ANTI FUNGAL DRUGS

Introduction

- Fungi are eukaryotic, heterotrophic (not self sustaining) organisms that live as saprobes or parasites.

- They are complex organisms in comparison to bacteria .Thus antibacterial agents are not effective against fungi.

- Fungal infections are also called as **mycoses**

Characteristics of fungal cell

- They have nucleus and **well defined nuclear membrane**, and chromosomes.
- they have **rigid cell wall** composed of chitin (N – acetylglucosamine)

  where as bacterial cell wall is composed of peptidoglycan

- fungal cell membrane contains **ergosterol** , human cell mebmrane is composed of cholesterol

TABLE 6.5 Clinical Types of Fungal Infection

Type	Disease State	Causative Organism
Superficial infections	Tinea versicolor	*Pityrosporum orbiculare*
	Piedra	*Trichosporon cutaneum* (white)
		Piedraia hortae (black)
Cutaneous infections	Ringworm of scalp, hairless skin, nails	Dermatophytes, *Microsporum, Trichophyton, Epidermophyton*
	Candidosis of skin, mucous membranes, nails; sometimes generalized	*Candida albicans* and related forms
Subcutaneous infections	Chromomycosis	*Fonsecaea* and related forms
	Mycotic mycetoma	*Allescheria boydii, Madurella mycetoma,* etc.
	Entomophthoromycosis	*Basidiobolus haptosporus, Conidiobolus coronatus*
Systemic infections	Histoplasmosis	*Histoplasma capsulatum*
	Blastomycosis	*Blastomyces dermatiditis*
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
	Coccidioidomycosis	*Coccidioides immitis*
	Cryptococcosis	*Cryptococcus neoformans*
	Sporotrichosis	*Sporothrix schenckii*
	Aspergillosis	*Aspergillus fumigates*
	Mucormycosis	*Mucor* spp., *Absidia* spp., *Rhizopus* spp.
	Histoplasmosis duboisii	*Histoplasma capsulatum* var. *duboisii*

Drug Classification

A) Drugs that disrupt fungal cell membrane

i) Polyene Antibiotics

Amphotericin
Nystatin
Natamycin

ii) Azoles

A) Imidazole

Ketoconazole
Clotrimazole
Miconazole

B) Triazole

Fluconazole
Itraconazole
Tioconazole

iii) Allylamines

Terbinafine
Naftifine
Butenafine

iv) Thiocarbamates:

Tolnaftate

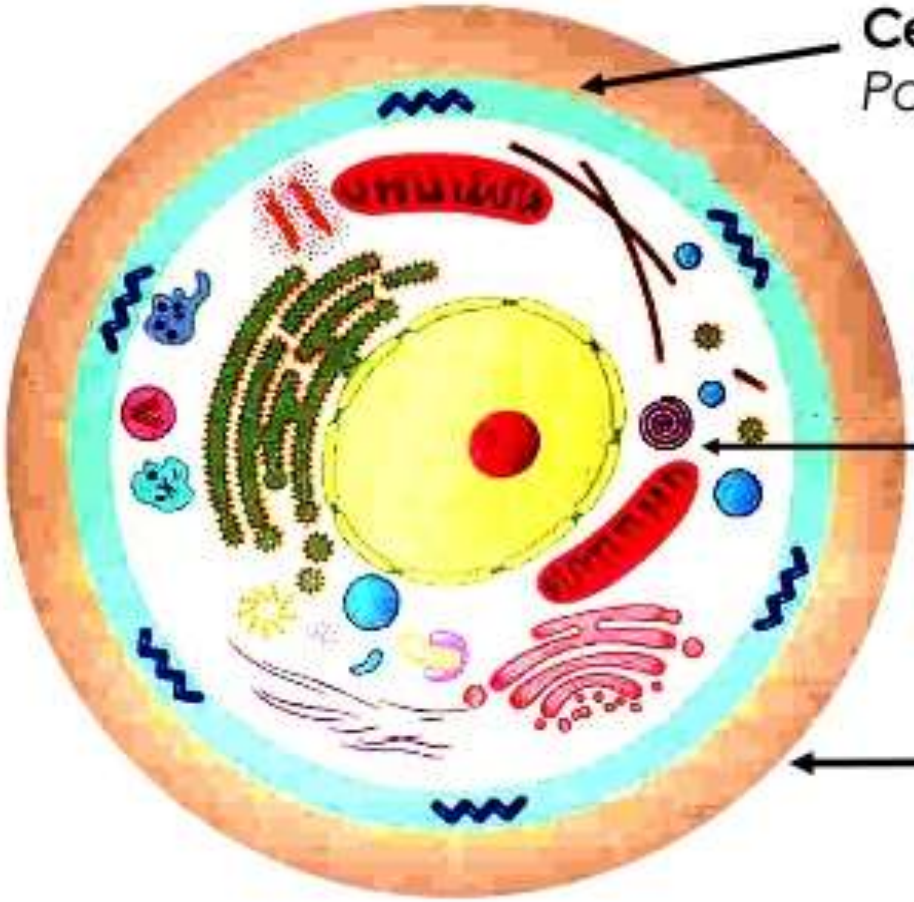
B) Drugs that inhibits mitosis

Griseofulvin

C) Drugs that inhibits DNA synthesis

flucytosine

Targets for antifungal therapy

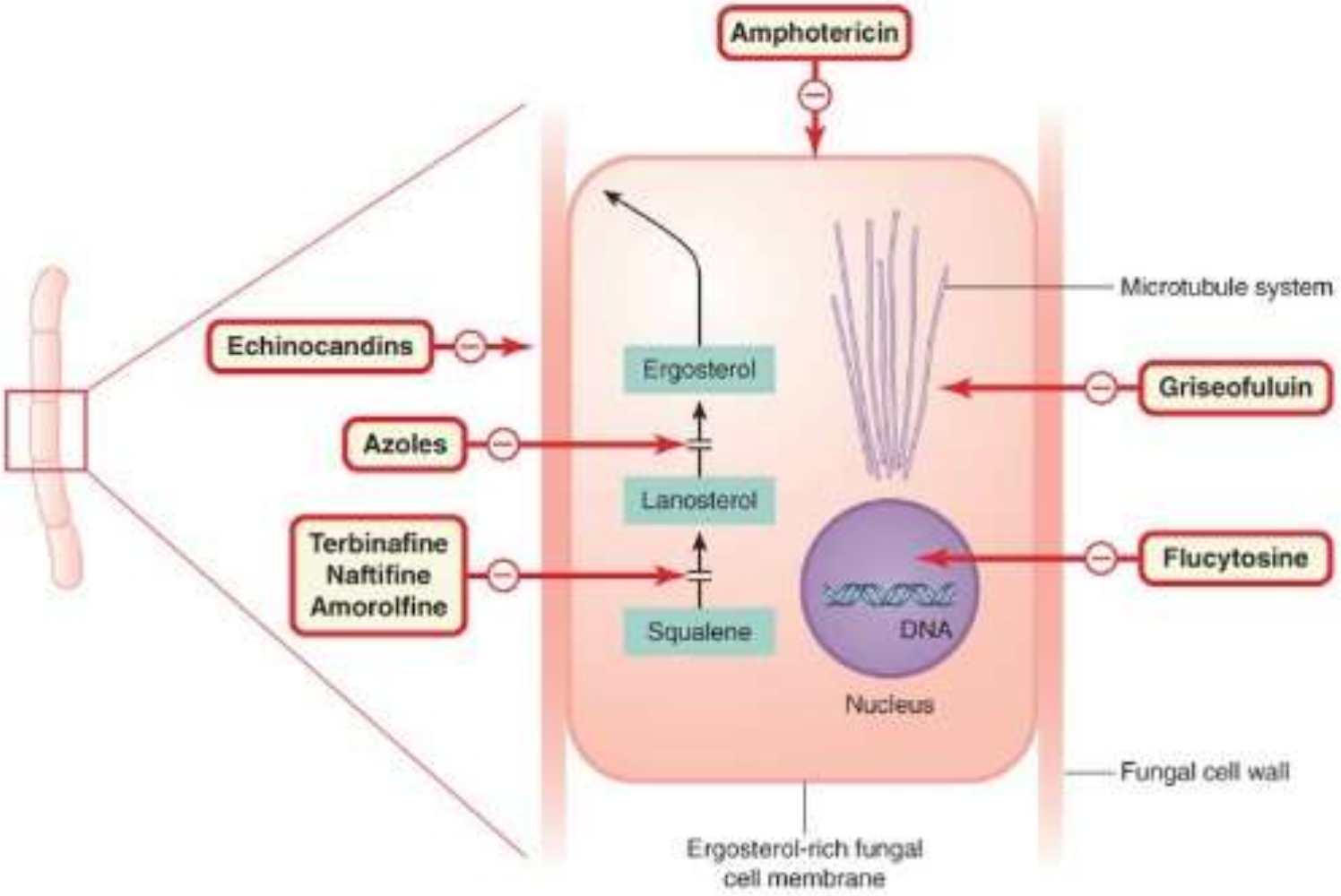


Cell membrane
Polyenes , Azoles , Allylamines
Morpholines

DNA synthesis
E.g-Flucytosin
Griseofulvin

Cell wall
E.g-Echinocandins

M/A of Antifungal drugs



Superficial Mycosis

- **a) Dermatophyte infection** (ring worm,tinea).
- **Benzoic acid** ointement for mild infection.
- **Topical imidazole** (like miconazole,clotrimazole) is preferred now a days
- **Tioconazole** for nail infection
- **Griseofulvin** orally for extensive scalp or nail tinea infection.

b) Candida infection.

- **Cutaneous infection**: by
  topical amphotericin,clotrimazole ,econazole, miconazole or nystatin

- **Candidiais of elementary tract mucosa**
  amphotericin,fluconazole, ketoconazole, miconazole or nystatin.

- **Vaginal candidiasis**:
  Clotrimazole,econazole,ketoconazole, miconazole or nystatin

1. Polyene Antibiotics

- they contain a system of conjugated double bonds in macrocyclic lactone rings Hence, they are called the *polyene antibiotics.*
- The polyenes have no activity against bacteria, rickettsia, or viruses, but they are highly potent, broad-spectrum antifungal agents.
- The use of the polyenes for the treatment of systemic infections is limited by

1. the toxicities of the drugs,
2. their low water solubilities, and
3. their poor chemical stabilities.

- Amphotericin B, the only polyene useful for the treatment of serious systemic infections.
- The other polyenes are indicated only as topical agents for superficial fungal infections.

Polyene-MOA

- Because of their three-dimensional shape, a barrel-like nonpolar structure capped by a polar group (the sugar), they penetrate the fungal cell membrane, acting as “false membrane components,” and bind closely with ergosterol, causing membrane disruption, cessation of membrane enzyme activity, and loss of cellular constituents, especially potassium ions.

‘Tunnelling molecules’

amphotericin B (Fig. 2.5) interacts with the lipids(ergosterol) of fungal cell membranes to build 'tunnels' through the membrane. Once in place, the contents of the cell are drained away and the cell is killed.

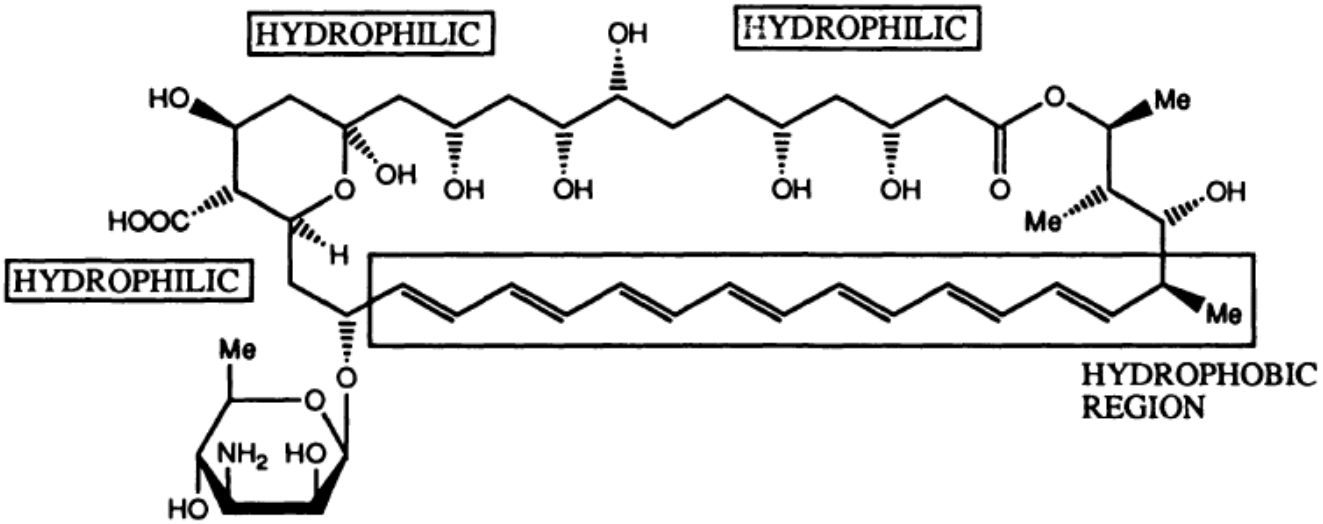


Fig. 2.5 Amphotericin B.

- Amphotericin is a fascinating molecule in that one half of the structure is made up of double bonds and is hydrophobic, while the other half contains a series of hydroxyl groups and is hydrophilic.
- It is a molecule of extremes and as such is ideally suited to act on the cell membrane in the way that it does. Several amphotericin molecules cluster together such that the alkene chains are to the exterior and interact favourably with the hydrophobic centre of the cell membrane.
- The tunnel resulting from this cluster is lined with the hydroxyl groups and so is hydrophilic, allowing the polar contents of the cell to escape (Fig. 2.6).

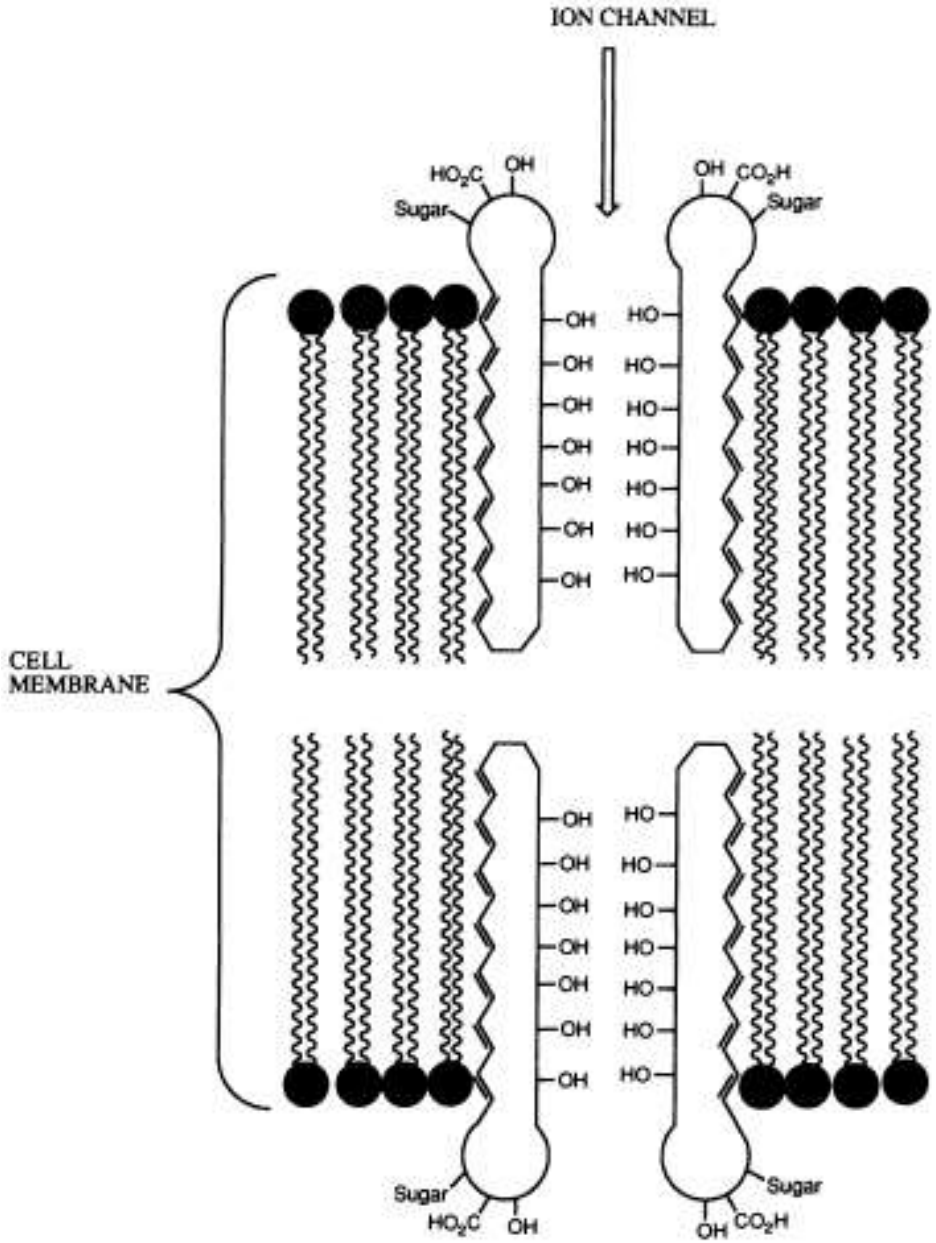
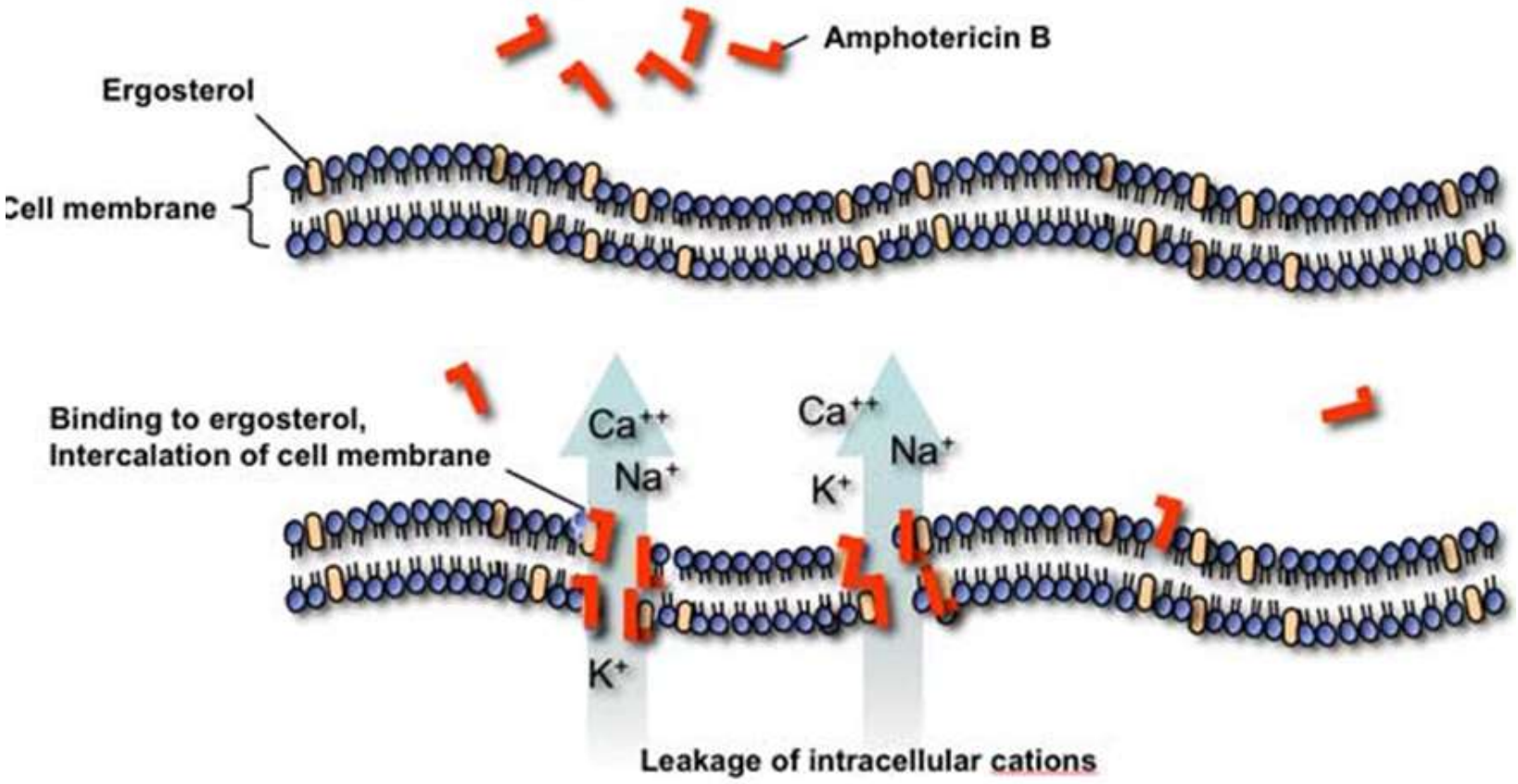
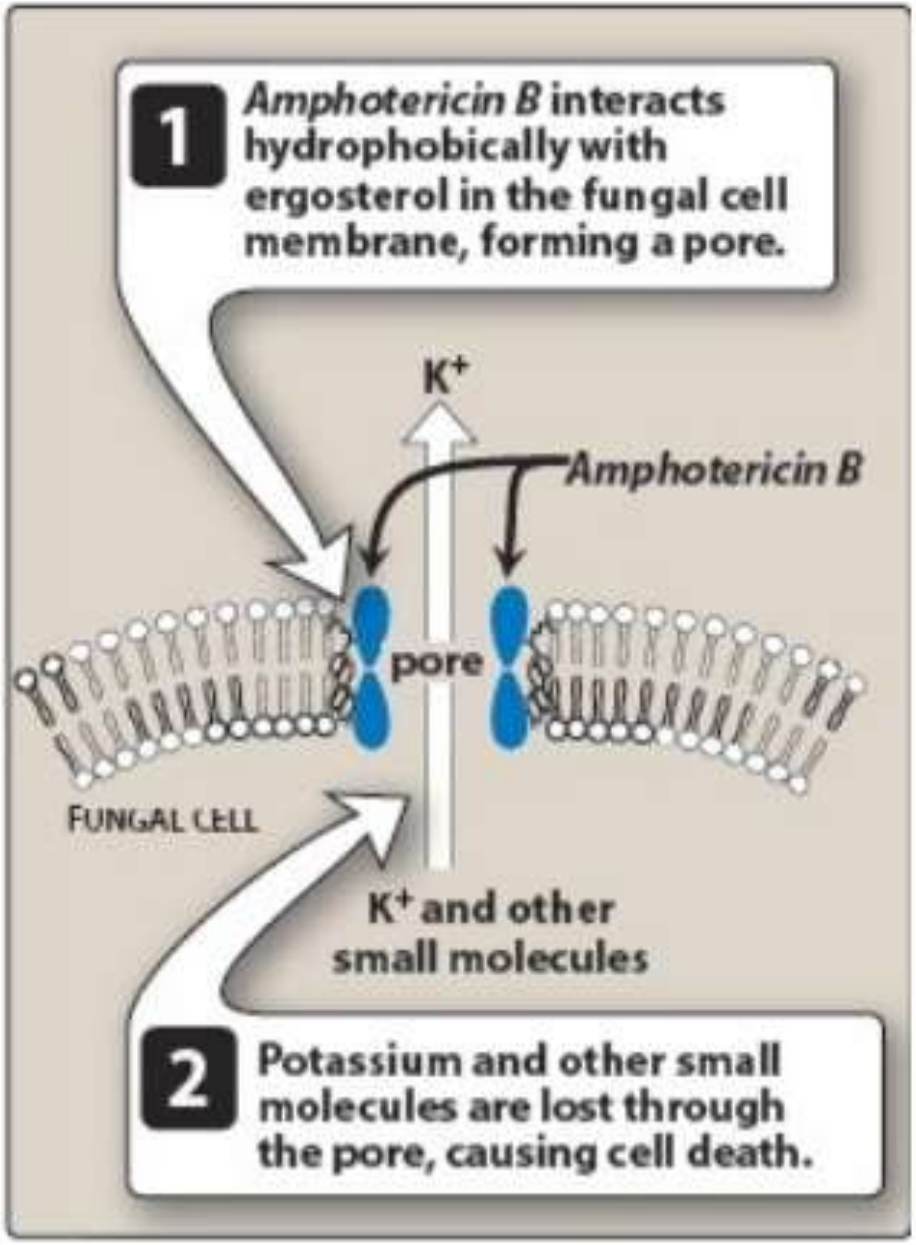


Fig. 2.6 Amphotericin-formed channel through the cell membrane.

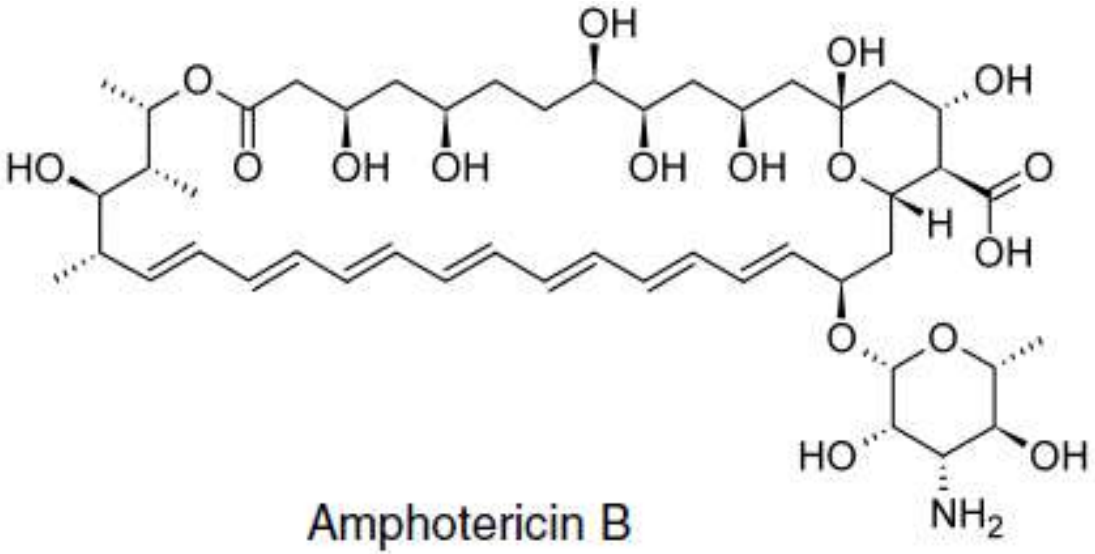
Amphotericin B is believed to interact with membrane sterols (ergosterol in fungi) to produce an aggregate that forms a transmembrane channel. Intermolecular hydrogen bonding interactions among hydroxyl, carboxyl, and amino groups stabilize the channel in its open form, destroying symport activity and allowing the cytoplasmic contents to leak out.




1
Amphotericin B interacts hydrophobically with ergosterol in the fungal cell membrane, forming a pore.
K+
Amphotericin B
pore
FUNGAL CELL
K+ and other small molecules
2
Potassium and other small molecules are lost through the pore, causing cell death.

amphotericin B

- As the name implies, amphotericin B is an **amphoteric substance**, with a primary amino group attached to the mycosamine ring and a carboxyl group on the macrocycle.



Amphotericin B

Adverse reactions

- Most serious is renal toxicity, which occurs in 80% of patients
- There may occur decrease in glomerular filtration, and renal function, drop in creatinine clearance,and loss of potassium and magnesium, nephrotoxcity may be potenciated by sodium depletion.

- Hypokalaemia in 25% of patients, requiring potassium supplementation.

- Hypomagnesaemia
- Anemia
- Impaired hepatic function
- Thrombocytopenia (Low platelet content)

Liposomal preparations of amphotericin B.

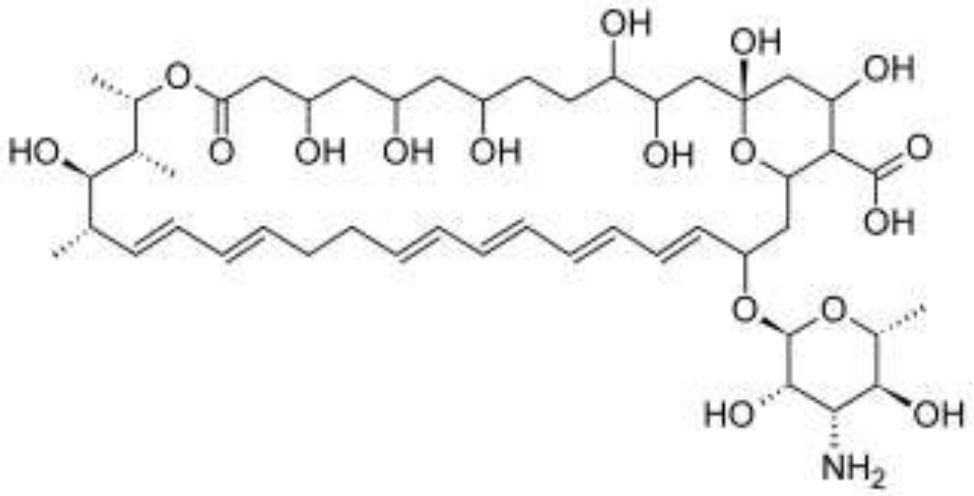
- To reduce the toxicity of amphotericin B ,several new formulations have been developed in which amphotericin B is packaged in a lipid-associated delivery system, to assume that they will less bind to mammalian cell. Lipid vehicle act as a reservoir, reducing binding to human cell. In this way it permits a larger doses, even five times more than colloidal preparation, they have better clearance .

- Clinically they have **more efficacy , less nephrotoxicity**.

- But these are very expansive.

NYSTATIN

- It is polyene macrolide similar in structure to amphotericin and with same mechanism of action
- Too toxic for systemic use
- Not absorbed from GIT, skin or vagina, therefore administered orally.



- Used to Prevent or treat superficial candidiasis of mouth, esophagus or intestinal tract, oral suspension of 100,000 U/ml 4 times a day and tablets 500,000 U are used to decrease GIT colonization with Candida

- For vaginal candidiasis in form of pessaries used for 2 weeks

- In Cutaneous infection available in cream, ointment or powder form and applied 2-3 times a day

- Can be used in combination with antibacterial agents and corticosteroids

AZOLES

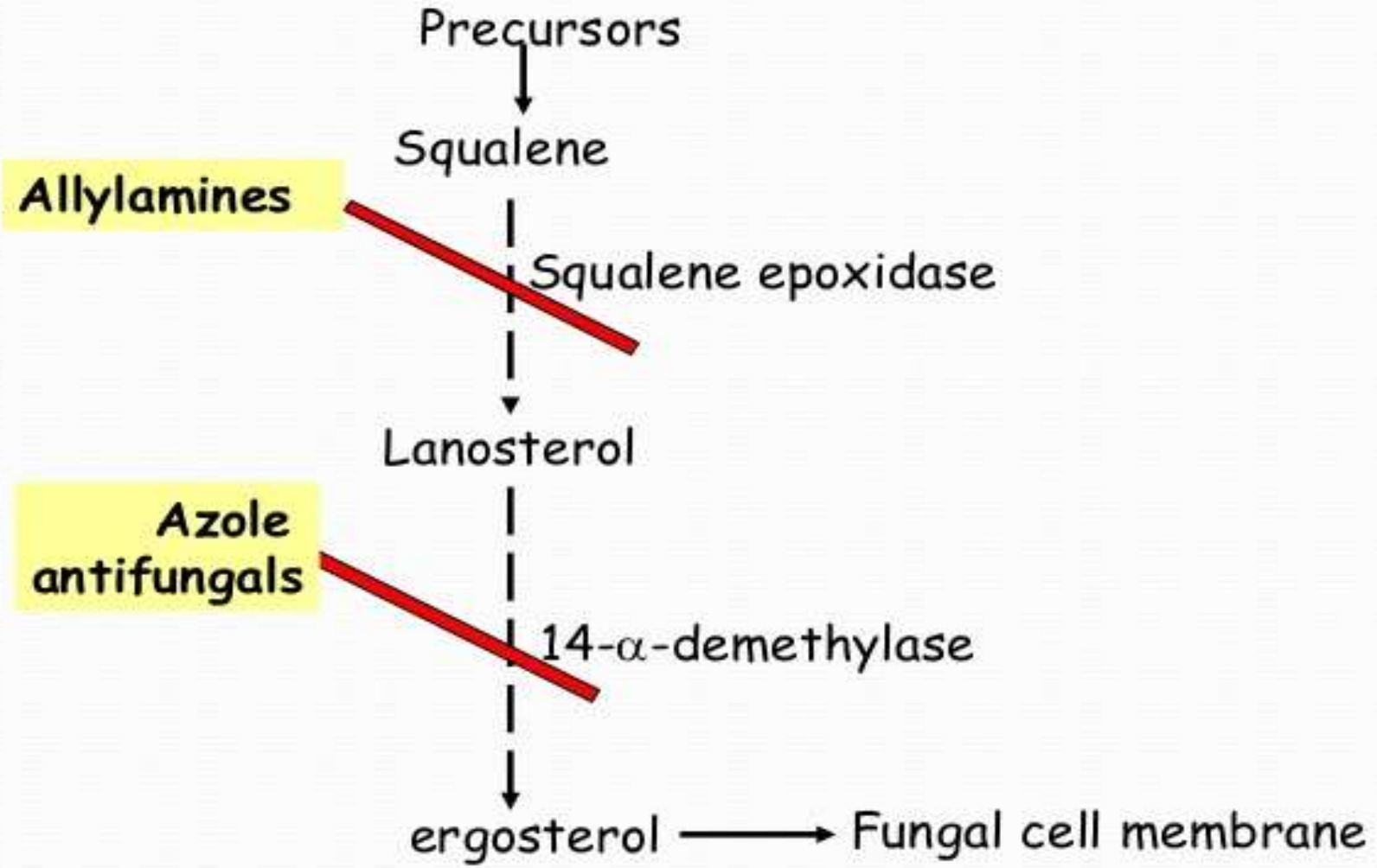
- The first members of the class were highly substituted **imidazoles**, such as clotrimazole and miconazole.
- Structure–activity studies revealed that the imidazole ring could be replaced with a bioisosteric **1,2,4-triazole** ring without adversely affecting the antifungal properties of the molecule. Hence, the more generic term ***azoles*** *refers to this class of antifungal agents.*
- *Hence two classes of azole antifungals are*

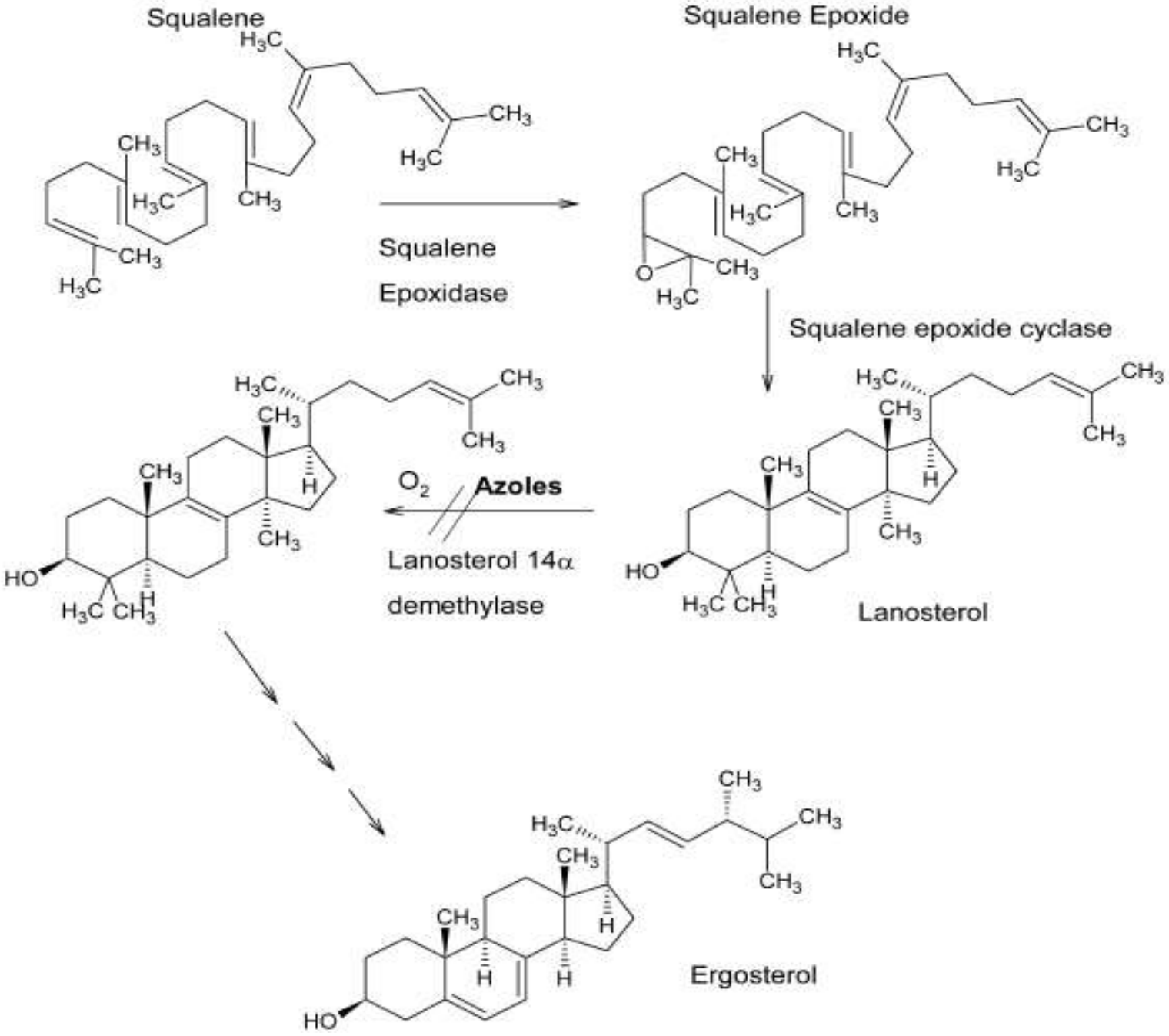
1. **Imidazoles**
2. **Triazoles**

MECHANISM OF ACTION

- The fungistatic effect is associated with inhibition of membrane-bound cytochrome P450-class enzyme, lanosterol -14-demethylase.
- P450 possesses a heme moiety as part of its structure (Fig. 6.5), 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.
- Lanosterol -14-demethylase is also required for mammalian biosynthesis of cholesterol, and the azoles are known to inhibit cholesterol biosynthesis but very high concentration of azole is required to inhibit the mammalian enzyme. This provides selectivity for antifungal action.

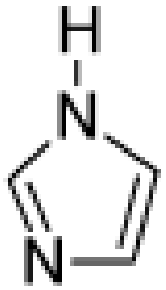
AZOLES & ALLYLAMINES

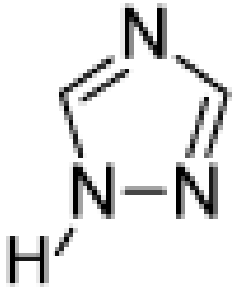


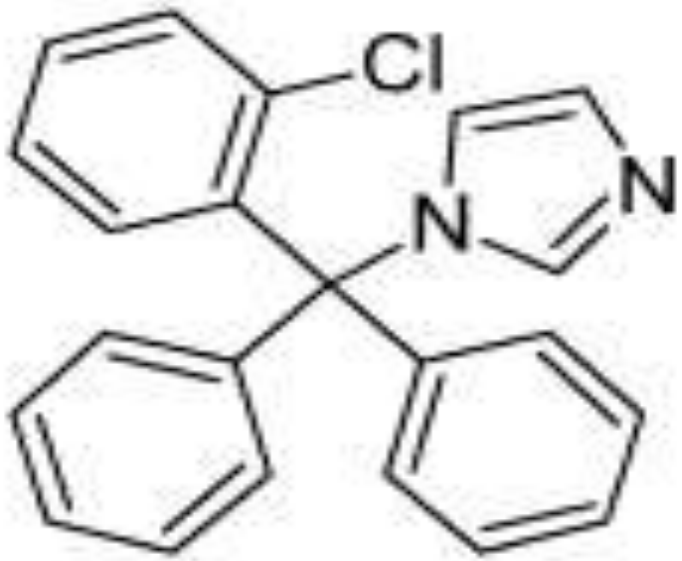

Squalene
Squalene Epoxide
Squalene
Epoxidase
Squalene epoxide cyclase
O_2
Azoles
Lanosterol 14α
demethylase
Lanosterol
Ergosterol

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.





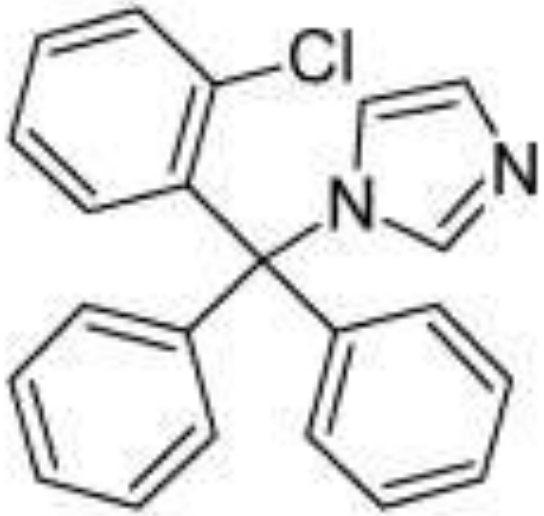

Cl
N
N

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 nonpolar 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.
6. Substitution at other positions of the ring yields inactive compounds.
7. The large nonpolar portion of these molecules mimics the nonpolar steroidal part of the substrate for lanosterol 14-demethylase, lanosterol, in shape and size.

a) Imidazoles.

- **Ketoconazole,**
- **miconazole,**
- **clotrimazole,**

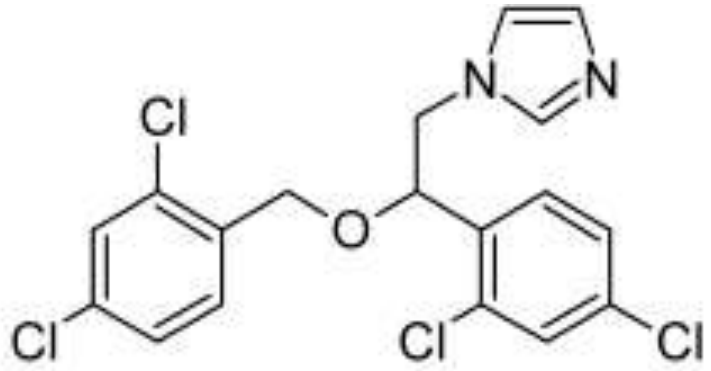
Clotrimazole:-



1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole

•broad-spectrum antifungal drug that
is used topically for the treatment of tinea infections and candidiasis.
•Indications includes the treatment of tinea pedis, tinea cruris, tinea capitis, tinea versicolor, or cutaneous candidiasis,athlete foot ,ringworm etc .
•It causes severe gastrointestinal disturbances
•Clotrimazole is not considered suitable for the treatment of systemic infections.

Miconazole:-



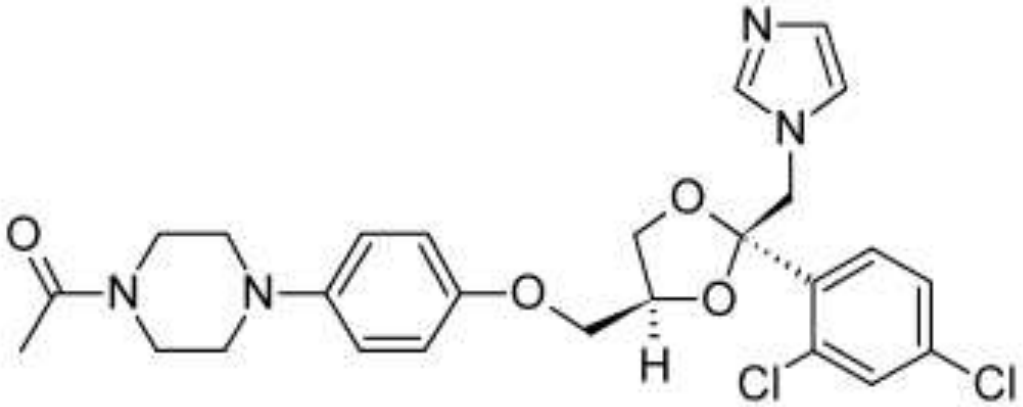
1-[2-(2,4-Dichlorophenyl)-2-[2,4-dichlorophenyl]-methoxy]ethyl]-1*H*-imidazole

•Intended for the treatment of serious systemic fungal infections, such
as candidiasis, coccidioidomycosis, cryptococcosis, petriellidiosis, and paracoccidioidomycosis.

• It may also be used for the treatment of chronic mucocutaneous candidiasis, Athlete foot ,ring worm etc .

•Although serious toxic effects from the systemic administration of miconazole are comparatively rare, thrombophlebitis, pruritus, fever, and gastrointestinal upset are relatively common.

Ketoconazole:-



1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1*H-imidazole-1-* ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine

- Ketoconazole is a racemic compound, consisting of the *cis-2S,4R and cis-2R,4S isomers.* The *2S,4R isomer was 2.5 times more active than its 2R,4S enantiomer.* The *trans-isomers, 2S,4S and 2R,4R, are* much less active.
- is a broad-spectrum imidazole antifungal agent that is administered orally for the treatment of systemic fungal infections.
- Hepatotoxicity, is the most serious adverse effect.

KETOCONAZOLE:

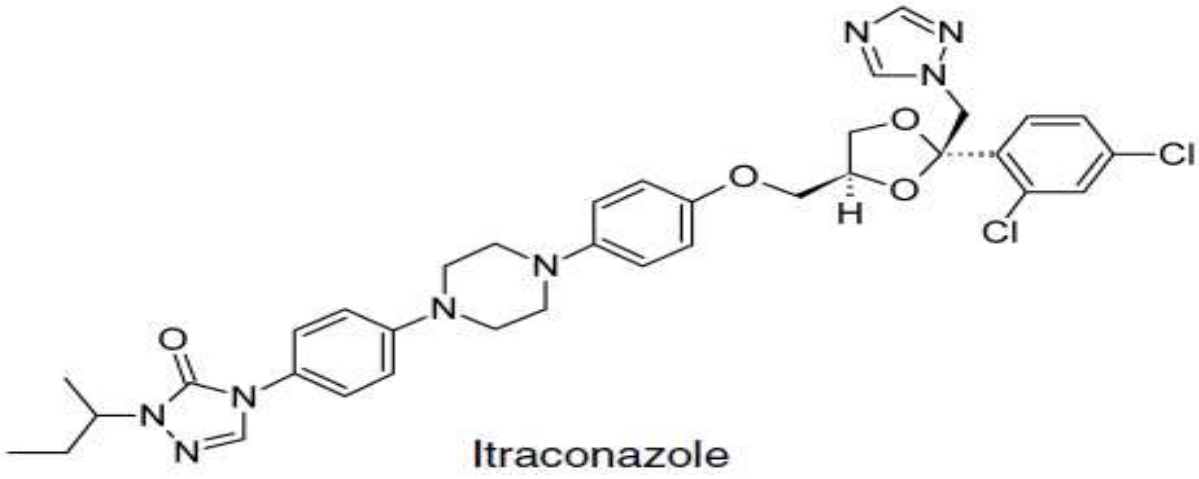
- First azole that could be given orally to treat systemic fungal infections.
- Well absorbed orally as acidic environment favors its dissolution.
- Only administered orally
- Bioavailability is decreased with H-2 blocking drugs, proton pump inhibitors and antacids and is impaired with food.
- cola drinks improve its absorption in patients with achlorhydria.
- After oral administration of 200,400 and 800 mg, plasma conc. reaches to 4.8 and 20 ug/ml.
- Half life increases with dose and it is 7-8 hrs with 800 mg

b).Triazoles.

- **Fluconazole,**
- **itraconazole,**
- **Voriconazole(new drug)**

- They are selective.
- Penetrate to CNS
- Resistant to degradation
- Cause less endocrine disturbance.

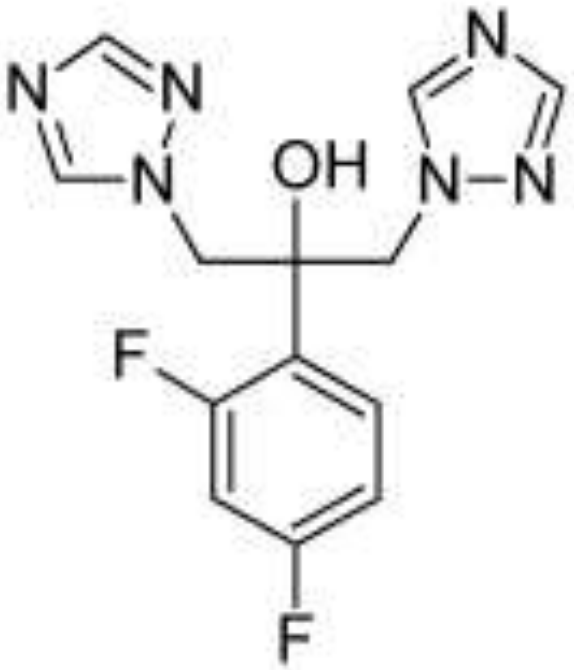
ITRACONAZOLE



- It is a synthetic triazole, contain two triaz
- It lacks hepatotoxicity and endocrine side effects of ketoconazole.
- Itraconazole is an orally active, broad-spectrum antifungal agent that has become an important alternative to ketoconazole.
- An acidic environment is required for optimum solubilization and oral absorption of itraconazole.
- Food greatly enhances the absorption of itraconazole, nearly doubling its oral bioavailability,it increses plasma level of terfenadine .
- Administered orally as well as I/V.

FLUCONAZOLE

- It is fluorinated bistriazole.
- Completely absorbed from GIT
- Excellent bioavailability by oral route.
- Concentration in plasma is same by oral or I/v route.
- Bioavailability not altered by food or gastric acidity/Little or no metabolism
- It has least effect on hepatic microsomal enzymes.
- Drug interactions are less common



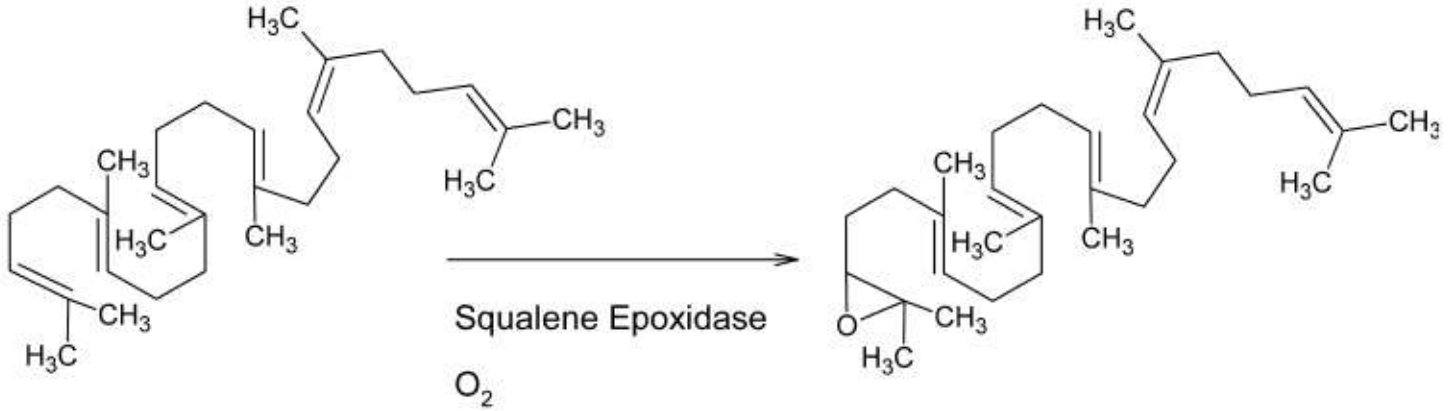
Comparison of Azoles fungistatic drugs

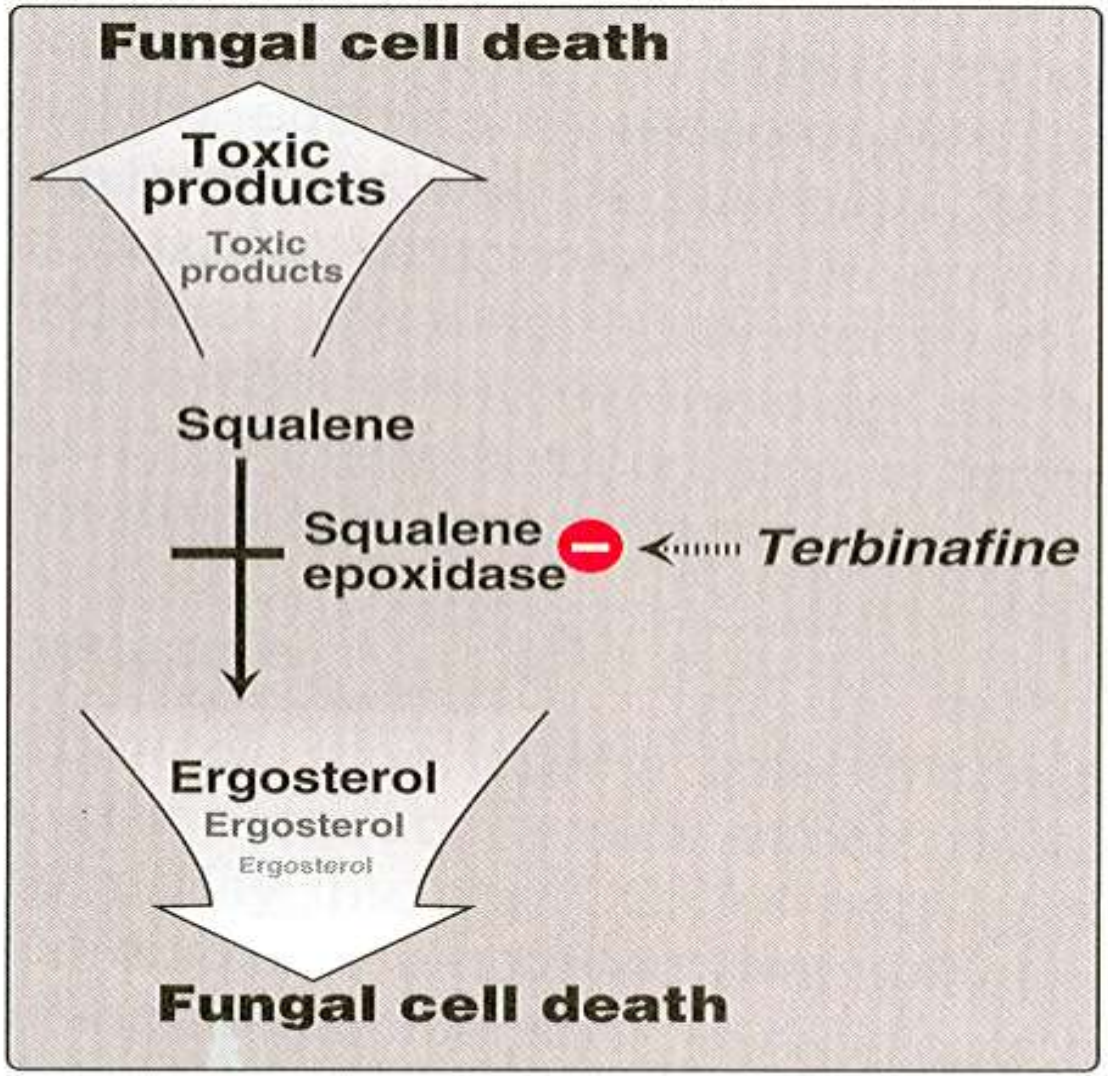
	Ketoconazole	Fluconazole	Itraconazole
spectum	narrow	expanded	expanded
Route of administration	Oral	Oral, i.v	oral
$T_{1/2}$	6-9	30	30-40
Csf penetration	no	yes	no
Renal excretion	no	yes	no
Interaction with other drugs	frequent	Occasional	occasional
Inhibition of mammalian sterol synthesis	Dose dependent inhibitory effect	no inhibition	NO inhibition

3. Allylamines(topical antifungal)

MOA:- interfere with an early step in ergosterol biosynthesis, namely, the epoxidation of squalene catalyzed by squalene epoxidase. Squalene epoxidase forms an epoxide at the C2–C3 position of squalene.

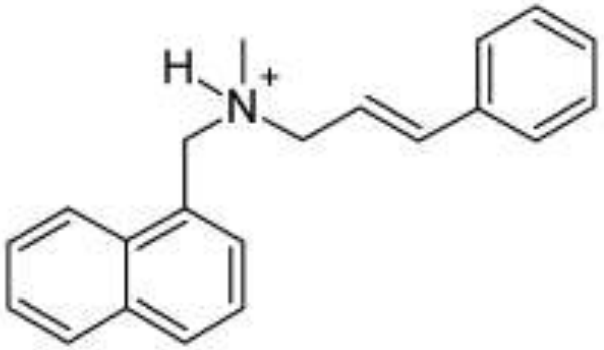
- Opening of the epoxide under acid catalysis yields a carbocation that initiates the “squalene zipper” reaction that forms the steroid nucleus.
- Inhibition of squalene epoxidase shuts down the biosynthesis of ergosterol and causes an accumulation of squalene, which destabilizes the fungal cell membrane.





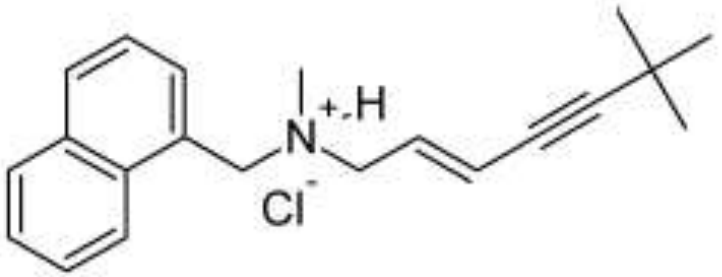
Mechanism of action of terbinafine

- Two allylamines, naftifine and terbinafine, have been approved as topical agents for the treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum, Trichophyton mentagrophytes, or Epidermophyton floccosum, respectively.*



Naftifine

N-Methyl-N-(3-phenyl2-propenyl)-1-naphthalene-methanamine

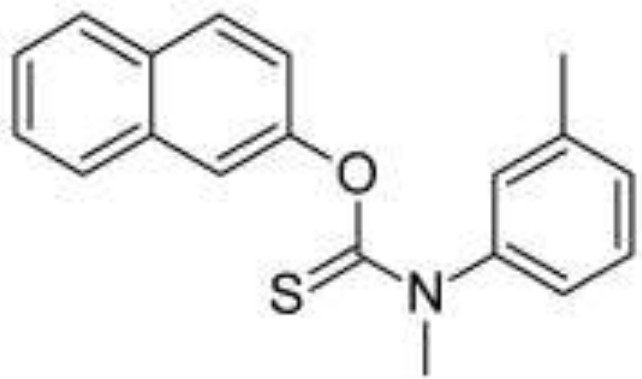


Terbinafine

(*E)-N-(6,6-dimethyl-2-hepten-4-ynyl)-N-methyl-1-naphthalene*-methanamine

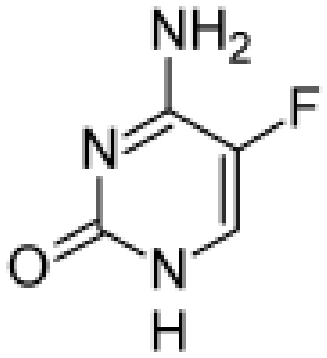
Thiocarbamates :-tolnaftate

- The topical agent Tolnaftate, inhibits squalene epoxidase and has a spectrum of activity similar to that of the allylamines.
- The compound is a thioester of β-naphthol
- It is fungicidal against dermatophytes, such as *Trichophyton, Microsporum, and Epidermophyton spp., that cause superficial* tinea infections.
- Tolnaftate is formulated into preparations mintended to be used with artificial fingernails to counteract the increased chance of ringworm of the nail beds



FLUCYTOSINE

- Has useful activity against Candida and Cryptococcus.
- it is synthetic pyrimidine antimetabolite that is often used in combination with amphotericin B
- it is fungistatic,effective in combination with itraconazole for treating chromoblastomycosis and with amphotericin for treating cryptococosis.

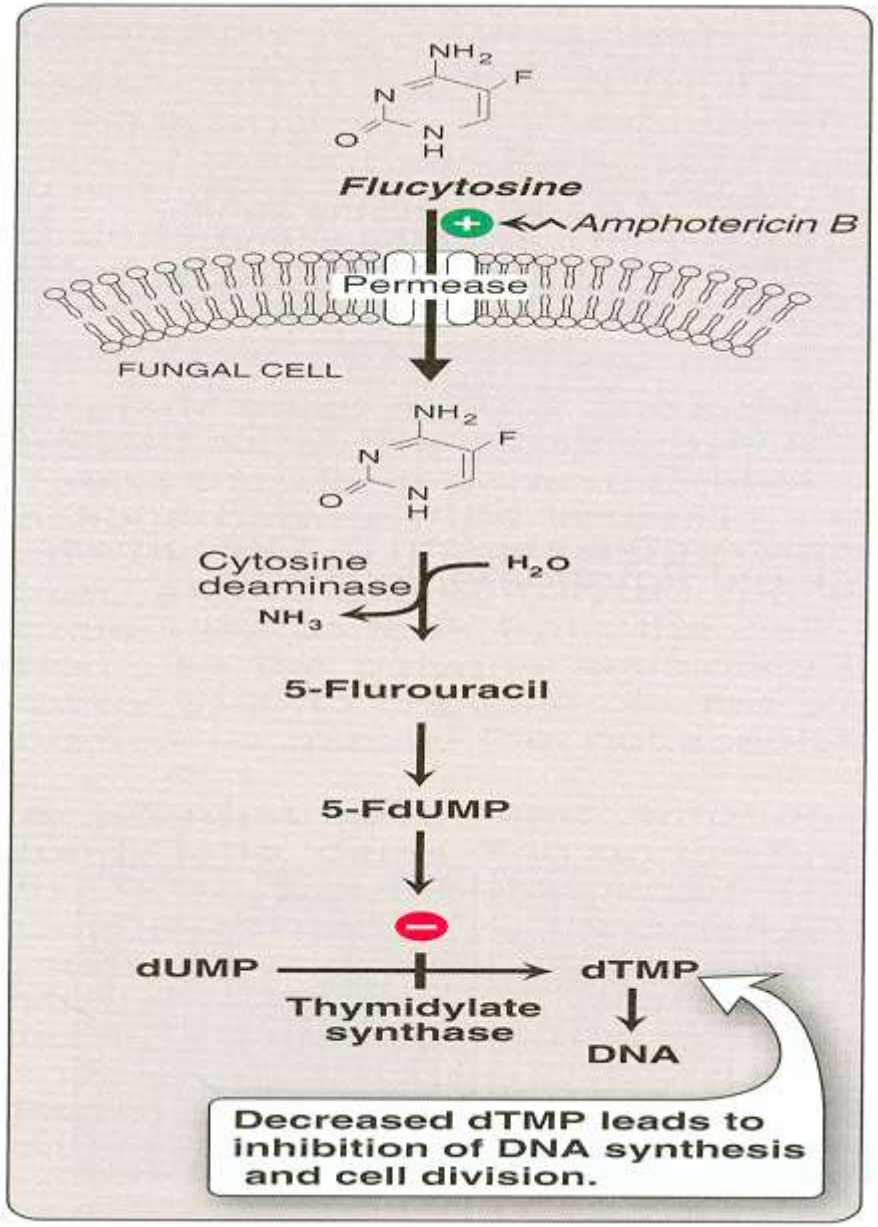


5-Fluorocytosine,
5-FC,
4-amino-5-fluoro-2(1*H*)-*pyrimidinone*

- **Mechanism of action**

It is converted to antimetabolite 5-florouracil in a fungal but not human cell. This 5-FU inhibits thymidylate synthetase enzyme and thus DNA synthesis. Resistant mutants may occur, should never be used alone.

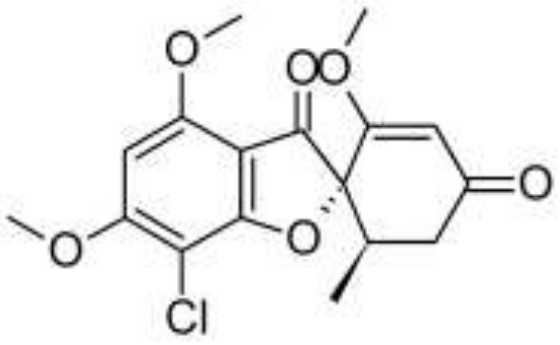
Fdump(fluorodeoxyuridne monophosphate



Mechanism of action of Flucytosine

GRISEOFULVIN

- Griseofulvin is an example of a rare structure in nature, a **spiro** compound.
- Isolated from fungus ***Pencillium griseofulvum***
- it has largely been replaced by terbinafine for treatment of dermatophytic infections of the nails.
- It is useful for dermatophytes

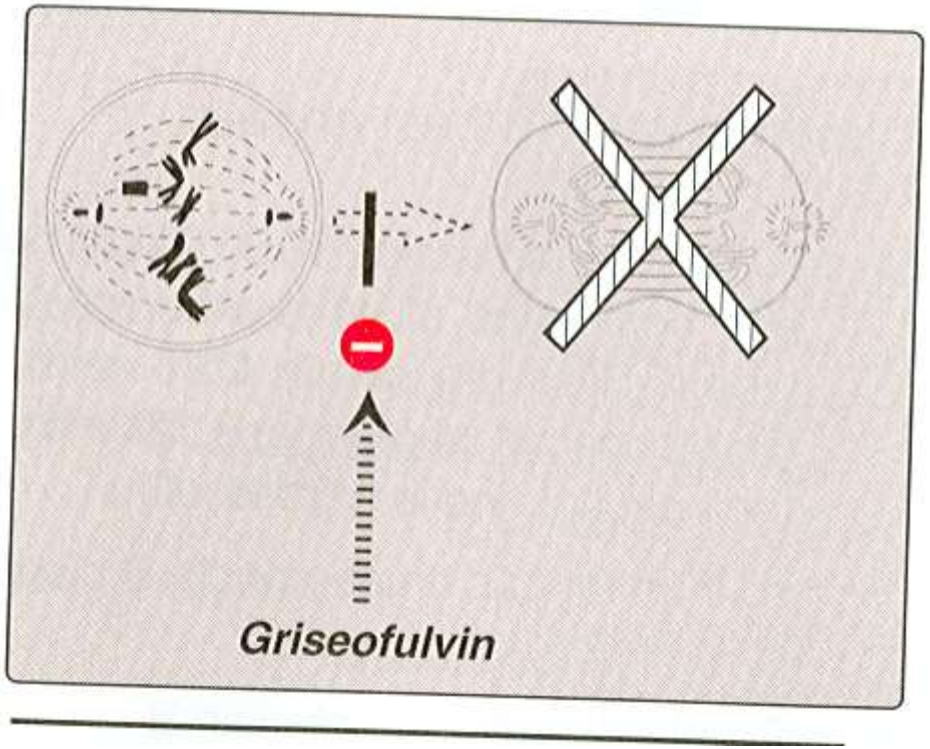


- It is fangistatic for species of dermatophytes.
- It has narrow spectrum.

MOA

- Griseofulvin is a mitotic spindle poison. In vitro, it rapidly arrests cell division in metaphase. It causes a rapid, reversible dissolution of the mitotic spindle apparatus, probably by binding with the tubulin dimer that is required for microtubule assembly. The selective toxicity to fungi is probably because of the propensity of the drug to concentrate in tissues rich in keratin, where dermatophytes typically establish infections.
- **Uses**
- Mycotic diseases of skin, hair (particularly for scalp) , nail.

- It is also highly effective in athlete's foot


Griseofulvin

Uses of antifungal drugs

Disease	Drug used
Systemic infections	
■ systemic candidiasis	■ Amphotericin, flucytocin, , fluconazole.
■ Cryptococcosis(meningitis)	■ Amphotericin, flucytocin , fluconazole, itraconazole
■ systemic aspergillosis	■ itraconazole Amphotericin,
■ Blastomycosis	■ itraconazole Amphotericin,
■ Histoplasmosis	■Amphotericin, itraconazole ,fluconazole.
■ Coccidiomycosis	■ fluconazole. itraconazole ,Amphotericin,
■ Paracoccidiomycosis	■ fluconazole. itraconazole ,Amphotericin,
■ Mucormycosis	■ Amphotericin, flucytocin ,Amphotericin,
■ Disseminated sportrichosis	■ Amphotericin, flucytocin