Quinolones

Antibiotics

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Description

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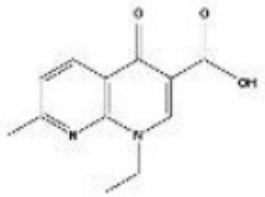
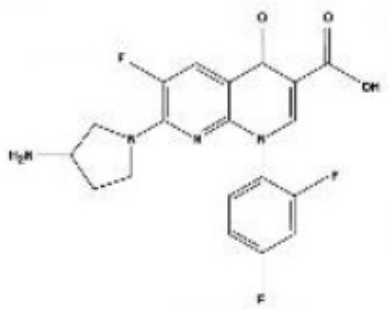
The fluorinated 4-quinolones, such as ciprofloxacin (CIPRO™), moxifloxacin (AVELOX™), and gatifloxacin (TEQUIN™), are orally effective for the treatment of a wide variety of infectious diseases and have relatively few side effects.

Chemistry

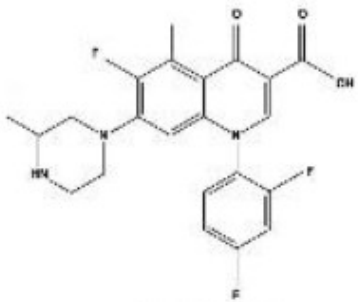
Compounds available in the U.S. contain a carboxylic acid moiety at position 3 of the primary ring structure. Many newer fluoroquinolones also contain a fluorine substituent at position 6 and a piperazine moiety at position 7.



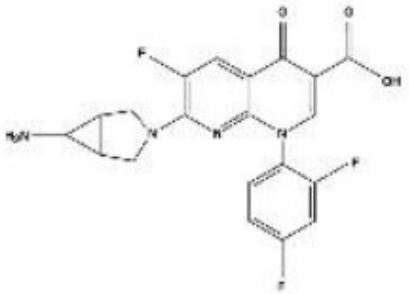
nalidixic acid



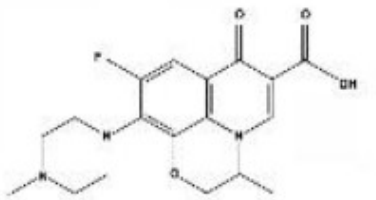
tosufloxacin



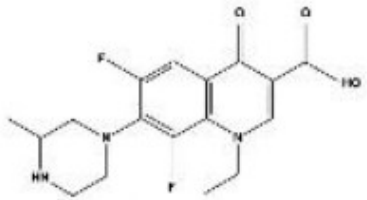
temafloxacin



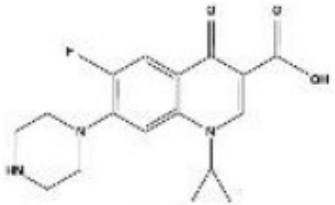
trovafloxacin



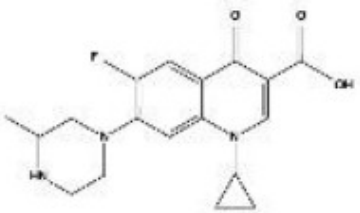
ofloxacin



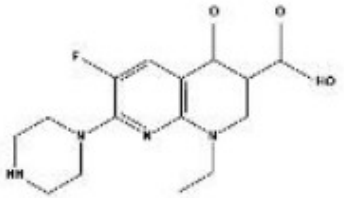
lomefloxacin



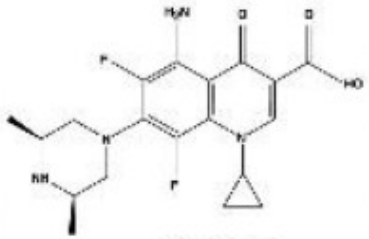
ciprofloxacin



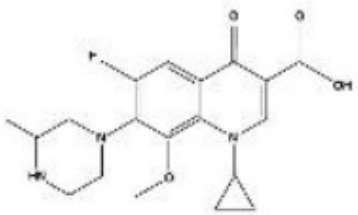
grepafloxacin



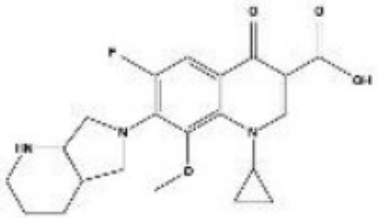
enoxacin



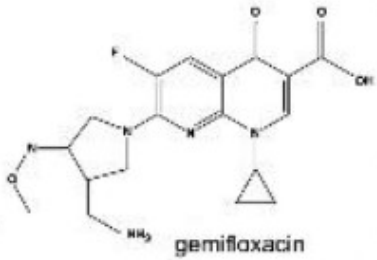
sparfloxacin



gatifloxacin



moxifloxacin

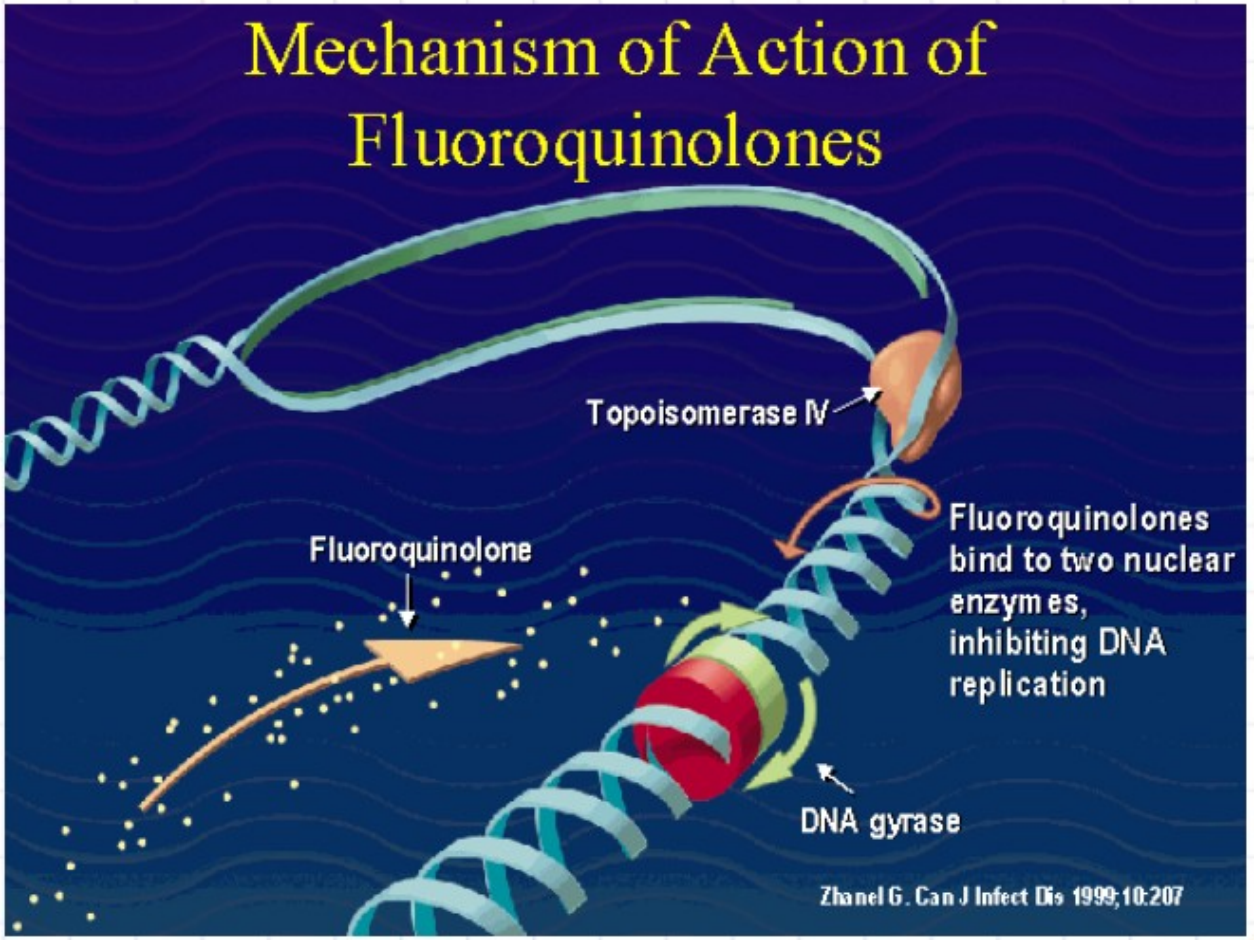


gemifloxacin

Suchen: bilanz Aufwärts Abwärts Hervorheben Groß-/Kleinschreibung

Mechanism of Action

The quinolone antibiotics target bacterial DNA gyrase and topoisomerase IV. For many gram positive bacteria, topoisomerase IV is the primary target. For many gram-negative bacteria, DNA gyrase is the primary quinolone target. The quinolones inhibit gyrase-mediated DNA supercoiling at concentrations that correlate well with their effective antibacterial actions. Mutations of gyrA can confer resistance to these drugs. Topoisomerase IV separates catenated DNA molecules that result from DNA replication, and also is a target for quinolones.



Antibacterial Spectrum

Quinolones Versus Gram +

	S. aureus	S. pyogenes	S. pneumoniae	E. faecalis	E. faecium
Ciprofloxacina	++	++	+	±	±
Levofloxacina	++	++	+	+	±
Moxifloxacina (*)	++	++	++	++	±

(*) active also against chlamydia, legionella, mycoplasma, brucella, mycobacterium (including mycobacterium tuberculosis).

Quinolones Versus Gram -

	E. Coli	K. pneumoniae	Enterebacter sp	Citrobacter sp.	Serratia marcescens	Shigella sp
Nalidixic acid	+	+	±	-	-	-
Ciprofloxacin	++	++	++	++	++	++
Levofloxacin	++	++	++	++	++	++
Moxifloxacin	++	++	++	++	+	++

	Salmonella sp	Proteus sp	P. aeruginosa	Haemophilus sp	Neisseria M	catarrhalis
Nalidixic acid	-	+	-	++	++	-
Ciprofloxacin	++	++	++	++	+	++
Levofloxacin	++	++	++	++	++	++
Moxifloxacin	++	±	-	++	++	++

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The fluoroquinolones are potent bactericidal agents against a broad variety of microorganisms, as outlined under Therapeutic Uses. Fluoroquinolones have good activity against staphylococci but not against methicillin-resistant strains. Activity against streptococci is limited to a subset of the quinolones, including levofloxacin (LEVAQUIN™), gatifloxacin (TEQUIN™), and moxifloxacin (AVELOX™).
Several intracellular bacteria are inhibited by fluoroquinolones; these include species of Chlamydia, Mycoplasma, Legionella, Brucella, and Mycobacterium (including Mycobacterium tuberculosis). Ciprofloxacin, ofloxacin (FLOXIN™), and pefloxacin inhibit M. fortuitum, M. Kansasii, and M. tuberculosis.

Moxifloxacin and pyrazinamide susceptibility testing in a complex case of multidrug-resistant tuberculosis. 2011

Resistance

Resistance to quinolones may develop via mutations in the bacterial chromosomal genes encoding DNA gyrase or topoisomerase IV or by active transport of the drug out of the bacteria.
No quinolone-inactivating mechanisms have been identified. Resistance has increased, especially in Pseudomonas and staphylococci. Fluoroquinolone resistance also is increasing in C. jejuni, Salmonella, Neisseria gonorrhoeae, and S. pneumoniae.

Characterization of nalidixic Acid-resistant and fluoroquinolone-reduced susceptible salmonella typhimurium in Swine. 2011

Absorption, Fate, And Excretion

The quinolones are well absorbed after oral administration and are widely distributed. Peak serum levels of the fluoroquinolones occur within 1–3 hours of an oral dose of 400 mg. Relatively low serum levels are reached with norfloxacin and limit its usefulness to the treatment of urinary tract infections. Food does not impair oral absorption but may delay the time to peak serum concentrations.
The volume of distribution of quinolones is high, with concentrations in urine, kidney, lung and prostate tissue, stool, bile, and macrophages and neutrophils higher than serum levels. Quinolone concentrations in CSF, bone, and prostatic fluid are lower than in serum.

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Pefloxacin and ofloxacin levels in ascites fluid approach serum levels, and ciprofloxacin, ofloxacin, and pefloxacin have been detected in human breast milk.
Most quinolones are cleared predominantly by the kidney, and dose must be adjusted for renal failure.
Pefloxacin and moxifloxacin are metabolized predominantly by the liver and should not be used in patients with hepatic failure.

Indications

Urinary Tract Infections

Norfloxacin is approved for use in the U.S. only for urinary tract infections. The fluoroquinolones are more efficacious than trimethoprim–sulfamethoxazole for the treatment of urinary tract infections.

Prostatitis

Norfloxacin, ciprofloxacin, and ofloxacin are effective for the treatment of prostatitis caused by sensitive bacteria.

Sexually Transmitted Diseases

The quinolones are contraindicated in pregnancy. Fluoroquinolones lack activity for Treponema pallidum but have activity in vitro against N. gonorrhoeae, Chlamydia Trachomatis, and Haemophilus ducreyi.

Gastrointestinal and Abdominal Infections

For traveler's diarrhea (frequently caused by enterotoxigenic E. coli), the quinolones are equal to trimethoprim–sulfamethoxazole in effectiveness. Norfloxacin, ciprofloxacin, and ofloxacin given for 5 days all are effective in the treatment of patients with shigellosis, with even shorter courses effective in many cases. Ciprofloxacin and ofloxacin cure most patients with enteric fever caused by S. typhi, as well as bacteremic nontyphoidal infections in AIDS patients. Shigellosis is treated effectively with either ciprofloxacin or azithromycin. The in vitro ability of the quinolones to induce the Shiga toxin (the cause of the hemolytic-uremic syndrome) in E. coli suggests that the quinolones should not be used for Shiga toxin–producing E. coli.

Shiga toxin-producing Escherichia coli urinary tract infection associated with hemolytic-uremic syndrome in an adult and possible adverse effect of ofloxacin therapy.2000

Respiratory Tract Infections

The major limitation to the use of quinolones for the treatment of community-acquired pneumonia and bronchitis was the poor activity against S. pneumoniae and anaerobic bacteria. Many of the newer fluoroquinolones, including gatifloxacin and moxifloxacin, have excellent activity against S. pneumoniae and have shown efficacy comparable to b-lactam antibiotics. The fluoroquinolones have activity against the rest of the common respiratory pathogens, including H. influenzae, Moraxella catarrhalis, S. aureus, Mycoplasma pneumoniae, Chlamydia pneumoniae, and Legionella pneumophila. Either a fluoroquinolone (ciprofloxacin or levofloxacin) or azithromycin is the antibiotic of choice for L. pneumophila.

Bone, Joint, and Soft Tissue Infections

The treatment of chronic osteomyelitis requires prolonged antimicrobial therapy with agents active against S. aureus and gram-negative rods. The fluoroquinolones, by virtue of their oral administration and antibacterial spectrum, may appropriately be used in some cases;
Clinical cures have been as high as 75% in chronic osteomyelitis in which gram-negative rods predominated. Failures have been associated with the development of resistance in S. aureus, P. aeruginosa, and Serratia marcescens. In diabetic foot infections, which commonly are polymicrobial, the fluoroquinolones in combination with an agent with antianaerobic activity are a reasonable choice.

Other Infections

Ciprofloxacin received wide usage for the prophylaxis of anthrax and is effective for the treatment of tularemia. The quinolones may be used as part of multiple-drug regimens for the treatment of multidrug-resistant tuberculosis and for the treatment of atypical mycobacterial infections and Mycobacterium avium complex infections in AIDS.

Adverse Effects

1. The most common adverse reactions involve the GI tract, with 3–17% of patients reporting mostly mild nausea, vomiting, and/or abdominal discomfort. Diarrhea and antibiotic-associated colitis have been unusual.

2. CNS side effects, predominately mild headache and dizziness, have been seenin 1–10% of patients. Rarely, hallucinations, delirium, and seizures have occurred, predominantly in patients who also were receiving theophylline or a nonsteroidal anti-inflammatory drug.
Ciprofloxacin and pefloxacin inhibit the metabolism of theophylline and may induce toxic levels.
Nonsteroidal anti-inflammatory drugs may augment displacement of g-aminobutyric acid (GABA) from its receptors by the quinolones.

3. Rashes, including photosensitivity reactions, also can occur.

4. Leukopenia, eosinophilia, and mild elevations in serum transaminases occur rarely.

5. Prolongation of the QTc interval has been observed with sparfloxacin and to a lesser extent with gatifloxacin and moxifloxacin. Quinolones probably should be used only with caution in patients who are taking certain antiarrhythmics, including amiodarone, quinidine, and procainamide. The prescribing information for gatifloxacin includes a contraindication in diabetic patients due to serious reports of hypoglycemia and hyperglycemia. Risk factors for this adverse effect include older age, renal insufficiency, and concomitant therapy with glucose-altering medications.

Quinolones And Tendons Damage

Achilles tendon rupture or tendinitis are a rare adverse effect. Renal disease, hemodialysis, and glucocorticoid use may be predisposing factors. Traditionally, the use of quinolones in children has been contraindicated because they have produced arthropathy in animal models. However, children with cystic fibrosis given ciprofloxacin, norfloxacin, and nalidixic acid have had few, and reversible, joint symptoms.

Fluoroquinolone-associated bilateral patellar tendon rupture: a case report and review of the literature. 2010

Fluoroquinolone-associated bilateral patellar tendon rupture: a case report and review of the literature. 2010

Tendinopathy resulting from the use of fluoroquinolones: managing risks.2010

Levofloxacin-induced Achilles tendinitis in a young adult in the absence of predisposing conditions.2011

Spontaneous tendon ruptures in patients with end-stage renal disease.2009

Why The Use Of Quinolones Can Create A Tendon Damage?
It's not clear the mechanism involved in tendons damage by quinolones, there are some studies that prove to explain this rare adverse effect:

Ciprofloxacin up-regulates tendon cells to express matrix metalloproteinase-2 with degradation of type I collagen.2011

Metalloproteinases (or metalloproteases) constitute a family of enzymes from the group of proteases, classified by the nature of the most prominent functional group in their active site. These are proteolytic enzymes whose catalytic mechanism involves a metal. Most metalloproteases are zinc, some use cobalt. The metal ion is coordinated to the protein via three ligands. The ligands co-ordinating the metal ion can vary with histidine, glutamate, aspartate, lysine and arginine all possible ligands. The fourth coordination position is taken up by a labile water molecule.

Possible involvement of DEC1 on the adverse effects of quinolone antibiotics.2010

Differentiated embryo-chondrocyte expressed gene 1 (DEC1) is an important transcription factor that has a basic helix-loop-helix domain and is ubiquitously expressed in both human embryonic and adult tissues, has a pivotal function in various biological phenomena, including neurogenesis, neuroregulation, chondrogenesis, cell growth, oncogenesis, immune balance and circandian rhythm.

Ciprofloxacin-mediated inhibition of tenocyte migration and down-regulation of focal adhesion kinase

Ciprofloxacin-mediated inhibition of tenocyte migration and down-regulation of focal adhesion kinase phosphorylation.2009

Age-dependent effects on redox status, oxidative stress, mitochondrial activity and toxicity induced by fluoroquinolones on primary cultures of rabbit tendon cells.2006

Is there a way to prevent the possible negative effect quinolones-induced on tendons?

The mitochondria targeted antioxidant MitoQ protects against fluoroquinolone-induced oxidative stress and mitochondrial membrane damage in human Achilles tendon cells. 2009

MitoQ--a mitochondria-targeted antioxidant.2007

MitoQ is an orally active antioxidant that has the ability to target mitochondrial dysfunction. The agent is currently under development by Antipodean Pharmaceuticals Inc in phase II clinical trials for Parkinson's disease and liver damage associated with HCV infection. MitoQ has demonstrated encouraging preclinical results in numerous studies in isolated mitochondria, cells and tissues undergoing oxidative stress and apoptotic death. MitoQ aims to not only mimic the role of the endogenous mitochondrial antioxidant coenzyme Q10, but also to augment substantially the antioxidant capacity of CoQ to supraphysiological levels in a mitochondrial membrane potential-dependent manner. MitoQ represents the first foray into the clinic in an attempt to deliver an antioxidant to an intracellular region that is responsible for the formation of increased levels of potentially deleterious reactive oxygen species. Results from the clinical trials with MitoQ will have important repercussions on the relevance of a mitochondrial-targeted approach.

Are There Studies In Which Is Shown The Efficacy Of MitoQ Against Pathological Situations Induced By Ossidative Stress?

Mitochondria-targeted antioxidant MitoQ10 improves endothelial function and attenuates cardiac hypertrophy.2009

The mitochondria-targeted antioxidant MitoQ protects against organ damage in a lipopolysaccharide-

relevance of a mitochondrial-targeted approach.

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The mitochondria-targeted antioxidant MitoQ protects against organ damage in a lipopolysaccharide-peptidoglycan model of sepsis.2008

Animal and human studies with the mitochondria-targeted antioxidant MitoQ.2010

MeSH

Antibiosis, Drug Resistance

Comments

2011-04-29 08:58:05.692416 - Paolo Pescarmona

CPK aumenta no con statine

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