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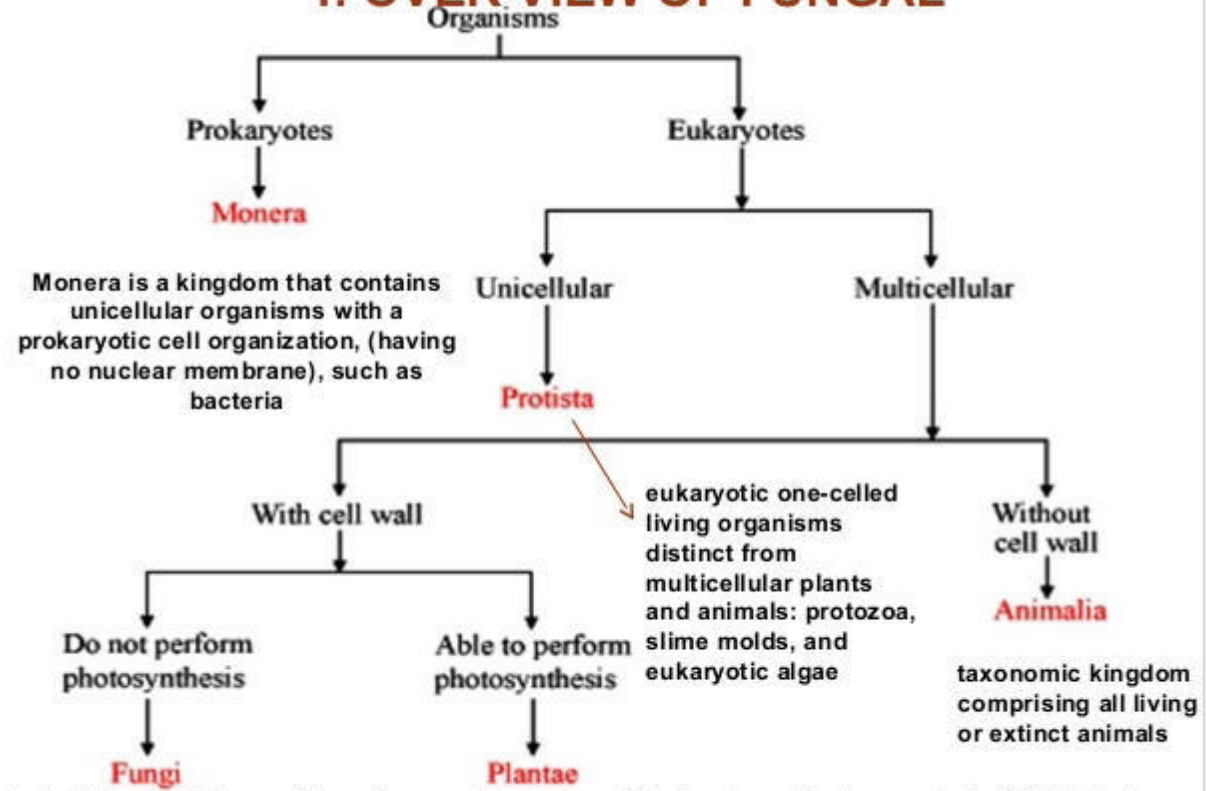
Designation: Professor
Department: Pharmacy
Subject: Medicinal Chemistry-III (BP 601T)
Unit: : IV
Topic: Antifungal Agents

3

ANTIFUNGAL DRUGS

Mr.Ganesh D.Mote

1. OVER VIEW OF FUNGAL



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**

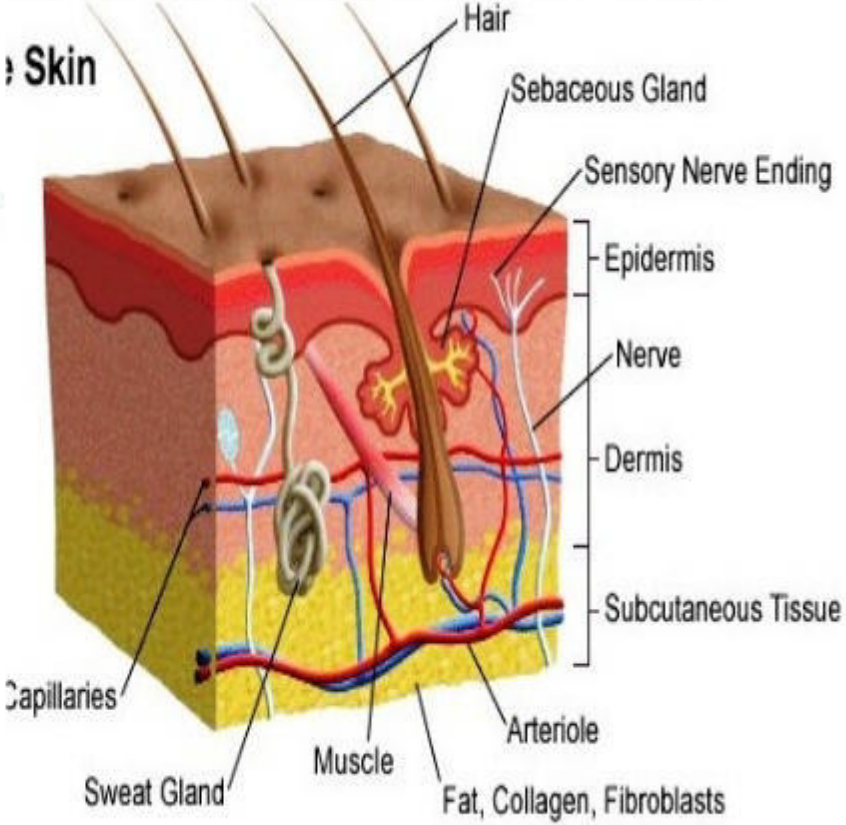
- they depend on other organisms for food

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

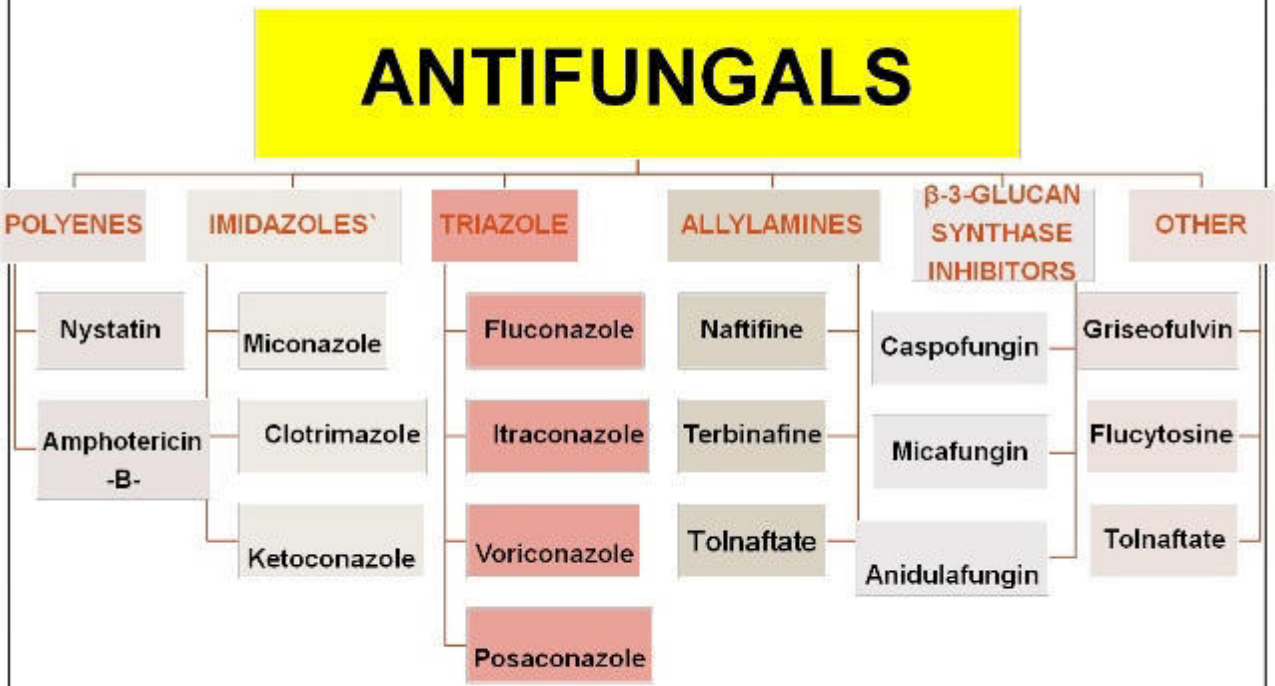


2. TYPES OF FUNGAL INFECTIONS

PATHOGENIC FUNGAI

1. CANDIDA
2. ASPERGILLUS
3. CRYPTOCOCCUS
4. HISTOPLASMA
5. PNEUMOCYSTIS
6. STACHYBOTRYS
7. MICROSPORUM
8. TRICHOPHYTON

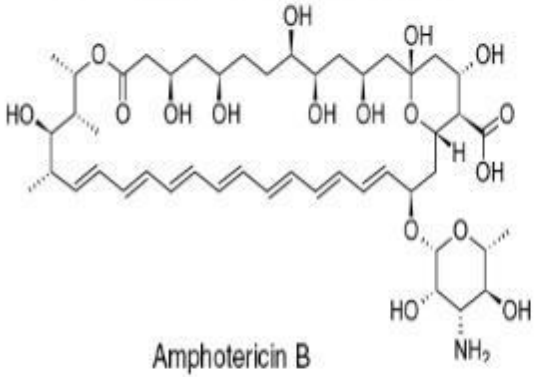
5.CLASSIFICATION



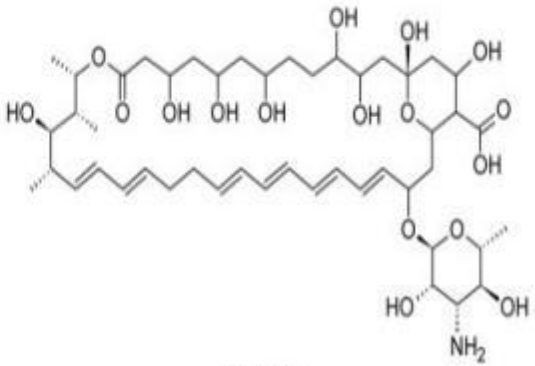
Chemical classification with structure

1.Antifunal antibiotics

a.Polyene antibiotics

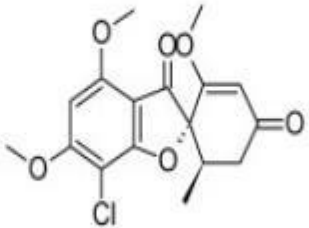


Amphotericin B



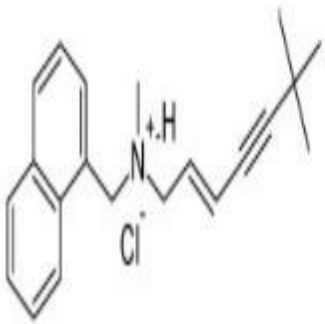
Nystatin

b.Other antifungal antibiotics

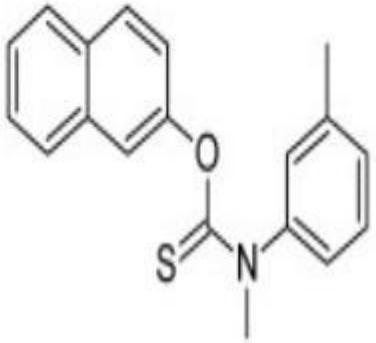


griseofulvin

2.Allyl amines

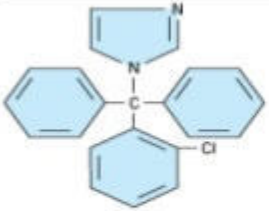


terbinafine

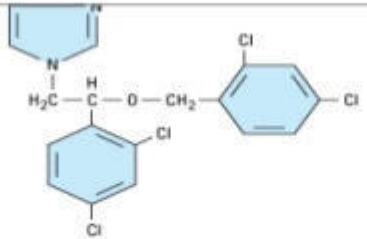


Tolnaftate

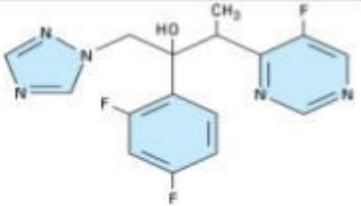
3. CHEMICAL STRUCTURES AZOLE ANTIFUNGAL DRUGS



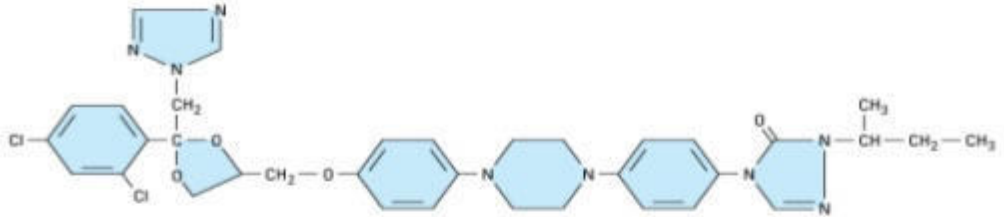
Clotrimazole



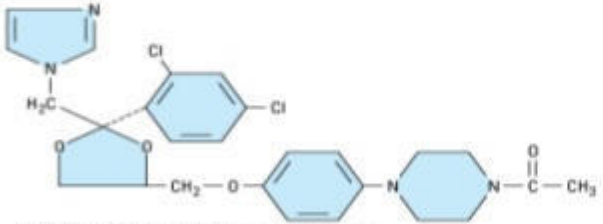
Miconazole



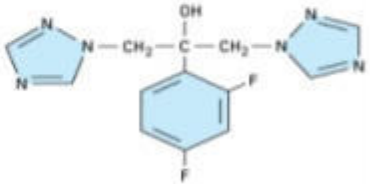
Voriconazole



Itraconazole



Ketoconazole



Fluconazole

5.CLASSIFICATION OF ANTIFUNGAL

DRUGS FOR SUBCUTANEOUS AND SYSTEMIC MYCOSES

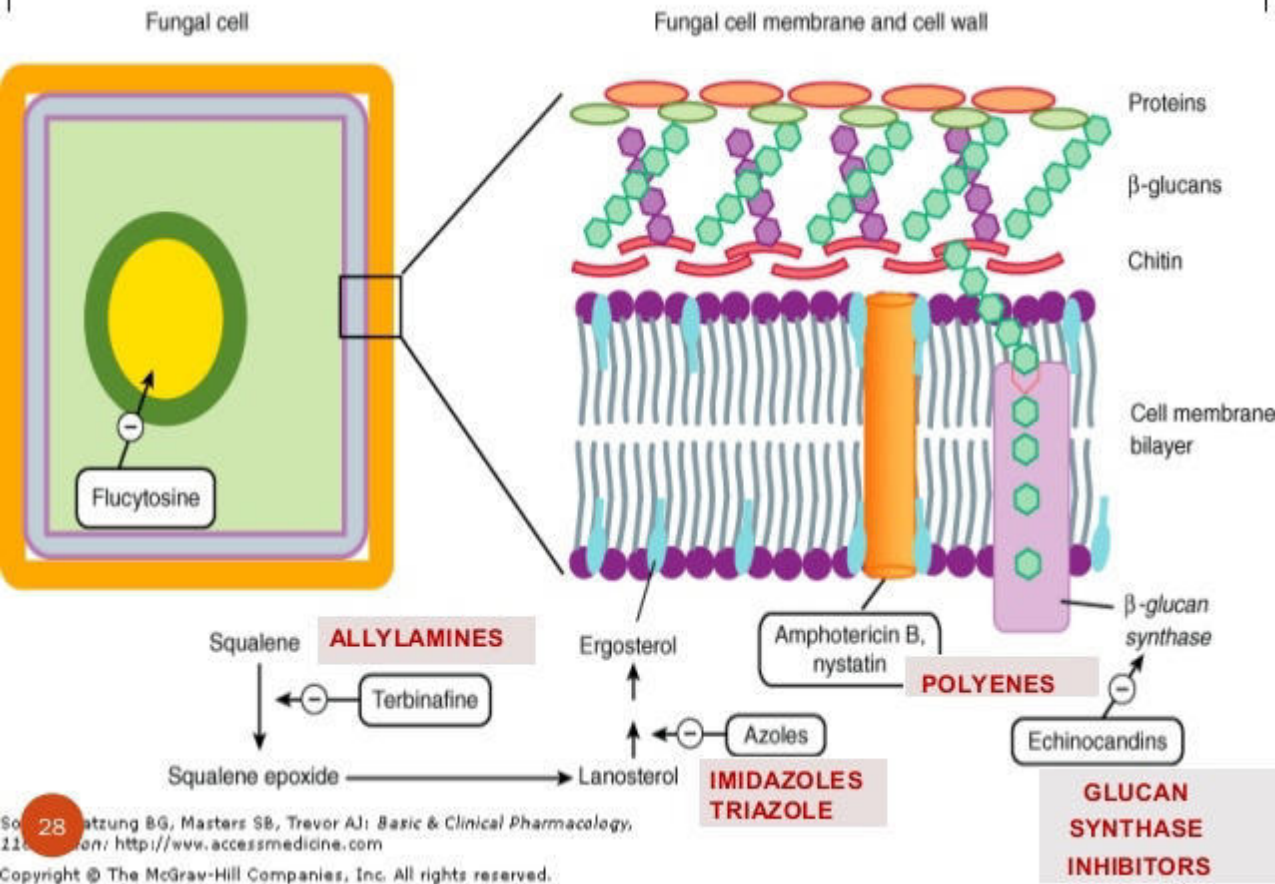
- *Amphotericin B* AMBISOME
- *Anidulafungin* ERAXIS
- *Caspofungin* CANCIDAS
- *Fluconazole* DIFLUCAN
- *Flucytosine* ANCOBON
- *Itraconazole* SPORANOX
- *Ketoconazole* NIZORAL
- *Micafungin* MYCAMINE
- *Posaconazole* NOXAFIL
- *Voriconazole* VFEND

DRUGS FOR CUTANEOUS MYCOSES

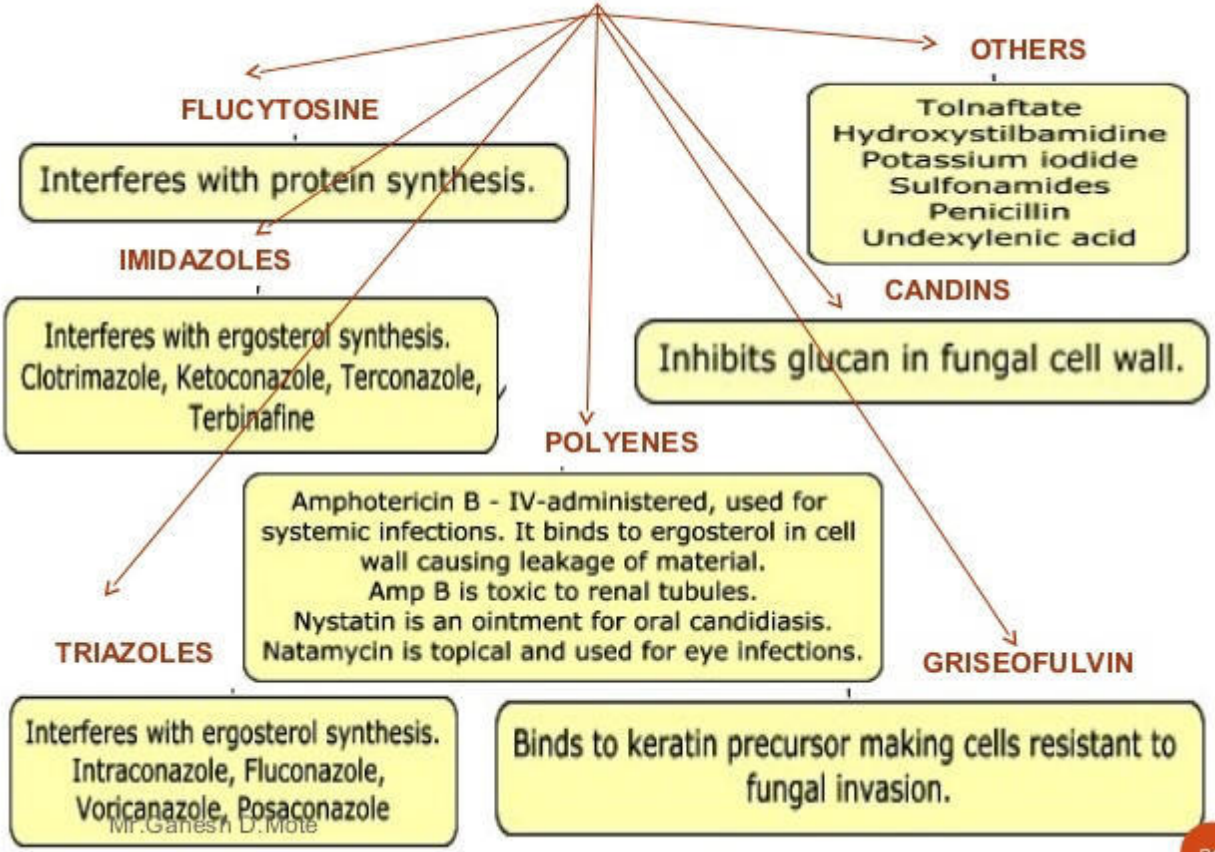
- *Butenafine* LOTRIMIN ULTRA
- *Clotrimazole*, LOTRIMIN AF
- *Ciclopirox* PENLAC
- *Econazole* ECONAZOLE NITRATE
- *Griseofulvin* GRIFULVIN V, GRIS-PEG
- *Miconazole* FUNGOID, MICATIN, MONISTAT
- *Naftifine* NAFTIN
- *Nystatin* MYCOSTATIN
- *Oxiconazole* OXISTAT
- *Sertaconazole* ERTACZO
- *Sulconazole*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

Con…

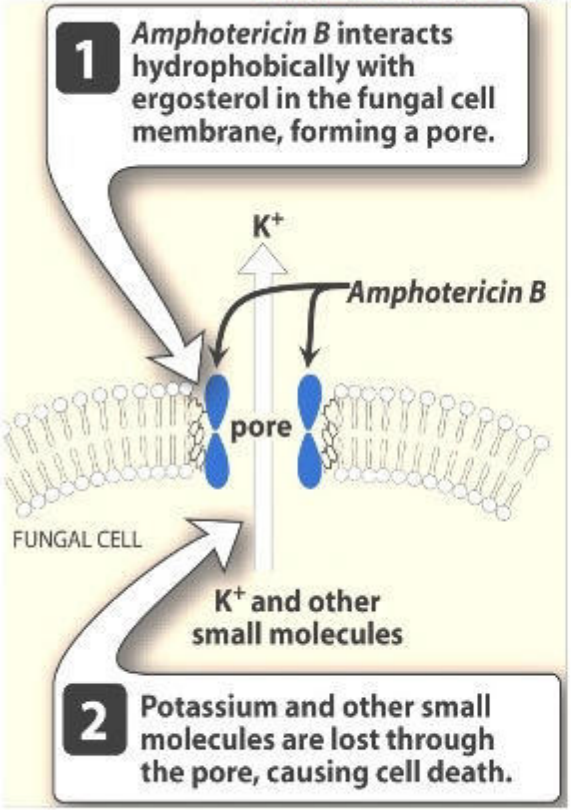
6.SITES OF ACTION OF COMMON ANTIFUNGAL DRUGS



7. ANTI FUNGAL DRUGS MECHANISAM



8.MECHANISM OF AMPHOTERICIN B

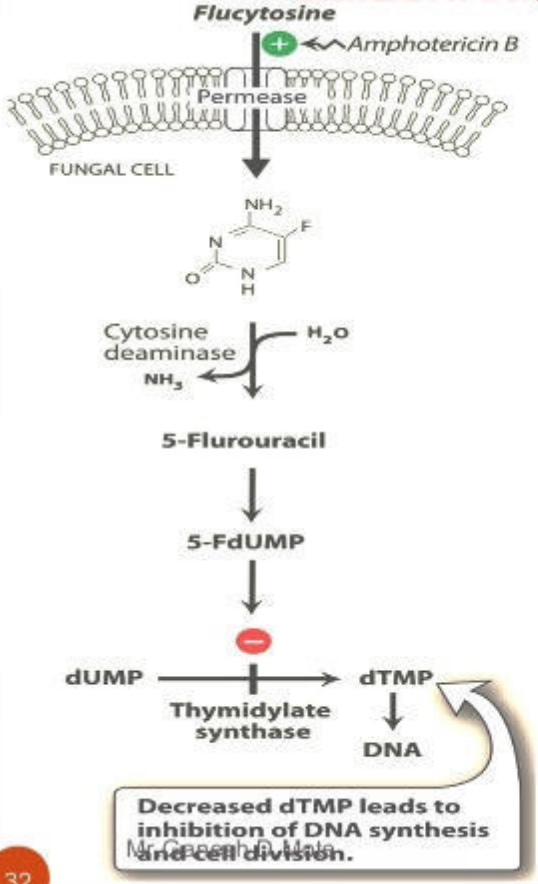


Several amphotericin B molecules bind to ergosterol in the plasma membranes of sensitive fungal cells.

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



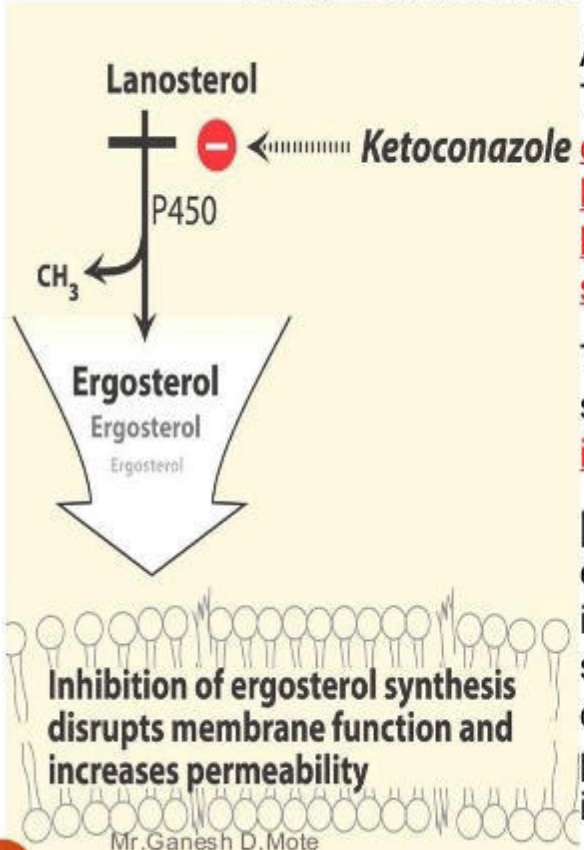
Flucytosine enters fungal cells via a cytosine-specific permease an enzyme not found in mammalian cells.

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

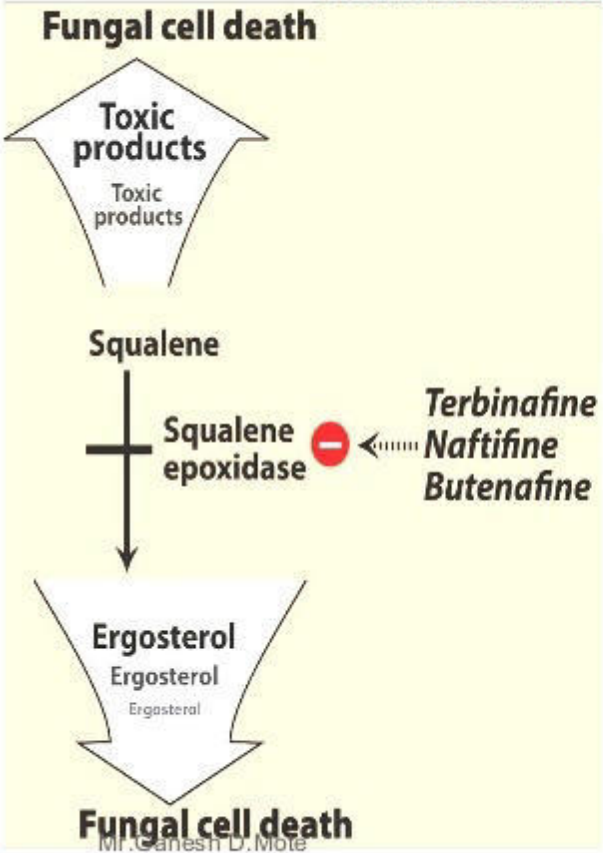


Azoles are predominantly fungistatic. They inhibit C-14 α-demethylase (a cytochrome P450 enzyme), thus blocking the demethylation of lanosterol to ergosterol the principal sterol of fungal membranes.

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]

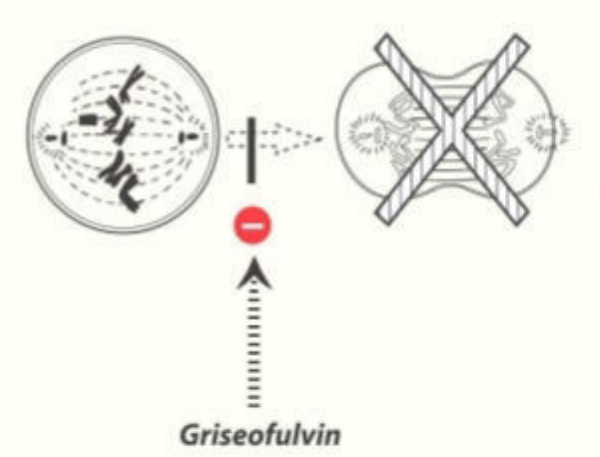
11.MECHANISM OF TERBINAFINE



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

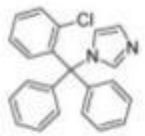


It is only fungistatic, and it causes a number of significant drug interactions.

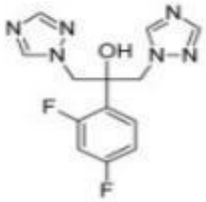
Griseofulvin accumulates in newly synthesized, keratin-containing tissue, where **it causes disruption of the mitotic spindle and inhibition of fungal mitosis .**

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.

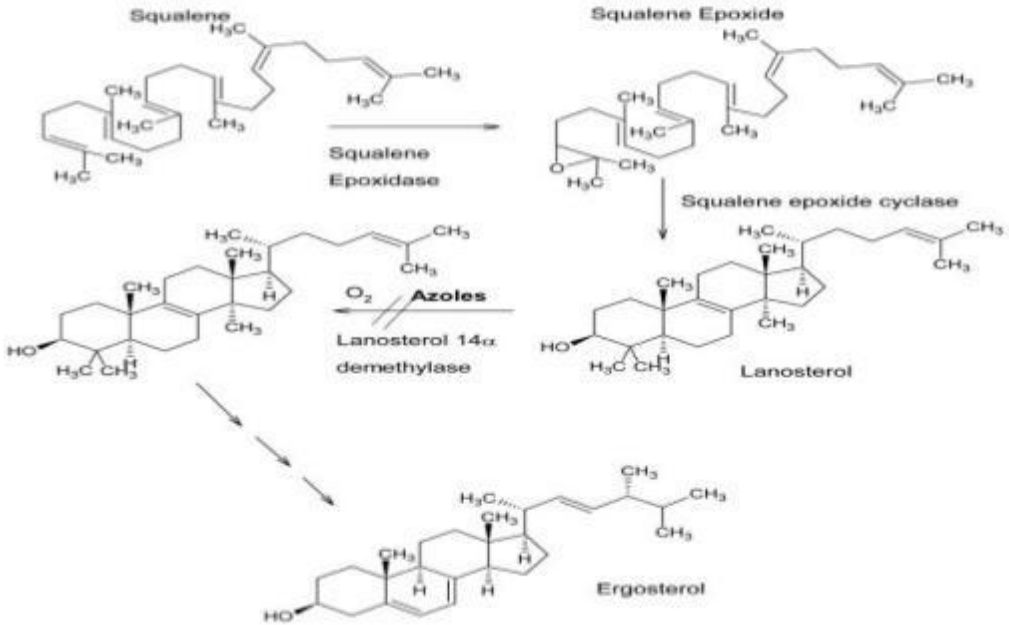


Clotrimazole

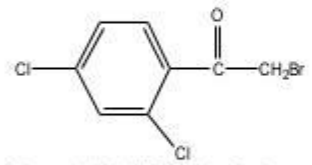


Fluconazole

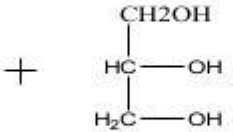
Mechanism action of squaline epoxidase(allyl amines and lanoseterol 14 ά demethylase inhibitor(Azoles derivatives)



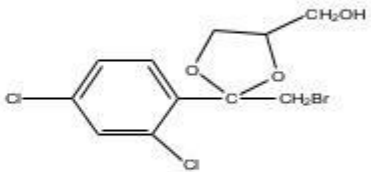
Synthesis of Ketoconazole



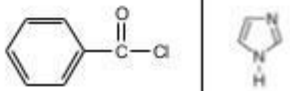
2-bromo-1-(2,4-dichlorophenyl)ethanone

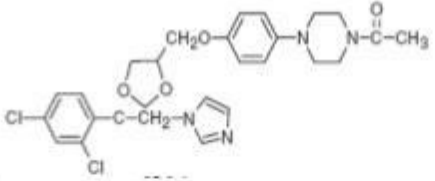


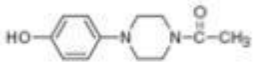
propane-1,2,3-triol

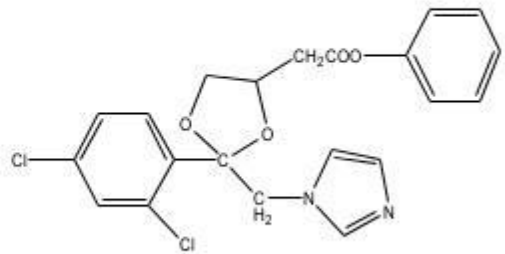


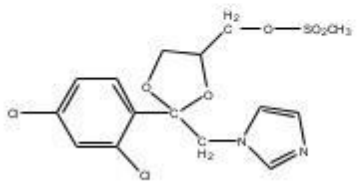
(2-(bromomethyl)-2-(2,4-dichlorophenyl)-1,3-dioxolan-4-yl)methanol



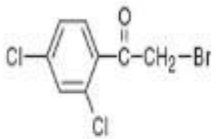




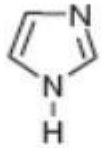




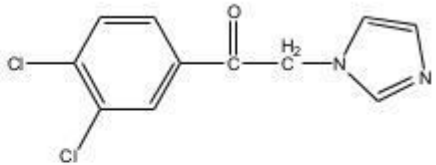
CH_3SO_3Cl



2,4-dichlorophenacylbromide



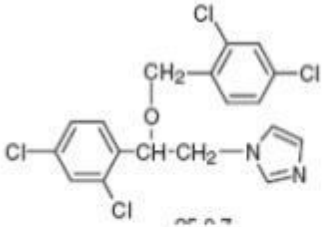
imidazole



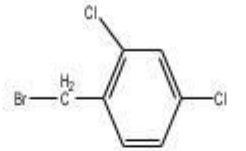
1-(3,4-dichlorophenyl)-2-(1H-imidazol-1-yl)ethanone

$NaBH_4$

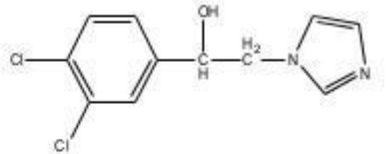
Synthesis of Miconazole



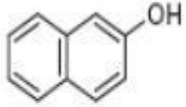
1-[2,4-dichloro-β-[(2,4-dichlorobenzyl)oxy]phenethyl]-imidazole



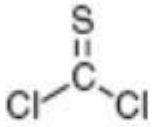
1-(bromomethyl)-2,4-dichlorobenzene



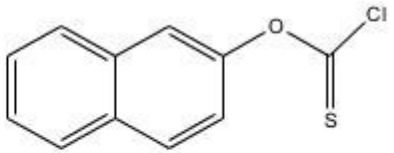
1-(3,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanol



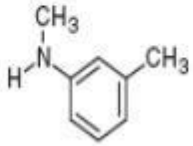
2-Naphthol



thiophosgene

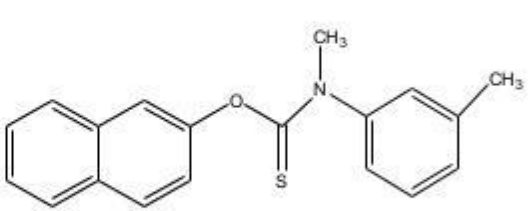


O-naphthalen-2-yl carbonochloridothioate



N-methyl 3-toludine

Synthesis of Tolnaftate



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