Antifungal agents

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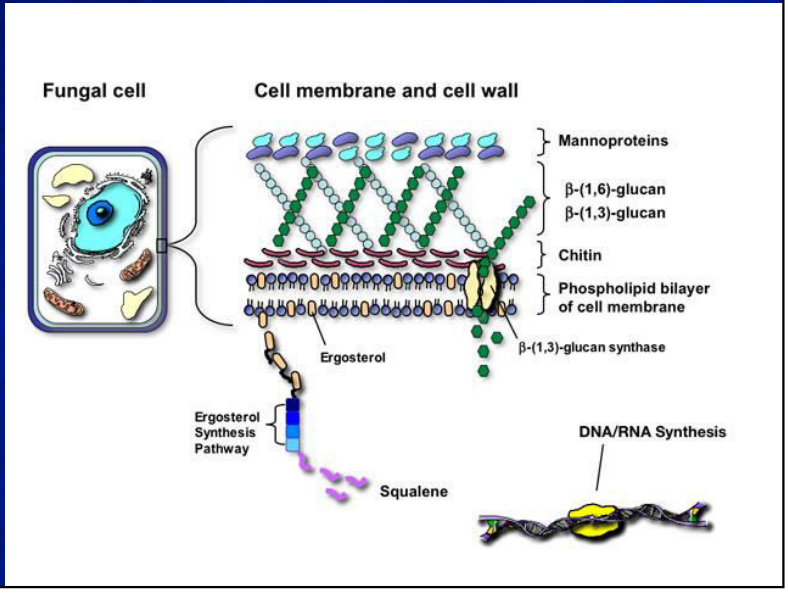
Overview

- Infectious diseases caused by fungi are called mycoses, and they are often chronic in nature.
- Fungal infections are iatrogenic/ drug induced ■ Infections majorly occur in immunocompromised people receiving immunosuppressants
- Human fungal infections have increased dramatically , owing mainly to advances in surgery, cancer treatment, and critical care accompanied by increases in use of broad-spectrum antimicrobials and the HIV epidemic

Fungal Cell Structure

- Fungi are eukaryotic organisms & possess cell wall.
- Fungi have rigid cell walls composed of chitin and glucans and glycoproteins.
- The fungal cell membrane contains ergosterol rather than the cholesterol found in mammalian membranes.



- Fungi may be classified as

1. Yeasts: fungi that can adopt a single-celled growth habit are called yeasts.

   E.g. Blastomyces, candida, histoplasma, coccidioides, cryptococcus

2. Moulds: A mold or mould is a fungus that grows in the form of multicellular filaments called hyphae.

- E.g. Aspergillus spp., Dermatophytes, mucor

- *Cryptococcus neoformans and Cryptococcus gattii are significant pathogens* of immunocompromised people. They are the species primarily responsible for **cryptococcosis, a** fungal disease that occurs in about one million HIV/AIDS patients, causing over 600,000 deaths annually.
- The cells of these yeast are surrounded by a rigid polysaccharide capsule, which helps to prevent them from being recognized and engulfed by white blood cells in the human body.
- Yeasts of the Candida genus, another group of opportunistic pathogens, cause oral and vaginal infections in humans, known as candidiasis. Candida is commonly found as a commensal yeast in the mucous membranes of humans and other warm-blooded animals.

- Aspergillosis is the group of diseases caused by *Aspergillus. The most common subtype* among paranasal sinus infections associated with aspergillosis is *A. fumigatus.*
- The symptoms include fever, cough, chest pain, or breathlessness, which also occur in many other illnesses, so diagnosis can be difficult. Usually, only patients with already weakened immune systems or who suffer other lung conditions are susceptible.

Classification of antifungal agents

1. ANTIBIOTICS

✓ Polyene: Amphotericin, Nystatin, Natamycin

✓ Hetrocyclic (benzofuran): Griseofulvin

2. ANTIMETABOLITE : Flucytosine

3. AZOLES :

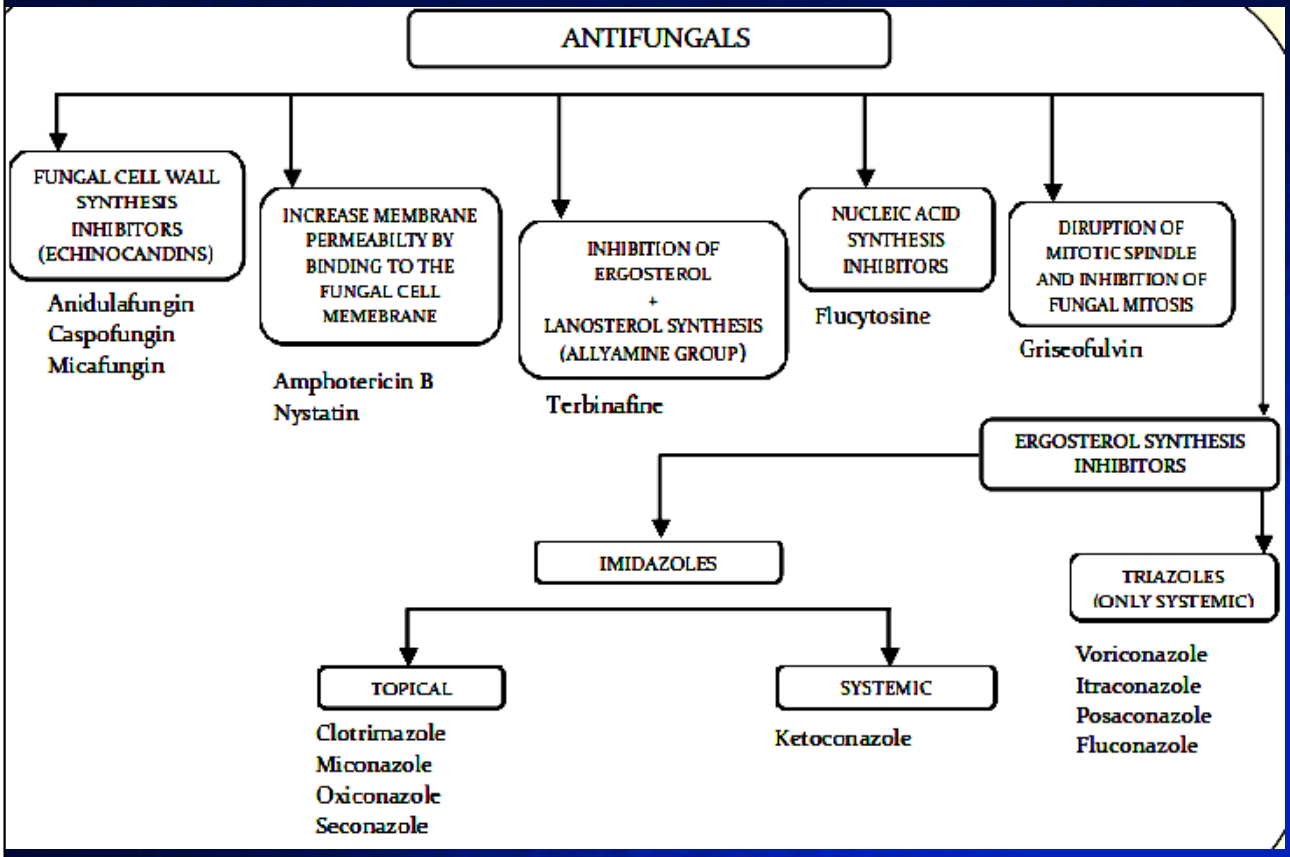
✓Imidazoles: Ketoconazole, Clotrimazole, Oxiconazole, Miconazole

✓Triazoles: Fluconazole, Itraconazole, Voriconazole,

4. ALLYLAMINES – Terbinafine, Naftifine

5. ECHINOCANDINS – Caspofungin, Anidulafungin, Micafungin

6. **OTHER TOPICAL AGENTS** – Tolnaftate, Undecyclinic acid, Benzoic acid



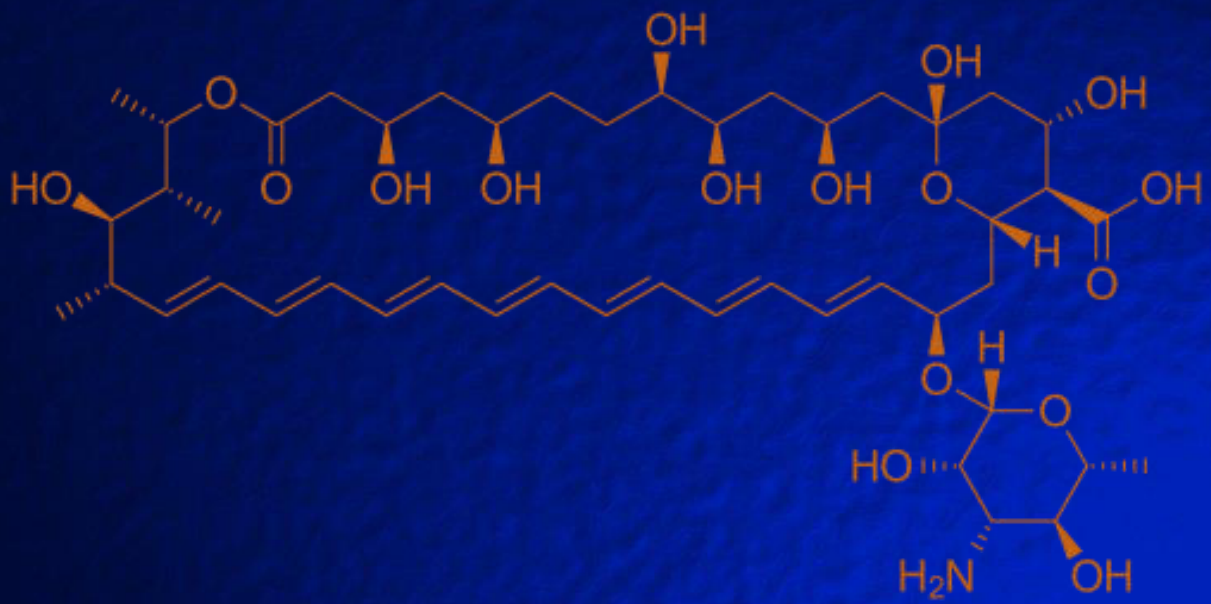
1. ANTIBIOTICS

Polyene antibiotics

- The polyene antibiotics comprise a class of molecules that are toxic to fungi but not to bacteria. They are produced by the bacteria Streptomyces.
- Although there are many polyene antibiotics only three are used clinically to treat fungal infections — nystatin, amphotericin B, and candicidin. All three are used in the treatment of topical infections, while only amphotericin B is used against systemic infections.
- Nystatin and amphotericin B are most frequently used clinically, and have been extensively studied experimentally.

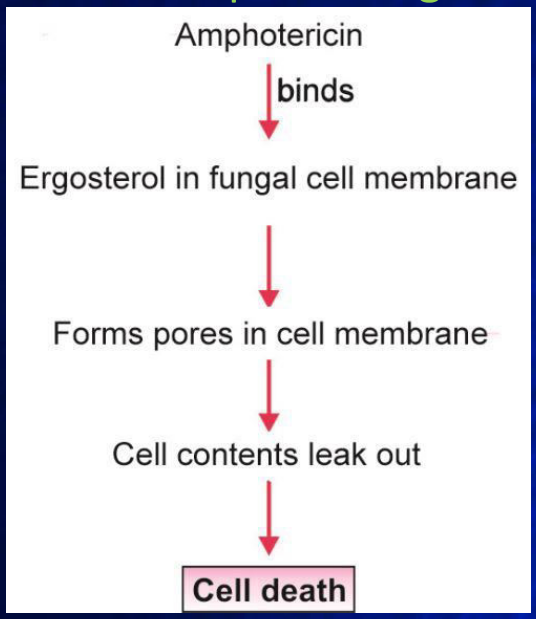
AMPHOTERICIN B

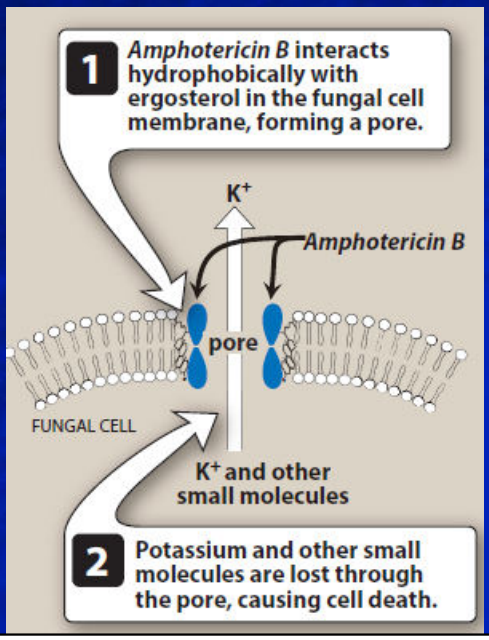
- Amphotericin B is a naturally occurring polyene antifungal produced by Streptomyces nodosus.
- In spite of its toxic potential, amphotericin B remains the drug of choice for the treatment of several life-threatening mycoses.
- It is a macromolecule and consists of both lipophilic and hydrophilic groups i.e., it is amphoteric in nature.
- Conjugated nature is responsible for lipophilicity and OH group is responsible for hydrophilicity
- The amphiphilicity of the drug is responsible for its unique mechanism of action



Mechanism of action

- Amphotericin B binds with ergosterol, a component of fungal cell membranes, forming pores that cause rapid leakage of monovalent ions (K^+, Na^+, H^+ and Cl^-) and subsequent fungal cell death.





Uses

The fungal infections it is used to treat include aspergillosis, blastomycosis, candidiasis, coccid ioidomycosis, and cryptococcosis.[

It is considered first line therapy for invasive mucormycosis infections, cryptococcal meningitis, and certain aspergillus and candidal infections.

Amphotericin B is used for life-threatening protozoan infections such as visceral leishmaniasis and primary amoebic meningoencephalitis.

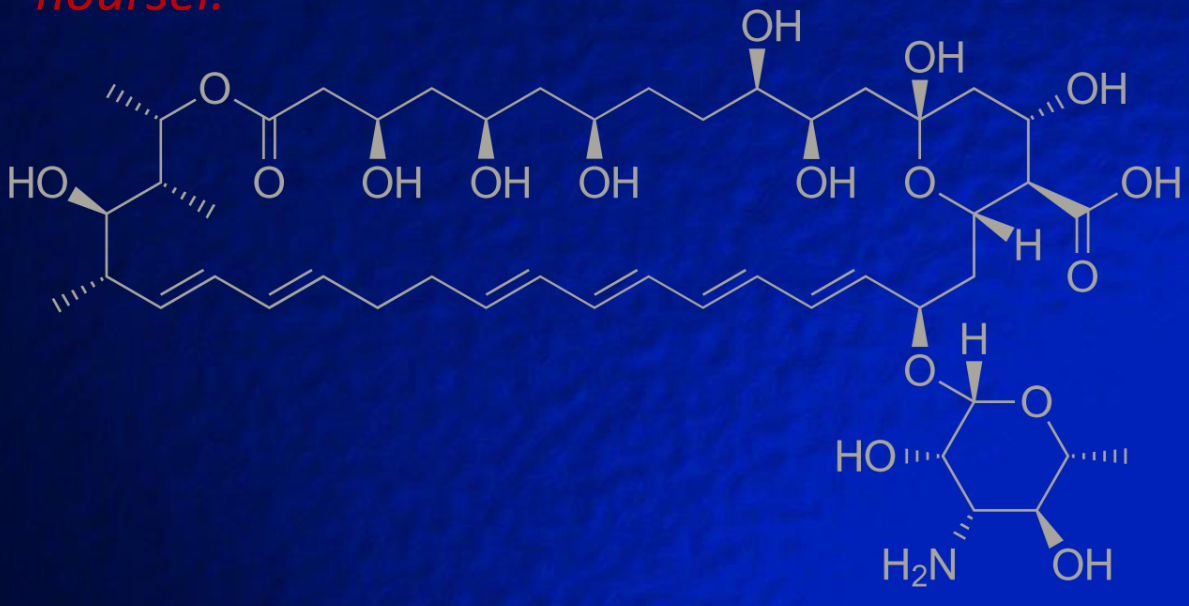
Adverse effects

- **Fever and chills:**
- These occur most commonly 1 to 3 hours after starting the IV administration but usually subside with repeated administration of the drug.
- Premedication with a corticosteroid or an antipyretic helps to prevent this problem.
- **Renal impairment**
- Patients may exhibit a decrease in glomerular filtration rate and renal tubular function. Serum creatinine may increase, creatinine clearance can decrease, and potassium and magnesium are lost. Renal function usually returns with discontinuation of the drug, but residual damage is likely at high doses.
- To minimize nephrotoxicity, sodium loading with infusions of normal saline and the lipid-based amphotericin B products can be used.

- Hypotension:
- A shock-like fall in blood pressure accompanied by hypokalemia may occur, requiring potassium supplementation. Care must be exercised in patients taking digoxin and other drugs that can cause potassium fluctuations.
- Thrombophlebitis:
- Adding heparin to the infusion can alleviate this problem.

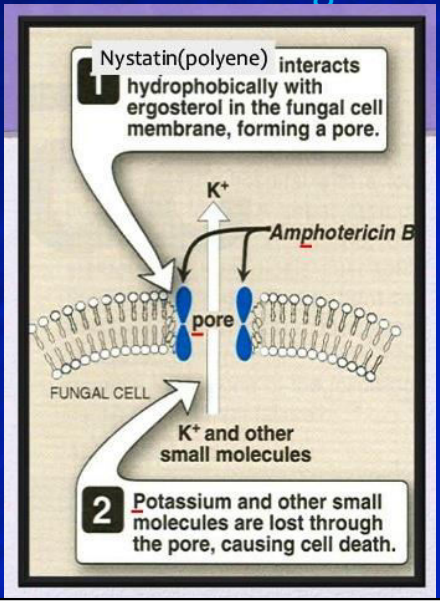
Nystatin

- It was the first polyene macrolide antifungal. It is made from the bacterium *Streptomyces noursei.*



Mechanism of action

- Like amphotericin B and natamycin, nystatin is an ionophore. 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.



- **Uses**

Skin, vaginal, mouth, and esophageal Candida infections usually respond well to treatment with nystatin. Infections of nails or hyperkeratinized skin do not respond well

Nystatin has been used to prevent the spread of mold on objects such as works of art.

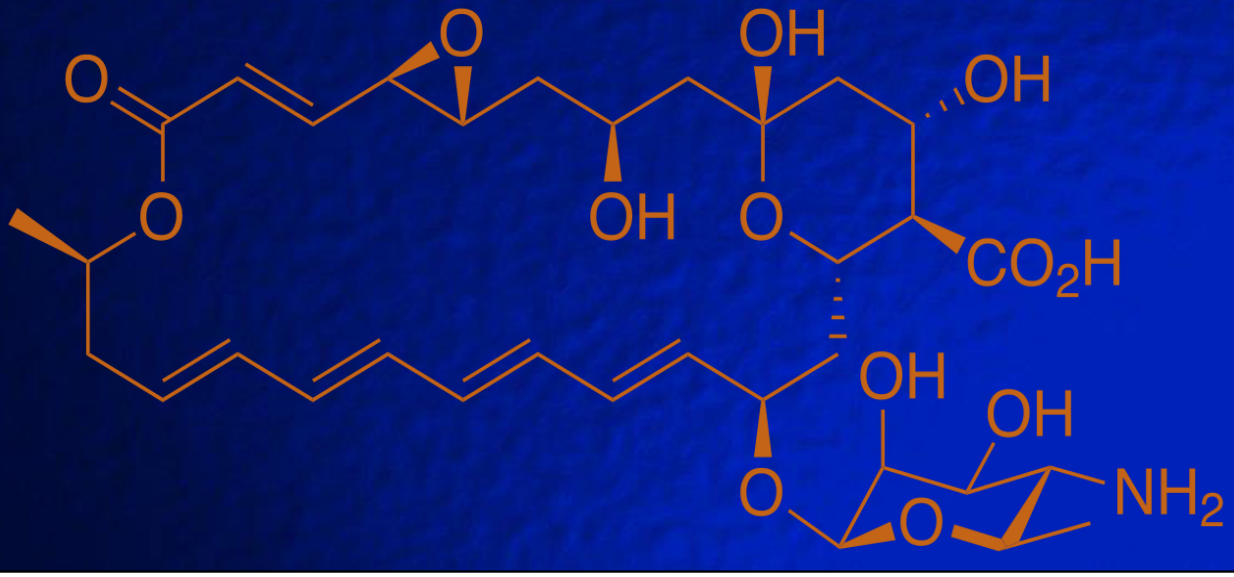
Adverse effects

Common Side effects of Nystatin include:

- Diarrhea.
- Nausea.
- Stomach pain or upset.
- Vomiting.
- Contact dermatitis.
- Stevens-Johnson syndrome.
- Hypersensitivity reactions.
- Skin irritation or redness.

Natamycin

- Natamycin is an antifungal drug for topical ophthalmic administration. It is a tetraene polyene antibiotic derived from *Streptomyces natalensis*.
- Natamycin is also known as pimaricin



- Mechanism of action

  Natamycin inhibits the growth of fungi by specifically binding to ergosterol present in fungal cell membranes. Natamycin inhibits amino acid and glucose transport proteins leading to a loss of nutrient transport across the plasma membrane.

- **Uses**

  Natamycin is used to treat fungal infections, including Candida, Aspergillus, Cephalosporium, Fusa rium, and Penicillium..

  It is applied topically as a cream, in eye drops, or (for oral infections) in a lozenge.

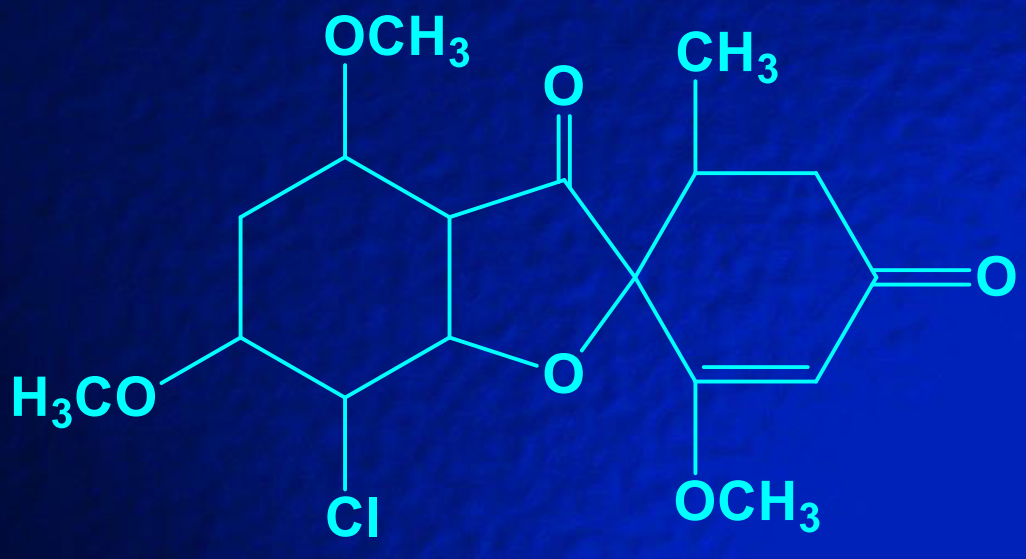
Adverse effects

Common side effects of Natacyn include:

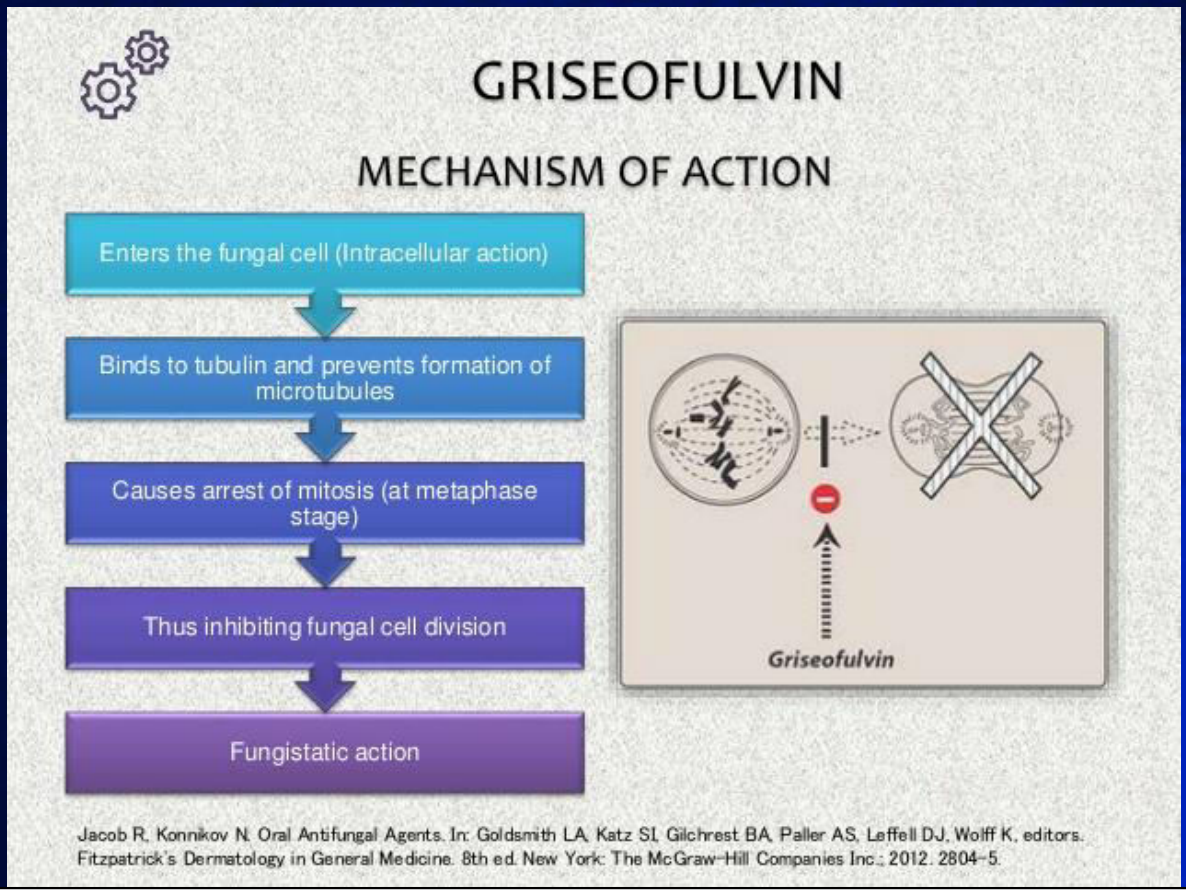
- mild eye irritation or discomfort (redness stinging or burning)
- allergic reaction.
- change in vision.
- chest pain.
- corneal opacity.
- shortness of breath.
- eye swelling.
- eye pain.

Hetrocyclic (benzofuran): Griseofulvin

- Griseofulvin was discovered in 1939 from the soil fungus *Penicillium griseofulvum.*
- *It is fungistatic*



Mechanism of action



Jacob R, Konnikov N. Oral Antifungal Agents. In: Goldsmith LA, Katz SI, Gilchrest BA, Paller AS, Leffell DJ, Wolff K, editors. Fitzpatrick's Dermatology in General Medicine. 8th ed. New York: The McGraw-Hill Companies Inc.; 2012. 2804-5.

- **Uses**

  Griseofulvin is indicated for the treatment of the following ringworm infections (Dermatophytosis):

- tinea corporis (ringworm of the body),
- tinea pedis (athlete's foot),
- tinea cruris (ringworm of the groin and thigh),
- tinea barbae (barber's itch),
- tinea capitis (ringworm of the scalp), and
- tinea unguium (ringworm of the nails)

  ❑ It is given orally, ineffective topically

Adverse effects

Griseofulvin may cause following side effects. :

- headache
- upset stomach
- vomiting
- diarrhea or loose stools
- thirst
- fatigue
- dizziness
- faintness

2. ANTIMETABOLITE

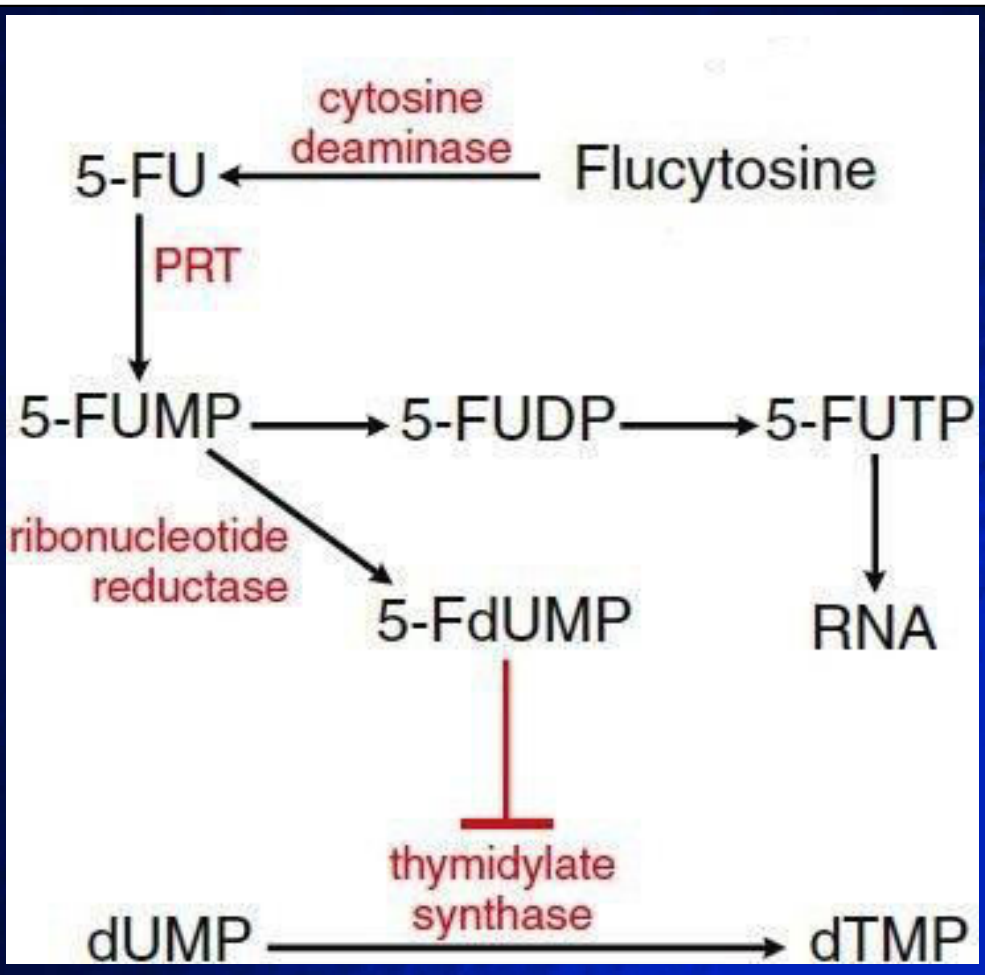
Flucytosine

It has relatively weak antifungal effects and fast developm.nt of resistance.

It is also known as 5-fluorocytosine (5-FC)

Mechanism of action

- ✓ Fungi are capable of deaminating flucytosine to 5-fluorouracil (5-FU).
- ✓ Fluorouracil is metabolized first to 5-fluorouracil-ribose monophosphate (5-FUMP) by the enzyme uracil phosphoribosyl transferase (UPRTase).
- ✓ 5-FUMP then is either incorporated into RNA (via synthesis of 5-fluorouridine triphosphate) or metabolized to 5-fluoro-2′-deoxyuridine-5′-monophosphate (5-FdUMP), a potent inhibitor of thymidylate synthetase and thus of DNA synthesis.
- ✓ Cytosine deaminase is absent in mammals, humans are not effected.
- ✓ Synergy with Amphotericin B and Azoles. Pores are formed or induced which facilitate entry of flucytosine in cell.



- **Uses**
- Flucytosine by mouth is used for the treatment of serious infections caused by susceptible strains of Candida or Cryptococcus neoformans..
- It can also be used for the treatment of chromomycosis (chromoblastomycosis).
- Flucytosine must not be used as a sole agent in life-threatening fungal infections rather in combination with amphotericin B and/or azole antifungals such as fluconazole or itraconazole.

- **Adverse effects**

Flucytosine may depress the bone marrow and lead to leucopenia.

Other untoward effects include

- rash
- nausea
- vomiting
- diarrhea
- severe enterocolitis

3. AZOLES

The azole group of antifungal drugs is divided into two subgroups: imidazoles and triazoles. Both classes are fungistatic agents .

A single representative of thiazole antifungals—abafungin—is also known.

A. Imidazole group

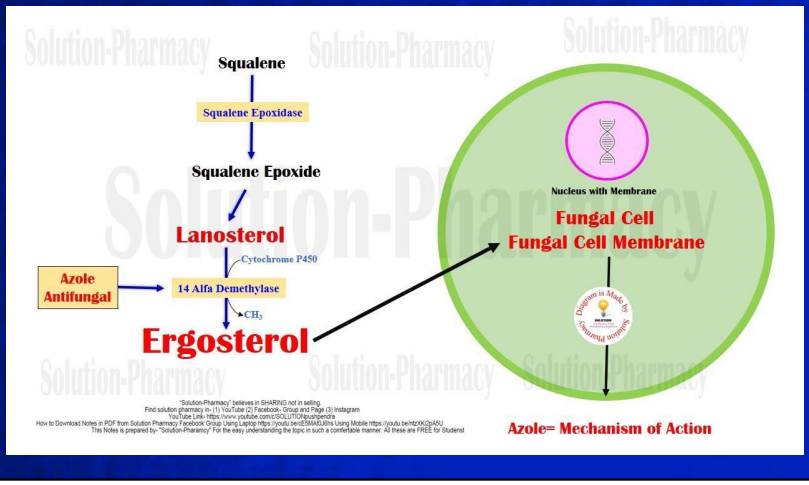
Clotrimazole,
Econazole
miconazole,
butaconazole,
Ketoconazole,
sulconazole,
oxiconazole

B. Triazole group

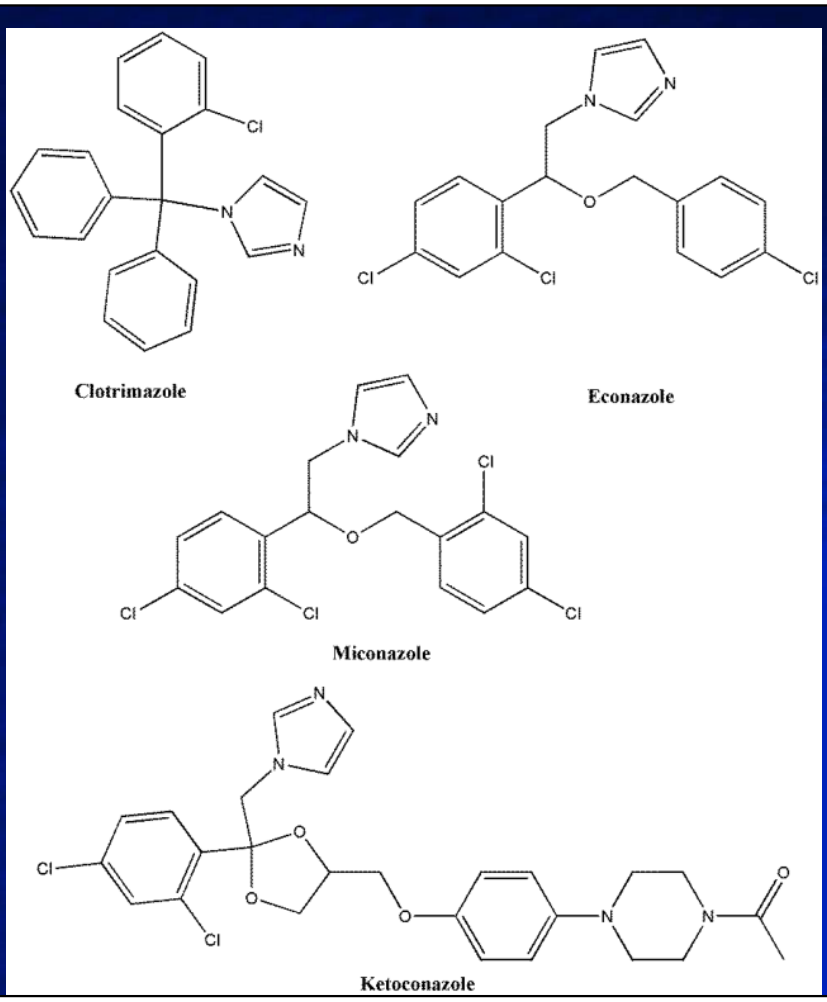
Terconazole,
fluconazole,
itraconazole,
voriconazole,
posaconazole

Mechanism of action

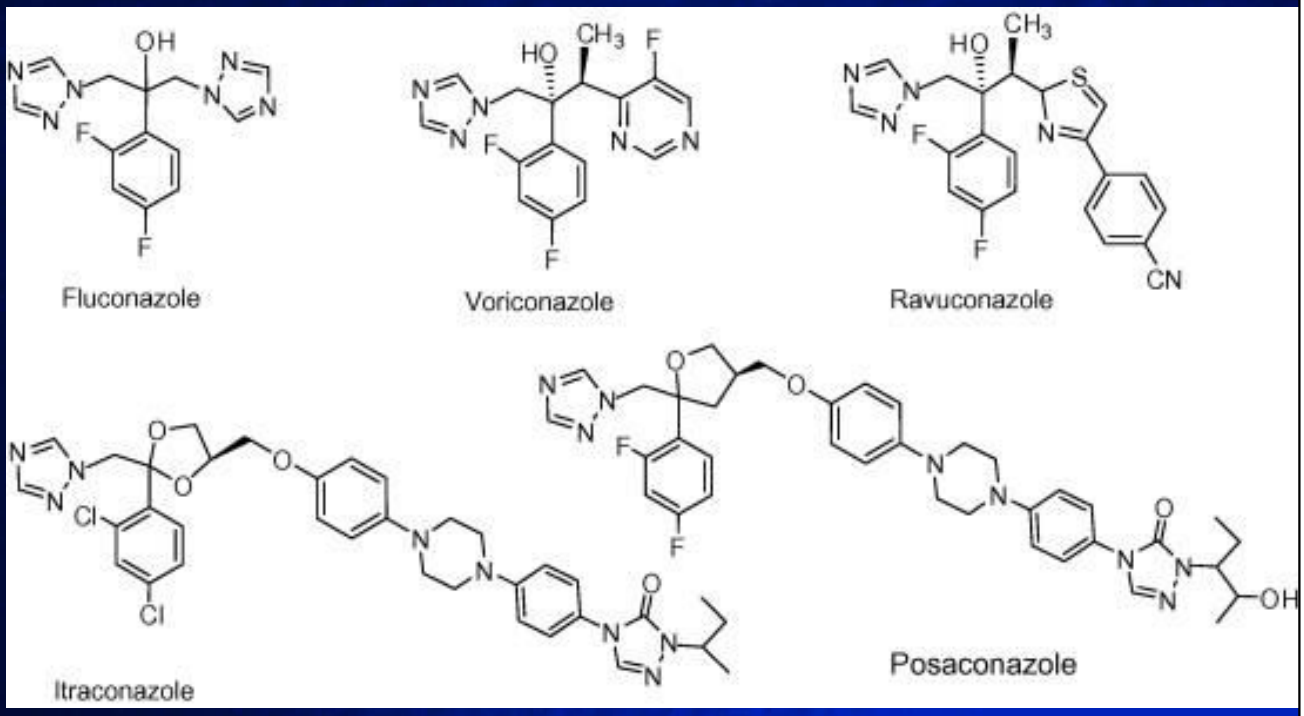
- The azoles interfere with the synthesis and permeability of fungal cell membranes by inhibiting cytochrome P450-dependent 14-α-sterol demethylase. This enzyme is required for the synthesis of ergosterol, the major sterol of most fungal cell membranes.



Imidazole derivatives



Triazole derivatives



Therapeutic uses

1. **Superficial fungal infections: [ketoconazole – itraconazole – miconazole]**

   A. Dermatophytes infection of the skin (tinea), hair, and nails (onychomycosis):

   For skin infection: treatment continued for 2-4 weeks.

   For hair infection: treatment continued for 6-8 weeks.

   For nail infection: treatment continued for 3-6 months.

   B. Mucocautaneous candidiasis: oropharyngeal, vulvovaginal, etc.

2. **Systemic fungal infections: [itraconazole – fluconazole – voriconazole]**

   Itraconazole (orally or IV) is the drug of choice for systemic blastomycosis.

   Fluconazole (orally or IV) is the drug of choice for systemic candidiasis, and cryptococcal meningitis (because it the only azole that can cross to CSF with good concentration).

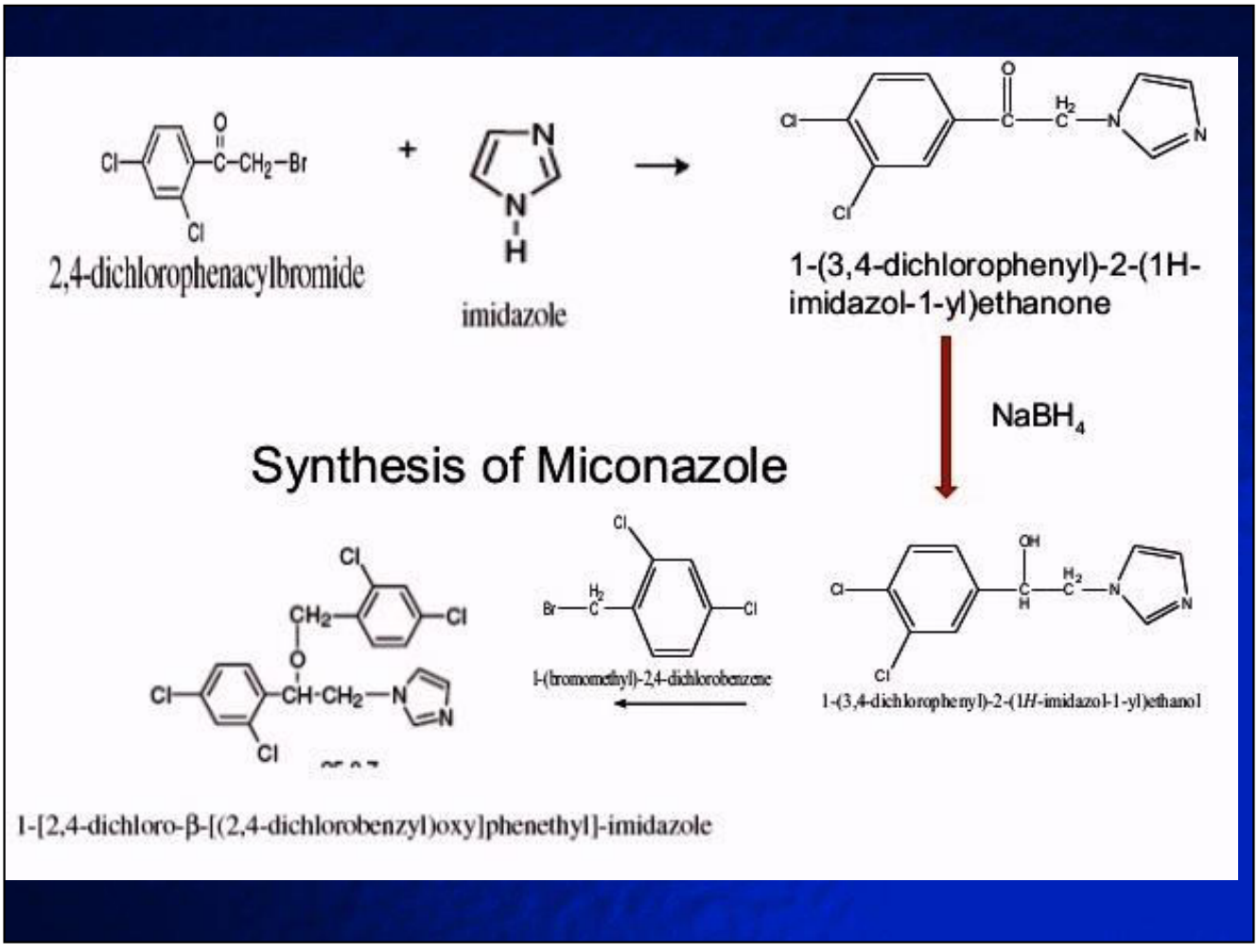
   Voriconazole is the drug of choice for invasive aspergillosis of the lung.

Adverse Effects Azole

Azoles are definitely efficient antifungal therapy but it has some harmful effects too.

Ketoconazole are more toxic as compared to other azoles. The most common adverse effects encountered with azoles are:

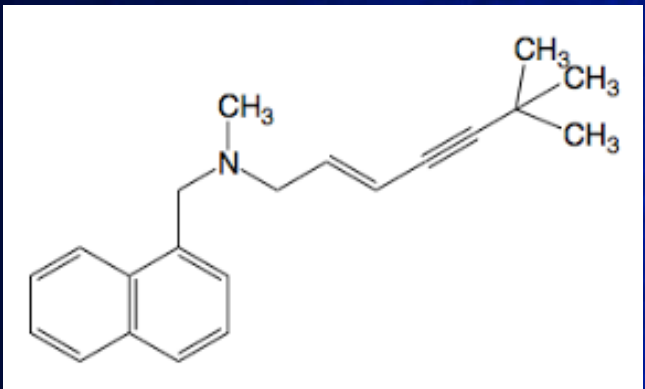
- Nausea and vomiting.
- Headache and abdominal pain.
- Skin infections
- Transient elevations in serum liver enzymes, noted occasionally.
- Gastrointestinal disturbances and pruiritus.
- Liver toxicity (rarely hepatitis).
- Inhibition of adrenocortical steroid and testosterone synthesis, thus resulting in gynecomastia in some male patients.



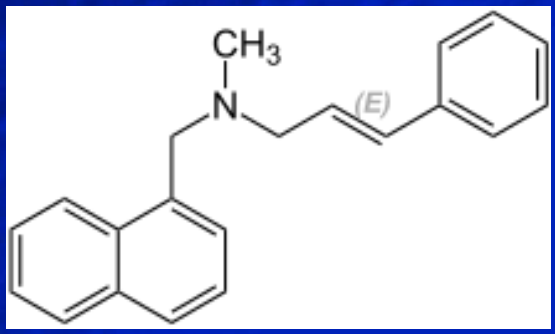
4. ALLYLAMINES

The allylamines have a more limited spectrum of activity than the azoles and triazoles and are only effective against dermatophytes. They are employed in the treatment of fungal infections of the skin and nails.

Terbinafine

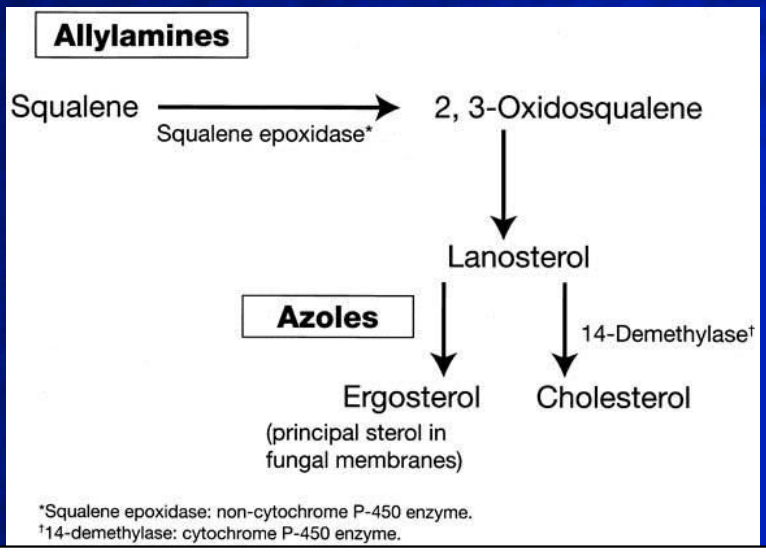


Naftifine



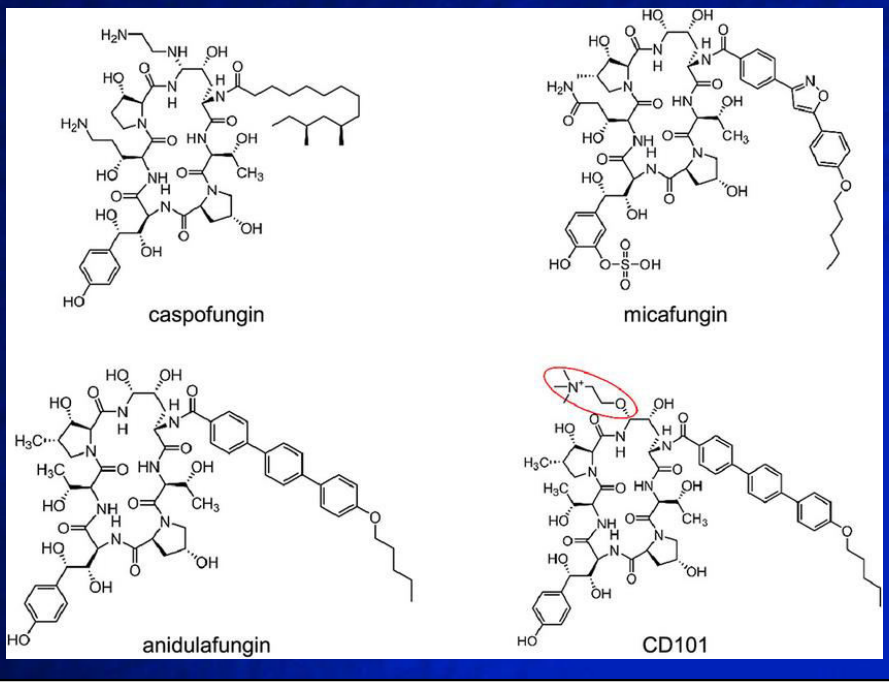
Mechanism of Action:

- These antifungal agents are reversible, noncompetitive inhibitors of the first step in ergosterol biosynthesis, the conversion of squalene to squalene-2,3- epoxide by squalene epoxidase. The buildup of squalene in the cell membrane is toxic to the cell, causing pH imbalances and malfunction of membrane bound proteins.



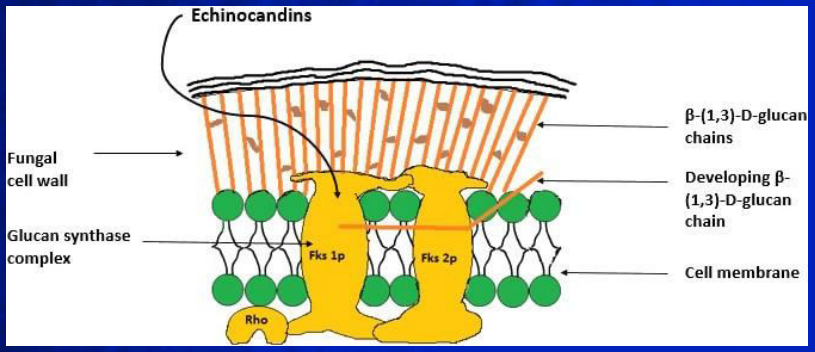
5. ECHINOCANDINS

The echinocandins are a class of semisynthetic antifungal lipopeptides that are structurally characterized by a cyclic hexapeptide core linked to a variably configured lipid side chain.



Mechanism of Action:

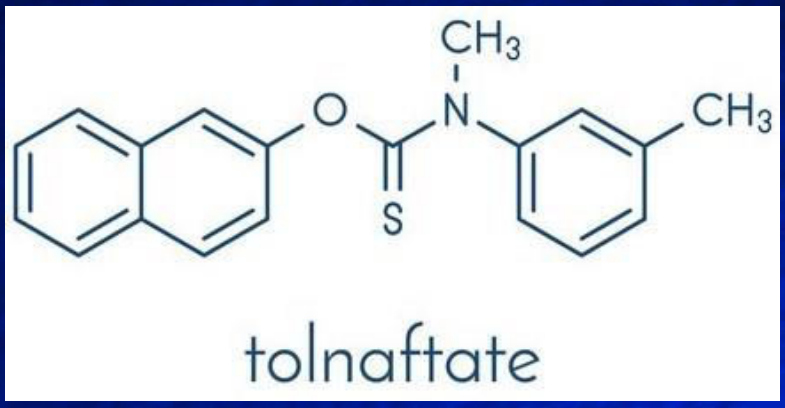
- The echinocandins, semi-synthetic lipopeptides derived from fungi. They non-competitively inhibit β1,3-d-glucan synthase, blocking the synthesis of β1,3-glucan.
- β-(1,3)-d-glucan synthase is a heteromeric glycosyltransferase enzyme complex present in the fungal cell membrane. It is composed of a catalytic Fks p subunit and a regulatory subunit belonging to the Rho GTPase family.
- This lessens cellular structural integrity and morphology and ultimately results in osmotic lysis of the cell



- The currently available echinocandins are anidulafungin (Versicor Inc, Freemont, CA), caspofungin (Merck & Co, Inc, Rahway, NJ), and micafungin (Fujisawa Inc, Deerfield, IL). They hav
- All three have potent and broad-spectrum antifungal activity against Candida species and Aspergillus species without cross-resistance to existing agents.
- The echinocandins are currently available only for intravenous administration.

6. OTHER TOPICAL AGENTS

Tolnaftate



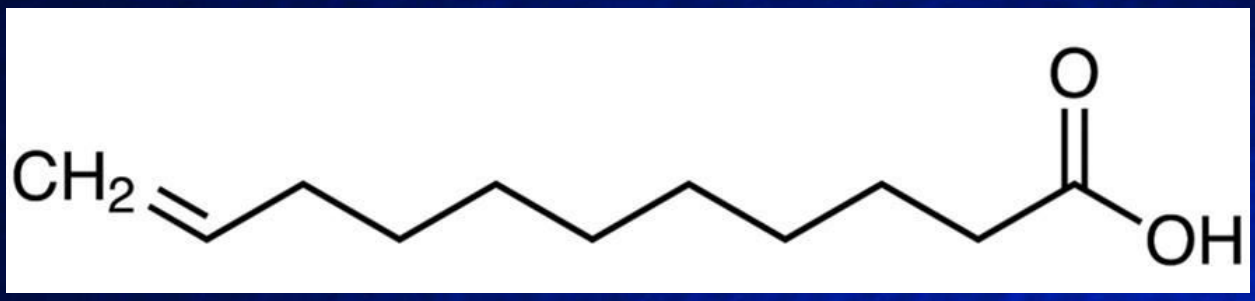
Tolnaftate is a synthetic thiocarbamate used as an anti-fungal agent. It is supplied as a cream, powder, spray, liquid, and liquid aerosol. Tolnaftate is used to treat fungal conditions such as jock itch, athlete's foot and ringworm.

- Although the exact mechanism of action is not entirely known, it is believed to inhibit squalene epoxidase, an important enzyme in the biosynthetic pathway of ergosterol (a key component of the fungal cell membrane) in a similar way to terbinafine.

- Side effects that may occur include:

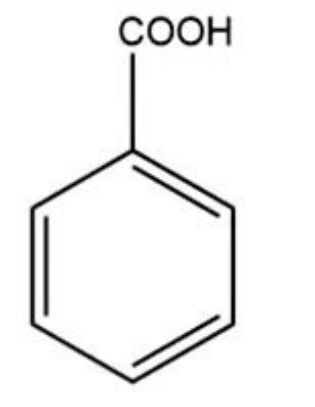
✓ allergic reactions like:
✓ skin rash
✓ itching or hives
✓ swelling of the face, lips, or tongue
✓ inflammation, redness, or pain at the affected area

- Undecyclinic acid



- Undecylenate, or undecylenic acid, is an unsaturated fatty acid with a terminal double bond that is derived from castor oil.
- Undecylenic acid is also found naturally in the human sweat.
- Undecylenic acid topical (for the skin) is used to treat skin infections that are caused by fungus, such as athlete's foot, jock itch, or ringworm.

- Benzoic acid



- A fungistatic compound that is widely used as a food preservative.
- Fungistatic. Needs prolonged application till keratin sheds off
- In Hyperkeratotic lesions, used with salicylic acid as WHITFIELDS OINTMENT (Benzoic acid-5% and Salicylic acid-3%). Salicylic acid helps to remove the infected tissue and promotes penetration of benzoic acid into the lesion.
- Irritation and burning sensation occurs