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Synthesis and Antinociceptive Activity of *N*-Substituted 4-Aryl-4-oxo-2-[(3-thiophen-2-yl)amino]but-2-enamides

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Abstract—2-{[5-Aryl-2-oxofuran-3(2*H*)-ylidene]amino}thiophene-3-carboxylic acid derivatives reacted with substituted amines to give new *N*-substituted 4-aryl-4-oxo-2-[(3-thiophen-2-yl)amino]but-2-enamides. Antinociceptive activity of the synthesized compounds was studied.

Keywords: antinociceptive activity, Gewald reaction, 2,4-dioxobutanoic acids, 3-(thiophen-2-yl)iminofuran-2(3*H*)-one

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Substituted Gewald aminothiophene derivatives are important heterocycles found in numerous biologically active and natural compounds [1–10]. Interest in this type of heterocycle starts from the chemistry of dyes to the modern design of drugs and much more. Generally, substituted 2-aminothiophenes with an electron-withdrawing group, such as cyano, ester or amide at position 3 and alkyl, aryl or hetaryl groups at position 4 or 5, can be obtained using the Gewald reaction [11–13].

Compounds containing 3-imino-3*H*-furan-2-one in their structure are represented in the literature by few examples of their preparation [14, 15]. Previously, we have proposed a simple method for the preparation of a number of ethyl esters of 2-[5-aryl-2-oxofuran-3(2*H*)-ylideneamino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acids by intramolecular cyclization of (*Z*)-4-aryl-4-oxo-2-[3-(ethoxycarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-2-ylamino]but-2-enoic acids under the action of acetic anhydride [16], and also their chemical properties were studied [17–19]. At the same time, this rare type of derivatives of 3-thienylimino-3*H*-furan-2-one seems to be very promising from the point of view of high reactivity and the possible presence of biologically active compounds in the series of furan derivatives.

It has been previously shown that 3-thienylimino-3*H*-furan-2-ones recyclize upon reaction with aliphatic amines to form amides of 4-aryl-4-oxo-2-thienylaminobut-2-enoic acids [20]. Herein, we proposed studies in the synthesis of new 3-thienylimino-3*H*-furan-2-ones and studied their reactions with aliphatic, aromatic, heteroaromatic and disubstituted amines.

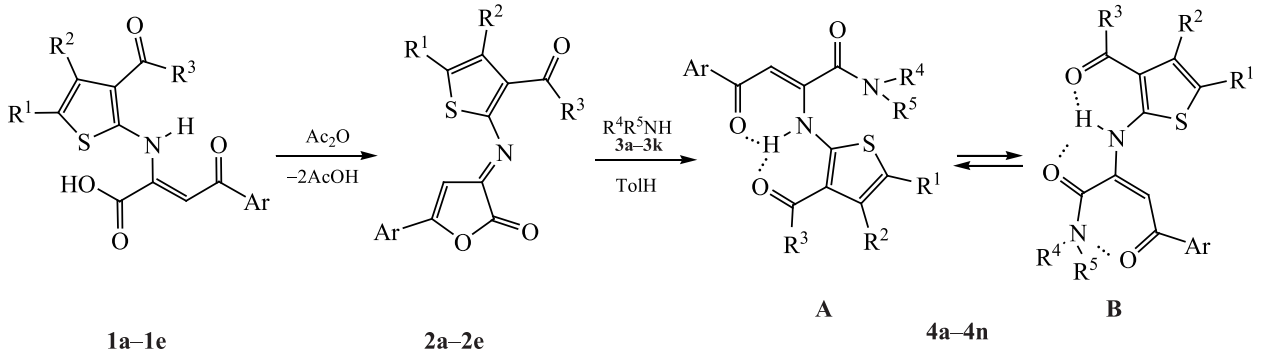
The starting 3-thienylimino-3*H*-furan-2-ones **2a–2e** were prepared according to the known methods [16] by intramolecular cyclization of the corresponding 4-aryl-4-oxo-2-thienylaminobut-2-enoic acids **1a–1e** in acetic anhydride. Compounds **2d** and **2e** were obtained for the first time (Scheme 1).

The IR spectra of compounds **2d** and **2e** contain absorption bands of stretching vibrations of the lactone carbonyl group of the furan ring at 1791–1794 cm^{-1} and C=N bonds at 1599–1606 cm^{-1}. In the ^1H NMR spectra, the singlet of the vinyl C^4H proton of the furan ring is observed at 7.22–7.23 ppm.

The reaction of 3-thienylimino-3*H*-furan-2ones **2a–2e** with alkyl, aryl, hetaryl, and disubstituted amines in an inert aprotic solvent proceeds with the formation of *N*-substituted butenoic acid amides **4a–4n** in yields of up to 97% (Scheme 1). It was found that the reaction proceeded through attack of the amino group at the carbon atom of the lactone C=O group of compounds **2a–2e** and led to the products of the furan ring opening. The ester group does not participate in the reaction with amines, which does not contradict the literature data [21–23].

Compounds **4a–4n** are crystalline orange or yellow substances. In the IR spectra of amides **4a–4n**, there is an

Scheme 1.



1, **2**, R^3 = OEt, R^1+R^2 = –$(CH_2)_4$–, Ar = Ph (**a**), 4-$CH_3OC_6H_4$ (**b**), 4-ClC_6H_4 (**c**); R^1, R^2 = CH_3, Ar = Ph (**d**); R^3 = NH_2, R^1+R^2 = –$(CH_2)_4$–, Ar = 4-$CH_3C_6H_4$ (**e**); **3**, R^4 = H, R^5 = Ad (**a**), Cy (**b**), Bn (**c**), Ph (**d**), 4-$EtOCOC_6H_4$ (**e**), 4-$CH_3OC_6H_4$ (**f**), 4-antipyryl (**g**); R^4 = Et, R^5 = Bn (**h**), Et (**i**); R^4+R^5 = –$(CH_2)_5$– (**j**), –$(CH_2)_2O(CH_2)_2$– (**k**); **4**, R^3 = OEt, R^1+R^2 = –$(CH_2)_4$–, Ar = Ph, R^4 = H, R^5 = Ad (**a**), Ph (**b**), 4-$EtOCOC_6H_4$ (**c**), 4-antipyryl (**d**); R^4+R^5 = –$(CH_2)_5$– (**e**); R^4 = Et, R^5 = Bn (**f**); Ar = 4-$CH_3OC_6H_4$, R^4 = H, R^5 = Ad (**g**), Cy (**h**); R^4+R^5 = –$(CH_2)_2O(CH_2)_2$– (**i**); R^4 = Et, R^5 = Bn (**j**), R^5= Et (**k**); Ar = 4-ClC_6H_4, R^4 = H, R^5 = Cy (**l**); R^1, R^2 = CH_3, Ar = Ph, R^4 = H, R^5 = 4-$CH_3OC_6H_4$ (**m**); R^3 = NH_2, R^1+R^2 = –$(CH_2)_4$–, Ar = 4-$CH_3C_6H_4$, R^4 = H, R^5 = Bn (**n**).

absorption band of the NH group of the amide fragment in the 3123–3395 cm^{-1} region and an absorption band of the carbonyl group at 1652–1694 cm^{-1}.

We studied the ^1H NMR spectra of compounds **4a–4n** in DMSO-d_6 and $CDCl_3$ solutions. It was found that compounds **4a**, **4e**, **4g–4i**, **4k–4n** in DMSO-d_6 solutions exist in form **A** and are characterized by a proton singlet of the NH group involved into a strong intramolecular hydrogen bonding (12.38–13.58 ppm), proton signals of the group NHCO (8.13–10.94 ppm) and a singlet of the proton of the CH group (6.12–6.48 ppm).

In $CDCl_3$ solutions, compounds **4a** and **4b** are in two forms, **A** and **B**. The presence of two forms in solutions of deuterated chloroform seems to be associated with greater thermodynamic stability due to several intramolecular hydrogen bonds of form **B**, which are destroyed by the more polar DMSO-d_6, and the gain in energy becomes predominant for solvated form **B**. Form **A** is characterized by a proton singlet of the NH group involved into a strong intramolecular hydrogen bond (13.14–14.86 ppm), proton of the CH group (6.20–7.23 ppm) and a proton signal of the NHCO group (5.91–9.73 ppm). Form **B** is

Table 1. Antinociceptive activity of compounds **4a–4g**, **4i**, **4j**, **4l–4n**[a]

Compound	Dosage, mg/kg	The latent period of the defensive reflex (120 min), s
4a	50	19.80 ± 1.24
4b	50	14.80 ± 0.49
4d	50	15.60 ± 0.75
4d	50	23.70 ± 3.23
4e	50	19.00 ± 1.22
4f	50	17.20 ± 1.77
4g	50	15.60 ± 1.33
4i	50	16.20 ± 1.71
4j	50	18.20 ± 0.20
4l	50	19.00 ± 0.84
4m	50	16.10 ± 1.50
4n	50	24.90 ± 1.18
Metamizole sodium	93 (ED_{50})	16.33 ± 3.02
		$p < 0.1$
Diclofenac sodium	10	26.20 ± 0.96
Control	–	10.30 ± 0.60

[a] Reliability compared to control $p < 0.05$.

characterized by a singlet of the proton of the NH group (12.31–13.89 ppm), a signal of the proton of the amide group (12.22–12.41 ppm), and a singlet of a proton of the CH group (6.06–7.05 ppm).

According to ^{1}H NMR data, in a DMSO-d_6 solution, disubstituted amides **4f** and **4l** exist in two conformations, mainly in a conformation with a larger group in a transoid position with respect to the oxygen atom. In ^{1}H NMR spectra, the *Z*-conformation is characterized by the NH proton singlet at 13.53–13.57 ppm involved into the intramolecular hydrogen bond and the CH proton singlet at 6.21–6.24 ppm. The proton singlet corresponds to the *E*-conformer NH groups at 13.46–13.49 ppm involved into the intramolecular hydrogen bond, and a proton singlet of the CH group at 6.16–6.19 ppm.

Earlier, antinociceptive activity has been detected in similar compounds [24, 25]; therefore, some of the obtained compounds were also studied on antinociceptive activity (Table 1). From the data obtained it follows that all the studied compounds have a pronounced analgesic effect. The most active compounds **4d** and **4n** are comparable in action to diclofenac sodium. It was found that the introduction of an antipyryl substituent into the amide fragment increases the activity of compound **4d**, while the introduction of a benzocaine fragment led to a significant decrease in activity. However, the replacement of the ester substituent at position 3 of the thiophene ring with an amide also led to a significant increase in the analgesic effect of compound **4n**. The data presented indicate the feasibility of further study of the antinociceptive activity of the obtained amides in order to search for substances with a pronounced analgesic effect.

EXPERIMENTAL

IR spectra were recorded on an FSM-1202 instrument from liquid paraffin. ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III instrument (400 and 100 MHz) from $CDCl_3$ and DMSO-d_6 solutions relative to residual signals of the non-deuterated solvent. Elemental analysis was performed on a Leco CHNS-932 instrument. Reaction progress and individuality of obtained compounds was monitored by TLC on Sorbfil plates, eluting with a diethyl ether–benzene–acetone system (10 : 9 : 1); detecting in UV light and iodine vapor. Melting points were determined on an SMP40 instrument.

The initial substituted 4-aryl-4-oxo-2-thienylaminobut-2-enoic acids **1a**–**1e** were obtained according to the procedure described in [26]; compounds **1a**–**1d** have been described previously.

2-[(3-(Aminocarbonyl)-4,5,6,7-tetrahydrobenzo[*b*]-thiophen-2-yl)amino]-4-(4-methylphenyl)-4-oxobut-2-enoic acid (1e). Yield 3.08 g (80%), red crystals, mp 150–151°C (dioxane). IR spectrum, ν, cm^{-1}: 1634 ($CONH_2$), 3189, 3396 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.57 m (2H, CH_2), 1.91 m (2H, CH_2), 2.45 s (3H, CH_3), 2.79 m (4H, CH_2), 5.89 br. s (2H, NH_2), 7.01 s (1H, C=CH), 7.33 m (2H, H_{Ar}), 7.94 m (2H, H_{Ar}), 12.65 s (1H, NH). Found, %: C 62.45; H 5.25; N 7.31; S 8.36. $C_{20}H_{20}N_2O_4S$. Calculated, %: C 62.48; H 5.24; N 7.29; S 8.34.

The substituted 3-thienylimino-3*H*-furan-2-ones **2a**–**2e** were obtained according to the procedure described in [16]; compounds **2a**–**2c** have been described previously.

Ethyl 4,5-dimethyl-2-{[2-oxo-5-phenylfuran-3(2*H*)-ylidene]amino}thiophene-3-carboxylate (2d). Yield 2.91 g (82%), dark red crystals, mp 169–170°C (toluene). IR spectrum, ν, cm^{-1}: 1606 (C=N), 1715 (COOEt), 1794 ($CO_{lactone}$). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.31 t (3H, CH_3CH_2O, J = 6.6 Hz), 2.13 s (3H, CH_3), 2.44 s (3H, CH_3), 4.31 q (2H, CH_3CH_2O, J = 6.6 Hz), 7.23 s (1H, H_{Ar}), 7.61 m (3H, H_{Ar}), 8.02 m (2H, H_{Ar}). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 12.1, 13.6, 14.1, 60.9, 98.3, 126.6, 126.7, 129.2, 132.5, 132.9, 135.3, 137.4, 145.2, 146.1, 162.6, 164.1, 165.6. Found, %: C 64.20; H 4.85; N 3.93; S 9.00. $C_{19}H_{17}NO_4S$. Calculated, %: 64.21; H 4.82; N 3.94; S 9.02.

2-{[5-(4-Methylphenyl)-2-oxofuran-3(2*H*)-ylidene]-amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxamide (2e). Yield 3.08 g (84%), red crystals, mp 231–232°C (toluene). IR spectrum, ν, cm^{-1}: 1599 (C=N), 1658 ($CONH_2$), 1791 ($CO_{lactone}$), 3165, 3348 (NH_2). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.78 m (2H, CH_2), 1.84 m (2H, CH_2), 2.44 s (3H, CH_3), 2.84 m (4H, $2CH_2$), 7.22 s (1H, H_{Ar}), 7.31 br. s (1H, NH_2), 7.42 m (2H, H_{Ar}), 7.92 m (2H, H_{Ar}), 8.08 br. s (1H, NH_2). Found, %: C 65.57; H 4.97; N 7.63; S 8.75. $C_{20}H_{18}N_2O_3S$. Calculated, %: C 65.55; H 4.95; N 7.64; S 8.75.

General procedure for the synthesis of *N*-substituted amides of 4-aryl-4-oxo-2-[(3-thiophen-2-yl)amino]-but-2-enoic acids 4a–4n. A mixture of 0.001 mol of compound **2a**–**2e** and 0.001 mol of the corresponding amine **3a**–**3k** in anhydrous toluene (20 mL) was stirred at 50°C for 2 h. After cooling the precipitate was filtered off and recrystallized.

Ethyl 2-{[1-(adamantylamino)-1,4-dioxo-4-phenylbut-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4a). Yield 0.52 g (97%), orange crystals, mp 200–201°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1665 br (CONH, COOEt), 3179, 3280 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.70 m (6H, CH_2), 1.74 m (7H, $2CH_2$ + 3CH), 2.11 m (6H, CH_2), 2.63 m (2H, CH_2), 2.75 m (2H, CH_2), 4.39 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.20 s (1H, C=CH), 7.57 m (2H, H_{Ar}), 7.65 m (1H, H_{Ar}), 8.03 m (2H, H_{Ar}), 8.58 s (1H, NH), 13.27 s (1H, NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: form **A** (46%), 1.38 m (3H, Me), 1.78 m (6H, CH_2), 2.10 m (7H, $2CH_2$ + 3CH), 2.23 m (6H, CH_2), 2.72 m (4H, CH_2), 4.40 m (2H, $CH_3\underline{CH_2}O$), 5.91 s (1H, NH), 6.17 s (1H, C=CH), 7.48 m (3H, H_{Ar}), 7.96 m (2H, H_{Ar}), 13.14 s (1H, NH); form **B** (54%), 1.38 m (3H, Me), 1.78 m (6H, CH_2), 2.10 m (7H, $2CH_2$ + 3CH), 2.23 m (6H, CH_2), 2.72 m (4H, CH_2), 4.40 m (2H, $CH_3\underline{CH_2}O$), 7.05 s (1H, C=CH), 7.48 m (3H, H_{Ar}), 7.96 m (2H, H_{Ar}), 12.22 s (1H, NH), 12.31 s (1H, NH). Found, %: C 69.93; H 6.80; N 5.22; S 6.07. $C_{31}H_{36}N_2O_4S$. Calculated, %: C 69.90; H 6.81; N 5.26; S 6.02.

Ethyl 2-{[1,4-dioxo-1-(phenylamino)-4-phenylbut-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4b). Yield 0.42 g (89%), orange crystals, mp 188–190°C (isopropanol). IR spectrum, ν, cm^{-1}: 1675 br (CONH, COOEt), 3188, 3312 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: form **A** (50%), 1.25 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.66 m (4H, CH_2), 2.37 m (2H, CH_2), 2.54 m (2H, CH_2), 4.15 m (2H, $CH_3\underline{CH_2}O$), 7.23 m (1H, C=CH; 2H, H_{Ar}), 7.52 m (4H, H_{Ar}), 7.84 m (2H, H_{Ar}), 8.08 m (2H, H_{Ar}), 9.73 s (1H, NH), 14.86 s (1H, NH); form **B** (50%), 1.44 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.87 m (4H, CH_2), 2.75 m (2H, CH_2), 2.87 m (2H, CH_2), 4.45 m (2H, $CH_3\underline{CH_2}O$), 6.06 s (1H, C=CH), 7.23 m (2H, H_{Ar}), 7.52 m (4H, H_{Ar}), 7.84 m (2H, H_{Ar}), 8.08 m (2H, H_{Ar}), 12.41 s (1H, NH), 13.89 s (1H, NH). Found, %: C 68.30; H 5.56; N 5.92; S 6.75. $C_{27}H_{26}N_2O_4S$. Calculated, %: C 68.33; H 5.52; N 5.90; S 6.76.

Ethyl 2-[(1,4-dioxo-1-{[4-(ethoxycarbonyl)phenyl]-amino}-4-phenylbut-2-en-2-yl)amino]-4,5,6,7-tetrahydro-benzo[b]thiophene-3-carboxylate (4c). Yield 0.38 g (70%), orange crystals, mp 179–180°C (isopropanol). IR spectrum, ν, cm^{-1}: 1688 (CONH), 1706, 1719 (COOEt), 3223, 3389 (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 m (3H, CH_3), 1.39 m (3H, CH_3), 1.73 m (4H, CH_2), 2.50 m (2H, CH_2), 2.69 m (2H, CH_2), 4.27 m (4H, CH_2O), 5.98 s (1H, C=CH), 7.19 m (2H, H_{Ar}), 7.35 m (2H, H_{Ar}), 7.69 m (3H, H_{Ar}), 8.09 m (2H, H_{Ar}), 10.35 s (1H, NH), 13.78 s (1H, NH). Found, %: C 65.90; H 5.57; N 5.15; S 5.82. $C_{30}H_{30}N_2O_6S$. Calculated, %: C 65.92; H 5.53; N 5.12; S 5.86.

Ethyl 2-{[1,4-dioxo-1-(4-antipyrylamino)-4-phenylbut-2-en-2-yl]amino}4,5,6,7-tetrahydrobenzo[*b*]-thiophen-3-carboxylate (4d). Yield 0.41 g (70%), orange crystals, mp 203–204°C (toluene). IR spectrum, ν, cm^{-1}: 1664 (CONH), 1712 (COOEt), 3123, 3236 br (NH). ^{1}H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.78 m (4H, CH_2), 2.08 s (3H, Me), 2.59 m (2H, CH_2), 2.79 m (2H, CH_2), 3.06 s (3H, NCH_3), 4.36 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.27 s (1H, C=CH), 7.37 m (10H, H_{Ar}), 8.39 s (1H, NH), 10.33 s (1H, NH). Found, %: C 65.70; H 5.53; N 9.55; S 5.47. $C_{32}H_{32}N_4O_5S$. Calculated, %: C 65.73; H 5.52; N 9.58; S 5.48.

Ethyl 2-{[1,4-dioxo-1-(piperidin-1-yl)-4-phenylbut-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4e). Yield 0.31 g (67%), orange crystals, mp 128–129°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1681 (CONH), 1726 (COOEt), 3370 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.56 m (6H, CH_2), 1.73 m (4H, CH_2), 2.72 m (2H, CH_2), 3.61 m (4H, NCH_2), 4.39 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.22 s (1H, C=CH), 7.52 m (2H, H_{Ar}), 7.60 m (1H, H_{Ar}), 8.01 m (2H, H_{Ar}), 13.61 s (1H, NH). Spectral data coincided with those reported in [6].

Ethyl 2-({1-[benzyl(ethyl)amino]-1,4-dioxo-4-phenylbut-2-en-2-yl}amino)-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carboxylate (4f). Yield 0.32 g (62%), yellow crystals, mp 119–120°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1652 (CONH), 1715 (COOEt), 3380 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: *Z*-conformer (57%), 1.13 m (3H, CH_3), 1.33 m (3H, CH_3), 1.73 m (4H, CH_2), 2.48 m (2H, CH_2), 2.71 m (2H, CH_2), 3.32 m (2H, CH_2N), 4.36 m (2H, CH_2O), 4.61 m (2H, $\underline{CH_2}Ph$), 6.24 s (1H, C=CH), 7.37 m (5H, H_{Ar}), 7.57 m (3H, H_{Ar}), 8.02 m (2H, H_{Ar}), 13.57 s (1H, NH); *E*-conformer (43%), 1.13 m (3H, CH_3), 1.33 m (3H, CH_3), 1.73 m (4H, CH_2), 2.48 m (2H, CH_2), 2.62 m (2H, CH_2), 3.25 m (2H, CH_2N), 4.36 m (2H, CH_2O), 4.71 m (2H, $\underline{CH_2}Ph$), 6.19 s (1H, C=CH), 7.37 m (5H, H_{Ar}), 7.57 m (3H, H_{Ar}), 7.76 m (2H, H_{Ar}), 13.49 s (1H, NH). Spectral data coincided with those reported in [6].

Ethyl 2-{[1-(adamantylamino)-1,4-dioxo-4-(4-methoxyphenyl)but-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophen-3-carboxylate (4g). Yield 0.47 g (83%), orange crystals, mp 200–202°C

(acetonitrile). IR spectrum, ν, cm^{-1}: 1686 br (CONH, COOEt), 3311 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.37 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.69 m (6H, CH_2), 1.76 m (7H, $2CH_2$ + 3CH), 2.09 m (6H, CH_2), 2.59 m (2H, CH_2), 2.73 m (2H, CH_2), 3.87 s (3H, OCH_3), 4.37 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.12 s (1H, C=CH), 7.05 m (2H, H_{Ar}), 7.97 m (2H, H_{Ar}), 8.13 s (1H, NH), 13.00 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.1, 22.1, 22.5, 24.1, 25.9, 28.9, 36.0, 40.5, 113.9, 114.3, 126.9, 129.5, 131.3, 132.5, 148.0, 151.3, 162.4, 162.6, 163.0, 188.4. Found, %: C 68.33; H 6.80; N 4.95; S 5.72. $C_{32}H_{38}N_2O_5S$. Calculated, %: C 68.30; H 6.81; N 4.98; S 5.70.

Ethyl 2-{[1,4-dioxo-4-(4-methoxyphenyl)-1-(cyclohexylamino)but-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4h). Yield 0.36 g (70%), yellow crystals, mp 177–179°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1660 (CONH), 1719 (COOEt), 3270 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.26 m (6H, CH_2), 1.36 t (3H, $\underline{CH_3}CH_2O$, J = 7.2 Hz), 1.73 m (8H, CH_2), 2.58 m (2H, CH_2), 2.71 m (2H, CH_2), 3.69 m (1H, CH), 3.86 s (3H, OCH_3), 4.36 q (2H, $CH_3\underline{CH_2}O$, J = 7.2 Hz), 6.18 s (1H, C=CH), 7.06 m (2H, H_{Ar}), 7.99 m (2H, H_{Ar}), 8.85 d (1H, NH J = 7.7 Hz), 13.13 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.2, 22.1, 22.4, 24.0, 24.4, 25.1, 25.9, 31.5, 48.2, 55.4, 60.0, 96.6, 113.9, 125.8, 129.6, 130.9, 132.4, 148.1, 150.5, 162.2, 162.6, 163.1, 188.3. Found, %: C 65.90, H 6.76, N 5.47, S 6.28. $C_{28}H_{34}N_2O_5S$. Calculated, %: C 65.86, H 6.71, N 5.49, S 6.28.

Ethyl 2-{[1,4-dioxo-1-morpholino-4-(4-methoxyphenyl)but-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4i). Yield 0.33 g (67%), yellow crystals, mp 104–106°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1679 ($CONH_2$), 1712 (COOEt), 3395 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz). 1.74 m (4H, CH_2), 2.60 m (2H, CH_2), 2.70 m (2H, CH_2), 3.60 m (8H, CH_2), 3.86 s (3H, OCH_3), 4.38 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.25 s (1H, C=CH), 7.04 m (2H, H_{Ar}), 8.01 m (2H, H_{Ar}), 13.53 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.1, 22.0, 22.4, 23.9, 26.0, 41.5, 46.8, 55.4, 60.1, 65.1, 65.2, 94.9, 113.8, 113.9, 126.0, 129.7, 130.8, 132.8, 148.8, 147.1, 162.1, 162.6, 163.0, 187.9. Spectral data coincided with those reported in [6].

Ethyl 2-({1-[benzyl(ethyl)amino]-1,4-dioxo-4-(4-methoxyphenyl)but-2-en-2-yl}amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (4j). Yield 0.53 g (97%), yellow crystals, mp 113–115°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1694 br (COOEt, $CONH_2$), 3370 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: *Z*-conformer (57%), 1.13 m (3H, CH_3), 1.33 m (3H, CH_3), 1.72 m (4H, CH_2), 2.46 m (2H, CH_2), 2.69 m (2H, CH_2), 3.31 m (2H, CH_2N), 3.86 s (3H, OCH_3), 4.35 m (2H, OCH_2), 4.65 m (2H, $\underline{CH_2}Ph$), 6.21 s (1H, C=CH), 7.05 m (2H, H_{Ar}), 7.36 m (5H, H_{Ar}), 8.01 m (2H, H_{Ar}), 13.53 s (1H, NH); *E*-conformer (43%), 1.13 m (3H, CH_3), 1.33 m (3H, CH_3), 1.72 m (4H, CH_2), 2.61 m (2H, CH_2), 2.69 m (2H, CH_2), 3.31 m (2H, CH_2N), 3.84 s (3H, OCH_3), 4.35 m (2H, OCH_2), 4.65 m (2H, $\underline{CH_2}Ph$), 6.16 s (1H, C=CH), 7.05 m (2H, H_{Ar}), 7.36 m (5H, H_{Ar}), 7.77 m (2H, H_{Ar}), 13.46 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: *Z*-conformer, 12.6, 14.1, 22.0, 22.3, 23.9, 25.9, 46.5, 55.4, 60.1, 94.2, 113.9, 114.5, 126.3, 127.4, 128.2, 129.0, 129.5, 130.8, 132.8, 135.8, 146.8, 150.3, 162.6, 162.8, 163.5, 187.9; *E*-conformer, 10.9, 14.1, 22.0, 22.4, 24.0, 26.0, 42.6, 50.1, 60.1, 94.7, 113.8, 114.4, 126.2, 127.1, 127.3, 128.2, 129.4, 130.7, 132.9, 135.9, 146.9, 159.8, 162.6, 162.8, 163.8, 187.8. Spectral data coincided with those reported in [6].

Ethyl (*Z*)-2-{[1,4-dioxo-1-(diethylamino)-4-(4-methoxyphenyl)but-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4k). Yield 0.30 g (62%), orange crystals 99–101°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1677 br (CON), 1710 (COOEt), 3368 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.13 t (3H, $\underline{CH_3}CH_2N$, J = 7.0 Hz), 1.20 t (3H, $\underline{CH_3}CH_2N$, J = 7.1 Hz), 1.36 t (3H, $\underline{CH_3}CH_2O$, J = 7.1 Hz), 1.73 m (4H, CH_2), 2.58 m (2H, CH_2), 2.71 m (2H, CH_2), 3.35 q (2H, $CH_3\underline{CH_2}N$, J = 7.0 Hz), 3.46 m (2H, $CH_3\underline{CH_2}N$), 3.85 s (3H, OCH_3), 4.38 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.13 s (1H, C=CH), 7.04 m (2H, H_{Ar}), 8.00 m (2H, H_{Ar}), 13.58 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 11.6, 13.0, 14.1, 22.0, 22.3, 23.9, 25.9, 38.6, 42.7, 55.4, 60.1, 94.2, 113.9, 114.0, 126.1, 129.5, 130.8, 132.8, 147.1, 150.2, 162.6, 162.9, 163.0, 187.8. Found, %: C 64.44, H 6.68, N 5.81, S 6.65. $C_{26}H_{32}N_2O_5S$. Calculated, %: C 64.44, H 6.66, N 5.78, S 6.62.

Ethyl 2-{[1,4-dioxo-4-(4-chlorophenyl)-1-(cyclohexylamino)but-2-en-2-yl]amino}-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylate (4l). Yield 0.27 g (53%), dark orange crystals, mp 164–166°C (isopropanol). IR spectrum, ν, cm^{-1}: 1679 (CONH), 1708 (COOEt), 3310 br (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.32 m (6H, CH_2), 1.37 t (3H, $\underline{CH_3}CH_2O$, J =

7.1 Hz), 1.73 m (8H, CH_2), 2.59 m (2H, CH_2), 2.71 m (2H, CH_2), 3.69 m (1H, CH), 4.36 q (2H, $CH_3\underline{CH_2}O$, J = 7.1 Hz), 6.19 s (1H, C=CH), 7.59 m (2H, H_{Ar}), 8.02 m (2H, H_{Ar}), 8.89 d (1H, NH, J = 7.7 Hz), 13.20 s (1H, NH). ^{13}C NMR spectrum (DMSO-d_6), δ_C, ppm: 14.1, 22.0, 22.4, 24.0, 24.37, 25.1, 25.90, 31.5, 48.3, 60.1, 96.2, 114.4, 126.6, 128.7, 129.2, 132.5, 136.9, 137.2, 147.4, 151.6, 161.9, 163.0, 188.0. Found, %: C 62.92; H 6.10; N 5.41; S 6.24. $C_{27}H_{31}ClN_2O_4S$. Calculated, %: C 62.96; H 6.07; N 5.44; S 6.22.

Ethyl 2-({1,4-dioxo-1-[(4-methoxyphenyl)amino]-but-2-en-2-yl}amino-4-phenyl)-4,5-dimethyl-thiophene-3-carboxylate (4m). Yield 0.38 g (80%), orange crystals, mp 210–211°C (acetonitrile). IR spectrum, ν, cm^{-1}: 1668 (CONH), 1702 (COOEt), 3288 br (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.39 t (3H, $\underline{CH_3}CH_2O$, J = 7.2 Hz), 2.16 s (3H, CH_3), 2.18 s (3H, CH_3), 3.75 s (3H, OCH_3), 4.39 q (2H, $CH_3\underline{CH_2}O$, J = 7.2 Hz), 6.48 s (1H, C=CH), 6.96 m (2H, H_{Ar}), 7.32 m (2H, H_{Ar}), 7.56 m (3H, H_{Ar}), 8.06 m (2H, H_{Ar}), 10.94 s (1H, NH), 13.28 s (1H, NH). Found, %: C 65.28; H 5.44; N 5.87; S 6.72. $C_{26}H_{26}N_2O_5S$. Calculated, %: C 65.25; H 5.48; N 5.85; S 6.70.

2-{[1-(Benzylamino)-1,4-dioxo-4-(4-methoxy-phenyl)but-2-en-2-yl]amino}-4,5,6,7-tetra-hydrobenzo[*b*]thiophene-3-carboxamide (4n). Yield 0.43 g (87%), yellow crystals, mp 215–217°C (toluene). IR spectrum, ν, cm^{-1}: 1652 ($CONH_2$, CONH), 3191 br (NH), 3291, 3373 (NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.71 m (4H, CH_2), 2.50 m (2H, CH_2), 2.57 m (2H, CH_2), 3.82 s (3H, OCH_3), 4.37 d (2H, CH_2N, J = 5.8 Hz), 6.19 s (1H, C=CH), 7.01 m (2H, H_{Ar}), 7.59 m (5H, H_{Ar}), 7.44 br. s (2H, NH_2), 7.96 m (2H, H_{Ar}), 9.55 t (1H, NH, J = 5.8 Hz), 12.38 s (1H, NH). Found, %: C 66.25; H 5.53; N 8.59; S 6.52. $C_{27}H_{27}N_3O_4S$. Calculated, %: C 66.24; H 5.56; N 8.58; S 6.55.

Studying antinociceptive activity was carried out in the Perm State National Research University, the Research Laboratory of Biologically Active Substances. Antinociceptive activity was determined on outbred white mice of both sexes weighing 18–22 g using the "hot plate" thermal stimulation technique [27]. The studied compounds were administered intraperitoneally in the form of a suspension in a 2% starch solution at a dose of 50 mg/kg 30 min before the animals were placed on a metal plate heated to 53.5°C [28]. Studies were performed 30, 60, 90, 120 min after administration of the compound.

The indicator of the change in pain sensitivity was the length of time the animals stay on the hot plate until a defensive pain reflex occurs—licking the hind legs or trying to tear off all four paws from the surface of the plate. The time of onset of this reflex from the beginning of the placement of the animal on the plate was measured in sec (latent period). The maximum duration of the latent period is the interval of 40 s. In the experiment we used animals with the initial time of the onset of the defensive reflex of no more than 15 sec. Each compound was tested on 6 animals. The results were evaluated by increasing the time of the onset of the defensive reflex compared with the initial data.

The control group of animals was injected with 2% starch mucus. Metamizole sodium (Farmkhimkomplekt LLC) at a dose of 93 mg/kg (ED50), ibuprofen (EnSiFarm) at a dose of 50 mg/kg, diclofenac sodium (AlfaAesar®) at a dose of 10 mg/kg were used as comparison compounds. Statistical processing of experimental data was carried out using Student's confidence criteria. The effect was considered significant at $p < 0.05$ [29].

The studies are carried out in accordance with all applicable international, national and institutional guidelines for the care and use of animals.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

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