especially at pH greater than 7. Under these conditions, chlorobutanol undergoes elimination. Solutions with a pH of approximately 5 are reasonably stable at 25°C. Chlorobutanol is stable in oils and organic solvents.

Benzyl Alcohol

Benzyl alcohol (phenylcarbinol, phenylmethanol) occurs naturally as the unesterified form in oil of jasmine and in esters of acetic, cinnamic, and benzoic acids in gum benzoin, storax resin, Peru balsam, tolu balsam, and some volatile oils. It is soluble in water and alcohol and is a clear liquid with an aromatic odor.

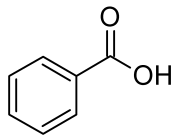
Benzyl alcohol is commonly used as a preservative in vials of injectable drugs in concentrations of 1% to 4% in water or saline solution. Benzyl alcohol has the added advantage of having a local anesthetic action. It is commonly used in ointments and lotions as an antiseptic in the treatment of various pruritic skin conditions.

Phenylethyl Alcohol

Phenylethyl alcohol (2-phenylethanol, orange oil, rose oil, $C_6H_5CH_2CH_2OH$) is a clear liquid that is sparingly soluble in water (~2%). It occurs naturally in rose oil and pine-needle oil. It is used primarily in perfumery.

Benzoic Acid

Benzoic acid and its esters occur naturally in gum benzoin and in Peru and tolu balsams. It is found as a white crystalline solid that slowly sublimes at room temperature and is steam distillable. It is slightly soluble in water (0.3%) but more soluble in alcohol and in other polar organic solvents. It has a pK_a of 4.2. Benzoic acid is used externally as an antiseptic in lotions, ointments, and mouthwashes. It is more effective as a preservative in foods and pharmaceutical products at low pH (less than the pK_a). When used as a preservative in emulsions, its effectiveness depends on both pH and distribution into the two phases.[16]



Sodium Benzoate

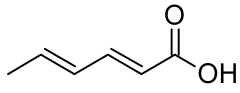
Sodium benzoate is a white crystalline solid that is soluble in water and alcohol. It is used as a preservative in acidic liquid preparations in which benzoic acid is released.

Sodium Propionate

Sodium propionate occurs as transparent colorless crystals that are soluble in water and alcohol. It is an effective antifungal agent that is used as a preservative. Sodium propionate is most effective at low pH.

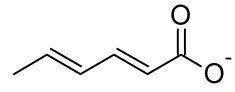
Sorbic Acid

2,4-Hexadienoic acid is an effective antifungal preservative. It is sparingly soluble in water and has a pK_a of 4.8. Sorbic acid is used to preserve syrups, elixirs, ointments, and lotions containing components such as sugars that support mold growth.



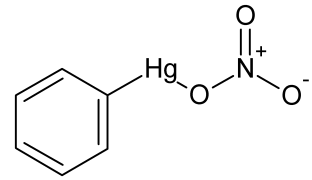
Potassium Sorbate

Potassium sorbate occurs as a white crystalline material that is soluble in water and alcohol. It is used in the same way as sorbic acid when greater water solubility is required.



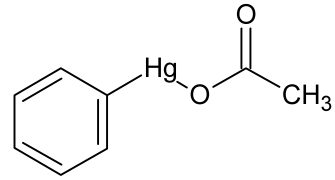
Phenylmercuric Nitrate

Phenylmercuric nitrate is a mixture of phenylmercuric nitrate and phenylmercuric hydroxide. It occurs as a white crystalline material that is sparingly soluble in water and slightly soluble in alcohol. It is used in concentrations of 1:10,000 to 1:50,000 to preserve injectable drugs against bacterial contamination. A disadvantage to organomercurials is that their bacteriostatic efficacy is reduced in the presence of serum.



Phenylmercuric Acetate

Acetoxyphenylmercury occurs as white prisms that are soluble in alcohol but only slightly soluble in water. It is used as a preservative.



ANTIFUNGAL AGENTS

General Introduction to Fungi: Medical Mycology

The discovery that some infectious diseases could be attributed to fungi actually preceded the pioneering work of Pasteur and Koch with pathogenic bacteria by several years. Two microbiologists, Schönlein and Gruby, studied the fungus *Trichophyton schoenleinii* in 1839. In that same year, Langenbeck reported the yeastlike microorganism responsible for thrush (*C. albicans*). Gruby isolated the fungus responsible for favus on potato slices, rubbed it on the head of a child, and produced the disease. Hence, he fulfilled Koch's postulates 40 years before they were formulated.[17] In spite of its earlier beginnings, medical mycology was quickly overshadowed by bacteriology, and it has only recently begun to receive the serious attention that it deserves. This is perhaps attributable to the relatively benign nature of the common mycoses, the rarity of the most serious ones, and the need for a morphological basis for differential identification of these structurally complex forms.

Cursory examination shows that fungal infections fall into two well-defined groups: the superficial and the deep-

seated mycoses.[18] The superficial mycoses are, by far, the most common and are caused, for the most part, by a relatively homogeneous group of fungi, the dermatophytes. These include the various forms of tinea, or ringworm, which are infections of the hair or hair follicles, the superficial infections of the intertriginous or flat areas of hairless skin, and infections of the nails. As a rule, these lesions are mild, superficial, and restricted. The causative microbes are specialized saprophytes with the unusual ability to digest keratin. They have their ultimate reservoir in the soil. Unlike the deep-seated mycoses, however, they are frequently transmitted from one host to another (e.g., athlete's foot). A species of yeast, *Candida*, also produces a dermatophyte-like disease.

Systemic Mycoses

The deep-seated, systemic mycoses have a sporadic distribution,[19] being common in some parts of the world and unknown in other geographical areas. These diseases have a heterogeneous etiology. Diseases caused by the systemic organisms include histoplasmosis, sporotrichosis, blastomycosis, coccidioidomycosis, cryptococcosis, and paracoccidioidomycosis. The causative agents for these diseases are soil-inhabiting saprophytes with the ability to adapt to the internal environment of their host. These organisms share a common route of infection. Fungal spores are inhaled into the lung, and a mild, coldlike condition may result. This may be the only symptom. In most cases, disease is inapparent. In asymptomatic disease, diagnosis is often made serendipitously. Sensitization, which reflects present or previous experience with the organism, may be detected by a skin test or other immunological procedure. The immune system deals with these infections by walling them off or by producing the giant cells that are common in type IV hypersensitivities. X-ray examination or autopsy frequently reveals these lesions. As stated previously, the causative organisms of the systemic infections are not typically transmitted from one host to another, but infection by the organism in an endemic area may be very common. Few infections develop into the severe, deep, spreading, and often-fatal disease seen in some persons. If the infection is symptomatic, the clinical signs may be those of a mild, self-limiting disease; or the infection may become progressive, with severe symptoms, tissue and organ damage, and, frequently, death. Recovery from a deep-seated infection of this type is accompanied by an uncertain anamnestic immune response.

Opportunistic Fungal Infections[20,21]

In recent years, because of overzealous use of antibacterial antibiotics, the use of immunosuppressive agents, cytotoxins, irradiation, and steroids, a new category of systemic mycoses has become prominent. These are the opportunistic fungal infections. There has been a precipitous rise in the incidence of these diseases. The patient, as a result of drug therapy, underlying disease, or medical manipulation, is deprived of the normal defenses conferred by microbial flora. This allows organisms of normally *low inherent virulence* to exploit the host. Such infections include systemic candidiasis, aspergillosis, and mucormycosis. Bacterial infections such as Gram-negative septicemia, nocardiosis, and *Pseudomonas* infection, fungal infections such as with *Pneumocystis carinii*, and viral opportunists such as cytomegalovirus also attack such patients. Multiple infections with various microorganisms are common. *C. albicans* is a particularly common opportunist. This yeast is a member of the normal microbial flora of human hosts, especially in the vagina. Use of contraceptives often predisposes a patient to infection by *Candida* spp. Fungal flora that inhabit the bowel may develop into a superinfection with the use of antibiotics to sterilize the bowel before surgery. Oral candidiasis is common in poorly nourished persons, in patients on immunosuppressive drugs, and in persons with acquired immunodeficiency syndrome (AIDS). Opportunists can grow in nearly every circumstance in which a patient's immune system is compromised.

Cutaneous Infections (Dermatophytoses)[22–24]

By far, the most common types of human fungal disease are among the dermatophytoses. These are superficial infections of the keratinized epidermis and keratinized epidermal appendages (i.e., the hair and nails). The severity of an infection depends largely on the location of the lesion and the species of the fungus involved. Though certain other fungi, notably *Candida* spp., produce clinically similar diseases, a somewhat homogeneous group of fungi, termed the *dermatophytes*, is responsible for most cases. The ability of these organisms to invade and parasitize the cornified tissues of hair, skin, and nails is closely associated with, and dependent on, their common physiological characteristic—metabolic use of the highly insoluble scleroprotein keratin. The biochemical use of keratin is rare and is shared by the dermatophyte species of the family Gymnoascaceae, with only a few species of the family Onygenaceae, and certain tineae. In humans, the genera *Trichophyton* (notably *T. rubrum* [nails, beard, smooth skin], *T. tonsurans* [scalp, beard, nails], *T. violaceum* [scalp, skin nails], *T. mentagrophytes* [commonest cause of athlete's foot], *T. verrucosum* [scalp, beard], and *T. rubrum* [psoriasis-like lesions of smooth skin, infections of nails]), *Microsporum* (*M. gypseum* [scalp], *M. fulvum* [scalp, hairless skin], and *M. canis* [scalp, hairless skin]), and *Epidermophyton* (eczema) contain the most common dermatophytes. These organisms cause the conditions known as tinea (ringworm). Some of the common tinea infections are listed in Table 6.4. The fungus *Pityrosporum orbiculare* causes an additional type, tinea versicolor. This organism, called *Malassezia furfur* in older literature, causes yellow to brown patches or continuous scaling over the trunk and occasionally the legs, face, and neck. The affected areas may be identified by the inability to tan in the sun.

Regardless of the type of fungus that is causing an infection (Table 6.5), treatment is extremely difficult because fungi, like mammalians, are eukaryotes. Many biochemical structures, especially the cell membranes, are nearly identi-

TABLE 6.4 Locations of the Common Types of Tinea (Ringworm)

Type	Location
Tinea manuum	Hand
Tinea cruris	Groin
Tinea sycosis	Beard
Tinea capitis	Scalp
Tinea unguium	Nails

TABLE 6.5 Clinical Types of Fungal Infection

Type	Disease State	Causative Organism
Superficial infections	Tinea versicolor	*Pityrosporum orbiculare*
	Piedra	*Trichosporon cutaneum* (white)
		Piedraia hortae (black)
Cutaneous infections	Ringworm of scalp, hairless skin, nails	Dermatophytes, *Microsporum, Trichophyton, Epidermophyton*
	Candidosis of skin, mucous membranes, nails; sometimes generalized	*Candida albicans* and related forms
Subcutaneous infections	Chromomycosis	*Fonsecaea* and related forms
	Mycotic mycetoma	*Allescheria boydii, Madurella mycetoma,* etc.
	Entomophthoromycosis	*Basidiobolus haptosporus, Conidiobolus coronatus*
Systemic infections	Histoplasmosis	*Histoplasma capsulatum*
	Blastomycosis	*Blastomyces dermatiditis*
	Paracoccidioidomycosis	*Paracoccidioides brasiliensis*
	Coccidioidomycosis	*Coccidioides immitis*
	Cryptococcosis	*Cryptococcus neoformans*
	Sporotrichosis	*Sporothrix schenckii*
	Aspergillosis	*Aspergillus fumigates*
	Mucormycosis	*Mucor* spp., *Absidia* spp., *Rhizopus* spp.
	Histoplasmosis duboisii	*Histoplasma capsulatum* var. *duboisii*

cal, as are many biochemical reactions. Consequently, drugs that will kill a fungus will have a toxic effect on human cells at normal doses.

A slight difference exists in the cell membranes. Lipid bilayers by themselves are unstable and would be unable to hold their shape and support their functions. Sterols are embedded in the bilayers to act as stiffening agents. The 3-hydroxyl group represents the polar "head" group, and the nonpolar sterol skeleton and side chain align perfectly with the nonpolar chains of the bilayer. In human cells, the sterol in the membrane is cholesterol (Fig. 6.1). In fungi, the sterol is ergosterol (Fig. 6.2). This difference amounts to the only source of selectivity that we have in treating fungal infections. New antifungal drug development has focused on this difference as a way to achieve selectivity, creating highly potent antifungal drugs that are much less toxic to the human host.

Subcutaneous Fungal Infections[22]

Subcutaneous mycosis refers to a group of fungal diseases in which both the skin and subcutaneous tissue are involved but typically no dissemination to the internal organs occurs. The causative agents are classified among several unrelated genera. They have the following characteristics in common: (a) they are primarily soil saprophytes of very low-grade virulence and invasive ability; and (b) in most human and animal infections, they gain access as a result of a trauma to the tissue. Many, if not all, organisms have the potential to establish local infections under certain circumstances, depending on their adaptability and the response of the host. The tissue reaction in most cases varies with the agent in question but usually remains a localized lesion similar to that elicited by a foreign body. The major disease types are chromomycosis, sporotrichosis, mycetoma, lobomycosis, and entomophthoromycosis. A type of dimorphism accompanies infection by agents of some of these groups. The organisms undergo a morphogenesis from their saprophytic form into a tissue or parasitic stage.

Tissue Reactions of Fungal Disease[23]

The tissue response of the host to the infecting fungus varies widely and depends somewhat on various invasive organisms. In dermatophyte infections, erythema is gener-

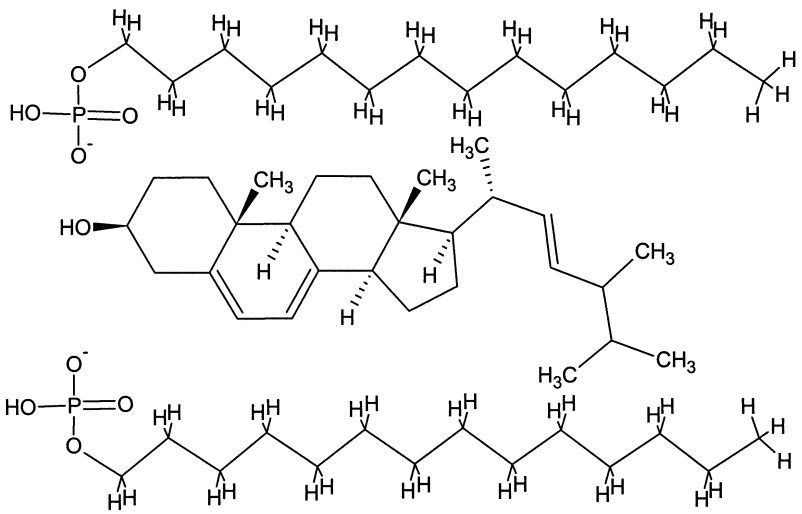


Figure 6.1 ● Cholesterol embedded in a lipid bilayer.

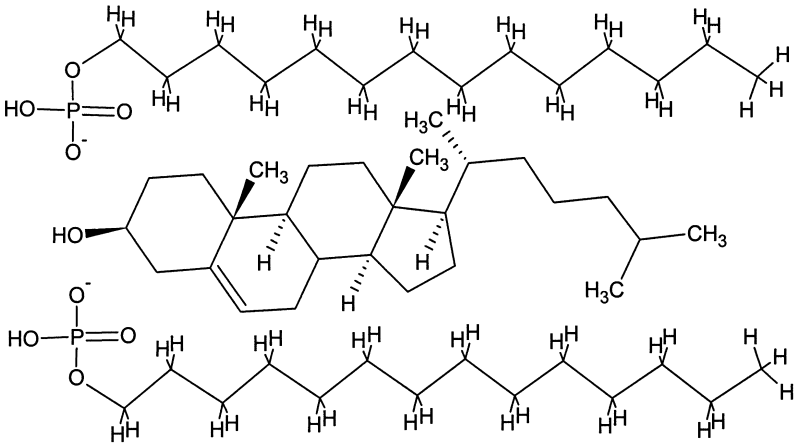


Figure 6.2 ● Ergosterol embedded in a lipid bilayer.

ally produced and is a result of the irritation of the tissues by the organism. Sometimes, severe inflammation, followed by scar tissue and keloid formation, occurs. This results from an exaggerated inflammatory response and an allergic reaction to the organism and its products.

With organisms that invade living tissue, such as those responsible for subcutaneous and systemic disease, there is generally a uniform acute pyogenic reaction that gives way to various chronic disease outcomes. Granuloma with caseation and fibrocaseous pulmonary granuloma are potential outcomes of infection with *Histoplasma capsulatum*, and thrombotic arteritis, a thrombosis characterized by a purulent coagulative necrosis and invasion of blood vessels, may be caused during aspergillosis and mucormycosis. The large numbers of fungal species of many morphotypes, their disease etiology, and the diversity of outcomes make medical mycology a complex field.

Topical Agents for Dermatophytoses

Collectively, the dermatophytoses are called *tinea*, or *ringworm*. Since these infections tend to be topical, their treatment has been directed to surface areas of the skin. The skin is a formidable barrier to drug penetration, and many of the topical agents work best if an adjuvant is added that opens the barrier function of the skin. Keratolytic agents such as salicylic acid or other α-hydroxy compounds perform this function reasonably well.

FATTY ACIDS

Adults have an acidic, fatty substance in and on the skin called *sebum*. Sebum functions as a natural antifungal agent, part of the innate immune system. Fatty acids have been used for years with the idea that if a substance similar to sebum could be applied to the infected area, the effect of the sebum would be augmented and fungi could be eradicated. The application of fatty acids or their salts does in fact have an antifungal effect, albeit a feeble one.

The higher–molecular-weight fatty acids have the advantage of having lower volatility. Salts of fatty acids are also fungicidal and provide nonvolatile forms for topical application.

Propionic Acid

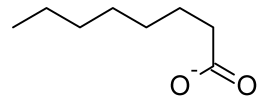
Propionic acid is an antifungal agent that is nonirritating and nontoxic. After application, it is present in perspiration in low concentration (~0.01%). Salt forms with sodium, potassium, calcium, and ammonium are also fungicidal. Propionic acid is a clear, corrosive liquid with a characteristic odor. It is soluble in water and alcohol. The salts are usually used because they are nonvolatile and odorless.

Zinc Propionate

Zinc propionate occurs as an anhydrous form and as a monohydrate. It is very soluble in water but only sparingly soluble in alcohol. The salt is unstable to moisture, forming zinc hydroxide and propionic acid. Zinc propionate is used as a fungicide, particularly on adhesive tape.

Sodium Caprylate

Sodium caprylate is prepared from caprylic acid, which is a component of coconut and palm oils. The salt precipitates as cream-colored granules that are soluble in water and sparingly soluble in alcohol.



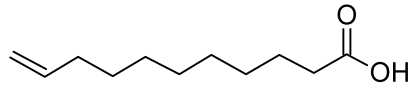
Sodium caprylate is used topically to treat superficial dermatomycoses caused by *C. albicans* and *Trichophyton*, *Microsporum*, and *Epidermophyton* spp. The sodium salt can be purchased in solution, powder, and ointment forms.

Zinc Caprylate

Zinc caprylate is a fine white powder that is insoluble in water or alcohol. The compound is used as a topical fungicide. The salt is highly unstable to moisture.

Undecylenic Acid

10-Undecenoic acid (Desenex, Cruex) obtained from the destructive distillation of castor oil. Undecylenic acid is a viscous yellow liquid. It is almost completely insoluble in water but is soluble in alcohol and most organic solvents.



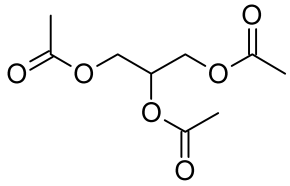
Undecylenic acid is one of the better fatty acids for use as a fungicide, although cure rates are low. It can be used in concentrations up to 10% in solutions, ointments, powders,

and emulsions for topical administration. The preparation should never be applied to mucous membranes because it is a severe irritant. Undecylenic acid has been one of the agents traditionally used for athlete's foot (*tinea pedis*). Cure rates are low, however.

Triacetin

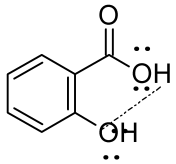
Glyceryl triacetate (Enzactin, Fungacetin) is a colorless, oily liquid with a slight odor and a bitter taste. The compound is soluble in water and miscible with alcohol and most organic solvents.

The activity of triacetin is a result of the acetic acid released by hydrolysis of the compound by esterases present in the skin. Acid release is a self-limiting process because the esterases are inhibited below pH 4.



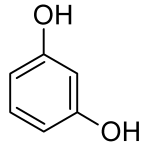
Salicylic Acid and Resorcinol

Salicylic acid is a strong aromatic acid (pK_a 2.5) with both antiseptic and keratolytic properties. It occurs as white, needlelike crystals or a fluffy crystalline powder, depending on how the compound was brought out of solution. Salicylic acid is only slightly soluble in water but is soluble in most organic solvents. The greater acidity of salicylic acid and its lower solubility in water compared with *p*-hydroxybenzoic acid are the consequence of intramolecular hydrogen bonding.



Salicylic acid is used externally in ointments and solutions for its antifungal and keratolytic properties. By itself, salicylic acid is a poor antifungal agent.

m-Hydroxyphenol (resorcinol) possesses antiseptic and keratolytic activity. It occurs as white, needlelike crystals and has a slightly sweet taste. Resorcinol is soluble in water, alcohols, and organic solvents.

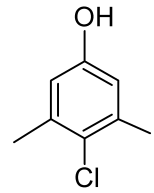


Benzoic Acid

Benzoic acid possesses appreciable antifungal effects, but it cannot penetrate the outer layer of the skin in infected areas. Therefore, benzoic acid when used as an antifungal agent must be admixed with a keratolytic agent. Suitable mixtures are benzoic acid and salicylic acid and benzoic acid and resorcinol. An old preparation that is still in use is Whitfield's Ointment, *USP*. This ointment contains benzoic acid, 6%, and salicylic acid, 6%, in a petrolatum base. The cure rates from preparations like these are low.

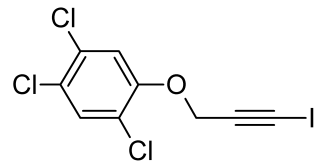
PHENOLS AND THEIR DERIVATIVES

Several phenols and their derivatives possess topical antifungal properties. Some of these, such as hexylresorcinols and parachlorometaxylenol have been used for the treatment of tinea infections. Two phenolic compounds, clioquinol and haloprogin, are still official in the *USP*. A third agent, ciclopirox olamine, is not a phenol but has properties like those of phenols. All of these agents appear to interfere with cell membrane integrity and function in susceptible fungi.



Haloprogin

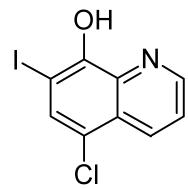
3-Iodo-2-propynyl-2,4,5-trichlorophenyl ether (Halotex) crystallizes as white to pale yellow forms that are sparingly soluble in water and very soluble in ethanol. It is an ethereal derivative of a phenol. Haloprogin is used as a 1% cream for the treatment of superficial tinea infections.



Formulations of haloprogin should be protected from light because the compound is photosensitive. Haloprogin is available as a solution and a cream, both in a 1% concentration. Haloprogin is probably not the first topical agent that should be recommended. Although the cure rates for topical fungal infections are relatively high, they come at a high price. The lesion typically worsens before it improves. Inflammation and painful irritation are common.

Clioquinol

5-Chloro-7-iodo-8-quinolinol, 5-chloro8-hydroxy-7-iodoquinoline, or iodochlorhydroxyquin (Vioform) occurs as a spongy, light-sensitive, yellowish white powder that is insoluble in water. Vioform was initially used as a substitute for iodoform in the belief that it released iodine in the tissues. It has been used as a powder for many skin conditions, such as atopic dermatitis, eczema, psoriasis, and impetigo. A 3% ointment or cream has been used vaginally as a treatment for *Trichomonas vaginalis* vaginitis. The best use for Vioform is in the topical treatment of fungal infections such as athlete's foot and jock itch. A combination with hydrocortisone (Vioform HC) is also available.



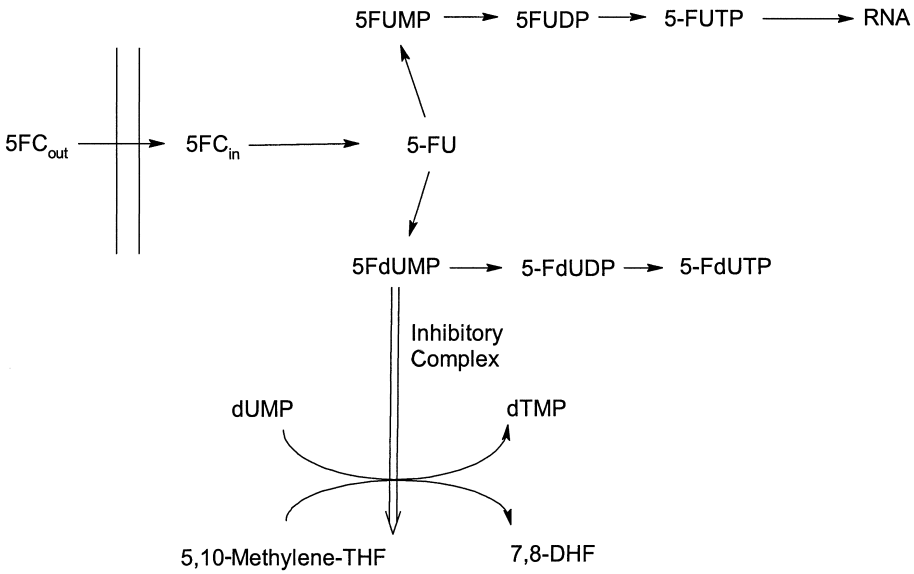
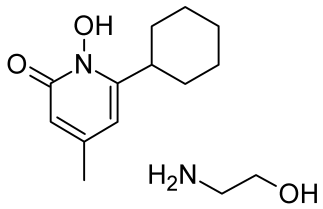


Figure 6.3 ● Mechanism of action of 5-fluorocytosine.

Ciclopirox Olamine[25]

6-Cyclohexyl-1-hydroxyl-4-methyl-2(1*H*)-pyridinone ethanolamine salt (Loprox) is a broad-spectrum antifungal agent intended only for topical use. It is active against dermatophytes as well as pathogenic yeasts (*C. albicans*) that are causative agents for superficial fungal infections.

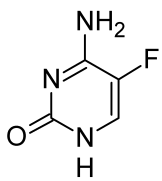


Ciclopirox is considered an agent of choice in the treatment of cutaneous candidiasis, tinea corporis, tinea cruris, tinea pedis, and tinea versicolor. It is a second-line agent for the treatment of onychomycosis (ringworm of the nails). Loprox is formulated as a cream and a lotion, each containing 1% of the water-soluble ethanolamine salt. Ciclopirox is believed to act on cell membranes of susceptible fungi at low concentrations to block the transport of amino acids into the cells. At higher concentrations, membrane integrity is lost, and cellular constituents leak out.

Nucleoside Antifungals

Flucytosine[26]

5-Fluorocytosine, 5-FC, 4-amino-5-fluoro-2(1*H*)-pyrimidinone, 2-hydroxy-4-amino-5-fluoropyrimidine (Ancobon). 5-Fluorocytosine is an orally active antifungal agent with a very narrow spectrum of activity. It is indicated only for the treatment of serious systemic infections caused by susceptible strains of *Candida* and *Cryptococcus* spp.



The mechanism of action of 5-fluorocytosine (5-FC) has been studied in detail and is presented in Figure 6.3. The drug enters the fungal cell by active transport on ATPases that normally transport pyrimidines. Once inside the cell, 5-fluorocytosine is deaminated in a reaction catalyzed by cytosine deaminase to yield 5-fluorouracil (5-FU). 5-Fluorouracil is the active metabolite of the drug. 5-Fluorouracil enters into pathways of both ribonucleotide and deoxyribonucleotide synthesis. The fluororibonucleotide triphosphates are incorporated into RNA, causing faulty RNA synthesis. This pathway causes cell death. In the deoxyribonucleotide series, 5-fluorodeoxyuridine monophosphate (F-dUMP) binds to 5,10-methylenetetrahydrofolic acid, interrupting the one-carbon pool substrate that feeds thymidylate synthesis. Hence, DNA synthesis is blocked.

Resistance to 5-FC is very common, and it occurs at several levels. A main one is at the step in which the drug is transported into the fungal cell. The transport system simply becomes impermeable to 5-FC. The cytosine deaminase step is another point at which resistance occurs, and the UMP pyrophosphorylase reaction is a third point at which fungal cells can become resistant. Regardless of which of these mechanisms operates, fungal resistance develops rapidly and completely when 5-FC is administered. After a few dosing intervals, the drug is essentially useless. One strategy used to decrease resistance and to prolong the effect of 5-FC is to administer it with the polyene antibiotic amphotericin B. The antibiotic creates holes in the fungal cell membrane, bypassing the transport step and allowing 5-FC to enter. Additionally, a lower dose of 5-FC can be used, preventing resistance by other mechanisms for a longer period.

Antifungal Antibiotics[27,28]

The antifungal antibiotics make up an important group of antifungal agents. All of the antibiotics are marked by their complexity. There are two classes: the polyenes, which contain a large number of agents with only a few being useful, and griseofulvin (one member of the class).

POLYENES

Several structurally complex antifungal antibiotics have been isolated from soil bacteria of the genus *Streptomyces*. The compounds are similar, in that they contain a system of conjugated double bonds in macrocyclic lactone rings. They differ from the erythromycin-type structures (macrolides; see Chapter 8), in that they are larger and contain the conjugated *-ene* system of double bonds. Hence, they are called the *polyene antibiotics*. The clinically useful polyenes fall into two groupings on the basis of the size of the macrolide ring. The 26-membered–ring polyenes, such as natamycin (pimaricin), form one group, whereas the 38-membered macrocycles, such as amphotericin B and nystatin, form the other group. Also common to the polyenes are (a) a series of hydroxyl groups on the acid-derived portion of the ring and (b) a glycosidically linked deoxyaminohexose called *mycosamine*.The number of double bonds in the macrocyclic ring differs also. Natamycin, the smallest macrocycle, is a pentaene; nystatin is a hexaene; and amphotericin B is a heptaene.

The polyenes have no activity against bacteria, rickettsia, or viruses, but they are highly potent, broad-spectrum antifungal agents. They do have activity against certain protozoa, such as *Leishmania* spp. They are effective against pathogenic yeasts, molds, and dermatophytes. Low concentrations of the polyenes in vitro will inhibit *Candida* spp., *Coccidioides immitis*, *Cryptococcus neoformans*, *H. capsulatum, Blastomyces dermatitidis*, *Mucor mucedo*, *Aspergillus fumigatus*, *Cephalosporium* spp., and *Fusarium* spp.

The use of the polyenes for the treatment of systemic infections is limited by the toxicities of the drugs, their low water solubilities, and their poor chemical stabilities. Amphotericin B, the only polyene useful for the treatment of serious systemic infections, must be solubilized with a detergent. The other polyenes are indicated only as topical agents for superficial fungal infections.

The mechanism of action of the polyenes has been studied in some detail. Because of their three-dimensional shape, a barrel-like nonpolar structure capped by a polar group (the sugar), they penetrate the fungal cell membrane, acting as "false membrane components," and bind closely with ergosterol, causing membrane disruption, cessation of membrane enzyme activity, and loss of cellular constituents, especially potassium ions. In fact, the first observable in vitro reaction upon treating a fungal culture with amphotericin B is the loss of potassium ions. The drug is fungistatic at low concentrations and fungicidal at high concentrations. This suggests that at low concentrations, the polyenes bind to a membrane-bound enzyme component, such as an ATPase.

Amphotericin B

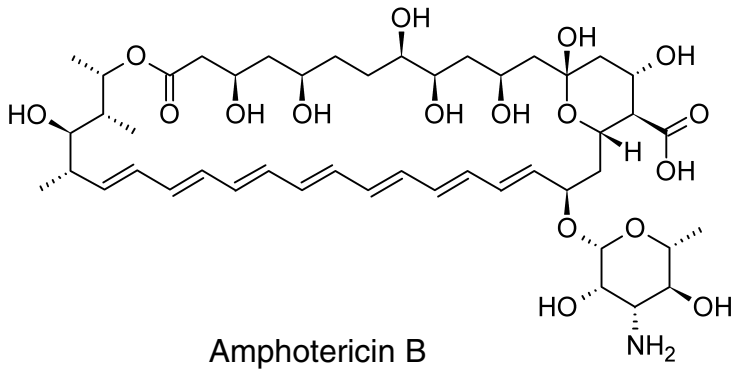
The isolation of amphotericin B (Fungizone) was reported in 1956 by Gold et al.[29] The compound was purified from the fermentation beer of a soil culture of the actinomycete *Streptomyces nodosus*, which was isolated in Venezuela. The first isolate from the streptomycete was a separable mixture of two compounds, designated amphotericins A and B. In test cultures, compound B proved to be more active, and this is the one used clinically.[30] The structure and absolute stereochemistry are as shown.

Amphotericin B is believed to interact with membrane sterols (ergosterol in fungi) to produce an aggregate that forms a transmembrane channel. Intermolecular hydrogen bonding interactions among hydroxyl, carboxyl, and amino groups stabilize the channel in its open form, destroying symport activity and allowing the cytoplasmic contents to leak out. The effect is similar with cholesterol. This explains the toxicity in human patients. As the name implies, amphotericin B is an amphoteric substance, with a primary amino group attached to the mycosamine ring and a carboxyl group on the macrocycle. The compound forms deep yellow crystals that are sparingly soluble in organic solvents but insoluble in water. Although amphotericin B forms salts with both acids and bases, the salts are only slightly soluble in water (~0.1 mg/mL) and, hence, cannot be used systemically. To create a parenteral dosage form, amphotericin B is stabilized as a buffered colloidal dispersion in micelles with sodium deoxycholate.[31] The barrel-like structure of the antibiotic develops interactive forces with the micellar components, creating a soluble dispersion. The preparation is light, heat, salt, and detergent sensitive.

Parenteral amphotericin B is indicated for the treatment of severe, potentially life-threatening fungal infections, including disseminated forms of coccidioidomycosis and histoplasmosis, sporotrichosis, North American blastomycosis, cryptococcosis, mucormycosis, and aspergillosis.

The usefulness of amphotericin B is limited by a high prevalence of adverse reactions. Nearly 80% of patients treated with amphotericin B develop nephrotoxicity. Fever, headache, anorexia, gastrointestinal distress, malaise, and muscle and joint pain are common. Pain at the site of injection and thrombophlebitis are frequent complications of intravenous administration. The drug must never be administered intramuscularly. The hemolytic activity of amphotericin B may be a consequence of its ability to leach cholesterol from erythrocyte cell membranes.

For fungal infections of the central nervous system (CNS) (e.g., cryptococcosis), amphotericin B is mixed with cerebrospinal fluid (CSF) that is obtained from a spinal tap.



Amphotericin B

The solution of amphotericin B is then reinjected through the tap. For severe infections, this procedure may need to be repeated many times.

Amphotericin B for injection is supplied as a sterile lyophilized cake or powder containing 50 mg of antibiotic with 41 mg of sodium deoxycholate to be dispersed in 10 mL of water. The infusion, providing 0.1 mg/mL, is prepared by further dilution (1:50) with 5% dextrose for injection. Normal saline cannot be used because it will break the micelles. The suspension should be freshly prepared and used within 24 hours. Even the powder should be refrigerated and protected from light.

Several sterile dosage forms[32] with amphotericin B admixed with a lipid carrier have been developed with the goal of counteracting the dose-limiting toxicity of the drug following parenteral administration. These include amphotericin B colloidal dispersion (Amphocil, Amphocyte), which contains nearly equal parts of the drug and cholesterol sulfate in a suspension of disklike particles; Abelcet, a 1:1 combination of amphotericin B with L-α-dimyristoylphosphatidylcholine (7 parts) and L-α-dimyristoylphosphatidylglycerol (3 parts) to create a suspension of ribbonlike sheets; and liposomal amphotericin B (AmBisome), a small laminar vesicular preparation consisting of an approximately 1:10 molar ratio of amphotericin B and lipid (hydrogenated soy phosphatidyl choline, cholesterol, and distearoylphosphatidylcholine in a 10:5:4 ratio) for an aqueous suspension.

The rationale behind these lipid preparations is simple: amphotericin B should have a greater avidity for the lipid vehicle than for cholesterol in cell membranes. Hence, toxicity should be reduced. Lipid-associated amphotericin B should be drawn into the reticuloendothelial system, concentrating in the lymphatic tissues, spleen, liver, and lungs, where infectious fungi tend to locate. Lipases elaborated by the fungi and the host should release the drug from the lipid carrier, making it available to bind ergosterol in fungal cell membranes to exert its fungistatic and fungicidal activities.

Clinical use of each of the approved lipid preparations has shown reduced renal toxicity. Liposomal amphotericin B has been approved specifically for the treatment of pulmonary aspergillosis because of its demonstrated superiority to the sodium deoxycholate-stabilized suspension.

Amphotericin B is also used topically to treat cutaneous and mucocutaneous mycoses caused by *C. albicans*. The drug is supplied in various topical forms, including a 3% cream, a 3% lotion, a 3% ointment, and a 100-mg/mL oral suspension. The oral suspension is intended for the treatment of oral and pharyngeal candidiasis. The patient should swish the suspension in his or her mouth and swallow it. The suspension has a very bad taste, so compliance may be a problem. A slowly developing resistance to amphotericin B has been described. This is believed to relate to alterations in the fungal cell membrane.

Nystatin

Nystatin (Mycostatin) is a polyene antibiotic that was first isolated in 1951 from a strain of the actinomycete *Streptomyces noursei* by Hazen and Brown.[33] It occurs as a yellow to light tan powder. Nystatin is very slightly soluble in water and sparingly soluble in organic solvents. The compound is unstable to moisture, heat, and light.

The aglycone portion of nystatin is called *nystatinolide*. It consists of a 38-membered macrolide lactone ring containing single tetraene and diene moieties separated by two methylene groups.[34] The aglycone also contains eight hydroxyl groups, one carboxyl group, and the lactone ester functionality. The entire compound is constructed by linking the aglycone to mycosamine. The complete structure of nystatin has been determined by chemical degradation and x-ray crystallography.[35]

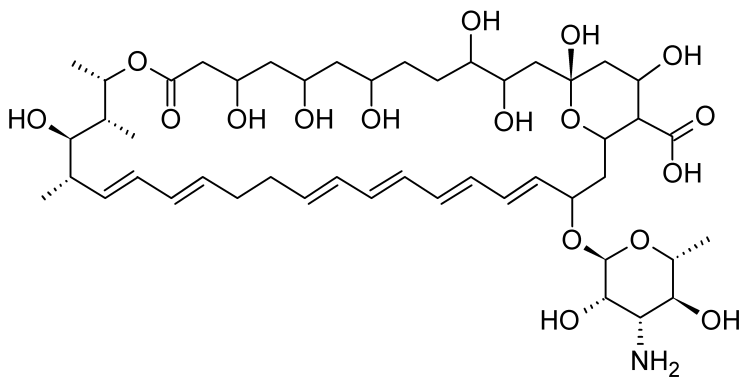
Nystatin is not absorbed systemically when administered by the oral route. It is nearly insoluble under all conditions. It is also too toxic to be administered parenterally. Hence, it is used only as a topical agent. Nystatin is a valuable agent for the treatment of local and gastrointestinal monilial infections caused by *C. albicans* and other *Candida* species. For the treatment of cutaneous and mucocutaneous candidiasis, it is supplied as a cream, an ointment, and a powder. Vaginal tablets are available for the control of vaginal candidiasis. Oral tablets and troches are used in the treatment of gastrointestinal and oral candidiasis. Combinations of nystatin with tetracycline can be used to prevent monilial overgrowth caused by the destruction of bacterial microflora of the intestine during tetracycline therapy.

Although nystatin is a pure compound of known structure, its dosage is still expressed in terms of units. One milligram of nystatin contains not less than 2,000 *USP* units.

Natamycin[36,37]

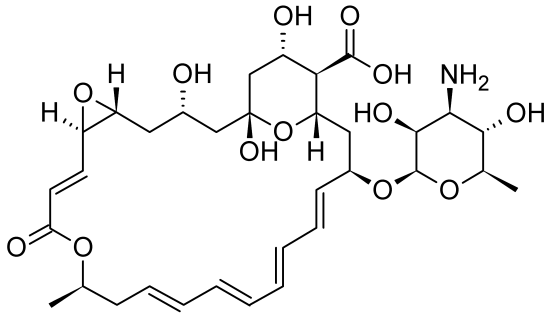
Natamycin (pimaricin; Natacyn) is a polyene antibiotic obtained from cultures of *Streptomyces natalensis*.

The natamycin structure consists of a 26-membered lactone ring containing a tetraene chromophore, an α,β-unsaturated lactone carbonyl group, three hydroxyl groups, a carboxyl



Nystatin

group, a *trans* epoxide, and a glycosidically joined mycosamine. Like the other polyene antibiotics, natamycin is amphoteric.



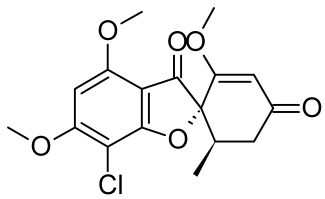
The mechanism action of the smaller polyenes differs from that of amphotericin B and nystatin. The 26-membered–ring polyenes cause both potassium ion leakage and cell lysis at the same concentration, whereas the 38-membered–ring polyenes cause potassium leakage at low, fungistatic concentrations and cell lysis at high, fungicidal concentrations. The smaller polyenes are fungistatic and fungicidal within the same concentration range.

Natamycin possesses in vitro activity against several yeasts and filamentous fungi, including *Candida*, *Aspergillus*, *Cephalosporium*, *Penicillium*, and *Fusarium* spp. The drug is supplied as a 5% ophthalmic suspension intended for the treatment of fungal conjunctivitis, blepharitis, and keratitis.

Other Antifungal Antibiotics

Griseofulvin

Griseofulvin (Grisactin, Gris-PEG, Grifulvin) was first reported in 1939 by Oxford et al.[38] as an antibiotic obtained from the fungus *Penicillium griseofulvum*. It was isolated originally as a "curling factor" in plants. Application of extracts containing the antibiotic to fungus-infected leaf parts caused the leaf to curl up. The drug has been used for many years for its antifungal action in plants and animals. In 1959, griseofulvin was introduced into human medicine for the treatment of tinea infections by the systemic route.



Griseofulvin is an example of a rare structure in nature, a spiro compound. The structure of griseofulvin was determined by Grove et al.[39] to be 7-chloro-2′,4,6-trimethoxy-6′,β-methylspiro[benzofuran-2(3*H*)-1′-[2]cyclohexene]-3,4′-dione. The compound is a white, bitter, heat-stable powder or crystalline solid that is sparingly soluble in water but soluble in alcohol and other nonpolar solvents. It is very stable when dry.

Griseofulvin has been used for a long time for the systemically delivered treatment of refractory ringworm infections of the body, hair, nails, and feet caused by species of dermatophytic fungi including *Trichophyton*, *Microsporum*, and *Epidermophyton*. After systemic absorption, griseofulvin is carried by the systemic circulation and capillary beds to the skin, nails, and hair follicles, where it concentrates in keratin precursor cells, which are gradually exfoliated and replaced by healthy tissue. Griseofulvin is a fungistatic agent, and as the new, healthy tissue develops, the drug prevents reinfection. Treatment must be continued until all of the infected tissue has been exfoliated, because old tissues will still support and harbor fungal growth. Therapy in slow-growing tissues, such as the nails, must be continued for several months. Compliance with the drug regimen is mandatory. In some cases, such as with the nails, it is possible to observe new, healthy tissue growing in to replace the infected tissue. Griseofulvin neither possesses antibacterial activity nor is effective against *P. obiculare*, the organism that causes tinea versicolor.

Few adverse effects have been reported for griseofulvin. The most common ones are allergic reactions such as rash and urticaria, gastrointestinal upset, headache, dizziness, and insomnia.

The oral bioavailability of griseofulvin is very poor. The compound is highly lipophilic with low water solubility. The most successful attempts at improving absorption have centered on creating micronized (ultramicrosized, microsized) griseofulvin. Reducing the particle size, in theory, should improve dissolution in the stomach and absorption. The efficiency of gastric absorption of griseofulvin ultramicrosized versus the microsized form is about 1.5, allowing a dosage reduction of one third. Several structural derivatives have been synthesized, but they have failed to improve absorption. Perhaps the best advice that the pharmacist can give a patient who is about to use griseofulvin is to take the drug with a fatty meal, as with salad dressing.

Griseofulvin is a mitotic spindle poison.[39,40] In vitro, it rapidly arrests cell division in metaphase. It causes a rapid, reversible dissolution of the mitotic spindle apparatus, probably by binding with the tubulin dimer that is required for microtubule assembly. The selective toxicity to fungi is probably because of the propensity of the drug to concentrate in tissues rich in keratin, where dermatophytes typically establish infections.

Allylamines and Related Compounds

The allylamine class of antifungal agents was discovered as a result of random screening of a chemical inventory for compounds with antifungal activity. Structure–activity studies in the series subsequently led to the discovery of compounds with enhanced potency and potential oral activity, such as terbinafine.[41,42] Investigation of the mechanism of action of the allylamines demonstrated that the compounds interfere with an early step in ergosterol biosynthesis, namely, the epoxidation of squalene catalyzed by squalene epoxidase. Squalene epoxidase[43] forms an epoxide at the C2–C3 position of squalene (Fig. 6.4). Opening of the epoxide under acid catalysis yields a carbocation that initiates the "squalene zipper" reaction that forms the steroid nucleus. Inhibition of squalene epoxidase shuts down the biosynthesis of ergosterol and causes an accumulation of squalene, which destabilizes the fungal cell membrane. The allylamines exert a fungicidal action against dermatophytes and other filamentous fungi, but their action against pathogenic yeasts, such as *Candida* spp., is largely fungistatic.

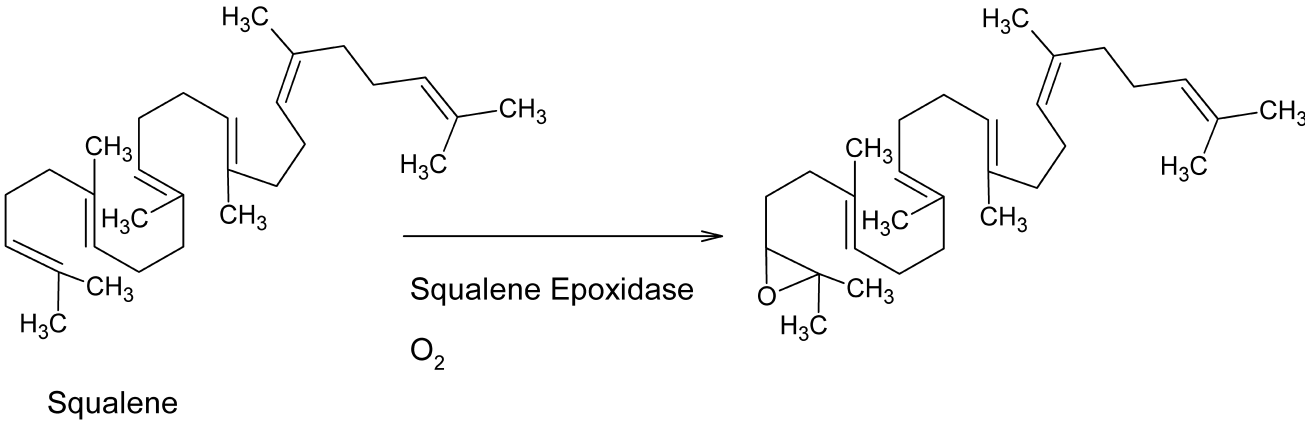


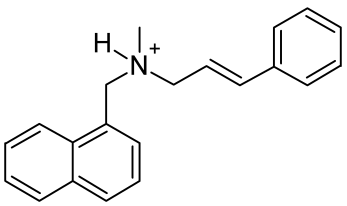
Figure 6.4 ● Squalene epoxidase reaction.

Although mammalian squalene epoxidase is weakly inhibited by the allylamines, cholesterol biosynthesis does not appear to be altered.

Two allylamines, naftifine and terbinafine, have been approved as topical agents for the treatment of tinea pedis, tinea cruris, and tinea corporis caused by *Trichophyton rubrum*, *Trichophyton mentagrophytes*, or *Epidermophyton floccosum*, respectively. The topical agent tolnaftate, although not an allylamine, inhibits squalene epoxidase and has a spectrum of activity similar to that of the allylamines. Hence, tolnaftate is classified with the allylamines. The allylamines are weak bases that form hydrochloride salts that are slightly soluble in water.

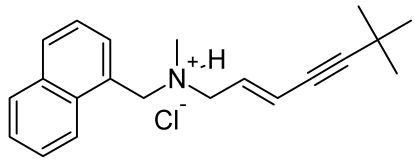
Naftifine Hydrochloride

N-Methyl-*N*-(3-phenyl2-propenyl)-1-naphthalenemethanamine hydrochloride (Naftin) is a white crystalline powder that is soluble in polar solvents such as ethanol and methylene chloride. It is supplied in a 1% concentration in a cream and in a gel for the topical treatment of ringworm, athlete's foot, and jock itch. Although unapproved for these uses, naftifine has shown efficacy for treatment of ringworm of the beard, ringworm of the scalp, and tinea versicolor.



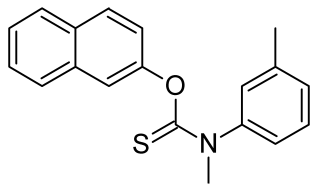
Terbinafine Hydrochloride

(*E*)-*N*-(6,6-dimethyl-2-hepten-4-ynyl)-*N*-methyl-1-naphthalene-methanamine hydrochloride (Lamisil) is an off-white crystalline material that is soluble in polar organic solvents such as methanol, ethanol, and methylene chloride but is only slightly soluble in water. The highly lipophilic free base is insoluble in water. Terbinafine hydrochloride is available in a 1% cream for topical administration for the treatment of tinea pedis, tinea corporis, and tinea cruris. Terbinafine is more potent than naftifine and has also demonstrated oral activity against onychomycosis (ringworm of the nails). It has not been approved in the United States for oral administration.



Tolnaftate

O,2-Naphthyl *m*,*N*-dimethylthiocarbanilate (Tinactin, Aftate, NP-27) is a white crystalline solid that is insoluble in water, sparingly soluble in alcohol, and soluble in most organic solvents. The compound, a thioester of β-naphthol, is fungicidal against dermatophytes, such as *Trichophyton*, *Microsporum*, and *Epidermophyton* spp., that cause superficial tinea infections. Tolnaftate is available in a concentration of 1% in creams, powders, aerosols, gels, and solutions for the treatment of ringworm, jock itch, and athlete's foot. Tolnaftate has been shown to act as an inhibitor of squalene epoxidase[44] in susceptible fungi, so it is classified with the allylamine antimycotics. Tolnaftate is formulated into preparations intended to be used with artificial fingernails to counteract the increased chance of ringworm of the nail beds.



Azole Antifungal Agents

The azoles represent a class of synthetic antifungal agents that possess a unique mechanism of action. With these drugs, one can achieve selectivity for the infecting fungus over the host. Depending on the azole drug used, one can treat infections ranging from simple dermatophytoses to life-threatening, deep systemic fungal infections. Research currently under way in the United States is aimed at developing more potent azoles and compounds that penetrate the blood-brain barrier more effectively. The first members of the class were highly substituted imidazoles, such as clotrimazole and miconazole. Structure–activity studies revealed that the imidazole ring could be replaced with a bioisosteric 1,2,4-triazole ring without adversely affecting the antifungal properties of the molecule. Hence, the more generic term *azoles* refers to this class of antifungal agents.

ANTIFUNGAL SPECTRUM

The azoles tend to be effective against most fungi that cause superficial infections of the skin and mucous membranes, including the dermatophytes such as *Trichophyton*, *Epidermophyton*, and *Microsporum* spp. and yeasts such as *C. albicans*. On the other hand, they also exhibit activity against yeasts that cause systemic infections, including *C. immitis*, *C. neoformans*, *Paracoccidioides brasiliensis*, *Petriellidium boydii*, *B. dermatitidis*, and *H. capsulatum*.

MECHANISM OF ACTION

The effects of the azoles on fungal biochemistry have been studied extensively, but there is still much to be learned.[45] At high in vitro concentrations (micromolar), the azoles are fungicidal; at low in vitro concentrations (nanomolar), they are fungistatic. The fungicidal effect is clearly associated with damage to the cell membrane, with the loss of essential cellular components such as potassium ions and amino acids. The fungistatic effect of the azoles at low concentration has been associated with inhibition of membrane-bound enzymes. A cytochrome P450-class enzyme, lanosterol 14α-demethylase, is the likely target for the azoles.[46] P450 possesses a heme moiety as part of its structure (Fig. 6.5), and the basic electron pairs of the azole rings can occupy a binding site on P450, preventing the enzyme from turning over. The function of lanosterol 14α-demethylase is to oxidatively remove a methyl group from lanosterol during ergosterol biosynthesis.

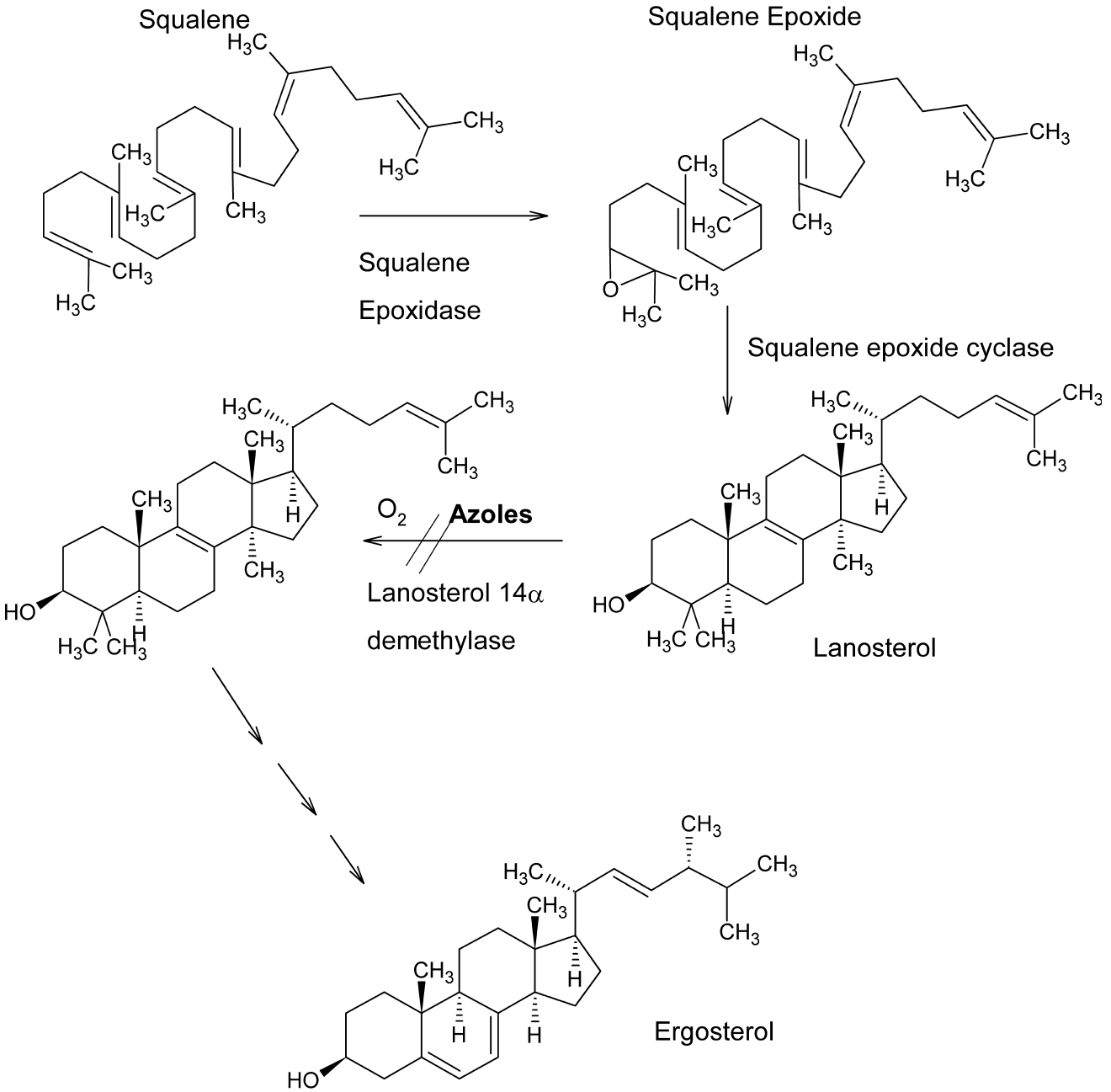


Figure 6.5 ● The inhibitory action of azole antifungal agents on the lanosterol 14-α-demethylase reaction.

When demethylation is inhibited, the 14α-sterol accumulates in the membrane, causing destabilization. As this happens, repair mechanisms, such as chitin synthesis, are initiated to patch the damage. This degrades membrane function further. Lanosterol 14α-demethylase is also required for mammalian biosynthesis of cholesterol, and the azoles are known to inhibit cholesterol biosynthesis.[47] In general, higher concentrations of the azoles are needed to inhibit the mammalian enzyme. This provides selectivity for antifungal action. The 1,2,4-triazoles appear to cause a lower incidence of endocrine effects and hepatotoxicity than the corresponding imidazoles, possibly because of a lower affinity for the mammalian cytochrome P450 enzymes involved.[48] The primary mode of resistance to the triazoles and imidazoles in *C. albicans* is the development of mutations in *ERG 11*, the gene coding for C14-α-sterol demethylase. These mutations appear to protect heme in the enzyme pocket from binding to azole but allow access of the natural substrate of the enzyme, lanosterol. Cross-resistance is conferred to all azoles. Increased azole efflux by the ATP-binding cassette (ABC-1, which normally transports cholesterol) and major facilitator superfamily transporters can add to fluconazole resistance in *C. albicans* and *C. glabrata*. Increased production of C14-α-sterol demethylase could be another cause of resistance.

STRUCTURE–ACTIVITY RELATIONSHIPS

The basic structural requirement for members of the azole class is a weakly basic imidazole or 1,2,4-triazole ring (pK_a of 6.5–6.8) bonded by a nitrogen–carbon linkage to the rest of the structure. 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. 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. Only 2, and/or 2,4 substitution yields effective azole compounds. 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. Substitution at other positions of the ring yields inactive compounds. Presumably, the large nonpolar portion of these molecules mimics the nonpolar steroidal part of the substrate for lanosterol 14α-demethylase, lanosterol, in shape and size.

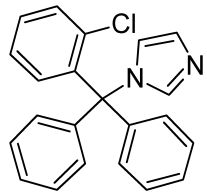
The nonpolar functionality confers high lipophilicity to the antifungal azoles. The free bases are typically insoluble in water but are soluble in most organic solvents, such as ethanol. Fluconazole, which possesses two polar triazole moieties, is an exception, in that it is sufficiently water soluble to be injected intravenously as a solution of the free base.

PRODUCTS

Clotrimazole

1-(*o*-Chloro-α,α-diphenylbenzyl)imidazole (Lotrimin, Gyne-Lotrimin, Mycelex) is a broad-spectrum antifungal drug that is used topically for the treatment of tinea infections and candidiasis. It occurs as a white crystalline solid that is sparingly soluble in water but soluble in alcohol and most organic solvents. It is a weak base that can be solubilized by dilute mineral acids.

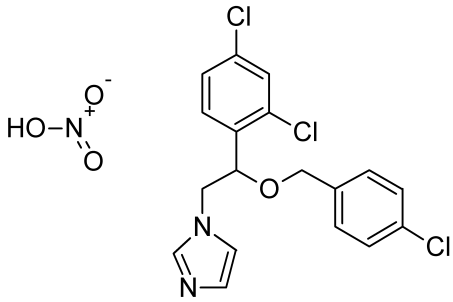
Clotrimazole is available as a solution in polyethylene glycol 400, a lotion, and a cream in a concentration of 1%. These are all indicated for the treatment of tinea pedis, tinea cruris, tinea capitis, tinea versicolor, or cutaneous candidiasis. A 1% vaginal cream and tablets of 100 mg and 500 mg are available for vulvovaginal candidiasis. Clotrimazole is extremely stable, with a shelf life of more than 5 years.



Although clotrimazole is effective against various pathogenic yeasts and is reasonably well absorbed orally, it causes severe gastrointestinal disturbances. It is also extensively protein bound and, hence, is not considered optimally bioavailable. Clotrimazole is not considered suitable for the treatment of systemic infections.

Econazole Nitrate

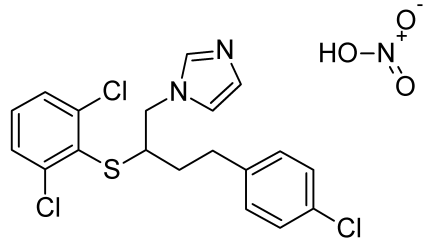
1-[2-[(4-Chlorophenyl)methoxy]-2-(2,4-dichlorophenyl)-ethyl]-1*H*-imidazole (Spectazole) is a white crystalline nitric acid salt of econazole. It is only slightly soluble in water and most organic solvents.



Econazole is used as a 1% cream for the topical treatment of local tinea infections and cutaneous candidiasis.

Butoconazole Nitrate

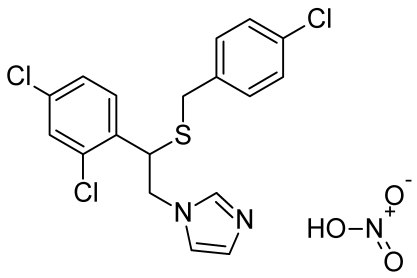
1-[4-(4-Chlorophenyl)-2-[(2,6-dichlorophenyl)-thio]butyl]-1*H*-imidazole (Femstat) is an extremely broad-spectrum antifungal drug that is specifically effective against *C. albicans*. It is supplied as a vaginal cream containing 2% of the salt. It is intended for the treatment of vaginal candidiasis.



Sulconazole Nitrate

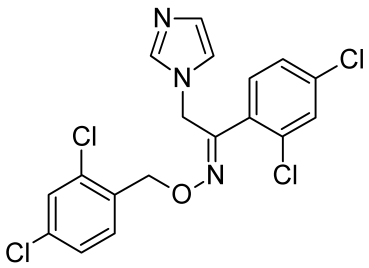
1-[2,4-Dichloro-β-[*p*-chlorobenzyl)thio]phenethyl]imidazole mononitrate (Exelderm) is the white crystalline nitric acid salt of sulconazole. It is sparingly soluble in water but soluble in ethanol. The salt is used in a solution and a cream

in 1% concentration for the treatment of local tinea infections, such as jock itch, athlete's foot, and ringworm.



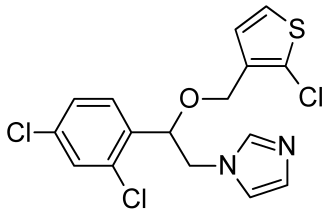
Oxiconazole Nitrate

(Z)-1-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-yl)ethanone-*O*-[2,4-dichlorophenyl)methyl]oxime mononitrate (Oxistat) is a white crystalline nitric acid salt. It is used in cream and lotion dosage forms in 1% concentration for the treatment of tinea pedis, tinea corporis, and tinea capitis.



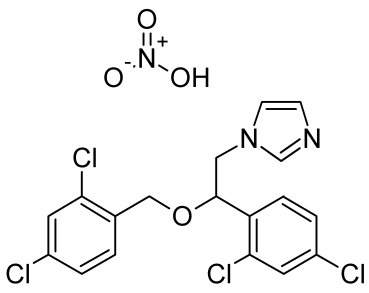
Tioconazole

1-[2-[(2-chloro-3-thienyl)methoxy]2-(2,4-dichlorophenyl)-ethyl]-1*H*-imidazole (Vagistat) is used for the treatment of vulvovaginal candidiasis. A vaginal ointment containing 6.5% of the free base is available. Tioconazole is more effective against *Torulopsis glabrata* than are other azoles.



Miconazole Nitrate

1-[2-(2,4-Dichlorophenyl)-2-[2,4-dichlorophenyl]-methoxy]ethyl]-1*H*-imidazole mononitrate (Monistat, Micatin) is a weak base with a pK_a of 6.65. The nitric acid salt occurs as white crystals that are sparingly soluble in water and most organic solvents.

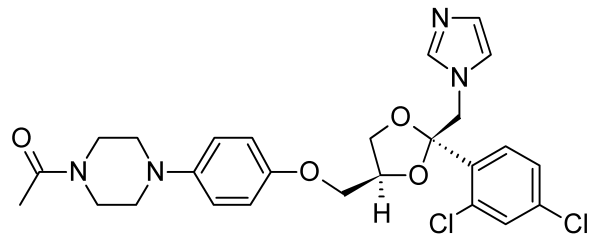


The free base is available in an injectable form, solubilized with polyethylene glycol and castor oil, and intended for the treatment of serious systemic fungal infections, such as candidiasis, coccidioidomycosis, cryptococcosis, petriellidiosis, and paracoccidioidomycosis. It may also be used for the treatment of chronic mucocutaneous candidiasis. Although serious toxic effects from the systemic administration of miconazole are comparatively rare, thrombophlebitis, pruritus, fever, and gastrointestinal upset are relatively common.

Miconazole nitrate is supplied in various dosage forms (cream, lotion, powder, and spray) for the treatment of tinea infections and cutaneous candidiasis. Vaginal creams and suppositories are also available for the treatment of vaginal candidiasis. A concentration of 2% of the salt is used in most topical preparations.

Ketoconazole

1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2(1*H*-imidazole-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (Nizoral) is a broad-spectrum imidazole antifungal agent that is administered orally for the treatment of systemic fungal infections. It is a weakly basic compound that occurs as a white crystalline solid that is very slightly soluble in water.



The oral bioavailability of ketoconazole depends on an acidic pH for dissolution and absorption. Antacids and drugs such as H_2-histamine antagonists and anticholinergics that inhibit gastric secretion interfere with its oral absorption. Ketoconazole is extensively metabolized to inactive metabolites, and the primary route of excretion is enterohepatic. It is estimated to be 95% to 99% bound to protein in the plasma.

Hepatotoxicity, primarily of the hepatocellular type, is the most serious adverse effect of ketoconazole. Ketoconazole is known to inhibit cholesterol biosynthesis,[47] suggesting that lanosterol 14α-demethylase is inhibited in mammals as well as in fungi. High doses have also been reported to lower testosterone and corticosterone levels, reflecting the inhibition of cytochrome P450-requiring enzymes involved in human steroid hormone biosynthesis.[48] Cytochrome P450 oxidases responsible for the metabolism of various drugs may also be inhibited by ketoconazole to cause enhanced effects. Thus, ketoconazole causes clinically significant increases in plasma concentrations of cyclosporine, phenytoin, and terfenadine. It may also enhance responses to sulfonylurea hypoglycemic and coumarin anticoagulant drugs.

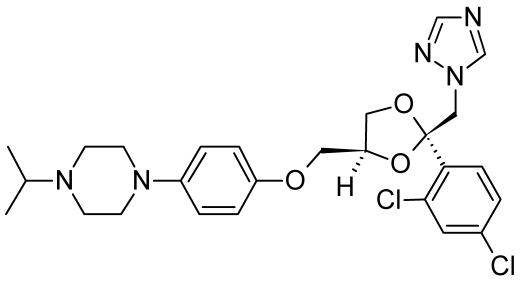
Ketoconazole is a racemic compound, consisting of the *cis*-2*S*,4*R* and *cis*-2*R*,4*S* isomers. An investigation of the relative potencies of the four possible diastereomers of ketoconazole against rat lanosterol 14α-demethylase[49] indicated that the 2*S*,4*R* isomer was 2.5 times more active than its 2*R*,4*S* enantiomer. The *trans*-isomers, 2*S*,4*S* and 2*R*,4*R*, are much less active.[49]

Ketoconazole is recommended for the treatment of the following systemic fungal infections: candidiasis (including oral thrush and the chronic mucocutaneous form), coccidioidomycosis, blastomycosis, histoplasmosis, chromomycosis, and paracoccidioidomycosis. It is also used orally to treat severe refractory cutaneous dermatophytic infections not responsive to topical therapy or oral griseofulvin. The antifungal actions of ketoconazole and the polyene antibiotic amphotericin B are reported to antagonize each other.

Ketoconazole is also used topically in a 2% concentration in a cream and in a shampoo for the management of cutaneous candidiasis and tinea infections.

Terconazole

cis-1-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl)methoxy]phenyl]-4-(1 methylethyl)piperazine (Terazol), or terconazole, is a triazole derivative that is used exclusively for the control of vulvovaginal moniliasis caused by *C. albicans* and other *Candida* species. It is available in creams containing 0.4% and 0.8% of the free base intended for 7-day and 3-day treatment periods, respectively. Suppositories containing 80 mg of the free base are also available.



Itraconazole

4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (Sporanox) is a unique member of the azole class that contains two triazole moieties in its structure, a weakly basic 1,2,4-triazole and a nonbasic 1,2,4-triazol-3-one.

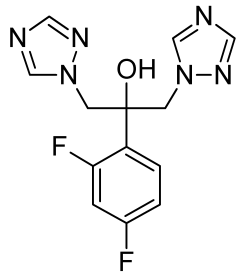
Itraconazole is an orally active, broad-spectrum antifungal agent that has become an important alternative to ketoconazole. An acidic environment is required for optimum solubilization and oral absorption of itraconazole. Drugs such as H_2-histamine antagonists and antacids, which reduce stomach acidity, reduce its gastrointestinal absorption. Food greatly enhances the absorption of itraconazole, nearly doubling its oral bioavailability. The drug is avidly bound to plasma proteins (nearly 99% at clinically effective concentrations) and extensively metabolized in the liver. Only one of the numerous metabolites, namely 1-hydroxyitraconazole, has significant antifungal activity. Virtually none of the unchanged drug is excreted in the urine. Thus, the dosage need not be adjusted in patients with renal impairment. The terminal elimination half-life of itraconazole ranges from 24 to 40 hours.

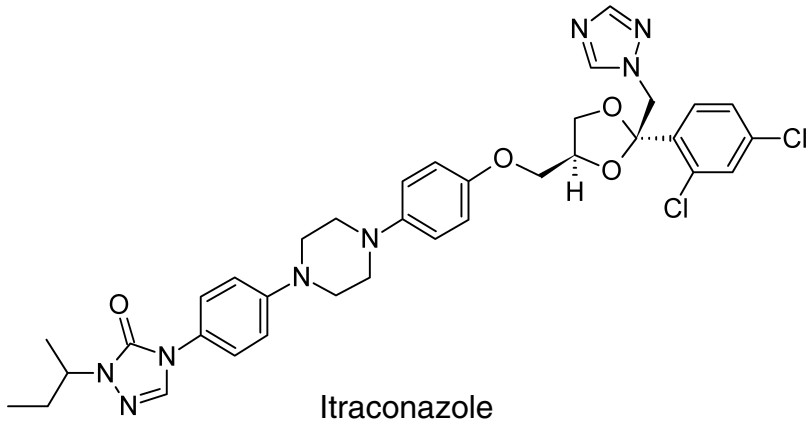
The primary indications for itraconazole are for the treatment of systemic fungal infections including blastomycosis, histoplasmosis (including patients infected with human immunodeficiency virus [HIV]), nonmeningeal coccidioidomycosis, paracoccidioidomycosis, and sporotrichosis. It may also be effective in the treatment of pergellosis, disseminated and deep organ candidiasis, coccidioidal meningitis, and cryptococcosis.

In general, itraconazole is more effective and better tolerated than is ketoconazole. Unlike ketoconazole, it is not hepatotoxic and does not cause adrenal or testicular suppression in recommended therapeutic doses.[14] Nonetheless, itraconazole can inhibit cytochrome P450 oxidases involved in drug and xenobiotic metabolism and is known to increase plasma levels of the antihistaminic drugs terfenadine and astemizole.

Fluconazole

α-(2,4-Difluorophenyl)-α-(1*H*-1,2,4-triazol-1-ylmethyl)-1*H*-1,2,4-triazole-1-ethanol or 2,4-difluoro-α,α-bis(1*H*-1,2,4-triazol-1-ylmethyl)benzyl alcohol (Diflucan) is a water-soluble bis-triazole with broad-spectrum antifungal properties that is suitable for both oral and intravenous administration as the free base. Intravenous solutions of fluconazole contain 2 mg of the free base in 1 mL of isotonic sodium chloride or 5% dextrose vehicle.





Itraconazole

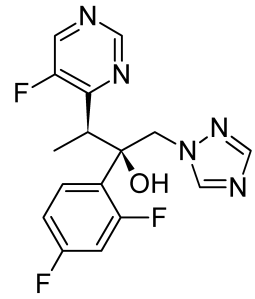
The oral bioavailability of fluconazole, following administration of either tablet or oral suspension dosage forms, is excellent. Apparently, the presence of two weakly basic triazole rings in the molecule confers sufficient aqueous solubility to balance the lipophilicity of the 2,4-difluorophenyl group. The oral absorption of fluconazole, in contrast to the oral absorption of ketoconazole or itraconazole, is not affected by alteration in gastrointestinal acidity or the presence of food.

Fluconazole has a relatively long elimination half-life, ranging from 27 to 34 hours. It penetrates well into all body cavities, including the CSF. Plasma protein binding of fluconazole is less than 10%; the drug is efficiently removed from the blood by hemodialysis. Fluconazole experiences little or no hepatic metabolism and is excreted substantially unchanged in the urine. A small amount of unchanged fluconazole (~10%) is excreted in the feces. Side effects of fluconazole are largely confined to minor gastrointestinal symptoms. Inhibition of cytochrome P450 oxidases by fluconazole can give rise to clinically significant interactions involving increased plasma levels of cyclosporine, phenytoin, and the oral hypoglycemic drugs (tolbutamide, glipizide, and glyburide). Fluconazole does not appear to interfere with corticosteroid or androgen biosynthesis in dosages used to treat systemic fungal infections.

Fluconazole is recommended for the treatment and prophylaxis of disseminated and deep organ candidiasis. It is also used to control esophageal and oropharyngeal candidiasis. Because of its efficient penetration into CSF, fluconazole is an agent of choice for the treatment of cryptococcal meningitis and for prophylaxis against cryptococcosis in AIDS patients. Although fluconazole is generally less effective than either ketoconazole or itraconazole against nonmeningeal coccidioidomycosis, it is preferred therapy for coccidioidal meningitis. Fluconazole lends itself to one-dose therapies for vaginal candidiasis.

NEWER ANTIFUNGAL STRATEGIES

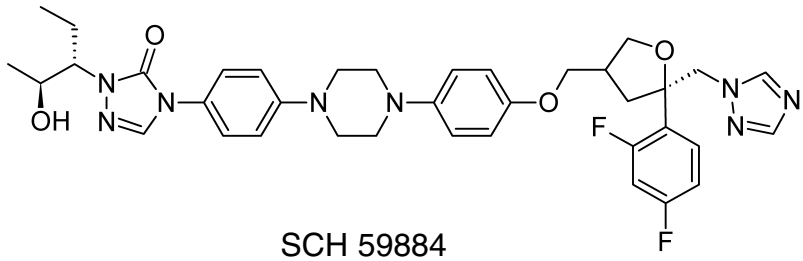
A newer azole is voriconazole.[50]



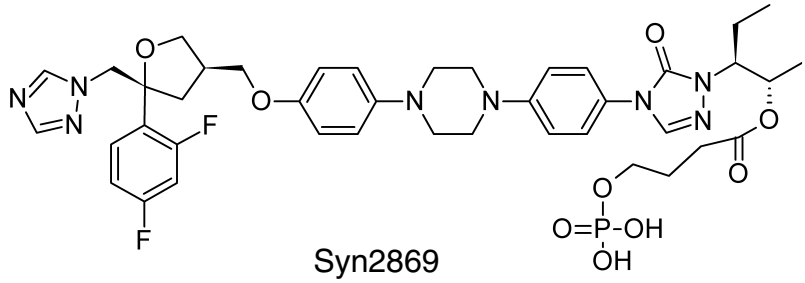
Unlike fluconazole, voriconazole has potent activity against a broad variety of fungi, including the clinically important pathogens. Several publications have substantiated the use of voriconazole against some of the newer and rarer fungal pathogens. Voriconazole is more potent than itraconazole against *Aspergillus* spp. and is comparable to posaconazole,[50] another azole that is in clinical trials, in its activity against *C. albicans*. In general, *Candida* spp. that are less susceptible to fluconazole possess higher MICs to voriconazole. The in vitro activity of posaconazole appears to be similar to that of voriconazole. Posaconazole is now in phase III clinical trials, and evidence of the efficacy of posaconazole against various fungal models, especially the rarer ones, continues to accumulate. Posaconazole exhibits high oral bioavailability, but its low water solubility makes its formulation into an intravenous solution impossible.

A search for potential prodrug forms of posaconazole has yielded a possible candidate, SCH 59884. The compound is inactive in vitro but is dephosphorylated in vivo to yield the active 4-hydroxybutyrate ester. This compound is hydrolyzed to the parent compound in the serum. Posaconazole undergoes extensive enterohepatic recycling, and most of the dose is eliminated in the bile and feces.

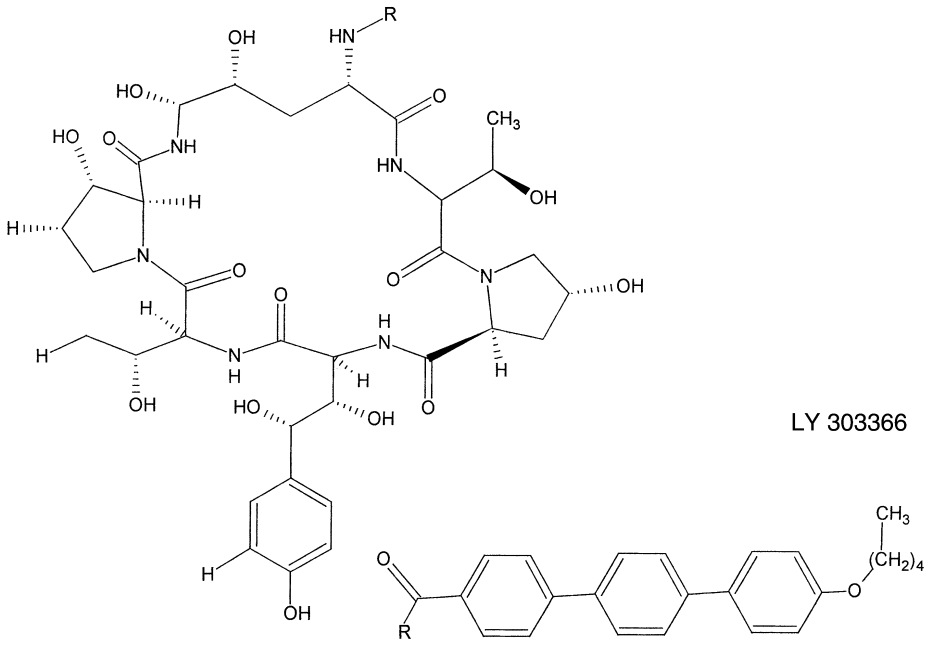
Syn2869 is a novel broad-spectrum compound that contains the piperazine-phenyl-triazolone side chain common to itraconazole and posaconazole, and it displays potency and an antifungal spectrum similar to those of the latter. Syn2869 demonstrates better activity than itraconazole in animal models of *C. albicans*, *C. glabrata*, and *C. neoformans*. The oral bioavailability (F) is 60%, and higher



SCH 59884



Syn2869



tissue-to-serum ratios than those found for itraconazole were claimed to contribute to the greater efficacy of the compound in a model of invasive pulmonary aspergillosis. Syn2869 also demonstrates considerable activity against the common mold pathogens.

ECHINOCANADINS AND PNEUMOCANADINS

Echinocanadins[51] and the closely related pneumocanadins[52] are natural products that were discovered in the 1970s. They act as noncompetitive inhibitors of (1,3)-β-*d*-glucan synthase,[53] an enzyme complex that forms stabilizing glucan polymers in the fungal cell wall. Three water-soluble derivatives of the echinocanadins and pneumocanadins are in end-stage clinical development but have not yet been marketed.

LY 303366 is a pentyloxyterphenyl side chain derivative of echinocanadin B that was discovered at Eli Lilly. It was licensed for parenteral use in 2000. Studies have shown that the MICs of LY 303366 against *Candida* spp. range from 0.08 to 5.12 μg/mL, and similar activity was obtained against *Aspergillus* spp. Studies show highly potent activity of the compound in animal models of disseminated candidiasis, pulmonary aspergillosis, and esophageal candidiasis.

AUREOBASIDINS[54]

Aureobasidin A is a cyclic depsipeptide that is produced by fermentation in cultures of *Aureobasidium pullulan*. Aureobasidin A acts as a tight-binding noncompetitive inhibitor of the enzyme inositol phosphorylceramide synthase (IPC synthase[55]), which is an essential enzyme for fungal sphingolipid biosynthesis. A unique structural feature of the aureobasidins is the *N*-methylation of four of seven amide nitrogen atoms. The lack of tautomerism dictated by *N*-methylation may contribute to forming a stable solution conformer that is shaped somewhat like an arrowhead, the presumed biologically active conformation of aureobasidin-A.

The pradimycins and benanomycins are naphthacenequinones that bind mannan in the presence of Ca^{2+} to disrupt the cell membrane in pathogenic fungi. Both demonstrate good in vitro and in vivo activity against *Candida* spp. and *C. neoformans* clinical isolates.

SYNTHETIC ANTIBACTERIAL AGENTS

Several organic compounds obtained by chemical synthesis on the basis of model compounds have useful antibacterial activity for the treatment of local, systemic, and/or urinary tract infections. Some chemical classes of synthetic antibacterial agents include the sulfonamides, certain nitroheterocyclic compounds (e.g., nitrofurans, metronidazole), and the quinolones. Some antibacterial agents that fail to achieve adequate concentrations in the plasma or tissues for the treatment of systemic infections following oral or parenteral administration are concentrated in the urine, where they can be effective for eradicating urinary tract infections. Nitrofurantoin (a nitrofuran), nalidixic acid (a quinolone), and methenamine are examples of such urinary tract antiinfectives.

Quinolones

The quinolones comprise a series of synthetic antibacterial agents patterned after nalidixic acid, a naphthyridine derivative introduced for the treatment of urinary tract infections in 1963. Isosteric heterocyclic groupings in this class include the quinolones (e.g., norfloxacin, ciprofloxacin, lomefloxacin), the naphthyridines (e.g., nalidixic acid, enoxacin), and the cinnolines (e.g., cinoxacin). Up to the present time, the clinical usefulness of the quinolones has been largely confined to the treatment of urinary tract infections. For urinary tract infections, good oral absorption, activity against common Gram-negative urinary pathogens, and comparatively higher urinary (compared with plasma and tissue) concentrations are the key useful properties. As a result of extensive structure–activity investigations leading to compounds with enhanced potency, extended spectrum of activity, and improved absorption and distribution properties, the class has evolved to the point that certain newer members