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Synthesis of Quinazolin-4(3H) Ones From Pyridine Based Chalcone By Conventional Method And Their Antimicrobial Studies *In Vitro*

N. B. Patel[1] and G. G. Barat[2*]

1. Department of Chemistry, VNSGU-Surat-395007, Gujarat, **INDIA**
2. Department of Chemistry, Arts, Science and Commerce College, Pilvai-382850, Gujarat, **INDIA**

Email: drnavinbpatel@gmail.com,gamanbarat@gmail.com

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ABSTRACT

*Quinazolin-4(3H) ones **6a-j** was synthesized by the cyclization of pyridine based chalcones 5**a-j** with hydrazine hydrate. The overall reaction was multistep base catalyzed cyclization of acid chloride **1** with 3:5-dibromo anthranilic acid yielded benzoxazinone **2**, which on reaction with hydrazine hydrate to afforded amino quinazolin-4(3H) one **3**. The structural confirmation of the synthesized compounds was carried out on the basis of elemental analysis, IR, ^{1}H NMR and ^{13}C NMR spectra results. The title compounds were screened for antimicrobial activity in vitro.*

Keywords: Antimicrobial activity, Chalcone, Quinazolin-4(3H) one, Pyrazole.

INTRODUCTION

Quinazolin-4(3*H*)-one and its derivatives are a class of hetero aromatic compounds that have drawn much attention due to their biological and pharmaceutical activities [1-3]. A brief survey on the biological activities of quinazolin-4(3*H*)-one derivatives showed anti-inflammatory [4-5], antitumor [6], anti HIV [7], antibacterial [8-9], as well as CNS depressant and anticonvulsant activities [10-11]. 4-Substituted quinazolines were also studied as anticancer agents for their strong ability to inhibit several receptor tyrosine kinases [12]. Derivatives of quinazolin-4-one are potential drugs which can possess hypnotic [13], analgesic [14], anthelmintic [15], neuroleptic [16], anti-allergic, anti-malarial and other effects [17]. On the other hand, it was found that not only quinazoline derivatives showed chemotherapeutic activity, but also pyrazole [18], pyrazolone [19], thiadiazoles [20] as well as triazole [21-22] moieties possess this activity. Moreover, the increasing biological importance of quinazolinone derivatives particularly in chemotherapy, promoted us to develop and synthesize the new pyrazolone, pyrazole, thiazolidine, triazole, thiadiazoles andtriazolo[3,4-*a*] isoindole molecules with a 6, 8-dibromoquinazoline substituent moiety, with the aim of obtaining some novel heterocyclic systems with potentially enhanced biological properties.

MATERIALS AND METHODS

The reagent grade chemicals were purchased from commercial sources and further purified before use. The melting points of all synthesized compounds were taken in open capillary tube and are uncorrected. The purities of all synthesized compounds were checked by TLC on Merck silica gel 60 F 254 using toluene: ethyl acetate (8:2) as mobile phase, and spots were visualized under UV radiation. The IR spectra of the synthesized compounds were recorded on Perkin-Elmer 1300 FTIR spectrophotometer using KBr pellets and frequencies are recorded in cm^{-1}. ^1H NMR and ^{13}C NMR spectra were recorded on Bruker Advance II 400 NMR spectrometer using deutero $CDCl_3$ as a solvent. The chemical shifts were reported in (δ ppm) downfield using tetra methyl silane as internal standard. Elemental analyses of newly synthesized compounds were carried out on Carlo Ebra 1108 analyzer.2-(2-phenylamino) phenyl acetyl chloride **1** was synthesized by literature procedure (Furniss et al., 1989).

2-[2-(phenylamino) phenylmethyl–6, 8-dibromo-3,1-benzoxazin-4(*H*) one (2): To the solution of 2–[(2-phenyl) amino] phenyl acetyl chloride (2.315 g. 0.01 mol) in pyridine (25mL) kept on an ice bath at 0-5 ^{0} C. Add each small portion of 3:5-dibromo anthranilic acid (2.94 g. 0.01 mol) was added portion wise and were stirred for 1 h to maintain temperature 0-5 ^{0}C. Further reaction mixture was stirred 1 h at room temperature. A pasty mass thus obtained which was washed thoroughly with sodium bicarbonate (5 %) to remove unreacted acid. A solid separated was filtered, dried and recrystalised from methanol.
M.P.:184-185^{0}CYield:73%.IR(KBr):3407(NH),3073,2861(C-H),1725(C=O),1614(C=N),1323 (C-N), 1236 (C-O-C), 750(NH wag), 614(C-Br). Anal.(%) for $C_{21}H_{14}N_2O_2Br_2$ Calcd; C, 51.85; H, 2.88; N, 5.76; Found; C, 51.87; H, 2.89; N, 5.80.

3-Amino 2-[2-(phenylamino)phenyl] methyl-6,8–dibromo quinazolin–4(3*H*) one (3): To a mixture of 2-[2- phenyl) amino] phenyl methyl- 6, 8-dibromo-3, 1-benzoxazine-4(*H*)-one (4.86 g. 0.01 mol) and hydrazine (99 %) (0.50 g. 0.01 mol) in 25.0 mL pyridine was heated at 180-200 ^{0} C in an oil bath for 5 - 6 h. The oily mass was slowly poured onto crushed acidic (HCl, 25mL) ice cold water with occasional stirring. The product obtained was filtered and washed several times with water. The crushed product was dried and recrystalised from ethanol.
M.P.**:**156-157 ^{0}C Yield**:** 68 %. IR(KBr) : 3403(NH), 3068, 2869(C-H), 1721(C=O), 1612(C=N), 1321(C-N), 611(C-Br).^{1}H NMR($CDCl_3$)**:** 9.79(s,1H, -NH-), 2.1(s, 2H, -N-NH_2), 6.34-7.91(m, 11H, Ar-H), 2.71(s, 2H, -CH_2).Anal. (%) for $C_{21}H_{16}N_4OBr_2$ Calcd; C, 50.40; H, 3.20; N, 11.20; Found; C, 50.45; H, 3.24; N, 11.22.

2-[2-(phenylamino)phenyl]methyl-3-acetamido-6,8-dibromo quinazolin-4(3*H*)-one (4): To a solution of 3-amino2-[2-(2-phenyl)amino]phenyl methyl-6, 8- dibromoquinazoline-4(3*H*)–one **(**5.00 g. 0.01 mol) in dry benzene (50 mL), acetyl chloride (0.785g. 0.01mol) was added drop by drop at 0-5 ^{0}C, for 1 h with constant stirring after completion of addition the reaction mixture was kept overnight. The excess of solvent was distilled off under reduced pressure and then poured onto ice, the solid thus obtained was recrystalised from methanol.
M.P**. :**171-173 ^{0}C Yield **: 7**6 %. IR(KBr): 3407(NH), 3062,2859(C-H),1727(C=O),1645(C=O of –CO CH_3),1320(C-N), 613(C-Br).^{1}H-NMR ($CDCl_3$) **:** 9.78(s, 1H, -NH-), 2.12(s, 1H, -N-NH-), 6.34- 7.96(m, 11H, Ar-H), 2.70(s, 3H, -CH_3), 2.71(s, 2H, -CH_2). Anal.(%) for $C_{23}H_{18}N_4O_2Br_2$ Calcd; C, 50.93; H, 3.32; N, 10.33; Found; C, 50.35; H, 3.37; N, 10.36.

2-[2-(phenylamino)phenyl]methyl-3-[(4-pyridinyl) acryl amido]-6, 8-dibromo quinazolin-4(3*H*)-one (5a): A solution of 2-(2-phenyl)amino]phenyl methyl-3-acetamido-6,8-dibromo quinazolin-4(3*H*)-one **(**5.42g. 0.01mol) in absolute ethanol (50 mL) and added benzaldehyde (0.01 mol) in 2 % NaOH was refluxed for 10-12 h. cooled and poured into ice cold water. The solid obtained was filtered, washed with water and recrystalised from methanol.

M.P.:91-92 ^{0}C Yield**:** 71 % IR(KBr) : 3411(NH), 3061, 2852(C-H), 1719(C =O), 1653(C=O of –$COCH_3$), 1576 (CH=CH), 1316(C-N), 611(C-Br).^{1}H-NMR($CDCl_3$) **:** 9.78(s, 1H, -NH-), 2.11(s, 1H, -N-NH), 6.34-7.91(m, 15H, Ar-H), 2.61(s, 2H, -CH_2), 6.80(d, 1H,COCH=), 8.62(d, 1H, =CH-Ar).^{13}C NMR:30.5(-CH_2), 36.4,41.6(CH=CH),160.8(immine-C),162.1(>C=O),173.1 (immine aromatic-C) 109.21-143.14 (aromatic-23C). Anal.(%) for $C_{29}H_{21}N_5O_2Br_2$ Calcd; C, 55.15; H, 3.32; N, 11.09; Found; C, 55.17; H, 3.34; N, 11.12.

The remaining 5b-j compounds were prepared by the above mention similar method.

5b: 2-[2-(phenylamino)phenyl]methyl-3-[(2-pyridinyl) acryl amido]-6, 8-dibromo quinazolin-4(3*H*)-one: M.P.: 103-104 ^{0}C Yield: 68% IR(KBr) : 3411(NH), 3061, 2852(C-H), 1719(C =O), 1617(C=O of –$COCH_3$), 1566 (CH=CH), 1317(C-N), 613(C-Br).^{1}H NMR($CDCl_3$) **:** 9.78(s, 1H, -NH-), 2.11(s, 1H, -N-NH), 6.34- 7.91(m, 15H, Ar-H), 3.63 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar).^{13}C NMR: 30.5(-CH_2), 36.4, 41.6 (CH=CH),160.8 (immine-C),162.1(>C=O),173.1(immine aromatic-C) 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{21}N_5O_2Br_2$ Calcd; C, 55.15; H, 3.32; N, 11.09; Found; C, 55.17; H, 3.34; N, 11.12.

5c:2-[2-(phenylamino)phenyl]methyl-3-[4-(2-bromopyridinyl)acrylamido]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 124-125 ^{0}C Yield: 75%. IR(KBr) : 3413(NH), 3071, 2852(C-H), 1729(C =O), 1613 (C=O of –$COCH_3$), 1575 (CH=CH), 1317(C-N), 616(C-Br).^{1}H NMR($CDCl_3$)**:**9.77(s, 1H, -NH-), 2.17(s, 1H, -N-NH), 6.34- 7.91(m, 14H, Ar-H), 3.61 (s, 2H, -CH_2), 6.82(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar). ^{13}C NMR:30.5 (-CH_2), 37.5, 42.9(CH=CH),161.2(immine -C),162.1(>C=O),173.2 (immine aromatic-C) 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{20}N_5O_2Br_3$ Calcd; C, 49.01; H, 2.81; N, 9.85; Found; C, 49.04; H, 2.84; N, 9.87.

5d: 2-[2-(phenylamino) phenyl]methyl-3-[2-(5-bromopyridinyl)acrylamido]-6,8-dibromo quinazolin -4(3*H*)-one: M.P.: 115-116 ^{0}C Yield: 64 % IR(KBr) : 3367(NH), 3064, 2852(C-H), 1719(C =O), 1611 (C=O of –$COCH_3$), 1572 (CH=CH), 1319(C-N), 615(C-Br).^{1}H NMR($CDCl_3$) **:** 9.78(s, 1H, -NH-), 2.11 (s, 1H, -N-NH), 6.34- 7.91(m, 14H, Ar-H), 3.65 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar). ^{13}C NMR : 30.6(-CH_2), 36.5,41.6(CH=CH),161.3(immine -C),162.1(>C=O),173.1 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{20}N_5O_2Br_3$ Calcd; C, 49.01; H, 2.81; N, 9.85; Found; C, 49.03; H, 2.85; N, 9.88.

5e: 2-[2-(phenylamino)phenyl]methyl-3-[2-(6-bromopyridinyl)acrylamido]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 131-132 ^{0}C Yeild: 70% IR(KBr) : 3365(NH), 3061, 2857(C-H), 1729(C =O), 1613(C=O of –$COCH_3$), 1578 (CH=CH), 1314(C-N), 617(C-Br).^{1}H NMR($CDCl_3$) **:** 9.78(s, 1H, -NH-), 2.13 (s, 1H, -N-NH), 6.38- 7.91(m, 14H, Ar-H), 3.63 (s, 2H, -CH_2), 6.82(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar).^{13}C NMR: 29.6(-CH_2), 36.0, 41.5(CH=CH), 160.9(immine -C),162.3(>C=O),173.1 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{20}N_5O_2Br_3$ Calcd; C, 49.01; H, 2.81; N, 9.85; Found; C, 49.05; H, 2.83; N, 9.87.

5f:2-[2-(phenylamino)phenyl]methyl-3-[2-(4-methylpyridinyl)acrylamido]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 143-144 ^{0}C Yield: 73% IR(KBr) : 3413(NH), 3067, 2853(C-H), 1729(C =O), 1615(C=O of –$COCH_3$), 1578 (CH=CH), 1318(C-N), 616(C-Br). ^{1}H NMR($CDCl_3$) **:** 9.79(s, 1H, -NH-), 2.11(s, 1H, -N-NH), 2.83(s, 3H, -CH_3), 6.39- 7.93(m, 14H, Ar-H), 3.63 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.60(d, 1H, =CH-Ar).^{13}C NMR: 31.3(-CH_2), 36.5, 41.1(CH=CH),46.7(-CH_3), 161.3(immine -C), 162.1(>C=O), 173.2(immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{30}H_{23}N_5O_2Br_2$ Calcd; C, 55.81; H, 3.56; N, 10.85; Found; C, 55.85; H, 3.58; N, 10.87.

5g:2-[2-(phenylamino)phenyl]methyl-3-[4-(2-nitropyridinyl)acrylamido]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 168-169 ^{0}C Yield: 69% IR(KBr) : 3369(NH), 3061, 2859(C-H), 1731(C =O), 1615(C=O of –$COCH_3$), 1576 (CH=CH), 1556, 1363(-NO_2), 1316(C-N), 618(C-Br).^{1}H NMR($CDCl_3$) **:** 9.78(s, 1H, -NH-), 2.11(s, 1H, -N-NH), 6.39- 7.94(m, 14H, Ar-H), 3.65 (s, 2H, -CH_2), 6.83(d, 1H, COCH=), 8.62(d,

1H, =CH-Ar).^{13}C NMR : 30.6(-CH_2),36.2, 41.7(CH=CH),161.2(immine -C),162.0(>C=O),172.8(immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{20}N_6O_4Br_2$ Calcd; C, 51.47; H, 2.95; N, 12.42; Found; C, 51.49; H, 2.98; N, 12.45.

5h:2-[2-(phenylamino)phenyl]methyl-3-[2-(4-nitropyridinyl)acrylamido]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 179-180 ^{0}C Yield: 72% IR(KBr) : 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), 617(C-Br).^{1}H NMR($CDCl_3$) **:** 9.79 (s, 1H, -NH-), 2.15(s, 1H, -N-NH), 6.39- 7.93(m, 14H, Ar-H), 3.63 (s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.64(d, 1H, =CH-Ar).^{13}C NMR : 30.5(-CH_2), 36.5,42.2(CH=CH),161.6(immine -C), 162.1 (>C=O), 173.1 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{20}N_6O_4Br_2$ Calcd; C, 51.47; H, 2.95; N, 12.42; Found; C, 51.48; H, 2.97; N, 12.46.

5i:2-[2-(phenylamino)phenyl]methyl-3-[2-(3:5-dibromopyridinyl)acrylamido]-6,8-dibromo quinazo lin -4(3*H*)-one. M.P.: 152-153 ^{0}C Yield: 67% IR(KBr) : 3411(NH), 3071, 2856(C-H), 1728(C =O), 1615 (C=O of –$COCH_3$), 1576 (CH=CH), 1317(C-N),613(C-Br).^{1}H NMR($CDCl_3$)**:** 9.78(s, 1H, -NH-),2.17 (s, 1H, -N-NH), 6.38- 7.93(m, 13H, Ar-H), 3.61 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar). ^{13}C NMR : 30.4(-CH_2),36.0, 41.6(CH=CH),160.9(immine -C),162.0(>C=O),172.9 (immine aromatic-C), 109.13-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{19}N_5O_2Br_4$ Calcd; C, 44.10; H, 2.40; N, 8.87; Found; C, 44.14; H, 2.42; N, 8.89.

5j:2-[2-(phenylamino)phenyl]methyl-3-[4-(2:6-dibromopyridinyl)acrylamido]-6,8-dibromo quina zolin-4(3*H*)-one. M.P.:161-162 ^{0}C Yield: 69% IR(KBr) : 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 ($CDCl_3$) **:** 9.79(s, 1H, -NH-), 2.17(s, 1H, -N-NH), 6.38- 7.93(m, 13H, Ar-H), 3.64 (s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.59 (d,1H, =CH-Ar).^{13}C NMR : 30.6(-CH_2),36.1, 42.7(CH=CH),161.2 (immine-C),162.3(>C=O),173.1 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{19}N_5O_2Br_4$ Calcd; C, 44.10; H, 2.40; N, 8.87; Found; C, 44.12; H, 2.43; N, 8.90.

2-[2-(phenylamino)phenyl]methyl-3–[(4-pyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one (6a): To a solution of 2-(2- phenyl) amino] phenyl methyl-3–[(4-pyridinyl) acryl amido)-6,8- dibromo quinazolin-4(3*H*)- one **(**6.31 g, 0.01 mol) in methanol, add hydrazine hydrate(99 %) (1.0 g, 0.02 mol) and few drops of glacial acetic acid. The reaction mixture was refluxed for 8-10 h, distilled and cooled. The separated solid was filtered, washed with water and recrystalised from methanol. M.P.: 121-123 ^{0}C Yield: 68% IR(KBr): 3369(N-H),3063,2854(C-H),1727(C=O),1616 (C=N), 1318(C-N),781, 617(C-Br). ^{1}H NMR($CDCl_3$):9.78(s,1H,-NH),2.17(d,1H,=N-NH),8.34(s,1H,-N-NH),3.61(s,2H,-CH_2),3.06(d,1Ha), 3.48(d,1Hb),6.53(t,1Hx), 6.34-7.91(m,15H,Ar-H).^{13}C NMR: 30.7(-CH_2),36.3, 41.2, 161.3(pyrazol-C), 162.3(>C=O),173.2(immine aromatic-C) 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{23}N_7OBr_2$ Calcd; C, 53.95; H, 3.56; N, 15.19; Found; C, 53.97; H, 3.58; N, 15.23.

The remaining 6b-j compounds were prepared by the above mention similar method.

6b:2-[2-(phenylamino)phenyl]methyl-3–[(2-pyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 131-133 ^{0}C Yield: 71% IR(KBr): 3412(N-H),3061,2855 (C-H),1732(C=O),1614(C=N), 1319 (C-N),618(C-Br).^{1}H NMR($CDCl_3$):9.79(s,1H,-NH),2.13(d,1H,=N-NH),8.31(s,1H,-N-NH), 3.59(s,2H,-CH_2), 3.05(d,1Ha), 3.46(d,1Hb),6.51(t,1Hx), 6.34-7.91(m,15H,Ar-H).^{13}C NMR: 30.5 (-CH_2), 36.4, 41.6,160.9 (pyrazol-C), 162.1(>C=O),164(immine aromatic-C) 109.21-143.14 (aromatic-23C). Anal.(%) for $C_{29}H_{23}N_7OBr_2$ Calcd; C, 53.95; H, 3.56; N, 15.19; Found; C, 53.96; H, 3.58; N, 15.21.

6c:2-[2-(phenylamino)phenyl]methyl-3-[4-(2-bromopyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 137-139 ^{0}C Yield: 69% IR(KBr):3409(N-H),3077,2854(C-H),1730(C=O),1614(C=N), 1313(C-N), 611(C-Br). ^{1}H NMR($CDCl_3$):9.78(s,1H,-NH),2.14(d,1H,=N-

NH),8.31(s,1H,-N-NH), 3.63(s,2H,-CH_2), 3.07(d,1Ha),3.48(d,1Hb),6.49(t,1Hx), 6.34-7.91(m,14H,Ar-H).^{13}C NMR :31.5 (-CH_2), 36.5, 42.9,161.2 (immine pyrazol-C),162.3(>C=O),172.9(immine aromatic-C) 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{22}N_7OBr_3$ Calcd; C, 48.06; H, 3.03; N, 13.53; Found; C, 48.09; H, 3.06; N, 13.55.

6d: 2-[2-(phenylamino)phenyl]methyl-3-[2-(5-bromopyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 141-143 ^{0}C Yield: 68% IR(KBr):3406(N-H),3061,2854 (C-H),1725(C=O), 1606(C=N), 1321(C-N Stretch), 617(C-Br).^{1}H NMR($CDCl_3$): 9.78(s,1H,-NH), 2.17 (d,1H, =N-NH),8.38(s,1H,-N-NH),3.61 (s,2H,-CH_2), 3.06 (d,1Ha), 3.45(d,1Hb),6.49(t,1Hx), 6.34-7.91(m, 14H, Ar-H).^{13}C NMR : 30.6(-CH_2), 36.5,41.6, 161.3 (immine pyrazol-C),162.1(>C=O),173.1(immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{22}N_7OBr_3$ Calcd; C, 48.06; H, 3.03; N, 13.53; Found; C, 48.08; H, 3.05; N, 13.56.

6e: 2-[2-(phenylamino)phenyl]methyl-3-[2-(6-bromopyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 139-140 ^{0}C Yield:70% IR(KBr):3361(N-H),3054,2864(C-H), 1732(C=O),1613(C=N), 1312(C-N), 620(C-Br).^{1}HNMR($CDCl_3$):9.77(s,1H,-NH),2.13(d,1H,=N-NH), 8.28(s,1H,-N-NH), 3.62(s,2H,-CH_2), 3.05 (d,1Ha),3.48(d,1Hb),6.49(t,1Hx), 6.34-7.91(m,14H,Ar-H).^{13}C NMR :29.6 (-CH_2),36.0, 41.5, 160.9 (immine pyrazol-C),162.3(>C=O),173.1(immine aromatic-C), 109.21 -143.14(aromatic-23C). Anal.(%) for $C_{29}H_{22}N_7OBr_3$ Calcd; C, 48.06; H, 3.03; N, 13.53; Found; C, 48.07; H, 3.05; N, 13.57.

6f:2-[2-(phenylamino)phenyl]methyl-3-[2-(4-methylpyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 146-148 ^{0}C Yield: 73% IR(KBr): 3412(N-H),3061, 2855(C-H),1732 (C=O),1614 (C=N), 1319(C-N), 618(C-Br).^{1}H NMR($CDCl_3$):9.79(s,1H,-NH),2.19(d,1H,=N-NH), 2.84(s, 3H, -CH_3), 8.31(s,1H,-N-NH),3.64(s,2H,-CH_2), 3.06(d,1Ha),3.51 (d,1Hb),6.53(t,1Hx), 6.34-7.91(m,14H,Ar-H).^{13}C NMR:31.3(-CH_2),36.5,41.1,161.3 (immine pyrazol-C),46.8(-CH_3), 162.3 (>C=O), 173.3 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{30}H_{25}N_7OBr_2$ Calcd; C, 54.62; H, 3.79; N, 14.87; Found; C, 54.66; H, 3.81; N, 14.89.

6g:2-[2-(phenylamino)phenyl]methyl-3-[4-(2-nitropyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 133-135 ^{0}C Yield:67% IR(KBr):3367(N-H),3060,2868(C-H), 1737(C=O),1616(C=N), 1563, 1365(-NO_2),1319(C-N), 611(C-Br). ^{1}H NMR($CDCl_3$):9.77(s,1H,-NH), 2.19(d,1H,=N-NH), 8.30(s,1H,-N-NH), 3.61(s,2H,-CH_2), 3.06(d,1Ha),3.48(d,1Hb),6.51(t,1Hx), 6.34-7.91(m,14H,Ar-H).^{13}C NMR : 30.6(-CH_2), 36.2, 41.7, 161.2(immine pyrazol-C),162.3 (>C=O), 172.8 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{22}N_8O_3Br_2$ Calcd; C, 50.43; H, 3.18; N, 16.23; Found; C, 50.46; H, 3.21; N, 16.25.

6h:2-[2-(phenylamino)phenyl]methyl-3-[2-(4-nitropyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 143-145 ^{0}C Yield: 70% IR(KBr): 3417(N-H),3065,2852 (C-H),1730(C=O),1615 (C=N), 1565,1361(-NO_2), 1322 (C-N), 620(C-Br).^{1}H NMR($CDCl_3$):9.79(s,1H,-NH), 2.14(d,1H,=N-NH), 8.31(s,1H,-N-NH), 3.62(s,2H,-CH_2), 3.07(d,1Ha),3.48(d,1Hb),6.49(t,1Hx), 6.34-7.91(m,14H,Ar-H).^{13}C NMR : 30.5(-CH_2), 36.5,42.2, 161.6(immine pyrazol-C),162.1 (>C=O), 173.1 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{22}N_8O_3Br_2$ Calcd; C, 50.43; H, 3.18; N, 16.23; Found; C, 50.45; H, 3.20; N, 16.24.

6i:2-[2-(phenylamino)phenyl]methyl-3-[2-(3:5-dibromopyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino] -6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 147-149 ^{0}C Yield: 75%. IR(KBr): 3410 (NH), 3075,2854(C-H),1732(C=O),1613(C=N), 1313(C-N), 613(C-Br).^{1}H NMR($CDCl_3$):9.77(s,1H,-NH),2.19 (d,1H,=N-NH),8.33(s,1H,-N-NH),3.61(s,2H,-CH_2), 3.06(d,1Ha), 3.48 (d,1Hb),6.54(t,1Hx), 6.34-7.91 (m,13H,Ar-H).^{13}C NMR: 30.4(-CH_2),36.0, 41.6,160.9 (immine pyrazol-C), 162.0(>C=O),172.9(immine

aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{21}N_7OBr_4$ Calcd; C, 43.03; H, 2.61; N, 12.20; Found; C, 43.05; H, 2.64; N, 12.24.

6j:2-[2-(phenylamino)phenyl]methyl-3-[4-(2:6-dibromopyridinyl)-1,5-dihydro-1*H*-pyrazol-3-ylamino]-6,8-dibromo quinazolin-4(3*H*)-one: M.P.: 152-153 ^{0}C Yield: 70% IR(KBr):3367(NH),3053, 2854(C-H),1729(C=O),1612(C=N), 1312 (C-N), 616(C-Br). ^{1}H NMR($CDCl_3$): 9.77(s,1H,-NH), 2.17(d, 1H,=N-NH),8.33(s,1H,-N-NH),3.61(s,2H,-CH_2), 3.05(d,1Ha),3.48 (d,1Hb) ,6.52 (t,1Hx), 6.34-7.91 (m,13H,Ar-H). ^{13}C NMR: 30.6(-CH_2), 36.1, 42.7, 161.2(immine pyrazol-C),162.3 (>C=O), 173.1 (immine aromatic-C), 109.21-143.14(aromatic-23C). Anal.(%) for $C_{29}H_{21}N_7OBr_4$ Calcd; C, 43.03; H, 2.61; N, 12.20; Found; C, 43.04; H, 2.65; N, 12.23.

RESULTS AND DISCUSSION

The title compounds quinazolin-4(3H) ones derivatives 6a-j was synthesized according to the conventional method based catalyzed cyclization of acid chloride 1 with 3:5 dibromoanthranilic acid in pyridine at 0-5 ^{0}C yielded benzoxazinone 2 which showed strong C=O stretching at 1734 cm^{-1}. The benzoxazinone 2 on condensation reaction with hydrazine hydrate and then acetylation with acetyl chloride afforded acetamido quinazolin-4(3H) one 4. The IR spectra showing strong stretching vibration at 1723 and 1649 cm^{-1} indicates the presence of C=O group of quinazolinone and actamide respectively. This was further confirming by ^{1}H NMR spectra which showed singlet at δ 2.24 ppm equivalent to three protons of actamide group. The acetamido quinazolin-4(3H) one 4 on based catalysed condensation with heterocyclic aldehydes yielded acrylamide 5a-j which showed CH=CH stretching at around 1576 cm^{-1} in IR spectrum while ^{1}H NMR spectra showed doublet of these protons at around δ 6.7 and δ 7.8 ppm with coupling constant *J*= 16.0-16.6 Hz. Further cyclization of acrylamide 5a-j with hydrazine hydrate yielded the desired compounds pyrazolyl quinazolin-4(3H) ones 6a-j. The IR spectra of of compounds 6a-j showed C=O and C=N stretching of quinazolinone at around 1720 and 1610 cm^{-1} respectively. The ^{1}H NMR spectra of compounds 6a-j indicates that the –CH_2 protons of the pyrazoline ring resonated as a pair of doublet of doublets (Ha and Hb) because of germinal and vicinal coupling. The CH proton appeared as a doublet of doublet (Hx) because of vicinal coupling with the two magnetically nonequivalent protons of methylene group at position 4 of pyrazolin ring. The Ha proton which is cis to Hx resonates upfield in the range δ 3.01-3.08 ppm as a doublet of doublet while Hb, the other proton which is trans to Hx resonates downfield in the range of δ 3.45-3.51 ppm as a doublet of doublet. The Hx proton which is vicinal to two methylene protons (Ha and Hb) resonates as a doublet of doublet in the range of δ 5.45-5.52 ppm. In ^{13}C NMR spectra, signals at around δ 36 ppm, δ 55 ppm and δ 161 ppm confirms the presence of CH_2, CH and C=N of pyrazoline ring respectively, whereas C=O and C=N signals of quinazolinone ring are appear at around δ 162 and δ 168 ppm respectively.

APPLICATIONS

Antimicrobial activity: The *in vitro* antimicrobial activity of compounds 6a-j was carried out by cup-plate method (Barry 1976). Antibacterial activity was screened against two gram positive bacteria (Staphylococcus aureus ATCC 9144 and Bacillus Subtilis ATCC 6633) and two gram negative bacteria(Escherichia coli ATCC 25922 and Pseudomonas aeruginosa ATCC 9027), by measuring the zone of inhibition on agar plates at two different concentrations 100 and 50 μg mL^{-1} (Table 1), whereas antifungal activity was tested by measuring the zone of inhibition on agar plates with two fungal species, Candida albicans ATCC 10231 and Aspergillus niger ATCC 6275, at two different concentrations 20 and 10 μg mL^{-1} (Table 2). Penicillin-G and fluconazole were used as standard drugs.

Table: 1 Anti-bacterial activity of compound 6a-j

Compd	R	Zone of inhibition in (mm)											
		S. aureus ATCC 9144			***B. subtilis*** ATCC 6633			**E.coli ATCC 25922**			**P.aeruginosa ATCC 9027**		
		C_H	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**
6a	2-H	12	10	42.34	13	11	44.60	12	10	42.34	13	11	44.60
6b	4-H	13	11	44.60	13	11	44.60	11	09	40.18	12	10	42.34
6c	2-Br	14	12	46.98	17	16	51.25	12	10	42.34	13	11	44.60
6d	5-Br	16	14	52.14	17	15	56.20	**18**	**14**	**62.76**	**19**	**15**	**65.36**
6e	6-Br	17	16	51.25	16	14	52.14	15	13	59.50	15	13	59.50
6f	4-CH_3	17	15	56.20	17	15	56.20	15	12	52.82	16	13	55.29
6g	2-NO_2	15	13	49.50	16	14	52.14	**17**	**13**	**60.27**	**18**	**14**	**62.76**
6h	4-NO_2	16	14	52.14	17	16	51.25	16	13	55.29	17	14	57.86
6i	3:5-Br	**18**	**17**	**60.96**	**20**	**17**	**66.34**	14	11	50.47	15	12	52.82
6j	4:-Br	**20**	**16**	**68.09**	**21**	**17**	**70.87**	15	13	49.50	16	14	52.14
Penicillin-G		30	25	100	30	25	100	30	25	100	30	25	100

C_H Zone of inhibition at concentration 100 µg mL^{-1},
C_L Zone of inhibition at concentration 50 µg mL^{-1},
potency of compound(%) as compared to penicillin-G.

Table: 2 Antifungal activity of compound 6a-j

Compd No.	R	Zone of inhibition in (mm)					
		C.albicans ATCC 10231			A.niger ATCC 6275		
		C_H	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**
6a	2-H	**17**	**13**	**61.80**	**18**	**14**	**64.86**
6b	4-H	**19**	**17**	**65.64**	**20**	**18**	**69.71**
6c	2-Br	17	16	55.76	16	13	57.05
6d	5-Br	15	12	54.08	15	13	51.60
6e	6-Br	14	12	48.59	14	12	48.59
6f	4-CH_3	13	11	45.75	12	10	43.08
6g	2-NO_2	12	10	43.08	11	09	40.53
6h	4-NO_2	11	09	40.53	10	08	38.19
6i	3:5-Br	11	09	40.53	11	10	36.91
6j	4:6-Br	10	08	38.19	11	09	40.53
Fluconazole		28	22	100	28	22	100

C_H Zone of inhibition at concentration 20 µg mL^{-1}, C_L Zone of inhibition at Concentration10 µg mL^{-1}, potency of compound (%) as compared to fluconazole.

CONCLUSIONS

We have used simple work with conventional methods and synthesizes the clean products of novel heterocycles 6, 8-dibromoquinazolin-4(3H) ones derivatives 6a-j. The newly synthesized compounds possess active pharmacophore. Antimicrobial screening results of synthesized compounds shows good activity *in vitro*. Compound 6i and 6j active against Gram positive bacteria, compound 6d and 6g active against Gram negative and compound 6a and 6b active against fungi compared to standard. Overall results lead to focus on identified for active inhibitor and better future for improvement of further research on these molecules.

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AUTHORS' ADDRESSES

1. **Dr. N. B. PATEL**
Professor, Department of Chemistry,
VNSGU-Surat-395007, Gujarat, India.
Mob: 09825350484, Email:drnavinbpatel@gmail.com
2. **Dr. G. G. BARAT**
Asso. Professor, Department of Chemistry,
Arts, Science and Commerce College, Pilvai-382850, Gujarat, India.
Mob No. 09429727545, Email: gamanbarat@gmail.com.