आईएफटीएम विश्वविद्यालय, मुरादाबाद, उत्तर प्रदेश

**IFTM University, Moradabad, Uttar Pradesh**

**NAAC ACCREDITED**

# E-Content

# IFTM University, Moradabad

# Unit IV (I)
# Antifungal drugs

Antifungal medicines are used to treat fungal infections, which most commonly affect your skin, hair and nails.

Fungi can be found throughout the world in all kinds of environments.

Most fungi don't cause disease in people. However, some species can infect humans and cause illness.

Antifungal drugs are medications that are used to treat fungal infections.

While most fungal infections affect areas such as the skin and nails, some can lead to more serious and potentially life threatening conditions like meningitis or pneumonia.

Antifungal drugs target structures or functions that are necessary in fungal cells but not in human cells, so they can fight a fungal infection without damaging your body's cells.

Two structures that are commonly targeted are the fungal cell membrane and the fungal cell wall.

Both of these structures surround and protect the fungal cell.

When either one becomes compromised, the fungal cell can burst open and die.

## Types of antifungal drugs

Antifungal drugs are very diverse. They can be given orally, as a topical treatment, or via IV

There are **many types of fungal infection**. One can get a fungal infection by coming into contact with a fungus or fungal spores that are present in the environment.

Some of the most common fungal infections are those of the skin, nails, and mucous membranes. Examples include:

**Ringworm (also known as tinea):** a fungal infection of the skin that can occur on your scalp, on your feet (athlete's foot), in your groin area (jock itch), and on other areas of your body

**Nail fungus:** an infection that typically affects your toenails but can also affect your fingernails

**Vaginal yeast infection:** an infection that occurs due to overgrowth of *Candida* yeast in and around the vagina

**Oral thrush:** a condition in which *Candida* yeast overgrows in your mouth

## CLASSIFICATION OF ANTIFUNGAL DRUGS

**Drugs for systemic fungal infections**

***Polyene antibiotics***

-Amphotericin B

***Pyrimidine antimetabolites***

-Flucytosine

***Antifungal azoles***

-Ketoconazole

-Fluconazole

-Itraconazole

**Echinocandins**

Caspofungin, micafungin, and anidulafungin

**Drugs for superficial fungal infections**

***Systemic drugs***

-Griseofulvin

-Iodide

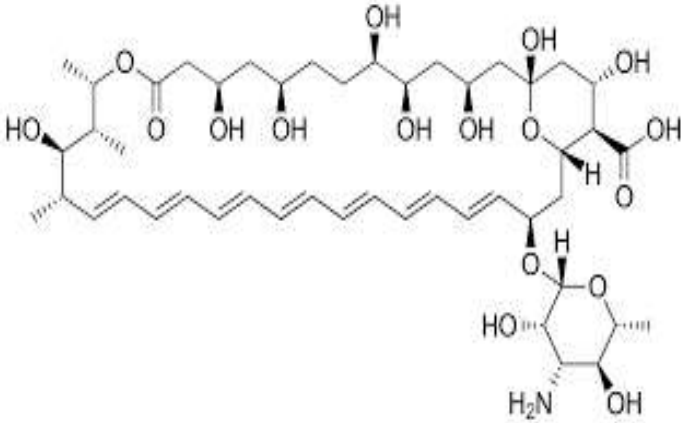
***Topical drugs***

-Nystatin

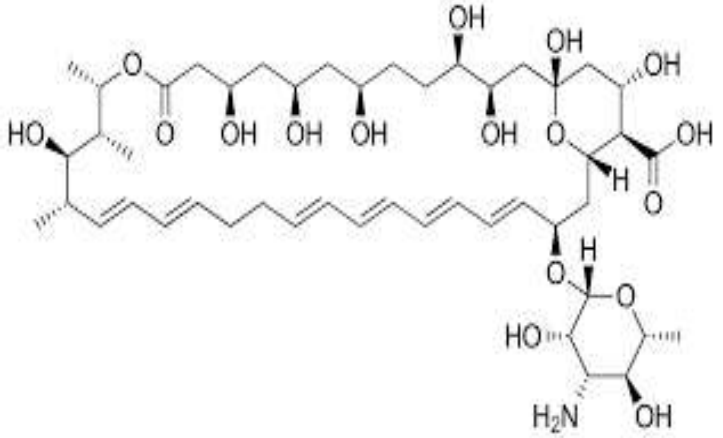
-Haloprogin

-Tolnaftate

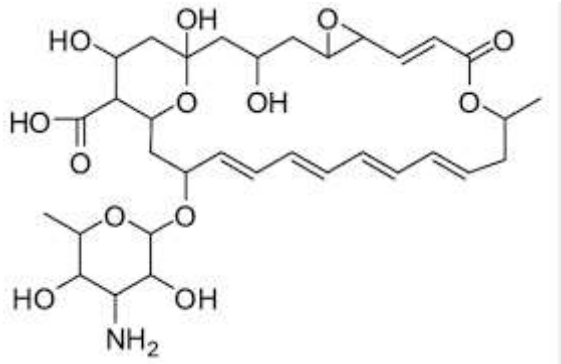
-Azoles (**miconazole**, econazole, clotrimazole, etc.)



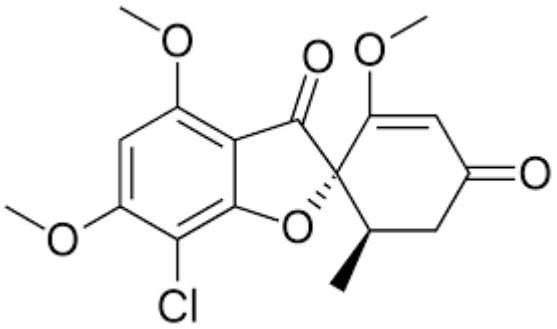
Amphotericin B



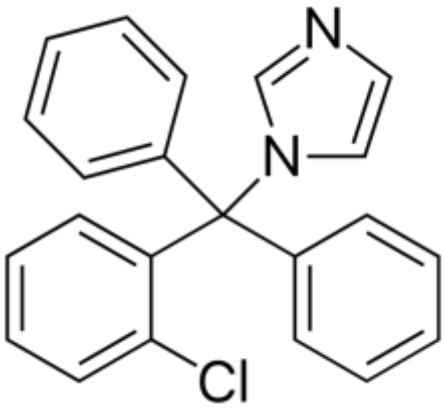
Nystatin



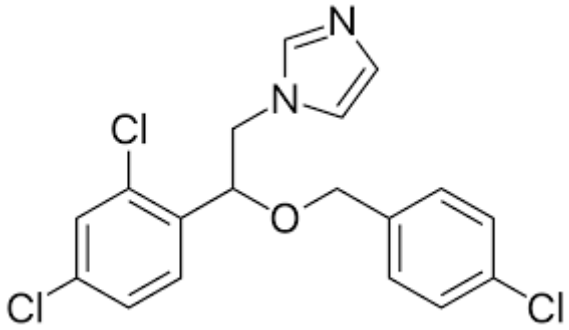
Natamycin



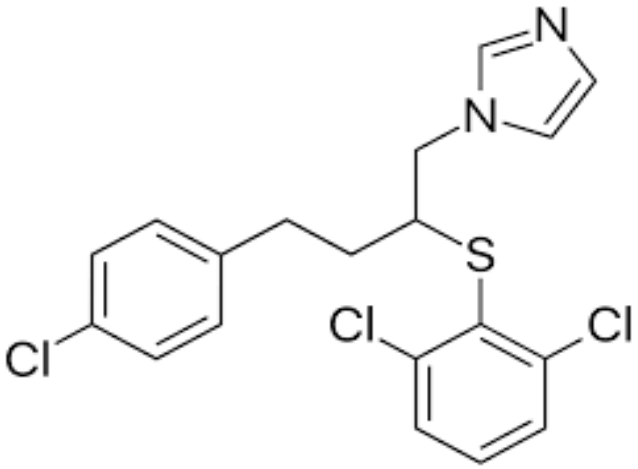
Griseofulvin



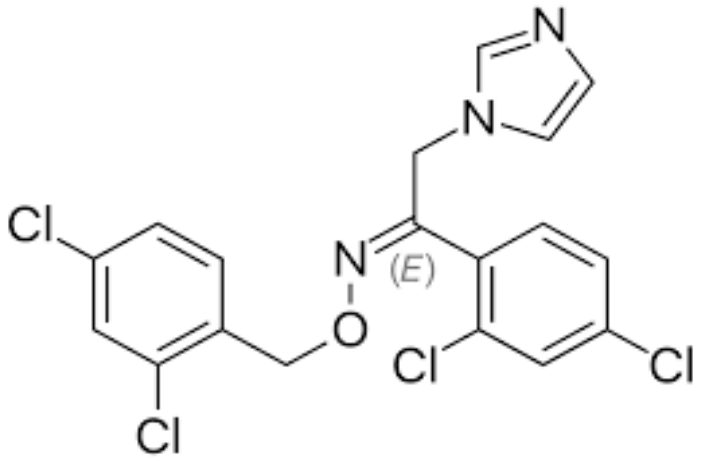

Clotrimazole



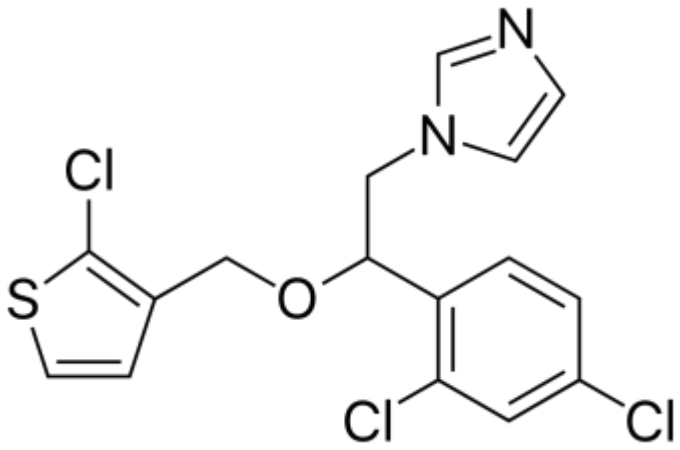

Econazole



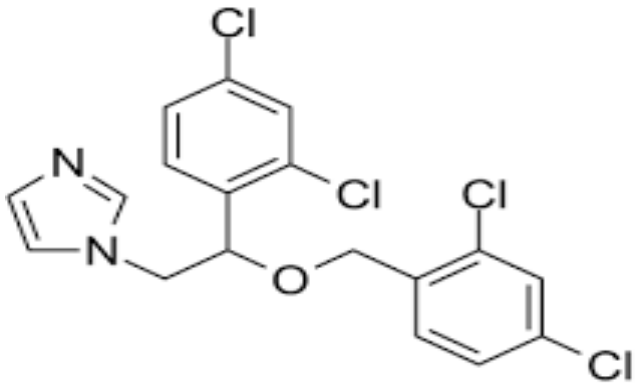

Butoconazole



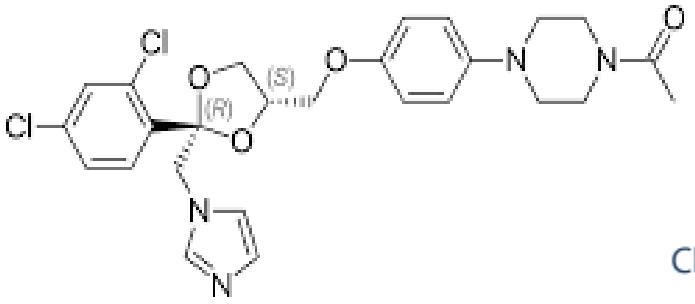

Oxiconazole



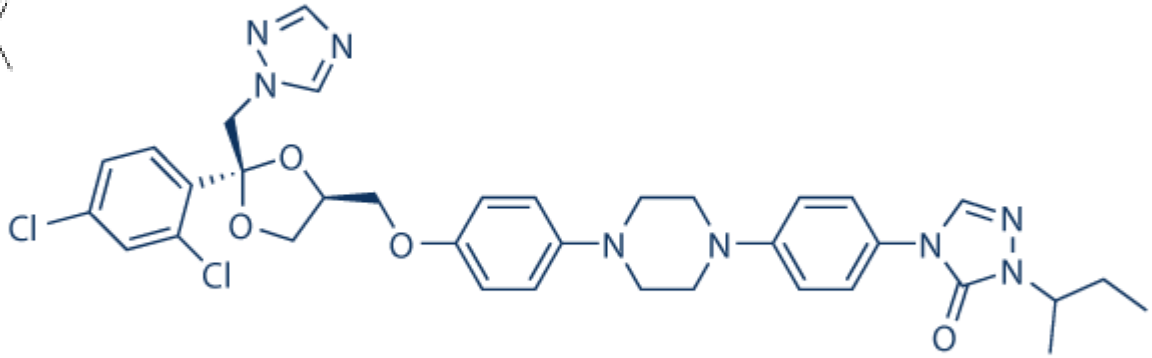

Tioconozole



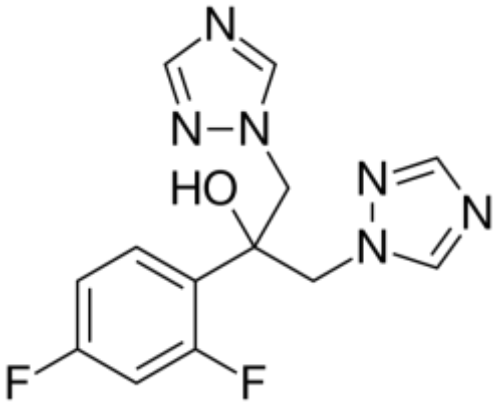

Miconazole



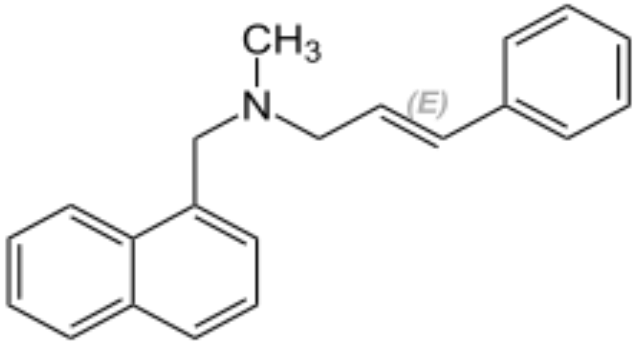

Ketoconazole



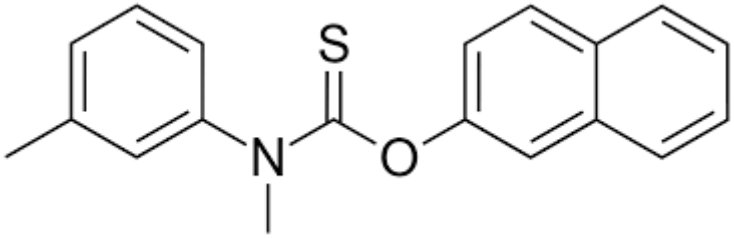

Itraconazole




Fluconazole

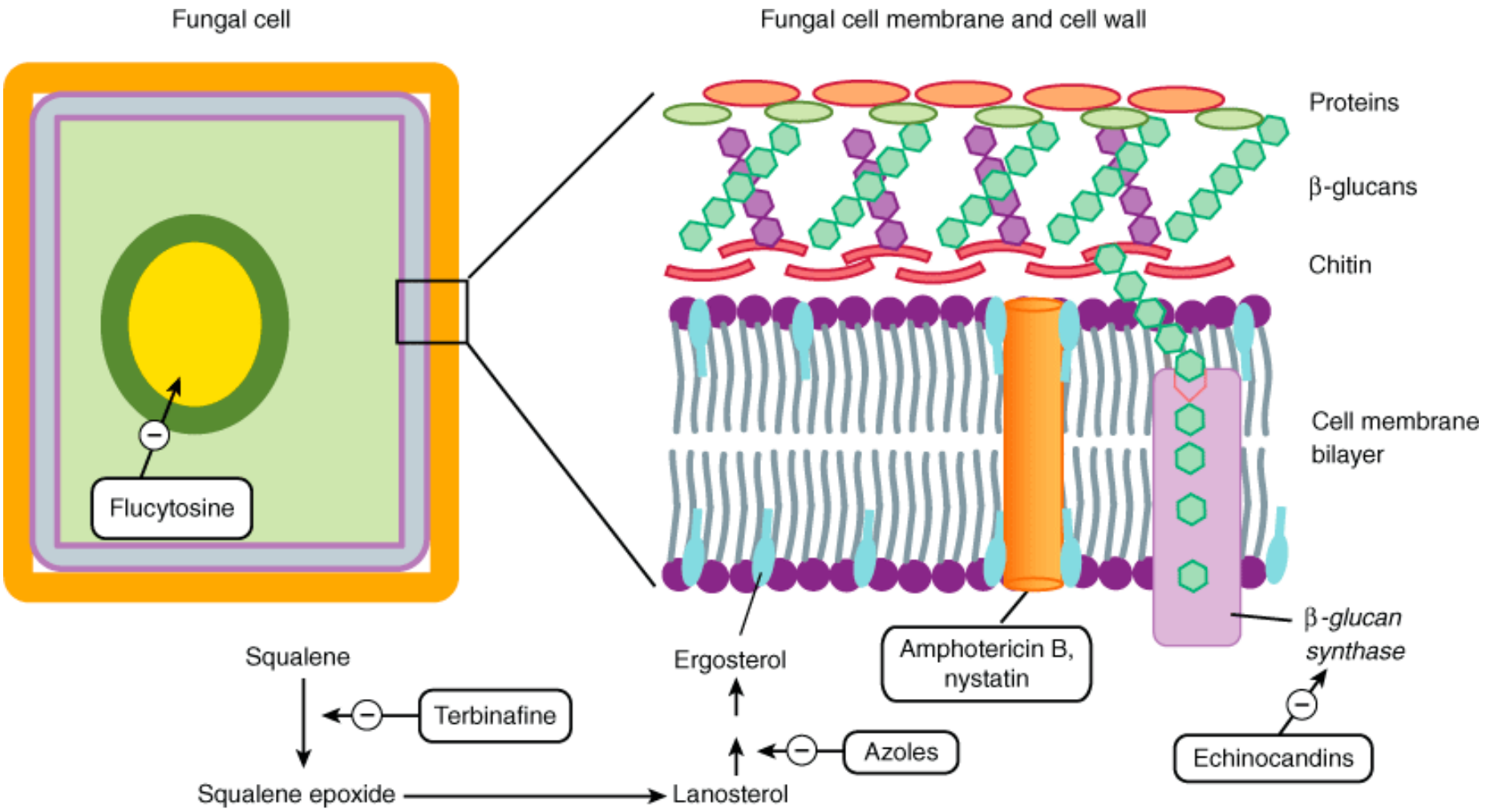


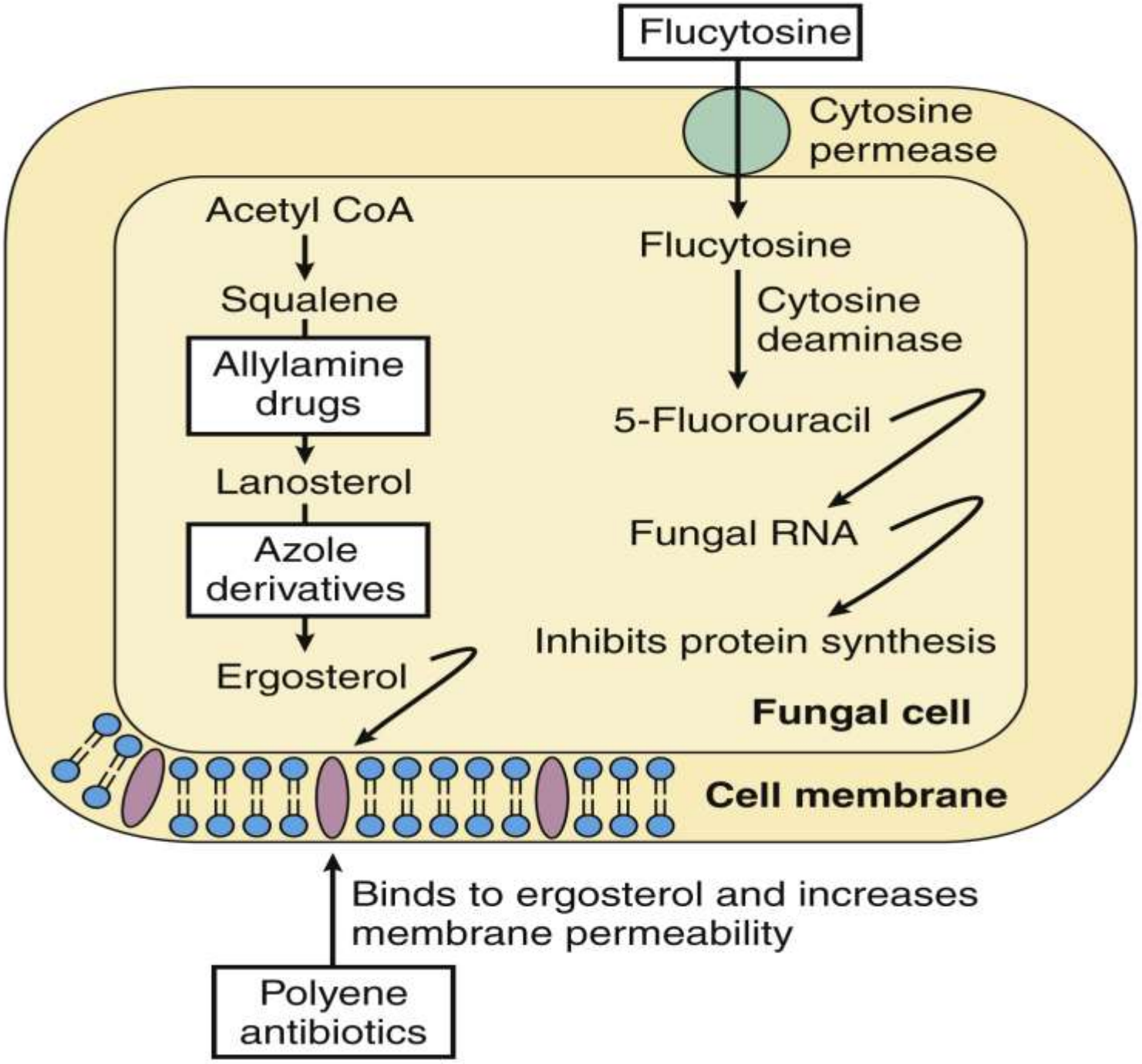

Naftifine hydrochloride




Tolnaftate

# Targets of antifungal drugs




Flucytosine
Cytosine permease
Acetyl CoA
Squalene
Allylamine drugs
Lanosterol
Azole derivatives
Ergosterol
Flucytosine
Cytosine deaminase
5-Fluorouracil
Fungal RNA
Inhibits protein synthesis
Fungal cell
Cell membrane
Binds to ergosterol and increases membrane permeability
Polyene antibiotics

# PHARMACOLOGY OF AMPHOTERICIN B

## Chemistry

-**Amphotericin B** is a polyene antibiotic (polyene: containing many double bonds)

## Mechanism of action

-Binding to ergosterol present in the membranes of fungal cells

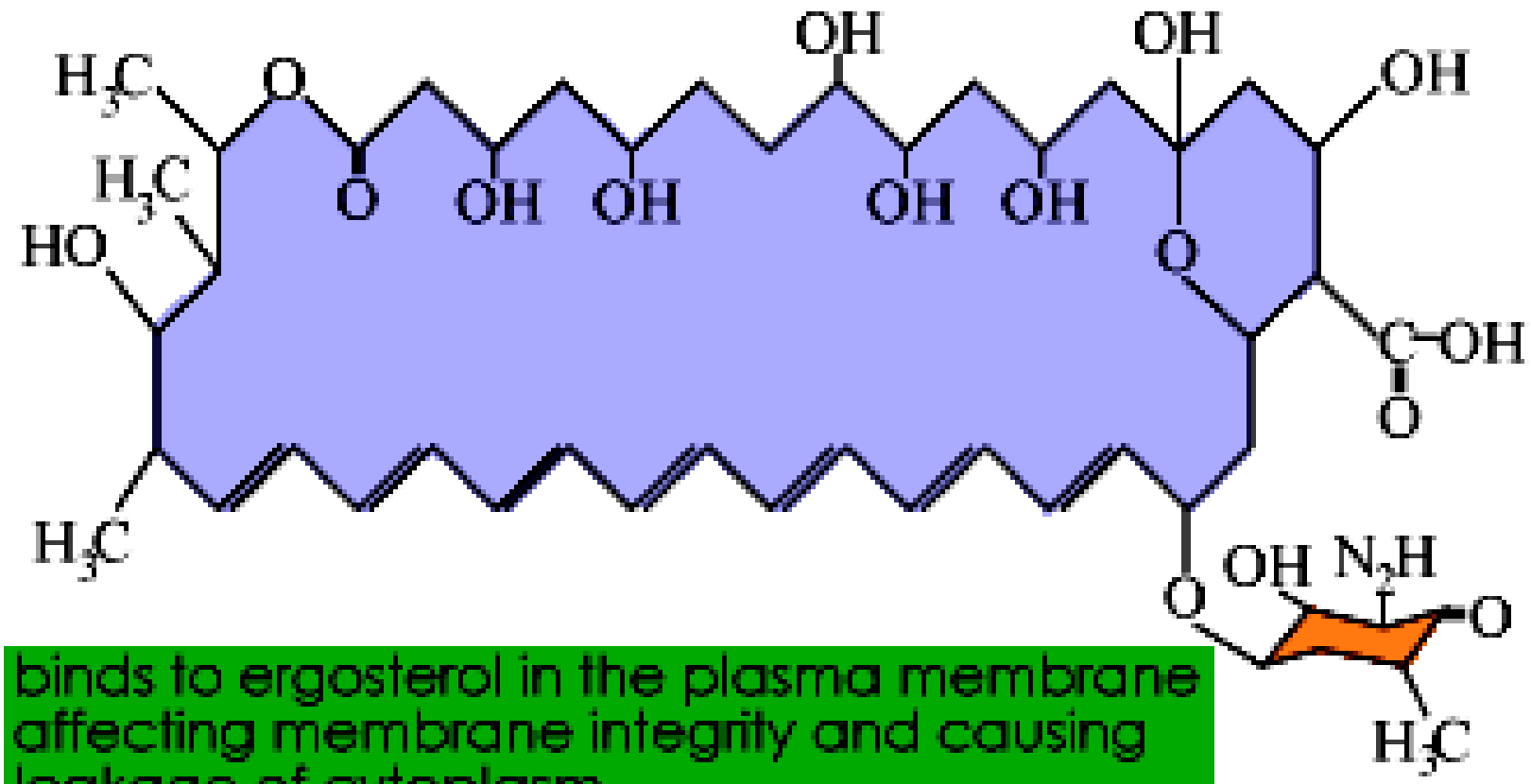
↓

Formation of "pores" in the membrane

↓

Leaking of small molecules (mainly K+) from the cells

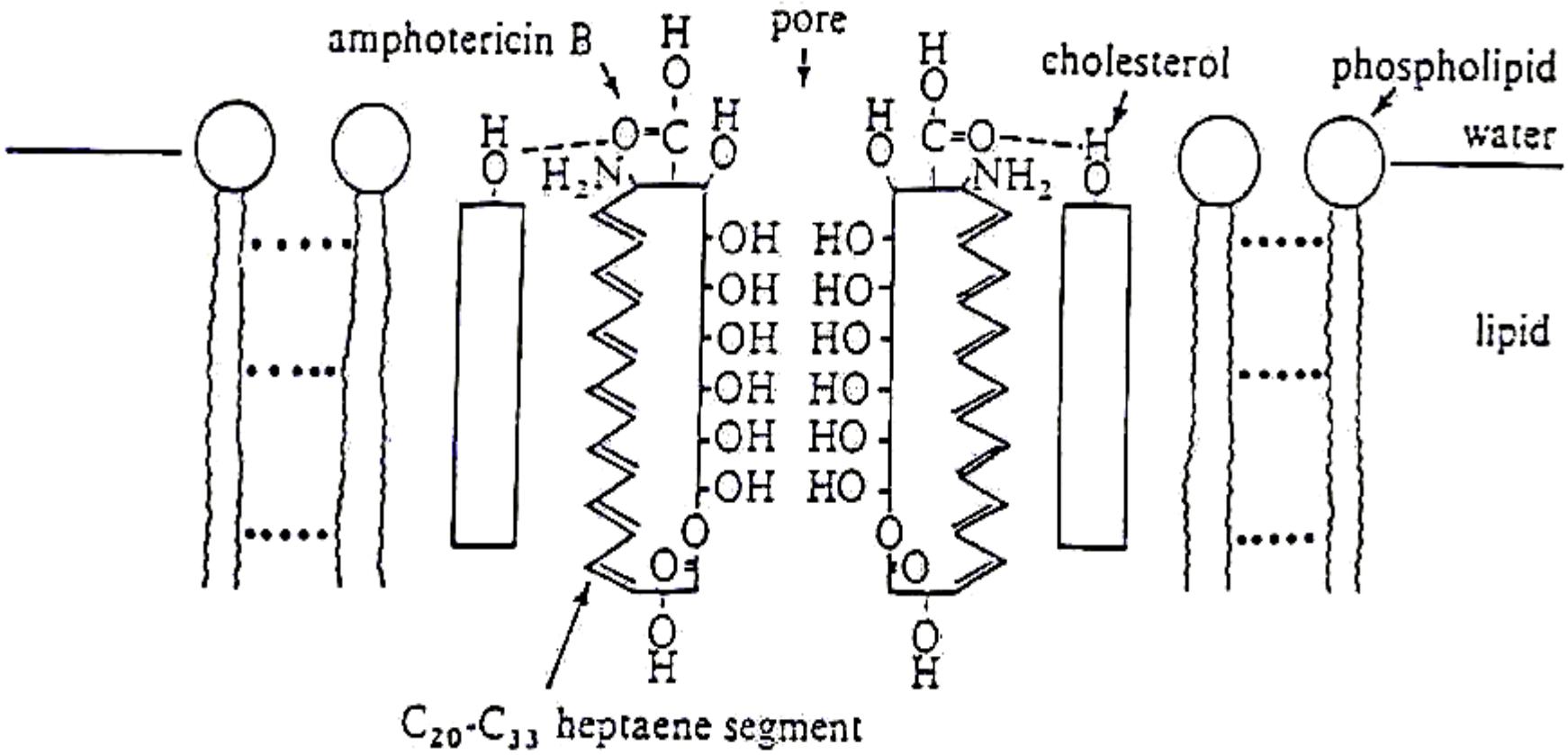
-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.




binds to ergosterol in the plasma membrane affecting membrane integrity and causing leakage of cytoplasm

Amphotericin B

# Model for Amphotericin B induced Pore in Cell Membrane



# Antifungal spectrum and resistance

-Antifungal spectrum includes:

- *Histoplasma capsulatus*
- *Coccidioides immitis*
- *Paracoccidioidoides braziliensis*
- *Aspergillus fumigatus*
- *Blastomyces dermatitidis*
- *Cryptococcus neoformans*
- *Candida albicans*
- *Sporothrix schenckii*
- *Mucor and Rhizopus spp*
- Resistance may occur but is very rare

# Pharmacokinetics

-F(oral): < 1% (too irritant to be given IM)

-Distribution in all body tissues, except CNS and eye

(concentrations in CSF are <10% than in plasma; however therapeutic concentrations in CNS can usually be achieved with parenteral administration)

-Biotransformation: > 95%

-Renal excretion: < 5%

-Half life: » 14 days

## Drug formulations and administration

-Formulations:

a) complex with deoxycholate

b) liposomal complex (adverse effects seem diminished)

-Administration:

IV infusion, intrathecal, topical, oral (to treat intestinal mycoses)

# Adverse effects

*(the therapeutic index of the drug is very narrow)*

-Headache, arthralgias, nausea and vomiting fever and chills, hyperpnea, shock-like fall in blood pressure (they may appear during IV infusion and may be reduced by concomitant administration of antipyretics or meperidine)

-Malaise, weight loss

-Nephrotoxicity (azotemia , decreased GFR, renal tubular acidosis, renal wasting of K+ and Mg++,). It is common (up to 80% of patients) and may be severe

-Normocytic anemia, likely due to decreased production of erythropoietin (frequent)

-Thrombophlebitis

-Delirium, seizures (after intrathecal injection)

## Therapeutic uses

***Amphotericin is the drug of choice for:***

-Disseminated histoplasmosis
-Disseminated and meningeal coccidioidomycosis
-Disseminated and meningeal cryptococcosis
-Invasive aspergillosis
-Deep candidiasis
-Mucormycosis

***Amphotericin is an alternative drug for:***

-Blastomycosis
-Paracoccidioidomycosis
-Extracutaneous sporotrichosis

[Amphotericin is preferred when these mycoses are rapidly progressive, occur in immunocompromised host or involve the CNS]

# PHARMACOLOGY OF FLUCYTOSINE

**Chemistry**

-Flucytosine is a fluorinated pyrimidine

**Mechanism of action**

-The drug is accumulated in fungal cells by the action of a ***membrane permease*** and is converted by a ***cytosine deaminase*** to 5-fluorouracil (selectivity occurs because mammalian cells do not accumulate and do not deaminate flucytosine)

↓

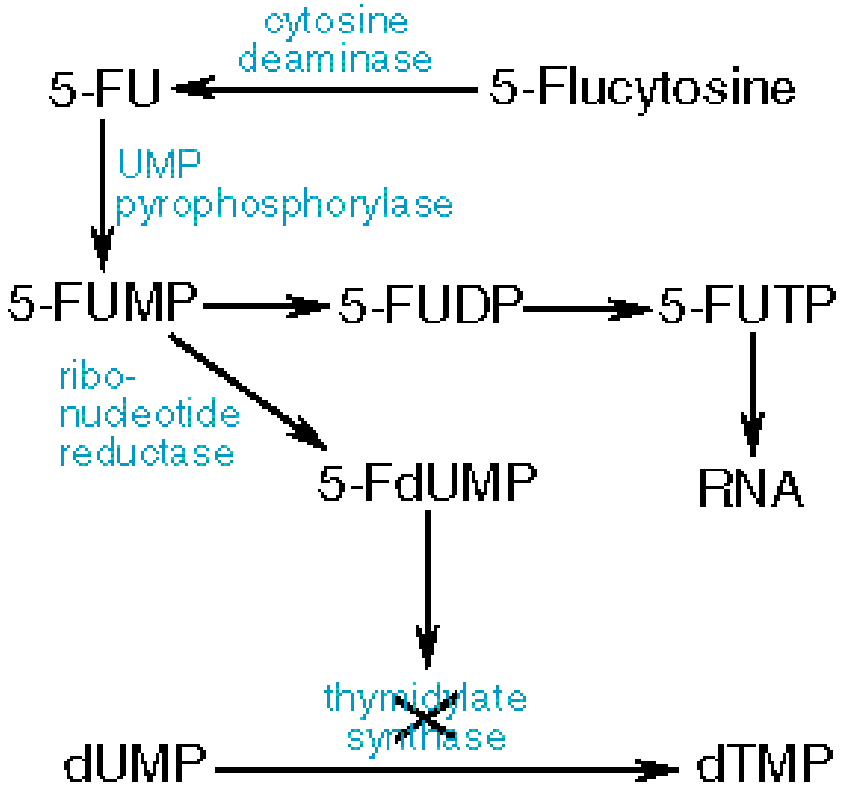
5-fluorouracil is metabolized to 5-fluorouridylic acid

which can be

a) incorporated into the RNA (this leads to a ***misreading of the fungal genetic code***)

b) further metabolized to 5-deoxyfluorouridylic acid, a potent inhibitor of thymidylate synthase (this leads to a ***blockade of fungal DNA synthesis***)

-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.




***Action of flucytosine in fungi.***

5-Flucytosine is transported into the fungal cell, where it is deaminated to 5-fluorouracil (5-FU). The 5-FU is then converted to 5-fluorouracil-ribose monophosphate (5-FUMP) and then is either converted to 5-FUTP and incorporated into RNA or converted by ribonucleotide reductase to 5-FdUMP, which is a potent inhibitor of thymidylate synthase.

## Antifungal spectrum and resistance

-Antifungal spectrum includes *Cryptococcus neoformans, Candida albicans, Aspergillus fumigatus, and several soil fungi which cause chromomycosis.*

-Resistance may arise rapidly during therapy and is an important cause of therapeutic failure when the drug is used alone.

## Pharmacokinetics and administration

-F(oral): > 80%

-Distribution in all body tissues, including CNS and the eye.

-Volume of distribution: » 42 L

-Renal excretion: » 99%

-Half-life: » 4 hours (in renal failure, half-life may be as long as 200 hours)

-Administration: oral, IV

## Adverse effects

*(toxicity is generally not pronounced)*

-Anorexia, nausea and vomiting, diarrhea

-Severe ulcerative enterocolitis (rare)

-Skin rashes

-Headache, dizziness, confusion

-Reversible bone marrow depression (8-13%)(leukopenia, thrombocytopenia)

-Liver dysfunction (5-10%)

-Alopecia, peripheral neuritis (rare)

[toxicity may be due to the conversion of flucytosine to 5-fluorouracil by the intestinal flora of the host]

## Therapeutic uses

-Deep candida infections, cryptococcal meningitidis (always in combination with amphotericin B)

-Chromomycosis (effectiveness is limited)

## Contraindications

-Pregnancy ( 5-fluorouracil is teratogenic)

# PHARMACOLOGY OF ANTIFUNGAL AZOLES

**Chemistry**

-Imidazole derivatives: **ketoconazole**, miconazole, econazole, clotrimazole

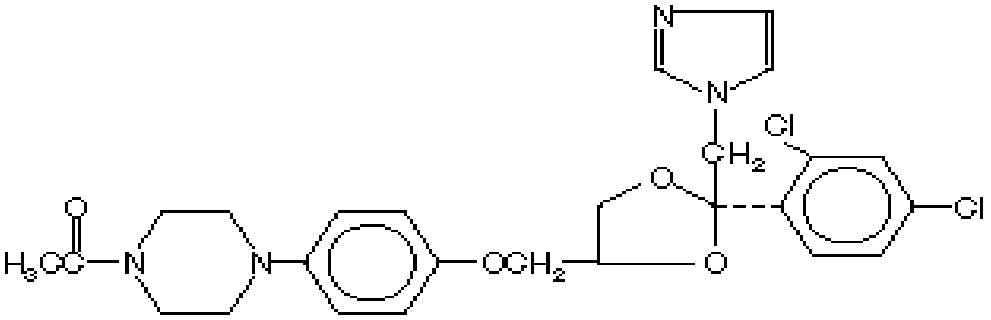
-Triazole derivatives: **itraconazole, fluconazole**.

**Mechanism of action**

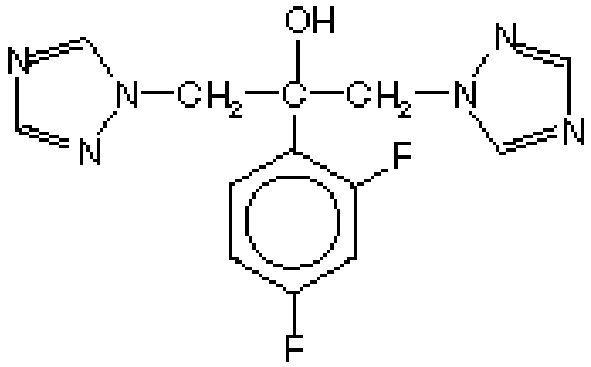
-Inhibition of sterol 14-alpha-demethylase, a cytochrome P450-dependent enzyme (relative selectivity occurs because the affinity for mammalian P450 isozymes is less than that for the fungal isozyme)

***blockade of the synthesis of ergosterol in fungal cell membranes***

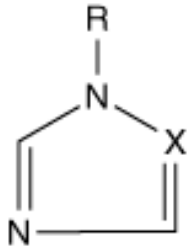
-The ultimate effect may be ***fungicidal*** or ***fungistatic*** depending on the organism and on drug concentration.



KETOCONAZOLE

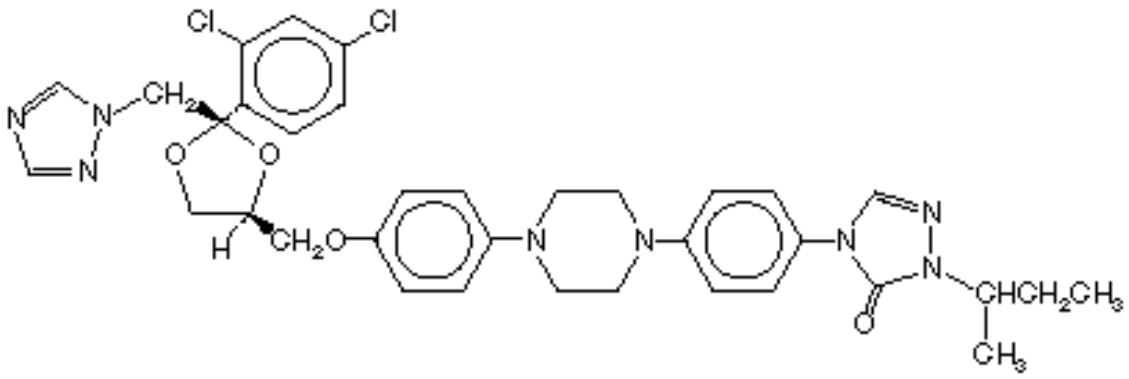


FLUCONAZOLE



**Azole nucleus**

X = C, imidazole
X = N, triazole



ITRACONAZOLE

## Antifungal spectrum and resistance

-Antifungal spectrum includes:

*Histoplasma capsulatus*, *Coccidioides immitis*

*Paracoccidioidoides braziliensis* , *Aspergillus fumigatus*

*Blastomyces dermatitidis*, *Cryptococcus neoformans*

*Candida albicans* , *Sporothrix schenckii*

*Dermatophytes (Microsporum, Epidermophyton, Trichophyton, Malassezia furfur)*

-Resistance can occur but is rare.

-Cross-resistance between azoles is a common finding.

## Other effects

-Azoles may inhibit certain mammalian cytochrome P450 isozymes and therefore they may

1) inhibit the synthesis of androgens and of corticosteroids

2) potentiate the effects of several drugs including cyclosporine, phenytoin, terfenadine, astemizole, tolbutamide and warfarin.

# Pharmacologic properties of five systemic azole drugs

| | **Water Solubility** | **Absorption** | **CSF: Serum Concentration Ratio** | ***t*** $_{1/2}$ **(Hours)** | **Elimination** | **Formulations** |
|---|---|---|---|---|---|---|
| Ketoconazole | Low | Variable | < 0.1 | 7–10 | Hepatic | Oral |
| Itraconazole | Low | Variable | < 0.01 | 24–42 | Hepatic | Oral, IV |
| Fluconazole | High | High | > 0.7 | 22–31 | Renal | Oral, IV |
| Voriconazole | High | High | . . . | 6 | Hepatic | Oral, IV |
| Posaconazole | Low | High | . . . | 25 | Hepatic | Oral |

## Pharmacokinetics and administration

-F(oral): itraconazole » 55%, fluconazole >90%.
(acidity favors oral absorption of ketoconazole)
-Distribution in all body tissues. Penetration into CNS is generally negligible, ***but good for fluconazole***.
-Renal excretion: fluconazole » 75%, others < 1%
-Half-lives (hrs): ketoconazole » 8, itraconazole » 35
-Administration: oral, IV, topical

## Adverse effects

-Anorexia, nausea and vomiting (they are dose-dependent and patients receiving high doses may require antiemetics)
-Gynecomastia, decreased libido, impotence, menstrual irregularities (with ketoconazole, due to blockade of adrenal steroid synthesis)
-Hepatitis (is rare, but can be fatal)
-Hypokalemia, hypertension (itraconazole)
-Azoles are potent teratogenic drugs in animals

## Therapeutic uses

***Azoles are first choice drugs for:***

-Blastomycosis (ketoconazole)
-Paracoccidioidomycosis (ketoconazole)
-Chronic pulmonary histoplasmosis
-Meningeal coccidioidomycosis (fluconazole)
-Meningeal cryptococcosis (fluconazole)
-Cutaneous and deep candidiasis

***Azoles are alternative drug for:***

-Invasive aspergillosis
-Sporotrichosis

***Topical azoles are used for:***

-Dermatophytoses (not of hair and nails)
-Tinea versicolor
-Mucocutaneous candidiasis

**Contraindications**

-Systemic azoles are contraindicated in pregnancy (potential teratogenic effects and endocrine toxicity for the fetus)

# PHARMACOLOGY OF GRISEOFULVIN

## Chemistry

-Griseofulvin is a benzofuran derivative

-The drug is practically insoluble in water

**Mechanism of action**

-An active transport accumulates the drug in sensitive fungal cells where

↓

griseofulvin causes disruption of the mitotic spindle by interacting with polymerized mycrotubules

-The ultimate effect is ***fungistatic***

**Antifungal spectrum and resistance**

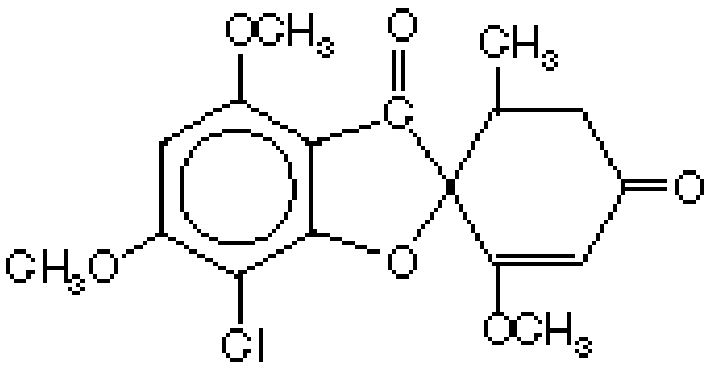
-Antifungal spectrum includes only *Dermatophytes (Microsporum, Epidermophyton, Trichophyton)*

-The drug is ineffective against other fungi producing superficial lesions (like *Candida* and *Malassezia furfur*) and those producing deep mycoses.

-Resistance is uncommon. It seems to be due to a decrease of the energy-dependent transport mechanism.

# Echinocandins

- Newest class of antifungal agents
- Intravenous
- inhibiting the synthesis of (1–3)-glucan
- Well tolerated
- **Caspofungin**
- **Micafungin**
- **Anidulafungin**




GRISEOFULVIN

## Pharmacokinetics and administration

-F(oral): » 50% (micronization of the drug and a high-fat food favor oral absorption)
-Distribution is ***mainly in keratinized tissues where the drug is tightly bound*** and where it can be detected 4-8 hours after oral administration. Concentration in other tissues and body fluids is negligible.
-Elimination: mainly in the feces.
-Half-life (hrs): » 24 hours
-Administration: oral

## Adverse effects

(*incidence is quite low)*
-Xerostomia, nausea and vomiting, diarrhea
-Headache (up to 15%), fatigue, blurred vision, vertigo, increased effects of alcohol
-Hepatotoxicity (rare)
-Leukopenia, neutropenia
-Allergic reactions (urticaria, skin rashes, serum sickness, angioedema)
-Teratogenic effects in several animal species

## Therapeutic uses

-Mycotic disease of the skin, hair and nails (long treatments are needed)

# TOPICAL ANTIFUNGAL DRUGS

**Nystatin**

-A polyene antibiotic useful only for local candidiasis.

-Administration: cutaneous, vaginal, oral.

**Haloprogin**

-The drug is fungicidal to various species of dermatophytes and candida.

-Principal use: in tinea pedis (cure rate » 80% )

**Tolnaftate**

-The drug is effective against most dermatophytes and *Malassezia furfur* but not against *Candida*

-In tinea pedis the cure rate is » 80%

**Antifungal azoles**

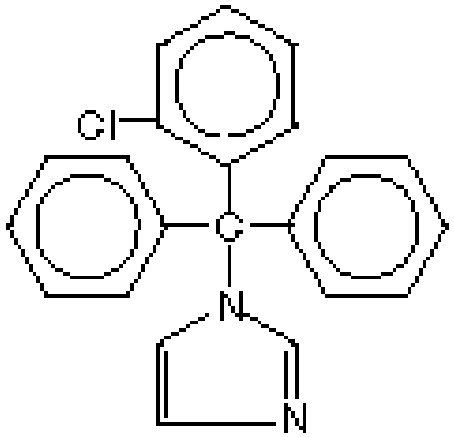
-Azoles are reported to cure dermatophyte infections in 60-100% of cases

-The cure rate of mucocutaneous candidiasis is > 80% and that of tinea versicolor > 90%.

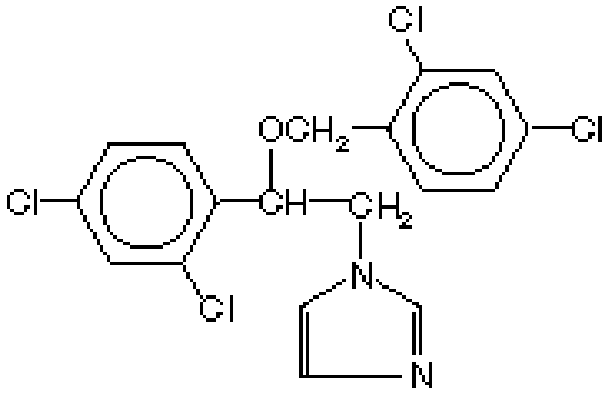
-Administration: cutaneous, vaginal.

-Cutaneous application rarely causes erythema, edema, vescication, desquamation and urticaria

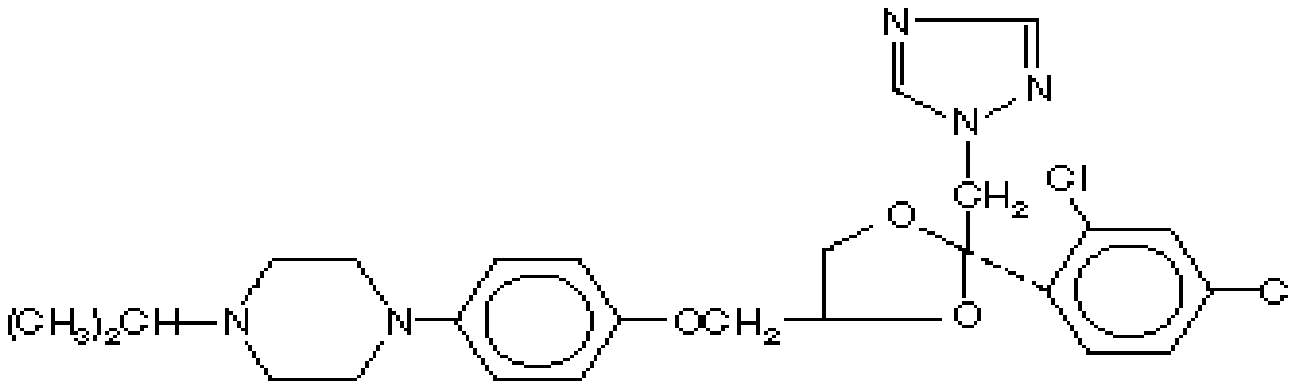
-Vaginal application may cause mild burning sensation and abdominal pain.



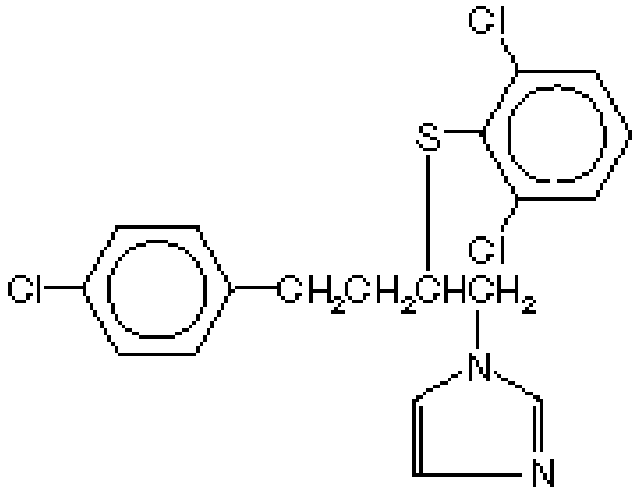

CLOTRIMAZOLE



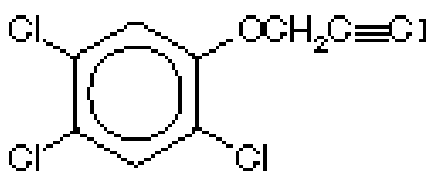

MICONAZOLE



TERCONAZOLE



BUTOCONAZOLE

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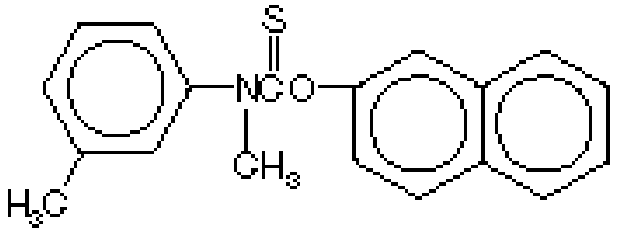


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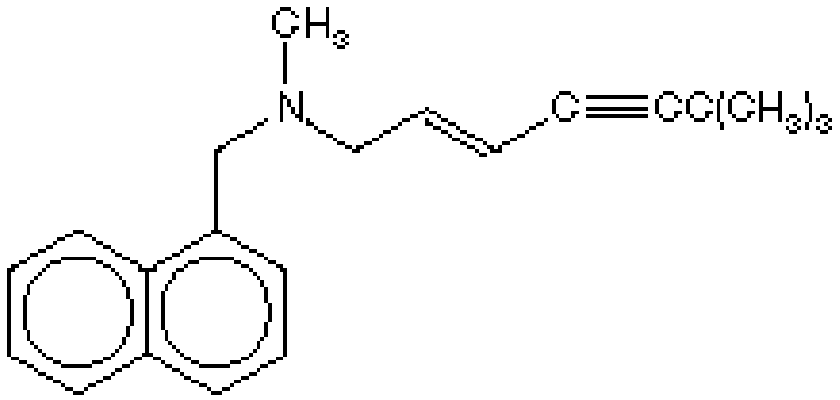


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