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Synthesis of New Derivatives of 5-(3,4-Dihydro-2*H*-pyrrol-5-yl)-pyrimidine

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Abstract—By one-stage condensation of 6-(arylamino)pyrimidine-2,4(1*H*,3*H*)-diones with pyrrolidin-2-one new potential antiviral compounds were obtained, analogs of pyrrolinylpyrimidine containing structural fragments of known drugs AZT and HEPT used in treating HIV-infections.

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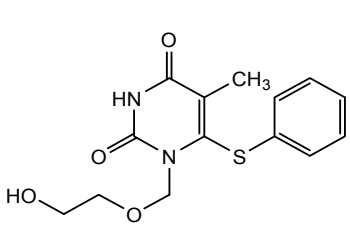
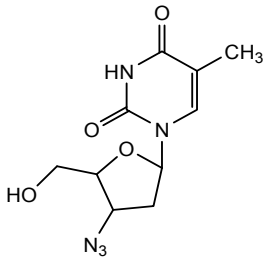
Derivatives of pyrimidine and its nucleosides are vitally important because they exhibit a wide spectrum of bioactivity, in particular, antitumor, antiviral, antifungal, antituberculosis, etc. [1]. After appearance of drugs with antitumor, antiviral, and especially anti-HIV activity in clinics, the interest to derivatives of uracyl and pyrimidine, substituted in the position *5* or *6* of pyrimidine ring grew significantly. To the series of compounds possessing positive effect against HIV belong 1-(2-hydroxyethoxy)methyl-6-(phenylsulfanyl)-thymine (HEPT) [2–4], 6-benzyl-5-isopropyl-1-(ethoxymethyl)-uracyl [5, 6], 2-alkoxy-6-benzyl-3,4-dihydropyrimidin-4(1*H*)-ones (DABOs) [7], 3'-azido-2',3'-dideoxythymidine (AZT) [8], and others.

Chemical modification of nucleosides is long proved as important way to increasing antiviral and antitumor activity [9–11]. In contrast to natural nucleosides in *C*-nucleosides the ribofuranosyl residue is bound with heterocyclic base with a glycoside bond C–C, resistant to chemical and enzymatic hydrolysis. On top of that the replacement of the glycoside oxygen atom in carbohydrate residue of *C*-nucleosides for nitrogen atom is known to result in *C*-azanucleosides, capable to inhibit glycohydrolases responsible for decomposition of glycoside bonds [12–14].



HEPT

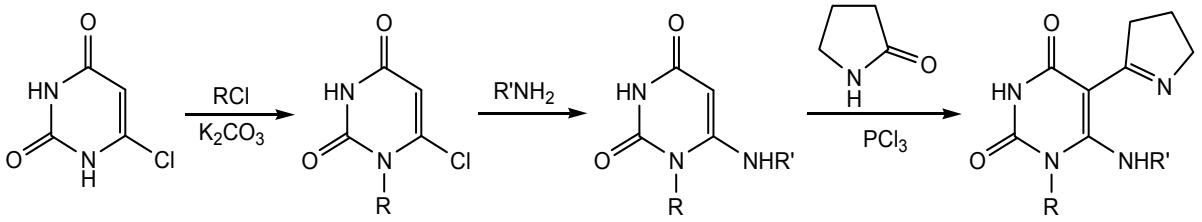


AZT

In the literature different methods of synthesis are described of *C*-azanucleosides, in particular, using Heck reaction, 1,3-dipolar cycloaddition, *C*-nucleosidation by Mannich type, cyclization of γ-azido ketones by Straudinger–aza-Wittig reaction, etc. [15–23]. All these methods are labor consuming and multistage, therefore developing more accessible methods of synthesis is an actual task.

Since pyrrolidin-2-ones possessing various bioactivities are applied in pharmacy [24, 25], it was desirable to introduce pyrrolidine ring as a substituent into pyrimidine molecule aiming to investigate biological properties of obtained compounds. Previously we suggested and realized a one-stage synthesis of new *C*-azanucleosides, derivatives of pyrrolinylpyrimidine [26], in conditions of Vilsmeier

Scheme 1.



R = Bn, R'= Ph (**2**, **4**, **7**), 3,5-$Me_2C_6H_3$ (**5**, **8**); R = $(CH_2)_3$Ph, R' = 3,5-$Me_2C_6H_3$ (**3**, **6**, **9**).

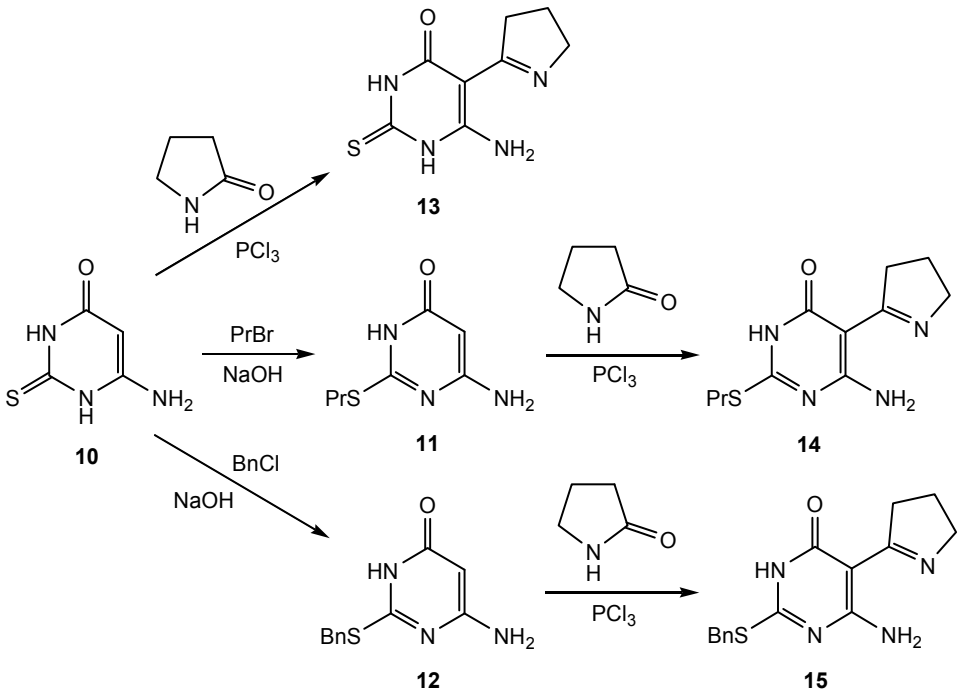
reaction, but using pyrrolidin-2-one instead of DMF. In this study we obtained new analogs of 5-(3,4-dihydro-2*H*-pyrrol-5-yl)pyrimidine **7–9**, **13–15**, and **20–23**.

As initial compound 6-chloropyrimidine-2,4-(1*H*,3*H*)-dione **1** [27] was used, which by reaction with benzyl chloride or phenylpropyl bromide in DMF in the presence of potassium carbonate afforded the corresponding N^1-derivatives **2** [28] and **3**. The reaction of compounds **2** and **3** with aniline or dimethylaniline results in 6-aniline-substituted pyrimidines **4–6**, by their condensation with pyrrolidin-2-one in the presence of PCl_3 under conditions of Vilsmeier reaction [26] derivatives of 5-(3,4-dihydro-2*H*-pyrrol-5-yl)pyrimidine-2,4(1*H*,3*H*)-dione **7–9** (Scheme 1) were synthesized.

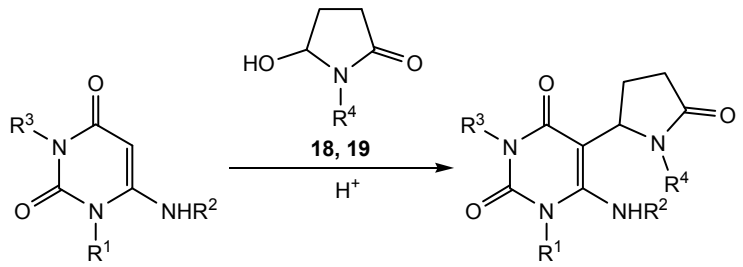
By the reaction of 6-amino-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one **10** with propyl bromide and benzyl chloride were similarly obtained the corresponding sulfanyl derivatives of pyrimidine **11** and **12** [29]. Compounds **10–12** were condensed with pyrrolidin-2-one in the presence of PCl_3 to obtain the corresponding products **13–15** resulting from the condensation at the position *5* of pyrimidine (Scheme 2).

The optimum path of producing derivatives of pyrrolinylpyrimidine is the reaction of *N*-substituted 5-hydroxypyrrolidin-2-ones with nucleophiles. Of many known methods producing 5-hydroxypyrrolidin-2-ones substituted at the nitrogen atom by the reduction with sodium borohydride of *N*-substituted succinimides the method of pH-controlled reduction turned out to be the

Scheme 2.



Scheme 3.



5, 16, 17 **20–23**

R^1 = Bn, R^2 = 3,5-$Me_2C_6H_3$, R^3 = H, R^4 = Bn (**5**, **18**, **20**); R^1 = R^2 = R^3 = H, R^4 = Bn (**16**, **21**); R^1 = R^3 = Me, R^2 = H, R^4 = Bn (**17**, **22**); R^1 = R^2 = R^3 = H, R^4 = 4-$MeOC_6H_4$ (**19**, **23**).

optimal [30]. Despite wide temperature range recommended by different authors (–20 to 0°C), only reduction at –30°C allowed the preparation of compounds **18** and **19** and prevented the opening of the pyrrolidine ring and undesired generation of amidoalcohol.

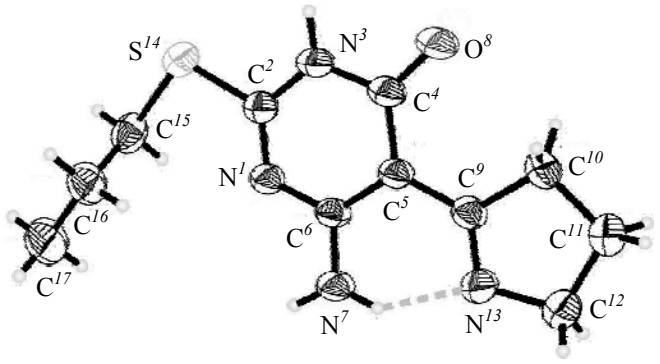


Fig. 1. Structure of the molecule of 6-amino-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-propylsulfanylpyrimidin-4(3*H*)-one **14** with random atom numeration, ellipsoids of anisotropic thermal oscillations are shown with 50% probability, intramolecular hydrogen bond is marked with dashed line.

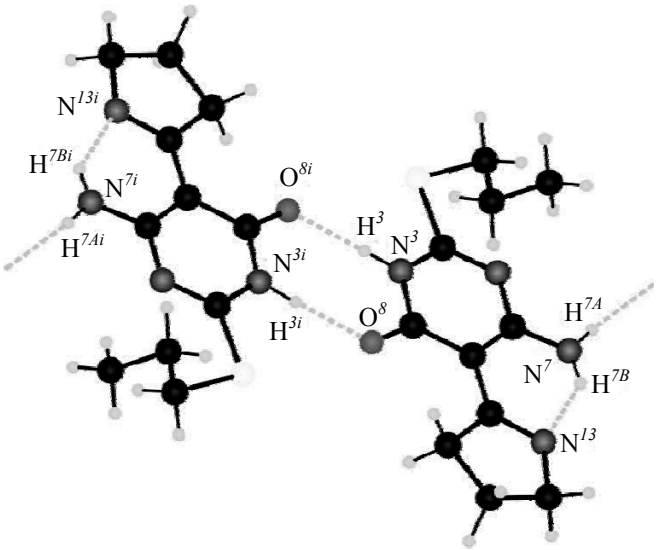


Fig. 2. Intermolecular and intramolecular bonds in structure of compound **14**, symmetry code *i* 1 – *x*, 1 – *y*, –*z*, hydrogen bonds are marked with dashed lines.

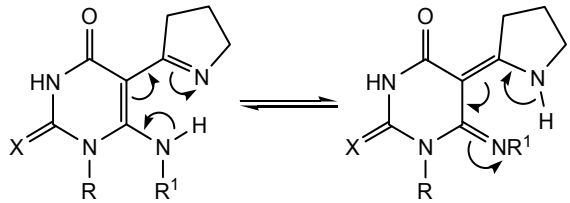
At heating the derivatives of pyrimidine **5**, **16**, and **17** with *N*-substituted 5-hydroxypyrrolidin-2-ones **18** [31], **19** [32] in glacial acetic acid by method [33] analogs were obtained of 5-(3,4-dihydro-2*H*-pyrrol-5-yl)pyrimidine-2,4(1*H*,3*H*)-dione **20–23** (Scheme 3).

The structure of obtained compounds was confirmed by IR and ^{1}H NMR spectra, and of compound **15** also by ^{13}C NMR spectrum.

Signals of protons of NH and NH_2 groups in ^{1}H NMR spectra are significantly broadened due to the formation of intermolecular and intramolecular hydrogen bonds in the solution. In ^{1}H NMR spectra of compounds **13–15** NH_2 group appears as two broad signals (of 1H) at 7.0 and 11.0 ppm that perhaps follows from the formation of the hydrogen bond between the nitrogen atom of pyrrolidine ring and NH_2 group.

For compounds **7–9** and **13–15** tautomeric transformations may occur (Scheme 4).

Scheme 4.



Structure of compound **14** was confirmed by X-ray diffraction analysis. Analysis of the conformations of cyclic fragments showed that deviation of atoms from the averaged plane of the pyrimidine ring does not exceed 0.0070(1) Å, and the pyrrolidine ring has a weakly pronounced *envelope* conformation, the

Table 1. Geometry of hydrogen bonds in crystal of compounds **14**

D–H···A	D–H, Å	H···A, Å	D–A, Å	Angle DHA, deg	Symmetry code
N^{3}–H^{3}···O^{8i}	0.892(19)	1.867(19)	2.7579(19)	178(2)	*i* 1 – *x*, 1 – *y*, –*z*
N^{7}–H^{7A}···N^{13ii}	0.93(2)	2.28(2)	3.196(2)	170(2)	*ii* 2 – *x*, 1/2 + *y*, 1/2 – *z*
N^{7}–H^{7B}···N^{13}	0.87(2)	1.96(2)	2.672(2)	138.3(19)	

deviation of C^{9}, C^{10}, C^{12} and N^{13} atoms from its plane does not exceed 0.0095(1) Å, of atom C^{11}, 0.1038(1) Å (Fig. 1). It turned out from the conformational calculations that cyclic fragments are coplanar, the dihedral angle between the averaged planes of pyrimidine and pyrrololidine rings is 1.141(2)°. In the structure of compound **14** between atoms N^{7}–H^{7B}···N^{13} intrarmolecular hydrogen bond exists, the length of the donor-acceptor bond is 2.672(2) Å (Fig. 1).

In the crystal lattice the molecules connected by hydrogen bonds (N^{3}–H^{3}···O^{8i}, N^{3i}–H^{3i}···O^{8} and N^{7}–H^{7A}···N^{13ii}) form two-dimensional nets parallel to the plane (1 0 –2) (Figs. 2, 3). Parameters of hydrogen bonds are compiled in Table 1.

New analogs of pyrrolinylpyrimidine **7–9**, **13–15**, and **20–23** obtained in this research are presently undergoing biological investigations, their result will be published separately.

EXPERIMENTAL

IR spectra were registered on a spectrometer Nicolet Avatar 330 FT-IR from thin layer. ^{1}H and ^{13}C NMR spectra were recorded at 303 K on a Varian Mercury-300VX instrument at operating frequencies 300 and 75 MHz correspondingly from compounds solutions in DMSO-d_6–CCl_4, 1 : 3. Chemical shifts were measured with respect to residual signal of DMSO (2.50 ppm). The reactions progress and compounds purity was monitored by TLC on Silufol UV-254 plates using eluent systems acetone–nonane, 2 : 1 (A), 1-butanol–acetic acid–water, 3 : 1 : 1 (B), 1-butanol saturated with NH_3 (C), development with iodine vapor and phosphorus molybdic acid.

X-ray diffraction analysis of compound **14** was realized at room temperature on an autodiffractometer CAD-4 Enraf-Nonius (graphite monochromator, MoK_α-radiation, θ /2θ-scanning). The extinction was taken into account by the method of psi-scanning [34]. The structure was solved by the direct method. Coordinates of hydrogen atoms were partially determined from differential Fourier synthesis. Coordinates of hydrogen atoms of methyl group were determined by geometrical calculations and refined in the *rider* model on the following conditions: bonds length C–H 0.96 Å, $U_{iso}(H) = 1.5U_{eq}(C)$. The structure was refined by full matrix least-squares method in anisotropic approximation for nonhydrogen atoms and in isotropic approximation for hydrogen. All calculations were performed using software complex SHELXTL [35]. Basic crystallographic characteristics and experimental data of compound **14** were collected in Table 2. Crystallographic data in CIF were deposited in Cambridge Crystallographic Data Centre, deposit number CCDC 1452678.

1-Benzyl-6-chloropyrimidine-2,4(1*H*,3*H*)-dione 2 was obtained by the method [28].

1-(3-Phenylpropyl)-6-chloropyrimidine-2,4-(1*H*,3*H*)-dione (3). A mixture of 1.47 g (10 mmol) of 6-chloropyrimidine-2,4(1*H*,3*H*)-dione **1** [27], 2.0 g (10 mmol) of (3-bromopropyl)benzene, 1.4 g (10 mmol) of K_2CO_3 in 10 mL of DMF was heated for 8 h at 65°C. The solvent was distilled off, the residue was triturated in 10 mL of water, the precipitate was filtered off, washed with water, dried, and recrystallized. Yield 1.9 g

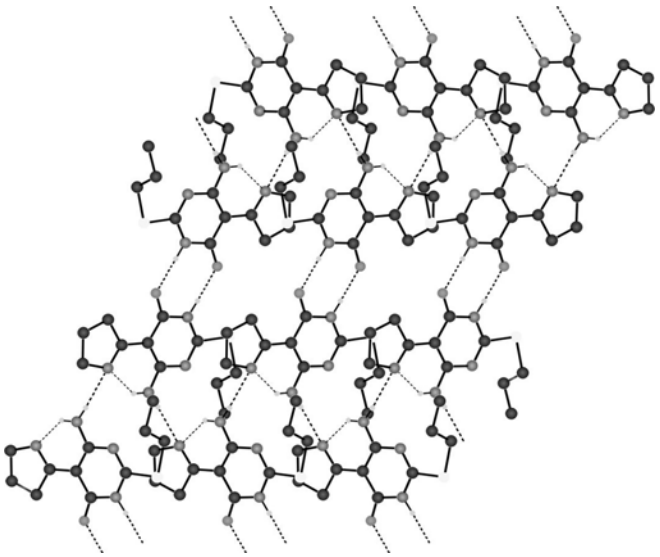


Fig. 3. Two-dimensional lattice parallel to the plane (1 0 –2) formed by intermolecular bonds, hydrogen bonds are marked with dashed lines.

Table 2. Basic crystallographic characteristics of 6-amino-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(propylsulfanyl)-pyrimidin-4(3*H*)-one **14**

Empirical formula	$C_{11}H_{16}N_4OS$
M	252.34
Crystal system	Monoclinic
Space group	*P*21/*c*
a, *b*, *c*, Å	10.623(2), 6.5812(13), 18.475(4)
β, deg	105.93(3)
V, Å^3	1242.0(5)
Z	4
D_{calc}, g/cm^3	1.349
μ(MoK_α) mm^{-1}, T_{min}, T_{max}	0.251, 0.30591, 0.33438
F(000)	536
Crystal size, mm	0.22 × 0.30 × 0.35
Temperature, K	293
Radiation wavelength, Å	0.71073
θ_{min}, θ_{max}, deg	2.0, 30.0
Scanning range	$0 \le h \le 14$, $0 \le k \le 9$, $-25 \le l \le 24$
Measured reflections	3786
Reflections with [$I>2.0\sigma(I)$]	2755
N_{ref}, N_{par}	3609, 207
R, WR_2, *S*	0.0422, 0.1223, 1.05
Weight scheme	$W = 1/[\sigma^2(Fo^2) + (0.0609P)^2 + 0.2601P]$, where $P = (Fo^2 + 2Fc^2)/3$

(72%), mp 140–142°C (2-propanol), R_f 0.73 (A). ^{1}H NMR spectrum, δ, ppm: 1.88–1.99 m (2H, CH_2), 2.65 t (2H, C<u>H</u>$_2$Ph, *J* 7.5 Hz), 3.71–3.78 m (2H, NCH_2), 5.71 d (1H, =CH, *J* 1.9 Hz), 7.09–7.24 m (5H$_{arom}$), 11.41 br.d (1H, NH, *J* 1.9 Hz). Found, %: C 58.80; H 4.73; N 10.29. $C_{13}H_{13}ClN_2O_2$. Calculated, %: C 58.99; H 4.95; N 10.58.

Compounds (4–6). General method. A mixture of 10 mmol of 1-R-pyrimidine-2,4(1*H*,3*H*)-dione **2** [28] or **3** and 20 mmol of aniline or dimethylaniline was boiled until reaction was completed (control with TLC). Then 10 mL of water was added, the reaction product was triturated, the formed precipitate was filtered off, washed with water, dried, and recrystallized.

6-Anilino-1-benzylpyrimidine-2,4(1*H*,3*H*)-dione (4). Yield 2.2 g (75%), mp 301–303°C (2-propanol), R_f 0.42 (A). IR spectrum, ν, cm^{-1}: 3267 (NH), 1681 (C=O). ^{1}H NMR spectrum, δ, ppm: 4.58 d (1H, =CH, *J* 1.6 Hz), 5.27 s (2H, NCH_2), 7.08–7.38 m (10H$_{arom}$), 8.24 s (1H, N<u>H</u>Ph), 10.59 br.s (1H, NH). Found, %: C 69.81; H 5.33; N 14.02. $C_{17}H_{15}N_3O_2$. Calculated, %: C 69.61; H 5.15; N 14.33.

1-Benzyl-6-(3,5-dimethylanilino)pyrimidine-2,4-(1*H*,3*H*)-dione (5). Yield 2.5 g (80%), mp 273–275°C (2-propanol), R_f 0.79 (B). IR spectrum, ν, cm^{-1}: 3277 (NH); 1690, 1638 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.29 s (6H, CH_3), 4.60 d (1H, =CH, *J* 1.4 Hz), 5.25 s (2H, NCH_2), 6.70 d (2H, C_6H_3, *J* 1.4 Hz), 6.77 br.t (1H, C_6H_3, *J* 1.4 Hz), 7.20–7.36 m (5H$_{arom}$), 8.07 s (1H, N<u>H</u>Ph), 10.44 br.s (1H, NH). Found, %: C 71.28; H 5.69; N 13.24. $C_{19}H_{19}N_3O_2$. Calculated, %: C 71.01; H 5.96; N 13.08.

6-(3,5-Dimethylanilino)-1-(3-phenylpropyl)-pyrimidine-2,4(1*H*,3*H*)-dione (6). Yield 2.4 g (69%), mp 240–242°C (2-propanol), R_f 0.74 (B). IR spectrum, ν, cm^{-1}: 3240, 3178 (NH); 1693, 1653 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.90–2.02 m (2H, CH_2), 2.33 s (6H, CH_3), 2.65–2.72 m (2H, C<u>H</u>$_2$Ph), 3.98–4.05 m (2H, NCH_2), 4.50 d (1H, =CH, *J* 2.0 Hz), 6.82 s (3H, C_6H_3), 7.09–7.14 m (1H$_{arom}$), 7.19–7.26 m (4H$_{arom}$), 8.08 s (1H, N<u>H</u>Ph), 10.25 br.d (1H, NH, *J* 2.0 Hz). Found, %: C 72.43; H 6.31; N 12.25. $C_{21}H_{23}N_3O_2$. Calculated, %: C 72.18; H 6.63; N 12.03.

Compounds (7–9 and 13–15). General method. To 1.9 g (20 mmol) of pyrrolidin-2-one in 5 mL of 1,4-dioxane at 0–5°C while vigorously stirring was added dropwise 2.74 g (20 mmol) of PCl_3. The reaction mixture was stirred for 15 min at 30°C and during 10 min was gradually added 10 mmol of compounds **4–6** or **10–12** dissolved in minimal amount of 1,4-dioxane. The reaction mixture was stirred for 3 h at 60°C, the temperature was raised to 100°C and the stirring continued for 15 min more. After cooling 50 mL of ice cold water was added, the solution was filtered from a little amount of precipitate, the filtrate was neutralized with 30% NH_4OH and held for one day at 5°C. The formed precipitate was filtered off and dried in air.

6-Anilino-1-benzyl-5-(3,4-dihydro-2*H*-pyrrol-5-yl)pyrimidine-2,4(1*H*,3*H*)-dione (7). Yield 2.1 g

(60%), mp 173–175°C, R_f 0.63 (B). IR spectrum, ν, cm^{-1}: 3320, 3204 (NH); 1698, 1637 (C=O). ^1H NMR spectrum, δ, ppm: 1.82–1.95 m (2H, CH_2), 2.44–2.83 m (2H, CH_2), 3.55 br.t (2H, CH_2, *J* 7.2 Hz), 4.95 br.s (2H, $NC\underline{H}_2Ph$), 6.65–6.69 m ($2H_{arom}$), 6.82–6.88 m ($1H_{arom}$), 7.00–7.23 m ($7H_{arom}$), 10.31 br.s (1H, NH), 11.08 br (1H, NH). Found, %: C 69.74; H 5.83; N 15.33. $C_{21}H_{20}N_4O_2$. Calculated, %: C 69.98; H 5.59; N 15.55.

1-Benzyl-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-6-(3,5-dimethylanilino)pyrimidine-2,4(1*H*,3*H*)-dione (8). Yield 2.5 g (64%), mp 198–199°C, R_f 0.71 (B). IR spectrum, ν, cm^{-1}: 3149 (NH), 1695 (C=O). ^1H NMR spectrum, δ, ppm: 1.88–2.01 m (2H, CH_2), 2.18 s (6H, CH_3), 2.72–3.00 m (2H, CH_2), 3.54–3.65 m (2H, NCH_2), 4.87 br.s (2H, $NC\underline{H}_2Ph$), 6.22 br.d (2H, C_6H_3, *J* 1.4 Hz), 6.49 br.t (1H, C_6H_3, *J* 1.4 Hz), 6.83–7.02 m ($2H_{arom}$), 7.10–7.23 m ($3H_{arom}$), 10.28 br.s (1H, NH), 11.55 br (1H, NH). Found, %: C 70.85; H 6.02; N 14.74. $C_{23}H_{24}N_4O_2$. Calculated, %: C 71.11; H 6.23; N 14.42.

5-(3,4-Dihydro-2*H*-pyrrol-5-yl)-6-(3,5-dimethylanilino)-1-(3-phenylpropyl)pyrimidine-2,4(1*H*,3*H*)-dione (9). Yield 2.4 g (58%), mp 224–225°C, R_f 0.66 (B). IR spectrum, ν, cm^{-1}: 3240, 3180 (NH); 1693 (C=O). ^1H NMR spectrum, δ, ppm: 1.63–1.77 m (2H, CH_2), 1.92–2.05 m (2H, CH_2), 2.16–2.34 m (2H, CH_2), 2.26 s (6H, CH_3), 3.11 br (2H, CH_2), 3.58–3.69 m (4H, NCH_2), 6.40 br.s (2H, $H^{2,2'}$, C_6H_3), 6.56 br.s (1H, H^4, C_6H_3), 7.00–7.20 m ($5H_{arom}$), 10.12 s (1H, NH), 11.96 br (1H, NH). Found, %: C 72.39; H 6.65; N 13.14. $C_{25}H_{28}N_4O_2$. Calculated, %: C 72.09; H 6.78; N 13.45.

6-Amino-2-(propylsulfanyl)pyrimidin-4(3*H*)-one (11). A mixture of 1.43 g (10 mmol) of 6-amino-2-sulfanylidene-2,3-dihydropyrimidin-4(1*H*)-one **10**, 1.25 g (10 mmol) of 1-bromopropane, and 0.4 g (10 mmol) of NaOH in a mixture of 10 mL of water and 2 ml of 2-propanol was boiled for 16 h. The reaction mixture was filtered from small amount of precipitate, the filtrate was neutralized with diluted acetic acid, the formed precipitate was filtered off and recrystallized from 2-propanol. Yield 1.5 g (82%), mp 201–203°C, R_f 0.80 (B). ^1H NMR spectrum, δ, ppm: 1.03 t (3H, CH_3, *J* 7.3 Hz), 1.70 sextet (2H, CH_2, *J* 7.3 Hz), 3.03 t (2H, SCH_2, *J* 7.3 Hz), 4.89 s (1H, =CH), 5.91 br.s (2H, NH_2), 11.34 br.s (1H, NH). Found, %: C 45.21; H 5.65; N 22.47. $C_7H_{11}N_3OS$. Calculated, %: C 45.39; H 5.99; N 22.68.

6-Amino-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-sulfanylidene-1,2-dihydropyrimidin-4(3*H*)-one (13). Yield 0.6 g (30%), mp 285°C (with decomposition), R_f 0.27 (B). IR spectrum, ν, cm^{-1}: 3529, 3370 (NH); 1636 (C=O). ^1H NMR spectrum, δ, ppm: 1.75–1.87 m (2H, CH_2), 3.06 br.t (2H, $=CCH_2$, *J* 8.0 Hz), 3.77 t (2H, NCH_2, *J* 7.4 Hz), 6.74 br.s (1H, =NH), 11.03 br.s (1H, NH), 11.39 br.s (2H, 2NH). Found, %: C 45.88; H 4.52; N 26.44. $C_8H_{10}N_4OS$. Calculated, %: C 45.70; H 4.79; N 26.65.

6-Amino-5-(3,4-dihydro-2*H*-pyrrol-5-yl)-2-(propylsulfanyl)pyrimidin-4(3*H*)-one (14). Yield 1.3 g (52%), mp 176°C (with decomposition), R_f 0.58 (B). IR spectrum, ν, cm^{-1}: 3351 (NH), 1642 (C=O). ^1H NMR spectrum, δ, ppm: 1.04 t (3H, CH_3, *J* 7.3 Hz), 1.72 sextet (2H, $C\underline{H}_2CH_3$, *J* 7.3 Hz), 1.75–1.87 m (2H, $NCH_2C\underline{H}_2CH_2$), 3.04–3.12 m (4H, SCH_2, $=CCH_2$), 3.81 br.t (2H, NCH_2, *J* 7.4 Hz), 6.83 br.s (1H, =NH), 10.51 br.s (1H, NH), 11.65 br.s (1H, NH). Found, %: C 52.61; H 6.12; N 22.52. $C_{11}H_{16}N_4OS$. Calculated, %: C 52.36; H 6.39; N 22.20.

6-Amino-2-benzylsulfanyl-5-(3,4-dihydro-2*H*-pyrrol-5-yl)pyrimidin-4(3*H*)-one (15). Yield 1.3 g (45%), mp 203°C (with decomposition), R_f 0.53 (B). IR spectrum, ν, cm^{-1}: 3347, 3135 (NH), 1636 (C=O). ^1H NMR spectrum, δ, ppm: 1.76–1.88 m (2H, CH_2), 3.09 br.t (2H, $=CCH_2$, *J* 8.0 Hz), 3.81 br.t (2H, NCH_2, *J* 7.4 Hz), 4.37 s (2H, SCH_2), 7.17–7.31 m ($3H_{arom}$), 7.38–7.43 m ($2H_{arom}$), 7.29 br.s (1H, =NH), 10.51 br.s (1H, NH), 11.62 br.s (1H, NH). ^{13}C NMR spectrum, δ, ppm: 21.6 (CH_2), 33.3 (CH_2), 38.1 (CH_2), 57.6 (NCH_2), 89.2 ($\underline{C}CO$), 126.6 (C^p), 127.9 and 128.7 ($C^{o,o'}$, $C^{m,m'}$), 137.0 (C^i), 160.4 br.s (N=C), 161.9, 171.2 br.s (N=C). Found, %: C 59.65; H 5.54; N 18.90. $C_{15}H_{16}N_4OS$. Calculated, %: C 59.98; H 5.37; N 18.65.

Compounds (20–23). General method. A mixture of 10 mmol of *N*-substituted 5-hydroxypyrrolidin-2-one **18** [31], **19** [32] and 10 mmol of compounds **5**, **16**, and **17** in 15 mL of glacial acetic acid was heated at 115–130°C for 2 h after the dissolution of reagents. After cooling the reaction mixture was diluted with water and neutralized with sodium carbonate. The formed precipitate was separated, dried, and recrystallized.

1-Benzyl-5-(1-benzyl-5-oxotetrahydro-1*H*-pyrrol-2-yl)-6-(3,5-dimethylanilino)pyrimidine-2,4(1*H*,3*H*)-dione (20). Yield 3.1 g (63%), mp 252–253.5°C (butan-1-ol), R_f 0.74 (C). IR spectrum, ν, cm^{-1}: 3260 (NH), 1699 (C=O). ^1H NMR spectrum, δ, ppm: 1.82–1.94 m

(2H, CHC<u>H</u>$_2$), 2.03–2.18 m (1H, O=CCH^B), 2.14 s (6H, 2CH$_3$), 2.52–2.68 m (1H, O=CCH^A), 3.76 d (1H, NCH$_2$, *J* 14.8 Hz), 4.24–4.32 m (1H, NCH), 4.41 d (1H, NCH$_2$, *J* 14.8 Hz), 4.85 d (1H, NCH$_2$, *J* 15.6 Hz), 5.13 d (1H, NCH$_2$, *J* 15.6 Hz), 6.07 br.s (2H, H$^{o,o'}$, C$_6$H$_3$), 6.38 br.s (1H, H^p, C$_6$H$_3$), 6.97–7.02 m (2H) and 7.08–7.25 m (8H, 2C$_6$H$_5$), 7.53 br.s (1H, NH), 11.03 s (1H, NH). Found, %: C 72.48; H 6.25; N 11.23. $C_{30}H_{30}N_4O_3$. Calculated, %: C 72.85; H 6.11; N 11.33.

6-Amino-5-(1-benzyl-5-oxotetrahydro-1*H*-pyrrol-2-yl)pyrimidine-2,4(1*H*,3*H*)-dione (21). Yield 1.9 g (64%), mp 286–287°C (butan-1-ol), R_f 0.52 (C). IR spectrum, ν, cm^{-1}: 3400, 3340, 3220 (NH$_2$, NH); 1715, 1695 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.92–2.29 m (3H) and 2.33–2.68 m (1H, CH$_2$CH$_2$), 3.72 br.s (0.5H) and 3.77 br.s (0.5H, CH), 4.38–4.90 br.s (2H, NCH$_2$), 5.47–5.89 br.s (2H, NH$_2$), 7.13–7.26 m (5H$_{arom}$), 9.79 s (1H, NH), 9.75–10.10 br.s (1H, NH). Found, %: C 60.31; H 4.98; N 18.91. $C_{15}H_{16}N_4O_3$. Calculated, %: C 59.99; H 5.37; N 18.66.

6-Amino-5-(1-benzyl-5-oxotetrahydro-1*H*-pyrrol-2-yl)-1,3-dimethylpyrimidine-2,4(1*H*,3*H*)-dione (22). Yield 2.7 g (82%), mp 278–279°C (butan-1-ol), R_f 0.42 (C). IR spectrum, ν, cm^{-1}: 3390, 3204 (NH$_2$); 1656 (C=O). ^{1}H NMR spectrum, δ, ppm: 1.92–2.32 m (3H) and 2.36–2.74 m (1H, CH$_2$CH$_2$), 2.97 s (2.1H) and 3.17 s (0.9H, CH$_3$), 3.27 s (3H, CH$_3$), 3.78 d (0.3H, *J* 14.0 Hz), 4.05 d (0.7H, *J* 14.0 Hz), 4.23 d (0.7H, *J* 14.0 Hz) and 4.53 d (0.3H, NCH$_2$, *J* 14.0 Hz), 4.59–4.68 m (0.7H) and 4.98–5.08 m (0.3H, CH), 5.96 br.s (0.6H) and 6.38 br.s (1.4H, NH$_2$), 7.07–7.25 m (5H$_{arom}$). Found, %: C 62.39; H 6.45; N 16.85. $C_{17}H_{20}N_4O_3$. Calculated, %: C 62.18; H 6.14; N 17.06.

6-Amino-5-[1-(4-methoxyphenyl)-5-oxotetrahydro-1*H*-pyrrol-2-yl]pyrimidine-2,4(1*H*,3*H*)-dione (23). Yield 2.0 g (65%), mp 293–294°C (methylcellozolv–water), R_f 0.43 (C). IR spectrum, ν, cm^{-1}: 3400, 3325, 3300, 3250, 3218 (NH$_2$, NH); 1713, 1688 (C=O). ^{1}H NMR spectrum, δ, ppm: 2.00–2.70 m (4H, CH$_2$CH$_2$), 3.71 s (3H, OCH$_3$), 5.19 br.s (0.7H) and 5.44 br.s (0.3H, CH), 5.88 br.s (0.6H) and 6.23 br.s (1.4H, NH$_2$), 6.80–6.86 m (2H) and 7.13–7.19 m (2H, C$_6$H$_4$), 9.68–9.86 br.s (1H, NH), 10.01–10.35 br.s (1H, NH). Found, %: C 56.72; H 5.31; N 17.87. $C_{15}H_{16}N_4O_4$. Calculated, %: C 56.96; H 5.10; N 17.71.

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