

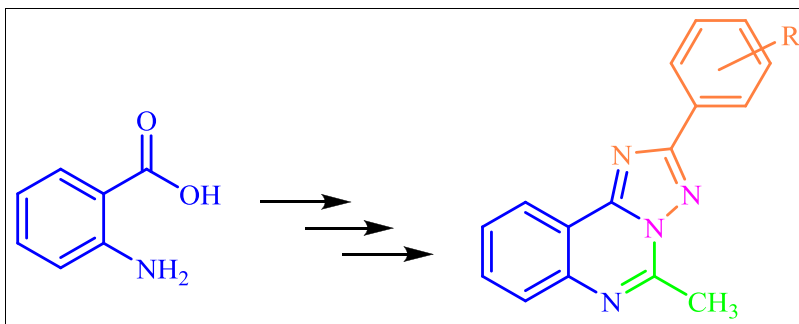
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A series of new 2-aryl-5-methyl-[1,2,4]triazolo[1,5-*c*]quinazoline derivatives (**5a–5g**) have been synthesized by the reaction of 3-amino-2-methylquinazolin-4(3*H*)-one (**3**) with aromatic nitriles in potassium *tert*-butoxide under reflux conditions. 3-Amino-2-methylquinazolin-4(3*H*)-one (**3**) was synthesized by the reaction 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**2**) with hydrazine hydrate. The chemical structure of products was confirmed by IR, ¹H, ¹³C NMR and elemental analysis. These compounds were screened for antibacterial [*Staphylococcus aureus* (ATCC 25923), *Bacillus cereus* (ATCC 11778), *Micrococcus luteus* (ATCC 9341), *Escherichia coli* (ATCC 25922), and *Pseudomonas aeruginosa* (ATCC 27853)] activities, using the zone inhibition method.

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INTRODUCTION

Among the heterocyclic nitrogen-containing compounds, quinazoline and their derivatives constitute an important class of compounds with a various pharmacological and therapeutic properties such as antimalarial [1], anticancer [2–5], antitumor [6], antimicrobial [7,8], antihypertensive [9,10], anticonvulsant [11,12], anti-inflammatory [13], anticholinesterase [14], anti-diabetic [15], cellular phosphorylation inhibition [16], dihydrofolate reductase inhibition [17,18], and kinase inhibitory activities [19–21]. In addition, a number of compounds with a quinazoline core are used as efficient drugs. Among them are erlotinib, gefitinib, and lapatinib for the treatment of different types of tumors, trimetrexate for the treatment of *Pneumocystis carinii* pneumonia, and prazosin for the treatment of hypertension [22,23] (Fig. 1).

Conversely, triazolo-quinazolines display diverse pharmacological and biological activities such as antihypertensive [7], anti-inflammatory [24], and phosphodiesterase 10A (PDE10A) inhibitors activities [25]. Some of the 1,2,4-triazolo[1,5-*a*]quinazolines have been proven as excellent agents for controlling the plant growth diseases caused by fungal pathogens, and some chlorinated derivatives have shown an interesting affinity

toward adenosine receptors [26]. Additionally, triazolo-quinazolines, which originated from *N*-cyanoimidocarbonates, have been described as potent protein kinase inhibitors [27]. As a part of our current studies in synthesis of *tris*-pyrazolines [28], *bis*-coumarines [29], triazepanes [30], and thiazolidine derivatives [31] here, we reported synthesis of novel triazolo-quinazolines and evaluation of their antibacterial activities.

RESULTS AND DISCUSSION

It was well known that the quinazoline moiety plays an important role in promoting the antibacterial properties of molecules. Therefore, study on the interesting pharmacological features of quinazolines has encouraged us to synthesize new triazolo-quinazoline derivatives **5a–5g**. Here, novel 2-aryl-5-methyl-[1,2,4]triazolo[1,5-*c*]quinazoline derivatives **5a–5g** were synthesized through the reaction of 3-amino-2-methylquinazolin-4(3*H*)-one (**3**) with aromatic nitriles **4a–4g** in the presence of bulky base potassium *tert*-butoxide under reflux conditions. 3-Amino-2-methylquinazolin-4(3*H*)-one (**3**) was prepared through the reaction 2-methyl-4*H*-benzo[*d*][1,3]oxazin-4-one (**2**) and hydrazine hydrate under microwave

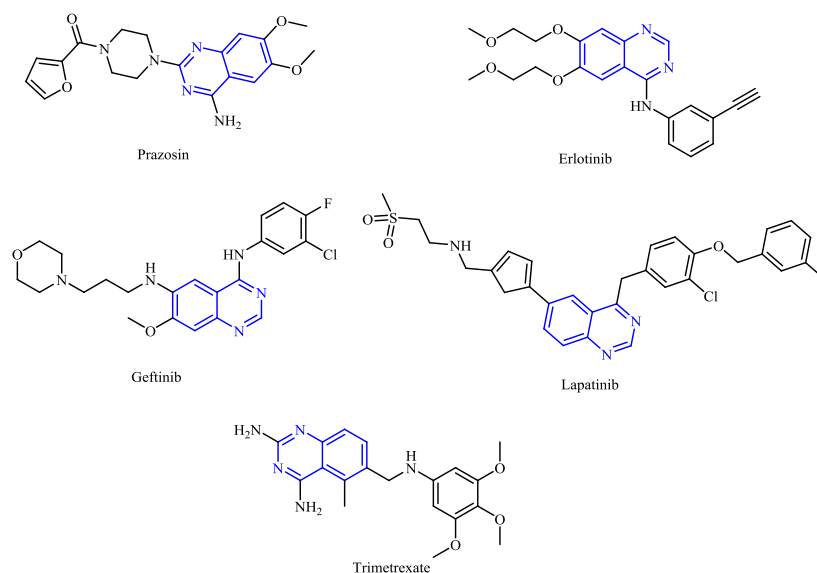


Figure 1. Selected drugs with a quinazoline core. [Color figure can be viewed at wileyonlinelibrary.com]

irradiation in absolute EtOH. It is remarkable that the reaction was completed in 27 h reflux in conventional methods. Alternatively, was completed efficiently, in 15 min, 94% yields under microwave condition. The total route for the synthesis of triazolo[1,5-*c*]quinazoline derivatives is illustrated in Scheme 1.

Addition of aromatic nitriles to 3-amino-2-methylquinazolin-4-(3*H*)-one is a regioselective reaction proceed via addition of the NH_2 of compound **3** to the carbon of nitrile group of **4**, and subsequent intramolecular cyclization of N–H to the carbonyl group of the amid **3** and elimination of water produce the corresponding triazolo-quinazolines (Scheme 1).

The structures of all synthesized triazolo-quinazolines **5a–5g** were assigned on the basis of their physical data

and spectral analysis. The Fourier transform infrared (FTIR) spectra of the compound **5a** reveal the presence of two band at 1523 and 1600 cm^{-1} for the C=N group. The ^1H NMR spectrum of **5a** in CDCl_3 showed methyl protons as singlet at 2.91 ppm that confirms the formation of the quinazolines moiety. Aromatic protons appear in the expected area (7.35–8.39 ppm). As well, in the ^{13}C NMR spectrum of **5a**, the methyl carbon appeared at 43.6 and three C=N resonate at δ 142.5, 153.5, and 169.5 ppm, respectively (according to the reference [32]).

The new triazolo-quinazolines **5a–5g** were evaluated for their *in vitro* antibacterial activity against three Gram-positive and two Gram-negative bacteria [*Staphylococcus aureus* (*S. aureus*) ATCC 25923, *Bacillus cereus* (*B. cereus*) ATCC 11778, and *Micrococcus luteus* (*M. luteus*) ATCC 9341] and Gram-negative bacteria [*Escherichia coli* (*E. coli*) ATCC 25922 and *Pseudomonas aeruginosa* (*P. aeruginosa*) ATCC 27853] using the zone inhibition method [33]. Dimethyl sulfoxide (DMSO) was used as a negative control and showed no activity against aforementioned bacterial strains. Penicillin was used as positive control and showed antibacterial activity against all bacterial strains. The antibacterial activity of quinazolines **5a–5g** was evaluated at a concentration of 1000 $\mu\text{g/mL}$ in DMSO. The experiments were performed in triplicate. The findings are reported as mean \pm standard deviation in millimeter and presented in Table 1. All the synthesized compounds possessed suitable antibacterial activity against Gram-positive and Gram-negative bacteria. Compound **5f** showed surprising activity against *P. aeruginosa* and *S. aureus*, while compound **5c** showed good activity against *B. cereus*.

Scheme 1. [Color figure can be viewed at wileyonlinelibrary.com]

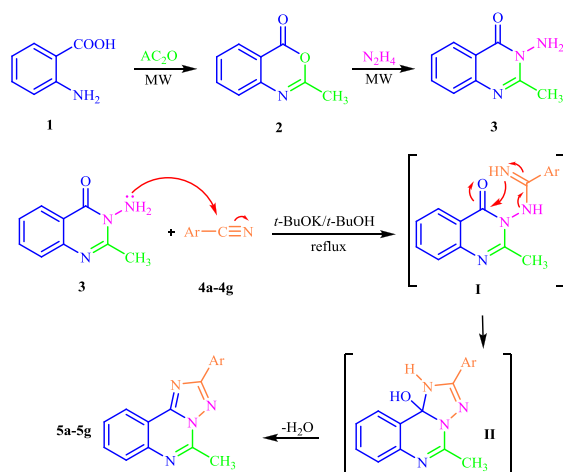


Table 1
Antimicrobial activity of triazolo-quinazolines **5a–5f**.

Entry	Compound	Antimicrobial activity (zone of inhibition in millimeters)				
		Gram-positive			Gram-negative	
		<i>Staphylococcus aureus</i>	<i>Bacillus subtilis</i>	<i>Micrococcus luteus</i>	<i>Escherichia coli</i>	<i>Pseudomonas aeruginosa</i>
1	5a	18	16	22	20	26
2	5b	13	11	18	10	12
3	5c	20	29	19	14	15
4	5d	10	15	11	8	17
5	5e	14	20	24	12	22
6	5f	24	17	20	19	27
7	5g	22	8	10	21	21
14	DMSO	—	—	—	—	—
15	Penicillin	48	33	49	21	47

CONCLUSIONS

In conclusion, we reported an efficient protocol for synthesis of 2-aryl-5-methyl-[1,2,4]triazolo[1,5-*c*]quinazoline derivatives (**5a–5g**) in good yields from reaction of 3-amino-2-methylquinazolin-4-(3*H*)-one (**3**) with aromatic nitriles **4** in potassium *tert*-butoxide under reflux conditions. The chemical structure of synthesized compound was characterized by FTIR, ¹H, ¹³C NMR spectroscopy, and elemental analysis. The antibacterial activities of triazolo[1,5-*c*]quinazolines were estimated versus five bacterial strains, including *S. aureus*, *B. cereus*, *M. luteus*, *E. coli*, and *P. aeruginosa*. The triazolo[1,5-*c*]quinazoline derivatives showed good antibacterial activity against Gram-positive bacteria (*S. aureus* and *M. luteus*) as well as Gram-negative bacteria (*E. coli* and *P. aeruginosa*).

EXPERIMENTAL

All materials, reagents, and biological cultures were obtained from commercial suppliers Merck, Sdfine, Quelab, and were used without further purification. All reactions were monitored by silica gel-coated thin-layer chromatography (TLC) plates (60 F254 Merck). FTIR spectra were recorded on a Shimadzu IR-470 spectrophotometer in anhydrous KBr. The ¹H and ¹³C NMR spectra were recorded at r.t. on a Bruker Avance 400 MHz and 100 MHz spectrometer using DMSO-*d*₆ and CDCl₃ as solvents. Elemental analyses were carried out on a Carlo-ErbaEA1110CNNO-Sanalyzer. All melting points were determined with a Mettler Fp5 apparatus and were uncorrected.

Synthesis of 2-methyl-4H-benzo[d][1,3]oxazin-4-one (2) [34]. A mixture of 2-aminobenzoic acid (10 mmol, 1.37 g) and acetic anhydride (10 mL) was irradiated under microwave at 650 W for 15 min in a scientific

oven (RAGA'S Electromagnetic System). The reaction was monitored by TLC (CHCl₃:MeOH 3:1). After completion of reaction, the mixture was allowed to cool at r.t. Separated solid product was recrystallized from H₂O to obtain the pure product. Yield% 94, m.p. (79–81).

Synthesis of 3-amino-2-methylquinazolin-4-(3H)-one (3) [34]. To a mixture of compound **2** (5 mmol, 0.8 g) in absolute EtOH (15 mL), NH₂NH₂ hydrate (99%) (2 mL) was added; the mixture was irradiated under microwave at 650 W for 30 min in a scientific oven. The reaction was monitored by TLC (CHCl₃:MeOH 3:1); after completion the reaction, the mixture was cooled and the precipitate was filtered and recrystallized from H₂O. Yield% 79, m.p. (148–150).

Synthesis of 2-aryl-5-methyl-[1,2,4]triazolo[1,5-*c*]quinazoline (5a–5g). 3-Amino-2-methylquinazolin-4-(3*H*)-one **3** (1 mmol, 0.175 g) and aromatic nitriles **4** (1 mmol) were dissolved in potassium *tert*-butoxide (10 mL) and refluxed for 48 h. The progress of the reaction was monitored by TLC (CHCl₃:MeOH 5:2). After completion of the reaction, the reaction mixture was poured into cold water and neutralize with dilute 1*N* HCl. Finally, the product was filtered, washed with water, dried, and recrystallized from EtOH 90% to recover the products in good yield with high purity.

3-Amino-2-methyl-4(3H)-quinazolinone (3). Yellow to brick red crystals; yield: 80%; m.p. 148–150°C; FTIR (KBr): 3448, 3252 (NH₂); 1586 (C=N) cm⁻¹.

5-Methyl-2-phenyl[1,2,4]triazolo[1,5-*c*]quinazoline (5a). Yellow crystals; yield: 72%; m.p. 230–232°C; FTIR (KBr): 3130 (C–H); 1600, 1523 (C=N) cm⁻¹; ¹H NMR (CDCl₃, δ, ppm): 2.91 (s, 3H, CH₃), 7.35 (m, 3H, Ar-H), 7.50 (t, 1H, *J* = 7.6 Hz, Ar-H), 7.63 (t, 1H, *J* = 7.2 Hz, Ar-H), 7.80 (d, 1H, *J* = 8.4 Hz, Ar-H), 8.19 (d, 2H, *J* = 7.6 Hz, Ar-H), 8.39 (d, 1H, *J* = 7.6 Hz, Ar-H); ¹³C NMR (100 MHz, CDCl₃, δ, ppm): 169.5, 153.5, 150.1, 142.5, 134.7, 130.5, 129.3, 127.3, 126.9, 126.3, 126.2,

122.0, 119.5, 21.5. *Anal.* Calcd for $C_{16}H_{12}N_4$: C, 73.83; H, 4.65; N, 21.52. Found: C, 73.85; H, 4.61; N, 21.56.

5-Methyl-2-(3-methylphenyl)[1,2,4]triazolo[1,5-c]quinazoline (5b). Yellow crystals; yield: 65%; m.p. 256–258°C; FTIR (KBr): 3067 (C–H); 1608 (C=N) cm^{-1} ; 1H NMR ($CDCl_3$, δ , ppm): 2.51 (s, 3H, CH_3), 3.11 (s, 3H, CH_3), 7.34 (d, 1H, $J = 7.2$ Hz, Ar-H), 7.44 (t, 1H, $J = 7.6$ Hz, Ar-H), 7.71 (t, 1H, $J = 7.6$ Hz, Ar-H), 7.83 (t, 1H, $J = 7.6$ Hz, Ar-H), 8.01 (d, 1H, $J = 7.2$ Hz, Ar-H), 8.21 (m, 2H, Ar-H), 8.60 (d, 1H, $J = 7.6$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ , ppm): 164.2, 151.4, 147.6, 142.7, 138.5, 131.8, 131.2, 130.1, 128.7, 128.1, 127.9, 127.8, 124.7, 123.7, 117.3, 21.4, 20.0. *Anal.* Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.47; H, 5.10; N, 20.46.

5-Methyl-2-(4-methylphenyl)[1,2,4]triazolo[1,5-c]quinazoline (5c). Yellow crystals; yield: 70%; m.p. 243–245°C; FTIR (KBr): 3053 (C–H); 1623, 1565 (C=N) cm^{-1} ; 1H NMR ($CDCl_3$, δ , ppm): 2.70 (s, 3H, CH_3), 3.12 (s, 3H, CH_3), 7.57 (d, 2H, $J = 5.6$ Hz, Ar-H), 7.71 (t, 1H, $J = 7.6$ Hz, Ar-H), 7.84 (t, 1H, $J = 7.2$ Hz, Ar-H), 8.01 (d, 1H, $J = 7.2$ Hz, Ar-H), 8.41 (d, 2H, $J = 7.6$ Hz, Ar-H), 8.60 (d, 1H, $J = 7.2$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ , ppm): 164.2, 151.7, 147.6, 142.7, 131.9, 130.4, 130.3, 128.7, 127.9, 127.8, 127.6, 123.8, 118.7, 22.0, 20.0. *Anal.* Calcd for $C_{17}H_{14}N_4$: C, 74.43; H, 5.14; N, 20.42. Found: C, 74.40; H, 5.19; N, 20.36.

2-(3-Chlorophenyl)-5-methyl-[1,2,4]triazolo[1,5-c]quinazoline (5d). Yellow crystals; yield: 87%; m.p. 302–305°C; IR (KBr): 3114 (C–H); 1623, 1578, 1445 (C=N, C=C) cm^{-1} ; 1H NMR ($CDCl_3$, δ , ppm): 2.82 (s, 3H, CH_3), 7.44 (d, 1H, $J = 8.00$ Hz, Ar-H), 7.51–7.55 (m, 3H, Ar-H), 7.78 (d, 1H, $J = 6.8$ Hz, Ar-H), 7.93 (s, 1H, Ar-H), 7.27–8.41 (m, 2H, Ar-H); ^{13}C NMR ($CDCl_3$, δ , ppm): 163.0, 160.1, 157.4, 151.9, 148.9, 132.4, 130.0, 129.1, 128.7, 127.7, 127.4, 126.8, 126.5, 122.8, 116.1, 21.6. *Anal.* Calcd for $C_{16}H_{11}ClN_4$: C, 65.20; H, 3.76; N, 19.01. Found: C, 65.17; H, 3.72; N, 19.06.

2-(4-Chlorophenyl)-5-methyl-[1,2,4]triazolo[1,5-c]quinazoline (5e). Yellow crystals; yield: 81%; m.p. 233–335°C; IR (KBr): 3097 (C–H); 1596, 1539, 1481 (C=N, C=C) cm^{-1} ; 1H NMR ($DMSO-d_6$, δ , ppm): 2.52 (s, 3H, CH_3), 7.22 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.30 (d, 1H, $J = 8.4$ Hz, Ar-H), 7.81–7.92 (m, 2H, Ar-H), 8.64 (d, 2H, $J = 8.4$ Hz, Ar-H), 8.81 (d, 1H, $J = 8.4$ Hz, Ar-H); ^{13}C NMR ($CDCl_3$, δ , ppm): 168.9, 160.9, 155.7, 138.5, 134.4, 131.8, 129.5, 129.3, 128.9, 127.8, 126.7, 121.6, 116.1, 21.5. *Anal.* Calcd for $C_{16}H_{11}ClN_4$: C, 65.20; H, 3.76; N, 19.01. Found: C, 65.26; H, 3.71; N, 19.05.

4-(5-Methyl-[1,2,4]triazolo[1,5-c]quinazolin-2-yl)phenol (5f). Yellow crystals; yield: 85%; m.p. 210–213°C; IR (KBr): 3383 (O–H); 3052 (C–H); 1637, 1514, 1412 (C=N, C=C); 1113 (C–O) cm^{-1} ; 1H NMR ($DMSO-d_6$, δ , ppm): 3.01 (s, 3H, CH_3), 7.03 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.53–7.60 (m, 2H, Ar-H), 7.67 (t, 1H, $J = 7.2$ Hz,

Ar-H), 7.85 (d, 2H, $J = 8.4$ Hz, Ar-H), 7.99 (d, H, $J = 8.4$ Hz, Ar-H), 11.54 (s, 1H, OH); ^{13}C NMR ($CDCl_3$, δ , ppm): 170.0, 159.4, 158.5, 155.8, 149.7, 132.0, 130.3, 127.1, 126.1, 125.1, 122.4, 116.7, 116.4, 21.7. *Anal.* Calcd for $C_{16}H_{12}N_4O$: C, 69.55; H, 4.38; N, 20.28. Found: C, 69.51; H, 4.43; N, 20.22.

2-(4-Methoxyphenyl)-5-methyl-[1,2,4]triazolo[1,5-c]quinazoline (5g). Yellow crystals; yield: 84%; m.p. 186–188°C; IR (KBr): 3135 (C–H); 1644, 1605, 1549, 1435 (C=N, C=C); 1268 (C–O) cm^{-1} ; 1H NMR ($DMSO-d_6$, δ , ppm): 2.90 (s, 3H, CH_3), 4.00 (s, 3H, OCH_3), 6.94 (d, 2H, $J = 8.00$ Hz, Ar-H), 7.44–7.58 (m, 2H, Ar-H), 7.70–7.81 (m, 1H, Ar-H), 7.86–8.04 (m, 3H, Ar-H); ^{13}C NMR ($CDCl_3$, δ , ppm): 168.9, 159.0, 157.9, 155.5, 149.7, 132.0, 129.7, 128.6, 127.5, 124.2, 122.1, 116.4, 114.3, 48.9, 21.5. *Anal.* Calcd for $C_{17}H_{14}N_4O$: C, 70.33; H, 4.86; N, 19.30. Found: C, 70.37; H, 4.82; N, 19.24.

Determination of antimicrobial activity. The antibacterial activity of triazolo-quinazolines **5a–5g** was measured biologically using the agar well-diffusion method. Then Mueller–Hinton agar (Merck) plates were readied similar to manufacturers' instructions in order to compare the antibacterial activities of products. The sterile Mueller–Hinton agar plates were inoculated with the bacteria; 0.001 g of test samples was dissolved in 1 mL DMSO to obtain a stock solution; 0.1 mL of each sample was dropped into each labeled well aseptically. The inoculated plates were then incubated for 24 h at 37°C. DMSO was used as a negative control and penicillin as a positive control. After incubation time, antimicrobial activity was estimated by measuring the zone of inhibition against the test organisms and compared with that of the standard. The results of our tests were presented as the inhibition zones, given in millimeters (mm). The experiment was carried out in repetitive and the average zone of inhibition was estimate.

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SUPPORTING INFORMATION

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