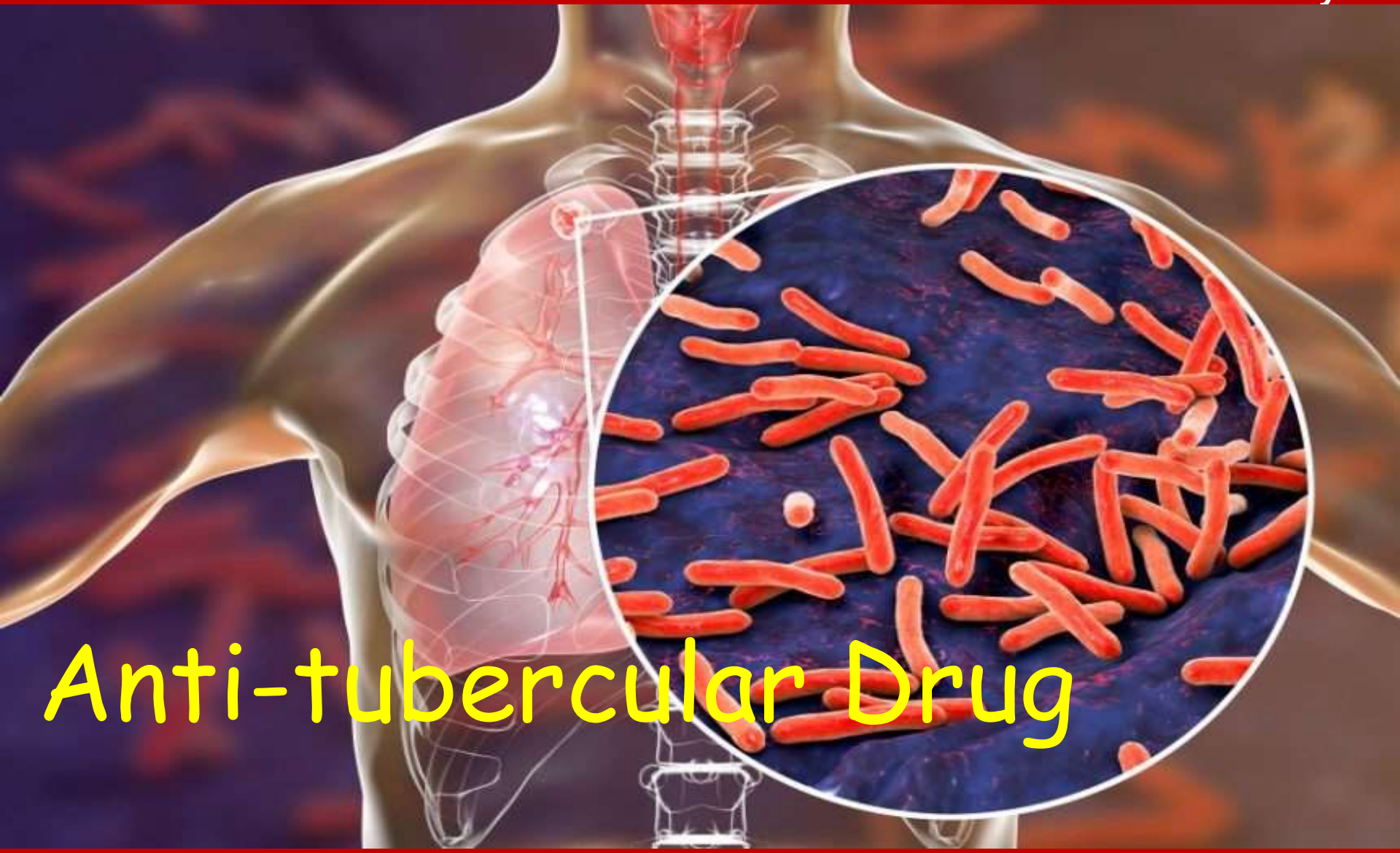
School of Medical & Allied Sciences

Course Code : BPHT6001 **Course Name: Medicinal Chemistry-III**



Anti-tubercular Drug

Name of the Faculty: Dr. Deepika **Program Name: B. Pharmacy**

Disclaimer

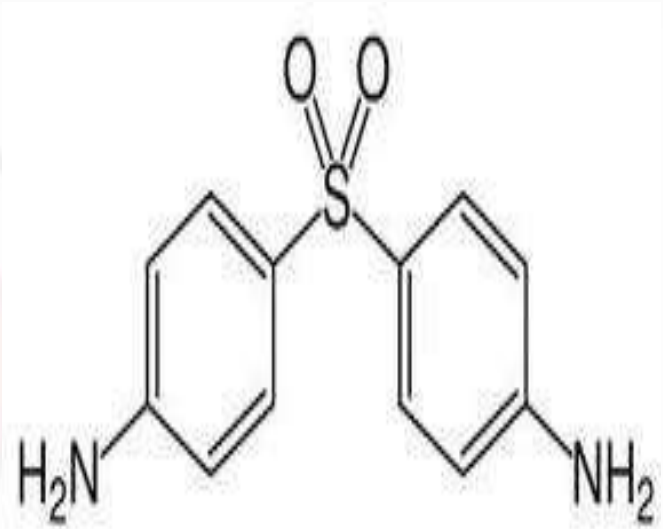
All the content material provided here is only for teaching purpose.

Tuberculosis (TB)

- TB is a communicable disease caused by *Mycobacterium tuberculosis*, which is a gram positive, acid fast bacilli
- MT has characteristic cell wall that is made up of peptydoglycan (amino acids and sugars)covered by a lipopolisaccharide made up of mainly mycolic acid
- Most of the antibiotics are not effective against MT due to its characteristic cell

Anti-TB drugs

- First agent used as an anti-TB drug was sulfanilamide, but, since, sulfonamides are bacteriostatic, resistance occurred rapidly
- Second agent tried was dapsone, though it was effective, but in long-term therapy found to be toxic…..discontinued



- In TB treatment, major breakthrough was the development of streptomycin-an aminoglycoside, that was highly effective against MT. Afterwards, many synthetic drugs were developed to eradicate TB, despite such developments, it is still prevailing due to emergence of multi-drug resistant stains

Classification of anti-TB drugs

- **First line drugs for tuberculosis**
- Isoniazid,
- Rifampicin,
- Ethambutol
- Pyrizanamide.
- Streptomycin.
- **Second line drugs**
- Amikacin, Kanamycin.
- Capreomycin.
- Ciprofloxacin, Levofloxacin, Moxifloxacin
- Ethionamide, Prothionamide
- Cycloserine
- Para aminosalicylic acid

Third line drugs for tuberculosis

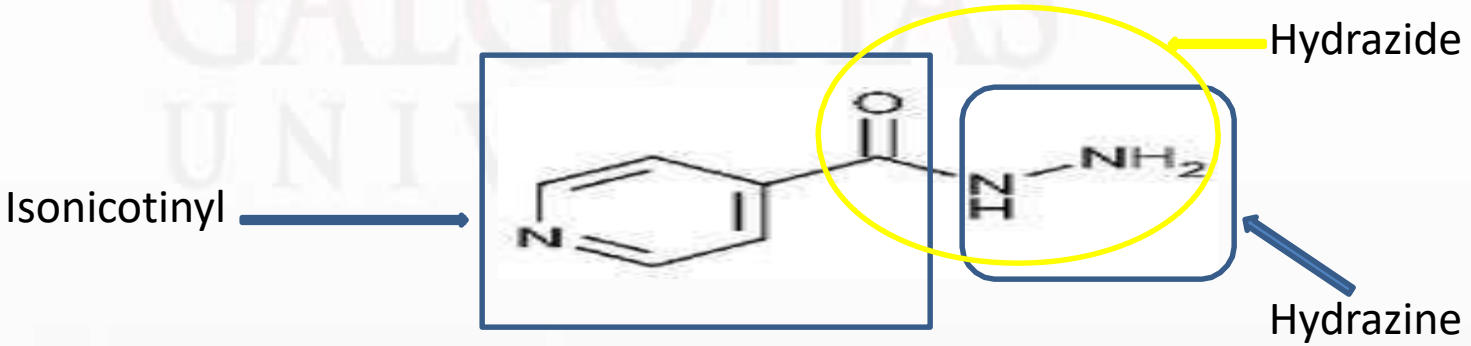
- Rifabutin
- Macrolides like clarythromycin
- Linezolid
- Thioacetazone
- Vitamin D
- Thioridazine

Antitubercular drugs are also classified on the basis of Chemical moiety as:-

1.Salicylic acid derivatives: Para amino salicylic acid.
2.Pyridine derivatives:Isoniazid (Isonicotinic acid hydrazine), Ethionamide, Prothionamide.
3.Pyrazine derivatives:Pyrazinamide
4.Ethylenediaminobutanol derivatives: Ethambutol.
5.**Antibiotics:**Streptomycin, Refampin (Refampicin), Kanamcin.
6.Miscellaneous drugs:Fluoroquinolones: Ofloxacin ,Ciprofloxacin.Macrolides: Clarithromycin, Azithromycin

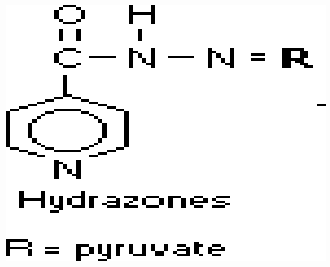
Isoniazid

- It is synthetic anti-TB drug introduced in 1950
- Chemically, it is isonicotinic acid derivative- combination of isonicotinic acid and hydrazine: (Hydrazide)
- It is a prodrug- in body is converted into electrophilic species which inhibit the synthesis of mycolic acid
- It is effective against rapidly dividing MTB but less effective against dormant and semi- dormant MTB

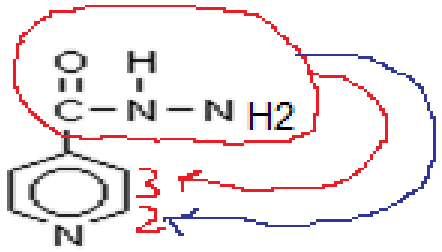


Structure activity relationship

- Pyridine ring, if replaced with piperidine then the compound is less active than the original
- Hydrazide linkage when converted into hydrazone derivatives, a series of active compounds are produced.

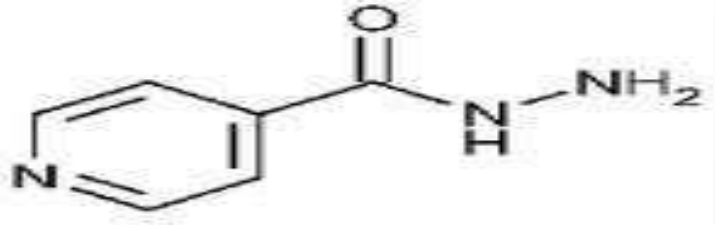


Later it was found that in the body Hydrzones are converted into isoniazid

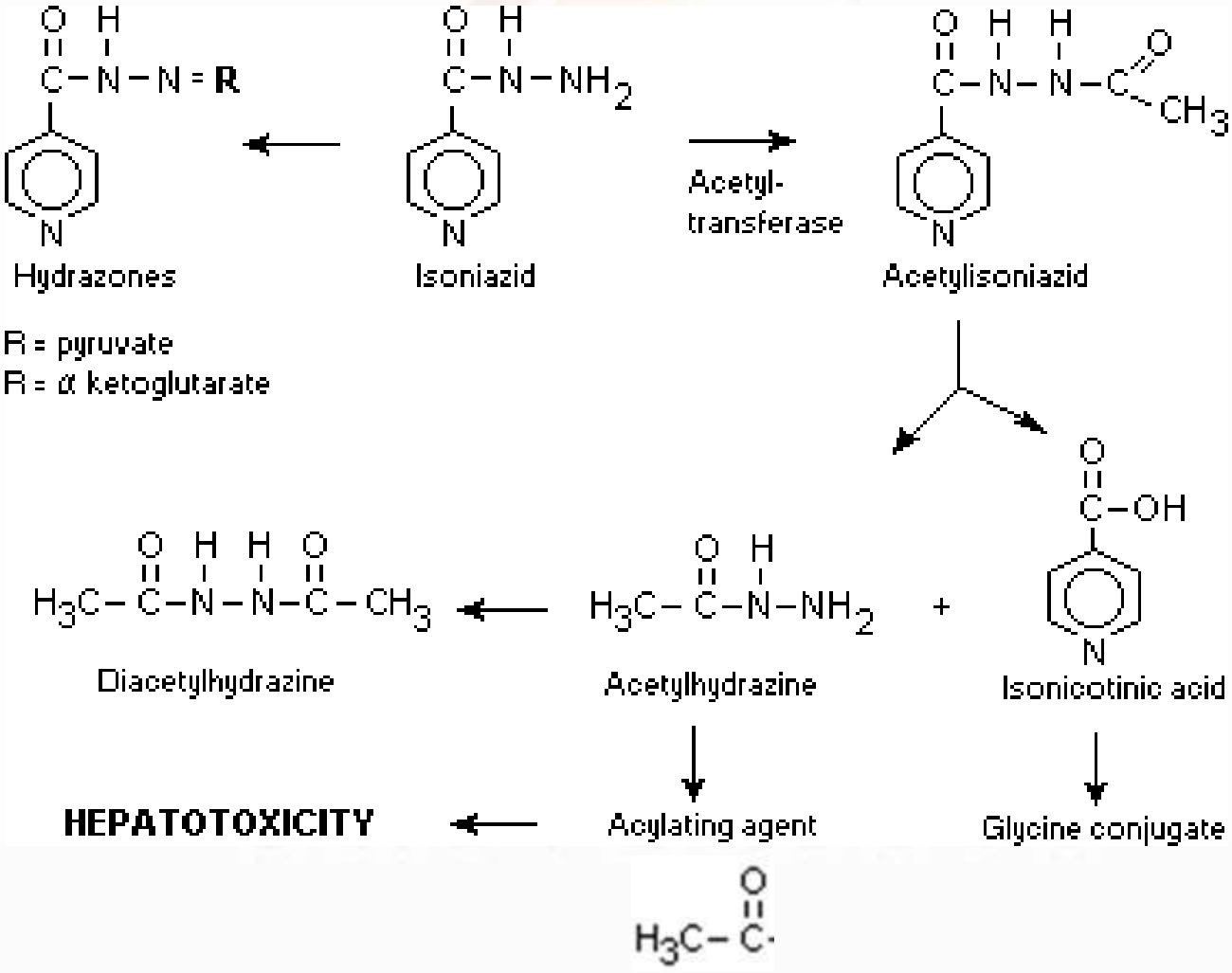


- If hydrazide is shifted to position 2 or 3 instead of 4 then the compound is less active

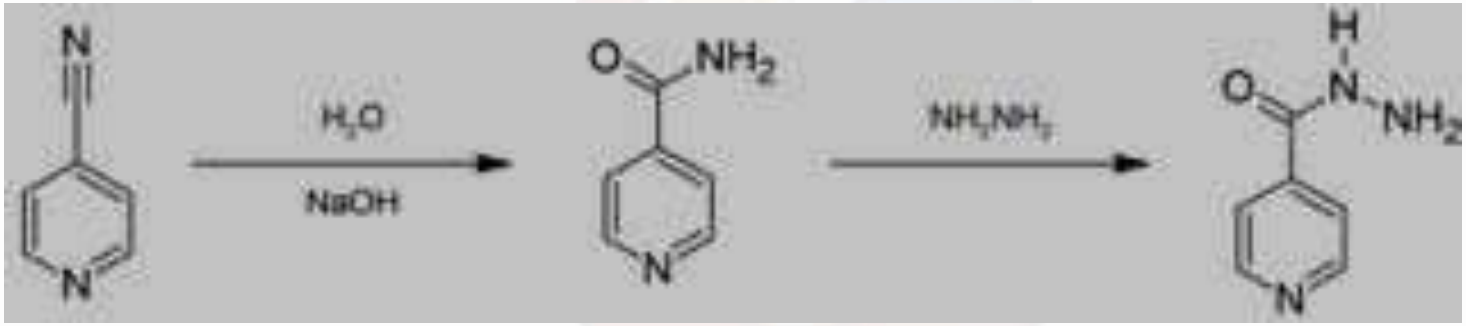
- INH contains two nitrogen atoms, when an alkyl group is introduced at N1 then the compound became inactive
- When any alkyl group is introduced at N2 then a series of active compounds are obtained but these are less active
- If hydarzide group is replaced totally by alkyl or aryl then the compound remains active but less than isonaizide



Metabolism of isoniazid



Chemical synthesis

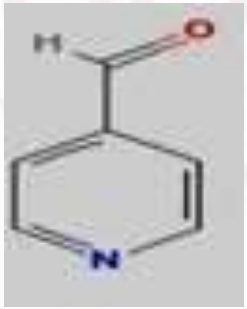


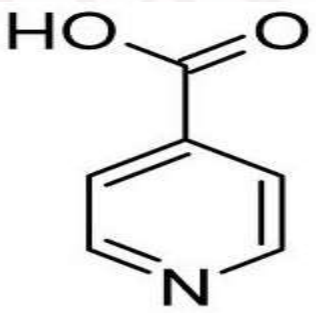
4-cyano pyridine Isonicotinamide Isoniazid

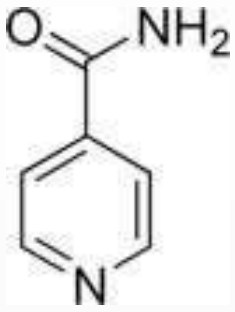
Basic hydrolysis of 4-cyano pyridine converts cyano/nitrile group to an amide- Isonicotinamide- which then reacts with hydrazine to produce isoniazid

Mechanism of action

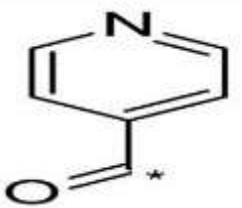
- INH undergoes oxidation reaction by endogenous catalyzing enzymes, producing reactive species capable of acylating the enzyme (*inhA*)-found in MT
- Under the influence of (kat G) a gene also called (*inhA*), INH is converted into isonicotinic aldehyde, isonicotinic acid and isonicotinamide

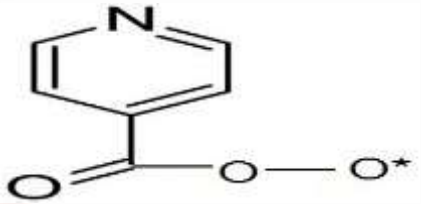






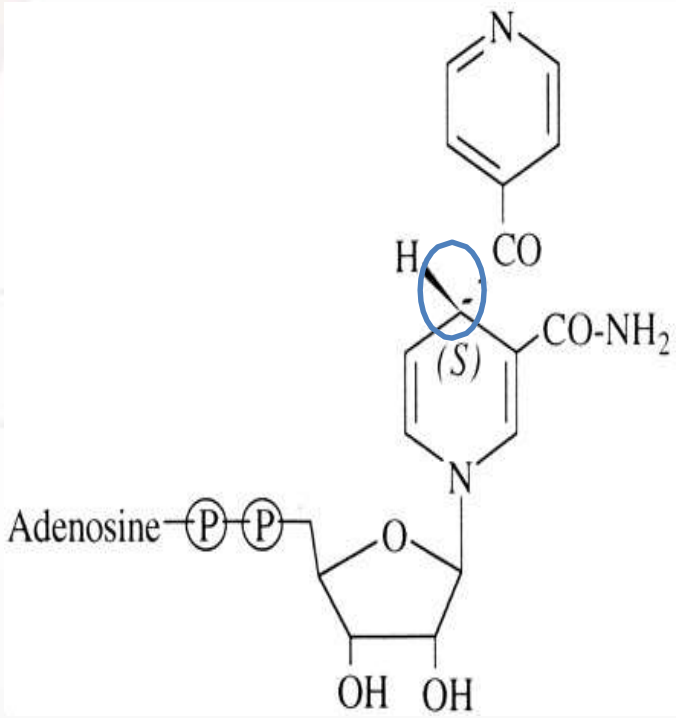
- From these compounds, highly reactive electrophilic species such as isonicotinyl radical and isonicotinyl peroxy radical are formed





- These radicals acylate NADPH dependent β-ketoacyl carrier protein reductase, involved in elongation of mycolic acid. It results in the inhibition of cell wall leading to cell death

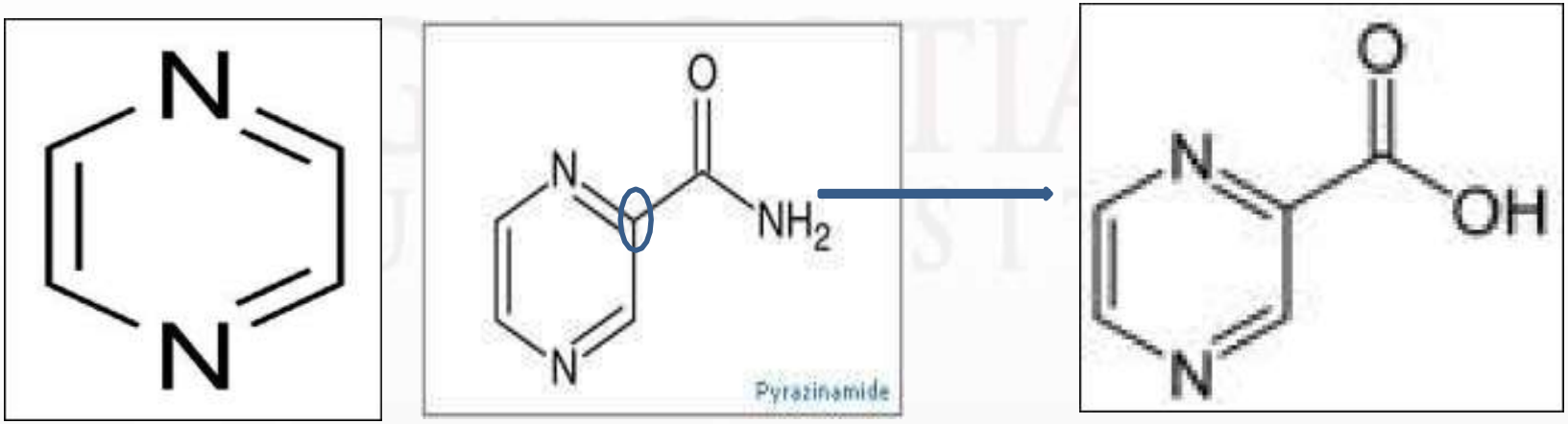
- This enzyme selectively acts on fatty acids (more than 26 carbon). Mycolic acid is a α-branched fatty acids having short arm of 20-24 carbon and long arm of 26-50 carbon
- Additionally, acylating agents combine with position 4 of the NADPH and make it inactive for reduction



- Its therapy causes peripheral neuritis /neuropathy, hence prescribed with vitamin-B6

Pyrazinamide (PZA)

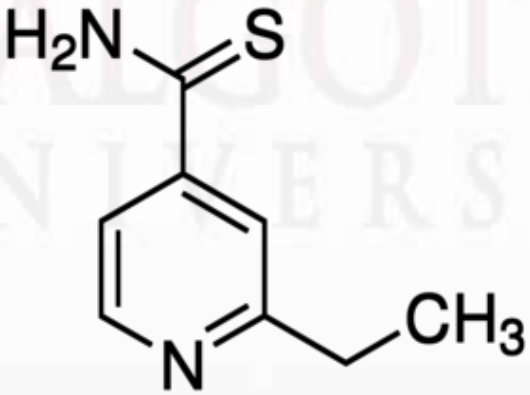
- Contains pyrazine ring in its structure, which is a six memberd heterocyclic ring containing two nitrogen at a distance of 2 carbon atoms
- Pyrazinamide has amide group at position 2
- It is a prodrug and converted into pyrazinoic acid in the body



- Activity is pH dependent and maximum activity takes place at pH 5.5
- It can be considered a derivative of isonicotinic acid, isonicotinic acid has 1 N while pyrazinamide has 2
- Both are called isosteres -those having same biological and physicochemical properties.
- Nitrogen has atomic number 7 whereas CH also has 7, hence isosteres
- OH group of isonicotinic acid/pyrazinoic acid is isosteric with NH_2 group of PZA because both have atomic number 9
- It is active against dormant MT

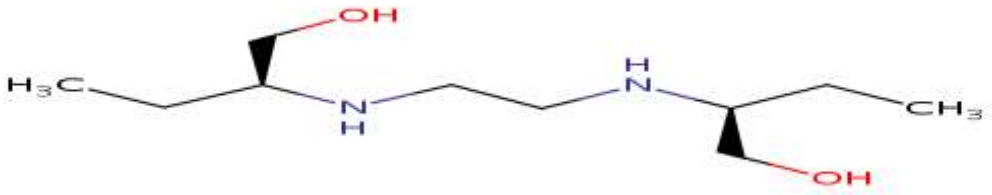
Ethionamide

- Ethionamide may be **bacteriostatic or bactericidal** in action, depending on the **concentration** of the drug attained at the site of infection and the susceptibility of the infecting organism.
- The exact *MECHANISM OF ACTION* of ETHIONAMIDE has not been fully elucidated, but the drug **appears to inhibit peptide synthesis in susceptible organisms**.
- Antimicrobial **spectrum** of Ethionamide comprises *M. tuberculosis*, *M. bovis* and *M. Segmatis.*
- Ethionamide is structurally similar to methimazole, has been shown to **inhibit thyroid hormone synthesis**, and was reported to cause hypothyroidism in several TB patients.



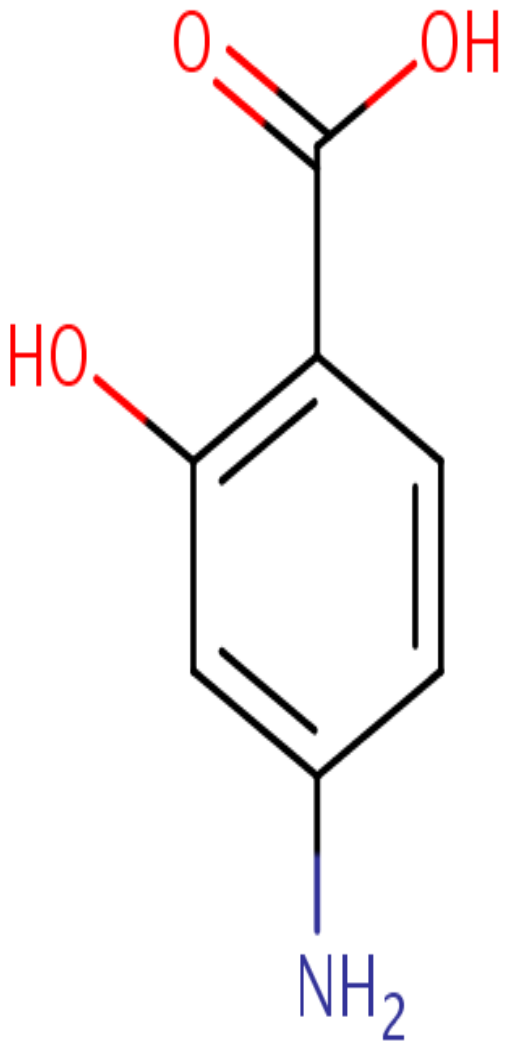
Ethambutol

- An antitubercular agent that **inhibits the transfer of mycolic acids into the cell wall of the tubercle bacillus.**
- It may also **inhibit the synthesis of spermidine in mycobacteria**.
- The action is usually **bactericidal**, and the drug can penetrate **human cell membranes to exert its lethal effect**.
- The most commonly recognized toxic effect of ethambutol is **optic neuropathy**, which generally is considered uncommon and reversible in medical literature.



Para-Aminosalicylic Acid

- Aminosalicylic acid is an anti-mycobacterial agent used with other anti-tuberculosis drugs (most often isoniazid) for the treatment of **all forms of active tuberculosis due to susceptible strains of tubercle bacilli.**



Para-Aminosalicylic Acid

- There are two mechanisms responsible for aminosalicylic acid's **bacteriostatic action** against *Mycobacterium tuberculosis*.
- **Firstly,** aminosalicylic acid **inhibits folic acid synthesis** (without potentiation with antifolic compounds). **The binding of para-aminobenzoic acid to pteridine synthetase acts as the first step in folic acid synthesis.**
- Aminosalicylic acid binds pteridine synthetase with greater affinity than para-aminobenzoic acid, **effectively inhibiting the synthesis of folic acid.**
- As bacteria are unable to use external sources of folic acid, **cell growth and multiplication slows**.
- **Secondly,** aminosalicylic acid may **inhibit the synthesis of the cell wall component, mycobactin**, thus **reducing iron uptake by *M. tuberculosis*.**

Rifampicin.

Mechanism of action: incorporation into DNA spiral, inhibition of DNA-dependent RNA-polymerase → inhibition of replication and transcription in microorganisms.

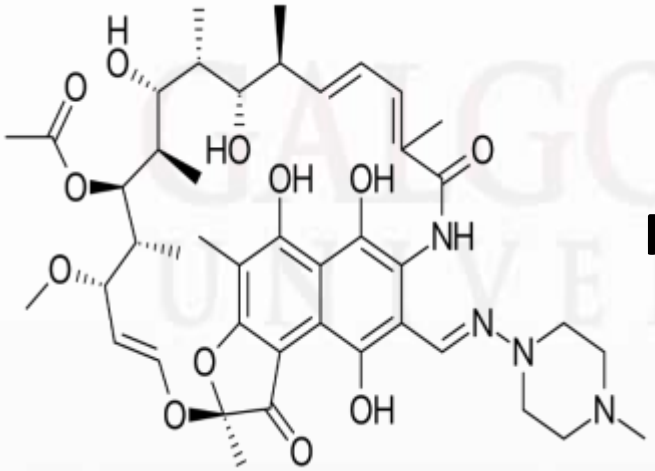
Spectrum of action: wide, Mycobacterium tuberculosis, leprosy.

Bactericidal.

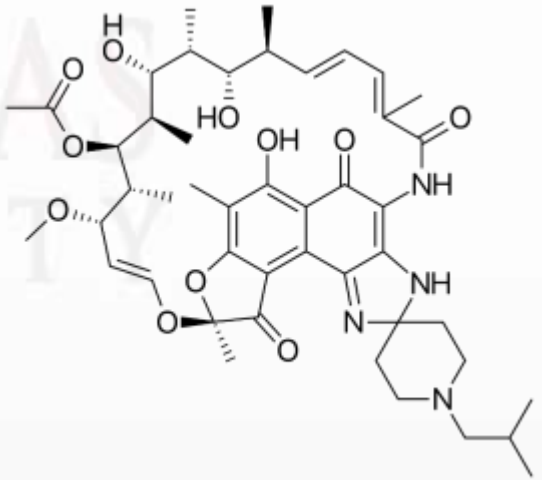
Indications: tuberculosis, leprosy, infections caused by multidrug-resistant pathogens.

Side effects: allergic reactions of heavy genesis, manifested by liver damage; flu-like syndrome, hemolytic anemia.

Rifampicin

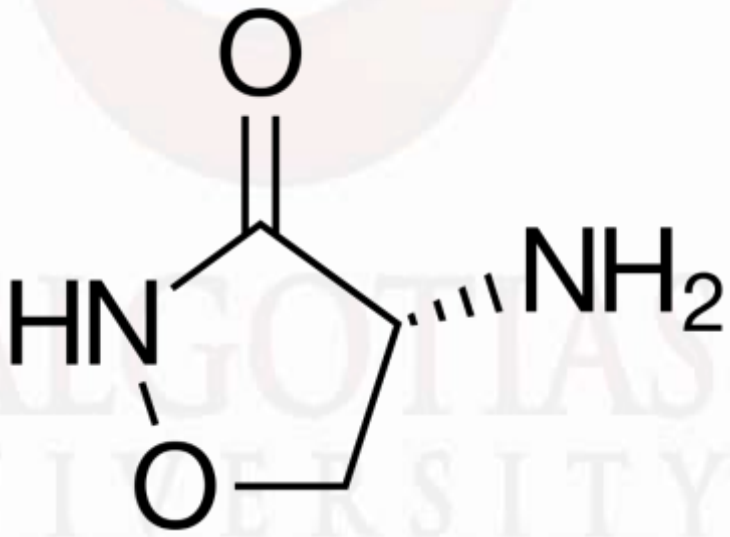


Rifabutin



Cycloserine

- Inhibitor of cell wall synthesis
- 0.5–1 g/d in two divided oral doses
- peripheral neuropathy and central nervous system dysfunction, including depression and psychotic reactions



Capreomycin

- Peptide protein synthesis inhibitor antibiotic obtained from Streptomyces capreolus
- Treatment of drug-resistant tuberculosis
- Strains of M tuberculosis that are resistant to streptomycin or amikacin - susceptible to capreomycin.
- Nephrotoxic and ototoxic - Tinnitus, deafness, and vestibular disturbances occur

Thank you!!!!

Reference

- William O. Foye.,Textbook of Medicinal Chemistry, Pg. no: 1089 -1106
- Sriram., Medicinal Chemistry, Pg. no: 295-309.
- Kadam., Textbook of Medicinal Chemistry, Pg. no: 68-82.
- Ilango., Principles of Medicinal chemistry(vol.1), Pg. no: 121-143.
- Good man And GilMan's; The Pharmacology Basis Of Therapeutics Tenth Edition, pg. no 1189-1225.
- JH Block & JM Beale., Wilson & Giswold's Textbook of Organic Medicinal Chemistry & pharmaceutical chemistry 12th Edition, 2011, pg. No. 260-294.