Synthesis and Antimicrobial Activity of Some Novel Quinoline, Chromene, Pyrazole Derivatives Bearing Triazolopyrimidine Moiety

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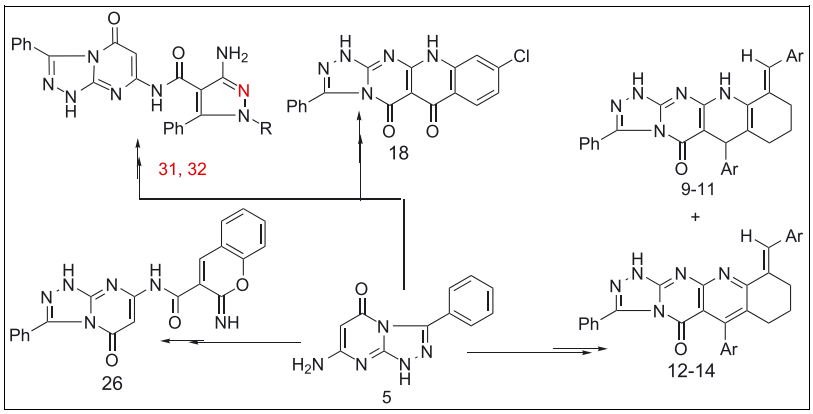

7-Amino-3-phenyl-[1,2,4]triazolo [4,3-a] pyrimidin-5(1*H*)-one (5) was utilized as key intermediate for the synthesis of some new, quinolines **9**–**14** and **18**–**20**, acrylonitrile **25** and **28**, coumarin **26**, and pyrazoles **31**–**34** incorporating triazolopyrimidines. The structures of the newly synthesized compounds were confirmed by elemental analysis, IR, ^{1}H NMR, and mass spectral data. Representative compounds of the synthesized products were tested and evaluated as antimicrobial. Compounds **25**, **28**, **31**, **32**, **33**, and **34** are the most promising.

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INTRODUCTION

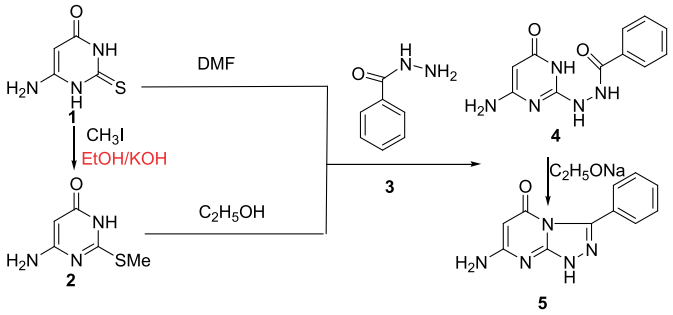
Triazolopyrimidines (TPs), a subtype of purine analogs, have been the subject of chemical and biological studies because of their interesting pharmacology including antibacterial [1], antifungal [2], antihypertensive [3], anticonvulsant [4], antitumor [5], cytotoxicity [6], potent and selective ATP site directed inhibition of the EGF-receptor protein tyrosine kinase [7], and cardiovascular [8] activities.

In addition, TPs are versatile ligands, and their derived coordination compounds can be considered as model systems for metal–ligand interactions observed in biological systems [9,10]. The simple molecule of Trapidil, the most widely known TP derivative, acts as a platelet-derived growth factor antagonist and as a phosphodiesterase inhibitor [9]. Essramycin was the first TP antibiotic isolated from nature. Essramycin represents a class of TP and was proved to be potent antibiotic agents [11].

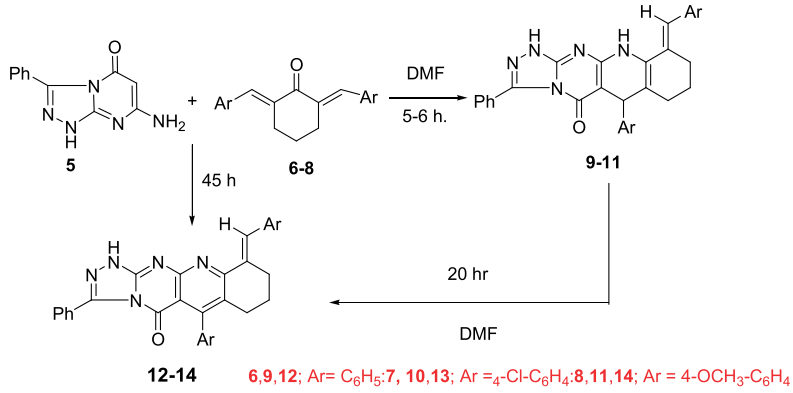
Furthermore, Pyrimidoquinolines are important compounds because of their biological properties, which are known to depend mainly on the nature and position of substituents, and include antimalarial [12], anticancer [13], antimicrobial [14], and anti-inflammatory activities [15]. Coumarin (2H-chromen-2-one) and its derivatives are widely distributed in nature and have been reported to exhibit diverse pharmacological properties such as anticancer [16], anti-coagulant, estrogenic, dermal, photosensitizing, antimicrobial, vasodilatory, molluscicidal, antihelminthic, sedative, hypnotic, and analgesic hypothermic [17,18]. Many biological properties for pyrazole derivatives have been reported such as anti-inflammatory [19], antiviral [20], antimicrobial [21], anticonvulsant [22], antitumor [23], fungicidal activities [24], and antihistaminic [25].

In view of these facts and as a continuation of our research program on the chemistry of 6-amino-2,3-dihydro-2-thioxopyrimidin-4(1*H*)-one [26–29], the present investigation aimed to synthesize and characterize newer quinoline, chromene, and pyrazole derivatives bearing TP moiety in order to evaluate their anti-microbial activities. It was found that 7-amino-3-phenyl-[1,2,4]triazolo [4,3-a] pyrimidin-5(1*H*)-one (5) is an excellent building block for the synthesis of the target objectives.

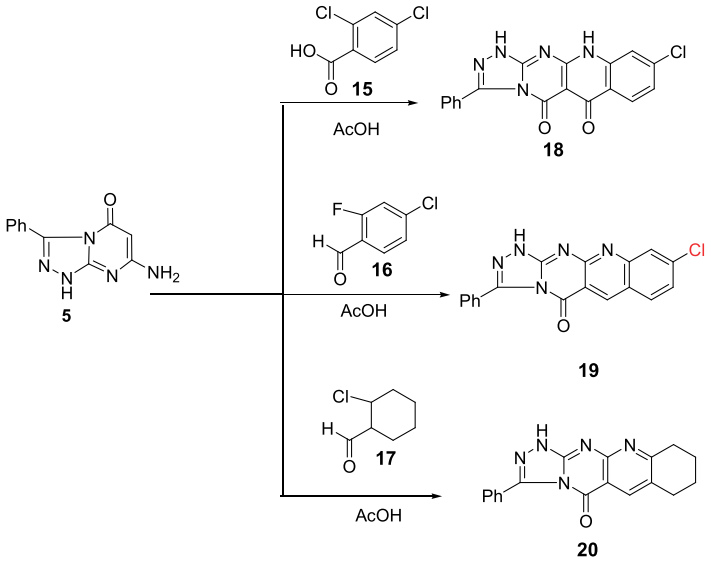
Scheme 1. Preparation of 7-amino-3-phenyl-[1,2,4]triazolo [4,3-a] pyrimidin-5(1H)-one (5). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



Scheme 2. Synthesis of [1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-b]quinoline derivatives 9–14. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



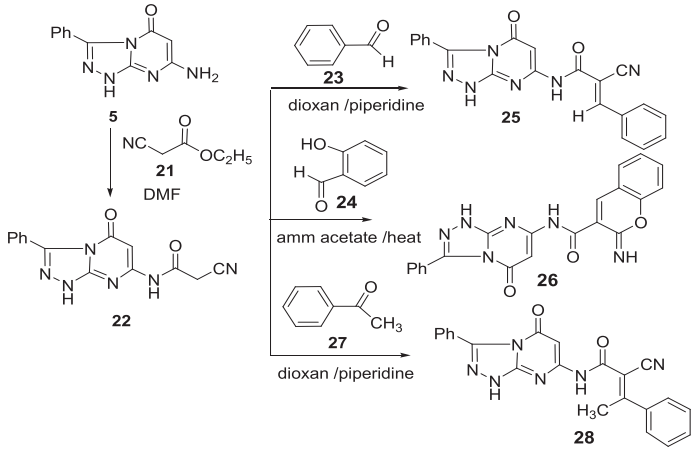
Scheme 3. Synthesis of [1,2,4]triazolo[4′,3′:1,2]pyrimido[4,5-b]quinoline derivatives 18–20.



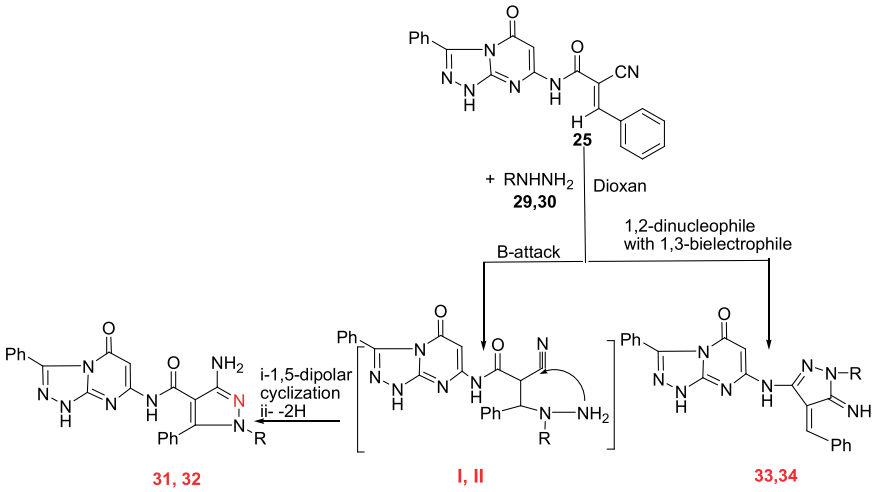
RESULTS AND DISCUSSION

Chemistry. The reaction sequences used for synthesis of the title compounds are depicted in Schemes 1, 2, 3, 4, and 5. The starting compound, 7-aminopyrimidin-5(1*H*)-one derivative (**5**), was prepared *via* heating under reflux of 6-aminothiouracil (**1**) with benzohydrazide (**3**) in dimethyl formamide, followed by stirring under reflux of the formed *N*′-(pyrimidin-2-yl)benzohydrazide derivative **4** in sodium ethoxide. In another route compound

Scheme 4. Synthesis of acrylonitrile derivatives 25, 28, iminocoumarin 28.



Scheme 5. Synthesis of pyrazole derivatives (31–34). [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]



4 was prepared by alkylation of **1** with methyl iodide in ethanolic potassium hydroxide solution to afford 6-amino-2-(methylthio) pyrimidin-4(3*H*)-one **(2)** [30], which reacted with benzohydrazide **(3)** in absolute ethanol to give the corresponding **4** (Scheme 1).

The starting compound, 7-amino-3-phenyl-[1,2,4]triazolo [4,3-a] pyrimidin-5(1*H*)-one **(5)** was used as versatile precursor to react with common reagents to obtain a variety of heterocyclic compounds. Thus, compound **5** reacted with cyclic α,β-unsaturated ketones type **(6–8)** in dimethylformamide for **6–7** h afforded compounds (**9–11**) in good yield. Whereas, triazolo pyrimido[4,5-b]quinolines **12–14** were achieved when the reaction mixture was refluxed for a longer time of 45 h. In another route compounds **12** were prepared by refluxing of **c**ompound **9** in DMF for 15 h (Scheme 2).

Furthermore, reaction of compound **5** with 2,4-dichlorobenzoic acid **15**, *o*-fluorobenzaldehyde **16**, 2-chlorocyclohexene carboxaldehyde **17** in glacial acetic acid produced the triazolopyrimidoquinolines **18–20** (Scheme 3).

Moreover, cyanoacetylation of compound **5** with ethylcyanoacetate **21** afforded the cyanoacetamide **22**. Knovenagel condensation of **22** with bezaldehyde **23** or salicyaldehyde **24** afforded the corresponding arylidine **25** and iminocoumarin **26**, respectively. Also, fusion of **22** with acetophenone **27** in the presence of ammonium acetate afford the corresponding arylidine **28** (Scheme 4).

Condensation of compound **25** with hydrazine derivatives **29, 30** afforded the 3-amino-*N*-(1,5-dihydro-5-oxo-3-phenyl [1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-5-phe-nyl-1H-pyrazole-4-carboxamide **(31)** and 3-amino-*N*-(1,5-dihydro-5-oxo-3-phenyl [1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,5-diphenyl-1H-pyrazole-4-carboxamide **(32)** as the major products. The formation of the pyrazole derivatives **31, 32** proceed via β-attack of hydrazine derivatives **29, 30** on the C=C moiety in **25** to give the non-isolable intermediates **I** and **II** which underwent 1,5-intramolecular dipolar cyclization and concomitant aromatization. Minor products **33, 34** were obtained in the mother liquor which proceeds via the condensation of hydrazine derivatives **29, 30** with the

carbonyl followed by addition on the cyano group afforded the pyrazole derivatives **33, 34**; similar behaviors were reported [31] (Scheme 5).

Assignment of the new synthesized compounds was based on elemental analyses, IR, ^{1}H, ^{13}C NMR, and mass spectral data (c.f. Exp. Part).

Biological evaluation. The new synthesized compounds were screened in vitro for their antimicrobial activity. The diameter of inhibition zone was measured as an indicator for the activity of the compounds. The results for antibacterial activities depicted in Table 1 revealed that compounds **10**, **11**, **25**, **28**, **31**, **32**, 33, and **34** were the most effective against *Staphylococcus aureus* and *Bacillus subtilis* and have moderate activity against *Pseudomonas aeruginosa*, and *Escherichia coli*. On the other hand, most of the prepared compounds exhibited low to moderate antifungal activities against the reference drugs, whereas compounds **25**, **28**, **31**, **32**, **33,** and **34** were the most effective against *Aspergillus fumigatus* and *Geotrichum candidum* and have moderate activity against *Candida albicans*, and *Syncephalastrum racemosum* (Table 2).

Comparing the results obtained for the antimicrobial activities of the compounds reported in this study with their structures, the following SAR are postulated (Fig. 1): (i) it seems that most of the quinolines, cyanoacetamid, coumarin, and pyrazole derivatives are more potent than the starting TP **5** which may be because of the presence of the quinoline, $NHCOCH_2CN$, coumarin, and pyrazole moieties respectively. (ii) The antimicrobial activities of quinoline **9–13** follow the order $\mathbf{9 < 11 < 10}$, which may be attributed to the electronic effect of the *p*-substituents, i.e. $Cl > OCH_3 > H$ by +M. (iii) Compounds **25** and **28** have good antimicrobial activities which may be attributed to presence of acrylonitrile moiety. (iv) Compound **33, 34** and **35**,**36**, have good antimicrobial activities than compound **5**, which may be attributed to the presence of aminopyrazole and iminopyrazole moieties respectively (**Fig.** 1).

CONCLUSION

Novel quinoline, cyanoacetamide, acrylonitrile, coumarin, and pyrazole derivatives incorporating the triazolepyrimidine

Table 1

Antibacterial activity of compounds.[a,b,c]

	Gram positive bacteria		Gram negative bacteria	
Compounds	*Staphylococcus aureus* (RCMB 000106)d	*Bacillus subtilis* (RCMB 000107)	*Pseudomonas aeruginosa* (RCMB 000102)	*Escherichia coli* (RCMB 000103)
1	10.30 ± 0.52	8.85 ± 0.45	NA	NA
2	11.10 ± 0.32	9.10 ± 0.60	NA	NA
3	NA	NA	NA	NA
4	12.90 ± 0.10	10.40 ± 0.20	NA	7.10 ± 0.52
5	14.40 ± 0.28	12.80 ± 0.50	NA	7.80 ± 0.74
9	23.20 ± 0.60	22.50 ± 0.80	14.50 ± 0.40	14.10 ± 0.30
10	25.30 ± 0.82	24.20 ± 0.50	16.70 ± 0.40	15.60 ± 0.15
11	24.10 ± 0.52	23.60 ± 0.70	15.80 ± 0.50	15.20 ± 0.20
12	17.50 ± 0.70	16.30 ± 0.50	NA	NA
13	19.10 ± 0.60	18.50 ± 0.20	10.40 ± 0.50	10.30 ± 0.70
14	18.20 ± 0.40	17.40 ± 0.10	NA	NA
18	22.50 ± 0.30	21.80 ± 0.60	13.70 ± 0.20	13.50 ± 0.60
19	14.20 ± 0.80	13.10 ± 0.60	NA	NA
20	20.20 ± 0.50	19.70 ± 0.30	11.50 ± 0.70	11.40 ± 0.80
22	21.60 ± 0.70	20.60 ± 0.50	12.80 ± 0.40	12.70 ± 0.90
25	26.50 ± 0.72	25.40 ± 0.40	17.80 ± 0.35	16.80 ± 0.10
26	16.40 ± 0.80	15.10 ± 0.90	NA	NA
28	26.90 ± 0.45	25.60 ± 0.55	18.50 ± 0.75	17.60 ± 0.85
31	29.50 ± 0.30	30.10 ± 0.90	22.80 ± 0.75	22.40 ± 0.60
32	29.70 ± 0.21	29.50 ± 0.80	24.30 ± 0.40	23.60 ± 0.50
33	27.50 ± 0.34	26.20 ± 0.42	19.70 ± 0.25	18.80 ± 0.95
34	28.60 ± 0.07	28.90 ± 0.70	20.80 ± 0.50	20.20 ± 0.30
Penicillin G	30.50 ± 0.62	34.25 ± 0.85	29.45 ± 0.20	35.40 ± 0.55
Streptomycin	28 ± 0.30	30 ± 0.50	26 ± 0.30	27 ± 0.46

RCMB, Regional Center for Mycology and Biotechnology Culture Collection.; NA, no activity.

[a]Mean zone of inhibition in mm ± standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (10 mg/mL) concentration of tested samples. The concentration used for the standard antibiotic was (30 μg/mL).

[b]The test was done using the diffusion agar technique. Well diameter: 6.0 mm (100 μL was tested).

[c]Data are expressed in the form of mean ± SD.

Table 2

Antifungal activity of compounds.[a,b,c]

Compounds	Fungi			
	Aspergillus fumigatus (RCMB 002003)	*Geotrichum candidum* (RCMB 052006)	*Candida albicans* (RCMB 005002)	*Syncephalastrum racemosum* (RCMB 005003)
1	NA	NA	NA	NA
2	NA	7.70 ± 0.60	NA	NA
3	NA	NA	NA	NA
4	8.10 ± 0.05	8.50 ± 0.80	7.10 ± 0.40	NA
5	9.50 ± 0.60	9.80 ± 0.50	8.60 ± 0.50	NA
9	18.40 ± 0.50	18.20 ± 0.30	10.70 ± 0.40	10.10 ± 0.50
10	20.20 ± 0.60	20.40 ± 0.50	12.50 ± 0.80	11.60 ± 0.30
11	19.50 ± 0.45	19.25 ± 0.60	11.20 ± 0.85	11.10 ± 0.35
12	10.90 ± 0.50	9.80 ± 0.30	NA	NA
13	14.60 ± 0.40	12.80 ± 0.60	NA	NA
14	13.70 ± 0.20	11.50 ± 0.40	NA	NA
18	17.30 ± 0.40	16.50 ± 0.40	9.40 ± 0.30	8.60 ± 0.70
19	14.20 ± 0.80	13.10 ± 0.60	NA	NA
20	NA	NA	NA	NA
22	16.40 ± 0.20	15.40 ± 0.80	NA	NA
25	21.40 ± 0.35	21.30 ± 0.90	13.10 ± 0.60	12.30 ± 0.40
26	9.20 ± 0.50	NA	NA	NA
28	22.10 ± 0.40	22.60 ± 0.75	14.30 ± 0.25	13.50 ± 0.65
31	25.30 ± 0.20	25.20 ± 0.40	19.60 ± 0.60	18.50 ± 0.30
32	25.60 ± 0.32	25.40 ± 0.70	20.20 ± 0.50	20.40 ± 0.20
33	23.60 ± 0.45	22.10 ± 0.90	16.70 ± 0.50	15.60 ± 0.80
34	24.20 ± 0.08	24.50 ± 0.40	18.30 ± 0.20	17.10 ± 0.50
Itraconazole	30 ± 0.08	29 ± 0.40	28 ± 0.05	24 ± 0.10
Clotrimazole	28 ± 0.20	25 ± 0.50	20 ± 0.30	22 ± 0.08

RCMB, Regional Center for Mycology and Biotechnology Culture Collection; NA, no activity.

[a]Mean zone of inhibition in mm ± standard deviation beyond well diameter (6 mm) produced on a range of environmental and clinically pathogenic microorganisms using (10 mg/mL) concentration of tested samples. The concentration used for the standard antibiotic was (30 µg/mL).

[b]The test was done using the diffusion agar technique. Well diameter: 6.0 mm (100 µL was tested).

[c]Data are expressed in the form of mean ± SD.

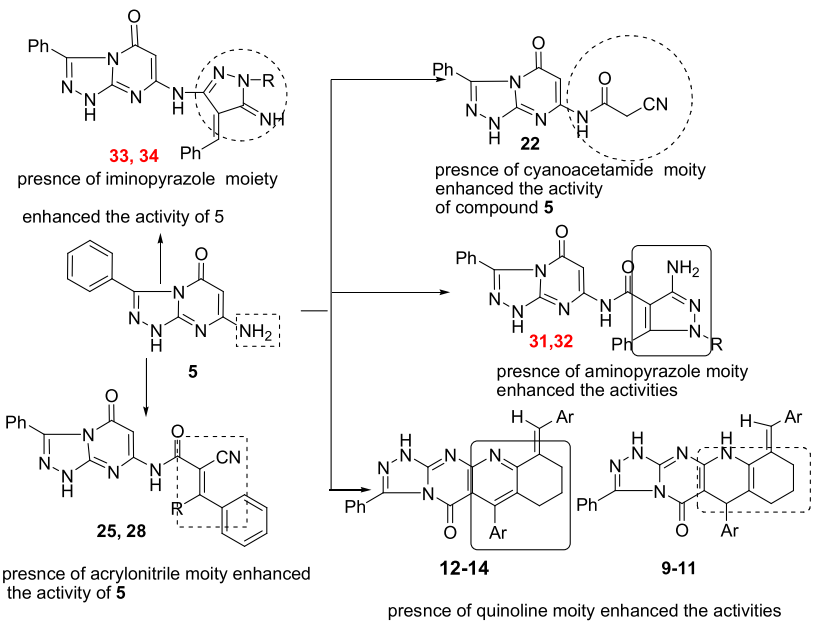


Figure 1. Structure–activity relationship of the more potent antimicrobial compounds. [Color figure can be viewed in the online issue, which is available at wileyonlinelibrary.com.]

moiety have been synthesized and their microbial activity evaluated. The results clearly showed that most of the compounds had mild to moderate activity, and that coupling of tiazolopyrimidine moiety to arylidine, pyrazole through a carboxamide linkage improves the antimicrobial activity.

EXPERIMENTAL

Chemistry. All melting points are in degree centigrade (uncorrected) and were determined on Gallenkamp electric melting point apparatus. TLC analysis was carried out on silica gel 60 F254 precoated aluminum sheets. The IR spectra were recorded (KBr) on a Perkin–Elmer 1430 spectrometer (λ, cm^{-1}) in the National Research Center, Egypt. ^{1}HNMR/^{13}CNMR spectra were measured on JEOL-ECA 500 and JEOL JNM-LA-400 FT NMR Spectrometers at 500 and 125 MHz, respectively, using tetramethylsilane (TMS) as an internal reference and DMSO-d6 as solvent at the Microanalytical Center in National Research Center, Egypt. The mass spectra (EI) were recorded on GCMS-QP 1000 EX (Shimadzu) at the National Research Center, Egypt. Elemental analyses (C, H, and N) were carried out at the Microanalytical Center in National Research Center, Egypt. The elemental analyses were found to agree favorably with the calculated values. Biological activities were carried in the Regional Center for Mycology and Biotechnology, Al-Azhar University, Nasr City, Cairo, Egypt.

Synthesis of N′-(6-amino-1, 2, 3, 4-tetrahydro-4-oxopyrimidin-2-yl) benzohydrazide (4). To a solution of compound **1**, (1.43 g, 10 mmol) or **2** (1.57 g, 10 mmol) in DMF (30 mL) and ethanol (25 mL) respectively, benzohydrazide (**3**) (1.36 g, 10 mmol) was added. The reaction mixture was heated under reflux for 9 h, and then allowed to cool, poured onto ice/water, and the formed solid product was collected by filtration and crystallized from ethanol/benzene to give compound **4**.

Yield 73% (78%); yellow crystals; mp > 325 °C; IR (KBr): (ν/cm^{-1}) = 3360 (br, NH, NH_2), 3035 (CH—Ar), 1690, 1680 (2CO), 1622 (C=N); 1555 (C=C); ^{1}H NMR (DMSO-d_6): δ (ppm):4.66 (s, 1H, C_5-H), 6. 35 (br, NH_2, D_2O exchangeable) 7.48–7.90 (m, 5H, ArH): 11.51, 11.61 (br, 2NH, D_2O exchangeable), 12.10 (br, NH, D_2O exchangeable); ^{13}CNMR (DMSO-d6): (δ ppm): 82.5 (C_5, pyrimidine), 127.5, 128.7, 132.1, 132.4 (6C, Ar—C), 158.6 (C_6, pyrimidine), 161.2 (C_4, pyrimidine), 164.5 (C_2 pyrimidine), 165.1(CONH); MS (EI, 70 eV): *m/z* (%) = 247 (M^++2, 2.1), 245 (M^+, 6.3), 242 (74.4), 241 (18.5), 229 (12.6), 196 (34.4), 184 (25.3), 156 (24.2), 125 (17.9), 110 (15.7), 97 (7.4), 68 (15.7), 67 (45.3), 59(11.6). Anal. Calcd. for $C_{11}H_{11}N_5O_2$ (245.24): Calcd.: C, 53.87; H, 4.52; N, 28.56%. Found: C, 53.80; H, 4.52; N, 28.56%.

Synthesis of 7-amino-3-phenyl-[1, 2, 4]triazolo[4,3-a] pyrimidin-5 (1H)-one (5). A solution of compound **4** (2.45 g, 10 mmol) in ethanol (50 mL) containing sodium ethoxide (prepared by dissolving sodium metal) (0.23 g, 10 mmol in ethanol) was heated under reflux for 9 h; the reaction mixture was cooled, and the deposited precipitate was filtered off and washed with ethanol. The formed salt was dissolved in water (50 mL) and acidified with 10% HCl; the formed precipitate was filtered, dried, and crystallized from methanol to afford **5**.

Yield 75%; mp > 325 °C; Yellowish crystals; IR (KBr): (ν/cm^{-1}) = 3312, 3352 (br, 2NH, NH_2), 3038 (CH aryl), 1675 (CO), 1620(C=N), 1558(C=C); ^{1}H NMR (DMSO-d_6): δ (ppm) = 4.66 (s, 1H, C_6—H), 6. 34 (br, 2H, NH_2, D_2O exchangeable), 7.49–7.91 (m, 5H, phenyl), 11.65 (br, 1H, NH, D_2O exchangeable); ^{13}CNMR (DMSO-d_6): δ (ppm): 83.1 (C_6, pyrimidine), 128.1, 128.6, 128.8, 131.2 (6C, ArC), 150.8 (C_3, triazole ring); 158.5 (C_7, pyrimidine), 160.4 (C_{8a}, pyrimidine); 162.5 (C_5, pyrimidine); MS (EI, 70 eV): *m/z* (%) = 229 (M^+ + 2, 11.6) 227 (M^+, 20.2), 203 (27.9), 125 (100), 103 (18.5), 91 (51.1), 77 (37.0), 63 (74.4); Anal. Calcd. for $C_{11}H_9N_5O$ (227.22): C, 58.14; H, 3.99; N, 30.82%; Found: C, 58.10; H, 3.95; N, 30.75%.

General procedure for synthesis of (*E*)-10-(arylidene)-6-(aryl)-3-phenyl-[1,2,4]triazolo[4′,3′:1,2]-pyrimido[4,5-b]quinoline-5 (1H, 4H, 6H, 7H, 8H, 9H, 11H)-one (9–11). A mixture of 7-amino-3-phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (**5**) (2.27 g, 10 mmol), (2*E*, 6*E*)-2,6-dibenzylidenecyclohexanone (**6**) (2.74 g, 10 mmol), (2*E*, 6*E*)-2,6-bis(4-chlorobenzylidene) cyclohexanone (7) (3.42 g, 10 mmol), (2*E*, 6*E*)-2,6-bis (4-methoxylbenzylidene) cyclohexanone (**8**) (3.34 g, 10 mmol), was refluxed in dimethylformamide (45 mL) for 5–7 h. The reaction mixture was cooled, then poured onto ice cold water, the formed precipitate was filtered off, washed with ethanol, and crystallized from the appropriate solvent to afford **9–11**.

(E)-10-(benzylidene)-6-(phenyl)-3-phenyl-[1,2,4]triazolo[4',3':1,2]-pyrimido[4,5-b]quinoline-5 (1H, 4H, 6H, 7H, 8H, 9H, 11H)-one (9). Yield 60%; mp 285–287 °C; yellow powder; reaction time 6 h, crystallized from EtOH/DMF; IR (KBr): (ν/cm^{-1}) = 3380 (br, 2NH), 3050 (CH aryl), 1680 (CO), 1632 (C=N; ^{1}H NMR (DMSO-d_6): δ (ppm): 1.60–1.62(m, 2H, CH_2), 2.20–2.25 (t, 2H, CH_2), 2.72–2.88 (t, 2H, CH_2), 5.50 (s, 1H, pyridine ring), 7.00–7.85 (m, 15H, ArH), 8.20 (s, 1H, methylenic proton), 10.40 and 12.10 (2brs,2H, 2NH, D_2O exchangeable); MS (EI, 70 eV): *m/z* (%) = 483 (M^+, 30.4), 358 (55.7), 443 (22.4), 342 (38.5), 301 (26.4), 278 (22.0), 243(10.2), 168 (26.1), 125 (100), 89(23), 84 (35.2), 54(61.1); Anal. Calcd. for $C_{31}H_{25}N_5O$ (483.56); C, 77.00; H, 5.21; N, 14.48%; Found: C, 77.10; H, 5.24; N, 14.56%.

(E)-10-(4-chlorobenzylidene)-6-(4-chlorophenyl)-3-phenyl-[1,2,4]triazolo [4',3':1,2]-pyrimido[4,5-b]quinoline-5 (1H, 4H, 6H, 7H, 8H, 9H, 11H)-one (10). Yield 65%; mp 315–317 °C; yellow powder; reaction time 5 h crystallized from EtOH/benzene; IR (KBr): (ν/cm^{-1}) = 3381 (br, 2 NH), 3052 (CH aryl), 1682 (CO), 1634 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.64–1.67 (m, 2H, CH_2), 2.27–2.37 (t, 2H, CH_2), 2.74–2.86 (t, 2H, CH_2), 5.43 (s, 1H, pyridine ring), 7.16–7.68 (m, 11H, Ar—H), 8.22 (s, 1H, CH=), 11.00 and 12.30 (2brs, 2H, 2NH, D_2O exchangeable); MS (EI, 70 eV): *m/z* (%) = 556 (M^++4, 2.3), 554 (M^++2, 6.2) 552 (M^+, 11.4), 474 (11.7), 369 (5.5), 339 (7.2), 177 (8.9), 125 (49.7), 107 (55.8), 90 (100), 79 (54.4); Anal. Calcd. for $C_{31}H_{23}Cl_2N_5O$ (552.4); C, 67.40; H, 4.20; N, 12.68%; Found: C, 67.45; H, 4.15; N, 12.63%.

(E)-10-(4-Methoxylbenzylidene)-6-(4-methoxylphenyl)-3-phenyl-[1,2,4]triazolo [4',3':1,2]-pyrimido[4,5-b]quinoline-5 (1H, 4H, 6H, 7H, 8H, 9H, 11H)-one (11). Yield 59%; mp 303–305 °C; yellow powder; reaction time 5 h, crystallized from EtOH/DMF; IR (KBr): (ν/cm^{-1}) = 3385 (br, 2NH), 3040 (CH aryl), 2910 (CH alkyl), 1681 (CO), 1635 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm):1.63–1.66 (m, 2H, CH_2), 2.26–2.36 (t, 2H, CH_2), 2.73–2.85 (t, 2H, CH_2), 3.88 (br, 6H, 2 methoxy groups), 5.42 (s, 1H, pyridine ring), 7.15–7.69 (m, 11H, ArH), 8.24 (s, 1H, CH=), 11.20 and 12.40 (2brs,2H, 2NH, D_2O exchangeable; MS (EI, 70 eV): *m/z* (%) = 543 (M^+, 2.5), 538 (15.7), 465 (71.6), 463 (85.2), 449 (73.3), 386 (15.8), 341(18.2),

239 (17.5), 175 (20.8), 151(29.1), 139 (44.1), 125(100), 115(20.0), 93 (25.0), 77 (20.1), 55 (21.6); Anal. Calcd. for $C_{33}H_{29}N_5O_3$ (543.6); C, 72.91; H, 5.38; N, 12.88%; Found: C, 72.88; H, 5.35; N, 12.80%.

General procedure for synthesis of (*E*)-10-(arylidene)-6-(aryl)-3-phenyl-[1,2,4]triazolo[4′,3′:1,2] Pyrimido[4,5-b]quinoline-5 (1H, 4H, 7H, 8H, 9H)-one (12–14) and 9–11. A suspension of 7-amino-3-phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-5 (1H)-one (**5**) (2.27 g, 10 mmol) and (2*E*, 6E)-2,6-dibenzylidenecyclohexanone (**6**) (2.74 g, 10 m*M*), (2*E*, 6*E*)-2,6-bis(4-chlorobenzylidene) cyclohexanone (**7**) (3.42 g, 10 m*M*) or 2*E*, 6*E*)-2,6-bis (4-methoxylbenzylidene) cyclohexanone (**8**) (3.34 g, 10 mmol) in dimethylformamide (45 mL) was refluxed for 45 h. The reaction mixture was cooled; the deposited precipitate was filtered off, washed with ethanol and dried, and crystallized from DMF to give **12–14** in a good yield. The filtrate was poured onto ice cold water, the formed precipitate was filtered off, and crystallized from appropriate solvent to afford **9–11.**

(E)-10-benzylidene–3,6-diphenyl-[1,2,4]triazolo-[4′,3′:1,2] pyrimido[4,5-b]quino-line-5 (1H, 4H, 7H, 8H, 9H)-one (12). Yield 65%; mp >325 °C; yellow powder; IR (KBr): (ν/cm^{-1}) = 3355 (brs, NH), 3030 (CH aryl), 1687 (CO), 1634 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): δ1.63–1.66 (m, 2H, CH_2), 2.28–2.31 (t, 2H, CH_2), 2.76–2.98 (t, 2H, CH_2), 7.01–7.873 (m, 15H, ArH), 8.21 (s, 1H, CH=) and 11.55 (br.,1H, NH, D_2O exchangeable); MS (EI, 70 eV): *m/z* (%) = 481 (M^+, 21.1), 477 (100), 464 (36.8), 450 (64.2), 405 (22.1), 366 (21.1), 342 (15.7), 302 (18.9), 220 (31.6), 125 (77.9), 115(7.3), 53(4.3); Anal. Calcd. for $C_{31}H_{23}N_5O$ (481.55); C, 77.32; H, 4.81; N, 14.54%; Found: C, 77.38; H, 4.74; N, 14.45%.

(E)-10-(4-chlorobenzylidene)-6-(4-chlorophenyl)-3-phenyl-[1,2,4]triazolo [4',3': 1,2] Pyrimido[4,5-b]quinoline-5 (1H, 4H, 7H, 8H, 9H)-one (13). Yield 66%; mp >325°C; yellow powder; IR (KBr): (ν/cm^{-1}) = 3375 (brs, NH), 3035 (CH aryl), 1688 (CO), 1630 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.65–1.68 (m, 2H, CH_2), 2.28–2.31 (t, 2H, CH_2) 2.74–2.96 (t, 2H, CH_2), 7.14–7.66 (m, 13H, ArH), 8.20 (s, 1H, CH=), 11.50 (br., 1H, NH, D_2O exchangeable); MS (EI, 70 eV): *m/z* (%) = 464 (M^++4, 5.2), 462 (M^++2, 15.3) 560 (M^+, 20.0), 549 (28.6), 448 (25.7), 390(5.7), 342 (22.8), 279 (20.0), 165 (25.6), 125 (100), 113 (45.2), 102 (45.2), 83 (20.7), 50 (48). Anal. Calcd. for $C_{31}H_{21}Cl_2N_5O$ (550.4); C, 67.64; H, 3.85; N, 12.72%; Found: C, 67.60; H, 3.81; N, 12.79%.

(E)-10-(4-methoxybenzylidene)-6-(4-methoxyphenyl)-3-phenyl-[1,2,4]triazolo-[4′,3′:1,2]-pyrim-ido[4,5-b]quinoline-5 (1H, 4H, 7H, 8H, 9H)-one (14). Yield 63%; mp > 325 °C; yellow powder; IR (KBr): (ν/cm^{-1}) = 3350 (brs, NH), 3035 (CH aryl), 2905 (CH alkyl), 1688 (CO), 1641 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.66–1.71 (m, 2H, CH_2), 2.28–2.31 (t, 2H, CH_2) 2.75–2.96 (t, 2H, CH_2), 3.79 (brs, 6H, OCH_3) 7.17–7.71(m, 13H, ArH), 8.24 (s, 1H, CH=), 11.65 (br.,1H, NH, D_2O exchangeable); Anal. Calcd. for $C_{33}H_{27}N_5O_3$ (541.6); C, 73.18; H, 5.02; N, 12.93; %; Found: C, 73.15; H, 5.10; N, 12.90%.

The yield of compounds **9** (13%), **10**, (15%), and **11** (14%), respectively.

General procedure for synthesis of [1,2,4]triazolo [4′,3′:1,2]-pyrimido[4,5-b]quinoline derivatives (18–20). To a solution of **5** (2.27 g, 10 mmol) glacial acetic acid (40 mL), 2,4-dichlorobenzoic acid (**15**) (1.89 g, 10 mmol), 2-fluorobenzaldehyde (**16**) (1.24 g, 10 mmol) or 2-chlorocyclohex-1-enecarbaldehyde (**17**) (1.46 g, 10 mmol) was added. The reaction mixture was stirred and heated under reflux for 12–20 h. The formed precipitate reaction after cooling was filtered off, dried, and recrystallized from the proper solvent to afford compounds (**18–20**).

9-Chloro-3-phenyl[1,2,4]triazolo [4′,3′:1,2]-pyrimido[4,5-b] quinoline-5,6(1H, 4H,11H) dione (18). Yield 70%; mp > 325 °C; brown powder; Reaction time 20 h, recrystallization from methanol; IR (KBr): (ν/cm^{-1}) = 3345 (br, 2NH), 1715, 1665 (2CO), 1628 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): 7.01–7.85 (m, 8H, ArH), 11.70, 12.35 (2brs, 2H, 2NH, D_2O exchangeable); MS (EI, 70 eV): *m/z* (%) = *m/z* 365 (M^+ + 2, 4.7), 363 (M^+, 14.2), 336 (39.3), 322 (28.9), 286 (10.7), 250 (14.0), 188 (32.1), 167 (46.4), 124 (100), 98 (17.3), 63 (50); Anal. Calcd. for $C_{18}H_{10}ClN_5O_2$ (363.7); C, 59.43; H, 2.77; N, 19.25%; Found: C, 59.40; H, 2.70; N, 19.15%**.**

3-Phenyl[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-b]quinoline-5 (1H, 4H) one(19). Yield, 60%; mp > 325 °C; white powder; reaction time 14 h, recrystallization from dioxane; IR (KBr): (ν/cm^{-1}) = 3340 (br, 2NH), 1680 (CO), 1630 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): 7.30–7.91 (m, 9H, ArH); 8.55 (s, 1H, C_5—H, pyridine ring), 11.60, (br., NH, D_2O exchangeable); Anal. Calcd. for $C_{18}H_{11}N_5O$ (313.3); C, 69.00; H, 3.54; N, 22.35%; Found: C, 69.10; H, 3.50; N, 22.31%.

3-Phenyl[1,2,4]triazolo-[4′,3′:1,2]pyrimido[4,5-b]quinoline-5 (1H, 4H, 7H, 8H, 9H,10H)-one (20). Yield, 68%; mp 270–272 °C; white powder; reaction time 12 h, recrystallization from DMF; IR (KBr): (ν/cm^{-1}) = 3349 (br, NH), 1682 (CO), 1632 (C=N); ^{1}H NMR (DMSO-d_6): δ (ppm): 1.70–1.74 (m, 2H, CH_2 of quinolone ring), 1.75–1.79 (m, 2H, CH_2 of quinolone ring), 2.70 (t, 2H, quinolone ring), 3.02 (t, 2H, quinolone ring), 7.37–7.43 (m, 5*H*, phenyl), 8.35 (s, 1H, pyridine ring), 11.70, (br., 1H, NH, D_2O exchangeable). MS (EI, 70 eV): *m/z* (%) = *m/z* 365(M^+, 11.4), 307 (100), 280 (81.8), 253 (31.8), 244 (45.5), 216 (36.4), 167 (22.7), 128 (54.5), 115 (95.4), 63 (36.4); Anal. Calcd. for $C_{18}H_{15}N_5O$ (317.3); C, 68.13; H, 4.76; N, 22.07%; Found: C, 68.06; H, 4.70; N, 22.01%.

Synthesis of 2-cyano-*N*-(5-oxo-3-phenyl-1,5-dihydro-[1,2,4] triazolo[4,3-a]pyrim-idin-7-yl)acetamide (22). To a solution of **5** (2.27 g, 10 mmol) in dimethylformamide (30 mL), ethyl cyanoacetate (1.13 g, 10 mmol) was added. The reaction mixture was heated under reflux for 7 h. The formed solid product upon pouring onto ice/water was collected by filtration and crystallized from benzene to give **22**.

Yield 73%; mp 268–270 C; yellow crystals; IR (KBr): (ν/cm^{-1}) = 3330, 3225 (2 NH), 3045 (CH aryl), 2915 (CH aliphatic), 2260 (CN), 1695, 1680 (2CO), 1630 (C=N), 1545 (C=C); ^{1}H NMR (DMSO-d_6): δ (ppm): δ 4.10 (s, 2H, CH_2), 6.88 (s, 1H, pyrimidine ring), 7.50–7.58 (m, 5H, ArH), 8.22 (br,1H, NH, D_2O exchangeable), 11.50 (br.,1H, NH, D_2O exchangeable); MS (EI, 70 eV): *m/z* (%) = 294 (100) Anal. Calcd. for $C_{14}H_{10}N_6O_2$ (294.27); C, 57.14; H, 3.43; N, 28.56%; Found C, 57.20; H, 3.35; N, 28.50%**.**

General procedure for synthesis of [1,2,4]triazolo [4′,3′:1,2]-pyrimido[4,5-b]quinolone derivatives 25–26. To a solution of (**22**) (2.94 g, 10 mmol) in 1,4-dioxane (30 mL) containing piperidine (1.00 mL) either benzaldehyde (**23**) (1.06 g, 10 mmol) or salicylaldehyde (**24**) (1.22 g, 10 mmol) was added. The reaction mixture, in each case, was heated under reflux for 6–8 h. The formed precipitate upon pouring onto ice-water mixture containing few drops of hydrochloric acid was collected by filtration to give (**25**) and (**26**), respectively.

(2E)-2-cyano-N-(1,5-dihydro-5-oxo-3-phenyl-[1,2,4]triazolo [4,3-a]pyrimidin-7-yl)-3-phenylacrylamide (25). Yield 78%; mp

186–188 °C; yellow powder; Reaction time 8 h, crystallization from DMF; IR (KBr): (ν/cm^{-1}) = 3335, 3230 (2NH), 3055 (CH aryl), 2920 (CH aliph), 2265 (CN), 1698, 1686 (2CO), 1628 (C=N), 1540 (C=C); ^{1}H NMR (DMSO-d$_6$): δ (ppm): δ 6.85 (s, 1H, pyrimidine ring), 7.35–7.85 (m, 10H, ArH), 8.05 (br.,1H, NH, D$_2$O exchangeable), 8.18 (s, 1H, CH=) 11.52 (br.,1H, NH, D$_2$O exchangeable); MS (EI, 70 eV): *m/z* (%) = *m/z* 382(M$^+$, 31.8), 380(M$^+$, −2, 100), 337 (13.6), 55 (18.2); Anal. Calcd. for $C_{21}H_{14}N_6O_2$ (382.37); C, 65.96; H, 3.69; N, 21.98%; Found: C, 65.91; H, 3.62; N, 21.90%.

N-(1,5-dihydro-5-oxo-3-phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-2-imino-2H-chromene-3-carboxamide (26). Yield 60%; mp 250–252 °C; orange powder; reaction time 6 h, recrystallization from dioxan; IR (KBr): (ν/cm^{-1}) = 3430–3240 (brs, NH), 3050 (CH aryl), 2930(CH alphatic), 1700, 1680 (3CO), 1632 (C=N), 1565 (C=C); ^{1}H NMR (DMSO-d$_6$): δ (ppm): 6.92 (s, 1H, pyrimidine ring), 7.35–7.68 (m, 10H, ArH), 7.83 (br 1H, NH, D$_2$O exchangeable), 8.14 (br.,1H, NH, D$_2$O exchangeable), 11.61 (br.,1H, NH, D$_2$O exchangeable); MS (EI, 70 eV): *m/z* (%) = 399 (M$^+$, 68.7), 352 (69.7), 291 (31.2), 253 (18.7), 214(16.7), 166(25.0), 125 (100), 89(56.2); Anal. Calcd. for $C_{21}H_{13}N_5O_4$ (398.37); C, 63.31; H, 3.54; N, 21.10%; Found: C, 63.15; H, 3.60; N, 21.02%.

Synthesis of (E)-2-cyano-N-(5-oxo-3-phenyl-1,5-dihydro-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-3-phenylbut-2-enamide (28). To a mixture of **22** (2.94 g, 10 mmol) and acetophenone (**27**) (1.20 g, 10 mmol), ammonium acetate (0.50 g) was added, and the reaction mixture was heated in an oil bath 140 °C for 50 min. Then, ethanol (65 mL) was added, and the reaction mixture was boiled for 15 min. The reaction mixture was poured onto ice/water, and the formed product was crystallized from methanol to give **28**.

Yield (70%); mp 212–214 °C; yellow powder; IR (KBr): (ν/cm^{-1}) = 3436–3231 (brs, NH), 3058 (CH aryl), 2922 (CH alkyl), 2262 (CN), 1699,1684 (2CO), 1629 (C=N), 1535 (C=C); ^{1}H NMR (DMSO-d$_6$): δ (ppm): 2.25 (s, 3H, CH$_3$), 6.90 (s, 1H, pyrimidine ring), 7.15–7.84 (m, 10H, ArH), 8.09 (br.,1H, NH, D$_2$O exchangeable), 11.54 (br., 1H, NH, D$_2$O exchangeable); MS (EI, 70 eV): *m/z* (%) = 396 (M$^+$, 55.5), 395 (100, M$^+$ − 1), 365 (90.9), 315 (40.9), 308(13.6), 276 (10.2), 249 (0.7), 91 (27.3) Anal. Calcd. for $C_{22}H_{16}N_6O_2$ (396.40); C, 66.66; H, 4.07; N, 21.20%; Found: C, 66.60; H, 4.15; N, 21.28%.

General procedure for synthesis of [1,2,4]triazolo [4′,3′:1,2]-pyrimido[4,5-b]quinolone derivatives 31–34. To a solution of compound *25 (3.82 g, 10* mmol*) in 1, 4-dioxane* (30 mL) and either hydrazine hydrate (**29**) (0.50 g, 10 mmol), or phenyl hydrazine (**30**) (1.08 g, 10 mmol) was added. The reaction mixture, in each case, was heated under reflux for 5 h and 6 h. The solid products formed, were collected by filtration, and crystallized from dimethylformamide and MeOH mixture to give **31** and **32** respectively. The mother liquor were poured onto ice/water mixture containing few drops of hydrochloric acid. The solid products formed, were collected by filtration, and crystallized from dimethylformamide to give **33** and **34**.

3-Amino-N-(1,5-dihydro-5-oxo-3-phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-5-phenyl-1H-pyrazole-4-carboxamide (31). Yield 60%; mp 218–220 °C; yellow crystals;; IR (KBr): (ν/cm^{-1}) = 3415–3205 (brs, NH$_2$, NH), 3042 (CH aryl), 1690, 1684 (2CO), 1632 (C=N), 1560 (C=C); ^{1}H NMR (DMSO-d$_6$): δ (ppm): 6.48 (br., 2H, NH$_2$, D$_2$O exchangeable), 6.95 (s, 1H, pyrimidine ring),7.40–7.85 (m, 10H, ArH), 8.10 (br., NH, D$_2$O exchangeable), 11.64, 12.10 (brs, 2NH, D$_2$O exchangeable); MS (EI, 70 eV): *m/z* (%) = 412(M$^+$, 57.8), 366 (52.6), 326 (42.2), 248 (18.4), 215 (21.1), 167 (23.7), 125 (100), 75 (31.5); Anal. Calcd. for $C_{21}H_{16}N_8O_2$ (412); C, 64.23; H, 4.16; N, 23.83%; Found: C, 64.15; H, 4.10; N, 23.91%.

3-Amino-N-(1,5-dihydro-5-oxo-3-phenyl [1,2,4]triazolo[4,3-a]pyrimidin-7-yl)-1,5-diphenyl-1H-pyrazole-4-carboxamide (32). Yield 66%, m.p. 238–240 °C; white crystals; IR (KBr): (ν/cm^{-1}) = 3412–3208 (brs, NH$_2$, NH), 3048 (CH aryl), 1692, 1686 (2CO), 1634 (C=N), 1564 (C=C; ^{1}H NMR (DMSO-d$_6$): δ (ppm): 6.50 (br., 2H, NH$_2$, D$_2$O exchangeable), 6.94 (s, 1H, pyrimidine ring), 7.15–7.85 (m, 15H, ArH), 8.09 (br.,1H, NH, D$_2$O exchangeable), 11.61 (br., 1H, NH, D$_2$O exchangeable); MS (EI, 70 eV): *m/z* (%) = 488 (M$^+$, 4.1), 448 (35.5), 423 (6.3), 369 (6.6), 344 (31.2), 264 (79.1), 235 (44.4), 213 (100), 185 (14.5), 164(62.5), 139 (31.3), 121 (93.7), 105 (83.3), 84 (10.4), 56(8.3); Anal. Calcd. for $C_{27}H_{20}N_8O_2$ (488.50); C, 68.98; H, 4.34; N, 20.11%; Found: C, 68.90; H, 4.48; N, 20.03%.

(E)-7-(4-benzylidene-5-imino-4,5-dihydro-1H-pyrazol-3-ylamino)-3-phenyl [1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (33). Yield 15%; mp 198–200 °C; white crystals; IR (KBr): (ν/cm^{-1}) = 3420–3210 (brs, 2NH), 3040 (CH aryl), 1685 (CO), 1633 (C=N), 1550 (C=C); ^{1}H NMR (DMSO-d$_6$): δ (ppm): 6.82 (br., NH, D$_2$O exchangeable), 7.32–7.84 (m, 10*H*, two phenyl), 8.08 (s, 1H, pyrimidine ring), 8.20 (s, 1H, CH=), 9.10, 10.25, 11.68 (brs, 3NH, D$_2$O exchangeable); Anal. Calcd. for $C_{21}H_{16}N_8O$ (396.40); C, 63.63; H, 4.07; N, 28.27%; Found: C, 63.60; H, 4.02; N, 28.20%.

(E)-7-(4-benzylidene-5-imino-1-phenyl-4,5-dihydro-1H-pyrazol-3-ylamino)-3-phenyl-[1,2,4]triazolo[4,3-a]pyrimidin-5(1H)-one (34). Yield 13%; mp 234–236 °C; white crystals; IR (KBr): (ν/cm^{-1}) = 3410–3230 (brs, 2NH), 3030 (CH aryl), 2920 (CH alkyl), 1682 (CO), 1630 (C=N), 1555 (C=C); ^{1}H NMR (DMSO-d$_6$): δ (ppm): 6.80 (s, 1H, pyrimidine ring)), 7.10–7.89 (m, 15H, ArH), 8.09 (br., NH, D$_2$O exchangeable), 8.19 (s, 1H, CH=), 10.20, 11.65 (brs, 2NH, D$_2$O exchangeable); MS (EI, 70 eV): *m/z* (%) = 472 (M$^+$, 100), 435 (95.6), 404 (78.3), 341 (52.2), 310 (60.8), 277 (26.1), 202 (34.8), 164 (47.8), 146 (52.2), 125 (86.9), 99 (56.5), 65 (69.5); Anal. Calcd. for $C_{27}H_{20}N_8O$ (472.50); C, 68.63; H, 4.27; N, 23.72%; Found: C, 68.63; H, 4.27; N, 23.72 5%.

In vitro antimicrobial activity. The tested compounds were evaluated by the agar diffusion technique [32] using a 2 mg/mL solution in DMSO. The test organisms were four bacterial strains: *S. aureus* and *B. subtilis* (as Gram positive bacteria) and *P. aeruginosa, E. coli*, and *Salmonella typhi* (as Gram negative bacteria). and two fungi: *A. fumigatus*, *G. candidum*, *C. albicans*, and *S. racemosum*. A control using DMSO without the test compound was included for each organism. Penicillin G and Streptomycin were purchased from the Egyptian market and used in a concentration 10 mg/mL as reference drugs for antibacterial activity, whereas, Itraconazole and Clotrimazole were used as reference drugs for antifungal activity The bacteria and fungi were tested on nutrient agar and potato dextrose agar media, respectively. Three plates were used for each compound as replicates. The plates were incubated for 24 h and seven days for bacteria and fungi, respectively. After the incubation period, the diameter of inhibition zone was measured as an indicator for the activity of the compounds.

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