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СИНТЕЗ, АНАЛЬГЕТИЧЕСКАЯ И ПРОТИВОМИКРОБНАЯ АКТИВНОСТЬ N-ГЕТАРИЛАМИДОВ 2-(2-(ДИАРИЛМЕТИЛЕН)ГИДРАЗОНО)-5,5-ДИМЕТИЛ-4-ОКСОГЕКСАНОВОЙ КИСЛОТЫ

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Новые N-гетарилзамещенные 2-((диарилметилен)гидразоно)-5,5-диметил-4-оксогексанамиды были получены в 4 стадии, которые включали конденсацию Кляйзена между пинаколином и диэтилоксалатом в присутствии метилата натрия, конденсацию пивалоилпировиноградной кислоты с диарилметиленгидразонами с образованием 2-диарилметиленгидразоно-4-оксо-5,5-диметилгексановой кислоты, внутримолекулярную циклизацию гидразонокислот в гидразонофураноны, дециклизацию последних под действием гетероциклических аминов. Выделение N-гетарил-2-((диарилметилен)гидразоно)-5,5-диметил-4-оксогексанамидов осуществлялось фильтрованием полученного осадка с последующей перекристаллизацией из этанола или пропан-2-ола. Структура полученных соединений подтверждена методами ^{1}H и ^{13}C ЯМР спектроскопии, элементного анализа. Установлено, что полученные замещенные гетариламиды существуют в растворах дейтерированного хлороформа и диметилсульфоксида в гидразоноформе, в отличие от ранее изученных растворов замещённых сложных эфиров аналогичных кислот, где наблюдалось не менее двух таутомерных форм. Изучена анальгетическая и противомикробная активность синтезированных соединений. Анальгетическая активность изучалась по методу термического раздражения «горячая пластина» на белых беспородных мышах обоего пола при внутрибрюшинном введении. Противомикробная активность изучалась методом двукратных серийных разведений в жидкой питательной среде по отношению к двум

штаммам - S. aureus ATCC 6538-P и E. coli ATCC 25922. У исследуемых соединений обнаружена выраженная анальгетическая активность, достоверно превышающая таковую препарата сравнения метамизола натрия, а в некоторых случаях соответствующая действию референтного диклофенака натрия. Следовательно, можно заключить, что наличие выраженной анальгетической активности у синтезированных гетариламидов при наличии слабой противомикробной активности или ее полном отсутствии обусловливает перспективность разработки на их основе новой фармакологической активной субстанции с обезболивающими свойствами.

Ключевые слова: 3-имино(гидразоно)-3Н-фуран-2-оны, реакция дециклизации, анальгетическая активность, противомикробная активность, 2,4-диоксобутановые кислоты

SYNTHESIS, ANALGESIC AND ANTIMICROBIAL ACTIVITY OF N-HETARYLAMIDES OF 2-(2-(DIARYLMETHYLENE)HYDRAZONO)-5,5-DIMETHYL-4-OXOHEXANOIC ACID

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New N-hetaryl substituted 2-((diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanamides were obtained in 4 steps: a) Claisen condensation between pinacolone and diethyl oxalate in the presence of sodium methylate; b) the condensation of pivaloyl pyruvic acid with diarylmethylene hydrazones to form 2-diarylmethylenehydrazono-4-oxo-5,5-dimethylhexanoic acid; c) intramolecular cyclization of hydrazonoacids in hydrazonofuranones; d) decyclization of the latter under the action of heterocyclic amines. Isolation of N-hetaryl-2-((diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanamides was carried out by filtration of the resulting precipitate with subsequent recrystallization from ethanol or propane-2-ol. The structure of the obtained compounds was confirmed by the methods of ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. It is established that the obtained substituted hetarylamides exist in solutions of deuterated chloroform and DMSO in hydrazonoform. The analgesic and antimicrobial activity of the synthesized compounds was evaluated. Analgesic activity was studied by the "hot plate" thermal irritation method on outbred white mice of both sexes with intraperitoneal injection. Antimicrobial activity of synthesized compounds was established via two-fold serial dilutions method in a liquid growth medium against two strains - S. aureus ATCC 6538-P and E. soli ATCC 25922. The studied compounds showed pronounced analgesic activity significantly exceeding that of the comparison drug metamizole sodium, and in

some cases corresponding to the action of the reference diclofenac sodium. Therefore, pronounced analgesic activity accompanied with weak antimicrobial activity of the synthesized hetarylamides determines the prospects for the development of a new pharmacological active substance with analgesic properties.

Key words: 3-imino(hydrazono)-3H-furan-2-ones, decyclyzation reaction, analgesic activity, antimicrobial activity, 2,4-dioxobutanoic acids

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INTRODUCTION

3-Imino(hydrazono)-3*H*-furan-2-ones are an interesting substrate in medicinal chemistry at least due to a moiety of 2,4-dioxobutanoic acid preserved in the decyclization reactions. 2,4-Dioxobutanoic acid derivatives ensured the presence of various biological action from analgesic [1, 2] and anti-inflammatory [3] to antiviral [4-13] and antifungal [14, 15], which makes it advisable to synthesize and study them.

However, 3-imino(hydrazono)-3*H*-furan-2-ones can be used not only to create new derivatives of aroyl- and pivaloyl pyruvic acids. The presence of several reaction centers in their structure makes it possible for obtaining of products with various structures [16-21]. The availability and diversity of preparation methods [22-29] is one more advantage of their use.

In this paper, the synthesis of new amides of pivaloyl pyruvic acid, as well as their analgesic and antimicrobial effects, are investigated. Based on these data, it will be possible to assume the expediency of further studying the compounds of this structure as pharmacologically active substances.

EXPERIMENTAL PART

The progress of reactions and the purity of the isolated compounds were monitored by TLC on Silufol plates using diethyl ether – benzene – acetone (10:9:1) as eluent; iodine vapor was used for the spots detection. The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III HD spectrometer at 400 and 100 MHz, respectively. The elemental analyses were obtained with a Leco CHNS-932 analyzer. The melting (decomposition) points were determined using an SMP40 apparatus.

N-hetaryl-2-((diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanamides 4a-i. *The general preparation procedure.* 20 ml of absolute toluene is added to the mixture of 1.0 mmol of the initial furanone **3a** or **3b** and 1.0 mmol of the corresponding heterocyclic amine. The reaction mixture is boiled with stirring for 10-20 min, then left at room temperature for 24 h. After removing the solvent, the precipitate is recrystallized.

2-((Diphenylmethylene)hydrazono)-5,5-dimethyl-4-oxo-*N*-(pyridin-2-yl)hexanamide (4a).

Yield 0.30 g (71%), yellow crystals, mp 156-157 °C (пропан-2-ол). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.15 s (9H, *t*-Bu), 4.16 s (2H, CH_2), 7.34 m (14H_{arom}), 9.16 s (1H, NH). Found, %: C 73.26; H 6.21; N 13.10. $C_{26}H_{26}N_4O_2$. Calculated, %: C 73.22; H 6.14; N 13.14.

2-((Diphenylmethylene)hydrazono)-5,5-dimethyl-*N*-(3-methylpyridin-2-yl)-4-oxohexanamide (4b).

Yield 0.31 g (70%), yellow crystals, mp 161-162 °C (from propane-2-ol). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.11 s (9H, *t*-Bu), 2.43 s (3H, CH_3), 4.08 s (2H, CH_2), 7.43 m (13H_{arom}), 8.93 s (1H, NH). Found, %: C 73.69; H 6.55; N 12.80. $C_{27}H_{28}N_4O_2$. Calculated, %: C 73.61; H 6.41; N 12.72.

2-((Diphenylmethylene)hydrazono)-5,5-dimethyl-*N*-(4-methylpyridin-2-yl)-4-oxohexanamide (4c).

Yield 0.32 g (73%), yellow crystals, mp 154-155 °C (from propane-2-ol). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.15 s (9H, *t*-Bu), 2.31 s (3H, CH_3), 4.15 s (2H, CH_2), 7.38 m (13H_{arom}), 9.21 s (1H, NH). Found, %: C 73.73; H 6.62; N 12.80. $C_{27}H_{28}N_4O_2$. Calculated, %: C 73.61; H 6.41; N 12.72.

2-((Diphenylmethylene)hydrazono)-5,5-dimethyl-*N*-(6-methylpyridin-2-yl)-4-oxohexanamide (4d).

Yield 0.33 g (74%), yellow crystals, mp 187-188 °C (from propane-2-ol). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.17 s (9H, *t*-Bu), 1.87 s (3H, CH_3), 4.19 s (2H, CH_2), 7.41 m (13H_{arom}), 8.88 s (1H, NH). Found, %: C 73.70; H 6.59; N 12.79. $C_{27}H_{28}N_4O_2$. Calculated, %: C 73.61; H 6.41; N 12.72. *M* 440.55.

2-((9*H*-fluoren-9-ylidene)hydrazono)-5,5-dimethyl-4-oxo-*N*-(thiazol-2-yl)hexanamide (4e).

Yield 0.41 g (96%), yellow crystals, mp 200-202 °C (from ethanol). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.18 s (9H, *t*-Bu), 4.17 s (2H, CH_2), 7.00 m (1H$_{arom}$), 7.30 m (2H$_{arom}$), 7.43 m (2H$_{arom}$), 7.54 m (1H$_{arom}$), 7.60 m (2H$_{arom}$), 7.80 m (1H$_{arom}$), 7.86 m (1H$_{arom}$), 10.60 br s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, м. д.: 26.47, 35.36, 44.83, 97.92, 113.78, 120.06, 120.23, 123.04, 128.20, 128.55, 129.88, 130.87, 131.70, 132.32, 135.97, 137.56, 141.63, 142.66, 151.92, 156.34, 157.98, 160.85, 208.88. Found, %: C 66.99; H 5.21; N 13.09; S 7.40. $C_{24}H_{22}N_4O_2S$. Calculated, %: C 66.96; H 5.15; N 13.01; S 7.45.

2-((9*H*-fluoren-9-ylidene)hydrazono)-5,5-dimethyl-4-oxo-*N*-(4-phenylthiazol-2-yl)hexanamide (4f).

Yield 0.40 g (79%), yellow crystals, mp 201-203 °C (from ethanol). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.07 s (9H, *t*-Bu), 4.11 s (2H, CH_2), 7.36 m (3H$_{arom}$), 7.44 m (2H$_{arom}$), 7.51 m (2H$_{arom}$), 7.73 m (1H$_{arom}$), 7.82 m (3H$_{arom}$), 7.96 m (3H$_{arom}$), 12.54 br s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, м. д.: 26.48, 27.34, 36.51, 44.70, 94.21, 102.19, 109.42, 121.11, 121.27, 123.13, 126.22, 128.18, 129.01, 130.35, 130.57, 132.32, 132.87, 134.65, 135.73, 141.23, 142.44, 149.87, 152.08, 154.41, 158.00, 162.41, 209.91. Found, %: C 71.25; H 5.28; N 11.00; S 6.25. $C_{30}H_{26}N_4O_2S$. Calculated, %: C 71.12; H 5.17; N 11.06; S 6.33.

2-((9*H*-fluoren-9-ylidene)hydrazono)-5,5-dimethyl-4-oxo-*N*-(1,3,4-thiadiazol-2-yl)hexanamide (4g).

Yield 0.34 g (78%), yellow crystals, mp 190-192 °C (from ethanol). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.17 s (9H, *t*-Bu), 4.16 s (2H, CH_2), 7.27 m (3H$_{arom}$), 7.45 m (4H$_{arom}$), 7.58 m (2H$_{arom}$), 7.65 m (1H$_{arom}$), 7.79 m (2H$_{arom}$), 8.90 s (1H, CONH). ^{13}C NMR spectrum ($CDCl_3$), δ, м. д.: 26.42, 35.40, 44.87, 98.52, 120.02, 120.38, 122.92, 123.16, 128.29, 128.59, 129.78, 129.88, 130.80, 130.95, 131.35, 131.89, 132.53, 135.84, 141.63, 142.83, 147.92, 151.38, 156.54, 160.87, 208.89. Found, %: C 64.11; H 5.01; N 16.32; S 7.36. $C_{23}H_{21}N_5O_2S$. Calculated, %: C 64.02; H 4.91; N 16.23; S 7.43.

2-((9*H*-fluoren-9-ylidene)hydrazono)-*N*-(5-bromo-1,3,4-thiadiazol-2-yl)-5,5-dimethyl-4-oxohexanamide (4h).

Yield 0.37 g (73%), yellow crystals, mp 203-204 °C (from ethanol). ^{1}H NMR spectrum (400 MHz, $CDCl_3$), δ, ppm: 1.18 s (9H, *t*-Bu), 4.14 s (2H, CH_2), 7.29 m (2H$_{arom}$), 7.43 m (2H$_{arom}$), 7.58 m (2H$_{arom}$), 7.74 m (1H$_{arom}$), 7.79 m (1H$_{arom}$), 10.94 br s (1H, CONH). ^{13}C NMR spectrum ($CDCl_3$), δ, м. д.: 26.40, 35.39, 44.90, 67.08, 98.64, 120.14, 120.42, 123.21, 128.42, 129.65, 130.80, 131.95, 132.61, 135.22, 135.80, 141.64, 142.87, 151.00, 156.57, 160.47, 161.07, 208.87. Found, %: C 54.21; H 4.06; N 13.79; S 6.15. $C_{23}H_{20}BrN_5O_2S$. Calculated, %: C 54.12; H 3.95; N 13.72; S 6.28.

2-((9*H*-fluoren-9-ylidene)hydrazono)-*N*-(benzo[*d*]thiazol-2-yl)-5,5-dimethyl-4-oxohexanamide (4i).

Yield 0.41 g (86%), yellow crystals, mp 234-236 °C (from ethanol). ^{1}H NMR spectrum (400 MHz, DMSO-d_6), δ, ppm: 1.08 s (9H, *t*-Bu), 4.12 s (2H, CH_2), 7.37 m (2H$_{arom}$), 7.51 m (3H$_{arom}$), 7.61 m (1H$_{arom}$), 7.79 m (5H$_{arom}$), 7.93 m (1H$_{arom}$), 11.11 br s (1H, CONH). Found, %: C 70.09; H 5.11; N 11.79; S 6.54. $C_{28}H_{24}N_4O_2S$. Calculated, %: C 69.98; H 5.03; N 11.66; S 6.67.

The study of biological activity was conducted at the Perm State National Research University and at the Perm State Pharmaceutical Academy. When conducting experiments on animals, the rules of laboratory practice and ethical requirements were observed.

Analgesic activity was determined on outbred white mice of both sexes weighing 18-22 g by the "hot plate" thermal irritation method [30]. The studied compounds were injected intraperitoneally in the form of a suspension in a 2% starch solution at a dose of 50 mg/kg. The animals were placed on a metal plate heated to 53.5 °C 30, 60, 90, 120 min after the injection of the compound. The indicator of the change in pain sensitivity (nociception) was the duration of the animals ' stay on the hot plate until the moment of the defensive pain reflex − licking the hind legs or trying to tear all four paws off the surface of the plate. The time of onset of this reflex from the beginning of placing the animal on the plate was measured in seconds (latency period). The maximum duration of the latent period (the cut off period) is 40 s, since the presence of the animal on the plate for a longer time could lead to burning of the paws and causing physical suffering to the animal. The experiment used animals with an initial time of onset of the defensive reflex of no more than 15 s. Each compound was tested on 6 animals. The results were evaluated by increasing the time of the offensive defensive reflex compared to the initial data. The control group of animals was injected with 2% starch mucus. As comparison drugs, dipyrone (metamizole, Farmkhimkomplekt Ltd.) was used at a dose of 93 mg/kg (ED_{50}), and diclofenac (AlfaAesar) at a dose of 10 mg/kg because of the toxicity of the substance.

The experimental results were processed statistically with the calculation of the Fisher-Student criterion [31]. The effect was considered reliable at $p < 0.05$.

To determine the antimicrobial activity, a two-fold serial dilutions method in a liquid growth medium was used against two strains – *S. aureus* ATCC 6538-P and *E. soli* ATCC 25922 [30]. To prepare stock solutions, the studied compound in an amount of 0.05 g was dissolved in 5 ml of dimethyl sulfoxide, obtaining a solution concentration of 10^4 μg/ml. Then working solutions of the substance was prepared as follows: 4 ml of a liquid growth medium was placed in a sterile test tube; 1 ml of the basic solution was added, obtaining a concentration of 2000 μg/ml. Next, a number of serial dilutions of compounds with a two-fold decreasing concentration (from 1000 μg/ml to 0.06 μg/ml) were prepared. An intact liquid growth medium was used as a negative control, and a medium with an introduced culture without the studied compound was used as a positive control.

The cultures were grown in test tubes on a beveled agarized medium (nutrient agar for bacteria); 24 h cultures were used. To prepare a working suspension of microorganisms, the grown culture was washed off with an isotonic sterile sodium chloride solution and the density of the microbial suspension was set according to the turbidity standard of five units. Next, a working solution with a concentration of $5 \cdot 10^6$ CFU/ml was prepared from the obtained microbial suspension. The microbial suspension was introduced into each tube in an amount of 0.1 ml. The microbial load was about $2.5 \cdot 10^5$ CFU/ml. The results were taken into account after 18-24 h of temperature control at 35-37 °C. Minimum inhibitory concentration (MIC) was determined by the absence of visual signs of microbial growth on the growth medium. Substances with a MIC value in the range of 125-1000 μg/ml were evaluated as having low bacteriostatic activity, 15.0-62.5 μg/ml − medium antibacterial activity, 7.8 μg/ml and less − high antibacterial activity. The antibacterial effect of the compounds was compared with that of dioksidin [2,3-bis(hydroxymethyl)quinoxaline 1,4-dioxide, 1% solution, Novosibkhimfarm).

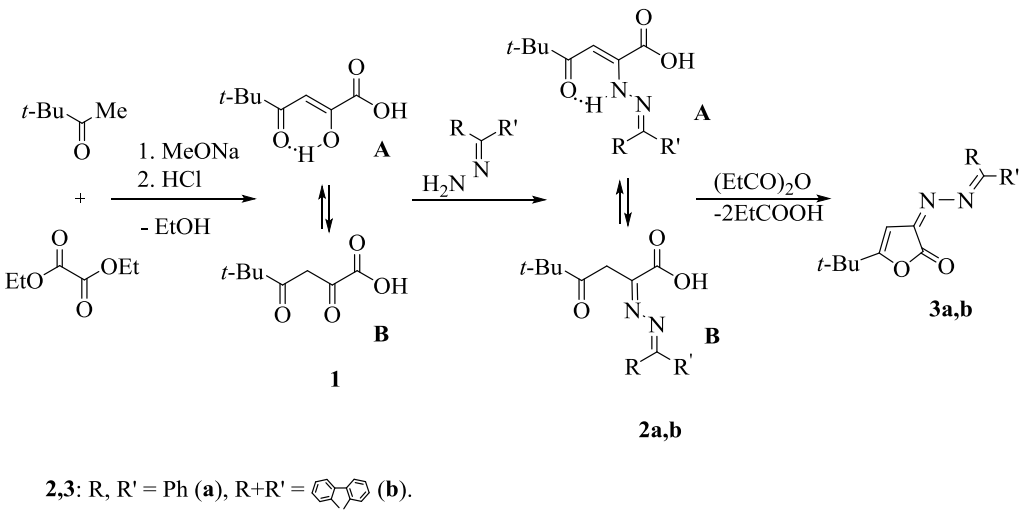
RESULTS AND DISCUSSION

Synthesis of starting hydrazonofuranones **3a,b** is shown on the scheme 1. Firstly, Claisen condensation between pinacolone and diethyl oxalate led to 5,5-dimethyl-2,4-dioxohexanoic acid (pivaloyl pyruvic acid) **1** [32], which interacting with the hydrazones of diarylmethylene ketones gave hydrazonic acids **2a,b** [33]. Hydrazonofuranones **3a, b** were obtained as a result of intramolecular cyclization of acids **2a,b** in a propionic anhydride medium [34, 35].

N-hetaryl-2-((diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanamides **4a-i** were obtained due to the interaction between hydrazonofuranones **3a,b** with heterocyclic amines (scheme 2).

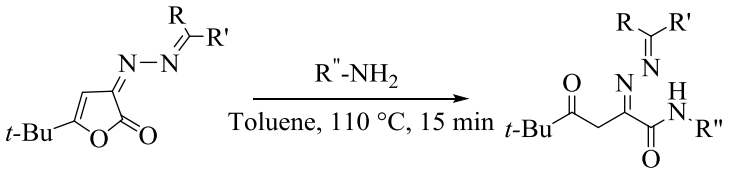
Amides **4a-i** are yellow crystalline compounds obtained with yields of up to 96%, insoluble in ether, hexane, water, hardly soluble in toluene, ethanol and propane-2-ole, easily soluble in dichloromethane, DMSO, chloroform, acetone.

In the ^{1}H NMR spectra of compounds **4a-i** recorded in $CDCl_3$ (**4c,f,i** in DMSO-d_6), a tautomer form of hydrazone is observed, as evidenced by the presence of the methylene group protons signal resonated at δ 4.08-4.17 ppm. In the ^{13}C NMR spectra of compounds **4a-i**, there are characteristic signals of carbonyl carbon C^4 located at δ 208.87-209.91 ppm and the signal of methylene carbon C^3 appeared at δ94.21-98.64 ppm.



2,3: R, R' = Ph (**a**), R+R' = (**b**).

Scheme 1
Схема 1



3a,b **4a-i**

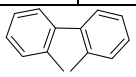
3: R, R' = Ph (**a**), R+R' =  (**b**).
4: R, R' = Ph, R" = pyridine-2-yl (**a**), 3-methylpyridine-2-yl (**b**), 4-methylpyridine-2-yl (**c**), 6-methylpyridine-2-yl (**d**); R+R' =  , thiazol-2-yl (**e**), 4-phenylthiazol-2-yl (**f**), thiadiazol-2-yl (**g**), 5-bromothiadiazol-2-yl (**h**), benzothiazol-2-yl (**i**).

Scheme 2
Схема 2

Table 1

Analgesic activity of compounds 4 studied by the "hot plate" method

Таблица 1. **Анальгетическая активность соединений 4, изученная по методу «горячая пластина»**

Compound no.	R"	c, mg/kg	Defensive response time at the maximum effect, s
R, R' = Ph			
4b	3-methylpyridine-2-yl	50	22.40 ± 3.36*
4c	4-methylpyridine-2-yl	50	12.18 ± 0.45
R + R' = 			
4e	**Thiazol-2-yl**	**50**	**24.20 ± 1.93***
4f	**4-Phenylthiazol-2-yl**	**50**	**26.00 ± 1.00***
4g	**1,3,4-Thiadiazol-2-yl**	**50**	**26.80 ± 2.24***
4h	**5-Bromo-1,3,4-thiadiazole-2-yl**	**50**	**25.60 ± 1.17***
4i	Benzothiazole-2-yl	50	20.60 ± 2.56*
Dipyrone	–	93 (ED_{50})	16.60 ± 1.00*
Diclofenac	–	10	26.20 ± 0.96*
Control	–	–	11.38 ± 0.93

Note: *Reliability with respect to control p <0.05
Примечание: *Надежность по отношению к контролю p<0,05

Analgesic and antimicrobial activities were evaluated for compounds **4**. It was found that the studied compounds have a pronounced analgesic activity, with the exception of compound **4c** (Table 1). The most active compounds were amides **4e-h**, which contain fragments of substituted thiazole or thiadiazole in the amide moiety.

According to the antimicrobial activity tests data, the MIC values of the examined amides are in the range of 500-1000 μg/ml or more, which indicates low bacteriostatic activity or its absence (Table 2).

Table 2

Antimicrobial activity of compounds 4

Таблица 2. **Противомикробная активность соединений 4**

Compound no.	MIC, μg/ml	
	S. aureus ATCC 6538P	*E. coli* ATCC 25922
4a	1000	1000
4b	>1000	>1000
4c	>1000	>1000
4d	500	1000
4e	1000	1000
4g	1000	1000
4i	1000	1000
Dioksidin, 1% solution	62.5	31.0

CONCLUSIONS

New *N*-hetaryl substituted 2-((diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanamides were obtained from commercially available pinacolone and diethyl oxalate in 4 steps with yields of up to 96%. The pronounced analgesic activity of the synthesized substances with low or absent bacteriostatic activity was established, which makes further in-depth research promising in order to develop a new pharmacologically active substance.

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