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ORIGINAL PAPER

Synthesis and antimicrobial activity of bis(azolyl)quinazoline-2,4-diamines

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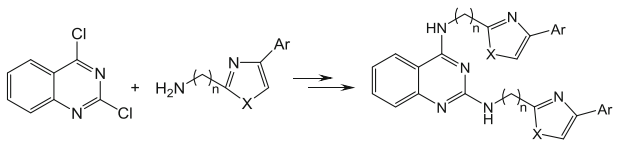
Abstract Some new bis(azolylamino)- and bis(azolylmethylamino)quinazolines were prepared from 2,4-dichloroquinazoline and azolyl amines under ultrasonication and tested for their antimicrobial activity. The chloro-, bromo-, and nitro-substituted bis(thiazolylamino)quinazolines displayed excellent antibacterial activity against *Bacillus subtilis* whereas unsubstituted, chloro-, bromo-, and nitro-substituted bis(imidazolylamino)quinazolines exhibited excellent antifungal activity against *Aspergillus niger*.

Graphical abstract



Keywords Quinazoline · Oxazole · Thiazole · Imidazole · Antimicrobial activity

Introduction

Quinazolines are privileged motifs present in a wide range of bioactive molecules and considered as attractive targets for medicinal chemists. Several antitumor drugs e.g., erlotinib [1] and gefitinib [2] have quinazoline moiety. Some of the derivatives of quinazoline also exhibit antimicrobial [3, 4], antimalarial [5], anti-inflammatory [6–8], antidiabetic [9], and anticancer activities [10–12]. Azoles having both electron donating (O/S/N) and electron withdrawing groups (C=N) gained importance synthetically and biologically. Oxazoles have excellent biological activities e.g., leucamide A and its analogues are used as anticancer agents [13]. Many thiazole derivatives have been reported in the drug development for the treatment of allergies [14], inflammation [15], bacterial infection [16], schizophrenia [17], and HIV infections [18]. Commonly used antifungal agents such as fluconazole, itraconazole, miconazole, and voriconazole possess imidazole moiety. Thus, the clinical efficacy of these aromatic heterocycles encouraged the chemists to construct a variety of novel molecules with different pharmacophoric units. Recently we have reported some pyrimidine/quinazoline benzazoles and studied their antimicrobial and cytotoxic properties [19, 20].

Ultrasound irradiation has emerged as a powerful technique for the promotion of organic reactions. The use of ultrasound in chemical reactions in solution provides specific activation based on acoustic cavitation. Thus, the rapid vibration causes cavitation, the formation and violent collapse of microscopic bubbles. The collapse of thousands of cavitation bubbles releases tremendous energy in the cavitation field. Hence this approach is more convenient and is easily controlled when compared with the traditional methods. The advantages of using ultrasound as an energy

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source to promote organic reactions include shorter reaction times and higher yields when compared with conventional thermal heating methods [21–23]. In fact, the synthesis of different heterocycles by applying ultrasound conditions was reported [24–27]. The beneficial effects of ultrasonic irradiation and our interest to develop and to improve the methodologies in chemical processes especially where classical methods require prolonged reaction times prompted to develop potential heterocycles—bis(azolyl)quinazoline-2,4-diamines under ultrasonication and study their antimicrobial activity.

Results and discussion

Chemistry

The synthetic intermediate 2,4-dichloroquinazoline (**1**) was prepared by the reaction of anthranilic acid with urea followed by chlorination with $POCl_3$ in the presence of *N*,*N*-dimethylaniline [28]. The compounds 4-aryloxazol-2-amines **2**, 4-arylthiazol-2-amines **3**, 4-aryl-1*H*-imidazol-2-amines **4**, (4-aryloxazol-2-yl)methanamines **8**, (4-arylthiazol-2-yl)methanamines **9**, and (4-aryl-1*H*-imidazol-2-yl)methanamines **10** were prepared as per the literature precedents [29–32]. The regioselective substitution of chlorine at C-4 of quinazoline was reported with appropriate amine at room temperature [33]. Moreover, the reaction of 2,4-dichloroquinazoline with cyclic amines was also reported under acidic conditions [34]. On the other hand, nucleophilic substitution of chlorine at C-2 of quinazoline was carried out at higher temperatures either in 2-propanol or in THF [33]. In fact, we have succeeded to prepare bis nucleophilic substituted products in the presence of conc. HCl in 2-propanol under ultrasonication for 30–45 min. Thus, amino linked heterocycles, N^2,N^4-bis(4-aryloxazol-2-yl)quinazoline-2,4-diamines **5**, N^2,N^4-bis(4-arylthiazol-2-yl)quinazoline-2,4-diamines **6**, and N^2,N^4-bis(4-aryl-1*H*-imidazol-2-yl)quinazoline-2,4-diamines **7** were prepared by the reaction **1** with **2**, **3**, and **4** sonicated in an ultrasonic bath at 46 kHz frequency (Scheme 1). In the ^{1}H NMR spectra of **5a**, **6a**, and **7a** a broad singlet was observed at $\delta = 9.45$, 9.54, 9.25 ppm due to two NH protons. A singlet due to $C_{5'}$-H was appeared at much downfield region and merged with aromatic protons. Besides, compound **7a** displayed another broad singlet at 11.32 ppm due to two NH protons of imidazole. The signals of highly acidic protons disappeared on deuteration.

In a much similar way, N^2,N^4-bis((4-aryloxazol-2-yl)methyl)quinazoline-2,4-diamines **11** were prepared by the reaction of **1** with **8** in the presence of conc. HCl in 2-propanol under ultrasonication for 60–90 min. Adopting similar methodology, N^2,N^4-bis(4-arylthiazol-2-ylmethyl)-quinazoline-2,4-diamines **12** and N^2,N^4-bis(4-aryl-1*H*-imidazol-2-ylmethyl)quinazoline-2,4-diamines **13** were also prepared by performing the reaction of **1** with **9** and **10**, respectively (Scheme 2). The ^{1}H NMR spectra of **11a**, **12a**, and **13a** exhibited two singlets at 4.35, 4.28, 4.29 and 4.39, 4.33, 4.34 ppm for methylene protons. A broad singlet was also observed at 9.40, 9.50, 9.18 ppm due to two NH protons. In addition to these, compound **13a** showed another broad singlet at 11.25 ppm due to two NH protons of imidazole. The signals of NH disappeared when D_2O was added. The signal corresponding to $C_{5'}$-H was appeared at downfield region and merged with aromatic protons. The structures of all the compounds were further ascertained by IR, ^{13}C NMR, mass and elemental analyses.

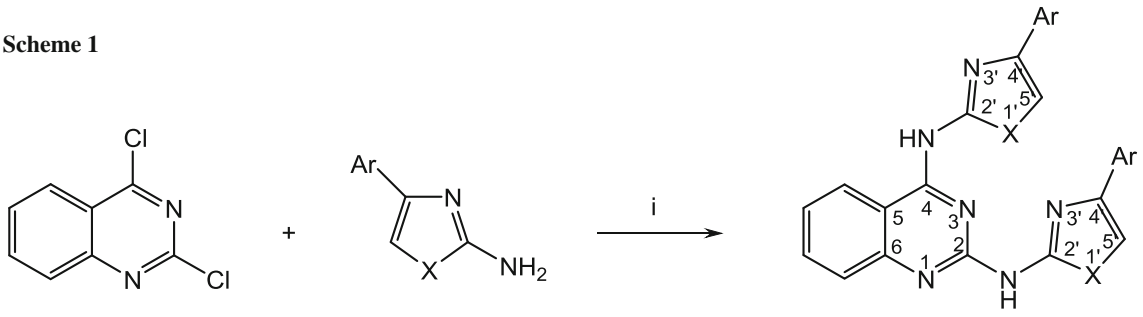
Antibacterial activity

The compounds **5–7** and **11–13** were evaluated for antibacterial activity at two concentrations 50 and 100 μg/well. The results showed in Table 1 and Fig. 1 indicated that Gram-positive bacteria were more susceptible towards the tested compounds than Gram-negative bacteria. The bis(azolyl)quinazolines linked by amino group (**5–7**) exhibited higher activity than those linked by aminomethane moiety (**11–13**). Further it was observed that the compounds having bis(thiazolyl)quinazolines (**6**, **12**) exhibited higher activity than the respective bis(oxazolyl)-(**5**, **11**) and bis(imidazolyl)quinazolines (**7**, **13**). Amongst the latter compounds **7**, **13** exhibited more activity than **5**, **11**. The effect of substituents on the activity indicated that unsubstituted, chloro-, bromo-, and nitro-substituted compounds displayed higher activity than those having methyl and *N*,*N*-dimethyl substituents. This may be due to +I effect of methyl and +M effect of *N*,*N*-dimethyl substituents on the aromatic ring. On the other hand bromo-substituted compounds showed slightly lower activity than chloro-substituted ones. In the literature it was also reported that quinazolines in combination with other heterocycles exhibited remarkable in vitro antimicrobial potency and the presence of electron withdrawing groups like chloro, bromo, fluoro, and nitro substituents on the aromatic ring increased the activity [35–37]. In fact, **6c** and **6f** showed activity against *Bacillus subtilis* greater than the standard drug chloramphenicol at all tested concentrations while **6d** exhibited similar activity to the standard drug. On the other hand, the compounds **5e**, **11b**, **11e**, **12e**, and **13e** displayed no activity.

Antifungal activity

The compounds **5–7** and **11–13** were also screened for antifungal activity against *Aspergillus niger* and *Penicillium chrysogenum* at two concentrations 50 and 100 μg/well and the

Scheme 1



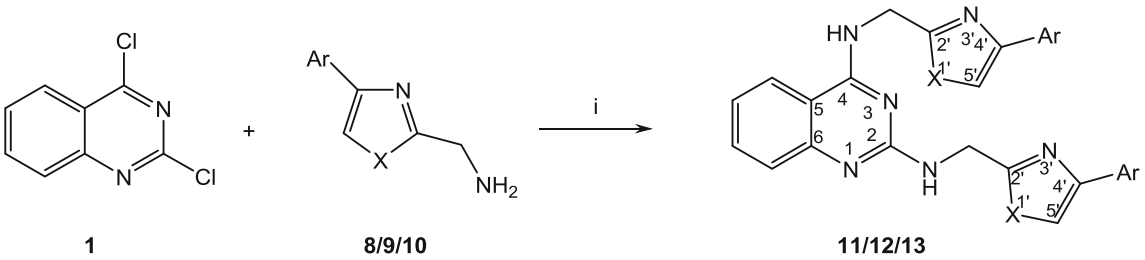
1 **2/3/4** **5/6/7**

i) 2- Propanol / conc. HCl /)))

2, **5**: X = O
3, **6**: X = S
4, **7**: X = NH

Ar
a) Ph
b) 4-Me-Ph
c) 4-Cl-Ph
d) 4-Br-Ph
e) 4-(Me_2N)-Ph
f) 4-NO_2-Ph

Scheme 2



1 **8/9/10** **11/12/13**

i) 2- Propanol / conc. HCl /)))

8, **11**: X = O
9, **12**: X = S
10, **13**: X = NH

Ar
a) Ph
b) 4-Me-Ph
c) 4-Cl-Ph
d) 4-Br-Ph
e) 4-(Me_2N)-Ph
f) 4-NO_2-Ph

results are presented in Table 2 and Fig. 2. All the tested compounds showed greater activity on *A. niger* than on *P. chrysogenum*. The bis(azolylamino)quinazolines **5**–**7** displayed slightly higher activity than bis(azolylmethylamino)-quinazolines **11**–**13**. The imidazolylquinazolines (**7**, **13**) displayed greater activity than thiazolyl- (**6**, **12**) and oxazolylquinazolines (**5**, **11**). Amongst the latter compounds **6** and **12** showed higher activity than **5** and **11**. The presence of electron withdrawing chloro, bromo, and nitro substituents on the aromatic ring increases the activity. In fact, the compounds **7a**, **7c**, **7d**, and **7f** displayed greater activity on *A. niger* than the standard drug ketoconazole at all tested concentrations. On the other hand, the compounds **5e**, **6e**, **11b**, **11e**, and **12e** exhibited no activity.

The compounds that exhibited higher antimicrobial activity are further assayed for MIC, MBC and MFC and the results are depicted in Table 3. MIC is the lowest concentration of an antimicrobial that will inhibit the visible growth of a microorganism (but it is not sure that the microorganisms are completely killed). The MBC/MFC is the lowest concentration of antibiotic required to kill a particular bacterium/fungus. The MBC/MFC involves an

Table 1 The in vitro antibacterial activity of compounds **5–7** and **11–13**

Compound	Zone of inhibition/mm							
	Gram-positive bacteria				Gram-negative bacteria			
	S. aureus		*B. subtilis*		*P. aeruginosa*		*K. pneumoniae*	
	50 μg/well	100 μg/well	50 μg/well	100 μg/well	50 μg/well	100 μg/well	50 μg/well	100 μg/well
5a	10 ± 2	12 ± 1	13 ± 3	15 ± 2	9 ± 3	10 ± 1	11 ± 2	12 ± 1
5b	9 ± 4	10 ± 3	10 ± 1	12 ± 1	8 ± 2	9 ± 1	9 ± 3	11 ± 1
5c	12 ± 1	14 ± 2	14 ± 2	16 ± 1	10 ± 1	12 ± 2	12 ± 1	13 ± 2
5d	10 ± 2	13 ± 3	12 ± 1	15 ± 2	8 ± 2	11 ± 1	10 ± 2	12 ± 1
5e	–	–	–	–	–	–	–	–
5f	14 ± 1	15 ± 3	16 ± 2	19 ± 1	11 ± 3	14 ± 1	13 ± 2	16 ± 1
6a	25 ± 3	28 ± 2	33 ± 1	36 ± 2	21 ± 1	23 ± 3	25 ± 3	28 ± 2
6b	17 ± 2	21 ± 1	20 ± 3	23 ± 3	13 ± 3	15 ± 1	14 ± 2	16 ± 1
6c	27 ± 2	30 ± 3	36 ± 1	39 ± 2	22 ± 2	25 ± 1	27 ± 2	29 ± 3
6d	29 ± 3	31 ± 2	34 ± 2	38 ± 2	20 ± 1	24 ± 2	26 ± 1	27 ± 3
6e	8 ± 1	10 ± 3	9 ± 2	12 ± 1	7 ± 2	9 ± 2	8 ± 1	9 ± 1
6f	28 ± 2	32 ± 1	38 ± 2	42 ± 2	24 ± 1	27 ± 2	30 ± 1	33 ± 2
7a	22 ± 4	25 ± 2	26 ± 3	27 ± 1	16 ± 1	19 ± 3	19 ± 1	21 ± 1
7b	16 ± 3	20 ± 2	20 ± 2	21 ± 3	12 ± 3	14 ± 2	13 ± 1	15 ± 2
7c	24 ± 2	28 ± 3	29 ± 1	31 ± 1	19 ± 3	22 ± 1	22 ± 3	25 ± 3
7d	22 ± 1	25 ± 3	28 ± 2	30 ± 2	17 ± 2	21 ± 3	20 ± 2	23 ± 1
7e	7 ± 1	9 ± 1	8 ± 2	10 ± 2	–	–	–	–
7f	27 ± 1	29 ± 2	31 ± 2	34 ± 2	21 ± 2	25 ± 1	23 ± 3	27 ± 1
11a	9 ± 1	11 ± 3	11 ± 1	13 ± 1	8 ± 1	10 ± 1	9 ± 1	11 ± 1
11b	–	–	–	–	–	–	–	–
11c	10 ± 3	12 ± 2	12 ± 3	14 ± 2	9 ± 4	11 ± 1	10 ± 1	12 ± 1
11d	8 ± 2	11 ± 1	10 ± 2	13 ± 1	8 ± 2	11 ± 2	9 ± 1	11 ± 2
11e	–	–	–	–	–	–	–	–
11f	11 ± 2	14 ± 1	13 ± 2	16 ± 3	11 ± 1	13 ± 2	13 ± 1	15 ± 2
12a	23 ± 2	26 ± 1	28 ± 3	30 ± 3	17 ± 3	21 ± 3	20 ± 2	23 ± 3
12b	14 ± 1	17 ± 2	18 ± 3	20 ± 1	12 ± 3	13 ± 1	13 ± 1	14 ± 1
12c	27 ± 2	29 ± 1	31 ± 1	33 ± 2	20 ± 2	22 ± 2	23 ± 3	27 ± 2
12d	25 ± 3	28 ± 2	30 ± 2	32 ± 1	18 ± 1	21 ± 2	22 ± 1	25 ± 2
12e	–	–	–	–	–	–	–	–
12f	29 ± 1	32 ± 2	33 ± 2	36 ± 1	21 ± 3	24 ± 2	26 ± 1	29 ± 2
13a	20 ± 2	22 ± 1	21 ± 4	24 ± 1	13 ± 1	17 ± 3	16 ± 1	19 ± 1
13b	12 ± 1	14 ± 1	15 ± 1	17 ± 2	11 ± 3	12 ± 2	12 ± 2	14 ± 2
13c	21 ± 3	23 ± 1	24 ± 2	26 ± 1	14 ± 1	18 ± 3	17 ± 1	20 ± 1
13d	19 ± 1	20 ± 2	21 ± 2	24 ± 3	12 ± 1	15 ± 2	16 ± 2	19 ± 1
13e	–	–	–	–	–	–	–	–
13f	23 ± 1	26 ± 2	25 ± 3	28 ± 2	17 ± 1	19 ± 2	19 ± 1	22 ± 2
Chloramphenicol	33 ± 1	35 ± 3	34 ± 2	38 ± 1	27 ± 2	30 ± 1	40 ± 3	42 ± 2
Control (DMSO)	–	–	–	–	–	–	–	–

additional set of steps performed once the MIC is determined. The antimicrobials are usually regarded as bactericidal/fungicidal if the MBC/MFC is not greater than four times the MIC [38]. The compounds **6c**, **6d**, and **6f** displayed low MIC values against *B. subtilis* and the MBC is 2 × MIC. However, the compounds **7a**, **7c**, **7d**, and **7f** exhibited low MIC values on *A. niger* and the MFC is 2 × MIC.

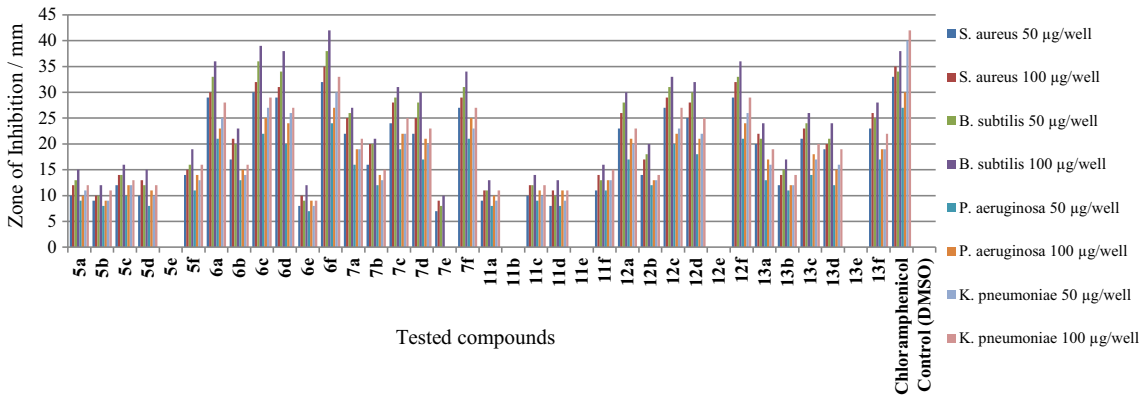


Fig. 1 The in vitro antibacterial activity of compounds **5–7** and **11–13**

Conclusion

Some new bis(azolylamino)- and bis(azolylmethylamino)quinazolines were prepared from 2,4-dichloroquinazoline and azolyl amines under ultrasonication and tested for their antimicrobial activity. The bis(azolyl)quinazolines linked by amino group (**5–7**) exhibited higher activity than those linked by aminomethane moiety. The chloro-, bromo-, and nitro-substituted bis(thiazolylamino)quinazolines **6c**, **6d**, and **6f** exhibited excellent antibacterial activity against *B. subtilis* with MIC value 6.25 and MBC is 2 × MIC. However, unsubstituted, chloro-, bromo-, and nitro-substituted bis(imidazolylamino) quinazolines **7a**, **7c**, **7d**, and **7f** showed excellent antifungal activity against *A. niger* with MIC value 6.25 and MBC is 2 × MIC.

Experimental

Melting points were determined in open capillaries on a Mel-Temp apparatus. The purity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate/hexane, 1:3). The IR spectra were recorded on a Thermo Nicolet IR 200 FT-IR spectrometer as KBr pellets and the wavenumbers were given in cm^{-1}. The ^1H NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 400 MHz. The ^{13}C NMR spectra were recorded in DMSO-d_6 on a Bruker spectrometer operating at 100 MHz. All chemical shifts are reported in δ/ppm using TMS as an internal standard. The high-resolution mass spectra were recorded on micromass Q-TOF micromass spectrometer using electrospray ionization. The microanalyses were performed on a Perkin-Elmer 240C elemental analyzer. Ultrasonication was performed in a Bandelin Sonorex RK 102H ultrasonic bath operating at a frequency of 46 kHz. The progress of the reaction was monitored by TLC using silica gel plates (silica gel 60 F254 0.25 mm) and components were visualized by observation under UV light (254 and 365 nm). The synthetic intermediates 2,4-dichloroquinazoline (**1**), 4-aryloxazol-2-amines **2**, 4-arylthiazol-2-amines **3**, 4-aryl-1*H*-imidazol-2-amines **4**, (4-aryloxazol-2-yl)methanamines **8**, (4-arylthiazol-2-yl)methanamines **9**, and (4-aryl-1*H*-imidazol-2-yl)methanamines **10** were prepared as per the literature precedents [28–32].

General procedure for the synthesis of N^2,N^4-bis(4-aryloxazol-2-yl)quinazoline-2,4-diamines ***5a–5f****, N^2,N^4-bis(4-arylthiazol-2-yl)quinazoline-2,4-diamines* ***6a–6f****, and N^2,N^4-bis(4-aryl-1H-imidazol-2-yl)quinazoline-2,4-diamines* ***7a–7f***

A solution of 2,4-dichloroquinazoline (**1**, 1.0 mmol), 4-aryloxazol-2-amine **2**/4-arylthiazol-2-amine **3**/4-aryl-1*H*-imidazol-2-amine **4** (2.5 mmol) and conc. HCl (2.0 mmol) in 5 cm^3 2-propanol was sonicated at room temperature for 30–45 min in an ultrasonic bath working at 46 kHz (constant frequency). After completion of the reaction (monitored by TLC), the separated solid was filtered, dried, and recrystallized from 2-propanol.

N^2,N^4-Bis(4-phenyloxazol-2-yl)quinazoline-2,4-diamine (**5a**, $C_{26}H_{18}N_6O_2$)

White crystals; yield 0.73 g (66%); m.p.: 123–125 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 7.25–7.81 (m, 16H, Ar–H, $C_{5'}$-H), 9.45 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.5, 140.6, 159.2, 173.9, 183.4, 114.5, 116.1, 123.8, 125.3, 127.4, 129.0, 131.6, 132.9, 136.0, 151.4 ppm; IR (KBr): $\bar{\nu}$ = 3297 (NH), 1649 (C=C), 1567 (C=N) cm^{-1}; HRMS: *m/z* = 469.4515 ([M+Na], calcd), 469.4507 (found).

N^2,N^4-Bis[4-(4-methylphenyl)oxazol-2-yl]quinazoline-2,4-diamine (**5b**, $C_{28}H_{22}N_6O_2$)

White crystals; yield 0.80 g (68%); m.p.: 115–117 °C; ^1H NMR (400 MHz, DMSO-d_6): δ = 2.34 (s, 6H, Ar–CH_3), 7.19–7.90 (m, 14H, Ar–H, $C_{5'}$-H), 9.50 (bs, 2H, NH) ppm;

Table 2 The in vitro antifungal activity of compounds **5–7** and **11–13**

Compound	Zone of inhibition/mm			
	A. niger		*P. chrysogenum*	
	50 μg/well	100 μg/well	50 μg/well	100 μg/well
5a	12 ± 3	14 ± 1	–	9 ± 2
5b	9 ± 1	10 ± 2	–	8 ± 1
5c	14 ± 2	17 ± 3	9 ± 1	10 ± 3
5d	13 ± 2	15 ± 1	8 ± 2	9 ± 2
5e	–	–	–	–
5f	16 ± 1	19 ± 2	12 ± 1	14 ± 2
6a	27 ± 2	29 ± 2	18 ± 3	21 ± 3
6b	20 ± 2	23 ± 1	13 ± 2	14 ± 1
6c	30 ± 2	32 ± 3	21 ± 3	25 ± 2
6d	30 ± 1	31 ± 3	20 ± 2	23 ± 2
6e	–	–	–	–
6f	32 ± 2	34 ± 1	24 ± 2	28 ± 1
7a	34 ± 2	37 ± 1	24 ± 3	26 ± 3
7b	22 ± 2	24 ± 1	14 ± 1	16 ± 2
7c	36 ± 1	38 ± 3	25 ± 3	28 ± 1
7d	35 ± 2	37 ± 1	24 ± 2	26 ± 2
7e	13 ± 1	15 ± 1	9 ± 2	10 ± 2
7f	38 ± 2	42 ± 2	27 ± 2	31 ± 1
11a	14 ± 3	17 ± 1	10 ± 1	11 ± 2
11b	–	–	–	–
11c	16 ± 3	19 ± 3	11 ± 1	12 ± 3
11d	14 ± 1	16 ± 2	9 ± 1	11 ± 2
11e	–	–	–	–
11f	17 ± 2	19 ± 1	13 ± 2	14 ± 2
12a	23 ± 3	25 ± 2	15 ± 3	18 ± 2
12b	19 ± 1	22 ± 1	12 ± 1	13 ± 1
12c	25 ± 2	26 ± 3	16 ± 2	20 ± 3
12d	22 ± 1	24 ± 2	16 ± 1	18 ± 2
12e	–	–	–	–
12f	26 ± 2	29 ± 3	19 ± 1	23 ± 2
13a	24 ± 1	26 ± 2	20 ± 3	22 ± 2
13b	19 ± 2	21 ± 2	13 ± 1	15 ± 1
13c	27 ± 3	30 ± 2	23 ± 2	26 ± 3
13d	25 ± 2	28 ± 1	20 ± 2	24 ± 2
13e	10 ± 1	12 ± 1	–	11 ± 1
13f	30 ± 2	32 ± 1	25 ± 1	29 ± 2
Ketoconazole	33 ± 1	36 ± 2	36 ± 3	38 ± 1
Control (DMSO)	–	–	–	–

– no activity, ± standard deviation

^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 24.9, 137.2, 141.1, 159.6, 173.5, 182.9, 117.7, 121.3, 122.6, 124.2, 128.0, 130.9, 133.5, 135.8, 139.3, 149.5$ ppm; IR (KBr): $\bar{\nu} = 3288$ (NH), 1645 (C=C), 1570 (C=N) cm^{-1}; HRMS: $m/z = 497.5031$ ([M+Na], calcd), 497.5036 (found).

N^2,N^4-Bis[4-(4-chlorophenyl)oxazol-2-yl]quinazoline-2,4-diamine (**5c**, $C_{26}H_{16}Cl_2N_6O_2$)

White crystals; yield 0.92 g (72%); m.p.: 136–138 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 7.33–7.82$ (m, 14H, Ar–H, $C_{5'}$-H), 9.48 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz,

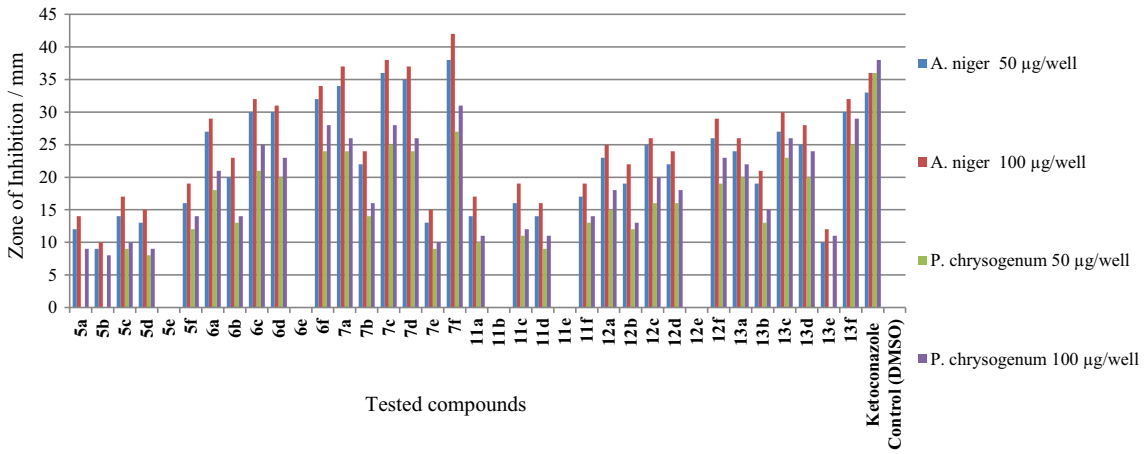


Fig. 2 The in vitro antifungal activity of compounds **5–7** and **11–13**

Table 3 MIC, MBC, and MFC of compounds **6a**, **6c**, **7a**, and **7c**

Compound	Minimum inhibitory concentration					
	MIC (MBC/MFC) µg					
	S. aureus	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. niger*	*P. chrysogenum*
6a	12.5 (50)	12.5(50)	100 (>200)	100 (>200)	50 (200)	100 (>200)
6c	12.5 (50)	6.25(12.5)	50 (200)	100 (>200)	25 (100)	100 (>200)
6d	12.5 (50)	6.25(12.5)	50 (200)	100 (>200)	25 (100)	100 (>200)
6f	12.5 (50)	6.25(12.5)	25 (100)	100 (>200)	25 (100)	100 (>200)
7a	100 (>200)	50 (200)	100 (>200)	200 (–)	6.25 (12.5)	100 (>200)
7c	100 (>200)	50 (200)	100 (>200)	200 (–)	6.25 (12.5)	100 (>200)
7d	100 (>200)	50 (200)	200 (–)	200 (–)	6.25 (12.5)	100 (>200)
7f	100 (>200)	50 (200)	100 (>200)	200 (–)	6.25(12.5)	50 (200)
12c	100 (>200)	50 (200)	100 (>200)	200 (–)	100 (>200)	100 (>200)
12f	12.5 (50)	50 (200)	100 (>200)	100 (>200)	50 (200)	100 (>200)
13c	200 (–)	50 (200)	100 (>200)	200 (–)	25 (100)	100 (>200)
13f	100 (>200)	50 (200)	200 (–)	200 (–)	12.5 (50)	100 (>200)
Chloramphenicol	6.25	6.25	6.25	12.5	–	–
Ketoconazole	–	–	–	–	6.25	12.5

– no activity

DMSO-d_6): δ = 136.3, 140.8, 156.9, 174.2, 182.7, 117.2, 118.7, 121.5, 124.8, 127.3, 130.8, 133.4, 134.9, 140.2, 148.6 ppm; IR (KBr): $\bar{\nu}$ = 3293 (NH), 1658 (C=C), 1563 (C=N) cm^{-1}; HRMS: *m/z* = 538.3400 ([M+Na], calcd), 538.3391 (found).

N^2,N^4-Bis[4-(4-bromophenyl)oxazol-2-yl]quinazoline-2,4-diamine (**5d**, $C_{26}H_{16}Br_2N_6O_2$)
White crystals; yield 0.96 g (64%); m.p.: 144–146 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.28–7.78 (m, 14H, Ar–H, $C_{5'}$-H), 9.43 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 136.1, 139.7, 155.4, 173.6, 181.5, 117.0, 118.9, 121.3, 124.6, 127.2, 129.1, 133.7, 134.8, 137.9, 148.3 ppm; IR (KBr): $\bar{\nu}$ = 3296 (NH), 1654 (C=C), 1565 (C=N) cm^{-1}; HRMS: *m/z* = 627.2351 ([M+Na], calcd), 627.2345 (found).

N^2,N^4-Bis[4-[4-(dimethylamino)phenyl]oxazol-2-yl]quinazoline-2,4-diamine (**5e**, $C_{30}H_{28}N_8O_2$)
White crystals; yield 0.86 g (65%); m.p.: 130–132 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.12 (s, 12H, $N(CH_3)_2$), 7.40–7.95 (m, 14H, Ar–H, $C_{5'}$-H), 9.41 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.8, 137.9, 141.5, 155.3, 173.5, 183.8, 119.2, 120.5, 123.5, 124.7, 128.1, 132.2, 134.0, 136.3, 139.4, 150.6 ppm; IR (KBr): $\bar{\nu}$ = 3282 (NH), 1640 (C=C), 1558 (C=N) cm^{-1}; HRMS: *m/z* = 555.5255 ([M+Na], calcd), 555.5862 (found).

N^2,N^4-Bis[4-(4-nitrophenyl)oxazol-2-yl]quinazoline-2,4-diamine (**5f**, $C_{26}H_{16}N_8O_6$)
White crystals; yield 0.92 g (69%); m.p.: 158–160 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.47–7.92 (m, 14H, Ar–H, $C_{5'}$-H), 9.46 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 137.8, 141.9, 159.1, 174.3, 183.6, 119.5, 121.7, 123.9, 125.8, 128.4, 132.0, 134.2, 136.5, 140.1, 150.7 ppm; IR (KBr): $\bar{\nu}$ = 3298 (NH), 1662 (C=C), 1574 (C=N) cm^{-1}; HRMS: *m/z* = 559.4391 ([M+Na], calcd), 559.4399 (found).

N^2,N^4-Bis(4-phenylthiazol-2-yl)quinazoline-2,4-diamine (**6a**, $C_{26}H_{18}N_6S_2$)
White crystals; yield 0.75 g (63%); m.p.: 157–159 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.22–7.72 (m, 16H, Ar–H, $C_{5'}$-H), 9.54 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.8, 148.3, 161.7, 173.0, 184.3, 117.2, 118.7, 121.5, 124.8, 127.3, 130.8, 133.4, 134.9, 140.2, 148.6 ppm; IR (KBr): $\bar{\nu}$ = 3309 (NH), 1651 (C=C), 1575 (C=N) cm^{-1}; HRMS: *m/z* = 501.5810 ([M+Na], calcd), 501.5802 (found).

N^2,N^4-Bis[4-(4-methylphenyl)thiazol-2-yl]quinazoline-2,4-diamine (**6b**, $C_{28}H_{22}N_6S_2$)
White crystals; yield 0.84 g (67%); m.p.: 162–164 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.31 (s, 6H, Ar–CH_3), 7.09–7.65 (m, 14H, Ar–H, $C_{5'}$-H), 9.50 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.3, 115.2, 147.6, 161.1, 173.2, 184.7, 118.3, 120.8, 124.6, 127.1, 129.5, 130.9, 132.4, 134.0, 136.8, 150.1 ppm; IR (KBr): $\bar{\nu}$ = 3306 (NH), 1660 (C=C), 1571 (C=N) cm^{-1}; HRMS: *m/z* = 529.6343 ([M+Na], calcd), 529.6338 (found).

N^2,N^4-Bis[4-(4-chlorophenyl)thiazol-2-yl]quinazoline-2,4-diamine (**6c**, $C_{26}H_{16}Cl_2N_6S_2$)
White crystals; yield 0.87 g (64%); m.p.: 176–178 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.16–7.70 (m, 14H, Ar–H, $C_{5'}$-H), 9.49 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.5, 147.1, 160.5, 173.9, 182.1, 119.2, 120.5, 121.9, 125.4, 127.2, 129.7, 130.1, 132.8, 135.2, 151.3 ppm; IR (KBr): $\bar{\nu}$ = 3315 (NH), 1656 (C=C), 1578 (C=N) cm^{-1}; HRMS: *m/z* = 570.4712 ([M+Na], calcd), 570.4705 (found).

N^2,N^4-Bis[4-(4-bromophenyl)thiazol-2-yl]quinazoline-2,4-diamine (**6d**, $C_{26}H_{16}Br_2N_6S_2$)
White crystals; yield 1.08 g (68%); m.p.: 183–185 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.13–7.69 (m, 14H, Ar–H, $C_{5'}$-H), 9.47 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 114.3, 147.5, 160.7, 173.8, 182.4, 118.2, 120.1, 121.6, 124.5, 127.9, 129.8, 130.2, 132.4, 135.7, 148.3 ppm; IR (KBr): $\bar{\nu}$ = 3318 (NH), 1659 (C=C), 1580 (C=N) cm^{-1}; HRMS: *m/z* = 659.3738 ([M+Na], calcd), 659.3731 (found).

N^2,N^4-Bis[4-[4-(dimethylamino)phenyl]thiazol-2-yl]quinazoline-2,4-diamine (**6e**, $C_{30}H_{28}N_8S_2$)
White crystals; yield 0.93 g (66%); m.p.: 167–169 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 3.06 (s, 12H, $N(CH_3)_2$), 7.27–7.81 (m, 14H, Ar–H, $C_{5'}$-H), 9.57 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.6, 115.7, 148.8, 161.3, 173.1, 183.6, 118.6, 119.3, 120.8, 121.6, 122.7, 126.9, 129.4, 134.7, 149.6, 150.4 ppm; IR (KBr): $\bar{\nu}$ = 3301 (NH), 1648 (C=C), 1582 (C=N) cm^{-1}; HRMS: *m/z* = 587.7167 ([M+Na], calcd), 587.7163 (found).

N^2,N^4-Bis[4-(4-nitrophenyl)thiazol-2-yl]quinazoline-2,4-diamine (**6f**, $C_{26}H_{16}N_8O_4S_2$)
White crystals; yield 0.88 g (62%); m.p.: 197–199 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.31–7.76 (m, 14H, Ar–H, $C_{5'}$-H), 9.53 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 115.9, 148.6, 161.8, 173.5, 184.2, 119.4, 120.9, 124.7, 125.3, 129.6, 130.5, 133.1, 134.8, 140.5, 151.2 ppm; IR (KBr): $\bar{\nu}$ = 3320 (NH), 1663 (C=C), 1584 (C=N) cm^{-1}; HRMS: *m/z* = 591.5705 ([M+Na], calcd), 591.5701 (found).

N^2,N^4-Bis(4-phenyl-1H-imidazol-2-yl)quinazoline-2,4-diamine (**7a**, $C_{26}H_{20}N_8$)
White crystals; yield 0.73 g (66%); m.p.: 210–212 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.43–8.15 (m, 16H, Ar–H, $C_{5'}$-H), 9.25 (bs, 2H, NH), 11.32 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 129.1, 138.6, 142.3, 172.5, 183.1, 115.7, 116.2, 124.5, 126.0, 128.8, 129.4, 132.1, 133.9, 136.0, 145.6 ppm; IR (KBr): $\bar{\nu}$ = 3285 (NH), 1643 (C=C), 1560 (C=N) cm^{-1}; HRMS: *m/z* = 467.4816 ([M+Na], calcd), 467.4808 (found).

N^2,N^4-Bis[4-(4-methylphenyl)-1H-imidazol-2-yl]quinazoline-2,4-diamine (**7b**, $C_{28}H_{24}N_8$)
White crystals; yield 0.76 g (65%); m.p.: 196–198 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.30 (s, 6H, Ar–CH_3), 7.20–7.98 (m, 14H, Ar–H, $C_{5'}$-H), 9.29 (bs, 2H, NH), 11.29 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.0, 130.5, 139.0, 142.7, 172.8, 182.7, 114.4, 116.8, 122.8, 125.3, 126.9, 128.1, 134.7, 136.0, 137.4, 148.9 ppm; IR (KBr): $\bar{\nu}$ = 3277 (NH), 1638 (C=C), 1565 (C=N) cm^{-1}; HRMS: *m/z* = 495.5335 ([M+Na], calcd), 495.5339 (found).

N^2,N^4-Bis[4-(4-chlorophenyl)-1H-imidazol-2-yl]quinazoline-2,4-diamine (**7c**, $C_{26}H_{18}Cl_2N_8$)
White crystals; yield 0.87 g (68%); m.p.: 220–222 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.29–7.60 (m, 14H, Ar–H, $C_{5'}$-H), 9.23 (bs, 2H, NH), 11.35 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 129.1, 138.4, 143.6, 173.1, 183.5, 115.8, 118.4, 121.3, 127.0, 128.9, 130.2, 131.5, 133.8, 135.6, 146.5 ppm; IR (KBr): $\bar{\nu}$ = 3271 (NH), 1647 (C=C), 1556 (C=N) cm^{-1}; HRMS: *m/z* = 536.3705 ([M+Na], calcd), 536.3700 (found).

N^2,N^4-Bis[4-(4-bromophenyl)-1H-imidazol-2-yl]quinazoline-2,4-diamine (**7d**, $C_{26}H_{18}Br_2N_8$)
White crystals; yield 0.91 g (61%); m.p.: 226–228 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.19–7.73 (m, 14H, Ar–H, $C_{5'}$-H), 9.27 (bs, 2H, NH), 11.31 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 129.4, 138.2, 142.8, 172.6, 182.9, 115.5, 116.1, 121.7, 125.2, 126.3, 128.4, 131.6, 133.5, 136.1, 146.0 ppm; IR (KBr): $\bar{\nu}$ = 3274 (NH), 1646 (C=C), 1559 (C=N) cm^{-1}; HRMS: *m/z* = 625.2659 ([M+Na], calcd), 625.2655 (found).

N^2,N^4-Bis[4-[4-(dimethylamino)phenyl]-1H-imidazol-2-yl]quinazoline-2,4-diamine (**7e**, $C_{30}H_{30}N_{10}$)
White crystals; yield 0.92 g (70%); m.p.: 216–218 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.91 (s, 12H, $N(CH_3)_2$), 7.41–8.11 (m, 14H, Ar–H, $C_{5'}$-H), 9.21 (bs, 2H, NH), 11.37 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 43.9, 131.6, 140.7, 143.1, 172.4, 183.8, 116.4, 118.7, 120.2, 123.6, 126.4, 129.7, 132.0, 134.7, 137.2, 149.0 ppm; IR (KBr): $\bar{\nu}$ = 3283 (NH), 1636 (C=C), 1551 (C=N) cm^{-1}; HRMS: *m/z* = 553.6160 ([M+Na], calcd), 553.6151 (found).

N^2,N^4-Bis[4-(4-nitrophenyl)-1H-imidazol-2-yl]quinazoline-2,4-diamine (**7f**, $C_{26}H_{18}N_{10}O_4$)
White crystals; yield 0.92 g (69%); m.p.: 235–237 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 7.48–8.17 (m, 14H, Ar–H, $C_{5'}$-H), 9.32 (bs, 2H, NH), 11.39 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 130.3, 139.4, 143.7, 173.2, 183.1, 116.6, 118.5, 122.9, 127.3, 128.4, 130.7, 134.8, 136.2, 137.6, 149.1 ppm; IR (KBr): $\bar{\nu}$ = 3286 (NH), 1649 (C=C), 1568 (C=N) cm^{-1}; HRMS: *m/z* = 557.4702 ([M+Na], calcd), 557.4711 (found).

General procedure for the synthesis of N^2,N^4-bis(4-aryloxazol-2-ylmethyl)quinazoline-2,4-diamines ***11a–11f****, N^2,N^4-bis(4-arylthiazol-2-ylmethyl)quinazoline-2,4-diamines* ***12a–12f****, and N^2,N^4-bis(4-aryl-1H-imidazol-2-ylmethyl)quinazoline-2,4-diamines* ***13a–13f***
The compounds 2,4-dichloroquinazoline (**1**, 1.0 mmol), (4-aryloxazol-2-yl)methanamine **8**/(4-arylthiazol-2-yl)methanamine **9**/(4-aryl-1*H*-imidazol-2-yl)methanamine **10** (2.5 mmol), conc. HCl (2.0 mmol), and 5 cm^3 2-propanol were sonicated at room temperature for 60–90 min. After completion of the reaction (monitored by TLC), the separated solid was filtered, dried, and recrystallized from 2-propanol.

N^2,N^4-Bis(4-phenyloxazol-2-ylmethyl)quinazoline-2,4-diamine (**11a**, $C_{28}H_{22}N_6O_2$)
White crystals; yield 0.79 g (67%); m.p.: 133–135 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.35 (s, 2H, CH_2), 4.39 (s, 2H, CH_2), 7.11–7.72 (m, 16H, Ar–H, $C_{5'}$-H), 9.40 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.3, 54.4, 140.8, 143.2, 149.6, 162.1, 182.7, 114.7, 120.3, 122.0, 123.2, 126.5, 132.7, 135.5, 138.1, 139.3, 147.8 ppm; IR (KBr): $\bar{\nu}$ = 3262 (NH), 1626 (C=C), 1514 (C=N) cm^{-1}; HRMS: *m/z* = 497.5049 ([M+Na], calcd), 497.5040 (found).

N^2,N^4-Bis[4-(4-methylphenyl)oxazol-2-ylmethyl]quinazoline-2,4-diamine (**11b**, $C_{30}H_{26}N_6O_2$)
White crystals; yield 0.87 g (70%); m.p.: 119–121 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.36 (s, 6H, Ar–CH_3), 4.30 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 7.30–7.88 (m, 14H, Ar–H, $C_{5'}$-H), 9.44 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 25.2, 51.6, 53.5, 139.1, 145.8, 149.2, 161.6, 183.0, 113.5, 119.1, 121.8, 124.3, 125.4, 126.5, 128.7, 133.9, 135.0, 150.4 ppm; IR (KBr): $\bar{\nu}$ = 3260 (NH), 1639 (C=C), 1536 (C=N) cm^{-1}; HRMS: *m/z* = 525.5562 ([M+Na], calcd), 525.5554 (found).

N^2,N^4-Bis[4-(4-chlorophenyl)oxazol-2-ylmethyl]quinazoline-2,4-diamine (**11c**, $C_{28}H_{20}Cl_2N_6O_2$)
White crystals; yield 0.93 g (69%); m.p.: 129–131 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.29 (s, 2H, CH_2), 4.33 (s, 2H, CH_2), 7.24–7.69 (m, 14H, Ar–H, $C_{5'}$-H), 9.47 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 53.2, 54.9, 137.6, 146.3, 150.4, 161.9, 182.2, 115.2, 117.7, 122.5, 124.0, 125.3, 128.8, 131.4, 132.9, 142.2, 151.6 ppm; IR (KBr): $\bar{\nu}$ = 3251 (NH), 1642 (C=C), 1540 (C=N) cm^{-1}; HRMS: *m/z* = 566.3932 ([M+Na], calcd), 566.3939 (found).

N^2,N^4-Bis[4-(4-bromophenyl)oxazol-2-ylmethyl]quinazoline-2,4-diamine (**11d**, $C_{28}H_{20}Br_2N_6O_2$)
White crystals; yield 1.01 g (64%); m.p.: 143–145 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.27 (s, 2H, CH_2), 4.31 (s, 2H, CH_2), 7.21–7.62 (m, 14H, Ar–H, $C_{5'}$-H), 9.43 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 51.4, 53.6, 137.8, 143.0, 149.5, 161.7, 180.3, 114.9, 117.6, 121.1, 123.4, 125.8, 128.2, 131.9, 133.0, 139.7, 147.5 ppm; IR (KBr): $\bar{\nu}$ = 3254 (NH), 1645 (C=C), 1542 (C=N) cm^{-1}; HRMS: *m/z* = 655.2949 ([M+Na], calcd), 655.2943 (found).

N^2,N^4-Bis[4-[4-(dimethylamino)phenyl]oxazol-2-ylmethyl]quinazoline-2,4-diamine (**11e**, $C_{32}H_{32}N_8O_2$)
White crystals; yield 1.00 g (72%); m.p.: 123–125 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.96 (s, 12H, $N(CH_3)_2$), 4.32 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 7.35–7.89 (m, 14H, Ar–H, $C_{5'}$-H), 9.39 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.1, 52.7, 54.3, 138.2, 145.1, 149.6, 162.3, 180.9, 116.2, 120.5, 123.5, 124.7, 128.1, 132.2, 134.0, 136.3, 139.4, 150.6 ppm; IR (KBr): $\bar{\nu}$ = 3246 (NH), 1635 (C=C), 1532 (C=N) cm^{-1}; HRMS: *m/z* = 583.6386 ([M+Na], calcd), 583.6391 (found).

N^2,N^4-Bis[4-(4-nitrophenyl)oxazol-2-ylmethyl]quinazoline-2,4-diamine (**11f**, $C_{28}H_{20}N_8O_6$)
White crystals; yield 0.95 g (68%); m.p.: 161–163 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.38 (s, 2H, CH_2), 4.36 (s, 2H, CH_2), 7.37–7.93 (m, 14H, Ar–H, $C_{5'}$-H), 9.48 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 52.1, 54.7, 139.3, 145.6, 150.8, 162.4, 182.5, 116.9, 119.0, 123.6, 124.1, 128.7, 132.3, 134.2, 136.8, 142.5, 150.9 ppm; IR (KBr): $\bar{\nu}$ = 3263 (NH), 1649 (C=C), 1547 (C=N) cm^{-1}; HRMS: *m/z* = 587.4950 ([M+Na], calcd), 587.4943 (found).

N^2,N^4-Bis(4-phenylthiazol-2-ylmethyl)quinazoline-2,4-diamine (**12a**, $C_{28}H_{22}N_6S_2$)
White crystals; yield 0.88 g (70%); m.p.: 141–143 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.28 (s, 2H, CH_2), 4.33 (s, 2H, CH_2), 7.32–7.86 (m, 16H, Ar–H, $C_{5'}$-H), 9.50 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.2, 56.5, 115.5, 153.7, 162.7, 170.1, 182.4, 115.1, 118.4, 119.5, 125.0, 130.6, 133.8, 135.9, 137.0, 143.2, 152.6 ppm; IR (KBr): $\bar{\nu}$ = 3367 (NH), 1632 (C=C), 1580 (C=N) cm^{-1}; HRMS: *m/z* = 529.6356 ([M+Na], calcd), 529.6349 (found).

N^2,N^4-Bis[4-(4-methylphenyl)thiazol-2-ylmethyl]quinazoline-2,4-diamine (**12b**, $C_{30}H_{26}N_6S_2$)
White crystals; yield 0.90 g (68%); m.p.: 137–139 °C; ^{1}H NMR (400 MHz, DMSO-d$_6$): δ = 2.35 (s, 6H, Ar–CH_3), 4.26 (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.18–7.75 (m, 14H, Ar–H, $C_{5'}$-H), 9.42 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 24.5, 54.6, 55.9, 116.9, 155.2, 163.0, 169.5, 182.1, 117.7, 119.5, 122.6, 124.1, 128.5, 131.9, 134.7, 136.3, 139.5, 149.2 ppm; IR (KBr): $\bar{\nu}$ = 3275 (NH), 1637 (C=C), 1541 (C=N) cm^{-1}; HRMS: *m/z* = 557.6874 ([M+Na], calcd), 557.6880 (found).

N^2,N^4-Bis[4-(4-chlorophenyl)thiazol-2-ylmethyl]quinazoline-2,4-diamine (**12c**, $C_{28}H_{20}Cl_2N_6S_2$)
White crystals; yield 1.03 g (72%); m.p.: 165–167 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.33 (s, 2H, CH_2), 4.35 (s, 2H, CH_2), 7.25–7.80 (m, 14H, Ar–H, C_5-H), 9.47 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.5, 56.3, 117.5, 155.9, 160.3, 162.5, 182.9, 118.2, 119.7, 120.3, 123.4, 125.2, 126.6, 129.1, 135.7, 138.5, 147.0 ppm; IR (KBr): $\bar{\nu}$ = 3269 (NH), 1640 (C=C), 1550 (C=N) cm^{-1}; HRMS: *m/z* = 598.5244 ([M+Na], calcd), 598.5236 (found).

N^2,N^4-Bis[4-(4-bromophenyl)thiazol-2-ylmethyl]quinazoline-2,4-diamine (**12d**, $C_{28}H_{20}Br_2N_6S_2$)
White crystals; yield 1.14 g (69%); m.p.: 174–176 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.31 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 7.23–7.79 (m, 14H, Ar–H, C_5-H), 9.45 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 54.3, 55.6, 116.2, 153.4, 162.9, 169.8, 182.5, 115.7, 118.6, 120.9, 123.2, 128.0, 131.4, 134.9, 136.1, 138.0, 147.3 ppm; IR (KBr): $\bar{\nu}$ = 3271 (NH), 1642 (C=C), 1553 (C=N) cm^{-1}; HRMS: *m/z* = 687.4219 ([M+Na], calcd), 687.4212 (found).

N^2,N^4-Bis[4-[4-(dimethylamino)phenyl]thiazol-2-ylmethyl]quinazoline-2,4-diamine (**12e**, $C_{32}H_{32}N_8S_2$)
White crystals; yield 1.08 g (73%); m.p.: 152–154 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.89 (s, 12H, N(CH_3)$_2$), 4.34 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 7.41–8.03 (m, 14H, Ar–H, $C_{5'}$-H), 9.40 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 42.5, 55.4, 57.1, 118.7, 156.3, 160.7, 162.1, 182.6, 117.4, 119.5, 122.0, 123.1, 125.6, 127.9, 131.3, 135.4, 146.2, 149.8 ppm; IR (KBr): $\bar{\nu}$ = 3258 (NH), 1629 (C=C), 1547 (C=N) cm^{-1}; HRMS: *m/z* = 615.7699 ([M+Na], calcd), 615.7691 (found).

N^2,N^4-Bis[4-(4-nitrophenyl)thiazol-2-ylmethyl]quinazoline-2,4-diamine (**12f**, $C_{28}H_{20}N_8O_4S_2$)
White crystals; yield 0.92 g (62%); m.p.: 188–190 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.37 (s, 2H, CH_2), 4.39 (s, 2H, CH_2), 7.46–8.12 (m, 14H, Ar–H, C_5-H), 9.49 (bs, 2H, NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 55.1, 57.3, 118.9, 155.7, 163.6, 170.4, 182.8, 117.2, 119.0, 122.3, 125.5, 130.1, 133.6, 135.4, 137.2, 146.7, 152.8 ppm; IR (KBr): $\bar{\nu}$ = 3276 (NH), 1643 (C=C), 1558 (C=N) cm^{-1}; HRMS: *m/z* = 619.6160 ([M+Na], calcd), 619.6167 (found).

N^2,N^4-Bis(4-phenyl-1H-imidazol-2-ylmethyl)quinazoline-2,4-diamine (**13a**, $C_{28}H_{24}N_8$)
White crystals; yield 0.83 g (71%); m.p.: 200–202 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 4.29 (s, 2H, CH_2), 4.34 (s, 2H, CH_2), 7.11–7.71 (m, 16H, Ar–H, $C_{5'}$-H), 9.18 (bs, 2H, NH), 11.25 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 44.6, 46.2, 127.4, 139.5, 141.9, 161.7, 181.3, 115.6, 116.2, 119.5, 123.0, 126.4, 127.9, 130.7, 133.5, 135.7, 151.9 ppm; IR (KBr): $\bar{\nu}$ = 3354 (NH), 1631 (C=C), 1581 (C=N) cm^{-1}; HRMS: *m/z* = 495.5352 ([M+Na], calcd), 495.5341 (found).

N^2,N^4-Bis[4-(4-methylphenyl)-1H-imidazol-2-ylmethyl]quinazoline-2,4-diamine (**13b**, $C_{30}H_{28}N_8$)
White crystals; yield 0.86 g (69%); m.p.: 179–181 °C; ^{1}H NMR (400 MHz, DMSO-d_6): δ = 2.38 (s, 6H, Ar–CH_3), 4.33 (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 7.19–7.74 (m, 14H, Ar–H, $C_{5'}$-H), 9.22 (bs, 2H, NH), 11.21 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): δ = 23.6, 44.8, 45.9, 128.9, 138.9, 141.5, 160.5, 180.6, 116.1, 119.6, 121.0, 127.8, 130.5, 133.9, 134.2, 137.8, 140.0, 148.5 ppm; IR (KBr): $\bar{\nu}$ = 3254 (NH), 1621 (C=C), 1527 (C=N) cm^{-1}; HRMS: *m/z* = 523.5867 ([M+Na], calcd), 523.5873 (found).

N^2,N^4-Bis[4-(4-chlorophenyl)-1H-imidazol-2-yl-methyl]quinazoline-2,4-diamine (**13c**, $C_{28}H_{22}Cl_2N_8$)
White crystals; yield 0.91 g (68%); m.p.: 214–216 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 4.28$ (s, 2H, CH_2), 4.32 (s, 2H, CH_2), 7.28–7.80 (m, 14H, Ar–H, $C_{5'}$-H), 9.14 (bs, 2H, NH) 11.23 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 44.1$, 46.2, 129.5, 137.2, 140.3, 160.9, 181.0, 116.2, 118.7, 120.5, 125.3, 127.6, 128.9, 132.7, 135.3, 139.4, 152.9 ppm; IR (KBr): $\bar{\nu} = 3249$ (NH), 1632 (C=C), 1539 (C=N) cm^{-1}; HRMS: $m/z = 564.4237$ ([M+Na], calcd), 564.4241 (found).

N^2,N^4-Bis[4-(4-bromophenyl)-1H-imidazol-2-yl-methyl]quinazoline-2,4-diamine (**13d**, $C_{28}H_{22}Br_2N_8$)
White crystals; yield 1.10 g (70%); m.p.: 219–221 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 4.25$ (s, 2H, CH_2), 4.30 (s, 2H, CH_2), 7.26–7.76 (m, 14H, Ar–H, $C_{5'}$-H), 9.13 (bs, 2H, NH) 11.19 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 44.3$, 45.7, 127.2, 138.6, 140.8, 160.1, 180.5, 115.4, 116.9, 119.3, 123.7, 126.6, 129.8, 132.0, 135.5, 139.2, 148.3 ppm; IR (KBr): $\bar{\nu} = 3252$ (NH), 1635 (C=C), 1542 (C=N) cm^{-1}; HRMS: $m/z = 653.3387$ ([M+Na], calcd), 653.3399 (found).

N^2,N^4-Bis[4-[4-(dimethylamino)phenyl]-1H-imidazol-2-yl-methyl]quinazoline-2,4-diamine (**13e**, $C_{32}H_{34}N_{10}$)
White crystals; yield 1.01 g (73%); m.p.: 207–209 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 2.84$ (s, 12H, $N(CH_3)_2$), 4.34 (s, 2H, CH_2), 4.37 (s, 2H, CH_2), 7.35–7.92 (m, 14H, Ar–H, $C_{5'}$-H), 9.11 (bs, 2H, NH), 11.20 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 41.4$, 44.9, 46.5, 128.7, 138.0, 140.9, 161.2, 181.8, 117.3, 118.8, 120.7, 124.6, 125.9, 129.2, 131.8, 137.1, 140.6, 150.7 ppm; IR (KBr): $\bar{\nu} = 3237$ (NH), 1627 (C=C), 1535 (C=N) cm^{-1}; HRMS: $m/z = 581.6691$ ([M+Na], calcd), 581.6683 (found).

N^2,N^4-Bis[4-(4-nitrophenyl)-1H-imidazol-2-yl-methyl]quinazoline-2,4-diamine (**13f**, $C_{28}H_{22}N_{10}O_4$)
White crystals; yield 0.92 g (66%); m.p.: 232–234 °C; ^{1}H NMR (400 MHz, DMSO-d_6): $\delta = 4.35$ (s, 2H, CH_2), 4.38 (s, 2H, CH_2), 7.39–7.81 (m, 14H, Ar–H, $C_{5'}$-H), 9.25 (bs, 2H, NH) 11.27 (bs, 2H, imidazole-NH) ppm; ^{13}C NMR (100 MHz, DMSO-d_6): $\delta = 44.5$, 46.9, 129.3, 139.6, 141.7, 161.8, 181.4, 117.0, 119.5, 121.2, 124.1, 127.8, 133.6, 134.3, 137.0, 140.9, 151.7 ppm; IR (KBr): $\bar{\nu} = 3257$ (NH), 1639 (C=C), 1546 (C=N) cm^{-1}; HRMS: $m/z = 585.5238$ ([M+Na], calcd), 585.5231 (found).

Antimicrobial activity

The compounds **5–7** and **11–13** were dissolved at two concentrations of 50 and 100 μg/cm^3.

Cells

Bacterial strains *Staphylococcus aureus*, *B. subtilis* (Gram-positive bacteria), *Pseudomonas aeruginosa*, *Klebsiella pneumoniae* (Gram-negative bacteria), and fungi *A. niger*, *P. chrysogenum* were obtained from the Department of Microbiology, S.V. University, Tirupati.

Antibacterial and antifungal assays

The in vitro antimicrobial studies were carried out by agar well diffusion method against test organisms [39, 40]. Nutrient broth (NB) plates were swabbed with 24-h old broth culture (100 mm^3) of test bacteria. Using the sterile cork borer, wells (6 mm) were made into each petri plate. The compounds (5 mg/cm^3) were dissolved in DMSO and from this 10 and 20 mm^3 (50 and 100 μg/well) were added into the wells using sterile pipettes. Simultaneously the standard antibiotics, chloramphenicol for antibacterial activity and ketoconazole for antifungal activity were tested as positive control against the pathogens. The samples dissolved in DMSO which showed no zone of inhibition acts as negative control. The plates were incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. After appropriate incubation, the diameter of zone of inhibition of each well was measured. Duplicates were maintained and the average values were calculated for eventual antibacterial activity. Broth dilution test was used to determine minimum inhibitory concentration (MIC) of the above mentioned samples [41, 42]. Freshly prepared nutrient broth was used as diluents. The 24 h old culture of the test bacteria *S. aureus*, *B. subtilis*, *P. aeruginosa*, and *K. pneumoniae* and the test fungi *A. niger* and *P. chrysogenum* were diluted 100 folds in nutrient broth (100 mm^3 bacterial cultures in 10 cm^3 NB). The stock solution of the synthesized compounds was prepared in DMSO by dissolving 5 mg of the compound in 1 cm^3 of DMSO. Increasing concentrations of the test samples (1.25, 2.5, 5, 10, 20, 40 mm^3 of stock solution contains 6.25, 12.5, 25, 50, 100, 200 μg of the compounds) were added to the test tubes containing the bacterial and fungal cultures. All the tubes were incubated at 37 °C for 24 h for bacteria and at 28 °C for 48 h for fungi. The tubes were examined for visible turbidity and using NB as control. Control without test samples and with solvent was assayed simultaneously.

The lowest concentration that inhibited visible growth of the tested organisms was recorded as MIC. To determine the minimum bactericidal concentration (MBC) [43] and minimum fungicidal concentration (MFC) [44] for each set of test tubes in the MIC determination, a loopful of broth was collected from those tubes which did not show any growth and inoculated on sterile nutrient broth (for

bacteria) and PDA (for fungi) by streaking. Plates inoculated with bacteria and fungi were incubated at 37 °C for 24 h and at 28 °C for 48 h, respectively. After incubation, the lowest concentration was noted as MBC (for bacteria) or MFC (for fungi) at which no visible growth was observed.

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