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Review Article

The fluoroquinolones as antibacterial compounds; an overview on biological and chemical activities aspects.

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ABSTRACT
Fluoroquinolones are the most promising anti-infective chemotherapy agents depicting broad spectrum and potent activity. Various substituted fluoroquinolones derivatives were evaluated against gram negative, gram positive and resistance bacteria strains. These drugs are having DNA gyrase and growth inhibition activity. They have a relatively simple molecular nucleus, which is willing to many structural modifications. These agents have several favorable properties such as good bioavailability, tissue penetrability and relatively low incidence of adverse and toxic effects. They are effective in treatment of various infectious diseases. This paper is an attempt to the therapeutic prospects of fluoroquinolones as antibacterial agents.

KEYWORDS
Fluoroquinolones, antibacterial agents, DNA gyrase.

1. INTRODUCTION

The quinolone classes of antimicrobial agents have considerable interest and divided into different generations based on their antibacterial spectrum [1]. The earlier-generation agents are narrow-spectrum than the later ones. The non-fluorinated drugs found within the 'first-generation' quinolones. The first generation is rarely used today. Nalidixic acid was list as a carcinogen on 1998. Substantial progress has been made in the molecular mechanisms of the action of quinolones against pathogenic bacteria, the induction of resistance to quinolones in these organisms, and the potential of each quinolone compound to induce toxicity in treated patients. However, the emergence of bacterial resistance to the quinolones is a major factor that will determine the future clinical effectiveness of these agents, so that intense investigation of mechanisms to either prevent or curtail resistance to quinolones is of prime importance to their future [2]. A number of the second, third, and fourth generation drugs have been removed from clinical practice due to severe toxicity. The drugs most frequently prescribed today consist of moxifloxacin, ciprofloxacin, levofloxacin etc [3,4]. These are quinolone antimicrobials having one or more fluorine substitutions. The efforts to develop better FQLs then the available ones with respect to activity or toxicity or resistance or all of these. The ‘first generation’ FQLs has one fluoro substitution. Compounds with additional fluoro and other substitution have been developed-further extending antimicrobial activity to gram positive cocci and anaerobes and conferring metabolic stability. These are referred to as ‘second generation’ FQLs.

The quinolone class of antimicrobial agents was not isolated from living organisms but, rather, was synthesized. The creative development of the quinolones began in 1962, made the accidental discovery of nalidixic acid as a by-product of the synthesis of the antimalarial compound chloroquine [5]. Other discoveries followed, but only a few were importance because they provided better understanding of the mechanisms of action of the quinolones; the ability to modify the quinolone nucleus to improve potency and the spectrum of antibacterial activity; the opportunity to prolong the elimination half-life and to improve the pharmacokinetic and pharmacodynamic properties of quinolones, resulting in effective once daily dosing; and a understanding of the importance of the structure-activity relationships of the quinolones, with respect to their relative susceptibilities to the development of bacterial resistance and their potential for causing adverse events in treated patients [6,7].

1.1. Classification of Quinolones

1.1.1. First-generation

Various first generation quinolones such as cinoxacin, flumequine (veterinary use), nalidixic acid, oxolinic acid, piromidic acid, pipemidic acid, and rosoxacin.

1.1. 2. Second-generation

The second-generation class are ciprofloxacin, enoxacin, fleroxacin, lomefloxacin, nadifloxacin, norfloxacin, ofloxacin, pefloxacin and rufloxacin.

1.1. 3. Third-generation

Unlike the first and second generations, the third-generation is active against streptococci. Examples are balofloxacin, Grepafloxacin, levofloxacin, pazufloxacin, sparfloxacin, temafloxacin, and tosufloxacin.

1.1. 4. Fourth-generation

Fourth-generation fluoroquinolones act at DNA gyrase and topoisomerase IV. This dual action slows development of resistance. This dual action slows development of resistance. Examples are clinafloxacin, gatifloxacin, gemifloxacin, moxifloxacin, sitafloxacin, trovafloxacin and prulifloxacin.

1.1. 5. In development

delafloxacin (an anionic fluoroquinoline in clinical trials), JNJ-Q2 (completed Phase II for MRSA), nemonoxacin.

1.2. Mechanisms of action

The quinolone nalidixic acid caused abnormal accumulation of single-stranded DNA precursors and that, when each chromosomal domain was supercoiled, it was also transiently nicked [8]. Furthermore, when supercoiling was completed, the single-stranded DNA state was abolished by the sealing action of an enzyme that was specifically inhibited by the quinolone. These observations helped to explain the mechanism of action of the quinolones against bacteria [9]. Subsequently, this enzyme that nicks double-stranded chromosomal DNA, introduces negative supercoils, and then seals the nicked DNA, and they called it "DNA gyrase" or topoisomerase II [10]. These observations provided a molecular basis for the potent antibacterial effects of the quinolones. Subsequently, 4 DNA topoisomerases were identified in bacteria. Topoisomerases I and III are not very susceptible to inhibition by the quinolones, whereas topoisomerases II and IV are the 2 major targets of quinolones. Both topoisomerases II and IV are tetrameric structures and are composed of 2 subunit pairs. There are 4 subunits in topoisomerase II: 2 A monomers and 2 B monomers, which are known as "Gyr A" and "Gyr B," to denote DNA gyrase. Topoisomerase IV also has A and B subunits that are encoded by the *parC* and *parE* genes. Topoisomerase IV is involved with decatenation of the linked DNA molecules in the bacterial cell [11]. Thus, topoisomerases II and IV are the lethal targets of the quinolones. Their identification has led to the development of new quinolones that have increased activity against topoisomerases II and IV [11,12].

1.3. Modifications to the quinolone nucleus

The evolution of quinolones was modification of the quinolone nucleus through the addition of different substituents at the N-1, C-6, C-7, and C-8 positions (Figure 1) [7,11]. These modifications altered the antimicrobial activity, pharmacokinetics, and metabolic properties of the quinolones. The addition of specifically selected substituents at these key positions on the quinolone nucleus made it possible to target specific groups of bacteria and to improve the pharmacokinetics quinolones [13-16]. Some key changes included the addition of a fluorine atom at position C-6, which increased DNA gyrase inhibitory activity, facilitated penetration into

the bacterial cell, and provided activity against staphylococci. The addition of a second fluorine group at position C-8 resulted in increased absorption and a longer elimination half-life but also increased phototoxicity. The addition of a piperazine group at position C-7 provided the greatest activity against aerobic gram-negative bacteria and increased the activity against staphylococci and *Pseudomonas* species. Alkylation of the C-7 ring improved the activity against aerobic gram-positive bacteria and increased the elimination half-life of quinolones. The addition of a methyl group to the distal nitrogen of the C-7 piperazine ring also increased the elimination half-life and improved bioavailability. Addition of a cyclopropyl group at position N-1 yielded ciprofloxacin, which has increased antibacterial activity against aerobic gram-positive and gram-negative pathogens. Increased activity against *Mycoplasma* and *Chlamydia* species was achieved by adding an amino group at C-5 and a fluorine group at C-8 to quinolone compounds that possessed a cyclopropyl group at N-1 [6]. Antibacterial activity could be enhanced by simply adding fluorine or chlorine at C-8 to compounds with a cyclopropyl group at N-1 [15]. The addition of a methoxy group, instead of a halide, at the C-8 position specifically targets both topoisomerase II and IV, which also may decrease the possibility of the development of resistance to quinolones [14,16]. Of the currently available agents, only gatifloxacin and moxifloxacin have a C-8 methoxy group in their chemical structure (Figure 2-4).

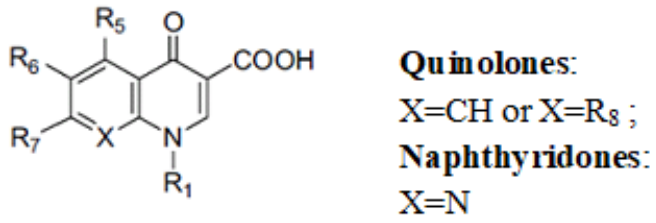


Figure 1. Common structure of 4-quinolones.

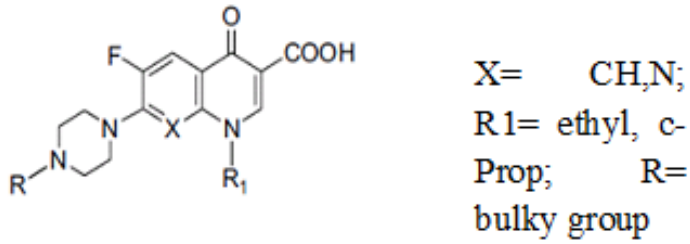
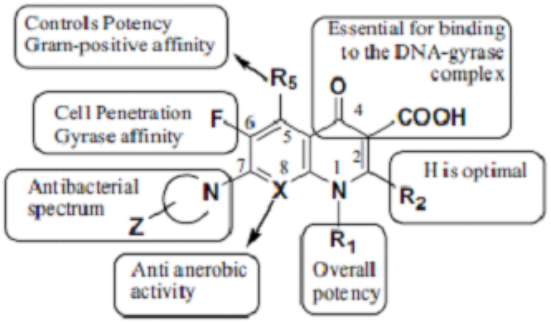


Figure 2. General structure of N-substituted piperazinyl quinolones.



R_1=Et, cyclopropyl, halo substituted aromating ring, etc.
R_2=H,-SMe, or R_1 and R_2 may join to form a ring.
R_5=H, -NH2, -OMe.
X=N, CH, C-OMe, or Xand R_1 may join to form a ring.
Z= attached group to cyclo-alkylamine ring.

Figure 3. Common structure feature of quinolones.

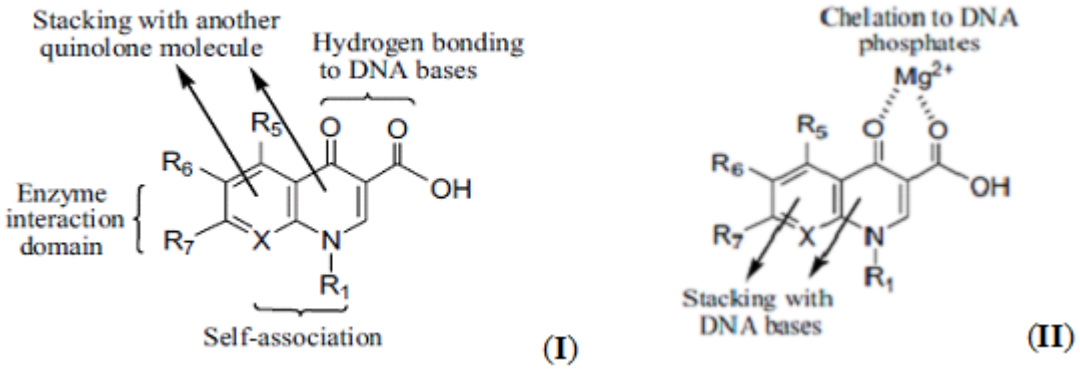


Figure 4. Two binding models (I and II) of quinolones.

A number of infectious diseases are successfully treated with quinolones. Clinical efficacy has been demonstrated for respiratory tract infections such as bronchitis, pneumonia, and bacterial sinusitis. Quinolones also have effectiveness for treating urinary tract infections, bacterial prostatitis, skin and other soft-tissue infections, bone and joint infections, gastrointestinal infections caused by *E. coli* or *Salmonella* species, and infection with *Shigella, Campylobacter, Aeromonas,* and *Vibrio* species and *Plesiomonas shigelloides.* The quinolones have also been effective in treating sexually transmitted diseases, such as gonococcal and chlamydial, chancroid, and pelvic infections. Some quinolones have also been useful in treating immunocompromised patients with febrile neutropenia [17-23]. Not all fluoroquinolones have been approved for use in the treatment of all of the aforementioned infections. The use of all FQLs interchangeably, especially for unapproved indications, is discouraged. At present in the United States, the most frequently prescribed FQLs are ciprofloxacin, levofloxacin, gatifloxacin, and moxifloxacin. Gemifloxacin became available for general use in 2004. Ciprofloxacin is approved for use for both uncomplicated and complicated urinary tract infections, including cystitis, pyelonephritis, and chronic bacterial prostatitis; uncomplicated urogenital and rectal gonorrhea; skin and other softtissue infections; bone and joint infections; infectious diarrhea and typhoid fever; intra-abdominal infections (used with metronidazole); sinusitis; nosocomial pneumonia. Cirpofloxacin is also approved for use as empirical therapy for patients with febrile neutropenia, as prophylaxis and treatment for anthrax, and for lower respiratory tract infections, including acute bacterial

exacerbations of chronic bronchitis, pneumonia (other than pneumococcal pneumonia), hospital-acquired pneumonia, and infection with *Legionella* species. Levofloxacin is approved for use in treating both uncomplicated and complicated urinary tract infections (including pyelonephritis and chronic bacterial prostatitis), skin and skin structure infections, acute maxillary sinusitis, acute bacterial exacerbations of chronic bronchitis, community-acquired pneumonia (including that due to penicillin-resistant *Streptococcus pneumoniae* [PRSP] and multidrug-resistant *S. pneumoniae* [MDRSP]), and nosocomial pneumonia. Gatifloxacin is approved for use in treating both uncomplicated and complicated urinary tract infections (including pyelonephritis), uncomplicated urogenital gonorrhea, uncomplicated skin and skin-structure infections, acute sinusitis, and acute bacterial exacerbations of chronic bronchitis and community-acquired pneumonia (including that due to PRSP and MDRSP). Moxifloxacin is approved for use in treating acute bacterial sinusitis, uncomplicated skin and skin-structure infections, and acute bacterial exacerbations of chronic bronchitis and community-acquired pneumonia (including that due to PRSP and MDRSP). Gemifloxacin is approved for use in treating acute bacterial exacerbations of chronic bronchitis and community-acquired pneumonia of mild-to-moderate severity. It is also worth noting that, although a quinolone may be approved to treat a specific infection, consideration must be given to the susceptibility of the infecting organism. In this context, all quinolones are not equal and should not be used interchangeably [24]. To use them most effectively, clinicians should be familiar with the specific properties and clinical indications of each quinolone. For example, ciprofloxacin continues to be an excellent choice for treating infections caused by aerobic gram-negative bacilli, including those caused by drug-susceptible *P. aeruginosa.* In contrast to other classes of antimicrobial agents, the appropriate use of the quinolones-in particular for the treatment of respiratory tract infections-continues to generate much discussion among clinical investigators [25-28]. One issue is the emergence of resistance to quinolones, particularly among *S. pneumoniae* and, more recently, among *Haemophilus influenzae*. Although the overall incidence of resistance to quinolones among pneumococci is currently relatively low, the incidence is increasing, and the justifiable concern is that it will continue to increase [28]. Importantly, resistance to quinolones among pneumococci has been observed to occur in association with those quinolones that have modest in vitro activity against pneumococci [29-32]. Therefore, the possibility exists that the use of those quinolones with the most potent in vitro activity against pneumococci may delay the emergence of resistance in these pathogens. However, future studies are required to answer this question. Another issue of concern is whether in vitro resistance to antimicrobial agents affects clinical outcomes, particularly in pathogens responsible for serious respiratory tract infections. Recent reports suggest that in vitro resistance to b-lactams and macrolides does not correlate with either therapeutic failure or increased mortality among patients with pneumococcal pneumonia [33]. If these observations are correct, then they are unique, compared with our earlier experiences with the resistance and clinical outcomes associated with infections caused by other pathogens. For instance, clinical failure was observed after the appearance of resistance to b-lactams among staphylococci, resistance to vancomycin and aminoglycoside among enterococci, multidrug resistance among *Mycobacterium tuberculosis,* and antiretroviral resistance among HIV. Recently, an alternative concept has been proffered that may help to explain the lack of

correlation between therapeutic failure and resistance to b-lactams and macrolides among pneumococci. Specifically, the problem may involve the methods used to identify pneumococci, so that misidentification results in a falsely elevated prevalence of resistance [34]. Misidentification obviously would also affect clinical evaluations. Clearly, correct identification of pneumococci in additional surveillance studies, as well as proper clinical investigation of outcomes, is needed to resolve the perplexing issue of the in vitro resistance to and clinical efficacy of quinolones used to treat respiratory tract infections.

1.4. Effect on antimicrobial activity

Differences in the in vitro activity of the fluoroquinolones (FQLs) primarily form the basis of their classification. The antimicrobial activity of the early, first-generation quinolones (i.e., nalidixic acid, oxolinic acid, cinoxacin, piromidic acid, pipemidic acid, and flumequine) was excellent against aerobic, gram-negative bacteria. However, first-generation quinolones were not very active against aerobic, gram-positive bacteria or anaerobic bacteria. Second-generation quinolones were introduced when norfloxacin was synthesized by adding a fluorine at C-6 and a cyclic diamine piperazine at C-7. These changes added antimicrobial activity against aerobic gram-positive bacteria and improved activity against gram-negative bacteria, compared with the first-generation compounds, but the second-generation quinolones still lacked activity against anaerobic bacteria. Norfloxacin was the first of the "fluoroquinolones," a name resulting from the addition of a fluorine at the C-6 position. Other second-generation quinolones include ciprofloxacin, ofloxacin, levofloxacin, enoxacin, fleroxacin, lomefloxacin, pefloxacin, and rufloxacin. Newer FQLs (i.e., third-generation fluoroquinolones, including grepafloxacin, gatifloxacin, sparfloxacin, temafloxacin, tosufloxacin, and pazufloxacin) were subsequently developed and had greater potency against gram-positive bacteria, particularly pneumococci; they also had good activity against anaerobic bacteria. The final group of compounds (trovafloxacin, clinafloxacin, sitafloxacin, moxifloxacin, and gemifloxacin) was termed "fourth-generation FQLs," because they had potent activity against anaerobes and increased activity against pneumococci [11]. Although there are a number of ways to categorize quinolones (by chemical structure, by SARs, by in vitro spectrum of antimicrobial activity, or by clinical efficacy), these classifications clearly are arbitrary. The aforementioned classification system- first to fourth generation- is based on the newest spectrum of antibacterial activity and potency against pneumococci and anaerobic organisms and provides a practical classification system for clinical use [7].

1.5. Effect on pharmacokinetics

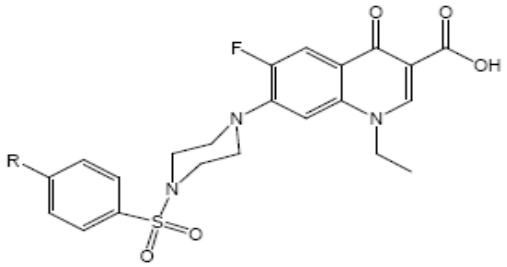
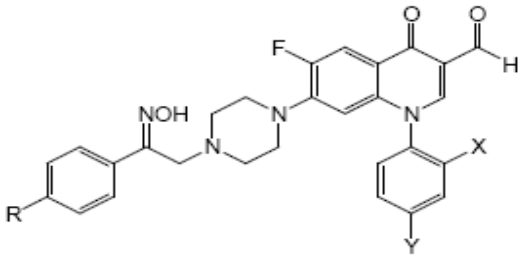
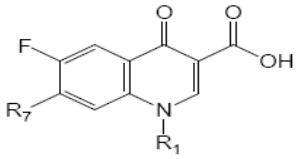
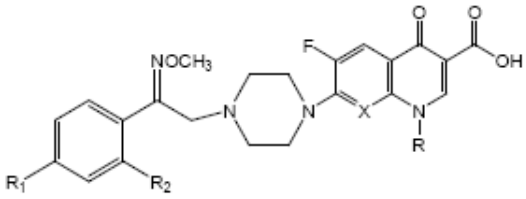
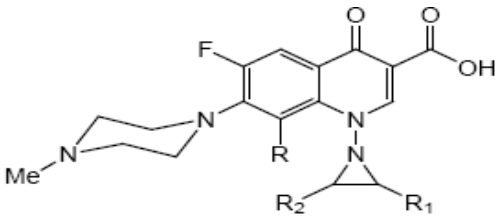
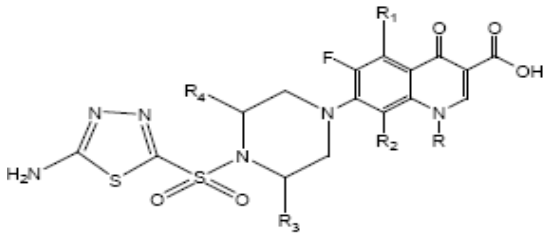
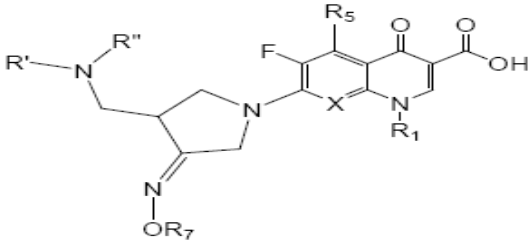
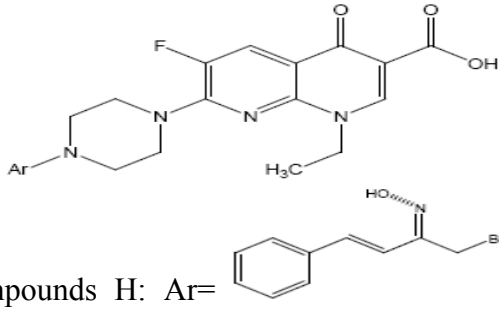
The quinolones were observed to have excellent oral absorption, good distribution in tissue, with excellent interstitial fluid levels, entry into phagocytic cells, and urinary concentrations that exceeded the MICs for many common pathogens [35]. Key structural modifications resulted in improved pharmacokinetics (e.g., a longer elimination half-life, which permitted once-daily dosing and better tissue penetration) of some of the newest quinolones, including gatifloxacin, gemifloxacin, grepafloxacin, moxifloxacin, sitafloxacin, sparfloxacin, and trovafloxacin [36,37]. Specific modifications included alkylation of the quinolones, which improved elimination half-

life and penetration into tissue; the addition of 2 methyl groups to the C-7 piperazine ring, which increased oral efficacy; the addition of an amino group at C-5, which increased lipophilicity; and the addition of a halogen at position C-8, which improved in vivo activity [7,11,15].

1.6. Effect on resistance and adverse events

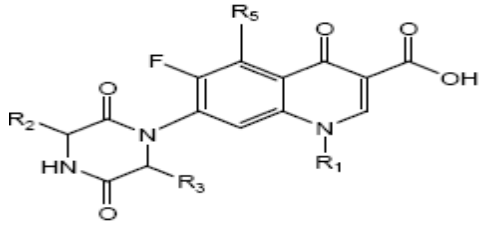
Progress in our understanding of the role of SARs, along with the application of current research techniques, has indicated that bacterial resistance to quinolones occurs either with the induction of amino acid changes in specific areas of the *parC* and *parE* genes of topoisomerase IV, particularly in pneumococci, and in the *gyr*A gene of topoisomerase II, in staphylococci, or with amino acid changes in both topoisomerases II and IV in many bacterial species [38-41]. The specific areas of these genes are known as "quinolone resistance-determining regions" (QRDRs). Moderate resistance can also occur because of increased efflux of the quinolone out of the bacterial cell, which reduces intracellular concentrations of the drug. Key observations have demonstrated that, not only is the level of resistance different among various quinolones, but it also is different among the various species of bacteria [42-45]. The incidence of adverse events observed in association with the early-generation quinolones was low; adverse events frequently appeared within the first several days of treatment and occurred with similar frequencies in both young and elderly patients, except that CNS adverse events occurred more frequently in elderly patients. The rate of adverse events associated with both oral and intravenous fluoroquinolones appears to be dose related, with an increasing incidence of adverse events associated with increasing doses and duration of therapy. In any event, FQLs are considered to be relatively safe, compared with other classes of commonly used antimicrobial agents [7,14]. Gastrointestinal disturbances have been reported most frequently, followed by CNS adverse effects, hypersensitivity reactions, and, quite rarely, hypotension, tachycardia, crystalluria, thrombocytopenia, leukopenia, and anemia. Some of the early quinolones interacted with theophylline and caffeine and other quinolone compounds (i.e., those that have a fluorine in the C-8 position) and produced moderate-to-severe phototoxicity, because they accumulated in high concentrations in skin. Phototoxicity is more common and more severe in association with the use of lomefloxacin, fleroxacin, and sparfloxacin and is much rarer in association with the use of (in descending order) grepafloxacin, ofloxacin, ciprofloxacin, levofloxacin, and trovafloxacin. Phototoxicity reactions have not been reported in association with moxifloxacin and gatifloxacin. Fortunately, phototoxicity is not a problem associated with the FQLs currently in common use. Three adverse events associated with quinolones-cardiotoxicity (e.g., prolongation of the corrected QT interval), hepatotoxicity, and hypoglycemia-currently command the most attention [7,46,47]. The naphthyridone quinolones (nalidixic acid, piromidic and pipemidic acid, enoxacin, tosufloxacin, trovafloxacin, and gemifloxacin) have 2 nitrogens in their basic nuclei-a traditional nitrogen in the 1 position and a second nitrogen in the 8 position. Some of the naphthyridone quinolones are associated with higher incidences of and a greater number of serious adverse events, compared with quinolones without a nitrogen in the 8 position.

Table 1: Antibacterial derivatives with standard drugs.

Structure	Standard Drug/Activity
	
Compounds A: R= NH2, NHCOCH3, N(CH3)COCH3, NHCH3, N(CH3)2, CH3, Cl4, H, OCH3, NO2	Compounds B: X= H, F Y= NO2, NH2 R= F, OMe
Ciprofloxacin, norfloxacin/Moderate to good for both G+ & Gbacteria [48].	Norfloxacin / Moderate to good for both G+ & G- bacteria [49].
	
Compounds C: R1= c-C3H5, 2,4-F2Ph, CH2CH3, (CH3)3C, (CH3)2CH, c-C4H7 R7= F	Compounds D: R= c-propyl, ethyl R1= H, F, Cl R2= H, F, Cl; X= CH, N
Moderate to good for both G+ & G-bacteria.	Ciprofloxacin, norfloxacin / Good activity for both G+ & Gbacteria [50].
	
Compounds E: R= H, F R1= H, R1R2=R3= C6H5, 4-fPh, 3-CF3Ph, pipridine, (CH2)4	Compounds F: R= c-propyl, CH2CH3 R1= H, NH2, NHCOCH3 R2= H, F, OCH3 R3= H, CH3 R4= H, CH3
Ciprofloxacin/Moderate for both G+ & G-bacteria [51].	Ciprofloxacin, norfloxacin/G+ good & G-moderate activity [52].
	
Compounds G: X= CF, CCl, CH, COMe, N	Compounds H: Ar= R1=

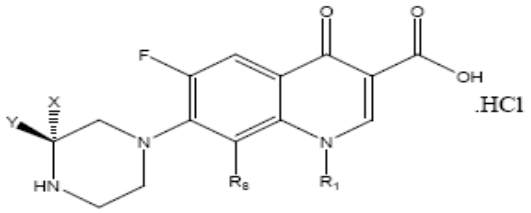
R1= c-propyl, 2,4-difluoroPh C2H5 R5= H, NH2 R7= H, Ph, benzyl, n-propyl, isopropyl, tertbutyl, CH3 R'= H,CH3 R"= H,CH3

Ciprofloxacin / G+ & G- good activity in both bacteria [53].



Compounds I: R1= C2H5, CH2- C6H5 R2= H, CH3 R3= H, CH3

Ciprofloxacin/Moderate activity for both G+ & Gbacteria [55].

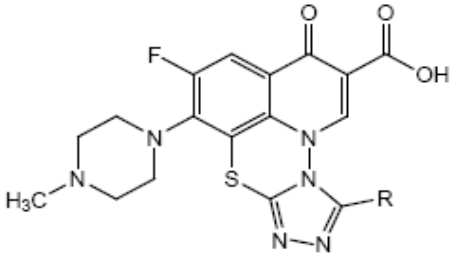


Compounds K: R8= H, F R1= (s)-OCH2CH(CH3), (R)- OCH2CH(CH3), c-C3H5, C6H3F2-2,4C6H3F2-3,4; C6H4F-3 Side chain= s-3-Methylpiprazine-1-yl R-3-Methylpiprazine-1-yl

Ciprofloxacin, ofloxacin.HCL/Not very significant [57].

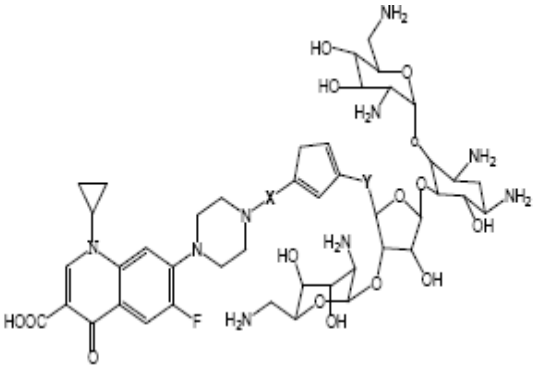
C2H5, CH2- C6H5 R2= H, CH3 R3= H, CH3

Ciprofloxacin, norfloxacin/Potent activity against G+ & G- bacteria [54].



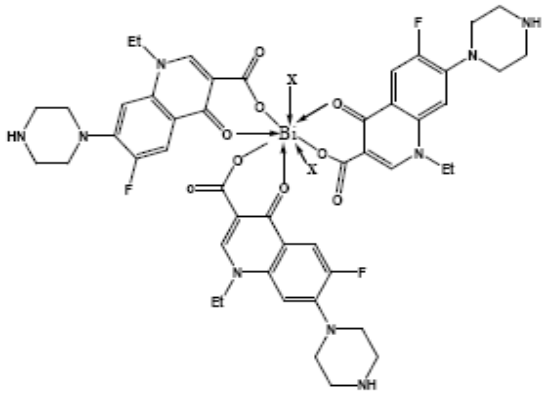
Compounds J: R= H, CH3, CH2CH3, n-C3H7, n-C4H9, n-C5H11, C6H5, p-CH3OC6H4, m-CH3OC6H4, p-CH3C6H4, 3,4-(CH3O)2C6H3, 3,4-(OCH2O)2C6H3, 3,4,5-(CH3O)3C6H2, p-FC6H4, p-ClC6H4

Ofloxacin/Good Activity against both G+ & G- (R=H or CH3) and R= aryl then no effect or poor activity against G+ & G [56]-



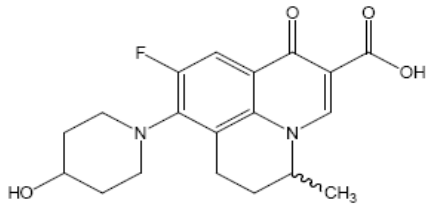
Compounds L: X= -(CH2)2-, -(CH2)3-, -(CH2)4-, -(CH2)5-, -(CH2)6-, -CH2CH(OH)CH2-, -(CH2)2-O-(CH2)2-, -CHmC6H4-CH2-, -CH2-pC6H4-CH2-,Y= -C6H4-NHCO-

Ciprofloxacin/Not very significant.



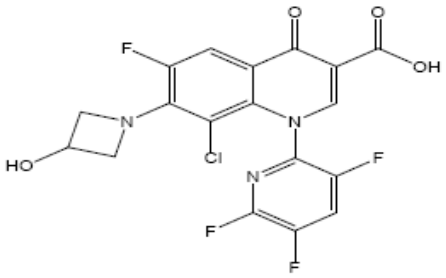
Compounds M: X= H2O

Ciprofloxacin / Significant action for both G+ & G- bacteria [58].



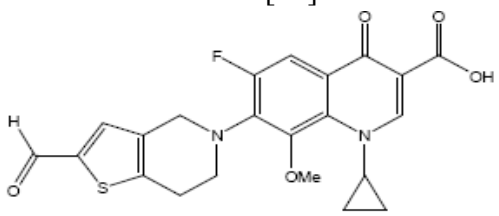
Compounds N:

Ciprofloxacin, norfloxacin /Excellent activity for both G+ & Gbacteria [59].



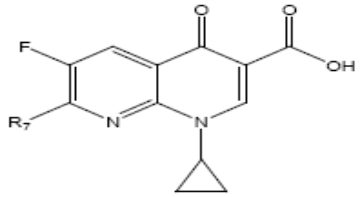
Compounds O:

Ciprofloxacin, norfloxacin/Excellent activity for both G+ & Gbacterial Resistance strain [59].



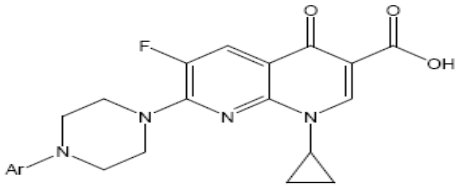
Compounds P:

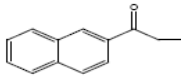
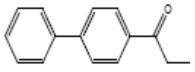
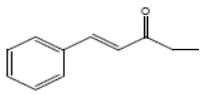
Ciprofloxacin, norfloxacin /Excellent activity for both G+ & Gbacterial Resistance strain [59].



Compounds Q:

Ciprofloxacin/Excellent activity for both G+ & G bacterial Resistance strain [59].



Compounds R: Ar =  ,  , 

Ciprofloxacin, norfloxacin/ Potent activity against G+ & G- bacteria.

The future of the quinolones is difficult to predict. The quinolone nucleus continues to provide opportunities for future modifications that may produce more valuable compounds. As mentioned in earlier reviews, future prospects of newer compounds may have greater potency, particularly against staphylococci and enterococci; better penetration into the CNS and cerebrospinal fluid; broader and more potent activity against anaerobic bacteria; greater activity against infections caused by mycobacteria and *Stenotrophomonas, Pseudomonas,* and *Alcaligenes* species, which currently are difficult to treat; decreased drug-drug interactions; and better patient tolerability, with lower incidences of adverse reactions and serioustoxicity. In addition, newer quinolones may be developed with greater activity against targets in infectious agents responsible for Lyme disease, malaria, nocardiosis, toxoplasmosis, pneumocystosis, leishmaniasis, fungi, and DNA viruses. However, research efforts are more likely to focus on more-common infections, rather than rare diseases or diseases for which effective therapy already exists. Another, albeit poorly explored, area is the development of new compounds with a high and specific affinity for the DNA (eukaryotic topoisomerases) in human malignant cells, which could be used alone or in combination with other chemotherapeutic agents. This potential would provide sufficient economic and humane rewards to justify the investment in such an effort [7]. If the use of quinolones in clinical medicine is to continue, the emergence of bacterial resistance to the quinolones should remain of primary importance as an area of current and future research. Although much progress has been made in our understanding of the important effect of amino acid changes in the QRDR of topoisomerases and their effect on bacterial resistance, the magnitude of the importance of efflux pumps in bacterial cells provides a different and potentially productive avenue for continued investigation [60-62]. The development of highly effective quinolone pump inhibitors that are safe for use in treating patients may provide a key advantage for patients receiving therapy with quinolones or other antimicrobial agents in the future.

1.7. Rapid color test identification system for screening of counterfeit fluoroquinolone Oxidation of ferrous ammonium sulfate Solution A: Ferrous ammonium sulfate solution 0.1% (w/v) in 1% H_2SO_4.

1.7.1. Procedure

To the solid sample, 0.5 mL solution A was added followed by sodium bicarbonate till effervescence ceased. Development of yellow-red color indicated presence of FQLs. The blank had no color.

Test for fluoride with Zr-EDTA-PV (Zirconium-Ethylene diamine tetracetic acid-Pyrocatechol violet) reagent

1.7.1. 1. Solution A:

The acetate buffer of pH 4.2 was prepared by dissolving 3.7 mL glacial acetic acid and 2.177 g sodium acetate trihydrate in 50 mL water.

1.7.1. 2. Solution B

0.02 g $ZrOCl_2$, 0.03 g EDTA and 0.001 g pyrocatechol violet were dissolved in water. To this 25 mL solution A was added and volume was made up to 100 mL. This reagent is stable for nearly 2 weeks at room temperature (~ 30 °C).

1.7.2. Procedure

The drug sample was fused with 50 mg of $NaNO_3$ in a wide mouth glass tube. After cooling, 25 mg NH_4Cl was added and heating was resumed till effervescence ceased. After cooling, the solid mass was dissolved in 0.5 mL water and 0.5 mL solution B was added. The color change of solution B from blue to yellow indicated positive test for FQLs [63].

The fluoroquinolones are frequently prescribed class of antibacterial agents. The fluoroquinolones have gained stupendous importance during the last two decades because of their potent antibacterial activity against wide varieties of gram-positive and gram-negative pathogenic bacteria with minimum toxic side-effects and somewhat different mechanism of action than other available antibacterial drugs [65-75]. To date, many fluoroquinolones antibacterial agents have been introduced into clinical use with significant improvement in antibacterial spectrum and activity. A vast array of fluoroquinolones having excellent broad-spectrum activity forms an invaluable part of the present anti-infective armory of the clinicians. A number of these compounds are today's blockbusters of the antibacterial market due to their therapeutic efficacy and tolerable side-effect even, challenging the predominance of well-established ß-lactam antibiotics which are becoming more prone to the resistant pathogenic bacteria. The fluoroquinolones are fastest growing antibacterial class in terms of global revenue, increasingly being used in both the hospital and community sectors to treat a broad range of infection. The boost in fluoroquinolones prescribing was attributable to the introduction and use of newer, broader–spectrum fluoroquinolones with activity against *S. Pneumoniae* (for example, levofloxacin, gatifloxacin, and moxifloxacin). However, increased prescribing has led to the recent emergence of fluoroquinolones-resistant bacteria which has necessitated the search or newer drugs with efficacy against resistant strains and efforts are on worldwide in this direction [75-85].

2. CONCLUSION

The new fluoroquinolones are potent synthetic antibacterial agents with broad spectra, including most urinary tract and gastrointestinal tract bacterial pathogens. The use of orally administered fluoroquinolones (when indicated) instead of intravenously administered antibiotics may provide significant advantages in terms of reduced hospitalization or home health care costs. Thus a judious and efficient use of these antibiotics is recommended. This review has attempted to highlight the key discoveries made during the evolution of the quinolone class of antimicrobial agents, as well as the effect of these discoveries on the development of newer and truly innovative compounds that have clearly been effective in clinical medicine. The currently approved indications for the most commonly used quinolones have also been reviewed, along with the concern of emerging bacterial resistance to these agents. In addition, a discussion of future potential uses for newer quinolone compounds, aside from their proven efficacy as

antibacterial agents, has been included. Clearly, the quinolones have captured the interest of investigators and clinicians during the past 2 decades.

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