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Research Article

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Synthesis of Quinoline Containing Pyrazolone Derivatives and their Biological Studies

Vineetha Telma D'Souza[1], Janardhana Nayak[2*], Shivaprasad Shetty M[2], Dayananda P[3] and Anil Kumar SH[4]

[1]*Department of Chemistry, MITE, Moodabidri, Karnataka, India*
[2]*Department of Chemistry, NMAMIT, Nitte-574 110, Udupi District, Karnataka, India*
[3]*Department of Chemistry, Excellent Science and Commerce PU College, Moodabidri, Karnataka, India*
[4]*Department of Biotechnology, NMAM IT, Nitte-574 110, Udupi District, Karnataka, India*

ABSTRACT

New series of (4E)-4-[(2-chloro/hydroxy quinolin-3-yl) methylidene]-2-substituted-5-methyl-2,4-dihydro-3H-pyrazol-3-ones derivatives were synthesized by the condensation of substituted 5-methyl-2,4-dihydro-pyrazol-3-ones with 6/8-substituted-2-chloro/hydroxy quinoline-3-carbaldehydes. The novel compounds were confirmed by Mass, NMR and IR spectroscopy and were also screened for their antimicrobial activities. Among them a few of the novel compounds showed tremendous bioactivities comparable with that of standard drug.

Keywords: Quinoline; Pyrazol-3-one; Antibacterial; Antifungal

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INTRODUCTION

In the wide variety of heterocyclic compounds quinoline derivatives are known to contribute to various pharmacological effects. Also the quinoline nucleus found in several natural products shows a varied biological activity. The derivatives of quinoline has been found to possess antimalarial [1], antibacterial [2,3], antifungal [4], antiviral [5], receptoragonists [6], antineoplastic agents [7] and antituberculotic [8] etc. Another heterocyclic compound, pyrazol-3-one has become a popular topic due to its manifold uses. The chemistry of pyrazol-3-one and its derivatives is particularly interesting because of their potential application in medicinal chemistry as analgesic [9,10], anti-inflammatory [11], antipyretic [12], antiparasitic [13], antimalarial [14], antifungal [15], antioxidant [16,17] and enzyme inhibitory agents [18,19] etc. These observations gave us additional motivations for the combination of quinoline derivatives with pyrazol-3-ones. In the present work the two heterocyclic moieties are combined together to enhance their antibacterial and antifungal activities.

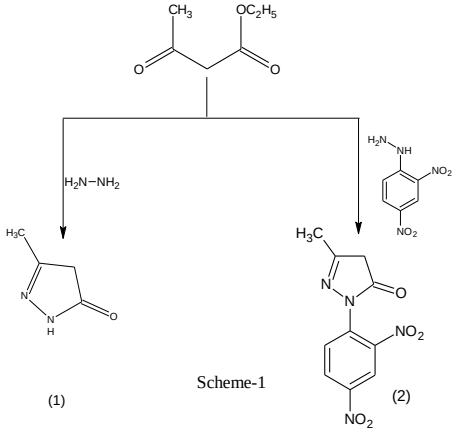
EXPERIMENTAL SECTION

All the materials used from Sigma Aldrich, Alfa, and Spectrochem Chemicals Pvt. Ltd. Melting points of all the synthesized compounds were recorded by melting point instrument. The completions of the process were checked by TLC. IR spectra were found on SHIMADZU FTIR spectrophotometer, 1H-NMR was recorded on BRUKER400

MHz spectrophotometer and mass of the compound was determined by LCMS: SHIMAZD LCMS2010A instrument.

General procedure for the synthesis of 5-methyl-2,4-dihydro-pyrazol-3-ones (1) and 2-(2, 4-dinitrophenyl)-5-methyl-2, 4-dihydro-3H-pyrazol-3-one (2) [20]:

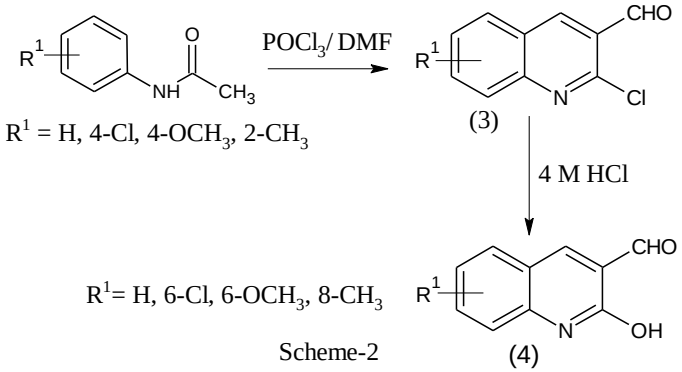
Ethylacetoacetate was taken in around bottomed flask and hydrazine hydrate and its derivatives were added to the flask dropwise with constant stirring at room temperature whereupon a vigorous reaction set in. A precipitate was formed quickly. As the reaction was exothermic, the reaction mixture was allowed to cool at room temperature. The resulting precipitate was collected by filtration. The crude product (1.5 g) was purified by recrystallization. The products were identified by spectroscopic techniques (Scheme-1).



Scheme-1

General procedure for the synthesis of 6/8-substituted-2-chloro-3-formylquinolones (3) [21]: To a solution of substituted acetanilide (5mmoles) in dry dimethylformamide (15mmoles) at 0-50C with stirring POCl3 (60 mmoles) was added dropwise and the mixture stirred at 80-900C for time ranging between 4-6 hour. The product obtained was poured into crushed ice, stirred for 5 minutes and the resulting solid mass was filtered, washed well with water and dried. The compounds were recrystallized from either ethylacetate or acetonitrile.

General procedure for the synthesis of 6/8-substituted-2-hydroxy-3-formyl quinolones (4) [22]: A mixture of 6/8-substituted chloroquinolines (0.01M) and HCl (35 ml, 4M) was subjected to heating for 4 hours. The product was poured into crushed ice. When hydroxyl quinolines separated as yellow solid, it was purified. It was recrystallized from aqueous acetic acid into yellow sticky needles (Scheme-2).



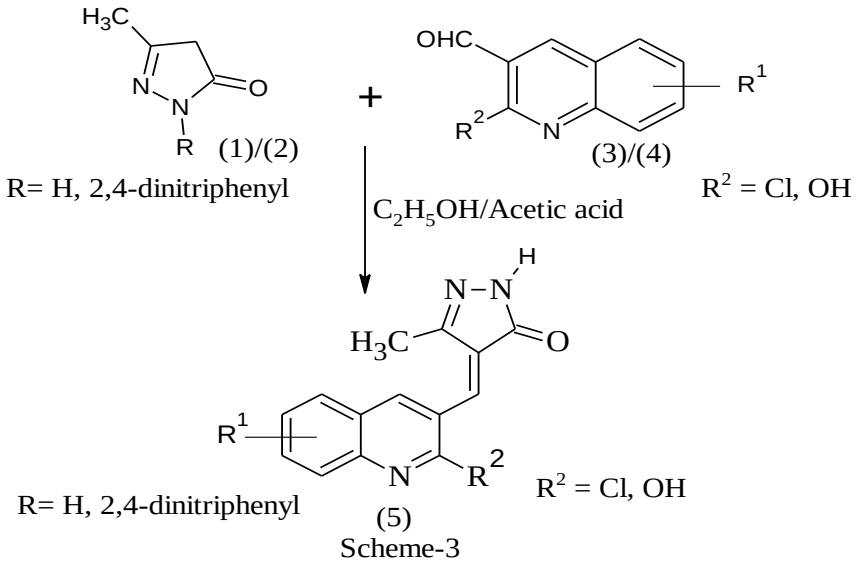
R^1 = H, 4-Cl, 4-OCH_3, 2-CH_3

R^1= H, 6-Cl, 6-OCH_3, 8-CH_3

Scheme-2

General procedure for the synthesis of (4*E*)-4-[(2-chloro/hydroxyquinolin-3-yl) methylidene]-2-substituted-5-methyl-2,4-dihydro-3*H*-pyrazol-3-ones (5):

Pyrazolones1 and 2 (1 mmol) and respective 6/8-substituted-2-chloro/hydroxy-3-formylquinolines 3 and 4 (1 mmol) were taken in ethanol (20-25ml) along with catalytic amount of acetic acid (0.1 mmol) and heated the reaction mass to reflux for about 20-25 minutes to obtain respective products. After completion of reaction (monitored by TLC), the reaction mass was allowed to cool to room temperature. The precipitated solid was filtered and dried. The crude product obtained was purified by recrystallization from ethanol/glacial acetic acid to obtain pure crystalline compounds (Scheme-3).



Scheme-3

The physical characterization data of the compounds are given in Table 1.

Table 1. Physical Characterization data of (4E)-4-[(2-chloro/hydroxy quinolin-3-yl) methylidene]-2-substituted-5-methyl-2,4-dihydro-3H-pyrazol-3-ones compounds (5)

Compound	R	R^1	R^2	Molecular formula	Melting point (^{0}C)	Yield (%)
5a	H	6-OCH_3	Cl	$C_{15}H_{12}ClN_3O_2$	277	62
5b	H	H	Cl	$C_{14}H_{10}ClN_3O$	280	82
5c	H	8-CH_3	Cl	$C_{15}H_{12}ClN_30$	273	73
5d	H	6-Cl	Cl	$C_{14}H_9Cl_2N_3O$	283	56

5e	H	H	OH	$C_{14}H_{11}N_3O_2$	295	77
5f	H	6-OCH_3	OH	$C_{15}H_{13}N_3O_3$	293	62
5g	H	8-CH_3	OH	$C_{15}H_{11}N_3O_2$	288	65
5h	H	6-Cl	OH	$C_{14}H_{10}ClN_3O_2$	303	59
5i	2, 4-dinitro phenyl	H	Cl	$C_{20}H_{12}ClN_5O_5$	270	79
5j	2, 4-dinitro phenyl	6-OCH_3	Cl	$C_{21}H_{14}ClN_5O_6$	267	61
5k	2, 4-dinitro phenyl	8-CH_3	Cl	$C_{21}H_{14}ClN_5O_5$	265	69
5l	2,4-dinitro phenyl	6-Cl	Cl	$C_{20}H_{11}Cl_2N_5O_5$	278	53

RESULT AND DISCUSSION

All the compounds (5a-l) were in solid state, stable to moisture and temperature. The structures were established by IR, ^{1}H NMR and Mass spectroscopy.

(4*E*)-4-[(2-chloroquinolin-3-yl)methylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (5b):

FT-IR (KBr, νcm^{-1}): 3462 (N-H stretch), 1654 (C=O stretch), 827 (C-Cl stretch), 1631.8 (- C=N stretch), 2926 (-C=CH).

^{1}H NMR (Solvent DMSO-d_6, 400 MHz, δ ppm): 2.5 (s, 3H, CH_3), 10.2 (s, 1H, -NH), 7.3 (s, 1H, -CH=C), 8.5 (s, 1H, quinoline H-4), 7.9 (m, 1H, quinoline H-5), 7.6 (m, 1H, quinoline H-8), 7.36 (m, 1H, quinoline H-6), 7.2 (m, 1H, quinoline H-7).

Mass spectra (m/z): 272.

(4*E*)-4-[(2-hydroxyquinolin-3-yl)methylidene]-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (5e): FT-IR (KBr, νcm^{-1}): 3462 (N-H stretch), 1647 (C=O stretch), 1643 (-C=N stretch), 2918 (-C=CH), 2849 (-OH stretch).

^{1}H NMR (Solvent DMSO-d_6, 400 MHz, δ ppm): 2.5 (s, 3H, CH_3), 10.2 (s, 1H, -NH), 7.2 (s, 1H, -CH=C), 8.4 (s, 1H, quinoline H-4), 7.8 (m, 1H, quinoline H-5), 7.6 (m, 1H, quinoline H-8), 7.3 (m, 1H, quinoline H-6), 7.2 (m, 1H, quinoline H-7).

Mass spectra (m/z): 254.

(4*E*)-4-[(2-chloroquinolin-3-yl)methylidene]-2-(2,4-dinitrophenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (5i):

FT-IR (KBr, νcm^{-1}): 1612 (C=O stretch), 833 (C-Cl stretch), 1589 (-C=N stretch), 3273 (- C=CH stretch), 1326(N-O stretch).

^{1}H NMR (Solvent DMSO-d_6, 400 MHz, δ ppm): 2.5 (s, 3H, CH_3), 7.3 (s, 1H, -CH=C), 8.8 (s, 1H, quinoline H-4), 8.1 (m, 1H, quinoline H-5), 8.0 (m, 1H, quinoline H-8), 7.69 (m, 1H, quinoline H-6), 6.7 (m, 1H, quinoline H-7), 7.4 (m, 3H, 2, 4-dinitrophenyl).

Mass spectra (m/z): 435.

(4*E*)-4-[(2-chloro-6-methoxyquinolin-3-yl)methylidene]-2-(2,4-dinitrophenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (5j):

FT-IR (KBr, νcm^{-1}): 1611 (C=O stretch), 835 (C-Cl stretch), 1543 (-C=N stretch), 3276 (- C=CH stretch), 1327(N-O stretch).

^{1}H NMR (Solvent DMSO-d_6, 400 MHz, δ ppm): 2.5 (s, 3H, CH_3), 3.9 (s, 1H, OCH_3), 7.6 (s, 1H, -CH=C), 9.1 (s, 1H, quinoline H-4), 8.2 (d, 1H, quinoline H-8), 7.6 (s, 1H, quinoline H-7), 7.5 (m, 1H, quinoline H-5), 8.3 (m, 3H, 2, 4-dinitrophenyl).

Mass spectra (m/z): 467.

(4*E*)-4-[(2-chloro-8-methylquinolin-3-yl)methylidene]-2-(2,4-dinitrophenyl)-5-methyl-2,4-dihydro-3*H*-pyrazol-3-one (5k):

FT-IR (KBr, νcm^{-1}): 1611 (C=O stretch), 832 (C-Cl stretch), 1586 (-C=N stretch), 3270 (- C=CH), 1324(N-O).

^{1}H NMR (Solvent DMSO-d_6, 400 MHz, δ ppm): 2.5 (s, 3H, CH_3), 2.6 (s, 1H, quinoline-CH_3), 7.7 (s, 1H, -CH=C), 8.8 (s, 1H, quinolone H-4), 7.5-8.0 (m, 3H, quinolone H-5, H-6 and H-7), 8.2 (m, 3H, 2, 4-dinitrophenyl).

Mass spectra (m/z): 452.

BIOLOGICAL ACTIVITY

The quinoline-pyrazolone derivatives were tested for antibacterial and antifungal activities.

Antibacterial Activity

Anti-bacterial activity was carried out by cup and plate method using *Bacillus substilis*, *Staphylococcus aureus*, *Staphylococcus epidermidis*, *Escherichia coli*, *Pseudomonas aeruginosa* and *Klebsiella pnenmoniae* organisms. The potency of synthesized compounds was determined against standard drug Penicillin and Streptomycin by measuring the minimum inhibitory concentration.

Preparation of test solution: 20 mg of the test compound was dissolved in 20 mL of DMF, from this stock solution, 1 ml of solution was taken and further diluted to required concentration with DMF. These sample solution were made in suitably labeled sterilized test tubes.

Preparation of standard solution: The standard drug used for the comparison are Penicillin and Streptomycin, the

solutions were prepared from sterile water soluble.

Method of testing: The prepared nutrient agar media sterilized using autoclave and is cooled to 45^{o}C with gentle shaking to bring about uniform cooling. To this 0.5-0.6 mL of 18-24 h old culture was injected aseptically and mixed well by gentle shaking. This was poured onto the petri dishes and was allowed to set for 1 h. Thereafter the cups were made by punching into the set agar with a sterile cork borer and scooping out the punched part of the agar. The diameter of each cup was 6 mm. To these cups 50 µL of the test compound was put, which was prepared in DMF. After adding the drug solution, it was allowed to diffuse for about 45 minutes, at room temperature. Then the plates were incubated at 37°C for 24 hours in an incubator. The minimum inhibitory concentration (MIC) is taken as a parameter of antibacterial activity, results were tabulated (Table 2).

The data in the Table 2 indicate that compound 5e show significant activity and compound 5d shows moderate activity against *Staphylococcus aureus*, and compound 5h shows moderate activity against *Bacillus subtilis* and compound 5d shows moderate activity against staphylococcus epidermidis and compound 5i shows significant activity and compound 5b and 5f shows moderate activity against *Escherichia coli* and compound 5b shows significant activity and compounds 5e and 5i shows moderate activity against *Pseudomonas aeruginosa* and compound 5e shows moderate activity against *Klebsiella pnenmoniae* and rest of the compounds were found to exhibit poor activity when compared to the standard Penicillin and Streptomycin.

Table 2. Antibacterial activity (4E)-4-[(2-chloro/hydroxy quinolin-3-yl) methylidene]-2-substituted-5-methyl-2,4-dihydro-3H-pyrazol-3-ones (5)

Compound	Minimum Inhibitory Concentration (µg/ml)					
	Gram Positive Organism			Gram Negative Organism		
	B. Subtilis	***S. aureus***	***S. epidermis***	***E. coli***	***P. aeroginosa***	***K. pneumoniae***
5a	23.15	150	17.10	75	150	18.0
5b	18.60	75	22.50	14.55	13.0	75
5c	75	30.15	75	150	150	75
5d	24.50	10.25	12.16	75	75	29.35
5e	24.75	4.65	75	75	17.75	16.75
5f	21.60	75	85	13.50	75	150
5g	18.65	75	150	150	150	18.66
5h	15.65	75	75	150	150	75
5i	26.15	18.65	16.75	12.25	16.0	75
5j	75	18.68	22.15	23.25	28.75	150
5k	16.15	18.75	28	75	75	23.75

5l	18.68	22.65	18.68	75	75	150
Penicillin	1.526	6.25	3.125	7.81	12.50	6.25
Streptomycin	6.25	1.56	1.56	3.125	3.125	3.125

Note: 20μg/ml and above poor activity, 14-20 μg/mL moderate activity and 4-13μg/mL significant activity.

Antifungal Activity

Antifungal activity was carried out by cup and plate method using Rhizopusoryzae, Aspergillusniger, Aspergillusflavus, *Candida albicans* and *Saccharomyces cerevisiae* on potato dextrose agar media. Amphotericin-B 100 mg/mL is used as standard.

Preparation of test solution: 10 mg of the compound was dissolved in 10 mL of DMF, from this stock solution further required concentration solutions were prepared by dilution using DMF.

Preparation of standard anti-fungal solution: Amphotericin-B was used as standard anti-fungal for comparison and solution were prepared by using sterile water, so that the concentrations of the solution were 100 μg/mL.

Method of testing: The method of testing for fungicidal activity is the same as that of antibacterial testing. DMF was used as a solvent control, zone of inhibition is taken as a parameter of antifungal activity and results were tabulated (Table 3) [23].

The data in Table 3 indicates that compounds 5d and 5j show significant activity and compounds 5b and 5e show moderate activity against Rhizopusoryzae and compound 5d show moderate activity against Aspergillusniger and compound 5l show significant activity and compound 5i show moderate activity against Aspergillusflavus and compound 5l show moderate activity against *Candida albicans* and compound 5e show significant activity and compounds 5c and 5h show moderate activity against *Saccharomyces cerevisiae* and rest of the compounds were found to exhibit poor activity when compared to the standard Amphotericin-B.

Table 3. Antifungal activity of (4*E*)-4-[(2-chloro/hydroxy quinolin-3-yl) methylidene]-2-substituted-5-methyl-2,4-dihydro-3*H*-pyrazol-3-ones (5)

Zone of Inhibition(mm)					
Compound (100 μg/mL)	***R. oryzae***	***A. niger***	***A. flavis***	***C. albicans***	***S. cerevisiae***
5a	16	16	-	-	-
5b	18	14	12	12	10
5c	12	14	16	-	18
5d	24	18	-	-	16
5e	18	16	12	14	22
5f	16	12	14	-	-
5g	14	10	12	14	16
5h	-	-	14	16	18

5i	16	14	18	12	12
5j	22	16	14	-	-
5k	-	-	14	`12	-
5l	14	-	21	18	16
Amphotericin-B	24	25	24	23.5	22

Note: '-'denotes no activity, 10-14 mm poor activity, 15-17 mm moderate activity, 18-25 mm significant activity.

CONCLUSION

The quinolino-pyrazol-3-one derivatives were synthesized and characterized by1HNMR, IR, and Mass spectral analysis. From the data of the antibacterial and antifungal activity, it is clearly concluded that the synthesized quinolino-pyrazol-3-one derivatives were found to be moderate antibacterial and antifungal agents.

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