


Chapter 9: Anti-tubercular Agents


Syllabus


Synthetic anti-tubercular agents: Isoniozid*, Ethionamide, Ethambutol, Pyrazinamide, Para amino salicylic acid.*


Anti-tubercular antibiotics: Rifampicin, Rifabutin, Cycloserine, Streptomycine, Capreomycin sulphate.


9.1. INTRODUCTION

 Tuberculosis is a serious infectious disease caused by *Mycobacterium tuberculosis* and *M. bovis*, collectively termed as tubercle bacilli.

 To achieve effective treatment of *M. tuberculosis* (a slow growing intracellular bacteria) require multidrug therapy for extended periods of time and prevent the emergence of resistance. The risk of adverse reactions therefore must be a major consideration in drug selection.

 A 6-month chemotherapy regimen are generally used for *tuberculosis* treatment by using a combination of 4 drugs (rifampicin, isoniazid, ethambutol, and pyrazinamide for 2 months, followed by rifampicin and isoniazid for 4 months).

 **1st Line Drugs:** These drugs are used in initial phase. These drugs have high antitubercular efficacy. Generally, three drugs are used concurrently. Agents used as first line drugs are: Isoniazid (H), Rifampicin (R), Ethambutol (E), Pyrazinamide (Z) and Streptomycin (S).

 **2nd Line Drugs:** These are indicated when the causative agent is resistant to the primary drugs. These drugs have low antitubercular efficacy and high toxicity. e.g. Paraaminosalicylic acid (PAS), Ethionamide, Cycloserine, Thiacetazone, Capreomycin, Kanamycin, Amikacin and Rifabutin

 **Daily Dose (WHO 2010 guideline)**

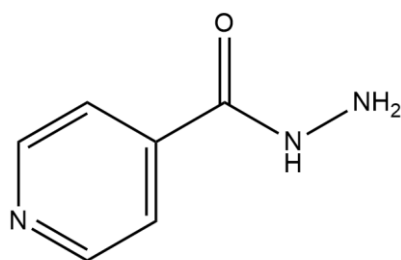
- INH: 5 mg/kg
- E: 15 mg/kg
- R: 10 mg/kg
- S: 15 mg/kg
- Z: 25 mg/kg

 **Regimen (RNTCP 2016 guideline)**

- For New Patients- 2 months HRZE + 4 months HRE
- For previously treated Patients- 2 months HRZES + 1 month HRZE + 5 months HRE

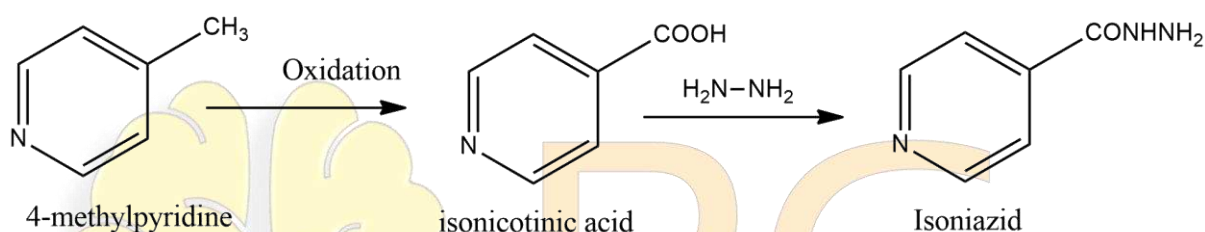
9.2. MEDICINAL CHEMISTRY

A) Isoniazid



isonicotinohydrazide

Synthesis:

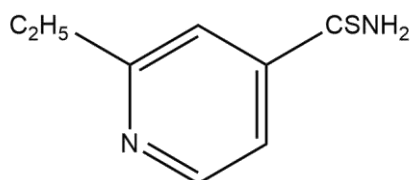


MOA: Isoniazid is a bacteriostatic on 'resting' bacilli but is bactericidal for actively dividing *M. tuberculosis*. Isoniazid act by inhibiting *mycolic acid* synthesis, which is an essential component of mycobacterial cell wall.

Uses:

- ✓ Isoniazid is the primary drug for chemotherapy of pulmonary or extrapulmonary tuberculosis
- ✓ Active against latent and active tuberculosis infection
- ✓ Also used in treatment of *Mycobacterium avium* complex

B) Ethionamide



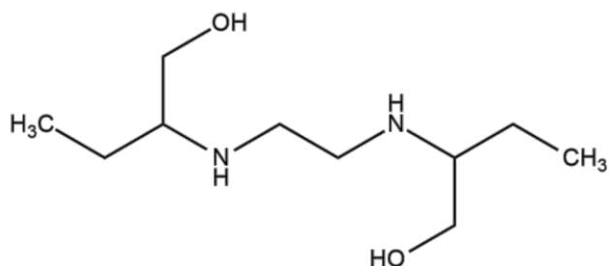
2-ethylpyridine-4-carbothioamide

MOA: Ethionamide is a bacteriostatic, act by inhibiting synthesis of *mycolic acid*

Uses:

- ✓ Used along with other antitubercular drugs, as part of second line of drug regimen
- ✓ Also used in treatment of Mycobacterium avium complex (MAC)

C) Ethambutol



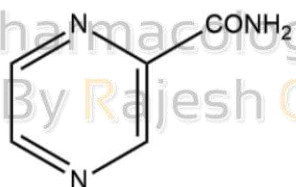
2,2'-(ethane-1,2-diybis(azanediy))bis(butan-1-ol)

[2-[[1-hydroxy butan-2yl]amino]ethyl amino] butanol

MOA: Ethambutol is a bacteriostatic, inhibits inhibit arabinosyl transferases (encoded by *embAB* genes) involved in arabinogalactan synthesis thereby interfering with mycolic acid incorporation in mycobacterial cell wall.

Uses: Used in treat of TB and MAC

D) Pyrazinamide



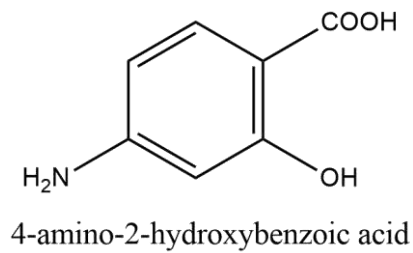
pyrazine-2-carboxamide

Chemically similar to INH, pyrazinamide (Z) was developed parallel to it in 1952. It is weakly tuberculocidal and more active in acidic medium. It is more lethal to intracellularly located bacilli and to those at sites showing an inflammatory response (pH is acidic at both these locations. Most effective during first 2 months.

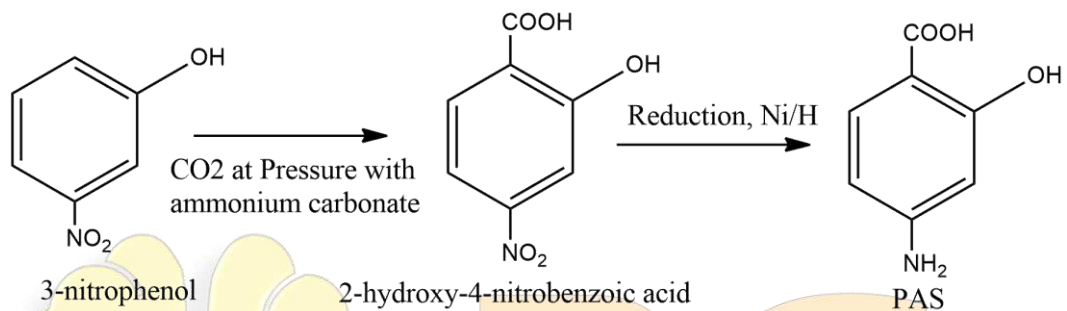
MOA: Within in mycobacterial cell it converts into pyrazinoic acid by an enzyme pyrazinamidase. This metabolite gets accumulated in acidic medium and probably inhibits mycolic acid synthesis, but by interacting with a different fatty acid synthase

Uses: It is bacteriocidal antitubercular drugs.

E) Para amino salicylic acid



Synthesis:

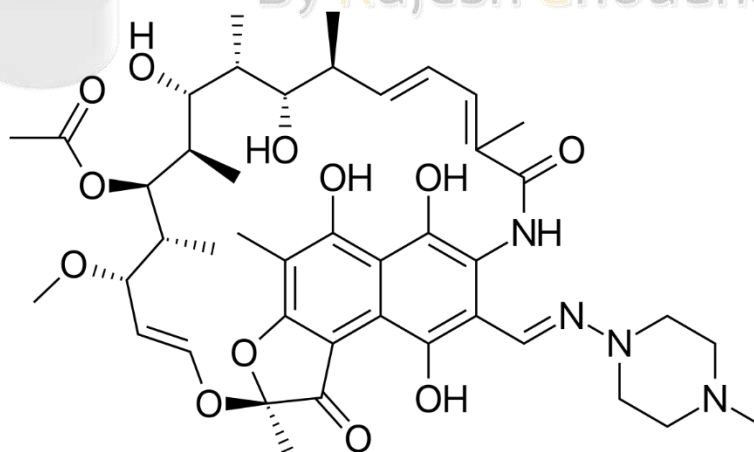


MOA: It is a folate synthesis antagonist (dihydro folate synthetase inhibitors). It is bacteriostatic.

Uses: only used in resistant TB and used in inflammatory bowel disease.

ANTITUBERCULAR ANTIBIOTICS

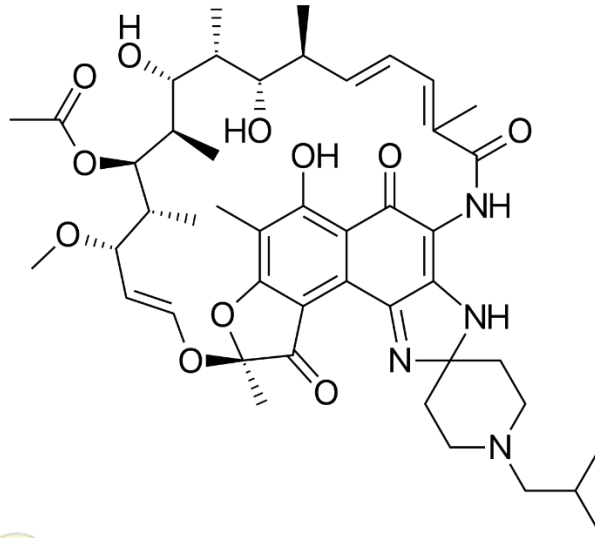
F) Rifampicin



MOA: Inhibit the DNA-dependent RNA polymerase

Uses: Used in bacterial, TB, MAC and leprosy

G) Rifabutin

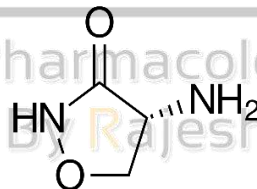


MOA: Inhibit the DNA-dependent RNA polymerase

Uses:

- ✓ Used in bacterial, TB, MAC and leprosy
- ✓ Also used in AIDS patient having *M. tuberculosis* infection

H) Cycloserine



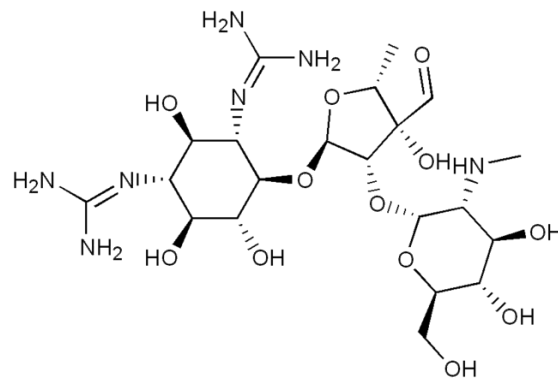
4-amino-1,2-oxazolidine-3-one

MOA: It inhibits the cell wall synthesis by inhibiting L-alanine racemase and D-alanylalanine synthetase which involve in the formation of peptidoglycan.

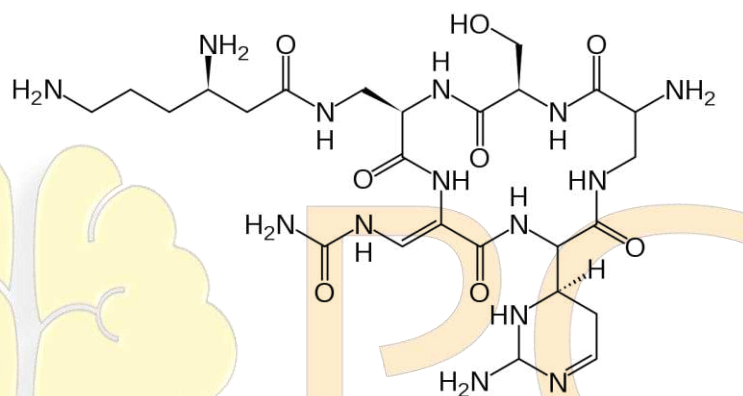
Uses:

- ✓ Uses along with other antitubercular drugs
- ✓ Also used as an antiinfective agent, as an antibiotic and antimetabolite
- ✓ Also used in treatment of *Mycobacterium avium* complex (MAC)

I) Streptomycine : discussed in Aminoglycoside chapter



J) Capreomycin sulphate.



MOA: Inhibits the protein synthesis by acting on 70s ribosomal unit.

Uses: used in antibacterial and antituberculous

Pharmacology Concepts

By Rajesh Choudhary