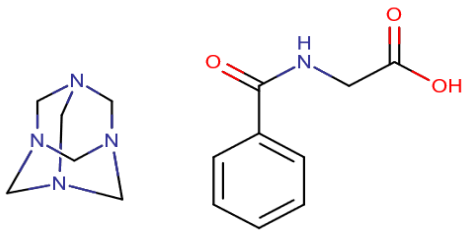
Urinary anti-infectives and Fluoroquinolones

Methenamine hippurate = Hexamethylenetetramine

it is used for the treatment of urinary tract infection as antiseptic.



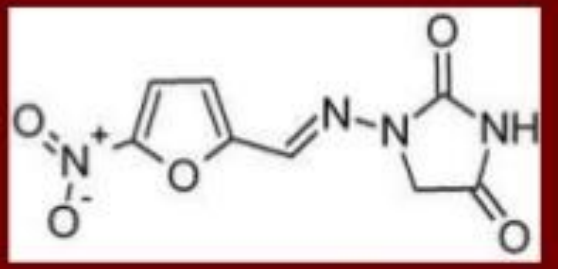
Methenamine is used to prevent or control returning urinary tract infections caused by certain bacteria. It is not used to treat an active infection. Other antibiotics must be used first to treat and cure the infection.

In some countries, this medicine may only be approved for veterinary use.

Furadonin *(Nitrofurantoin – Tab. 0.05 g, Caps. 0.1 g) is*

an effective urinary antiseptic.

- Is a bacteriostatic compound, but may be cidal at higher concentrations and in acidic urine: its activity is enhanced at lower pH 5.5 or below.
- Ihibits many Gr(+) and Gr(–) bacteria.
- It antagonizes the action of Nalidixic acid.

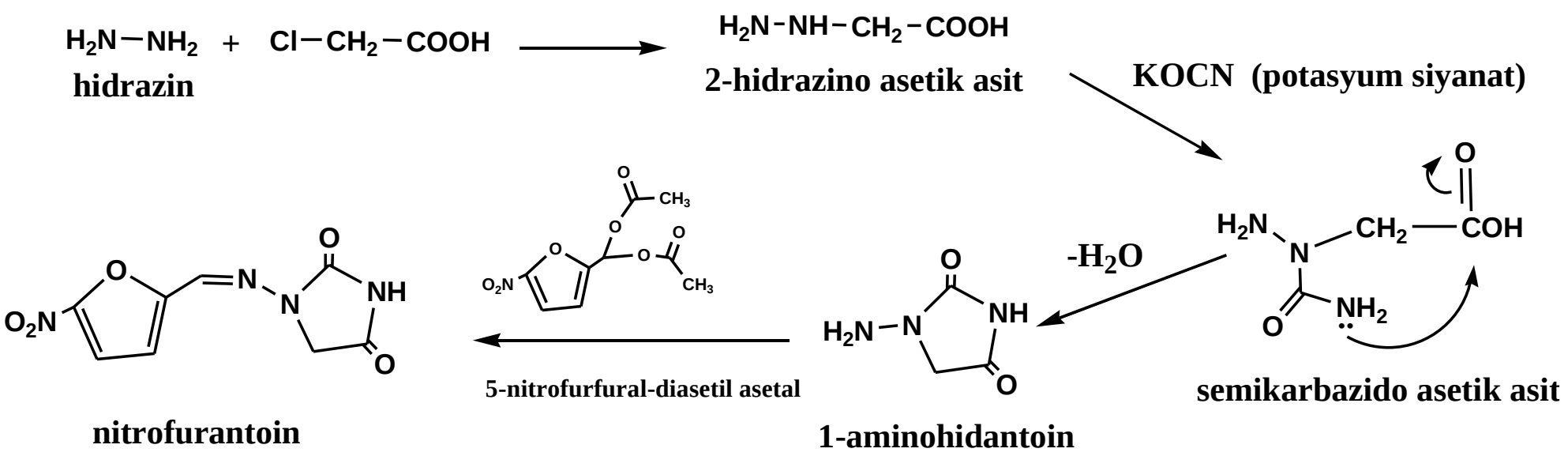


- Mechanism of action. Susceptible bacteria appear to enzymetically reduce furadonin to generate the active form: it is highly reactive and damages DNA.

Clinical uses: urinary tract infection.

Adverse reactions: Interstitial changes in the lung, bronchoobstructive syndrome, cough; neuropathies and hemolytic anaemia occur in glucose-6-phosphate dehydrogenase deficiency.

Rashes, pulmonary infiltration and other hypersensitivity reactions (chills, fever, anaphylaxis); nausea, epigastric pain, diarrhoea.


H2N−NH2 + Cl−CH2−COOH
hidrazin
H2N−NH−CH2−COOH
2-hidrazino asetik asit
KOCN (potasyum siyanat)
semikarbazido asetik asit
-H2O
1-aminohidantoin
5-nitrofurfural-diasetil asetal
nitrofurantoin

The urinary tract includes the bladder, ureters, urethra, and kidneys. When bacteria travels up the urethra, it can travel into the bladder or kidneys, causing infection.

In most cases, antibiotics are used. Commonly prescribed antibiotics to treat bacterial urinary tract infections and bladder infections include

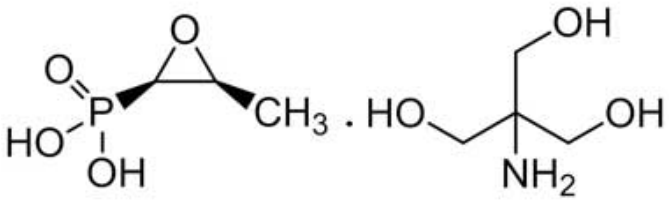
Keflex (cephalexin)

Bactrim (trimethoprim/sulfamethoxazole),

Monurol (Fosfomycin)

Fosfomycin Tromethamine MONUROL

(1R,2S)-(1,2-Epoxypropyl)phosphonic acid, compound with 2-amino-2-(hydroxymethyl)-1,3-propanediol (1:1)



Treatment of uncomplicated UTIs (acute cystitis) in women caused by susceptible *Escherichia coli* or *Enterococcus faecalis*.

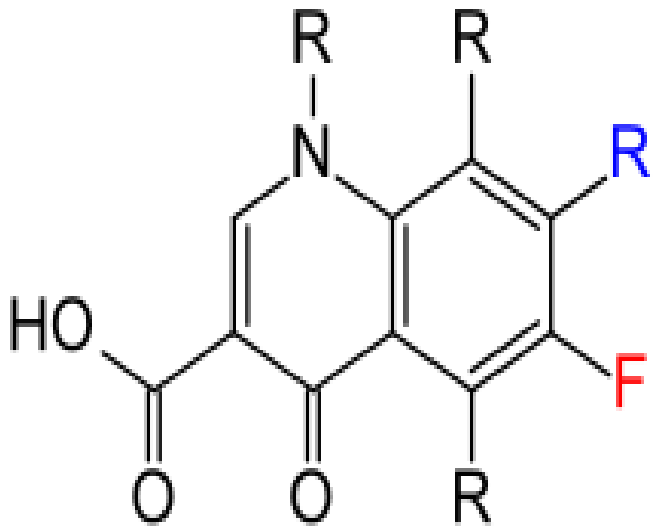
Has been effective when used in a limited number of men for treatment of chronic prostatitis caused by multidrug-resistant Enterobacteriaceae (e.g., *E. coli*)

Quinolones

- The quinolones are a family of synthetic broad-spectrum antibiotics. The term quinolone(s) refers to potent synthetic chemotherapeutic antibacterial agent.
- The first generation of the quinolones begins with the introduction of nalidixic acid in 1962 for treatment of urinary tract infections in humans. Nalidixic acid was discovered by *George Lesher* and co-workers in a distillate during an attempt at chloroquine synthesis.
- They prevent bacterial DNA from unwinding and duplicating

Fluoroquinolones

- The Fluoroquinolones are a relatively new group of antibiotics. Fluroquinolones were first introduced in 1986, but they are really modified quinolones, a class of antibiotics, whose accidental discovery occurred in the early 1960.



- The fluoroquinolones are a family of synthetic, broad-spectrum antibacterial agents with bactericidal activity. 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.*

History

- The first quinolone was nalidixic acid introduced in 1962 for treatment of urinary tract infections in humans. Nalidixic acid was discovered by George Lesher and coworkers in a distillate during an attempt at chloroquine synthesis. Nalidixic acid is thus considered to be the predecessor of all members of the quinolone family, including the second, third and fourth generations commonly known as fluoroquinolones.

- This first generation also included other quinolone drugs, such as pipemidic acid, oxolinic acid, and cinoxacin, which were introduced in the 1970s. They proved to be only marginal improvements over nalidixic acid.
- Since the introduction of nalidixic acid in 1962, more than 10,000 analogs have been synthesized, but only a handful have found their way into clinical practice.

Classification

- **Quinolones (1st generation)**
  - Highly protein bound
  - Mostly used in UTIs
- **Fluoroquinolones (2nd, 3rd and 4th generation)**
  - **Modified 1st generation quinolones**
  - Not highly protein bound
  - Wide distribution to urine and other tissues; limited CSF penetration.

Generation	Drug Names	Spectrum
Nonfluorinated Quinolone	nalidixic acid Cinoxacin rosoxacin	Gram- but not Pseudomonas species.
First generation Fluoroquinolones	norfloxacin ciprofloxacin enoxacin ofloxacin	Gram- (including Pseudomonas species), some Gram+ (S. aureus) and some atypicals.

Second generation Fluoroquinolones	levofloxacin sparfloxacin moxifloxacin Gatifloxacin moxifloxacin	Same as 2nd generation with extended Gram+ and atypical coverage.
Third generation Fluoroquinolones	trovafloxacin clinafloxacin gemifloxacin moxifloxacin sitafloxacin prulifloxacin	Same as 3rd generation with broad anaerobic coverage Fourth-generation fluoroquinolones act at DNA gyrase and topoisomerase IV. This dual action slows development of resistance.

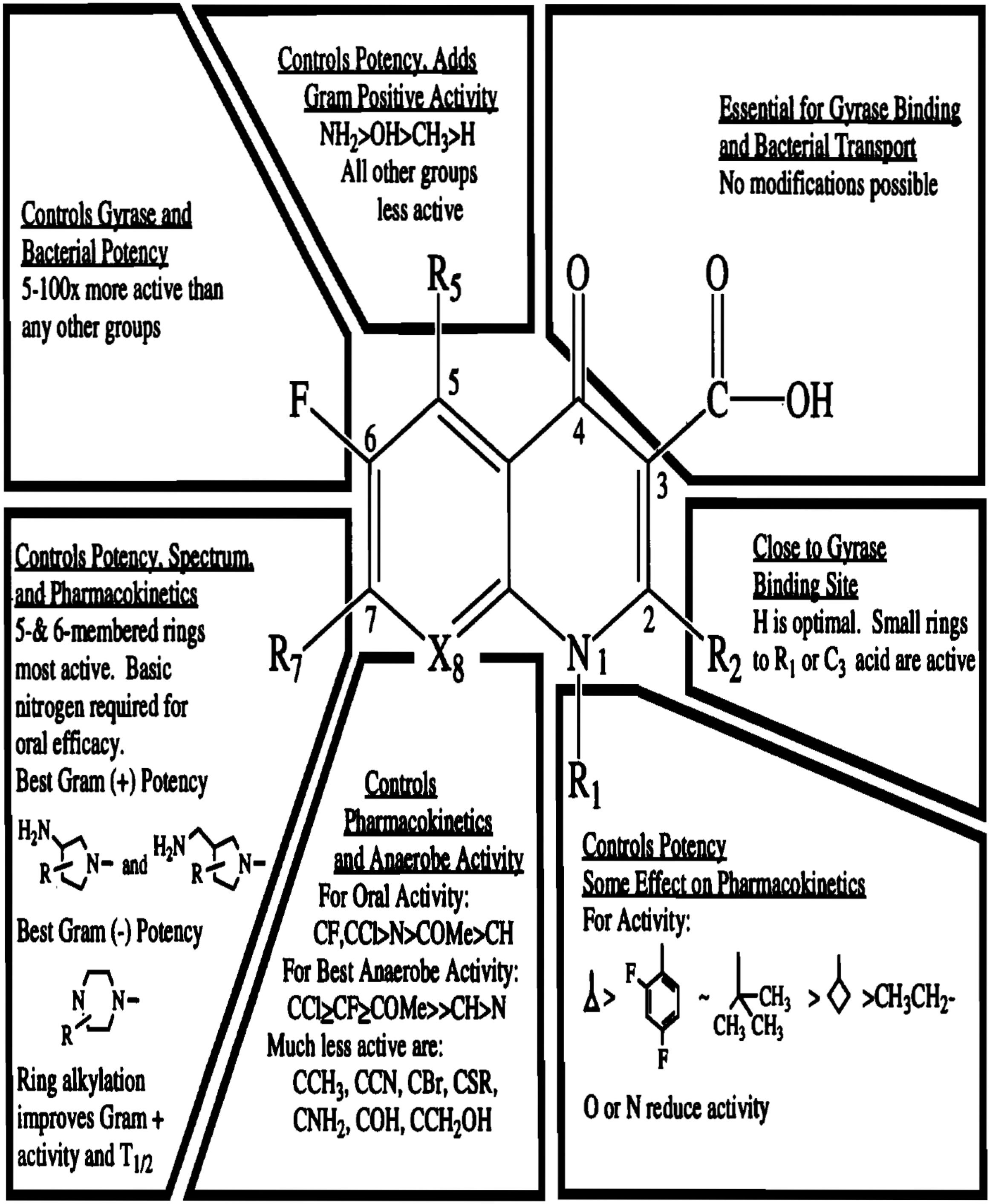


Figure 1. Summary of quinolone antibacterial structure activity relationships. Gram(−), Gram-negative; Gram(+), Gram-positive.

first-generation

The first-generation agents include cinoxacin and nalidixic acid, which are the oldest and least often used quinolones. These drugs had poor systemic distribution and limited activity and were used primarily for gram-negative urinary tract infections. Cinoxacin and nalidixic acid require more frequent dosing than the newer quinolones, and they are more susceptible to the development of bacterial resistance.

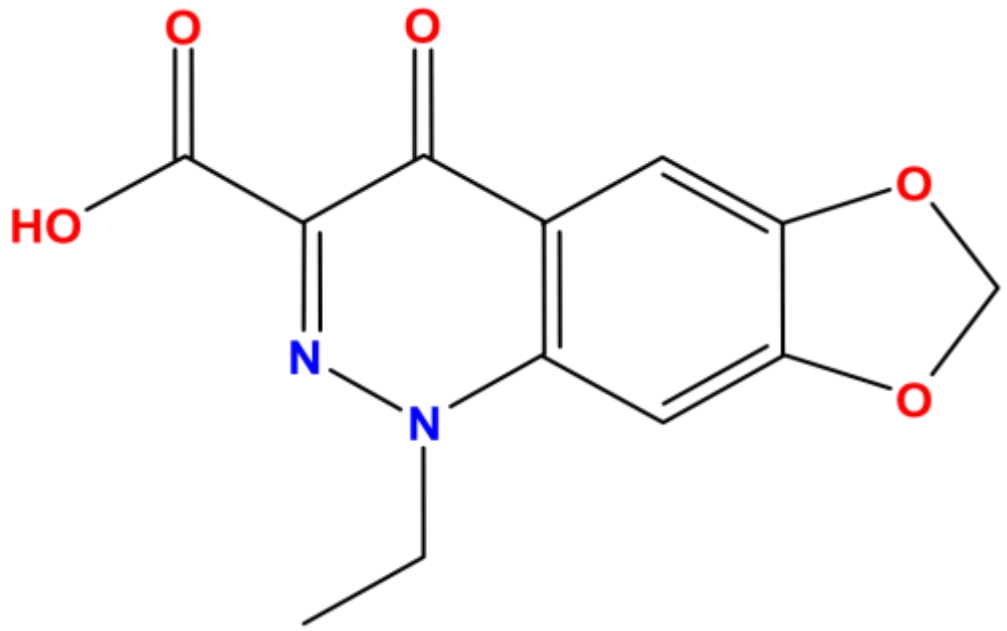
Second Generation

The second-generation fluoroquinolones have increased gram-negative activity, as well as some gram-positive and atypical pathogen coverage. Compared with first-generation quinolones, these drugs have broader clinical applications in the treatment of complicated urinary tract infections and pyelonephritis, sexually transmitted diseases, selected pneumonias and skin infections

Second-generation agents include ciprofloxacin, enoxacin, lomefloxacin, norfloxacin and ofloxacin. Ciprofloxacin is the most potent fluoroquinolone against P. aeruginosa. Ciprofloxacin and ofloxacin are the most widely used second-generation quinolones because of their availability in oral and intravenous formulations and their broad set of FDA-labeled indications.

First generation drug Cinoxacin

- Cinoxacin was an older synthetic antimicrobial related to the quinolone class of antibiotics with activity similar to oxolinic acid and nalidixic acid. It was commonly used thirty years ago to treat urinary tract infections in adults.



(IUPAC) name

1-Ethyl-1,4-dihydro-4-oxo[1,3]dioxolo[4,5-*g*]cinnoline-3-carboxylic acid

History

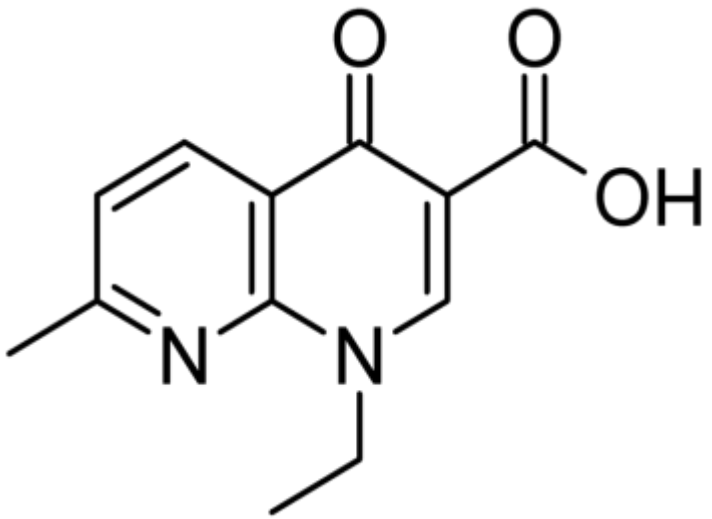
- Cinoxacin is one of the original quinolone drugs, which were introduced in the 1970s. Commonly referred to as the first generation quinolones.
- Cinoxacin was patented in 1972 and assigned to Eli Lilly. Eli Lilly obtained approval from the FDA to market cinoxacin in the United States as Cinobac on June 13, 1980. Prior to this cinobac was marketed in the U.K. and Switzerland in 1979.

Mode of action

- Cinoxacin mode of action involves the inhibiting of DNA gyrase, a type II topoisomerase, and topoisomerase iv, which is an enzyme necessary to separate replicated DNA, thereby inhibiting cell division.
- **Adverse reactions**
- Hypersensitivity resulting in an anaphylactic reactions

Nalidixic acid

- It is a naphthyridone, not a quinolone its ring structure is a 1,8-naphthyridine nucleus that contains two nitrogen atoms, unlike quinoline, which has a single nitrogen atom.



(IUPAC) name

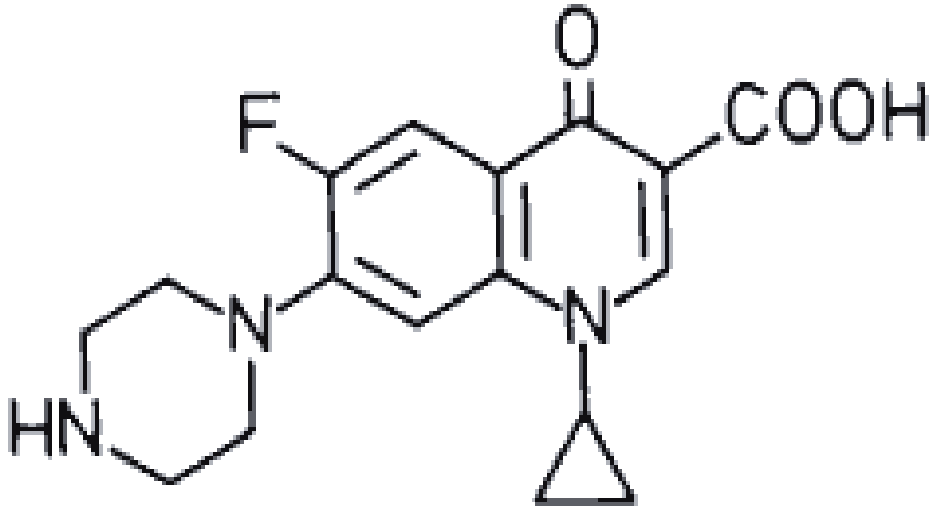
1-Ethyl-7-methyl-4-oxo-[1,8]naphthyridine-3-carboxylic acid

- Synthetic quinolone antibiotics were discovered by George Lesher and coworkers as a byproduct of chloroquine manufacture in the 1960s. Used clinically from 1967.
- Nalidixic acid is effective primarily against gram-negative bacteria, with minor anti-gram-positive activity. In lower concentrations, it acts in a bacteriostatic manner; that is, it inhibits growth and reproduction. In higher concentrations, it is bactericidal, meaning that it kills bacteria instead of merely inhibiting their growth.

- It has historically been used for treating urinary tract infections, caused, for example, by *Escherichia coli*, *Proteus*, *Shigella*, *Enterobacter*, and *Klebsiella*. It is no longer clinically used for this indication in the USA as less toxic and more effective agents are available.

Second Generation Fluoroquinolone
Ciprofloxacin

- Second generation fluoroquinolone that was synthesized for first time in 1987. A well known antibacterial drug with a wide spectrum of activity, it is extremely useful for the treatment of a variety of infections.
- Ciprofloxacin can usually act as a bidentate ligand through the pyridone oxygen and one carboxylate oxygen

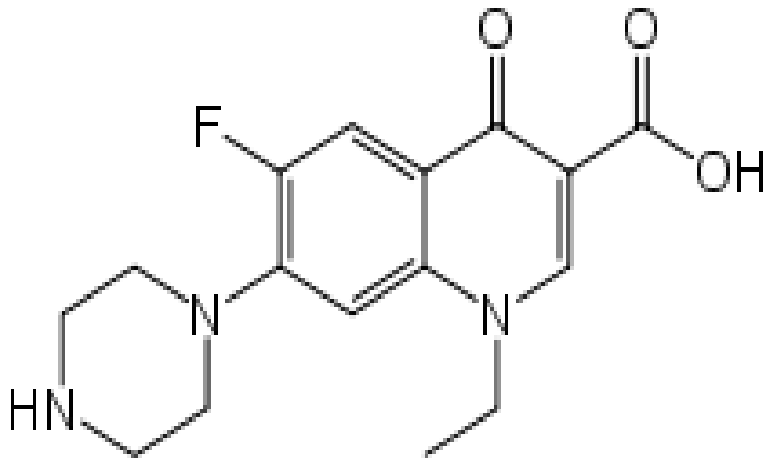


(IUPAC) name

1- cyclopro-pyl-6-fluoro-1,4- dihydro-4-oxo-7- (1- piperaz- inil)- 3-quinolone carboxylic acid

Norfloxacin

- Norfloxacin is synthetic chemotherapeutic antibacterial agent occasionally used to treat common as well as complicated urinary tract infections.



(IUPAC) name

1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1*H*-quinoline-3-carboxylic acid

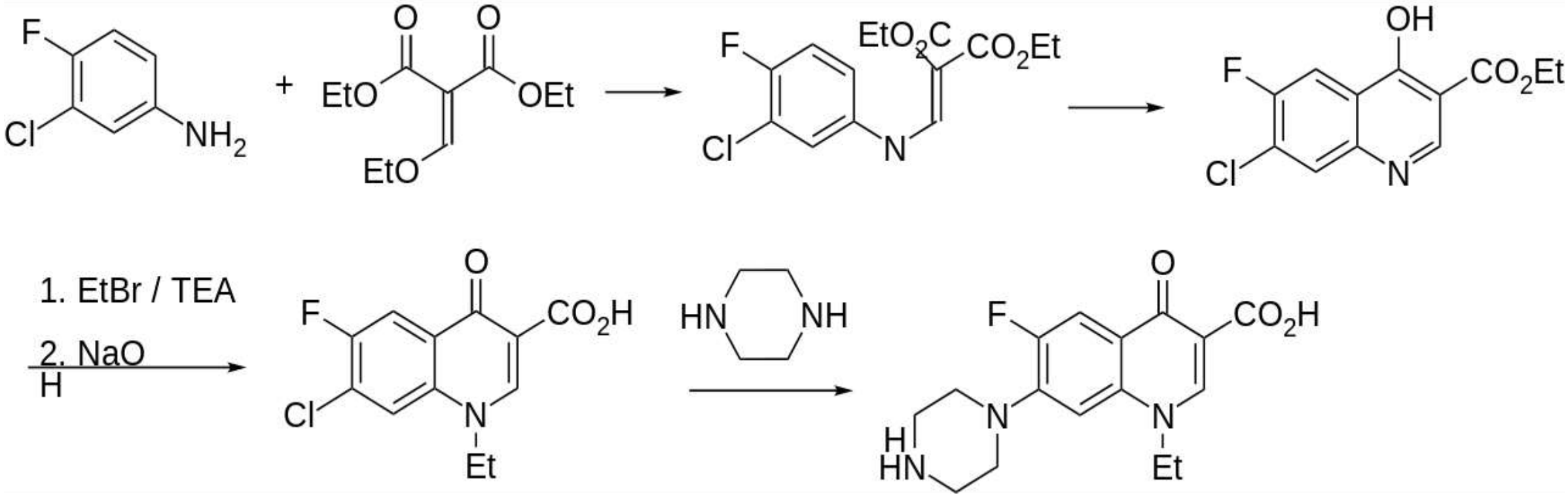
History

- In 1979 the publication of a patent filed by the pharmaceutical arm of *Kyorin Seiyaku Kabushiki Kaisha* disclosed the discovery of norfloxacin, and the demonstration that certain structural modifications including the attachment of a fluorine atom to the quinolone ring leads to dramatically enhanced antibacterial potency.

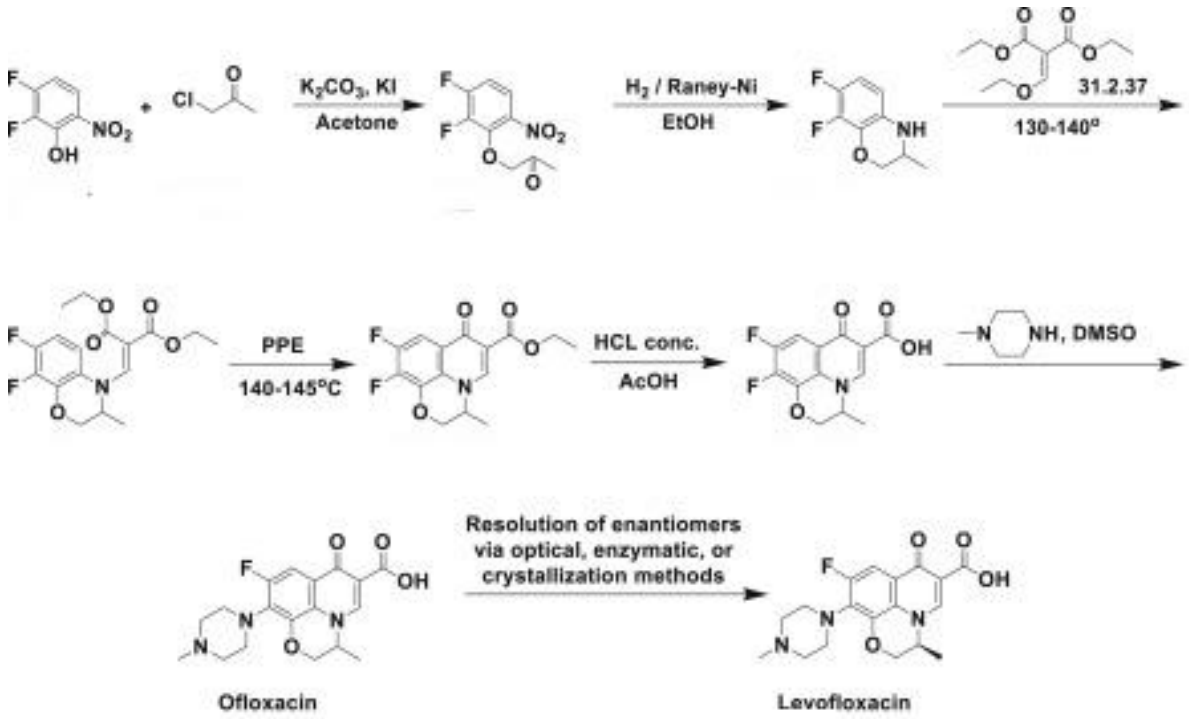
Mode of action

- Norfloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type topoisomerase II, and topoisomerase IV, enzymes necessary to separate bacterial DNA, thereby inhibiting cell division. Norfloxacin does not bind to DNA gyrase but does bind to the substrate DNA.

Synthesis

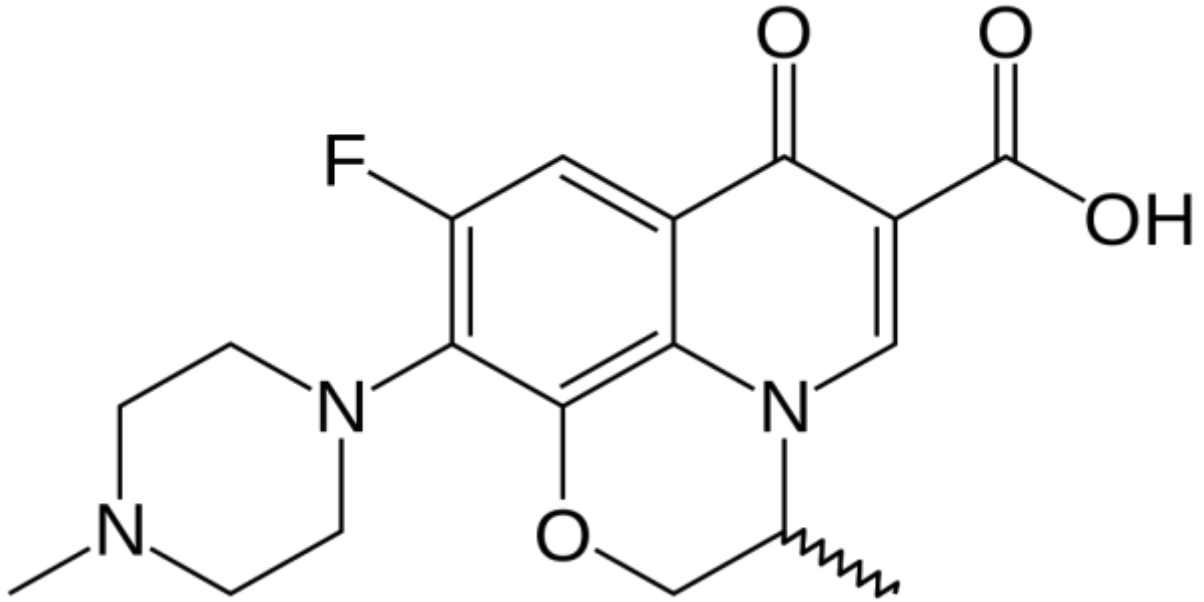


1-ethyl-6-fluoro-4-oxo-7-piperazin-1-yl-1*H*-quinoline-3-carboxylic acid


K2CO3, KI
Acetone
H2 / Raney-Ni
EtOH
31.2.37
130-140°
PPE
140-145°C
HCL conc.
AcOH
NH, DMSO
Resolution of enantiomers via optical, enzymatic, or crystallization methods
Ofloxacin
Levofloxacin

Ofloxacin

- Ofloxacin is a racemic mixture, which consists of 50% levofloxacin (the biologically active component) and 50% of its “mirror image” or enantiomer dextrofloxacin.
- Ofloxacin was first patented in 1982 (European Patent Daiichi) and received approval from the U.S. Food and Drug Administration(FDA) on December 28, 1990.



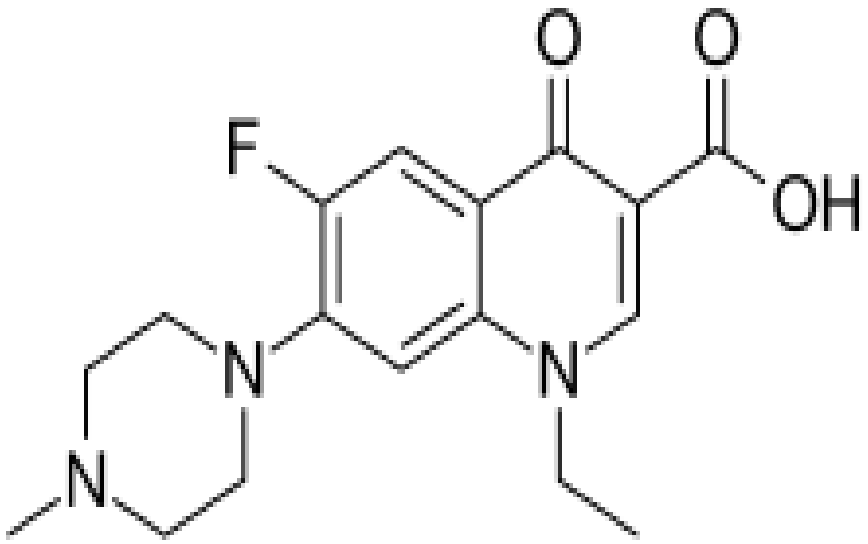
(IUPAC) name

(*RS*)-7-fluoro-2-methyl-6-(4-methylpiperazin-1-yl)-10-oxo-4-oxa-1-azatricyclo[7.3.1.$0^{5,13}$]trideca-5(13),6,8,11-tetraene-11-carboxylic acid

- Mode of action

- Ofloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type II topoisomerase, and topoisomerase IV, which is an enzyme necessary to separate (mostly in prokaryotes, in bacteria in particular) replicated DNA, thereby inhibiting bacterial cell division.

Pefloxacin



(IUPAC) name

1-ethyl-6-fluoro-7-(4-methylpiperazin-1-yl)-4-oxo-quinoline-3-carboxylic acid

- History:-

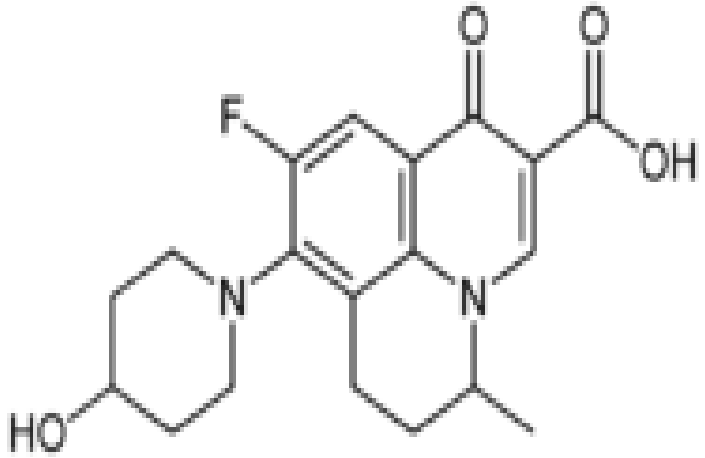
Pefloxacin was developed in 1979 and approved in France for human use in 1985.

- Mode of action:-

Pefloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria. It functions by inhibiting DNA gyrase, a type topoisomerase II, and topoisomerase IV, which is an enzyme necessary to separate, replicated DNA, thereby inhibiting cell division.

Nadifloxacin

- Nadifloxacin is a topical fluoroquinolone antibiotic for the treatment of acne vulgaris. It is also used to treat bacterial skin infections.



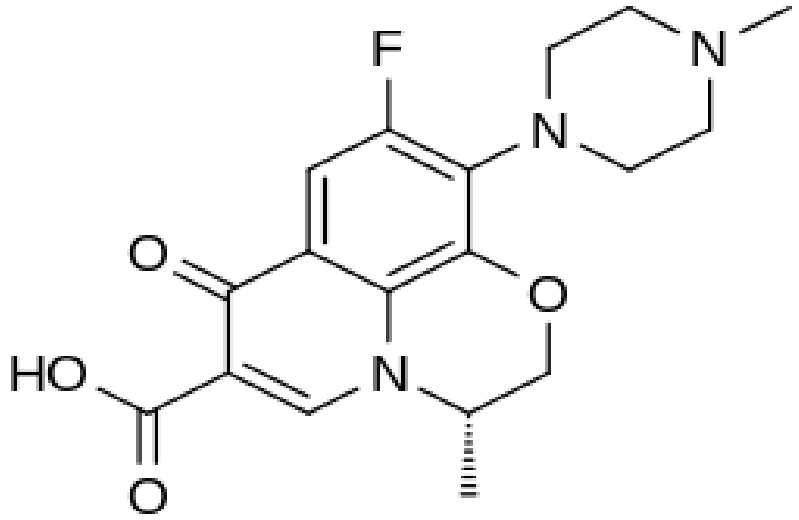
- (IUPAC) name:-

(*RS*)-9-Fluoro-8-(4-hydroxy-piperidin-1-yl)-5-methyl-1-oxo-6,7-dihydro-1*H*,5*H*-pyrido[3,2,1-ij]quinoline-2-carboxylic acid.

- **Antibacterial spectrum**
- In vitro studies of nadifloxacin showed potent and broad-spectrum antibacterial activity against aerobic Gram-positive, Gram-negative and anaerobic bacteria, including *Propionibacterium acnes* and *Staphylococcus* epidermidis. Nadifloxacin showed potent antibacterial activity against *methicillin-resistant Staphylococcus aureus* (MRSA), which was similar to potency against methicillin-sensitive Staphylococcus aureus (MSSA). The drug was also active against new quinolone-resistant MRSA. Nadifloxacin does not show cross-resistance with other new quinolones.

- **Mechanism of action**
- Nadifloxacin inhibits the enzyme DNA gyrase that is involved in bacterial DNA synthesis and replication, thus inhibiting the bacterial multiplication. Nadifloxacin in addition to determine a therapeutic antibacterial action, can have a sebostatic and anti-inflammatory action, thus contributing to the improvement of the clinical condition of the patient.

Third-generation
Levofloxacin



- IUPAC) name

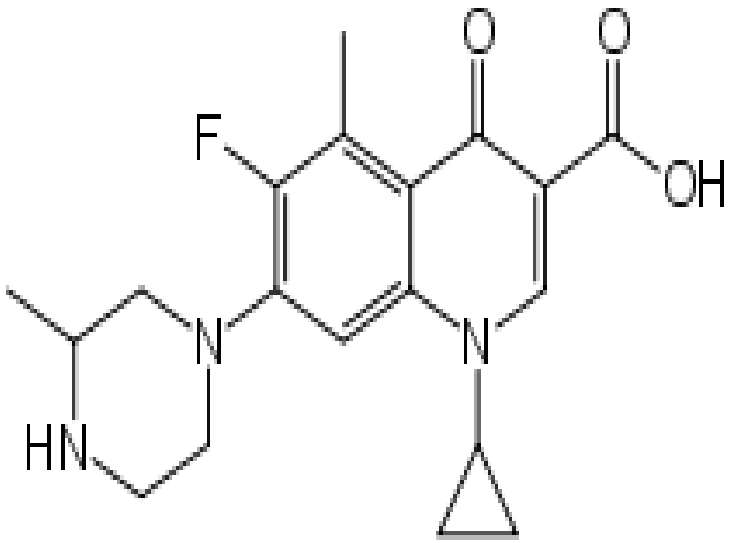
(*S*)-9-fluoro-2,3-dihydro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-7*H*-pyrido[*1,2,3-de*]-1,4-benzoxazine-6-carboxylic acid

- Levofloxacin is the levo isomer of the racemate ofloxacin, another quinolone antimicrobial agent. In layman terms, this means that levofloxacin is the 50% of ofloxacin that have been found to be effective against bacteria, while the other 50% have been removed. In chemical terms, levofloxacin, a chiral fluorinated carboxyquinolone, is the pure (−)-(*S*)-enantiomer of the racemic ofloxacin.
- The substance is used as the hemihydrate, which has the empirical formula $C_{18}H_{20}FN_3O_4 \cdot ½\ H_2O$ and a molecular mass of 370.38 g/mol. Levofloxacin is a light-yellowish-white to yellow-white crystal or crystalline powder.

Mechanism of action

- Like all quinolones, it functions by inhibiting the two type topoisomerase II enzymes, namely DNA gyrase and topoisomerase IV. Topoisomerase IV is necessary to separate DNA that has been replicated (doubled) prior to bacterial cell division. With the DNA not being separated, the process is stopped, and the bacterium cannot divide. DNA gyrase, on the other hand, is responsible for supercoiling the DNA, so that it will fit in the newly formed cells.

Grepafloxacin

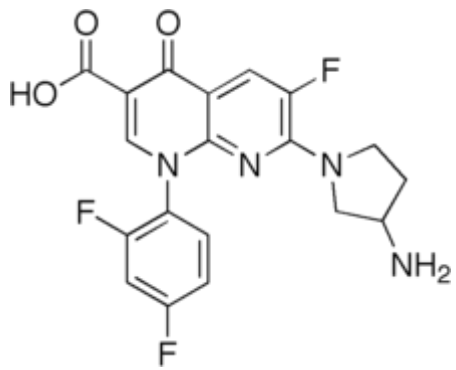


- (IUPAC) name

  (*RS*)-1-cyclopropyl-6-fluoro-5-methyl-7-(3-methylpiperazin-1-yl)- 4-oxo-quinoline- 3-carboxylic acid.

- Grepafloxacin hydrochloride was an oral broad-spectrum fluoroquinolone antibacterial agent used to treat bacterial infections. Grepafloxacin was withdrawn worldwide from markets in 1999, owing to its side effect of lengthening the QT interval on the electrocardiogram, leading to cardiac events and sudden death.

Tosufloxacin



Sparfloxacin

- (IUPAC) name

  5-Amino-1-cyclopropyl-7-[(3*R*,5*S*)3,5-dimethylpiperazin-1-yl]-6,8-difluoro-4-oxo-quinoline-3-carboxylic acid