Chapter 10: Urinary Tract Anti-infective Agents

Syllabus

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

Miscellaneous: Furazolidine, Nitrofurantoin*, Methanamine

10.1. URINARY TRACT INFECTION

- A urinary tract infection, or UTI, is an infection in any part of your urinary system, which includes your kidneys, bladder, ureters, and urethra.
- **Types: Based on location**
  - ✓ **Cystitis or Lower UTI (bladder):** Symptoms from a lower urinary tract infection include pain with urination, frequent urination, and feeling the need to urinate despite having an empty bladder. You might also have lower belly pain and cloudy or bloody urine.
  - ✓ **Pyelonephritis or Upper UTI (kidneys):** This can cause fever, chills, nausea, vomiting, and pain in your upper back or side.
  - ✓ **Urethritis(urethra):** This can cause a discharge and burning when you pee.
- **Causative Agents:** The most common cause of infection is ***Escherichia coli***, though other bacteria or fungi may sometimes be the cause.

10.2. DRUGS USED IN UTI

A) Urinary Antiseptics: Some orally administered AMAs attain antibacterial concentration only in urine, with little or no systemic antibacterial effect. E.g., **Nitrofurantoin*, Methanamine**

B) Urinary Analgesics: to reduce pain, E.g., Phenazopyridine,

C) Antimicrobial Agents: Quinolones (Norfloxacin, Ciprofloxacin, Ofloxacin), Cephalosporins (Cephalexin, Cefpodoxime), Cotrimoxazole, Amoxicillin

Treatments

Antimicrobial regimens for acute UTI (all given orally for 3–5 days)*

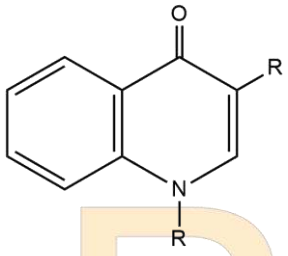
1. Norfloxacin 400 mg 12 hourly
2. Ciprofloxacin 250–500 mg 12 hourly
3. Ofloxacin 200–400 mg 12 hourly
4. Cotrimoxazole 960 mg 12 hourly
5. Cephalexin 250–500 mg 6 hourly

6. Cefpodoxime proxetil 200 mg 12 hourly
7. Amoxicillin + clavulanic acid (500 + 125 mg) 8 hourly
8. Nitrofurantoin 50 mg 8 hourly or 100 mg 12 hourly × 5–7 days

** For upper UTI (pyelonephritis), the same drugs may be given for 2–3 weeks. Nitrofurantoin is not suitable for pyelonephritis.*

10.3. QUINOLONES

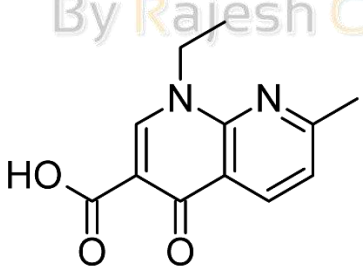
- These are synthetic antimicrobials having a quinolone structure that are active primarily against gram-negative bacteria, though the newer fluorinated compounds also inhibit gram-positive ones.



Basic Quinolone Ring

(1) First Generation Quinolones :

- The first member *Nalidixic acid* introduced in mid-1960s had usefulness limited to urinary and g.i. tract infections because of low potency, modest blood and tissue levels, restricted spectrum and high frequency of bacterial resistance
- These have limited antibacterial spectrum. e.g. Nalidixic acid, Miloxacin, Oxolinic acid, Flumequine, Pipemidic acid, Rosoxacin

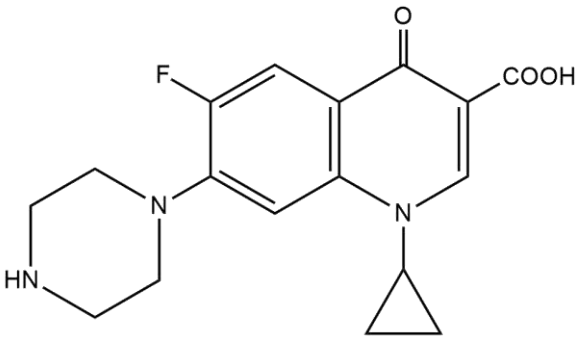


Nalidixic acid

(2) Second Generation Quinolones (Fluoroquinolones)

- A breakthrough was achieved in the early 1980s by fluorination of the quinolone structure at position 6 and introduction of a piperazine substitution at position 7 resulting in derivatives called *fluoroquinolones* with high potency, expanded spectrum, slow development of resistance, better tissue penetration and good tolerability.

These have extended antibacterial spectrum. e.g. Ciprofloxacin, Norfloxacin, Pefloxacin, Ofloxacin, Amifloxacin



Ciprofloxacin
1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid

Mechanism of Action:

- ✓ *Quinolones block bacterial DNA synthesis by inhibiting bacterial DNA gyrase and topoisomerase IV that are type of Type II topoisomerase.*
- ✓ Inhibition of *topoisomerase II* prevents the relaxation of positively supercoiled DNA (required from normal transcription and replication). Inhibition of *topoisomerase IV* interferes with separation of replicated chromosomal DNA into the daughter cells during cell division

Antibacterial spectrum:

- ✓ First generation quinolones are effective against certain gram negative bacteria (e.g. *Shigella, E. Coli*) and ineffective against gram positive organisms
- ✓ Second generation quinolones are effective against gram positive and gram negative organisms including *Enterobacteriaceae*, *Pseudomonas*, *Neisseria*, *Haemophilus*, *Campylobacter* and *Staphylococci*

General Uses: UTI, Gonorrhea, Bacterial gastroenteritis, Typhoid, RTI, Soft tissue infection, and tuberculosis

ADR: It may damage growing cartilage and cause an arthropathy

10.4. SAR of Quinolones

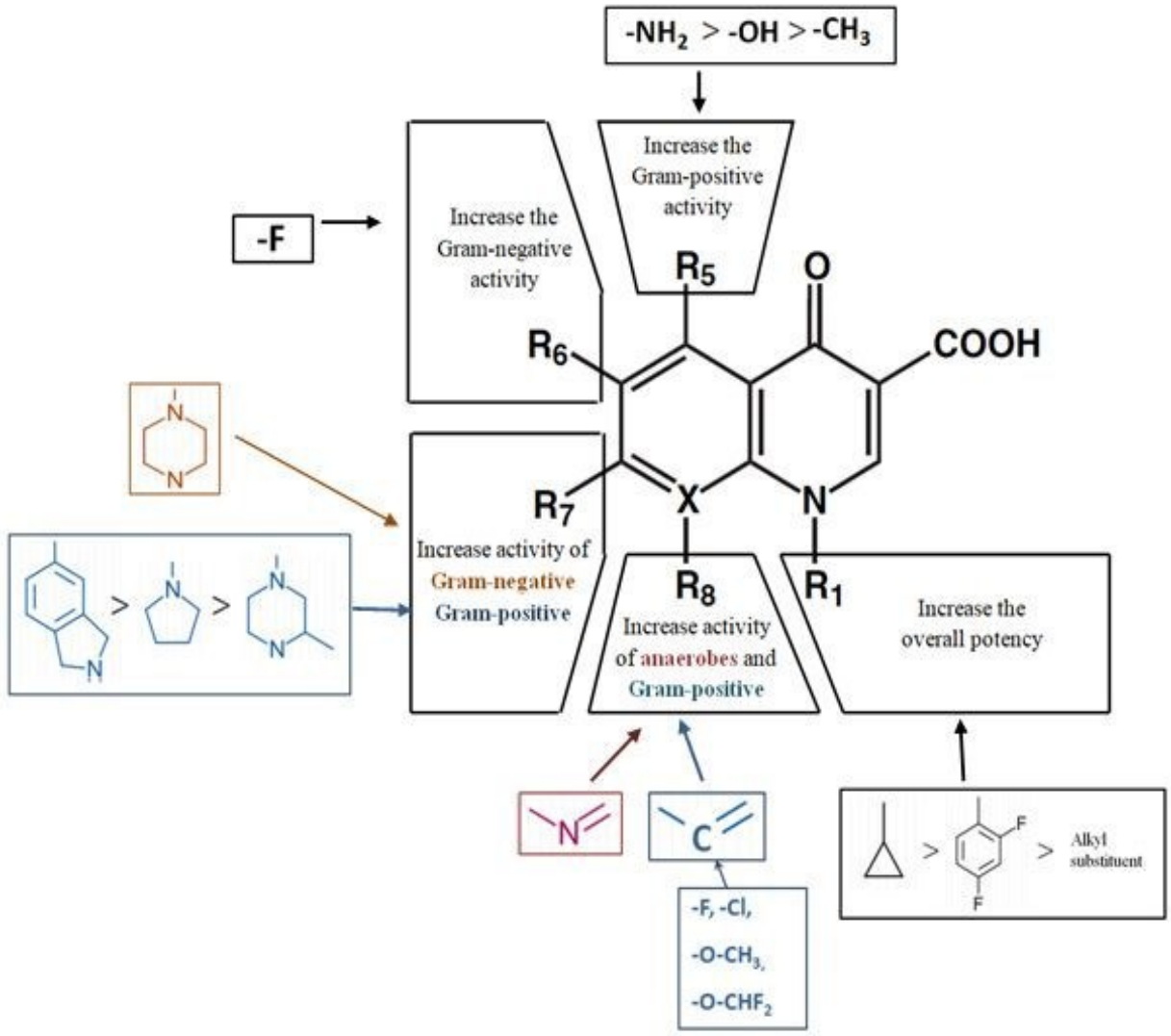
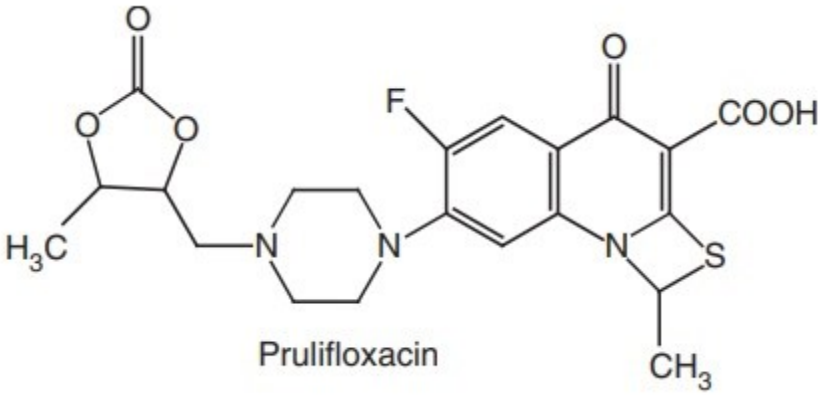


Figure: Basic Ring. There are 6 important positions for modifications to improve the activity of the drug: R_1, R_5, R_6, R_7, R_8. *X=C defines quinolones, X=N defines naphthyridones.* Source*:* T. D. M. Pham, Z. Ziora and M. Blaskovich*, Med. Chem. Commun.*, 2019, DOI: 10.1039/C9MD00120D.

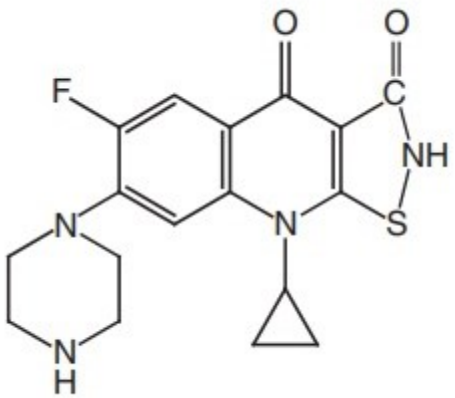
1. Substituent at N-1 position: The optimum substituents at position 1 appear to be ethyl, butyl, cyclopropyl, and difluorophenyl, and these substituents have resulted in potent compounds. Addition of a fluorine atom into the N-1 cyclopropyl group or the 1-butyl substituent resulted in compounds with overall improved activity against gram-positive bacteria.

2. **Substitution at C-2:** The simple replacement of C-2 hydrogen has been generally disadvantageous (e.g. C-2 methyl or hydroxy groups); however, some derivatives containing a suitable C-1, C-2 ring have shown to possess notable activity.



Prulifloxacin

3. The carboxy functions at position: Modification of C-3 carboxylic acid group leads to decrease in antibacterial activity. However, replacement of C-3 carboxylic group with isothiazole group afforded most active isothiazolo-quinolone, which has been 4–10 times greater in *in vitro* antibacterial activity than ciprofloxacin. The isothiazolo system possesses aromatic character and the nitrogen proton is very acidic and can be considered as a carboxylic acid mimic, whereas other groups, such as sulphonic acid, phosphonic acid, tetrazole as well as derivatization, as an ester lead to loss of antibacterial activity.

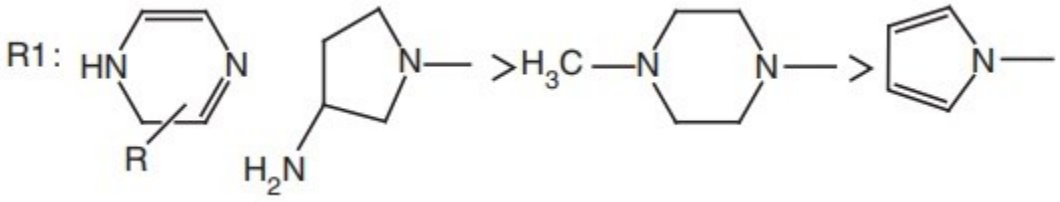


4. **The C-4-oxo group** of the quinolone nucleus appears to be essential for antibacterial activity. Replacement with 4-thioxo or sulphonyl group leads to a loss of activity.

5. Substitution at C-5 position: The incorporation of a group at the C-5 position has proven beneficial in terms of antibacterial activity. The order of activity is NH_2>OH> CH_3>F.

6. **Substitution at C-6 position**: The incorporation of a **fluorine** atom at the C-6 position of the quinolone is monumental. The order of activity is F>Cl, Br, CH_3>CN.

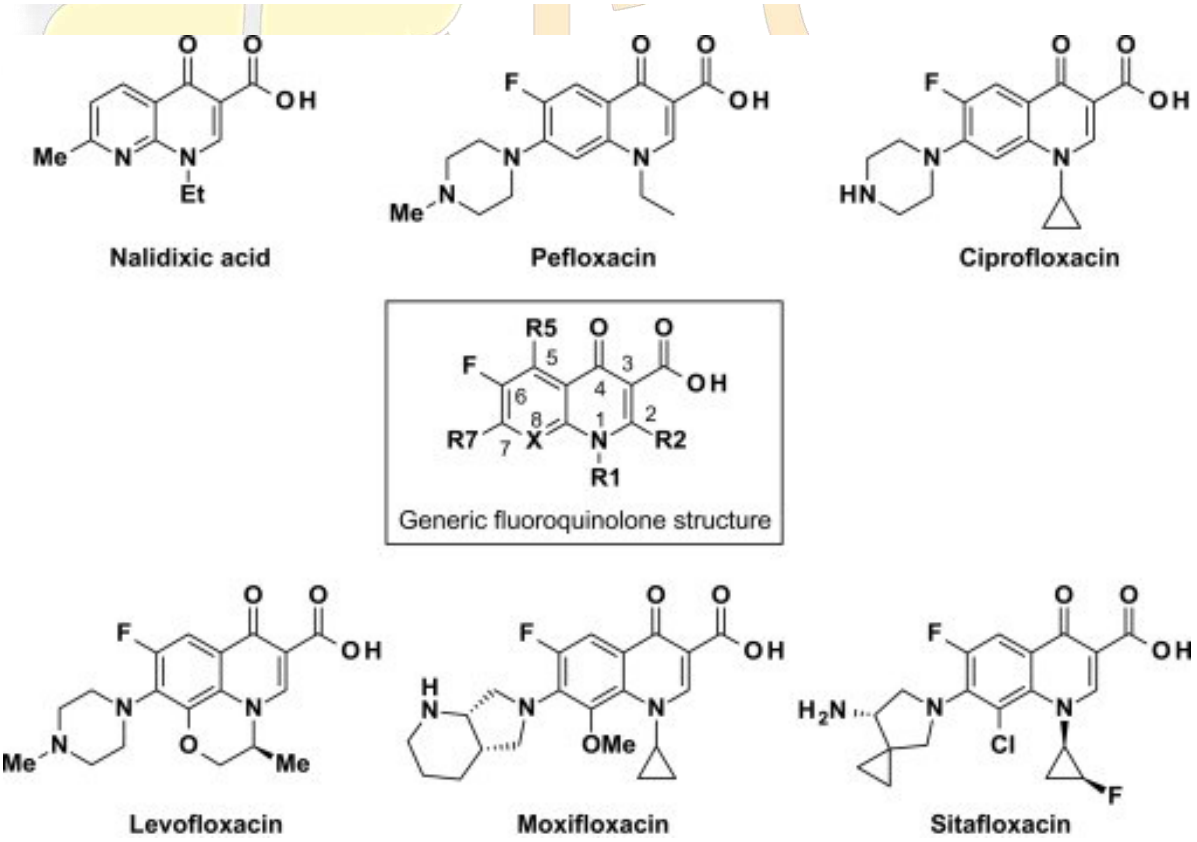
7. **Substitution at C-7 position**: The introduction of a piperazine moiety at the C-7 position is essential. Other aminopyrrolidines also are compatible for activity.



8. **Substitution at C-8 position:** In general, a C-8 fluoro substituent offers good potency against gram-negative pathogens, while a C-8 methoxy moiety is active against gram-positive bacteria. The order of activity is F, Cl, OCH_3>H, CF_3>methyl, vinyl, propargyl.

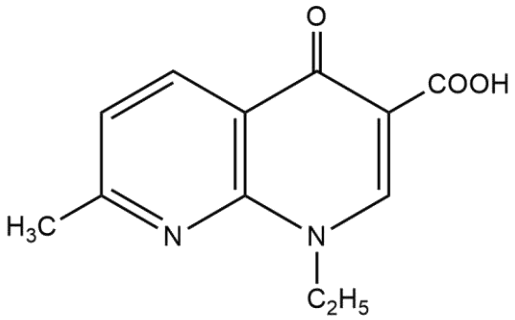
9. A halogen (F or Cl) at the C-8 position improves oral absorption.

10. Linking of N-1 group to the C-8 position with oxazine ring leads to active oflaxacin.



10.5. MEDICINAL CHEMISTRY OF QUINOLONES

A) Nalidixic Acid



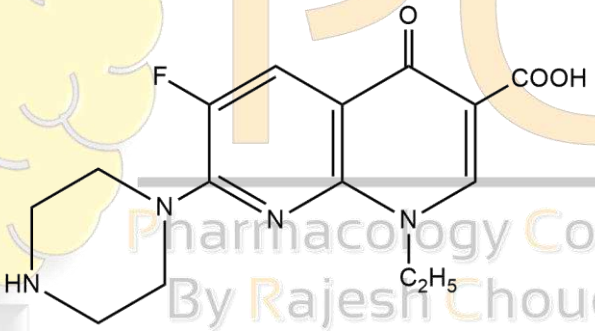
1-ethyl-7-methyl-4-oxo-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

MOA: DNA gyrase inhibitor (binds to the A Site)

Uses:

- ✓ Mainly used in Lower UTI
- ✓ Used as a tool in studying the regulation of bacterial division.

B) Enoxacin

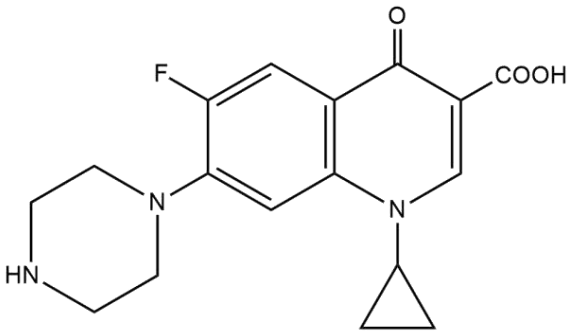


1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydro-1,8-naphthyridine-3-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses: Lower UTI, Diarrhoea, RTI

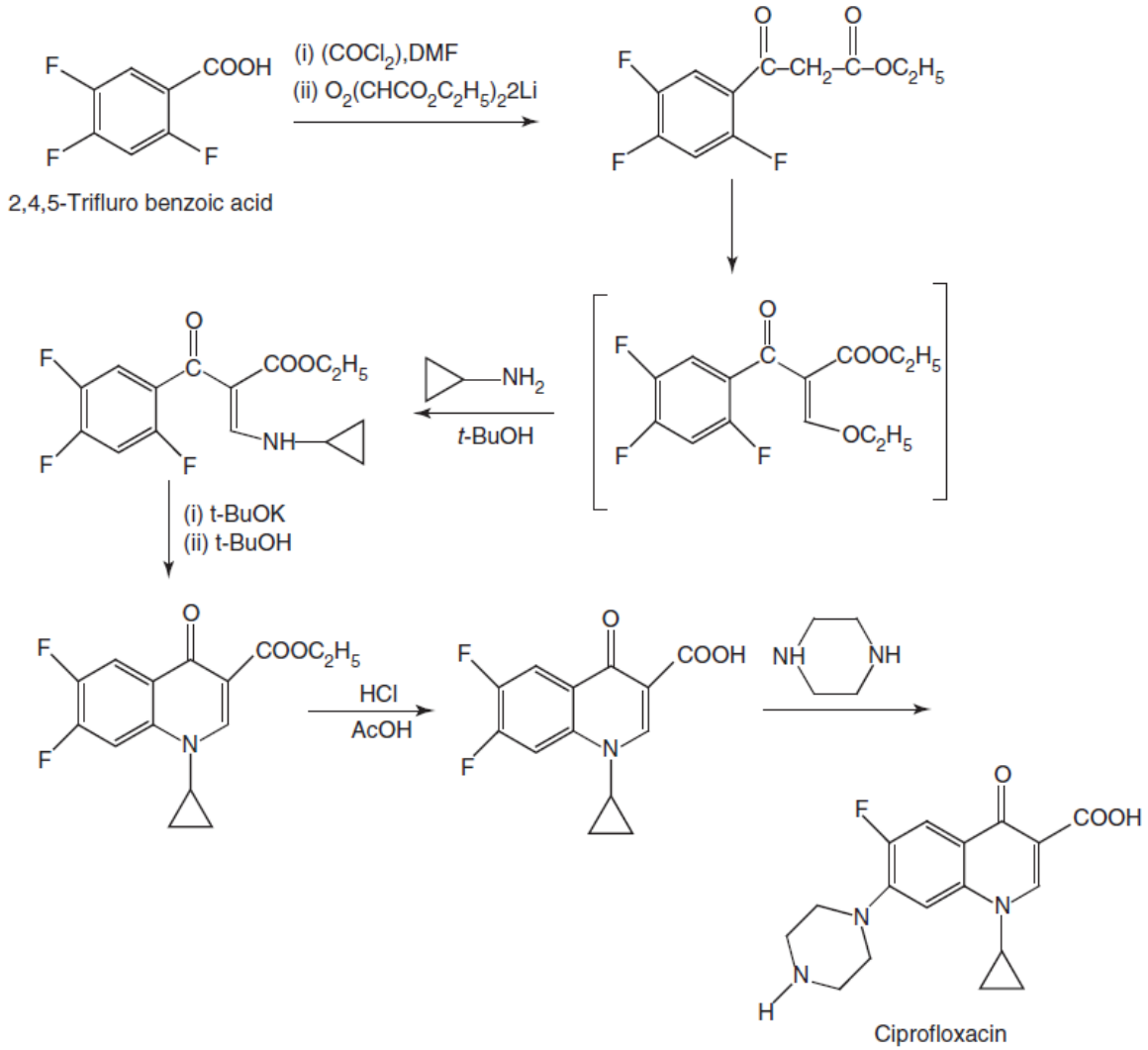
C) Ciprofloxacin



Ciprofloxacin

1-cyclopropyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid

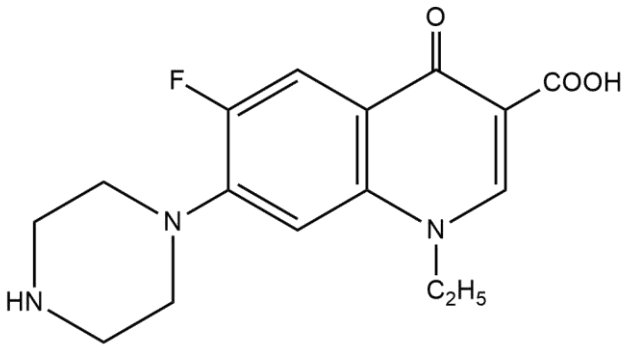
Synthesis:



MOA: Inhibits the topoisomerase II and topoisomerase IV

- ✓ **Uses**: Lower and upper UTI, pneumonia, skin infection, meningitis
- ✓ Along with metronidazole used in complicated abdominal infection caused by E. coli

D) Norfloxacin

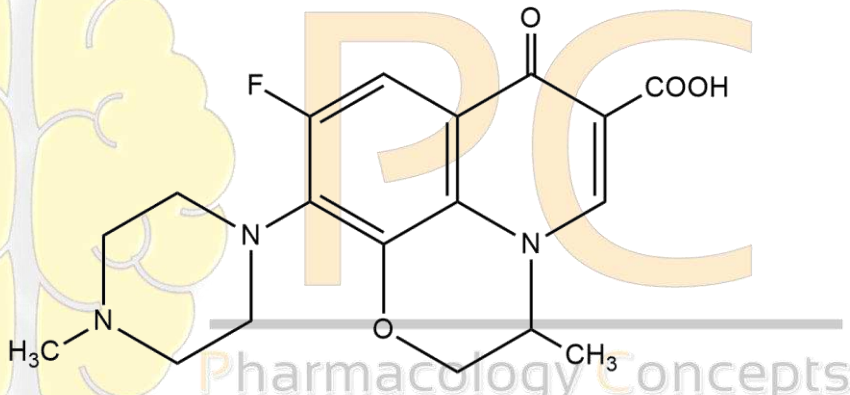


1-ethyl-6-fluoro-4-oxo-7-(piperazin-1-yl)-1,4-dihydroquinoline-3-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses: UTI and prostatitis caused by E. coli and Gastroenteritis

E) Ofloxacin



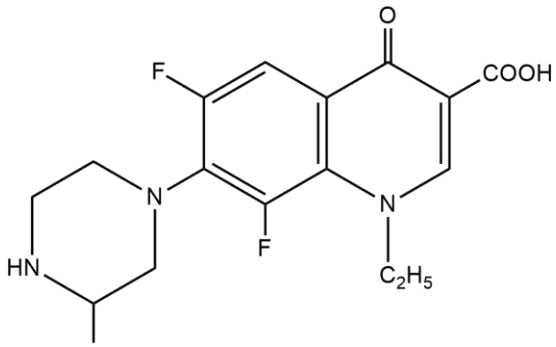
9-fluoro-3-methyl-10-(4-methylpiperazin-1-yl)-7-oxo-3,7-dihydro-2*H*-[1,4]oxazino[2,3,4-*ij*]quinoline-6-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses:

- ✓ Lower and upper UTI, lower RTI, Infection Diarrhea, Chronic Prostatitis
- ✓ Also used in treatment of acute pelvic inflammatory disease (PID)

F) Lomefloxacin

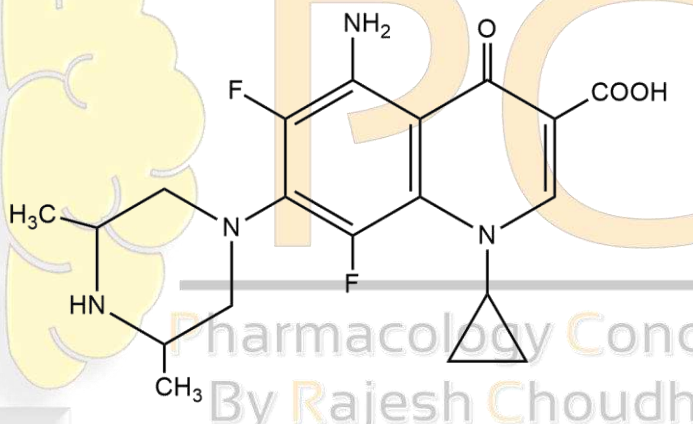


1-ethyl-6,8-difluoro-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses: Acute UTI, lower RTI, bronchitis, and other bacterial infection

G) Sparfloxacin

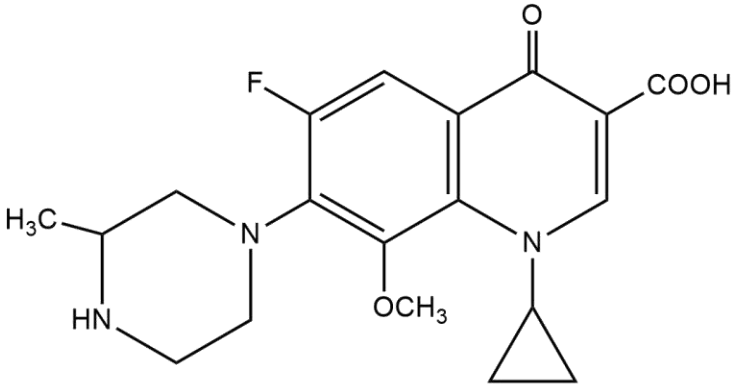


5-amino-1-cyclopropyl-7-(3,5-dimethylpiperazin-1-yl)-6,8-difluoro-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses: Acute UTI, lower RTI, bronchitis, and other bacterial infection

H) Gatifloxacin

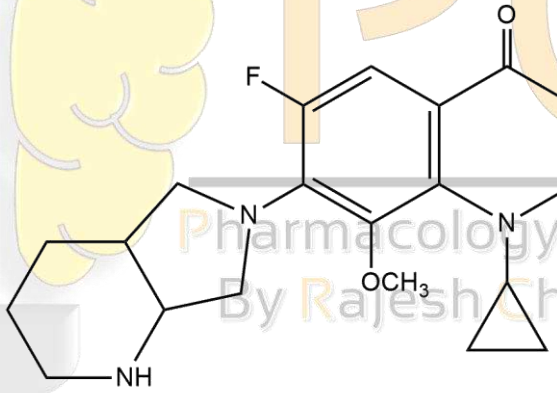


1-cyclopropyl-6-fluoro-8-methoxy-7-(3-methylpiperazin-1-yl)-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses: Acute UTI, lower RTI, bronchitis, sinusitis, community acquired pneumonia, and skin infection

I) Moxifloxacin



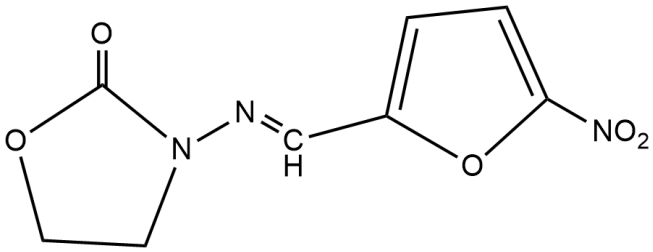
1-cyclopropyl-6-fluoro-7-(hexahydro-1*H*-pyrrolo[3,4-*b*]pyridin-6(2*H*)-yl)-8-methoxy-4-oxo-1,4-dihydroquinoline-3-carboxylic acid

MOA: Inhibits the topoisomerase II and topoisomerase IV

Uses: Acute UTI, ophthalmic solution of conjunctivitis, acute bacterial sinusitis, skin infection, pneumonia, and complicated intra-abdominal infection.

10.5. MEDICINAL CHEMISTRY OF URINARY ANTISEPTICS AND OTHERS

A) Furazolidine

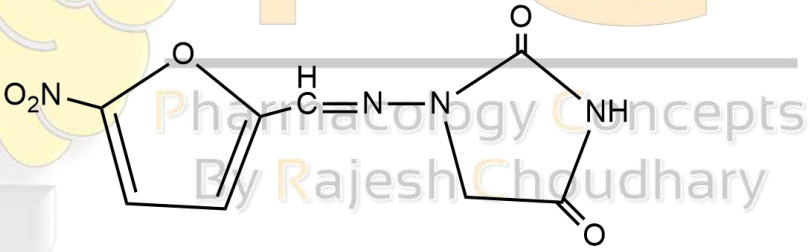


(*E*)-3-(((5-nitrofuran-2-yl)methylene)amino)oxazolidin-2-one

MOA: It cause crosslinking the bacterial DNA

Uses: Used in treatment of UTIs, Diarrhea, enteritis, cholera, giardiasis, and amoebiasis

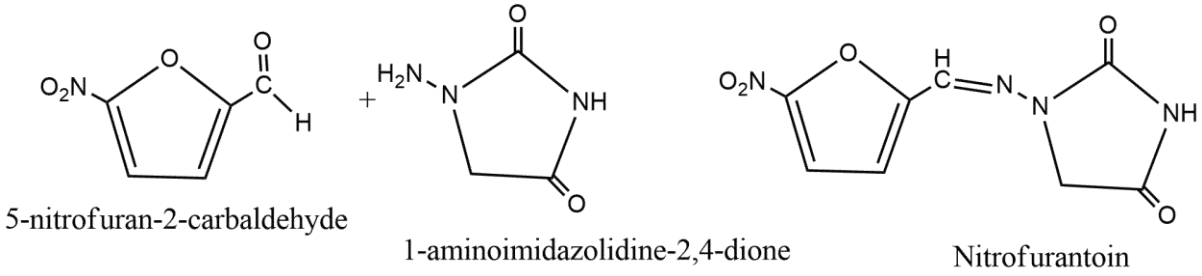
B) Nitrofurantoin



1-(((5-nitrofuran-2-yl)methylene)amino)imidazolidine-2,4-dione

It is primarily bacteriostatic but may be bactericidal at higher concentrations and in acidic urine. Its activity is enhanced at lower pH.

Synthesis:

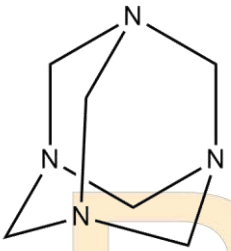


5-nitrofuran-2-carbaldehyde + 1-aminoimidazolidine-2,4-dione → Nitrofurantoin

MOA: Susceptible bacteria enzymatically reduce nitrofurantoin to generate reactive intermediates which damage DNA and Inhibits the DNA, RNA, Protein synthesis further leads to inhibition of bacterial growth.

Uses: Prophylaxis and treatment of uncomplicated lower urinary tract infection caused by E. coli, Enterococci, and Staphylococcus aureus.

D) Methenamine



1,3,5,7-tetraazaadamantane

MOA: It is hexamethylene-tetramine, which is inactive as such; decomposes slowly in acidic urine to release formaldehyde which inhibits all bacteria

Methenamine is administered in enteric coated tablets to protect it from decomposing in gastric juice. Mandelic acid, given as methenamine mandelate, is excreted in urine→lowers urinary pH and promotes decomposition of methenamine.

Uses: Used in prophylaxis of recurrent UTI.

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