

# WELCOME TO



This is an Education Platform

We Provide PDF Notes for Pharmacy Students

Web Site <http://www.fdspharmacy.in/>

You tube <https://www.youtube.com/c/FDSpharmacy>

Telegram <https://t.me/Fdspharmacy>

App <https://play.google.com/store/apps/details?id=com.FDSPharmacyMedia.FDSPharmacy>

E-mail [fdspharmacyinfo@gmail.com](mailto:fdspharmacyinfo@gmail.com)

## Bachelor of Pharmacy Biopharmaceutics and Pharmacokinetics

### NOTES

- ✓ Unit 1 **All Unit**
- ✓ Unit 2 **in**
- ✓ Unit 3 **One PDF**
- ✓ Unit 4
- ✓ Unit 5

Visit our Website  
[WWW.fdspharmacy.in](http://WWW.fdspharmacy.in)



## Bachelor of Pharmacy Herbal Drug Technology

### NOTES

- ✓ Unit 1 **All Unit**
- ✓ Unit 2 **in**
- ✓ Unit 3 **One PDF**
- ✓ Unit 4
- ✓ Unit 5

Visit our Website  
[WWW.fdspharmacy.in](http://WWW.fdspharmacy.in)



## Bachelor of Pharmacy Medicinal Chemistry III

### NOTES

- ✓ Unit 1 **All Unit**
- ✓ Unit 2 **in**
- ✓ Unit 3 **One PDF**
- ✓ Unit 4
- ✓ Unit 5

Visit our Website  
[WWW.fdspharmacy.in](http://WWW.fdspharmacy.in)



## Bachelor of Pharmacy Pharmaceutical Biotechnology

### NOTES

- ✓ Unit 1 **All Unit**
- ✓ Unit 2 **in**
- ✓ Unit 3 **One PDF**
- ✓ Unit 4
- ✓ Unit 5

Visit our Website  
[WWW.fdspharmacy.in](http://WWW.fdspharmacy.in)



## Bachelor of Pharmacy Pharmacology III

### NOTES

- ✓ Unit 1 **All Unit**
- ✓ Unit 2 **in**
- ✓ Unit 3 **One PDF**
- ✓ Unit 4
- ✓ Unit 5

Visit our Website  
[WWW.fdspharmacy.in](http://WWW.fdspharmacy.in)



## Bachelor of Pharmacy Quality Assurance

### NOTES

- ✓ Unit 1 **All Unit**
- ✓ Unit 2 **in**
- ✓ Unit 3 **One PDF**
- ✓ Unit 4
- ✓ Unit 5

Visit our Website  
[WWW.fdspharmacy.in](http://WWW.fdspharmacy.in)





## D.Pharma B.Pharma

- 👉 PDF Notes
- 👉 Practical Manual
- 👉 Important Questions
- 👉 Assignment etc

 Download Now



# www.fdpharmacy.in

# 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  $\beta$ -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  $\beta$ -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 Macrocylic 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

