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Synthesis and Antimicrobial Activity of New Functionalized Derivatives of [1,2,4]Triazolo[4,3-*a*]pyrimidin-5(1*H*)-one

Ahmad S. Shawali,[1] Asma M. Mahran,[2] and Afaf A. Nada[2]

[1]*Department of Chemistry, Faculty of Science, University of Cairo, Giza, Egypt*

[2]*Photochemistry Department, National Research Center, Dokki, Giza, Egypt*

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ABSTRACT: *New functionalized 1,7-diaryl-6-cyano-1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one derivatives (***5a–j***) were synthesized via reaction of 5-cyano-6-phenyl-2-thiouracil* **1** *with the respective hydrazonoyl halides* **2a–j** *and their biological activity was evaluated. The mechanism and the regioselectivity of the studied reactions are discussed.* © 2007 Wiley Periodicals, Inc. Heteroatom Chem 18:393–398, 2007; Published online in Wiley InterScience (www.interscience.wiley.com). DOI 10.1002/hc.20311

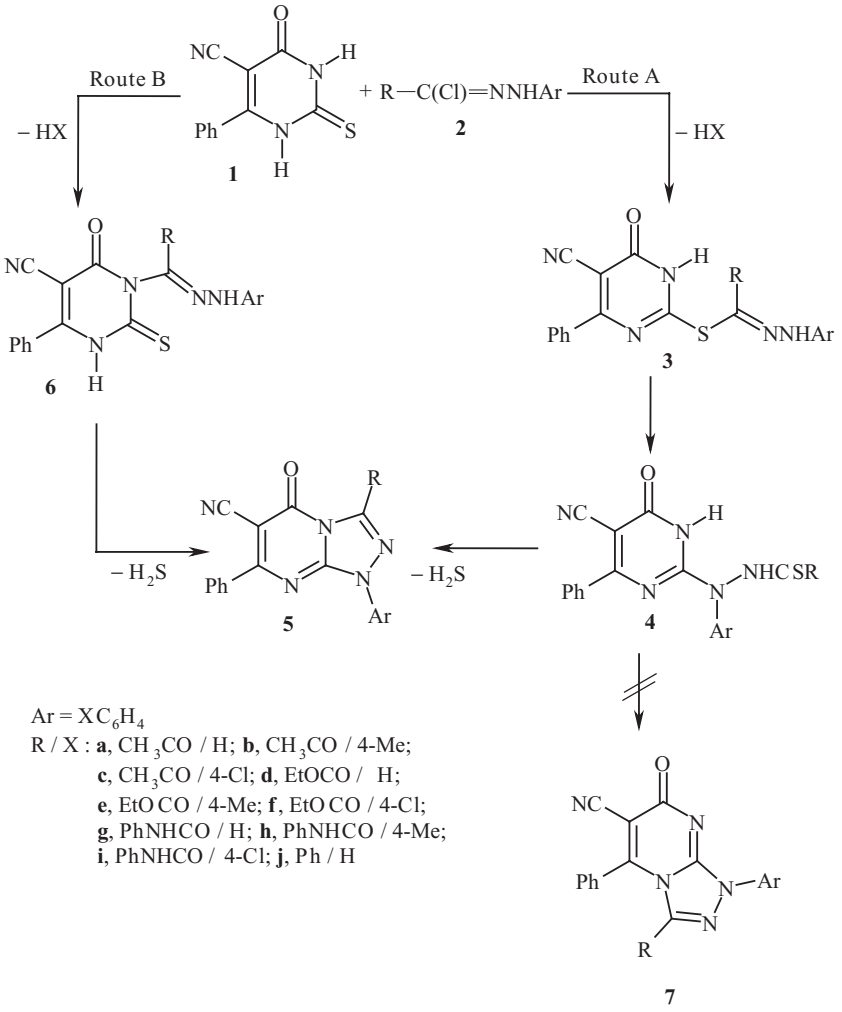
INTRODUCTION

Various derivatives of 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one were reported to be useful as calcium-channel–blocking vasodilators, some have antihypertensive [1], cardiovascular [2,3] and anxiolytic activities [4] and other are used as components in photographic materials [5]. These pharmacological activities have prompted us to develop a new synthetic strategy for functionalized derivatives of such a ring system. This is because at present the main synthetic strategy reported in literature for synthesis of 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones involves cyclization of the 2-hydrazino-3,4-dihydropyrimidin-4-one derivatives with carbon-inserting agents such as ortho esters [6]. The required hydrazine derivatives are usually prepared by hydrazinolysis of the respective 2-thiouracils [7,8]. This general route is, however, limited for synthesis of only 1-unsubstituted-1,2,4-triazolo[4,3-*a*]pyrimidin-5(1H)-ones. In the present paper, we wish to report one-step synthesis of functionalized 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones directly from 2-thiouracils **1** (Scheme 1) and the biological activity of the compounds prepared.

RESULTS AND DISCUSSION

The starting 5-cyano-6-phenyl-3,4-dihydro-2-thiouracil **1** [9] and the hydrazonoyl halides **2a–j** [10] were prepared by literature methods. Reaction of **1** with each of **2a–j** in refluxing ethanol in the presence of sodium ethoxide gave, in each case, one isolable product as evidenced by TLC analysis of the crude product. This finding indicates that the studied reactions are regioselective. On the basis of elemental analyses and IR and ^{1}H and ^{13}C NMR spectra, which showed all the expected signals (see Experimental), the isolated products were assigned the structure of 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one **5** rather than the isomeric structure of 1,3,4-triazolo[4,3-*a*]pyrimidin-7(1*H*)-one **7** (Scheme 1). Formation of compound **5** could be accounted for by one of the two pathways indicated in Scheme 1. As depicted in the latter,

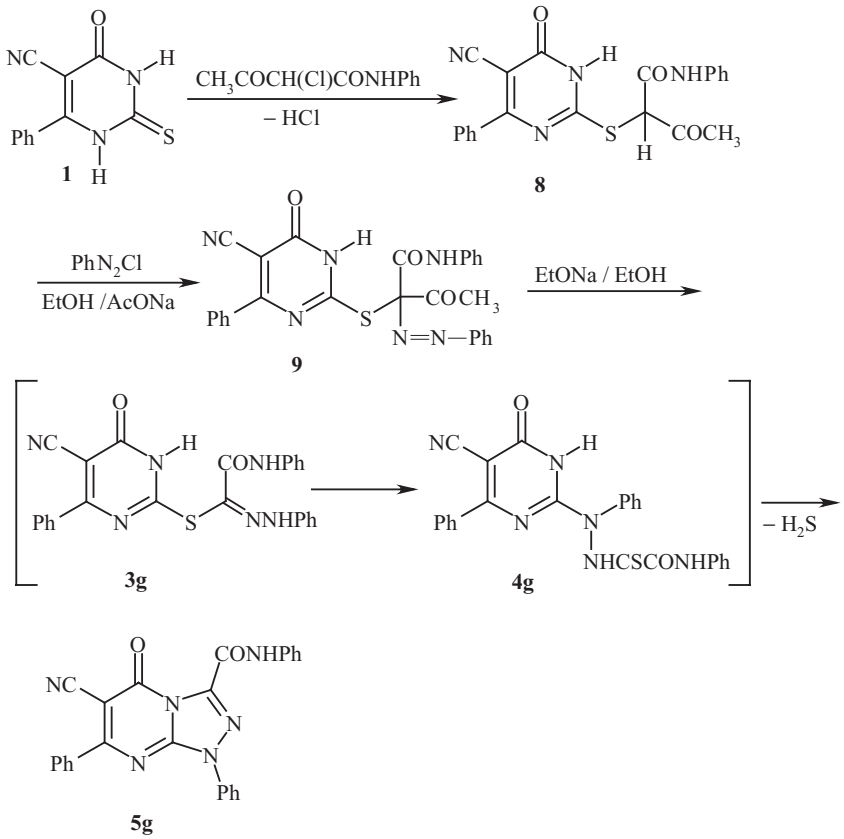
Correspondence to: Asma M. Mahran; e-mail: dr_asma_chem@yahoo.com.



SCHEME 1

it is suggested that the studied reactions started with the hydrazonoylation of **1** to give the thiohydrazonate esters **3**. This is followed by Smiles-type rearrangement [11] of the latter esters to form the respective thiohydrazides **4**, which in turn underwent cyclization to give **5** as end products (Route A, Scheme 1). It seems that both intermediates **3** and **4** are consumed, under the employed reaction conditions, as soon as they are formed since all attempts to isolate them failed. However, by varying the reaction conditions, we succeeded in isolation of one of these intermediates. For example, when **1** was reacted with **2i** in ethanol in the presence of triethylamine at room temperature, it gave **4i**. The structure of the latter was established on the basis of its microanalysis and spectra (IR, MS, and ^{1}H NMR) (see Experimental) and its conversion into **5i** upon refluxing it with ethanolic sodium ethoxide. Alternatively, the formation of **5** can also be accomplished via cyclization of the amidrazone intermediates **6** (Route B, Scheme 1). This latter alternative pathway has been ruled out, however, because alkylation and acylation of 2-thiouracil derivatives have been known to give S-alkyl and S-acyl derivatives, respectively [12–16].

The involvement of **3** and **4** as intermediates in the formation of **5** was further evidenced by alternate synthesis of **5g** (Scheme 2). Thus, treatment of **1** with α-chloroacetoacetanilide in ethanol in the presence of sodium ethoxide afforded the substituted product **8**. Coupling of **8** with benzenediazonium chloride in ethanol in the presence of sodium acetate yielded the coupling product **9** (Scheme 2). Treatment of the latter with sodium ethoxide in refluxing ethanol, in an attempt to effect Japp-Klingemann cleavage of the acetyl group in **9** [17] to give the respective thiohydrazonate (**3g**), was found to give **5g** directly (Scheme 2). This finding indicates that **3** and **4** are



SCHEME 2

intermediates in the studied reactions and they are consumed as soon as they are formed.

Finally, the suggestion that cyclization of the thiohydrazide intermediates **4** to give 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones **5** rather than the isomeric 1,2,4-triazolo[4,3-*a*]pyrimidin-7(1*H*)-ones **7** (Scheme 1) is consistent with literature reports. For example, it has been reported that cyclization of 2-substituted uracil derivatives having no substituent at N-3 proceeds regioselectively to give the respective 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-ones [18–21].

Antimicrobial Activity

The compounds **5a–j** were tested for their antimicrobial activities against four fungal species, namely *Aspergillus fumigatus* (AF), *Penicillium italicum* (PI), *Syncephalastrum racemosum* (SR), and *Candida albicans* (CA) as well as four bacteria species, namely *Staphylococcus aureus* (SA), *Pseudomonas aeruginosa* (PA), *Bacillus subtilis* (BS), and *Escherichia coli* (EC). The organisms were tested against the activity of solutions of concentration of 1.0 mg/mL of each compound and using inhibition zone diameter (IZD) in centimeter as the criterion for antimicrobial activity. Terbinafin as an antifungal agent and chloramphenicol as an antibacterial agent were used as references to evaluate the potency of the tested compounds under the same conditions. The results are depicted in Table 1. The results reveal that compounds **5a** and **5e** exhibited the highest degree of inhibition against the tested organisms SA and BS, respectively, whereas compounds **5h** and **5j** exhibited maximum inhibition against AF. Their activity is similar to that of the standard antifungal and antibacterial agents used. All other compounds either exhibit no activity or are less active against the tested species (Table 1).

EXPERIMENTAL

Melting points were determined on a Gallenkamp apparatus and are uncorrected. IR spectra were recorded in potassium bromide using PU 9712 spectrophotometer. ^{1}H and ^{13}C NMR spectra were recorded in deuterated chloroform using a Varian Gemini 300 NMR spectrometer. Mass spectra were

TABLE 1 Antimicrobial Activity of the Products **5a–j***

	Microorganism IZD (cm)†							
Compound	*Aspergillus Fumigatus*	*Penicillium Italicum*	*Syncephalastrum Racemosum*	*Candida Albicans*	*Staphylococcus Aureus*	*Pseudomonas Aeruginosa*	*Bacillus Subtilis*	*Escherichia Coli*
5a	+	+	0	+	++	0	+	0
5b	+	0	+	0	+	0	+	0
5c	0	0	0	0	+	+	+	0
5d	0	0	0	0	0	+	0	0
5e	+	0	0	0	+	+	++	+
5f	+	0	0	0	0	0	0	0
5g	+	0	0	0	0	0	0	0
5h	++	0	+	+	0	0	+	0
5i	+	0	0	+	0	0	+	0
5j	++	0	+	0	+	+	+	0
CA‡						++	++	++
TE§	++	++	++	++	++			

**Note*: IZD, inhibition zone diameter; ++, inhibition value 0.6–1.0 cm; +, inhibition value 0.1–0.5 cm beyond control; 0, no inhibition detected.
†50 mL of solution in DMF, whose concentration of 1.0 mg/mL was tested.
‡Chloramphenicol as standard antibacterial agent.
§Terbinafin as standard antifungal agent.

recorded on a 75 Kratos spectrometer. Elemental analyses were carried out at the Microanalytical Laboratory of National Research Center, Giza, Egypt. 5-Cyano-6-phenyl-3,4-dihydro-2-thiouracil (**1**) [9] and hydrazonoyl halides (**2a–j**) [10] were prepared as previously described.

Synthesis of Compounds **5a–j**

General Procedure: To a stirred ethanolic sodium ethoxide solution, prepared by dissolving sodium metal (0.01 g.atom) in ethanol (30 mL), was added 5-cyano-6-phenyl-2-thiouracil (**1**) (2.30 g, 0.01 mol). To the resulting mixture was added the appropriate hydrazonoyl halide (**2**) (0.01 mol) portionwise. After the addition was complete, the reaction mixture was refluxed until hydrogen sulfide ceased to evolve. The reaction mixture was then evaporated in a rotatory evaporator and the residue was triturated with methanol. The solid that precipitated was filtered, washed with water and dried, and finally crystallized from the proper solvent to give the respective 1,2,4-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one derivative (**5**).

*3-Acetyl-6-cyano-1,7-diphenyl[1,2,4]triazolo[4,3-a]pyrimidin-5(1*H*)-one (***5a***)*. White crystals, yield 2.48 g (70%), mp 148–149°C (EtOH). IR (KBr) ν cm^{-1}: 2225, 1685, 1660. MS *m/z* (%): 356 ($M^+ + 1$, 72), 355 (M^+, 2), 327 (4), 313 (100), 285 (62), 258 (28), 127 (3), 103 (10), 77 (13). ^{1}H NMR ($CDCl_3$) δ_H: 2.36 (s, 3H, $COCH_3$), 7.20–8.10 (m, 10H, ArH). Anal. Calcd. for $C_{20}H_{13}N_5O_2$ (355): C, 67.66%; H, 3.68%; N, 19.72%. Found: C, 67.65%; H, 3.67%; N, 19.71%.

*3-Acetyl-6-cyano-7-phenyl-1-(4-methylphenyl)-[1,2,4]triazolo[4,3-a]-pyrimidin-5(1*H*)-one (***5b***)*. White crystals, yield 2.65 g (72%), mp 221–222°C (EtOH). IR (KBr) ν cm^{-1}: 2221, 1685, 1660. MS *m/z* (%): 370 ($M^+ + 1$, 68), 369 (M^+, 9), 341 (4), 327 (100), 299 (32), 272 (21), 127 (3), 104 (11), 77 (10). ^{1}H NMR ($CDCl_3$) δ_H: 2.30 (s, 3H, CH_3), 2.36 (s, 3H, $COCH_3$), 7.52–8.10 (m, 9H, ArH). Anal. Calcd. for $C_{21}H_{15}N_5O_2$ (369): C, 68.35%; H, 4.09%; N, 18.97%. Found: C, 68.34%; H, 4.10%; N, 18.96%.

*3-Acetyl-6-cyano-7-phenyl-1-(4-chlorophenyl)-[1,2,4]triazolo[4,3-a]-pyrimidin-5(1*H*)-one (***5c***)*. White crystals, yield 2.80 g (72%), mp 238–240°C (EtOH). IR (KBr) ν cm^{-1}: 2219, 1685, 1660. MS *m/z* (%): 392 ($M^+ + 2$, 2), 390 (M^+, 2), 363 (2), 347 (41), 321 (10), 293 (6), 127 (58), 104 (15), 77 (42). ^{1}H NMR ($CDCl_3$) δ_H: 2.36 (s, 3H, $COCH_3$), 7.20–8.10 (m, 9H, ArH). Anal. Calcd. for $C_{20}H_{12}ClN_5O_2$ (390): C, 61.15%; H, 3.09%; N, 17.95%. Found: C, 61.00%; H, 3.11%; N, 17.80%.

*Ethyl-6-cyano-1,7-diphenyl-[1,2,4]triazolo[4,3-a]-pyrimidin-5(1*H*)-one-3-carboxylate (***5d***)*. White crystals, yield 2.77 g (72%), mp 209–210°C (EtOH). IR (KBr) ν cm^{-1}: 2225, 1685. MS *m/z* (%): 385 (M^+, 100), 357 (5), 312 (14), 259 (6), 258 (6), 127 (10), 103 (10), 77 (9). ^{1}H NMR ($CDCl_3$) δ_H: 1.5 (t, 3H, CH_3), 4.62 (q, 2H, CH_2) 7.20–8.10 (m, 10H, ArH). Anal. Calcd. for $C_{21}H_{15}N_5O_3$ (385): C, 65.51%; H, 3.92%; N, 18.18%. Found C, 65.32%; H, 3.90%; N, 18.20%.

*Ethyl-6-cyano-7-phenyl-1-(4-methylphenyl)-[1,2,4]-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one-3-carboxylate (**5e**).* White crystals, yield 2.87 g (72%), mp 155–156°C (EtOH). IR (KBr) ν cm^{-1}: 2225, 1685. MS *m/z* (%): 399 (M^+, 3), 371 (9), 326 (100), 299 (33), 272 (18), 127 (2), 104 (9), 77 (4). ^{1}H NMR ($CDCl_3$) δ_H: 1.51 (t, 3H, CH_3), 2.36 (s, 3H, CH_3), 4.62 (q, 2H, CH_2), 7.20–8.10 (m, 9H, ArH). Anal. Calcd. for $C_{22}H_{17}N_5O_3$ (399): C, 66.22%; H, 4.29%; N, 17.55%. Found: C, 66.01%; H, 4.10%; N, 17.60%.

*Ethyl-6-cyano-7-phenyl-1-(4-chlorophenyl)-[1,2,4]-triazolo[4,3-*a*]pyrimidin-5(1*H*)-one-3-carboxylate (**5f**).* Brown crystals, yield 2.89 g (72%), mp 239–240°C (EtOH). IR (KBr) ν cm^{-1}: 2225, 1700, 1685. MS *m/z* (%): 421 ($M^+ + 2$, 31), 419 (M^+, 100), 391 (2), 346 (14), 319 (8), 292 (2), 127 (9), 103 (1), 77 (5). ^{1}H NMR ($CDCl_3$) δ_H: 1.5 (t, 3H, CH_3), 4.62 (q, 2H, CH_2), 7.20–8.10 (m, 9H, ArH). ^{13}C NMR ($CDCl_3$) δ: 13.89, 64.70, 114.91, 122.41, 128.75, 129.15, 129.82, 132.24, 134.11, 134.78, 135.37, 136.45, 146.47, 154.00, 155.43, 170.69. Anal. Calcd. for $C_{21}H_{14}ClN_5O_3$ (419): C, 60.19%; H, 3.36%; N, 16.71%. Found: C, 60.20%; H, 3.40%; N, 16.80%.

N-*Phenyl-6-cyano-1,7-diphenyl-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one-3-carboxamide (**5g**).* Yellow crystals, yield 3.09 g (72%), mp 218–220°C (EtOH). IR (KBr) ν cm^{-1}: 3080, 2225, 1685. MS *m/z* (%): 433 ($M^+ + 1$, 33), 432 (M^+, 65), 404 (2), 327 (100), 312 (25), 286 (4), 358 (3), 127 (3), 104 (21), 77 (29). ^{1}H NMR ($CDCl_3$) δ_H: 7.20–8.10 (m, 15H, ArH), 8.51 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 13.89, 29.67, 64.71, 87.95, 114.9, 122.41, 128.75, 129.15, 129.82, 132.24, 134.11, 134.76, 135.37, 136.45, 146.47, 154.00, 155.43, 170.69. Anal. Calcd. for $C_{25}H_{16}N_6O_2$ (432): C, 69.50%; H, 3.72%; N, 19.45%. Found: C, 69.40%; H, 3.80%; N, 19.41%.

N-*Phenyl-6-cyano-7-phenyl-1-(4-methylphenyl)-[1,2,4]triazolo[4,3-*a*]pyrimidin-5(1*H*)-one-3-carboxamide (**5h**).* Yellow crystals, yield 3.2 g (72%), mp 211–212°C (EtOH). IR (KBr) ν cm^{-1}: 3072, 2225, 1685, 1660. MS *m/z* (%): 447 ($M^+ + 1$, 18), 446 (M^+, 80), 419 (2), 341 (100), 327 (40), 300 (15), 272 (10), 127 (6), 103 (18), 77 (18). ^{1}H NMR ($CDCl_3$) δ_H: 2.30 (s, 3H, CH_3), 7.20–8.10 (m, 14H, ArH) 8.52 (s, 1H, NH). Anal. Calcd. for $C_{26}H_{18}N_6O_2$ (446): C, 69.95%; H, 4.03%; N, 18.83%; Found: C, 69.89%; H, 4.00%; N, 18.79%.

N-*Phenyl-6-cyano-7-phenyl-1-(4-chlorophenyl)-[1,2,4]triazolo[4,3-*a*]-pyrimidin-5(1*H*)-one-3-carboxamide (**5i**).* Yellow crystals, yield 3.2 g (70%), mp 250–251°C (EtOH). IR (KBr) ν cm^{-1}: 2225, 1685, 1664. MS *m/z* (%): 468 ($M^+ + 2$, 17), 466 (M^+, 70), 446 (2), 361 (100), 347 (25), 319 (13), 127 (9), 114 (4), 77 (16). ^{1}H NMR ($CDCl_3$) δ_H: 7.20–8.10 (m, 14H, ArH), 8.52 (s, 1H, NH). ^{13}C NMR ($CDCl_3$) δ: 86.99, 116.61, 120.71, 124.31, 125.80, 129.45, 129.52, 129.86, 130.51, 132.61, 133.93, 134.80, 136.32, 138.13, 139.55, 147.84, 153.28, 155.77, 170.63. Anal. Calcd. for $C_{25}H_{15}ClN_5O_2$ (466): C, 64.43%; H, 3.24%; N, 18.03%. Found: C, 64.50%; H, 3.24%; N, 18.00%.

*1,3,7-Triphenyl-6-cyano-[1,2,4]triazolo[4,3-*a*]-pyrimidin-5(1*H*)-one (**5j**).* White crystals, yield 2.8 g (72%), mp 302–303°C (EtOH). IR (KBr) ν cm^{-1}: 2225, 1685. MS *m/z* (%): 399 ($M^+ + 1$, 5), 389 (M^+, 100), 360 (24), 258 (10), 127 (2), 103 (5), 77 (9). ^{1}H NMR (DMSO-d_6) δ_H: 7.20–8.16 (m, 15H, ArH). ^{13}C NMR (DMSO-d_6) δ: 67.90, 87.23, 117.86, 123.52, 126.84, 129.27, 129.95, 103.12, 131.01, 132.06, 132.47, 132.98, 137.27, 137.57, 146.62, 149.75, 157.57, 170.58; Anal. Calcd. for $C_{24}H_{15}N_5O_2$ (389): C, 74.10%; H, 3.88%; N, 18.00%. Found: C, 74.10%; H, 3.90%; N, 18.01%.

*Synthesis of the Thiohydrazide (**4i**)*

To a mixture of the thione **1** and **2i** (0.01 mol each) in ethanol (50 mL) was added triethylamine (1.4 mL, 0.01 mol) and the reaction mixture was stirred for 3 h at room temperature. The solid that was precipitated was filtered and crystallized from ethanol to give **4i**: yellow crystals, yield 3.21 g (76%), mp 195–196°C (EtOH). IR (KBr) ν cm^{-1}: 3160, 2219, 1698, 1664, 1465. MS *m/z* (%): 425 ($M^+ + 2$, 12), 423 (M^+, 50). ^{1}H NMR ($CDCl_3$) δ_H: 1.53 (s, 3H, CH_3), 7.00–7.60 (m, 9H, ArH), 8.50 (s, 1H, NH), 11.83 (s, 1H, NH). Anal. Calcd. for $C_{20}H_{14}ClN_5O_2S$ (423): C, 56.73%; H, 3.30%; N, 16.54%; Found C, 56.68%; H, 3.23%; N, 16.60%.

*2-(5-Cyano-6-phenyl-3*H*-4-oxo-2-pyrimidinylthio)acetoacetanilide (**8**)*

To a mixture of equimolar amounts of 2-chloroacetoacetanilide and **1** (0.01 mol each) in absolute ethanol (25 mL) was added triethylamine (1.4 mL, 0.01 mol). The resulting mixture was stirred at room temperature for 10 h. The solid that precipitated was filtered and crystallized from ethanol to give **8**: white crystals, yield 3.0 g (75%), mp 197–198°C (EtOH). IR (KBr) ν cm^{-1}: 3430, 3124, 2223, 1700, 1685, 1650. MS *m/z* (%): 406 ($M^+ + 1$, 1), 405 (M^+, 2). ^{1}H NMR ($CDCl_3$) δ_H: 1.53 (s, 3H, CH_3), 5.9 (s, 1H, CH), 7.00–7.60 (m, 10H, ArH), 8.50 (s, 1H, NH), 11.83 (s, 1H, NH). Anal. Calcd. for $C_{21}H_{16}N_4O_3S$ (404): C, 62.22%; H, 3.95%; N, 13.82%; Found C, 62.13%; H, 4.00%; N, 13.19%.

*2-Phenylazo-2-(5-cyano-6-phenyl-3*H*-4-oxo-2-pyrimidinylthio)acetoacetanilide (**9**)*

To a stirring solution of **8** (10 m moles) in ethanol (50 mL) was added sodium acetate trihydrate (3 g) and the mixture was cooled in an ice bath to 0–5°C. To the resulting cold solution was added portionwise a cold solution of benzenediazonium chloride, prepared by diazotizing aniline (10 mmol) in hydrochloric acid (6 mL, 6M) with sodium nitrite (0.7 g, 10 mmol) in a low amount of water. After all of the diazonium salt solution was added, the reaction mixture was stirred for 1 h in ice bath and left in the refrigerator. The solid that precipitated was filtered off, washed with water, air dried, and finally crystallized from ethanol to give **9**: brown powder, yield 3.45 g (68%), mp 161–162°C. (EtOH). IR (KBr) ν cm^{-1}: 3421, 3100, 2217, 1700, 1687, 1650, 1567, 1508. MS *m/z* (%): 509 ($M^+ + 1$, 2), 508 (M^+, 5). ^1H NMR (DMSO-d_6) δ_H : 1.50 (s, 3H, CH_3), 7.3–8.1 (m, 15H, ArH), 8.5 (s, 1H, NH), 10.9 (s, 1H, NH); Anal. Calcd. for $C_{27}H_{20}N_6O_3S$ (508): C, 63.77%; H, 3.93%; N, 16.53%; Found C, 63.69%; H, 3.92%; N, 16.50%.

*Cyclization of 2-phenylazo-2-(5-cyano-6-phenyl-3*H*-4-oxo-2-pyrimidinylthio)acetoacetanilide (**9**)*

To a stirred sodium ethoxide solution, prepared from sodium metal (0.69 g, 0.003 g.atom) and absolute ethanol (20 ml), compound **9** (1.524 g, 0.003 mol) was added and the mixture was refluxed, while being stirred, till all hydrogen sulfide ceased to evolve (3 h), then cooled. The solid that precipitated was filtered off, washed with water, air dried, and finally crystallized from ethanol to give a yellow crystaline product that proved identical in all respects with **5g** (mp 220°C, yield 65%) obtained above from **1** and **2g**.

Antimicrobial Assay

Cultures of four fungal species, namely, *Aspergillus fumigatus*, *Penicillium italicum*, *Syncephalastrum racemosum*, and *Candida albicans*, as well as four bacterial species, namely, *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Bacillus subtilis*, and *Escherichia coli* were used to investigate the antimicrobial activity of compounds **5a–j**. The antimicrobial activity was assayed biologically using the diffusion plate technique. The latter technique involved pouring a spore suspension of the fungal species (1 mL of sterile water contains approximately 10^8 conidia) or spreading bacterial suspension over a solidified malt agar medium. The layer is allowed to set for 30 min. A solution of the test compound **5** (1.0 mg/mL) in dimethylformamide was placed onto sterile 5-mm filter paper discs and allowed to dry; then the discs were placed on the centre of the malt agar plate and incubated at optimum incubation temperature 28 ± 2°C. Test organism growth may be affected by the inhibitory action of the test compound, so a clear zone around the disc appears as an indication of the inhibition of test organism growth. The size of the clearing zone is proportional to the inhibitory action of the compound. The fungicide Terbinafin and the bactericide chloramphenicol were used as standards under the same conditions. Measurements were considered after 72 h for fungi and 24 h for bacteria. The results are summarized in Table 1.

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