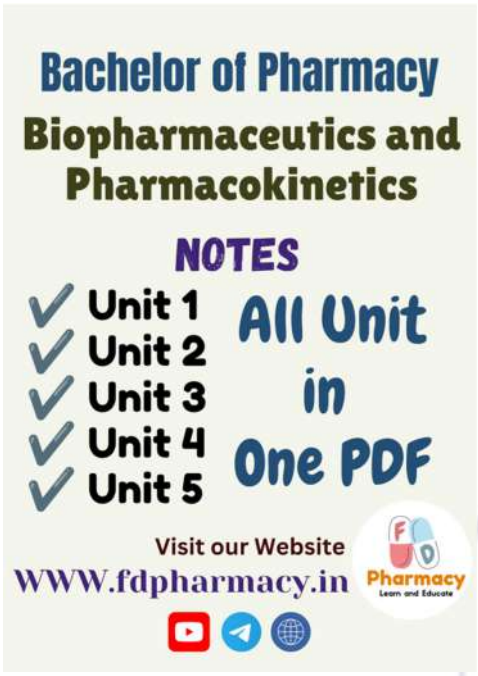
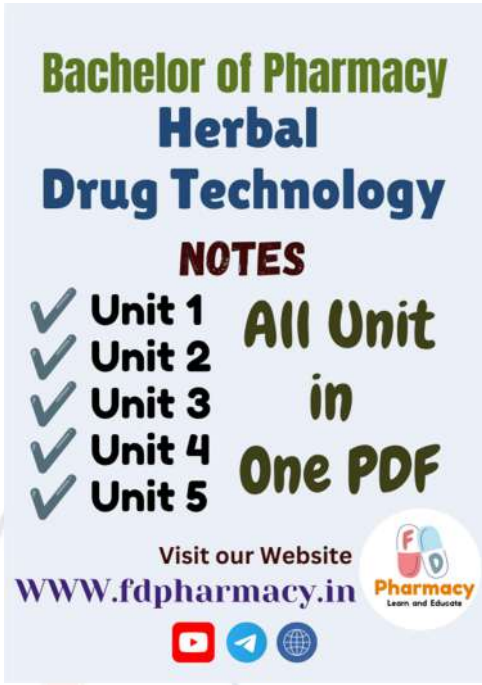
WELCOME

TO


Bachelor of Pharmacy
Biopharmaceutics and Pharmacokinetics
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Herbal Drug Technology
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Pharmaceutical Biotechnology
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Medicinal Chemistry III
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Pharmacology III
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate


Bachelor of Pharmacy
Quality Assurance
NOTES
Unit 1
Unit 2
Unit 3
Unit 4
Unit 5
All Unit in One PDF
Visit our Website
WWW.fdpharmacy.in
Pharmacy
Learn and Educate

MEDICINAL CHEMISTRY - III

UNIT 4

TOPIC :

- **Synthetic Antifungal agents :** Clotrimazole, Econazole, Butoconazole, Oxiconazole Tioconozole, Miconazole, *Ketoconazole, Terconazole, Itraconazole, Fluconazole, Naftifine hydrochloride, Tolnaftate*.

Synthetic Antifungal Agents

- Synthetic antifungal agents are chemically synthesized drugs used to treat fungal infections (mycoses).
- They act mainly by inhibiting ergosterol synthesis, damaging fungal cell membrane, or inhibiting nucleic acid synthesis.

Classification

A. Azoles

1. Imidazoles

- Ketoconazole, Clotrimazole, Miconazole, Econazole

2. Triazoles

- Fluconazole, Itraconazole
- Voriconazole, Posaconazole

B. Allylamines

- Terbinafine, Naftifine

C. Echinocandins

- Caspofungin, Micafungin, Anidulafungin

D. Antimetabolites

- Flucytosine

Mechanism of Action

A. Azoles

- Inhibit 14-α-demethylase enzyme
- Block conversion of lanosterol to ergosterol
- Disrupt fungal cell membrane
- Fungistatic

B. Allylamines

- Inhibit squalene epoxidase
- Decrease ergosterol synthesis
- Accumulation of toxic squalene
- Fungicidal

C. Echinocandins

- Inhibit β-(1,3)-D-glucan synthesis
- Weakens fungal cell wall

- Fungicidal

D. Flucytosine

- Converted to 5-fluorouracil in fungal cells
- Inhibits DNA and RNA synthesis
- Fungistatic

Spectrum of Activity

Class	Effective Against
Azoles	Candida, Cryptococcus, Aspergillus
Allylamines	Dermatophytes
Echinocandins	Candida, Aspergillus
Flucytosine	Candida, Cryptococcus

Therapeutic Uses

Azoles

- Candidiasis
- Systemic and superficial fungal infections

Allylamines

- Tinea infections, Onychomycosis

Echinocandins

- Invasive candidiasis
- Refractory fungal infections

Flucytosine

- Cryptococcal meningitis (with Amphotericin-B)

Adverse Effects

Azoles

- Hepatotoxicity,GI disturbances

Allylamines

- GI upset
- Taste disturbance

Echinocandins

- Mild GI upset, Fever

Flucytosine

- Bone marrow suppression
- GI toxicity

Clotrimazole

- Clotrimazole is a synthetic broad-spectrum imidazole antifungal.
- It is used topically for cutaneous, vaginal, and oral fungal infections, and systemically in some cases.
- Clotrimazole inhibits ergosterol synthesis, disrupting fungal cell membranes and growth.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – skin, mucous membranes
- Oral and vaginal infections

Structure

- Imidazole ring attached to chlorophenyl and dichlorophenyl groups
- Lipophilic side chain → membrane penetration

Molecular formula: $C_{22}H_{17}ClN_2$

Structural Characteristics

- Lipophilic → allows penetration into skin and mucous membranes
- Imidazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as cream, lotion, solution, vaginal tablets

Nomenclature

- Clotrimazole → generic name
- Brand names: Canesten, Lotrimin
- Formulations: topical cream, lotion, vaginal tablets, lozenges, solution

Mechanism of Action

- Clotrimazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- Blocks conversion of lanosterol to ergosterol.
- Leads to accumulation of methylated sterols → altered membrane structure.
- Disrupts membrane permeability → inhibits fungal growth.
- Hence, clotrimazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Candida spp. – C. albicans, C. tropicalis, C. glabrata
- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Malassezia spp. – causes pityriasis versicolor
- Limited activity against Aspergillus

Uses

- Cutaneous candidiasis – skin infections
- Oral thrush – lozenges or solution
- Vaginal candidiasis – vaginal tablets or cream

Adverse Effects

- Topical: burning, itching, redness
- Oral: nausea, vomiting, taste disturbances

Chemical Degradation

- Sensitive to light and heat
- Poor water solubility → formulated in ointments, creams, and solutions
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Imidazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance membrane penetration
- Chlorophenyl groups → increase antifungal potency
- Fungistatic/fungicidal activity → concentration-dependent

Econazole

- Econazole is a synthetic broad-spectrum imidazole antifungal.
- It is primarily used topically for cutaneous fungal infections including dermatophytosis and candidiasis.
- It inhibits ergosterol synthesis, disrupting fungal cell membranes and fungal growth.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – skin, mucous membranes

Structure

- Imidazole ring attached to dichlorophenyl and phenyl groups
- Lipophilic side chain → enhances membrane penetration

Molecular formula: $C_{18}H_{15}Cl_3N_2$

Structural Characteristics

- Lipophilic → penetrates skin and nails
- Imidazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as cream, lotion, or solution

Nomenclature

- Econazole → generic name
- Brand names: Spectazole, Ecostatin
- Formulations: topical cream, lotion, solution

Mechanism of Action

- Econazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- Blocks conversion of lanosterol to ergosterol.
- Leads to accumulation of methylated sterols → altered membrane structure.
- Disrupts membrane permeability → inhibits fungal growth.
- Hence, econazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Candida spp. – C. albicans, C. tropicalis
- Malassezia spp. – causes pityriasis versicolor
- Limited activity against Aspergillus

Uses

- Tinea infections – corporis, cruris, pedis
- Cutaneous candidiasis – skin infections
- Pityriasis versicolor – Malassezia infection
- Topical fungal infections resistant to other azoles

Adverse Effects

- Topical: burning, itching, redness, irritation
- Rare: hypersensitivity reactions
- Systemic toxicity negligible due to poor absorption

Chemical Degradation

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

Structure–Activity Relationship (SAR)

- Imidazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance skin penetration and potency
- Chlorophenyl groups → increase antifungal activity
- Fungistatic/fungicidal activity → concentration-dependent

Butocconazole

- Butoconazole is a synthetic imidazole antifungal agent.
- It is primarily used for topical treatment of vaginal fungal infections, especially vulvovaginal candidiasis.
- It works by inhibiting ergosterol synthesis, disrupting fungal cell membrane function.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – vaginal infections

Structure

- Imidazole ring attached to chlorophenyl and phenyl groups
- Lipophilic side chain → enhances membrane penetration

Molecular formula: $C_{18}H_{17}ClN_2S$

Structural Characteristics

- Lipophilic → penetrates vaginal mucosa effectively
- Imidazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as vaginal cream or suppository

Nomenclature

- Butoconazole → generic name
- Brand names: Femstat, Gynazole
- Formulations: vaginal cream, vaginal suppository

Mechanism of Action

- ❖ Butoconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- ❖ Blocks conversion of lanosterol to ergosterol.
- ❖ Leads to accumulation of methylated sterols → disrupted membrane structure.
- ❖ Disrupts membrane permeability → inhibits fungal growth.
- ❖ Hence, butoconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- ▪ Candida spp. – C. albicans, C. tropicalis
- ▪ Some dermatophytes – Trichophyton spp.
- ▪ Primarily effective for vaginal candidiasis
- ▪ Limited activity against other fungi

Uses

- ⇨ Vulvovaginal candidiasis – single-dose or short-course therapy
- ⇨ Topical vaginal fungal infections
- ⇨ Alternative for patients resistant or intolerant to other azoles

Adverse Effects

- ❍ Local irritation: burning, itching, redness
- ❍ Rare: hypersensitivity reactions, urticaria
- ❍ Systemic absorption negligible → minimal systemic toxicity

Chemical Degradation

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

Structure–Activity Relationship (SAR)

- ⅄ Imidazole ring → binds fungal cytochrome P450
- ⅄ Lipophilic side chains → enhance mucosal penetration and potency
- ⅄ Chlorophenyl groups → increase antifungal activity
- ⅄ Fungistatic/fungicidal activity → concentration-dependent

Oxiconazole

- Oxiconazole is a synthetic broad-spectrum imidazole antifungal.
- It is used primarily for topical treatment of cutaneous fungal infections, including dermatophytosis and candidiasis.
- Oxiconazole works by inhibiting ergosterol synthesis, disrupting fungal cell membrane integrity and growth.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – skin infections

Structure

- Imidazole ring attached to chlorophenyl and phenyl groups
- Lipophilic side chain → enhances skin penetration

Molecular formula: $C_{18}H_{14}Cl_3N$

Structural Characteristics

- Lipophilic → penetrates skin and nails effectively
- Imidazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as cream or lotion

Nomenclature

- Oxiconazole → generic name
- Brand names: Oxistat, Oxicon
- Formulations: topical cream, lotion

Mechanism of Action

- ❖ Oxiconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- ❖ Blocks conversion of lanosterol to ergosterol.
- ❖ Leads to accumulation of methylated sterols → altered membrane structure.
- ❖ Disrupts membrane permeability → inhibits fungal growth.
- ❖ Hence, oxiconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Candida spp. – C. albicans, C. tropicalis
- Effective for cutaneous fungal infections
- Limited activity against other fungi

Uses

- Tinea infections – corporis, cruris, pedis
- Cutaneous candidiasis – skin infections
- Topical fungal infections resistant to other azoles

Adverse Effects

- Topical: burning, itching, redness, irritation
- Rare: hypersensitivity reactions
- Systemic toxicity negligible due to poor absorption

Chemical Degradation

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

Structure–Activity Relationship (SAR)

- Imidazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance skin penetration and potency
- Chlorophenyl groups → increase antifungal activity
- Fungistatic/fungicidal activity → concentration-dependent

Tioconazole

- Tioconazole is a synthetic imidazole antifungal.
- It is primarily used for topical treatment of vulvovaginal candidiasis and other superficial fungal infections.
- Tioconazole inhibits ergosterol synthesis, disrupting fungal cell membrane integrity and growth.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – vaginal infections

Structure

- Imidazole ring attached to dichlorophenyl and thiazole groups
- Lipophilic side chain → enhances mucosal penetration

Molecular formula: $C_{14}H_{14}Cl_3NOS$

Structural Characteristics

⇨ Lipophilic → penetrates vaginal mucosa effectively
⇨ Imidazole ring → binds to fungal cytochrome P450 enzyme
⇨ Poor water solubility → formulated as vaginal cream or ointment

Nomenclature

- Tioconazole → generic name
- Brand names: Trosyd, Vagistat
- Formulations: vaginal cream, ointment

Mechanism of Action

- Tioconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- Blocks conversion of lanosterol to ergosterol.
- Leads to accumulation of methylated sterols → altered membrane structure.
- Disrupts membrane permeability → inhibits fungal growth.
- Hence, tioconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Candida spp. – *C. albicans*, *C. tropicalis*
- Effective for vaginal candidiasis
- Limited activity against dermatophytes and other fungi

Uses

- Vulvovaginal candidiasis – single-dose or short-course therapy
- Topical treatment of cutaneous fungal infections
- Alternative for patients resistant to other azoles

Adverse Effects

- Local irritation: burning, itching, redness
- Rare: hypersensitivity reactions
- Systemic absorption negligible → minimal systemic toxicity

Chemical Degradation

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

Structure–Activity Relationship (SAR)

- Imidazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance mucosal penetration and potency
- Chlorophenyl and thiazole groups → increase antifungal activity
- Fungistatic/fungicidal activity → concentration-dependent

Miconazole

- Miconazole is a synthetic broad-spectrum imidazole antifungal.
- It is used topically for cutaneous, vaginal, and oral fungal infections and is effective against dermatophytes and Candida species.
- Miconazole inhibits ergosterol synthesis, disrupting fungal cell membrane structure and function.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – skin, mucous membranes, vaginal infections

Structure

- Imidazole ring attached to chlorophenyl and dioxolane groups
- Lipophilic side chain → enhances membrane penetration

Molecular formula: $C_{18}H_{14}Cl_4N_2O$

Structural Characteristics

- Lipophilic → penetrates skin and mucous membranes effectively
- Imidazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as cream, lotion, powder, solution, or vaginal tablet

Nomenclature

- Miconazole → generic name
- Brand names: Daktarin, Micatin, Monistat
- Formulations: topical cream, powder, lotion, vaginal tablets, oral gel

Mechanism of Action

- ⇨ Miconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- ⇨ Blocks conversion of lanosterol to ergosterol.
- ⇨ Leads to accumulation of methylated sterols → altered membrane structure.
- ⇨ Disrupts membrane permeability → inhibits fungal growth.
- ⇨ Hence, miconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- ⮝ Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- ⮝ Candida spp. – C. albicans, C. tropicalis
- ⮝ Malassezia spp. – causes pityriasis versicolor
- ⮝ Limited activity against Aspergillus

Uses

- Tinea infections – corporis, cruris, pedis
- Cutaneous candidiasis – skin infections
- Oral thrush – oral gel
- Vaginal candidiasis – vaginal tablets or cream
- Pityriasis versicolor – Malassezia infection

Adverse Effects

- Topical: burning, itching, redness, irritation
- Rare: hypersensitivity reactions
- Systemic toxicity negligible due to poor absorption

Chemical Degradation

- Sensitive to light and heat
- Poor water solubility → formulated as cream, powder, solution, or gel
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- ❖ Imidazole ring → binds fungal cytochrome P450
- ❖ Lipophilic side chains → enhance skin and mucosal penetration
- ❖ Chlorophenyl and dioxolane groups → increase antifungal activity
- ❖ Fungistatic/fungicidal activity → concentration-dependent

Ketoconazole

- Ketoconazole is a synthetic broad-spectrum imidazole antifungal.
- It is effective against dermatophytes, yeasts (Candida), and some systemic mycoses.
- It can be administered topically or orally, but systemic use is limited due to hepatotoxicity.
- Ketoconazole inhibits ergosterol synthesis, disrupting fungal cell membrane integrity.

Classification

Based on Chemical Class

- Imidazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical therapy – cream, shampoo, lotion
- Systemic therapy – oral tablets (restricted due to toxicity)

Structure

- Imidazole ring attached to dichlorophenyl and piperazine groups
- Lipophilic side chains → enhance membrane penetration

Molecular formula: $C_{26}H_{28}Cl_2N_4O_4$

Structural Characteristics

- Lipophilic → penetrates skin, hair, and nails
- Imidazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as cream, lotion, shampoo, or oral tablet

Nomenclature

- Ketoconazole → generic name
- Brand names: Nizoral, Ketozol
- Formulations: topical cream, shampoo, oral tablet

Mechanism of Action

- ❖ Ketoconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- ❖ Blocks conversion of lanosterol to ergosterol.
- ❖ Leads to accumulation of methylated sterols → altered membrane structure.
- ❖ Disrupts membrane permeability → inhibits fungal growth.
- ❖ Hence, ketoconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Candida spp. – C. albicans, C. tropicalis
- Malassezia spp. – causes dandruff and pityriasis versicolor
- Some systemic fungi – Histoplasma, Blastomyces
- Less effective against Aspergillus

Uses

- Dermatophytosis – tinea corporis, cruris, pedis
- Cutaneous candidiasis – skin infections
- Seborrheic dermatitis/dandruff – topical shampoo

Adverse Effects

- Topical: burning, itching, irritation
- Oral: nausea, vomiting, hepatotoxicity (rare but serious), gynecomastia, menstrual irregularities

Chemical Degradation

- Sensitive to light and heat
- Poor water solubility → formulated as cream, shampoo, lotion, or tablet
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Imidazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance skin and mucosal penetration
- Dichlorophenyl and piperazine groups → increase antifungal potency
- Fungistatic/fungicidal activity → concentration-dependent

Terconazole

- Terconazole is a synthetic triazole antifungal.
- It is primarily used for topical treatment of vulvovaginal candidiasis.
- Terconazole works by inhibiting ergosterol synthesis, disrupting fungal cell membrane integrity and fungal growth.
- It is more potent and less irritating compared to imidazole antifungals.

Classification

Based on Chemical Class

- Triazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – vaginal infections

Structure

- Triazole ring attached to dichlorophenyl and cyclohexyl groups
- Lipophilic side chain → enhances mucosal penetration

Molecular formula: $C_{22}H_{24}Cl_2N_4O$

Structural Characteristics

- Lipophilic → penetrates vaginal mucosa effectively
- Triazole ring → binds to fungal cytochrome P450 enzyme
- Poor water solubility → formulated as vaginal cream or suppository

Nomenclature

- Terconazole → generic name
- Brand names: Terazol, Tercon
- Formulations: vaginal cream, vaginal suppository

Mechanism of Action

- Terconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- Blocks conversion of lanosterol to ergosterol.
- Leads to accumulation of methylated sterols → altered membrane structure.
- Disrupts membrane permeability → inhibits fungal growth.
- Hence, terconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Candida spp. – *C. albicans*, *C. tropicalis*
- Effective for vaginal candidiasis
- Limited activity against dermatophytes

Uses

- Vulvovaginal candidiasis – single-dose or short-course therapy
- Topical treatment of vaginal fungal infections
- Alternative for patients resistant to imidazoles

Adverse Effects

- Local irritation: burning, itching, redness
- Rare: hypersensitivity reactions
- Systemic absorption negligible → minimal systemic toxicity

Chemical Degradation

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

Structure–Activity Relationship (SAR)

- Triazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance mucosal penetration and potency
- Dichlorophenyl and cyclohexyl groups → increase antifungal activity
- Fungistatic/fungicidal activity → concentration-dependent

Itraconazole

→ Itraconazole is a synthetic triazole antifungal.
→ It is used for systemic and superficial fungal infections, including dermatophytosis, candidiasis, and systemic mycoses.
→ Itraconazole inhibits ergosterol synthesis, disrupting fungal cell membrane integrity and growth.
→ It is more potent and less hepatotoxic than ketoconazole.

Classification

Based on Chemical Class

- Triazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Systemic antifungal therapy – oral capsules or solution
- Topical therapy – creams for skin infections

Structure

❖ Triazole ring attached to dichlorophenyl and dioxolane groups
❖ Lipophilic side chains → enhance tissue penetration

Molecular formula: $C_{32}H_{38}Cl_2N_8O_4$

Structural Characteristics

⅄ Lipophilic → penetrates skin, nails, and systemic tissues
⅄ Triazole ring → binds to fungal cytochrome P450 enzyme
⅄ Poor water solubility → formulated as oral capsules, solution, or cream

Nomenclature

- Itraconazole → generic name
- Brand names: Sporanox, Onmel
- Formulations: oral capsule, oral solution, topical cream

Mechanism of Action

- Itraconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- Blocks conversion of lanosterol to ergosterol.
- Leads to accumulation of methylated sterols → altered membrane structure.
- Disrupts membrane permeability → inhibits fungal growth.
- Hence, itraconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Candida spp. – C. albicans, C. tropicalis, C. glabrata
- Systemic fungi – Aspergillus, Histoplasma, Blastomyces, Sporothrix
- Malassezia spp. – causes pityriasis versicolor

Uses

- Dermatophytosis – tinea corporis, cruris, pedis
- Cutaneous candidiasis – skin infections
- Vulvovaginal candidiasis

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Hepatotoxicity (rare but serious) – monitor liver function
- Headache, dizziness
- Rash, pruritus
- Rare: cardiac issues (negative inotropic effect)

Chemical Degradation

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

Structure–Activity Relationship (SAR)

- Triazole ring → binds fungal cytochrome P450
- Lipophilic side chains → enhance tissue and keratin penetration
- Dichlorophenyl and dioxolane groups → increase antifungal potency
- Fungistatic/fungicidal activity → concentration-dependent

Fluconazole

- Fluconazole is a synthetic triazole antifungal with high oral bioavailability.
- It is widely used for systemic and superficial fungal infections, including candidiasis, cryptococcosis, and prophylaxis in immunocompromised patients.
- Fluconazole works by inhibiting ergosterol synthesis, leading to disruption of fungal cell membranes.

Classification

Based on Chemical Class

- Triazole derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits lanosterol 14α-demethylase → blocks ergosterol synthesis

Based on Use

- Systemic therapy – oral or intravenous
- Topical therapy – creams for mucocutaneous infections

Structure

- Triazole ring attached to difluorophenyl and hydroxyl groups
- Highly water-soluble compared to other azoles

Molecular formula: $C_{13}H_{12}F_2N_6O$

Structural Characteristics

- Hydrophilic → excellent oral bioavailability and tissue penetration
- Triazole ring → binds to fungal cytochrome P450 enzyme
- Poor lipid solubility → formulated as oral capsules, tablets, suspension, or IV solution

Nomenclature

- Fluconazole → generic name
- Brand names: Diflucan, Flucan
- Formulations: oral capsules, tablets, suspension, IV solution

Mechanism of Action

- Fluconazole inhibits fungal cytochrome P450 enzyme lanosterol 14α-demethylase.
- Blocks conversion of lanosterol to ergosterol.
- Leads to accumulation of methylated sterols → altered membrane structure.
- Disrupts membrane permeability → inhibits fungal growth.
- Hence, fluconazole is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Candida spp. – C. albicans, C. tropicalis, C. glabrata (limited)
- Cryptococcus neoformans – treatment and prophylaxis
- Coccidioides spp. – systemic mycoses
- Effective for mucocutaneous candidiasis
- Limited activity against Aspergillus

Uses

- Oropharyngeal, esophageal, and systemic candidiasis
- Vulvovaginal candidiasis – single-dose or short-course therapy
- Cryptococcal meningitis – treatment and prophylaxis

Adverse Effects

- Gastrointestinal: nausea, vomiting, diarrhea
- Headache, dizziness
- Hepatotoxicity (rare) – monitor liver function

Chemical Degradation

- Stable under normal storage conditions
- Sensitive to extreme heat
- Store in cool, dry place, protected from light

Structure–Activity Relationship (SAR)

- Triazole ring → binds fungal cytochrome P450
- Difluorophenyl group → improves potency and water solubility
- Hydroxyl group → increases systemic bioavailability
- Fungistatic/fungicidal activity → concentration-dependent

Naftifine Hydrochloride

- Naftifine hydrochloride is a synthetic allylamine antifungal.
- It is primarily used for topical treatment of dermatophytosis, tinea infections, and cutaneous candidiasis.
- It works by inhibiting squalene epoxidase, leading to ergosterol synthesis inhibition and accumulation of squalene, which is toxic to fungal cells.

Classification

Based on Chemical Class

- Allylamine derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungicidal – kills fungi at therapeutic concentrations
- Inhibits squalene epoxidase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – cream, gel, or solution

Structure

- Allylamine nucleus with naphthalene and tertiary amine groups

Molecular formula: $C_{20}H_{25}N{\cdot}HCl$

Structural Characteristics

- Lipophilic → penetrates skin and nails effectively
- Allylamine group → targets squalene epoxidase
- Formulated as topical cream, gel, or solution

Nomenclature

- Naftifine hydrochloride → generic name
- Brand names: Naftin, Exoderil (in some countries)
- Formulations: topical cream, gel, solution

Mechanism of Action

- Naftifine inhibits the fungal enzyme squalene epoxidase.
- Prevents conversion of squalene to lanosterol.
- Leads to ergosterol depletion → impaired fungal cell membrane synthesis.
- Accumulation of squalene → toxic to fungal cells.
- Hence, naftifine is fungicidal.

Spectrum of Activity

- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Candida spp. – C. albicans
- Some molds – limited activity
- Effective for cutaneous fungal infections

Uses

- Tinea infections – corporis, cruris, pedis
- Cutaneous candidiasis
- Onychomycosis (adjunct therapy)
- Seborrheic dermatitis (off-label in some cases)

Adverse Effects

- Local irritation: burning, itching, redness
- Rare: hypersensitivity reactions
- Systemic absorption negligible → minimal systemic toxicity

Chemical Degradation

- Sensitive to light and heat
- Store in cool, dry place, protected from light
- Formulated as cream, gel, or solution for topical stability

Structure–Activity Relationship (SAR)

- Allylamine group → inhibits squalene epoxidase
- Lipophilic side chains → enhance skin and nail penetration
- Naphthalene group → increases antifungal potency
- Fungicidal activity → concentration-dependent

Tolnaftate

- Tolnaftate is a synthetic thiocarbamate antifungal.
- It is primarily used topically for the treatment of dermatophytosis, including tinea pedis (athlete's foot), tinea corporis (ringworm), and tinea cruris (jock itch).
- Tolnaftate works by inhibiting squalene epoxidase, which blocks ergosterol synthesis, leading to fungal cell membrane disruption and growth inhibition.

Classification

Based on Chemical Class

- Thiocarbamate derivative
- Synthetic antifungal

Based on Antifungal Action

- Fungistatic/fungicidal depending on concentration
- Inhibits squalene epoxidase → blocks ergosterol synthesis

Based on Use

- Topical antifungal agent – cream, powder, lotion, solution

Structure

- Thiocarbamate nucleus with tolyl and naphthyl groups

Molecular formula: $C_{10}H_9NOS_2$

Structural Characteristics

- Lipophilic → penetrates skin effectively
- Thiocarbamate group → targets squalene epoxidase
- Poor water solubility → formulated as topical cream, powder, solution, or spray

Nomenclature

- Tolnaftate → generic name
- Brand names: Tinactin, Desenex
- Formulations: topical cream, powder, solution, spray

Mechanism of Action

- Tolnaftate inhibits fungal squalene epoxidase.
- Prevents conversion of squalene to lanosterol.
- Leads to ergosterol depletion → impaired fungal cell membrane synthesis.
- Accumulation of squalene → toxic to fungal cells.
- Hence, tolnaftate is fungistatic at lower concentrations and fungicidal at higher concentrations.

Spectrum of Activity

- Dermatophytes – Trichophyton, Microsporum, Epidermophyton
- Limited activity against Candida spp.
- Effective for cutaneous fungal infections

Uses

- Tinea pedis (athlete's foot)
- Tinea corporis (ringworm)
- Tinea cruris (jock itch)
- Prevention of fungal reinfection in susceptible individuals

Adverse Effects

- Local irritation: burning, itching, redness, stinging
- Rare: hypersensitivity reactions
- Systemic absorption negligible → minimal systemic toxicity

Chemical Degradation

- Sensitive to light and heat
- Store in cool, dry place, protected from light
- Formulated as cream, powder, solution, or spray for topical stability

Structure–Activity Relationship (SAR)

- Thiocarbamate group → inhibits squalene epoxidase
- Lipophilic side chains → enhance skin penetration and potency
- Aromatic groups → increase antifungal activity
- Fungistatic/fungicidal activity → concentration-dependent