World Journal of Pharmaceutical Science and Research
www.wjpsronline.com
Review Article
ISSN: 2583-6579
SJIF Impact Factor: 3.454
Year - 2024
Volume: 3; Issue: 3
Page: 222-239

A REVIEW BASED ON ANTIMICROBIAL ACTIVITY OF QUINOLONES AND THEIR DERIVATIVES

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Article Received: 30 April 2024 | | ***Article Revised: 21 May 2024*** | | ***Article Accepted: 10 June 2024***

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DOI: https://doi.org/10.5281/zenodo.12640666

ABSTRACT

The main aim of review is to learn the antimicrobial activity of Quinolone and their derivatives and to study the type and uses of quinolones and fluroquinolones. It is done to clarify the study regarding the first generation and second-generation fluroquinolones along with its working and spectrum also, to understand the study regarding to the different type antimicrobial drugs.

KEYWORDS: Antimicrobials, hybrid antimicrobials, Quinolones, Fluroquinolones.

Microorganisms

Microorganisms are a heterogeneous group of several distinct classes of living beings. They were originally classified under the plant and animal kingdoms. As this proved unsatisfactory, they were classified under a third kingdom, the Protista. Based on differences in cellular organisation and biochemistry, the kingdom Protista has been divided into two groups prokaryotes and eukaryotes. Bacteria and blue green algae are prokaryotes, while fungi, other algae, slime moulds and protozoa are eukaryotes.

- Classification

1. Prokaryotes:-

A) Bacteria e.g. E.coli

2. Eukaryotes:-

A) Fungi e.g. Agaricus

B) Protozoa e.g. Amoeba

C) Algae e.g. Brown Algae

- **Antimicrobial agents**

The term antimicrobial agents are broader in meaning because it includes drugs synthesised in the laboratory (precisely called antibacterial agents) as well as those obtained from fermentation of microorganisms (antibiotics). There are

many antimicrobial agents wherein the key portion of the chemical structure is derived from the microbial source but its chemical structure is then modified by attaching different chemical moieties (called semisynthetic antibiotics), Hence, the distinction between the terms “Antibacterial”, “antibiotics” and “semisynthetic antibiotics” is somewhat blurred and has lost the original precise meaning in today’s context. We shall be using these terms for which they stand for, but virtually many texts and many physicians use this term interchangeable. Again, these days, the term chemotherapy has been extended to cover “cancer chemotherapy” as well, because the same definition can cover this aspect also. However, in this introductory chapter we stick to the original meaning, i.e., treatment of infectious diseases caused by the microbes (i.e., bacteria, fungi and viruses) and the parasites (i.e., protozoa and helminthics). That leaves the mysterious protein agents, lacking nucleic acids, called prions which cause certain fatal diseases, and defy proper classification.

Antimicrobial agents may act as either bacteriostatic or bactericidal. Bacteriostatic drugs arrest the growth and replication of the bacteria and thus limit the spread of infection. In case of antifungal drugs, the term used is fungistatic. Examples of bacteriostatic drugs include: macrolide group of antibiotics, oxazolidinones, chloramphenicol, tetracyclines, Sulphonamides, trimethoprim, clindamycin, nitrofurantoin and ethambutol.

Antimicrobials, the magic bullets to target microbial Infections has come to verge of losing efficacy due to Emergence of antimicrobial resistance (AMR). As Per Darwin’s theory of evolution, evolution is the key to Adapt the changes in the environment, in turn increasing the probability of survival. Therefore, bacteria, fungi, Viruses, and parasites evolve (mutations) to adapt the environmental changes (attack of antimicrobials). This evolution and indiscriminate use antimicrobials have led to Rise of antimicrobial resistance. Moreover, this resistance has led physicians to increase the dose of Antimicrobials which in turn increases the drug toxicity or emergence of multidrug-resistant microbes. This emergence has led to arise of antimicrobial resistance (AMR) and has led to scarcity of novel drugs that can combat this Resistance. Therefore, AMR confers a serious challenge to the healthcare system worldwide in the terms of mortality, morbidity, and economic burden. In fact, the centres for Disease Control and Prevention claimed 23,000 Deaths per year in the US due to antibiotic resistance and this could reach millions in the coming decades.

- **Antimicrobial spectrum**

Antimicrobial agents that are active against a single or limited group of pathogens are said to have a narrow spectrum, e.g., antitubercular drugs which act mainly on Mycobacterium tuberculosis and procaine penicillin-G or cloxacillin which act primarily on Gram-positive bacteria. Agents which act against a wide range of pathogens (i.e., Gram positive, Gram-negative, Spirochetes, Chlamydia and Rickettsia etc) are called broad-spectrum drugs. Antibiotics that are effective against Gram-positive organisms and also against some Gram-negative pathogens (e.g., amoxycillin and ampicillin) are h. referred to as extended-spectrum drugs. A broad-spectrum antibiotic is more likely to cause Superinfection or pseudomembranous colitis (PMC) by destroying the normal flora of the gut which prevents the growth of other pathogenic flora.

First generation drugs (. c. ciprofloxacin group) These are most effect against: Gram-negative aerobes which include Enterobacteriaceae (E. coli, Klehsiella, Salmonella, Shigella and Proteus mirabilis): other Gram-negative bacteria such as Haemophilus influenzae, H. dhcreyi, Legionella pneumophila. Pseudomonas aeruginosa, and to some extent Vibrio cholerae, Some Gram-negative cocci such as Neisseria b gororrhoeae and N. meningitidis. Recently ciprofloxacin has gained popular attention in providing protection against Bacillus anthracis (Gram-positive bacilli), a major bioterrorism

agent. Otherwise. These drugs are d least effective against other Gram-positive bacilli. These have moderate activity against Gram-positive cocci such as Staphylococcus aureus. Among other microorganisms, these are effective against Mycobacterium tuberculosis, and Rick such as Chlamydia trachomatis and Chlamydia pneumoniae. These drugs show no activity against methicillin-resistant Staph. Aureus (MRSA), Streptococcus pneumonia and anaerobes such as Bacteroides fragilis and Fusobacterium species. These are not reliably active against Mycoplasma ma pneumonia cither. Second generation drugs have similar spectrum as first generation plus better activity against gram-positive cocci such as Streptococcus pneumonia and for other microorganisms like, Legionella and Chlamydia. Third generation drugs have enhanced activity against Gram-positive cocci such as Streptococcus, Staphylococcus and Enterococcus as well as for Mycobacterium tuberculosis, Mycoplasma pneumonia and M. aviun complex in AIDS. These are active against anaerobes also. Fourth generation drugs, not only show enhanced activity against Gram-positive organisms, but exhibit significantly greater activity against anaerobes (for details see individual agents). Fluoroquinolones, like aminoglycosides (Ch. S6), exhibit concentration dependent killing and a post-antibiotic effect which usually) for 3 to 6 hrs. Only moxifloxacin, trovafloxacin and persists.

- Classification

1. First Generation
   Norfloxacin, Pefloxacin and Lomefloxacin Ciprofloxacin
2. Second Generation
   Levofloxacin and Prulifloxacin
3. Third Generation
   Quinolones
4. fourth Generation
   Gatifloxacin, Sparfloxacin and Gemifloxacin Ofloxacin, ag Moxifloxacin, Trovafloxacin, Alatrofloxacin and Finafloxacin.
   Some text classifies nalidixic acid as first-generation drug: but it is a quinolone not fluoroquinolone

- **FIRST GENERATION FLUOROQUINOLONES**

Examples: Norfloxacin, Ciprofloxacin, Ofloxacin, Pefloxacin and Lomefloxacin

- **Pharmacokinetics**

In this group, norfloxacin has a poor bioavailability (30-35%). Its plasma levels are therefore not sufficient to treat systemic infections. For others, oral bioavailability ranges from 80-100%. An average plasma protein binding is only 20 40% and therefore tissue penetration of these drugs is high. These drugs get concentrated in mucosal tissues of GIT. Genitourinary and respiratory tract; in prostate, lungs, heart and macrophages. These drugs penetrate placental barrier and concentrate in amniotic fluid. These are metabolised in liver and eliminated through kidney deposit their short half-life, which ranges from 3 S hrs (norfloxacin) to 8 10 hrs (pefloxacm), these agents can be administered twice daily because of their post-antibiotic effect which varies from 36 hrs.

- **Therapeutic Uses**

Norfloxacin is less potent than ciprofloxacin and is not used to treat systemic infections because of its poor bioavailability. It has restricted use in urinary, genital and GIT infection only. Pseudomonas and Gram-positive cocci

are not inhibited by norfloxacin. Ofloxacin is intermediate between norfloxacin and ciprofloxacin in activity against Gram negative bacteria; but it has slightly better action against Gram-positive organisms and still better action against Chlamydia and Mycoplasma pared to ciprofloxacin. Pefloxacin is similar to ciprofloxacin but penetrates tissues better and accumulate in CSF in high concentration than other drugs in this group. It also attains higher plasma concentration as it is completely absorbed and exhibits cumulation on repeated dosing. Lomefloxacin is also similar to ciprofloxacin but has a long plasma half-life and needs single daily dose administration. It is more active against some Gram-negative bacteria and Chlamydia.

- **SECOND GENERATION FLUOROQUINOLONES**

Levofloxacin and Prulifloxacin Levofloxacin has an extended spectrum against Gram positive bacteria (especially Streptococcus pneumoniae), atypical pathogens (Chlamydia, Mycoplasma) and also against anaerobes. These are equally effective against Gram-negative organisms d including Pseudomonas, Legionella, Proteus. Morella catarrhalis.) Pharmacokinetics Its main use is in: acute bacterial exacerbation of chronic bronchitis, community acquired pneumonia, nosocomial pneumonia, acute sinusitis, uncomplicated skin and soft tissue infections, uncomplicated UTI, complicated UTI and ophthalmic practice as eve drops or ointment for bacterial conjunctivitis and corneal ulcer. Its usual dose is 500 mg orally, once daily. Prulifloxacin also has an extended spectrum of activity against Gram-negative organisms (especially E. coli, Pseudomonas, Proteus, Haemophilus, Klebsiella and Moraxella catarrhalis) as well as against Gram-positive organisms (especially Streptococcus pneumoniae, Enterococcus and Staphylococcus aureus).

Prulifloxacin is mainly used to treat acute uncomplicated urinary tract infection, complicated lower urinary tract infection and for acute exacerbation of chronic bronchitis. Its usual dose is 600 mg orally once daily. After oral absorption the bioavailability of these drugs is 95-100%. Hence, their oral and I.V. doses are simi lar. Their protein binding is poor (30-45%) and hence have a wider distribution in body fluids and tissues but penetration into CSF is relatively poor. These have relatively longer half-lives (levofloxacin 8 hrs; prulifloxacin 10 hrs), which permits once daily dose Ing. The primary route of elimination of these drugs is renal. Prulifloxacin is a prodrug of Ulifloxacin.

- **Antimicrobial: As a Bifunctional antimicrobial conjugates and hybrid**

Bacterial resistance to antimicrobial drugs might become one of the biggest threats to human health in our times. The Increasing occurrence of infections with multi-drug-resistant Pathogens is associated with high mortality and morbidity, And the prevailing lack of new efficient antimicrobial drugs for Treatment of these infections has led to serious concerns of an Imminent fall-back into a so-called pre-antibiotic era. Bacterial resistance to antimicrobial drugs has to be understood as An intrinsic part of bacterial evolution, and its genetic basis Can arise via two main ways:9 either direct via chromosomal mutation leading to viable mutants or, more commonly, Through an acquisition of resistance genes from other bacteria Via horizontal gene transfer (HGT) by mobile plasmids, Transposons or outer membrane vesicles (OMVs). HGT can Lead to easy and fast spread of resistance genes through the Whole pan-genome of the global microbiome. Considering Further that every administered antibiotic has a significant Influence on the resistome,which is defined as the collection Of all genes in pathogenic and non-pathogenic bacteria that Could contribute to a phenotype of antibiotic resistance, Even the evolution of resistance in non-pathogenic bacteria, Originally not targeted by the treatment in patients or ulcer Clearance of the drug into the general environment, can lead to Resistance in pathogenic bacteria .The most frequently occurring genetic mechanisms leading To bacterial resistance include the modification or over-Expression of the antibiotics target, the decrease of the intra-Cellular

antibiotic concentration (by either expression of efflux Systems actively transporting the drug out of the cell or by Mechanism , and the expression of Enzymes able to deactivate the antibiotic. It is therefore clear That the need for novel antimicrobial drugs is a continuous one In order to counteract the development of bacterial resistance. Nowadays, this need has been potentiated by a pronounced Innovation gap in antibiotic drug discovery, which has grown Over a period of almost 40 years aer the "golden era of anti-Biotic drug discovery" lasting from the 1930s to the mid-1960s. In this period the majority of the antibiotics used today have Been discovered.[40]

- **Strategies to overcome resistance in antimicrobial drug development**

Several national and international programs and research initiatives for the development of novel antimicrobials have been started to secure the access to efficient antibiotics, Able to overcome resistance, for the future. Therefore, a Multitude of different approaches have been investigated to restock the therapeutic arsenal, including the modification of Existing drugs, the discovery of novel antibiotic templates The design of patho blockers that don't kill bacteria, but only Inhibit their infectivity, the use of biological formats like Antibodies or phases or combination treatments For the Treatment of critical infections with Gram-negative bacterial ,Combination therapies are controversially discussed and it is Less understood what determines the efficacy of a particular Drug combination. While combination treatments of b-lac-Tams and aminoglycosides showed significant synergistic Effects in vitro and slowed the emergence of resistance, no Evidence could be found for synergy in vivo.[40]

- **Hybrid antimicrobials**

The hybridization of two antimicrobial drugs can be associated with several advantages. The dual targeting can lead to an Enhanced antibacterial potency due to synergistic effects of the Single components. Hybrid antimicrobials can surpass the efficacy of their component drugs, either alone or in combination, by Maintaining their antibacterial activity against pathogens that are Resistant to one or both components of the hybrid antimicrobial and they can decrease the frequency of resistant mutations. Especially when resistance to one of the antimicrobial Components leads to a higher sensitivity of the pathogen against the second component due to a cost, such hybrid antimicrobials can significantly impair the development of resistance. The covalent linkage of two or more antimicrobial drugs Makes the pharmacokinetic and dynamic properties of the Resulting hybrid antimicrobial more predictable compared to the administration of the single antimicrobial components in A combination therapy approach. Furthermore, the physicochemical properties of the covalently linked drug moieties have been reported to be beneficial for their uptake and retention in the bacterial cell. For example, a high membrane Penetration capacity of one antimicrobial moiety can lead to an increased penetration and bioavailability of a second drug. also, Toxicities can be significantly reduced in hybrid molecules. Large variety of Synthetic approaches for the hybridization of antimicrobial drugs have been realized in the last decades. Among those, hybrids Containing either quinolones or fluoroquinolones as one Component are by far the most comprehensively represented.[40]

- **Development of the quinolones**

The prototypical quinolone, nalidixic acid (technically a naphthyridine), was discovered in the 1960s as a by-product During the synthesis of anti-malarial quinine compounds. It was soon found to act by inhibiting the activity of bacterial Topoisomerase type II enzymes, inhibiting the bacterial replication. In 1967, nalidixic acid was approved for clinical Treatment for urinary tract infections (UTIs) caused by Gram-Negative bacteria. However, its use was limited because

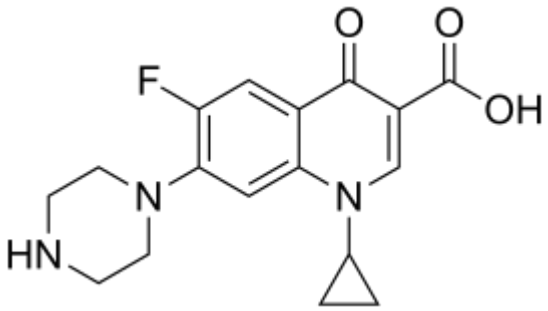
of the narrow spectrum of activity, low serum concentrations Achieved, high inhibitory concentration required, and several Adverse effects.[5]

- **Development in activity**

The first second-generation quinolone, flumequine, exemplified the discovery that a key modification, adding a fluorine (F) atom at the R6 position, could significantly improve the spectrum of activity. This change dramatically increased the quinolone activity, since almost all quinolone antibiotics have been designated as fluoroquinolones, with the exception of the most recent compounds from the fourth generation. Other fluoroquinolones from the second generation include enoxacin, norfloxacin, and ciprofloxacin, which were able to grepafloxacin and gatifloxacin; the MIC90 of gatifloxacin (8-MeO) improved significantly compared with that of grepafloxacin (8-H). These modifications expanded the Gram-positive activity of the third generation, including penicillin-sensitive and penicillin resistant S. pneumoniae, while the activity against atypical organisms, reducing its effectiveness and leading to investigations to discover analogues with improved properties. The first second-generation quinolone, flumequine, exemplified the discovery that a key modification, adding a fluorine (F) atom at the R6 position, could significantly improve the spectrum of activity. This change dramatically increased the quinolone activity, since almost all quinolone antibiotics have been designated as fluoroquinolones, with the exception of the most recent compounds from the fourth generation. Other fluoroquinolones from the second generation include enoxacin, norfloxacin, and ciprofloxacin, which were able to inhibit all Gram-negative organisms, including Pseudomonas organisms, reducing its effectiveness17 and leading to investigations to discover analogues with improved properties. The first second-generation quinolone, flumequine, exemplified the discovery that a key modification, adding a fluorine (F) atom at the R6 position, could significantly improve the spectrum of activity.[18] This change dramatically increased the quinolone activity, since almost all quinolone antibiotics have been designated as fluoroquinolones, with the exception of the most recent compounds from the fourth generation. Other fluoroquinolones from the second generation include enoxacin, norfloxacin, and ciprofloxacin, which were able to inhibit all Gram-negative organisms, including Pseudomonasspecies.19 In addition to the fluoro substituent, these drugs were further modified by addition of a piperazine ring to the R7 position and addition of a cyclopropyl group to the R1 position. The R7 piperazine ring improved the Gram-negative potency, while the cyclopropyl group was found to improve the overall activity of the compounds. This combination made ciprofloxacin the most active compound among the early compounds of the second generation and made it the first choice used against Pseudomonas aeruginosa today. Subsequent development of the second generation produced analogues with activity against some Gram-positive bacteria, including Staphylococcus aureus but not Streptococcus pneumoniae, and some atypical organisms (Mycoplasma pneumoniae and Chlamydia pneumoniae). The presence of an alkylated piperazine group at the R7 position, as in ofloxacin, marked the first modifications that help inhibit Gram-positive organisms. ofloxacin is considered as the most powerful as it combines all the new substituents and it is now still being used for clinical treatment. Ofloxacin is a chiral molecule and its L-isomer is the only active compound, which is known as levofloxacin. It was proposed to have 4-fold higher activity compared with ofloxacin and is also more active than ciprofloxacin in treating some strains.[5] With the synthesis of fleroxacin, the quinolones entered their third generation. The improvements of this generation included addition of alkylated piperazine and pyrrolidinyl groups to the R7 position, and –NH2, –OH, and –CH3 groups to the R5 position to the pharmacophore. The cyclopropyl group at the R1 position and the –OCH3 group at position R8 were kept unchanged from the second generation. The third generation also added new substituents, such as a chloro group (Cl) at the R8 position; this was verified to improve the anti-Gram-positive activity of the drug. Among all modifications at

this position, 8-methoxyquinolone was shown to surpass other compounds in activity and spectrum. These modifications expanded the Gram-positive activity of the third generation, including penicillin-sensitive and penicillin-resistant S. pneumoniae, while the activity against a typical resistant.[5]

Quinolones - The quinolones are a family of antibiotics containing a bicyclic core structure related to the compound 4-quinolone. Since their discovery in the early 1960s, they have gained increasing importance as key therapies to treat both community acquired and severe hospital-acquired infections. The first quinolone antibiotic is generally considered to be nalidixic acid, which was reported in 1962 as part of a series of 1-alkyl-1,8 naphthyridines prepared at the Sterling Winthrop Research Institute. However, a 2015 perspective that examined the origins of quinolone antibiotics in greater detail points out that the author of the 1962 publication (George Lesher) described the isolation of-chloro-1-ethyl-1,4-dihydro-4-oxo-3-quinolinecarboxylic acid in the late 1950s as a by-product of chloroquine synthesis, with modest antibacterial activity leading to further work on analogues, including nalidixic acid. Around the same time, Imperial Chemical.



Industries (ICI) published patent applications with anti-bacterial quinolones, including a 6-fluoroquinolone.

- **Chemistry**

The compounds that are currently available for clinical use in the United States are 4-quinolones that all contain a carboxylic acid moiety in the 3 positions of the basic ring structure. The newer fluoroquinolones also contain a fluorine substituent at position 6, and many of these compounds contain a piperazine moiety at position 7.

- **Mechanism of Action**

The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV (Drlica and Zhao, 1997). For many gram-positive bacteria (such as S. aureus), topoisomerase IV is the primary activity inhibited by the quinolones (Ng et al., 1996). In contrast, for many gram-negative bacteria (such as E. coli) DNA gyrase is the primary quinolone target (Hooper, 2000a; Alovero et al., 2000). The two strands of double-helical DNA must be separated to permit DNA replication or transcription. However, anything that separates the strands results in "overwinding" or excessive positive supercoiling of the DNA in front of the point of separation. To combat this mechanical obstacle, the bacterial enzyme DNA gyrase is responsible for the continuous introduction of negative super-coils into DNA. This is an ATP-dependent reaction requiring that both strands of the DNA be cut to permit passage of a segment of DNA through the break; the break is then resealed.

One class of antimicrobial compounds that has traditionally been used systemically to combat infections is the quinolones. These materials are a class of compounds originating from a by-product of anti-malarial research in 1962 known as nalidixic acid. Through an incremental process over the last 40 years, nalidixic acid derivatives have grown

to be an important class of antimicrobial chemicals including the well-known antimicrobial drugs, norfloxacin, ciprofloxacin, ofloxacin, levofloxacin, and moxifloxacin. Ciprofloxacin, which is effective toward Gram-negative bacteria as well as some resistant strains of bacteria, was introduced in the mid-1980s. Further developments led to levofloxacin, an advanced, broad-spectrum antibiotic with strong activity toward a variety of pathogenic Gram-negative and Gram-positive bacteria. Levofloxacin is typically prescribed for a wide range of infections and is the only respiratory fluoroquinolone approved by the US FDA for the treatment of nosocomial pneumonia.[37]

Quinolones are an important class of synthetic antibiotics. They have been widely used to treat various bacterial diseases such as urinary, digestive and pulmonary infections.[1] These drugs can inhibit bacterial DNA function and thus exhibit obvious inhibitory effects on Gram-negative bacteria, Gram-positive bacteria, and mycoplasma. Until now, the quinolones have been developed to the fourth generation. They have been widely used in clinical treatment. However, the side effects of quinolones are non-negligible, such as diarrhoea, vomiting, arthralgia and joint swelling. Thus, a convenient and sensitive assay for quinolones is highly needed. To date, a variety of analysis methods have been proposed for quinolone detection, including microbiological assays, electrochemical techniques, high-performance liquid chromatography, flow-injection chemiluminescence, and capillary electrophoresis. Although they showed promising results for quinolone detection, these strategies possess obvious shortcomings, including being time-consuming, limited sensitivity, and so on. Fluorometry has attracted much interest owing to its high sensitivity, convenient operation, and on-site detection.[36]

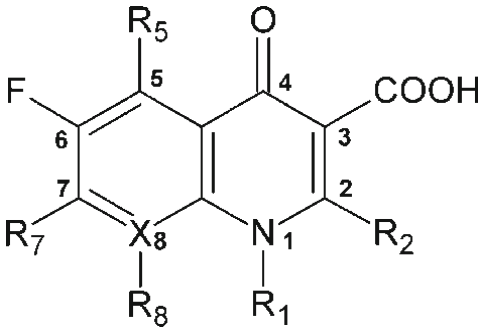
In order to solve the above problem, we have focused on the conventional organic fluorophore. o-Phenylenediamine (OPD) is an important precursor for synthesizing abundant heterocyclic compounds or polymers with unique properties. Certain metal ions can oxidize OPD to form 2,3-diaminophenazine (OPDox) exhibiting orange-yellow fluorescence. As a kind of promising organic fluorophore, OPDox has been used for the development of a series of fluorescence assay.[36]

- **Fluroquinolons**

Currently the Fluoroquinolones Cinoxacin, Enoxacin, Norfloxacin, Ciprofloxacin, Levofloxacin, Lomefloxacin, Ofloxacin, Pefloxacin, Sparfloaxacin-are used clinically.[3]

These drugs are chemically related to nalidixic acid and fluoroquinolones because of the fluorine in their chemical structure Inclusion of fluorine increases their activity manifold and broadens the spectrum. They are: Highly effective orally. Rapidly bactericidal antibacterial spectrum COOH "Relatively safe with broad Effective against bacteria resistant to beta-lactam and aminoglycoside antibiotics; and Antibacterial Activity: They are highly active against many Grams negative and some Gram-positive organisms, in a concentration dependent manner. Thus, they possess excellent manifestations include headache, malaise drowsiness and myalgia. Convulsions may appear with overdosage, particularly in children. It may cause haemolytic anaemia which has been reported in a two-week-old baby fed on breast milk, due to the presence of the drug in the breast milk. It may cause increase in intracranial pressure (pseudotumor cerebri) in young children. Erosion of weight bearing joints has been reported in growing animals. Because of its toxicity, limited utility and availability of fluoroquinolones, its use has now diminished.

Basic Structure of fluroquinolones[2]



Fluoroquinolone action

As pointed out above, the hallmark of quinolone action is the formation of ternary, cleaved complexes containing quinolone, DNA, and gyrase or topoisomerase IV. The formation of cleaved complexes, which is reversible,61 constitutes the mechanistic basis for MIC, a measure of growth inhibition-ray crystallography of cleaved complexes shows gyrase and to Po isomerase IV as hetero tetramers in which one fluoroquinolone molecule binds to each GyrA/GyrB dimer (ParC/ParE for topoisomerase IV). These structures show the binding of the drug at a pair of sites in which the drug intercalates into DNA; the C7 ring system extends into GyrB (ParE), and the C3–C4 keto/carboxyl interacts with helix-4 of GyrA (ParC) through a water–magnesium bridge.25 This important drug–target interaction at GyrA would be blocked by complexing of fluoroquinolone to 99mTc.Quinolone resistance arises from the failure of the compounds to avidly form cleaved complexes. One mechanism is the restriction of intracellular drug concentration (mutations that reduce uptake or increase efflux). Another is blockage of the drug–target interaction, largely by amino acid substitutions in GyrA and ParC that interfere with the formation of the water–Mg2+ bridge between quinolone and enzyme. The importance of the drug–enzyme bridge is emphasized by the behavior of fluoroquinolone-like compounds called quinoxalinediones These agents lack the C3-carboxyl, cannot form the water–Mg2+ bridge with amino acids in helix-4 of GyrA and ParC, and require higher concentrations to form cleaved complexes. Nevertheless, diones bypass the effects of existing resistance substitutions in GyrA and would therefore be unaffected by widespread fluoroquinolone resistance. Thus, they might be useful substitutes for ciprofloxacin as an 18F-based imaging agent. We note that gyrase-based resistance is unlikely to affect imaging by 99mTc-labeled compounds, because the compounds do not target gyrase, as pointed out above. Thus, diones would not confer an advantage for 99mTc-based diagnosis. Moreover, diones lack the C3 carboxyl group used to form 99mTc complexes. Recent drug–enzyme cross-linking experiments identified a second binding interaction between fluoroquinolones and gyrase.[34]

1. Ciprofloxacin-It is a pencil graphite electrode modified with polypyrene, single wall carbon nanotubes and ds-DNA as a highly sensitive DNA label-free biosensor for the determination of ciprofloxacin in pharmaceutical samples. The PGE/PP/SWCNTs/DNA showed high sensitivity for the determination of ciprofloxacin at the nano-molar level. In addition, docking simulations were used as a high-performance tool for studying and clarifying the mode of interaction between DNA and ciprofloxacin.[31]

- **Interaction of 99mTc-ciprofloxacin with bacterial cells**

99mTc-ciprofloxacin behaviour differs from that of its component parts when tests are performed with bacteria. For example, pure ciprofloxacin does not compete with 99mTc-ciprofloxacin for binding to S. aureus. Moreover, when two commonly studied efflux pumps are overexpressed in cultured S. aureus (NorA) or Pseudomonas aeruginosa (MexAB-

OprM), no effect on the accumulation of 99mTcciprofloxacin is observed. However, both pumps do reduce the intracellular concentration of free ciprofloxacin. 99mTc by itself is not taken up by the cells. Thus, studies of bacterial interactions with 99mTc-fluoroquinolones cannot be advanced by examining only the quinolone or the 99mTc component. An approach for studying the binding mechanism is to obtain mutants that fail to carry out binding. Such mutants should allow growth under conditions in which a 99mTc-fluoroquinolone blocks wild-type growth. To our knowledge, this avenue has not been explored. A third issue concerns DNA gyrase, the intracellular target of ciprofloxacin. Part of the initial enthusiasm for 99mTc-ciprofloxacin as an imaging agent rested on the broad-spectrum nature of the antimicrobial, which was due to the widespread distribution of gyrase. It has become clear that gyrase is not the target of 99mTc-ciprofloxacin, as seen in a biochemical test in which the formation of complexes containing ciprofloxacin, gyrase, and plasmid DNA was examined. These ternary complexes (cleaved complexes) are the hallmark of quinolone action, as they rapidly block DNA replication and interfere with the movement of transcription complexes.[34]

- **Ciprofloxacin initial concentration**

Quantity of ciprofloxacin adsorbed on [Cu (Glu)2(H2O)]- H2O with increase in concentration of ciprofloxacin up to 20 ppm before desorption set in. The interaction of the adsorbate and adsorbent resulted from the immediate relationship between the drug concentration and the available binding sites on the MOF surface. The maximum concentration of ciprofloxacin adsorbed onto the MOF was 84.2 mg g^{-1}[Cu (Glu)2(H2O).[13]

- **Contact time of ciprofloxacin**

The effect of contact time on the ciprofloxacin adsorption over [Cu (Glu)2(H2O)]. H2O at concentrations of 20 ppm is displayed in). The ciprofloxacin adsorbed by [Cu (Glu)2(H2O)].H2Owas fast as the contact time increases and after which it approaches equilibrium. Availability of the huge vacant adsorption sites gives room for rapid adsorption at the initial stage of adsorption.[13]

- **Ciprofloxacin temperature**

Ciprofloxacin adsorption over [Cu (Glu)2(H2O)]. H2O was experimented for 2 hours contact time at pH of 6. The result of the Temperature effect is displayed in Fig. S7 (ESI†), indicating That the amounts of ciprofloxacin adsorbed decrease with Increasing temperature of the ciprofloxacin solution through-Out the study. The maximum uptake of 50.8 mg g1 was Recorded at a temperature of 27 1C.[13]

- **Ciprofloxacin pH**

Ciprofloxacin pH (ESI†) shows the pH effect on the drug adsorption. The result clearly reveals that the amount of adsorbed ciprofloxacin is fairly low at low pH and after that continues to increase with increasing pH. The optimum uptake of 90 mg per gram of them OF was adsorbed at pH of 4.0 after which the quantity adsorbed begins to reduce with additional increase in the pH of the ciprofloxacin solution. Research as shown that at a pKa value higher than 5, the polar compound is mostly in an ionic form due to deprotonation. Ciprofloxacin displaying a pKa value of 7.0 and 8.0 signifies the existence of its ionic form in the whole range of the experimental conditions. It was reported that at the pH range of 7–8, ciprofloxacin exists in its cationic form.[13]

2. **Levofloxacin: -** Levofloxacin is a third-generation quinolone antimicrobial agent with a broad-spectrum bactericidal activity against gram-positive and gram-negative bacteria (aerobic and anaerobic). It is used to treat diverse infections

such as those of the sinuses, skin, lungs, ears, airways, bones, and joints caused by susceptible bacteria, urinary infections, prostatitis, misstates and infectious diarrhea caused by E. coli, Campylobacter jejuna and Shigella bacteria.1b, Levofloxacin is the pure (-)-(S)-enantiomer of the racemic drug substance ofloxacin and is much more potent than the racemic mixture that constitutes the parent drug. A thorough survey of the literature has revealed the existence of the crystal structures of only two levofloxacin to complexes; a Mg (II) complex and a Cu (II) one.[22]

Levofloxacin It is the active levo(S) isomer of ofloxacin having improved activity against Strep. pneumoniae, M. tuberculosis and some other gram-positive and gram-negative bacteria Anaerobes are moderately susceptible. Oral bioavailability of levofloxacin is nearly 100%; oral and iv doses are similar. It is mainly excreted unchanged, and a single daily dose is sufficient because of slower elimination and higher potency. Theophylline, warfarin, cyclosporine and zidovudine pharmacokinetics has been found to remain unchanged during levofloxacin treatment.

The primary indication of levofloxacin is community acquired pneumonia and exacerbations of chronic bronchitis in which up to 90% cure rate has been obtained. High cure rates have been noted in sinusitis, pyelonephritis, prostatitis and other UTI, as well as skin/soft tissue infections. Levofloxacin is an alternative drug for chlamydial urethritis. It is the second most active FQ for TB, and in India it is a component of the standardized regimen for MDR-TB.

Photocatalytic degradation of levofloxacin

The influence of process parameters such as pH, catalyst dose and initial drug concentration on the degradation efficiency of levofloxacin was evaluated by varying the pH of the drug solution. Explaining the effect of pH on the photocatalytic degradation of fluoroquinolones is a very difficult task because it is dependent on many factors such as the electrostatic contact between the photocatalyst surface, drug molecules, charged radicals and solvent molecules formed during the photocatalytic reaction process, the drug behaves like a cation. The adsorption of positively charged drug molecules on the catalyst surface decreased due to the repulsion between both catalyst and drug molecules. Secondly, the levofloxacin zwitterion generates three ionic forms, which are dependent on the pH of the drug solution.[30]

- **Structural diversity and activity of Levofloxacin**

Levofloxacin is the active levoisomer (S- (−) isomer) of ofloxacin, an antibiotic drug known for its antibacterial efficacy against a variety of infections such as respiratory tract, genitourinary, obstetric, gynaecological, skin and soft tissue infections. Levofloxacin belongs to the fluoroquinolone family of compounds that are known to inhibit cell division by acting on the bacterial topoisomerase II (DNA gyrase) and topoisomerase IV complex which interferes with bacterial DNA replication, transcription, repair, and recombination a similar PXRD profile.8 Recently, Niddam-Hildesheim et al. had claimed the isolation of six new forms (A, B, C, F, G and H) of levofloxacin obtained from a polar solvent mixture at elevated temperatures (70–120 °C) characterized by distinct PXRD profiles. The presence of solvent in the A, C, G and H forms was confirmed from the TGA and DSC thermograms.[7]

3. Cinoxacin: **–** It has half-life of two hours.it is slightly more active than nalidixic acid and attains higher concentration in urine and produces fewer side effects. Like nalidixic acid it is used for urinary tract infections, but not when renal function is impaired.

4. Enoxacin:- It has half-life of 8.5 hours. It may be used for urinary tract and cutaneous infections. It interferes with the metabolism of theophylline and warfarin and thus enhances their effects.

5. Norfloxacin:- It is the least potent FQ: MIC values for most gram-negative bacteria are 2-8 times higher than that of ciprofloxacin. Many Pseudo monas and gram-positive organisms are not inhibited. Moreover, it attains lower concentration in tissues which are non-therapeutic. Norfloxacin is primarily used for urinary tract infections. Given for 8-12 weeks, it can treat chronic UTI. It is also good for bacterial diarrheas, because high concentrations are present in the gut, and anaerobic flora of the gut is not disturbed. NORBACTIN, NORFLOX 200, 400, 800 mg tab, 3 mg/ml eye drops; UROFLOX, NORILET 200, 400 mg tab. BACIGYL 400 mg tab, 100 mg/5 ml susp.

6. Lomefloxacine:- It is a second generation difluorinated quinolone, more active against some gram-negative bacteria and chlamydia. However, due to higher incidence of photo toxicity and Q-T prolongation, it has been withdrawn in USA and some other countries, but is available in India, though infrequently used.

***7. Ofloxacin*:-** Ofloxacin This FQ is somewhat less active than ciprofloxacin against gram-negative bacteria, but equally or more potent against Strep. pyogenes and other gram-positive cocci and certain anaerobes. Good activity against Chlamydia and Mycoplasma has been noted. It is an alternative drug for nonspecific urethritis, cervicitis and atypical pneumonia caused by Chlamydia trachomatis. It also inhibits M. tuberculosis; can be used in resistant cases of TB. High activity is exhibited against M. leprae, and it is being used in alternative multidrug therapy regimens.

Ofloxacin is relatively lipid soluble; oral bioavailability is high, and higher plasma concentrations are attained. Food does not interfere with its absorption. It is excreted largely unchanged in urine; dose needs to be reduced in renal failure.

Ofloxacin is comparable to ciprofloxacin in the therapy of systemic and mixed infections. It is suitable for chronic bronchitis and other respiratory or ENT infections as well as for chlamydia urethritis as an alternative drug. Inhibition of theophylline metabolism is less marked.

ZANOCIN, TARIVID 100, 200, 400 mg tab; 200 mg/100 ml i.v. infusion, ZENFLOX also 50 mg/5 ml susp.
ZANOCIN, OFLOX, EXOCIN 0.3% eye drops.

8. Pefloxacin:- It is the methyl derivative of norfloxacin which is more lipid soluble, completely absorbed orally, penetrates tissues better and attains higher plasma concentrations. Passage into CSF is greater than other FQs can be used for meningeal infections. It is highly metabolized partly to norfloxacin which contributes to its activity. Pefloxacin has longer t/: cumulates on repeated dosing achieving plasma concentrations twice as high as after a single dose. Because of this it is effective in some systemic infections as well. Dose of pefloxacin needs to be reduced in liver disease, but not in renal insufficiency.

PELOX, 200, 400 mg tab, to be taken with meals; 400 mg/5 ml inj (to be diluted in 100-250 ml of glucose solution but not saline, because it precipitates in presence of Cl ions).

9. Sparfloxacin:- Another second generation difluorinated quinolone which has enhanced activity against gram-positive bacteria, Bacteroides fragilis, other anaerobe's and mycobacteria. Its major indications include pneumonia, exacerbations of chronic bronchitis, sinusitis and other ENT infections. However, it has frequently caused phototoxic reactions: recipients should be cautioned not to go out in the sun. Prolongation of QTe interval has been noted in 3% recipients; fatal arrhythmias have occurred. It has been discontinued in many countries including USA, but not yet in India. Dose: 200-400 mg OD oral.

TOROSPAR 200, 400 mg tab; SPARTA, SPARQUIN, SPAR-DAC 100, 200 mg tab, ZOSPAR, SPARC, EYPAR 0.3% eye drops.

Sparfloxacin is the first marketed aminodifluoroquinolone with increased absorption, is active against Gram-positive species such as staphylococci and is mainly used for the treatment of acute exacerbations of chronic bronchitis and community-acquired pneumonia.[22]

10. Moxifloxacin hydrochloride (MX): - Is a synthetic fluroquinolone antibiotic with bactericidal effects. It binds to DNA gyrase (a bacterial enzyme) and inhibits DNA replication. It is active against Gram-positive bacteria such as Micrococcus luteus and Staphylococcus aureus, in addition to aerobic Gram-negative bacteria such as Actinobacter lwoffli and H. inuenza. It is available as tablets, ophthalmic solutions and infusion bags for treatment of skin infections and respiratory infections such as pneumonia and bronchitis.[39] MX has a reduced activity against anaerobic pathogens. Therefore, a combination of MX with an antimicrobial agent active against anaerobes, such as MT, is of extreme importance for the treatment of mixed aerobic/anaerobic infections. The combination therapy of MX and MT is effective for patients having intra-abdominal abscesses.[39]

- ***Spectrofluorimetric determination of moxifloxacin***

For moxifloxacin determination in aqueous solution, aliquots of working solutions of moxifloxacin were pipetted into 25 mL calibrated flasks after which 5 mL of 0.1 M phosphoric acid– sodium phosphate buffer (pH 8.2) were added and the solution was diluted to the mark with high-purity water. The moxifloxacin concentration range was 0.030–1.2 mg/mL. The solutions were thermostated at 25 ± 0.1 °C and the fluorescence was measured at 465 nm using an excitation wavelength of 287 nm against a blank solution. The concentration of moxifloxacin in the sample was determined from a calibration graph prepared under identical conditions. The prepared solutions remain stable for at least 24 h.[38]

- ***Methods of analysis of Moxifloxacin***

Several methods for the analysis of MX, such as high-performance liquid chromatography (HPLC), 3 spectrophotometry, 4 electrochemical approaches,5 high performance liquid chromatography-ultraviolet visible spectroscopy (HPLC-UV), and liquid chromatography/mass spectrometry7 have been reported. However, most of these methods are time-consuming and require sophisticated procedures/instrumentation. Development of a rapid, simple, sensitive, and accurate analytical method for MOX detection is important. Fluorescence has attracted much attention because of its high sensitivity, selectivity, simplicity and rapidity.[33]

MOX was analysed in several steps. First, MOX (0.0041 g) was dissolved in a beaker and transferred to a 100 mL volumetric flask to prepare a MOX solution of concentration 104 M. Then, 60 mL of CQDs solution and different

volumes (0–60 mL) of MOX were mixed and allowed to react for 10 min at room temperature. Finally, the fluorescence spectrum and fluorescence intensity were measured by a fluorescence spectrometer (excitation wavelength: 360 nm; solvent: deionized water). The fluorescence intensity at 435 nm and 497 nm was expressed as I435 and I497, respectively.[33]

Therapeutic uses –Fluoroquinolones have proved to be very effective in the treatment of:

(1) Urinary tract infection &prostatitis.
(2) For acute diarrheal disease caused by E. coli, shigella, Salmonella, campylobacter.
(3) Bone and soft tissue infections caused by staphylococci and gram-negative organisms respond well to ciprofloxacin.
(4) In serious staphylococcal infections rifampicin should probably be given together.
(5) In neutropenic patients the incidence of infections is reduced.
(6) To reduce the meningococcal and Typhoid.

CONCLUSION

Microorganism are heterogeneous groups of several distinct classes of living organisms like plant, animals, Protista. Were as bacteria and blue green algae being prokaryotes and fungi, protozoa are eukaryotes. Antimicrobial agents are drugs synthesized in laboratory or by the fermentation of microorganism. Key portion of antimicrobial agents are derived from microbial source but its chemical structure is modified by attaching different chemical moieties. These agents may act as bacteriostatic or bactericidal. Bacteriostatic drugs arrest growth and replication of bacteria and limit spread of drug. Bactericidal drugs are used to killed the harmful microorganism. And fungistatic drugs are the antifungal drugs.

Narrow spectrum of antimicrobial agents is active against single or limited group of pathogens. Like antitubercular drugs mainly on mycobacterium tuberculosis. Were as broad-spectrum agents act against wide range of pathogens i.e., Gram-positive bacteria, gram-negative bacteria, spirochetes, chlamydia and rickettsia etc.

Increasing occurrence of infection with multi drug resistance pathogens associated with high mortality and morbidity. Bacterial resistance to antimicrobial drugs has to be understand as an intrinsic part of bacterial evolution it may occur on genetic basis by- A) Direct chromosomal mutation, leading to viable mutants. B) By acquisition of resistance genes transfer from other bacteria via horizontal gene transfer, transgenes and membrane vehicles may cause easy spread resistance genes.

Hybrid antimicrobials overcome from resistance of this antimicrobial can be associated with several advantages due to hybridization. It enhances antibacterial activity due to synergistic effect of single component is bypassed by hybrid antimicrobial. In combination or alone covalent linkage of two or more antimicrobial drugs makes the pharmacokinetics and pharmacodynamic properties of resulting hybrid antimicrobial more predictable compared to administration of single antimicrobial component. Toxicities in hybrid molecules can be reduced.

Quinolones are a family of antibiotics containing bicyclic core structure related to compound 4-quinnolones. This quinolone antibiotics target bacterial DNA gyrase and Topo isomers. Topo isomers primary activity is inhibited by quinolones. Many gram-negative bacteria DNA gyrases are primary quinolones target to combat positive overwinding

of DNA stands bacterial enzyme DNA gyrase is responsible for continuous introduction og negative supercoils into DNA.

Currently Cinoxacin, Enoxacin, Norfloxacin, Ciprofloxacin, Levofloxacin, Lomefloxacin, Ofloxacin, Pefloxacin, Sparfloaxacin etc. fluroquinolones are clinically used. Fluroquinolones have the bactericidal antimicrobial spectrum. These are broad effective against bacterial resistant and aminoglycoside antibiotics.

Name of compund	Antimicrobial spectrum	Modifications	Conclusion
Ciprofloxacin	All Gram-negative pathogens' and some atypical pathogens (including Mycoplasma pneumoniae and Chlamydia pneumoniae)	Addition of (1) piperazine toC7 position, (2) –F to C6position, and (3) cyclopropyl at the N1 position	(1) Improves anti-Gram-negative activity (2) Increases potency
Enoxacin	All Gram-negative pathogen's and some atypical pathogens (including Mycoplasma pneumoniae and Chlamydia pneumoniae)	Addition of (1) piperazine to C7 position, and (2) –F to C6 position	Improves activity Against Gram-negative organisms (inhibits the efflux mechanism)
Norfloxacin	All Gram-negative pathogens' and some atypical pathogens (including Mycoplasma pneumoniae and Chlamydia pneumoniae)	Addition of (1) piperazine to C7 position (quinolone), and (2) –F to C6 position	(1) Improves bioavailability, side effects Improves activity against Gram-negative organisms (inhibits the efflux mechanism)
Moxifloxacin	Covers all the activities of third generation drugs and extra anaerobic activity	Addition of (1) azabicyclo group to C7 position, (2) –OCH3 at C8 position, and (3) cyclopropyl ring at N1position	(1) Improves anti-Gram-positive activity but may result in low water solubility and oral bioavailability (2) Improves anti-Gram-positive activity, tissue penetration, half-life (3) Improves potency of the drug
Ofloxacin (L-isomer = levofloxacin)	All Gram-negative pathogen's and some Gram-positive bacteria (including Staphylococcus aureus, except Streptococcus pneumoniae) and some atypical organisms	Addition of (1) methylated piperazine to C7 position and (2) –OCH2 at C8 position	(1) Increases anti-Gram-positive activity (2) Increases anti-Gram-positive activity, tissue penetration, half-life (3) L-Isomer is 4-fold more active
Sparfloxacin	Retains the activity of second-generation drugs and possesses expanded Gram-positive coverage (penicillin-sensitive and penicillin-resistant S. pneumoniae) and improved activity against atypical pathogens	Addition of (1) dimethylated piperazine to C7 position, (2) –F at C6 and C8 positions, (3) –NH2 at C5 position, and (4) cyclopropyl ring at N1 position	(1) Increases anti-Gram-positive activity(2) Increases anti-Gram-positive activity, tissue penetration, half-life (3) Improves activity against Gram-positive pathogens (4) Improves potency of the drug
Gatifloxacin	Retains the activity of second-generation drugs and possesses expanded Gram-positive coverage (penicillin-sensitive and penicillin-resistant S. pneumoniae) and improved activity against atypical pathogens	Addition of (1) methylated piperazine group to C7 position, (2) methoxy group at C8 position, and (3)cyclopropyl ring at N1position	(1) Improves anti-Gram-positive activity (2) Improves anti-Gram-positive activity, tissue penetration, half-life (3) Improves potency of the drug
Nalidixic acid	Gram-negative organisms (except Pseudomonas species)	N at X8 position = naphthyridone	First molecule to be discovered in quinolone class

ACKNOWLEDGMENT

Author would like to thank miss. Shital Patil and The Department of Chemistry of Mahatma Gandhi Vidya mandir's Pharmacy college Panchvati, Nashik.

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