Antifungal agents

Part 1

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Introduction

The main characteristics of fungi:

Fungi are eukaryotic (Nuclei & mitochondria)

Heterotrophs (They depend on other organisms for food: Saprobes or parasite)

Multicellular (Complex organism in comparison to bacteria)

Cannot move on their own

Similarity to mammalian cell is great.

Antibacterial agents are not effective against fungi

Introduction

The **main difference** between fungal- and mammalian cells

Fungal cells have **a cell wall** composed of chitin (bacterial cell wall is composed of peptidoglycan)

Fungal cell membrane contains **ergosterol** , human cell membrane is composed of cholesterol

Introduction

Systemic fungal infections

Affect internal organs as : lung ,heart , brain leading to pneumonia , endocarditis , meningitis

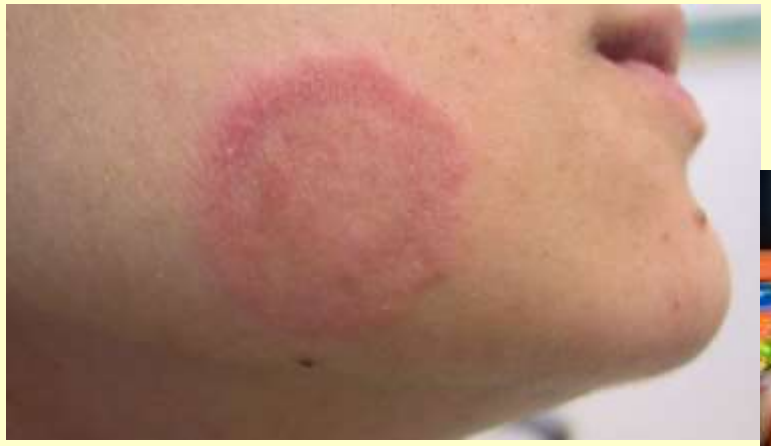
A major cause of death (Immune system is compromised – cancer or its chemotherapy, – organ transplantation – HIV-1 infection).

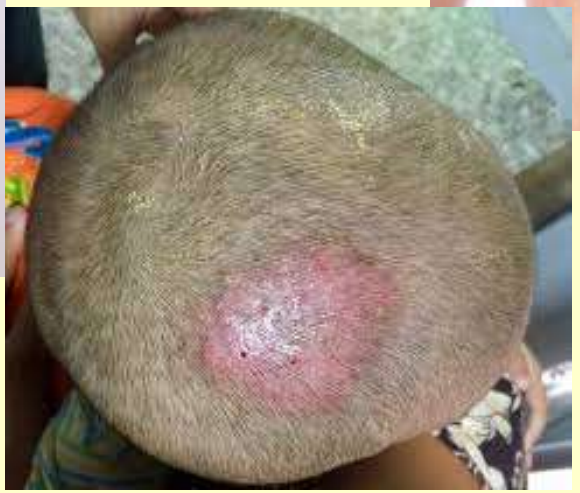
Superficial infections

Skin (Cutaneous, subcutaneous) and other soft tissue structures

Dermatophytes: Affect keratin layer of skin, hair, nail. e.g. tinea pedis, ring worm infection

Candidiasis: Oral thrush, vulvo-vaginitis .



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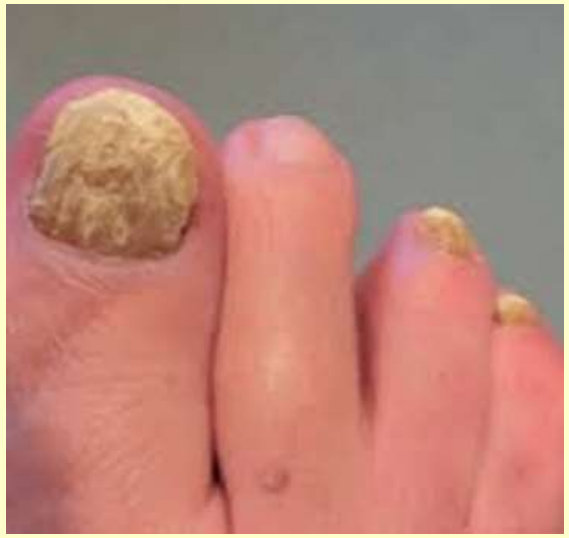
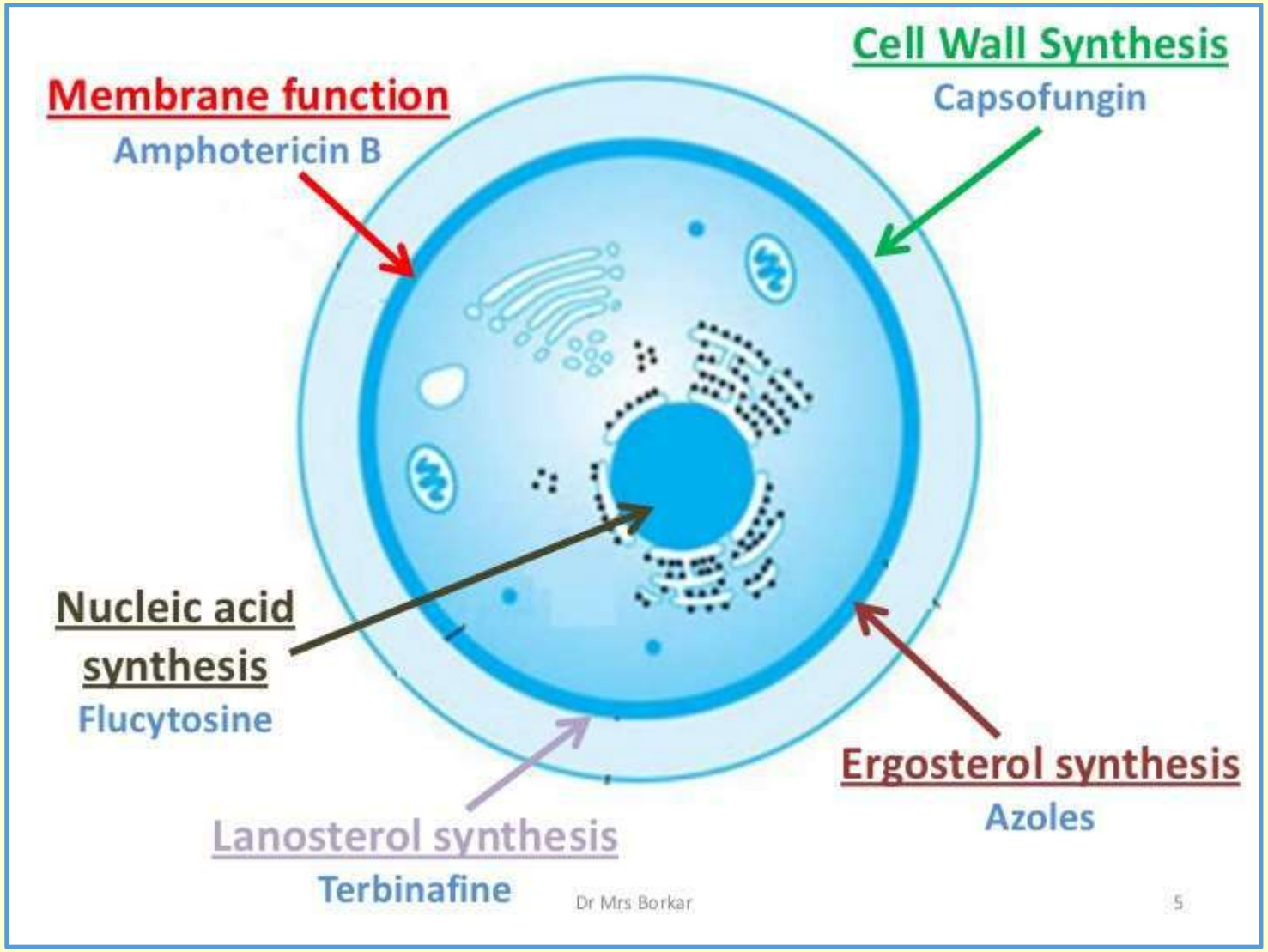


Antifungal agents: Targets

SITES OF ACTION OF COMMON ANTIFUNGAL DRUGS



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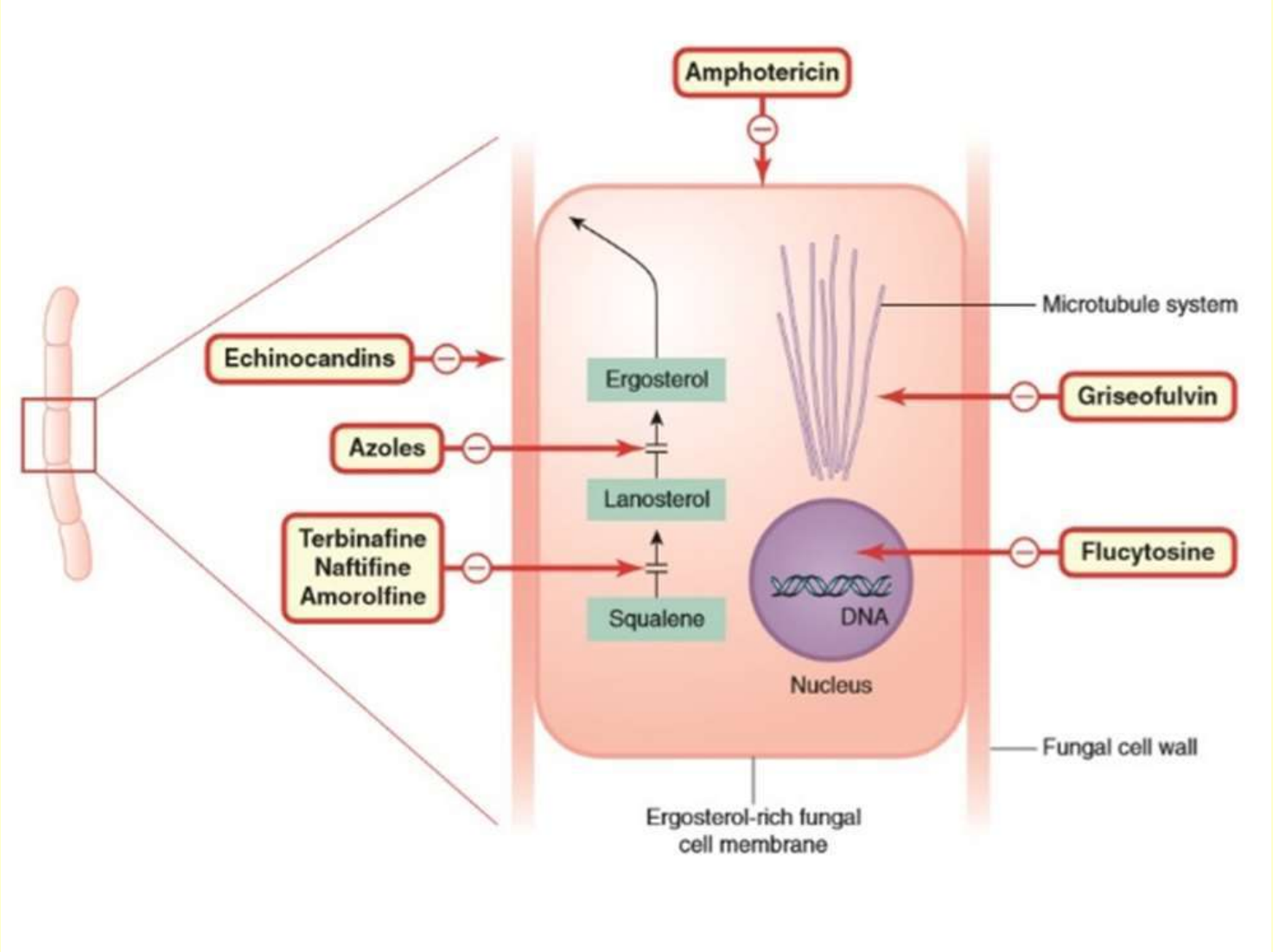


Antifungal agents: Targets

Mechanism of action of Antifungal agents

Disrupt fungal cell membrane

Polyenes : Amphotericin, Nystatin

Azoles: **Imidazole** (Ketoconazole, Miconazole, Clotrimazole)

Triazole (Fluconazole, Itraconazole, voriconazole, posaconazole)

Allylamines: Terbinafine

Morpholine: Amorolfine

Inhibit mitosis: Gresiofulvin

Inhibit DNA synthesis: Flucytosine

Inhibit cell wall synthesis: Echinocandins e.g. Caspofungin

Miscellaneous: Tolnaftate, Cyclopirox

Antifungal agents: Classification

Antifungal drugs

- Antifungal drugs are used for the treatment of fungal infections (mycoses) that may be superficial or deep infections.
- Fungal infections are susceptible to the immunocompromised patients due to chemotherapy or antibiotic use.
- Antifungal drugs can be broadly classified into systemic agent & topical agents.

1.Systemic Agents

a.Antibiotics: **Amphotericin B, Griseofulvin**

b.Antimetabolites: **Flucytosine (5-FC)**

c.Azoles: **Ketoconazole, Fluconazole, Itraconazole,Vericonazole**

d.Allylamine: **Terbinafine**

e.Echinocandins: **Caspofungin, Micafungin, Anidulafungin**

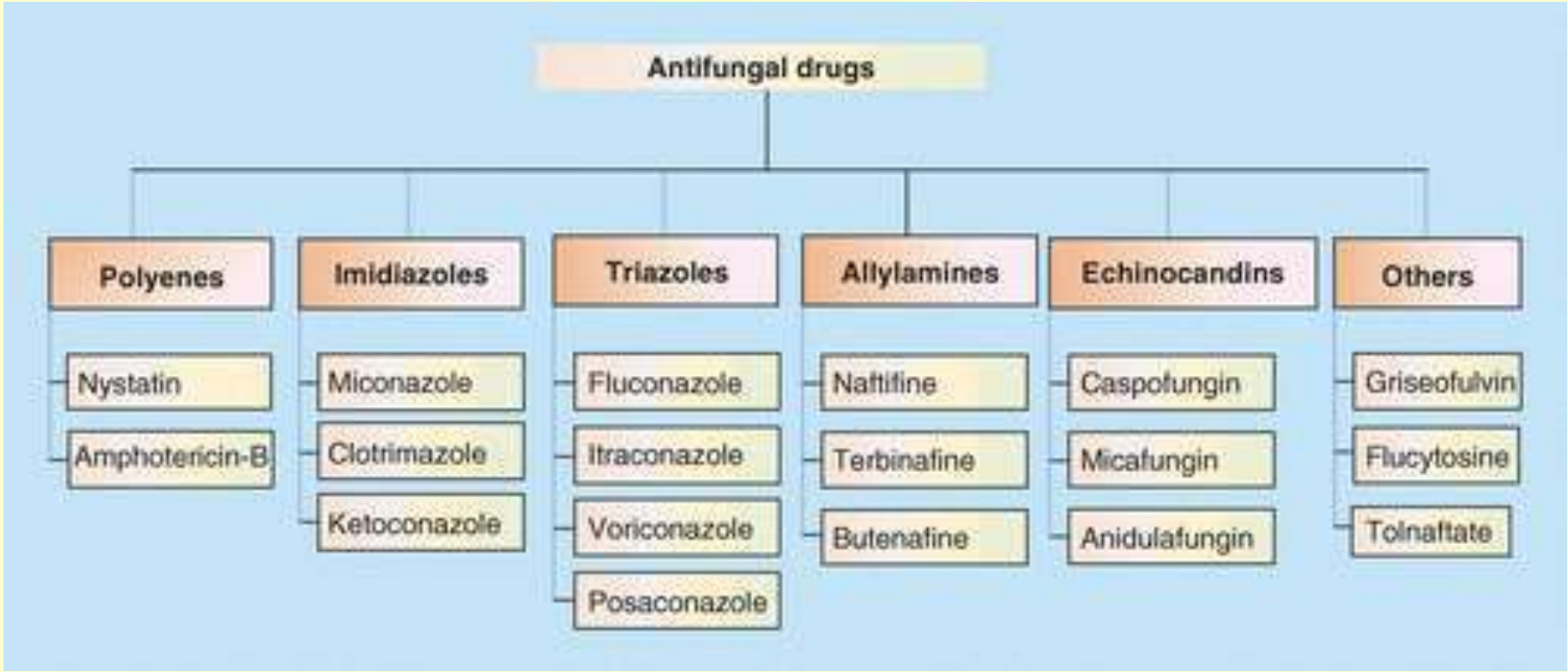
2.Topical Agents

a.Polyene Antibiotics: **Nystatin, Hamycin, Natamycin**

b.Imidazole: Clotrimazole, Miconazole, Econazole

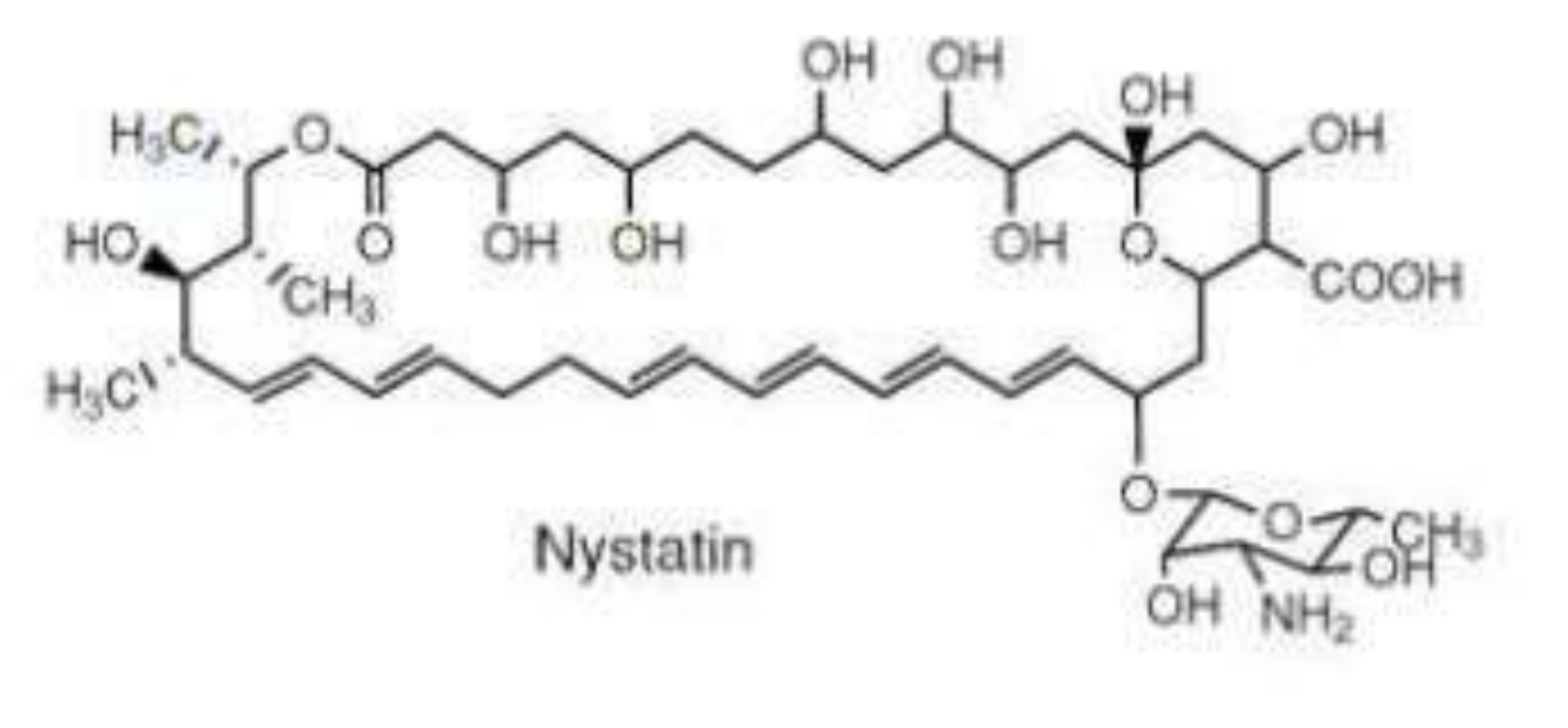
c.Miscellaneous: **Tolnaftate, Undecylenic acid, Benzoic acid**

Antifungal agents: Classification



Antifungal agents: Polyenes

Nystatin



Antifungal agents:

Polyenes *: Membrane Disruptors*

- ❑ The polyene antibiotic produced by actinomycete
- ❑ Macrocyclic lactones (Macrolide) with distinct hydrophilic and lipophilic regions.
- **The hydrophilic part:** several alcohols, a carboxylic acid, and usually, a sugar (Mycosamine) .
- **Lipophilic part:** in part 4-7 double bonds, unsubstituted.

- ❑ Ring size varied from 12 to 38 atom size
- ❑ The conjugated system is usually all-trans configuration so that the ring contain a planner lipophilic segment.
- ❑ With increase conjugation (double bond) the activity and toxicity will increase.
- ❑ Amphotericin B have 7conjugated double bond while nystatin have 6 conjugated double bond so, amphotericin B more active and more toxic.

Antifungal agents:

Polyenes *: Membrane Disruptors*

Mechanism of Action

The polyenes have an affinity for sterol-containing membranes, insert into the membranes, and disrupt membrane functions.

The membranes become leaky, loss of essential cell constituents like K+, small molecules

Polyenes have a demonstrably higher affinity for membranes containing ergosterol over cholesterol-containing membranes.

Greater toxicity to fungal cells

Antifungal agents: Polyenes

Examples: Nystatin, Amphotercin B, Natamycin

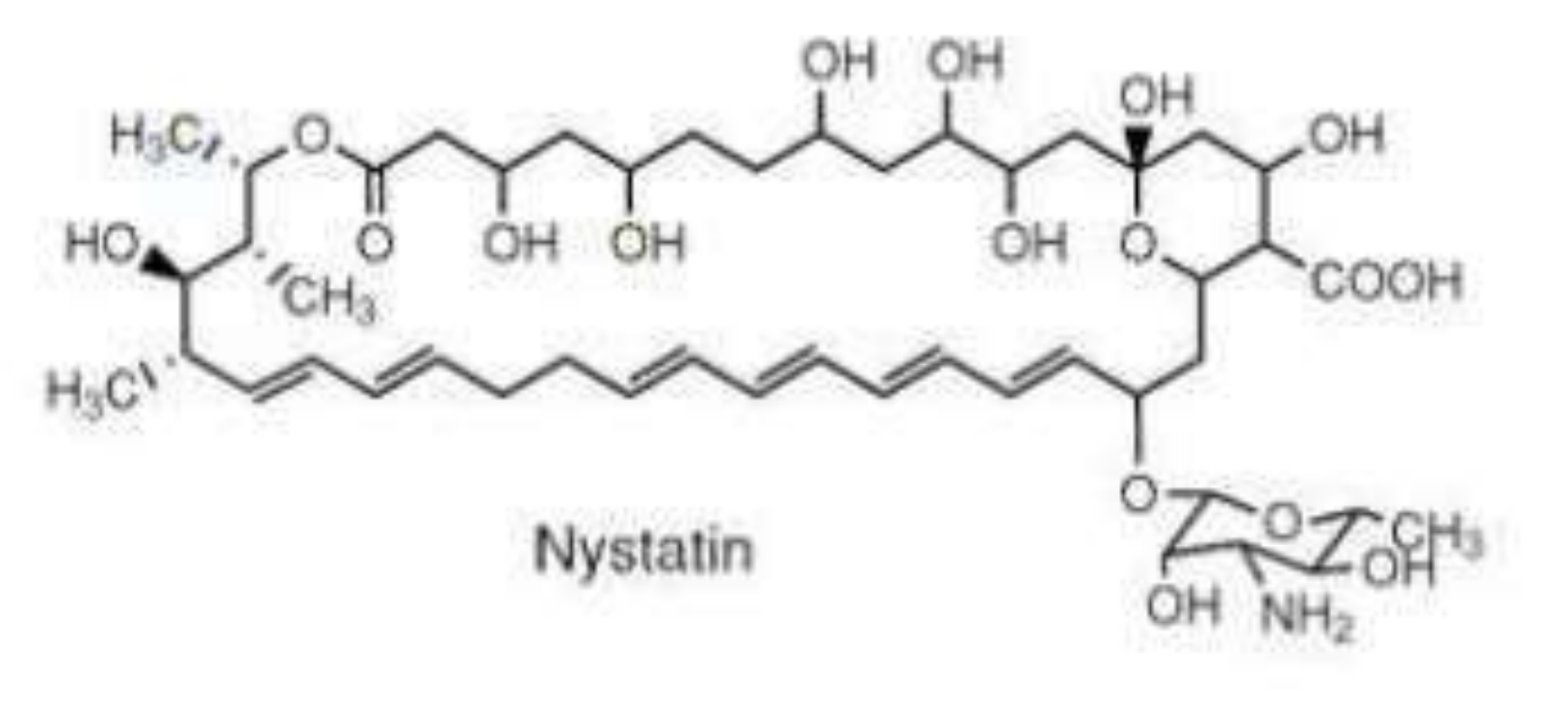
These compounds are poor water soluble

High toxicity

Chemical stability

Antifungal agents: Polyenes

Nystatin



Antifungal agents: Polyenes

Nystatin

Isolated from cultures of the bacterium *Streptomyces noursei*

Not absorbed from GIT

Toxic for systemic use

Used topically (ointment, cream)

Orally for fungal infections of the mouth and gastrointestinal tract

Antifungal agents: Polyenes

Amphotericin B

Antifungal agent with **the broadest spectrum of activity**

Produced by Streptomyces nodosus

Amphoteric polyene macrolide (38 membered ring)

Heptaene macrolide - large lactone ring with multiple ketone and hydroxyl group

The drug of choice **for many systemic, life- threatening fungal infections.**

Cannot cross the blood-brain barrier.

Amphotericin B : Antifungal Spectrum

- Aspergillus
- Blastomyces dermatitidis
- Candida albicans
- Cryptococcus neoformans
- Coccidioides immitis
- Histoplasma capsulatum
- Mucor spp.

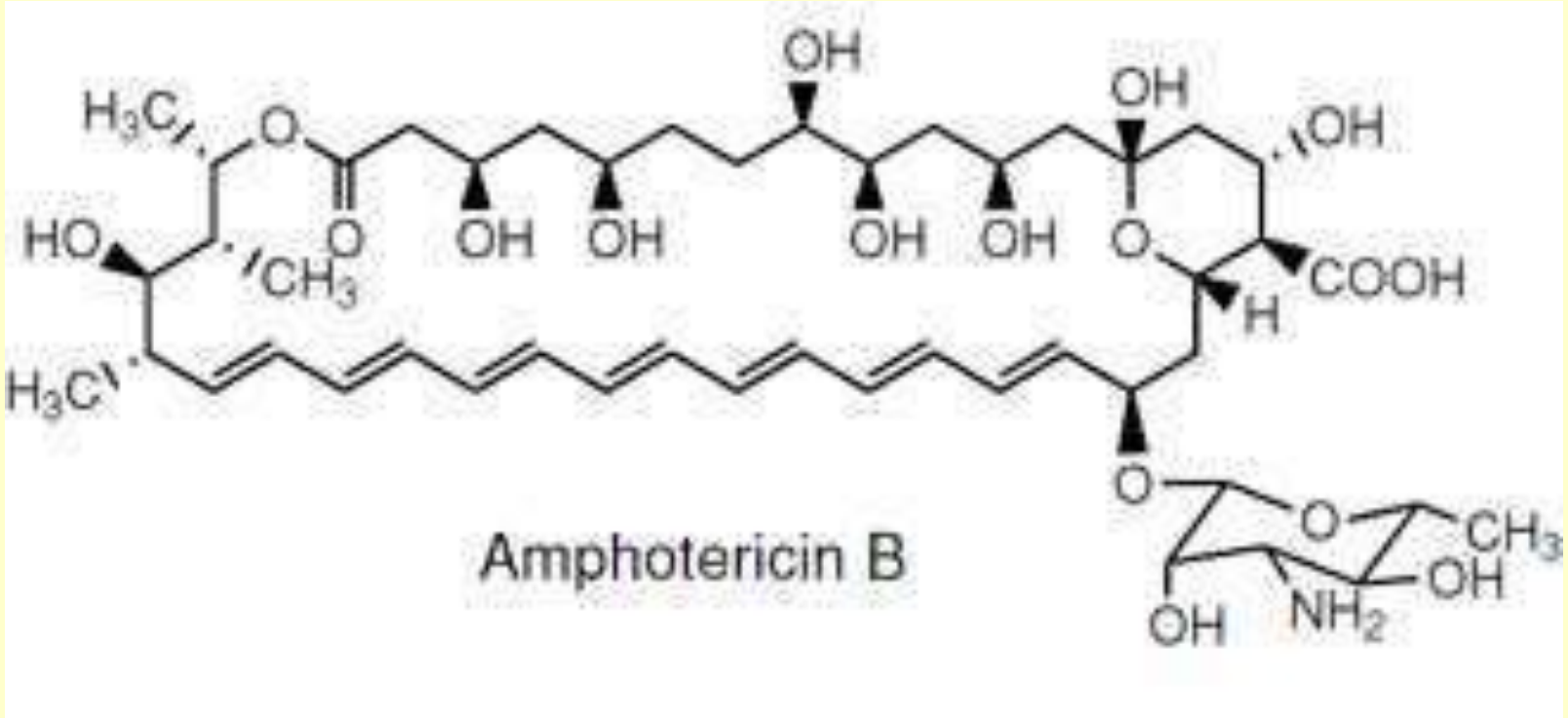
Also active against Leshmania

Broadest spectrum of action

Fungicidal at high & static at low conc.

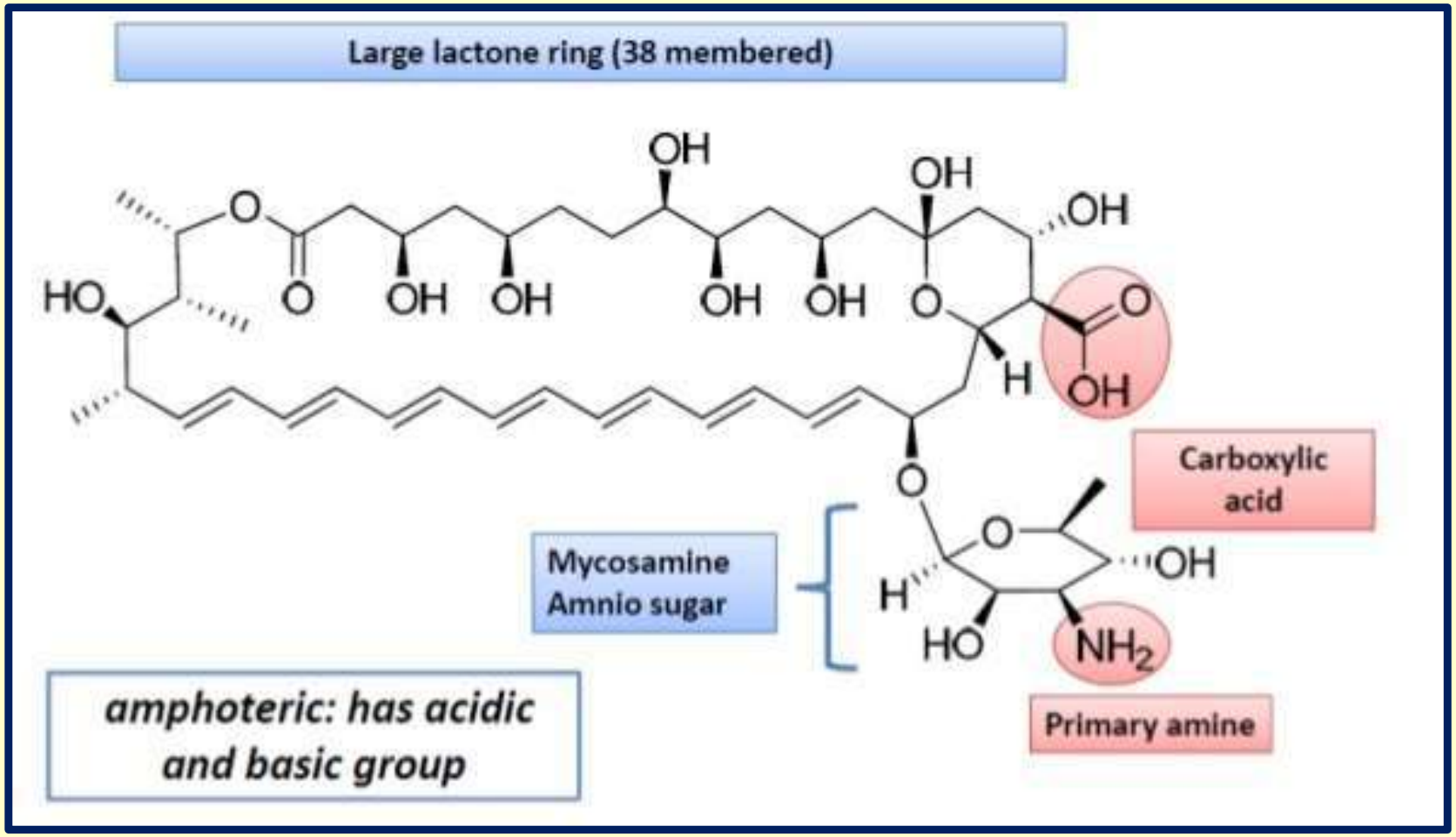
Antifungal agents: Polyenes

Amphotericin B

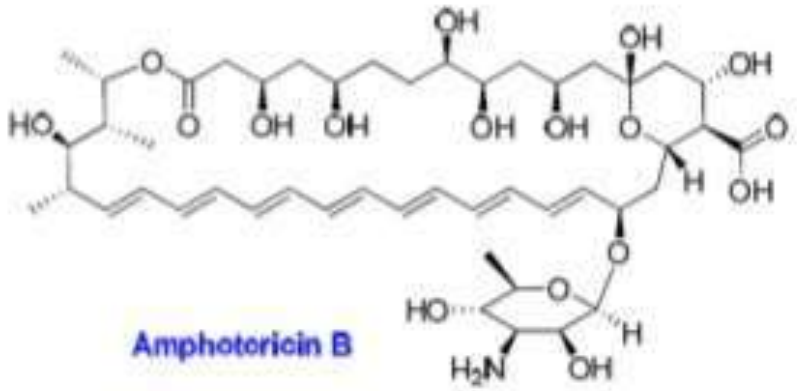


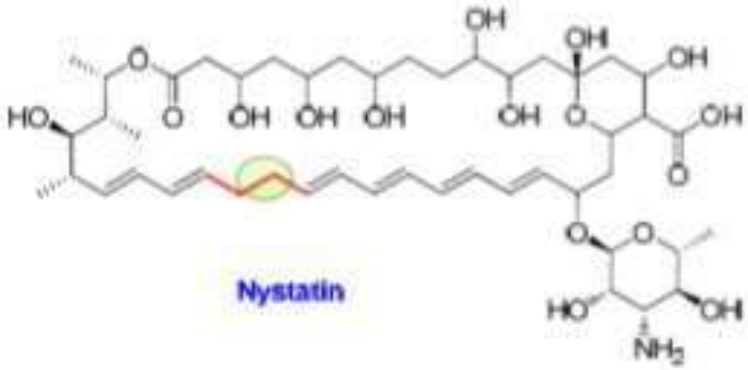
Antifungal agents: Polyenes

Amphotericin B



Antifungal agents: Polyenes





- The number of conjugated double bonds (nystatin = 4; amphotericin = 7)

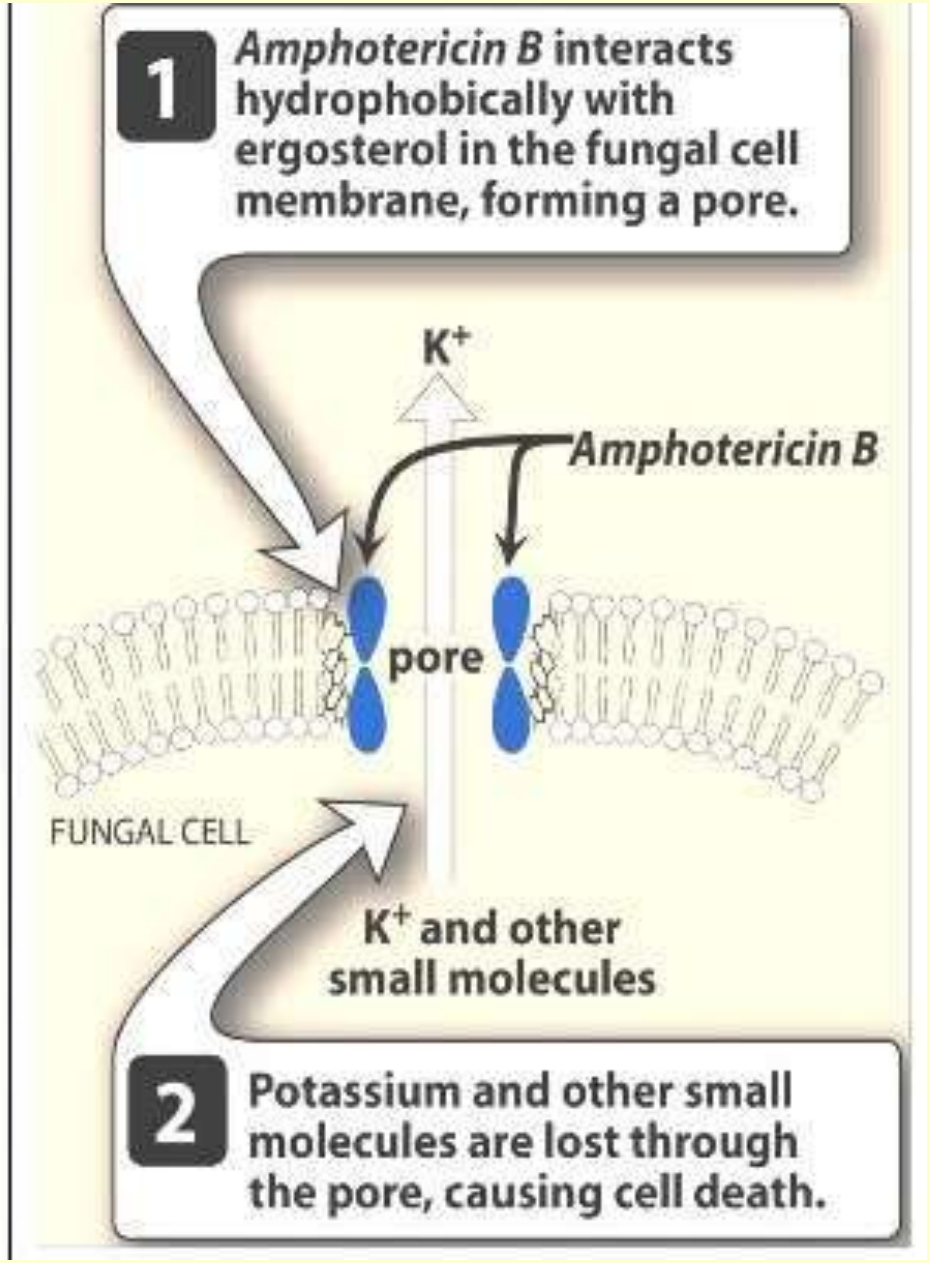
⇑ No. of conjugated double bonds → ⇑ Antifungal activity

⇑ No. of conjugated double bonds → ⇓ Degree of toxicity to mamallian cells

- Amphotericin B: the highest activity and the lowest toxicity

MECHANISM OF AMPHOTERICIN B

Amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells. There, they form pores (channels) that require hydrophobic interactions between the lipophilic segment of the polyene antibiotic and the sterol. The pores disrupt membrane function, allowing electrolytes (particularly potassium) and small molecules to leak from the cell, resulting in cell death.



Antifungal agents: Polyenes

Amphotericin B

Slow IV infusion for systemic fungal disease [For solubilization complex with deoxycholic acid, liposomes].

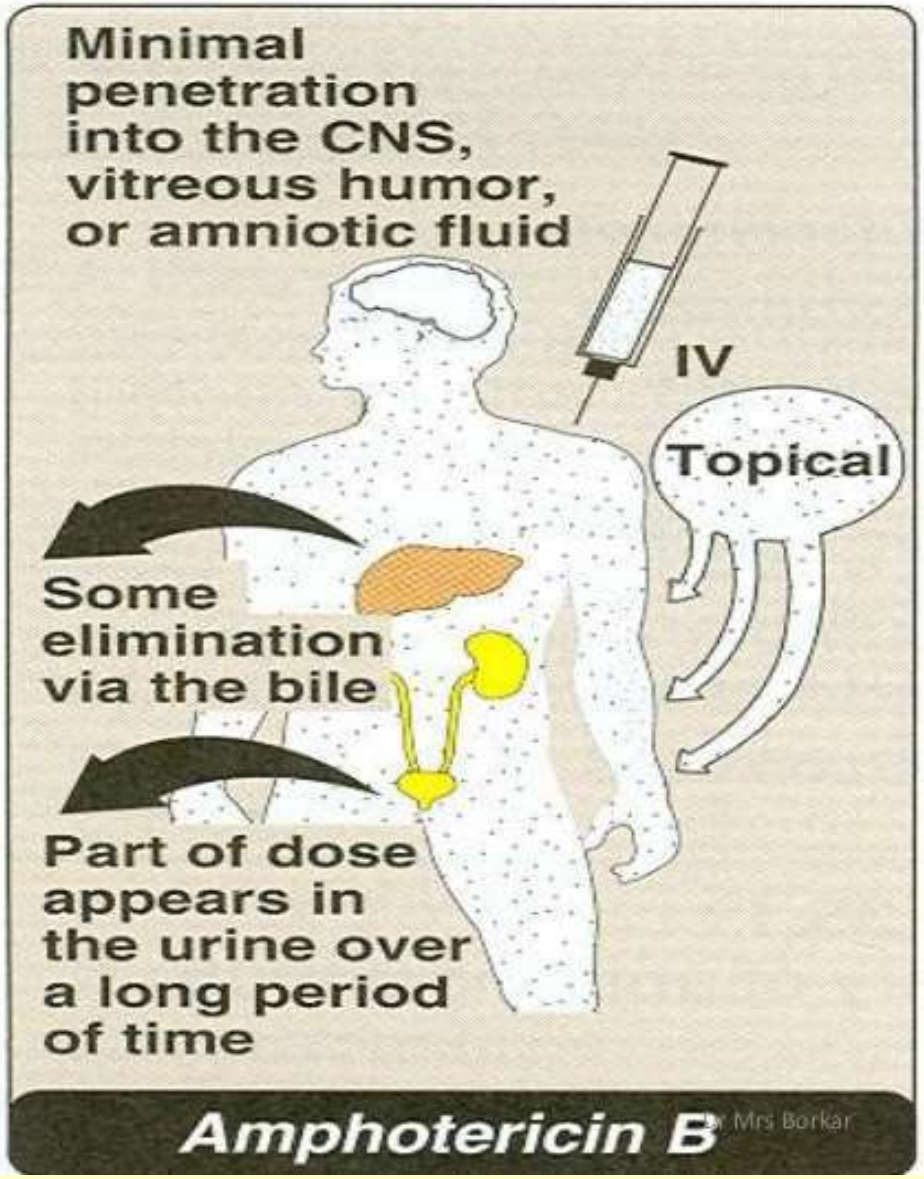
Intrathecal for fungal CNS infections.

Topical drops & direct subconjunctival injection for Mycotic corneal ulcers & keratitis.

Local injection into the joints in fungal arthritis.

Bladder irrigation in Candiduria

The main side effect: Nephrotoxicity



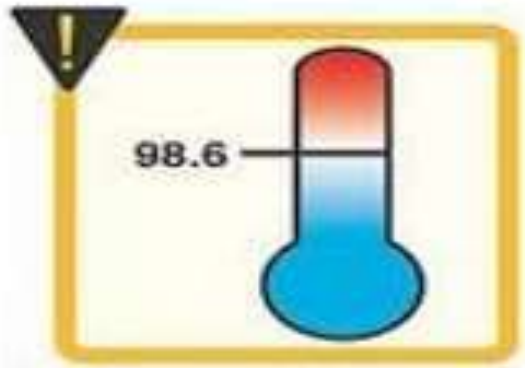
Amphotericin ADME

Highly protein bound - > 90%

Excreted slowly via kidneys, traces found in urine for months after cessation of drugs.

Half life 15 days

SOME ADVERSE REACTIONS OF AMPHOTERICIN B.



Fever

Chills

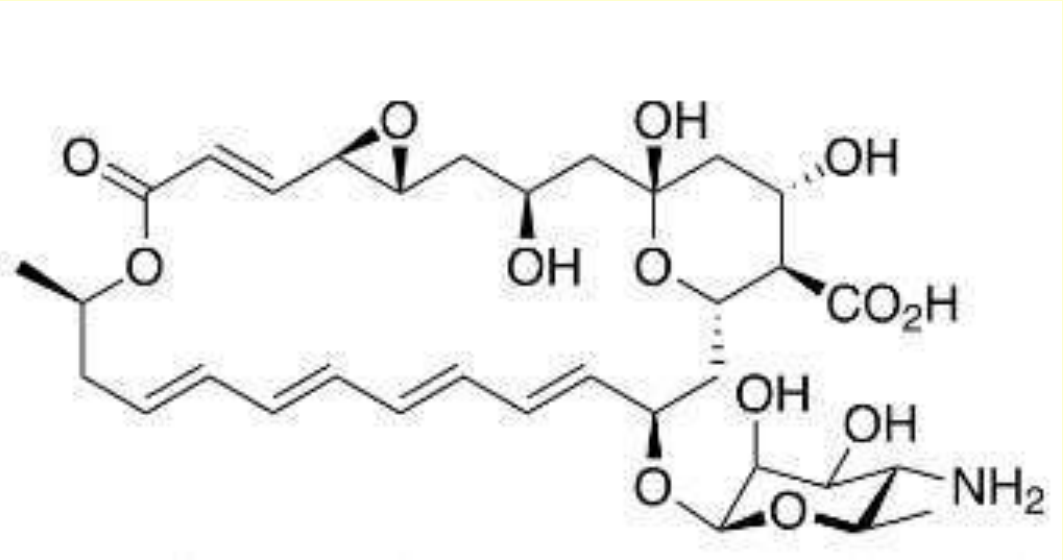
Kidny failure

Hypotensior

Anemia

Antifungal agents: Polyenes

Natamycin



33 Carbons

Natamycin performs this function by specifically binding to ergosterol and inhibiting membrane transport proteins

Very low solubility in water

Produced by Streptomyces natalensis

Antifungal agents: Polyenes

Natamcyin

Topically as a cream, in eye drops, or (for oral infections) in a lozenge.

It shows negligible absorption into the body when administered in these ways.

When taken orally, little or none is absorbed from the gastrointestinal tract, making it inappropriate for systemic infections>

Treat fungal infections around the eye. This includes infections of the eyelids, conjunctiva, and cornea. It is used as eye drops

Antifungal agents:

Azoles: Imidazole and triazole

A five-membered aromatic ring containing either two nitrogen (Imidazole) or three nitrogen atoms (Triazole).

N1 of azole ring is attached to a side chain containing at least one aromatic ring

The largest class of antimycotic (Over 20 drugs)

Synthetic drugs

Fungistatic and fungicidal depening on concentration of drug

Broad spectrum

Antifungal agents:

Imidazole

Topically : Econazole, miconazole, clotrimazole

Systemic: Ketconazole

Newer: oxiconazole, sulconazole

to treat superficial dermatophytic and yeast infections

Orally for the treatment of systemic fungal infections

Triazole

Systemic : Fluconazole, itraconazole, voriconazole, posaconazole

To treat invasive candidiasis.

Antifungal agents:

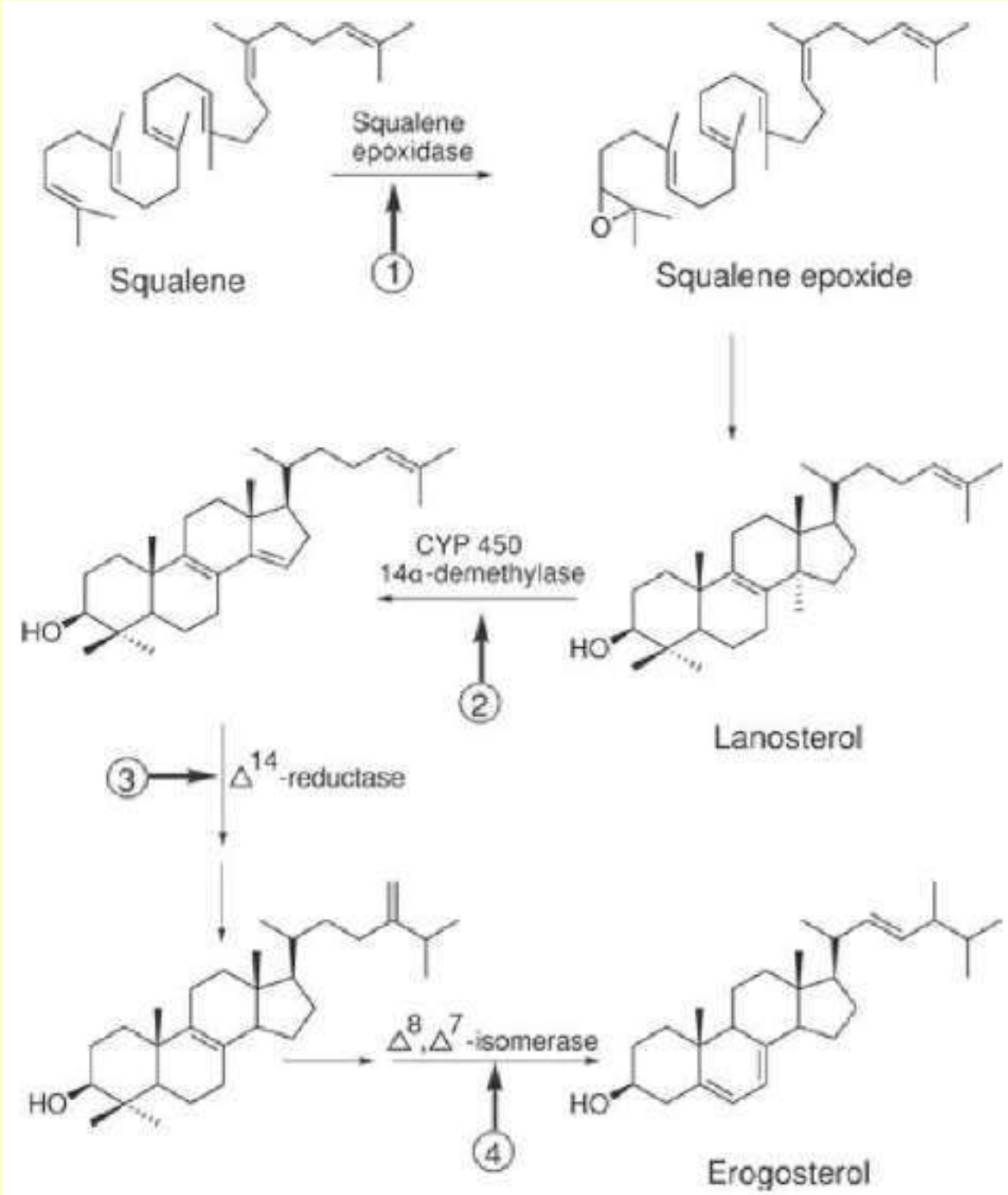
Azoles: Imidazole and triazole

Mechanism of action:

Azoles are predominantly fungistatic.

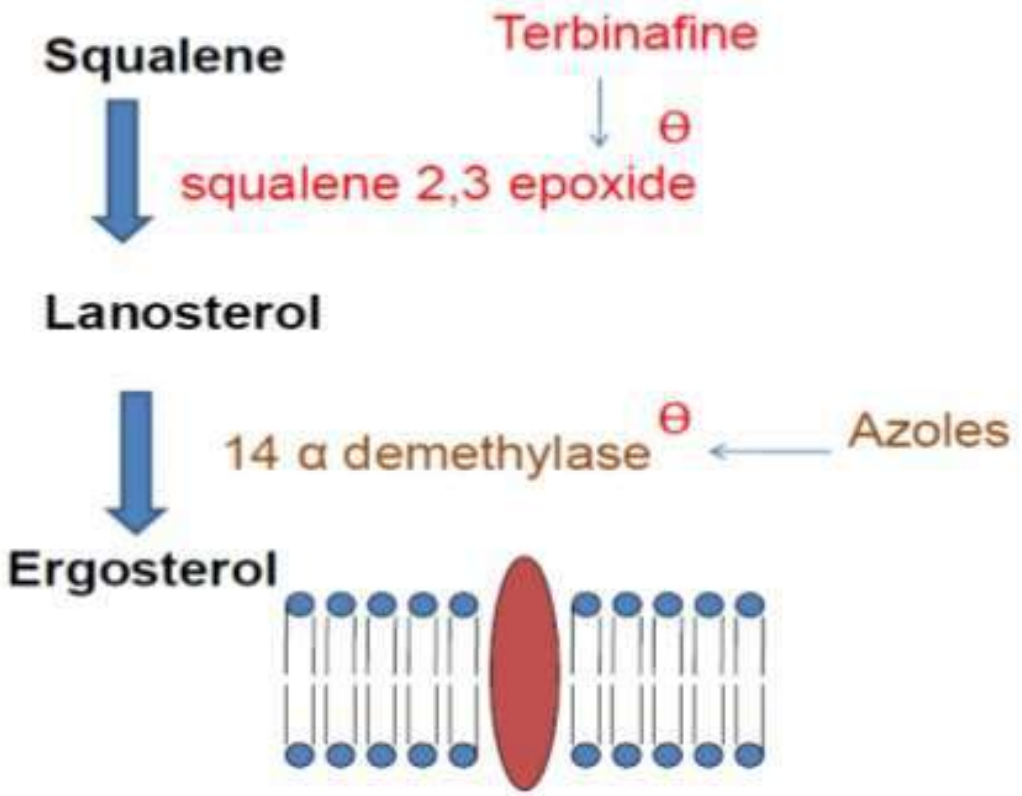
They inhibit C-14 α-demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterol.

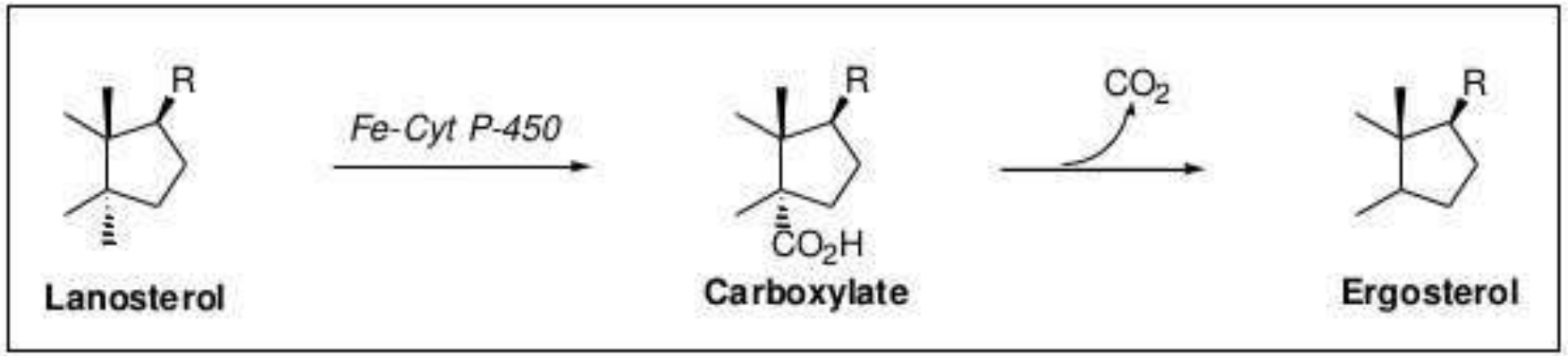
The basic N3 atom of the azole forms a bond with the heme iron of the CYP450 prosthetic group in the position normally occupied by the activated oxygen.
The remainder of the azole antifungal forms bonding interactions with the apoprotein in a manner that determines the relative selectivity of the drug for the fungal demethylase versus other CYP450 enzymes

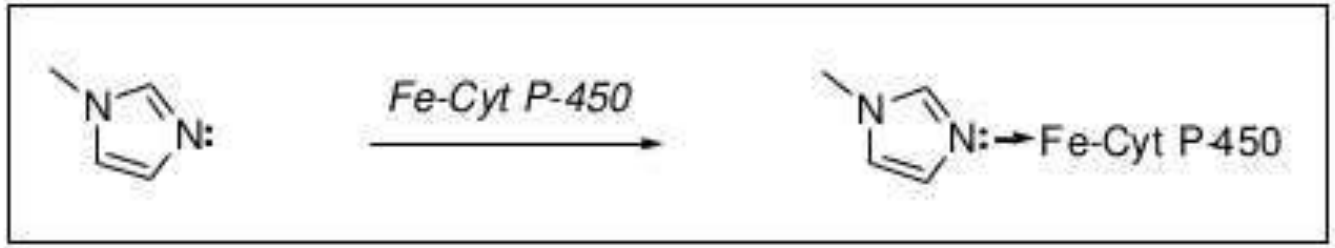


Ergosterol biosynthesis from squalene: Enzymatic steps known to be the site of action of currently employed antifungal agents are indicated by an arrow and a number.

Azoles Mechanism of Action

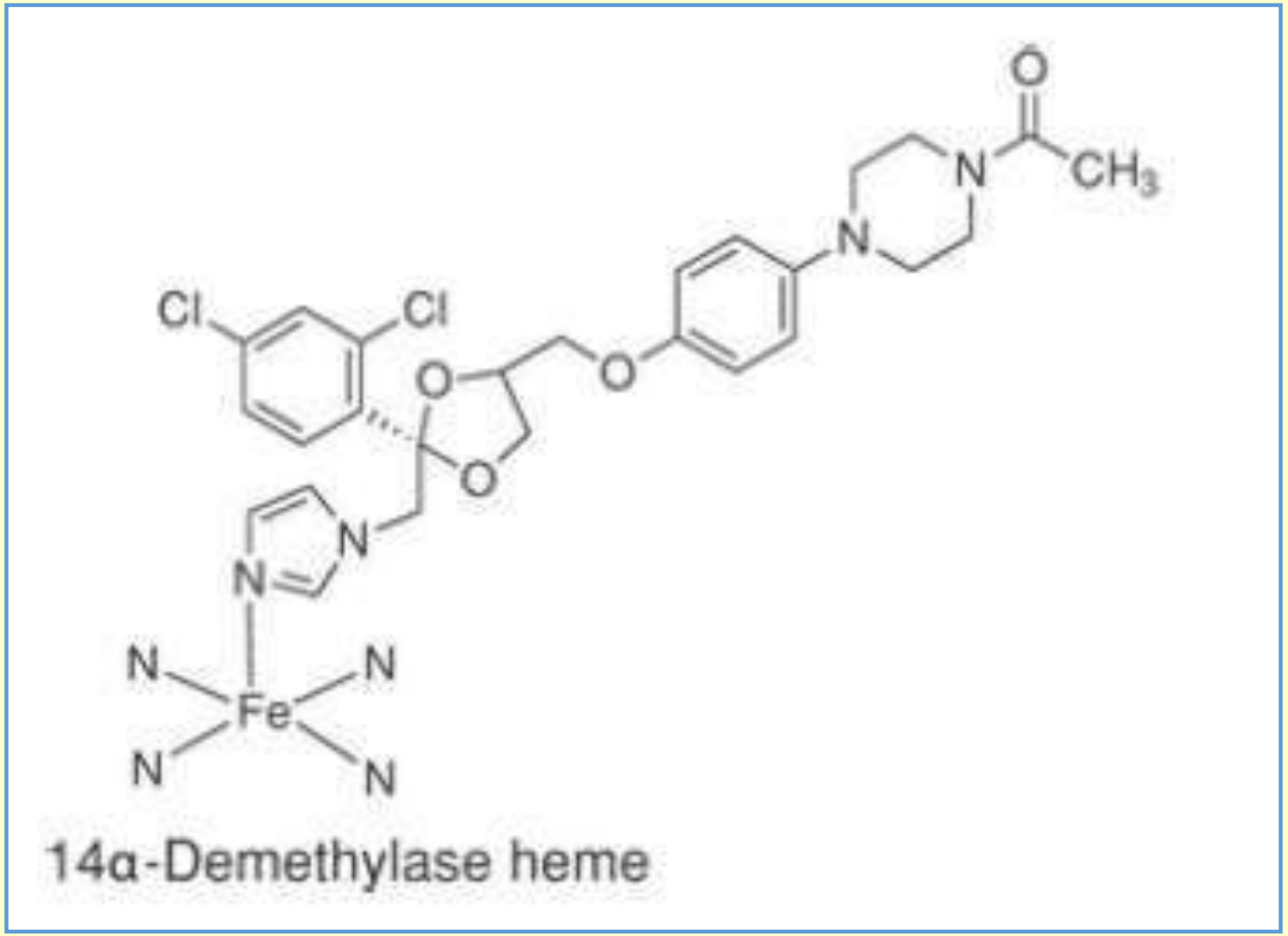






Mechanism of action of Azoles

Azoles: Mechanism of action



14α-Demethylase heme

Ketoconazole is representative of the azole antifungals

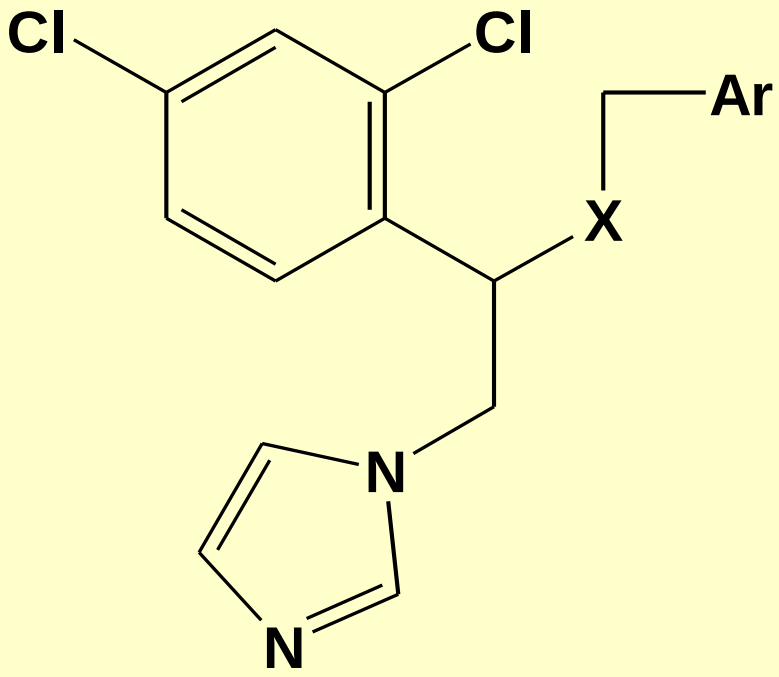
Question

What is the difference between Cholestrol and Ergosterol? LOOK in your Textbook

14-α-demethylase enzyme is important for cholestrol and ergosterol synthesis. Can azoles antifungal inhibit cholestrol biosynthsis in human cells? Explain

Triazole is bioisosteric replacement of imidazole. What is bioisoster ?

SAR OF AZOLE ANTIFUNGAL AGENTS



1. The basic structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pKa of 6.5–6.8) bonded by (**N-1**) a nitrogen–carbon linkage to the rest of the structure.

SAR OF AZOLE ANTIFUNGAL AGENTS

2. At the molecular level, the amidine nitrogen atom (**N-3** in the imidazoles, **N-4** in the triazoles) is believed to bind to the heme iron of enzyme-bound cytochrome P450 (**Coordination bond**) to inhibit activation of molecular oxygen and prevent oxidation of steroidal substrates by the enzyme.

3. The most potent antifungal azoles possess two or three aromatic rings, at least one of which is halogen substituted (e.g., 2,4-dichlorophenyl, 4-chlorophenyl, 2,4-difluorophenyl), and other non-polar functional groups.

4. Only 2, and/or 2,4 substitution yields effective azole compounds.

5. The halogen atom that yields the most potent compounds is **fluorine**, although functional groups such as sulfonic acids have been shown to do the same.

SAR OF AZOLE ANTIFUNGAL AGENTS

6. Substitution at other positions of the ring yields **inactive** compounds.

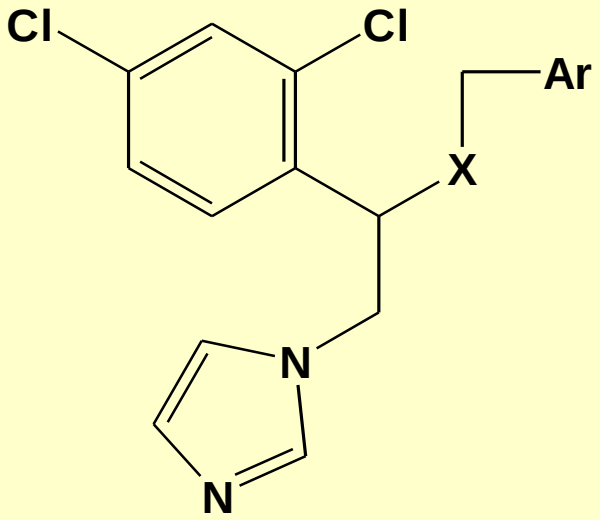
7. Presumably, the large nonpolar portion of these molecules mimics the nonpolar steroidal part of the substrate for lanosterol 14-demethylase, lanosterol, in shape and size.

8. The nonpolar functionality confers high lipophilicity to the antifungal azoles.

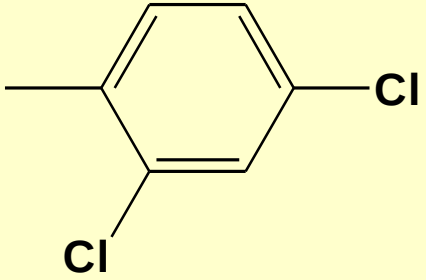
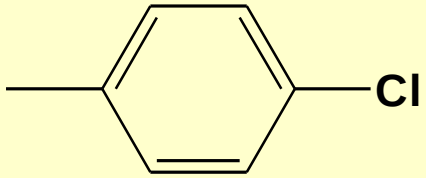
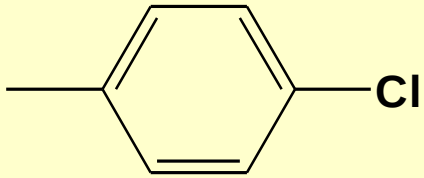
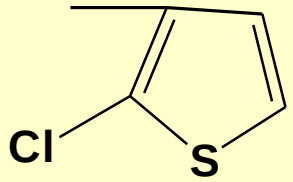
9. The free bases are typically insoluble in water but are soluble in most organic solvents, such as ethanol.

10.Fluconazole, which possesses two polar triazole moieties, is an exception, in that it is sufficiently water soluble to be injected IV as a solution of the free base.

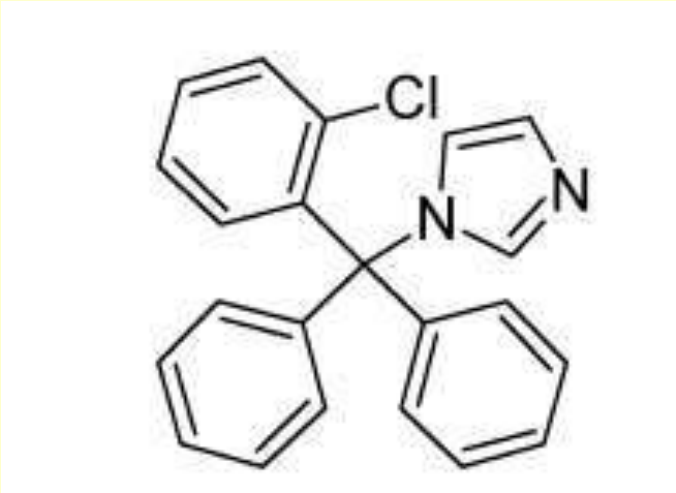
Chemical structure of azoles: Imidazole



Ground structure of imidazole antifungal

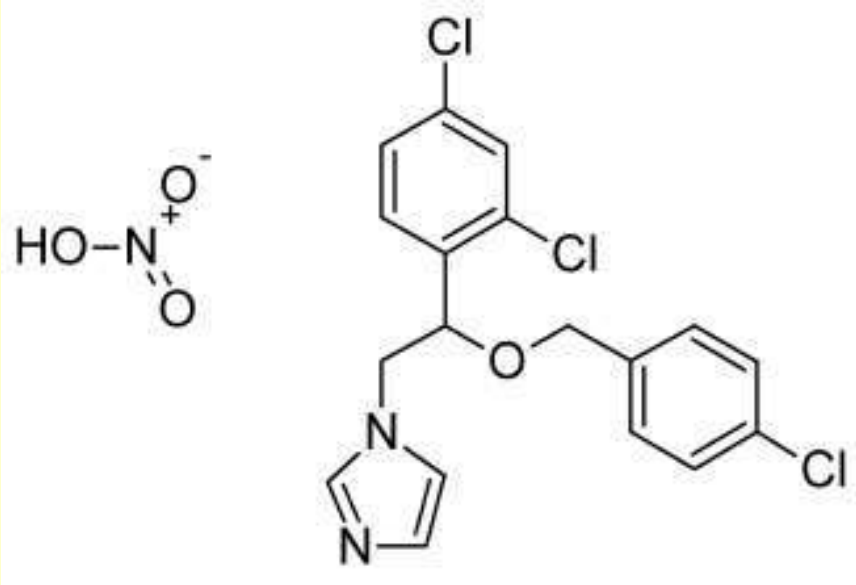
	X	Ar
Miconazole	O	
Ecoconazole	O	
Sulconazole	S	
Tioconazole	O	

Chemical structure of azoles: Imidazole



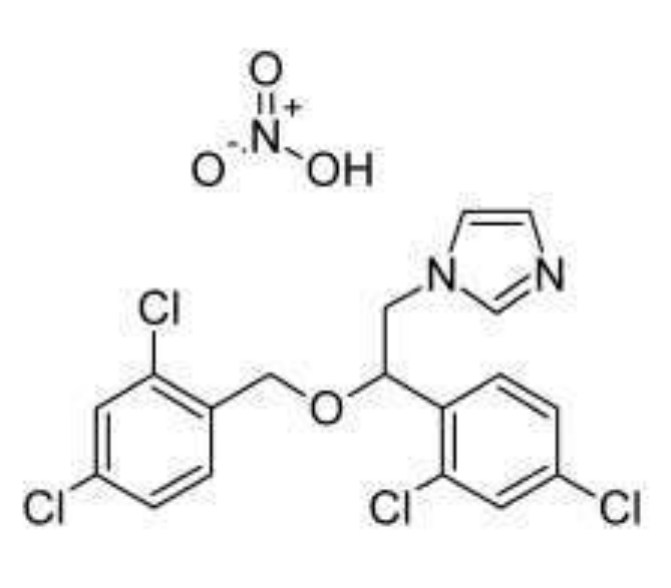
Clotrimazole

Only Topically



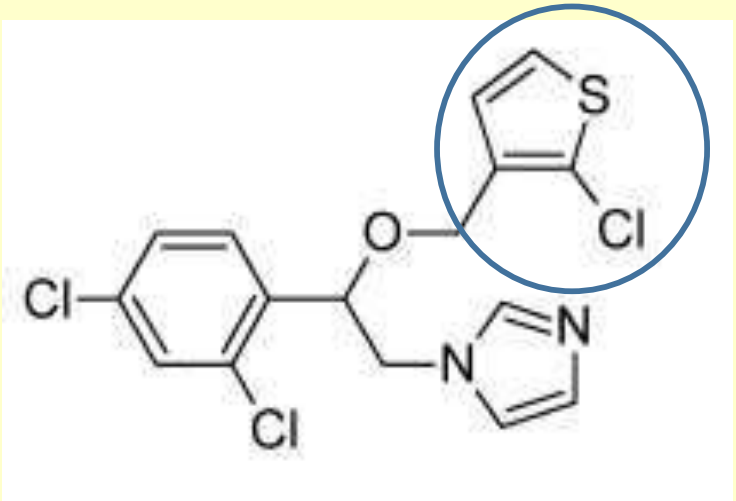
Econazole nitrate topical treatment of local tinea infections and cutaneous candidiasis

Chemical structure of azoles: Imidazole



Miconazole nitrate

Poor soluble in water, topically
Free base injectable
Solubilized [polyethylene glycol and castor oil] the treatment of serious systemic fungal infections



Ticonazole

Treatment of vulvovaginal candidiasis.

Antifungal agents: Imidazole

Ketoconazole

Very slightly soluble in water

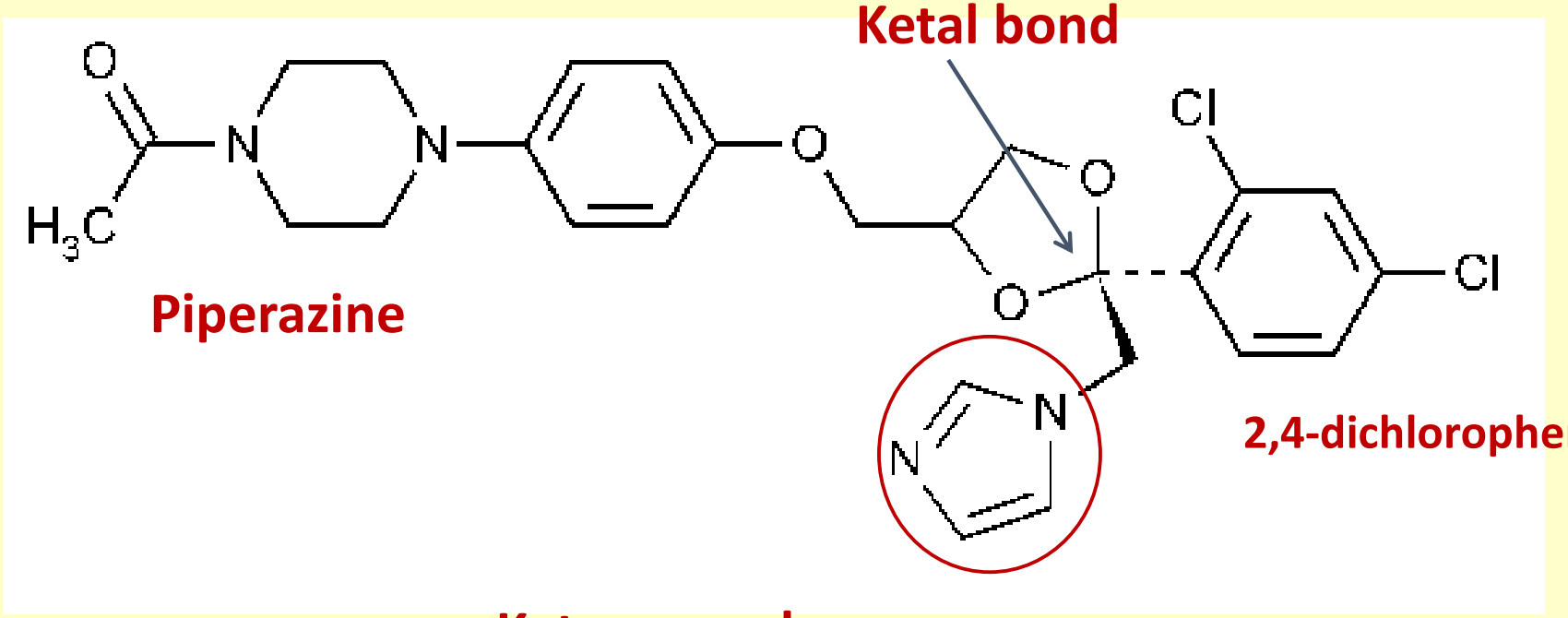
Extensively metabolized by microsomal enzymes, All metabolite are inactive

Powerful inhibitor of CYP3A4 (Hypnotic triazolam)

Weak inhibitor of CYP2C9 (Warfarin)

Application:
Treatment of candidiasis, dermatophytes, deep mycosis
locally to reduce toxicity (hepatotoxicity)
Drug interaction

Antifungal agents: Imidazole



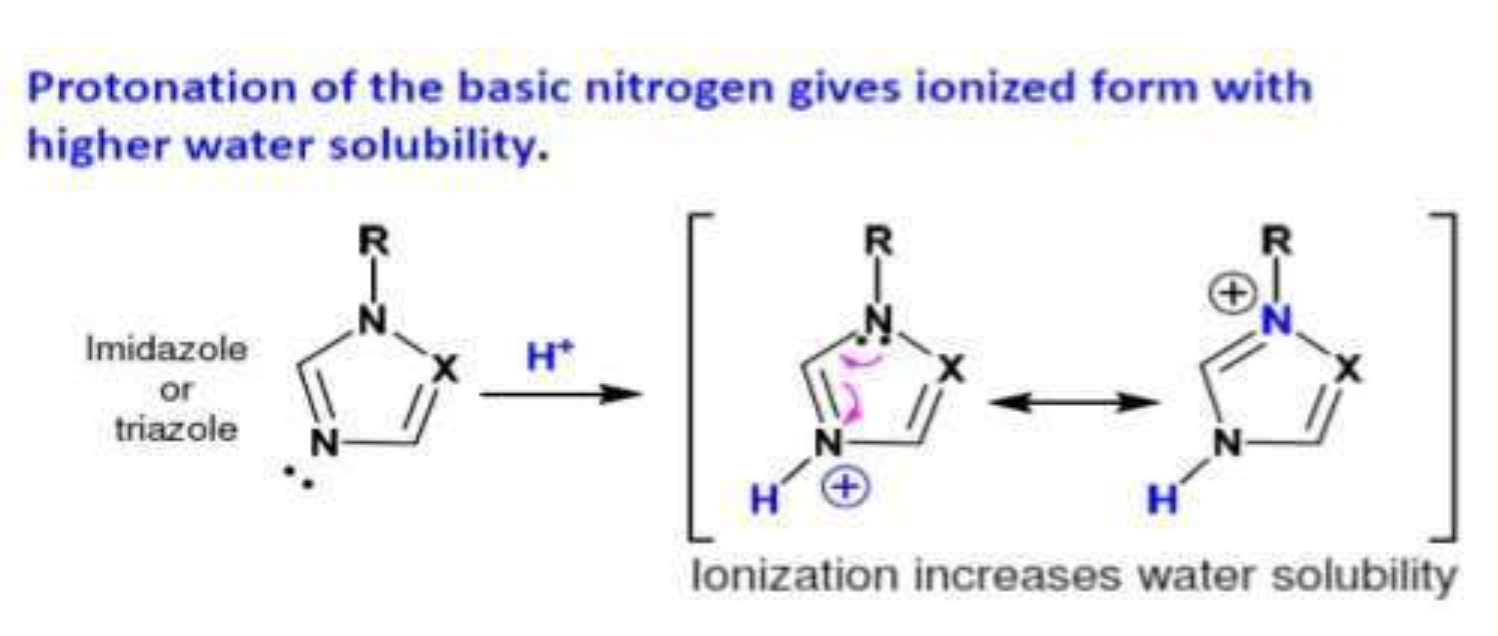
Ketoconazole

Antifungal agents: Imidazole

Ketoconazole

- The first orally active azole

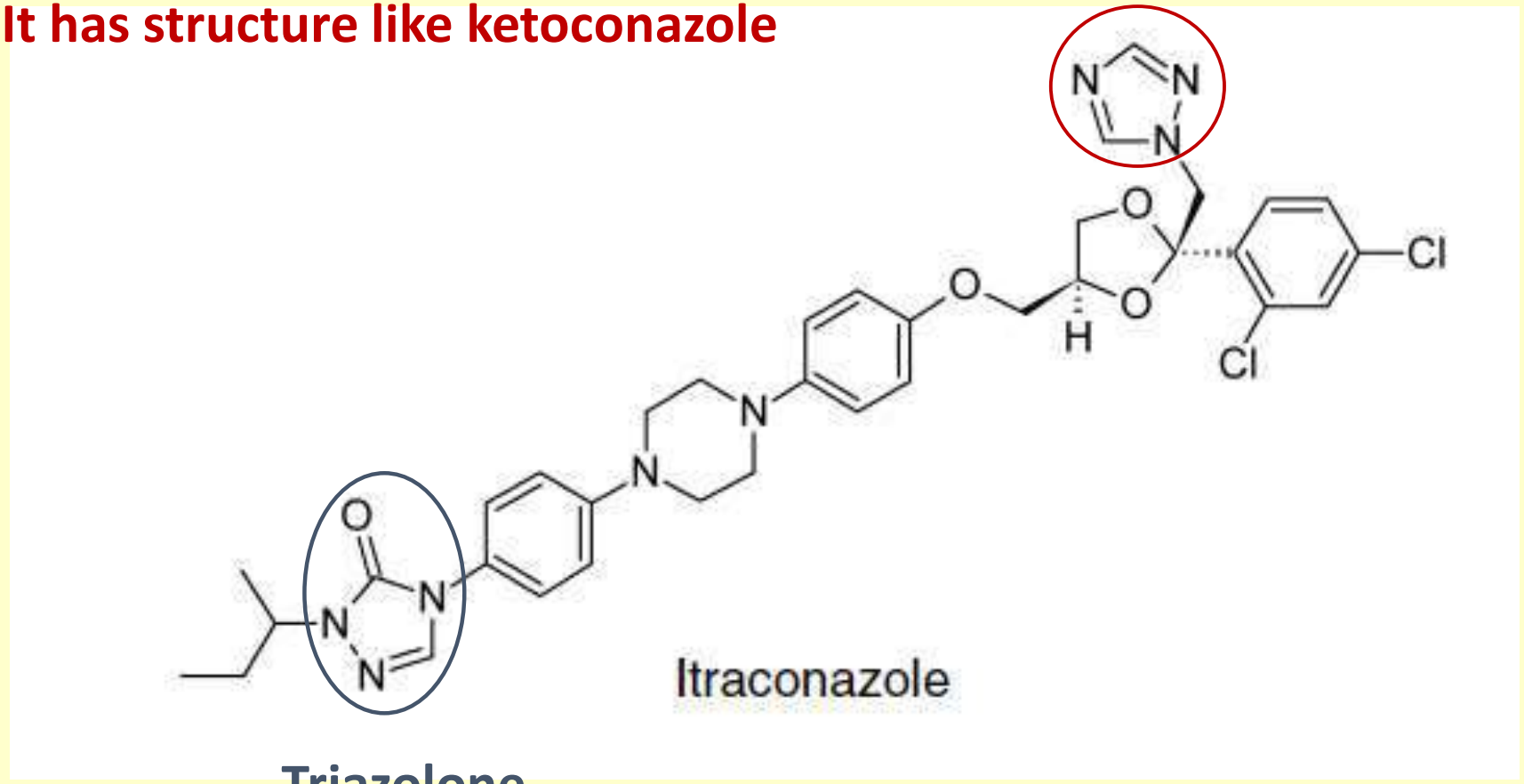
- Oral bioavailability only at low stomach pH less than 4
Antiacid, H_2-antagononist reduce absorption Acid medium is required for solubilization of the drug



Antifungal agents: Triazole

Itraconazole

It has structure like ketoconazole



Triazolone

Antifungal agents: Triazole

Itraconazole

Itraconazole is an orally active, broad-spectrum antifungal agent that has become an important alternative to ketoconazole.

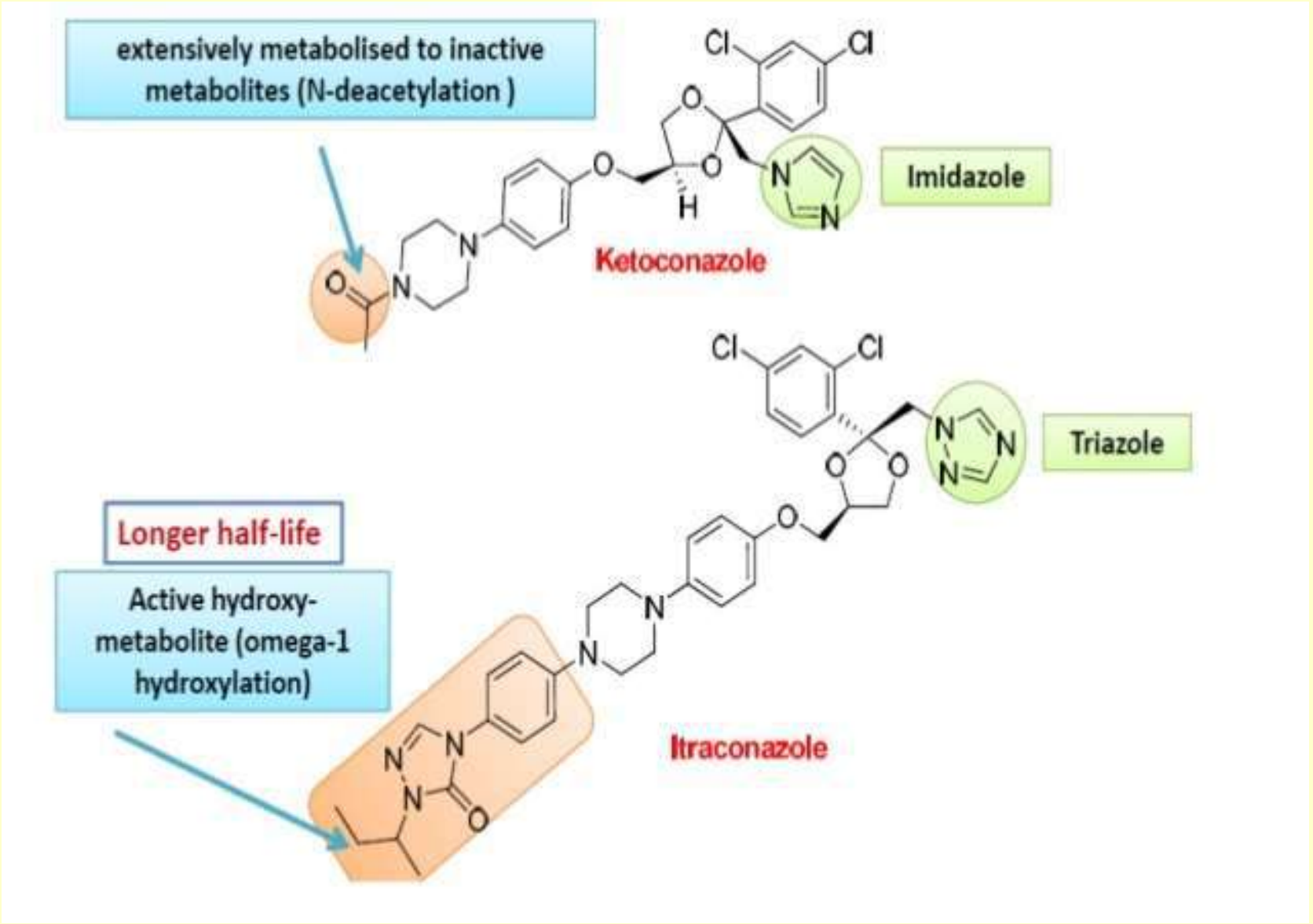
For treatment of systemic fungal infections

Oral bioavailability is variable and is influenced by food and stomach pH

Itraconazole has been demonstrated to be a strong inhibitor of CYP3A4

Clinically significant drug interaction (Lovastatin)

Unlike ketoconazole, it is not hepatotoxic and does not cause adrenal or testicular suppression in recommended therapeutic doses


extensively metabolised to inactive metabolites (N-deacetylation)
Imidazole
Ketoconazole
Triazole
Longer half-life
Active hydroxy-metabolite (omega-1 hydroxylation)
Itraconazole

Itraconazole	Ketoconazole
Better tolerated, not hepatotoxic, no anti-androgenic effects. Generally triazole derivatives are safer	Inhibits the synthesis of cholesterol and other steroid hormones → anti-androgenic effects (loss of libido gynecomastia).
More effective, Broad spectrum antifungal agent than ketoconazole Also effective against Aspergillus infections. Generally triazole derivatives are more active	not effective against *Aspergillus* .
Longer half-life (20-30 h) than ketoconazole (6-9 h), active hydroxy-metabolite	Ketoconazole is extensively metabolized to the inactive deacetylated product

Antifungal agents: Triazole

Fluconazole

Water soluble bis-triazole with broad-spectrum antifungal properties that is suitable for both oral and intravenous administration as the free base.

Taken orally: tablet, suspension. Absorption is not affected by GIT acidity

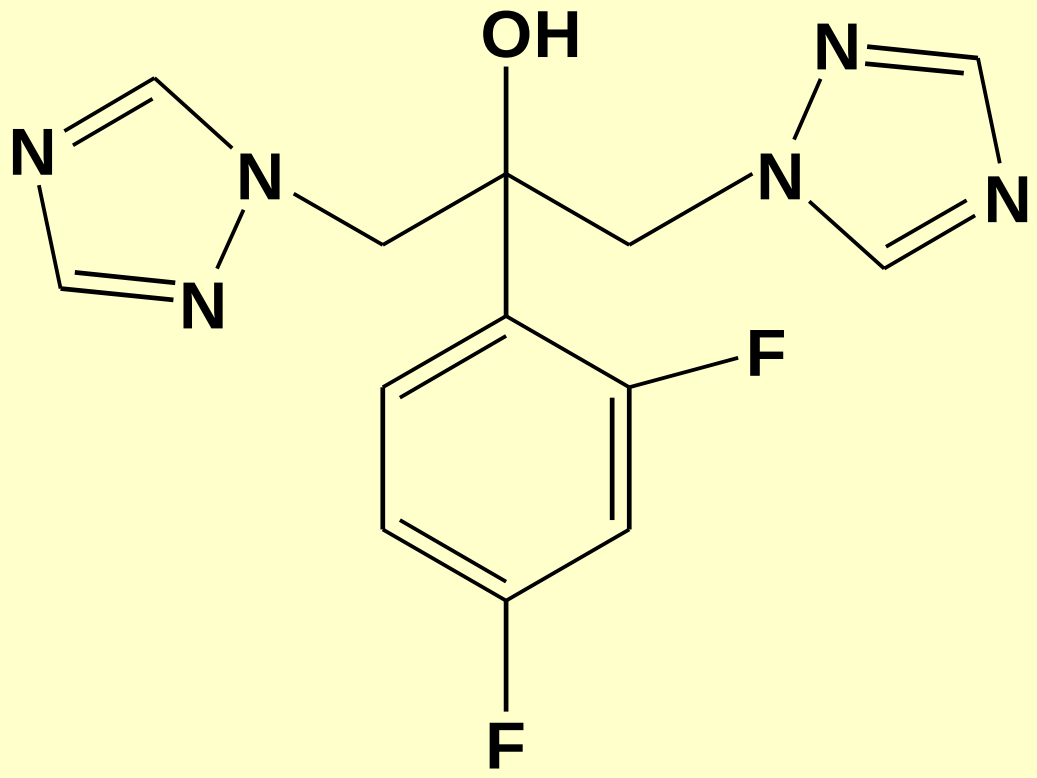
It can cross the blood-brain barrier

A weak inhibitor of CYP3A4 but a strong inhibitor of CYP2C9 (Interaction with warfarin)

little or no hepatic metabolism

Antifungal agents: Triazole

Chemical structure of azoles: Triazole



Fluconazole

Antifungal agents

Part 2

Dr. Mai Ramadan

AZOLES

IMIDAZOLES

TOPICAL

CLOTRIMAZOLE

SECONAZOLE

OXICONAZOLE

MOCONAZOLE

ECONAZOLE

BUTOCONAZOLE

SULCONAZOLE

TERCONAZOLE

SYSTEMIC

KETOCONAZOLE

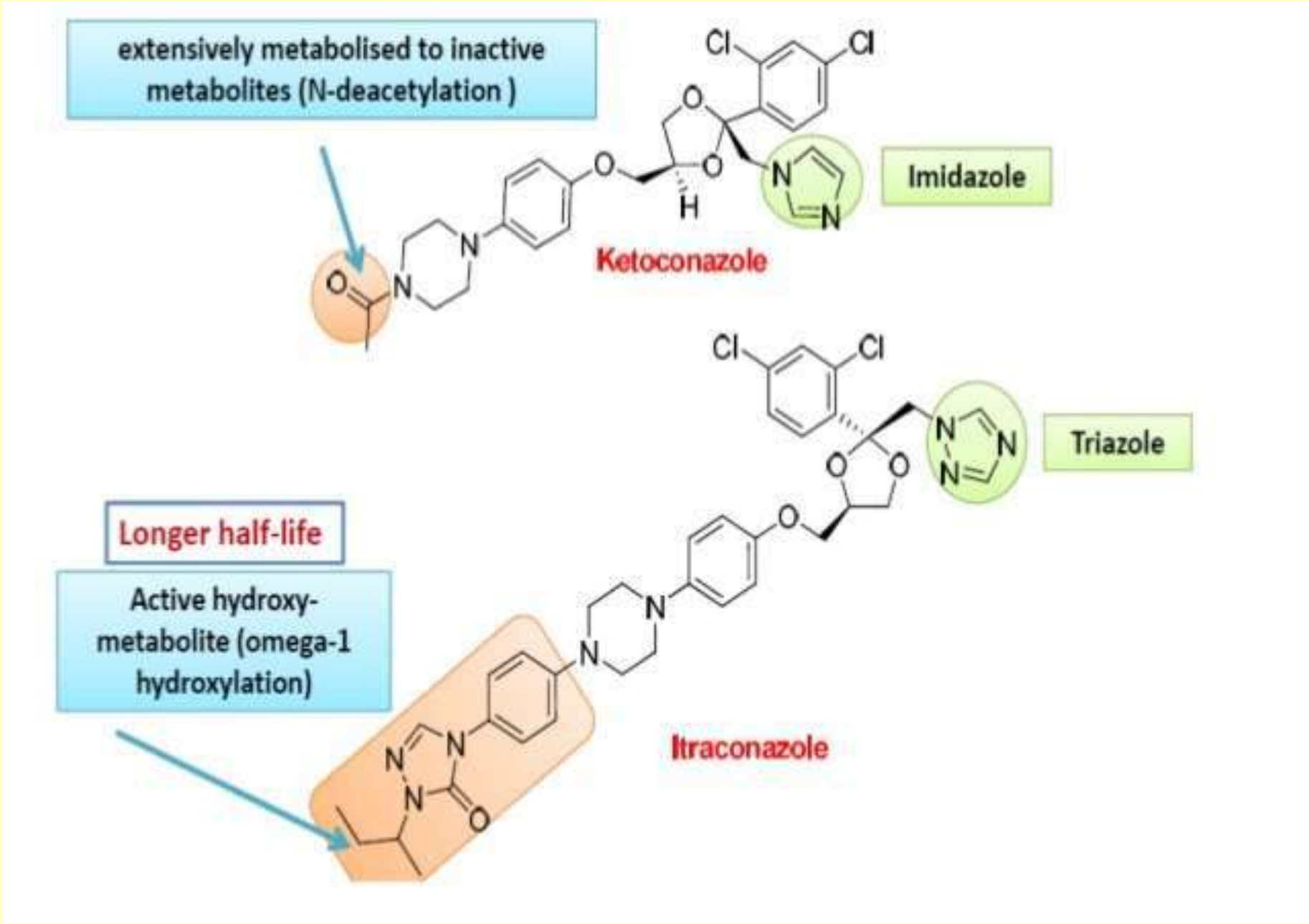
TRIAZOLES

VORICONAZOLE

ITRACONAZOLE

POSACONAZOLE

FLUCONAZOLE


extensively metabolised to inactive metabolites (N-deacetylation)
Imidazole
Ketoconazole
Triazole
Longer half-life
Active hydroxy-metabolite (omega-1 hydroxylation)
Itraconazole

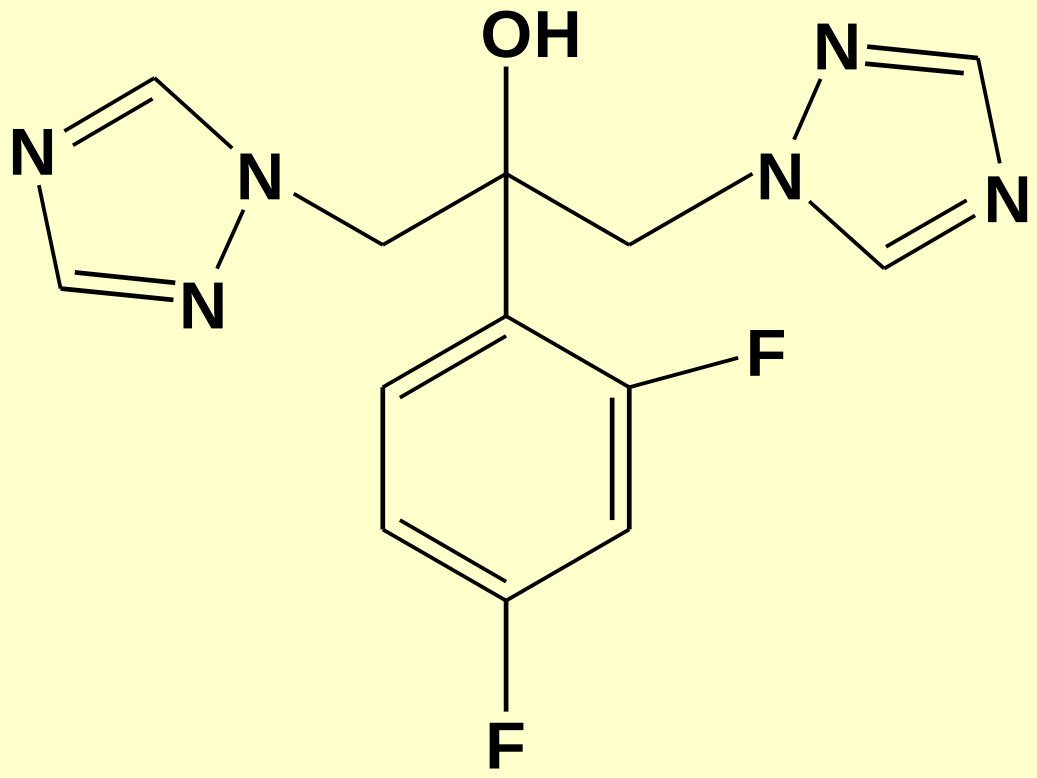
Antifungal agents: Triazole

Itraconazole

- Orally well absorbed
- IV can be given in serious infections
- **Not effective against fungal meningitis**
- Adverse effects include nausea, vomiting, rash hypokalemia, hypertension, edema, and headache, hepatotoxicity.
- It has **a negative inotropic effect** and should be avoided in patients with evidence of ventricular dysfunction, such as heart failure.

Antifungal agents: Triazole

Chemical structure of azoles: Triazole



Fluconazole

Antifungal agents: Triazole

Fluconazole

Water soluble bis-triazole with broad-spectrum antifungal properties that is suitable for both oral and intravenous administration as the free base.

Taken orally: tablet, suspension. Absorption is not affected by GIT acidity

It can cross the blood-brain barrier

A weak inhibitor of CYP3A4 but a strong inhibitor of CYP2C9 (Interaction with warfarin)

little or no hepatic metabolism

Antifungal agents: Triazole

Fluconazole

Completely absorbed from GIT, > 90% renal excretion unchanged.

Half life 25-30 hour

It is the drug of choice of cryptococcal meningitis

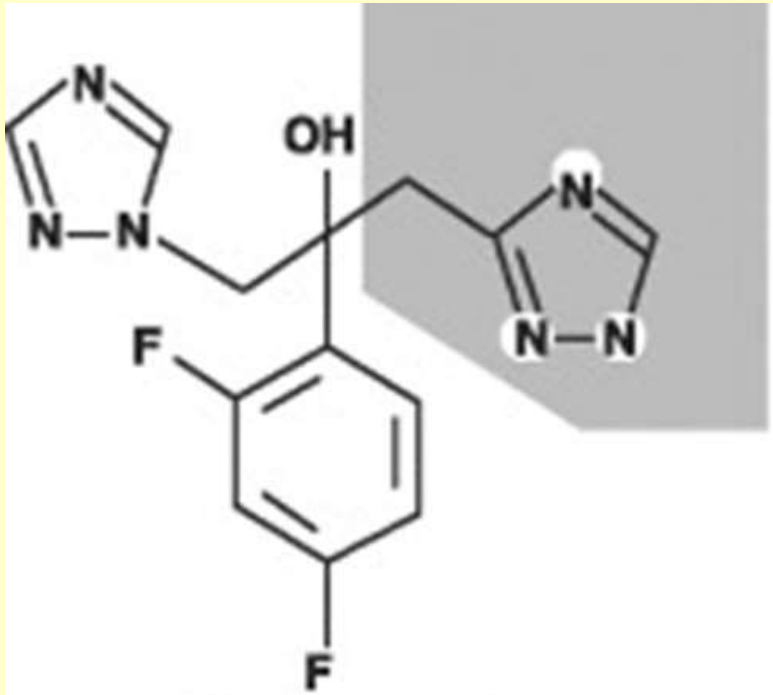
It is not effective in aspergillosis

It is commonly used as **a single-dose oral** treatment for vulvovaginal candidiasis

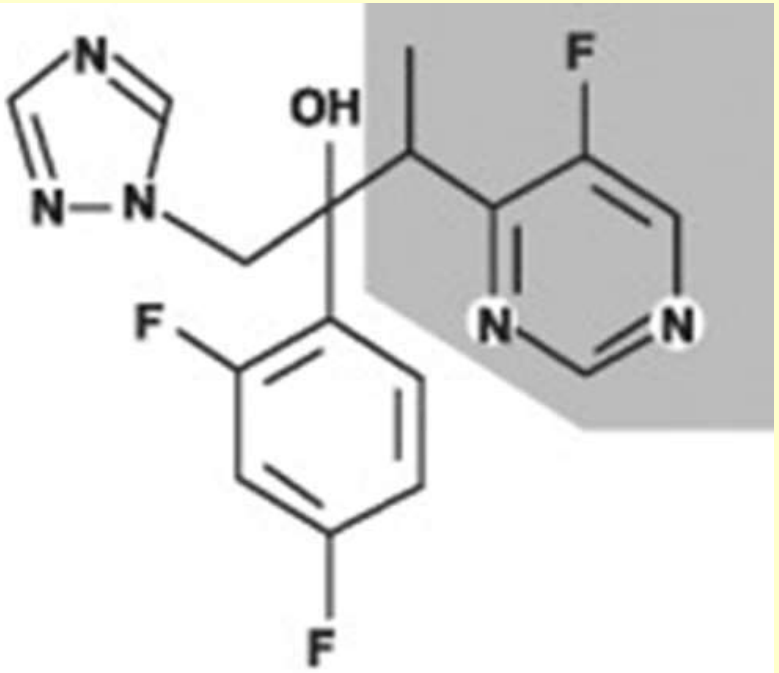
No endocrine side effects

Antifungal agents: Triazole

Voriconazole: second generation



Fluconazole



Voriconazole

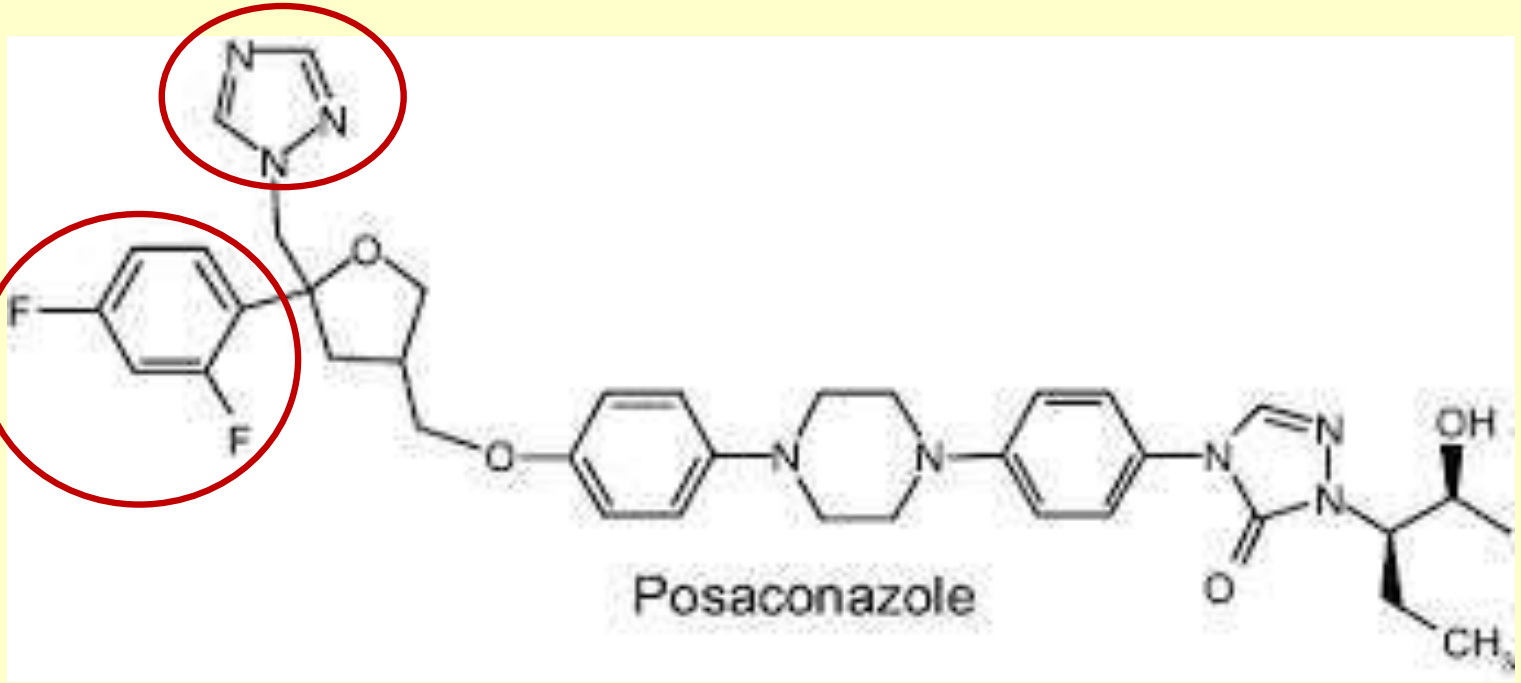
Voriconazole: second generation

- Voriconazole was discovered during developing an antifungal agent with a spectrum of activity beyond that of fluconazole.

- It is relatively insoluble in water.
- Intravenous formulation contains voriconazole in a sulphobutylether β-cyclodextrin (SBECD) solute to allow for parenteral administration.
- It **has replaced amphotericin B as the drug of choice for invasive aspergillosis, and invasive candidiasis.**
- High concentrations are associated with visual and auditory hallucinations and an increased incidence of hepatotoxicity.

Antifungal agents: Triazole

Posaconazole: second generation



Posaconazole

Posaconazole: second generation

The broadest spectrum azole and most expensive one to date.

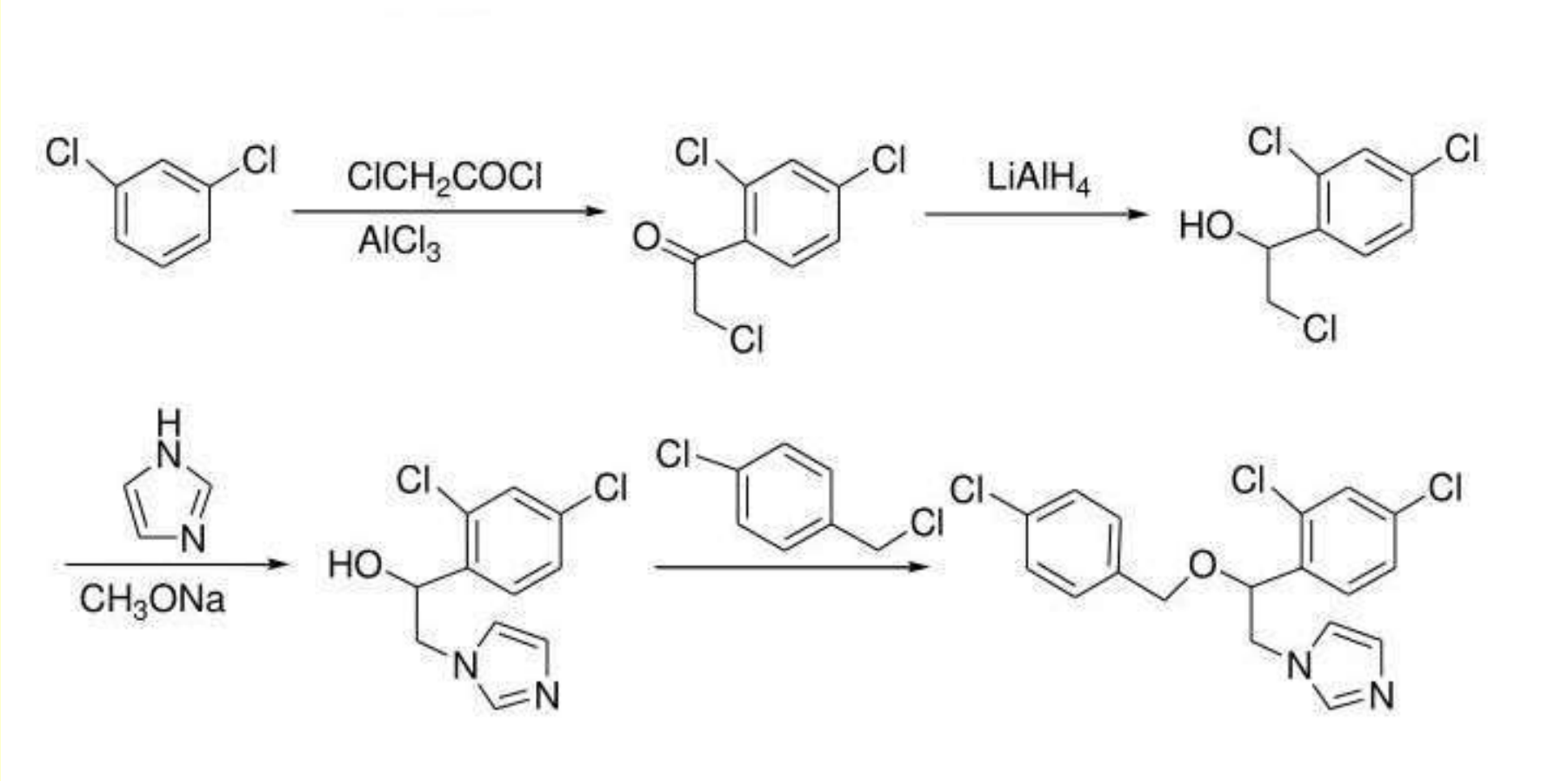
Cyp inhibitor

Posaconazole is the only azole with clinical activity against zygomycete fungilts

Absorption is improved when taken with food

IV formulation and two oral formulations of NOXAFIL **for prophylaxis against invasive Aspergillus and Candida infections** in severely immunocompromised patients
For patients older than 18 years.

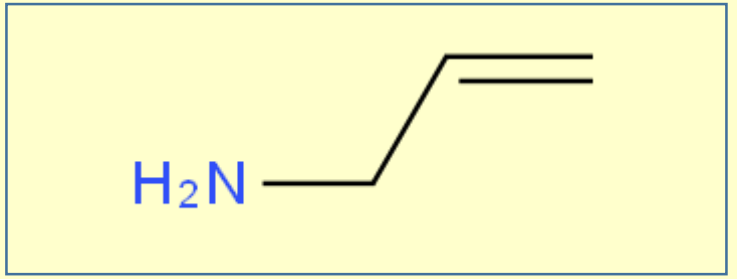
Antifungal agents: Econazole synthesis



	FLUCONAZOLE	ITRACONAZOLE	VORICONAZOLE	POSACONAZOLE
SPECTRUM OF ACTIVITY	+	++	+++	++++
ROUTE(S) OF ADMINISTRATION	Oral, IV	Oral	Oral, IV	Oral, IV
ORAL BIOAVAILABILITY (%)	95	55 (solution)	96	Variable
DRUG LEVELS AFFECTED BY FOOD OR GASTRIC PH	No	Yes	No	Yes
PROTEIN BINDING (%)	10	99	58	99
PRIMARY ROUTE OF ELIMINATION	Renal	Hepatic CYP3A4	Hepatic CYP2C19, 2C9, 3A4	Hepatic Glucuronidation
CYTOCHROME P450 ENZYMES INHIBITED	CYP3A4, 2C9, 2C19	CYP3A4, 2C9	CYP2C19, 2C9, 3A4	CYP3A4
HALF-LIFE ($t_{1/2}$)	25 hours	30–40 hours	Dose Dependent	20–66 hours
CSF PENETRATION	Yes	No	Yes	Yes
RENAL EXCRETION OF ACTIVE DRUG (%)	>90	<2	<2	<2

Antifungal agents: Allylamine

- Terbinafine
- Naftifine
- Butenafine



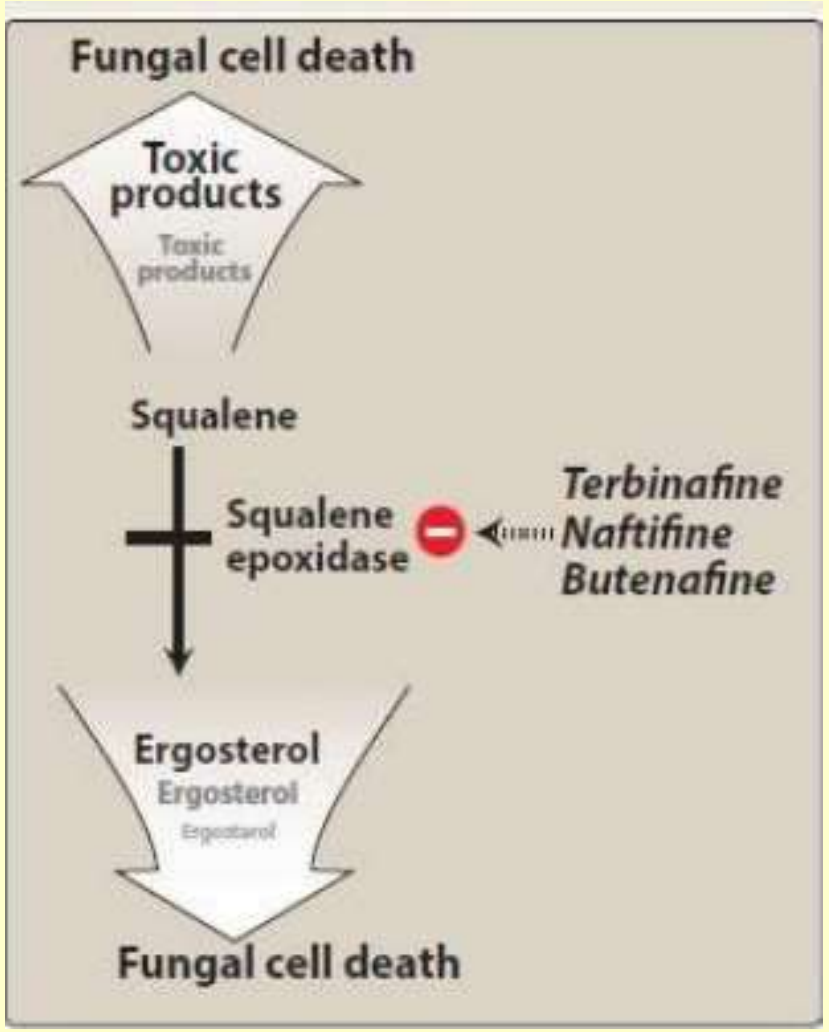
limited spectrum of activity than the azoles.

Effective only against dermatophytes.

Squalene epoxidase inhibitors

Mechanism of action:

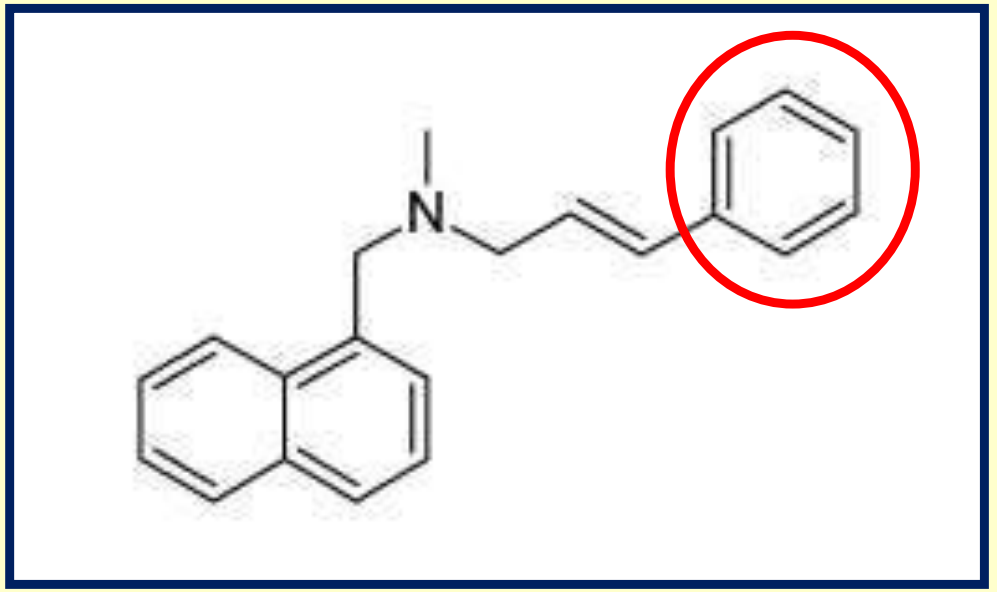
Inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol , and lead to accumulation of toxic amounts of squalene result in the death of the fungal cell



Antifungal agents: Allylamine

Naftifine

The first drug of this class



Only in topical preparations

against various tinea infections of the skin

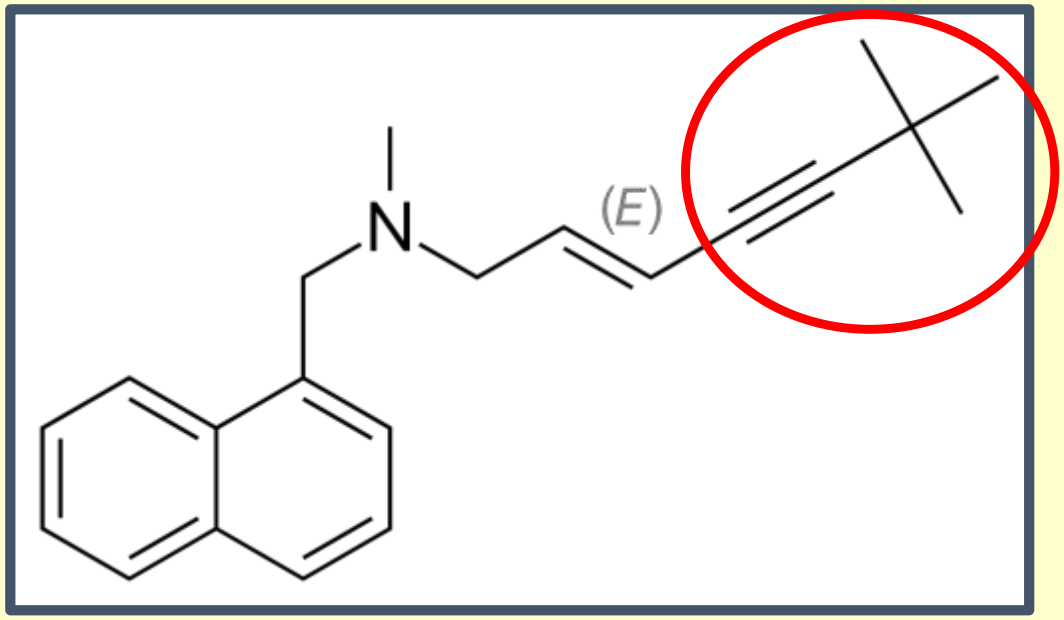
Antifungal agents: Allylamine

Terbinafine (Lamisil)

Synthetic analog of naftifine

Tert-butyl acetylene substitution

Increase oral efficacy 10 to 100 times the in vitro activity of naftifine



Effective topically or systemically for nail infection (Onychomycoses)

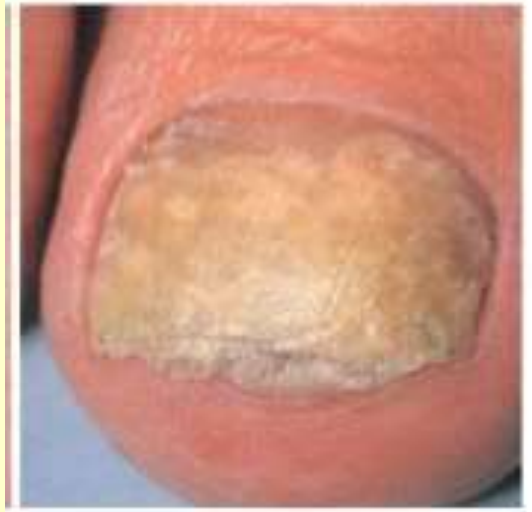
Antifungal effect of Candida

Antifungal agents: Allylamine

Terbinafine (Lamisil)

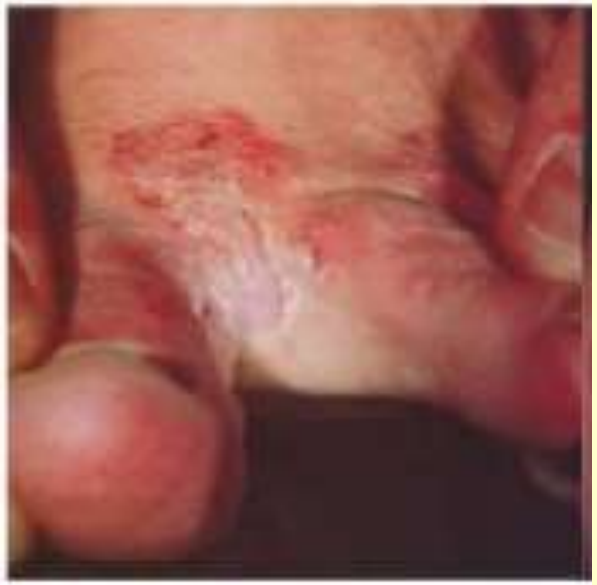
Oral terbinafine is the drug of choice for treating dermatophyte onychomycoses
(Fungal infections of nails, therapy requires 3 months)
Given orally, the highly lipophilic drug redistributes from the plasma into the nail bed and into the nail itself.

Topical terbinafine (1% cream, gel or solution) is used to treat tinea pedis, tinea corporis (ringworm), and tinea cruris (infection of the groin). Duration of treatment is usually 1 week

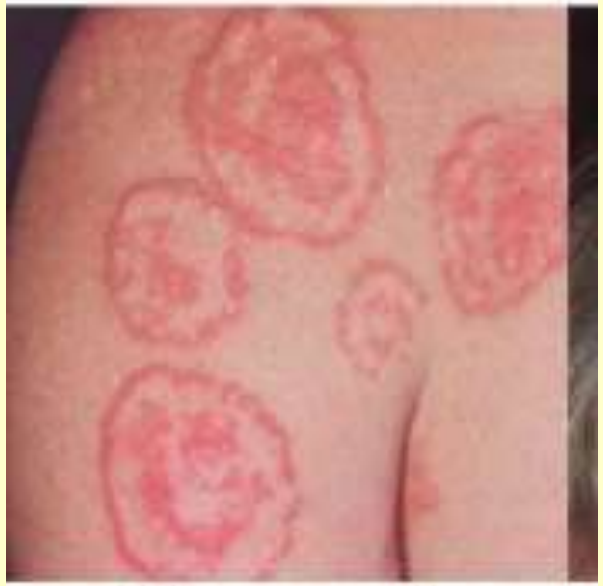


Tinea unguium

Tinea capitis



Tinea pedis



Tinea corporis

Antifungal agents: Allylamine

Terbinafine (Lamisil)

Terbinafine is available for oral and topical administration

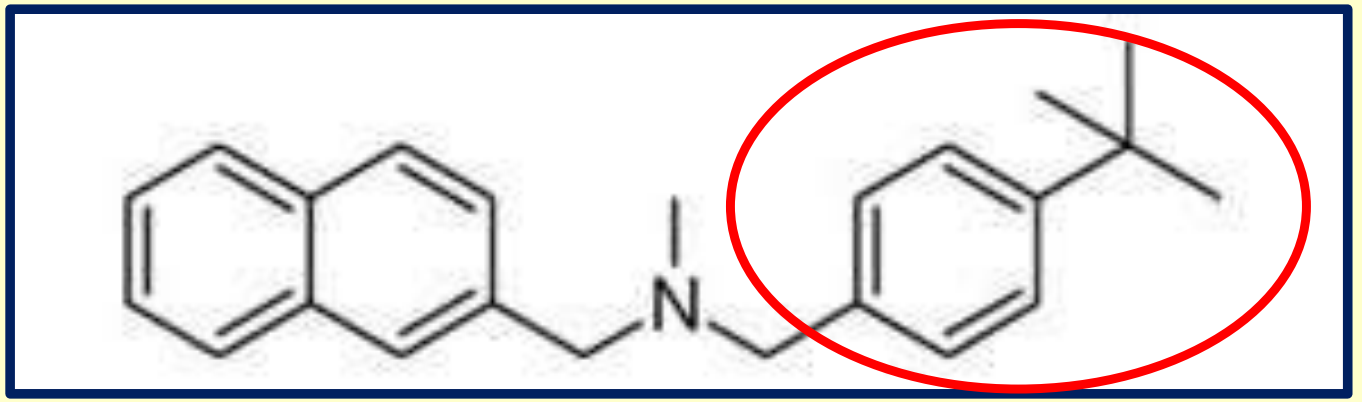
Bioavailability is only 40% due to first-pass metabolism.

It is highly protein bound and is deposited in the skin, nails, and adipose tissue.

It accumulates in breast milk

Antifungal agents: Allylamine

Butenafine



Synthetic benzylamine antifungal agent.

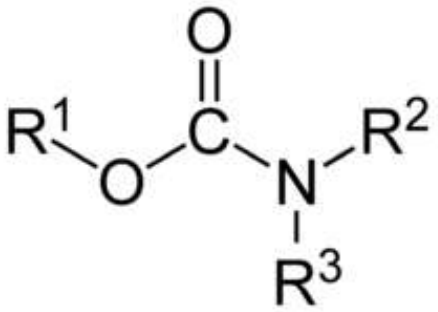
Mechanism of action: Inhibit the activity of the squalene epoxidase enzyme

Mainly active against dermatophyte

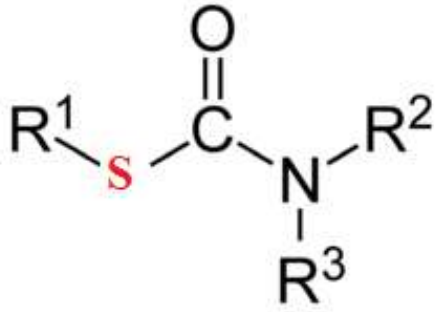
Superior fungicidal activity against dermatophyte when compared to that of terbinafine, naftifine, tolnaftate

Antifungal agents: Allylamine

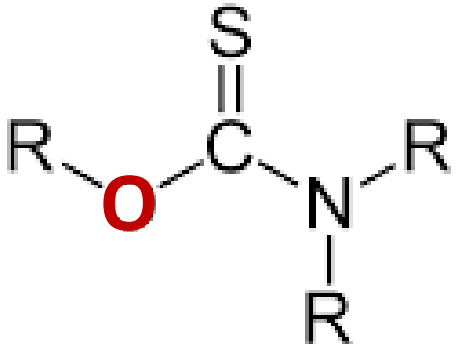
Tolnaftate



Carbamate



S-Thiocarbamate



O-Thiocarbamate

A thioester of β-naphthol. (O-thiocarbamate)

Inhibitor of squalene epoxidase

Classified with allylamine

Antifungal agents: Allylamine

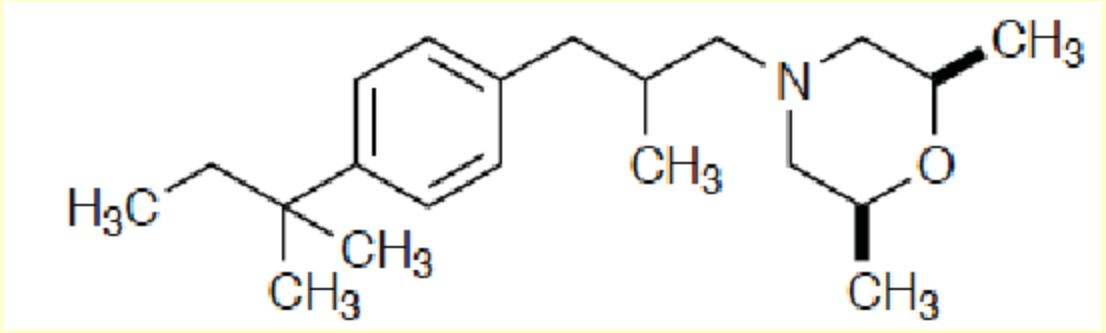
Tolnaftate

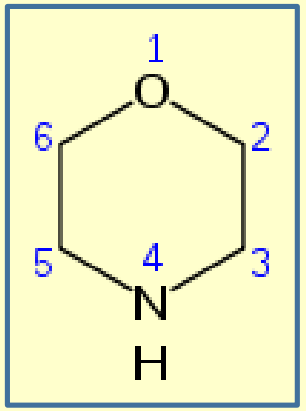
Tolnaftate is available in 1% creams, powders, and solutions

Treatment of ringworm, jock itch, and athlete's foot

Tolnaftate is used to treat tinea pedis, tinea cruris, and tinea corporis

Antifungal agents: Morpholines





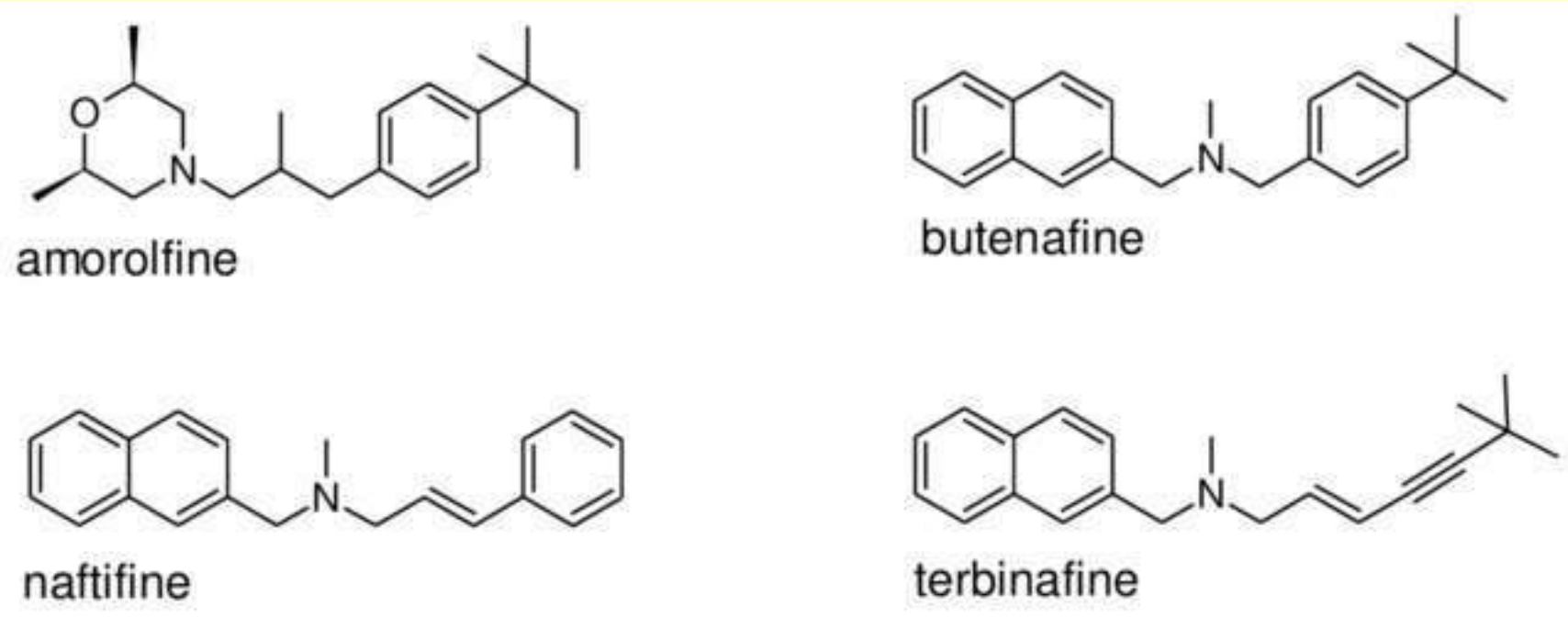
Amorolfine

Morpholine antifungals inhibit ergosterol biosynthesis by acting on the enzymes Δ^{14}- reductase and Δ^{8},Δ^{7-} isomerase

Antifungal agents: Morpholines

Amorolfine is the only drug in this class that is employed clinically in the treatment of dermatophytic infections **topically**.

Disrupt fungal cell membrane



Antifungal agents: Targets

Mechanism of action of Antifungal agents

1] Disrupt fungal cell membrane

Polyenes : Amphotericin B, Nystatin, Natamycin

Azoles: **Imidazole** (Ketoconazole, Miconazole, Clotrimazole)
Triazole (Fluconazole, Itraconazole, Voriconazole, posaconazole)

Allylamines: Terbinafine, Naftifine, Butenafine, Tolnaftate

Morpholine: Amorolfine

Antifungal agents
Part 3

Dr. Mai Ramadan

Antifungal agents: Targets

Mechanism of action of Antifungal agents

✓ **Disrupt fungal cell membrane**

Polyenes / Azoles / Allylamines / Morpholine

- **Inhibit cell wall synthesis:** Echinocandins e.g. Caspofungin
- **Inhibit mitosis:** Gresiofulvin
- **Inhibit DNA synthesis**: Flucytosine
- **Miscellaneous:** Ciclopirox

Antifungal agents: *Echinocandins*

- Echinocandins, a group of cyclic peptides with long lipophilic side chains.
- Discovered serendipitously
- During fermentation process, some metabolites were found to inhibit Candida sp., and they were named Echinocandins.
- The echinocandins have **potent activity against Aspergillus and most Candida species**, including those species resistant to azoles.

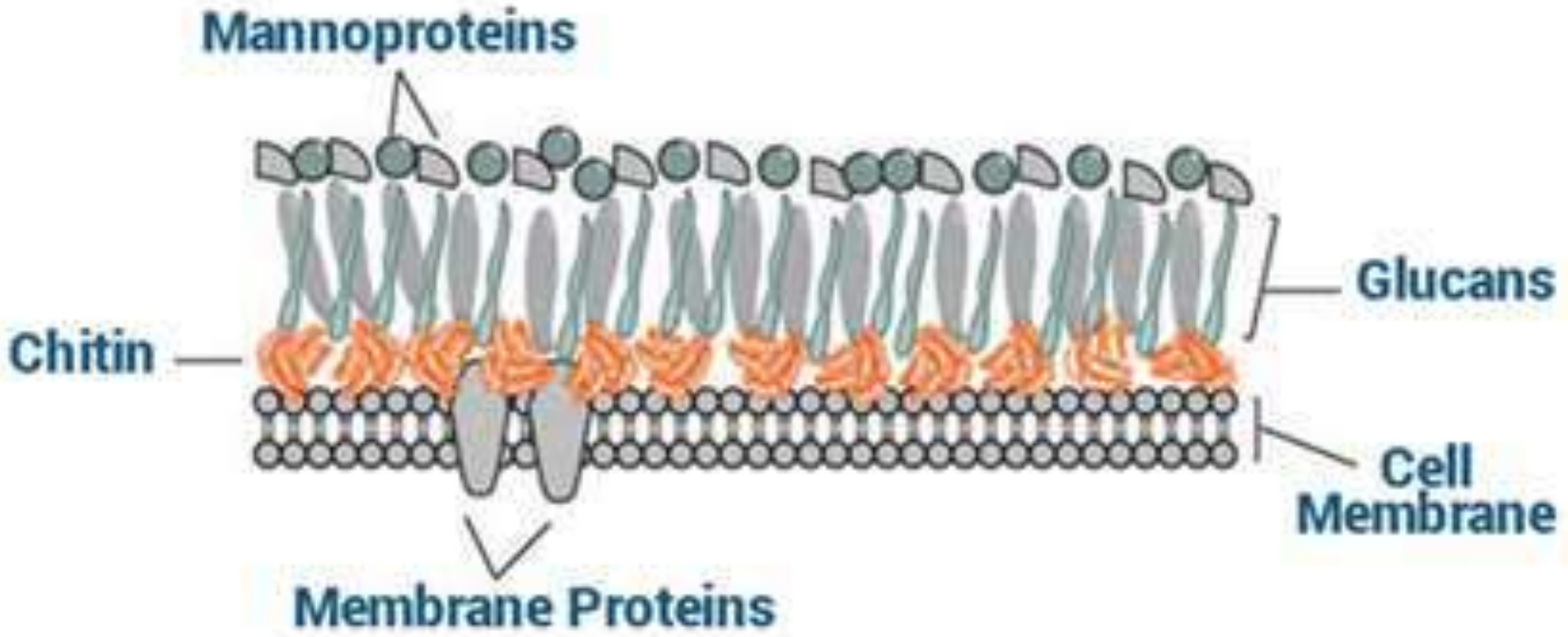
Antifungal agents: *Echinocandins*

❑ **Mechanism of action: Inhibitors of Cell Wall Biosynthesis**

Inhibit enzyme β-1,3-glucan synthase via noncompetitive inhibition of the enzyme 1,3-β glucan synthase and are thus called "penicillin of antifungals“ resulting in the inhibition of cell wall, leading to lysis and death.

β-Glucan is an important polymer component of many fungal cell wall.

Fungal Cell Wall



Antifungal agents: *Echinocandins*

- One of the first echinocandins, discovered in 1974, echinocandin B, could not be used clinically due to risk of high degree of hemolysis.

- Example: Caspofungin, micafungin, and anidulafungin are semisynthetic echinocandin derivatives with clinical use due to their solubility, antifungal spectrum, and pharmacokinetic properties

- **Advantages of echinocandins:**

Broad range (especially against all Candida)

Can be used in case of azole-resistant Candida or use as a second-line agent for refractory aspergillosis

Long half-life

Antifungal agents: *Echinocandins*

❑ Pharmacokinetics

Due to the large molecular weight of echinocandins, they have poor oral bioavailability and are administered by intravenous infusion. **Orally inactive**, IV administered

In addition, their large structures limit penetration into cerebrospinal fluid, urine, and eyes.

In plasma, echinocandins have a high affinity to serum protein

Echinocandins **do not have interactions with CYP450** or **P-glycoprotein pumps. (Minimal drug interaction)**

Antifungal agents: *Echinocandins*

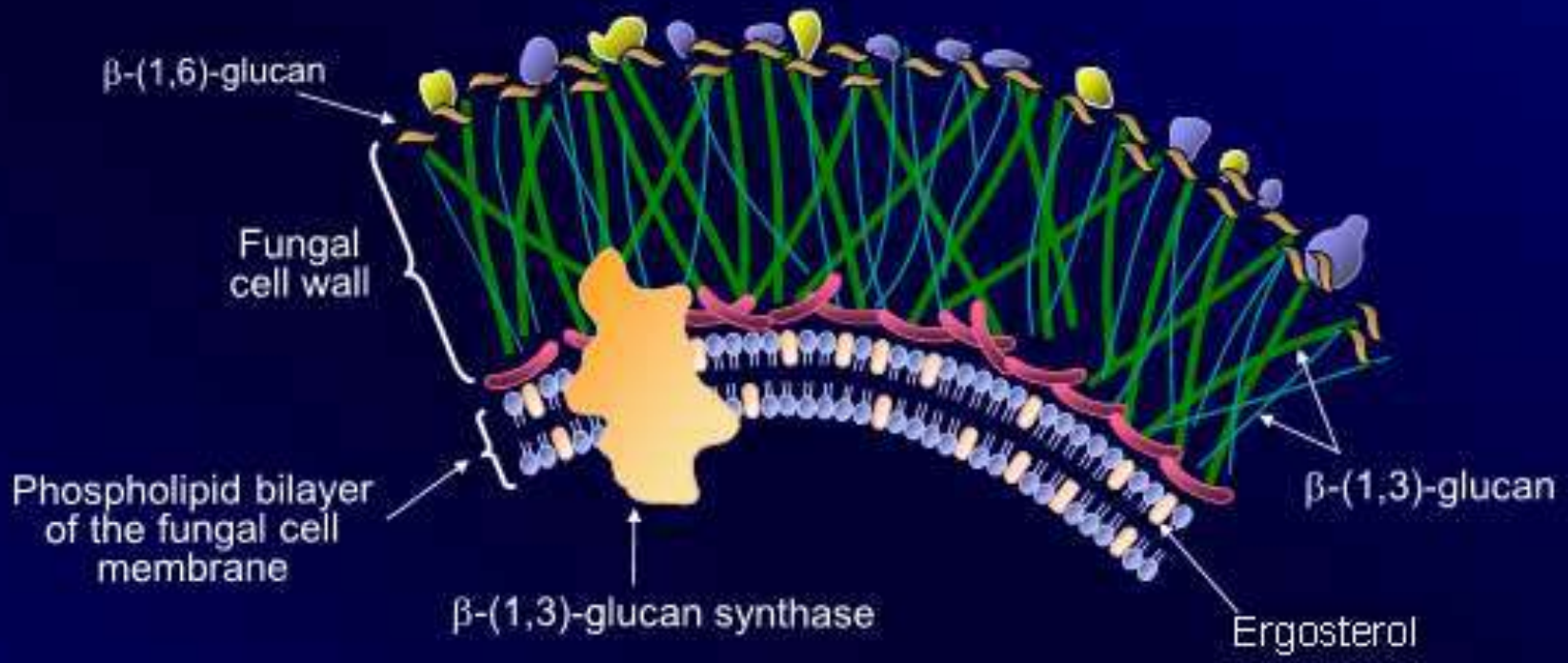
❑ **Chemistry:**

Lipopeptide in nature, consisting of large cyclic (hexa)peptide.

Caspofungin, micafungin, and anidulafungin are similar cyclic hexapeptide structures linked to long modified N-linked acyl fatty acid chains.

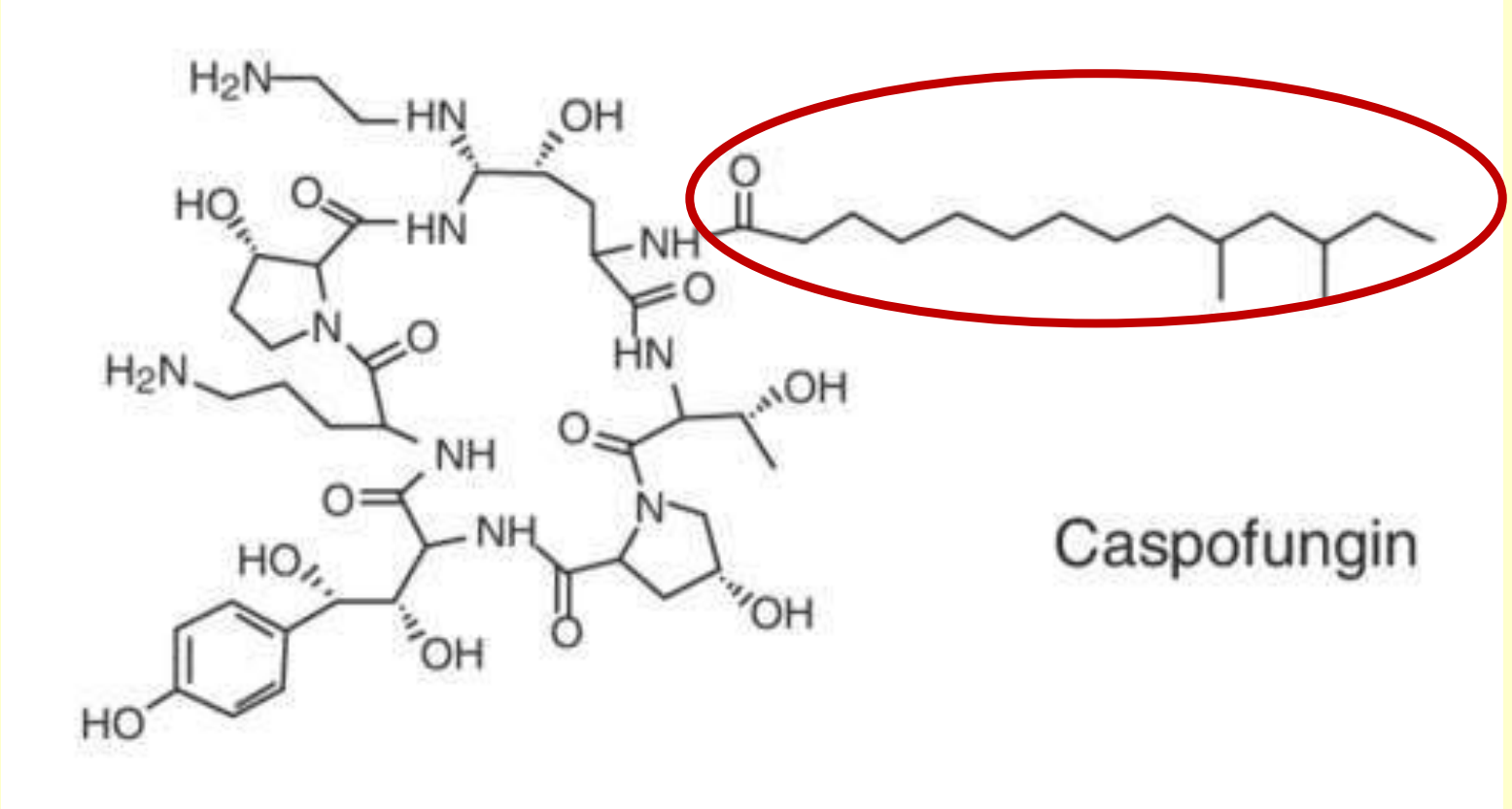
The chains act as anchors on the fungal cell membrane to help facilitate antifungal activity Chemistry

Caspofungin: Mechanism of Action

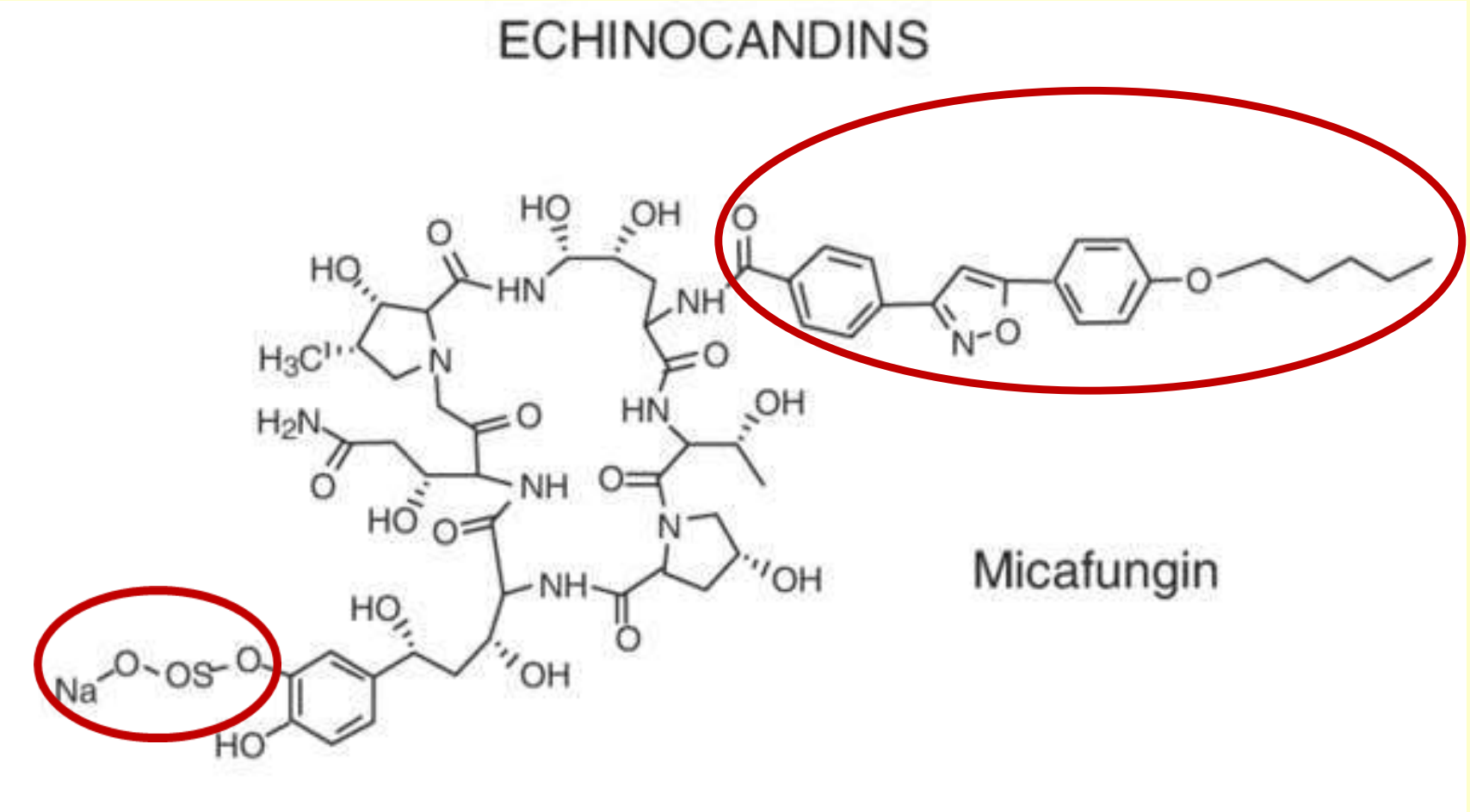


- Caspofungin specifically inhibits beta (1-3)-D-glucan synthesis, essential to the cell-wall integrity of many fungi, including *Aspergillus* and *Candida* spp, thereby compromising the integrity
- As a result, the fungal cell wall becomes permeable, and cell lysis
- Beta (1-3)-D-glucan synthesis does not occur in human cells

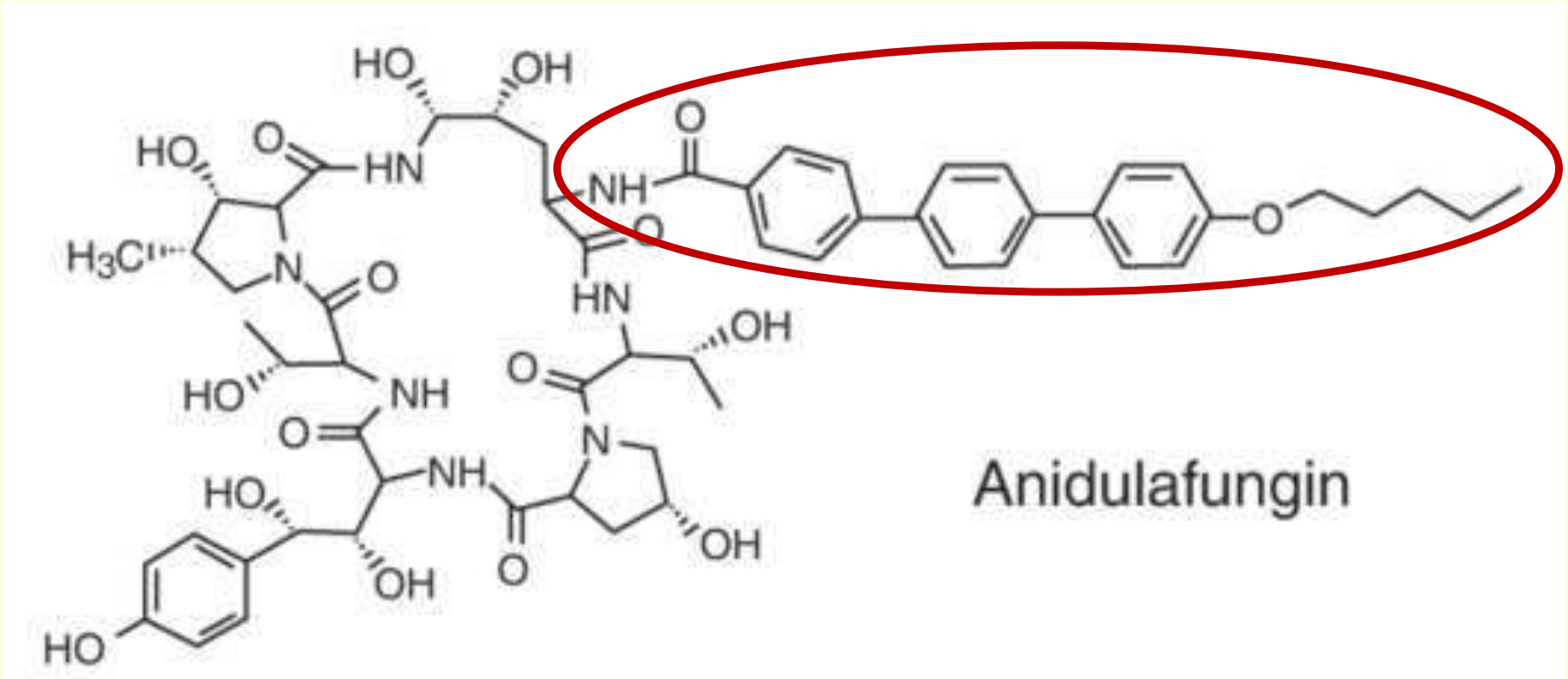
Antifungal agents: *Echinocandins*



Antifungal agents: *Echinocandins*



Antifungal agents: *Echinocandins*



Antifungal agents: *Echinocandins*

Caspofungin

First-line option for patients with invasive candidiasis, including candidemia,

Second-line option for invasive aspergillosis in patients who have failed or cannot tolerate amphotericin B or an azole.

Micafungin and Anidulafungin:

First-line options for the treatment of invasive candidiasis, including candidemia.

Micafungin is also indicated for the prophylaxis of invasive Candida infections in patients who are undergoing hematopoietic stem cell transplantation

Antifungal agents: Griseofulvin

Produced by a strain of Penicillium

Effective against dermatophytes

A spiro compound

Griseofulvin

Orally to treat superfacial infection fingernail and toenail infections.
It does not penetrate skin or nails if used topically

Mechanism of action:
Inhibition of fungal mitosis. (fungistatic)

MECHANISM OF ACTION

GRISEOFULVIN

↓ Binds to

Tubulins

↓ inhibiting

Mitotic spindle formation

↓ Resulting in

Inhibition of separation of daughter nuclei

↓

FUNGISTATIC EFFECT

Antifungal agents: Griseofulvin

Pharmacokinetics

Well absorbed orally

Absorption is enhanced in the presence of lipophilic substances

Accumulation is enhanced in tissues made up of keratin such as skin, nails, and hair

Can prevent further spread but cannot treat already infected keratinocytes **Fungistatic**

Antifungal agents: Griseofulvin

Indication

It has been largely replaced by oral terbinafine for the treatment of onychomycosis, although it is still used for dermatophytosis of the scalp and hair.

Griseofulvin is fungistatic and requires a long duration of treatment (for example, 6 to 12 months for onychomycosis).

Duration of therapy

The infection is cured when the diseased tissue is replaced by new, healthy skin and nails, which can take months.

Antifungal agents: Flucytosine

Flucytosine Antimetabolite, inhibit DNA synthesis

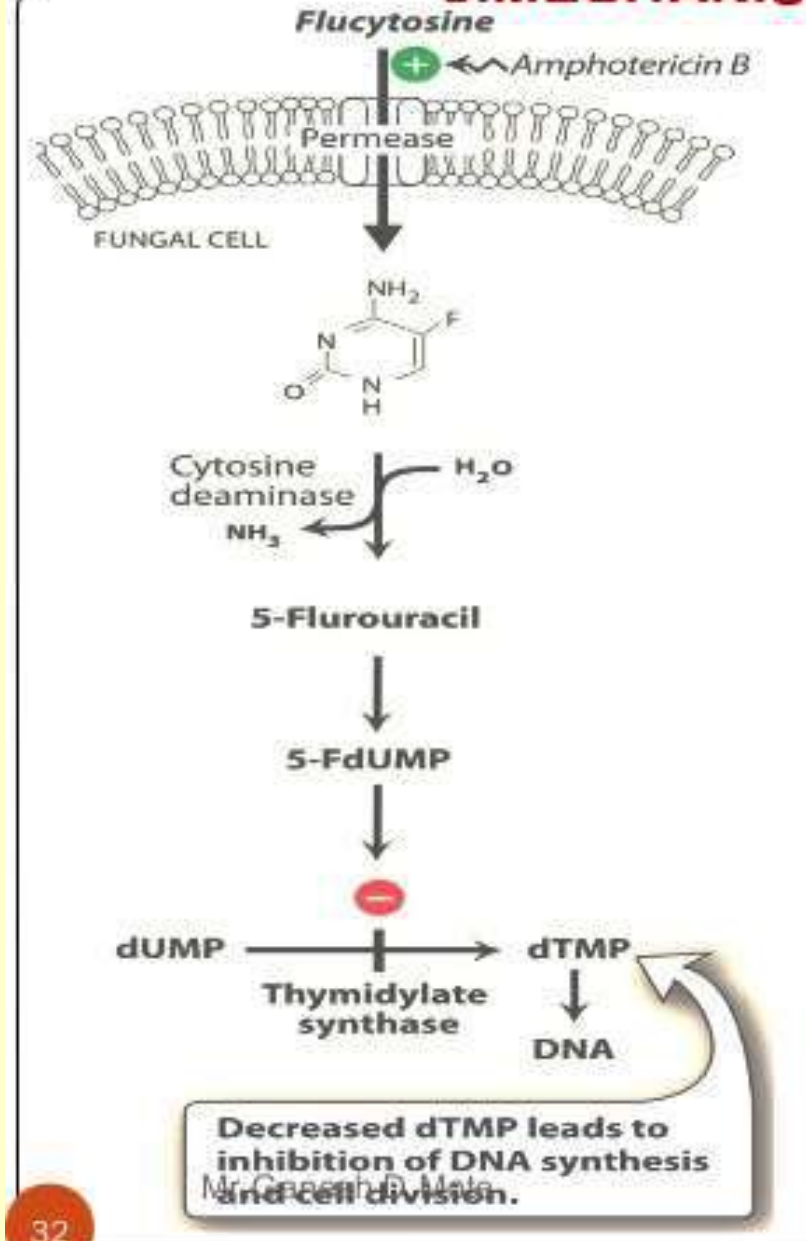
Enters fungal cells via a **cytosine-specific permease**, an enzyme not found in mammalian cells.

A pro-drug

Metabolized to 5-fluorouracil (5-FU) by **fungal** cytidine deaminase., then converted by a series of steps to 5-fluorodeoxyuridine 5'-monophosphate.

This false nucleotide inhibits thymidylate synthase, thus depriving the organism of thymidylic acid an essential DNA component.

9.MECHANISM OF FLUCYTOSINE



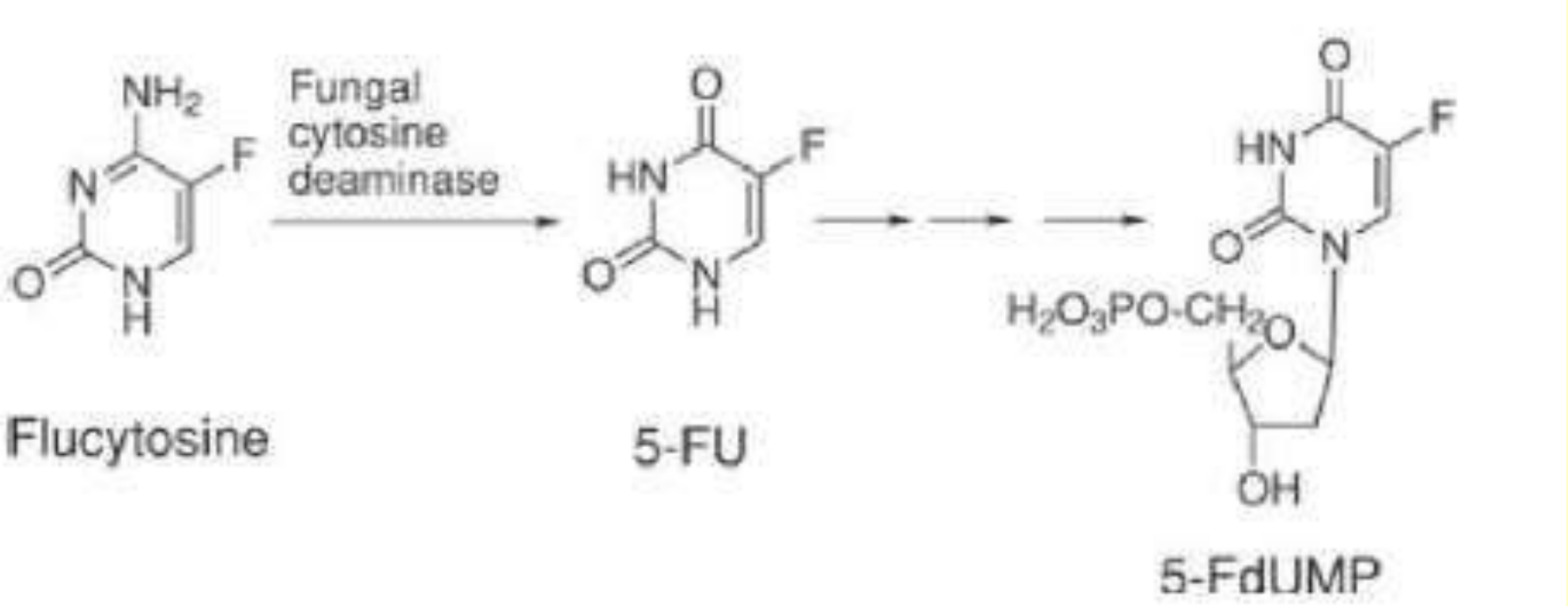
Flucytosine enters fungal cells via a cytosine-specific permease an enzyme not found in mammalian cells.

Flucytosine is then converted by a series of steps to 5-fluorodeoxyuridine 5'-monophosphate.

This false nucleotide **inhibits thymidylate synthase, thus depriving the organism of thymidylic acid an essential DNA component.**

Note: [Amphotericin B increases cell permeability, allowing more 5-FC to penetrate the cell. Thus, 5-FC and amphotericin B are synergistic.]

Antifungal agents: Flucytosine



Flucytosine, a pro-drug, is converted by fungal cytosine deaminase to 5-fluorouracil (5-FU). This reaction does not occur in mammalian cells. A further transformation of 5-FU to the actual cytotoxic agent, 5-fluorodeoxyuridine monophosphate (5-FdUMP), also occurs.

Antifungal agents: Miscellaneous

Ciclopirox

Mechanism of action:

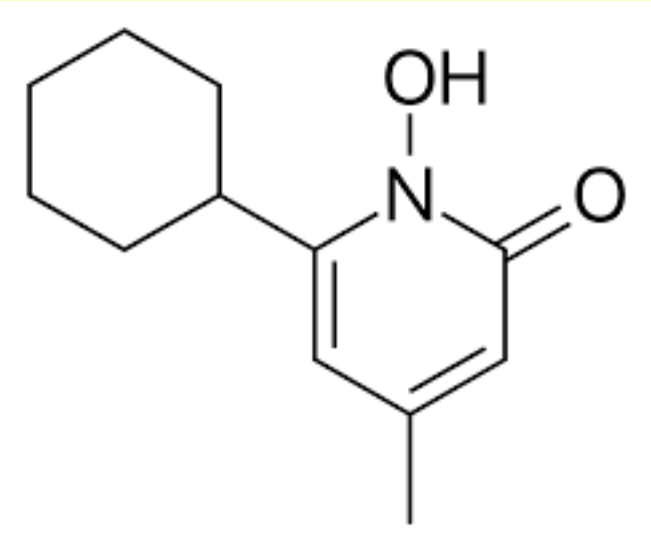
Ciclopirox is thought to act through the chelation of polyvalent metal cations, such as Fe^{3+} and Al^{3+}. These ions are incorporated in function of important enzymes, including cytochromes. Thus, disrupting cellular activities such as mitochondrial electron transport processes and energy production.

Ciclopirox also appears to modify the plasma membrane of fungi, resulting in the disorganization of internal structures.

Ciclopirox may exert its effect by disrupting DNA repair, cell division signals and structures (mitotic spindles) as well as some elements of intracellular transport.

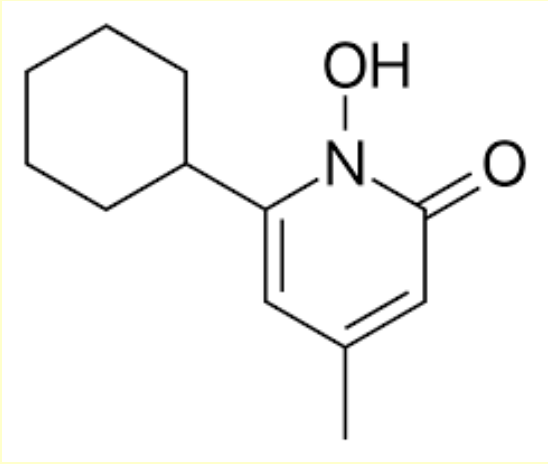
Antifungal agents: Miscellaneous

Ciclopirox



Antifungal agents: Miscellaneous

Ciclopirox



Ciclopirox 1% shampoo is used for treatment of seborrheic dermatitis.

Tinea pedis, tinea corporis, tinea cruris, cutaneous candidiasis, and tinea versicolor may be treated with the 0.77% cream, gel, or suspension.