FirstHope Notes | Pharm D Year - 3

Anti-tubercular Agents

Tuberculosis (TB)

What is Tuberculosis?

- Tuberculosis (TB) is a bacterial infection caused by Mycobacterium tuberculosis.
- While it primarily affects the lungs, it can also spread to other parts of the body, such as the kidneys, spine, and brain.

How is TB Spread?

- TB is an **airborne disease**, meaning it spreads when an infected person **coughs or sneezes**, releasing bacteria into the air.
- It can also be transmitted through **sharing needles** or other injection equipment contaminated with infected blood.

Symptoms of Tuberculosis

- Symptoms of TB can vary but commonly include:
  - **Persistent cough** (lasting more than three weeks)
  - **Chest pain**
  - **Coughing up blood**
  - **Fatigue**
  - **Fever**
  - **Night sweats**
  - **Unexplained weight loss**
- However, not everyone infected with TB develops symptoms.
- The bacteria can **remain dormant** in the body for years, a condition known as **latent TB infection (LTBI)**.

TB Treatment

- Tuberculosis is treatable with antibiotics, but treatment is long and complex, typically lasting six to nine months or longer.
- It involves a combination of several medications to prevent the development of drug-resistant TB strains.

Importance of Completing Treatment

- Even if symptoms improve, it is essential to complete the full course of treatment to ensure complete eradication of the bacteria.

- Incomplete treatment can lead to drug resistance, making TB harder to treat and more dangerous.

Prevention of Tuberculosis

- Prevention strategies include:
    - **Avoiding close contact** with infected individuals
    - **Vaccination** (*BCG vaccine*) in high-risk populations
    - **Early diagnosis and treatment** to prevent the spread of TB

Screening and High-Risk Groups

- **Screening for TB is recommended for individuals at higher risk, including:**
    - People with weakened immune systems (e.g., HIV patients)
    - Those who have had close contact with an infected person

Anti-Tubercular Agents

- Anti-tubercular agents are medications used to treat **tuberculosis (TB)**, a potentially serious and contagious bacterial infection that primarily affects the lungs but can also involve other parts of the body.
- These medications work by **killing or inhibiting the growth of Mycobacterium tuberculosis**, the bacteria responsible for TB.

Factors Influencing Treatment Selection

- The choice of anti-tubercular agents and the duration of treatment depend on several factors, including:
    - The **severity** of the disease
    - The **patient's age and overall health**
    - The **drug susceptibility** of the TB bacteria

Treatment Duration and Importance

- Tuberculosis treatment typically involves a combination of multiple drugs taken for several months to ensure complete eradication of the bacteria and prevent the development of drug resistance.
- Adherence to the prescribed regimen is crucial to achieving successful treatment outcomes.

Classification of Anti-Tubercular Agents

- Anti-tubercular agents are used to treat infections caused by ***Mycobacterium tuberculosis*** and can be classified based on their mechanism of action and chemical structure.

- They are often categorized into first-line and second-line drugs, and further grouped into two main types:

1. Synthetic Anti-Tubercular Agents

- These are chemically synthesized drugs that target various biochemical pathways in M. tuberculosis.
- Examples:
    1. Isoniazid
    2. Ethionamide
    3. Ethambutol
    4. Pyrazinamide
    5. Para-aminosalicylic acid

2. Anti-Tubercular Antibiotics

- These agents are naturally derived or semi-synthetic and work by inhibiting mycobacterial growth through mechanisms such as interfering with bacterial RNA synthesis, protein synthesis, or cell wall formation.
- Examples:
    1. Rifampicin
    2. Rifabutin
    3. Cycloserine
    4. Streptomycin
    5. Capreomycin sulphate

Brand Names Of Important Marketed Products

Used for the treatment of tuberculosis (TB). Often used in combinations.

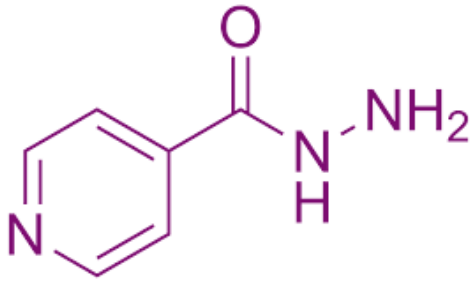
Drug Name	Brand Name(s)	Formulation	Use
Isoniazid (INH)	**Isonex, Nydrazid**	Tablet	First-line TB drug
Rifampicin	**R-cin, Rifadin, R-cinex**	Capsule, Tablet	Bactericidal in TB
Pyrazinamide	**PZA, Zinamide**	Tablet	First 2 months of therapy
Ethambutol	**Myambutol, Combutol**	Tablet	Prevent resistance
Streptomycin	**Streptomycin injection**	Injection	Severe TB, 2nd line
Fixed Dose Combinations (FDCs)	**R-cinex, Forecox, AKT-4**	Tablet	Combination for compliance

Various Synthetic Anti-Tubercular Agents Drugs

1. Isoniazid (INH)*

Chemical Structure / Formula

- **Formula:** C6H7N3O
- **Structure:** Pyridine ring with a hydrazide (-CONHNH$_2$) group.



Mechanism of Action

- **Prodrug** that is activated by **KatG enzyme** (catalase-peroxidase) in *Mycobacterium tuberculosis*.
- Once activated, it forms **isonicotinoyl radical**, which inhibits:
    1. **Enoyl-acyl carrier protein reductase (InhA)** → prevents mycolic acid synthesis (essential for the mycobacterial cell wall).
    2. **Dihydrofolate reductase** → interferes with nucleic acid synthesis.

Uses

- **First-line treatment for tuberculosis (TB)**.
- Used **alone** for **latent TB infection** (LTBI).
- Combined with **rifampicin, ethambutol, and pyrazinamide** for active TB.

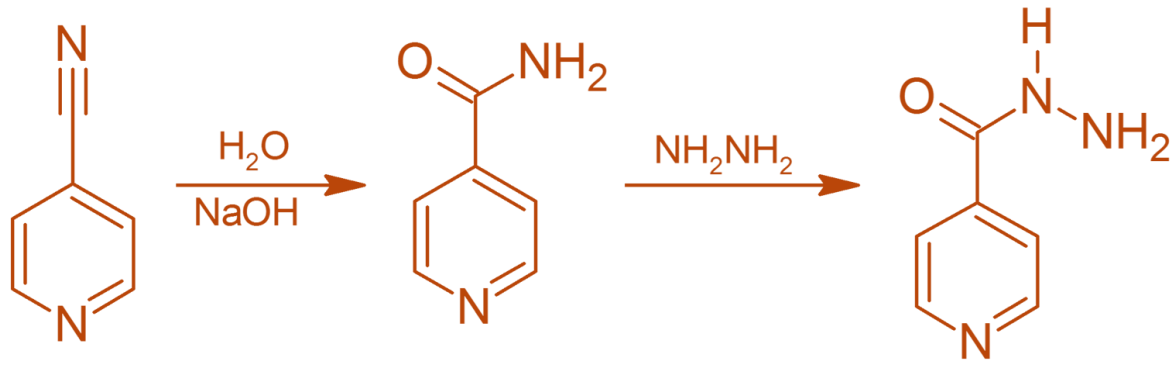
Side Effects

- **Hepatotoxicity** (elevated liver enzymes, hepatitis).
- **Peripheral neuropathy** (due to pyridoxine deficiency – prevented by vitamin B6 supplementation).
- **Neurotoxicity** (seizures, ataxia, dizziness).
- Hemolysis in G6PD-deficient patients.
- Drug-induced lupus (rare).

Structure-Activity Relationship (SAR) of Isoniazid

Structural Feature	SAR Insight
Isonicotinic acid hydrazide core	Essential for activity. Modifications to the hydrazide group generally reduce or eliminate activity.
Hydrazide (-$CONHNH_2$) group	Important for activation by the bacterial catalase-peroxidase enzyme (KatG). Oxidation is necessary for its prodrug activation.
Free –NH_2 group	Critical for forming the isonicotinoyl radical that inhibits InhA (mycolic acid synthesis enzyme).
Substitutions on pyridine ring	Generally, reduce antitubercular activity.
Electron-donating groups	Usually decrease activity by altering binding or red

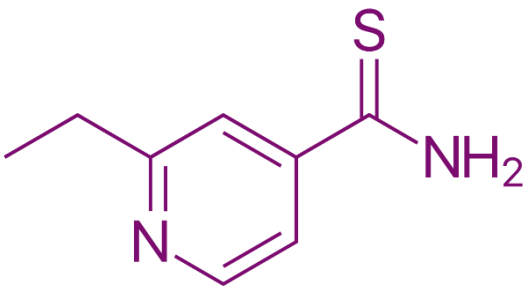
Synthesis of Isoniazid



2. Ethionamide

Chemical Structure / Formula

- **Formula:** C8H10N2S
- **Structure:** Similar to isoniazid but contains a **thioamide (-$CSNH_2$) group** instead of a hydrazide.



Mechanism of Action

- **Prodrug**, activated by mycobacterial **EthA enzyme**.

- Inhibits InhA enzyme, blocking mycolic acid synthesis, disrupting the bacterial cell wall.

Uses

- Second-line drug for multidrug-resistant TB (MDR-TB).

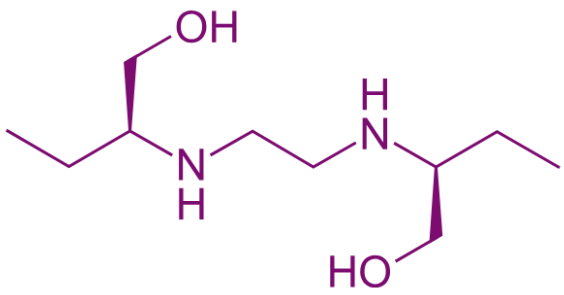
Side Effects

- Hepatotoxicity, neurotoxicity (peripheral neuropathy, psychosis).
- GI disturbances (nausea, vomiting, abdominal pain).
- Hypothyroidism (interferes with thyroid hormone synthesis).

3. Ethambutol

Chemical Structure / Formula

- **Formula:** C10H24N2O2
- **Structure:** A **polyhydroxy ethylenediamine** derivative.



Mechanism of Action

- Inhibits arabinosyl transferase, preventing arabinogalactan polymerization, an essential component of the mycobacterial cell wall.

Uses

- First-line TB treatment (in combination therapy).

Side Effects

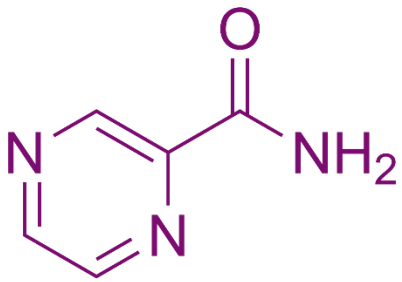
- Optic neuritis (dose-dependent, reversible) – red-green color blindness.
- Hyperuricemia (gout-like symptoms).

4. Pyrazinamide

Chemical Structure / Formula

- **Formula:** C5H5N3O

- **Structure:** A **nicotinamide analog**.



Mechanism of Action

- Prodrug converted into pyrazinoic acid (POA) by pyrazinamidase (pncA enzyme).
- POA disrupts membrane potential and fatty acid synthesis, leading to bacterial death.

Uses

- **First-line TB treatment**, especially in **short-course regimens**.

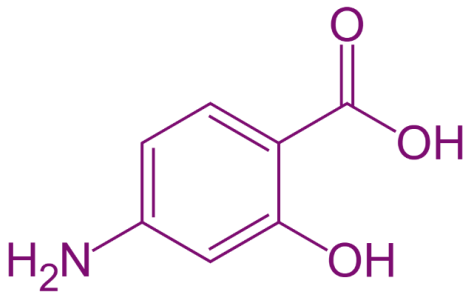
Side Effects

- Hepatotoxicity, hyperuricemia (gout), GI upset.

5. Para-Aminosalicylic Acid (PASA)

Chemical Structure / Formula

- **Formula:** C7H7NO3
- **Structure:** A **p-aminobenzoic acid (PABA) analog**.



Mechanism of Action

- Inhibits **dihydrofolate reductase (DHFR)**, disrupting folic acid metabolism.

Uses

- Second-line treatment for MDR-TB.

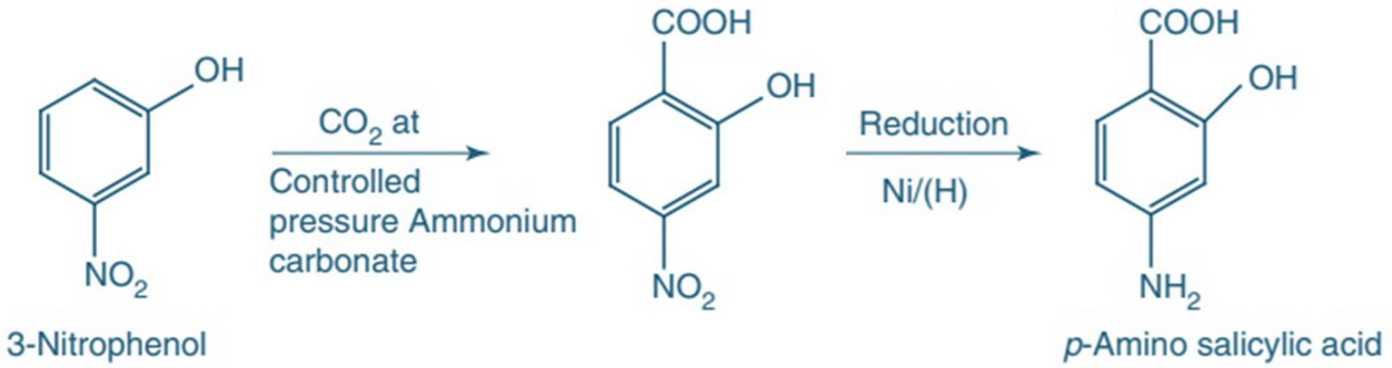
Side Effects

- GI disturbances, hepatotoxicity, hypersensitivity reactions.

Structure-Activity Relationship (SAR)

Structural Feature	SAR Insight
Amino group at para-position	Essential for antimycobacterial activity; mimics PABA to inhibit dihydropteroate synthase.
Carboxylic acid (COOH) at ortho position	Required for activity; interacts with bacterial enzyme system.
Phenolic –OH group	Increases solubility and mimics salicylic acid. Important but not absolutely essential.
Any major substitution on benzene ring	Typically results in loss of activity.
Methyl esters of PAS	May reduce GI side effects while retaining activity.

Synthesis of Para-Aminosalicylic Acid (PASA)



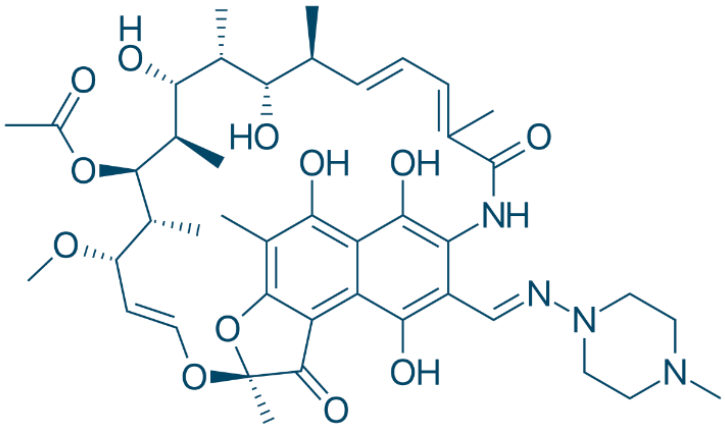
3-Nitrophenol — *p*-Amino salicylic acid

Various Anti-Tubercular Antibiotics Drugs

1. Rifampicin

Chemical Structure / Formula

- **Formula:** C43H58N4O12
- **Structure:** A **rifamycin derivative** with an **ansamycin ring**.



Mechanism of Action

- Binds to **DNA-dependent RNA polymerase**, preventing mRNA transcription.

Uses

- **First-line TB treatment**, also used for **leprosy and MRSA infections**.

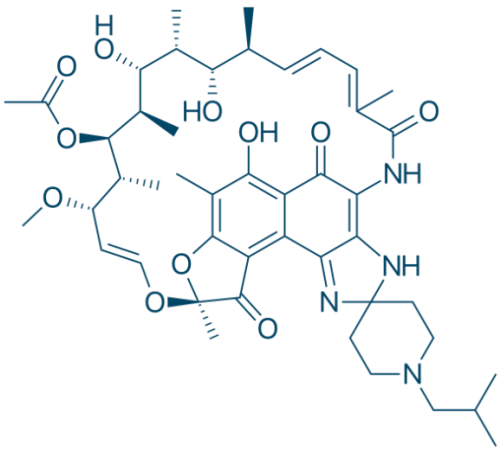
Side Effects

- Hepatotoxicity, red-orange body fluids, strong CYP450 inducer.

2. Rifabutin

Chemical Structure / Formula

- **Formula:** C46H62N4O11
- **Structure:** Similar to rifampicin but with **less CYP450 induction**.



Mechanism of Action

- **Inhibits bacterial RNA polymerase**, preventing mRNA synthesis.

Uses

- **TB treatment in HIV patients** (less interaction with antiretrovirals).

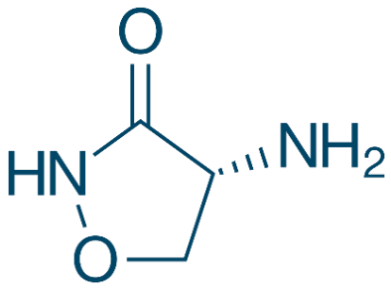
Side Effects

- GI upset, myalgia, uveitis.

3. Cycloserine

Chemical Structure / Formula

- **Formula:** C3H6N2O2
- **Structure:** A **D-alanine analog**.



Mechanism of Action

- Inhibits **D-alanine racemase and D-Ala-D-Ala ligase**, disrupting **peptidoglycan synthesis**.

Uses

- Second-line for MDR-TB.

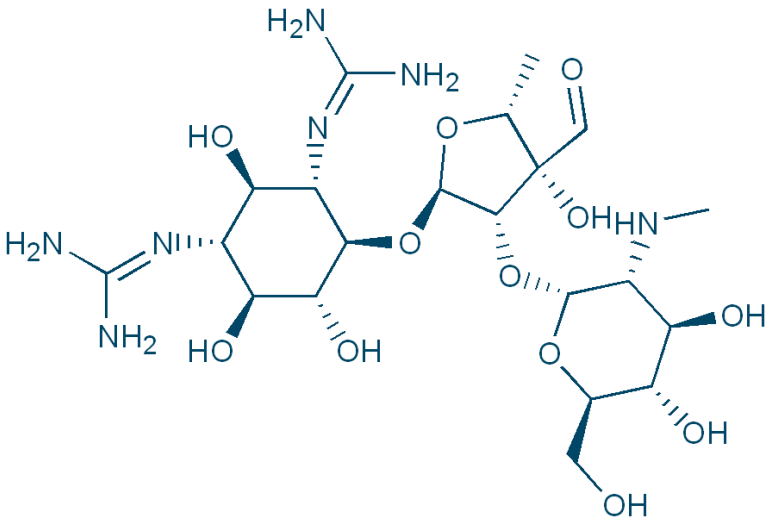
Side Effects

- Neurotoxicity (psychosis, seizures, depression).

4. Streptomycin

Chemical Structure / Formula

- **Formula:** C21H39N7O12
- **Structure:** An **aminoglycoside** with an **aminocyclitol ring**.



Mechanism of Action

- Binds to **30S ribosome**, inhibiting protein synthesis.

Uses

- Second-line for MDR-TB.

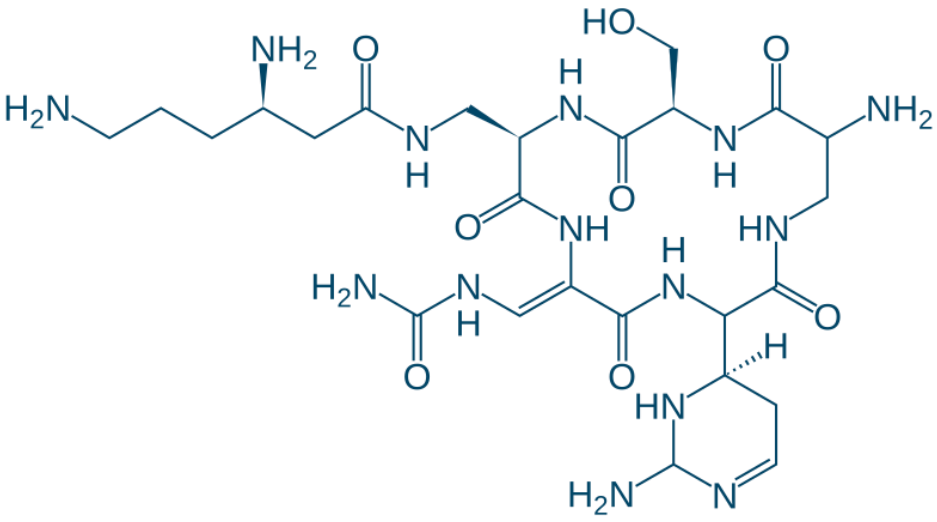
Side Effects

- Ototoxicity, nephrotoxicity, neuromuscular blockade.

5. Capreomycin Sulfate

Chemical Structure / Formula

- **Formula:** C25H44N14O8
- **Structure:** A **cyclic polypeptide antibiotic**.



Mechanism of Action

- Inhibits **ribosomal protein synthesis**.

Uses

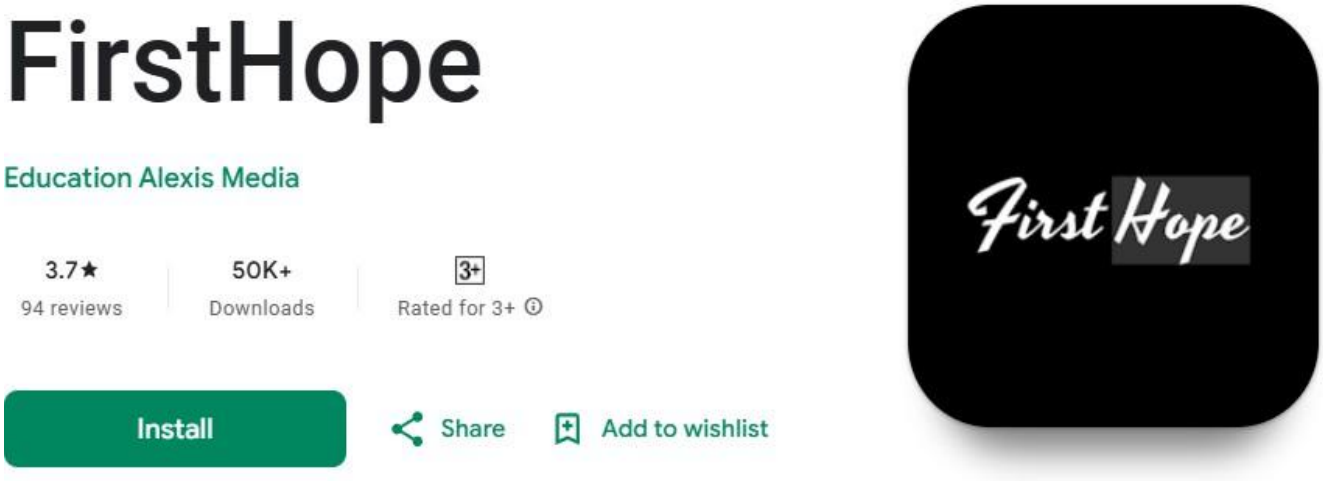
- Second-line treatment for MDR-TB.

Side Effects

- Ototoxicity, nephrotoxicity, hypokalemia.

First Hope

Easy Short Notes Designed to Help You Score Better



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