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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

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В настоящей работе представлены результаты продолжения изучения синтетических превращений под действием нуклеофильных реагентов замещенных 3-тиенилимино-3Н-фуран-2-онов, содержащих нитрильный заместитель в третьем положении тиофенового кольца. Данный класс соединений вызывает большой интерес для изучения благодаря содержанию в своей структуре нескольких реакционных центров, что позволяет получать продукты разнообразного строения, сохраняя при этом важные фармакофорные группы (фрагмент 2-аминотиофена и фрагмент 2,4-диоксобутановой кислоты). Нами были синтезированы и изучены на предмет биологической активности эфиры замещенных 4-оксо-2-(3-циано-4,5,6,7-тетрагидробензо[b]тиофен-2-иламино)бут-2-еновых кислот, которые были получены многостадийным синтезом. Предложенный метод обеспечивает высокие выходы целевых продуктов и включает в себя взаимодействие 4-арил-2-гидрокси-4-оксобутановых кислот с нитрилом 2-амино-4,5,6,7-тетрагидробензо[b]тиофен-3-карбоновой кислоты, последующую внутримолекулярную циклизацию полученных продуктов под действием пропионового ангидрида, а также дециклизацию полученных замещенных 3-тиенилимино-3Н-фуран-2-онов под действием первичных спиртов. Подтверждение структуры выделенных итоговых соединений проводилось методами ^{1}H и ^{13}C ЯМР спектроскопии, а также элементного анализа. Полученные соединения 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, основанном 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 эфиры замещенных 4-оксо-2-(3-

циано-4,5,6,7-тетрагидробензо[b]тиофен-2-иламино)бут-2-еновых кислот 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(3*H*)-оны, антиноцицептивная активность, токсичность, *in vivo*

SYNTHESIS AND STUDY OF ANTINOCICEPTIVE ACTIVITY OF SUBSTITUTED 2-(3-CYANO-4,5,6,7-TETRAHYDROBENZO[B]THIOPHEN-2-YLAMINO)-4-OXOBUT-2-ENOATES

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In the current work, we present results the study of synthetic transformations of substituted 3-thienylimino-3H-furan-2-one derivatives containing a nitrile substituent in the third position of the thiophene ring under the action of nucleophilic reagents. This class of compounds is of great for study due to the presence of several reaction centers in its structure, which makes it possible to obtain products of various structures, while retaining important pharmacophore groups - fragments of 2-aminothiophene and a fragment of 2,4-dioxobutanoic acid. We have synthesized and studied for biological activity substituted 2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino)-4-oxobut-2-enoates, which were obtained by a multistep synthesis method. The proposed method provides high yields of target compounds and includes the reaction of 4-aryl-2-hydroxy-4-oxobutanoic acids with 2-amino-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carbonitrile, followed by intramolecular cyclization of the resulting products under the action of propionic anhydride, as well as decyclization of the resulting substituted 3-thienylimino-3H-furan-2-ones under the action of primary alcohols. The structure of the finally isolated compounds was confirmed by ^{1}H and ^{13}C NMR spectroscopy and the elemental analysis. The resulting compounds were screened in vivo to detect and evaluate their biological activity and acute toxicity. Antinociceptive activity was studied in white outbred mice of both sexes by the hot plate test with intraperitoneal injection. Acute toxicity was studied according to the Pershin method, based on monitoring the condition of mice for 10 days after intraperitoneal injection of the test compounds. According to the results obtained, the tested compounds have a pronounced antinociceptive activity, and the assessment of acute toxicity indicates that they belong to the V class of practically non-toxic drugs. The high values of antinociceptive activity in combination with low toxicity make the considered substituted 2-(3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-ylamino)-4-oxobut-2-enoates a highly promising class for further study in order to search for and develop new biologically active compounds with analgesic effect.

Key words: 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

The synthesis of biologically active compounds with low toxicity has always been and remains one of the most important tasks of modern pharmaceutical and medicinal chemistry [1-4]. It has long been known that substances containing 2-aminothiophene or 2,4-dioxobutanoic acid fragments in their structure provide various biological activities. Derivatives of 2,4-dioxobutanoic acids and 2-aminothiophenes have analgesic [5-7], antimicrobial [8-10], antitumor [11-12] and other types of biological activity [13-15].

It was previously shown that 3-imino(hydrazono)furan-2(3*H*)-ones have in their structure several electrophilic centers, which causes their high reactivity with various nucleophilic reagents [16-17]. We proposed a convenient method for the synthesis of 3-hydrazonofuran-2(3*H*)-ones [18-19] and 3-(thiophene-2-ylimino)furan-2(3*H*)-ones [20], and also carried out studies, during which it was found that the obtained substances are derivatives of 3-imino(hydrazono)furan-2(3*H*)-ones have pronounced antinociceptive [21-23], anti-inflammatory [24-26], antimicrobial [27], antitumor [28] activity, as well as photoluminescent properties [29-30]. In addition, we studied the substituted esters and amides of 2-(3-cyano-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino)-4-oxobut-2-enoic acids and found that they have analgetic [31-32] and antimicrobial [33] activities.

The purpose of this work is the synthesis of new derivatives of 2,4-dioxobutanoic acid, the study of the interaction of substituted 3-(thiophene-2-ylimino)furan-2(3*H*)-ones with primary alcohols, as well as the study of the antinociceptive activity of the obtained compounds.

EXPERIMENTAL PART

The reaction course and purity of the synthesized compounds were monitored by TLC using Silufol 254 UV precoated plates. The plates were developed with ethyl 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 $CDCl_3$. Melting points were measured on a Stuart SMP40 apparatus and are given incorrected. All reagents used are commercially available and were used as purchased.

Synthesis of 2-(3-cyano-4,5,6,7-tetrahy-drobenzo[b]thiophen-2-ylamino)-4-oxobut-2-enoates. To 1 mmol of compounds **4a-d** in 5 mL of anhydrous toluene was added 3 mmol of the corresponding alcohol and 1 mmol of DIPEA. The resulting suspension was refluxed for 5 min until complete dissolution of the starting compounds. The solution was cooled, the formed precipitate was filtered off and recrystallized from toluene if necessary [32].

Benzyl 2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)amino)-4-(4-fluorophenyl)-4-oxobut-2-enoate 5a. Yield 0.33 g (71%), orange crystals, mp 172.7-173.5 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.83 m (4H, CH_2), 2.56 m (4H, CH_2), 5.29 s (2H, OCH_2), 6.70 s (1H, C=CH), 7.16 m ($2H_{Ar}$), 7.37 m ($5H_{Ar}$), 8.00 m ($2H_{Ar}$), 12.09 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9, 23.0, 24.3, 24.5, 68.4, 99.5, 103.4, 113.5, 115.6, 115.9, 127.0, 127.6, 128.6, 128.7, 130.3, 130.4, 131.2, 134.1, 134.4, 148.0, 149.2, 162.6, 190.2.

4-Nitrobenzyl 2-((3-cyano-4,5,6,7-tetrahydro-benzo[b]thiophen-2-yl)amino)-4-(4-fluorophenyl)-4-oxobut-2-enoate 5b. Yield 0.35 g (70%), orange crystals, mp 71.1-75.1 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.83 m (4H, CH_2), 2.58 m (4H, CH_2), 5.37 s (2H, OCH_2), 6.72 s (1H, C=CH), 7.50 m ($4H_{Ar}$), 8.00 m ($2H_{Ar}$), 8.24 m ($2H_{Ar}$), 12.05 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.8, 22.9, 24.4, 24.5, 66.7, 99.9, 103.5, 113.4, 115.7, 116.0, 123.8, 129.0, 130.4, 130.5, 131.4, 134.2, 134.3, 141.3, 147.1, 148.1, 149.2, 162.4, 190.2.

Isobutyl 4-(4-chlorophenyl)-2-((3-cyano-4,5,6, 7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-oxobut-2-enoate 5c. Yield 0.36 g (81%), brown crystals, mp 108.1-108.9 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 0.90 d (6H, J = 6.6 Hz, $2CH_3$), 1.82 m (4H, $2CH_2$), 1.94 m (1H, CH), 2.61 m (4H, $2CH_2$), 4.03 d (2H, J = 6.6 Hz, OCH_2), 6.64 s (1H, C=CH), 7.45 m ($2H_{Ar}$), 7.90 m ($2H_{Ar}$), 12.16 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 18.9, 22.0, 23.0, 24.4, 24.6,

27.5, 72.8, 99.1, 103.4, 113.5, 129.0, 129.2, 131.4, 134.2, 136.5, 139.2, 148.5, 149.3, 162.7, 190.3.

Benzyl 4-(4-chlorophenyl)-2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-oxobut-2-enoate 5d. Yield 0.34 g (72%), orange crystals, mp 130.7-131.2 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.81 m (4H, $2CH_2$), 2.54 m (4H, $2CH_2$), 5.26 s (2H, OCH_2), 6.65 s (1H, C=CH), 7.30 m ($2H_{Ar}$), 7.35 m ($3H_{Ar}$), 7.44 m ($2H_{Ar}$), 7.89 m ($2H_{Ar}$), 12.10 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9, 23.0, 24.3, 24.5, 68.4, 99.3, 103.6, 113.4, 128.6, 128.7, 128.7, 129.0, 129.2, 131.4, 134.1, 134.3, 136.4, 139.2, 148.2, 149.0, 162.5, 190.3.

4-Nitrobenzyl 4-(4-chlorophenyl)-2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-oxobut-2-enoate 5e. Yield 0.39 g (74%), orange crystals, mp 138.9-139.7 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.82 m (4H, CH_2), 2.56 m (4H, CH_2), 5.37 s (2H, OCH_2), 6.70 s (1H, C=CH), 7.48 m ($4H_{Ar}$), 7.91 m ($2H_{Ar}$), 8.23 m ($2H_{Ar}$), 12.08 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.8, 22.9, 24.4, 24.5, 66.7, 99.8, 103.6, 113.4, 123.8, 129.0, 129.2, 131.6, 134.3, 136.3, 139.5, 141.3, 147.4, 149.0, 162.3, 190.4.

Methyl 2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)amino)-4-oxo-4-(p-tolyl)but-2-enoate 5f. Yield 0.32 g (84%), brown crystals, mp 161.2-161.8 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.86 m (4H, $2CH_2$), 2.44 s (3H, CH_3), 2.53 m (2H, CH_2), 3.08 m (2H, CH_2), 3.90 s (3H, OCH_3), 6.71 s (1H, C=CH), 7.29 m ($2H_{Ar}$), 7.89 m ($2H_{Ar}$), 12.24 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.6, 21.9, 23.0, 24.4, 24.5, 53.2, 99.9, 102.4, 113.6, 127.9, 129.4, 130.6, 134.0, 135.5, 143.7, 146.9, 149.7, 163.2, 191.4.

Benzyl 2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]-thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate 5g. Yield 0.35 g (74%), red crystals, mp 136.1-136.7 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.83 m (4H, CH_2), 2.56 m (4H, CH_2), 3.90 s (3H, OCH_3), 5.28 s (2H, OCH_2), 6.74 s (1H, CH), 6.98 m ($2H_{Ar}$), 7.32 m ($2H_{Ar}$), 7.37 m ($3H_{Ar}$), 7.97 m ($2H_{Ar}$), 12.11 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9, 23.0, 24.3, 24.4, 55.5, 68.2, 102.8, 113.6, 113.9, 127.0, 128.5, 128.6, 128.6, 130.1, 130.7, 131.0, 134.0, 134.5, 147.0, 149.9, 162.9, 163.6, 190.4.

Nitrobenzyl 2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate 5h. Yield 0.40 g (77%), orange crystals, mp 168.2-168.7 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.82 m (4H, CH_2), 2.56 m (4H, CH_2), 3.90 s (3H, OCH_3), 5.37 s (2H, OCH_2), 6.77 s (1H, C=CH), 6.98 m ($2H_{Ar}$), 7.50 m ($2H_{Ar}$), 7.97 m ($2H_{Ar}$), 8.23 m ($2H_{Ar}$), 12.07 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 21.9, 23.0, 24.4, 24.5, 55.5, 66.6, 102.9, 113.6, 114.0, 123.8, 127.0, 129.0, 130.1, 130.8, 130.9, 134.1, 141.5, 146.2, 148.1, 149.8, 162.6, 163.7, 190.4.

Furan-2-ylmethyl 2-((3-cyano-4,5,6,7-tetrahydrobenzo[b]thiophen-2-yl)amino)-4-(4-methoxyphenyl)-4-oxobut-2-enoate 5i. Yield 0.33 g (71%), red crystals, mp 140.9-141.1 °C (toluene). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.85 m (4H, CH_2), 2.61 m (4H, $2CH_2$), 3.90 s (3H, OCH_3), 5.25 s (2H, OCH_2), 6.39 m ($1H_{Ar}$), 6.45 m ($1H_{Ar}$), 6.71 s (1H, C=CH), 6.97 m ($2H_{Ar}$), 7.44 m ($1H_{Ar}$), 7.97 m ($2H_{Ar}$), 12.12 s (1H, NH). ^{13}C NMR spectrum ($CDCl_3$), δ, ppm: 22.0, 23.0, 24.3, 24.5, 55.7, 59.6, 100.2, 102.7, 110.6, 111.6, 113.6, 113.9, 130.1, 130.6, 130.9, 133.9, 143.5, 146.6, 148.2, 149.8, 162.6, 163.5, 190.3.

Antinociceptive activity and acute toxicity of compounds **5a-i** 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 [34]. 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 [35]. 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}) and sodium diclofenac (Alfa Aesar) was used as a reference drug.

Acute toxicity of compounds **5a-i** was evaluated by the method described by Pershin [36]. The median lethal doses (LD_{50}) were determined. Compounds **5a-i** were administered intraperitoneally to the mice as

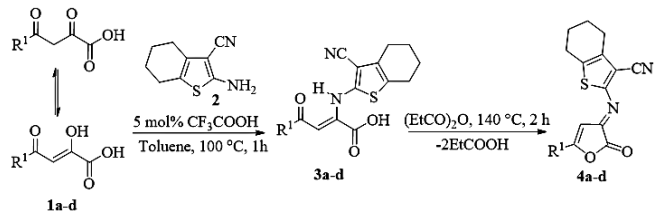
a suspensions in 2% starch solution and the behavior and mortality of the animals were observed for 10 days. The LD_{50} values for compounds **5a-i** were >1500 mg/kg. According to the toxicity classification system, compounds **5a-i** belong to the toxicity class V (practically nontoxic substances) [37].

Statistical analysis of the results was carried out by the student's test. The effect was considered significant at $p < 0.05$ [38].

RESULTS AND DISCUSSION

Earlier described 4-aryl-2-hydroxy-4-oxobut-2-enic acids **1a-d** [39], 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile **2** [40] were synthesized by the published procedures. Melting points and the ^{1}H NMR spectral data of these compounds coincide with those published earlier.

Substituted 2-[2-oxofuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitriles **4a-d** were synthesized in two steps using a previously developed method [20]. For this, (*Z*)-4-aryl-4-oxo-2-(thiophen-2-ylamino)but-2-enoic acids **3a-d** were obtained by a condensation of 4-aryl-2-hydroxy-4-oxobut-2-enoic acids **1a-d** with 2-amino-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitrile **2** in toluene at 100 °C in 1 h with adding 5 mol% of trifluoroacetic acid. Then, 3-(thiophen-2-ylimino)furan-2(3*H*)-ones were acquired by intramolecular cyclization of acids **3a-d** using propionic anhydride at 140 °C (Scheme 1).

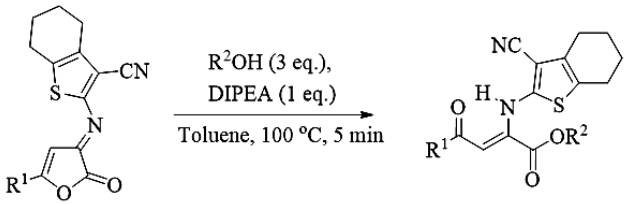


1,3,4: R^1 = 4-FC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**).

Scheme 1
Схема 1

4-Aryl-4-oxo-2-(thiophen-2-ylamino)but-2-enoates **5a-i** were isolated as products of interaction of 2-[2-oxofuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carbonitriles **4a-d** and primary alcohols in the presence of diisopropylethylamine in anhydrous toluene at 100 °C and vigorous stirring for 5 min (Scheme 2).

Compounds **5a-i** are orange, red or brown crystalline substances well soluble in DMSO, chloroform, soluble in toluene, methanol, ethanol at heating, and insoluble in water and alkanes. According to the ^{1}H NMR data for $CDCl_3$ solution compounds **5a-5i**, spectra are characterized by existence of a singlet of the CH groups at 6.12-6.77 ppm and a singlet of the proton of the NH group at 9.98-12.24 ppm. The ^{13}C NMR spectra of compounds **5a-i** shows the characteristic signals of the carbonyl carbons of the aroyl moiety in the δ_C 190.2-191.4 ppm, signals of nitrile group in the δ_C 113.4-113.6 ppm and the signals of the methine group carbons in the δ_C 102.2-103.6 ppm.



4: R^1 = 4-FC_6H_4 (**a**), 4-ClC_6H_4 (**b**), 4-MeC_6H_4 (**c**), 4-$MeOC_6H_4$ (**d**);
5: R^1 = 4-FC_6H_4, R^2= Bn (**a**), 4-$NO_2C_6H_4CH_2$ (**b**); R^1 = 4-ClC_6H_4, R^2= *i*-Bu (**c**), Bn (**d**), 4-$NO_2C_6H_4CH_2$ (**e**); R^1 = 4-MeC_6H_4, R^2= Me (**f**); R^1 = 4-$MeOC_6H_4$, R^2= Bn (**g**), 4-$NO_2C_6H_4CH_2$ (**h**), furan-2-ylmethyl (**i**).

Scheme 2
Схема 2

Table

Antinociceptive activity of the studied compounds 5a-i[a], studied by the "hot plate" method

***Таблица*. Антиноцицептивная активность исследованных соединений 5a-i[a], изученная по методу «горячая пластина»**

Compound no.	c, mg/kg	Defensive response time at the maximum effect, s
5a	50	19.92±0.82
5b	50	21.12±0.98
5c	50	19.28±0.42
5d	50	20.67±1.97
5e	50	19.24±0.86
5f	50	19.08±3.86
5g	50	**22.00±0.71**
5h	50	19.17±3.52
5i	50	**21.70±3.23**
Sodium metamizole	93 (ED_{50})	16.33±3.02
Sodium diclofenac	10	26.20±0.96
Control	_	10.30±0.60

Note: [a] $p < 0.05$ compared to control
Примечание: [a] $p < 0,05$ по сравнению с контролем

According to the antinociceptive activity data from Table, it can be seen that the obtained esters **5a-i** has a highly analgesic effect. It was found that the introduction of benzyl and furan-2-yl substituents into the ester function significantly increases the analgesic effect, so compounds **5g** and **5i** exhibit the highest activity among structures containing methoxy groups as

a substituent in the aromatic ring. It was found that the replacement of a chlorine atom by a fluorine atom in the aryl fragment of compounds **5** does not significantly affect their antinociceptive activity (compounds **5d**,**e** and **5a**,**b**).

Acute toxicity (LD_{50}, mg/kg) of compounds **5a-i** was found to be >1500 mg/kg. According to the toxicity classification of drugs, they belong to the V class of toxicity (practically non-toxic drugs).

CONCLUSIONS

Thus, by decyclization of substituted 3-(thiophene-2-ylamino)furan-2(3*H*)-ones under the action of primary alcohols, novel 4-aryl-4-oxo-2-(thiophene-2-ylamino)but-2-enoates. Determination of the antinociceptive activity of the obtained compounds showed that all esters have an analgesic effect, while being practically non-toxic substances, so, 4-aryl-4-oxo-2-(thiophene-2-ylamino)but-2-enoates can be a highly promising class for further study in order to search for and developing new biologically active compounds with analgesic effect.

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