Chapter 21

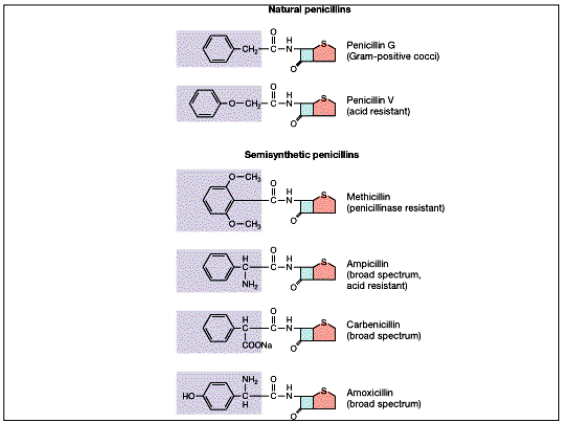
Antimicrobial chemotherapy

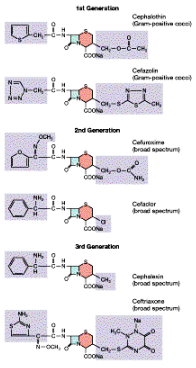
Key terms

- Chemotherapy
  - Chemical substances used to treat disease
- Antimicrobial agents
  - Chemotherapeutic agents used to treat diseases caused by microbes
- Antibiotic
  - An antimicrobial agent produced by a bacteria
- Synthetic drugs - synthesized in the lab
- Semisynthetic drugs - combination of antibiotic and synthetic

History of Chemotherapy

- Drugs
  - Salvarsan (~1907)
    - Paul Ehrlich
    - Arsenic (salvation & arsenic = Salvarsan)
    - Treatment for syphilis
  - Sulfa drugs (~1932)
    - Gerhard Domagk
    - Prontosil (Red Dye)
    - Sulfaninlamide
- Antibiotics
  - Penicillin (1928)
    - Alexander Fleming (Chain and Florey purified it 10 years later)
  - Streptomycin
    - Selman Waksman





MICROBE	ANTIBIOTICS
FUNGI	
Aspergillus fumigatus	Fumagillin
Cephalosporium species	Cephalosporins
Penicillium griseofulvum	Griseofulvin
Penicillium notatum and P. chrysogenum	Penicillin
STREPTOMYCETES	
Streptomycies nodosus	Amphotericin B
Streptomyces venezuelae	Chloramphenicol
Streptomyces erythraeus	Erythromycin
Streptomyces griseus	Steptomycin
Streptomyces kanamyceticus	Kanamycin
Streptomyces fradiae	Neomycin
Streptomyces noursei	Nystatin
Streptomyces antibioticus	Vidarabine
ACTINOMYCETES	
Micronomonospora	Gentamicin
BACTERIA	
Bacillus subtilis	Bacitracin
Bacillus polymyxa	Polymyxins
Bacillus brevis	Tyrothricin

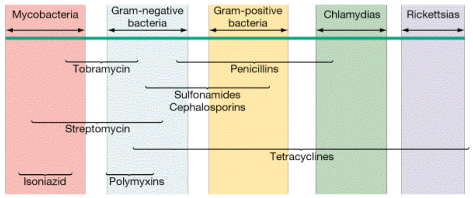
Toxicity

- Selective toxicity
  - – Harm the microbes without harming the host
- Toxic dosage
  - – Dosage given which causes host damage
- Therapeutic dosage
  - – Dosage given that controls or kills the microbe
- Therapeutic index
  - – Toxic dose divided by the therapeutic dose
  - – Therapeutic index of 8 is much better than 1

Spectrum of activity

- Broad spectrum
  - – Effective against many taxonomic groups
    - Gram + and Gram -
    - Can damage the normal flora
- Narrow spectrum
  - – A single taxonomic group or a small number of microbes
    - Best is the infecting organism is known

Spectrum of antibiotic activity



Broad and narrow spectrum agents

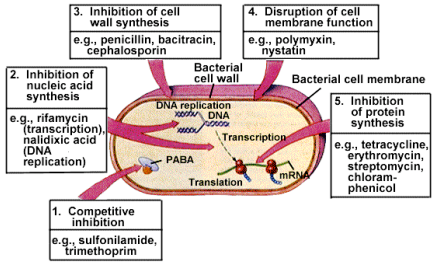
ORGANISMS AFFECTED	BROAD-SPECTRUM AGENTS*	NARROW-SPECTRUM AGENTS
Gram-positive bacteria	Ampicillin	Erythromycin
Bacteroides and other anaerobes	Cephalosporins	Lincomycin
Yeasts	Chloramphenicol	Nystatin
Gram-positive bacteria	Gentamicin	Penicillin
Gram-negative bacteria	Kanamycin	Polymyxins
Streptococci and some gram-negative bacteria	Tetracyclines	Streptomycin
Staphylococci, entero-cocci, and some tridia	Tobramycin	Vancomycin

* Broad-spectrum agents affect most bacteria.

Modes of Action

✓Inhibition of cell wall synthesis
  ✓Peptidoglycan
✓Disruption of cell membrane
✓Inhibition of protein synthesis
✓Inhibition of nucleic acid synthesis
✓Action of antimetabolites/metabolic pathways
  ✓Folate biosythesis

Modes of action (fig 13.2)



Agent	Used to Treat	Common Method of Administration*	Side Effects
Agents that inhibit cell wall synthesis			
Penicillin (natural)	Wide variety of infections, mostly of Gram-positive bacteria	IM, O	Relatively few side effects, but allergies do occur
Penicillin (semisynthetic)	Infections resistant to natural penicillin	O, IV	Same as natural penicillin
Cephalosporins	Wide variety of infections when allergy or toxicity make other agents unsuitable	IV, IM, O	Relatively nontoxic but can lead to superinfections
Carbapenems	Mixed infections, nosocomial infections, infections of unknown etiology	IV	Allergic reactions, superinfections, seizures, gastrointestinal disturbances
Bacitracin	Skin infections (topical application)	T	Internal use toxic to kidneys

Imipenem (a carbapenem)

Bacitracin

Agents that interfere with cell membrane function			
Polymyxins	Skin infections (topical application, with bacitracin)	T, IV	Internal use highly toxic
Tyrocidins	Skin infections caused by Gram-positive cocci (topical application)	T, IV	Internal use highly toxic

Polymyxin B

Tyrocidin

Antimetabolites and other agents			
Sulfonamides	Some kinds of meningitis and to supress intestinal flora before colon surgery	O, IV	Early forms caused kidney damage, but ones now in use do not
Isoniazid	Tuberculosis (used with ethambutol)	O	May cause pyridoxine deficiency
Ethambutol	Tuberculosis (used with isoniazid)	O	
Nitrofurantoin	Urinary tract infections	O	Nausea and vomiting

Sulfanilamide (a sulfonamide)

Isoniazid

Ethambutol

Nitrofurantoin

* IM = intramuscular, IV = intravenous, O = oral, T = topical

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Para-aminobenzoic acid (PABA)

Sulfanilamide

(a)

Precursor #1

PABA

Enzyme #1

Sulfa drugs

Precursor #2

Glutamate

Enzyme #2

Dihydrofolate

Enzyme #3

Trimethoprim

Tetrahydrofolate

Multiple enzymes and reactions

Thymine, guanine, and adenine nucleotides

(b)

Agent	Used to Treat	Common Method of Administration*	Side Effects
Agents that inhibit protein synthesis			
Streptomycin	Tuberculosis (used with isoniazid and rifampin)	IM, O	Damages kidneys and inner ear
Gentamicin and other aminoglycosides	Antibiotic-resistant and hospital-acquired infections (used synergistically with other drugs)	IM, T (burns)	Varying degrees of kidney and inner ear damage
Tetracyclines	A broad spectrum of bacterial infections and some fungal infections	O	Stain teeth; cause gastrointestinal symptoms; can lead to superinfections
Chloramphenicol	A broad spectrum of bacterial infections, brain abscesses and penicillin-resistant infections	O	Can damage bone marrow and cause aplastic anemia
Erythromycin	Gram-positive bacterial infections, some penicillin-resistant infections, and Legionnaires' disease	O	One of the least toxic of commonly used antibiotics

Erythromycin

Gentamicin

Tetracycline

Chloramphenicol

Streptomycin

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Aminoglycosides
Block the initiation of translation and causes the misreading of mRNA

Tetracyclines
Block the attachment of tRNA to the ribosome

Streptogramins
Each interferes with a distinct step of protein synthesis

30S

50S

Macrolides
Prevent the continuation of protein synthesis

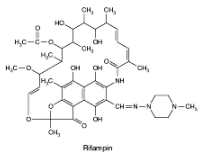
Chloramphenicol
Prevents peptide bonds from being formed

Lincosamides
Prevent the continuation of protein synthesis

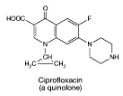
Oxazolidinones
Interfere with the initiation of protein synthesis

Agents that inhibit nucleic acid synthesis

Rifampin	Tuberculosis and to eliminate meningococci from the nasopharynx	O	Bright orange or red urine, saliva, tears, and skin; liver damage; many disorders when used with other agents
Quinolones	Urinary tract infections, traveller's diarrhea; effective against many drug-resistant organisms	O	Nausea; headaches and other nervous system disturbances



Rifampin



Ciprofloxacin (a quinolone)

Side effects

- Toxicity
  - Aminoglycosides damage kidneys
    - Therapeutic index
      - Ratio of toxic dose to therapeutic dose
- Allergy
  - Penicillin
    - Anaphylactic shock
- Disruption of normal microflora
  - Broad spectrum antibiotics
  - Lead to secondary infections
    - *Candida albicans*
    - *Clostridia* - produces toxins

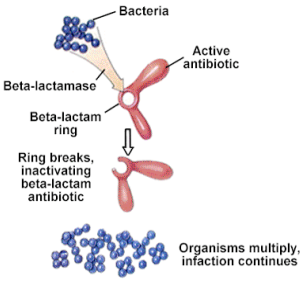
Microbial resistance

- Resistance - the microbe is no longer susceptible to the antimicrobial agent
  - Chromosomal resistance
    - A mutation on the chromosomal DNA
  - Extrachromosomal resistance
    - Resistance plasmid or R factors
      - A plasmid with resistance genes

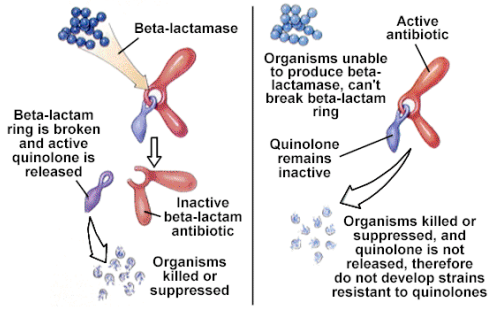
Mechanisms of resistance

- Alteration of targets
  - Bacterial ribosomes
- Alteration of membrane permeability
  - Alteration transport pores
- Development of enzymes
  - ß-lactamase - destroys penicillin
- Alteration of an enzyme
  - Active site no longer recognizes the drug - sulfa drugs
- Alteration of a metabolic pathway
  - Pathway bypass to get around block caused by the drug

Penicillin resistance



Double antibiotic therapy



Ideal qualities...

- broad spectrum.
- work so as to prevent evolution of antibiotic-resistant strains of pathogens.
- no undesirable side-effects.
- not destroy normal flora.
- not inactivated by body fluids.
- highly soluble in body.
- reach high enough concentration to work.

Antibiotics

- Natural chemotherapeutic agents.
- produced by microorganisms, particularly actinomycetes (G+ filamentous bacteria)

Families of antibiotics

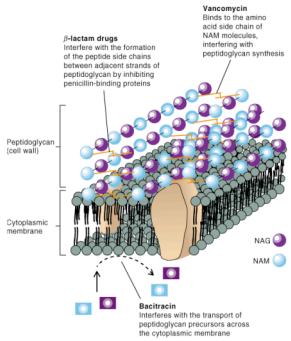
(based on structure)

- Cell Wall Synthesis
- β-lactam antibiotics
- Vancomycin
- Protein synthesis
- Macrolides
- Aminoglycosides
- Tetracyclines
- Choramphenicol
- Cell membrane
- polypeptides
- polyenes

β-lactam antibiotics

- penicillins
- monobactams
- cephalosporins
- carbapenems

- inhibit cell wall synthesis



Macrolides

- Erythromycin
- Azithromycin
- Clarithromycin
  - interfere with protein synthesis.

- Flouroquinolones
  - Ciprofloxin, ofloxacin
- quinolones
  - inhibit DNA synthesis

Aminoglycosides

- streptomycin
- Neomycin
- Gentamicin
- Tobramycin
- Amikacin

- induce abnormal protein synthesis.

Tetracyclines

- chlortetracycline
- oxytetracycline
- tetracycline
- doxycycline
- minocycline

- interfere with protein synthesis

Polypeptides

- bacitracin
  - inhibit cell wall formation
- polymyxins
  - cause deterioration of cell membrane.

Polyenes

- nystatin
- amphotericin B

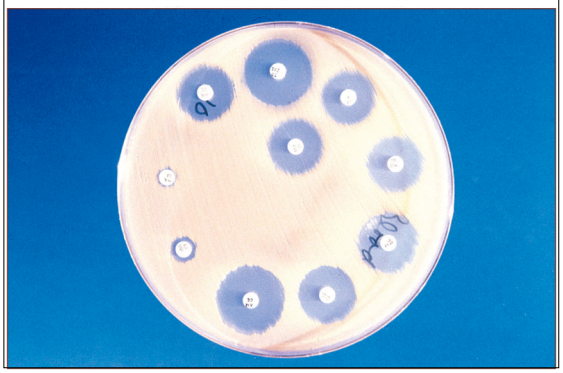
- Damage cell membrane.
- Interfere with membrane function.

Others

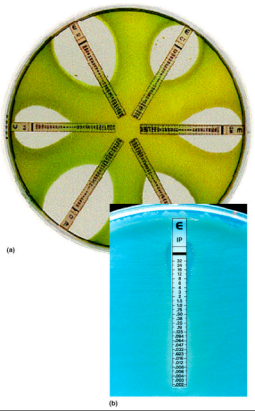
- Chloramphenicol
- Sulfonamides
- Isoniazid
- Ethambutol
- Nitrofurans
  - protein synthesis inhibitors

MIC

Kirby-Bauer disk susceptibility



E-Test



Mechanisms of resistance

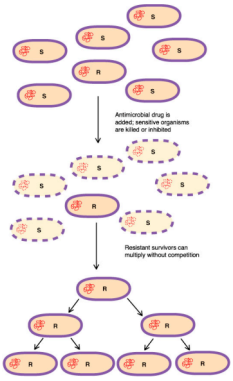
- Drug inactivating enzymes
  - ß-lactamase - destroys penicillin
- Alteration of targets
  - Bacterial ribosomes
- Alteration of membrane permeability
  - Decrease uptake of the drug
- Efflux pumps
  - Pump the drug out of the cell
- Alteration of an enzyme
  - Active site no longer recognizes the drug - sulfa drugs
- Alteration of a metabolic pathway
  - Pathway bypass to get around block caused by the drug

Mechanisms of resistance

- Spontaneous mutations
- Gene Transfer
  - R plasmids

Why resistance?

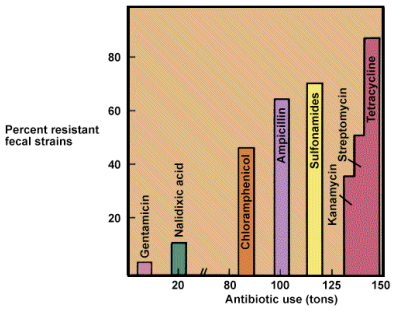
- Indiscriminate use of antibiotics.
- Use of insufficiently high concentrations that fail to kill the bacteria.
  - Not following prescription through.
- Mutation



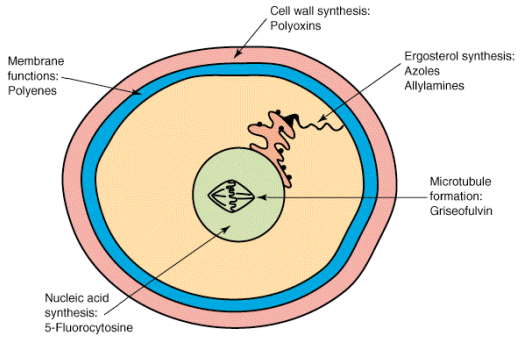
Preventing resistance

- Avoid indiscriminate use of antibiotics.
- Use high enough dosages.
- Use combinations of antibiotics.
- Switching antibiotics as soon as signs of resistance

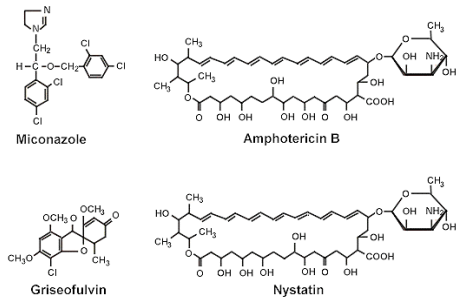
Use verses resistance



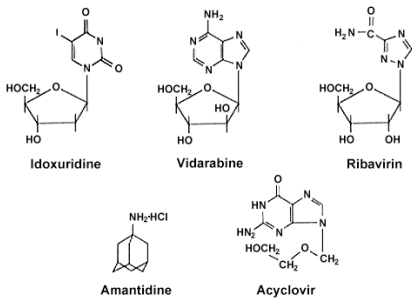
Antifungal drug mechanisms

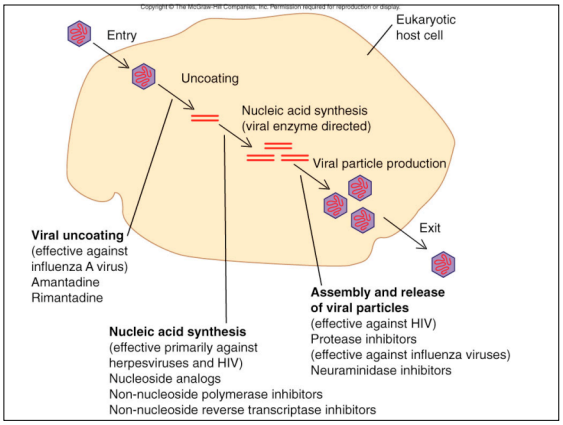


Antifungal agents

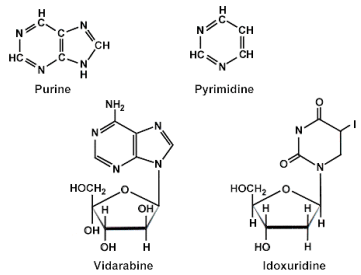


Antiviral agents

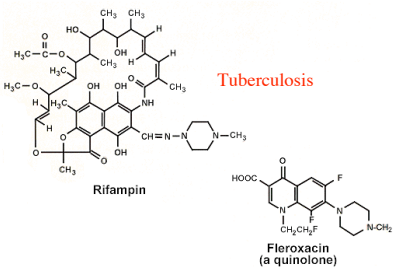




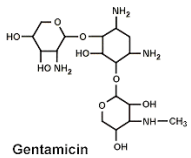
Antivirals are base analogs



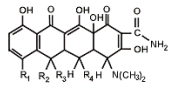
Nucleic acid synthesis inhibitors



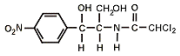
Antibacterial - protein synthesis inhibitors



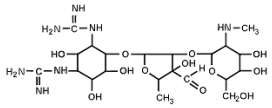
Gentamicin



Tetracycline

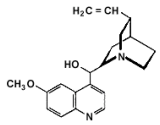


Chloramphenicol

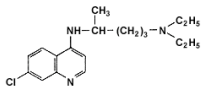


Streptomycin

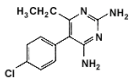
Antiprotozoan agents



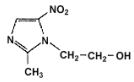
Quinine



Chloroquine



Pyrimethamine

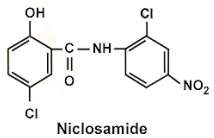


Metronidazole

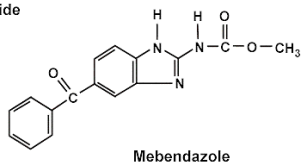
Table 21.5 Characteristics of Some Antiprotozoan and Antihelminthic Drugs

Causative Agent/Drug	Comments
Intestinal protozoa	
Iodoquinol	Mechanism unknown. Poorly absorbed but taken orally to eliminate amebic cysts in the intestine.
Nitroimidazoles Metronidazole	Activated by the metabolism of anaerobic organisms. Interferes with electron transfer and alters DNA. Does not reliably eliminate the cyst stage. Metranidazole is also used to treat infections caused by anaerobic bacteria.
Quinacrine	Mechanism of action is unknown, but it may be due to interference with nucleic acid synthesis.
Plasmodium* (Malaria) and *Toxoplasma	
Folate antagonists Pyrimethamine, sulfonamide	Interferes with folate metabolism. Used to treat toxoplasmosis and malaria.
Quinolones Chloroquine, mefloquine, primaquine, tafenoquine	The mechanism of action is not completely clear. Chloroquine is concentrated in infected red blood cells and is the drug of choice for preventing or treating the red blood cell stage of the malarial parasite. Its effects may be due to inhibition of an enzyme that protects the parasite from the toxic by-products of hemoglobin degradation. Primaquine and tafenoquine destroy the liver stage of the parasite and are used to treat relapsing forms of malaria. Mefloquine is used to treat infections caused by chloroquine-resistant strains of the malarial parasite.
Trypanosomes and *Leishmania*	
Eflornithine	Used to treat infections caused by some types of *Trypanosoma*. It inhibits the enzyme ornithine decarboxylase.
Heavy metals Melarsoprol, sodium stibogluconate, meglumine antimonate	These inactivate sulfhydryl groups of parasitic enzymes, but they are very toxic to host cells as well. Melarsoprol is used to treat trypanosomiasis, but the treatment itself is often lethal. Sodium stibogluconate and meglumine antimonate are used to treat leishmaniasis.
Nitrofurtimox	Widely used to treat acute Chagas' disease; it forms reactive oxygen radicals that are toxic to the parasite as well as the host.

Antihelminthic agents



Niclosamide

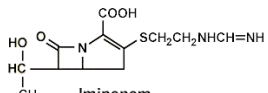


Mebendazole

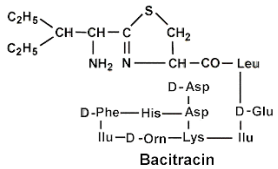
Table 21.5 Characteristics of Some Antiprotozoan and Antihelminthic Drugs

Causative Agent/Drug	Comments
Intestinal and Tissue Helminths	
Avermectins Ivermectin	Ivermectin causes neuromuscular paralysis in parasites. It is used to treat infections caused by *Strongyloides* and tissue nematodes.
Benzimidazoles Mebendazole, thiabendazole, albendazole	Mebendazole binds to tubulin of helminths, blocking microtubule assembly and inhibiting glucose uptake. It is poorly absorbed in the intestine, making it effective for treating intestinal, but not tissue, helminths. Thiabendazole may have a similar mechanism, but it is well absorbed and has many toxic side effects. Albendazole is used to treat tissue infections caused by *Echinococcus* and *Taenia solium*.
Phenols Niclosamide	Absorbed by cestodes in the intestinal tract, but not by the human host.
Piperazines Piperazine, diethylcarbamazine	Piperazine causes a flaccid paralysis in worms and can be used to treat infections caused by *Ascaris*. Diethylcarbamazine immobilizes filarial worms and alters their surface, which enhances killing by the immune system. The resulting inflammatory response, however, causes tissue damage.
Pyrazinoisoquinolines Praziquantel	A single dose of praziquantel is effective in eliminating a wide variety of trematodes and cestodes. It is taken up but not metabolized by the worm, ultimately causing tetanic contractions of the worm.
Tetrahydropyrimidines Pyrantel pamoate, oxantel	Pyrantel pamoate interferes with neuromuscular activity of worms, causing a type of paralysis. It is not readily absorbed from the gastrointestinal tract and is active against intestinal worms including pinworm, hookworm, and *Ascaris*. Oxantel can be used to treat *Trichuris* infections.

Antibacterial - cell wall synthesis inhibitors

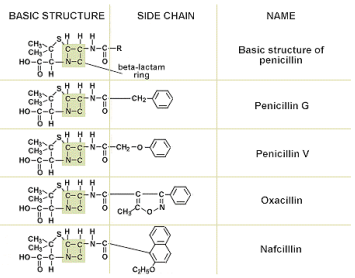


Imipenem
(a carbapenem)

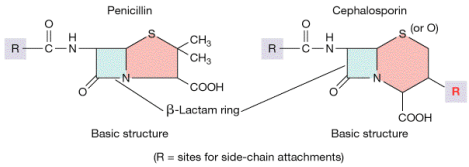


Bacitracin

Structures of Penicillin



Penicillin verses cephalosporin



Sulfa drugs are competitive inhibitors with PABA