ANTIFUNGAL AGENTS

Classification

I. Antibiotics

A. Polyenes

Amphotericin B (AMB)
Nystatin
Hamycin
Natamycin

B. Heterocyclic benzofuran

Griseofulvin

C. Echinocandins

Caspofungin, Micafungin, Anidulafungin

II. Antimetabolites

Flucytocine (5-FC)

III. Azoles

A. Imidazoles (topical)

Clotrimazole
Econazole
Miconazole
Oxiconazle

B. Imidazoles (systemic)

Ketoconazole

C. Triazoles (systemic)

Fluconazole, Itraconazole, Voriconazole
Posaconazole

IV. Allylamine

Terbinafine

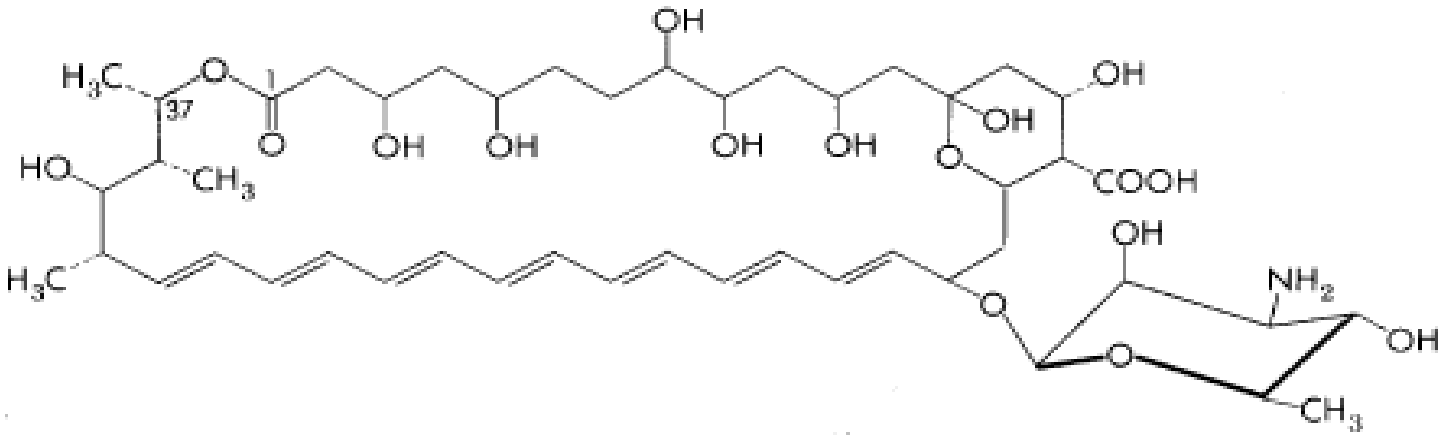
V. Other topical agents: Tolnaflate, Undecylenic acid, Benzoic acid, Quiniodochlor, Ciclopririx olamine, Butenafine, Sod. thiosulfate

Pharmacology of Polyene Antibiotic

Amphotericin B (AMB)

Amphotericin (also called amphotericin B) is a mixture of antifungal substances derived from cultures of *Streptomyces nodosus*

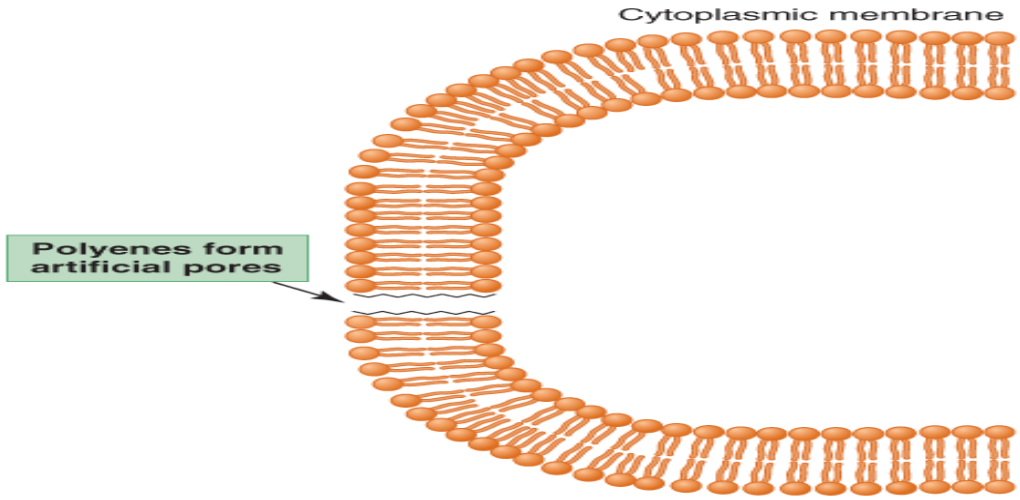
Chemistry



AMPHOTERICIN B

1. Amphotericin B is a heptaene macrolide containing seven conjugated double bonds in the *trans* position and 3-amino-3,6-dideoxymannose (mycosamine) connected to the main ring by a glycosidic bond.
2. The amphoteric behavior for which the drug is named derives from the presence of a **carboxyl group** on the main ring and a **primary amino group** on mycosamine; these groups confer aqueous solubility at extremes of pH.

Mechanism of action



1. AMB acts by inhibiting fungal cell membrane function.

2. The site of amphotericin action is the fungal cell membrane, where it interferes with permeability and with transport functions.

3. It forms binds to **ergosterol** of fungal cell membrane to from large pores (ion channels) in the cell membrane leading to loss of intracellular K^+ ions.

Antifungal Spectrum

Amphotericin B is used to treat systemic disseminated fungal infections caused by

1. *Candida* spp., *Cryptococcus neoformans* and

2. Dimorphic fungi (*Aspergillus* spp) like

Histoplasma capsulatum

Coccidioides immitis

Blastomyces dermatitidis, and

Sporothrix schenckii.

It is the **gold standard** for treating disseminated infections caused by several organisms including *Aspergillus* and *Candida*.

Pharmacokinetics

Absorption: Amphotericin B is primarily an intravenous drug; absorption from the intestinal tract is minimal.

Distribution: 90% of the drug is bound to protein. Its initial half-life is about 24 hours; the second elimination phase has a half-life of 15 days. Drug concentrations in pleural fluid, peritoneal fluid, synovial fluid, aqueous humor, and vitreous humor approach two-thirds of the serum concentration when local inflammation is present. Meningeal and amniotic fluid penetration, with or without local inflammation.

Metabolism: About 60% of drug is metabolized in liver

Excretion: About 5% of amphotericin B is excreted in the urine as active drug, with drug still detectable in the urine 7 or more weeks after the last dose.

Adverse effects

1. *Renal toxicity:* Some degree of reduction of renal function occurs in more than 80% of patients receiving the drug.
2. *Impaired hepatic function*
3. *Thrombocytopenia*
4. *Anaphylactic reactions*
5. *Others*

a) Injection frequently results initially in chills, fever, tinnitus and headache, and about one in five patients vomits.

b) The drug is irritant to the endothelium of the veins, and local thrombophlebitis is sometimes seen after intravenous injection.

c) Intrathecal injections can cause neurotoxicity, and topical applications cause a skin rash.

Interactions

1. Flucytocine has supra additive action with AMB.
2. Rifampin and minocycline potentiate AMB action.
3. Aminogycosides, vancomycin, and cyclosporine enhance renal toxicity of AMB.

Uses

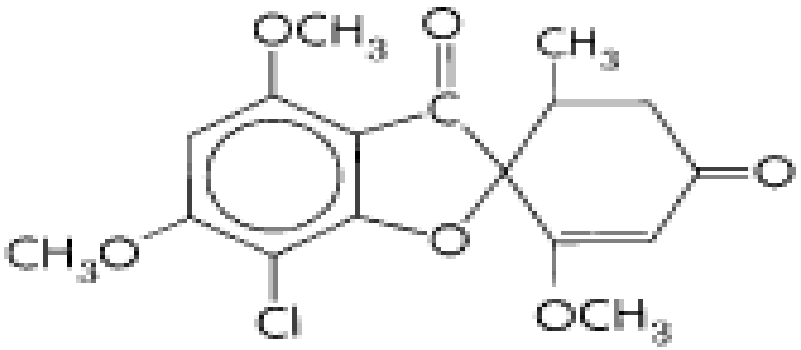
1. Candida esophagitis responds to much lower doses than deeply invasive mycoses.
2. Intrathecal infusion of C-AMB is useful in patients with meningitis caused by *Coccidioides.*
3. Intravenous administration of amphotericin B is the treatment of choice for mucormycosis and is used for initial treatment of cryptococcal meningitis, severe or rapidly progressing histoplasmosis, blastomycosis, coccidioidomycosis, and penicilliosis marneffei, as well as in patients not responding to azole therapy of invasive aspergillosis, extracutaneous sporotrichosis, fusariosis, alternariosis, and trichosporonosis.

Brands: MYCOL 50mg i.v

Pharmacology of Antibiotic Heterocyclic benzofuran

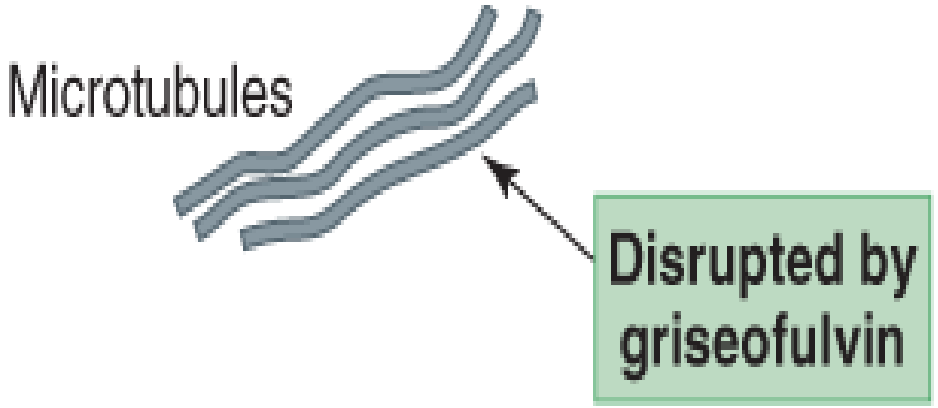
Griseofulvin: Produced by the mold *Penicillium griseofulvin*,

Strucutre



GRISEOFULVIN

Mechanism of action



1. Griseofulvin inhibits microtubule function and thereby disrupts assembly of the mitotic spindle and forms multinucleate cells as the drug inhibits fungal mitosis.
2. In addition to its binding to tubulin, griseofulvin interacts with microtubule-associated protein.

Antifungal Spectrum

1. Griseofulvin is fungistatic *in vitro* for various species of the dermatophytes like
   Microsporum
   Epidermophyton, and *Trichophyton*

2. The drug has no effect on bacteria or on other fungi.

Pharmacokinetics

1.Griseofulvin is given orally. It is poorly soluble in water, and absorption varies with the type of preparation, in particular with particle size.

2. It is taken up selectively by newly formed skin and concentrated it the keratin.

3. The plasma half-life is 24 h, but it is retained in the skin for much longer.

4. It potently induces cytochrome P450 enzymes and causes several clinically important drug interactions.

Adverse effects

1. Gastrointestinal upsets, headache and photosensitivity.

2. Allergic reactions (rashes, fever) may also occur.

3. The drug should not be given to pregnant women.

Interactions

1. Griseofulvin induces hepatic CYPs, thereby increasing the rate of metabolism of warfarin .

2.The drug may reduce the efficacy of low-estrogen oral contraceptive agents, probably by a similar mechanism.

Uses

1.Mycotic disease of the skin, hair, and nails due to *Microsporum*, *Trichophyton*, or *Epidermophyton*

2.For tinea capitis in children, efficacy is best for tinea capitis caused by *Microsporum canis*, *Microsporum audouinii*, *Trichophyton schoenleinii*, and *Trichophyton verrucosum*.

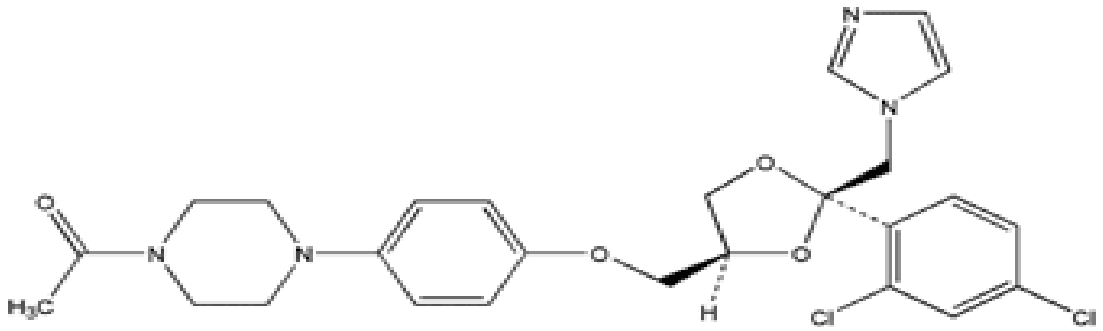
3.Griseofulvin also is highly effective in tinea pedis, the vesicular form of which is most commonly due to *T. mentagrophytes* and the hyperkeratotic type to *T. rubrum.*

4.Griseofulvin is also effective for ringworm of the glabrous skin; tinea cruris and tinea corporis caused by *M. canis*, *Trichophyton rubrum*, *T. verrucosum*, and *Epidermophyton floccosum;* and tinea of the hands (*T. rubrum* and *T. mentagrophytes*) and beard (*Trichophyton* species).'

Brands: GRISOVIN-FP, WALAVIN, GRISORAL 250mg tab

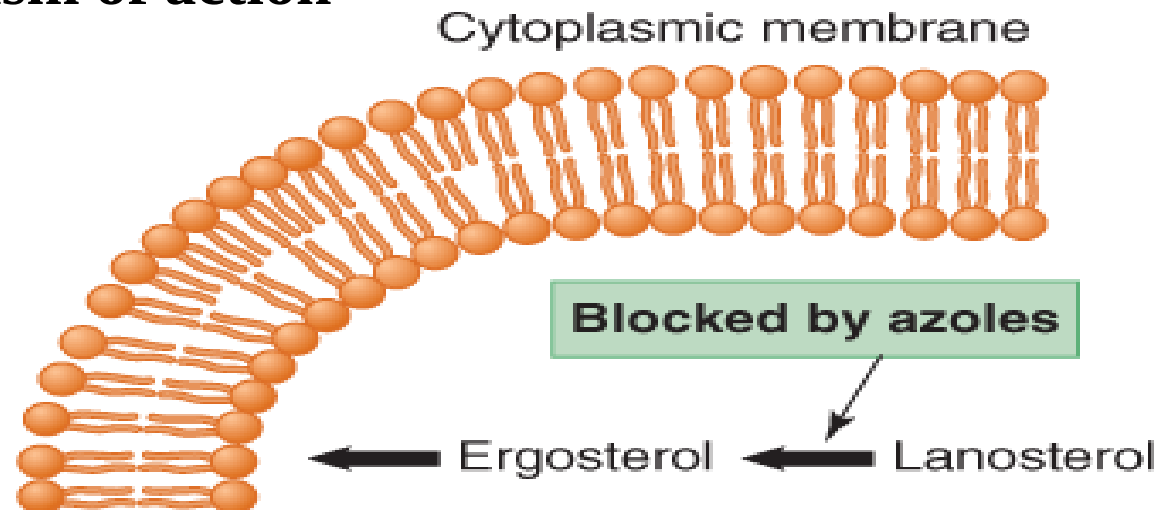
Pharmacology of Imidazole

Ketoconazole



ketoconazole

Mechanism of action



1. Ketoconazole acts by inhibiting fungal cell membrane synthesis.

2. Important molecular target in the ergosterol synthesis pathway is **14a-sterol demethylase**, a microsomal cytochrome P450 enzyme that converts lanosterol to ergosterol.

3. The **azoles** are antifungal agents that inhibit fungal 14a-sterol demethylase. The resulting decrease in ergosterol synthesis and accumulation of 14a-methyl sterols disrupt the tightly packed acyl chains of the phospholipids in fungal membranes.

4. Destabilization of the fungal membrane leads to dysfunction of membrane-associated enzymes, including those in the electron transport chain, and may ultimately lead to cell death.

Antifungal spectrum

1. Azoles as a group have clinically useful activity against *Candida albicans*,

Candida tropicalis

Candida parapsilosis

Candida glabrata

Cryptococcus neoformans

2.Blastomyces dermatitidis

3. Histoplasma capsulatum

4.Coccidioides spp., *Paracoccidioides brasiliensis*, and ringworm fungi (dermatophytes).

5. Aspergillus spp., *Scedosporium apiospermum (Pseudallescheria boydii)*, *Fusarium*, and *Sporothrix schenckii* are intermediate in susceptibility.

6.These drugs do not have any useful antibacterial or antiparasitic activity.

Adverse effects

1.The main hazard of ketoconazole is liver toxicity, which is rare but can prove fatal. Liver function is monitored before and during treatment.

2.Other side effects that occur are gastrointestinal disturbances and pruritus.

3. Inhibition of adrenocortical steroid and testosterone synthesis has been recorded with high doses, the latter resulting in gynaecomastia in some male patients.

Interactions

1. Ciclosporin and astemizole all interfere with cytochrome P450 drug-metabolising enzymes, causing increased plasma concentrations of ketoconazole or the interacting drug or both.

2. Rifampicin, histamine H_2 receptor antagonists and antacids decrease the absorption of ketoconazole.

Uses

1. Ketoconazole remains useful in the treatment of cutaneous and mucous membrane dermatophyte and yeast infections, but it has been replaced by the newer triazoles in the treatment of most serious *Candida* infections and disseminated mycoses.

2. Ketoconazole is ineffective in the treatment of cryptococcosis, aspergillosis, and mucormycosis.

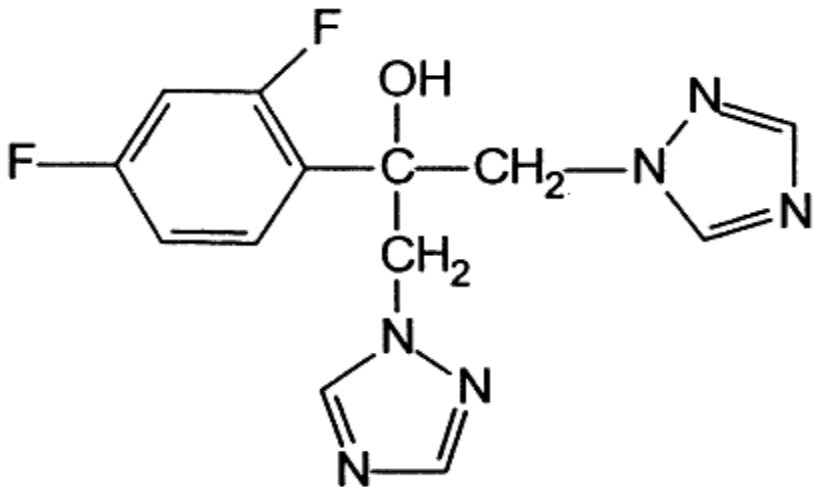
3. Widespread dermatophyte infections on skin surfaces can be treated easily with oral ketoconazole.

Brands: FUNGICIDE,, KETOVATE 200mg tab.

NIZORAL ANTIDANRUF 2% shampoo

Pharmacology of Triazole

FLUCONAZOLE



Fluconazole

Pharmacokinetics

1. It is 94% absorbed orally. Bioavailability not affected by food or gastric pH.
2. Its $t_{1/2}$ is 25-30 hr.
3. Fungicidal concentration is obtained in nails, vagina & saliva.
4. Excreted unchanged in urine.

Mechanism of action

Same as that of KTZ

Adverse effects

1. Few side effects than KTZ due to more selectivity for cytochrome P450.
2. Nausea, vomiting, abdominal pain, rash and headache.
3. Elevation of hepatic transaminase in AIDS patients.
4. Contraindicated in pregnancy and lactation.

Interactions

1. Plamsa levels of phenytoin, astemizole, cisapride, warfarin, Zidovudine and sulphonylureas have been observed.

Uses

1. Fluconazole is a drug of choice in esophageal and oropharyngeal candidiasis and for most infections caused by Coccidioides.

2. A single oral dose usually eradicates vaginal candidiasis.

3. Fluconazole is the drug of choice for treatment and secondary prophylaxis against cryptococcal meningitis and is an alternative drug of choice (with amphotericin B) in treatment of active disease due to Cryptococcus neoformans.

Brands

SYSCAN, ZOCON, FORCAN 50, 100, 150, 200 mg caps

200mg/100ml i.v. infusion