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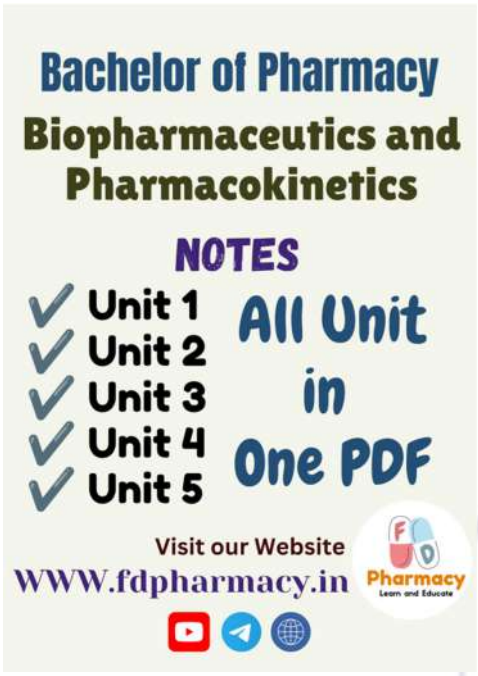
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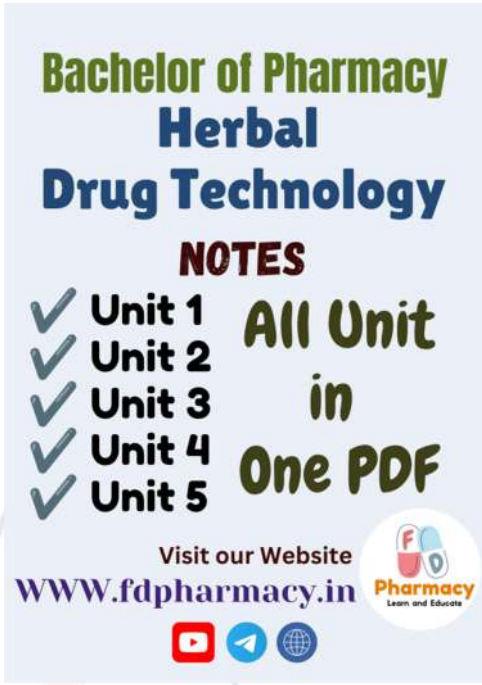
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MEDICINAL CHEMISTRY - III

UNIT 2

TOPIC :

- **Antibiotics**

  Historical background, Nomenclature, Stereochemistry, Structure activity relationship, Chemical degradation classification and important products of the following classes.

  Macrolide : Erythromycin Clarithromycin, Azithromycin.

Macrolide Antibiotics

- Macrolides are broad-spectrum antibiotics characterized by the presence of a large macrocyclic lactone ring (14, 15, or 16-membered).
- They are mainly bacteriostatic drugs that inhibit bacterial protein synthesis by acting on the 50S ribosomal subunit.

Classification

A. 14-Membered Ring Macrolides

- Erythromycin
- Clarithromycin
- Roxithromycin

B. 15-Membered Ring Macrolides

- Azithromycin

C. 16-Membered Ring Macrolides

- Spiramycin
- Josamycin

Mechanism of Action

- Macrolides penetrate bacterial cells by diffusion.
- They bind to the 50S ribosomal subunit.
- They inhibit translocation of peptidyl-tRNA.
- This prevents elongation of the peptide chain.
- Protein synthesis is inhibited, stopping bacterial growth.
- Hence, macrolides are bacteriostatic antibiotics (may be bactericidal at high concentrations).

Spectrum of Activity

Effective Against:

A. Gram-Positive Bacteria

- *Streptococcus*
- *Staphylococcus*

B. Gram-Negative Bacteria

- *Haemophilus influenzae*
- *Neisseria*

C. Atypical Organisms

- *Mycoplasma pneumoniae*
- *Chlamydia trachomatis*
- *Legionella pneumophila*

Resistance

- Resistance to macrolides occurs due to:
- Alteration of ribosomal binding site (methylation of 23S rRNA)
- Efflux pumps decreasing drug concentration
- Enzymatic inactivation
- Cross-resistance among macrolides

Therapeutic Uses

- Respiratory tract infections
- Community-acquired pneumonia
- Skin and soft tissue infections
- Sexually transmitted infections (Chlamydia)
- Diphtheria
- Pertussis (whooping cough)

Adverse Effects

Common Adverse Effects

- Nausea, vomiting, diarrhea
- Abdominal cramps

Serious Adverse Effects

- Hepatotoxicity (cholestatic hepatitis)
- QT interval prolongation

Erythromycin

- Erythromycin is a macrolide antibiotic obtained from Streptomyces erythreus.
- It is a broad-spectrum, bacteriostatic antibiotic, mainly active against Gram-positive organisms and atypical pathogens.
- Erythromycin is often used as an alternative to penicillin in penicillin-allergic patients.
- It acts by inhibiting bacterial protein synthesis.

Classification

Based on Chemical Class

Macrolide antibiotics

- Erythromycin
- Clarithromycin
- Azithromycin

Based on Source

Naturally occurring macrolide

- Erythromycin

Structure

Erythromycin contains a 14-membered macrocyclic lactone ring.

Two important sugar moieties are attached:

- Desosamine (basic sugar)
- Cladinose (neutral sugar)

Key structural features:

- Large lactone ring
- Multiple hydroxyl (–OH) groups
- Dimethylamino group on desosamine sugar

Molecular formula: $C_{37}H_{67}NO_{13}$

Structural Characteristics

- Acid-labile structure
- Poor stability in gastric acid
- Bulky molecule → limited Gram-negative penetration

Nomenclature

Erythro → red (derived from producing organism)
Mycin → antibiotic obtained from microorganisms
Marketed as:

- Erythromycin base
- Erythromycin stearate
- Erythromycin estolate
- Erythromycin ethylsuccinate

Stereochemistry

- Erythromycin contains multiple chiral centers.
- Proper three-dimensional orientation of lactone ring and sugar moieties is essential.
- Stereochemistry is crucial for binding to 50S ribosomal subunit.
- Any change in configuration reduces antibacterial activity.

Mechanism of Action

- Erythromycin penetrates bacterial cell membrane.
- Binds reversibly to the 50S ribosomal subunit.
- Inhibits translocation step of protein synthesis.
- Prevents movement of peptidyl-tRNA from A-site to P-site.
- Protein synthesis stops → bacterial growth inhibited.
- Hence, erythromycin is bacteriostatic (may be bactericidal at high concentrations).

Spectrum of Activity

Gram-positive bacteria:

- *Streptococcus*
- *Staphylococcus*

Atypical organisms:

- *Mycoplasma pneumoniae*
- *Chlamydia*
- *Legionella*

Some Gram-negative organisms:

- *Neisseria*
- *Haemophilus influenzae*

Uses

- Upper and lower respiratory tract infections
- Skin and soft tissue infections
- Diphtheria
- Whooping cough (*Bordetella pertussis*)

Chemical Degradation

1. Acid Degradation

- Highly acid-labile
- Undergoes intramolecular rearrangement in stomach acid
- Forms inactive degradation products

2. Alkaline Degradation

- More stable than in acidic conditions

3. Photodegradation

- Sensitive to light exposure

4. Thermal Degradation

- Heat accelerates degradation

Prevention

- Given as enteric-coated tablets
- Use of ester prodrugs

Structure–Activity Relationship (SAR)

Macrocyclic Lactone Ring

- Essential for antibacterial activity
- Ring opening → loss of activity

Desosamine Sugar

- Basic dimethylamino group
- Required for ribosomal binding
- Removal → reduced activity

Cladinose Sugar

- Contributes to antibacterial potency
- Modifications improve acid stability

Hydroxyl Groups

- Important for binding and activity
- Excessive modification reduces potency

Clarithromycin

→ Clarithromycin is a semi-synthetic macrolide antibiotic derived from erythromycin.

→ It is more acid-stable, better absorbed orally, and has a longer half-life than erythromycin.

→ Clarithromycin is mainly bacteriostatic but may show bactericidal action at higher concentrations.

→ It is effective against Gram-positive, Gram-negative, and atypical organisms.

Classification

Based on Chemical Class

Macrolide antibiotics

- Erythromycin
- Clarithromycin
- Azithromycin

Based on Origin

Semi-synthetic macrolide

Structure

→ Clarithromycin contains a 14-membered macrocyclic lactone ring similar to erythromycin.

→ It is a 6-O-methyl derivative of erythromycin.

Important structural features:

- Macrocyclic lactone ring
- Methoxy ($-OCH_3$) group at C-6
- Desosamine and cladinose sugar moieties
- Dimethylamino group on desosamine sugar

Molecular formula: $C_{38}H_{69}NO_{13}$

Structural Advantages

- Increased acid stability
- Reduced formation of inactive degradation products
- Improved oral bioavailability

Nomenclature

Clari → indicates structural modification of erythromycin
Mycin → antibiotic derived from microorganisms
Available as:

Clarithromycin base
Clarithromycin tablets and suspension

Stereochemistry

- Clarithromycin contains multiple chiral centers.
- Correct stereochemical orientation of:
  - Lactone ring
  - Sugar moieties

  is essential for activity.
- Stereochemistry is necessary for effective binding to 50S ribosomal subunit.

Mechanism of Action

⇨ Clarithromycin enters bacterial cells.
⇨ Binds reversibly to the 50S ribosomal subunit.
⇨ Inhibits translocation of peptides.
⇨ Prevents protein chain elongation.
⇨ Bacterial growth is inhibited.
⇨ Hence, clarithromycin is bacteriostatic.

Spectrum of Activity

Gram-positive bacteria

- *Streptococcus*
- *Staphylococcus*

Gram-negative bacteria

- *Haemophilus influenzae*
- *Moraxella catarrhalis*

Atypical organisms

- *Mycoplasma*
- *Chlamydia*
- *Legionella*

Helicobacter pylori

Uses

- Upper and lower respiratory tract infections
- Community-acquired pneumonia
- Skin and soft tissue infections
- Helicobacter pylori eradication (with PPI + amoxicillin/metronidazole)
- Sinusitis
- Pharyngitis
- Otitis media

Chemical Degradation

1. Acid Degradation

- Much less acid-labile than erythromycin
- C-6 methoxy group prevents intramolecular cyclization

2. Alkaline Degradation

- Relatively stable

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid excessive heat

Structure–Activity Relationship (SAR)

Macrocyclic Lactone Ring

- Essential for antibacterial activity

C-6 Methoxy Group

- Increases acid stability
- Improves oral bioavailability

Desosamine Sugar

- Dimethylamino group essential for ribosomal binding

Cladinose Sugar

- Contributes to antibacterial potency
- Modification improves stability

Azithromycin

→ Azithromycin is a semi-synthetic, broad-spectrum macrolide antibiotic belonging to the azalide subclass.
→ It is derived from erythromycin and is more acid-stable with an extended half-life.
→ Azithromycin is mainly bacteriostatic, but may be bactericidal at high concentrations.
→ It is widely used due to once-daily dosing and short treatment duration.

Classification

Based on Chemical Class

Macrolide antibiotics

- Erythromycin
- Clarithromycin
- Azithromycin

Based on Subclass

- Azalide macrolide

Based on Origin

- Semi-synthetic macrolide

Structure

- Azithromycin contains a 15-membered macrocyclic lactone ring.
- One nitrogen atom is inserted into the lactone ring, differentiating it from erythromycin.

Important structural features:

- Enlarged 15-membered azalide ring
- Desosamine sugar attached
- Absence of cladinose sugar
- Tertiary amine nitrogen in ring

Molecular formula: $C_{38}H_{72}N_2O_{12}$

Structural Advantages

- High acid stability
- Reduced gastrointestinal irritation
- Long tissue half-life

Nomenclature

- **Azi** → indicates nitrogen insertion (azalide)
- **Mycin** → antibiotic derived from microorganisms
- Marketed as:
  - Azithromycin dihydrate
  - Azithromycin tablets, capsules, suspension

Stereochemistry

→ Azithromycin contains multiple chiral centers.

→ Correct stereochemistry of:

- Lactone ring
- Sugar moiety

is essential for antibacterial activity.

→ Proper spatial configuration ensures binding to 50S ribosomal subunit.

Mechanism of Action

- Azithromycin enters bacterial cells.
- Binds reversibly to the 50S ribosomal subunit.
- Inhibits translocation of peptide chains.
- Blocks protein synthesis.
- Inhibits bacterial growth.
- Hence, azithromycin is bacteriostatic.

Spectrum of Activity

Gram-positive bacteria

- *Streptococcus*
- *Staphylococcus*

Gram-negative bacteria

- *Haemophilus influenzae*
- *Moraxella catarrhalis*

Atypical organisms

- *Chlamydia*
- *Mycoplasma*
- *Legionella*

Mycobacterium avium complex (MAC)

Uses

- Upper and lower respiratory tract infections
- Community-acquired pneumonia
- Skin and soft tissue infections
- Sexually transmitted infections (*Chlamydia trachomatis*)
- Typhoid fever
- Traveller's diarrhea
- Prophylaxis of MAC in HIV patients

Chemical Degradation

1. Acid Degradation

- Highly acid-stable
- No intramolecular cyclization

2. Alkaline Degradation

- Stable under mild alkaline conditions

3. Photodegradation

- Sensitive to light exposure

4. Thermal Degradation

- Heat accelerates degradation

Prevention

- Store in cool, dry place
- Protect from light
- Avoid excessive heat

Structure–Activity Relationship (SAR)

15-Membered Azalide Ring

- Essential for antibacterial activity
- Increases acid stability

Insertion of Nitrogen Atom

- Improves pharmacokinetic properties
- Increases tissue penetration

Desosamine Sugar

- Dimethylamino group required for ribosomal binding

Absence of Cladinose Sugar

- Reduces drug interactions
- Improves metabolic stability