Acta Poloniae Pharmaceutica – Drug Research, Vol. 66 No. 6 pp. 587–604, 2009 ISSN 0001-6837
Polish Pharmaceutical Society

REVIEV

FLUOROQUINOLONE ANTIBACTERIALS: A REVIEW ON CHEMISTRY, MICROBIOLOGY AND THERAPEUTIC PROSPECTS

PRABODH CHANDER SHARMA[1]*, ANKIT JAIN[1] and SANDEEP JAIN[2]

[1] Institute of Pharmaceutical Sciences, Kurukshetra University, Kurukshetra-136119, India

[2] Department of Pharmaceutical Sciences, Guru Jambheshwar University of Science and Technology, Hisar-125001, India

Abstract: Fluoroquinolones are one of the most promising and vigorously pursued areas of contemporary anti-infective chemotherapy depicting broad spectrum and potent activity. They have a relatively simple molecular nucleus, which is amenable to many structural modifications. These agents have several favorable properties such as excellent bioavailability, good tissue penetrability and a relatively low incidence of adverse and toxic effects. They have been found effective in treatment of various infectious diseases. This paper is an attempt to review the therapeutic prospects of fluoroquinolone antibacterials with an updated account on their development and usage.

Keywords: fluoroquinolone, antibacterial, ciprofloxacin, therapeutic

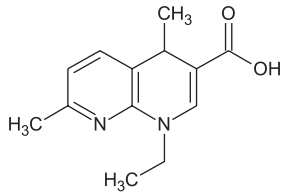
Antiinfective chemotherapy is the science of administering chemical agents to treat infectious diseases. This practice has proven to be one of the most successful of all pharmaceutical studies (1). Historically, the use of anti-infective agents can be credited with saving more human lives than any other area of medicinal therapy discovered to date. Antibacterial chemotherapy accounts for the majority of antiinfective agents in comparison to antifungal, antiviral and antiparasitic agents. It is a highly valued medical science, which has shaped modern humanity in a phenomenal fashion (1, 2). Ehrlich successfully developed the first purely synthetic revolutionary antimicrobial drug salvarsan in 1910 (2). Afterwards, beta-lactam antibiotic penicillins and sulfonamides have been the most promising or dominating drugs in clinical usage (3).

Quinolones and fluoroquinolones are a relatively new class of synthetic antibiotics with potent bactericidal, broad spectrum activity against many clinically important pathogens which are responsible for variety of infections including urinary tract infections (UTI), gastrointestinal infections (4), respiratory tract infections (RTI), sexually transmitted diseases (STD) and skin infections (5, 6). They are primarily used against urinary tract infections and are also clinically useful against prostatitis, infections of skin and bones and penicillin resistant sexually transmitted diseases (4). These agents are also employed against bacterial enteric infections, prophylaxis in the immuno compromised neutropenic host. New quinolones provide a valid alternative antibacterial therapy, especially in areas where the prevalence of pencillin resistant and macrolide resistant organisms exist (7).

Historical background

The first clinically useful quinolone was naldixic acid, discovered by Lesher and co-workers in 1962, which was generated from chloroquine, an antimalarial agent (3). It was active against some Gram negative bacteria and had limited usefulness because of its high protein binding (approximately 90%) and little half life (about 1.5 h) (8). Unfortunately, bacteria could develop a rapid resistance to this agent (9, 10).

* Corresponding author: e-mail: sharma_prabodh@rediffmail.comkg_ju@hotmail.com.



Naldixic acid

In 1968, Kaminsky and Melfezer discovered an oxolinic acid, which was lately approved by the United States Food and Drug Administration (USFDA) (9). Since then, extensive efforts has been undertaken for the development and to derive an array of significantly active drugs of this class. Molecular modification for the lead optimization by bioisosteric replacements, homologation of side chain or branching of side chain, stereochemistry and other useful techniques of analogs design and development of fluoroquinolones have given rise to agents with broad spectrum activity and minimum toxic or side effects. Development of new antibiotics has been achieved from derivatives of known antimicrobial agents or by identification of novel agents active against previously unexploited targets. The development has been focused on the following aspects (3):

Increasing activity against resistant strains of microbes, anaerobes and atypical organisms.

Reducing rate of emergence of resistance.

Improving pharmacokinetics and pharmacodynamic profile.

Targeted towards selectivity of drugs.

Flumequine was the first fluoroquinolone which was patented in 1973, after that many fluoroquinolones have been patented and are still used today, including norfloxacin (1978), pefloxacin (1979), enoxacin (1980), fleroxacin (1981), ciprofloxacin (1981) and ofloxacin (1982) (3). An advantage of these compounds over previous ones is their broad spectrum. A big revolution was made in 1980's when an analog of naldixic acid, enoxacin was derived with significantly increased spectrum of activity against Gram negative or Gram positive bacteria (2).

The most successful and widely used fluoroquinolone, ciprofloxacin was marketed in 1986, and since then the value of fluoroquinolones for the treatment of a wide range of infections have become widely recognized (3, 11). This class of compounds has enhanced pharmacokinetic properties as well as extensive and potent activities against various parasites, bacteria and mycobacteria, including resistant strains as compared to previously existing bactericidal drugs (11, 12).

Classification

Fluoroquinolones are classified (Table 1) on the basis of their spectrum of activity and their pharmacokinetic profile (13).

Structure-activity relationships (SAR)

Essential structural features

All clinically important compounds of fluoroquinolone class are synthetic fluorinated analogues of naldixic acid, a 1,8-naphthyridine and possess a 4-quinolone nucleus (14).

In general, pharmacophore required for significant antibacterial activity is 4-pyridone-3-carboxylic

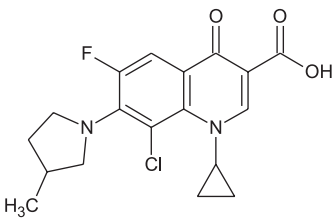
Table 1. Classification of fluoroquinolones

Generation	Drug	Characteristic features
First	Naldixic acid Oxolinic acid Pipemidic acid	Active against some Gram negative bacteria. Highly protein bound drugs. Short half life.
Second	Norfloxacin Enoxacin Ciprofloxacin Ofloxacin Lomefloxacin	Protein binding (50%). Longer half life than previous agents. Improved activity against Gram negative bacteria.
Third	Temafloxacin Sparafloxacin Grepafloxacin	Active against Gram negative bacteria. Also active against Gram positive bacteria.
Fourth	Clinafloxacin Trovafloxacin Moxifloxacin Gatifloxacin	Show extended activity against both strains of bacteria. Active against anaerobes and atypical bacteria.

acid with a ring at 5 or 6 position (Fig. 1). Now considerable information is available about the effects of modifications on nucleus. Although various alterations were done to improve antibacterial activity (3, 4, 15-31), two major pathways of lead optimization of original 1,8-naphthyridine nucleus were pursued. Both the strategies are based on modification of 6-fluoro and 7-piperazinyl quinolone (6).

It is pertinent to mention here that a similarity is seen in many fluoroquinolones with beta lactams, wherein a reciprocal relationship is seen in both the classes where an increase in Gram positive activity is associated with a decrease in Gram negative activity (3).

The first route of lead optimization involved replacement of nitrogen atom by carbon atom at position-8, as well as other side chain modifications, resulting in fluoroquinolones such as 1-cyclopropyl (ciprofloxacin) and 1,8-cyclo compounds such as ofloxacin and levofloxacin (6). Additional molecular substitution at 6-fluoro, 7-piperazinyl yielded second generation agents with improved activity and pharmacokinetic profile, such as sparfloxacin and clinafolxacin (6, 32). These compounds demonstrated greatly improved activity against many Gram positive species without compromising on their activity against Gram negative bacteria, contrary to the earlier agents of this class (3).



Clinafloxacin

The second major route of chemical modifications retained the naphthyridine core, yielding agents such as enoxacin and tosufloxacin (32). The 7-azabicyclo evolutionary modification lead to third generation molecule of trovafloxacin, which showed, increased spectrum of antibacterial activity and also improved potency (6, 33).

Dynamic approach towards optimization

The essential features for improving lead compound of fluoroquinolone class (Fig. 2) are summarized below:

4-Oxo group is essential for the activity (9).

Reduction of 2, 3- double bond eliminates the activity (4).

Position 1 (nitrogen in ring A): The side chain attached to ring nitrogen significantly affects the

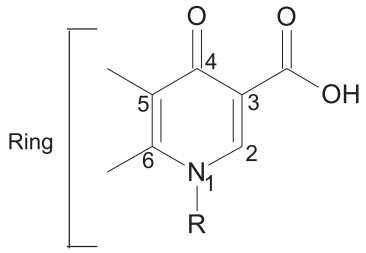


Figure 1. Required pharmacophore of quinolone

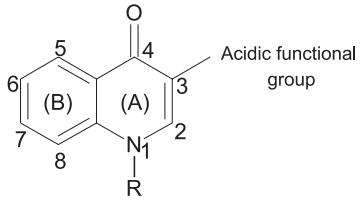
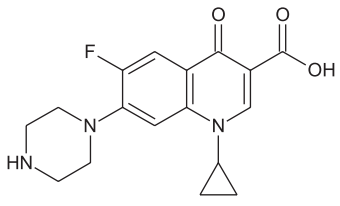
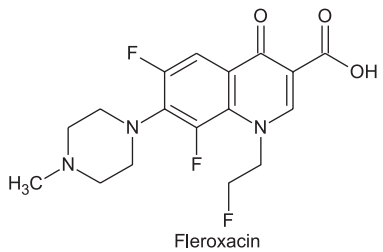


Figure 2. Basic quinolone nucleus for SAR

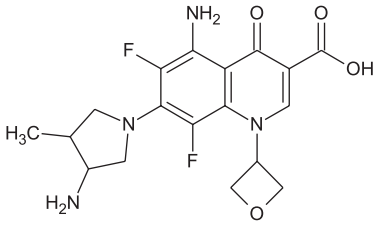
potency of the drug. The earlier compounds such as naldixic acid, pipemidic acid, norfloxacin, enofloxacin, cinoxacin, rosoxacin etc. had an ethyl group as side chain at the nitrogen atom (9). So the optimal substituent at position one appeared to be ethyl, but cyclopropyl and difluorophenyl have resulted in increased potency (3). Addition of some small group at cyclopropyl, as fluorine in case of fleroxacin, results in overall improved activity against Gram positive bacteria. Replacement of cyclopropyl group of ciprofloxacin by an oxetane (compound A) had increased Gram positive activity relative to ciprofloxacin. Connecting the methoxy or hydroxy group at carbon-8 atom to a dimethylamino group at nitrogen-1 atom (compound B) displayed superior *in vitro* and *in vivo* antibacterial activity as compared to ofloxacin and ciprofloxacin in addition to having good bioavailability (94%) and half life of 4.6 h (6).



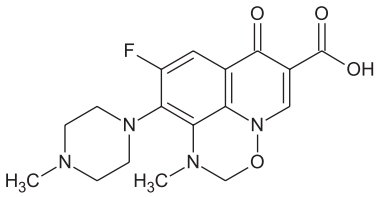
Ciprofloxacin



Fleroxacin

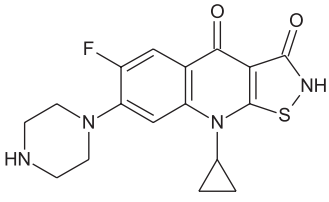


Compound A



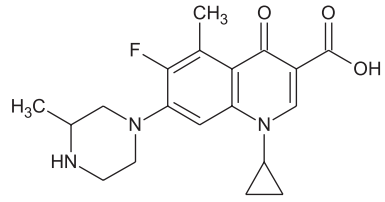
Compound B

Position 2 and 3: One part of the molecule where modifications are rarely attempted is at positions 2 and 3 (1, 3). The carboxylic moiety at position 3 is believed to be the portion of the pharmacophore that binds to the DNA gyrase of the bacterial cell, and thus it is important do not interfere with the stereochemistry around this area (3). Generally, modification of the 3-carboxylic acid group produced compounds with decreased activity. However, some attempts have been made where incorporation of an aldehyde (formaldehyde) group at carbon-3 position, as well as certain labile carboxylate esters afforded derivatives, which displayed antibacterial properties, but the activity was due to their conversion (*in vivo*) to corresponding carboxylic acids. Replacement of 3-carboxyl group with isothiazole group produced the most potent isothiazquinolone (1), which have 4 to 10 times greater *in vitro* antibacterial activity than ciprofloxacin, but it appeared to suffer from some undesirable properties such as insolubility and mammalian toxicity (9).

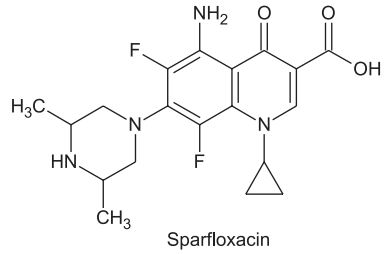


Isothiazquinolone derivative

Position 5: Improved antibacterial activity has been reported against Gram positive strain by modifying or substituting this position (3). It has been found that bulky substituents at this position reduce activity markedly, while other substituents result in improved activity, such as methyl and amino substituents in case of grepafloxacin and sparfloxacin, respectively (3, 17).



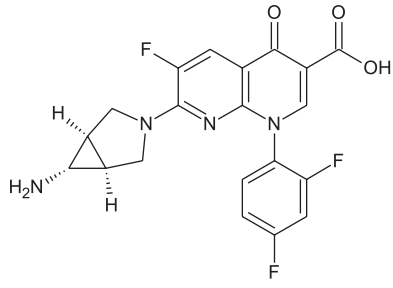
Grepafloxacin



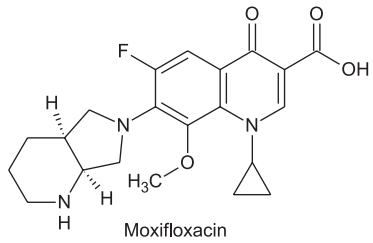
Sparfloxacin

Position 6: fluorine atom seems to be essential as it helps in binding with DNA topoisomerase enzyme of bacteria (9).

Position 7: The evolution in quinolones mainly arises from the modification at this position of the basic molecule. This is the position where modification can bring about the major changes in potency. Attachment of heterocyclic nitrogen containing rings results in improved activity and it also affects the pharmacokinetics of the compound (34, 35). Some examples of the earlier compounds with such modifications using unsubstituted piperazine are pipemidic acid, norfloxacin, enoxacin, and ciprofloxacin, which have shown good activity against Gram negative strain of viable bacteria. Substitution with a methyl group at position 3 or 4 of piperazine leads to improved pharmacokinetics. Amino pyrrolidines also possess good activity. The other unusual type of the side chain at position 7 is a bicyclic ring system such as in trovafloxacin, moxifloxacin etc. (3).

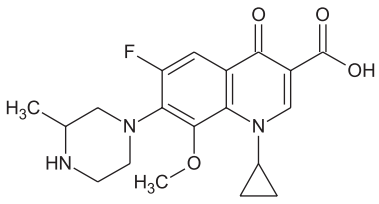


Trovafloxacin



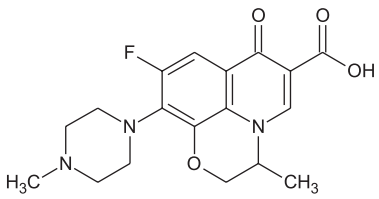
Moxifloxacin

Position 8: Modification at this position affects the *in vivo* properties and antibacterial activities, particularly against anaerobes (11). A fluorine or chlorine substituent at this position provides potentially active compounds. Methoxy group at this position confers good anaerobic activity, for example in gatifloxacin and moxifloxacin. This carbon atom can be replaced with nitrogen atom with retention of activity (3).



Gatifloxacin

The stereochemistry of methyl group in the third ring of ofloxacin exhibits a significant affect on the antibacterial activity (2). The (S)-enantiomer is significantly 10 folds more potent than (R)-enantiomer and is rather more water soluble than the racemate (9).



Ofloxacin

The quinolones show amphoteric nature due to the presence of both basic (tertiary nitrogen) and acidic (carboxylic acid) group(s) in their pharmacophore. Their solubility is low, except between pH 6 to 8. Within this range, they have low water solubility and are prone to precipitation under more acidic conditions. Due to this property crystalluria, as an adverse effect has been observed (10).

Mechanism of action

Pharmacology

Fluoroquinolones inhibit the replication and transcription of bacterial DNA, which eventually culminate in cell death (36, 37). They either inhibit the activity of DNA gyrase, an essential adenosine triphosphate-hydrolyzing topoisomerase II enzyme or/and prevent the detachment of gyrase from DNA. The topoisomerases exert their bactericidal activity by interacting with the DNA (38). During the processes of replication and transcription, enzymes called helicases unwind/uncoil the DNA double helix leading to excess supercoiling of the remaining DNA double helix. A tension is created in this remaining double helix which must be relived in order to continue the process. The topoisomerase II enzyme allows the relaxation of supercoiled DNA by breaking both strands of DNA chain, crossing them over, and then resealing them (Fig. 3). Bacterial gyrase is different enough from mammalian topoisomerase so that quinolones and fluoroquinolones show about 1000 fold selectivity towards bacteria over the corresponding enzyme in humans (2).

Fluoroquinolones have also been found to inhibit the *in vitro* activities of topoisomerase IV, having structure similar to DNA gyrase (4). This enzyme has an important role in partitioning of chromosomal DNA during bacterial cell division and may be the primary target of fluoroquinolone activity in Gram positive bacteria. This mechanism is consistent with apoptosis rather than necrosis (6).

Medicinal chemistry

Inhibition of DNA synthesis occurs by the formation of a ternary complex involving the drug, the enzyme and bound DNA segment. Fluoroquinolones bind with DNA in a stacking arrangement such that their aromatic ring is coplanar and the bonding interactions also take place between the substituents at the first position (2). The carbonyl and carboxylate groups of fluoroquinolones bind with DNA by hydrogen bonding, while the fluoro substituent, substituent at carbon-7 and carboxylate ion are involved in binding interactions with the enzyme (Fig. 4). The resulting complex is stable and so the activity of fluoroquinolones arises. Chemical modifications for improvement of activity and pharmacology of this class of the drugs are mainly focused over the stacking domain and the binding sites to enzyme and DNA (20).

ACQUIRED RESISTANCE

Resistance against antibiotics is a worldwide problem. In recent years, the rate of emergence of resistance has outpaced the development of new agents (39). The complacency associated with infectious diseases in the 1960's and the general confi-

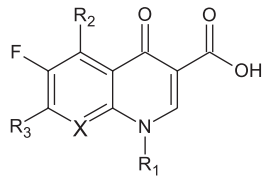


Table 2. Structure, pharmacokinetics and important clinical indications of fluoroquinolones.

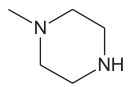
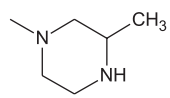
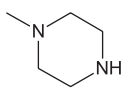
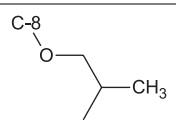
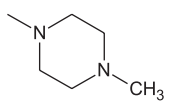
Compound		Structure				Pharmacokinetic average			Clinical indication	References
No.	Name	R_1	R_2	R_3	X	AUC (mg/h/L)	$t_{1/2}$ life (h)	C_{max} (mg/L)		
1	Norfloxacin					1.77	3.7	0.33	Uncomplicated urinary tract infections.	62, 112-118
2	Enoxacin	-do-	-do-	-do-		4.36	3.54	0.66	Uncomplicated urinary tract infections.	10, 62, 63, 116
3	Lomefloxacin	-do-	-do-			9.84	7.73	1.06	Uncomplicated urinary tract infections.	62, 63, 119, 120
4	Ciprofloxacin		-do-			2.56	4.16	0.56	Complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections, sexually transmitted diseases, anthrax.	50, 63, 121, 122
5	Ofloxacin		-do-		-do-	7.67	5.32	0.87	Complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections, sexually transmitted diseases, anthrax.	62, 63, 123-127

Table 2. Cont.

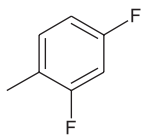
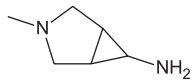
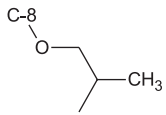
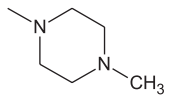
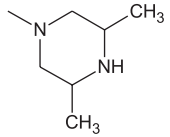
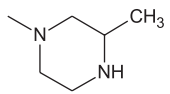
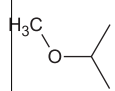
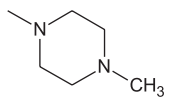
Compound		Structure				Pharmacokinetic average			Clinical indication	References
No.	Name	R_1	R_2	R_3	X	AUC (mg/h/L)	$t_{1/2}$ life (h)	C_{max} (mg/L)		
6	Trovafloxacin		-do-			11.91	9.66	1.23	Intra abdominal infections, acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities.	6, 62, 128-130
7	Levofloxacin		-do-			9.33	6.78	0.24	Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	6, 62, 121, 131, 132
8	Sparfloxacin		—NH_2			8.35	20.06	0.34	Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	6, 62, 63, 133-136
9	Gatifloxacin	-do-	—H			7.87	7.46	0.9	Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	62, 63, 111, 137-141
10	Grepafloxacin	-do-	—CH_3	-do-		3.43	11.53	0.32	Acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities.	6, 53, 101, 121, 142, 143
11	Amifloxacin	—NH—CH_3			-do-	5.57	4.14	1.14	Genitor urinary, respiratory, gastrointestinal, skin and soft tissue infections.	9, 62, 144, 145

Table 2. Cont.

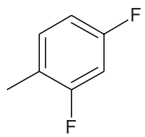
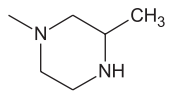
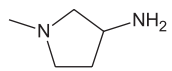
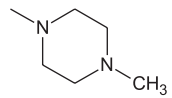
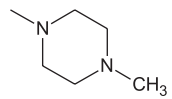
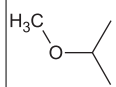
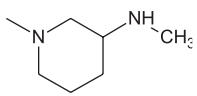
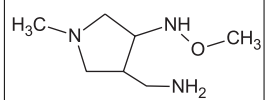
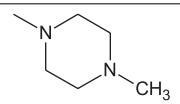
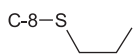
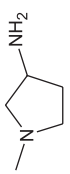
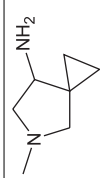
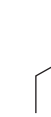
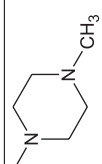
Compound		Structure				Pharmacokinetic average			Clinical indication	References
No.	Name	R_1	R_2	R_3	X	AUC (mg/h/L)	$t_{1/2}$ life (h)	C_{max} (mg/L)		
12	Temafloxacin		-do-			8.45	8.55	0.74	Respiratory and urinary tract infections, sexually transmitted diseases, skin and soft tissue infections.	9, 62, 146-148
13	Tosufloxacin	-do-	-do-			2.62	4.02	0.34	Respiratory and urinary tract infections, sexually transmitted diseases, skin and soft tissue infections.	9, 62, 149-151
14	Difloxacin	-do-	-do-			27.8	25.7	1.04	Genitor urinary, respiratory, gastrointestinal, skin and soft tissue infections.	9, 62, 152
15	Moxifloxacin		-do-			30.8	9.6	3.1	Community acquired pneumonia, complicated urinary tract infections, gastroenteritis with severe diarrhea prostatitis and nosocomial infections.	6, 10, 63, 111, 137
16	Balofloxacin	-do-	-do-		-do-	8.55	7.8	1.08	Uncomplicated urinary tract infections.	63, 142, 153
17	Gemifloxacin	-do-	-do-			3.02	6.65	0.56	Community acquired pneumonia, acute exacerbation of chronic bronchitis.	154-158
18	Pefloxacin		-do-			29.97	14.63	1.44	Acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities.	62, 159
19	Rufloxacin		-do-	-do-	-do-	39.43	34.25	0.99	Acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities.	63, 160-163

Table 2. Cont.

Compound		Structure				Pharmacokinetic Average			Clinical indication	Reference s
No.	Name	R_1	R_2	R_3	X	AUC (mg/h/L)	$t_{1/2}$ life (h)	C_{max} (mg/L)		
20	Clinafloxacin		-do-			5.34	5.74	0.72	Acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities.	62, 164-166
21	Sitafloxacin		-do-		-do-	5.88	5.4	0.92	Acute exacerbation of chronic bronchitis, community acquired pneumonia, uncomplicated gonorrhea, urethritis, cervicities .	62, 167, 168
22	Fleroxicin		-do-			18.13	11.02	0.34	Urinary tract infections, sexually transmitted diseases, skin and soft tissue infections.	62, 121, 169, 170

dence in existing antibiotics resulted in a lag in production of new classes of antimicrobial agents. The danger of new and reemerging infections is compounded by the increase in antibiotic resistant bacteria (40). Drug selection for treatment of infections are increasingly limited and in some cases it has become nonexistent. Although defining the precise public health risk of emergent antibiotic resistance is not simple, there is a little doubt in that the problem is global in scope and is very serious (41).

With increasing utilization of fluoroquinolones in both human and veterinary medicines, emerging resistance for these agents is also a growing concern. These findings ponder upon the need for the continued monitoring of quinolone resistance among bacterial pathogens (41). The mechanism of acquired resistance to the fluoroquinolones is consistent among currently available drugs of this class and is expected to be similar for new and developing agents as well (40). Resistance to this class of agents occurs primarily *via* two fundamental processes. First, by spontaneous mutations at various locations on the gyrase enzymes subunit A, which lower the affinity of the drug at the gyrase DNA complex. Mutations of subunit A are found in both Gram negative and Gram positive strains and involve amino acid alterations (42). These alterations are clustered between amino acid 67 and 106 in the amino terminus of subunit A, which is near the active binding site of the enzyme. For example, the substitution of leucine or tryptophan at the place of serine 83 is the most commonly observed alteration (43) and causes a largest increase in resistance. Similar alterations have been seen in topoisomerase IV. Combination of both alterations results in fluoroquinolone resistance in *S. pneumonae* (44-47).

Second mechanism that entails resistance to the fluoroquinolones is slow to appear, but when it appears it is mainly due to the efflux mechanism, which pumps the drug back to the cell (2, 6). This is due to the mutation in the genes that code for porins, which are membrane proteins by which quinolones enter Gram negative cells (4). These mutations raise tolerance limit of antibiotics to four folds and result in either reduced production of outer membrane proteins or stimulated cell efflux system, which lead to active drug expulsion. This type of resistance has been described in both *E. coli* and *P. aeruginosa*. Similar evidence of enhanced quinolone efflux has been found in *S. aureus*, which lacks an outer cell membrane (42, 47).

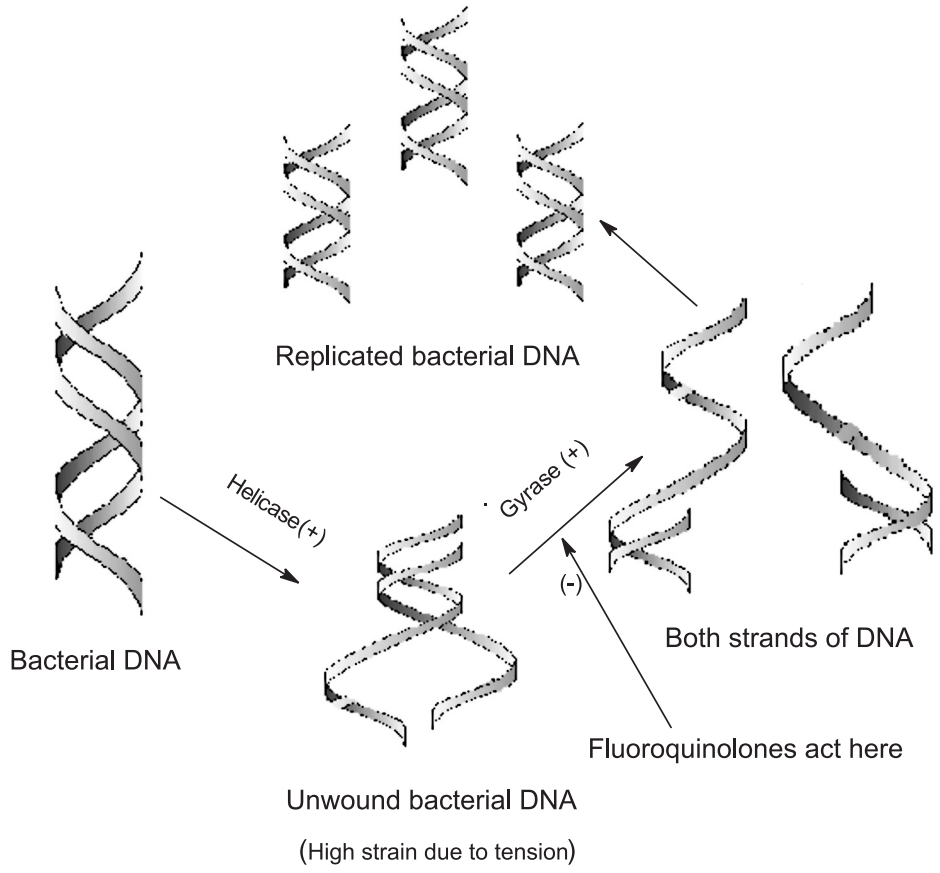


Figure 3. Schematic representation of mechanism of action of fluoroquinolones

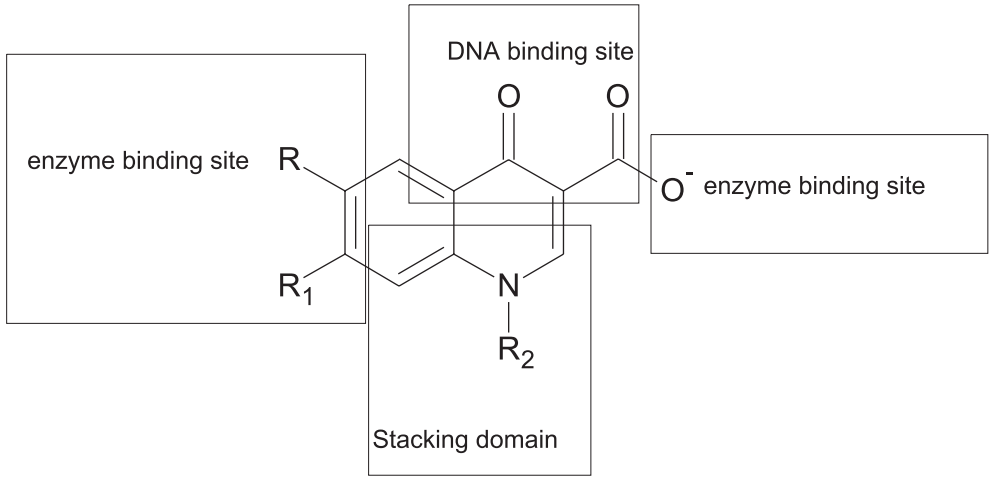


Figure 4. Complex formed between DNA, topoisomerase and fluoroquinolones

These mutations also account for the cross resistance common with these agents. On the contrary, clinical resistance is rarely encountered in some families of microorganisms (such as the Enterobacteriaceae) (6) which are innately highly susceptible to quinolones. For example, resistant mutants of *P. aeruginosa* and *S. aureus* are selected far more frequently than resistant *E. coli* mutants (6, 48).

A problem associated with first and second generation fluoroquinolones is that they generally show moderate activity against *S. aureus,* with resistance being rapid to arise and only marginal inhibito-

ry activity is shown against anaerobes and *S. pneumoniae*. To overcome these issues, third generation fluoroquinolones were developed in 1990's (2).

Because of unique mechanism of action of fluoroquinolones, plasmid mediated transferable resistance probably does not occur and is rarely observed with them (49).

DRUG INTERACTIONS

Potentially hazardous interactions, which have been documented only in human studies of fluoroquinolones are limited. Absorption of fluoroquinolones by oral route of administration is drastically decreased by antacid containing magnesium, aluminum and other agents such as sucralfate (10). Without exception, all of the new compounds interact with multivalent cation-containing products. Ranitidine does not alter the oral absorption of ciprofloxacin, but it decreases the oral bioavailability of enoxacin, suggesting that the gastric pH affects the oral absorption of the some fluoroquinolones, perhaps through alteration in dissolution (50). These interactions of fluoroquinolones with antacids might be hazardous during the treatment of serious infections (8).

A more disturbing interaction occurs between the fluoroquinolones and theophylline or other methylxanthines such as caffeine. This interaction involves isoenzyme 1A2 of the cytochrome P-450 pathway and appears to be most pronounced with ciprofloxacin, norfloxacin and grepafloxacin, the use of which can raise serum theophylline concentration to much greater extent. Clinical consequence of this interaction requires dose reduction and serum concentration monitoring of the xanthines. The interaction is not clinically significant when occurs between theophylline and sparfloxacin, trovafloxacin, levofloxacin or third generation fluoroquinolones (6, 51).

Concurrent administration of the non-steroidial anti-inflammatory agent fenbufen with enoxacin has been associated with seizures in humans. Patients given other fluoroquinolones concurrently with non steroidal anti-inflammatory agents except fenbufen did not develop seizures (10).

Some other significant drug interactions of fluoroquinolones are as follows:

- Elevated serum levels of cyclosporine have been reported with concomitant use of fluoroquinolones.
- Serum concentration of antineoplastics decrease due to the interaction with ciprofloxacin (50).
- Ciprofloxacin and norfloxacin serum concentrations increase and decrease in their clearance as observed in these drugs by significant interaction with azlocillin, cimetidine and probenecid (8, 50, 51).
- Drugs, such as sodium bicarbonate, carbonic anhydrase inhibitors and citrates which cause the urine alkaline, reduce the solubility of norfloxacin and may increase the possibility of crystalluria (8).

PHARMACOKINETICS AND PHARMACODYNAMICS

Pharmacokinetic and pharmacodynamic properties of different antimicrobial compounds depend on the dosage form and dose of drug required for inhibiting the viability of pathogens. This difference in absorption, distribution, metabolism and excretion of quinolones may affect the endophthalmitis (ocular complication) incidences after cataract surgery (52). Fluoroquinolones, however, kill pathogens in a concentration dependent manner. Consequently, it is their peak concentration that is important and not the time above the minimum inhibitory concentration. In general, the pharmacokinetic profile of newer analogs of fluoroquinolones is considerably improved over the older agents of this class. Their longer serum half life permits the once daily dosing and greater maximum plasma concentration offers more extensive coverage above the minimum inhibitory concentration. Also, the increased volume of distribution improves their tissue penetration (53-60). Important pharmacokinetic parameters of some fluoroquinolones are summarized in Table 2. Fluoroquinolones are distributed rapidly (61) and extensively in tissues except for the brain. It was hypothesized that P-glycoprotein at the blood brain barrier may play a role in this fact (62).

Adsorption

Fluoroquinolones are readily absorbed but their complete absorption is not always achieved following oral administration (10). The oral bioavailability varies with the individual compounds of the class. The bioavailability of new fluoroquinolones after oral doses is equal to or greater than that of ciprofloxacin, ranging from a low of 70% with grepafloxacin to a high of 99% with levofloxacin. Although drug food interactions may prolong the time required to reach maximum plasma concentration (t_{max}) and thus affect the area under the concentration-time curve, this does not significantly alter the bioavailability of the drugs (6).

Distribution

Distribution of fluoroquinolones to tissues is superior to that of most other drugs because there is

little binding to plasma proteins (4). After oral administration, fluoroquinolones have good penetration into various fluids and tissues of body except central nervous system (CNS). The newer fluoroquinolones achieve a higher serum concentration well in excess than that of required for efficacy against infections (62, 63). A remarkable drug level is achieved in kidney, prostate gland, liver and lung. The penetration into the cerebrospinal fluid is poor, except when the meninges are inflamed. Their urinary drug concentration is higher than minimum inhibitory concentration and thus fluoroquinolones are mainly used in urinary tract infections (13).

Metabolism and elimination

The fluoroquinolones differ greatly in the degree to which they are eliminated by metabolism in liver or by renal excretion. Their metabolism is inactivating and is primarily by glucuronides conjugation at the 3-carboxylic group. The piperazine ring is readily metabolized resulting in decreased antimicrobial activity (4). Elimination occurs by both renal and nonrenal routes but the primary route of elimination of most of fluoroquinolones is through kidney by glomerular filtration and tubular secretion. Thus, in patients with renal impairment and in geriatrics, dosage adjustment is required. The secondary route of excreation is *via* the lever. They are poorly cleared by both peritoneal dialysis and hemodialysis (13).

Some change in pharmacokinetics is observed in disease conditions (10), although, diarrhea or cutaneous infections in human beings does not alter the oral absorption of fluoroquinolones. In the case of bacteriaemia, serum concentrations remain sufficient for effective treatment of Gram negative infections, although differences can be observed in different analogs. Metabolism of ciprofloxacin to oxociprofloxacin is reduced in hepatic cirrhosis. In a study conducted on healthy volunteers, pharmacokinetics and lung disposition of danofloxacin were not altered when compared to pneumonic claves although the volume of distribution was somewhat larger in case of pneumonic claves (64, 65).

ANTIMICROBIAL SPECTRUM

Many studies have been reported on the activity of the fluoroquinolones (3, 6, 10). The newer and developmental fluoroquinolones are distinguished by their enhanced spectrum of antimicrobial activity against clinically important pathogens such as *S. pneumoniae,* Enterococcus spp*, S. pyrogenes, S. aureus,* and multidrug resistant isolates (6). In general, these agents have an excellent activity against Enterobacteriaceae*,* fastidious Gram negative bacteria and *Pseudomonas aeruginosa,* moderate activity against staphylococci, mycobacteria, chlamydia, mycoplasma and ureaplasma, less activity against streptococci (particularly group D. streptococci), and anaerobic bacteria. The term "post antibiotic effect" describes the continuous suppression of an organism's growth after short exposure to an antibacterial agent such that there is an inhibitory effect in the absence of the antibiotic. Such an effect of fluoroquinolones has been shown to be of 4-8 hours against *E. coli, Klebsiella, Serratia* and *Pseudomonas aeruginosa* (10, 66).

Activity against Gram positive organisms

Streptococcus pneumoniae is the commonest cause of community-acquired respiratory tract infection (RTI) and strains resistant to penicillins and macrolides have become increasingly prevalent in all parts of the world (6). Activity against pneumococci was lacking in the early 4-quinoloes and was only marginal in the first generation of fluoroquinolones. Their activity has improved steadily with the newer compounds such as trovafloxacin and moxifloxacin (67-74). Bauernfeind observed that the enhanced activity of the newer fluoroquinolones against Gram positive cocci is limited to agents whose chemical structure at position 7 of the basic ring contains an azabicyclo, a 3-amino-pyrolidinyl, or a 3-methyl-piperazinyl ring (6).

Fluoroquinolones are bactericidal compounds and a number of studies have shown their ability to kill pneumococci at concentration about 2 to 8 times higher than their minimum inhibitory concentration (MIC). Although resistance to this class of antibiotics in pneumococci is rare, however, recent reports indicate that resistance to ciprofloxacin and ofloxacin is increasing (75, 76).

The newer compounds have greatly improved activity against *Streptococcus pyogenes* (77, 78). The activity of earlier fluoroquinoloes is only modest against methicillin-sensetive *S. aureus* and *Staphylococcus epidermidis* strains, with minimum inhibitory concentration 0.5-1.0 mg/l (3).

Activity against Gram negative organisms

In the development of newer analogs of fluoroquinolones, research work has been primarily focused on improving their potency against Gram positive organisms while retaining the favorable activity against Gram negative organisms (6). Resistance to ciprofloxacin has been most often seen in strains of *Escherichia coli, Enterobacter,* and

Klebsiella spp and also observed in some members of Enterobacteriaceae (3).

Infectious Gram negative pathogens are mainly *P. aeruginosa, Acinetobacter, Alcaligenes, Stenotrophomonas* and *Burkholderia* species. The activities of different fluoroquinolones considerably vary, particularly among strains of *P. aeruginosa*. Ciprofloxacin is generally more active than the newer analogs of this class against most species of *P. aeruginosa*. However, clinafloxacin and sitafloxacin have activity that is equal to or better than ciprofloxacin. Species of non fermentative Gram negative rods are of increasing importance in the hospital settings (78-80).

Haemophilus influenzae and *Moraxella catarrhalis* species are both highly susceptible to most of the fluoroquinolones. Ciprofloxacin (50) and ofloxacin have demonstrated excellent activity and lower minimum inhibitory concentrations against these Gram negative bacteria (39). Newer agents gatifloxacin and moxifloxacin offered no apparent advantages over ciprofloxacin and levofloxacin, however, this activity has been retained in newer compounds (72).

Activity against anaerobic pathogens

Until the introduction of newer analogs of fluoroquinolones, the more serious deficiency of the quinolones was their lack of anaerobic activity. The limited anaerobic activity was shown by the second generation of fluoroquinolones (81). The activity of these agents against important anaerobic species, such as the *Bacteroides fragilis* group, species of *Fusobacterium, Prevotella, Porphyromonas* and *Clostridium* was only marginal and variable. Activity of most of the newer fluoroquinolones against *Clostridium difficile* is good, showing improvements in potency relative to ciprofloxacin (82).

Activity against atypical pathogens

A notable improvement in most of the newer analogs of this class is their enhanced activity against atypical respiratory tract pathogens such as *Mycoplasma pneumoniae, Chlamydia pneumonia,* and *Legionella pneumophila*. These agents also show their significant activities against most of genital pathogens. The findings regarding the performance of the new quinolones in clinical studies of respiratory tract infections involving atypical pathogens have generally been favorable (53, 79, 83-96).

TOXICITES AND ADVERSE EVENTS

With few exceptions, the adverse effects of fluoroquinolones are not too severe consequences when compared to the beneficial features they exhibit. Toxicity is mild at therapeutic doses, and is generally limited to gastrointestinal disturbances such as nausea, vomiting and diarrhea (10). Recently, ciprofloxacin has been reported to be an effective therapeutic for anthrax (97, 98); however, a large dose is needed due to blood brain barrier (BBB) and heavy use of ciprofloxacin in such cases has been suspected to induce aseptic meningitis (61) and arthritis damage (99) and hence there is a need to increase uptake by the brain (63). These drugs are still effective as antibiotic prophylaxis for prostate biopsies but there is an increase in infective complications and fluoroquinolones resistance (100). Newer drugs of this class have greater epithelial toxicity than do the previous fluoroquinolones. In addition, there can be a significant difference in toxicity between any two newer fluoroquinolones.

Some focused adverse events

- Skin photosensitivity reactions have been reported during treatment with fluoroquinolone antibiotics. The incidence and severity of such reactions, however, appear to differ between different drugs (6, 13).
- The greatest concern with ciprofloxacin use in children is potential bone and joint damage (50).
- CNS effects are second most common type of adverse events associated with quinolone therapy. Dizziness, insomnia, and mood alterations have frequently been observed during treatment with fluoroquinolones. Seizures or hallucination have also been described (6, 10, 13, 63).
- Unpleasant taste was reported fairly by greapafloxacin treated patients during the clinical trials but at a much lesser extent (101).
- Rarely, anaphylaxis and agranulocytosis have been reported (13).
- These drugs have been associated with potentially life threatening dysglycemic reactions (102, 103).
- The use of these drugs to treat multidrug resistant tuberculosis in children has led to the emergence of invasive pneumococcal diseases (104).
- Prolongation of the QT interval in electrocardiogram (ECG) is another serious adverse event reported with sparfloxacin and grepafloxacin but not with the levofloxacin and trovafloxacin. Although this effect has not been found to be associated with arrhythmia (101, 105, 106).

CLINICAL AND THERAPEUTIC ROLE

Numerous factors govern the selection of a specific antimicrobial agent, including severity of infec-

tion, likely pathogen or pathogens, pharmacokinetic profile, safety, dosing convenience, cost, and increasing patterns of antimicrobial resistance in particular community or hospital setting. Fluoroquinolones have many favorable properties including broad spectrum of activity (107), excellent bioavailability when given orally, good tissue penetrability and a relative low incidence of adverse and toxic effects (6).

Although fluoroquinolones have several clinical applications, yet few of important indications are as below:

- In the treatment of urinary tract infections and prostatitis (108).
- The ideal treatment of *Neisseria gonorrhoea* infections should be safe, effective, affordable and available as a single dose regimen for which fluoroquinolones are appropriate (109).
- Effective against bacterial enteric infections, prophylaxis in the immuno compromised neutropenic host (13).
- They have been used in treatment and prophylaxis of ocular infections (110).
- Some fluoroquinolones are the drugs of first choice in prevention and treatment of diarrheal disease (63).

The fluoroquinolones are presently found to be effective in tuberculosis, primarily in cases involving resistance or intolerable to first line antituberculosis therapy. However, there is concern about the development of fluoroquinolone resistance in *Mycobacterium tuberculosis,* particularly when administered as monotherapy or as the only active agent in a failing multidrug regimen (111). Important fluoroquinolones along with their structures, pharmacokinetics and indications have been summarized in Table 2.

REFERENCES

1. Dax S.L.: Quinolone antibacterials, in Antibacterial Chemotherapeutic Agents, The R W Johnson Pharmaceutical Research Institute, Spring House, Pennsylvania, USA, p. 298-345, Blackie Academic and Professional, London 1997.
2. Patrick G.L.: Antibacterial agents, in An Introduction to Medicinal Chemistry, p. 379-435, Oxford University Press, Oxford, New York 2003.
3. Appelbaum P.C., Hunter P.A.: Int. J. Antimicrob. Agents 16, 5 (2000).
4. Abraham D.J.: Quinolone, in Burger's Medicinal Chemistry Drug Discovery, p. 582-587, John Wiley and Sons, Hoboken, New Jersey 2003.
5. Guneysel O., Onur O., Erdede M., Dehizbasi A.: J. Emerg. Med. 36, 338 (2009).
6. Blondeau J.M.: Clin. Ther. 21, 3 (1999).
7. Balkhy H.H., Memish Z.A., Shibl A., Elbashier A., Osoba A.: EMHJ 11, 36 (2005).
8. Dollery C.: Norfloxacin, in Therapeutic Drugs, Churchill Livingstone, p. N137-N140, Harcourt Brace and Co. Ltd., London 1999.
9. Pandey S.N.: Antimicrobial Agents-Sulphonamides and Quinolones, in A Text Book of Medicinal Chemistry (Synthetic and Biochemial Approach), p. 547-585, Mahavir Press, Bhelpur, S.G. Publisher, Varanasi 2003.
10. Sarkozy G.: Vet. Med. Czech. 46, 257 (2001).
11. De Almeida M.V., Saraiva M.F., De Souza M.V.N., Da Costa C.F., Vincente F.R.C., Lourenco M.C.S.: Bioorg. Med. Chem. Lett. 17, 5661 (2007).
12. Anquetin G., Greiner J., Mahmoud N., et al.: Eur. J. Med. Chem. 41, 1478 (2006).
13. Scholar E.M.: Am. J. Pharm. Educ. 66, 164 (2003).
14. Moshirfar M., Chew J., Werner L., Meyer J.J., Hunter B., Stevens S., Jensen M., Kleinmann G., Mamalis N.: Graefes Arch. Clin. Exp. Ophthalmol. 246, 1455 (2008).
15. Sharma P.C., Jain S.: Acta Pol. Pharm. Drug Res. 65, 551 (2008).
16. Sharma P.C., Jain S.: Acta Pharm. Sci. 50, 35 (2008).
17. Domagala J.M.: J. Antimicrob. Chemother. 33, 685 (1994).
18. Foroumadi A., Emami S., Hassanzadeh A., Rajaee M., Sokhanavr K., Moshafi M.H., Shafiee A.: Bioorg. Med. Chem. Lett. 15, 4488 (2005).
19. Nagawade R.R., Khanna V.V., Bhagwat S.S., Shinde D.B.: Eur. J. Med. Chem. 40, 1325 (2005).
20. Foroumadi A., Oboudiat M., Emami S., Karimollah A., Saghaee L., Moshafi M.H., Shafiee A.: Bioorg. Med. Chem. 14, 3421 (2005).
21. Sriram D., Yogeeswari P., Basha J.S., Radha D.R., Nagaraja V.: Bioorg. Med. Chem. 13, 5774 (2003).
22. Foroumadi A., Emami S., Mehni M., Moshafi M.H., Shafiee A.: Bioorg. Med. Chem. Lett. 15, 4536 (2005).
23. Zhao Y.L., Chen Y.L., Sheu J.Y., Chen I.L., Wang T.C., Tzeng C.C.: Bioorg. Med. Chem. 13, 3921 (2005).
24. Reddy G.V., Kanth S.R., Maitraie D., et al.: Eur. J. Med. Chem. 44, 1570 (2009).
25. Jazayeri S., Moshafi M.H., Firoozpour L., et al.: Eur. J. Med. Chem. 44, 1205 (2009).

26. German N., Wei P., Kaatz G.W., Kerns R.J.: Eur. J. Med. Chem. 43, 2453 (2008).
27. El-Gazzar A.B.A., Youssef M.M., Youssef A.M.S., Abu-Hashem A.A., Badria F.A.: Eur. J. Med. Chem. 44, 609 (2009).
28. Winter R.W., Kelly J.X., Smilkstein M.J., Dodean R., Hinrichs D., Riscoe M.K.: Exp. Parasitol. 118, 487 (2008).
29. Vargas F., Zoltan T., Rivas C., et al.: J. Photochem. Photobiol. B: Biology 92, 83 (2008).
30. Wall M.J., Chen J., Meegalla S., et al.: Bioorg. Med. Chem. Lett. 18, 2097 (2008).
31. Senthilkumar P., Dinakaran M., Yogeeswari P., Sriram D., China A., Nagaraja V.: Eur. J. Med. Chem. 44, 345 (2009).
32. Ball P., Fernald A., Tillotson G.: Exp. Opin. Invest. Drugs 7, 761 (1998).
33. Radl S.: Pharmacol. Ther. 48, 1 (1990).
34. Stein G.E.: Pharmacotherapy 8, 301 (1988).
35. Tillotson G.: J. Med. Microbiol. 44, 320 (1996).
36. Cozzarelli N.R.: Science 207, 953 (1980).
37. Schmidt F.J., Hofmann B., Hansen B., et al.: J. Antimicrob. Chemother. 41, 481 (1998).
38. Walters J.D., Zhang F., Nakkula R.J.: Antimicrob. Agents Chemother. 43, 2710 (1999).
39. Aydemir S., Tunger A., Cilli F.: West Indian Med. J. 55, 9 (2006).
40. Cassell G.H., Mekalanos J.: JAMA 285, 601 (2001).
41. Rubin J., Walker R.D., Blickenstaff K., Jones S.B., Zhao S.: Vet. Microbiol. 131, 164 (2008).
42. Hooper D.C.: Emerg. Infect. Diseases 7, 337 (2001).
43. Cattoir V., Nectoux J., Lascols C., Deforges L., Delchier J.C., Megraud F., Soussy C.J., Cambau E.: Int. J. Antimicrob. Agents 29, 389 (2007).
44. Hooper D.C., Wolfson J.S.: Mechanisms of bacterial resistance to quinolones, in The quinolone antimicrobial agents, Hooper D.C., Wolfson J.S., Eds., 2nd ed., p. 97-118, American Society for Microbiology, 1993.
45. Piddock L.J.V.: Drugs 49, 29 (1995).
46. Taba H., Kusano N.: Antimicrob. Agents Chemother. 42, 2193 (1998).
47. Livermore D.M.: Eur. J. Clin. Microbiol. Infect. Dis. 9, 1 (2004).
48. Wiedemann B., Heisig P.: Infection 22, S73 (1994).
49. Scheld W.M.: Emerg. Infect. Diseases 9, 1 (2003).
50. Buck M.L.: Pediatr. Pharm. 4, 12 (1998).
51. Efthymiopoulos C., Blum B., Maroli A., Bramer S.L.: Clin. Pharmacokinet. 33, 39 (1997).
52. Jensen M.K., Fiscella R.G., Moshirfar M., Mooney B.: J. Cataract. Refract. Surg. 34, 1460 (2008).
53. Child J., Andrews J.M., Wise R.: Antimicrob. Agents Chemother. 39, 513 (1995).
54. Haria M., Lamb H.M.: Drugs 54, 435 (1997).
55. Bron N.J., Dorr M.B., Mant T.G., Webb C.L., Vasso A.B.: J. Antimicrob. Chemother. 38, 1023 (1996).
56. Nakashima M., Uematsu T., Kosuge K., et al.: Antimicrob. Agents Chemother. 39, 2635 (1995).
57. Chein S.C., Rogge M.C., Gisclon L.G., et al.: Antimicrob. Agents Chemother. 41, 2256 (1997).
58. Fish D.N., Chow A.T.: Clin. Pharmacokinet. 32, 101 (1997).
59. Johnson J.H., Wise R. Andrews J.M., Cooper M.A.: Antimicrob. Agents Chemother. 36, 2444 (1992).
60. Teng R., Dogolo L.C., Willavize S.A., Friedman H.L., Vincent J.: J. Antimicrob. Chemother. 39, 87 (1997).
61. Kepa L., Oczko-Grzesik B., Stolarz W., Sobala S.B.: J. Clin. Neurosci. 12, 562 (2005).
62. Cheng D., Xu W.R., Liu C.X.: World J. Gastroenterol. 13, 2496 (2007).
63. Oliphant C.M., Green G.M.: Am. Fam. Physician 65, 455 (2002).
64. Wolfson J.S., Hooper D.C.: Eur. J. Clin. Microbiol. Infect. Dis. 10, 267 (1991).
65. Apley M.D., Upson D.W.: Am. J. Vet. Res. 54, 937 (1993).
66. Neu H.C., Kumada T., Chin N.X., Mandell W.: Drugs Exp. Clin. Res. 13, 63 (1987).
67. Jacobs M.R., Appelbaum P.C.: Rev. Med. Microbiol. 6, 77 (1995).
68. Klugman K.P.: Clin. Microbiol. Rev. 3, 171 (1990).
69. Felmingham D., O'Hare M.D., Robbins M.J., et al.: Drugs Exp. Clin. Res. 11, 317 (1985).
70. Gruneberg R.N., Felmingham D., O'Hare M.D.: J. Antimicrob. Chemother. 22, 9 (1988).
71. Ridgway G.L., O'Hare M.D., Felmingham D., Gruneberg R.N.: Drugs Exp. Clin. Res. 11, 259 (1985).
72. Bauernfeind A.: J. Antimicrob. Chemother. 40, 639 (1997).
73. Hoellman D.B., Lin G., Jacobs M.R., Appelbaum P.C.: J. Antimicrob. Chemother. 43, 645 (1999).
74. Visalli M.A., Jacobs M.R., Appelbaum P.C.: Antimicrob. Agents Chemother. 41, 2786 (1997).
75. Ho P.L., Que T.L., Tsang D.N.C., Ng T.K., Chow K.H., Seto W.H.: Antimicrob. Agents Chemother. 43, 1310 (1999).

76. Chen D.K., McGeer A., De Azaevedo J.C., Low D.E.: New Engl. J. Med. 341, 233 (1999).
77. Nakane T., Iyobe S., Sato K., Mitsuhashi S.: Antimicrob. Agents Chemother. 39, 2822 (1995).
78. Cormican M.G., Jones R.N.: Antimicrob. Agents Chemother. 41, 204 (1997).
79. Woodcock J.M., Andrews J.M., Boswell J.F., Brenwald N.P., Wise R.: Antimicrob. Agents Chemother. 41, 101 (1997).
80. Visalli M.A., Bajaksouzain S., Jacobs M.R., Appelbaum P.C.: Antimicrob. Agents Chemother. 41, 1475 (1997).
81. Davis R., Markham A., Balfour J.A.: Drugs 51, 1019 (1996).
82. MacGowan A.P., Bowker K.E., Holt H.A., Wootton M., Reeves D.S.: J. Antimicrob. Chemother. 40, 503 (1997).
83. Prosser B.L.T., Beskid G.: Diagn. Microbiol. Infect. Dis. 21, 33 (1995).
84. Holden H.E., Barrett J.F., Huntington C.M., Muehlbauer P.A., Wahrenburg M.G.: Environ. Mol. Mutagen 13, 238 (1989).
85. Dalhoff A., Peterson U., Endermann R.: Chemotherapy 42, 410 (1996).
86. Krueger S., Zaccai G., Woldawer A., Lanqowski J., O'Dea M., Maxwell A., Gellert M.: J. Mol. Biol. 211, 211 (1990).
87. Hirai K., Yasue T., Hosaka M., Wakabayashi E., Tomizawa H., Nishino K.: Drugs 45, 182 (1993).
88. Miyashita N., Niki Y., Kishimoto T., Nakajima M., Matsushima T.: Antimicrob. Agents Chemother. 41, 1331 (1997).
89. Kenny G.E., Cartwright F.D.: Antimicrob. Agents Chemother. 37, 1726 (1993).
90. Roblin P.M., Montalban G., Hammerschlag M.R.: Antimicrob. Agents Chemother. 38, 1402 (1994).
91. Ridgway G.L., Salman H., Robbins M.J., Dencer C., Felmingham D.: Antimicrob. Agents Chemother. 40, 31 (1997).
92. Hammerschlag M.R., Hyman C.L., Roblin P.M.: Antimicrob. Agents Chemother. 36, 682 (1992).
93. Edelstein P.H., Edelstein M.A., Lehr K.H., Ren J.: J. Antimicrob. Chemother. 37, 117 (1996).
94. Roblin P.M., Hammerschlag M.R.: Antimicrob. Agents Chemother. 42, 951 (1998).
95. Kenny G.E., Cartwright F.D.: Antimicrob. Agents Chemother. 35, 587 (1991).
96. Roblin P.M., Kutlin A., Hammerschlag M.R.: Antimicrob. Agents Chemother. 41, 2033 (1997).
97. Liu L., Guo K., Lu J., et al.: Biomaterials 29, 1509 (2008).
98. Book I.: J. Antimicrob. Agents 20, 320 (2002).
99. Mao Z., Ma L., Gao C., Shen J.: J. Control. Release 104, 193 (2005).
100. Feliciano J., Teper E., Ferrandino M., Macchia R.J., Blank W., Grunberger I., Colon I.: J. Urol. 179, 952 (2008).
101. Lode H., Vogel F., Elies W.: Clin. Ther. 21, 61 (1999).
102. Oneyenwenyi A.J., Winterstein A.G., Hatton R.C.: Pharma World Sci. 30, 544 (2008).
103. Malak K., Naipaul R., Mika Ng, Ruddock B.: CPJ/RPC 140, 327 (2007).
104. Gottberg A.V., Klugman K.P., Cohen C., et al.: Lancet 371, 1108 (2008).
105. Fillastre J.P., Leroy A., Humbert G.: Antimicrob. Agents Chemother. 31, 156 (1987).
106. Lipsky B.A., Dorr M.B., Magner D.J., Talbot G.H.: Clin. Ther. 21, 148 (1999).
107. Torriero A.A.J., Ruiz-Diaz J.J.J., Salinas E., Marchevsky E.J., Sanz M.I., Raba J.: Talanta 69, 691 (2006).
108. Prajapati B.S., Prajapati R.B., Patel B.S.: Indian J. Pediatr. 75, 809 (2008).
109. Farhi D., Dupin N.: Swiss Med. Wkly. 138, 223 (2008).
110. Scoper S.V.: Adv. Ther. 25, 979 (2008).
111. Ginsburg A.S., Grosset J.H., Bishai W.R.: Lancet Infect. Dis. 3, 432 (2003).
112. Lee C., Ronald A.R.: Am. J. Med. 82, 27 (1987).
113. Corrado M.L., Struble W.E., Peter C., Hoagland V., Sabbaj J.: Am. J. Med. 82, 22 (1987).
114. Heseltine P.N.R., Corrado M.L.: Am. J. Med. 82, 88 (1987).
115. Kaplowitz L.G., Vishniavsky N., Evans T., Vartivarian S., Dalton H., Simpson M., Gruninger R.P.: Am. J. Med. 82, 35 (1987).
116. Hooper D.C., Wolfson J.S.: Antimicrob. Agents Chemother. 28, 716 (1985).
117. Adhami Z.N., Wise R., Weston D., Crump B.: J. Antimicrob. Chemother. 13, 87 (1984).
118. Lehto P., Kivisto K.T.: Antimicrob. Agents Chemother. 38, 248 (1994).
119. Stone J.W., Andrews J.M., Ashby J.P., Griggs D., Wise R.: Antimicrob. Agents Chemother. 32, 1508 (1988).
120. Kovarik J.M., Hoepelman A.I., Smit J.M., Sips P.A., Rozenberg A.M., Glerum J.H., Verhoef J.: Antimicrob. Agents Chemother. 36, 2458 (1992).
121. Lubasch A., Keller I., Borner K., Koeppe P., Lode H.: Antimicrob. Agents Chemother. 44, 2600 (2000).

122. Boy D., Well M., Kinzig S.M., Sorgel F., Ankel F.D., Naber K.G.: Int. J. Antimicrob. Agents 23, S6 (2004).
123. Yuk J.H., Nightingale C.H., Quintiliani R., Sweeney K.R.: Antimicrob. Agents Chemother. 35, 384 (1991).
124. Immanuel C., Hemanthkumar A.K., Gurumurthy P., Venkatesan P.: Int. J. Tuberc. Lung Dis. 6, 1017 (2002).
125. Hameed A., Iqbal T., Nawaz M., Batool F., Baig T.T., Ali S., Nurjis F.: Pak. J. Biol. Sci. 5, 1098 (2002).
126. Israel D., Gillum J.G., Turik M., et al.: Antimicrob. Agents Chemother. 37, 2193 (1993).
127. Lode H. Hoffken G., Olschewski P., Sievers B., Kirch A., Borner K., Koeppe P.: Antimicrob. Agents Chemother. 31, 1338 (1987).
128. Teng R., Liston T.E., Harris S.C.: J. Antimicrob. Chemother. 37, 955 (1996).
129. Vincent J., Venitz J., Teng R., Baris B.A., Willavize S.A., Polzer R.J., Friedman H.L.: J. Antimicrob. Chemother. 39, 75 (1997).
130. Wise R., Mortiboy D., Child J., Andrews J.M.: Antimicrob. Agents Chemother. 40, 47 (1996).
131. Chein S.C., Rogge M.C., Gisclon L.G., et al.: Antimicrob. Agents Chemother. 41, 1562 (1997).
132. Chein S.C., Chow A.T., Natarajan J., Williams R.R., Wong F.A., Rogge M.C., Nayak R.K.: Antimicrob. Agents Chemother. 41, 2256 (1997).
133. Struwe M., Greulich K.O., Perentes E., Martus H.J., Suter W., Helbig U.P.: J. Invest. Dermatol. 263, 1 (2008).
134. Johnson J.H., Cooper M.A., Andrews J.M., Wise R.: Antimicrob. Agents Chemother. 36, 2444 (1992).
135. Zix J.A., Geerdes F.H.F., Rau M., Vockler J., Borner K., Koeppe P., Lode H.: Antimicrob. Agents Chemother. 41, 1668 (1997).
136. Mody V.D., Panday K.K., Satia M.C., Modi I.A., Modi R.I., Gandhi T.P.: J. Pharm. Biomed. Anal. 16, 1289 (1998).
137. Santos A., Cremades R., Rodriguez J.C., Pachon E.G., Ruiz M., Royo G.: J. Infect. Chemother. 14, 262 (2008).
138. Trampuz A., Laifer G., Wenk M., Rajacic Z., Zimmerli W.: Antimicrob. Agents Chemother. 46, 3630 (2002).
139. Lober S., Ziege S., Rau M., Schreiber G., Mignot A., Koeppe P., Lode H.: Antimicrob. Agents Chemother. 43, 1067 (1999).
140. Liu X.D., Xie L., Wang J., Liang Y., Li L., Lu L.: Asian J. Drug Metab. Pharmacokinet. 5, 71 (2005).
141. Wise R., Andrews J.M., Ashby J.P., Marshall J.: J. Antimicrob. Chemother. 44, 701 (1999).
142. Kozawa O., Uematsu T., Matsuno H., Niwa M., Nagashima S, Kanamaru M.: Antimicrob. Agents Chemother. 40, 2824 (1996).
143. Efthymiopoulos C.: J. Antimicrob. Chemother. 40, 35 (1997).
144. Cook J.A., Silverman M.H., Schelling D.J., Nix D.E., Schentag J.J., Brown R.R., Stroshane R.M.: Antimicrob. Agents Chemother. 34, 974 (1990).
145. Stroshane R.M., Silverman M.H., Sauerschell R., Brown R.R., Boddy A.W., Cook J.A.: Antimicrob. Agents Chemother. 34, 751 (1990).
146. Matsuoka M., Banno K., Sato T.: J. Chromatogr. B. Biomed. Appl. 676, 117 (1996).
147. Granneman G.R., Carpentier P., Morrison P.J., Pernet A.G.: Antimicrob. Agents Chemother. 35, 436 (1991).
148. Granneman G.R., Braeckman R., Kraut J., Shupien S., Craft J.C.: Antimicrob. Agents Chemother. 35, 2345 (1991).
149. Minami R., Inotsume N., Nakamura C., Nakano M.: Eur. J. Clin. Pharmacol. 45, 489 (1993).
150. Niki Y.: J. Infect. Chemother. 8, 1 (2002).
151. Minami R., Nakamura C., Inotsume N., Nakano M.: Antimicrob. Agents Chemother. 42, 453 (1998).
152. Granneman G.R., Snyder K.M., Shu V.S.: Antimicrob. Agents Chemother. 30, 689 (1986).
153. Wagenlehner F.M.E., Naber K.G.: Eur. Urol. 49, 235 (2006).
154. Cada J.D., Levien T., Baker D.E.: Hosp. Pharm. 38, 851 (2003).
155. Chagan L.: Drug Forecast 28, 769 (2003).
156. Allen A., Bygate E., Oliver S., et al.: Antimicrob. Agents Chemother. 44, 1604 (2000).
157. Gee T., Andrews J.M., Ashby J.P., Marshall G., Wise R.: J. Antimicrob. Chemother. 47, 431 (2001).
158. Allen A., Bygate E., Vousden M., et al.: Antimicrob. Agents Chemother. 45, 540 (2001).
159. De Lepeleire I., Van H.A., Verbesselt R., Tjandra M.T.B., De Schepper P.J.: J. Antimicrob. Chemother. 22, 197 (1988).

160. Imbimbo B.P., Broccali G., Cesana M., Crema F., Attardo P.G.: Antimicrob. Agents Chemother. 35, 390 (1991).
161. Wise R., Jhonson J., O'sullivan N., Andrews J.M., Imbimbo B.P.: J. Antimicrob. Chemother. 28, 905 (1991).
162. Perry G., Mant T.G., Morrison P.J., Sacks S., Woodcock J., Wise R. Imbimbo B.P.: Antimicrob. Agents Chemother. 37, 637 (1993).
163. Kisicki J.C., Griess R.S., Ott C.L., Cohen G.M., McCormack R.J., Troetel W.M., Imbimbo B.P.: Antimicrob. Agents Chemother. 36, 1296 (1992).
164. Randinitis E.J., Bordfuehrer J.I., Eiseman I, Vassos A.B.: Antimicrob. Agents Chemother. 45, 2529 (2001).
165. Randinitis E.J., Koup J.R., Rausch G., et al.: Antimicrob. Agents Chemother. 45, 2536 (2001).
166. Wise R., Jones S., Das I., Andrews J.M.: Antimicrob. Agents Chemother. 42, 428 (1998).
167. O'Grady J., Briggs A., Atarashi S., Kobayashi H., Smith R.L., Ward J., Ward C., Milatovic D.: Xenobiotica 31, 811 (2001).
168. Nakashima M., Uematsu T., Kosuge K., Umemura K., Hakusui H., Tanaka M.: Antimicrob. Agents Chemother. 39, 170 (1995).
169. Stass H., Dalhoff A., Kubitza D., Schuhly U.: Antimicrob. Agents Chemother. 42, 2060 (1998).
170. Siefert H.M., Domdey B.A., Henninger K., Hucke F., Kohlsdorfer C., Stass H.H.: J. Antimicrob. Chemother. 43, 69 (1999).

Received: 19. 11. 2008