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Biological Screening of Novel 1-cyclopropyl-6-fluoro-8-methoxy-7-susbstituted-4-oxo-1, 4-dihydroquinolin-3-carboxylic acids

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Abstract: Herein, we report the biological activity of novel 1-cyclopropyl-6-fluoro-8-methoxy-7-susbstituted-4-oxo-1,4-dihydroquinolin-3-carboxylic acids. Almost all the series of compounds **3a-i** showed moderate to excellent activity towards the bacteria and fungi under investigation. Some of them, particularly **3h** and **3i** can be exploited for formulation of bactericide and fungicide after detailed study by disc method and agardisc diffusion method. Chloroamphenicol and Fluconazole are used as standard positive control.

Keywords: antifungal and antibacterial activity, disc method, agardisc diffusion method, hydroquinolin.

Introduction:

Nitrogen containing heterocyclic ring such quinoline is a promising structural moiety for drug design[1,2]. Among them, quinoline derivatives are exceptional nitrogen-containing heterocycles which concerned specific attention having superior place as building blocks of various pharmaceutical agents, natural products and biological active molecules[3-5].

. The quinoline is found in many naturally occurring alkaloids. Quinine is an anti-malarial drug and has been isolated from the bark of cinchona trees. Since the discovery of the natural product quinine, many compounds with a quinoline scaffold have displayed good antimalarial activity, leading to the development of effective antimalarial agents, including Chloroquine, Primaquine, Pamaquine, Mefloquine, Amodiaquine and Mepacrine (Figure 1).

Nalidixic acid is the oldest member of the quinolone class of synthetic antimicrobial agents[6], and has been used for the treatment of urinary tract infections for many years. This drug is of relatively minor significance because of its limited therapeutic utility and the rapid development of bacterial resistance. Against this backdrop, fluorinated 4-quinolones like norfloxacin, ciprofloxacin, ofloxacin, *etc*. have been developed. Since these agents have broad antimicrobialprofile, they are effective after oral administration for the treatment of a wide variety of infectious diseases[7,8].However, serious side effects are associated with thesedrugs along with development of

antimicrobial resistance. Both the discovery and development of new antimicrobial agents are required to overcome these drawbacks. For this purpose extensive literature surveyhas been carried out, which has indicated that derivatives of quinoline[9-11] exhibit good antimicrobial profile.

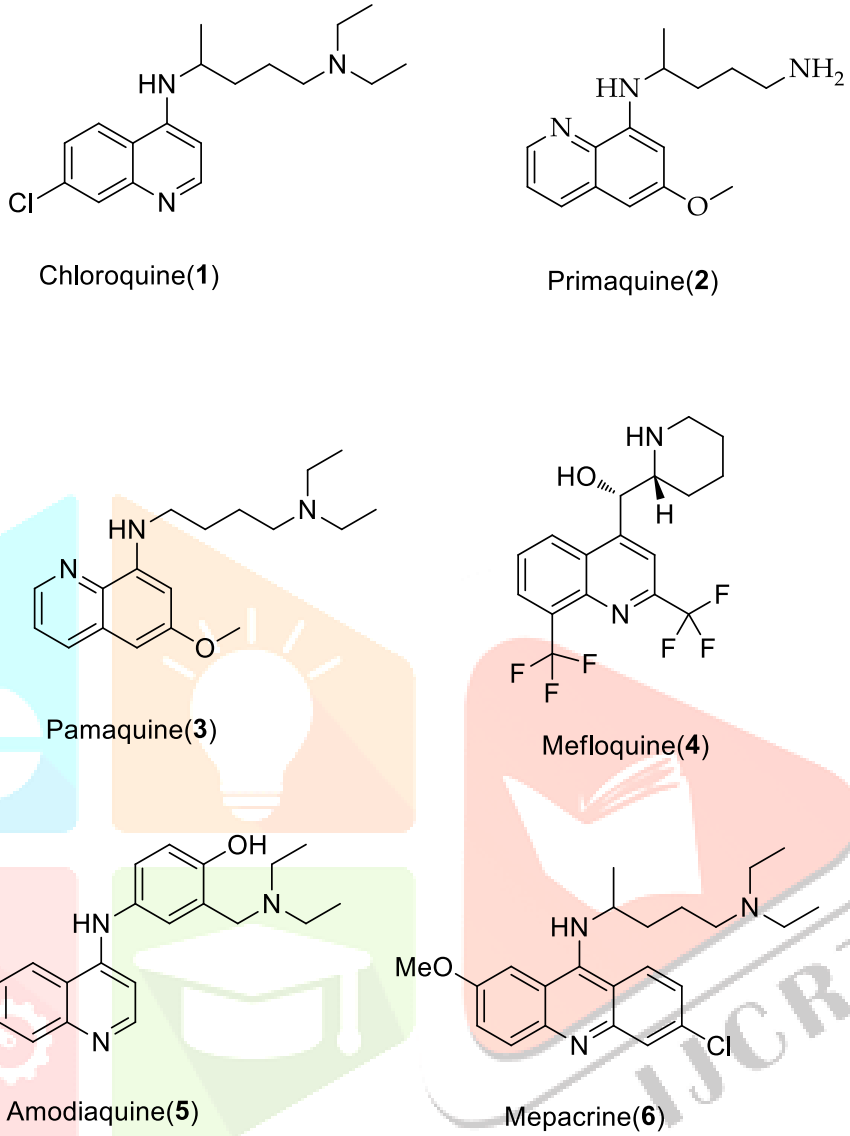


Figure 1 — Quinoline based anti-malarial agents

Anti-microbial screening

All the compounds **3(a-i)** prepared herein were screened for antibacterial and antifungal activities against different strains of bacteria and fungi shown in Fig 2.

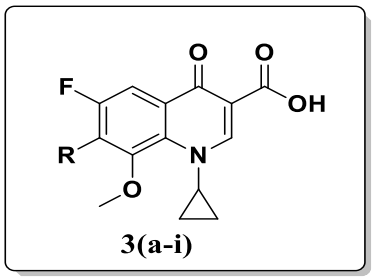


Figure 2 — Structure of designed Target

Materials and Method

Minimal inhibitory concentration (MIC)

The antimicrobial activity was assayed *in vitro* by two-fold broth dilution[12] against bacteria: *Eschericia coli, Bacillus subtilis* and *Staphylococcus aureus* and fungi: *Candida albicans, Aspergillus niger* and *Candida krusei*. Theminimal inhibitory concentrations (MIC in µg/mL)were defined as the lowest concentrations of compound that completely inhibited the growth ofeach strain. All compounds dissolved in dimethylsulfoxide (DMSO) were added to culture media. Mueller-Hinton Broth for bacteria and Sabouraud Liquid Medium for fungi were used to obtain the finalconcentrations ranging from125 µg/mL to 1.592 µg/mL. The amount of DMSO never exceeded 1%v/v. Inocula consisted of 5.0 x 10^4 bacteria/mL and 1.0 x 10^3 fungi/mL. The MICs were noted after incubation at 37°C for 24 hr (bacteria) and at 30°C for 48 hr (fungi). Media with 1% v/v DMSO were employed as growth controls. Chloroamphenicol and fluconazole were used as reference antibacterial and anti-fungal drugs, respectively.

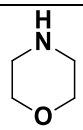
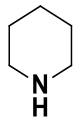
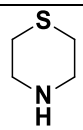
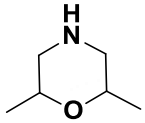
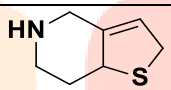
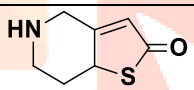
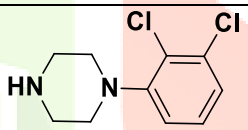
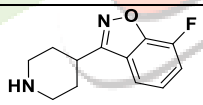
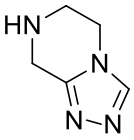
Antibacterial activity

The newly synthesized compounds **3a-i** and standard drug, chloroamphenicol were screened forantibacterial activity against bacterial strains namely *Eschericia coli* , *Bacillus subtilis* and *Staphylococcus aureus* at a concentration of 250 µg/mL by using filter paper disc method[13]. DMSO served as control. The discs of Whatman filter paper were prepared with standardsize (7.0 mm) and kept into 1.0 Oz screw-cappedwide-mouthed containers for sterilization. These bottles were kept in a hot-air oven at a temperature of 150°C. Then, the prepared solution of test compoundsand standard drug (DMSO) of desired concentration were poured into their respective bottles. Further, the discs were transferred to the inoculated plates with a pair of fine pointed tweezers. To prevent contamination, tweezers may be kept with their tips in 70% alcohol and flamed off before used. Before using the test organisms, which were grown onnutrient agar, they were sub-cultured in nutrient broth at a temperature of 37°C for 18-20 hr. Each disc was applied carefully to the surface of agar without lateral movement once the surface had been touched. Thereafter, the plates were incubated for 24 hr at a temperature of 37°C. Care was taken not to stockpile the plates. Clear zones of inhibition in millimetershave indicated the relative susceptibility of thebacteria to the compounds **3a-i** and standard drug, chloroamphenicol.

Antifungal activity

The newly synthesized compounds **3a-i** and standard drug, fluconazole, were evaluated for their antifungal activity by employing the standard agardisc diffusion method[14]. The following strains of fungi have been used in this study: *Candida albicans* *Aspergillus niger* and*Candida krusei*. All cultures were maintained on Sabouraud Dextrose Agar (SDA) and incubated at 30˚C. To prepare homogeneous sus- pensions of the above-mentioned fungi for the disc assays, they were grown in Sabouraud broth, centrifuged to collect the pellet, and buffered withsaline. The fungal pellet was homogenized in a sterile hand held homogenizer. This suspension was then plated onto SDA using a fungal spreader to obtain an even growth field. The discs of Whatman filter paper were prepared with standard size (6.0 mm) and kept into 1.0 Oz screw capped wide mouthed containers for sterilization. These sterilized discs were impregnated with 250 µg/mL concentrations of the various test compounds and standard drug, fluconazole. These discs were then placed in the centre of each quadrant of an SDA plate. Each plate had one control disc impregnated with DMSO. The plates were incubated at 30°C. After 48 hr, the plates were removed and the radius of the zone of inhibition (in mm) was measured. Care was taken not to stockpile the plates.

Table I – Substituent structures of 3(a-i)

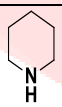
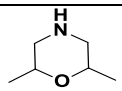
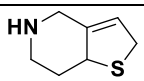
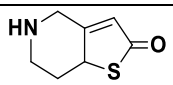
R	Structure
3a	
3b	
3c	
3d	
3e	
3f	
3g	
3h	
3i	

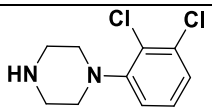
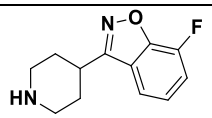
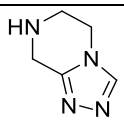
Results and discussions

Antimicrobial activity

All the newly synthesized compounds 3a-i of the present study were evaluated *in vitro* to determinetheir antibacterial and antifungal activities against numerous pathogens. The results of screening are given in **Table II**. The effects of various substitutions on antibacterial and antifungal activities were examined and after reviewing the results for the compounds **3a-i**, a few conclusions could be drawn, such as: It has been observed that compounds **3h** and **3i** bearing benzo-isoxazole, 1,2,4-triazole moieties reflected most potent antibacterial and antifungal activities. Compounds having dihydrothieno [3,2-c]pyridine, oxo-dihydrothieno[3,2-c]pyridine groups as in compounds **3e** and **3f** yielded remarkable inhibitory action againstbacteria and fungi. Compounds **3c**, **3g** bearing thiomorpholine and 2,3-dichloorophenyl-piperazinyl groupfurnished adequate antibacterial and antifungal activity. It is also interesting to point out that substitution of morpholine, piperidine, 2, 6-dimethylmorpholine as in compounds **3a**, **3b** and **3d** respectively, yielded less antibacterial activity. And these compounds have not exhibited antifungal activity.

Table II — Antimicrobial data of compounds **3a-i** against tested bacterial and fungal strains

Compd	R	Antibacterial activity[#]			Antifungal activity[#]		
		E.coli	*B.substilis*	*S.aureus*	*C.albicans*	*A.nigar*	*C.krusei*
3a		15	10	14	—	—	—
		(100)	(100)	(>125)			
3b		21	19	17	—	—	—
		(50)	(12.5)	(>125)			
3c		21	16	18	20	12	11
		(25)	(20)	(50)	(30)	(25)	(25)
3d		12	13	10	—	—	—
		(>125)	(50)	(>125)			
3e		22	25	25	30	24	18
		(20.5)	(12.5)	(15.2)	(18)	(12)	(17)
3f		20	22	19	25	22	18
		(21.5)	(15.5)	(16.5)	(20)	(10)	(12)
3g		20	16	19	12	9	10

		(24)	(25)	(30)	(25)	(28)	(34)
3h		27	23	22	26	23	21
		(12.0)	(6.25)	(11.5)	(8.25)	(10.5)	(7.5)
3i		30	26	28	28	23	21
		(6.25)	(3.125)	(6.25)	(3.125)	(12.5)	(1.592)
[a] Control		0	0	0	0	0	0
Chloroamphenicol		26	23	22			
		(12.5)	(6.25)	(12.5)			
Fluconazole					29	22	19
					(6.25)	(12.5)	(3.125)

Concentration was 250 µg/mL.

[a]DMSO served as control

'-' Denotes no inhibition zone was observed

Values in brackets are of MIC

Conclusion

In conclusion, we report the biological activity of novel 1-cyclopropyl-6-fluoro-8-methoxy-7-susbstituted-4-oxo-1,4-dihydroquinolin-3-carboxylic acids. Almost all the series of compounds **3a-i** showed moderate to excellent activity towards the bacteria and fungi under investigation. Some of them, particularly **3h** and **3i** can be exploited for formulation of bactericide and fungicide after detailed study.

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