Quinolones: Recent Structural and Clinical Developments

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Abstract

Quinolones are a very important family of antibacterial agents that are widely prescribed for the treatment of infections in humans. Since their discovery in the early 1960s, the quinolone group of antibacterials has generated considerable clinical and scientific interest. Two major groups of compounds have been developed from the basic molecule: quinolones and naphthyridones. The 4-pyridone-3-carboxylic acid associated with a 5, 6-fused aromatic ring is the common chemical feature of bactericidal quinolones. In the resulting bicyclic ring, the 1-, 5-, 6-, 7-, and 8-positions are the major targets of chemical variation. Manipulations of the basic molecule, including replacing hydrogen with fluorine at position 6, substituting a cyclic amine residue at position 7 and adding new residues at position 1 of the quinolone ring, have led to improved breadth and potency of antibacterial activity and pharmacokinetics. One of the most significant developments has been the improved anti-Gram-positive activity of the newer compounds, such as moxifloxacin and garenoxacin. However, some of these structural changes have been found to correlate with specific adverse effects: the addition of fluorine or chlorine at position 8 being associated with photoreactivity, e.g. sparfloxacin; and the substitution of an amine or a methyl group at position 5 having a potential role in QTc prolongation, e.g. sparfloxacin and grepafloxacin. The clinical utility of this expanding class of antimicrobial agents, and the lower propensity for the development of resistance with the newer quinolones will need to be continually monitored in the changing therapeutic environment. Antibiotic drug choice will remain difficult in the presence of increasing resistance, but introduction of the new quinolones has created a new and exciting era in antimicrobial chemotherapy.

Keywords: Antibacterial agents; Quinolones; Structure-activity relationships.
from the discovery of nalidixic acid 1 (4) in 1962 as a by-product of antimalarial research, the first representative of the quinolones which was found effective against some Gram-negative microorganisms and possessed pharmacokinetic properties for treating urinary tract infections (UTIs).

However, following the introduction of nalidixic acid for the treatment of uncomplicated UTIs caused by enteric bacteria, the quinolones became a neglected group of antimicrobials until the development of the fluoroquinolones in the 1970s and 1980s. The fluoroquinolones have an extended spectrum of activity and improved pharmacokinetics compared with the earlier compounds. In two decades, the quinolones moved from a relatively small and unimportant group of drugs used predominantly for the treatment of UTIs, to molecules with potent activity against a wide spectrum of significant bacterial pathogens (5). Recently, there has been a considerable increase in the number of agents that are in development, and to date over 10 000 molecules have been patented. The subsequent four decades have seen the identification of many thousands of molecules, now generically classified as ‘the quinolones’, although strictly, these are derivatives of either the 4-quinolone or 1, 8-napthyridine ring structures. Therefore, the quinolones cover the modern era of antibiotic drug discovery. Quinolones have been not only widely used, but also intensively studied and, as such, have probably added more to our knowledge of antimicrobial science than any other class of antibiotics or antimicrobial chemotherapeutic agents.

Although some excellent reviews on SAR, biological and clinical aspects are available in the literature, this article attempts to overview the recent developments that have taken place in the areas related to chemical and biological aspects in a concise manner, while focussing on structural development, structure-activity and structure-side effect relationships, generation, prediction of the future position of the quinolone class of agents in antimicrobial chemotherapy and the future trends for further development of this group of compounds. It also points out to their structural manipulations to obtain newer fluoroquinolones, being more potent with better pharmacokinetic profile than the parent compounds.

**Generation and development of quinolones**

Based on the 4-quinolone nucleus (Fig. 1), the quinolones comprise a relatively large and expanding group of synthetic compounds. An alkaloid having quinolone structure was first prepared by Price (6) but it possessed no biological activity. In 1960, Barton et al. (7) isolated 6-chloro-1H-ethyl-4-oxo-quinoline-3-carboxilic acid during antimalarial research, which showed antibacterial activity. In 1962, during the process of synthesis and purification of chloroquine (an antimalarial agent), a naphthyridine derivative, nalidixic acid 1, was discovered which possessed bactericidal activity (4). However, its clinical use was limited to the treatment of UTIs caused by the majority of Gram-negative bacteria, with the exception of *Pseudomonas aeruginosa*. The clinical usefulness of nalidixic acid, in the treatment of other infections than UTIs, was limited by its low serum concentrations and high minimum inhibitory concentrations (MIC 4–16 mg/L) (8).

Thereafter, novel compounds of this family, such as oxolinic acid 2, pipemidic acid 3, and cinoxacin 4 were synthesized and introduced...
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into clinical practice (Figures 2 and 3), although the clinical indication for these quinolones still remained only for UTIs (9, 10). These early agents, however, proved invaluable in the treatment of uncomplicated UTIs, such as cystitis. Nalidixic acid 1 has several structural features retained by the newer compounds, and is based on a 4-oxo-1, 8-naphthyridin-3-carboxylic acid nucleus (11). Two major groups have been developed from the basic structure: quinolones and naphthyridones (11-15). The presence of a nitrogen at position 8 identifies the naphthyridones, a carbon and associated group at position 8 identifies the quinolones (Fig. 1). The quinolones and naphthyridones were further improved by the addition of groups to the N-1, C-5, C-6 and C-7 positions of their respective basic molecules. Until the development of flumequine 5, the first monofluoroquinolone in 1976, none of the earlier compounds had offered any significant improvements over nalidixic acid 1. Flumequine 5 was the first compound to be developed with a fluoro- group at position 6, and gave the first indications that modifications of the basic chemical structure could improve Gram-positive activity (5). Its range of activity embraced the Enterobacteriaceae, including some strains that were resistant to nalidixic acid with useful activity against uncomplicated gonorrhoea, albeit with a two- or three-dose regimen.

In 1978 norfloxacin 6, a 6-fluorinated quinolone with a piperazinyl side-chain at position 7, was developed. Norfloxacin 6 had a longer half-life than the earlier compounds (3–4 h), less protein binding (50%) and improved Gram-negative activity (16). The addition of a fluorine atom at position 6 was one of the earliest changes of the basic structure. This single alteration provides a more than 10-fold increase in gyrase inhibition and up to 100-fold improvement in MIC. During the 1980s, a great number of fluoroquinolones were developed. In addition to fluorine atom at the C-7 position, a cyclopropyl group was introduced to the N-1 position and is best exemplified by ciprofloxacin 7, which was first synthesized in 1983 (Figures 2 and 3). This increases the potency of the drug and many subsequent quinolones have a cyclopropyl group. The benzopyridone nucleus (quinolone) proved to be more responsive to chemical manipulation which made in order to enhance antibacterial potency. Subsequent discovery of fluorine atom and piperazinyl ring on the quinolone ring namely norfloxacin 6, ciprofloxacin 7, pefloxacin 8, ofloxacin 9 revolutionized the chemistry of fluoroquinolones (5, 9-13). These agents showed potent activity against Gram-negative bacteria, but not against the Gram-positive bacteria or anaerobes. In the 1990s, further alterations of the quinolones resulted in the discovery of novel compounds that not only showed potent activity against Gram-negative bacteria but also against the Gram-positives. A number of other structural manipulations have been tried to improve the anti-Gram-positive activity of fluoroquinolones. One of the first additions was an NH$_2$ group at position C-5, which resulted in a general increase in anti-Gram-positive activity (5, 12-15). This is seen with sparfl oxacin 10 which otherwise has a very similar structure to

![Figure 2. Clinical development of quinolones](image)
ciprofloxacin. Sparfloxacin also has a fluorine at position C-8, a piperazine at position C-7 and is alkylated (17). Grepafloxacin 11 is also substituted at position C-5 but by a CH₃ group which improved anti-Gram-positive potency compared with ciprofloxacin (18). Other new quinolones containing 7-piperazinyl group are gatifloxacin 12, lomefloxacin 13 and levofloxacin 14 (the (S)-enantiomer of ofloxacin 9). Gatifloxacin 12 is a racemic compound that bears a C-7 3-methylpiperazinyl and a C-8 methoxy substituents. Gatifloxacin is active against penicillin-resistant *S. Penumoniae* and has proven highly effective in the treatment of lower respiratory tract infections.

Pyrrolidine rings (five-membered) are also common substituents at position 7 (Fig. 4), and are associated with enhanced potency against Gram-positive bacteria. However, this group is associated with low water solubility and low oral bioavailability, so in-vivo activity may be compromised. Introduction of methyl groups on the pyrrolidine ring helps to overcome some of these physical properties. Naphthyridine derivatives, tosufloxacin 16 and gemifloxacin 17 (Fig. 4) are example of the
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Advantages and disadvantages associated with a pyrrolidine ring at position 7 (5, 19). The addition of azabicyclo groups onto position 7 (Fig. 4) has resulted in agents (moxifloxacin 18 and trovafloxacin 19) with significant anti-Gram-positive activity, marked lipophilicity and half-lives of >10 h (20, 21). Sitafloxacin 20 is another new fluoroquinolone that is in limited development due to photosensitivity. Unique structural features of sitafloxacin 20, which is being developed as a single enantiomer, include a novel aminopyrrolidine substituent at C-7 and a fluorocyclopropyl group at N-1 (5).

Manipulation of the group at position 8 has also been shown to play a role in altering oral pharmacokinetics, broadening the spectrum of activity and reducing the selection of mutants (22-25). Whilst alkylation has been shown to increase further anti-Gram-positive activity, it also improves tissue penetration and increases the half-life by increasing lipophilicity, as with grepafloxacin 11, levofloxacin 14 and sparfloxacin 10.

In addition, some of the new compounds, such as trovafloxacin 19 (having 2, 4-difluorophenyl group at position 1), also showed promising activity against the anaerobes (26).

Thus, continuous efforts were directed to further modify the quinolone pharmacophore with more complex newer fluoroquinolones, namely danofloxacin 21, pazufloxacin 22, clinafloxacin 23 and prulifloxacin 24 (Fig. 5).

Recently, non-fluorinated quinolones, such as garenoxacin 25 (Fig. 6) have been developed, which further opens novel avenues in the development of quinolone antibiotics (27).

The targets in fluoroquinolone research during the last few years include improving the pharmacokinetic properties, increasing the activity against Gram-positive cocci and...
anaerobes and against fluoroquinolone-resistant strains, and improving activity against nonfermentative Gram-negative species (28-30).

**Mechanism of action**

Quinolones rapidly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death (3, 31, 32). The molecular organization of the complex is presently unknown although several models have been suggested (3, 31, 32). According to one model, four quinolone molecules bound as two pairs of noncovalently associated drug dimers in a single-stranded DNA bubble opened up by topoisomerase action (Fig. 7). Based on another model, the affinity of quinolones to metal ions seems to be an important prerequisite of their antibacterial activity: probably, quinolones bind to the DNA-enzyme-complex via a magnesium ion (Fig. 7) (33). As a general rule, Gram-negative bacterial activity correlates with inhibition of DNA gyrase, and Gram-positive bacterial activity corresponds with inhibition of DNA type IV topoisomerase (31).

**Structure-activity relationships**

The minimum pharmacophore required for significant antibacterial activity consists of the 4-pyridone ring with a 3-carboxylic acid group (Fig. 8). Indeed, Quinolones consist of a bicyclic ring structure in which there is a substitution at position N-1, with various moieties. Most of the current agents have a fluorine atom at position 6, and a nitrogen heterocycle moiety at the C-7 position (34). In general, β-keto carboxylic acid moiety (positions 3 and 4) is essentially required for hydrogen bonding interactions with DNA bases in the single-stranded regions of duplex DNA created by the action of the enzyme, (Fig. 7 and Fig. 8) (35, 36). Thus, the 1-, 2-, 5-, 6-, 7-, and 8-positions are the major targets of chemical variation (Fig. 8).

The structure-activity relationships (SAR) of quinolones have been the subject of extensive review (5, 9-14). The antibacterial activity of 4-quinolones depends on the nature of peripheral substituents and their spatial arrangements (37). These substituents play a major role to influence the antibacterial activity and pharmacokinetic
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Properties through affinity for binding with bacterial enzymes (Fig. 8).

The purpose of our brief discussion is to demonstrate the changes or effects occur due to modifications or manipulation of different substituents in particular positions of the pharmacophore, and their influence on the chemotherapeutic properties, as well as side effects of quinolone class.

**Position 1**

Antibacterial activity is greatly influenced by the steric bulk of N-1 substituent and optimal groups in order of activity being cyclopropyl, ethyl, followed by fluorosubstituted phenyl and t-butyl (13). It is also found that substituent with more steric bulk e.g. fluoroethyl (fleroxacin 26, Fig. 9), 2, 4-difluorophenyl (tosufloxacin 16 and temafloxacin 27, Fig. 9) group have also enhanced activity against anaerobes. From the X-ray crystallography and molecular modeling studies, it has been observed that in N-1 aryl substituted quinolones, the N-1 aryl ring is twisted out of the plane of the quinolone nucleus (21, 38). Another structure at this position is found in ofloxacin 9, levofloxacin 14, pazufloxacin 22, nadifloxacin 28 and rufloxacin 29 which has a fused ring between positions 1 and 8 (Fig. 10).

**Position 2**

Very little is known about the SAR of quinolone having substituents at C-2 position; as loss of bioactivity has been found with methyl, hydroxyl or methylthio substituents. However a ring between C-1 and C-2 position was shown to have biological activity. The C-2 position is left unsubstituted because of its proximity to the enzyme binding site (9-14).

**Position 5**

Introduction of some substituents such as halogen, nitro, amino, hydroxy and alkyl groups at C-5 were initially thought to reduce antibacterial activity of the quinolones. However, 5-amino substitution in the 6, 8-difluoroquinolone series having N-1 cyclopropyl group showed enhanced in-vitro activity, especially against Gram-positive organisms. Thus, substitutions at this position are thought to contribute to potency against Gram-positive organisms. The influence of 5-amino group depends on the substitution pattern at C-8 and N-1 and a few potent analogues in this series are sparfloxacin 10 and PD 124816 30 (Fig. 11); having improved Gram-positive activity as well as anaerobic activity. Moreover,

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**Figure 7.** Two binding models of quinolones

**Figure 8.** Common structural features of quinolones

R₁= Et, cyclopropyl, halo substituted aromatic ring, etc.
R₃= H, -SMe, or R₁ & R₂ may join to form a ring.
R₄= H, -NH₂, -OMe
X= N, CH, CF, C-OMe, or X & R₁ may join to form a ring.
Z= attached group to cycloalkylamine ring.
Several substituents besides fluorine have been introduced into position 6. All of the quinolones having those substituents were less active than 6-fluoroquinolones. The influence of fluorine at C-6 is essential for high activity as evidenced by its enhanced gyrase inhibition and cell penetration which has become the basis for generic name fluoroquinolones. However, there has been a recent interest in quinolones without a fluorine at this position. The non-fluorinated quinolones, for example garenoxacin, show greater potency than the newer fluoroquinolone moxifloxacin against both sensitive and resistant Gram-positive organisms, thus casting doubt on the validity of the necessity of the C-6 fluorine. Garenoxacin does however have a difluoromethoxy at position 8, although an analog of this compound without the C-8 moiety is still as potent as moxifloxacin. Recently, fluorine at C-6 is replaced by NO₂ group to get highly potent nitroquinolones. They are potent inhibitor of *Streptococcus* and *Staphylococcus* species.

**Position 7**

Substituent at position 7 are closely associated with properties of the quinolones such as their antibacterial spectrum, bioavailability, and side effects. Introduction of a basic group at C-7 of the quinolone ring was found to enhance antibacterial activity, as this substituent greatly influences antibacterial and pharmacokinetic properties. A five- or six-membered cycloamino moiety (e.g., pyrrolidine or piperazine rings) is the most commonly used substitutions at C-7 position. Piperazine rings are particularly
common (e.g. norfloxacin 6, ciprofloxacin 7, pefloxacin 8, ofloxacin 9, sparfloxacin 10, lomefloxacin 13, levofloxacin 14, enoxacin 15 and fleroxacin 26), and confer potency against Gram-negative bacteria (34, 41). The addition of methyl groups can improve both oral absorption and in-vivo activity. However, the improved activity against Gram-positive bacteria can sometimes be at the expense of activity against *Pseudomonas aeruginosa*. The piperazine moiety of 7-piperazinyl quinolones possess enough structural flexibility to allow product optimization. In addition, a position on the 7-piperazinyl quinolone molecule, where substitutions of bulky groups are permitted, is at the N-4 of piperazine ring (42). Accordingly, a number of *N*-substituted piperazinyl quinolones 31 (Fig. 12) with a specific substituents in the piperazine unit of 7-piperazinyl quinolones were described by our research team and others (43-53).

Pyrrolidine rings (five-membered) are also common substituents at position 7, and are associated with enhanced potency against Gram-positive bacteria. However, this group is associated with low water solubility and low oral bioavailability, and therefore in-vivo activity may be compromised. Introduction of methyl groups on the pyrrolidine ring helps to overcome some of these physical properties. Gemifloxacin 17, a naphthyridone, is a good example of the advantages and disadvantages associated with a pyrrolidine ring at position 7 (19). In a series of compounds, it was shown that antibacterial activity against Gram-negative bacteria increased in the following order 4'-methyl piperazinyl < 3'-methyl piperazinyl < piperazinyl < 3'- amino pyrrolidinyl; whereas the Gram-positive activity follows the sequence piperazinyl < 3'-methyl piperazinyl < 4'-methyl piperazinyl < 3'-amino pyrrolidinyl (54). Alkylamino and alkyl oximino substituents in the ring further enhances bactericidal action and serum half life of the compounds (55).

The addition of azabicyclo groups onto position 7 has resulted in agents (moxifloxacin 18 and trovafloxacin 19) with significant anti-Gram-positive activity and marked lipophilicity (20, 21).

**Position 8**

Manipulation of the group at position 8 has also been shown to play a role on oral pharmacokinetics and broadening the spectrum of activity (22-25, 56). Among many modifications investigated in C-8 position, a few substituents such as fluoro, chloro, methyl and methoxy group offered good antibacterial activity, especially against Gram-positive bacteria; while other substituents tend to decrease the activity (11). Also, the introduction of halogen atoms, methoxy or methyl groups enhances potency of the compound against anaerobes.

A number of naphthyridines in which C-8 of quinolone is replaced by a nitrogen atom, showed excellent activity.
Structure-side effect relationships

The structural changes to the quinolone molecule and correlation with adverse events are now well documented (13, 57). Photoreactivity is probably mostly influenced by position 8, with fluoro or chlorine producing the most phototoxic potential (e.g. sparfloxacin 10, lomefloxacin 13 and clinafloxacin 23) and methoxy groups the least effect (e.g. gatifloxacin 12 or moxifloxacin 18). Garenoxacin 25 has fluorine incorporated through a C-8 difluoromethyl ether linkage, as there is no fluorine at C-6. It has been suggested that substitution at position 5 may have a role in QTc prolongation as those agents that have been associated with significant problems, such as sparfloxacin 10 and grepafloxacin 11, have either a NH₂ or a CH₃ group in this position (17, 58). Many speculations have also surrounded the likely structural correlates of the haemolytic uraemic-like syndrome caused by temafloxacin 27 (59), hepatic eosinophilia caused by trovafloxacin 19 (60), pulmonary interstitial eosinophilia and other immunological side-effects caused by tosufloxacin 16 and gemifloxacin 17 (61), and the hypoglycaemia seen with clinafloxacin 23 and temafloxacin 27 (62, 63). Although a number of these agents are naphthyridones (tosufloxacin 16, gemifloxacin 17 and trovafloxacin 19), others are fluoroquinolones (temafloxacin 27), hence it is unclear whether this difference is relevant. A more powerful association is that of the 2,4-difluorophenyl group at position 1, as this is shared by tosufloxacin 16, trovafloxacin 19 and temafloxacin 27 and not by gemifloxacin 17. A further hypothesis is that metabolites of these agents (as yet not fully identified), which share common structures, may be responsible for some of the immunologically mediated adverse events seen with these drugs.

Quinolone generations based on antimicrobial activity

The quinolones can be classified into four generations based on potency and spectrum of their antimicrobial activity (64).

1. First-generation agents include nalidixic acid 1, cinoxacin 4 and the progenitor fluorinated agent, flumequine 5, and 7-piperazinyl derivatives, pipemidic acid 3. These drugs, which are used less often today, have moderate Gram-negative activity and minimal systemic distribution.

2. Second-generation quinolones: norfloxacin 6, ciprofloxacin 7, pefloxacin 8, ofloxacin 9, lomefloxacin 13, enoxacin 15, fleroxacin 26, possessing expanded gram-negative activity and atypical pathogen coverage, but limited gram-positive activity.

3. Third-generation quinolones: sparfloxacin 10, gatifloxacin 12, levofloxacin 14, moxifloxacin 18, having expanded gram-negative and atypical intracellular activity but have improved gram-positive coverage.

4. Fourth-generation agents including trovafloxacin 19 with improved Gram-positive coverage, while maintain Gram-negative coverage, and gain anaerobic coverage (65).

Generally, marginal susceptibility and acquired resistance limit the usefulness of second-generation quinolones in the treatment of staphylococcal, streptococcal, and enterococcal infections (66). The presently available fluoroquinolones with in-vitro activity against Streptococcus pneumoniae (including current penicillin-resistant strains) are sparfloxacin 10, gatifloxacin 12, levofloxacin 14, moxifloxacin 18, and trovafloxacin 19. Sparfloxacin 10 and levofloxacin 14 exhibit inferior in-vitro anti-streptococcal activity compared with gatifloxacin 12, moxifloxacin 18, and trovafloxacin 19. Gatifloxacin 12 is two to four times and moxifloxacin 18 is 4-8 times more active than levofloxacin 14 against S. pneumoniae in vitro (67). Compared with ciprofloxacin 7 and levofloxacin 14, the fluoroquinolones gatifloxacin 12, moxifloxacin 18, and trovafloxacin 19 have greater in-vitro activity against S. aureus and some Enterococcus strains (67, 68). Although gatifloxacin 12 and moxifloxacin 18 have in-vitro anaerobic activity, only trovafloxacin 19 is labeled for the treatment of anaerobic infections. Clinafloxacin 23, an investigational fluoroquinolone, has the most in-vitro potency against anaerobic bacteria (69).

Resistance to Quinolones

Quinolones resistance has multiple mechanisms
and significant clinical impact. It is clear that there are essentially three types of resistance mechanisms deployed by bacteria to evade the action of an antibiotic (70). Firstly, there is prevention of access of the drug to the target site; which may occur by reducing entry of the drug into the cell (influx) or by pumping of the drug out of the cell (i.e. efflux). Secondly, bacteria can produce novel enzymes that inactivate or modify the molecules. Thirdly, the target site can be altered so that the interaction of the drug is reduced in such a way that higher concentration of the drug is required to achieve the same level of inhibition of enzyme activity. Quinolone resistance is mediated by target changes or reduced intercellular accumulations as yet there is no bacterial enzyme described in the literature which is capable of modifying, hydrolysing or altering the quinolones molecule (71). Mutations may occur rapidly during quinolone therapy and may be the most significant factor limiting the use of these antimicrobials. *In vitro* susceptibility to methicillin-resistant *S. aureus*, methicillin-resistant *Staphylococcus epidermidis*, and vancomycin-resistant Enterococcus species is variable and unpredictable. Although the newer quinolones have shown promising *in-vitro* activity against Gram-positive bacteria based on MIC data, physicians should be cautious when using quinolone antibiotics to treat life threatening Gram-positive infections. Continued overuse of these antimicrobials in clinical medicine and agricultural feed will promote Gram-positive and Gram-negative resistance and is likely to limit the effectiveness of the quinolones in the near future. Overuse of a single agent will ultimately result in resistance to the entire class (31).

**Quinolones and future trends**

Without doubt, the newer quinolones have very attractive properties, combining high potency, a broader spectrum of activity, better bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating higher concentrations in tissues and a potentially low incidence of side-effects. Since the introduction of nalidixic acid 1, the principle successor of quinolones; more than 10000 analogues belonging to approximately variety of ring systems, have established themselves as clinical drugs and there are more are in the horizon to be introduced. Such an explosive growth of this group of compounds occured mainly due to three factors: (1) unprecedented mode of action (inhibition of DNA gyrase and topoisomerase IV), (2) high potency and broad antimicrobial spectrum equally comparative to the desired fermentation-based semisynthetic antimicrobials, (3) simple chemical preparation from readily available intermediates or chemicals. Further rapid progress has been made towards broadening their spectrum of activity (based on SAR to treat various systemic infections), improving their pharmacokinetic properties and reducing adverse reactions (72, 73). Some of these modern quinolones contain modifications not only in basic ring structure or bearing no fluorine atom at position 6 of the pharmocophore, but also uses new cyclic amines or appropriately substituted nitrogen heterocycles in its 7 position. Despite of explosive growth in the different aspects of quinolones such as structural modification or improvement in pharmacokinetics, pharmacology and toxicity, concerted efforts are being made to design newer compounds possessing excellent dual action properties or multi functional activity with greater clinical efficacy (2) in respiratory, intra-abdominal, pelvic and pediatric infections (74); Based on our present understanding of the mode of action of these compounds on molecular level at the target site. It is inevitable that with increasing use of the quinolones, bacterial resistance will also increase, despite the remarkable features of these new agents. Our present knowledge in the topics provide wide scope for developing newer quinolones to inhibit the highly resistant bacteria (75). Furthermore, it is recognized that new clinical strategies need to be developed to delay or minimize development of the risk of antibiotic resistance, and the quinolones are no exception to this. Strategies may include the more widespread adoption of clinical guidelines advocating the use of appropriate dose/duration and/or combination with other agents, and the continuous monitoring of local resistance patterns.
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