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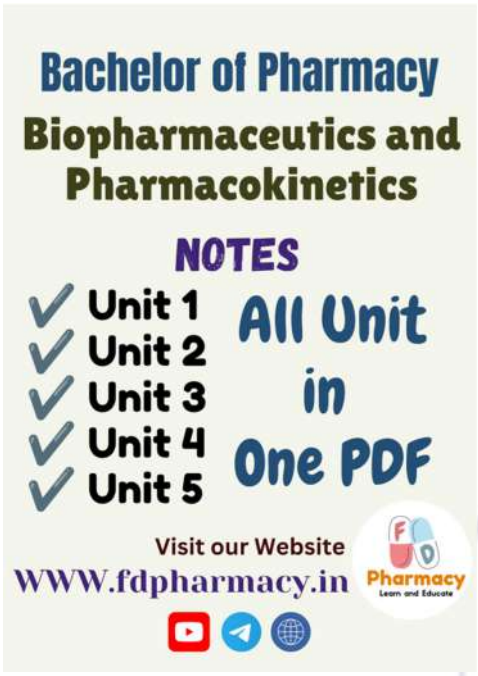
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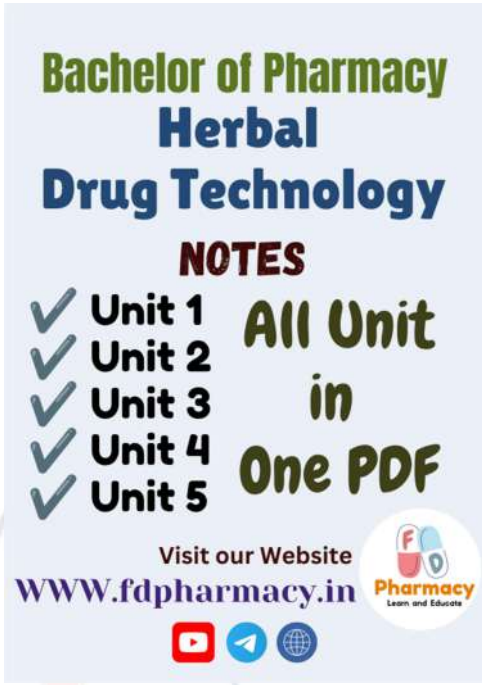
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MEDICINAL CHEMISTRY - III

UNIT 1

TOPIC :

- **Tetracyclines :** Tetracycline, Oxytetracycline, Minocycline, Doxycycline

Tetracyclines

→ Tetracyclines are broad-spectrum antibiotics obtained from *Streptomyces* species or prepared semi-synthetically.

→ They are bacteriostatic drugs that inhibit bacterial protein synthesis by acting on the 30S ribosomal subunit.

Classification

A. Natural Tetracyclines

- Tetracycline
- Oxytetracycline
- Chlortetracycline

B. Semi-Synthetic Tetracyclines

- Doxycycline
- Minocycline
- Methacycline

C. Long-Acting Tetracyclines

- Doxycycline
- Minocycline

Mechanism of Action

→ Tetracyclines enter bacterial cells by passive diffusion and active transport.

→ They bind reversibly to the 30S ribosomal subunit.

→ Prevent attachment of aminoacyl-tRNA to the A-site of the ribosome.

→ Protein synthesis is inhibited.

→ Bacterial growth is stopped.

→ Therefore, tetracyclines are bacteriostatic antibiotics.

Spectrum of Activity

Effective Against

Gram-positive bacteria

Staphylococcus, Streptococcus

Gram-negative bacteria

E. coli, Haemophilus influenzae

Atypical organisms

Chlamydia

Mycoplasma

Rickettsia

Spirochetes

Treponema pallidum

Protozoa

Plasmodium (malaria)

Resistance

Bacterial resistance to tetracyclines occurs due to:

Decreased drug accumulation

Efflux pumps remove drug from bacteria

Ribosomal protection proteins

Prevent tetracycline binding

Enzymatic inactivation (rare)

Cross-resistance among tetracyclines

Therapeutic Uses

- Acne vulgaris
- Respiratory tract infections
- Urinary tract infections
- Sexually transmitted infections (Chlamydia)
- Rickettsial infections
- Lyme disease
- Malaria prophylaxis
- Brucellosis (with rifampicin)

Adverse Effects

Common Adverse Effects

- Nausea, vomiting, diarrhea
- Photosensitivity

Serious Adverse Effects

- Tooth discoloration in children
- Bone growth inhibition in fetus
- Hepatotoxicity (high dose)

Tetracycline

→ Tetracycline is a broad-spectrum antibiotic obtained from Streptomyces species.

→ It is bacteriostatic in nature and acts by inhibiting bacterial protein synthesis.

→ Tetracyclines are effective against Gram-positive, Gram-negative, intracellular organisms, and atypical bacteria.

Classification

A. Natural Tetracyclines

- Tetracycline
- Chlortetracycline
- Oxytetracycline

B. Semi-Synthetic Tetracyclines

- Doxycycline
- Minocycline

Structure

Tetracycline has:

- Four fused hydrocarbon rings (A, B, C, D) → hence the name *tetracycline*
- Multiple hydroxyl (–OH), keto (=O), and amide groups
- A dimethylamino group at C-4, essential for activity

Key Structural Features

- Polycyclic naphthacene ring system
- Amphoteric nature (acidic and basic groups)

Nomenclature

Name derived from:

Tetra → four

Cycline → rings

Generic names usually end with "**-cycline**"

Example: tetracycline, doxycycline, minocycline

Stereochemistry

→ Tetracycline has several chiral centers
→ 4-dimethylamino group must be in α-configuration
→ Epimerization at C-4 → reduced antibacterial activity
→ Correct stereochemistry is essential for ribosomal binding

Mechanism of Action

- Tetracycline enters bacterial cells by passive diffusion and active transport.
- Binds reversibly to the 30S ribosomal subunit.
- Prevents attachment of aminoacyl-tRNA to the A-site.
- Inhibits protein synthesis.
- Results in growth inhibition of bacteria.
- Hence, tetracycline is bacteriostatic.

Uses

- Respiratory tract infections
- Urinary tract infections
- Acne vulgaris
- Sexually transmitted diseases (Chlamydia)
- Rickettsial infections
- Mycoplasma infections
- Cholera
- Brucellosis (with other drugs)

Chemical Degradation

1. Acid Degradation
   - Dehydration at C-6 → anhydrotetracycline (toxic)
2. Alkaline Degradation
   - Epimerization at C-4 → 4-epitetracycline (less active)
3. Photodegradation
   - Light exposure causes degradation
4. Thermal Degradation
   - Heat accelerates breakdown

Prevention

- Store in cool, dry place
- Protect from light
- Avoid acidic & alkaline conditions

Structure–Activity Relationship (SAR)

Four-Ring System

- Essential for antibacterial activity

C-4 Dimethylamino Group

- Essential for ribosomal binding
- Removal → loss of activity

Substitutions at C-5, C-6, C-7

- Modify pharmacokinetics & potency
- Example: doxycycline (better absorption)

Keto-Enol System (C-1 to C-3)

- Necessary for metal ion chelation

Stereochemistry

- Correct 3D configuration essential for activity

Oxytetracycline

- Oxytetracycline is a broad-spectrum tetracycline antibiotic obtained from Streptomyces rimosus.
- It is bacteriostatic in nature and acts by inhibiting bacterial protein synthesis.
- Oxytetracycline is effective against Gram-positive, Gram-negative, intracellular and atypical organisms.

Classification

A. Based on Origin

Natural tetracycline

- Oxytetracycline
- Tetracycline
- Chlortetracycline

B. Tetracycline Group

- First-generation tetracycline antibiotic

Structure

- Oxytetracycline has a four-ring (naphthacene) system labeled A, B, C and D rings.
- Contains:
  - Hydroxyl (–OH) group at C-5
  - Dimethylamino group at C-4 (essential)
  - Multiple keto (=O) and phenolic –OH groups
- Molecular formula: $C_{22}H_{24}N_2O_9$

Key Structural Features

- Polycyclic structure
- Amphoteric in nature
- Strong metal ion chelation property

Nomenclature

Name derived from:

Oxy → presence of additional hydroxyl group

Tetracycline → four fused rings

Ends with "**-cycline**"

Common salt form: **Oxytetracycline hydrochloride**

Stereochemistry

- Oxytetracycline has several chiral centers
- C-4 dimethylamino group must be in α-orientation
- Epimerization at C-4 produces 4-epioxytetracycline (less active)
- Correct stereochemistry is essential for antibacterial activity

Mechanism of Action

- Oxytetracycline enters bacterial cells by diffusion and active transport.
- Binds reversibly to the 30S ribosomal subunit.
- Blocks binding of aminoacyl-tRNA to the A-site.
- Inhibits protein synthesis.
- Stops bacterial growth.
- Hence, oxytetracycline is bacteriostatic.

Uses

- Respiratory tract infections
- Urinary tract infections
- Acne vulgaris
- Sexually transmitted diseases (Chlamydia)
- Rickettsial infections

Chemical Degradation

1. Acid Degradation
    - Dehydration at C-6
    - Forms anhydro-oxytetracycline (toxic)
2. Alkaline Degradation
    - Epimerization at C-4
    - Produces less active epimers
3. Photodegradation
    - Sensitive to light
4. Thermal Degradation
    - Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid acidic and alkaline conditions

Structure–Activity Relationship (SAR)

Four-Ring System

- Essential for antibacterial activity

C-4 Dimethylamino Group

- Required for ribosomal binding
- Removal → loss of activity

Hydroxyl Group at C-5

- Increases polarity
- Influences pharmacokinetics

Keto-Enol System (C-1 to C-3)

- Necessary for metal ion chelation

Stereochemistry

- Correct spatial orientation is critical

Chlortetracycline

- Chlortetracycline is a broad-spectrum tetracycline antibiotic obtained from Streptomyces aureofaciens.
- It was the first tetracycline antibiotic discovered.
  Chlortetracycline is bacteriostatic and acts by inhibiting bacterial protein synthesis.
- It is effective against Gram-positive, Gram-negative, rickettsiae, chlamydia, and mycoplasma.

Classification

A. Based on Origin

Natural tetracyclines

- Chlortetracycline
- Tetracycline
- Oxytetracycline

B. Based on Generation

First-generation tetracycline antibiotic

Structure

Chlortetracycline has a four fused ring system (A, B, C, D) known as the naphthacene nucleus.

Key functional groups:

Chloro (–Cl) group at C-7

Dimethylamino group at C-4 (essential)

Multiple keto (=O) and hydroxyl (–OH) groups

Molecular formula: $C_{22}H_{23}ClN_2O_8$

Key Structural Features

- Polycyclic structure
- Amphoteric nature
- Strong chelation with metal ions (Ca^{2+}, Mg^{2+})

Nomenclature

- Name derived from:
  - **Chloro** → presence of chlorine atom
  - **Tetracycline** → four fused rings
- Generic names end with "**-cycline**"
- Common salt form: **Chlortetracycline hydrochloride**

Stereochemistry

- Chlortetracycline contains multiple chiral centers.
- C-4 dimethylamino group must be in α-orientation for activity.
- Epimerization at C-4 forms 4-epichlortetracycline, which is less active.
- Correct stereochemistry is essential for ribosomal binding.

Mechanism of Action

- Chlortetracycline enters bacterial cells by passive diffusion and active transport.
- Binds reversibly to the 30S ribosomal subunit.
- Prevents binding of aminoacyl-tRNA to the A-site.
- Inhibits protein synthesis.
- Stops bacterial growth.
- Hence, chlortetracycline is bacteriostatic.

Uses

- Respiratory tract infections
- Urinary tract infections
- Acne
- Rickettsial infections
- Chlamydial infections
- Veterinary infections
  (Use in humans is now limited due to better alternatives.)

Chemical Degradation

1. Acid Degradation
    - Dehydration at C-6
    - Forms **anhydrochlortetracycline (toxic)**
2. Alkaline Degradation
    - Epimerization at C-4
    - Produces less active epimers
3. Photodegradation
    - Sensitive to light
4. Thermal Degradation
    - Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid extreme pH conditions

Structure–Activity Relationship (SAR)

Four-Ring (Naphthacene) System

- Essential for antibacterial activity

C-4 Dimethylamino Group

- Necessary for ribosomal binding
- Removal → loss of activity

Chloro Substitution at C-7

- Increases lipophilicity
- Enhances antibacterial potency

Keto-Enol System (C-1 to C-3)

- Required for metal ion chelation

Stereochemistry

- Correct 3D configuration essential for activity

Minocycline

- Minocycline is a semi-synthetic, broad-spectrum tetracycline antibiotic.
- It is derived from tetracycline by chemical modification and shows greater lipid solubility and potency.
- Minocycline is bacteriostatic and acts by inhibiting bacterial protein synthesis.
- It is effective against Gram-positive, Gram-negative, intracellular and atypical organisms, including some tetracycline-resistant strains.

Classification

Based on Origin

Semi-synthetic tetracycline

Minocycline

Doxycycline

Based on Generation

Second-generation tetracycline antibiotic

Structure

Minocycline has a four-ring (naphthacene) system like other tetracyclines.

Important structural features:

Dimethylamino group at C-4 (essential)

Dimethylamino substitution at C-7

Absence of hydroxyl group at C-6

Molecular formula: $\mathbf{C_{23}H_{27}N_3O_7}$

Key Properties

- Increased lipophilicity
- Better tissue penetration
- Improved oral absorption

Nomenclature

Name derived from:

Mino → modified tetracycline

Cycline → four-ring system

Generic names end with "**-cycline**"

Common salt: **Minocycline hydrochloride**

Stereochemistry

- Minocycline contains multiple chiral centers.
- C-4 dimethylamino group must be in α-configuration for activity.
- Epimerization at C-4 → 4-epiminocycline (less active).
- Correct stereochemistry is crucial for ribosomal binding.

Mechanism of Action

- Minocycline enters bacterial cells by passive diffusion and active transport.
- Binds reversibly to the 30S ribosomal subunit.
- Blocks binding of aminoacyl-tRNA to the A-site.
- Inhibits protein synthesis.
- Prevents bacterial growth.
- Hence, minocycline is bacteriostatic.

Uses

- Acne vulgaris (common use)
- Respiratory tract infections
- Urinary tract infections
- Sexually transmitted infections (Chlamydia)
- Rickettsial infections
- MRSA infections
- Rheumatoid arthritis (anti-inflammatory action)

Chemical Degradation

1. Acid Degradation
    - Dehydration at C-6 may occur
    - Produces toxic degradation products
2. Alkaline Degradation
    - Epimerization at C-4
    - Reduced antibacterial activity
3. Photodegradation
    - Sensitive to light exposure
4. Thermal Degradation
    - Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid extreme pH conditions

Structure–Activity Relationship (SAR)

Four-Ring (Naphthacene) System

- Essential for antibacterial activity

C-4 Dimethylamino Group

- Required for binding to 30S ribosomal subunit
- Removal → loss of activity

C-7 Dimethylamino Substitution

- Increases lipophilicity
- Improves potency and tissue penetration

Absence of C-6 Hydroxyl Group

- Increases chemical stability
- Reduces acid-catalyzed degradation

Stereochemistry

- Correct 3D configuration essential for activity

Doxycycline

- Doxycycline is a semi-synthetic, broad-spectrum tetracycline antibiotic.
- It is more lipid-soluble, better absorbed orally, and more stable than older tetracyclines.
- Doxycycline is bacteriostatic and acts by inhibiting bacterial protein synthesis.
- It shows activity against Gram-positive, Gram-negative, intracellular and atypical organisms.

Classification

Based on Origin

Semi-synthetic tetracyclines

- Doxycycline
- Minocycline

Based on Generation

Second-generation tetracycline antibiotic

Structure

Doxycycline possesses the four fused ring (naphthacene) tetracycline nucleus.

Important structural features:

Dimethylamino group at C-4 (essential for activity)
Hydroxyl group at C-5
Absence of hydroxyl group at C-6 → increased stability
Multiple keto and enol groups

Molecular formula: $C_{22}H_{24}N_2O_8$

Structural Advantages

- Less prone to acid-catalyzed degradation
- Reduced chelation with calcium

Nomenclature

Name derived from:

Doxy → deoxy (absence of oxygen at C-6)

Cycline → four-ring system

Generic names end with "**-cycline**"

Common salt: **Doxycycline hyclate / doxycycline monohydrate**

Stereochemistry

- Doxycycline contains multiple chiral centers.
- The C-4 dimethylamino group must be in α-configuration for antibacterial activity.
- Epimerization at C-4 produces 4-epidoxycycline, which is less active.
- Correct stereochemistry is essential for ribosomal binding.

Mechanism of Action

- Doxycycline enters bacterial cells by passive diffusion and active transport.
- Binds reversibly to the 30S ribosomal subunit.
- Prevents binding of aminoacyl-tRNA to the A-site.
- Inhibits protein synthesis.
- Stops bacterial growth.
- Hence, doxycycline is bacteriostatic.

Uses

- Acne vulgaris
- Respiratory tract infections
- Urinary tract infections
- Sexually transmitted infections (Chlamydia)
- Rickettsial infections
- Malaria prophylaxis
- Lyme disease
- Brucellosis (with rifampicin)

Chemical Degradation

1. Acid Degradation
    - Less susceptible than tetracycline
    - Minimal dehydration due to absence of C-6 OH
2. Alkaline Degradation
    - Epimerization at C-4

    Reduced antibacterial activity
3. Photodegradation
    - Sensitive to light exposure
4. Thermal Degradation
    - Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid alkaline conditions

Structure–Activity Relationship (SAR)

Four-Ring (Naphthacene) System

- Essential for antibacterial activity

C-4 Dimethylamino Group

- Required for binding to 30S ribosomal subunit
- Removal → loss of activity

Absence of C-6 Hydroxyl Group

- Increases chemical stability
- Reduces toxic degradation products

Hydroxyl and Keto Groups

- Required for metal ion chelation and activity

Lipophilicity

- Improved absorption
- Longer half-life