

Antifungal Agents

1. The biochemical basis for antifungal therapy. Antifungal drug development has presented medicinal chemists with a significant challenge. Unlike bacteria, which are prokaryotes, both fungi and mammals are eukaryotes, and thus the differences in cellular structure and metabolism are less pronounced. One main difference between the fungal cell and the mammalian cell is the

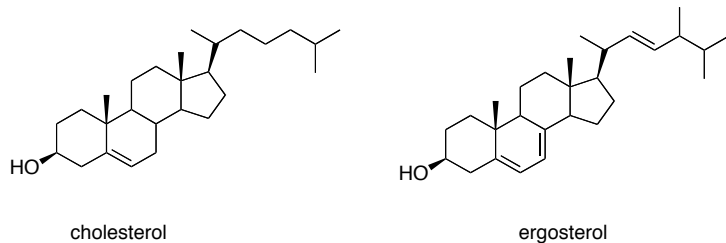


Figure 1. Chemical structures for cholesterol and ergosterol.

presence of a fungal cell wall, and thus cell wall inhibitors could represent a promising class of antifungal agents. However, only recently have efficient cell wall biosynthesis inhibitors called echinocandins been studied as antifungal agents.

Sterols are important constituents of both mammalian and fungal cell membranes, but there is a significant difference that allows fungal cells to be selectively targeted. Mammalian cell membranes contain cholesterol as the predominant sterol component, while fungal cell membranes contain ergosterol as the primary sterol component (Figure 1). These two sterols are quite similar in structure, but this structural difference has become the basis for the activity of many available antifungal agents.

2. Polyene membrane disruptors. Prior to 1950, antifungal therapy consisted of topical application

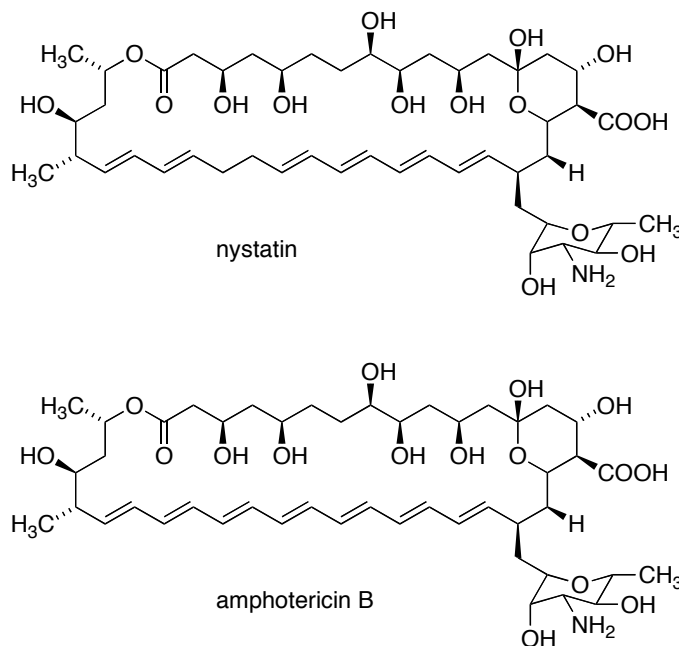


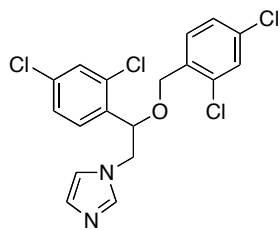
Figure 2. The polyene membrane disrupting antifungal agents nystatin and amphotericin B.

of undecylenic acid derivatives, or of mixtures of salicylic and benzoic acid. The discovery of polyene antifungal agents (Figure 2) can be considered the first significant breakthrough in antifungal therapy. Polyene antibiotics such as nystatin and amphotericin B have an affinity for cell membranes that contain ergosterol rather than cholesterol, and as such are reasonably well targeted to fungal cell membranes. These antibiotics integrate themselves into the cell membrane of fungi, causing the membranes to become leaky, and ultimately to lyse, killing the organism. However, both drugs are quite toxic to the mammalian host, and thus must be used with caution. Nystatin is too toxic to be used systemically. However, it has very poor bioavailability when given orally, and thus it can be used to treat fungal infections of the mouth and GI tract. Amphotericin B has a low enough toxicity to be used systemically by IV

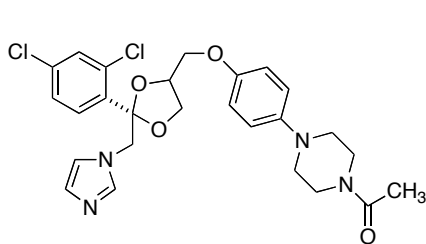
administration, but can produce significant nephrotoxicity that limits its use as a systemic

antibiotic. Some newer formulations of amphotericin B have been developed with a somewhat attenuated toxicity profile.

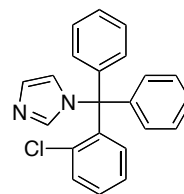
3. Azoles, imidazoles and triazoles. A number of agents have been developed that target the



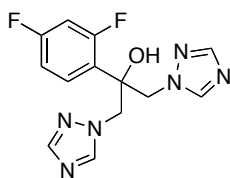
miconazole



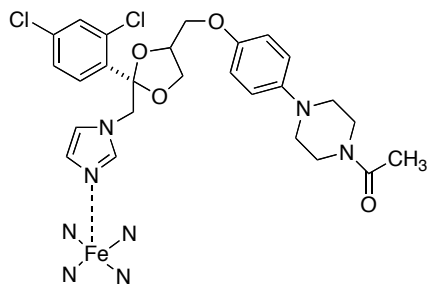
ketoconazole



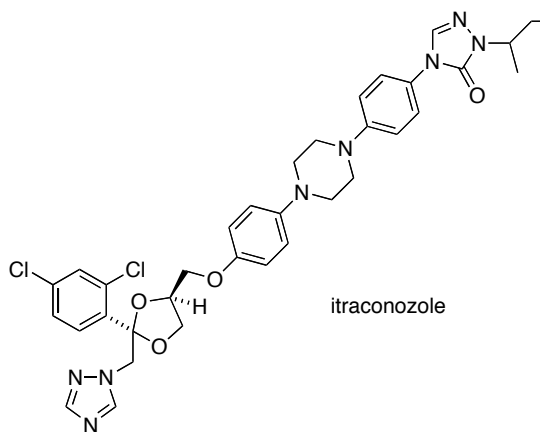
clotrimazole



fluconazole



ketoconazole bound to heme iron in CYP51

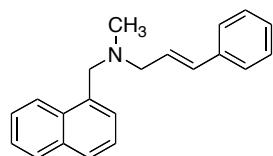


itraconazole

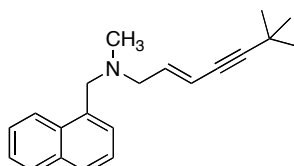
biosynthesis of ergosterol, which is unique to the organism. A key step in the fungal biosynthesis of ergosterol is the cytochrome P450 enzyme 14- α -demethylase (known as CYP51), and many of the available agents target this enzyme as their primary mechanism of action. Treatment with an azole such as those shown in Figure 3 results in the accumulation of sterols still bearing a 14-

methyl substituent, and this results in permeability changes, leaky membranes and malfunction of membrane-bound proteins.

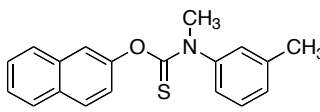
4. Inhibitors of squalene synthase. A group of allyl amines and some related derivatives (Figure 4)



naftifine



terbinafine



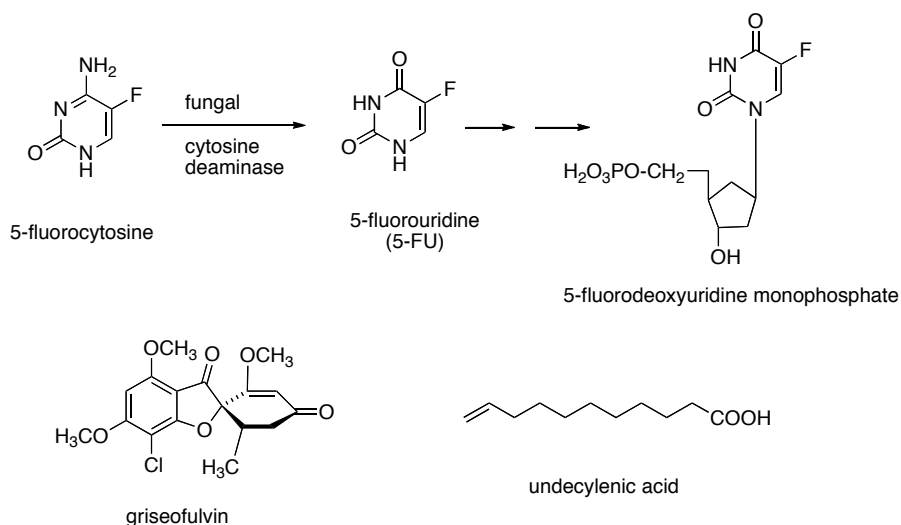
tolnaftate

Figure 4. Antifungal agents that inhibit fungal squalene synthase.

have been developed that inhibit the fungal enzyme squalene synthase, a step in the synthesis of cholesterol and ergosterol. Selectivity for the fungus is based on

the fact that fungal squalene synthase is much more sensitive to drug treatment than the mammalian form of the enzyme.

5. *Miscellaneous agents.* There are several miscellaneous agents (Figure 5) that can be used to treat fungal infections. In fungi, the drug flucytosine is converted to 5-fluorouracil by fungal cytosine deaminase, and then



through a series of steps to 5-fluorodeoxyuridine monophosphate. 5-Fluorodeoxyuridine monophosphate acts as a thymidylate synthase inhibitor in fungi, which interferes with the ability to synthesize RNA and some proteins, resulting in the death of the organism. These transformations do not occur in mammalian cells. However, some bacteria in the human intestinal flora can convert flucytosine to 5-

Figure 5. The antifungal drugs 5-fluorocytosine, griseofulvin and undecylenic acid, and the metabolic activation of 5-fluorocytosine.

fluorouracil, which is used as a cytotoxic agent in cancer chemotherapy, so human toxicity can result. Resistance to flucytosine is a significant problem, and as such the drug is generally used in combination with amphotericin B.

Griseofulvin is an antifungal antibiotic that is produced by a strain of penicillium. It can be used orally for the treatment of fungal infections of the fingernails and toenails. Topical griseofulvin does not penetrate skin or nails, but when given orally, it is incorporated into keratin precursor cells, and ultimately into the keratin that makes up skin and nail tissue. This form of keratin cannot support fungal growth. The mechanism of action for griseofulvin involves binding to tubulin, which inhibits cell division, and it may also interfere with DNA replication.

Undecylenic acid is widely employed in OTC preparations, and is fungistatic when applied topically, presumably because it interacts with constituents of the fungal cell membrane.