ISSN 1070-3632, Russian Journal of General Chemistry, 2014, Vol. 84, No. 10, pp. 1950–1952. © Pleiades Publishing, Ltd., 2014.
Original Russian Text © T.M. Zamaraeva, T.F. Odegova, A.Yu. Fedotov, M.V. Tomilov, V.L. Gein, P.A. Slepukhin, 2014, published in Zhurnal Obshchei Khimii, 2014, Vol. 84, No. 10, pp. 1672–1675.

Synthesis and Antimicrobial Activity of 6-Aryl-3,4-dimethyl-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides

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Received May 5, 2014

Abstract—Three-component reaction of acetoacetanilide, aromatic aldehydes, and *N*-methylurea afforded 6-aryl-3,4-dimethyl-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides. IR, ^{1}H NMR spectroscopy, mass spectrometry, and X-ray diffraction analysis data confirmed the structure of the compounds obtained. Antimicrobial activity of these compounds was investigated.

Keywords: three-component synthesis, 1,2,3,6-tetrahydropyrimidine-5-carboxamide, antimicrobial activity

DOI: 10.1134/S1070363214100168

Currently the chemistry of the nitrogen-containing heterocyclic compounds is one of rapidly developing areas of organic and pharmaceutical chemistry. The application in medical practice of preparations containing pyrimidine ring in their structures shows the usefulness of the search for new biologically active compounds among pyrimidine derivatives. Compounds having a pyrimidine ring have been known as antibacterial and antifungal agents; some pyrimidine derivatives show a pronounced antiviral and antitumor activity [1–5].

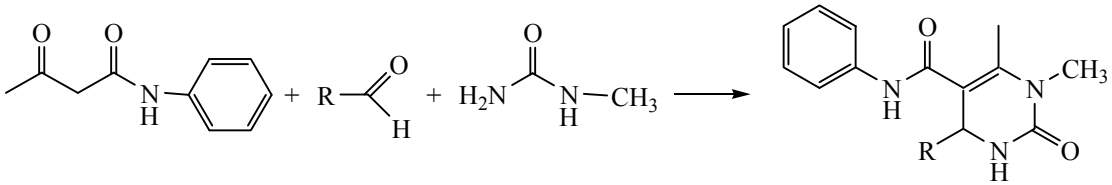
Aiming to obtain the previously unknown pyrimidine derivatives and to study their antimicrobial activity, we synthesized 6-aryl-3,4-dimethyl-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides **I–VI** by reacting acetoacetanilide, aromatic aldehydes, and *N*-methylurea as described in [6] (Scheme 1).

Compounds **I–VI** are colorless crystalline solids soluble in DMF, DMSO, in acetic acid and ethanol upon heating, insoluble in water, toluene, and benzene.

The IR spectra of **I–VI** contained the absorption bands of amide groups (1644–1688 cm^{-1}), N–H (3200–3384 cm^{-1}) and C=C bonds (1608–1640 cm^{-1}).

In the ^{1}H NMR spectra of **I–VI** there were the signals of the protons of 4-CH_3 and 3-CH_3 moieties

Scheme 1.



I–VI

R = 4-$NO_2C_6H_4$ (**I**), 4-FC_6H_4 (**II**), 4-$EtOC_6H_4$ (**III**), 4-ClC_6H_4 (**IV**), 3-$NO_2C_6H_4$ (**V**), 3-$MeOC_6H_4$ (**VI**).

(2.14–2.20 and 3.05–3.23 ppm, respectively), H^6 (5.17–5.38 ppm), H^1 (7.14–7.91 ppm, $J_{1,6}$ 2.95–3.30 Hz), and NH of the amide group (9.58–9.84 ppm).

The spatial structure of **V** was established by X-ray diffraction analysis (see Figure). Single crystals were obtained by slow evaporation of ethanol solution.

General geometric parameters of the molecule (bond lengths and angles) are close to the standard. In the crystal packing there are 2 types of hydrogen bonds: chained intermolecular hydrogen bonds NH···O between the amide moieties, and dimeric bonds NH···O between the pyrimidinone moieties.

Antimicrobial activity of these compounds against strains of *St. aureus, E. coli, C. albicans* (see table) was determined by serial dilutions of the test compound solution in meat-peptone broth and Sabouraud liquid medium. Bacterial load on 1 mL of the culture liquid reached 250 000 microbial cells. Control and test samples were incubated at 36–37°C for 18–20 h. The performed biological tests indicate that the compounds obtained show weak antimicrobial activity.

Antimicrobial activity of compounds **I–VI**

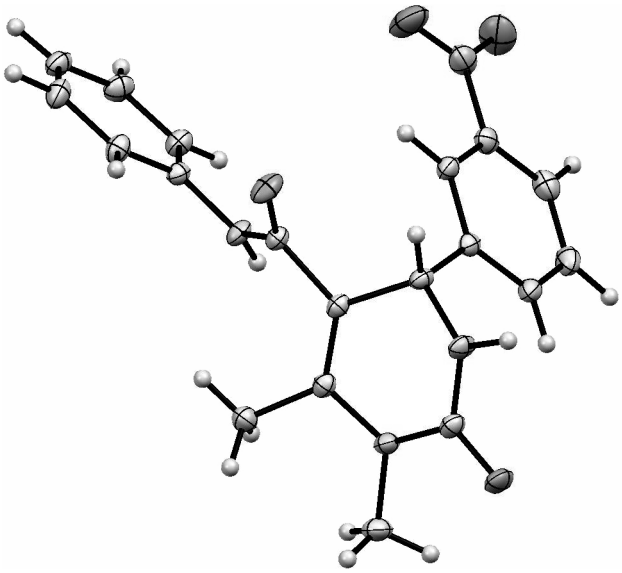
Compound	Minimum inhibitory concentration, mg mL^{-1}		
	St. aureus	*E. coli*	*Candida albicans*
I	1000	1000	250
II	1000	1000	250
III	1000	1000	500
IV	500	1000	125
V	500	1000	125
VI	1000	1000	250
Dioxidine	62.5–1000	3.9–62.5	–
Chloramine B	500	250	–
Fluconazole	–	–	8–32

EXPERIMENTAL

IR spectra were recorded on a Specord M-80 spectrometer from mulls in mineral oil. ^{1}H NMR spectra were registered on a Bruker 500 spectrometer (500.13 MHz) in DMSO-d_6, internal reference TMS. Mass spectra were obtained on a Finnigan MAT INCOS-50 spectrometer with ionization energy of electrons 70 eV. Elemental analysis was performed on a Perkin Elmer 2400 instrument. Melting points were determined on a Melting Point M-565 apparatus.

X-Ray diffraction analysis of compound V was performed on a Xcalibur E automatic diffractometer (MoK_α-radiation, graphite monochromator, ω-scanning, 140 K). Data collection and processing were performed using the CrysAlisPro software package [7]; the structure was solved and refined using the OLEX2 program [8]. The main crystallographic parameters and results of structure refinement are as follows: crystals monoclinic, space group $P2_1/c$, a 15.0841(6), b 5.0547(2), c 22.7354(11) Å, β 96.371(4)°, d_{calc} 1.413 g cm^{-3}, μ 0.102 mm^{-1}; 9279 reflections collected, 4727 independent, R_{int} 0.0208, for reflections with $I > 2\sigma(I)$ R_1 0.0438, wR_2 0.1192. Crystallographic data were deposited in the Cambridge Crystallographic Data Center (CCDC 996028).

3,4-Dimethyl-6-(4-nitrophenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (I). A mixture of 0.01 mol of acetoacetanilide, 0.01 mol of 4-nitrobenzaldehyde, and 0.01 mol of *N*-methylurea was heated at 120–150°C for 10–15 min until gas evolution ceased and the reaction mixture solidified. After cooling, the residue was treated with ethanol, filtered, and recrystallized from ethanol. Yield 2.85 g (78%), mp 236–238°C (EtOH). IR spectrum, ν, cm^{-1}: 1610 (C=C), 1680 (CON), 3200 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.20 s (3H, 4-CH_3), 3.23 s (3H, 3-CH_3), 5.38 d (1H, CH, $J_{1,6}$ 3.30 Hz), 6.87–8.21 m (9H, C_6H_5, $NO_2C_6H_4$), 7.91 d (1H, 1-NH, $J_{1,6}$ 3.30 Hz), 9.84 s (1H, NH, amide). Found, %: C 62.42, 62.15; H 5.02, 4.86; N 15.40, 15.19. $C_{19}H_{18}N_4O_4$. Calculated, %: C 62.29; H 4.95; N 15.29.



General view of the molecule of 3,4-dimethyl-6-(3-nitrophenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide **V**.

Compounds **II**–**VI** were prepared similarly.

3,4-Dimethyl-6-(4-fluorophenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (II). Yield 2.78 g (82%), mp 251–253°C (EtOH). IR spectrum, ν, cm^{-1}: 1620 (C=C), 1675 (CON), 3232 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.15 s (3H, 4-CH_3), 3.10 s (3H, 3-CH_3), 5.30 d (1H, CH, $J_{1,6}$ 3.1 Hz), 6.91–7.57 m (9H, C_6H_5, FC_6H_4), 7.75 d (1H, 1-NH, $J_{1,6}$ 3.1 Hz), 9.80 s (1H, NH, amide). Mass spectrum (70 eV), *m*/*z* (I_{rel}, %): 339 $[M]^+$, 247 $[M - C_6H_5NH]^+$, 219 $[M - C_6H_5NHCO]^+$, 123 $[M - C_6H_5NHCO - FC_6H_4]^+$, 77 $[Ph]^+$. Found, %: C 67.36, 67.11; H 5.43, 5.26; N 12.51, 12.28. $C_{19}H_{18}FN_3O_2$. Calculated, %: C 67.25; H 5.35; N 12.38.

3,4-Dimethyl-6-(4-ethoxyphenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (III). Yield 2.34 g (64%), mp 244–246°C (EtOH). IR spectrum, ν, cm^{-1}: 1640 (C=C), 1672 (CON), 3248 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 1.36 t (3H, $\underline{CH_3}CH_2O$, *J* 6.4 Hz), 3.87 q (2H, $CH_3\underline{CH_2}O$, *J* 6.4 Hz), 2.14 s (3H, 4-CH_3), 3.05 s (3H, 3-CH_3), 5.17 d (1H, CH, $J_{1,6}$ 2.8 Hz), 6.67–7.50 m (9H, C_6H_5, $C_2H_5O\underline{C_6H_4}$), 7.14 d (1H, 1-NH, $J_{1,6}$ 2.8 Hz), 9.58 s (1H, NH, amide). Found, %: C 69.12, 68.89; H 6.42, 6.28; N 11.62, 11.39 $C_{21}H_{23}N_3O_3$. Calculated, %: C 69.02; H 6.34; N 11.50.

3,4-Dimethyl-6-(4-chlorophenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (IV). Yield 2.52 g (71%), mp 263–265°C (EtOH). IR spectrum, ν, cm^{-1}: 1608 (C=C), 1672 (CON), 3288 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.15 s (3H, 4-CH_3), 3.05 s (3H, 3-CH_3), 5.28 d (1H, CH, $J_{1,6}$ 2.9 Hz), 7.61 m (9H, C_6H_5, ClC_6H_4), 7.77 d (1H, 1-NH, $J_{1,6}$ 2.9 Hz), 9.80 s (1H, NH, amide). Mass spectrum (70 eV), *m*/*z* (I_{rel}, %): 355 $[M]^+$, 340 $[M - CH_3]^+$, 263 $[M - C_6H_5NH]^+$, 77 $[Ph]^+$. Found, %: C 64.27, 64.03; H 5.17, 5.01; N 11.93, 11.73. $C_{19}H_{18}ClN_3O_2$. Calculated, %: C 64.14; H 5.10; N 11.81.

3,4-Dimethyl-6-(3-nitrophenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (V). Yield 2.96 g (81%), mp 238–240°C (EtOH). IR spectrum, ν, cm^{-1}: 1608 (C=C), 1644 (CON), 3288 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.18 s (3H, 4-CH_3), 3.06 s (3H, 3-CH_3), 5.31 d (1H, CH, $J_{1,6}$ 2.8 Hz), 6.90–8.05 m (9H, C_6H_5, $NO_2C_6H_4$), 7.84 d (1H, 1-NH, $J_{1,6}$ 2.8 Hz), 9.70 s (1H, NH, amide). Found, %: C 62.38, 62.21; H 5.05, 4.89; N 15.42, 15.16. $C_{19}H_{18}N_4O_4$. Calculated, %: C 62.29; H 4.95; N 15.29.

3,4-Dimethyl-6-(3-methoxyphenyl)-*N*-phenyl-2-oxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (VI). Yield 2.17 g (62%), mp 198–200°C (EtOH). IR spectrum, ν, cm^{-1}: 1616 (C=C), 1688 (CON), 3384 (NH). ^{1}H NMR spectrum (DMSO-d_6), δ, ppm: 2.15 s (3H, 4-CH_3), 3.10 s (3H, 3-CH_3), 3.70 s (3H, CH_3O), 5.25 d (1H, CH, $J_{1,6}$ 3.0 Hz), 6.60–7.60 m (9H, C_6H_5, $CH_3O\underline{C_6H_4}$), 7.77 d (1H, 1-NH, $J_{1,6}$ 3.0 Hz), 9.80 s (1H, NH, amide). Mass spectrum (70 eV), *m*/*z* (I_{rel}, %): 351 $[M]^+$, 336 $[M - CH_3]^+$, 259 $[M - C_6H_5NH]^+$. Found, %: C 68.44, 68.26; H 6.09, 5.93; N 12.08, 11.85. $C_{20}H_{21}N_3O_3$. Calculated, %: C 68.36; H 6.02; N 11.96.

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