Synthesis and Antimicrobial Activity of Some Novel Substituted Piperazinyl-quinazolin-3(4*H*)-ones

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Received 26 July 2007; Accepted 20 September 2007

Abstract: Several substituted-quinazolin-3(4*H*)-ones were synthesized by condensation of 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides with various substituted piperazines through single step reaction. Elemental analysis, IR, ¹HNMR and mass spectral data confirmed the structure of the newly synthesized compounds. Synthesized quinazolin-4-one derivatives were investigated for their antibacterial and antifungal activities.

Keywords: Quinazolin-4-ones, Piperazinyl quinazolin-4-ones, Antibacterial activity, Antifungal activity.

Introduction

Pharmacologically, quinazolin-4-ones are among the most important classes of heterocyclic compounds. These compounds possess versatile type of biological activities; some of these are well known for their anticancer¹⁻², antitubercular³, antibacterial⁴, antifungal⁵, anti-HIV⁶, anthelmintic⁷, anti-inflammatory⁸ and antihypertensive activities⁹. Piperazines are found to be antimicrobial agents¹⁰⁻¹¹. Structure activity relationship studies of quinazolinone ring system revealed in various literatures¹²⁻¹⁴ 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.

Keeping in view the potential biological activities of quinazolin-4-ones and piperazines, it was perceived that if both the heterocyclic moieties are synergized in a single nucleus, the new compounds obtained were likely to possess significant antimicrobial activities. In this quest, novel 2-(1*H*-substituted-piperazin-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8-30** were synthesized by reacting different piperazines with 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides and subjected to antimicrobial activity.

In Scheme-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 **4,5ab**. 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**, which were later treated with piperazine derivatives in presence of anhydrous potassium carbonate to yield 2-(1*H*-substituted-piperazin-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8-30**. 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 NH₂, which were disappeared by the formation of 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **6,7ab**. Similarly the ¹HNMR 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=OCH₂Cl protons. Presence of signals at δ 2.2-2.4 due to piperazine protons established that all the 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides had converted into 2-(1*H*-substituted-piperazin-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8-30**. The ¹HNMR, mass spectra, IR and elemental analysis supported the structure of title compounds. The synthesis of compounds **8-30** is mentioned in Scheme 1 and their physico-chemical data are given in Table 1.

Scheme 1

Table 1. Physico-chemical data of synthesized compounds (**8-30**)

Compounds	X	R	R ¹	Yield, %	M.P °C
8	H	C ₆ H ₅	piperazin-1-yl	60	250
9	H	C ₆ H ₅	4-methylpiperazin-1-yl	45	210
10	H	C ₆ H ₅	4-ethylpiperazin-1-yl	48	125
11	H	C ₆ H ₅	4-phenylpiperazin-1-yl	50	112
12	H	C ₆ H ₅	4-(4-fluorophenyl)piperazin-1-yl	38	128
13	H	C ₆ H ₅	4-(2-fluorophenyl)piperazin-1-yl	40	200
14	Br	C ₆ H ₅	piperazin-1-yl	65	285
15	Br	C ₆ H ₅	4-methylpiperazin-1-yl	55	209
16	Br	C ₆ H ₅	4-ethylpiperazin-1-yl	50	189
17	Br	C ₆ H ₅	4-phenylpiperazin-1-yl	50	149
18	Br	C ₆ H ₅	4-(4-fluorophenyl)piperazin-1-yl	45	205
19	Br	C ₆ H ₅	4-(2-fluorophenyl)piperazin-1-yl	47	125
20	Br	CH ₃	piperazin-1-yl	68	250
21	Br	CH ₃	4-methylpiperazin-1-yl	45	230
22	Br	CH ₃	4-ethylpiperazin-1-yl	54	160
23	Br	CH ₃	4-(4-fluorophenyl)piperazin-1-yl	52	191
24	Br	CH ₃	4-(2-fluorophenyl)piperazin-1-yl	48	126
25	Br	C ₃ H ₇	piperazin-1-yl	69	235
26	Br	C ₃ H ₇	4-methylpiperazin-1-yl	57	160
27	Br	C ₃ H ₇	4-ethylpiperazin-1-yl	54	120
28	Br	C ₃ H ₇	4-phenylpiperazin-1-yl	49	227
29	Br	C ₃ H ₇	4-(4-fluorophenyl)piperazin-1-yl	55	123
30	Br	C ₃ H ₇	4-(2-fluorophenyl)piperazin-1-yl	56	179

Experimental

Thin layer chromatography was used to reach the completion of the reaction and purity of the compounds synthesized. Melting points were taken in open glass capillary tubes by using Thermanik melting point apparatus and were uncorrected. IR spectra in KBr were recorded on a Shimadzu-8400 FTIR spectrophotometer. ¹HNMR spectra were recorded on Bruker spectrophotometer (400 MHz) in DMSO-d₆/CDCl₃ using TMS as an internal standard (chemical shifts are expressed in δ, ppm), mass spectra were recorded in Shimadzu QP 5050A Mass spectrometer and micro analysis were recorded on Thermo Finnigan FLASH EA 1122 CHNS Analyzer.

Synthesis of substituted-4H-3,1-benzoxazin-4-one (2,3)ab

These compounds were synthesized by methods reported earlier¹⁵⁻¹⁸

General procedure for the synthesis of 2, 6, 8-substituted-3-amino-4-oxoquinazolin-3(4H)-one (4,5)ab

Respective benzoxazin-4-ones (**2,3)ab** (0.01 M) 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 were recrystallized from ethyl acetate and used in the next step.

3-Amino-2-phenyl-quinazolin-4(3H)-one (4a)

Yield 40%; mp 172 °C; IR (KBr) ν (cm⁻¹): 3307, 3215 (N-H), 3062 (ArC-H), 1662 (C=O), 1564, 1471 (ArC=C), 1338 (C-N); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.15–8.25 (d, 1H, J=7.0Hz, ArH), 7.8–8.1 (m, 3H, ArH), 7.71–7.73 (d, 1H, J=8.0Hz, ArH), 7.55–7.6 (t, 1H, J=5.6Hz, ArH), 7.45–7.5 (d, 3H, J=6.73Hz, ArH), 5.2 (s, 2H, NH₂).

3-Amino-6,8-dibromo-2-phenyl-quinazolin-4(3H)-one (4b)

Yield 65%; mp 235 °C; IR (KBr) ν (cm⁻¹): 3311, 3274 (N-H), 3082 (ArC-H), 1670 (C=O), 1568 (ArC=C), 694 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.4 (s, 1H, ArH), 8.2–8.3 (s, 1H, ArH), 7.8–7.9 (d, 2H, J=6.4Hz, ArH), 7.4–7.6 (m, 3H, ArH), 5.72–5.75 (s, 2H, NH₂).

3-Amino-6,8-dibromo-2-methyl-quinazolin-4(3H)-one (5a)

Yield 65%; mp 225 °C; IR (KBr) ν (cm⁻¹): 3305, 3247 (N-H), 3076 (ArC-H), 2952, 2862 (CH₃), 1664 (C=O), 1542, 1448 (ArC=C), 694 (C-Br); ¹HNMR (400MHz, CDCl₃): δ 8.4 (s, 1H, ArH), 8.2–8.3 (s, 1H, ArH), 5.8–5.9 (s, 2H, NH₂), 2.6 (s, 3H, CH₃).

3-Amino-6,8-dibromo-2-propyl-quinazolin-4(3H)-one (5b)

Yield 60%; mp 182 °C; IR (KBr) ν (cm⁻¹): 3313, 3211 (N-H), 3086 (ArC-H), 2978, 2861 (CH₃), 2817 (CH₂), 1666 (C=O), 1606, 1589 (ArC=C), 792 (CH₂), 692 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.34 (s, 1H, ArH), 8.1–8.2 (s, 1H, ArH), 5.8 (s, 2H, NH₂), 2.9–3.1 (m, 4H, CH₂), 1.2–1.4 (t, 3H, J=7.3Hz, CH₃).

General method for the synthesis of 2-chloro-N-(2, 6, 8-substituted-4-oxo-quinazolin-3(4H)-yl)-acetamide (6,7)ab

2, 6, 8-Substituted-3-amino-4-oxo-quinazolin-3(4H)-one (**4,5**)ab (0.018 M) was dissolved in 50 mL of dry toluene and cooled to 15 °C. To this chloroacetyl chloride (2.3 mL, 0.020 M) 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 F₂₅₄ 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(4H)-yl)-acetamide (6a)

Yield 55%; mp 148 °C; IR (KBr) ν (cm⁻¹): 3205 (N-H), 3010 (ArC-H), 2935 (CH₂), 1690 (C=O), 1568, 1475 (ArC=C), 1328 (C-N), 775 (C-Cl); ¹HNMR (400MHz, DMSO-*d*₆): δ 11.5 (s, 1H, Enol), 8.1–8.2 (d, 2H, J=6.7Hz, ArH), 7.89–7.90 (t, 1H, J=7.0Hz, ArH), 7.75–7.77 (d, 1H, J=7.9Hz, ArH), 7.48–7.54 (m, 5H, ArH), 4.08–4.18 (dd, 2H, J=13.6Hz, diastereotopic-CH₂).

2-Chloro-N-(6,8-dibromo-4-oxo-2-phenyl-quinazolin-3(4H)-yl)-acetamide (6b)

Yield 58%; mp 238 °C; IR (KBr) ν (cm⁻¹): 3230 (N-H), 3070 (ArC-H), 2943 (CH₂), 1710 (C=O), 1542, 1488 (ArC=C), 700 (C-Cl), 694 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 11.6–11.8 (s, 1H, Enol), 8.4–8.5 (s, 1H, ArH), 8.2–8.3 (s, 1H, ArH), 7.4–7.7 (m, 5H, ArH), 4.05–4.20 (dd, 2H, J=13.7Hz, diastereotopic-CH₂).

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 (N-H), 3010 (ArC-H), 2962, 2856 (CH₃), 1685 (C=O), 1583, 1438 (ArC=C), 756 (C-Cl), 663 (C-Br); ¹HNMR (400MHz, CDCl₃): δ 8.35-8.4 (s, 1H, ArH), 8.15-8.2 (s, 1H, ArH), 4.3-4.5 (dd, 2H, J=13.6Hz, diastereotopic-CH₂), 2.35-2.4 (s, 3H, CH₃).

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 (N-H), 3070 (ArC-H), 2939 (CH₃), 1683 (C=O), 1585, 1442 (ArC=C), 788 (CH₂), 756 (C-Cl), 696 (C-Br); ¹HNMR (400MHz, CDCl₃): δ 11.5 (b, 1H, Enol), 8.45 (s, 1H, ArH), 8.3 (s, 1H, ArH), 4.3-4.5 (dd, 2H, J=13.7Hz, diastereotopic-CH₂), 2.58-2.88 (m, 4H, CH₂), 1.1-1.3 (t, 3H, J=7.2Hz, CH₃).

General method for the synthesis of 2-(substituted-piperazin-1-yl)-*N*-(2,6,8-substituted-4-oxo-quinazolin-3(4*H*)-yl)-acetamide (8-13, 20-30)

2-Chloro-*N*-(2, 6, 8-substituted-4-oxoquinazolin-3(4*H*)-yl)-acetamide (**6a,7ab**) (0.006 M) was dissolved in 50 mL of dry toluene, to this freshly dried anhydrous potassium carbonate (0.9 g, 0.0065 M) and substituted piperazine (0.0067 M) 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 F₂₅₄ precoated TLC plates by using ethyl acetate, petroleum ether and methanol (1:1:0.3) as the eluent and observed in UV light.

***N*-(4-Oxo-2-phenyl-quinazolin-3(4*H*)-yl)-2-piperazin-1-yl-acetamide (8)**

IR (KBr) ν (cm⁻¹): 3180 (N-H), 3020 (ArC-H), 2930, 2829 (CH₂), 1710 (C=O), 1568, 1440 (ArC=C); ¹HNMR (400MHz, DMSO-*d*₆): δ 10.9 (s, 1H, Enol), 8.15-8.25 (d, 1H, J=7.8Hz, ArH), 7.9-7.95 (t, 1H, J=7.0 Hz, ArH), 7.75-7.8 (d, 1H, J=8.0Hz, ArH), 7.45-8.25 (m, 6H, ArH), 2.8-2.9 (d, 1H, J=15.4Hz, diastereotopic-CH₂), 3.05-3.15 (d, 1H, J=15.4Hz, diastereotopic-CH₂), 2.3 (s, 4H, Piperazine), 2.1 (s, 4H, Piperazine).

***N*-(2-Phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(4-methylpiperazin-1-yl)-acetamide (9)**

IR (KBr) ν (cm⁻¹): 3141 (N-H), 3060 (ArC-H), 2937, 2808 (CH₂), 1712 (C=O), 1593, 1469 (ArC=C); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 7.8-8.25 (m, 3H, ArH), 7.72-7.74 (d, 1H, J=7.9Hz, ArH), 7.50-7.65 (m, 5H, ArH), 2.8-2.9 (d, 1H, J=15.4Hz, diastereotopic-CH₂), 3.0-3.2 (d, 1H, J=15.4Hz, diastereotopic-CH₂), 2.2 (s, 4H, Piperazine), 2.1 (s, 4H, Piperazine), 1.7 (s, 3H, CH₃).

***N*-(2-Phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(4-ethylpiperazin-1-yl)-acetamide (10)**

IR (KBr) ν (cm⁻¹): 3142 (N-H), 3060 (ArC-H), 2937, 2810 (CH₂), 1710 (C=O), 1593, 1469 (ArC=C); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 7.5-8.25 (m, 9H, ArH), 2.8-2.9 (d, 1H, J=15.3Hz, diastereotopic-CH₂), 3.0-3.2 (d, 1H, J=15.3Hz, diastereotopic-CH₂), 2.2-2.3 (s, 6H, Piperazine + CH₂), 2.1 (s, 4H, Piperazine), 1.9 (s, 3H, CH₃).

***N*-(2-Phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(4-phenylpiperazin-1-yl)-acetamide (11)**

IR (KBr) ν (cm⁻¹): 3487 (N-H), 3020 (ArC-H), 2930, 2829 (CH₂), 1710 (C=O), 1568, 1440 (ArC=C); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.18-8.25 (d, 1H,

J=7.8Hz, ArH), 7.9-8.0 (t, 2H, J=7.0Hz, ArH), 7.4-7.8 (m, 6H, ArH), 6.9-7.3 (m, 4H, ArH), 6.71-6.73 (t, 1H, J=7.1Hz, ArH), 3.1-3.2 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.9-3.0 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.4-2.6 (m, 4H, Piperazine), 2.2-2.3 (m, 4H, Piperazine).

N-(2-Phenyl-4-oxo-quinazolin-3(4H)-yl)-2-[4-(4-fluorophenyl)piperazin-1-yl]-acetamide (**12**)

IR (KBr) ν (cm⁻¹): 3489 (N-H), 2920, 2818 (CH₂), 1683 (C=O), 1508, 1447 (ArC=C), 1233 (C-F); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.15-8.25 (d, 1H, J=7.1Hz, ArH), 7.9-8.0 (t, 1H, J=8.2Hz, ArH), 7.75-7.8 (d, 1H, J=8.0Hz, ArH), 7.4-7.8 (m, 7H, ArH), 6.9-7.1 (m, 5H, ArH), 3.1-3.2 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.9-3.0 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.4-2.6 (m, 4H, Piperazine), 2.2-2.3 (m, 4H, Piperazine).

N-(2-Phenyl-4-oxo-quinazolin-3(4H)-yl)-2-[4-(2-fluorophenyl)piperazin-1-yl]-acetamide (**13**)

IR (KBr) ν (cm⁻¹): 3489 (N-H), 2920, 2818 (CH₂), 1683 (C=O), 1508, 1447 (ArC=C), 1233 (C-F); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.1-8.2 (d, 1H, J=7.6Hz, ArH), 7.88-7.93 (t, 1H, J=7.3Hz, ArH), 7.7-7.8 (d, 1H, J=8.0Hz, ArH), 7.4-7.7 (m, 7H, ArH), 6.9-7.2 (m, 4H, ArH), 3.0-3.1 (d, 1H, J=14.8Hz, diastereotopic-CH₂), 2.8-2.9 (d, 1H, J=14.8Hz, diastereotopic-CH₂), 2.4-2.6 (m, 4H, Piperazine), 2.2-2.3 (m, 4H, Piperazine).

N-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4H)-yl)-2-piperazin-1-yl-acetamide (**20**)

IR (KBr) ν (cm⁻¹): 3282 (N-H), 3030 (ArC-H), 2932, 2844 (CH₂), 1728 (C=O), 1604, 1444 (ArC=C), 684 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 10.9 (br, 1H, Enol), 8.4 (s, 1H, ArH), 8.2 (s, 1H, ArH), 3.6 (s, 1H, NH), 3.3-3.4 (d, 1H, J=15.7Hz, diastereotopic-CH₂), 3.1-3.2 (d, 1H, J=15.7Hz, diastereotopic-CH₂), 2.8 (br, 4H, Piperazine), 2.6-2.7 (br, 4H, Piperazine), 2.4 (s, 3H, CH₃).

N-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4H)-yl)-2-(4-methylpiperazin-1-yl)-acetamide (**21**)

IR (KBr) ν (cm⁻¹): 3269 (N-H), 3030 (ArC-H), 2968, 2917 (CH₂), 1733 (C=O), 1602, 1465 (ArC=C), 680 (C-Br); ¹HNMR (400MHz, CDCl₃): δ 8.3-8.35 (s, 1H, ArH), 8.15 (s, 1H, ArH), 3.3-3.4 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 3.1-3.2 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.6-2.5 (s, 4H, Piperazine), 2.1-2.2 (s, 4H, Piperazine), 1.25 (s, 3H, CH₃), 0.9 (s, 3H, CH₃).

N-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4H)-yl)-2-(4-ethylpiperazin-1-yl)-acetamide (**22**)

IR (KBr) ν (cm⁻¹): 3270 (N-H), 3072 (ArC-H), 2964, 2818 (CH₂), 1697 (C=O), 1598, 1440 (ArC=C); ¹HNMR (400MHz, CDCl₃): δ 8.2-8.3 (s, 1H, ArH), 8.15 (s, 1H, ArH), 3.4-3.6 (d, 1H, J=15.8Hz, diastereotopic-CH₂), 3.2-3.4 (d, 1H, J=15.8Hz, diastereotopic-CH₂), 3.0-3.2 (br, 4H, Piperazine), 2.8 (br, 4H, Piperazine), 2.8 (br, 2H, CH₂), 2.7 (s, 3H, CH₃), 1.1-1.2 (t, 1H, J=6.8Hz, CH₃).

N-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-2-[4-(4-fluorophenyl)-piperazin-1-yl]-acetamide (**23**)

IR (KBr) ν (cm⁻¹): 3507 (N-H), 3068 (ArC-H), 2929, 2820 (CH₂), 1695 (C=O), 1597, 1443 (ArC=C), 1240 (C-F), 672 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.4 (s, 1H, ArH), 8.15 (s, 1H, ArH), 6.9-7.1 (m, 4H, ArH), 3.3-3.4 (d, 1H, J=15.2Hz, diastereotopic-CH₂), 3.1-3.2 (d, 1H, J=15.3Hz, diastereotopic-CH₂), 2.75-2.85 (m, 4H, Piperazine), 2.65-2.75 (m, 4H, Piperazine), 2.45 (s, 3H, CH₃).

N-(6,8-Dibromo-2-methyl-4-oxo-quinazolin-3(4*H*)-yl)-2-[4-(2-fluorophenyl)-piperazin-1-yl]-acetamide (**24**)

IR (KBr) ν (cm⁻¹): 3510 (N-H), 3030 (ArC-H), 2929, 2820 (CH₂), 1695 (C=O), 1597, 1443 (ArC=C), 1240 (C-F), 700 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (br, 1H, Enol), 8.45 (s, 1H, ArH), 8.23 (s, 1H, ArH), 6.9-7.2 (m, 4H, ArH), 3.4-3.6 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 3.2-3.3 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.8-2.9 (br, 4H, Piperazine), 2.6-2.8 (br, 4H, Piperazine), 2.43 (s, 3H, CH₃).

N-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-piperazin-1-yl-acetamide (**25**)

IR (KBr) ν (cm⁻¹): 3244 (N-H), 3030 (ArC-H), 2945, 2835 (CH₂), 1731 (C=O), 1606, 1444 (ArC=C), 675 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (br, 1H, Enol), 8.4 (s, 1H, ArH), 8.2 (s, 1H, ArH), 3.6 (s, 1H, NH), 3.4-3.5 (d, 1H, J=15.8Hz, diastereotopic-CH₂), 3.1-3.2 (d, 1H, J=15.8Hz, diastereotopic-CH₂), 2.7-2.9 (m, 6H, Piperazine + CH₂), 2.6-2.7 (br, 6H, Piperazine + CH₂), 1.2-1.3 (t, 3H, J=7.2Hz, CH₃).

N-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-(4-methylpiperazin-1-yl)-acetamide (**26**)

IR (KBr) ν (cm⁻¹): 3298 (N-H), 3030 (ArC-H), 2937, 2819 (CH₂), 1720 (C=O), 1600, 1469 (ArC=C), 684 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 10.9 (br, 1H, Enol), 8.4-8.5 (s, 1H, ArH), 8.2 (s, 1H, ArH), 3.4-3.5 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 3.1-3.2 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.7-2.8 (m, 2H, CH₂), 2.6-2.7 (m, 2H, CH₂), 2.4-2.6 (br, 4H, Piperazine), 2.3-2.4 (br, 4H, Piperazine), 1.2-1.3 (t, 3H, J=7.3Hz, CH₃); MS *m/z*: 501 (M)⁺; Calcd. (%) for C₁₈H₂₃Br₂N₅O₂: C, 43.13; H, 4.63; N, 13.97; Found: C, 43.48; H, 4.32; N, 13.73.

N-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-(4-ethylpiperazin-1-yl)-acetamide (**27**)

IR (KBr) ν (cm⁻¹): 3420 (N-H), 2922 (CH₂), 1688 (C=O), 1605, 1443 (ArC=C), 694 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.4 (s, 1H, ArH), 8.2 (s, 1H, ArH), 3.1-3.2 (d, 2H, J=15.7Hz, diastereotopic-CH₂), 2.7-2.8 (m, 6H, Piperazine + CH₂), 2.6-2.7 (m, 6H, Piperazine + CH₂), 2.3 (t, 3H, J=7.1Hz, CH₃), 1.2-1.25 (t, 3H, J=7.0Hz, CH₃); MS *m/z*: 515 (M)⁺; Calcd. (%) for C₁₉H₂₅Br₂N₅O₂: C, 44.29; H, 4.89; N, 13.59; Found: C, 44.37; H, 4.56; N, 13.26.

N-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4*H*)-yl)-2-(4-phenylpiperazin-1-yl)-acetamide (**28**)

IR (KBr) ν (cm⁻¹): 3440 (N-H), 2921, 2830 (CH₂), 1674 (C=O), 1586, 1445 (ArC=C), 685 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.4 (s, 1H, ArH), 8.2 (s, 1H, ArH), 6.8-7.4 (m, 5H,

ArH), 3.0-3.25 (m, 2H, diastereotopic-CH₂), 2.5-3.0 (m, 12H, Piperazine + CH₂), 1.25 (t, 3H, J=7.0Hz, CH₃).

N-(6,8-dibromo-4-oxo-2-propyl-quinazolin-3(4H)-yl)-2-[4-(4-fluorophenyl)-piperazin-1-yl]-acetamide (**29**)

IR (KBr) ν (cm⁻¹): 3510 (N-H), 3045 (ArC-H), 2935, 2820 (CH₂), 1695 (C=O), 1597, 1444 (ArC=C), 1240 (C-F), 672 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 10.9 (s, 1H, Enol), 8.4 (s, 1H, ArH), 8.2 (s, 1H, ArH), 6.9-7.1 (m, 4H, ArH), 3.4-3.5 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 3.0-3.2 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.7-2.9 (m, 6H, Piperazine + CH₂), 2.6-2.7 (m, 6H, Piperazine + CH₂), 1.2-1.3 (t, 3H, J=7.3Hz, CH₃).

N-(6,8-Dibromo-4-oxo-2-propyl-quinazolin-3(4H)-yl)-2-[4-(2-fluorophenyl)-piperazin-1-yl]-acetamide (**30**)

IR (KBr) ν (cm⁻¹): 3510 (N-H), 3045 (ArC-H), 2935, 2820 (CH₂), 1695 (C=O), 1597, 1444 (ArC=C), 1240 (C-F), 672 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 10.9 (s, 1H, Enol), 8.4 (s, 1H, ArH), 8.2 (s, 1H, ArH), 6.9-7.2 (m, 4H, ArH), 3.4-3.5 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 3.2-3.3 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.8-3.0 (m, 6H, Piperazine + CH₂), 2.6-2.7 (m, 6H, Piperazine + CH₂), 1.25 (t, 3H, J=7.2Hz, CH₃).

General method for the synthesis of 2-(substituted-imidazol-1-yl)-N-(2,6,8-substituted-4-oxo-quinazolin-3(4H)-yl)-acetamide (**14-19**)

2-Chloro-*N*-(6,8-dibromo-4-oxo-2-phenyl-quinazolin-3(4H)-yl)-acetamide(**3b**), 0.006 M) was dissolved in 50 mL of dry dioxan, to this freshly dried anhydrous potassium carbonate (0.9 g, 0.0065 M) and different piperazines (0.0067 M) 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 F₂₅₄ 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(4H)-yl)-2-piperazin-1-yl-acetamide (**14**)

IR (KBr) ν (cm⁻¹): 3480 (N-H), 3062 (ArC-H), 2943, 2819 (CH₂), 1697 (C=O), 1589, 1448 (ArC=C), 700 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.5 (s, 1H, ArH), 8.2 (s, 1H, ArH), 7.4-7.7 (m, 5H, ArH), 3.0-3.1 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.8-2.9 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.2-2.3 (br, 4H, Piperazine), 2.0-2.1 (br, 4H, Piperazine); MS *m/z*: 521 (M)⁺; Calcd. (%) for C₂₀H₁₉Br₂N₅O₂: C, 46.09; H, 3.67; N, 13.44; Found: C, 46.35; H, 3.42; N, 13.37.

N-(6,8-Dibromo-2-phenyl-4-oxo-quinazolin-3(4H)-yl)-2-(4-methylpiperazin-1-yl)-acetamide (**15**)

IR (KBr) ν (cm⁻¹): 3294(N-H), 3030 (ArC-H), 2945, 2839 (CH₂), 1737 (C=O), 1587, 1444 (ArC=C); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (br, 1H, Enol), 8.45-8.55 (s, 1H, ArH), 8.25-8.30 (s, 1H, ArH), 7.4-7.7 (m, 5H, ArH), 3.0-3.1 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.8-2.9 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.2-2.4 (br, 4H, Piperazine), 2.14 (s, 3H, CH₃), 2.0-2.1 (m, 4H, Piperazine).

N-(6,8-Dibromo-2-phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(4-ethylpiperazin-1-yl)-acetamide (**16**)

IR (KBr) ν (cm⁻¹): 3431 (N-H), 3010 (ArC-H), 2948, 2812 (CH₂), 1697 (C=O), 1593, 1444 (ArC=C); ¹HNMR (400MHz, DMSO-*d*₆): δ 8.45-8.55 (s, 1H, ArH), 8.25 (s, 1H, ArH), 7.45-7.7 (m, 7H, ArH), 3.0-3.1 (d, 1H, J=15.7Hz, diastereotopic-CH₂), 2.8-2.9 (d, 1H, J=15.7Hz, diastereotopic-CH₂), 2.2-2.3 (m, 6H, Piperazine + CH₂), 2.0-2.1 (m, 4H, Piperazine), 0.9-1.0 (t, 3H, J=7.1Hz, CH₃); MS *m/z*: 549 (M)⁺; Calcd. (%) for C₂₂H₂₃Br₂N₅O₂: C, 48.11; H, 4.22; N, 12.75; Found: C, 48.45; H, 4.35; N, 12.53.

N-(6,8-Dibromo-2-phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-(4-phenylpiperazin-1-yl)-acetamide (**17**)

IR (KBr) ν (cm⁻¹): 3245 (N-H), 2919, 2842 (CH₂), 1687 (C=O), 1585, 1456 (ArC=C), 700 (C-Br); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.5 (s, 1H, ArH), 8.3 (s, 1H, ArH), 7.5-7.7 (m, 5H, ArH), 6.7-7.2 (m, 5H, ArH), 3.2-3.25 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 3.15-3.25 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.93-2.98 (br, 4H, Piperazine), 2.2 (br, 4H, Piperazine).

N-(6,8-Dibromo-2-phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-[4-(4-fluorophenyl)-piperazin-1-yl]-acetamide (**18**)

IR (KBr) ν (cm⁻¹): 3206 (N-H), 3068 (ArC-H), 2948, 2825 (CH₂), 1691 (C=O), 1580, 1453 (ArC=C), 1240 (C-F); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.5 (s, 1H, ArH), 8.3 (s, 1H, ArH), 7.5-7.7 (m, 5H, ArH), 6.9-7.1 (m, 5H, ArH), 3.18-3.22 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.93-2.97 (d, 1H, J=15.6Hz, diastereotopic-CH₂), 2.4-2.5 (br, 4H, Piperazine), 2.2-2.3 (br, 4H, Piperazine).

N-(6,8-Dibromo-2-phenyl-4-oxo-quinazolin-3(4*H*)-yl)-2-[4-(2-fluorophenyl)-piperazin-1-yl]-acetamide (**19**)

IR (KBr) ν (cm⁻¹): 3206 (N-H), 3068 (ArC-H), 2948, 2825 (CH₂), 1691 (C=O), 1580, 1453 (ArC=C), 1240 (C-F); ¹HNMR (400MHz, DMSO-*d*₆): δ 11 (s, 1H, Enol), 8.5 (s, 1H, ArH), 8.3 (s, 1H, ArH), 7.5-7.7 (m, 5H, ArH), 6.9-7.2 (m, 5H, ArH), 3.1-3.2 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.9-3.0 (d, 1H, J=15.5Hz, diastereotopic-CH₂), 2.5 (br, 4H, Piperazine), 2.4 (br, 4H, Piperazine).

Antibacterial and antifungal activities

The antimicrobial activity of title compounds was determined in vitro by using paper disc method¹⁹ against variety of pathogenic bacteria like *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 fungi *Aspergillus awamori* (*A. awamori*) (MTCC 2879), *Aspergillus oryzae* (*A. oryzae*) (MTCC 1122), *Candida albicans* (*C. albicans*) (MTCC 183), *Candida tropicalis* (*C. tropicalis*) (MTCC 461). The agar media for each microorganism were prepared as per by Institute of Microbial Technology, Chandigarh, India. The zone of inhibition in mm was measured. Concentration of 100 μ g/mL of test compounds were prepared by dissolving the compounds in dimethyl sulfoxide (DMSO). The standard drugs used were ciprofloxacin and griseofulvin. Antimicrobial activity of tested compounds towards various bacteria and fungi is recorded in Table 2.

Table 2. Antimicrobial activity of compounds **8-30**[©]

Compound	<i>S. aureus</i>	<i>B. subtilis</i>	<i>P. aeruginosa</i>	<i>K. pneumoniae</i>	<i>A. awamori</i>	<i>A. oryzae</i>	<i>C. tropicalis</i>
8	—	—	+	—	—	—	—
9	—	—	+	+	—	—	—
10	—	—	+	—	—	—	—
11	—	—	—	—	—	++	+
12	—	—	—	—	—	++	+
13	—	—	+	—	—	++	—
14	—	—	—	—	++	++	—
15	—	—	+	—	—	—	—
16	—	+	—	—	—	++	++
17	—	+	—	—	—	++	++
18	—	—	++	—	—	++	++
19	—	—	++	—	—	++	++
20	—	—	—	—	—	+	—
21	—	—	+	—	++	—	—
22	—	—	++	—	—	++	++
23	—	—	—	—	—	++	++
24	—	—	—	—	—	+	++
25	++	—	++	—	—	++	++
26	—	—	+	—	—	+	+
27	—	—	—	—	—	+	+
28	—	—	++	—	—	++	++
29	—	+	++	+	—	++	++
30	—	—	+	—	—	—	—
Standard [§]	++++	++++	++++	++++	++++	++++	++++

[©] = The compounds were used at concentration of 100 µg/mL, zone of inhibition was measured in mm (—, 0; +, <10; ++, 10-20; +++++, 30-40mm); [§]Ciprofloxacin for bacteria and Griseofulvin for fungi, were used at the concentration of 10 µg.

Conclusion

Simple and moderate yielding reactions of 2-chloro-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides with various substituted piperazines to form novel 2-(1*H*-substituted-piperazin-1-yl)-*N*-(4-oxo-substituted-quinazolin-3(4*H*)-yl)-acetamides **8-30** are reported. The antimicrobial screening results revealed that some of the compounds are moderately active. However, the activities of the tested compounds are much less than those of standard antifungal and antibacterial agents used.

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.

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