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СИНТЕЗ, ВНУТРИМОЛЕКУЛЯРНАЯ ЦИКЛИЗАЦИЯ И АНТИНОЦИЦЕПТИВНАЯ АКТИВНОСТЬ 4-(ГЕТ)АРИЛ-4-ОКСО-2-{[4-(4-R-ФЕНИЛ)-3-(ЭТОКСИКАРБОНИЛ)ТИОФЕН-2-ИЛ]АМИНО}БУТ-2-ЕНОВЫХ КИСЛОТ

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В данной работе были изучены новые замещенные 4-(гет)арил-4-оксо-2-{[4-(4-R-фенил)-3-(этоксикарбонил)тиофен-2-ил]амино}бут-2-еновые кислоты. Было установлено, что внутримолекулярная циклизация данных кислот под действием дегидратирующего агента приводит к образованию соответствующих замещенных 3-(тиофен-2-ил)имино-3Н-фуран-2-онов, представляющих большой интерес для дальнейшего изучения. Наличие в структуре изучаемых кислот нескольких реакционных центров позволяет получать продукты гетероциклического и ациклического строения, которые, при этом, сохраняют такие важные фармакофоры как фрагмент 2-аминотиофена и фрагмент 2,4-диоксобутановой кислоты. Исследованные 4-(гет)арил-4-оксо-2-{[4-(4-R-фенил)-3-(этоксикарбонил)тиофен-2-ил]амино}бут-2-еновые кислоты были получены одностадийным способом, обеспечивающим высокие выходы и включающим в себя взаимодействие замещенных 4-(гет)арил-2-гидрокси-4-оксобут-2-еновых кислот с замещенными этиловыми эфирами 2-амино-4-(4-R-фенил)тиофен-3-карбоновых кислот. Подтверждение структуры выделенных итоговых соединений проводилось методами ^{1}H и ^{13}C ЯМР спектроскопии, а также элементного анализа. Затем замещенные 4-(гет)арил-4-оксо-2-тиениламинобут-2-еновые кислоты подвергались скринингу in vivo с целью обнаружения и оценки их биологической активности и острой токсичности. Антиноцицептивная активность изучалась на белых беспородных мышах обоих полов посредством термического раздражения «горячая пластинка» при внутрибрюшинном введении. Острая токсичность изучалась по методу Першина, основанному на наблюдении за состоянием мышей в течении 10 сут после внутрибрюшинного введения тестируемых соединений. Согласно полученным результатам, протестированные соединения обладают выраженной антиноцицептивной активностью, а оценка острой токсичности указывает на их принадлежность к V классу практически нетоксичных препаратов. Высокие значения антиноцицептивной активности в сочетании с низкой токсичностью делают рассмотренные 4-(гет)арил-4-оксо-2-{[4-(4-R-фенил)-3-(этоксикарбонил)тиофен-2-ил]амино}бут-2-еновые кислоты высоко перспективным классом для дальнейшего изучения с целью поиска и разработки новых биологически активных соединений с обезболивающим действием и низкой токсичностью.

Ключевые слова: 2-аминотиофены, 2,4-диоксобутановые кислоты, 3-(тиофен-2-илимино)фуран-2(3Н)-оны, антиноцицептивная активность, токсичность, лекарства, *in vivo*

SYNTHESIS, INTRAMOLECULAR CYCLIZATION AND ANTINOCICEPTIVE ACTIVITY OF 4-(HET)ARYL-2-{[3-(ETHOXYCARBONYL)-4-(4-R-PHENYL)THIOPHEN-2-YL]AMINO}-4-OXOBUT-2-ENOIC ACIDS

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In this work, new substituted 4-(het)aryl-4-oxo-2-{[4-(4-R-phenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}but-2-enoic acids were studied. It was found that the intramolecular cyclisation of these acids under the action of a dehydrating agent leads to the formation of the corresponding substituted 3-(thiophen-2-yl)imino-3H-furan-2-ones, which are of great interest for further study. A content of several reaction centers in its structure allows to obtain products of heterocyclic and acyclic structure, which, at the same time, retain such important pharmacophore groups as the 2-aminothiophene fragment and 2,4-dioxobutanoic acid fragment. The studied 4-(het)aryl-4-oxo-2-{[4-(4-R-phenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}but-2-enoic acids were obtained by a one-step method, providing high yields and involving the interaction of substituted 4-(het)aryl-2-hydroxy-4-oxobut-2-enoic acids with substituted ethyl 2-amino-4-(4-R-phenyl)thiophen-3-carboxylates. The structure of the isolated final compounds was confirmed by ^{1}H and ^{13}C NMR spectroscopy and elemental analysis. Substituted 4-(het)aryl-4-oxo-2-thienylaminobut-2-enoic acids were then screened in vivo to detect and evaluate their biological activity and acute toxicity. The antinociceptive activity was studied in white mice of both sexes by hot plate thermal irritation intraperitonally. Acute toxicity was studied according to Pershin's method, based on observation of mice condition during 10 days after intraperitoneal injection of tested compounds. According to the results obtained, the tested compounds have a pronounced antinociceptive activity, and the acute toxicity assessment indicates that they belong to the V class of practically non-toxic drugs. High values of antinociceptive activity in combination with low toxicity makes the considered 4-(het)aryl-4-oxo-2-{[4-(4-R-phenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}but-2-enoic acids a highly promising class for further study in order to search and develop new biologically active compounds with analgesic action and low toxicity.

Keywords: 2-aminothiophenes, 2,4-dioxobutanoic acids, 3-(thiophene-2-ylimino)furan-2(3*H*)-ones, antinociceptive activity, toxicity, *in vivo*

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INTRODUCTION

Modern medicine is rapidly developing, and entire generations of drugs are becoming obsolete, so there is an urgent need to develop new, more advanced biologically active compounds with low toxicity [1-3].

In the search for new drugs, it is necessary to develop a universal basic structure that combines different pharmacophores and allows a wide range of potentially biologically active compounds to be obtained. Various biological activities are provided by substances that contain 2-aminothiophene or 2,4-dioxobutanoic acid fragments in their structure. They exhibit an anticancer [4-5], antimicrobial [6-9], analgesic [10-12] and other pharmacological effects [13-15].

The 3-imino(hydrazono)furan-2(3*H*)-one derivatives can combine in its structure both pharmacophoric fragments, possess high reactivity and scalability of methods for their synthesis [16-17] and have several reaction centers, that provide the obtaining acyclic [18-21] and heterocyclic products [22-23]. We have found that compounds based on these derivatives possess antinociceptive [24-26], anti-inflammatory [27-30], antimicrobial [31-32] and anticancer properties [33], can also photoluminesce [34-36] and can be used as optical materials [37-38].

EXPERIMENTAL PART

The progress of the reaction and purity of the synthesized compounds were monitored by TLC using Sorbfil precoated plates, eluent – diethyl ether-benzene-acetone (10 : 9 : 1). The ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (working frequencies of 400 and 100 MHz) in $CDCl_3$ and DMSO-d_6. Melting points were measured on a Stuart SMP40 apparatus. Elemental analysis was performed on a Leco CHNS-932 analyser. All reagents used are commercially available and were used as purchased.

The starting 2-aminothiophenes **1a,b** and 4-(het)aryl-2-hydroxy-4-oxobut-2-enoic acids **2a-h** were prepared according to previously published procedures, their melting points and ^{1}H NMR spectra were in agreement with those published [39-40].

Synthesis of 4-(het)aryl-2-{[3-(ethoxycarbonyl)4-(4-R-phenyl)thiophen-2-yl]amino}-4-oxobut-2-enoic acids 3a-h. To a solution of 1.0 mmol of ethyl 2-amino-4-(4-aryl)thiophen-3-carboxylates **1a,b** in 15 mL of methanol was added 1.0 mmol of 4-(het)aryl-2-hydroxy-4-oxobut-2-enoic acids **2a-h**. The resulting solution was stirred for 30 min at 60 °C and then evaporated at a rotary evaporator until the solvent volume is halved. The resulting precipitate was filtered off and washed with cold methanol.

2-{[3-(ethoxycarbonyl)-4-phenylthiophen-2-yl]amino)}-4-(4-fluorophenyl)-4-oxobut-2-enoic acid 3a. Yield 0.43 g (96%), orange crystals, mp 174.5-177.0 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 t (3H, J = 7.1 Hz, CH_3), 4.14 q (2H, J = 7.1 Hz, OCH_2), 6.62 s (1H, N–C=CH), 7.08 s (1H, S–CH=C), 7.32 m (2H, H_{Ar}), 7.37 m (5H, H_{Ar}), 8.12 m (2H, H_{Ar}), 12.69 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.0, 60.8, 98.9, 115.9, 116.2, 116.4, 117.1, 127.7, 128.2, 128.9, 131.0, 131.1, 135.0, 138.0, 141.1, 148.9, 150.4, 163.5, 164.1, 165.0, 166.6, 189.3. Found, %: C, 62.83; H, 4.15; N, 3.17; S, 7.34. $C_{23}H_{18}FNO_5S$. Calculated, %: C, 62.86; H, 4.13; N, 3.19; S, 7.30.

4-(3,4-dichlorophenyl)-2-{[3-(ethoxycarbonyl)-4-phenylthiophen-2-yl]amino}-4-oxobut-2-enoic acid 3b. Yield 0.46 g (93%), orange crystals, mp 192.7-193.4 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 t (3H, J = 7.1 Hz, CH_3), 4.14 q (2H, J = 7.1 Hz, OCH_2), 6.63 s (1H, N–C=CH), 7.11 s (1H, S–CH=C), 7.32 m (2H, H_{Ar}), 7.37 m (3H, H_{Ar}), 7.80 m (1H, H_{Ar}), 8.01 m (1H, H_{Ar}), 8.23 m (1H, H_{Ar}), 12.76 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.0, 60.9, 98.1, 100.0, 116.4, 117.5, 127.7, 128.2, 128.9, 129.9, 131.6, 132.4, 136.0, 136.9, 138.6, 141.1, 145.6, 149.9, 163.4, 164.9, 188.1. Found, %: C, 56.31; H, 3.47; N, 2.89; S, 6.56. $C_{23}H_{17}Cl_2NO_5S$. Calculated, %: C, 56.34; H, 3.49; N, 2.86; S, 6.54.

2-{[3-(ethoxycarbonyl)-4-phenylthiophen-2-yl]amino}-4-(4-hydroxyphenyl)-4-oxobut-2-enoic acid 3c. Yield 0.41 g (94%), red crystals, mp 154.4-155.6 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 t (3H, J = 7.1 Hz, CH_3), 4.13 q (2H, J = 7.1 Hz, OCH_2), 6.59 s (1H, N–C=CH), 6.89 m (2H, H_{Ar}), 7.01 s (1H, S–CH=C), 7.32 m (2H, H_{Ar}), 7.36 m (3H, H_{Ar}), 7.93 m (2H, H_{Ar}), 10.32 s (1H, OH), 12.61 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.0, 60.7, 99.9, 115.1, 116.0, 116.4, 127.6, 128.2, 129.0, 129.7, 130.7, 137.1, 141.03, 147.4, 151.3, 162.5, 163.5, 165.2, 189.4. Found, %: C, 63.13; H, 4.39; N, 3.22; S, 7.31. $C_{23}H_{19}NO_6S$. Calculated, %: C, 63.15; H, 4.38; N, 3.20; S, 7.33.

2-{[3-(ethoxycarbonyl)-4-phenylthiophen-2-yl]amino}-4-(4-nitrophenyl)-4-oxobut-2-enoic acid 3d. Yield 0.35 g (74%), red crystals, mp 169.3-172.5 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.03 t (3H, J = 7.1 Hz, CH_3), 4.15 q (2H, J = 7.1 Hz, OCH_2), 6.63 s (1H, N–C=CH), 7.13 s (1H, S–CH=C), 7.33 m (2H, H_{Ar}), 7.37 m (3H, H_{Ar}), 8.26 m (2H, H_{Ar}), 8.34 m (2H, H_{Ar}), 12.84 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.1, 60.9, 98.2, 105.6, 116.7, 124.3, 127.6, 128.2, 129.0, 129.4, 131.2, 136.9, 138.8, 141.1, 143.4, 150.1, 164.8, 165.5, 188.7. Found, %: C,

59.25; H, 3.87; N, 6.03; S, 6.84. $C_{23}H_{18}N_2O_7S$. Calculated, %: C, 59.22; H, 3.89; N, 6.01; S, 6.87.

{[3-(ethoxycarbonyl)-4-phenylthiophen-2-yl]amino}-4-(5-methylfuran-2-yl)-4-oxobut-2-enoic acid 3e. Yield 0.40 g (94%), orange crystals, mp 191.5-192.0 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.03 t (3H, *J* = 7.1 Hz, CH_3), 2.50 s (3H, CH_3), 4.20 q (2H, *J* = 7.1 Hz, OCH_2), 6.33 d (1H, *J* = 3.5 Hz, H_{Ar}), 6.87 s (1H, N–C=CH), 7.23 s (1H, S–CH=C), 7.31 m (2H, H_{Ar}), 7.37 m (3H, H_{Ar}), 7.41 d (1H, *J* = 3.5 Hz, H_{Ar}), 11.98 s (1H, NH).^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.7, 14.5, 61.4, 97.6, 111.1, 114.9, 117.8, 122.4, 127.8, 127.8, 129.1, 136.9, 142.9, 145.6, 148.0, 151.5, 160.4, 162.2, 164.2, 176.8. Found, %: C, 62.13; H, 4.52; N, 3.25; S, 7.53. $C_{22}H_{19}NO_6S$. Calculated, %: C, 62.11; H, 4.50; N, 3.29; S, 7.54.

2-{(4-chlorophenyl)-[4-(4-chlorophenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}-4-oxobut-2-enoic acid 3f. Yield 0.37 g (75%), orange crystals, mp 182.0-183.0 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.06 t (3H, *J* = 7.1 Hz, CH_3), 4.16 q (2H, *J* = 7.1 Hz, OCH_2), 6.35 s (1H, N–C=CH), 7.02 s (1H, S–CH=C), 7.34 m (2H, $H_{Ar.}$), 7.42 m (2H, $H_{Ar.}$), 7.56 m (2H, $H_{Ar.}$), 7.98 m (2H, $H_{Ar.}$), 13.02 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.2, 60.8, 98.9, 106.1, 116.2, 127.6, 128.1, 129.3, 130.8, 131.7, 132.4, 136.1, 137.6, 139.3, 139.6, 151.4, 165.0, 165.7, 188.8. Found, %: C, 56.32; H, 3.50; N, 2.87; S, 6.54. $C_{23}H_{17}Cl_2NO_5S$. Calculated, %: C, 56.34; H, 3.49; N, 2.86; S, 6.54.

2-{[4-(4-chlorophenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}-4-(furan-2-yl)-4-oxobut-2-enoic acid 3g. Yield 0.32 g (72%), orange crystals, mp 198.6-200.9 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.06 t (3H, *J* = 7.1 Hz, CH_3), 4.15 q (2H, *J* = 7.1 Hz, OCH_2), 6.16 s (1H, N–C=CH), 6.69 m (1H, $H_{Ar.}$), 6.98 s (1H, S–CH=C), 7.32 m (2H, $H_{Ar.}$), 7.35 m (1H, $H_{Ar.}$), 7.42 m (2H, $H_{Ar.}$), 7.93 m (1H, $H_{Ar.}$), 12.76 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.1, 60.7, 98.4, 106.1, 113.2, 115.8, 116.2, 128.1, 130.8, 132.3, 136.3, 137.6, 139.2, 147.2, 151.8, 153.6, 163.4, 165.1, 179.0. Found, %: C, 56.59; H, 3.62; N, 3.12; S, 7.21. $C_{21}H_{16}ClNO_6S$. Calculated, %: C, 56.57; H, 3.62; N, 3.14; S, 7.19.

2-{[4-(4-chlorophenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}-4-oxo-6-phenylhexa-2,5-dienoic acid 3f. Yield 0.38 g (79%), orange crystals, mp 191.4-192.9 °C. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.06 t (3H, *J* = 7.1 Hz, CH_3), 4.15 q (2H, *J* = 7.1 Hz, OCH_2), 6.26 s (1H, N–C=CH), 7.07 s (1H, S–CH=C), 7.13 d (1H, *J* = 16.0 Hz, CH=CH-Ph), 7.34 m (2H, $H_{Ar.}$), 7.45 m (5H, $H_{Ar.}$), 7.67 d (1H, *J* = 16.0 Hz, CH=CH-Ph), 7.75 m (2H, $H_{Ar.}$), 12.63 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ, ppm: 14.1, 60.8, 103.9, 115.9, 116.1, 128.0, 128.2, 129.0, 129.4, 130.8, 130.9, 132.5, 135.2, 136.0, 139.7, 141.9, 147.3, 151.4, 163.3, 165.0, 189.7. Found, %: C, 62.33; H, 4.20; N, 2.92; S, 6.66. $C_{25}H_{20}ClNO_5S$. Calculated, %: C, 62.30; H, 4.18; N, 2.91; S, 6.65.

Synthesis of ethyl 2-{[5-(het)aryl-2-oxofuran-3(2*H*)-ylidene]amino}-4-(4-R$_1$-phenyl)thiophene-3-carboxylates 4a-h. To 1 mmol of 4-(het)aryl-4-oxo-2-{[4-(4-R-phenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}but-2-enoic acids 3a-h was added 4 mL of propionic anhydride and slowly heated under vigorous stirring to 100-110 °C for 2h, monitoring the reaction by TLC. Then the solution was cooled, the precipitate formed was filtered and dried in a vacuum desiccator for 1h.

Ethyl 2-{[5-(4-fluorophenyl)-2-oxofuran-3(2*H*)-ylidene]amino}-4-phenylthiophene-3-carboxylate 4a. Yield 0.27 g (65%), orange crystals, mp 149.7-154.4 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, *J* = 7.1 Hz, CH_3), 4.33 q (2H, *J* = 7.1 Hz, OCH_2), 6.91 s (1H, O–C=CH), 7.25 m (2H, $H_{Ar.}$), 7.36 s (1H, S–CH=C), 7.43 m (5H, $H_{Ar.}$), 7.92 m (2H, $H_{Ar.}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0, 61.8, 97.4, 116.7, 116.9, 123.2, 127.9, 128.1, 128.5, 129.2, 129.2, 134.1, 135.0, 142.3, 147.1, 151.0, 162.1, 164.5, 166.4, 166.9. Found, %: C, 65.57; H, 3.85; N, 3.30; S, 7.59. $C_{23}H_{16}FNO_4S$. Calculated, %: C, 65.55; H, 3.83; N, 3.32; S, 7.61.

Ethyl 2-{[5-(3,4-dichlorophenyl)-2-oxofuran-3(2*H*)-ylidene]amino}-4-phenylthiophene-3-carboxylate 4b. Yield 0.32 g (70%), orange crystals, mp 171.2-173.0 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.25 t (3H, *J* = 7.1 Hz, CH_3), 4.34 q (2H, *J* = 7.1 Hz, OCH_2), 6.95 s (1H, O–C=CH), 7.40 s (1H, S–CH=C), 7.42 m (5H, $H_{Ar.}$), 7.63 m (1H, $H_{Ar.}$), 7.72 m (1H, $H_{Ar.}$), 7.97 m (1H, $H_{Ar.}$). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0, 61.9, 98.6, 124.0, 125.5, 126.9, 127.9, 128.2, 128.2, 128.5, 131.4, 134.1, 134.8, 135.0, 137.5, 142.4, 146.3, 150.6, 161.6, 164.5, 164.8. Found, %: C, 58.47; H, 3.23; N, 2.96; S, 6.77. $C_{23}H_{15}Cl_2NO_4S$. Calculated, %: C, 58.49; H, 3.20; N, 2.97; S, 6.79.

Ethyl 2-{[5-(4-hydroxyphenyl)-2-oxofuran-3(2*H*)-ylidene]amino}-4-phenylthiophene-3-carboxylate 4c. Yield 0.27 g (62%), red crystals, mp 139.3-141.1 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, *J* = 7.1 Hz, CH_3), 4.33 q (2H, *J* = 7.1 Hz, OCH_2), 6.93 s (1H, O–C=CH), 7.32 m (2H, H_{Ar}), 7.36 s (1H, S–CH=C), 7.43 m (5H, H_{Ar}), 7.92 m (2H, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0, 61.7, 97.6, 122.6, 123.3, 124.3, 127.9, 128.0, 128.2, 128.5, 134.0, 135.1, 142.2, 147.2, 154.6, 162.2, 164.5, 166.7, 172.1.

Found, %: C, 65.83; H, 4.11; N, 3.31; S, 7.66. $C_{23}H_{17}NO_5S$. Calculated, %: C, 65.86; H, 4.09; N, 3.34; S, 7.64.

Ethyl 2-{[5-(4-nitrophenyl)-2-oxofuran-3(2*H*)-ylidene]amino}-4-phenylthiophene-3-carboxylate 4d. Yield 0.28 g (63%), red crystals, mp 170.0-172.3 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, *J* = 7.1 Hz, CH_3), 4.34 q (2H, *J* = 7.1 Hz, OCH_2), 7.11 s (1H, O–C=CH), 7.43 m (5H, H_{Ar}), 7.46 s (1H, S–CH=C), 8.07 m (2H, H_{Ar}), 8.40 m (2H, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 13.9, 62.0, 100.2, 123.5, 124.4, 124.8, 127.8, 128.3, 128.6, 129.1, 132.6, 137.2, 142.7, 145.9, 148.7, 162.5, 164.4, 169.0, 170.0. Found, %: C, 61.62; H, 3.59; N, 6.23; S, 7.18. $C_{23}H_{16}N_2O_6S$. Calculated, %: C, 61.60; H, 3.60; N, 6.25; S, 7.15.

Ethyl 2-{[5'-methyl-5-oxo-[2,2'-bifuran]-4(5*H*)-ylidene]amino}-4-phenylthiophene-3-carboxylate 4e. Yield 0.27 g (66%), red crystals, mp 188.8-190.0 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.24 t (3H, *J* = 7.1 Hz, CH_3), 2.50 s (3H, CH_3), 4.33 q (2H, *J* = 7.1 Hz, OCH_2), 6.32 d (1H, *J* = 3.4 Hz, H_{Ar}), 6.76 s (1H, O–C=CH), 7.13 d (1H, *J* = 3.4 Hz, H_{Ar}), 7.32 s (1H, S–CH=C), 7.35 m (5H, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0, 14.2, 61.6, 95.8, 110.4, 114.5, 117.7, 118.9, 122.6, 127.9, 128.4, 137.0, 141.3, 143.1, 145.6, 147.7, 151.4, 160.0, 164.7, 167.0. Found, %: C, 64.83; H, 4.23; N, 3.41; S, 7.89. $C_{22}H_{17}NO_5S$. Calculated, %: C, 64.85; H, 4.21; N, 3.44; S, 7.87.

Ethyl 4-(4-chlorophenyl)-2-{[5-(4-chlorophenyl)-2-oxofuran-3(2*H*)-ylidene]amino}thiophene-3-carboxylate 4f. Yield 0.37 g (76%), red crystals, mp 190.3-191.6 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 t (3H, *J* = 7.1 Hz, CH_3), 4.34 q (2H, *J* = 7.1 Hz, OCH_2), 6.92 s (1H, O–C=CH), 7.35 s (1H, S–CH=C), 7.39 m (4H, H_{Ar}), 7.54 m (2H, H_{Ar}), 7.84 m (2H, H_{Ar}). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 14.0, 61.9, 97.8, 115.5, 123.5, 125.4, 128.0, 128.7, 129.3, 129.7, 133.5, 134.2, 139.7, 141.1, 147.4, 151.3, 161.6, 164.3, 166.6. Found, %: C, 58.21; H, 3.60; N, 2.97; S, 6.75. $C_{23}H_{17}Cl_2NO_4S$. Calculated, %: C, 58.24; H, 3.61; N, 2.95; S, 6.76.

Ethyl 4-(4-chlorophenyl)-2-{[5-oxo-[2,2'-bifuran]-4(5*H*)-ylidene]amino}thiophene-3-carboxylate 4g. Yield 0.31 g (72%), red crystals, mp 136.5-140.8 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.27 m (3H, CH_3), 4.34 m (2H, CH_2), 6.82 s (1H, O–C=CH), 6.89 m (1H, $H_{Ar.}$), 7.22 m (1H, $H_{Ar.}$), 7.33 s (1H, S–CH=C), 7.35 m (4H, $H_{Ar.}$), 7.47 m (1H, $H_{Ar.}$). Found, %: C, 58.96; H, 3.31; N, 3.26; S, 7.51. $C_{21}H_{14}ClNO_5S$. Calculated, %: C, 58.95; H, 3.30; N, 3.27; S, 7.49.

Ethyl 4-(4-chlorophenyl)-2-{[2-oxo-5-(styryl)furan-3(2*H*)-ylidene]amino}thiophene-3-carboxylate 4h. Yield 0.33 g (70%), red crystals, mp 196.2-201.0 °C. ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.17 m (3H, CH_3), 4.26 m (2H, CH_3), 6.73 s (1H, O–C=CH), 6.94 d (1H, *J* = 15.6 Hz, CH=CH-Ph), 7.25 m (2H, $H_{Ar.}$), 7.29 s (1H, S–CH=C), 7.33 m (5H, H_{Ar}), 7.38 m (2H, $H_{Ar.}$), 7.96 d (1H, *J* = 15.6 Hz, CH=CH-Ph). Found, %: C, 64.73; H, 3.92; N, 3.01; S, 6.94. $C_{25}H_{18}ClNO_4S$. Calculated, %: C, 64.72; H, 3.91; N, 3.02; S, 6.91.

Antinociceptive activity and **acute toxicity** of compounds **3a-h** was studied at the Laboratory of Biologically Active Compounds of the Perm State University. The experiments were carried out on outbred albino mice of both sexes weighted 18-22 g Animal care, maintenance, and testing has been carried out in accordance with good laboratory practice and ethical requirements.

Antinociceptive activity was evaluated using the hot plate test [41]. The pain sensitivity was estimated using an OrchidScientific EH-01 analgesia meter. The test compounds were administered intraperitoneally at the doses of 50 mg/kg as the suspensions in 2% starch solution 30-min before the mice were placed on a metal surface maintained at 53.5 °C [42]. The pain response was recorded 30-, 60-, 90- and 120- min after the test compounds were administered.

Nociceptive threshold was assessed as the latency for nocifensive response, which was the time taken to observe nocifensive behavior, namely, hind paw-licking or jumping. The latency was recorded in seconds as the time between placement of the animal on the hot plate and nocifensive response. The cut off time for the hot plate test was 40 s in order to avoid unnecessary nociceptive stimulation and burns of the paws. The animals with the reaction to pain less than 15 s were used. Each compound was tested in the group of six mice. The results were evaluated by the increase in the latency compared with the animals in the control group. Animals in the control group received a 2% starch solution. Sodium metamizole (FarmKhimKomplect) at a dose of 93 mg·kg^{-1} (ED_{50}) was used as a reference drug.

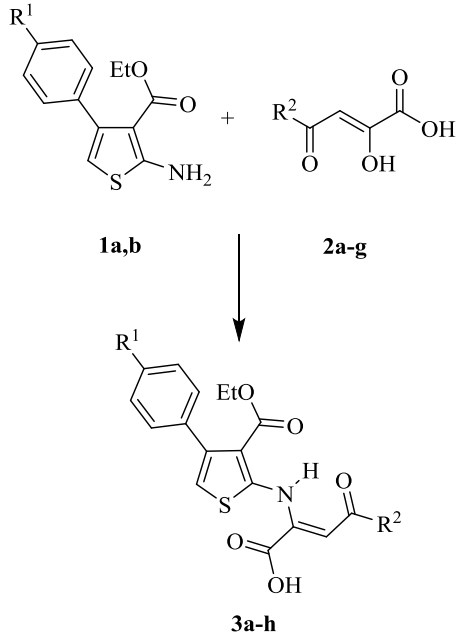
Acute toxicity of compounds **3a-h** was evaluated by the method described by Pershin [43]. The median lethal doses (LD_{50}) were determined. Compounds **3a-h** were administered intraperitoneally to the mice as a suspension in 2% starch solution and the behavior and mortality of the animals were observed for 10 days. The LD_{50} values for compounds **3a-h** were > 1500 mg/kg. According to the toxicity classification system, compounds **3a-h** belong to the toxicity class V (practically nontoxic substances) [44].

Statistical analysis of the results was carried out by the student's test. The effect was considered significant at $p < 0.05$ [45].

RESULTS AND DISCUSSION

It has been previously demonstrated that 4-(het)aryl-2-hydroxy-4-oxobut-2-enoic acids can react with substituted 2-amino-4-arylthiophenes to form the corresponding substituted 4-(het)aryl-4-oxo-2-thienylaminobut-2-enoic acids [46]. In this study, we considered to use the same approach for synthesize new series of 4-(het)aryl-4-oxo-2-thienylaminobut-2-enoic acids containing the pharmacophore moiety [4-(4-R-phenyl)thiophen-2-yl]amine in order to study their biological activity.

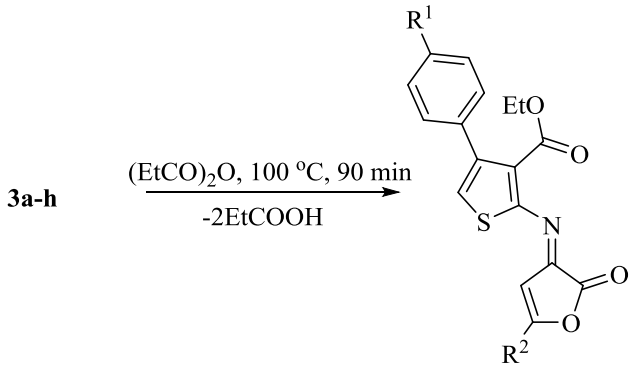
In this way, the interaction of substituted ethyl 2-amino-4-(4-aryl)thiophen-3-carboxylates **1a,b** with substituted 4-(het)aryl-2-hydroxy-4-oxobut-2-enoic acids **2a-h** in methanol at 60 °C leads to the formation of the corresponding 4-(het)aryl-4-oxo-2-{[4-(4-R-phenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}but-2-enoic acids **3a-h** in yields of 74-96% (Scheme 1).



1: R^1 = H (**a**), Cl (**b**);
2: R^2 = 4-ClC_6H_4 (**a**), 4-FC_6H_4 (**b**), 3,4-ClC_6H_3 (**c**), 4-HOC_6H_4 (**d**), 4-$O_2NC_6H_4$ (**e**), furan-2-yl (**f**), 5-methylfuran-2-yl (**g**), styryl (**h**);
3: R^1 = H, R^2 = 4-FC_6H_4 (**a**), 3,4-ClC_6H_3 (**b**), 4-HOC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), 5-methylfuran-2-yl (**e**); R^1 = Cl, R^2 = 4-ClC_6H_4 (**f**), furan-2-yl (**g**), styryl (**h**).

Scheme 1
Схема 1

Further we investigated the intramolecular condensation of the obtained compounds **3a-h** under the action of propionic anhydride. It was found that the reaction carried out by vigorous stirring of a solution of compounds **3a-h** in propionic anhydride at 90-100 °C for 90 min leads to the formation of substituted ethyl 2-{[2-oxofuran-3(2*H*)-ylidene]amino}-4-(4-R-phenyl)-thiophene-3-carboxylates **4a-h** with yields of 62-76% (Scheme 2).



3,4: R^1 = H, R^2 = 4-FC_6H_4 (**a**), 3,4-ClC_6H_4 (**b**), 4-HOC_6H_4 (**c**), 4-$O_2NC_6H_4$ (**d**), 5-methylfuran-2-yl (**e**); R^1 = Cl, R^2 = 4-ClC_6H_4 (**f**), furan-2-yl (**g**), styryl (**h**).

Scheme 2
Схема 2

Compounds **3a-h** and **4a-h** are crystalline substances of orange or red color, well soluble in DMSO at room temperature, in chloroform and methanol at heating, insoluble in alkanes and water. The ^{1}H NMR spectra of compounds **3a-h** in $CDCl_3$ and DMSO-d_6 solutions are characterized by the presence of the singlet signal of the proton of the NH-group in the region of 11.98-13.02 ppm. In the ^{1}H NMR spectra of compounds **4a-h** recorded for their solutions in $CDCl_3$, contains singlet signals of the protons of the CH group of the furan-2-one cycle in the 6.73-7.11 ppm. region.

According to the data from **Table**, it can be seen that the obtained acids **3a-h** has a highly analgesic effect. The antinociceptive activity of all compounds **3a-e** exceeds the activity of the comparison drug – sodium metamizole. The most active compound (**3a**) combines phenyl at the 4th position of thiophene ring and 4-fluorophenyl at the 4th position of acid.

Acute toxicity (LD_{50}, mg/kg) of compounds **3a-h** was found to be >1500 mg/kg, which demonstrates that they belong to the V class of toxicity (practically non-toxic drugs).

Table

Antinociceptive activity of the studied compounds 3a-h, studied by the "hot plate" method

***Таблица.* Антиноцицептивная активность исследованных соединений 3a-h, изученная по методу «горячая пластинка»**

Compound no.	c, mg/kg	Defensive response time at the maximum effect, s
3a	50	**22.92±1.01**
3b	50	21.00±1.25
3c	50	20.90±0.64
3d	50	19.80±0.78
3e	50	21.08±0.68
3f	50	19.58±0.51
3g	50	20.25±0.54
3h	50	20.83±0.38
Sodium metamizole	93 (ED_{50})	16.33±3.02
Control	_	10.30±0.60

Note. a) $p < 0.05$ compared to control

Примечание. а) $p < 0.05$ по сравнению с контролем

CONCLUSIONS

Thus, methods of synthesis and intramolecular cyclization of substituted 4-(het)aryl-2-{[3-(ethoxycarbonyl)4-(4-R-phenyl)thiophen-2-yl]amino}-4-oxobut-2-enoic acids were described. It was found that this series of compounds has pronounced antinociceptive activity and low toxicity.

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

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ЛИТЕРАТУРА

1. **Huang L., Yang J., Wang T., Gao J., Xu D.** Engineering of small-molecule lipidic prodrugs as novel nanomedicines for enhanced drug delivery. *J. Nanobiotechnol.* 2022. V. 20. N 49. P. 1-15. DOI: 10.1186/s12951-022-01257-4.
2. **Samy K.E., Gampe C.** Medicinal chemistry strategies to extend duration of action of inhaled drugs for intracellular targets. *Bioorg. Med. Chem. Lett.* 2022. V. 62. P. 128627. DOI: 10.1016/j.bmcl.2022.128627.
3. **Babushkina A.A., Dogadina A.V., Egorov D.M., Piterskaia J.L., Shtro A.A., Nikolaeva Y.V., Galochkina A.V., Kornev A.A., Boitsov V.M.** Efficient synthesis and evaluation of antiviral and antitumor activity of novel 3-phosphonylated thiazolo[3,2-a]oxopyrimidines. *Med. Chem. Res.* 2021. V. 30. N 12. P. 2203-2215. DOI: 10.1007/s00044-021-02801-x.
4. **Bobrovskaya O.V., Russkih A.A., Yankin A.N., Dmitriev M.V., Bunev A.S., Gein V.L.** Straightforward synthesis of novel spiroether derivatives. *Synth. Commun.* 2021. V. 51. N 11. P. 1731-1741. DOI: 10.1080/00397911.2021.1903930.
5. **Khalifa M.E., Algothami W.M.** Gewald synthesis, antitumor profile and molecular modeling of novel 5-acetyl-4-((4-acetylphenyl)amino)-2-aminothiophene-3-carbonitrile scaffolds. *J. Mol. Struct.* 2020. V. 1207. P. 127784. DOI: 10.1016/j.molstruc.2020.127784.
6. **Singla N., Singh G., Bhatia R., Kumar A., Kaur R., Kaur S.** Design, Synthesis and Antimicrobial Evaluation of 1, 3, 4-Oxadiazole/1,2,4-Triazole-Substituted Thiophenes. *Chem. Select.* 2020. V. 5. N 13. P. 3835-3842. DOI: 10.1002/slct.202000191.
7. **Cvijetić I.N., Verbić T.Ž., de Resende E.P., Stapleton P., Gibbons S., Juranić I.O., Drakulić B.J., Zloh M.** Design, synthesis and biological evaluation of novel aryldiketo acids with enhanced antibacterial activity against multidrug resistant bacterial strains. *Eur. J. Med. Chem.* 2018. V. 143. P. 1474-1488. DOI: 10.1016/j.ejmech.2017.10.045.

REFERENCES

1. **Huang L., Yang J., Wang T., Gao J., Xu D.** Engineering of small-molecule lipidic prodrugs as novel nanomedicines for enhanced drug delivery. *J. Nanobiotechnol.* 2022. V. 20. N 49. P. 1-15. DOI: 10.1186/s12951-022-01257-4.
2. **Samy K.E., Gampe C.** Medicinal chemistry strategies to extend duration of action of inhaled drugs for intracellular targets. *Bioorg. Med. Chem. Lett.* 2022. V. 62. P. 128627. DOI: 10.1016/j.bmcl.2022.128627.
3. **Babushkina A.A., Dogadina A.V., Egorov D.M., Piterskaia J.L., Shtro A.A., Nikolaeva Y.V., Galochkina A.V., Kornev A.A., Boitsov V.M.** Efficient synthesis and evaluation of antiviral and antitumor activity of novel 3-phosphonylated thiazolo[3,2-a]oxopyrimidines. *Med. Chem. Res.* 2021. V. 30. N 12. P. 2203-2215. DOI: 10.1007/s00044-021-02801-x.
4. **Bobrovskaya O.V., Russkih A.A., Yankin A.N., Dmitriev M.V., Bunev A.S., Gein V.L.** Straightforward synthesis of novel spiroether derivatives. *Synth. Commun.* 2021. V. 51. N 11. P. 1731-1741. DOI: 10.1080/00397911.2021.1903930.
5. **Khalifa M.E., Algothami W.M.** Gewald synthesis, antitumor profile and molecular modeling of novel 5-acetyl-4-((4-acetylphenyl)amino)-2-aminothiophene-3-carbonitrile scaffolds. *J. Mol. Struct.* 2020. V. 1207. P. 127784. DOI: 10.1016/j.molstruc.2020.127784.
6. **Singla N., Singh G., Bhatia R., Kumar A., Kaur R., Kaur S.** Design, Synthesis and Antimicrobial Evaluation of 1, 3, 4-Oxadiazole/1,2,4-Triazole-Substituted Thiophenes. *Chem. Select.* 2020. V. 5. N 13. P. 3835-3842. DOI: 10.1002/slct.202000191.
7. **Cvijetić I.N., Verbić T.Ž., de Resende E.P., Stapleton P., Gibbons S., Juranić I.O., Drakulić B.J., Zloh M.** Design, synthesis and biological evaluation of novel aryldiketo acids with enhanced antibacterial activity against multidrug resistant bacterial strains. *Eur. J. Med. Chem.* 2018. V. 143. P. 1474-1488. DOI: 10.1016/j.ejmech.2017.10.045.

8. **Бабушкина А.А., Питерская Ю.Л., Штро А.А., Николаева Ю.В., Галочкина А.В., Клабуков А.М., Егоров Д.М.** Синтез, фосфорилирование и противовирусная активность некоторых 6-арил-5-циано-2-тиоурацилов. *Журн. общ. химии.* 2022. Т. 92. Вып. 1. С. 31-37. DOI: 10.31857/S0044460X2201005X.
9. **Сюткина А.И., Чащина С.В., Махмудов Р.Р., Новикова В.В., Чернов И.Н., Игидов Н.М.** Синтез, анальгетическая и противомикробная активность N-гетариламидов 2-(2-(диарилметилен)гидразоно)-5,5-диметил-4-оксогексановой кислоты. *Изв. вузов. Химия и хим. технология.* 2022. Т. 65. Вып. 3. С. 74-82. DOI: 10.6060/ivkkt.20226503.6522.
10. **Гейн О.Н., Замараева Т.М., Гейн В.Л.** Оценка острой токсичности и анальгетической активности этил-6-амино-4-арил-5-циано-2,4-дигидропирано-2,3-С]-пиразол-3-карбоксилатов. *Хим. Фарм. Журн.* 2019. Т. 53. Вып. 1. С. 40-42. DOI: 10.30906/0023-1134-2019-53-1-41-43.
11. **Mulla J.A.S., Khazi M.I.A., Panchamukhi S.I., Gong Y.D., Khazi I.A.M.** Synthesis and pharmacological evaluation of novel thienopyrimidine and triazolothienopyrimidine derivatives. *Med. Chem. Res.* 2014. V. 23. P. 3235-3243. DOI: 10.1007/s00044-013-0900-1.
12. **Siutkina A.I., Chashchina S.V., Makhmudov R.R., Kizimova I.A., Shipilovskikh S.A., Igidov N.M.** Synthesis and Biological Activity of Substituted 2-[2-(Diphenylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enoates. *Russ. J. Org. Chem.* 2021. V. 57. P. 1874-1881. DOI: 10.1134/S1070428021110105.
13. **Шаравьёва Ю.О., Горбунова И.А., Махмудов Р.Р., Шипиловских Д.А., Силайчев П.С., Шипиловских С.А.** Синтез и противовоспалительная активность эфиров 4-арил-4-оксо-2-[(3-цианотиофен-2-ил)амино]бут-2-еновых кислот. *Изв. АН. Сер. Хим.* 2023. Т. 72. Вып. 12. С. 3005-3012. DOI: 10.1007/s11172-023-4112-7.
14. **Joksimović N., Janković N., Davidović G., Bugarčić Z.** 2,4-Diketo esters: Crucial intermediates for drug discovery. *Bioorg. Chem.* 2020. V. 105. P. 104343. DOI: 10.1016/j.bioorg.2020.104343.
15. **Kathiravan M.K., More K.D., Raskar V.K., Jain K.S., Maheshwar M., Gadhwe S., Jain D.P., Nagras M.A., Phoujdar M.S.** Synthesis and antihyperlipidemic activity of novel condensed 2-fluoromethylpyrimidines. *Med. Chem. Res.* 2013. V. 22. P. 4286-4292. DOI: 10.1007/s00044-012-0263-z.
16. **Игидов С.Н., Турышев А.Ю., Махмудов Р.Р., Шипиловских Д.А., Игидов Н.М., Шипиловских С.А.** Синтез, внутримолекулярная циклизация и анальгетическая активность 4-арил-4-оксо-2-[2-(фуран-2-илкарбонил)гидразинилиден]бутановых кислот. *Журн. общ. химии.* 2022. Т. 92. Вып. 9. С. 1378-1386. DOI: 10.31857/S0044460X22090062.
17. **Горбунова И.А., Шипиловских Д.А., Рубцов А.Е., Шипиловских С.А.** Синтез и внутримолекулярная циклизация замещенных 4-(гет)арил-4-оксо-2-тиениламинобут-2-еновых кислот, содержащих нитрильный заместитель в тиофеновом кольце. *Журн. общ. химии.* 2021. Т. 91. Вып. 9. С. 1333-1339. DOI: 10.31857/S0044460X21090043.
18. **Липин Д.В., Денисова Е.И., Шипиловских Д.А., Махмудов Р.Р., Игидов Н.М., Шипиловских С.А.** Дециклизация замещенных 3-(4-нитробензоил)гидразоно-3Н-фуран-2-онов, под действием первичных спиртов и исследование анальгетической активности и острой токсичности продуктов реакции. *Журн. орган. химии.* 2023. Т. 59. Вып. 4. С. 516-524. DOI: 10.31857/S0514749223040109.

8. **Babushkina A.A., Piterskaya Yu.L., Shtro A.A., Nikolaeva Yu.V., Galochkina A.V., Klabukov A.M., Egorov D.M.** Synthesis, Phosphonylation, and Anti-Viral Activity of Some 6-Aryl-5-cyano-2-thiouracils. *Russ. J. Gen. Chem.* 2022. V. 92. N 1. P. 18-23. DOI: 10.1134/S1070363222010042.
9. **Siutkina A.I., Chashchina S.V., Makhmudov R.R., Novikova V.V., Chernov I.N., Igidov N.M.** Synthesis, analgesic and antimicrobial activity of N-hetarylamides of 2-(2-(diarylmethylene)hydrazono)-5,5-dimethyl-4-oxohexanoic acid. *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.]*. 2022. V. 65. N 3. P. 74-82. DOI: 10.6060/ivkkt.20226503.6522.
10. **Gein O.N., Zamaraeva T.M., Gein V.L.** Assessment of the Acute Toxicity and Analgesic Activity of Ethyl-6-Amino-4-Aryl-5-Cyano-2,4-Dihydropyrano-2,3-C]-Pyrazole-3-Carboxylates. *Khim. Farm. Zhurn.* 2019. V. 53. N 1. P. 40-42 (in Russian). DOI: 10.1007/s11094-019-01952-x.
11. **Mulla J.A.S., Khazi M.I.A., Panchamukhi S.I., Gong Y.D., Khazi I.A.M.** Synthesis and pharmacological evaluation of novel thienopyrimidine and triazolothienopyrimidine derivatives. *Med. Chem. Res.* 2014. V. 23. P. 3235-3243. DOI: 10.1007/s00044-013-0900-1.
12. **Siutkina A.I., Chashchina S.V., Makhmudov R.R., Kizimova I.A., Shipilovskikh S.A., Igidov N.M.** Synthesis and Biological Activity of Substituted 2-[2-(Diphenylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enoates. *Russ. J. Org. Chem.* 2021. V. 57. P. 1874-1881. DOI: 10.1134/S1070428021110105.
13. **Sharavyeva Yu.O., Gorbunova I.A., Makhmudov R.R., Shipilovskikh D.A., Silaichev P.S., Shipilovskikh S.A.** Synthesis and anti-inflammatory activity of 4-aryl-2-[(3-cyanothiophen-2-yl)amino]-4-oxobut-2-enoates. *Izv. AN Ser. Khim.* 2023. V. 72. N. 12. P. 3005-3012 (in Russian). DOI: 10.1007/s11172-023-4112-7.
14. **Joksimović N., Janković N., Davidović G., Bugarčić Z.** 2,4-Diketo esters: Crucial intermediates for drug discovery. *Bioorg. Chem.* 2020. V. 105. P. 104343. DOI: 10.1016/j.bioorg.2020.104343.
15. **Kathiravan M.K., More K.D., Raskar V.K., Jain K.S., Maheshwar M., Gadhwe S., Jain D.P., Nagras M.A., Phoujdar M.S.** Synthesis and antihyperlipidemic activity of novel condensed 2-fluoromethylpyrimidines. *Med. Chem. Res.* 2013. V. 22. P. 4286-4292. DOI: 10.1007/s00044-012-0263-z.
16. **Igidov S.N., Turyshev A.Yu., Makhmudov R.R., Shipilovskikh D.A., Igidov N.M., Shipilovskikh S.A.** Synthesis, Intramolecular Cyclization, and Analgesic Activity of Substituted 2-[2-(Furancarbonyl)hydrazinylydene]-4-oxobutanoic Acids. *Russ. J. Gen. Chem.* 2022. V. 92. N 9. P. 1629-1636. DOI: 10.1134/S1070363222090067.
17. **Gorbunova I.A., Shipilovskikh D.A., Rubtsov A.E., Shipilovskikh S.A.** Synthesis and Intramolecular Cyclization of Substituted 4-(Het)aryl-4-oxo-2-thienylaminobut-2-enoic Acids Containing Nitrile Group in the Thiophene Ring. *Russ. J. Gen. Chem.* 2021. V. 91. N 9. P. 1623-1628. DOI: 10.1134/S1070363221090048.
18. **Lipin D.V., Denisova E.I., Shipilovskikh D.A., Makhmudov R.R., Igidov N.M., Shipilovskikh S.A.** Ring Opening of Substituted 3-[2-(4-Nitrobenzoyl) hydrazinylidene]furan-2(3H)-ones with Primary Alcohols. Analgesic Activity and Acute Toxicity of the Products. *Russ. J. Org. Chem.* 2023. V. 59. N 4. P. 631-638. DOI: 10.1134/S1070428023040103.
19. **Lipin D.V., Denisova E.I., Devyatkin I.O., Okoneshnikova E.A., Shipilovskikh D.A., Makhmudov R.R., Igidov N.M., Shipilovskikh S.A.** Synthesis and Antinociceptive

19. **Липин Д.В., Денисова Е.И., Девяткин И.О., Оконешникова Е.А., Шипиловских Д.А., Махмудов Р.Р., Игидов Н.М., Шипиловских С.А.** Синтез и антиноцицептивная активность замещенных 5-(гет)арил-3-(4-метилбензоил)гидразоно-3Н-фуран-2-онов. *Журн. общ. химии.* 2021. Т. 91. Вып. 12. С. 1962-1968. DOI: 10.31857/S0044460X21120167.
20. **Липин Д.В., Козлов Д.А., Шадрин В.М., Пархома К.Ю., Старкова А.В., Шипиловских Д.А., Пулина Н.А., Шипиловских С.А.** Синтез и гемостатическая активность замещенных 5-оксо-1-циано-3-{(3-циано-4,5,6,7-тетрагидробензо[b]тиофен-2-ил)амино}пента-1,3-диен-2-олятов калия. *Журн. орган. химии.* 2023. Т. 59. Вып. 8. С. 1041-1049. DOI: 10.31857/S0514749223080050.
21. **Шаравьева Ю.О., Махмудов Р.Р., Шипиловских Д.А., Силайчев П.С., Горбунова И.А.** Синтез и исследование антиноцицептивной активности замещенных эфиров 4-оксо-2-(3-циано-4,5,6,7-тетрагидробензо[b]тиофен-2-иламино)бут-2-еновых кислот. *Изв. вузов. Химия и хим. технология.* 2024. Т. 67. Вып. 7. С. 19-27. DOI: 10.6060/ivkkt.20246707.7029.
22. **Игидов С.Н., Турышев А.Ю., Махмудов Р.Р., Шипиловских Д.А., Дмитриев М.В., Зверева О.В., Силайчев П.С., Игидов Н.М., Шипиловских С.А.** Дециклизация замещенных 2-[2-оксофуран-3(2Н)-илиден]фуран-2-карбогидразидов под действием спиртов и анальгетическая активность полученных соединений. *Журн. общ. химии.* 2023. Т. 93. Вып. 2. С. 188-199. DOI: 10.31857 /S0044460X2302004X.
23. **Липин Д.В., Пархома К.Ю., Шадрин В.М., Махмудов Р.Р., Шипиловских Д.А., Силайчев П.С., Шипиловских С.А.** Синтез и антиноцицептивная активность нитрилов, эфиров и амидов 2-амино-1-(3-циано-4,5,6,7-тетрагидробензо[b]-тиофен-2-ил)-4-оксо-5-(2-оксо-2-арилэтилиден)-4,5-дигидро-1Н-пиррол-3-карбоновых кислот. *Изв. АН. Сер. Хим.* 2023. Т. 72. Вып. 8. С. 1913-1920. DOI: 10.1007/s11172-023-3976-x.
24. **Горбунова И.А., Шаравьёва Ю.О., Махмудов Р.Р., Шипиловских Д.А., Шадрин В.М., Пулина Н.А., Шипиловских С.А.** Синтез и антиноцицептивная активность замещенных первичных эфиров 4-оксо-2-(3-циано-4,5,6,7-тетрагидробензо[b]тиофен-2-иламино)бут-2-еновых кислот. *Журн. общ. химии.* 2022. Т. 92. Вып. 10. С. 1520-1527. DOI: 10.31857/S0044460X22100043.
25. **Денисова Е.И., Липин Д.В., Пархома К.Ю., Шипиловских Д.А., Чащина С.В., Махмудов Р.Р., Игидов Н.М., Шипиловских С.А.** Синтез, внутримолекулярная циклизация и антиноцицептивная активность замещенных 2-[2-(4-нитробензоил)гидразоно]-4-оксобут-2-еновых кислот. *Журн. орган. химии.* 2021. Т. 57. Вып. 12. С. 1736-1743. DOI: 10.31857/S0514749221120089.
26. **Горбунова И.А., Оконешникова Е.А., Махмудов Р.Р., Шипиловских Д.А., Шадрин В.М., Силайчев П.С., Шипиловских С.А.** Синтез и антиноцицептивная активность замещенных амидов 4-арил-4-оксо-2-[(3-циано-4,5,6,7-тетрагидробензо[b]тиофен-2-ил)-амино]бут-2-еновых кислот. *Изв. АН. Сер. Хим.* 2023. Т. 72. Вып. 8. С. 1905-1912. DOI: 10.1007/s11172-023-3975-y.
27. **Липин Д.В., Денисова Е.И., Шипиловских Д.А., Махмудов Р.Р., Игидов Н.М., Шипиловских С.А.** Синтез, внутримолекулярная циклизация и противовоспалительная активность замещенных 2-[2-(4-R-бензоил)гидразоно]4-оксобут-2-еновых кислот. *Журн. орган. химии.* 2022. Т. 58. Вып. 12. С. 1354-1365. DOI: 10.31857/S0514749222120047.

Activity of Substituted 5-(Het)aryl-3-(4-methylbenzoyl)hydrazono-3H-furan-2-ones. *Russ. J. Gen. Chem.* 2021. V. 91. N 12. P. 2469-2474. DOI: 10.1134/S1070363221120161.

20. **Lipin D.V., Kozlov D.A., Shadrin V.M., Parkhoma K.Yu., Starkov A.V., Shipilovskikh D.A., Pulina N.A., Shipilovskikh S.A.** Synthesis and Hemostatic Activity of Substituted Potassium 1-Cyano-3-{(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino}-5-oxopenta-1,3-dien-2-olates. *Russ. J. Org. Chem.* 2023. V. 59. N 8. P. 1322-1328. DOI: 10.1134/S1070428023080055.
21. **Sharavyeva Yu.O., Makhmudov R.R., Shipilovskikh D.A., Silaichev P.S., Gorbunova I.A.** Synthesis and study of antinociceptive activity of substituted 2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino)-4-oxobut-2-enoates. *ChemChemTech [Izv. Vyssh. Uchebn. Zaved. Khim. Khim. Tekhnol.].* 2024. V. 67. N 7. P. 19-27. DOI: 10.6060/ivkkt.20246707.7029.
22. **Igidov S.N., Turyshev A.Yu., Makhmudov R.R., Shipilovskikh D.A., Dmitriev M.V., Zvereva O.V., Silaichev P.S., Igidov N.M., Shipilovskikh S.A.** Decyclization of Substituted 2-[2-Oxofuran-3(2H)-ylidene)furan-2-carbohydrazides by the Action of Alcohols and Analgesic Activity of the Obtained Compounds. *Zhurn. Obshch. Khim.* 2023. V. 59. N 2. P. 188-199 (in Russian). DOI: 10.1134/S1070363223020044.
23. **Lipin D.V., Parkhoma K.Yu., Shadrin V.M., Makhmudov R.R., Shipilovskikh D.A., Silaichev P.S., Shipilovskikh S.A.** Synthesis and antinociceptive activity of nitriles, esters, and amides of 2-amino-1-(3-cyano-4, 5,6,7-tetrahydrobenzo[b]thiophen-2-yl)-4-oxo-5-(2-oxo-2-arylethylidene)-4,5-dihydro-1H-pyrrole-3-carboxylic acids. *Izv. AN Ser. Khim.* 2023. V. 72. N 8. P. 1913-1920 (in Russian). DOI: 10.1007/s11172-023-3976-x.
24. **Gorbunova I.A., Sharavyeva Yu.O., Makhmudov R.R., Shipilovskikh D.A., Shadrin V.M., Pulina N.A., Shipilovskikh S.A.** Synthesis and Antinociceptive Activity of Substituted 2-(3-Cyano-4,5,6,7-tetrahydrobenzo[b]thiophene-2-ylamino)-4-oxobut-2-enoates. *Russ. J. Gen. Chem.* 2022. V. 92. N 10. P. 1899-1905. DOI: 10.1134/S1070363222100048.
25. **Denisova E.I., Lipin D.V., Parkhoma K.Yu., Devyatkin I.O., Shipilovskikh D.A., Chashchina S.V., Makhmudov R.R., Igidov N.M., Shipilovskikh S.A.** Synthesis, Intramolecular Cyclization, and Antinociceptive Activity of Substituted 2-[2-(4-Nitrobenzoyl)hydrazinylidene]-4-oxobut-2-enoic Acids. *Russ. J. Org. Chem.* 2021. V. 57. N 12. P. 1955-1960. DOI: 10.1134/S1070428021120083.
26. **Gorbunova I.A., Okoneshnikova E.A., Makhmudov R.R., Shipilovskikh D.A., Shadrin V.M., Silaichev P.S., Shipilovskikh S.A.** Synthesis and antinociceptive activity of N-substituted 4-aryl-2-[(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino]4-oxobut-2-enamides. *Izv. AN Ser. Khim.* 2023. V. 72. N 8. P. 1905-1912 (in Russian). DOI: 10.1007/s11172-023-3975-y.
27. **Lipin D.V., Denisova E.I., Shipilovskikh D.A., Makhmudov R.R., Igidov N.M., Shipilovskikh S.A.** Synthesis, Intramolecular Cyclization, and Anti-inflammatory Activity of Substituted 2-[2-(4-R-Benzoyl)hydrazinylidene]-4-oxobutanoic Acids. *Russ. J. Org. Chem.* 2022. V. 58. N 12. P. 1759-1768. DOI: 10.1134/S1070428022120041.
28. **Siutkina A.I., Sharavyeva Yu.O., Chashchina S.V., Shipilovskikh S.A., Igidov N.M.** Synthesis and anti-inflammatory activity of N′-substituted 2-[2-(diarylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enehydrazides. *Izv. AN Ser. Khim.* 2022. V. 71. N 3. P. 496-501 (in Russian). DOI: 10.1007/s11172-022-3439-9.

28. **Сюткина А.И., Шаравьёва Ю.О., Чащина С.В., Шипиловских С.А., Игидов Н.М.** Синтез и противовоспалительная активность N'-замещенных 2-[2-(диарилметилен)гидразинил]-5,5-диметил-4-оксогекс-2-енегидразидов. *Изв. АН. Сер. Хим.* 2022. Т. 71. Вып. 3. С. 496-501. DOI: 10.1007/s11172-022-3439-9.
29. **Липин Д.В., Метлякова С.К., Шипиловских Д.А., Махмудов Р.Р., Силайчев П.С., Игидов Н.М., Шипиловских С.А.** Синтез, противовоспалительная активность и токсичность замещенных 2-[2-(4-нитробензоил)гидразоно]-4-оксобутаноатов. *Изв. АН. Сер. Хим.* 2023. Т. 72. Вып. 8. С. 1887-1893. DOI: 10.1007/s11172-023-3973-0.
30. **Игидов С.Н., Турышев А.Ю., Чащина С.В., Шипиловских Д.А., Чернов И.Н., Зверева О.В., Силайчев П.С., Игидов Н.М., Шипиловских С.А.** Синтез и противовоспалительная активность N-ариламидов 4-арил- и 4-(тиофен-2-ил)-2-[2-(фуран-2-илкарбонил)гидразоно]-4-оксобутановых кислот. *Изв. АН. Сер. Хим.* 2023. Т. 72. Вып. 9. С. 2241-2248. DOI: 10.1007/s11172-023-4021-9.
31. **Горбунова И.А., Шадрин В.М., Пулина Н.А., Новикова В.В., Дубровина С.С., Шипиловских Д.А., Шипиловских С.А.** Синтез и антибактериальная активность 4-оксо-2-тиениламинобут-2-еновых кислот. *Журн. общ. химии*. 2023. Т. 93. Вып. 1. С. 22-30. DOI: 10.31857/S0044460X23010031.
32. **Шаравьёва Ю.О., Сюткина А.И., Чащина С.В., Новикова В.В., Махмудов Р.Р., Шипиловских С.А.** Синтез, анальгетическая и противомикробная активность замещенных 2-(3-циано-4,5,6,7-тетрагидробензо[b]тиофен-2-иламино)-4-оксо-4-фенилбут-2-еноатов. *Изв. АН. Сер. Хим.* 2022. Т. 71. Вып. 3. С. 538-542. DOI: 10.1007/s11172-022-3445-y.
33. **Rogova A., Gorbunova I.A., Karpov T.E., Sidorov R.Yu., Domracheva N., Rubtsov A.E., Shipilovskikh D.A., Muslimov A.R., Zyuzin M.V., Timin A.S., Shipilovskikh S.A.** Synthesis of thieno[3,2-e]pyrrolo[1,2-a]pyrimidine derivatives and their precursors containing 2-aminothiophenes fragments as anticancer agents for therapy of pulmonary metastatic melanoma. *Eur. J. Med. Chem.* 2023. V. 254. P. 115325. DOI: 10.1016/j.ejmech.2023.115325.
34. **Gunina E., Timofeeva M., Kenzhebaeva Yu.A., Bachinin S., Gorbunova I.A., Shipilovskikh D.A., Milichko V.A., Shipilovskikh S.A.** Thiophene-based thin films with tunable red photoluminescence. *Photonics Nanostruct.* 2023. V. 56. P. 101168. DOI: 10.1016/j.photonics.2023.101168.
35. **Gunina E., Zhestkij N., Bachinin S., Fisenko S.P., Shipilovskikh D.A., Milichko V.A., Shipilovskikh S.A.** The influence of substitutes on the room temperature photoluminescence of 2-amino-4-oxobut-2-enoic acid molecular crystals. *Photon. Nanostruct. Fund. Appl.* 2022. V. 48. P. 100990. DOI: 10.1016/j.photonics.2021.100990.
36. **Kenzhebayeva Yu., Gorbunova I., Dolgopolov A., Dmitriev M.V., Atabaev T.S., Stepanidenko E.A., Efimova A.S., Novikov A.S., Shipilovskikh S., Milichko V.A.** Self-Assembly of Hydrogen-Bonded Organic Crystals on Arbitrary Surfaces for Efficient Amplified Spontaneous Emission. *Adv. Photonics.* 2023. P. 2300173. DOI: 10.1002/adpr.202300173.
37. **Gorbunova I.A., Timofeeva M., Gunina E., Sharavyeva Yu.O., Parkhoma K.Yu., Shipilovskikh D.A., Shipilovskikh S.A.** Self-assembly of thiophene-based luminescent thin films on flexible substrates. *Photonics Nanostruct.* 2024. V. 58. P. 101220. DOI: 10.1016/j.photonics.2023.101220.
38. **Gunina E.V., Gorbunova I., Rzhevskiy S., Kenzhebayeva Y., Bachinin S., Shipilovskikh D., Mitusova K.,**
29. **Lipin D.V., Metlyakova S.K., Shipilovskikh D.A., Makhmudov R.R., Silaichev P.S., Igidov N.M., Shipilovskikh S.A.** Synthesis, anti-inflammatory activity, and acute toxicity of the substituted 2-[2-(4-nitrobenzoyl)hydrazono]-4-oxobutanoates. *Izv. AN Ser. Khim.* 2023. V. 72. N 8. P. 1887-1893 (in Russian) DOI: 10.1007/s11172-023-3973-0.
30. **Igidov S.N., Turyshev A.Yu., Chashchina S.V., Shipilovskikh D.A., Chernov I.N., Zvereva O.V., Silaichev P.S., Igidov N.M., Shipilovskikh S. A.** Synthesis and anti-inflammatory activity of N-arylamides of 4-aryl- and 4-(thiophen-2-yl)-2-[2-(furan-2-carbonyl)hydrazono]-4-oxobutanoic a(in Russian)cids. *Izv.AN Ser. Khim.* 2023. V. 72. N 9. P. 2241-2248 (in Russian). DOI: 10.1007/s11172-023-4021-9.
31. **Gorbunova I.A., Shadrin V.M., Pulina N.A., Novikova V.V., Dubrovina S.S., Shipilovskikh D.A., Shipilovskikh S.A.** Synthesis and Antibacterial Activity of 4-Oxo-2-thienylaminobut-2-enoic Acids. *Russ. J. Gen. Chem.* 2023. V. 93. N 1. P. 8-15. DOI: 10.1134/S1070363223010024.
32. **Sharavyeva Yu.O., Siutkina A.I., Chashchina S.V., Novikova V.V., Makhmudov R.R., Shipilovskikh S.A.** Synthesis, analgesic and antimicrobial activity of substituted 2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino)-4-oxo-4-phenylbut-2-enoates. *Izv. AN Ser. Khim.* 2022. V. 71. N 3. P. 538-542 (in Russian). DOI: 10.1007/s11172-022-3445-y.
33. **Rogova A., Gorbunova I.A., Karpov T.E., Sidorov R.Yu., Domracheva N., Rubtsov A.E., Shipilovskikh D.A., Muslimov A.R., Zyuzin M.V., Timin A.S., Shipilovskikh S.A.** Synthesis of thieno[3,2-e]pyrrolo[1,2-a]pyrimidine derivatives and their precursors containing 2-aminothiophenes fragments as anticancer agents for therapy of pulmonary metastatic melanoma. *Eur. J. Med. Chem.* 2023. V. 254. P. 115325. DOI: 10.1016/j.ejmech.2023.115325.
34. **Gunina E., Timofeeva M., Kenzhebaeva Yu.A., Bachinin S., Gorbunova I.A., Shipilovskikh D.A., Milichko V.A., Shipilovskikh S.A.** Thiophene-based thin films with tunable red photoluminescence. *Photonics Nanostruct.* 2023. V. 56. P. 101168. DOI: 10.1016/j.photonics.2023.101168.
35. **Gunina E., Zhestkij N., Bachinin S., Fisenko S.P., Shipilovskikh D.A., Milichko V.A., Shipilovskikh S.A.** The influence of substitutes on the room temperature photoluminescence of 2-amino-4-oxobut-2-enoic acid molecular crystals. *Photon. Nanostruct. Fund. Appl.* 2022. V. 48. P. 100990. DOI: 10.1016/j.photonics.2021.100990.
36. **Kenzhebayeva Yu., Gorbunova I., Dolgopolov A., Dmitriev M.V., Atabaev T.S., Stepanidenko E.A., Efimova A.S., Novikov A.S., Shipilovskikh S., Milichko V.A.** Self-Assembly of Hydrogen-Bonded Organic Crystals on Arbitrary Surfaces for Efficient Amplified Spontaneous Emission. *Adv. Photonics.* 2023. P. 2300173. DOI: 10.1002/adpr.202300173.
37. **Gorbunova I.A., Timofeeva M., Gunina E., Sharavyeva Yu.O., Parkhoma K.Yu., Shipilovskikh D.A., Shipilovskikh S.A.** Self-assembly of thiophene-based luminescent thin films on flexible substrates. *Photonics Nanostruct.* 2024. V. 58. P. 101220. DOI: 10.1016/j.photonics.2023.101220.
38. **Gunina E.V., Gorbunova I., Rzhevskiy S., Kenzhebayeva Y., Bachinin S., Shipilovskikh D., Mitusova K., Rogova A., Kulakova A.N., Timin A.S., Shipilovskikh S., Milichko V.A.** Inkjet Printing of Biocompatible Luminescent Organic Crystals for Optical Encryption. *ACS Appl. Opt. Mater.* 2023. V. 1. N 12. P. 2013-2020. DOI: 10.1021/acsaom.3c00340.
39. **Gewald K., Schinke E., Böttcher H.** Heterocyclen aus CH-aciden Nitrilen, VIII. 2-Amino-thiophene aus meth-

Rogova A., Kulakova A.N., Timin A.S., Shipilovskikh S., Milichko V.A. Inkjet Printing of Biocompatible Luminescent Organic Crystals for Optical Encryption. *ACS Appl. Opt. Mater.* 2023. V. 1. N 12. P. 2013-2020. DOI: 10.1021/acsaom.3c00340.

39. **Gewald K., Schinke E., Böttcher H.** Heterocyclen aus CH-aciden Nitrilen, VIII. 2-Amino-thiophene aus methylenaktiven Nitrilen, Carbonylverbindungen und Schwefel. *Chem. Ber.* 2006. V. 99. N 1. P. 94-100. DOI: 10.1002/cber.19660990116.
40. **Verbić T., Drakulić B., Zloh M., Pecelj J., Popović G., Juranić I.** An LFER study of the protolytic equilibria of 4-aryl-2,4-dioxobutanoic acids in aqueous solutions. *J. Serbian Chem. Soc.* 2007. V. 72. N 12. P. 1201-1216. DOI: 10.2298/jsc0712201v.
41. **Eddy N.B., Leimbach D.J.** Synthetic analgesics. II. Dithienylbutenyl-and dithienylbutylamines. *J. Pharmacol. Exp. Ther.* 1953. V. 107. N 3. P. 385.
42. **Миронов А.Н.** Руководство по проведению доклинических исследований лекарственных веществ. М.: Гриф и К. 2012. 509 с.
43. **Першин Г.Н.** Методы экспериментальной химиотерапии. М.: Медицина. 1971. 109 с.
44. **Измеров Н.Ф., Саноцкий И.В., Сидоров К.К.** Параметры токсикометрии промышленных ядов при однократном воздействии. М.: Справочник, Медицина. 1977. 196 с.
45. **Беленький М.Л.** Элементы количественной оценки фармакологического эффекта. Л.: Медгиз. 1963. 146 с.
46. **Горбунова И.А., Никонов И.П., Махмудов Р.Р., Шипиловских Д.А., Силайчев П.С., Шипиловских С.А.** Синтез, внутримолекулярная циклизация и антиноцицептивная активность 4-(гет)арил-4-оксо-2-{[4-(4-хлорфенил)-3-(этоксикарбонил)тиофен-2-ил]амино}бут-2-еновых кислот. *Изв. АН. Сер. Хим.* 2023. Т. 72. Вып. 9. С. 2255-2262. DOI: 10.1007/s11172-023-4023-7.

ylenaktiven Nitrilen, Carbonylverbindungen und Schwefel. *Chem. Ber.* 2006. V. 99. N 1. P. 94-100. DOI: 10.1002/cber.19660990116.

40. **Verbić T., Drakulić B., Zloh M., Pecelj J., Popović G., Juranić I.** An LFER study of the protolytic equilibria of 4-aryl-2,4-dioxobutanoic acids in aqueous solutions. *J. Serbian Chem. Soc.* 2007. V. 72. N 12. P. 1201-1216. DOI: 10.2298/jsc0712201v.
41. **Eddy N.B., Leimbach D.J.** Synthetic analgesics. II. Dithienylbutenyl-and dithienylbutylamines. *J. Pharmacol. Exp. Ther.* 1953. V. 107. N 3. P. 385.

42. **Mironov A.N.** Guidelines for conducting preclinical studies of medicinal substances. M.: Grif and K. 2012. 509 p. (in Russian).
43. **Pershin G.N.** Methods of experimental chemotherapy. M.: Medicine. 1971. 109 p. (in Russian).
44. **Izmerov N.F., Sanotsky I.V., Sidorov K.K.** Parameters of toxicometry of industrial poisons at a single exposure. M.: Spravochnik, Meditsina. 1977. 196 p. (in Russian).
45. **Belenky M. L.** Elements of a quantitative assessment of the pharmacological effect. L.: Medgiz. 1963. 146 p. (in Russian).
46. **Gorbunova I.A., Nikonov I.P., Makhmudov R.R., Shipilovskikh D.A., Silaichev P.S., Shipilovskikh S.A.** Synthesis, intramolecular cyclization, and antinociceptive activity of 4-(het)aryl-2-{[4-(4-chlorophenyl)-3-(ethoxycarbonyl)thiophen-2-yl]amino}-4-oxobut-2-enoic acids. *Izv. AN Ser. Khim.* 2023. V. 72. N 9. P. 2255-2262 (in Russian). DOI: 10.1007/s11172-023-4023-7.

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