Antimycobacterial agents

OR

Antitubercular agents

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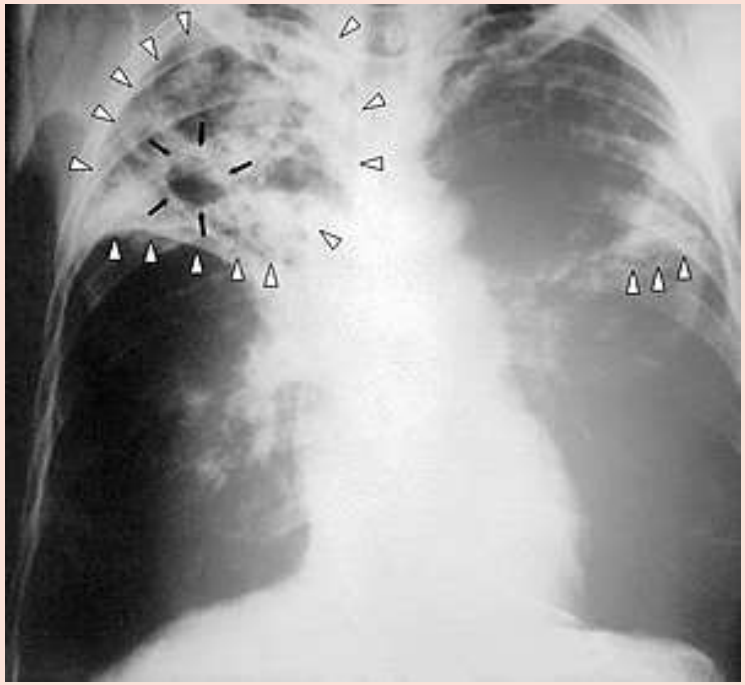
- **Tuberculosis**
- Tuberculosis (TB) is a chronic infectious disease.
- **Caused by strains of *Mycobacterium especially Mycobacterium tuberculosis* which is an acid fast, aerobic bacillus**.
- Tuberculosis may be **latent TB or active TB.**
- **Latent TB do not have symptoms and noncontagious.**
- **Active TB have symptoms and contagious.**
- It generally affects lungs but can spread through blood stream and lymphatic system to the brain, bones, eyes and skin.
- The classic symptoms of active TB are a **chronic cough with blood-containing sputum, fever, night sweats, and weight loss.**
- **Tuberculosis is spread through the air when active TB peoples spit, speak, or sneeze. People with latent TB do not spread the disease.**

Diagnosis is based on **chest X-rays**, as well as microscopic examination and culture of body fluids.
Diagnosis of latent TB relies on the **tuberculin skin test** (TST).



Antitubercular drugs are medicines used to treat tuberculosis, an infectious disease that can affect the lungs and other organs.

Classification:

First-line drugs –

ethambutol is EMB or E, isoniazid is INH or H, pyrazinamide is PZA or Z, rifampicin is RMP or R, streptomycin is SM or S.

Second-line drugs –

Capreomycin, Cycloserine, Kanamycin, Thioacetazone, Clarithromycin, Paraaminosalicylic acid (PAS), Ciprofloxacin, Levofloxacin, Rifabutin, Clofazimine, Amikacin, Ethionamide.

Third line: Third-line drugs include drugs that may be useful, but have doubtful or unproven efficacy: Rifabutin macrolides: e.g., clarithromycin (CLR); linezolid (LZD); thioacetazone (T); thioridazine; arginine;

First line drugs, are only used for the treatment of new patients who are very unlikely to have resistance to any of the TB drugs.

The second line drugs, that are only used for the treatment of drug resistant TB.

Most current TB drugs those that are effective against actively metabolizing and rapidly growing bacilli.

Drug Resistant TB:

A person with active TB disease has drug resistant TB if the TB bacteria that the person is infected with, will not respond to, and are therefore resistant to, at least one of the main TB drugs.

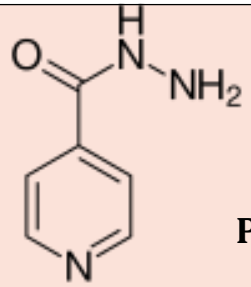
Types of drug resistant TB:

MDR (multi drug resistant) TB is the name given to TB when the bacteria that are causing it are resistant to at least isoniazid and rifampicin.

Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

First line agents

Isoniazid :
isonicotinylhydrazide (INH)



Pyridine-4-carbohydrazide

Mechanism of action:

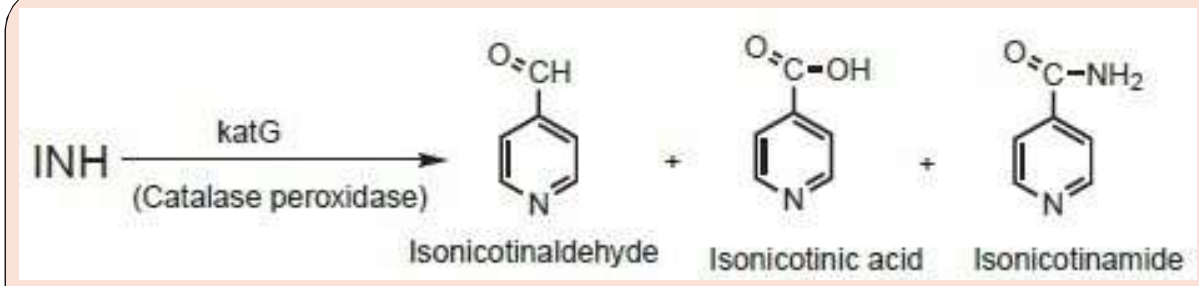
It inhibit the synthesis of mycolic acids, high–molecular-weight, branched – hydroxy fatty acids, are important constituents of the mycobacterial cell wall in that they provide a permeability barrier to hydrophilic solutes.

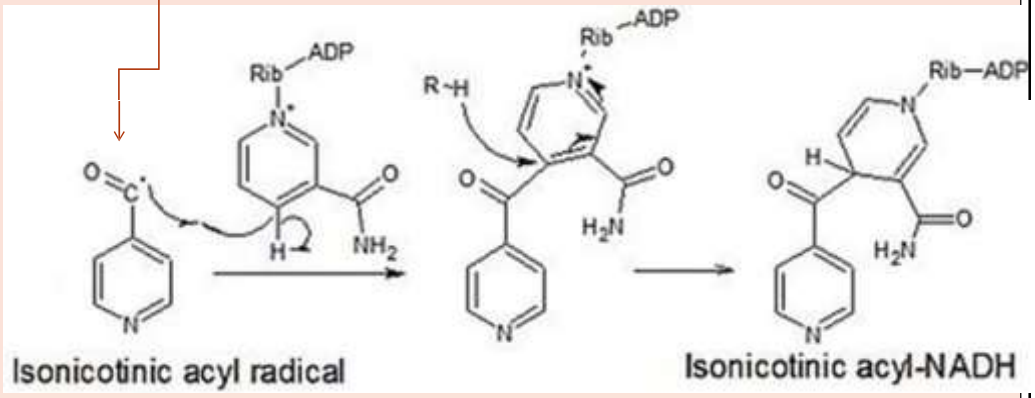
It is a prodrug, activated through an oxidation reaction by endogenous enzyme katG which exhibits catalase-peroxidase activity.

This enzyme convert INH to a reactive species which are capable of acylation of an enzyme system found exclusively in *M. tuberculosis.*

Reaction of INH with catalase-peroxidase results in formation of isonicotinaldehyde, isonicotinic acid, and isonicotinamide.

These reactive species reacts with the NAD. The resulting adducts inhibit the enzyme enoyl-reductase enzyme (inhA).





For active tuberculosis it is often used together with Rifampicin, Pyrazinamide, and either Streptomycin or Ethambutol. For latent tuberculosis it is often used by itself.

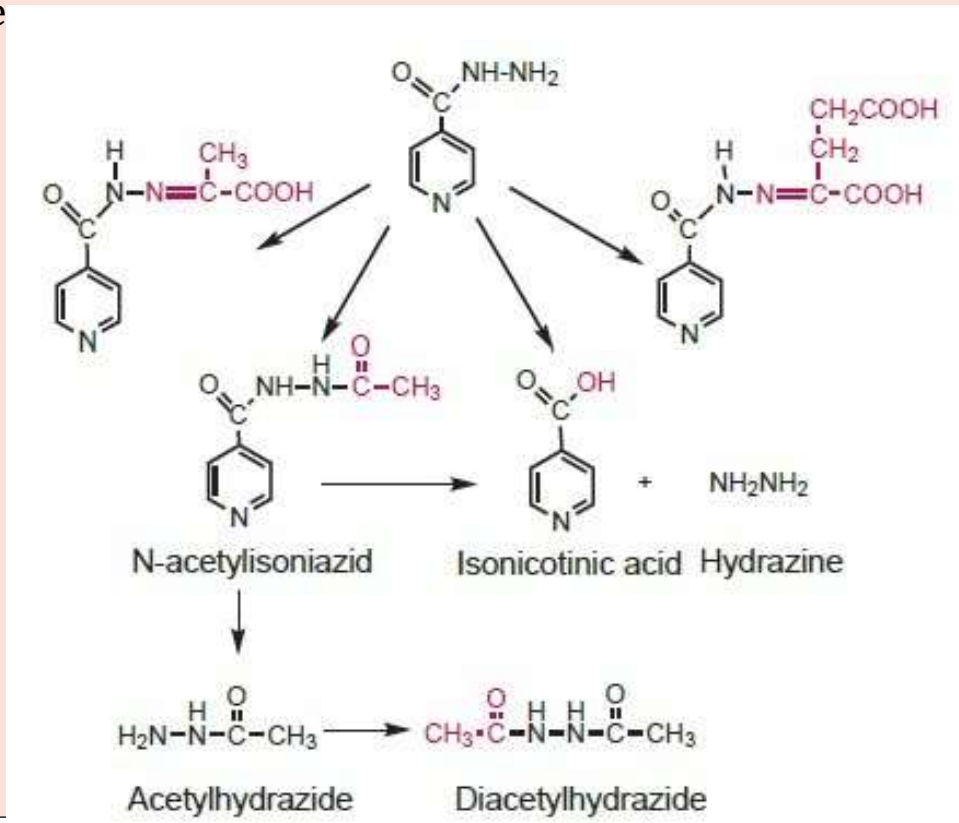
Structure–activity Relationship of INH:

- Substitution of the hydrazine portion of INH with alkyl and aralkyl substituent resulted in a series of active and inactive derivatives.

- Any substitution of the N-1 hydrogen with alkyl groups destroyed the activity (R1 and R2 = H; R3 = alkyl).
- Substitution on the N-2 position resulted in active compounds (R1 and/or R2 = alkyl; R3 = H).
- None of these changes produced compounds with activity superior to that of INH.
- Replacement of pyridine nucleus with other aromatic ring such as benzene or piperidine or thiazole ring diminished the antitubercular activity.

Metabolism of INH

Enzyme responsible for acetylation, cytosolic N-acetyltransferase present in liver and small intestine



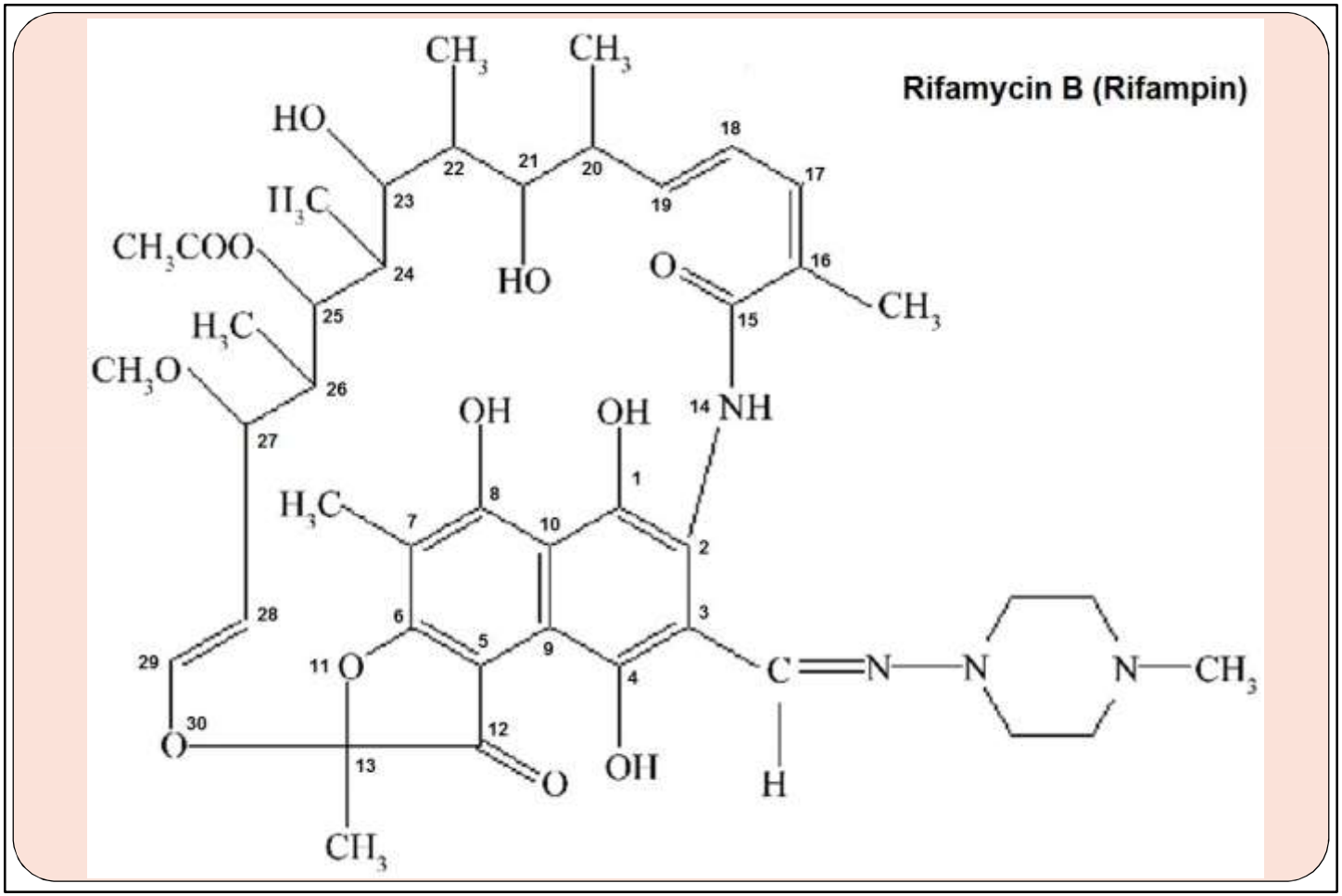
Rifamycins

These are ansamycins antibiotics obtained by fermentation from cultures of ***Streptomyces mediterranei***.

The rifamycins and many of their semisynthetic derivatives have a broad spectrum of antimicrobial activity. They are most notably active against Gram-positive bacteria and M. tuberculosis.

All of the rifamycins (A, B, C, D, and E) are biologically active.

Some of the semisynthetic derivatives e.g. Rifamycin B (Rifampin) are the most potent known inhibitors of DNA directed RNA polymerase in bacteria, and their action is bactericidal.


Rifamycin B (Rifampin)
CH3
CH3
HO
H3C
CH3COO
HO
O
CH3
H3C
CH3O
OH
OH
NH
H3C
O
O
O
O
OH
H
CH3
N
N
N
CH3

Mechanism of action:

Rifamycins inhibit bacterial DNA-dependent RNA polymerase (DDRP) by binding to the β-subunit of the enzyme and are highly active against rapidly dividing intracellular and extracellular bacilli.

Inhibition of DDRP leads to blocking the initiation of chain formation in RNA synthesis.

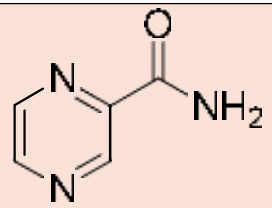
The DDRP is a metalloenzyme that contains two zinc atoms.

It is postulated that the oxygen at C-1 and C-8 of a rifamycin can chelate to a zinc atom, which increases the binding to DDRP, and finally, the oxygen at C-21 and C-23 form strong hydrogen bonds to the DDRP. The binding of the rifamycins to DDRP results in the inhibition of the RNA synthesis.

SAR

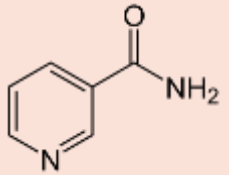
1) Free –OH groups are required at C-1, C-8, C-21, and C-23;
2) These groups appear to lie in a plane and to be important binding groups for attachment to DDRP, as previously indicated;
3) Acetylation of C-21 and/or C-23 produces inactive compounds;
4) Reduction of the double bonds in the macro ring results in a progressive decrease in activity;
5) Opening of the macro ring also gives inactive compounds.

Pyrazinamide



Pyrazinamide

pyrazine-2-carboxamide



Nicotinamide

It is a **bioisoster of nicotinamide** and possess bactericidal action against M. tuberculosis.

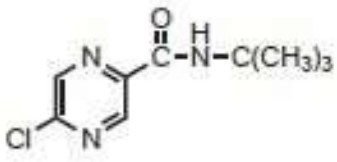
Mechanism of action:

Susceptible organisms produce **pyrazinamidase**, which is responsible for conversion of **pyrazinamide to pyrazinoic acid** intracellularly.

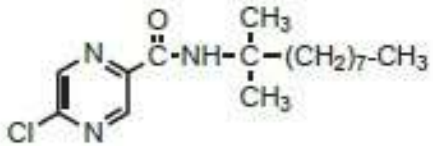
Pyrazinoic acid has been shown to possess biologic activity at a pH 5.4. Pyrazinoic acid can lower the pH in the immediate surroundings of the M. tuberculosis to such an extent that the organism is unable to grow.

SAR of Pyrazinamide:

- Substitution on the pyrazine ring or use of alternate heterocyclic aromatic rings has given compounds with reduced activity.
- Hydrophilic groups are essential for sufficient plasma concentration and to deliver the drugs to the site of action.
- Liphophilic groups are essential to allow penetration into the mycobacterial cell.
- Susceptibility to hydrolysis such that the prodrug is unaffected by the "extracellular" enzymes but is readily hydrolyzed at the site of action.

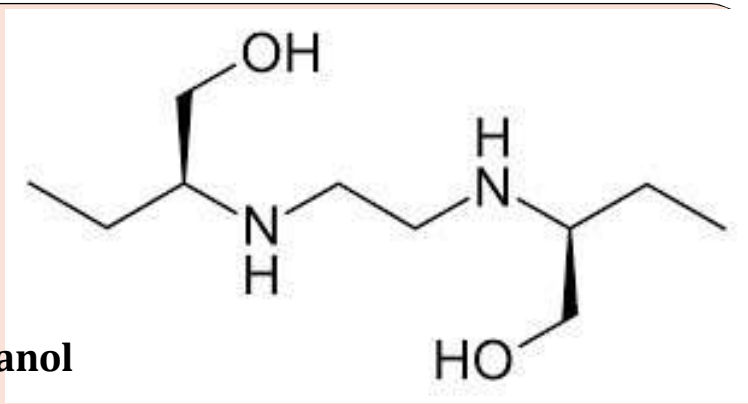


tert -butyl 5-chloropyrazinamide



2'-(2'-methyldecyl) 5-chloropyrazinamide

Ethambutol (EMB)



(+)-2,2'-(ethylenediimino)di-1-butanol

It is an ethylenediiminobutanol.

(+)-enantiomer is 200 – 500 fold more active than (-)- enantiomer.

Mechanism of action:

It inhibits **mycobacterial arabinosyl transferases** which are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

SAR:

Extension of the ethylene diamine chain, replacement of either nitrogen, increasing the size of the nitrogen substituents, and moving the location of the alcohol groups are all changes that drastically reduce or destroy biologic activity

Streptomycin (STM)

It is aminoglycoside antibiotic, obtained from actinomycetes, genus *Streptomyces griseus.*

Mechanism of action:

STM inhibit protein synthesis.

It binds to 30s subunit of the bacterial ribosome interfering with the binding of formyl-methionyl-tRNA to the 30s subunit.

The binding of molecule to the 30s subunit interferes with 50s subunit association with the mRNA strand. This leads to codon misreading. Thus results in an unstable ribosomal mRNA complex leading to mutation and defective protein synthesis; leading to cell death.

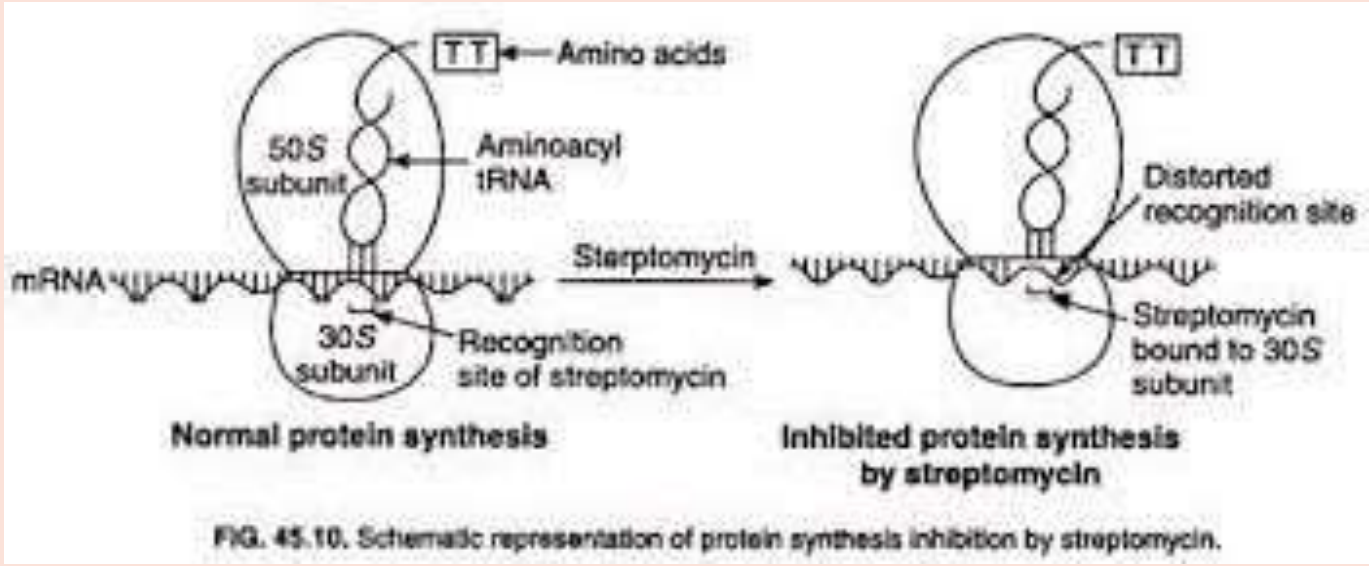


FIG. 45.10. Schematic representation of protein synthesis inhibition by streptomycin.

Chemistry of streptomycin

Streptomycin is a triacidic base and has aldose sugar.

The hydrophilic nature results in poor absorption from GIT.

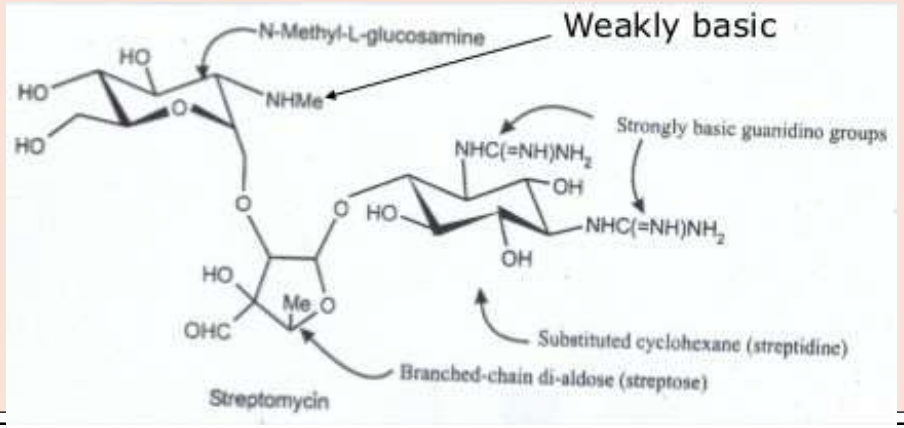
It is made of 3 basic strucutral subunits

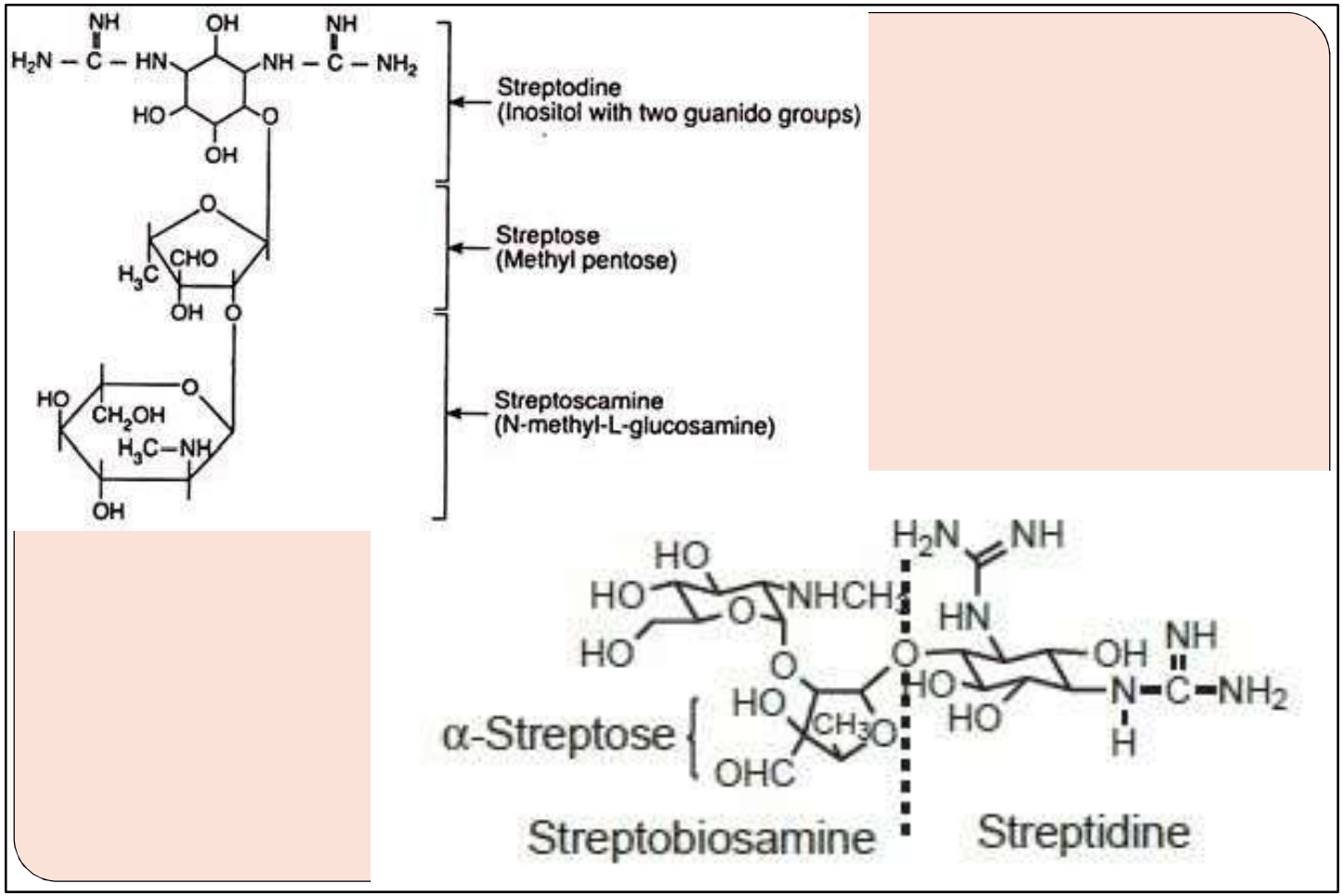
- streptidine (diguanidino compound)
- Streptose ((a aldose suagr)
- streptoscamine (N-methyl-L-glucosamine unit)

The two guanidino groups attached to the streptidine exhibits strong basic nature.

The amino sugar attached to streptidine by means of glycosidic linkage.

The methyl amino group attached to N-methyl-L-glucosamine exhibit weakly basic nature.



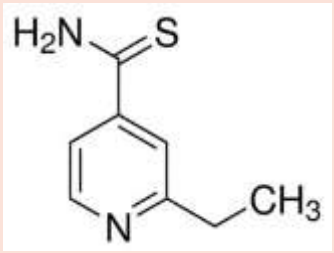

Streptodine
(Inositol with two guanido groups)
Streptose
(Methyl pentose)
Streptoscamine
(N-methyl-L-glucosamine)
α-Streptose
Streptobiosamine
Streptidine

SAR of strptomycin

- Modification of the α-streptose portion of STM has been extensively studied. Reduction of the aldehyde to the alcohol results in a compound, dihydrostreptomycin that has activity similar to STM but with a greater potential for producing delayed, severe deafness.
- Oxidation of the aldehyde to a carboxyl group or conversion to Schiff base derivatives (oxime, semicarbazone, or phenylhydrazone) results in inactive analogs.
- Oxidation of the methyl group in α-streptose to a methylene hydroxy gives an active analog that has no advantage over STM.

- Modification of the aminomethyl group in the glucosamine portion of the molecule by demethylation or by replacement with larger alkyl groups reduces activity
- Removal or modification of either guanidine in the streptidine nucleus also decreases activity

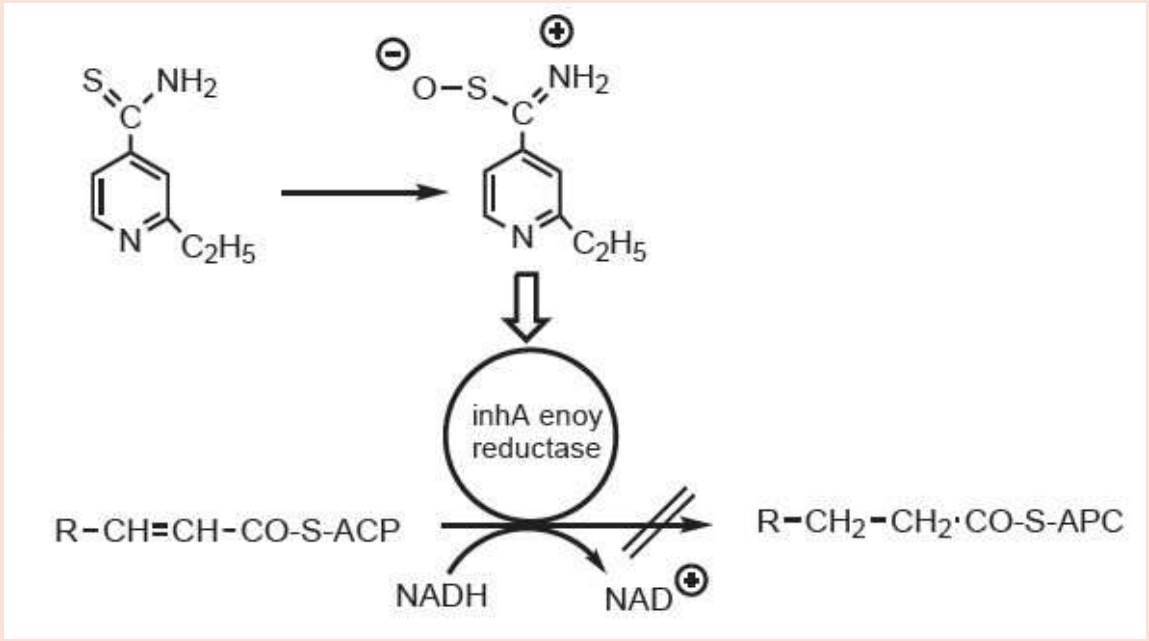
Second line agents
Ethionamide:



2-ethylpyridine-4-carbothioamide

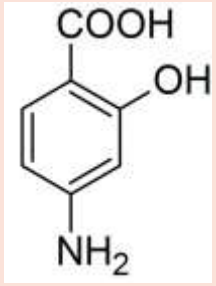
Mechanism of action:

It is a prodrug that is **converted via oxidation** by **catalase-peroxidase** to an active acylating agent, **ethionamide sulfoxide**, which in turn **inactivates the inhA enoyl reductase enzyme**. In the case of ethionamide, it has been proposed that the ethionamide sulfoxide acylates Cys-243 in inhA protein.


S
NH2
C
N
C2H5
O–S
NH2
C
N
C2H5
inhA enoy
reductase
R–CH=CH–CO-S-ACP
R–CH2–CH2·CO-S-APC
NADH
NAD

p-Aminosalicylic acid

4-amino-2-hydroxybenzoic acid

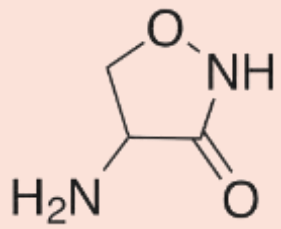


As a bacteriostatic agent, PAS is used at a dose of up to 12 g/day, which causes considerable GI irritation.

Mechanism of Action

PAS is thought to act as an antimetabolite **interfering with the incorporation of *p-aminobenzoic* acid into folic acid**. When co-administered with INH, PAS is found to reduce the acetylation of INH, itself being the substrate for acetylation, thus increasing the plasma levels of INH.

Cycloserine (Seromycin)



(*R*)-4-Amino-1,2-oxazolidin-3-one

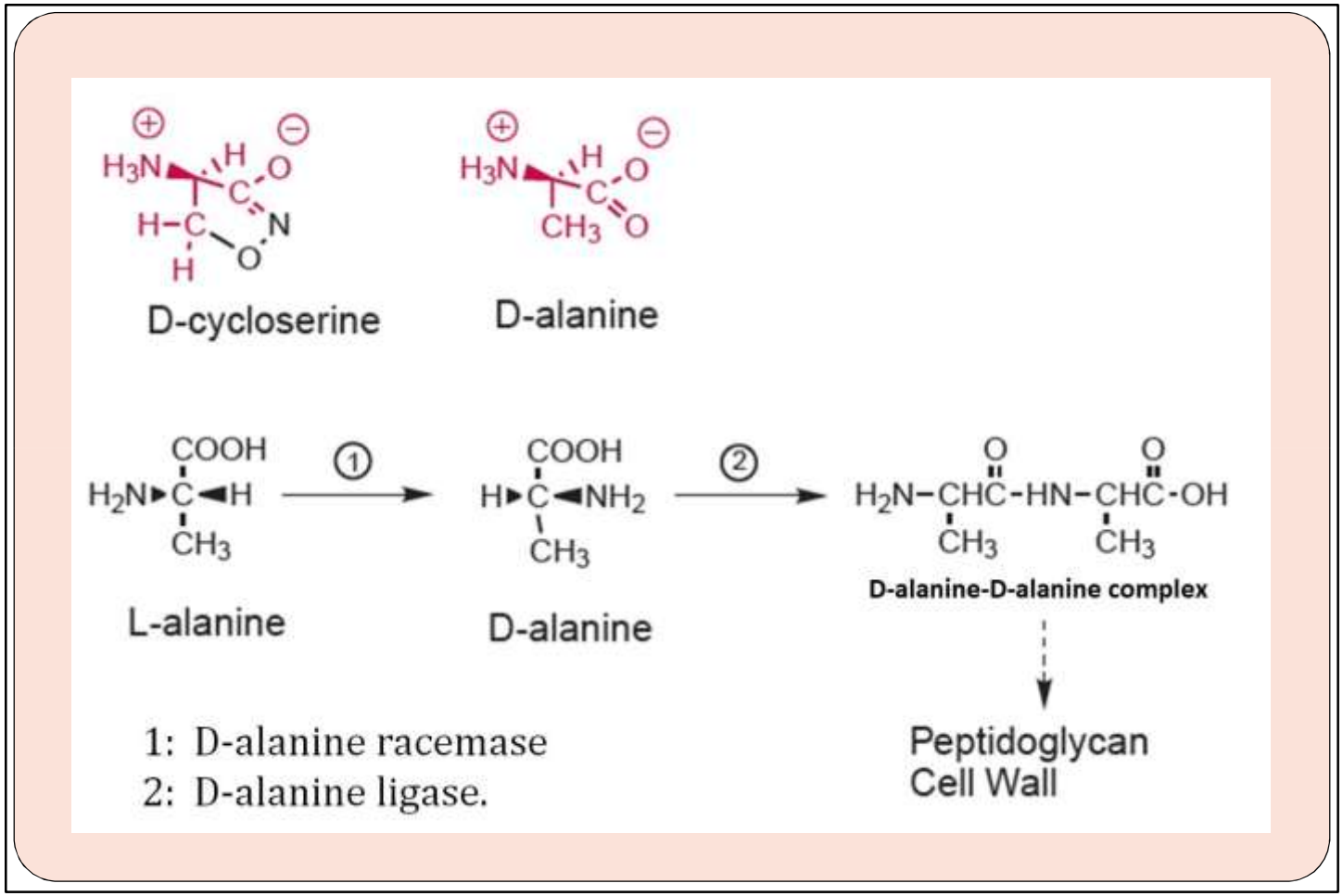
Cycloserine is a natural product isolated from ***Streptomyces orchidaceus*** as the d-(+)-enantiomer

MOA:

It is a structural analogue of D-alanine.

It inhibit two key enzyme: **D-alanine recemase and D-alanine ligase**.

It competitively inhibits the binding of d-alanine to both of these enzymes and its incorporation into the peptidoglycan.


D-cycloserine
D-alanine
L-alanine
D-alanine
D-alanine-D-alanine complex
Peptidoglycan
Cell Wall
1: D-alanine racemase
2: D-alanine ligase.

Problems in Chemotherapy:

1. Chemotherapy of tuberculosis faced some special problems because of **slow growth rate of mycobacteria and their intracellular location**.

2.Since the disease is chronic by its nature, the **therapy needs to be continued for at least about 1–2 years** in most of the cases. In such a chronic treatment, if only single drug is used, **the risk of development of drug resistant strains** of mycobacteria is always high. This is coupled with the risk of drug toxicity due to high doses of a single drug needed.

4.The solution to this problem is to use combination therapy. **When two or more effective drugs are used in combination, resistance will not develop**. However drugs with similar toxicological profiles should not be used together.

5.The drugs used in the combination therapy are usually selected from ethambutol, isoniazid and rifampin.

Combination Therapy:

As single drug may cause resistance as well drug toxicity, to avoid such problem, different combination are used.

1. Standard regimens:

- Anti-TB drugs are given as 2/3/4 drug combination regimens for different durations.
- Combination regimen should include at least two drugs to which mycobacteria are sensitive.
- The response to chemotherapy is slow so given for months to years.

Standard regimens:

May be given in two phases.

1. Initial Intensive Phase for 2 months
2. Continuation Phase for 4 months

Initial Intensive Phase for 2 months:

Therapy is initiated with 4 drug regimen.

Isoniazid , Rifampin , Pyrazinamide & Ethambutol or Streptomycin.

Neither Ethambutol nor Streptomycin decreases the duration of the regimen, but they provide additional coverage for mycobacteria if isolate proves to be resistant to Isoniazid / Rifampin or to both

Continuation Phase for 4 months:

A few bacilli are left, only 2/ 3 drugs are enough.

- Isoniazid and Rifampin
- Isoniazid , Rifampin , Pyrazinamide / Ethambutol
- Pyridoxine: 25 to 50mg/day, to minimize adverse reactions to isoniazid.

Standard regimen may be given as DOTS : Directly Observed Treatment Short Course. Recommended by WHO in 1995. For noncompliant patient.

DOTS is a strategy used to reduce the number of tuberculosis (TB) cases.

DOTS have five main components:

i. Political commitment with increased and sustained financing.
ii. Case detection through quality-assured bacteriology (sputum smear microscopy).
iii. Standardized treatment, with supervision and patient support.
iv. An effective drug supply and management system.
v. A standardized recording and reporting system that allows assessment of treatment results

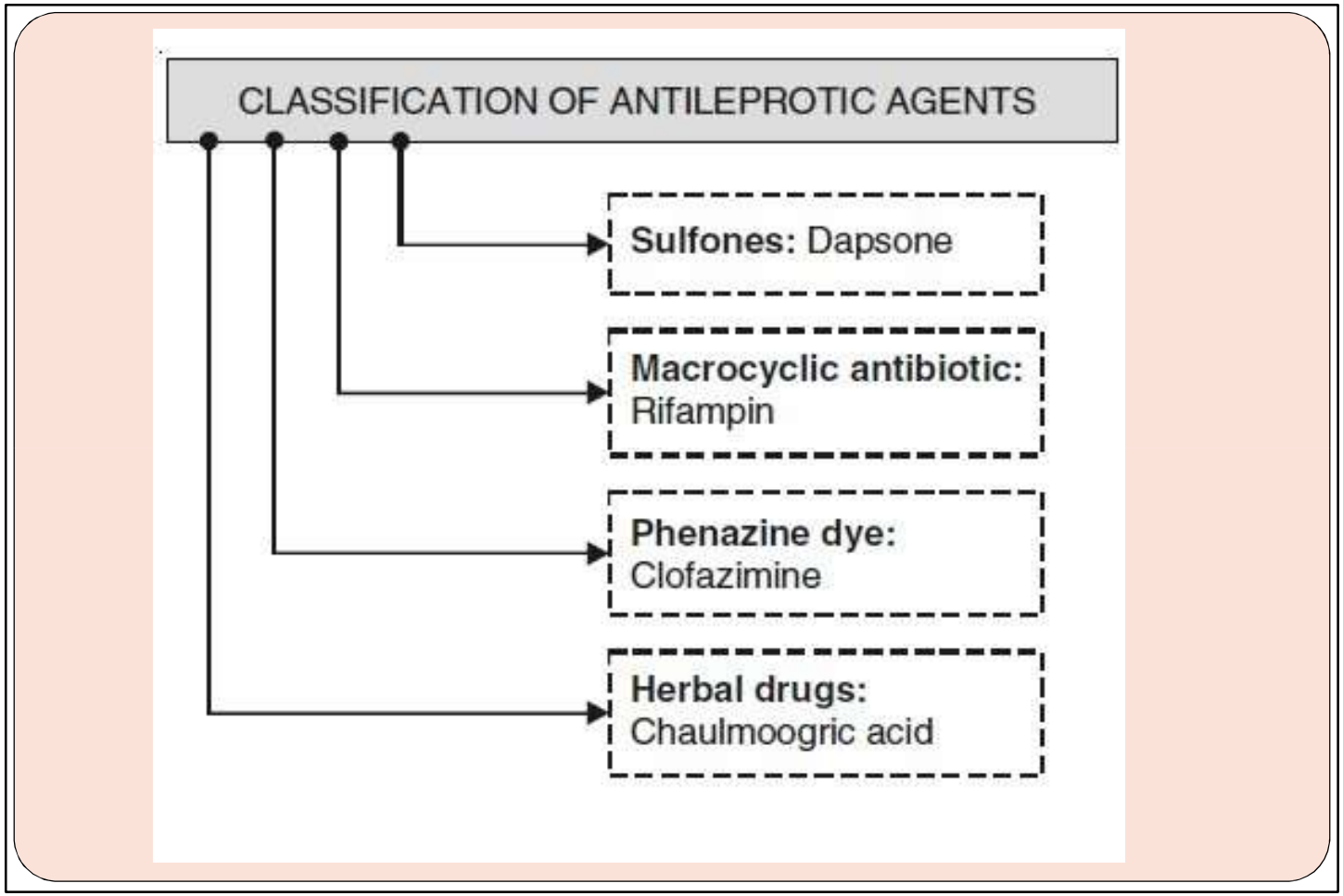
Leprosy

➢Leprosy or Hansen's disease is a chronic human disease caused due to an acid-fast bacillus which produces nodules in the skin and loss of sensation in the affected region.

➢This dermatological infection is caused by ***Mycobacterium leprae*** and the disease develops very slowly over a period of years.

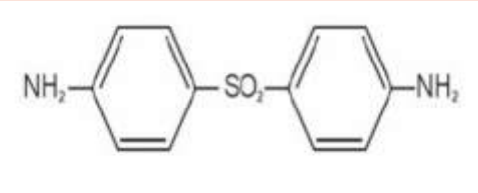
Antileprotic agents

Antileprotic drugs are that interferes with proliferation of bacterium that causes leprosy.


CLASSIFICATION OF ANTILEPROTIC AGENTS
Sulfones: Dapsone
Macrocyclic antibiotic: Rifampin
Phenazine dye: Clofazimine
Herbal drugs: Chaulmoogric acid

Sulfones: The diaryl sulfones represent the major class of agents used to treat leprosy.

Dapsone:



4-[(4-aminobenzene)sulfonyl]aniline

Dapsone, a diaminodiphenylsulfone, is a nearly water insoluble agent that is very weakly basic (pKa ~ 1.0). The lack of solubility can account for the occurrence of GI irritation.

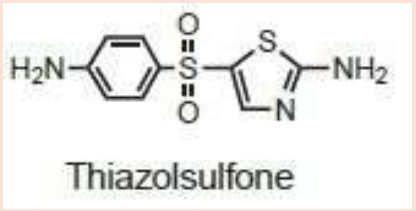
It is commonly used in combination with clofazimine and rifampin for the treatment of leprosy.

MOA:

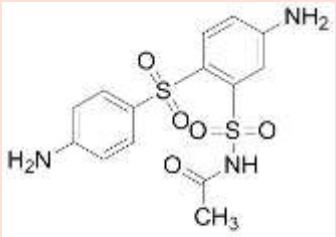
It is a bacteriostatic agent, act through competitive inhibition of p-aminobenzoic acid incorporation into folic acid.

SAR of Dapsone

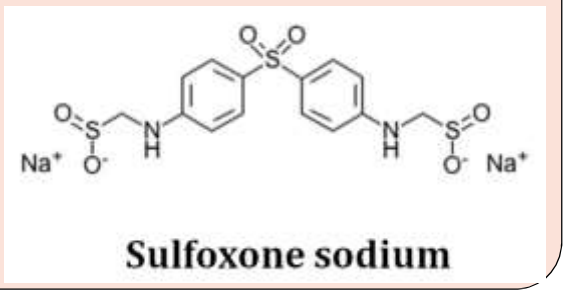
- Isosteric replacement of one benzene ring resulted in the formation of thiazolsulfone. Although still active, it is less effective than dapsone.
- Substitution on the aromatic ring, to produce acetosulfone, reduced activity while increasing water solubility and decreasing GI irritation.
- A successful substitution consists of adding methanesulfinate to dapsone to give sulfoxone sodium. This water-soluble form of dapsone is hydrolyzed in-vivo to produce dapsone. Sulfoxone sodium is used in individuals who are unable to tolerate dapsone because of GI irritation, but it must be used in a dose threefold that of dapsone because of inefficient metabolism to dapsone.



Thiazolsulfone



Acetosulfone



Sulfoxone sodium

Clofazimine:

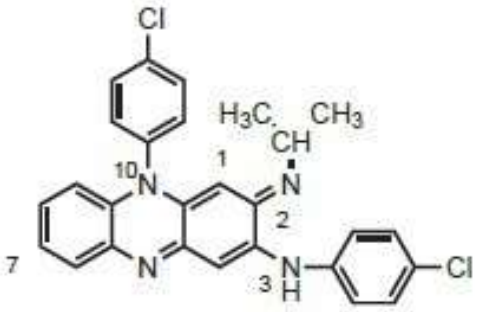
It is a phenazine derivative, is a water-insoluble dye (darkred crystals) that leads to pigmentation of the skin. In addition, discoloration (pink, red, or brownish-black) of the feces, eyelid lining, sputum, sweat, tears, and urine is seen.

Mechanism of action:

The molecule possesses direct antimycobacterial and immunosuppressive properties. It has been shown that clofazimine increases prostaglandin synthesis and the generation of antimicrobial reactive oxidants like superoxide from neutrophils, which in turn could have a lethal effect on the organism

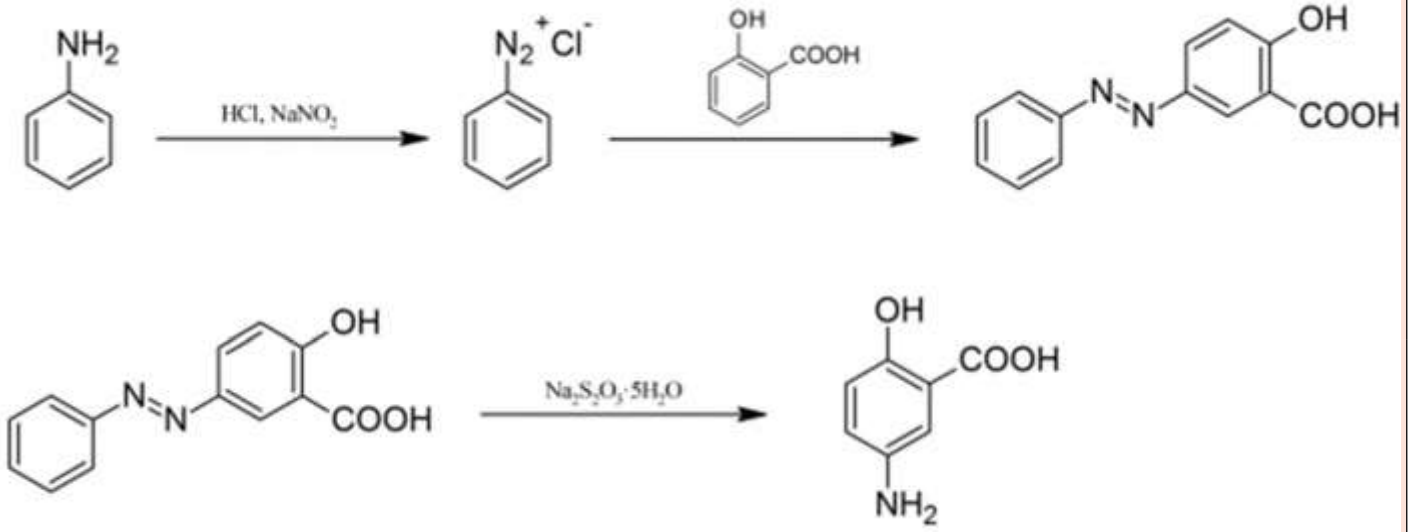
SAR

- The imino group at C-2 appears to be essential for activity. Alkyl and cycloakyl substitution at C-2 imino group increases the activity.
- Halogen substitution on the para position of the two phenyls at C-3 and N-10 enhance activity but are not essential to activity. The following order of activity has been reported: Br > Cl > CH3 > EtO > H or F.
- In the analogs studied, the increased activity correlates well with pro-oxidative activities of the molecule (e.g., ability to generate superoxide anion) as well as increased lipophilicity.

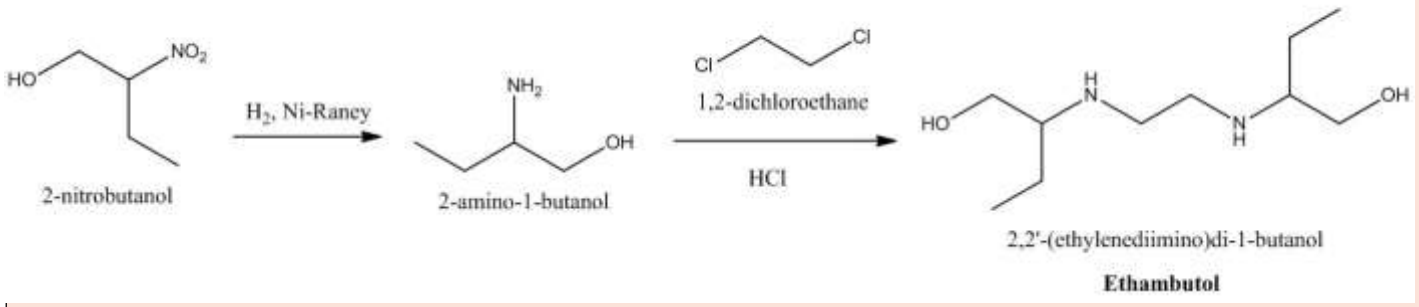


Clofazimine

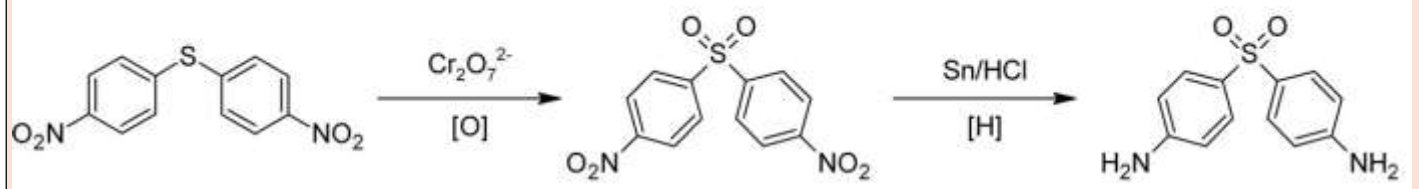
Synthesis of p-amino salicylic acid



Synthesis of Ethambutol



Synthesis of Dapsone



Antimycobacterial agents

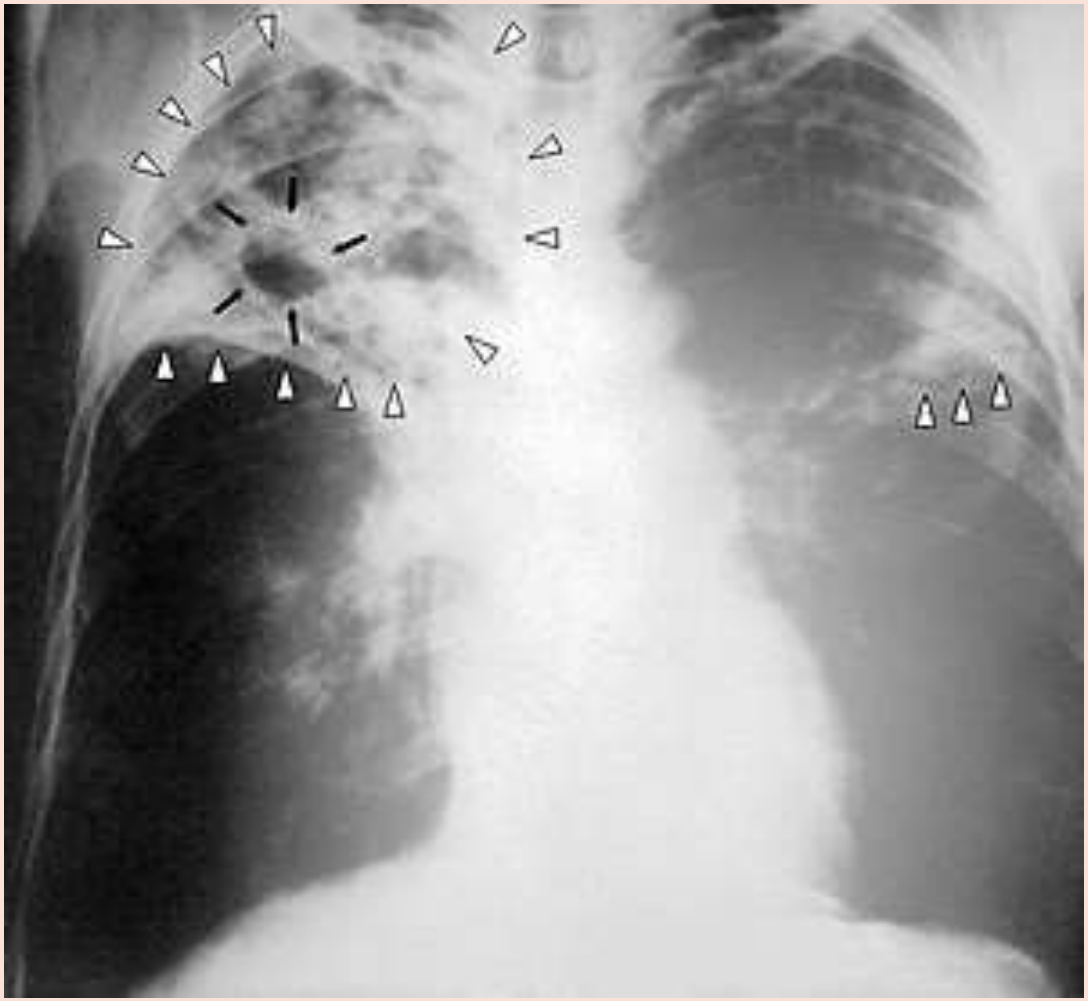
OR

Antitubercular agents

Ms. Rina P. Patil
Assistant Professor M. Pharm
Department of PPharmaceutical Chemistry
JES'S College of Pharmacy Nandurbar

- **Tuberculosis**
- Tuberculosis (TB) is a chronic infectious disease.
- **Caused by strains of *Mycobacterium especially Mycobacterium tuberculosis* which is an acid fast, aerobic bacillus**.
- Tuberculosis may be **latent TB or active TB.**
- **Latent TB do not have symptoms and noncontagious.**
- **Active TB have symptoms and contagious.**
- It generally affects lungs but can spread through blood stream and lymphatic system to the brain, bones, eyes and skin.
- The classic symptoms of active TB are a **chronic cough with blood-containing sputum, fever, night sweats, and weight loss.**
- **Tuberculosis is spread through the air when active TB peoples spit, speak, or sneeze. People with latent TB do not spread the disease.**

Diagnosis is based on **chest X-rays**, as well as microscopic examination and culture of body fluids.
Diagnosis of latent TB relies on the **tuberculin skin test** (TST).



Antitubercular drugs are medicines used to treat tuberculosis, an infectious disease that can affect the lungs and other organs.

Classification:

First-line drugs –

ethambutol is EMB or E, isoniazid is INH or H, pyrazinamide is PZA or Z, rifampicin is RMP or R, streptomycin is SM or S.

Second-line drugs –

Capreomycin, Cycloserine, Kanamycin, Thioacetazone, Clarithromycin, Paraaminosalicylic acid (PAS), Ciprofloxacin, Levofloxacin, Rifabutin, Clofazimine, Amikacin, Ethionamide.

Third line: Third-line drugs include drugs that may be useful, but have doubtful or unproven efficacy: Rifabutin macrolides: e.g., clarithromycin (CLR); linezolid (LZD); thioacetazone (T); thioridazine; arginine;

First line drugs, are only used for the treatment of new patients who are very unlikely to have resistance to any of the TB drugs.

The second line drugs, that are only used for the treatment of drug resistant TB.

Most current TB drugs those that are effective against actively metabolizing and rapidly growing bacilli.

Drug Resistant TB:

A person with active TB disease has drug resistant TB if the TB bacteria that the person is infected with, will not respond to, and are therefore resistant to, at least one of the main TB drugs.

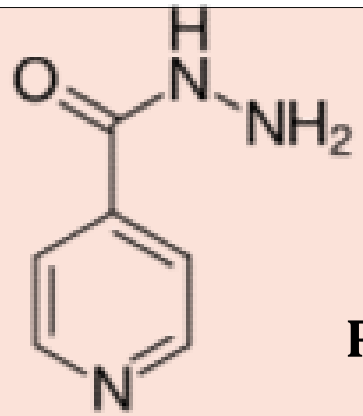
Types of drug resistant TB:

MDR (multi drug resistant) TB is the name given to TB when the bacteria that are causing it are resistant to at least isoniazid and rifampicin.

Extensively drug-resistant TB (XDR TB) is a rare type of MDR TB that is resistant to isoniazid and rifampin, plus any fluoroquinolone and at least one of three injectable second-line drugs (i.e., amikacin, kanamycin, or capreomycin).

First line agents

Isoniazid : isonicotinylhydrazide (INH)



Pyridine-4-carbohydrazide

Mechanism of action:

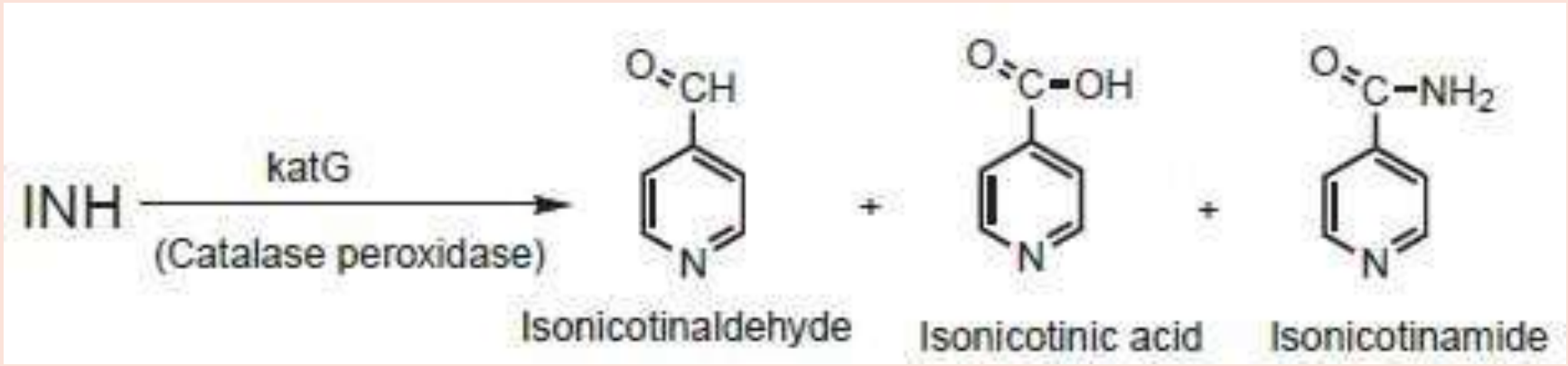
It inhibit the synthesis of mycolic acids, high–molecular-weight, branched – hydroxy fatty acids, are important constituents of the mycobacterial cell wall in that they provide a permeability barrier to hydrophilic solutes.

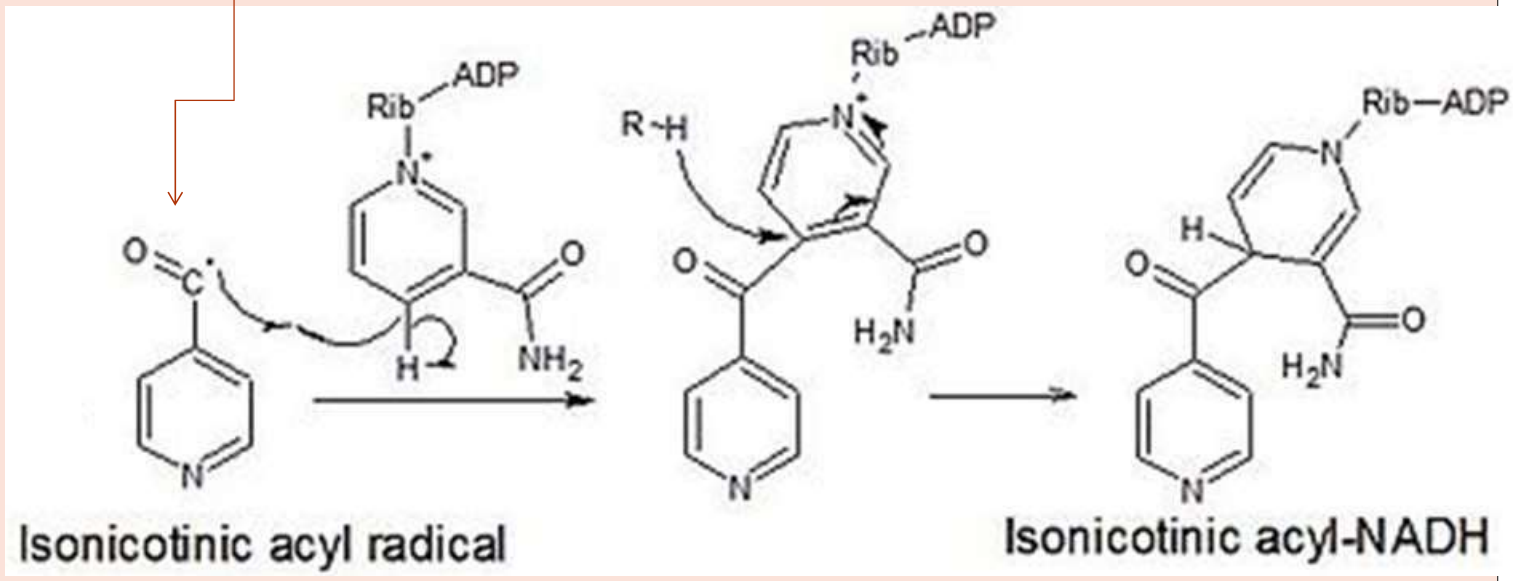
It is a prodrug, activated through an oxidation reaction by endogenous enzyme katG which exhibits catalase-peroxidase activity.

This enzyme convert INH to a reactive species which are capable of acylation of an enzyme system found exclusively in *M. tuberculosis.*

Reaction of INH with catalase-peroxidase results in formation of isonicotinaldehyde, isonicotinic acid, and isonicotinamide.

These reactive species reacts with the NAD. The resulting adducts inhibit the enzyme enoyl-reductase enzyme (inhA).

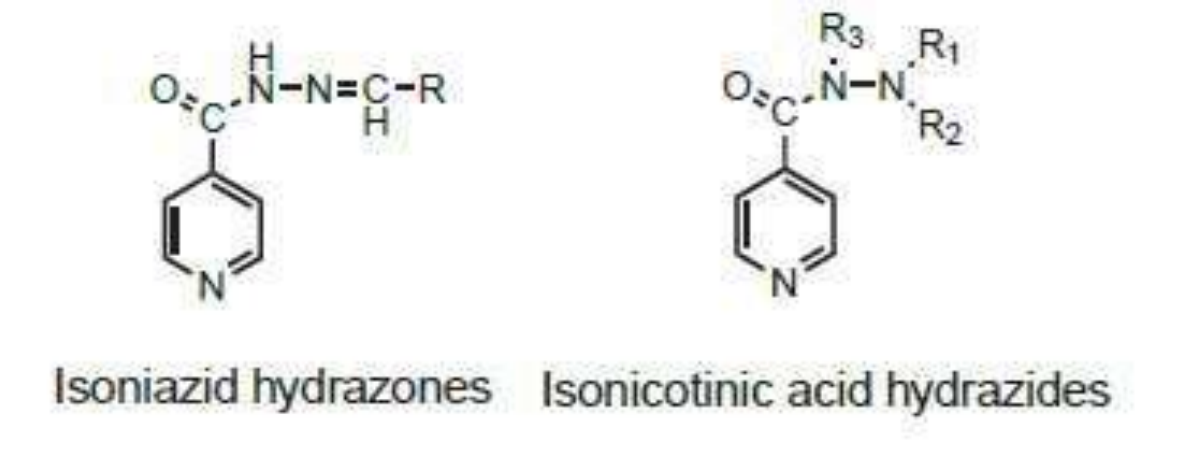




For active tuberculosis it is often used together with Rifampicin, Pyrazinamide, and either Streptomycin or Ethambutol. For latent tuberculosis it is often used by itself.

Structure–activity Relationship of INH:

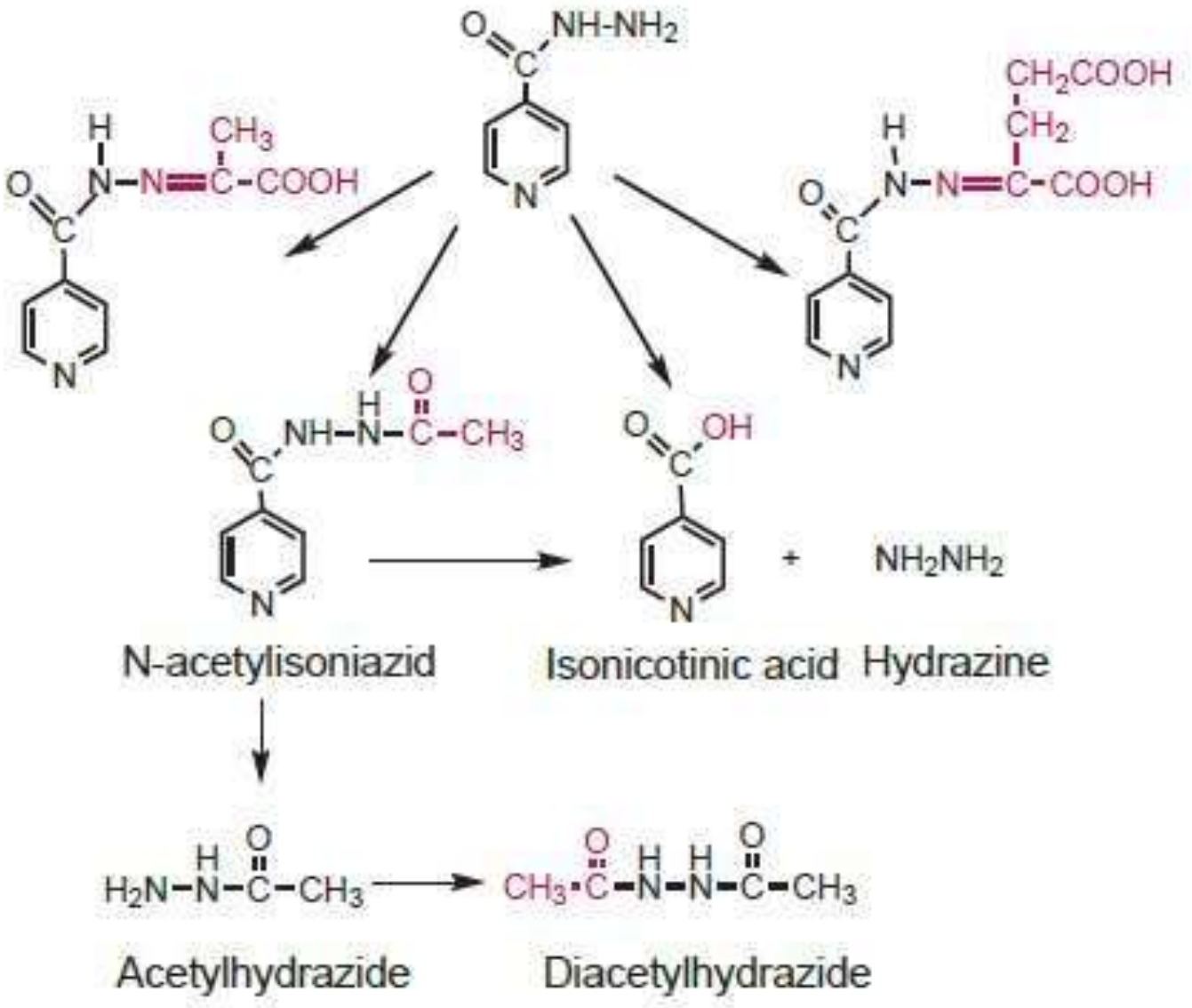
- Substitution of the hydrazine portion of INH with alkyl and aralkyl substituent resulted in a series of active and inactive derivatives.



- Any substitution of the N-1 hydrogen with alkyl groups destroyed the activity (R1 and R2 = H; R3 = alkyl).
- Substitution on the N-2 position resulted in active compounds (R1 and/or R2 = alkyl; R3 = H).
- None of these changes produced compounds with activity superior to that of INH.
- Replacement of pyridine nucleus with other aromatic ring such as benzene or piperidine or thiazole ring diminished the antitubercular activity.

Metabolism of INH

Enzyme responsible for acetylation, cytosolic N-acetyltransferase present in liver and small intestine



Rifamycins

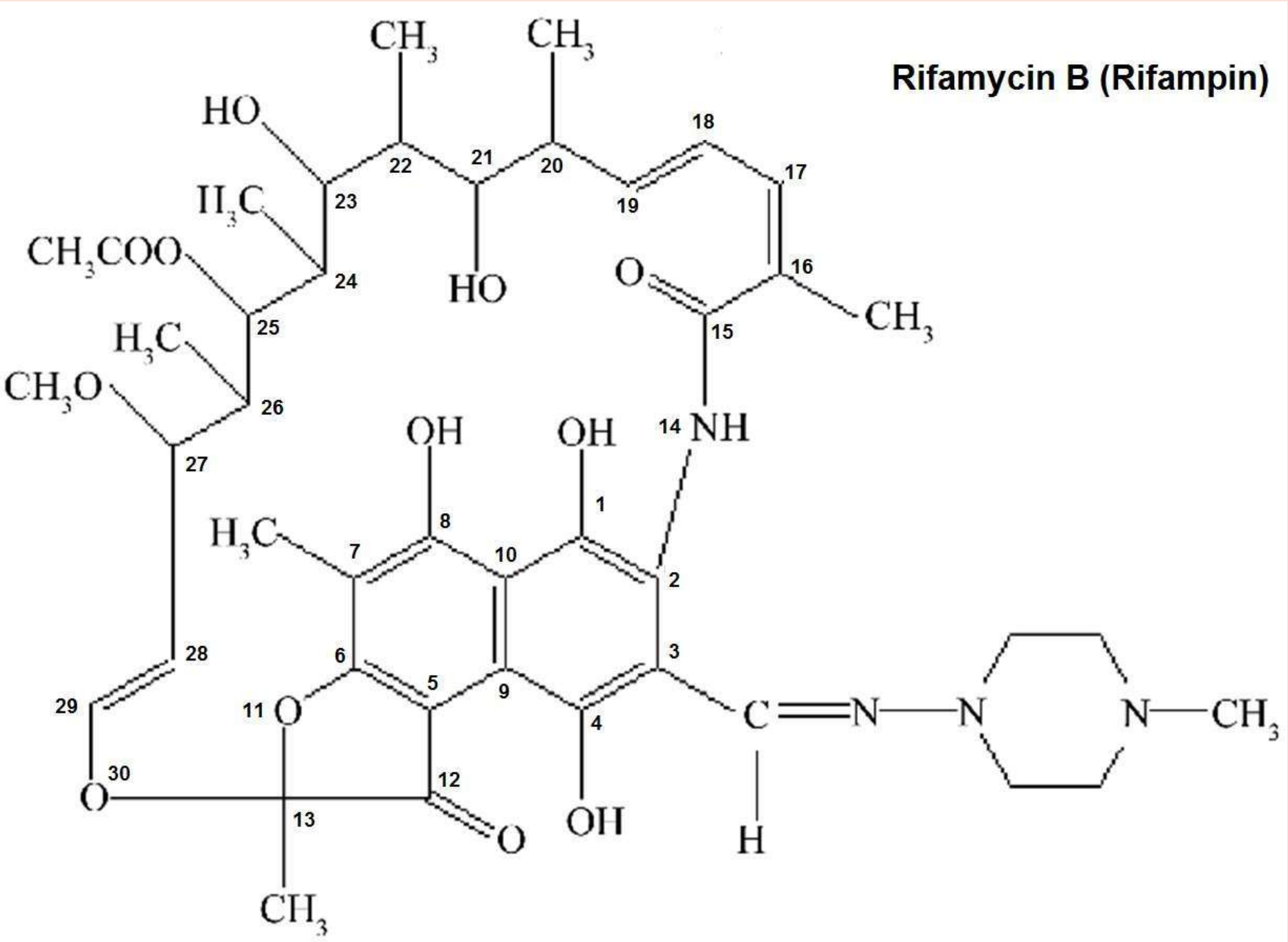
These are ansamycins antibiotics obtained by fermentation from cultures of ***Streptomyces mediterranei*** .

The rifamycins and many of their semisynthetic derivatives have a broad spectrum of antimicrobial activity. They are most notably active against Gram-positive bacteria and M. tuberculosis.

All of the rifamycins (A, B, C, D, and E) are biologically active.

Some of the semisynthetic derivatives e.g. Rifamycin B (Rifampin) are the most potent known inhibitors of DNA directed RNA polymerase in bacteria, and their action is bactericidal.

Rifamycin B (Rifampin)



Mechanism of action:

Rifamycins inhibit bacterial DNA-dependent RNA polymerase (DDRP) by binding to the β-subunit of the enzyme and are highly active against rapidly dividing intracellular and extracellular bacilli.

Inhibition of DDRP leads to blocking the initiation of chain formation in RNA synthesis.

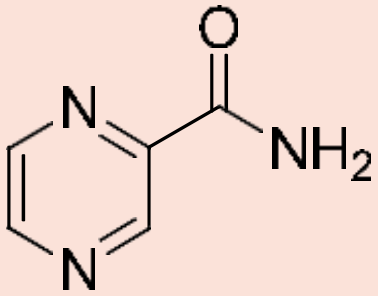
The DDRP is a metalloenzyme that contains two zinc atoms.

It is postulated that the oxygen at C-1 and C-8 of a rifamycin can chelate to a zinc atom, which increases the binding to DDRP, and finally, the oxygen at C-21 and C-23 form strong hydrogen bonds to the DDRP. The binding of the rifamycins to DDRP results in the inhibition of the RNA synthesis.

SAR

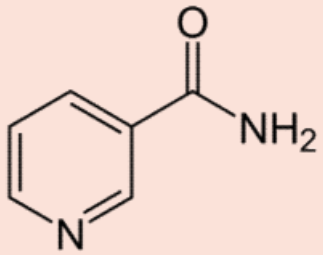
1) Free –OH groups are required at C-1, C-8, C-21, and C-23;
2) These groups appear to lie in a plane and to be important binding groups for attachment to DDRP, as previously indicated;
3) Acetylation of C-21 and/or C-23 produces inactive compounds;
4) Reduction of the double bonds in the macro ring results in a progressive decrease in activity;
5) Opening of the macro ring also gives inactive compounds.

Pyrazinamide



Pyrazinamide

pyrazine-2-carboxamide



Nicotinamide

It is a **bioisoster of nicotinamide** and possess bactericidal action against M. tuberculosis.

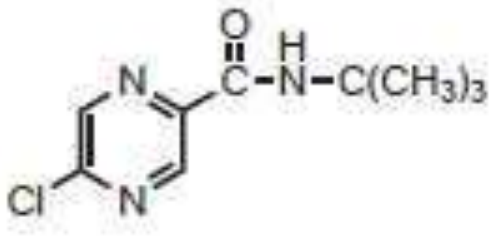
Mechanism of action:

Susceptible organisms produce **pyrazinamidase**, which is responsible for conversion of **pyrazinamide to pyrazinoic acid** intracellularly.

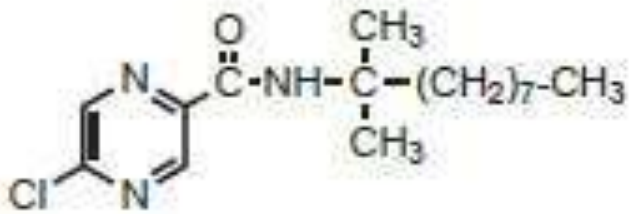
Pyrazinoic acid has been shown to possess biologic activity at a pH 5.4. Pyrazinoic acid can lower the pH in the immediate surroundings of the M. tuberculosis to such an extent that the organism is unable to grow.

SAR of Pyrazinamide:

- Substitution on the pyrazine ring or use of alternate heterocyclic aromatic rings has given compounds with reduced activity.
- Hydrophilic groups are essential for sufficient plasma concentration and to deliver the drugs to the site of action.
- Liphophilic groups are essential to allow penetration into the mycobacterial cell.
- Susceptibility to hydrolysis such that the prodrug is unaffected by the "extracellular" enzymes but is readily hydrolyzed at the site of action.

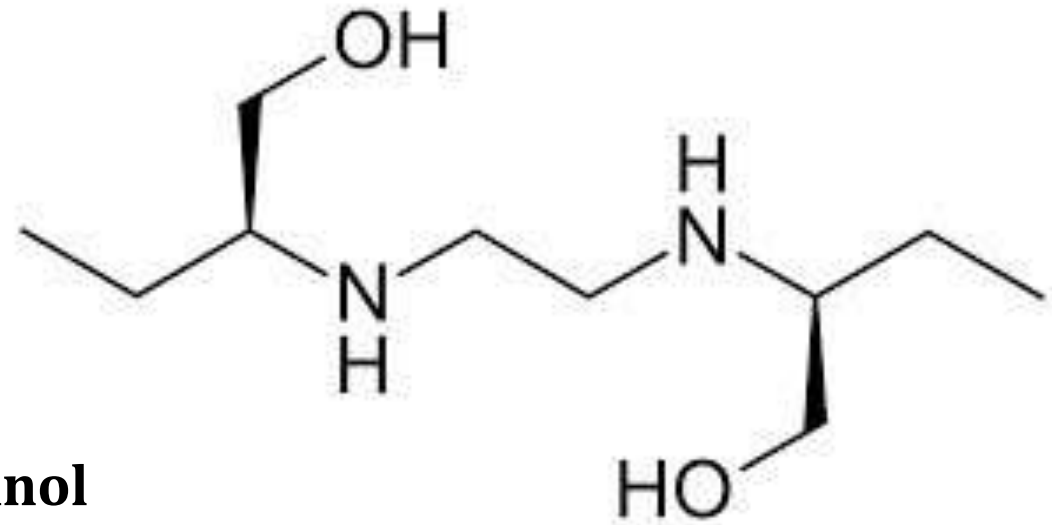


tert -butyl 5-chloropyrazinamide



2'-(2'-methyldecyl) 5-chloropyrazinamide

Ethambutol (EMB)



(+)-2,2'-(ethylenediimino)di-1-butanol

It is an ethylenediiminobutanol.

(+)-enantiomer is 200 – 500 fold more active than (-)- enantiomer.

Mechanism of action:

It inhibits **mycobacterial arabinosyl transferases** which are involved in the polymerization reaction of arabinoglycan, an essential component of the mycobacterial cell wall.

SAR:

Extension of the ethylene diamine chain, replacement of either nitrogen, increasing the size of the nitrogen substituents, and moving the location of the alcohol groups are all changes that drastically reduce or destroy biologic activity

Streptomycin (STM)

It is aminoglycoside antibiotic, obtained from actinomycetes, genus *Streptomyces griseus.*

Mechanism of action:

STM inhibit protein synthesis.

It binds to 30s subunit of the bacterial ribosome interfering with the binding of formyl-methionyl-tRNA to the 30s subunit.

The binding of molecule to the 30s subunit interferes with 50s subunit association with the mRNA strand. This leads to codon misreading. Thus results in an unstable ribosomal mRNA complex leading to mutation and defective protein synthesis; leading to cell death.

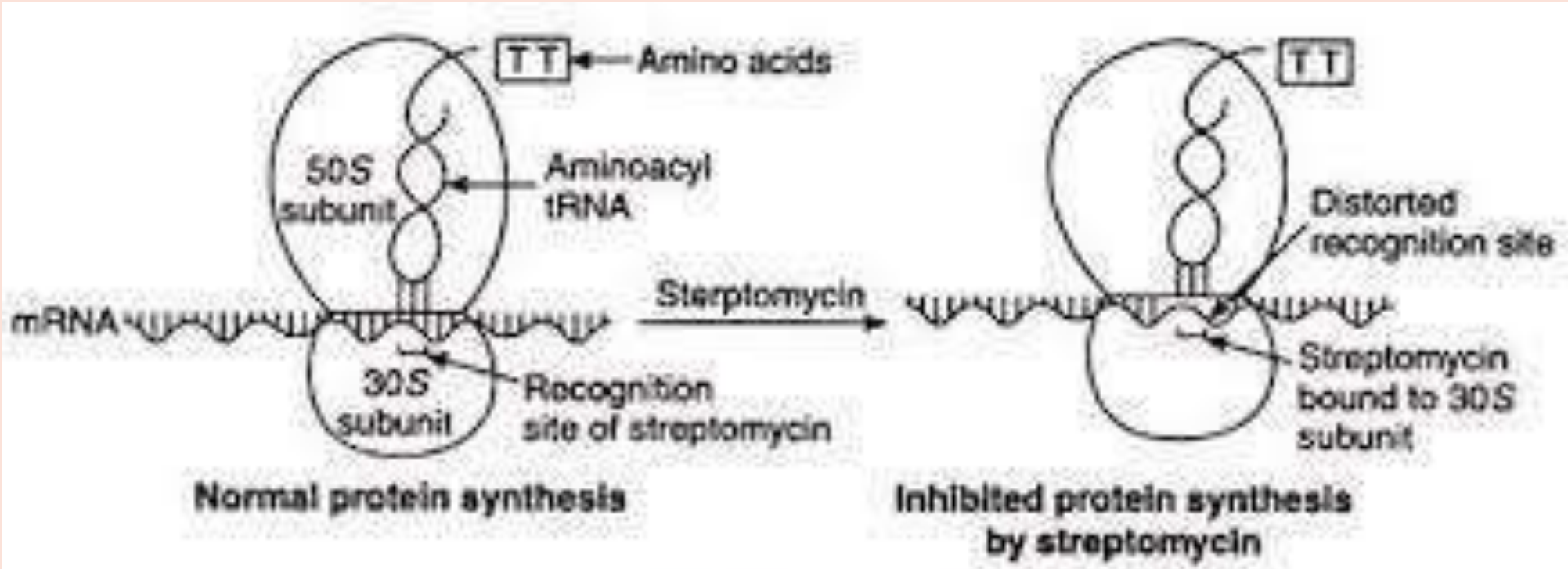


FIG. 45.10. Schematic representation of protein synthesis inhibition by streptomycin.

Chemistry of streptomycin

Streptomycin is a triacidic base and has aldose sugar.

The hydrophilic nature results in poor absorption from GIT.

It is made of 3 basic strucutral subunits

streptidine (diguanidino compound)

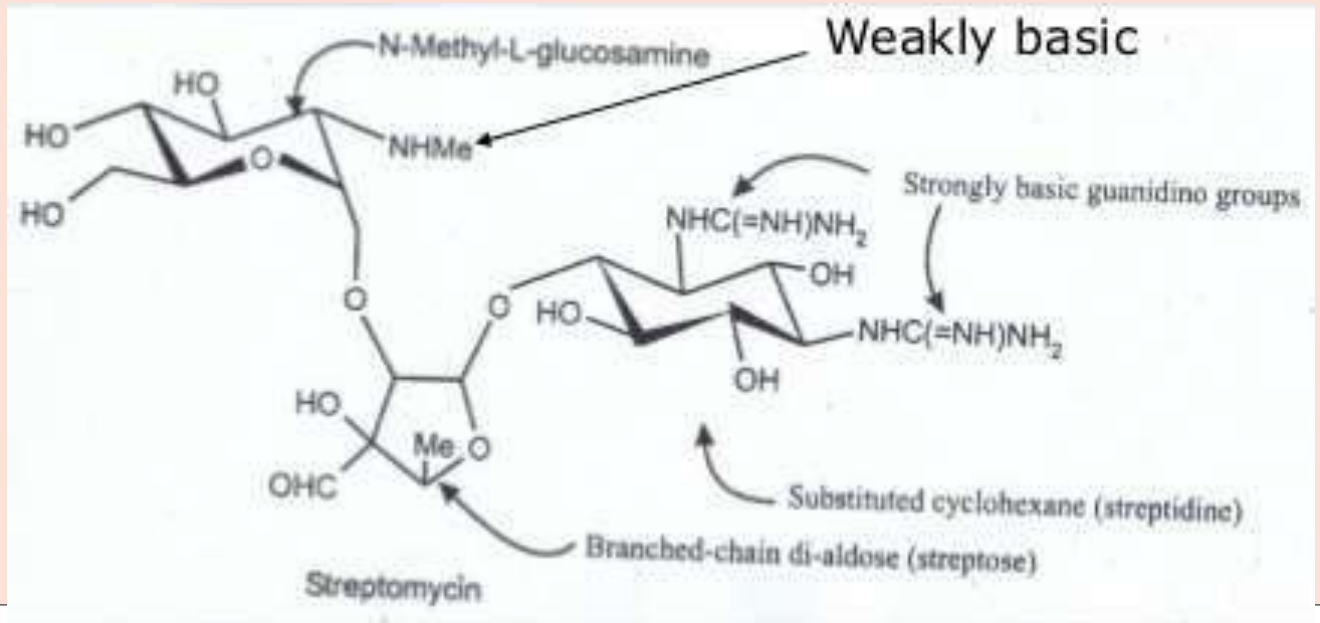
Streptose ((a aldose suagr)

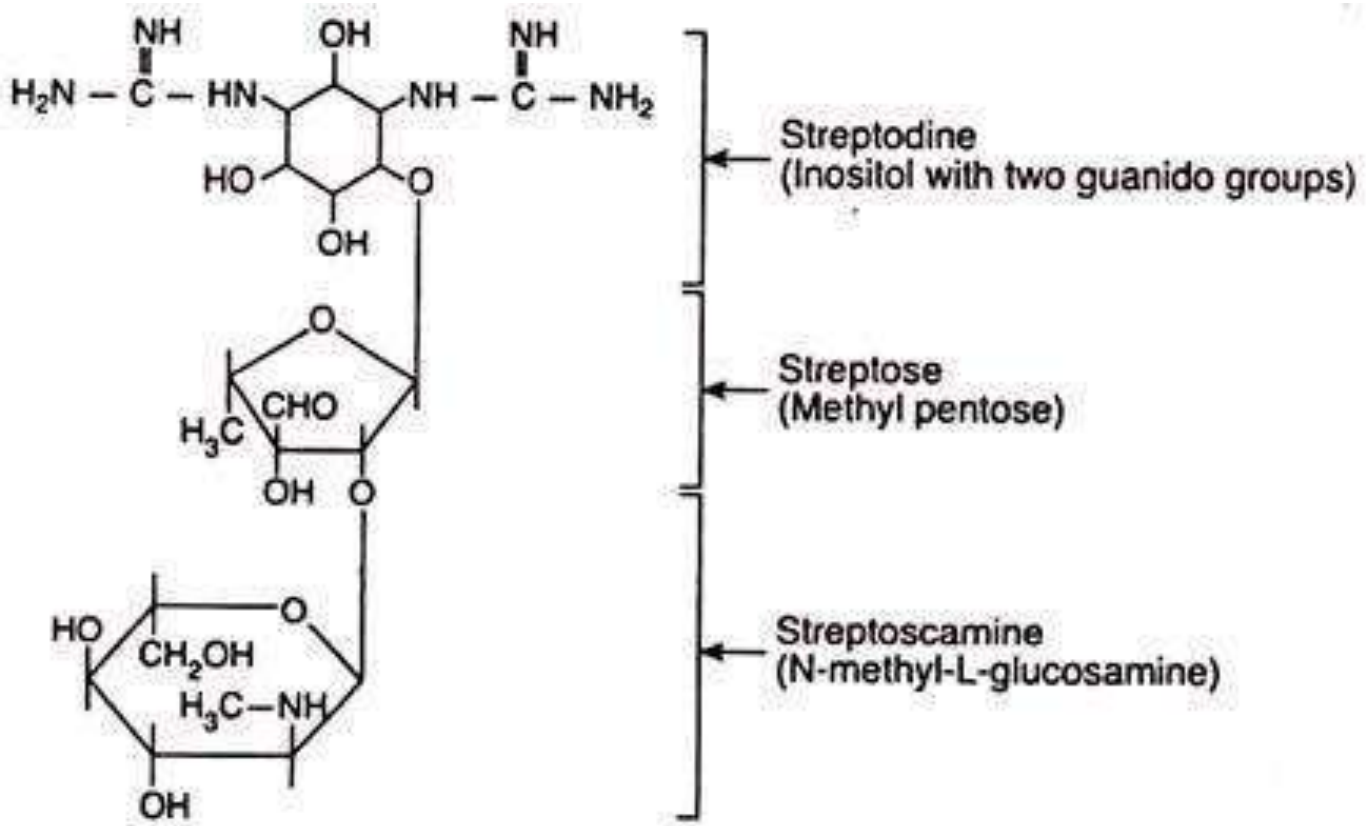
streptoscamine (N-methyl-L-glucosamine unit)

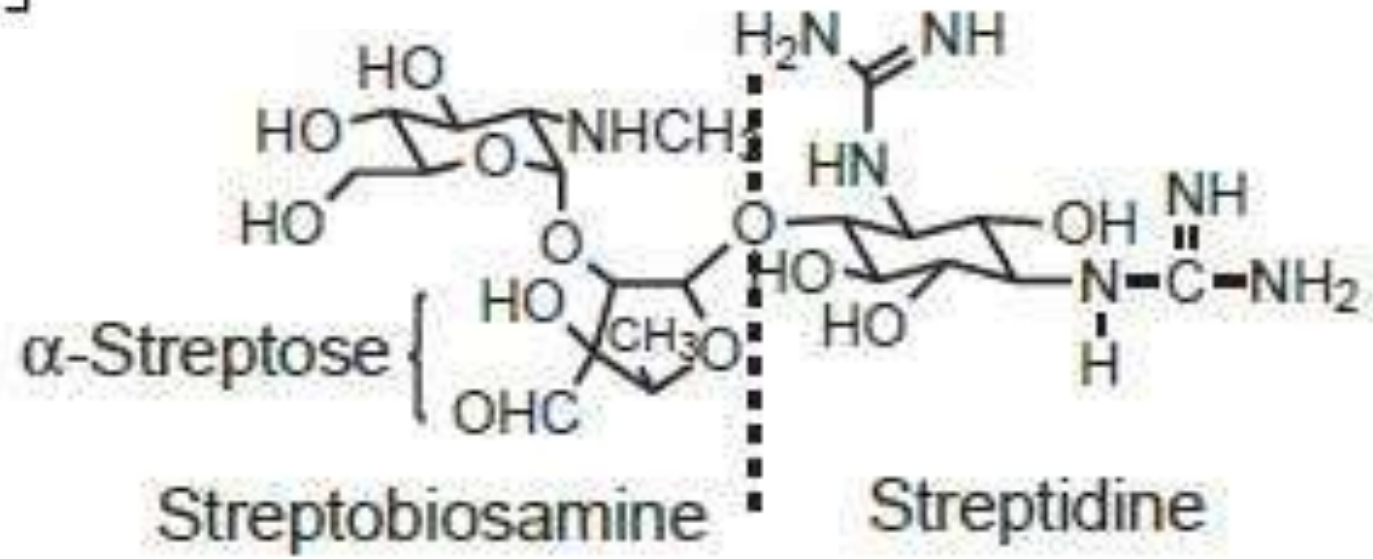
The two guanidino groups attached to the streptidine exhibits strong basic nature.

The amino sugar attached to streptidine by means of glycosidic linkage.

The methyl amino group attached to N-methyl-L-glucosamine exhibit weakly basic nature.




Streptodine
(Inositol with two guanido groups)
Streptose
(Methyl pentose)
Streptoscamine
(N-methyl-L-glucosamine)


α-Streptose
Streptobiosamine
Streptidine

SAR of strptomycin

- Modification of the α-streptose portion of STM has been extensively studied. Reduction of the aldehyde to the alcohol results in a compound, dihydrostreptomycin that has activity similar to STM but with a greater potential for producing delayed, severe deafness.
- Oxidation of the aldehyde to a carboxyl group or conversion to Schiff base derivatives (oxime, semicarbazone, or phenylhydrazone) results in inactive analogs.
- Oxidation of the methyl group in α-streptose to a methylene hydroxy gives an active analog that has no advantage over STM.

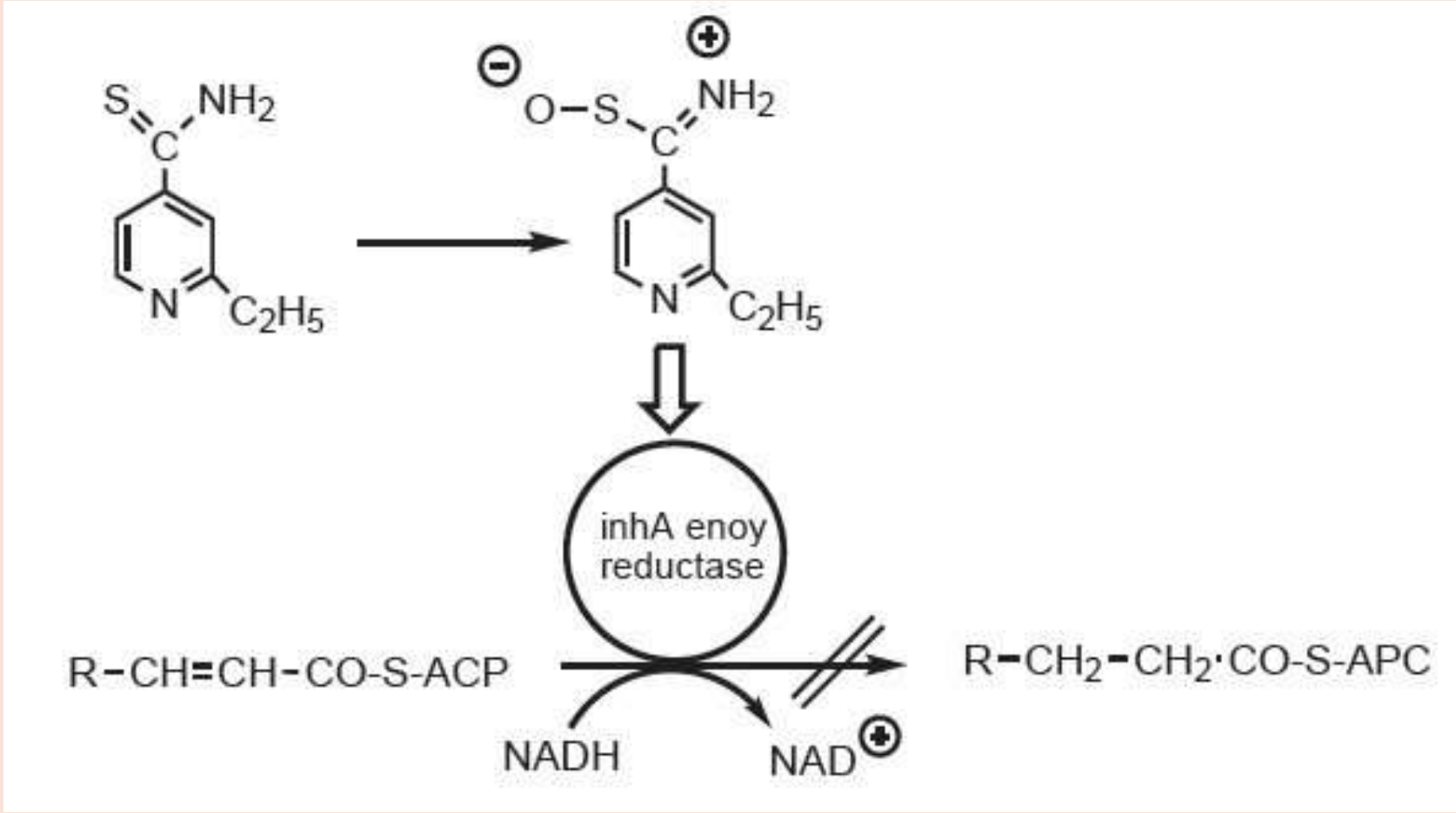
- Modification of the aminomethyl group in the glucosamine portion of the molecule by demethylation or by replacement with larger alkyl groups reduces activity
- Removal or modification of either guanidine in the streptidine nucleus also decreases activity

Second line agents
Ethionamide:

2-ethylpyridine-4-carbothioamide

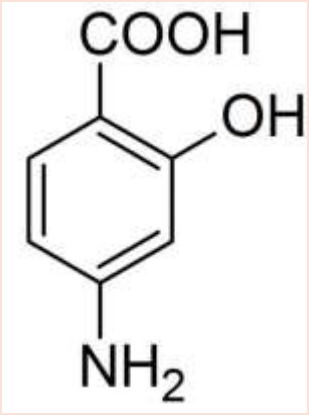
Mechanism of action:

It is a prodrug that is **converted via oxidation** by **catalase-peroxidase** to an active acylating agent, **ethionamide sulfoxide**, which in turn **inactivates the inhA enoyl reductase enzyme**. In the case of ethionamide, it has been proposed that the ethionamide sulfoxide acylates Cys-243 in inhA protein.


S
NH2
C
N
C2H5
O
S
NH2
C
N
C2H5
inhA enoy
reductase
R-CH=CH-CO-S-ACP
NADH
NAD
R-CH2-CH2·CO-S-APC

p-Aminosalicylic acid

4-amino-2-hydroxybenzoic acid

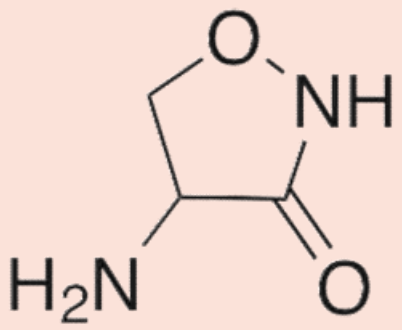


As a bacteriostatic agent, PAS is used at a dose of up to 12 g/day, which causes considerable GI irritation.

Mechanism of Action

PAS is thought to act as an antimetabolite **interfering with the incorporation of *p-aminobenzoic* acid into folic acid**. When co-administered with INH, PAS is found to reduce the acetylation of INH, itself being the substrate for acetylation, thus increasing the plasma levels of INH.

Cycloserine (Seromycin)



(*R*)-4-Amino-1,2-oxazolidin-3-one

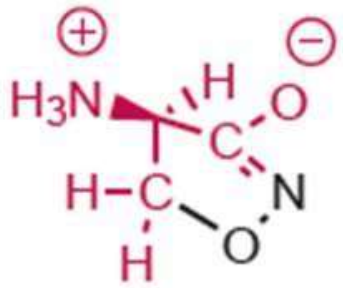
Cycloserine is a natural product isolated from ***Streptomyces orchidaceus*** as the d-(+)-enantiomer

MOA:

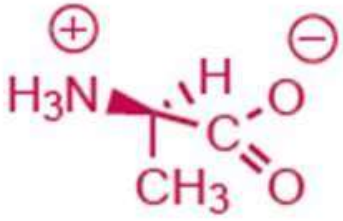
It is a structural analogue of D-alanine.

It inhibit two key enzyme: **D-alanine recemase and D-alanine ligase**.

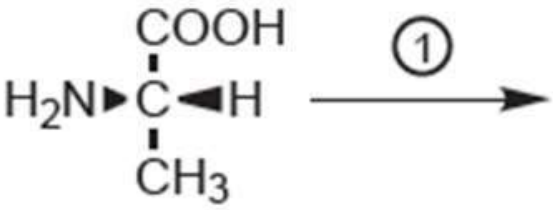
It competitively inhibits the binding of d-alanine to both of these enzymes and its incorporation into the peptidoglycan.



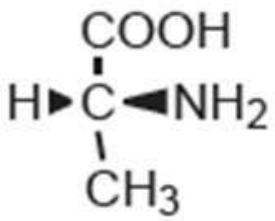
D-cycloserine



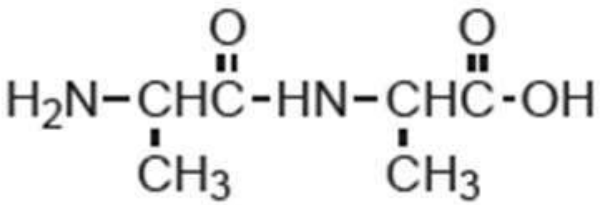
D-alanine



L-alanine



D-alanine



D-alanine-D-alanine complex

Peptidoglycan
Cell Wall

1: D-alanine racemase
2: D-alanine ligase.

Problems in Chemotherapy:

1.Chemotherapy of tuberculosis faced some special problems because of **slow growth rate of mycobacteria and their intracellular location**.

2.Since the disease is chronic by its nature, the **therapy needs to be continued for at least about 1–2 years** in most of the cases. In such a chronic treatment, if only single drug is used, **the risk of development of drug resistant strains** of mycobacteria is always high. This is coupled with the risk of drug toxicity due to high doses of a single drug needed.

4.The solution to this problem is to use combination therapy. **When two or more effective drugs are used in combination, resistance will not develop**. However drugs with similar toxicological profiles should not be used together.

5. The drugs used in the combination therapy are usually selected from ethambutol, isoniazid and rifampin.

Combination Therapy:

As single drug may cause resistance as well drug toxicity, to avoid such problem, different combination are used.

1. Standard regimens:

- Anti-TB drugs are given as 2/3/4 drug combination regimens for different durations.
- Combination regimen should include at least two drugs to which mycobacteria are sensitive.
- The response to chemotherapy is slow so given for months to years.

Standard regimens:

May be given in two phases.

1. Initial Intensive Phase for 2 months
2. Continuation Phase for 4 months

Initial Intensive Phase for 2 months:

Therapy is initiated with 4 drug regimen.

Isoniazid , Rifampin , Pyrazinamide & Ethambutol or Streptomycin.

Neither Ethambutol nor Streptomycin decreases the duration of the regimen, but they provide additional coverage for mycobacteria if isolate proves to be resistant to Isoniazid / Rifampin or to both

Continuation Phase for 4 months:

A few bacilli are left, only 2/ 3 drugs are enough.

- Isoniazid and Rifampin
- Isoniazid , Rifampin , Pyrazinamide / Ethambutol
- Pyridoxine: 25 to 50mg/day, to minimize adverse reactions to isoniazid.

Standard regimen may be given as DOTS : Directly Observed Treatment Short Course. Recommended by WHO in 1995. For noncompliant patient.

DOTS is a strategy used to reduce the number of tuberculosis (TB) cases.

DOTS have five main components:

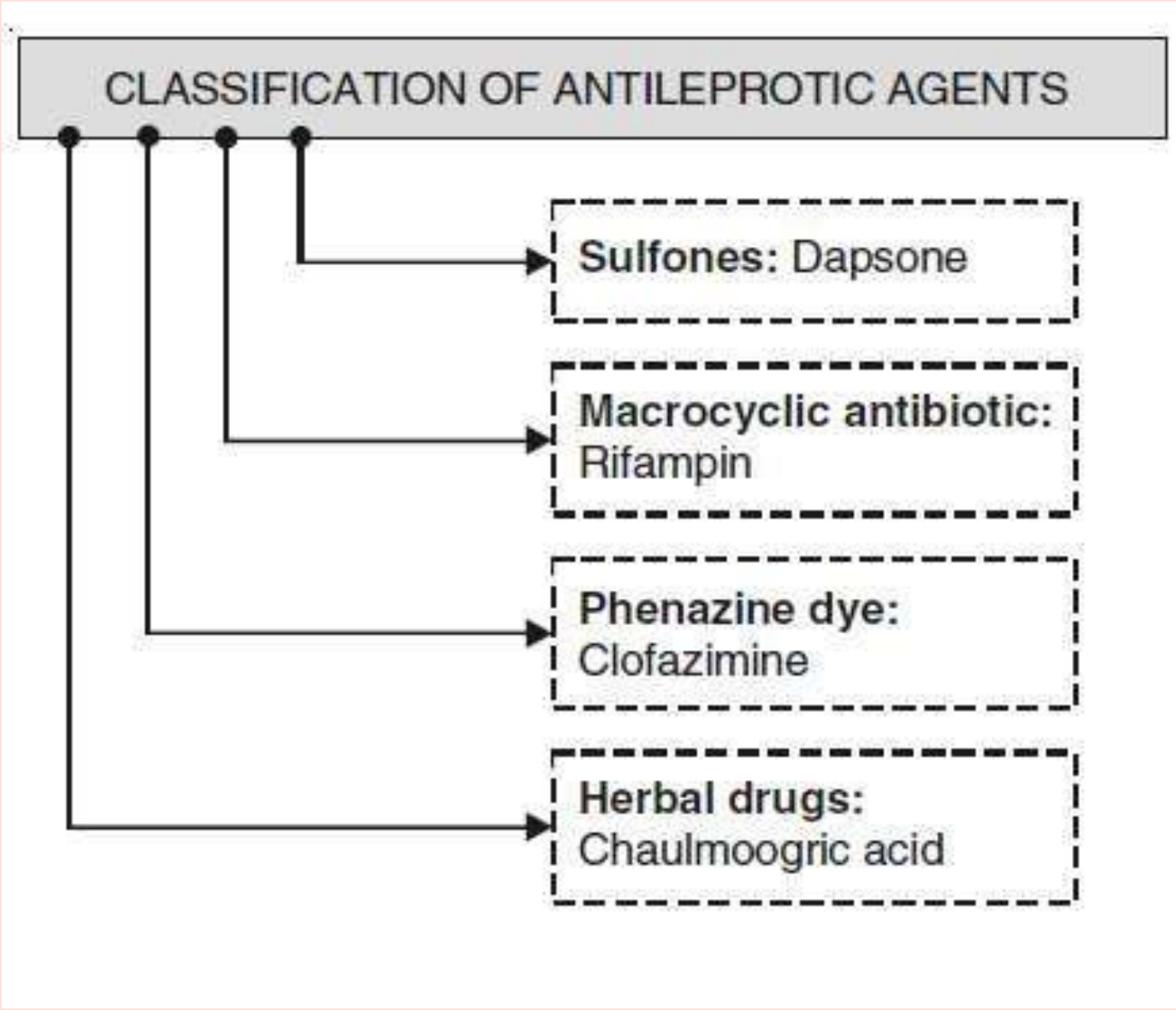
i. Political commitment with increased and sustained financing.
ii. Case detection through quality-assured bacteriology (sputum smear microscopy).
iii. Standardized treatment, with supervision and patient support.
iv. An effective drug supply and management system.
v. A standardized recording and reporting system that allows assessment of treatment results

Leprosy

- Leprosy or Hansen's disease is a chronic human disease caused due to an acid-fast bacillus which produces nodules in the skin and loss of sensation in the affected region.
- This dermatological infection is caused by ***Mycobacterium leprae*** and the disease develops very slowly over a period of years.

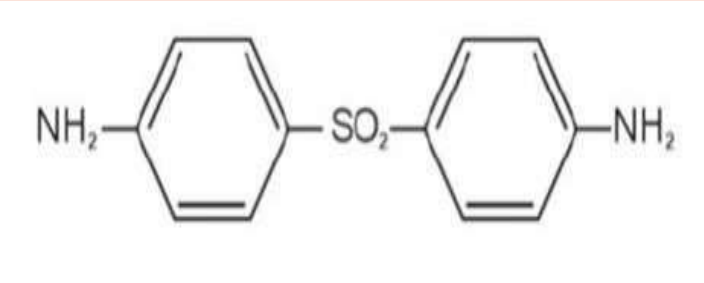
Antileprotic agents

Antileprotic drugs are that interferes with proliferation of bacterium that causes leprosy.


CLASSIFICATION OF ANTILEPROTIC AGENTS
Sulfones: Dapsone
Macrocyclic antibiotic: Rifampin
Phenazine dye: Clofazimine
Herbal drugs: Chaulmoogric acid

Sulfones: The diaryl sulfones represent the major class of agents used to treat leprosy.

Dapsone:



4-[(4-aminobenzene)sulfonyl]aniline

Dapsone, a diaminodiphenylsulfone, is a nearly water insoluble agent that is very weakly basic (pKa ~1.0). The lack of solubility can account for the occurrence of GI irritation.

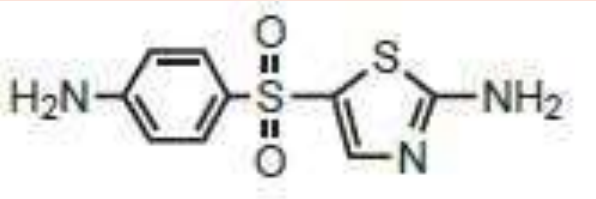
It is commonly used in combination with clofazimine and rifampin for the treatment of leprosy.

MOA:

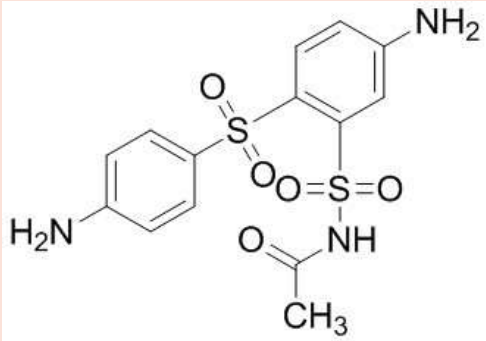
It is a bacteriostatic agent, act through competitive inhibition of p-aminobenzoic acid incorporation into folic acid.

SAR of Dapsone

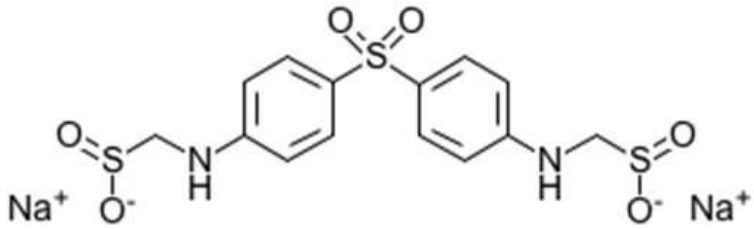
- Isosteric replacement of one benzene ring resulted in the formation of thiazolsulfone. Although still active, it is less effective than dapsone.
- Substitution on the aromatic ring, to produce acetosulfone, reduced activity while increasing water solubility and decreasing GI irritation.
- A successful substitution consists of adding methanesulfinate to dapsone to give sulfoxone sodium. This water-soluble form of dapsone is hydrolyzed in-vivo to produce dapsone. Sulfoxone sodium is used in individuals who are unable to tolerate dapsone because of GI irritation, but it must be used in a dose threefold that of dapsone because of inefficient metabolism to dapsone.



Thiazolsulfone



Acetosulfone



Sulfoxone sodium

Clofazimine:

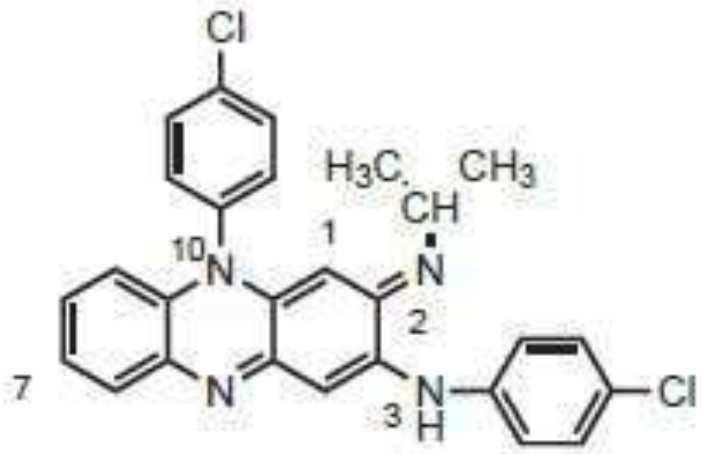
It is a phenazine derivative, is a water-insoluble dye (darkred crystals) that leads to pigmentation of the skin. In addition, discoloration (pink, red, or brownish-black) of the feces, eyelid lining, sputum, sweat, tears, and urine is seen.

Mechanism of action:

The molecule possesses direct antimycobacterial and immunosuppressive properties. It has been shown that clofazimine increases prostaglandin synthesis and the generation of antimicrobial reactive oxidants like superoxide from neutrophils, which in turn could have a lethal effect on the organism

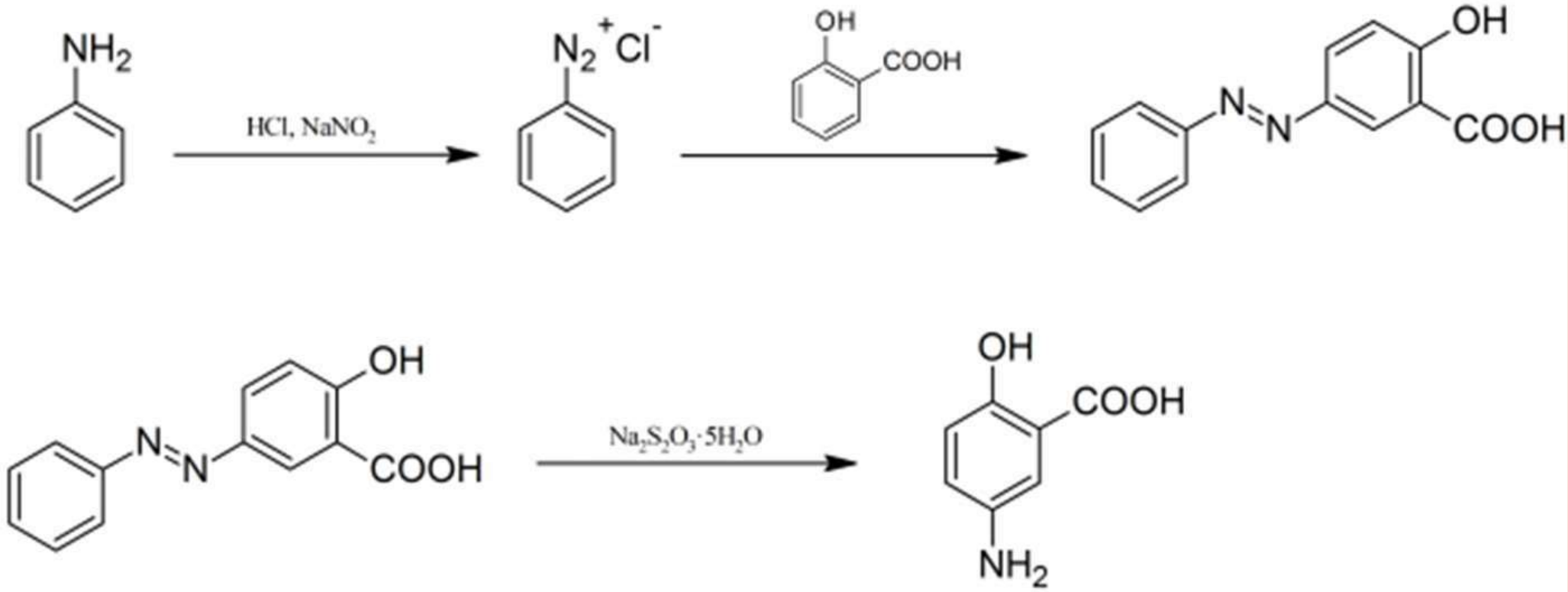
SAR

- The imino group at C-2 appears to be essential for activity. Alkyl and cycloakyl substitution at C-2 imino group increases the activity.
- Halogen substitution on the para position of the two phenyls at C-3 and N-10 enhance activity but are not essential to activity. The following order of activity has been reported: Br > Cl > CH3 > EtO > H or F.
- In the analogs studied, the increased activity correlates well with pro-oxidative activities of the molecule (e.g., ability to generate superoxide anion) as well as increased lipophilicity.

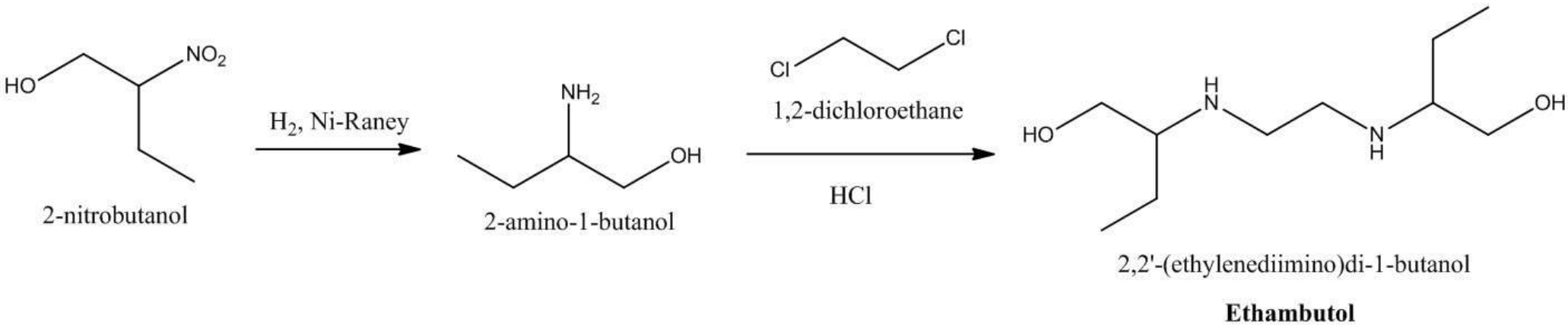


Clofazimine

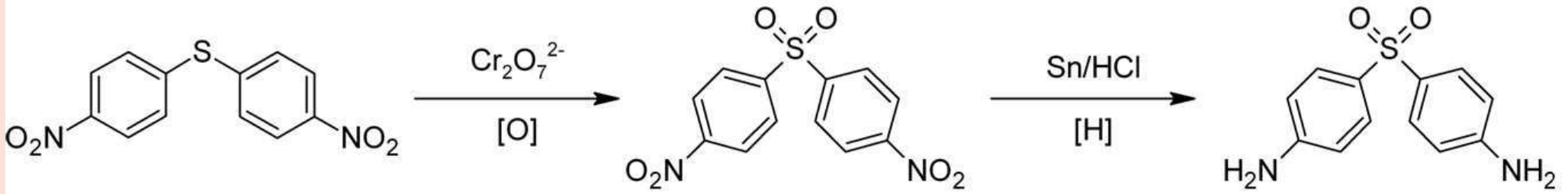
Synthesis of p-amino salicylic acid



Synthesis of Ethambutol



Synthesis of Dapsone



Antiviral Agent

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Assistant Professor
Department of Pharmceutical Chemistry

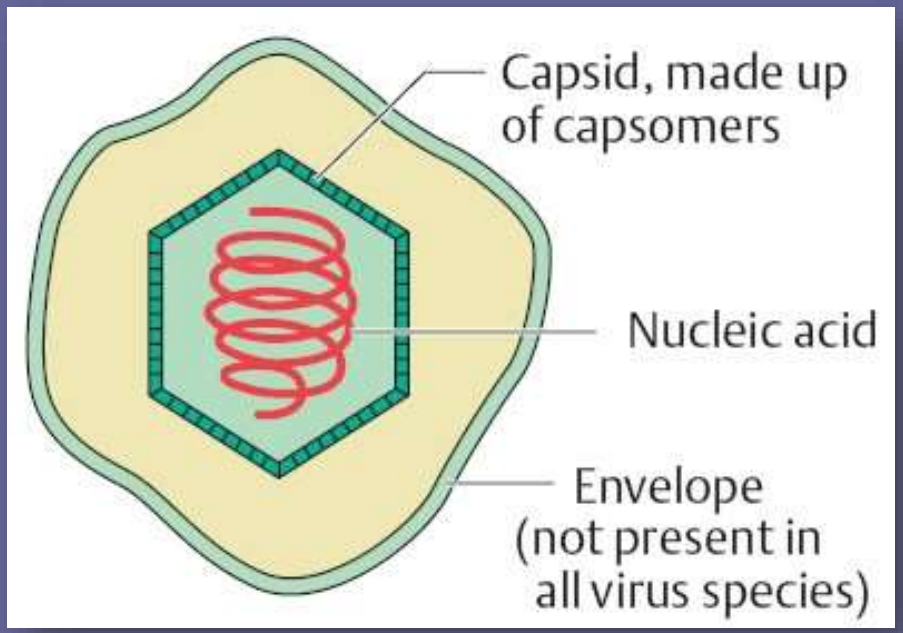
JES'S College of Pharmacy Nandurbar 425412

Virus

Definition

- Viruses are complexes consisting of protein and an RNA or DNA genome.
- They lack both cellular structure and independent metabolic processes.
- They replicate solely by exploiting living cells based on the information in the viral genome.

Structure



Classification of viruses

- **Capsid symmetry:** cubic, helical, or complex symmetry.
- **Presence or absence of an envelope.**
- **Diameter of the virion, or of the nucleocapsid with helical symmetry.**

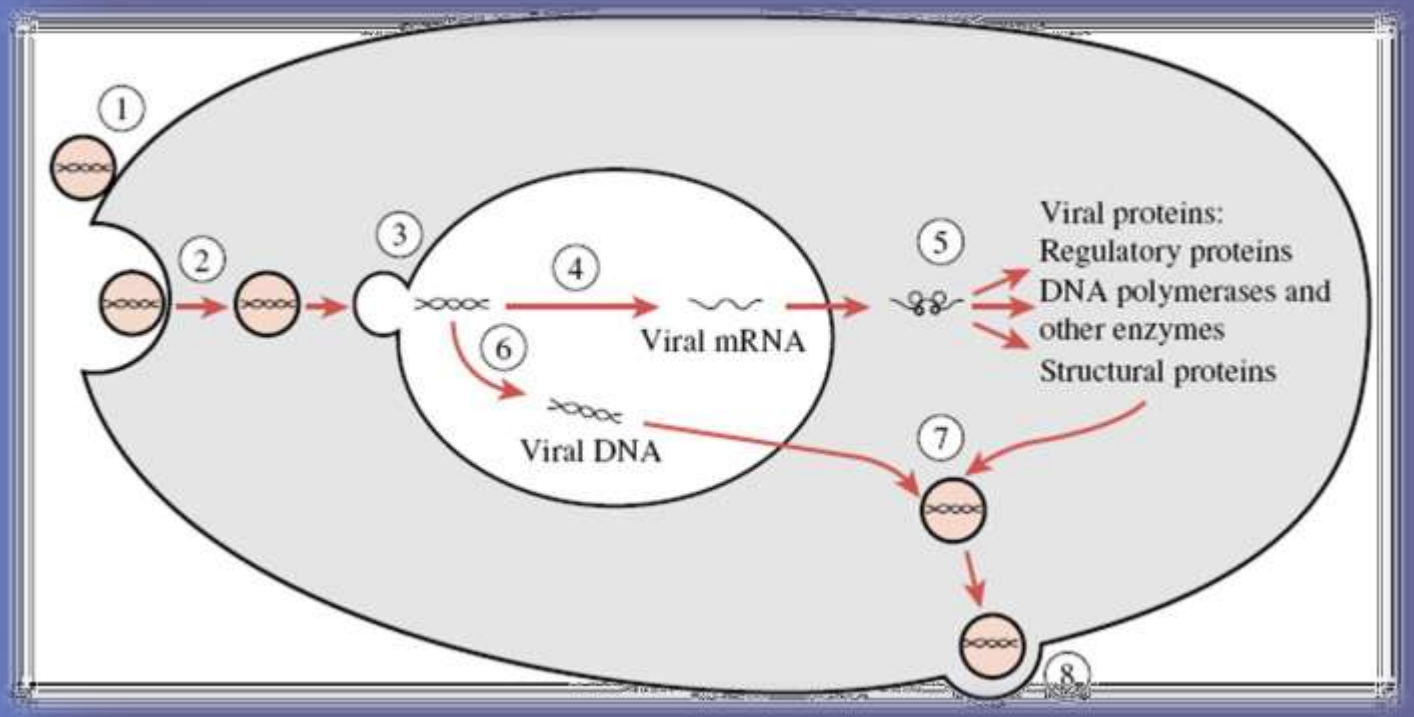
In short

Viruses are classified on the basis of several features:

- Nucleic acid content (DNA or RNA)
- Viral morphology (helical, icosahedral)
- Site of replication in cell (cytoplasm or nucleus)
- Coating (enveloped or nonenveloped)
- Serological typing (antigenic signatures)
- Cell types infected (B lymphocytes, T lymphocytes, monocytes)

Process of viral infection

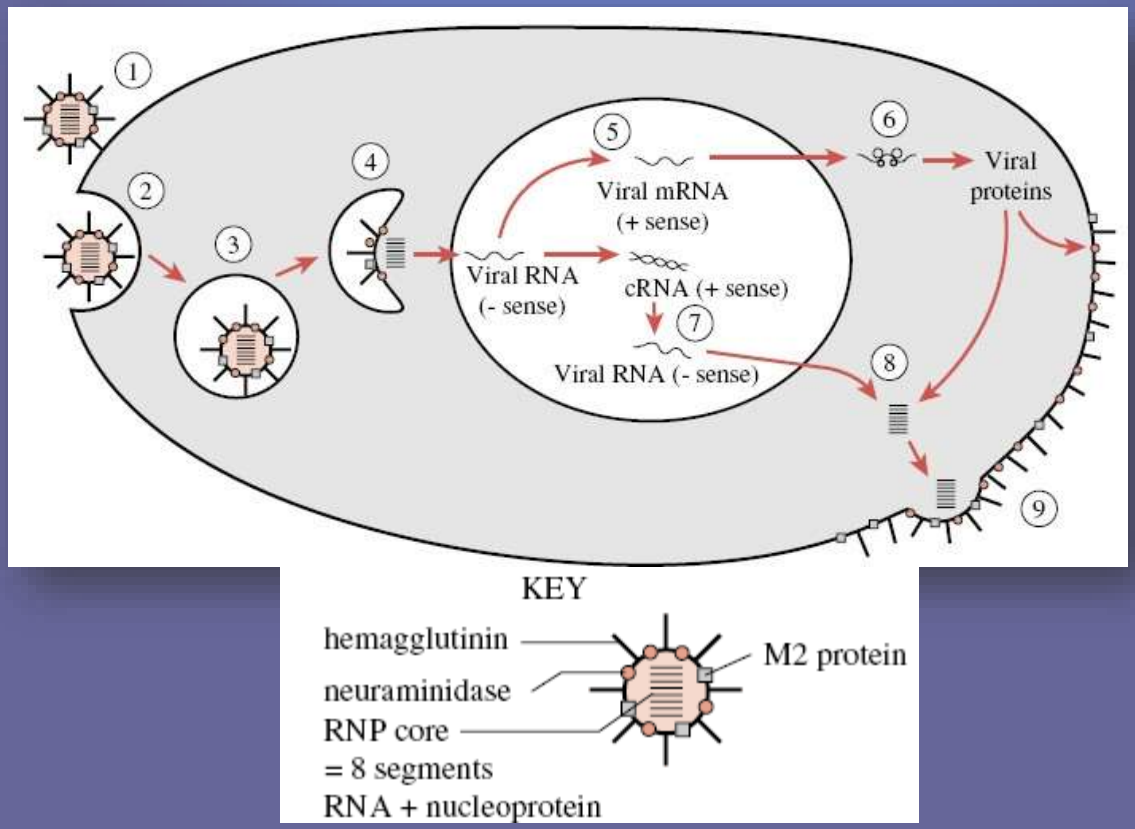
- The steps in viral replication are as follows:
- ***Adsorption*** of the virus to specific receptors on the cell surface.
- ***Penetration*** by the virus and intracellular release of nucleic acid.
- ***Proliferation*** of the viral components: virus-coded synthesis of capsid and noncapsid proteins, replication of nucleic acid by viral and cellular enzymes.
- ***Assembly*** of replicated nucleic acid and new capsid protein.
- ***Release*** of virus progeny from the cell.



Replicative cycles of representative DNA viruses.

Replicative cycle of a herpes virus, an example of a DNA virus.

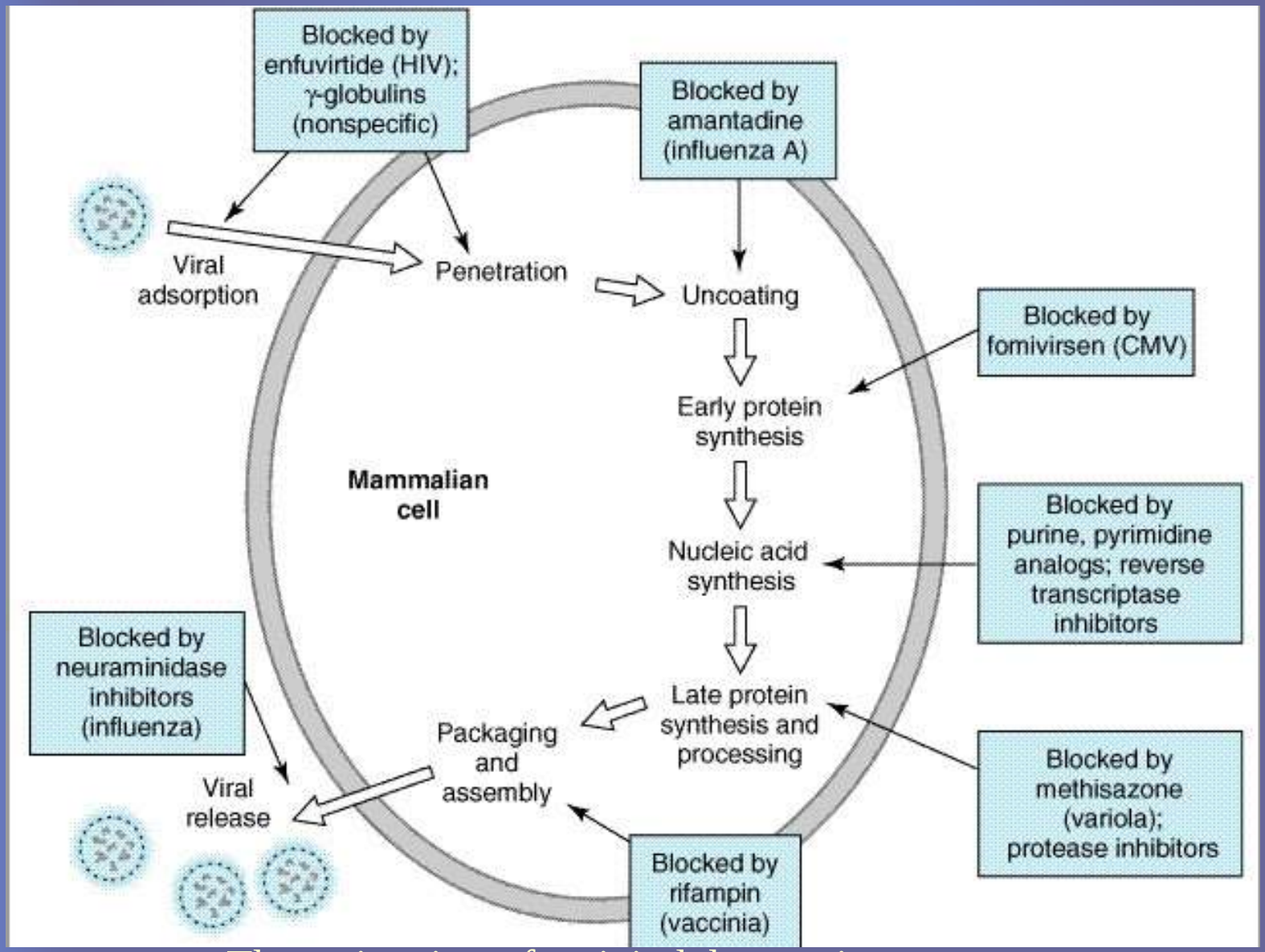
1. Attachment. 2. Membrane fusion. 3. Release of viral DNA through nuclear pores. 4. Transcription of viral mRNA. 5. Synthesis of viral proteins by host cell's ribosomes. 6. Replication of viral DNA by viral polymerases. 7. Assembly of virus particles. 8. Budding and release of progeny virus.



Replicative cycles of representative RNA viruses.

Replicative cycle of an influenza virus, an example of an RNA virus.

1. *Attachment.* ***2.*** *Endocytosis.* ***3.*** *Influx of H through M2 protein.* ***4.*** *Fusion of the* viral envelope with the endosomes membrane, dissociation of the RNP complex, and entry of viral RNA into the nucleus. ***5.*** *Synthesis of viral mRNA by viral RNA polymerase.* ***6.*** *Translation of viral* mRNA by host cell's ribosomes. ***7.*** *Replication of viral RNA, using viral RNA polymerase, via cRNA* replicative form. ***8.*** *Assembly of virus particles. and 9. Budding and release of progeny virus.*



The major sites of antiviral drug action

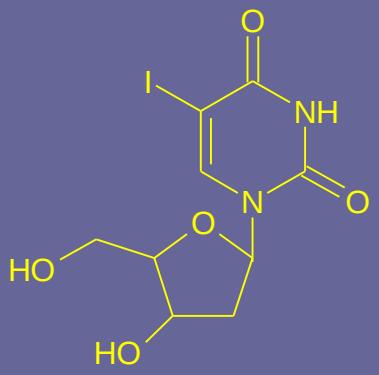
Problem in developing antiviral drugs

- Low level of specificity
- Late diagnosis of viral disease
- Development of resistance to chemotherapeutics.

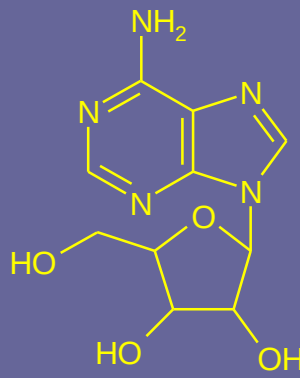
- Low level of specificity of the agents in some cases (toxic effects because cellular metabolism is also affected): viral replication is completely integrated in cell metabolism. The virus supplies only the genetic in formation for proteins to be synthesized by the cell.
- Late diagnosis of viral disease: Necessity of administering chemotherapeutics early, preferably before clinical symptoms manifest, since the peak of viral replication is then usually already past.
- Development of resistance to chemotherapeutics: Acyclovir-resistant strains of herpesviruses, in particular herpes simplex viruses, are occasionally isolated. Less frequently, cytomegaly viruses resistant to ganciclovir are also found.

Classification of antiviral agents

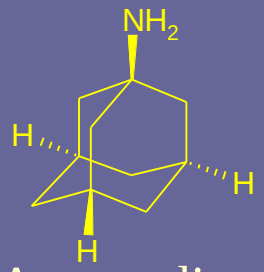
- Nucleoside analogs
  - Pyrimidine derivatives
  - Purine derivatives
- Nonnucleoside derivatives
- Adamantane amine derivatives
- Interferons
- Phosphorous derivatives



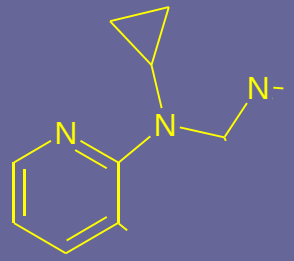
Idoxuridine



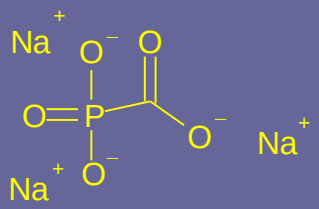
Vidarabine



Amantadine



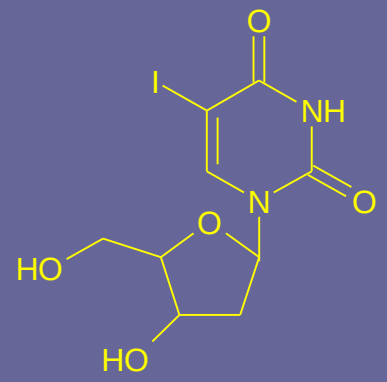
Nevirapine



Foscarnet sodium

Cyclic Nucleoside Analog

- Pyrimidine derivative



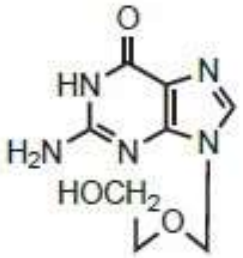
Idoxuridine

It substituting itself for thymidine in viral DNA. This in turn inhibits thymidylate phosphorylase and viral DNA polymerases from properly functioning

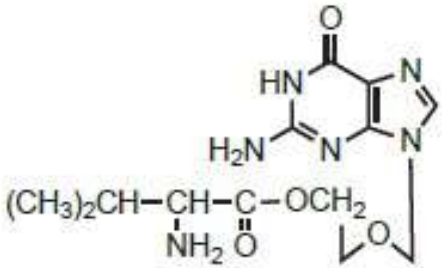
Idoxuridine is an iodinated analogue of deoxyuridine, with antiviral activity against herpes simplex virus (HSV)

Upon ocular administration, idoxuridine is converted to its mono-, di-, and triphosphate forms, is incorporated into DNA and disrupts viral replication.

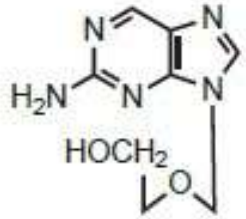
Agents Interfering with Viral Nucleic Acid Replication
-Acyclic Nucleoside Analogs



Acyclovir

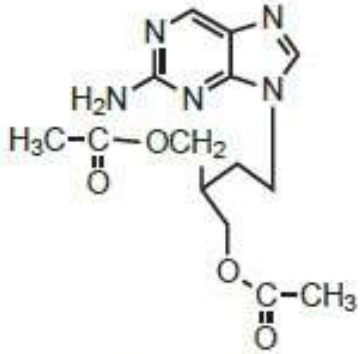


Valacyclovir

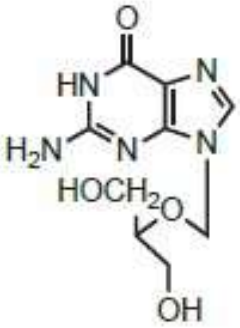


6-Deoxyacyclovir

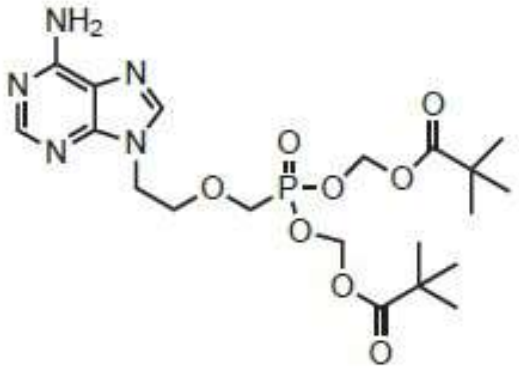
Cidofovir



Famciclovir

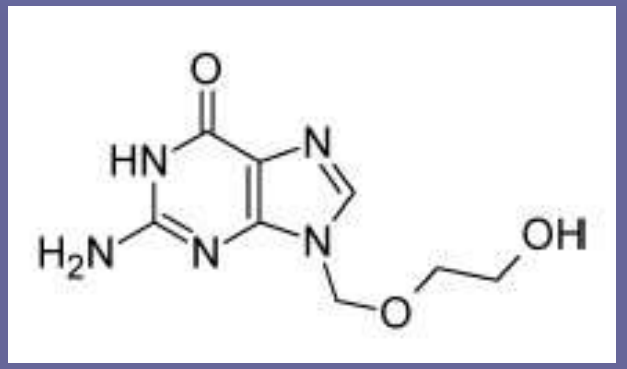


Ganciclovir



Adefovir dipivoxil

- Purine derivatives



ACYCLOVIR

9-[2-(hydroxyethoxy)methyl]-9H-guanine

• Acyclovir is a synthetic analog of deoxyguanosine in which the carbohydrate moiety is acyclic
• acyclovir possesses a unique mechanism of antiviral activity
• consists of three consecutive mechanisms

•MOA

- viral DNA polymerase is competitively inhibited by acyclovir triphosphate

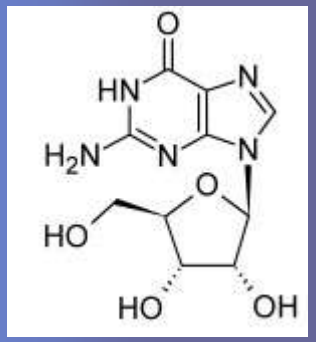
- Acyclovir triphosphate is incorporated into the viral DNA chain during DNA synthesis

- acyclovir triphosphate lacks the 3’-hydroxyl group of a cyclic sugar, it terminates further elongation of the DNA chain.

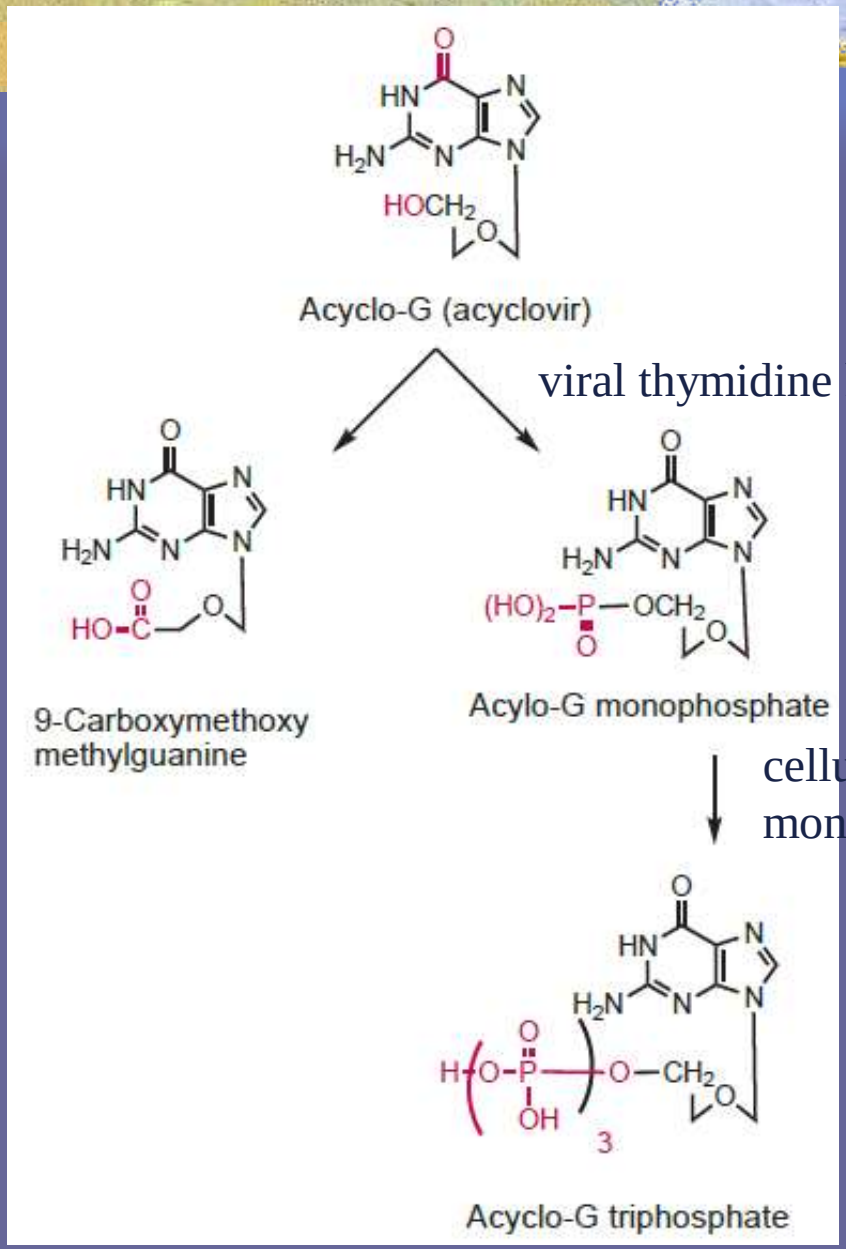
Clinical applications

for treatment of herpes zoster infection.

HSV-1 and HSV-2 infections in immunocompromised patients



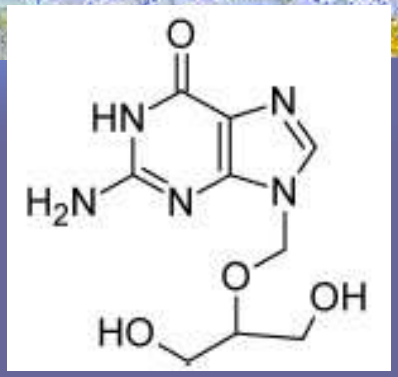
Guanosine



Metabolic reactions of acyclovir

- Purine derivatives

Ganciclovir



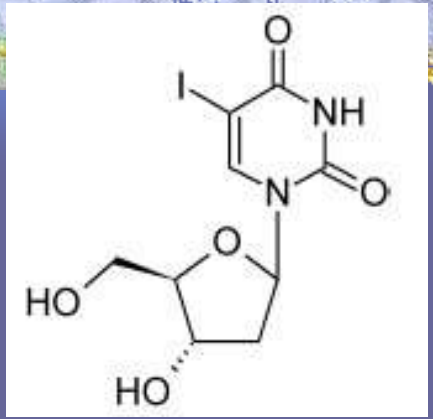
9-[(1,3-dihydroxy-2-propoxy) methyl]guanine)

- The mechanism of action is similar to that of acyclovir
- however, ganciclovir is more toxic to human cells than is acyclovir.
- It has greater activity than acyclovir against CMV and EBV infection in immunocompromised patients.
- It is also active against HSV infection

CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HSV, herpes simplex virus; VZV, varicella-zoster virus.

- Nucleoside analogs

Pyrimidine derivatives



5-iodo-2-deoxyuridine

•iodinated analog of thymidine that inhibits replication of several DNA viruses

• biotransformation to a triphosphate

• triphosphate is believed to be both a substrate and an inhibitor of viral DNA polymerase, causing inhibition of viral DNA synthesis

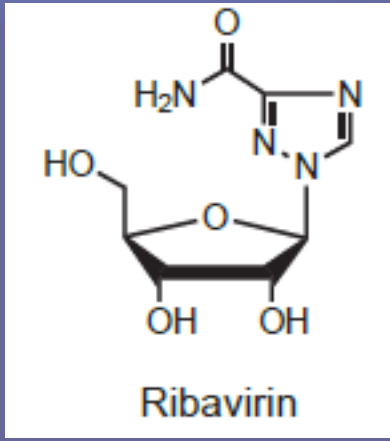
•Facilitating the synthesis of DNA that contains the iodinated pyrimidine.

•altered DNA is more susceptible to strand breakage and leads to faulty transcription

Idoxuridine is available as ophthalmic drops (0.1%) and ointment (0.5%) for the treatment of HSV keratoconjunctivitis

Ribavirin, a guanosine analog, has broad-spectrum antiviral activity against both DNA and RNA viruses

triphosphate, inhibts viral-specifi c RNA polymerase, disrupting messenger RNA and nucleic acid synthesis.

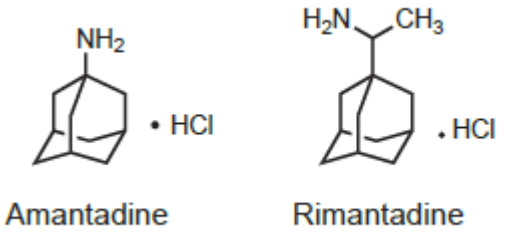


Ribavirin

Ribavirin is highly active against influenza A and B and the parainfl uenza group of viruses
genital herpes, herpes zoster, measles, and acute hepatitis types A, B, and C.

Aerosolized ribavirin has been approved by the FDA for the treatment of lower respiratory tract infections (bronchiolitis and pneumonia)

Agents Inhibiting Virus Attachment, Penetration, and Early Viral Replication



Amantadine

MECHANISM OF ACTION

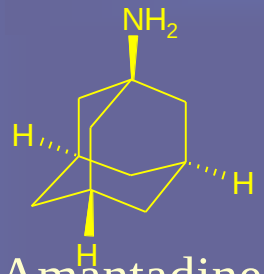
•inhibits penetration of RNA virus particles into the host cell

•It also inhibits the early stages of viral replication by blocking the uncoating of the viral genome.

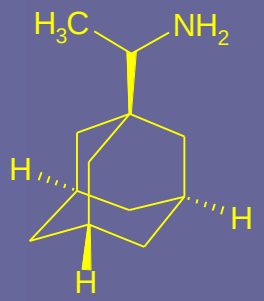
• inhibits viral replication by blocking the infl uenza A virus M2 proton-selective ion channel

CLINICAL APPLICATION Amantadine is clinically effective in preventing and treating all A strains of infl uenza, particularly A2 strains of Asian infl uenza virus and, to a lesser extent, German measles (rubella) or togavirus

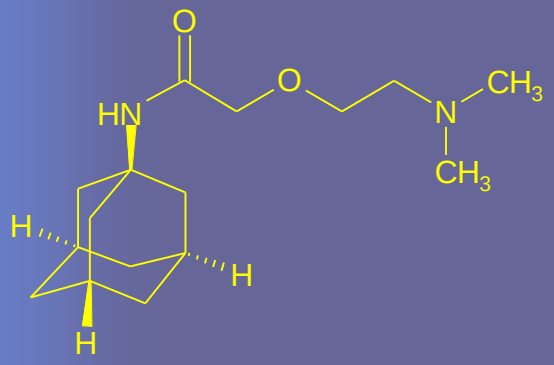
Adamantane amines



Amantadine



Rimantadine



Tromantadine

- SAR:
- N-alkyl and N,N-dialkyl derivatives of amantadine exhibit antiviral activity similar to that of amantadine .
- N-acyl derivatives show reduced antiviral activity except glycyl derivative and tromantadine possesses efficacy against clinical herpes labialis and herpes genitalis.
- Replacement of the amino group with a OH, SH, CN or halogen produced inactive compounds.
- Optical isomers and the racemic mixture of rimantadine are equally active.
- Adamantanespiro-3’-pyrrolidine derivative has greater activity than that of amantadine against influenza A_2 virus.

Amantadine

Mode of action

- Two mechanisms
- They inhibit an early step in viral replication, most likely viral uncoating, and
- In some strains they affect later step that probably involves viral assembly, possibly by interfering with hemagglutinin processing.

Uses

- Amantadine is used in treatment of parkinson's disease
- Inhibit replication if influenza type A virus at low concentrations
- Rimantadine is 4 to 10 times more active than amantadine.

Antiretroviral (Anti-HIV) Agents

Classification of Anti-Retroviral drugs (Anti-HIV drugs):

- The Anti-HIV drugs can be classified into

1. **Nucleoside reverse transcriptase inhibitors (NRTIs):** Zidovudine (AZT,ZDV), Stavudine (d4T), Lamivudine (3TC), Abacavir (ABC), Zalcitabine, Emtricitabine (FTC), Didanosine (ddI).

2. **Non nucleoside reverse transcriptase inhibitors (NNRTIs):** Efavirenz (EFV), Nevirapine (NVP), Delaviridine.

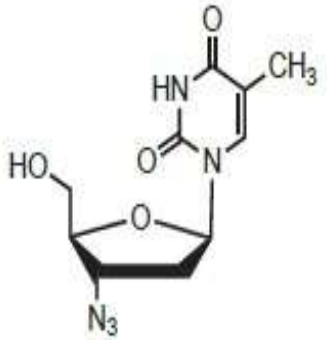
3. **Nucleotide reverse transcriptase inhibitors (NTRTIs):** Tenofovir (TDF)

4. **Protease inhibitors (PIs):** Saquinavir (SQV), Indinavir (IDV), Nelfinavir (NFV), Amprenavir, Fosamprenavir, Ritonavir (RTV), Lopinavir (LPV) , Atazanavir (ATV).

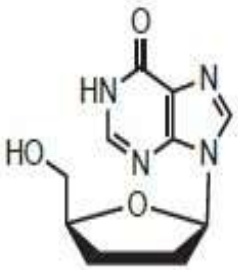
5. **Entry/Fusion inhibitors:** Enfuvirtide

Antiretroviral (Anti-HIV) Agents

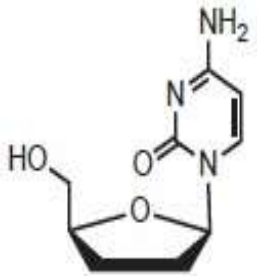
Nucleoside Reverse Transcriptase Inhibitors



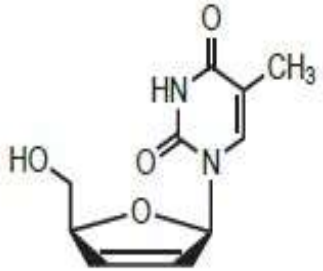
Zidovudine(AZT)



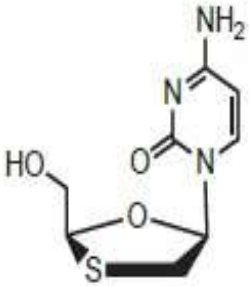
Didanosine(ddI)



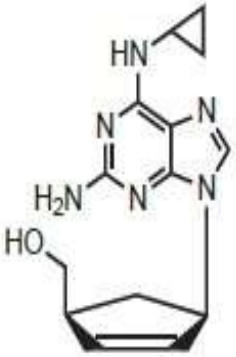
Zalcitabine
(2',3'-Dideoxycytidine, ddC)



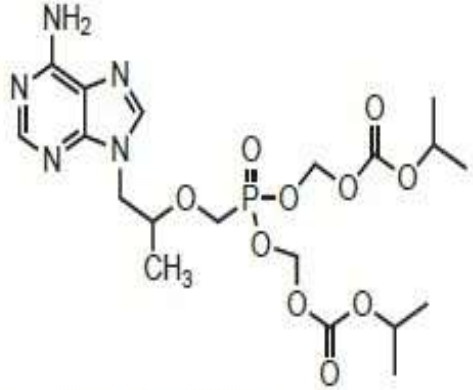
Stavudine
(2',3'-Dideoxy-2',3'-didehydro-thymidine, D4T)



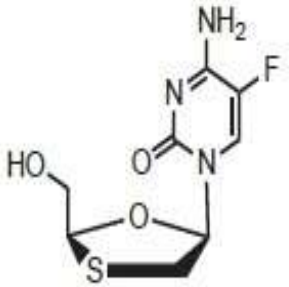
Lamivudine
(2'-Deoxy-3'-thiacytidine, 3TC)



Abacavir (ABC)



Tenofovir disoproxil

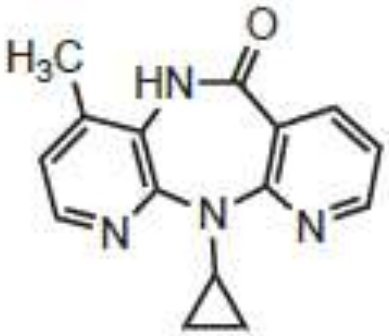


Emtricitabine

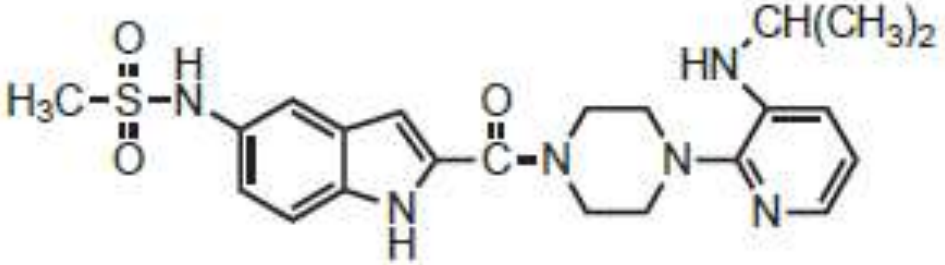
MOA Zidovudine

- ZDV-triphosphate get incorporated into proviral DNA by RT
- This process results in termination of DNA chain elongation due to the presence of an azido group in ZDV.
- The multiplication of HIV is halted by selective inhibition of RT

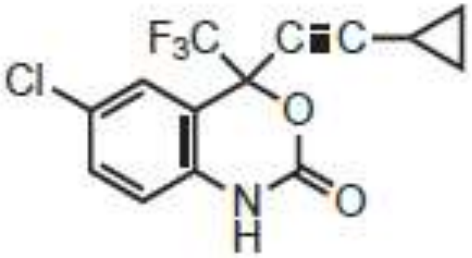
Nonnucleoside Reverse Transcriptase Inhibitors



Nevirapine

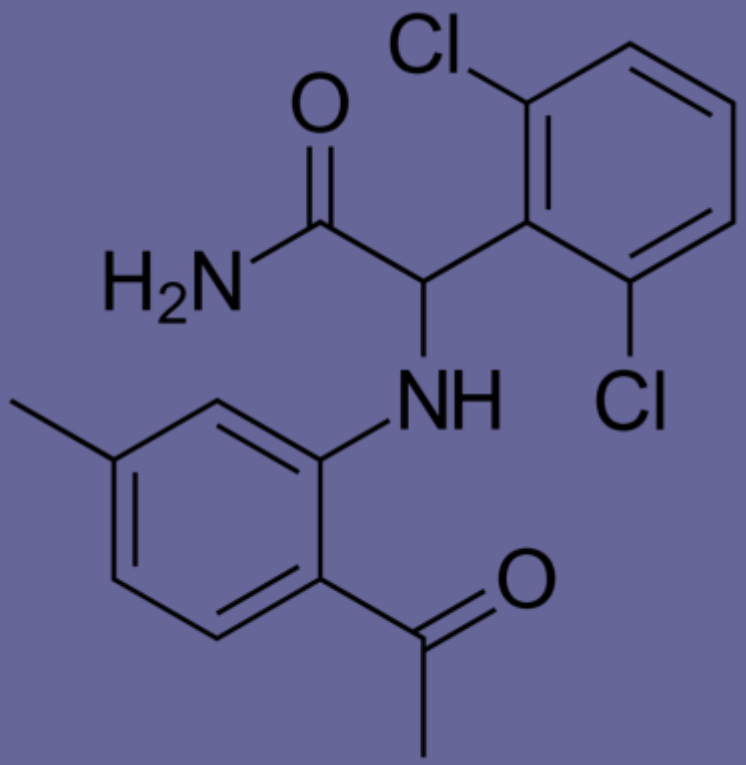


Delavirdine



Efavirenz

Loviride



Nonnucleoside Reverse Transcriptase Inhibitors (NNRTI)

MOA NNRTIs

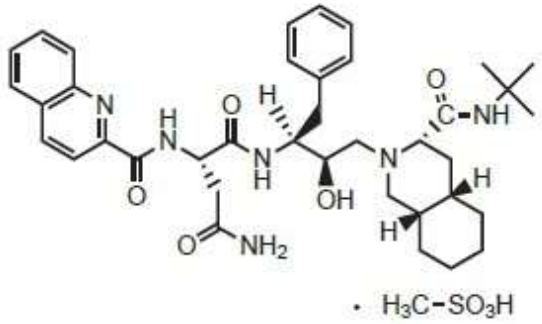
•Unlike the nucleoside antimetabolites, the NNRTIs do not require bioactivation by kinases to yield phosphate esters. \

•They are not incorporated into the growing DNA chain.
Instead, they bind to an allosteric site that is distinct from the substrate (nucleoside triphosphate)-binding site of RT.

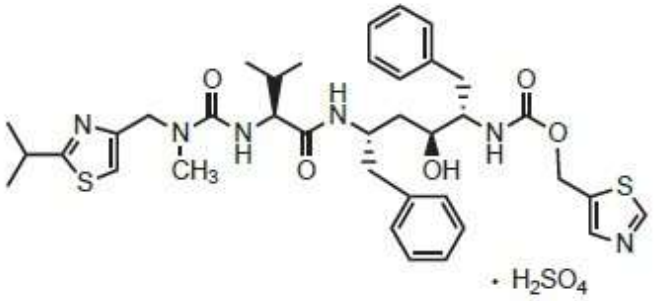
•Such binding distorts the enzyme, so that it cannot form the enzyme–substrate complex

HIV Protease Inhibitors

Protease inhibitors are synthetic drugs that inhibit the action of HIV-1 **protease**, an enzyme that cleaves two precursor proteins into smaller fragments. These fragments are needed for viral growth, infectivity and replication.



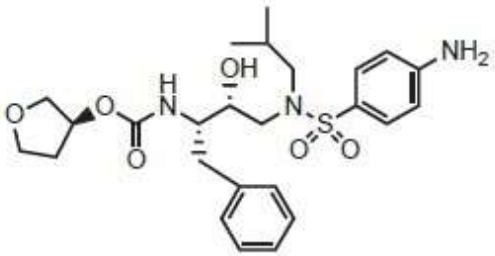
Saquinavir



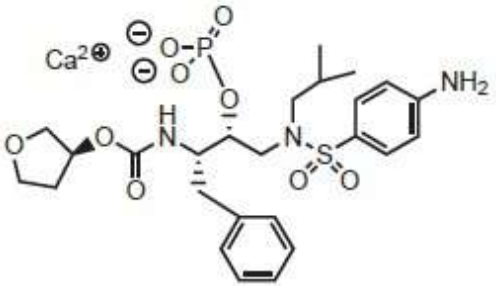
Ritonavir

Indinavir

Nelfinavir

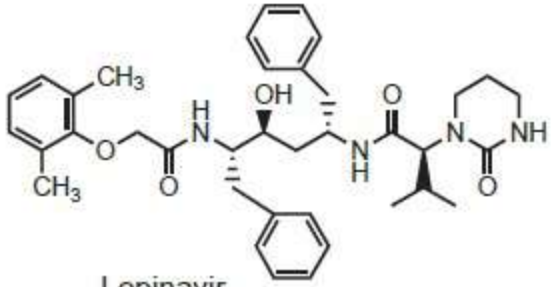


Amprenavir

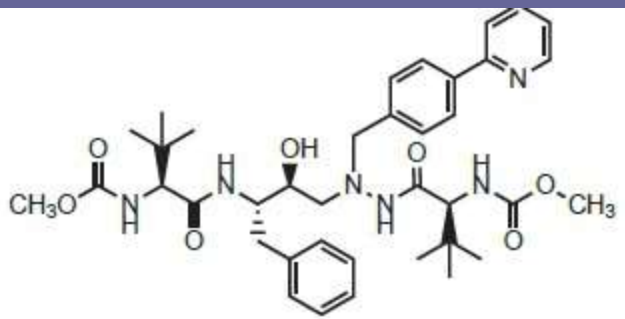


Fosamprenavir calcium

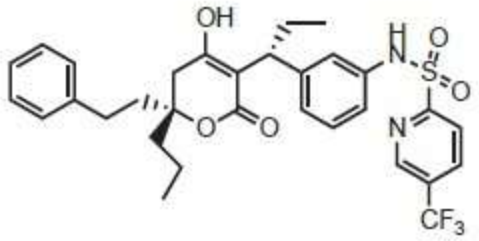
HIV Protease Inhibitors



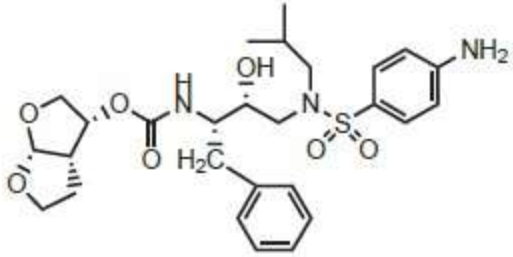
Lopinavir



Atazanavir

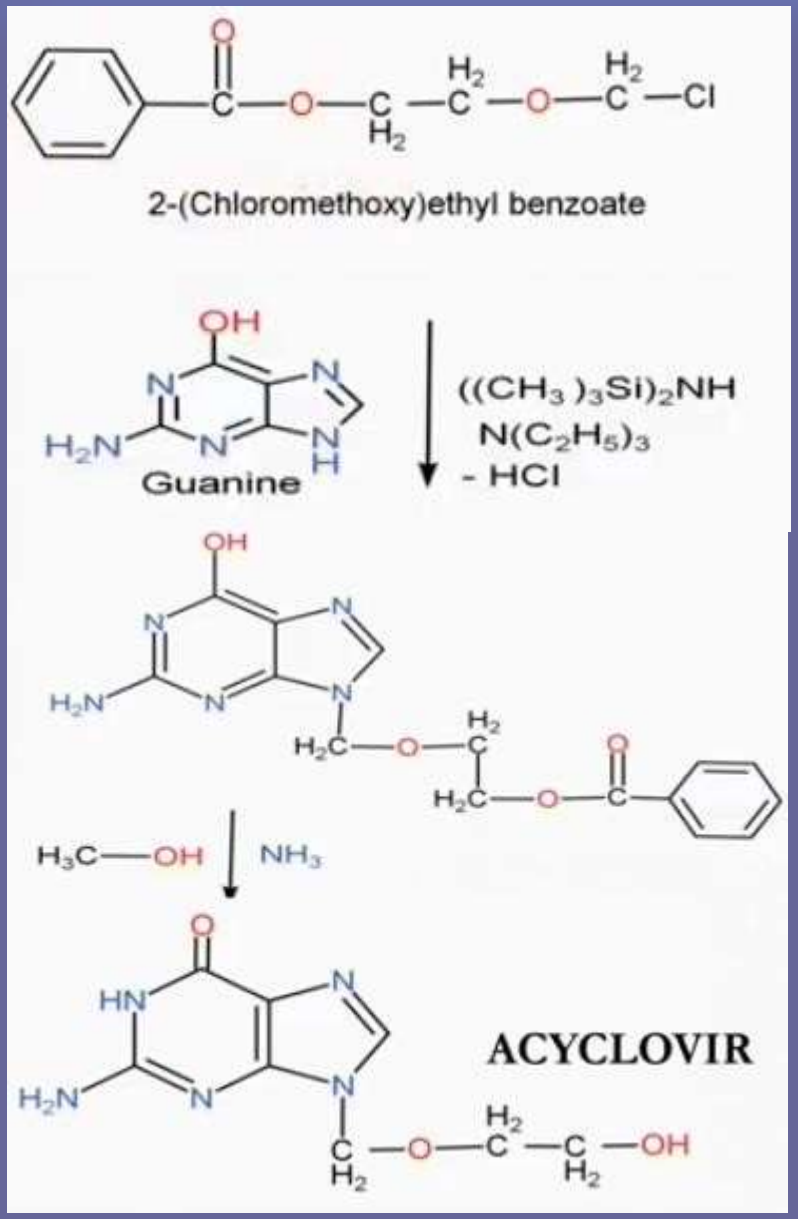


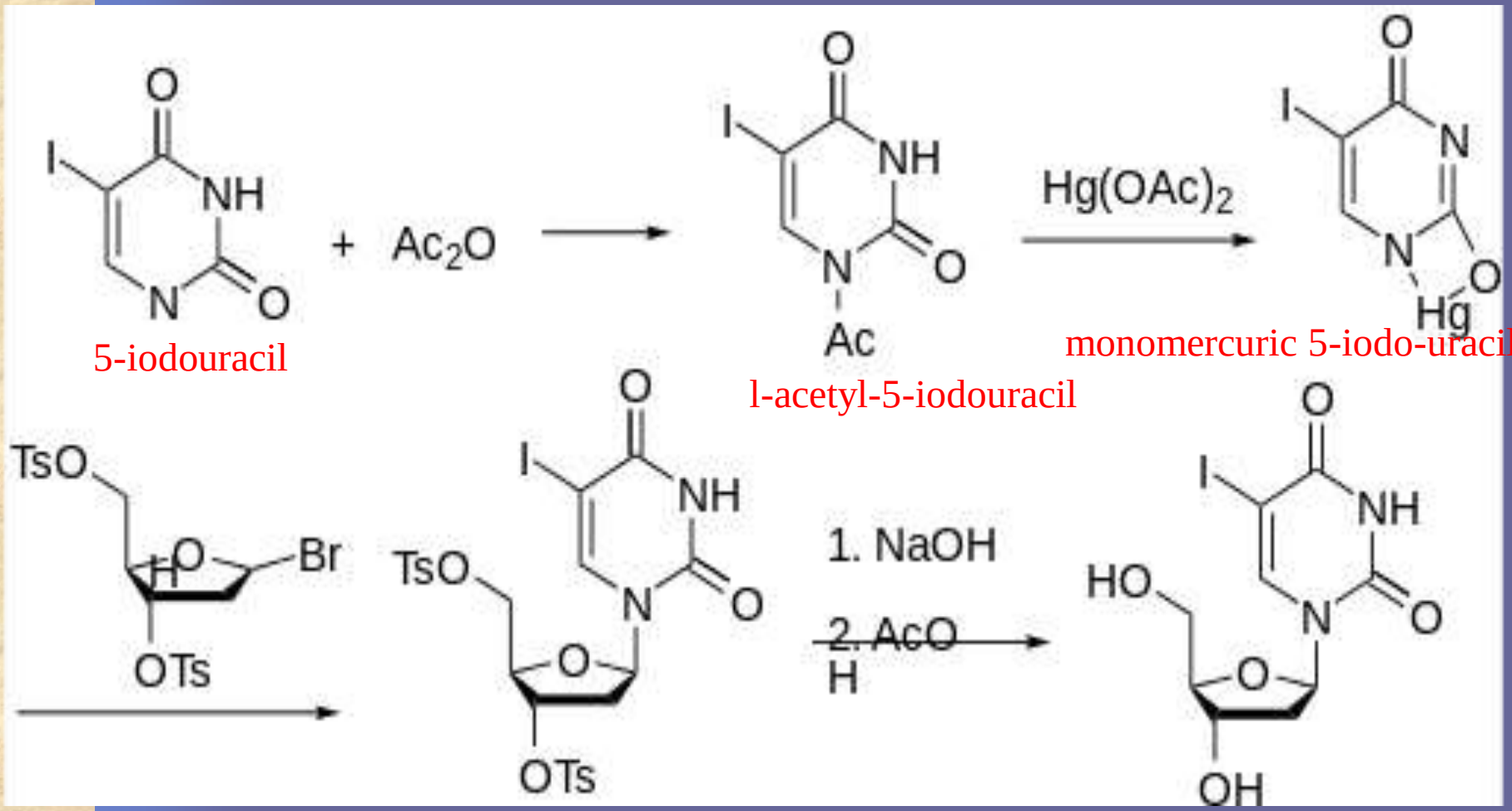
Tipranavir



Darunavir

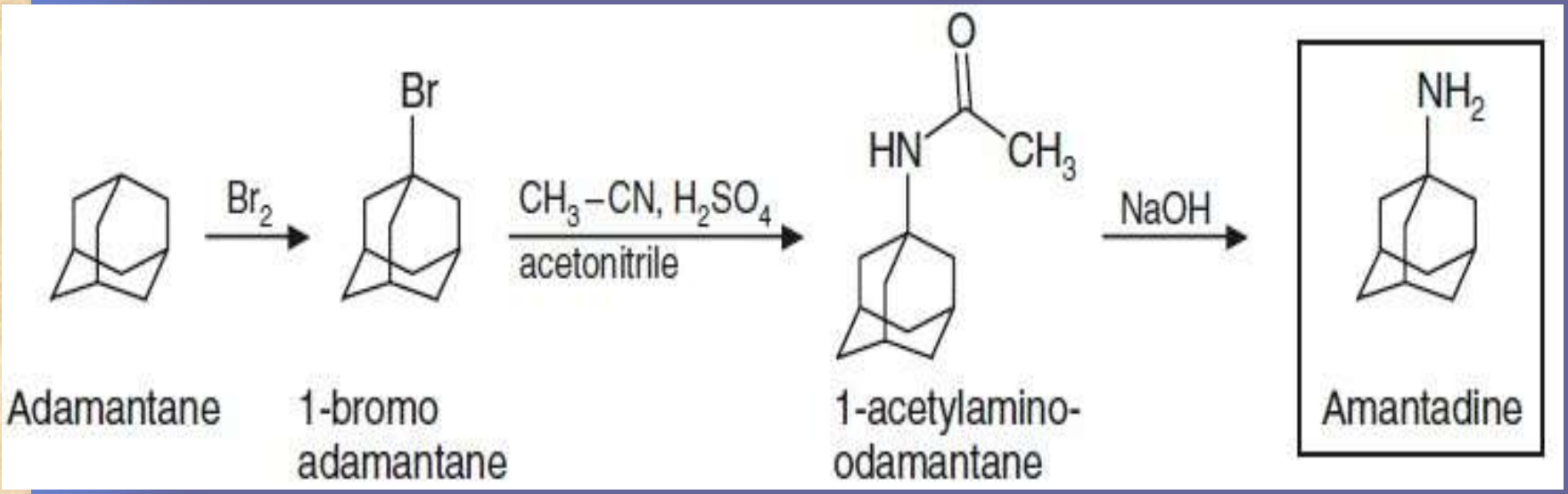
Synthesis of Acyclovir





3,5-di-p-toluylribofuranosyl bromide

Idoxuridine


Br
Br_2
CH_3-CN, H_2SO_4
acetonitrile
O
HN
CH_3
NaOH
NH_2
Adamantane
1-bromo adamantane
1-acetylamino-odamantane
Amantadine

Combination Antiviral Therapy

Combination antiviral therapy, in which a mixture of drugs possessing different mechanisms of action, has been shown to be advantageous for several reasons.

The antiviral effect of the combination is excellent, toxicities are decreased, and resistance to any drug in the combination is slow to develop.

Resistance to single drugs such as amantadine, ganciclovir, and acyclovir is problematic.

Administration of a given agent in combination with other types of drugs retards the development of such resistance.

Combination treatment is especially important in antiretroviral therapy.

Typical antiretroviral therapy, as exemplified by HIV treatment, includes combinations of NRTI or NNRTI along with PIs. The key that makes the combination work is that the drugs act to inhibit HIV virus replication at different stages of the viral infective cycle.
The RT inhibitors (NRTIs or NNRTIs) prevent RNA formation or viral protein synthesis or inactivate the catalytic site of RT (NNRTIs).
The PIs act once the provirus integrates into the host's genes.
Protease is necessary to split viral precursor polypeptides into new virus.

The combination of RTs and PIs is synergistic.

There are many two- and three-drug combinations that have been reported to be useful in various viral infections.

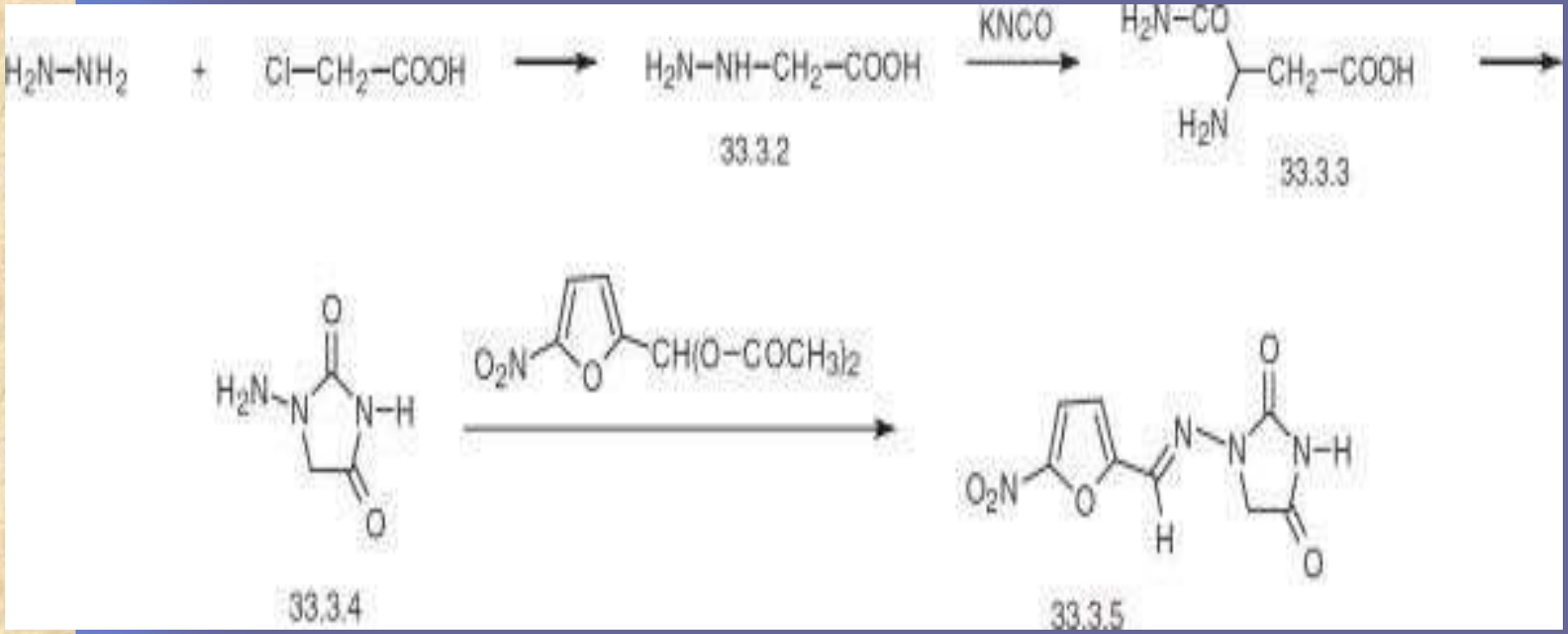
- **WHEN TO START:**
- All adolescents and adults including pregnant women with HIV infection and CD4 counts of ≤350 cells/mm3, should start ART, regardless of the presence or absence of clinical symptoms.

- Those with severe or advanced clinical disease (WHO clinical stage 3 or 4) should start ART irrespective of their CD4 cell count

- **WHAT TO START:**
- **First-line therapy should consist of**
- NNRTI(1) + NRTIs (2), one of which should be zidovudine (AZT) or tenofovir (TDF).
- Take steps to progressively reduce the use of stavudine (d4T) in first-line regimens because of its well-recognized toxicities.
- **Second-line ART should consist of**
- A Ritonavir-boosted PI + NRTIs (2), one of which should be AZT or TDF, based on what was used in first-line therapy.
- Ritonavir-boosted atazanavir (ATV/r) or lopinavir/ritonavir (LPV/r) are the preferred PIs.

Nitrofurantoin synthesis

1-(5-nitrofurfurylidenamino)hydantoin (33.3.5), is synthesized from hydrazinoacetic acid (33.3.2), which is synthesized by reacting chloroacetic acidwith hydrazine. Reacting hydrazinoacetic acid with potassium cyanate gives the semicarbazidoacetic acid (33.3.3), which upon heating cyclizes into 1-aminoidantoin (33.3.4). Reacting this with diacetylacetal of 5-nitrofurfurol gives the desired



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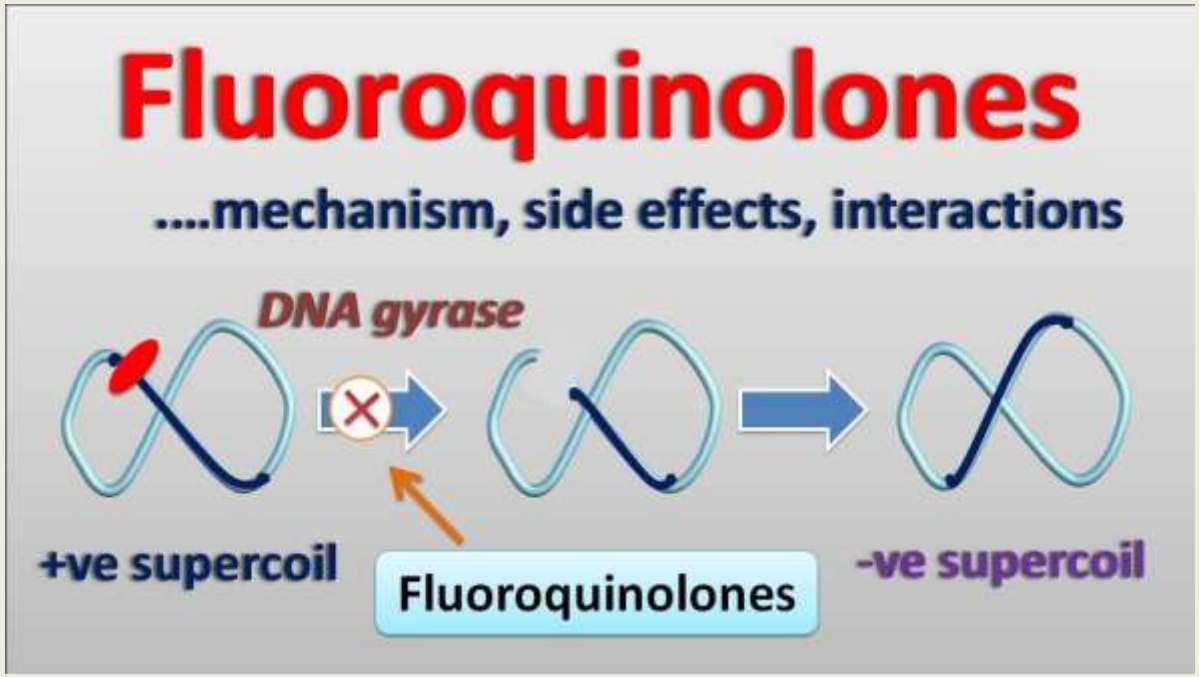
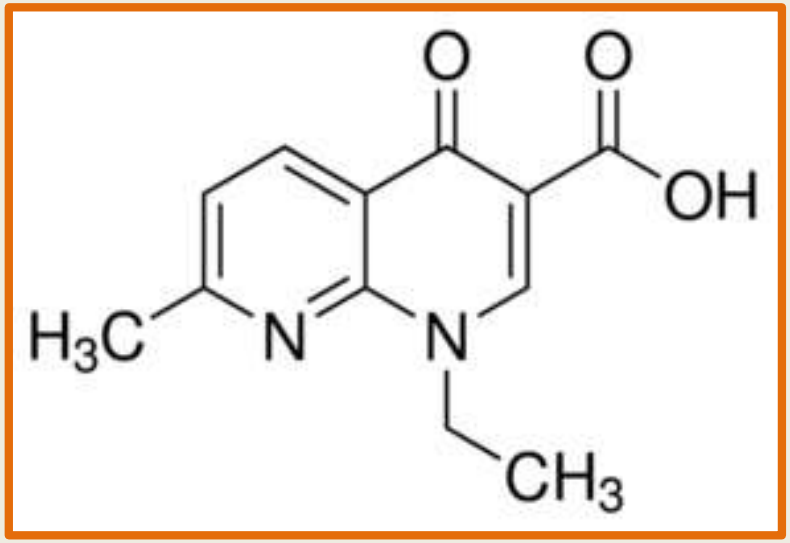
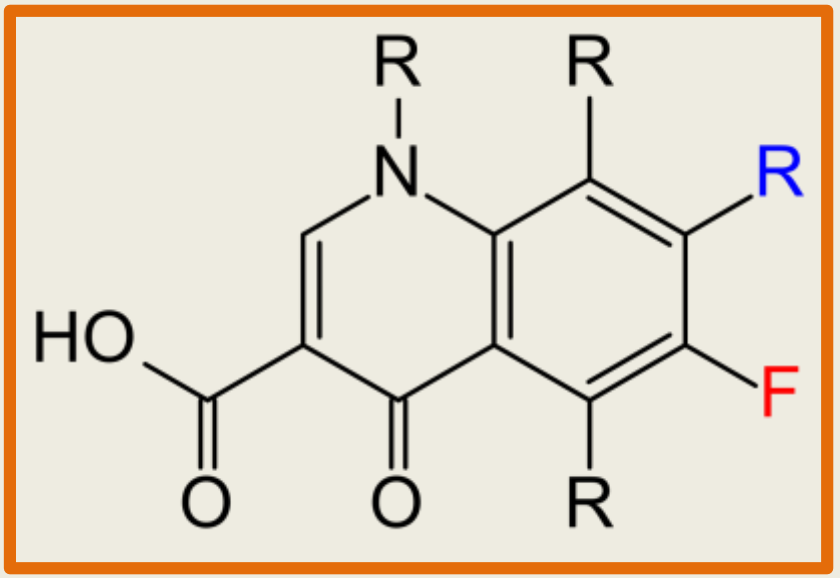


Ms. Rina P. Patil
Assistant Professsor
M Pharm
Department of Pharmaceutical Chemistry

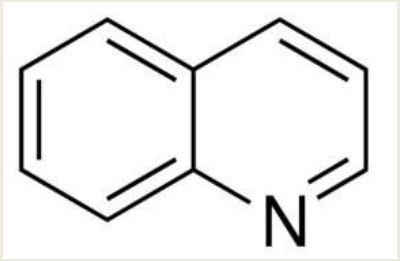
Quinolone Antibacterials



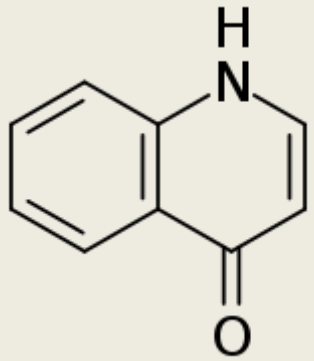
Nalidixic acid



4-Fluoroquinolones



Quinoline



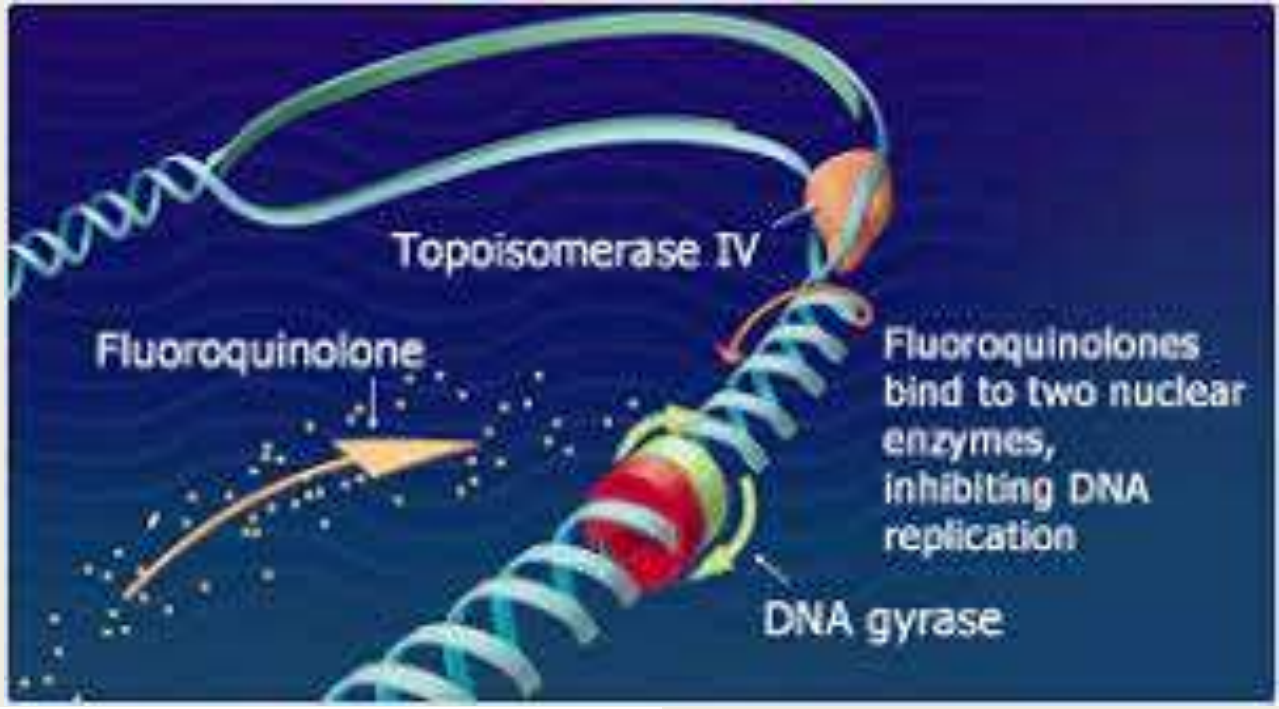
Qiunolone

- **Quinolones** are synthetic antibacterial agents that are highly effective in the treatment of many types of infectious diseases.

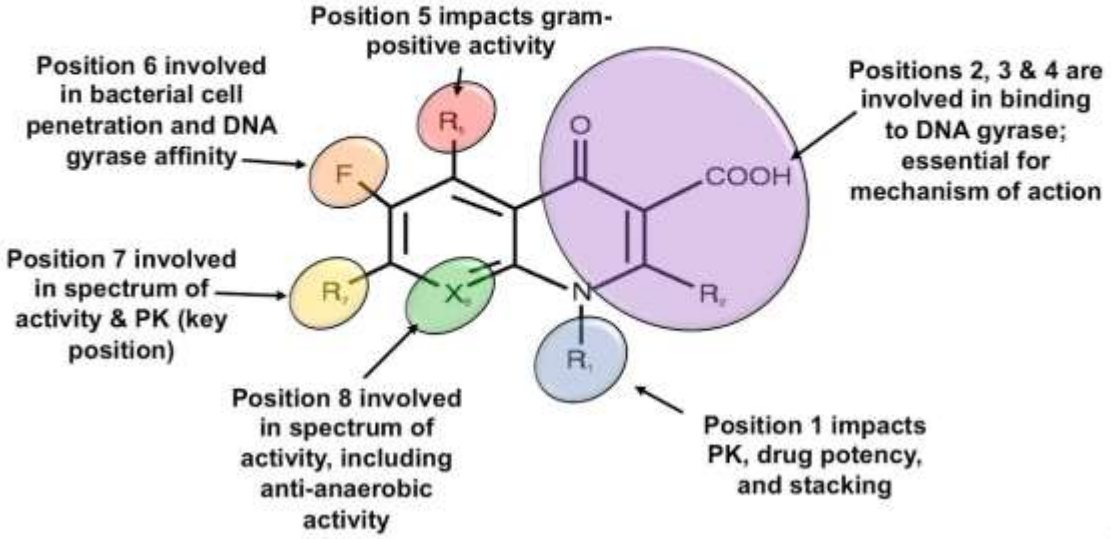
- First quinolone antibacterial, **nalidixic acid**, a **naphthyridine derivative** introduced for the treatment of urinary tract infections in 1963.

- Modern generation of fluoroquinolones (containing C-6 Fluoro substituent and cyclic basic amine moiety at C-7) are more potent and having broad spectrum of activity.

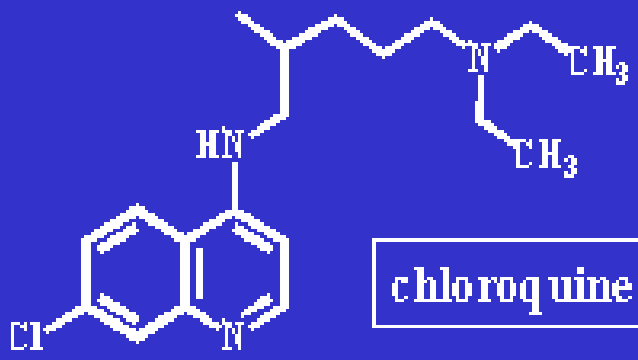
- They are used against a variety of gram negative as well as gram positive pathogens.



FQ Structure-Activity Relationship



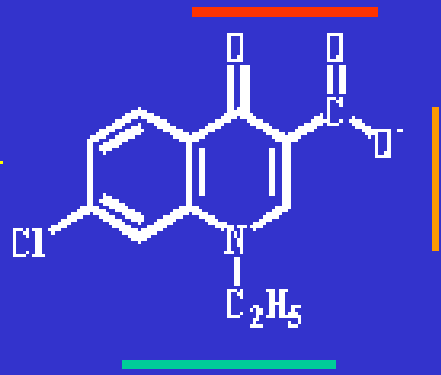
From chloroquine to nalidixic acid...



chloroquine

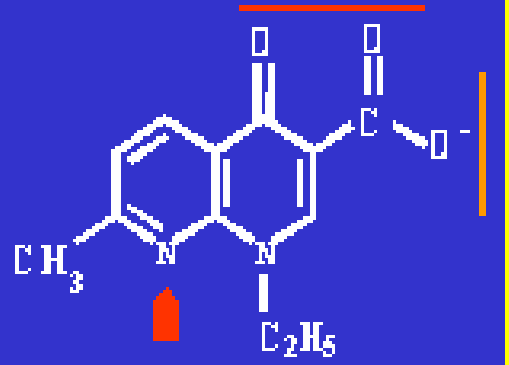
1939

1958



7-chloroquinoline
(synthesis intermediate found to display antibacterial activity)

nalidixic acid



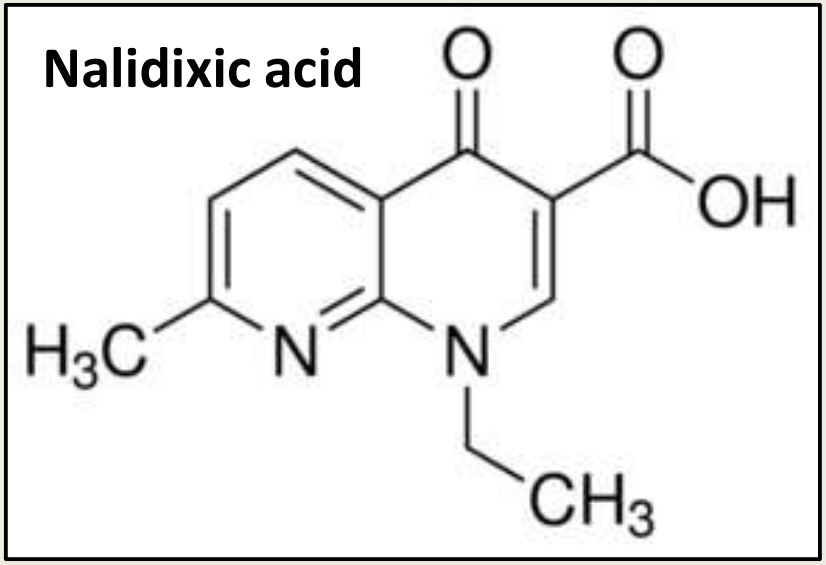
1962

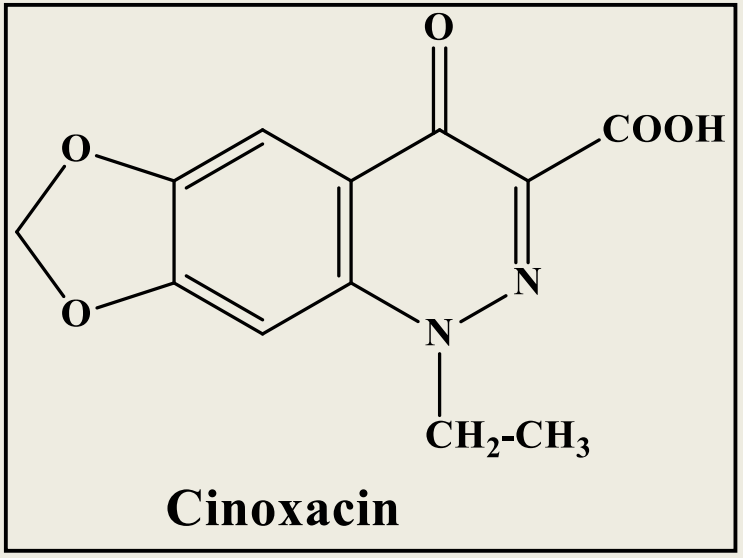
Classification of Quinolone antibacterials

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.

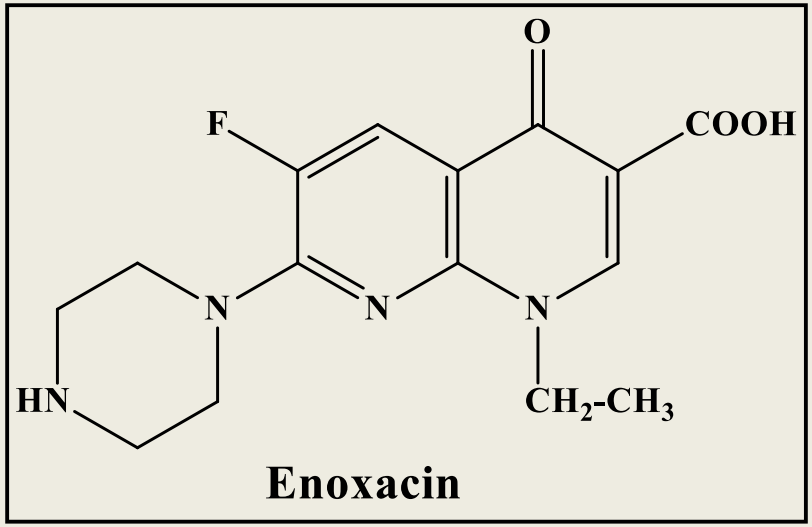
Classification of Quinolones

I) First generation

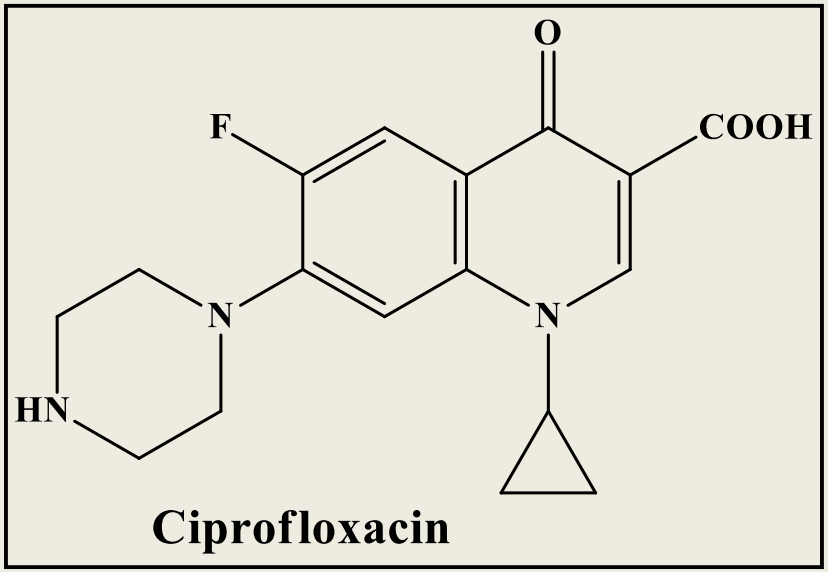




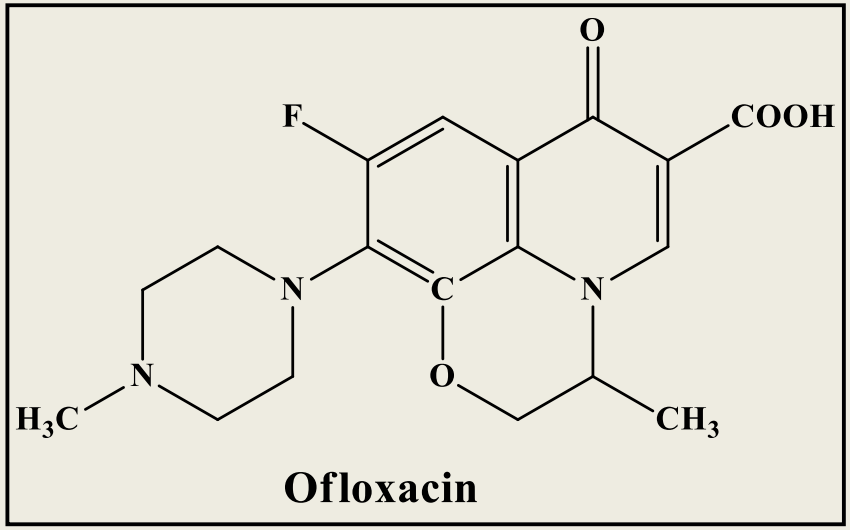
II) Second generation



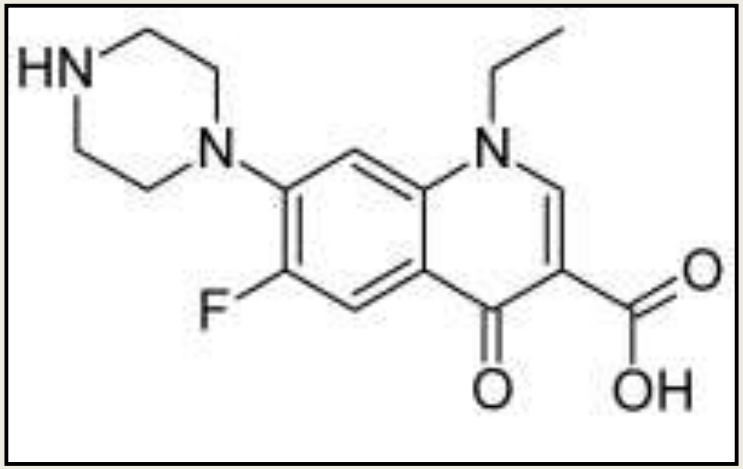
Enoxacin



Ciprofloxacin

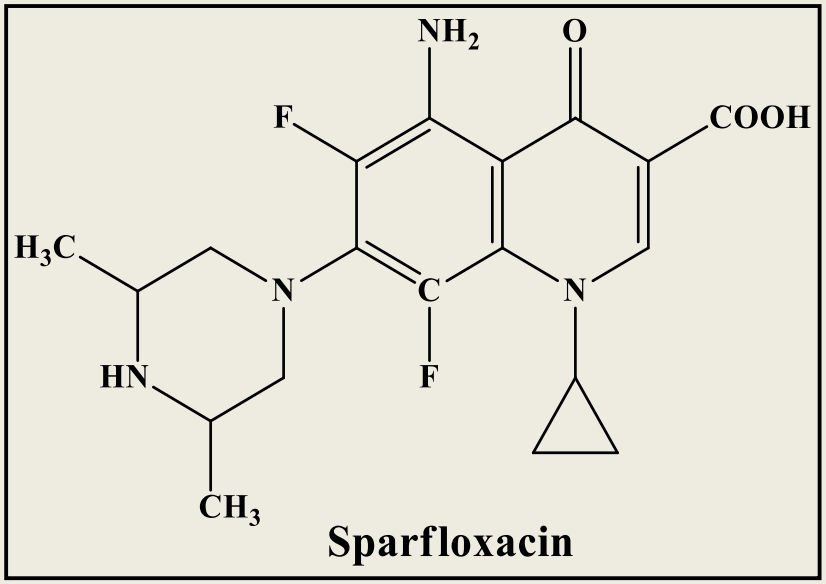


Ofloxacin



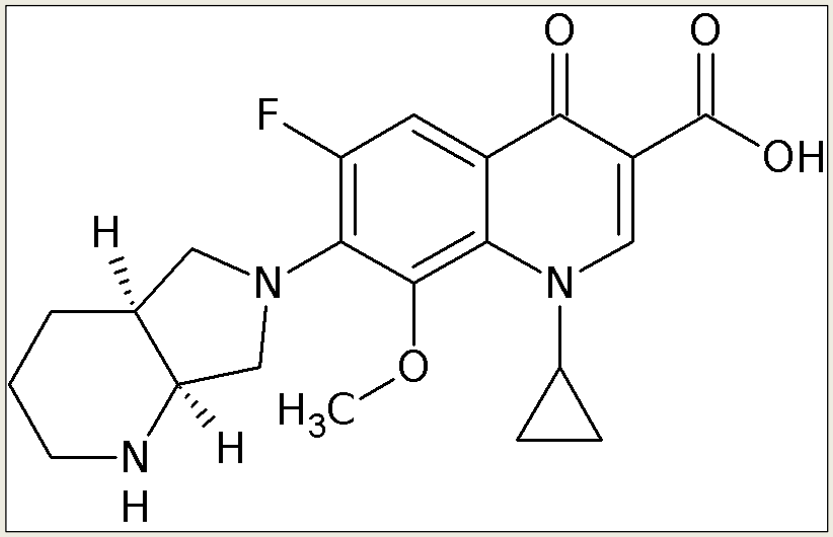
Norfloxacin

III) Third generation

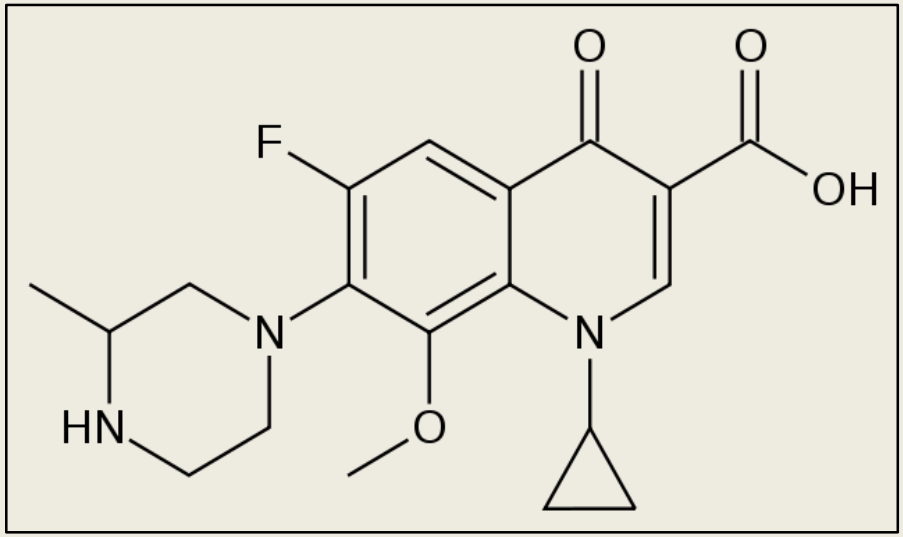


Sparfloxacin

IV) Fourth generation



Moxifloxacin

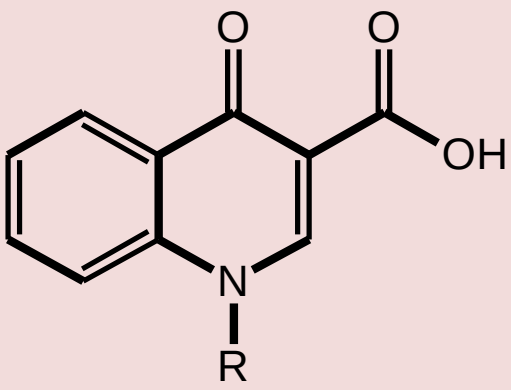


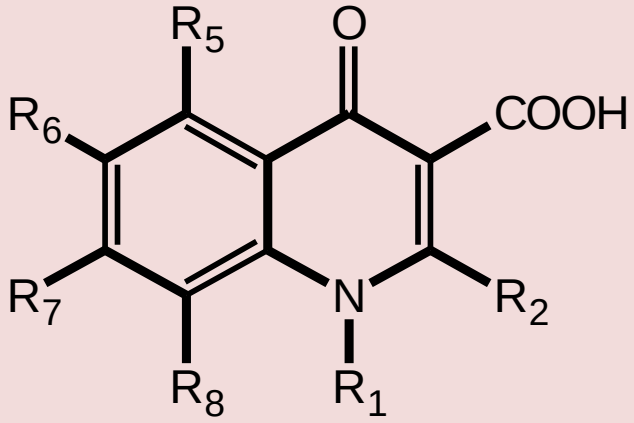
Gatifloxacin

SAR of Quinolones

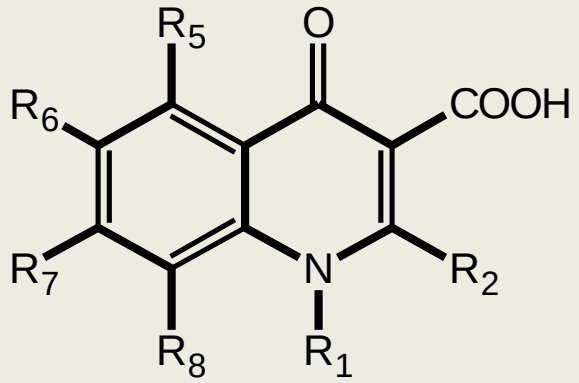
1) Studies have shown that the **1,4-dihydro-4-oxo-3-pyridinecarboxylic acid** moiety is essential for antibacterial activity.

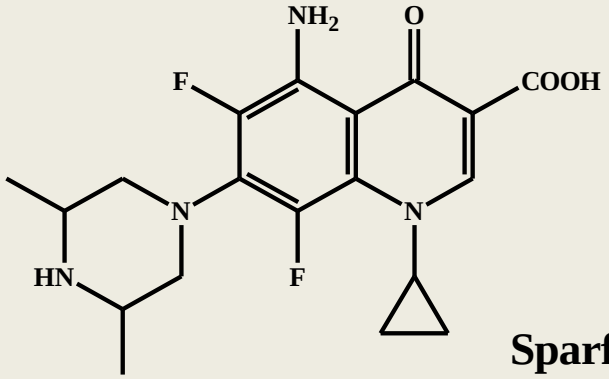
- The **pyridone system** must be annulated with an aromatic ring





2) Isosteric replacements of nitrogen for carbon atoms at positions 2 (cinnolines), 5 (1,5-napthyridines), 6 (1,6-naphthyridines), and 8 (1,8-naphthyridines) leads to retention of antibacterial activity.

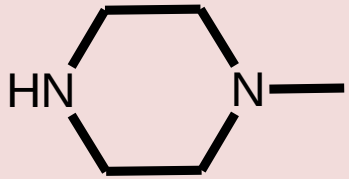




Sparfloxacin

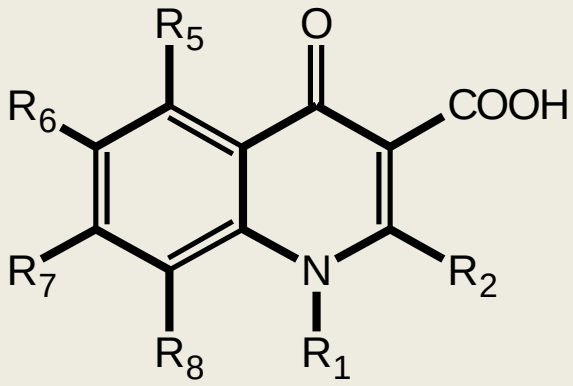
3) Introduction of substituents at position **2** greatly reduces or abolishes activity

- But substitution at positions **5, 6, 7** (especially), and **8** of the annulated ring produce good effects.
- For e.g., **piperazinyl and 3-aminopyrrolidinyl** substitutions at position 7, enhanced activity against *P. aeruginosa.*



- Amino group at C-5 position increases the activity

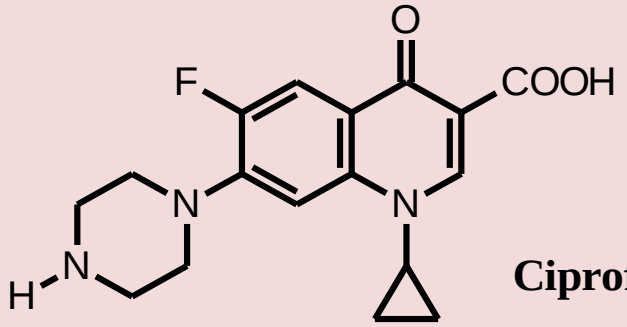
4) Fluorine *atom substitution at* position **6** is also associated with significantly enhanced antibacterial activity.



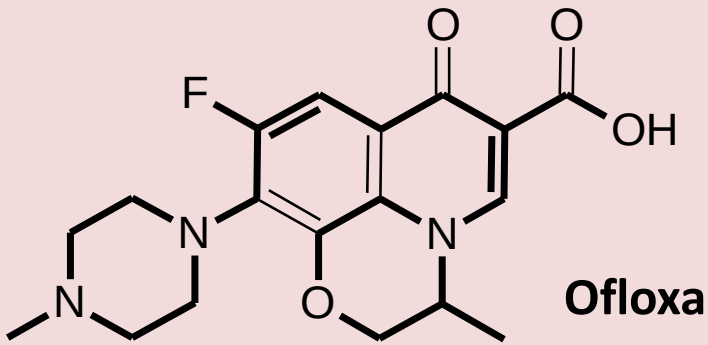
5) Alkyl substitution at the 1-position is essential for activity

- Lower alkyl (methyl, ethyl, cyclopropyl) compounds generally having greater potency.
- Aryl substitution at the 1-position is also consistent with antibacterial activity

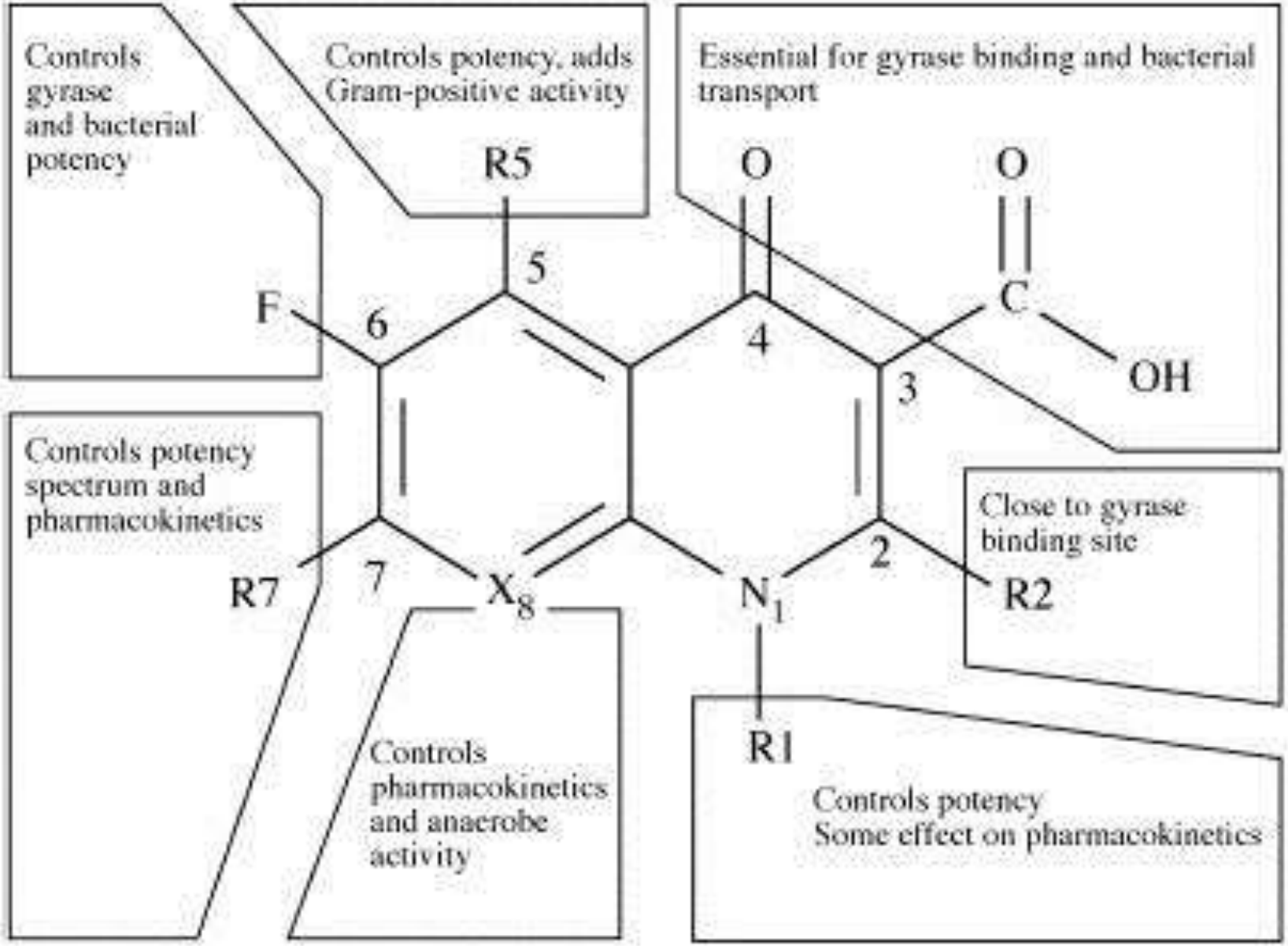
6) Ring condensations at the 1,8-, 5,6-, 6,7-, and 7,8-positions also lead to active compounds



Ciprofloxacin



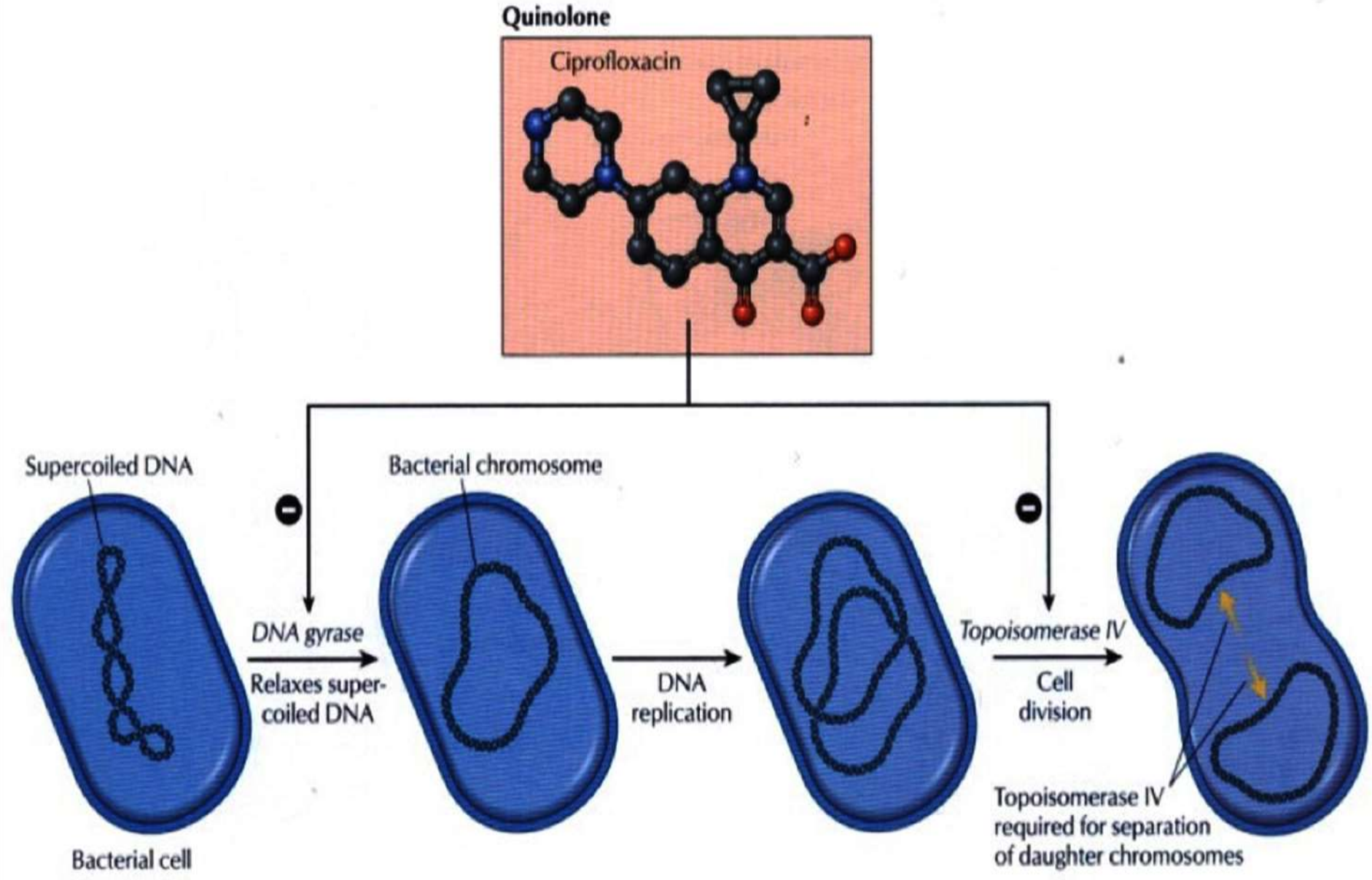
Ofloxacin


Controls gyrase and bacterial potency
Controls potency, adds Gram-positive activity
Essential for gyrase binding and bacterial transport
R5
O
O
5
F
6
4
C
OH
3
Controls potency spectrum and pharmacokinetics
Close to gyrase binding site
2
R7
7
X8
N1
R2
R1
Controls pharmacokinetics and anaerobe activity
Controls potency
Some effect on pharmacokinetics

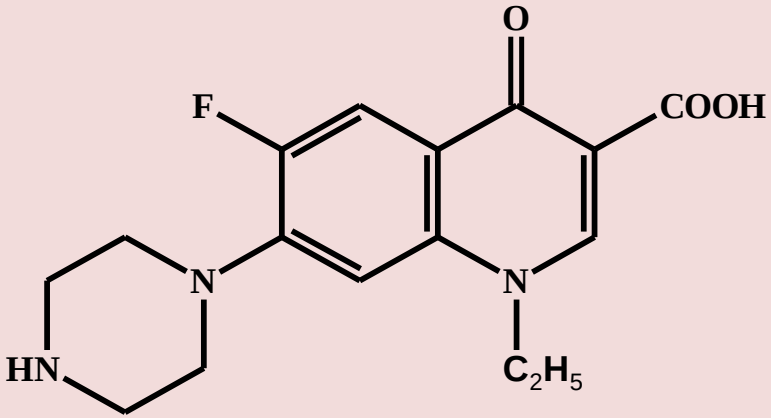
Mechanism of action

- The antibacterial action of quinolones result from the inhibition of DNA synthesis.
- This effect is caused by the inhibition of bacterial DNA gyrase (topoisomerase II), an enzyme responsible for introducing negative supercoils into circular duplex DNA
- The FQs inhibit the enzyme *bacterial DNA gyrase* (primarily active in gram negative bacteria), which nicks double stranded DNA, introduces negative supercoils and then reseals the nicked ends.
- This is necessary to prevent excessive positive supercoiling of the strands when they separate to permit replication or transcription.
- 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.
- 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.
- The bactericidal action probably results from digestion of DNA by exonucleases whose production is signalled by the damaged DNA.
- 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.


Quinolone
Ciprofloxacin
Supercoiled DNA
Bacterial chromosome
DNA gyrase
Relaxes super-coiled DNA
DNA replication
Topoisomerase IV
Cell division
Bacterial cell
Topoisomerase IV required for separation of daughter chromosomes

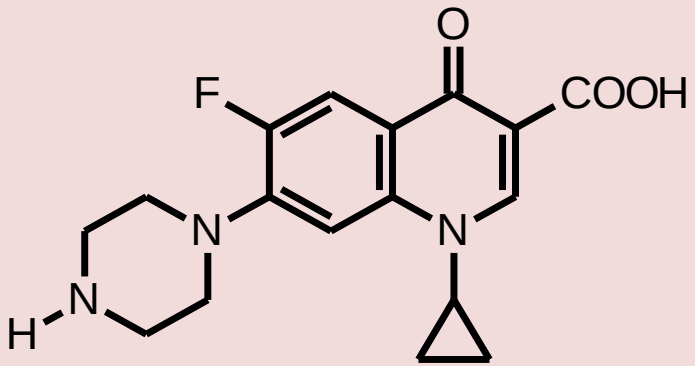
Norfloxacin



1-Ethyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinolinecarboxylic acid

- It has broad-spectrum activity against Gram-negative and Gram-positive aerobic bacteria.
- The **fluorine** atom provides increased potency against Gram-positive organisms, whereas the **piperazine** moiety improves antipseudomonal activity.
- **Norfloxacin is indicated for the treatment of urinary tract infections** caused by *E. coli, K. pneumoniae, Enterobacter cloacae, Proteus mirabilis etc.*

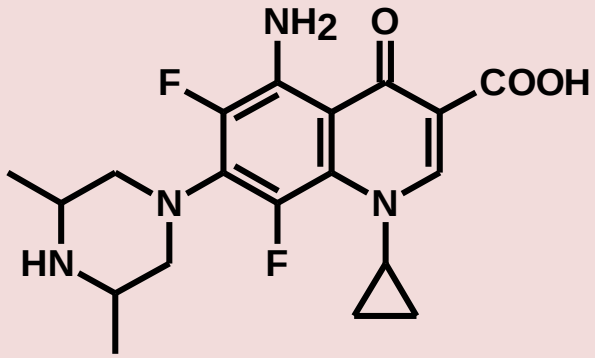
Ciprofloxacin



1-Cyclopropyl-6-fluoro-1,4-dihydro-4-oxo-7-(1-piperazinyl)-3-quinoline Carboxylic acid

- It is an agent of choice for the treatment of **bacterial gastroenteritis** caused by Gram-negative bacilli such as enteropathogenic *E. coli, Salmonella spp. etc*
- It is widely used for the treatment of respiratory tract infections and is particularly effective for controlling bronchitis and pneumonia caused by Gram-negative bacteria.
- It is also used for combating infections of the skin, soft tissues, bones, and joints.
- **It is widely distributed to virtually all parts of the body, including the CSF**
- Ciprofloxacin exhibits higher potency against most Gram-negative bacterial species, including ***P. aeruginosa,*** than other quinolones

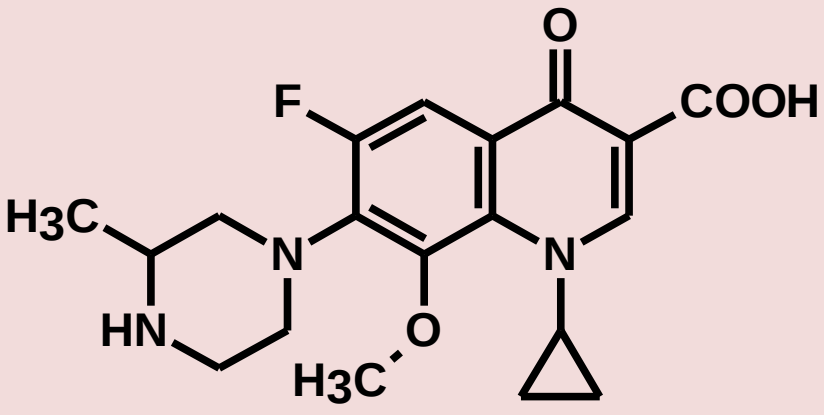
Sparfloxacin



5-amino-1-cyclopropyl-7-(3,5-dimethyl)-1-piperazinyl)-6,8-difluoro-1,4-dihydro - 4-oxo-3-quinolinecarboxylic acid

- It exhibits higher potency against Gram positive bacteria, especially staphylococci and streptococci & its activity against Gram-negative bacteria is also very impressive.
- It is also more active against chlamydia and the anaerobe *Bacteroides fragilis*
- Used in the treatment of skin and soft tissue infections, lower respiratory infections, and pelvic inflammatory disease caused by gonorrhea and chlamydia.
- Sparfloxacin has also recommended for the treatment of bacterial gastroenteritis and cholecystitis (gallbladder inflammation).

Gatifloxacin



Properties of Quinolones / OR Toxicities due to quinolones

- **CNS effects**

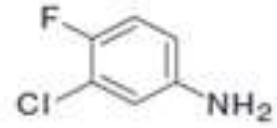
  (irritability, tremors, sleep disorders, vertigo, anxiety, agitations, convulsions)

- **Phototoxicity**

- **Chelating Properties**

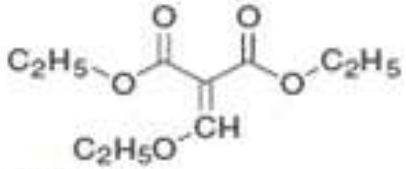
Therapeutic applications

Drugs	Therapeutic Applications
Nalidixic acid Cinoxacin	Uncomplicated urinary tract infections
Norfloxacin	Urinary tract infections, Prostatitis, Gonorrhea
Ciprofloxacin	Upper respiratory tract infections, bone infections, septicemia, staphylococcal and pseudomonal endocarditis, meningitis, and anthrax infections
Levofloxacin, Gatifloxacin, Gemifloxacin	Chronic bronchitis and community-acquired pneumonia
Moxifloxacin	Second-line agents for tuberculosis

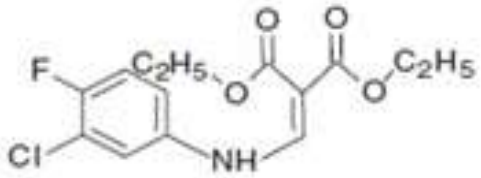


3-chloro-4-fluoroaniline

+

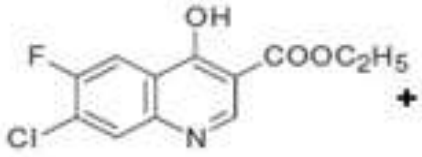


ethyl ethoxymethylenmalonate



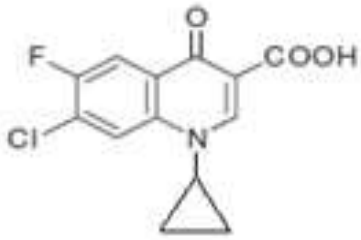
substitution product

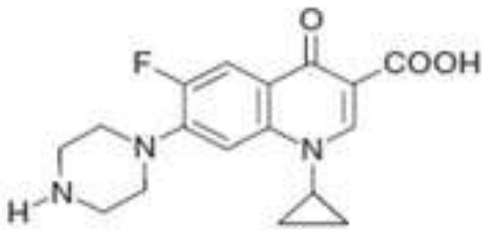
Diphenyl ether



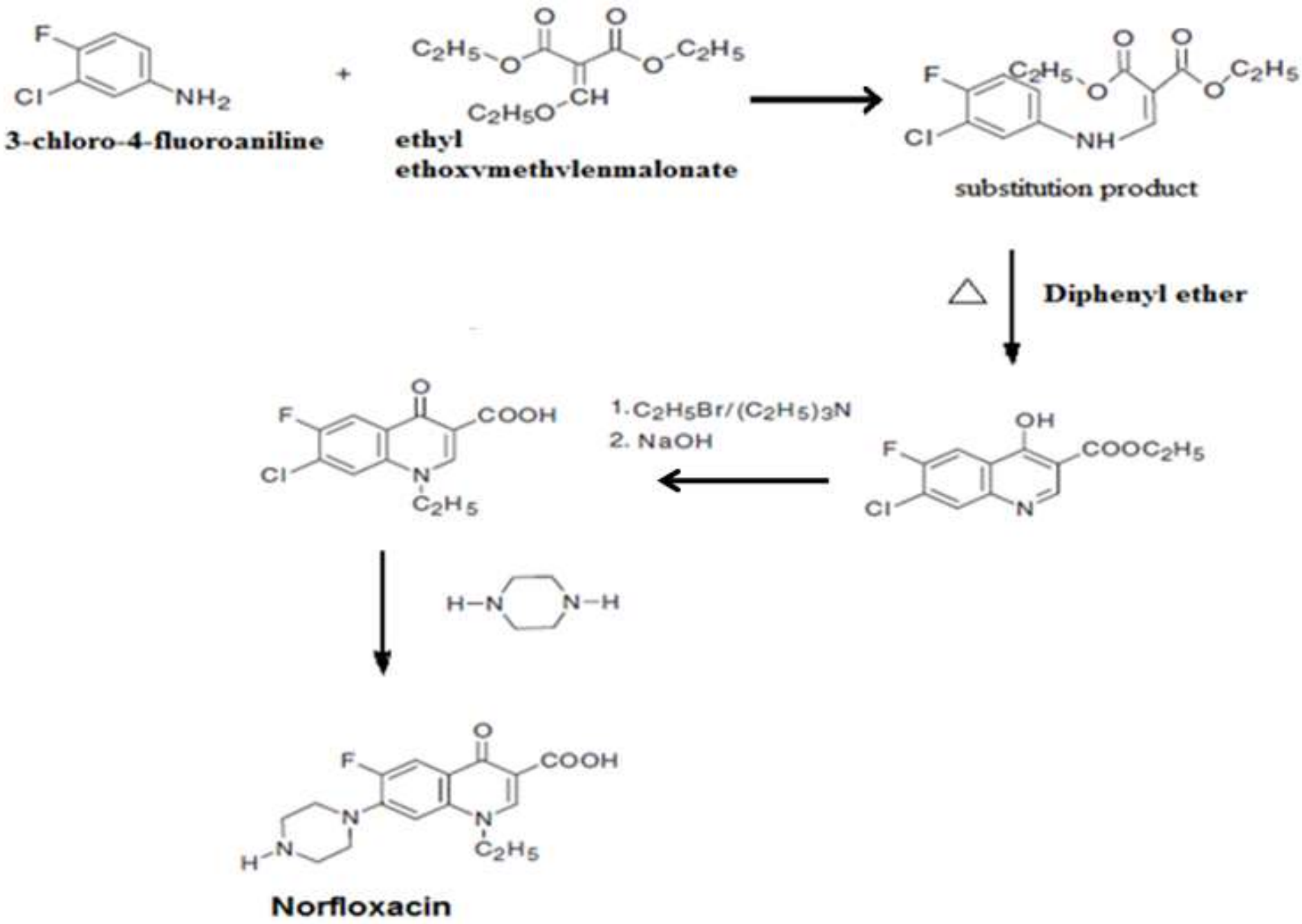
+

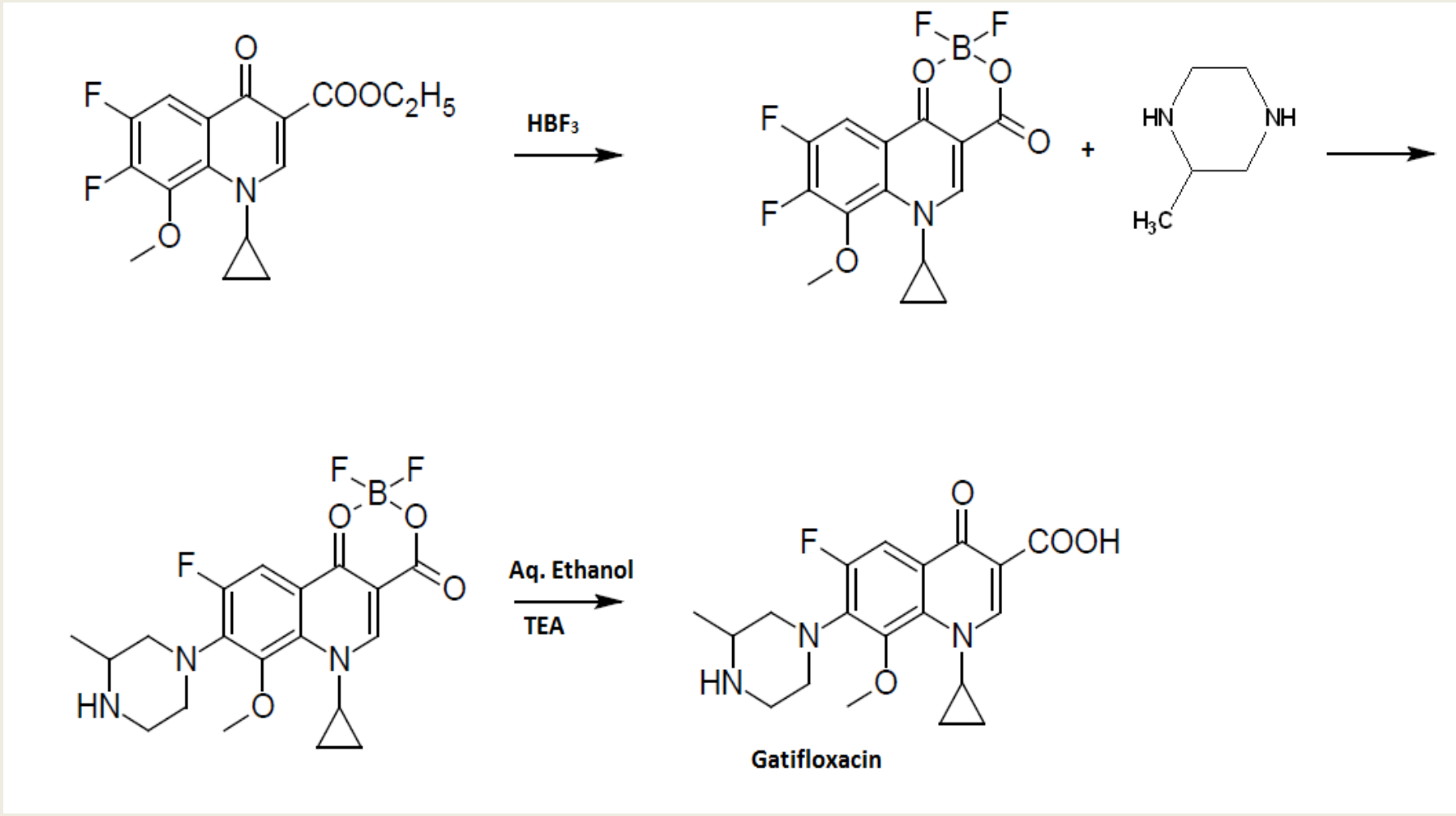
1. $(C_2H_5)_3N$
2. NaOH



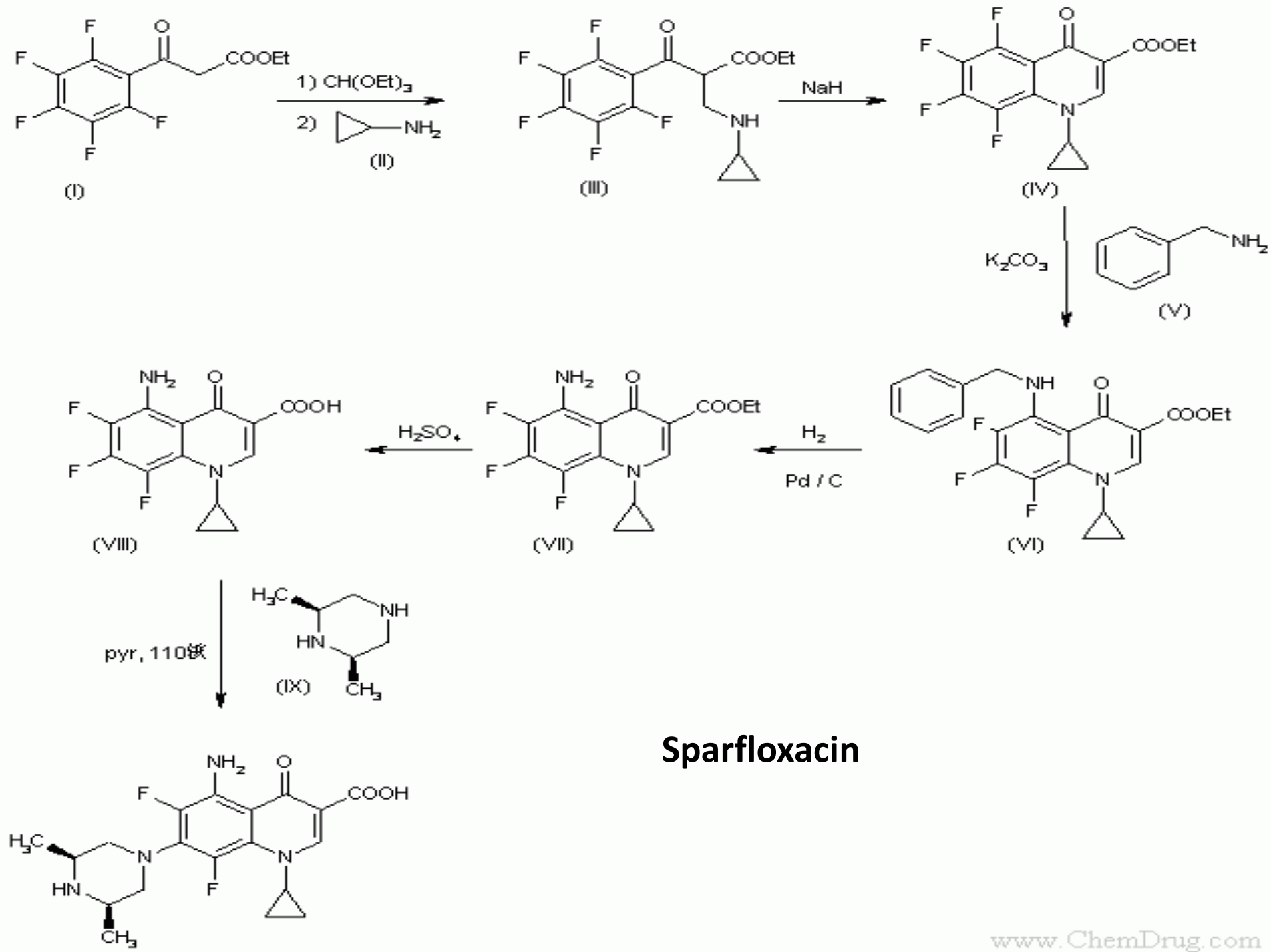


Ciprofloxacin


3-chloro-4-fluoroaniline
ethyl
ethoxymethylenmalonate
substitution product
Diphenyl ether
1. C2H5Br/(C2H5)3N
2. NaOH
Norfloxacin



Gatifloxacin



Sparfloxacin