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

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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, ^{1}HNMR 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.

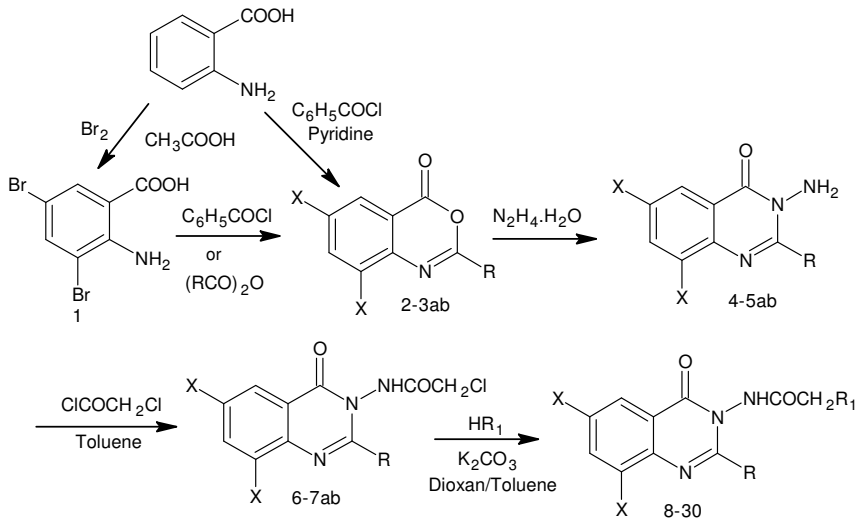
Keywords: Quinazolin-4-ones, Piperazinyl quinazolin-4-ones, Antibacterial activity, Antifungal activity.

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 anticancer[1-2], antitubercular[3], antibacterial[4], antifungal[5], anti-HIV[6], anthelmintic[7], anti-inflammatory[8] and antihypertensive activities[9]. Piperazines are found to be antimicrobial agents[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.

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 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}HNMR 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_2Cl 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 ^{1}HNMR, 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.

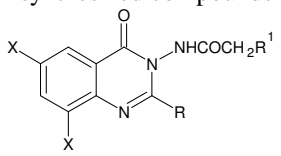


2a, 4a, 6a: X = H; R = C_6H_5 3a, 5a, 7a: X = Br; R = CH_3

2b, 4b, 6b: X = Br; R = C_6H_5 3b, 5b, 7b: X = Br; R = C_3H_7

Scheme 1

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



Compounds	X	R	R^1	Yield, %	M.P °C
8	H	C_6H_5	piperazin-1-yl	60	250
9	H	C_6H_5	4-methylpiperazin-1-yl	45	210
10	H	C_6H_5	4-ethylpiperazin-1-yl	48	125
11	H	C_6H_5	4-phenylpiperazin-1-yl	50	112
12	H	C_6H_5	4-(4-fluorophenyl)piperazin-1-yl	38	128
13	H	C_6H_5	4-(2-fluorophenyl)piperazin-1-yl	40	200
14	Br	C_6H_5	piperazin-1-yl	65	285
15	Br	C_6H_5	4-methylpiperazin-1-yl	55	209
16	Br	C_6H_5	4-ethylpiperazin-1-yl	50	189
17	Br	C_6H_5	4-phenylpiperazin-1-yl	50	149
18	Br	C_6H_5	4-(4-fluorophenyl)piperazin-1-yl	45	205
19	Br	C_6H_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_3H_7	piperazin-1-yl	69	235
26	Br	C_3H_7	4-methylpiperazin-1-yl	57	160
27	Br	C_3H_7	4-ethylpiperazin-1-yl	54	120
28	Br	C_3H_7	4-phenylpiperazin-1-yl	49	227
29	Br	C_3H_7	4-(4-fluorophenyl)piperazin-1-yl	55	123
30	Br	C_3H_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 Thermonik melting point apparatus and were uncorrected. IR spectra in KBr were recorded on a Shimadzu-8400 FTIR spectrophotometer. ^{1}HNMR spectra were recorded on Brucker spectrophotometer (400 MHz) in DMSO-d_6/$CDCl_3$ 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 earlier [15-18]

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); ^{1}HNMR (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, NH_2).

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); ^{1}HNMR (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, NH_2).

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 (CH_3), 1664 (C=O), 1542, 1448 (ArC=C), 694 (C-Br); ^{1}HNMR (400MHz, $CDCl_3$): δ 8.4 (s, 1H, ArH), 8.2-8.3 (s, 1H, ArH), 5.8-5.9 (s, 2H, NH_2), 2.6(s, 3H, CH_3).

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 (CH_3), 2817 (CH_2), 1666 (C=O), 1606, 1589 (ArC=C), 792 (CH_2), 692 (C-Br); ^{1}HNMR (400MHz, DMSO-d_6): δ 8.34 (s, 1H, ArH), 8.1-8.2 (s, 1H, ArH), 5.8 (s, 2H, NH_2), 2.9-3.1 (m, 4H, CH_2), 1.2-1.4 (*t*, 3H, J=7.3Hz, CH_3).

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(4*H*)-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 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(4H)-yl)-acetamide ***(6a)***

Yield 55%; mp 148 °C; IR (KBr) ν (cm^{-1}): 3205 (N-H), 3010 (ArC-H), 2935 (CH_2), 1690 (C=O), 1568, 1475 (ArC=C), 1328 (C-N), 775 (C-Cl); ^{1}HNMR (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-CH_2).

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 (CH_2), 1710 (C=O), 1542, 1488 (ArC=C), 700 (C-Cl), 694 (C-Br); ^{1}HNMR (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-CH_2).

2-Chloro-N-(6,8-dibromo-2-methyl-4-oxo-quinazolin-3(4H)-yl)-acetamide ***(7a)***

Yield 60%; mp 188 °C; IR (KBr) ν (cm^{-1}): 3188 (N-H), 3010 (ArC-H), 2962, 2856 (CH_3), 1685 (C=O), 1583, 1438 (ArC=C), 756 (C-Cl), 663 (C-Br); ^{1}HNMR (400MHz, $CDCl_3$): 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-CH_2), 2.35-2.4 (s, 3H, CH_3).

2-Chloro-N-(6,8-dibromo-4-oxo-2-propyl-quinazolin-3(4H)-yl)-acetamide ***(7b)***

Yield 75%; mp 192 °C; IR (KBr) ν (cm^{-1}): 3301 (N-H), 3070 (ArC-H), 2939 (CH_3), 1683 (C=O), 1585, 1442 (ArC=C), 788 (CH_2), 756 (C-Cl), 696 (C-Br); ^{1}HNMR (400MHz, $CDCl_3$): 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-CH_2), 2.58-2.88 (m, 4H, CH_2), 1.1-1.3 (t, 3H, J=7.2Hz, CH_3).

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

IR (KBr) ν (cm^{-1}): 3180 (N-H), 3020 (ArC-H), 2930, 2829 (CH_2), 1710 (C=O), 1568, 1440 (ArC=C); ^{1}HNMR (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-CH_2), 3.05-3.15 (d, 1H, J=15.4Hz, diastereotopic-CH_2), 2.3 (s, 4H, Piperazine), 2.1 (s, 4H, Piperazine).

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

IR (KBr) ν (cm^{-1}): 3141 (N-H), 3060 (ArC-H), 2937, 2808 (CH_2), 1712 (C=O), 1593, 1469 (ArC=C); ^{1}HNMR (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-CH_2), 3.0-3.2 (d, 1H, J=15.4Hz, diastereotopic-CH_2), 2.2 (s, 4H, Piperazine), 2.1 (s, 4H, Piperazine), 1.7 (s, 3H, CH_3).

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

IR (KBr) ν (cm^{-1}): 3142 (N-H), 3060 (ArC-H), 2937, 2810 (CH_2), 1710 (C=O), 1593, 1469 (ArC=C); ^{1}HNMR (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-CH_2), 3.0-3.2 (d, 1H, J=15.3Hz, diastereotopic-CH_2), 2.2-2.3 (s, 6H, Piperazine + CH_2), 2.1 (s, 4H, Piperazine), 1.9 (s, 3H, CH_3).

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

IR (KBr) ν (cm^{-1}): 3487 (N-H), 3020 (ArC-H), 2930, 2829 (CH_2), 1710 (C=O), 1568, 1440 (ArC=C); ^{1}HNMR (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-CH_2), 2.9-3.0 (d, 1H, J=15.5Hz, diastereotopic-CH_2), 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 (CH_2), 1683 (C=O), 1508, 1447 (ArC=C), 1233 (C-F); ^{1}HNMR (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-CH_2), 2.9-3.0 (d, 1H, J=15.5Hz, diastereotopic-CH_2), 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 (CH_2), 1683 (C=O), 1508, 1447 (ArC=C), 1233 (C-F); ^{1}HNMR (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-CH_2), 2.8-2.9 (d, 1H, J=14.8Hz, diastereotopic-CH_2), 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 (CH_2), 1728 (C=O), 1604, 1444 (ArC=C), 684 (C-Br); ^{1}HNMR (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-CH_2), 3.1-3.2 (d, 1H, J=15.7Hz, diastereotopic-CH_2), 2.8 (br, 4H, Piperazine), 2.6-2.7 (br, 4H, Piperazine), 2.4 (s, 3H, CH_3).

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 (CH_2), 1733 (C=O), 1602, 1465 (ArC=C), 680 (C-Br); ^{1}HNMR (400MHz, $CDCl_3$): δ 8.3-8.35 (s, 1H, ArH), 8.15 (s, 1H, ArH), 3.3-3.4 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 3.1-3.2 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 2.6-2.5 (s, 4H, Piperazine), 2.1-2.2 (s, 4H, Piperazine), 1.25 (s, 3H, CH_3), 0.9 (s, 3H, CH_3).

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 (CH_2), 1697 (C=O), 1598, 1440 (ArC=C); ^{1}HNMR (400MHz, $CDCl_3$): δ 8.2-8.3 (s, 1H, ArH), 8.15 (s, 1H, ArH), 3.4-3.6 (d, 1H, J=15.8Hz, diastereotopic-CH_2), 3.2-3.4 (d, 1H, J=15.8Hz, diastereotopic-CH_2), 3.0-3.2 (br, 4H, Piperazine), 2.8 (br, 4H, Piperazine), 2.8 (br, 2H, CH_2), 2.7 (s, 3H, CH_3), 1.1-1.2 (t, 1H, J=6.8Hz, CH_3).

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

IR (KBr) ν (cm^{-1}): 3507 (N-H), 3068 (ArC-H), 2929, 2820 (CH_2), 1695 (C=O), 1597, 1443 (ArC=C), 1240 (C-F), 672 (C-Br); ^{1}HNMR (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-CH_2), 3.1-3.2 (d, 1H, J=15.3Hz, diastereotopic-CH_2), 2.75-2.85 (m, 4H, Piperazine), 2.65-2.75 (m, 4H, Piperazine), 2.45 (s, 3H, CH_3).

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

IR (KBr) ν (cm^{-1}): 3510 (N-H), 3030 (ArC-H), 2929, 2820 (CH_2), 1695 (C=O), 1597, 1443 (ArC=C), 1240 (C-F), 700 (C-Br); ^{1}HNMR (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-CH_2), 3.2-3.3 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 2.8-2.9 (br, 4H, Piperazine), 2.6-2.8 (br, 4H, Piperazine), 2.43 (s, 3H, CH_3).

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

IR (KBr) ν (cm^{-1}): 3244 (N-H), 3030 (ArC-H), 2945, 2835 (CH_2), 1731 (C=O), 1606, 1444 (ArC=C), 675 (C-Br); ^{1}HNMR (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-CH_2), 3.1-3.2 (d, 1H, J=15.8Hz, diastereotopic-CH_2), 2.7-2.9 (m, 6H, Piperazine + CH_2), 2.6-2.7 (br, 6H, Piperazine + CH_2), 1.2-1.3 (t, 3H, J=7.2Hz, CH_3).

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

IR (KBr) ν (cm^{-1}): 3298 (N-H), 3030 (ArC-H), 2937, 2819 (CH_2), 1720 (C=O), 1600, 1469 (ArC=C), 684 (C-Br); ^{1}HNMR (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-CH_2), 3.1-3.2 (d, 1H, J=15.5Hz, diastereotopic-CH_2), 2.7-2.8 (m, 2H, CH_2), 2.6-2.7 (m, 2H, CH_2), 2.4-2.6 (br, 4H, Piperazine), 2.3-2.4 (br, 4H, Piperazine), 1.2-1.3 (t, 3H, J=7.3Hz, CH_3); MS m/z: 501 $(M)^+$; Calcd. (%) for $C_{18}H_{23}Br_2N_5O_2$: 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(4H)-yl)-2-(4-ethylpiperazin-1-yl)-acetamide ***(27)***

IR (KBr) ν (cm^{-1}): 3420 (N-H), 2922 (CH_2), 1688 (C=O), 1605, 1443 (ArC=C), 694 (C-Br); ^{1}HNMR (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-CH_2), 2.7-2.8 (m, 6H, Piperazine + CH_2), 2.6-2.7 (m, 6H, Piperazine + CH_2), 2.3 (t, 3H, J=7.1Hz, CH_3), 1.2-1.25 (t, 3H, J=7.0Hz, CH_3); MS m/z: 515 $(M)^+$; Calcd. (%) for $C_{19}H_{25}Br_2N_5O_2$: 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(4H)-yl)-2-(4-phenylpiperazin-1-yl)-acetamide ***(28)***

IR (KBr) ν (cm^{-1}): 3440 (N-H), 2921, 2830 (CH_2), 1674 (C=O), 1586, 1445 (ArC=C), 685 (C-Br); ^{1}HNMR (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-CH_2), 2.5-3.0 (m, 12H, Piperazine + CH_2), 1.25 (t, 3H, J=7.0Hz, CH_3).

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 (CH_2), 1695 (C=O), 1597, 1444 (ArC=C), 1240 (C-F), 672 (C-Br); ^{1}HNMR (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-CH_2), 3.0-3.2 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 2.7-2.9 (m, 6H, Piperazine + CH_2), 2.6-2.7 (m, 6H, Piperazine + CH_2), 1.2-1.3 (*t*, 3H, J=7.3Hz, CH_3).

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 (CH_2), 1695 (C=O), 1597, 1444 (ArC=C), 1240 (C-F), 672 (C-Br); ^{1}HNMR (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-CH_2), 3.2-3.3 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 2.8-3.0 (m, 6H, Piperazine + CH_2), 2.6-2.7 (m, 6H, Piperazine + CH_2), 1.25 (*t*, 3H, J=7.2Hz, CH_3).

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(4*H*)-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 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(4H)-yl)-2-piperazin-1-yl-acetamide ***(14)***

IR (KBr) ν (cm^{-1}): 3480 (N-H), 3062 (ArC-H), 2943, 2819 (CH_2), 1697 (C=O), 1589, 1448 (ArC=C), 700 (C-Br); ^{1}HNMR (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-CH_2), 2.8-2.9 (d, 1H, J=15.5Hz, diastereotopic-CH_2), 2.2-2.3 (br, 4H, Piperazine), 2.0-2.1 (br, 4H, Piperazine); MS m/z: 521 $(M)^+$; Calcd. (%) for $C_{20}H_{19}Br_2N_5O_2$: 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 (CH_2), 1737 (C=O), 1587, 1444 (ArC=C); ^{1}HNMR (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-CH_2), 2.8-2.9 (d, 1H, J=15.5Hz, diastereotopic-CH_2), 2.2-2.4 (br, 4H, Piperazine), 2.14 (s, 3H, CH_3), 2.0-2.1 (m, 4H, Piperazine).

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

IR (KBr) ν (cm^{-1}): 3431 (N-H), 3010 (ArC-H), 2948, 2812 (CH_2), 1697 (C=O), 1593, 1444 (ArC=C); ^{1}HNMR (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-CH_2), 2.8-2.9 (d, 1H, J=15.7Hz, diastereotopic-CH_2), 2.2-2.3 (m, 6H, Piperazine + CH_2), 2.0-2.1 (m, 4H, Piperazine), 0.9-1.0 (t, 3H, J=7.1Hz, CH_3); MS m/z: 549 $(M)^+$; Calcd. (%) for $C_{22}H_{23}Br_2N_5O_2$: 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(4H)-yl)-2-(4-phenylpiperazin-1-yl)-acetamide ***(17)***

IR (KBr) ν (cm^{-1}): 3245 (N-H), 2919, 2842 (CH_2), 1687 (C=O), 1585, 1456 (ArC=C), 700 (C-Br); ^{1}HNMR (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-CH_2), 3.15-3.25 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 2.93-2.98 (br, 4H, Piperazine), 2.2 (br, 4H, Piperazine).

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

IR (KBr) ν (cm^{-1}): 3206 (N-H), 3068 (ArC-H), 2948, 2825 (CH_2), 1691 (C=O), 1580, 1453 (ArC=C), 1240 (C-F); ^{1}HNMR (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-CH_2), 2.93-2.97 (d, 1H, J=15.6Hz, diastereotopic-CH_2), 2.4-2.5 (br, 4H, Piperazine), 2.2-2.3 (br, 4H, Piperazine).

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

IR (KBr) ν (cm^{-1}): 3206 (N-H), 3068 (ArC-H), 2948, 2825 (CH_2), 1691 (C=O), 1580, 1453 (ArC=C), 1240 (C-F); ^{1}HNMR (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-CH_2), 2.9-3.0 (d, 1H, J=15.5Hz, diastereotopic-CH_2), 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 method[19] 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 μg/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	*S. aureus*	*B. subtilis*	*P. aeruginosa*	*K. pneumoniae*	*A. awamori*	*A. oryzae*	*C. tropicalis*
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.

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