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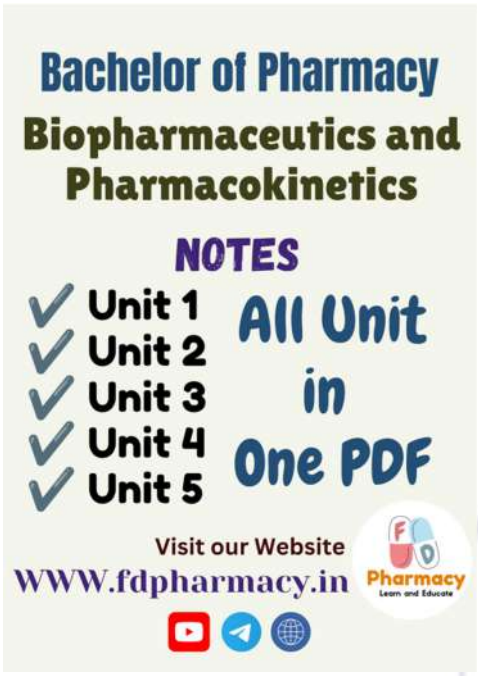
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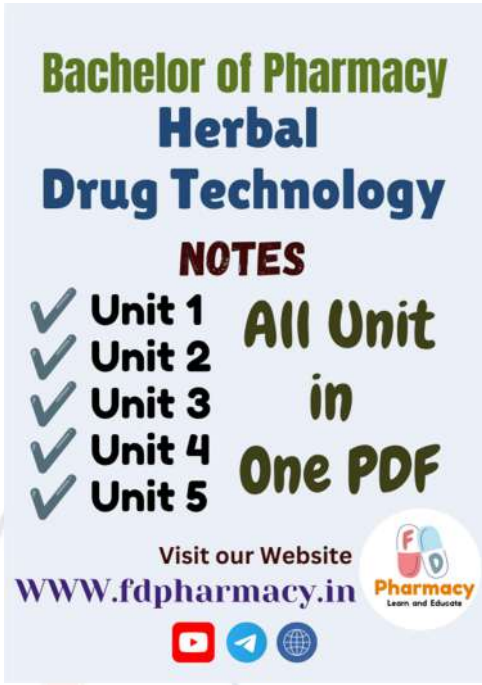
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MEDICINAL CHEMISTRY - III

UNIT 1

TOPIC :

- **Antibiotics**

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

  β-Lactam antibiotics : Penicillin, Cepholosporins, β- Lactamase inhibitors,

  Monobactams

Antibiotics

→ Antibiotics are chemical substances produced by microorganisms or synthesized artificially which, in low concentrations, inhibit the growth of or destroy other microorganisms, especially bacteria.
→ Antibiotics represent one of the greatest milestones in medical science and have revolutionized the treatment of infectious diseases.
→ Origin: The first antibiotic discovered was Penicillin, by Sir Alexander Fleming in 1928.

History of Antibiotics

→ The development of antibiotics began with the acceptance of the germ theory of disease. Louis Pasteur was among the first scientists to recognize that microorganisms could inhibit the growth of other microorganisms.

Important Milestones

1871 – Joseph Lister observed that urine contaminated with mould could inhibit bacterial growth.
1890s – Rudolf Emmerich and Oscar Löw prepared *Pyocyanase* from microbes. It was the first antibiotic used in hospitals, but it was not clinically successful.
1909 – Paul Ehrlich discovered Salvarsan, the first modern chemotherapeutic agent used for the treatment of syphilis.
1928 – Sir Alexander Fleming discovered the enzyme Lysozyme and the antibiotic substance Penicillin from *Penicillium notatum*.
1932 – Gerhard Domagk discovered Prontosil, a prodrug of sulfonamides.
1936 – Sulfanilamide was introduced as the first synthetic sulfonamide used in human medicine.
1940 – Concept of Modern Drug Discovery introduced by Paul Ehrlich through the concept of the “Magic Bullet”, a compound that selectively targets disease-causing organisms without harming human tissues.
1940 – Howard Florey and Ernst Chain first used Penicillin therapeutically.

1944 – Selman Waksman discovered Streptomycin from soil bacteria, effective against tuberculosis.
1948 – Chlortetracycline was discovered.
1957 – Nystatin was introduced for the treatment of fungal infections.
1970s – Discovery of early quinolones such as Pipemidic acid, Oxolinic acid, and Cinoxacin.
1980 – Norfloxacin, the first fluoroquinolone, was introduced.
1980 – Enrofloxacin was developed for veterinary use.
1998 – SmithKline Beecham patented Amoxicillin + Clavulanate Potassium combination.

Classification of Antibiotics

Antibiotics can be classified based on different criteria:

A. Classification Based on Origin

Natural Antibiotics

Obtained directly from microorganisms.

Examples: Penicillin G, Streptomycin

Semisynthetic Antibiotics

Chemically modified forms of natural antibiotics to improve activity or stability.

Examples: Amoxicillin, Cephalexin

Synthetic Antibiotics

Completely synthesized in the laboratory.

Examples: Ciprofloxacin, Sulfonamides

B. Classification Based on Spectrum of Activity

Narrow-Spectrum Antibiotics

Effective against specific groups of bacteria (either Gram-positive or Gram-negative).

Example: Penicillin G (mainly Gram-positive)

Broad-Spectrum Antibiotics

Effective against both Gram-positive and Gram-negative bacteria.

Examples: Tetracycline, Chloramphenicol

C. Classification Based on Mechanism of Action

Inhibition of Cell Wall Synthesis
Examples: Penicillins, Cephalosporins
Inhibition of Protein Synthesis
Examples: Tetracyclines, Aminoglycosides, Macrolides
Inhibition of Nucleic Acid Synthesis
Examples: Fluoroquinolones, Rifampicin
Alteration of Cell Membrane Permeability
Examples: Polymyxins
Antimetabolite Action (Interference with Metabolic Pathways)
Examples: Sulfonamides, Trimethoprim

D. Classification Based on Chemical Structure

β-Lactam Antibiotics
Penicillins, Cephalosporins, Carbapenems
Aminoglycosides
Streptomycin, Gentamicin
Tetracyclines
Doxycycline, Minocycline
Macrolides
Erythromycin, Azithromycin
Quinolones / Fluoroquinolones
Ciprofloxacin, Levofloxacin

β-Lactam Antibiotics

→ β-Lactam antibiotics are a large group of antibacterial agents that contain a β-lactam ring in their chemical structure. They exert their action by inhibiting bacterial cell wall synthesis, which leads to cell lysis and bacterial death.
→ They are mainly bactericidal in nature.

Classification of β-Lactam Antibiotics

Penicillins
Examples: Penicillin-G, Ampicillin, Amoxicillin

Cephalosporins
Examples: Cephalexin, Ceftriaxone

Carbapenems
Examples: Imipenem, Meropenem

Monobactams
Example: Aztreonam

β-Lactamase Inhibitors
Examples: Clavulanic acid, Sulbactam, Tazobactam

Mechanism of Action

→ β-Lactam antibiotics bind to Penicillin-Binding Proteins (PBPs) present in the bacterial cell membrane.
→ They inhibit the transpeptidation step in peptidoglycan synthesis.
→ This results in weakening of the bacterial cell wall.
→ Ultimately leads to cell lysis and death of bacteria.
→ *(Hence, β-lactam antibiotics are bactericidal.)*

Spectrum of Activity

- Spectrum varies with different subclasses and generations.
- Active against Gram-positive bacteria and many Gram-negative bacteria.
- Several broad-spectrum derivatives are available.

Resistance to β-Lactam Antibiotics

- Bacteria produce β-lactamase enzymes which break the β-lactam ring.
- This enzymatic degradation makes the antibiotic inactive.

Overcoming Resistance

Combination therapy with β-lactamase inhibitors such as:

- Clavulanic acid
- Sulbactam
- Tazobactam

Example: Amoxicillin + Clavulanic acid

Therapeutic Uses

- Respiratory tract infections
- Urinary tract infections (UTI)
- Skin and soft tissue infections
- Septicemia
- Meningitis
- Surgical prophylaxis

Adverse Effects

- Allergic reactions (rash, urticaria, anaphylaxis)
- Gastrointestinal upset (nausea, diarrhea)
- Rare adverse effects:
  - Neurotoxicity
  - Nephrotoxicity

Penicillins

→ Penicillins are β-lactam antibiotics obtained from *Penicillium* species. They were the first antibiotics used clinically, discovered by Sir Alexander Fleming in 1928.
→ They inhibit bacterial cell wall synthesis.
→ Mainly active against Gram-positive bacteria, though several derivatives show broad and extended spectrum activity.

Classification of Penicillins

A. Based on Source / Production

1. Natural Penicillins
Penicillin-G (Benzylpenicillin)
Penicillin-V (Phenoxymethylpenicillin)
2. Semisynthetic Penicillins
Aminopenicillins: Ampicillin, Amoxicillin
Antistaphylococcal penicillins: Cloxacillin, Dicloxacillin
Extended-spectrum (Antipseudomonal): Ticarcillin, Piperacillin

B. Based on Spectrum of Activity

Narrow spectrum: Penicillin-G, Penicillin-V
Broad spectrum: Ampicillin, Amoxicillin
Extended spectrum: Piperacillin, Ticarcillin

Structure of Penicillin

Consists of two fused rings:

β-Lactam ring

Thiazolidine ring

An amide side chain (R-CO-NH) at position-6

Intact β-lactam ring is essential for activity

Nomenclature of Penicillins

→ **Penam nucleus:** 6-acylamino-2,2-dimethylpenam-3-carboxylic acid
→ **Penicillanic acid nucleus:** 6-carbonylaminopenicillanic acid
→ **Penicillin nucleus:** Substitution at R determines type (e.g. benzyl → Penicillin-G)
→ Related nuclei: Penam, Carbapenam, Penem, Carbapenem, Monobactam, Cephem

Stereochemistry

- Three chiral carbons: C-3, C-5, C-6
- Absolute configuration: 3S, 5R, 6R
- Acylamino and carboxyl groups are trans
- Derived from L-cysteine and D-valine

Mechanism of Action

- Bind to PBPs (transpeptidase enzymes)
- Inhibit transpeptidation of peptidoglycan
- Cell wall weakens → cell lysis
- Bactericidal action

Uses

- Skin and soft tissue infections
- Dental infections
- Ear, nose, throat infections
- Respiratory tract infections

Chemical Degradation

◈ Acidic & alkaline hydrolysis
◈ β-lactamase enzyme degradation
◈ Amidase → 6-aminopenicillanic acid
◈ (All degradation products are inactive)

Structure–Activity Relationship (SAR)

- Sulfur oxidation ↑ acid stability, ↓ activity
- Dimethyl groups at C-2 essential
- Free carboxyl group at C-3 required
- Side-chain substitution at C-6 allowed
- Bulky groups ↑ β-lactamase resistance

Cephalosporins

→ Cephalosporins are β-lactam antibiotics originally isolated from the fungus Cephalosporium acremonium (Acremonium).
→ They are structurally related to penicillins but show greater resistance to β-lactamase enzymes.
→ Cephalosporins are bactericidal and act by inhibiting bacterial cell wall synthesis.
→ They are widely used due to their broad spectrum, safety, and good tolerability.

Classification (Based on Generations)

First Generation

- **Mainly** Gram-positive
- **Examples:** Cephalexin, Cefazolin, Cefadroxil

Second Generation

- **Increased** Gram-negative activity
- **Examples:** Cefuroxime, Cefaclor, Cefotetan

Third Generation

- **Strong Gram-negative,** CNS penetration
- **Examples:** Ceftriaxone, Cefotaxime, Ceftazidime

Fourth Generation

- Broad spectrum, high β-lactamase resistance
- **Example:** Cefepime

Fifth Generation

- **Active against** MRSA
- **Example:** Ceftaroline

Structure

The basic nucleus of cephalosporins is 7-aminocephalosporanic acid (7-ACA).

Structural Components

- β-lactam ring (essential for activity)
- Dihydrothiazine ring (6-membered)
- R_1 side chain at position-7 → antibacterial activity
- R_2 side chain at position-3 → pharmacokinetic properties

Nomenclature

All cephalosporins start with "cef-" or "ceph-"

Example:

Ceftriaxone

Cephalexin

Position-7 substitution defines antibacterial potency

Position-3 substitution affects metabolism & excretion

Stereochemistry

- Cephalosporins have specific stereochemical configuration
- Correct β-lactam ring orientation is necessary for binding to PBPs
- Change in stereochemistry → loss of antibacterial activity
- Natural configuration is essential for biological action

Mechanism of Action

- Cephalosporins bind to Penicillin Binding Proteins (PBPs)
- Inhibit transpeptidation step of peptidoglycan synthesis
- Cell wall becomes weak
- Leads to osmotic lysis of bacteria
- Bactericidal action

Uses

- Respiratory tract infections
- Urinary tract infections
- Skin & soft tissue infections
- Meningitis (3rd generation)
- Septicemia

Chemical Degradation of Cephalosporins

1. Hydrolysis
   - β-lactam ring is hydrolyzed by moisture
   - Causes loss of activity
2. β-Lactamase Degradation
   - Enzymes break β-lactam ring
   - Newer generations show resistance
3. Photodegradation
   - Light-sensitive drugs degrade on exposure

Prevention

- Store in dry, cool place
- Use light-resistant containers

Structure–Activity Relationship (SAR)

β-Lactam Ring

Essential for antibacterial activity

Opening → inactive drug

Dihydrothiazine Ring

Provides stability

Enhances resistance to β-lactamase

R_1 Side Chain (Position-7)

Determines:

Antibacterial spectrum

β-lactamase resistance

Bulky groups → enzyme resistance

R_2 Side Chain (Position-3)

Controls:

Metabolism

Duration of action

Oral bioavailability

Polar Substituents

Increase Gram-negative activity

β-Lactamase Inhibitors

→ β-Lactamase inhibitors are drugs that inhibit bacterial β-lactamase enzymes, which are responsible for destroying β-lactam antibiotics like penicillins and cephalosporins.

→ They have little or no antibacterial activity alone, but when combined with β-lactam antibiotics, they restore or enhance antibacterial efficacy.

Common combinations:

- Amoxicillin + Clavulanic acid
- Piperacillin + Tazobactam
- Ampicillin + Sulbactam

Classification

A. β-Lactam Based Inhibitors

- Clavulanic acid
- Sulbactam
- Tazobactam

B. Non-β-Lactam Inhibitors (Newer Agents)

- Avibactam
- Vaborbactam
- Relebactam

Structure

General Structural Features

Most inhibitors contain a β-lactam ring.
Structural similarity to penicillins.
Clavulanic acid has:
β-lactam ring
Oxazolidine ring
Sulbactam & Tazobactam are penicillanic acid sulfone derivatives.

Nomenclature

- Names usually end with "-bactam"
- Indicates their action against β-lactamase enzymes

Examples:

- Clavulanic acid
- Sulbactam
- Tazobactam
- Avibactam

Stereochemistry

- Correct stereochemical configuration is essential for enzyme binding.
- β-lactam ring orientation must match the active site of β-lactamase.
- Change in stereochemistry → reduced inhibitory activity.
- Natural stereochemistry allows irreversible enzyme inhibition.

Mechanism of Action

- β-lactamase inhibitor binds to β-lactamase enzyme.
- Forms a covalent, irreversible complex (suicide inhibition).
- Enzyme becomes inactive.
- β-lactam antibiotic remains intact.
- Bacteria become susceptible again.
- No direct antibacterial effect

Uses

- Respiratory tract infections
- Urinary tract infections
- Skin and soft tissue infections
- Intra-abdominal infections
- Hospital-acquired infections

Chemical Degradation

1. Hydrolysis
    - β-lactam ring is sensitive to moisture
    - Causes loss of inhibitory action
2. Thermal Degradation
    - High temperature increases degradation rate
3. pH-Dependent Degradation
    - Acidic or alkaline pH causes ring opening
4. Enzymatic Degradation
    - Can degrade during improper storage

Prevention

- Store in cool, dry place
- Protect from light & moisture
- Maintain suitable pH

Structure–Activity Relationship (SAR)

β-Lactam Ring

- Essential for β-lactamase binding
- Ring opening → inactive inhibitor

Substituted Sulfone Group

- Present in sulbactam & tazobactam
- Enhances enzyme inhibition

Electron-Withdrawing Groups

- Increase stability of acyl-enzyme complex
- Improve inhibitory potency

Stereochemistry

- Correct configuration necessary for irreversible inhibition

Ring System

- Modified ring structures improve:
    - Spectrum of enzyme inhibition
    - Resistance to hydrolysis

Monobactams

→ Monobactams are a special class of β-lactam antibiotics that contain a single (mono) β-lactam ring without a fused second ring.
→ They are synthetic antibiotics and are mainly active against aerobic Gram-negative bacteria.
→ Monobactams are resistant to many β-lactamase enzymes and show minimal cross-allergy with penicillins.
→ Example: Aztreonam

Classification

→ Monobactams have very limited members:
Clinically Used
- Aztreonam

Experimental / Less Used
- Tigemonam
- Carumonam

Structure

Core structure is a single β-lactam ring (not fused).

Contains:

β-lactam ring

Sulfonic acid group (–SO_3H) attached to nitrogen

Side chain similar to ceftazidime

Key Feature

Absence of thiazolidine or dihydrothiazine ring
→ hence called monobactam

Nomenclature

Names usually end with "**-treonam**"
Derived from:
Mono = single
Bactam = β-lactam ring
Example: Az-tre-onam

Stereochemistry

- Correct stereochemical configuration of the β-lactam ring is essential.
- Side-chain orientation affects binding to PBPs.
- Improper stereochemistry → loss of antibacterial activity.

Mechanism of Action

- Monobactams bind to Penicillin Binding Protein-3 (PBP-3).
- Inhibit peptidoglycan cross-linking.
- Cell wall synthesis stops.
- Bacterial cell lysis occurs.
- Bactericidal action

Uses

Infections caused by aerobic Gram-negative bacteria, especially:
Pseudomonas aeruginosa
E. coli
Klebsiella
Urinary tract infections
Respiratory tract infections

Chemical Degradation

1. Hydrolysis
   - β-lactam ring undergoes hydrolytic cleavage.
   - Leads to inactivation.
2. pH-Dependent Degradation
   - Unstable in extreme acidic or alkaline conditions.
3. Thermal Degradation
   - High temperature accelerates degradation.

Prevention

- Store in cool, dry place
- Protect from moisture
- Maintain proper pH

Structure–Activity Relationship (SAR)

β-Lactam Ring

- Essential for antibacterial activity.
- Ring opening → inactive drug.

Sulfonic Acid Group

- Increases β-lactamase resistance
- Enhances Gram-negative activity

Side Chain at β-Lactam Ring

- Determines:
  - Spectrum of activity
  - PBP affinity
- Similar side chain to ceftazidime improves activity against *Pseudomonas*.

Absence of Fused Ring

- Reduces cross-allergenicity with penicillins.

Stereochemistry

- Correct configuration essential for PBP binding.