



Fluoroquinolones: Chemistry & Action – A Review

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ABSTRACT: Fluoroquinolones 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. 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. The growth in understanding of structure activity relationships with fluoroquinolones has enabled the development of even better compounds. The targets in fluoroquinolone research during the last few years include: improvements in pharmacokinetic properties, greater activity against gram-positive cocci and anaerobes, activity against fluoroquinolone-resistant strains, and improvements in activity against non-fermentative gram-negative species. The compounds developed in the recent years have fulfilled some but not all of these goals; improved bioavailability is one target achieved with most of the more recent compounds allowing for once-daily dosing. © 2011 IGJPS. All rights reserved.

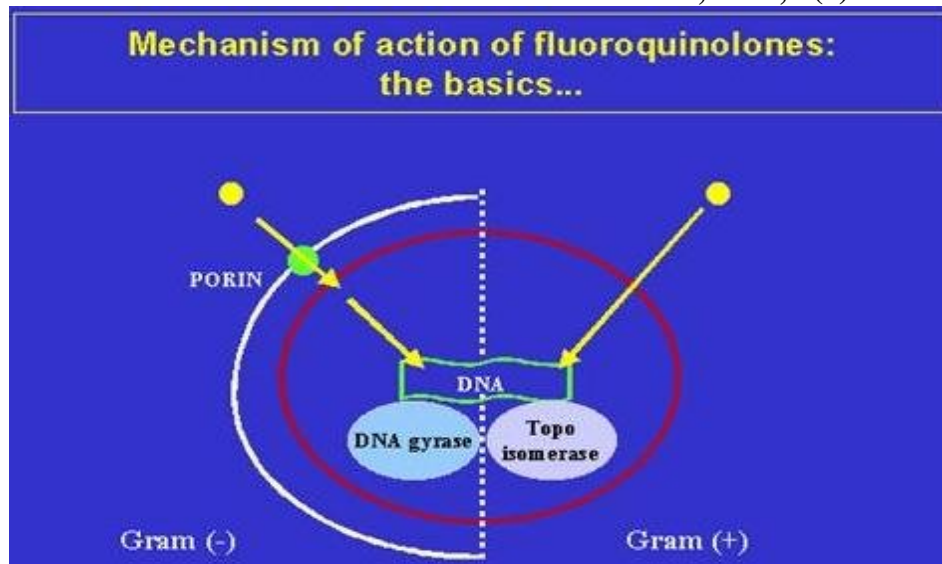
KEYWORDS: *Fluoroquinolones; Medicinal Chemistry; Anti-infective agents.*

INTRODUCTION

The fluoroquinolones are a family of synthetic, broad-spectrum antibacterial agents with bactericidal activity. The parent of the group is nalidixic acid, discovered in 1962 by Lescher and colleagues. The first fluoroquinolones were widely used because they were the only orally administered agents available for the treatment of serious infections caused by gram-negative organisms, including *Pseudomonas* species. The newer fluoroquinolones have a wider clinical use and a broader spectrum of antibacterial activity including gram-positive and gram-negative aerobic and anaerobic organisms. Some of the newer fluoroquinolones have an important role in the treatment of community-acquired pneumonia and intra-abdominal infections.[1,7]

MECHANISM OF ACTION

The mechanism of action of quinolones is through the inhibition of bacterial gyrase, an enzyme involved in DNA replication, recombination and repair. By interfering with gyrase, quinolones arrest bacterial cell growth. The affinity of quinolones to metal ions seems to be an important prerequisite of their antibacterial activity: probably, quinolones bind to the DNA-gyrase-complex via a magnesium ion.[2]



Fluoroquinolones disadvantages or side effects [1,9]

- Tendonitis or tendon rupture
- Multiple drug interactions
- Not used in children
- Newer quinolones produce additional toxicities to the heart that were not found with the older agents
- Gastrointestinal 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.
- Musculoskeletal effects.
- Hepatotoxicity
- Cardiovascular effects
- Hypoglycemia/Hyperglycemia
- Hypersensitivity

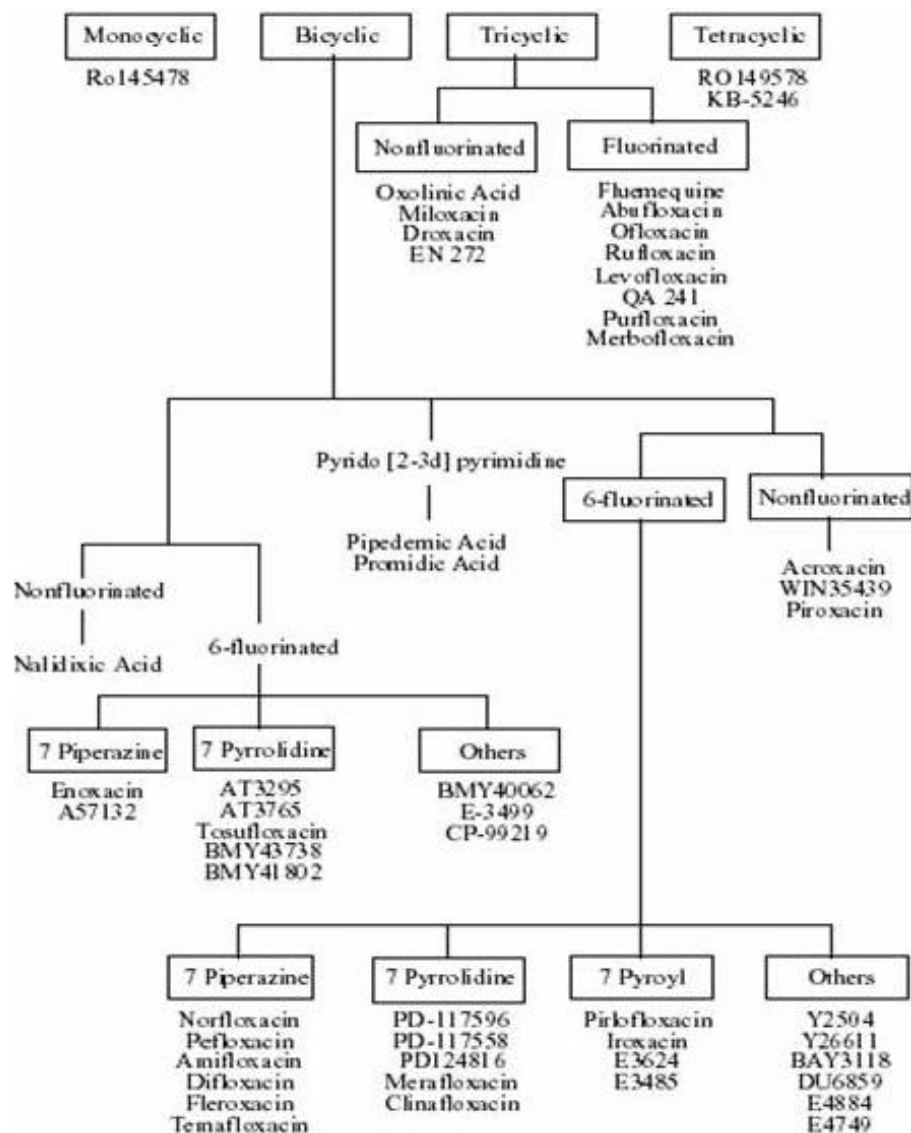
Fluoroquinolone advantages: [1]

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

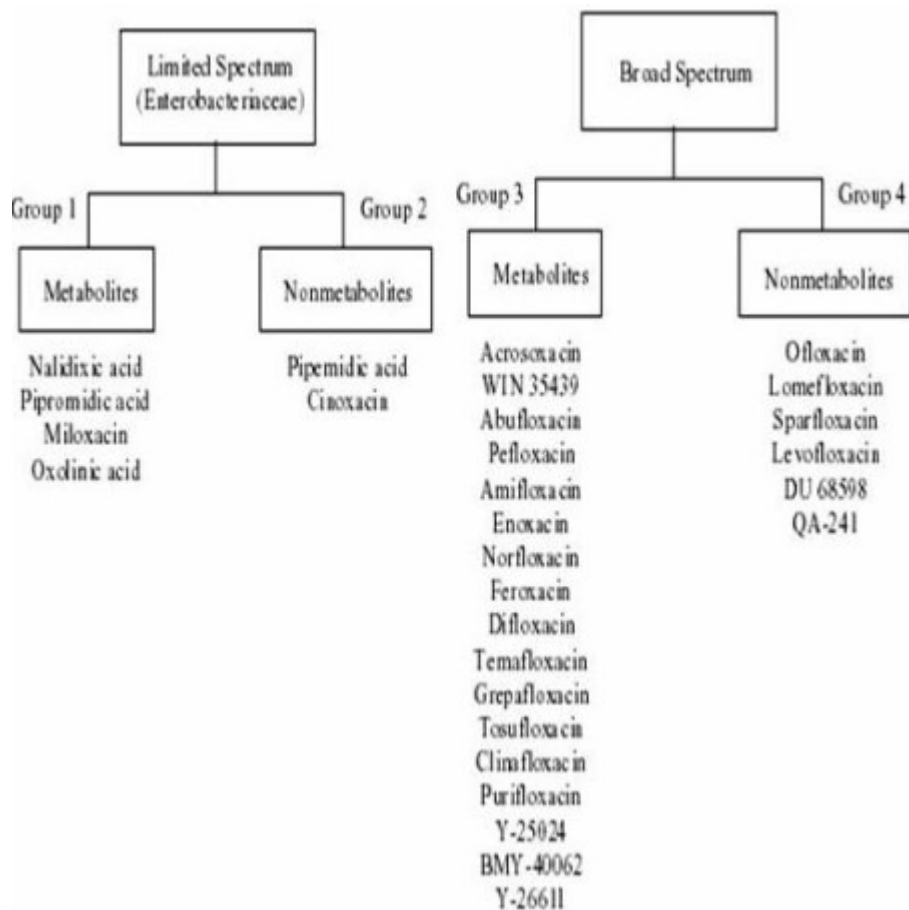
CLASSIFICATION

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

Chemical classification of Fluoroquinolones [3]



Biological classification of fluoroquinolones [3]



Classification On The Basis Of Spectrum Of Activity [4,10,11,12,13,14,15]

Class and agent	Half-life*	Route of administration	Dosage adjustment required	Significant adverse effects†	Significant drug interactions‡
First generation					
Nalidixic acid (NegGram)	60 to 90 minutes	Oral	Renal impairment		Warfarin (Coumadin)
Cinoxacin (Cinobac)	1.1 to 2.7 hours	Oral	Renal impairment	Hypersensitivity (fewer than 3 percent of recipients)	
Second generation					
Norfloxacin (Noroxin)	2.3 to 5.5 hours	Oral	Renal impairment		Warfarin, cyclosporine (Sandimmune)
Lomefloxacin (Maxaquin)	7 to 8.5 hours	Oral	Renal impairment	Phototoxicity, headache (3 to 44 percent of	

Class and agent	Half-life*	Route of administration	Dosage adjustment required	Significant adverse effects†	Significant drug interactions‡
				recipients), abdominal pain (11 percent), nausea (5.6 percent)	
Enoxacin (Penetrex)	3.3 to 7 hours	Oral	Renal or hepatic impairment (patients with advanced cirrhosis)	Phototoxicity (mild)	Warfarin, ranitidine (Zantac), bismuth subsalicylate, theophylline, caffeine
Ofloxacin (Floxin)	5 to 8 hours	Oral, intravenous	Renal or hepatic impairment (patients with severe disease)	Insomnia (13 percent of recipients)	Warfarin
Ciprofloxacin (Cipro)	3 to 5.4 hours	Oral, intravenous	Renal impairment	Nausea, vomiting, abdominal pain	Warfarin, theophylline, caffeine, cyclosporine, glyburide (Micronase)
Third generation					
Levofloxacin (Levaquin)	6 hours	Oral, intravenous	Renal impairment	Headache, nausea (6.6 percent of recipients), diarrhea	
Sparfloxacin (Zagam)	21 hours	Oral	Renal impairment	Phototoxicity (8 percent of recipients), QT-interval prolongation, torsades des pointes	Drugs that prolong the QT interval, including class I antiarrhythmics, tricyclic antidepressants, phenothiazines, cisapride (Propulsid),§ pentamidine (Pentam) and erythromycin
Gatifloxacin (Tequin)	7 hours	Oral, intravenous	Renal impairment		Same as for sparfloxacin
Moxifloxacin (Avelox)	12 hours	Oral	Hepatic impairment	QT-interval prolongation	Same as for sparfloxacin
Fourth generation					
Trovfloxacin (Trovan)Alatrofloxacin (Trovan IV)	7.8 hours	Oral	Hepatic impairment (patients with mild to moderate cirrhosis)	Dizziness (2.4 to 11 percent of recipients), severe hepatotoxicity (rare), candidal vaginitis (1 to 10 percent)	Morphine, citric acid–sodium citrate (Bicitra)
		Intravenous			

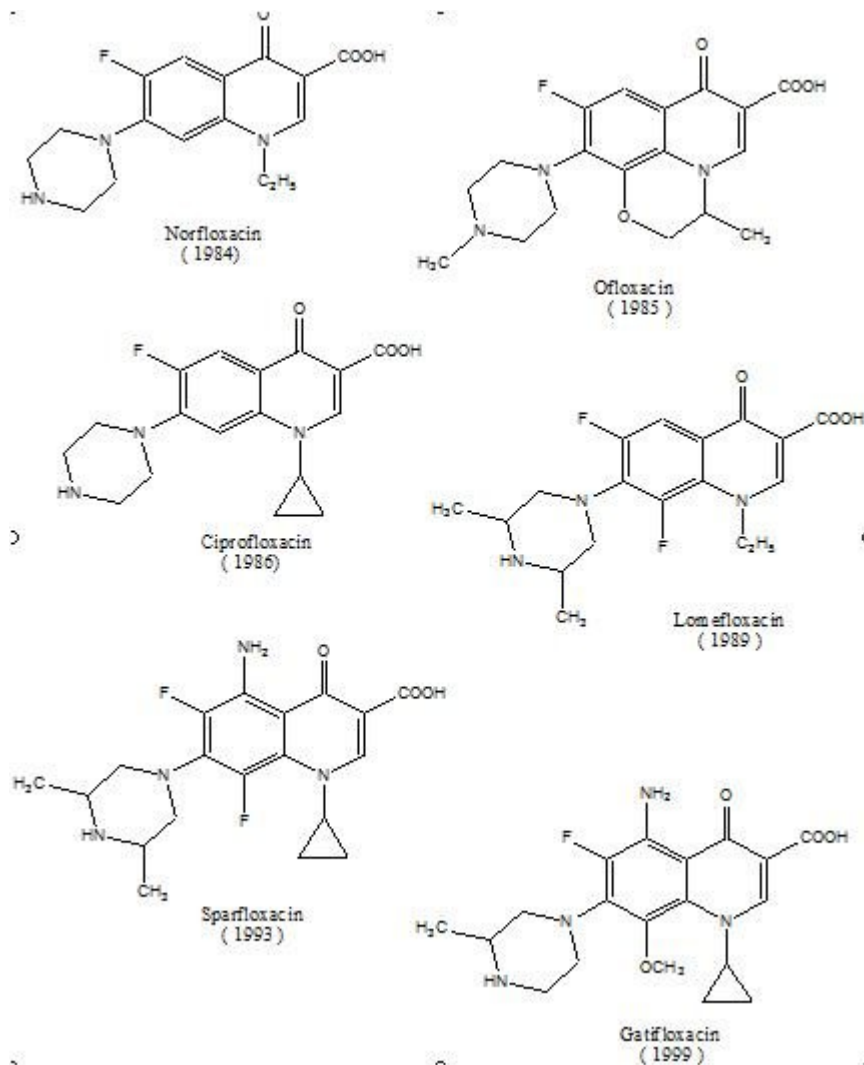
*—Half-lives are significantly increased for renally eliminated compounds.

†—All quinolones cause nausea, insomnia, headache and dizziness (3 percent or more of recipients); tendon rupture and cartilage damage are considered a possible effect of any quinolone.

‡—All quinolones interact with sucralfate (Carafate), antacids containing aluminum or magnesium, iron, calcium and zinc.

§—As of July 14, 2000, cisapride will be available only to patients who meet specific clinical eligibility criteria for a limited-access protocol.

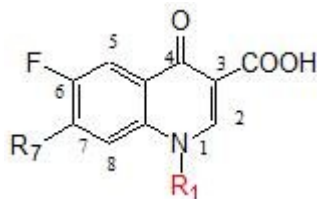
Chemical structures of some commonly used fluoroquinolones[3]



Structure-Activity Relationship:[3,6,8]

Position 1:

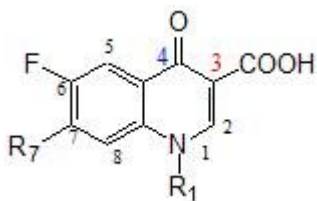
- Earlier study indicated that substitution at N-1 position is important for Anti-bacterial activity .
- QSAR analysis of a set of N-1 allyl and alkyl derivatives suggested an optimum STERIMOL length of 0.42 nm , corresponding approximately to an ethyl group.



- STERIMOL is a program that calculates a set of five parameters characterizing size and shape of a substituent .
- STERIMOL length is defined as length of substituent along the axis of bond between the substituent and the parent molecule.
- Subsequently, the discovery of potent quinolones with N-1 phenyl and N-1 cyclopropyl substitutions indicated that with respect to an N-1 substituent, in addition to steric bulk , there are other factors such as electronic- π donation and ideal spatial effects that also have a great influence on their biological activities .
- Introduction of a t-butyl group at N-1 produced quinolones with enhanced activity against gram positive bacteria with minor reduction of activity against gram negative bacteria .
- In general , cyclopropyl group appears to be optimum for activity. e.g Ciprofloxacin.

Position - 3 :

- Position 3 and 4 , having a link between the carboxylic acid group and the keto group are generally considered necessary for binding of quinolones to DNA gyrase .

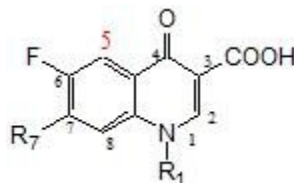


- Classical studies have produced no active quinolone with a significant modification of C-3 carboxylic acid group , with exception of groups which are converted in vivo to carboxylic acid group .

Position - 4 :

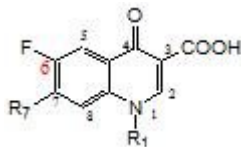
- Position - 4 has not been extensively explored and replacement of 4- keto group with other groups has generally produced inactive or weakly active compounds.

Position - 5 :



- Compounds with small substituents such as nitro, amino , halo, alkyl groups have been synthesized . Among them , C-5 amino group enhances absorption and / or tissue distribution . e.g Sparfloxacin .
- The incidence of photo toxicity of Sparfloxacin is the lowest of the fluoroquinolones , because of the presence of the 5- amino group , which counteracts the effect of the 8- fluoro substituent .

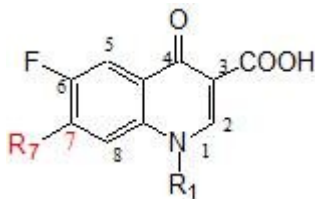
Position - 6 :



- Of various C-6 substituents, H, Cl, Br, F, CH₃, S-CH₃, CO-CH₃, CN, NO₂ etc the addition of a fluorine atom resulted in a dramatic increase in anti-bacterial potency.
- Fluoro group at C-6 seems to improve both the DNA gyrase complex binding (2 to 17 folds) and cell penetration (1 to 70 folds) of the corresponding derivatives with no substitution at C-6.

Position - 7 :

- C-7 piperazinyl group in addition to C-6 fluorine substituent has anti-bacterial potency for superior to that of earlier classical quinolones against both gram-positive and gram-negative bacteria.
- In general, quinolones with small or linear C-7 substituents (H, Cl, CH₃, NH₂-CH₂-CH₂-NH₂, NH-CH₃, NH-NH₂) possess moderate to weak anti-bacterial activities.



- Various substitutions tried at C-7 position are -
- substituted piperazinyl
- substituted pyrrolidinyl
- substituted morpholinyl
- In general, the substitution of methyl at C-4 position of the piperazinyl group enhances gram-positive anti-bacterial activity with slight decrease in gram-negative activity.

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.

BACTERIAL RESISTANCE

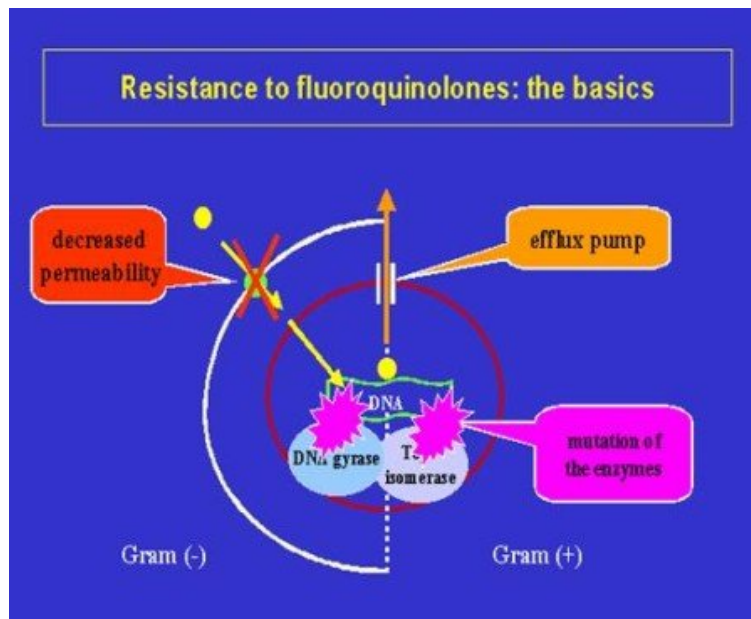
Gram-positive and gram-negative bacteria have been reported to be resistant to quinolones. This resistance appears to be the result of one of three mechanisms: alterations in the quinolone enzymatic targets (DNA gyrase), decreased outer membrane permeability or the development of efflux mechanisms.

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The accumulation of several bacterial mutations (DNA gyrase and bacterial permeability) has been associated with the development of very high minimum inhibitory concentrations to ciprofloxacin in isolates of *Staphylococcus aureus*, *Enterobacteriaceae* species and *P. aeruginosa*.

Resistance to quinolones can also develop because of alterations in bacterial permeability and the development of efflux pumps. This resistance mechanism is shared with antimicrobial agents structurally unrelated to the quinolones, such as the betalactams, tetracyclines and chloramphenicol (Chloromycetin).

Cross-resistance among the quinolones is expected, but the extent to which the minimum inhibitory concentration is affected varies from agent to agent. Therefore, the bacterial susceptibility and pharmacokinetic profiles of each quinolone should be considered in determining the effectiveness of specific agents.[4,9]



Some Recent Trends In Chemical Modifications:[3]

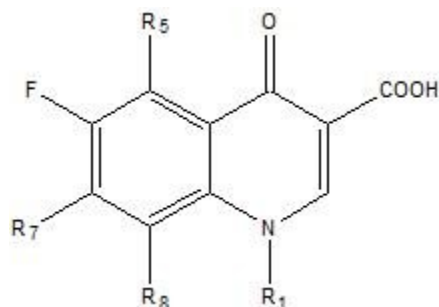
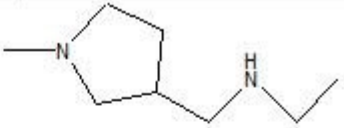

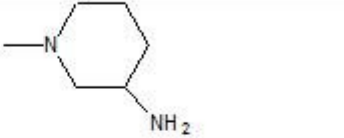

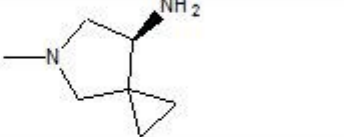
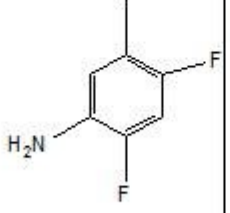

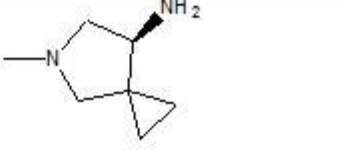


Table No. 6

Name	R ₁	R ₅	R ₇	R ₈
Merafloxacin (preclinical phase)	-C ₂ H ₅	H		F
Balofloxacin (phase -II)		H		OCH ₃
Olamfloxacin (phase -III)		NH ₂		CH ₃
WQ-2944 (preclinical phase)		H	-NH-CH ₃	CH ₃
DK- 507 K (phase-I)		H		OCH ₃

Rapid Color Test Identification System for Screening of Counterfeit Fluoroquinolone

Oxidation of ferrous ammonium sulfate

Solution A: Ferrous ammonium sulfate solution 0.1% (w/v) in 1% H₂SO₄.

Procedure: To the solid sample, 0.5 mL solution A was added followed by sodium bicarbonate till effervescence ceased. Development of yellow-red color indicated presence of fluoroquinolones. The blank had no color.

Test for fluoride with Zr-EDTA-PV (Zirconium-Ethylene diamine tetracetic acid-Pyrocatechol violet) reagent Solution A

The acetate buffer of pH 4.2 was prepared by dissolving 3.7 mL glacial acetic acid and 2.177 g sodium acetate trihydrate in 50 mL water.

Solution B

0.02 g ZrOCl₂, 0.03 g EDTA and 0.001 g pyrocatechol violet were dissolved in water. To this 25 mL solution A was added and volume was made up to 100 mL. This reagent is stable for nearly 2 weeks at room temperature (~ 30 oC).

Procedure

The drug sample was fused with 50 mg of NaNO₃ in a wide mouth glass tube. After cooling, 25 mg NH₄Cl was added and heating was resumed till effervescence ceased. After cooling, the solid mass was dissolved in 0.5 mL water and 0.5 mL solution B was added. The color change of solution B from blue to yellow indicated positive test for fluoroquinolones.[5]

CONCLUSION

This review is an attempt to provide the readers with the information related to fluoroquinolone class of drugs. The new fluoroquinolones are potent synthetic antibacterial agents with broad spectra, including most urinary tract and gastrointestinal tract bacterial pathogens. The use of orally administered fluoroquinolones (when indicated) instead of intravenously administered antibiotics may provide significant advantages in terms of reduced hospitalization or home health care costs. Thus a judicious and efficient use of these antibiotics is recommended.

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