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Synthesis and analgesic activity evaluation of derivatives of 2-[(1,4-dioxo-1-amino-4-arylbutyl-2-en-2-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid

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Abstract

The synthesis of new derivatives of 2-[(1,4-dioxo-1-amino-4-arylbutyl-2-en-2-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid is described. Starting 2-{[5-aryl-2-oxofuran-3(2*H*)-ylidene]amino}thiophene-3-carboxylic acids were obtained by intramolecular cyclisation of substituted 4-aryl-4-oxo-2-thienylaminobut-2-enoic acids in acetic anhydride. New derivatives of 2-[(1,4-dioxo-1-amino-4-arylbutyl-2-en-2-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acids were obtained via decyclization reaction of 2-{[5-aryl-2-oxofuran-3(2*H*)-ylidene]amino}thiophene-3-carboxylic acids. The structure of the compounds obtained was confirmed by the ^{1}H and ^{13}C NMR spectroscopy, IR spectrometry and elemental analysis methods. Analgesic activity of new compounds has been studied by the “hot plate” method on outbred white mice of both sexes with intraperitoneal injection. It was found that derivatives of 2-[(1,4-dioxo-1-amino-4-arylbutyl-2-en-2-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid possess analgesic effect exceeding the effect of the comparison drug metamizole.

Keywords

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

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1. Introduction

The Gewald aminothiophene fragment is a promising pharmacophore group, since it was found in both natural and synthetic physiologically active compounds [1–6]. The synthesis of substituted Gewald aminothiophenes can be carried out using the Gewald reaction [7–9]. In turn, 3-imino(hydrazono)-3*H*-furan-2-ones have high reactivity, leading to the production of compounds of various structures [10–17]. Decyclization reactions of 3-imino-3H-furan-2-ones lead to the production of 2,4-dioxobutanoic acid derivatives, for which antiviral [18–22], analgesic [23], anti-inflammatory [24], antimicrobial [25] activity was determined.

It was previously shown that 3-imino(hydrazono)-3*H*-furan-2-ones can be decyclized under the action of aliphatic, aromatic, and heterocyclic amines to form amides of 4-aryl(tert-butyl)-4-oxo-2-amino(hydrazono)-2-eno acids [26, 27]. In this paper, synthesis and analgesic activity of new 2-[(1,4-dioxo-1-amino-4-arylbutyl-2-en-2-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid derivatives is discussed.

2. 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.

Starting substituted 4-aryl-4-oxo-2-thienylaminobut-2-enoic acids **1a,b** and substituted 3-thienylimino-3H-furan-2-ones **2a,b** were obtained according to the procedure described in [28–30]. All data correspond to the previously obtained ones.

2.1. General procedure for the synthesis of N-substituted amides of 4-aryl-4-oxo-2-[(3-thiophen-2-yl)amino]-but-2-enoic acids 3a–e

A mixture of 0.001 mol of compound **2a–e** and 0.001 mol of the corresponding amine in anhydrous toluene (20 mL) was stirred at 50 °C for 2 h. After cooling, the precipitate was filtered off and recrystallized.

2.2. Ethyl 2-((1-((4-methylpyrimidin-2-yl)amino)-1,4-dioxo-4-phenylbut-2-en-2-yl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3a)

Yield 0.36 g (74%), orange crystals, mp 172–173 °C (isopropanol). IR spectrum, *ν*, cm^{-1}: 1671 (CONH), 1738, (COOEt), 3186, 3351 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.31 t (3H, CH_3CH_2O, J_{HH} = 7.2 Hz), 1.76 m (4H, $2CH_2$), 2.40 s (3H, CH_3), 2.57 m (2H, CH_2), 2.80 m (2H, CH_2), 4.37 q (2H, CH_3CH_2O, J_{HH} = 7.1 Hz), 6.19 s (1H, C=CH), 6.83 m (2H, H_{arom}), 7.22 m (3H, H_{arom}), 7.45 m (2H, H_{arom}), 8.43 s (1H, NH), 10.21 s (1H, NH). Found, %: C 63.60; H 5.37; N 11.43; S 6.52. $C_{26}H_{26}N_4O_4S$. Calculated, %: C 63.66; H 5.34; N 11.42; S 6.54.

2.3. Ethyl 2-((1-((5-bromopyridin-2-yl)amino)-1,4-dioxo-4-phenylbut-2-en-2-yl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3b)

Yield 0.40 g (73%), orange crystals, mp 188–189 °C (isopropanol). IR spectrum, *ν*, cm^{-1}: 1667 (CONH), 1708, (COOEt), 3323, 3416 (NH). ^1H NMR spectrum ($CDCl_3$), δ, ppm: 1.40 t (3H, CH_3CH_2O, J_{HH} = 6.9 Hz), 1.76 m (4H, $2CH_2$), 2.58 m (2H, CH_2), 2.77 m (2H, CH_2), 4.36 q (2H, CH_3CH_2O, J_{HH} = 6.9 Hz), 6.17 s (1H, C=CH), 6.71 s (1H, NH), 7.27 m (3H, H_{arom}), 7.38 m (2H, H_{arom}), 7.83 m (1H, H_{arom}), 8.13 m (1H, H_{arom}), 8.37 m (1H, H_{arom}), 10.49 s (1H, NH). Found, %: C 56.37; H 4.33; N 7.56; S 5.74. $C_{26}H_{24}BrN_3O_4S$. Calculated, %: C 56.32; H 4.36; N 7.58; S 5.78.

2.4. Ethyl 2-((1,4-dioxo-4-phenyl-1-(thiazol-2-ylamino)but-2-en-2-yl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxylate (3c)

Yield 0.41 g (85%), yellow crystals, mp 200–201 °C (isopropanol). IR spectrum, *ν*, cm^{-1}: 1663 (CONH), 1718, (COOEt), 3234, 3439 (NH). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.38 t (3H, CH_3CH_2O, J_{HH} = 7.2 Hz), 1.74 m (4H, $2CH_2$), 2.63 m (2H, CH_2), 2.75 m (2H, CH_2), 4.35 q (2H, CH_3CH_2O, J_{HH} = J 7.2 Hz), 6.25 s (1H, C=CH), 7.38 m (5H, H_{arom}), 7.62 m (2H, H_{arom}), 8.12 s (1H, NH), 10.44 s (1H, NH). Found, %: C 59.83; H 4.85; N 8.72; S 13.36. $C_{24}H_{23}N_3O_4S_2$. Calculated, %: C 59.86; H 4.81; N 8.73; S 13.31.

2.5. 2-((1-((4-Bromophenyl)amino)-4-(4-methoxyphenyl)-1,4-dioxobut-2-en-2-yl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (3d)

Yield 0.47 g (84%), orange crystals, mp 193–195 °C (isopropanol). IR spectrum, *ν*, cm^{-1}: 1666, 1686 (CONH, $CONH_2$), 3294 (NH, NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.69 m (4H, CH_2), m 2.50 (2H, CH_2), 2.58 m (2H, CH_2), 3.84 s (3H, OCH_3), 6.37 s (1H, C=CH), 7.04 m (2H, H_{arom}), 7.47 m (2H, NH_2; 4H, H_{arom}), 8.02 m (2H, H_{arom}), 11.17 s (1H, NH), 12.67 s (1H, NH). Found, %: C 56.30, H 4.35, N 7.53, S 5.77. $C_{26}H_{24}BrN_3O_4S$. Calculated, %: C 56.32, H 4.36, N 7.58, S 5.78.

2.6. 2-((4-(4-methoxyphenyl)-1-morpholino-1,4-dioxobut-2-en-2-yl)amino)-4,5,6,7-tetrahydrobenzo[b]thiophene-3-carboxamide (3e)

Yield 0.41 g (87%), yellow crystals, mp 146–148 °C (isopropanol). IR spectrum, *ν*, cm^{-1}: 1658 (CON, $CONH_2$), 3169, 3344 (NH, NH_2). ^1H NMR spectrum (DMSO-d_6), δ, ppm: 1.73 m (4H, $2CH_2$), 2.62 m (4H, $2CH_2$), 3.48 m (8H, $4CH_2$), 3.83 s (3H, OCH_3), 6.14 s (1H, C=CH), 7.00 m (2H, H_{arom}), 7.40 br s (1H, NH_2), 7.49 br s (1H, NH_2), 7.97 m (2H, H_{arom}), 12.94 s (1H, NH). Found, %: C 61.35, H 5.82, N 8.96, S 6.80. $C_{24}H_{27}N_3O_5S$. Calculated, %: C 61.39, H 5.80, N 8.95, S 6.83.

Evaluation of analgesic activity was carried out in the Perm State National Research University, the Research Laboratory of Biologically Active Substances. Analgesic activity was determined on outbred white mice of both sexes weighing 18–22 g using the “hot plate” method [31]. 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 [32]. 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 seconds (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 s. 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 (ED_{50}) was used as a comparison compound.

Statistical processing of experimental data was carried out using Student's confidence criteria. The effect was

considered significant at $p<0.05$ [33]. The studies were carried out in accordance with all applicable international, national and institutional guidelines for the care and use of animals.

3. Results and discussion

Starting furanones **2a,b** were obtained by known literature method via intramolecular cyclization of 4-aryl-4-oxo-2-tienylaminobut-2-enoic acids **1a,b** in acetic anhydride. The reaction of 3-thienylimino-3*H*-furan-2-ones **2a,b** with alkyl-, aryl-, hetarylamines in inert aprotic solvent proceeded with the formation of *N*-substituted amides of but-2-enic acids **3a-e** (Scheme 1). As a result, it was found that the attack of the amino group was directed at the carbon atom of the lactone carbonyl moiety of compounds **2a,b** and led to the products of the furanone cycle decyclization. The ester and amide groups under the conditions of the reaction did not participate in interaction with amines, which does not contradict the literature data.

The mechanism of the decyclization reaction of 5-aryl-2,3-dihydro-2,3-furandiones under the action of nucleophilic reagents was published based on the detailed large-scale study of kinetic data [34–36] as well as quantum chemical calculations [37]. Assuming the similarity of these structures with the iminofuranones discussed in the current paper, we can assume the validity of this mechanism for the transformations 3-thienylimino-3*H*-furan-2-ones **2a,b** under the action of amines as nucleophiles (NuH) described here (Scheme 2).

If the solvent cannot be a donor or acceptor of an electron pair (aprotic nonpolar or weakly polar solvents), a non-catalytic reaction occurs. The use of a nonpolar solvent contributes to the displacement of the equilibrium from the transition state **TS1** to the intermediate **I** that leads to the limiting stage of the process with the formation of the transition state **TS2**.

Compounds **3a-e** are crystalline substances of orange or yellow color, obtained with yields up to 87%.

We have studied the ^{1}H NMR spectra of compounds **3a,b** in DMSO-d_6 and **3c-e** $CDCl_3$. It was established that compounds **3a-e** are characterized by a proton singlet of the NH group involved in a strong intramolecular hydrogen bond at 10.44–12.94 ppm, proton signals of the NHCO group at 6.71, 8.12–11.17 ppm and a proton singlet of the CH group at 6.14–6.37 ppm.

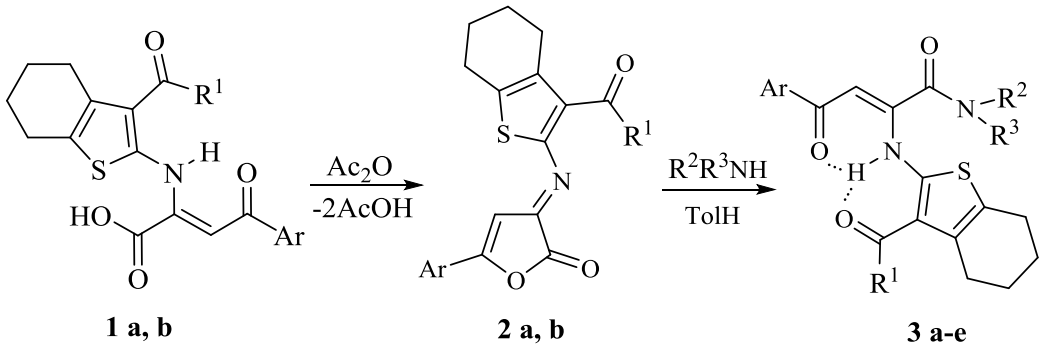
Some of the compounds obtained were examined for analgesic activity. It is shown in Table 1 that all the studied compounds have a pronounced analgesic effect, surpassing the effect of the comparison drug metamizole.

Table 1 Analgesic activity of amides **3a-c**

Compound	Dosage, mg/kg	The latent period of the defensive reflex (120 min), s
3a	50	21.20±1.24
3b	50	22.40±1.83
3c	50	21.00±1.46
Metamizole	93 (ED_{50})	16.60±1.00
Control	–	10.30±0.60

4. Conclusions

New derivatives of 2-[(1,4-dioxo-1-amino-4-arylbutyl-2-en-2-yl)amino]-4,5,6,7-tetrahydrobenzo[*b*]thiophene-3-carboxylic acid were obtained with 73-87% yields by the decyclization reaction of 2-{[5-aryl-2-oxofuran-3(2*H*)-ylidene]amino}thiophene-3-carboxylic acids under the action of aliphatic, aromatic and heterocyclic amines. It was found that the obtained compounds exhibited significant analgesic activity, reliably exceeding the effect of a referral drug.

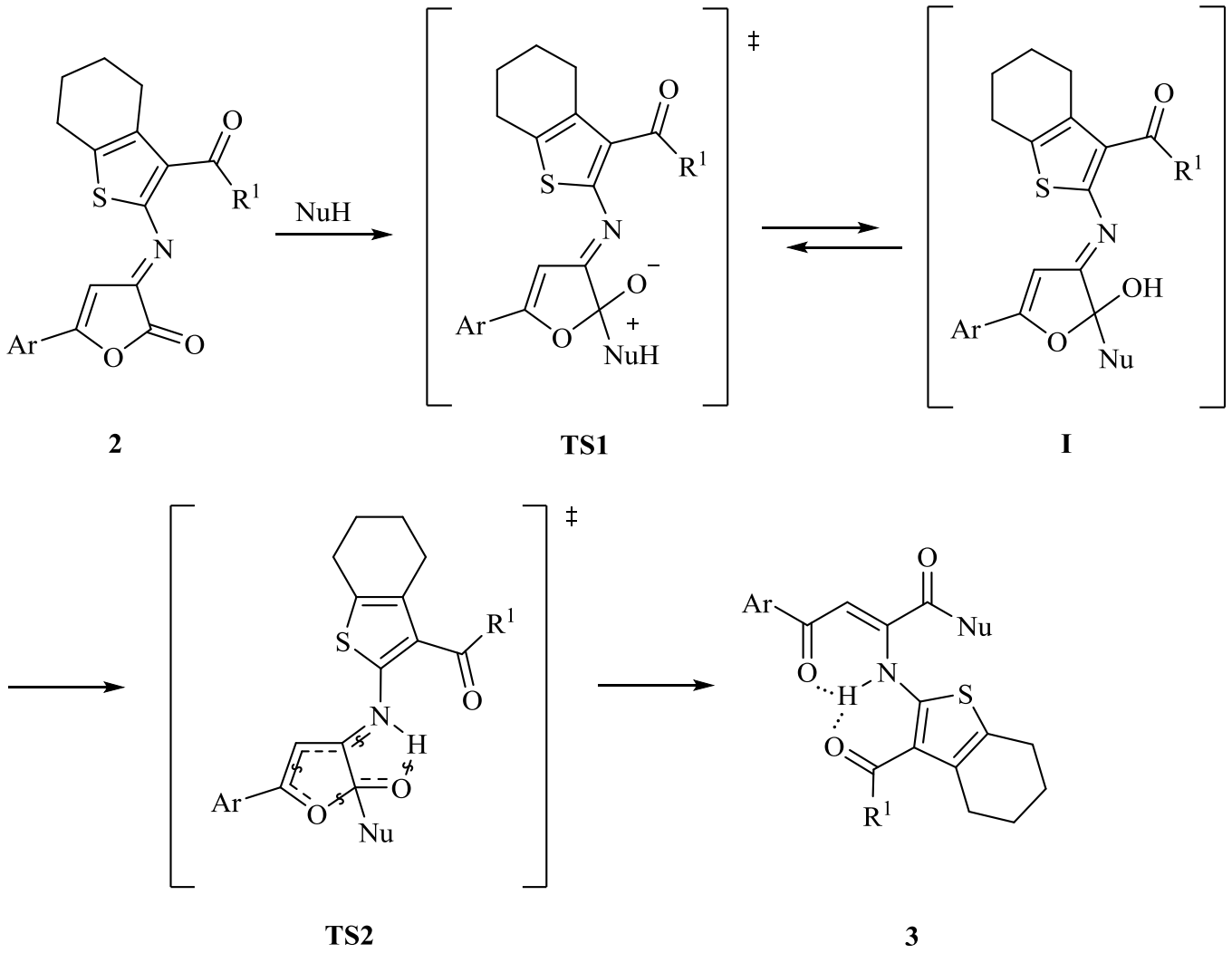


1 a, b **2 a, b** **3 a-e**

1, 2: R^1 = OEt, Ar= Ph (a), $R^1 = NH_2$, Ar= 4-$CH_3OC_6H_4$(b).

3: R^1 = OEt, Ar= Ph, R^2= H, R^3=4-methylpyrimidin-2-yl (a), 5-bromopyridin-2-yl (b), thiazol-2-yl (c); $R^1 = NH_2$, Ar= 4-$MeOC_6H_4$, R^2= H, R^3=4-BrC_6H_4 (d); $R^1 = NH_2$, Ar= 4-$MeOC_6H_4$, R^2+R^3= morpholine (e).

Scheme 1 The reaction of 3-thienylimino-3H-furan-2-ones 2a,b with alkyl-, aryl-, hetarylamines in inert aprotic solvent



Scheme 2 The transformations 3-thienylimino-3H-furan-2-ones 2**a,b** under the action of amines as nucleophiles (NuH)

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