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Synthesis and Pharmacological Aspects of Some Novel Nitrogen Containing Heterocycles With 6-Iodo Quinazolin-4(3H) Ones

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ABSTRACT

*Several 6-iodo quinazolin-4(3H) ones **6a-l** were synthesized by the cyclization of acrylamide 5**a-l** with hydrazine hydrate. The overall reaction was carried out by multistep process. The base catalyzed cyclization of acid chloride **1** with 5-iodo 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 as well as IR and NMR spectra results. The title compounds were evaluated for antibacterial and antifungal activity in vitro.*

Keywords: Acryl amide, Antimicrobial activity, Quinolin, Quinazolin-4(3H) one.

INTRODUCTION

Quinolin nucleus is an important pharmacophore in medicinal chemistry, since a large number of its derivatives possess useful biological properties. 4(3*H*)-quinazolinones have emerged as an important class of nitrogenated heterocyclic that have attached synthetic interest because of they possess good pharmacological and therapeutic properties, along with quinolin moiety played vital role in the medicinal chemistry. The large number of synthetic compounds with pyrazoline and quinolin nucleus used for antibacterial[1-2], antimycobacterial[3], analgesics[4], antifungal[5-6], anticonvulsant[7], rheumatic arthritis[8], antinociceptive[9], anxiolytic activity[10] ,anti-inflammatory and anti-breast cancer agent[11]. A Quinazolinones system possess pyrazoline moiety at C-3 positions to yield the potential anti-tumor and antidiabetic activities[12]. Its halogenated derivatives possess potential antihyperlipidemic activity[13] and have no significant toxic side effects at the drop sub lethal dose level (2mg/kg). There are broad spectrum of therapeutic values of pyrazoline with 4(3H)-Quinazolinones for the pharmacological activity [14-20]. In the light of these findings, the synthesis of new chemical entities incorporating the quinolin and pyrazoles with quinazolinones may prove to be useful from the biological activity point of view.

MATERIALS AND METHODS

The melting points of all synthesized compounds were taken in open capillary tube and are uncorrected. 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 shift are 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 providing satisfactory results. The purities of all the compounds were checked by TLC on Merck silica gel 60 F 254 using toluene : ethylacetate (8:2) as mobile phase, and spots were visualized under UV radiation. The reagent grade chemicals were purchased from commercial sources and further purified before use. 3-(6-chloro-2-phenylquinolin) acetyl chloride **1** was synthesized by literature procedure (Furniss et al., 1989).

Synthesis of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl] methyl–6-iodo-3, 1-benzoxazin-4(3*H*) one 2: To the solution of 3-(6-chloro-2-phenylquinolin)acetyl chloride (3.16 g, 0.01 mol) in pyridine (25ml) kept on an ice bath at 0-5 ^{0}C. Add each small portion of 5-iodo anthranilic acid (2.63 g, 0.01 mol) was added portion wise and were stirred for 1 h. to maintain temperature 0-5 ^{0}C. Furthere reaction mixture was stirred 1h 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 recrystallized from methanol. M.P.: 162 ^{0}C. Yeild : 79 % IR(KBr):3071,2859(C-H),1723(C=O),1616(C=N),1325(C-N),1237(C-O-C), 781(C-Cl),504(C-I).Anal. (%) for $C_{24}H_{14}N_2O_2ICl$ Calcd; C, 54.90; H, 2.66; N, 5.33; Found; C, 54.93; H, 2.67; N, 5.35.

Synthesis of 3-Amino-2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl–6-iodoquinazolin–4(3*H*) one 3: To a mixture of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl–6-iodo-3,1-benzoxazin-4(3*H*) one (5.245 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 recrystallized from ethanol. M.P. **:**145 ^{0}C. Yeild **:** 74 % IR(KBr) : 3405(NH), 3068, 2865(C-H), 1719(C=O), 1614(C=N), 1323(C-N), 778(C-Cl), 508(C-I). ^{1}HNMR($CDCl_3$)**:** 2.1(s, 2H, -N-NH_2), 6.37-7.94(m, 12H, Ar-H), 2.72(s, 2H, -CH_2). Anal. (%) for $C_{24}H_{16}N_4OICl$ Calcd; C, 53.48; H, 2.97; N,10.40; Found; C, 53.49; H, 2.99; N, 10.42.

Synthesis of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-acetamido-6-iodoquinazolin-4(3*H*)-one 4 : To a solution of 3-Amino-2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl–6-iodoquinazolin–4(3*H*) one **(**5.385 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 recrystallized from methanol. M.P. **:**173 ^{0}C. Yeild **:** 69 % IR(KBr): 3405(NH), 3063,2860(C-H),1723(C=O), 1642(C=O of –$COCH_3$), 1321(C-N), 779(C-Cl), 513(C-I). ^{1}H-NMR($CDCl_3$) **:** 2.12(s, 1H, -N-NH-), 6.33- 7.96(m, 12H, Ar-H), 2.72(s, 3H, -CH_3), 2.62(s, 2H, -CH_2). Anal. (%) for $C_{26}H_{18}N_4O_2ICl$ Calcd; C, 53.74; H, 3.10; N, 9.64; Found; C, 53.76; H, 3.11; N, 9.66.

Synthesis of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-substituted phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one 5a : A solution of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-acetamido-6-iodoquinazolin-4(3*H*)-one **(**5.805g, 0.01 mol) 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 recrystallized from methanol. M.P.**:** 137 ^{0}C. Yeild**:** 76 % IR(KBr) : 3409(NH), 3061, 2857(C-H), 1718(C =O), 1651(C=O of –$COCH_3$), 1577 (CH=CH), 1317(C-N), 780(C-Cl), 511(C-I).^{1}H-NMR($CDCl_3$) **:** 2.11(s, 1H, -N-NH), 6.34- 7.91(m, 17H, Ar-H), 2.61 (s, 2H, -CH2),

6.81(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar). Anal; (%) $C_{33}H_{22}N_4O_2ICl$ Calcd; C, 59.23; H, 3.29; N, 8.37; Found; C, 59.24; H, 3.30; N, 8.39.

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

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(2-chloro)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5b) : M.P.**:** 131-133 ^{0}C. Yeild**:** 70 % IR(KBr) : 3367(NH), 3061, 2855(C-H), 1727(C =O), 1613(C=O of –$COCH_3$), 1579 (CH=CH), 1314(C-N), 781(C-Cl), 511(C-I). ^{1}H NMR($CDCl_3$) **:** 2.13(s, 1H, -N-NH), 6.38- 7.91(m, 16H, Ar-H), 3.63 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar). ^{13}C NMR: 29.5(-CH_2), 36.1, 41.6(CH=CH), 160.9 (immine>C=O), 162.1 (>C=O), 173.1(immine aromatic-C), 109.20-143.16(aromatic-27C). Anal; (%) $C_{33}H_{21}N_4O_2ICl_2$ Calcd; C, 56.33; H, 2.99; N,7.96; Found; C, 56.34; H, 3.01; N, 7.97.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(3-chloro)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5c) : M.P.**:** 134-135 ^{0}C. Yeild**:** 72 % IR(KBr) : 3371(NH), 3065, 2858(C-H), 1729(C =O), 1615(C=O of –$COCH_3$), 1577 (CH=CH), 1316(C-N), 779(C-Cl), 509(C-I). ^{1}H NMR($CDCl_3$) **:** 2.11(s, 1H, -N-NH), 6.39- 7.93(m, 16H, Ar-H), 3.61 (s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar). ^{13}C NMR: 31.3(-CH_2), 36.5, 41.1(CH=CH), 161.3(immine>C=O), 162.3(>C=O), 173.2(immine aromatic-C), 109.13-143.17(aromatic-27C). Anal; (%) $C_{33}H_{21}N_4O_2ICl_2$ Calcd; C, 56.33; H, 2.99; N,7.96; Found; C, 56.35; H, 3.02; N, 7.98.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(4-chloro)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5d) : M.P.**:** 127-129 ^{0}C. Yeild**:** 72 % IR(KBr) : 3368(NH), 3063, 2856(C-H), 1727(C =O), 1617(C=O of –$COCH_3$), 1578(CH=CH), 1317(C-N), 781(C-Cl), 513(C-I). ^{1}H NMR($CDCl_3$) **:**2.11(s, 1H, -N-NH), 6.37- 7.96(m, 16H, Ar-H), 3.63(s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar). ^{13}C NMR: 30.6(-CH_2), 36.2, 41.3(CH=CH), 161.4 (immine >C=O),162.0(>C=O), 173.1(immine aromatic-C), 109.17-143.21(aromatic-27C). Anal; (%) $C_{33}H_{21}N_4O_2ICl_2$ Calcd; C, 56.33; H, 2.99; N,7.96; Found; C, 56.35; H, 3.01; N, 7.97.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(2-hydroxy)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5e) : M.P.**:** 146-148 ^{0}C. Yeild**:** 71 % IR (KBr) : 3549(-OH),3413(NH), 3061, 2854(C-H), 1719(C =O), 1619(C=O of –$COCH_3$), 1572 (CH=CH), 1319(C-N), 779(C-Cl), 507(C-I). ^{1}H NMR($CDCl_3$) **:**2.11(s, 1H, -N-NH),6.34- 7.91(m,16H, Ar-H),3.62 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar), 10.36(s, 1H,-OH). ^{13}C NMR: 30.7(-CH_2), 36.3, 41.4(CH=CH),160.9 (immine>C=O),162.1 (>C=O), 173.1(immine aromatic-C), 109.3-143.4(aromatic-27C). Anal; (%) $C_{33}H_{22}N_4O_3ICl$ Calcd; C, 57.85; H, 3.21; N,8.18; Found; C, 57.86; H, 3.23; N, 8.19.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3-(3-hydroxy)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5f) : M.P.**:**151-153 ^{0}C. Yeild**: 6**7 % IR(KBr) : 3552(-OH),3416(NH), 3067, 2852(C-H), 1721(C =O), 1615(C=O of –$COCH_3$), 1574 (CH=CH), 1318(C-N), 780(C-Cl), 510(C-I). ^{1}H NMR($CDCl_3$) **:**2.17(s, 1H, -N-NH), 6.36- 7.96(m, 16H, Ar-H), 3.63 (s, 2H, -CH_2), 6.82(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar),10.38(s,1H,-OH).^{13}C NMR: 30.8(-CH_2), 37.5, 42.7(CH=CH), 161.2 (immine>C=O),162.2 (>C=O), 173.3(immine aromatic-C), 109.21-143.27(aromatic-27C). Anal; (%) $C_{33}H_{22}N_4O_3ICl$ Calcd; C, 57.85; H, 3.21; N,8.18; Found; C, 57.87; H, 3.23; N, 8.20.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3-(4-hydroxy)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5g) : M.P.**:** 157-159 ^{0}C. Yeild**:**70 % IR(KBr): 3557(-OH),3411(NH), 3064, 2854(C-H), 1720(C =O), 1613(C=O of –$COCH_3$), 1571(CH=CH), 1319(C-N), 782(C-Cl), 509(C-I). ^{1}H NMR($CDCl_3$)**:** 2.11(s, 1H, -N-NH),6.35- 7.93(m,16H, Ar-H),3.62 (s, 2H, -CH_2), 6.80(d, 1H, COCH=), 8.61(d, 1H, =CH-Ar), 10.36(s,1H,-OH).^{13}C NMR: 30.7(-CH_2), 36.5,41.5 (CH=CH), 161.1

(immine>C=O),162.3(>C=O),173.1 (immine aromatic-C), 108.78-143.24 (aromatic-27C). Anal; (%) $C_{33}H_{22}N_4O_3ICl$ Calcd; C, 57.85; H, 3.21; N,8.18; Found; C, 57.86; H, 3.21; N, 8.20.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(2-nitro)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5h) : M.P.**:** 169-171 ^{0}C. Yeild**:** 68 % IR(KBr) : 3413(NH), 3061, 2852(C-H), 1721(C =O), 1614(C=O of –$COCH_3$), 1572(CH=CH), 1317(C-N),1565,1367(-NO_2) 779(C-Cl), 507(C-I). ^{1}H NMR($CDCl_3$)**:** 2.15(s, 1H, -N-NH), 6.36- 7.91(m, 16H, Ar-H), 3.61 (s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar). ^{13}C NMR: 30.5(-CH_2), 36.6, 42.3(CH=CH),161.4(immine >C=O), 162.1(>C=O), 173.2 (immine aromatic-C), 108.89-143.13(aromatic-27C). Anal; (%) $C_{33}H_{21}N_5O_4ICl$ Calcd; C, 55.50; H, 2.94; N,9.81; Found; C, 55.53; H, 2.96; N, 9.83.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(3-nitro)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5i) : M.P.**:** 174-176 ^{0}C. Yeild**:** 66 % IR(KBr) : 3411(NH), 3063, 2854(C-H), 1723(C =O), 1615(C=O of –$COCH_3$), 1574(CH=CH), 1319(C-N),1561,1363(-NO_2), 781(C-Cl), 509(C-I). ^{1}H NMR($CDCl_3$)**:** 2.17(s, 1H, -N-NH), 6.37- 7.92(m, 16H, Ar-H), 3.63(s, 2H, -CH_2), 6.80(d, 1H, COCH=),8.61(d,1H,=CH-Ar).^{13}CNMR:30.6(-CH_2), 36.4,42.2(CH=CH), 161.1(immine>C=O), 162.0 (>C=O), 173.3 (immine aromatic-C), 109.13-143.14(aromatic-27C). Anal; (%) $C_{33}H_{21}N_5O_4ICl$ Calcd; C, 55.50; H, 2.94; N,9.81; Found; C, 55.51; H, 2.95; N, 9.82.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(4-nitro)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5j) : M.P.**:** 181-182 ^{0}C. Yeild**:** 70 % IR(KBr) : 3415(NH), 3059, 2857(C-H), 1724(C =O), 1613(C=O of –$COCH_3$), 1572 (CH=CH),1563,1366(-NO_2),1317(C-N), 778(C-Cl), 507(C-I). ^{1}H NMR($CDCl_3$)**:** 2.16(s, 1H, -N-NH), 6.39- 7.94(m, 16H, Ar-H), 3.62 (s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.60(d, 1H, =CH-Ar).^{13}CNMR:30.4(-CH_2), 36.3,42.3(CH=CH),161.2(immine>C=O), 162.1 (>C=O),173.2 (immine aromatic-C),109.19-143.13(aromatic-27C). Anal; (%) $C_{33}H_{21}N_5O_4ICl$ Calcd; C, 55.50; H, 2.94; N, 9.81; Found; C, 55.53; H, 2.96; N, 9.84.

Spectral data of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-(2-methoxy)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5k) : M.P.**:**141-143 ^{0}C. Yeild**:** 72 % IR(KBr) : 3412(NH), 3061, 2856(C-H), 1723(C =O), 1614(C=O of –$COCH_3$),1573(CH=CH),1319(C-N),1243,1109(C-O-C),781(C-Cl),509(C-I).^{1}H-NMR($CDCl_3$)**:** 2.15(s, 1H, -N-NH),6.38- 7.91(m,16H, Ar-H), 3.63 (s, 2H, -CH_2),6.80(d,1H, COCH=),8.62(d,1H, =CH-Ar), 3.77(s,3H,-OCH_3).^{13}CNMR:30.5(-CH_2),36.5,41.9(CH=CH), 59.5(-OCH_3) 161.3(immine >C=O), 162.2 (>C=O),173.1(immine aromatic-C),109.17-143.21(aromatic-27C).Anal;(%) $C_{34}H_{24}N_4O_3ICl$ Calcd; C, 58.41; H, 3.43; N,8.01; Found; C, 58.43; H, 3.45; N, 8.03.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl] methyl-3-(4-methoxy)phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (5l) : M.P.**:** 149-151 ^{0}C. Yeild**:** 75 % IR(KBr) : 3409(NH), 3063, 2859(C-H), 1721(C =O), 1615(C=O of –COCH3), 1575(CH=CH), 1317(C-N),1245,1108(C-O-C),778(C-Cl), 509(C-I). ^{1}H NMR($CDCl_3$)**:** 2.16(s, 1H, -N-NH), 6.39- 7.93(m, 16H, Ar-H), 3.62 (s, 2H, -CH_2), 6.81(d, 1H, COCH=), 8.62(d, 1H, =CH-Ar), 3.80(s,3H,-OCH_3).^{13}C NMR: 30.6(-CH_2), 36.6,42.4(CH=CH),59.7(-OCH_3),161.1(immine >C=O),162.3 (>C=O), 173.2(immine aromatic-C), 109.21-143.20(aromatic-27C). Anal; (%) $C_{34}H_{24}N_4O_3ICl$ Calcd; C, 58.41; H, 3.43; N,8.01; Found; C, 58.42; H, 3.44; N, 8.04.

Synthesis of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl] methyl-3–(5-phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino)-6-iodo quinazolin-4(3*H*)-one 6a : To a solution of 2-[3-(6-chloro-2-phenyl)quinolin-3-yl]methyl-3-substituted phenyl acryl amido-6-iodoquinazolin-4(3*H*)-one (6.685 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 recrystallized from methanol. M.P.**:** 141-143 ^{0}C. Yeild**:** 78 % IR(KBr): 3369(N-H),3063,2857(C-H),1725(C=O),1616(C=N), 1319(C-N),780(C-Cl),507(C-I).^{1}H NMR($CDCl_3$): 2.17(d,1H,=N-NH), 8.32(s,1H,-N-NH), 3.61(s,2H,-CH_2), 3.06 (d,1Ha), 3.47(d,1Hb), 6.53(t,1Hx), 6.43-7.95(m,17H,Ar-H). ^{13}C

NMR: 30.6(-CH_2), 36.4, 41.1, 161.3(pyrazol-C), 162.2 (>C=O), 173.1(immine aromatic-C) 109.1-143.2(aromatic-27C). Anal; (%) $C_{34}H_{24}N_6OICl$ Calcd; C, 58.02; H, 3.51; N,12.30; Found; C, 58.04; H, 3.54; N, 12.32.

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

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(2-chloro)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6b) : M.P.**:** 135-137 ^{0}C. Yeild**:** 68 % IR(KBr):3368(N-H),3059,2861(C-H),1729(C=O),1616(C=N), 1315(C-N), 782(C-Cl), 509(C-I). ^{1}H NMR($CDCl_3$): 2.13(d,1H,=N-NH),8.28(s,1H,-N-NH),3.63(s,2H,-CH_2), 3.05 (d,1Ha), 3.47(d,1Hb), 6.52 (t,1Hx), 6.42-7.96(m,16H,Ar-H).^{13}C NMR: 30.4(-CH_2), 36.2, 41.5, 160.7 (immine pyrazol-C),162.2 (>C=O),173.1(immine aromatic-C), 108.92-143.25(aromatic-27C). Anal; (%) $C_{33}H_{23}N_6OICl_2$ Calcd; C, 55.23; H, 3.20; N,11.71; Found; C, 55.24; H, 3.22; N, 11.73.

Spectral data of 6c: 2-[3-(6-chloro-2-phenyl) quinolin-3-yl] methyl-3–[5-(3-chloro) phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6c) : M.P.**:** 123-124 ^{0}C. Yeild**:** 72 % IR(KBr): 3371(N-H),3061, 2856(C-H),1731 (C=O),1614(C=N), 1318(C-N), 780(C-Cl),511(C-I). ^{1}H NMR($CDCl_3$):2.16(d,1H,=N-NH),8.30(s,1H,-N-NH),3.64(s,2H,-CH_2), 3.06 (d,1Ha), 3.51(d,1Hb), 6.57 (t,1Hx), 6.43-7.96(m,16H,Ar-H). ^{13}C NMR: 31.3(-CH_2), 36.4, 41.3,161.3 (immine pyrazol-C),162.1 (>C=O),173.3(immine aromatic-C), 109.13-143.17(aromatic-27C). Anal; (%) $C_{33}H_{23}N_6OICl_2$ Calcd; C, 55.23; H, 3.20; N,11.71; Found; C, 55.25; H, 3.21; N, 11.72.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl] methyl-3–[5-(4-chloro) phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6d) : M.P.**:**132-133 ^{0}C. Yeild**:** 75 % IR(KBr):3367(N-H),3060,2866(C-H),1735(C=O),1616(C=N),1317(C-N), 782(C-Cl),510(C-I). ^{1}H NMR ($CDCl_3$): 2.18 (d,1H,=N-NH),8.32 (s,1H,-N-NH),3.61(s,2H,-CH_2), 3.05 (d,1Ha), 3.48(d,1Hb), 6.53(t,1Hx), 6.44-7.95(m,16H,Ar-H).^{13}C NMR: 31.6(-CH_2), 36.2, 41.5, 161.2 (immine pyrazol-C),162.2 (>C=O),172.9(immine aromatic-C), 109.17-143.21(aromatic-27C). Anal; (%) $C_{33}H_{23}N_6OICl_2$ Calcd; C, 55.23; H, 3.20; N,11.71; Found; C, 55.26; H, 3.22; N, 11.73.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(2-hydroxy)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6e) : M.P.**:**152-153 ^{0}C.Yeild**:** 70 % IR(KBr):3548(O-H),3415(N-H),3063,2856 (C-H),1733(C=O),1614 (C=N), (C-N), 780(C-Cl),511(C-I).^{1}H NMR($CDCl_3$): 2.14(d,1H,=N-NH), 8.32(s,1H,-N-NH), 3.62(s,2H,-CH_2), 3.06(d,1Ha), 3.45(d,1Hb), 6.52(t,1Hx), 6.44-7.96(m,16H,Ar-H),10.39(s,1H,-OH). ^{13}C NMR: 30.6(-CH_2), 36.4, 41.5,160.8(pyrazol-C), 162.1(>C=O),172.9(immine aromatic-C) 109.23-143.21(aromatic-27C). Anal; (%) $C_{33}H_{24}N_6O_2ICl$ Calcd; C, 56.69; H, 3.43; N,12.02; Found; C, 56.70; H, 3.45; N, 12.03.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(3-hydroxy)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6f) : M.P.**:** 157-159 ^{0}C.Yeild**:** 69 %IR(KBr): 3549(O-H), 3409(N-H), 3067,2855(C-H), 1731(C=O), 1617 (C=N),1314(C-N), 782(C-Cl),508(C-I). ^{1}H NMR($CDCl_3$): 2.16(d,1H,=N-NH), 8.34(s,1H,-N-NH), 3.63 (s,2H,-CH_2), 3.05(d,1Ha), 3.46 (d,1Hb), 6.51(t,1Hx), 6.43-7.96(m,16H,Ar-H),10.35(s,1H,-OH). ^{13}C NMR: 30.7(-CH_2), 36.5, 41.9,161.2 (immine pyrazol-C), 162.3(>C=O),172.7 (immine aromatic-C) 109.15-143.19 (aromatic-27C). Anal; (%) $C_{33}H_{24}N_6O_2ICl$ Calcd; C, 56.69; H, 3.43; N,12.02; Found; C, 56.71; H, 3.44; N, 12.05.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(4-hydroxy)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6g) : M.P.: 163-165 ^{0}C.Yield: 72 % IR(KBr): 3553(O-H), 3411(N-H), 3061,2856 (C-H),1725(C=O), 1614 (C=N),1316(C-N), 778(C-Cl), 513(C-I). ^{1}H NMR($CDCl_3$): 2.17(d,1H,=N-NH), 8.36(s,1H,-N-NH), 3.61 (s,2H,-CH_2), 3.06(d,1Ha), 3.46(d,1Hb), 6.52(t,1Hx), 6.44-7.96(m,16H,Ar-H), 10.34(s,1H,-OH). ^{13}C NMR: 30.6(-CH_2), 36.3,41.6,161.1(immine

pyrazol-C),162.1(>C=O),173.1(immine aromatic-C), 109.17-143.16(aromatic-27C). Anal; (%) $C_{33}H_{24}N_6O_2ICl$ Calcd; C, 56.69; H, 3.43; N,12.02; Found; C, 56.71; H, 3.45; N, 12.04.

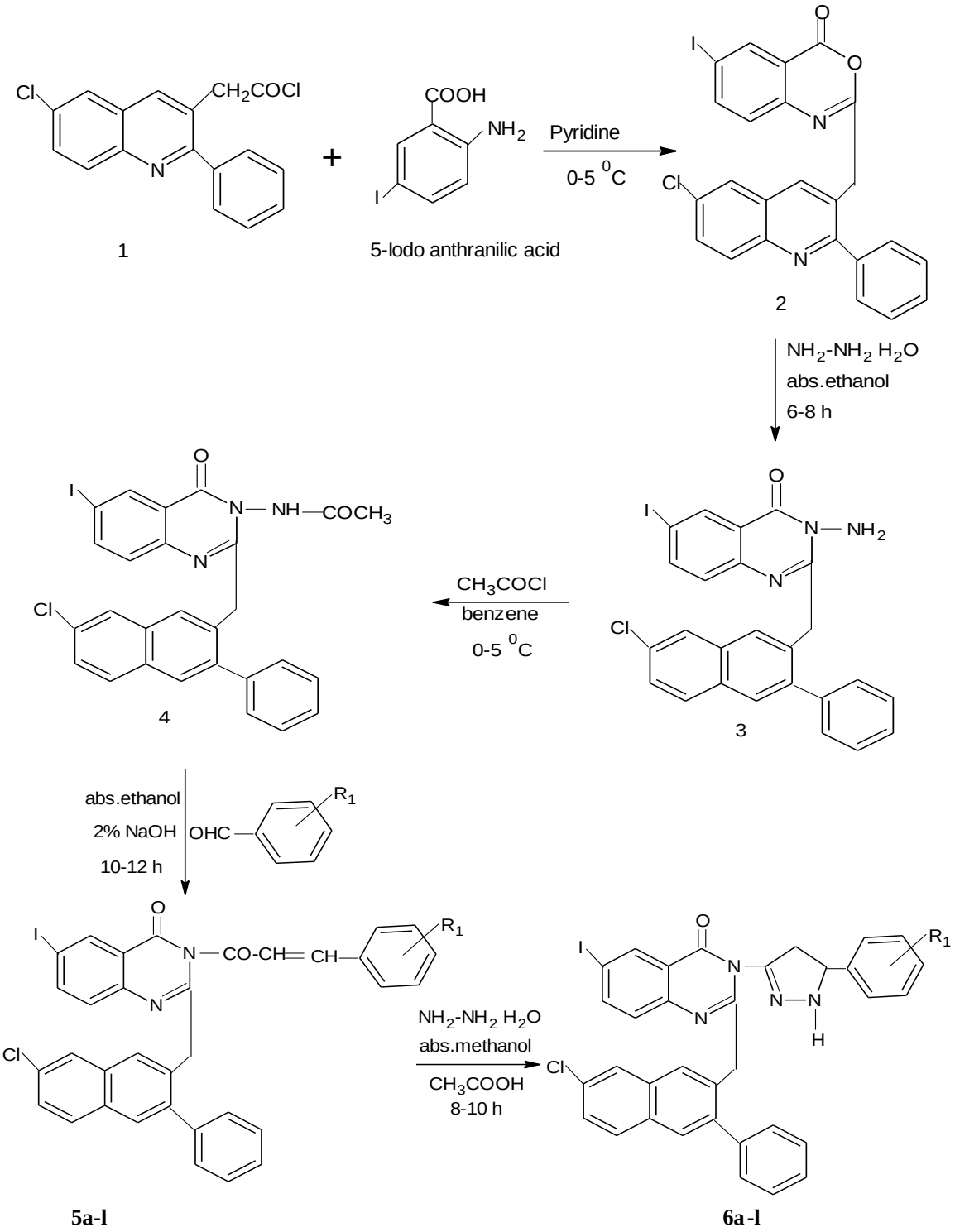
Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(2-nitro)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6h) : M.P.**:** 173-175 ^{0}C.Yeild**:** 67 % IR(KBr): 3415(N-H),3063,2856(C-H),1728(C=O),1615(C=N), 1564, 1363(-NO_2), 1318(C-N),781(C-Cl),510(C-I).^{1}H NMR($CDCl_3$): 2.16(d,1H,=N-NH), 8.32(s,1H,-N-NH), 3.62(s,2H,-CH_2), 3.07(d,1Ha), 3.48(d,1Hb),6.55(t,1Hx), 6.43-7.96(m,16H,Ar-H).13C NMR : 30.5(-CH_2), 36.5,42.2,161.6(immine pyrazol-C),162.1(>C=O),173.1(immine aromatic-C), 109.19-143.16(aromatic-27C). Anal; (%) $C_{33}H_{23}N_7O_3ICl$ Calcd; C, 54.43; H, 3.16; N,13.47; Found; C, 54.45; H, 3.17; N, 13.48.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(3-nitro)phenyl-4,5-dihydro -1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6i) : M.P.**:** 184-186 ^{0}C.Yeild**:** 65 % IR(KBr):3411(NH),3065,2854(C-H),1729(C=O),1613(C=N),1565, 1361(-NO_2),1316(C-N), 779(C-Cl),513 (C-I). ^{1}H NMR($CDCl_3$): 2.17(d,1H,=N-NH), 8.33(s,1H,-N-NH), 3.61 (s,2H,-CH_2), 3.06(d,1Ha), 3.46 (d,1Hb),6.52(t,1Hx), 6.43-7.96(m,16H,Ar-H). ^{13}C NMR: 30.4(-CH_2),36.1, 41.8,160.9(immine pyrazol-C),162.3(>C=O),172.9(immine aromatic-C), 109.19-143.16 (aromatic-27C). Anal; (%) $C_{33}H_{23}N_7O_3ICl$ Calcd; C, 54.43; H, 3.16; N,13.47; Found; C, 54.44; H, 3.18; N, 13.49.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(4-nitro)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6j) : M.P.**:** 195-197 ^{0}C.Yeild**:** 69 % IR (KBr): 3415(NH), 3060,2855(C-H), 1726(C=O),1615(C=N), 1563, 1359(-NO_2),1318(C-N), 783(C-Cl),516(C-I). ^{1}H NMR($CDCl_3$): 2.18(d,1H,=N-NH), 8.31(s,1H,-N-NH), 3.63(s,2H,-CH_2), 3.05(d,1Ha), 3.48 (d,1Hb),6.53(t,1Hx), 6.43-7.96(m,16H,Ar-H). ^{13}C NMR: 30.6(-CH_2), 36.2, 42.3,161.2(immine pyrazol-C),162.3(>C=O),173.1(immine aromatic-C), 109.19-143.11 (aromatic-27C). Anal; (%) $C_{33}H_{23}N_7O_3ICl$ Calcd; C, 54.43; H, 3.16; N,13.47; Found; C, 54.45; H, 3.19; N, 13.48.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(2-methoxy)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6k) : M.P.**:** 144-145 ^{0}C. Yeild**:** 71 % IR(KBr): 3408 (N-H),3065,2859 (C-H), 1730 (C=O), 1611 (C=N),1319 (C-N), 1241, 1109(C-O-C), 784(C-Cl), 502(C-I). ^{1}H NMR($CDCl_3$):2.16(d,1H,=N-NH), 8.30(s,1H,-N-NH) 3.62(s,2H,-CH_2), 3.05(d,1Ha), 3.46(d,1Hb), 6.51(t,1Hx), 6.43-7.96 (m,16H,Ar-H), 3.81(s,3H,-OCH_3).^{13}C NMR : 31.3(-CH_2),36.4, 42.4,161.1(immine pyrazol-C),162.0(>C=O), 173.3 (immine aromatic-C),58.3(-OCH_3),109.14-143.17(aromatic-27C). Anal; (%) $C_{34}H_{26}N_6O_2ICl$ Calcd; C, 57.26; H, 3.64; N,11.79; Found; C, 57.28; H, 3.65; N, 11.80.

Spectral data of 2-[3-(6-chloro-2-phenyl) quinolin-3-yl]methyl-3–[5-(4-methoxy)phenyl-4,5-dihydro-1*H*-pyrazol-3-yl amino]-6-iodo quinazolin-4(3*H*)-one(6l) : M.P.**:**147-149 ^{0}C. Yeild**:** 74 % IR (KBr): 3405(N-H), 3066, 2861 (C-H), 1729(C=O), 1613(C=N), 1317 (C-N), 1243,1108 (C-O-C), 786(C-Cl), 507(C-I).^{1}H NMR($CDCl_3$):2.17(d,1H,=N-NH) ,8.32 (s,1H,-N-NH), 3.61(s,2H,-CH_2), 3.06(d,1Ha), 3.46(d,1Hb),6.52(t,1Hx), 6.43-7.96(m,16H,Ar-H), 3.80(s,3H,-OCH_3). ^{13}C NMR : 31.2(-CH_2), 36.5,42.6,161.3(immine pyrazol-C),162.1(>C=O), 173.2 (immine aromatic-C),58.2(-OCH_3),109.14-143.17(aromatic-27C). Anal; (%) $C_{34}H_{26}N_6O_2ICl$ Calcd; C, 57.26; H, 3.64; N,11.79; Found; C, 57.27; H, 3.66; N, 11.81.



R_1 = H, 2-Cl, 3-Cl, 4-Cl, 2-OH, 3-OH, 4-OH, 2-NO_2, 3-NO_2, 4-NO_2, 2-OCH_3, 4-OCH_3

Scheme I

RESULTS AND DISCUSSION

The title compound pyrazolyl 6-iodoquinazolin-4(3H) ones **6a-l** was synthesized according to the described procedure in **scheme-I.** Based catalyzed cyclization of acid chloride **1** with 5- iodoanthranilic 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 hydration 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 acetamide respectively. This was further confirming by ^{1}H NMR spectra which showed singlet at δ 2.24 ppm equivalent to three protons of acetamide group. The acetamido quinazolin-4(3H) one **4** on based catalysed condensation with aromatic 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 6-iodoquinazolin-4(3H) ones **6a-l**. 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 (H_a and H_b) 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 up field 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-l 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}, penicillin-G were used as a standard, 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, fluconazole were used as a standard.

From the screening results compound **6d (R = 4-Cl), 6b (R = 2-Cl), and 6c(R = 3-Cl)** were active against gram positive bacteria, while compound **6i (R_1 = 3-NO_2)** were active against gram negative bacteria compared to penicillin-G. Compound **6a (R_1 = H), 6k(R_1 = 2-OCH_3)** and **6l(R_1 = 4-OCH_3)** showed very good antifungal activity compared to fluconazole.

In the present study the derivatives of quinazolin-4(3H) ones were synthesized and screened for their antimicrobial activity which have active pharmacophore and promising results were obtained. Results were also useful to further studies undergoing to explore the scope of varieties of biological activity.

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

Compd	R_1	Zone of inhibition in (mm)											
		S. aureus ATCC9144			***B. subtilis*** ATCC6633			**E.coli** ATCC25922			**P.aeruginosa** ATCC9027		
		C_H	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**
6a	H	10	08	41.44	11	09	43.86	10	08	41.44	11	09	43.86
6b	**2-Cl**	**18**	**14**	**68.69**	**19**	**17**	**68.29**	15	12	52.44	13	11	49.15
6c	**3-Cl**	**16**	**13**	**60.81**	**16**	**12**	**62.87**	14	11	55.05	15	12	52.44
6d	**4-Cl**	**19**	**16**	**70.60**	**20**	**17**	**73.48**	15	13	54.00	16	13	59.84
6e	2-OH	11	09	43.86	12	10	46.40	11	09	43.86	12	10	46.40
6f	3-OH	11	08	47.42	12	10	46.40	11	09	43.86	12	10	46.40
6g	4-OH	12	10	46.40	13	11	49.15	12	10	46.40	13	11	49.15
6h	2-NO_2	15	13	54.00	16	13	59.84	16	13	59.84	**17**	**14**	**62.99**
6i	3-NO_2	14	11	55.05	14	11	54.96	**16**	**14**	**61.69**	**18**	**15**	**66.29**
6j	4-NO_2	15	12	52.44	15	13	54.00	14	11	55.05	16	13	59.84
6k	2-OCH_3	11	08	41.44	12	10	46.40	11	08	47.42	13	11	49.15
6l	4-OCH_3	13	11	49.15	13	11	49.15	11	08	47.42	13	11	49.15
Penicillin-G		27	22	100	27	22	100	27	22	100	27	22	100

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

Table: 2 Antifungal activity of compound 6a-l

Compd No.	R_1	Zone of inhibition in (mm)					
		C.albicans ATCC 10231			A.niger ATCC 6275		
		C_H	**C_L**	**Pot %**	**C_H**	**C_L**	**Pot %**
6a	H	**17**	**13**	**70.13**	**17**	**14**	**68.92**
6b	2-Cl	11	08	50.90	12	09	53.75
6c	3-Cl	11	09	47.09	12	10	49.89
6d	4-Cl	12	09	53.75	13	11	52.86
6e	2-OH	15	13	59.36	14	12	56.03
6f	3-OH	14	12	56.03	14	12	56.03
6g	4-OH	14	11	59.36	14	11	59.36
6h	2-NO_2	12	10	49.89	10	08	38.19
6i	3-NO_2	09	07	41.93	11	10	36.91
6j	4-NO_2	11	09	47.09	11	09	40.53
6k	2-OCH_3	**15**	**12**	**62.38**	**15**	**13**	**59.36**
6l	4-OCH_3	**16**	**13**	**65.88**	**16**	**13**	**65.88**
Fluconazole		25	21	100	25	21	100

C_H Zone of inhibition at concentration 20 µg mL^{-1}, C_L Zone of inhibition at concentration 10 µg mL^{-1}, potency of compound(%) as compared to fluconazole.

CONCLUSIONS

The title compound pyrazolyl quinazolin-4(3H) ones bearing quinolin moiety 6a-l were comprehensively synthesized by well organized methods. In addition, some of the compounds possessed good antibacterial as well as antifungal activity in vitro. Phenyl nucleus containing chloro group on *ortho, para* position showed very good activity against gram positive bacteria compared to *meta* chloro containing compounds. On the other hand *meta* nitro group containing compounds displayed higher activity than *para* nitro group containing compound against gram nerative bacteria, while *ortho* nitro group containing compounds showed good activity against *P.aeruginosa* gram negative bacteria. Phenyl group, *ortho* and *para* methoxy substituted compounds showed very good antifungal activity compared to nitro, chloro and hydroxyl substituted compounds. Therefore, these results will give some idea about further research on this molecule.

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