Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIBACTERIAL AGENTS, QUINOLONES

1. Introduction

The fluoroquinolones became one of the most important and successful classes of antibacterial agents in the 1990s (1–4). The rudimentary structure of the fluoroquinolone carboxylic acid (shown below in Fig. 1), depicts the common core, which has been combined with a wide variety of chemical modifications to produce numerous analogues in this class of totally synthetic antibacterial agents. The generic structure in Figure 1 exemplifies the contemporary fluoroquinolones, of which the 6-fluoro-4-oxo-3-quinolinecarboxylic acids are by far the predominant quinolones marketed to the human population. These contemporary fluoroquinolones include ciprofloxacin [85721-33-1],ofloxacin [82419-36-1],levofloxacin [100986-85-4], moxifloxacin [151096-09-2], and gatifloxacin [112811-59-3] (Fig 2).

As shown in Figure 1, two general heterocyclic nuclei are found in this class of compounds. The quinolones contain a single nitrogen at position 1, while the naphthyridones possess a second nitrogen at position 8. While the 6-fluoro series of the quinolones are clinically the most important, there is still interest in the 1,8-naphthyridone analogues.

Early quinolone agents such as the 1,8-naphthyridones, cinnolines, and pyrido[2,3-*d*]pyrimidines were the predecessors of the modern day fluoroquinolones (Fig. 3). These older classes are exemplified by nalidixic acid [389-08-2],cinoxacin [28657-80-9],piromidic acid [19562-30-2], and norfloxacin [70458-96-7]. Although nalidixic acid was the first quinolone-like agent introduced into clinical practice, its clinical utility is currently limited due to its inferior properties, especially when compared to the improved newer quinolones (5).

After the introduction of nalidixic acid in the early 1960s (previously used for urinary tract infections) numerous advances were made in developing structure–activity relationships (SAR) of quinolone antibacterials. These have resulted in improvements in the target specificity (1, 2), the balance of activity against both DNA gyrase and topoisomerase IV (6, 7), antibacterial potency and spectrum (3, 4), pharmacokinetic properties (8), and safety (3, 4). Enhancements in absorption, bioavailability, and tissue distribution have made the quinolones useful for the treatment of a variety of systemic infections including those of the upper and lower respiratory tract, skin, soft tissue, the gastrointestinal tract, bones, joints, and sexually transmitted diseases (3, 4). The broad spectrum of activity, lack of rapidly transmissible resistance, reasonable cost, and acceptable safety of quinolone antibacterial agents has positioned them as a key part of the antimicrobial arsenal available to the physician in both the hospital and community settings (3, 4).

The quinolone antimicrobials have been developed most fully for clinical use in human medicine (9, 10), but they are also used in a limited fashion for the treatment of animal infection (11). The first two generations of the quinolone class, including nalidixic acid, ciprofloxacin, enoxacin, [74011-58-8] ofloxacin, levofloxacin, and sparfloxacin, displayed the greatest potency against gram-negative bacteria but the third generation quinolones, trovafloxacin [147059-72-1], gatifloxacin, and moxifloxacin, also exhibit increased potency against gram-positive bacteria, providing a broader spectrum of activity (3, 4). Bacterial resistance resulting from clinical use has occurred widely in staphylococci (12, 13) and *Pseudomonas aeruginosa* (14). Specifically,

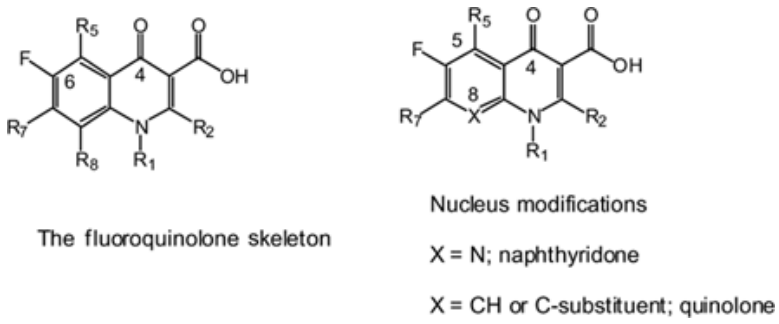


Fig. 1.

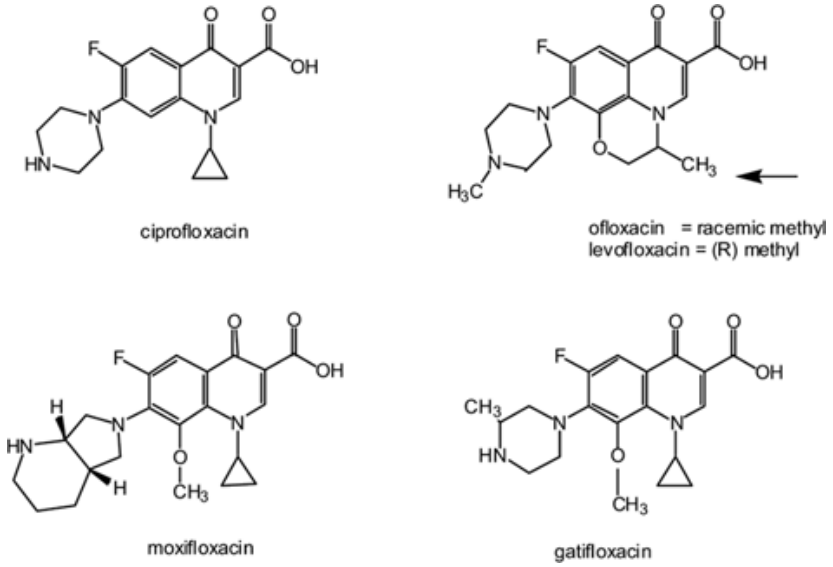


Fig. 2.

increasingly high quinolone resistance is being noted in methicillin-resistant *Staphylococcus aureus* (MRSA) and coagulase-negative staphylococci (12, 13). Widespread clinical use of quinolones and the ability of resistant pathogens to clonally spread have contributed to the development of resistance in more susceptible pathogens such as *Escherichia coli* and *Neisseria gonorrhoeae*, where quinolone usage is high (15–17). The antibacterial activity of the more significant commercialized fluoroquinolone antibacterial agents is summarized in Table 1.

2. Mechanism of Inhibition by Quinolones

The antibacterial targets of quinolones are the two intracellular enzymes, DNA gyrase and topoisomerase IV (6). Both of these enzymes are Type II DNA topoisomerases that modulate the state of genetic material by effecting topological changes in the three-dimensional (3D) structure of DNA, which is 'twisted' during DNA replication (6). Type II topoisomerases achieve their effects by passing an intact DNA helix through a temporary

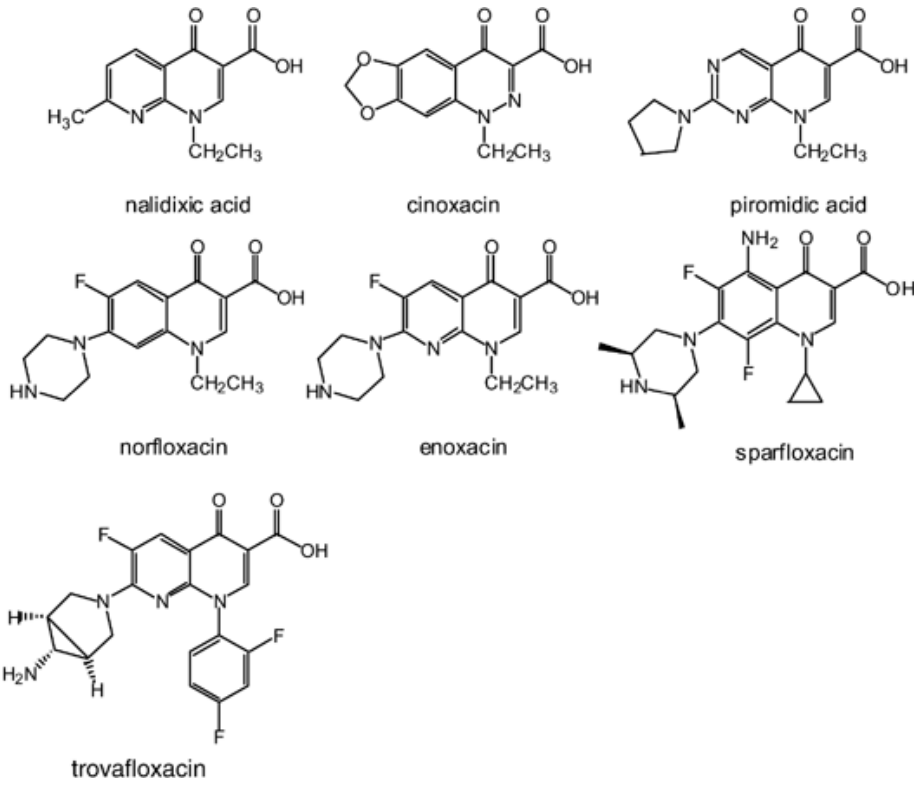


Fig. 3.

double stranded break in another segment of the same DNA molecule facilitated by the tetramer [see figure on page 307 of (56)] of the two A and two B subunits of the topoisomerase. DNA gyrase is involved in controlling DNA supercoiling/relaxation homeostasis (over or underwinding) and relieving the topological stress caused by alterations in linking number by repeated DNA strand passages (see below), during transcription regulation and DNA replication (3). This enzyme introduces negative supercoils into chromosomal and plasmid bacterial DNA (18). Topoisomerase IV functions in the decatenation of daughter chromosomes after replication (19, 20) but also plays a key role in the relaxation of DNA. These enzymes share a common reaction mechanism, in which breaks are introduced into both strands of duplex DNA, after which another strand is passed through the break and finally the DNA breaks are resealed (21, 22).

2.1. Gyrase Inhibition by Quinolones

DNA gyrase was initially recognized as the target for this class of compounds when it was found that the progenitors of modern quinolone compounds, nalidixic acid and oxolinic acid, inhibited the enzyme's activity *in vitro* (23, 24). DNA gyrase exists as a tetramer, with two subunits encoded by the *gyrA* gene and two subunits encoded by the *gyrB* gene making up the complex that is the active enzyme (22, 25, 26). The enzyme has been proposed to have a "two gate" open clamp structure (27) that works by a mechanism depicted in the literature (22). It is believed that initially, a section of double stranded DNA (G strand) enters and passes through the open clamp and associates with the enzyme complex. The gyrase creates a break in each strand of the enzyme bound section of double stranded DNA but the ends of the breaks remain closed, held in place by the top gate of

Table 1. Antibacterial Activity of Fluoroquinolones (MIC_{90}s in μg/mL)[a]

Pathogen	Ciprofloxacin	Norfloxacin[b]	Levofloxacin	Trovafloxacin	Gatifloxacin	Moxifloxacin
Staphylococcus aureus methicillin-S	0.5	2	0.5	0.03	0.12	0.03–0.12
Staphylococcus aureus methicillin-R	16–64	>16	16	1.0–8	2–4	2–4
Streptococcus pneumoniae	2	16	1–2	0.12	0.5	0.25
Enterococcus faecalis	2–64	>16	1–4	0.25–2	4	0.5
Escherichia coli	0.03–0.25	0.25–1	0.06–0.25	0.05–0.5	0.05–1	0.5–1
Klebsiella spp.	0.03–0.25	0.25–1	0.06–1	0.5–1	0.06–0.25	0.06–0.25
Proteus mirabilis	0.06	0.12–0.5	0.12–0.25	0.25–0.5	N/A	0.25
Morganella morgani	0.06	0.12–0.5	0.12	1	4	0.25
Salmonella spp.	0.06	0.25	0.12	0.12	N/A	0.12
P. aeruginosa	0.5–4	2	1–8	1–8	4–32	8
Neisseria spp.	<0.01	0.03	<0.01	<0.01	0.06	0.015
Moraxella catarrhalis	0.03	0.25	0.06	<0.01	0.03	0.12
Haemophilus influenzae	0.015	0.06	0.03	0.01	0.03	0.03
Bacteroides fragilis	2–16	4–32	1–8	0.25–0.5	1–2	0.25–2
Chlamydia pneumoniae	1	N/A	1	0.12	0.12	0.06
Mycoplasma pneumoniae	1–2	N/A	0.5–1	0.25	0.06	0.12
Legionella pneumophila	0.03–0.12	N/A	0.05	0.01–0.06	0.03	0.015

[a] Adapted from (4).
[b] N/A is not applicable.

the enzyme. Approximately 130 base pairs of DNA from the break wrap around the tetrameric holoenzyme in a right-handed configuration. As a result, a second section of double stranded DNA is brought in close proximity to the section of double stranded DNA that was cleaved by the enzyme. This second section of double stranded DNA (the T-strand) is grasped by the clamp portion of the gyrase tetramer and is passed through the top gate while the previously formed DNA breaks in the G strand are simultaneously forced open. The breaks in the first segment of DNA are then resealed thus closing the top gate. Then a bottom gate in the enzyme opens and the DNA is released. The overall result is that one double stranded portion of DNA has been passed through another and the overall supercoiling (twist) in the molecule has been increased. Gyrase can also cause uncoiling (relaxing) rather than supercoiling. The enzyme can catalyze either reaction via the same mechanism by passing an intact segment of DNA from opposite sides (3′ or 5′) of the DNA that is temporarily cleaved. In the process described above, nucleophilic tyrosines create the break in each of the strands of DNA, staggered four base pairs apart. The tyrosines at position 122 (*E. coli* GyrA) of both GyrA subunits form covalent linkages with

the 5′ phosphoryl groups of the resultant broken DNA strands. The 3′ ends are held by noncovalent interactions with the protein, thus forming an enzyme bridge that controls the broken ends (27). adenosinetriphosphate (ATP) supplies the energy required for supercoiling. ATP binding to the 43 kDa-domains of GyrB is postulated to cause the clamp to close around the T-strand and force the breaks in the DNA open in the process described above. Subsequent to passage, the duplex DNA is rejoined, ATP hydrolysis (required for enzyme turnover [21, 27, 28]) by the N terminal regions of GyrB occurs, and the annealed double stranded product is released.

Quinolones have been shown to form a ternary complex with DNA gyrase and DNA (3, 6, 22). Quinolone binding to the enzyme–DNA complex can be dissociated from quinolone-mediated DNA cleavage by DNA gyrase. Several experiments have established that DNA cleavage is not required for drug binding; rather quinolones are believed to stabilize a conformational change that occurs in the DNA gyrase–DNA complex. This conformational change is believed to be the enzyme trapped in the closed gate form. In this model, the DNA cleavage is a result of extended stabilization of the ternary complex rather than a prerequisite of quinolone binding (29–32).

DNA gyrases isolated from quinolone-resistant organisms have changes in amino acids in both the GyrA and GyrB subunits (33, 34). The GyrA changes are more common and occur at amino acids in α helices close to the active site tyrosine. They are formed along a positively charged surface that may act to bind DNA in the region where quinolones bind to the DNA–enzyme complex. This region has been designated the quinolone resistance determining region (QRDR), due to the common changes in key amino acids repeatedly isolated from resistant strains. It is unclear at present whether the GyrB changes leading to resistance are also in proximity to the drug binding site, although recent models suggest that this may be the case in certain conformations of the enzyme (35).

2.2. Topoisomerase IV Inhibition

Recognition of the role of topoisomerase IV in drug action came later, after identification of the enzyme and the finding that some newer quinolones had a higher affinity for this enzyme than for gyrase (36–39). Similar to gyrase, topoisomerase IV consists of two subunits of each of the proteins ParC and ParE (designated GrlA and GrlB in *S. aureus*). Furthermore, there are striking similarities in primary amino acid sequences both in key regions of GyrA and ParC, and regions of GyrB and ParE. Topoisomerase IV is believed to operate very similarly to DNA gyrase, and detailed studies of the interactions of quinolones with topoisomerase IV have been recently published (23, 40, 41). Topoisomerase IV does not, however, wrap the DNA in the region adjacent to the scission site around the enzyme, as is the case with DNA gyrase (42). It plays a critical role in chromosome segregation by catalyzing intermolecular strand passage (decatenation) as well as relaxing DNA *in vivo* (19). The latter role indicates that this enzyme, along with DNA gyrase, plays an important role in maintaining levels of DNA supercoiling. Resistance to quinolones can arise by point mutations that lead to changes in the amino acid sequence of ParC and, less commonly, ParE in regions that are similar in the structure of the protein and in sequence to the QRDR areas in GyrA and GyrB (as described above). As described below, with certain combinations of antibiotics and bacteria, either GyrA or ParC can be the primary target for quinolone inhibition. First level resistance mutants will arise in the primary target for a given drug and bacterium. A recent compilation of fluoroquinolone resistance changes in the target proteins among a broad range of bacteria has been published (42).

2.3. Dual Inhibition (DNA Gyrase and Topoisomerase IV)

In gram-negative bacteria, DNA gyrase appears to be the primary target of quinolones while in gram-positive species, topoisomerase IV assumes that role (23). Most of the early studies were performed with *E. coli* gyrase and early generation quinolones (20, 21). When topoisomerase IV was discovered and purified from *E. coli*, it was found that it could also be inhibited by quinolones but higher concentrations were required (43, 44).

Mutants of *S. aureus* that were moderately resistant to ciprofloxacin, have been found to have amino acid changes in the QRDR of ParC (GrlA), rather than GyrA, which suggests that the primary target for quinolones in *S. aureus* is topoisomerase IV (45). Similarly, the emergence of resistance to ciprofloxacin in *S. pneumoniae* is associated with amino acid changes in ParC in moderately resistant strains, but higher resistance in *S. pneumoniae* and *S. aureus* is associated with both ParC and GyrA changes (46, 47). Subsequently, it was found that sparfloxacin [110871-86-8], a newer quinolone, preferred GyrA as a target in *S. pneumoniae*, as mutations resulting in resistance arose first in this protein (48). Clinafloxacin [105956-97-6] has also been found to target both enzymes, with a slightly greater potency for DNA gyrase (49). Measurements of *in vitro* inhibition of *S. pneumoniae* enzymes (GyrAB and ParCE) with quinolones led to the unexpected finding that topoisomerase IV was more sensitive to all the quinolones in *S. pneumoniae* than DNA gyrase (49). This is at variance with mutational studies, in which different drugs select different primary resistance mutations. These results were interpreted as a possible difference in the actual killing pathway of the two targets, which is a complex process involving downstream events necessary to convert the drug–enzyme–DNA complex (cleavable complex measured in the *in vitro* experiments) into a lethal double stranded break (34). The authors postulate that cleavable complex formation through topoisomerase IV or gyrase may be more lethal for some quinolones than for others (48, 49).

The idea that it may be possible to optimize the future design of fluoroquinolones with regard to target specificity is raised with a series of C-7 modified molecules based on ciprofloxacin (50). It was possible to change the target specificity from topoisomerase IV to gyrase in *S. pneumoniae* by the addition of benzenesulfonylamido groups to the C-7 piperazinyl ring. This raises the possibility of generating compounds that are equally effective against both gyrase and topoisomerase IV (50). Such a compound would demand mutations in gyrase and topoisomerase IV for resistance to occur. Strains with double mutations would be expected to be rarer and slower to develop than those with only a single change.

2.4. Quinolone Lethality

The earliest experiments indicated that quinolones rapidly inhibited DNA synthesis in bacteria (3, 4, 51). However, inhibition of DNA synthesis was reversible upon removal of the drug. Several additional lines of evidence led to the conclusion that inhibition of DNA synthesis is itself not the lethal event in quinolone-induced killing. The interactions of fluoroquinolone compounds with bacteria lead to the formation of a quinolone–enzyme–DNA complex, with either gyrase or topoisomerase IV as the enzyme (52, 53). This complex contains DNA that has two single stranded breaks within the complex. A key finding is that the complex formation is reversible (6, 52, 53). Thus the formation of the complex itself is also not the lethal event. It is believed that cell death results from the release of double stranded DNA breaks from the drug–enzyme–DNA complex (51–53), which is based on studies in which the sedimentation of chromosomes from quinolone-treated and untreated bacteria are compared (52). The DNA breaks in the drug–enzyme–DNA complex are released, leading to lethal double stranded breaks that can be observed as a change in sedimentation velocity in sucrose gradient centrifugation. It is currently postulated that quinolone treatment may also induce expression of a protein that leads to the release of the topoisomerase (gyrase or topoisomerase IV) from the complex and release of the DNA with the double strand break (52, 53). Thus, there are two steps to quinolone action: formation of bacteriostatic drug–enzyme–DNA complexes, followed by release of lethal double stranded DNA breaks (53). Quinolones may vary in their ability to promote the second step, thereby leading to differences in lethality. Quinolones are known to induce the SOS response pathway, but the occurrence of cell lethality as a result has not been developed (4).

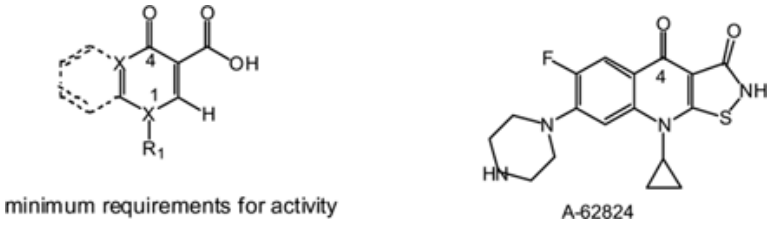


Fig. 4.

3. Structure–Activity Relationships

Many quinolone analogues have been prepared to date and a number of reviews of the extensive SAR have been published (1, 5, 54–57). The structural features that are essential for meaningful antibacterial activity in this class of compounds are the pyridone carboxylic acid and a small alkyl, aryl, or heteroaryl group in the 1-position (Fig. 4). Monocyclic 2-and 4-pyridones retain some activity but all of the clinically important compounds contain a second fused ring (Fig. 4) (58, 59). The essential carboxylic acid at position 3 has been replaced with prodrug moieties such as aldehydes or esters that generate the key carboxylic acid after dosing (56). The replacement of the carboxylate with an isothiazolone ring fused between the 2- and 3-position of the quinolone nucleus is described in most recent quinolone SAR reviews but this modification is not utilized in any clinically important or notable compounds (60, 61). A-62824 [111279-87-9] (62) illustrates this structural modification as applied to ciprofloxacin (Fig. 4).

Replacement of the 4-keto moiety has not been successful. The hydrogen at position 2 is also maintained in compounds with clinical importance and only a few, nonsterically demanding fused substituents at this position have been identified, which do not appreciably reduce antibacterial activity (56).

The important clinical compounds of the last decade and many highly active preclinical newer generation quinolones have a fluorine attached to the 6-position. The 6-fluorine substituent frequently provides a significant enhancement in antibacterial activity and a broader antimicrobial spectrum, presumably by increasing cellular penetration (9, 63) and by increasing the innate inhibitory activity against the target enzymes. The fluorine can provide greater than 10-fold increases in gyrase inhibition and up to 100-fold enhancements in MIC. In some cases, the effect of the 6-fluorine is much smaller, depending on the group at the 7-position (64, 65). The 6-fluoro substituent has also been incorporated into the naphthyridone nucleus where enoxacin, trovafloxacin (Fig. 3), tosufloxacin [100490-36-6], andgemifloxacin [175463-14-6] (Fig. 5), are the compounds of clinical relevance.

Bromo, chloro, methyl, and cyano groups are tolerated at C-6 but do not have the same effect as fluorine. Because the C-6 fluorine may also increase toxicity or other side effects, a current focus of considerable research is to find compounds that lack the 6-fluoro but that retain impressive potency. These are collectively referred to as des-F(6)-quinolones and since the best results have come from compounds containing certain modifications at C-7 these are discussed below.

The 7-position is a key position for modifiying the potency, properties, and spectrum of quinolone antibiotics. While a wide variety of substituents have been evaluated at this position, many of the more recent efforts have employed heteroalicyclic diamines, which generally confer excellent antibacterial properties and selectivity over human topoisomerases. A saturated nitrogen heterocycle is attached via a ring nitrogen to the 7-position and serves to increase antibacterial activity by increasing penetration into the bacterial cell. This heterocycle, which is often a piperazine or pyrrolidine derivative, generally increases gram-negative or gram-positive potency, respectively.

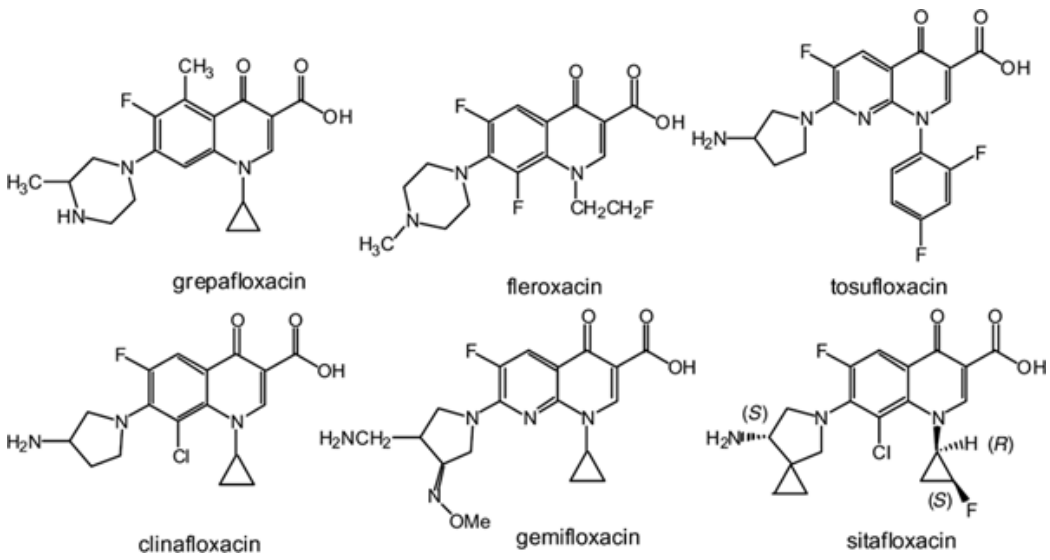


Fig. 5.

Norfloxacin, enoxacin, and ciprofloxacin (Fig. 2 and 5), have an unsubstituted piperazine ring that gives good activity against gram-negative organisms (66). A number of compounds contain substituted piperazines: [119914-60-2]: grepafloxacin, gatifloxacin, and fleroxacin [79660-72-3] have a 3-methyl piperazine, ofloxacin, and levofloxacin a 4-methyl piperazine, and sparfloxacin has a 3,5-dimethyl piperazine. These compounds have greater activity against gram-positive bacteria and the substituted piperazines [119914-60-2] they contain are believed to enhance penetration into the bacterial cell (67,68).

Amino-substituted pyrrolidines confer good activity and generally improve the activity of compounds against gram-positive organisms. For these reasons, a number of novel substitution patterns have been incorporated into the amino pyrrolidine in order to favorably modulate the antibacterial and pharmacokinetic properties of quinolones. Although there are exceptions, in general, both five- and six-membered amino-linked rings at the 7-position require the presence of a second amine for optimal activity. Tosufloxacin and clinafloxacin both have a 3-amino pyrrolidine substituent (Fig. 5). The des-F(6)-quinolone compounds PGE-9262932 [221221-18-7] andPGE-4175997 [341520-51-2] (Fig. 6), incorporate methyl or dimethyl substituents, respectively, on the exocyclic amino-containing methyl moiety. A third member of this series, PGE-9509924 [221221-39-2] (Fig. 6), contains a 3-amino, 4-cyclohexyl group. Gemifloxacin is unusual in that the pyrrolidine ring has a 3-aminomethyl and an additional 4-oximinomethyl group. The oximinoalkyl group on the pyrrolidine provided an opportunity to modulate the antibacterial and pharmacokinetic properties by varying the size of the substituents (69). Gemifloxacin (Fig. 5) provided optimal properties, particularly against gram-positive strains (69). Another novel type of side chain in position 7 is a bicyclic diamine, in which a second ring is fused to the pyrrolidine ring. Moxifloxacin has a diazabicyclic ring and trovafloxacin an azabicyclic ring. Sitafloxacin [127254-12-0] incorporates still another novel C-7 variation, and contains a novel spirocyclopropane moiety on the pyrrolidine ring (Fig. 5). All of these compounds have good activity against gram-positive organisms (70). Wakunaga Seiyaku has published patents claiming broad spectrum quinolones [329014-26-8] and [198013-83-1] (Fig. 7) containing novel hydroxy-azetidine or amino-azetidine substituents that are incorporated into compounds having difluoroanilines or difluoroaminopyridines attached to position 1 (71, 72). Interestingly, some recent des-F(6)-quinolone derivatives have incorporated five- or six-membered ring heteroaryls at C-7 (Fig. 8 and 9).

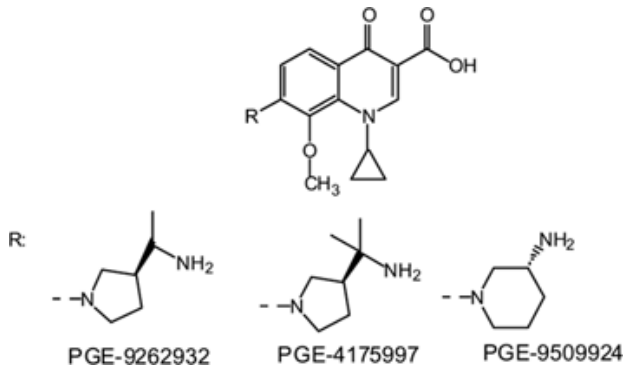
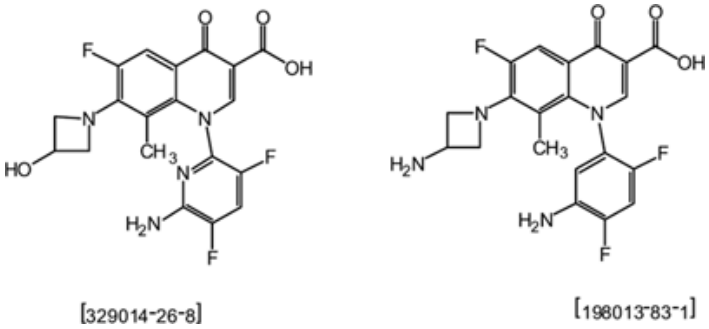


Fig. 6.



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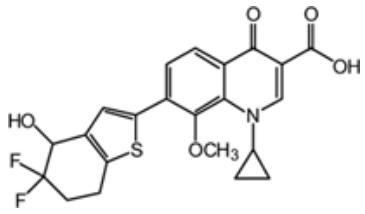

Fig. 8.

Earlier quinolones that contained an ethyl or 2-fluoroethyl group at the 1-position were more active than compounds containing a methyl or propyl group and possessed good activity against gram-negative organisms, particularly *E. coli* (73). Subsequent replacement of the ethyl moieties with a cyclopropyl group provided compounds with major improvements against both gram-negative and gram-positive organisms. The increase in activity afforded by the cyclopropyl substituent compared to the ethyl moiety cannot be explained simply on steric grounds and it has been suggested that through-space electronic interactions may be important (74). The cyclopropyl moiety is incorporated into a majority of the most important quinolones including ciprofloxacin, sparfloxacin, grepafloxacin, clinafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, and BMS-284756 [223652-82-2] (Fig. 9). Sitafloxacin contains a fluorinated cyclopropyl moiety. The 2,4-difluorophenyl group was initially thought to be sub-optimal for potency but tosufloxacin (75) and temafloxacin [105784-61-0] (76) contain this moiety and possess antibacterial activity comparable to that found for the cyclopropyl-containing

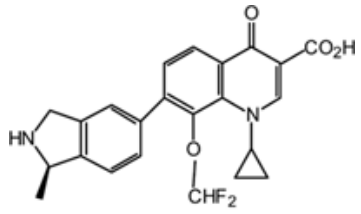

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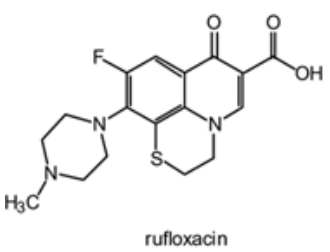
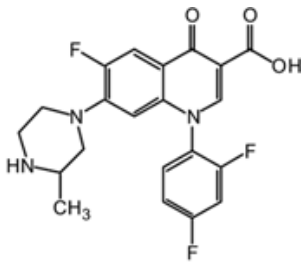
Fig. 9.



rufloxacin



temafloxacin

Fig. 10.

ciprofloxacin. More recently, trovafloxacin, which also possesses a difluorophenyl at position 1, has demonstrated improved activity against gram-positives, although hepatic toxicity has restricted its clinical use (77). The 2,4-difluorophenyl moiety can provide enhanced *in vivo* activity when compared to ciprofloxacin and may slightly enhance activity against anaerobes. Quinolones with a *tert*-butyl group at the 1-position can also compare favorably with ciprofloxacin (78). Introduction of a 1,8-bridge was initially utilized in flumequine, a poorly active analogue; but ofloxacin, its (*R*) isomer levofloxacin (Fig. 2), and rufloxacin [101363-10-4] (Fig. 10), had better activity. It is believed that the 1,4-benzoxazine ring represents a conformationally constrained 1-ethyl group. *in vitro* activity improvements are found to be more or less comparable to the improvements noted with ciprofloxacin (79–82). Removing the methyl group on the 1,8-bridge of ofloxacin and substituting a sulfur in place of the oxygen attached to the 8-position provided rufloxacin. Rufloxacin, although less potent than ofloxacin, was well absorbed and had a longer half-life than ofloxacin (83, 84) (Fig. 10).

Ofloxacin was first sold as the racemate but later the optical isomers were prepared and it was found that the (*S*)-enantiomer, DR 3355 (levofloxacin), was substantially more active (8–128-fold) than the (*R*) isomer against a broad range of bacteria (85–88). This chiral preference is not unique to ofloxacin, having been demonstrated in other quinolones as well (89, 90).

The 5-position of quinolones can be substituted by small groups such as halogens, hydroxyl, or amino (91–93). However, this does not always provide advantages since many of the best optimized quinolones including ciprofloxacin, clinafloxacin, moxifloxacin, gatifloxacin, gemifloxacin, levofloxacin, ofloxacin, sitafloxacin, trovafloxacin, and BMS-284756, contain only a hydrogen at this position. An amino group at the 5-position can be advantageous, as seen for sparfloxacin (94), a compound that displays modest improvements in gram-positive activity as well as increased *in vivo* potency when compared with either ciprofloxacin or ofloxacin. Replacement of the 5-amino group with methylamine or dimethylamine causes activity to drop substantially (95) but the addition of a methyl group at the 5-position imparts improved gram-positive activity to grepafloxacin.

The 8-position of the quinolone nucleus can often be advantageously substituted by fluorine (96) or chlorine (97) to give compounds with improved antibacterial potency over compounds with a hydrogen in this position.

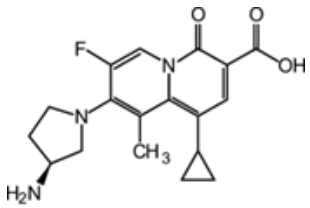
However, the chlorine-containing compounds in particular have been associated with phototoxicity and none of these compounds have yet successfully completed clinical development. Fluorine-containing compounds also have shown phototoxicity, which has limited their utility. A recent and important development, which represents the state of the art, has been the discovery that an 8-alkoxy group can provide good anaerobic activity without causing phototoxicity (54). The potent quinolones gatifloxacin and moxifloxacin both contain an 8-methoxy moiety and have negligible potential for phototoxicity (54). The 8-methoxy group of gatifloxacin, one of the most recently registered compounds to assume a position of clinical importance, has been shown to cause reduced selection for mutant strains (98). Thus, the methoxy group enhances activity against both native and mutant strains of bacteria. Incorporation of a difluoromethyl moiety at C-8 also results in compounds such as BMS-284756, which display improved properties and seem to take advantage of both the positive effects of an 8-alkoxy group and the activity enhancements arising from incorporation of fluorine into the molecule (99–102). BMS-284756 represents one of the more promising des-F(6)-quinolone antibacterials. Another more recent approach, aimed at achieving the same effects, utilized the 8-methoxy group in combination with a novel fluorine containing tetrahydrobenzothiophene at the 7-position to give [339053-37-1] (103).

The relatively simple change of removing the C-6 fluorine from the bicyclic nucleus and incorporating fluorines at the the C-8 position in a difluoromethoxy group resulted in some remarkable and unexpected changes in the properties of this new generation of quinolones (99–102). The first of these des-F(6)-quinolones identified and characterized in detail is BMS-284756 (T-3811), first reported by Toyama Chemical Co. in 1997, and subsequently licensed to Bristol-Myers Squibb.

The structure of BMS-284756 is shown in Fig. 9. BMS-284756 (garenoxacin) contains a 1-(*R*)-2,3-dihydro-1-methyl-1*H*-isoindol-5-yl group at position 7. This molecule exhibits an excellent spectrum of coverage, including some strains frequently not susceptible to quinolones. The broad spectrum of activity and increased potency of BMS-284756 compared to five other quinolones (trovafloxacin, moxifloxacin, levofloxacin, ofloxacin, and ciprofloxacin) against over 400 pathogens was reported (100). BMS-284756 was equal to or more active against gram-positive pathogens than the other quinolones tested (100). BMS-284756 retains *in vitro* activity and displays greater potency against ciprofloxacin-resistant *S. pneumoniae*, as compared to trovafloxacin, moxifloxacin, levofloxacin, ofloxacin, and ciprofloxacin (100). This activity was independently confirmed in several other *in vitro* studies reported showing the same rank-order of susceptibility (based on MIC_{90}s) with BMS-284756 > trovafloxacin > gatifloxacin > levofloxacin > ciprofloxacin against all *S. pneumoniae* isolates (including ciprofloxacin-resistant organisms) (101). BMS-284756 has an advantage in laboratory-based resistance emergence, which may be predictive of clinical outcome when compared to other clinically used quinolones, ie, ciprofloxacin (102).

Similarly, a series of Des-F(6)-quinolones have been reported by Proctor & Gamble (Fig. 6) in which all halogens, including the C-6 fluorine, have been removed from the quinolone (1 (104,105,106,107)).

The strategy in the design of non-fluorinated compounds is based on a desire to move away from the toxicity believed to be associated with the presence of the 6-fluorine. It was found that it was possible to synthesize a series of compounds without this substituent that are as potent *in vitro* and *in vivo* as the fluorinated analogues (105–107). A methoxy group at C-8, in combination with a C-7 diamine, produces a compound with excellent antimicrobial activity that is equipotent with many fluoroquinolones. Profiling of the target specificity of these compounds by monitoring microbial growth (DNA, RNA, protein, and cell wall synthesis) in *S. aureus*, indicated that the DNA synthesis inhibition was similar in potency to that of fluoroquinolones (105–107). In general, the non-fluoroquinolones were found to be rapidly bactericidal *in vitro*, to have *in vivo* potency matching the *in vitro* activities and improved safety profiles (based on animal models). A series of *S. aureus* mutants resistant to the non-fluoroquinolone compounds were selected *in vitro* and found to have mutations at sites outside the QRDR in which fluoroquinolone mutations are usually found. These nontraditional mutations include His_{103}-Tyr and Ser_{52}-Arg in GrlA, Glu*472*-Val in GrlB, and Glu_{477}-Val in GyrB (105–107).



ABT-719

Fig. 11.

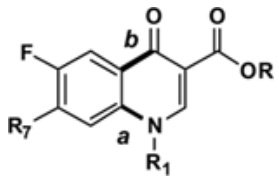


Fig. 12.

3.1. Other Important Approaches

A good deal of research has been focused on identifying antibacterial agents that possess novel ring systems that could mimic or improve on the properties of quinolones. One important series, which has recently been identified and reviewed (108), incorporates the bioisosteric exchange of the N-1 atom and C-4a atom of quinolones. These compounds, designated 2-pyridones, have been reported to possess potent antibacterial activity against both gram-positive and gram-negative organisms including anaerobes. Selected compounds, such as ABT-719 [162763-53-3] (Fig. 11), are thought to be progressing through clinical trials (108).

4. Preparation of Quinolones

While the clinical utility of quinolone derivatives has spawned a range of elegant synthetic approaches, two methods that exploit complementary heterocycle ring closure procedures based on forming bond *a* or *b* have emerged as general preparative strategies (Fig. 12) (56).

Ring formation relying on closure of bond *a* provides versatility at several steps of the approach, as depicted in Scheme 1. The introduction of the R_1 substituent can be accomplished either by alkylation of the quinolone nitrogen atom after ring formation or incorporated into a precursor as the amine derivative, preferable when R_1 is a poor electrophile, such as a bulky alkyl element or an aromatic moiety. The introduction of R_7 is accomplished by a nucleophilic displacement of the halogen X_2 if R_7 is an amine moiety or by Pd-catalyzed methods if R_7 is a carbon-linked moiety. Ester hydrolysis under alkaline or acidic conditions completes the synthesis.

The second approach, which relies upon forming bond *b* of the heterocycle, is a process referred to as the Gould–Jacobs cyclization and constitutes a particularly useful and practical method, summarized in Scheme 2. Reaction of an aniline with an alkoxymethylenemalonate ester affords the corresponding anilinomethylene malonate that is cyclized either thermally or under acidic conditions, the latter preferable for N-substituted aniline derivatives. The Gould–Jacobs method is limited to quinolone targets in which the group on the 1-position is derived from a reasonably reactive alkyl halide (109).

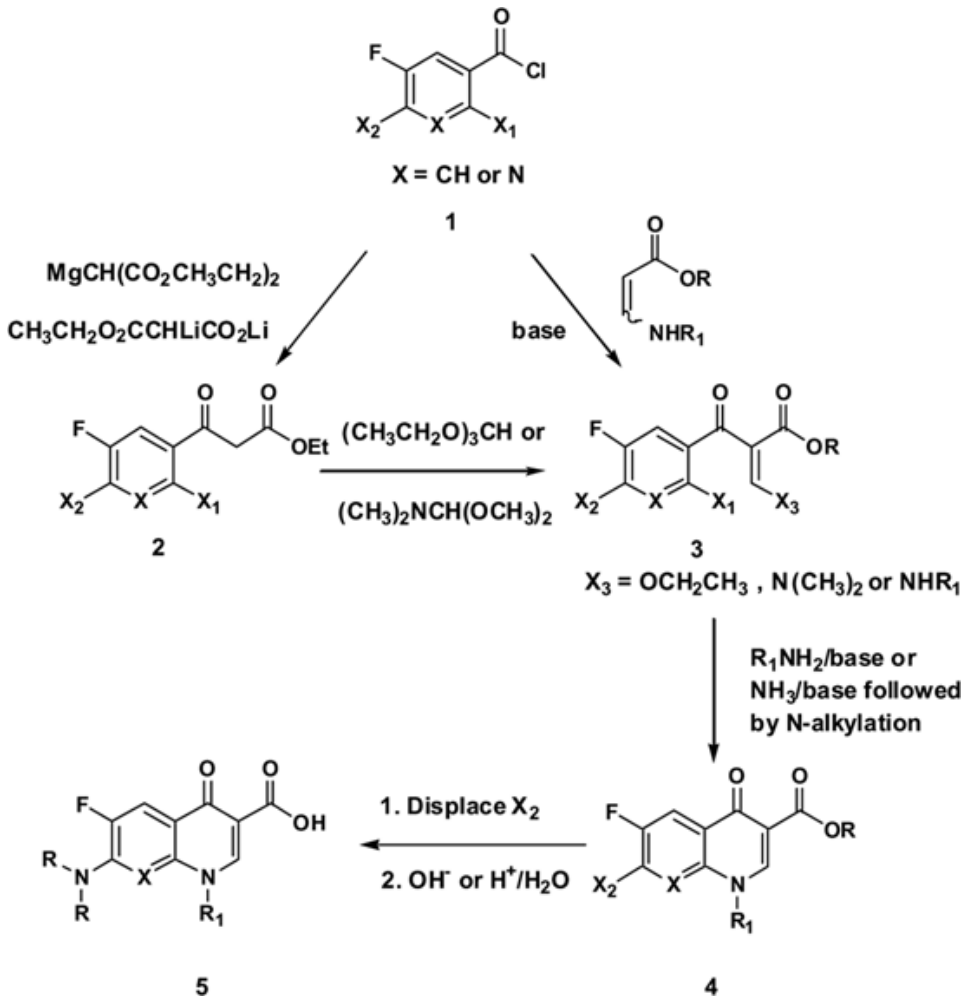


Fig. 13.

A variant of the Gould–Jacobs cyclization procedure has been developed to provide access to the pyridopyrimidone chemotype, as summarized in Scheme 3 (108). Generation of the nucleophile for coupling with diethylethoxymethylene malonate required excess strong base (BuLi). This process is not applicable when R_1 is cyclopropyl, necessitating an alternate approach for this substituent. Ester exchange, from ethyl to benzyl, is necessary due to the sensitivity of the pyridone chemotype toward base during liberation of the essential free carboxylate moiety in the final step.

5. Safety of Quinolone

Fluoroquinolones are considered to be a well-tolerated class of clinically effective antibacterial agents. The most common side effects associated with this class include those affecting the gastrointestinal tract, central nervous system (CNS) and skin, which are mild and reversible (111). Gastrointestinal tract effects are most commonly

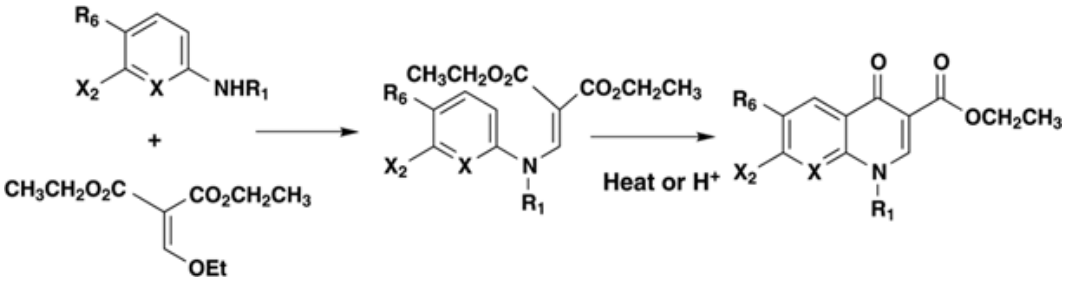


Fig. 14.

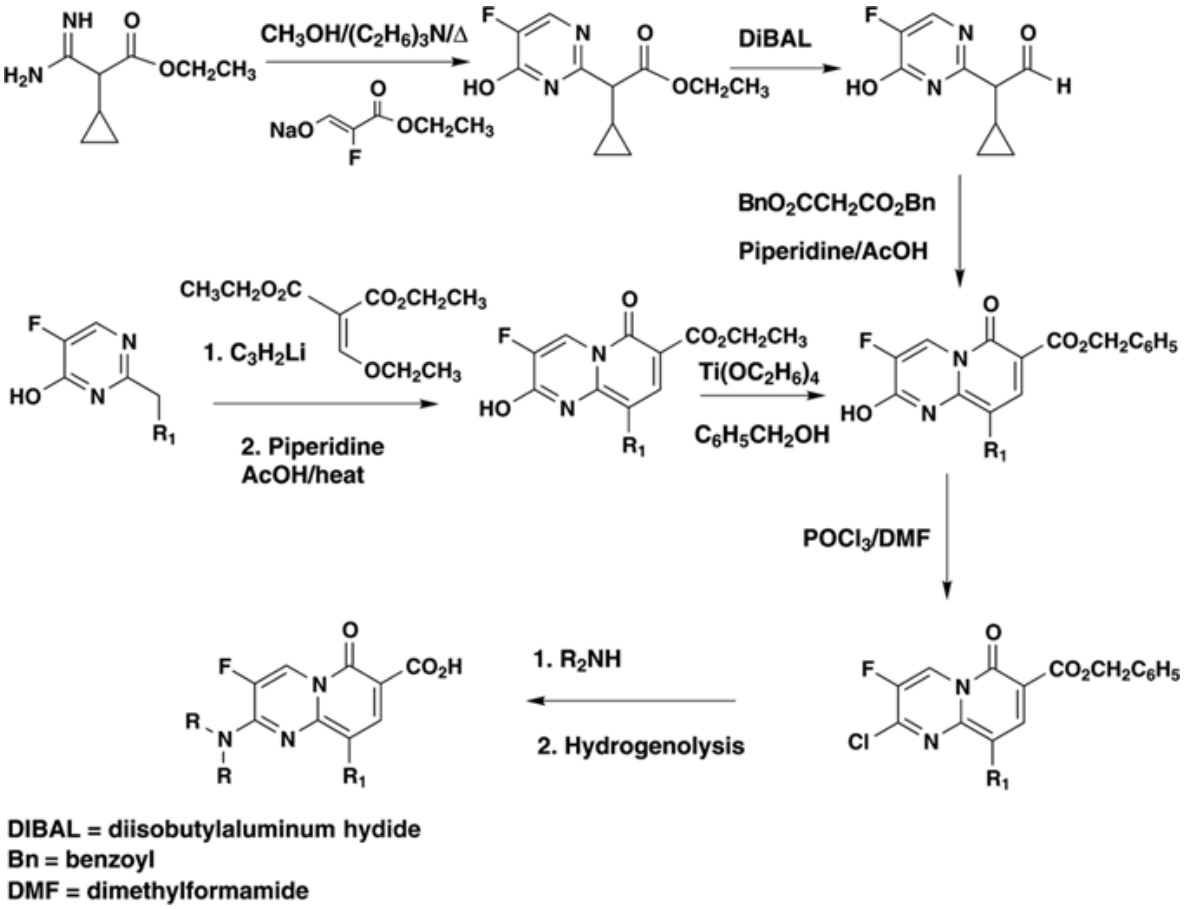


Fig. 15.

diarrhea, nausea, and vomiting (∼1–5 %), while the CNS effects are primarily headache and dizziness (∼1–2 %) and the skin problems seen are predominantly rash and pruritus (< 2.5 %) (112).

Less common but more serious adverse events include phototoxicity, cardiotoxicity, hepatic toxicity, neurotoxicity, and problems affecting connective tissue structure. Phototoxicity is a commonly associated side effect of some fluoroquinolones that is induced by exposure to sunlight, including indirect exposure to sunlight and

artificial ultraviolet (uv) sources (113, 114). Phototoxic side effects are most commonly associated with the eight-halogenated fluoroquinolones (111). The cardiotoxicity reported for some fluoroquinolones results from a prolongation of the QT_c interval and appears to be a class effect. Both sparfloxacin and grepafloxacin induced QT_c prolongation in humans at the upper limit of normal values (111). Moxifloxacin also induces a prolongation of the QT_c interval, although this is not expected to be clinically significant (115).

Hepatotoxicity has been observed with some fluoroquinolones, with the most common manifestation a mild increase in liver transaminase (111). Significant hepatotoxicity has been associated with trovafloxacin that caused increased transaminase levels and eosinophilic hepatitis in patients, resulting in FDA restrictions on its clinical use (111).

Severe neurotoxicity is a rare occurrence (< 0.5 %) (111) but reactions include convulsions, hallucinations, depression, and confusion (111, 112). These side effects begin several days after therapy is initiated and resolve at the end of treatment (112).

Tendinopathy induced by fluoroquinolone treatment has been reported to occur with an incidence of ≤ 1.5 % and is most commonly reported in the elderly (113). Severe arthropathy has been seen in all juvenile animals treated with prolonged high doses of fluoroquinolones (111). Due to the potential development of arthropathy in children, fluoroquinolones have, to date, not been approved for use in the pedriatric population in the United States. However, several fluoroquinolones have been used on a compassionate basis for children and adolescents, with no drug-related cases of arthropathy being reported (111, 112). Fluoroquinolones are commonly used in the pedriatric population in Japan and developing countries (111).

Some of the adverse effects of fluoroquinolones can be correlated to the SAR of the fluoroquinolones. Structural modifications are responsible not only for imparting antimicrobial activity, but also moderate the safety of the fluoroquinolones. The specific side-chain modifications that affect the safety profile are not clearly understood (114), but several modifications are known to affect safety: substituents at position 7 appear to impact CNS toleration; substitutions at position 8 affect phototoxicity; and substitutions at position 7 affect interactions with non-steroidal antiinflammatory drugs (NSAIDS) (111, 115). Further study of the SAR of fluoroquinolones may provide an additional understanding of the physicochemical properties of fluoroquinolones in relation to their safety.

6. Economic Aspects

The domestic antibacterial market is in excess of $9 billion and the worldwide market is > $25 billion. Whereas the early generation quinolones enoxacin, nalidixic acid, cinoxacin, and norfloxacin had minimal impact on the market, the newer quinolones, ciprofloxacin, ofloxacin, and levofloxacin, have had a major effect as their utility in the treatment of respiratory infections increases. The large impact of quinolones as one of the fastest growing classes of antibacterial agents comes despite their usage being limited to the adult population. The more recent quinolones, moxifloxacin, gatifloxacin, and BMS-284756 (garenoxacin), join ciprofloxacin in promising to expand quinolone usage into serious infections due to their improved gram-positive activity.

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