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INVESTIGATIONS ON 5-(2-ARYL-2-OXO-ETHYLIDENE)-1,3-DIMETHYLBARBITURIC AND THIOBARBITURIC ACIDS: REACTIONS WITH THIOUREAS AND THIOACETAMIDE

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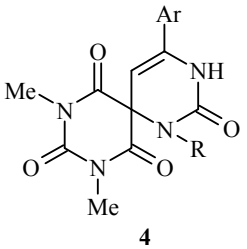
Derivatives of 2-amino- and 2-methylthiazole have been synthesized by the reaction of 5-(2-aryl-2-oxoethylidene)-1,3-dimethylbarbituric and thiobarbituric acids with thioureas and thioacetamide, and also by a one-pot synthesis involving thiourea (or thioacetamide), arylglyoxals, 1,3-dimethyl-barbituric (or thiobarbituric) acids. The mechanisms of the studied reactions are discussed.

Keywords: 5-(2-amino-4-arylthiazol-5-yl)-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones, 5-(2-amino-4-arylthiazol-5-yl)-1,3-dimethylpyrimidine-2,4-diones, 5-(2-aryl-2-oxoethylidene)-1,3-dimethyl-barbituric and 5-(2-aryl-2-oxoethylidene)thiobarbituric acids, thioacetamide, thioureas, one-pot synthesis, cyclocondensation.

It is well known that heterocyclization involving α,β-unsaturated ketones and thioureas is a convenient method of synthesis of 3,4-dihydropyrimidine-2-thiones [1-3]. However an alternative direction is also mentioned in the literature for the interaction of α,β-unsaturated ketones with thioureas leading to the formation of a dihydrothiazine ring. Nucleophilic addition of mercapto group with subsequent cyclization is characteristic of cyclic unsaturated ketones [4, 5], and also on using N-arylthioureas in the reaction [6, 7].



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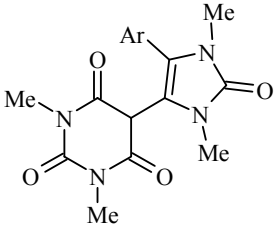

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R = H, Ar

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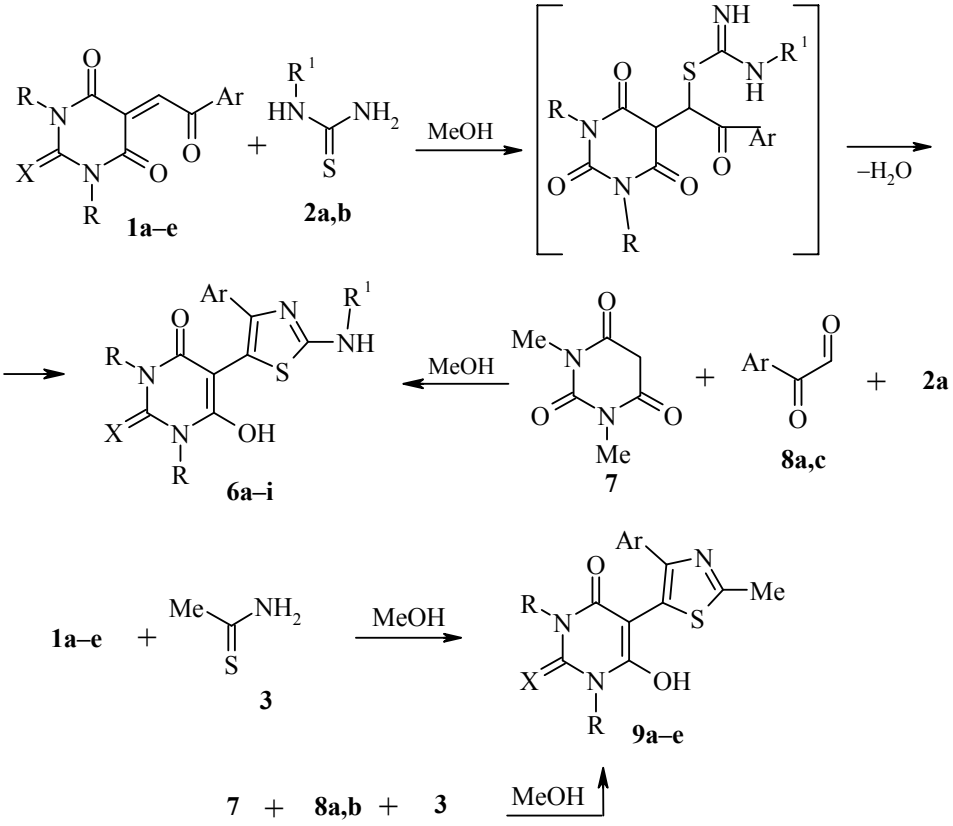
The aim of the present investigation was the study of the reactivity of 5-(2-aryl-2-oxoethylidene)-1,3-dimethylbarbituric or thiobarbituric acids **1a-e** in relation to thioureas **2a,b** and thioacetamide **3**. Compounds **1** belong to the polarized olefins, the vinyl bond of which tests the effect of two electron-withdrawing fragments, *viz*. a carbonyl group and a pyrimidinetrione (thioxopyrimidinedione), which generates intrigue on investigating the direction of their interaction in reactions with 1,3-binucleophiles. It was established previously in [8], that reactions with ureas in alcohols lead to spiropyrimidine **4**, while N,N-dimethylurea under analogous experimental conditions forms imidazolones **5**.

The hypothesis has been expressed that a weak nucleophile (urea) initially attacks an exocyclic carbonyl group of enones **1** while an increase in nucleophilicity of the reagent (N,N-dimethylurea) may change the direction of the interaction. Such a hypothesis is in good agreement with the data obtained by us previously for reactions of enones with a series of azabinucleophiles [9-11].

To verify the hypothesis we have studied the interaction of ketones **1** with thioureas **2**. It was carried out by briefly heating (30-45 min) the initial components in ethanol. The reaction products proved to be compounds **6a-i**, light-yellow crystalline substances, readily soluble in polar organic solvents. In the ^{1}H NMR spectra of products **6a-e** a six-proton singlet was observed for the methyl groups of the pyrimidine fragment, doublets for the aromatic protons, and also broadened singlets in the region of 8.5 and 12.7 ppm, of intensity two and one



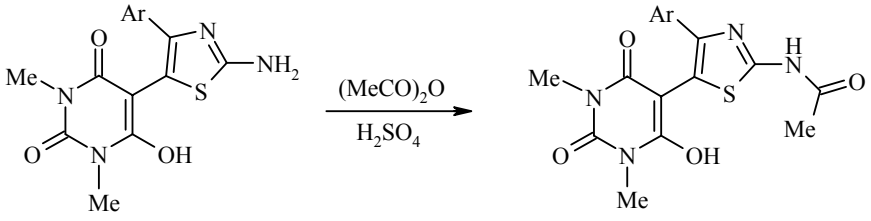
1 a–e R = Me(H), X = O(S); **a** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 4-FC_6H_4, **d** Ar = 4-MeOC_6H_4, **e** Ar = 2-thienyl; **2 a** R^1 = H, **b** R^1 = 2-BrC_6H_4CO; **6 a–d** R = Me, R^1 = H, X = O, **a** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 4-FC_6H_4, **d** Ar = 4-MeOC_6H_4; **e** R = Me, R^1 = 4-BrC_6H_4CO, Ar = 2-thienyl, X = O; **f–i** R = H, X = S, **f** R^1 = H, Ar = 4-BrC_6H_4, **g** R^1 = H, Ar = 4-MeOC_6H_4, **h** R^1 = 2-BrC_6H_4CO, Ar = Ph, **i** 2-BrC_6H_4CO, Ar = 4-FC_6H_4; **8 a** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 4-FC_6H_4; **9 a–c** R = Me, **a–c** X = O, **a** Ar = Ph, **b** Ar = 4-BrC_6H_4, **c** Ar = 4-FC_6H_4; **d, e** R = H, X = S, **d** Ar = 4-MeOC_6H_4, **e** Ar = 2-thienyl

proton respectively, disappearing on carrying out deuterium exchange. In the IR spectra (KBr disks) of compounds **6a,d,g** two absorption bands of moderate intensity were seen at 3220 and 3320 cm^{-1}, confirming the presence of a primary amino group. In the mass spectra of compounds **6a,c,h** peaks were displayed for the molecular ions, and their fragmentation confirmed the formation of a thiazole ring.

The products of reacting enones **1** with thioureas **2** are therefore 5-(2-amino-4-arylthiazol-5-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4-diones **6a**-e or 5-(2-amino-4-arylthiazol-5-yl)-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones **6f-i**. The synthesized compounds **6a-i** and the imidazolin-2-ones **5** exist in DMSO-d_6 solution in the 6-hydroxy form. In thiazoles **6a-d** the clear influence is observed of conjugation of the *p*-substituent in the aromatic nucleus on the chemical shift of the proton of the hydroxyl group (see Experimental). However the introduction of electron-withdrawing groups into the molecule (**6e,h,i**) increases the acidity of the 6-hydroxyl group. This does not appear in the ^{1}H NMR spectra due to the rapid exchange with water present in the DMSO-d_6. Thiazoles **6a,c** were also obtained by the one-pot method using acid **7**, arylglyoxals **8a,c** and thiourea, however the reaction time doubled. In addition, in the case of the interaction in stages the yields were 70-80%, while under one-pot conditions of synthesis the yield of product **6** was reduced significantly (see Experimental). Thioacetamide **3** reacts analogously with ketones **1a-e** forming thiazoles **9a-e**.

The structure of compounds **9a-e** was confirmed by spectral methods. In the ^{1}H NMR spectra singlets were present for the methyl groups of the pyrimidine and thiazole rings, and multiplets for the aromatic protons. The signal of the 6-hydroxyl group of the uracil ring is in this case readily exchanged with water and is not seen in the spectrum. In the mass spectrum of product **9b** peaks were present for the molecular ion with *m/z* 407 (409).

The presence of the amino group in thiazoles **6** was additionally confirmed by an acylation reaction. Boiling compounds **6a,b** in acetic anhydride did not lead to the N-acetyl derivative, while reaction in the presence of sulfuric acid (procedure for acylating difficultly acylable amines [12]) enabled amides **10a,b** to be synthesized.



6a,b **10a,b**

6, 10 **a** Ar = Ph, **b** Ar = 4-BrC_6H_4

Consequently the ketones **1** investigated by us are characterized by a vinyl group with a large π-deficiency in comparison with chalcones, which also leads to a regioselective interaction with 1,3-N,S-binucleophiles. Thioureas and thioacetamide react with the electron-deficient C(2) atom of the vinylic bond of ketones **1** *via* the sulfur atom with the highest nucleophilic strength. This enables convenient methods to be developed for the synthesis of new derivatives of 2-amino- and 2-methylthiazole **6a-i** and **9a-e** respectively, including a one-pot, starting from dimethylbarbituric (or thiobarbituric) acid, arylglyoxals and thioureas (or thioacetamide).

EXPERIMENTAL

The IR spectra were obtained on a Specord IR-75 spectrometer in KBr disks. The ^{1}H and ^{13}C NMR spectra were measured with a Varian VX-200 Mercury instrument (200 and 50 MHz respectively) in DMSO-d_6, internal standard was TMS. The mass spectra were obtained on a Hewlett-Packard LC/MSD 1100 instrument

with ionization by electron impact (voltage 70 eV). Elemental analysis was carried out on a LECO CHNS 900 instrument. Melting points were determined on a Koefler block. A check on the progress of reactions and the purity of the obtained compounds was carried out by TLC on Silufol UV-254 plates in the system toluene–ethyl acetate, 1:1, and toluene–hexane, 1:10 (visualization with iodine vapor).

5-(2-Amino-4-arylthiazol-5-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4-diones 6a-e, 5-(2-Amino-4-arylthiazol-5-yl)-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones 6f-i (General Method). A. Equimolar quantities of enone **1** and thiourea **2** (about 1 mmol) were boiled in ethanol (10 ml) for 30-45 min. The resulting light-yellow solid was filtered off and crystallized from EtOH.

B. (one-pot). Arylglyoxal monohydrate **8** and thiourea **2** (about 1 mmol) were added to a solution of compound **7** (1 mmol) in EtOH (10 ml). The reaction mixture was boiled for 30 min to 1 h until precipitation from the hot solution of a solid, which was crystallized from EtOH.

5-(2-Amino-4-phenylthiazol-5-yl)-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6a). Yield 76% (A), 40% (B); mp 300-301°C (EtOH). IR spectrum, ν, cm^{-1}: 1622 (C=C), 1665 (C=O), 1676 (C=O), 3220 (NH_2^s), 3326 (NH_2^{as}). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.01 (6H, s, CH_3); 7.26-7.36 (3H, m, *p*- + *m*-Ph); 7.42 (2H, d, *J* = 7.2, *o*-Ph); 8.55 (2H, s, NH_2); 12.76 (1H, br. s, OH). ^{13}C NMR spectrum, δ, ppm: 27.8 (2N–CH_3); 78.0 (C-5 Pyr); 119.3 (C-5 thiazole); 132.0 (C-4 thiazole); 127.6, 128.6, 128.8, 131.6 (Ph); 153.1, 161.8, 168.5 (C=O); 167.0 (C-2 thiazole). Mass spectrum, *m/z* (I_{rel}, %): 330 $[M]^+$ (100), 331 $[M+1]^+$ (8), 216 (100), 187 (8), 160 (8), 155 (10), 146 (37), 102 (13), 77 (13). Found, %: C 54.44; H 4.32; N 16.80. $C_{15}H_{14}N_4O_3S$. Calculated, %: C 54.53; H 4.27; N 16.96.

5-[2-Amino-4-(4-bromophenyl)thiazol-5-yl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6b). Yield 64%; mp >300°C (EtOH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.01 (6H, s, CH_3); 7.43 (2H, d, *J* = 8.4, *o*-Ar); 7.52 (2H, d, *J* = 8.4, *m*-Ar); 8.55 (2H, s, NH_2); 12.51 (1H, br. s, OH). Found, %: C 43.94; H 3.13; N 13.76. $C_{15}H_{13}BrN_4O_3S$. Calculated, %: C 44.02; H 3.20; N 13.69.

5-[2-Amino-4-(4-fluorophenyl)thiazol-5-yl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6c). Yield 72% (A), 39% (B); mp >300°C (EtOH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.01 (6H, s, CH_3); 7.17 (2H, t, *J* = 8.8, *m*-Ar); 7.41-7.49 (2H, m, *o*-Ar); 8.57 (2H, s, NH_2); 12.62 (1H, br. s, OH). Mass spectrum, *m/z* (I_{rel}, %): 348 $[M]^+$ (100), 349 $[M+1]^+$ (16), 234 (100), 235 (12), 172 (12), 164 (64), 120 (13), 107 (7). Found, %: C 51.64; H 3.70; N 15.99. $C_{15}H_{13}FN_4O_3S$. Calculated, %: C 51.72; H 3.76; N 16.08

5-[2-Amino-4-(4-methoxyphenyl)thiazol-5-yl)]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (6d). Yield 61%; mp >300°C (EtOH). IR spectrum, ν, cm^{-1}: 1628 (C=C), 1668 (C=O), 1675 (C=O), 3225 NH_2^s), 3323 (NH_2^{as}). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.01 (6H, s, CH_3); 3.73 (3H, s, OCH_3); 6.91 (2H, d, *J* = 8.4, *m*-Ar); 7.37 (2H, d, *J* = 8.4, *o*-Ar); 8.57 (2H, s, NH_2); 12.44 (1H, br. s, OH). Found, %: C 53.40; H 4.53; N 15.49. $C_{16}H_{16}N_4O_4S$. Calculated, %: C 53.32; H 4.47; N 15.55.

N-[5-(6-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-(2-thienylthiazol-2-yl]-2-bromobenzamide (6e). Yield 48%; mp >300°C (EtOH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.08 (6H, s, CH_3); 7.28-7.50 (3H, m, thienyl); 7.56-7.64 (3H, m, *m*-, *p*-BrC_6H_4); 7.72 (1H, d, *J* = 7.2, *o*-BrC_6H_4); 12.69 (1H, s, NH). Found, %: C 46.35; H 2.83; N 10.84. $C_{20}H_{15}BrN_4O_4S_2$. Calculated, %: C 46.25; H 2.91; N 10.79.

5-[2-Amino-4-(4-bromophenyl)thiazol-5-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (6f). Yield 3%; mp 298-299°C (EtOH). ^1H NMR spectrum, δ, ppm (*J*, Hz): 7.33 (2H, d, *J* = 8.4, *o*-Ar); 7.53 (2H, d, *J* = 8.4, *m*-Ar); 8.39 (2H, s, NH_2); 10.89 (2H, s, NH); 12.80 (1H, br. s, OH). Found, %: C 39.24; H 2.20; N 14.19. $C_{13}H_9BrN_4O_2S_2$. Calculated, %: C 39.30; H 2.28; N 14.10.

5-[2-Amino-4-(4-methoxyphenyl)thiazol-5-yl]-6-hydroxy-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (6g). Yield 57%; mp 281-282°C (EtOH). IR spectrum, ν, cm^{-1}: 1195 (C=S), 1620 (C=C), 1667 (C=O), 3250 (NH_2^s), 3350 (NH_2^{as}). ^1H NMR spectrum, δ, ppm (*J*, Hz): 3.73 (3H, s, CH_3); 6.92 (2H, d, *J* = 8.4, *o*-Ar); 7.36 (2H, d, *J* = 8.4, *m*-Ar); 8.56 (2H, s, NH_2); 10.82 (2H, s, NH); 12.82 (1H, br. s, OH). Found, %: C 48.34; H 3.56; N 16.12. $C_{14}H_{12}N_4O_3S_2$. Calculated, %: C 48.26; H 3.47; N 16.08.

N-[5-(6-Hydroxy-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-phenylthiazol-2-yl]-2-bromo-benzamide (6h). Yield 45%; mp >300°C (from EtOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.24 (1H, m, *p*-Ph); 7.30-7.49 (4H, m, *o*- + *m*-Ph); 7.56-7.62 (3H, m, *m*-, *p*-BrC_6H_4); 7.72 (1H, d, *J* = 7.0, *o*-BrC_6H_4); 12.01 (2H, s, NH); 12.71 (1H, s, NH). Mass spectrum, *m/z* (I_{rel}, %): 500 $[M]^+$ (50), 502 $[M]^+$ (50), 421 (5), 201 (10), 185 (97), 179 (100), 157 (35), 105 (6). Found, %: C 47.84; H 2.69; N 11.12. $C_{20}H_{13}BrN_4O_3S_2$. Calculated, %: C 47.91; H 2.61; N 11.17.

N-[4-(4-Fluorophenyl)-5-(6-hydroxy-4-oxo-2-thioxo-1,2,3,4-tetrahydropyrimidin-5-yl)thiazol-2-yl]-2-bromobenzamide (6i). Yield 49%; mp >300°C (EtOH). IR spectrum, ν, cm^{-1}: 1193 (C=S), 1620 (C=C), 1655 (C=O), 1692 (C=O), 3403 (NH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 7.19 (2H, t, *J* = 8.4, *o*-Ar); 7.44-7.64 (5H, m, *m*-Ar + *m*-, *p*-BrC_6H_4); 7.72 (1H, d, *J* = 6.6, *o*-BrC_6H_4); 12.17 (2H, s, NH); 12.76 (1H, s, NH). Found, %: C 46.32; H 2.40; N 10.86. $C_{20}H_{12}BrFN_4O_3S_2$. Calculated, %: C 46.25; H 2.33; N 10.79.

6-Hydroxy-1,3-dimethyl-5-(4-aryl-2-methylthiazol-5-yl)pyrimidine-2,4-(1H,3H)-diones 9a-c and 6-Hydroxy-5-[4-aryl-2-methylthiazol-5-yl]-2-thioxo-2,3-dihydropyrimidin-4(1H)-ones 9d,e (General Method). A. A mixture of enone **1** (1 mmol) and thioacetamide **3** (1 mmol) in MeOH (10-15 ml) was boiled for 15-30 min. The finely crystalline white solid precipitated on cooling was filtered off and washed on the filter or crystallized from MeOH.

B. (one-pot). Arylglyoxal monohydrate **8** (1 mmol) and thioacetamide **3** (1 mmol) were added to compound **7** (1 mmol) in MeOH (10 ml). The reaction mixture was boiled for 1 h until precipitation of a white solid from the hot solution. The solid was crystallized from MeOH.

6-Hydroxy-1,3-dimethyl-5-(2-methyl-4-phenylthiazol-5-yl)pyrimidine-2,4(1H,3H)-dione (9a). Yield 51% (A), 73% (B); mp 279-280°C (MeOH). IR spectrum, ν, cm^{-1}: 1619 (C=C), 1670 (C=O), 1687 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.77 (3H, s, CH_3); 3.06 (6H, s, CH_3); 7.27-7.38 (3H, *p*-, *m*-Ph); 7.51 (2H, d, *J* = 6.8, *o*-Ph). Found, %: C 58.44; H 4.62; N 12.83. $C_{16}H_{15}N_3O_4S$. Calculated, %: C 58.34; H 4.59; N 12.76.

5-[4-(4-Bromophenyl)-2-methylthiazol-5-yl]-6-hydroxy-1,3-dimethylpyrimidine-2,4(1H,3H)-dione (9b). Yield 56% (A), 75% (B); mp 288-289°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.74 (3H, s, CH_3); 3.06 (6H, s, CH_3); 7.46 (2H, d, *J* = 8.7, *o*-Ar); 7.53 (2H, d, *J* = 8.7, *m*-Ar). Mass spectrum, *m/z* (I_{rel}, %): 407 $[M]^+$ (50), 409 $[M]^+$ (50), 235 (12), 214 (100), 198 (28), 183 (21), 145 (9), 107 (7). Found, %: C 46.98; H 3.54; N 10.34. $C_{16}H_{14}BrN_3O_3S$. Calculated, %: C 47.07; H 3.46; N 10.29.

6-Hydroxy-1,3-dimethyl-5-[2-methyl-4-(4-fluorophenyl)thiazol-5-yl]pyrimidine-2,4(1H,3H)-dione (9c). Yield 39%; mp 251-252°C (MeOH). IR spectrum, ν, cm^{-1}: 1621 (C=C), 1675 (C=O), 1689 (C=O). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.75 (3H, s, CH_3); 3.06 (6H, s, CH_3); 7.17 (2H, t, *J* = 8.8, *m*-Ar); 7.51-7.58 (2H, m, *o*-Ar). Found, %: C 55.24; H 3.99; N 12.03. $C_{16}H_{14}FN_3O_3S$. Calculated, %: C 55.32; H 4.06; N 12.10.

6-Hydroxy-5-[2-methyl-4-(4-methoxyphenyl)thiazol-5-yl]-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (9d). Yield 55%; mp >300°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.75 (3H, s, CH_3); 3.75 (3H, s, OCH_3); 6.93 (2H, d, *J* = 8.6, *m*-Ar); 7.44 (2H, d, *J* = 8.6, *o*-Ar); 11.49 (2H, s, NH). Found, %: C 51.78; H 3.83; N 12.01. $C_{15}H_{13}N_3O_3S$. Calculated, %: C 51.86; H 3.77; N 12.10.

6-Hydroxy-5-[2-methyl-4-(2-thienyl)thiazol-5-yl]-2-thioxo-2,3-dihydropyrimidin-4(1H)-one (9e). Yield 37%; mp >300°C (MeOH). ^{1}H NMR spectrum, δ, ppm (*J*, Hz): 2.64 (2H, s, CH_3); 7.02 (1H, t, *J* = 3.8; *J* = 4.6, β-thienyl); 7.27 (1H, d, *J* = 2.8, β-thienyl); 7.42 (1H, d, *J* = 4.6, α-thienyl); 12.01 (2H, s, NH). Found, %: C 44.49; H 2.73; N 13.04. $C_{12}H_9N_3O_2S_3$. Calculated, %: C 44.56; H 2.80; N 12.99.

N-[5-(6-Hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl)-4-phenylthiazol-2-yl]-acetamide (10a). Conc. H_2SO_4 (2 drops) was added to a solution of compound **6a** (1 mmol) in Ac_2O (2 ml) and the mixture was boiled for 30 min. The reaction mixture was poured onto ice and the obtained solid crystallized from EtOH. Yield 76%; mp 280-282°C (EtOH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.13 (3H, s, CH_3); 3.15 (6H, s, CH_3); 7.21-7.30 (3H, m, *p*-, *m*-Ph); 7.61 (2H, d, *J* = 6.8, *o*-Ph); 12.07 (1H, s, NH). Found, %: C 54.90; H 4.30; N 14.97. $C_{17}H_{16}N_4O_4S$. Calculated, %: C 54.83; H 4.33; N 15.04.

N-[4-(4-Bromophenyl)-5-(6-hydroxy-1,3-dimethyl-2,4-dioxo-1,2,3,4-tetrahydropyrimidin-5-yl]thiazol-2-yl)acetamide (10b) was obtained analogously. Yield 69%; mp 254-256°C (EtOH). ^{1}H NMR spectrum, δ, ppm, (*J*, Hz): 2.13 (3H, s, CH_3); 3.14 (6H, s, $2CH_3$); 7.49 (2H, d, *J* = 8.0, *o*-Ar); 7.55 (2H, d, *J* = 8.0, *m*-Ar); 12.05 (1H, s, NH). Found, %: C 45.30; H 3.42; N 12.33. $C_{17}H_{15}BrN_4O_4S$. Calculated, %: C 45.24; H 3.35; N 12.41.

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