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Synthesis and Analgesic Activity of *N*,6-Diaryl-4-hydroxy-4-methyl-2-oxocyclohexane-1-carboxamides and Their Dehydration Products

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Abstract—A series of new *N*,6-diaryl-4-hydroxy-4-methyl-2-oxocyclohexane-1-carboxamides was obtained through the reaction of *N*-arylamides of acetoacetic acid with benzalacetone and 4-chlorobenzalacetone under basic conditions (KOH) in methanol at room temperature. Increasing of the amount of potassium hydroxide used in the reaction led to the formation of dehydration products, namely *N*,6-diaryl-4-methyl-2-oxocyclohex-3-ene-1-carboxamides. The latter were also formed by using unsubstituted acetoacetamide and *N*-methylacetoacetamide. The synthesized compounds were tested for analgesic activity.

Keywords: acetoacetic acid *N*-arylamides, benzalacetone, 4-chlorobenzalacetone, *N*,6-diaryl-4-hydroxy-4-methyl-2-oxocyclohexane-1-carboxamides, analgesic activity

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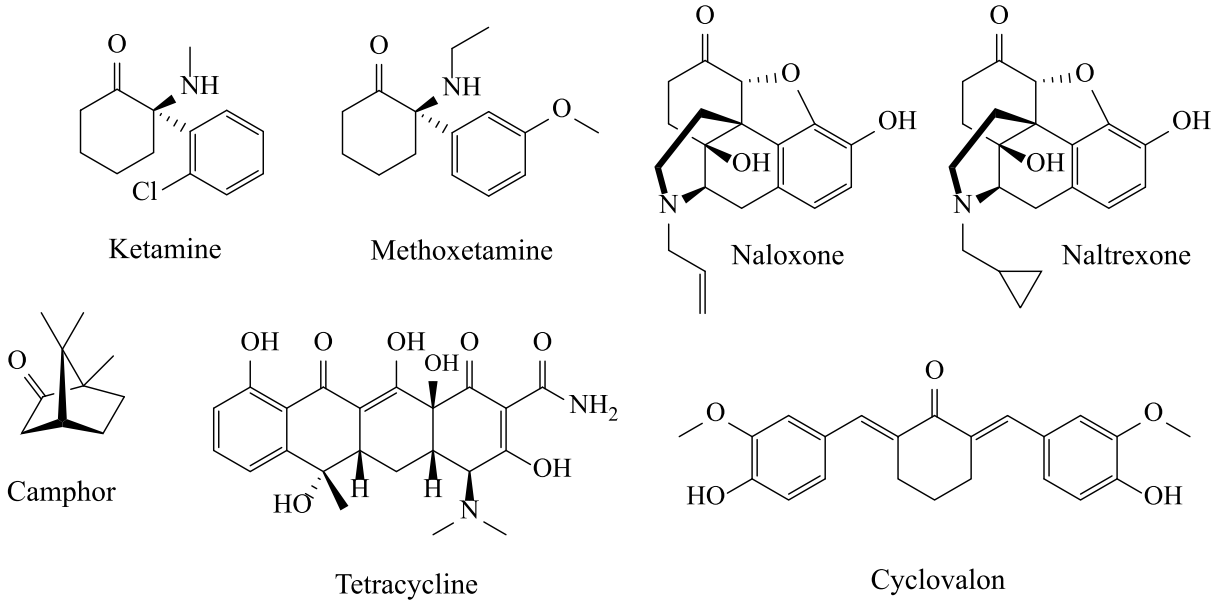
The synthesis of cyclohexanones attracts the attention of researchers both in theoretical and practical aspects. This is due to the fact that the cyclohexanone fragment is the main structural unit of a number of widely used natural and synthetic drugs [1, 2]. The best-known representative of this class is camphor (Scheme 1), a structural terpenoid found in camphor laurel oil (*Cinnamomum camphora*) and used as an analeptic drug [3]. Functionalized cyclohexanone derivatives are used as fluorescent agents [4] and have anthelmintic [5], anti-inflammatory [6], antibacterial [7–9], anticonvulsant [10], antitumor [11, 12], antiviral [13] and herbicidal activity [14]. Some of them are phosphodiesterase inhibitors and can be used as anti-inflammatory agents for the treatment of chronic obstructive pulmonary disease [15, 16]. There are a number of well-known drugs containing a cyclohexanone fragment in their structure (Scheme 1). For example, ketamine and methoxetamine are non-inhalation anesthetics that exhibit analgesic activity [17, 18], while naloxone and naltrexone are opioid receptor antagonists [19, 20]. Tetracycline is a broad-spectrum antibiotic [21], and cyclovalon is a synthetic choleretic drug, which in addition to the main effect (bile formation) also has an anti-inflammatory effect [22].

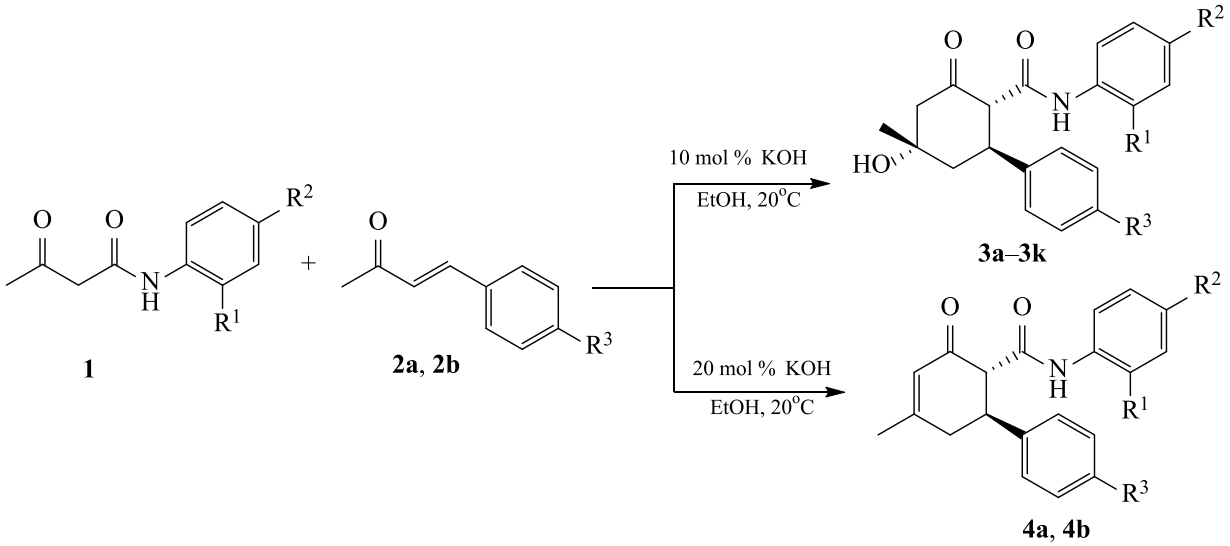
Earlier, we have obtained derivatives of 2-acetyl-4-hydroxy-5-methyl-3-phenyl-1-cyclohexanone and alkyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylates [23] through the reaction of benzalacetone with acetylacetone and acetoacetic acid esters, respectively, under basic catalysis. In addition, their reactions with *N*-nucleophilic reagents have been performed [24] and antimicrobial action against *St. aureus* and *E. coli* have been studied [23].

Continuing research in the field of the chemistry of cyclohexanones [23–26] and aiming to obtain new potentially biologically active compounds, we for the first time carried out the synthesis of *N*,6-diaryl-4-hydroxy-4-methyl-2-oxocyclohexane-1-carboxamides **3a–3k** by reacting benzalacetone **2a** and 4-chlorobenzalacetone **2b** with acetoacetic acid arylamides **1** in ethanol at room temperature in the presence of potassium hydroxide as the catalyst (Scheme 2).

Scheme 1.



Scheme 2.



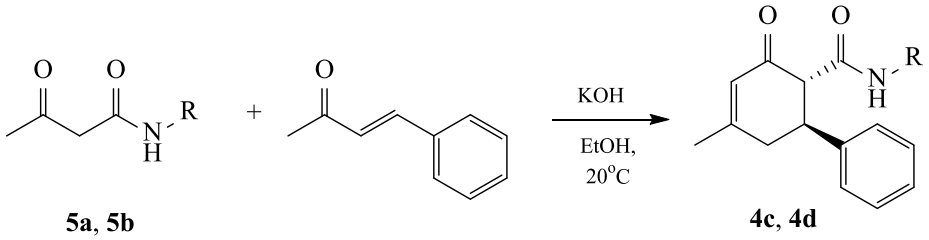
$R^1 = R^2 = R^3 = H$ (**3a**); R^1 = Me, $R^2 = R^3 = H$ (**3b**); $R^1 = R^3 = H$, R^2 = Cl (**3c**); $R^1 = R^2$ = Me , $R^3 = H$ (**3d**); R^1 = MeO, $R^2 = R^3 = H$ (**3e**); R^1 = Cl, $R^2 = R^3 = H$ (**3f**); $R^1 = R^2 = H$, R^3 = Cl (**3g**); $R^1 = R^3$ = Cl, $R^2 = H$ (**3h**); $R^1 = H$, $R^2 = R^3$ = Cl (**3i**); R^1 = MeO, R^2 = H, R^3 = Cl (**3j**); $R^1 = R^2$ = Me, R^3 = Cl (**3k**); $R^1 = R^2 = R^3 = H$ (**4a**); $R^1 = R^3 = H$, R^2 = Cl (**4b**).

Compounds **3a–3k** contain a hydroxyl group at position 4 of the alicycle. Under similar conditions, *N*,6-diaryl-4-methyl-2-oxo-3-cyclohexene-1-carboxamides **4a** and **4b** were obtained when increasing the concentration of potassium hydroxide to 20 mol %. In the case of unsubstituted acetoacetic acid amide **5a** and *N*-methylacetoacetamide **5b**, regardless of the concentration of potassium hydroxide, the products of dehydration, 3-cyclohexene-1-carboxamides **4c** and **4d**, were obtained (Scheme 3).

When *N*,*N*-dimethyl- and *N*,*N*-diethylacetoacetamides were used, the reaction products were not isolated due to resinification of the reaction mixture.

The obtained cyclohexanones **3a–3k** are colorless crystalline substances, soluble in DMSO and DMF, with

Scheme 3.



5a, **5b** **4c**, **4d**

R = H (**4c**, **5a**), Me (**4d**, **5b**).

heating in ethanol, isopropanol, and acetone, insoluble in ethyl acetate, diethyl ether and water.

The IR spectra of compounds **3a–3k** contain strong absorption bands of the amide carbonyl group (1660–688 cm^{-1}), ketone group (1704–1712 cm^{-1}), NH (3302–3408 cm^{-1}), and hydroxyl groups (3432–3538 cm^{-1}). In the ^1H NMR spectra of compounds **3a–3k**, in addition to the signals of aromatic protons (6.80–7.93 ppm), there is a singlet of methyl group protons at the C^4 atom of the ring (1.23–1.28 ppm), a doublet of doublets and a triplet of two protons at the C^5 atom in the form of an AB system (1.83–2.12 ppm, J = 11.13–14.7 Hz), two doublets of protons at the C^3 atom (2.33–2.71 ppm, J = 13.0–14.8 Hz), a doublet of triplet of the C^6H proton (3.54–3.80 ppm, J = 11.1–14.7 Hz), a doublet of the C^1H proton (3.60–4.15 ppm, J = 12.0–12.1 Hz), singlets of the OH (4.72–4.85 ppm) and NH groups (8.79–9.92 ppm). The ^{13}C NMR spectra of compounds **3a–3k** contain signals from the carbonyl groups of the alicycle (205.35–206.02 ppm), the amide (166.48–167.18 ppm), and methyl groups at the C^4 atom of the alicycle (30.20–30.33 ppm).

The mass spectrum of compound **3e** contains a molecular ion peak with m/z 353 $[M]^+$, as well as peaks of fragment ions with m/z 335 $[M - H_2O]^+$, 203 $[M - CONHC_6H_4OCH_3]^+$, and 185 $[M - H_2O - CONHC_6H_4OCH_3]^+$, confirming the proposed structure.

To establish the spatial structure, including the relative configuration of chiral centers, an X-ray diffraction study of a single crystal of compound **3e** was performed. According to X-ray diffraction data (Fig. 1), the studied crystal consists of molecules of one pair of enantiomers with the configuration S*, R*, and S* for C^1, C^4, and C^5 atoms, respectively. The cyclohexanone ring adopts the *chair* conformation. The phenyl and arylcarbamoyl substituents lie in equatorial positions in a *trans* position relative to each other. The hydroxyl group located in the axial position forms intermolecular hydrogen bonds O^3–$H^3\cdots O^2$ [1 – x, 1 – y, 2 – z], due to which the molecules in the crystal are bound into centrosymmetric dimers.

The IR spectra of compounds **4b** and **4c** contain strong absorption bands of the amide carbonyl group (1660–1688 cm^{-1}), the ketone (1704–1712 cm^{-1}), and NH groups (3302–3408 cm^{-1}). In the ^1H NMR spectra of compounds **4a**–**4d**, in addition to the signals of aromatic protons (6.80–7.48 ppm), there is a singlet of methyl group protons at the C^4 atom of the ring (1.95–2.01 ppm), a doublet and a doublet of doublets of two protons at the C^5 atom in the form of an AB system (2.42–2.68 ppm, J = 8.0–12.0 Hz), a doublet of triplets of the C^6H moiety (3.58–3.70 ppm, J = 8.0–12.0 Hz), a doublet of the C^1H group (3.51–3.82 ppm, J = 12.0 Hz), a singlet of the =CH group (5.81–5.98 ppm) and a singlet of the NH protons of the amide residue (6.75–10.04 ppm). The ^{13}C NMR spectra of compounds **4a**–**4d** contain signals from the carbonyl groups of the alicycle (194.66–194.99 ppm), the amide (167.39–168.75 ppm), and methyl groups at the C^4 atom of the alicycle (23.52–23.72 ppm).

To establish the spatial structure of compounds **4a–4d**, an X-ray diffraction analysis of a single crystal of compound **4d** was performed. The independent part of the

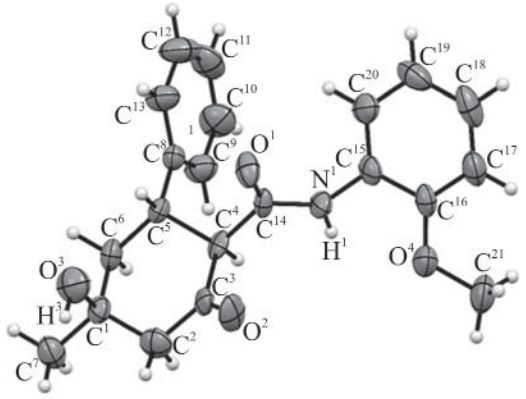
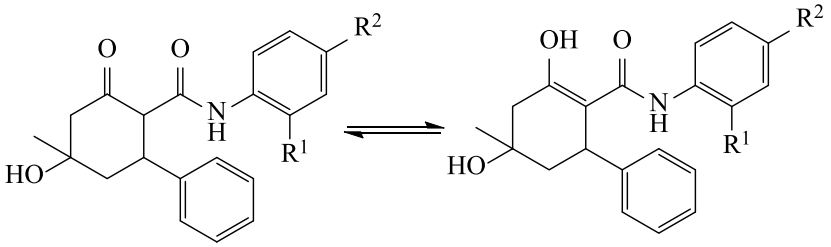


Fig. 1. General view of the molecule of compound **3e** in the crystal.

Scheme 4.



3A **3B**

unit cell contains two crystallographically independent molecules with similar geometry, which are enantiomers with the *S** and *R** configurations of the C^2 and C^3 atoms. Fig. 2 shows one of the molecules. The cyclohexenone ring of both independent molecules takes on a *half-chair* conformation. The C^4, C^5, C^6, and C^1 atoms or the C^{4A}, C^{5A}, C^{6A}, and C^{1A} atoms for the second independent molecule lie in the same plane. The C^2 and C^3 atoms are deflected on opposite sides of the plane of the other four atoms of the ring by 0.34 and –0.38 Å, the C^2 and C^3 atoms are deflected by 0.33 and –0.38 Å, respectively. The phenyl and methylcarbamoyl substituents are expected to be in more favorable equatorial positions in the *trans* position relative to each other. In a crystal, independent molecules of enantiomers, alternating with each other, are linked into infinite chains along the *a* direction of the unit cell due to intermolecular hydrogen bonds $N^{1A}–H^{1A}\cdots O^2$ and $N^1–H^1\cdots O^{2A}$ [–1 + *x*, *y*, *z*].

In solution, the obtained compounds **3a**–**3k** can exist in ketone (**3A**) and enol (**3B**) forms due to proton migration between the C^1 atom of the cyclohexane ring and the carbonyl oxygen atom at the C^2 atom of the ring (Scheme 4). The presence of two isomeric forms **3A** and **3B** with a predominance of the ketone form in the solution

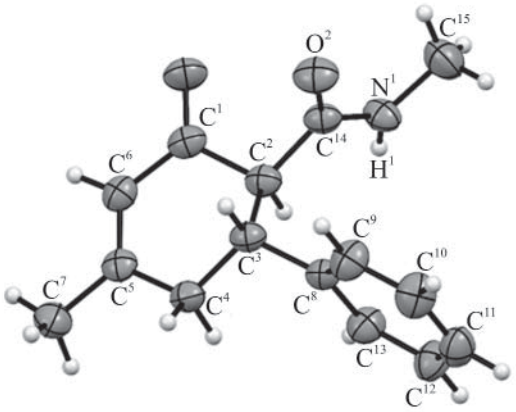


Fig. 2. General view of the molecule of compound **4d** in the crystal.

does not contradict early studies [27, 28]. Based on the data of IR, ^{1}H NMR spectroscopy, a qualitative reaction with an alcoholic solution of iron(III) chloride, as well as X-ray diffraction data, it can be concluded that *N*,6-diaryl-4-hydroxy-4-methyl-2-oxocyclohexane-1-carboxamides **3a–3k** in the crystalline state and in solution exist mainly in the ketone form **3A**.

A plausible mechanism for the formation of *N*,6-diaryl-4-hydroxy-4-methyl-2-oxocyclohexane-1carboxamides **3a–3k** is shown in Scheme 5. Initially, the Michael addition of enolized acetoacetamide **1A** to the unsaturated benzalacetone molecule **2** with the formation of intermediate **A** takes place. In the basic medium, enol **B** is formed, followed by intramolecular aldol condensation and the formation of a six-membered ring of cyclohexanone derivatives **3a–3k**. In the case of a potassium hydroxide concentration of 20 mol %, dehydration occurs with the participation of the proton at the C^3 atom and the formation of compounds **4a**–**4d**.

The acute toxicity and analgesic activity of compounds **3e** and **3f** was investigated. The results are presented in Tables 1, 2. Studies have shown that compounds **3e** and **3f** can be attributed to the fourth hazard class (low toxicity) according to the classification of K.K. Sidorov [30], since the LD_{50} value of these compounds is in doses greater than 2000 mg/kg when administered intraperitoneally.

As you can see from Table 1, compounds **3e** and **3f** exhibit analgesic activity at a dose of 50 mg/kg when administered intraperitoneally in the hot plate test. The investigated compounds increased the duration of the stay of the animals on the heated surface before the onset of the defensive reaction compared to the control. However, the increase in the duration of the latent period with the introduction of these compounds is less pronounced in comparison with the reference drug, metamizole sodium, which was injected intraperitoneally at the same dose.

Compounds **3e** and **3f** also exhibit analgesic activity in the acetic acid-induced writhing test (Table 2). It

Table 1. Acute toxicity and analgesic activity of cyclohexaneone derivatives **3e** and **3f** in the hot plate test[a]

Compound	LD_{50}, mg/kg	Latent period, sec	*p* compared to control
Control	–	11.52 ± 0.92 (*n* = 9)	–
Metamizole sodium	2900[b] (2160–3340)	17.79 ± 1.86 (*n* = 6)	< 0.05
3e	> 2000 (*n* = 8)	16.35 ± 1.23 (*n* = 9)	< 0.05
3f	>2000 (*n* = 8)	16.97 ± 1.18 (*n* = 9)	< 0.01

[a] The results are presented as mean and its standard error (*M* ± *m*); (*n*) number of animals.
[b] Literature data [29].

Table 2. Analgesic activity of cyclohexaneone derivatives **3e** and **3f** in the acetic acid-induced writhing test

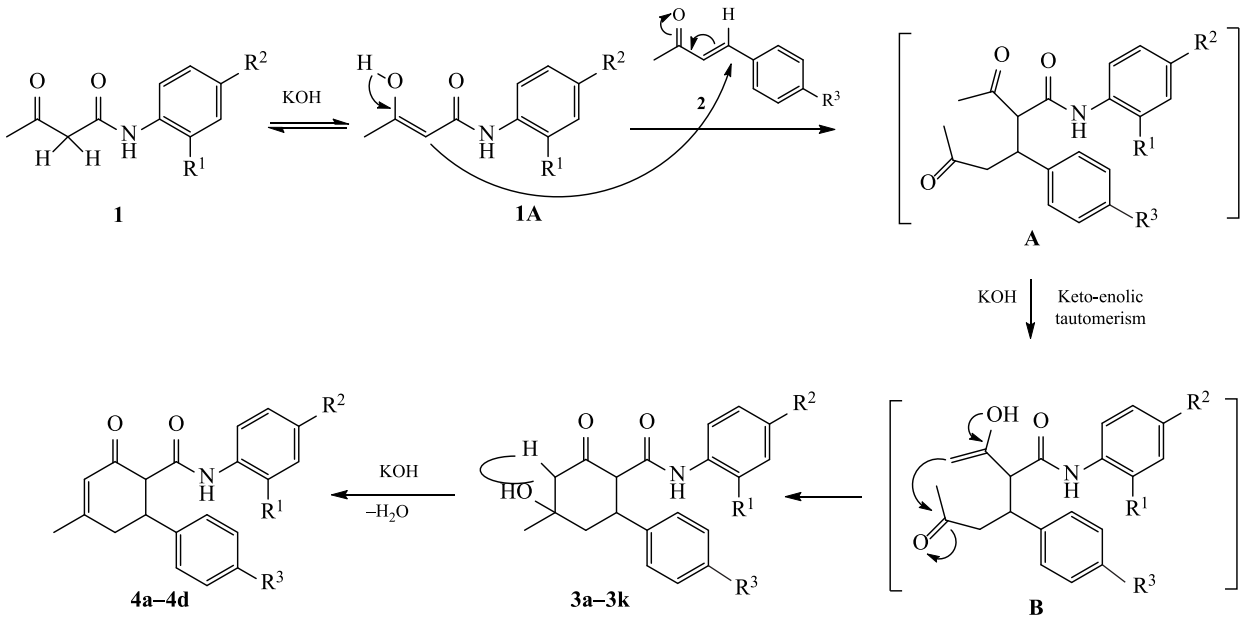
Compound	Number of cramps	Decrease in writhing compared to control, %	*p* compared to control
Control	28.55 ± 2.4 5 (*n* = 11)	–	–
Metamizole sodium	16.38 ± 3.13 (*n* = 8)	42.63	< 0.02
3e	14.50 ± 4.31 (*n* = 9)	49.21	< 0.05
3f	0.50 ± 0.22 (*n* = 10)	98.25	< 0.001

[a] The results are presented as mean and its standard error (*M* ± *m*); (*n*) number of animals.

was found that when the animals were administered compounds **3e** and **3f**, the number of writhing decreased compared to the control group. The most pronounced decrease in the number of writhing was observed in the group of animals that were administered compound **3f**: the decrease in writhing was more than 90% compared to the control. The effect of reducing writhing against when using compound **3f** was also more pronounced in comparison with the reference drug, metamizole sodium (p <0.001).

In conclusion, the reaction of *N*-arylacetoacetamides with benzalacetone and 4-chlorobenzalacetone under basic catalysis conditions furnished new cyclohexanone derivatives, among which substances exhibiting pronounced analgesic activity were found. It was shown that with a two-fold increase in the concentration of the

Scheme 5.



basic catalyst, as well as in the case of unsubstituted acetoacetamide and *N*-methylacetoacetamide, 2-oxo-3-cyclohexene-1-carboxamides are formed under similar conditions due to dehydration of the obtained cyclohexanones.

EXPERIMENTAL

IR spectra were obtained on a Shimadzu IRAffinity-1 instrument in the range of 4000–400 cm^{-1} from KBr pellets. ^1H and ^{13}C NMR spectra were recorded on a Bruker AVANCE 400SX instrument with an operating frequency of 400 and 100 MHz, respectively, using DMSO-d_6 as the solvent. Mass spectrum of compound **3e** was recorded on a Finnigan MAT INCOS-50 instrument (70 eV). High resolution mass spectra were recorded on a Bruker maXis instrument with ESI ionization. Elemental analysis was performed on an elemental analyzer Euro EA3028-NT for the simultaneous determination of C, H, N. Melting points were determined on a Melting Point M-565 instrument.

Single crystal X-ray diffraction analysis was performed on an Xcalibur Ruby diffractometer with a CCD detector according to the standard method [MoK_α radiation, 295(2) K, ω-scanning with a step of 1°]. Absorption was taken into account empirically using the SCALE3 ABSPACK algorithm [31]. Structures were solved using the SHELXS program [32] and refined by full-matrix least squares in F^2 in the anisotropic approximation for all non-hydrogen atoms using the SHELXL program [33] with the OLEX2 graphical interface [34]. Hydrogen atoms were included into the refinement in the *rider* model (except for the hydrogen atoms of the OH and NH groups, refined independently in the isotropic approximation). The X-ray diffraction data were deposited at the Cambridge Crystallographic Data Center [CCDC 1994223 (**3e**) and 1994224 (**4e**)].

4-Hydroxy-4-methyl-2-oxo-*N*,6-diphenylcyclohexanecarboxamide (3a). To a solution of 0.020 mol of acetoacetanilide **1** in 10 mL of ethanol was added 10 mol % of potassium hydroxide. The resulting mixture was stirred for 5 min, then 0.025 mol of benzalacetone **2** was added. The resulting mixture was stirred until the reagents were completely dissolved and kept for 1–2 days until a precipitate was formed. The resulting precipitate was filtered off and recrystallized from ethanol. Yield 47%, mp 184–186°C. IR spectrum, ν, cm^{-1}: 3520 (OH), 3328 (NH), 1712 (CO), 1660 (CONHAr). ^1H NMR spectrum, δ, ppm: 9.75 s (1H, NH), 7.44 d. d (2H, H-Ar, J = 8.5, 0.9 Hz), 7.34–7.25 m (4H, H-Ar), 7.22 d. d (2H, H-Ar, J = 10.8, 5.1 Hz), 7.18–7.13 m (1H, H-Ar), 6.98 t (1H, H-Ar, J = 7.4 Hz), 4.82 s (1H, OH), 3.87–3.77 m (2H, C^6H, C^1H), 2.69 d (1H, $C^3\underline{H}_AH_B$, J = 13.6 Hz), 2.36 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.7, 2.3 Hz), 2.09 d. d (1H, $C^5H_A\underline{H}_B$, J = 18.1, 7.2 Hz), 1.85 d. d (1H, $C^5\underline{H}_AH_B$, J = 9.4, 6.8 Hz), 1.28 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 206.0 (CO), 166.7 (CON), 143.5, 139.0, 128.5, 128.3, 127.2, 126.3, 123.0, 118.9, 71.7, 62.4, 53.4, 45.6, 41.0, 30.3 ($C^4\underline{Me}$). Found, %: C 74.53; H 6.58; N 4.09. $C_{20}H_{21}NO_3$. Calculated, %: C 74.28; H 6.55; N 4.33.

Compounds **3b**–**3k** were prepared similarly.

4-Hydroxy-4-methyl-2-oxo-6-phenyl-*N*-(*o*-tolyl)-cyclohexanecarboxamide (3b). Yield 51%, mp 200–202°C. IR spectrum, ν, cm^{-1}: 3512 (OH), 3304 (NH), 1712 (CO), 1660 (CONHAr). ^1H NMR spectrum, δ, ppm: 9.06 s (1H, NH), 7.36–7.28 m (4H, H-Ar), 7.22–7.17 m (1H, H-Ar), 7.12–6.97 m (4H, H-Ar), 4.77 s (1H, OH), 3.89 d. d (1H, C^1H, J = 12.6, 5.3 Hz), 3.80 t. d (1H, C^6H, J = 12.3, 3.8 Hz), 2.68 d (1H, $C^3H_A\underline{H}_B$, J = 13.8 Hz), 2.37 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.9, 2.3 Hz), 2.09 d. d (1H, $C^5H_A\underline{H}_B$, J = 25.2, 12.4 Hz), 1.91–1.85 m (1H, $C^5\underline{H}_AH_B$), 1.88 s (3H, Me), 1.28 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 205.9 (CO), 166.7 (CON), 143.4, 136.1, 131.9, 130.0, 128.2, 127.5, 127.4, 126.3, 125.6, 125.2, 125.1, 71.6, 61.9, 53.5, 40.2, 30.3 ($C^4\underline{Me}$), 17.39 ($\underline{Me}$). Mass spectrum (ESI), *m/z*: 360.2570 $[M + Na]^+$ (calcd. for $C_{21}H_{23}NO_3Na$: 360.1579).

***N*-(4-Chlorophenyl)-4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexanecarboxamide (3c).** Yield 89%, mp 175–176°C. IR spectrum, ν, cm^{-1}: 3488 (OH), 3304 (NH), 1712 (CO), 1688 (CONHAr). ^1H NMR spectrum, δ, ppm: 9.84 s (1H, NH), 7.48–7.43 m (2H, H-Ar), 7.36–7.33 m (2H, H-Ar), 7.31–7.26 m (4H, H-Ar), 7.21–7.16 m (1H, H-Ar), 4.78 s (1H, OH), 3.73–3.65 m (2H, C^6H, C^1H), 2.70 d (1H, $C^3\underline{H}_AH_B$, J = 13.7 Hz), 2.36 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.7, 2.1 Hz), 2.09 d. d (1H, $C^5H_A\underline{H}_B$, J = 14.8, 10.3 Hz), 1.89–1.82 m (1H, $C^5\underline{H}_AH_B$), 1.27 s (3H, Me). Mass spectrum (ESI), *m/z*: 380.1024 $[M + Na]^+$ (calcd. for $C_{20}H_{20}ClNO_3Na$: 380.1029).

4-Hydroxy-4-methyl-*N*-(2,4-dimethylphenyl)-2-oxo-6-phenylcyclohexanecarboxamide (3d). Yield 54%, mp 203–205°C. IR spectrum, ν, cm^{-1}: 3430 (OH), 3397 (NH), 1704 (CO), 1680 (CONHAr). ^1H NMR spectrum, δ, ppm: 9.03 s (1H, NH), 7.35–7.28 m (4H, H-Ar), 7.22–7.17 m (1H, H-Ar), 6.96–6.84 (3H, H-Ar), 4.81 s (1H, OH), 3.86 d (1H, C^1H, J = 12.3 Hz), 3.80 t. d (1H, C^6H, J = 12.1, 3.6 Hz), 2.67 d (1H, $C^3\underline{H}_AH_B$, J = 13.8 Hz), 2.36 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.8, 2.2 Hz), 2.19 s (3H, Me), 2.08 t (1H,

$C^5H_A\underline{H}_B$, J = 12.8 Hz), 1.90–1.84 m (1H, $C^5\underline{H}_AH_B$), 1.81 s (3H, Me), 1.28 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 206.5 (CO), 167.1 (CON), 143.9, 134.6, 134.0, 132.4, 128.7, 127.9, 126.7, 126.6, 125.8, 72.2, 62.4, 53.9, 46.0, 30.8 ($C^4\underline{Me}$), 20.9 (Me), 17.39 (Me). Mass spectrum (ESI), *m/z*: 380.1735 $[M + Na]^+$ (calcd. for $C_{22}H_{25}NO_3Na$: 374.1727).

4-Hydroxy-4-methyl-*N*-(2-methoxyphenyl)-2-oxo-6-phenylcyclohexanecarboxamide (3e). Yield 78%, mp 186–188°C. IR spectrum, ν, cm^{-1}: 3450 (OH), 3409 (NH), 1705 (CO), 1679 (CONHAr). ^{1}H NMR spectrum, δ, ppm: 8.92 s (1H, NH), 7.93 d (1H, H-Ar, J = 12.3 Hz), 7.33–7.25 m (4H, H-Ar), 7.18–7.13 m (1H, H-Ar), 7.01–6.94 m (2H, H-Ar), 6.80 d. d. d (1H, H-Ar, J = 8.6, 6.3, 2.5 Hz), 4.81 s (1H, OH), 4.20 d (1H, C^1H, J = 12.2 Hz), 3.81–3.73 m (1H, C^6H), 3.78 s (3H, OMe), 2.62 d (1H, $C^3\underline{H}_AH_B$, J = 13.5 Hz), 2.34 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.6, 2.1 Hz), 2.19 s (3H, Me), 1.99 t (1H, $C^5H_A\underline{H}_B$, J = 13.2 Hz), 1.89–1.83 m (1H, $C^5\underline{H}_AH_B$), 1.27 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 206.6 (CO), 167.5 (CON), 148.9, 144.1, 128.7, 127.8, 126.7, 124.1, 121.0, 120.6, 111.5, 72.1, 62.5, 56.1, 54.0, 46.4 (OMe), 41.6, 30.8 ($C^4\underline{Me}$). Mass spectrum, *m/z* (I_{rel}, %): 335 (56) $[M - H_2O]^+$, 203 (24) $[M - CONHC_6H_4OCH_3]^+$, 185 (36) $[M - H_2O - CONHC_6H_4OCH_3]^+$. Mass spectrum (ESI), *m/z*: 376.1531 $[M+Na]^+$ (calcd. for $C_{21}H_{23}NO_4Na$: 376.1519).

Crystals of compound **3e** are triclinic, space group *P*-1, $C_{21}H_{23}NO_4$, M 353.40, a = 5.6959(19), b = 12.519(2), c = 13.128(4) Å, α = 89.692(20)°, β = 79.57(3)°, γ = 81.71(2)°, V = 910.8(4) Å^3, Z = 2, d_{calc} = 1.289 g/cm^3, μ = 0.089 mm^{-1}. The crystal was refined using a data file with the reflection intensities of the HKLF 5 format as a twin with two components. Final refinement parameters are: R_1 = 0.1223 [for 2688 reflections with $I > 2\sigma(I)$], wR_2 = 0.3172 (for all 5601 independent reflections), S = 1.034, ratio of twinning components is 0.605(3) : 0.395(3).

***N*-(2-Chlorophenyl)-4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexanecarboxamide (3f).** Yield 69%, mp 192–194°C. IR spectrum, ν, cm^{-1}: 3487 (OH), 3379 (NH), 1711 (CO), 1665 (CONHAr). ^{1}H NMR spectrum, δ, ppm: 9.28 s (1H, NH), 7.60 d (1H, H-Ar, J = 7.3 Hz), 7.39 d. d (1H, H-Ar, J = 8.0, 1.4 Hz), 7.35–7.27 m (4H, H-Ar), 7.26–7.15 m (2H, H-Ar), 7.09 t. d (1H, H-Ar, J = 7.8, 1.5 Hz), 4.83 s (1H, OH), 4.13 d (1H, C^1H, J = 12.3 Hz), 3.78 t. d (1H, C^6H, J = 12.6, 3.9 Hz), 2.66 d (1H, $C^3\underline{H}_AH_B$, J = 13.6 Hz), 2.36 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.6, 2.2 Hz), 2.04 t (1H, $C^5H_A\underline{H}_B$, J = 13.2 Hz), 1.90–1.83 m (1H, $C^5\underline{H}_AH_B$), 1.28 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 206.3 (CO), 167.8 (CON), 143.8, 135.2, 129.8, 128.8, 127.8, 127.6, 126.8, 126.1, 125.6, 125.5, 72.2, 62.2, 53.9, 46.3, 41.7, 30.8 ($C^4\underline{Me}$). Mass spectrum (ESI), *m/z*: 358.1159 $[M + H]^+$ (calcd. for $C_{20}H_{21}ClNO_3$: 358.1204).

6-(4-Chlorophenyl)-4-hydroxy-4-methyl-2-oxo-*N*-phenylcyclohexanecarboxamide (3g). Yield 52%, mp 218–220°C. IR spectrum, ν, cm^{-1}: 3526 (OH), 3315 (NH), 1716 (CO), 1671 (CONHAr). ^{1}H NMR spectrum, δ, ppm: 9.90 s (1H, NH), 7.44 d (2H, H-Ar, J = 7.6 Hz), 7.40–7.33 m (4H, H-Ar), 7.26–7.20 m (2H, H-Ar), 7.00 q. d (1H, H-Ar, J = 2.3, 1.1 Hz), 4.80 s (1H, OH), 3.79 d (1H, C^1H, J = 12.7 Hz), 3.76–3.67 m (1H, C^6H), 2.69 d (1H, $C^3\underline{H}_AH_B$, J = 13.8 Hz), 2.37 d (1H, $C^3H_A\underline{H}_B$, J = 13.7, 2.3 Hz), 2.10 t (1H, $C^5H_A\underline{H}_B$, J = 13.2 Hz), 1.88–1.82 m (1H, $C^5\underline{H}_AH_B$), 1.28 s (3H, Me). Mass spectrum (ESI), *m/z*: 380.1037 $[M + Na]^+$ (calcd. for $C_{20}H_{20}ClNO_3Na$: 380.1024).

***N*-(2-Chlorophenyl)-6-(4-chlorophenyl)-4-hydroxy-4-methyl-2-oxocyclohexanecarboxamide (3h).** Yield 63%, mp 203–205°C. IR spectrum, ν, cm^{-1}: 3512 (OH), 3317 (NH), 1705 (CO), 1668 (CONHAr). ^{1}H NMR spectrum, δ, ppm: 9.25 s (1H, NH), 7.60 d (1H, H-Ar, J = 7.3 Hz), 7.40 d. d (1H, H-Ar, J = 8.0, 1.4 Hz), 7.38–7.32 m (4H, H-Ar), 7.27–7.21 m (1H, H-Ar), 7.13–7.08 m (1H, H-Ar), 4.81 s (1H, OH), 4.07 d (1H, C^1H, J = 12.3 Hz), 3.78 t. d (1H, C^6H, J = 12.6, 3.9 Hz), 2.66 d (1H, $C^3\underline{H}_AH_B$, J = 13.7 Hz), 2.37 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.7, 2.3 Hz), 2.06 t (1H, $C^5H_A\underline{H}_B$, J = 13.2 Hz), 1.90–1.83 m (1H, $C^5\underline{H}_AH_B$), 1.28 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 205.4 (CO), 167.2 (CON), 142.3, 134.7, 130.9, 129.3, 129.2, 128.2, 127.2, 125.8, 125.3, 125.2, 71.6, 61.7, 53.4, 40.7, 40.0, 30.3 ($C^4\underline{Me}$). Found, %: C 67.45; H 4.72; N 3.78. $C_{20}H_{19}Cl_2NO_3$. Calculated, %: C 67.37; H 4.86; N 3.58.

***N*,6-Di-(4-chlorophenyl)-4-hydroxy-4-methyl-2-oxocyclohexanecarboxamide (3i).** Yield 42%, mp 220–224°C. IR spectrum, ν, cm^{-1}: 3523 (OH), 3302 (NH), 1709 (CO), 1665 (CONHAr). ^{1}H NMR spectrum, δ, ppm: 9.90 s (1H, NH), 7.47 d (2H, H-Ar, J = 8.9 Hz), 7.37–7.32 m (4H, H-Ar), 7.28 d. d (2H, H-Ar, J = 9.4, 2.4 Hz), 4.85 s (1H, OH), 3.87–3.78 m (1H, C^6H), 3.76 d (1H, C^1H, J = 12.2 Hz), 2.71 d (1H, $C^3\underline{H}_AH_B$, J = 13.6 Hz), 2.36 d. d (1H, $C^3H_A\underline{H}_B$, J = 13.6, 1.9 Hz), 2.12 t (1H, $C^5H_A\underline{H}_B$, J = 12.8 Hz), 1.87–1.80 m (1H, $C^5\underline{H}_AH_B$), 1.27 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 205.6 (CO), 166.8 (CON), 142.4, 137.7, 130.9, 129.2, 128.5, 128.3, 126.7, 120.5, 71.7, 62.4, 53.4, 45.6, 40.5, 30.2 ($C^4\underline{Me}$). Found, %: C 67.54; H 4.98; N

3.74. $C_{20}H_{19}Cl_2NO_3$. Calculated, %: C 67.37; H 4.86; N 3.58.

6-(4-Chlorophenyl)-4-hydroxy-*N*-(2-methoxyphenyl)-4-methyl-2-oxocyclohexanecarboxamide (3j). Yield 49%, mp 180–182°C. IR spectrum, ν, cm^{-1}: 3530 (OH), 3331 (NH), 1712 (CO), 1662 (CONHAr). ^1H NMR spectrum, δ, ppm: 8.89 s (1H, NH), 7.92 d (1H, H-Ar, *J* = 7.5 Hz), 7.42–7.30 m (4H, H-Ar), 7.02–6.94 m (2H, H-Ar), 6.81 d. d. d (1H, H-Ar, *J* = 14.6, 8.5, 5.0 Hz), 4.77 s (1H, OH), 4.15 d (1H, C^1H, *J* = 12.2 Hz), 3.82–3.74 m (1H, C^6H), 3.78 s (3H, OMe), 2.62 d (1H, $C^3\underline{H}_AH_B$, *J* = 13.6 Hz), 2.35 d. d (1H, $C^3H_A\underline{H}_B$, *J* = 13.6, 2.3 Hz), 2.01 d. d (1H, $C^5H_A\underline{H}_B$, *J* = 15.3, 11.0 Hz), 1.88–1.82 m (1H, $C^5\underline{H}_AH_B$), 1.27 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 205.6 (CO), 166.8 (CON), 148.6, 142.6, 130.8, 129.4, 129.2, 128.2, 127.4, 123.8, 120.7, 120.2, 111.1, 71.6, 62.0, 55.7, 53.5 (OMe), 40.7, 30.3 ($C^4\underline{Me}$). Found, %: C 65.32; H 5.81; N 3.50. $C_{21}H_{22}ClNO_4$. Calculated, %: C 65.10; H 5.68; N 3.62.

6-(4-Chlorophenyl)-4-hydroxy-4-methyl-*N*-(2,4-dimethylphenyl)-2-oxocyclohexanecarboxamide (3k). Yield 57%, mp 220–222°C. IR spectrum, ν, cm^{-1}: 3538 (OH), 3368 (NH), 1708 (CO), 1680 (CONHAr). ^1H NMR spectrum, δ, ppm: 9.01 s (1H, NH), 7.41–7.32 m (4H, H-Ar), 6.97–6.85 m (3H, H-Ar), 4.78 s (1H, OH), 3.85–3.73 m (2H, C^1H, C^6H), 2.66 d (1H, $C^3\underline{H}_AH_B$, *J* = 13.8 Hz), 2.36 d. d (1H, $C^3H_A\underline{H}_B$, *J* = 13.9, 2.2 Hz), 2.18 s (3H, OMe), 2.13–2.04 m (1H, $C^5H_A\underline{H}_B$), 1.88–1.83 m (1H, $C^5\underline{H}_AH_B$), 1.84 s (3H, OMe), 1.28 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 205.5 (CO), 166.5 (CON), 142.5, 134.2, 133.5, 131.9, 130.8, 130.6, 129.3, 128.1, 126.2, 125.3, 71.6, 61.8, 53.4, 44.8, 40.2, 30.3 ($C^4\underline{Me}$), 20.4 (Me), 17.3 (Me). Found, %: C 68.27; H 6.41; N 3.48. $C_{22}H_{24}ClNO_3$. Calculated, %: C 68.55; H 6.23; N 3.64.

4-Methyl-2-oxo-*N*,6-diphenyl-3-cyclohexenecarboxamide (4a). To a solution of 0.020 mol of acetoacetanilide **1** in 10 mL of ethanol was added 20 mol % of potassium hydroxide. The resulting mixture was stirred for 5 min, then 0.025 mol of benzalacetone **2** was added. The mixture was stirred until the reagents were completely dissolved and kept for 1–2 days until a precipitate was formed. The precipitate was filtered off and recrystallized from ethanol. Yield 62%, mp 206–208°C. ^1H NMR spectrum, δ, ppm: 9.83 s (1H, NH), 7.44 d. d (2H, H-Ar, *J* = 8.5, 1.0 Hz), 7.38–7.34 m (2H, H-Ar), 7.29 t (2H, H-Ar, *J* = 7.6 Hz), 7.25–7.16 m (3H, H-Ar), 6.99 d. d (1H, H-Ar, *J* = 10.6, 4.2 Hz), 5.99 s (1H, =C^3H), 3.83 d (1H, C^1H, *J* = 12.9 Hz), 3.76–3.65 m (1H, C^6H), 2.67 d. d (1H, $C^3\underline{H}_AH_B$, *J* = 18.6, 11.5 Hz), 2.36 d. d. d (1H, $C^3H_A\underline{H}_B$, *J* = 8.8, 8.2, 4.7 Hz), 2.01 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 194.9 (CO), 167.4 (CON), 163.2, 142.2, 138.8, 128.6, 128.3, 127.3, 126.7, 124.9, 123.2, 119.0, 59.3, 42.8, 38.5, 23.7 ($C^4\underline{Me}$). Mass spectrum (ESI), *m/z*: 328.1320 $[M + Na]^+$ (calcd. for $C_{20}H_{19}NO_2Na$: 328.1308).

***N*-(4-Chlorophenyl)-4-methyl-2-oxo-6-phenyl-3-cyclohexenecarboxamide (4b)** was prepared similarly. Yield 58%, mp 168–170°C. IR spectrum (mineral oil), ν, cm^{-1}: 3314 (NH), 1673 (CO), 1664 (CONHAr). ^1H NMR spectrum, δ, ppm: 10.04 s (1H, NH), 7.48–7.45 m (2H, H-Ar), 7.37–7.33 m (2H, H-Ar), 7.31–7.36 m (4H, H-Ar), 7.21–7.16 m (1H, H-Ar), 5.98 s (1H, =C^3H), 3.80 d (1H, C^1H, *J* = 12.8 Hz), 3.74–3.66 m (1H, C^6H), 2.68 d. d (1H, $C^3\underline{H}_AH_B$, *J* = 17.2, 11.7 Hz), 2.52 d. d. d (1H, $C^3H_A\underline{H}_B$, *J* = 8.8, 5.9, 3.5 Hz), 2.01 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 194.7 (CO), 167.6 (CON), 163.3, 142.1, 137.7, 128.5, 128.3, 127.8, 126.7, 124.8, 120.6, 59.5, 42.8, 38.5, 23.7 ($C^4\underline{Me}$). Found, %: C 70.51; H 5.38; N 4.34. $C_{20}H_{18}ClNO_2$. Calculated, %: C 70.69; H 5.30; N 4.12.

4-Methyl-2-oxo-6-phenyl-3-cyclohexenecarboxamide (4c). To a solution of 0.020 mol of acetoacetanilide **1** in 10 mL of ethanol was added 10 or 20 mol % of potassium hydroxide. The resulting mixture was stirred for 5 min, then 0.025 mol of benzalacetone **2** was added. The mixture was stirred until the reagents were completely dissolved and kept for 1–2 days until a precipitate was formed. The precipitate was filtered off and recrystallized from ethanol. Yield 26%, mp 116–118°C. IR spectrum (mineral oil), ν, cm^{-1}: 3429 (NH), 1662 (CO), 1610 (CON). ^1H NMR spectrum, δ, ppm: 7.35–7.27 m (5H, H-Ar, $N\underline{H}_AH_B$), 7.24–7.19 m (1H, H-Ar), 6.80 s (1H, H-Ar, $NH_A\underline{H}_B$), 5.91 s (1H, =C^3H), 3.61–3.50 m (2H, C^1H, C^6H), 2.61–2.53 m (1H, $C^3\underline{H}_AH_B$), 2.49–2.42 m (1H, $C^3H_A\underline{H}_B$), 1.97 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 195.5 (CO), 170.8 (CON), 163.0, 143.0, 128.7, 127.9, 127.0, 125.5, 58.6, 43.3, 24.1 ($C^4\underline{Me}$). Mass spectrum (ESI), *m/z*: 252.0995 $[M + Na]^+$ (calcd. for $C_{14}H_{15}NO_2Na$: 252.1004).

***N*,4-Dimethyl-2-oxo-6-phenyl-3-cyclohexenecarboxamide (4d)** was prepared similarly. Yield 32%, mp 168–170°C. ^1H NMR spectrum, δ, ppm: 7.75 d. d (1H, NH, *J* = 8.6, 4.1 Hz), 7.30–7.27 m (4H, H-Ar), 7.24–7.17 m (1H, H-Ar), 5.91 s (1H, =C^3H), 3.58 d. d. d (1H, C^6H, *J* = 12.6, 10.8, 4.7 Hz), 3.51 d (1H, C^1H, *J* = 12.5 Hz), 2.59 d. d (1H, $C^3\underline{H}_AH_B$, *J* = 18.3, 10.7 Hz), 2.47 d (1H, $C^3H_A\underline{H}_B$, *J* = 4.7 Hz), 2.47 d (3H, NMe, *J* = 4.6 Hz), 1.97 s (3H, Me). ^{13}C NMR spectrum, δ_C, ppm: 195.0 (CO), 168.8 (CON),

162.6, 142.5, 128.2, 127.3, 126.5, 125.0, 55.4, 42.7, 38.3, 25.3 (NMe), 23.7 (C^4Me).Found, %: C 74.29; H 6.78; N 5.83. $C_{15}H_{17}NO_2$. Calculated, %: C 74.03; H 6.99; N 5.76.

Crystals of compound **4d** are triclinic, space group *P*-1, $C_{15}H_{17}NO_2$, *M* 243.29, $a = 9.4105(13)$, $b = 11.5562(15)$, $c = 12.882(2)$ Å, $\alpha = 75.761(13)$, $\beta = 87.700(12)$, $\gamma = 89.897(11)°$, $V = 1356.8(4)$ Å^3, $Z = 4$, $d_{calc} = 1.191$ g/cm^3, $\mu = 0.079$ mm^{-1}. Final refinement parameters are: $R_1 = 0.0727$ [for 3344 reflections with $I>2\sigma(I)$], $wR_2 = 0.2477$ (for all 6286 independent reflections), $S = 1.019$.

The acute toxicity of cyclohexanone derivatives was studied using the Prozorovskii express method [35]. The tested substances were injected intraperitoneally at doses of 1000, 1260, 1500, and 2000 mg/kg. The results are shown in Table 1.

The analgesic activity was assessed by the "hot plate" thermal stimulation method and the acetic cramps model [36]. In the "hot plate" test, the test substances were injected intraperitoneally at a dose of 50 mg/kg as a suspension in 2% starch mucus 60 min before placing the animals on a metal plate heated to 52°C. An indicator of nociception was the duration of the animal's stay on the hot plate before the onset of a defensive reaction (licking, shaking, jumping), measured in seconds.

The pain reaction in the acetic cramps model test was induced by intraperitoneal administration of 0.75% acetic acid (at the rate of 0.1 mL per 10 g of animal weight) 30 min after intraperitoneal administration of the test compounds at a dose of 50 mg/kg. During the next 20 min after the injection of acetic acid, the number of writhing was counted for each animal. The control group of animals was injected with an equivalent volume of 2% starch mucus. Metamizole sodium (analgin) at a dose of 50 mg/kg, administered similarly to the test compounds, was used as a comparison standard. The results were statistically processed using Student's t test. The effect was considered significant at $p < 0.05$.

The studies were performed in compliance with all applicable international, national and institutional guidelines for the care and use of animals.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

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