Synthesis and anti-inflammatory activity of *N′*-substituted 2-[2-(diarylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enehydrazides

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New *N′*-substituted 2-(2-(diarylmethylene)hydrazinyl)-5,5-dimethyl-4-oxohex-2-enehydrazides were synthesized by the ring opening reaction of 3-diarylmethylenehydrazono-5-*tert*-butyl-3*H*-furan-2-ones under the action of aliphatic, aromatic, and heterocyclic acid hydrazides. The structures of the obtained compounds were confirmed by ^{1}H and ^{13}C NMR spectroscopy, IR spectroscopy, and elemental analysis. Their anti-inflammatory activity was studied.

Key words: lactones, 3-imino(hydrazono)-3*H*-furan-2-ones, 2,4-dioxobutanoic acid derivatives, aliphatic acid hydrazides, aromatic acid hydrazides, heterocyclic acid hydrazides, anti-inflammatory activity.

Derivatives of 2,4-dioxobutanoic acids have long been known as biologically active compounds, which is regularly confirmed by new research in the field of medicinal chemistry. This type of compounds inhibit such target enzymes as influenza virus endonuclease,[1—3] 2-keto-3-deoxy-6-phosphogluconataldolase,[4] integrase,[5—9] human immunodeficiency virus ribonuclease[10] and polymerase,[11] protein tyrosine phosphatase 1B,[12] and acetylcholinesterase.[13] Derivatives of 2,4-dioxobutanoic acid, interacting with undefined targets, exhibit analgesic,[14—20] anti-inflammatory,[20] antibacterial[20—22] (including against multi-resistant strains *Staphylococcus aureus*[23]) action, antifungal,[24,25] antiviral,[26] antioxidant,[21] and other types of biological activity.

The variety of chemical properties of 3-imino(hydrazono)-3*H*-furan-2-ones is ensured by the presence of several reaction centers in their structure, as well as by the possibility of changing the nature of substituents in the furan ring and the imino(hydrazono) group. There are known several approaches to the synthesis of 3-imino(hydrazono)-3*H*-furan-2-ones: the introduction of an imino(hydrazono) group into an already existing furan ring[27—32] and intramolecular cyclization of the corresponding 2-imino(hydrazono) acids[33—37] obtained by treatment of carbonyl compounds with amines (hydrazones) or amides (hydrazides).[38—40] In the reactions with nucleophiles, 3-imino(hydrazono)-3*H*-furan-2-ones undergo attack at the carbonyl group of the lactone fragment, which, depending on the reagent nature and reaction conditions, leads to new acyclic[41—46] or heterocyclic[27—29,47—53] products. In this case, the ring opening products formed contain a fragment of 2,4-dioxobutanoic acid, which makes them interesting starting compounds for the search of new biologically active substances.

An analysis of the literature shows that the search for new biologically active substances among the products of conversion of imino(hydrazono)furanones is promising. In addition, it is interesting to examine poorly studied imino(hydrazono)furanones containing a *tert*-butyl fragment at position 5 of the furan ring, which are distinguished by storage stability. In the present work, we describe the reaction of 3-(diarylmethylene)hydrazono-5-*tert*-butylfuran-2(3*H*)-ones with a number of *NH*-nucleophiles (aliphatic, aromatic, and heterocylic acid hydrazides) and study the anti-inflammatory activity of the synthesized compounds.

Results and Discussion

First, we optimized the conditions for the reaction of hydrazonofuranones with acid hydrazides, using hydrazonofuranone **1a** and 2-phenylacetohydrazide as model

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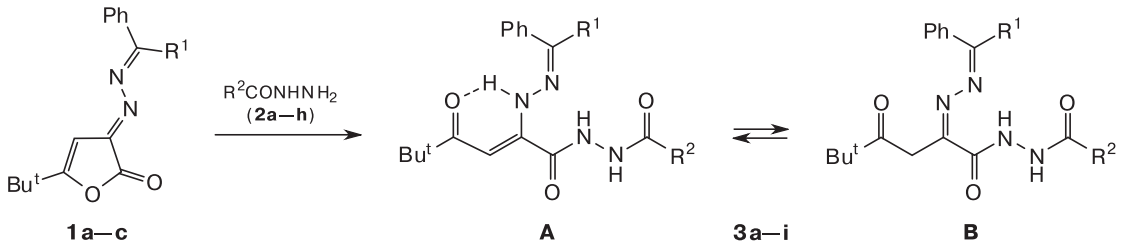
Scheme 1



1: R^1 = Ph (**a**), C(O)Ph (**b**), 4-$MeOC_6H_4$ (**c**)
2: R^2 = Bn (**a**), 2,4-$Cl_2C_6H_3OCH_2$ (**b**), PhCH(OH) (**c**), 4-BrC_6H_4 (**d**) pyridin-4-yl (**e**), *N*-(4-bromophenyl)-2-aminoquinolin-4-yl (**f**), 3-HOC_6H_4 (**g**), 2-HOC_6H_4 (**h**)

Compound **3**	R^1	R^2	Compound **3**	R^1	R^2
a	Ph	Bn	**f**	Ph	*N*-(4-bromophenyl)-2-aminoquinolin-4-yl
b	Ph	2,4-$Cl_2C_6H_3OCH_2$			
c	Ph	PhCH(OH)	**g**	C(O)Ph	3-HOC_6H_4
d	Ph	4-BrC_6H_4	**h**	4-$MeOC_6H_4$	2-HOC_6H_4
e	Ph	pyridin-4-yl	**i**	4-$MeOC_6H_4$	3-HOC_6H_4

starting compounds (Scheme 1). We studied the influence of the solvent, temperature, ratio of reagents, and reaction time on the yield of the target product **3a** (Table 1).

Heating of reagents **1a** and **2a** in the ratio of 2 : 1 at 50 °C for 1 h in dioxane practically did not cause the reaction, the yield of product **3a** was only 4% (see Table 1, entry *1*). When the reaction was carried out with an equimolar ratio of hydrazonofuranone **1a** and hydrazide **2a** without changing the other reaction conditions, the yield of product **3a** increased to 10% (entry *2*). An increase in the reaction time to 12 and 24 h led to an increase in the yield of product **3a** to 34% and 51%, respectively (entries *3* and *4*). The use of toluene as a solvent (50 °C, 24 h) slightly increased the yield of the target product **3a** up to 56% (entry *5*). The reaction in MeCN and diethyl ether gave lower yields of product **3a** (entries *6* and *7*), therefore, these solvents were not used in further studies. The yield of product **3a** was significantly increased by carrying out the reaction in refluxing solvents: up to 86% in dioxane and up to 89% in toluene (entries *8* and *9*). Reducing the reaction time to 15 min had almost no effect on the yield of compound **3a** (entries *10* and *11*). Thus, the optimal conditions are: the reagent ratio 1 : 1, toluene as the solvent (or dioxane, if the starting hydrazide is insoluble in toluene), reflux, and the reaction time of 15 min. Compounds **3a—i** were obtained under the optimal conditions by the reaction of furanones **1a—c** with hydrazides of aliphatic, aromatic, and heterocyclic acids (see Scheme 1).

Table 1. Optimization of the reaction conditions for hydrazonofuranone **1a** with phenylacetic acid hydrazide (**2a**)[a]

Entry	Solvent	*T*/°C	*t*/h	Yield of **3a** (%)
1[b]	Dioxane	50	1	4
2	Dioxane	50	1	10
3	Dioxane	50	12	34
4	Dioxane	50	24	51
5	Toluene	50	24	56
6	MeCN	50	24	31
7	Et_2O	40	24	15
8	Dioxane	101	1	86
9	Toluene	110	1	89
10	Dioxane	101	0.25	84
11	Toluene	110	0.25	88

[a] The reactions were carried out at a molar ratio **1a** : **2a** = = 1 : 1, unless stated otherwise.
[b] The molar ratio **1a** : **2a** = 2 : 1.

Hydrazides **3a—e** are crystalline substances from white to orange in color, readily soluble in dioxane, poorly soluble in ethanol and toluene, practically insoluble in hexane and water.

The structures of the synthesized compounds were confirmed by IR spectroscopy and ^1H and ^{13}C NMR spectroscopy. The IR spectra of hydrazides **3a—i** exhibit an absorption band of the hydrazide NH groups in the region of 3268—3442 cm^{-1}, an absorption band of the carbonyl group in the range of 1633—1712 cm^{-1}, as well as an absorption band in the region of 1533—1612 cm^{-1} characteristic of the stretching vibrations of the C=C and C=N bonds. The ^1H NMR spectra of compounds **3b—d** recorded in $CDCl_3$ and compounds **3a,f,i** recorded in DMSO-d_6 showed the presence of only the enehydrazine form **A**, as evidenced by the signal for the methine proton in the range of δ 5.48—6.44 and the absence of the signal for the methylene group. The ^1H NMR spectrum of compound **3e** recorded in $CDCl_3$ showed the presence of both forms **A** and **B**, which is confirmed by the presence of the signals for both the methine proton of form **A** at δ 6.37 and the methylene group protons of form **B** at δ 4.18. The ^1H NMR spectra of compounds **3g,h** recorded in DMSO-d_6

Table 2. Anti-inflammatory activity of hydrazides **3a,f—i**

Compound	Increase in foot volume after 3 h (%)	Edema inhibition after 3 h (%)
3a	21.31±4.61*	67.94
3f	35.16±3.81*	47.10
3g	44.93±5.97	32.41
3h	42.38±7.33	36.24
3i	45.58±8.45	31.43
Nimesulide	33.90±6.78	48.99
Control	66.47±10.19	—

* $p < 0.05$ compared to control.

showed the presence of only hydrazone form **B**, as evidenced by the presence of a singlet signal for the methylene group protons at δ 3.79—4.18 and the absence of the methine proton signal.

Taking into account the wide range of biological activity of 2,4-dioxobutanoic acid derivatives, it was of interest to study the activity of compounds **3**. Additional interest arose due to the fact that the degradation in the body of this type of compounds leads to pyruvic acid and other organic acids, which are natural metabolites. This allows one to synthesize practically non-toxic compounds in the considered series of derivatives.

We studied the anti-inflammatory effect of hydrazides **3a,f—i** on the model of acute inflammatory edema caused by the administration of a solution of carrageenan into the hind paw of a rat. Statistically processed results are presented in Table 2. According to the obtained data, hydrazides **3a,f—i** manifest an anti-inflammatory effect. The activity of compounds **3a,f** is comparable or significantly exceeds that of the reference drug nimesulide.

In conclusion, we synthesized new *N*′-substituted 2-[2-(diarylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enehydrazides by the reaction of 3-(diarylmethylene)hydrazono-5-*tert*-butylfuran-2(3*H*)-ones with aliphatic, aromatic, and heterocyclic acid hydrazides in 63—99% yields. The anti-inflammatory activity of the compounds obtained was revealed. Two compounds were found to exhibit pronounced anti-inflammatory activity, which indicates the appropriacy of further search for new anti-inflammatory substances in this series.

Experimental

Reaction progress was monitored by TLC on Silufol 254 UV or Sorbfil PTLC P-A-UV-254 plates in the system diethyl ether—benzene—acetone (10 : 9 : 1), spots of compounds were detected in iodine vapors. IR spectra were recorded on a FSM-1201 spectrometer in Nujol, ^{1}H and ^{13}C NMR spectra were recorded on a Bruker Avance III spectrometer (400 (^{1}H) and 100 MHz (^{13}C)) in $CDCl_3$ and DMSO-d_6, using residual signal of the solvent as a reference. Melting (decomposition) points of the products were determined on PTP-2 and SMP40 apparatuses. Elemental analysis was performed on a Leco CHNS-932 instrument.

The starting hydrazonofuranones **1a—c** were synthesized by known procedures.[54,55]

***N*′-Substituted 2-[2-(diarylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enehydrazides 3a—i (general procedure).** A suspension of hydrazonofuranone **1a—c** (0.6 mmol) and hydrazide **2a—h** (0.6 mmol) in anhydrous toluene (5 mL) (for compounds **3a,b,d,f,h**) or anhydrous dioxane (for compounds **3c**,**e,g,i**) was refluxed for 10—15 min with stirring. The solution was cooled and left at room temperature for 24—72 h. The precipitate formed was collected by filtration and recrystallized. If the precipitate was not formed, the solvent was evaporated and the resulting residue was recrystallized.

2-[2-(Diphenylmethylene)hydrazinyl]-5,5-dimethyl-4-oxo-*N*′-(2-phenylacetyl)hex-2-enehydrazide (3a). The yield was 0.25 g (88%), yellow crystals, m.p. 136—138 °C (from toluene). IR, ν/cm^{-1}: 3271 (NH); 1633 (C=O); 1604, 1582 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR (DMSO-d_6), δ, form **A**: 1.01 (s, 9 H, Bu^t); 3.59 (s, 2 H, C$\underline{H}_2$CONH); 5.48 (s, 1 H, CH); 7.27 (m, 2 H, Ar); 7.30 (m, 3 H, Ar); 7.37 (m, 4 H, Ar); 7.51 (m, 4 H, Ar); 7.68 (m, 2 H, Ar); 10.36 (s, 1 H, CON$\underline{H}$NHCO); 10.50 (s, 1 H, CONHN$\underline{H}$CO); 12.19 (s, 1 H, NH). ^{13}C NMR (DMSO-d_6), δ: 27.42 (3 C), 42.42, 91.35, 126.99, 127.82 (2 C), 128.59, 128.69 (2 C), 128.64, 128.80 (2 C), 129.47, 129.56 (2 C), 129.98, 130.35 (2 C), 130.43, 132.37, 136.12, 137.17, 151.76, 153.39, 162.25, 169.31, 205.84. Found (%): C, 72.20; H, 6.29; N, 11.64. $C_{29}H_{30}N_4O_3$. Calculated (%): C, 72.18; H, 6.27; N, 11.61.

2-[2-(Diphenylmethylene)hydrazinyl]-5,5-dimethyl-4-oxo-*N*′-[2-(2,4-dichlorophenoxy)acetyl]hex-2-enehydrazide (3b). The yield was 0.24 g (69%), yellow crystals, m.p. 156—158 °C (from toluene). IR, ν/cm^{-1}: 3268 (NH); 1712, 1642 (C=O); 1574 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR ($CDCl_3$), δ, form **A**: 1.10 (s, 9 H, Bu^t); 4.76 (s, 2 H, OCH_2); 6.44 (s, 1 H, CH); 7.28 (m, 2 H, Ar); 7.37 (m, 3 H, Ar); 7.42 (m, 3 H, Ar); 7.65 (m, 3 H, Ar); 7.72 (m, 2 H, Ar); 9.73 (d, 1 H, CON$\underline{H}$NHCO, J = 6.6 Hz), 12.37 (d, 1 H, CONHN$\underline{H}$CO, J = 6.6 Hz); 13.04 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 26.99 (3 C), 42.88, 67.97, 95.72, 114.89, 127.97, 128.21 (2 C), 128.48 (2 C), 128.51 (2 C), 129.48, 129.83 (2 C), 130.06, 130.19, 130.31, 130.42, 132.05, 136.49, 144.84, 151.59, 153.28, 157.73, 162.09, 206.38. Found (%): C, 61.40; H, 5.00; Cl, 12.51; N, 9.89. $C_{29}H_{28}Cl_2N_4O_4$. Calculated (%): C, 61.38; H, 4.97; Cl, 12.49; N, 9.87.

2-[2-(Diphenylmethylene)hydrazinyl]-*N*′-(2-hydroxy-2-phenylacetyl)-5,5-dimethyl-4-oxohex-2-enehydrazide (3c). The yield was 0.209 g (70%), yellow crystals, m.p. 153—155 °C (from propan-2-ol). IR, ν/cm^{-1}: 3371 br. (NH); 1701, 1654 (C=O); 1598 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR ($CDCl_3$), δ, form **A**: 1.08 (s, 9 H, Bu^t); 4.16 (s, 1 H, OH); 5.32 (s, 1 H, C$\underline{H}$OH); 6.34 (s, 1 H, CH); 7.37 (m, 2 H, Ar); 7.41 (m, 3 H, Ar); 7.45 (m, 4 H, Ar); 7.53 (m, 4 H, Ar); 7.65 (m, 2 H, Ar); 9.73 (br.s, 1 H, CON$\underline{H}$NHCO); 12.04 (br.s, 1 H, CONHN$\underline{H}$CO); 12.96 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 27.00 (3 C), 42.85, 73.74, 95.44, 126.86 (2 C), 127.85 (2 C), 128.15 (2 C), 128.45 (2 C), 128.51 (2 C), 128.79, 128.88 (2 C), 129.47 (2 C), 129.81 (2 C), 130.27, 145.22, 153.18, 158.25, 167.69, 206.34. Found (%): C, 69.88; H, 6.10; N, 11.27. $C_{29}H_{30}N_4O_4$. Calculated (%): C, 69.86; H, 6.07; N, 11.24.

4-Bromo-*N*′-{2-[2-(diphenylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enoyl}benzhydrazide (3d). The yield was 0.267 g (69%), orange crystals, m.p. 138—140 °C (from toluene).

IR, ν/cm^{-1}: 3442 br. (NH); 1674 (C=O); 1592 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR ($CDCl_3$), δ, form **A**: 1.09 (s, 9 H, Bu^t); 6.38 (s, 1 H, CH); 7.20 (m, 2 H, Ar); 7.38 (m, 3 H, Ar); 7.43 (m, 2 H, Ar); 7.64 (m, 3 H, Ar); 7.76 (m, 2 H, Ar); 7.81 (m, 2 H, Ar); 9.74 (d, 1 H, CONHNHCO, *J* = 6.2 Hz); 12.42 (d, 1 H, CONHNHCO, *J* = 6.2 Hz); 13.04 (s, 1 H, NH). ^{13}C NMR ($CDCl_3$), δ: 27.03 (3 C), 42.84, 95.43, 125.29, 128.21 (2 C), 128.28 (2 C), 128. 49 (2 C), 128.55 (2 C), 128.83 (2 C), 128.93 (2 C), 129.02, 129.83 (2 C), 132.04 (2 C), 136.48, 145.13, 153.46, 157.90, 206.29. Found (%): C, 61.46; H, 4.99; Br, 14.62; N, 10.25. $C_{28}H_{27}BrN_4O_3$. Calculated (%): C, 61.43; H, 4.97; Br, 14.60; N, 10.23.

***N′*-{2-[2-(Diphenylmethylene)hydrazinyl]-5,5-dimethyl-4-oxohex-2-enoyl}isonicotinehydrazide (3e).** The yield was 0.206 g (73%), white crystals, m.p. 132.5—134.4 °C (from propan-2-ol). IR, ν/cm^{-1}: 3327 br. (NH); 1692, 1654 (C=O); 1612, 1557 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR ($CDCl_3$), δ, form **A** (36%): 1.08 (s, 9 H, Bu^t); 6.37 (s, 1 H, CH); 7.37 (m, 2 H, Ar); 7.48 (m, 3 H, Ar); 7.64 (m, 4 H, Ar); 7.69 (m, 3 H, Ar); 7.75 (m, 2 H, Ar); 10.09 (d, 1 H, CONHNHCO, *J* = 5.3 Hz), 12.46 (d, 1 H, CONHNHCO, *J* = 5.3 Hz); 13.03 (s, 1 H, NH); form **B** (64%): 1.16 (s, 9 H, Bu^t); 4.18 (s, 2 H, CH_2); 7.37 (m, 2 H, Ar); 7.48 (m, 3 H, Ar); 7.64 (m, 4 H, Ar); 7.69 (m, 3 H, Ar); 7.75 (m, 2 H, Ar); 9.21 (s, 1H, CONHNHCO); 9.37 (s, 1 H, CONHNHCO). ^{13}C NMR ($CDCl_3$), δ: 26.45 (3 C), 27.01 (3 C), 35.68, 44.84, 95.50, 99.97, 120.95 (2 C), 121.05 (2 C), 127.88 (2 C), 128.21 (2 C), 128.25 (2 C), 128.46 (2 C), 128.56 (2 C), 129.51 (2 C), 129.84 (2 C), 129.94 (2 C), 130.10, 130.22, 130.30 (2 C), 130.82 (2 C), 132.05, 134.57, 136.47, 137.27, 138.74, 145.01, 150.60 (2 C), 150.69 (2 C), 153.54, 154.43, 158.43, 161.12, 162.50, 165.27, 206.32, 210.35. Found (%): C, 69.09; H, 5.83; N, 14.95. $C_{27}H_{27}N_5O_3$. Calculated (%): C, 69.07; H, 5.80; N, 14.92.

2-[(4-Bromophenyl)amino]-*N′*-[2-(2-(diphenylmethylene)-hydrazinyl]-5,5-dimethyl-4-oxohex-2-enoyl)quinoline-4-carbohydrazide (3f). The yield was 0.196 g (63%), yellow crystals, m.p. 188—191 °C (from propan-2-ol). IR, ν/cm^{-1}: 3377 (NH); 1700, 1657 (C=O); 1610, 1533 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR (DMSO-d_6), δ, form **A**: 1.05 (s, 9 H, Bu^t); 5.58 (s, 1 H, CH); 7.37 (m, 4 H, Ar); 7.52 (m, 3 H, Ar); 7.58 (m, 3 H, Ar); 7.70 (m, 4 H, Ar); 7.80 (m, 2 H, Ar); 8.05 (m, 2 H, Ar); 8.09 (m, 1 H, Ar); 10.02(s, 1 H, NHC$_6$H$_4$Br); 10.81 (s, 1 H, CONHNHCO); 10.85 (s, 1 H, CONHNHCO); 12.25 (s, 1 H, NHN). ^{13}C NMR (DMSO-d_6), δ: 27.47 (3 C), 42.50, 53.19, 91.39, 113.13, 120.97 (2 C), 123.93, 124.42, 125.60, 127.18, 127.89 (2 C), 128.59 (4 C), 128.79 (2 C), 129.78, 130.00, 130.40 (2 C), 131.84 (4 C), 132.37, 137.13, 142.16, 151.86, 153.41, 162.65, 166.22, 205.94. Found (%): C, 64.46; H, 4.85; Br, 11.61; N, 12.22. $C_{37}H_{33}BrN_6O_3$. Calculated (%): C, 64.44; H, 4.82; Br, 11.59; N, 12.19.

***N′*-{5,5-Dimethyl-4-oxo-2-[(2-oxo-1,2-diphenylethylidene)-hydrazono]hexanoyl}-3-hydroxybenzhydrazide (3g).** The yield was 0.304 g (99%), yellow crystals, m.p. 191—193 °C (from a toluene—acetonitrile mixture). IR, ν/cm^{-1}: 3356 br. (NH); 1681 (C=O); 1651 (C=O); 1599, 1559 (C=C, C=N). ^{1}H NMR (DMSO-d_6), δ, form **B**: 1.19 (s, 9 H, Bu^t); 4.18 (s, 2 H, CH_2); 7.42 (m, 14 H, Ar); 10.26 (br.s, 1 H, CONHNHCO); 10.53 (br.s, 1 H, CONHNHCO). Found (%): C, 67.95; H, 5.51; N, 10.92. $C_{29}H_{28}N_4O_5$. Calculated (%): C, 67.96; H, 5.51; N, 10.93.

2-Hydroxy-*N′*-(2-{[(4-methoxyphenyl)(phenyl)methylene]-hydrazono}-5,5-dimethyl-4-oxohexanoyl)benzhydrazide (3h). The yield was 0.293 g (95%), yellow crystals, m.p. 197—199 °C (from toluene). ^{1}H NMR (DMSO-d_6), δ, form **B**: 1.06 (s, 9 H, Bu^t); 3.79 (s, 2 H, CH_2); 7.38 (m, 13 H, Ar); 10.75 (br.s, 1 H, CONHNHCO); 11.90 (br.s, 1 H, CONHNHCO). Found (%): C, 67.67; H, 5.90; N, 10.88. $C_{29}H_{30}N_4O_5$. Calculated (%): C, 67.69; H, 5.88; N, 10.89.

3-Hydroxy-*N′*-(2-{2-[(4-methoxyphenyl)(phenyl)methylene]-hydrazinyl}-5,5-dimethyl-4-oxohex-2-enoyl)benzhydrazide (3i). The yield was 0.231 g (75%), yellow crystals, m.p. 191—193 °C (from a toluene—acetonitrile mixture). IR, ν/cm^{-1}: 3331 br. (NH); 1698, 1641 (C=O); 1611, 1582 (C=O$_{chel}$, C=C, C=N). ^{1}H NMR (DMSO-d_6), δ, form **A**: 1.04 (s, 9 H, Bu^t); 5.59 (s, 1 H, CH); 7.47 (m, 13 H, Ar); 10.76 (br.s, 1 H, CONHNHCO); 10.88 (s, 1 H, CONHNHCO); 12.23 (s, 1 H, NH). Found (%): C, 67.68; H, 5.89; N, 10.87. $C_{29}H_{30}N_4O_5$. Calculated (%): C, 67.69; H, 5.88; N, 10.89.

The anti-inflammatory activity of the synthesized compounds was studied at the Perm State Pharmaceutical Academy. Experiments on animals were conducted under the rules of laboratory practice and the requirements of ethics. The study was carried out on white non-linear female rats weighing 160—180 g obtained from the Andreevka nursery (Moscow region). The animals were kept in a typical vivarium with a natural 12-hour day and night cycle at an air temperature of 20±2 °C; they were fed in accordance with the feed norms for experimental animals. The control and experimental groups included six animals each. Acute inflammatory edema was induced by subplantar injection of 0.1 mL of a 1% aqueous solution of carrageenan into the hind paw of a rat. Foot volume was assessed oncometrically[56] before and 3 h after carrageenan administration. An increase in the volume of the foot indicating the development of edema was calculated as a percentage to the initial value. The test compounds were administered orally at a dose of 50 mg kg^{-1} 1 h before the administration of the phlogogenic agent. Animals in the control group received 1% starch solution in the equivolume amounts. Nimesulide (Unimark Remedies, India) was used as a reference drug, which was administered orally at a dose of 50 mg kg^{-1}. The presence of an anti-inflammatory effect was judged by the severity of inhibition of the inflammatory reaction. The results of the experiments were processed statistically with the calculation of the Fisher—Student criterion.[57] The effect was considered significant at $p < 0.05$.

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All experiments involving animals and their maintenance complied with the rules of laboratory practice at conducting preclinical studies in the Russian Federation (GOST ISO/MEK 17025-2009 "General requirements for testing laboratories"; GOST 33044-2014 "Principles of good laboratory practice"), the rules of good laboratory practice of the Eurasian Economic Union in the field of circulation of medicines (Decision of the Council of the Eurasian Economic Commission dated November 3, 2016, No. 81), and the Order of the Ministry of Health of the Russian Federation dated April 1, 2016, No. 199n "On Approval of the Rules of Good Laboratory Practice" (GLP) in compliance with the International Recommendations

of the European Convention for the Protection of Vertebrate Animals used for Experimental and other Scientific Purposes (1997). The performed studies comply with the principles of ethics in accordance with the protocol of the Commission on Bioethics of the Perm State Pharmaceutical Academy No. 02/21-n-zh dated July 14, 2021.

The authors declare no competing interests.

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