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Synthesis, intramolecular cyclization and anti-inflammatory activity of substituted 2-(2-(Furan-2-carbonyl)hydrazono)-4-oxobutanoic acids

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Abstract

A method was proposed for the synthesis of substituted 2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acids by the reaction of substituted 2,4-dioxobut-2-enoic acids with furan-2-carbohydrazide. It was found that substituted 2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acids undergo intramolecular cyclization in the presence of propionic anhydride to form the corresponding N'-(2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazides. The anti-inflammatory activity of the obtained compounds was studied. It was found that the obtained compounds have pronounced anti-inflammatory activity.

Keywords

dioxobutanoic acids
2-hydrazono-4-oxobutanoic acids
3-hydrazonofuran-2(3*H*)-ones
anti-inflammatory activity
drugs

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Key findings

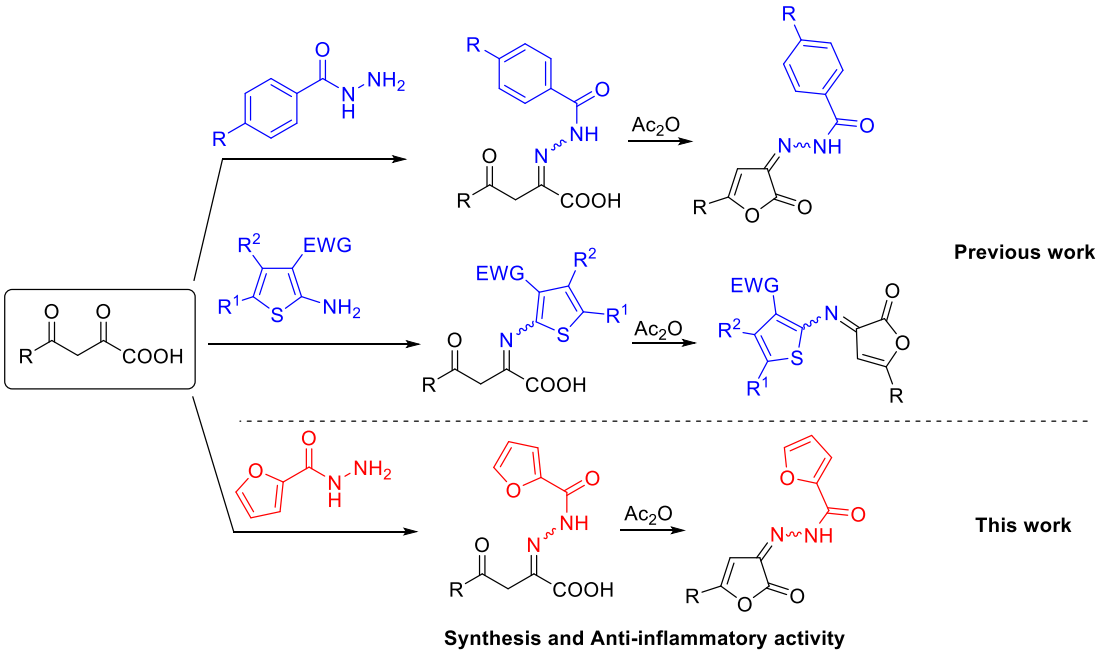
- A synthesis method for obtained to produce methyl-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acids and N'-(2-oxofuran-3(2H)-ylidene]furan-2-carbohydrazides.
- Sixteen new biologically active compounds have been obtained and described.
- It was found that some of the compounds obtained have a significant anti-inflammatory effect.

1. Introduction

The priority direction in pharmaceuticals and medical chemistry is the development and creation of new dosage forms with low toxicity [1–7]. The main cause is the chaotic usage of medicines, which leads to a loss of their efficiency. The main problem of drug development now is the choice of suitable frameworks that would make it possible to transform compounds at various stages of synthesis.

Derivatives of 3-imino- and 3-hydrazonofuran-2(3H)-one are excellent for this role because of their chemical availability, scalability of synthetic methods [8–12] and high reactivity [13–17]. Derivatives of 3-imino- and 3-hydrazonofuran-2(3H)-ones are capable of interacting with various nucleophilic reagents to form acyclic structures preserving the pharmacophore fragment of 2,4-dioxobutanoic acid [18–27].

Previously, we proposed a simple method for the preparation of 3-hydrazinylidenefuran-2(3H)-one derivatives by intramolecular cyclization of substituted 2-(2-(4-R-benzoyl)hydrazono)-4-oxobutanoic acids in the presence of acetic or propionic anhydride [28, 29]. Furthermore, this method was applied to the synthesis of 3-(imino(thien-2-yl))furan-2(3H)-ones derivatives, which include the pharmacophore fragment, Gewald aminothiophene [30] (Scheme 1). It was found that 2-(2-(4-R-benzoyl)hydrazono)-4-oxobutanoic and 2-(thiophen-2-ylamino)-4-oxobut-2-enoic acids and their derivativities exhibit analgesic [31, 32], anti-inflammatory [16] antimicrobial activity [24] and photoluminescent properties [33, 34].
We continue to search for new biologically active compounds with low toxicity [35] and expand the methods for the synthesis of 2,4-dioxobutanoic acid and 3-hydrazonofuran-2(3H)-one derivatives.



Scheme 1 Synthesis of 3-hydrazono- and 3-(imino(thien-2-yl))furan-2(3H)-ones.

In this paper, synthesis and anti-inflammatory activity of new 2,4-dioxobutanoic acids derivatives are discussed.

2. Experimental

IR spectra were recorded on an FSM-1202 instrument in vaseline oil. ^{1}H NMR spectra were obtained on a Bruker Avance III spectrometer (operating frequency of 400 MHz) in DMSO-d$_6$, the internal standard was the residual signal of the deuterium solvent.

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.

2.1. General procedure for the synthesis of substituted 2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acids (3a–h)

To a solution of 0.01 mol of furan-2-carboxylic acid hydrazide **2** in 30 mL of acetonitrile was added 0.01 mol of 2,4-dioxobutanoic acid **1a–h**. 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 acetonitrile or 1,4-dioxane.

2.1.1. 5,5-Dimethyl-4-oxo-2-(2-(furan-2-carbonyl)hydrazono)hexanoic acid (3a)

Yield 1.96 g (70%), pale yellow crystals, m.p. 144–145 °C (MeCN). IR spectrum, ν, cm^{-1}: 3324, 3204 br., 3119, 1717, 1676, 1595. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (24%): 1.16 *s* (3H, *t*-Bu), 4.04 *s* (2H, CH$_2$), 6.62 *dd* (1H, H$_{arom}$, J_{HH} 3.5, 1.8 Hz), 7.02–7.95 *m* (2H, H$_{arom}$), 11.09 *br. s* (1H, NH); form **B** (61%): 1.12 *d* (3H, *t*-Bu), 3.21 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.35 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz) , 6.56 *dd* (1H, J_{HH} 3.5, 1.8 Hz), 7.03–7.95 *m* (2H, H$_{arom}$, 1H, OH); form **C** (15%): 1.14 *s* (3H, *t*-Bu), 3.80 *s* (2H, CH$_2$), 6.70 *dt* (1H, H$_{arom}$, J_{HH} 1.7, 0.8 Hz), 7.03–7.95 *m* (2H, H$_{arom}$), 13.48 *br. s* (1H, NH). Found, %: C 55.74; H 5.73; N 10.03. C$_{13}$H$_{16}$N$_2$O$_5$. Calculated, %: C 55.71; H 5.75; N 10.00.

2.1.2. 4-Methylphenyl-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acid (3b)

Yield 2.29 g (73%), yellow crystals, m.p. 179–180 °C (1,4-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$_4$H$_2$, J_{HH} 20.0 Hz), 3.32 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 6.70 *dd* (1H, J_{HH} 3.5, 1.7 Hz), 7.14–7.98 *m* (6H, H$_{arom}$; 1H, 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$_2$O$_5$. Calculated, %: C 61.14; H 4.49; N 8.91.

2.1.3. (4-Ethylphenyl)-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acid (3c)

Yield 2.10 g (64%), yellow crystals, m.p. 143–144 °C (MeCN). IR spectrum, ν, cm^{-1}: 3245, 3126, 1736, 1684, 1641, 1612. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (12%), 1.20 *m* (3H, Me), 2.65 *m* (2H, CH$_2$), 4.51 *s* (2H, CH$_2$), 6.68 *dd* (1H, H$_{arom}$, J_{HH} 3.6, 1.8 Hz), 7.15–7.94 *m* (6H, H$_{arom}$), 11.30 *br. s* (1H, NH); form **B** (81%), 1.20 *m* (3H, Me), 3.20 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.33 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 2.65 *m* (2H, CH$_2$), 6.66 *dd* (1H, H$_{arom}$, J_{HH} 3.5, 1.6 Hz), 7.15–7.94 *m* (7H, 6H$_{arom}$ and OH); form **C** (7%), 1.20 *m* (3H, Me), 2.64 *m* (2H, CH$_2$), 4.23 *s* (2H, CH$_2$), 6.71 *dd* (1H, H$_{arom}$, J_{HH} 3.6, 1.7 Hz), 7.15–7.94 *m* (6H, H$_{arom}$), 13.83 *br. s* (1H, NH). Found, %: C 62.21; H 4.89; N 8.56. C$_{17}$H$_{16}$N$_2$O$_5$. Calculated, %: C 62.19; H 4.91; N 8.53. M 328.32.

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2.1.4. (4-Ethoxyphenyl)-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acid (3d)

Yield 2.89 g (84%), yellow crystals, m.p. 134–135 °C (MeCN). IR spectrum, ν, cm^{-1}: 3232, 3121, 1744, 1652, 1641, 1607. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (47%), 1.33 *m* (3H, Me), 4.13 *m* (2H, CH$_2$), 4.48 *s* (2H, CH$_2$), 6.68 *dd* (1H, H$_{arom}$, J_{HH} 3.5, 1.8 Hz), 6.85–7.98 *m* (6H, H$_{arom}$), 11.29 *s* (1H, NH); form **B** (32%), 1.33 *m* (3H, Me), 3.21 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.30 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 4.13 *m* (2H, CH$_2$), 6.66 *dd* (1H, H$_{arom}$, J_{HH} 3.5, 1.8 Hz), 6.85–7.98 *m* (7H, 6H$_{arom}$ and OH); form **C** (21%), 1.33 *m* (3H, Me),4.13 *m* (2H, CH$_2$), 4.24 *s* (2H, CH$_2$), 6.71 *m* (1H, H$_{arom}$, J_{HH} 3.5, 1.8 Hz), 6.85–7.98 *m* (6H, H$_{arom}$), 13.35 *br. s* (1H, NH). Found, %: C 59.32; H 4.69; N 8.17. $C_{17}H_{16}N_2O_6$. Calculated, %: C 59.30; H 4.68; N 8.14. M 344.32.

2.1.5. (4-Fluorophenyl)-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acid (3e)

Yield 2.32 g (73%), yellow crystals, m.p. 132–133 °C (MeCN). IR spectrum, ν, cm^{-1}: 3237, 3131, 1741, 1683, 1617, 1585. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (6%), 4.51 *s* (2H, CH$_2$), 6.71 *m* (1H, H$_{arom}$), 7.28–7.92 *m* (6H, H$_{arom}$), 11.30 *br. s* (1H, NH); form **B** (90%), 3.24 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.30 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 6.68 *m* (1H, H$_{arom}$), 7.28–7.92 *m* (7H, 6H$_{arom}$ and OH); form **C** (4%), 4.13 *s* (2H, CH$_2$), 6.85 *m* (1H, H$_{arom}$), 7.28–7.92 *m* (6H, H$_{arom}$), 13.04 *br. s* (1H, NH). Found, %: C 56.63; H 3.46; N 8.82. $C_{15}H_{11}FN_2O_5$. Calculated, %: C 56.61; H 3.48; N 8.80. M 318.26.

2.1.6. 4-(4-Chlorophenyl)-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acid (3f)

Yield 2.58 g (77%), m.p. 182–183 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3237, 3131, 1741, 1683, 1617, 1585. 1H NMR spectrum (DMSO-d6), δ, ppm: form **A** (9%), 4.49 *s* (2H, CH$_2$), 6.71 *m* (1H, H$_{arom}$), 7.22–7.96 *m* (6H, H$_{arom}$), 11.43 *br. s* (1H, NH); form **B** (86%), 3.21 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.30 *d* (1H, C$_4$H$_2$, 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.

2.1.7. 2-(2-(Furan-2-carbonyl)hydrazono)-4-(naphthalen-1-yl)-4-oxobutanoic acid (3g)

Yield 2.38 g (68%), yellow crystals, m.p. 199–200 °C (MeCN). IR spectrum, ν, cm^{-1}: 3247, 3124, 1703, 1675, 1654, 1581. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (23%), 4.63 *s* (2H, CH$_2$), 6.71 *m* (1H, H$_{arom}$), 7.33–8.57 *m* (9H, H$_{arom}$), 11.44 *br. s* (1H, NH); form **B** (66%), 3.39 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.44 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 6.71 *m* (1H, H$_{arom}$), 7.33–8.57 *m* (10H, 9H$_{arom}$ and OH); form **C** (11%), 4.38 *s* (2H, CH$_2$), 6.71 m (1H, H$_{arom}$), 7.33–8.57 m (9H, H$_{arom}$), 13.52 br. s (1H, NH). Found, %: C 65.17; H 4.01; N 8.03. $C_{19}H_{14}N_2O_5$. Calculated, %: C 65.14; H 4.03; N 8.00.

2.1.8. 2-(2-(Furan-2-carbonyl)hydrazono)-4-(naphthalen-2-yl)-4-oxobutanoic acid (3h)

Yield 2.49 g (71%), m.p. 198–199 °C (MeCN). IR spectrum, ν, cm^{-1}: 3251, 3118, 1705, 1681, 1649, 1583. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (13%), 4.69 *s* (2H, CH$_2$), 6.70 *m* (1H, H$_{arom}$), 7.47–8.73 *m* (9H, H$_{arom}$), 11.33 *br. s* (1H, NH); form **B** (81%), 3.34 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 3.40 *d* (1H, C$_4$H$_2$, J_{HH} 20.0 Hz), 6.70 *m* (1H, H$_{arom}$), 7.47–8.73 *m* (10H, 9H$_{arom}$ and OH); form **C** (6%), 4.42 *s* (2H, CH$_2$), 6.71 *m* (1H, H$_{arom}$), 7.33–8.57 *m* (9H, H$_{arom}$) 13.77 *br. s* (1H, NH). Found, %: C 65.13; H 4.05; N 8.02. $C_{19}H_{14}N_2O_5$. Calculated, %: C 65.14; H 4.03; N 8.00.

2.2. General procedure for the synthesis of N′-(2-oxofuran-3(2H)-ylidene]furan-2-carbohydrazides 4a–h

Propionic anhydride (8 mL) was added to 0.01 mol of acid **3a–h**. The resulting mixture was slowly heated with stirring to 150 °C and kept for 5 min at this temperature. The precipitate formed after cooling was filtered off, washed with anhydrous diethyl ether, and recrystallized from anhydrous toluene or 1,4-dioxane.

2.2.1. N'-(5-(t-Butyl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4a)

Yield 1.36 g (52%), light yellow crystals, m.p. 215–216 °C (1,4-dioxane). IR spectrum, ν, cм$^{-1}$: 3186, 1793, 1699, 1663, 1622, 1592. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (88%): 1.22 *s* (9H, t-Bu), 6.73 *dd* (1H, J_{HH} 3.6, 1.8 Hz), 6.83 *s* (1H, CH), 7.52 *dd* (1H, J_{HH} 3.6, 0.7 Hz), 7.98 *dd* (1H, J_{HH} 1.8, 0.8 Hz), 11.63 *br. s* (1H, NH): form **B** (12 %): 1.23 *s* (9H, t-Bu), 6.28 *s* (1H, CH), 6.76 *dd* (1H, H$_{arom}$, J_{HH} 3.6, 1.8 Hz), 7.39 *d* (1H, J_{HH} 3.6, 0.7 Hz), 8.02 *dd* (1H, J_{HH} 1.8, 0.8 Hz), 12.36 *br. s* (1H, NH). Found, %: C 59.57; 5.35; N 10.66. $C_{13}H_{14}N_2O_4$. Calculated, %: C 59.54; H 5.38; N 10.68.

2.2.2. N'-(2-Oxo-5-(p-tolyl)furan-3(2H)-ylidene)furan-2-carbohydrazide (4b)

Yield 1.57 g (53%), yellow crystals, m.p. 258–259 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3125, 1799, 1693, 1672, 1622. ^{1}H NMR spectrum (DMSO-d$_6$), δ, ppm: form **A** (100%): 2.41 *s* (3H, CH$_3$), 6.72 *dd* (1H, HAr, J_{HH} 3.5, 1.8 Hz), 7.36–7.67 *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; H 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-Ethylphenyl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4c)

Yield 1.89 g (61%), yellow crystals, m.p. 189–190 °C (toluene). IR spectrum, ν, cm^{-1}: 3132, 1806, 1697, 1666, 1616. ^{1}H NMR spectrum (DMSO-d6), δ, ppm: form **A** (25%), 1.22 *m* (3H, CH$_3$), 2.70 *m* (2H, CH$_2$), 6.78 *dd* (1H, H$_{arom}$, J_{HH} 3.6, 1.8 Hz), 7.44 *m* (2H, H$_{arom}$), 7.45 *s* (1H, CH), 7.59 *d* (1H, H$_{arom}$, J_{HH} 3.4 Hz), 7.70 *m* (2H, H$_{arom}$), 8.04 *d* (1H, H$_{arom}$, J_{HH} 1.5 Hz), 11.83 *br. s* (1H, NH); form **B** (75%), 1.22 *m* (3H, CH$_3$), 2.70 *m* (2H, CH$_2$), 6.80 *dd* (1H, H$_{arom}$, J_{HH} 3.6, 1.8 Hz), 7.17 *s* (1H, CH), 7.40 *m* (2H, H$_{arom}$), 7.70 *d* (1H, H$_{arom}$, J_{HH}

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8.3 Hz), 7.78 *d* (2H, Harom, J_{HH} 8.3 Hz), 8.07 *d* (1H, Harom, J_{HH} 1.5 Hz), 12.53 *br. s* (1H, NH). Found, %: C 49.87; H 2.53; N 7.73. $C_{17}H_{14}N_2O_4$. Calculated, %: C 65.80; H 4.55; N 9.03.

2.2.4. N'-(5-(4-Ethoxyphenyl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4d)

Yield 1.89 g (58%), yellow crystals, mp. 259–260 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3123, 3118, 1811, 1694, 1662, 1615. ^1H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (47%): 1.37 *t* (3H, CH_3 , J_{HH} 7.0 Hz), 4.15 *m* (2H, CH_2), 6.77 *dd* (1H, Harom, J_{HH} 3.5, 1.8 Hz), 7.40 *s* (1H, CH), 7.58 *d* (1H, Harom, J_{HH} 3.5 Hz), 7.72 *m* (2H, Harom), 7.80 *m* (2H, Harom), 8.03 *d* (1H, Harom, J_{HH} 1.5 Hz), 11.75 *br. s* (1H, NH): form **B** (75%): 1.37 *t* (3H, CH_3, J_{HH} 7.0 Hz), 4.15 *m* (2H, CH_2), 6.79 *dd* (1H, Harom, J_{HH} 3.5, 1.8 Hz), 7.06 *s* (1H, CH), 7.09 *m* (2H, Harom), 7.14 *m* (2H, Harom), 7.42 *d* (1H, Harom, J_{HH} 3.5 Hz), 8.06 *m* (1H, Harom), 12.50 *br. s* (1H, NH). Found, %: C 62.55; 4.35; N 8.61. $C_{17}H_{14}N_2O_5$. Calculated, %: C 62.57; H 4.32; N 8.59.

2.2.5. N'-(5-(4-Fluorophenyl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4e)

Yield 1.89 g (63%), yellow crystals, mp. 287–288 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3116, 1808, 1662, 1615. ^1H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (16%), 6.75 *dd* (1H, Harom, J_{HH} 3.6, 1.7 Hz), 7.42 *m* (2H, Harom), 7.49 *s* (1H, CH), 7.56 *m* (1H, Harom), 7.82 *m* (2H, Harom), 8.00 *m* (1H, Harom), 11.77 *br. s* (1H, NH); form **B** (84%): 6.80 *dd* (1H, Harom, J_{HH} 3.6, 1.7 Hz), 7.17 *s* (1H, CH), 7.38 *m* (2H, Harom), 7.43 *dd* (1H, Harom, J_{HH} 3.5, 0.6 Hz) , 7.76 *m* (2H, Harom), 8.07 *dd* (1H, Harom, J_{HH} 1.6, 0.6 Hz), 12.54 *s* (1H, NH). Found, %: C 60.04; H3.00; N 9.35. $C_{15}H_9N_2O_4$. Calculated, %: C 60.01; H 3.02; N 9.33.

2.2.6. N'-(5-(4-Chlorophenyl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4f)

Yield 2.34 g (74%), yellow crystals, mp. 268–269 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 1619, 1694, 1776, 3137. ^1H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (16%): 6.78 *dd* (1H, Harom, J_{HH} 3.6, 1.7 Hz), 7.50 *s* (1H, CH), 7.59 *m* (1H, Harom), 7.63 *m* (2H, Harom), 7.88 *m* (2H, Harom), 8.04 *m* (1H, Harom), 11.75 *br. s* (1H, NH). form **B** (84%): 6.80 *dd* (1H, Harom, J_{HH} 3.6, 1.7 Hz), 7.17 *s* (1H, CH), 7.38 *m* (2H, Harom), 7.43 *dd* (1H, Harom, J_{HH} 3.5, 0.6 Hz), 7.76 *m* (2H, Harom), 8.07 *dd* (1H, Harom, J_{HH} 1.6, 0.6 Hz), 12.54 *s* (1H, NH). Found, %: C 56.87; H 2.88; N 8.87. $C_{15}H_9N_2O_4$. Calculated, %: C 56.89; H 2.86; N 8.85.

2.2.7. N'-(5-(Naphthalene-1-yl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4g)

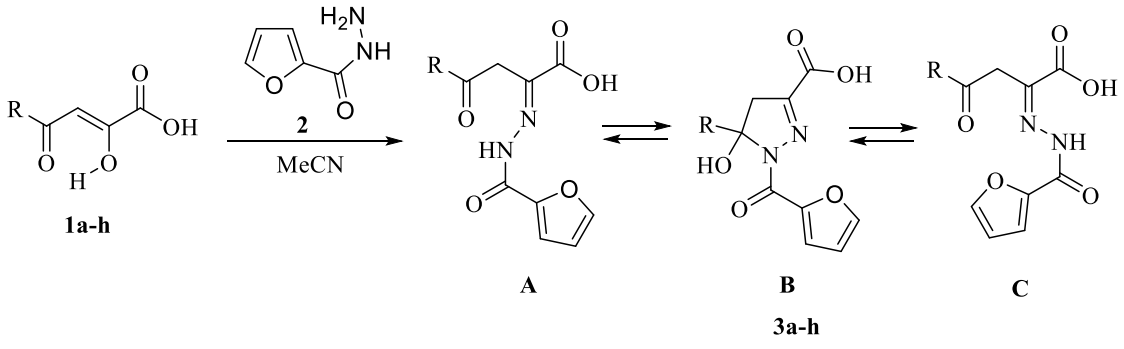
Yield 2.59 g (78%), yellow crystals, mp. 236–237 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3163, 1808, 1660, 1612. ^1H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (100%): 6.77 *dd* (1H, Harom, J_{HH} 3.6, 1.8 Hz), 7.60 *s* (1H, CH), 7.68 *m* (3H, Harom), 7.97 *dd* (1H, Harom, J_{HH} 7.3, 1.2 Hz), 8.02 *dd* (1H, Harom, J_{HH} 1.7, 0.8 Hz), 8.08 *dd* (1H, Harom, J_{HH} 3.4 , 1.1 Hz), 8.16 *m* (1H, Harom), 8.42 *m* (1H, Harom), 11.96 *br. s* (1H, NH). Found, %: C 68.65; H 3.66; N 8.44. $C_{19}H_{12}N_2O_4$. Calculated, %: C 68.67; H 3.64; N 8.43.

2.2.8. N'-(5-(Naphthalene-2-yl)-2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazide (4h)

Yield 2.79 g (84%), yellow crystals, mp. 264–265 °C (1,4-dioxane). IR spectrum, ν, cm^{-1}: 3137, 1805, 1662, 1617. ^1H NMR spectrum (DMSO-d_6), δ, ppm: form **A** (100%): 6.79 *dd* (1H, Harom, J_{HH} 3.6, 1.8 Hz), 7.64 *m* (3H, Harom), 7.68 *s* (1H, CH), 7.79 *dd* (1H, Harom, J_{HH} 3.7, 1.7 Hz), 8.01 *m* (1H, Harom), 8.05 *m* (1H, Harom, J_{HH} 1.7, 0.8 Hz), 8.12 *m* (2H, Harom), 8.39 *d* (1H, Harom, J_{HH} 0.9 Hz), 11.91 *br. s* (1H, NH). Found, %: C 68.69; H 3.67; N 8.42. $C_{19}H_{12}N_2O_4$. Calculated, %: C 68.67; H 3.64; N 8.43.

2.3. Anti-inflammatory activity

Anti-inflammatory activity tests were carried out at the Perm State Pharmaceutical Academy. The study was performed on rats of both sexes (the group included 6 animals) weighing 210–240 g on a model of acute inflammatory edema caused by subplantar injection of 0.1 ml of 1% aqueous solution of carrageenan into the hind paw of a rat. An increase in the volume of the foot, indicating the development of edema, was assessed oncometrically [36] before and 3 hours after the administration of carrageenan. The test substances were administered orally at a dose of 50 mg/kg 1 hour before the administration of the phlogogenic agent. Animals that did not receive the drug served as controls. Statistical processing was carried out according to the Student's method. The effect of inhibition of inflammation was determined as a percentage of the control level. The presence of anti-inflammatory action was judged by the severity of inhibition of the inflammatory response.



1,3,4: R= t-Bu (**a**), 4-MeC_6H_4(**b**), 4-EtC_6H_4 (**c**), 4-$EtOC_6H_4$ (**d**), 4-FC_6H_4 (**e**), 4-ClC_6H_4 (**f**), naphthalen-1-yl (**g**), naphthalen-2-yl (**h**).

Scheme 2 Synthesis of 4-R-2-(2-(furan-2-ylcarbonyl)hydrazono)-4-oxobutanoic acids **3a–h**.

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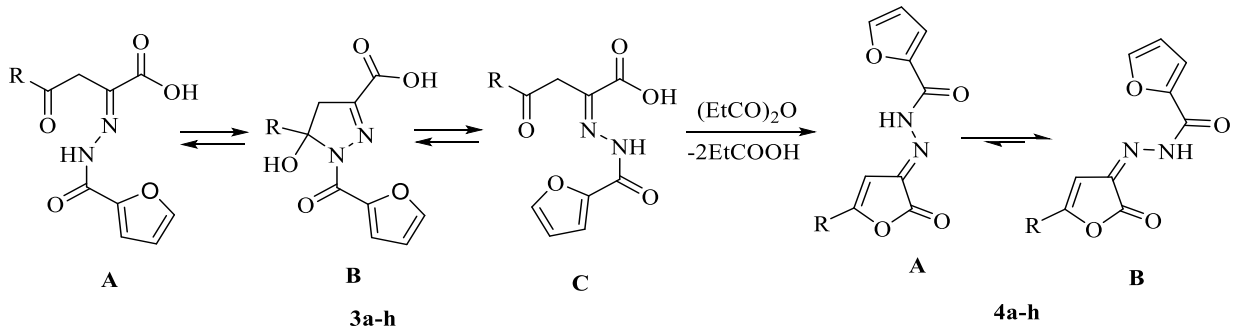

1,3,4: R= t-Bu (**a**), 4-MeC_6H_4(**b**), 4-EtC_6H_4 (**c**), 4-$EtOC_6H_4$ (**d**), 4-FC_6H_4 (**e**), 4-ClC_6H_4 (**f**), naphthalen-1-yl (**g**), naphthalen-2-yl (**h**).

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

All applicable international, national, and/or institutional guidelines for the care and use of animals were followed.

3. Results and Discussion

Substituted 2-[2-(furan-2-ylcarbonyl)hydrazono]-4-oxobutanoic acids **3a–h** were obtained in 64–84% yields by the reaction of corresponding 2,4-dioxobutanoic acids **1a–h** with furan-2-carbohydrazide **2** in acetonitrile at 50 °C (Scheme 2).

Compounds **3a–h** are crystalline yellow substances, easily soluble in chloroform, DMSO, and when heated, in toluene, dioxane, and ethanol, and insoluble in water and alkanes.

The IR spectra of compounds **3a–h** contain an absorption band at 1703–1744 cm^{-1}, which is characteristic of the stretching vibrations of the carbonyl amide group, and absorption bands at 3119–3131 and 3204–3251 cm^{-1}, which are characteristic of the stretching vibrations of the amino group. The ^1H NMR spectra (DMSO-d_6) of compounds **3a–h** in the tautomeric form **A** are characterized by singlet signals of the NH protons (11.09–11.44 ppm) and CH_2 (4.04–4.69 ppm) groups. Form **B** is characterized by the presence in the spectrum of a doublet of protons of the CH_2 group at 3.30–3.44 and 3.20–3.39 ppm, and for form **C**, singlets of the NH protons (13.04–13.83 ppm) and CH_2 (3.80–4.42 ppm). The spectral data of compounds **3a–h** are in good agreement with the corresponding spectral data of alkyl 4-oxo-4-aryl-2-[2-(arylcarbonyl)hydrazinylidene]butanoates, which have a similar structure and also exist in three forms [37].

Intramolecular cyclization of acids **3a–h** occurs upon slow heating to 150 °C in propionic anhydride and led to the formation of substituted N'-(2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazides **4a–h** (Scheme 3). Compounds **4a–h,** obtained in 52–84% 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–h** contain an absorption band in the region 1776–1811 cm^{-1}, which is characteristic of the stretching vibrations of the lactone carbonyl of the furan-2(3H)-one ring, and an absorption band in the region 3116–3186 cm^{-1}, which is characteristic of the stretching vibrations of the amino group. According to ^1H NMR data in DMSO-d_6, compounds **4a**, **4c–f** 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 [11.63–11.83 (*E*-**A**) and 12.36–12.54 ppm (*Z*-**B**)]. Compounds **4b**, **4g**, **4h** exist only as the *E*-isomer, δ(NH) 11.89–11.96 ppm. The spectral data of compounds **4a–h** are in good agreement with the corresponding spectral data of N-[5-aryl-2-oxofuran-3(2H)-ylidene]-4-methylbenzohydrazides, which have a similar structure [28].

Some of the obtained compounds were examined for anti-inflammatory activity. It is shown in Table 1 that compounds **3e, g** and **4d, f, g** have a pronounced anti-inflammatory effect, surpassing the effect of the comparison drug nimesulide.

Table 1 Anti-inflammatory activity of substances **3a**, **c–e**, **g**.

Compound	Increase in foot volume after 3 hours (%)	Braking swelling after 3 h, %
3a	57.59±3.54	13.36
3c	44.12±3.22*,**	33.62
3d	55.91±5.82	15.89
3e	26.71±5.47*	59.82
3g	30.49±3.55*	54.13
Nimesulide	33.90±6.78*	48.99
Control	66.47±10.19	–

* – the difference is reduced compared to the decrease at $p<0.05$; ** – the difference is significant compared with nimesulide at $p<0.05$.

Table 2 Anti-inflammatory activity of substances **4a**, **b**, **d–h.**

Compound	Increase in foot volume after 3 hours (%)	Braking swelling after 3 h, %
4a	41.32±3.26*	37.84
4b	39.61±1.73*	40.41
4d	28.96±5.58*	56.43
4e	45.34±3.62*,**	31.79
4f	24.04±5.68*	63.83
4g	24.29±3.73*	63.45
4h	114.76±16.45*	–72.64
Nimesulide	33.90±6.78*	48.99
Control	66.47±10.19	–

* – the difference is reduced compared to the decrease at $p<0.05$; ** – the difference is significant compared with nimesulide at $p<0.05$.

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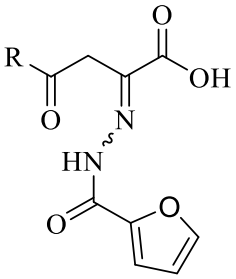

Figure 1 The structure of the **3a, c–e, g** compounds.

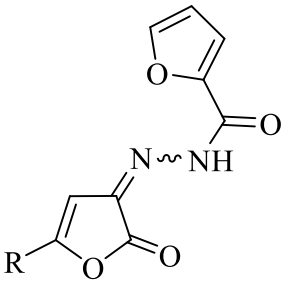

Figure 2 The structure of the **4a**, **b**, **d–h** compounds.

4. Limitations

We have received new methyl-2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acids with yields of 64–84% and N'-(2-oxofuran-3(2H)-ylidene]furan-2-carbohydrazides with yields of 52–84%, after recrystallization of the obtained compounds, yields are significantly reduced. In the course of our further research, we are going to improve the purification method in order to achieve a significantly higher yield of the product.

5. Conclusions

New derivatives of 2-(2-(furan-2-carbonyl)hydrazono)-4-oxobutanoic acids and N'-(2-oxofuran-3(2H)-ylidene)furan-2-carbohydrazides were obtained. It was found that some of the obtained compounds (**3e**, **4g** and **4f**) exhibited significant anti-inflammatory activity, reliably exceeding the effect of a referral drug nimesulide. Compounds **3** and **4** have LD_{50} > 1500 mg/kg and, according to the drug toxicity classification [38], belong to the V class (practically non-toxic substances).

• 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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