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Synthesis and Structure of New Substituted Pyrimidinone with Unsaturated Side Chain

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Abstract—Melting of a mixture of 5-substituted 2,4-dimethyl-1,6-dihydropyrimidin-6-ones with cinnamic aldehyde, 1-methylindoline-2,3-dione and 6-methoxy-2-chloroquinoline-3-carbaldehyde in the presence of $ZnCl_2$ led to the formation of substituted pyrimidines with conjugated bonds in the position *2*. The structure of synthesized compounds as 2-isomers was confirmed by 2D ^{1}H NMR NOESY data.

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The interest to the synthesis of pyrimidines with a system of unsaturated double bonds in the side chain is due both to the high biological activity of styryl derivatives of pyrimidines [1, 2] and to the optical absorption and emission properties of heteroconjugated pyrimidines [3]. Here we report on a series of new substituted pyrimidines containing in the position *2* of the pyrimidine ring 1-methyl-2-oxo-3-indolylidenemethyl, 2-(3-quinolyl)ethylene, and 1-phenyl-1,3-butadiene groups. The initial 2,4-dimethyl-1,6-dihydropyrimidin-6-ones **1a–1f** were prepared by the reaction of 2-substituted ethyl 3-oxobutanoates [4] with acetamide in anhydrous methanol in the presence of sodium methylate. Pyrimidines **1a**, **1c**, and **1e–1g** were synthesized in [5], **1b**, in [6].

The structure of 5-butyl-2,4-dimethyl-1,6-dihydropyrimidin-6-one **1c** was proved by X-ray diffraction (XRD) analysis (Figs. 1, 2).

The heterocyclic fragment $N^1C^2N^3C^4C^5C^6$ is practically planar with a maximum deviation from the mean square plane 0.0091(3) Å. The molecules of compound **1c** form in the crystal centrosymmetric cyclic dimers (Fig. 2) owing to intermolecular hydrogen bonds N^1–$H^1\cdots O^7$ [the length of the donor-acceptor bond is 2.804(2) Å].

The reaction of 5-substituted 2,4-dimethyl-1,6-dihydropyrimidin-6-ones **1a–1g** with 1-methyl-indoline-2,3-dione **2**, 6-methoxy-2-chloro-3-quinolinecarbaldehyde **3**, and cinnamic aldehyde **4** in the presence of $ZnCl_2$

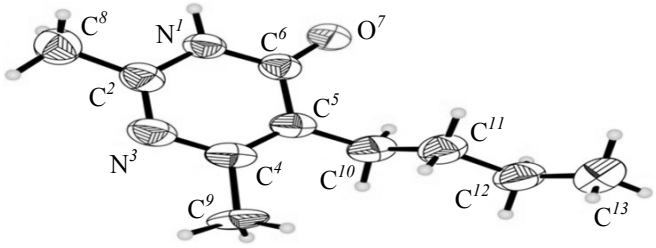


Fig. 1. General arrangement of the molecule of 5-butyl-2,4-dimethyl-1,6-dihydropyrimidin-6-one **1c** by XRD data.

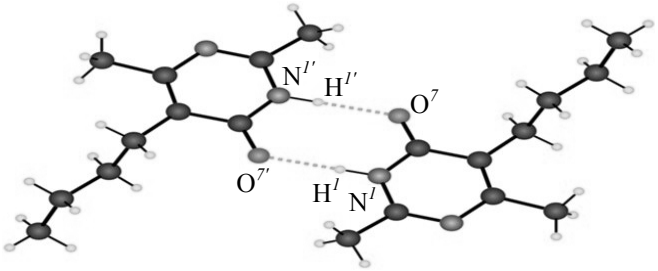
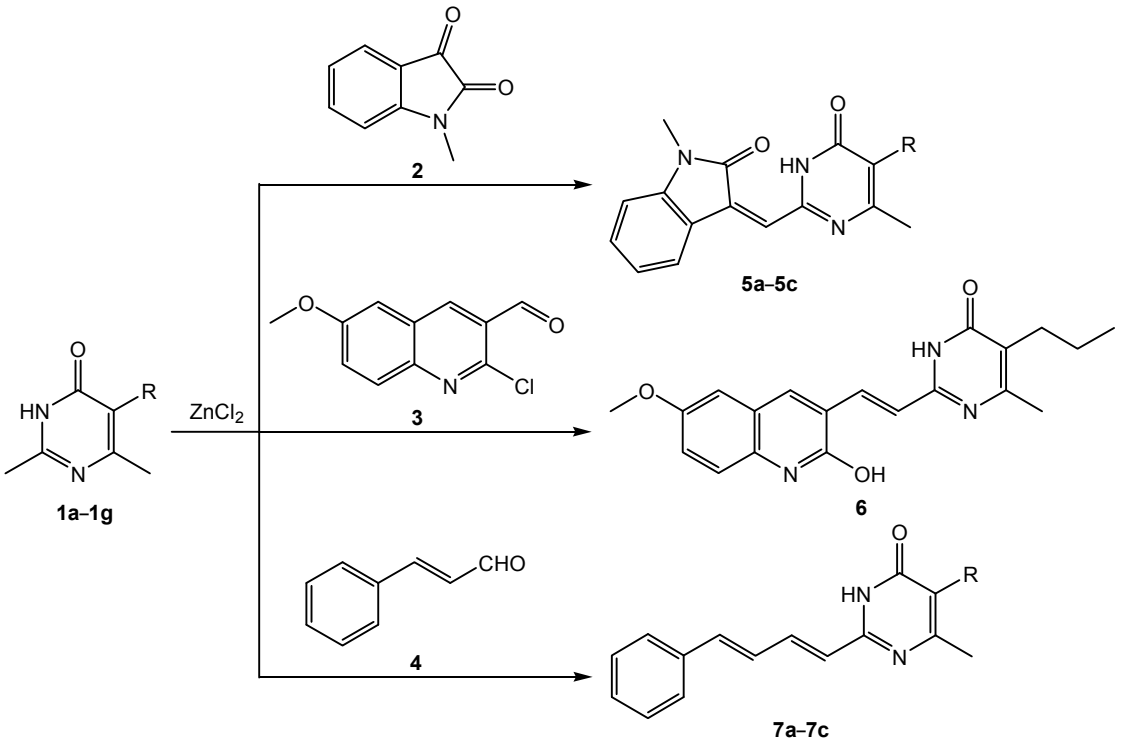


Fig. 2. Fragment of crystal packing of 5-butyl-2,4-dimethyl-1,6-dihydropyrimidin-6-one **1c** showing the formation of centrosymmetric dimer.

Scheme 1.



1, R = $(CH_2)_2Me$ (**a**), $CH_2CH{=}CH_2$ (**b**), $(CH_2)_3Me$ (**c**), $CH(CH_2)_4$ (**d**), $CH_2CH_2CHMe_2$ (**e**), $(CH_2)_5Me$ (**f**), Bn (**g**); **5**, R = $(CH_2)_3Me$ (**a**), $CH(CH_2)_4$ (**b**), Bn (**c**); **7**, R = $CH_2CH{=}CH_2$ (**a**), $(CH_2)_3Me$ (**b**), $CH_2CH_2CHMe_2$ (**c**).

afforded 3-substituted 1-methylindolin-2-ones **5a–5c**, substituted 2-(3-quinolyl)-pyrimidone **6**, and 5-substituted buta-1,3-dienyl-1,6-dihydropyrimidin-6-ones **7a–7c** (Scheme 1).

The condensation of 6-methoxy-2-chloro-3-quinolinecarbaldehyde with pyrimidinone **1a** is accompanied with a hydrolytic substitution of the chlorine atom in the position *2* of the quinolone ring with the formation of quinolinol derivative **6**. The consideration of computer molecular models of compounds **5a–5c** (program product Cambridge Soft Corporation Chem. 3D 5.0) did not give unambiguous indication of the prevailing formation of one among regioisomeros (2- or 4-styryl-substituted pyrimidine), yet such preliminary indications were obtained for geometric isomers. In *trans*-isomers of compounds **5a–5c** unfavorable steric interactions were revealed between the atoms H^4 of isatin benzene ring and HN^1 of pyrimidine in case of coplanar location of the pyrimidine and isatin rings, whereas in the *cis*-isomers such interactions are less significant (Fig. 3).

The comparison of the reactivity of groups 2- and 4 -CH_3 of 1,6-dihydropyrimidin-6-one in the reactions with carbonyl compounds where the methyl group

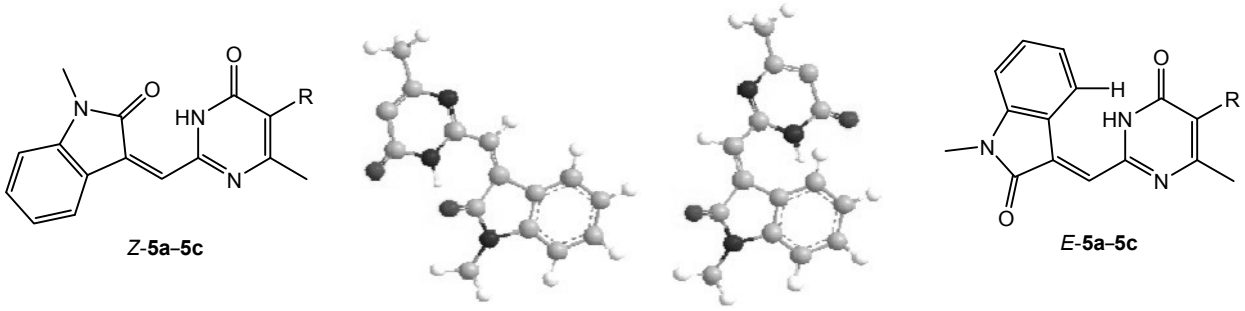


Fig. 3. Molecular models of compounds **5a–5c**.

plays the role of a nucleophilic site with a partial negative sign shows the greater chemical activity of the 2-CH_3 group due to more efficient delocalization of the negative sign. The discussed assumptions were proved by the study of NMR spectra of compounds **5a**, **5c**, and **7b**.

As show the 2D NOESY NMR spectra of compounds **5a**, **5c**, and **7b** the reaction proceeds at the 2-methyl group of the pyrimidine ring. It is confirmed by the NOE between the 6-methyl and the group α-CH_2 of substituents in the position *5* of the ring. Moreover, the presence of intensive NOE between the proton of the exocyclic double bond and H^4 of the aromatic ring of 1- methylisatin shows that compounds **5a** and **5c** have *Z*-configuration.

EXPERIMENTAL

IR spectra were recorded on a spectrophotometer Nicolet Avatar 330 in mineral oil. ^{1}H NMR spectra were registered on a spectrometer Varian Mercury-300 at operating frequency 300 MHz in a mixture DMSO-d_6–CCl_4, 1 : 3, internal reference TMS. Elemental analysis was carried out on an automatic analyzer EA 3000 Eurovector (Italy). X-ray diffraction analysis was performed on a single crystal of compound **1c** at room temperature using automatic diffractometer Enraf-Nonius CAD-4 (graphite monochromator, MoK_α-radiation, θ/2θ-scanning). The structure was solved by the direct method, hydrogen atoms coordinates were partially found from the difference Fourier syntheses. The coordinates of hydrogen atoms of methyl groups were geometrically calculated and refined in the *rider* model with the following restrictions: length of the bond C–H 0.96 Å, U_{iso}(H) = 1.5 U_{eq}(C). The structure was refined by full-matrix least-squares method in anisotropic approximation for nonhydrogen atoms and in isotropic approximation for hydrogen atoms. All structural computations were carried out using SHELXTL software [6]. TLC was performed on a Silufol UV-254 plates, eluent ethanol–chloroform, 1 : 10, development in iodine vapor.

Crystallographic data of compound **1c** are deposited in the Cambridge Crystallographic Data Centre (CCDC 1536234).

5-Substituted 2,4-dimethyl-1,6-dihydropyrimidin-6-ones. General procedure. To a solution of alkali metal ethylate prepared from 0.46 g (0.02 mol) of metal sodium or potassium and 40 mL of anhydrous ethanol was added 0.95 g (0.01 mol) of preliminary dried acetamidine hydrochloride and 0.01 mol of 2-substituted ethyl 3-oxobutanoate. The mixture was boiled for 6 h, alcohol was distilled off to dryness, the residue was dissolved in 10 mL of water and acidified with AcOH to pH 6. On cooling the separated crystals were filtered off, dried, and recrystallized from aqueous ethanol.

Table 1. Main crystallographic characteristics and experimental data for 5-butyl-2,4-dimethyl-1,6-dihydro-6-pyrimidinone **1c**

Parameter	Value
Empirical formula	$C_{10}H_{16}N_2O$
Molecular mass	180.25
Crystal system	Triclinic
Space group	*P*-1
a, *b*, *c*, Å	4.8866(10), 10.088(2), 11.577(2)
α, β, γ, deg	114.58(3), 96.59(3), 90.66(3)
V, Å^3	514.4(2)
Z	2
D_{calc}, g/cm^3	1.164
μ(MoK_α), mm^{-1}	0.076
F(000)	196
Crystal size, mm	0.18×0.23×0.35
Temperature, K	293
Radiation, Å	0.71073
Θ_{min}, θ_{max}, deg	2.0, 30.0
Scan range	$-6 \le h \le 6$, $-14 \le k \le 14$, $-16 \le l \le 16$
Number of measured reflections	5966
Observed reflections with $I > 3.0\sigma(I)$	1344
N_{ref}, N_{par}	2983, 160
R, wR_2, *S*	0.0593, 0.1609, 0.96

5-Allyl-2,4-dimethyl-1,6-dihydropyrimidin-6-one (1c), mp 151–152°C [7]. ^{1}H NMR spectrum, δ, ppm: 2.14 s (3H, CH_3), 2.22 (3H, CH_3), 3.13 d.t (2H, CH_2, *J* 6.0, 1.6 Hz), 4.93 d.d.t (1H, CH_2, *J* 10.1, 1.8, 1.6 Hz), 4.96 d.d.t (1H, CH_2, *J* 17.1, 1.8, 1.6 Hz), 5.76 d.d.t (1H, CH, *J* 17.1, 10.1, 6.0 Hz), 12.14 br.s [1H, NH (OH)].

2,4-Dimethyl-5-cyclopentyl-1,6-dihydropyrimidin-6-one (1d) was obtained from ethyl 2-cyclopentyl-

3-oxobutanoate. Yield 39%, mp 180–182°C, R_f 0.51 (2-propanol–dichloroethane, 1 : 9), IR spectrum, ν, cm^{-1}: 3290, 3130 (NH), 1850, 1639 (CO), 1610 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 1.51–1.66 m (4H), 1.78–2.02 m (4H) and 2.90–3.02 m (1H, C_5H_9), 2.18 s (3H) and 2.19 s (3H, $2CH_3$), 11.95 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 20.2 (CH_3), 21.1 (CH_3), 26.0 ($2CH_3$), 28.8 ($2CH_3$), 37.7 (CH), 122.8, 153.9, 158.0, 161.4. Found, %: C 68.89; H 8.51; N 14.65. $C_{11}H_{16}N_2O$. Calculated, %: C 68.72; H 8.39; N 14.57.

2-Substituted pyrimidin-6-ones (5a–5c, 6, 7a–7c) *(general procedure).* A mixture of 0.01 mol of 5-substituted 2,4-dimethyl-1,6-dihydro-6-pyrimidinone, 0.01 mol of *N*-methylisatin **2**, substituted 3-quinolinealdehyde **3** or cinnamic aldehyde **4**, 100 mg of anhydrous $ZnCl_2$ was heated at 170–180°C for 1 h. On cooling the product was triturated with ethanol, filtered off, and dried. The compounds obtained were purified by recrystallization from alcohol or by hot filtration of a dispersion of the compound in alcohol. Compounds **5a–5c** are red-orange powders, **6**, and **7a–7c** are yellow or light yellow powders.

3-[(*Z*)-1-(5-Butyl-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)methylidene]-1-methylindolin-2-one (5a) was prepared from 1-methylindoline-2,3-dione and pyrimidine **1a**. Yield 60%, mp 243–245°C, R_f 0.75 (ethanol–dichloroethane, 1 : 1). IR spectrum, ν, cm^{-1}: 1701, 1674, 1641 (CO), 1602 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 0.97 t (3H, CH_3, *J* 6.9 Hz), 1.35–1.52 m (4H, $\underline{CH_2}\underline{CH_2}CH_3$), 2.31 s (3H, 4-$CH_3$), 2.44–2.50 m (2H, 5-$\underline{CH_2}CH_2$), 3.36 s (3H, NCH_3), 7.02 br.d (1H, C_6H_4, $H^7_{indolinone}$, *J* 7.7 Hz), 7.11 t.d (1H, C_6H_4, $H^5_{indolinone}$, ^1J 7.6, ^2J 1.0 Hz), 7.26 s (1H, 2-CH=C), 7.38 t.d (1H, C_6H_4, $H^6_{indolinone}$, ^1J 7.7, ^2J 1.0 Hz), 7.73 br.d (1H, C_6H_4, $H^4_{indolinone}$, *J* 7.6 Hz), 14.15 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 13.5 (CH_3), 20.5 (CH_3), 22.2 (CH_2), 25.2 (CH_2), 26.0 (NCH_3), 29.7 (CH_2), 108.8 (CH), 120.5 (CH), 121.9, 122.6 (CH), 126.4, 129.1 (CH), 130.8 (CH), 131.8, 142.4, 149.9, 158.2, 160.3, 166.4. Found, %: C 70.68; H 6.31; N 12.85. $C_{19}H_{21}N_3O_2$. Calculated, %: C 70.57; H 6.54; N 12.99.

3-[(*Z*)-1-(4-Methyl-6-oxo-5-cyclopentyl-1,6-dihydropyrimidin-2-yl)methylidene]-1-methylindolin-2-one (5b) was prepared from 1-methylindoline-2,3-dione and pyrimidine **1b**. Yield 51%, mp 263–265°C, R_f 0.78 (ethanol–dichloroethane, 1 : 1). IR spectrum, ν, cm^{-1}: 1671, 1641 (CO), 1605 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 1.56–1.74 m (4H) and 1.84–2.11 m [4H, $(CH_2)_4$], 2.35 s (3H, 4-CH_3), 3.00–3.13 m (1H, $CH_{cyclopentyl}$), 3.36 s (3H, NCH_3), 7.01 d (1H, C_6H_4, *J* 7.8 Hz), 7.10 t (1H, C_6H_4, *J* 7.6 Hz), 7.26 s (1H, 2-CH=C), 7.38 d.d (1H, C_6H_4, ^1J 7.8, ^2J 7.6 Hz), 7.73 d (1H, C_6H_4, *J* 7.6 Hz), 14.01 br.s (1H, NH). Found, %: C 71.77; H 6.18; N 12.40. $C_{20}H_{21}N_3O_2$. Calculated, %: C 71.62; H 6.31; N 12.53.

3-[(*Z*)-1-(5-Benzyl-4-methyl-6-oxo-1,6-dihydropyrimidin-2-yl)methylidene]-1-methylindolin-2-one (5c) was prepared from 1-methylindoline-2,3-dione and pyrimidine **1g**. Yield 62%, mp 228–230°C, R_f 0.82 (ethanol–dichloroethane, 1 : 1). IR spectrum, ν, cm^{-1}: 1703, 1675 (CO), 1642, 1601 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 2.31 s (3H, CH_3), 3.36 s (3H, NCH_3), 3.87 s (2H, CH_2), 7.02 br.d (1H, H^7_{isatin}, *J* 7.8 Hz), 7.11 t.d (1H, C_6H_4, *J* 7.8, 0.9 Hz), 7.09–7.16 m (1H, C_6H_5), 7.20–7.23 m (4H, C_6H_5), 7.29 s (1H, =CH), 7.38 t.d (1H, C_6H_4, *J* 7.8, 1.0 Hz), 7.74 br.d (1H, H^4_{isatin}, *J* 7.6 Hz), 14.32 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.0 (CH_3), 25.6 (CH_3), 30.6 (NCH_3), 108.9 (CH), 120.6 (CH), 121.8, 122.6 (CH), 124.8, 125.4 (CH), 127.7 (2CH, Ph), 127.8 (2CH, Ph), 129.6 (CH), 130.9 (CH), 132.2, 149.9, 138.8, 142.5, 150.5, 159.7, 160.7. Found, %: C 74.05; H 5.53; N 11.90. $C_{22}H_{19}N_3O_2$. Calculated, %: C 73.93; H 5.36; N 11.76.

2-[(*E*)-2-(2-Hydroxy-6-methoxyquinol-3-yl)-1-ethenyl]-4-methyl-5-propyl-1,6-dihydropyrimidin-6-one (6) was prepared from 6-methoxy-2-chloro-3-quinolinecarbaldehyde and pyrimidinone **1a**. Yield 38%, mp 320°C, R_f 0.67 (isobutanol–H_2O–AcOH, 2 : 2 : 1). IR spectrum, ν, cm^{-1}: 1640 (CO), 1584 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 0.92 t (3H, $\underline{CH_3}CH_2CH_2$, *J* 7.3 Hz), 1.39–1.50 m (2H, $\underline{CH_2}CH_3$), 2.28 s (3H, CH_3), 2.37–2.43 m (2H, $CH_2C_2H_5$), 3.87 s (3H, OCH_3), 7.21 d.d (1H, H^7, C_6H_3, *J* 8.9, 2.8 Hz), 7.27 d (1H, H^5, C_6H_3, *J* 2.8 Hz), 7.28 d (1H, H^8, C_6H_3, *J* 8.9 Hz), 7.57 d [1H, (*E*) =CH, *J* 15.9 Hz], 7.83 d [1H, (*E*) =CH, *J* 15.9 Hz], 8.17 s (1H, H^4), 11.96 s (1H, OH), 12.34 br.s (1H, NH). Found, %: C 68.57; H 5.85; N 11.67. $C_{20}H_{21}N_3O_3$. Calculated, %: C 68.36; H 6.02; N 11.96.

5-Allyl-4-methyl-2-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]-1,6-dihydropyrimidin-6-one (7a) was prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dienal and pyrimidine **1b**. Yield 48%, mp 200–202°C, R_f 0.57 (acetone–hexane, 2 : 3). IR spectrum, ν, cm^{-1}: 1649, 1625 (CO), 1585 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 2.23 s (3H, CH_3), 3.18 d.t (2H, CH_2, *J* 6.2, 1.5 Hz), 4.95 d.q (1H, =C$\underline{H}$H, *J* 10.0, 1.5 Hz), 5.00 d.q (1H, =C$\underline{H}$H, *J* 17.1, 1.5 Hz), 5.79 d.d.t (1H, =CH, *J* 17.1,

10.0, 6.2 Hz), 6.32 d [1H, (*E*)=CH, *J* 15.2 Hz], 6.86 d [1H, (*E*)=CH, *J* 15.5 Hz], 6.98 d.d [1H, (*E*)=CH, *J* 15.5, 10.5 Hz], 7.20–7.34 m (3H, $H_{Ph}^{3',4',5'}$), 7.45–7.50 m (2H, $H_{Ph}^{2',6'}$), 7.62 d.d [1H, (*E*)=CH, *J* 15.2, 10.5 Hz], 12.20 br.s (1H, NH). Found, %: C 77.83; H 6.47; N 10.30. $C_{18}H_{18}N_2O$. Calculated, %: C 77.67; H 6.52; N 10.06.

5-Butyl-4-methyl-2-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]-1,6-dihydropyrimidin-6-one (7b) was prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dienal and pyrimidine **1c**. Yield 59%, mp 184–186°C, R_f 0.61 (acetone–hexane, 2 : 3). IR spectrum, ν, cm^{-1}: 1646, 1626 (CO), 1570 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 0.96 t (3H, CH_3, *J* 7.0 Hz), 1.32–1.48 m (4H, CH_2CH_2Me), 2.23 s (3H, CH_3), 2.35–2.44 m (2H, $CH_2C_3H_7$), 6.30 d [1H, H^1 (*E*)=CH, *J* 15.3 Hz], 6.85 d [1H, H^4 (*E*)=CH, *J* 15.6 Hz], 6.97 d.d [1H, H^3 (*E*)=CH, *J* 15.6, 10.6 Hz], 7.20–7.35 m (3H, $H_{Ph}^{3',4',5'}$), 7.45–7.50 m (2H, $H_{Ph}^{2',6'}$), 7.59 d.d [1H, H^2 (*E*)=CH, *J* 15.3, 10.6 Hz], 12.09 br.s (1H, NH). Found, %: C 77.37; H 7.68; N 9.40. $C_{19}H_{22}N_2O$. Calculated, %: C 77.52; H 7.53; N 9.52.

5-Isopentyl-4-methyl-2-[(1*E*,3*E*)-4-phenylbuta-1,3-dienyl]-1,6-dihydropyrimidin-6-one (7c) was prepared from (2*E*,4*E*)-5-phenylpenta-2,4-dienal and pyrimidine **1e**. Yield 51%, mp 192–194°C, R_f 0.60 (acetone–hexane, 2 : 3). IR spectrum, ν, cm^{-1}: 1644, 1630 (CO), 1582 (C=C–C=N). ^{1}H NMR spectrum, δ, ppm: 0.97 d (6H, 2Me, *J* 6.6 Hz), 1.26–1.35 m (2H, $\underline{CH_2}CH$), 1.62 nonet (1H, CH, *J* 6.6 Hz), 2.23 s (3H, CH_3), 2.36–2.43 m (2H, $\underline{CH_2}CH_2CH$), 6.30 d [1H, (*E*) =CH, *J* 15.3 Hz], 6.85 d [1H, (*E*)=CH, *J* 15.5 Hz], 6.97 d.d [1H, (*E*)=CH, *J* 15.5, 10.5 Hz], 7.20–7.34 m (3H, $H_{Ph}^{3',4',5'}$), 7.45–7.50 m (2H, $H_{Ph}^{2',6'}$), 7.59 d.d [1H, (*E*)=CH, *J* 15.3, 10.5 Hz], 12.08 br.s (1H, NH). Found, %: C 78.05; H 7.53; N 9.28. $C_{20}H_{24}N_2O$. Calculated, %: C 77.89; H 7.84; N 9.08.

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