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# Synthesis of new pyrazole and pyrazolin-5-one bearing 2-(quinolin-8-yloxy) acetohydrazide analogs as potential antimicrobial agents

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**ABSTRACT**

*2-(quinolin-8-yloxy)acetohydrazide **(3)** was prepared using ethyl 2-(quinolin-8-yloxy)acetate **(2)** and hydrazine hydrate. The acetohydrazide **(3)** derivative was used as a precursor for the preparation of 1-(3,5-dimethyl-4-(substitutedphenyldiazenyl)-1H-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanone **(8a-d)** and 3-methyl-4-(2-substitutedphenyl hydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1H-pyrazol-5(4H)-one **(9a-e)**. The newly synthesized pyrazoles and pyrazolin-5-ones have been characterized by elemental analysis, IR, $^{1}H$ NMR, $^{13}C$ NMR and mass spectral data. The newly synthesized compounds have been screened for their antimicrobial activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, Pseudomonas aeruginosa, Salmonella typhi and fungi Aspergillus niger, Ustilago maydis, as compared to the standard drugs Gentamicin and Nystatin for bacterial and fungal growth respectively, using the agar disc diffusion method. All the compounds showed significant activity against both the strains.*

**Keywords:** 8-hydroxy quinoline, hydrazide, pyrazoles, pyrazolin-5-ones, antibacterial and antifungal activities.

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## INTRODUCTION

Heterocyclic compounds have enormous potential as the most promising molecules as lead structures for the design of new drugs [1-4]. Moreover, in tune with the present trend 'scientists to the door steps of common man' there is always a challenging task in search of more and more new scientific accomplishments. This is reflected by the voluminous data available in the literature on heterocyclic chemistry and many useful drugs indeed have emerged from such investigations which strengthen the trend. But the evolution of antibiotic resistance strains is of principally severe concern due to the biochemical fickleness of several bacteria and the over use of many of these antibiotics. Multidrug resistant bacteria have become a major public health crisis because existing antibiotics are no longer effective in many cases. Considering the rapid advance of multidrug resistance to the existing variety of marketed antibiotics, new approaches are of an immediate need. Among the various heterocyclic rings, quinolines posses a wide spectrum of biological activities. Quinoline and their derivatives could be considered as possible antimalarial, anti-bacterial, antifungal, anthelmintic, cardiovascular, anticonvulsant, anti-inflammatory and analgesic [5-10]. It was observed from the literature that certain five membered heterocyclic compounds possess interesting biological activity. Among them the compounds bearing pyrazole nucleus have wide applications in medicinal chemistry. Pyrazoles and several N-substituted pyrazoles are known to possess numerous chemical, biological and medicinal applications because of their versatile biological activities such as antitumour [11], antileukemia [12], antidepressant [13,14] and antitubercular [15]. A typical model of the pyrazole containing diaryl-heterocyclic

template that is known to selectively inhibit cyclooxygenase enzyme COX-2 [16], Celecoxib is a safe anti-inflammatory and analgesic agent. Fascinated by the varied biological activity of quinoline and pyrazole derivatives it was contemplated to synthesize a series of pyrazolin-5-ones and pyrazoles carrying quinoline scaffold with a view to kill multidrug resistant bacteria.

In view of the above the synthesis of some 3-methyl-4-(2-phenylhydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones and 1-(3,5-dimethyl-4-(phenyldiazenyl)-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanones was reported [17]. In the present paper we report the synthesis, characterization and antimicrobial evaluation of some more pyrazole and pyrazolin-5-one derivatives (**8a-d** and **9a-e**) containing quinoline moiety.

## MATERIALS AND METHODS

Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The homogeneity of the compounds was checked by TLC (silica gel H, BDH, ethyl acetate-hexane, 3:5). The IR spectra were recorded on Perkin Elmer precisely spectrum 100 FT-IR spectrometer as KBr pellets. The wave numbers are given in $cm^{-1}$. The $^1H$ NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$ on a Jeol JNM λ-400 MHz machine. The $^{13}C$ NMR spectra were recorded in $CDCl_3$/DMSO-$d_6$ on a Jeol JNM spectrometer operating at 100 MHz. All chemical shifts are reported in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on VG 7070H mass spectrometer. The micro analyses were performed on Perkin-Elmer 240C elemental analyzer.

All newly synthesized compounds yielded spectral data consistent with the proposed structure and microanalysis data are in agreement with the theoretical values.

**General procedures for the synthesis of the title compounds**

**Synthesis of ethyl 2-(quinolin-8-yloxy)acetate (2)**

A mixture of 8-hydroxy quinoline (**1**) (0.01 mole), ethyl chloroacetate (0.01 mole), anhydrous $K_2CO_3$ (1.38 g., 0.01 mole) and 10 ml of DMF was subjected to agitation at room temperature for 8 hr. The reaction mixture was diluted with ice cold water and the separated product was filtered, washed with water and recrystallized from ethanol. 80% yield, mp 56°-58°C.

IR ($cm^{-1}$): 3065, 2920 (CH stretch in $CH_3/CH_2$), 1730 (C=O stretch in ester), 1215, 1015 ($sp^2/sp^3$ C-O stretch); $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 1.22 (t,3H,$CH_3$), 4.20 (q,2H,$CH_2$), 4.94 (d,2H,$OCH_2$), 7.14 (d,1H,H7 quinoline ring), 7.49 (t,1H,H3 quinoline ring), 7.54 (d,1H,H5 quinoline ring), 7.56 (t,1H, H6 quinoline ring), 8.32 (d,1H,H4 quinoline ring), 8.88 (d,1H,H2 quinoline ring); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 153.5(C2), 122.5(C3), 136.2(C4), 121.4(C5), 124.0(C6), 112.3(C7), 155.2(C8), 139.2(C9), 129.1(C10), 67.1(C11), 165.6(C=O acetate), 63.1($CH_2$ of ethyl), 13.8($CH_3$ of ethyl); Anal. Calcd. for $C_{13}H_{13}NO_3$: C, 67.52; H, 5.67; N, 6.06. Found: C, 66.48 ; H, 5.53; N, 5.98.

**Synthesis of 2-(quinolin-8-yloxy)acetohydrazide (3)**

To a solution of ethyl 2-(quinolin-8-yloxy)acetate **(2)** (0.01 mole) in methanol, hydrazine hydrate (0.02 mole) was added and the reaction mixture was refluxed for 8 hr. The excess of solvent was distilled off and the reaction mixture was cooled. The separated solid was filtered, washed with pet. ether (40°-60°C) and recrystallized from water. 76% yield, mp 122°-126°C.

IR ($cm^{-1}$): 3325 (N-H str.), 3060, 2895 (CH stretch in $CH_2$), 1660 (C=O stretch in amide), 1285, 1035 ($sp^2/sp^3$ C-O stretch); $^1H$ NMR (DMSO-$d_6$, 400 MHz): δ 4.44 (s,2H,$NH_2$), 4.75 (s,2H,$OCH_2$), 7.25 (d,1H,H7 quinoline ring), 7.52 (t,1H, H3 quinoline ring), 7.56 (d,1H,H5 quinoline ring), 7.59 (t,1H, H6 quinoline ring), 8.36 (d,1H,H4 quinoline ring ), 8.90 (d, 1H, H2 quinoline ring), 9.47 (s,1H,NH); $^{13}C$ NMR (DMSO-$d_6$, 100 MHz): δ 153.5(C2), 122.5(C3), 135.9(C4), 121.6(C5), 123.6(C6), 112.4(C7), 154.6(C8), 139.4(C9), 130.0(C10), 67.51(C11), 162.7(C=O amide); Anal. Calcd. for $C_{11}H_{11}N_3O_2$: C, 60.82; H, 5.10; N, 19.34. Found: C, 60.13; H, 4.96; N, 19.16.

**General procedure for the synthesis of 1-chloro-2-substitutedphenyldiazene (5a-e)**

The required primary amine **(4a-e)** was dissolved in a suitable volume of water containing 2.5-3.5 equivalents of hydrochloride acid or (sulphuric acid) by the application of heat if necessary [18]. The solution thus obtained was cooled to $0^oC$ where the amine hydrochloride or (sulphate) usually crystallizes. The temperature was maintained at 0° to $5^oC$ and the aqueous sodium nitrite solution was added portion wise till there was free nitrous acid. The

solution was tested for the later with an external indicator paper (moist potassium iodide–starch paper). An excess of acid was maintained to stabilize the diazonium salt solution. However, in those cases where a large excess of acid was harmful, the concentration of the acid was reduced to optimum value.

**General procedure for the synthesis of 3-(substitutedphenyldiazenyl)pentane-2,4-dione (6a-d)**
A solution of sodium acetate (100 g) in 100 ml aqueous alcohol (50%) was added to a solution of acetylacetone (100 g) in 500 ml of ethanol and the mixture was cooled. To this cold mixture, the corresponding diazonium chloride (**5a-d)** was added gradually till turbidity was observed [19]. The addition was continued till yellow crystals separated out. These crystals were filtered, washed with water and recrystallized from ethanol. 70-85% yield; mp 6a, 92$^{o}$; 6b, 233$^{o}$; 6c, 112$^{o}$; 6d, 120-122°C.

**General procedure for the synthesis of ethyl-3-oxo-2-(substitutedphenyldiazenyl)butanoate (7a-e)**
A solution of sodium acetate (100 g) in 100 ml aqueous alcohol (50%) was added to a solution of ethyl acetoacetate (100 g) in 500 ml of ethanol and the mixture was cooled. To this cold mixture, the corresponding diazonium chloride **(5a-e)** was added gradually till turbidity was observed [19]. The addition was continued till yellow crystals separated out. These crystals were filtered, washed with water and recrystallized from ethanol. 70-85% yield; mp 7a, 184$^{o}$; 7b, 119-120$^{o}$; 7c, 125-126$^{o}$; 7d, 89-91°; 7e, 116-118°C.

**General procedure for the synthesis of compounds (8a-d)**
A mixture of 3-(phenyldiazenyl)pentane-2,4-dione (**6a-d**) (0.01 mol) and 2-(quinolin-8-yloxy)acetohydrazide (**3**) (0.01 mol) in ethanol (20 ml) was heated under reflux for 8 hr. on a water bath. After completion of the reaction, ethanol was evaporated. The residue was dissolved in water, neutralized with $NaHCO_3$ and extracted with ether. The ether solution was evaporated under reduced pressure to furnish the pure compound.

**1-(3,5-dimethyl-4-(phenyldiazenyl)-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanone (8a)**
Recrystallised from ethanol as yellow crystals in 85% yield; mp 224-226$^{0}$C;
IR (cm$^{-1}$): 3060 (CH stretch in aromatic ring), 2925 (CH stretch in $CH_3$/$CH_2$), 1660 (C=O stretch in amide), 1610 (C=N stretch), 1415 (N=N stretch), 1270, 1015 ($sp^2$/$sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.28 (s, 3H,pyrazole $CH_3$), 2.52 (s, 3H, pyrazole $CH_3$), 4.81 (s, 2H,$OCH_2$), 7.08- 7.23 (m, 5H, phenyl ring), 7.27 (d,1H,H7 quinoline ring), 7.50 (t,1H,H3 quinoline ring), 7.55 (d,1H,H5 quinoline ring), 7.59 (t,1H,H6 quinoline ring), 8.36 (d,1H,H4 quinoline ring), 8.89 (d,1H,H2 quinoline ring);$^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 8.25 ($CH_3$ pyrazole ring), 14.6 ($CH_3$ pyrazole ring), 152.9(C2), 122.2(C3), 136.1(C4), 121.8(C5), 123.9(C6), 111.9(C7), 154.5(C8), 139.8(C9), 130.2(C10), 73.41(C11), 163.0(C=O), 143.6, 108.2, 137.6 (pyrazole ring), 128.9, 129.4, 129.0, 129.1 (phenyl ring); MS m/*z*: found 385 [$M^+$], calcd. 385; Anal. Calcd. for $C_{22}H_{19}N_5O_2$: C, 68.56; H, 4.97; N, 18.17. Found: C, 67.49; H, 4.72; N, 17.74.

**1-(3,5-dimethyl-4-((4-nitrophenyl)diazenyl)-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanone (8b)**
Recrystallised from ethanol as yellow crystals in 74% yield. mp 240$^{0}$-244$^{0}$C.
IR (cm$^{-1}$): 3055 (CH stretch in aromatic ring), 2920 (CH stretch in $CH_3$/$CH_2$), 1685 (C=O stretch in amide), 1620 (C=N stretch), 1510, 1360 (asym/aym. N-O stretching),1405 (N=N stretch), 1270, 1085 ($sp^2$/$sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.17 (s, 3H, pyrazole $CH_3$), 2.31 (s, 3H, pyrazole $CH_3$), 5.00 (s,2H,$OCH_2$), 7.18 (d, 2H, phenyl ring), 8.16 (d, 2H, phenyl ring), 7.29 (d, 1H,H7 quinoline ring),7.48 (t,1H,H3 quinoline ring), 7.58 (d, 1H,H5 quinoline ring), 7.60 (t, 1H,H6 quinoline ring), 8.36 (d,1H,H4 quinoline ring), 8.88 (d, 1H,H2 quinoline ring); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 8.16 ($CH_3$ pyrazole ring), 14.27 ($CH_3$ pyrazole ring), 153.1(C2), 122.3(C3), 136.3(C4), 121.8(C5), 123.6(C6), 114.7(C7), 156.8(C8), 139.4(C9), 129.1(C10), 73.5(C11), 164.9(C=O), 143.1, 110.2, 138.8 (pyrazole ring), 133.0, 123.4, 123.1, 151.8 (phenyl ring);MS m/*z*: found 430 [$M^+$], calcd. 430;Anal.Calcd for $C_{22}H_{18}N_6O_4$: C, 61.39; H, 4.22; N, 19.53. Found: C, 60.84; H, 4.09; N, 18.96.

**1-(4-((2-methoxyphenyl) diazenyl)-3,5-dimethyl-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanone (8c)**
Recrystallised from ethanol as brown crystals in 76% yield. mp 188$^{0}$-190$^{0}$C.
IR (cm$^{-1}$):3060 (CH stretch in aromatic ring), 2925 (CH stretch in $CH_3$/$CH_2$), 1670 (C=O stretch in amide), 1610 (C=N stretch), 1515 (N=N stretch), 1250, 1030 ($sp^2$/$sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.45 (s,3H,pyrazole $CH_3$), 2.56 (s,3H,pyrazole $CH_3$), 3.91 (s,3H,Ph-$OCH_3$), 4.82 (s, 2H,$OCH_2$), 6.48-7.12 (m,4H, phenyl ring), 7.22(d, 1H,H7 quinoline ring), 7.54 (t,1H,H3 quinoline ring), 7.58 (d, 1H,H5 quinoline ring), 7.61 (t,1H,H6 quinoline ring), 8.33 (d,1H, H4 quinoline ring), 8.89 (d, 1H, H2 quinoline ring); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 7.94 ($CH_3$ pyrazole ring), 13.06 ($CH_3$ pyrazole ring), 56.92($OCH_3$), 153.2(C2), 121.7(C3), 136.2(C4), 121.0(C5),

123.9(C6), 112.8(C7), 155.4(C8), 138.9(C9), 128.7(C10), 73.51(C11), 165.1(C=O), 141.3, 108.4, 137.9 (pyrazole ring), 102.6, 158.7, 117.2, 123.0, 121.4, 131.5 (phenyl ring);MS m/z: found 415 [$M^+$], calcd. 415;Anal.Calcd for $C_{23}H_{21}N_5O_2$: C, 66.49; H, 5.09; N, 16.86. Found: C, 65.52; H, 4.91; N, 16.30.

**1-(3,5-dimethyl-4-((2-nitrophenyl)diazenyl)-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanone (8d)**
Recrystallised from ethanol as orange crystals in 81% yield. mp $172^0$-$174^0$C.
IR ($cm^{-1}$): 3080 (CH stretch in aromatic ring), 2930 (CH stretch in $CH_3/CH_2$), 1680 (C=O stretch in amide), 1620 (C=N stretch), 1560, 1370 (asym/aym. N-O stretching), 1415 (N=N stretch), 1275, 1080 ($sp^2/sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.19 (s,3H, pyrazole $CH_3$), 2.35 (s, 3H, pyrazole $CH_3$), 5.02 (s, 2H,$OCH_2$), 7.46 (d, 1H, phenyl ring), 7.69 (t,1H, phenyl ring), 8.04-8.17 (m,2H, phenyl ring), 7.31(d,1H,H7 quinoline ring), 7.46 (t,1H,H3 quinoline ring), 7.57 (d,1H,H5 quinoline ring), 7.61 (t, 1H,H6 quinoline ring), 8.36 (d,1H, H4 quinoline ring), 8.90 (d,1H, H2 quinoline ring); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 8.06 ($CH_3$ pyrazole ring), 13.64 ($CH_3$ pyrazole ring), 153.4(C2), 122.2(C3), 136.2(C4), 121.9(C5), 123.7(C6), 111.7(C7), 155.7(C8), 140.4(C9), 129.6(C10), 72.95(C11), 165.2(C=O), 145.0, 107.3, 139.3 (pyrazole ring), 122.8, 154.2, 123.0, 130.8, 134.3, 131.0 (phenyl ring); MS m/*z*: found 430 [$M^+$], calcd. 430; Anal. Calcd for $C_{22}H_{18}N_6O_4$: C, 61.39; H, 4.22; N, 19.53. Found: C, 60.82; H, 4.06; N, 19.14.

**General procedure for the synthesis of compounds (9a-e)**
A mixture of ethyl 3-oxo-2-(phenyldiazenyl)butanoate **(7a-e)** (0.01 mole) and 2-(quinolin-8-yloxy)acetohydrazide **(3)** (0.01 mole) in ethanol (20 ml) was heated under reflux for 8 hr. on a water bath. After completion of the reaction, ethanol was evaporated. The residue was dissolved in water, neutralized with $NaHCO_3$ and extracted with ether. The ether solution was evaporated under reduced pressure to furnish the pure compound.

**3-methyl-4-(2-phenylhydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one (9a)**
Recrystallised from ethanol as yellow crystals in 87% yield. mp $190^0$-$192^0$C.
IR ($cm^{-1}$): 3320 (NH stretch), 3075 (CH stretch in aromatic ring), 2910 (CH stretch in $CH_3/CH_2$), 1675 (C=O stretch in pyrazolin-5-one), 1630 (C=O stretch in amide), 1610 (C=N stretch), 1270, 1060 ($sp^2/sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.51 (s, 3H, pyrazolin-5-one $CH_3$), 4.90 (s, 2H,$OCH_2$), 7.09-7.48 (m, 5H, phenyl ring), 7.53 (d, 1H, H7 quinoline ring), 7.55 (t,1H,H3 quinoline ring), 7.59 (d, 1H,H5 quinoline ring), 7.62 (t,1H,H6 quinoline ring), 8.38 (d,1H,H4 quinoline ring), 8.93 (d, 1H,H2 quinoline ring), 11.63 (s, 1H,NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ12.2 ($CH_3$ pyrazolin-5-one ring), 153.7(C2), 122.0(C3), 136.0(C4), 121.9(C5), 123.8(C6), 111.9(C7), 154.9(C8), 139.6(C9), 129.0(C10), 67.86(C11), 165.0(C=O), 149.4, 126.7, 164.7 (pyrazolin-5-one ring), 142.0, 115.0, 129.3, 121.0 (phenyl ring);MS m/*z*: found 387 [$M^+$], calcd. 387;Anal.Calcd for $C_{21}H_{17}N_5O_3$: C, 65.11; H, 4.42; N, 18.08. Found: C, 64.72; H, 4.15; N, 17.85.

**3-methyl-4-(2-(4-nitrophenyl)hydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one (9b)**
Recrystallised from ethanol as brown crystals in 84% yield. mp $202^0$-$206^0$C.
IR ($cm^{-1}$): 3310 (NH stretch), 3070 (CH stretch in aromatic ring), 2915 (CH stretch in $CH_3/CH_2$), 1670 (C=O stretch in pyrazolin-5-one), 1645 (C=O stretch in amide), 1610 (C=N stretch), 1240, 1070 ($sp^2/sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.31 (s,3H,pyrazolin-5-one $CH_3$), 4.91 (s,2H,$OCH_2$), 7.38 (d, 2H, phenyl ring), 7.54 (d, 1H,H7 quinoline ring), 7.56 (t,1H,H3 quinoline ring), 7.58 (d, 1H,H5 quinoline ring), 7.63 (t,1H,H6 quinoline ring), 8.04 (d,2H, phenyl ring), 8.40 (d,1H,H4 quinoline ring), 8.93 (d, 1H,H2 quinoline ring), 10.58 (s,1H,NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ12.24 ($CH_3$ pyrazolin-5-one ring), 148.4(C2), 122.5(C3), 136.2(C4), 121.7(C5), 123.6(C6), 111.6(C7), 156.3(C8), 139.3(C9), 129.0(C10), 66.82(C11), 166.1(C=O), 147.6, 127.9, 163.8 (pyrazolin-5-one ring), 148.9, 130.3, 123.1, 138.1 (phenyl ring);MS m/*z*: found 432[$M^+$], calcd. 432;Anal.Calcd for $C_{21}H_{16}N_6O_5$: C, 58.33; H, 3.73; N, 19.44. Found: C, 58.06; H, 3.59; N, 18.96.

**4-(2-(2-methoxyphenyl)hydrazono)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one (9c)**
Recrystallised from ethanol as orange crystals in 81% yield. mp $210^0$-$212^0$C.
IR ($cm^{-1}$): 3380 (NH stretch), 3040 (CH stretch in aromatic ring), 2860 (CH stretch in $CH_3/CH_2$), 1690 (C=O stretch in pyrazolin-5-one ring), 1680 (C=O stretch in amide), 1610 (C=N stretch), 1240, 1020 ($sp^2/sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.52 (s,3H,pyrazoin-5-one $CH_3$), 3.92 (s,3H,$PhOCH_3$), 4.89 (s,2H,$OCH_2$), 7.03-7.29 (m, 4H, phenyl ring), 7.51 (d,1H,H7 quinoline ring), 7.57 (t,1H,H3 quinoline ring), 7.62 (d, 1H,H5 quinoline ring), 7.65 (t, 1H,H6 quinoline ring), 8.38 (d,1H,H4 quinoline ring), 8.88 (d, 1H,H2 quinoline ring), 10.58 (s,1H,NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ12.35($CH_3$ pyrazolin-5-one ring), 57.26($OCH_3$), 152.6(C2), 122.5(C3), 136.4(C4), 121.7(C5), 123.4(C6), 109.0(C7), 155.1(C8), 138.1(C9), 128.7(C10), 67.91(C11), 166.2(C=O), 147.9, 126.3,

164.5(pyrazolin-5-one ring), 127.5, 146.3, 117.8, 120.2, 122.8, 119.5 (phenyl ring);MS m/z: found 417[$M^+$], calcd. 417;Anal.Calcd for $C_{22}H_{19}N_5O_4$: C, 63.30; H, 4.59; N, 16.78. Found: C, 62.94; H, 4.41; N, 16.52.

**3-methyl-4-(2-(2-nitrophenyl)hydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one (9d)**
Recrystallised from ethanol as orange crystals in 78% yield. mp $236^0$-$238^0$C.
IR ($cm^{-1}$): 3215 (NH stretch), 3075 (CH stretch in aromatic ring), 2920 (CH stretch in $CH_3/CH_2$), 1680 (C=O stretch in pyrazolin-5-one ring), 1630 (C=O stretch in amide), 1610 (C=N stretch), 1270, 1095 ($sp^2/sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.51 (s, 3H,$CH_3$ pyrazolin-5-one), 4.90 (s,2H,$OCH_2$), 7.18 (d,1H, phenyl ring), 7.30 (t, 1H, phenyl ring), 7.48 (d, 1H, H7 quinoline ring),7.51 (t,1H, phenyl ring ), 7.54 (t,1H,H3 quinoline ring), 7.58 (d, 1H,H5 quinoline ring), 7.62 (t, 1H,H6 quinoline ring), 8.02 (d,1H, phenyl ring), 8.37 (d,1H,H4 quinoline ring), 8.91 (d,1H,H2 quinoline ring), 10.59 (s,1H,NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ12.43(CH3 pyrazolin-5-one ring), 154.6(C2), 123.0(C3), 136.2(C4), 120.3(C5), 125.1(C6), 112.3(C7), 156.2(C8), 138.9(C9), 129.5(C10), 67.52(C11), 165.2(C=O), 149.0, 126.4, 164.5 (pyrazolin-5-one ring), 138.0, 137.4, 116.9, 121.4, 133.9, 122.2 (phenyl ring);MS m/z: found 432[$M^+$], calcd. 432;Anal.Calcd for $C_{21}H_{16}N_6O_5$: C, 58.33; H, 3.73; N, 19.44. Found: C, 58.13; H, 3.62; N, 19.28.

**4-(2-(3-methyl-5-oxo-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-4(5*H*)-ylidene)hydrazinyl)benzenesulfonamide (9e)**
Recrystallised from ethanol as yellow crystals in 82% yield. mp $108^0$-$110^0$C.
IR ($cm^{-1}$): 3320 (NH stretch), 3060 (CH stretch in aromatic ring), 2850 (CH stretch in $CH_3/CH_2$), 1675 (C=O stretch in pyrazolin-5-one), 1660 (C=O stretch in amide), 1610 (C=N stretch), 1220, 1060 ($sp^2/sp^3$ C-O stretch); $^1$H NMR (DMSO-$d_6$, 400 MHz): δ 2.09 (s, 2H,$NH_2$), 2.49 (s, 3H,$CH_3$ pyrazolin-5-one), 4.91 (s, 2H,$OCH_2$), 7.12(d, 2H, phenyl ring), 7.56 (d, 2H, phenyl ring), 7.52 (d,1H,H7 quinoline ring), 7.57 (t,1H,H3 quinoline ring), 7.58 (d,1H,H5 quinoline ring), 7.60 (t,1H,H6 quinoline ring), 8.38 (d,1H,H4 quinoline ring), 8.92 (d,1H,H2 quinoline ring), 10.52(s, 1H,NH); $^{13}$C NMR (DMSO-$d_6$, 100 MHz): δ 12.3 ($CH_3$ pyrazolin-5-one ring), 152.8(C2), 122.1(C3), 136.7(C4), 121.1(C5), 124.6(C6), 111.6(C7), 156.9(C8), 139.1(C9), 128.8(C10), 68.25(C11), 165.8(C=O), 148.7, 127.2, 164.1 (pyrazolin-5-one ring), 145.0, 118.1, 131.6, 132.8 (phenyl ring);MS m/z: found 466 [$M^+$], calcd. 466;Anal.Calcd for $C_{21}H_{18}N_6O_5S$: C, 54.07; H, 3.89; N, 18.02. Found: C, 53.86; H, 3.71; N, 17.84.

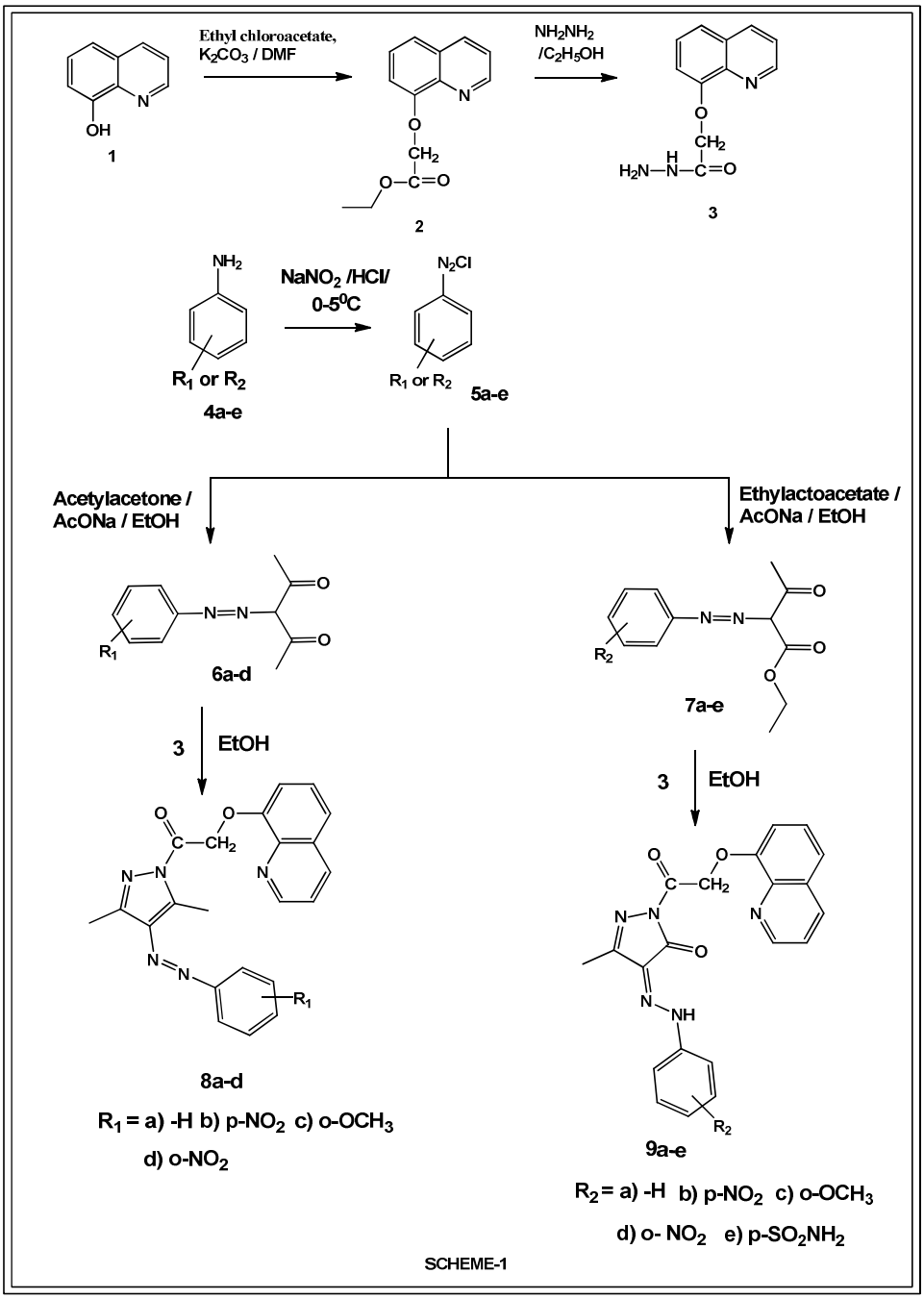
## RESULTS AND DISCUSSION

Ethyl-2-(quinoline-8-yloxy)acetate (2) was prepared by agitating a mixture of quinoline-8-ol (**1**) with ethyl chloroacetate in the presence of $K_2CO_3$ in DMF. Compound (**2**) was converted into corresponding acetohydrazide by heating with hydrazine hydrate to give 2-(quinolin-8-yloxy)acetohydrazide (**3**). The newly synthesised compounds **8a-d** and **9a-e** were prepared as depicted in **SCHEME–1.** The reaction of phenyl diazonium chlorides **(5a-e)** with acetylacetone and ethyl acetoacetate yielded the corresponding 3-(phenyldiazenyl)pentane-2,4-dione **(6a-d)** and ethyl-2-(phenyl hydrazono)-3-oxo-butanoate **(7a-e)** respectively.

Reaction of compound (**3**) with **6a-d** in the presence of ethanol resulted in the formation of 1-(3,5-dimethyl-4-(substitutedphenyldiazenyl)-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanone (**8a-d**) in good yields. IR spectrum of **8a** revealed a band at 1415$cm^{-1}$ due to N=N group. The $^1$H NMR spectrum of **8a** showed two singlets at δ 2.28 and 2.52 indicating the presence of a pair of $CH_3$ groups in the pyrazole ring. A singlet was also observed at δ 4.81 due to $OCH_2$ protons. The mass spectrum of 8a showed molecular ion peak $M^+$ at m/z 385 corresponding to molecular formula $C_{22}H_{19}N_5O_2$.

Reaction of compound **(3)** with **7a-e** in ethanol resulted in the formation of 3-methyl-4-(2-substitutedphenylhydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one **(9a-e)** in good yields. The spectral data of **9a-e** confirmed that these compounds exist in hydrazono form. The spectral data of **9a** revealed a strong band at 1630 $cm^{-1}$ due to C=O group. Low frequency carbonyl band may be assigned to C=O group in pyrazolone participating in intra- molecular hydrogen-bonding with NH group. The $^1$H NMR spectrum of **9a**, showed a singlet at δ 11.63 due to the presence of hydrogen-bonded NH group. The mass spectrum of **9a** showed molecular ion peak $M^+$ at m/z 387 corresponding to molecular formula $C_{21}H_{17}N_5O_3$.

Elemental analyses and spectral data of **8a-d** and **9a-e** are consistent with the assigned structures.




SCHEME-1

**Antimicrobial activity**

The antibacterial and antifungal activity of the synthesized compounds was examined by cup plate method [20, 21] against the following bacterial strains: *Staphylococcus aureus*, *Bacillus subtilis*, *Escherichia coli*, *Pseudomonas aeruginosa*, *Salmonella typhi* and fungi *A. niger*, *U. maydis*, as compared to the standard drugs Gentamicin and Nystatin for bacterial and fungal growth respectively. The antimicrobial results are summarized in **Table-1.**

The investigation of antibacterial screening data revealed that all the tested compounds showed moderate to good bacterial inhibition. But majority of the compounds did not exhibit any significant antifungal inhibition.

**Table 1: *In vitro* antibacterial and antifungal activity**

| Compound | Zone of inhibition, mm, Concentration, ppm | | | | | | | | | | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Gram-positive organisms[a] | | | | | | Gram-negative organisms[a] | | | | | | | | | Fungi[b] | | | | | |
| | *Stapylococcus aureus* | | | *Bacillus subtilis* | | | *Escherichia coli* | | | *Pseudomonas aeruginosa* | | | *Salmonella typhi* | | | *Aspergillus niger* | | | *Ustilago maydis* | | |
| | 1000 | 500 | 200 | 1000 | 500 | 200 | 1000 | 500 | 200 | 1000 | 500 | 200 | 1000 | 500 | 200 | 1000 | 500 | 200 | 1000 | 500 | 200 |
| 3 | 4.3 | 2.3 | 1.4 | 4.8 | 3.3 | 2.5 | 4.3 | 3.1 | 2.0 | 4.1 | 2.4 | 1.4 | 3.4 | 2.5 | 1.4 | 2.0 | 1.7 | 1.1 | 1.9 | 1.4 | 1.0 |
| 8a | 4.5 | 3.2 | 1.8 | 4.3 | 3.2 | 2.0 | 3.4 | 2.1 | 1.2 | 3.1 | 2.4 | 1.3 | 4.3 | 3.0 | 1.4 | NA* | NA* | NA* | 0.5 | NA* | NA* |
| 8b | 4.1 | 2.5 | 1.2 | 2.1 | 1.1 | 0.8 | 2.4 | 1.7 | 1.0 | 2.2 | 1.0 | 0.8 | 4.7 | 3.3 | 1.7 | NA* | NA* | NA* | 1.6 | NA* | NA* |
| 8c | 4.5 | 2.9 | 1.8 | 3.5 | 2.4 | 1.2 | 2.8 | 2.0 | 1.2 | 2.0 | 1.8 | 1.2 | 4.5 | 3.4 | 2.1 | NA* | NA* | NA* | NA* | NA* | NA* |
| 8d | 4.7 | 3.4 | 1.3 | 3.4 | 2.0 | 1.4 | 3.6 | 2.4 | 1.0 | 2.3 | 1.8 | 1.1 | 4.2 | 2.8 | 1.4 | NA* | NA* | NA* | NA* | NA* | NA* |
| 9a | 5.1 | 3.9 | 1.6 | 4.3 | 2.9 | 1.7 | 3.8 | 2.6 | 1.4 | 3.4 | 2.0 | 1.4 | 4.9 | 3.2 | 1.3 | NA* | NA* | NA* | 2.0 | 1.3 | 0.6 |
| 9b | 4.1 | 3.1 | 1.8 | 3.8 | 2.5 | 1.6 | 4.1 | 2.6 | 1.5 | 3.1 | 2.3 | 1.4 | 4.9 | 3.6 | 2.2 | NA* | NA* | NA* | NA* | NA* | NA* |
| 9c | 4.9 | 3.4 | 2.1 | 3.1 | 2.4 | 1.5 | 2.8 | 2.2 | 1.6 | 2.9 | 2.5 | 1.2 | 4.3 | 3.1 | 1.4 | NA* | NA* | NA* | NA* | NA* | NA* |
| 9d | 4.4 | 3.1 | 1.8 | 3.4 | 2.8 | 1.4 | 2.8 | 1.7 | 1.2 | 3.3 | 2.6 | 2.0 | 4.1 | 3.2 | 1.8 | NA* | NA* | NA* | NA* | NA* | NA* |
| 9e | 4.6 | 3.5 | 1.0 | 3.8 | 2.7 | 1.5 | 3.5 | 2.2 | 1.5 | 3.8 | 2.1 | 1.0 | 4.3 | 2.6 | 1.7 | NA* | NA* | NA* | NA* | NA* | NA* |

[a] *Reference drug: Gentamicin*
[b] *Reference drug : Nystatin*
** No activity*

All the tested compounds 3, 8a, 8b, 8c, 8d, 9a, 9b,9c, 9d and 9e were found to be potent against *S. aureus* and *Salmonella typhi* as compared to the control Gentamicin.

Compounds 3, 8a, 8c, 8d, 9a, 9b, 9c, 9d and 9e were found more potent against *Bacillus subtilis*. Compound 8b was moderately potent against *Bacillus subtilis.*

Compounds 3, 8a, 8c, 8d, 9a, 9b and 9e were more potent against *Escherichia coli* and the remaining compounds i.e. 8b, 9c and 9d were moderately potent.

Compounds 3, 8a, 9a, 9b, 9d and 9e were more potent against *Pseudomonas aeruginosa* whereas the remaining compounds 8a, 8b, 8c and 9c were moderately potent.

Surprisingly majority of the compounds did not exhibited significant antifungal activity against *A. niger* and *U. maydis*. Compounds 3, 8a, 8b and 9a exhibited feeble activity against *A. Niger* and *U. maydis.*

## CONCLUSION

Two series of diversely substituted 1-(3,5-dimethyl-4-(substitutedphenyldiazenyl)-1*H*-pyrazol-1-yl)-2-(quinolin-8-yloxy)ethanones **(8a-d)** and 3-methyl-4-(2-substitutedphenyl hydrazono)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones **(9a-e)** were synthesized in good yields. Structures of all the newly synthesized pyrazoles and pyrazolin-5-ones has been established by elemental analysis, IR, $^{1}$H NMR, $^{13}$C NMR and mass spectral data. The results of antibacterial screening revealed that all the tested compounds showed moderate to good bacterial inhibition with compounds 8a, 9a, 9b and 9e being more potent. But majority of the compounds did not exhibit any significant antifungal inhibition. Only compounds 3, 8a, 8b and 9a exhibited feeble antifungal activity.

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