An Efficient Method for the Synthesis of *N*-uracil-4-oxo-thiazolidines without Catalyst

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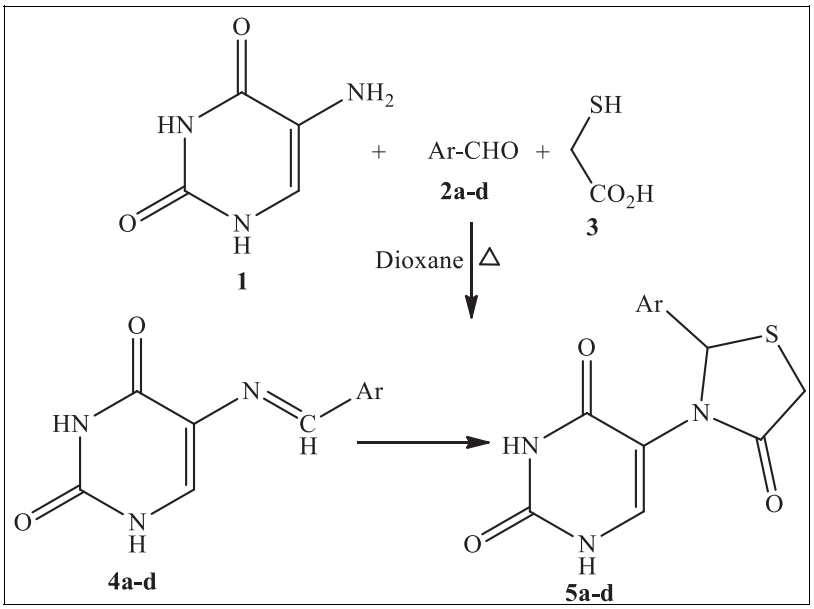

We have developed highly efficient, one-pot three component reaction of 5-amino-uracil and aromatic aldehydes with thioglycolic acid for the synthesis of N-uracil-thiazolidinones in excellent yields. The same products were also prepared by the reaction of Schiff bases of 5-amino-uracil with thioglycolic acid. In addition, benzylation of thiazolidinone derivatives and Schiff bases by using benzyl chloride was investigated. The results obtained from elemental microanalysis and different spectral data are in agreement with the assigned structures.

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INTRODUCTION

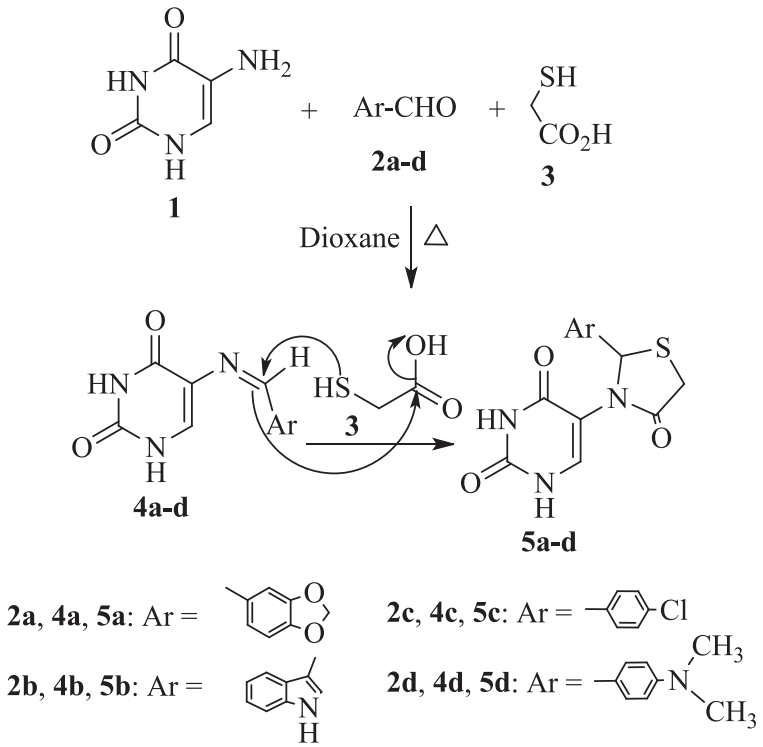
In recent years, the chemistry of 4-thiazolidinone derivatives has been the subject of intense research by biologists and organic chemists because such compounds represent substantial scaffolds in drug discovery [1,2]. According to this approach, thiazolidin-4-ones have been reported to own wide spectrum of biological activity such as antimicrobial [3–7], antitubercular [8,9], antitumoral [10], anticancer [11,12], anti-inflammatory [13], antiglioma [14], anticonvulsant [15], anti-HIV-1 [16], antioxidant [5,12], and analgesic properties [17].

The most well-known and classical method for the synthesis of these compounds includes two-component and three-component reactions involving primary amines, an oxo-compound and thiolic acids in the presence of diverse catalysts, such as hexafluorophosphate benzotriazole tetramethyl uronium [18], *N*,*N*′-dicyclohexylcarbodiimide [19], silica gel [20], [bmim][PF_6] [21], $ZnCl_2$ [22], ferrite [23], Hunig's base [24], [BmIm]OH [25], molecular sieves [26], sodium sulfate [27], montmorillonite K-10 [28], nano-Fe_3O_4@SiO_2 [29], [Et_3NH][HSO_4] [30], DBSA [31], and baker's yeast [32].

In addition, the structure of uracil still attracts the attendance of organic chemists and biologist [33–38], because of wide array of biological activities, synthetic accessibility, and ability to grant drug like properties to the compound libraries suffixed on it at the N^1, N^3, C^5, and C^6 positions [39].

In continuation of our interest in the development of new and simple methods for the synthesis of polyfunctionally substituted heterocyclic compounds starting from 5-amino-uracil [40–44], we wish to report an efficient one-pot method for the synthesis of *N*-uracil-thiazolidinones.

Scheme 1. Synthesis of *N*-uracil-thiazolidinones **5a–d**.



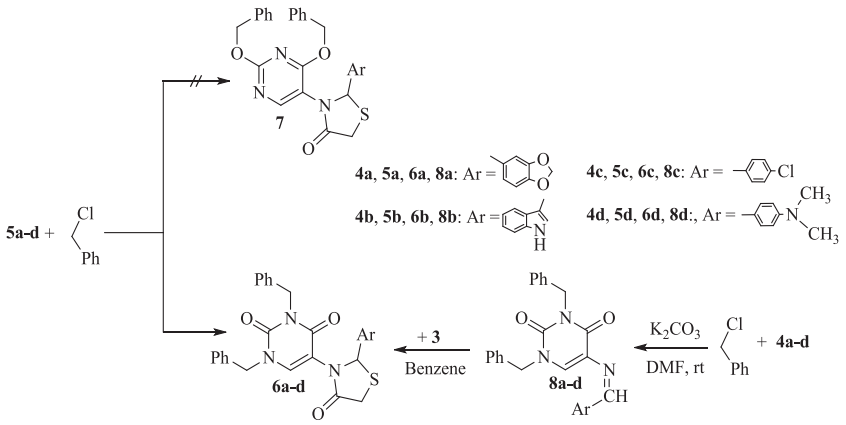
RESULTS AND DISCUSSION

Scheme 1 outlines the synthesis of 5-(4-oxo-2-aryl thiazolidin-3-yl)pyrimidine-2,4(1*H*,3*H*)-dione **5a–d** *via* one-pot three-component reaction of 5-aminouracil (**1**), aromatic aldehydes **2a–d**, and thioglycolic acid (**3**) without catalyst in dioxane as a solvent. The structure of the thiazolidinones **5a–d** was further supported by an alternative synthesis. Thus, cyclocondensation of Schiff bases **4a–d** with compound **3** in equimolar proportions in dioxane gave the same products **5a–d**. The formation of compounds **5a–d** was rationalized by initial formation of an imine **4a–d**, which undergoes attack by the sulfur nucleophile, followed by intramolecular cyclization on elimination of water. All products have been fully characterized by analytical and spectroscopic data. For example, compound **5a** exhibited an IR spectrum with strong absorption bands at 3439 and 3292 cm^{-1}, belonging to stretching vibrations of the NH groups, in addition to the absorption bands at 1718, 1685, and 1659 cm^{-1} for carbonyl groups. Its ^1H NMR spectrum revealed three sharp singlet signals at 11.50, 9.37, and 8.11 (two NH groups and CH for uracil ring, 3-NH, 1-NH, and 6-CH, respectively) and three singlet signals at 6.00, 5.23, and 3.92 ppm (CH_2 of pipronal, CH and CH_2 of thiazolidinone ring, respectively).

It has been known that the uracil ring has a high potential to form polar intermolecular and hydrogen bond interactions [35]. The electrophilic attack at uracil ring involves nitrogen's (N^1, N^3), oxygen's (O^2 and O^4), or (C^6), so the formation of compounds **6** and **7** was possible when we studied the alkylation of **5a–d** with benzyl chloride in the presence of potassium carbonate as a base. The benzylated derivatives **6a–d** was formed in 75–78% yield. The support for the structure of **6** was provided from spectral data and elemental analysis. For example, the ^{13}C NMR spectrum of compound **6a** showed three values for 3C═O at 171.59, 159.73, and 150.29 ppm that exhibited strong absorption bands at 1702, 1634, and 1600 cm^{-1} in its IR spectrum, and these facts allowed us to discard the structure **7**. The ^1H NMR spectrum of **6a** revealed that the alkylation occurs only at the N-1 and N-3 atoms, which showed disappearance of two NH protons and showed signals for the N^1CH_2 (δ = 4.75) and N^3CH_2 protons (δ = 4.79 ppm). Furthermore, the fragmentation patterns of the mass spectra of **6a** showed the molecular ion peak at *m/z* = 514 (M^{+1}) and *m/z* 513 (M^+), respectively.

Further confirmation of structures **6a–d** was made *via* the synthesis of alkylated Schiff base **8a–d**, prepared from the reaction of compounds **4a–d** with benzyl chloride. Subsequent refluxing of **8a–d** with 2-

Scheme 2. Benzylation of compounds **5a**–**d**.



mercaptoacetic acid (**3**) in benzene smoothly converts it to the final products **6a**–**d** (Scheme 2).

CONCLUSION

We have reported a simple method for the synthesis of N-uracilthiazolidinones by using one-pot three-component reaction of 5-amino uracil, thioglycolic acid and some aromatic aldehydes. The alkylation of thiazolidinones with benzyl chloride in the presence of K_2CO_3 was studied. In addition, the definite structures of the novel products have been confirmed by spectral data.

EXPERIMENTAL

General remarks. All reagents were purchased from Alfa Aesar or Fluka and were used without further purification. Melting points were measured in capillary tubes using a Büchi 530 melting point apparatus and are uncorrected. IR spectra were measured using a Bruker Tensor 27 instrument. ^{1}H NMR (300 or 400 MHz) and ^{13}C NMR (75 or 101 MHz) spectra were recorded in DMSO-d_6 on BrukerAvance II-300 and Avance DRX-400 spectrometers with trimethylsilyl (for ^{1}H) or the solvent (for ^{13}C, δ_C = 77.01 ppm) as the internal standards. Mass spectral measurements (EI, 70 eV) were performed using a Finnigan MAT 8430 spectrometer.

Synthesis of compounds 4a–d. To a mixture of compound **1** (2 mmol) and the aldehydes **2a**–**d** (2 mmol) in DMSO (10 mL), *p*-TSA (10 mg) was added. The reaction mixture was stirred for 24 h at room temperature. The precipitated solid was obtained by pouring the reaction mixture onto cold water, and then filtered off. The products **4a**–**d** were obtained in very good yields.

(E)-5-((benzo[d][1,3]dioxol-5-ylmethylene)amino)pyrimidine-2,4(1H,3H)-dione (4a). Pale yellow solid; mp 358–360°C; yield 89%; IR (KBr): *v*max/cm^{-1} = 3269 (NH), 1624 (CO), 1608 (C═N). ^{1}H NMR (400 MHz, DMSO): δ_H = 6.10 (s, 2H, *CH*$_2$), 6.99–7.01 (d, 1H, *J* = 8.0 Hz, Ar—*H*), 7.25–7.27 (d, 1H, *J* = 8.0 Hz, Ar—*H*), 7.38 (s, 1H, Ar—*H*), 7.53 (s, 1H, N═*CH*), 9.23 (s, 1H, C$_6$H), 11.10 (s, 1H, NH), 11.31 (s, 1H, NH).^{13}C NMR (100 MHz, DMSO): δ_C = 102.05 (*C*H$_2$), 105.87, 108.79, 122.74, 125.23, 132.19 (*C*H—Ar), 137.84, 148.45, 150.13 (*C*—Ar), 150.58 (*C*═N), 158.08 (*C*O), 161.89 (*C*O). MS, (*m/z*) (%): 259 (M$^+$, 85). *Anal*. for $C_{12}H_9N_3O_4$ (259.22): calcd C, 55.60; H, 3.50; N, 16.21; found: C, 55.78; H, 3.55; N, 16.37.

(E)-5-(((1H-indol-3-yl)methylene)amino)pyrimidine-2,4(1H,3H)-dione (4b). Yellow crystals; mp 344–346°C; yield 85%, IR (KBr): *v*max/cm^{-1} = 3245, 3159 (NH), 1640 (CO), 1622 (C═N). ^{1}H NMR (400 MHz, DMSO): δ = 7.13–7.11 (t, 1H, *J* = 8.0 Hz, Ar—*H*), 7.20–7.18 (t, 2H, *J* = 2.0 Hz, Ar—*H*), 7.49–7.46 (m, 2H, Ar—*H* + N═C*H*), 7.89–7.88 (d, 1H, *J* = 2.8 Hz, C*H*-Indol), 8.36–8.34 (d, 1H, *J* = 8.0 Hz, Ar—*H*), 9.34 (s, 1H, C*H*-6), 10.91 (s, 1H, N*H*), 11.63 (s, 1H, N*H*), 11.21 (s, 1H, N*H*).^{13}CNMR (100 MHz, DMSO): δ = 112.22 (*C*-3-indol), 115.59 (*C*-5), 120.64, 122.50, 123.20, 124.98 (*C*H—Ar), 132.95 (*C*-6), 134.38, 137. 88 (*C*—Ar), 150.83 (*C*═N), 155.90 (*C*O), 162.49 (*C*O). MS, (*m/z*) (%): 256.16 (M^{+2}), 254 (M$^+$, 100). *Anal*. for $C_{13}H_{10}N_4O_2$ (254.24): calcd C, 61.41; H, 3.96; N, 22.04. Found: C, 61.61; H, 4.03; N, 22.23.

(E)-5-((4-chlorobenzylidene)amino)pyrimidine-2,4(1H,3H)-dione (4c). Pale yellow solid; mp 346–348°C; yield 93% (Gouvea *et al*. 13 345–346°C).

(E)-5-((4-(dimethylamino)benzylidene)amino)pyrimidine-2,4(1H,3H)-dione(4d). Pale yellow solid, yield 86%; mp 322–324°C (Rawal *et al*. 18 322–324°C).

General procedures for the synthesis of compounds 5a–d.

Method A. (three-component reaction): Refluxing a mixture of compound (**1**) (1 mmol), 2-mercaptoacetic acid (**3**, 2 mmol), and the appropriate aldehyde (1 mmol) in dioxane for 10 h. The collected water was removed by using the Dean–Stark trap and then the reaction mixture was neutralized by a solution of sodium carbonate after cooling. The solvent was removed under reduced pressure and then the oily residue was powdered by treatment with diethyl ether to afford compounds **5a**–**d**.

Method B. (two-component reaction): To a well-stirred suspension of the appropriate **4a**–**d** (1 mmol) in dioxane (10 mL), 2-mercaptoacetic acid (**3**, 2 mmol) was added. The reaction mixture was refluxed for 8 h and the collected water was removed by using the Dean–Stark trap. After cooling, the deposited solid was filtered off and crystallized from dimethylformamide (DMF)/ethanol to give the title compounds **5a**–**d**.

5-(2-(Benzo[d][1,3]dioxol-5-yl)-4-oxothiazolidin-3-yl)pyrimidine-2,4(1H,3H)-dione (5a). Yellow crystals; mp 328–330°C; yield (A) 83%, (B) 83%; IR (KBr): *ν*max/cm^{-1} = 3439–3292 (NH), 1718 (CO), 1685 (CO), 1659 (CO). ^{1}H NMR (400 MHz, DMSO): δ = 3.92 (s, 2H, C*H*$_2$), 5.23 (s, 1H, C*H*-thiazolidinone), 6.00 (s, 2H, C*H*$_2$), 7.23 (s, 1H, Ar—*H*), 7.43–7.36 (m, 2H, Ar—*H*), 8.11 (s, 1H, *H*C-6), 9.37 (s, 1H, N*H*), 11.50 (s, 1H, N*H*). ^{13}CNMR (100 MHz, DMSO): δ = 53.18 (*C*H$_2$), 63.45 (*C*H-thiazolidinone), 101.56 (*C*H$_2$), 108.18 (*C*-5), 113.52, 113.72, 114.15 (*C*H—Ar), 126.15 (H*C*-6), 130.07, 149.89, 150.13 (*C*—Ar), 161.00 (*C*O), 169.54 (*C*O), 171.57 (*C*O). MS, (*m/z*) (%): 333 (M^+, 22). *Anal*. for $C_{14}H_{11}N_3O_5S$ (333.32): calcd C, 50.45; H, 3.33; N, 12.61; S, 9.62; found: C, 50.65; H, 3.38; N, 12.79; S, 9.54.

5-(2-(1H-indol-3-yl)-4-oxothiazolidin-3-yl)pyrimidine-2,4(1H,3H)-dione (5b). Yellow crystals; mp 330–332°C; yield (A) 78%, (B) 80%; IR (KBr): *ν*max/cm^{-1} = 3269–3166 (NH), 1680 (CO), 1666 (CO), 1640 (CO). ^{1}H NMR (400 MHz, DMSO): δ = 4.13 (s, 2H, C*H*$_2$), 6.20 (s, 1H, C*H*-thiazolidinone), 7.70–7.69 (m, 2H, Ar—*H*), 8.17 (m, 2H, Ar—*H*), 8.27 (s, 1H, C*H*), 8.29 (s, 1H, *H*C-6), 9.50 (s, 1H, N*H*), 9.92 (s, 1H, N*H*-indol), 11.50 (s, 1H, N*H*). ^{13}CNMR (100 MHz, DMSO): δ = 49.06 (*C*H$_2$), 94.80 (*C*H-thiazolidinone), 108.18 (*C*-5), 109.52, 115.88, 117.00, 120.25, 122.00, 125.00 (*C*H—Ar), 128.27 (H*C*-6), 131.25, 146.96 (*C*—Ar), 162.00 (*C*O), 164.00 (*C*O), 166.00 (*C*O). MS, (*m/z*) (%): 328 (M^+, 42). *Anal*. for $C_{15}H_{12}N_4O_3S$ (328.38): calcd C, 54.87; H, 3.68; N, 17.06; S, 9.77; found: C, 55.09; H, 3.72; N, 17.21; S, 9.71.

5-(2-(4-Chlorophenyl)-4-oxothiazolidin-3-yl)pyrimidine-2,4(1H,3H)-dione (5c). Pale yellow solid; mp 340–342°C; yield (A) 80%, (B) 80%; IR (KBr): *ν*max/cm^{-1} = 3206 (NH), 1705 (CO), 1654 (CO), 1645 (CO). ^{1}H NMR (400 MHz, DMSO): δ = 3.93 (s, 2H, C*H*$_2$), 6.03 (s, 1H, C*H*-thiazolidinone), 7.35–7.48 (m, 4H, Ar—*H*), 8.09 (s, 1H, *H*C-6), 9.30 (s, 1H, N*H*), 11.40 (s, 1H, N*H*).^{13}C NMR (100 MHz, DMSO): δ = 32.25 (C*H*$_2$), 62.29 (*C*H-thiazolidinone), 108.51 (*C*-5), 129.02,129.13, 129.96 (*C*H—Ar), 132.07 (H*C*-6), 132.17, 133.48, 139.86 (*C*—Ar), 162.12 (*C*O), 167.47 (*C*O), 171.39 (*C*O). MS, (*m/z*) (%): 325 (M^{+2}, 25), 323 (M^+, 60). *Anal*. for $C_{13}H_{10}ClN_3O_3S$ (323.75): calcd C, 48.23; H, 3.11; N, 12.98; S, 9.90; found: C, 48.41; H, 3.16; N, 13.14, S; 9.85.

5-(2-(4-(Dimethylamino)phenyl)-4-oxothiazolidin-3-yl)pyrimidine-2,4(1H,3H)-dione (5d). Pale yellow solid; mp 328–330°C; yield (A) 79%, (B) 80%; IR (KBr): *ν*max/cm^{-1} = 3217 (NH), 1698 (CO), 1665 (CO), 1649 (CO). ^{1}H NMR (400 MHz, DMSO): δ = 2.87 (s, 3H, C*H*$_3$), 3.17 (s, 3H, C*H*$_3$), 3.79 (s, 2H, C*H*$_2$), 5.23 (s, 1H, C*H*-thiazolidinone), 6.62–6.65 (d, 1H, *J* = 8.0 Hz, Ar—H), 7.17–7.19 (d, 1H, *J* = 8.0 Hz, Ar—H), 8.09–8.11 (m, 2H, Ar—H), 9.37 (s, 1H, *H*C-6), 10.69 (s, 1H, N*H*), 11.50 (s, 1H, N*H*).^{13}C NMR (100 MHz, DMSO): δ = 27.86 (2*C*H$_3$), 42.33 (*C*H$_2$), 69.60 (*C*H-thiazolidinone), 112.38 (*C*-5), 113.63, 113.70, 128.82, 129.28 (*C*H—Ar), 129.67 (H*C*-6), 138.90, 150.03 (*C*—Ar), 160.96 (*C*O), 167.62 (*C*O), 169.41 (*C*O). MS, (*m/z*) (%): 332 (M^+, 12). *Anal*. for $C_{15}H_{16}N_4O_3S$ (332.38): calcd C, 54.20; H, 4.85; N, 16.86; S, 9.65; found: C, 54.40; H, 4.89; N, 17.01; S, 9.59.

General procedures for the synthesis of compounds 6a–d.

Method A. The reaction mixture of **5a**–**d** (1 mmol) and solid K_2CO_3 (4 mmol) in 5-mL dry DMF was stirred for 30 min. The first fraction of benzyl chloride (3 mmol) was added, and then the reaction mixture was stirred for 3–4 h at room temperature. The next fraction of benzyl chloride (1 mmol) was added; the reaction mixture was stirred for further 10 h and poured onto cold water. The pale yellow precipitate was filtered, washed with water, and crystallized from ethanol.

Method B. To a well-stirred suspension of the appropriate **8a**–**d** (1 mmol) in dry benzene (20 mL), 2-mercaptoacetic acid (**3**, 2 mmol) was added. The reaction mixture was refluxed for 8 h. The collected water was removed by using the Dean–Stark trap. After cooling, the deposited solid was filtered off and crystallized from ethanol to give the title compounds.

5-(2-(Benzo[d][1,3]dioxol-5-yl)-4-oxothiazolidin-3-yl)-1,3-dibenzylpyrimidine-2,4(1H,3H)-dione (6a). White solid; mp 168–170°C; yield (A) 75%, (B) 77%; IR (KBr): *ν*max/cm^{-1} = 1702 (CO), 1634 (CO), 1600 (CO), 1435 (CH$_2$). ^{1}H NMR (400 MHz, DMSO): δ = 3.95 (s, 2H, C*H*$_2$), 4.75 (s, 2H, C*H*$_2$), 4.79 (s, 2H, C*H*$_2$), 6.00 (s, 1H, C*H*-thiazolidinone), 6.03 (s, 2H, C*H*$_2$), 6.81–7.09 (m, 3H, Ar—*H*), 7.23–7.29 (m, 10H, Ar—*H*), 8.04 (s, 1H, *H*C-6). ^{13}C NMR (100 MHz, DMSO): δ = 32.51 (*C*H$_2$), 44.43 (N—*C*H$_2$), 52.36 (N—*C*H$_2$), 63.32 (*C*H-thiazolidinone), 101.83 (*C*H$_2$), 108.35 (*C*-5), 110.75, 122.73, 127.57,

127.69, 127.76, 128.28, 128.79 (*C*H—Ar), 128.97 (H*C*-6), 132.43, 136.47, 136.92, 148.19, 148.38 (*C*—Ar), 150.29 (*C*O), 159.73 (*C*O), 171.59 (*C*O). MS, (*m/z*) (%): 513 (M^+, 12). *Anal*. for $C_{28}H_{23}N_3O_5S$ (513.56): calcd C, 65.48; H, 4.51; N, 8.18; S, 6.24; found: C, 65.66; H, 4.56; N, 8.30; S, 6.19.

1,3-Dibenzyl-5-(2-(1-benzyl-1H-indol-3-yl)-4-oxothiazolidin-3-yl)pyrimidine-2,4(1H,3H)-dione (6b). Pale yellow solid; mp 190–192°C; yield (A) 73%, (B) 73%; IR (KBr): *ν*max/cm^{-1} = 1701 (CO), 1675 (CO), 1650 (CO), 1440 (CH_2). ^{1}H NMR (400 MHz, DMSO): δ = 3.45 (s, 2H, CH_2), 4.13 (s, 4H, 2CH_2), 4.74 (s, 2H, CH_2), 5.00 (s, 1H, C*H*-thiazolidinone), 6.80–6.82 (m, 2H, Ar—*H* + C*H*-indol), 7.16–7.32 (m, 19H, Ar—*H* + H*C*-6).^{13}C NMR (100 MHz, DMSO): δ = 30.26 (*C*H_2), 44.11 (N—*C*H_2), 52.00 (N—*C*H_2), 55.80 (N—*C*H_2), 64.50 (*C*H-thiazolidinone), 122.40, 126.22, 127.29, 127.54, 127.59, 127.65, 127.80, 128.02, 128.13, 128.68, 128.78, 128.88 (*C*H—Ar), 129.05 (H*C*-6), 136.97, 137.16, 137.53, 138.51 (*C*—Ar), 150.20 (*C*O), 161.27 (2*C*O). MS, (*m/z*) (%): 598 (M^+, 20). *Anal*. for $C_{36}H_{30}N_4O_3S$ (598.71): calcd C, 72.22; H, 5.05; N, 9.36; 5.36; found: C, 72.41; H, 5.09; N, 9.52; S, 5.32.

1,3-Dibenzyl-5-(2-(4-chlorophenyl)-4-oxothiazolidin-3-yl) pyrimidine-2,4(1H,3H)-dione (6c). White crystal; mp 184–186°C; yield (A) 75%, (B) 76%; IR (KBr): *ν*max/cm^{-1} = 1698 (CO), 1630 (CO), 1610 (CO), 1420 (CH_2). ^{1}H NMR (400 MHz, DMSO): δ = 3.94 (s, 2H, CH_2), 4.71 (s, 2H, N—CH_2), 4.76 (s, 2H, N—CH_2), 6.05 (s, 1H, C*H*-thiazolidinone), 6.98–7.07 (m, 5H, Ar—*H*), 7.24–7.28 (m, 4H, Ar—*H*), 7.38–7.47 (m, 5H, Ar—*H*), 8.08 (s, 1H, H*C*-6). ^{13}C NMR (100 MHz, DMSO): δ = 31.90 (*C*H_2), 43.92 (N—*C*H_2), 51.86 (N—*C*H_2), 62.02 (*C*H-thiazolidinone), 110.04 (*C*-5), 121.17, 127.13, 127.25, 127.76, 128.27, 128.46, 128.65 (*C*H—Ar), 129.99 (H*C*-6), 133.52, 135.91, 136.36, 137.52, 145.61, 149.68 (*C*—Ar), 159.15 (*C*O), 171.20 (2*C*O). MS, (*m/z*) (%): 503 (M^{-1}, 22), 505 (M^{+1}, 10). *Anal*. for $C_{27}H_{22}ClN_3O_3S$ (504.00): calcd C, 64.34; H, 4.40; N, 8.34; S, 6.36; found: C, 64.51; H, 4.45; N, 8.54; S, 6.31.

1,3-Dibenzyl-5-(2-(4-(dimethylamino)phenyl)-4-oxothiazolidin-3-yl)pyrimidine-2,4(1H,3H)-dione (6d). Pale yellow crystal; mp 190–192°C; yield (A) 73%, (B) 73%; IR (KBr): *ν*max/cm^{-1} = 1702 (CO), 1628 (CO), 1615 (CO), 1445 (CH_2). ^{1}H NMR (400 MHz, DMSO): δ = 3.69 (s, 3H, CH_3), 3.74 (s, 3H, CH_3), 3.95 (s, 2H, CH_2), 5.00 (s, 2H, N—CH_2), 5.07 (s, 2H, N—CH_2), 6.10 (s, 1H, C*H*-thiazolidinone), 7.36–7.24 (m, 14H, Ar—*H*), 8.14 (s, 1H, H*C*-6).^{13}C NMR (100 MHz, DMSO): δ = 31.24 (*C*H_2), 44.20 (N—*C*H_2), 51.90 (N—*C*H_2), 67.52 (*C*H-thiazolidinone), 109.49 (*C*-5), 120.96, 121.17, 127.13, 127.25, 127.44, 127.75, 128.20 (*C*H—Ar), 128.55 (H*C*-6), 136.19, 136.65, 145.93, 150.45 (*C*—Ar), 159.94 (*C*O), 168.71 (*C*O), 170.85 (*C*O). MS, (*m/z*) (%): 512 (M^+, 14). *Anal*. for $C_{29}H_{28}N_4O_3S$ (512.62): calcd C, 67.95; H, 5.51; N, 10.93; S, 6.26; found: C, 68.11; H, 5.55; N, 11.11; S, 6.21.

General procedure for the synthesis of compounds 8a–d. The reaction mixture of **4a**–**d** (1 mmol) and solid K_2CO_3 (4 mmol) in 5-mL dry DMF was stirred for 30 min. Then, the first fraction of benzyl chloride (3 mmol) was added, and the reaction mixture was stirred for 3–4 h at room temperature. Then, the next fraction of benzyl chloride (1 mmol) was added; the reaction mixture was stirred for further 10 h and poured onto cold water. The pale yellow precipitate was filtered, washed with water, and crystallized from ethanol.

(E)-5-((benzo[d][1,3]dioxol-5-ylmethylene)amino)-1,3-dibenzylpyrimidine-2,4(1H,3H)-dione (8a). Pale yellow solid; mp 156–158°C; yield 76%, IR (KBr): *ν*max/cm^{-1} = 1633 (CO), 1618 (C═N), 1448 (CH_2). ^{1}H NMR (400 MHz, DMSO): δ = 5.04 (s, 2H, N—CH_2), 5.07 (s, 2H, N—CH_2), 6.10 (s, 2H, CH_2), 7.00–7.02 (d, 1H, *J* = 8.0 Hz, Ar—*H*), 7.23–7.38 (m, 12H, Ar—*H*), 8.13 (s, 1H, *H*C-6), 9.25 (s, 1H, *H*C═N).^{13}C NMR (100 MHz, DMSO): δ = 44.60 (N—*C*H_2), 52.27 (N—*C*H_2), 102.12 (*C*H_2), 105.91 (*C*H—Ar), 108.86 (*C*-5), 122.88, 125.54, 127.67, 128.04, 128.13, 128.29, 128.82, 129.15, 129.30, 131.95, 132.19 (*C*H—Ar), 137.01, 137.44, 139.90, 148.50 (*C*—Ar), 150.40 (H*C*-6), 150.45 (*C*═N), 159.14 (*C*O), 160.19 (*C*O). MS, (*m/z*) (%): 439 (M^+, 16). *Anal*. for $C_{26}H_{21}N_3O_4$ (439.46): calcd C, 71.06; H, 4.82; N, 9.56; found: C, 71.25; H, 4.86; N, 9.60.

(E)-1,3-dibenzyl-5-(((1-benzyl-1H-indol-3-yl)methylene)amino)pyrimidine-2,4(1H,3H)-dione (8b). Pale yellow solid; mp 98–100°C; yield 70%; IR (KBr): *ν*max/cm^{-1} = 1634 (CO), 1620 (C═N), 1450 (CH_2). ^{1}H NMR (400 MHz, DMSO): δ = 4.75 (s, 2H, N—CH_2), 5.00 (s, 2H, N—CH_2), 5.55 (s, 2H, N—CH_2), 6.81–6.83 (m, 2H, Ar—*H*), 7.23–7.39 (m, 11H, Ar—*H* + C*H*indol), 7.58–7.60 (d, 1H, *J* = 8.0 Hz, Ar—*H*), 8.12–8.14 (d, 1H, *J* = 8.0 Hz, Ar—*H*), 8.48 (s, 1H, *H*C-6), 9.95 (s, 1H, *H*C═N). ^{13}C NMR (100 MHz, DMSO): δ = 50.29 (N—*C*H_2), 52.00 (N—*C*H_2), 55.88 (N—*C*H_2), 111.88 (*C*-5), 117.89, 121.56, 122.40, 123.03, 124.10, 125.30, 127.32, 127.53, 127.58, 127.69, 127.79, 127.83, 127.92, 128.07, 128.15, 128.27, 128.68, 128.77, 128.88, 128.97, 129.06, 129.14, 129.21 (*C*H—Ar), 137.45 (H*C*-indol), 137.57, 138.54, 141.45 (*C*—Ar), 150.40 (*C*═N), 150.28 (*C*O), 161.26 (*C*O). MS, (*m/z*) (%): 524 (M^+, 10). *Anal*. for $C_{34}H_{28}N_4O_2$ (524.61): calcd C, 77.84; H, 5.38; N, 10.68; found: C, 77.99; H, 5.41; N, 10.87.

(E)-1,3-dibenzyl-5-((4-chlorobenzylidene)amino)pyrimidine-2,4(1H,3H)-dione (8c). Pale yellow solid; mp 184–186°C; yield 77%; IR (KBr): *ν*max/cm^{-1} = 1645 (CO), 1625 (C═N), 1455 (CH_2). ^{1}H NMR (400 MHz, DMSO): δ = 5.05 (s, 2H, CH_2), 5.07 (s, 2H, CH_2), 7.30–7.38 (m, 10H, Ar—*H*), 7.51–7.54 (d, *J* = 9.0 Hz, 2H, Ar—*H*),

7.82–7.85 (d, J = 9.0 Hz, 2H, Ar—*H*), 8.21 (s, 1H, *H*C-6), 9.41 (s, 1H, C*H*═N). MS, (*m/z*) (%): 429 (M^+, 20). *Anal*. for $C_{25}H_{20}ClN_3O_2$ (429.90): calcd C, 69.85; H, 4.69; N, 9.77; found: C, 70.03; H, 4.72; N, 9.96.

(E)-1,3-dibenzyl-5-((4-(dimethylamino)benzylidene)amino) pyrimidine-2,4(1H,3H)-dione (8d). Pale yellow solid; mp 164–166°C; yield 76%; IR (KBr): *v*max/cm^{-1} = 1702 (CO), 1663 (C═N), 1567 (CH_2). ^1H NMR (400 MHz, DMSO): δ = 2.98 (s, 6H, 2C*H*$_3$), 5.01(s, 2H, C*H*$_2$), 5.06 (s, 2H, C*H*$_2$), 6.73–6.76 (d, 2H, J = 9.0 Hz, Ar—*H*), 7.26–7.37 (m, 10H, Ar—*H*), 7.61–7.64 (d, 2H, J = 9.0 Hz, Ar—*H*), 7.92 (s, 1H, *H*C-6), 9.04 (s, 1H, C*H*═N). MS, (*m/z*) (%): 438 (M^+, 18). *Anal*. for $C_{27}H_{26}N_4O_2$ (438.52): calcd C, 73.95; H, 5.98; N, 12.78; found: C, 74.16; H, 6.02; N, 12.92.

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