Antimicrobial Agents

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PhD

Antibacterial agents

Antibacterial Agents

- **Substances that kill bacteria without harming the host.**

- **History:**
  - **Arsenic: 1800s for syphilis.**
  - **Sulfonamides: 1935.:** synthetic antimicrobial agents
  - **Penicillin(Antibiotics): 1940.**
  - **Antimicrobials have revolutionized the treatment of bacterial infections as well as enhanced the advancement of medical and surgical treatment.**
  - **Patient's natural resistance plays a major role.**

Antibacterial Agents

- **Choosing an Antibiotic:**
  - **The infecting organism.**
  - **The correct antibiotic.**
  - **Site of infection.**
  - **Route of administration.**
  - **Drug history of the patient.**
  - **Complicating factors such as pregnancy.**
  - **Cost.**

Problems associated

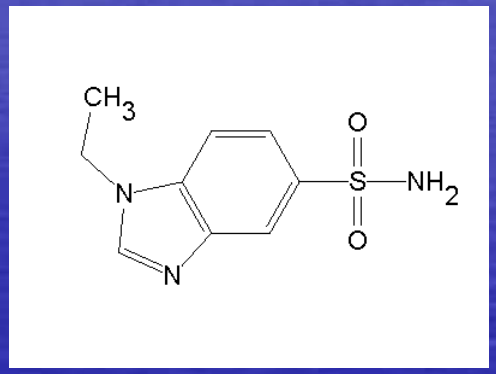
Overprescribing

due to

- patient demand
- time pressure on clinicians
- diagnostic uncertainty

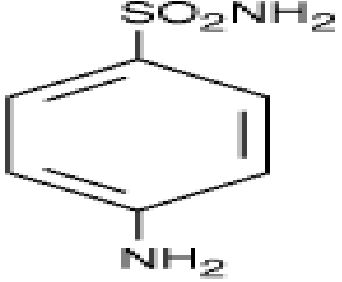
Sulphonamides

- **Almost obsolete nowadays because of:**
  - **Bacterial resistance.**
  - **bacteriostatic**
  - **Toxicity:**
    - **Nausea.**
    - **Rashes**
    - **Blood dyscrasia.:**

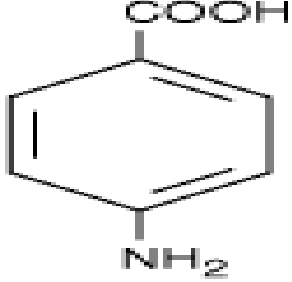


the presence of abnormal material in the **blood**, usually applied to diseases affecting **blood** cells or platelets. Evidence of **dyscrasia** can be present with a WBC count of over 1,000,000.

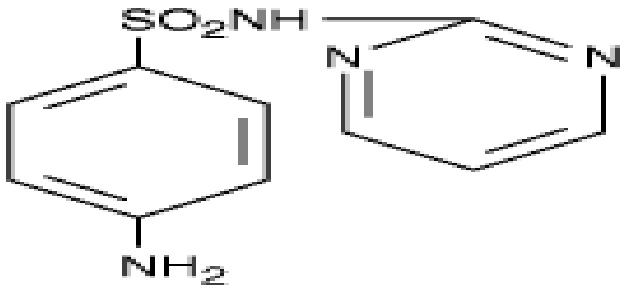
- **Precipitation (crystallization) in urinary tract and stone formation.**



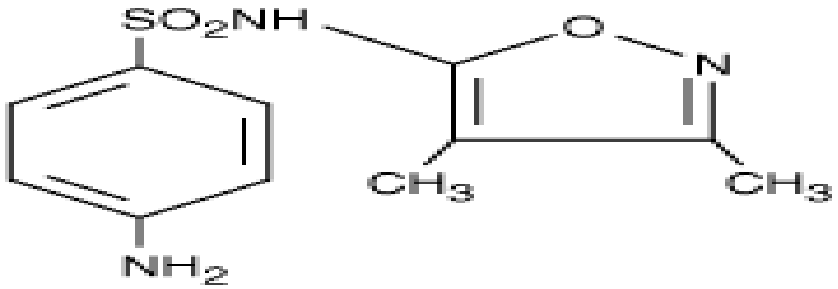
Sulfanilamide



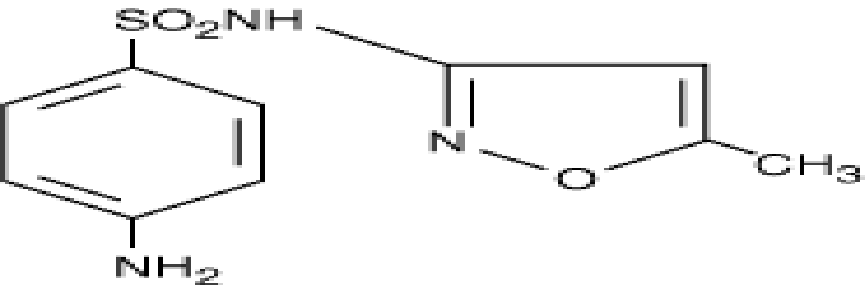
***p*-Aminobenzoic acid (PABA)**



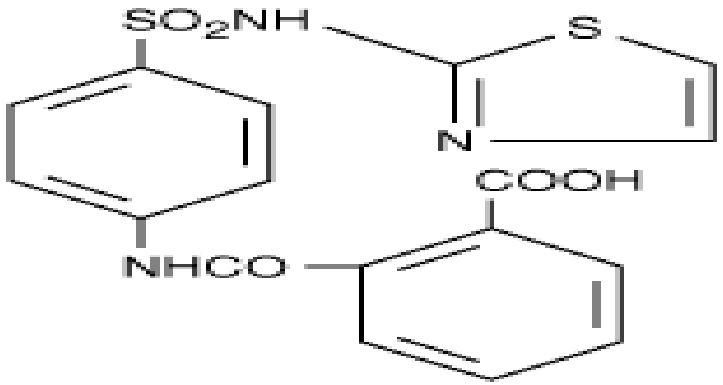
Sulfadiazine



Sulfisoxazole



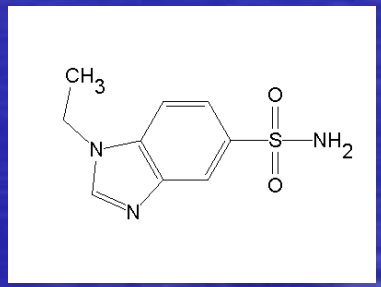
Sulfamethoxazole



Sulfathalidine
(phthalylsulfathiazole)

Chemical features

- SO2NH2 group is not essential as such
- the important feature is that the sulfur is linked directly to the benzene Ring
- The NH2 group is essential



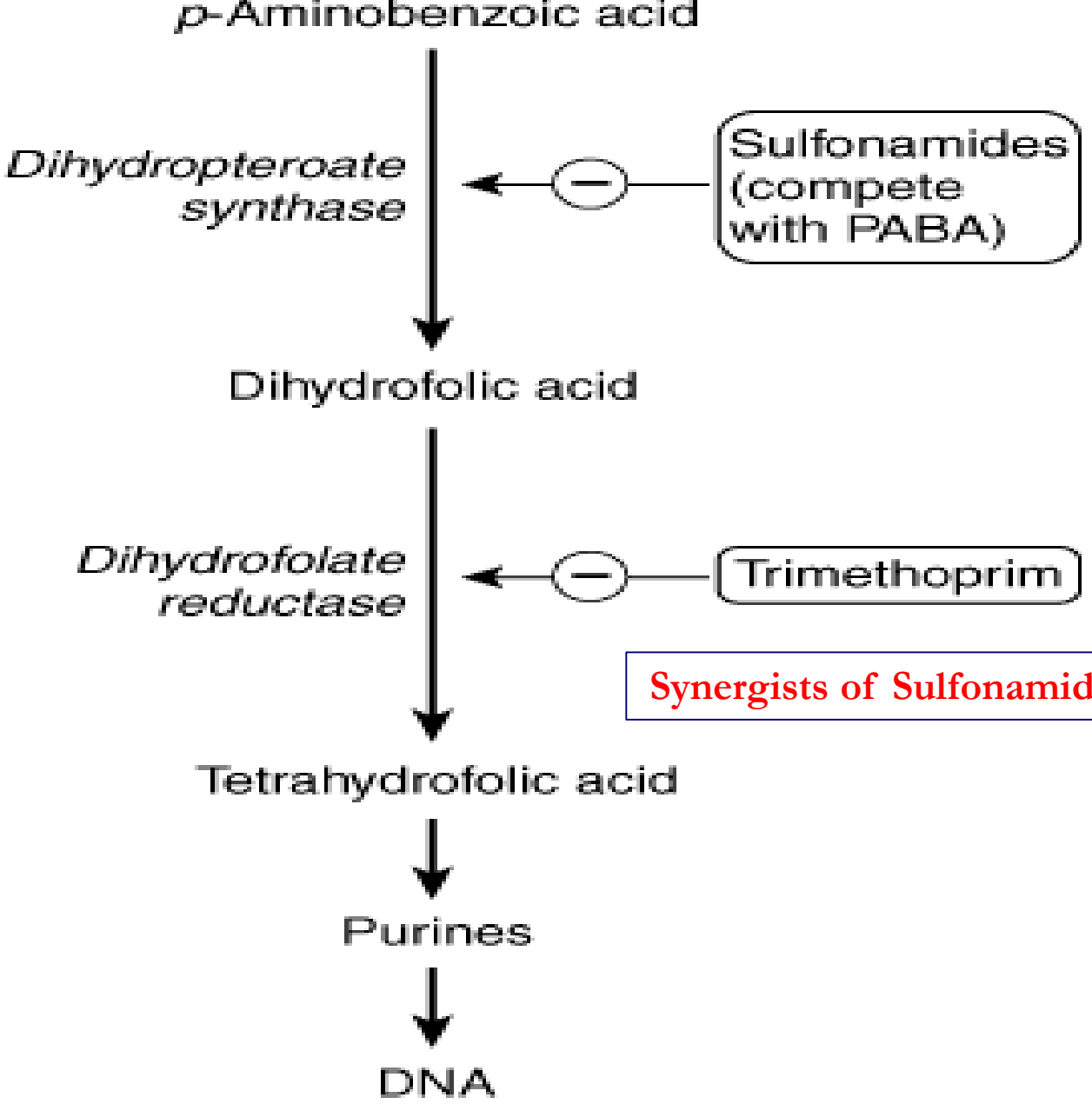
Sulphonamides

- **Cotrimoxazole- Trimethoprim Combination (Bactrim, Septrin, Balakatrin):**
  - One of the few, still used, sulfa drugs.
  - Very effective fixed combination.
  - No resistance.
  - Very useful in UTI, RTI, Salmonella, and Pneumocystis pneumonia, an opportunistic infection in AIDS patients.

Mechanism of Action

Sulfonamides: structural analogs and competitive antagonists of para-aminobenzoic acid (PABA)

Prevent normal bacterial utilization of PABA for the synthesis of folic acid



Synergists of Sulfonamide

Sensitive microorganisms are those that must synthesize their own folic acid; bacteria that can use preformed folate are not affected like mamalin cells

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Quinolones

- **Interfere with cell division of bacteria.**
- **Nalidixic Acid:**
  - **Very old urinary antiseptic.**
- **Norfloxacin:**
  - **Used only for UTI.**
  - **3-day course.**

- **fluorinated 4-quinolones**

such as ciprofloxacin (CIPRO), moxifloxacin (AVELOX), and gatifloxacin (TEQUIN)

Ciprofloxacin:

Wide range of activity, even Botulinum.

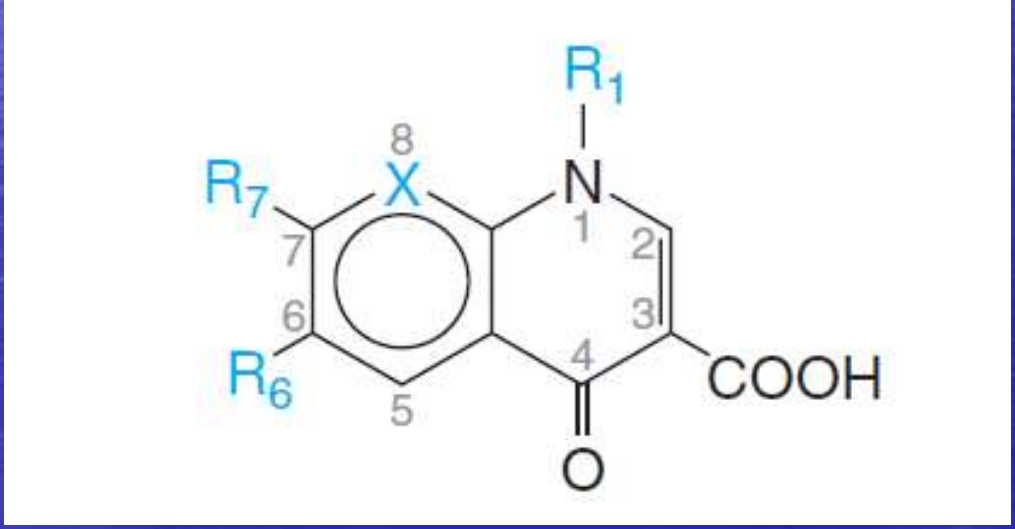
Expensive.

Prophylaxis for meningitis.

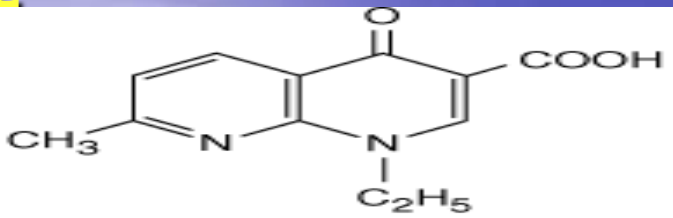
Can cause g.i upset, and epilepsy

Botulinum toxin is produced by Clostridium **botulinum** bacteria

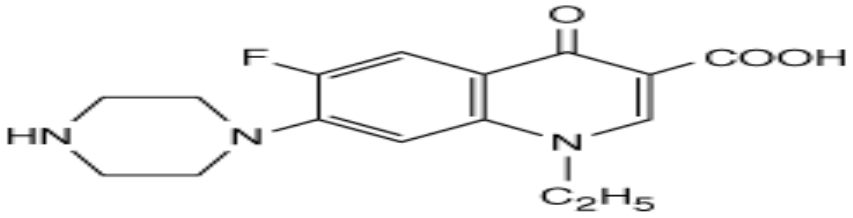
Quinolones available for use are containing a carboxylic acid moiety at position 3 of the primary ring structure



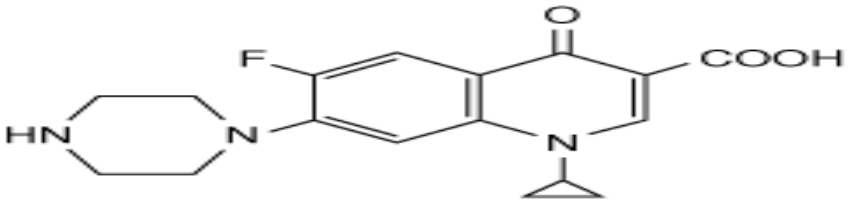
Quinolones.



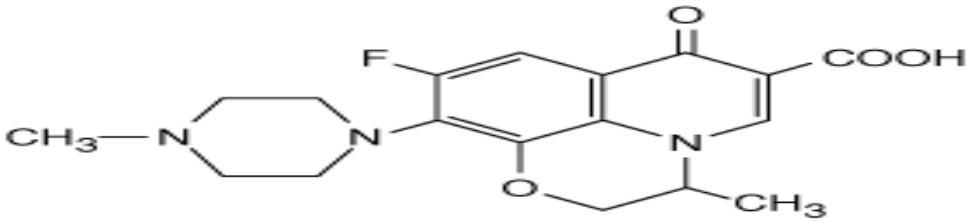
Nalidixic acid



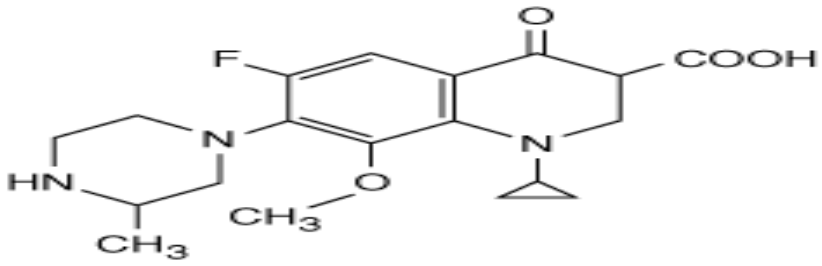
Norfloxacin



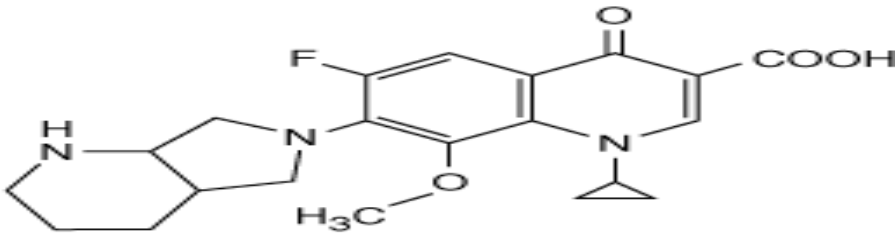
Ciprofloxacin



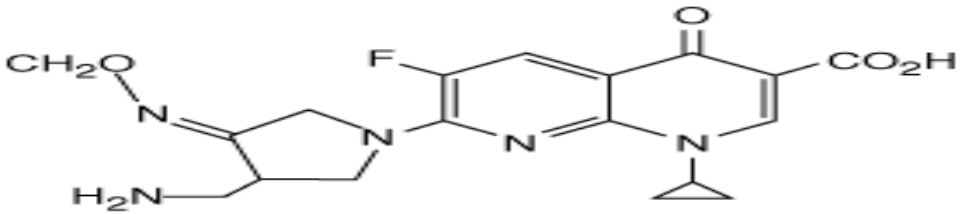
Levofloxacin



Gatifloxacin



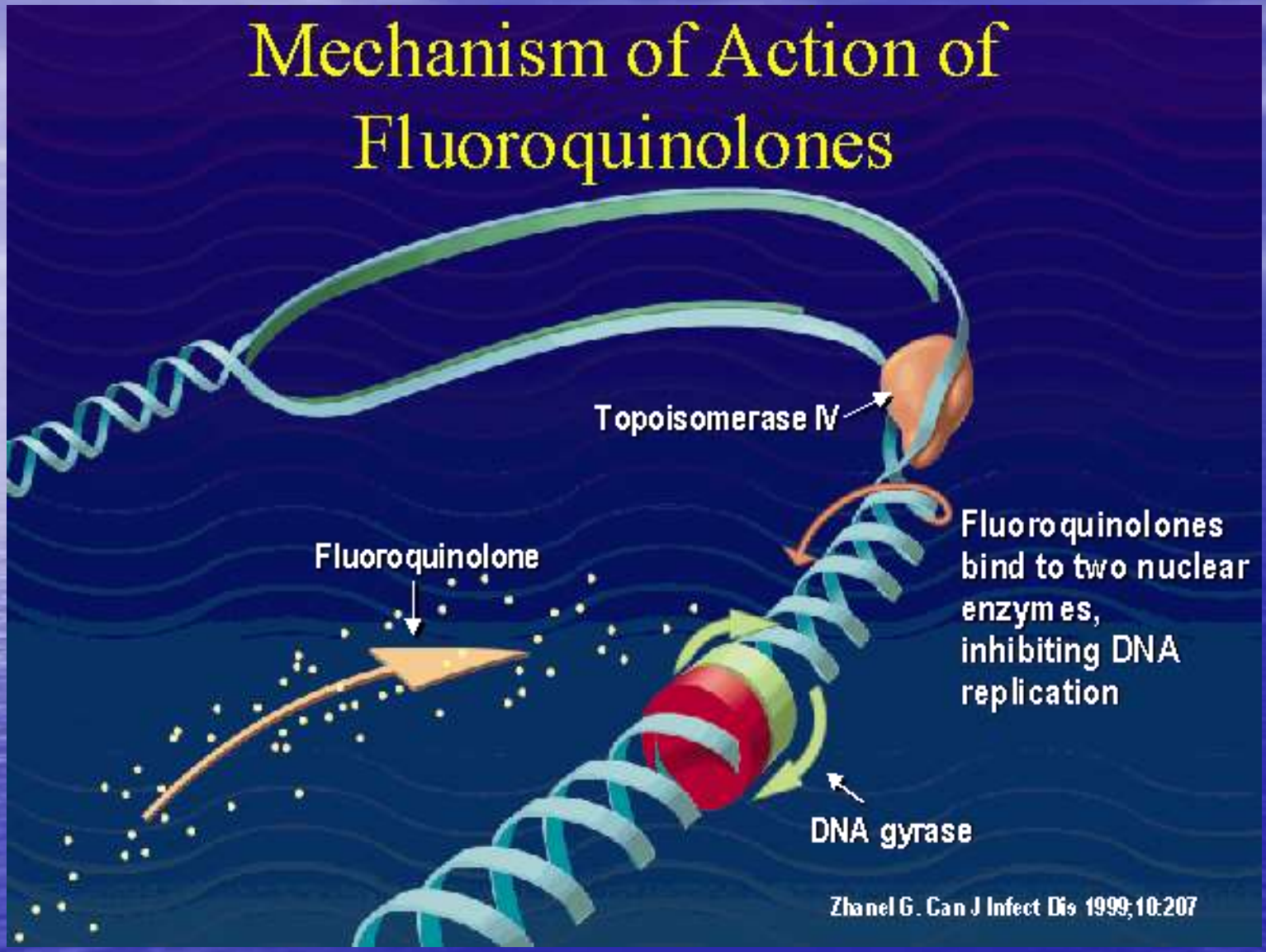
Moxifloxacin



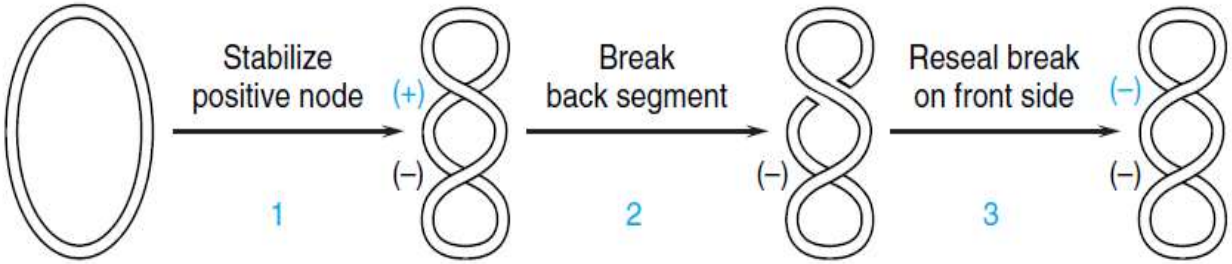
Gemifloxacin

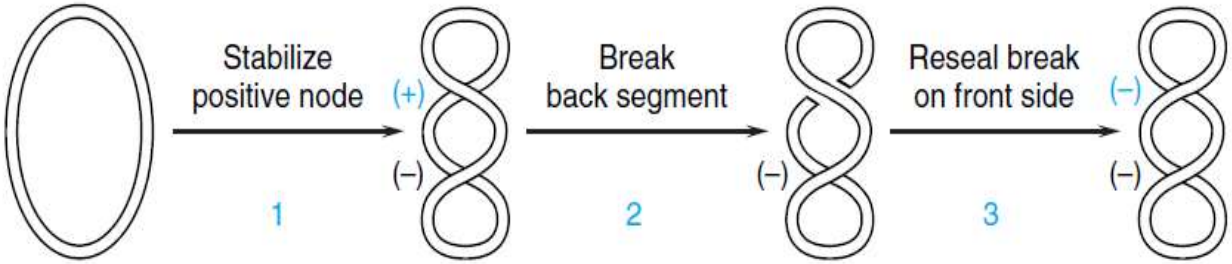
Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Mechanism of Action of Fluoroquinolones

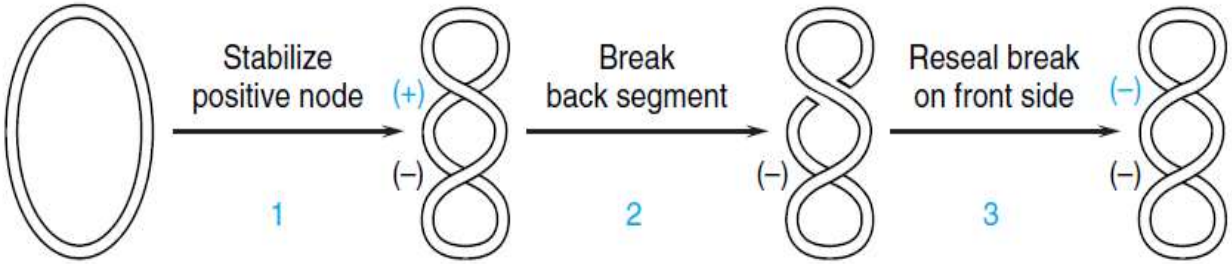


The quinolone antibiotics target bacterial DNA gyrase and Topoisomeras which is responsible for the continuous introduction of negative supercoils into DNA



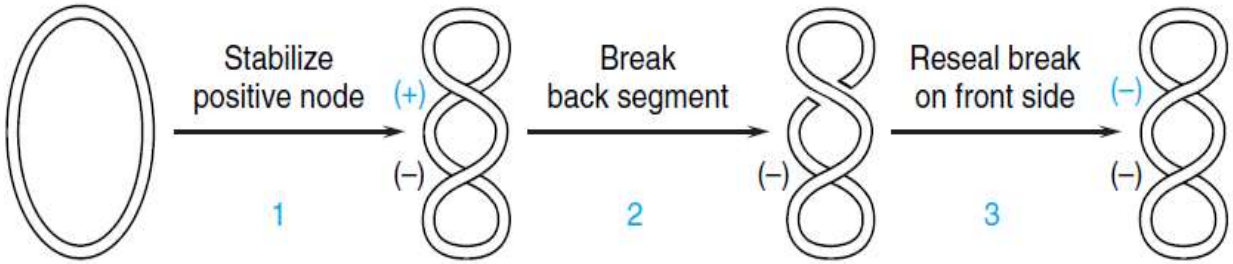


The individual strands of double-helical DNA must be separated to permit DNA replication or transcription. However, anything that separates the strands results in "overwinding" of the DNA. To combat this mechanical obstacle, the bacterial enzyme DNA gyrase is responsible for the continuous introduction of negative supercoils into DNA



The enzyme binds to two segments of DNA (1), creating a node of positive (+) superhelix. The enzyme then introduces a double-strand break in the DNA and passes the front segment
through the break (2). The break is then resealed (3), creating a negative (−) supercoil.

Quinolones inhibit the nicking and closing activity of the gyrase and also block the activity of topoisomerase IV



Nitrofurans (Nitrofurantoin)
Chemistry and Mechanism of Action

- A number of 5-nitro-2-furaldehyde derivatives, called nitrofurans,
- are used in the treatment and/or prophylaxis of microbial infections, primarily in the urinary tract

- modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis

It is presumed that the nitrofurans are selectively toxic to microbial cells because in humans, the slower reduction by mammalian cells prevents high serum concentrations.

Nitrofurantoin is primarily
active against gram-negative bacteria (E. coli, P. mirabilis
is variable) and some susceptible gram-positive organisms, such as S. aureus and Enterococcus faecalis

Development
of resistant strains is virtually unknown, and crossresistance
with other antimicrobials has not been reported

because

Intermediate metabolites modify various bacterial macromolecules that affect a variety of biochemical processes (e.g., DNA and RNA synthesis, protein synthesis);
this observation may explain the lack of resistance development to these drugs.

Clinical Use

- The singular indication for nitrofurantoin is the treatment and long-term prophylaxis of lower UTIs caused by susceptible bacteria
- it is not used as a bacterial suppressant.
- It is often used prophylactically post intercourse in women with chronic UTIs.

The bacteriostatic or bactericidal activity of nitrofurantoin is concentration dependent; a urinary concentration greater than 100 ug/mL ensures bactericidal activity

Nausea and vomiting are the most commonly observed adverse effects.

Methenamine

- Methenamine (hexamethylenetetramine) is an aromatic acid
- hydrolyzed at an acid pH (less than 6) to liberate ammonia and the active alkylating agent formaldehyde
- formaldehyde denatures protein and is bactericidal.

- Methenamine is usually administered as a salt
- this salt is either mandelic (Mandelamine) or hippuric (Hiprex, Urex) acid.
- these acids acidify the urine, which is necessary to generate formaldehyde.
- also, the resulting low urine pH is by itself bacteriostatic for some organisms

- Methenamine is administered orally and is well absorbed from the intestinal tract.
- 10 to 30% decomposes in the stomach unless the tablets are protected by an enteric coating.
- The inactive form (methenamine) is distributed to virtually every bodyfluid.
- Almost all of the methenamine moiety is excreted into the urine by 24 hours

- Methenamine is primarily used for the long-term prophylactic or suppressive therapy of recurring UTIs.
- It is not a primary drug for therapy of acute infections.
- It should be used to maintain sterile urine after appropriate antimicrobial agents have been employed to eradicate the infection.