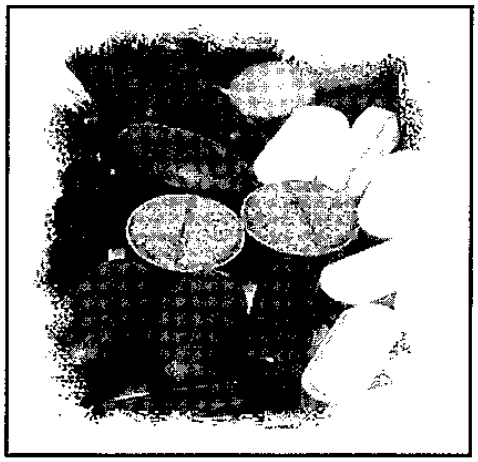
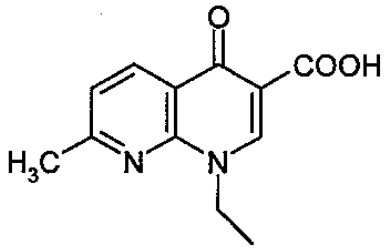
Quinolone



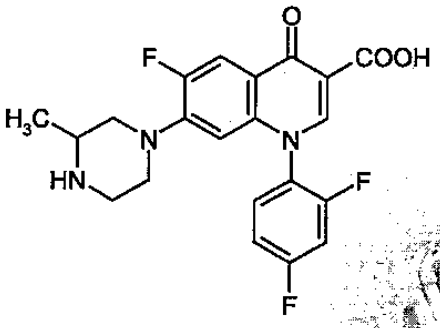
Dr. Sommai Patitungkho*

A. History:

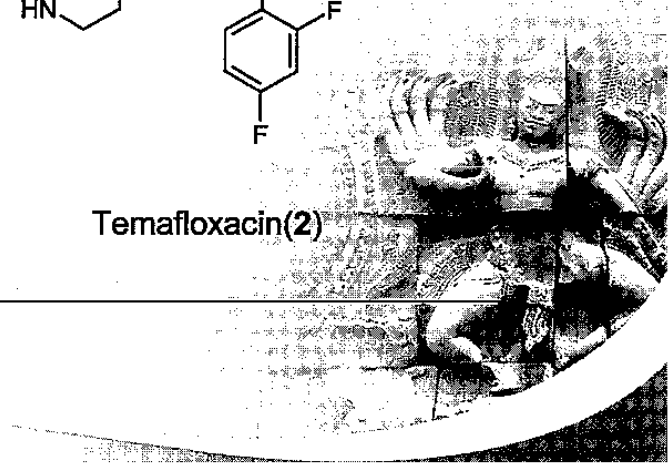
The development of quinolone antibacterials was initiated after the discovery of the naphthyridine agent, viz. nalidixic acid (1), as a by-product of the chloroquine synthesis in the early 1960s [1]. Further progress was achieved with the introduction of oxolinic acid and cinoxacin with improved activity against gram-negative bacteria. Another compound, viz. pipemidic acid, synthesized around the same time had limited activity against Pseudomonas aeruginosa [2]. The broad-spectrum antibacterial activity was introduced into this class of quinolone compounds though fluorination at C-6 position giving rise to class of compounds which are commonly known as fluoroquinolones [2]. They constitute a major group of synthetic antibiotics with activity that ranges against the enterobacteriaceae to gram-positive pathogens including streptococci and staphylococci.



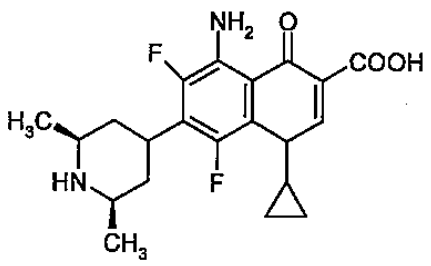
Nalidixic acid(**1**)



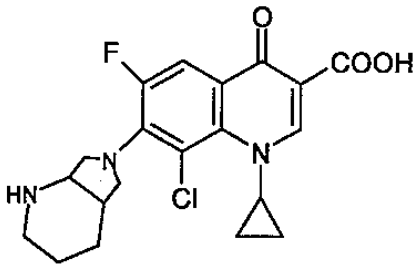
Temafloxacin(**2**)



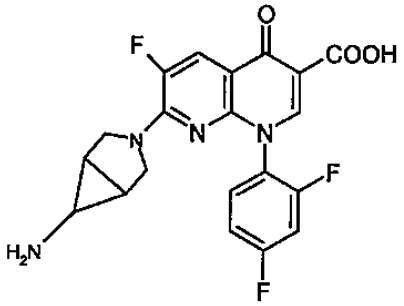
*Faculty of Science, Buriram Rajabhat University



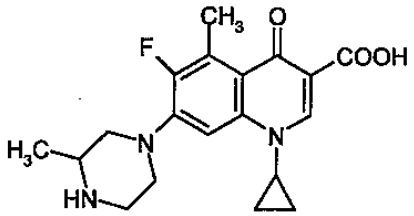
Sparfloxacin(**3**)



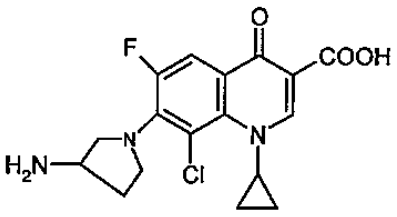
BAY 3118 (**4**)



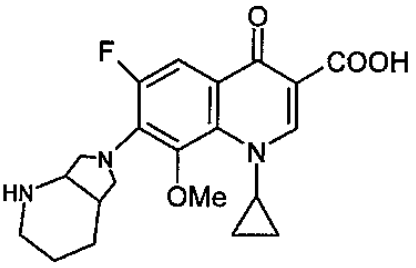
Trovafloxacin(**5**)



Grepafloxacin (**6**)



Clinafloxacon (**7**)



Moxifloxacin (**8**)

The next significant advance in the quinolone chemistry occurred in the early 1990s with the synthesis of temafloxacin (2), which had four- to eight-fold greater activity against Streptococcus pneumonia and good activity against anaerobes, such as the Bacteroides and Prevotella spp [3]. However, an unexpected toxicity resulted in its withdrawal only months after its launch. The development of several other compounds such as Sparfloxacin (3) and Bay-3118 (4), having superior antibacterial activity against gram-positive bacteria, had been delayed due to an unacceptable incidence of phototoxicity. In spite of this, molecules differing in the quinolone side chains continued to be synthesized leading to the discovery of compounds such as trovafloxacin (5), grepafloxacin (6), clinafloxacin (7), and moxifloxacin (8), which

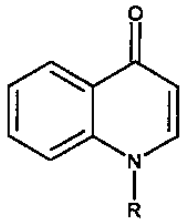
exhibit significantly improved activity against gram-positive bacterial species. Clinical trials have confirmed their high efficacy in treating pneumococcal infections together with high potency against Haemophilus influenzae and Moraxella catarrhalis respectively.

These compounds have excellent penetration into respiratory tissues including the intracellular habitat of clamydiae and legionellae which has led to anticipation that modification of earlier compounds may lead to quinolones having superior antibacterial activities with reduced adverse effects.

B. General Structural Features of the Quinolones:

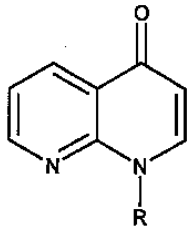
The fluoroquinolones are synthetic derivatives of nalidixic acid that display broad-spectrum anti-bacterial activity including anti-mycobacterial activity [4]. Modifications of fluoroquinolone structure for optimization of more potency for mycobacterial infections and development of the structure-activity relationships (SAR) in the fluoroquinolones have led to preparation of a large number of analogous compounds. Presently, more than 10,000 structurally related agents have been synthesized which exhibit improved activity against gram-positive pathogens compared to ciprofloxacin. Some of them also show potent activity against anaerobes and pathogens that are resistant to many other groups of antimicrobials [5].

Compounds containing a bicyclic aromatic core containing carbon atom at the C-8 position are considered as true quinolone moieties (9) while those having nitrogen, at the same position are technically termed as a naphthyridone (10). The presence of the pyridone ring, a carboxylate group at the C-3 position and the ketonic function at C-4 as shown in 11 are essential for the antibacterial activity.



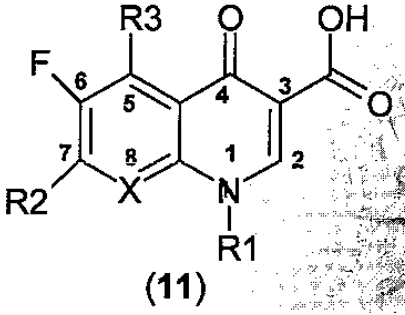
quinolone nucleus

(9)



naphthyridone nucleus

(10)



(11)

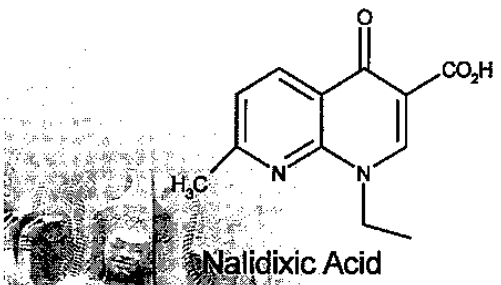
It is observed that a fluorine atom at C-6 position and a piperazine ring at C-7 position greatly enhance the spectrum of biological activity of these compounds. These compounds are much more active against aerobic gram-negative microorganisms but less active against gram-positive ones and hence are extremely useful for treatment of a wide variety of infections [6].

C. Classification of Quinolones:

It should be recognized that there are a number of ways to categorize quinolones such as by their chemical structure, by their structure - activity relationships or by their specific in vitro spectrum of antimicrobial activities. However, at the present time, it is convenient to classify the quinolones into generations. Such classifications are clearly arbitrary. The classification provided here is based on the potency and spectrum of antibacterial activity against some "problem" bacterial organisms [7]. The newer fluoroquinolones have broad-spectrum activity, excellent oral bioavailability, good tissue penetration, favorable safety and tolerability profiles. In the following discussion we have provided a brief account of the four-generations of quinolone drugs taking into account their expanded antimicrobial spectrum and clinical indications.

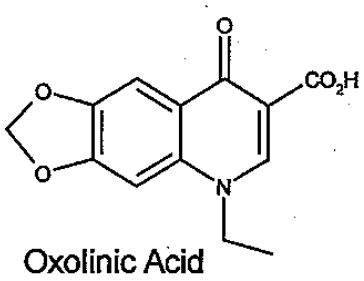
(i) First generation quinolones:

The first generation quinolone derivative (Figure 3.1) reflect the early experimentation with the original nalidixic acid structure. For example, all of these quinolones retain a nitrogen atom at the C-1 position while modifying the naphthyridone structure of nalidixic acid returning to the quinolone nucleus [8]. Compounds belonging to this generation attain high concentrations in the urinary tract and hence are useful therapeutically for the treatment of urinary tract infections. However, they achieve minimal serum levels.



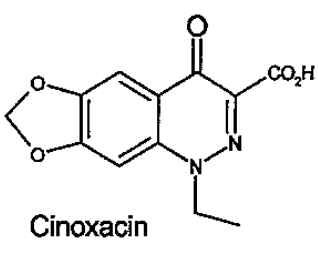
Nalidixic Acid

(12)



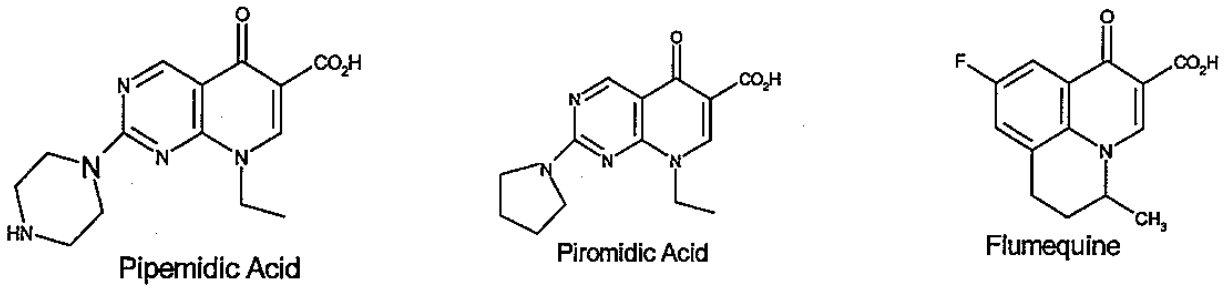
Oxolinic Acid

(13)



Cinoxacin

(14)



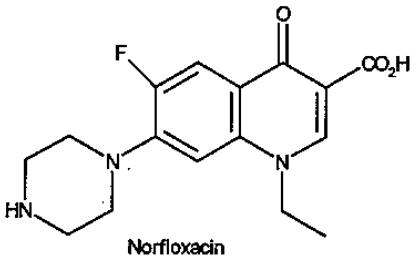
(15) (16) (17)

Figure 3.1: First generation quinolone compounds

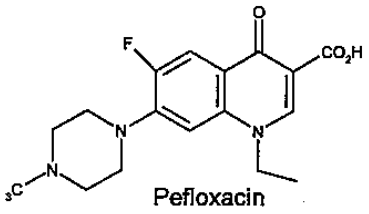
(ii) Second generation quinolones:

One of the major developments in the quinolone compounds took place sometimes in 1980s, when chemists at the Kyorin company reported the preparation of norfloxacin (18), which was the first fluoroquinolone having fluoro group at the C-6 position which resulted in enhancement of the quinolone activity against the enzyme target DNA gyrase and enzyme facilitated penetration into the bacterial cell [9]. Subsequently other modifications to the norfloxacin structure (19, 20) were introduced including an addition of a methyl group at the distal nitrogen of the piperazine ring, which extended drugs half-life more than twice than that of norfloxacin [10]. Enoxacin, the naphthyridone analogue of norfloxacin, possesses roughly similar antibacterial activity but improved bioavailability over norfloxacin [11]. Introduction of fluorine atom and addition of a methyl group onto the piperazine ring of norfloxacin produced fleroxacin (21) and lomefloxacin (22) which exhibit extended half -lives and significantly improved oral absorption [12]. Replacement of N-1 ethyl group of norfloxacin by a cyclopropyl group yielded ciprofloxacin (23) which displays improved MIC values against gram-positive and gram-negative pathogens [13]. Ciprofloxacin is the first quinolone to be useful in a variety of infections beyond those of the urinary tract and sexually transmitted diseases and is widely prescribed in the treatment of lower respiratory tract, skin, and joint infections. It remains as the most potent fluoroquinolone against gram-negative bacterial pathogens including Pseudomonas aeruginosa [14]. Ofloxacin (24) is another fluoroquinolone that has been used in the treatment of a variety of systemic infections [15]. Rufloxacin (25) which is derived from ofloxacin by replacement of the ring oxygen by a sulfur atom has significantly longer half life than any of the other quinolones [16]. The presence of a second amine, in addition to the nitrogen at C-7 of the quinolone nucleus, is not required for in vitro activity but has been found to be important for good activity in vivo [17]. These second generation

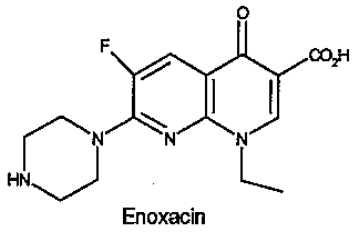
compounds are characterized by good to excellent activity against gram-negative bacteria, with ciprofloxacin exhibiting the strongest gram-negative spectrum. These potency improvements are directly related to enhanced potency against the target DNA gyrase enzymes. A linear correlation has been identified between the MIC against E. coli for these agents and interaction with gyrases, as measured either by inhibition of super coiling or cleavable complex formation. The gram-positive potency of these agents is also enhanced over that of the first generation quinolone agents [18].



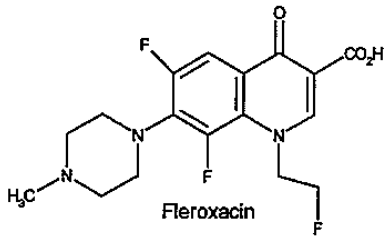
(18)



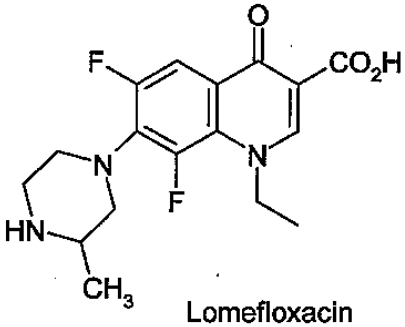
(19)



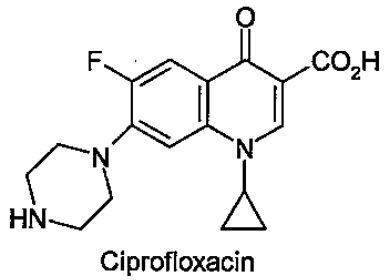
(20)



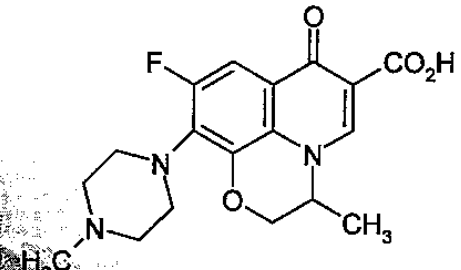
(21)



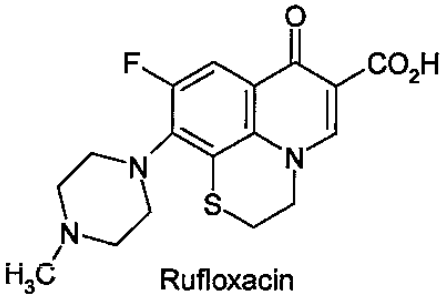
(22)



(23)



(24)

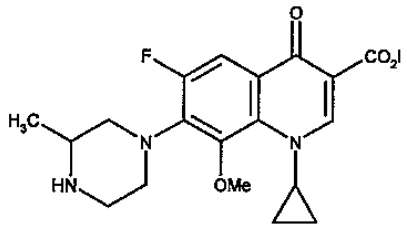


(25)

Figure 3.2 : Second generation quinolones

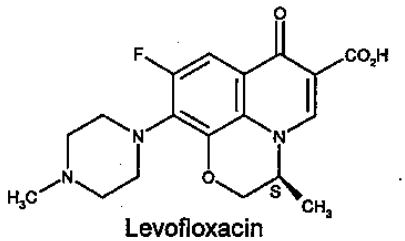
(iii) Third generation quinolones:

The third-generation quinolones (26-31) are characterized by increasing structural novelty and complexity which endows them with some new and useful characteristics such as activity against gram-positive cocci and in some select cases activity against anaerobes and specific pathogens. For example, these agents have an expanded activity against gram-positive penicillin-sensitive and penicillin-resistant S. pneumoniae and inhibitory properties against atypical pathogens such as Mycoplasma pneumoniae and Chlamydia pneumoniae.



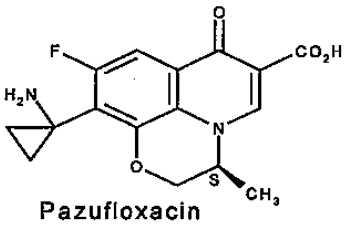
Gatifloxacin

(26)



Levofloxacin

(27)

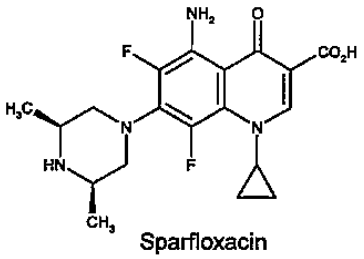


Pazufloxacin

(28)

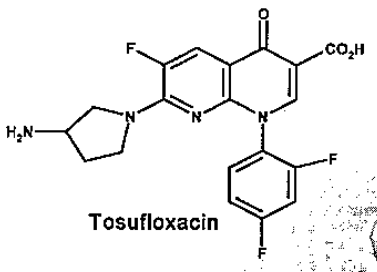
Grepafloxacin

(29)



Sparfloxacin

(30)



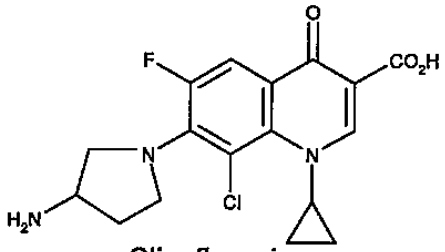
Tosufloxacin

(31)

Figure 3.3 : Third generation quinolones

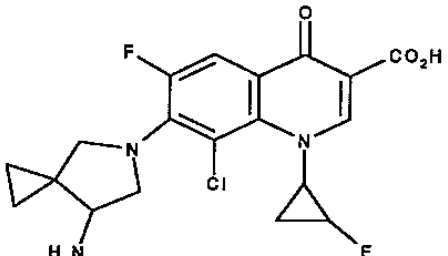
(iv) Fourth generation quinolones:

These newer quinolones have significant antimicrobial activity against anaerobes and pneumococcus while maintaining the gram-positive and gram-negative activity as well as activity against Pseudomonas species. They include clinafloxacin (32), DU-6859a (33), trovafloxacin (34), and moxifloxacin (35) [19].



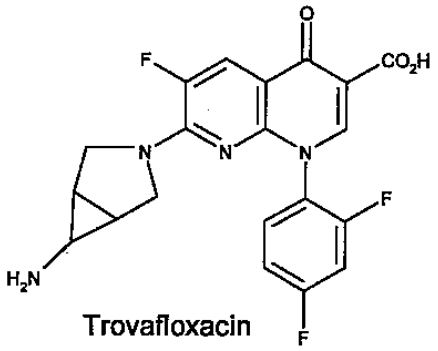
Clinafloxacin

(32)



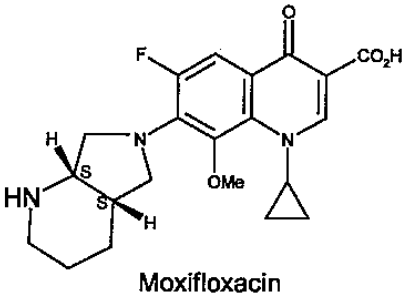
DU-6859a

(33)



Trovafloxacin

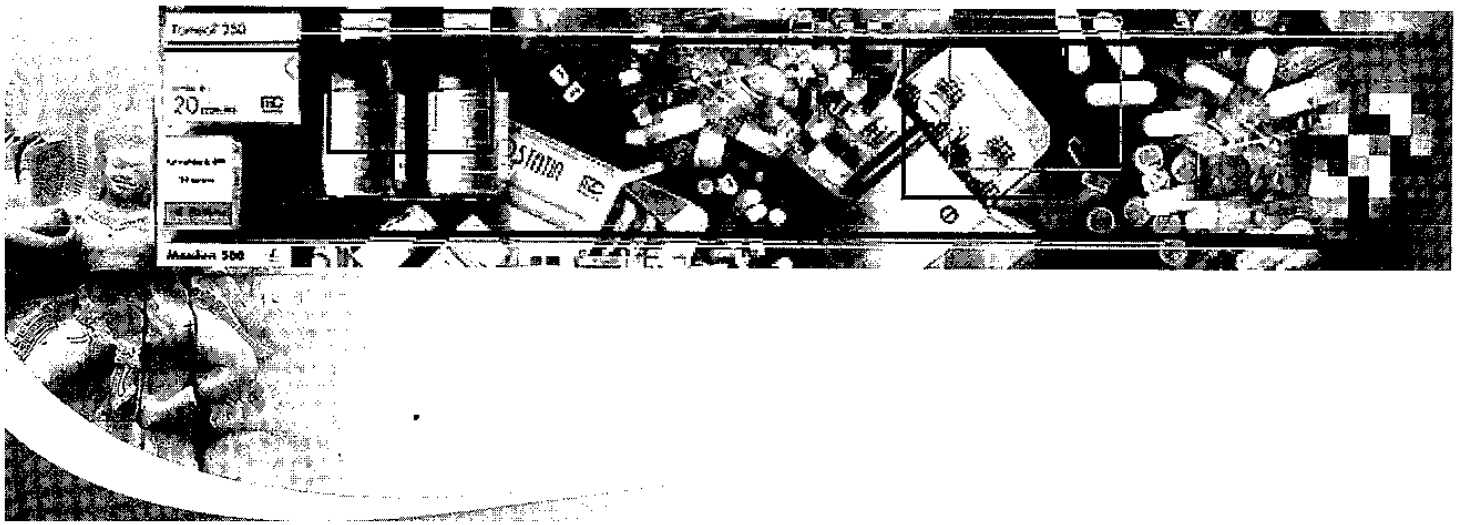
(34)



Moxifloxacin

(35)

Figure 3.4 : Fourth generation quinolones



References:

1. G.Y. Lesher, E.D. Froelich, M.D. Gruet, *J. Med.Pharmacol.Chem.*, **5,** 1063 (1962).
2. P. Ball, *Int.J. Clin. Practice,* **54,** 329 (2000).
3. D. Blum, D.J. Grahm, C.A. McCloskey, *Clin.Infect.Dis.*,**18,** 946 (1994).
4. I.Chopra, P.Brennan, *Mol. Action Antimycobac.Agents,* **78,** 89 (1998).
5. E.M.Brown, D.S.Reeves, Quinolones, In:F.ÕGrady,H.P.Lambert, R.G.Finch, D.Greenwood, eds, *Antibiotic and Chemotherapy,* 7th Ed. Edinburgh: Churchill Livingstone (1997).
6. K.E. Brighty and T. D. Gootz, *J. Antimicrob. Chemother.*, **39** (suppl.B), 1 (1997).
7. I.Turel, *Coord.Chem.Rev.*, **232,** 27(2002).
8. T.D. Gootz and K.E. Brighty, *Med.Res.Rev.*, **16,** 433(1996).
9. J.M. Domagala, *J. Antimicrob.Chemother.*, **33,** 685 (1994).
10. R. Wise, *J. Antimicrob.Chemother.*, **13,** Suppl. D, 71(1986).
11. D.C. Hooper and J.S. Wolfson, *Antimicrob. Agents Chemother.*, **28,** 716 (1985).
12. D.T.W. Chu and P.B. Fernandes, *Adv.Drug Res.*, **21,** 39 (1991).
13. J.S. Wolfson and D.C. Hooper, *Antimicrob.Agents Chemother.*, **28,** 581(1985).
14. J.P.Monk and D.M.Campoli-Richards, *Drugs,* **33,** 346 (1987).
15. T.D. Gootz and P.R.McGuirk, *Expert.Opin. Invest. Drugs,* **3,** 93 (1996).
16. J.M. Domagala, A.J. Bridge, T.P. Culbertson, L. Gambino, S.E. Hagen, G. Karrick, K. Porter, J.P. Sanchez, J.A. Sesnie, G. Spense, D. Szotek and J. Wemple, *J. Med. Chem.*, **34,** 1142 (1991).
17. G.C. Cruplin and J.T. Smith, *Nature,* **260,** 643 (1976).
18. G.C. Crumplin, Molecular effects of 4-quinolones upon DNA gyrase: DNA system, In *"The 4-quinolones"* Sringer-Verlag, New York, (1990).
19. P. Ball, **J. Antimicrob. Chemother., 51** (supply. S1), 21 (2003).