Annals of Pharmacology and Pharmaceutics

Short Communication
Published: 20 Sep, 2017

Quinolones: Understanding the Drug Designing to Combat Drug Resistance

Rina Das, Dinesh Kumar Mehta and Vaibhav Sharma*

Department of Pharmacy, MM University, India

Short Communication

Incidences of drug resistances have increased in the recent past and with the ongoing discoveries of new infectious diseases, medicine practice in management of infections and treatment of ailments have become a challenging situation in the medical care settings. Therefore, there is an urgent demand for a new class of antimicrobial agent with a different mode of action and it led medicinal chemists to explore a wide variety of chemical structures. In pursuit of this goal, research efforts have been directed towards the discovery of new chemical entities that are effective antimicrobial agents. The discovery and development of antimicrobial agents that has met with enormous success over the past few years provided many classes of natural products and semi-synthetic or synthetic compounds. Nitrogen containing heterocyclic compounds is well studied for their broad spectrum of activities. Among them quinolones and their derivatives constitute a crucial class of organic compounds which have been reported to posses versatile activities. The quinolones are a family of synthetic broad-spectrum antibiotic drugs [1-3]. Quinolones and their derivatives occur in numerous natural products, many of which possess interesting physiological and biological properties [1].

Isolated as a by-product of the synthesis of chloroquinine, nalidixic acid was the first therapeutically potential quinolone moiety and used for the treatment of urinary tract infections for many years. Ciprofloxacin, moxifloxacin, and gatifloxacin are some fluorinated-quinolones (FQ) which have broad spectrum antimicrobial activity for the cure of diverse pathogenic diseases. Side effects are relatively few with the use of these fluoroquinolones (FQs). Microbial resistance may be developed. In some cases rare and potentially fatal side effects were also reported and few drugs such as clinafloxacin, grepafloxacin, trovafloxacin, and temafloxacin were withdrawn from the market due to severe toxic side effects [1-3].

The FQs are potent bactericidal agents against *E. coli* and various species of Salmonella, Shigella, Enterobacter, Campylobacter, and Neisseria, *P. aeruginosa*, staphylococci, but not against methicillin-resistant strains. Activity against streptococci is limited to a subset of the quinolones, including le ofloxacin, moxifloxacin and gatifloxacin [4]. Several intracellular bacteria are inhibited by FQs which include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium [5,6]. Several of FQs have activity against anaerobic bacteria, like garenoxacin and gemifloxacin [7].

The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV [8]. For many gram-positive bacteria (such as *S. aureus*), topoisomerase IV is the primary activity inhibited by the FQs. In contrast, for many gram-negative bacteria (such as *E. coli*), DNA gyrase is the primary quinolone target [9]. The drugs inhibit gyrase-mediated DNA super coiling at concentrations that correlate well with those required to inhibit bacterial growth. Mutations of the gene that encodes the A subunit polypeptide can confer resistance to these drugs [8]. This enzyme is the target for some anti-neoplastic agents. Quinolones inhibit eukaryotic type II topoisomerase only at much higher concentrations (100 mg/ml to 1000 mg/ml) [10].

Resistance to quinolones may develop during therapy via mutations in the bacterial chromosomal genes encoding DNA gyrase or topoisomerase IV or by active transport of the drug out of the bacteria [11]. Resistance has increased after the introduction of FQs, especially in *Pseudomonas* and *staphylococci* [12]. Increasing FQ resistance also is being observed in *C. jejuni*, *Salmonell*a, *N. gonorrhoeae*, and *S.pneumonia* [13].

FQs and various quinolone derivatives are used in treatment of various urinary tract infection; prostatitis, sexually transmitted diseases; gastrointestinal and abdominal infections; respiratory tract infections; bone, joint, and soft tissue infections, etc [14-17].

OPEN ACCESS

Correspondence:
Dinesh Kumar Mehta, Department of Pharmacy, MM University, India, E-mail: dkmehta17@rediffmail.com

Received Date: *19 Jul 2017*
Accepted Date: *11 Sep 2017*
Published Date: *20 Sep 2017*

Citation:
Das R, Mehta DK, Sharma V. Quinolones: Understanding the Drug Designing to Combat Drug Resistance. Ann Pharmacol Pharm. 2017; 2(17): 1092.

Table 1: Description and possible chemical modifications at each position of the pharmacore
Our main focus is on the establishment of the structures of a wide variety of novel quinolones on the basis of their spectral characteristics and SAR studies, and to study the effect of such modifications on their biological potential. In future, the design and synthesis of the hybrids of quinolones may engender a lot of opportunities in the field of medicinal chemistry.

Position	Description	SAR studies
1	This position is part of the enzyme-DNA binding complex, and has a hydrophobic interaction with the major grove of DNA.	Most potent modification here are a cyclopropyl substituent, followed by addition of a 2,4-difluorophenyl.
2	This position is very close to the site for DNA gyrase (or topoisomerase IV) binding so it is believed that any added bulk inhibits access and results in a lower level of microbiological activity.	A sulfur, incorporated into a small ring, has been able to replace hydrogen at the R-2 position.
3 and 4	These two positions on the quinolone nucleus are considered critical for binding to DNA, and no useful substitutions have yet been reported.	3-carboxylate and 4-carbonyl groups are considered essential for antimicrobial activity.
5	Substituents at this position of the basic quinolone nucleus appear to have the capacity to alter overall stearic configuration (planar structure) of the molecule, which is how changes here are thought to affect activity.	Modestly sized additions, such as an amino, hydroxyl, or methyl group can noticeably increase in vitro activity against gram-positive bacteria while halide and methoxy substituents tend to reduce activity.
6	Substituents at this position **c**ontrols gyrase and antibacterial potency	The addition of a fluorine molecule here markedly improved antimicrobial activity compared to the original quinolone agents, and gave rise to widely used and clinically successful fluoroquinolone compounds.
7	This position is considered to be one that directly interacts with DNA gyrase, or topoisomerase IV.	The best possible substituents at this position have been found to be groups that contain, at a minimum, a 5- or 6-membered nitrogen heterocycle.
8	This position affects overall molecular stearic configuration, similar to position 5. Hence, changes made here affect target affinity, probably by altering drug access to the enzyme or DNA binding sites.	Most useful groups employed on this position are CF, CCl and COMe.

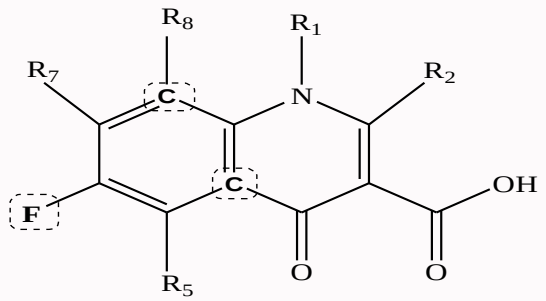

Figure 1: Quinolone pharmacore.

The focus of our current review is the most recent data on how various structural modifications affect the activity of quinolones, interpreting structural effects in the light of work on budding microbial resistance, and highlighting ongoing drug development that points to a continued useful future for this important class of antimicrobial agents.

Structure of the quinolone molecule, using the accepted numbering scheme for positions on the molecule is shown in Figure 1. The huge majority of useful antibacterial agents in this class rely upon variation of peripheral substituents (mainly, C-5, C-6 and C-7 positions of quinoline ring), leaving the 3-carboxy-6-fluoro-4-quinolone core essentially intact. It is known that this type of quinolones rapidly inhibits DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of type II topoisomerase, DNA gyrase and topoisomerase IV, resulting in rapid bacterial death. An R indicates possible sites for structural modification. Molecules at positions marked in dotted line can also be changed [18-19].

A detailed examination of the quinolone pharmacore may help to explain some of the features found on the quinolones available presently, as well as those under development. The possible chemical modifications at each position of the pharmacore is mentioned in Table 1 [18-25].

Our main focus is on the establishment of the structures of a wide variety of novel quinolones on the basis of their spectral characteristics and SAR studies, and to study the effect of such modifications on their biological potential. In future, the design and synthesis of the hybrids of quinolones may engender a lot of opportunities in the field of medicinal chemistry.

References

1. Carlos M. Melendez Gomez, Vladimir V. Kouznetsov. Recent Developments on Antimicrobial Quinoline Chemistry. Formatex. 2013;666-677.
2. Andersson MI, MacGowan AP. Development of the quinolones. J Antimicrob Chemother. 2003;51(1):1-11.
3. Ivanov DV, Budanov SV. Ciprofloxacin and antibacterial therapy of respiratory tract infections]. Antibiot Khimioter. 2006;51(5):29-37.
4. Eliopoulos GM, Eliopoulos CT. Activity in vitro of the quinolones. In Quinolone Antimicrobial Agents, 2nd (edn). Hooper DC, Wolfson JS (eds), American Society for Microbiology. Washington. 1993;161-193.
5. Alangaden GJ, Lerner SA. The clinical use of fluoroquinolones for the treatment of mycobacterial diseases. Clin Infect Dis. 1997;25(5):1213-21.
6. Hooper DC. Quinolones. In Mandell Douglas and Bennett's, Principles and Practice of Infectious Diseases. 5 th (edn). Mandell GL, Bennett JE, Dolin R (eds), Churchill Livingstone. New York. 2000;404-423.
7. [No authors listed]. Gatifloxacin and moxifloxacin: two new fluoroquinolones. Med Lett Drugs Ther. 2000;42(1072):15-7.
8. Drlica K, Zhao X. DNA gyrase, topoisomerase IV, and the 4-quinolones. Microbiol Mol Biol Rev. 1997;61(3):377-92.
9. Alovero FL, Pan XS, Morris JE, Manzo RH, Fisher LM. Engineering the specificity of antibacterial fluoroquinolones: benzenesulfonamide modifications at C-7 of ciprofloxacin change its primary target in Streptococcus pneumoniae from topoisomerase IV to gyrase. Antimicrob Agents Chemother. 2000;44(2): 320-325.
10. Mitscher LA, Ma Z. Structure-activity relationships of quinolones. In Fluoroquinolone Antibiotics. Ronald AR, Low DE (eds), Birkhauser Basel. 2003;11-48.
11. Oethinger M, Kern WV, Jellen-Ritter AS, McMurry LM, Levy SB. Ineffectiveness of topoisomerase mutations in mediating clinically significant fluoroquinolone resistance in Escherichia coli in the absence of the AcrAB efflux pump. Antimicrob Agents Chemother. 2000;44(1):10-13.
12. Peterson LR, Postelnick M, Pozdol TL, Reisberg B, Noskin GA.

Management of fluoroquinolone resistance in Pseudomonas aeruginosa: Outcome of monitored use in a referral hospital. Int J Antimicrob Agents. 1998;10(3):207-214.

13. Thornsberry C, Ogilvie P, Kahn J, Mauriz Y. Surveillance of antimicrobial resistance in Streptococcus pneumoniae Haemophilus influenzae and Moraxella catarrhalis in the United States in 1996-1997 respiratory season The Laboratory Investigator. Diagn Microbiol Infect Dis. 1997;29(4):249-57.
14. Hooper DC, Wolfson JS. Fluoroquinolone antimicrobial agents. N Engl J Med. 1991;324(6):384-94.
15. Asif M. Study of Antimicrobial Quinolones and Structure Activity Relationship of AntiTubercular Compounds. JCHEM. 2015;4(2): 28-70.
16. Bennish ML, Salam MA, Khan WA, Khan AM. Treatment of shigellosis: III. Comparison of one- or two-dose ciprofloxacin with standard 5-day therapy. A randomized, blinded trial. Ann Intern Med. 1992;117(9):727-34.
17. Khan WA, Seas C, Dhar U, Salam MA, Bennish ML. Treatment of shigellosis: V Comparison of azithromycin and ciprofloxacin A double-blind randomized controlled trial. Ann Intern Med 1997; 126:697-703.
18. Tillotson GS1. Quinolones: structure-activity relationships and future predictions. J Med Microbiol. 1996;44(5):320-4.
19. Llorente B, Leclerc F, Cedergren R. Using SAR and QSAR analysis to model the activity and structure of the quinolone-DNA complex. Bioorg Med Chem. 1996;4(1):61-71.
20. Domagala JM. Structure-activity and structure side-effect relationships for the quinolone antibacterials. J Antimicrob Chemother. 1994;33(4):685-706.
21. Morrissey I, Hoshino K, Sato K. Mechanism of differential activities of ofloxacin enantiomers. Antimicrob Agents Chemother. 1996;40(8):1775-84.
22. Ma Z, Chu DT, Cooper CS. Synthesis and antimicrobial activity of 4-H-4-oxoquinolizine derivatives: consequences of structural modification at the C-8 position. J Med Chem. 1999;42(20):4202-13.
23. Yoshida T, Yamamoto Y, Orita H. Studies on quinolone antibacterials. IV. Structure-activity relationships of antibacterial activity and side effects for 5- or 8-substituted and 5,8-disubstituted-7(3-amino-1-pyrrolidinyl)-1-cyclopropyl-1,4-dihydro-4-oxoquinoline-3- carboxylic acids. Chem Pharm Bull (Tokyo). 1996;44(5):1074-85.
24. Kahn AA, Araujo FG, Brightly KE, Gootz TD, Remington JS. AntiToxoplasma gondii activities and structure-activity relationships of novel fluoroquinolones related to trovafloxacin. Antimicrob Agents Chemother. 1999;43(7):1783-7.
25. Ledoussal B, Almstead JK, Flaim CP. Novel fluoroquinolone, structureactivity, and design of new potent and safe agents. In: Program and abstracts of the 39th Interscience Conference on Antimicrobial Agents and Chemotherapy (San Francisco). Washington, DC: American Society for MicrobiologyEmerg Infect Dis. 2003;9(1): 1-9.