ISSN 1070-3632, Russian Journal of General Chemistry, 2016, Vol. 86, No. 12, pp. 2666–2670. © Pleiades Publishing, Ltd., 2016.
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# Synthesis and Antimicrobial Activity of *N*,6-Diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides

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Received April 14, 2016

**Abstract**—Three-component reactions of acetoacetic acid *N*-arylamides, aromatic aldehydes, and thiourea afforded *N*,6-diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides. Structure and antimicrobial activity of the compounds obtained were examined.

**Keywords:** three-component reaction, *N*,6-diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides, antimicrobial activity

**DOI:** 10.1134/S107036321612015X

Dihydropyrimidine-2-one(thione) derivatives are of interest due to wide spectrum of biological activity. Structure of these pyrimidine derivatives includes ester group at the position 5 of heterocycle [1–5]. Some of alkoxycarbonyl derivatives of pyrimidine show cardiovascular [6, 7], antihypertensive [8], antiarrhythmic [9], anticancer [10–12], antioxidant [13, 14], anti-inflammatory [15], fungicidal [16, 17], and antimicrobial [18, 19] activity.

Data on the synthesis of 5-carbamoyl derivatives of dihydropyrimidine-2-ones and -2-thiones are scarce. It is known that biological activity is retained when changing ester moiety at the position 5 of hydrogenated pyrimidine ring with amide group [1–5].

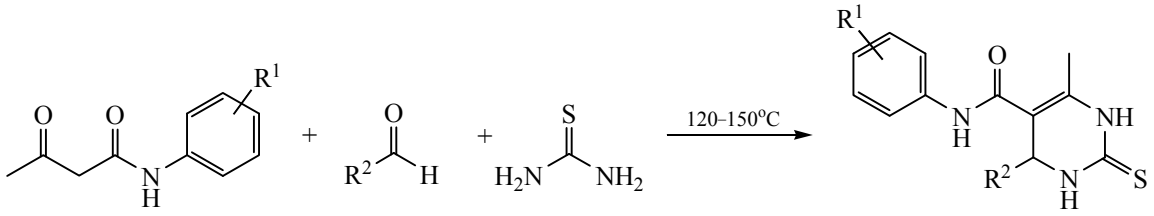
Currently principles of green chemistry are preferred that make promising the synthesis of pyrimidine derivatives without using expensive catalysts and toxic solvents.

In order to obtain new pyrimidine derivatives, study their spatial structure and antimicrobial activity, we synthesized new *N*,6-diaryl-4-methyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamides **1–12** by reacting acetoacetic acid *N*-arylamides with aromatic aldehydes and thiourea. The reactions were carried out without solvent under conditions analogous to those described in [20] (Scheme 1).

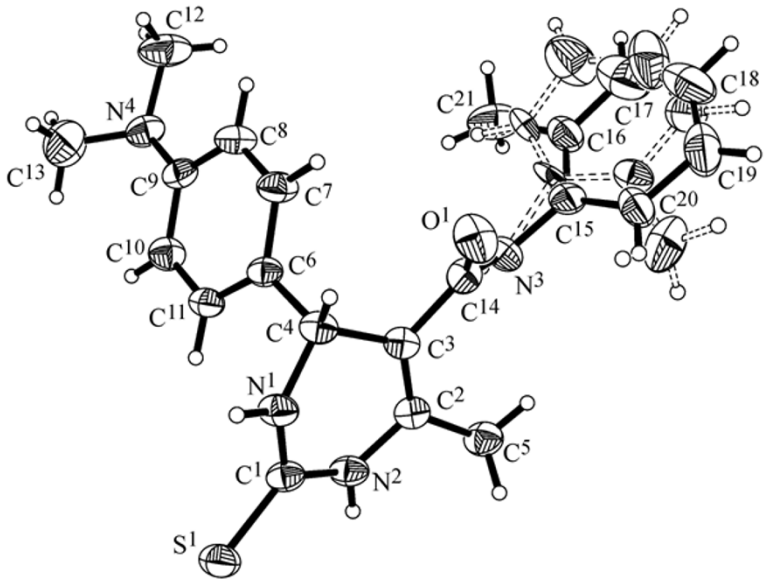
Compounds **1–12** were colorless crystalline substances, soluble in DMF, DMSO, as well as in acetic acid and ethanol on heating, and insoluble in water, benzene and toluene.

The IR spectra of compounds **1–12** contained the absorption bands due to stretching vibrations of amide

**Scheme 1.**




$R^1$ = 2-$CH_3$ (**1–6**), 2,4-$(CH_3)_2$ (**7–9**), 2-Cl (**10–12**); $R^2$ = 4-$FC_6H_4$ (**1**), 4-$CH_3OOCC_6H_4$ (**2**, **9**), 4-$(CH_3)_2NC_6H_4$ (**3**), 2,4-$Cl_2C_6H_3$ (**4**, **10**), 4-$BrC_6H_4$ (**5**), 2-$NO_2C_6H_4$ (**6**, **11**), 3-pyridyl (**7**), 2-thienyl (**8**), 2-$FC_6H_4$ (**12**).




Crystal structure of 4-methyl-6-(4-dimethylaminophenyl)-*N*-2-methylphenyl-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide **3**.

groups (1660–1688 $cm^{-1}$), N–H (3120–3400 $cm^{-1}$) and C=C bonds (1600–1630 $cm^{-1}$).

Compounds **1**–**12** showed characteristically in the $^1H$ NMR spectra a singlet of $C^4H_3$ group (1.85–2.15 ppm), doublets of $H^1$ and $H^6$ protons (5.20–6.02 and 9.05–9.39 ppm, $J_{1,6}$ = 1.9–3.0 Hz), a singlet of amide NH proton (8.91–9.37 ppm), and a broad signal of $N^3H$ moiety (9.74–10.07 ppm). Signals from the corresponding aryl substituents were also present. In the mass spectrum of compound **5** we observed the molecular ion peak $[M]^+$ of *m*/*z* 417 and the fragment ion peaks of *m*/z 311 $[M - CH_3C_6H_4NH]^+$, 106 $[CH_3C_6H_4NH]^+$. These data confirmed the structure of the obtained compounds.

The crystal structure of compound **3** was determined by X-ray diffraction analysis (see figure) of a single crystal obtained by slow crystallization from ethanol. Compound **3** crystallizes in the centrosymmetric space group belonging to the monoclinic crystal system. The tetrahydropyrimidine ring adopts a distorted *boat* conformation; deviations of the $C^1$ and $N^1$ atoms from the $C^4C^3C^2N^2$ plane equal 0.395 and 0.559 Å, respectively. The dimethylaminophenyl moiety occupies pseudo-axial position. The carbonyl group is turned with respect to the $C^4C^3C^2N^2$ plane: the torsion angle $C^2C^3C^{14}O^1$ is –137.1(3)°. The tolylcarbamoyl substituent is not planar: the torsion angles $O^1C^{14}N^3C^{15}$ and $C^{14}N^3C^{15}C^{20}$ are 8.9(8)° and 50(1)°, respectively. The *ortho*-tolyl fragment is disordered by two positions with populations of 0.703(8) and 0.297(8) that indicates the presence of two conformers of compound **3** in the crystal. Molecules of **3** in the crystal are linked to each other through intermolecular hydrogen bonds to form infinite two-dimensional network parallel to the plane (1 0 0). Hydrogen bonding parameters are shown in Table 1.

Antimicrobial activity of compounds **1**–**12** was determined in relation to *St. aureus*, *E. coli*, *C. albicans* strains (Table 2). According to the data obtained, they posses weak antimicrobial activity.

**Table 1.** Hydrogen bonds parameters in the molecule of **3**

| D–H···A | *d*(D–H), Å | *d*(H···A), Å | *d*(D···A), Å | Angle DHA, deg |
|---|---|---|---|---|
| $N^1$–$H^1$···$N^4$ [*x*, –*y* + 1/2, *z* − 1/2] | 0.85(2) | 2.22(2) | 3.031(3) | 160(2) |
| $N^2$–$H^2$···$S^1$ [–*x* + 1, –*y*, –*z* + 2] | 0.83(3) | 2.56(3) | 3.378(3) | 169(3) |
| $N^3$–$H^3$···$O^1$ [*x*, –*y* + 1/2, *z* + 1/2] | 0.82(2) | 2.00(2) | 2.819(3) | 174(3) |

**Table 2.** Antimicrobial activity of compounds **1–12**

| Compound | MIC, μg/mL | | |
|---|---|---|---|
| | *St. aureus* ATCC 6538 | *E. coli* ATCC 25922 | *C. albicans* ATCC 24433 |
| **1** | 500 | 500 | н/а |
| **2** | 500 | 500 | 1000 |
| **3** | 500 | 1000 | 1000 |
| **4** | 500 | 1000 | 500 |
| **5** | 500 | 1000 | – |
| **6** | 500 | 500 | 250 |
| **7** | 1000 | 1000 | 125 |
| **8** | 500 | 500 | 250 |
| **9** | 500 | 500 | 1000 |
| **10** | 1000 | 1000 | 500 |
| **11** | 1000 | 1000 | 250 |
| **12** | 500 | 500 | 1000 |
| Dioxidine | 62.5–1000 | 3.9–62.5 | – |
| Chloramine B | 500 | 250 | – |
| Fluconazole | – | – | 8–32 |

## EXPERIMENTAL

IR spectra in mineral oil were recorded on a Specord M-80 spectrometer. $^1$H NMR spectra of the solutions in DMSO-$d_6$ were registered on a Bruker 500 spectrometer (500.13 MHz) relative to internal TMS. Mass spectrum was obtained on a Finnigan MAT INCOS-50 instrument (ionization energy 70 eV). Elemental analysis was performed on a Perkin Elmer 2400 analyzer. Melting points were determined on a M-565 instrument.

**X-ray diffraction analysis** of compound **3** was performed on a Xcalibur R diffractometer equipped with a CCD-detector [Mo$K_\alpha$-radiation, 295(2) K, ω-scanning]. A correction for absorption was applied empirically using SCALE3 ABSPACK algorithm [21]. Crystals of compound **3**, $C_{21}H_{24}N_4O_3S$, monoclinic, space group $P21/c$, unit cell parameters: $a$ = 11.630(5), $b$ = 19.765(6), $c$ = 9.414(3) Å, β = 101.47(3)°, $V$ 2120.6(14) Å$^3$, $d_{calc}$ = 1.192 g/cm$^3$, μ = 0.170 mm$^{-1}$, $Z$ = 4. The structure was solved by the direct full-matrix method and refined by anisotropic approximation for all non-hydrogen atoms. Hydrogen atoms were refined according to a *rider* model in isotropic approximation with dependent thermal parameters; the NH hydrogen atoms were localized from difference electron density synthesis and refined independently in an isotropic approximation. Atomic coordinates of the disordered components were determined taking into account SAME soft limits. All calculations were performed using SHELX-97 [22] and OLEX2 [23] program packages. The final divergence factors: $R_1$ = 0.0657, $wR_2$ = 0.1243 for 2288 reflections with $I > 2\sigma(I)$, $R_1$ = 0.1609, $wR_2$ = 0.1659 for all 4943 independent reflections, $S$ = 1.002. The crystallographic data for compound **3** were deposited to the Cambridge Crystallographic Data Centre (CCDC 1471336).

**4-Methyl-*N*-(2-methylphenyl)-6-(4-fluorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (1).** A mixture of 0.01 mol of 2-methylacetoacetanilide, 0.01 mol of 4-fluorobenzaldehyde, and 0.01 moles of thiourea was heated at 120–150°C for 5–10 min until gas evolution ceased and the reaction mixture solidified. After cooling, the solid was treated with ethanol, filtered, and recrystallized from ethanol. Yield 2.56 g (72%), mp 170–172°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1616 (C=C), 1688 (CON), 3216 (NH). $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.89 s (3H, 4-$CH_3$), 2.12 s (3H, $\underline{CH_3}C_6H_4$), 5.34 d (1H, CH, $J_{1,6}$ = 1.9 Hz), 7.02–7.24 m (8H, $CH_3C_6\underline{H_4}$, $FC_6H_4$), 9.10 s (1H, NH, amide), 9.30 d (1H, N$^1$H, $J_{1,6}$ = 1.9 Hz), 9.88 br.s (1H, N$^3$H). Found, %: C 64.10, 64.33; H 5.02, 5.19; N 11.71, 11.95. $C_{19}H_{18}FN_3OS$. Calculated, %: C 64.21; H 5.10; N 11.82.

Compounds **2–12** were prepared similarly.

**6-(4-Carbomethoxyphenyl)-4-methyl-*N*-(2-methylphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (2).** Yield 3.08 g (78%), mp 234–236°C (EtOH). IR spectrum, ν, cm$^{-1}$: 1630 (C=C), 1680 (CON), 1720 (CO), 3150, 3200, 3360 (NH). $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.90 s (3H, 4-$CH_3$), 2.12 s (3H, $\underline{CH_3}C_6H_4$), 3.79 s (3H, $\underline{CH_3}OOCC_6H_4$), 5.42 d (1H, CH, $J_{1,6}$ = 2.1 Hz), 7.02–7.93 m (8H, $CH_3C_6\underline{H_4}$, $CH_3OOCC_6\underline{H_4}$), 9.14 s (1H, NH, amide), 9.36 d (1H, N$^1$H, $J_{1,6}$ = 2.1 Hz), 9.93 br.s (1H, N$^3$H). Found, %: C 63.67, 63.90; H 5.27, 5.45; N 10.49, 10.75. $C_{21}H_{21}N_3O_3S$. Calculated, %: C 63.78; H 5.35; N 10.62.

**4-Methyl-*N*-(2-methylphenyl)-6-(4-dimethylaminophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (3).** Yield 2.21 g (58%), mp 238–240°C (EtOH). $^1$H NMR spectrum (DMSO-$d_6$), δ, ppm: 1.89 s (3H, 4-$CH_3$), 2.10 s (3H, $\underline{CH_3}C_6H_4$), 2.82 s [6H, $(\underline{CH_3})_2NC_6H_4$], 5.20 d (1H, CH, $J_{1,6}$ = 2.1 Hz), 6.57–7.02 m [8H, $CH_3C_6\underline{H_4}$, $(CH_3)_2NC_6\underline{H_4}$], 8.95 s (1H, NH, amide), 9.18 d (1H, N$^1$H, $J_{1,6}$ = 2.1 Hz), 9.74 br.s (1H, N$^3$H). Found, %: C 66.17, 66.41; H 6.26, 6.45; N

14.59, 14.84. $C_{21}H_{24}N_4OS$. Calculated, %: C 66.29; H 6.36; N 14.72.

**4-Methyl-*N*-(2-methylphenyl)-6-(2,4-dichlorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (4).** Yield 2.76 g (68%), mp 262–264°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1610 (C=C), 1660 (CON), 3180, 3210, 3352 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.91 s (3H, 4-$CH_3$), 2.08 s (3H, $\underline{CH_3}C_6H_4$), 5.67 d (1H, CH, $J_{1,6}$ = 2.8 Hz), 6.99–7.34 m (7H, $CH_3C_6\underline{H_4}$, 2,4-$Cl_2C_6H_3$), 9.02 s (1H, NH, amide), 9.05 d (1H, $N^1H$, $J_{1,6}$ = 2.8 Hz), 9.82 br.s (1H, $N^3H$). Found, %: C 56.04, 56.27; H 4.13, 4.30; N 10.22, 10.47. $C_{19}H_{17}Cl_2N_3OS$. Calculated, %: C 56.16; H 4.22; N 10.34.

**4-Methyl-6-(4-bromophenyl)-*N*-(2-methylphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (5).** Yield 2.87 g (69%), mp 246–248°C (EtOH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.91 s (3H, 4-$CH_3$), 2.11 s (3H, $\underline{CH_3}C_6H_4$), 5.31 d (1H, CH, $J_{1,6}$ = 3.0 Hz), 6.85–7.55 m (8H, $CH_3C_6\underline{H_4}$, 4-$BrC_6H_4$), 9.13 s (1H, NH, amide), 9.20 d (1H, $N^1H$, $J_{1,6}$ = 3.0 Hz), 10.00 br.s (1H, $N^3H$). Found, %: C 54.68, 54.93; H 4.28, 4.45; N 9.98, 10.22. $C_{19}H_{18}BrN_3OS$. Calculated, %: C 54.81; H 4.36; N 10.09.

**4-Methyl-*N*-(2-methylphenyl)-6-(2-nitrophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (6).** Yield 2.44 g (64%), mp 216–218°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1620 (C=C), 1670 (CON), 3180, 3280, 3400 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.86 s (3H, 4-$CH_3$), 2.10 s (3H, $\underline{CH_3}C_6H_4$), 6.02 d (1H, CH, $J_{1,6}$ = 2.8 Hz), 7.00–7.89 m (8H, $CH_3C_6\underline{H_4}$, 2-$NO_2C_6H_4$), 9.07 d (1H, $N^1H$, $J_{1,6}$ = 2.8 Hz), 9.16 s (1H, NH, amide), 10.02 br.s (1H, $N^3H$). Found, %: C 59.56, 59.80; H 4.64, 4.83; N 14.52, 14.77. $C_{19}H_{18}N_4O_3S$. Calculated, %: C 59.67; H 4.74; N 14.65.

**4-Methyl-6-(3-pyridyl)-*N*-(2,4-dimethylphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (7).** Yield 2.64 g (75%), mp 266–268°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1600 (C=C), 1660 (CON), 3200 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.85 s (3H, 4-$CH_3$), 2.12 s and 2.19 s [6H, $(\underline{CH_3})_2C_6H_3$], 5.35 d (1H, CH, $J_{1,6}$ = 2.1 Hz), 6.86–7.63 m [7H, $(CH_3)_2C_6\underline{H_3}$, $C_5H_4N$], 9.08 s (1H, NH, amide), 9.32 d (1H, $N^1H$, $J_{1,6}$ = 2.1 Hz), 9.90 br.s (1H, $N^3H$). Found, %: C 64.64, 64.87; H 5.62, 5.81; N 15.78, 16.03. $C_{19}H_{20}N_4OS$. Calculated, %: C 64.75; H 5.72; N 15.90.

**4-Methyl-6-(2-thienyl)-*N*-(2,4-dimethylphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (8).** Yield 2.26 g (63%), mp 240–242°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1610 (C=C), 1660 (CON), 3120, 3210, 3320 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.94 s (3H, 4-$CH_3$), 2.13 s and 2.22 s [6H, $(\underline{CH_3})_2C_6H_3$], 5.59 d (1H, CH, $J_{1,6}$ = 2.8 Hz), 6.79–7.33 m [6H, $(CH_3)_2C_6\underline{H_3}$, $C_4H_3S$], 8.91 s (1H, NH, amide), 9.39 d (1H, $N^1H$, $J_{1,6}$ = 2.8 Hz), 9.90 br.s (1H, $N^3H$). Found, %: C 60.37, 60.61; H 5.28, 5.45; N 11.62, 11.87. $C_{18}H_{19}N_3OS_2$. Calculated, %: C 60.48; H 5.36; N 11.75.

**6-(4-Carbomethoxyphenyl)-4-methyl-*N*-(2,4-dimethylphenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (9).** Yield 3.24 g (79%), mp 240–242°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1630 (C=C), 1680 (CON), 1720 (CO), 3200, 3150, 3380 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 1.86 s (3H, 4-$CH_3$), 2.11 s and 2.19 s [6H, $(\underline{CH_3})_2C_6H_3$], 3.79 s (3H, $\underline{CH_3}OOCC_6H_4$), 5.41 d (1H, CH, $J_{1,6}$ = 2.1 Hz), 6.86–7.92 m [7H, $(CH_3)_2C_6\underline{H_3}$, $CH_3OOCC_6\underline{H_4}$], 9.06 s (1H, NH, amide), 9.34 d (1H, $N^1H$, $J_{1,6}$ = 2.1 Hz), 9.92 br.s (1H, $N^3H$). Found, %: C 64.42, 64.65; H 5.58, 5.75; N 10.14, 10.39. $C_{22}H_{23}N_3O_3S$. Calculated, %: C 64.53; H 5.66; N 10.26.

**4-Methyl-6-(2,4-dichlorophenyl)-*N*-(2-chlorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (10).** Yield 3.50 g (82%), mp 256–258°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1620 (C=C), 1680 (CON), 3190, 3220, 3390 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 2.10 s (3H, 4-$CH_3$), 5.66 d (1H, CH, $J_{1,6}$ = 1.9 Hz), 7.06–7.49 m (7H, $ClC_6H_4$, 2,4-$Cl_2C_6H_3$), 9.23 d (1H, $N^1H$, $J_{1,6}$ = 1.9 Hz), 9.37 s (1H, NH, amide), 9.99 br.s (1H, $N^3H$). Found, %: C 50.55, 50.79; H 3.24, 3.39; N 9.73, 9.98. $C_{18}H_{14}Cl_3N_3OS$. Calculated, %: C 50.66; H 3.31; N 9.85.

**4-Methyl-6-(2-nitrophenyl)-*N*-(2-chlorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (11).** Yield 3.17 g (79%), mp 200–202°C (EtOH). IR spectrum, ν, $cm^{-1}$: 1620 (C=C), 1680 (CON), 3190, 3320, 3410 (NH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 2.15 s (3H, 4-$CH_3$), 6.01 d (1H, CH, $J_{1,6}$ = 1.9 Hz), 7.06–7.89 m (8H, $ClC_6H_4$, 2-$NO_2C_6H_4$), 9.09 d (1H, $N^1H$, $J_{1,6}$ = 1.9 Hz), 9.30 s (1H, NH, amide), 10.07 br.s (1H, $N^3H$). Found, %: C 53.55, 53.80; H 3.65, 3.84; N 13.78, 14.04. $C_{18}H_{15}ClN_4O_3S$. Calculated, %: C 53.67; H 3.75; N 13.91.

**4-Methyl-6-(2-fluorophenyl)-*N*-(2-chlorophenyl)-2-thioxo-1,2,3,6-tetrahydropyrimidine-5-carboxamide (12).** Yield 3.15 g (84%), mp 210–212°C (EtOH). $^1H$ NMR spectrum (DMSO-$d_6$), δ, ppm: 2.11 s (3H, 4-

$CH_3$), 5.57 d (1H, CH, $J_{1,6}$ = 1.9 Hz), 6.99–7.36 m (8H, $ClC_6H_4$, $FC_6H_4$), 9.20 d (1H, $N^1H$, $J_{1,6}$ = 1.9 Hz), 9.30 s (1H, NH, amide), 9.91 br.s (1H, $N^3H$). Found, %: C 57.41, 57.64; H 3.93, 4.10; N 11.06, 11.31. $C_{18}H_{15}ClFN_3OS$. Calculated, %: C 57.52; H 4.02; N 11.18.

Antimicrobial activity of the compounds obtained against strains of *St. aureus*, *E. coli* and *C. albicans* was determined by serial dilutions of the test compound solution with meat-peptone broth and Sabouraud liquid medium and examined activity. Bacterial load on 1 mL of culture liquid was 250 000 microbial cells. Control and test tubes were incubated at 36–37°C for 18–20 h. Growth of bacterial cultures or inhibition due to the bacteriostatic action of the test compounds was registered. Minimum inhibitory concentration of the substance (MIC, μg/mL), which inhibits the growth of bacterial cultures, was determined. Dioxidine, chloramine B, and fluconazole were used as comparison drugs.

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