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Review Article

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.

Introduction

Quinolones comprise a relatively large, growing and most interesting group of antibacterial drugs which have made a major impact on the field of antimicrobial chemotherapy, particularly in the past few years (1-3). This is because they potentially offer many of the attributes of an ideal antibiotic, combining high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating concentration in tissues and a potentially low incidence of side-effects. More researches have attempted to make these potential attributes real.

The evolution of quinolones actually emanated

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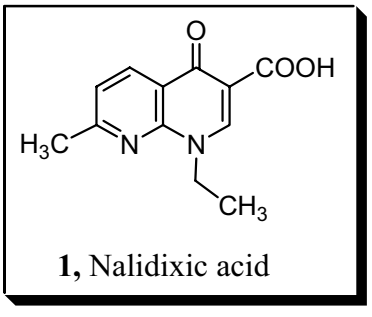
from the discovery of nalidixic acid **1** (4) in 1962 as a by-product of antimalarial research, the first representative of the quinolones which was found effective against some Gram-negative microorganisms and possessed pharmacokinetic properties for treating urinary tract infections (UTIs).

However, following the introduction of nalidixic acid for the treatment of uncomplicated



1, Nalidixic acid

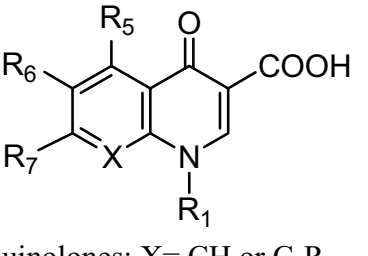
UTIs caused by enteric bacteria, the quinolones became a neglected group of antimicrobials until the development of the fluoroquinolones in the 1970s and 1980s. The fluoroquinolones have an extended spectrum of activity and improved pharmacokinetics compared with the earlier compounds. In two decades, 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 has 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 fluoroqunolones, 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-1*H*- 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 aeroginosa.* 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



quinolones: X= CH or C-R_8
naphthyridones: X= N

Figure 1. Common structure of 4-quinolones.

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 napththyridones 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 sparfloxacin **10** which otherwise has a very similar structure to

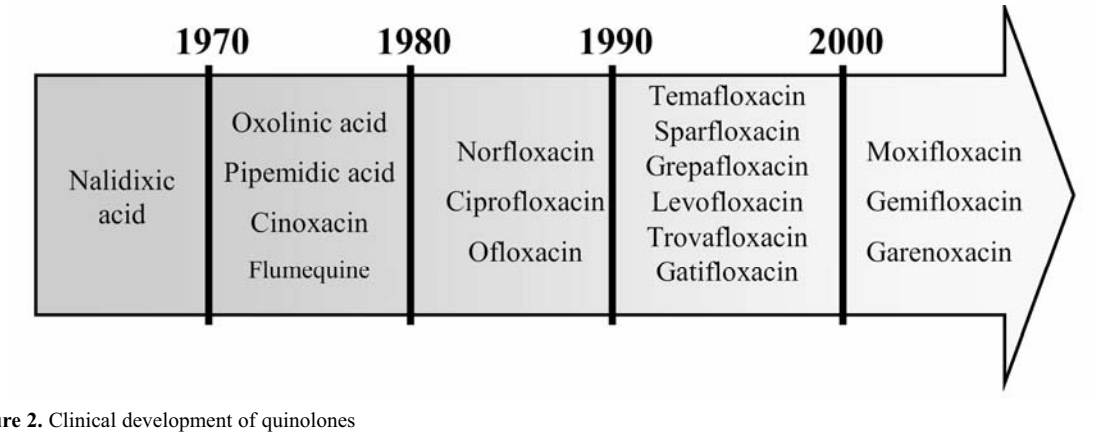


Figure 2. Clinical development of quinolones

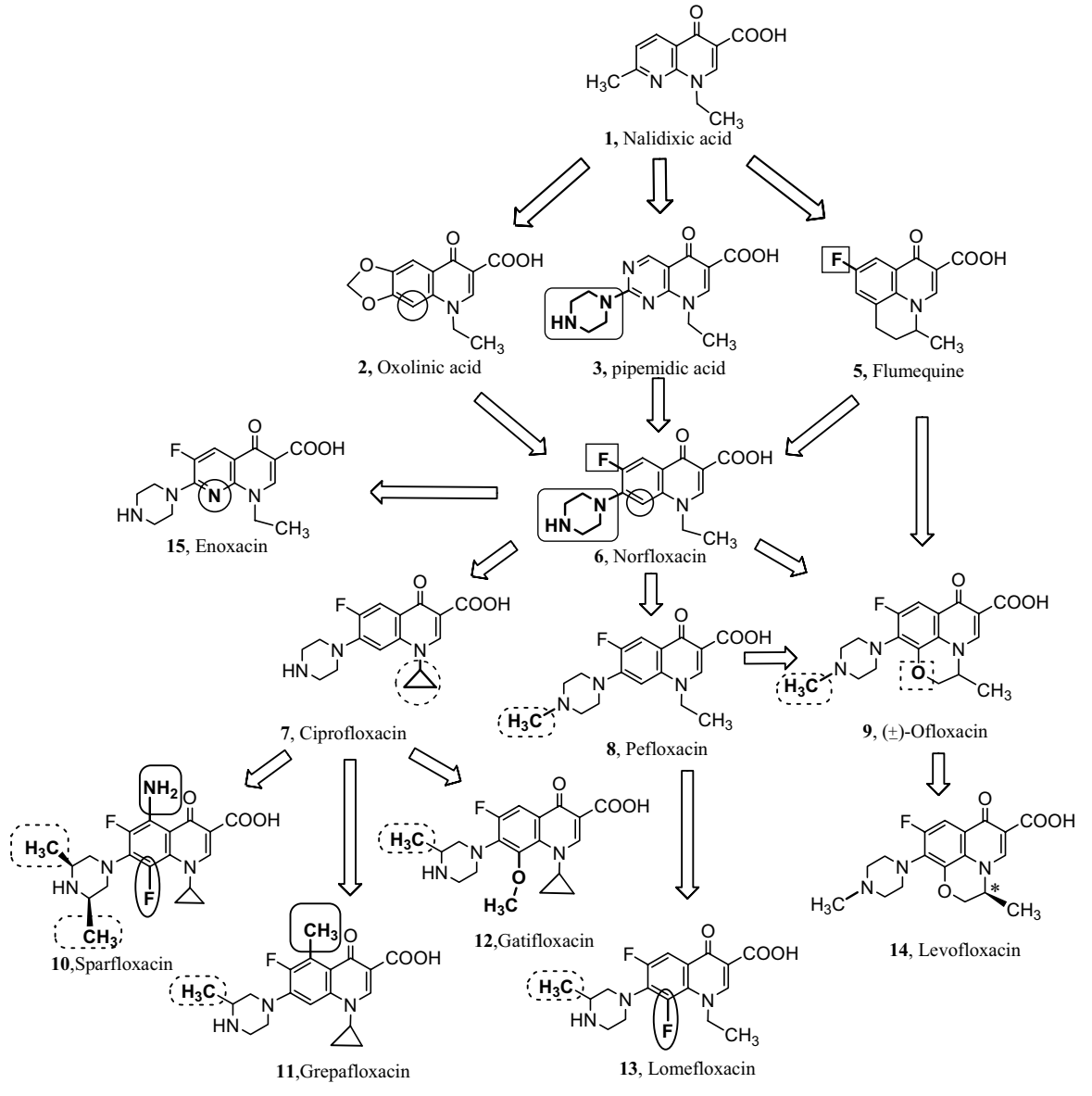
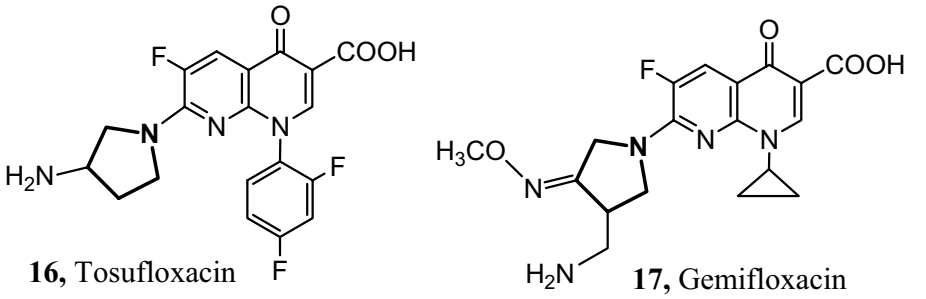


Figure 3. Structural development of 7-piperazinylquinolones from primary quinolones

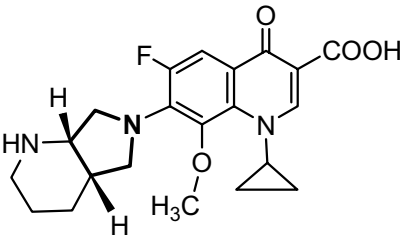
ciprofloxacin. Sparfloxacin also has a fluorine at position C-8, a piperazine at position C-7 and is alkylated (17). Grepafloxacin **11** is also substituted at position C-5 but by a CH_3 group which improved anti-Gram-positive potency compared with ciprofloxacin (18). Other new quinolones containing 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 infectins.

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

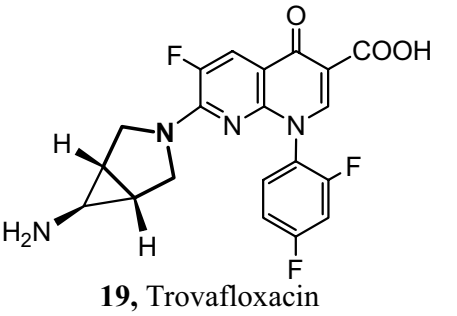


16, Tosufloxacin

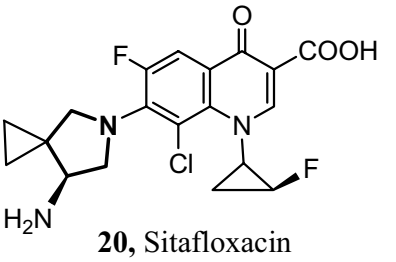
17, Gemifloxacin



18, Moxifloxacin



19, Trovafloxacin



20, Sitafloxacin

Figure 4. Quinolones containing pyrrolidine skeleton at C-7 position

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).

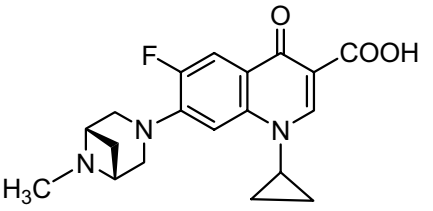
Manipulation of the group at position 8 has also been shown to play a role in altering oral pharmacokinetics, broadening the spectrum of activity and reducing the selection of mutants (22-25). Whilst alkylation has been shown to increase further anti-Gram-positive activity, it also improves tissue penetration 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).

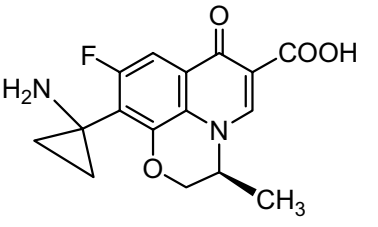
Thus, continuous efforts were directed to further modify the quinolone pharmacophore with more complex newer fluroquinolones, namely danofloxacin **21**, pazufloxacin **22**, clinafloxacin **23** and prulifloxacin **24** (Fig. 5).

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).

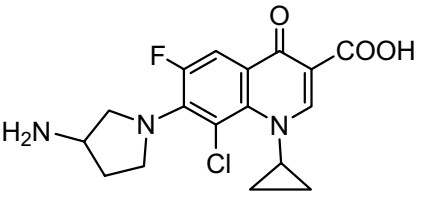
The targets in fluoroquinolone research during the last few years include improving the pharmacokinetic properties, increasing the activity against Gram-positive cocci and



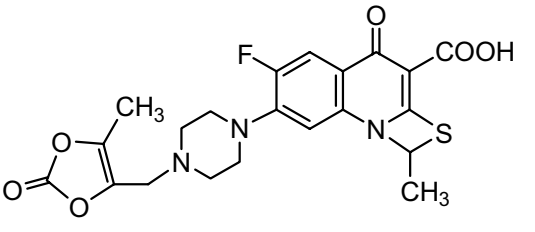
21, Danofloxacin



22, Pazufloxacin



23, Clinafloxacin



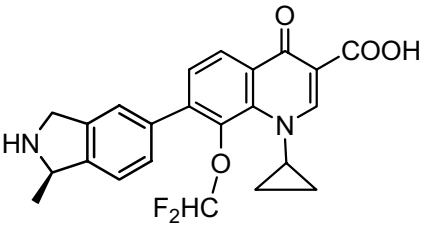
24, Prulifloxacin

Figure 5

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).



25, Garenoxacin

Figure 6. Structure of garenoxacin, a 6-desfluoroquinolone

Stracture-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 essentioally required for hydrogen bonding interactions with DNA bases in the single-stranded regions of dublex 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

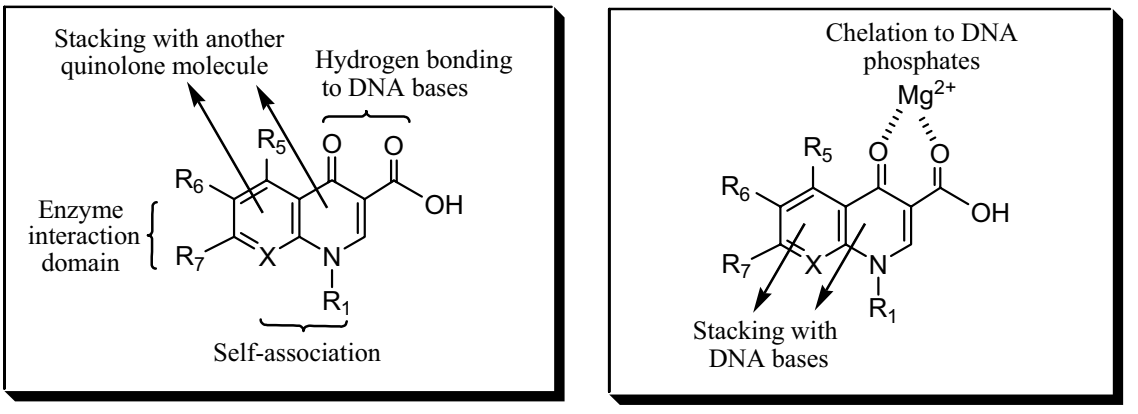


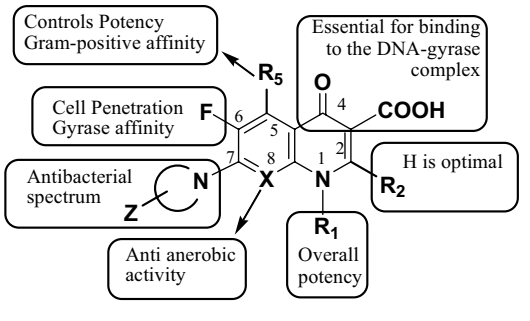
Figure 7. Two binding models of quinolones

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



R_1= Et, cyclopropyl, halo substituted aromatic ring , etc.
R_2= H, -SMe, or R_1& R_2 may join to form a ring.
R_5= H, -NH_2 ,-OMe
X= N, CH, CF, C-OMe, or X & R_1 may join to form a ring.
Z= attached group to cycloalkylamine ring.

Figure 8. Common structural features of quinolones

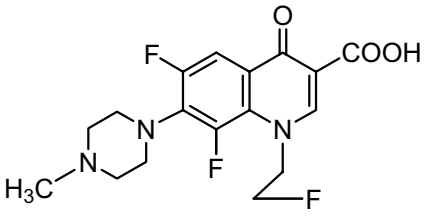
X-ray crystallography and molecular modeling studies, It has been observed that in N-1 aryl substituted quinolones, the N-1 aryl ring is twisted out of the plane of the quinolone nucleus (21, 38). Another structure at this position is found in ofloxacin **9**, levofloxacin **14**, pazufloxacin **22**, nadifloxacin **28** and rufloxacin **29** which has a fused ring between positions 1 and 8 (Fig. 10).

Position 2

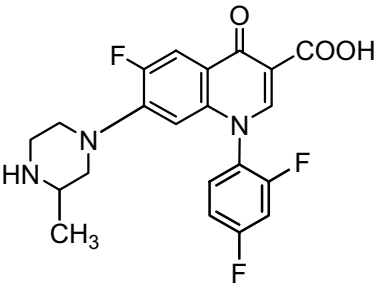
Very little is known about the SAR of quinolone having substituents at C-2 position; as loss of bioactivity has been found with methyl, hydroxyl or methylthio substituents. However a ring between C-1 and C-2 position was shown to have biological activity. The C-2 position is left unsubstituted because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



26, Fleroxacin



27, Temafloxacin

Figure 9. Structure of two quinolones with certain substituent at N-1

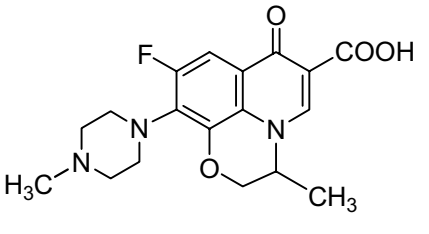
grepafloxacin **11** with a methyl group at C-5 exhibits increased activity (9-14).

Position 6

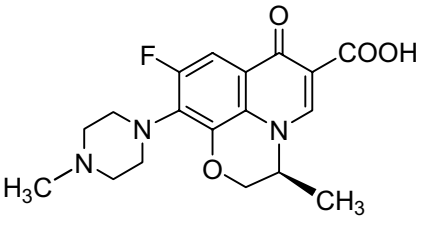
Several substituents besides fluorine have been introduced into position 6. All of the quinolones having those substituents were less active than 6-fluoroquinolones. The influence of fluorine at C-6 is essential for high activity as evidenced by its enhanced gyrase inhibition and cell penetration which 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 **25**, show greater potency than the newer fluoroquinolone moxifloxacin **18** against both sensitive and resistant Gram-positive organisms, thus casting doubt on the validity of the necessity of the C-6 fluorine. Garenoxacin **25** 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 (39). Recently, fluorine at C-6 is replaced by NO_2 group to get highly potent nitroquinolones (40). They are potent inhibitor of *Streptococcus* and *Staphylococcus* species.

Position 7

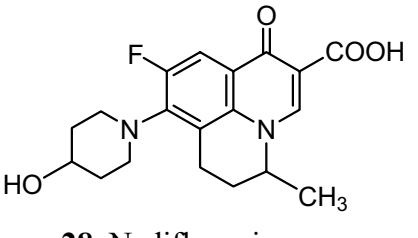
Substituent at position 7 are closely associated with properties of the quinolones such as their antibacterial spectrum, bioavailability, and side effects. Introduction of a basic group at C-7 of the quinolone ring was found to enhance antibacterial activity, as this substituent greatly influences antibacterial 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



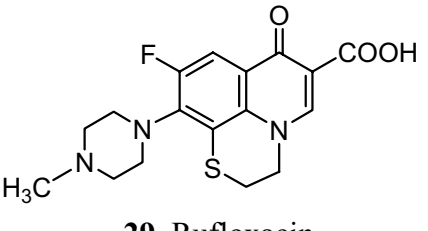
9, Ofloxacin



14, Levofloxacin

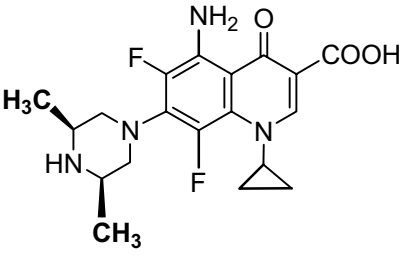


28, Nadifloxacin

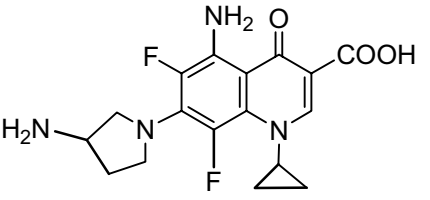


29, Rufloxacin

Figure 10. Tricyclic quinolones



10, Sparfloxacin

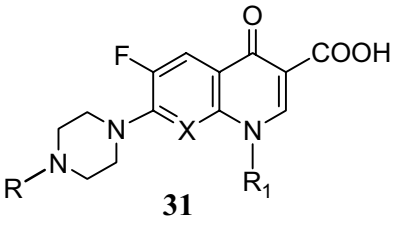


30, PD 124816

Figure 11. 5-Aminoquinolones: sparfloxacin and PD 124816

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



31

X= CH, N
R_1= Et, c-Pr
R= bulky groups

Figure 12. General structure of *N*-substituted piperazinylquinolones

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.

Stracture-side effect relationships

The structural changes to the quinolone molecule and correlation with adverse events are now well documented (13, 57). Photo-reactivity is probably mostly influenced by position 8, with fluorine 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 NH_2 or a CH_3 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

Quinolone 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 antibiotics, (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 hetrocycles in its 7 position. Despite of explosive growth in the different aspects of quinolones such as structural modification or improvement in pharmocokinetics, 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.

References

(1) Gootz TD, Brighty KE. Chemistry and mechanism of action of the quinolone antibacterials. In: Andriole VT (ed.), *The Quinolones*. 2nd ed. Academic Press, San Diego (1998) 29-80

(2) Andriole VT. The future of the quinolones. *Drugs* (1999) 58 (Suppl 2): 1-5

(3) Hooper DC. Mode of action of fluoroquinolones. *Drugs* (1999) 58 (Suppl 2): 6-10

(4) Lescher GY, Froelich EJ, Gruett MD, Bailey JH and Brundage RP. 1,8-Naphthyridine derivatives: a new class of chemotherapy agents. *J. Med. Pharm. Chem.* (1962) 5: 1063–8

(5) Appelbaum PC and Hunter PA. The fluoroquinolone antibacterials: past, present and future perspectives. *Int. J. Antimicrob. Agents* (2000) 16: 5–15

(6) Price JR. Some reactions of 1-methyl-4-quinolone-3-carboxylic acid, a degradation product of the alkaloids. *Aust. J. Sci. Res*. (1949) 2A: 272-281

(7) Barton N, Crowther AF, Hepworth W, Richardson DN and Driver GW. New quinolones and therapeutic compositions containing them. *GB* 830832 (1960) [*Chem. Abstr.* (1961) 55: 7442e]

(8) Wise R. Norfloxacin – a review of pharmacology and tissue penetration. *J. Antimicrob. Chemother.* (1984) 13 (Suppl. B): 59–64

(9) Norris S, Mandell GL. The quinolones: history and overview. In: Andriole VT (ed.) *The Quinolones*. Academic Press, San Diego (1988) 1- 22

(10) Norrby SR. Treatment of urinary tract infections with quinolone antimicrobial agents. In: Hooper DC, Wolfson JS (eds.) *Quinolone Antimicrobial Agents.* 2nd ed. American Society for Microbilogy, Washington DC (1993) 273-83

(11) Domagala JM. Structure-activity and structure side effect relationships for the quinolone antibacterials. *J. Antimicrob. Chemother.* (1994) 33: 685–706

(12) Tillotson GS, Blondeau JM. Structure–activity–function evaluation of the fluoroquinolones. In: Adam D, Finch RG, Hunter PA (eds.) *Moxifloxacin in Practice*. Maxim Medical, Oxford (1999) 91–101

(13) Asahina Y, Ishizaki T and Suzue S. Recent advances in structure activity relationships in new quinolones. *Prog. Drug Res.* (1992) 38: 57–106

(14) Tillotson GS. Quinolones: structure–activity relationships and future predictions. *J. Med. Microbiol.* (1996) 44: 320–4

(15) Ball P, Fernald A and Tillotson G. Therapeutic advances of new fluoroquinolones. *Expert Opin. Inv. Drugs* (1998) 7: 761–83

(16) Koga H, Itoh A, Murayama S, Suzue S and Irikura T. Structure-activity relationships of antibacterial 6,7- and 7,8-disubstituted 1-alkyl-1,4-dihydro-4-oxoquinoline-3-carboxylic acids. *J. Med. Chem*. (1980) 23: 1358-63

(17) Jaillon P, Morganroth J, Brumpt I and Talbot G. Overview of electrocardiographic and cardiovascular safety data for sparfloxacin. Sparfloxacin Safety Group. *J. Antimicrob. Chemother.* (1996) 37 (Suppl. A): 161–7

(18) Wiedemann B and Heisig P. Antibacterial activity of grepafloxacin. *J. Antimicrob. Chemother.* (1997) 40 (Suppl. A): 19–25

(19) Lowe MN and Lamb HM. Gemifloxacin. *Drugs* (2000) 59: 1137–47

(20) Ball P. Moxifloxacin (Avelox): an 8-methoxyquinolone antibacterial with enhanced potency. *Int. J. Clin. Pract.* (2000) 54: 329–32

(21) Brighty KE and Gootz TD. The chemistry and biological profile of trovafloxacin. *J. Antimicrob. Chemother.* (1997) 39 (Suppl. B): 1–14

(22) Dong Y, Xu C, Zhao X, Domagala J. and Drlica K. Fluoroquinolone action against mycobacteria: effects of C-8 substituents on growth, survival, and resistance. *Antimicrob. Agents Chemother.* (1998) 42: 2978–84

(23) Lu T, Zhao X and Drlica K. Gatifloxacin activity against quinolone-resistant gyrase: allele-specific enhancement of bacteriostatic and bactericidal activities by the C-8-methoxy group. *Antimicrob. Agents Chemother.* (1999) 43: 2969–74

(24) Cecchetti V, Fravolini A, Lorenzini MC, Tabarrini O, Terni P and Xin T. Studies on 6-aminoquinolones: synthesis and antibacterial evaluation of 6-amino-8-methylquinolones. *J. Med. Chem.* (1996) 39: 436–45

(25) Ma Z, Chu DT, Cooper CS, Li Q, Fung AK, Wang S, Shen LL, Flamm RK, Nilius AM, Alder JD, Meulbroek JA and Or YS. Synthesis and antimicrobial activity of 4H-4-oxoquinolizine derivatives: consequences of structural modification at the C-8 position *J. Med. Chem.* (1999) 42: 4202–13

(26) Spangler SK, Jacobs MR and Appelbaum PC. Susceptibility of anaerobic bacteria to trovafloxacin: comparison with other quinolones and non-quinolone antibiotics. *Infect. Dis. Clin. Pract.* (1996) 5 (Suppl. 3): S101–9

(27) Dalhoff A and Schmitz F-J. *In vitro* antibacterial activity and pharmacodynamics of new quinolones. *Eur. J. Clin. Microbiol. Infect. Did.* (2003) 22: 203-221

(28) Fung-Tomc J, Minassian B, Kolek B, Washo T, Huczko E and Bonner D. *In vitro* antibacterial spectrum of a new broad-spectrum 8-methoxy fluoroquinolone, gatifloxacin. *J. Antimicrob. Chemother.* (2000) 45: 437–446

(29) Garcia-Garrote F, Cercenado E, Martin-Pedroviejo J, Cuevas O and Bouza E. Comparative *in-vitro* activity of the new quinolone gemifloxacin (SB-265805) with other fluoroquinolones against respiratory tract pathogens. *J. Antimicrob. Chemother.* (2001) 47: 681–684

(30) Kim JH, Kang JA, Kim YG, Kim JW, Lee JH, Choi EC and Kim BK. *In vitro* and *in-vivo* antibacterial efficacies of CFC-222, a new fluoroquinolone. *Antimicrob. Agents Chemother.* (1997) 41: 2209–2213

(31) Hooper D. Quinolones. In: Mandell GL, Bennett JE, Dolin R (eds.) *Mandell, Douglas, and Bennett's Principles and practice of infectious diseases.* 5th ed.

Churchill Livingstone, Philadelphia (2000) 404-23
(32) Hooper DC and Wolfson JS. *Quinolone antimicrobial agents.* 2d ed. American Society for Microbiology (1993) 53-7
(33) Palù G, Valisena S, Ciarrocchi G, Gatto B and Palumbo M. Quinolone binding to DNA is mediated by magnesium ions. *Proc. Natl. Acad. Sci. USA* (1992) 89: 9671-5
(34) De Sarro A and De Sarro G. Adverse reactions to fluoroquinolones. an overview on mechanistic aspects. *Current Med. Chem.* (2001) 8: 371-84
(35) Domagala JM, Heifetz CL, Hutt MP, Mich TF, Nichols JB, Solomon M and Worth D F. 1-Substituted 7-[3-[(ethylamino)methyl]-1-pyrrolidinyl]-6,8- difluoro-1,4-dihydro-4-oxo-3-quinolinecarboxylic acids. New quantitative structure-activity relationships at N1 for the quinolone antibacterials. *J. Med. Chem.* (1988) 31: 991-1001
(36) Chu DTW, Fernandes PB, Claiborne AK, Pihuleac E, Nordeen CW, Maleczka RE and Pernet AG. Synthesis and structure-activity relationships of novel arylfluoroquinolone antibacterial agents. *J. Med. Chem*. (1985) 28: 1558-64
(37) Bryskier A and Chantot JF. Classification and structure-activity relationships of fluoroquinolones. *Drugs* (1995) 49: 16-28
(38) Ohta M and Koga H. Three-dimensional structure-activity relationships and receptor mapping of N_1-substituents of quinolone antibacterials. *J. Med. Chem.* (1991) 34: 131-9
(39) Lawrence LE, Wu P, Fan L, Gouveia KE, Card A, Casperson M, Denbleyker K and Barret JF. The inhibition and selectivity of bacterial topoisomerases by BMS-284756 and its analogues. *J. Antimicrob. Chemother.* (2001) 48: 195-201
(40) Artico M, Mai A, Spardella G, Massa S, Musiu C, Lostia S, Demontis F and La Colla F. Nitroquinolones with broad-spectrum antimycobacterial activity *in-vitro*. *Bioorg. Med. Chem. Lett.* (1999) 9: 1651-6
(41) Anderson VE and Osheroff N. Type II topoisomerases as targets for quinolone antibacterials. *Curr. Pharm. Des.* (2001) 7: 337-53
(42) Shen LL, Mitscher LA, Sharma PN, O'Donnell T. J, Chu DWT, Cooper CS, Rosen T and Pernet AG. Mechanism of inhibition of DNA gyrase by quinolone antibacterials: a cooperative drug-DNA binding model. *Biochemistry* (1989) 28: 3886-94
(43) Foroumadi A, Emami S, Davood A, Moshafi MH, Sharifian A, Tabatabaiee M, Tarhimi Farimani H, Sepehri G and Shafiee A. Synthesis and *in-vitro* antibacterial activities of N-substituted piperazinyl quinolones. *Pharm. Sci.* (1997) 3: 559-563
(44) Foroumadi A, Emami S, Haghighat P and Moshafi MH. Synthesis and *in-vitro* antibacterial activity of new N-substituted piperazinyl quinolones. *Pharm. Pharmacol. Commun.* (1999) 5: 591-4
(45) Foroumadi A, Davood A, Mirzaei M, Emami S and Moshafi MH. Synthesis and antibacterial activity of some novel N-substituted piperazinyl quinolones. *Boll. Chim. Farm.* (2001) 140: 411-16
(46) Foroumadi A, Soltani F, Emami S and Davood A. Antituberclusis agents. III. *In vitro* evaluation of antimycobacterial activity and cytotoxicity of some N-substituted piperazinyl quinolones. *Boll. Chim. Farm.* (2002) 141: 247-9
(47) Foroumadi A, Ashraf-Askari R, Moshafi MH and Emami S. Synthesis and in-vitro antibacterial activity of N-[5-(5-nitro-2-furyl)-1,3,4-thiadiazol-2-yl]piperazinyl quinolone derivatives. *Pharmazie* (2003) 58: 432-33
(48) Mirzaei M and Foroumadi A. Synthesis and *in-vitro* antibacterial activity of *N*-piperazinyl quinolone derivatives with a 2-thienyl group. *Pharm. Pharmacol. Commun.* (2000) 6: 351-4
(49) Foroumadi A, Mansouri S, Kiani Z and Rahmani A. Synthesis and *in-vitro* antibacterial evaluation of *N*-[5-(5-nitro-2-thienyl)-1,3,4-thiadiazole-2-yl] piperazinyl quinolones. *Eur. J. Med.Chem.* (2003) 38: 851-4
(50) Foroumadi A, Soltani F, Moshafi MH and Ashraf-Askari R. Synthesis and *in-vitro* antibacterial activity of some N-(5-aryl-1,3,4-thiadiazole-2-yl)piperazinyl quinolone derivatives. *Il Farmaco* (2003) 58: 1023-28
(51) Kondo H, Sakamoto F, Koders Y and Tsukamoto G. Studies on prodrugs. 5. Synthesis and antimicrobial activity of N-(oxoalkyl)norfloxacin derivatives. *J. Med. Chem.* (1986) 29: 2020-4
(52) Fang K C, Chen Y L, Sheu J Y, Wang T C and Tzeng C C. Synthesis, antibacterial, and cytotoxic evaluation of certain 7-substituted norfloxacin derivatives. *J. Med. Chem.* (2000) 43: 3809-12
(53) Sheu J Y, Chen Y L and Tzeng C C. Synthesis, and antimycobacterial and cytotoxic evaluation of certain fluoroquinolone derivatives. *Helv. Chim. Acta* (2003) 86: 2481-9
(54) Wise R, Andrews JM and Brenwald N. The *in-vitro* activity of Bay y 3118, a new chlorofluoroquinolone. *J. Antimicrob. Chemother.* (1993) 31: 73-80
(55) Hong CY, Kim YK, Chang JH, Kim SH, Choi H, Nam DH, Kim YZ and Kwak JH. Novel fluoroquinolone antibacterial agents containing oxime-substituted (aminomethyl)pyrrolidines: synthesis and antibacterial activity of 7-(4-(aminomethyl)-3-(methoxyimino)pyrrolidin-1-yl)-1-cyclopropyl-6- fluoro-4-oxo-1,4-dihydro[1,8]naphthyridine-3-carboxylic acid (LB20304). *J. Med. Chem*. (1997) 40: 3584-93
(56) Zhao X, Wang JY, Xu C, Dong Y, Zhou J and Domagala J and Drlica K. Killing of *Staphylococcus aureus* by C-8-methoxy fluoroquinolones. *Antimicrob. Agents Chemother.* (1998) 42: 956–8
(57) Gootz TD and Brighty KE. Fluoroquinolone antibacterials: SAR mechanism of action, resistance, and clinical aspects. *Med. Res. Rev.* (1996) 16: 433–86
(58) Lipsky BA and Baker CA. Fluoroquinolone toxicity profiles: a review focusing on newer agents. *Clin. Infec. Dis.* (1999) 28: 352–64

(59) Blum MD, Graham DJ and McCloskey CA. Temafloxacin syndrome: review of 95 cases. *Clin. Infec. Dis.* (1994) 18: 946–50
(60) Ball P, Mandell L, Niki Y and Tillotson G. Comparative tolerability of the newer fluoroquinolone antibacterials. *Drug Safety* (1999) 21: 407–21
(61) Yamamoto T, Tanida T, Ueta E, Kimura T, Doi S and Osaki T. Pulmonary infiltration with eosinophilia (PIE) syndrome induced by antibiotics, PIPC and TFLX during cancer treatment. *Oral Oncology* (2001) 37: 471–5
(62) Zhanel GG, Ennis K, Vercaigne L, Walkty A, Gin AS, Embil J, Smith H and Hoban DJ. A critical review of the fluoroquinolones: focus on respiratory infections. *Drugs* (2002) 62: 13–59
(63) Rubinstein E. History of quinolones and their side effects. *Chemotherapy* (2001) 47 (Suppl. 3): 3–8
(64) Owens RC Jr and Ambrose PG. Clinical use of the fluoroquinolones. *Med. Clin. North Am.* (2000) 84: 1447-69
(65) Ambrose PG, Owens RC Jr, Quintiliani R and Nightingale CH. New generations of quinolones: with particular attention to levofloxacin. *Conn. Med.* (1997) 61: 269-72
(66) Hooper DC. New uses for new and old quinolones and the challenge of resistance. *Clin. Infect. Dis.* (2000) 30: 243-54
(67) No authors listed. Gatifloxacin and moxifloxacin: two new fluoroquinolones. *Med. Lett. Drugs Ther.* (2000) 42: 15-7
(68) Eliopoulos GM. Activity of newer fluoroquinolones *in-vitro* against gram-positive bacteria. *Drugs* (1999) 58(suppl 2): 23-8
(69) Applebaum PC. Quinolone activity against anaerobes. *Drugs* (1999) 58 (suppl 2): 60-4
(70) Piddock LJ. Mechanisms of fluoroquinolone resistance: an update 1994-1998. *Drugs* (1999) 58: 11-8
(71) Masecar BL, Clelesk RA and Robillard H. Analysis of acquired ciprofloxacin resistance in a clinical strain of Pseudomonas aeruginosa. *J. Antimicrob. Agents Chemother.* (1990) 34: 281-6
(72) Wolfson JS, Hooper DC. Mechanisms of killing of bacteria by 4-quinolones. In: Crumplin GG (ed.) *The 4-Quinolones, Antibacterial Agents in vitro*. Springer-Verlag, London (1990) 53-68
(73) Ball P. Adverse drug reactions: implications for the development of fluoroquinolones. *J. Antimicrob. Chemother.* (2003) 51 (Suppl. S1): 21-7
(74) Jafri HS and McCracken GH Jr. Fluoroquinolones in paediatrics. *Drugs* (1999) 58: 43-8
(75) Nicolle LE. Quinolones in the aged. *Drugs* (1999) 58: 49-51

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