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Synthesis and characterization of some new quinoline based derivatives endowed with broad spectrum antimicrobial potency

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ABSTRACT

The synthesis of a novel series of 2-(5-(2-chloro-6-fluoroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-ones (**4a–l**) and *N*-(4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)-2-morpholinoacetamides (**7a–l**) are described in the present paper. The chemical structures of compounds have been elucidated by IR, ^{1}H NMR, ^{13}C NMR and mass spectral data. Antimicrobial activity was measured against *Escherichia coli* (MTCC 443), *Pseudomonas aeruginosa* (MTCC 1688), *Staphylococcus aureus* (MTCC 96), *Streptococcus pyogenes* (MTCC 442), *Candida albicans* (MTCC 227), *Aspergillus niger* (MTCC 282) and *Aspergillus clavatus* (MTCC 1323) by serial broth dilution. Evaluation of antimicrobial activity showed that several compounds exhibited greater activity than reference drugs and thus could be promising new lead molecules.

The current interest in the development of new antimicrobial agents can be partially ascribed both to the increasing emergence of bacterial resistance to antibiotic therapy and to newly emerging pathogens.[1,2] Over the past few years, we have been principally engrossed in the synthesis of quinoline incorporating structures for antimicrobial evaluations[3] on the premise that quinoline moiety is found in a large variety of naturally occurring compounds. In fact, introducing chloroquine into treatment of malaria more than 60 years ago triggered a new era of quickly developing antimicrobial drugs. In synthetic medicinal chemistry the quinoline motif is widely exploited revealing a spectrum of activity covering antimalarial,[4] anticancer,[5] antifungal, antibacterial, antiprotozoic antibiotic,[6] and anti-HIV[7] effects. Moreover, 2-pyrazoline and thiazolidinone derivatives have been reported to exhibit various pharmacological activities such as antimicrobial,[8] anti-inflammatory[9] and antihypertensive.[10] The design concepts have been drawn in Figure 1, which explains the structural similarity of our new target compounds with renowned drugs.

As quinoline compounds are known to be effective antimicrobial compounds,[11] we initiated a program to synergies the antimicrobial activity of quinoline and other reported heterocycles by preparing hybrid molecules having the features of these scaffolds in an effort to discover potent antimicrobial. To derivatize the resulting heterocyclic system, we have used several functional groups such as chloro, nitro, methoxy, fluoro etc at positions 3 and 6 of pyrazoline and pyrimidine ring 'respectively'. It has been hoped that combination of these active groups in the new molecular design would lead to better antimicrobial agents. In continuation of our research activity on quinoline derivatives, several compounds were prepared and tested against bacteria and fungi, potent compounds are given in Table 1.

In this communication, we report the synthesis of newly developed two series of compounds 2-(5-(2-chloro-6-fluoroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-ones (**4a–l**) and *N*-(4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)-2-morpholinoacetamides (**7a–l**) starting from 2-chloro-6-fluoroquinoline-3-carbaldehyde (**1**).

The Vilsmeier–Haack reaction on acetanilide provided a vital and efficient intermediate for synthesis of several newer substituted heterocyclic compounds. The reaction was performed at 100 °C for 15–20 h, using typical Vilsmeier-Haack reagent derived from phosphorus oxychloride-dimethylformamide.[12] Although, the reaction proceeded uneventfully, products formed were isolated using silica gel column chromatography. The reaction sequences employed for synthesis of target compounds (**4a–l**) and (**7a–l**) are illustrated in Scheme 1. Key chalcone intermediates (**2a–l**) were synthesized through Claisen–Schmidt condensation of equimolar amounts of acetophenone derivatives and 2-chloro-6-fluoroquinoline-3-carbaldehyde (**1**) by stirring the reactants in aqueous ethanolic solution containing 20% sodium hydroxide at room temperature for 24 h.[13] Newly synthesized compounds

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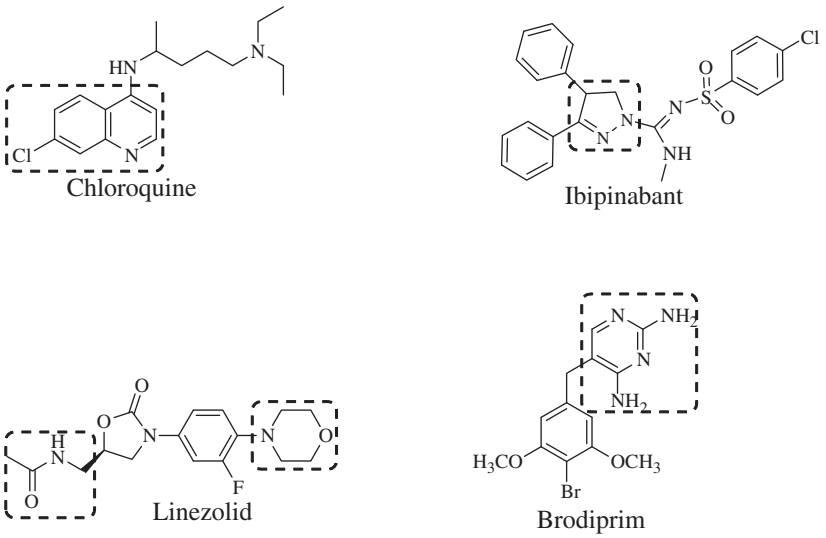


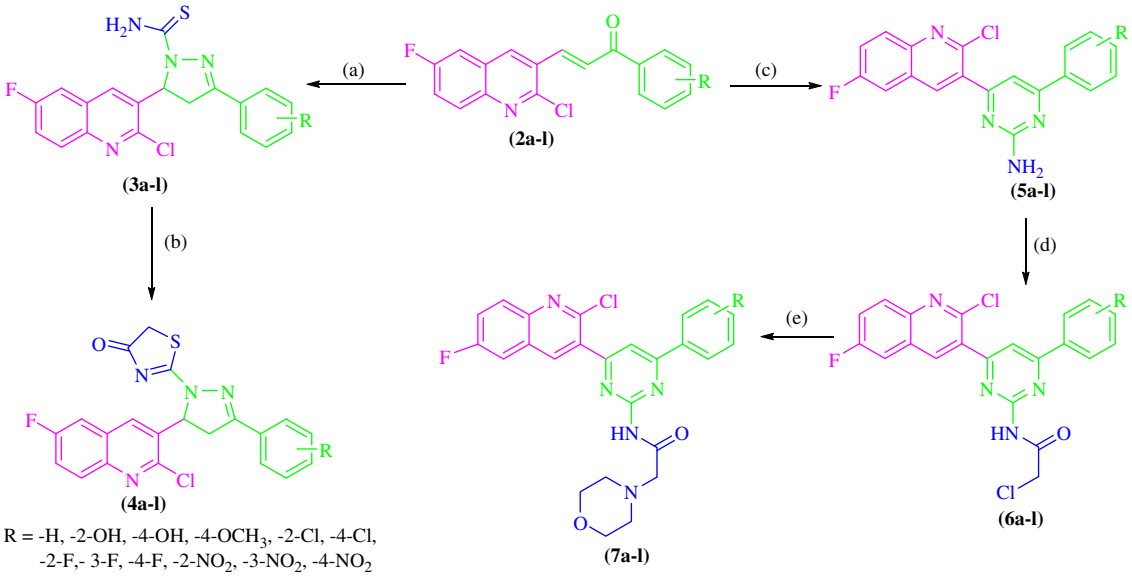
Figure 1. Structure of drugs containing reported heterocycles.

Table 1
Structures and antimicrobial activity of promising compounds

Compounds	Microorganisms	MIC, μg/mL
4i	*S. pyogenes*	25
4j	*P. aeruginosa*	12.5
	S. pyogenes	25
	A. niger	25
	A. clavatus	12.5
7g	*E. coli*	12.5
	P. aeruginosa	25
	A. clavatus	25
7l	*E. coli*	25

5-(2-chloro-6-fluoroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides (**3a–l**) were obtained by heating at reflux equimolar amounts of thiosemicarbazide and the corresponding α,β-unsaturated ketones (**2a–l**) in hot ethanolic sodium hydroxide solution for 8 h (Scheme 1).[14] Moreover, aforementioned 1-thiocarbamoyl pyrazole derivatives (**3a–l**) were cyclized to (**4a–l**) through their reaction with ethyl bromoacetate in hot ethanol for 1 h.[15] When 3-(2-chloro-6-fluoroquinolin-3-yl)-1-(aryl)prop-2-en-1-ones (**2a–l**) were refluxed with guanidine nitrate in presence of sodium hydroxide, 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-amines (**5a–l**) were formed.[16] Various substituted 2-chloro-*N*-(4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)acetamides (**6a–l**) were synthesized by electrophilic substitution reaction of chloroacetyl chloride with corresponding parent 4-(2,6-dichloroquinolin-3-yl)-6-(aryl)pyrimidin-2-amines (**5a–l**) in presence of triethylamine as base and toluene as solvent.[17] Condensation of 2-chloro-*N*-(4-(2,6-dichloroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)acetamides (**6a–l**) with morpholine in presence of anhydrous potassium carbonate furnished *N*-(4-(2,6-dichloroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)-2-morpholinoacetamides (**7a–l**).[18]

All the newly synthesized compounds were evaluated against Gram-positive bacteria (*Staphylococcus aureus, Staphylococcus pyogenes*), Gram-negative bacteria (*Escherichia coli, Pseudomonas*



(a) $NH_2CSNHNH_2$, Ethanol, Reflux 8 h **(b)** $BrCH_2COOC_2H_5$, Ethanol, Reflux 1 h **(c)** $NH_2C(=NH)NH_2$. HNO_3, Ethanol, Reflux 10 h, NaOH **(d)** $ClCH_2COCl$, Chloroform, Reflux 12 h, Et_3N **(e)** Morpholine, Dry toluene, Reflux 8 -10 h, Anhyd. K_2CO_3

Scheme 1. Synthetic scheme for the title compounds **4a–l** and **7a–l**.

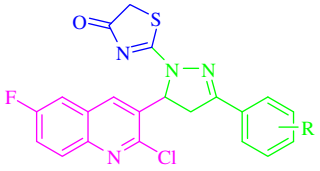
aeruginosa) and fungi (*Candida albicans*, *Aspergillus niger* and *Aspergillus clavatus*) strains. Individual minimum inhibitory concentration (MIC, μg/mL) values of tested compounds (**4a–l**) and (**7a–l**) against the test microbes are listed in Table 2 along with MIC values of reference compounds ciprofloxacin (for bacteria) and griseofulvin (for fungi). Results revealed that majority of synthesized compounds showed varying degrees of inhibition against the test panel of species. The obtained antimicrobial activity of tested compounds could be correlated to structural variations and modifications. Key precursors, chalcones (**2a–l**) showed poor antimicrobial activity. Compounds (**3a–l**) displayed moderate to mild antibacterial activity. Finally, cyclized target molecules (**4a–l**) showed significant to potent activity. On the other hand pyrimidine counterparts (**5a–l**) and (**6a–l**) did not significantly affect the antimicrobial potential and showed poor antibacterial activity. Compounds (**7a–l**) led to a noticeable improvement in the antimicrobial activity. Collectively, compounds (**4a–l**) and (**7a–l**) could be considered as significant to potent active broad spectrum antimicrobial agents identified in this study. Compounds **4g** (2-F) and **4j** (2-NO_2) of pyrazole series and compounds **7g** (2-F) and **7l** (4-NO_2) of pyrimidine series showed excellent activity against *E. coli*. Amongst them, compound **7g** (2-F) was potent at MIC = 12.5 μg/mL against *E. coli*. Compound **4j** (2-NO_2) of pyrazole series and **7g** (2-F) of pyrimidine series possessed highest inhibition against *P. aeruginosa* at MIC = 12.5 μg/mL and MIC = 25 μg/mL respectively. Compounds **4f** (4-Cl), **7g** (2-F) and **7j** (2-NO_2) were equipotent to ciprofloxacin at MIC = 50 μg/mL against *S. aureus*. Compounds **4i** (4-F) and **4j** (2-NO_2) were more potent than standard drug at MIC = 25 μg/mL, while compounds **7g** (2-F) and **7j** (2-NO_2) were equipotent to ciprofloxacin at MIC = 50 μg/mL against *S. pyogenes*.

MIC values of antifungal activity showed similar trend as antibacterial activity. Intermediates exhibited poor or no activity against all the tested panel of fungal strains. Introduction of thiazolone and morpholine moiety afforded compounds to display good inhibition against three fungal strains. Among tested compounds, **4h** (3-F) and **4j** (2-NO_2) from pyrazole series and compounds **7g** (2-F), **7i** (4-F), **7j** (2-NO_2) and **7l** (4-NO_2) from pyrimidine series displayed significant inhibition compared to other compounds at MIC = 100 μg/mL against *C. albicans*. Compound **7g** (2-F) exhibited highest inhibition at MIC = 25 μg/mL against *A. clavatus*. Compound **4j** (2-NO_2) showed excellent potency at MIC = 25 μg/mL and MIC = 12.5 μg/mL against *A. niger* and *A. clavatus* respectively which were more potent than griseofulvin. The comparison of antibacterial and antifungal activity was discussed on the basis of standard drugs ciprofloxacin and griseofulvin, 'respectively'.

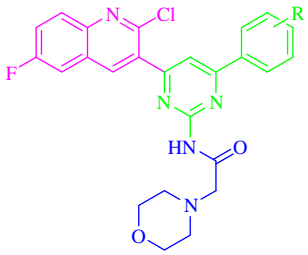
Antimicrobial activity (Table 2) revealed that target compounds (**4a–l**) and (**7a–l**) represented broadly potent molecules. Presence of a phenyl group (compounds **4a** and **7a**) did not seem to make either a negative or a positive contribution to antimicrobial activity against any of the analyzed microorganisms. Comparison of compounds **4a–l** and **7a–l** with other derivatives also pointed out that existence of electron withdrawing group at position 2 and 4 of the benzene ring in both core structures was essential. Compounds containing 2-NO_2, 4-NO_2, 2-F and 4-F exhibited pronounced activity. Presence of 2-NO_2 and 2-F group caused enhancement in antimicrobial activity against analyzed microorganisms. In fact, in case of *P. aeruginosa* and *A. clavatus*, it even boosted antimicrobial activity. Amongst all synthesized compounds fluoro derivatives at second and fourth position also exerted significant activity. This attributed to smaller size of fluorine atom, which may give stability to compound and reduce ring strain. In both serieses, compounds containing hydrophilic substituents hydroxy and methoxy did not lead to show potent antimicrobial effect but strongly reduced the activity. In summary, compounds from both of these new classes of antimicrobial agents showed promising in vitro antibacterial and antifungal activities.

In conclusion, in the present article, we have reported the synthesis, characterization and antimicrobial activity of some new series of quinoline based pyrazoline and pyrimidine derivatives.

Table 2
Results of antibacterial and antifungal screening of compounds **4a–l** and **7a–l**



(4a-l)



(7a-l)

Comp	–R	Minimum Inhibitory Concentration (MIC) for bacteria (μg/mL)				Minimum Inhibitory Concentration (MIC) for fungi (μg/mL)		
		Gram-negative		Gram-positive				
		E. coli MTCC 443	*P. aeruginosa* MTCC 1688	*S. aureus* MTCC 96	*S. pyogenes* MTCC 442	*C. albicans* MTCC 227	*A. niger* MTCC 282	*A. clavatus* MTCC 1323
4a	–H	500	250	500	1000	1000	1000	500
4b	–2-OH	250	500	1000	500	1000	1000	1000
4c	–4-OH	500	250	500	250	1000	500	1000
4d	–4-OCH_3	1000	1000	500	1000	1000	500	500
4e	–2-Cl	50	100	250	50	500	100	50
4f	–4-Cl	500	250	50	50	500	50	100
4g	–2-F	25	50	100	100	250	50	500
4h	–3-F	500	250	500	500	100	500	500
4i	–4-F	50	50	100	25	1000	250	100
4j	–2-NO_2	25	12.5	100	25	100	25	12.5
4k	–3-NO_2	250	500	1000	500	500	100	50
4l	–4-NO_2	50	100	250	50	250	100	100
7a	–H	250	500	500	250	1000	500	250
7b	–2-OH	1000	500	500	500	1000	250	500
7c	–4-OH	500	1000	1000	1000	500	500	1000
7d	–4-OCH_3	500	250	500	250	1000	250	500
7e	–2-Cl	50	100	100	100	500	100	100
7f	–4-Cl	100	50	250	100	250	100	100
7g	–2-F	12.5	25	50	50	100	50	25
7h	–3-F	100	100	250	250	250	250	250
7i	–4-F	50	50	100	100	100	100	100
7j	–2-NO_2	100	100	50	50	100	50	100
7k	–3-NO_2	250	100	250	100	250	100	500
7l	–4-NO_2	25	50	100	100	100	100	50
	Ciprofloxacin	25	25	50	50	—	—	—
	Griseofulvin	—	—	—	—	500	100	100

Preliminary in vitro results of antimicrobial screening of the title compounds, reported here, evidenced that some of the compounds from both new series have emerged as potential lead antimicrobials endowed with significant to potent activity. Further improvements in activity can possibly be achieved by slight modifications in the ring substituents. Yet, extensive additional functioning warrants further investigations. Finally, clinical potential of these types of compounds awaits the results of additional structure activity studies and the in vivo evaluation of their efficacies. Our findings will have impact on medicinal chemists and pharmacists for further investigations in this field for search of potent antimicrobial agents.

Characterization data and antimicrobial assay of all synthesized compounds are described in supplementary data file.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.bmcl.2012.09.039.

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13. General procedure for preparation of 3-(2-chloro-6-fluoroquinolin-3-yl)-1-(aryl)prop-2-en-1-ones (**2a–l**). A mixture of 2-chloro-6-fluoroquinoline-3-carbaldehyde (**1**) (0.01 mol) and substituted acetophenones (0.01 mol) was stirred in ethanolic sodium hydroxide for 24 h at room temperature. The yellow crystals formed were filtered off, washed with water and crystallized from ethanol (95%).
14. General procedure for preparation of 5-(2-chloro-6-fluoroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazole-1-carbothioamides (**3a–l**). A suspension of chalcones (0.01 mol), sodium hydroxide (0.025 mol) in ethanol (95%) (50 mL) and thiosemicarbazide (0.01 mol) was added. Mixture was refluxed for 8 h. The

product was poured into crushed ice and the solid mass which separated out was filtered, dried and recrystallized from ethanol (95%).

15. General procedure for preparation of 2-(5-(2-chloro-6-fluoroquinolin-3-yl)-3-(aryl)-4,5-dihydro-1*H*-pyrazol-1-yl)thiazol-4(5*H*)-ones **(4a–l)**. To a suspension of compounds (**3a–l**) (0.01 mol) in ethanol (95%), ethyl bromoacetate (0.01 mol) was added and heated at reflux for 1 h. After cooling, the separated product was filtered and washed. The product was crystallized from aqueous DMF.
16. General procedure for preparation of 4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-amines (**5a–l**). A mixture of compounds (**2a–l**) (0.01 mol) and guanidine nitrate (0.01 mol) in ethanol (95%) was refluxed, while a solution of sodium hydroxide (0.05 mol) in water was added portion-wise for 2 h. Refluxing was continued for a further 10 h and the mixture was poured into ice-cold water. The formed solid was separated by filtration. Crude product was dried and crystallized from ethanol (95%).
17. General procedure for preparation of 2-chloro-*N*-(4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)acetamides (**6a–l**). An equimolar amount of compounds (**5a–l**) (0.01 mol) and chloroacetyl chloride (0.01 mol) in chloroform was refluxed in presence of catalytic amount of triethylamine for about 12 h. Excess of solvent was removed under reduced pressure and the residue was stirred with water. Crude product was dried and recrystallized from aqueous DMF.
18. General procedure for preparation of *N*-(4-(2-chloro-6-fluoroquinolin-3-yl)-6-(aryl)pyrimidin-2-yl)-2-morpholinoacetamides (**7a–l**). A mixture of compounds (**6a–l**) (0.01 mol), anhydrous potassium carbonate (0.02 mol) and morpholine (0.01 mol) in dry toluene was refluxed for about 8–10 h. After completion of the reaction, potassium carbonate was removed by filtration and excess of solvent was removed under reduced pressure. The obtained residues were filtered, dried and recrystallized from aqueous DMF.