Available online on www.ajper.com

Asian Journal of Pharmaceutical Education and Research

Vol -5, Issue-3, July-September 2016 **SJIF Impact Factor 4.101**

ISSN: 2278-7496

REVIEW ARTICLE

A SHORT REVIEW ON QUINOLONE

Sanjay Kumar Vishwakarma*, Alka Pradhan

Department of Chemistry

Sarojini Naidu Govt. Girls PG College, Bhopal (M.P.), India

Article Received on 12/06/2016

Revised on 18/06/2016

Accepted on 22/06/2016

***Correspondence for Author**

Sanjay Kumar Vishwakarma *

Sarojini Naidu Govt. Girls PG College, Bhopal (M.P.), India

Email:

viceleducation@gmail.com

ABSTRACT:

The discovery of first quinolone as antibacterial compound nalidixic acid was synthesised by Lesher and co-workers in 1962, led to the interest in 2-quinolone and 4-quinolones.Quinolones comprise a relatively large, growing and most interesting group of antibacterial drugs, which have made a major impact on the field of antimicrobial chemotherapy, particularly in the past few decades.

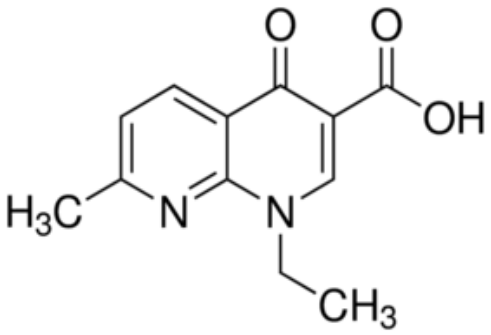
Keywords: Quinolone, Nilidixic acid, DNA

.

Introduction:

In recent years, the numbers of life frightening infections caused worldwide by multi-drug resistant Gram-positive and Gram-negative pathogenic bacteria have extended to an alarming level. The quinolone antibacterial establish a major addition with a broad spectrum of *in-vitro* and *in-vivo* chemotherapeutic efficiency. A number of quinolones like ciprofloxacin, norfloxacin, levofloxacin and moxifloxacin are being marketed and many are nowadays in clinical examination[1].

The discovery of first quinolone as antibacterial compound nalidixic acid was synthesised by Lesher and co-workers in 1962, led to the interest in 2-quinolone and 4-quinolones[2].Quinolones comprise a relatively large, growing and most interesting group of antibacterial drugs, which have made a major impact on the field of antimicrobial chemotherapy, particularly in the past few decades[3].



Nilidixic acid

Quinolones are regarded as a big family of multi-faceted drugs; their chemical synthesis is flexible and can be easily adapted to prepare new congeners with rationally devised structures. QSAR, which is essential for effective drug design also gave us the chance to discover new unprecedented activities, which makes quinolones an endless source of hope and enables further development of new clinically useful drugs[4].

They are a class of 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, respiratory tract infections (RTI), sexually transmitted diseases (STD) and skin infections[5].

Literature survey reveals that quinolones derivatives have potent anticancer, antitubercular, antiulcer, antimicrobial activity. Further quinolones have potent anticonvulsant activity and antagonist of NMDA receptor[6].Quinolone 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 simpler molecular nucleus, which is amenable to many structural modifications[7].

This is because they potentially offer many of the attributes of an ideal antibiotic, combining high potency, a broad spectrum of activity, good bioavailability, oral and intravenous formulations, high serum levels, a large volume of distribution indicating concentration in tissues and a potentially low incidence of side-effects[8].

Classification of Quinolone:

Based on oxygen atom attached with the respect of nitrogen atom of quinolone ring quinolone can divided into two types:

1. 2-quinolone and
2. 4-quinolone

Classification On The Basis Of Spectrum of Activity quinolone are broadly classified generation by generation as

First-generation quinolones.

The success of first generation quinolones spurred the research in this area, which led to the obtainment through synthesis, after 1980, of a new series of compounds with stronger antibacterial properties and a broader spectrum of antibacterial activity, which included gram positive and gram-negative organisms, and which defined by their ability to be applied on all localized infections. Koga and his collaborators introduced Norfloxacin into clinical use in 1980, the first quinolone with a fluorine atom substituted at the C-6 position and a piperazine C-7. Norfloxacin was the first quinolone with increased antimicrobial activity, acting on a large spectrum of gram positive and gram-negative microorganisms, including Pseudomonas aeruginosa[9]. It is based on fluoroquinolone derivatives like ciprofloxacin, norfloxacin, pefolxacin and ofloxacin.

Second-generation quinolones.

Research in the field of derivatives with a quinolone structure have lead to new compounds obtained recently, which have been classified as third and fourth generation systemic quinolones, largely effective against Staphilococcus aureus. Their large antibacterial spectrum includes anaerobes, Chlamydia and Mycoplasma. (Brighty & Gootz, 2000)[10]. Second generation quinolones are lomefloxacin, levofloxacin and prulioxacin.

Third-generation quinolones.

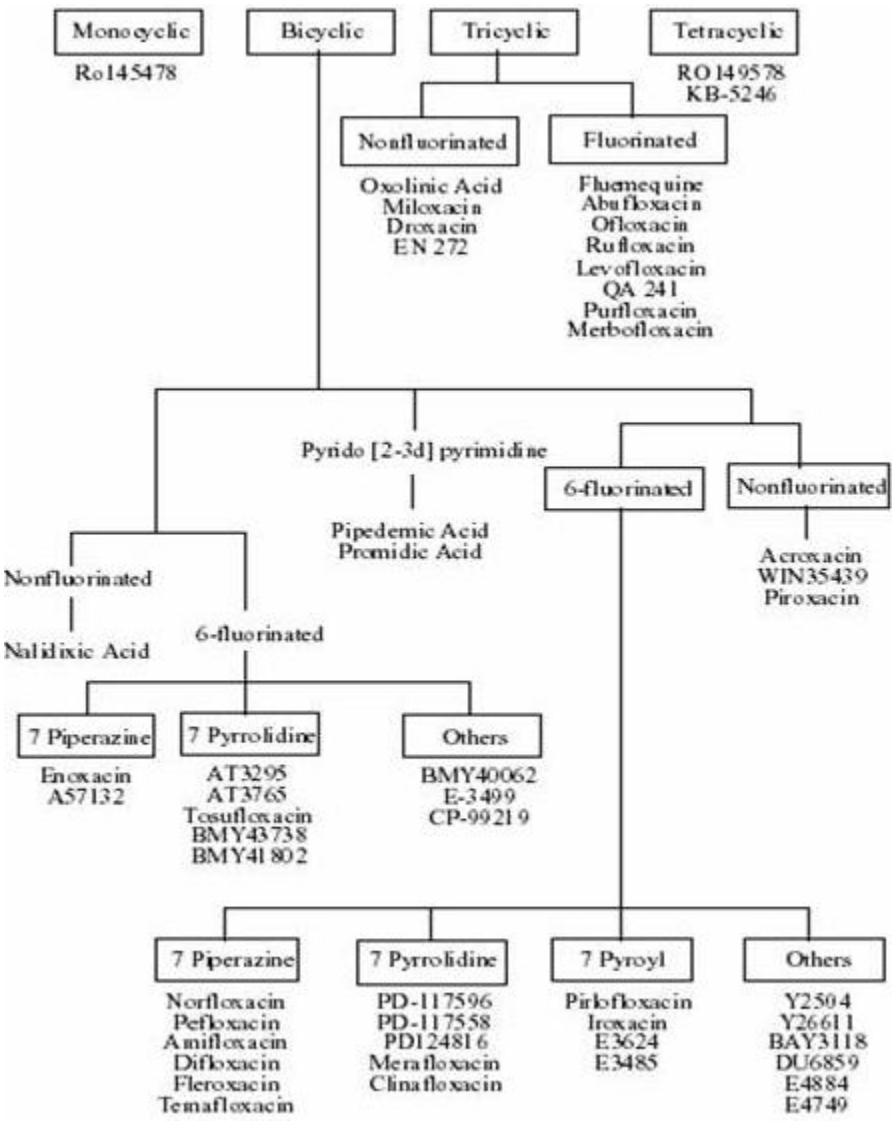
The four generations have the following common aspects: an identical mechanism of action by inhibition the A subunit of DNA-gyrasa, an exclusively chromosomal bacteria resistance and some similar bacteria effects: photo toxicity, neurotoxicity, cartilage toxicity. Eg. Gatifloxacin, Gemifloxacin and moxifloxacin.

Fourth- generation quinolones.

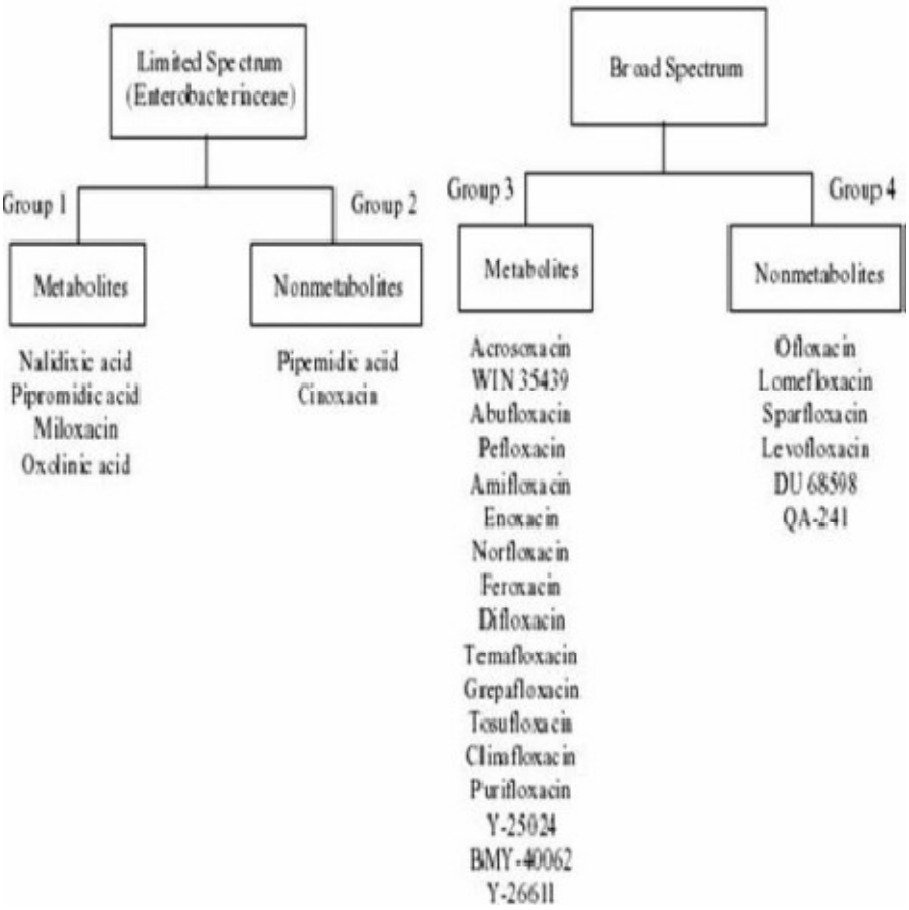
Until now a large number of antibacterial substances belonging to the above mentioned class have been used in medicine. Quinolones are used when treating infections of the urinary tract, the respiratory tract, intestinal infections, ear/nose/throat infections, STD's, soft tissue and skin infections, meningitis caused by gram negative and Staphylococci bacteria, liver and bile infections, septicaemia and endocarditic, prophylaxis and surgical infections and on patients with immune deficiencies. E.g. Finalfloxacin, alatrofloxacin and trovafloxacin.

Two main classifications for fluoroquinolones based on chemical structure and biological properties respectively has been described by Bryskier & Chantot[11] , which logically embraces the majority of active compounds known till date.

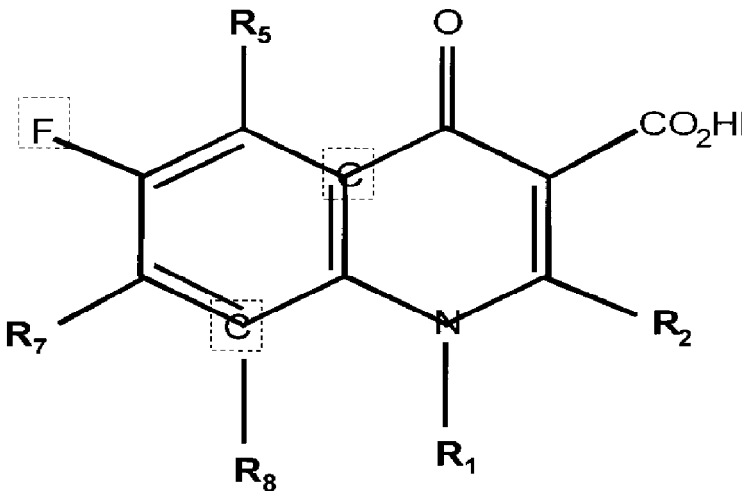
Chemical classification of quinolones:



Biological classification of fluoroquinolones:



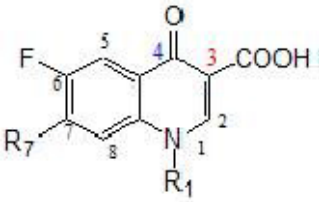
Structure activity relation of quinolone



Position 1. This position is part of the enzyme-DNA binding complex, and has a hydrophobic interaction with the major grove of DNA.[12]

Position 2. This location is very close to the site for DNA gyrase (or topoisomerase IV) binding so it is believed that any added bulk inhibits access and results in a lower level of microbiological activity[13-14]. Only a sulfur, incorporated into a small ring, has been able to replace hydrogen at the R-2 position[14]. To accomplish this, researchers reconfigured positions 3 and 4.

Positions 3 and 4. These two positions on the quinolone nucleus are considered critical for binding to cleaved or perturbed DNA, and no useful substitutions have yet been re ported.Therefore, the 3-carboxylate and 4-carbonyl groups are considered essential for antimicrobial activity[15].

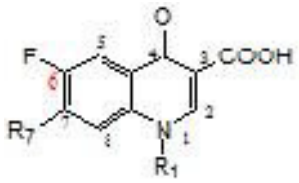


Position 5. Substituents at this position of the basic quinolone nucleus appear to have the capacity to alter overall stearic configuration (planar structure) of the molecule, which is how changes here are thought to affect activity[12].

Modestly sized additions, such as an amino, hydroxyl, or methyl group can markedly increase in vitro activity against gram-positive bacteria[16-17], as well as enhance potency against Toxoplasma gondii[18].

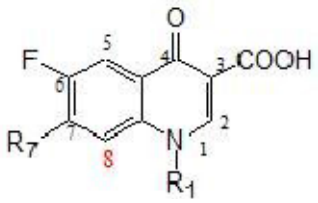
Position 6. The addition of a fluorine molecule here markedly improved antimicrobial activity compared to the original quinolone agents, and gave rise to the now widely used and

clinically successful fluoroquinolone compounds. New 6-Hquinolones are currently under development that appear very promising[19].



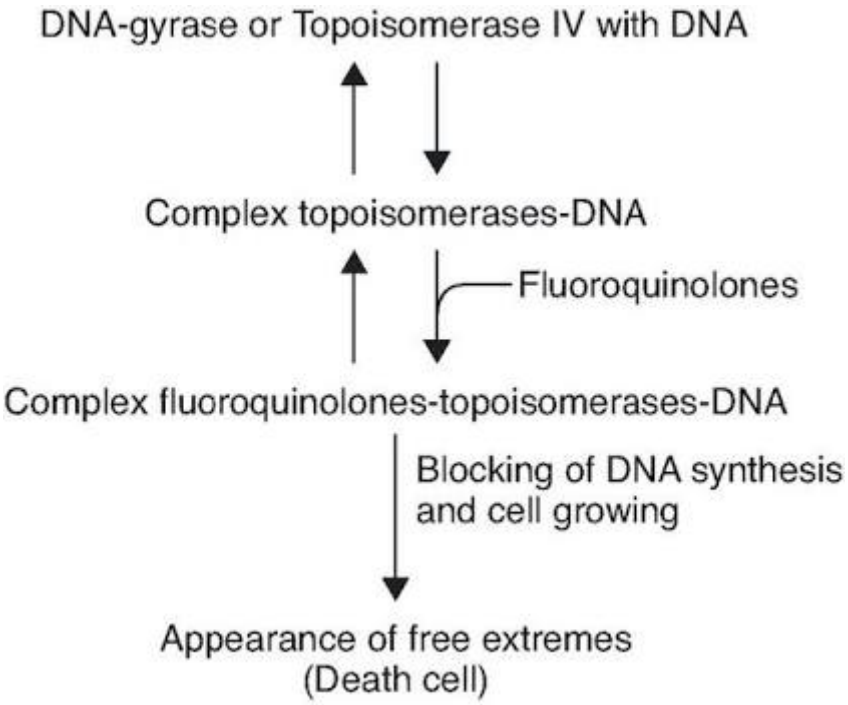
Position 7. This position is considered to be one that directly interacts with DNA gyrase,or topoisomerase IV. The optimal substituents at this position have been found to be groups that contain, at a minimum, a 5- or 6-membered nitrogen heterocycle. The most common of these are aminopyrrolidines and piperazines.

Position - 8 :C-8 fluoro or chloro derivatives are more active in-vivo , owing to better oral absorption . Oxygen substituent at C-8 position , where substituent is part of ring system has been shown to have better in vivo efficacy .C-8 methoxy or ethoxy group appears to increase the spectrum of activity .C-8 methoxy (e.g Gatifloxacin) has been shown to contribute significant activity against anaerobes .



Mechanism of Action

Quinolones quickly inhibit DNA synthesis by promoting cleavage of bacterial DNA in the DNA-enzyme complexes of DNA gyrase and type IV topoisomerase, resulting in rapid bacterial death[20-21]. As a rule, gram-negative bacterial activity correlates with inhibition of DNA gyrase, and gram-positive activity corresponds with inhibitionof DNA type IV topoisomerase[20].



Quinolone advantages:[22]

- Prolonged half-lives
- Efficacy
- Excellent oral absorption
- Ease of administration
- Daily or twice daily dosing
- Significant entry into phagocytic cells.
- Excellent tissue penetration

Quinolones disadvantages or side effects[22-23]**.**

- Tendonitis or tendon rupture
- Gastrointestinal effects
    - Multiple drug interactions
    - Newer quinolones produce additional toxicities to the heart that were not found with the older agents

- Musculoskeletal effects
- CNS effects: Headache, dizziness, and drowsiness have been reported with all fluoroquinolones.
- Phototoxicity: The degree of phototoxic potential of fluoroquinolones is as follows: lomefloxacin > sparfloxacin >ciprofloxacin > norfloxacin = ofloxacin = levofloxacin = gatifloxacin = moxifloxacin.
- Hypoglycemia/Hyperglycemia
- Hepatoxicity

- Cardiovascular effects
- Not used in children
- Hypersensitivity

THERAPEUTIC USES

Norfloxacin and ciprofloxacin have received the most extensive clinical trials. Norfloxacin has mostly been used for the treatment of urinary tract infections. In one study[24], 408 out of 417 (98%) gram-negative isolates and 58 out of 62 (94%) gram-positive isolates were susceptible to norfloxacin. Norfloxacin is active against pathogens that often require parenteral therapy, and therefore, the entire spectrum of urinary pathogens can be treated with a single oral drug. Therefore many patients who once needed long-term hospitalization for parenteral therapy of difficult urinary tract infections can now be discharged earlier and treated with these oral fluoroquinolones.

In dogs, a therapeutically equivalent dose of ciprofloxacin has been suggested to be 4–5 times the dose (on a mg/kg basis) of enrofloxacin which is 2.5 mg/kg twice a day; however, the scientific justification for this recommendation is questionable. Studies have been published indicating that enrofloxacin was effective in the treatment of acute salmonella infections in calves, and produced negative fecal cultures in salmonella carrier calves 5 and 12 days after treatment [25]. In swine, enrofloxacin is reported to eliminate the carrier state for Salmonella with an oral dose of 200 ppm in the feed for 10 days[25]. Clinical field studies were

conducted with enrofloxacin and difloxacin in swine colibacillosis, poultry colibacillosis, and other poultry bacterial and mycobacterial diseases, with therapeutic success[25].

Parenteral enrofloxacin and oxytetracycline were both effective, and in terms of clinical efficacy, indistinguishable from each other, against Actinobacillus pleuropneumoniae in swine as determined by rectal temperature and lung weight[26].

The fluoroquinolones have shown efficacy against a variety of bacterial diseases and are indicated in the treatment of local and systemic diseases caused by a wide range of gram-positive and gram-negative bacteria, mycoplasma and chlamydia. Due to the wide array of spectrum the use of fluoroquinolones has been proposed in conditions such as deep-seated infections, prostatitis, CNS infections, bone and joint infections, and nosocomial infections resistant to other antibacterial agents. In human beings, the fluoroquinolones are used for the treatment of a variety of severe infections that are either located in tissues inaccessible to other antibacterial agents or caused by bacterial pathogens resistant to other antimicrobial agents. These include (but are not limited to) purulent exacerbations of chronic respiratory infections[27],complicated and uncomplicated urinary tract infections, Salmonella spp. infections, and other infections, such as otitis externa and ophthalmitis, which are resistant to agents[28].

Efficacy rates of enrofloxacin for treating pneumonia and diarrhea in cattle and swine are from 76% to 100%[29]., those of danofloxacin for cattle and swine pneumonia from 83% to 86%[30].Enrofloxacin decreases mortality rates in poultry flocks with respiratory infections[31],similarly like difloxacin, norfloxacin and danofloxacin. Danofloxacin may cause temporal sedentariness, and orbifloxacin may cause temporal walk failure. The oral norfloxacin therapy of dogs suffering from acute enteritis removed the disease in 100%[32], and in another study the urinary tract infection[33].

CONCLUSION

Hypersensitivity, Gastrointestinal effects, musculoskeletal effects ,cardiovascular effects, Tendonitis or tendon ruptures like those that adverse effect makes quinolone-based medicine less useful, but study reveals that their Excellent oral absorption, efficacy and excellent tissue penetration properties open the door of possibilities. Quinolone can be bringing into more uses by modifying their substituent, which may reduce their adverse effect. Literature also reveals that there are lots of work has to done on 2-quinolone which is not in much use in

medicine world and not much work done by researchers. So works on 2-quinolone may open the door of new possibilities, which may be more effective in different disease whether it is caused by bacterial, viral or neuro, or psychological disordered.

REFERENCES

1. Al-Hiari YM and Al-Mazari IS. Molecules. 2007; 12: 1240-1258.
2. Appelbaum PC and Hunter PA, Int. J. Antimicrob. Agents. 2000;16:5.
3. Verma V. CIBTech Journal of Pharmaceutical Sciences. 2014;3 (4): 32-38.
4. Ahmed A and Daneshtalab M. J Pharm Pharmaceut Sci. 2011; 1:52 – 72
5. Soni K. Indo Global Journal of Pharmaceutical Sciences. 2012; 2(1): 43-53.
6. Sathe V amd Vilegave K. International Journal of Pharmacy and Pharmaceutical Science Research. 2012; 2(3) 45-49.
7. Sharma PC. Acta Poloniae Pharmaceutica-Drug Research, 2009; 66(6): 587-604.
8. Emami S and Shafiee A, Iranian Journal of Pharmaceutical Research. 2005; 3: 123-136.
9. Koga, H., Itoh, A and Murayama, *Journal of Medicinal Chemistry*, Vol. 23, No.12, (dec. 1980), pp. 1358-1363, ISSN-0022-2623.
10. Brighty K and Gootz T. Vincent Andriole, Academic Press, 2000; 33-97. ISBN 978-0-12-059517-4
11. Lodha SR, Fluoroquinolones : An Overview, Pharmainfo net.
12. Llorente B, Leclerc F and Cedergren R, Bioorg Med Chem 1996; 4:61–71.
13. Tillotson GS, J Med Microbiol 1996; 44:320–4.
14. Domagala JM. J Antimicrob Chemother. 1994; 33:685–706.
15. Tillotson GS. J Med Microbiol 1996; 44:320–4.
16. Domagala JM. J Antimicrob Chemother. 1994; 33:685–706.)
17. Yoshida T and Yamamoto Y. Chem Pharm Bull (Tokyo). 1996; 44:1074–85.

18. Kahn AA, Araujo FG and Brightly KE, Antimicrob Agents Chemother. 1999; 43:1783–7.

19. Ledoussal B, Almstead JK and Flaim CP. American Societyfor Microbiology, 1999.

20. Hooper D. Quinolones. In: Mandell GL, 5th ed. Philadelphia: Churchill Livingstone, 2000:404-23.

21. Hooper DC. *Drugs* 1999;58(suppl 2):6-10.)

22. Overall safety Yury Bayarski, Fluoroquinolone Antibiotics Classification, Uses and Side Effects, http://EzineArticles.com/?expert=Yury_Bayarski)

23. Appelbaum PC andHunter PA., Int J Antimicrob Agents. 2000 Sep; 16(1):5-15.)

24. Friis C. (Acta Vet. Scand., (Suppl.). 1991; 87, 104–106.

25. Berg J. Clinical indications for enrofloxacin in domestic animals and poultry. In: Quinolones: A new class of antimicrobial agents for use in veterinary medicine. In: Proc. West Vet. Conf, Las Vegas, Nevada: Mobay Corporation. 1988

26. Pijpers A, Vernooy JCM, Cruijsen ALM., Van Leengoed LAMG, Koeman J, Hessels AH, Vandenhoek J and Verheijden JHM. Efficacy of parenteral treatment with oxytetracycline and enrofloxacin against Actinobacillus pleuropneumoniae in swine. In: Proceedings of the Sixth Congress of the European Association for Veterinary Pharmacology and Toxicology. Edinburgh, Scotland. 1994; 93.

27. Maesen FPV, Davies BI, Geraeds WH and Baur C. Drugs. 1987; 34 (1), 74–79.

28. Barza M. Eur. J. Clin. Microbiol. Infect. Dis. 1991; 10: 296–303.

29. Lekeux P and Art T. Vet. Rec., 1988;123, 205–207.

30. Grimshaw WTR, Magonigle RA, Giles CJ, Tanner AC, Risk JE, Lynch MJ and Rice JR. The pharmacokinetics of danofloxacin in cattle. In: XVI World Buiatrics Congress, Salvador, Bahia, Brazil. 1990.

31. Hinz KH and Rottmann S. Studies in vivo on the efficacy of enrofloxacin against Mycoplasma gallisepticum. Avian Pathol. 1990; 19: 511–522.

32. Bhaumik A Indian Vet. J. 1997; 74: 246–247.

33. Patil VK, Keskar DV and Jagadish S. Indian Vet. J., 1997;72:374–377.