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SYNTHESIS AND EVALUATION OF HYPOGLYCEMIC ACTIVITY OF NEW PYRAZOLOTHIAZOLIDINE HYBRID STRUCTURES

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Abstract. New promising pyrazolothiazolidine hybrid structures, containing a methylenehydrazone linker between functionalized pyrazole and thiazolidine cycles, have been obtained using cyclocondensation of 3-aryl-4-formylpyrazole thiosemicarbazones and diethyl acetylenedicarboxylate in mild reactional conditions. The acetic acid was proposed as a catalytic agent for the synthesis of ambident bi-center thiosemicarbazones as reagents for further formation of the thiazolidine cycle. The obtained pyrazolothiazolidines were found to exhibit hypoglycemic activity by *in vivo* study of glucose level in the blood of rats after oral administration of synthesized derivatives

Keywords: pyrazoles, thiazolidinones, hybrid structures, hypoglycemic activity.

1. Introduction

In recent years the search for new effective and safe hypoglycemic drugs for the therapy of type 2 diabetes (T2D) has become especially important [1]. The oral synthetic preparations of various structures are usually used for the treatment of T2D. Some thiazolidinediones or glitazones such as troglitazone, rosiglitazone, pioglitazone (Fig. 1) are widely used in therapy of T2D [2-4].

The chemical modification of the thiazolidine ring with such pharmacophore as a functionalized pyrazole system is a promising way for the creation of new antidiabetic drugs. This approach has been successfully used in development of hypoglycemic drugs such as teneligliptin (Fig. 1), remogliflozin, atorvastatin. But, at the same time, these drugs have a number of side effects, such as anemia risk, swelling of legs or ankles, a high toxicity to hepatocytes and an increase in the incidence of myocardial infarction.

Therefore, the structural modification and synthesis of new pyrazole-1,3-thiazolidine hybrid structures are important in the search for new antidiabetic drugs. In particular, the high hypoglycemic activity *in vitro* of pyrazole-1,3-thiazolidine hybrid molecules was determined in a number of works [5-11]. Also, studies of this type of compounds have shown that they play an important role in modern drug development methodologies, as they are characterized by powelful biological potential [12-17].

Here, we report the design and synthesis of new pyrazolothiazolidines connected with the hydrazone linker, which were then evaluated for hypoglycemic action.

2. Experimental

^{1}H and ^{13}C NMR spectra were acquired on a Varian VXR-400 Spectrometer (400 and 100 MHz, respectively) in DMSO-d_6 with TMS as an internal standard. IR-spectra were recorded on a Bruker Vertex 70 instrument for samples in KBr pellets. Liquid chromatography-mass (LC-MS) spectra were recorded on an Agilent LC/MSD SL using Zorbax SB-C18 column, 4.6×15 mm, 1.8 μm (P/V 82(C) 75-932): solvent DMSO, electrospray ionization at atmospheric pressure (70 eV). Elemental analysis was performed on a Perkin Elmer 2400 series II CHN analyzer, and their results were found to be in good agreement with the calculated values. Melting points were determined on a Kofler bench and are uncorrected. Thin-layer chromatography (TLC) was performed on Merck silica gel plates (60F254) and detection was carried out with ultraviolet light (254 nm).

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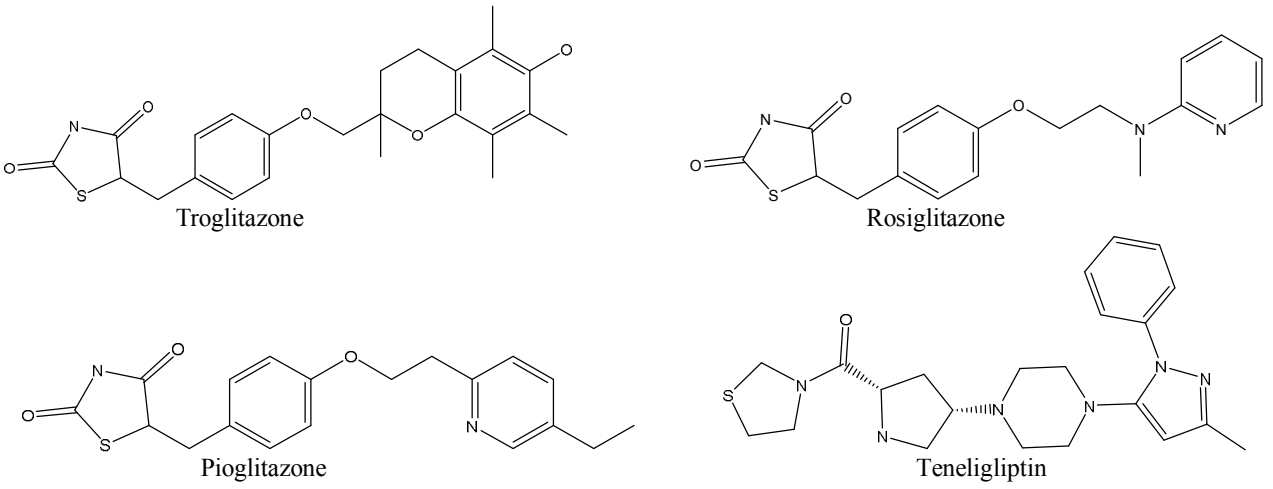


Fig. 1. Known drugs among thiazolidinedione and pyrazole derivatives

3-Aryl-1-phenyl-1*H*-pyrazole-4-carbaldehyde thiosemicarbazones II a-d. 0.46 g (0.005 mol) of thiosemicarbazide and one drop of acetic acid were added to the solution of 0.005 mol of aldehyde **I a-d** in 10 ml of methanol. The mixture was stirred under reflux for 2 h. The obtained precipitate was filtered, washed with water, dried, and recrystallized from methanol.

2-((3-(3-Chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide II a. Yield 76 %. Mp. = 524–526 K. ^{1}H NMR spectra, δ ppm: 7.38 (t, 1H, J = 8.0 Hz, CH_{Ar}); 7.52-7.78 (m, 7H, CH_{Ar}, NH), 7.90 (d, 2H, J = 7.8 Hz, CH_{Ar}); 8.24 (s, 1H, CH=N), 8.28 (s, 1H, NH), 9.19 (s, 1H, $CH_{pyrazol}$), 11.37 (s, 1H, NH). LC-MS, *m/z* (I_{rel}, %): 356 [M+1] (100 %). Found, %: C 57.22; H 3.85; N 19.85. $C_{17}H_{14}ClN_5S$. Calculated, %: C 57.38; H 3.97; N 19.68.

2-((3-(3-Methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide II b. Yield 73 % Mp. = 501–503 K. ^{1}H NMR spectra, δ ppm: 3.85 (s, 3H, CH_3O); 7.03 (d, 1H, J = 8.0 Hz, CH_{Ar}); 7.21 (s, 1H, NH), 7.26 (s, 1H, CH_{Ar}); 7.37-7.45 (m, 3H, CH_{Ar}); 7.56 (t, 2H, J = 8.0 Hz, CH_{Ar}), 7.83 (s, 1H, NH), 7.90 (d, 2H, J=7.8 Hz, CH_{Ar}); 8.25 (s, 1H, CH=), 9.19 (s, 1H, $CH_{pyrazol}$), 11.38 (s, 1H, NH). LC-MS, *m/z* (I_{rel}, %): 352 [M+1] (100 %). Found, %: C 61.24; H 4.99; N 19.71. $C_{18}H_{17}N_5OS$. Calculated, %: C 61.52; H 4.88; N 19.93.

2-((3-(3-(Difluoromethoxy)phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide II c. Yield 81 %. Mp. = 516-518 K. ^{1}H NMR spectra, δ ppm: 7.14–7.51 (m, 4H, CH_{Ar}, CHF_2); 7.56 (t, 2H, J =7.8 Hz, CH_{Ar}), 7.74 (d, 2H, J =7.8 Hz, CH_{Ar}); 7.78 (s, 1H, NH), 7.89 (d, 2H, J = 7.8 Hz, CH_{Ar}), 8.22 (s, 1H, CH=N), 8.25 (s, 1H, NH), 9.17 (s, 1H, $CH_{pyrazol}$), 11.32 (s, 1H, NH). LC-MS, m/z (I_{rel}, %): 388 [M+1] (100 %). Found, %: C 55.52; H 4.01; N 17.87. $C_{18}H_{15}F_2N_3OS$. Calculated, %: C 55.81; H 3.90; N 18.08.

2-((1-Phenyl-3-(pyridin-3-yl)-1*H*-pyrazol-4-yl)methylene)hydrazine-1-carbothioamide II d. Yield 83 %. Mp. = 505-507 K. ^{1}H NMR spectra, δ ppm: 7.39 (t, 1H, J = 7.8 Hz, CH_{Ar}); 7.52–7.58 (m, 3H, CH_{Ar}); 7.48 (s, 1H, NH), 7.90 (d, 2H, J =7.8 Hz, CH_{Ar}), 8.09 (d, 1H, J=8.0 Hz, CH_{Ar}); 8.24 (s, 1H, CH=N-), 8.29 (s, 1H, NH); 8.66 (d, 1H, J = 7.8 Hz, CH_{Ar}); 8.90 (s, 1H, CH_{Ar}); 9.21 (s, 1H, $CH_{pyrazol}$); 11.21 (s, 1H, NH). LC-MS, *m/z* (I_{rel}, %): 323 [M+1] (100 %). Found, %: C 59.87; H 4.49; N 25.86. $C_{16}H_{14}N_6S$. Calculated, %: C 59.01; H 3.8; N 26.07.

Ethyl 2-(2-(((3-aryl-1-phenyl-1*H*-pyrazol-4-yl) methylene)hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate III a-d. 0.22 g (0.0013 mmol) of dimethyl acetylenedicarboxylate were added to the solution of 0.0013 mmol of thiosemicarbazide **II a-d** in 20 ml of methanol. The mixture was stirred under reflux for 1 h. The obtained precipitate was filtrated, washed with water, dried, and recrystallized from methanol.

Ethyl 2-(2-(((3-(3-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate III a. Yield 82 %. Mp. = 509–511 K. IR spectra, ν cm^{-1}: 3396 (NH), 1717 (C=O), 1703 (C=O). ^{1}H NMR spectra, δ ppm: 1.25 (t, 3H, J = 7.2 Hz, CH_3); 4.23 (q, 2H, J = 7.2 Hz, CH_2O); 6.60 (s, 1H, CH=); 7.39-7.57 (m, 5H, CH_{Ar}); 7.84-7.99 (m, 4H, CH_{Ar}); 8.43 (s, 1H, CH=N–); 8.99 (s, 1H, $CH_{pyrazol}$); 12.78 (s, 1H, NH). ^{13}C NMR spectra, δ ppm: 13.7, 60.8, 114.1, 116.1, 118.7, 127.0, 127.2, 127.6, 128.2, 129.3, 129.4, 130.0, 130.4, 130.6, 132.9, 133.6, 138.0, 142.4, 149.7, 159.1, 164.9. LC-MS, *m/z* (I_{rel}, %): 480 [M+1] (100 %). Found, %: C 57.31; H 3.86; N 14.42. $C_{23}H_{18}ClN_5O_3S$. Calculated, %: C 57.56; H 3.78; N 14.59.

Ethyl 2-(2-(((3-(3-methoxyphenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate III b. Yield 93 %. Mp. = 527–529 K. IR spectra, ν cm^{-1}: 3389 (NH), 1715 (C=O), 1705 (C=O). ^{1}H NMR spectra, δ ppm: 1.27 (t, 3H, *J*=7.4 Hz, CH_3); 3.83 (s, 3H, CH_3O); 4.24 (s, 2H, CH_2O); 6.62 (s, 1H, CH=); 7.05 (d, 1H, *J*=7.6 Hz, CH_{Ar}); 7.30-7.58 (m, 6H, CH_{Ar}); 8.00 (d, 2H, *J*=8.0 Hz, CH_{Ar}); 8.49 (s, 1H, CH=N–); 8.99 (s, 1H, $CH_{pyrazol}$); 12.77 (br.s, 1H, NH). ^{13}C NMR spectra, *δ* ppm: 14.0, 55.2, 61.2, 113.8, 114.3, 114.5, 116.3, 119.0, 121.1, 127.2, 129.4, 129.5, 129.6, 129.7, 132.6, 133.0, 138.8, 143.0, 151.5, 152.0, 159.3, 165.4. LC-MS, *m/z* (I_{rel}, %): 476 [M+1] (100 %). Found, %: C 60.52; H 4.30; N 14.96. $C_{24}H_{21}N_5O_4S$. Calculated, %: C 60.62; H 4.45; N 14.73.

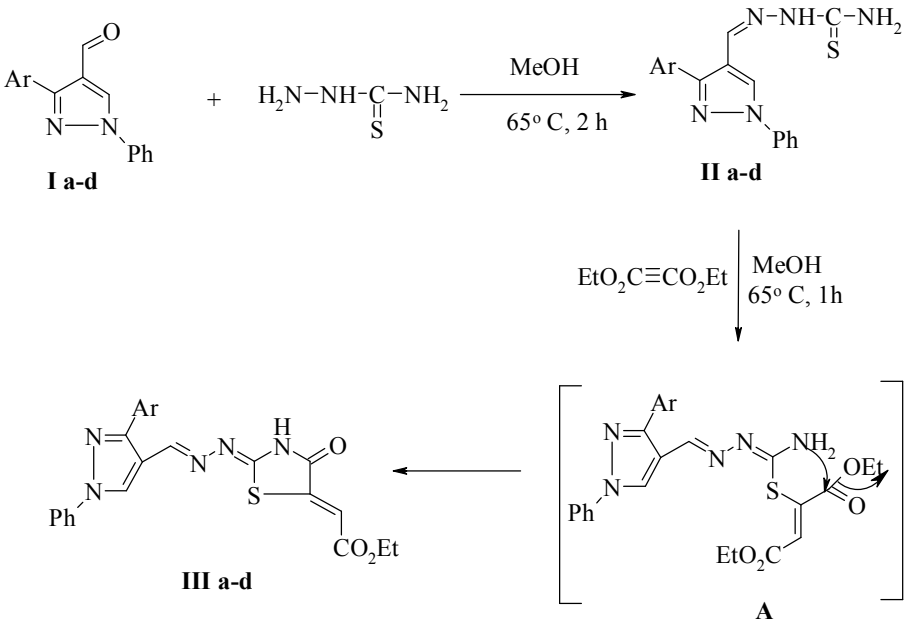
Ethyl 2-(2-(((3-(3-(difluoromethoxy)phenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene)-hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate III c. Yield 88 %. Mp. = 494–496 K. IR spectra, ν cm^{-1}: 3391 (NH), 1719 (C=O), 1701 (C=O). ^{1}H NMR spectra, *δ* ppm: 1.27 (t, 3H, *J* = 7.2 Hz, CH_3); 4.26 (t, 2H, *J* = 7.2 Hz, CH_2O); 6.61 (s, 1H, CH=); 7.13-7.57 (m, 6H, CH_{Ar}, CHF_2O); 7.92-7.99 (m, 4H, CH_{Ar}); 8.51 (s, 1H, CH=N); 9.00 (s, 1H, $CH_{pyrazol}$); 12.76 (br s, 1H, NH). ^{13}C NMR spectra, *δ* ppm: 13.9, 61.2, 114.2, 116.3, 116.4 (t, J_{C-F} = 257.7 Hz), 118.2, 118.8, 127.2, 128.9, 129.6, 129.8, 130.5, 130.6, 131.5, 138.7, 143.2, 150.6, 151.4, 151.5, 159.0, 165.5, 165.8. LC-MS, *m/z* (I_{rel}, %): 512 [M+1] (100 %). Found, %: C 56.18; H 3.65; N 13.87. $C_{24}H_{19}F_2N_5O_4S$. Calculated, %: C 56.36; H 3.74; N 13.69.

Ethyl 2-(4-oxo-2-(((1-phenyl-3-(pyridin-3-yl)-1*H*-pyrazol-4-yl)methylene)hydrazineylidene) thiazolidin-5-ylidene)acetate III d. Yield 91 %. Mp. = = 487–489 K. IR spectra, *ν* cm^{-1}: 3384 (NH), 1714 (C=O), 1703 (C=O). ^{1}H NMR spectra, *δ* ppm: 1.26 (t, 3H, *J*=7.2 Hz, CH_3); 4.25 (d, 2H, *J* =7.2 Hz, CH_2O); 6.59 (s, 1H, CH=); 7.40 (t, 1H, *J*= 8.00 Hz, CH_{Ar}); 7.49-7.58 (m, 3H, CH_{Ar}); 7.94 (d, 2H, *J*= 8.2 Hz, CH_{Ar}); 8.30 (d, 1H, *J*= 8.0 Hz, CH_{Ar}); 8.51 (s, 1H, 1H, CH=N–); 9.66 (s, 1H, CH_{Ar}); 8.95 (s, 1H, CH_{Ar}); 9.05 (s, 1H, $CH_{pyrazol}$); 12.64 (br s, 1H, NH). ^{13}C NMR spectra, *δ* ppm: 14.0, 61.3, 114.4, 116.8, 118.9, 123.4, 127.3, 128.0, 129.6, 131.4, 136.5, 138.7, 142.8, 148.8, 149.0, 149.4, 151.2, 158.9, 165.3, 165.7. LC-MS, *m/z* (I_{rel}, %): 447 [M+1] (100 %). Found: C 59.27; H 3.96; N 19.03. $C_{22}H_{18}N_6O_3S$. Calculated, %: C 59.47; H 4.06; N 18.82.

Experimental in vivo study of hypoglycemic action of (1,3-thiazolidine-5-ylidene)hydrazones of 3-aryl-pyrazole-4-carbaldehydes **III a-d** was conducted with adult non-pedigree male rats (*Rattus rattus* L.) with a body mass of 0.16–0.18 kg. For one month before and during the experiment, the animals were kept in a vivarium under conditions of constant temperature (291–294 K), air humidity (50–55 %) in standard animal cages with free access to drinking water and food to adapt to the experimental conditions. The animals were separated into two subgroups: control (intact rats) and experimental. The selection of derivatives with the ability to influence the concentration of glucose in the blood and a comparison of their hypoglycemic effect was carried out using a primary screening. The evaluation was conducted by comparison of glucose concentration changes in the blood before administration of the studied compounds and after 1, 3, 5, 8, and 24 h. Glucose level in the capillary blood from the rats tail was analyzed using the glucose meter BIONIME Rightest GM 110 (Switzerland). The compounds have been administered in the dose of 17.3 mg/kg. The obtained results of dynamics of the rats blood glucose levels were statistically processed using *Microsoft Excel* [18]. Alloxan-induced diabetes were modeled using intraperitoneal administration of 5 % solution of alloxan monohydrate in the dose of 150 mg/kg.

3. Results and Discussion

4-Formylpyrazoles **I a-d** [19] with aryl and pyridine substituents in the position 3 of the heterocycle were chosen as basic substrates for the synthesis of target hybrid compounds. The corresponding thiosemicarbazones **II a-d** as ambident bi-center reagents for formation of the thiazolidine nucleus were successfully synthesized (yields of 73–83 %) using the structural modification of formyl group of compounds **I a-d** with thiosemicarbazide in a boiling methanol in the presence of acetic acid as a catalytic agent (Scheme 1). It was shown that the cyclocondensation of thiosemicarbazones **II a-d** and diethyl acetylenedicarboxylate, as highly electrophilic and widely used in heterocyclic synthesis [20] reagent, during 1 hour is highly regioselective and leads to undescribed (1,3-thiazolidine-5-ylidene)hydrazones of 3-arylpyrazole-4-carbaldehydes **III a-d** with yields of 82–93 % (Scheme 1). Recently the authors of work [21] have proposed a similar type of transformation, which includes the stage of primary N^5-acylation of the thioureido fragment of the compounds **IIa-d** by acetylenedicarboxylate. However, the majority of publications devoted to this problem [22-25] is shown that the reaction proceeds through the initial formation of the addition Michael's product **A** with the subsequent formation of the thiazolidine ring.



Ar = 3-ClC_6H_4 (a), 3-$MeOC_6H_4$ (в), 3-$F_2CHOC_6H_4$ (c), 3-Pyridyl (d)

Scheme 1. Synthesis of (1,3-thiazolidine-5-ylidene)hydrazones of 3-arylpyrazole-4-carbaldehydes **III a-d**

Table

Change of the glucose level in the rats blood after administration of the compounds III a-d

Compound	Dose, mg/kg	Base value	Time after compound administration, h				
			1	3	5	8	24
III a	17.3	5.5±0.7	7.0±0.4	6.7±0.8	6.1±0.4	5.6±0.6	5.3±0.4
III b	17.3	5.7±1.5	7.25±0.22	5.85±0.22	5.40±0.01	5.15±0.22	6.5±0.5
III c	17.3	5.55±0.22	6.2±0.5	5.25±0.22	4.9±0.43	4.7±0.43	5.6±1.5
III d	17.3	5.75±0.22	7.4±0.22	5.9±0.5	5.6±0.5	5.0±0.4	5.9±0.2
5% solution of alloxan monohydrate	150	5.5±0.7	12.8±0.6	12.6±0.5	12.4±0.5	10.8±0.5	8.8±0.5
III c in the conditions of alloxan-induced DM	17.3	8.8±0.5	7.0±0.4	5.7±0.6	5.4±0.6	5.1±0.6	5.2±0.8
Control		5.4±0.2	5.6±0.2	5.1±0.5	4.9±0.2	5.0±0.2	4.8±0.2

Note: $P \leq 0.05$ (in relation to the base level); DM is diabetes mellitus

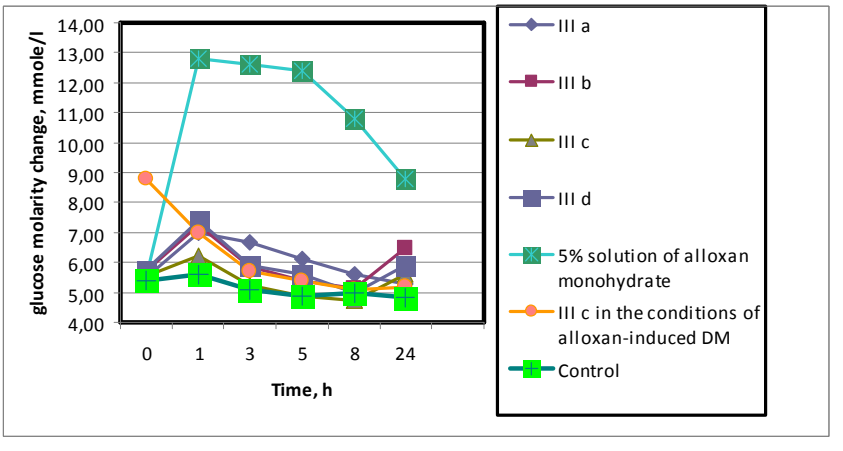


Fig. 2. Influence of the studied compounds **III a-d** on the change of glucose level in the rats blood

The structures of synthesized compounds were confirmed by the data of their ^{1}H, ^{13}C NMR, IR, and LC-MS spectra. In particular, the absorption bands of N–H groups (3384–3396 cm^{-1}) and C=O (1714–1719 and 1701–1705 cm^{-1}) are presented in IR spectra. In the ^{1}H and ^{13}C NMR spectra of compounds **III a-d**, for which rotation around a bond is possible, only one set of resonance signals is present, which indicates the existence of these derivatives in the form of one geometric isomer. Characteristic singlets of protons of exocyclic group CH= at 6.59–6.62 ppm, CH=N at 8.43–8.51 ppm, and broad singlets of NH-protons of the thiazolidine cycle at 12.64–12.78 ppm are presented in ^{1}H NMR spectra. The presence of singlet signal in the range of 6.59–6.62 ppm in the ^{1}H NMR spectra of the obtained compounds confirms the Z-configuration of the exocyclic ethoxycarbonylvinyl fragment [22, 25]. ^{13}C NMR spectra of the formed thiazolidine hybride molecules **III a-d** contain signals of carbon atoms in the ranges of 149.7–152.0 ppm (C^{5}), 158.9–159.3 ppm (C^{2}), and 167.5–165.8 ppm (C^{4}), respectively.

The results of *in vivo* studies of changes in rats blood glucose level after oral administration of the studied compounds **III a-d** have shown the following structure-activity relationship. It was established that the replacement of the phenyl substituent in the pyrazole ring with the pyridyl residue reduces the hypoglycemic effect. The presence of a halogen atom in the phenyl substituent of the pyrazole ring decreases the level of glucose in the blood. It was determined, that the compound **III c**, containing difluoromethoxyphenyl substituent, decreases the glucose concentration the most effectively. Ethyl 2-(2-(((3-(3-(difluoromethoxy)phenyl) -1-phenyl-1H-pyrazol-4-yl)methylene)-hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate **III c** was chosen for the following study of hypoglycemic effect in animals with induced alloxan-induced diabetes mellitus. The last one was induced by an intraperitoneal injection of 150 mg/kg body weight of alloxan monohydrate.

The obtained results are given in the Table and Fig. 2. It was determined that the hypoglycemic activity of the compound **III c** at a dose of 17.3 mg/kg causes a rapid decrease of the glucose concentration in the blood of rats after its introduction. Thus, after 3 h a glucose level decreased on average by 35.2 %, after 5 h – by 38.6 %. It was established that the effect of decrease of the glucose concentration lasted for more than 8 h.

4. Conclusions

Therefore, the synthesis of (1,3-thiazolidine-5-ylidene)hydrazones of 3-arylpyrazole-4-carbaldehydes **III a-d** with high yields of 82–93 % using cyclocondensation of corresponding thiosemicarbazones of 3-aryl-4-formylpyrazoles with diethyl acetylenedicarboxylate was carried out. The convenient use of acetic acid as a catalyst for the synthesis of compounds **II a-d** obtained by the structural modification of formyl group of 3-aryl-4-formylpyrazoles **I a-d**, containing aryl and pyridine substituents in the position 3 of the heterocycle, was shown. It was determined that the proposed cyclocondensation of ambident bi-center reagents **II a-d** with highly electrophilic dipolarophile diethyl acetylenedicarboxylate is regioselective. The hypoglycemic effect in the conditions of oral administration of synthesized compounds **III a-d** has been determined by *in vivo* study. It was found that ethyl 2-(2-(((3-(3-chlorophenyl)-1-phenyl-1*H*-pyrazol-4-yl)methylene) hydrazineylidene)-4-oxothiazolidin-5-ylidene)acetate **III c** is a promising hypoglycemic substance with the effect of more than 8 h in the conditions of alloxan-induced diabetes mellitus at a concentration of 17.3 μg/kg.

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СИНТЕЗ ТА ОЦІНКА ГІПОГЛІКЕМІЧНОЇ АКТИВНОСТІ НОВИХ ПІРАЗОЛО-ТІАЗОЛІДИНОВИХ ГІБРИДНИХ СТРУКТУР

Анотація. *Циклоконденсацією тіосемикарбазонів 3-арил-4-формілпіразолів із діетиловим естером ацетилендикарбонової кислоти у м'яких реакційних умовах отримані перспективні гібридні структури, в яких функціоналізовані піразольний і тіазолідиновий цикли з'єднані метиленгідразоновим лінкером. Запропоновано використання оцтової кислоти як каталітичної добавки у реакції одержання амбідентних біцентрових тіосемикарбазонів - реагентів для подальшого формування тіазолідинового циклу. In vivo дослідженням змін рівня глюкози у крові щурів після перорального введення синтезованих похідних встановлено сполуки з вираженим гіпоглікемічним ефектом.*

Ключові слова: *піразоли, тіазолідинони, гібридні структури, гіпоглікемічна активність.*