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Research Article

SYNTHESIS AND ANTIMICROBIAL ACTIVITY OF SOME NOVEL PYRAZOLE DERIVED QUINOLINES

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ABSTRACT

A series of diversely substituted Pyrazole derived quinoline (**4a-g)** were obtained by the reaction of various chalcones **(3a-g)** with hydrazine hydrate. New compounds were characterized by FT-IR, 1H- NMR and Elemental analysis. Antibacterial and antifungal activities of those compounds were determined by disc diffusion method against *A. niger, A. flavus* (fungal strains), *E. coli and P. aeruginosa* (Gram negative bacteria), *S. aureus and S. pyogenes* (Gram positive bacteria) using Nystatin (for fungi) and ciprofloxacin (for bacteria) as a standard drugs. The in vitro antifungal and antibacterial screening of the pyrazole derived quinoline **(4a-g)** revealed that most of the compounds in the series showed potent activity.

Key Words: Pyrazole, Quinoline, Antibacterial activity, Antifungal activity.

1.INTRODUCTION

Pyrazoles are five member ring heterocyclic compounds, have some structural features with two nitrogen atoms in adjacent position and are also called as Azoles. The term Pyrazole was given by Ludwig Knorr in1883. Pyrazole refers to the class of simple aromatic ring organic compounds of the heterocyclic series characterized by a 5 membered ring structure composed of three carbon atoms and two nitrogen atoms in adjacent positions. Being so composed and having pharmacological effects on humans, they are classified as alkaloids, although they are rare in nature. In 1959, the first natural pyrazole, 1-pyrazolyl-alanine, was isolated from seeds of watermelons[1]. Pyrazole derivatives have a long history of application in agrochemicals and pharmaceutical industry as herbicides and active pharmaceuticals. The recent success of pyrazole COX-2 inhibitor has further highlighted the importance of these heterocyclic rings in medicinal chemistry. A systematic investigation of this class of heterocyclic compounds revealed that pyrazole containing pharmacoactive agents play important role in medicinal chemistry. The prevalence of pyrazole cores in biologically active molecules has stimulated the need for elegant and efficient ways to make these heterocyclic lead[1]. There is continuing interest in quinoline derivatives due to their large variety of industrial and biological activities[2-4]. It was reported that quinoline derivatives which incorporating another heterocyclic ring displayed an impressive properties, for example, the presence of pyrazole moiety with quinoline have antimicrobial[5-6] and industrial importance.[7-8].The

heterocyclic compounds results in enormous significance in the field of drug discovery process. Substituted pyrazole and their analogues have been used as precursors for synthesis of various biologically dynamic molecules, pyrazole derivatives as brain-derived neurotrophic factor inducers,[9] analgesic,[10] trypanocidal activity,[11] anti-mitotic agents with pro-apoptotic activity,[12] antifungal activity,[13] anti-depressant,[14] anti-cancer,[15] anti-diabetic and anti- obesity.[16] Compounds which contain the pyrazole functionality continue to attract great interest due to their varied and significant pharmacological effects. For example, the identification of new and selective cox-2 inhibitors, [17] for the relief of pain and the treatment of the symptom of arthritis and related diseases has been an important advance in modern anti-inflammatory therapy. In a related area, heterocycle appended pyrazoles have been reported to be potent and selective in inhibitors of the mitogen activated proteinkinase p38 and consequently provide a novel approach for the treatment of rheumatoid arthritis and related inflammatory diseases.[18]Taking into consideration the important biological activities of pyrazoles, we have decided to devote some attention for the synthesis and antimicrobial activity of new substituted pyrazoles.

2.MATERIALS AND METHODS

2.1 General

Reagent and solvents were purchased from commercial sources and used without further purification unless otherwise specified. All melting points were taken using open glass capillaries and were found uncorrected. Reactions were monitored by thin- layer chromatography carried out on 0.15-0.20mm silica gel 60F254 aluminum plates (MERCK company) using UV light as visualizing agent. The IR spectra in KBr were recorded on Shimadzu spectrophotometer and ^{1}HNMR spectra were recorded in DMSO on Varian Inova 300 FT MHz spectrophotometer (δ ppm) using TMS as internal standard (δ ppm). Elemental Analysis was carried out using Perkin-Elmer 240 CHN elemental analyzer.

2.1.2 General procedure for synthesis of a novel series of differently substituted pyrazole derived quinoline (4a-g)

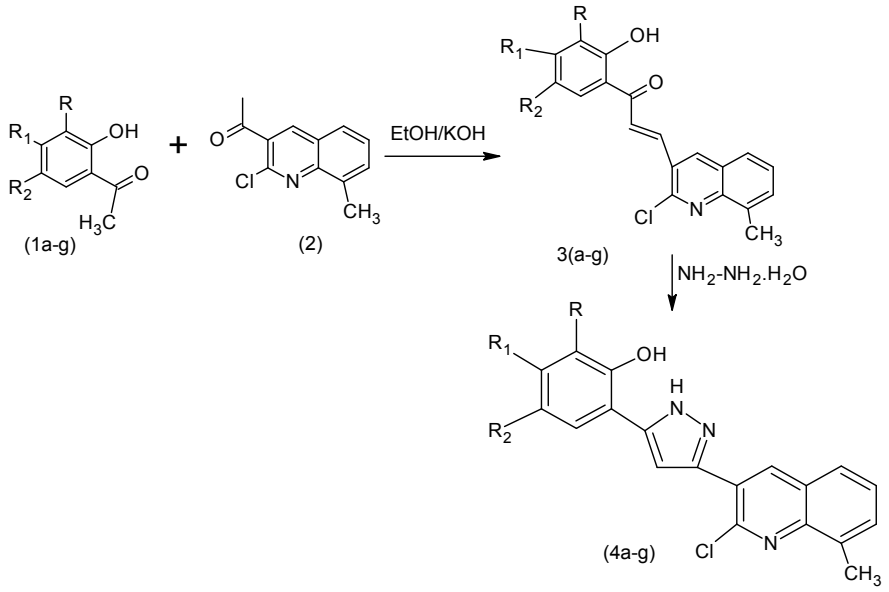
Equimolar quantities of substituted 2-hydroxyacetophenone 1a-g (0.01 mol) and 2-choloro-8-methylquinolone-3-carbaldehyde (2) (0.01 mol) were dissolved in ethanol (15 ml), under stirring and aqueous KOH (50%, 10 mL) was added drop wise. The reaction mixture was stirred at room temperature and kept for 14-16 hours. The reaction mixture was diluted with water and acidified with 10% HCl. The separated solid was filtered and crystallized using acetic acid to give compounds 3a-g. A mixture of chalcone (3a-g) (5mmoles) and hydrazine hydrate (5mmoles) was dissolved in absolute alcohol (25ml) and refluxed for 9-10 hrs. The reaction mixture was poured onto crushed ice and stirred; the solid thus obtained was filtered off and washed with water to obtain compounds 4a-g *(scheme 1).*

2.2 Microbiology

2.2.1 In vitro antibacterial and antifungal activity

The test compounds **4a-g**, in measured quantities, was dissolved in Dimethyl Sulphoxide (DMSO) in a final concentration of 50µg/mL. The synthesized compounds were evaluated for antibacterial and antifungal activity by disc diffusion method (Biljana et al, 2010) against A. niger, A. Flavus (fungal strains), E. coli and P. Aeruginosa (Gram negative bacteria), S. aureus and S. Pyogenes (Gram positive bacteria) using Nystatin (for fungi) and ciprofloxacin (for bacteria) as a standard drugs. The bacterial (24 h) and fungal (48 h) cultures from the slants were diluted with sterile water and mixed thoroughly to prepare a clear homogeneous suspension. These suspensions were spread on solidified agar, potato dextrose agar for fungi and nutrient agar for bacteria medium. The filter paper disks prepared by only DMSO (as negative control) and with solution of 50 µg/L concentrations of test compounds **4a-g** as well as standard compounds (Ciprofloxacin and Nystatin as positive control) were carefully placed over the spread cultures and incubated at 37 ºC for 24 h for bacteria and 28-30 ºC for 48 h for fungi. After the incubation period, the plates were examined for the zone of inhibition. The diameter of zones of inhibition was measured including the diameter of disk also. All

determinations were made in triplicate for each of the compounds and the average value was taken.



Scheme 1: Synthesis of Pyrazole derived quinoline

3. RESULT AND DISCUSSION

3.1 Compound characterization

3.1.1 (2Z)-3-(2-chloro-8-methylquinolin-3-yl)-1-(2,4-dihydroxy-3,5-diiodophenyl)prop-2-en-1-one (3a):

m.p. 185 °C. IR (KBr) cm-1: 3393 (-OH), 1635 (C=O), 1574, 1485 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 9.54 (s, 1H), 8.47 (d, J= 1.6 Hz, 1H), 8.08 (d, J= 15.1 Hz, 1H), 7.93 (s, 1H), 7.87-7.73 (m, 2H), 7.62 (t, J= 7.5 Hz, 1H), 7.42 (d, J= 15.1 Hz, 1H).

3.1.2 (2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(2-hydroxy-3-iodo-5-ethylphenyl)prop-2-en-1-one(3b):

m.p. 173 °C. IR (KBr) cm-1:3066(-OH), 1632 (C=O), 1569, 1487 (ring C=C), 1HNMR (300 MHz, DMSO-d6): δ 8.52 (d, J= 1.5 Hz. 1H), 8.11 (d, J= 15.1 Hz, 1H), 7.89-7.73 (m, 4H), 7.68-7.55 (m, 2H), 7.46 (d, J= 15.1 Hz, 1H), 2.30 (d, J= 1.0 Hz, 4H).

3.1.3 (2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(2-hydroxy-3,5-diiodophenyl)prop-2-en-1-one(3c):

m.p. 148°C. IR (KBr) cm-1: 2995(-OH), 1635(C=O), 1569,1492(ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.48 (d, J= 1.6 Hz, 1H), 8.24 (dd, J= 11.5, 1.5 Hz, 3H), 8.10 (d, J= 15.1 Hz, 1H), 7.88-7.73 (m, 3H), 7.62(t, J= 7.5 Hz, 1H),7.44 (d, J= 15.1 Hz, 1H).

3.1.4(2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(3,5-dichloro-2,4-dihydroxyphenyl)prop-2-en-1-one(3d):

m.p. 156°C. IR (KBr) cm-1: 3405 (-OH), 1635 (C=O), 1575, 1485 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.47 (d, J= 1.6 Hz, 1H), 8.10 (d, J= 15.1 Hz, 2H), 7.87-7.73 (m, 3H), 7.68-7.55 (m, 3H), 7.47 (d, J= 15.0 Hz, 1H).

3.1.5(2E)-3-(2-chloro-8-methylquinolin-3-yl)-1-(3,5-dibromo-2,4-dihydroxyphenyl)prop-2-en-1-one(3e):

m.p. 179°C. IR (KBr) cm-1: 3396 (-OH), 1637(C=O), 1570, 1480 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.47 (d,J= 1.6 Hz, 1H), 8.09 (d, J= 15.1 Hz, 2H), 7.87-7.72 (m, 4H), 7.62 (t, J= 7.5 Hz, 1H), 7.45 (d, J= 15.1 Hz, 2H).

3.1.6 (2E)-1-(5-chloro-2-hydroxy-3-iodophenyl)-3-(2-chloro-8-methylquinolin-3-yl)prop-2-en-1-one(3f):

m.p. 162°C. IR (KBr) cm-1: 3032(-OH), 1630(C=O), 1569, 1496(ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.48 (d, J= 1.6 Hz, 1H), 8.17-8.00 (m, 4H), 7.88-7.73 (m, 3H), 7.62 (t, J= 7.5 Hz. 1H), 7.46 (d, J= 15.1 Hz, 1H).

3.1.7 (2E)-1-(3-bromo-5-chloro-2-hydroxyphenyl)-3-(2-chloro-8-methylquinolin-3-yl)prop-2-en-1-one(3g):

m.p. 160°C. IR (KBr) cm-1: 3078 (-OH), 1637 (C=O), 1571, 1490 (ring C=C). 1HNMR (300 MHz, DMSO-d6): δ 8.48 (d,J=1.5 Hz, 1H), 8.18-8.01(m, 3H), 7.88-7.73 (m,4H), 7.62 (t, J= 7.5 Hz, 1H), 7.47 (d, J= 15.1 Hz, 1H) .

3.1.8 4-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]-2,6-diiodobenzene-1,3-diol (4a):

m.p. 213 °C. IR (KBr) cm-1: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C), 3300 (secondary N-H, broad), 3400 (-OH, broad); 1HNMR (300 MHz, DMSO-d6): δ 9.54 (s, 2H), 8.40 (d, J= 1.6 Hz, 1H), 7.84 (dd, J= 7.4, 1.7 Hz, 1H), 7.68 (t,J=7.4 Hz, 1H), 7.59 (dt, J= 7.5, 1.6 Hz, 1H), 7.40 (s, 1H), 7.21 (s, 1H).

3.1.9.2-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]-6-iodo-4-methylphenol (4b):

m.p. 204 °C. IR (KBr) cm-1: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C, narrow), 3300 (secondary N-H, broad), 3400 (-OH, broad); 1HNMR (300 MHz, DMSO-d6): δ 9.54 (s, 1H), 8.40 (d, J= 1.5 Hz, 1H), 7.84 (dd, J= 7.4, 1.6 Hz, 1H), 7.74-7.62 (m, 2H), 7.65- 7.50 (m, 2H), 7.45 (s, 1H), 2.28 (d, J= 1.0 Hz, 4H).

3.1.10 2-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]-4,6-diiodophenol (4c):

m.p. 237°C. IR (KBr) cm^{-1}: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C, narrow), 3300 (secondary N-H, broad), 3400 (-OH, broad); ^{1}HNMR (300 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.40 (d, J= 1.6 Hz,1H), 8.12 (d, J= 1.6 Hz, 1H), 7.93 (d, J= 1.5Hz, 1H), 7.85(dd, J= 6.9, 2.2 Hz, 1H),7.75- 7.59 (m, 2H), 7.35 (s, 1H).

3.1.11 4-chloro-6-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]-2-iodobenzene-1,3-diol (4d):

m.p. 224°C. IR (KBr) cm^{-1}: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C, narrow), 3300 (secondary N-H, broad), 3400 (-OH, broad); ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.40 (d, J= 1.5 Hz, 2H), 7.84 (dd, J= 7.4, 1.7 Hz, 2H), 7.68 (t, J= 7.4 Hz, 2H), 7.58 (dt, J= 7.5, 1.5 Hz, 2H), 7.25 (s, 2H), 6.87 (s, 2H).

3.1.12 2,4-dibromo-6-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]benzene-1,3-diol (4e):

m.p. 243°C. IR (KBr) cm^{-1}: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C, narrow), 3300 (secondary N-H, broad), 3400 (-OH, broad); ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.40 (d, J= 1.6 Hz, 2H), 7.84 (dd, J= 7.4, 1.7 Hz, 2H), 7.68 (t, J= 7.5 Hz, 2H), 7.59 (dt, J= 7.4, 1.5 Hz, 2H), 7.24 (s, 2H), 7.01 (s, 2H).

3.1.13. 4-chloro-2-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]-6-iodophenol (4f):

m.p. 268°C. IR (KBr) cm^{-1}: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C, narrow), 3300 (secondary N-H, broad), 3400 (-OH, broad); ^{1}HNMR (300 MHz, DMSO-d_6): δ 9.54 (s, 1H), 8.40 (d, J= 1.6 Hz, 1H), 7.91-7.79 (m, 2H), 7.78- 7.62 (m, 2H), 7.59 (dt, J= 7.5, 1.6 Hz, 1H), 7.48 (s, 1H).

3.1.14. 4-chloro-2-[3-(2-chloro-8-methylquinolin-3-yl)-1H-pyrazol-5-yl]-6-iodophenol (4g):

m.p. 259°C. IR (KBr) cm^{-1}: 1660-1600(C=C), 1350- 1000 (C-N), 1690-1640 (C=N), 3000 (C-H, broad), 1600 (C=C, aromatic ring, narrow), 1475 (C=C, narrow), 3300 (secondary N-H, broad), 3400 (-OH, broad); ^{1}HNMR (300 MHz, DMSO-d_6): δ 8.40 (d, J=1.6 Hz, 1H), 7.84(dd, J= 7.4, 1.7 Hz, 1H), 7.76-7.62 (m,4H), 7.59 (dt, J= 7.5, 1.6 Hz, 1H), 7.50 (s, 1H).

3.2 Biological activity

Newly synthesized pyrazole derived quinoline **4a-g** exhibited a varying pattern of antibacterial and antifungal activities; the results are tabulated in Table 3. In case of *E. coli*, compound **4f** showed excellent activity with respect to ciprofloxacin, compounds **4b** and **4e** displayed equipotent activity, while remaining compounds showed moderate activity.

Table 1. Physical and analytical data of the newly synthesized compounds 3a-g

Compound	R	R_1	R_2	Mol. Formula	Yield (%)	Elemental analysis% found (calculated)		
						C	H	N
3a	I	OH	I	$C_{19}H_{12}ClI_2NO_3$	72	38.59 (38.54)	2.0 (2.02)	2.28 (2.36)
3b	I	H	CH_3	$C_{20}H_{15}ClINO_2$	70	51.71 (51.75)	3.19 (3.23)	3.08 (3.01)
3c	I	H	I	$C_{19}H_{12}ClI_2NO_2$	75	39.66 (39.61)	2.04 (2.08)	2.40 (2.43)
3d	Cl	OH	Cl	$C_{19}H_{12}Cl_3NO_3$	70	55.71 (55.79)	2.95 (2.93)	3.46 (3.42)
3e	Br	OH	Br	$C_{19}H_{12}Br_2ClNO_3$	73	45.80 (45.82)	2.38 (2.41)	2.86 (2.81)
3f	I	H	Cl	$C_{19}H_{12}Cl_2INO_2$	68	47.13 (47.09)	2.43 (2.47)	2.93 (2.89)
3g	Br	H	Cl	$C_{19}H_{12}BrCl_2NO_2$	71	52.12 (52.16)	2.76 (2.74)	3.25 (3.20)

Table 2. Physical and analytical data of the newly synthesized compounds 4a-g

Compound	R	R_1	R_2	Mol. Formula	Yield (%)	Elemental analysis % found (calculated)		
						C	H	N
4a	I	OH	I	$C_{19}H_{12}ClI_2N_3O_2$	73	37.59 (37.81)	2.98 (3.18)	6.28 (6.96)
4b	I	H	CH_3	$C_{20}H_{15}ClIN_3O$	71	50.11 (50.50)	3.03 (3.18)	8.18 (8.83)
4c	I	H	I	$C_{19}H_{12}ClI_2N_3O$	78	38.54 (38.84)	2.01 (2.06)	7.08 (7.15)
4d	Cl	OH	Cl	$C_{19}H_{12}Cl_3N_3O_2$	73	53.89 (54.25)	2.35 (2.88)	9.36 (9.99)
4e	Br	OH	Br	$C_{19}H_{12}Br_2ClN_3O_2$	73	44.10 (44.78)	2.10 (2.37)	7.96 (8.25)
4f	I	H	Cl	$C_{19}H_{12}Cl_2IN_3O$	69	45.53 (46.00)	2.21 (2.44)	8.17 (8.47)
4g	Br	H	Cl	$C_{19}H_{12}BrCl_2N_3O$	72	50.45 (50.81)	2.16 (2.69)	9.20 (9.36)

Table 3. Results of Antibacterial and antifungal activity of newly synthesized compounds4a-g

Compound	**Gram Negative bacteria**		**Gram Positive Bacteria**		**Fungi**	
	E. coli	***P. aeruginosa***	***S. aureus***	***S. pyogenes***	***A. niger***	***C. albicans***
	Zone of Inhibition (mm)					
4a	25	23	25	27	29	27
4b	28	23	22	26	28	26
4c	26	22	23	27	25	28
4d	26	23	23	24	27	29
4e	29	25	25	25	24	25
4f	30	24	26	28	25	25
4g	24	25	27	28	26	23
Ciprofloxacin	29	24	26	28	-	-
Nystatin	-	-	-	-	27	27

Compound **4g** showed excellent activity and compounds **4f** showed equipotent activity while compounds **4a, 4b** and **4d** showed moderate activity while **4c** showed good activity against *P. aeruginosa.* In case of S*. aureus*, compound **4g** showed excellent activity with respect to ciprofloxacin and **4a, 4e** and **4f** showed equipotent activity while compounds **4b, 4c, 4d** showed moderate activity with respect to ciprofloxacin. Compounds **4a, 4c** and **4g** showed equipotent activity while compounds **4b, 4d** and **4e** exhibited moderate activity against *S. pyogenes*. Most of the compounds showed a significant level of activity in comparison with standard antifungal (Nystatin, 50µg/L concentration). Compounds **4a** and **4b** showed excellent activity, compound **4d** showed equipotent activity, compounds **4c, 4f**, and **4g** showed moderate inhibitory activity against *A. niger.* In case of *C. albicans*, compound **4c** and **4d** showed excellent activity, compound **4a** displayed equipotent inhibitory activity and compounds **4e** and **4f** showed moderate activity. The preliminary in vitro antifungal and antibacterial screening of the compounds 4a-g revealed that most of the compounds showed potent activity. Therefore, the present study is valuable for finding the new drugs against bacterial and fungal diseases.

4.CONCLUSION

We have synthesized some bioactive pyrazole derived quinolines by using conventional method and it is found that all the synthesized compounds showed significant antibacterial and antifungal activities. The antimicrobial study show that these heterocycles accommodating both subunits i.e. pyrazole and quinoline are expected to prove the therapeutic relevance and its utility in medicinal chemistry and drug development.

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