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Synthesis, recyclization under the action of methanol and analgetic activity of N'-(5-aryl-2-oxofuran-3(2*H*)-ylidene)furan-2-carbohydrazides

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Abstract

New methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates were obtained via decyclization reaction of N'-(5-aryl-2-oxofuran-3(2*H*)-ylidene)furan-2-carbohydrazides under the action of methanol. Starting N'-(5-aryl-2-oxofuran-3(2*H*)-ylidene)furan-2-carbohydrazides were obtained by intramolecular cyclization of substituted 4-aryl-2-[2-(furan-2-ylcarbonyl)hydrazinylidene]-4-oxobutanoic acids in propionic anhydride. The structure of the compounds obtained was confirmed by the ^{1}H NMR spectroscopy, IR spectrometry and elemental analysis methods. Analgesic activity of some obtained compounds was studied by the “hot plate” method on outbred white mice of both sexes with intraperitoneal injection.

Keywords

2,4-dioxobutanoic acid
2-hydrazono-4-oxobutanoic acids
3-hydrazonofuran-2(3*H*)-one
analgesic activity
drugs

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Key findings

- The synthesis method for obtaining methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates developed.
- Five new compounds not previously described in the literature were obtained.
- Some of the compounds obtained have been found to have significant analgetic effects.

1. Introduction

The development and creation of new drug forms with lower toxicity is one of the most important tasks of modern pharmaceutical and medicinal chemistry [1–7], since modern medicine is always in need of new drugs. It is necessary to create a universal basic structure that will allow obtaining a wide diversity of different structures possessing biological activity. Such a universal structural fragment can be found among the 3-imino-(hydrazinylidene)-furan-2(3*H*)-one derivatives, which results from their chemical availability due to the scalability of the synthetic methods [8] and the reactivity [9–15]. For example, the reactions of 3-imino-(hydrazinylidene)-furan-2(3*H*)-ones derivatives with various nucleophilic reagents lead to the attack on the carbonyl group of the lactone fragment and to the formation of acyclic or heterocyclic structures [16–21] that retain the pharmacophore fragment of 2,4-dioxobutanoic acid [22–32]. This fragment was found in the structure of various biologically active and natural compounds [33, 34], which indicates that this idea is worth developing. Previously, we proposed a simple method for the preparation of 3-hydrazinylidenefuran-2(3*H*)-one derivatives by intramolecular cyclization of substituted 2-[2-(4-R-benzoyl)hydrazinylidene]-4-oxobutanoic acids in the presence of acetic or propionic anhydride [35, 36]. Furthermore, this method was applied to 3-imino(thiophen-2-yl)furan-2(3*H*)-ones derivatives, which include the pharmacophore fragment, Gewald aminothiophene [37–41]. Compounds that contain this pharmacophore fragment exhibit analgesic [42–44], anti-inflammatory [45, 46], antimicrobial [47–49] and photoluminescent properties [50, 51] and other biological activities [52–54]. Also,

we showed that N′-[5-aryl-2-oxofuran-3(2*H*)-ylidene]furan-2-carbohydrazides and its precursor 4-aryl-2-[2-(furan-2-ylcarbonyl)hydrazinylidene]-4-oxobutanoic acids have analgesic activity in the previous studies [55]. The interaction of 3-hydrazinylidenefuran-2(3*H*)-one with alcohols in the presence of triethylamine, which leading to the formation of a mixture of alkyl 2-hydrazinylidene-4-oxobutanoates and alkyl 5-hydroxy-4,5-dihydro-1*H*-pyrazole-3-carboxylates, was described earlier [56] (Scheme 1). In the this study, the research into the reactivity of 3-hydrazinylidenefuran-2(3H)-one towards alcohols was continued. Namely, we considered the interaction of N′-[5-aryl-2-oxofuran-3(2*H*)-ylidene]furan-2-carbohydrazides with methanol in the presence of *p*-toluenesulfonic acid, which leads to the formation of methyl 1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates as sole products (Scheme 1). In addition, the analgesic activity of the original N′-[5-aryl-2-oxofuran-3(2*H*)-ylidene]furan-2-carbohydrazides and the resulting methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates was studied.

2. Experimental

IR spectra were recorded on an FSM-1202 instrument in vaseline oil. The ^{1}H NMR spectra were recorded at 400 MHz at the temperature of 313 K; the chemical shifts (δ) were measured in ppm with respect to the solvent ([D_6] DMSO, ^{1}H: δ= 2.50 ppm). The coupling constants (J_{HH}) are given in Hertz. The splitting patterns of apparent multiplets associated with an averaged coupling constants were designated as *s* (singlet), *d* (doublet), *t* (triplet), *q* (quartet), *m* (multiplet), *dd* (doublet of doublets) and *br* (broadened). Elemental analysis was performed on a LECO CHNS-932 instrument. The chemical purity of the compounds and the reactions progress were monitored by TLC on Sorbfil plates in the diethyl ether–benzene–acetone (10:9:1) system, detection in UV light and iodine vapor. Melting points were determined on an SMP40 apparatus.

Furan-2-carbohydrazide **1** [57] and 4-aryl-2,4-dioxobutanoic acids **2a–e** [58, 59] were prepared according to the literature methods.

2.1. General procedure for the synthesis of 4-aryl-2-[2-(furan-2-carbonyl)hydrazinylidene]-4-oxobutanoic acids 3a–e

To a solution of 0.01 mol of furan-2-carboxylic acid hydrazide (**1**) in 30 mL of acetonitrile was added 0.01 mol of 4-aryl-2,4-dioxobutanoic acid **2a–e**. The resulting mixture was heated to 50 °C and kept for 5 min at this temperature. The solution was cooled to 0 °C; the formed precipitate was filtered off and recrystallized from dioxane.

2.1.1. 2-[2-(Furan-2-carbonyl)hydrazinylidene]-4-oxo-4-phenylbutanoic acid (3a)

Yield 2.52 g (84%), yellow crystals, mp 165–166 °C (dioxane). IR spectrum, ν, cm^{-1}: 3379, 3299, 3137, 1735, 1645, 1600. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (14%): 4.53 *s* (2H, CH_2), 6.71 *dd* (1H, H_{arom}, J_{HH} 3.5, 1.6 Hz), 7.24–8.01 *m* (7H, H_{arom}), 11.32 *br. s* (1H, NH); form **B** (79%): 3.21 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 3.33 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 6.68 *dd* (1H, J_{HH} 3.5, 1.8 Hz), 7.24–8.01 *m* (7H, H_{arom} and OH); form **C** (7%): 4.27 c (2H, CH_2), 6.71 dd (1H, H_{arom}, J_{HH} 3.5, 1.6 Hz), 7.24–8.01 *m* (7H, H_{arom}) 13.72 *br. s* (1H, NH). Found, %: C 60.02; H 4.01; N 9.36. $C_{15}H_{12}N_2O_5$. Calculated, %: C 60.00; H 4.03; N 9.33.

2.1.2. 2-[2-(Furan-2-carbonyl)hydrazinylidene]-4-(4-methylphenyl)-4-oxobutanoic acid (3b)

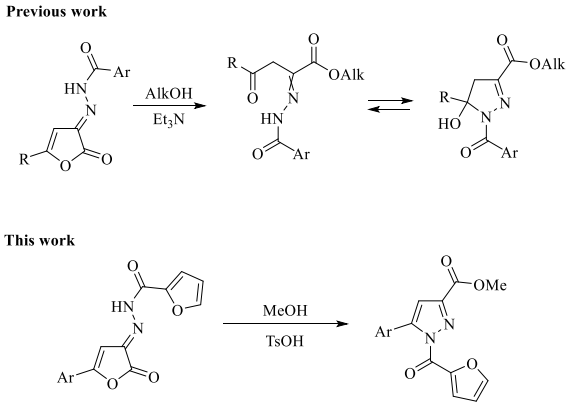
Yield 2.29 g (73%), yellow crystals, mp 179–180 °C (dioxane). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (30%): 2.41 *s* (3H, CH_3), 4.52 *s* (2H, CH_2), 6.73 *dd* (1H, H_{arom}, J_{HH} 3.4, 1.7 Hz), 7.14–7.99 *m* (6H, H_{arom}), 11.38 *br. s* (1H, NH); form **B** (58%): 2.30 *c* (3H, CH_3), 3.22 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 3.32 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 6.70 *dd* (1H, J_{HH} 3.5, 1.7 Hz), 7.14–7.98 *m* (6H, H_{arom} and OH); form **C** (12%): 2.40 *s* (3H, CH_3), 4.29 *s* (2H, CH_2), 6.73 *dd* (1H, H_{arom}, J_{HH} 3.4, 1.7 Hz), 7.14–7.99 *m* (6H, H_{arom}) 13.47 *br. s* (1H, NH). Found, %: C 61.12; H 4.47; N 8.94. $C_{16}H_{14}N_2O_5$. Calculated, %: C 61.14; H 4.49; N 8.91.

2.1.3. 2-[2-(Furan-2-carbonyl)hydrazinylidene]-4-(4-methoxyphenyl)-4-oxobutanoic acid (3c)

Yield 2.81 g (85%), yellow crystals, mp 159–160 °C (dioxane). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (43%): 3.86 *s* (3H, CH_3O), 4.48 *s* (2H, CH_2), 6.71 *dd* (1H, H_{arom}, J_{HH} 3.2, 1.7 Hz), 6.87–8.00 *m* (6H, H_{arom}), 11.29 *br. s* (1H, NH); form **B** (37%): 3.21 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 3.31 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 6.68 *dd* (1H, J_{HH} 3.4, 1.6 Hz), 6.87–8.00 *m* (6H, H_{arom} and OH); form **C** (20%): 3.81 *s* (3H, CH_3O), 4.24 *s* (2H, CH_2), 6.71 *dd* (1H, H_{arom}, J_{HH} 3.2, 1.7 Hz), 6.87–8.00 *m* (6H, H_{arom}), 13.40 br. *s* (1H, NH). Found, %: C 58.16; H 4.31; N 8.46. $C_{16}H_{14}N_2O_6$. Calculated, %: C 58.18; H 4.27; N 8.48.

2.1.4. 4-(4-Chlorophenyl)-2-[2-(furan-2-carbonyl)hydrazinylidene]-4-oxobutanoic acid (3d)

Yield 2.58 g (77%), yellow crystals, mp 182–183 °C (dioxane). IR spectrum, ν, cm^{-1}: 3237, 3131, 1741, 1683, 1617, 1585. ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (9%), 4.49 *s* (2H, CH_2), 6.71 *m* (1H, H_{arom}), 7.22–7.96 *m* (6H, H_{arom}),



Scheme 1 Reaction of 3-hydrazinylidenefuran-2(3*H*)-one with alcohols in basic and acidic conditions.

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11.43 *br. s* (1H, NH); form **B** (86%), 3.21 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 3.30 *d* (1H, C_4H_2, J_{HH} 20.0 Hz), 6.69 *m* (1H, H_{arom}), 7.22–7.96 *m* (7H, $6H_{arom}$ and OH); form **C** (5%), 4.31 *s* (2H, CH_2), 6.84 *m* (1H, H_{arom}), 7.22–7.96 *m* (6H, H_{arom}), 13.50 *br. s* (1H, NH). Found, %: C 53.85; H 3.29; N 8.39. $C_{15}H_{11}ClN_2O_5$. Calculated, %: C 53.83; H 3.31; N 8.37.

2.1.5. (4-Bromophenyl)-2-[2-(furan-2-ylcarbonyl)hydrazinylidene]-4-oxobutanoic acid (3e)

Yield 2.99 g (79%), yellow crystals, mp 179–180 °C (dioxane). IR spectrum, ν, cm^{-1}: 3242, 3148, 1734, 1666, 1614, 1583. ^1H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (8%), 4.51 *s* (2H, CH_2), 6.66 *dd* (1H, H_{arom}, J_{HH} 3.5, 1.6 Hz), 7.37–7.94 *m* (6H, H_{arom}), 11.29 *br. s* (1H, NH); form **B** (87%), 3.25 *d* (1H, C^4H_2, J_{HH} 20.0 Hz), 3.32 *d* (1H, C^4H_2, J_{HH} 20.0 Hz), 6.68 *dd* (1H_{Ar}, J_{HH} 3.6, 1.7 Hz), 7.37–7.94 *m* (7H, $6H_{arom}$ and OH); form **C** (5%), 4.25 *s* (2H, CH_2), 6.71 *dd* (1H, H_{arom}, J_{HH} 3.5, 1.8 Hz), 7.37–7.94 *m* (6H, H_{arom}), 13.06 br. *s* (1H, NH). Found, %: C 47.55; H 2.88; N 7.41. $C_{15}H_{11}BrN_2O_5$. Calculated, %: C 47.52; H 2.92; N 7.39.

2.2. General method of synthesis of N'-(5-aryl-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazides 4a–e

Propionic anhydride (8 mL) was added to 0.01 mol of acid **3a–e**. The resulting mixture was slowly heated with stirring to 150 °C and kept for 5 min. The precipitate formed after cooling was filtered off, washed with anhydrous diethyl ether, and recrystallized from anhydrous toluene or dioxane.

2.2.1. N'-(2-Oxo-5-phenylfuran-3(2H)-ylidene)furan-2-carbohydrazide (4a)

Yield 2.20 g (78%), yellow crystals, mp 246–248 °C (dioxane). IR spectrum, ν, cm^{-1}: 3188, 1801, 1698, 1667, 1617. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): form **A** (69%): 6.78 *dd* (1H, H_{arom}, J_{HH} 3.5, 1.8 Hz), 7.52 *m* (5H, H_{arom}, 2H, 2CH), 8.04 *d* (1H, J_{HH} 1.0 Hz), 11.90 *br. s* (1H, NH); form **B** (31%): 6.80 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.7 Hz), 7.25 *s* (1H, CH), 7.65 *m* (5H, H_{arom}, 1H, CH) 8.07 *d* (1H, H_{arom}, J_{HH} 1.0 Hz), 12.55 *s* (1H, NH). Found, %: C 63.80; 3.55; N 9.91. $C_{15}H_{10}N_2O_4$. Calculated, %: C 63.83; H 3.57; N 9.93.

2.2.2. N'-[5-(4-Methylphenyl)-2-oxofuran-3(2H)-ylidene]furan-2-carbohydrazide (4b)

Yield 1.57 g (53%), yellow crystals, mp 258–259 °C (dioxane). IR spectrum, ν, cm^{-1}: 3125, 1799, 1693, 1672, 1622. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.41 *s* (3H, Me), 6.72 *dd* (1H, H_{arom}, J_{HH} 3.5, 1.8 Hz), 7.51 *m* (5H, H_{arom}, 1H, CH), 7.98 *d* (1H, J_{HH} 1.0 Hz), 11.89 *br. s* (1H, NH). Found, %: C 64.84; 4.11; N 9.48. $C_{16}H_{12}N_2O_4$. Calculated, %: C 64.86; H 4.08; N 9.46.

2.2.3. N'-[5-(4-Methoxyphenyl)-2-oxofuran-3(2H)-ylidene]furan-2-carbohydrazide (4c)

Yield 1.75 g, (56%), yellow crystals, mp 265–266 °C (dioxane). IR spectrum, ν, cm^{-1}: 3137, 1801, 1666, 1622, 1592. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): form **A** (76%): 3.86 *s* (3H, MeO), 6.74 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.7 Hz), 7.14 *d* (2H, H_{arom}, J_{HH} 8.0 Hz), 7.38 *s* (1H, CH), 7.56 *dd* (1H, H_{arom}, J_{HH} 3.6, 0.8 Hz), 7.72 *d* (2H, H_{arom}, J_{HH} 8.0 Hz), 7.99 *dd* (1H, J_{HH} 1.6, 0.8 Hz), 11.66 *br. s* (1H, NH); form **B** (24%): 3.85 *s* (3H, MeO), 6.76 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.7 Hz), 7.03 s (1H, CH), 7.11 *d* (2H, H_{arom}, J_{HH} 9.0 Hz) , 7.40 *d* (1H, H_{arom}, J_{HH} 1.0 Hz), 7.80 *d* (2H, H_{arom}, J_{HH} 9.0 Hz), 8.02 *d* (1H, H_{arom}, J_{HH} 1.0 Hz), 12.44 *s* (1H, NH). Found, %: C 61.53; 3.85; N 8.99. $C_{16}H_{12}N_2O_5$. Calculated, %: C 61.54; H 3.87; N 8.97.

2.2.4. N′-[5-(4-Chlorophenyl)-2-oxofuran-3(2H)-ylidene]furan-2-carbohydrazide (4d)

Yield 2.35 g, (74%), yellow crystals, mp 268–269 °C (dioxane). IR spectrum, ν, cm^{-1}: 3137, 1776, 1694, 1619. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): form **A** (16%), 6.78 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.7 Hz), 7.50 *s* (1H, CH), 7.59 *m* (1H, H_{arom}), 7.63 *m* (2H, H_{arom}), 7.88 *m* (2H, H_{arom}), 8.04 *m* (1H, H_{arom}), 11.75 *br. s* (1H, NH); form **B** (84%), 6.80 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.7 Hz), 7.17 *s* (1H, CH), 7.38 *m* (2H, H_{arom}), 7.43 *dd* (1H, H_{arom}, J_{HH} 3.5, 0.6 Hz), 7.76 *m* (2H, H_{arom}), 8.07 *dd* (1H, H_{arom}, J_{HH} 1.6, 0.6 Hz), 12.54 *s* (1H, NH). Found, %: C 56.87; H 2.88; N 8.87. $C_{15}H_9ClN_2O_4$. Calculated, %: C 56.89; H 2.86; N 8.85.

2.2.5. N′-[5-(4-Bromophenyl)-2-oxofuran-3(2H)-ylidene]-furan-2-carbohydrazide (4e)

Yield 2.35 g, (65%), yellow crystals, mp 267–268 °C (dioxane). IR spectrum, ν, cm^{-1}: 3181, 1803, 1683, 1614. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 6.78 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.7 Hz), 7.27 *s* (1H, CH), 7.42 *dd* (1H, H_{arom}, J_{HH} 3.6, 0.6 Hz), 7.74 *m* (4H, H_{arom}), 8.04 *m* (1H, H_{arom}), 12.37 *br. s* (1H, NH). Found, %: C 49.87; H 2.53; N 7.73. $C_{15}H_9BrN_2O_4$. Calculated, %: C 49.89; H 2.51; N 7.76

2.3. General method of synthesis of methyl 5-aryl-1-(furan-2-carbonyl)-1H-pyrazole-3-carboxylates 5a–e.

To a suspension of 0.0025 mol N'-[5-aryl-2-oxofuran-3(2*H*)-ylidene]furan-2-carbohydrazide **4a–e** in 20 ml of methanol was added 1.16 mmol (0.2 g) of *p*-toluenesulfonic acid, stirred at 64 °C for 20–60 min and cooled to 0 °C. The formed precipitate was filtered off, washed with cold methanol and recrystallized from propan-2-ol.

2.3.1. Methyl 1-(furan-2-ylcarbonyl)-5-phenyl-1H-pyrazole-3-carboxylate (5a)

Yield 0.43 g, (58%), colorless crystals, mp 122–123 °C (propan-2-ol). IR spectrum, ν, cm^{-1}: 1746, 1706, 1557. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 3.94 *s* (3H, MeO), 6.92 *dd* (1H, H_{arom}, J_{HH} 3.7, 1.7 Hz), 7.18 *s* (1H, CH), 7.87 *m* (7H, H_{arom}). Found, %: s, 64.88; H 4.06; H 9.44; $C_{16}H_{12}N_2O_4$. Calculated, %: C, 64.86; H, 4.08; N, 9.46.

2.3.2. Methyl 1-(furan-2-ylcarbonyl)-5-(4-methylphenyl)-1H-pyrazole-3-carboxylate (5b)

Yield (0.53 g, 68%), colorless crystals, mp 223–224 °C (propan-2-ol). IR spectrum, ν, cm^{-1}: 1730, 1618, 1587. ^1H

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NMR (DMSO-d_6, 400 MHz) δ (ppm): 2.34 *s* (3H, Me), 3.89 *s* (3H, MeO), 6.82 *dd* (1H, H_{arom}, J_{HH} 3.7, 1.7 Hz), 7.02 *s* (1H, CH), 7.23 *d* (2H, H_{arom}, J_{HH} 7.9 Hz), 7.35 *d* (2H, H_{arom}, J_{HH} 7.9 Hz), 7.74 *dd* (1H, H_{arom}, J_{HH} 3.7, 0.7 Hz), 8.14 *dd* (1H, H_{arom}, J_{HH} 1.6, 0.6 Hz). Found, %: C, 65.83; H, 4.48; N, 9.05; $C_{17}H_{14}N_2O_4$. Calculated, %: C, 65.80; H, 4.55; N, 9.03.

2.3.3. Methyl 1-(furan-2-ylcarbonyl)-5-(4-methoxyphenyl)-1H-pyrazole-3-carboxylate (5c)

Yield 0.56 g (69%), colorless crystals, mp 155–156 °C (propan-2-ol). IR spectrum, ν, cm^{-1}: 1730, 1714, 1616, 1560. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 3.80 *s* (3H, MeO), 3.89 *s* (3H, MeO), 6.87 *dd* (1H, H_{arom}, J_{HH} 3.6, 1.8 Hz), 6.99 *d* (2H, H_{arom}, J_{HH} 8.0 Hz) 7.07 *s* (1H, CH), 7.43 *d* (2H, H_{arom}, J_{HH} 8.0 Hz), 7.77 *dd* (1H, H_{arom}, J_{HH} 3.7, 0.6 Hz), 8.21 *m* (1H, H_{arom}). Found, %: C, 62.54; H, 4.34; N, 8.62. $C_{17}H_{14}N_2O_5$. Calculated, %: C, 62.57; H, 4.32; N, 8.59.

2.3.4. Methyl 5-(4-chlorophenyl)-1-(furan-2-ylcarbonyl)-1H-pyrazole-3-carboxylate (5d)

Yield 0.54 g (65%), colorless crystals, mp 85–86 °C (propan-2-ol). IR spectrum, ν, cm^{-1}: 1751, 1724, 1600. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 3.91 *s* (3H, MeO), 6.89 *dd* (1H, H_{arom}, J_{HH} 3.7, 1.7 Hz), 7.17 *s* (1H, CH), 7.77 *m* (6H, H_{arom}). Found, %: C, 58.09; H, 3.37; N, 8.51. $C_{16}H_{11}ClN_2O_4$. Calculated, %: C, 58.11; H, 3.35; N, 8.47.

2.3.5. Methyl 5-(4-bromophenyl)-1-(furan-2-ylcarbonyl)-1H-pyrazole-3-carboxylate (5e)

Yield 0.58 g (62%), colorless crystals mp 183–184 °C (propan-2-ol). IR spectrum, ν, cm^{-1}: 1743, 1685, 1616, 1584. ^1H NMR (DMSO-d_6, 400 MHz) δ (ppm): 3.91 *s* (3H, MeO), 6.89 *dd* (1H, H_{arom}, J_{HH} 3.7, 1.7 Hz), 7.15 *s* (1H, CH), 7.48 *d* (2H, H_{arom}, J_{HH} 8.0 Hz) 7.65 *d* (2H, H_{arom}, J_{HH} 8.0 Hz), 7.83 *dd* (1H, H_{arom}, J_{HH} 3.7, 0.7 Hz), 8.23 *dd* (1H, H_{arom}, J_{HH} 3.7, 0.7 Hz, J_{HH} 1.7, 0.8 Hz). Found, %: C, 51.24; H, 2.93; N, 7.50. $C_{16}H_{11}BrN_2O_4$. Calculated, %: C, 51.22; H, 2.96; N, 7.47.

2.4. Evaluation of biological activity of target compounds

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 [60]. 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 [61]. 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 adefensive 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.

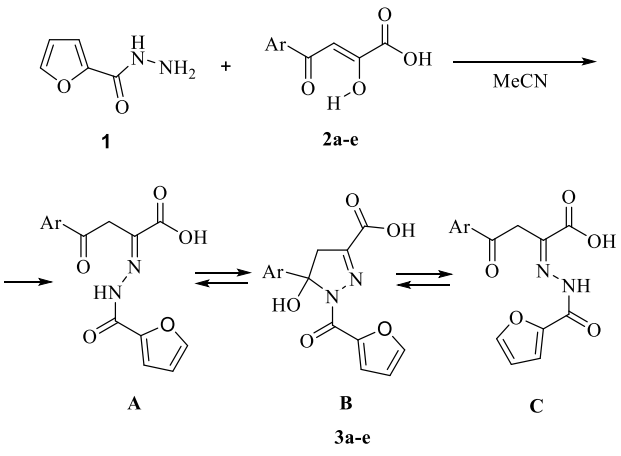
Statistical processing of experimental data was carried out using Student's confidence criteria. The effect was considered significant at $p<0.05$ [62]. The studies were carried out in accordance with all applicable international, national and institutional guidelines for the care and use of animals.

3. Results and Discussion

Substituted 2-[2-(furan-2-ylcarbonyl)hydrazinilydene]-4-oxobutanoic acids **3a–e** were obtained in 73–85% yields by reaction of furan-2-carbohydrazide **1** with corresponding 2,4-dioxobutanoic acids **2a–e** in acetonitrile at 50 °C (Scheme 2).

Compounds **3a–e** are crystalline yellow substances, readily soluble in chloroform, DMSO, and, when heated, in toluene, dioxane, and ethanol, and insoluble in water and alkanes. The IR spectra of compounds **3a–e** contains an absorption band at 1734–1741 cm^{-1}, which is characteristic of the stretching vibrations of the carbonyl amide group, and absorption bands at 3131–3148 and 3237–3299 cm^{-1}, which are characteristic of the stretching vibrations of the NH group.

The ^1H NMR spectra (DMSO-d_6) of compounds **3a–e** in the tautomeric form **A** are characterized by singlet signals of the NH protons (11.29–11.43 ppm) and CH_2 (4.48–4.53 ppm) groups. Form **B** is characterized by the presence in the spectrum of a doublet of protons of the CH_2 group at 3.21–3.25 and 3.30–3.33 ppm, and for form **C**, singlets of the NH protons (13.06–13.72 ppm) and CH_2 (4.24–4.31 ppm).



Ar= Ph (**a**), 4-MeC_6H_4(**b**), 4-$MeOC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**).

Scheme 2 Synthesis of 2-[2-(furan-2-ylcarbonyl)hydrazynilidene]-4-oxobutanoic acids **3a–e**.

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Intramolecular cyclization of acids **3a–e** occurs upon slow heating to 150 °C in propionic anhydride and leads to the formation of substituted N'-(2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazides **4a–e** (Scheme 3).

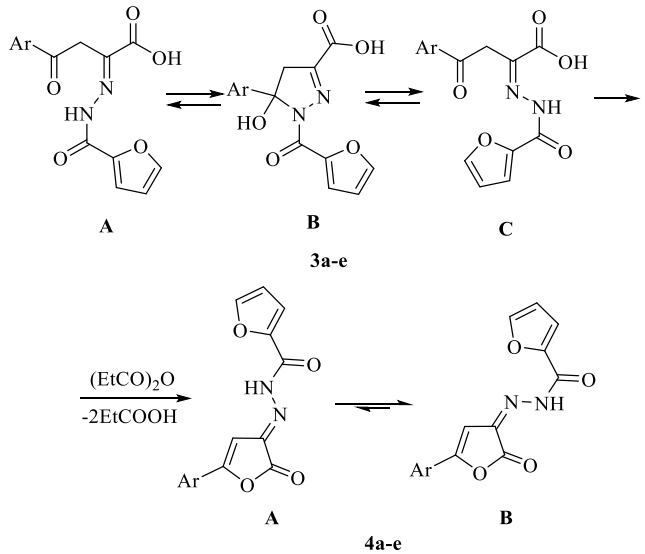
Compounds **4a–e**, obtained in 53–78% yields, are yellow crystalline substances, readily soluble in DMSO, when heated – in toluene and ethanol, and insoluble in water and alkanes. The IR spectra of compounds **4a–e** contain an absorption band in the region 1776–1803 cm^{-1}, which is characteristic of the stretching vibrations of the lactone carbonyl of the furan ring, and an absorption band in the region 3125–3188 cm^{-1}, which is characteristic of the stretching vibrations of the NH group.

According to ^1H NMR data in DMSO-d_6, compounds **4a**, **4c, 4d** are present as two geometric isomers **A** and **B**. The spectra of the isomers are characterized by the presence of signals of the NH groups [11.66–11.90 (*E*-**A**) and 12.44–12.55 ppm (*Z*-**B**)]. Compound **4b** exists only as the *E*-isomer [δ(NH) 11.89 ppm], but compound **4e** exists only as the *Z*-isomer [δ(NH) 12.37 ppm].

It was found that the reaction of N'-(2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazides **4a–e** with methanol in present of *p*-toluenesulfonic acid led to the formation of methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates **5a–e** (Scheme 3).

Compounds **5a–e** are apparently formed due to the addition of methanol to the lactone carbonyl group of furanones **4a–e**, opening of the furanone ring at the O1–C2 bond, and subsequent closing of the pyrazole ring due to the addition NH group to carbonyl group of aroyl fragment followed by dehydration (Scheme 4).

Compounds **5a–e**, obtained in 58–69% yields, are colorless crystalline substances. The IR spectra of compounds **5a–e** are characterized by the absence of NH group signal, in contrast to the spectra of compounds **4a–e**, and the presence of the absorption band of two carbonyl groups in region 1685–1751 cm^{-1}.



Ar = Ph (**a**), 4-MeC_6H_4(**b**), 4-$MeOC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**).

Scheme 3 Synthesis of N'-(2-oxofuran-3(2*H*)-ylidene)furan-2-carbohydrazides **4a–e.**

In ^1H NMR spectra, in addition to the signals of the protons of arylic and heterocyclic fragments, there are singlet signals of the methoxycarbonyl groups in the region 3.89–3.94 ppm.

Some of the compounds obtained were examined for analgesic activity.

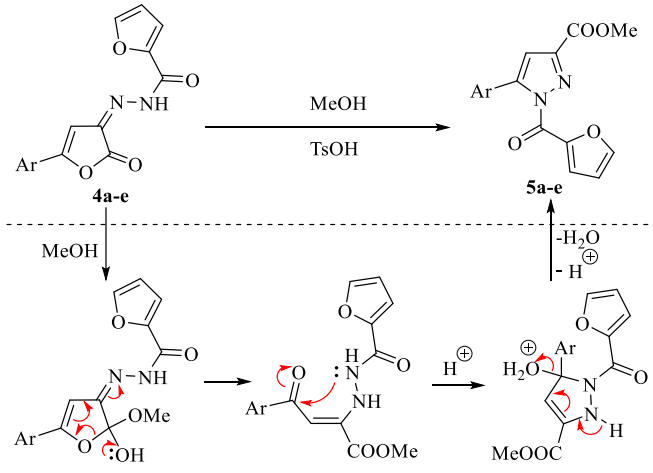
It is shown in Table 1 that all the studied compounds have a pronounced analgesic effect, surpassing the effect of the comparison drug metamizole.

4. Limitations

We have obtained new methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates with 58-69% yields, yields are significantly declining after recrystallisation of obtained compounds. Therefore, we are going to improve a method of purification for achievement higher product yields in our further studies.

5. Conclusions

New methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates were obtained with 58-69% yields by the recyclization of N'-(5-aryl-2-oxofuran-3(2*H*)-ylidene)furan-2-carbohydrazides under the action methanol in the presence of *p*-toluenesulfonic acid. It was found that N'-(5-aryl-2-oxofuran-3(2*H*)-ylidene)furan-2-carbohydrazides and methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates exhibit significant analgesic activity, reliably exceeding the effect of a reference drug. Further study of biological activity of the compounds obtained is planned.



Ar = Ph (**a**), 4-MeC_6H_4(**b**), 4-$MeOC_6H_4$ (**c**), 4-ClC_6H_4 (**d**), 4-BrC_6H_4 (**e**).

Scheme 4 Synthesis and proposed pathway of formation of methyl 5-aryl-1-(furan-2-carbonyl)-1*H*-pyrazole-3-carboxylates **5a–e.**

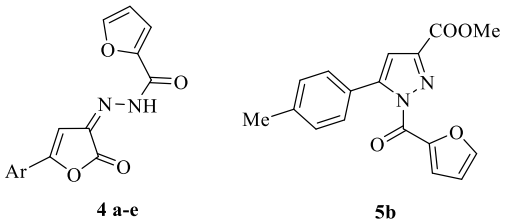


Figure 1 The structure of the **4a–e** and **5b** compounds.

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Table 1 Analgetic activity of substances **4a–e** and **5b.**

Compound	Dosage, mg/kg	The latent period of the defensive reflex (120 min), s
4a	50	24.80±0.97
4b	50	26.60±1.36
4c	50	19.48±0.82
4d	50	21.66±0.46
4e	50	24.64±1.38
5b	50	22.18±0.34
Metamizole sodium	93 (ED_{50})	16.60±1.00
Control	–	10.30±0.60

• Supplementary materials

No supplementary materials are available.

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• Conflict of interest

The authors declare no conflict of interest.

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