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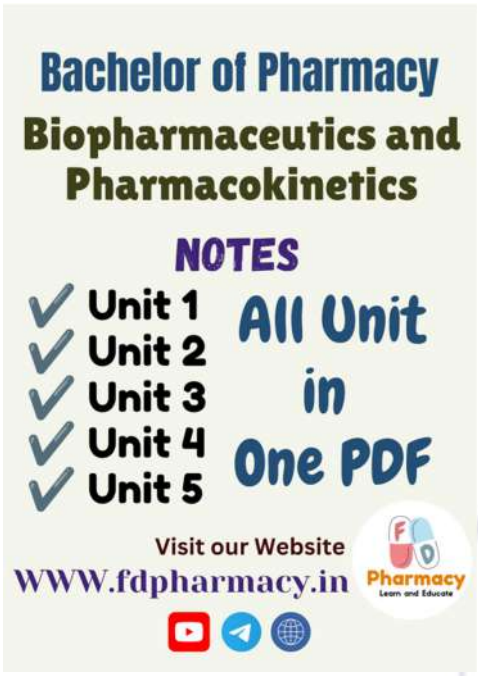
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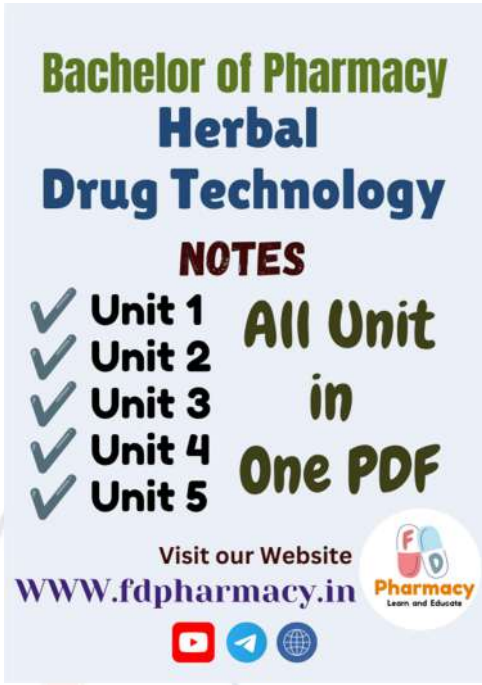
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MEDICINAL CHEMISTRY - III

UNIT 3

TOPIC :

- **Anti-tubercular Agents**

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

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

- **Urinary tract anti-infective agents**

  Quinolones : SAR of quinolones, Nalidixic Acid,Norfloxacin, Enoxacin, Ciprofloxacin, *Ofloxacin, Lomefloxacin, Sparfloxacin, Moxifloxacin* **Miscellaneous :** *Furazolidine, Nitrofurantoin*, Methanamine.

- **Antiviral agents :**

  Amantadine hydrochloride, Rimantadine hydrochloride, Idoxuridine trifluoride, Acyclovir*, Gancyclovir, Zidovudine, Didanosine, Zalcitabine, Lamivudine, Loviride, Delavirding, Ribavirin, Saquinavir, Indinavir, Ritonavir.

Anti-Tubercular Agents

→ Tuberculosis (TB) is a chronic infectious disease caused by Mycobacterium tuberculosis, primarily affecting the lungs but may involve other organs.

→ Anti-tubercular agents (ATAs) are drugs used to treat and prevent tuberculosis. They inhibit the growth of Mycobacterium tuberculosis or kill the bacteria.

Classification

Anti-tubercular drugs are classified based on **effectiveness and usage**:

A. First-Line (Primary) Drugs

- Used for initial treatment of TB. Highly effective with fewer side effects.
  - Isoniazid (INH)
  - Rifampicin (RIF)
  - Pyrazinamide (PZA)
  - Ethambutol (EMB)
  - Streptomycin (SM) – injectable aminoglycoside
- First-line drugs form the standard short-course therapy (6 months).

B. Second-Line (Reserve) Drugs

- Used for multi-drug resistant TB (MDR-TB) or when first-line drugs are ineffective.
  - Aminoglycosides: Amikacin, Kanamycin
  - Fluoroquinolones: Levofloxacin, Moxifloxacin
  - Thioamides: Ethionamide, Prothionamide
  - Cycloserine
  - Para-aminosalicylic acid (PAS)

C. Other Anti-TB Agents

- Clofazimine (for resistant TB)
- Bedaquiline (newer agent for MDR-TB)

Mechanism of Action

Drug	Mechanism
Isoniazid	Inhibits synthesis of mycolic acid, an essential component of mycobacterial cell wall
Rifampicin	Inhibits RNA polymerase, preventing RNA synthesis
Pyrazinamide	Disrupts mycobacterial membrane metabolism in acidic environment
Ethambutol	Inhibits arabinosyl transferase, preventing cell wall formation
Streptomycin	Binds 30S ribosomal subunit, inhibiting protein synthesis

Drug Resistance

- Primary resistance: inherent resistance of bacteria
- Secondary resistance: develops due to incomplete or irregular therapy

Mechanisms:

- Mutation in target enzymes (e.g., RNA polymerase for Rifampicin)
- Drug inactivation
- Reduced drug uptake

Synthetic Anti-Tubercular Agents

→ Synthetic anti-tubercular agents are chemically synthesized drugs used to treat tuberculosis (TB) caused by Mycobacterium tuberculosis.

→ They act by inhibiting bacterial cell wall synthesis, protein synthesis, or nucleic acid synthesis.

Classification

Synthetic anti-TB drugs can be classified based on primary mechanism of action:

A. Rifamycins (RNA synthesis inhibitors)

- Rifampicin
- Rifabutin
- Rifapentine

B. Inhibitors of Mycolic Acid Synthesis (Cell wall inhibitors)

- Isoniazid (INH)
- Ethionamide

C. Others / Miscellaneous Synthetic Agents

- Pyrazinamide
- Ethambutol (technically partially synthetic)
- Cycloserine
- Capreomycin

Mechanism of Action

A. Rifamycins (Rifampicin)

- Inhibit DNA-dependent RNA polymerase
- Prevent RNA synthesis
- Bactericidal

B. Isoniazid (INH)

- Inhibits mycolic acid synthesis
- Interferes with cell wall formation
- Bactericidal (actively dividing bacteria)

C. Ethionamide

- Similar to INH

- Prodrug → inhibits mycolic acid synthesis

D. Pyrazinamide

- Converted to pyrazinoic acid
- Lowers intracellular pH
- Effective against semi-dormant bacilli in acidic environments

Spectrum of Activity

⇨ Effective against Mycobacterium tuberculosis

⇨ Some drugs active against M. bovis, M. kansasii

⇨ Pyrazinamide → effective against latent/semi-dormant TB bacilli

Therapeutic Uses

→ First-line treatment of active TB → Rifampicin, INH, Pyrazinamide, Ethambutol (RIPE regimen)

→ Latent TB treatment → INH

→ Drug-resistant TB → Ethionamide, Cycloserine, Capreomycin

Adverse Effects

Drug	Major Adverse Effects
Rifampicin	Hepatotoxicity, orange discoloration of body fluids, flu-like syndrome
Isoniazid	Hepatitis, peripheral neuropathy (give pyridoxine)
Ethionamide	Gastrointestinal upset, hepatotoxicity, neuropathy
Pyrazinamide	Hepatotoxicity, hyperuricemia (gout)
Ethambutol	Optic neuritis (red-green color blindness)
Cycloserine	CNS effects – headache, psychosis, seizures
Capreomycin	Nephrotoxicity, ototoxicity

Resistance

- INH resistance → mutation in *katG* gene
- Rifampicin resistance → mutation in *rpoB* gene
- Combination therapy is essential to prevent resistance

Isoniazid (INH)

→ Isoniazid is a first-line synthetic antitubercular drug used in the treatment and prophylaxis of tuberculosis (TB).
→ It is bactericidal against actively growing *Mycobacterium tuberculosis* and bacteriostatic against dormant bacilli.
→ Isoniazid selectively inhibits mycolic acid synthesis, which is essential for mycobacterial cell wall integrity.
→ It is highly effective, orally active, and widely used in combination therapy for TB.

Classification

Based on Chemical Class

- Hydrazide of isonicotinic acid

Based on Antitubercular Action

- First-line antitubercular agent
- Bactericidal against replicating bacilli

Based on Origin

- Synthetic antitubercular agent

Structure

→ Isoniazid is the isonicotinic acid hydrazide.

Important structural features:

- Pyridine ring (isonicotinic acid)
- Hydrazide functional group (-$CONHNH_2$)

Molecular formula: $C_6H_7N_3O$

Structural Characteristics

- Small, polar molecule → good oral absorption
- Requires activation by mycobacterial catalase-peroxidase (KatG) to exert activity
- Hydrazide group interacts with NAD^+ cofactor in fatty acid synthesis

Nomenclature

- Iso → isonicotinic acid
- Niazid → hydrazide functional group
- Available as isoniazid tablets or injections

Stereochemistry

Isoniazid is **achiral**

Activity depends on **activation by mycobacterial KatG enzyme**

Mechanism of Action

- ⇨ Isoniazid is activated by mycobacterial catalase-peroxidase (KatG).
- ⇨ Forms a reactive intermediate that inhibits enoyl-acyl carrier protein reductase (InhA).
- ⇨ Blocks mycolic acid synthesis → essential for cell wall formation.
- ⇨ Results in bacterial death (bactericidal) in replicating bacilli and growth inhibition (bacteriostatic) in dormant bacilli.
- ⇨ Hence, isoniazid is a cell wall synthesis inhibitor specific for mycobacteria.

Spectrum of Activity

- *Mycobacterium tuberculosis* (primary)
- *Mycobacterium bovis*
- Ineffective against most other bacteria
- Active against both intracellular and extracellular bacilli

Uses

- Treatment of active tuberculosis (usually in combination with rifampicin, pyrazinamide, ethambutol)
- Prophylaxis of latent TB infection
- Part of short-course and long-course TB chemotherapy

Adverse Effects

- Hepatotoxicity (monitor liver function)
- Peripheral neuropathy (prevented with pyridoxine supplementation)
- Gastrointestinal: nausea, vomiting
- CNS: headache, dizziness
- Rare: lupus-like syndrome, hematological effects (anemia, thrombocytopenia)

Chemical Degradation

1. Acid Degradation

- Stable in mild acidic conditions

2. Alkaline Degradation

- Decomposes in strong alkali

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light

Structure–Activity Relationship (SAR)

Hydrazide Group (-$CONHNH_2$)

- Essential for activation by KatG enzyme

Pyridine Ring

- Ensures selectivity for mycobacterial enzymes

Activation Requirement

- Must be metabolized by mycobacteria → selective toxicity

Oral Bioavailability

- Small, polar structure ensures good absorption

Ethionamide

→ Ethionamide is a synthetic second-line antitubercular drug used to treat multidrug-resistant tuberculosis (MDR-TB).
→ It is structurally similar to isoniazid and acts as a bactericidal agent against actively growing *Mycobacterium tuberculosis*.
→ Ethionamide inhibits mycolic acid synthesis, thereby compromising mycobacterial cell wall integrity.
→ It is orally active and used in combination therapy for resistant TB strains.

Classification

Based on Chemical Class

- Thioamide derivative

Based on Antitubercular Action

- Second-line antitubercular agent
- Bactericidal against replicating bacilli

Based on Origin

- Synthetic antitubercular agent

Structure

Ethionamide contains:

- Thioamide functional group (-$CSNH_2$)
- Pyridine ring

Important structural features:

- Thiocarbonyl group (essential for activation)
- Pyridine nucleus similar to isoniazid

Molecular formula: $C_8H_{10}N_2S$

Structural Characteristics

- Lipophilic → good oral absorption
- Activated by mycobacterial monooxygenase (EthA) to form reactive species
- Blocks mycolic acid biosynthesis

Nomenclature

- Ethionamide → thioamide derivative of ethylpyridine
- Available as oral tablets or suspensions

Stereochemistry

- Ethionamide is achiral
- Activity depends on activation by mycobacterial enzyme EthA

Mechanism of Action

- Ethionamide is a prodrug activated by mycobacterial flavin monooxygenase (EthA).
- The activated species inhibits enoyl-acyl carrier protein reductase (InhA).
- Blocks mycolic acid synthesis, essential for the mycobacterial cell wall.
- Leads to bactericidal action against replicating bacilli.
- Hence, ethionamide is a cell wall synthesis inhibitor similar to isoniazid, but used for resistant TB.

Spectrum of Activity

- *Mycobacterium tuberculosis* (including MDR strains)
- Limited activity against other mycobacteria
- Active against intracellular and extracellular bacilli

Uses

- Treatment of multidrug-resistant tuberculosis (MDR-TB)
- Part of second-line combination therapy
- Used when first-line agents (isoniazid, rifampicin) cannot be used

Adverse Effects

- Gastrointestinal: nausea, vomiting, abdominal discomfort
- Hepatotoxicity (monitor liver function)
- Peripheral neuropathy (prevented with pyridoxine)
- CNS: dizziness, depression, lethargy
- Rare: hypothyroidism, gynecomastia

Chemical Degradation

1. Acid Degradation

- Stable in mild acidic conditions

2. Alkaline Degradation

- Sensitive in strong alkali

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light and moisture

Structure–Activity Relationship (SAR)

Thioamide Group (-$CSNH_2$)

- Essential for activation by EthA enzyme

Pyridine Ring

- Ensures selectivity for mycobacterial enzymes

Prodrug Nature

- Requires enzymatic activation → selective toxicity

Lipophilicity

- Facilitates oral absorption and tissue penetration

Combination Therapy

- Reduces resistance and enhances efficacy in MDR-TB

Ethambutol (EMB)

→ Ethambutol is a first-line antitubercular drug used in combination therapy for tuberculosis (TB).
→ It is bacteriostatic, acting primarily on actively growing *Mycobacterium tuberculosis*.
→ Ethambutol interferes with mycobacterial cell wall synthesis by inhibiting arabinosyl transferases, which are essential for the formation of arabinogalactan.
→ It is orally active and widely used in initial TB therapy and for treatment of drug-resistant TB.

Classification

Based on Chemical Class

- Diaminobutanol derivative

Based on Antitubercular Action

- First-line antitubercular agent
- Bacteriostatic against replicating bacilli

Based on Origin

- Synthetic antitubercular agent

Structure

Ethambutol contains:

- Diaminobutanol chain
- Two primary amine groups (-NH_2)

Important structural features:

- Linear aliphatic chain with terminal amino groups
- Hydroxyl group for solubility

Molecular formula: $C_{10}H_{22}N_2O_2$

Structural Characteristics

- Water-soluble → good oral absorption
- Selectively inhibits arabinogalactan synthesis in mycobacterial cell wall
- Minimal activity against non-mycobacterial organisms

Nomenclature

- Ethambutol → ethyl-substituted diaminobutanol
- Available as ethambutol hydrochloride tablets or oral solution

Stereochemistry

- Ethambutol contains one chiral center
- (+)-enantiomer is active, while the (–)-enantiomer is inactive
- Correct stereochemistry is important for antibacterial activity

Mechanism of Action

- Ethambutol inhibits arabinosyl transferases (EmbB) in *Mycobacterium tuberculosis*.
- Blocks polymerization of arabinose into arabinogalactan, an essential component of the mycobacterial cell wall.
- Weakens the cell wall → inhibits bacterial growth (bacteriostatic).
- Hence, ethambutol is a cell wall synthesis inhibitor specific for mycobacteria.

Spectrum of Activity

- *Mycobacterium tuberculosis* (primary)
- *Mycobacterium kansasii* and other slow-growing mycobacteria
- Active against **extracellular and intracellular bacilli**

Uses

- Initial therapy for TB in combination with isoniazid, rifampicin, and pyrazinamide
- Treatment of drug-resistant TB
- Prophylaxis in some high-risk cases (less common)

Adverse Effects

- Optic neuritis (red-green color blindness; dose-dependent)
- Peripheral neuropathy (rare)
- Gastrointestinal: nausea, vomiting
- Mild hepatotoxicity (rare)
- Generally well tolerated at recommended doses

Chemical Degradation

1. Acid Degradation

- Stable in mild acidic conditions

2. Alkaline Degradation

- Sensitive in strong alkali

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light

Structure–Activity Relationship (SAR)

Diaminobutanol Chain

- Essential for inhibition of arabinosyl transferase

Hydroxyl Group

- Enhances solubility and absorption

Chirality (+)-enantiomer

- Active form for mycobacterial inhibition

Bacteriostatic Action

- Inhibits cell wall synthesis → slows growth

Pyrazinamide (PZA)

→ Pyrazinamide is a first-line antitubercular drug used in combination therapy for tuberculosis (TB).
→ It is bactericidal against *Mycobacterium tuberculosis* in acidic environments, such as those found in phagolysosomes of macrophages.
→ Pyrazinamide shortens the duration of TB therapy when used in combination with isoniazid and rifampicin.
→ It is orally active and widely used in initial intensive TB treatment phase.

Classification

Based on Chemical Class

- Pyrazine derivative

Based on Antitubercular Action

- First-line antitubercular agent
- Bactericidal against intracellular bacilli

Based on Origin

- Synthetic antitubercular agent

Structure

Pyrazinamide contains:

- Pyrazine ring
- Amide functional group (-$CONH_2$)

Important structural features:

- Small polar molecule → good oral absorption
- Active at acidic pH

Molecular formula: $C_5H_5N_3O$

Structural Characteristics

- Orally absorbed and distributed intracellularly
- Converted in vivo by mycobacterial pyrazinamidase (PncA) to pyrazinoic acid, the active form
- Targets bacteria in acidic environments

Nomenclature

- Pyraza → pyrazine ring
- Namide → amide functional group
- Available as pyrazinamide tablets

Stereochemistry

- Pyrazinamide is achiral
- Activity depends on conversion to pyrazinoic acid by mycobacterial enzyme PncA

Mechanism of Action

- Pyrazinamide is a prodrug converted by mycobacterial pyrazinamidase into pyrazinoic acid (POA).
- POA accumulates in acidic intracellular environment, disrupting membrane potential and energy production.
- Inhibits fatty acid synthase I → impairs mycolic acid synthesis.
- Leads to bactericidal activity against intracellular bacilli.
- Hence, pyrazinamide is a bactericidal, intracellular-specific antitubercular drug.

Spectrum of Activity

- *Mycobacterium tuberculosis* (primary)
- Active against intracellular, dormant, and slowly replicating bacilli
- Ineffective against other mycobacteria

Uses

- Initial intensive therapy of TB (with isoniazid, rifampicin, ethambutol)
- Shortens TB treatment duration
- Used in drug-sensitive and some resistant TB regimens

Adverse Effects

- Hepatotoxicity (monitor liver function)
- Hyperuricemia → gout attacks
- Gastrointestinal: nausea, vomiting, loss of appetite
- Arthralgia (joint pain)
- Rare: rash, photosensitivity
- Generally well tolerated at recommended doses

Chemical Degradation

1. Acid Degradation

- Stable under normal acidic conditions

2. Alkaline Degradation

- Sensitive in strong alkali

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light and moisture

Structure–Activity Relationship (SAR)

Pyrazine Ring

- Essential for prodrug conversion by pyrazinamidase

Amide Group (-$CONH_2$)

- Required for formation of pyrazinoic acid

Prodrug Nature

- Selective toxicity toward intracellular acidic environments

Lipophilicity & Small Size

- Facilitates entry into macrophages and acidic compartments

Para-Amino Salicylic Acid (PAS)

→ Para-aminosalicylic acid (PAS) is a second-line antitubercular drug used to treat multidrug-resistant tuberculosis (MDR-TB).
→ It is bacteriostatic and acts primarily on actively growing *Mycobacterium tuberculosis*.
→ PAS inhibits folate synthesis in mycobacteria, thereby interfering with DNA, RNA, and protein synthesis.
→ It is orally active and usually administered in combination therapy to prevent resistance.

Classification

Based on Chemical Class

- P-aminobenzoic acid (PABA) analogue

Based on Antitubercular Action

- Second-line antitubercular agent
- Bacteriostatic

Based on Origin

- Synthetic antitubercular agent

Structure

PAS contains:

- Salicylic acid moiety (ortho-hydroxybenzoic acid)
- Para-amino group ($-NH_2$)

Important structural features:

- Aromatic ring with hydroxyl and amino substitutions
- Analog of para-aminobenzoic acid (PABA)

Molecular formula: $C_7H_7NO_3$

Structural Characteristics

- Orally absorbable
- Competes with PABA → inhibits dihydropteroate synthase in folate pathway
- Weak antibacterial activity alone; used mainly in combination

Nomenclature

- Para-amino → amino group at para position of benzene ring
- Salicylic acid → ortho-hydroxybenzoic acid moiety
- Available as PAS granules or tablets

Stereochemistry

- PAS is achiral
- Activity depends on structural mimicry of PABA

Mechanism of Action

→ PAS acts as a competitive antagonist of para-aminobenzoic acid (PABA).
→ Inhibits dihydropteroate synthase, an enzyme in folic acid synthesis.
→ Reduces production of tetrahydrofolate, essential for DNA, RNA, and protein synthesis.
→ Leads to inhibition of bacterial growth (bacteriostatic).
→ Hence, PAS is a folate synthesis inhibitor specific for mycobacteria.

Spectrum of Activity

- *Mycobacterium tuberculosis* (including MDR strains)
- Active against slow-growing and intracellular bacilli
- Limited activity against other bacteria

Uses

- Treatment of multidrug-resistant tuberculosis (MDR-TB)
- Used in combination therapy with isoniazid, rifampicin, ethionamide, or streptomycin
- Reduces development of drug resistance

Adverse Effects

- Gastrointestinal: nausea, vomiting, abdominal pain
- Hypersensitivity reactions: rash, fever
- Hepatotoxicity (rare)
- Gastrointestinal intolerance is common → often given with meals

Chemical Degradation

1. Acid Degradation
- Stable in mild acidic conditions

2. Alkaline Degradation
- Decomposes in strong alkali

3. Photodegradation
- Sensitive to light

4. Thermal Degradation
- Heat accelerates decomposition

Prevention

- Store in cool, dry place
- Protect from light and moisture

Structure–Activity Relationship (SAR)

Para-Amino Group (-NH_2)

- Essential for competitive inhibition of PABA

Salicylic Acid Moiety

- Ensures bacterial uptake and activity

Structural Analogy to PABA

- Blocks folate synthesis selectively in mycobacteria

Combination Therapy

- Increases efficacy and prevents resistance