VI. Antifungal Agents

Fungal Infections

Fungal infections are caused by microscopic organisms that can invade the epithelial tissue. The fungal kingdom includes yeasts, molds, rusts and mushrooms. Fungi, like animals, are hetrotrophic, that is, they obtain nutrients from the environment, not from endogenous sources (like plants with photosynthesis). Most fungi are beneficial and are involved in biodegradation, however, a few can cause opportunistic infections if they are introduced into the skin through wounds, or into the lungs and nasal passages if inhaled.

Diseases caused by fungi include superficial infections of the skin by dermatophytes in the Microsporum, Trichophyton or Epidermophyton genera. These dermophytic infections are named for the site of infection rather than the causative organism.

Dermophytic Infection	Causative Organism
Tinea corporis (ringworm)	*Microsporum canis, Trichophyton mentagrophytes*
Tinea pedis (athlete's foot)	*T. rubrum, T. mentagrophytes, Epidermophyton floccosum*
Tinea cruis (jock itch)	*T. rubrum, T. mentagrophytes, E. floccosum*
Tinea capis (scalp)	*M. canis T. tonsurans*
Tinea barbae (beard/hair)	*T. rubrum, T. mentagrophytes*
Tinea unguium (nails)	*T. rubrum, T. mentagrophytes, E. floccosum*

Systemic infections are caused by the inhalation of spores and cause fungal pneumonia. This pneumonia cannot be transmitted from human to human. These infections can occur in otherwise healthy individuals. Many of the organisms that cause systemic fungal infections are confined to specific geographic locations due to favorable climates for their proliferation.

Systemic Infections	Causative Organism	Geographic Location
Coccidioidomycosis	*Cocidioides immitis*	Southwestern U.S. and parts of Latin America
Histoplasmosis	*Histoplasma capsulatum*	Central and Eastern U.S.
Brazilian Blastomycosis	*Paracoccidioides brasiliensis*	South America
Blastomycosis	*Blastomyces dermatitidis*	Southeastern U.S. and Mississippi River valley

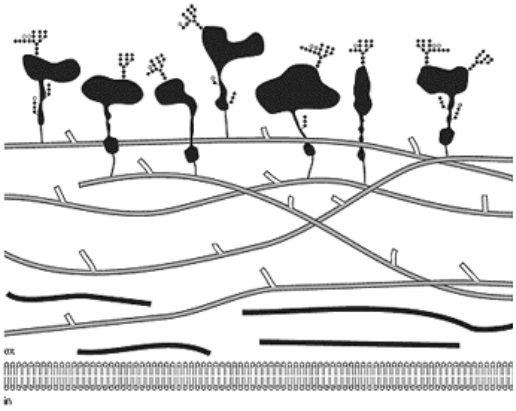
Organisms that cause opportunistic infections will not gain a foothold in healthy individuals, but in the immunocompromised they can cause serious, sometimes life-threatening infections. Patients especially susceptible to these infections include individuals with leukemia and other blood diseases, cancer, HIV and other immunodeficiencies, and diabetes. These organisms can be found throughout the U.S.

Opportunistic Infections	Causative Organism	Target Organs
Candidaisis, Thrush, Vulvovaginitis	*Candida albicans*	GI tract and vagina
Cryptococcal meningitis	C*ryptococcus neoformans*	Through inhalation, may cause mild lung infection. Mainly affects CNS
Aspergillosis	*Aspergillus* sp.	Lung, brain, sinuses and other organs
Mucormycosis	*Murcor* sp.	Sinuses, eyes, blood and brain
Pneumocystis carinii pneumonia	*Pneumocystis carinii*	Lungs (especially prevalent in HIV patients)

Biochemical Targets for Antifungal Chemotherapy

Fungal cells are complex organisms that share many biochemical targets with other eukaryotic cells. Therefore, agents that interact with fungal targets not found in eukaryotic cells are needed. The fungal cell wall is a unique organelle that fulfills the criteria for selective toxicity.

The fungal cell wall differs greatly from the bacterial cell wall and is not affected by antibacterial cell wall inhibitors such as the β-lactams or vancomycin.



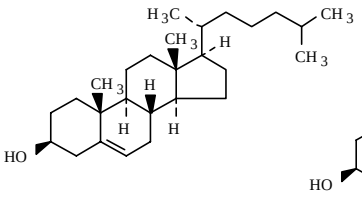
Arrangement of the biomolecular components of the cell wall accounts for the individual identity of the organism. Although, each organism has a different biochemical composition, their gross cell wall structure is similar. There are three general mechanisms of action for the antifungal agents: cell membrane disruption, inhibition of cell division and inhibition of cell wall formation.

Inhibition of Cell Wall Formation

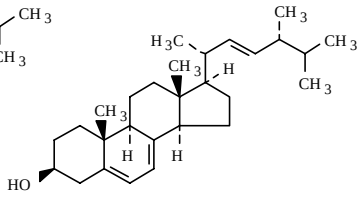
Interference with fungal cell wall biosynthesis has not been as successful and effective as penicilins and cephalosporins against bacteria. Many chemicals have been discovered that interfere with various steps in fungal cell wall synthesis with excellent antifungal activity in vitro. Unfortunately, development of these agents into useful drugs has proven very difficult. Many of these agents are developed to target β-glucan synthesis.

Cell Membrane Disruption

Antifungal agents that disrupt the cell membrane do so by targeting ergosterol, either by binding to the sterol, forming pores and causing the membrane to become leaky (as with polyene antifungals), or inhibiting ergosterol biosynthesis (as seen with azole antifungal agents). Ergosterol is similar to mammalian cholesterol, thus agents binding ergosterol may have a cytotoxic effect in the host tissue. Ergosterol has two conjugated double bonds that are lacking in mammalian sterols.



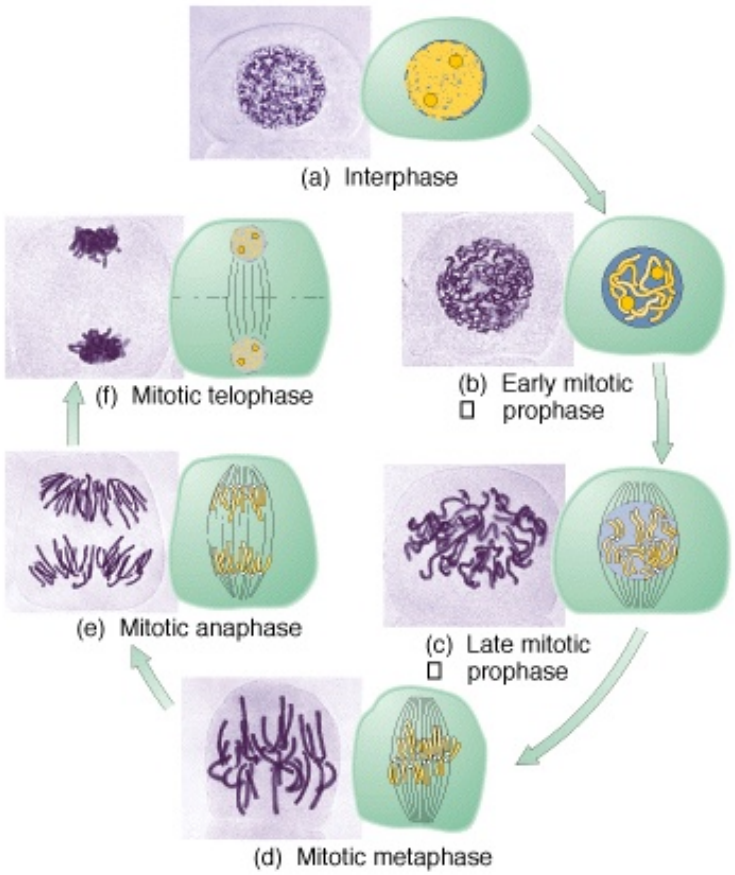
Cholesterol



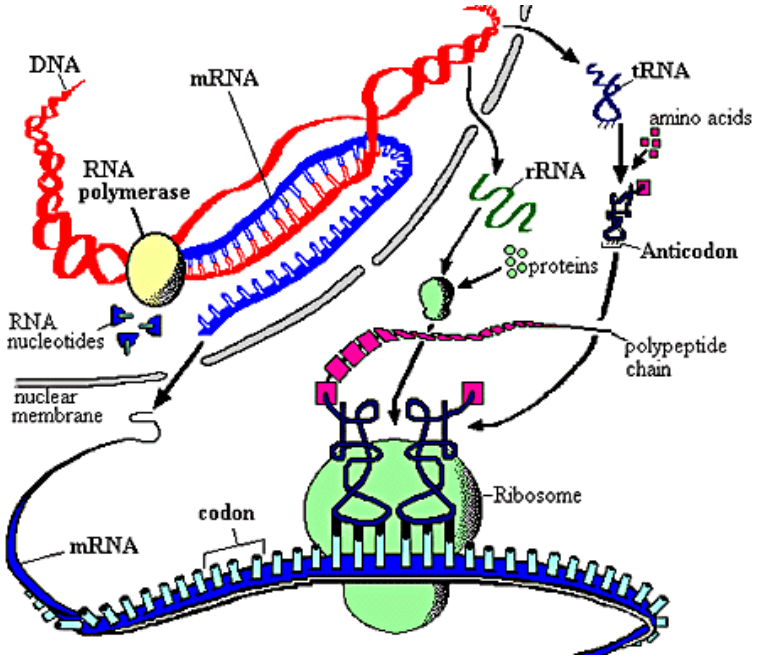
Ergosterol

Inhibition of Cell Division

Nucleoside antifungal agents affect cell division by targeting the microtubule effects in forming the mitotic spindle:



or by inhibiting DNA transcription:



Polyene Antifungal Agents *(Cell Membrane Disruption)*

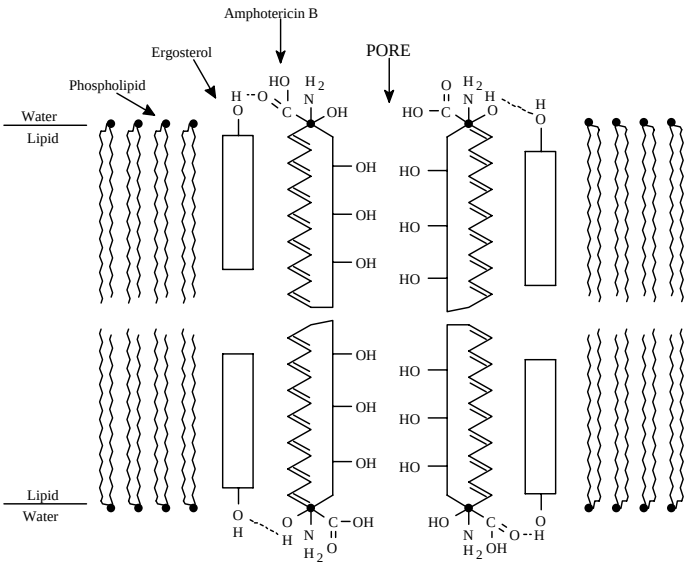
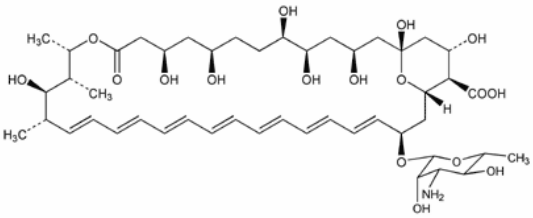


Fig. 1: Mechanism of Action of Polyenes
(Amphotericin B as example)



AMPHOTERICIN B

Class of Antifungal: Polyene

Mechanism of Action: Binds to ergosterol in fungal membrane causing membrane to become leaky (see Fig. 1)

Indications: Amp. B is indicated for treatment of severe, potentially life threatening fungal infections. Unfortunately, it must be given IV and is toxic (due to nonselective action on cholesterol in mammalian cell membranes). Serious fungal infections involve long therapy.

Resistance is due to lower production of membrane sterols or altered sterols, but is relatively rare at present. Target modification and reduced access to target. Antifungal resistance to date generally involves emergence of naturally resistant species. No data to suggest that antibiotic modification in an important antifungal resistance mechanism.

Disposition: Amp. B is not absorbed orally. It is given as a colloidal dispersion by slow IV infusion. It is highly bound to cholesterol-lipoprotein and has a plasma T1/2 of about 1 day and 1-2 weeks from tissues. It is excreted in urine over a long time. Penetration into the CNS is poor. However, for fungal infections of the CNS, amphotericin B is mized with cerebrospinal fluid

(CSF) that is obtained from a spinal tap. The solution of amphotericin is then reinjected through the tap.

Adverse Effects

Headache, fever, chills, anorexia, vomiting, muscle and joint pain.

Pain at site of injection and thrombophlebitis (Drug must never be given intramuscular)
Can give aspirin, meperidine, steroids, antiemetics etc.

Nephrotoxicity - chronic renal tox in up to 80% of patients taking the drug for prolonged periods. It is reversible but can be irreversible in high doses. Test for kidney function regularly. This is the most common limiting toxicity of the drug.

Hematologic - hemolytic anemia due to effects on rbc membrane.

Other less common reactions - cardiac, convulsions, neuropathy, hearing loss, allergic, etc.

The use of liposomal preparations will decrease some adverse effects particularly nephrotoxicity. It is believed the lipid preps decrease nonspecific binding to mammalian membranes.

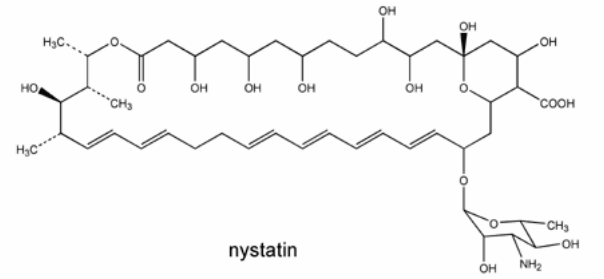
Products

Fungizone (Bristol Myers Squibb) 50 mg/vial with 41mg of sodium deoxycholate. Reconstitute with water. Give a test dose and gradually increase dose. Don't exceed 1.5mg/kg/d. Alternate day therapy is sometimes used. Several months of therapy is usually needed.

Abelcet (Liposome Co.) 1:1 mixture of amphotericin and lipid complex, 100 mg/20 ml. Rationale for this lipid preparation is that amphotericin B should have a greater affinity for the lipid vehicle than for cholesterol in cell membranes, thus lower toxicity. Lipid associated amphotericin B is drawn into the reticuloendothelial system, concentrating in lymphatic tissues, spleen, liver and lungs where infectious fungi concentrate. Lipases excreted from fungi release drug from lipid carrier allowing to bind to ergosterol in fungal cell membranes to exert fungistatic and fungicidal activities.

Aphotec (Sequus Pharmaceuticals) cholesterol colloidal dispersion, 50 or 100 mg/20 ml (not on UW formulary) Supplied in variety of topical forms including a 3% cream, lotion or ointment and 100mg/mL oral suspension to treat cutaneous and mucocutaneous mycoses caused by *Candida albicans*

AmBiosome (Fujisawa) liposomal, 50mg/vial.



nystatin

NYSTATIN

Class of Antifungal: Polyene

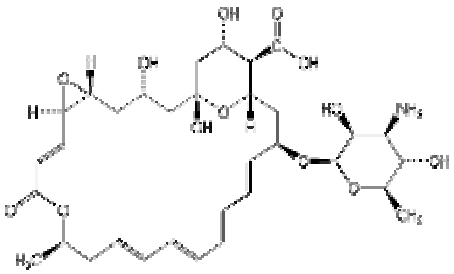
Mechanism of Action: Binds to ergosterol in fungal membrane causing membrane to become leaky (see Fig. 1)

Indications: Nystatin was originally isolated from Streptomyces noursei in 1951. A conjugated tetraene, it was the first clinically useful polyene antifungal antibiotic.

Disposition: Available in oral tablets, powder for suspension, vaginal tablets, pastilles, for local therapy only (not absorbed). Nystatin will treat gut candidiasis, and is used in a "swish and swallow" routine for oral candidiasis.

Adverse Effects: No significant adverse effects with these uses, however itching, irritation and burning may occur. Rarely nystatin can cause diarrhea and nausea Nystatin can be combined with tetracycline to prevent monilial overgrowth caused by the destruction of bacterial microflora of the intestine during tetracycline therapy.

Product: Mycostatin ® and other generic products.



natamycin

NATAMYCIN (Pimaricin, Natacyn)

Class of Antifungal: Polyene

Mechanism of Action: Binds to ergosterol in fungal membrane causing membrane to become leaky (see Fig. 1)

Indications: Natamycin was first isolated from cultures of Streptomyces natalensis. suspension intended for the treatment of fungal conjunctivitis, blepharitis and keratitis. Structures consists of 26-membered lactone instead of the 38 for Nystatin and Amphotericin B. The 26-membered polyenes cause both K leakage and cell lysis at same concentration.

Disposition: Natamycin is supplied as a 5% ophthalmic suspension intended for the treatment of fungal conjunctivitis, blepharitis and keratitis.

Adverse Effects: Eye irritation, redness and swelling not present prior to use.

Product: Natacyn

Azoles and Triazole Antifungal Agents: Ergosterol Biosynthesis Inhibitors

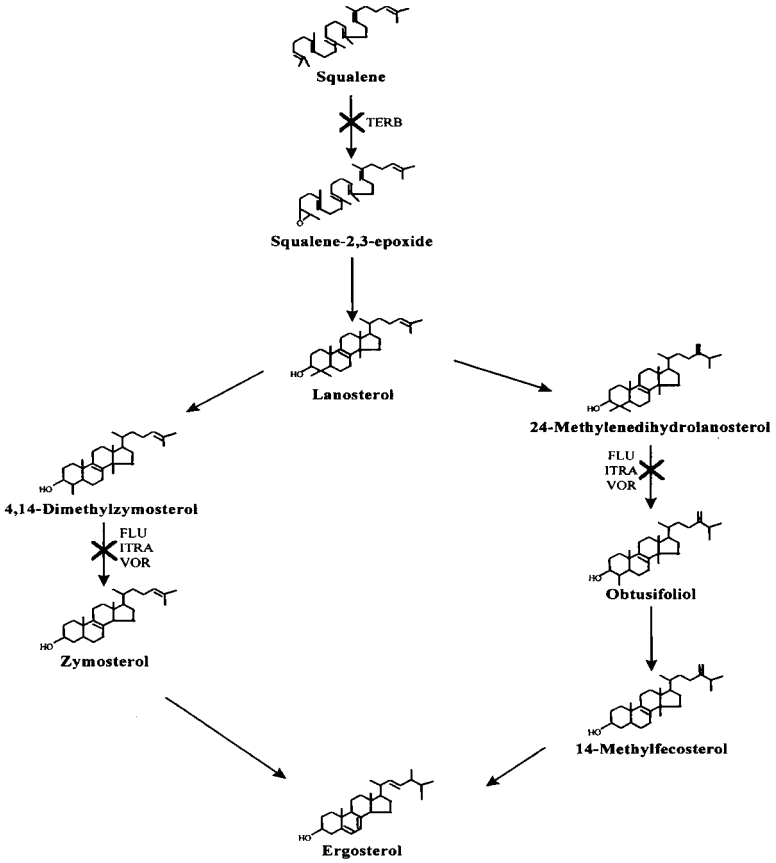


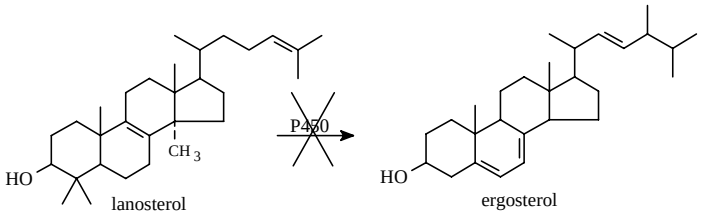
Fig. 2: Ergosterol biosynthesis from squalene.
Site of action of azole antifungals (Flu, Itra, Vor) and Terbinafine (Terb) indicated.

Azole antifungal agents are the largest class of synthetic antimycotics. About 20 agents on the market today. Some used topically to treat superficial dermatophytic and yeast infections. Others used systemically to treat severe fungal infections. Antifungal activity stems from the presence of an aromatic five member heterocyclic, either an imidazole or a triazole.

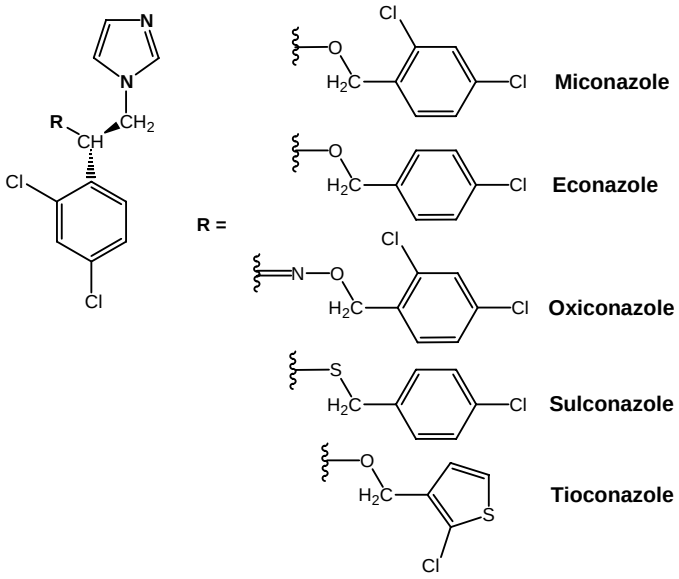
The first members of the class were highly substituted imidazoles (clotrimazole, miconazole) were not absorbed orally. Ketoconazole introduced in 1984 was the first effective oral therapy for *Candida*. Structure activity studies revealed that the imidazole ring can be replaced by a bioisosteric triazole ring without affecting the antifungal activity but achieving higher selectivity of the fungal targets vs. host. Itraconazole and Fluconazole are more potent, less toxic and provide effective oral therapy for many systemic fungal infections. These two are triazoles. Another triazole has been recently introduced (voriconazole). That said, amphotericin B is usually the preferred drug for life threatening systemic fungal infections. It is still the "gold standard".

*Mechanism of Action***:** These imidazoles and triazoles inhibit CYP P450 14 α- demethylase in fungi. This enzyme is involved in the conversion of lanosterol to ergosterol. Other P450s in sterol biosynthesis may be affected. The basic nitrogen of the azole ring forms a tight bond with

the heme iron of the fungal P450 preventing substrate and oxygen binding. Inhibition of the C14α-demethylase results in accumulation of sterols still bearing a C14 methyl group changing the exact shape and physical properties of the membrane causing permeability changes and malfunction of membrane imbedded proteins. They have a lower affinity for mammalian P450's. The effect is fungistatic, but may be fungicidal at higher concentrations.



Spectrum and Uses of Azole and Triazole Antifungals



Five azole antifungals, miconazole, econazole, oxiconazole, sulconazole and tioconazole share a common general structure but differ by the additional structural elements attached to the central methylene carbon. All five antifungals are used in topical application only.

MICONAZOLE (developed by Janssen Pharmaceutica) is used for skin infections such as tinea pedis, tinea cruris and vulvovaginitis. It comes in cream, lotion, powder, spray liquid and spray powder, and also in suppository form for vaginal use. Miconazole is used once or twice a day for one month for tinea pedis or two weeks for other skin infections. For vaginal infections it is used once a day at bedtime for three or seven days.

Adverse effects include: increased burning, itching or irritation of the skin or vagina, stomach pain, fever or foul-smelling vaginal discharge.

Products: Micatin, Monistat-3, Monistat-7, Monistat-Derm, Monistat Dual-Pak

ECONAZOLE (developed by Janssen Pharmaceutica) is a topical cream applied to the skin to treat fungal infections including: tinea corporis, tinea pedis, tinea cruris, and superficial candidiasis.

Adverse effects include: Burning, itching, stinging, redness and skin rash.

Products: Spectrazole, Ecostatin

OXICONAZOLE (developed by F. Hoffmann-LaRoche and Siegfried AG) is a cream or lotion applied to the skin in the treatment of tinea corporis, tinea pedis and tinea cruris.

Adverse effects include: Burning, itching, blistering, crusting, dryness or flaking of the skin, scaling, severe redness, soreness, swelling and pain in hairy areas with pus at the root of hair.

Products: Oxistat, Oxizole

SULCONAZOLE (developed by Syntex Research) is a topical cream or solution to treat tinea corporis, tinea pedis and tinea cruris.

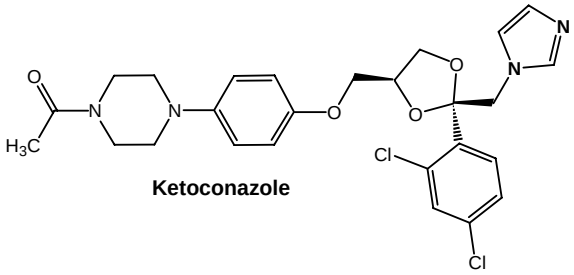
Adverse effects include: Burning, stinging, itching and redness of the skin.

Products: Exelderm

TIOCONAZOLE (developed by Pfizer U.K.) is a cream to treat tinea corporis, tinea pedis, tinea cruris and cutaneous candidiasis.

Adverse effects include: Burning, itching, redness, skin rash and swelling.

Products: Trosyd AF, Trosyd J

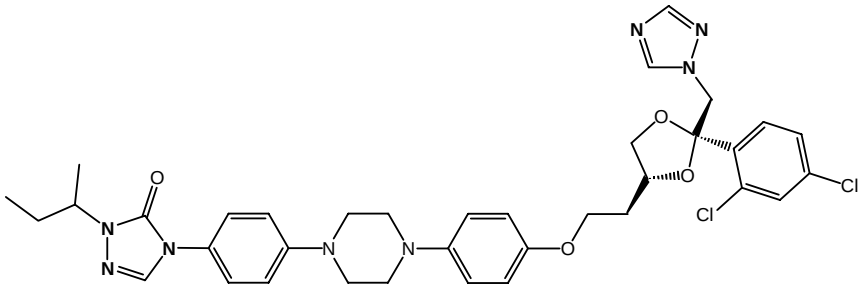


Ketoconazole

KETOCONAZOLE is supplied as a cream or in shampoos at one- or two-percent, for the treatment of tinea pedis, tinea corporis, tinea cruris and cutaneous candidiasis.

Adverse effects include: itching, stinging, skin rash, dry skin, and dry or oily scalp.

Products: Nizoral Cream, Nizoral A-D Shampoo (1%), Nizoral Shampoo (2%)



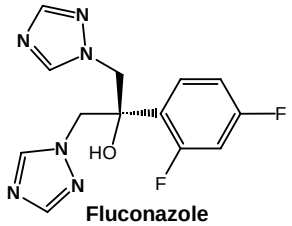
Itraconazole

ITRACONAZOLE is taken orally in capsule form to treat fungal infections that start in the lungs and spread throughout the body. Itraconazole can also be used to treat fungal infections of the nails, although it is important to point out that treatment of nail fungal infections does not result in healthier looking nails. Normal nail appearance will occur only with new growth, which can take up to six months for full nail growth. Oral solutions of this antifungal agent can be used to treat oral candidiasis.

Drug Interactions: Patients on proton pump inhibitors should take itraconazole with a cola soft drink to aid in bioavailability.

Adverse effects include: diarrhea, constipation, gas, stomach pain, heartburn, sore or bleeding gums, sores in and around the mouth, headache, dizziness, sweating, muscle pain, decreased sexual desire or ability, nervousness, depression and runny nose. More severe side effects can include: excessive tiredness, loss of appetite, upset stomach, vomiting, tingling or numbness in the extremities, fever, chills, rash, hives and difficulty breathing or swallowing. HEPATOXICITY: yellowing of the eyes or skin, dark urine or pale stools.

Product: Sporanox

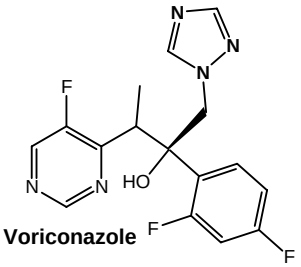


Fluconazole

FLUCONAZOLE is a one-a-day tablet or suspension to treat yeast infections of the vagina, mouth, throat, esophagus, abdomen, lungs, blood and other organs. Fluconazole is also used to treat meningitis and can prevent yeast infections in patients who are likely to become infected due to chemotherapy or radiation therapy before a bone marrow transplant.

Adverse effects include: headache, dizziness, diarrhea, stomach pain, heartburn and changes in the ability to taste food. More severe side effects can include: excessive tiredness, loss of appetite, upset stomach, vomiting, tingling or numbness in the extremities, fever, chills, rash, hives and difficulty breathing or swallowing. HEPATOXICITY: yellowing of the eyes or skin, dark urine or pale stools.

Product: Diflucan



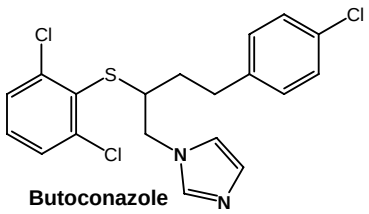
Voriconazole

VORICONAZOLE is formulated in an oral suspension, tablets or parenteral injection. It is used to treat different kinds of serious fungal infections and may be used in patients who have not responded to other antifungal agents.

Drug interactions: Xanax, Versed, Halcion, Agenernase, Viracept, Invirase, Hismanal, barbiturates, cyclosporine, ergot alkaloids, HMG CoA reductase inhibitors and warfarin.

Adverse effects include: rash, bloating or swelling of face, arms, hands, lower legs or feet, stomach pain, blurred vision, chills, convulsions, dizziness, dry mouth, headache and muscle pain. HEPATOXICITY: dark urine or pale stools.

Product: VFEND

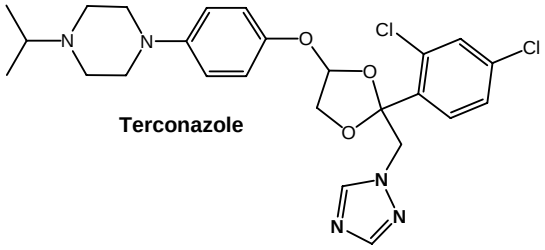


Butoconazole

BUTOCONAZOLE is a cream suppository used to treat vulvovaginitis. It is used either once or in a seven-day regimen at bedtime.

Adverse effects include: burning or irritation in the vagina when cream is inserted, stomach pain, fever or foul-smelling vaginal discharge.

Product: Gynazole-1

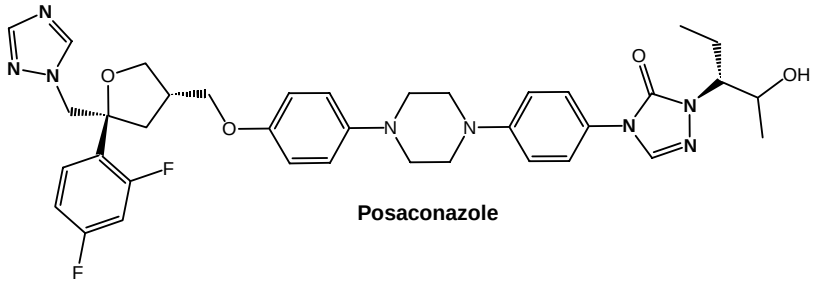


Terconazole

TERCONAZOLE is supplied as a cream or suppository to treat vulvovaginitis. It is usually used daily at bedtime for either three or seven days.

Adverse effects include: headache, missed menstrual periods, burning or irritation in vagina when cream or suppository is inserted, stomach pain, fever, or foul-smelling vaginal discharge.

Product: Terazol 3, Terazol 7.



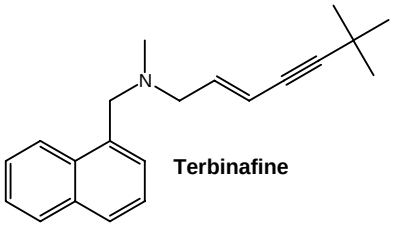
Posaconazole

POSACONAZOLE (Schering-Plough) is a novel triazole in Phase II clinical trials to be used as an oral suspension to treat invasive fungal infections caused by Candida and aspergillus. The current clinical trial will conclude in October 2006.

Antifungal Agents Targeting Squalene Epoxidase: Ergosterol Biosynthesis Inhibitors

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.

Mechanism of Action: These antifungal agents are reversible, noncompetitive inhibitors of the first step in ergosterol biosynthesis (see fig. 2), 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.



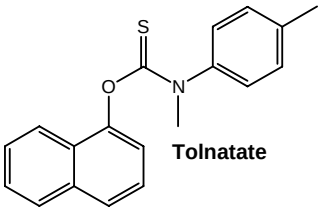
Terbinafine

TERBINAFINE comes as a tablet to take orally or as a topical cream It is used to treat fungal infections of the nails.

Drug interactions: warfarin, antidepressant drugs, beta-blockers, proton pump inhibitors and drugs to suppress the immune system.

Adverse effects include: headache, dizziness, diarrhea, stomach pain, heartburn and changes in the ability to taste food. More severe side effects can include: excessive tiredness, loss of appetite, upset stomach, vomiting, tingling or numbness in the extremities, fever, chills, rash, hives and difficulty breathing or swallowing. HEPATOXICITY: yellowing of the eyes or skin, dark urine or pale stools.

Product: Lamisil,



Tolnatate

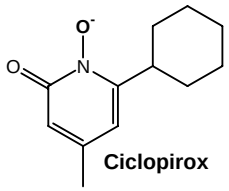
TOLNAFTATE is is a topical cream to treat tinea infections of the skin.

Mechanism of Action: The exact mechanism unknown; however, it has been reported to distort the hyphae and to stunt mycelial growth in susceptible organisms. Inhibition of squalene epoxidation has also been reported.

Adverse effects are rare. Skin irritation has been reported.

Products:Aftate, Tinactin, Ting, Breezee

Other Antifungals Affecting Cell Membrane Stability



Ciclopirox

CICLOPIROX is a topical solution used to treat fungal infections of the nails and hair.It is a broad-spectrum antifungal medication that also has antibacterial and anti-inflammatory properties.

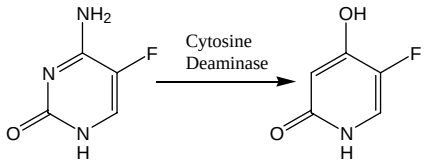
Mechanism of Action: Its main mode of action is thought to be its high affinity for trivalent cations, which inhibit essential co-factors in enzymes. Ciclopirox exhibits either fungistatic or fungicidal activity in vitro against a broad spectrum of fungal organisms, such as dermatophytes, yeasts, dimorphic fungi, eumycetes, and actinomycetes. In addition to its broad spectrum of action, ciclopirox also exerts antibacterial activity against many Gram-positive and Gram-negative bacteria. Furthermore, the anti-inflammatory effects of ciclopirox have been demonstrated in human polymorphonuclear cells, where ciclopirox has inhibited the synthesis of prostaglandin and leukotriene. Ciclopirox can also exhibit its anti-inflammatory effects by inhibiting the formation of 5-lipoxygenase and cyclooxygenase.

Ciclopirox is thought to act through the chelation of polyvalent metal cations, such as Fe^{3+} and Al^{3+}. These cations inhibit many enzymes, including cytochromes, possibly disrupting the biosynthesis of ergosterol. Ciclopirox also appears to modify the plasma membrane of fungi, resulting in the disorganization of internal structures.

Adverse effects: redness, irritation, burning, blistering or swelling at the site of application and discoloration of the nails or surrounding area. Treated nails may become ingrown.

Product: Loprox, Penlac nail lacquer

Inhibitors of Cell Division



FLUCYTOSINE was synthesized in 1957 as an antitumor agent. It was inactive but it was found to have antifungal activity.

Mechanism of Action: The drug enters the fungal cell through active transport on ATPases that normally transport pyrimidines. Once inside cells, fungal cytosine deaminase convert the drug to active 5-fluorouracil (5FU, a very effective antitumor agent, by the way!) which is incorporated into RNA causing faulty RNA synthesis and also is a strong, non competitive inhibitor of thymidylate synthesis interrupting the one carbon pool substrate. Mammalian cells do not contain cytosine deaminase.

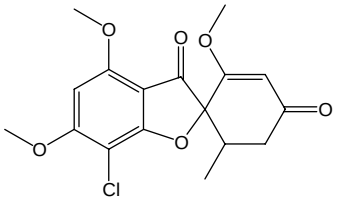
Resistance develops rapidly and occurs on many levels e.g. transport into the cell and cytosine deaminase steps. After a few dosing intervals the drug is essentially useless. To avoid rapid resistance, combination with Amphotericin B, and the combination is synergistic. It is also synergistic with itraconazole and fluconazole, and interest in these combinations for treatment of

systemic Candida infections is increasing. Amphotericin B damaged membranes are thought to allow better entry of flucytosine. Used (with Amp. B) for Cryptococcal meningitis, systemic Candida infections, and some other systemic fungal infections. This is an oral drug. Good also for fungal UTI.

Disposition: The drug is well absorbed and well distributed. CSF levels are 65-90% of plasma levels. Is eliminated unchanged largely in the urine.

Adverse Effects: GI upset, hepatic involvement seen in the increase in transaminases, Hematologic involvement include anemia, leucopenia. Thrombocytopenia is the major complication of therapy and may be due to low levels of 5-FU circulating.

Product: Ancobon (Roche)



Griseofulvin

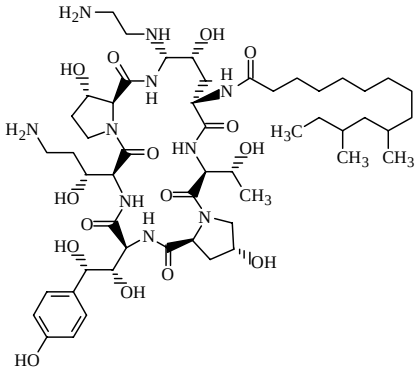
GRISEOFULVIN is an antifungal produced from *Penicillium griseofulvin*. Therapy must continue until new tissue replaces old diseased tissue. When given orally, plasma-borne griseofulvin becomes incorporated into keratin precursor cells and ultimately into kearatin that cannot support fungal growth.

Mechanism of Action: Griseofulvin inhibits microtubule polymerization thus inhibiting the formation of the mitotic spindle.

Adverse effects: Headache is a common adverse effect. May cause aplastic anemia. Being gradually replaced by newer agents.

Products: Fulvicin-U/F, Grifulvin V, Gris-PEG

Cell Wall Inhibitors



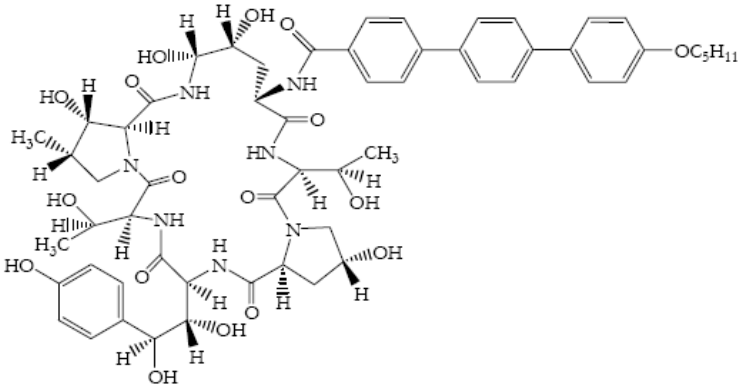
CASPOFUNGIN acetate is an parenteral injection used in the treatment of invasive aspergillosis in patients refractory to or intolerant of other antifungal therapies. Studies have shown caspofungin to be effective against invasive candidaisis. It is a semisynthetic lipopeptide (echinocandin) derived from a fermentation product of *Glarea lozoyensis*.

Mechanism of Action: Caspofungin is a (1,3)-D-glucan synthesis inhibitor, thus disrupting the formation of β-glucan in the cell walls. β-glucan is essential to the structural integrity of the cell wall.

Drug interactions: Reduces AUC, Cmax and concentration of tacrolimus. Cyclosporine increases AUC of caspofungin.

Adverse effects: thrombophlebitis, vein irritation, histamine-related symptoms, anaphylaxis has been reported.

Product: Cancidas

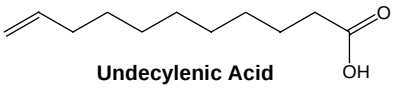


ANIDULAFUNGIN (Pfizer) has recently been approved to treat infections by Candida.

Mechanism of Action: It inhibits glucan synthase, disrupting the formation of b-glucan. It is especially effective against fluconazole-resistant Candida.

Adverse Effects: Diarrhea, elevation of liver enzymes.

Product: Eraxis



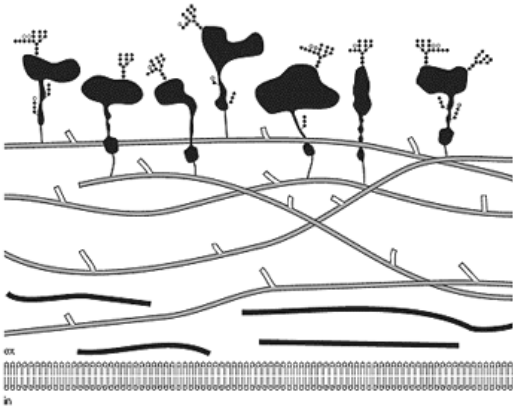
UNDECYLENIC ACID is widely used topically as the zinc salt in OTC preparations for topical treatment of infections by dermatophytes.

Mechanism of Action: This organic acid will interact non-specifically with components in the cell membrane. It can be used in concentrations up to 10% in solution, powder and emulsions. Traditionally used for athlete's foot (tinea pedis) although cure rates are low.

Adverse effects are rare. Skin irritation has been reported.

Products: Desenex, Cruex, Decylenes Powder, Caldesene, Gordochom Solution

Other Inhibitors of Fungal Cell Wall Synthesis: Under Development



Other β-1,3 glucan synthetase inhibitors: Papulacandins – glycolipid antifungal produced by Papularia sp. Loss of b-glucan results in weakening of the cell wall, thus internal pressures can cause the cells to lyse

Chitin Synthase inhibitors: Polyoxins and Nikkomycins– nucleoside peptides. Chitin is also a major component to the cell wall and its loss will also weaken the cell walls.

C Mannan binding antifungals: Pradimicins and benanomicins. C-mannan is a cell wall glycoprotein that combats the host immune response through disruption of cytokine response and possibly T-lymphocyte action.