



THERAPEUTIC SIGNIFICANCE OF QUINOLINE DERIVATIVES AS ANTIMICROBIAL AGENTS

Rajeev Kharb*, Hardeep Kaur

CT Institute of Pharmaceutical Sciences, Jalandhar-144020, Punjab, India

E-mail: rajeevkharb_2007@rediffmail.com

Article Received on: 15/01/13 Revised on: 01/02/13 Approved for publication: 10/03/13

DOI: 10.7897/2230-8407.04311

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ABSTRACT

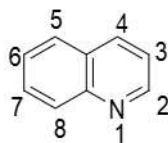
Microbial infections are one of the leading diseases which are responsible for millions of deaths every year because of lack of effective antimicrobial therapy and this situation becomes more complicated because of microbial resistance towards conventional antibiotics. Quinoline derivatives have proved their medicinal importance by having broad spectrum of pharmacological activities like antimicrobial, anticancer, antiviral and anti-inflammatory activities etc. This review article deals with the antimicrobial potential of novel quinoline derivatives as an effort to provide better treatment for microbial infections.

KEY WORDS: Quinoline, antibacterial, antifungal activities.

INTRODUCTION

Microorganisms like bacteria and fungi are becoming resistant to conventional antimicrobial therapy because of acquired resistance which is encoded by resistance genes in the DNA of the microbe. Resistance genes can arise through spontaneous mutations in the microbial DNA and these genes can also transfer from drug-resistant microbes to drug-sensitive ones¹. Therefore, antibiotic resistance problem demand continuous discovery and development of new antibacterial agents by modification of existing classes including fluoroquinolones, tetracyclines, aminoglycosides, β -lactams and identification of inhibitors against previously unexploited antibacterial targets by different mode of action^{2,3}.

Various heterocyclic compounds have shown antimicrobial potential and quinoline is one of the most promising heterocyclic nuclei having prominent antibacterial and antifungal activity. Quinoline (1) is characterized by a double ring structure composed of benzene and pyridine ring fused at two adjacent carbon atoms. The benzene ring contains six carbon atoms, while the pyridine ring contains five carbon atoms and a nitrogen atom having molecular formula of C_9H_7N ⁴.



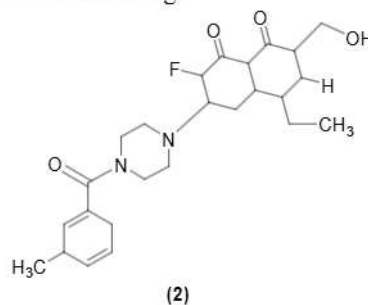
(1)

Antimicrobial Activities

Quinoline derivatives are known for their potent antibacterial and antifungal activity which is illustrated by the literature survey presented as below:

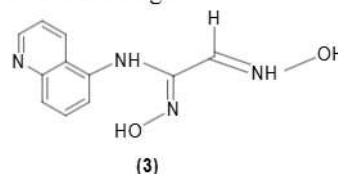
A series of six novel 1-ethyl-6-fluoro-7-[4-(1-alkyl-1,4-dihydropyridine-3-carbonyl)-piperazin-1-yl]-4-oxo-1,4-dihydro-quinoline-3-carboxylate derivatives (2) were evaluated for antibacterial activity against two Gram positive bacteria i.e. *Staphylococcus aureus* (NCDC 110), *Bacillus subtilis* (NCDC 71) and two Gram-negative bacteria i.e. *Escherichia coli* (NCDC 134), *Pseudomonas aeruginosa* (NCDC 105). Some compounds exhibited moderate to

significant minimum inhibitory concentration when compared with standard drug⁵.



(2)

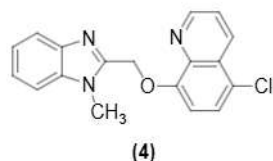
Some novel N-(8-hydroxyquinolin-5-yl)-aminoglyoximes (3) were synthesized and evaluated for *in-vitro* antimicrobial activity. Their antibacterial activities against five Gram-negative (*Escherichia coli*, *Salmonella enteridis*, *Enterococcus faecalis*, *Klebsiella pneumonia* and *Pseudomonas aeruginosa*) and four Gram-positive (*Streptococcus mutans*, *Bacillus cereus*, *Staphylococcus aureus* and Methicillin-resistant *S. aureus*) and antifungal activities against *Candida albicans* were measured by using disc diffusion and broth microdilution techniques. Some compounds showed significant antimicrobial activity when compared with standard drug⁶.



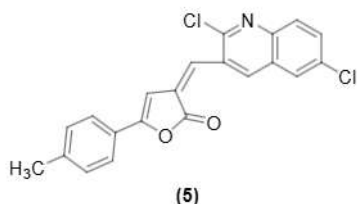
(3)

8-(1-alkyl/alkylsulphonyl/alkoxycarbonyl-benzimidazol-2-ylmethoxy)-5-chloro quinoline derivatives (4) were synthesized and evaluated for antimicrobial activity. Almost all the compounds exhibited promising antibacterial activity against *Salmonella typhimurium* and *Staphylococcus aureus*. Some of the compounds showed good antifungal activities against *Aspergillus niger* but antifungal activity against *Candida albicans* was disappointing. Most of the compounds showed very good antibacterial activities against *Staphylococcus aureus* and *Salmonella typhimurium* which

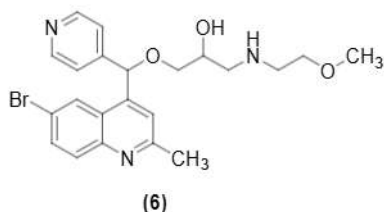
were almost competitive with standard drugs like chloramphenicol and ciprofloxacin⁷.



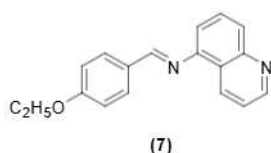
A novel series of 5-aryl-3-[(2-chloroquinolin-3-yl)methylene]furan-2(3*H*)-ones (5) was evaluated for antimicrobial activity. The antibacterial activities were performed against *Staphylococcus aureus* and *Escherichia coli*. Some compounds showed significant antimicrobial activity against both *S. aureus* and *E. coli* having minimum inhibitory concentration (MIC) value of 6.25 µg/mL as compared with standard drug⁸.



Quinoline derivatives (6) were evaluated for antimicrobial activity. SAR analysis indicated that presence of hydroxyl group and nature of substituents on piperazinyl-phenyl ring was critical in dictating antimicrobial activity of newly synthesized compounds. One compound was found to be the most active compound having MIC value of 6.25 mg/mL⁹.

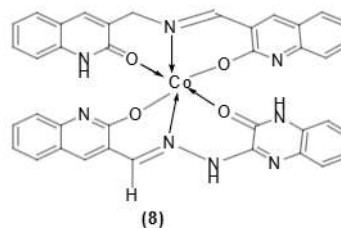


5-aminoquinoline derivatives (7) were evaluated for their *in-vitro* antimicrobial activity. Antibacterial activity of compounds were compared with bacteriomycin and gentamycin as standard antibacterial drugs whereas antifungal activity of compounds were evaluated and compared with nystatin as standard antifungal drug. Some compounds showed good antimicrobial activities against tested bacterial and fungal stains¹⁰.

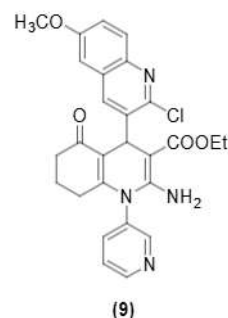


3-[(2*E*)-2-[(2-hydroxyquinolin-3-yl)methylidene]hydrazinyl]quinoxalin-2-ol derivatives (8) were tested for antibacterial and antifungal activities at concentrations of 100, 50 and 25 mg/L in DMF solvent using two bacteria (*Escherichia coli*, *Staphylococcus aureus*) and two fungi (*Aspergillus niger* and *Penicillium chrysogenum*) stains by zone of inhibition method. These bacterial and fungal stains were incubated for 24h and 48h at 37°C

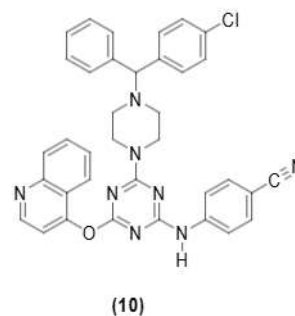
respectively. Standard antibacterial (gentamycin) and antifungal drugs (fluconazole) were used for comparison under similar conditions. Activity was determined by measuring the diameter of the zone of inhibition (mm)¹¹.



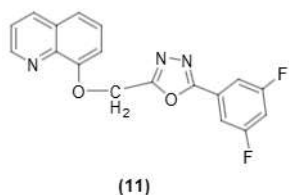
2-Chloro-3-formyl quinoline compounds (9) were screened for their antibacterial activity against Gram-positive bacteria (*Bacillus subtilis*, *Clostridium tetani*, *Streptococcus pneumoniae*), Gram-negative bacteria (*Escherichia coli*, *Salmonella typhi*, *Vibrio cholerae*) and antifungal activity against *Aspergillus fumigates* and *Candida albicans*. Some of the biquinoline compounds were found to be more potent or equipotent than the first line standard drugs. The compounds were evaluated for their *in-vitro* antitubercular activity against *Mycobacterium tuberculosis* H37Rv strain using Lowenstein-Jensen medium. One compound showed a compelling activity at concentration of 6.25 µg/mL with 96% inhibition and could be ideally suited for further modifications to obtain more efficacious compounds in the fight against tuberculosis¹².



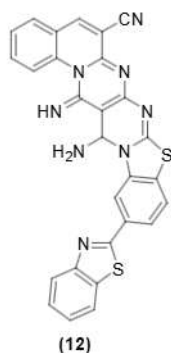
2-(4-cyanophenyl amino)-4-quinoline (quinazoline)-4-ylloxy-6-piperazinyl-(piperidinyl)-1,3,5-triazines (10) were evaluated for antimicrobial activity against eight bacteria (*S. aureus*, *B. cereus*, *E. coli*, *P. aeruginosa*, *K. pneumoniae*, *S. typhi*, *P. vulgaris*, *S. flexneria*), four fungi (*A. niger*, *A. fumigatus*, *A. clavatus*, *C. albicans*) and *Mycobacterium tuberculosis* H37Rv and the effects of various substituents on biological profiles of final analogues were investigated. One of the final analogues displayed good antimycobacterial activity having MIC value of 12.5 µg/mL when compared with standard drug¹³.



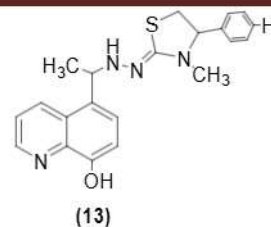
1,3,4-oxadiazole and quinoline derivatives (**11**) were investigated for their antibacterial activity against four different strains like *Staphylococcus aureus* (NCIM 2079), *Bacillus subtilis* (NCIM 2708), *Pseudomonas aeruginosa* (NCIM 2242) and *Escherichia coli* (NCIM 2685) and compared with standard drug ampicillin while antifungal activity was determined against stains like *Candida albicans* (NCIM 22491) and compared with standard drug griseofulvin. Some of the compounds showed remarkable antimicrobial activity¹⁴.



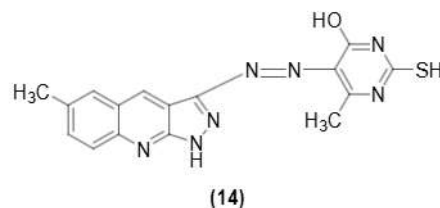
8-cyano-15,16-diimino benzothiazolo [2, 3-b] pyrimido [5, 6-e] pyrimido [3, 2-a] quinoline derivatives (**12**) were screened for their antifungal and antibacterial activity against species like *Aspergillus flavus*, *Aspergillus niger*, *E.coli* and *B. Subtilis*. The synthesized compounds exhibited zone of inhibitions in range of 10-31 mm in diameter, where as standard drug fluconazole exhibited zone of inhibition of 26 and 25 mm against *Aspergillus flavus* and *Aspergillus niger*. Streptomycin exhibited zone of inhibition of 32 and 30 mm in diameter against *E. Coli* and *B. Subtilis*. Amongst the synthesized compounds, few compounds showed higher zone of inhibition against *Aspergillus flavus* and *Aspergillus niger* whereas other compounds showed higher zone of inhibition against *B. subtilis*¹⁵.



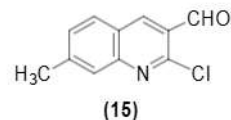
5-Acyl-8-hydroxyquinoline-2-(3-substituted-4'-aryl-2,3-dihydrothiazol-2'ylidene)hydrazone derivatives (**13**) were evaluated for antimicrobial activity. Twenty-eight new compounds were tested for their possible antimicrobial activities. Most of the tested compounds showed weak to moderate antibacterial activity against most of the bacterial strains used in comparison with gatifloxacin as a reference drug. Test compounds showed weak to moderate antifungal activity against tested fungi in comparison with ketoconazole as a reference drug¹⁶.



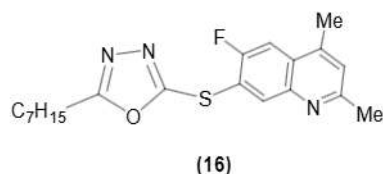
3-Amino-6-methyl-1H-pyrazolo[3,4-b]quinolines (**14**) were screened for antimicrobial activity. Antibacterial activities of synthesized compounds were examined *in-vitro* by known agar diffusion cup method. All the compounds were tested for activity against gram-positive bacteria like *Bacillus cereus* ATCC 10987, *Staphylococcus aureus* ATCC 6538 and *Bacillus subtilis* ATCC 6633 and gram-negative bacteria *Escherichia coli* ATCC 10536. The culture medium was nutrient agar. Norfloxacin was employed as the standard drug. Some compounds showed significant antimicrobial activity¹⁷.



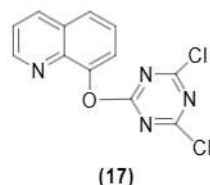
2-Chloro-7-methyl-3-formyl quinolines (**15**) were assayed *in-vitro* for their antimicrobial activity; the antimicrobial activities were determined by using agar cup plate method by measuring the zone of inhibition in mm. All newly synthesized compounds were screened *in-vitro* for their antibacterial activity against gram-positive species (*Bacillus subtilis*, *Bacillus megaterium*) and gram-negative species (*Escherichia coli*, *Pseudomonas aeruginosa*), while antifungal activity was tested against *Aspergillus niger* and *C. albicans* at concentration of 75 µg/ml. Streptomycin was used as a standard drug for antibacterial screening, while Imidil was used as a standard drug for antifungal screening. It was revealed that some of the synthesized derivatives were exhibiting competent biological activity against bacterial species (gram-negative and gram-positive) and fungal microorganisms¹⁸.



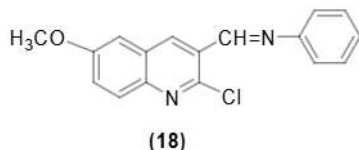
7-(5'-Alkyl-1',3',4'-thiadiazol-2-ylthio)-6-fluoro-2,4-dimethylquinolines (**16**) were evaluated for antimicrobial activity against *Klebsiella aerogens* and *Escherichia coli* and compared well with standard drug norfloxacin. All compounds showed promising antibacterial activity¹⁹.



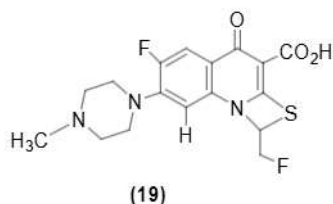
8-hydroxy quinolines (17) were assayed for antimicrobial activity. All the synthesized compounds were screened for their antibacterial activity against the *E. coli*, *P. auregenosa*, *S. aureus*, *S. Pyogenus* and antifungal activity against fungi *C. albicans*, *A. niger*, and *A. clavatus*. The compounds were tested at concentrations of 500, 250, 100 and 50 µg/mL by using nutrient agar tubes. The highest dilution showing at least 99% inhibition was taken as MBC (minimal bacterial concentration). Control experiment was carried out under similar condition by using gentamycine, ampicillin and chloramphenicol for antibacterial activity and nystatin, griseofulvin for antifungal activity as standard drugs respectively²⁰.



2-Chloro-3-formyl-6-methoxyquinolines (18) were tested for their antimicrobial activity against different stains of gram-positive bacteria, gram-negative bacteria and fungi. The antifungal activity of all the synthesized compounds were carried out against the fungi *Candida albicans*, *Aspergillus niger* and *Aspergillus paracitica* at concentration of 500 µg/ml by using griseofulvin as standard antifungal drug. SAR studies showed that compounds containing chloro and bromo group showed good activity against *S. aureus* and *B. subtilis* whereas nitro group containing compounds showed moderate activity against gram-negative stain of microorganisms²¹.

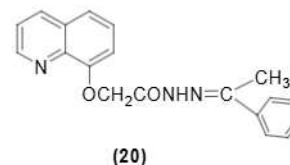


7-substituted-6-fluoro-1-fluoromethyl-4-oxo-4H-[1,3]thiazeto[3,2-a]quinoline-3-carboxylic acid derivatives (19) were evaluated for antibacterial activity against *E. coli* and Methicillin-resistant *Staphylococcus aureus* and their minimum inhibitory concentrations (MICs) were determined by the agar dilution method. One of the synthesized compounds showed significant antibacterial activity when compared with standard drug²².

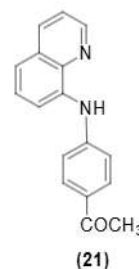


N'-(1-phenylethylidene)-2-(quinolin-8-yloxy) acetohydrazides derivatives (20) were screened for their antibacterial and antifungal activities by cup-plate method. The antimicrobial activity was carried out against *P. aeruginosa*, *E. coli*, *B. subtilis*, *S. aureus* and for antifungal activity against *A. niger*, *C. albicans* by measuring the zone of inhibition in mm. The activities were performed at a concentration of 50 µg/ml. Streptomycin and griseofulvin

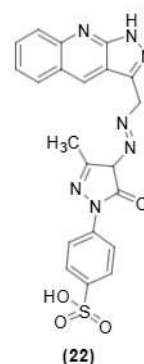
were used as standard drugs for comparison of antibacterial and antifungal activities respectively. Some of the compounds showed good antibacterial activity against all the tested microorganisms²³.



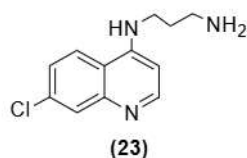
1-[4-(quinolin-8-yl-amino)phenyl]ethanone derivatives (21) were studied for their antibacterial activity against four different bacterial stains like *E. coli*, *B. subtilis*, *Pseudomonas aeruginosa* and *S. aureus* by measuring the zone of inhibition in mm on agar plates. All compounds possessed moderate to good antibacterial activity against all stains in comparison with standard drug²⁴.



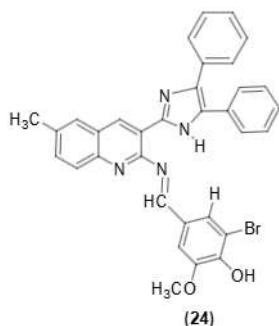
3-methyl-1-phenyl-4-[(E)-2-{1H-pyrazolo[3,4-b]quinolin-3-yl}diazen-1-yl]-4,5-dihydro-1H-pyrazol-5-one derivatives (22) were evaluated *in-vitro* for antibacterial activity against gram-positive bacteria like *Staphylococcus aureus*, *Bacillus subtilis* and gram-negative bacteria like *Escherichia coli* and *Pseudomonas aeruginosa* and antifungal activity against *Candida albicans* at concentrations of 100 µg/ml and 200 µg/ml. Synthesized compounds showed moderate to good antibacterial and antifungal activity with respect to standard drugs ciprofloxacin and fluconazole²⁵.



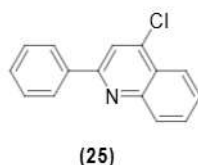
7-chloro-4-aminoquinoline derivatives (23) were evaluated for antimicrobial activity. The synthesized compounds were studied for antibacterial activity against six different stains of gram-positive (*Bacillus subtilis*, *Bacillus cereus*, *Staphylococcus aureus*) and gram-negative bacteria (*Escherichia coli*, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*) at two different tested doses like 25 mg/ml and 50 mg/ml by disc diffusion method. All the compounds were found to be active against the tested organisms, but were less active as compared to standard drug ofloxacin²⁶.



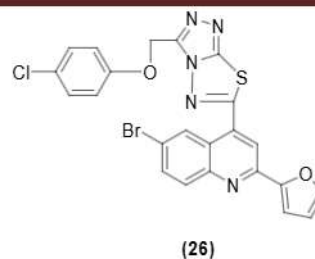
3-(4,5-diphenyl-1*H*-imidazol-2-yl)-6-methyl-quinoline derivatives (**24**) were assayed for antibacterial activity against *Escherichia coli* (MTCC2939) *Salmonella typhi* (MTCC 98), *Staphylococcus aureus* (MTCC 96) and *Bacillus subtilis* (MTCC 441). The antifungal activity was evaluated against *Aspergillus niger* (MTCC 281), *Candida albicans* (MTCC 183) and *Penicillium chrysogenum* (MTCC 160). Some compounds showed considerable antimicrobial activity when compared with their respective standard drugs²⁷.



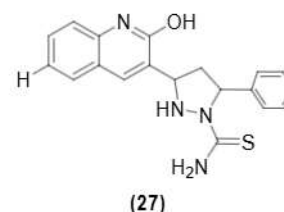
A new series of 4-chloro-2-phenyl quinoline derivatives (**25**) were screened for their antibacterial activity against different bacterial stains like *B. subtilis*, *S. aureus*, *P. aeruginosa*, *E. coli* and *S. typhi*. The antibacterial activity study revealed that some derivatives possessed significant inhibitory activity against gram-negative and gram-positive bacteria including multidrug resistant stains of *S. aureus* (MSRA) while other derivatives showed moderate antibacterial activity. The MIC value of the most active compounds was found to be 50 µg/ml when compared with ciprofloxacin as a standard drug²⁸.



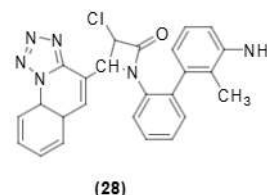
2-(2-furyl)-4-(3-aryloxymethyl-1,2,4-triazolo[3,4-b]-1,3,4-thiadiazol-6-yl)quinolines (**26**) were screened for their antibacterial activity against *E. coli*, *S. aureus*, *P. aeruginosa* and *B. subtilis* by using furacin as a standard drug. The screening data indicated that all the compounds showed moderate to excellent antibacterial activity compared with the standard drug furacin²⁹.



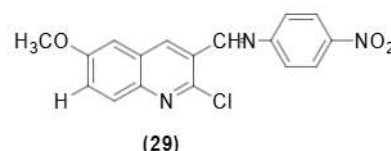
3-(2-hydroxyquinolin-3-yl)-5-phenyl-4,5-dihydro-1*H*-pyrazole-1-carbothioamide (**27**) derivatives were tested for their antibacterial activity against *Pseudomonas aeruginosa* and *S. aureus* and antifungal activity against *A. niger* and *Candida albicans*. All compounds showed significant antibacterial activity³⁰.



A series of potentially active quinoline based azetidinones and thiazolidinones analogues (**28**) were synthesized and examined for antimicrobial activity against two gram-negative bacteria (*E. coli*, *P. aeruginosa*), two gram-positive bacteria (*S. aureus*, *B. subtilis*) and two fungal species (*C. albicans*, *A. niger*) to develop novel class of antimicrobial agents with varied mode of action. Some analogues emerged as lead molecules with excellent MIC values against above mentioned microorganisms when compared with standard drugs like ciprofloxacin and nystatin³¹.

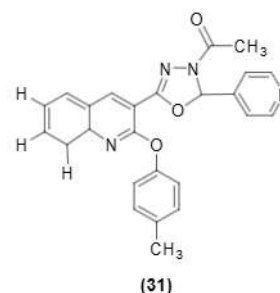
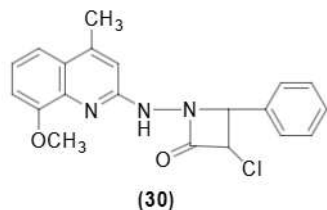


A series of novel quinoline schiff bases (**29**) were prepared and screened for their antibacterial activity against *S. aureus*, *B. subtilis*, *S. typhi* and *E. coli* by using disc diffusion technique. Some compounds showed good antibacterial activity when compared with standard drug ampicillin³².



8-methoxy-4-methyl-2-amino-(3'-chloro-2'-oxo-4'-substituted aryl-1'-azetidinyl)quinolines (**30**) were screened *in-vitro* for antibacterial activity against gram-positive bacteria: *Staphylococcus aureus* ATCC 25923, *Bacillus subtilis* ATCC 6051 and *Staphylococcus epidermis* ATCC 14940 and gram-negative bacteria: *Escherichia coli* ATCC 25922, *Klebsiella pneumoniae* ATCC 10031 and *Pseudomonas aeruginosa* ATCC 27853 at concentration of 250 µg/mL. Some

compounds were found to exhibit potent antibacterial activity as compared to the standard drug ampicillin³³.



A new series of 1-(5-(2-tolyloxyquinoline-3-yl)-2-(pyridine-4-yl)-1,3,4-oxadiazol-3(2H)-yl)ethanones (31) were synthesized and screened for their antibacterial activities against various bacterial strains including two gram-positive bacteria, *Bacillus subtilis* (ATCC 6633), *Staphylococcus aureus* (ATCC 25923) and two gram-negative bacteria, *Salmonella typhimurium* (ATCC 23564), *Pseudomonas aeruginosa* (ATCC 27853). Several of these compounds showed potent antibacterial activity when compared with standard drug ampicillin³⁴.

Quinoline nucleus is known to have antimicrobial activity as mentioned in this manuscript and its derivatives are utilized as medicinal agents which are available in the market for treatment of microbial infections. Some of the quinoline nucleus based clinically used drug have been compiled in the table 1.

Table 1: Quinoline Nucleus Based Clinically Used Drugs³⁵⁻³⁶

S. No.	Drug	Chemical Structure	Pharmacological Activity
1.	Ciprofloxacin		Antibacterial
2.	Sparfloxacin		Antibacterial
3.	Ofloxacin		Antibacterial
4.	Norfloxacin		Antibacterial
5.	Gatifloxacin		Antibacterial

CONCLUSION

Quinoline nucleus has occupied a pivotal position in the modern medicinal chemistry as per literature. This manuscript has compiled updated information about the antimicrobial potential of various quinoline derivatives. This valuable information may be utilized further by the researchers for drug design and development of better antimicrobial agents for future to save the valuable life of patients which is the ultimate aim of writing this review article.

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Cite this article as:

Rajeev Kharb, Hardeep Kaur. Therapeutic significance of Quinoline derivatives as antimicrobial agents. *Int. Res. J. Pharm.* 2013; 4(3):63-69

Source of support: Nil, Conflict of interest: None Declared