Kirk-Othmer Encyclopedia of Chemical Technology.

ANTIPARASITIC AGENTS, ANTIMYCOTICS

Since the 1960s, there has been such a rapid evolution in the pharmacotherapy of mycoses that three phases of the development of antimycotic agents can be distinguished: (*1*) compounds that existed before griseofulvin (1939); (*2*) compounds presently available on the market, including itraconazole (1987); (*3*) new antimycotics that are being studied now and will be prescribed tomorrow. Both milestones (griseofulvin and itraconazole) are intended for oral administration. Topical treatment of superficial dermatomycoses (trichophytosis, favus, and microsporosis) has been complemented by systemic oral treatment.

The world market for antimycotics in 1980 was valued at a total of $350 million. About 10% of this came from the sale of systemic (intravenous or oral) antifungals. In 1990, the antifungal world market was estimated at $1560 million of which almost $280 million was accounted for by systemic antifungals. This important increase in market value has induced more interest in research activities in the field of antifungals leading to more and more costly new treatment modalities. The five most prescribed antifungals today are miconazole, clotrimazole, ketoconazole, nystatin, and econazole. As this list indicates, among antifungal drugs the azoles are most significant; roughly 70% of all antifungals used today belong to this chemical category.

Though highly pathogenic, fungi represent only a minority; the importance of opportunistic infections is increasing from year to year. Human resistance against fungal infections is undermined by a number of factors and both exogenous and endogenous factors are capable of increasing the pathogenicity of certain fungi. Fungal growth may be stimulated when the host is treated with antibiotics, oral contraceptives, or cytostatics. Exogenous factors such as protheses, catheters, and valves may give rise to an increased incidence of mycoses. In immunocompromised patients and diabetics, saprophytic fungi may become pathogenic due to disturbances in the internal environment. These patients may present chronic mucocutaneous candidosis (CMC) due to *Candida albicans*. *Aspergillus fumigatus* and *A. niger* may become moderately to highly pathogenic in the presence of previously mentioned predisposing factors.

To mycologists, each fungal infection has something specific, either in its symptomatology or its etiology. However, this is less obvious to practitioners. The incidence and the severity of the pathology are sometimes underestimated. Mycoses may be classified as follows:

The physician must decide whether to opt for systemic or topical treatment and which arguments will convince the patient to use one or both forms for the minimum period recommended. It is typical for mycoses that the period of treatment generally exceeds one week and may even last a few months. There is still a

Superficial	Deep	
dermatophytosis	aspergillosis	histoplasmosis
trichophytosis	blastomycosis	maduromycosis
microsporosis	candidosis	paracoccidioidomycosis
epidermophytosis	chromomycosis	sporotrichosis
pityriasis	coccidioidomycosis	
candidosis	cryptococcosis	

strong tendency to treat the organ or the part of the organ affected by the pathogenic microorganism. This is justifiable in the case of localized unifocal mycoses of the skin caused by dermatophytes.

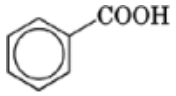
Oral treatment offers the advantage of bringing all the lesions at all sites under control, in addition to the absence of unpleasant cosmetic effects. In certain cases, it may be preferable to use oral treatment for *C. albicans* vaginitis and for extensive and persistent pityriasis versicolor, a skin disorder caused by *Pityrosporum orbiculare*. In the case of onychomycosis, a combination treatment, topical plus systemic, is required. It is preferable to use oral treatment for deep and systemic mycoses, though intravenous or intrathecal treatment is sometimes required.

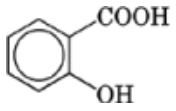
The final choice of a suitable antimycotic and the route of administration are determined by many factors: safety of the antimycotic, easy administration, broad-spectrum activity, and rapid clinical improvement associated with mycological cure.

1. Topical Antimycotics

1.1. Older Compounds

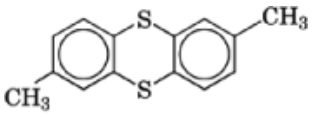
Some antimycotics have been used for a long time; Whitfield's ointment is a typical example (1907). The ointment usually contains 6% benzoic acid [65-85-0], $C_7H_6O_2$, and 3% salicylic acid [69-72-7], $C_7H_6O_3$. The action is attributed to the keratolytic effect of the salicylic acid and the direct effect of benzoic acid on the fungus.





The main advantage of this ointment is its low price. This combination has now been replaced by more active modern antimycotics. Long ago, the antimycotic effect of aliphatic carboxylic acids with an increasing number of C-atoms was discovered. The optimum is 11 C-atoms and $CH_2{=}CH(CH_2)_8COOH$, undecylenic acid [112-38-9], $C_{11}H_{20}O_2$, is used in several ointments.

Other drugs are a combination of a keratolytic agent (mesulfen [135-58-0], $C_{14}H_{12}S_2$) and the well-known antimycotic zinc undecylenate [557-08-4], $C_{22}H_{38}O_4Zn$.



mesulfen

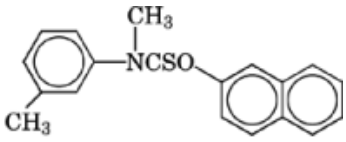
This cream also contains zinc naphthenate, terpineol, chlorcresol, and methyl salicylate [119-36-8]. s The latter has a deeply penetrative effect. It combines antimycotic and antibacterial properties and is used to treat swimmer's eczema. The cream must not be used on open skin areas infected by bacteria. Some foot powders are a combination of zinc undecylenate, boric acid, hexachlorophene, and salicylic acid.

Table 1. Polyene Antimycotic Antibiotics [a]

Structurenumber	Name	CAS Registry Number	Molecular formula	Trade name
(1)[b]	nystatin	[1400-61-9]	[b]	Fungicidin, Biotanal, Diastatin, CandexMycostatin[c], Mioronal, Multilind, Nystan, Nystarescent
(2)	natamycin	[7681-93-8]	$C_{33}H_{47}NO_{13}$	Pimaricin, Mycophyt, Myprozine, Natacyn, Pimatucin, Synogil
(3)	amphotericin B	[1397-89-3]	$C_{47}H_{73}NO_{17}$	Amphozone, Fungizone[c], Fungilin, Ampho-Mioronal
(4)[c]	candicidin	[1403-17-4]	[d]	Levorin, Candeptin, Candimon, Vanobid
	filipin	[11078-21-0]	[e]	Filimarisin
	homycin	[1403-71-0]	[e]	Primamycin
(5)	etruscomycin[f]	[13058-67-8]	$C_{36}H_{53}NO_{13}$	Etruscomycin
	trichomycin[g]	[1394-02-1]	[e]	Cabimicina, Trichonat

[a] See Figure 1.
[b] Nystatin has three biologically active components: A_1, A_2, and A_3. Figure 1 depicts A_1.
[c] Squibb is the U.S. producer.
[d] A 4-component mixture; candicidin D shown in Figure 1 is the primary component.
[e] Multicomponent mixture.
[f] Also known as lucensomycin.
[g] Also known as hachimycin.

Tolnaftate [2398-96-1], $C_{19}H_{17}NOS$, which is active against dermatophytes, is the active component in another antifungal powder; it also contains cetylpyridinium chloride and talcum venetum.



tolnaftate

In addition to tolnaftate and cetylpyridinium chloride, the ointment also contains poly(ethylene glycol). This preparation is not active against *C. albicans*.

1.2. Antimycotic Antibiotics

1.2.1. Nystatin

This compound 1 belongs to the group of polyene antimycotic antibiotics (Table 1). Since the early 1960s, approximately 200 polyenes have been isolated from different *Streptomyces* strains.

Nystatin is obtained from *Streptomyces noursei*. The polyenes are characterized by a macrolide ring and differ from one another by the number (12–37) of carbon atoms in the ring structure, the number (6–14) of hydroxyl groups, and the presence or absence of a carbohydrate (1). Polyenes alter the membrane permeability of sensitive cells by forming a complex with the sterol present in the membranes. Due to this binding to sterols, potassium ions are lost. Both nystatin and amphotericin B bind more strongly to ergosterol than to cholesterol. Ergosterol is the principal sterol in the membrane of yeasts and fungi, whereas the cell membrane in mammals contains mainly cholesterol. This difference in binding capacity is probably responsible for the selectivity (1, 2). Since bacteria, with the exception of *Mycoplasma* and *Acholeplasma*, contain no sterols; polyenes have no antibacterial activity.

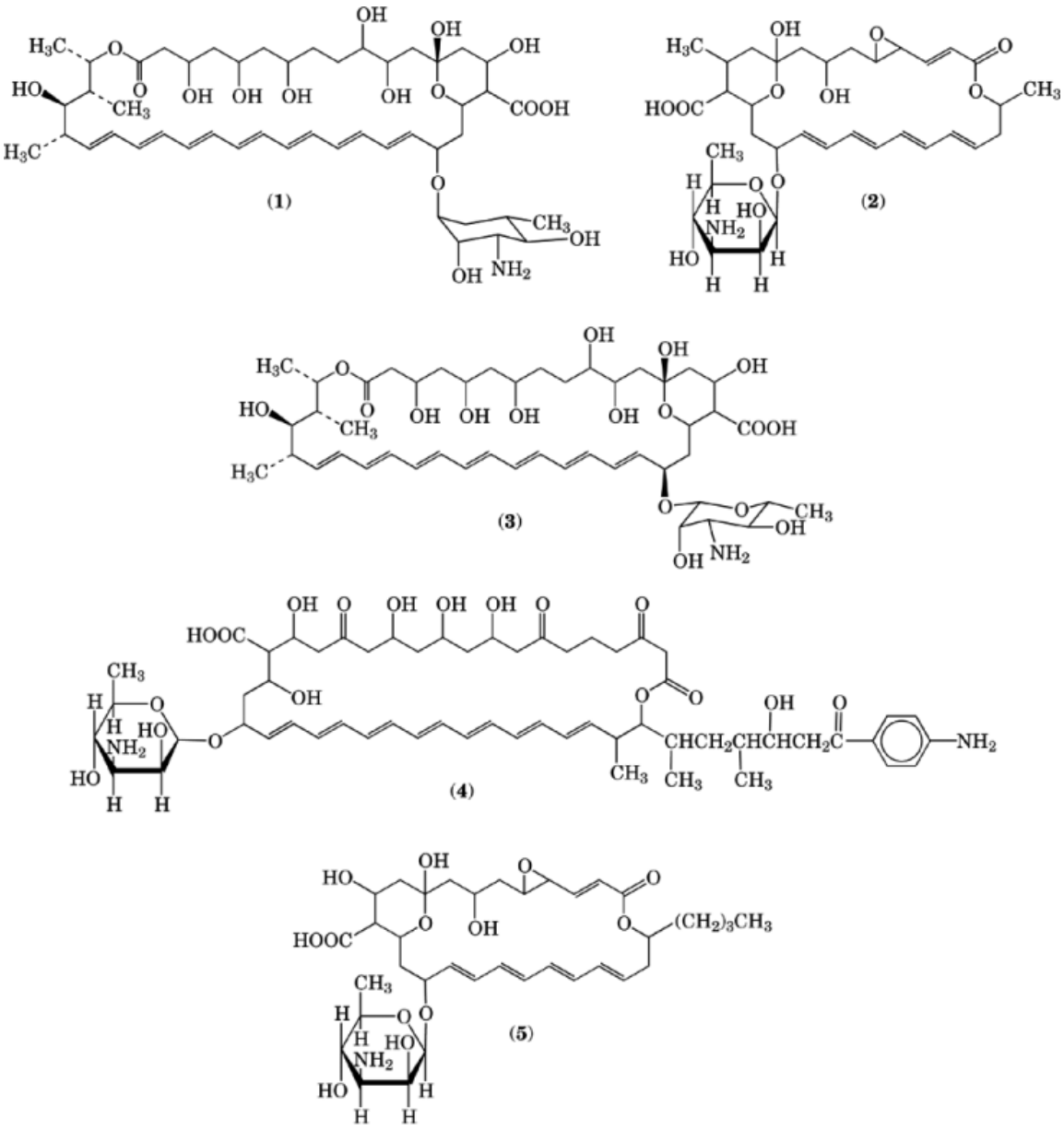


Fig. 1. Polyene antibiotics (see Table 1).

Nystatin has a local fungicidal and fungistatic action against *C. albicans*. This polyene is not water-soluble. It is absorbed to a limited extent from the digestive tract, which limits the field of indications after oral administration to candidoses of the oral cavity, the esophagus, and the intestines. Oral administration of large doses may cause gastrointestinal disorders (nausea, vomiting, diarrhea). Nystatin is too toxic for parenteral administration. More information concerning chemical, mycological, and clinical properties of the polyenes is available (1, 3, 4).

Nystatin is mainly used to treat vaginal and oral infections and localized skin lesions, including *Candida* intertrigo and Candida nappy dermatitis. It may also be used as prophylaxis during treatment with antibiotics.

Nystatin (100,000 IU) is also available in combination with neomycin sulfate [1405-10-3] (35,000 IU), polymyxin B sulfate [1405-20-5] (35,000 IU), acetarsol [97-44-9] (150 mg), and dimethicone [8050-81-5] (2,500 mg). One or two ovules per day are inserted vaginally for at least 6–12 days. This combination has an antibacterial, antimycotic, and antitrichomonas action (see also Antibiotics, oligosaccharides; Antiparasitic agents, antiprotozoals).

1.2.2. Natamycin

Natamycin or pimaricin 1 is a polyene with only four conjugated double bonds. This tetraene is obtained from *Streptomyces natalensis*. Like the other polyenes, pimaricin induces K^+ release from cells with membranes containing 20–40 mol % ergosterol. This is also the ergosterol concentration in the membrane of *Saccharomyces cerevisiae*.

Natamycin is not water-soluble or soluble in most organic solvents. It is not absorbed in the digestive tract. It is indicated for skin and nail infections with *C. albicans*, intertrigo and fissures at the corners of the mouth (perleche) caused by *C. albicans*, *Candida vulvitis*, and vaginitis. Natamycin plays an important role in the treatment of mycotic keratitis. Natamycin also appears to be active against the protozoan *Trichomonas vaginalis*. Side effects are nausea or diarrhea during oral treatment. Dosage is application of cream several times a day.

Combination creams or ointments contain 3.5 mg neomycin base and 10 mg hydrocortisone [50-23-7] per g, in addition to 10 mg natamycin. The combination as a lotion contains 1.75 mg neomycin and 5 mg hydrocortisone/g, in addition to 10 mg natamycin. This combination has an antiinflammatory, antibacterial, and antimycotic action. It is applied 2–4 times per day.

1.2.3. Amphotericin B

Amphotericin B 1, an important polyene antibiotic, is administered almost exclusively via the intravenous route and is therefore discussed in more detail under the systemic antimycotics. The vaginal tablets contain 50 mg amphotericin B, and 100 mg tetracycline base per tablet (see also Antibiotics, tetracyclines). The tablets for oral use contain 50 mg amphotericin B, 250 mg tetracycline base, and 125 mg sodium hexametaphosphate. A combination ointment contains 1 mg fludrocortisone acetate, 2.5 mg neomycin, 0.25 mg gramicidin, and 1 g plastibase in addition to 30 mg amphotericin B (see also Antibiotics, peptides).

1.3. Synthetic Antimycotics

Because of their limited activity, small spectrum, and side effects, the older topical antimycotics have generally been surpassed by newer antimycotic chemotherapeutic agents. These newer antimycotics for topical use include the imidazole derivatives clotrimazole, miconazole, econazole, isoconazole, sulconazole, fenticonazole, oxiconazole, bifonazole, butoconazole, zinoconazole, tioconazole, and the triazole derivative, terconazole (Table 2) (5–7). The introduction of the azole derivatives represents a milestone in the treatment of mycoses.

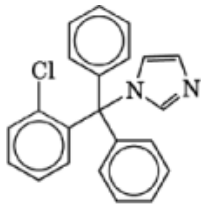
1.3.1. Clotrimazole

The imidazole derivative clotrimazole **(6)** was introduced in 1969. Clotrimazole [23593-75-1] or 1-(*o*-chloro-α,α-diphenylbenzyl)imidazole is a water-insoluble antimycotic for topical application, with a broad-spectrum activity against mycoses of the skin and the vagina.

Table 2. Azole Antimycotics[a]

Name	CAS Registry Number	Structure number	Molecular formula	Trade name
clotrimazole	[23593-75-1]	**(6)**	$C_{22}H_{17}ClN_2$	Canesten, Canifug, Expecid, Lotrimin, Mycofug, Pedisafe, Rimazole, Tibatin, Trimysten
miconazole	[22916-47-8]	**(7a)**	$C_{18}H_{14}Cl_4N_2O$	Fungisdin, Aflorix[b], Albistat[b], Andergin[b], Brentan[b], Conoderm[b], Constite[b], Daktor[b], Deralbine[b], Dermonistat[b], Florid[b], Micatin[b], Monistat[b], Prilagin[b], Vodol[b]
econazole	[27220-47-8]	**(7b)**	$C_{18}H_{15}Cl_3N_2O$	Ecostatin[b], Ifenec[b], Micofugal[b], Micogin[b], Palavale[b], Pargin[b], Pevaryl[b], Spectazole[b]
isoconazole	[27523-40-6]	**(7c)**	$C_{17}H_{14}Cl_4N_2O$	Fazol[b], Travogen[b]
ketonazole	[65277-42-1]	**(10)**	$C_{26}H_{28}Cl_2N_4O_4$	Fungarest, Fungoral, Ketoderm, Ketoisdin, Nizoral, Orifungal M, Panfungol
butoconazole	[64872-76-0]	**(11)**	$C_{19}H_{17}Cl_3N_2S$	Exelgyn[b], Femstat[b], Gynomyk[b]
oxiconazole	[64211-46-7][b]	**(12)**	$C_{18}H_{13}Cl_4N_3O$	Myfungar[b], Oceral[b], Oxistat[b]
omoconazole	[74512-12-2]	**(13)**	$C_{20}H_{17}Cl_3N_2O_2$	Fangorex[b], Fongarex[b]
sulconazole	[61318-90-9]	**(14)**	$C_{18}H_{15}Cl_3N_2S$	Exelderm[b], Myk[b], Sulcosyn[b]
itraconazole	[84625-61-6]	**(18)**	$C_{35}H_{38}Cl_2N_8O_4$	Sporanox
fluconazole	[86386-73-4]	**(19)**	$C_{13}H_{12}F_2N_6O$	Diflucan, Triflucan
saperconazole	[110558-57-3]			
fenticonazole	[72479-26-6]		$C_{24}H_{20}Cl_2N_2OS$	Falvin[b], Lomexin[b]
bifonazole	[60628-96-8]		$C_{22}H_{18}N_2$	Amycor, Amolmen, Bedriol, Mycospor, Mycosporan
terconazole	[67915-31-5]		$C_{26}H_{31}Cl_2N_5O_3$	Fungistat, Panlomyc, Terazol, Tercospor
tioconazole	[65899-73-2]		$C_{16}H_{13}Cl_3N_2OS$	Fungibacid, Trosyd, Trosyl, Zoniden
zinoconazole	[80168-44-1]			

[a] U.S. producers include Ortho Pharmaceutical (eg, Monistat), Schering-Plough (eg, Lotrimin), and Syntex (Femstat).
[b] The nitrate.

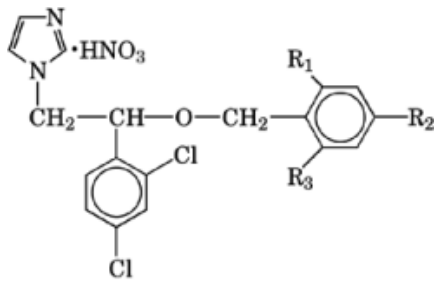


(6)

This antimycotic, which was introduced for topical use, shows *in vitro* activity against dermatophytes, species of *Candida*, *Aspergillus*, *Coccidioides immitis*, *Histoplasma capsulatum*, *Cryptococcus neoformans*, and *Madurella* species. *Petriellidium (Allescheria) boydii* and *Phialophora* species are less sensitive.

Clotrimazole and other azole derivatives have a different mode of action than the polyenes, eg, amphotericin B. The latter bind to the ergosterol present in the membranes of yeasts and fungi, but azole derivatives inhibit the cytochrome P-450 dependent biosynthesis of ergosterol (8–11). This inhibition not only results in a reduction of ergosterol, but also in an accumulation of C-14 methyl sterols. They disturb membrane permeability, inhibit cell replication, and are basically responsible, in combination with the reduction of ergosterol levels, for the antifungal action.

Clotrimazole is only partly absorbed in the digestive tract. It is a microsomal enzyme (cytochrome P-450) inductor and induces its own metabolism. This explains why it is not active *in vivo* against the etiologic agents



(7)

Fig. 2. Miconazole nitrate (**7a**) R_1=R_2=Cl, R_3=H; econazole nitrate (**7b**) R_1=R_3=H, R_2=Cl; isoconazole nitrate (**7c**) R_1=R_3=Cl, R_2=H.

of deep mycoses, including *H. capsulatum*, *C. immitis*, and *C. neoformans*. Enzyme induction also produces increased levels of other liver enzymes, such as transaminases. Because of this and possible side effects such as nausea, vomiting, and hallucinations (cerebral toxicity), the use of clotrimazole is limited to topical application. Topical application of clotrimazole is well tolerated; local allergic reactions and generalized skin irritations may occur occasionally.

1.3.2. Miconazole

Miconazole nitrate [22832-87-7] (Fig. 2), the 1-phenethyl-imidazole derivative first described in 1969, interferes at low doses with the cytochrome P-450 dependent ergosterol biosynthesis in yeasts and fungi. The result is accumulation of C-14 methylated sterols on the one hand and reduction of the ergosterol levels in the membranes on the other hand (12). Analogous to clotrimazole, this leads to a disturbance in the membranes; it results in inhibition of cell replication, mycelium development (in *C. albicans*), and finally, cell death. High concentrations of miconazole, which may be achieved with topical use, disturb the orientation of phospholipids in the membranes, which produces leaks (13).

Miconazole [22916-47-8] has a potent antifungal action against dermatophytes and *Candida* species. It is also active against gram-positive bacilli and cocci. *In vitro*, it is also effective against *Trichomonas*, *Leishmania*, and *Plasmodium*. Miconazole is only moderately absorbed in the digestive tract. After intravenous administration, it is rapidly metabolized.

This drug is indicated for infections of skin and nails due to dermatophytes or *Candida* species and vulvovaginal infections due to *Candida* species. Miconazole is used orally for prophylactic purposes in patients who have been treated with cytostatics or immunosuppressants, in particular, to prevent candidosis of the mouth and digestive tract. Side effects include possible nausea during oral treatment. Miconazole tablets may increase the anticoagulant effect of coumarin derivatives. Topical treatment with cream or powder is well tolerated. Local irritation and allergic reactions of the skin and mucosa occur only rarely.

Daktacort is a combination product. It combines a broad-spectrum antimycotic with antibacterial action against gram-positive bacilli and cocci, miconazole and hydrocortisone. This corticosteroid was added for its antiinflammatory and antipruriginous properties. Daktacort is indicated for skin infections due to dermatophytes or *Candida* species associated with inflammatory symptoms. For this reason, daktacort is used mainly during the initial phase of treatment. Afterwards, it is possible to switch to a cream containing only miconazole nitrate.

1.3.3. Econazole

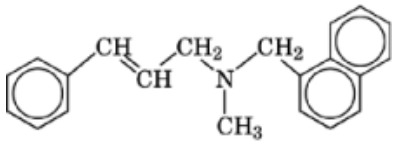
Econazole and isoconazole are structurally very similar to miconazole; they differ only in the pattern of chlorine substitution on the terminal phenyl ring. Chemically, econazole (Fig. 2, 2) is closely related to miconazole. The clinical indications are almost identical. Econazole [27220-47-9] is available as a vaginal cream and ovule containing respectively 1% and 150 mg econazole nitrate. For mycoses of the skin, several forms are available including cream, spray-powder, spray-solution, and lotion. All these formulations contain 1% econazole nitrate [68797-31-9]. The dosages are practically identical to those of miconazole.

1.3.4. Isoconazole

Like econazole, both the chemical structure and the clinical indications of this imidazole derivative (Fig. 2, 2) closely resemble those of miconazole. It is available as a vaginal tablet (300 mg isoconazole nitrate per tablet). In some countries isoconazole [27523-40-6] is also available as a cream for dermatological use and as a cream and ovules for treatment of vaginal candidosis.

1.3.5. Naftifine

Naftifine **(8)** belongs to the allylamines, a new class of antimycotics (14). It is used to treat superficial mycoses and is particularly active against dermatophytes.

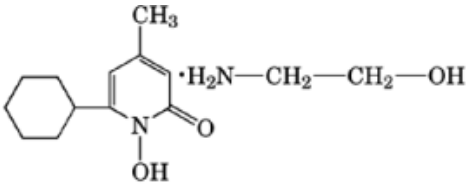


(8)

Like the azole derivatives, it inhibits the biosynthesis of ergosterol. However, naftifine [65472-88-0] does not inhibit the cytochrome P-450 dependent C-14-demethylase, but the epoxidation of squalene. Squalene epoxidase catalyzes the first step in the conversion of squalene via lanosterol to ergosterol in yeasts and fungi or to cholesterol in mammalian cells. The squalene epoxidase in *C. albicans* is 150 times more sensitive to naftifine, $C_{21}H_{21}N$, than the enzyme in rat liver (15). Naftifine is available as a 1% cream.

1.3.6. Ciclopiroxolamine

This ethanolamine salt, $C_{14}H_{24}N_2O_3$, of ciclopirox **(9)** is a topically active antimycotic, available as a cream and powder (16).

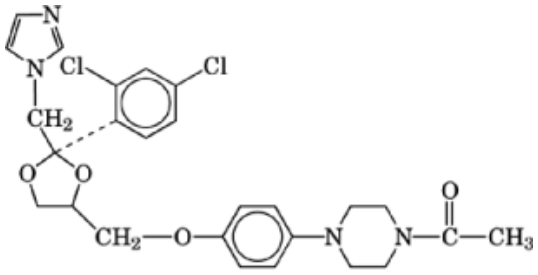


(9)

The biochemical basis for its action in fungi has not been totally elucidated. Ciclopiroxolamine [41621-49-2] is used mainly in the treatment of mycoses of the skin and nails.

1.3.7. Ketoconazole

Initial observations indicating that oral administration of ketoconazole **(10)** produced good results in seborrheic eczema and dandruff, led to the development of a 2% cream and a 2% shampoo (scalp gel) of this antimycotic (17, 18). Naturally, these two topical forms of ketoconazole [65277-42-1] are highly active against superficial mycoses.

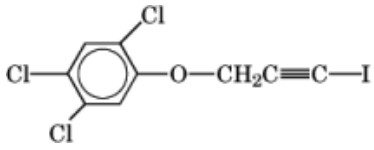


(10)

The main application of these two topical forms is the treatment of seborrheic eczema and dandruff. Ketoconazole's potent pityrosporicidal effect at concentrations of 100 ng/mL to 1 μg/mL forms the rationale of this activity.

1.3.8. Haloprogin

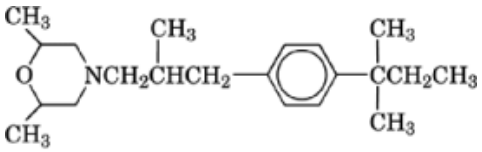
3-Iodo-2-propynyl 2,4,5-trichlorophenyl ether, $C_9H_4Cl_3IO$, is an almost insoluble antifungal for topical use, available in the United States. Haloprogin [777-11-7] was developed in 1963 and it is active against dermatophytes. The drug's effect against *Candida* sp. is rather limited.



1.3.9. Developmental Topical Antimycotics

Most of the topical antimycotics still being developed are azole derivatives (mostly imidazole), including butoconazole, oxiconazole, omoconazole, zinoconazole, and sulconazole (Fig. 3). Generally speaking, these newer azoles offer no additional therapeutic advantages compared to existing substances. These drugs are already available in certain countries, but are not yet commercialized on a worldwide scale.

Amorolfine [78613-35-1] is a molecule that is totally different from this group; it is a morpholine derivative **(15)** (19). This substance has a broad-spectrum activity and has a fungicide effect at fairly low concentrations. The development of a nail varnish for treatment of onychomycoses could be very interesting.



(15)

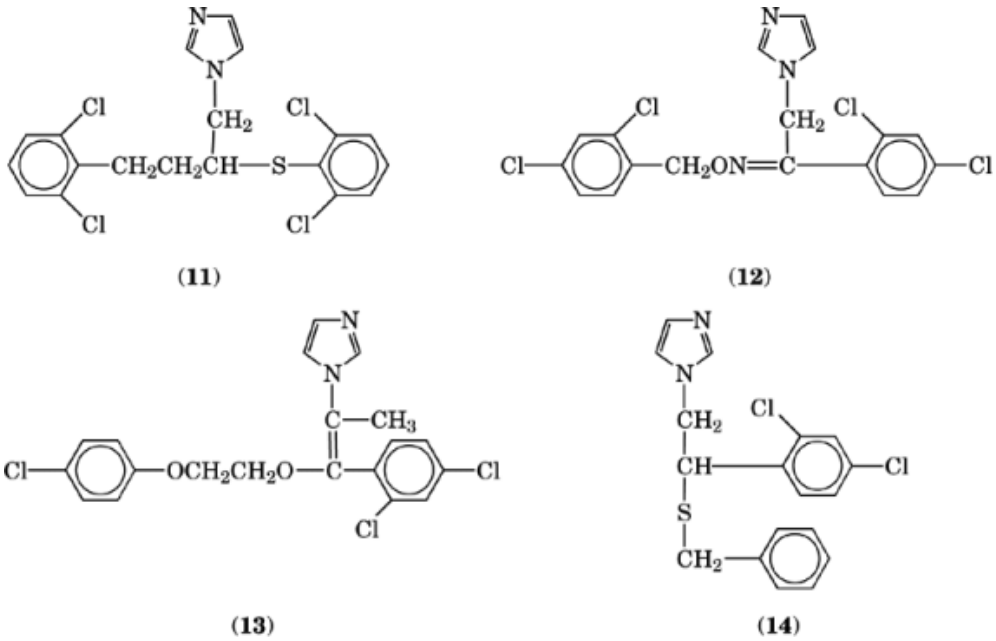


Fig. 3. Developmental topical antimycotics. Butoconazole 3, oxiconazole 3, omoconazole 3, and sulconazole 3.

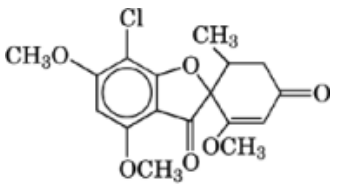
2. Systemic Antimycotics

2.1. Potassium Iodide

When potassium iodide [7681-11-0] is administered orally for several (6–8) weeks, a therapeutic effect may be obtained in the subcutaneous form of sporotrichosis. Amphotericin B is used intravenously to treat systemic sporotrichosis. The KI dosage is usually a saturated solution in water (1 g/mL). The usual oral dose is 30 mg/kg/d. Children should receive five droplets, three times a day (after meals); the dose may be increased to 15–20 droplets. Side effects include digestive disorders, swelling of the salivary glands, and lacrimation. Thyroid function tests may be disturbed.

2.2. Griseofulvin

Although this antibiotic was first isolated in 1939 and was described as a metabolite of *Penicillium griseofulvum* (20), its action against *Microsporum* and *Trichophyton* was only discovered in 1958. Several modes of action were suggested for (+) 7 chloro-4,6-dimethoxycoumaran-3-one-2-spiro-1′-(2′-methoxy-6′-methylcyclohex-2′-en-4′-one) ($C_{17}H_{17}ClO_6$) **(16)**, this antibiotic derived from *P. griseofulvum*.



(16)

It interferes with the synthesis of the hyphal walls, the biosynthesis of nucleic acids, and the synthesis of chitin. The interaction with microtubules has also been described. The sensitivity of a cell seems to depend particularly on the ability to form griseofulvin–nucleic acid complexes. Further information concerning griseofulvin is available (21).

After oral administration, griseofulvin [126-07-8] is absorbed moderately. The absorption is increased when it is administered together with oil or fat. Micronization also increases the absorption greatly in the digestive tract; griseofulvin with a particle diameter of 2.7 μm reaches twice the plasma levels of griseofulvin with a particle diameter of 10 μm. Griseofulvin is found in the outer layers of the stratum corneum. Perspiration probably plays an important role in bringing it there.

Indications are mycoses of the skin, hair, and nails due to species of *Trichophyton*, *Epidermophyton floccosum*, and *Microsporum*. Yeasts and bacteria are not sensitive. Griseofulvin has a very weak effect against *Aspergillus*. Side effects may include headaches and gastrointestinal disorders, but they are usually only temporary. Occasionally, urticaria, erythema, or photosensitivity are observed. Griseofulvin is a strong inducer of the mixed function oxidase in the liver. It therefore has a stimulating effect on the conversion of various other drugs, including oral anticoagulants. It also affects the biosynthesis of porphyrin; this may result in accumulation of protoporphyrin in hepatocytes.

In the case of tinea corporis, treatment may last longer than six weeks. The treatment of onychomycosis may last up to twelve months, certainly if the toenails are involved. Caution is required in patients with impaired kidney or liver function or hematological disorders. Also, use is contraindicated during pregnancy.

2.3. Amphotericin B

This heptaene macrolide antibiotic 1 is produced by *Streptomyces nodosus*. It has fungistatic and fungicide properties and is effective against *Candida* species and the etiologic agents of systemic mycoses, including *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, and *Cryptococcus neoformans*. It is also active against *Sporothrix schenckii*. Like nystatin, this polyene has a greater affinity for ergosterol than cholesterol. Consequently, much lower levels of amphotericin B are required to induce potassium release in *C. albicans* than in mammalian cells. Potassium release is secondary to the increased flux of protons (1). In yeasts, the proton gradient plays an important role in the function of the plasma membrane. The transport of amino acids and other nutrients depends on this proton gradient (22).

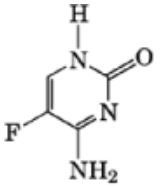
Absorption is minimal after oral and topical administration. In order to obtain a systemic effect, the compound must be administered intravenously. Plasma levels are fairly stable during the first 24 hours; only a small fraction is eliminated via urine during this period. The polyene can be detected in urine up to three weeks after treatment. Diffusion of amphotericin B into cerebrospinal fluid is only moderate. More information concerning polyene antibiotics is available (1–4, 23). Several side effects should be taken into account during intravenous administration. The main side effects are noted in the glomeruli of the renal parenchyma and include thickening of the basal membrane with hyalinisation, and in the tubuli, where focal or generalized degeneration and nephrocalcinosis may occur. Hypokalemia is an important consequence of nephrotoxicity. Headache, nausea, and vomiting are usually the first signs of toxicity. The dosage should be reduced until these side effects disappear. Vomiting, fever, and headache may be prevented by the administration of antihistamines and corticosteroids. Amphotericin B is administered over a 6-h period by a slow intravenous infusion. The recommended concentration is 0.1 mg/mL. The initial dose is 0.1–0.2 mg/kg/d. The dose is then increased to 1 mg/kg/d. The daily dose must never exceed 1.5 mg/kg. The duration of the treatment depends on the nature and the extent of the infection.

A marked improvement is generally noted after 4–8 weeks of treatment. Treatment is often continued until a total dose of 3 g is reached. In the case of coccidioidomycosis, for example, treatment with 0.4–0.8 mg/kg/d may last months. The polyene is administered intrathecally to treat *Coccidioides* meningitis. However, the

results are only moderate. It is very important to check renal and hepatic function during treatment with amphotericin B.

2.4. Flucytosine

Flucytosine **(17)** or 5-fluorocytosine (4-amino-5-fluoro-2-pyrimidone, 5-FC), $C_4H_4FN_3O$, is a pyrimidine derivative, that is efficient against *Candida albicans*, *Cryptococcus neoformans*, and *Torulopsis glabrata*.



(17)

It is also active against *Aspergillus*, *Phialophora*, and *Cladosporium*. The protozoa *Acanthamoeba culbertsoni* and *Leishmania* are sensitive to flucytosine (1, 24).

Flucytosine [2022-85-7] is well absorbed in the digestive tract, which is why oral administration is preferable. Plasma levels of 30–40 mg/L are obtained after a dose of 30 mg/kg body weight. Approximately 90% of the pyrimidine derivative is found unaltered in urine, indicating that it is highly suitable for the treatment of renal candidosis. High concentrations were also noted in cerebrospinal fluid; the average concentration is approximately 75% of the plasma concentration.

With the aid of cytosine permease, flucytosine reaches the fungal cell where it is converted by cytosine deaminase into 5-fluorouracil [51-21-8]. Cytosine deaminase is not present in the host, which explains the low toxicity of 5-FC. 5-Fluorouracil is then phosphorylated and incorporated into RNA and may also be converted into 5-fluorodeoxyuridine monophosphate, which is a potent and specific inhibitor of thymidylate synthetase. As a result, no more thymidine nucleotides are formed, which in turn leads to a disturbance of the DNA-synthesis. These effects produce an inhibition of the protein synthesis and cell replication (1, 23, 24). 5-Fluorouracil cannot be used as an antimycotic. It is poorly absorbed by the fungus to begin with and is also toxic for mammalian cells.

Flucytosine-resistant strains can develop very rapidly. These mutants may have a disturbed 5-FC-metabolism, or a compensatory mechanism for the disturbed nucleic acid functions. No cytosine permease was found in a resistant *Cryptococcus neoformans* strain, whereas cytosine deaminase was absent in resistant *C. albicans* strains. A deficiency of uridine monophosphate pyrophosphorylase occurs frequently in resistant *C. albicans* strains (1).

The dosage of flucytosine is 150–200 mg/kg orally in four portions every six hours. A 1% flucytosine solution has been developed for intravenous administration. In some countries, a 10% ointment is also available. In patients with normal renal function, flucytosine is seldom toxic, but occasionally severe toxicity may be observed (leukopenia and thrombocytopenia). Plasma levels should be determined and the dose in patients with impaired renal function should be checked. Liver function tests (transaminases and alkaline phosphatase) should be performed regularly. In some patients with high flucytosine plasma levels, hepatic disorders have been observed (24).

2.5. Miconazole

Miconazole (Fig. 2, 7a) is also available as a sterile solution for intravenous infusion. Miconazole has a therapeutic effect on systemic mycoses due to *C. albicans*, *Aspergillus fumigatus*, *Cryptococcus neoformans*, *Blastomyces dermatitidis*, *Histoplasma capsulatum*, *Coccidioides immitis*, *Paracoccidioides brasiliensis*, and *Petriellidum boydii*.

The recommended dosage produces plasma levels that exceed the *in vitro* MIC-values for the previously mentioned fungi. Doses >9 mg/kg generally produce plasma levels of ≥ 1 mg/L. Large doses may cause loss of appetite, nausea, and vomiting. Very rapid infusion may lead to transitory cardiac arrhythmia and tachycardia. During prolonged and repeated intravenous administration, liver function tests are recommended. Cremophor, the solvent, may induce hypertriglyceridemia.

2.6. Ketoconazole.

For treatment of systemic mycoses with amphotericin B or miconazole, the patient must be admitted to a hospital. This is not always possible, particularly in areas where systemic mycoses occur frequently, nor is it always desirable, because of the expense. For these reasons, it was desirable to find an antimycotic that combined safety and broad-spectrum activity with oral administration. Ketoconazole **(10)**, which is orally active, met most of these requirements. This inhibitor of the ergosterol biosynthesis is an *N*-substituted imidazole, that differs from its precursors by the presence of a dioxolane ring (6, 7). Ketoconazole is rapidly absorbed in the digestive system after oral administration. Sufficient gastric acid is required to dissolve the compound and for absorption. Therefore, medication that affects gastric acidity (for example, cimetidine and antacids) should not be combined with ketoconazole.

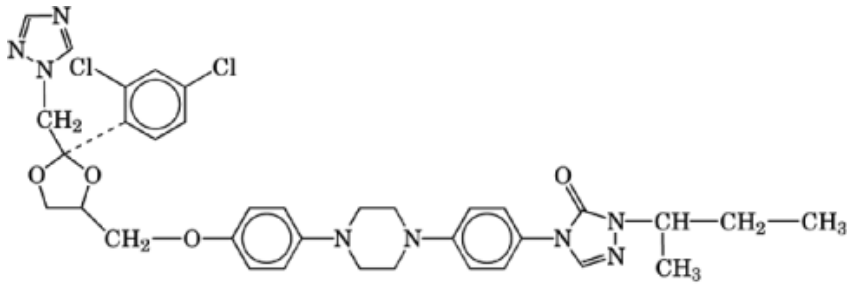
Plasma levels of 3–5 μg/mL are obtained two hours after administration of 200 mg ketoconazole. No accumulation in the bloodstream was noted after a 30-wk treatment with this dose. The half-life is approximately eight hours. When ketoconazole is taken with meals, higher plasma levels are obtained. Distribution studies using radioactive ketoconazole in rats show radioactivity mainly in the liver and the connective tissue. Radioactivity is also present in the subcutaneous tissue and the sebaceous glands. After one dose of 200 mg in humans, ketoconazole is found in urine, saliva, sebum, and cerumen. Like miconazole, the mode of action is based on inhibition of the cytochrome P-450 dependent biosynthesis of ergosterol. This results in disturbed membrane permeability and membrane-bound enzymes (8, 10, 23, 25).

Ketoconazole is active against dermatophytes (*Microsporum*, *Trichophyton*, *Epidermophyton*), yeasts (*Candida* species, *Cryptococcus*), and the dimorphous fungi (*Coccidioides*, *Histoplasma*, and *Paracoccidioides*). Activity has also been demonstrated in patients with aspergillosis and in a limited number of patients with chromomycosis and sporotrichosis; promising results were obtained. Some *Leishmania* species are sensitive.

It is indicated for infections of the skin and nails due to dermatophytes and/or yeasts, yeast infection of the gastrointestinal tract, chronic recurring vaginal candidosis, and systemic fungal infections. Ketoconazole is well tolerated by most patients. Gastrointestinal symptoms or pruritus have been noted in 1–3% of the patients. Occasionally, liver enzymes may be increased temporarily. Normalization usually occurs during treatment. Of the estimated 4,000,000 patients treated, 300 developed hepatitis, ie, one per 15,000 patients (26). Treatment with ketoconazole should be discontinued when clinical and/or laboratory indications of hepatitis are present (7, 27). In the case of prolonged treatment, it is advisable to check liver function twice a month during the first month of treatment, followed by monthly checks. With large doses (600 mg–1.2 g/d) a reversible inhibition of testosterone synthesis is observed (28). The period of treatment, with the exception of vaginal candidosis, depends on the clinical and mycological results. In the case of recurrent vaginal candidosis, 400 mg/d is prescribed for five days, but more recent studies with *Pityriasis versicolor* have demonstrated that shorter treatments also produce good results. Ketoconazole is contraindicated during pregnancy.

2.7. Itraconazole

Itraconazole **(18)** is a highly lipophilic compound with a triazole structure. Compared to ketoconazole, itraconazole has a broader spectrum (including *Aspergillus* spp.) (29, 30) and an *in vitro* activity that is 10 times higher than ketoconazole for most species.



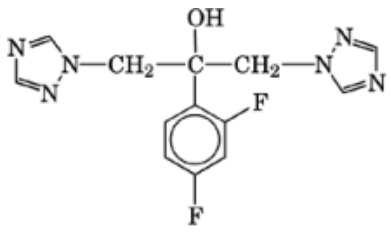
(18)

This *in vitro* superiority is also confirmed by animal experiments. Compared to ketoconazole, itraconazole [84625-61-6] is a much more selective inhibitor of the cytochrome P-450 dependent ergosterol biosynthesis in yeasts and fungi (29, 31). Pharmacokinetically, itraconazole has a much longer bioavailability ($\pm 24-\mathrm{h}$) and a greater tissue affinity. In general, itraconazole tissue levels are significantly higher than the corresponding plasma levels. It has been established toxicologically that therapeutic doses of itraconazole do not interfere with steroid metabolism in humans. Itraconazole does not affect the liver as much as ketoconazole.

There are few side effects including headache, nausea, vertigo, intestinal disorders, etc. Itraconazole is used to treat vaginal candidosis, pityriasis versicolor, tinea corporis–tinea cruris, tinea pedis–tinea manus, and most of the systemic mycoses including aspergillosis cryptococcal meningitis. Itraconazole is contraindicated during pregnancy (32).

2.8. Fluconazole

This substance **(19)** is a water-soluble bis-triazole tertiary alcohol (33). Fluconazole [86386-73-4] has a broad spectrum, but has little activity *in vitro*. However, animal experiments reveal a broad spectrum and a potent effect.



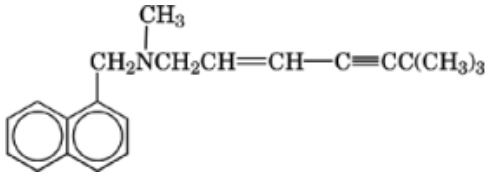
(19)

At the tested daily dose of 50 mg, fluconazole appears to be slightly less active against dermatophytes. The substance is used mainly to treat vaginal candidosis (a single capsule of 150 mg) and oral and esophageal candidosis (50 mg od for 14 d). In a number of countries, ie, England, the maximal period of treatment is 14 d.

Toxicological studies have demonstrated that there are no important problems with fluconazole. Therapeutic doses of fluconazole may cause enzyme induction in the liver. This suggests that interactions with other drugs cannot be excluded. The side effects are similar to those of itraconazole and include nausea, headache, and vertigo. Occasionally, increased liver enzymes may be noted. Like itraconazole, fluconazole is contraindicated during pregnancy.

2.9. Future Antimycotics for Systemic Treatment

Two new antimycotics for systemic use have now reached the stage of clinical development. The first is a triazole and fluoride analogue of itraconazole. This compound (saperconazole) is extremely active against *Aspergillus* spp. and slightly more soluble. Consequently, intravenous administration might be possible (34). The second molecule is terbinafine [91161-71-6], an allylamine, $C_{21}H_{25}N$, that appears to be particularly active against dermatophytes, just like topical naftifine (35).



Both substances will probably become available for more widespread clinical use in the following three to four years.

BIBLIOGRAPHY

Cited Publications

1. D. Kerridge and L. E. Whelan in A. P. J. Trinci and J. F. Ryley, eds., *Mode of Action of Antifungal Agents*, British Mycological Society Symposium 9, Cambridge University Press, Cambridge, UK, 1984, 343–375.
2. E. F. Gale, E. Cundliffe, P. E. Reynolds, M. H. Richmond, and M. J. Waring, *The Molecular Basis of Antibiotic Action*, 2nd ed., John Wiley & Sons, Inc., 1981, 201–219.
3. G. Medoff and G. A. Kobayashi in D. C. E. Speller, ed., *Antifungal Chemotherapy*, John Wiley & Sons, Inc., New York, 1980, 3–33.
4. G. Medoff, J. Brajtburg, and G. S. Kobayashi, *Ann. Rev. Pharmacol. Toxicol.* **23**, 303–330 (1983).
5. R. J. Holt in Ref. 3, 107–147.
6. H. B. Levine, *Ketoconazole in the Management of Fungal Disease*, Adis Press, Sydney, Australia, 1982.
7. H. E. Jones in R. Fleischmajer, ed., *Progress in Diseases of the Skin*, Vol. **2**, Grune & Stratton, New York, 1984, 217–249.
8. H. Vanden Bossche and co-workers, *Pestic. Sci.* **15**, 188–198 (1984).
9. H. Vanden Bossche, G. Willemsens, P. Marichal, W. Cools, and W. Lauwers in Ref. 1, 21–41.
10. H. Vanden Bossche in M. McGinnes, ed., *Current Topics in Medical Mycology*, Vol. **1**, Springer-Verlag, New York, 1985, 313–351.
11. H. Vanden Bossche and co-workers, *Pestic. Sci.* **21**, 289–306 (1987).
12. H. Vanden Bossche, G. Willemsens, W. Cools, W. F. J. Lauwers, and L. Le Jeune, *Chem. Biol. Interact.* **21**, 59–78 (1978).
13. H. Vanden Bossche and co-workers, *Biochem. Pharmacol.* 2609–2617 (1982).
14. G. Petranyi, N. S. Ryder, and A. Stütz, *Science* **224**, 1239–1241 (1984).

15. N. S. Ryder in C. Nombela, ed., *Microbial Cell Wall Synthesis and Autolysis*, Elsevier Science Publishers, Amsterdam, The Netherlands, 1984, 313–312.
16. B. Farkas, L. Kem;aaeny, and M. Csato in E. Tümbay, ed., *The Efficacy of Cyclopyroxolamine in the Treatment of Mycosis and Its Influence on the Keratinocyte Killing Activity*, The Turkish Microbiological Society No. 5, 1986, p. 35.
17. J. D. Stratigos and co-workers, *J. Am. Acad. Dermatol.* **19**(5) (part 1), 850–853 (1987).
18. G. Cauwenbergh, P. De Doncker, P. Schrooten, and H. Degreef, *Int. J. Dermatol.* **25**(8), 541 (1986).
19. A. Polak and D. M. Dixon in R. A. Fromtling, ed., *Recent Trends in the Discovery, Development and Evaluation of Antifungal Agents*, J. R. Prous Science Publishers, SA, 1987, 555–573.
20. A. E. Oxford, H. Raistrick, and P. Simonart, *Biochem. J.* **33**, 240–248 (1939).
21. R. R. Davies in Ref. 3, 49–82.
22. F. Foury and A. Goffeau, *J. Biol. Chem.* **250**, 2354–2362 (1974).
23. H. Vanden Bossche, G. Willemsens, and P. Marichal, *CRC Crit. Rev. Microbiol.* **15**, 57–72 (1987).
24. H. J. Scholer in Ref. 3, 35–106.
25. H. Vanden Bossche and co-workers, *Antimicrob. Agents Chemother.* **17**, 922–928 (1980).
26. J. H. Lewis, H. J. Zimmerman, G. D. Benson, and K. G. Ishak, *Gastroenterology* **86**(3), 503–513 (1986).
27. P. A. J. Janssen and J. E. Symoens, *Am. J. Med.* 80–85 (1983).
28. H. Vanden Bossche, W. Lauwers, G. Willemsens, and W. Cools in F. Schroeder, ed., *European Organisation for Research on Treatment of Cancer*, Monograph 2, Alan E. Liss Inc., New York, 1985, 187–196.
29. J. Van Cutsem, F. Van Gerven, M-A. Van De Ven, M. Borgers, and P. A. J. Janssen, *Antimicrob. Agents Chemother.* **26**, 527–534 (1984).
30. H. Vanden Bossche, D. W. R. Mackenzie, and G. Cauwenbergh, eds., *Aspergillus and Aspergillosis*, Plenum Press, New York, 1988.
31. H. Vanden Bossche in Ref. 19, 207–221.
32. G. Cauwenbergh and P. De Doncker, *Drug Dev. Res.* **8**, 317–323 (1986).
33. P. F. Troke in Ref. 19, 103–112.
34. J. Van Cutsem and P. A. J. Janssen, *28th Interscience Conference on Antimicrobial Agents and Chemotherapy*, Los Angeles, Calif., 1988, p. 141.
35. N. S. Ryder in Ref. 19, 451–459.

GEERT CAUWENBERGH
Janssen Research Foundation

Related Articles

Oligosaccharides; Antiparasitic agents, antiprotozoals, Tetracyclines; Peptides