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Reactions of 2-Acetyl-5-hydroxy-5-methyl-3-phenylcyclohexanone and Alkyl 4-Hydroxy-4-methyl-2-oxo-6-phenylcyclohexanecarboxylates with Nucleophilic Reagents

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Abstract—A series of novel enamines, bis(enamines), benzisoxazoles, tetrahydroindazoles, benzophenone hydrazones were obtained via reactions of 2-acetyl-5-hydroxy-5-methylcyclohexanone and alkyl 4-hydroxy-4-methyl-2-oxocyclohexanecarboxylates with nucleophilic reagents such as aliphatic and aromatic amines, diamines, hydroxylamine, hydrazine, phenylhydrazine, benzophenone hydrazone. The structures of the compounds obtained were proved by IR and ^{1}H NMR spectroscopy methods.

Keywords: 2-acetylcyclohexanone, alkyl 2-oxocyclohexanecarboxylates, enamines, indazoles, benzisoxazoles, hydrazones

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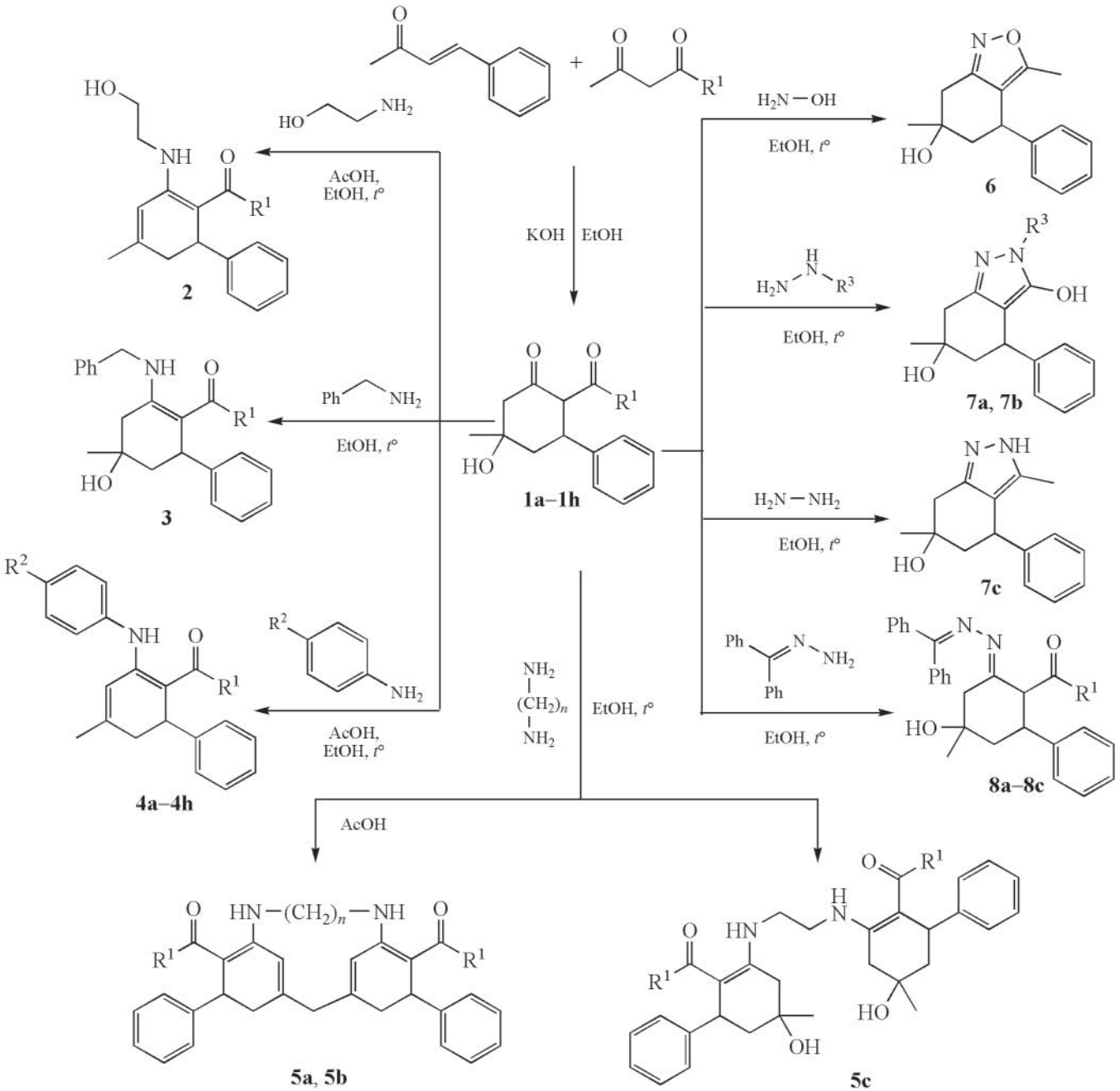
Cyclohexanones and their derivatives are an important scaffolds for the synthesis of new heterocyclic compounds with antimicrobial [1–4], analgesic [5], anti-phage [6], antiarrhythmic [7], hypoglycemic [8], anti-cancer [9], anti-convulsive [10], anti-inflammatory [11] and sedative activity [5, 10]. It is known that the products of reaction of compounds bearing a cyclohexanone fragment with nucleophilic reagents are good diuretics [12], enzyme inhibitors such as cholinesterase [13], and can be used as antiprotozoal [14], antitripanosomal [15] and anthelmintic pharmaceuticals [16]. In addition, there are positive results of studies of these compounds as ligand agonists of H1 receptors of the body, which has pharmacotherapeutic potential in the treatment of neuro-degenerative and neuropsychiatric disorders, as well as various types of allergies [17, 18].

Recently, we have obtained 2-acetyl-5-hydroxy-5-methyl-3-phenylcyclohexanone **1a** and alkyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexanecarboxylates **1b**–**1h** by reacting benzalacetone with acetylacetone and acetoacetates, respectively, in the presence of potassium hydroxide in ethanol at room temperature and studied their antimicrobial action against the strains of *St. aureus* and *E. coli* [19]. Herein we reported the synthesis of new enamines, bis(enamines), benzisoxazoles, tetrahydroindazoles, and benzophenone hydrazones **2–8** based on reactions of cyclohexanones **1b**–**1h** with some *N*-nucleophilic reagents.

The reactions of 2-acetyl-cyclohexanone **1a** and alkyl 2-oxocyclohexane-carboxylates **1b**, **1d**, and **1e** with mononucleophilic reagents, such as alkyl and aryl amines, were performed when boiling equimolar amounts of the reagents in ethyl alcohol, in some cases with the addition of a catalytic amount of acetic acid. The amination of the carbonyl group of the alicyclic compound took place, which led to the formation of the corresponding enamines **2–4** (Scheme 1).

Alkyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylates **1d** and **1e** reacted with aliphatic diamines, such as ethylene diamine and 1,3-propanediamine, in ethanol when heated for 2–4 h. The reactions proceeded regioselectively with the participation of both amino groups of the diamine and the carbonyl group of the alicycle of two cyclohexanone molecules with the formation of new bis(enamine) derivatives **5a**–**5c** (Scheme 1).

Scheme 1.



R^1 = Me (**1a**, **6**); R^1 = OMe (**1b**, **2**, **3**); R^1 = Me, R^2 = OMe (**4a**); R^1 = OMe, R^2 = OMe (**4b**); R^1 = OMe, R^2 = F (**4c**); R^1 = OMe, R^2 = H (**4d**); R^1 = OMe, R^2 = Cl (**4e**); R^1 = O-*i*Pr, R^2 = Me (**4f**); R^1 = O-*i*Bu, R^2 = Me (**4g**); R^1 = O-*i*Bu, R^2 = Me (**4h**); R^1 = O-*i*Pr, n = 2 (**5a**); R^1 = O-*i*Pr, n = 3 (**5b**); R^1 = O-*i*Bu, n = 2 (**5c**); R^1 = OEt, R^3 = Ph (**7a**); R^1 = OEt, R^3 = H (**7b**); R^1 = OBn (**8a**); R^1 = O-*i*Pr (**8b**); R^1 = OEt (**8c**).

The resulting compounds **2–5** are yellow crystalline substances, soluble in acetone, DMSO, DMF, and when heated, in ethyl, isopropyl, *n*-butyl alcohols and acetonitrile, insoluble in water.

In the IR spectra of enamines **3**, **4a**–**4h** and bis-(enamines) **5a**–c, there are strong absorption bands of the NH group (3296–3266 cm^{-1}) and the ester moiety (1696–1740 cm^{-1}). The absorption band of the C=C bond

(1596–1564 cm^{-1}) is present in the spectra of compounds **4a**–**4h**. The ^{1}H NMR spectra of compounds **2–5** contain singlet signals of the methyl group at the C^5 atom of the ring (1.21–1.78 ppm), multiplets of the aromatic protons (6.98–7.40 ppm) and doublets of the protons at the C^6 atom (1.82–2.88 ppm) with spin-spin coupling constants within 15.8–17.0 Hz. The absence of a signal from the C^{2}H proton in the spectrum of compound **1a** (C^{1}H for compounds **1b**, **1d**, **1e**), and the presence of a signal from the proton of the NH group (9.07–13.07 ppm) confirms the enamine formation. The mass spectrum of compound **4g** contains a peak of a molecular ion with *m*/z 375, as well as peaks of fragmentary ions with c *m/z* 360 $[M-CH_3]^+$, 318 $[M-CH_2CH(CH_3)_2]^+$, 298 $[M-C_6H_5]^+$ and 274 $[M-COOCH_2CH(CH_3)_2]^+$ that confirms the proposed structure.

The formation of enamine form of compounds **2–5** is explained by the existence of an intramolecular hydrogen bond between the hydrogen atom of the amino group and the oxygen atom of the ester carbonyl group. Dehydration of compounds **2–5** involving the C^{3}H proton is due to the presence of a catalytic amount of acetic acid in the reaction medium.

In order to obtain new bicyclic derivatives containing biologically active isoxazole and pyrazole fragments, we performed the reactions of cyclohexanones **1a** and **1c** with hydroxylamine, phenylhydrazine and hydrazine hydrate in ethyl alcohol when heated. During the interaction of these reagents, nucleophilic substitution of the oxygen atom of the carbonyl group of the ring was observed, followed by heterocyclization and the formation of 4,5,6,7-tetrahydrobenzo[*c*]isoxazole **6** and 4,5,6,7-tetrahydro-2*H*-indazoles **7a**–**7c** with yield of 41 and 61–93%, respectively (Scheme 1). The yield of compound **6** is lower in comparison with derivatives **7a**–**7c** due to the lower nucleophilicity of the reagent.

Benzisoxazole **6** and tetrahydroindazoles **7a**–**7c** are colorless crystalline substances, soluble in DMF and DMSO, poorly soluble in ethyl and *n*-butyl alcohols, acetonitrile, dioxane and insoluble in water.

In the IR spectra of compounds **6** and **7a**–**7c**, there are strong absorption bands of the OH group (3312–3400 cm^{-1}) and the conjugated C=N bond (1600–1640 cm^{-1}). There are no bands due to stretching vibrations of the carbonyl groups characteristic of the starting cyclohexanones in the spectra of compounds **6**, **7a**–**7c**. In the spectrum of **7c**, a band is observed due to vibrations of the secondary NH group (3312 cm^{-1}). The ^{1}H NMR spectra of compounds **6** and **7a**–**7c** contain singlet signals of the methyl groups at the C^6 atom (1.21–1.32 ppm), a triplet (2.46–2.62 ppm, J = 14.3–16.8 Hz) and a doublet of doublets of the protons of the methylene group at the C^5 atom (2.56–2.74 ppm, J = 14.3–16.5, 1.4–1.6 Hz), as well as doublets from the C^{7}H proton (1.40–1.62 and 1.62–1.96 ppm) as the AB system with spin-spin coupling constants within 11.6–13.4 Hz, and multiplet signals of aromatic protons (7.13–7.68 ppm). In the spectra of compounds **6** and **7c**, additional singlet signals of the methyl groups at the C^3 atom (1.72 and 1.48 ppm) are observed. In the case of tetrahydroindazole **7b**, a broad singlet of two protons of the OH and NH groups was found (10.20 ppm).

Compounds **7a**, **7b** reacted with an alcoholic solution of iron(III) chloride to form an intense violet-purple solution. This fact, along with literature data for analogous compounds, whose structure was confirmed using X-ray diffraction data [20] and the results of IR, ^{1}H NMR spectroscopy, indicates enolization of the carbonyl group at the C^3 atom of heterocycle.

The reaction of alkyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylates **1b**, **1d**, and **1f** with benzophenone hydrazone led to the formation of the corresponding hydrazones **8a**–**8c** (Scheme 1). Structure of compounds **8a**–**8c** was confirmed by the data of IR, ^{1}H NMR spectroscopy and mass spectrometry.

In conclusion, the reaction of 2-acetyl-5-hydroxy-5-methylcyclohexanone and alkyl 4-hydroxy-4-methyl-2-oxocyclohexanecarboxylates with alkyl and aryl amines leads to the formation of the corresponding enamines and bis(enamines). The interaction of functionalized cyclohexanones with binucleophilic reagents, such as hydroxylamine and hydrazine, is accompanied by cyclization with the formation of new benzisoxazole and 4,5,6,7-tetrahydro-2*H*-indazole derivatives. In the case of the reaction of cyclohexanones with benzophenone hydrazone, the corresponding hydrazones form.

EXPERIMENTAL

IR spectra were taken on a Specord M-80 instrument from mineral oil. ^{1}H NMR spectra were recorded on a Bruker AM-300 spectrometer with an operating frequency of 300 MHz from DMSO-d_6 solutions, the internal standard was tetramethylsilane. Mass spectra were taken on a Finnigan MAT INCOS-50 instrument (70 eV). Elemental analysis was performed on a PerkinElmer 2400 instru-

ment. Melting points were determined on a Melting Point M-565 instrument.

2-Acetyl-5-hydroxy-5-methyl-3-phenylcyclohexanone **1a** and alkyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexanecarboxylates **1b**–**1h** were prepared according to a known procedure [19].

Methyl 5-hydroxy-3-[(2-hydroxyethyl)amino]-5-methyl-1,4,5,6-tetrahydro-(1,1'-biphenyl)-2-carboxylate (2). To a solution of 0.01 mol of methyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylate **1b** in 19.6 mL of ethanol were added 0.02 mol of ethanolamine and 0.4 mL of glacial acetic acid. The resulting mixture was boiled for 6 h. The precipitate formed was filtered off, dried and recrystallized from ethanol. Yield 51%, mp 143–145°C. ^{1}H NMR spectrum, δ, ppm: 1.76 s (3H, Me), 2.22 d. d (1H, $C^6H_A\underline{H}_B$, J = 16.9, 1.4 Hz), 2.71 d. d (1H, $C^6\underline{H}_AH_B$, J = 16.5, 8.1 Hz), 3.33 m (2H, $NH\underline{CH_2}CH_2OH$), 3.44 s (3H, OMe), 3.53 m (2H, $NHCH_2\underline{CH_2}OH$), 3.98 m (1H, C^1H), 4.76 t (1H, $NHCH_2CH_2\underline{OH}$, J = 5.5 Hz), 6.20 s (1H, C^4H), 7.05–7.17 m (5H, Ph), 9.13 t (1H, $\underline{NH}CH_2CH_2OH$, J = 5.8 Hz). Found, %: C 71.23; H 7.41; N 4.68. $C_{17}H_{21}NO_3$. Calculated, %: C 71.06; H 7.37; N 4.87.

Methyl 3-(benzylamino)-5-hydroxy-5-methyl-1,4,5,6-tetrahydro-(1,1'-biphenyl)-2-carboxylate (3). To a solution of 0.01 mol of methyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylate **1b** in 10 mL of ethanol was added 0.01 mol of benzyl amine. The resulting mixture was boiled for 10 min, then cooled. The formed precipitate was filtered off, dried and recrystallized from ethanol. Yield 24%, mp 115–117°C. IR spectrum, ν, cm^{-1}: 3472 (OH), 3272 (NH), 1740 (C=O), 1592 (Ar). ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, Me), 1.82 d (1H, $C^6H_A\underline{H}_B$, J = 15.8 Hz), 1.98 d (1H, $C^6\underline{H}_AH_B$, J = 15.9 Hz), 2.26 d (1H, $C^4H_A\underline{H}_B$, J = 12.8 Hz), 2.72 d (1H, $C^4\underline{H}_AH_B$, J = 12.8 Hz), 3.38 s (3H, OMe), 3.71 m (1H, C^1H), 4.35 d (2H, $NH\underline{CH_2}C_6H_5$, J = 6.5 Hz), 7.01–7.25 m (10H, 2Ph), 9.15 t (1H, NH, J = 6.3 Hz). Found, %: C 75.01; H 7.14; N 4.10. $C_{22}H_{25}NO_3$. Calculated, %: C 75.19; H 7.17; N 3.99.

General procedure for the synthesis of compounds 4a–4h. To a solution of 0.005 mol of 4-hydroxy-4-methyl-6-phenyl-cyclohexanone **1a** in 5 mL of ethyl alcohol were added 0.005 mol of the corresponding aryl amine and 0.1 mL of glacial acetic acid. The resulting mixture was boiled for 3–4 h, then cooled. The precipitate was filtered off, dried and recrystallized from ethanol.

5-Methyl-1-{3-[(4-methoxyphenyl)amino]-1,6-dihydro-(1,1'-biphenyl)-2-yl}ethanone (4a). Yield 60%, mp 120–122°C. IR spectrum, ν, cm^{-1}: 3223 (NH), 1660 (C=O), 1592 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.69 s (3H, Me), 1.88 s (3H, COMe), 2.33 d (1H, $C^6H_A\underline{H}_B$, J = 16.8 Hz), 2.93 d (1H, $C^6\underline{H}_AH_B$, J = 16.5 Hz), 3.77 s (3H, OMe), 4.08 m (1H, C^1H), 5.99 s (1H, C^4H), 6.98–7.21 m (9H, Ph, C_6H_4), 13.07 s (1H, NH). Found, %: C 79.06; H 7.00; N 4.02. $C_{22}H_{23}NO_2$. Calculated, %: C 79.25; H 6.95; N 4.20.

Methyl 5-methyl-3-[(4-methoxyphenyl)amino]-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate (4b). Yield 57%, mp 132–134°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1664 (C=O), 1592 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.67 s (3H, Me), 2.27 d (1H, $C^6H_A\underline{H}_B$, J = 15.9 Hz), 2.83 d (1H, $C^6\underline{H}_AH_B$, J = 16.1 Hz), 3.51 s (3H, OMe), 3.76 s (3H, OMe), 4.07 m (1H, C^1H), 5.90 s (1H, C^4H), 6.96–7.23 m (9H, Ph, C_6H_4), 10.52 s (1H, NH). Found, %: C 75.48; H 6.67; N 4.19. $C_{22}H_{23}NO_3$. Calculated, %: C 75.62; H 6.63; N 4.01.

Methyl 5-methyl-3-[(4-fluorophenyl)amino]-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate (4c). Yield 44%, mp 127–128°C. IR spectrum, ν, cm^{-1}: 3260 (NH), 1670 (C=O), 1580 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.70 s (3H, Me), 2.32 d (1H, $C^6H_A\underline{H}_B$, J = 16.7 Hz), 2.78 d (1H, $C^6\underline{H}_AH_B$, J = 16.7 Hz), 3.49 s (3H, OMe), 4.06 m (1H, C^1H), 5.86 s (1H, C^4H), 6.98–7.16 m (9H, Ph, C_6H_4), 10.44 s (1H, NH). Found, %: C 74.98; H 5.92; N 4.29. $C_{21}H_{20}FNO_2$. Calculated, %: C 74.76; H 5.97; N 4.15.

Methyl 5-methyl-3-(phenylamino)-1,6-dihydro-(1,1′-biphenyl)-2-carboxylate (4d). Yield 29%, mp 96–97°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1668 (C=O), 1572 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.69 s (3H, Me), 2.29 d (1H, $C^6H_A\underline{H}_B$, J = 15.9 Hz), 2.86 d (1H, $C^6\underline{H}_AH_B$, J = 16.1 Hz), 3.52 s (3H, OMe), 4.07 m (1H, C^1H), 6.01 s (1H, C^4H), 7.12–7.38 m (10H, 2Ph), 10.55 s (1H, NH). Found, %: C 78.74; H 6.55; N 4.57. $C_{21}H_{21}NO_2$. Calculated, %: C 78.97; H 6.63; N 4.39.

Methyl 5-methyl-3-[(4-chlorophenyl)amino]-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate (4e). Yield 37%, mp 120–121°C. IR spectrum, ν, cm^{-1}: 3296 (NH), 1660 (C=O), 1584 (C=C). ^{1}H NMR spectrum, δ, ppm: 1.70 s (3H, Me), 2.30 d (1H, $C^6H_A\underline{H}_B$, J = 15.9 Hz), 2.86 d (1H, $C^6\underline{H}_AH_B$, J = 16.0 Hz), 3.53 s (3H, OMe), 4.07 m (1H, C^1H), 5.99 s (1H, C^4H), 7.14–7.40 m (9H, Ph, C_6H_4), 10.55 s (1H, NH). Found, %: C 71.54; H 5.63; N 4.19. $C_{21}H_{20}ClNO_2$. Calculated, %: C 71.28; H 5.70; N 3.96.

Isopropyl 5-methyl-3-(*p*-tolylamino)-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate (4f). Yield 61%, mp 83–84°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1660 (C=O),

1564 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.89 d (3H, CH$\underline{Me}_2$, J = 6.0 Hz), 1.17 d (3H, OCH$\underline{Me}_2$, J = 6.0 Hz), 1.72 s (3H, Me), 2.28 d (1H, C^{6}H$_A\underline{H}_B$, J = 16.2 Hz), 2.29 s (3H, 4-$\underline{Me}$-C$_6$H$_4$), 2.85 d (1H, C$^6\underline{H}_A$H$_B$, J = 17.0 Hz), 4.04–4.06 m (1H, C^{1}H), 4.82 m (1H, O$\underline{CH}$Me$_2$), 5.97 s (1H, C^{4}H), 6.99–7.22 m (9H, Ph, C$_6$H$_4$), 10.59 s (1H, NH). Found, %: C 79.69; H 7.55; N 3.52. $C_{24}H_{27}NO_2$. Calculated, %: C 79.74; H 7.53; N 3.87.

Isobutyl 5-methyl-3-(*p*-tolylamino)-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate (4g). Yield 59%, mp 87–89°C. IR spectrum, ν, cm^{-1}: 3296 (NH), 1696 (C=O), 1567 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.69 d (3H, OCH$_2$CH$\underline{Me}_2$, J = 6.0 Hz), 0.71 d (3H, OCH$_2$CH$\underline{Me}_2$, J = 6.0 Hz), 1.67–1.68 m (3H, OCH$_2\underline{CH}$Me$_2$), 1.69 s (3H, Me), 2.26 d (1H, C^{6}H$_A\underline{H}_B$, J = 16.1 Hz), 2.30 s (3H, 4-$\underline{Me}$-C$_6$H$_4$), 2.87 d (1H, C$^6\underline{H}_A$H$_B$, J = 16.8 Hz), 3.67–3.68 m (1H, O$\underline{CH}_2$CHMe$_2$), 3.77–3.78 m (1H, O$\underline{CH}_2$CHMe$_2$), 4.11 m (1H, C^{1}H), 5.99 s (1H, C^{4}H), 6.01–7.17 m (9H, Ph, C$_6$H$_4$), 10.59 s (1H, NH). Mass spectrum, *m/z* (I_{rel}, %): 375 (56) [M]$^+$. Found, %: C 79.73; H 7.72; N 3.89. $C_{25}H_{29}NO_2$. Calculated, %: C 79.96; H 7.78; N 3.73.

Isobutyl 5-methyl-3-[(4-fluorophenyl)amino]-1,6-dihydro(1,1′-biphenyl)-2-carboxylate (4h). Yield 66%, mp 80–82°C. IR spectrum, ν, cm^{-1}: 3240 (NH), 1664 (C=O), 1580 (C=C). ^{1}H NMR spectrum, δ, ppm: 0.68 d (3H, OCH$_2$CH$\underline{Me}_2$, J = 6.0 Hz), 0.70 d (3H, OCH$_2$CH$\underline{Me}_2$, J = 6.0 Hz), 1.67–1.68 m (3H, OCH$_2\underline{CH}$Me$_2$), 1.69 s (3H, Me), 2.26 d (1H, C^{6}H$_A\underline{H}_B$, J = 16.3 Hz), 2.88 d (1H, C$^6\underline{H}_A$H$_B$, J = 16.6 Hz), 3.68–3.69 m (1H, O$\underline{CH}_2$CHMe$_2$), 3.78–3.79 m (1H, O$\underline{CH}_2$CHMe$_2$), 4.09 m (1H, C^{1}H), 5.94 s (1H, C^{4}H), 7.16–7.21 m (9H, Ph, C$_6$H$_4$), 10.56 s (1H, NH). Found, %: C 79.71; H 7.02; N 3.90. $C_{24}H_{26}FNO_2$. Calculated, %: C 75.96; H 6.91; N 3.69.

General procedure for the synthesis of compounds 5a, 5b. To a solution of 0.01 mol of alkyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylate in 9.5 mL of ethanol were added 0.01 mol of diamine and 0.5 mL of glacial acetic acid. The resulting mixture was boiled for 2–4 h. The solvent was evaporated. The precipitate was filtered off, washed with water, dried and recrystallized from ethanol.

Diisopropyl 3,3''-[ethane-1,2-diylbis(azanediyl)bis-[5-methyl-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate] (5a). Yield 26%, mp 154–155°C. IR spectrum, ν, cm^{-1}: 3300 (NH), 1750 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.87 d (6H, OCH$\underline{Me}_2$, J = 6.0 Hz), 1.14 d (6H, OCH$\underline{Me}_2$, J = 6.0 Hz), 1.78 s (6H, 2Me), 2.22 d (2H, 2C^{6}H$_A\underline{H}_B$, J = 16.1 Hz), 2.68 d (2H, 2C$^6\underline{H}_A$H$_B$, J = 16.2 Hz), 3.47 m (4H, 2$\underline{CH}_2$NH), 3.94 m (2H, 2C^{1}H), 4.78 m (2H, 2O$\underline{CH}$Me$_2$), 6.21 s (2H, 2C^{4}H), 7.12–7.24 m (10H, 2Ph), 9.09 s (2H, 2NH). Found, %: C 76.26; H 7.75; N 5.19. $C_{36}H_{44}N_2O_4$. Calculated, %: C 76.02; H 7.80; N 4.93.

Diisopropyl 3,3''-[propane-1,2-diylbis(azanediyl)]bis-[5-methyl-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate] (5b). Yield 34%, mp 103–104°C. IR spectrum, ν, cm^{-1}: 3256 (NH), 1736 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.86 d (6H, 2OCH$\underline{Me}_2$, J = 6.0 Hz), 1.13 d (6H, 2OCH$\underline{Me}_2$, J = 6.0 Hz), 1.77 s (6H, 2Me), 1.82 m [2H, $\underline{CH}_2$(CH$_2$NH)$_2$], 2.25 d (2H, 2C^{6}H$_A\underline{H}_B$, J = 17.1 Hz), 2.70 d (2H, 2C$^6\underline{H}_A$H$_B$, J = 16.7 Hz), 3.40 m [4H, CH$_2$($\underline{CH}_2$NH)$_2$], 3.95–3.96 m (2H, 2C^{1}H), 4.77–4.78 m (2H, 2O$\underline{CH}$Me$_2$), 6.20 s (2H, 2C^{4}H), 7.11–7.23 m (10H, 2Ph), 9.07 s (2H, 2NH). Found, %: C 76.54; H 7.83; N 5.14. $C_{37}H_{46}N_2O_4$. Calculated, %: C 76.26; H 7.96; N 4.81.

Diisobutyl 3,3''-[ethane-1,2-diylbis(azanediyl)]bis[5-methyl-1,6-dihydro-(1,1'-biphenyl)-2-carboxylate] (5c). To a solution of 0.01 mol of isobutyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylate **1e** in 20 mL of ethanol was added 0.01 mol of ethylenediamine. The resulting mixture was boiled for 3 h. The solvent was evaporated. The precipitate was filtered off, washed with water, then with alcohol, dried and recrystallized from ethanol. Yield 11%, mp 171–172°C. IR spectrum, ν, cm^{-1}: 3408 (OH), 3266 (NH), 1720 (C=O). ^{1}H NMR spectrum, δ, ppm: 0.47 d (6H, OCH$_2$CH$\underline{Me}_2$, J = 7.5 Hz), 0.57 d (6H, OCH$_2$CH$\underline{Me}_2$, J = 7.5 Hz), 1.16 s (6H, 2Me), 1.32 m (6H, 2OCH$_2\underline{CH}$Me$_2$), 1.65 d (2H, 2C^{4}H$_A\underline{H}_B$, J = 13.2 Hz), 1.87 d (2H, 2C$^4\underline{H}_A$H$_B$, J = 13.2 Hz), 2.22 d (2H, 2C^{6}H$_A\underline{H}_B$, J = 16.5 Hz), 2.45 d (2H, 2C$^6\underline{H}_A$H$_B$, J = 16.5 Hz), 3.38 m (4H, 2OCH$_2\underline{CH}$Me$_2$), 3.41 m (4H, 2$\underline{CH}_2$NH), 3.86 m (2H, 2C^{1}H), 4.78 m (2H, 2O$\underline{CH}$Me$_2$), 4.32 s (1H, OH), 7.02–7.11 m (10H, 2Ph), 9.18 s (2H, 2NH). Found, %: C 71.47; H 8.25; N 4.17. $C_{38}H_{52}N_2O_4$. Calculated, %: C 71.12; H 8.28; N 4.43.

3,6-Dimethyl-4-phenyl-4,5,6,7-tetrahydrobenzo[*c*]-isoxazole-6-ol (6). Potassium hydroxide (0.1 mol) was added to a solution of 0.1 mol of hydroxylamine hydrochloride in 30 mL of ethanol. The precipitate was filtered off. 2-Acetyl-5-hydroxy-5-methyl-3-phenylcyclohexanone **1a** (0.05 mol) was added to the filtrate. The mixture was boiled for 2 h. The solvent was evaporated. The precipitate was filtered off and recrystallized from ethanol. Yield 41%, mp 134–136°C. IR spectrum, ν, cm^{-1}: 3376 (OH), 1640 (C=N). ^{1}H NMR spectrum, δ, ppm:

1.32 s (3H, Me), 1.62 d (1H, C^{7}H$_A$H$_B$, J = 13.2 Hz), 1.72 s (3H, Me), 1.94 d (1H, C^{7}H$_A$H$_B$, J = 13.4 Hz), 2.62 t (1H, C^{5}H$_A$H$_B$, J = 16.5 Hz), 2.74 d. d (1H, C^{5}H$_A$H$_B$, J = 16.5, 1.6 Hz), 3.98 m (1H, C^{4}H), 4.67 s (1H, OH), 7.22–7.31 m (5H, Ph). Found, %: C 74.34; H 7.01; N 5.93. $C_{15}H_{17}NO_2$. Calculated, %: C 74.05; H 7.04; N 5.76.

6-Methyl-2,4-diphenyl-4,5,6,7-tetrahydro-2*H*-indazole-3,6-diol (7a). To a solution of 0.01 mol of ethyl 4-hydroxy-4-methyl-2-oxo-6-phenylcyclohexane-1-carboxylate **1b** in 20 mL of ethanol was added 0.01 mol of phenylhydrazine. The mixture was boiled for 6 h. After removing the solvent, the precipitate was filtered off, treated with acetone and recrystallized from ethanol. Yield 74%, mp 217–219°C. IR spectrum, ν, cm^{-1}: 3312 (OH), 3200 (OH), 1680 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.26 s (3H, Me), 1.47 d (1H, C^{7}H$_A$H$_B$, J = 12.2 Hz), 1.96 d (1H, C^{7}H$_A$H$_B$, J = 13.2 Hz), 2.46 t (1H, C^{5}H$_A$H$_B$, J = 14.3 Hz), 2.63 d. d (1H, C^{5}H$_A$H$_B$, J = 14.3, 1.6 Hz), 3.76 q (1H, C^{4}H, J = 14.1 Hz), 4.67 s (1H, OH), 7.15–7.68 m (10H, 2Ph), 10.68 s (OH). Found, %: C 74.61; H 6.31; N 8.96. $C_{20}H_{20}N_2O_2$. Calculated, %: C 74.98; H 6.29; N 8.74.

6-Methyl-4-phenyl-4,5,6,7-tetrahydro-2*H*-indazole-3,6-diol (7b). A mixture of 0.005 mol of 4-hydroxy-4-methyl-6-phenylcyclohexanone, 10 mL of ethanol and 0.005 mol of hydrazine hydrate was boiled for 30 min. The precipitate was filtered off and washed with ethanol. Yield 61%, mp 261–263°C. IR spectrum, ν, cm^{-1}: 3360 (OH), 3280 (NH), 1600 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.21 s (3H, Me), 1.40 d (1H, C^{7}H$_A$H$_B$, J = 13.2 Hz), 1.89 d (1H, C^{7}H$_A$H$_B$, J = 13.2 Hz), 2.47 t (1H, C^{5}H$_A$H$_B$, J = 16.8 Hz), 2.56 d. d (1H, C^{5}H$_A$H$_B$, J = 16.5, 1.4 Hz), 3.82 q (1H, C^{4}H, J = 16.1 Hz), 4.45 s (1H, OH), 7.13–7.23 m (5H, Ph), 10.20 br. s (2H, NH, OH). Found, %: C 68.60; H 6.66; N 11.73. $C_{14}H_{16}N_2O_2$. Calculated, %: C 68.83; H 6.60; N 11.47.

3,6-Dimethyl-4-phenyl-4,5,6,7-tetrahydro-2*H*-indazole-6-ol (7c) was prepared analogously. Yield 93%, mp 226–228°C. IR spectrum, ν, cm^{-1}: 3400 (OH), 3312 (NH), 1600 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.24 s (3H, Me), 1.48 s (3H, Me), 1.62 d (1H, C^{7}H$_A$H$_B$, J = 11.6 Hz), 1.85 d (1H, C^{7}H$_A$H$_B$, J = 12.0 Hz), 2.57 m (2H, C^{5}H$_2$), 3.87 q (1H, C^{4}H, J = 16.0 Hz), 4.37 s (1H, OH), 7.14–7.26 m (5H, Ph), 11.76 s (1H, NH). Found, %: C 74.61; H 7.56; N 11.77. $C_{15}H_{18}N_2O$. Calculated, %: C 74.35; H 7.49; N 11.56.

General procedure for the synthesis of compounds 8a–8c. A mixture of 0.005 mol of the corresponding cycloketol, 0.005 mol of benzophenone hydrazone and 10 mL of ethanol was boiled for 2–3 h. After removing the solvent, the precipitate was filtered off and recrystallized from ethanol.

Benzyl 2-[(diphenylmethylene)hydrazono]-4-hydroxy-4-methyl-6-phenylcyclohexanecarboxylate (8a). Yield 87%, mp 195–196°C. IR spectrum, ν, cm^{-1}: 3440 (OH), 1728 (C=O), 1624 (C=N). ^{1}H NMR spectrum, δ, ppm: 1.23 s (3H, Me), 1.76 t (1H, C^{5}H$_A$H$_B$, J = 12.5 Hz), 1.89 d (1H, C^{5}H$_A$H$_B$, J = 13.0 Hz), 2.15 d (1H, C^{3}H$_A$H$_B$, J = 14.2 Hz), 3.34 d (1H, C^{3}H$_A$H$_B$, J = 14.2 Hz), 3.60–3.61 m (1H, C^{6}H), 3.75 d (1H, C^{1}H, J = 12.1 Hz), 4.48 s (2H, CH$_2$Ph), 4.78 s (1H, OH), 7.18–7.57 m (20H, 4Ph). Found, %: C 78.71; H 6.29; N 5.73. $C_{34}H_{32}N_2O_3$. Calculated, %: C 79.04; H 6.24; N 5.42.

Isobutyl 2-[(diphenylmethylene)hydrazono]-4-hydroxy-4-methyl-6-phenylcyclohexanecarboxylate (8b). Yield 88%, mp 165–166°C. IR spectrum, ν, cm^{-1}: 3424 (OH), 1728 (C=O), 1624 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.50 d (3H, OCH$_2$CHMe$_2$, J = 6.0 Hz), 0.51 d (3H, OCH$_2$CHMe$_2$, J = 6.0 Hz), 1.23 s (3H, Me), 1.32 m (1H, OCH$_2$CHMe$_2$), 1.75 t (1H, C^{5}H$_A$H$_B$, J = 12.3 Hz), 1.85 d (1H, C^{5}H$_A$H$_B$, J = 13.0 Hz), 2.14 d (1H, C^{3}H$_A$H$_B$, J = 14.2 Hz), 3.16 m (2H, OCH$_2$CHMe$_2$), 3.32 d (1H, C^{3}H$_A$H$_B$, J = 14.2 Hz), 3.56–3.57 m (1H, C^{6}H), 3.67 d (1H, C^{1}H, J = 12.1 Hz), 4.68 s (1H, OH), 7.16–7.56 m (15H, 3Ph). Found, %: C 77.26; H 7.17; N 5.61. $C_{31}H_{34}N_2O_3$. Calculated, %: C 77.15; H 7.10; N 5.80.

Ethyl 2-[(diphenylmethylene)hydrazono]-4-hydroxy-4-methyl-6-phenylcyclohexanecarboxylate (8c). Yield 63%, mp 178–179°C. IR spectrum, ν, cm^{-1}: 3496 (OH), 1728 (C=O), 1624 (C=N). ^{1}H NMR spectrum, δ, ppm: 0.66 t (3H, OCH$_2$Me$_2$, J = 7.5 Hz), 1.23 s (3H, Me), 1.32 m (1H, OCH$_2$CHMe$_2$), 1.73 t (1H, C^{5}H$_A$H$_B$, J = 13.0 Hz), 1.87 d (1H, C^{5}H$_A$H$_B$, J = 12.8 Hz), 2.13 d (1H, C^{3}H$_A$H$_B$, J = 14.1 Hz), 3.31 d (1H, C^{3}H$_A$H$_B$, J = 14.1 Hz), 3.43 q (2H, OCH$_2$Me$_2$, J = 7.5 Hz), 3.55–3.56 m (1H, C^{6}H), 3.61 d (1H, C^{1}H, J = 12.1 Hz), 4.67 s (1H, OH), 7.17–7.56 m (15H, 3Ph). Found, %: C 76.92; H 6.73; N 6.38. $C_{29}H_{30}N_2O_3$. Calculated, %: C 76.63; H 6.65; N 6.16.

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CONFLICT OF INTEREST

No conflict of interest was declared by the authors.

REFERENCES

1. Rajveer, Ch., Stephenrathinaraj, B., Sudharshini, S., Kumaraswamy, D., Shreshtha, B., and Choudhury, P.K., *Res. J. Pharm. Biol. Chem. Sci*., 2010, vol. 1, no. 3, p. 99.
2. Vyas, D.H., Tala, S.D., Akbari, J.D., Dhaduk, M.F., and Joshi, H.S., *Indian J. Chem. (B)*, 2009, vol. 48, no. 10, p. 1405.
3. Gein, V.L., Zorina, A.A., Nosova, N.V., Voronina, E.V., Vahrin, M.I., and Kriven'ko, A.P., *Pharm. Chem. J*., 2007, vol. 41, no. 6, p. 319. doi 10.1007/s11094-007-0072-8
4. Gein, V.L., Prusakova, A.S., Nosova, N.V., Vahrin, M.I., Voronina, E.V., and Kriven'ko, A.P., *Pharm. Chem. J*., 2010, vol. 44, no. 8, p. 427. doi 10.1007/s11094-010-0483-9
5. Ghodse, A.H. and Galea, S., *Side Effects of Drugs Annual*, 2011, vol. 33, p. 205. doi 10.1016/B978-0-444-53741-6.00008-8
6. Sorokin, V.V., Kriven'ko, A.P., Vinogradova, N.A., and Plotnikov, O.P., *Pharm. Chem. J*., 2001, vol. 35, no. 9, p. 488. doi 10.1023/A:1014090608261
7. Puchina, G.R., *Candidate Dissert. (Chem.)*, Ufa, 2007.
8. Zorina, A.A., *Candidate Dissert. (Pharm.)*,Perm, 2006.
9. Sharma, A., Chakravarti, B., Gupt, M. P., Siddiqui, J.A., Konwar, R., and Tripathi, R.P., *Bioorg. Med. Chem*., 2010, vol. 18, no. 13, p. 4711. doi 10.1016/j.bmc.2010.05.015
10. Said, M.M., Ahmed, A.A.E., and El-Alfy, A.T., *Arch. Pharm. Res*., 2004, vol. 27, p. 1194. doi 10.1007/BF02975880
11. RU Patent 2428410, 2011.
12. Cooling, M.J. and Sim, M.F., *Br. J. Pharmacol*., 1977, vol. 60, no. 4, p. 569. doi 10.1111/j.1476-5381.1977.tb07536.x
13. Colović, M.B., Krstić, D.Z., Lazarević-Pašti, T.D., Bondžić, A.M., and Vasić, V.M., *Curr. Neuropharmacol*., 2013, vol. 11, no. 3, p. 315. doi 10.2174/ 1570159X11311030006
14. Seebacher, W., Kaiser, M., Brun, R., Saf, R., and Weis, R., *Monatsh. Chem.*, 2007, vol. 138, p. 709. doi 10.1007/s00706-007-0670-x
15. Weis, R., Berger, H., Kaiser, M., Brun, R., Saf, R., and Seebacher, W., *Arch. Pharm. Res*., 2008, vol. 3, no. 6, p. 688. doi 10.1007/s12272-001-1214-5
16. Niwas, S., Kumar, S., and Bhaduri, A.P., *Indian J. Chem*., 1985, vol. 24, no. 7, p. 747.
17. Bucholtz, E.C., Brown, R. L., Tropsha, A., Booth, R.G., and Wyrick, S.D., *J. Med. Chem.*, 1999, vol. 42, no. 16, p. 3041. doi 10.1021/jm980428x
18. Ghoneim, O.M., Legere, J.A., Golbraikh, A., Tropsha, A., and Booth, R.G., *Bioorg. Med. Chem*., 2006, vol. 14, no. 19, p. 6640. doi 10.1016/j.bmc.2006.05.077
19. Gein, V.L., Vagapov, A.V., Nosova, N.V., Voronina, E.V., Vahrin, M.I., and Krivenko, A.P., *Pharm. Chem. J*., 2010, vol. 44, no. 5, p. 245. doi 10.1007/s11094-010-0440-7
20. Usova, E.B., Lysenko, L.I., Krapivin, G.D., Zavodnik, V.E., and Kul'nevich, V.G., *Chem. Heterocycl. Compd*., 1997, vol. 33, no. 11, p. 1259. doi 10.1007/BF02320324