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SYNTHESIS AND *IN VITRO* ANTIMICROBIAL EVALUATION OF PYRAZOLYL-QUINAZOLIN-4(3*H*)-ONES

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Abstract: A new series of 2-[2-(2,6-dichlorophenyl)amino]phenyl methyl -3-[(1-phenyl-5-substituted phenyl)-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-ones $\mathbf{C}_{1\text{-}13}$ have been synthesized by the reaction of 2-[2-(2,6-dichlorophenyl)amino]phenylmethyl-3-substituted phenyl chromene amido-6,8-dibromoquinazolin-4(3*H*)-ones with phenylhydrazine in the presence of glacial acetic acid. The chalcones $\mathbf{B}_{1\text{-}13}$ have been synthesized by the condensation of 2-[2-(2, 6-dichloro phenyl)amino]phenylmethyl-3-acetamido-6,8-dibromoquinazolin-4(3*H*)-one **A** with different substituted aromatic aldehydes. The structures of newly synthesized compounds have been confirmed on the basis of their elemental analysis and spectral data: IR, ^{1}H NMR, ^{13}C NMR. All the compounds have been screened for antibacterial and antifungal activity.

Keywords: antibacterial; antifungal; pyrazoline; chromen; quinazolinone

Heterocyclic derivatives are pharmaceutically important compounds which were developed for better result in the medicinal chemistry. Among these, pyrazoline and its analogs represent one of the most active classes of compounds possessing a wide spectrum of biological activity (1). During the past years, considerable evidence has been accumulated to domestic efficacy of pyrazoles including antibacterial (2), antifungal (3), herbicidal (4), insecticidal and other biological activities (5–7). The large number of synthetic compounds with pyrazoline nucleus are used as anti-inflammatory agents (8–10), analgesics (11), anticonvulsants (12), as well as rheumatic arthritis (13), anxiolytic (14), and enzyme inhibitory agents (15).

The quanazolin-4(3*H*)-one ring system is considered as an interesting moiety because of its several analogs, which have been found to possess broad spectrum of biological and pharmacological properties which include anti-tubercular (16), anticancer (17), anti-HIV (18), anthelmintic (19), antihypertensive (20), anti-diabetic (21), CNS depressant (22), calcilytic activity (23) and antimicrobial and anti-inflammatory (24–26) activities etc.

In order to see the effect of incorporation of pyrazoline moiety in quinazoline nucleus at C-3 position and in continuation of earlier work on nitrogen heterocycles, we decided to synthesize a new series of compounds – 2-[2-(2,6-dichlorophenyl)amino]phenylmethyl-3-[(1-phenyl-5-substituted phenyl)-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-ones $\mathbf{C}_{1\text{-}13}$ and to study their antimicrobial activities.

EXPERIMENTAL

All reagents and solvents were obtained from Rankem, Sisco, Qualigens and Spectrochem and were of the highest commercial quality and used without further purification. Solvents were freshly distilled and used. Melting points were determined in open capillaries and are uncorrected. TLC analyses were done on glass plates coated with silica gel GF-254 and detection was done using iodine/UV lamp. IR absorption spectra were recorded on Perkin–Elmer RX-1 FTIR spectrophotometer using KBr pellets and the proton magnetic resonance spectra ^{1}H-NMR at 400 MHz and ^{13}C-NMR at 100 MHz were recorded on Bruker Avance II in $CDCl_3$ using tetramethylsilane (TMS) as an internal reference. Elemental analysis was performed on Carlo Erba 1108 analyzer. The compounds were analyzed for carbon, hydrogen and nitrogen and the results were varying within ± 0.04% of the calculated values. The starting compound **A** was prepared according to the reported method (29–31).

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2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-(phenylchromen amido)-6,8-dibromoquinazolin-4(3*H*)-one (B_1)

To a solution of 2-[2-(2,6-dichlorophenyl)amino]phenylmethyl-3-acetamido-6,8-dibromoquinazolin-4(3*H*)-one (5.82 g, 0.01 mol) in absolute ethanol (50 mL), benzaldehyde (0.01 mol) and 2% NaOH were added and the mixture was refluxed for 10–12 h., cooled and poured into icecold water. The solid obtained was filtered, washed with water and recrystallized from methanol. M.p.: 146–148°C. Yield**:** 67%, IR (KBr, cm^{-1}): 3413 (NH), 3059, 2856 (C-H), 1720 (C=O), 1655 (C=O of $–COCH_3$), 1578 (CH=CH), 1317 (C-N), 781 (C-Cl), 609 (C-Br).^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.77 (s, 1H, -NH-), 8.61 (d, 1H, =CH-Ar), 6.80 (d, 1H, COCH=), 6.34–7.91 (m, 14H, Ar-H), 2.63 (s, 2H, $-CH_2$), 2.10 (s, 1H, -N-NH).

2-[2-(2, 6-Dichlorophenyl)amino]phenylmethyl-3-[(2-hydroxy)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B_2)

IR (KBr, cm^{-1}): 3547 (-OH), 3411 (NH), 3061, 2852 (C-H), 1719 (C =O), 1617 (C=O of $–COCH_3$), 1566 (CH=CH), 1317 (C-N), 779 (C-Cl), 613 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 10.34 (s, 1H, -OH), 9.78 (s, 1H, -NH-), 8.62 (d, 1H, =CH-Ar), 6.34–7.91 (m, 13H, Ar-H), 6.80 (d, 1H, COCH=), 3.63 (s, 2H, $-CH_2$), 2.11 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.5 ($-CH_2$), 36.4, 41.6 (CH=CH), 109.3–143.4 (aromatic 24C), 160.8 (imine C), 162.1 (>C=O), 173.1 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(3-hydroxy)phenylchromen amido]-6,8-dibromoquinazoline-4(3*H*)-one (B_3)

IR (KBr, cm^{-1}): 3551 (-OH), 3413 (NH), 3071, 2852 (C-H), 1729 (C =O), 1613 (C=O of $–COCH_3$), 1575 (CH=CH), 1317 (C-N), 780 (C-Cl), 616 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 10.38 (s, 1H,-OH), 9.77 (s, 1H, -NH-), 8.61 (d, 1H, =CH-Ar), 6.34–7.91 (m, 13H, Ar-H), 6.82 (d, 1H, COCH=), 3.61 (s, 2H, $-CH_2$), 2.17 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.5 ($-CH_2$), 37.5, 42.9 (CH=CH), 109.21–143.27 (aromatic 24C), 161.2 (imine C), 162.1 (>C=O), 173.2 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(4-hydroxy)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B_4)

IR (KBr, cm^{-1}): 3557 (-OH), 3367 (NH), 3064, 2852 (C-H), 1719 (C =O), 1611 (C=O of $–COCH_3$), 1572 (CH=CH), 1319 (C-N), 780 (C-Cl), 615 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 10.35 (s, 1H,-OH), 9.78 (s, 1H, -NH-), 8.62 (d, 1H, =CH-Ar), 6.34–7.91 (m, 13H, Ar-H), 6.80 (d, 1H, COCH=), 3.65 (s, 2H, $-CH_2$), 2.11 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.6 ($-CH_2$), 36.5, 41.6 (CH=CH), 108.7–143.2 (aromatic 24C), 161.3 (imine C), 162.1 (>C=O), 173.1 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(2-chloro)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B_5)

IR (KBr, cm^{-1}): 3365 (NH), 3061, 2857 (C-H), 1729 (C =O), 1613 (C=O of $–COCH_3$), 1578 (CH=CH), 1314 (C-N), 781 (C-Cl), 617 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm) **:** 9.78 (s, 1H, -NH-), 8.61 (d, 1H, =CH-Ar), 6.82 (d, 1H, COCH=), 6.38–7.91 (m, 13H, Ar-H), 3.63 (s, 2H, $-CH_2$), 2.13 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 29.6 ($-CH_2$), 36.0, 41.5 (CH=CH), 109.2–143.1 (aromatic 24C), 160.9 (imine C), 162.3 (>C=O), 173.1 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(3-chloro)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B_6)

IR (KBr, cm^{-1}): 3413 (NH), 3067, 2853 (C-H), 1729 (C =O), 1615 (C=O of $–COCH_3$), 1578 (CH=CH), 1318 (C-N), 779 (C-Cl), 616 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.79 (s, ^{1}H, -NH-), 8.60 (d, 1H, =CH-Ar), 6.80 (d, 1H, COCH=), 6.39–7.93 (m, 13H, Ar-H), 3.63 (s, 2H, $-CH_2$), 2.11 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.3 ($-CH_2$), 36.5, 41.1 (CH=CH), 109.1–143.1 (aromatic 24C), 161.3 (imine C), 162.1 (>C=O), 173.2 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(4-chloro)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B_7)

IR (KBr, cm^{-1}): 3369 (NH), 3061, 2859 (C-H), 1731 (C =O), 1615 (C=O of $–COCH_3$), 1576 (CH=CH), 1316 (C-N), 782 (C-Cl), 618 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.78 (s, 1H, -NH-), 8.62 (d, 1H, =CH-Ar), 6.83 (d, 1H, COCH=), 6.39–7.94 (m, 13H, Ar-H), 3.65 (s, 2H, $-CH_2$), 2.11 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.6 ($-CH_2$), 36.2, 41.7 (CH=CH), 109.1–143.2 (aromatic 24C), 161.2 (imine C), 162.0 (>C=O), 172.8 (immine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(2-nitro)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B_8)

IR (KBr, cm^{-1}): 3416 (NH), 3066, 2856 (C-H), 1727 (C =O), 1617 (C=O of $–COCH_3$), 1578 (CH=CH), 1319 (C-N), 1567, 1363 ($-NO_2$), 779 (C-

Cl), 617 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.79 (s, 1H, -NH-), 8.64 (d, 1H, =CH-Ar), 6.81 (d, 1H, COCH=), 6.39–7.93 (m, 13H, Ar-H), 3.63 (s, 2H, -CH_2), 2.15 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.5 (-CH_2), 36.5, 42.2 (CH=CH), 108.9–143.1 (aromatic 24C), 161.6 (imine C), 162.1 (>C=O), 173.1 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(3-nitro)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B$_9$)

IR (KBr, cm^{-1}): 3411 (NH), 3071, 2856 (C-H), 1728 (C =O), 1615 (C=O of –$COCH_3$), 1576 (CH=CH), 1317 (C-N), 1550, 1356 (-NO_2), 785 (C-Cl), 613 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.78 (s, 1H, -NH-), 8.62 (d, 1H, =CH-Ar), 6.80 (d, 1H, COCH=), 6.38–7.93 (m, 13H, Ar-H), 3.61 (s, 2H, -CH_2), 2.17 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.4 (-CH_2), 36.0, 41.6 (CH=CH), 109.1–143.1 (aromatic 24C), 160.9 (imine C), 162.0 (>C=O), 172.9 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(4-nitro)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B$_{10}$)

IR (KBr, cm^{-1}): 3411 (NH), 3059, 2853 (C-H), 1727 (C =O), 1613 (C=O of –$COCH_3$), 1574 (CH=CH), 1561, 1359 (-NO_2), 1319 (C-N), 783 (C-Cl), 617 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.79 (s, 1H, -NH-), 8.59 (d, 1H, =CH-Ar), 6.81 (d, 1H, COCH=), 6.38–7.93 (m, 13H, Ar-H), 3.64 (s, 2H, -CH_2), 2.17 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.6 (-CH_2), 36.1, 42.7 (CH=CH), 109.2–143.1 (aromatic 24C), 161.2 (imine-C), 162.3 (>C=O), 173.1 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{[4-(dimethylamino)]phenyl chromen amido}-6,8-dibromoquinazolin-4(3*H*)-one (B$_{11}$)

IR (KBr, cm^{-1}): 3379 (NH), 3066, 2859 (C-H), 1727 (C =O), 1614 (C=O of –$COCH_3$), 1578 (CH=CH), 1317 (C-N), 780 (C-Cl), 613 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.78 (s, 1H, -NH-), 8.62 (d, 1H, =CH-Ar), 6.81 (d, 1H, COCH=), 6.39–7.93 (m, 13H, Ar-H), 3.61 (s, 2H, -CH_2), 2.83 (s, 6H,-CH_3), 2.17 (s, ^{1}H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.2 (-CH_2), 36.2, 41.6 (CH=CH), 46.2 (N-CH_3), 108.9–142.9 (aromatic 24C), 160.9 (imine C), 162.3 (>C=O), 172.8 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(2-methoxy)phenylchromen amido]-6,8-dibromoquinazoline-4(3*H*)-one (B$_{12}$)

IR (KBr, cm^{-1}): 3411 (NH), 3061, 2857 (C-H), 1722 (C =O), 1613 (C=O of –$COCH_3$), 1574 (CH=CH), 1317 (C-N), 1242, 1107 (C-O-C), 781 (C-Cl), 605 (C-Br). ^{1}H-NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.77 (s, 1H, -NH-), 8.61 (d, 1H, =CH-Ar), 6.81 (d, 1H, COCH=), 6.39–7.93 (m, 13H, Ar-H), 3.79 (s, 3H,-OCH_3), 3.65 (s, 2H, -CH_2), 2.14 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.2 (-CH_2), 36.8, 41.7(CH=CH), 59.4 (-OCH_3), 109.1–143.1 (aromatic 24C), 161.1 (immine-C), 162.0 (>C=O), 173.1 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(4-methoxy)phenylchromen amido]-6,8-dibromoquinazolin-4(3*H*)-one (B$_{13}$)

IR (KBr, cm^{-1}): 3401 (NH), 3068, 2861 (C-H), 1721 (C =O), 1613 (C=O of –$COCH_3$), 1577 (CH=CH), 1319 (C-N), 1245, 1107 (C-O-C), 783 (C-Cl), 609 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm)**:** 9.78 (s, 1H, -NH-), 8.61 (d, 1H, =CH-Ar), 6.82 (d, 1H, COCH=), 6.38–7.95 (m, 13H, Ar-H), 3.80 (s, 3H, -OCH_3), 3.63 (s, 2H, -CH_2), 2.17 (s, 1H, -N-NH). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.7 (-CH_2), 36.5, 42.6 (CH=CH), 58.7 (-OCH_3), 109.1–143.1 (aromatic 24C), 161.3 (imine C), 162.3 (>C=O), 173.2 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3–(1,5-diphenyl-5-hydro-1*H*-pyrazol-3-ylamino)-6, 8-dibromoquinazolin-4(3*H*)-one (C$_1$)

To a solution of 2-[2-(2,6-dichlorophenyl) amino] phenylmethyl-3-(phenylchromen amido)-6,8-dibromoquinazolin-4(3*H*)-one (6.71 g, 0.01 mol) in methanol, phenylhydrazine (99%, 2.16 g, 0.02 mol) and few drops of glacial acetic acid were added. The reaction mixture was refluxed for 8–10 h, distilled and cooled. The separated solid was filtered, washed with water and recrystallized from methanol. M.p.: 131–133^{o}C. Yield: 68%, IR (KBr, cm^{-1}): 3371 (N-H), 3063, 2856 (C-H), 1727 (C=O), 1615 (C=N), 1317 (C-N), 779 (C-Cl), 611 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.78 (s, 1H, -NH), 8.33 (s, 1H, -N-NH), 6.55 (t, 1Hx), 6.43–7.95 (m, 19H, Ar-H), 3.61 (s, 2H, -CH_2), 3.46 (d, 1Hb), 3.05 (d, 1Ha). 13C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.6 (-CH_2), 36.4, 41.3, 161.4 (pyrazole 3C), 109.1–143.2 (aromatic 30C), 162.1 (>C=O), 173.2 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(2-hydroxyphenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C$_2$)

IR (KBr, cm^{-1}): 3549 (O-H), 3413 (N-H), 3061, 2855 (C-H), 1730 (C=O), 1613 (C=N), 1319 (C-N),

780 (C-Cl), 608 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.39 (s, 1H, -OH), 9.79 (s, 1H, -NH), 8.32 (s, 1H, -N-NH), 6.55 (t, 1Hx), 6.43–7.95 (m, 18H, Ar-H), 3.58 (s, 2H, -CH_2), 3.46 (d, 1Hb), 3.05 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.4 (-CH_2), 36.4, 41.5, 160.9 (pyrazole 3C), 109.3–143.4 (aromatic 30C), 162.3 (>C=O), 164 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(3-hydroxyphenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazoline-4(3*H*)-one (C$_3$)

IR (KBr, cm^{-1}): 3549 (O-H), 3411 (N-H), 3074, 2856 (C-H), 1727 (C=O), 1614 (C=N), 1313 (C-N), 789 (C-Cl), 610 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.34 (s, 1H, -OH), 9.77 (s, 1H, -NH), 8.31 (s, 1H, -N-NH), 6.49 (t, 1Hx), 6.43–7.96 (m, 18H, Ar-H), 3.63 (s, 2H, -CH_2), 3.45 (d, 1Hb), 3.07 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.5 (-CH_2), 36.5, 42.7, 161.2 (imine pyrazole 3C), 109.12–143.15 (aromatic 30C), 162.2 (>C=O), 172.9 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(4-hydroxyphenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C$_4$)

IR (KBr, cm^{-1}): 3551 (O-H), 3407 (N-H), 3063, 2857 (C-H), 1725 (C=O), 1606 (C=N), 1317 (C-N), 782 (C-Cl), 607 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 10.34 (s, 1H, -OH), 9.78 (s, 1H, -NH), 8.36 (s, 1H, -N-NH), 6.47 (t, 1Hx), 6.44–7.96 (m, 18H, Ar-H), 3.63 (s, 2H, -CH_2), 3.45 (d, 1Hb), 3.06 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.6 (-CH_2), 36.4, 41.6, 161.3 (imine pyrazole 3C), 109.17–143.13 (aromatic 30C), 162.1 (>C=O), 173.3 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(2-chlorophenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C$_5$)

IR (KBr, cm^{-1}): 3359 (N-H), 3054, 2861 (C-H), 1729 (C=O), 1613 (C=N), 1312 (C-N), 779 (C-Cl), 611 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.77 (s, 1H, -NH), 8.27 (s, 1H, -N-NH), 6.51 (t, 1Hx), 6.44–7.96 (m, 18H, Ar-H), 3.63 (s, 2H, -CH_2), 3.48 (d, 1Hb), 3.06 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.4 (-CH_2), 36.2, 41.5, 160.9 (imine pyrazole 3C), 108.92–143.2 (aromatic 30C), 162.3 (>C=O), 173.2 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(3-chlorophenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C$_6$)

IR (KBr, cm^{-1}): 3413 (N-H), 3066, 2855 (C-H), 1730 (C=O), 1614 (C=N), 1316 (C-N), 780 (C-Cl), 608 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.79 (s, 1H, -NH), 8.31 (s, 1H, -N-NH), 6.53 (t, 1Hx), 6.43–7.95 (m, 18H, Ar-H), 3.64 (s, 2H, -CH_2), 3.51 (d, 1Hb), 3.06 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.1 (-CH_2), 36.4, 41.2, 161.3 (immine pyrazole 3C), 109.13–143.17 (aromatic 30C), 162.1 (>C=O), 173.2 (imine aromatic-C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(4-chlorophenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino-6,8-dibromoquinazolin-4(3*H*)-one (C$_7$)

IR (KBr, cm^{-1}): 3377 (N-H), 3060, 2861 (C-H), 1727 (C=O), 1616 (C=N), 1319 (C-N), 781 (C-Cl), 611 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.78 (s, 1H, -NH), 8.32 (s, 1H, -N-NH), 6.53 (t, 1Hx), 6.44–7.95 (m, 18H, Ar-H), 3.63 (s, 2H, -CH_2), 3.49 (d, 1Hb), 3.06 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.6 (-CH_2), 36.2, 41.4, 161.2 (imine pyrazole 3C), 109.17–143.21 (aromatic 30C), 162.3 (>C=O), 172.8 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(2-nitrophenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C$_8$)

IR (KBr, cm^{-1}): 3411 (N-H), 3061, 2856 (C-H), 1726 (C=O), 1615 (C=N), 1565, 1361 (-NO_2), 1318 (C-N), 778 (C-Cl), 612 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.79 (s, 1H,-NH), 8.31 (s, 1H, -N-NH), 6.49 (t, 1Hx), 6.43–7.96 (m, 18H, Ar-H), 3.62 (s, 2H, -CH_2), 3.48 (d, 1Hb), 3.07 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.3 (-CH_2), 36.4, 42.5, 161.4 (imine pyrazole 3C), 162.2 (>C=O), 173.1 (imine aromatic C), 108.9–143.1 (aromatic 30C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(3-nitrophenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C$_9$)

IR (KBr, cm^{-1}): 3410 (NH), 3073, 2854 (C-H), 1727 (C=O), 1613 (C=N), 1547, 1349 (-NO_2), 1313 (C-N), 781 (C-Cl), 613 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.78 (s, 1H, -NH), 8.33 (s, 1H, -N-NH), 6.51 (t, 1Hx), 6.43–7.96 (m, 18H, Ar-H), 3.62 (s, 2H, -CH_2), 3.48 (d, 1Hb), 3.06 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.4 (-CH_2), 36.2, 41.4, 161.1 (imine pyrazole 3C), 109.13–143.14 (aromatic 30C), 162.0 (>C=O), 172.9 (imine aromatic C).

Table 1. Physical properties of compounds $\mathbf{B}_{1\text{-}13}$ and $\mathbf{C}_{1\text{-}13}$.

Compound	R	Molecular formula	M.p. (± 2°C)	Yield (%)	C H N analysis Calculated(found)		
					%C	%H	%N
$\mathbf{B}_1$	H	$C_{30}H_{20}N_4O_2Br_2Cl_2$	146–148	67	51.51 (51.53)	2.86 (2.88)	8.01 (8.03)
$\mathbf{B}_2$	2-OH	$C_{30}H_{20}N_4O_3Br_2Cl_2$	156–158	72	50.36 (50.39)	2.79 (2.81)	7.83 (7.85)
$\mathbf{B}_3$	3-OH	$C_{30}H_{20}N_4O_3Br_2Cl_2$	171–173	66	50.36 (50.39)	2.79 (2.81)	7.83 (7.85)
$\mathbf{B}_4$	4-OH	$C_{30}H_{20}N_4O_3Br_2Cl_2$	184–186	73	50.36 (50.39)	2.79 (2.81)	7.83 (7.85)
$\mathbf{B}_5$	2-Cl	$C_{30}H_{19}N_4O_2Br_2Cl_3$	145–147	72	49.09 (49.11)	2.59 (2.61)	7.63 (7.65)
$\mathbf{B}_6$	3-Cl	$C_{30}H_{19}N_4O_2Br_2Cl_3$	163–165	65	49.09 (49.11)	2.59 (2.61)	7.63 (7.65)
$\mathbf{B}_7$	4-Cl	$C_{30}H_{19}N_4O_2Br_2Cl_3$	176–178	69	49.09 (49.11)	2.59 (2.61)	7.63 (7.65)
$\mathbf{B}_8$	2-NO_2	$C_{30}H_{19}N_5O_4Br_2Cl_2$	202–204	70	48.39 (48.41)	2.55 (2.57)	9.41 (9.43)
$\mathbf{B}_9$	3-NO_2	$C_{30}H_{19}N_5O_4Br_2Cl_2$	227–229	68	48.39 (48.41)	2.55 (2.57)	9.41 (9.43)
$\mathbf{B}_{10}$	4-NO_2	$C_{30}H_{19}N_5O_4Br_2Cl_2$	238–239	63	48.39 (48.41)	2.55 (2.57)	9.41 (9.43)
$\mathbf{B}_{11}$	4-$N(CH_3)_2$	$C_{32}H_{25}N_5O_2Br_2Cl_2$	161–163	67	51.76 (51.78)	3.37 (3.39)	9.43 (9.45)
$\mathbf{B}_{12}$	2-OCH_3	$C_{31}H_{22}N_4O_3Br_2Cl_2$	157–159	65	51.04 (51.06)	3.01 (3.03)	7.68 (7.70)
$\mathbf{B}_{13}$	4-OCH_3	$C_{31}H_{22}N_4O_3Br_2Cl_2$	173–175	68	51.04 (51.06)	3.01 (3.03)	7.68 (7.70)
$\mathbf{C}_1$	H	$C_{36}H_{26}N_6OBr_2Cl_2$	131–133	68	54.76 (54.77)	3.17 (3.19)	10.64 (10.66)
$\mathbf{C}_2$	2-OH	$C_{36}H_{26}N_6O_2Br_2Cl_2$	152–153	62	53.67 (53.65)	3.22 (3.23)	10.43 (10.45)
$\mathbf{C}_3$	3-OH	$C_{36}H_{26}N_6O_2Br_2Cl_2$	163–165	67	53.67 (53.65)	3.22 (3.23)	10.43 (10.45)
$\mathbf{C}_4$	4-OH	$C_{36}H_{26}N_6O_2Br_2Cl_2$	173–175	73	53.67 (53.65)	3.22 (3.23)	10.43 (10.45)
$\mathbf{C}_5$	2-Cl	$C_{36}H_{25}N_6OBr_2Cl_3$	139–141	69	52.47 (52.49)	3.03 (3.05)	10.20 (10.22)
$\mathbf{C}_6$	3-Cl	$C_{36}H_{25}N_6OBr_2Cl_3$	147–149	67	52.47 (52.49)	3.03 (3.05)	10.20 (10.22)
$\mathbf{C}_7$	4-Cl	$C_{36}H_{25}N_6OBr_2Cl_3$	159–161	65	52.47 (52.49)	3.03 (3.05)	10.20 (10.22)
$\mathbf{C}_8$	2-NO_2	$C_{36}H_{25}N_7O_3Br_2Cl_2$	171–173	69	51.81 (51.83)	2.99 (3.01)	11.75 (11.47)
$\mathbf{C}_9$	3-NO_2	$C_{36}H_{25}N_7O_3Br_2Cl_2$	188–190	61	51.81 (51.83)	2.99 (3.01)	11.75 (11.47)
$\mathbf{C}_{10}$	4-NO_2	$C_{36}H_{25}N_7O_3Br_2Cl_2$	203–205	63	51.81 (51.83)	2.99 (3.01)	11.75 (11.47)
$\mathbf{C}_{11}$	4-$N(CH_3)_2$	$C_{38}H_{31}N_7OBr_2Cl_2$	149–151	68	54.82 (54.84)	3.72 (3.75)	11.77 (11.79)
$\mathbf{C}_{12}$	2-OCH_3	$C_{37}H_{28}N_6O_2Br_2Cl_2$	139–141	63	54.22 (54.24)	3.41 (3.43)	10.25 (10.24)
$\mathbf{C}_{13}$	4-OCH_3	$C_{37}H_{28}N_6O_2Br_2Cl_2$	153–155	69	54.22 (54.24)	3.41 (3.43)	10.25 (10.24)

Table 2. Antimicrobial activity of compounds $\mathbf{B}_{1\text{-}13}$ and $\mathbf{C}_{1\text{-}13}$.

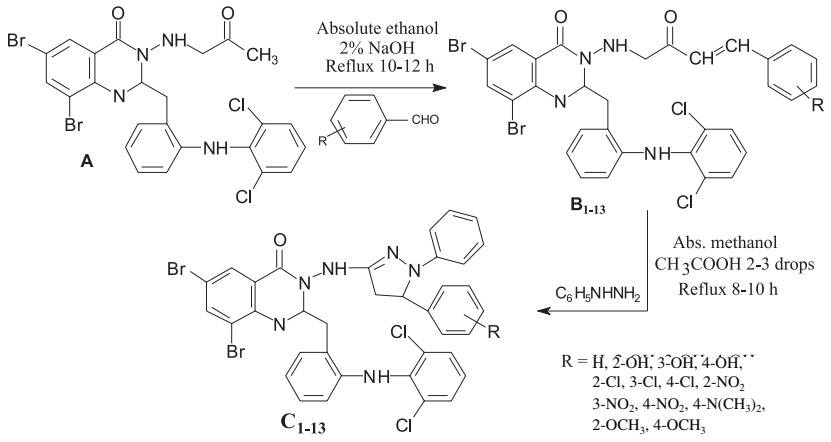
Compd. No.	R	Conc. (μM) in DMF	Zone of inhibition in mm					
			Antibacterial activity				Antifungal activity	
			S. aureus	*B. subtilis*	*E. coli*	*Certium*	*A. niger*	*C. albicans*
$\mathbf{B}_1$	H	143.01	20	20	11	10	12	12
$\mathbf{B}_2$	2-OH	139.81	12	13	14	13	09	10
$\mathbf{B}_3$	3-OH	139.81	11	11	14	14	NA	NA
$\mathbf{B}_4$	4-OH	139.81	13	12	12	11	07	08
$\mathbf{B}_5$	2-Cl	136.30	11	10	11	10	20	23
$\mathbf{B}_6$	3-Cl	136.30	11	11	12	12	16	17
$\mathbf{B}_7$	4-Cl	136.30	12	13	14	13	21	19
$\mathbf{B}_8$	2-NO_2	134.36	18	19	23	24	13	12
$\mathbf{B}_9$	3-NO_2	134.36	12	13	21	21	11	12
$\mathbf{B}_{10}$	4-NO_2	134.36	13	15	17	16	12	13
$\mathbf{B}_{11}$	4-$N(CH_3)_2$	134.71	10	12	10	09	13	14
$\mathbf{B}_{12}$	2-OCH_3	137.12	11	11	16	17	NA	NA
$\mathbf{B}_{13}$	4-OCH_3	137.12	11	12	18	18	NA	NA
$\mathbf{C}_1$	H	126.68	23	21	12	11	15	15
$\mathbf{C}_2$	2-OH	124.17	15	14	16	15	09	10
$\mathbf{C}_3$	3-OH	124.17	13	12	17	16	NA	07
$\mathbf{C}_4$	4-OH	124.17	15	15	16	15	09	09
$\mathbf{C}_5$	2-Cl	121.39	13	12	14	13	22	22
$\mathbf{C}_6$	3-Cl	121.39	13	12	12	11	18	19
$\mathbf{C}_7$	4-Cl	121.39	14	13	13	13	24	21
$\mathbf{C}_8$	2-NO_2	119.85	19	19	25	22	15	16
$\mathbf{C}_9$	3-NO_2	119.85	15	14	23	20	12	13
$\mathbf{C}_{10}$	4-NO_2	119.85	16	15	17	16	14	15
$\mathbf{C}_{11}$	4-$N(CH_3)_2$	120.13	13	12	11	10	15	15
$\mathbf{C}_{12}$	2-OCH_3	122.04	14	13	18	17	NA	NA
$\mathbf{C}_{13}$	4-OCH_3	122.04	15	14	18	17	NA	NA
Penicillin		319.48	30	27	31	28	–	–
Fluconazole		326.50	–	–	–	–	28	26

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(4-nitrophenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one ($\mathbf{C}_{10}$)

IR (KBr, cm^{-1}): 3369 (NH), 3057, 2856 (C-H), 1729 (C=O), 1614 (C=N), 1561, 1356 (-NO_2), 1312 (C-N), 789 (C-Cl), 611 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.78 (s, 1H, -NH), 8.31 (s, 1H, -N-NH), 6.51 (t, 1Hx), 6.43–7.96 (m, 18H, Ar-H), 3.63 (s, 2H, -CH_2), 3.48 (d, 1Hb), 3.05 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.4 (-CH_2), 36.3, 42.5, 161.2 (imine pyrazole 3C), 109.2–143.1 (aromatic 30C), 162.3 (>C=O), 173.2 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-{5-[4-(dimethylamino)phenyl]-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino}-6,8-dibromoquinazolin-4(3*H*)-one ($\mathbf{C}_{11}$)

IR (KBr, cm^{-1}): 3377 (N-H), 3066, 2859 (C-H), 1727 (C=O), 1614 (C=N), 1319 (C-N), 781 (C-Cl), 612 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.78 (s, 1H, -NH), 8.33 (s, 1H, -N-NH), 6.53 (t, 1Hx), 6.44–7.95 (m, 18H, Ar-H), 3.62 (s, 2H, -CH_2),



Scheme 1.

3.50 (d, 1Hb), 3.07 (d, 1Ha), 2.82 (s, 6H, -CH_3). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.5 (-CH_2), 36.2, 41.6, 161.2 (imine pyrazole 3C), 46.2 (N-CH_3), 108.9–142.99 (aromatic 30C), 162.3 (>C=O), 173.3 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(2-methoxyphenyl)-1-phenyl-5-hydro-1H-pyrazol-3-yl-amino]-6,8-dibromoquinazoline-4(3*H*)-one (C_{12})

IR (KBr, cm^{-1}): 3406 (N-H), 3066, 2859 (C-H), 1725 (C=O), 1611 (C=N), 1319 (C-N), 1240, 1105 (C-O-C), 778 (C-Cl), 608 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.79 (s, 1H, -NH), 8.30 (s, 1H, -N-NH), 6.52 (t, 1Hx), 6.43–7.96 (m, 18H, Ar-H), 3.81 (s, 3H, -OCH_3), 3.63 (s, 2H, -CH_2), 3.48 (d, 1Hb), 3.05 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 31.1 (-CH_2), 36.4, 41.5, 161.3 (imine pyrazole 3C), 58.4 (-OCH_3), 109.1–143.2 (aromatic 30C), 162.1 (>C=O), 173.3 (imine aromatic C).

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[5-(4-methoxyphenyl)-1-phenyl-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-one (C_{13})

IR (KBr, cm^{-1}): 3394 (N-H), 3066, 2863 (C-H), 1729 (C=O), 1611 (C=N), 1317 (C-N), 1243, 1109 (C-O-C), 781 (C-Cl), 607 (C-Br). ^{1}H NMR (400 MHz, $CDCl_3$, δ, ppm): 9.78 (s, 1H, -NH), 8.33 (s, 1H, -N-NH), 6.53 (t, 1Hx), 6.43–7.95 (m, 18H, Ar-H), 3.83 (s, 3H, -OCH_3), 3.62 (s, 2H, -CH_2), 3.48 (d, 1Hb), 3.06 (d, 1Ha). ^{13}C NMR (100 MHz, $CDCl_3$, δ, ppm): 30.4 (-CH_2), 36.5, 42.6, 161.1 (imine pyrazole 3C), 59.3 (-OCH_3), 109.1–143.2 (aromatic 30C), 162.3 (>C=O), 173.2 (imine aromatic C).

Antimicrobial activity

Following common standard strains were used for screening of antibacterial and antifungal activities: The stains were produced from Microbiology Department of Ahmedabad Textile Industries Research Association, Ahmedabad. *S. aureus* (Gram-positive) ATCC-12228, *B. subtilis* (Gram-positive) ATCC-11778, *E. coli* (Gram-negative) ATCC-8739, *Certium* (Gram-negative) ATCC-27957, *A. niger* (fungus) ATCC-16404, *C. albicans* (fungus) ATCC-10231; by broth dilution method, all the newly synthesized compounds were tested for antibacterial activities against *S.* aureus, *B. subtilis*, *E. coli* and *Certium* bacteria, the zone of inhibition measured in mm and compared with standard drug penicillin; antifungal activities against *A. niger* and *C. albicans* by the same method were measured and compared with fluconazole. All the compounds were tested at 100 μg/mL concentration (27, 28).

RESULTS

2-[2-(2,6-Dichlorophenyl)amino]phenylmethyl-3-[(1-phenyl-5-substituted phenyl)-5-hydro-1*H*-pyrazol-3-yl-amino]-6,8-dibromoquinazolin-4(3*H*)-ones $\mathbf{C}_{1\text{-}13}$ have been synthesized by the reaction of 2-[2-(2,6-dichlorophenyl)amino]phenyl methyl-3-substituted phenylchromen amido-6,8-

dibromoquinazolin-4(3*H*)-ones with phenylhydrazine in the presence of glacial acetic acid. The chalcones $\mathbf{B}_{1\text{-}13}$ have been synthesized by the condensation of 2-[2-(2,6-dichlorophenyl)amino]phenylmethyl-3-acetamido-6,8-dibromoquinazolin-4(3*H*)-one **A** with different substituted aromatic aldehydes. The conversion of compounds from **A** to $\mathbf{C}_{1\text{-}13}$ is showed in Scheme 1. Physical properties of $\mathbf{B}_{1\text{-}13}$ and $\mathbf{C}_{1\text{-}13}$ are given in Table 1. The structures of synthesized compounds were conformed by IR and NMR spectral data. The MIC values in µg/mL of compounds are presented in Table 2.

DISCUSSION AND CONCLUSION

Antibacterial activity

From the *in vitro* antibacterial screening results compounds $\mathbf{B}_1$, $\mathbf{B}_8$ (R = H, 2-NO_2) and $\mathbf{C}_1$, $\mathbf{C}_8$ (R = H, 2-NO_2) showed better activity against *S. aureus* and *B. subtilis* compared to penicillin. Compound $\mathbf{C}_2$, $\mathbf{C}_9$, $\mathbf{C}_{10}$ (R = 2-OH, 2-NO_2, 3-NO_2) showed good activity against *S. aureus* and *B. subtilis* compared to penicillin. Compound $\mathbf{B}_5$ (R = 2-Cl) showed moderate to weak activity against *B. subtilis* and $\mathbf{C}_{11}$ (R = 4-$N(CH_3)_2$) showed moderate to weak activity against *S. aureus* compared to penicillin.

Compounds $\mathbf{B}_8$, $\mathbf{B}_9$, (R = 2-NO_2, 3-NO_2) and $\mathbf{C}_8$, $\mathbf{C}_9$ (R = 2-NO_2, 3-NO_2) showed excellent activity against *E. coli* and *Certium* compared to penicillin. Compounds $\mathbf{C}_2$, $\mathbf{C}_3$, $\mathbf{C}_4$, $\mathbf{C}_{10}$, $\mathbf{C}_{12}$ and $\mathbf{C}_{13}$ (R = 2-OH, 3-OH, 4-OH, 4-NO_2, 2-OCH_3, 4-OCH_3) showed better activity against *E. coli* and *Certium* compared to penicillin. Compounds $\mathbf{C}_1$, $\mathbf{C}_5$, $\mathbf{C}_6$, $\mathbf{C}_7$ and $\mathbf{C}_{11}$ (R = H, 2-Cl, 3-Cl, 4-Cl, 4-$N(CH_3)_2$) showed weak activity against *E. coli* and *Certium* compared to penicillin.

Antifungal activity

From the *in vitro* antifungal screening results compounds $\mathbf{B}_7$ and $\mathbf{C}_7$ (R = 3-Cl, 3-Cl) showed excellent activity against *A. niger* and *C. albicans* compared to fluconazole. Compounds $\mathbf{B}_6$, $\mathbf{C}_6$, and $\mathbf{C}_{11}$ (R = 2-Cl, 2-Cl, 4-$N(CH_3)_2$) showed good activity against *A. niger* and *C. albicans* compared to fluconazole. Compounds $\mathbf{B}_3$, $\mathbf{B}_{12}$, $\mathbf{B}_{13}$, $\mathbf{C}_{12}$ and $\mathbf{C}_{13}$ (R = 3-OH, 2-OCH_3, 4-OCH_3, 2-OCH_3, 4-OCH_3) showed no activity against *A. niger* and *C. albicans*. Compound $\mathbf{C}_3$ (R = 3-OH) showed no activity against *A. niger.*

In conclusion, a quite simple procedure, low consumption of solvent, mild reaction conditions and good yield of the reaction make this protocol an attractive and useful contribution to the preparation. The present investigation is centered on the studies of reactions, synthesis, spectral analysis and antimicrobial activity.

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