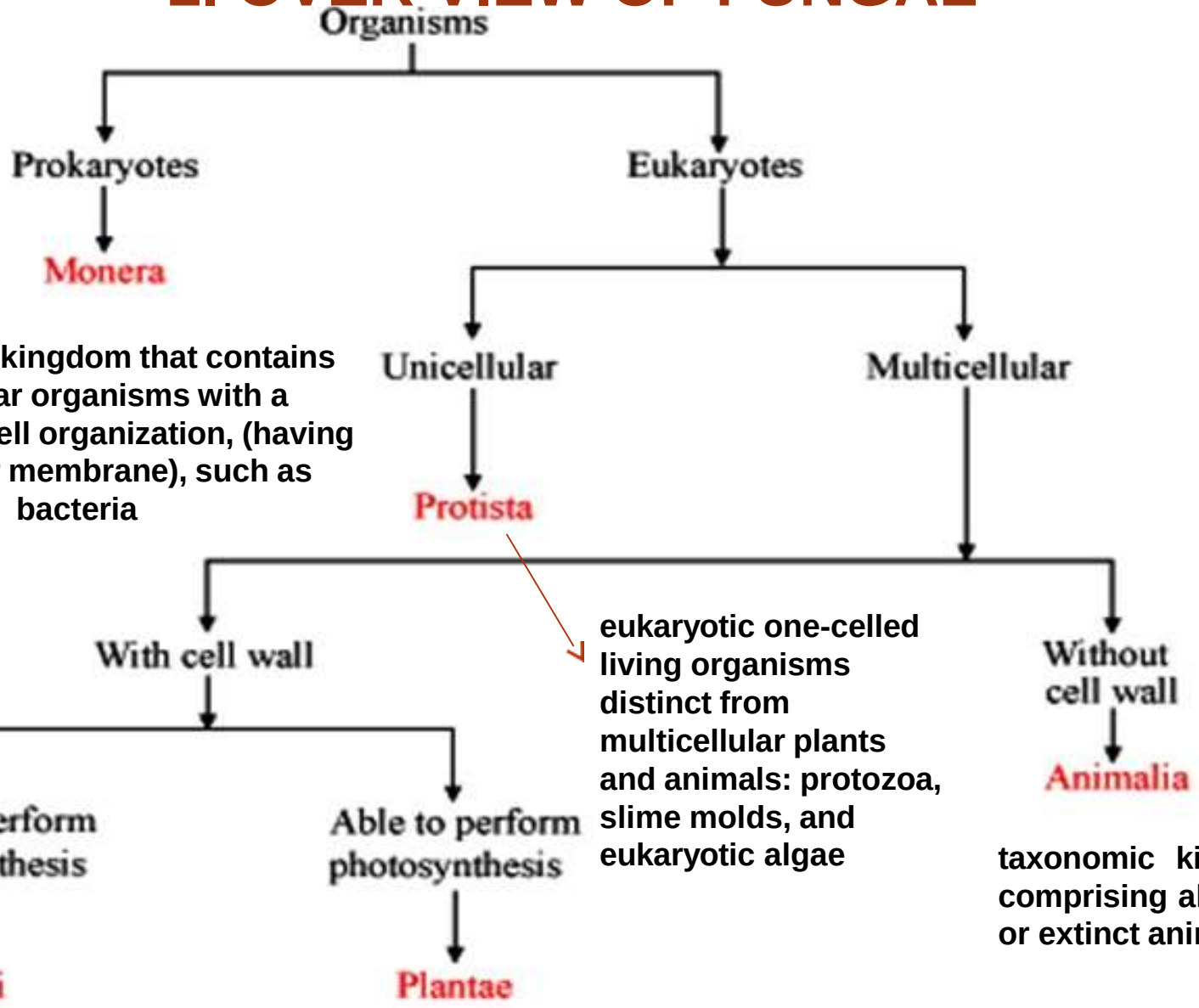
School of Medical & Allied Sciences

Course Code : BPHT6001 **Course Name: Medicinal Chemistry-III**

Anti-fungal agents

Name of the Faculty: Dr. Deepika **Name: B. Pharmacy**

1. OVER VIEW OF FUNGAL



Monera is a kingdom that contains unicellular organisms with a prokaryotic cell organization, (having no nuclear membrane), such as bacteria

eukaryotic one-celled living organisms distinct from multicellular plants and animals: protozoa, slime molds, and eukaryotic algae

taxonomic kingdom comprising all living or extinct animals

Lack chlorophyll, leaves, true stems, and roots, reproduce by spores, and live as saprotrophs or parasites

Plants, also called green plants (Viridiplantae in Latin), are living multicellular organisms of thekingdom Plantae.

1. OVER VIEW OF FUNGAL

THE FUNGI KINGDOM

Mycology - *the study of fungi*

fungi - *singular*

fungus - *plural*

4 Main Characteristics of Fungi

1) fungi are **eukaryotic**

- they have a nuclei & mitochondria

2) they are **heterotrophs**

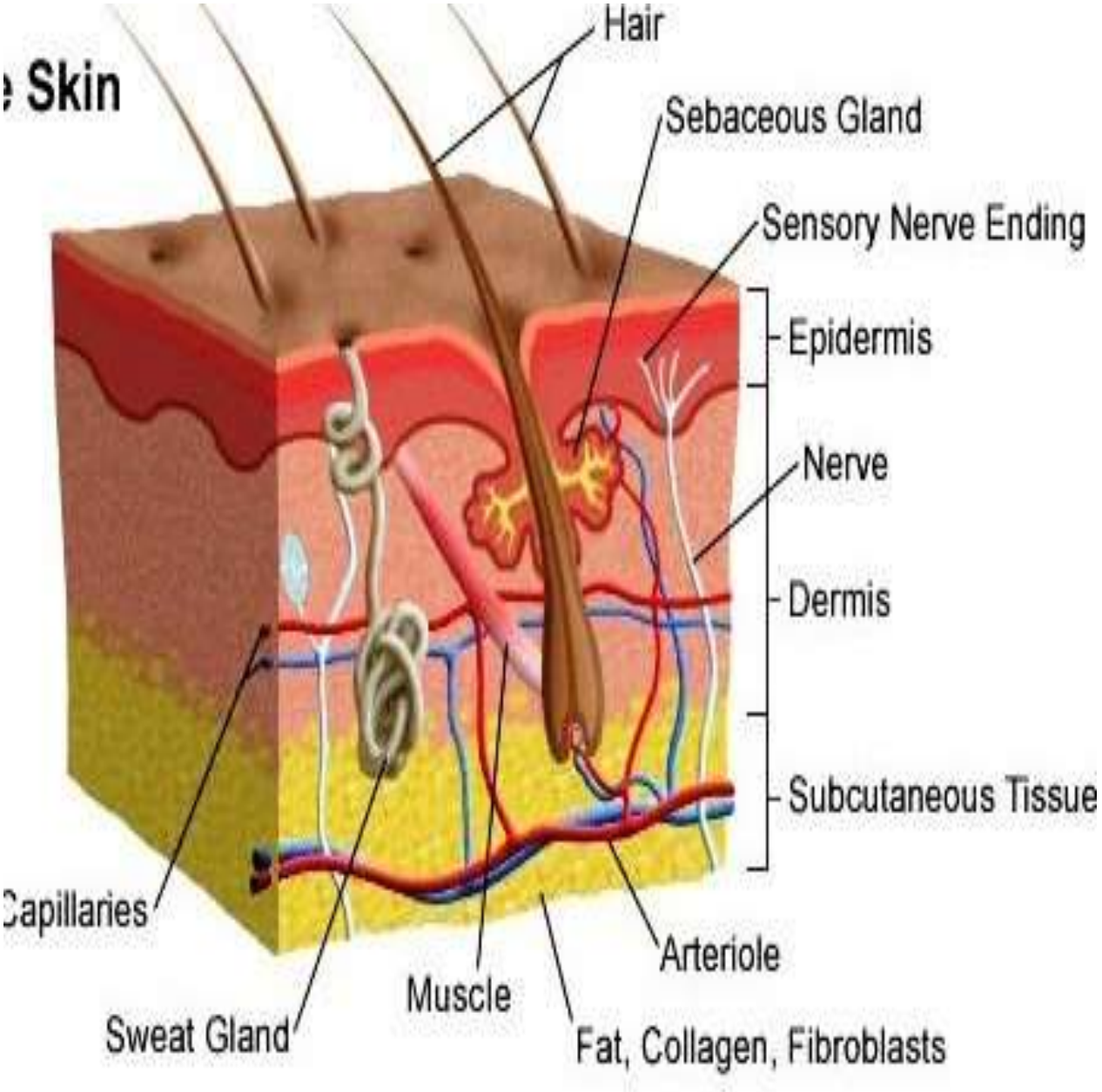
- they depend on other organisms for food

3) they are **multicellular**

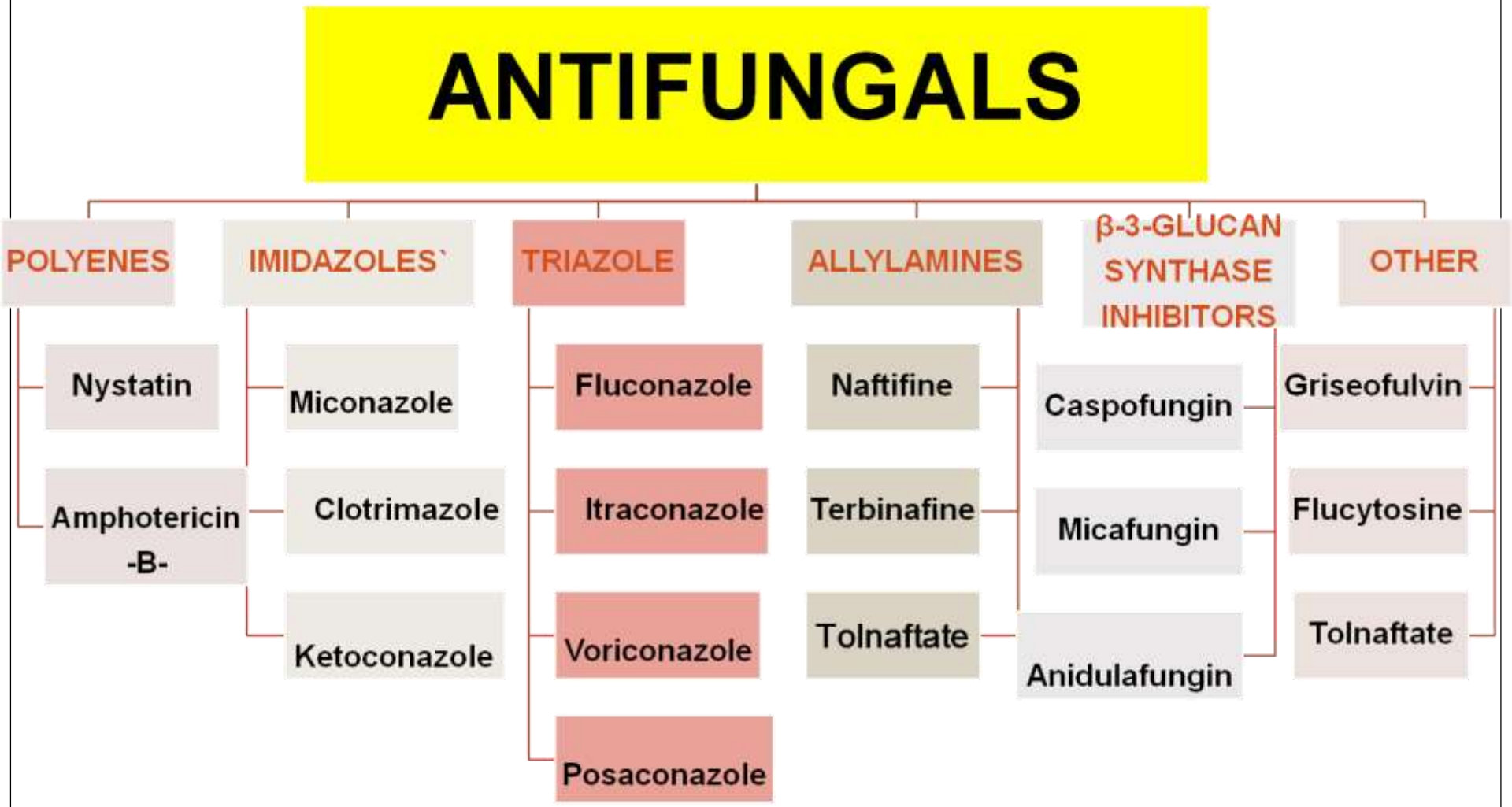
4) they cannot move on their own

1. OVER VIEW OF FUNGAL INFECTION

- **Major Types of Mycoses**
  - superficial
  - cutaneous
  - subcutaneous
  - systemic
  - opportunistic



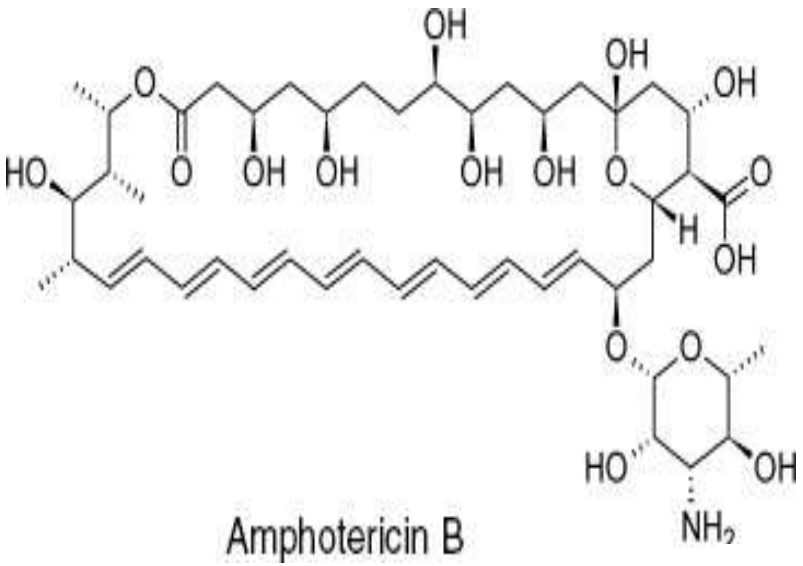
5.CLASSIFICATION



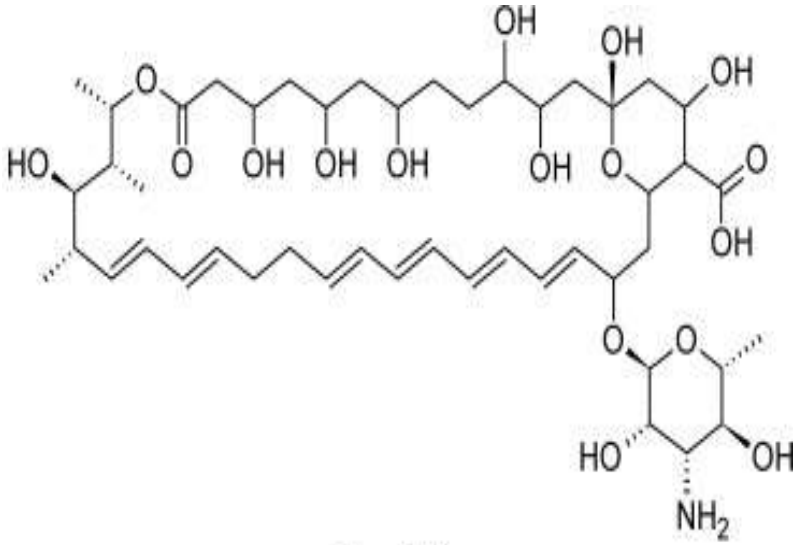
Chemical classification with structure

1.Antifunal antibiotics

a.Polyene antibiotics

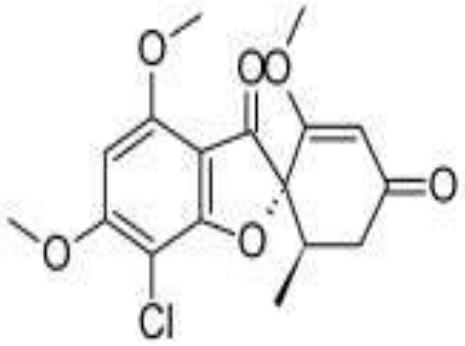


Amphotericin B



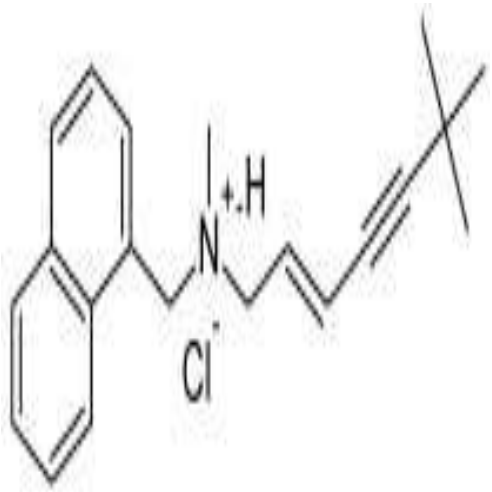
Nystatin

b.Other antifungal antibiotics

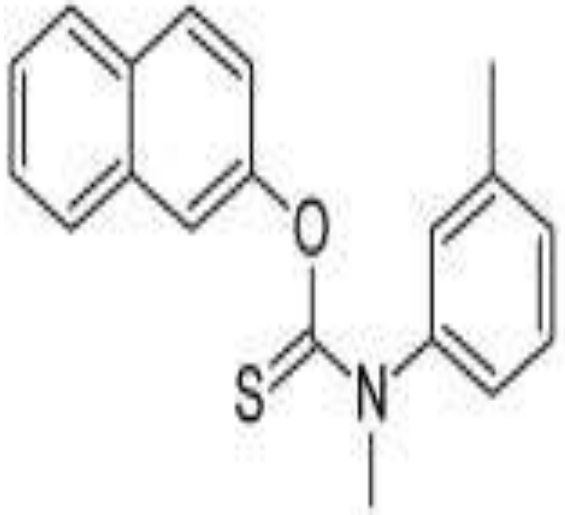


griseofulvin

2.Allyl amines

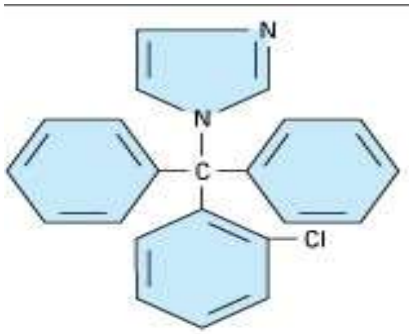


terbinafine

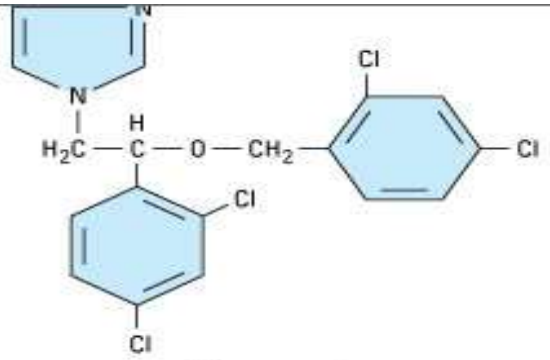


Tolnaftate

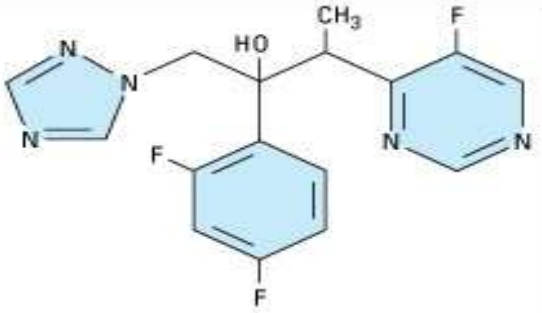
3. CHEMICAL STRUCTURES AZOLE ANTIFUNGAL DRUGS



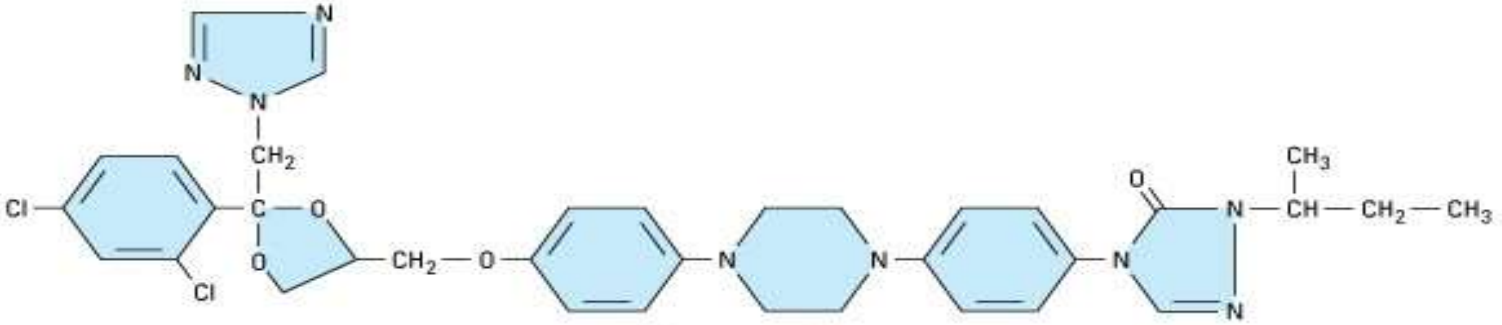
Clotrimazole



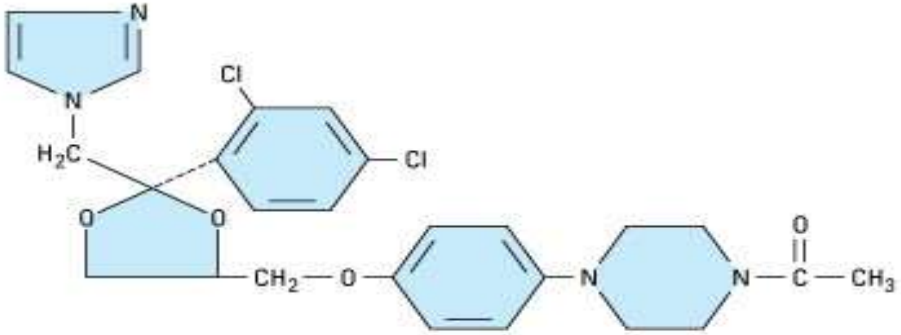
Miconazole



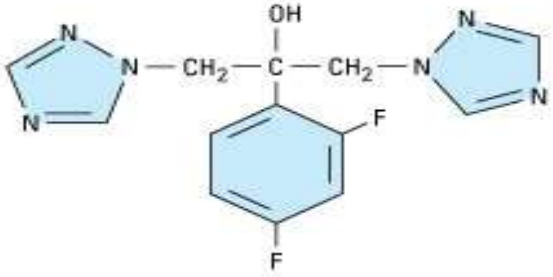
Voriconazole



Itraconazole



Ketoconazole



Fluconazole

5.CLASSIFICATION OF ANTIFUNGAL

DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

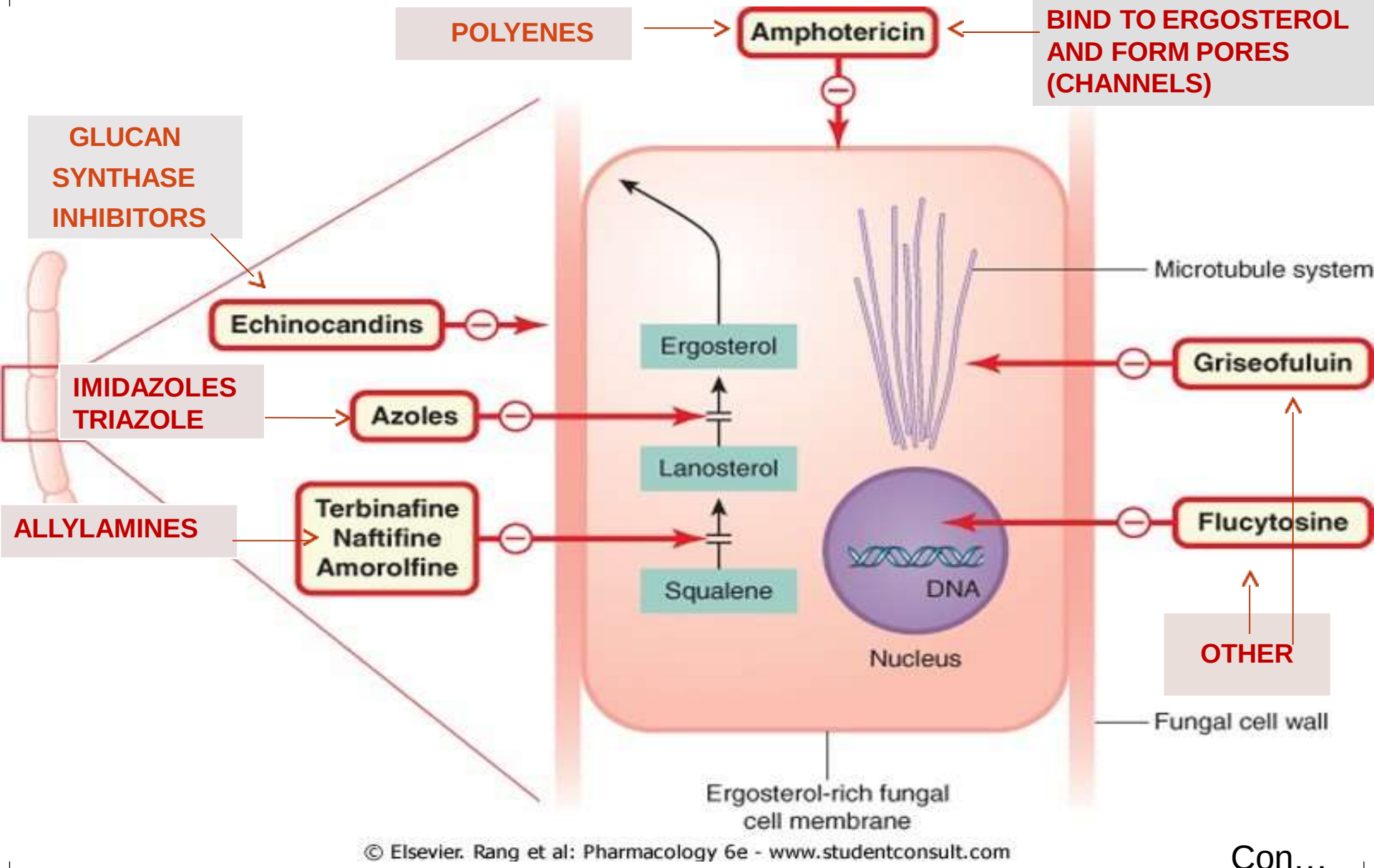
- ***Amphotericin B*** AMBISOME
- ***Anidulafungin*** ERAXIS
- ***Caspofungin*** CANCIDAS
- ***Fluconazole*** DIFLUCAN
- ***Flucytosine*** ANCOBON
- ***Itraconazole*** SPORANOX
- ***Ketoconazole*** NIZORAL
- ***Micafungin*** MYCAMINE
- ***Posaconazole*** NOXAFIL
- ***Voriconazole*** VFEND

DRUGS FOR CUTANEOUS MYCOSES

- ***Butenafine*** LOTRIMIN ULTRA
- ***Clotrimazole***, LOTRIMIN AF
- ***Ciclopirox*** PENLAC
- ***Econazole*** ECONAZOLE NITRATE
- ***Griseofulvin*** GRIFULVIN V, GRIS-PEG
- ***Miconazole*** FUNGOID, MICATIN, MONISTAT
- ***Naftifine*** NAFTIN
- ***Nystatin*** MYCOSTATIN
- ***Oxiconazole*** OXISTAT
- ***Sertaconazole*** ERTACZO
- ***Sulconazole*** EXELDERM
- ***Terbinafine*** LAMISIL
- ***Terconazole*** TERAZOL
- ***Tioconazole*** VAGISTAT-1
- ***Tolnaftate*** TINACTIN

Con…

6.SITES OF ACTION OF COMMON ANTIFUNGAL DRUGS



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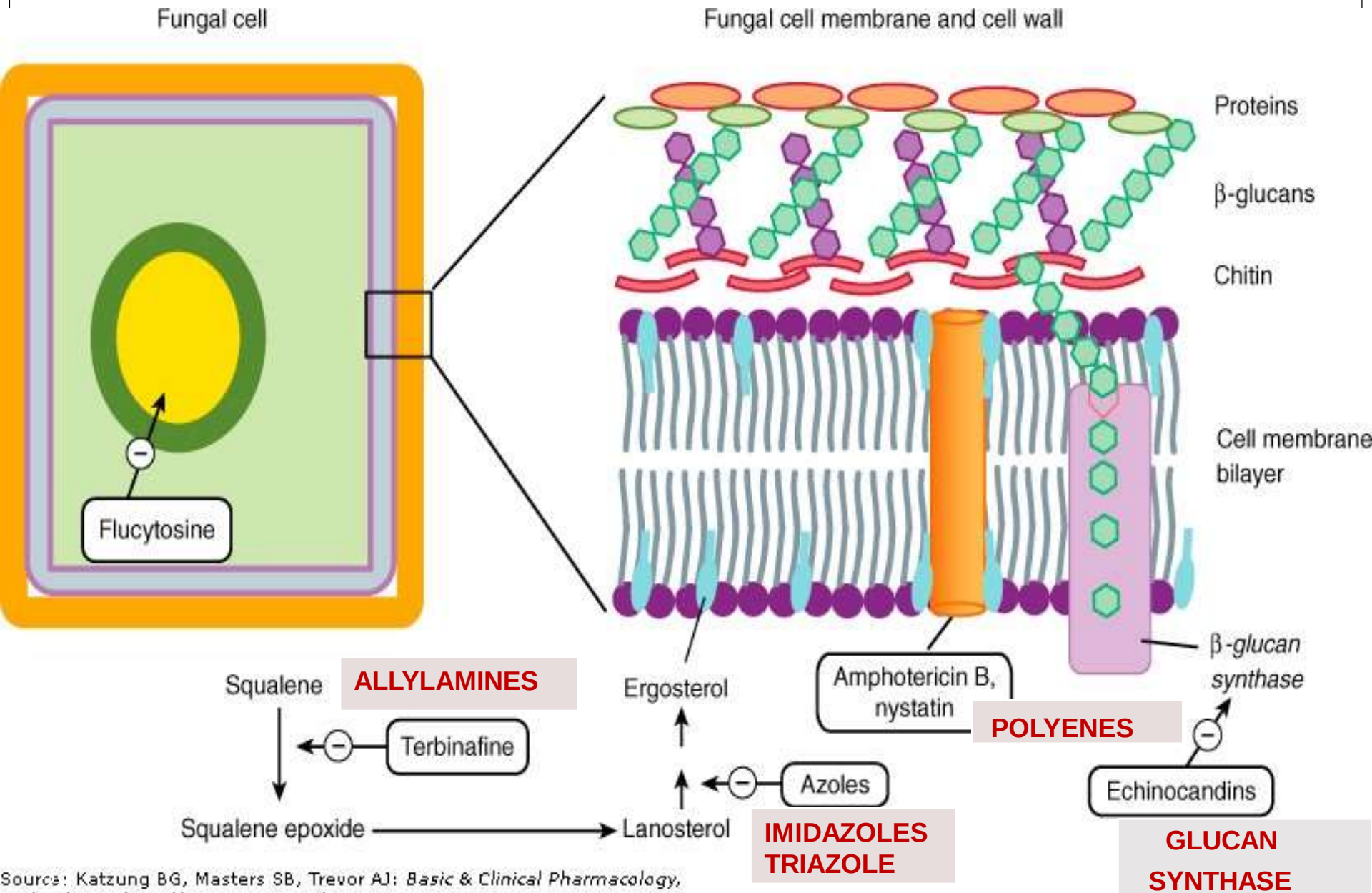
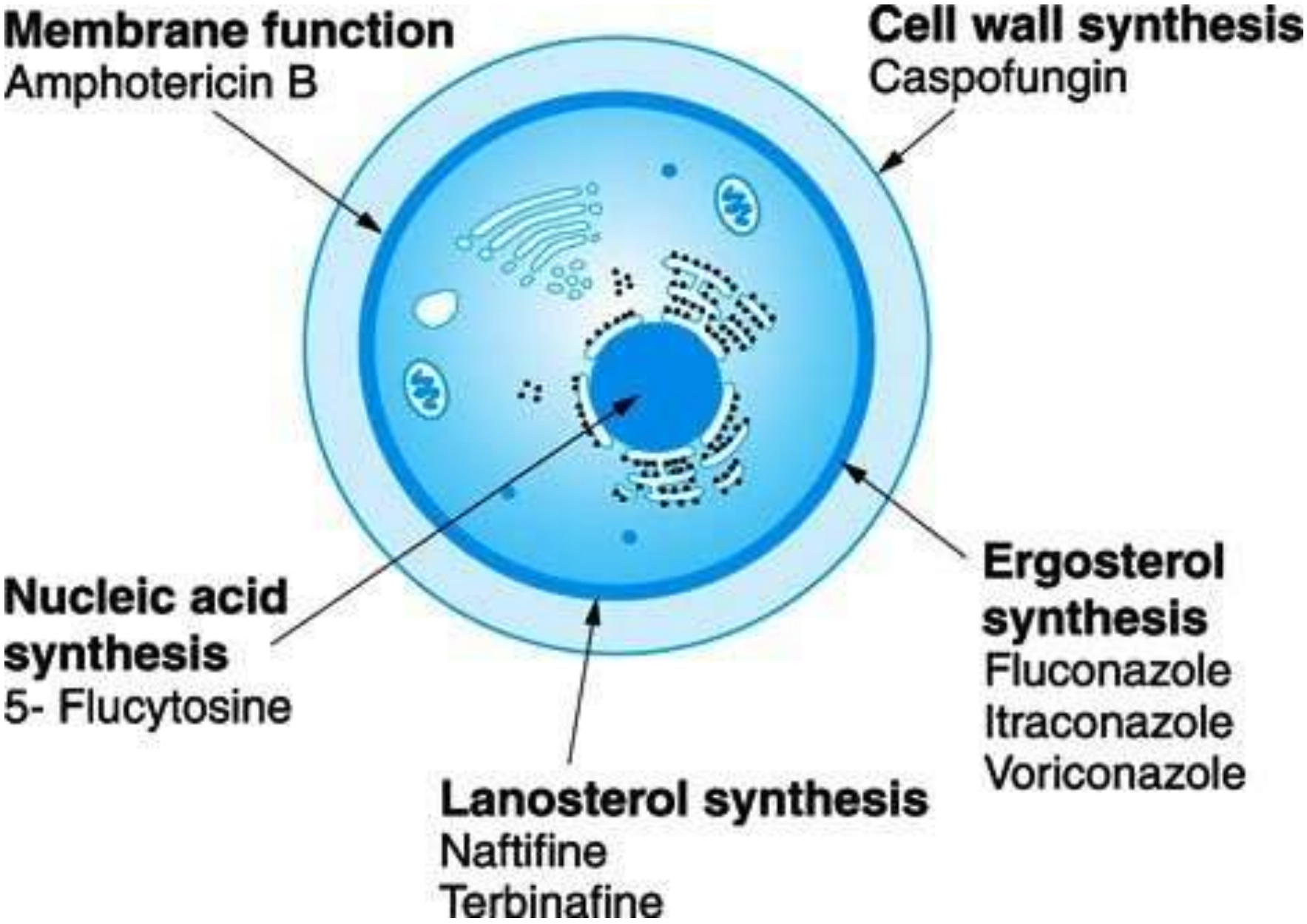
6.SITES OF ACTION OF COMMON ANTIFUNGAL DRUGS

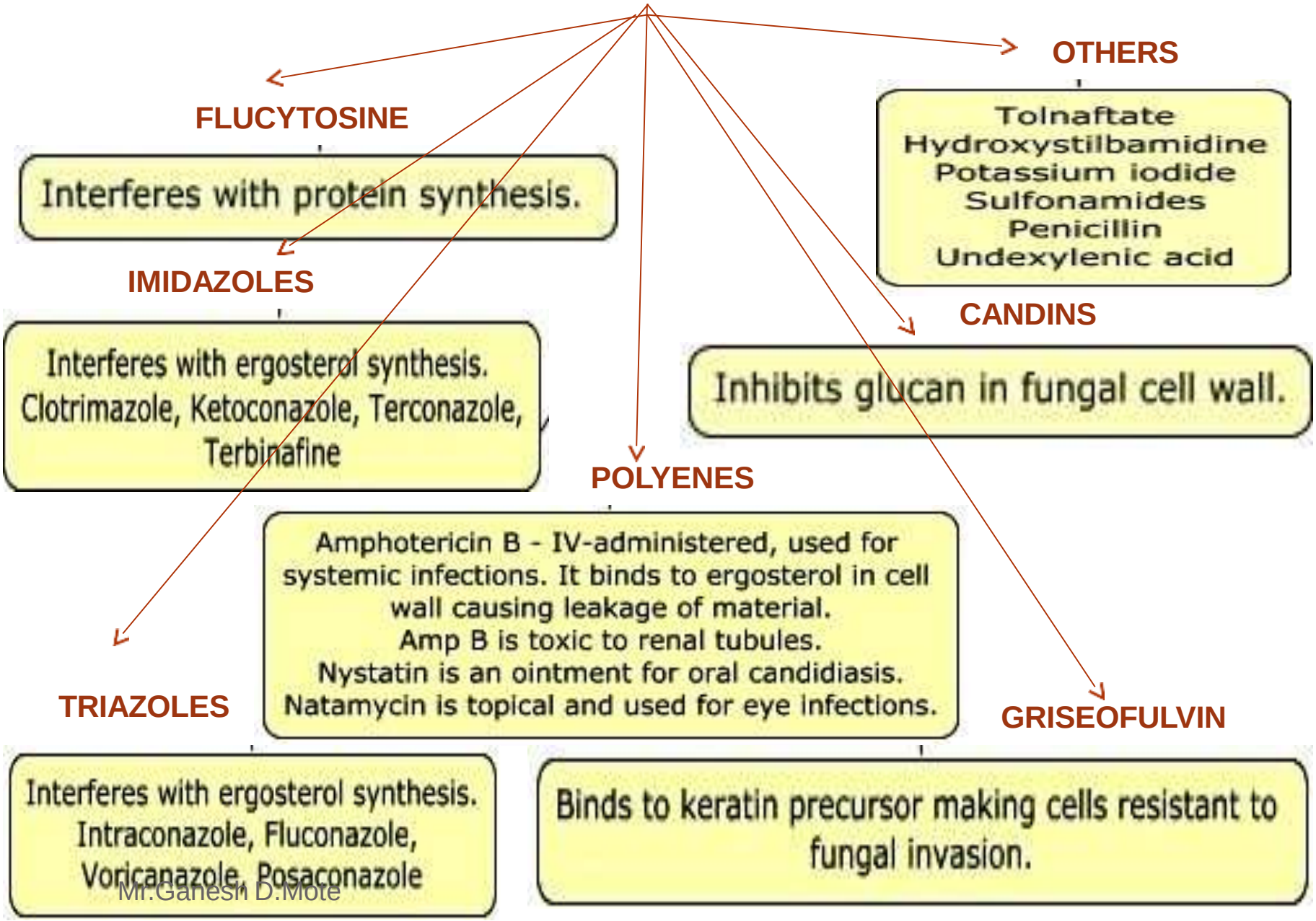


Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

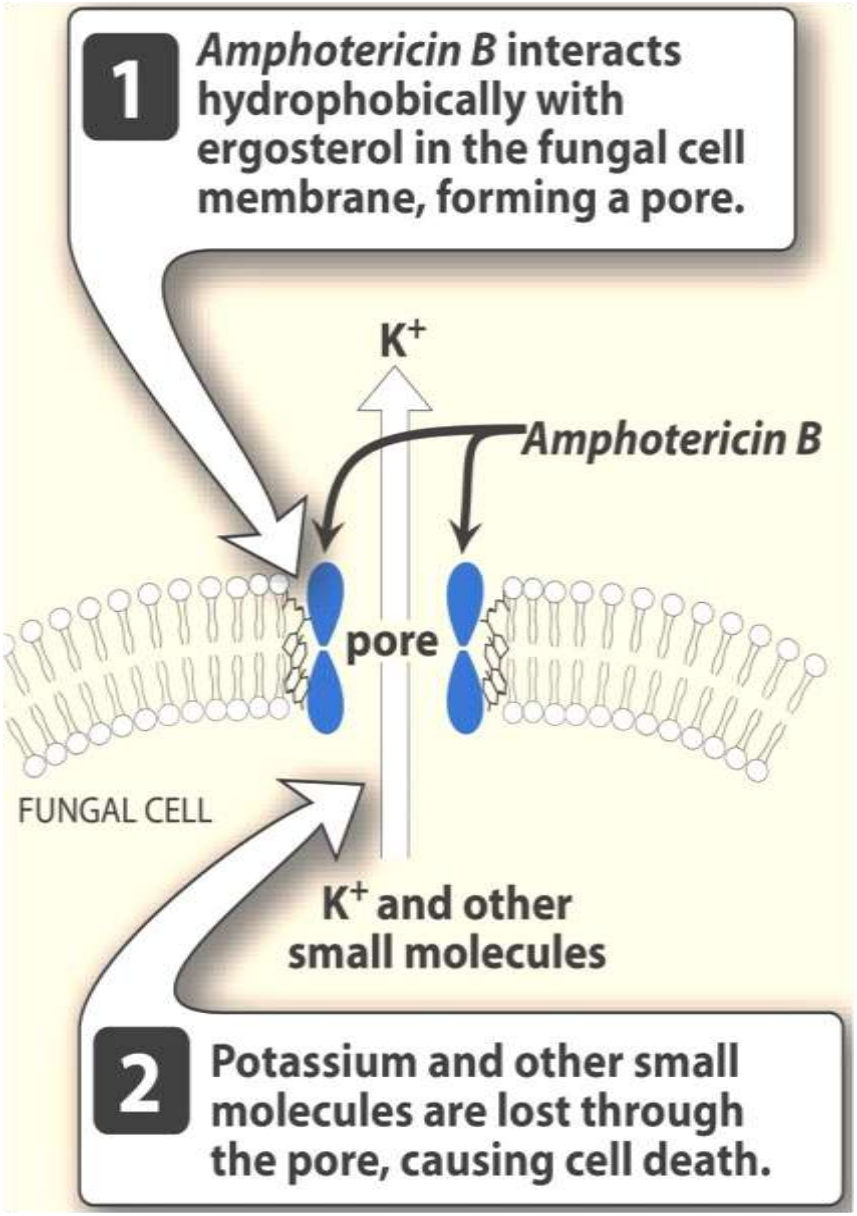
6.SITES OF ACTION OF COMMON ANTIFUNGAL DRUGS



7. ANTI FUNGAL DRUGS MECHANISAM



8.MECHANISM OF AMPHOTERICIN B

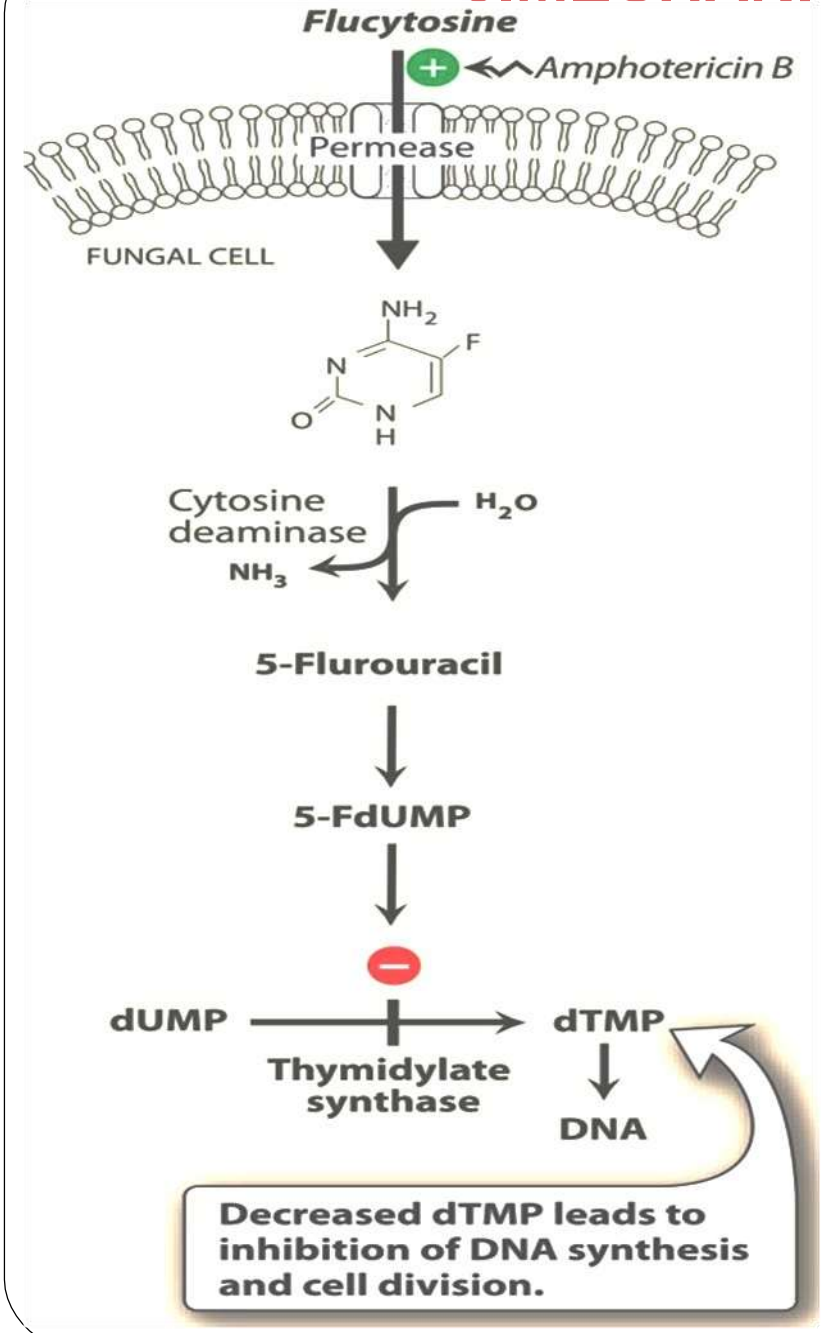


Several amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells.

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.**

9.MECHANISM OF FLUCYTOSINE



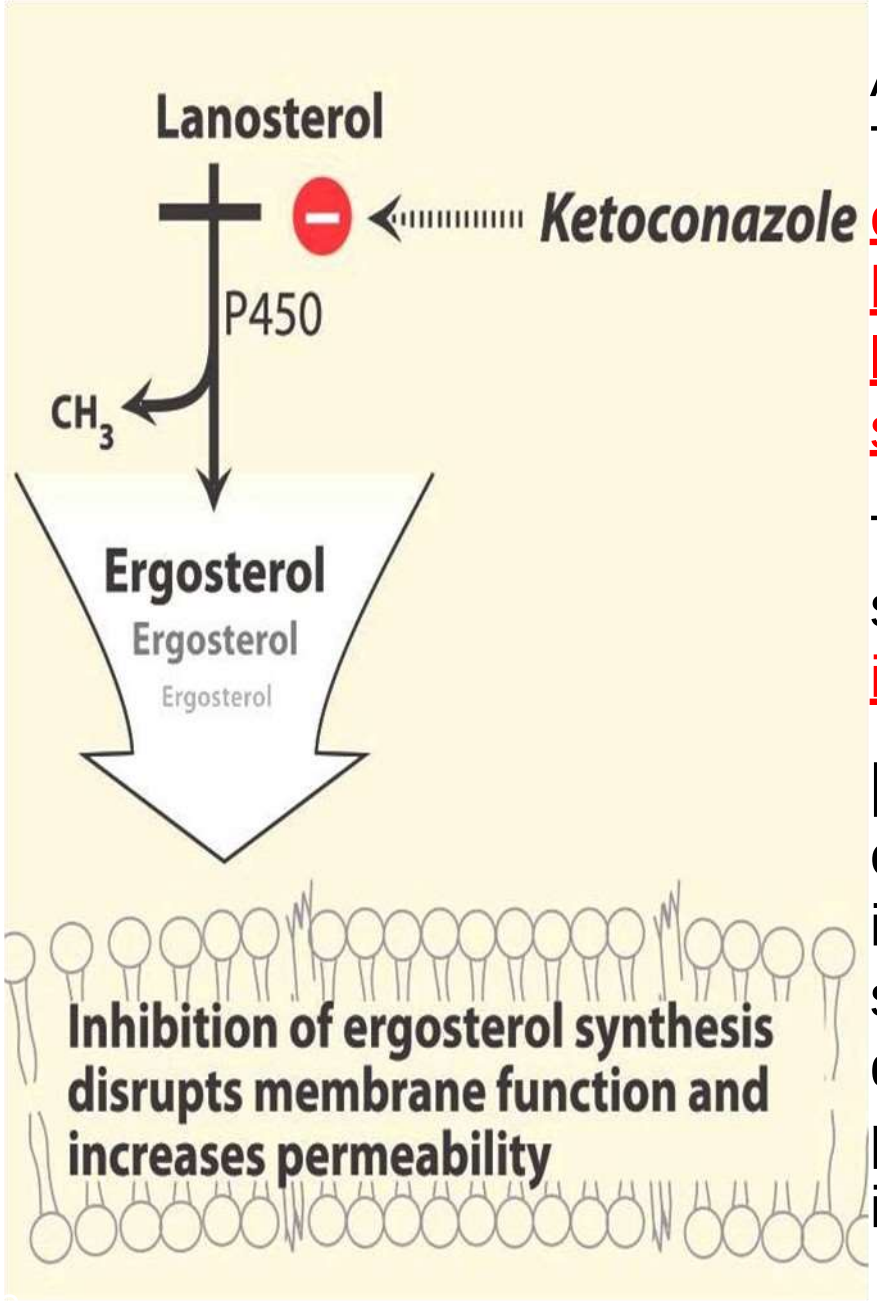
Flucytosine enters fungal cells via a cytosine-specific permease an enzyme not found in mammalian cells.

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.]

10.MECHANISM OF KETOCONAZOLE

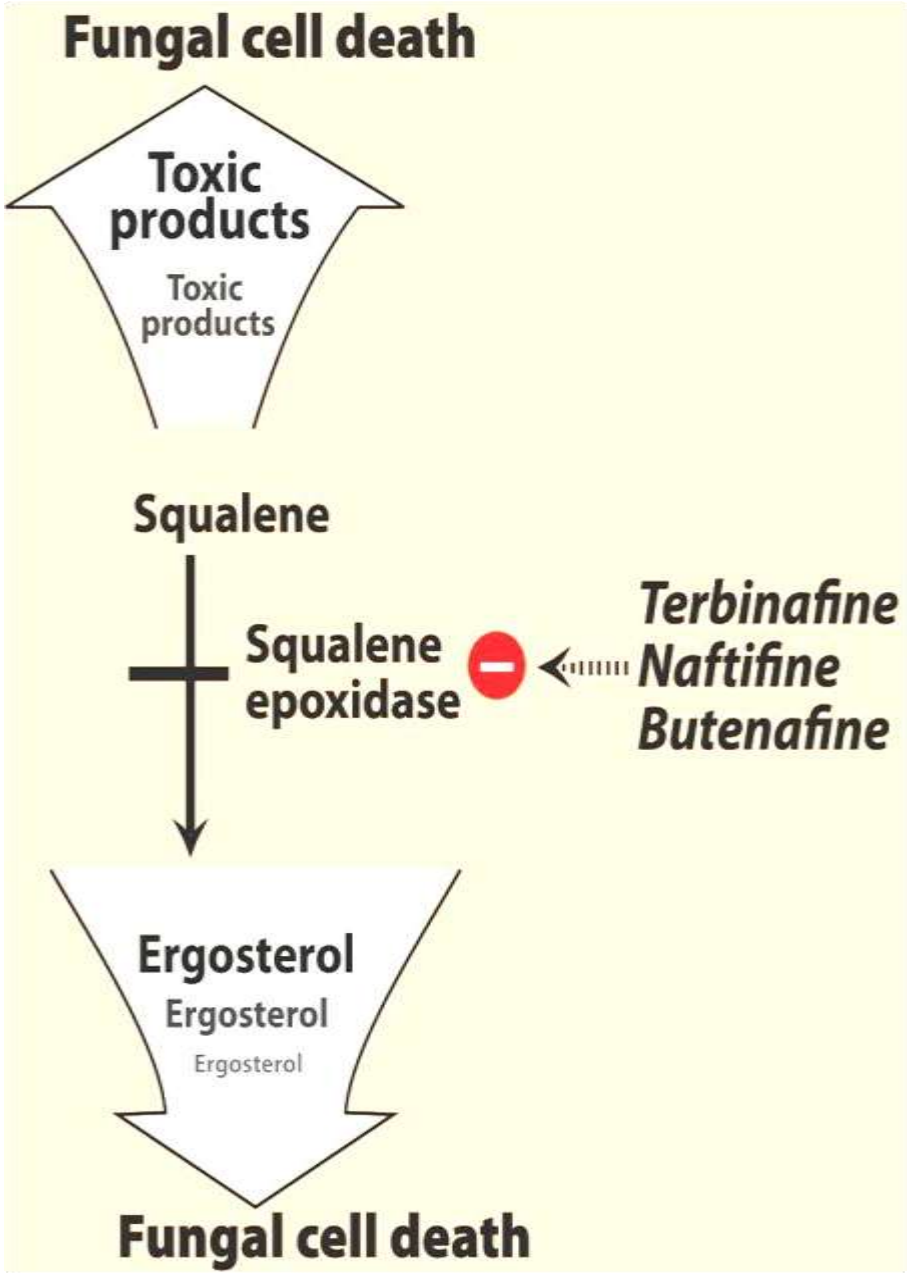


Azoles are predominantly fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterol the principal sterol of fungal membranes.

This inhibition disrupts membrane structure and function and, thereby, inhibits fungal cell growth.

[Note:In addition to blocking fungal ergosterol synthesis, the drug also inhibits human gonadal and adrenal steroid synthesis, leading to decreased testosterone and cortisol production. In addition, ketoconazole inhibits cytochrome P450]

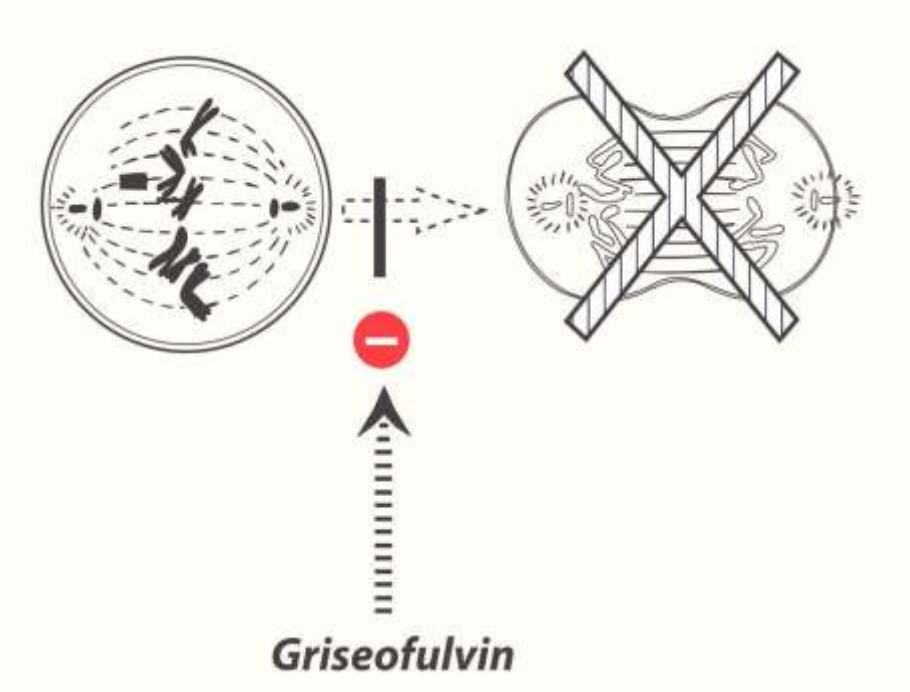
11.MECHANISM OF TERBINAFINE



Terbinafine inhibits fungal squalene epoxidase, thereby decreasing the synthesis of ergosterol .

This plus the accumulation of toxic amounts of **squalene result in the death of the fungal cell.**

12. MECHANISM OF GRISEOFULVIN



It is only fungistatic, and it causes a number of significant drug interactions.

Griseofulvin accumulates in newly synthesized, keratin-containing tissue, where **it causes disruption of the mitotic spindle and inhibition of fungal mitosis .**

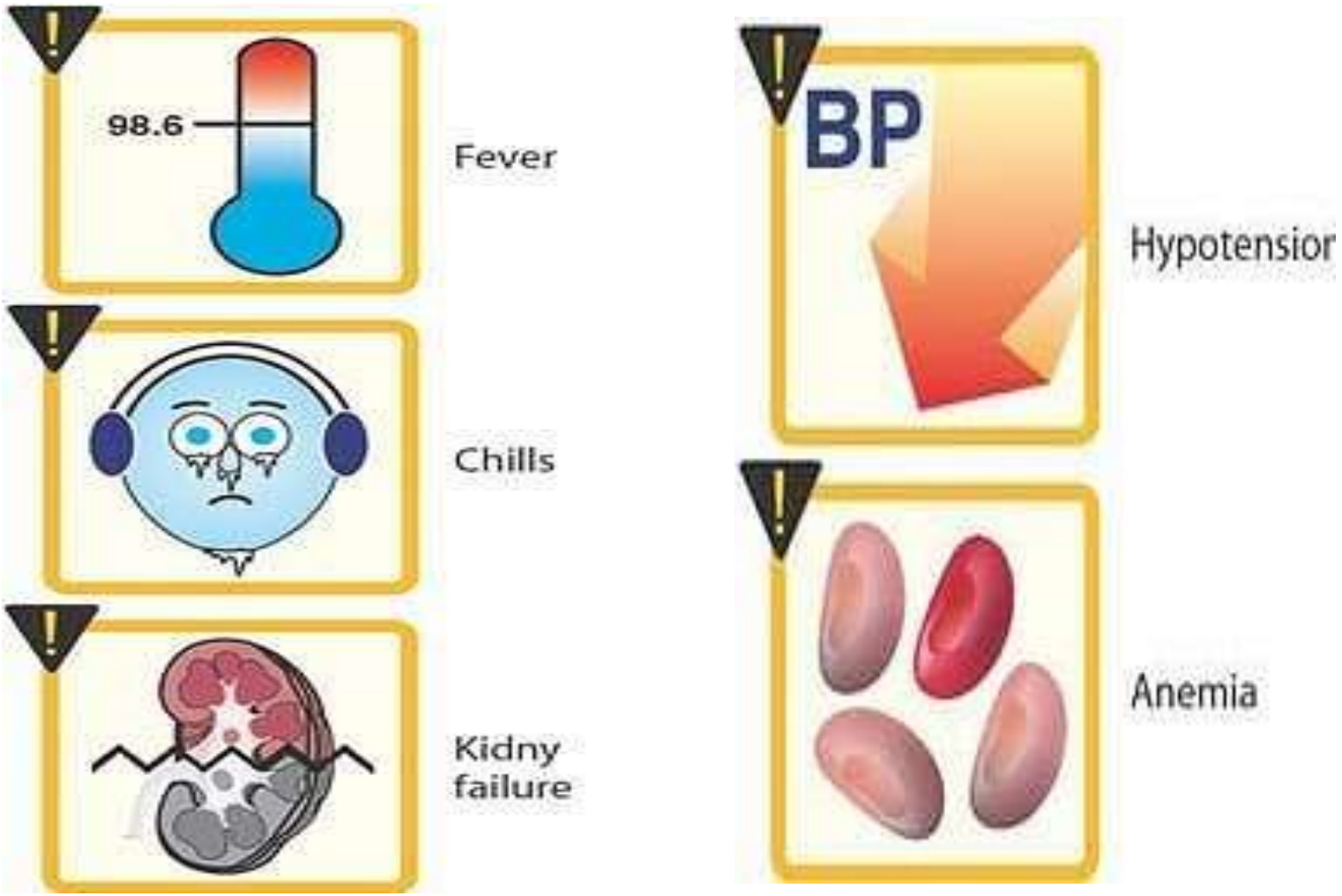
13. SOME ADVERSE REACTIONS OF ANTIFUNGAL DRUGS

Medscape

Antifungal agent	Form	Strength	Adverse events
Topical			
Nystatin	Pastille	200,000 units	Nausea, vomiting and diarrhea
	Suspension	–	
Clotrimazole	Oral troche	10 mg troche	Nausea, vomiting, local discomfort and anorexia
Amphotericin B	Suspension Lozenge Tablet	1 mg/ml 100 mg 10 mg	Nephrotoxicity, hypokalemia, hypomagnesemia, anemia, thrombocytopenia, infusion-related reactions, nausea, vomiting and fever
Miconazole Lauriad®	Lauriad	10 mg	Local discomfort
Systemic			
Ketoconazole	Tablets	200 mg	Hepatotoxicity, nausea, vomiting, edema and diarrhea
Fluconazole	Tablet Solution iv. piggyback	100 mg 10 mg/ml –	Hepatotoxicity, photosensitivity dermatitis, nausea, vomiting and rash
Itraconazole	Capsule Solution	100 mg 10 mg/ml	Hepatotoxicity, edema, hypokalemia, nausea, vomiting, rash and diarrhea
Posaconazole	Suspension	100 mg/2.5 ml	Nausea, vomiting, diarrhea, hepatotoxicity and edema

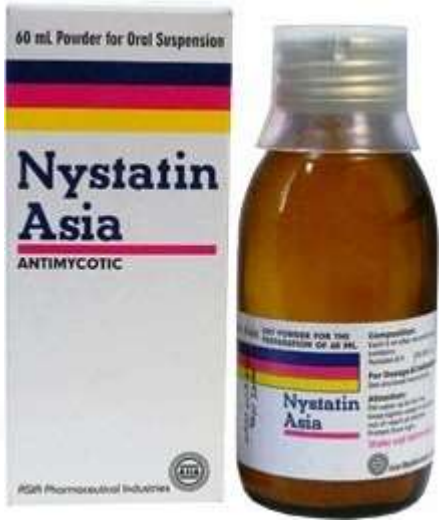
Oral therapy is preferred when tolerated.
iv.: Intravenous.

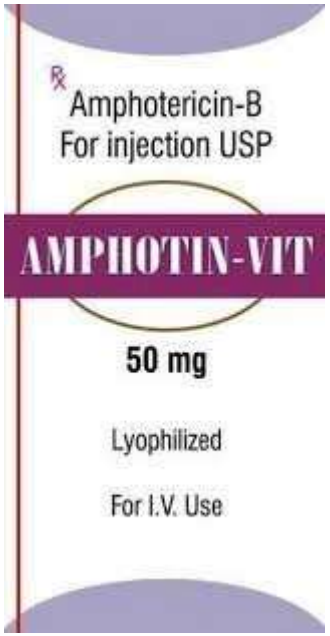
14. SOME ADVERSE REACTIONS OF AMPHOTERICIN B.



POLYENES

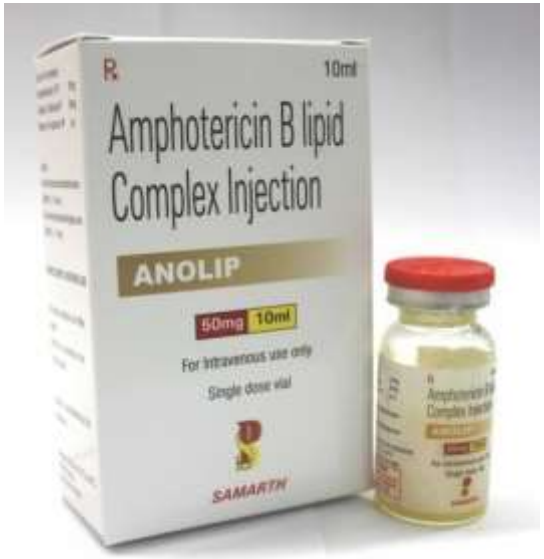

1 x 14 Tablets
Nystatin
Vaginal
Tablets Usp


60 mL Powder for Oral Suspension
Nystatin
Asia
ANTIMYCOTIC
Nystatin
Asia


Amphotericin-B
For injection USP
AMPHOTIN-VIT
50 mg
Lyophilized
For I.V. Use


Nystatin and Triamcinolone
Acetonide Cream, USP
TARO


Nystatin and Triamcinolone
Acetonide Cream, USP
TARO


10ml
Amphotericin B lipid
Complex Injection
ANOLIP
50mg 10ml
For Intravenous use only
Single dose vial
SAMARTH

IMIDAZOLES


Micogel 15g
Micogel 15g


15 ml
CLOTRIMAZOLE
TOPICAL
SOLUTION USP
Canazole
lotion
Broad Spectrum
Antimycotic
With Fungicidal
Action
LUPIN


Nizoral®
dandruff shampoo
Treats & prevents
dandruff &
seborrhoeic dermatitis
Dry, flaky, red, itchy scalp
Dermatologically tested
Fragrance free
For a healthier scalp
100 ml
up to 5 months treatment

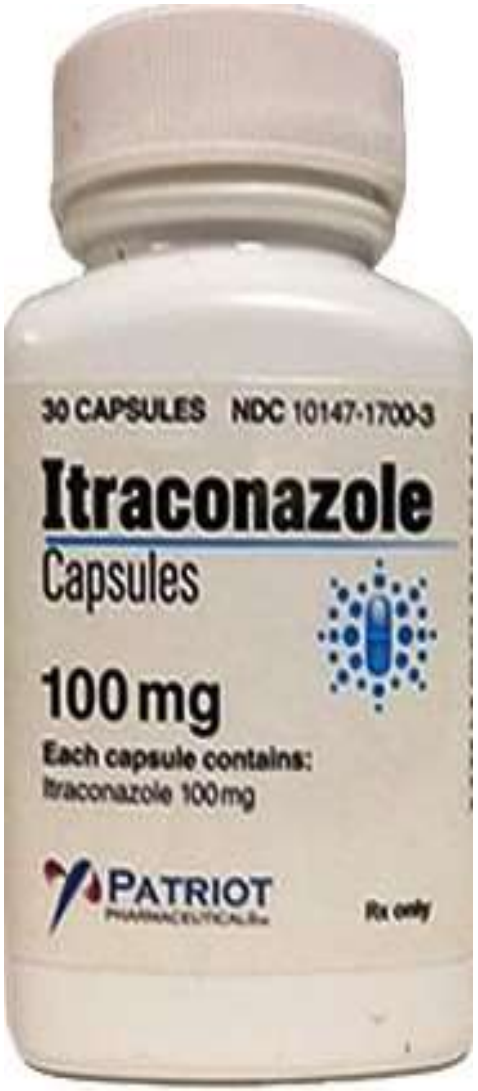

Nizoral
A-D
Nizoral
A-D


NDC 49884-062-26
ORAVIG
miconazole buccal tablets
50 mg
Rx only
14 Tablets

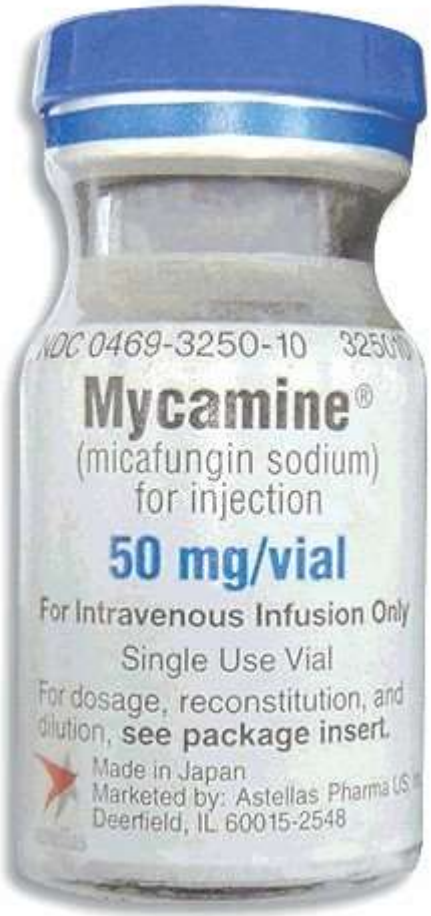

CLOTRIMAZOLE CREAM I.P.
Broad Spectrum antifungal cream
CLOTRIMAZOLE CREAM I.P.
Broad Spectrum Antifungal Cream
15 g

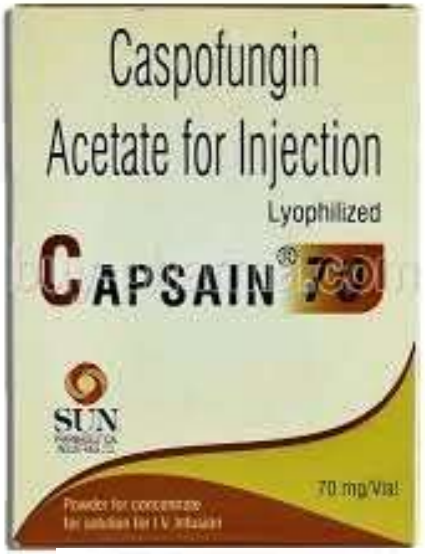
TRIAZOLE

ALLYLAMINES



B-3-GLUCAN SYNTHASE INHIBITORS





Griseofulvin

Flucytosine

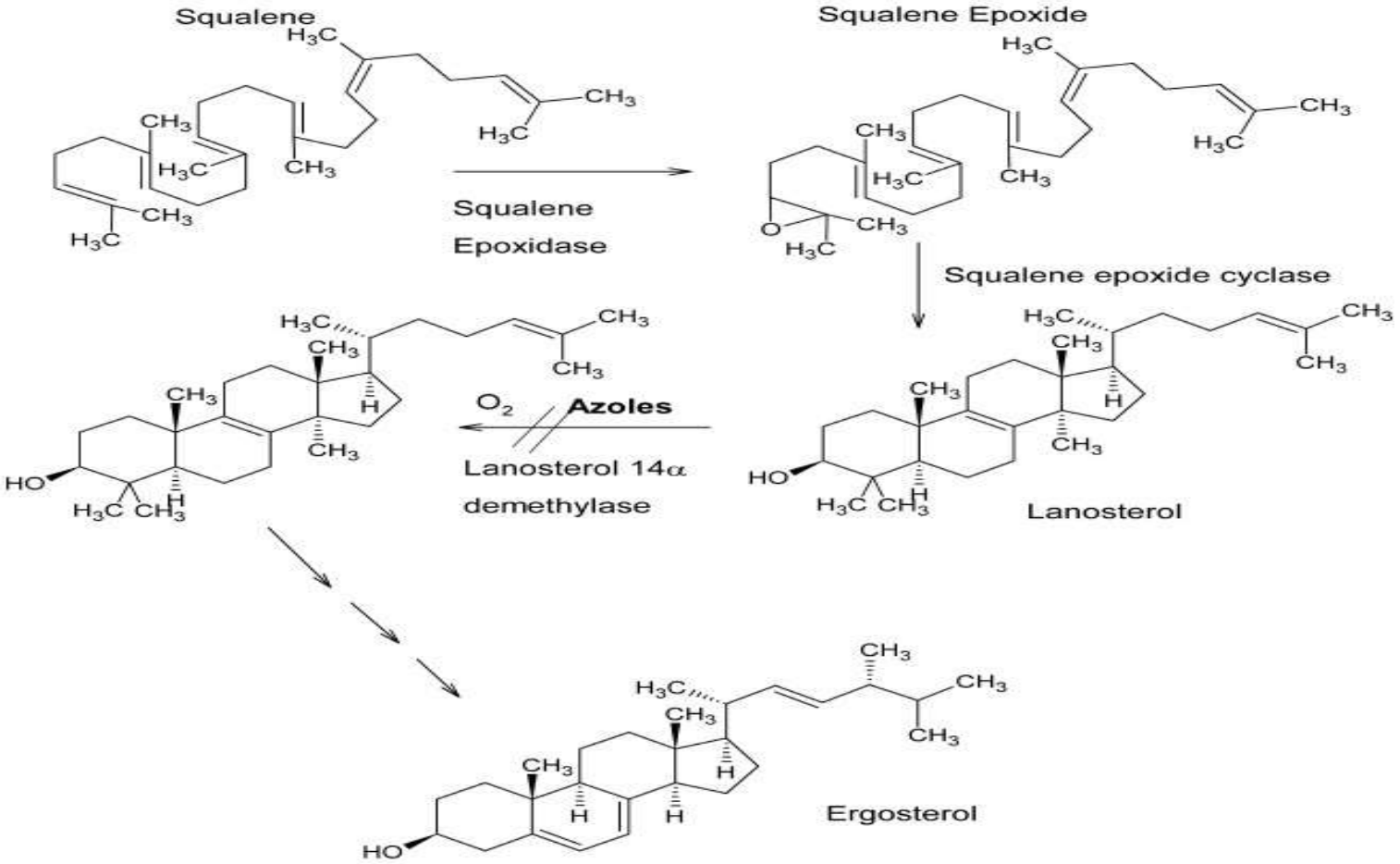
SAR OF AZOLE ANTIFUNGAL AGENTS

1. The basic structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pKaof 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 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, although functional groups such as sulfonic acids have been shown to do the same.
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 intravenously as a solution of the free base.

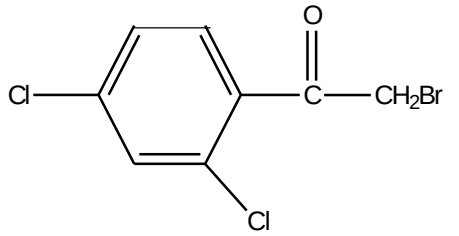
Clotrimazole

Fluconazole

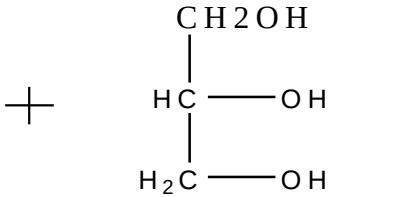
Mechanism action of squaline epoxidase(allyl amines and lanoseterol 14 ά demethylase inhibitor(Azoles derivatives)



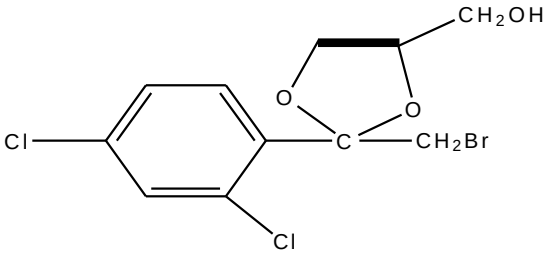
Synthesis of Ketoconazole



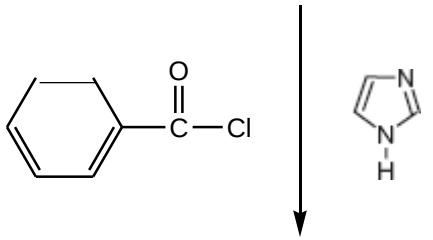
2-bromo-1-(2,4-dichlorophenyl)ethanone

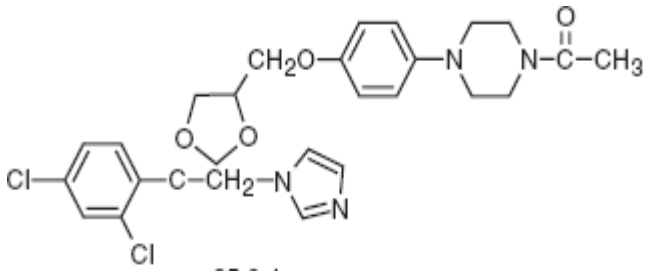


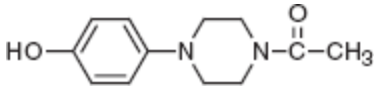
propane-1,2,3-triol

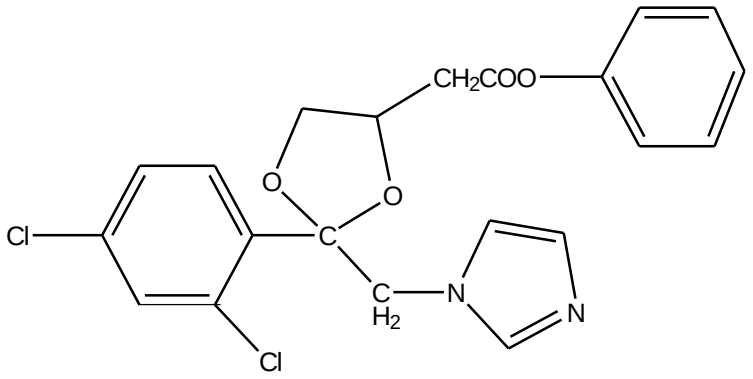


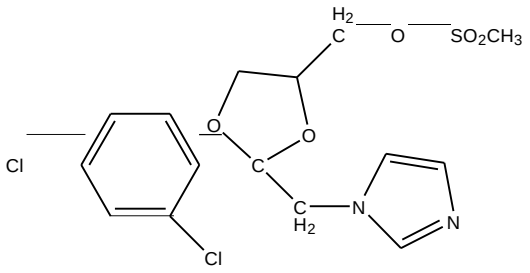
(2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methanol





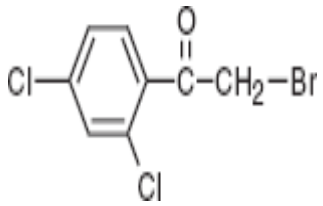






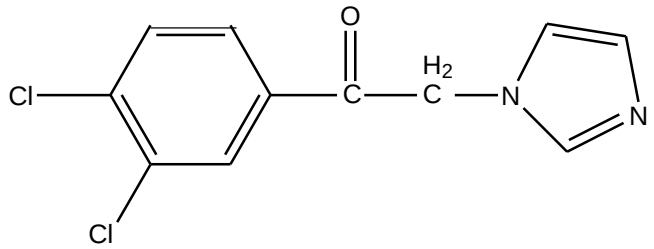
CH_3SO_3Cl

Synthesis of Miconazole



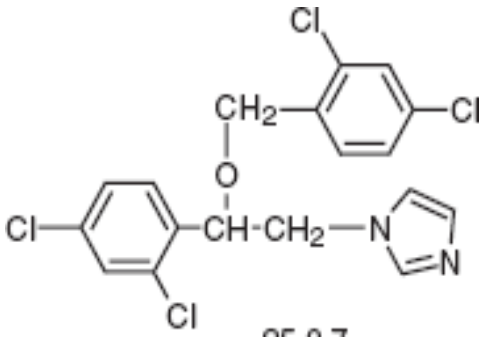
2,4-dichlorophenacylbromide

imidazole

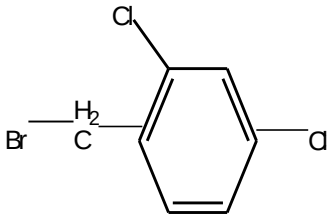


1-(3,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone

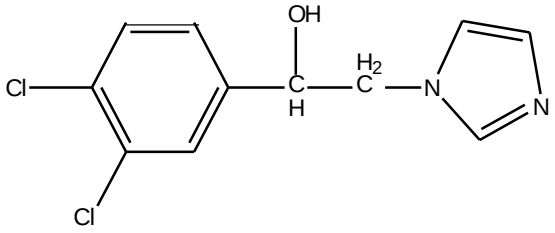
$NaBH_4$



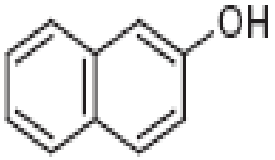
1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]-imidazole



1-(bromomethyl)-2,4-dichlorobenzene

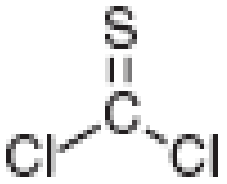


1-(3,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol



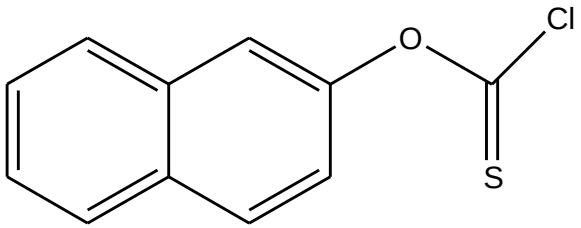
2-Naphthol

+



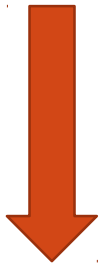
thiophosgene

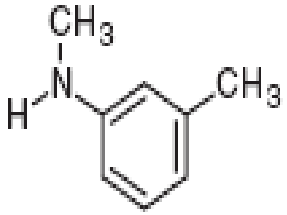
→



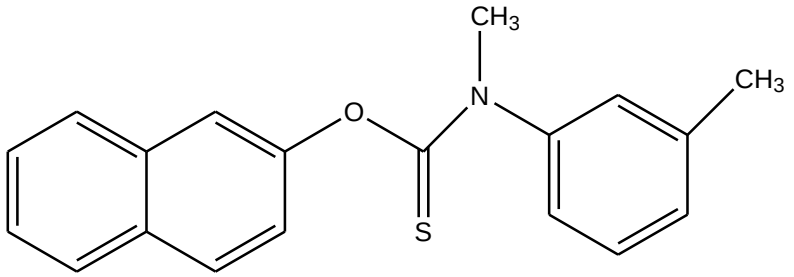
O-naphthalen-2-yl carbonochloridothioate

Synthesis of Tolnaftate





N-methyl 3-toludine



O-naphthalen-2-yl methyl(*m*-tolyl)carbamothioate

Reference

- William O. Foye.,Textbook of Medicinal Chemistry, Pg. no: 1089 -1106
- Sriram., Medicinal Chemistry, Pg. no: 295-309.
- Kadam., Textbook of Medicinal Chemistry, Pg. no: 68-82.
- Ilango., Principles of Medicinal chemistry(vol.1), Pg. no: 121-143.
- Good man And GilMan's; The Pharmacology Basis Of Therapeutics Tenth Edition, pg. no 1189-1225.
- JH Block & JM Beale., Wilson & Giswold's Textbook of Organic Medicinal Chemistry & pharmaceutical chemistry 12th Edition, 2011, pg. No. 260-294.