International Journal of Pharmacy and Analytical Research (IJPAR)

IJPAR |Vol.13 | Issue 4 | Oct - Dec -2024

www.ijpar.com

DOI : https://doi.org/10.61096/ijpar.v13.iss4.2024.618-622

ISSN: 2320-2831

Review

Fluoroquinolone as anticancer agents: An overview

G. Tamilarasi*[1], Dr. G. Umarani[2], P. Keerthana[3], I. Selvamatha[3], R. Thirupathi[3]

Assistant professor[1], Associate professor[2], II year M.Pharm[3]
Department of Pharmaceutical chemistry, College of pharmacy, Madurai medical college, Madurai, Tamilnadu, India.

*Author for Correspondence: Mrs. G. Tamilarasi, M.Pharm.
Email: thamilarasi.mmc@gmail.com

Published on: 04 Nov 2024

Published by:
DrSriram Publications

Abstract

Quinolones and fluoroquinolones are the most kind of antibacterial agents. Fluoroquinolones one of the type of antibacterial agents extensively used from the past few years and will be continued to be used in the next decade. Fluoroquinolones exerting the antibacterial activity through binding to type 2 bacterial topoisomerase enzymes, DNA gyrase and topoisomerase 4 are mainstays in chemotherapy. Antibacterial agents are chemical agents which is used to treat the infection by bacterial, viral, fungal and microorganism infection. This review aims to highlight the classification, structural activity relationship and recent update for fluoroquinolone as anticancer and antibacterial activity.

Keywords: Quinolone, fluoroquinolone, DNA gyrase, topoisomerase 4, antibiotic, anticancer.

INTRODUCTION

Bacterial infections can cause a wide range of diseases such as listeriosis, anthracnose, urinary tract infections and gastroenteritis. Bacterial infections leads one third of global mortality (1,2). Thus , bacterial infections represent a major threat to human health. Antibiotic therapy has been used as an effective way to treat bacterial infections, but more and more antibiotic-resistant bacteria have emerged asfatal threats to human beings due to the misuse and abuse of antibiotics (3,4).

Once antibiotic –resistant pathogens emerge, these organisms can spread rapidly around the globe and acquire resistance to additional drug classes(5,6). Antibiotic resistant bacteria are associated with an increase in morbidity and mortality, and more than 700000 patients die from resistant infections annually because of the lack of treatment (7,8). Therefore, the discovery of novel antibacterial agents plays a key role in solving the current crisis issue.

Antibacterial agents are chemical agents, which is used to treat the infection by bacterial, viral, fungal, micro-organism infection. A variety of antimicrobial agents were used in past decades to treat different types of

infection, beta lactam antibiotic penicillins and sulphonamide were commonly used in clinical usage (9). Antimicrobial is an agent that kills microorganisms or stop their growth (bacteriostatic agent)(10).

Quinolone and fluoroquinolones were established as new class of antibiotic with broad spectrum activity.It is potent bacteriostatic agent which are active against to important pathogen that cause variety of infections urinary tract infections, respiratory tract infections, sexually transmitted disease, gastro intestinal infection, and skin infections(11).

Quinolones are a class of broad-spectrum antibiotics with excellent oral bioavailability and can be used to treat a wide variety of bacterial infections. Their clinical utility is restricted, particularly in the outpatient setting, due to their potential for severe side effects. Due to these safety concerns, quinolones are not recommended as first-line agents by the FDA if there are other available antibiotic options with less potential for severe adverse events. There are currently four generations of quinolones. While initial quinolones were effective only against Gram-negative bacteria, succeeding generations gained activity against *Pseudomonas sp.*, Gram-positive, and atypical bacterial strains. Many different quinolones have undergone development, and among them, the ones currently approved by the FDA for systemic use include moxifloxacin, ciprofloxacin, gemifloxacin, levofloxacin, delafloxacin and ofloxacin. A few key differences exist in the spectrum of activity between the quinolones(12).

The fluoroquinolones are a family of broad spectrum, systemic antibacterial agents that have been used widely as therapy of respiratory and urinary tract infections. Fluoroquinolones are active against a wide range of aerobic gram-positive and gram-negative organisms. Gram-positive coverage includes penicillinase- and non-penicillinase producing Staphylococci, Streptococcus pneumoniae and viridans, Enterococcus faecalis, Listeria monocytogenes, and Nocardia species. Gram negative coverage includes Neisseria meningitides and gonorrhoeae, Haemophilus influenzae, and most clinically important Enterobacteriaceae species, Pseudomonas aeruginosa and Vibrio species.

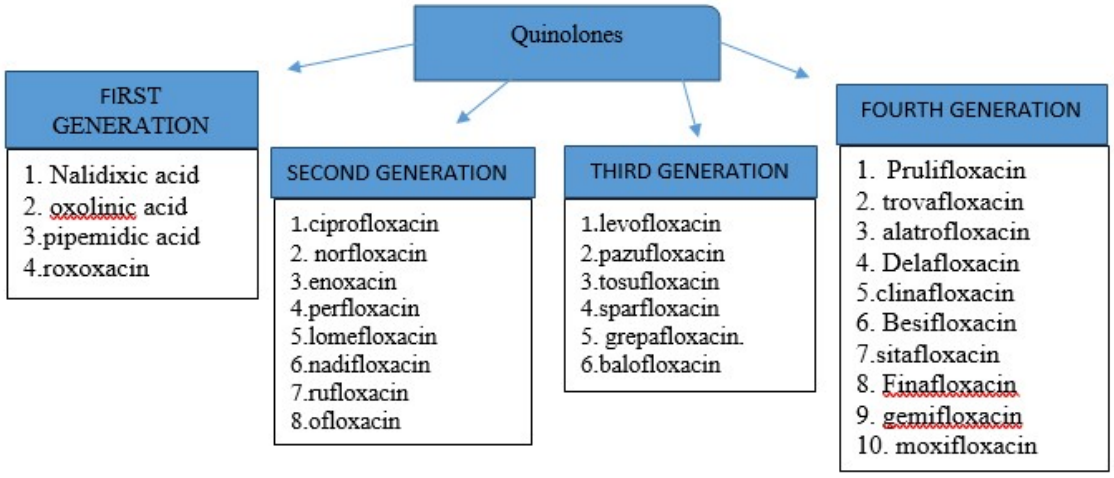
The fluoroquinolones are believed to act by inhibition of type II DNA topoisomerases (gyrases) that are required for synthesis of bacterial mRNAs (transcription) and DNA replication. The fluoroquinolones currently available in the United States include ciprofloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. These agents are well absorbed orally and well tolerated with a low rate of adverse effects. Several quinolones and fluoroquinolones were introduced but were subsequently withdrawn after spontaneous reports of severe adverse events including hepatotoxicity: temafloxacin (1992), gatifloxacin (2006), and trovafloxacin (1999)(13).

Mechanism of action

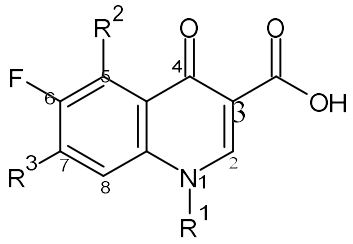
Quinolones are bactericidal antibiotics that directly kill bacterial cells. They act on bacterial type II topoisomerases, DNA gyrase, and topoisomerase IV, inhibiting their function and converting them into toxic enzymes that produce permanent double-stranded breaks in the bacterial chromosome. DNA topoisomerases are essential for normal physiologic functions of the bacteria, such as DNA replication, transcription, recombination, and condensed DNA remodeling. They function by performing transient single- and double-stranded breaks, which help to facilitate their fundamental roles in removing torsional stress and knots in the bacterial chromosome that form during regular nucleic acid processes. Quinolone antibiotics stabilize the enzyme-DNA cleavage complexes by inhibiting DNA ligation. When the gyrase and topoisomerase IV create breaks in the bacterial chromosome to perform their physiological functions, it leads to fragmentation of the bacterial chromosome. When the DNA strand breaks overwhelm the cell's ability to repair the DNA, it leads to cell death(14,15).

Fluoroquinolones inhibit the replication and transcription of bacterial DNA, which eventually culminate in cell death.[16] They either inhibit the activity of DNA gyrase, an essential adenosine triphosphate-hydrolyzing topoisomerase II enzyme and/or prevent the detachment of gyrase from DNA.[17] The topoisomerase inhibitors exert their bactericidal activity by interacting with the DNA.[18,19] During the processes of replication and transcription, enzymes called helicases unwind/uncoil the DNA double helix leading to excess supercoiling of the remaining DNA double helix. A tension is created in this remaining double helix, which must be relived in order to continue the process.[19] The topoisomerase II enzyme allows the relaxation of supercoiled DNA by breaking both strands of DNA chain, crossing them over, and then resealing them . Bacterial gyrase is different enough from mammalian topoisomerase so that quinolones and fluoroquinolones are 1000-fold more selective toward bacteria over the corresponding enzyme in humans.[19] Fluoroquinolones have also been found to inhibit the in vitro activities of topoisomerase IV ligase domain, having structure similar to DNA gyrase[19]. This enzyme has an important role in the partitioning of chromosomal DNA during bacterial cell division and may be the primary target of fluoroquinolone activity in Gram-positive bacteria. This mechanism is consistent with apoptosis rather than necrosis.[19–21]

Claasification



Structural activity relationship



Position 1

Small alkyl or aryl group broadens spectrum of activity and it is the part of enzyme DNA binding complex and has hydrophobic interaction with the major grove of DNA (22). A cyclopropyl moiety is now considered the most potent modification(23).

Position 2

It is very close to the site for DNA gyrase (or topoisomerase IV) binding. So it is believed that any bulky substituent can inhibit access to DNA gyrase and results in a lower level of microbiological activity(24,25).

Position 3&4

positions 3 and 4 are considered critical for binding to cleaved or perturbed DNA. Therefore the 3-carboxylate and 4-carbonyl groups are considered essential for antimicrobial activity(26).

Position 5

substituents at position 5 of the basic quinolone nucleus appear to have the capacity to alter overall steric configuration (planar structure) of the molecule. Changes at this position are thought to affect activity; an amino, hydroxyl, or methyl group can markedly increase in vitro activity against Gram-positive bacteria, as well as enhance potency against Toxoplasma gondii. It was found that the methyl group enhances action against Gram-positive but not Gram-negative bacteria; halide and methoxy substituent tends to diminish activity(27).

Position 6

Addition of fluorine into position 6 markedly improves antimicrobial activity compared to the original quinolone agents and gives rise to the nowadays widely used and clinically successful fluoroquinolone compounds(28).

Position 7

Substituents at positions 1, 7, and 8 continue to be key determinants of overall biological activity in the

compounds under development[29]. A tetrahydroisoquinoline substituent at C-7 seems to be a most useful addition for the 6-amino agents, increasing in vitro activity anywhere from 4-fold to over 100-fold, compared with ciprofloxacin.[27,30] The substituent at position 7 is considered to be one that directly interacts with DNA gyrase[30] or topoisomerase IV. The optimal substituents at this position have been found to be groups that contain, at a minimum, a five- or six-membered nitrogen heterocycle.[24] The most common of these are aminopyrrolidines and piperazines. Placement of an aminopyrrolidine can improve Gram-positive activity, whereas a piperazine generally enhances potency against Pseudomonas. Alkylation of the five-membered or six-membered heterocycle (pyrrolidines or piperazines) also enhances activity against Gram-positive bacteria(31).

Recent advances as anti cancer agents

Increasing development costs and higher failure rate in clinical trials has reduced the newer drugs in the market for clinical use. Most appropriate approach to end the search for newer drugs is drug repurposing. Drug repurposing also known as drug repositioning, reprofilling, re-tasking, or redirecting. Drug repositioning is the process of finding new implication of an existing or failed drug apart from its original indication and as it requires less time and money (32,33). Anticancer drugs are broadly classified either as cytotoxic (cell killing drugs) or cytostatic (anti-proliferative drugs), these leads to tumor growth. Levofloxacin invivo activity, dose 0.1-1.0 m mol/l (0-72 h), type of tumor cell is MCF7, MDA MB-231, MDA MB-468, SkBr3 (Breast cancer), mode of anticancer activity- Apoptosis, S / G2 - phase arrest Inhibition of mitochondrial biogenesis& respiration, pPI3K (down regulated), pAKT (down regulated), mTOR(down regulated), pc-Raf(down regulated), pERK (down regulated)(34). Levofloxacin invivoactivity, dose 200 µg/ml (0-72 h) , type of tumor cell is H460, H3255, A549 (Lung cancer), mode of anticancer activity-Apoptosis Oxidative stress, mitochondrial dysfunction(35). Ciprofloxacin -dose 330 µg/ml (5 days), type of tumor cell is LOVO (Colon cancer) , Apoptosis is mode of anticancer activity ,mechanism of action - ERK1/2(↑)(36). Ciprofloxacin-dose 0-2000 µg/ml (24- 96 h), type of tumor cell is HTB9, T24, TccSup (Bladder cancer), mode of anticancer activity- Inhibits proliferation (37).

CONCLUSION

Fluoroquinolone and development of fluoroquinolone derivatives or hybrids mainly ar C -7 position and it have the chance for invention of new drugs with improved activity, especially with better pharmacokinetic profile and effective against anaerobic organism. Fluoroquinolone have become the second largest claases of chemotherapeutic drug used in clinical practice and seems to be bright as anticancer drugs which may attributed to their non-genotoxic nature and higher bioavailability rate as compared to present day anticancer drugs. Fluoroquinolone in cancer therapy and their mechanism of action and sensitivity varies against different cancer cells. In conclusion, fluoroquinolones have the valuable drugs that have enormous potential to battle of humans against cancer and in future ,researcher aim to discovering optimal antibiotics.

REFERENCES

1. C.Deusenbery Y. Wang A. Shula Recent Innovation In Bacterial Infection Detection And Treatment
2. M. Li. B Mai A. Wang Y. Gao. X. Yang X. Liu S.SongQ.LiuS.Wei P. Wang Photodynamic Anti MicrobialChemotheraphy With Cationic Phthalocyanines Against Escherichia Coil Planktonic And Biofilm Cultures RscAdv
3. D. Van Duin D.L. Paterson, Multidrug Resistant Bacteria In The Community; An Update. Infect Dis. Clin
4. D. Van. Duin D.L Paterson Multidrug Resistant Bacteria In The Community Trends And Lessons Learned Infect
5. J. O'Neill, Tackling Drug-Resistant Infections Globally: Final Report and Recommendations (The Review on Antimicrobial Resistance, 2016. Assess, https://apo.org.au/sites/default/files/resource-files/2016-05/apo-nid63983. pdf.
6. S.B. Levy, B. Marshall, Antibacterial resistance worldwide: Causes, challenges and responses, Nat. Med. 10 (Suppl) (2004) S122eS129.
7. K.U. Jansen, C. Knirsch, A.S. Anderson, The role of vaccines in preventing bacterial antimicrobial resistance, Nat. Med. 24 (2018) 10e19.
8. Q. Han, J.W. Lau, T.C. Do, Z. Zhang, B. Xing, Near-infrared light brightens bacterial disinfection: recent progress and perspectives, ACS Appl. Bio. Mater. 4 (5) (2021) 3937e3961.
9. Ramanjeetkaurbrar, umajyoti, rajesh kumara patil, Hanumanth raochader shekarpatil, fluoroquinolone antibiotic review.
10. National center for biotechnology information, national library of medicine.2020
11. Abraham DJ. Quinolone. In: Burgerís Medicinal Chemistry Drug Discovery. Hoboken, New Jersey: John Wiley and Sons; 2003. p. 582-7

12. Amanda Yan; Emily E. Bryant. 2023 National center for biotechnology information, national library of medicine.
13. Liver Tox: Clinical and Research Information on Drug-Induced Liver Injury National center for biotechnology information, national library of medicine 2020.
14. Aldred KJ, Kerns RJ, Osheroff N. Mechanism of quinolone action and resistance. Biochemistry. 2014 Mar 18;53(10):1565-74
15. Naeem A, Badshah SL, Muska M, Ahmad N, Khan K. The Current Case of Quinolones: Synthetic Approaches and Antibacterial Activity. Molecules. 2016 Mar 28;21(4):268
16. N. R. Cozzarelli, Science 1980, 207, 953.
17. J. D. Walters, F. Zhang, R. J. Nakkula, Antimicrob. Agents Chemother. 1999, 43, 2710.
18. F. Schmitz, J. Antimicrob. Chemother. 1998, 41, 481.
19. A. Gutierrez, J. Stokes, I. Matic, Antibiotics 2018, 7, 32.
20. N. H. Nasser, M. Abdulbary, S. H. Shaalan, E. S. Hadi, World J. Pharm. Pharm. Sci. 2018, 7, 175.
21. J. M. Blandeau, Clin. Ther. 1999, 21, 3
22. G. P. Vitorino, M. C. Becerra, G. D. Barrera, M. R. Caira, M. R. Mazzieri, Biol. Pharm. Bull. 2017, 40, 758.
23. B. Quintero, M. Miranda, Ars Pharm. 2000, 41, 27.
24. J. M. Domagala, J. Antimicrob. Chemother. 1994, 33, 685.
25. E. Rubinstein, Chemotherapy 2001, 47, 3.
26. G. S. Tillotson, J. Med. Microbiol. 1996, 44, 320.
27. P. G. Higgins, A. C. Fluit, F.-J. Schmitz, Curr. Drug Targets 2003, 4, 181.
28. V. Cecchetti, E. Filipponi, A. Fravolini, O. Tabarrini, D. Bonelli, M. Clementi, G. Cruciani, S. Clementi, J. Med. Chem. 1997, 40, 1698.
29. S. Nawaz, R. Bodla, R. Kant, S. P. Singh, R. Bhutani, G. Kapoor, Int. J. Pharm. Sci. Res. 2017, 2, 57.
30. M. I. Andersson, J. Antimicrob. Chemother. 2003, 51, 1.
31. M. Daneshtalab, A. Ahmed, J. Pharm. Pharm. Sci. 2011, 15, 52.
32. T.T. Ashburn, K.B. Thor, Drug repositioning: identifying and developing new uses for existing drugs, Nat. Rev. Drug Discov. 3 (8) (2004) 673–683.
33. S. Murteira, Z. Ghezaiel, S. Karray, Drug reformulations and repositioning in pharmaceutical industry and its impact on market access: reassesmant of nomenclature, J. Mark. Access Health Policy 1 (2013) 21131.
34. M. Yu, R. Li, J. Zhang, Repositioning of antibiotic levofloxacin as a mitochondrial biogenesis inhibitor to target breast cancer, Biochem. Biophys. Res. Commun. 471 (4) (2016) 639–645
35. M. Song, H. Wu, S. Wu, T. Ge, G. Wang, Y. Zhou, S. Sheng, J. Jiang, Antibiotic drug levofloxacin inhibits proliferation and induces apoptosis of lung cancer cells through inducing mitochondrial dysfunction and oxidative damage, Biomed. Pharmaco. Ther. 84 (2016) 1137–1143.
36. I. Jemel-Oualha, J. Elloumi-Mseddi, A. Beji, B. Hakim, S. Aifa, Controversial effect on Erk activation of some cytotoxic drugs in human LOVO colon cancer cells, J. Recept. Transduct. Res. 36 (1) (2016) 21–25. 58]
37. A.M. Kamat, D.L. Lamm, Antitumor activity of common antibiotics against superficial bladder cancer, Urology 63 (3) (2004) 457–460.