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ORIGINAL ARTICLE

Synthesis and biological evaluation of 1-(5-(2-chloroquinolin-3-yl)-3-phenyl-1H-pyrazol-1-yl)ethanone derivatives as potential antimicrobial agents

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Abstract A novel series of 2-Chloroquinoline nucleus clubbed with the pyrazole ring has been synthesized and screened for antibacterial and antifungal activity. The results obtained were promising against both bacterial and fungal strains. Among the series, compound **MB-N** was found moderately active against *Aspergillus fumigatus*, *Penicillium notatum* and *Bacillus subtilis* having MIC 48, 46 and 44 μg/ml, respectively whereas compound **MB-A** was found active against *P. notatum*, *B. subtilis* and *Escherichia coli* having MIC 57, 54 and 43 μg/ml, respectively as compared to standard.

1. Introduction

The rise in antibiotic-resistant microorganisms in recent years has led to an increasing search for new antibiotics [11]. Therefore, there is a prime need to discover new antimicrobial agents to avert the emergence of resistance and ideally shorten the duration of therapy.

Among the essential pharmacophores reported for antimicrobial activity, the quinoline scaffold is still considered a viable lead structure for the synthesis of more efficacious and broad spectrum antimicrobial agents [16]. The quinoline ring has various activities, such as antimicrobial [3], antituberculosis [7], antimalarial [13], anti-inflammatory [6], anticancer [1], antibiotic [10], antihypertensive [12], tyrokinase PDGF-RTK inhibiting agents [9], and antiHIV [21,19]. In addition, the recent literature is enriched with progressive findings about the synthesis and pharmacological activities of pyrazoline derivatives. Pyrazolines have been found to possess antimicrobial [22], antitubercular [18], anti-inflammatory [15], anti-tumor [5] and antiviral activities [17].

On the other hand, being a valuable alternative to conventional methods, syntheses of a variety of organic compounds by microwave irradiation is gaining the attention of medicinal chemists during the last decades [8,20]. Prompted by these

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above observations and considering the significant role of quinoline and pyrazoline in biological applications, we wish to report here the synthesis of a new series of quinolines–pyrazoline derivatives and their anti-microbial activities.

2. Method

2.1. Experimental

Conventional method of synthesis has drawbacks of lower yields and being time consuming. Here we have made attempts to report novel chloroquinoline derivatives by combination of both conventional as well as microwave irradiation method. Purity of starting materials was confirmed by TLC using Merck silica gel precoated plate and with appropriate solvent system. All the melting points were recorded on a Veego apparatus and were uncorrected. IR spectra were recorded on Jasco model 4100 FI-IR (KBr Pellet in the 4000-400 cm^{-1} range).

The ^1H NMR spectra were obtained at 300 MHz in $CDCl_3$, by using Varian instrument using TMS as internal standard and chemical shift values are given in ppm downfield to TMS (tetramethylsilane). ESI-MS was recorded on a Micromass Quattro II triple quadrupole mass spectrometer. The starting material acetanilide (**1a**) was procured from commercial source and *p*-bromo (**1b**) and *p*-nitro acetanilide (**1c**) were prepared from acetanilide by standard procedure reported by Furniss et al [23].

2.1.1. Step 1: synthesis of 2-chloroquinoline-3-carbaldehyde derivatives (Meth-Cohn et al., 1981) [24]

Acetanilide derivatives, **1a**–**1c** (13.5 g, 0.1 mol) were dissolved in 33 ml of dimethyl formamide (0.25 mol) and to this solution phosphorus oxychloride was added gradually at 0 °C. The reaction mixture was taken in a round bottom flask (RBF) equipped with reflux condenser and refluxed for 5–6 h on oil bath at 80–90 °C. The solution was cooled to room temperature and then poured on 250 ml ice water. The precipitate was collected by filtration and recrystallized from ethyl acetate to yield title compounds (**2a**–**2c**). Scheme of synthesis of 2-chloroquinoline-3-carbaldehyde derivatives is described in Fig. 1 and their respective characterization data in Table 1.

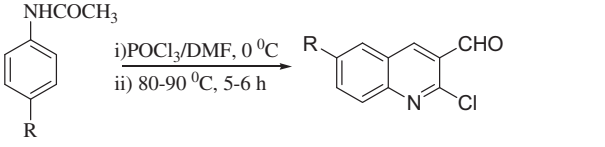


Figure 1 Synthesis of compounds **2a**–**2c**.

2.1.2. Step 2: synthesis of 2-chloroquinoline chalcones [2]

In a round bottom flask equipped with sealed mechanical stirrer, 40% sodium hydroxide solution and 15–20 ml methanol were stirred in an ice-bath. Then compounds **2a**–**2c** (1 mol) and substituted acetophenones (1 mol) were added into the above mixture and stirred for 24 h at room temperature. At the end of the period, the reaction mixture was poured in ice cold water, neutralized with dilute hydrochloric acid and the resultant solid was filtered, dried to give titled compounds **3a**–**3f**. Scheme of synthesis of 2-chloroquinoline chalcones is described in Fig. 2 and their characterization data in Table 2.

2.1.3. Step 3: synthesis of 2-chloroquinoline pyrazole derivatives [4]

A mixture of compounds **3a**–**3f** (1.0 mmol), hydrazine hydrate (1.3 mmol) and AcOH (10 ml) was placed into an open Pyrex-glass vessel. The above mixtures were subjected to microwave irradiation with magnetic stirring for 5–7 min and with a maximum power of 300 W. Reaction progress was monitored by TLC and the reaction mixture was poured in ice cold water. The precipitate formed was filtered off and recrystallized from ethanol to yield **MB-A** to **MB-BB**. Scheme of synthesis of 2-chloroquinoline pyrazole derivatives is described in Fig. 3 and their characterization data in Table 3.

2.2. Spectral characterizations of synthesized compounds MB A –BB are given below

2.2.1. MB-A: 1-(5-(2-chloroquinolin-3-yl)-3-phenyl-1H-pyrazol-1-yl)ethanone

IR (KBr): ν cm^{-1} (C=O) 1677.77, (C–H, Ar) 3061.44, (C=N) 1594.84, (C–Cl) 780.17. ^1H NMR (300 MHz $CDCl_3$) δ: 7.56–8.37 (s, 5H, Quinoline), 7.20–7.48 (s, 5H, aromatic), 4.18 (s, 1H, pyrazole), 2.53 (s, 1H, CH_3).

2.2.2. MB-Br: 1-(3-(4-bromophenyl)-5-(2-chloroquinolin-3-yl)-1H-pyrazol-1-yl)ethanone

IR (KBr): ν cm^{-1} (C=O) 1681.82, (C–H, Ar) 2922.50, (C=N) 1582.31, (C–Br) 807.06, (C–Cl) 756.92. ^1H NMR (300 MHz $CDCl_3$) δ: 8.51 (s, 1H, Quinoline), 8.05 (s, 1H, Quinoline), 7.43–7.68 (s, 3H, Quinoline), 7.37–7.49 (s, 4H, aromatic), 4.30 (s, 1H, pyrazole), 2.25 (s, 1H, CH_3). MS: m/z 450.15 $(M+Na)^+$.

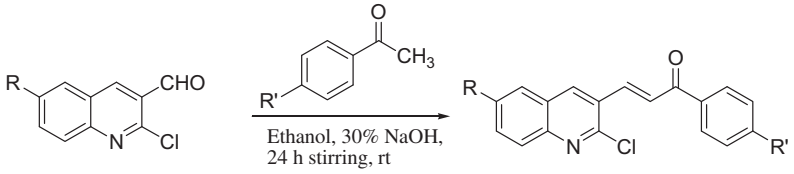
2.2.3. MB-F: 1-(5-(2-chloroquinolin-3-yl)-3-(4-fluorophenyl)-1H-pyrazol-1-yl)ethanone

IR (KBr): ν cm^{-1} (C=O) 1681.62, (C–H) 3071.09, (C=N) 1594.84, (C–F) 1236.15, (C–Cl) 756.92. ^1H NMR (300 MHz $CDCl_3$) δ: 8.73 (s, 1H, Quinoline), 8.26 (s, 1H, Quinoline), 7.43–7.75 (s,3H, quinoline), 7.49–7.68 (s,2H, aromatic), 7.13

Table 1 Characteristic data for compounds **2a**–**2c**.

Compound code	Mol. formula	M. W.	% Yield	m. p. (°C)[a]	R_f[b] value
2a	$C_{10}H_6ClNO$	191.1	63	125–127	0.69
2b	$C_{10}H_5BrClNO$	268.92	55	164–166	0.52
2c	$C_{10}H_5ClN_2O_3$	236.61	60	212–215	0.48

[a] Uncorrected.
[b] Solvent system: chloroform:ethanol (3:2).



2a-2c **3a-3f**

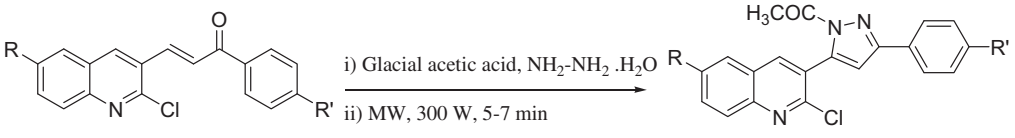
Compound code	R	R'
3a	H	H
3b	H	Br
3c	H	F
3d	H	NH_2
3e	NO_2	Br
3f	Br	Br

Figure 2 Synthesis of compounds **3a**–**3f**.

Table 2 Characteristic data for compounds **3a**–**3f**.

Compound code	Mol. formula	M. W.	% Yield	m. p. (°C)[a]	R_f[b] value
3a	$C_{18}H_{12}ClNO$	293.1	78	132–140	0.65
3b	$C_{18}H_{11}BrClNO$	372.48	69	223–226	0.59
3c	$C_{18}H_{11}ClFNO$	331.79	71	210–215	0.61
3d	$C_{18}H_{13}ClN_2O$	308.56	81	157–161	0.68
3e	$C_{18}H_{10}BrClN_2O_3$	417.36	67	248–250	0.58
3f	$C_{18}H_{10}Br_2ClNO$	451.54	64	198–203	0.60

[a] Uncorrected.
[b] Solvent system: n-hexane:ethyl acetate (3:2).



3a-3f **MB-A- MBBB**

Figure 3 Synthesis of compounds **MB-A**–**MBBB**.

Table 3 Characteristic data for compounds **MB-A** to **MB-BB**.

Compound code	Substituent		Mol. formula	M. W.	% Yield	m. p.[a] (^{0}C)	R_f[b] value
	R	R′					
MB-A	H	H	$C_{20}H_{14}ClON_3$	347.08	72	180–183	0.63
MB-Br	Br	H	$C_{20}H_{13}BrClON_3$	426.69	76	160–162	0.72
MB-F	F	H	$C_{20}H_{13}ClFON_3$	365.07	78	186–188	0.68
MB-N	NH_2	H	$C_{20}H_{15}ClON_4$	362.81	80	192–194	0.64
MB-BN	NO_2	Br	$C_{20}H_{12}BrClO_3N_4$	471.69	81	182–186	0.59
MB-BB	Br	Br	$C_{20}H_{12}Br_2ClON_3$	505.59	85	133–135	0.78

[a] Uncorrected.
[b] Solvent system: n-hexane:ethyl acetate (4:1).

(s, 2H, aromatic), 5.02 (s, 1H, pyrazole), 2.65 (s, 1H, CH_3). MS: m/z 388.23 $(M+Na)^+$.

2.2.4. MB-N: 1-(3-(4-aminophenyl)-5-(2-chloroquinolin-3-yl)-1H-pyrazol-1-yl)ethanone

IR (KBr): ν cm^{-1} (C═O) 1670.05, (N–H) 3341.07, (C–H) 3021.26, (C═N) 1559.17, (C–Cl) 780.78. ^1H NMR (300 MHz $CDCl_3$) δ: 8.51 (s, 1H, Quinoline), 8.05 (s, 1H, Quinoline), 7.57–7.59 (s, 2H, quinoline), 7.43–7.70 (s,3H,quinoline), 7.53 (s, 2H, aromatic), 6.52 (s, 2H, aromatic), 4.85 (s, 1H, pyrazole), 4.23(s, 2H,aromatic amine), 2.78 (s, 1H, CH_3).

2.2.5. MB-BN: 1-(3-(4-bromophenyl)-5-(2-chloro-7-nitroquinolin-3-yl)-1H-pyrazol-1-yl)ethanone

IR (KBr): ν cm^{-1}(C═O) 1681.62, (C–H) 2922.50, (C═N) 1582.31, (C–NO_2) 1397.17, (C–Br) 807.06, (C–Cl) 756.92. ^1H NMR (300 MHz $CDCl_3$) δ: 9.72 (s, 1H, NO_2), 7.56–8.37 (s, 3H, Quinoline), 7.12–7.36 (s, 2H, aromatic), 7.46–7.51(s, 2H, aromatic), 4.25 (s, 1H, pyrazole), 2.23 (s, 1H, CH_3).

2.2.6. MB-BB: 1-(5-(7-bromo-2-chloroquinolin-3-yl)-3-(4-bromophenyl)-1H-pyrazol-1-yl)ethanone

IR (KBr): ν cm^{-1}(C═O) 1666.2, (C–H) 3059.51, (C═N) 1590.21, (C–Br) 840.81, (C–Cl) 750.17. ^1H NMR (300 MHz $CDCl_3$) δ: 8.43 (s, 1H, Quinoline), 8.28 (s, 1H, Quinoline), 7.57–7.59 (s, 2H, quinoline), 7.37 (s, 2H, aromatic), 7.49 (s, 2H, aromatic), 4.89 (s, 1H, pyrazole), 2.53 (s, 1H, CH_3).

3. Results and discussion

3.1. Chemistry

Cyclization of chalcones (**3a**–**3f**) with hydrazine hydrate by using the microwave irradiation method to give various chloroquinoline substituted pyrazole is described in Fig. 3. From the IR spectra, it was observed that functional groups present in the molecule appeared at their characteristic frequency. C═N str. between 1540 and 1590 cm^{-1}, C–Cl str. between 746 and 780 cm^{-1}, C═O str. between 1666 and 1682 cm^{-1} etc. The chemical shift (δ) for 2-chloroquinoline hydrogen was observed in the range of 7.56–8.37 ppm, δ value for aromatic hydrogen was observed in the range of 7.20–7.48 ppm. The m/e value was observed, e.g., in case of MB-Br and MB-F at 450.15 $(M+Na)^+$ and 388.23 $(M+Na)^+$, respectively. So, from the physical and spectral data, we can conclude that the desired compounds synthesized successfully.

3.2. Antibacterial and antifungal activity

All the synthesized compounds were screened for both antimicrobial and antifungal activity. Compounds were screened for *in vitro* against two Gram positive strains *Staphylococcus aureus* (*S. aureus*, NCIM 2079), *Bacillus subtilis* (*B. subtilis*, NCIM 2711) and Gram negative *Escherichia coli* (*E. coli*, NCIM 2685) bacteria for antibacterial and two fungal species *Aspergillus fumigatus* (*A. fumigatus*, NCIM 535) and *Penicillium notatum* (*P. notatum*, NCIM 745) for antifungal activity, respectively using the broth microdilution method [14].

Minimum inhibitory concentration (MIC) was determined and compared with standard drugs Gatifloxacin for antibacterial activity (Table 4) and Fluconazole for antifungal activity (Table 5).

Table 4 MIC values (μg/ml) against *S. aureus*, *B. subtilis*, *E. coli*.

Compound code	*S. aureus*	*B. subtilis*	*E. coli*
MB-A	200	54	43
MB-Br	213	103	77
MB-F	245	82	93
MB-N	225	44	87
MB-BN	246	108	97
MB-BB	289	104	96
Gatifloxacin	32.5	30	28.5

Table 5 MIC values (μg/ml) against *A. fumigatus*, *P. notatum*.

Compound code	*A. fumigatus*	*P. notatum*
MB-A	77	57
MB-Br	98	102
MB-F	95	66
MB-N	48	46
MB-BN	89	93
MB-BB	96	113
Fluconazole	32.5	30.5

From *in vitro* antifungal results, compound **MB-N** (*p*-amino derivative) was found to have significant activity as compared to reference standard Fluconazole against *A. fumigatus* and *P. Notatum*, while derivative **MB-A** (acetophenone derivative), **MB-F** (*para*-fluro derivative) having moderate activity as that of standard against *P. notatum*. The compounds **MB-Br**, **MB-BN** and **MB-BB** showed least activity against both the fungal strains (Fig. 4). So, from this study it can be concluded that the electron-donating group i.e., (*p*-amino) on the phenyl ring is contributing positively for the antifungal activity whereas the unsubstituted phenyl ring as well as the electron-withdrawing group are able to maintain the moderate antifungal activity. Fluro substituted compound (**MB-F**) having high electronegativity is showing moderate activity as compared to bromo substitution (**MB-Br**) on the phenyl ring.

In case of anti-bacterial activity, all the tested derivatives showed least activity against *S. aureus* with MIC in the range of 200–250 μg/ml. In case of *B. subtilis* and *E. coli* derivative **MB-A** was found to have good activity which is 1–2 folds less than the standard drug Gatifloxacin while compound **MB-N** showed significant activity against *B. subtilis*. All other compounds **MB-Br**, **MB-F**, **MB-BN** and **MB-BB** showed least activity against *B. subtilis* and *E. coli* (Fig. 4). Thus from the obtained antibacterial activity data we can conclude that compounds with the unsubstituted phenyl ring (**MB-A**) were active against gram negative as well as gram positive bacteria whereas compounds with electron-donating group substituent (**MB-N**) on the phenyl ring were active against *B. subtilis*. Compounds with both electron-withdrawing and electron-donating groups on the phenyl ring resulted in decreased activity.

As far as quinoline nucleus is considered for all the synthesized compounds, substitution at 7-position with the electron-withdrawing group (**MB-BN** and **MB-BB**) results in poor

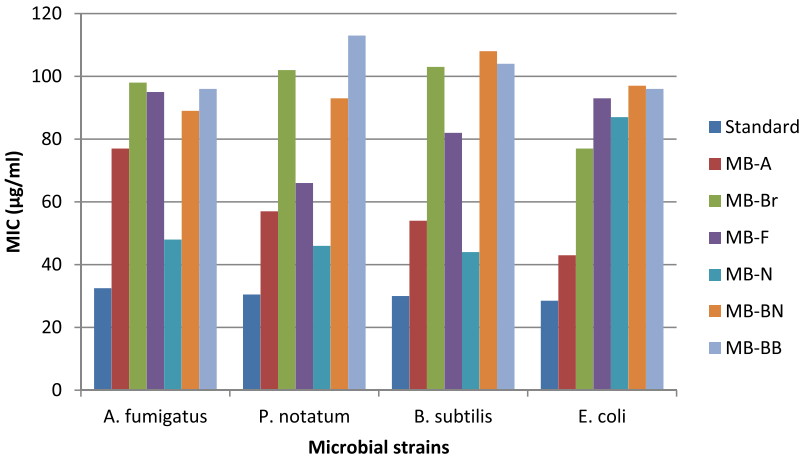


Figure 4 MIC of synthesized compounds in comparison with standard against different microbial strains.

antibacterial as well as antifungal activity. The chloro substitution at 2-position was a key factor for both antibacterial as well as antifungal activities.

4. Conclusion

A series of 2-chloroquinolines condensed with pyrazole nucleus have been synthesized and evaluated for antibacterial and antifungal activity. The compound **MB-N** was found to be having moderate activity against *A. fumigatus* and *P. notatum*, whereas compounds **MB-A** and **MB-F** were found active against *P. notatum*. As far as antibacterial activity is concerned compound **MB-A** showed good activity against *B. subtillis* and *E. coli* whereas compound **MB-N** has promising activity only against *B. subtillis*. All the synthesized compounds showed very poor activity against *S. aureus*.

So, the results obtained from antibacterial and antifungal activities are more promising as the compounds showed significant activity as compared to standard or marketed drugs, Gatifloxaicn and Fluconazole. These results can be used further to design and develop novel antimicrobial agents.

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