to 127.9 seconds, which is 7.7 times more than after the use of sodium metamizole.

Three samples showed pronounced analgesic activity – compounds with the codes AZ023, AZ331 and AZ383. Moreover, the time rats of the experimental groups treated with AZ331 and AZ383 for preventive purposes spend on the heated plate was 158.8 seconds and 164.9 seconds on average for the groups, which is 9.56 and 9.93 times more than the same indicator in the reference group, respectively. Animals treated with condensed thienopyridine with the code AZ023 were characterized by an increase in the latent reaction time to 241.2 seconds, which is 14.53 times higher than that in rats injected with sodium metamizole.

CONCLUSIONS

When conducting pharmacological studies *in vivo* and modelling dextran edema of rat paw for ten new derivatives of condensed 3-aminothieno[2,3-b]pyridines and 1,4-dihydropyridines with potential analgesic activity, it was found that four samples with the following laboratory codes have the most pronounced antiexudative properties at a dose of 5 mg/kg: AZ023 (3-amino-4-(5-methyl-2-furyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-2-yl](phenyl) methanone); AZ331 (5-cyano-4-(2-furyl)-N-(2-methoxyphenyl)-6-{[2-(4-methoxyphenyl)-2-oxoethyl]thio}-2-methyl-1,4-dihydropyridine-3-carboxamide), AZ420 (5-cyano-4-(2-furyl)-N-(2-methoxyphenyl)-6-({2-[(3- methoxyphenyl) amino]-2-oxoethyl}thio)-2-methyl-1,4-dihydropyridine-3-carboxamide) and AZ383 (3-amino-4-(5-methyl-2-furyl)-5,6,7,8-tetrahydrothieno[2,3-b]quinolin-2-yl](phenyl)methanone). They are 2.5 times more effective than nimesulide in terms of antiexudative properties, and 2.2 times more effective than acetylsalicylic acid.

Three new studied heterocyclic compounds of 1,4-dihydrothiopyridine derivatives with the codes AZ729, AZ213 and AZ169 show antiedemic activity similar to acetylsalicylic acid.

In addition, a hot plate test performed on white mongrel rats showed the presence of analgesic activity in seven studied derivatives of condensed 3-aminothieno[2,3-b] pyridines. Among them, the compound AZ023 [3-amino-4-(5-methyl-2-furyl)-5,6,7,8-tetrahydrothieno[2,3-*b*]quinolin-2-yl](phenyl)methanone] is 14.53 times more effective than sodium metamizole.

DISCUSSION OF THE STUDY RESULT

Literature data indicate that partially cyanothioacetamide derivatives have a variety of pharmacological properties. For example, 1,4-dihydropyridine-3-carbonitriles are hepatoprotectors, pyrido-1,3,5-thiadiazines have antiviral effects against Powassan virus and tick-borne encephalitis virus, and also demonstrate an analeptic effect and adaptogenic effect. Hexahydroquinoline derivatives are known to be active against HIV. In addition, saturated nicotinonitriles exhibit an inhibitory effect against autotaxin. A hybrid molecule combining thiophene and hexahydroquinoline fragments inhibits the formation of β-amyloid peptide and thus prevents the formation of amyloid plaques, a factor concomitant with a number of serious diseases such as Alzheimer's disease, hemodialysis amyloidosis, lysozyme amyloidosis.

In the last decade, the polypharmacological approach in the industry of creating new medicines has become particularly relevant. It involves moving away from the concept of "one drug – one target – one disease" and creating and/or using a single pharmaceutical product that can simultaneously bind several protein targets or act on different biochemical routes [25]. The strategy of the polypharmacological approach is to create hybrid or multimodal compounds. The latter consist of residues of two or more pharmacophore subunits covalently bound by a flexible spacer. This combination allows the molecule to interact with several protein targets at once, which sometimes gives a synergistic effect. Therefore, the use of hybrid bioactive molecules allows for the combined therapy of multifactorial diseases using a single drug.

The results obtained in our experimental study on white rats allowed us to identify new heterocyclic compounds with pronounced anti-inflammatory and analgesic properties. This may be due to the fact that a sample with the laboratory code AZ331, selected according to virtual bioscreening data from an extensive library of new organic compounds synthesized in the ChemEx laboratory, can bind to phospholipase *A2* and arachidonate-5-lipoxygenase. A new dihydropyridine derivative with the laboratory code AZ383 can also potentially bind to arachidonate-5-lipoxygenase and cyclooxygenase-2.

The 1,4-dihydropyridine derivative with the laboratory code AZ420 can affect the activity of serine threonine protein kinase, phospholipase *A2*, arachidonate-5-lipoxygenase. The heterocyclic compound – condensed thienopyridine with the laboratory code AZ023 – according to the results of virtual bioscreening is potentially capable of binding to prostanoid receptors of types *EP1*, *EP2* and *EP4*, *CB1* type cannabinoid receptors and arachidonate-5-lipoxygenase.

In terms of discussion, we assume that it is common for the leading samples in the experimental study of proto-inflammatory and analgesic activity to consider their effect on the activity of the enzyme arachidonate-5-lipoxygenase as a biomishen for these new derivatives of thienopyridines and dihydropyridines according to the results of virtual bioscreening. At the same time, the ability of individual samples to bind to cyclooxygenase-2 and phospholipase*A2* only enhances their potential anti-inflammatory activity.

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Conflict of interest

The authors of this article declare the absence of a conflict of interest.

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