Synthesis and Antimicrobial Activities of Some Novel Substituted 2-Imidazolyl-*N*-(4-oxo-quinazolin-3(4*H*)-yl)-acetamides

Nulgulmnalli Manjunathiah RAGHAVENDRA,*[,a] Parameshwaran THAMPI,[a] Purvarga Mattada GURUBASAVARAJASWAMY,[a] and Dharmarajan SRIRAM[b]

[a] *Medicinal Chemistry Research Laboratory, Acharya and B.M. Reddy College of Pharmacy; Bangalore, Karnataka 560090, India: and* [b] *Medicinal Chemistry Research Laboratory, Pharmacy Group, Birla Institute of Technology and Science; Pilani, Rajasthan 333031, India.* Received July 24, 2007; accepted September 3, 2007

Several substituted-quinazolin-3(4*H*)-ones 8—11ad were synthesized by condensation of 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides with various substituted imidazoles through one pot reaction. Elemental analysis, IR, ^{1}H-NMR and mass spectral data confirmed the structure of the newly synthesized compounds. Synthesized quinazolin-4-one derivatives were investigated for their antitubercular, antibacterial and antifungal activities. Some of the tested compounds showed good antitubercular activity. None of the synthesized compounds showed significant antibacterial and antifungal activity.

Key words quinazolin-4-one; imidazolyl quinazolin-4-one; antitubercular activity; imidazole

Quinazolin-4-one ring system has been consistently rewarded as a promising molecule because of its broad spectrum pharmacological activities like antitubercular,[1)] antibacterial,[2)] antifungal,[3)] anticancer,[4,5)] anti-HIV,[6)] anthelmintic,[7)] anti-inflammatory[8)] and antihypertensive activities.[9)] Imidazoles are one of the oldest and potent heterocyclic compounds having antimicrobial activities.[10,11)] Structure activity relationship studies of quinazolinone ring system revealed in various literatures[12—14)] suggest position 2, 6 and 8 are very much important for structure activity studies and position 3 should be attached to different heterocyclic rings for better chemotherapeutic activity.

As these two heterocycles are present in biologically active compounds, we were interested in preparing compounds containing them. In view of these observations, we report herein the reactions of imidazoles with 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides to give appropriate 2-(1*H*-substituted-imidazol-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8**—**11ad** and their antimicrobial activities.

Chemistry

In Chart 1, *o*-aminobenzoic acid was brominated at 15 °C in presence of glacial acetic acid to form 2-amino-3,5-dibromobenzoic acid **1**. Different anthranilic acids on treatment with benzoyl chloride/acid anhydrides yields substituted-4*H*-3,1-benzoxazin-4-one **2**, **3ab**, which on condensation with hydrazine hydrate gives 3-amino-substituted-quinazolin-4(3*H*)-one **4ab**,[15,16)] **5a**[17)] and **5b**. These 3-amino-quinazolin-4(3*H*)-ones **4**, **5ab** were reacted with chloroacetyl chloride in toluene to form 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **6**, **7ab** (compound **7a** was reported as an intermediate for various quinazolin-4-one derivatives as anthelmintic agents,[7)] which were later treated with imidazole derivatives in presence of anhydrous potassium carbonate to yield 2-(1*H*-substituted-imidazol-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8**—**11ad**. The infrared spectra of the 3-amino-quinazolin-4(3*H*)-ones **4**, **5ab** showed characteristic absorption bands at 3200—3300 cm^{-1}, was attributed to NH_2, which were disappeared by the formation of 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **6**, **7ab**. Similarly the ^{1}H-NMR spectra of 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **6**, **7ab** showed characteristic diastereotopic two doublets at δ 4.1—4.4 due to C=OCH$_2$Cl protons. Presence of singlet at δ 6.6—7.3 due to imidazole protons established that all the 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides had converted into 2-(1*H*-substituted-imidazol-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides and **8**—**11ad**. The ^{1}H-NMR, MS, IR and elemental analysis supported the structure of title compounds.

Antitubercular Activity Compounds were evaluated for their *in vitro* antimycobacterial activity by agar dilution method[18)] against *Mycobacterium tuberculosis* H_{37}Rv and *M. smegmatis* in duplicate. The agar dilution method was performed using Middlebrook 7H10 medium supplemented with Middlebrook OADC medium (Hi-Media). After solidification of the agar, the plates were inoculated with 0.1 ml of 10^{-4} dilutions of a McFarland 1.0 concentration of a suspension of organism. The inoculated plates were then incubated at 37 °C for 4 weeks. The minimum inhibitory concentration (MIC) was considered to be the lowest concentration that completely inhibited growth on agar plates, disregarding a

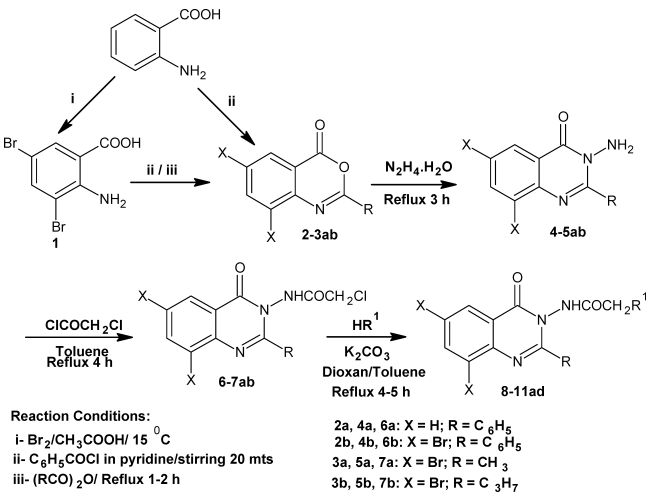


Chart 1. Synthesis of 2-(1*H*-Substituted-imidazol-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8**—**11ad**

* To whom correspondence should be addressed. e-mail: nmraghu76@yahoo.co.in

single colony or a faint haze caused by the inoculums. *In vitro* antimycobacterial activity of tested compounds are reported in Table 1.

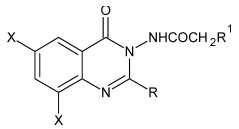
Antibacterial and Antifungal Activity The antibacterial and antifungal activity of title compounds was determined *in vitro* by using paper disc method.[19] The agar media for each microorganism were prepared as per by Institute of Microbial Technology, Chandigarh, India. The zone of inhibition (ZI) in mm was measured. The concentration (100 μg/ml) of test compounds were prepared by dissolving the compounds in dimethyl sulfoxide (DMSO). Under identical conditions, ciprofloxacin and griseofulvin were tested as standard drug (100 μg/ml) for bacteria and fungi respectively. Antibacterial and antifungal activity shown by moderately active compounds towards various bacteria is recorded in Table 2.

Results and Discussion

In vitro antitubercular screening reveals that some of the tested compounds are promising candidates having good activity against *M. tuberculosis* $H_{37}Rv$ and *M. smegmatis*. Compounds **8b**, **9b** and **11c** showed good antitubercular activities comparable to standard antitubercular agents (Table 1). Compound **9b** exhibited the highest degree of antitubercular activity than ciprofloxacin against *M. tuberculosis* $H_{37}Rv$. Rest of the compounds does not show any significant antitubercular activity as compared with standard agents.

The results of the antibacterial and antifungal effect of the

Table 1. *In Vitro* Antimycobacterial Activity of Compounds **8**—**11ad**



Compounds	X	R	R^1	MIC in (μg/ml) *M. tuberculosis*	MIC in (μg/ml) *M. smegmatis*
8a	H	C_6H_5	Imidazolyl	>12.5	50
8b	H	C_6H_5	2-Methyl imidazolyl	1.56	6.25
8c	H	C_6H_5	2-Methyl benzimidazolyl	6.25	25
8d	H	C_6H_5	Benzimidazolyl	12.5	25
9a	Br	C_6H_5	Imidazolyl	>12.5	25
9b	Br	C_6H_5	2-Methyl imidazolyl	0.4	0.78
9c	Br	C_6H_5	2-Methyl benzimidazolyl	>12.5	50
9d	Br	C_6H_5	Benzimidazolyl	12.5	25
10a	Br	CH_3	Imidazolyl	12.5	50
10b	Br	CH_3	2-Methyl imidazolyl	6.25	50
10c	Br	CH_3	2-Methyl benzimidazolyl	6.25	25
10d	Br	CH_3	Benzimidazolyl	12.5	50
11a	Br	C_3H_7	Imidazolyl	>12.5	50
11b	Br	C_3H_7	2-Methyl imidazolyl	6.25	50
11c	Br	C_3H_7	2-Methyl benzimidazolyl	1.56	25
11d	Br	C_3H_7	Benzimidazolyl	6.25	25
Ciprofloxacin				1.56	<0.78
Gatifloxacin				0.39	0.78
Isoniazid				0.05	6.25
Rifampicin				0.2	1.56

Table 2. Antibacterial and Antifungal Activity of Compounds **8**—**11ad**[a]

Compounds[b]	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. oryzae*	*C. albicans*	*C. tropicalis*
8a	—	9±0.00	—	—	—	10±0.00
8b	11.5±0.50[c]	8±0.00	7±0.00	—	—	—
8c	11±0.00	8.5±0.50	8±0.00	—	—	11±0.50
9a	—	8±0.00	—	—	12.5±0.50	—
9b	—	8±1.00	—	—	11.5±0.50	—
9c	9±0.00	11±0.00	10.5±0.50		10±0.00	—
9d	8±0.00	11±0.00	9±0.00	9±0.00	—	—
10a	—	6.5±0.50	8±0.00	—	—	—
10b	12±1.00	9±0.00	—	—	—	
10c	—	8±0.00	—	—	—	—
10d	9±0.00	—	—	—	—	—
11b	8.5±0.50	—	10±0.00	9.5±0.50	—	—
11c	8.5±0.50	—	8.5±0.50	—	—	—
11d	12±0.00	—	9.5±0.50	—	—	—
Standard[d]	42±0.50	43±0.50	41±0.50	33±0.50	34±0.50	31±0.50

a) Zone of inhibition in mm at concentration of 100 μg/ml (inactive, —; mild, <10; moderate, 10—20; good, 20—30; potent, 30—45 mm), all the compounds were inactive against *S. aureus* and *A. awamori*. *b*) Compounds **8d** and **11a** were found to be inactive against all tested microorganisms. *c*) Standard error. *d*) Ciprofloxacin for bacteria and griseofulvin for fungi.

newly synthesized compounds are reported as MIC against *Staphylococcus aureus* (*S. aureus*) (MTCC 3160), *Bacillus subtilis* (*B. subtilis*) (MTCC 441) (gram-positive bacteria), *Pseudomonas aeruginosa* (*P. aeruginosa*) (MTCC 424), *Klebsiella pneumoniae* (*K. pneumoniae*) (MTCC 3384) (gram-negative bacteria) and four fungi *Aspergillus awamori* (*A. awamori*) (MTCC 2879), *Aspergillus oryzae* (*A. oryzae*) (MTCC 1122), *Candida albicans* (*C. albicans*) (MTCC 183) and *Candida tropicalis* (*C. tropicalis*) (MTCC 461). Compounds **8bc**, **10b** and **11d** exhibit moderate activity against *B. subtilis*. Compounds **9ac** were moderately active against *C. albicans* (Table 2); **9c** was found to have similar activity against *P. aeruginosa* and *K. pneumoniae* also. Compounds **8ac**, **9d** and **11b** showed moderate activity against *C. tropicalis*, *P. aeruginosa* and *K. pneumoniae* respectively. Compounds **8ac**, **9ab** and **10c** were mild in activity against *P. aeruginosa*. **8bc**, **9d**, **10a** and **11cd** were mild in activity against *K. pneumoniae*. Compounds **9cd**, **10d** and **11bc** showed mild activity against *B. subtilis*. As noted, against *A. oryzae* compounds **9d** and **11b** exhibit mild activity. However, the activities of the tested compounds are much less than those of standard antifungal and antibacterial agents used.

Structure activity relationship studies of the title compounds for antitubercular activity against *M. tuberculosis* indicates compound **9b** (MIC, 0.4 μg/ml) having phenyl group at position 2 of the quinazolinone ring is more active than propyl derivative compound **11b** (MIC, 6.25 μg/ml) and methyl derivative compound **10b** (MIC, 6.25 μg/ml). Methyl substituted azoles attached to acetamido side chain at position 3 of quinazolinone proves more beneficial than unsubstituted azoles as compound **8b** (MIC, 1.56 μg/ml), **11c** (MIC, 1.56 μg/ml) are more active than compound **8a** (MIC, $>$12.5 μg/ml) and **11a** (MIC, $>$12.5 μg/ml) respectively. Replacement of hydrogen by bromine at position 6 and 8 of the quinazolinone ring as in compound **9b** (MIC, 0.4 μg/ml) favors antitubercular activity than non halogen derivative compound **8b** (MIC, 1.56 μg/ml).

Structured activity relationship studies for antibacterial and antifungal studies reveals that the presence of bromine at position 6 and 8 of the quinazolinone ring favors antifungal activity as compound **9a** (ZI, 12.5 mm) is more active than compound **8a** (ZI, 0 mm) against *C. albicans*; based on the same structural features compound **9c** (ZI, 11 mm) is more active than **8c** (ZI, 8.5 mm) against *P. aeruginosa*. On the other hand, in case of *C. tropicalis* it is the presence of bromine atom at position 6 and 8 of quinazolinone ring decreases activity as compound **9c** (ZI, 0 mm) is inactive compared to moderately active compound **8c** (ZI, 11 mm). As noted, methyl substituted azole moiety of **8b** (ZI, 11.5 mm) increased activity against *B. subtilis* relative to **8a** (ZI, 0 mm) that has unsubstituted azole; similarly compound **10b** (ZI, 12 mm) is more active than compound **10a** (ZI, 0 mm).

In summary, in view of these observations, we conclude that this series could be developed as a novel class of antimycobacterial agents. However, further structural evaluation is required to identify the potent molecule among the series.

Experimental

All the chemicals were purchased from Merck and used without purification. Analytical TLC was performed on Silica Gel F_{254} plates (Merck) with visualization by UV light. Melting points were determined in open capillaries on a Thermonik melting point apparatus, Mumbai, India and are uncorrected. The IR spectra (KBr, γMax, cm^{-1}) were run on Shimadzu-8400 FTIR spectrophotometer. ^{1}H-NMR (δ ppm, $CDCl_3$/DMSO-d_6) spectra were recorded using Brucker WM-400 spectrometer with TMS as internal standard. Mass spectra were recorded on Micromass Q-TOF and Shimadzu LCMS 2010A Mass spectrometer. Elemental analyses were performed on Thermo Finnigan FLASH EA 1122 CHNS Analyzer and were within $\pm$0.4% of theoretical values.

Synthesis of Substituted-4*H*-3,1-benzoxazin-4-one (2, 3)ab These compounds were synthesized by methods reported earlier.[20—22]

General Method for the Synthesis of 2,6,8-Substituted-3-amino-4-oxo-quinazolin-3(4*H*)-one (4, 5ab) Respective benzoxazin-4-ones (**2**, **3ab**) (1.0 mmol) was refluxed with hydrazine hydrate (50 ml) for 3 h with occasional shaking. The reaction mixture was cooled to room temperature. The crystals formed were filtered, washed with water and dried. The products thus formed was recrystallized from ethyl acetate and used in the next step.

3-Amino-2-phenyl-quinazolin-4(3*H*)-one (4a) Yield 40%; mp 172 °C; IR (KBr) ν cm^{-1}: 3307, 3215, 3062, 1662, 1564, 1471, 1338. ^{1}H-NMR (DMSO-d_6) δ: 8.15—8.25 (1H, d, J=7.0 Hz), 7.8—8.1 (3H, m), 7.71—7.73 (1H, d, J=8.0 Hz), 7.55—7.6 (1H, t, J=5.6 Hz), 7.45—7.5 (3H, d, J=6.73 Hz), 5.2 (2H, s).

3-Amino-6,8-dibromo-2-phenyl-quinazolin-4(3*H*)-one (4b) Yield 65%; mp 235 °C; IR (KBr) ν cm^{-1}: 3311, 3274, 3082, 1670, 1568, 694. ^{1}H-NMR (DMSO-d_6) δ: 8.4 (1H, s), 8.2—8.3 (1H, s), 7.8—7.9 (2H, d, J=6.4 Hz), 7.4—7.6 (3H, m), 5.72—5.75 (2H, s).

3-Amino-6,8-dibromo-2-methyl-quinazolin-4(3*H*)-one (5a) Yield 65%; mp 225 °C; IR (KBr) ν cm^{-1}: 3305, 3247, 3076, 2952, 2862, 1664, 1542, 1448, 694. ^{1}H-NMR ($CDCl_3$) δ: 8.4 (1H, s), 8.2—8.3 (1H, s), 5.8—5.9 (2H, s), 2.6 (3H, s).

3-Amino-6,8-dibromo-2-propyl-quinazolin-4(3*H*)-one (5b) Yield 60%; mp 182 °C; IR (KBr) ν cm^{-1}: 3313, 3211, 3086, 2978, 2861, 2817, 1666, 1606, 1589, 792, 692. ^{1}H-NMR (DMSO-d_6) δ: 8.34 (1H, s), 8.1—8.2 (1H, s), 5.8 (2H, s), 2.9—3.1 (4H, m), 1.2—1.4 (3H, t, J=7.3 Hz).

General Method for the Synthesis of 2-Chloro-*N*-(2,6,8-substituted-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (6, 7)ab 2,6,8-Substituted-3-amino-4-oxoquinazolin-3(4*H*)-one (**4**, **5**)**ab** (1.8 mmol) was dissolved in 50 ml of dry toluene and cooled to 15 °C. To this chloroacetyl chloride (2 mmol, 2.3 ml) was added drop wise with stirring. The temperature was brought slowly to room temperature and then refluxed for 4 h. Excess toluene was distilled off; precipitate obtained was filtered, washed several times with dry benzene, dried and recrystallized from aqueous dioxan. The completion of the reaction was monitored on silica gel 60 F_{254} precoated TLC plates by using ethyl acetate, petroleum ether and methanol (1 : 1 : 0.3) as the eluent and observed in UV light.

2-Chloro-*N*-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (6a) Yield 55%; mp 148 °C; IR (KBr) ν cm^{-1}: 3205, 3010, 2935, 1690, 1568, 1475, 1328, 775. ^{1}H-NMR (DMSO-d_6) δ: 11.5 (1H, s), 8.1—8.2 (2H, d, J=6.7 Hz), 7.89—7.90 (1H, t, J=7.0 Hz), 7.75—7.77 (1H, d, J=7.9 Hz), 7.48—7.54 (5H, m), 4.08—4.18 (2H, q, J=13.6 Hz).

2-Chloro-*N*-(6,8-dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (6b) Yield 58%; mp 238 °C; IR (KBr) ν cm^{-1}: 3230, 3070, 2943, 1710, 1542, 1488, 700, 694. ^{1}H-NMR (DMSO-d_6) δ: 11.6—11.8 (1H, s), 8.4—8.5 (1H, s), 8.2—8.3 (1H, s), 7.4—7.7 (5H, m), 4.05—4.20 (2H, q, J=13.7 Hz).

2-Chloro-*N*-(6,8-dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (7a) Yield 60%; mp 188 °C; IR (KBr) ν cm^{-1}: 3188, 3010, 2962, 2856, 1685, 1583, 1438, 756, 663. ^{1}H-NMR ($CDCl_3$) δ: 8.35—8.4 (1H, s), 8.15—8.2 (1H, s), 4.3—4.5 (2H, q, J=13.6 Hz), 2.35—2.4 (3H, s).

2-Chloro-*N*-(6,8-dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-acetamide (7b) Yield 75%; mp 192 °C; IR (KBr) ν cm^{-1}: 3301, 3070, 2939, 1683, 1585, 1442, 788, 756, 696. ^{1}H-NMR ($CDCl_3$) δ: 11.5 (1H, b), 8.45 (1H, s), 8.3 (1H, s), 4.3—4.5 (2H, q, J=13.7 Hz), 2.58—2.88 (4H, m), 1.1—1.3 (3H, t, J=7.2 Hz).

General Method for the Synthesis of 2-(Substituted-imidazol-1-yl)-*N*-(2,6,8-substituted-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (8, 10, 11)ad 2-Chloro-*N*-(2,6,8-substituted-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (**6a**, **7ab**) (0.6 mmol) was dissolved in 50 ml of dry toluene, to this freshly dried anhydrous potassium carbonate (0.65 mmol, 0.9 g) and substituted imidazole (0.67 mmol) were added and refluxed for 4—5 h. Excess toluene was distilled off; precipitate obtained was washed with petroleum ether, hot water, dried and recrystallized from aqueous dioxan. The completion of the reaction was monitored on silica gel 60 F_{254} precoated TLC plates by using ethyl acetate, petroleum ether and methanol (1 : 1 : 0.3) as the eluent and observed in UV light.

2-(1*H*-Imidazol-1-yl)-*N*-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (8a) Yield 35%; mp 248 °C; IR (KBr) ν cm^{-1}: 3422, 3000, 2926, 2856, 1679, 1560, 1467, 1338. ^{1}H-NMR ($CDCl_3$) δ: 11.5 (1H, s), 8.1—8.25 (2H, d, J=7.8 Hz), 7.9—8.0 (1H, t, J=8.8 Hz), 7.7—7.8 (1H, d, J=8.1 Hz), 7.5—7.67 (5H, m), 7.4 (1H, s), 6.85 (1H, s), 6.75 (1H, s), 4.8—4.95 (1H, d, J=16.3 Hz), 4.6—4.75 (1H, d, J=16.3 Hz). MS *m/z*: 345 (M^+). *Anal.* Calcd for $C_{19}H_{15}N_5O_2$: C, 66.08; H, 4.38; N, 20.28. Found: C, 66.37; H, 4.32; N, 20.20.

2-(2-Methyl-1*H*-imidazol-1-yl)-*N*-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (8b) Yield 55%; mp 269 °C; IR (KBr) ν cm^{-1}: 3420, 3010, 2952, 2869, 2848, 1708, 1566, 1471, 1338. ^{1}H-NMR (DMSO-d_6) δ: 11.5 (1H, s), 8.1—8.3 (2H, d, J=7.5 Hz), 7.9—8.0 (1H, t, J=7.1 Hz), 7.7—7.8 (1H, d, J=8.0 Hz), 7.4—7.7 (5H, m), 6.85 (1H, s), 6.65 (1H, s), 4.75—4.85 (1H, d, J=17.0 Hz), 4.5—4.6 (1H, d, J=17.0 Hz), 1.90 (3H, s). MS *m/z*: 360.1 (M^++1). *Anal.* Calcd for $C_{20}H_{17}N_5O_2$: C, 66.84; H, 4.77; N, 19.49. Found: C, 66.55; H, 4.52; N, 19.20.

2-(2-Methyl-1*H*-benzimidazol-1-yl)-*N*-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (8c) Yield 40%; mp 287 °C; IR (KBr) ν cm^{-1}: 3450, 3045, 2972, 2889, 2848, 1722, 1604, 1469, 1346. ^{1}H-NMR (DMSO-d_6) δ: 11.62—11.64 (1H, s), 8.2—8.25 (2H, d, J=6.9 Hz), 7.9—7.95 (1H, t, J=7.1 Hz), 7.5—7.8 (1H, d, J=8.0 Hz), 7.4—7.67 (5H, m), 7.02—7.16 (4H, m), 4.75—4.90 (1H, d, J=17.6 Hz), 5.0—5.15 (1H, d, J=17.6 Hz), 2.25 (3H, s). MS *m/z*: 410.1 (M^++1). *Anal.* Calcd for $C_{24}H_{19}N_5O_2$: C, 70.40; H, 4.68; N, 17.10. Found C, 70.44; H, 4.68; N, 17.09.

2-(1*H*-Benzimidazol-1-yl)-*N*-(4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (8d) Yield 60%; mp 242 °C; IR (KBr) ν cm^{-1}: 3500, 3030, 2849, 1658, 1568, 1469, 1346. ^{1}H-NMR ($CDCl_3$) δ: 11.5—11.6 (1H, s), 8.15—8.25 (1H, d, J=7.8 Hz), 7.9—8.0 (1H, t, J=7.8 Hz), 7.75—7.85 (1H, d, J=8.0 Hz), 7.4—7.7 (10H, m), 4.1—4.2 (2H, dd, J=13.7 Hz). MS *m/z*: 395 (M^+). *Anal.* Calcd for $C_{23}H_{17}N_5O_2$: C, 69.86; H, 4.33; N, 17.71. Found: C, 69.72; H, 4.51; N, 17.62.

***N*-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(1*H*-imidazol-1-yl)-acetamide (10a)** Yield 50%; mp 271 °C; IR (KBr) ν cm^{-1}: 3136, 3029, 2952, 2864, 1716, 1585, 1444, 1340, 694. ^{1}H-NMR ($CDCl_3$) δ: 8.4 (1H, s), 8.2 (1H, s), 7.8 (1H, s), 7.2 (1H, s), 6.9 (1H, s), 5.2 (1H, s), 5.0—5.1 (2H, dd, J=16.8 Hz), 2.4 (3H, s). MS *m/z*: 441.9 (M^++1). *Anal.* Calcd for $C_{14}H_{11}Br_2N_5O_2$: C, 38.12; H, 2.51; N, 15.88. Found: C, 37.9; H, 2.71; N, 15.52.

***N*-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(2-methyl-1*H*-imidazol-1-yl)-acetamide (10b)** Yield 55%; mp 276 °C; IR (KBr) ν cm^{-1}: 3147, 3068, 2941, 2871, 1712, 1541, 1488, 1340, 694. ^{1}H-NMR (DMSO-d_6) δ: 8.4 (1H, s), 8.2 (1H, s), 7.0—7.2 (1H, s), 6.7—6.8 (1H, s), 4.9—5.1 (2H, dd, J=17.0 Hz), 2.4 (3H, s), 2.25 (3H, s). MS *m/z*: 455.9 (M^++1). *Anal.* Calcd for $C_{15}H_{13}Br_2N_5O_2$: C, 39.59; H, 2.88; N, 15.39. Found: C, 39.33; H, 3.13; N, 15.14.

***N*-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(2-methyl-1*H*-benzimidazol-1-yl)-acetamide (10c)** Yield 60%; mp 247 °C; IR (KBr) ν cm^{-1}: 3544, 3070, 2983, 2918, 1716, 1606, 1446, 1311, 692. ^{1}H-NMR (DMSO-d_6) δ: 11.6—11.7 (1H, s), 8.4 (1H, s), 8.2 (1H, s), 7.0—7.6 (4H, m), 5.1—5.4 (2H, dd, J=17.5 Hz), 2.42 (3H, s), 2.58 (3H, s). MS *m/z*: 505 (M^+). *Anal.* Calcd for $C_{19}H_{15}Br_2N_5O_2$: C, 45.17; H, 2.99; N, 13.86. Found: C, 45.28; H, 3.03; N, 13.78.

2-(1*H*-Benzimidazol-1-yl)-*N*-(6,8-dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (10d) Yield 65%; mp 280 °C; IR (KBr) ν cm^{-1}: 3534, 3010, 2963, 2871, 1728, 1585, 1444, 1338, 692. ^{1}H-NMR (DMSO-d_6) δ: 9.9 (1H, s), 8.25 (1H, s), 8.1 (1H, s), 7.6—8.05 (4H, m), 5.35—5.55 (2H, dd, J=5.7 Hz), 2.25 (3H, s). MS *m/z*: 491 (M^+). *Anal.* Calcd for $C_{18}H_{13}Br_2N_5O_2$: C, 44.02; H, 2.67; N, 14.26. Found: C, 44.15; H, 2.78; N, 14.29.

***N*-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-(1*H*-imidazol-1-yl)-acetamide (11a)** Yield 65%; mp 268 °C; IR (KBr) ν cm^{-1}: 3500, 3072, 2985, 2935, 1718, 1608, 1542, 1442, 1363, 788, 696. ^{1}H-NMR ($CDCl_3$) δ: 9.2—9.3 (1H, s), 8.23 (1H, s), 8.09 (1H, s), 7.6—7.8 (3H, s), 4.8—5.1 (2H, s), 2.7—2.9 (4H, m), 1.05—1.35 (3H, t, J=7.1 Hz). MS *m/z*: 470 (M^++1). *Anal.* Calcd for $C_{16}H_{15}Br_2N_5O_2$: C, 40.96; H, 3.22; N, 14.93. Found: C, 40.51; H, 3.07; N, 14.66.

***N*-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-(2-methyl-1*H*-imidazol-1-yl)-acetamide (11b)** Yield 65%; mp 258 °C; IR (KBr) ν cm^{-1}: 3128, 3080, 2983, 2937, 1714, 1585, 1444, 1359, 786, 713. ^{1}H-NMR ($CDCl_3$) δ: 8.23 (1H, s), 8.09 (1H, s), 7.6—7.7 (2H, s), 4.9—5.05 (2H, s), 3.4 (1H, b), 2.54—2.8 (4H, m), 2.4—2.5 (3H, s), 1.15—1.25 (3H, t, J=7.2 Hz). MS *m/z*: 483 (M^+). *Anal.* Calcd for $C_{17}H_{17}Br_2N_5O_2$: C, 42.26; H, 3.55; N, 14.49. Found: C, 42.46; H, 3.42; N, 14.51.

***N*-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-(2-methyl-1*H*-benzimidazol-1-yl)-acetamide (11c)** Yield 60%; mp 249 °C; IR (KBr) ν cm^{-1}: 3128, 3080, 2983, 2937, 2850, 1714, 1585, 1444, 1359, 786, 713. ^{1}H-NMR ($CDCl_3$) δ: 8.35—8.4 (1H, s), 8.20 (1H, s), 7.1—8.1 (4H, m), 5.2—5.3 (2H, q, J=17.3 Hz), 3.4 (1H, b), 2.54—2.8 (4H, m), 2.58—2.6 (3H, s), 1.15—1.25 (3H, t, J=7.2 Hz). MS *m/z*: 533 (M^+). *Anal.* Calcd for $C_{21}H_{19}Br_2N_5O_2$: C, 47.30; H, 3.59; N, 13.13. Found: C, 47.23; H, 3.65; N, 13.15.

2-(1*H*-Benzimidazol-1-yl)-*N*-(6,8-dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-acetamide (11d) Yield 70%; mp 262 °C; IR (KBr) ν cm^{-1}: 3534, 3068, 2983, 2912, 2875, 1722, 1542, 1444, 1359, 745, 692. ^{1}H-NMR (DMSO-d_6) δ: 9.8 (1H, s), 8.24 (1H, s), 7.95—8.15 (5H, m), 7.7 (1H, s), 5.3—5.55 (2H, q, J=16.0 Hz), 2.5—2.8 (4H, m), 1.1—1.2 (3H, t, J=7.4 Hz). MS *m/z*: 519 (M^+). *Anal.* Calcd for $C_{20}H_{17}Br_2N_5O_2$: C, 46.27; H, 3.30; N, 13.49. Found: C, 46.38; H, 3.24; N, 13.36.

General Method for the Synthesis of 2-(Substituted-imidazol-1-yl)-*N*-(2,6,8-substituted-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (9ad) 2-Chloro-*N*-(6,8-dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (**6b**), (0.6 mmol) was dissolved in 50 ml of dry dioxan, to this freshly dried anhydrous potassium carbonate (0.65 mmol, 0.9 g) and different imidazoles (0.67 mmol) were added and refluxed for 4 h. Excess dioxan was distilled off; precipitate obtained was washed with hot water, dried and recrystallized from aqueous dioxan. The completion of the reaction was monitored on silica gel 60 F_{254} precoated TLC plates by using ethyl acetate, petroleum ether and methanol (1 : 1 : 0.3) as the eluent and observed in UV light.

***N*-(6,8-Dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-2-(1*H*-imidazol-1-yl)-acetamide (9a)** Yield 50%; mp 258 °C; IR (KBr) ν cm^{-1}: 3522, 3064, 2954, 2856, 1685, 1539, 1444, 1319, 775, 702. ^{1}H-NMR (DMSO-d_6) δ: 8.8 (1H, s), 8.28 (1H, s), 8.18 (1H, s), 7.6—7.7 (2H, d, J=7.0 Hz), 7.3—7.5 (5H, m), 7.24 (1H, s), 4.5—4.53 (2H, q, J=14.0 Hz). MS *m/z*: 503.9 (M^++1). *Anal.* Calcd for $C_{19}H_{13}Br_2N_5O_2$: C, 45.36; H, 2.60; N, 13.92. Found: C, 45.21; H, 2.80; N, 13.63.

***N*-(6,8-Dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-2-(2-methyl-1*H*-imidazol-1-yl)-acetamide (9b)** Yield 55%; mp 250 °C; IR (KBr) ν cm^{-1}: 3521, 3068, 2920, 2848, 1668, 1558, 1443, 1340, 775, 700. ^{1}H-NMR ($CDCl_3$) δ: 8.3 (1H, s), 8.18 (1H, s), 7.64—7.67 (2H, d, J=7.3 Hz), 7.3—7.55 (5H, m), 4.5—4.8 (2H, q, J=15.6 Hz), 2.12 (3H, s). MS *m/z*: 517 (M^+). *Anal.* Calcd for $C_{20}H_{15}Br_2N_5O_2$: C, 46.45; H, 2.92; N, 13.54. Found: C, 46.32; H, 2.72; N, 13.47.

***N*-(6,8-Dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-2-(2-methyl-1*H*-benzimidazol-1-yl)-acetamide (9c)** Yield 55%; mp 250 °C; IR (KBr) ν cm^{-1}: 3510, 3066, 2954, 2848, 1695, 1589, 1404, 1340, 774, 700. ^{1}H-NMR (DMSO-d_6) δ: 8.3 (1H, s), 8.18 (1H, s), 7.3—7.7 (9H, m), 4.9—5.2 (2H, q, J=15.9 Hz), 2.4 (3H, s). MS *m/z*: 567 (M^+). *Anal.* Calcd for $C_{24}H_{17}Br_2N_5O_2$: C, 50.82; H, 3.02; N, 12.35. Found: C, 50.73; H, 3.13; N, 12.57.

2-(1*H*-Benzimidazol-1-yl)-*N*-(6,8-dibromo-4-oxo-2-phenyl-quinazolin-3(4*H*)-yl)-acetamide (9d) Yield 65%; mp 257 °C; IR (KBr) ν cm^{-1}: 3542, 3066, 2954, 2856, 1722, 1585, 1541, 1340, 775, 700. ^{1}H-NMR (DMSO-d_6) δ: 9.52 (1H, s), 8.25 (1H, s), 8.16 (1H, s), 7.62—7.64 (2H, d, J=8.3 Hz), 7.3—7.7 (8H, m), 4.75—4.95 (2H, q, J=16.1 Hz). MS *m/z*: 553.9 (M^++1). *Anal.* Calcd for $C_{23}H_{15}Br_2N_5O_2$: C, 49.94; H, 2.73; N, 12.66. Found: C, 49.54; H, 2.80; N, 12.33.

Acknowledgements The authors are thankful to Indian Institute of Science, Bangalore, for the spectral analysis. The authors are also thankful to Sri. Premnath Reddy, Chairman, Acharya Institutes and Dr. Divakar Goli, Principal, Acharya and B.M. Reddy College of Pharmacy, Bangalore, for laboratory facilities.

References

1) Trivedi P. B., Undavia N. K., Dave A. M., Bhatt K. N., Desai N. C., *Indian J. Chem.*, **32B**, 497—500 (1993).
2) Gangwal N. A., Kothawade U. R., Galande A. D., Pharande D. S., Dhake A. S., *Indian J. Heterocycl. Chem.*, **10**, 291—294 (2001).
3) Bartroli J., Turmo E., Alguero M., Boncompte E., Vericat M. L., Conte L., Ramis J., Merlos M., Rafanell J. G., Forn J., *J. Med. Chem.*, **41**, 1869—1882 (1998).
4) Jiang J. B., Hesson D. P., Dusak B. A., Dexter D. L., Kang G. J., Hamel E., *J. Med. Chem.*, **33**, 1721—1728 (1990).
5) Xia Y., Yang Z. Y., Hour M. J., Kuo S. C., Xia P., Bastow K. F., Nakanishi Y., Nampoothiri P., Hackl T., Hamel E., Lee K. H., *Bioorg. Med. Chem. Lett.*, **11**, 1193—1196 (2001).
6. Alagarsamy V., Revathi R., Meena S., Ramaseshu K. V., Rajasekaran S., De-Clerco E., *Indian J. Pharm. Sci.*, **4**, 459—462 (2004).
7) Gupta D. P., Ahmad S., Ashok K., Shanker K., *Indian J. Chem.*, **27B**,

1060—1062 (1988).
8) Chao Q., Deng L., Shih H., Leoni L. M., Genini D., Carson D. A., Cottam H. B., *J. Med. Chem.*, **42**, 3860—3873 (1999).
9) Wright W. B., Tomcufcik A. S., Chan P. S., Marsico J. W., Press J. B., *J. Med. Chem.*, **30**, 2277—2283 (1987).
10) Goudgaon N. M., Dhondiba V., Vijayalaxmi A., *Indian J. Heterocycl. Chem.*, **13**, 271—272 (2004).
11) Joaquin V. M., Juan L. R., *Antimicrob. Agents Chemother.*, **39**, 1512—1516 (1995).
12) Hour M. J., Huang L. J., Kuo S. C., Xia Y., Bastow K., Nakanishi Y., Hamel E., Lee K. H., *J. Med. Chem.*, **43**, 4479—4487 (2000).
13) Kumar S., Shrivastava A. K., Sarkar P. C., *Indian J. Heterocycl. Chem.*, **7**, 51—54 (1997).
14) Ghorab M. M., Abdel-Hamide S. G., El-Hakim A. E., *Indian J. Heterocycl. Chem.*, **5**, 115—120 (1995).
15) Alagarsamy V., Meena S., Vijayakumar S., Ramseshu K. V., Revathi R., *Pharmazie*, **58**, 233—236 (2003).
16) Husain M. I., Srivastava V. P., *Indian Drugs*, **21**, 241—244 (1984).
17) Kumar A., Singh S., Saxena A. K., Shanker K., *Indian J. Chem.*, **27B**, 443—447 (1988).
18) Siddiqi S., "Clinical Microbiology Handbook," Vol. I, ASM Press, Washington, DC, 1992.
19) Mathew V., Keshavayya J., Vaidya V. P., *Eur. J. Med. Chem.*, **41**, 1048—1058 (2006).
20) Girija K., Selvam P., Nagarajan R., De-Clerco E., Gopal V., *Indian J. Heterocycl. Chem.*, **14**, 255—256 (2005).
21) Selvam P., Girija K., Nagarajan G., De-Clerco E., *Indian J. Pharm. Sci.*, **67**, 484—487 (2005).
22) El-Naser Ossman A. R., El-Sayed Barakat S., *Arzneim.-Forsch.*, **44**, 915—919 (1994).