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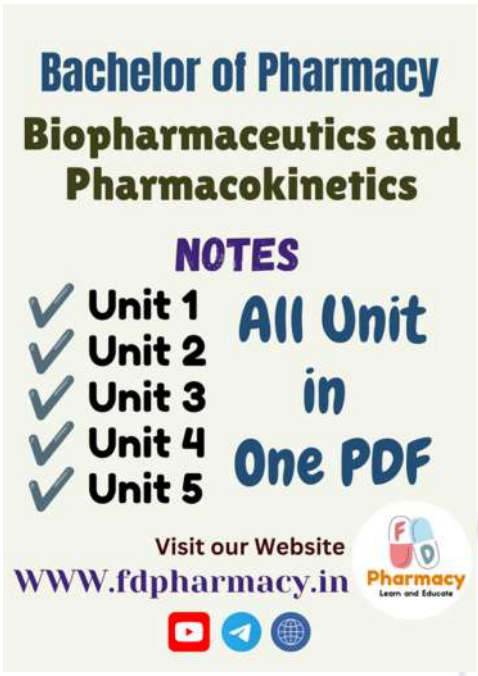
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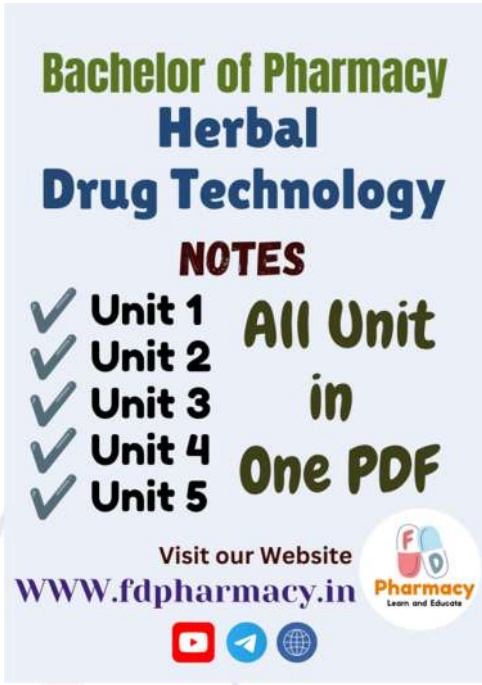
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MEDICINAL CHEMISTRY - III

UNIT 4

TOPIC :

- **Antifungal agents :**

  Antifungal antibiotics : Amphotericin-B, Nystatin, Natamycin, Griseofulvin.

Antifungal Agents

- Antifungal agents are drugs used to treat infections caused by fungi. Fungal infections are classified as:
  - Superficial – affect skin, hair, nails (e.g., dermatophytes, Candida)
  - Systemic – affect internal organs (e.g., Candida, Aspergillus, Cryptococcus)
- Antifungal agents work by inhibiting fungal cell wall synthesis, membrane integrity, or nucleic acid synthesis.

Classification of Antifungal Agents

- Antifungal agents are classified based on mechanism of action and chemical structure**:**

A. Polyenes

- Bind to ergosterol in fungal cell membrane → forms pores → cell death

Examples:

- Amphotericin B (systemic infections)
- Nystatin (topical, oral candidiasis)

Key points:

- Broad-spectrum
- Mainly fungicidal
- Toxicity: nephrotoxicity, infusion reactions (Amphotericin B)

B. Azoles

- Inhibit lanosterol 14α-demethylase, blocking ergosterol synthesis → defective cell membrane

Examples:

- Imidazoles: Ketoconazole, Clotrimazole, Miconazole
- Triazoles: Fluconazole, Itraconazole, Voriconazole

Key points:

- Fungistatic (some fungicidal at high dose)
- Used for systemic and superficial mycoses
- Adverse effects: hepatotoxicity, drug interactions (CYP450 inhibition)

C. Echinocandins

- Inhibit β-(1,3)-D-glucan synthase, disrupting fungal cell wall
- Examples: Caspofungin, Micafungin, Anidulafungin
- Used for invasive Candida and Aspergillus infections
- Fungicidal against Candida, fungistatic against Aspergillus

D. Allylamines

- Inhibit squalene epoxidase, blocking ergosterol synthesis → accumulation of squalene → cell death
- Examples: Terbinafine, Naftifine
- Mainly used for dermatophyte infections (skin and nails)

E. Flucytosine (5-FC)

- Converted to 5-fluorouracil in fungi → inhibits DNA and RNA synthesis
- Used in combination with Amphotericin B for cryptococcal meningitis
- Adverse effects: bone marrow suppression, hepatotoxicity

F. Other Agents

- Griseofulvin: Interferes with microtubule formation → inhibits mitosis; used for dermatophyte infections
- Tolnaftate, Ciclopirox: Topical antifungals for skin infections

Mechanism of Action

Class	Example	Mechanism	Type
Polyenes	Amphotericin B	Binds ergosterol → membrane pores	Fungicidal
Azoles	Fluconazole	Inhibits ergosterol synthesis	Fungistatic/Fungicidal
Echinocandins	Caspofungin	Inhibits β-(1,3)-D-glucan synthesis	Fungicidal (Candida)
Allylamines	Terbinafine	Inhibits squalene epoxidase	Fungicidal
Flucytosine	5-FC	Inhibits DNA/RNA synthesis	Fungistatic
Griseofulvin	Griseofulvin	Inhibits microtubule formation	Fungistatic

Indications

- Superficial fungal infections: Clotrimazole, Terbinafine, Nystatin
- Systemic fungal infections: Amphotericin B, Fluconazole, Echinocandins
- Combination therapy: Flucytosine + Amphotericin B (Cryptococcus)

Adverse Effects

Drug/Class	Common Adverse Effects
Amphotericin B	Fever, chills, nephrotoxicity, anemia
Azoles	Hepatotoxicity, GI upset, drug interactions
Echinocandins	Mild GI upset, liver enzyme elevation
Flucytosine	Bone marrow suppression, hepatotoxicity
Griseofulvin	Headache, GI upset, photosensitivity

Antifungal Antibiotics

- Antifungal antibiotics are drugs used to treat fungal infections (mycoses) caused by yeasts and molds.
- They act by damaging fungal cell membrane, inhibiting ergosterol synthesis, or interfering with nucleic acid synthesis.

Classification of Antifungal Antibiotics

A. Polyene Antibiotics

- Amphotericin-B
- Nystatin

B. Griseofulvin

- Griseofulvin (unique class)

Mechanism of Action

A. Amphotericin-B

- Binds to ergosterol in fungal cell membrane
- Forms pores/channels
- Leakage of intracellular contents
- Fungal cell death
- Fungicidal

B. Nystatin

- Similar to Amphotericin-B
- Binds to ergosterol
- Causes membrane damage
- Used only topically or orally (not absorbed)
- Fungicidal

C. Griseofulvin

- Inhibits mitosis by binding to microtubules
- Prevents fungal cell division
- Deposits in keratinized tissues (skin, hair, nails)
- Fungistatic

Spectrum of Activity

Drug	Effective Against
Amphotericin-B	Candida, Cryptococcus, Aspergillus, Histoplasma
Nystatin	Candida species
Griseofulvin	Dermatophytes (*Trichophyton, Microsporum, Epidermophyton*)

Therapeutic Uses

Amphotericin-B

- Severe systemic fungal infections
- Cryptococcal meningitis
- Disseminated candidiasis

Nystatin

- Oral candidiasis (thrush)
- Vaginal candidiasis
- Topical fungal infections

Griseofulvin

- Dermatophytosis
- Ringworm
- Tinea infections (skin, hair, nails)

Adverse Effects

Amphotericin-B

- Nephrotoxicity (most important)
- Fever, chills
- Hypokalemia
- Anemia

Nystatin

- Nausea, vomiting (oral use)
- Minimal systemic toxicity

Griseofulvin

- Headache
- GI upset
- Photosensitivity

Amphotericin B

- Amphotericin B is a polyene macrolide antifungal antibiotic obtained from *Streptomyces nodosus*.
- It is broad-spectrum, effective against most systemic fungal infections.
- It is used intravenously for systemic mycoses and topically for superficial fungal infections.

Classification

Based on Chemical Class

- Polyene macrolide antibiotic
- Large macrocyclic lactone ring with conjugated double bonds

Based on Antifungal Action

- Fungicidal (primarily)
- Binds to ergosterol in fungal cell membrane → increases membrane permeability

Based on Use

- Systemic and topical antifungal agent

Structure

- Macrocyclic lactone ring with conjugated double bonds (polyene)
- Hydroxyl groups along the ring → hydrophilic portion

Molecular formula: $C_{47}H_{73}NO_{17}$

Structural Characteristics

- Amphipathic molecule: hydrophobic polyene portion + hydrophilic hydroxyl portion
- Forms pores in fungal membranes by binding ergosterol
- Poor water solubility → available as deoxycholate or lipid formulations

Nomenclature

- Amphotericin B → generic name
- Available as Fungizone, Abelcet, AmBisome (lipid formulations)
- Formulations: IV infusion, topical creams, eye drops

Mechanism of Action

- Amphotericin B binds to ergosterol in fungal cell membrane.
- Forms transmembrane pores → leakage of intracellular ions (K^+, Mg^{2+}).
- Disrupts membrane integrity → fungal cell death.
- Selectivity due to binding affinity to ergosterol vs cholesterol in mammalian cells.
- Hence, amphotericin B is fungicidal by membrane disruption.

Spectrum of Activity

- Candida spp. – C. albicans, C. tropicalis, C. glabrata
- Cryptococcus neoformans
- Aspergillus spp.
- Histoplasma capsulatum, Blastomyces dermatitidis, Coccidioides spp.
- Mucor and Rhizopus spp. (less sensitive)
- Not effective against bacteria

Uses

- Systemic mycoses: candidiasis, cryptococcosis, aspergillosis
- Severe fungal infections in immunocompromised patients
- Topical fungal infections: skin and mucosal candidiasis

Adverse Effects

- Infusion-related: fever, chills, rigors, hypotension
- Nephrotoxicity: azotemia, electrolyte imbalance (K^+, Mg^{2+} loss)
- Anemia (due to decreased erythropoietin)

Chemical Degradation

- Sensitive to light and heat
- Store protected from light, at 2–8°C

Structure–Activity Relationship (SAR)

- Conjugated polyene system → binds ergosterol effectively
- Hydrophilic hydroxyl groups → insertion into membrane and pore formation
- Amphipathic nature → allows interaction with lipid bilayer
- Lipid formulations → reduce toxicity while retaining antifungal activity

Nystatin

- Nystatin is a polyene macrolide antifungal antibiotic obtained from *Streptomyces noursei*.
- It is broad-spectrum against Candida species and is used topically, orally, or as vaginal preparations.
- Unlike amphotericin B, nystatin is not absorbed systemically when given orally, limiting its use to localized infections.

Classification

Based on Chemical Class

- Polyene macrolide antibiotic
- Macrocyclic lactone ring with conjugated double bonds

Based on Antifungal Action

- Fungicidal (primarily)
- Binds to ergosterol in fungal cell membrane → causes pore formation

Based on Use

- Topical and oral antifungal agent
- Used for cutaneous, mucosal, and oral Candida infections

Structure

- Macrocyclic lactone ring with conjugated double bonds (polyene)
- Multiple hydroxyl groups → hydrophilic portion

Molecular formula: $C_{47}H_{75}NO_{17}$

Structural Characteristics

- Amphipathic molecule: hydrophobic polyene + hydrophilic hydroxyls
- Forms pores in fungal membranes by binding to ergosterol
- Poor water solubility → formulated in creams, ointments, powders, suspensions

Nomenclature

- Nystatin → generic name
- Brand names include Nilstat, Mycostatin
- Formulations: topical cream, powder, oral suspension, vaginal tablets

Mechanism of Action

- ❖ Nystatin binds to ergosterol in fungal cell membrane.
- ❖ Forms transmembrane channels → leakage of intracellular ions (K^+, Mg^{2+}).
- ❖ Disrupts membrane integrity → fungal cell death.
- ❖ Selectivity due to higher affinity for ergosterol than cholesterol.
- ❖ Hence, nystatin is fungicidal by membrane disruption.

Spectrum of Activity

- Candida albicans – primary activity
- Candida tropicalis, Candida glabrata
- Limited activity against Aspergillus spp. and other fungi
- No activity against bacteria

Uses

- Oral candidiasis (thrush) – oral suspension
- Cutaneous candidiasis – creams and powders
- Vaginal candidiasis – vaginal tablets or cream
- Prevention of Candida infections in immunocompromised patients

Adverse Effects

- ▪ Topical: mild irritation, redness, itching
- ▪ Oral: nausea, vomiting, diarrhea (rare)
- ▪ Systemic toxicity: negligible (not absorbed orally)
- ▪ Hypersensitivity reactions – rare

Chemical Degradation

- ❖ Sensitive to light and heat
- ❖ Poor water solubility → store as suspension, cream, or powder
- ❖ Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- ⅄ Conjugated polyene system → binds ergosterol effectively
- ⅄ Hydroxyl groups → insertion into membrane and pore formation
- ⅄ Amphipathic nature → allows interaction with lipid bilayer
- ⅄ Non-absorbable orally → useful for local infections without systemic toxicity

Natamycin (Pimaricin)

- Natamycin is a polyene macrolide antifungal antibiotic obtained from *Streptomyces natalensis*.
- It is primarily used for topical fungal infections of the eye, skin, and mucous membranes, and as a food preservative against yeasts and molds.
- Natamycin is poorly absorbed orally, limiting systemic use.

Classification

Based on Chemical Class

- Polyene macrolide antibiotic
- Macrocyclic lactone ring with conjugated double bonds

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Binds to ergosterol in fungal cell membrane → inhibits membrane function

Based on Use

- Topical antifungal agent (ophthalmic, dermatologic)
- Food preservative (prevents mold and yeast growth)

Structure

- Macrocyclic lactone ring with conjugated double bonds (polyene)
- Multiple hydroxyl groups → hydrophilic portion

Molecular formula: $C_{33}H_{47}NO_{13}$

Structural Characteristics

- Amphipathic molecule: hydrophobic polyene + hydrophilic hydroxyls
- Forms specific interactions with ergosterol in fungal membranes
- Poor water solubility → formulated in ophthalmic suspensions, creams, and powders

Nomenclature

- Natamycin → generic name
- Also called Pimaricin
- Brand names: Natacyn (ophthalmic), Pactamycin
- Formulations: ophthalmic suspension, topical cream, food-grade powder

Mechanism of Action

- Natamycin binds specifically to ergosterol in fungal cell membranes.
- Unlike other polyenes, it does not form pores; instead, it inhibits membrane-associated transport.
- Disrupts fungal membrane function → inhibits growth and replication.
- Selectivity due to high affinity for ergosterol over cholesterol.
- Hence, natamycin is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Candida spp. – C. albicans, C. tropicalis
- Aspergillus spp.
- Fusarium spp.
- Effective for ocular and superficial fungal infections
- Minimal systemic activity due to poor absorption

Uses

- Ophthalmic fungal infections – keratitis, conjunctivitis
- Food preservation – prevents spoilage by molds and yeasts
- Alternative for patients intolerant to other polyenes

Adverse Effects

- Topical/ophthalmic: mild irritation, burning, redness
- Rare systemic toxicity due to minimal absorption
- Hypersensitivity reactions – very rare

Chemical Degradation

- Sensitive to light and heat
- Poor water solubility → store as suspension or cream
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Conjugated polyene system → binds specifically to ergosterol
- Hydroxyl groups → interact with membrane lipids
- Amphipathic nature → allows membrane binding without forming pores
- Low systemic absorption → effective for topical and ophthalmic use

Griseofulvin

- Griseofulvin is a fungistatic antibiotic derived from *Penicillium griseofulvum*.
- It is used primarily for superficial fungal infections of the skin, hair, and nails, especially caused by dermatophytes.
- Griseofulvin is orally active and accumulates in keratinized tissues, providing prolonged protection against fungal infections.

Classification

Based on Chemical Class

- Benzofuran derivative
- Fungistatic antibiotic

Based on Antifungal Action

- Fungistatic – inhibits fungal growth rather than killing fungi
- Interferes with mitosis by binding to fungal microtubules

Based on Use

- Systemic therapy for dermatophytic infections of skin, hair, and nails

Structure

- Benzofuran ring system with chloro-substituents

Molecular formula: $C_{21}H_{22}Cl_2O_4$

Structural Characteristics

- Lipophilic → concentrates in keratin-rich tissues
- Methoxy and phenyl groups → improve binding to fungal microtubules
- Poor water solubility → formulated as oral tablets or suspensions

Nomenclature

- Griseofulvin → generic name
- Brand names: Grisovin, Fulcin
- Formulations: oral tablets, capsules, oral suspension

Mechanism of Action

- Griseofulvin binds to fungal microtubules, inhibiting mitotic spindle formation.
- Prevents fungal cell division (mitosis).
- Deposits in keratin precursor cells, providing resistance to reinfection.
- Fungistatic action allows host immune system to eliminate the infection.
- Hence, griseofulvin is a fungistatic mitotic inhibitor.

Spectrum of Activity

- Dermatophytes: Trichophyton spp., Microsporum spp., Epidermophyton spp.
- Limited activity against Candida and other fungi
- Not effective against systemic mycoses

Uses

- Tinea infections – corporis, cruris, pedis
- Onychomycosis – fungal infection of nails
- Scalp ringworm (tinea capitis)
- Prophylaxis in recurrent dermatophyte infections

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- CNS: headache, dizziness, fatigue
- Hypersensitivity reactions: rash, urticaria

Chemical Degradation

- Sensitive to light and heat
- Poor water solubility → store as tablets or suspension
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Benzofuran ring → essential for antifungal activity
- Lipophilic groups → accumulation in keratin-rich tissues
- Chloro-substituents → increase potency against dermatophytes
- Fungistatic action → allows slow eradication of fungi in keratinized tissues