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Synthesis and Hypoglycemic Activity of New Nicotinonitrile-Furan Molecular Hybrids

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Abstract—Objective: Synthesis of some new nicotinonitrile-furan hybrids and evaluation of their hypoglycemic activity. **Methods:** Three-component pyridine synthesis based on tandem reactions of Knoevenagel condensation-Michael addition-heterocyclization using furfural, cyanothioacetamide and Meldrum's acid (or allyl acetoacetate) as the starting reagents. Hypoglycemic effects was studied on the model of dexamethasone-induced diabetes mellitus in rats. **Results and Discussion:** All four new compounds (**XX–XXIII**) were characterized by spectral methods and found to have remarkable hypoglycemic activity. **Conclusions:** Some new nicotinonitrile-furan hybrids were prepared and tested *in vivo* for hypoglycemic activity. The compound (**XX**) showed more potent hypoglycemic effect that of the reference drug metformin without pronounced hepatotoxicity.

Keywords: cyanothioacetamide, furfural, partially saturated nicotinonitriles, hypoglycemic effects, steroid-induced diabetes mellitus

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INTRODUCTION

In recent years, the concept of molecular hybridization has been used to develop pharmacological drugs of increased efficacy. This concept consists of combining two or more pharmacophore scaffolds in one molecule [1–3] and is based on the assumption that the combined molecule exhibits the structural features of two (or more) parent pharmacophore molecules, which act independently on two different pharmacological targets. The presence of two or more pharmacophore subunits in one molecule often leads to a synergistic effect, which exceeds the sum effect of individual compounds [3]. Molecular hybrids are actively used in the combined therapy of Alzheimer's disease [4–7], parasitic diseases [4, 5], oncological diseases [5, 8], tuberculosis and fungal diseases [9–11], neurodegenerative processes [12], malaria [13, 14], HIV + tuberculosis coinfections [15], and others.

It is known that 1,4-dihydro- and tetrahydronicotinonitrile derivatives have a variety of biological effects. For example, 1,4-dihydropyridine-3-carbonitriles (**I** and **II**) exhibit antioxidant and hepatoprotective properties [16, 17], and compounds (**III** and **IV**) have antiviral activity [18] (Fig. 1). In addition, related pyrido-1,3,5-thiadiazines (**IV**) exhibit an analeptic [19], anti-inflammatory [20], adaptogenic [21], and analgesic [22] effects. It was reported [23] that compound (**V**) has an antiviral effect, compounds (**VI** and **VII**) are strong analgesics [22], and compound (**VIII**) inhibits autotaxin [24]. 1,4-Dihydropyridine-3-

Abbreviations: Mp, Morpholine; NMM, *N*-methylmorpholine; ALT, alanine aminotransferase; AST, aspartate aminotransferase; GCS, glucocorticosteroid; DMSO, dimethyl sulfoxide; DMF, dimethylformamide; DM, diabetes mellitus; thyroid, thyroid gland.

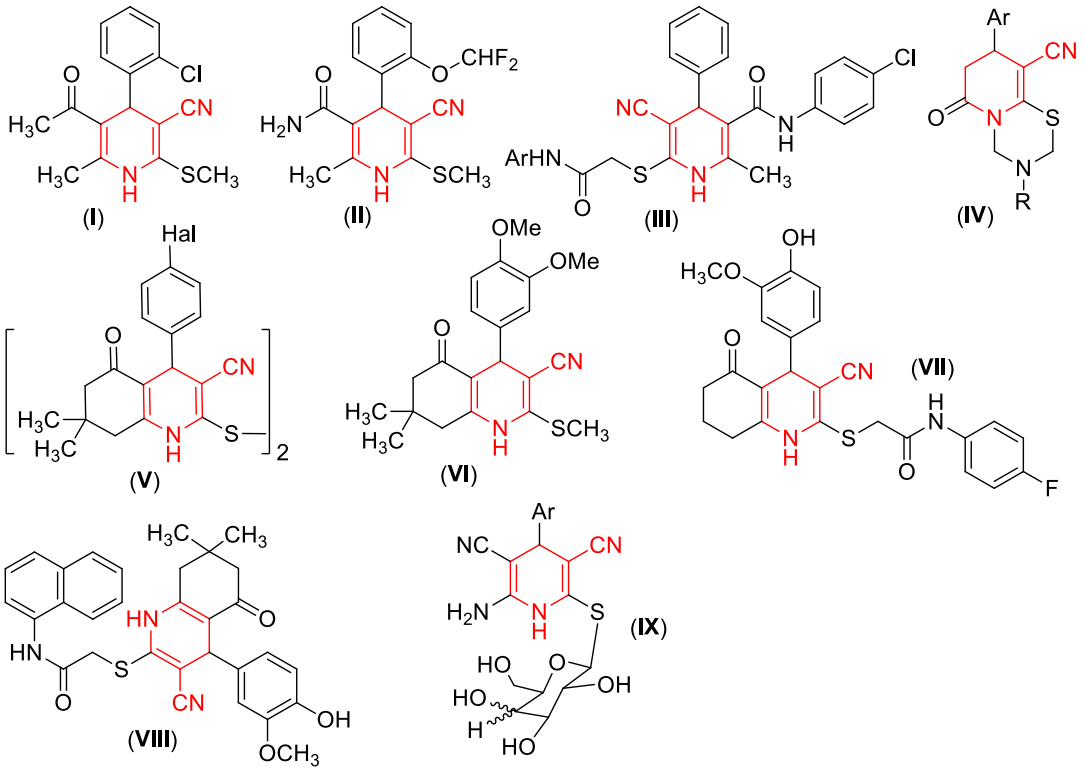


Fig. 1. Biologically active 1,4-dihydro nicotinonitriles.

carbonitriles conjugated with α-D-gluco- or galacto-pyranose residues (structure (**IX**)), Fig. 1) have a remarkable antitumor effects [25]. Some selenium-containing partially saturated nicotinonitriles are active against tick-borne encephalitis virus at micromolar concentrations *in vitro* [26]. In general, the high potential of nicotinonitrile derivatives in the search for new biologically active substances should be noted (see reviews [27–35]).

Several molecular hybrids based on furan derivatives are already used in modern medical practice. It is worth noting the analgesic mirfentanil, antimicrobial furazolin and furadonin, diuretic furosemide, hypotensive prazosin, and some other drugs. Biological activity has been documented for many furan derivatives [36, 37], and the 2-furyl fragment is a well-known pharmacophore residue.

It is known from the literature that hybrid molecules of the general structure (**X**) (Fig. 2), which combines the 2-furyl and 1,4-dihydronicotinonitrile fragments, are active against the Omsk hemorrhagic fever virus [18] and have analgesic [38–43] and anti-inflammatory [44] effects. Compound (**XI**) [26, 45] exhibits a moderately pronounced antiviral effect. According to virtual screening data, compound (**XII**) has an affinity for the adenosine receptor A2A [46]. Dihydropyridine (**XIII**) is a selective modulator of glucocorticoid receptors with potential anti-inflammatory efficacy [47]. According to patent data [48], compounds (**XIV**) inhibit c-Met tyrosine kinase. Compound (**XV**) is a strong acetylcholinesterase inhibitor, which is promising for the treatment of Alzheimer's disease [49]. 1,4-Dihydronicotinonitrile (**XVI**) was identified as an AmpC β-lactamase inhibitor by high-throughput screening [50]. 4-(2-Furyl)quinolines (**XVII**) in the *in vitro* experiments showed insignificant antitumor activity [51, 52], whereas 4-(2-furyl)-1,4-dihydronicotinonitriles (**XVIII**) [53] and (**XIX**) [54] showed high cytotoxicity against some cancer cell lines. Data on molecular hybrids that contain the 2-furyl and 1,4,5,6-tetrahydronicotinonitrile fragments are less numerous. The antiviral [26] and analgesic [38, 41] effects of such compounds are mentioned in the literature.

Thus, the creation of hybrid molecules that combine the residues of the furan cycle and 1,4-dihydro- or

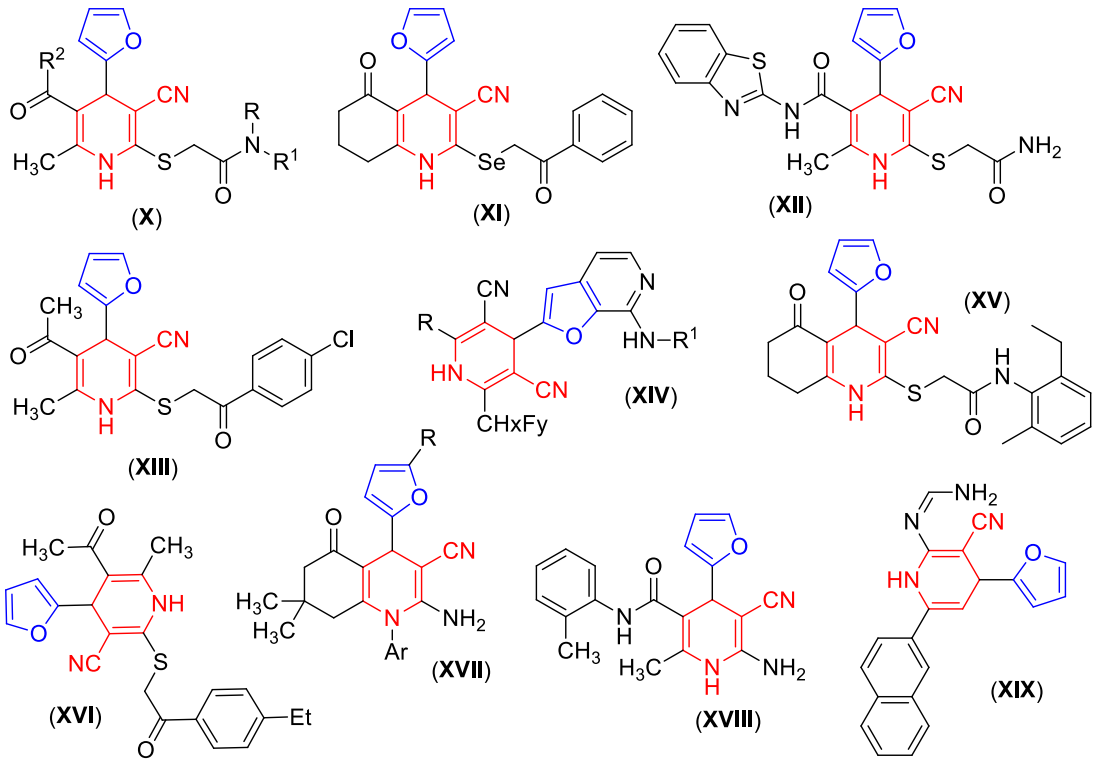


Fig. 2. Biologically active hybrid molecules with 2-furyl and 1,4-dihydronicotinonitrile fragments.

1,4,5,6-tetrahydronicotinonitrile seems to be a promising direction in the search for new biologically active compounds.

The goal of this work is to synthesize new nicotinonitrile furan hybrid molecules based on cyanothioacetamide and to study their hypoglycemic activity.

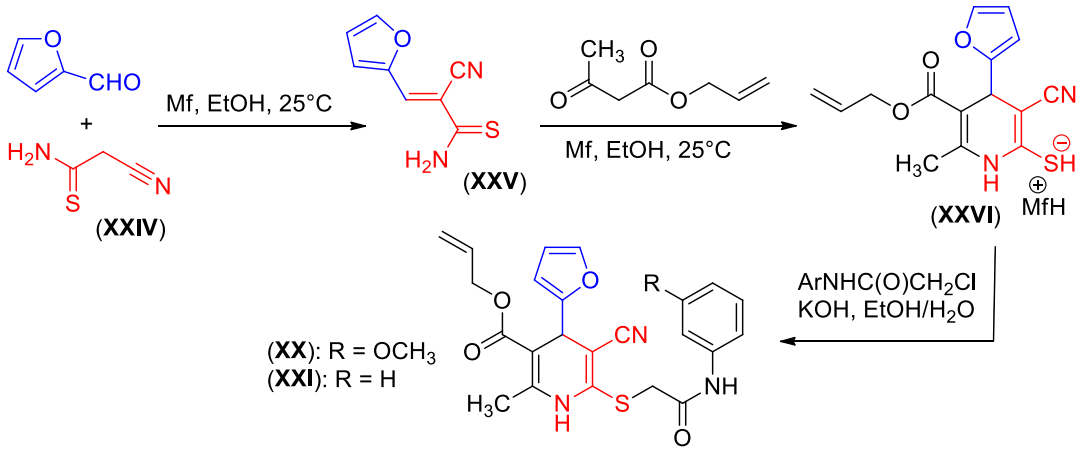
RESULTS AND DISCUSSION

Synthesis of Nicotinonitrile-Furan Hybrid Molecules

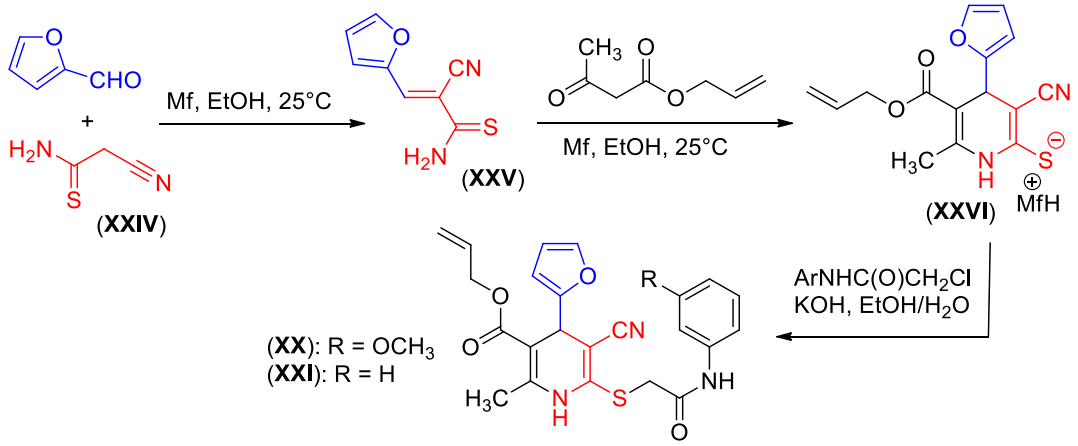
Four compounds (**XX–XXIII**) (Schemes 1, 2) were selected from the synthesized library of 4-(2-furyl)-nicotinonitriles (>100 compounds) to study their hypoglycemic effect. The protein targets for compounds (**XX–XXIII**) were searched using the GalaxySagittarius protein-ligand docking protocol [55] based on the GalaxyWeb web server [56, 57] and the SwissTarget Prediction service [58]. The search showed the affinity for the following targets: 1) G-protein-bound receptor GPR119 responsible for regulating glucose-dependent secretion of incretins and insulin [59]; 2) rhodopsin-like receptor GPR142 stimulating insulin secretion [60, 61]; 3) kinase-3-glycogen synthase (GSK3B), inhibitors of which reduce the blood glucose level [62]; 4) glucokinase (hexokinase VI, GCK) [63–65]; 5) receptors activated by peroxisomal proliferators PPARα, PPARγ (the binding to these receptors helps to decrease insulin resistance, reduce blood glucose levels, and normalize lipid metabolism [66, 67]); 6) free fatty acid receptors FFAR1 (GPR40) regulating insulin secretion [68, 69]. In general, a hypoglycemic effect in vivo can be assumed for compounds (**XX–XXIII**) with affinity to these targets.

Compounds (**XX**) and (**XXI**) were prepared as shown in Scheme 1. Cyanothioacetamide (**XXIV**) reacted with furfural in the presence of a catalytic amount of morpholine (Mp). The Knoevenagel condensation product (**XXV**) was further reacted in situ with allyl acetoacetate and an excess of morpholine. The resulting pyridine-2-thiolate (**XXVI**) was S-alkylated with the corresponding α-chloroacetanilides in the presence of alkali.

Compounds (**XXII**) and (**XXIII**) were also prepared from cyanothioacetamide (**XXIV**). *N*-Methyl-



Scheme 1. Synthesis of compounds (**XX**) and (**XXI**).



Scheme 2. Synthesis of compounds (**XXII**) and (**XXIII**).

morpholinium 4-(2-furyl)-3-cyano-6-oxo-1,2,3,4-tetrahydropyridine-2-thiolate (**XXVII**) was synthesized by the reaction of thioamide (**XXIV**) with furfural and Meldrum's acid in the presence of an excess of *N*-methylmorpholine (NMM) according to the known method [38, 70–72]. Alkylation of thiolate (**XXVII**) with substituted α-chloroacetanilides in an aqueous alcohol solution led to the formation of target nicotinonitriles (**XXII**) and (**XXIII**) (Scheme 2).

Compounds (**XX–XXIII**) are fine crystalline substances of white or beige color, poorly soluble in ethanol, moderately soluble in acetone, and well soluble in DMF and DMSO. Their structure was confirmed by ^{1}H and ^{13}C NMR spectroscopy and FT-IR spectrophotometry.

Hypoglycemic Effect of Compounds (XX–XXIII) In Vivo

The hypoglycemic activity (the ability to reduce blood glucose levels) of synthesized hybrid compounds (**XX–XXIII**) was studied in rats with pronounced senile changes in the course of dexamethasone-induced diabetes mellitus (DM).

Dexamethasone is a fluorinated glucocorticosteroid (GCS). The prolonged use of GCS is known to cause hyperglycemia because of immediate stimulation of gluconeogenesis. A direct damaging effect on the beta cells of the pancreas was also noted. GCS at high doses disrupts the secretory function of β cells and leads to the development of insulin resistance. The mechanism of

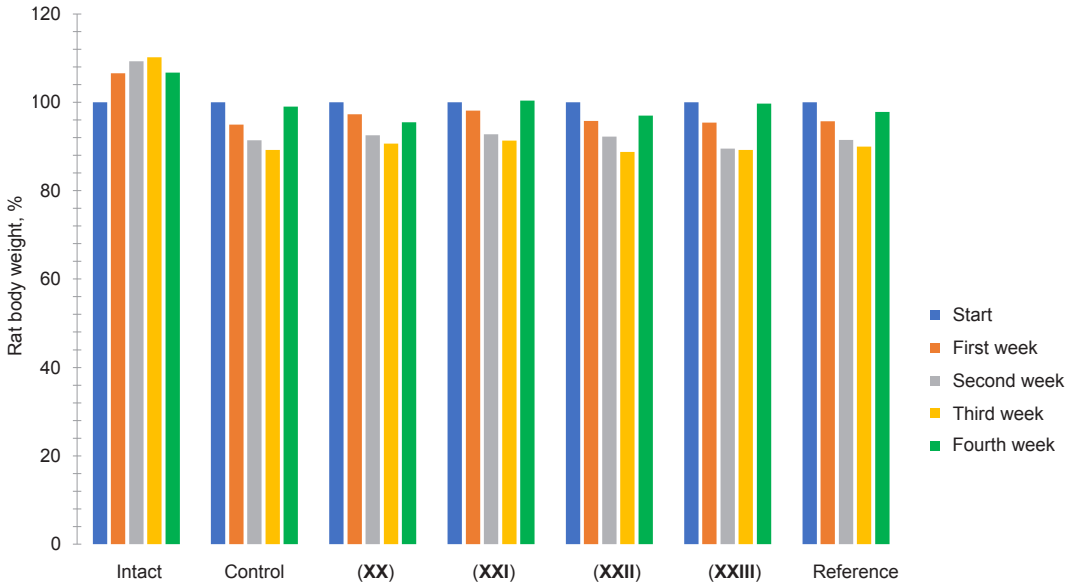


Fig. 3. Dynamics of changes in rat body weight against the background of modeling dexamethasone diabetes mellitus with subsequent pharmacocorrection with compounds (**XX–XXIII**) and the reference drug metformin. The differences in the values in the experimental, control, and reference groups are significant in comparison with the intact group ($p \leq 0.05$).

impaired regulation of carbohydrate and lipid metabolism is mainly associated with the direct effect of GCS on the expression of the GLUT1 and GLUT4 glucose transporters and inactivation of mitochondrial FAD-glycerophosphate dehydrogenase, which leads to insulin resistance, decreased glucose utilization by adipocytes, and impaired glucose-induced insulin secretion.

The experiment was carried out on white mongrel rats, which were divided into seven groups, i.e., intact, control, reference, and four experimental groups (for each of the studied compounds (**XX–XXIII**)). Dexamethasone was administered to all rats except for animals of the intact group for the development of diabetes (at a dosage of 125 μg/kg daily for 13 days) [73]. The pharmacocorrection of DM was performed for three weeks. The hypoglycemic agent metformin (1,1-dimethylbiguanide hydrochloride) was used as a reference drug for DM pharmacocorrection in the reference group. The range of metformin doses is 1000–3000 mg per day according to the approved instructions. Given the average human body weight for the Eurasian continent (70 kg), it is possible to calculate the dose for a person, which is 14.29–42.86 mg/kg. Using the method of dose extrapolation proposed in [74] and taking into account the coefficients for a laboratory rat (3.62) and a human (0.57), we have multiplied these coefficients and calculated a total coefficient, which can be used to obtain the dose of metformin. Thus, the dose of the reference drug metformin is in the range of 90.74–272.16 mg/kg. Taking into account the relative safety of metformin and the literature data on using doses up to 400 mg/kg in experiments with rats, we decided to use this drug at a dose close to the upper limit of the norm, i.e., 200 mg/kg. The studied new heterocyclic compounds (**XX–XXIII**) were administered to animals at a dose of 1 mg/kg of body weight. The experimental compounds and the reference drug were administered per os as a freshly prepared suspension through an atraumatic probe daily for three weeks. Placebo (saline solution) was administered to animals of the control group. The dynamics of body weight changes in all experimental groups of rats is shown in Fig. 3.

Figure 3 demonstrates the entire period of the experiment. The first column is the average initial weight of rats (taken as 100%). The second and third columns are the two-week steps of DM modeling at the first stage of

Table 1. Results of measurements of the thyroid gland of rats in a model of dexamethasone diabetes mellitus after pharmacocorrection with compounds (**XX–XXIII**)

Parameter, cm	Statistical parameters*	Animal group						
		intact	control	(**XX**)	(**XXI**)	(**XXII**)	(**XXIII**)	reference
Height	M	1.63	1.61	2.00	1.84	1.88	1.96	1.93
	m	0.1	0.1	0.09	0.12	0.12	0.12	0.04
	σ^2	0.1242	0.0936	0.15	0.2386	0.1814	0.2176	0.0309
	σ	0.3525	0.3060	0.3872	0.4885	0.4259	0.4664	0.1759
	V	7.62	5.82	7.5	12.97	9.65	11.1	100.01
	n	12	9	17	17	14	13	17
Width	M	2.61	2.57	2.56	2.38	2.33	2.34	2.47
	m	0.28	0.22	0.17	0.13	0.19	0.24	0.06
	σ^2	0.9717	0.4400	0.4650	0.2994	0.4490	0.7709	0.0560
	σ	0.9858	0.6633	0.6819	0.5471	0.6701	0.8780	0.2366
	V	37.23	17.12	23.25	5.46	8.15	32.9	22.7
	n	12	9**	17	17	14**	13**	17

* For each data set, the mean value (M), standard error (m), standard deviation (σ), variance of values (σ^2), and coefficient of variation (**V**) were calculated.
** In these groups, the death of rats from complications of diabetes was recorded.

the experiment. The last two columns are the weight of animals at the pharmacocorrection stage. Throughout the experiment, the animals of the intact group gained body weight at an average rate typical for this age category. The body weight of the animals of the other groups steadily decreased during the DM modeling. The administration of dexamethasone to animals was discontinued after the third week, and pharmacocorrection with compounds (**XX–XXIII**) and metformin was initiated. Starting from now on, the weight of rats began to gradually increase. This phenomenon was also observed in the control group, which suggests that this result is caused by the withdrawal of dexamethasone. The weight gain was observed in animals of all groups except the intact group but the body weight of animals did not reach the initial values only in three groups, which received metformin (97.83%) and compounds (**XX**) and (**XXII**) (95.51% and 97.03%, respectively). This fact suggests the ability of metformin and compounds (**XX**) and (**XXII**) to reduce the intensity of GCS withdrawal syndrome. It should be noted that according to the in silico virtual screening data, corticotropin-releasing hormone type 1 (CRHR1) receptors were noted among the potential targets of compounds (**XX**) and (**XXII**). It is known that the CRHR1 receptor gene is involved in the regulation of endogenous corticosteroid levels and may influence the response to exogenously prescribed glucocorticosteroids [75, 76].

Visual observations showed changes in the appearance and behavioral reactions of the dexamethasone-treated animals during the development of the expected diabetes. The death of ten animals was observed in the experiment. The death was caused by a complication of DM because the dead rats had all the signs of macroangiopathies (gangrenous changes in the muzzle, tail, and limbs). The dead animals were in the control group and experimental groups treated with compounds (**XXII**) and (**XXIII**). There were no deaths in the intact, reference, and experimental groups of rats, the latter of which were treated with compounds (**XX**) and (**XXI**).

The organometric parameters of the thyroid gland (Table 1) show that the height and width of the thyroid gland of rats in the intact and control groups are within the statistical error. In addition, the height of the thyroid gland in all animals treated with one of the compounds (**XX–XXIII**) was higher than that in the intact and control groups. Regarding the width of the organ, this indicator was approximately the same (within the statistical error) in rats of the intact, control, and experimental (**XX**)

Table 2. The length of the liver lobes of rats of experimental groups (M ± m, n = 9–17)

Animal group	Lobe length, cm					
	first	second	third	fourth	fifth	sixth
Intact	4.09 ± 0.25	2.78 ± 0.18	2.55 ± 0.24	2.08 ± 0.19	1.92 ± 0.23	2.30 ± 0.13
Control	5.50 ± 0.46*	3.12 ± 0.22*	2.97 ± 0.30*	2.58 ± 0.18*	1.93 ± 0.25	2.71 ± 0.20*
(**XX**)	4.68 ± 0.16	3.09 ± 0.16	2.52 ± 0.20	2.24 ± 0.19	2.14 ± 0.18	2.49 ± 0.16
(**XXI**)	4.40 ± 0.10	3.35 ± 0.13*	2.68 ± 0.16	2.36 ± 0.13	2.44 ± 0.13*	2.42 ± 0.15
(**XXII**)	4.86 ± 0.12*	3.64 ± 0.19*	2.24 ± 0.13	2.16 ± 0.12	3.03 ± 0.12*	3.03 ± 0.17*
(**XXIII**)	4.74 ± 0.19*	3.37 ± 0.24*	2.55 ± 0.16	2.28 ± 0.13	2.43 ± 0.24*	2.89 ± 0.12*
Reference	4.71 ± 0.09*	3.28 ± 0.1*	2.5 ± 0.04	2.35 ± 0.06	2.44 ± 0.09*	2.51 ± 0.07

* Significant differences relative to the intact group ($p \leq 0.05$).

Table 3. The height of the liver lobes of rats of experimental groups (M ± m, n = 9–12)

Animal group	Lobe height, cm					
	first	second	third	fourth	fifth	sixth
Intact	2.27 ± 0.06	1.75 ± 0.11	1.58 ± 0.19	1.20 ± 0.15	0.75 ± 0.07	1.74 ± 0.17
Control	2.53 ± 0.18*	1.83 ± 0.17	1.82 ± 0.17*	1.61 ± 0.18*	0.89 ± 0.04	2.31 ± 0.09*
(**XX**)	2.39 ± 0.10	1.49 ± 0.16	1.04 ± 0.07	0.94 ± 0.06	0.97 ± 0.09	2.46 ± 0.18*
(**XXI**)	2.52 ± 0.10*	1.65 ± 0.13	1.65 ± 0.12	1.12 ± 0.07	1.00 ± 0.06	2.02 ± 0.13
(**XXII**)	2.59 ± 0.12*	2.89 ± 0.17*	1.26 ± 0.14	1.07 ± 0.06	0.95 ± 0.05	2.65 ± 0.16*
(**XXIII**)	2.62 ± 0.17*	2.28 ± 0.20*	1.75 ± 0.14	1.18 ± 0.08	1.04 ± 0.08	2.229 ± 0.09*
Reference	2.49 ± 0.08	1.64 ± 0.06	1.39 ± 0.04	1.05 ± 0.06	0.92 ± 0.06	2.28 ± 0.08*

* Significant differences relative to the intact group ($p \leq 0.05$).

groups. The thyroid width index of the other experimental groups insignificantly changed but the average value of this indicator was lower than in the above three groups.

After the slaughter of rats, the liver was extracted from the abdominal cavity to measure organometric parameters of all liver lobes. The results are presented in Tables 2 and 3. The most pronounced changes at the organometric level were found in rats of the control group. The measured linear sizes of the liver lobes of rats vary in different groups. Significant differences in the length of all liver lobes except the fifth lobe were revealed in the control group of animals. We did not observe significant differences in the liver lobe length in the intact group in comparison with the indicators in rats treated with compound (**XX**). A significant increase in the lengths of the first, second, fifth, and sixth liver lobes was noted in rats of the experimental groups, which received pharmacocorrection of dexamethasone-induced DM with compounds (**XXII**) and (**XXIII**). The most pronounced changes at the organometric level in the height of the liver lobes were found in the control group of animals treated with dexamethasone without pharmacocorrection. The height of the first, third, fourth, and sixth liver lobes in the control group significantly ($p < 0.05$) increased compared with the values in the intact group (Table 3). The measurements of the height of the liver lobes in rats of the experimental groups indicate an increase in the first, second, and sixth liver lobes of rats treated with compounds (**XXII**) and (**XXIII**) for pharmacocorrection of dexamethasone-induced DM.

The studies of morphological parameters of the liver (changes in relative and absolute weight, volume, and density) revealed the most pronounced hepatomegaly in animals of the control group, which had an averaged absolute liver weight of 16.43 g (3.4% of body weight) in comparison with an average of 14.44 g (2.8% of body weight) in animals of the intact group [77]. At the same time, the average liver weight of rats treated with compound (**XX**) slightly differed from that of the intact group and amounted to 12.90 g (2.74% of body weight). The maximum number of pathological changes (88.9%) was revealed in animals of the control dexamethasone-treated rats without correction. In 77.8% of cases, the liver of rats from this group had a whitish-gray color, which is characteristic of GCS-induced cholestatic hepatitis. Visual examination and monitoring of the dynamics of changes in the condition of the skin were also performed to assess the severity of steroid diabetes and the effectiveness of pharmacocorrection with compounds (**XX–XXIII**). The presence of non-healing wounds and ulcers, the dynamics of recovery, and the severity of alopecia were taken into account. The results are presented in Tables 4 and 5.

Table 4 shows skin changes in the animals of the experimental groups, which were treated with compounds (**XX–XXIII**) for pharmacocorrection of simulated DM. The control group of rats showed a low number of wounds in the healing stage. It is noteworthy that 11 out of 17 animals had no wounds at all after using compound (**XXI**) as a corrector of metabolic disorders in diabetes mellitus.

In general, modeling of dexamethasone-induced DM has led to a change in the appearance of the coat. The results in Table 5 demonstrate that administration

Table 4. Quantitative characteristics of rats of experimental groups with wound defects

Animal group	Wounds				In total
	absent	purulent-necrotic	non-purulent	in the healing stage	
Intact	11	0	0	1	12
Control	4	0	3	2	9
(**XX**)	3	1	4	9	17
(**XXI**)	11	1	1	4	17
(**XXII**)	4	1	4	5	14
(**XXIII**)	4	1	3	5	13
Reference	4	2	4	7	17

Table 5. Severity of alopecia in rats in experimental groups

Animal group	Severity of alopecia				In total
	absent	weakly pronounced	moderately pronounced	strongly pronounced	
Intact	12	0	0	0	12
Control	2	1	2	4	9
(**XX**)	3	1	12	1	17
(**XXI**)	6	4	5	2	17
(**XXII**)	1	4	5	4	14
(**XXIII**)	1	4	4	4	13
Reference	5	4	6	2	17

Table 6. Results of biochemical analysis of rat blood in an experiment of modeling steroid diabetes mellitus followed by pharmacocorrection with compounds (**XX–XXIII**)

Animal group		Glucose, mM	Bilirubin, μ	ALT, mM	AST, mM	Thymol, U	Cholesterol, mM	TGL, mM
Intact	M	5.53	10.98	1.45	1.62	1.28	2.48	2.05
	m	0.21	2.74	0.15	0.24	0.10	0.09	0.22
Control	M	11.73	15.83	2.75	2.04	2.31	4.11	4.38
	m	0.27	2.48	0.29	0.21	0.64	0.60	1.42
(**XX**)	M	6.47	10.95	1.31	1.51	0.88	2.22	1.44
	m	0.48	1.58	0.16	0.15	0.10	0.08	0.10
(**XXI**)	M	5.59	16.32	1.46	1.95	1.11	2.49	2.10
	m	0.21	2.98	0.15	0.14	0.08	0.09	0.20
(**XXII**)	M	5.42	13.21	0.98	1.68	0.83	2.36	1.58
	m	0.20	1.91	0.11	0.16	0.08	0.07	0.11
(**XXIII**)	M	5.18	11.85	1.66	1.42	1.21	2.28	1.37
	m	0.32	2.62	0.17	0.19	0.11	0.14	0.08
Reference	M	7.12	12.63	2.62	2.02	2.15	2.88	2.5
	m	0.26	0.93	0.12	0.12	0.18	0.14	0.25

M, the average value; m, the standard error; ALT, alanine aminotransferase; AST, aspartate aminotransferase; TGL, triglycerides.

of compound (**XXI**) to rats for three weeks prevents the occurrence of dexamethasone-induced alopecia (baldness) in 35% of cases and significantly affects the degree of its severity in other cases. Severe alopecia was developed in seven rats of the control group.

At the end of the experiment, animal blood was sampled to determine biochemical parameters and liver markers. Table 6 demonstrates that the maximum level of glycemia is observed in rats of the control group (i.e., in animals, which received no pharmacocorrection after exposure to dexamethasone). Although this indicator was significantly lower than that after the first stage of DM modeling, it was still high enough to diagnose steroid DM. It has been found that all four compounds (**XX–XXIII**) have pronounced hypoglycemic activity. The values of glucose levels are close to the values for intact animals. The reference drug metformin turned out to be less effective in comparison with the action of studied compounds (**XX–XXIII**). In addition to hyperglycemia in animals of the control group, the highest possible values of other biochemical markers should be noted except the bilirubin level.

In general, the biochemical parameters of rat blood indicate that all the studied compounds (**XX–XXIII**) showed hypoglycemic activity. The glucose concentration was 6.47, 5.59, 5.42, and 5.18 mM for compounds (**XX**), (**XXI**), (**XXII**), and (**XXIII**), respectively, which is significantly lower than the values in the control and even reference groups (11.73 and 7.12 mM, respectively). The main indicators of hepatic metabolism (bilirubin levels and ALT and AST enzyme activity) and lipid metabolism (cholesterol and THR levels) were maximal in the control group rats. The exception was the indicator of bilirubin level in the experimental group after using 1,4-dihydropyridine (**XXI**). The bilirubin level was minimal in the experimental group against the background of dihydropyridine (**XX**) administration and was comparable to the same indicator in the intact group (10.95 and 10.98 μM, respectively) versus 15.83 μM in the control group. There were no significant differences in the activity of both studied transaminases in the blood of

rats of the experimental groups treated with compounds (**XX–XXIII**) and the intact group. The concentration of cholesterol and triglycerides in the experimental group of rats treated with compound (**XX**) was also lower than the corresponding values in the group of intact animals. The cholesterol and triglyceride levels in the blood of rats of the experimental group against the background of using 1,4-dihydropyridine (**XXI**) were similar to those in animals of the intact group.

EXPERIMENTAL

The IR spectra were recorded on a Vertex 70 spectrophotometer (Bruker, Germany) equipped with an ATR device on a diamond crystal (± 4 cm^{-1} accuracy). The NMR spectra were recorded on an Avance III HD 400 MHz spectrometer (400.17 MHz for ^1H, and 100.63 MHz for ^{13}C; Bruker, Germany) in a DMSO-d_6 solution. The residual DMSO signal was used as a reference signal (δ_H 2.49, δ_C 39.50 ppm). The purity of the synthesized samples was controlled by TLC on Sorbfil-A plates (Imid Ltd, Krasnodar, Russia) using acetone-petroleum ether (1 : 1) or ethyl acetate-hexane (1 : 1) eluent mixtures and stained with iodine vapors and UV detector.

Synthesis of allyl 6-[(2-(arylamino-2-oxoethyl)thio]-5-cyano-4-(2-furyl)-2-methyl-1,4-dihydropyridine-3-carboxylates (XX, XXI) (general procedure). **Morpholinium 5-((allyloxy)carbonyl)-3-cyano-4-(2-furyl)-6-methyl-1,4-dihydropyridine-2-thiolate (XXVI).** Trace amounts of morpholine (10 μL) were added to a mixture of freshly distilled furfural (3.0 mL, 36.2 mmol) and cyanothioacetamide (**XXIV**) [78] (3.63 g, 36.2 mmol) in EtOH (15 mL) under intensive stirring and stirred at 25°C until complete conversion according to TLC (precipitation of a dark-yellow Knoevenagel condensation product, 3-(2-furyl)-2-cyanothioacrylamide (**XXV**) was observed). Allyl acetoacetate (5.1 mL, 37 mmol) and morpholine (4.3 mL, 50 mmol) were then added dropwise to the suspension of thioacrylamide (**XXV**) under vigorous stirring. The resulting mixture was stirred at 25°C for 3 h and then was kept for 24 h. The precipitate was filtered off, washed with acetone and dried at 60°C. Thiolate (**XXVI**) was obtained with a yield of 12.1 g (83%) as a pinkish-beige powder.

Alkylation of thiolate (XXVI). Thiolate (**XXVI**) (1.5 g, 3.85 mmol) was suspended in 15 mL of EtOH, and 10% aqueous KOH (2.0 ml, 3.86 mol) was added under stirring. The mixture was stirred until dissolution, followed by dipping through a paper filter to a solution of α-chloroacetanilide or *N*-(3-methoxyphenyl)-α-chloroacetamide (3.85 mmol) in EtOH (10 mL). The mixture was stirred for 3 h, and the precipitate was filtered off and washed with aqueous EtOH, and dried at 60°C.

Allyl 5-cyano-4-(2-furyl)-6-{[2-(3-methoxyphenyl)-amino-2-oxoethyl]thio}-2-methyl-1,4-dihydropyridine-3-carboxylate (XX). White powder; yield: 82%. IR, ν, cm^{-1}: 3300 br, s, 3180 br, s (N–H), 2204 s (C≡N), 1675 br, s (COOR, CONH); ^1H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.31 s (3H, Py-CH_3), 3.74 s (3H, OCH_3), 3.92 *AB*-pattern (SC$\underline{H}_2$, ^2J 15.0), 4.48–4.56 m (2H, OC$\underline{H}_2$CH=), 4.68 s (1H, C^4H Py), 5.13–5.19 m (2H, signals overlapped =CH_2), 5.83–5.92 m (1H, $OCH_2C\underline{H}$=CH_2), 6.05 d (1H, H^3 furyl, ^3J 3.1), 6.31–6.33 m (1H, H^4 furyl), 6.70 dd (1H, H^4 3-$MeOC_6H_4NH$, ^3J 8.2, ^4J 2.1), 7.11 d (1H, H^6 3-$MeOC_6H_4NH$, ^3J 8.5), 7.22–7.25 m (2H, H^2, H^5 3-$MeOC_6H_4NH$), 7.50–7.51 m (1H, H^5 furyl), 9.96 s (1H, NH Py), 10.00 s (1H, C(O)NH); ^{13}C NMR DEPTQ (101 MHz, DMSO-d_6), δ_C, ppm: 18.5* (CH_3-Py), 35.6* (C^4H Py), 36.9 (SCH_2), 55.0* (MeO), 64.0 ($\underline{C}H_2O$), 85.5 (C^5 Py), 97.3 (C^3 Py), 105.4* (C^2H 3-$MeOC_6H_4NH$), 105.5* (C^3H furyl), 109.3* (C^4H 3-$MeOC_6H_4NH$), 110.5* (C^4H furyl), 111.9* (C^6H 3-$MeOC_6H_4NH$), 117.1 (=CH_2), 118.7 (C≡N), 129.7* (C^5H 3-$MeOC_6H_4NH$), 132.9* (C$\underline{H}$=CH_2), 139.5 (C^1 3-$MeOC_6H_4NH$), 142.4* (C^5H furyl), 144.0 (C^6 Py), 146.9 (C^2 Py), 155.9 (C^1 furyl), 159.5 (C^3 3-$MeOC_6H_4NH$), 165.6 (COOR), 167.1 (C(O)NH). Calculated, %: C, 61.92; H, 4.98; N, 9.03; Found, %: C, 61.88; H, 5.08; N, 8.96. $C_{24}H_{23}N_3O_5S$ (M 465.52).

*The signal is in the opposite phase.

Allyl 5-cyano-4-(2-furyl)-2-methyl-6-{[2-(phenyl-amino)-2-oxoethyl]thio}-1,4-dihydro-pyridine-3-carboxylate (XXI). White powder; yield: 84%. IR, ν, cm^{-1}: 3302 br, s, 3146 br, s (N–H), 2201 s (C≡N), 1699 s,

1653 m (2 C=O); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.31 s (3H, Py-CH_3), 3.94 *AB*-q (S$\underline{CH}_2$, ^2J 14.9), 4.48–4.56 m (2H, O$\underline{CH}_2$CH=), 4.67 s (1H, C^{4}H Py), 5.12–5.20 m (2H, signals overlapped =CH_2), 5.83–5.92 m (1H, OCH$_2$C$\underline{H}$=CH_2), 6.05 d (1H, H^3 furyl, ^3J 3.2), 6.32–6.33 m (1H, H^4 furyl), 7.07–7.10 m (1H, H^4 PhNH), 7.31–7.35 m (2H, H^3 H^5 PhNH), 7.51–7.52 m (1H, H^5 furyl), 7.55 d (2H, H^2 H^6 PhNH, ^3J 7.6), 10.08 br.s (1H, NH), 10.39 br.s (1H, CONH). ^{13}C NMR DEPTQ (101 MHz, DMSO-d_6), δ_C, ppm: 18.5* (CH_3-Py), 35.5* (C^{4}H Py), 36.7 (SCH_2), 64.1 ($\underline{C}H_2$O), 85.2 (C^5 Py), 97.4 (C^3 Py), 105.5* (C^{3}H furyl), 110.6* (C^{4}H furyl), 117.1 (=CH_2), 118.9 (C≡N), 119.6* (2C, C^{2}H C^{6}H NHPh), 124.1* (C^{4}H NHPh), 128.9* (2C, C^{3}H C^{5}H CH NHPh), 132.9* (C$\underline{H}$=CH_2), 138.3 (C^1 NHPh), 142.5* (C^{5}H furyl), 144.3 (C^6 Py), 147.2 (C^2 Py), 156.0 (C^1 furyl), 165.6 (COOR), 167.0 ($\underline{C}$(O)NHPh); Calculated, %: C, 63.43; H, 4.86; N, 9.65; Found, %: C, 63.40; H, 4.95; N, 9.60. $C_{23}H_{21}N_3O_4S$ (M 435.50).

*The signal is in the opposite phase.

Synthesis of *N*-(3,4-dichlorophenyl)-2-{[3-cyano-4-(2-furyl)-6-oxo-1,4,5,6-tetrahydro-pyridine-2-yl]-thio}acetamide (XXII). A sample (1.00 g, 3.1 mmol) of *N*-methylmorpholinium 6-oxo-4-(2-furyl)-3-cyano-tetrahydropyridine-2-thiolate (**XXVII**) [70, 71] was dissolved in hot 60% EtOH (mL). The resulting solution was added through a paper filter to the hot solution (50–60°C) of 2-chloro-*N*-(3,4-dichlorophenyl)acetamide (0.74 g, 3.1 mmol) in EtOH (15 mL). The mixture was brought to a boil with stirring and left for 24 h. The precipitate was filtered off after 24 h, washed with 60% EtOH and petroleum ether and dried at 60°C. Beige powder; yield: 76%; IR, ν, cm^{-1}: 3302, 3113 br, s (N–H), 2212 s (C≡N), 1703 s, 1666 s (2 C=O); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.65 dd (1H, *cis*-C^{5}H, ^2J 16.5, ^3J 4.4), 2.91 dd (1H, *trans*-C^{5}H, ^2J 16.4, ^3J 7.1), 3.97 br.s (2H, SC$\underline{H}_2$), 4.12 dd (1H, H^4, ^3J 4.4, ^3J 7.1), 6.21 d (1H, H^3 furyl, ^3J 3.3), 6.39 dd (1H, H^4 furyl, ^3J 3.3, ^3J 1.8), 7.45 dd (1H, C^{6}H NHAr, ^3J 8.8, ^4J 2.4), 7.59 d (1H, C^{5}H NHAr, ^3J 8.8), 7.61 dd (1H, H^5 furyl, ^3J 1.8, ^4J 0.7), 7.94 d (1H, C^{2}H NHAr, ^4J 2.4), 10.64 s (1H, NH), 10.68 s (1H, NH); ^{13}C NMR DEPTQ (101 MHz, DMSO-d_6), δ_C, ppm: 33.3* (C^{4}H), 34.6 (C^{5}H$_2$), 36.0 (S$\underline{C}$H$_2$), 89.8 (C^3), 106.4* (C^3 furyl), 110.5* (C^4 furyl), 117.8 (C≡N), 119.5* (CH Ar), 120.6* (CH Ar), 125.4 (C–Cl), 130.9* (CH Ar), 131.1 (C–Cl), 138.6 (C^1 ArNH), 143.2* (C^5 furyl), 147.4 (C^2), 152.3 (C^1 furyl), 167.0 (C(O)NHAr), 168.4 (CONH Py); Calculated, %: C, 51.20; H, 3.10; N, 9.95; Found, %: C, 51.16; H, 3.15; N, 9.93. $C_{18}H_{13}Cl_2N_3O_3S$ (M 422.29).

*The signal is in the opposite phase.

Synthesis of 4-(2-{[3-cyano-4-(2-furyl)-6-oxo-1,4,5,6-tetrahydropyridine-2-yl]thio}acet-amido)-benzoic acid (XXIII). A sample (1.00 g, 3.1 mmol) of *N*-methylmorpholinium 6-oxo-4-(2-furyl)-3-cyano-tetrahydropyridine-2-thiolate (**XXVII**) [70, 71] was dissolved in hot 60% EtOH (15 mL). The resulting solution was added through a paper filter to a warm solution (40–50°C) of 4-(2-chloroacetamido)benzoic acid (0.72 g, 3.1 mmol), pre-neutralized by an equimolar amount of $NaHCO_3$ in 60% ethanol (15 mL). The mixture was stirred for 6 h and left for 24 h. Then 10% HCl was added dropwise to the resulting suspension under stirring to adjust pH to 3–4. The precipitate was filtered off after 6 h, washed with 60% NaOH and petroleum ether, and dried at 60°C. Beige powder; yield: 74%; IR, ν, cm^{-1}: 3306, 3269, 3200, 3126 br, m (N–H, O–H), 2210 s (C≡N), 1688 br. s 1668 br. s (3 C=O); ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 2.65 dd (1H, *cis*-C^{5}H, ^2J 16.3, ^3J 3.7), 2.91 dd (1H, *trans*-C^{5}H, ^2J 16.3, ^3J 6.9), 4.01 br.s (2H, SC$\underline{H}_2$), 4.11–4.14 m (1H, H^4), 6.21–6.22 m (1H, H^3 furyl), 6.38–6.39 m (1H, H^4 furyl), 7.61–7.62 m (1H, H^5 furyl), 7.68 d (2H, CH NHAr, ^3J 8.2), 7.91 d (2H, CH NHAr, ^3J 8.2), 10.66 s (1H, NH), 10.71 br.s (1H, NH), 12.78 br.s (1H, COOH); ^{13}C NMR DEPTQ (101 MHz, DMSO-d_6), δ_C, ppm: 33.3* (C^{4}H), 34.7 (C^{5}H$_2$), 36.1 (S$\underline{C}$H$_2$), 89.5 (C^3), 106.4* (C^3 furyl), 110.6* (C^4 furyl), 117.9 (C≡N), 118.8* (2 CH Ar), 125.8 (C^4 Ar), 130.6* (2 CH Ar), 142.5 (C^1 ArNH), 143.2* (C^5 furyl), 147.6 (C^2), 152.3 (C^1 furyl), 166.9 (C(O)NHAr), 167.1 (COOH), 168.4 (CONH Py); Calculated, %: C, 57.42; H, 3.80; N, 10.57; Found, %: C, 57.36; H, 3.88; N, 10.55. $C_{19}H_{15}N_3O_5S$ (M 397.40).

*The signal is in the opposite phase.

Hypoglycemic effect of compounds (XX–XXIII). The experiments were carried out at the Department of Fundamental and Clinical Pharmacology of St. Luke Lugansk State Medical University in the autumn-winter period to exclude the influence of seasonal rhythms. The white mongrel rats from the vivarium were randomly (by the envelope method) divided into groups of ten rats. All laboratory animals were quarantined for two weeks before the experiment. Throughout the experiment, all animals were kept in a vivarium under the same conditions, i.e., in plastic cages for up to six individuals under natural light, the air temperature of 22–24°C, and the relative humidity of 40–50%. There were no restrictions on the amount of standard feed and water. Weekly weighing of animals was carried out throughout the experiment to study the dynamics of changes in body weight. The appearance and behavioral reactions of the animals were monitored daily.

The experiment was performed with 114 male rats (18 months of age), which were divided into seven groups, i.e., intact (12 rats), control (17 rats), experimental (four groups of 17 rats), and reference (17 rats) groups.

In all rats, except for the intact group, steroid diabetes was modeled by administration of glucocorticosteroid dexamethasone (KRKA, Novo Mesto, Slovenia) daily in the morning by intramuscular injection for 13 days at a dose of 125 μg/kg of the body weight [73]. Weekly control weighing of animals was carried out to monitor the dynamics of the body weight.

After 13 days, pharmacocorrection was performed for rats with experimental diabetes. The rats of the experimental, reference, and control groups were treated with studied compounds (**XX–XXIII**), reference drug metformin (2 mL), and a placebo (saline solution, 2 mL), respectively, which were administered *per os* through an atraumatic probe daily for three weeks. Animals of the experimental groups received one of the compounds (**XX–XXIII**) at a dose of 1 mg/kg of weight. Numerous studies previously performed in our department demonstrated the biological activity of other cyanothioacetamide derivatives in various models. The animals of the reference group received metformin at a dose of 200 mg/kg. The dose of the drug was chosen according to the calculated method of dose extrapolation [74].

Wound effects and alopecia were observed visually and recorded at the end of the experiment.

At the end of the experiment, we assessed the severity of DM and the pharmacocorrection results after using compounds (**XX–XXIII**) and the reference drug metformin. For this purpose, we analyzed blood taken during slaughter from the femoral vein of rats of all experimental groups. After the slaughter of rats, the liver and thyroid glands were extracted from the abdominal cavity to measure organometric parameters. An autopsy was performed immediately after slaughter to exclude possible autolysis of tissues and cells by intracellular enzymes.

The levels of glucose, total bilirubin, triglycerides, and cholesterol and the activity of ALT and AST aminotransferases were evaluated using standard techniques using a SOLAR PM 2111 spectrophotometer (SOLAR CJSC, Republic of Belarus). A thymol test (thymol turbidity test) was also performed. Biochemical studies were carried out in the laboratory of the Lugansk Republican Clinical Neuropsychiatric Hospital.

Statistical processing of the results was performed using standard methods of mathematical statistics characterizing quantitative variability. The average value (M), standard error (m), standard deviation σ, variance of values σ^2, and coefficient of variation V were calculated using the Microsoft Excel 6.0 program. The Student's criterion ($p < 0.05$) was used to assess the statistical significance.

CONCLUSIONS

We have described the synthesis of four new hybrid molecules that contain the 4-(2-furyl)-1,4-dihydronicotinonitrile and 4-(2-furyl)-1,4,5,6-tetrahydronicotinonitrile fragments. The structure of the synthesized compounds is confirmed by spectral methods. We have shown a noticeable hypoglycemic effect of all four studied compounds on the model of dexamethasone-induced diabetes mellitus in rats in the state of pronounced senile changes. The results of visual examination and analysis

of organometric parameters of the thyroid gland and liver and biochemical parameters of blood and liver markers have shown that pharmacocorrection with 1,4-dihydropyridine (**XX**) leads to the best metabolic and somatic changes in rats with dexamethasone-induced diabetes mellitus. The hypoglycemic effect of compound (**XX**) exceeds that of the reference drug metformin. At the same time, hybrid compounds with a fragment of 4-(2-furyl)-1,4,5,6-tetrahydronicotinonitrile (structures (**XXII**) and (**XXIII**)) have a noticeable hypoglycemic effect but do not have a hepatoprotective effect.

The presented work shows the prospects for further study of hybrid nicotinonitrile derivatives. Compound (**XX**) has shown the best hypoglycemic effect without pronounced hepatotoxicity.

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ETHICS APPROVAL AND CONSENT TO PARTICIPATES

All manipulations with animals were carried out in accordance with the principles of bioethics, the rules of laboratory practice (GLP), the requirements of the Federal Law of the Russian Federation on 05/14/1993 N 4979-1 "On Veterinary Medicine" (as amended on 07/02/2021), Directive 2010/63/EU of the European Parliament and the Council of the European Union "On the protection of animals used for scientific purposes."

The study was approved by the Bioethics Commission of St. Luke Lugansk State Medical University of the Ministry of Health of the Lugansk Republic (Protocol no. 6 on 11/01/2021).

CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

AUTHOR CONTRIBUTION

All authors made equal contributions to the writing of the article.

DATA AVAILABILITY

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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