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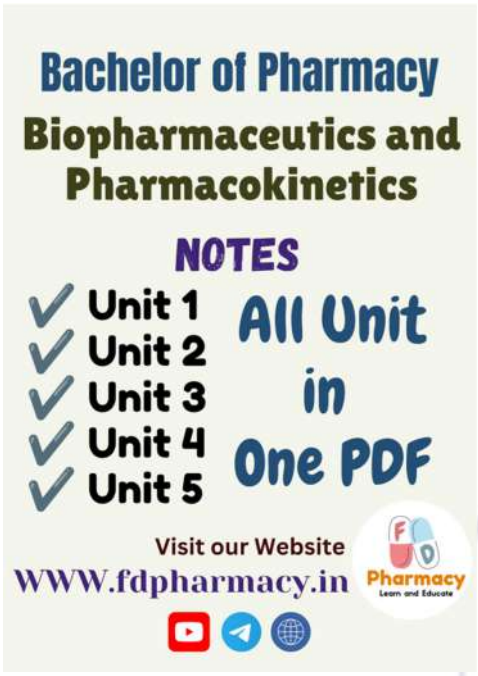
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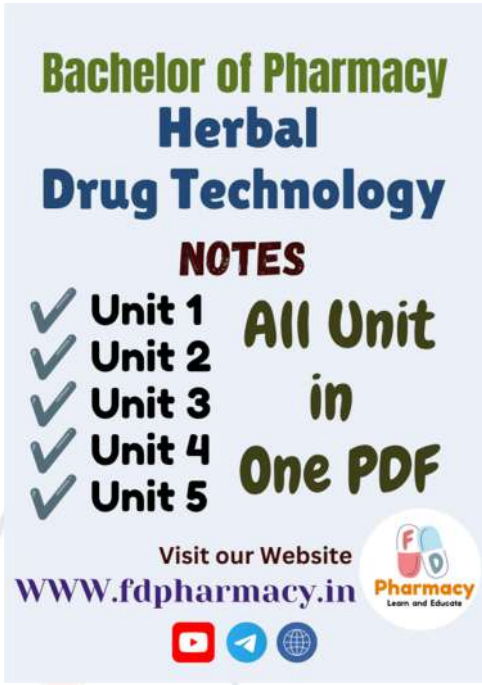
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MEDICINAL CHEMISTRY - III

UNIT 3

TOPIC :

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

Anti-Tubercular Antibiotics

→ Anti-tubercular antibiotics are drugs used to treat tuberculosis (TB) caused by Mycobacterium tuberculosis.

→ They act by inhibiting bacterial cell wall synthesis, protein synthesis, or nucleic acid synthesis, leading to bactericidal or bacteriostatic effects.

Classification

A. First-Line Anti-TB Antibiotics (RIPE Regimen)

Rifampicin – RNA polymerase inhibitor
Isoniazid (INH) – Mycolic acid synthesis inhibitor
Pyrazinamide – Active in acidic environment (semi-dormant bacilli)
Ethambutol – Inhibits arabinosyl transferase (cell wall synthesis)

B. Second-Line Anti-TB Antibiotics

Aminoglycosides

Streptomycin, Kanamycin, Amikacin → Protein synthesis inhibitor (30S ribosome)

Fluoroquinolones

Levofloxacin, Moxifloxacin → DNA gyrase inhibitor

Other synthetic drugs

Ethionamide, Cycloserine, Capreomycin → Various mechanisms

Mechanism of Action

Drug	MOA	Type
Isoniazid (INH)	Inhibits mycolic acid synthesis	Bactericidal
Rifampicin	Inhibits DNA-dependent RNA polymerase	Bactericidal
Pyrazinamide	Converted to pyrazinoic acid → lowers pH → kills semi-dormant bacilli	Bactericidal
Ethambutol	Inhibits arabinogalactan synthesis in cell wall	Bacteriostatic
Streptomycin	Inhibits 30S ribosome → protein synthesis	Bactericidal
Ethionamide	Inhibits mycolic acid synthesis	Bactericidal
Cycloserine	Inhibits D-alanine incorporation in peptidoglycan	Bacteriostatic
Capreomycin	Inhibits protein synthesis	Bactericidal

Spectrum of Activity

- Mycobacterium tuberculosis
- Mycobacterium bovis
- Some activity against non-tubercular mycobacteria (NTM)
- Pyrazinamide → acts on latent/semi-dormant bacilli

Therapeutic Uses

- Active TB treatment → RIPE regimen
- Latent TB treatment → Isoniazid
- Drug-resistant TB → Fluoroquinolones, Aminoglycosides, Ethionamide, Cycloserine
- Combination therapy prevents resistance

Adverse Effects

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

Resistance

- INH resistance → mutation in *katG* gene
- Rifampicin resistance → mutation in *rpoB* gene
- Resistance prevented by combination therapy

Rifampicin (RIFAMPIN)

→ Rifampicin is a first-line antitubercular drug used for the treatment of tuberculosis (TB) and leprosy.
→ It is bactericidal against actively growing and dormant *Mycobacterium tuberculosis*.
→ Rifampicin inhibits bacterial RNA synthesis by targeting DNA-dependent RNA polymerase, leading to rapid bacterial death.
→ It is orally active, widely distributed in tissues, and a cornerstone of short-course combination therapy for TB.

Classification

Based on Chemical Class

- Rifamycin derivative (macrocyclic antibiotic)

Based on Antitubercular Action

- First-line antitubercular agent
- Bactericidal against both replicating and dormant bacilli

Based on Origin

- Semi-synthetic antibiotic derived from *Streptomyces rifamycinica*

Structure

Rifampicin contains:

- Ansamycin macrocyclic ring
- Multiple hydroxyl and keto groups

Important structural features:

- Naphthohydroquinone nucleus
- Macrocyclic ansa bridge connecting aromatic rings

Molecular formula: $C_{45}H_{58}N_4O_{12}$

Structural Characteristics

- Lipophilic → good tissue penetration
- Inhibits DNA-dependent RNA polymerase
- Active against intracellular and extracellular mycobacteria

Nomenclature

- **Rifa** → derived from rifamycin
- **Mpicin** → antibiotic suffix
- Available as **Rifampicin capsules, tablets, or injections**

Stereochemistry

- Rifampicin contains multiple chiral centers
- Correct stereochemistry is essential for binding to RNA polymerase

Mechanism of Action

→ Rifampicin binds to the β-subunit of bacterial DNA-dependent RNA polymerase.
→ Inhibits transcription initiation.
→ Prevents RNA synthesis → blocks protein production.
→ Leads to rapid bactericidal activity against *Mycobacterium tuberculosis*.
→ Hence, rifampicin is a RNA synthesis inhibitor.

Spectrum of Activity

- *Mycobacterium tuberculosis*
- *Mycobacterium leprae* (leprosy)
- Gram-positive cocci (Staphylococcus aureus, Streptococcus spp.)
- Some Gram-negative bacteria (Haemophilus influenzae, Neisseria meningitidis)

Uses

◈ Treatment of active tuberculosis (in combination with isoniazid, pyrazinamide, ethambutol)
◈ Short-course therapy for leprosy
◈ Prophylaxis for meningococcal carriers
◈ Part of therapy for MDR-TB in combination with other drugs

Adverse Effects

→ Gastrointestinal: nausea, vomiting
→ Hepatotoxicity (monitor liver function)
→ Orange-red discoloration of urine, sweat, tears (harmless but permanent)
→ Flu-like syndrome (rare)

Chemical Degradation

1. Acid Degradation

- Stable in acidic medium

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)

Ansamycin Macrocyclic Ring

- Essential for binding to RNA polymerase

Hydroxyl and Keto Groups

- Important for hydrogen bonding with enzyme

Lipophilicity

- Facilitates tissue penetration and intracellular activity

Chirality

- Maintains high-affinity binding to RNA polymerase

Rifabutin

→ Rifabutin is a semi-synthetic rifamycin antibiotic used primarily in the treatment and prevention of tuberculosis (TB), especially in HIV-infected patients.

→ It is bactericidal against *Mycobacterium tuberculosis* and *Mycobacterium avium complex (MAC)*.

→ Rifabutin is structurally related to rifampicin but has a longer half-life and fewer drug interactions, making it suitable for patients on antiretroviral therapy.

Classification

Based on Chemical Class

- Rifamycin derivative (macrocyclic antibiotic)

Based on Antitubercular Action

- First-line/rifamycin-class antitubercular agent
- Bactericidal against replicating and some dormant bacilli

Based on Origin

- Semi-synthetic antibiotic

Structure

Rifabutin contains:

- **Ansamycin macrocyclic ring**
- Multiple hydroxyl and keto groups
- Substitutions at **C-25 position** to reduce CYP450 induction

Molecular formula: $C_{45}H_{58}N_4O_{11}$

Structural Characteristics

- Lipophilic → good tissue and intracellular penetration
- Less potent inducer of cytochrome P450 enzymes than rifampicin
- Inhibits bacterial RNA polymerase

Nomenclature

- Rifa → rifamycin class
- Butin → distinguishes from rifampicin
- Available as oral capsules or tablets

Stereochemistry

- Rifabutin contains multiple chiral centers
- Correct stereochemistry is essential for binding to RNA polymerase

Mechanism of Action

- Rifabutin binds to the β-subunit of bacterial DNA-dependent RNA polymerase.
- Inhibits transcription initiation → prevents RNA synthesis.
- Leads to rapid bactericidal activity against mycobacteria.
- Hence, rifabutin is an RNA synthesis inhibitor.

Spectrum of Activity

- *Mycobacterium tuberculosis*
- *Mycobacterium avium complex (MAC)*
- Some Gram-positive cocci and other slow-growing mycobacteria

Uses

- Treatment of tuberculosis, especially in HIV-infected patients
- Prophylaxis and treatment of MAC infections
- Used in combination therapy for TB to reduce resistance

Adverse Effects

- Gastrointestinal: nausea, vomiting
- Hepatotoxicity (monitor liver function)
- Orange discoloration of body fluids (harmless)
- Uveitis (rare, dose-dependent)
- Myalgia and arthralgia
- Fewer drug interactions than rifampicin (advantage in ART patients)

Chemical Degradation

1. Acid Degradation

- Stable in acidic medium

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)

Ansamycin Macrocyclic Ring

- Essential for RNA polymerase inhibition

Hydroxyl and Keto Groups

- Required for hydrogen bonding with enzyme

C-25 Substitution

- Reduces CYP450 induction → fewer drug interactions

Lipophilicity

- Ensures intracellular penetration, especially in macrophages

Cycloserine (CS)

→ Cycloserine 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*.
→ Cycloserine interferes with cell wall synthesis by inhibiting enzymes required for peptidoglycan formation.
It is orally active and usually administered in combination therapy.

Classification

Based on Chemical Class

- D-Alanine analogue (cyclic amino acid derivative)

Based on Antitubercular Action

- Second-line antitubercular agent
- Bacteriostatic

Based on Origin

- Synthetic derivative of D-serine

Structure

Cycloserine contains:

- 4-Amino-1,2-oxazolidin-3-one ring
- Amino and hydroxyl functional groups

Molecular formula: $C_3H_6N_2O_2$

Structural Characteristics

- Small, polar molecule → good oral absorption
- Mimics D-alanine, competing with it in peptidoglycan synthesis

Nomenclature

- Cyclo → cyclic structure
- Serine → amino acid analogue
- Available as oral tablets or injectable solutions

Stereochemistry

- Contains a chiral center
- Only D-cycloserine is active
- Correct stereochemistry essential for enzyme inhibition

Mechanism of Action

- Cycloserine inhibits D-alanine racemase and D-alanine–D-alanine ligase.
- Blocks incorporation of D-alanine into peptidoglycan.
- Weakens bacterial cell wall → bacteriostatic effect.
- Hence, cycloserine is a cell wall synthesis inhibitor.

Spectrum of Activity

- *Mycobacterium tuberculosis* (including MDR strains)
- Limited activity against other mycobacteria
- Not effective against most Gram-negative and Gram-positive bacteria

Uses

- Treatment of multidrug-resistant TB (MDR-TB)
- Used in combination therapy with other second-line drugs
- Reserved for resistant TB cases

Adverse Effects

- CNS toxicity: headache, drowsiness, confusion, seizures (dose-dependent)
- Peripheral neuropathy
- Gastrointestinal disturbances: nausea, vomiting
- Rare hypersensitivity reactions

Chemical Degradation

- Stable in acidic medium
- Decomposes in strong alkaline conditions
- Sensitive to light and heat
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- D-alanine mimicry → essential for peptidoglycan inhibition
- Cyclic oxazolidinone ring → required for enzyme binding
- Correct stereochemistry (D-form) → active

Streptomycin (STM)

→ Streptomycin is a first-line aminoglycoside antibiotic used in the treatment of tuberculosis (TB).
→ It is bactericidal, primarily against extracellular *Mycobacterium tuberculosis*.
→ Streptomycin inhibits protein synthesis by binding to the 30S ribosomal subunit, causing misreading of mRNA.
→ Administered parenterally (intramuscular or intravenous) due to poor oral absorption.

Classification

Based on Chemical Class

- Aminoglycoside antibiotic

Based on Antitubercular Action

- First-line/second-line antitubercular agent
- Bactericidal

Based on Origin

- Natural antibiotic produced by *Streptomyces griseus*

Structure

Streptomycin contains:

- Amino sugars linked to a streptidine ring
- Multiple amino and hydroxyl groups

Molecular formula: $C_{21}H_{39}N_7O_{12}$

Structural Characteristics

- Highly polar → poor oral absorption
- Requires parenteral administration
- Targets bacterial 30S ribosomal subunit

Nomenclature

- Strepto → Streptomyces origin
- Mycin → antibiotic suffix
- Available as injectable solution

Stereochemistry

- Contains multiple chiral centers
- Correct stereochemistry is essential for ribosomal binding

Mechanism of Action

- Streptomycin binds to the 30S ribosomal subunit.
- Causes misreading of mRNA and inhibition of initiation complex.
- Leads to production of defective proteins → bacterial cell death.
- Hence, streptomycin is a protein synthesis inhibitor.

Spectrum of Activity

- *Mycobacterium tuberculosis* (extracellular)
- Some Gram-negative bacteria (e.g., *E. coli, Pseudomonas*)
- Limited activity against Gram-positive bacteria

Uses

- Treatment of TB, especially in combination therapy
- Second-line drug for MDR-TB
- Occasionally used for plague and tularemia

Adverse Effects

- Ototoxicity (hearing loss)
- Nephrotoxicity
- Vestibular disturbances (dizziness, vertigo)
- Neuromuscular blockade (rare)
- Local pain at injection site

Chemical Degradation

- Stable in dry form
- Sensitive to acidic and alkaline hydrolysis
- Heat and light can cause degradation
- Store in cool, dry place

Structure–Activity Relationship (SAR)

- Amino sugars → essential for ribosomal binding
- Streptidine ring → required for activity
- Multiple hydroxyl and amino groups → hydrogen bonding with ribosome

Capreomycin Sulphate

→ Capreomycin sulphate is a second-line antitubercular antibiotic used to treat multidrug-resistant tuberculosis (MDR-TB).
→ It is bactericidal against *Mycobacterium tuberculosis* and acts by inhibiting protein synthesis.
→ Capreomycin is a cyclic polypeptide antibiotic administered parenterally (intramuscular or intravenous) due to poor oral absorption.
→ It is often used in combination therapy for resistant TB cases.

Classification

Based on Chemical Class

- Cyclic polypeptide antibiotic

Based on Antitubercular Action

- Second-line antitubercular agent
- Bactericidal against actively growing bacilli

Based on Origin

- Natural antibiotic produced by *Streptomyces capreolus*

Structure

Capreomycin contains:

- Cyclic polypeptide backbone
- Multiple amino acid residues including unusual amino acids

Molecular formula: $C_{36}H_{58}N_{10}O_{14}$ (Capreomycin A)

Structural Characteristics

- Highly polar → poor oral absorption
- Requires parenteral administration
- Binds to bacterial ribosome → inhibits protein synthesis

Nomenclature

- Capreo → derived from *Streptomyces capreolus*
- Mycin → antibiotic suffix
- Available as injectable solution (sulfate salt)

Stereochemistry

- ⇨ Contains multiple chiral centers
- ⇨ Correct stereochemistry is essential for ribosomal binding and activity

Mechanism of Action

- ⮝ Capreomycin binds to the 30S and 50S ribosomal subunits.
- ⮝ Interferes with protein elongation, causing misreading of mRNA.
- ⮝ Leads to production of defective proteins → bacterial cell death.
- ⮝ Hence, capreomycin is a protein synthesis inhibitor.

Spectrum of Activity

- ⮝ *Mycobacterium tuberculosis*, including MDR strains
- ⮝ Limited activity against other mycobacteria
- ⮝ Minimal activity against Gram-negative and Gram-positive bacteria

Uses

- ▪ Treatment of multidrug-resistant TB (MDR-TB)
- ▪ Used in combination therapy with other second-line drugs
- ▪ Reserved for resistant TB cases

Adverse Effects

- ⮝ Ototoxicity (hearing loss, tinnitus)
- ⮝ Nephrotoxicity
- ⮝ Vestibular disturbances (dizziness, vertigo)
- ⮝ Pain at injection site

Chemical Degradation

- ⮝ Sensitive to acidic and alkaline hydrolysis
- ⮝ Heat and light can cause decomposition
- ⮝ Store in cool, dry place
- ⮝ Protect from light

Structure–Activity Relationship (SAR)

- → Cyclic polypeptide backbone → essential for ribosomal binding
- → Amino acid residues → interact with rRNA
- → Multiple hydroxyl and amino groups → hydrogen bonding with ribosome
- → Parenteral administration ensures bioavailability