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# Synthesis of New Derivatives of 4-(1,4-Benzodioxan-2-yl)thiophene

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**Abstract**—Ethyl 2-amino-4-(1,4-benzodioxan-2-yl)thiophene-3-carboxylate was synthesized by the Gewald reaction of 2-acetyl-1,4-benzodioxane with ethyl 2-cyanoacetate and sulfur in the presence of diethylamine. The product was used to synthesize a series of amido ester derivatives with various pharmacophoric fragments. The antihypoxic properties of the synthesized amido esters were investigated.

**Keywords:** 2-acetyl-1,4-benzodioxane, thiophene, ethyl 2-amino-4-(1,4-benzodioxan-2-yl)thiophene-3-carboxylate, amido ester, antihypoxic activity

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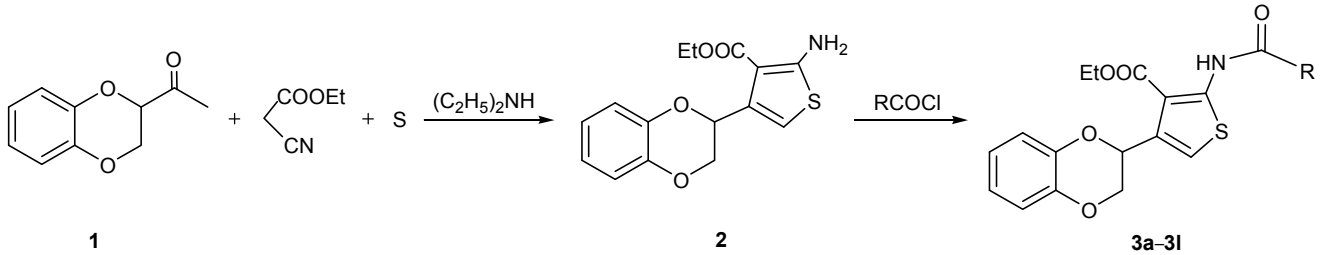
1,4-Benzodioxane derivatives containing a substituted thiophene ring are of interest as potential pharmacological active compounds, since they combine in their structure two pharmacophoric heterocycles present in the composition of a wide range of drugs [1–5]. Many of them exhibit antihypertensive, antibacterial, antiinflammatory, antihypoxic, sedative, analgesic, antitumor, fungicidal, and other activities.

The key compound in the presented syntheses is 2-acetyl-1,4-benzodioxane (**1**), which was prepared from 2-cyano-1,4-benzodioxane by the Grignard reaction in a yield of 47–50% [6]. Compound **1** was reacted with cyanoacetic ester and sulfur in the presence of diethylamine under the Gewald reaction conditions to obtain biheterecycle **2** comprising, along with the 1,4-benzodioxane core, a substituted thiophene ring.

The molecule of compound **2** contains two functional groups (amino and ethoxycarbonyl), which can be used for further transformations in the search for biologically active derivatives of thiophenodioxanes. In the present work we synthesized a series of biheterocyclic amides with a 3-ethoxycarbonyl substituent in the thiophene ring, as well as diverse pharmacophoric substituents on the nitrogen atom. Target compounds **3a–3l** were prepared by the condensation of thiophenodioxane **2** [ethyl 2-amino-4-(1,4-benzodioxan-2-yl)thiophene-3-catboxyli acid] with mono- and dichlorides of mono- and disubstituted benzoic acids, as well as acetic, phenylacetic, and phenoxyacetic acids in absolute dioxane in the presence of pyridine. The yields of amides were 64–71% (Scheme 1).

The purity and structure of all the synthesized compounds were confirmed by TLC and physicochemical methods. Thus, the IR spectra of compounds **3a–3l** display, along with the ester

**Scheme 1.**




**1** **2** **3a–3l**

R = $CH_3$ (**a**), $C_6H_5$ (**b**), 4-$BrC_6H_4$ (**c**), 4-$C_3H_7OC_6H_4$ (**d**), 4-*i*-$C_4H_9OC_6H_4$ (**e**), 3,4-$(CH_3O)_2C_6H_3$ (**f**), 4-$C_4H_9O$-3-$CH_3O$-$C_6H_3$ (**g**), $CH_2C_6H_5$ (**h**), $CH_2OC_6H_5$ (**i**), 4-$NO_2$-$C_6H_4$ (**k**), 3,5-$(NO_2)_2C_6H_3$ (**l**).

carbonyl absorption bands at 1730–1740 $cm^{-1}$, the absorption bands of the amido carbonyl group at 1640–1652 $cm^{-1}$. The $^1H$ NMR spectra of amides **3a–3l** contain a signal assignable to the amide NH proton (11.0–12.3 ppm).

The synthesized compounds were tested for antihypoxic activity under conditions of acute hypoxia by the procedure in [7]. All the test compounds at a dose of 50 mg/kg showed moderate antihypoxic activity, increasing the survival rate of animals under the conditions of oxygen deficiency in the inhaled air by 20–30% ($P < 0.001$). Compound **3g** containing the butoxy substituent in the aromatic ring showed the highest activity.

## EXPERIMENTAL

The IR spectra were measured on a Nicolet Avatar 330 FTIR spectrometer in mineral oil. The $^1H$ NMR spectra were obtained on a Varian Mercury-300 spectrometer (300 MHz) in DMSO-$d_6$, internal reference TMS. The melting points were measured on a Boëtius hot stage. The reaction progress and purity of the synthesized compounds were monitored by TLC on Silufol UV-254 plates (eluent benzene–acetone, 3 : 1; development in iodine vapor).

**2-Acetyl-1,4-benzodioxane (1)** was prepared as described in [6].

**Ethyl 2-amino-4-(1,4-benzodioxan-2-yl)thiophene-3-carboxylate (2).** Sulfur, 3.2 g (0.1 g-at) and 11.3 g (0.1 mol) of ethyl cyanoacetate was added to 17.8 g (0.1 mol) of 2-acetyl-1,4-benzodioxane (**1**). The mixture was heated with stirring to 50–53°C, and a solution of 5.7 g (0.08 mol) of diethylamine in 10 mL of ethanol was then added dropwise. The reaction mixture was stirred at this temperature until sulfur dissolved completely (about 30–40 min) and then poured into a beaker, cooled, and acidified with 10% HCl to pH 3–4. The crystals that formed were filtered off, dried, and recrystallized from ethanol. Yield 12.1 g (40%), mp 150–151°C, $R_f$ 0.37. IR spectrum, ν, $cm^{-1}$: 3318, 3107 ($NH_2$), 1732 (ester C=O), 1594 (arom). $^1H$ NMR spectrum, δ, ppm: 1.35 t (3H, $CH_3$, *J* 7.1 Hz), 3.74 d.d (1H, $OCH_2CH$, *J* 11.0, 7.7 Hz), 4.18–4.35 m (2H, $OCH_2CH_3$), 4.51 d.d (1H, $OCH_2CH$, *J* 11.0, 2.1 Hz), 5.44 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.23 d (1H, SCH, *J* 1.0 Hz), 6.74–6.89 m (4H, $C_6H_4$), 7.33 br.s (2H, $NH_2$). Found, %: C 59.34; H 5.07; N 4.79. $C_{15}H_{15}NO_4S$. Calculated, %: C 59.00; H 4.95; N 4.59.

***N*-Substituted amides 3a–3l** (*general procedure*). A solution of 0.005 mol of corresponding acid chloride, in 10 mL of absolute dioxane was added to a solution of 1.5 g (0.005 mol) of amine **2** and 0.4 g (0.005 mol) of pyridine in 50 mL of absolute dioxane. The reaction mixture was poured into 200 mL of cold water, the crystals that formed were filtered off, dried, and recrystallized from ethanol.

**Ethyl 2-acetamido-4-(1,4-benzodioxan-2-yl)thiophene-3-carboxylate (3a).** Yield 68%, mp 138–140° C, $R_f$ 0.64. IR spectrum, ν, $cm^{-1}$: 3331 (NH), 1732 (ester C=O), 1645 (amide C=O), 1590 (arom). $^1H$ NMR spectrum, δ, ppm: 1.41 t (3H, $CH_3$, *J* 7.1 Hz), 2.28 s (3H, $COCH_3$), 3.80 d.d (1H, $OCH_2CH$, *J* 11.1, 7.7 Hz), 4.30–4.47 m (2H, $OCH_2CH_3$), 4.52 d.d (1H, $OCH_2CH$, *J* 11.1, 2.2 Hz), 5.55 d.d.d (1H, OCH, *J* 7.7, 2.2, 1.0 Hz), 6.77–6.92 m (4H, $C_6H_4$), 6.93 br.s (1H, SCH), 11.11 s (1H, NH). Found, %: C 58.45; H 5.21; N 4.38. $C_{17}H_{17}NO_5S$. Calculated, %: C 58.78; H 4.93; N 4.03.

**Ethyl 2-benzamido-4-(1,4-benzodioxan-2-yl)thiophene-3-carboxylate (3b).** Yield 66%, mp 160–161°C, $R_f$ 0.52. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1648 (amide C=O), 1600 (arom). $^1H$ NMR spectrum, δ, ppm: 1.45 t (3H, $CH_3$, *J* 7.1 Hz), 3.85 d.d (1H, $OCH_2CH$, *J* 11.1, 7.7 Hz), 4.36–4.54 m (2H, $OCH_2CH_3$), 4.56 d.d (1H, $OCH_2CH$, *J* 11.1, 2.2 Hz), 5.60 d.d.d (1H, OCH, *J* 7.7, 2.2, 1.0 Hz), 6.80–6.93 m (4H, $C_6H_4$), 7.03 br.s (1H, SCH), 7.56–7.68 m (3H) and 7.96–8.00 m (2H, $C_6H_5$), 12.24 s (1H, NH). Found, %: C 64.83; H 4.97; N 3.70. $C_{22}H_{19}NO_5S$. Calculated, %: C 64.53; H 4.68; N 3.42.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(4-bromobenzamido)thiophene-3-carboxylate (3c).** Yield 69%, mp 182–183°C, $R_f$ 0.61. IR spectrum, ν, $cm^{-1}$: 3330 (NH), 1735 (ester C=O), 1646 (amide C=O), 1593 (arom). $^1H$ NMR spectrum, δ, ppm: 1.45 t (3H, $CH_3$, *J* 7.1 Hz), 3.84 d.d (1H, $OCH_2CH$, *J* 11.1, 7.7 Hz), 4.36–4.52 m (2H, $OCH_2CH_3$), 4.55 d.d (1H, $OCH_2CH$, *J* 11.1, 2.1 Hz), 5.59 d.d (1H, OCH, *J* 7.7, 2.1 Hz), 6.77–6.92 m (4H, $C_6H_4$), 7.03 s (1H, SCH ), 7.72–7.77 m (2H) and 7.86–7.91 m (2H, $C_6H_4Br$), 12.21 br.s (1H, NH). Found, %: C 54.42; H 3.98; N 3.02. $C_{22}H_{18}BrNO_5S$. Calculated, %: C 54.11; H 3.72; N 2.87.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(4-propoxybenzamido)thiophene-3-carboxylate (3d).** Yield 68%, mp 132–133°C, $R_f$ 0.56. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1640 (amide C=O), 1600 (arom). $^1H$ NMR spectrum, δ, ppm: 1.08 t (3H,

$CH_3$, Pr, *J* 7.4 Hz), 1.45 t (3H, $CH_3$, Et, *J* 7.1 Hz), 1.79–1.91 m (2H, $CH_2$, Pr), 3.83 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 4.03 t (2H, $OCH_2$, Pr, *J* 6.5 Hz), 4.36–4.52 m (2H, OC$\underline{H}_2CH_3$), 4.55 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.2 Hz), 5.59 d.d (1H, OCH, *J* 7.7, 2.2 Hz), 6.79–6.92 m (4H, $C_6H_4$), 6.98 br.s (1H, SCH), 7.02–7.07 m (2H) and 7.88–7.93 m (2H, $C_6H_4$OPr), 12.14 br.s (1H, NH). Found, %: C 64.52; H 5.71; N 3.37. $C_{25}H_{25}NO_6S$. Calculated, %: C 64.22; H 5.39; N 3.00.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(4-isobutoxybenzamido)thiophene-3-carboxylate (3e).** Yield 64%, mp 120–121°C, $R_f$ 0.48. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1648 (amide C=O), 1600 (arom). $^1$H NMR spectrum, δ, ppm: 1.06 d (6H, $CH_3$, *i*-Bu, *J* 6.7 Hz), 1.45 t (3H, $CH_3$, Et, *J* 7.1 Hz), 2.12 d (1H, CH, *i*-Bu, *J* 6.6 Hz), 3.83 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 3.83 d (2H, $CH_2$, *i*-Bu, *J* 6.6 Hz ), 4.35–4.53 m (2H, OC$\underline{H}_2CH_3$), 4.55 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 5.58 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.78–6.92 m (4H, $C_6H_4$), 6.97 br.s (1H, SCH), 7.01–7.06 m (2H) and 7.87–7.92 m (2H, $C_6H_4$OBu), 12.13 s (1H, NH). Found, %: C 65.11; H 5.89; N 3.28. $C_{26}H_{27}NO_6S$. Calculated, %: C 64.85; H 5.65; N 2.91.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(3,4-dimethoxy-benzamido)thiophene-3-carboxylate (3f).** Yield 71%, mp 158–160°C, $R_f$ 0.50. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1645 (amide C=O), 1600 (arom). $^1$H NMR spectrum, δ, ppm: 1.45 t (3H, $CH_3$, *J* 7.1 Hz), 3.83 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 3.91 s (3H, $OCH_3$), 3.92 s (3H, $OCH_3$), 4.36–4.52 m (2H, OC$\underline{H}_2CH_3$), 4.55 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 5.59 d.d (1H, OCH, *J* 7.7, 2.1 Hz), 6.79–6.92 m (4H, $C_6H_4$), 6.97 br.s (1H, SCH), 7.06 d (1H, $C_6H_3$, *J* 7.7 Hz ), 7.48–7.54 m (2H, $C_6H_3$), 12.14 s (1H, NH). Found, %: C 61.90; H 5.18; N 3.31. $C_{24}H_{23}NO_7S$. Calculated, %: C 61.40; H 4.94; N 2.98.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(4-butoxy-3-methoxybenzamido)thiophene-3-carboxylate (3g).** Yield 65%, mp 110–111°C, $R_f$ 0.54. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1649 (amide C=O), 1600 (arom). $^1$H NMR spectrum, δ, ppm: 1.02 t (3H, $CH_3$, Bu, *J* 7.4 Hz), 1.45 t (3H, $CH_3$, Et, *J* 7.1 Hz), 1.48–1.60 m (2H, $CH_2$, Bu),1.77–1.87 m (2H, $CH_2$, Bu), 3.84 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 3.92 s (3H, $OCH_3$), 4.06 t (2H, $OCH_2$, Bu, *J* 6.4 Hz), 4.36–4.53 m (2H, OC$\underline{H}_2CH_3$), 4.55 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 5.59 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.78–6.93 m (4H, $C_6H_4$), 6.98 br.s (1H, SCH), 7.03 d (1H, $C_6H_3$, *J* 8.9 Hz), 7.47–7.51 m (2H, $C_6H_3$), 12.12 br.s (1H, NH). Found, %: C 63.65; H 5.89; N 3.02. $C_{27}H_{29}NO_7S$. Calculated, %: C 63.39; H 5.71; N 2.74.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(2-phenylacetamido)thiophene-3-carboxylate (3h).** Yield 69%, mp 124–125°C, $R_f$ 0.37. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1650 (amide C=O), 1600 (arom). $^1$H NMR spectrum, δ, ppm: 1.34 t (3H, $CH_3$, *J* 7.1 Hz), 3.77 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 3.86 s (2H, $CH_2$Ph), 4.21–4.38 m (2H, OC$\underline{H}_2CH_3$), 4.49 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 5.53 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.76–6.90 m (4H, $C_6H_4$), 6.93 br.s (1H, SCH), 7.26–7.40 m (5H, $C_6H_5$), 11.03 br.s (1H, NH). Found, %: C 65.52; H 4.99; N 3.59. $C_{23}H_{21}NO_5S$. Calculated, %: C 65.23; H 5.00; N 3.31.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(2-phenoxyacetamido)thiophene-3-carboxylate (3i).** Yield 68%, mp 147–148°C, $R_f$ 0.49. IR spectrum, ν, $cm^{-1}$: 3334 (NH), 1732 (ester C=O), 1647 (amide C=O), 1600 (arom). $^1$H NMR spectrum, δ, ppm: 1.41 t (3H, $CH_3$, *J* 7.1 Hz), 3.82 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 4.33–4.51 m (2H, OC$\underline{H}_2CH_3$), 4.54 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 4.80 s (2H, $CH_2$OPh), 5.58 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.78–6.93 m (4H, $C_6H_4$), 6.98–7.10 m (3H, $C_6H_5$), 7.01 br.s (1H, SCH), 7.29–7.36 m (2H, $C_6H_5$), 12.00 s (1H, NH). Found, %: C 63.04; H 4.94; N 3.45. $C_{23}H_{21}NO_6S$. Calculated, %: C 62.86; H 4.82; N 3.19.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(4-nitrobenzamido)thiophene-3-carboxylate (3k).** Yield 63%, mp 201–202°C, $R_f$ 0.45. IR spectrum, ν, $cm^{-1}$: 3332 (NH), 1739 (ester C=O), 1652 (amide C=O), 1592 (arom). $^1$H NMR spectrum, δ, ppm: 1.45 t (3H, $CH_3$, *J* 7.1 Hz), 3.86 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 4.38–4.54 m (2H, OC$\underline{H}_2CH_3$), 4.56 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 5.61 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.79–6.93 m (4H, $C_6H_4$), 7.10 br.s (1H, SCH), 8.19–8.23 m (2H) and 8.42–8.46 m (2H, $C_6H_4NO_2$), 12.31 br.s (1H, NH). Found, %: C 58.38; H 4.11; N 6.41. $C_{22}H_{18}N_2O_7S$. Calculated, %: C 58.14; H 3.99; N 6.16.

**Ethyl 4-(1,4-benzodioxan-2-yl)-2-(3,5-dinitrobenzamido)thiophene-3-carboxylate (3l).** Yield 65%, mp 219–220°C, $R_f$ 0.38. IR spectrum, ν, $cm^{-1}$: 3331 (NH), 1735 (ester C=O), 1649 (amide C=O), 1590 (arom). $^1$H NMR spectrum, δ, ppm: 1.47 t (3H, $CH_3$, *J* 7.1 Hz), 3.87 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 7.7 Hz), 4.43–4.57 m (2H, OC$\underline{H}_2CH_3$), 4.58 d.d (1H, OC$\underline{H}_2$CH, *J* 11.1, 2.1 Hz), 5.62 d.d.d (1H, OCH, *J* 7.7, 2.1, 1.0 Hz), 6.79–6.93 m (4H, $C_6H_4$), 7.14 br.s (1H, SCH), 9.07–9.12 m (3H, $C_6H_3$), 12.26 br.s (1H, NH). Found, %: C

52.67; H 3.58; N 8.77. $C_{22}H_{17}N_3O_7S$. Calculated, %: C 52.91; H 3.43; N 8.41.

## CONFLICT OF INTEREST

The authors declare no conflict of interest.

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