ANTITUBERCULAR DRUGS

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ANTI-TUBERCULAR DRUGS (Anti mycobacterial drugs)

Tuberculosis (often called TB) is chronic bacterial infection caused by *MYCOBACTERIUM TUBERCULOSIS, M. Bovos.

It contains unusual cell wall. The cell wall has a high lipid content,resulting high degree of hydrophobicity and resistance to alcohol,acids, alkalies and some disinfefectants.

This organism usually attacks or affects almost any tissue and lungs, but can also affect the ...

1. CNS (meningitis),Circulatory system,Genitourinary system,Bones,joints. It is characterized by the formation of nodular bodies or tubercles(hence the name tuberculosis)

- It is one of the most deadly and common major infectious disease today, more than 2 billion people have been suffering the world's population.

1000 people have been dieing daily in India by TB.

TB spread person to person through the air.

When people with TB in their lungs or throat cough, laugh, sneeze, sing or even talk the germs that cause TB may be spread into the air, if another person breaths in these germs there is a chance that they will become infected with TB.

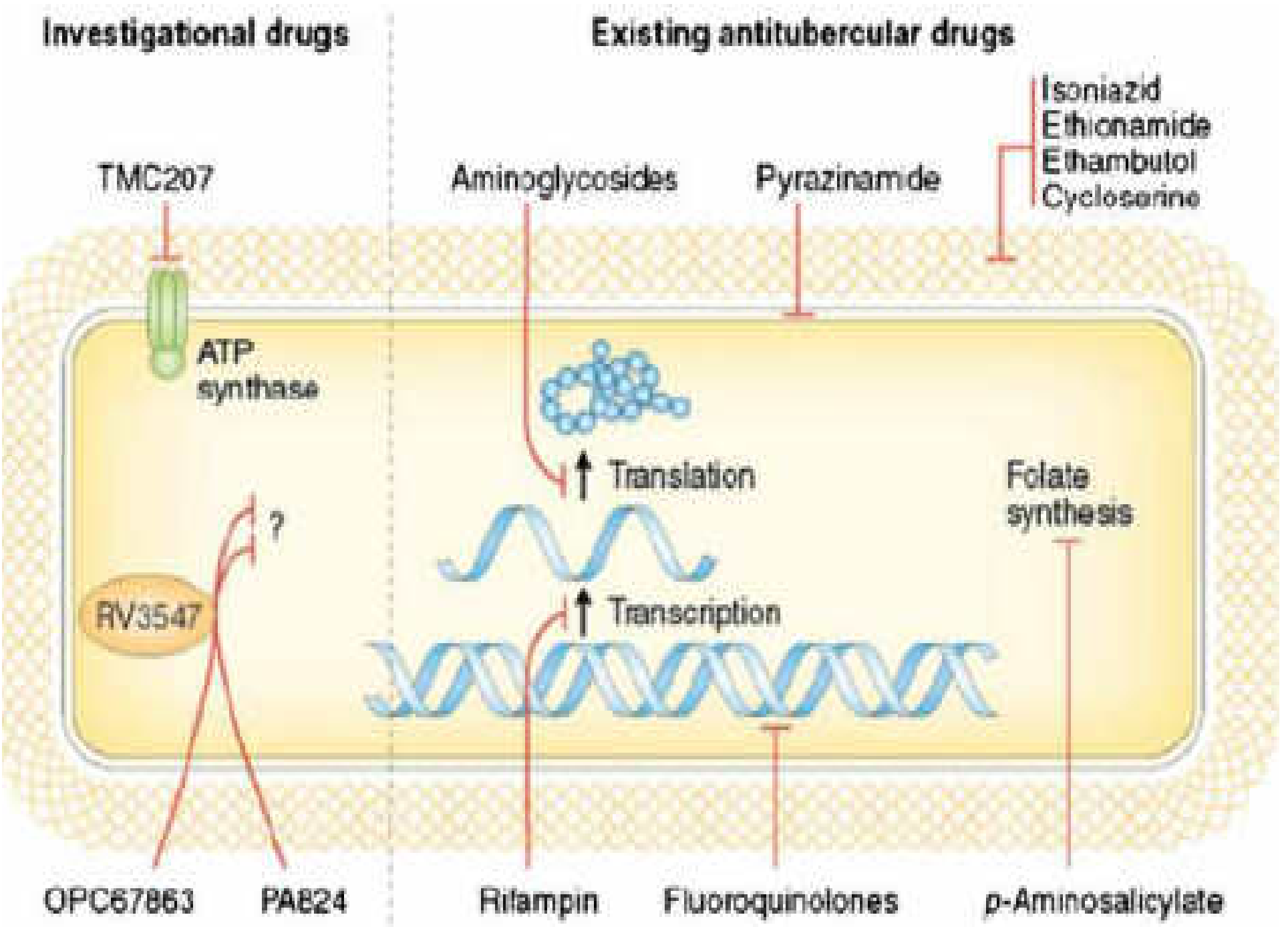
Tuberculosis—a chronic infectious disease caused by *Mycobacterium tuberculosis*

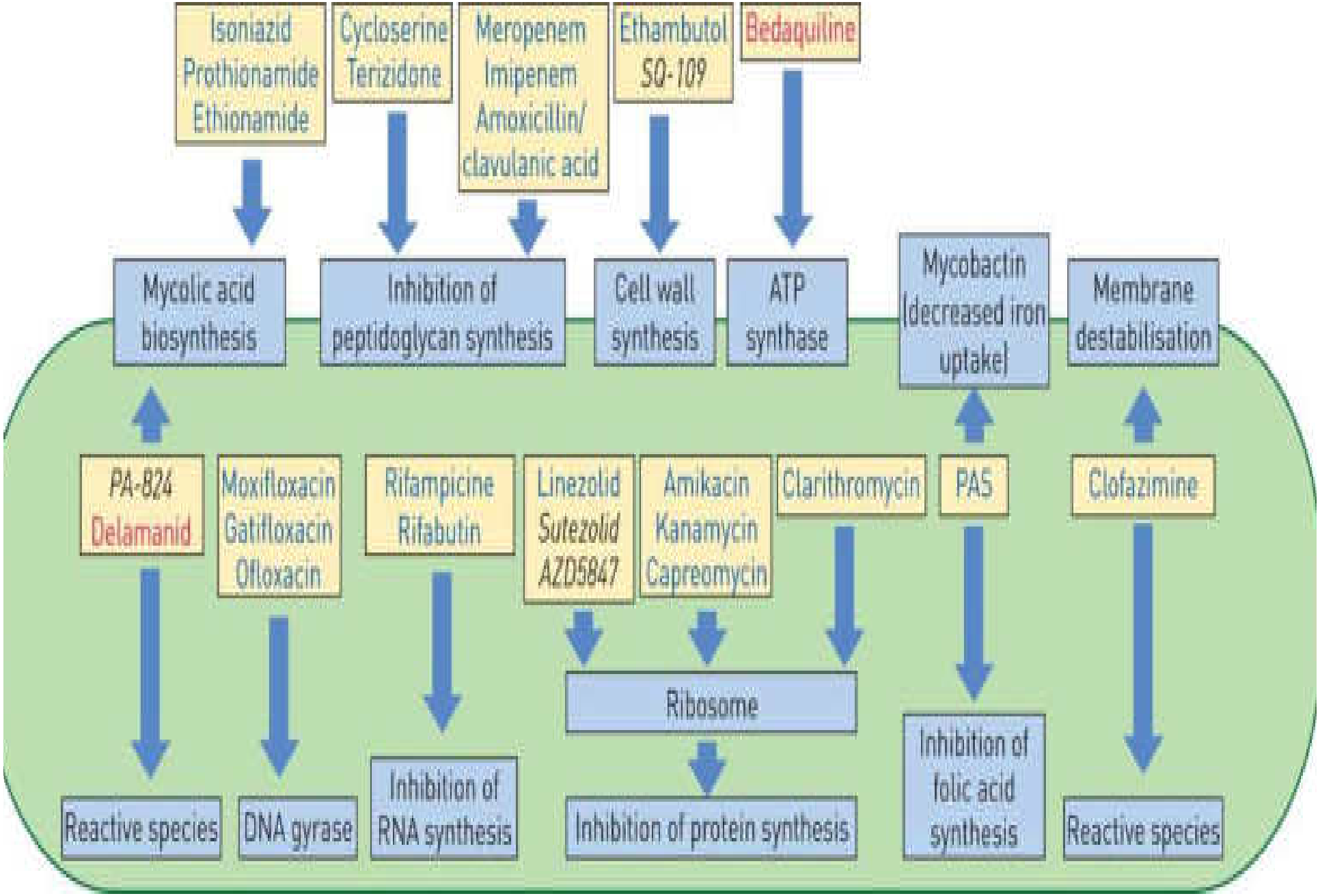
Transmitted via respiratory route

Organism appears in water droplets expelled during coughing & sneezing or talking.

Mainly affects lungs but can spread through blood stream and lymphatic system to brain , bones, eyes & skin.

Drugs used to treat tuberculosis are called as antitubercular drugs.


Investigational drugs
Existing antitubercular drugs
Isoniazid
Ethionamide
Ethambutol
Cycloserine
TMC207
Aminoglycosides
Pyrazinamide
ATP synthase
Translation
Folate synthesis
?
RV3547
Transcription
OPC67863
PA824
Rifampin
Fluoroquinolones
p-Aminosalicylate


Isoniazid
Prothionamide
Ethionamide
Cycloserine
Terizidone
Meropenem
Imipenem
Amoxicillin/
clavulanic acid
Ethambutol
SQ-109
Bedaquiline
Mycolic acid biosynthesis
Inhibition of peptidoglycan synthesis
Cell wall synthesis
ATP synthase
Mycobactin (decreased iron uptake)
Membrane destabilisation
PA-824
Delamanid
Moxifloxacin
Gatifloxacin
Ofloxacin
Rifampicine
Rifabutin
Linezolid
Sutezolid
AZD5847
Amikacin
Kanamycin
Capreomycin
Clarithromycin
PAS
Clofazimine
Ribosome
Reactive species
DNA gyrase
Inhibition of RNA synthesis
Inhibition of protein synthesis
Inhibition of folic acid synthesis
Reactive species

Classification

- According to clinical utility the anti TB drugs can be divided into 2 groups
  - **First Line** : high antitubercular efficacy as well as low toxicity – routinely used
    - **Isoniazid (H) , Rifampin (R), Pyrazinamide (Z), Ethambutol (E), Streptomycin (S) - HRZES**
  - **Second Line** : low antitubercular efficacy or high toxicity
    - **Paraminosallcylic Acid, Cycloserine, Kanamycin, Amikacin, Ciprofloxacin, Olfloxacin, Clarithromycin, Azithromycin**

Classification Of ATT Drugs

FIRST line drugs [HRZSE]

- F Field defects causing drug i.e. Ethambutol [E]
- I Isoniazid (INH) [H]
- R Rifampicin [R]
- S Streptomycin [S]
- T Twice a day given drug i.e. Pyrazinamide [Z]

(All other first line antitubercular are given once a day)

SECOND line drugs

- S Salicylates like Para-amino salicylate
- E Ethionamide
- C Cycloserine
- O Old drug: Thiacetazone
- N Newer Drugs:
  Quinolones e.g. Ciprofloxacin, Levofloxacin, gatifloxacin and Moxifloxacin Macrolides e.g. Clarithromycin, Azithromycin
- D Drugs rarely used: Aminoglycosides e.g. Capreomycin, Kanamycin, Amikacin
- Rifabeutin

Isoniazid (INH)

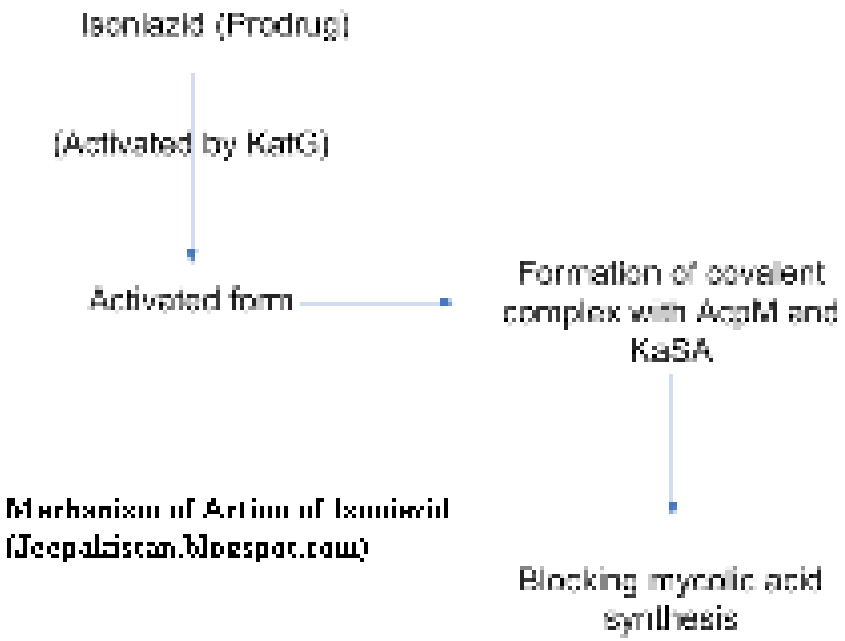
Mechanism of Action

Mycolic acid ⇒ Essential components of mycobacterial cell wall

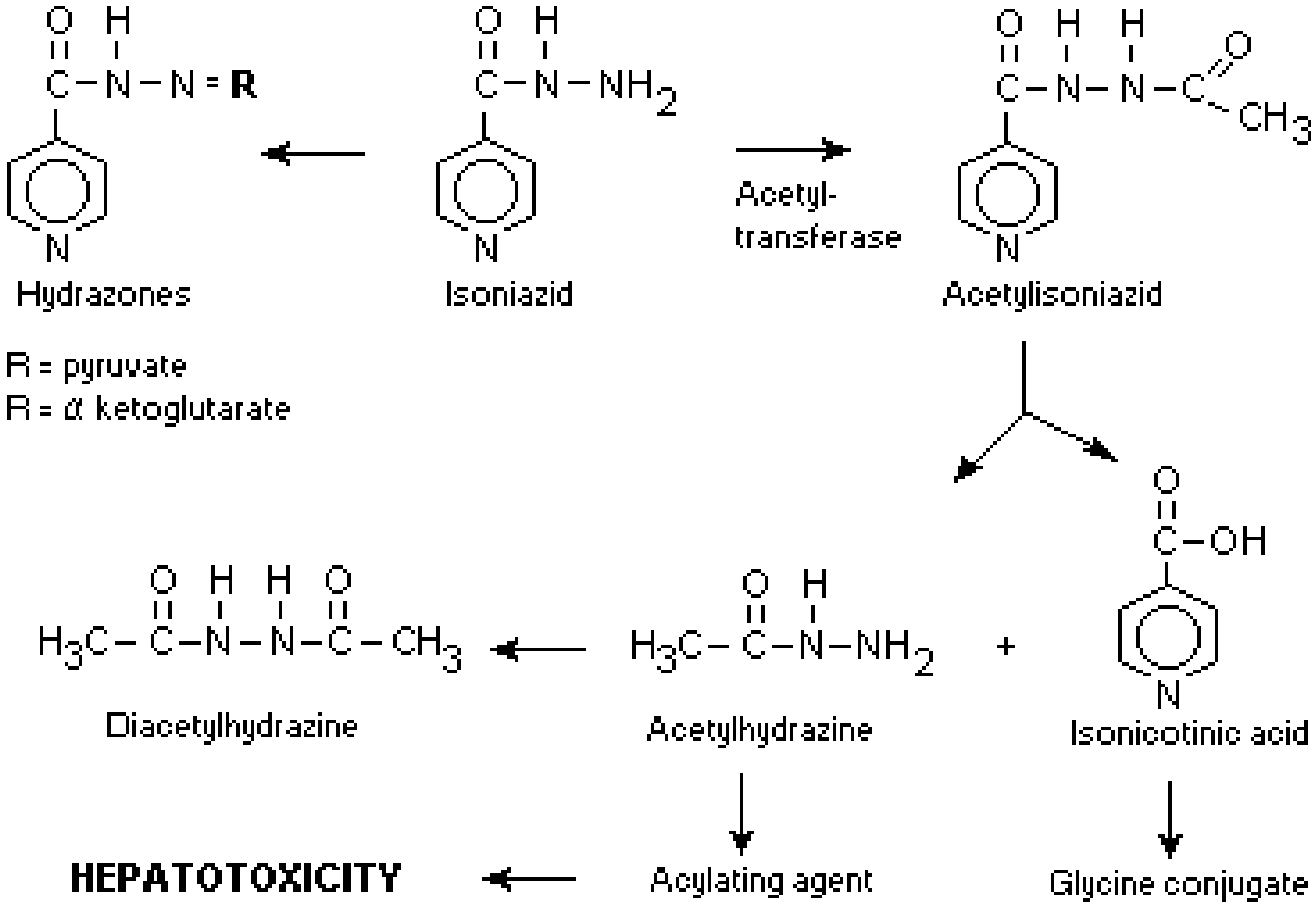
- INH form complex with
  - Acyl carrier protein (Acp M)
  - Beta ketoacyl carrier protein synthase (Kas A)

Inhibit mycolic acid synthesis

- Need mycobacterial catalase peroxidase (Kat G) to become active



Mechanism of Action of Isoniazid (Deepakiscan.blogspot.com)


Hydrazones
Isoniazid
Acetyl-
transferase
Acetylisoniazid
R = pyruvate
R = α ketoglutarate
Diacetylhydrazine
Acetylhydrazine
Isonicotinic acid
HEPATOTOXICITY
Acylating agent
Glycine conjugate

RIFAMPICIN

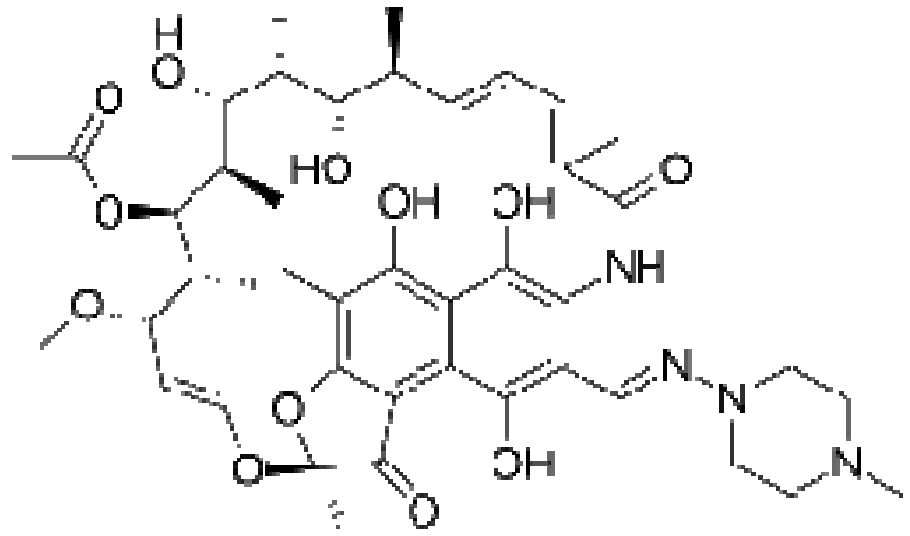
Rifampin is a semisynthetic derivative of rifamycin, an antibiotic produced by Streptomyces mediterranei.

It is active against gram positive and gram negative cocci, some enteric bacteria, mycobacteria and chlamydia.

Mechanism

- Rifampin binds to the β subunit of bacterial DNA–dependent RNA polymerase and thereby inhibits RNA synthesis.

Resistance results from any one of several possible point mutations in repoB, the gene for the β subunit of RNA polymerase.


H
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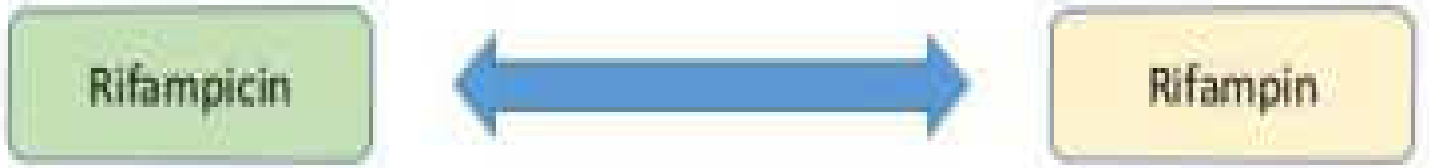
Introduction

- Rifamycins are a family of antibiotics, with the first agent, rifamycin V, derived in 1957 in Italy, from the soil mold Amycolaptis rifamycinica (formerly Streptomyces mediterranei)

- In 1959, a more stable semisynthetic rifamycin, 'rifampicin' was discovered.



Rifampicin (Rifampin)

•Refamycins are a group of macrocyclic antibiotics which are Produced by

Refamycins inhibit the enzyme RNA polymerase and prevent RNA synthesis.Than in turn prevent protein synthesis.

•So they are useful in treating tuberculosis, leprosy, Mycobacterium avium complex (MAC) infection, and Staphylococcus infections.

•Eventually 7, rifamycins were developed they are Rifamycin A,B,C,D,E,S,SV.

•Refampicin is a semi-synthetic rifamycin made from Rifamycin-B isolated from streptomyces mediterranei in 1957

•Among the various rifamycins, rifamycin-B was the first Commercial product.

Rifampicin —esterase→ Deacetyl rifampicin

ETHAMBUTOL(Myambutol)

(Ethylenediaminobutanol derivatives)

- Ethambutol abbreviated as EMB.
- The dextro enantiomer (+) is almost 200-500 times more potent than the meso(-) -enantiomer.
- Levo isomer is pharmacologically inert.
- Structurally it possesses aliphatic diamine and two butanol moieties.
- Ethambutol is a water-soluble,bacteriostatic agent that is readily absorbed (75-80%) following oral administration.

2,2'-(1,2-ethanediyldiamino)bis-1-butanol.

Ethambutol

Mechanism of action

- Inhibit mycobacterial arabinosyl transferase enzyme

Enzyme in arabinoglycan polymerization

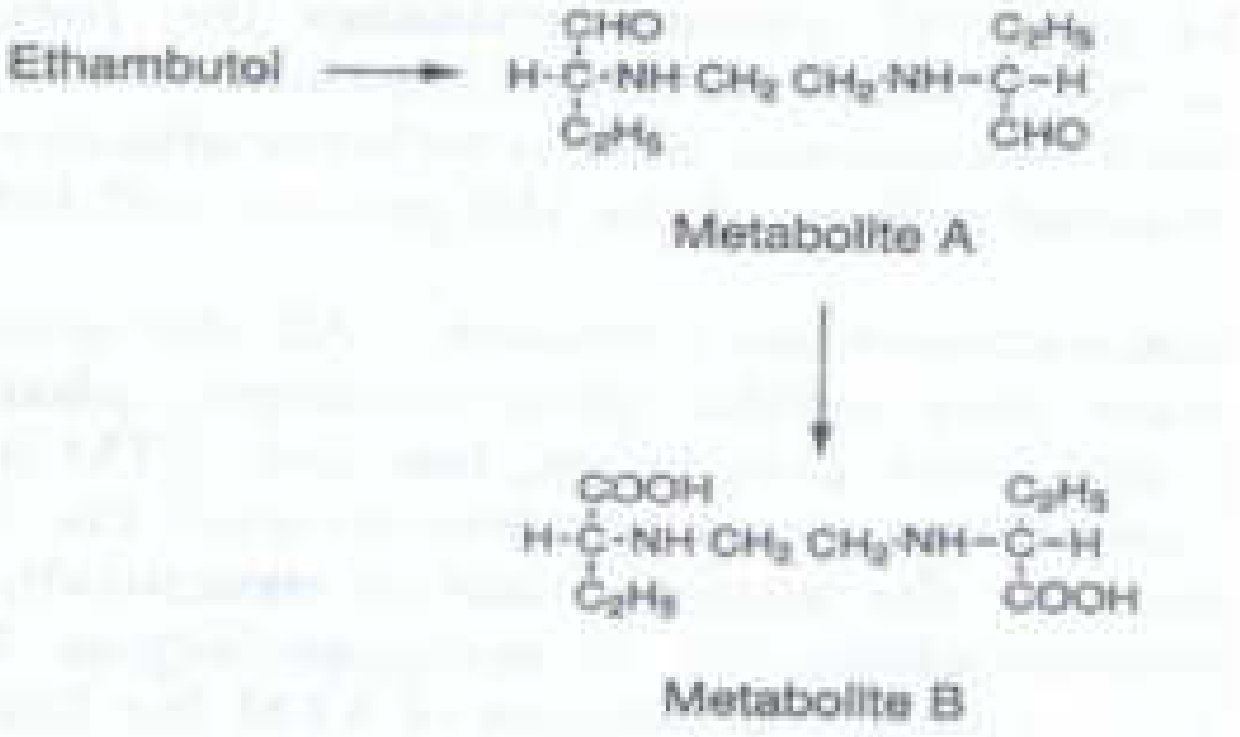
Arabinoglycan = Essential component of mycobacterial cell wall

Mechanism of resistance

Mutation of mycobacterial arabinosyl transferase enzyme

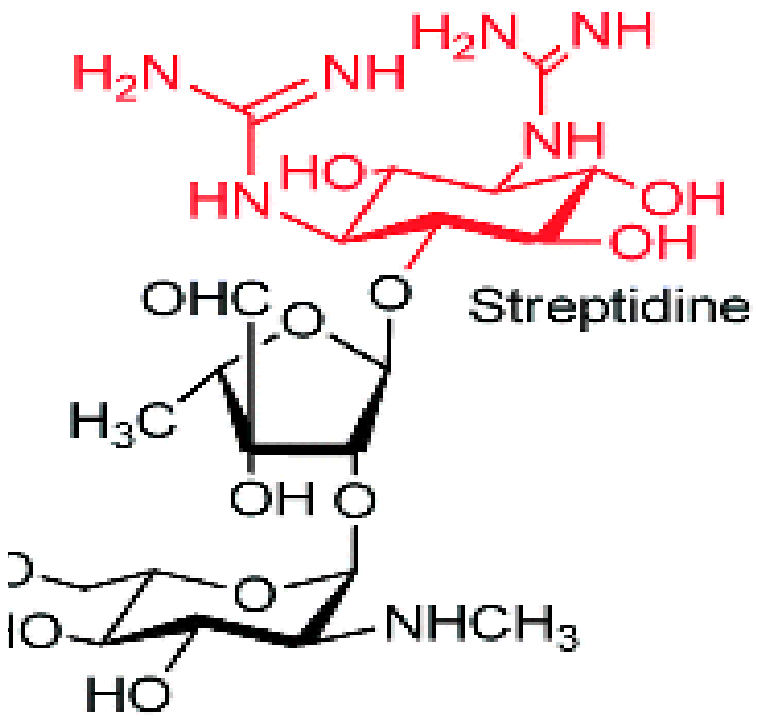
- Metabolism of ethambutol:

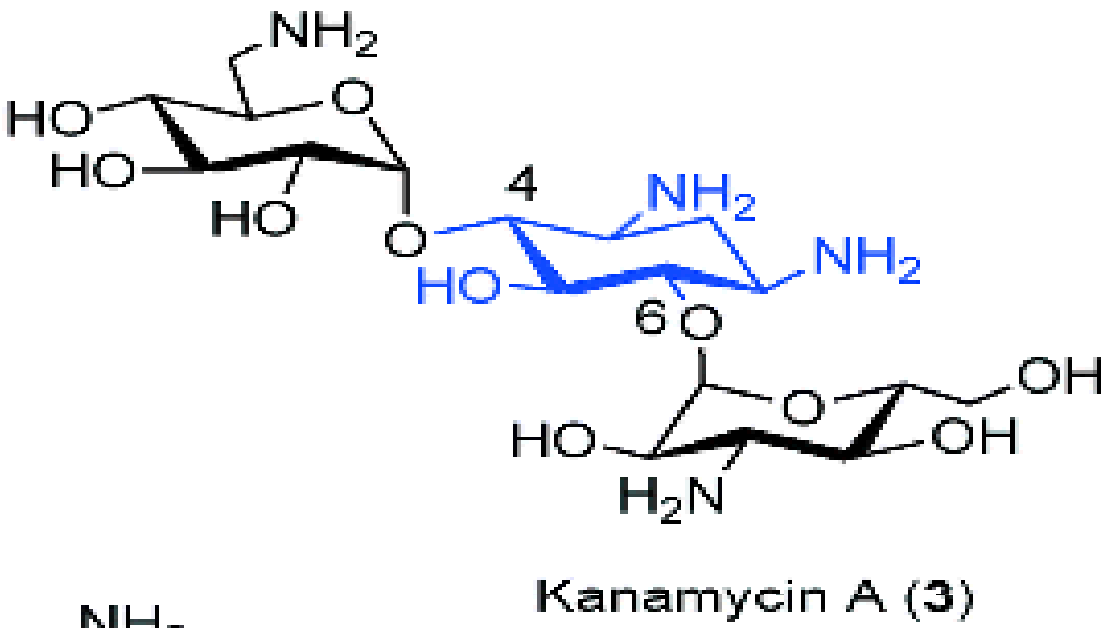
The majority of the administered EMB is excreted nchanged (73%),with no more than 15% appearing in the urine as either motabolite A or Metabolite B.
Both metabolites are devoid of biological activity.

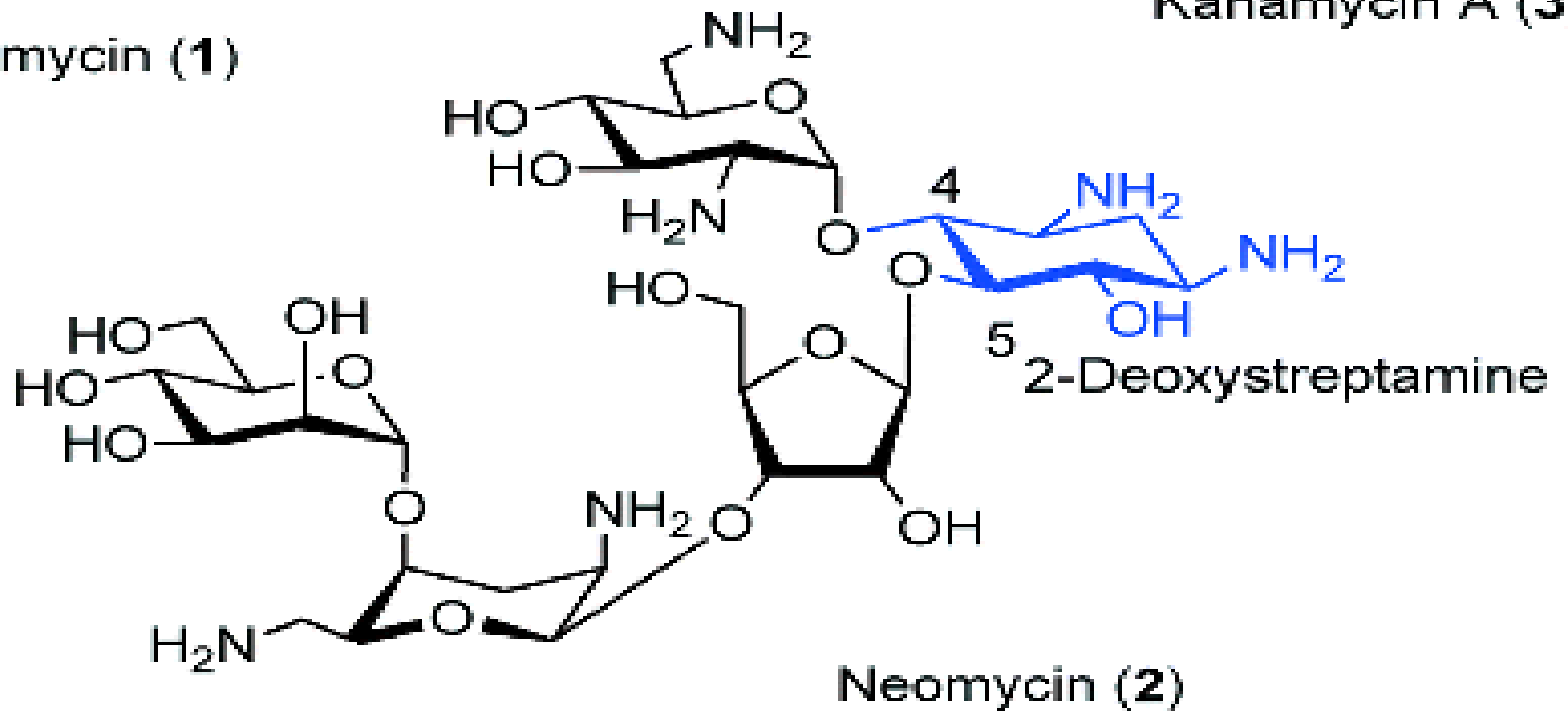


STREPTOMYCIN

- Streptomycin is an antibiotic (antimycobacterial) drug, the first of a class of drugs called aminoglycosides to be discovered, and it was the first antibiotic remedy for tuberculosis.
- It is derived from the actinobacterium "Streptomyces griseus".
- Streptomycin is a bactericidal antibiotic.
- Streptomycin cannot be given orally, but must be administered by regular intramuscular injections.
- Adverse effects of this medicine are ototoxicity, nephrotoxicity, fetal auditory toxicity, and neuromuscular paralysis.
- **Ototoxicity** due to neurotoxicity to the 8th cranial nerve can lead to vertigo and irreversible deafness.
- **Nephrotoxicity** due to kidney tubular necrosis may also arise. The reason for these toxicities is the affinity of Aminoglycosides to these tissues and their long $t_{1/2}$ within these tissues.


Streptidine
Streptomycin (1)


Kanamycin A (3)


2-Deoxystreptamine
Neomycin (2)

Adverse effects of ATT drugs

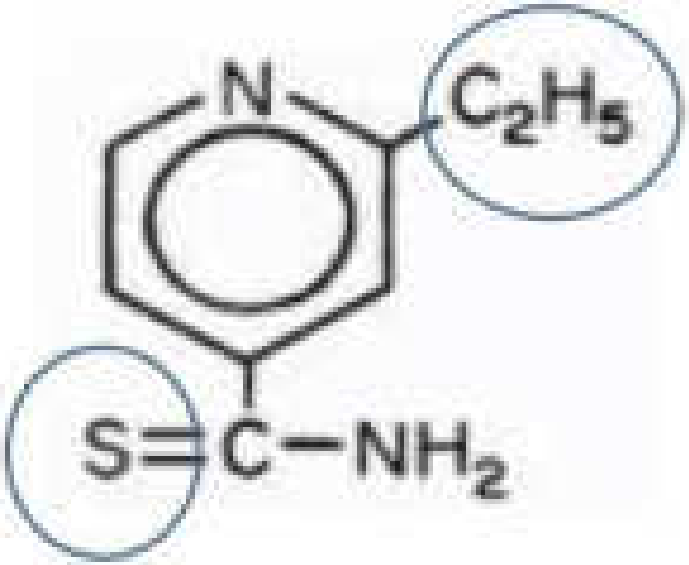
Drug	Adverse effects
Isoniazid	Hepatotoxicity, peripheral neuritis, hypersensitive reactions may precipitate epilepsy, drug induced lupus, psychotic changes
Rifampicin	Hepatotoxicity, gastrointestinal, autoimmune reactions (more with intermittent administration), which include flu syndrome, thrombocytopenias, purpura, respiratory shock syndrome, acute hemolytic anemia, ARF)
Pyrazinamide	Hepatotoxicity, arthralgia, hyperuricemia, gastrointestinal, allergic reactions
Ethambutol	Optic neuritis, colour blindness, gastrointestinal, allergic reactions, hyperuricemia
Streptomycin	Vestibular dysfunction, deafness, nephrotoxicity, neuromuscular blockade, peripheral neuritis

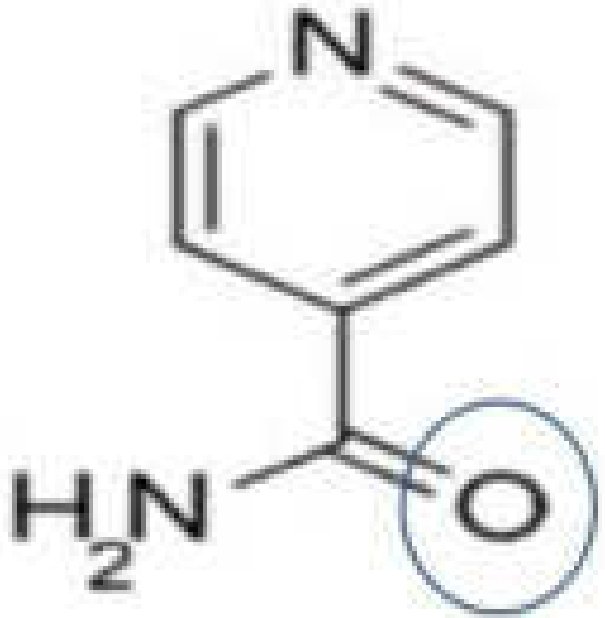
SECOND line drugs

- S Salicylates like Para-amino salicylate
- E Ethionamide
- C Cycloserine
- O Old drug: Thiacetazone
- N Newer Drugs:
  Quinolones e.g. Ciprofloxacin, Levofloxacin, gatifloxacin and Moxifloxacin Macrolides e.g. Clarithromycin, Azithromycin
- D Drugs rarely used: Aminoglycosides e.g. Capreomycin, Kanamycin, Amikacin
- Rifabeutin

Ethionamide

- A 2nd line anti TB agent, analogue of isonicotinamide but it is di-substituted and contains S in place of O
- It contains ethyl group at position 2





Ethionamide

Mechanism of action:

- Bacteriostatic against metabolically active M.tuberculosis.
- *Inhibits InhA gene product enoyl-acyl carrier* protein reductase which is involved in mycolic acid synthesis.

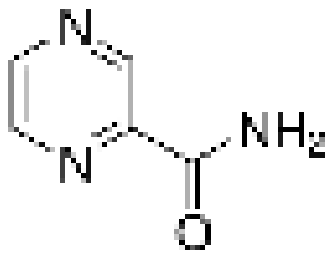
CYCLOSERINE :

- Streptomyces orchidaceus

- Structural analog of D- alanine

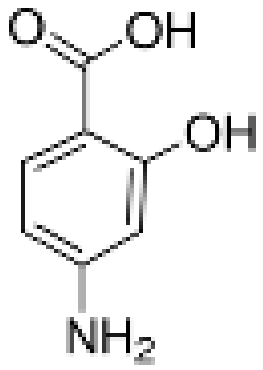
Mechanism of action :

- Inhibits incorporation of D- alanine into peptidoglycan pentapeptide & inhibits mycobacterial cell wall synthesis



Pyrazinamide (PZA)

- Contains pyrazine ring in its structure, which is a six memberd heterocyclic ring containing two nitrogen at a distance of 2 carbon atoms
- Pyrazinamide has amide group at position 2
- It is a prodrug and converted into pyrazinoic acid in the body



SECOND LINE DRUGS
Para amino salicylic acid

Mechanism of action

Aminosalicylic acid is a folate synthesis antagonist that is active almost exclusively against mycobacterium tuberculosis.

It is structurally similar to p-amino benzoic acid(PABA) and the sulfonamides.

Pharmacokinetics

Absorption

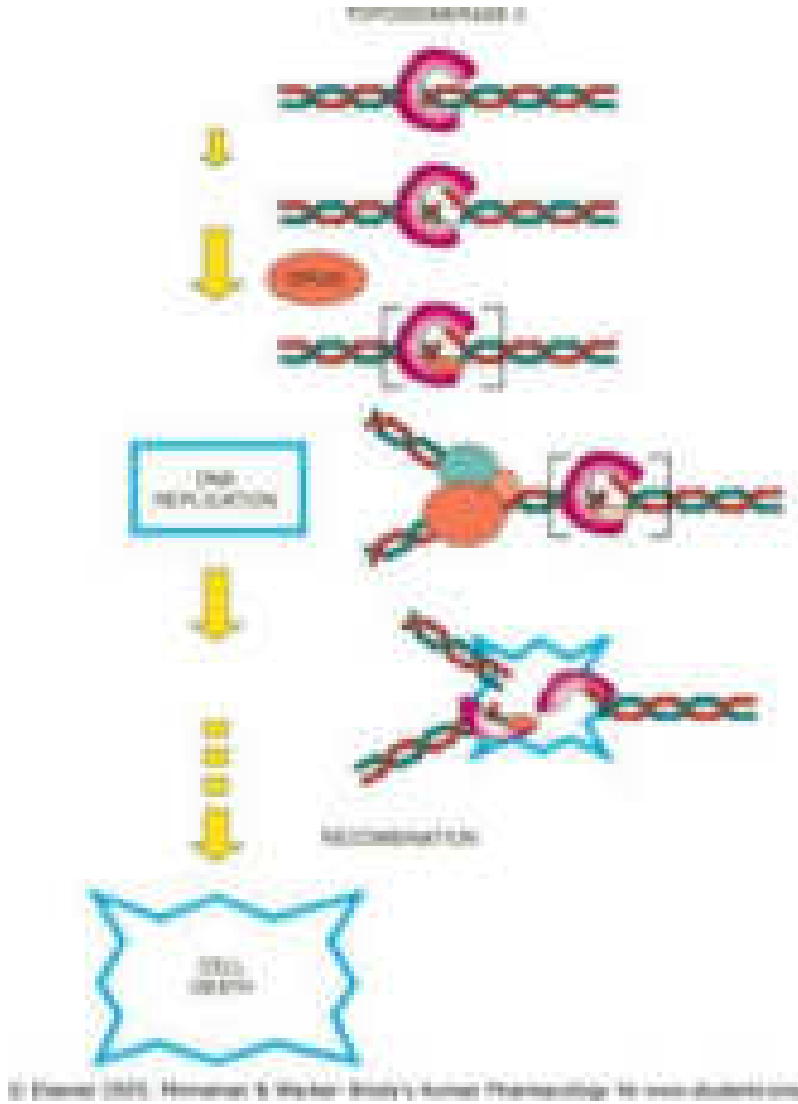
- T_{max} is about 6 h

Distribution

- About 50% to 60% is protein bound.

Elimination

- 80% is excreted in the urine with at least 50% excreted in acetylated form.
- The $t_{1/2}$ of free aminosalicylic acid is 26.4 min.

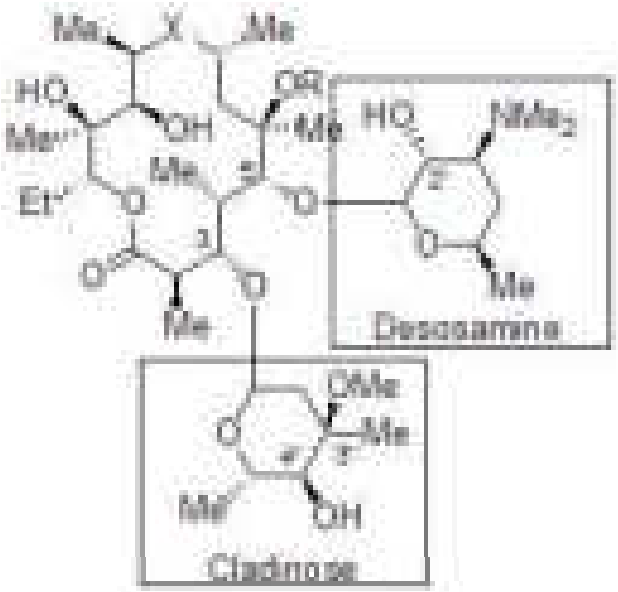


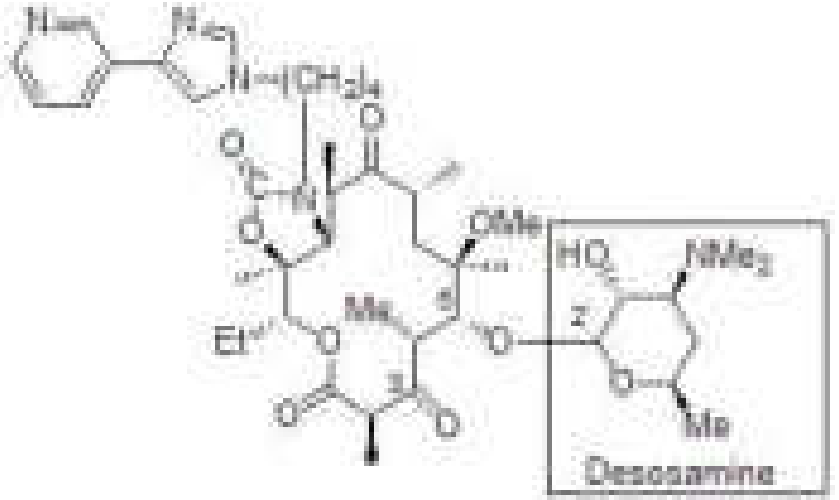
The fluoroquinolones act by inhibiting **type 2 bacterial DNA topoisomerases**, **DNA gyrase** and **topoisomerase IV**. They bind to and trap the enzyme-DNA complex. This blocks DNA synthesis and cell growth and ultimately has a lethal effect on the cell.

levofloxacin

MACROLIDES

- The macrolides are a group of antibiotics with a macrocyclic **lactone** structure to which one or more **deoxy sugars** are attached.
- Macrolides includes ,
    - **Erythromycin**
    - **Clarithromycin**
    - **Azithromycin -methyl-substituted nitrogen** in the lactone ring that improves acid stability and tissue penetration and broadens the activity spectrum.
    - **Roxithromycin .**
- Macrolides are narrow spectrum antibiotic. More commonly bacteriostatic in nature ocassionaly bactericidal depends upon the microorganism.
- Macrolides are also bacterial protein synthesis inhibitors.
- **Mechanism of action**
    - The macrolides bind irreversibly to a site on the 50S subunit of the bacterial ribosome, thus inhibiting the translocation steps of protein synthesis .
    - They may also interfere at other steps, such as transpeptidation.
    - Their binding site is either identical or in close proximity to that for clindamycin and chloramphenicol.





1 R=H, X = CO Erythromycin
2 R=Me, X = CO Clarithromycin
3 R=H, X=N(Me)CH_2 Azithromycin

4 Telithromycin

Anti Leprotic Drugs

Leprosy

- Leprosy, also known as Hansen's disease
- It is a chronic infection caused by the bacteria *Mycobacterium leprae* and *Mycobacterium lepromatosis*.
- **Antileprotic Drugs**

Sulfone	Dapsone (DDS)
Phenazine derivative	Clofazimine
Antitubercular drugs	Rifampin Ethionamide
Other antibiotics	Ofloxacin Moxifloxacin Minocycline Clarithromycin

Multidrug therapy (MDT) of leprosy

- To deal with dapsone resistant strains of M. leprae
- to shorten the duration of treatment
- Multidrug therapy with rifampin, dapsone and clofazimine was introduced by the WHO in 1981.

- Though the burden of leprosy has fallen drastically after introduction of MDT, both globally and in India, WHO data (2010) show that 65% of all new leprosy cases worldover are from India.

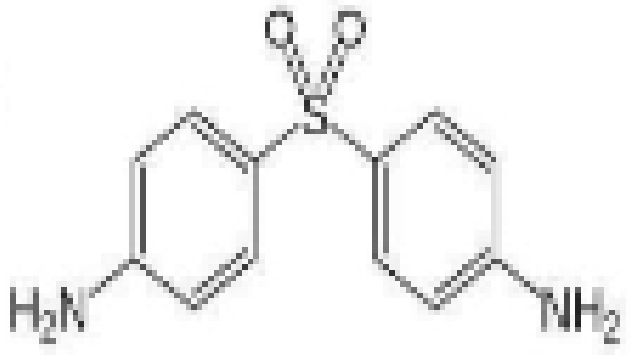
TREATMENT

Classification of Antileprotic drugs:

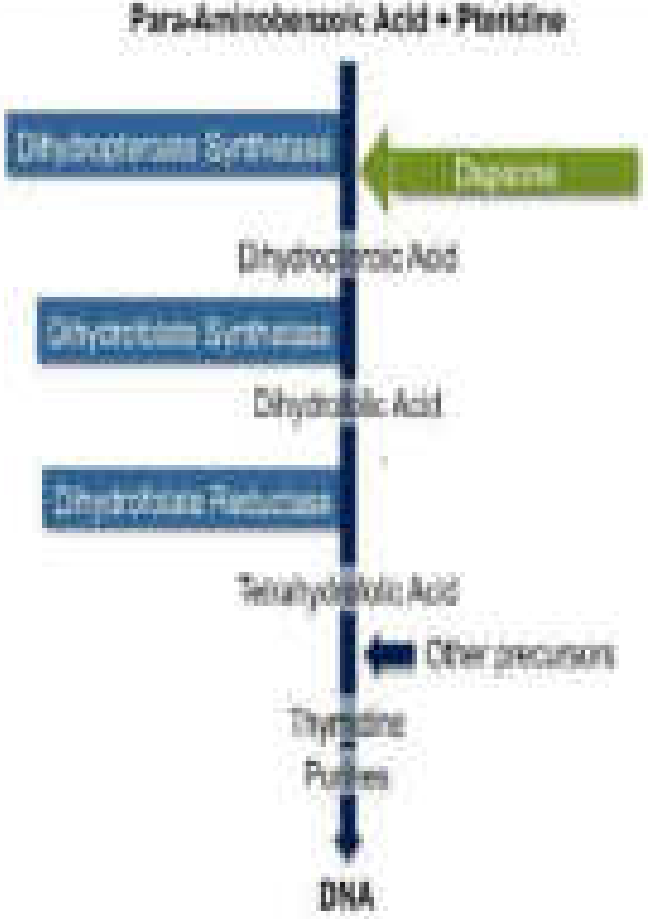
1) Sulfone - Dapsone(DDS)
2) Phenazine derivative - Clofazimine
3) Antitubercular drugs – Rifampicin, Ethionamide
4) Other antibiotics – Ofloxacin, Minocycline

DAPSONE

- Dapsone is an aniline derivative.
- All sulfones share the structure of a sulfur atom linking to two carbon atoms
- 4-4'-diamino-diphenyl sulfone (DDS
- Available as 25 & 100-mg tablets
- Inexpensive drug



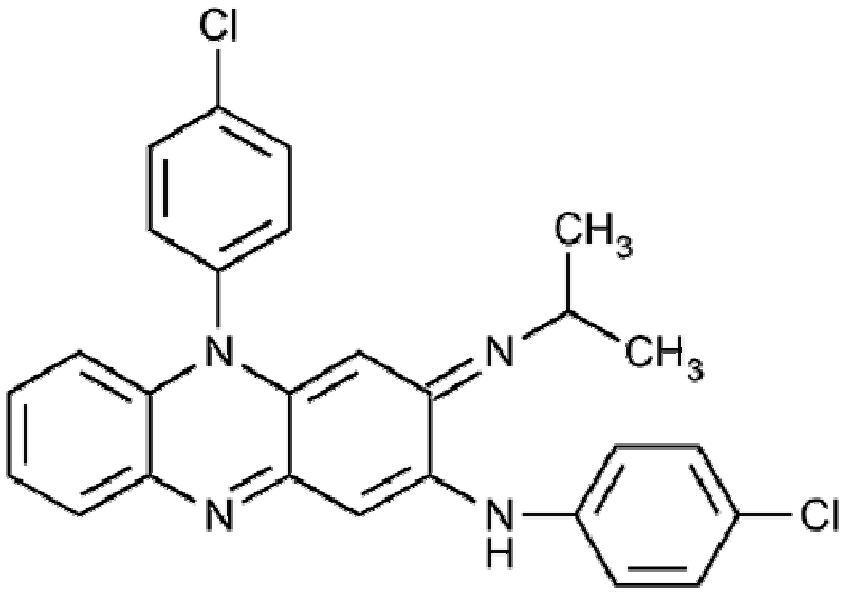
MECHANISM OF ACTION



Clofazimine (Clo)

The putative mechanisms of anti-leprotic action of clofazimine are:

- Interference with template function of DNA in M.leprae
- Alteration of membrane stucture and its transport function.
- Disruption of mitochondrial electron transport chain.


Cl
CH3
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