Lecture 7

Pharmaceutical Chemistry

Antibacterial - Antibiotics

Antifungal drugs

AL-Mustaqbal University

Faculty of Pharmacy

- An **Antifungal medication**, also known as an **Antimycotic medication:**
- is a pharmaceutical fungicide or fungistatic used to treat and prevent mycosis such as athlete's foot, ringworm, candidiasis (thrush), serious systemic infections such as cryptococcal meningitis, and others.
- Such drugs are usually obtained by doctor's prescription, but a few are available over the counter (OTC).
- The evolution of antifungal resistance is a growing threat to health globally.

الرياضيين

Antifungal Drugs

Fungi are traditionally important in plant pathology. They have gained much importance for **causing serious human diseases**, mainly due to indiscriminate use of suppressive immunotherapy. So development of antifungal is gaining importance.

Fungal infections are usually **more difficult to treat than bacterial infections,** because fungal organisms grow slowly and because fungal infections often occur in tissues that are poorly penetrated by antimicrobial agents (e.g., devitalized or a vascular tissues).

Therapy of fungal infections usually requires prolonged treatment

Classification of antifungal drugs

1. **Anti fungals damaging permeability of the cell membrane**

Imidazoles: Bifonazole, Clotrimazole, Econazole, Ketoconazole, Miconazole

Triazoles: Fluconazole, Itraconazole, Voriconazole

Allylamines: Terbinafine, Naftifine

Thiocarbamates: Tolciclate, Tolnaftate

Substituted pyridones: Ciclopirox

Polyene antibiotics: Amphotericin B, Nystatin

II. Antifungals inhibiting chitin synthesis in the cell wall

Caspofungin, Griseofulvin

III. Antifungals inhibiting synthesis of nucleic acids

Flucytosine

Biochemical targets for antifungal chemotherapy

Mechanism of action

There are three general mechanisms of action for the antifungal agents:

A. cell membrane disruption.

B. inhibition of cell division .

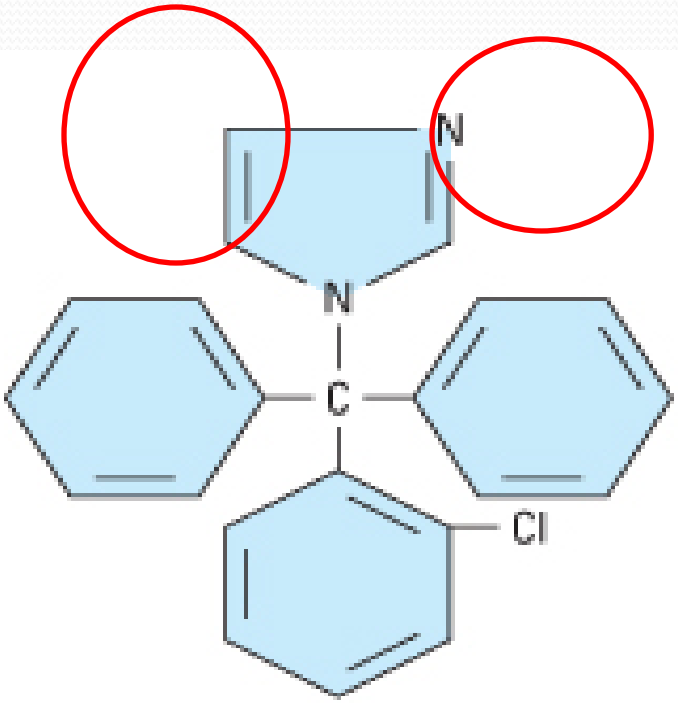
C. inhibition of cell wall formation.

Antifungal azoles

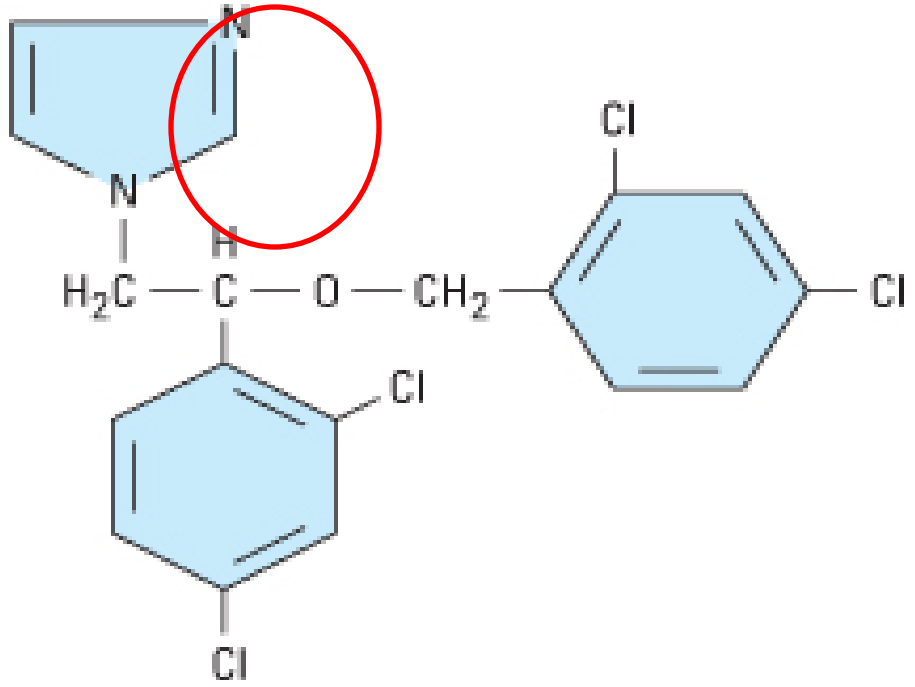
Antifungal Azoles are
i-synthetic drugs with
Ii-broad-spectrum
Iii-fungistatic activity.
Azoles can be divided into two groups: **the older**
a - **imidazole agents**
(clotrimazole, ketoconazole, miconazole) in which the five-member azole nucleus contains two nitrogens
b - and **the newer triazole compounds**
(fluconazole, itraconazole, and voriconazole)in which the azole nucleus contains three nitrogens.

The azoles tend to be effective against most fungi that cause superficial infections of the skin and mucous membranes.

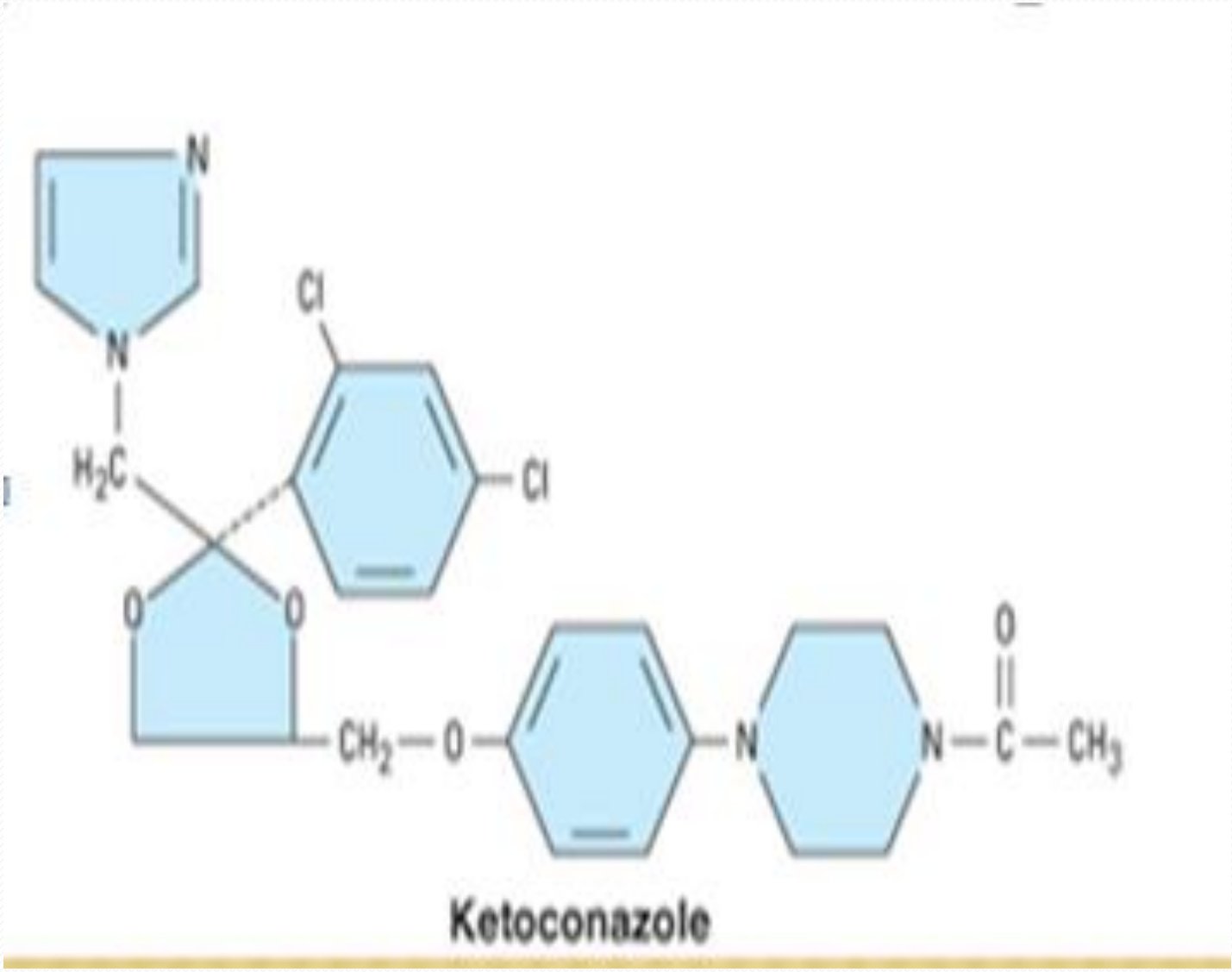
imidazole agents



Clotrimazole



Miconazole



Ketoconazole

Canesten

More details

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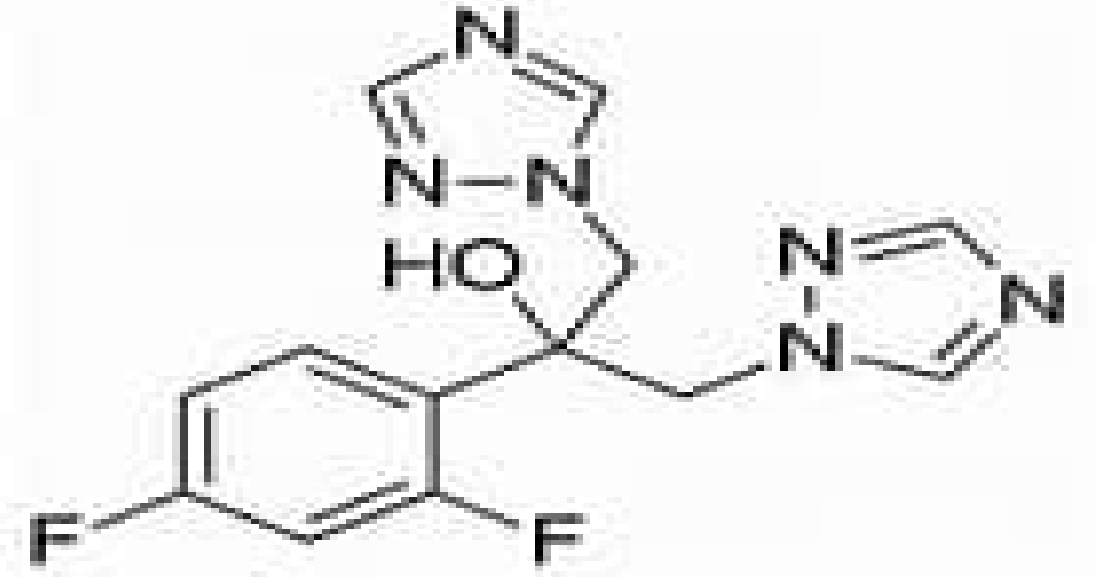
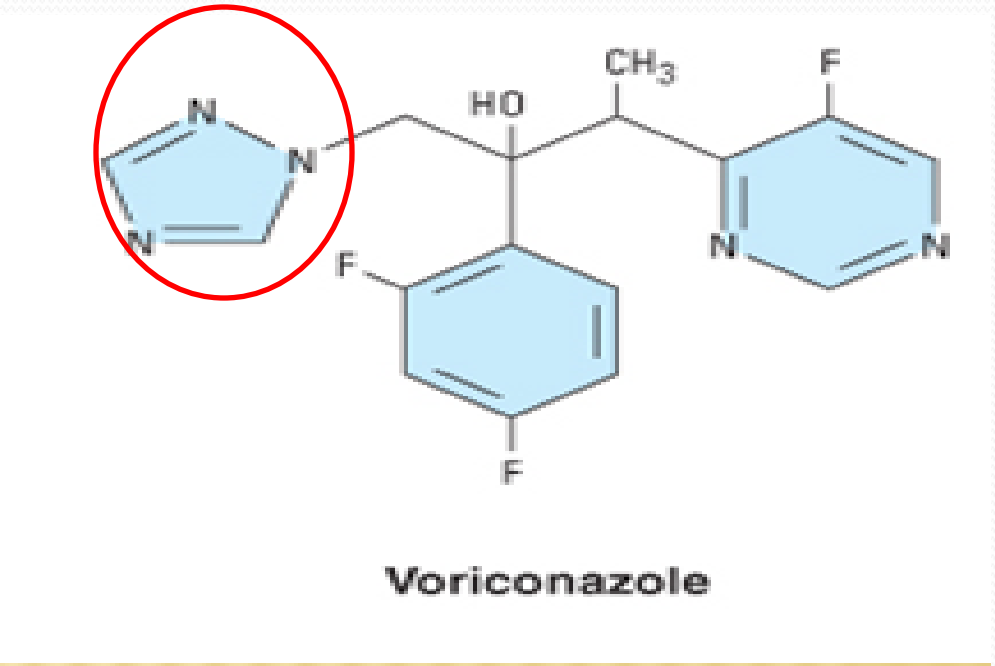
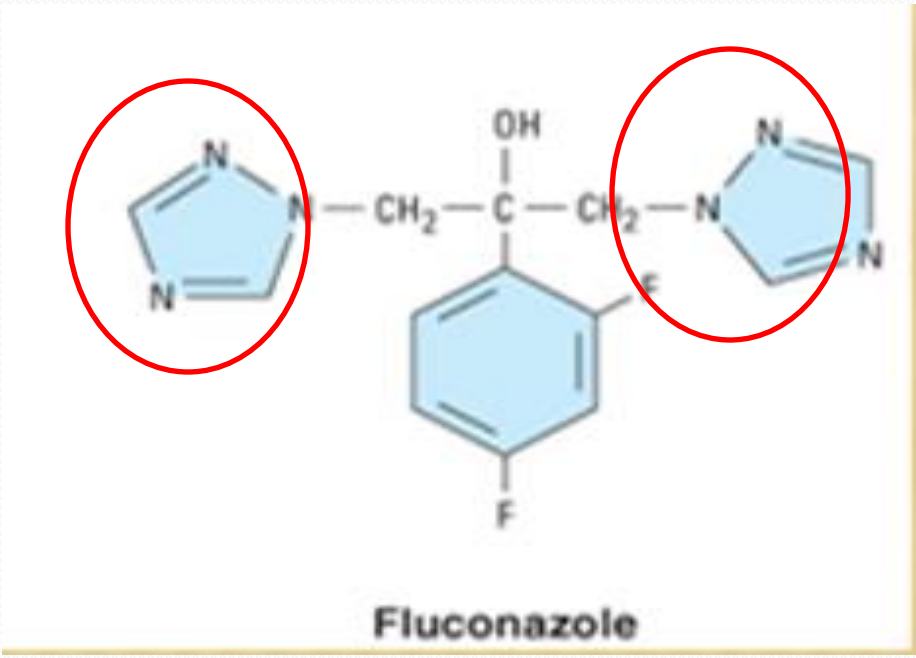
FLUCONAZOLE
150 mg CAPSULES
Single Dose
1 Capsule
FLUCONAZOLE
150 mg CAPSULES
Relief From Thrush
1
Capsule
BRISTOL


N
N–N
HO
N
N
N
F
F

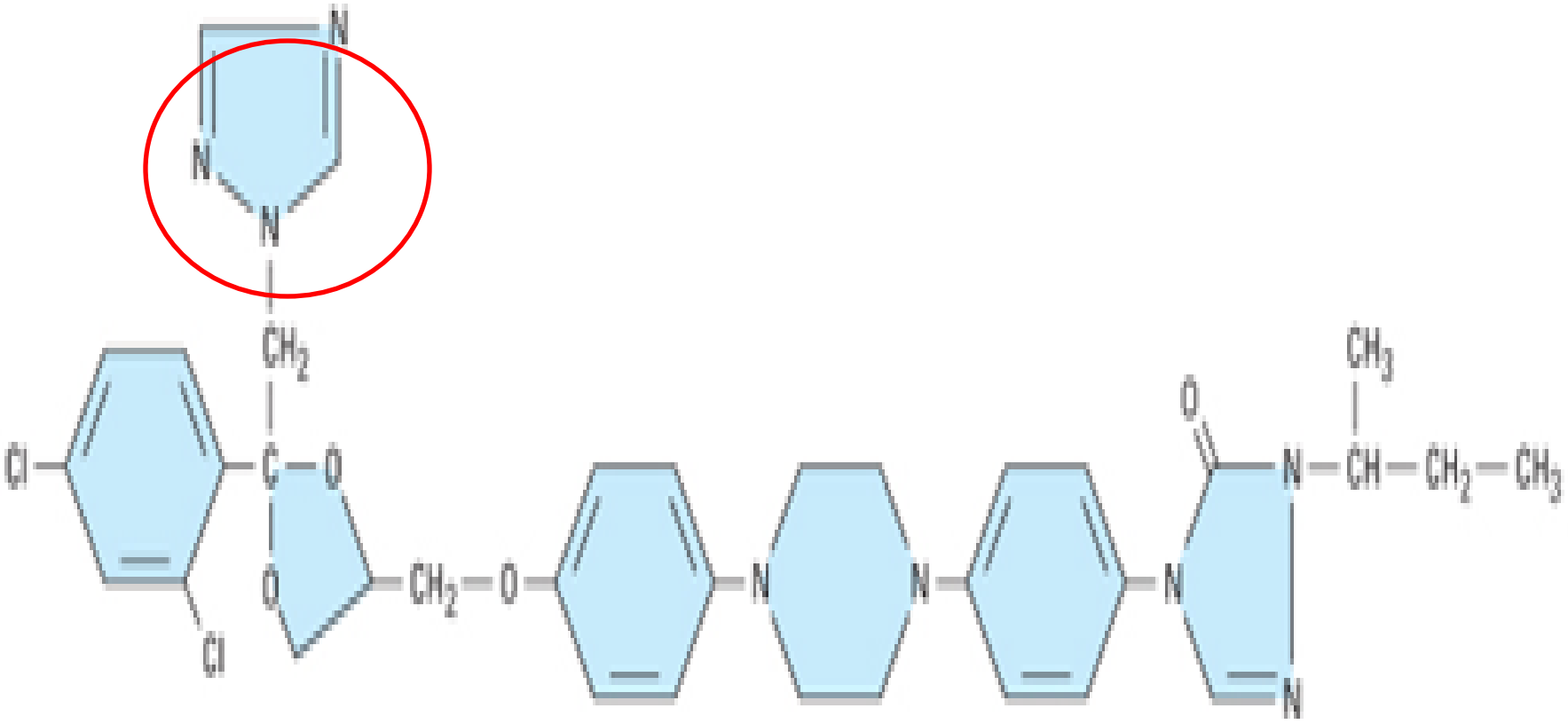
Triazole compounds



Voriconazole



Fluconazole



Itraconazole

All azoles exert antifungal activity by **inhibiting cytochrome P450 enzymes** responsible for the demethylation of lanosterol to ergosterol.

Reduced fungal membrane ergosterol concentrations result in **damaged, leaky cell membranes**.

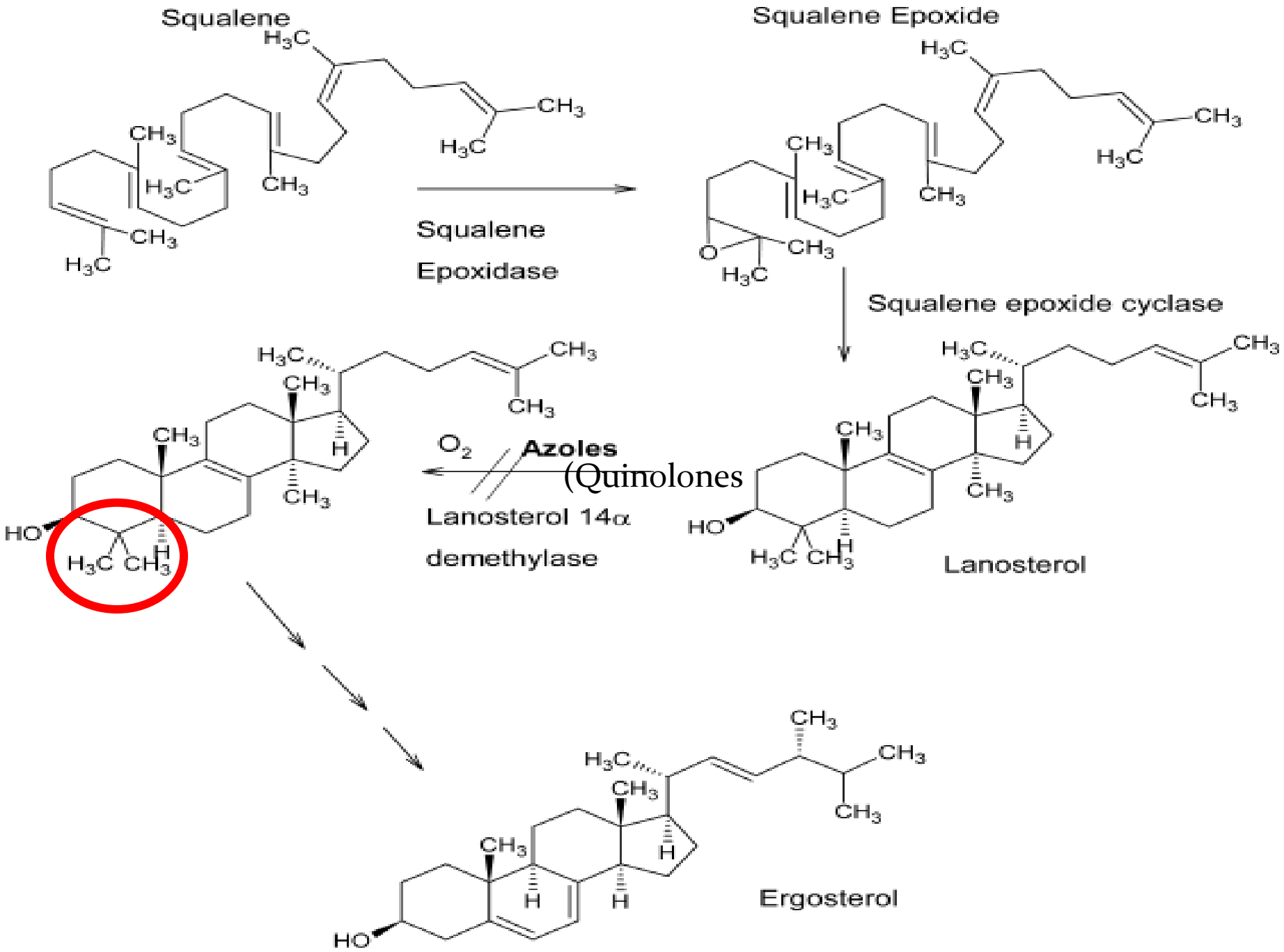
The toxicity of these drugs depends on their relative affinities for mammalian and fungal cytochrome P450 enzymes.

The fungicidal effect is clearly associated with **damage to the cell membrane,** with the loss of essential cellular components such as potassium ions and amino acids.

The fungistatic effect of the azoles at low concentration has been associated with **inhibition of membrane-bound enzymes.**

Cytochrome P450-class enzyme, lanosterol 14-demethylase, is the likely target for the azoles.

P450 possesses a heme moiety as part of its structure and the basic electron pairs of the azole rings can occupy a binding site on P450, preventing the enzyme from turning over. The function of lanosterol 14-demethylase is to oxidatively remove a methyl group from lanosterol during ergosterol biosynthesis. When demethylation is inhibited, the 14-sterol accumulates in the membrane, causing destabilization


Squalene
Squalene Epoxide
Squalene
Epoxidase
Squalene epoxide cyclase
O_2
Azoles
(Quinolones
Lanosterol 14α
demethylase
Lanosterol
Ergosterol

Structure–activity relationships

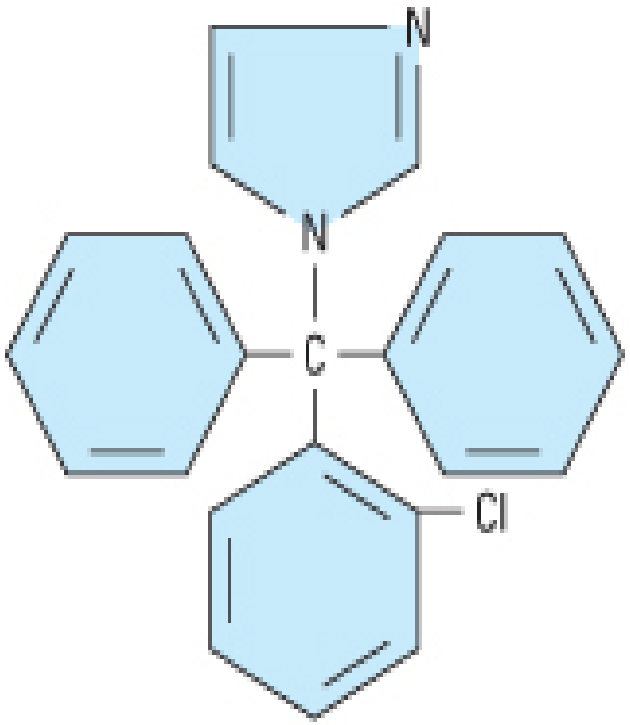
1. The basic structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pKa of 6.5–6.8) bonded by a nitrogen–carbon linkage to the rest of the structure.

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 to inhibit activation of molecular oxygen and prevent oxidation of steroidal substrates by the enzyme.

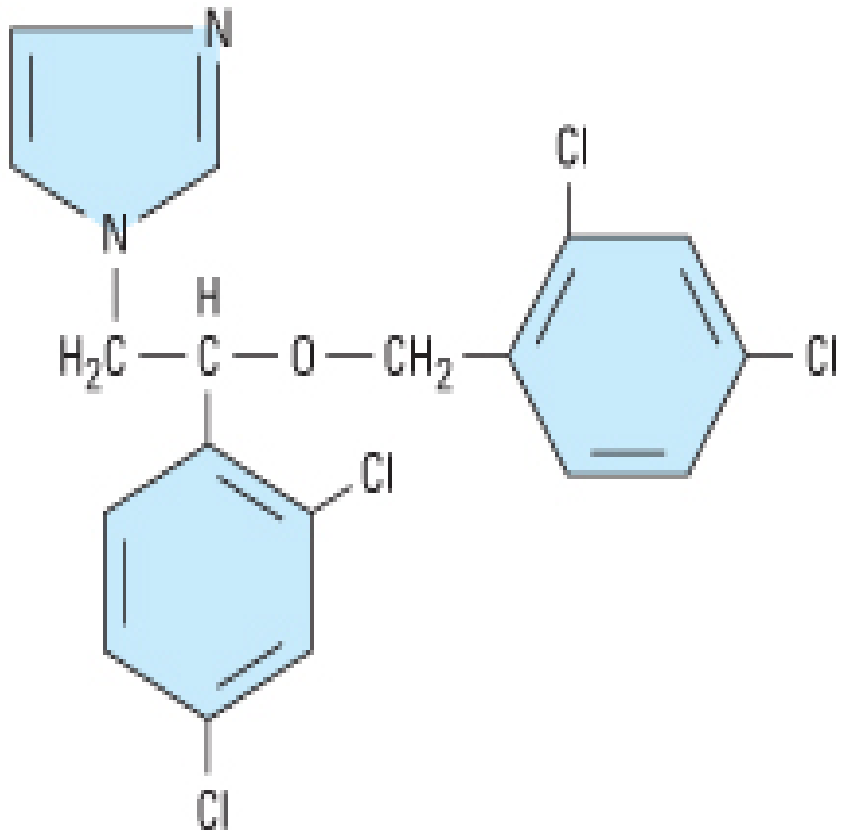
3.The most potent antifungal azoles possess two or three aromatic rings, at least one of which is halogen substituted (e.g., 2,4-dichlorophenyl, 4-chlorophenyl, 2,4-difluorophenyl), and other non polar functional groups. Only 2, and/or 2,4 substitution yields effective azole compounds.

4.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.

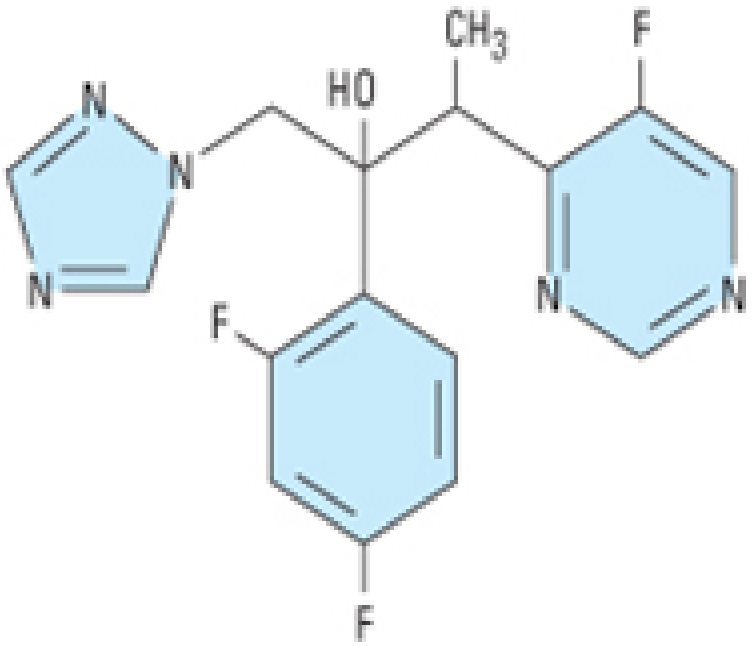
5.Substitution at other positions of the ring yields inactive compounds.



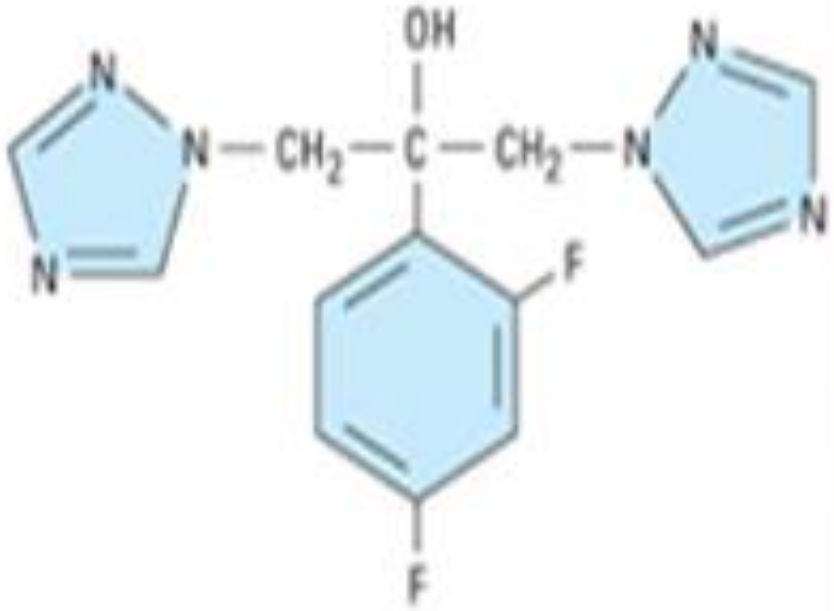
Clotrimazole



Miconazole



Voriconazole



Fluconazole

The triazoles **(second generation**) tend to have fewer side effects, better absorption, better drug distribution in body tissues, and fewer drug interactions.

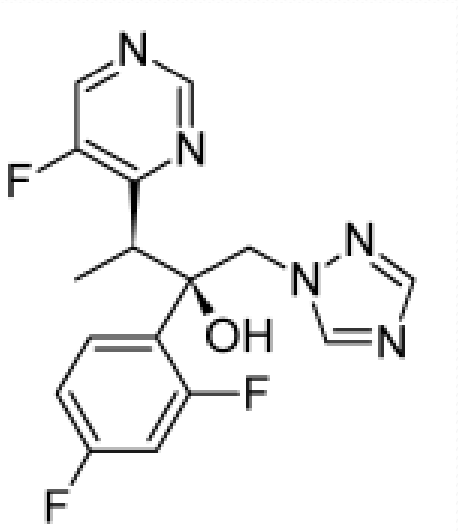
Fluconazole does not require an acidic environment, as does ketoconazole, for GI absorption.

Itraconazole is lipophilic and water insoluble and requires a low gastric pH for absorption.

Ketoconazole can be absorbed orally, but it requires an acidic gastric environment.

Clotrimazole is a broad-spectrum fungistatic imidazole drug used in the topical treatment of oral, skin, and vaginal infections with C. albicans.

A newer azole is **voriconazole**



Voriconazole has potent activity against a broad variety of fungi, including the clinically important pathogens.

Several publications have substantiated the use of voriconazole against some of the newer and rarer fungal pathogens.

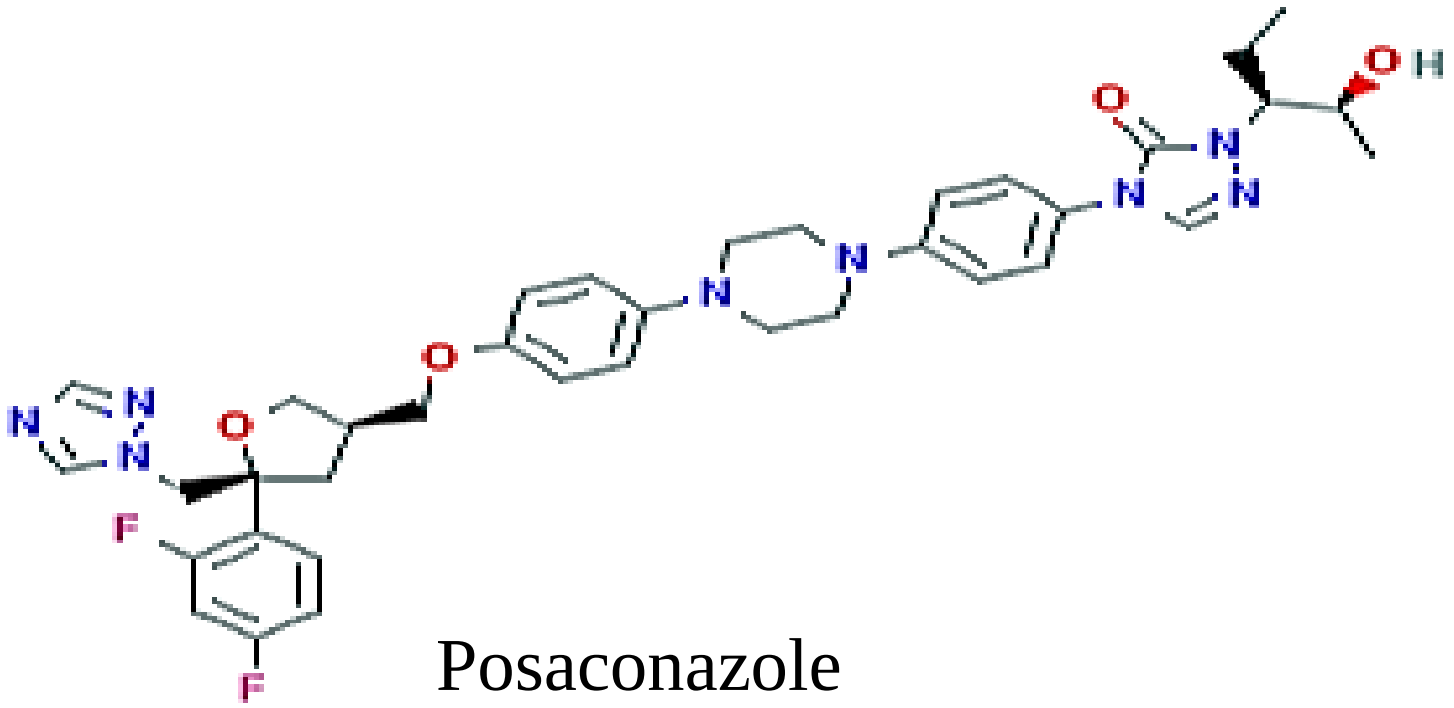
Voriconazole is more potent than itraconazole against Aspergillus spp. and is comparable to **posaconazole,** another azole that is in clinical trials, in its activity against C.albicans

Posaconazole

Posaconazole, sold under the brand names **Noxafi**l and Posanol, is **a triazole** antifungal medication

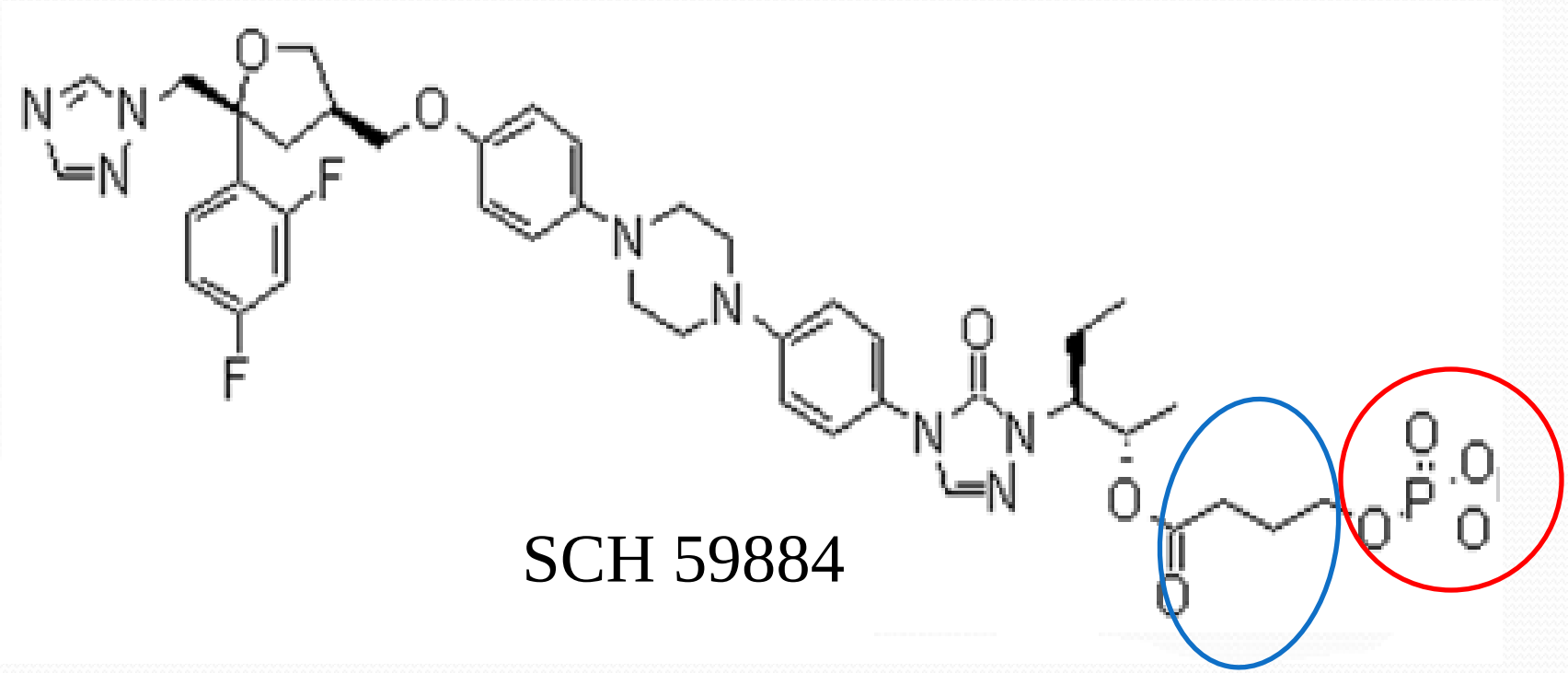
Posaconazole is a broad-spectrum, second generation, triazole compound with antifungal activity. Posaconazole strongly inhibits 14-alpha demethylase, a cytochrome P450-dependent enzyme. Inhibition of 14-alpha-demethylase prevents the conversion of lanosterol to ergosterol, an important component of the fungal cell wall. Inhibition of ergosterol synthesis changes the fungal cell membrane composition and integrity, alters membrane permeability and eventually leads to fungal cell lysis. Compared to other azole antifungals, posaconazole is a significantly more potent inhibitor of sterol 14-alpha demethylase.

Posaconazole is the newest triazole antifungal agent. It is structurally related to itraconazole and has activity against Candida species, Aspergillus species, Cryptococcus neoformans, the zygomycetes, and other filamentous fungi.



Posaconazole

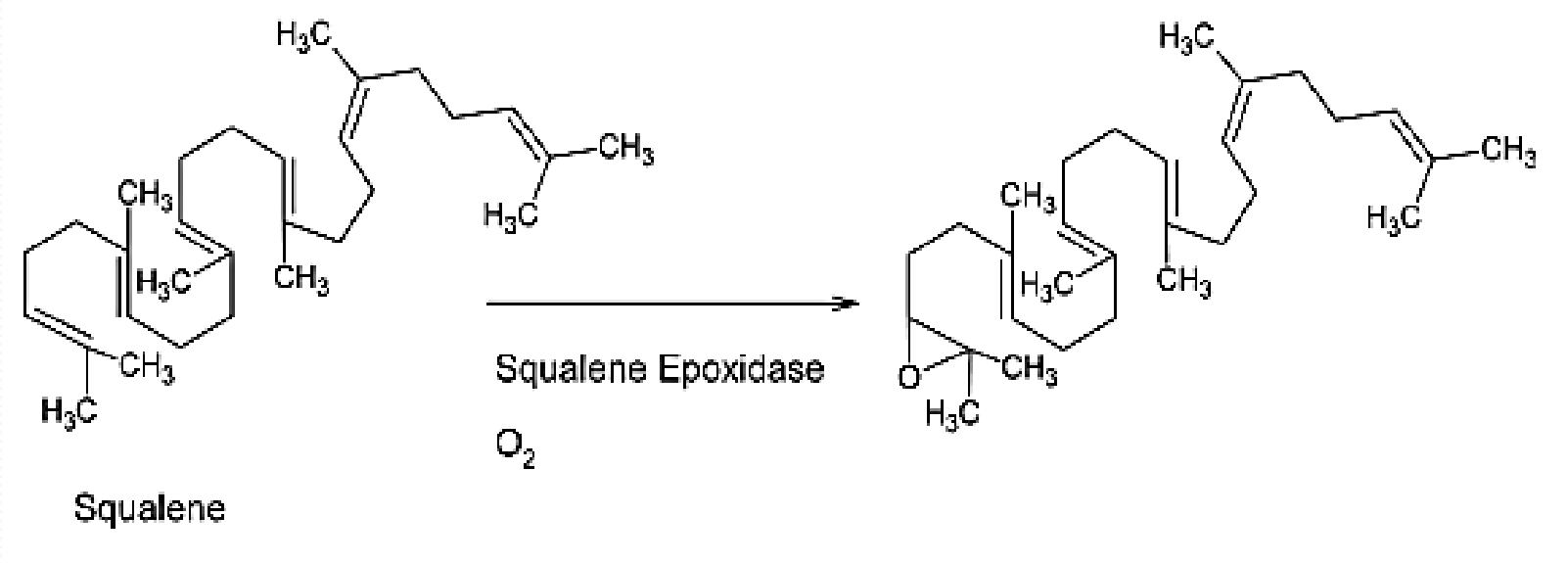
A search for potential prodrug forms of posaconazole has yielded a possible candidate, SCH 59884. The compound is inactive in vitro but is dephosphorylated in vivo to yield the active 4-hydroxy butyrate ester. This compound is hydrolyzed to the parent compound in the serum.



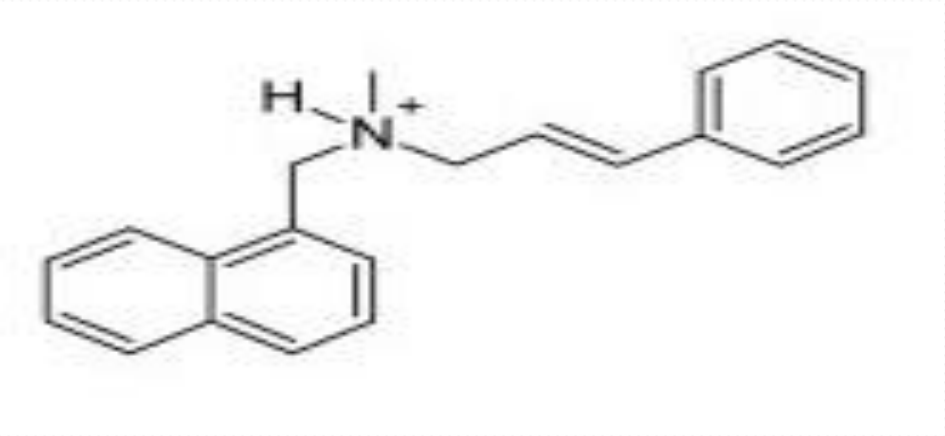
SCH 59884

Allylamines

Reversible noncompetitive **inhibitors of the fungal enzyme squalene monooxygenase**, which *converts squalene to lanosterol*.(first step in ergosterol biosynthesis). With a decrease in lanosterol production, ergosterol production is also diminished, affecting fungal cell membrane synthesis and function.

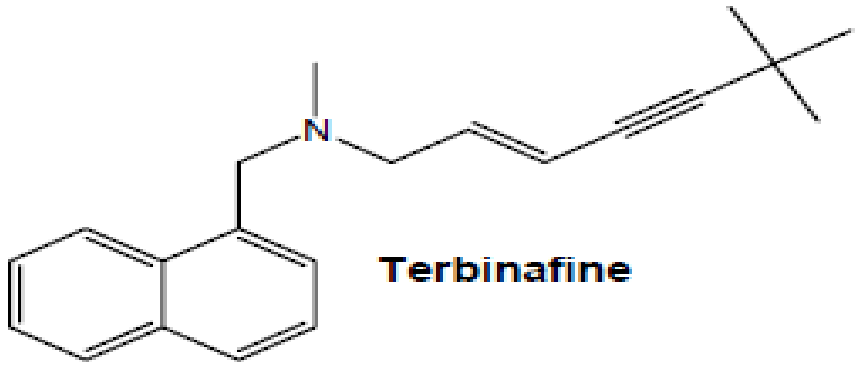


Naftifine is available **for topical use only** in the treatment of cutaneous dermatophyte and Candida infections.



Terbinafine (Lamisil®)

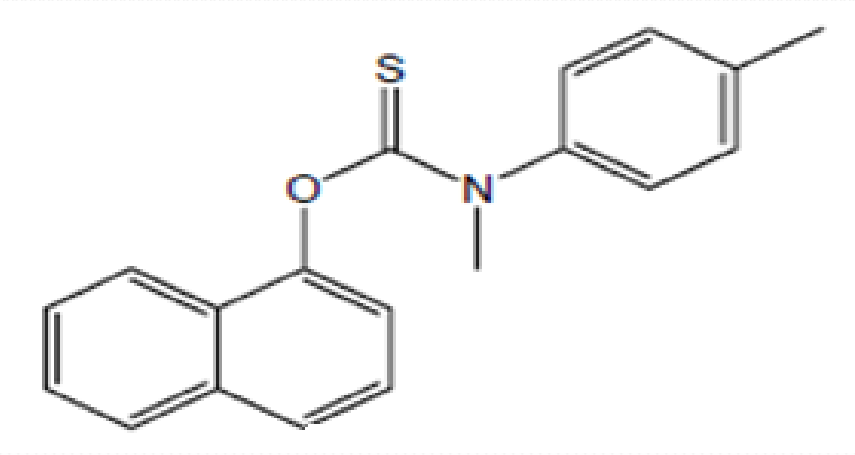
is available **for topical and systemic** use (oral tablet) in the treatment of dermatophyte skin and nail infections.



Thiocarbamates:

Tolnaftate :

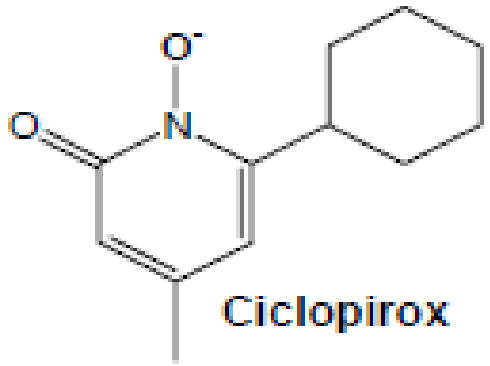
The compound, a thioester of β- naphthol, is **fungicidal a**gainst dermatophytes, such as Trichophyton, has been shown to act as an **inhibitor of squalene epoxidase** in susceptible fungi, so it is classified with the allylamine antimycotics.



Tolnaftate

Antifungals affecting cell membrane stability

Ciclopirox is a topical solution used to treat fungal infections of the nails and hair. It is a broad-spectrum antifungal medication that also has antibacterial and anti-inflammatory properties.



Ciclopirox

Mechanism of Action: Its main mode of action is thought to be its high affinity for trivalent cations, which inhibit essential co-factors in enzymes.

Ciclopirox is thought to act through the chelation of polyvalent metal cations, such as $Fe^{+3}$and Al^{+3} . These cations inhibit many enzymes, including cytochromes, possibly disrupting the biosynthesis of ergosterol.

Antifungal Antibiotics

The antifungal antibiotics make up an important group of antifungal agents. All of the antibiotics are marked by their complexity. There are two classes:

- The **polyenes,** which contain a large number of agents with only a few being useful,
- The **griseofulvin** (one member of the class).

The **polyenes compounds are similar, in that they contain a system of conjugated double bonds in macrocyclic lactone rings.**

They differ from the erythromycin-type structures (macrolides), in that they are larger and **contain the conjugated-ene system of double bonds**. Hence, they are called the polyene antibiotics.

The clinically useful polyenes fall into two groupings on the basis of the size of the macrolide ring.

1. **The 26-membered–ring** polyenes, such as natamycin (**pimaricin**),

2. **The 38-membered macrocycles**, such as amphotericin B and **nystatin,.**

Also common to the polyenes are :

(a) A series of hydroxyl groups on the acid-derived portion of the ring

(b) A glycosidically linked deoxyaminohexose called mycosamine.

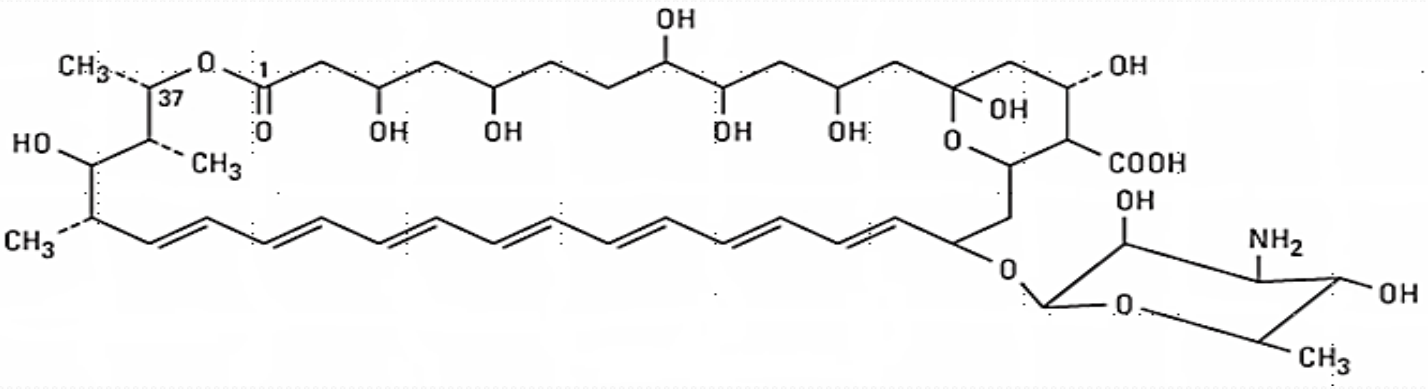
(c) The number of double bonds in the macrocyclic ring differs also.

Natamycin, the smallest macrocycle, is a pentaene; nystatin is a hexaene; and amphotericin B is a heptaene.

Polyene antifungal agents

Amphotericin B (heptene **)** and **Nystatin** (hexene) bind to the fungal cell membrane component ergosterol, leading to **increased fungal cell membrane permeability** and the **loss of intracellular constituents.** Amphotericin B is indicated for treatment of severe, potentially life threatening fungal infections. Unfortunately, **it must be given IV** and is toxic (due to nonselective action on cholesterol in mammalian cell membranes).

Serious fungal infections involve long therapy. The drug must **never be administered intramuscularly**.



- **The polyenes have no activity against bacteria, rickettsia, or viruses, but they are highly potent, broad-spectrum antifungal agents.**

They do have activity against certain protozoa, such as Leishmania spp. **They are effective against pathogenic yeasts, molds, and dermatophytes**. Low concentrations of the polyenes in vitro will inhibit Candida spp.

- The usefulness of amphotericin B is limited by a high prevalence of adverse reactions. Nearly 80% of patients treated with amphotericin B **develop nephrotoxicity.**
- **The hemolytic activity of amphotericin** B may be a consequence of its ability to leach cholesterol from erythrocyte cell membranes.

Amphotericin B is believed to interact with membrane sterols (ergosterol in fungi) to produce an aggregate that forms a transmembrane channel.

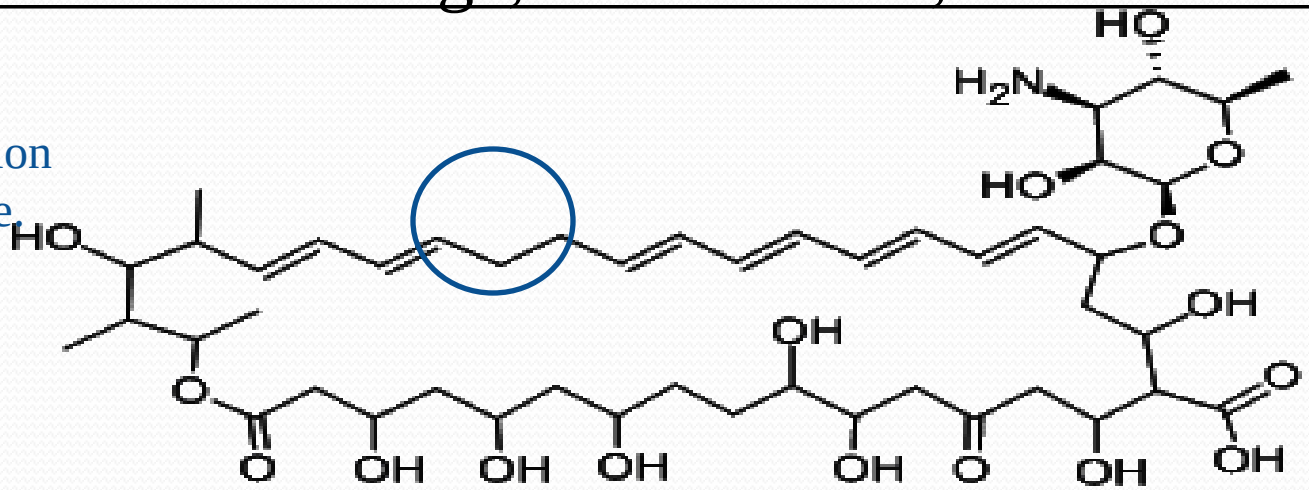
Intermolecular hydrogen bonding interactions among hydroxyl, carboxyl, and amino groups stabilize the channel in its open form, destroying symport activity and allowing the cytoplasmic contents to leak out.

The effect is similar with cholesterol. This explains the toxicity in human patients. Amphotericin B is also used topically to treat cutaneous and mucocutaneous mycoses caused by C. albicans.

The oral suspension is intended for the treatment of oral and pharyngeal candidiasis.

Nystatin is **a polyene** antifungal drug with **a ring structure** and a mechanism of action similar to that of amphotericin B. Nystatin **is an ionophore** (Ionophore means "ion carrier"). It binds to ergosterol, a major component of the fungal cell membrane. When present in sufficient concentrations, it forms pores in the membrane that lead to K+ leakage, acidification, and death of the fungus.

aglycone portion
nystatinolide



The aglycone portion (the compound remaining after the glycosyl group on a glycoside is replaced by a hydrogen atom) of **nystatin** is called nystatinolide.

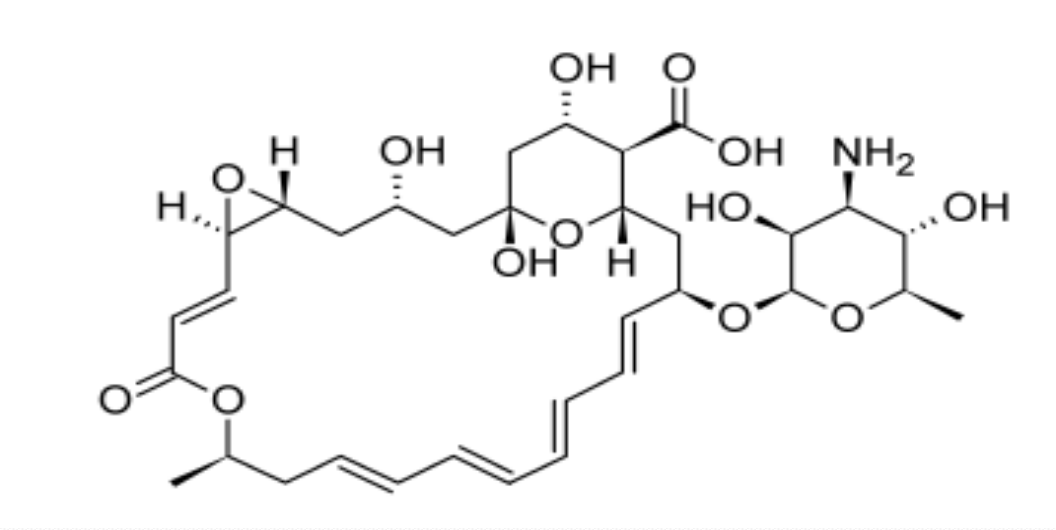
It consists of a **38-membered macrolide lactone ring** containing single tetraene and diene moieties separated by two methylene groups.

The aglycone also contains eight hydroxyl groups, one carboxyl group, and the lactone ester functionality. The entire compound is constructed by linking the aglycone to mycosamine.

Natamycin (pimaricin; Natacyn)

The natamycin structure consists of **a 26-membered lactone** ring **containing a tetraene** chromophore, an ,β-unsaturated lactone carbonyl group, three hydroxyl groups, a carboxyl group, a trans epoxide, and a glycosidically joined mycosamine.

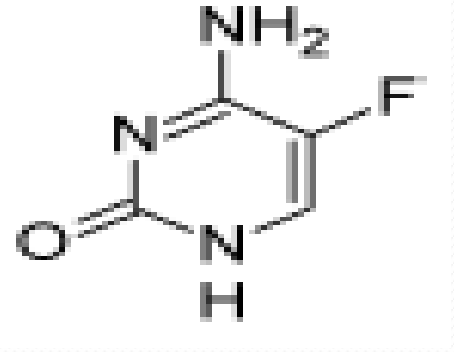
Like the other polyene antibiotics, natamycin is amphoteric.



- The 26-membered–ring polyenes cause both potassium ion leakage and cell lysis at the same concentration,
- The 38-membered–ring polyenes cause potassium leakage at low, fungistatic concentrations and cell lysis at high, fungicidal concentrations.
- The smaller polyenes are fungistatic and fungicidal within the same concentration range.

Nucleoside Antifungals (Inhibitors of cell division)

Flucytosine (5-flucytosine, 5-FC) is an **analogue of cytosine** that was originally synthesized for possible **use as an antineoplastic agent**.



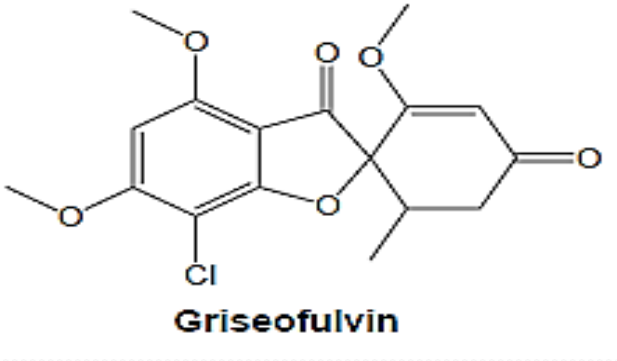
5-FC is converted to 5-fluorouracil inside the cell by the fungal enzyme cytosine deaminase. The active metabolite 5-fluorouracil **interferes with fungal DNA synthesis** by inhibiting thymidylate synthetase.

Incorporation of these metabolites into fungal RNA inhibits protein synthesis. Flucytosine has a significant antifungal activity against Candida spp. and the fungal organisms responsible for chromomycosis.


NDC 42794-009-08
Flucytosine
Capsules, USP
250 mg
SigmaPharm
Rx only
30 Capsules

Cell wall inhibitors

Griseofulvin is an antifungal produce from penicillium griseofulvin.



Griseofulvin

Mechanism of action: griseofulvin inhibits microtubule polymerization thus inhibiting the formation of the mitotic spindle.

It binds to keratin in keratin precursor cells and makes them resistant to fungal infections.

The drug reaches its site of action only when hair or skin is replaced by the keratin-griseofulvin complex.

Griseofulvin then enters the dermatophyte through energy-dependent transport processes and bind to fungal microtubules.

This alters the processing for mitosis and also underlying information for deposition of fungal cell walls. Griseofulvin is an oral fungistatic agent used in the long-term treatment of dermatophyte infections caused by Epidermophyton, Microsporum, and Trichophyton spp.


GlaxoSmithKline
GRISEOFULVIN TABLETS IP 250 mg
GRISOVIN® FP
Griseofulvin IP 250 mg
Store at temperature below 30°C
Keep out of reach of children.
For oral use only.
B.No.RE197
MFD.APR.2008 EXP.MAR.2011
MRP FOR 10 TABS. Rs.13.34.
INCLUSIVE OF ALL TAXES

Caspofungin acetate

Caspofungin acetate is an parenteral injection used in the treatment of invasive aspergillosis in patients refractory to or intolerant of other antifungal therapies.

Studies have shown caspofungin to be effective against invasive candidaisis.

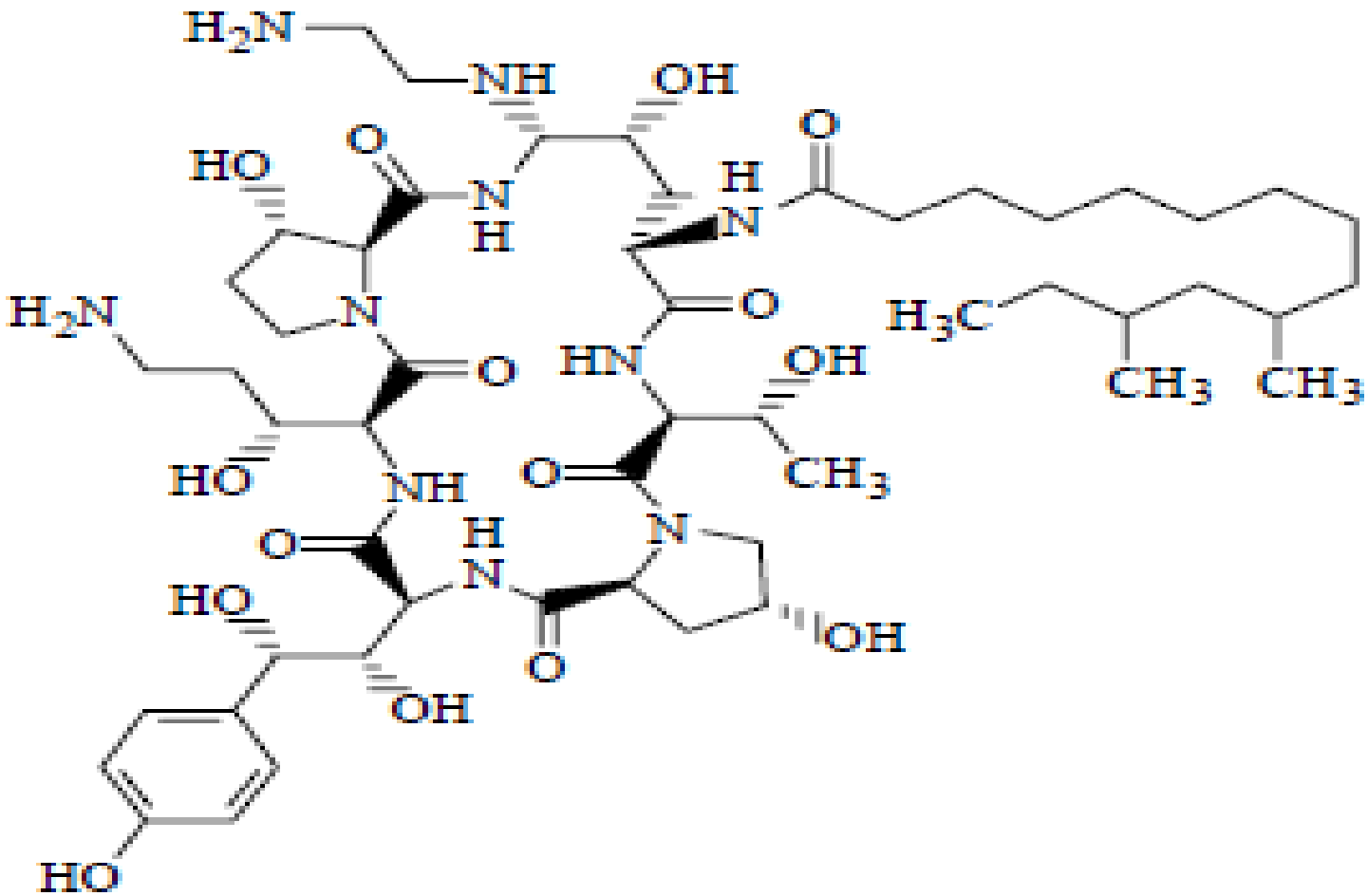
It is a semisynthetic lipopeptide (echinocandin) derived from a fermentation product of Glarea lozoyensis.

Mechanism of Action:

Caspofungin is a (1,3)-D-glucan synthesis inhibitor, thus disrupting the formation of β-glucan in the cell walls.

β-glucan is essential to the structural integrity of the cell wall.

Caspofungin




Caspofungin
Acetate
for Injection
50 mg per vial*
Caspofungin
Acetate
for Injection
70 mg per vial*