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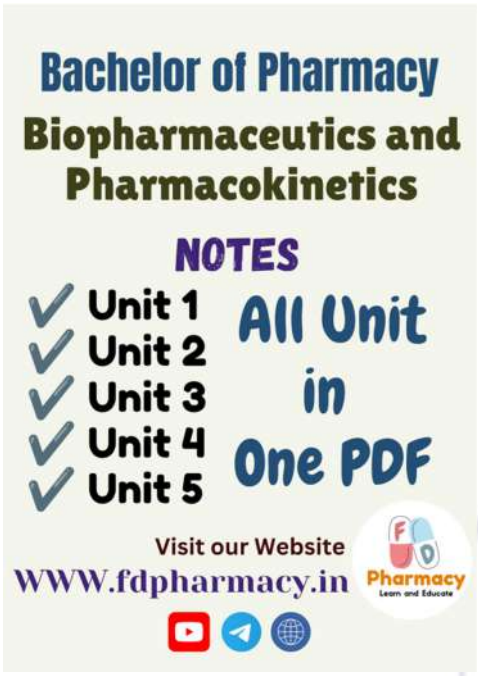
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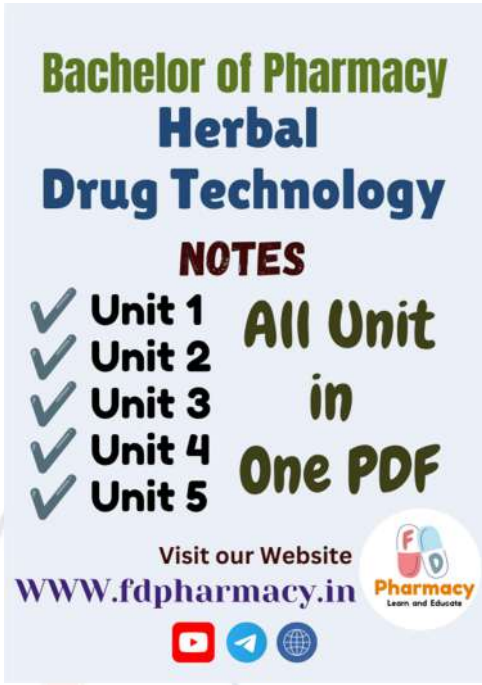
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MEDICINAL CHEMISTRY - III

UNIT 2

TOPIC :

- **Miscellaneous :** Chloramphenicol*, Clindamycin.

Miscellaneous Antibiotics

→ Miscellaneous antibiotics are a group of antibacterial agents that do not fit into major antibiotic classes based on structure or mechanism of action.

→ They possess different mechanisms, spectrums, and therapeutic uses.

Classification

Common miscellaneous antibiotics include:

- Chloramphenicol
- Vancomycin
- Metronidazole
- Rifampicin
- Fosfomycin
- Nitrofurantoin
- Linezolid

Mechanism of Action

A. Chloramphenicol

- Binds to 50S ribosomal subunit
- Inhibits peptidyl transferase enzyme
- Prevents protein synthesis

  ➡Bacteriostatic

B. Vancomycin

- Inhibits bacterial cell wall synthesis
- Binds to D-Ala-D-Ala terminus

  ➡Bactericidal

C. Metronidazole

- Reduced in anaerobic bacteria
- Forms toxic free radicals
- Damages DNA

  ➡Bactericidal

D. Rifampicin

- Inhibits DNA-dependent RNA polymerase

- Blocks RNA synthesis

  ➡Bactericidal

E. Nitrofurantoin

- Reduced by bacterial enzymes
- Produces reactive intermediates
- Damages DNA and proteins

Spectrum of Activity

Drug	Effective Against
Chloramphenicol	Gram +, Gram –, anaerobes
Vancomycin	Gram + (MRSA)
Metronidazole	Anaerobes, protozoa
Rifampicin	Mycobacterium tuberculosis
Nitrofurantoin	Urinary pathogens
Linezolid	Gram + resistant strains

Therapeutic Uses

Chloramphenicol

- Typhoid fever
- Meningitis (alternative drug)

Vancomycin

- MRSA infections
- Severe *C. difficile* infection

Metronidazole

- Amoebiasis
- Giardiasis
- Anaerobic infections
- *H. pylori* infections

Rifampicin

- Tuberculosis
- Leprosy
- Meningococcal prophylaxis

Nitrofurantoin

- Urinary tract infections (UTI)

Adverse Effects

Chloramphenicol

- Bone marrow suppression
- Aplastic anemia
- Gray baby syndrome

Vancomycin

- Nephrotoxicity
- Ototoxicity
- Red man syndrome

Metronidazole

- Metallic taste
- Peripheral neuropathy
- Disulfiram-like reaction with alcohol

Rifampicin

- Hepatotoxicity
- Orange discoloration of body fluids

Nitrofurantoin

- Pulmonary fibrosis (long term)
- GI disturbances

Resistance

Resistance occurs due to:

- Enzyme inactivation
- Altered target sites
- Decreased permeability
- Efflux mechanisms

Chloramphenicol

→ Chloramphenicol is a broad-spectrum antibiotic originally isolated from *Streptomyces venezuelae* and now produced synthetically.
→ It is primarily bacteriostatic, but may be bactericidal against certain organisms at high concentrations.
→ Chloramphenicol inhibits bacterial protein synthesis and shows activity against Gram-positive, Gram-negative, and anaerobic bacteria.

Classification

Based on Source
Synthetic antibiotic (originally natural)
Based on Spectrum
Broad-spectrum antibiotic
Based on Mechanism
Protein synthesis inhibitor

Structure

→ Chloramphenicol is a nitrobenzene derivative.
Important structural features:

- p-Nitro phenyl ring
- Dichloroacetamide side chain
- Propane-1,3-diol moiety
- Two chiral centers at C-1 and C-2

Molecular formula: $C_{11}H_{12}Cl_2N_2O_5$

Structural Characteristics

→ Small, non-bulky molecule
→ Highly lipophilic
→ Easily penetrates bacterial cell membrane
→ Crosses blood–brain barrier

Nomenclature

Chloro → presence of chlorine atoms
Amphenicol → amide + phenyl structure
Available forms:

- Chloramphenicol
- Chloramphenicol palmitate (oral prodrug)
- Chloramphenicol sodium succinate (injectable)

Stereochemistry

- Chloramphenicol contains two asymmetric carbon atoms.
- Only the D-(–)-threo isomer is antibacterially active.
- L-isomer and erythro forms are inactive or toxic.
- Correct stereochemistry is essential for ribosomal binding.

Mechanism of Action

- Chloramphenicol enters bacterial cell by passive diffusion.
- Binds to 50S ribosomal subunit.
- Inhibits peptidyl transferase enzyme.
- Prevents peptide bond formation.
- Protein synthesis stops.
- Hence, chloramphenicol is bacteriostatic.

Spectrum of Activity

Gram-positive bacteria
Gram-negative bacteria
Anaerobes

- *Salmonella typhi*
- *Haemophilus influenzae*
- *Neisseria meningitidis*
- *Rickettsia*

Uses

- Typhoid fever
- Bacterial meningitis
- Severe anaerobic infections
- Eye infections (topical)
- Alternative drug when no safer antibiotic is available

Adverse Effects

Aplastic anemia (rare but fatal)

- Dose-related bone marrow suppression

Gray baby syndrome

- Gastrointestinal disturbances

Chemical Degradation

1. Acid Degradation

- Relatively stable in acidic conditions

2. Alkaline Degradation

- Hydrolysis of amide linkage

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat causes degradation

Prevention

→ Store in cool, dry place
→ Protect from light
→ Avoid moisture

Structure–Activity Relationship (SAR)

p-Nitro Group

- Essential for antibacterial activity
- Removal → loss of activity

Dichloroacetamide Side Chain

- Required for activity
- Contributes to toxicity

Propane-1,3-diol Moiety

- Necessary for proper binding

Stereochemistry

- Only D-threo form is active

Clindamycin

→ Clindamycin is a semi-synthetic lincosamide antibiotic derived from lincomycin.
→ It is primarily bacteriostatic, but may be bactericidal at high concentrations.
→ Clindamycin is especially effective against anaerobic bacteria and Gram-positive cocci.
→ It inhibits bacterial protein synthesis and is commonly used in penicillin-allergic patients.

Classification

Based on Chemical Class

Lincosamide antibiotics

- Lincomycin
- Clindamycin

Based on Origin

Semi-synthetic antibiotic

Structure

→ Clindamycin is a chlorinated derivative of lincomycin.

Important structural features:

- Amino acid (proline-like) moiety
- Octose sugar unit
- Chlorine atom substitution (increases potency)
- Thioether linkage

Molecular formula: $C_{18}H_{33}ClN_2O_5S$

Structural Advantages

- Increased lipophilicity
- Better oral absorption

Nomenclature

Clin-da → chemical modification of lincomycin
Mycin → antibiotic of microbial origin
Available as:

- Clindamycin hydrochloride
- Clindamycin phosphate (injectable/topical)

Stereochemistry

- Clindamycin contains multiple chiral centers.
- Correct stereochemical configuration is required for:
  - Ribosomal binding
  - Antibacterial activity
- Change in configuration reduces potency significantly.

Mechanism of Action

→ Clindamycin penetrates bacterial cell.
→ Binds reversibly to the 50S ribosomal subunit.
→ Inhibits peptide chain initiation and translocation.
→ Blocks protein synthesis.
→ Bacterial growth is inhibited.
→ Hence, clindamycin is bacteriostatic.

Spectrum of Activity

Gram-positive cocci

- *Streptococcus*
- *Staphylococcus* (including some MRSA)

Anaerobic bacteria

- *Bacteroides fragilis*
- *Clostridium*

Protozoa

- *Toxoplasma gondii* (with pyrimethamine)

Uses

→ Anaerobic infections
→ Skin and soft tissue infections
→ Bone and joint infections (osteomyelitis)
→ Dental infections
→ Acne vulgaris (topical)
→ Alternative in penicillin allergy
→ Toxoplasmosis (with pyrimethamine)

Adverse Effects

- ◈ Pseudomembranous colitis (*Clostridioides difficile*)
- ◈ Diarrhea
- ◈ Abdominal pain
- ◈ Skin rashes
- ◈ Hepatotoxicity (rare)

Chemical Degradation

1. Acid Degradation

- Relatively stable

2. Alkaline Degradation

- Hydrolysis of ester linkage

3. Photodegradation

- Sensitive to light

4. Thermal Degradation

- Heat accelerates degradation

Prevention

→ Store in cool, dry place
→ Protect from light
→ Avoid moisture

Structure–Activity Relationship (SAR)

Chlorine Substitution

- Increases antibacterial potency
- Improves lipid solubility

Amino Acid Moiety

- Essential for ribosomal binding

Sugar Moiety

- Important for activity and solubility