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SYNTHESIS OF PYRAZOLIN-5-ONE DERIVATIVES CONTAINING QUINOLINE MOIETY USING KNOEVENAGEL CONDENSATION : A NOVEL CLASS OF POTENTIAL ANTIBACTERIAL AND ANTIFUNGAL AGENTS

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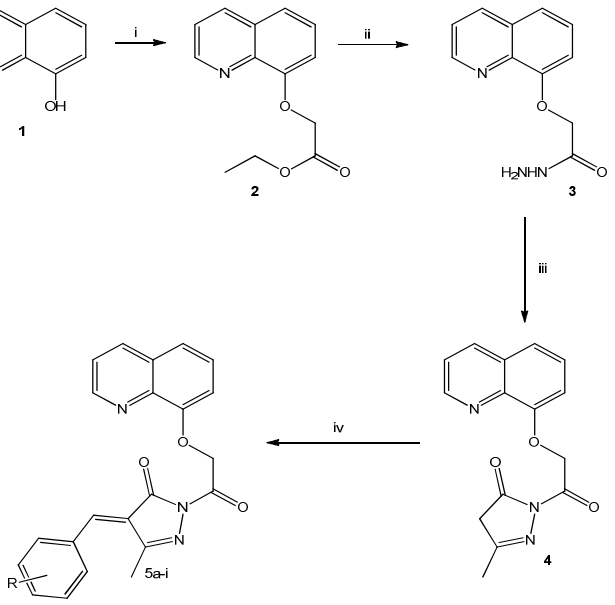
ABSTRACT
In the present investigation, a new series of 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones have been designed and synthesized by condensation of 3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one with various substituted aromatic aldehydes in presence of imidazole. These newly synthesized quinoline derivatives containing pyrazolin-5-one moiety were screened for their minimum inhibitory concentration by antibacterial activity against two kinds of strains i.e. *Staphylococcus aureus, Escherichia coli* and antifungal activity against *Aspergillus niger*. The results showed that some of the compounds exhibited moderate to good antibacterial activity against both the strains and a few compounds were active in antifungal activity. The structure–activity relationships were briefly discussed. The studies indicated that variation of substituent in the aromatic rings changes the antibacterial activity.

KEYWORDS : Quinolin-8-ol, ethyl chloroacetate, hydrazine hydrate, pyrazolin-5-one, antibacterial activity and antifungal activity.

INTRODUCTION:
A wide range of antimicrobial agents have been discovered to prolong the lifespan of people but unfortunately microbial resistance resulted in a dwindling pool of effective antibiotics. At this instance, resistance to existing antifungal agents is also a major threat and hence there is a pressing need for the development of new antimicrobial agents which may be effective against the resistant microbes.
Quinoline[i-v] has its own prominence in drug discovery programs. Quinoline along with its derivatives is reported to exhibit a wide spectrum of biological properties such as antimicrobial[vi], antimalarial[vii] and antitubercular[viii] activities. Quinoline and its derivatives are widely used as fungicides, biocides, antibiotics, alkaloids, dyes, rubber chemicals and flavoring agents. They are also used in manufacturing oil soluble dyes, food colorants, pharmaceuticals, pH indicators and other organic compounds.
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 are known to possess numerous chemical, biological and medicinal applications because of their versatile biological activities such as antitumour[ix], antileukemia[x], antidepressant[xi,xii] and antitubercular[xiii].
Looking at the importance of quinoline and pyrazole nuclei, it was thought that it would be worthwhile to design and synthesize some new quinoline derivatives bearing pyrazole moiety and screen them for potential biological activities.

RESULTS AND DISCUSSION:
A novel series of ring systems derived from quinolin-8-ol **1** have been synthesized in good yields using the synthetic route outlined in Scheme 1. IR, ^{1}H NMR, ^{13}C NMR, Mass and chemical analysis data were in agreement with the proposed structures of all newly synthesized compounds.



Scheme-I

(i) $ClCH_2COOC_2H_5$, K_2CO_3, DMF (ii) $N_2H_4.H_2O$, EtOH
(iii) $CH_3COCH_2COOC_2H_5$, Et_3N, EtOH, reflux, 8hr.
(iv)  , imidazole (cat.), CH_2Cl_2, reflux, 1hr.

R = (a) -H, (b) 2-OH, (c) 4-OH, (d) 2-OCH_3, (e) 4-OCH_3, (f) 2-NO_2, (g) 4-NO_2, (h) 2-Cl, (i) 4-Cl

The precursor 3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one **4** was obtained by condensing 2-(quinolin-8-yloxy)acetohydrazide **3** with ethyl acetoacetate in ethanol and refluxing for 8 hr. IR spectrum of **4** revealed a band at 1601 cm^{-1} due to C=N stretching in pyrazolin-5-one ring. A singlet was observed at δ 4.93 due to OCH_2 protons and a singlet at δ 2.55 corrresponding to the methylene proton of heterocyclic ring. The mass spectrum of **4** showed molecular ion peak M^+ at m/z 283 corresponding to molecular formula $C_{15}H_{13}N_3O_3$.
The next step involves Knoevenegel condensation of compound **4** containing active methylene group with various substituted aromatic aldehydes in presence of imidazole to yield 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones

5a-i. A singlet was observed at δ 4.91 due to OCH_2 protons. The disappearance of the characteristic signal of methylene group of compound **4** and the appearance of new signal at around δ 7.64 corresponding to the methine proton of Knovenegel adducts along with other characteristic peaks confirms the successful formation of the adducts **5a-i**. The mass spectrum of **5a** showed molecular ion peak M^+ at m/z 371 corresponding to molecular formula $C_{22}H_{17}N_3O_3$.

These newly synthesized quinoline derivatives containing pyrazole **5a-i** were screened for their minimum inhibitory concentration by antibacterial activity against two kinds of strains i.e. gram-positive organism *Staphylococcus aureus* and gram-negative organism *Escherichia coli* and antifungal activity against *Aspergillus niger*. The newly synthesized quinoline derivatives containing pyrazole moiety were found potent in the concentration range 100 – 50 µg/ml compared to the standard drugs, 0.19 µg/ml for Ofloxacin and 1.56 µg/ml for Fluconazole.

The compounds 5e and 5h were more potent against *Staphylococcus aureus* and 5c and 5f have moderate potencies. Compound 5a, 5b, 5d, 5g and 5i were weakly potent towards *S. aureus.*

Compound 5i was more potent towards *Escherichia coli* and 5a, 5b, 5d and 5h have moderate potencies. Compounds 5c, 5e, 5f and 5g were weakly potent towards *E. coli.*

But only five compounds showed significant antifungal inhibition with 5e and 5d being more potent and 5c, 5f & 5g were weakly potent towards *Aspergillus niger.*

The results showed that some of the compounds exhibited moderate to good activity against both the strains in antibacterial activity and few compounds were active in antifungal activity. The studies indicated that variation of substituent in the aromatic rings changes the antibacterial activity significantly.

EXPERIMENTAL

Materials and methods:

All chemicals and reagents were procured from Merck India limited. Melting points were determined in open capillary on a Mel-Temp apparatus and are uncorrected. The progress of the reaction was monitored by TLC (silica gel H, BDH, ethyl acetate-hexane, 3:5). The IR spectra were recorded on IR 200 FT-IR spectrometer as KBr pellets. The wave numbers were 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 125 MHz. All chemical shifts were measured in δ (ppm) using TMS as an internal standard. The mass spectra were recorded on VG 7070H mass spectrometer. The microanalyses were performed on Perkin-Elmer 240C elemental analyzer.

Biological activity:

Following common standard strains were used for screening of antibacterial and antifungal activities: *Staphylococcus aureus*, *Escherichia coli* and fungi *Aspergillus niger*. DMSO was used as diluent to get desired concentration of synthesized compounds to test upon standard bacterial strains. Each synthesized compound was diluted for obtaining 2000 µg/mL concentration, as a stock solution. In primary screening 1000 µg/mL concentrations of the synthesized compounds were taken. The synthesized compounds found active in this primary screening were further tested in a second set of dilution against all microorganisms. The compounds found active in primary screening were similarly diluted to obtain 500, 200, 100, 87.5, 75, 62.5, 50, 37.5, 25, 12.5, 6.25, 3.13, 1.56, 0.78, 0.39, 0.19 and 0.09 µg/mL and 2 ml of these solutions were taken in test tubes. The highest dilution showing at least 99%

inhibition zone was taken as MIC. The results of this were much affected by the size of the inoculums. The test mixture should contain 10^8 microorganism/mL. The Minimum Inhibitory Concentration[xiv-xvii] of the compounds was determined by broth dilution method. The respective clinical strain was spread separately on the Mueller-Hinton broth[xviii,xix] medium for antibacterial activity and Sabouraud dextrose agar (SDA) broth for antifungal activity. Then 2µl of test organism suspension was added and incubated at 37ºC for 24 hr. for bacteria and 48 hr. for fungi studies. The drugs Ofloxacin and Fluconazole were used as standards for comparison of antibacterial and antifungal activities respectively. The Minimum Inhibitory Concentration (MIC) was the lowest concentration of test compound that inhibit the visible growth of the organism and was determined in triplicates. The results are tabulated in **Table-I**.

Table I - Minimum Inhibitory Concentration (MICs) of 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones 5a-i

Minimum Inhibitory concentration (Concentration in µg/ml)				
S. No.	Compound	Gram-positive organisms[a]	Gram-negative organisms[a]	Fungi[b]
		Staphylococcus aureus	*Escherichia coli*	*Aspergillus niger*
1	**5a**	100	87.5	_
2	**5b**	100	75	_
3	**5c**	75	100	100
4	**5d**	100	75	_
5	**5e**	62.5	100	75
6	**5f**	75	100	100
7	**5g**	100	100	100
8	**5h**	50	75	_
9	**5i**	100	62.5	62.5
10	**Ofloxacin**	0.19	0.19	
11	**Fluconazole**			1.56

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

A mixture of quinolin-8-ol **1** (0.01 mol), ethyl chloroacetate (0.01 mol), anhydrous K_2CO_3 (1.38 g, 0.01 mol) and DMF was stirred at room temperature for 8 hr. The reaction mixture was diluted with ice-cold water. The separated solid was filtered, washed with water and recrystallized from ethanol to afford ethyl 2-(quinolin-8-yloxy)acetate **2**.

Characterization data of 2

Yield 80%. m.p. 56-58 ºC.

IR (KBr)ν_{max} : 3065 (C-H stretch in aromatics), 2920 (C-H stretch in CH_3/CH_2), 1730 (C=O stretch), 1215, 1015 (sp^2/sp^3 C-O stretch) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 1.28 (t, J = 6.8 Hz, 3H, ester CH_3), 4.29 (q, J = 7.2 Hz, 2H, ester CH_2), 4.95 (s, 2H, OCH_2), 6.98 (d, J = 2.4 Hz , 1H, quinoline-H_7), 7.44-7.47 (m, 3H, quinoline-H_3, -H_5, -H_6), 8.15 (dd, J = 2.0, 6.8, 1.6 Hz, 1H, quinoline-H_4), 8.96 (dd, J = 1.6, 2.4, 2.0 Hz, 1H, quinoline-H_2) ppm.

MS m/*z*: found 231 [M^+]; calcd. 231. Anal. $C_{13}H_{13}NO_3$. Found C 66.48 (67.52), H 5.53 (5.67), N 5.98 (6.06).

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

A solution of ethyl 2-(quinolin-8-yloxy)acetate **2** (0.01 mole) and hydrazine hydrate (0.015 mole) in ethanol (25 ml) was refluxed for 5 hr. The excess of solvent was distilled off and the reaction mixture was cooled. The separated solid was filtered, washed with petroleum ether and recrystallized from water to afford **3**.

Characterization data of 3

Yield 76%. m.p. 124-126 ºC.

IR (KBr)ν_{max} : 3325 (N-H stretch), 3060 (C-H stretch in aromatics), 2895 (C-H stretch in CH_3/CH_2), 1660 (C=O stretch), 1285, 1035 (sp^2/sp^3 C-O stretch) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 3.98 (s, 2H, NH_2), 4.87 (s, 2H, CH_2O), 7.17 (dd, J = 1.2, 5.6, 1.6 Hz, 1H, quinoline-H_7), 7.47-7.54 (m, 3H, quinoline-H_3, -H_5, -H_6), 8.20 (dd, J = 2.0, 6.8, 1.2 Hz, 1H, quinoline-H_4), 8.93 (dd, J = 1.2, 3.2, 1.2 Hz, 1H, quinoline-H_2), 9.75 (s, 1H, NH) ppm.

MS m/*z*: found 217 [M^+]; calcd. 217. Anal. $C_{11}H_{11}N_3O_2$. Found C 60.14 (60.82), H 4.98 (5.10), N 19.17 (19.34).

Synthesis of 3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 4

To a mixture of ethyl acetoacetate (0.01 mol.) and 2-(quinolin-8-yloxy)acetohydrazide **3** (0.01 mol.) in **abso**lute ethanol (20 ml), catalytic amount of triethyl amine (1ml) was added. The reaction mixture was refluxed for 8 hr. at 80ºC and after the completion of the reaction, the resultant heavy reddish syrup was allowed to cool to room temperature. The residue was dissolved in water, neutralized with $NaHCO_3$, filtered and washed thoroughly with ether to remove impurities. The crude solid thus separated out was filtered off and purified by recrystallization from ethanol to furnish the pure compound **4**.

Characterization data of 4

Yield 70%. m.p. 238-240 ºC.

IR (KBr)ν_{max} : 3214 (C-H stretching in aromatics), 1700 (C=O stretching), 1601 (C=N stretching), 1504 (C=C stretching in aromatics), 1118, 1026 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.36 (s, 3H, CH_3), 2.55 (s, 2H, CH_2 in pyrazolin-5-one), 4.93 (s, 2H, OCH_2), 7.52 (m, 4H, quinoline-H_3, H_5, H_6 & H_7), 8.18 (d, 1H, quinoline-H_4), 8.96 (d, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 16.5 (CH_3), 28.4 (CH_2 in pyrazolin-5-one), 66.3 (OCH_2), 108.2, 117.8, 121.8, 126.9, 129.8, 135.6, 140.4, 150.1, 155.9 (quinoline carbons), 159.8 (pyrazolin-5-one carbon), 163.2 (C=O in pyrazolin-5-one), 170.4 (C=O) ppm.

MS m/*z*: found 283 [M^+]; calcd. 283. Anal. $C_{15}H_{13}N_3O_3$. Found C 63.31 (63.60), H 4.59 (4.63), N 14.62 (14.83).

Synthesis of 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones 5a-i

A mixture of 3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one **4** (0.01 mol.) and different aldehydes (0.01 mol.) was suspended in dichloromethane (20 ml) and refluxed for 1 hr. at 70ºC using imidazole as a catalyst. On cooling, the crude product was precipitated, filtered under vacuum and washed with cold methanol to remove impurities and recrystallized with ethanol to afford **5**.

Characterization data of 5a-i

4-benzylidene-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5a

Yield 68%. m.p. 192-194 ºC.

IR (KBr)ν_{max} : 3064 (C-H stretching in aromatics), 2925 (aliphatic C-H stretching), 1620 (C=O stretching), 1506 (C=C stretching in aromatics), 1109, 1024 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.38 (s, 3H, CH_3), 4.91 (s, 2H, OCH_2), 7.11 (t, J = 5.8 Hz, 1H, Ar-H), 7.35 (t, J = 6.2 Hz, 2H, Ar-H), 7.38 (d, J = 6 Hz, 2H, Ar-H), 7.64 (s, 1H, Ar-CH=), 7.53-7.62 (m, 4H, quinoline-H_3, H_5, H_6 & H_7), 8.39 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.94 (d, J = 7.2 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.7 (CH_3), 65.8 (OCH_2), 107.4, 116.9, 121.4, 127.2, 129.8, 135.9, 140.4, 148.6, 155.6 (quinoline carbons), 143.8 (=CH), 126.6, 147.8 (pyrazolin-5-one carbons), 171.8 (C=O in pyrazolin-5-one), 127.8, 128.4, 128.7, 133.1 (aromatic carbons), 170.9 (C=O) ppm.

MS m/*z*: found 371 [M^+]; calcd. 371. Anal. $C_{22}H_{17}N_3O_3$. Found C 70.62 (71.15), H 4.56 (4.61), N 11.09 (11.31).

4-(2-hydroxybenzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5b

Yield 84%. m.p. 184-186 ºC.

IR (KBr)ν_{max} : 3328 (O-H stretching), 3075 (C-H stretching in aromatics), 2946 (aliphatic C-H stretching), 1641 (C=O stretching), 1493 (C=C stretching in aromatics), 1133, 1028 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.37 (s, 3H, CH_3), 4.91 (s, 2H, OCH_2), 5.36 (s, 1H, OH), 6.98-7.54 (m, 4H, Ar-H), 7.66 (s, 1H, Ar-CH=), 7.46-7.65 (m, 3H, quinoline-H_3, H_5 & H_7), 7.74 (t, J = 7.2 Hz, 1H, quinoline-H_6), 8.34 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.86 (d, J = 6.8 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.7 (CH_3), 66.9 (OCH_2), 108.1, 117.6, 121.6, 126.9, 129.2, 135.8, 140.0, 149.5, 155.8 (quinoline carbons), 143.4 (=CH), 126.2, 147.8 (pyrazolin-5-one carbons), 172.3 (C=O in pyrazolin-5-one), 117.8, 120.1, 121.4, 128.9, 133.1, 156.8 (aromatic carbons), 170.7 (C=O) ppm.

MS m/*z*: found 387 [M^+]; calcd. 387. Anal. $C_{22}H_{17}N_3O_4$. Found C 67.84 (68.21), H 4.38 (4.42), N 10.63 (10.85).

4-(4-hydroxybenzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5c

Yield 76%. m.p. 200-202 ºC.

IR (KBr)ν_{max} : 3340 (O-H stretching), 3053 (C-H stretching in aromatics), 2922 (aliphatic C-H stretching), 1634 (C=O stretching), 1511 (C=C stretching in aromatics), 1111, 1031 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.37 (s, 3H, CH_3), 4.95 (s, 2H, OCH_2), 5.37 (s, 1H, OH), 6.87 (d, J = 5.8 Hz, 2H, Ar-H), 7.95 (d, J = 6 Hz, 2H, Ar-H), 7.69 (s, 1H, Ar-CH=), 7.41-7.68 (m, 3H, quinoline-H_3 H_5 & H_7), 7.79 (t, J = 6.8 Hz, 1H, quinoline-H_6), 8.31 (d, J = 6.4 Hz, 1H, quinoline-H_4), 8.86 (d, J = 6.8 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.6 (CH_3), 66.5 (OCH_2), 107.8, 117.6, 121.9, 126.4, 128.9, 136.1, 140.2, 149.3, 155.7 (quinoline carbons), 143.5 (=CH), 126.5, 148.3 (pyrazolin-5-one carbons), 172.0 (C=O in pyrazolin-5-one), 115.9, 125.8, 130.4, 157.8 (aromatic carbons), 170.6 (C=O) ppm.

MS m/*z*: found 387 [M^+]; calcd. 387. Anal. $C_{22}H_{17}N_3O_4$. Found C 67.82 (68.21), H 4.37 (4.42), N 10.61 (10.85).

4-(2-methoxybenzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5d

Yield 64%. m.p. 194-196 ºC.

IR (KBr)ν_{max} : 3058 (C-H stretching in aromatics), 2925 (aliphatic C-H stretching), 1665 (C=O stretching), 1598 (C=C stretching in aromatics), 1228, 1017 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.38 (s, 3H, CH_3), 3.84 (s, 3H, OCH_3), 4.92 (s, 2H, OCH_2), 6.94-7.26 (m, 4H, Ar-H), 8.06 (s, 1H, Ar-CH=), 7.51-7.63 (m, 3H, quinoline-H_3, H_5 & H_7),

7.78 (t, J = 7.0 Hz, 1H, quinoline-H_6), 8.31 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.82 (d, J = 6.8 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.8 (CH_3), 56.2 (OCH_3), 66.5 (OCH_2), 108.8, 117.6, 121.9, 127.3, 128.8, 136.1, 140.3, 148.8, 155.6 (quinoline carbons), 143.5 (=CH), 126.8, 147.9 (pyrazolin-5-one carbons), 173.1 (C=O in pyrazolin-5-one), 114.8, 121.1, 122.3, 128.6, 134.1, 160.3 (aromatic carbons), 170.6 (C=O) ppm.

MS m/*z*: found 401 [M^+]; calcd. 401. Anal. $C_{23}H_{19}N_3O_4$. Found C 68.18 (68.82), H 4.71 (4.77), N 10.38 (10.47).

4-(4-methoxybenzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5e

Yield 78%. m.p. 206-208 ºC.

IR (KBr)ν_{max} : 3061 (C-H stretching in aromatics), 2927 (aliphatic C-H stretching), 1673 (C=O stretching), 1603 (C=C stretching in aromatics), 1278, 1013 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.37 (s, 3H, CH_3), 3.81 (s, 3H, OCH_3), 4.94 (s, 2H, OCH_2), 6.91 (d, J = 6.0 Hz, 2H, Ar-H), 8.36 (d, J = 5.8 Hz, 2H, Ar-H), 7.81 (s, 1H, Ar-CH=), 7.49-7.64 (m, 3H, quinoline-H_3, H_5 & H_7), 7.78 (t, J = 7.2 Hz, 1H, quinoline-H_6), 8.32 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.81 (d, J = 7.2 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.7 (CH_3), 55.4 (OCH_3), 66.2 (OCH_2), 107.2, 116.9, 121.7, 126.7, 129.6, 135.8, 140.1, 149.3, 155.5 (quinoline carbons), 143.9 (=CH), 126.5, 147.6 (pyrazolin-5-one carbons), 171.8 (C=O in pyrazolin-5-one), 114.6, 125.6, 130.1, 160.1 (aromatic carbons), 170.3 (C=O) ppm.

MS m/*z*: found 401 [M^+]; calcd. 401. Anal. $C_{23}H_{19}N_3O_4$. Found C 68.22 (68.82), H 4.72 (4.77), N 10.39 (10.47).

3-methyl-4-(2-nitrobenzylidene)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5f

Yield 78%. m.p. 224-226 ºC.

IR (KBr)ν_{max} : 3078 (C-H stretching in aromatics), 2950 (aliphatic C-H stretching), 1628 (C=O stretching), 1554 (N-O stretching), 1502 (C=C stretching in aromatics), 1121, 1026 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.36 (s, 3H, CH_3), 4.94 (s, 2H, OCH_2), 7.80-8.14 (m, 4H, Ar-H), 8.34 (s, 1H, Ar-CH=), 7.51-7.65 (m, 3H, quinoline-H_3, H_5 & H_7), 7.78 (t, J = 7.2 Hz, 1H, quinoline-H_6), 8.36 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.87 (d, J = 7.2 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.5 (CH_3), 66.4 (OCH_2), 106.8, 117.2, 121.5, 126.6, 129.3, 135.6, 140.3, 148.8, 155.5 (quinoline carbons), 143.4 (=CH), 126.8, 147.7 (pyrazolin-5-one carbons), 172.1 (C=O in pyrazolin-5-one), 123.7, 128.6, 129.9, 130.3, 134.8, 147.6 (aromatic carbons), 170.7 (C=O) ppm.

MS m/*z*: found 416 [M^+]; calcd. 416. Anal. $C_{22}H_{16}N_4O_5$. Found C 62.74 (63.46), H 3.83 (3.87), N 13.35 (13.46).

3-methyl-4-(4-nitrobenzylidene)-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5g

Yield 70%. m.p. 208-210 ºC.

IR (KBr)ν_{max} : 3062 (C-H stretching in aromatics), 2946 (aliphatic C-H stretching), 1632 (C=O stretching), 1559 (N-O stretching), 1504 (C=C stretch in aromatics), 1126, 1024 (sp^2/sp^3 C-O-C stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.37 (s, 3H, CH_3), 4.93 (s, 2H, OCH_2), 8.08 (d, J = 6.0 Hz, 2H, Ar-H), 8.24 (d, J = 5.8 Hz, 2H, Ar-H), 7.96 (s, 1H, Ar-CH=), 7.50-7.63 (m, 3H, quinoline-H_3, H_5 & H_7), 7.78 (t, J = 7.2 Hz, 1H, quinoline-H_6), 8.35 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.87 (d, J = 6.8 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.8 (CH_3), 66.2 (OCH_2), 106.9, 117.2, 121.6, 126.7, 130.1, 135.6, 140.5, 149.8, 155.5 (quinoline carbons), 143.6 (=CH), 126.2, 148.2 (pyrazolin-5-one carbons), 172.1 (C=O in pyrazolin-5-one), 123.8, 132.5, 139.4, 147.5 (aromatic carbons), 170.9 (C=O) ppm.

MS m/*z*: found 416 [M^+]; calcd. 416. Anal. $C_{22}H_{16}N_4O_5$. Found C 62.89 (63.46), H 3.81 (3.87), N 13.37 (13.46).

4-(2-chlorobenzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5h

Yield 68%. m.p. 182-184 ºC.

IR (KBr)ν_{max} : 3065 (C-H stretching in aromatics), 2924 (aliphatic C-H stretching), 1672 (C=O stretching), 1509 (C=C stretch in aromatics), 1238, 1128 (sp^2/sp^3 C-O-C stretching), 1094 (aromatic C-Cl stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.35 (s, 3H, CH_3), 4.95 (s, 2H, OCH_2), 7.26-7.43 (m, 4H, Ar-H), 8.08 (s, 1H, Ar-CH=), 7.48-7.69 (m, 3H, quinoline-H_3, H_5 & H_7), 7.78 (t, J = 7.0 Hz, 1H, quinoline-H_6), 8.33 (d, J = 6.8 Hz, 1H, quinoline-H_4), 8.92 (d, J = 6.8 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 14.9 (CH_3), 66.5 (OCH_2), 108.3, 117.5, 122.1, 127.2, 129.9, 136.5, 140.5, 149.3, 155.6 (quinoline carbons), 143.7 (=CH), 126.8, 147.9 (pyrazolin-5-one carbons), 171.8 (C=O in pyrazolin-5-one), 126.9, 127.8, 129.5, 130.2, 133.6, 134.7 (aromatic carbons), 171.2 (C=O) ppm.

MS m/*z*: found 407 [M+2], 405 [M^+]; calcd. 405. Anal. $C_{22}H_{16}ClN_3O_3$. Found C 64.56 (65.11), H 3.93 (3.97), N 10.24 (10.35).

4-(4-chlorobenzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-one 5i

Yield 74%. m.p. 194-196 ºC.

IR (KBr)ν_{max} : 3058 (C-H stretching in aromatics), 2913 (aliphatic C-H stretching), 1685 (C=O stretching), 1504 (C=C stretch in aromatics), 1336, 1180 (sp^2/sp^3 C-O-C stretching), 1045 (aromatic C-Cl stretching) cm^{-1}.

^{1}H NMR (DMSO-d_6) : δ 2.36 (s, 3H, CH_3), 4.94 (s, 2H, OCH_2), 7.44 (d, J = 6.0 Hz, 2H, Ar-H), 7.69 (d, J = 5.8 Hz, 2H, Ar-H), 7.82 (s, 1H, Ar-CH=), 7.46-7.69 (m, 3H, quinoline-H_3, H_5 & H_7), 7.77 (t, J = 7.2 Hz, 1H, quinoline-H_6), 8.35 (d, J = 6.4 Hz, 1H, quinoline-H_4), 8.90 (d, J = 6.8 Hz, 1H, quinoline-H_2) ppm.

^{13}C NMR (DMSO-d_6) : δ 15.2 (CH_3), 67.2 (OCH_2), 107.5, 117.6, 122.3, 126.5, 129.3, 135.9, 140.3, 149.2, 155.3 (quinoline carbons), 143.6 (=CH), 126.5, 148.2 (pyrazolin-5-one carbons), 172.4 (C=O in pyrazolin-5-one), 128.9, 131.3, 133.8, 135.2 (aromatic carbons), 170.8 (C=O) ppm.

MS m/*z*: found 407 [M+2] 405 [M^+]; calcd. 405. Anal. $C_{22}H_{16}ClN_3O_3$. Found C 64.48 (65.11), H 3.91 (3.97), N 10.25 (10.35).

DISCLOSURE OF INTEREST :

The authors declare that they have no conflicts of interest concerning this article.

CONCLUSION:

The compounds 4-(substituted benzylidene)-3-methyl-1-(2-(quinolin-8-yloxy)acetyl)-1*H*-pyrazol-5(4*H*)-ones **5a-i** have been successfully synthesized and the structures are established by spectral analysis. The spectral data are consistent with the structure of the newly synthesized compounds. The Minimum Inhibitory Concentration (MIC) of the synthesized compounds was studied using broth dilution method. The results revealed that majority of the tested

compounds exhibited moderate to good activity against the control Ofloxacin in antibacterial activity and few compounds exhibit significant antifungal inhibition.

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