आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

IFTM University, Moradabad, Uttar Pradesh

NAAC ACCREDITED

E-Content

IFTM University, Moradabad

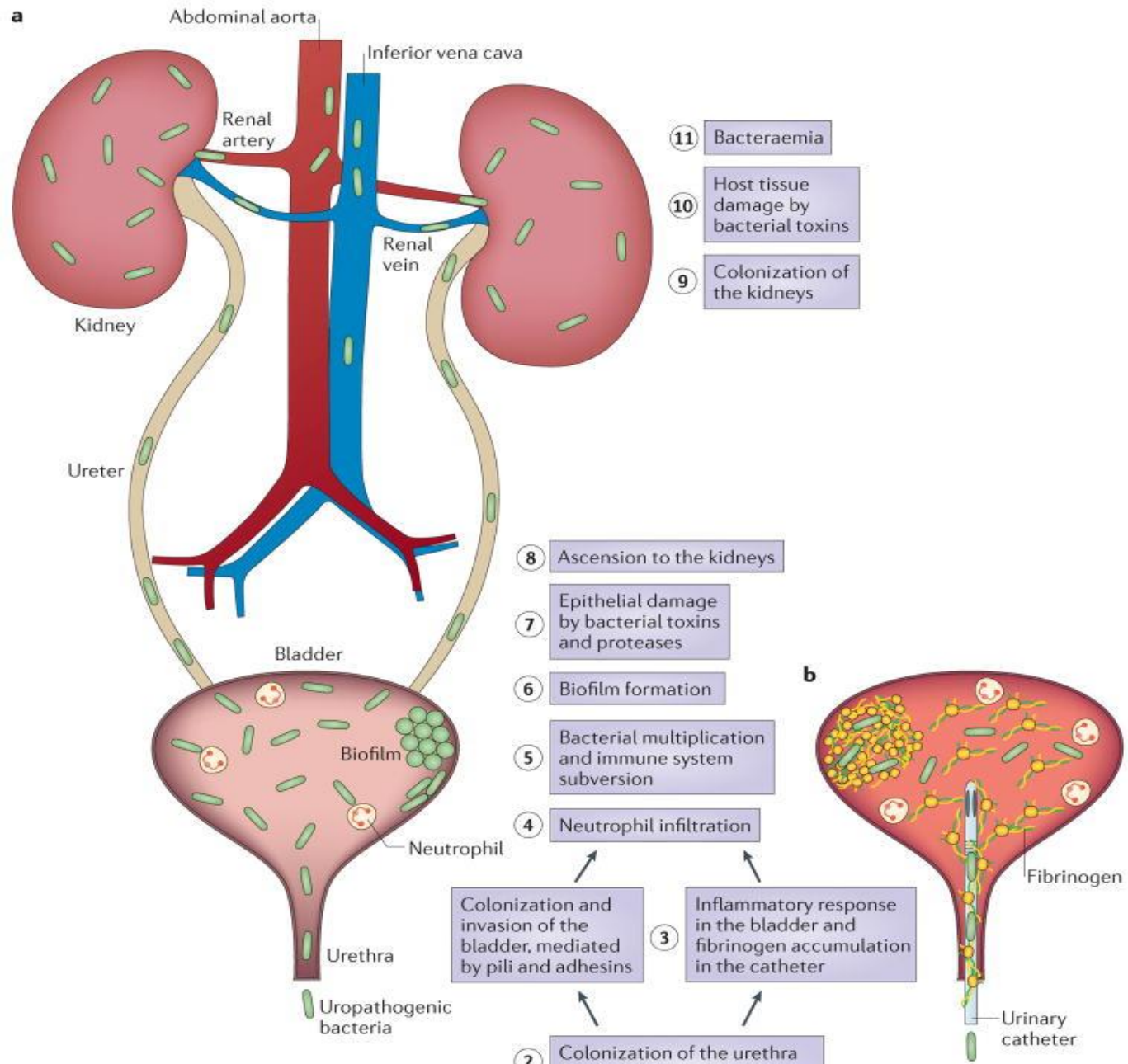
Urinary tract anti-infective agents

Quinolones: SAR of quinolones, Nalidixic Acid,Norfloxacin, Enoxacin, Ciprofloxacin*, Ofloxacin, Lomefloxacin, Sparfloxacin, Gatifloxacin, Moxifloxacin

Miscellaneous: Furazolidine, Nitrofurantoin*, Methanamine.

Urinary tract infections (UTIs) are a severe public health problem and are caused by a range of pathogens, but most commonly by

Escherichia coli*, *Klebsiella pneumoniae*, *Proteus mirabilis*, *Enterococcus faecalis* and *Staphylococcus saprophyticus.


a
Abdominal aorta
Inferior vena cava
Renal artery
Renal vein
Kidney
Ureter
Bladder
Biofilm
Neutrophil
Urethra
Uropathogenic bacteria
11 Bacteraemia
10 Host tissue damage by bacterial toxins
9 Colonization of the kidneys
8 Ascension to the kidneys
7 Epithelial damage by bacterial toxins and proteases
6 Biofilm formation
5 Bacterial multiplication and immune system subversion
4 Neutrophil infiltration
3
Colonization and invasion of the bladder, mediated by pili and adhesins
Inflammatory response in the bladder and fibrinogen accumulation in the catheter
2 Colonization of the urethra and migration to the bladder
1 Contamination of the periurethral area with a uropathogen from the gut
b
Fibrinogen
Urinary catheter

Urinary Tract Infection

some facts

i. Very common
ii. Significant cause of morbidity and mortality.
iii. Occurs anywhere between the glomerulus and urethra
iv. Upper UTI is above the bladder
v. Lower UTI is from the bladder down

UTI - Who is susceptible?

i. Mostly females due to the (20cm) shorter urethra (30:1)
ii. Exceptions are neonatal boys who are 4X more likely than neonatal girls to have an UTI – reasons not clear.
iii. Elderly men become more susceptible due to prostatic hyperplasia

iv. One in five women will have at least one UTI in her lifetime.
v. About 80 to 90 percent of UTIs are caused by a single type of bacteria.
vi. UTIs can be treated effectively with medications called **antibiotics**. (Quinolones)
vii. People who get repeated UTIs may need additional tests to check for other health problems.
viii. Most UTIs stay in the bladder, the pouch-shaped organ where urine is stored before it passes out of the body. If a UTI is not treated promptly, the bacteria can travel up to the kidneys and cause a more serious type of infection, called pyelonephritis

- **Pyelonephritis** is an actual infection of the kidney, where urine is produced. This may result in fever and back pain.
- About 80 to 90 percent of UTIs are caused by a type of bacteria, called ***E. coli***

- These bacteria normally live in your intestines, but they sometimes get into the urinary tract.

What are the symptoms of a UTI?

Some people don't have any symptoms with a UTI. However, most get at least one or some of the following:

- an urgent need to urinate, often with only a few drops of urine to pass
- a burning feeling when urinating
- an aching feeling, pressure or pain in the lower abdomen
- cloudy or blood-tinged urine
- a strong odor to your urine.

If the infection spreads to the kidneys and becomes more severe, you may also have:

- pain in your lower back
- fever and chills

What will the doctor do to check for a uti?

- Doctor will test a sample of your urine for bacteria and blood cells. This is called a urinalysis.
- Different antibiotics may also be tested to see which works best against the bacteria.

If an infection does not clear up with treatment, or if you have repeated infections, your doctor may refer you to a urologist, a physician who specializes in diseases of the urinary tract. Often, the urologist will order some special tests such as:

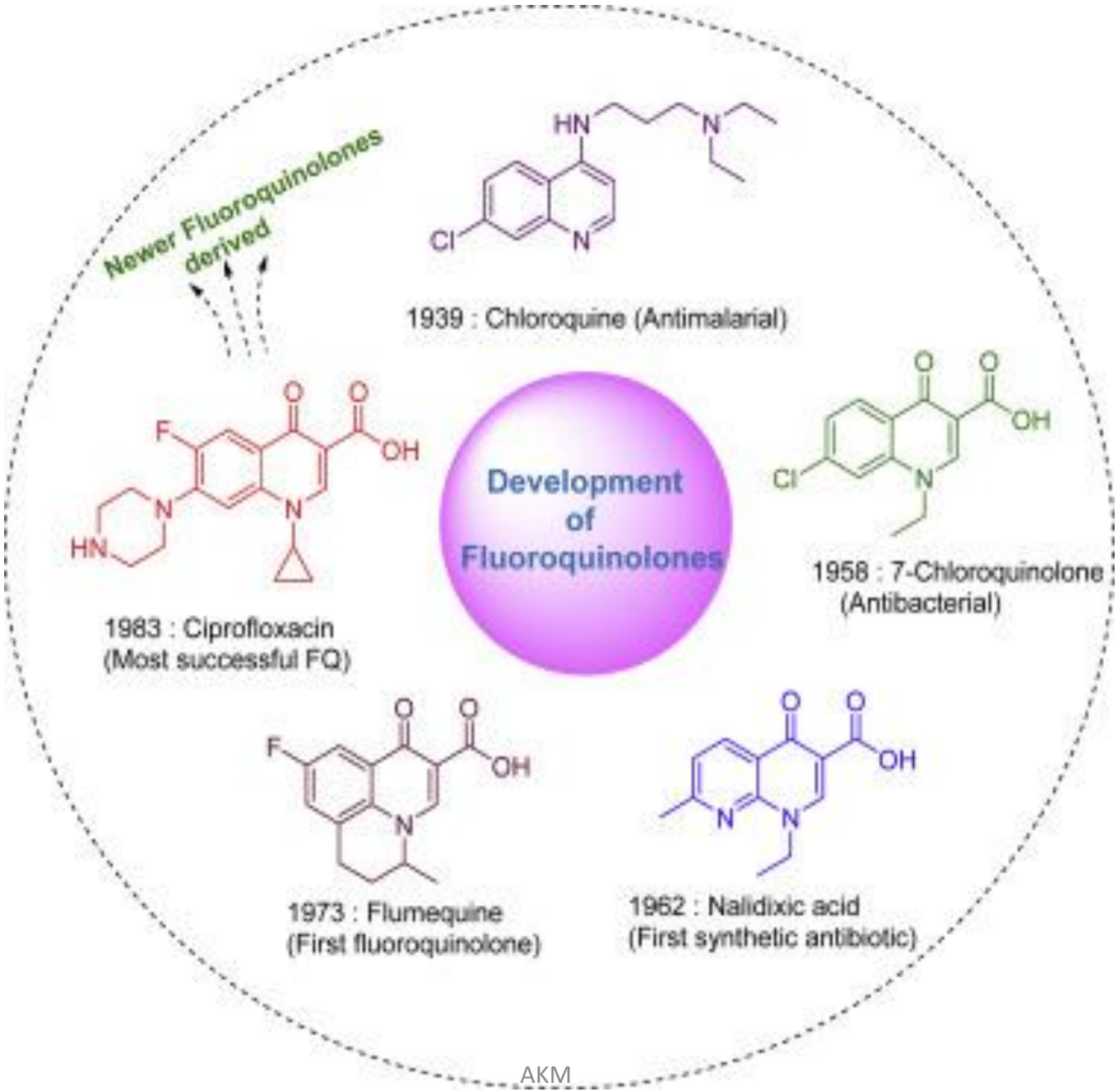
- An ultrasound exam, which gives a picture of your kidneys and bladder using sound waves.
- A cystoscopic exam, which uses a hollow tube with special lenses to look inside the bladder

How are UTI is treated?

- UTI are treated with antibiotics.
- Your doctor may ask you to take the antibiotics for a week or two to make sure the infection has been cured.
- If your infection has spread to your kidneys, you may need several weeks of antibiotic treatment.
- In addition to antibiotics, your doctor may also tell you to **drink plenty of fluids.**

Susceptibility

- People who have diabetes may have changes in their body's immune system, making it easier for them to get UTIs.
- People with blockages in their urinary tract, such as a kidney stone, are more likely to get UTIs.
- An enlarged prostate gland in a man can also block the flow of urine and cause a UTI.
- Infants who are born with an abnormality of their urinary tract have an increased chance of getting a UTI.
- Surgery is sometimes needed to correct the problem.
- People who have a catheter, or tube, placed in their bladder for a long time are more prone to UTIs.

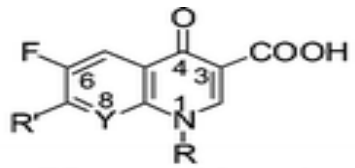

Newer Fluoroquinolones derived
1939 : Chloroquine (Antimalarial)
Development of Fluoroquinolones
1983 : Ciprofloxacin
(Most successful FQ)
1958 : 7-Chloroquinolone
(Antibacterial)
1973 : Flumequine
(First fluoroquinolone)
1962 : Nalidixic acid
(First synthetic antibiotic)

The most frequently used fluoroquinolones include **ciprofloxacin, levofloxacin, norfloxacin, ofloxacin, and gatifloxacin**.

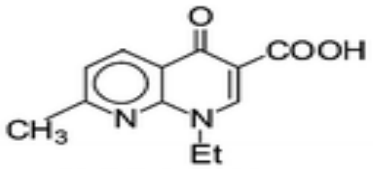
With increasing availability of newer-generation drugs and a broad spectrum of antibiotic effectiveness, the role of fluoroquinolones in UTI treatment may have changed.

Table 1. Classification of fluoroquinolones

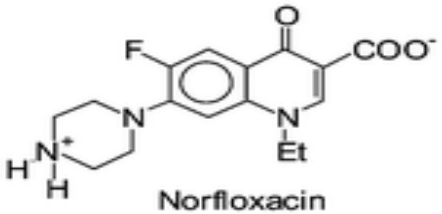
Generation	Drug	Characteristic features
First	Naldixic acid Oxolinic acid Pipemidic acid	Active against some Gram negative bacteria. Highly protein bound drugs. Short half life.
Second	Norfloxacin Enoxacin Ciprofloxacin Ofloxacin Lomefloxacin	Protein binding (50%). Longer half life than previous agents. Improved activity against Gram negative bacteria.
Third	Temafloxacin Sparafloxacin Grepafloxacin	Active against Gram negative bacteria. Also active against Gram positive bacteria.
Fourth	Clinafloxacin Trovafloxacin Moxifloxacin Gatifloxacin	Show extended activity against both strains of bacteria. Active against anaerobes and atypical bacteria.



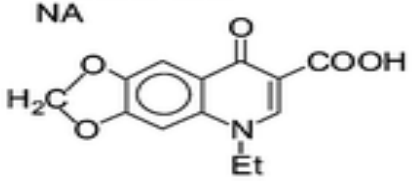
FQ general formula



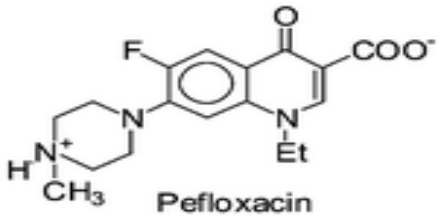
Nalidixic acid
NA



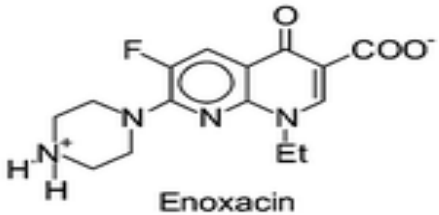
Norfloxacin
NOR



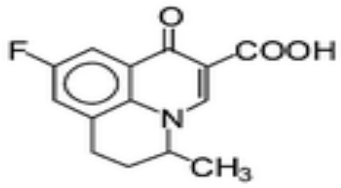
Oxolinic acid
OA



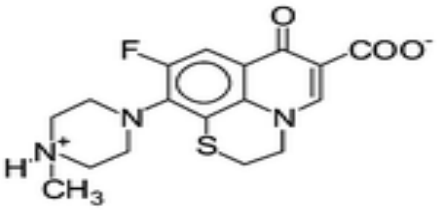
Pefloxacin
PEF



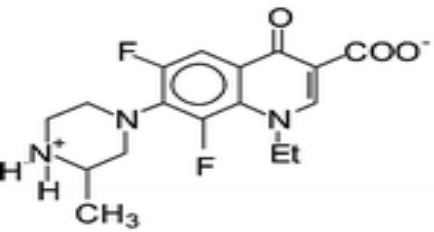
Enoxacin
ENX



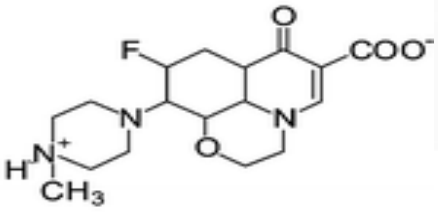
Flumequine
FLU



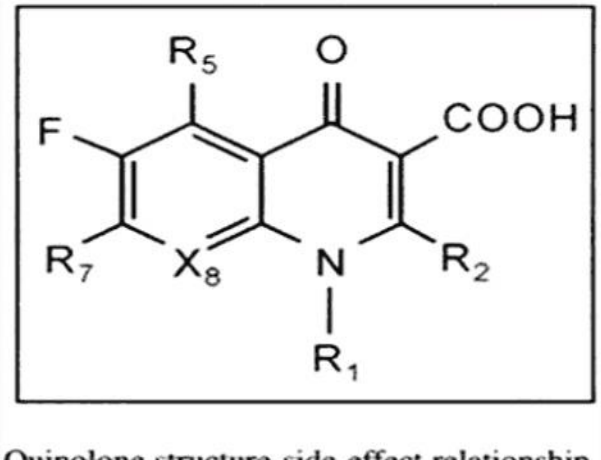
Rufloxacin
RFX



Lomefloxacin
LOM

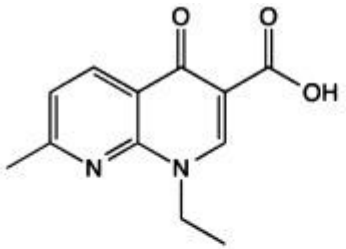


Ofloxacin
OFL

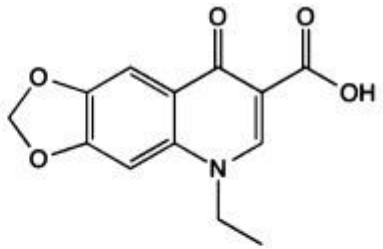


Quinolone structure-side-effect relationship.

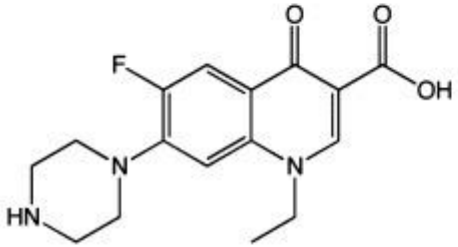
Basic Structure of 4-quinolones
(Short for 4-oxo-1, 4-hydroquinoline)



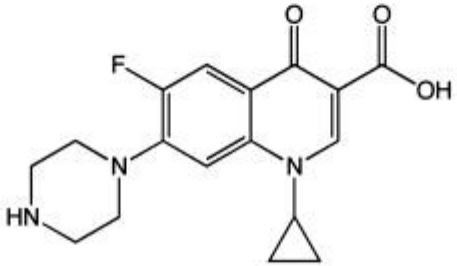
Nalidixic acid



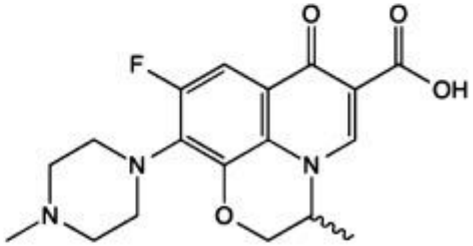
Oxolinic acid



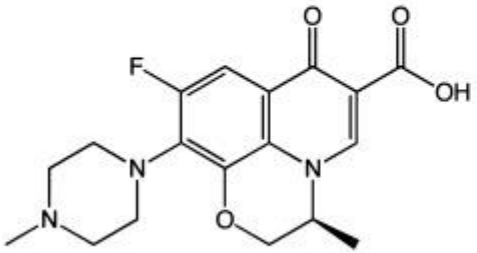
Norfloxacin



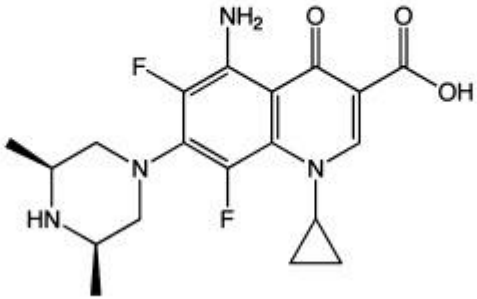
Ciprofloxacin



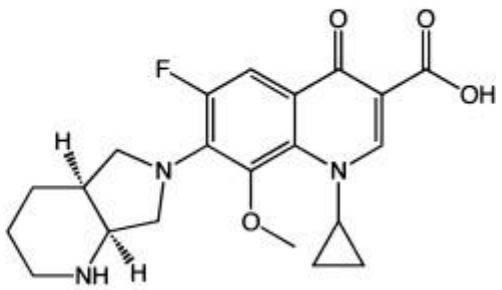
Ofloxacin



Levofloxacin



Sparfloxacin



Moxifloxacin

Mechanism Of Action

The FQs inhibit the enzyme bacterial DNA gyrase, which nicks double-stranded DNA, introduces negative supercoils and then reseals the nicked ends.

The DNA gyrase consists of two A and two B subunits:

The A subunit carries out nicking of DNA, B subunit introduces negative supercoils and then A subunit reseals the strands.

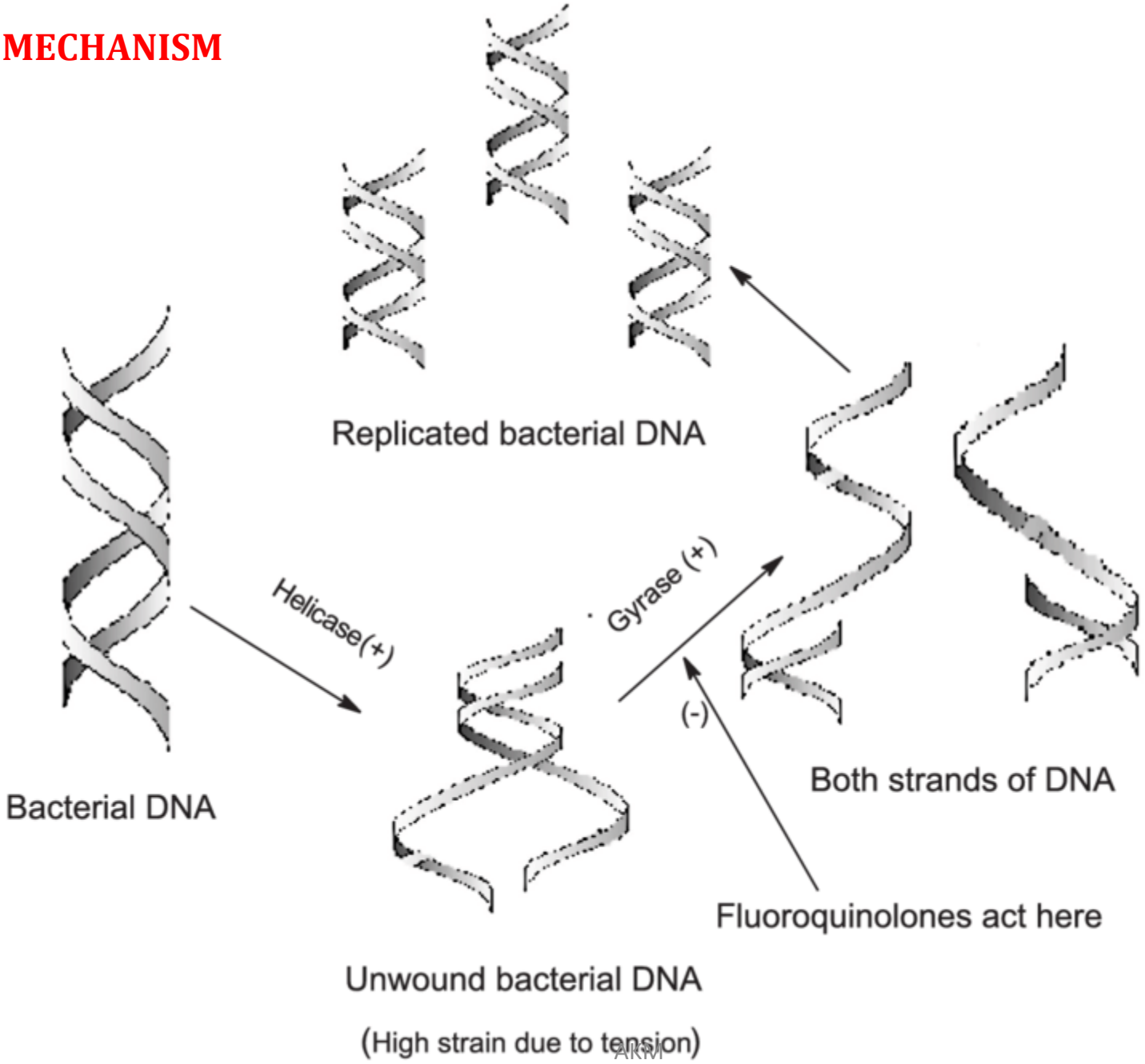
FQs bind to A subunit with high affinity and interfere with its strand cutting and resealing function.

Recent evidence indicates that in gram-positive bacteria the major target of FQ action is a similar enzyme *topoisomerase IV* which nicks and separates daughter DNA strands after DNA replication.

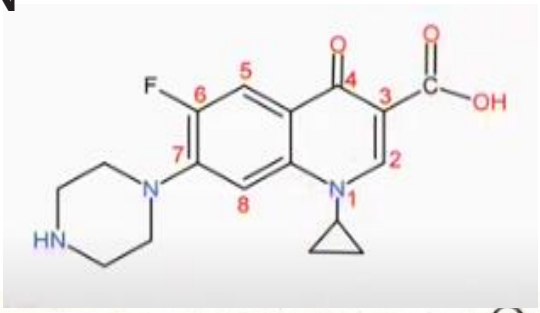
Greater affinity for topoisomerase IV may confer higher potency against gram-positive bacteria.

In place of DNA gyrase or topoisomerase IV, the mammalian cells possess an enzyme topoisomerase II (that also removes positive supercoils) which has very low affinity for FQs— hence the low toxicity to host cells.

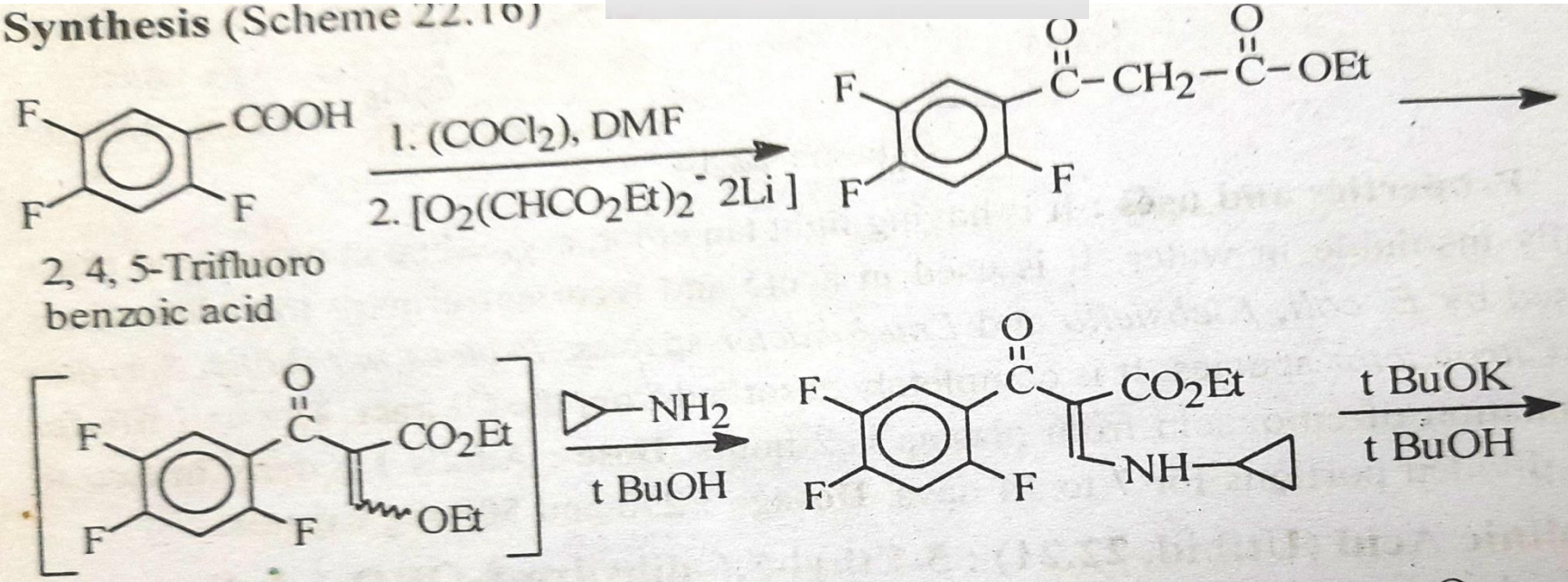
MECHANISM


Replicated bacterial DNA
Helicase(+)
Gyrase (+)
(-)
Bacterial DNA
Both strands of DNA
Fluoroquinolones act here
Unwound bacterial DNA
(High strain due to tension)

SYNTHESIS OF CIPROFLOXACIN



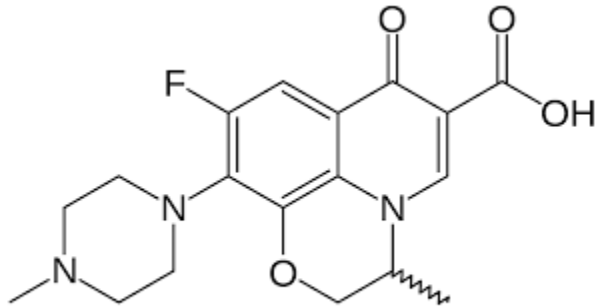
Synthesis (Scheme 22.16)



Ciprofloxacin (22.25)

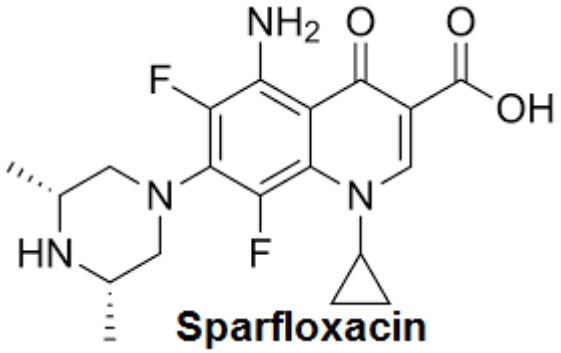
SAR OF FLUROQUINOLONES

- 1. Presence of 4-oxo group is essential.



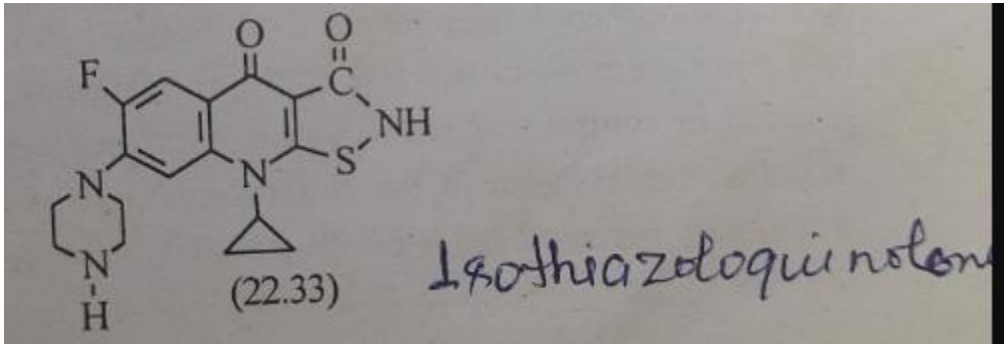
Ofloxacin

- 2. Presence of trisubsitituted nitrogen as hetero atom at position 1 is essential.

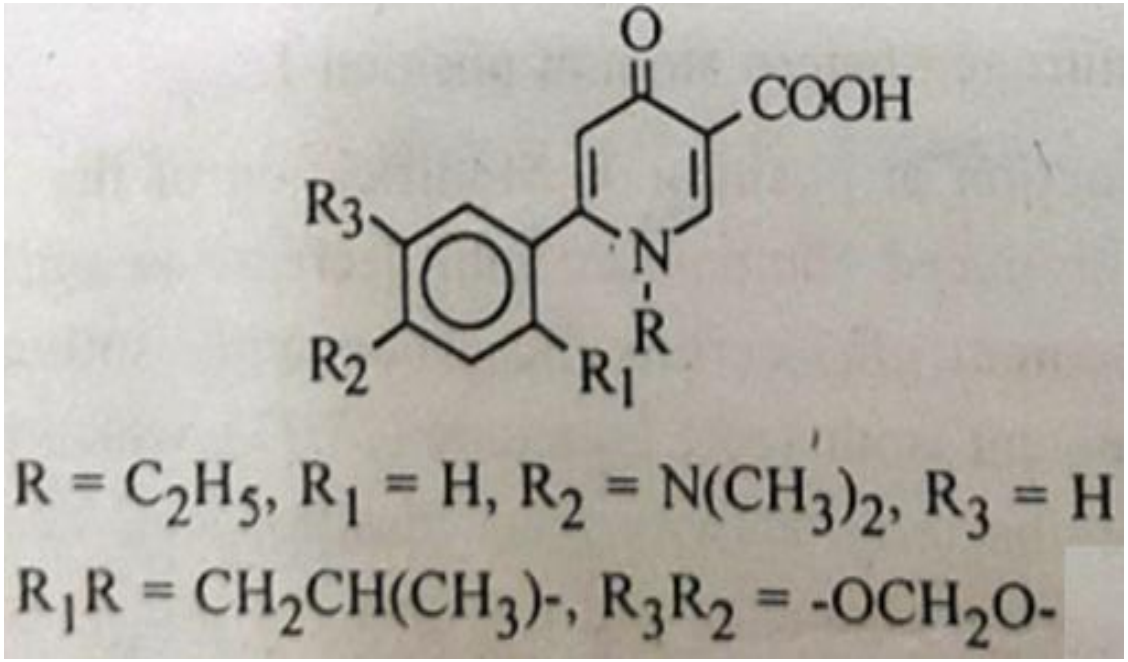


Sparfloxacin

▪3. Carboxy group at psition 3 is essential. Modification of the 3-carboxylic group produces a compound with reduced activity. But replacement of 3-carboxyli group with isothiazologroup produced most potent isothiazoloquinolone which is 4-10 times more active than ciprofloxacin.

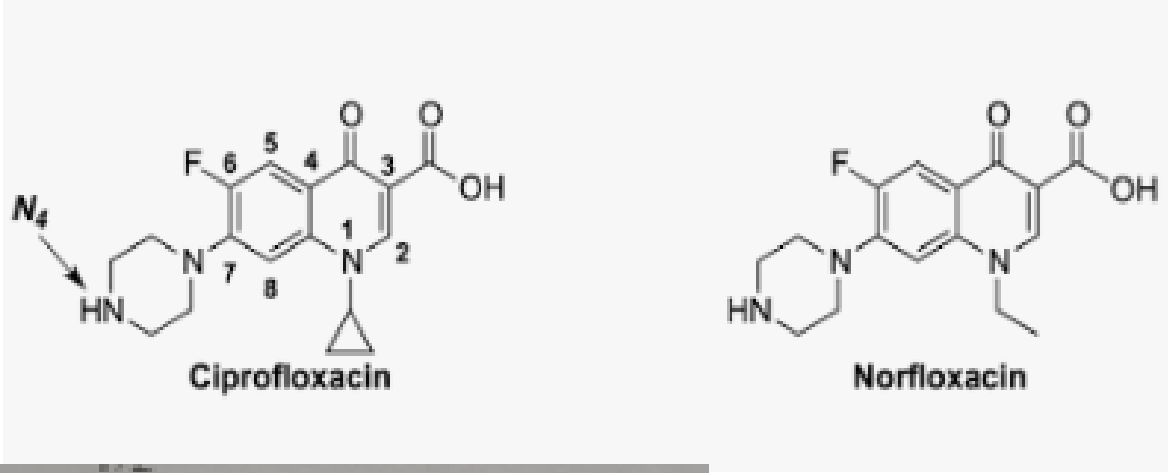


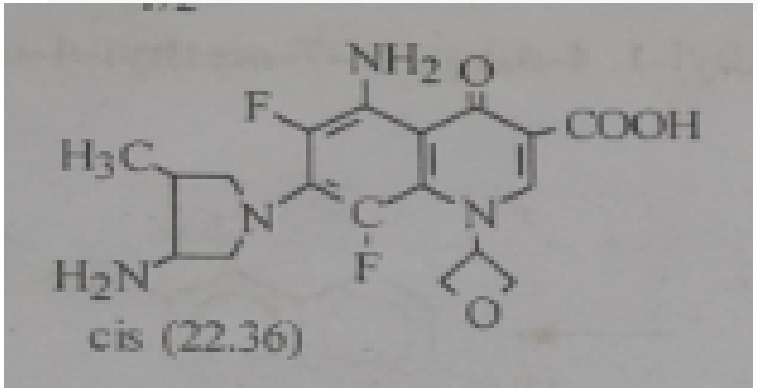
▪4. A second ring attached to pyridone ring at position 5 and 6 may be done. These derived compounds have antibacterial activities equal to nalidix acid.



▪5. Optimum substituent at C-1 may be ethyl but **cyclopropyl and diflurophenyl have resulted in potent compounds.**

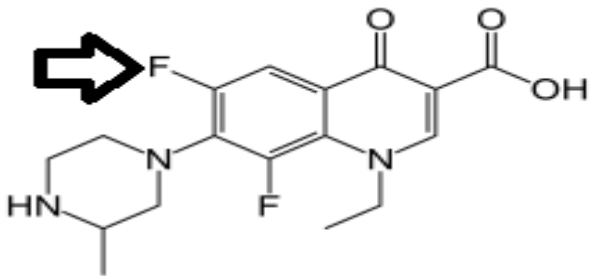
▪Replacement of **N-1 cyclopropyl with oxetane** resulted in increased activity.





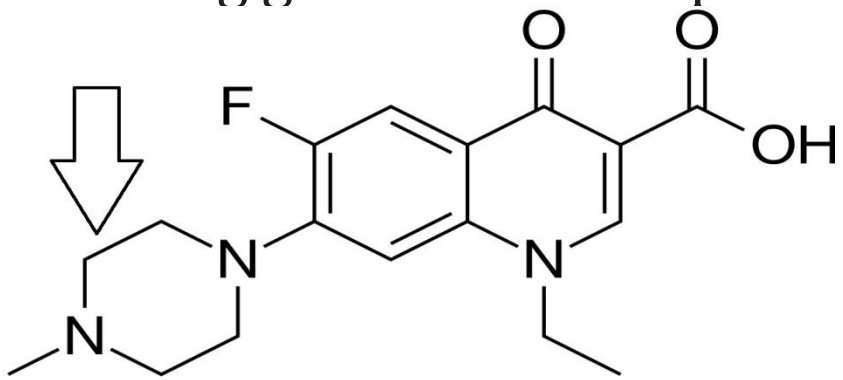
- 6. At position 5 of quinoline ring, an amino substituent gave active compounds.

- 7. At position 6 of quinoline ring, fluorine atom seems to be essential.



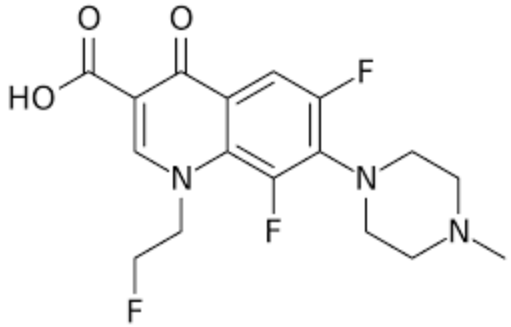
Lomefloxacin

▪.8. At position 7, piperazine, n-methyl piperazine and pyrrolidine ring gave active compounds.



Pefloxacin

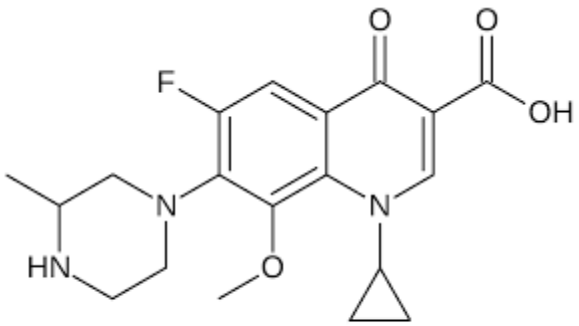
▪9. At position 8, fluorine or chlorine gives active compounds., 8 carbon can also be replaced with nitrogen resulting in an active compound.



fleroxacin structure

▪10. In ofloxacin, the S-Enatiomer is slightly more potent than its antipode.

Gatifloxacin

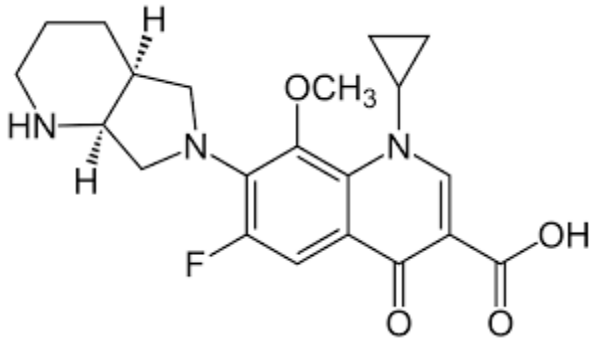


Gatifloxacin

Gatifloxacin is an antibiotic of the fourth-generation fluoroquinolone family, that like other members of that family, inhibits the bacterial enzymes DNA gyrase and topoisomerase IV. It was patented in 1986 and approved for medical use in 1999.

Gatifloxacin eye drops may cause side effects including red, irritated, itchy, or teary eyes, blurred vision. eye pain. eye discharge. swollen eyelids. broken blood vessels in the eyes. headache.

Moxifloxacin

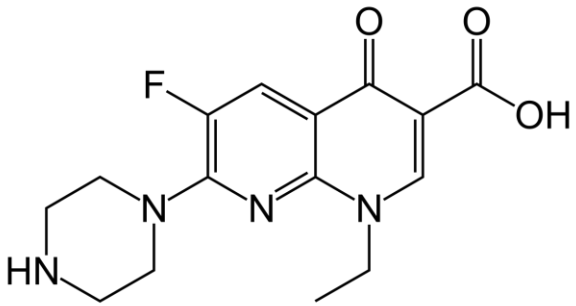


Moxifloxacin is an antibiotic, used to treat bacterial infections, including **pneumonia, conjunctivitis, endocarditis, tuberculosis, and sinusitis**.

It can be given by mouth, by injection into a vein, and as an eye drop. Common side effects include diarrhea, dizziness, and headache.

Moxifloxacin is a broad-spectrum antibiotic that is active against both Gram-positive and Gram-negative bacteria.

Enoxacin,

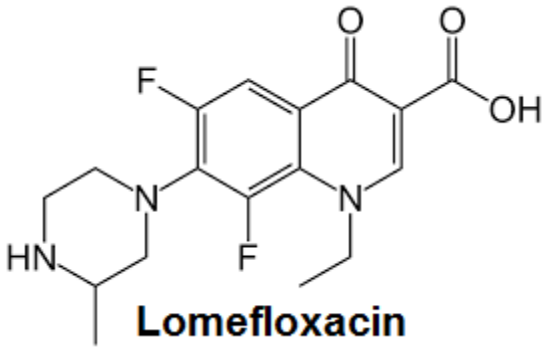


Enoxacin is an oral broad-spectrum fluoroquinolone antibacterial agent used in the treatment of urinary tract infections and gonorrhea.

Insomnia is a common adverse effect.

It is no longer available in the United States. It has been shown recently that it may have cancer inhibiting effect.

Lomefloxacin



Lomefloxacin

Lomefloxacin hydrochloride is a fluoroquinolone antibiotic used to treat bacterial infections including bronchitis and urinary tract infections.

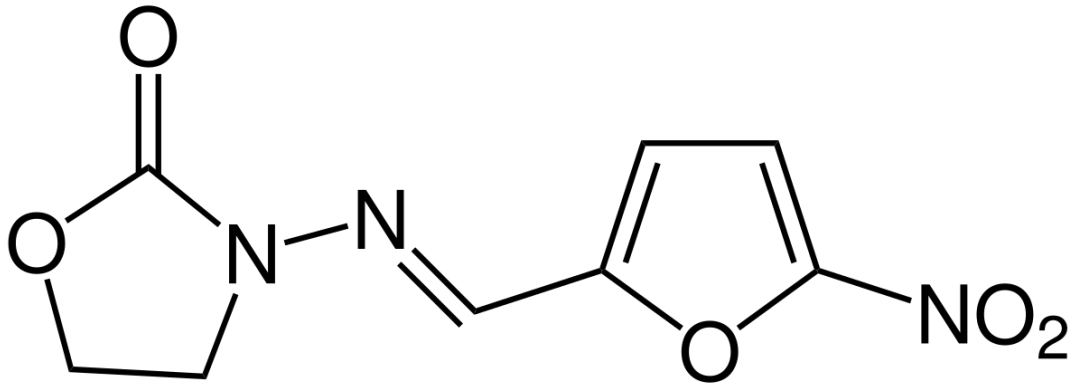
It is also used to prevent urinary tract infections prior to surgery.

Lomefloxacin is associated with phototoxicity and central nervous system adverse effects.

Miscellaneous

Furazolidine, Nitrofurantoin*, Methanamine.

Furazolidone



Furazolidone is a nitrofuran antibacterial agent and monoamine oxidase inhibitor.

Its bactericidal activity is based upon its **interference with DNA replication and protein production**;

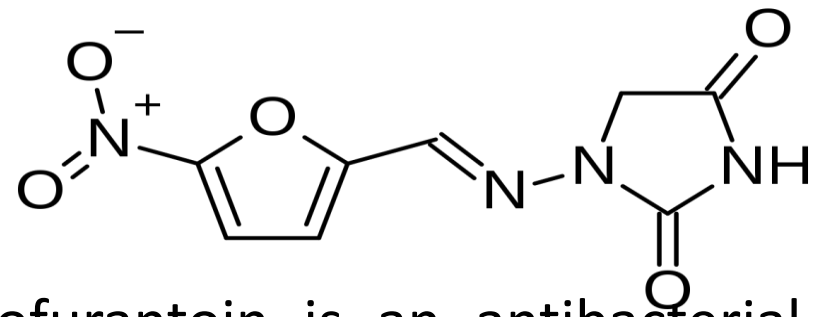
this antimicrobial action minimizes the development of resistant organisms. Furazolidone and its related free radical products are believed to bind DNA and induce cross-links.

Furazolidone is used **to treat bacterial and protozoal infections.** It works by killing bacteria and protozoa**.**

USES: This medication is **used in the treatment of diarrhea or enteritis caused by bacteria.** It may also be useful in treating traveler's diarrhea, typhoid fever, cholera and salmonella infections**.**

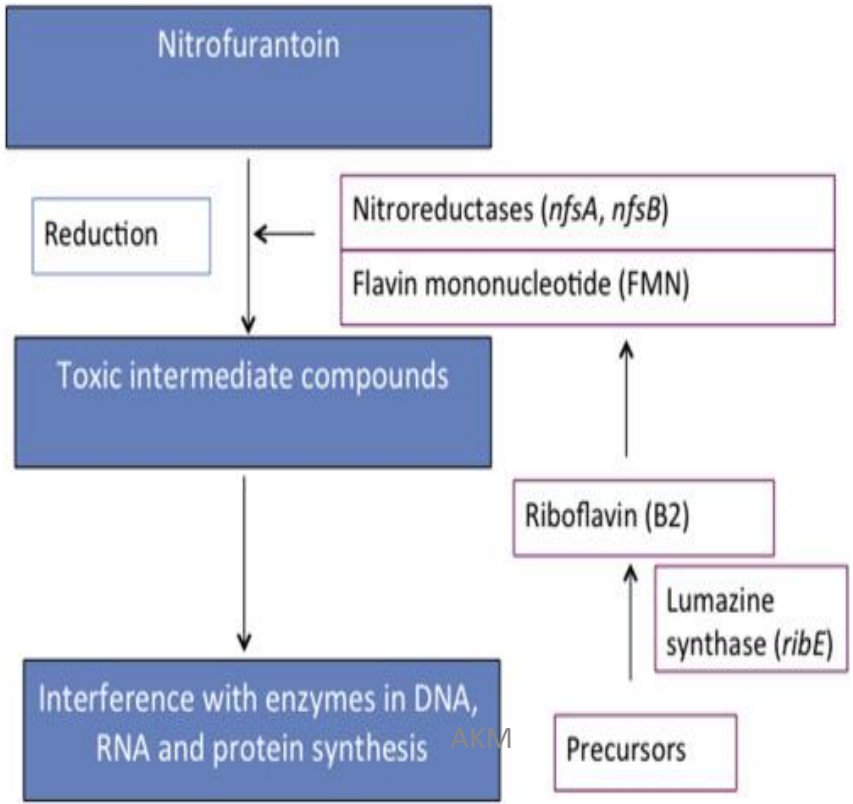
Common side effects of Furoxone (furazolidone) include: lowered blood pressure,fever,joint pain, rash

Nitrofurantoin



Nitrofurantoin is an antibacterial medication used **to treat bladder infections**, but it is not as effective for kidney infections. Orally given Common side effects include nausea, loss of appetite, diarrhea, and headaches.

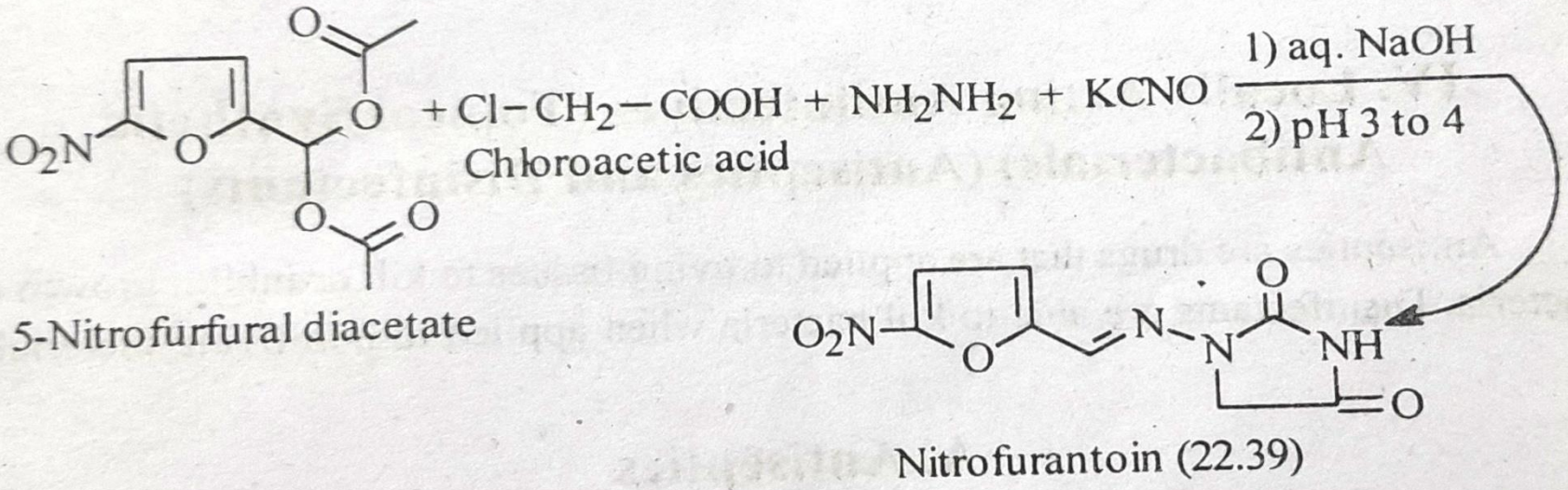
Mechanism



Synthesis

Nitrofurantoin (Furandanti, Furalan; 1-[[(5-nitro-2-furanyl) methylene] amino]-2,4-imidazolidinedione (22.39).

Synthesis (Scheme 22.24)

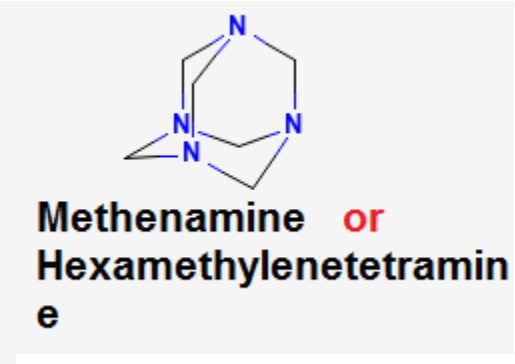


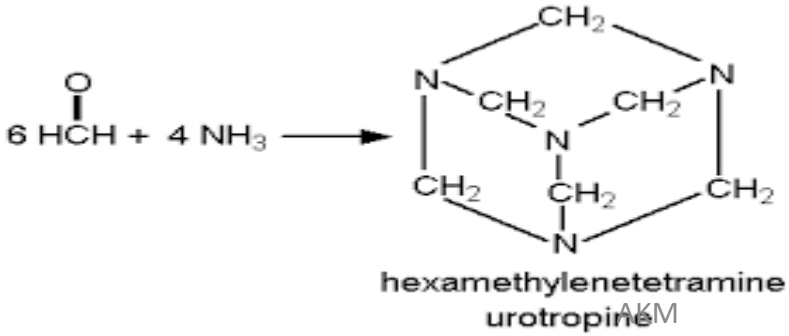
Uses:

Nitrofurantoin is used to treat urinary tract infections.

Methanamine

Hexamethylenetetramine, also known as methenamine, hexamine, or urotropin, is a heterocyclic organic compound with the formula $(CH_2)_6N_4$. This white crystalline compound is highly soluble in water and polar organic solvents. It has a cage-like structure similar to adamantane.





Mechanism

- In an acidic environment, methenamine is hydrolyzed to ammonia and formaldehyde. Its mechanism of action is driven by the formation of bactericidal formaldehyde, which possesses nonspecific antimicrobial activity by denaturing proteins and nucleic acid of bacteria.
- Methenamine belongs to the family of medicines called anti-infectives.
- It is used to help prevent the urinary tract infections.
- It will not work for colds, flu, or other viral infections.
- Methenamine is not effective for an active (current) urinary tract infection. It's used instead for prevention if you have recurrent UTIs.

Methenamine may cause side effects. including
upset stomach.
vomiting.
diarrhea.
stomach cramps.
loss of appetite.