CLINICAL MICROBIOLOGY REVIEWS, Apr. 1988, p. 187–217
0893-8512/88/020187-31$02.00/0

Vol. 1, No. 2

Overview of Medically Important Antifungal Azole Derivatives

ROBERT A. FROMTLING

Department of Basic Microbiology, Merck Institute for Therapeutic Research, Rahway, New Jersey 07065-0900

INTRODUCTION

From 10 to 12 years and $125 million may be required to take a successful drug from discovery to its use to treat and protect patients. In recent years the pharmaceutical industry has directed serious attention toward the discovery and development of antifungal agents. The purpose of this review is to present an overview of the azole antifungal drugs that have been developed and are in use, as well as the azole agents that are under development and evaluation for use in the chemotherapy of both systemic and superficial fungal diseases.

BRIEF OVERVIEW OF ANTIFUNGAL CHEMOTHERAPY AND DRUG DEVELOPMENT

Fungi were recognized as pathogens prior to bacteria, and antifungal chemotherapy was successfully attempted before antibacterial chemotherapy. However, the development of effective antifungal agents has been disappointingly slow. Thrush, an oral manifestation of *Candida albicans* infection, was recorded in 1665 as a fatal disease (63). In 1835, Bassi de Lodi determined that the causative agent of muscardine, i.e., silkworm disease, was a fungus that multiplied within and on the insect. Bassi is considered to be the founder of the concept of parasitic infection with his research on the pathogenesis of the etiologic agent of silkworm disease, *Beauvaria bassiana* (3). Thus, the first organism scientifically established to cause disease was a fungus. The treatment of sporotrichosis with potassium iodide in 1903 is believed to be among the first reports of antifungal chemotherapy (312). In spite of this early beginning, the discovery of the first major antifungal drug, nystatin, was not until 1949 (39). Azole antifungal drugs, the subject of this review, were not introduced for clinical use until 1969. In comparison to antibacterial agents, the field of antifungal chemotherapy has not progressed rapidly.

Until recently, infections caused by fungi were not considered to be a major problem. Fungal diseases are not reportable; thus, documentation of their incidence and trends in this field is difficult (42). However, with the increase in the number of patients compromised by human immunodeficiency virus, cancer chemotherapy, organ transplants, and long-term antimicrobial therapy, the incidence of opportunistic fungal infections is increasing. One analysis of data from 1970 to 1976 revealed increases of 158 and 78% in aspergillosis and cryptococcosis, respectively (87). A more recent study revealed that the incidences of certain opportunistic or hospital-acquired fungal infections or both almost doubled from 1976 to the period of 1980 to 1982 (234). The human immunodeficiency virus (acquired immunodeficiency syndrome) patient population also has greatly added to the incidence of opportunistic fungal infections (51, 282).

Fungi are eucaryotic and thus are biochemically similar to the human host. This similarity makes the development of a drug that is effective against the invading fungus, but safe for the host, an arduous and lengthy study in basic and clinical research. The objective of basic research in the field of antimicrobial chemotherapy is to rationally design, synthesize, and/or isolate novel chemical entities that can be used to treat diseases effectively and safely; for antifungal agents, directing research to a specific fungal target is one logical approach. This multidisciplinary task involves chemistry, biochemistry, molecular biology, pharmacology, immunology, microbiology, endocrinology, and enzymology, as well as other scientific disciplines. Once a product candidate is identified, research is conducted on the safety, bioavailability, formulation, and drug delivery system for the potential drug. Following the successful completion of these basic and developmental research steps, clinical research ensues (Table 1). The drug progresses through rigorous tests in humans to determine efficacy and safety. Beginning with phase I, i.e., clinical pharmacology, initial tolerance tests are conducted on small numbers of normal, healthy adults. If the product is determined to be safe, it then progresses to tests on larger numbers of patients with the target disease (phases II and III) to determine efficacy and continued safety. After

TABLE 1. Phases of development of pharmaceutical products[a]

Compound status	Stage of development
Basic research	Discovery of compound, including interaction of chemistry, biochemistry, microbiology, pharmacology, and enzymology
Pharmacology	All stages of preclinical investigations, including in vitro and in vivo (animal models) assays, safety assessment in animal models, pharmacology, and formulation studies
Clinical trials	
Phase I	Clinical pharmacology: first tolerance and pharmacokinetics tests in normal, healthy volunteers
Phase II	Efficacy and safety tests in a limited number of patients with the target disease
Phase III	Controlled clinical trials to determine efficacy and safety in large numbers of patients with the target disease; data are used for registration of the compound with government agency for marketing approval
Launched (marketed)	Marketing started in one or more countries
Phase IV studies	Surveillance after approval of drug; based on government request
Phase V studies	Studies to seek additional marketing claims, new formulations, and combinations

[a] These terms are used in the text to describe the stage of development of each antifungal azole. From discovery to launch may take 10 to 12 years and $125 million.

regulatory approval (the Food and Drug Administration in the United States or an international equivalent), surveillance of the drug continues based on government request (phase IV). The phase V stage in clinical research involves further marketing claims and new formulations and combinations.

HISTORY OF ANTIFUNGAL AZOLES

The first report of antifungal activity of an azole compound, benzimidazole, was in 1944 by Woolley (343), who was studying biotin deficiency in animals and microbes. He noted the structural similarity of biotin and purines to benzimidazole, but the biological effects of benzimidazole were not reversed by biotin, whereas they were reversed by the purines adenine and guanine. Since mycotic diseases were of minimal interest in 1944, Woolley's initial discovery was largely ignored, although his data were confirmed in 1949 (M. C. Goldsworthy and S. J. Gertler, Chem. Abstr. 43:6351, 1949). Thirty years later, Vanden Bossche observed that phenethylimidazole, another azole moiety with antifungal activity, inhibited the uptake of purines in yeast form *Candida* spp. by interference at the cell membrane (324).

In 1952, Jerchel et al. (151) revived Woolley's work and reported that certain substituted benzimidazole compounds had significant antifungal activity. This publication encouraged other investigators to screen this group of chemicals in search of a clinically useful antifungal agent. The breakthrough came in 1958 to 1959 when chlormidazole, a chlorobenzyl imidazole, was developed and studied in clinical trials (132, 261). Chlormidazole was sold as a 5% topical cream, the first azole derivative developed and marketed as an antifungal drug.

With the introduction of chlormidazole, interest in the antifungal activity of azole compounds began to increase. For example, after the introduction of thiabendazole, a thiazolyl-benzimidazole, in 1961 by Merck Sharp & Dohme for use as a broad-spectrum antihelminthic drug, Robinson et al. (241) tested the compound for antifungal activity in vitro. It was effective against many dermatophytes and *Aspergillus* species, but since its activity against yeast-like fungi was minimal, the compound was not developed as an antifungal agent. Similarly, mebendazole, a benzoyl-benzimidazole developed by Janssen Pharmaceutica (Beerse, Belgium) in 1973 as a broad-spectrum antihelminthic agent, was shown to have antifungal activity (40). Despite the fact that the antifungal activity of these two compounds was not pursued, the data supported the concept that two azole compounds had potential as antifungal drugs for human use.

In the late 1960s, three compounds from two different laboratories were introduced in the literature; these drugs firmly established azoles as antifungal agents. Clotrimazole, developed by Bayer AG (Wuppertal, Federal Republic of Germany), and miconazole and econazole, developed by Janssen Pharmaceutica, were introduced within months of each other. This era of azole antifungal compounds was so new and competitive that the less descriptive report of clotrimazole antifungal activity (221) was published 3 years prior to the more detailed description of the chemical synthesis (41). These three imidazoles continue to be used today for treatment of fungal infections, demonstrating the success of these early discoveries. Unfortunately, their use also reveals the slow evolution of the azole class of antifungal drugs during the past two decades.

Although progress with this group of antifungal agents has been slow, several clinically useful compounds have been developed, and many, which appear promising, are presently under development and clinical evaluation. A few imidazole compounds (ketoconazole, in particular) represent major advances in antifungal chemotherapy. New triazole derivatives, e.g., fluconazole and itraconazole, appear to be less toxic and more active than ketoconazole (92). These and several other antifungal azole derivatives are discussed in this review.

ANTIFUNGAL IMIDAZOLES AVAILABLE FOR CLINICAL USE

The imidazoles represent one of the two major classes of antifungal azole derivatives. Many of these drugs are limited in their clinical use by their spectrum of activity, potency, solubility, or side effects, but the imidazole group has contributed significantly to the therapy of both superficial and systemic mycotic infections. Chemical structures, marketed name(s), formulations, route of administration, and clinical uses are listed in Table 2.

Clotrimazole

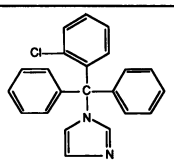
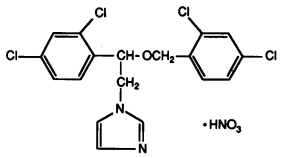
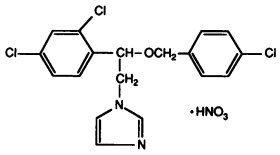
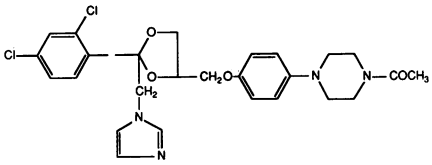
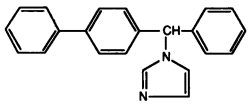
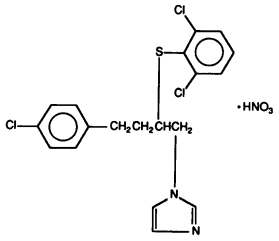
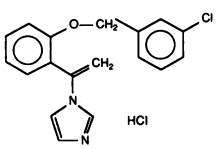
Clotrimazole was among the first of the imidazole antifungal drugs developed. It was synthesized in 1969 by chemists at Bayer AG, although the synthesis was not reported until 1972 (41). Clotrimazole has well-established in vitro activity against isolates of dermatophytes, pathogenic yeasts, and filamentous and dimorphic fungi, as well as some gram-positive bacteria. The drug is useful in the treatment of dermatophytic infections, superficial fungal infections, i.e., tinea versicolor, and various *Candida* infections, including oral thrush and vaginal candidiasis. Since its effectiveness has been proven, clotrimazole has been used as a control drug in many clinical trials of the newer azole derivatives.

The in vitro activity of clotrimazole against most systemic pathogens is comparable to that of amphotericin B (262). Clotrimazole is more active than griseofulvin and nystatin against dermatophytes as well. Its broad spectrum and potent activity have been confirmed in many studies (26, 43, 220, 264, 345). Very short contact time is required for clotrimazole to effect its antifungal activity (246), and as with the other imidazoles, the suggested mode of action appears to be disturbance of the fungal cell membrane. In one study, clotrimazole inhibited the uptake and intracellular pooling of leucine, lysine, and other amino acids in the absence of glucose (348).

Although several in vivo studies showed the drug to be active orally (263), problems with toxicity and other side effects have limited the use of clotrimazole to topical applications. Pharmacokinetic studies in humans demonstrated a progressive decline over several days in the serum concentrations of clotrimazole after oral administration; these data supported the hypothesis of liver enzyme induction by the drug (43, 141). Unacceptable side effects include high incidences of gastrointestinal disturbances following oral administration of clotrimazole (43, 47, 339) and alterations in hepatic and adrenal functions (300).

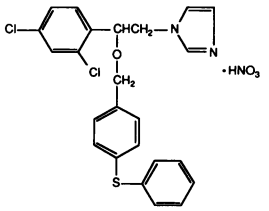
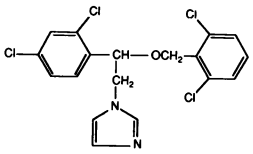
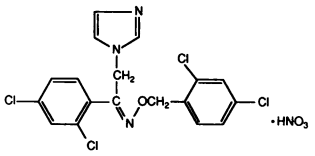
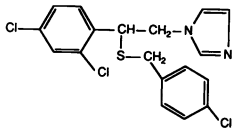
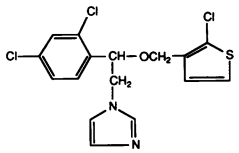
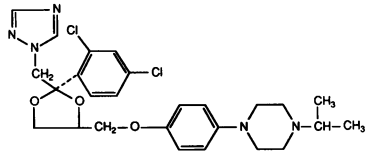
Clotrimazole has been shown to be safe and effective for topical treatment of both cutaneous and vaginal candidiasis, as well as dermatophytic and other cutaneous fungal infections. In an early study, Clayton and Connor (52) demonstrated that clotrimazole was as effective as nystatin in the therapy of superficial candidiasis. Moreover, several cases of vaginal candidiasis refractory to therapy with other agents reportedly responded to treatment with pessaries of clotrimazole (46). The advantages of this drug, with particular

TABLE 2. Generic and trade (marketing) names, chemical structures, formulations, and indications of antifungal imidazoles and Terconazole, a triazole derivative, currently available for clinical use

Generic name	Trade name(s)	Chemical structure	Formulations	Indications
Clotrimazole	Canesten Mycelex Mycelex-G Lotrimin Gyne-Lotrimin		1% cream and solution 100-, 200-, and 500-mg vaginal tablets 10-mg oral troches	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Miconazole	Monistat Monistat-Derm Monistat I.V.		2% cream and lotion 200-mg vaginal suppositories 10-mg/ml sterile solution for i.v. use	Systemic fungal infections, including coccidioidomycosis, candidiasis, cryptococcosis, paracoccidioidomycosis, pseudallescheriosis, and chronic mucocutaneous candidiasis Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Econazole	Spectazole Pevaryl		1% topical and vaginal creams 1% soln, spray, and powder	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Ketoconazole	Nizoral Fungarol Fungarest Orifungal		200-mg tablets for oral use 2% cream and solution	Systemic fungal infections, including blastomycosis, certain forms of coccidioidomycosis and histoplasmosis, chronic mucocutaneous candidiasis, chromoblastomycosis, paracoccidioidomycosis, and pseudallescheriosis; NOT recommended for fungal meningitis Superficial fungal infections, including dermatomycoses and tinea versicolor
Bifonazole	Mycospor Mycosporan		1% cream and solution	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous candidiasis
Butoconazole	Femstat		2% vaginal cream 100-mg vaginal ovules	Vaginal candidiasis
Croconazole	Pilzcin		1% cream and gel	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous candidiasis

Continued on next page

TABLE 2—*Continued*

Generic name	Trade name(s)	Chemical structure	Formulations	Indications
Fenticonazole	Lomexin		2% topical and vaginal creams	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Isoconazole	Travogen Gyne-Travogen		2% topical and vaginal creams	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Oxiconazole	Oceral Myfungar Gyno-Myfungar Okinazole Derimine		1% cream, spray, and powder	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Sulconazole	Exelderm Sulcosyn		1% cream	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous candidiasis
Tioconazole	Trosyd Gyne-Trosyd		1% cream, lotion, spray, and powder	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Terconazole (triazole)	Terazol Gyne-Terazol Fungistat		0.8% vaginal cream 40- and 80-mg vaginal ovules	Vaginal candidiasis

emphasis on reduced dosage and shorter-term therapy, have been reviewed by Plempel (218).

Clotrimazole also is effective in the treatment of oral candidiasis. In one drug-versus-placebo study (159), all 10 of 10 patients reported improvement of symptoms and regression of oral candidal lesions following administration of oral troches of clotrimazole five times a day; only one of ten patients in the placebo-treated group reported improvements. Another study (350) by other investigators revealed similar data; 2 weeks of therapy were recommended for optimal mycological cures.

Miconazole

In vitro activity and mode of action. Miconazole is a phenethyl imidazole derivative that was synthesized by Janssen Pharmaceutica in 1969 (107). It was one of the first azole derivatives synthesized and developed for antifungal therapy and the first azole derivative of sufficiently low toxicity to permit intravenous (i.v.) administration for the therapy of systemic fungal infections. Miconazole has well-established activity against isolates of dermatophytes, pathogenic yeasts, dimorphic fungi, and filamentous fungi, including *Aspergillus* species and mycetoma-causing fungi, as well as some gram-positive bacteria (55, 107, 147, 202, 255, 268, 323, 345). Miconazole's primary utility is in the treatment of dermatophytic infections, tinea versicolor, and cutaneous, vaginal, and systemic candidiasis. This azole derivative has proven to be an effective topical antifungal agent for more than a decade. However, miconazole administered i.v. has only limited use against certain cases of pseudallescheriosis (181). It also has been used rarely as a second-line agent for refractory cryptococcal meningitis (23). This imidazole has been used as the control in many clinical trials of the newer azole derivatives (see following sections for specific references).

Mode of action studies suggest that miconazole may cause direct membrane damage and inhibit ergosterol synthesis, as well as adversely affect other physiologic parameters of

exposed fungi; some studies have shown miconazole to be fungicidal. In one study, miconazole was shown to inhibit the uptake and intracellular pooling of amino acids; the investigators suggested that this may be responsible for the antifungal activity of the drug (348). Pye and Marriott (231) demonstrated that miconazole inhibited sterol C-14 demethylation in *Candida* species, which led to inhibition of ergosterol synthesis in the fungal cell membrane and death of the fungus. Morita and Nozawa (195) subsequently confirmed this observation in both *C. albicans* and *Trichophyton mentagrophytes*. Scott et al. (259) demonstrated a reduction in ergosterol levels in *T. mentagrophytes* following exposure to miconazole as well. In contrast, Taylor et al. (299) have presented data indicating that inhibition of C-14 demethylation is not a fungicidal event. They have proposed that direct membrane damage to the fungus may be the key antifungal activity of miconazole and other imidazole drugs.

Miconazole is fungicidal against *Candida parapsilosis* (16) and *C. albicans* (20); however, its fungicidal activity appears to be highly pH dependent (19). In other studies, adenosine 5′-triphosphate (ATP) levels in cells of *C. albicans* were suppressed (203), enzyme-catalyzed release of spheroplasts from young yeast cells of *C. albicans* was inhibited (13), and hyphal development in *T. mentagrophytes* (258) and *C. albicans* was prevented (205).

Experimental in vivo activity. The effectiveness of miconazole has been demonstrated in several experimental animal models. Van Cutsem and Thienpont (323) demonstrated the efficacy of miconazole given orally or topically against cutaneous infections with *T. mentagrophytes*, *Microsporum canis*, and *C. albicans* in guinea pigs. In another study, all mice given miconazole intramuscularly and subcutaneously 4 days after infection with 50 or 100% lethal doses of *Coccidioides immitis* were protected, whereas 60 to 100% of the untreated mice succumbed (178). Cultural assays of lung tissue confirmed that the drug limited proliferation of the fungus at that site. In this animal model, side effects of miconazole administration (i.v., intramuscular, or subcutaneous) included hematomas, fibrotic lesions, bleeding, and ulcerations. Miconazole at concentrations of 1.0 and 2.0% was shown to be effective in the topical treatment of experimental dermatophytosis and at 2.0% in the treatment of vaginal candidiasis (318). When administered i.v. to rabbits with experimentally induced *Candida* keratitis, the drug proved effective in reducing inflammation and producing mycological cures (148). Miconazole was not effective, however, in an experimental model of aspergillosis (2). A potentially serious side effect of miconazole noted in male rats was the induction of hepatic drug-metabolizing enzymes (171). Assuming that this occurs in humans as well, it would be a contraindication for long-term i.v. therapy.

Clinical studies. Clinically, miconazole can be administered either topically or i.v. In humans, i.v. doses of the drug have been shown to reach serum or plasma concentrations in excess of the minimum inhibitory concentrations (MICs) for a wide variety of fungal organisms (28, 79, 245, 286, 291), but serum levels decrease significantly within hours (28). A cause for concern in the i.v. administration of this drug is that it must be solubilized in polyethoxylated castor oil (10% Cremophor EL [Janssen Pharmaceutica]) for administration. The vehicle, therefore, may be the primary cause of many of the undesirable side effects of i.v. therapy (126). Foremost among side effects are persistent phlebitis, pruritis, nausea, fever, and chills. Despite these problems, miconazole has been used successfully to treat systemic candidiasis in compromised patients (153, 155, 190, 248), disseminated coccidioidomycosis (136, 284–286), cryptococcal meningitis (114), and severe cutaneous fungal infections (333) in humans. Relapse rates and clinical failures remain unacceptable when miconazole is used to treat coccidioidomycosis, however (284, 285).

Miconazole is effective in the treatment of superficial fungal infections including dermatophytoses, cutaneous candidiasis, and candidal vaginal infections (4, 31, 119, 240). Miconazole cream, lotion, and vaginal pessary formulations are widely prescribed for treating these non-life-threatening infections. In one recent study (61), it was shown that miconazole was only minimally absorbed systemically following the insertion of a 1,200-mg vaginal pessary. For example, the mean peak serum concentration of miconazole in 11 healthy adult females was 10.4 μl/liter, and the mean elimination half-life was 56.8 h. These data, as well as those of Odds and MacDonald (206), demonstrated that miconazole remains in the vagina for extended periods of time following administration and suggest that miconazole may be useful in a single-dose formulation for treating vaginal candidiasis, a procedure that would improve patient compliance.

Econazole

Econazole is an antifungal imidazole derivative having a structure identical to that of miconazole with the absence of one chlorine atom on one benzene ring. It was synthesized by Janssen Pharmaceutica in 1969 (107) and has been developed for topical therapy of dermatophytoses, superficial mycoses, e.g., tinea versicolor, and cutaneous candidiasis. Since econazole appears to be bound strongly by serum proteins, it is unsuitable for systemic therapy. The in vitro antifungal activity of econazole is comparable to that of miconazole; broad-spectrum activity against dermatophytes, *Candida* species, other pathogenic yeasts, filamentous fungi, and some gram-positive bacteria (26, 202, 255, 303).

The mode of action of econazole is not clearly defined. Ultrastructurally, the cell wall of *C. albicans* appeared to be distorted after treatment with the drug (13), and the plasmalemma and mitochondria appeared to be altered in the dermatophyte *M. canis* (188). The mitochondria, in fact, appeared to be the first organelles damaged by econazole. To the contrary, Preusser and Rostek (230) found no mitochondrial damage in their ultrastructural studies of the effect of econazole on *Trichophyton rubrum* and *C. albicans*. Biochemically, inhibition of enzyme-catalyzed release of spheroplasts of young cells of *C. albicans* has been shown (13), as well as suppression of ATP concentrations in the fungus (202). Others have demonstrated complete release of [^{14}C]aminoisobutyric acid from cells of *C. albicans*, suggesting direct membrane damage to the yeast (103).

In animal models, econazole was effective in the treatment of experimental cutaneous candidiasis and dermatophytoses in guinea pigs (303), vaginal candidiasis in the rat (303), and selected ocular fungal diseases in the rabbit (210). The drug was less effective in the treatment of aspergillosis (255) and coccidioidomycosis in the mouse (176). In the latter disease, for example, despite the fact that survival time was prolonged, cultures of organs remained positive. Econazole has not been approved for use in human ocular fungal diseases.

Clinically, econazole has been shown in a number of open studies to be an effective agent for treating superficial mycoses (106, 183, 340). Since econazole, one of the first antifungal azole derivatives discovered, has been used clinically for more than a decade, several comparative studies of

the drug versus clotrimazole and some of the newer azole derivatives have been done. It was proven to be comparable or superior to clotrimazole in clinical studies of vaginal candidiasis (22, 119), intertriginous candidiasis (59), and a variety of dermatophytic infections (88). In the therapy of dermatophytic infections, econazole appears comparable to the newer azole derivatives tioconazole (118), oxiconazole (104), and sulconazole (167).

Ketoconazole

Ketoconazole is an orally active, antifungal imidazole derivative synthesized and developed by Janssen Pharmaceutica in 1977 (127, 302). It is considered to be the "gold standard" among the azole derivative antifungal drugs. It has proven to be the most successful and most widely used antifungal azole derivative to date. Ketoconazole is indicated as a drug of choice for blastomycosis, disseminated histoplasmosis in stable nonimmunocompromised patients, chronic cavitary histoplasmosis, paracoccidioidomycosis, and chronic mucocutaneous candidiasis. It may be used in some cases of chromoblastomycosis and subcutaneous pseudallescheriosis and in certain subgroups of coccidioidomycosis (97), including soft-tissue and cutaneous lesions, draining sinus tracts, and possibly osteomyelitis and synovitis (T. J. Walsh, Methods Find. Exp. Clin. Pharmacol., in press). Ketoconazole is not recommended in the treatment of fungal meningitis as the drug penetrates the blood brain barrier poorly.

Ketoconazole is the most extensively studied antifungal azole derivative. Much of the published information regarding ketoconazole up to 1984 has been summarized in several reviews (89, 125, 145, 162). It is an impractical task to review all of the published reports relating to ketoconazole; thus, only selected papers in each area of interest will be discussed in this overview.

In vitro activity. The in vitro activity of ketoconazole was first reported by Dixon et al. (73) in 1978. These investigators studied 175 isolates of pathogenic yeasts and filamentous fungi and observed that ketoconazole was comparable to miconazole in all cases and was more active than miconazole against isolates of *Coccidioides immitis*. It was, however, less active against isolates of *Sporothrix schenckii*. Other in vitro studies also have confirmed the broad-spectrum activity of ketoconazole against pathogenic yeasts and dermatophytes (207, 269, 315) and dematiaceous fungi (55). A recent study by Shadomy et al. (269) demonstrated that emergence of ketoconazole-resistant clinical isolates of systemic and pathogenic fungi was not apparent but that in vitro data did not necessarily correlate with the clinical outcome of treatment, a common problem among tests with the antifungal azole derivatives.

The relative inhibition factor (RIF), an in vitro measure of antifungal activity, of ketoconazole was tested by Odds et al. (208). The RIF approaches 100% for a drug that either does not or only poorly inhibits the growth of a test fungus; the RIF approaches 0% for a drug that effectively inhibits fungal growth. The RIF values for 26 isolates of *Candida* species, 6 isolates of dermatophytes, and 8 isolates of *Aspergillus* species were 54, 18, and 55%, respectively. Activity was greatest at neutral pH. Thus, ketoconazole had substantial activity against all fungi tested in this assay; the data support ketoconazole as a broad-spectrum antifungal agent.

As with many of the antifungal azole derivatives, in vitro activity of ketoconazole is affected by several factors, including pH, culture medium, presence of serum, temperature and time of incubation, and growth phase of the fungus. Odds (201) and Hoeprich and Merry (139) have specifically addressed many of these issues. Historically, in vitro/in vivo correlation of data with ketoconazole has been poor.

Ketoconazole also has been reported to suppress the chemiluminescence response of murine immune cells (1) and the lymphocyte blastogenesis of human cells (5, 330) in vitro at therapeutic concentrations. The clinical significance of these in vitro studies remains unknown.

Experimental in vivo activity. Ketoconazole has been tested in experimental animal models of dermatophytic as well as systemic (e.g., candidiasis, cryptococcosis, blastomycosis, aspergillosis, coccidioidomycosis, histoplasmosis, and phaeohyphomycosis) infections, usually with favorable results. Heel et al. (125) have reviewed this area extensively; thus, only a few of the more recent papers will be discussed in this article.

In a study of the efficacy of orally administered ketoconazole in experimental systemic candidiasis in guinea pigs, the drug was effective in clearing the yeast from internal organs with resolution of tissue lesions (317). It demonstrated efficacy in the treatment of experimental paracoccidioidomycosis in mice as well (310), especially when therapy was begun early in the infection and continued for extensive periods of time. Polak and Dixon (226) demonstrated apparent fungicidal activity of ketoconazole against experimental murine histoplasmosis, using a quantitative spleen culture technique. Ketoconazole was comparable to fluconazole and superior to amphotericin B in this study. However, in another study by the same investigators, ketoconazole was the least active of five drugs tested in the treatment of experimental phaeohyphomycosis caused by three different genera of the dematiaceous fungi (72).

In a comprehensive study by Polak et al. (227), the outcome of combination therapy of ketoconazole and amphotericin B was variable. For example, in the treatment of experimental candidiasis produced by several strains of *Candida*, sp. synergistic activity was noted with some strains and antagonistic activity was noted with others. Effects that were primarily additive were noted in cryptococcosis, while antagonistic effects were observed in models of aspergillosis. Combination therapy of ketoconazole and another antifungal drug, 5-fluorocytosine, was not advantageous for the treatment of candidiasis, cryptococcosis, or aspergillosis. Schaffner and Frick (254) noted antagonism between ketoconazole and amphotericin B in an experimental model of aspergillosis. Ketoconazole alone is not effective therapy for aspergillosis.

Pharmacokinetics. Peak plasma concentrations of ketoconazole administered orally to normal human volunteers (200-mg tablet, suspension, or solution) have been reported to be 4.2, 5.0, and 6.2 μg/ml at 1.7, 1.2, and 1.0 h, respectively, after administration of the tablet, suspension, and solution, respectively. Mean elimination half-life ranged from 7.5 to 7.9 h (143). In another study in human volunteers and in mongrel dogs, ketoconazole solution was more readily absorbed and gave higher peak plasma concentrations than a tablet formulation (14). Thus, bioavailability of the solution was greater than that of the tablet. In general, the absorption of orally administered ketoconazole varies greatly from patient to patient, as shown by Shadomy et al. (267), who studied ketoconazole plasma concentrations by bioassay and high-pressure liquid chromatography techniques in patients undergoing therapy for systemic mycoses. Of interest was the observation that ketoconazole serum levels and therapeutic responses did not correlate.

Serum levels of ketoconazole are markedly decreased by concurrent administration of antacids or H-2 receptor-blocking agents due to elevated gastric pH, which impairs absorption of ketoconazole (62). Serum levels of ketoconazole also are decreased by concomitant administration of rifampin, apparently due to accelerated hepatic metabolism (35). Adverse interaction of ketoconazole and cyclosporin is well described, leading to elevated toxic levels of cyclosporin (70, 85, 271, 276).

Clinical studies. Ketoconazole has undergone clinical studies for a number of years. Many of the earlier studies have been summarized by Heel et al. (125). Some of the more recent clinical studies will be reviewed here. Ketoconazole is effective in the treatment of a wide variety of infections caused by *Candida* species. In a study of vaginal candidiasis, ketoconazole administered orally for 5 days produced 97% cures, with 10% relapses (260). In another study, 5 days of oral ketoconazole was as effective as 14 days of topical nystatin in treating vaginal candidiasis (294). A recent study of 13 cases of chronic mucocutaneous candidiasis demonstrated that ketoconazole was effective in producing clinical improvements or clinical and mycological cures with few side effects (192). Sobel (277) demonstrated that oral ketoconazole was effective in the prophylactic treatment of recurrent vaginal candidiasis, but he cautioned that the incidence of hepatic injury by the drug must be considered in treating patients with this syndrome. A study by Slotman and Buchard (274) demonstrated that oral ketoconazole was effective in the prevention of *Candida* sepsis in critically ill surgical patients; patients with hepatic dysfunction were excluded from the study. A randomized, double-blind study by Hansen et al. (120) tested the efficacy of using ketoconazole prophylactically in cancer patients. Ketoconazole was most effective in preventing oral candidiasis, but cases of vaginal and esophageal candidiasis occurred during the trial. The authors concluded that the routine prophylactic use of ketoconazole in this patient group was not justified.

A multicenter, randomized trial to test the efficacy of low-dose (400 mg/day) and high-dose (800 mg/day) oral ketoconazole in the treatment of blastomycosis and histoplasmosis was done by the National Institute of Allergy and Infectious Diseases Mycoses Study Group (198). The following recommendations resulted from this study: (i) oral ketoconazole may be used in the initial therapy of immunocompetent patients with chronic cavitary histoplasmosis and in patients with localized or disseminated histoplasmosis; (ii) ketoconazole is effective in the treatment of non-life-threatening, nonmeningeal forms of blastomycosis in immunocompetent patients; and (iii) low-dose (400 mg/day) therapy is safer and more effective than the high-dose (800 mg/day) therapy.

The importance of immunocompetency in the patient treated with ketoconazole should be stressed, because the drug is largely fungistatic and requires an immunocompetent host to effect mycological cure. An example of the ineffectiveness of ketoconazole in the immunocompromised host was provided by Greene et al. (117), who treated such a patient with oral ketoconazole at 400 mg/day; the fungal disease progressed systemically and required amphotericin B for resolution. In diabetic patients, a physiologically compromised group, cure rates with ketoconazole were not as high as those seen with nondiabetic patients (10). Prophylactic administration of ketoconazole to neutropenic immunosuppressed patients, however, was more efficaceous than nystatin in reducing colonization with *Candida* spp. and preventing opportunistic fungal disease (272). Ketoconazole treatment was associated with increased rates of *Torulopsis glabrata* colonization, however. Another comparative study of prophylactic use of ketoconazole and amphotericin B in neutropenic cancer patients demonstrated that, in general, the two drugs were comparable. Ketoconazole was not recommended for use in institutions in which a high frequency of *Aspergillus* species and *Candida tropicalis* cases occur, however (82). In general, clinical trials of ketoconazole used prophylactically to protect immunocompromised patients have demonstrated that 400 to 600 mg of drug per day provides adequate protection. Problems, however, include a tendency to select for *Aspergillus* species and *Torulopsis glabrata*, a reduction in drug absorption by the patient, and the question of whether prophylactic therapy with ketoconazole promotes colonization by certain other fungi (48).

Ketoconazole has been evaluated for efficacy in the treatment of superficial fungal infections as well. In a double-blind, placebo-versus-drug study, ketoconazole 2.0% cream was shown to be effective in the treatment of tinea versicolor (116). In another study, oral ketoconazole was shown to be inferior to griseofulvin in the treatment of tinea capitis (99). Ketoconazole was effective, but was significantly slower than griseofulvin in producing cures. Cullen and Cullen (58) reported that orally administered ketoconazole (200 mg/day) was more effective than griseofulvin (1 g/day) in the treatment of toenail dermatophyte onychomycosis. In a review by Cacciaglia et al. (44), it was noted that rates of cure for toenail and fingernail fungal infections treated with oral ketoconazole ranged from 13 to 95%. In spite of these clinical studies, however, it is important to note that orally administered ketoconazole is not recommended for the treatment of superficial fungal infections; 2.0% topical cream is recommended.

Toxicity and adverse reactions. Major adverse reactions to ketoconazole include nausea and vomiting (71); each is a serious dose-limiting side effect. More serious adverse reactions to ketoconazole have been reported. Ketoconazole has clearly been demonstrated to cause hepatotoxicity and the inhibition of adrenal steroid synthesis. Symptomatic hepatotoxicity during therapy with ketoconazole occurs at an incidence of 1:10,000 to 1:15,000 (150, 179). Although the toxicity is usually reversible following discontinuance of therapy, recovery may take several months (179). Transient minor elevations of liver enzymes in serum have been reported to occur in 5 to 10% of patients receiving the drug (179). Fatal cases of ketoconazole-associated hepatotoxicity have been reported (75, 179). Though low in incidence, this potentially fatal side effect of ketoconazole therapy must be considered before deciding upon therapy for certain types of fungal infection.

Ketoconazole also blocks adrenal steroid synthesis by inhibiting cytochrome P-450-dependent enzymes (164, 180, 229, 233) and has been suggested to be a universal inhibitor of cytochrome P-450 isozymes (134). One recent report documented a chronic adrenal insufficiency in a patient undergoing low-dose (400 mg/day) ketoconazole treatment for blastomycosis (27). The syntheses of testosterone (250) and cholesterol (165) are directly affected by ketoconazole. Gynecomastia has been reported to occur in 3 to 8% of patients receiving ketoconazole, although this is reversible when the drug is discontinued (65). Interestingly, the endocrine effects of ketoconazole have suggested a new use for the drug: the treatment of prostatic cancer (6, 305). Excellent reviews on hepatotoxicity (166) and endocrine effects of ketoconazole have been published recently (84, 280, 281).

The reader is referred to these articles for a more comprehensive review of the adverse reactions associated with ketoconazole.

Bifonazole

Bifonazole is a halogen-free imidazole antifungal agent synthesized and developed by Bayer AG (24, 222). Clinical trials in the United States and England have been conducted (R. Sochynsky and J. Hardcastle [ed.], Pharma Projects, p. m 107, May 1987, V&O Publications, Ltd., Richmond, Surrey, U.K.). Bifonazole has a broad spectrum of antifungal activity in vitro, including many pathogenic yeasts, dimorphic pathogens, dermatophytes, the agent of tinea versicolor, and several pathogenic filamentous fungi (222, 223, 345, 347). The drug is very lipophilic and has poor water solubility. These factors must be taken into consideration when in vitro susceptibility testing is done (222).

The RIF of bifonazole was tested by Odds et al. (208). RIF values for 26 isolates of *Candida* species, 6 isolates of dermatophytes, and 8 isolates of *Aspergillus* species were 77, 23, and 71%, respectively. Thus, bifonazole had relatively poor activity against *Candida* and *Aspergillus* species, but strong activity against dermatophytes under these conditions.

Other in vitro studies have shown that bifonazole inhibits the normal growth of hyphal tips of *T. mentagrophytes* and induces degenerative changes in hyphal structure at subinhibitory concentrations (212, 347). Using light and scanning electron microscopy, Barug et al. (12) demonstrated that the morphology of *C. albicans* was markedly altered following exposure to low concentrations of bifonazole. Yeast cells formed chains and clusters of interconnected cells rather than individual buds; yeast-to-hypha conversion was adversly affected also by exposure to bifonazole at subinhibitory concentrations. The authors concluded that these alterations could be a reflection of inhibition of fungal sterol biosynthesis. Hector and Braun (124) studied the effect of bifonazole on chitin synthesis in cells of *C. albicans*. They determined that its effect was stimulatory at low concentrations, but they were unable to elucidate the mechanisms or significance of the interaction in relation to antifungal activity.

Bifonazole has been shown to be effective in the treatment of experimental dermatophytic and *Candida* infections (222, 223, 265). In guinea pigs, topical application of bifonazole at concentrations of 0.05 and 1.0% produced a high percentage of mycological cures in experimentally induced trichophytosis (223). The efficacy of the drug was attributed to its long retention time in skin and therapeutically achievable (topically) fungicidal effect against dermatophytes. Once-daily application was efficaceous for the treatment of these infections. In a model of systemic candidiasis in mice, bifonazole was only moderately effective; the data were based on oral administration of the drug, and the results were dose dependent (222).

Pharmacokinetic studies in animals and humans have shown bifonazole to be tolerated well as a topical antifungal agent (238, 239, 256, 283, 337). Absorption following topical application in experimental animals (238, 239, 337) and in humans has been minimal (238). Percutaneous absorption in humans was <1.0% when the drug was applied to unbroken skin and 4.0% when it was applied to inflamed skin (238). Studies on the penetration of and retention time in skin following topical application of bifonazole have shown the drug to be compatible with once-daily application (225, 238), with a half-life in humans ranging from 19 to 32 h (238).

Clinical trials also have demonstrated the efficacy of bifonazole as a topical antifungal agent. Many of the clinical studies reported have been summarized in a recent review article (90) and in the proceedings of an antifungal telesymposium (92). Bifonazole appears to be comparable or superior to other antifungal azole derivatives in the treatment of tinea versicolor (90, 193, 275), dermatophytic infections (90, 108, 275), and cutaneous candidiasis (90). Advantages seem to be its once-daily application with few side effects.

Butoconazole

Butoconazole is an antifungal imidazole developed for the treatment of vaginal candidiasis by Syntex Research Laboratories (Palo Alto, Calif.) (91). The synthesis and initial antifungal properties of this compound were first reported in 1978 (335). Butoconazole has a broad spectrum of antifungal activity, including clinically important yeasts and dermatophytes (335). RIF values for 26 isolates of *Candida* species, 6 isolates of dermatophytes, and 8 isolates of *Aspergillus* species were 59, 16, and 87%, respectively (208). In this assay, butoconazole was comparable to ketoconazole, with the exception that ketoconazole was superior against the *Aspergillus* species, i.e., RIF value of 55% for ketoconazole versus 87% for butoconazole. Thus, in a sensitive assay, butoconazole was comparable to ketoconazole in relative antifungal activity against *Candida* species and dermatophytes.

Beggs (16, 18) has studied the mode of action of butoconazole. It was found to have intermediate activity against resting cells of *C. parapsilosis* (16), but to be fungicidal against logarithmic phase cells of *C. albicans* (18). Butoconazole was superior to ketoconazole against *C. parapsilosis* (16). Pye and Marriott (231) determined that a butoconazole concentration of 60 nM reduced synthesis of C-4,14-desmethyl sterols (ergosterol) by 50% in cells of *C. albicans*. The concentrations of ketoconazole, clotrimazole, and miconazole required to produce the same effect were 50, 120, and 200 nM, respectively. Thus, butoconazole was comparable to ketoconazole and superior to clotrimazole and miconazole in this study.

Few experimental in vivo studies have been done. One evaluation study that compared the efficacy of butoconazole with that of miconazole in the treatment of experimental vaginal candidiasis in mice demonstrated that butoconazole was superior to miconazole (335). Butoconazole also was shown to be superior to miconazole in the treatment of experimental vaginal candidiasis in mice caused by a mixture of 10 isolates of *C. albicans* (187, 335).

Butoconazole has been tested in clinical trials primarily for its efficacy in the treatment of vaginal candidiasis. In a multicenter, parallel, double-blind study of 274 nonpregnant patients, butoconazole nitrate cream (2.0%) administered once a day was more effective than clotrimazole vaginal tablets administered twice a day in producing and maintaining mycological cures (74). By using radiolabeled butoconazole, it was determined that the drug had a slow rate of systemic absorption, with maximum plasma levels of 19 to 44 ng/ml occurring 24 h after intravaginal administration. Total radioactivity was excreted in the urine and feces in the form of unidentified breakdown products of butoconazole. Butoconazole itself was not detected in the specimens (74). Another study of similar design, but involving 107 nonpregnant patients with confirmed vaginal candidiasis treated once a day with butoconazole vaginal inserts (50 and 100 mg) or twice a day with clotrimazole 200-mg vaginal tablets, each

for 3 days, confirmed the efficacy of butoconazole over clotrimazole in producing mycological cures (39). The first cultural evaluation was at 8 days. When patients were recultured at 30 days posttreatment, the cure rate for butoconazole remained higher than that of clotrimazole, but the data were not statistically significant.

In other clinical trials, butoconazole was compared to miconazole, and the former was more efficaceous. For example, in a multicenter, parallel, double-blind trial of 130 nonpregnant patients with culture-proven vaginal candidiasis, 1.0 or 2.0% butoconazole cream was more effective than 2.0% miconazole cream in producing mycological and clinical cures, as well as in reducing vaginal discharges (149). Thirty days after the completion of therapy, the cure rates were 80, 80, and 68% for butoconazole 2.0%, butoconazole 1.0%, and miconazole 2.0%, respectively. Minor side effects, including itching, burning, cream leakage, and headache, were reported for each of the drugs tested. Butoconazole 2.0% cream administered for 3 days was compared to miconazole 2.0% cream administered for 7 days in a single-blind study of 68 nonpregnant patients (32). The mycological cures in the two groups were found to be comparable. The results were perceived as indicating an advantage of butoconazole because of the shorter dosing schedule, a condition that improves patient compliance. These data have been confirmed by additional clinical studies (37, 328), with the exception of one study in which miconazole administered for 7 days was more effective than butoconazole 2.0% cream administered for either 3 or 6 days (338).

Croconazole

Croconazole (710674-S; cloconazole) is an imidazole derivative with antifungal activity developed by Shionogi Research Laboratories (Osaka, Japan) (209). It is indicated in the topical treatment of dermatomycoses and candidiasis (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 1163, May 1987).

Croconazole has broad-spectrum antifungal activity in vitro. The range of MICs against isolates of *T. mentagrophytes*, *T. rubrum*, *M. canis*, *Microsporum gypseum*, and *Epidermophyton floccosum* were 0.16 to 1.25 μg/ml. Five isolates of *Aspergillus* species and two isolates of *Penicillium* species were susceptible, with MICs of 0.63 to 5.0 μg/ml. However, this compound was less active (MICs, 10 to 80 μg/ml) against yeastlike fungi, including isolates of *C. albicans*, *Candida* species, *Torulopsis glabrata*, and *Cryptococcus neoformans* (209).

Croconazole was compared in vitro with clotrimazole, econazole, and miconazole against a large panel of dermatophytes. The geometric mean MICs of croconazole were comparable to those of clotrimazole and econazole when tested against isolates of *T. mentagrophytes* and quantitatively superior to all three imidazoles when tested against isolates of *T. rubrum*. When tested against isolates of *C. albicans*, croconazole was superior to clotrimazole, but less active than miconazole and econazole (209).

Studies designed to assay the fungistatic or fungicidal effects of croconazole, econazole, miconazole, and clotrimazole against an isolate of *C. albicans* determined that croconazole was fungicidal at 80 μg/ml. Miconazole and econazole were fungicidal at 40 and 80 μg/ml, respectively; clotrimazole was not fungicidal in this assay. In a similar assay with *T. rubrum*, croconazole and econazole were fungicidal at 40 μg/ml; miconazole and clotrimazole were not fungicidal at the same concentration (209).

A gel formulation of croconazole was more effective than clotrimazole tincture in the treatment of *Trichophyton asteriodes*-induced dermatomycosis in guinea pigs. In the same experimental model, but with a different treatment regimen, croconazole 1.0% cream was comparable to clotrimazole 1.0% cream (209). Croconazole had no marked effects on pharmacologic parameters following oral administration in experimental animals (349) and did not produce any notable contact sensitivity, phototoxicity, or photoallergy following topical application in guinea pigs (293).

Although the drug has been marketed, no reports on the efficacy of the compound in clinical trials have been published to date.

Fenticonazole

Fenticonazole is an antifungal imidazole derivative developed by Recordati SpA (Milan, Italy). It is indicated for the treatment of superficial mycoses and vaginal candidiasis. The compound is in phase III clinical trials in the United Kingdom and the Federal Republic of West Germany; France discontinued development after phase III clinical trials (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 1007-m 1008, May 1987). Fenticonazole has broad-spectrum in vitro antifungal activity, but it is most active against dermatophytes (56, 332). Its activity decreases significantly at alkaline pH and in the presence of serum. At acidic pH, activity was demonstrated against *Cryptococcus neoformans* and *C. albicans*.

Studies of its mode of action and efficacy in experimental animal models have been limited. A scanning electron microscopic study of the effect of fenticonazole on cells of *C. albicans* revealed the induction of cytoskeletal changes and alterations in plasma membrane architecture with increasing concentrations of the drug (57). Moreover, at concentrations approaching the MIC, the drug inhibited the formation of pseudohyphae of *C. albicans*; filamentation was completely inhibited at the MIC and higher (60). In experimental models of dermatomycoses and candidiasis in guinea pigs, fenticonazole was comparable to miconazole and clotrimazole (331). Formulations of 1 to 3% produced complete healing of infected skin without relapses.

Several clinical trials have been published. Fenticonazole was shown to be more effective than miconazole, econazole, and clotrimazole in phase III clinical trials (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m1007–m1008, May 1987). In one report of a double-blind, clinical study of 54 patients with vaginal candidiasis, topical application of fenticonazole 2.0% cream for 7 days produced a 95% rate of cure with no significant side effects (36). The clinical cures were comparable to those obtained with clotrimazole, although four of the fenticonazole-treated patients relapsed within 4 to 6 weeks as compared to none of the clotrimazole-treated patients. In a double-blind trial with 30 patients with vaginal candidiasis, fenticonazole 100 mg as ovules was compared with miconazole 100 mg as ovules; both compounds were administered twice daily (101). All patients from both groups were cured, but the onset of action of fenticonazole was more rapid than that of miconazole; 13 of 15 patients treated with fenticonazole were cured in weeks 1 and 2 compared to 4 of 15 patients treated with miconazole.

In several trials, fenticonazole was more effective than econazole or clotrimazole. When 52 patients with culture-proven dermatomycoses were treated with fenticonazole 2.0% cream or econazole 1.0% cream, fenticonazole produced more cures (163). Likewise, fenticonazole 2.0% cream

produced more cures in 21 patients with dermatophytoses when compared with clotrimazole 1.0% cream (86). Fenticonazole was significantly more effective than clotrimazole in producing cures in week 3 of treatment. In contrast to the above, in another randomized, double-blind, parallel, multicenter clinical trial of 60 patients with dermatomycoses or tinea versicolor, fenticonazole 2.0% cream was comparable to miconazole 2.0% cream in producing mycological cures. No or minimal side effects followed twice-daily applications for up to 4 weeks (9). A once-a-day dosage formulation is in phase II and III clinical trials (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 1007-m 1008, May 1987).

Isoconazole

Isoconazole is structurally related to miconazole and econazole and was synthesized by Janssen Pharmaceutica. The compound has been marketed in several countries, but not in the United States. It has broad-spectrum activity in vitro against dermatophytes, pathogenic yeasts, pathogenic filamentous fungi, gram-positive bacteria, and trichomonads (157). The mode of action appears to include rapid reduction in ATP concentrations caused by damage to the fungal cell membrane (203). An ultrastructural study of the effect of various imidazoles on the cell wall of *C. albicans* showed that isoconazole interacted with the cell wall and caused convolutions and wrinkles. Isoconazole also inhibited the enzyme-catalyzed release of spheroplasts from young yeast cells (13). An in vitro study with mouse Leydig cells demonstrated a direct reversible inhibition of testosterone biosynthesis by isoconazole (257); thus, like ketoconazole, isoconazole is capable of altering steroid synthesis.

This compound appears to be active only when administered topically. Oral or parenteral administration in experimental animal models of fungal and bacterial infections has yielded negative data. In one such study, oral treatment of mice with gastrointestinal candidiasis failed to protect the animals from progressive disease (158). Only a small reduction in the number of animals excreting the yeast in the feces was observed. A recent study has demonstrated that application of the free base of isoconazole in combination with a volatile/nonvolatile vehicle, e.g., ethanol/propylene glycol, can increase drug bioavailability in the skin by a factor of 10 (297). This observation may lead to newer formulations of isoconazole and broaden its use for topical (e.g., spray) treatment of yeast and dermatophytic infections.

Isoconazole has been developed and marketed primarily as a once-a-day, topical anti-*Candida* agent for the treatment of vaginal candidiasis. In clinical studies, very little of the drug entered the blood after a single vaginal application of a 600-mg dose; the same dose did not adversely affect intestinal flora by inducing a proliferation of yeastlike species following prolonged administration (140). Studies evaluating isoconazole have demonstrated that 80 to 90% of patients with vaginal candidiasis who were treated once a day with the drug remained clinically and mycologically cured (336). Following insertion of two 300-mg tablets, concentrations of isoconazole in the vagina remained above minimum inhibitory and minimum fungicidal levels for at least 72 h (298). Another open, randomized, comparative study of isoconazole and orally administered ketoconazole in the treatment of vaginal candidiasis showed that there were no statistically significant differences in the rates of cure between the two drugs. Fewer side effects were reported with the isoconazole-treated group than with the ketoconazole-treated group (83).

Oxiconazole

Oxiconazole (Ro-13-8996) is an antifungal imidazole jointly developed by F. Hoffmann-LaRoche and Siegfried AG, both of Basel, Switzerland (191). It is marketed for the treatment of dermatomycoses and vaginal candidiasis (Sochynsky and Hardcastle [ed.], Pharma Projects, p. a 299, May 1986).

Oxiconazole has broad-spectrum antifungal activity in vitro, although its degree of activity varies over a wide range. Fungicidal activity was found against isolates of *Aspergillus fumigatus*, *Cryptococcus neoformans*, *C. albicans*, and *T. mentagrophytes* (224). It appears to be less active than miconazole against *C. albicans* and less active than ketoconazole against *C. parapsilosis* (102). Oxiconazole was the most active drug against both *Mucor* and *Rhizopus* species. Subinhibitory concentrations inhibited synthesis of deoxyribonucleic acid (224) and suppressed intracellular concentrations of ATP (203). Synthesis of ribonucleic acid, protein, and carbohydrate were decreased only slightly (224). Oxiconazole RIF values for isolates of *Candida* species, *Aspergillus* species, and dermatophytes were 67, 72, and 20%, respectively (208), suggesting good activity against the dermatophytes and only moderate activity against the other fungi tested. Polak-Wyss et al. (228) demonstrated that oxiconazole-treated cells of *C. albicans* had reduced concentrations of ergosterol, but increased concentrations of other sterols, indicating an inhibition of C-14 demethylation. This observation was made by Hiratani and Yamaguchi as well (135). Beggs (18) demonstrated that oxiconazole was a fungistatic agent against both early stationary phase and early logarithmic phase cells of *C. albicans*. In a second study, the same investigator noted that it was lethal to resting cells of *C. parapsilosis*, although the lethal activity was intermediate when compared with that of other imidazole antifungal drugs; oxiconazole was more active than ketoconazole in this assay (16).

In experimental studies, oxiconazole was more potent than other imidazole drugs in the treatment of trichophytosis in the guinea pig and vaginal candidiasis in the rat (224). Oral activity against experimental systemic infections was variable. Oxiconazole was effective in treating experimental histoplasmosis, but had poor activity against systemic candidiasis and no activity against cryptococcosis and aspergillosis in mouse models (224). Based on the irregular responses obtained in experimental animal models following oral administration, oxiconazole was developed as a topical antifungal agent.

In a guinea pig model, oxiconazole had a retention time in the dermis sufficient for once-daily application (228). When three drugs were evaluated ≥48 h after application, oxiconazole was the most active, followed by an experimental compound (Ro 14-4767/002) and bifonazole. Radiolabeled drug applied to human cadaver skin penetrated into the deeper layers of epidermis and into hair follicles (288). Fungistatic concentrations of the drug were found in the upper corium and in deeper hair follicles as well. Others have shown that oxiconazole penetrated into the horny layer of skin and nail layers in sufficient amounts to inhibit fungal growth; dissolutions in tinctures gave better nail penetration than in ointments (287). Thus, the deep skin penetration and long retention time of oxiconazole make this imidazole a useful topical antifungal agent.

In clinical studies, oxiconazole was compared with econazole in a double-blind evaluation of 120 patients with dermatomycoses (104). From both clinical and mycological

perspectives, oxiconazole was shown to be comparable to econazole (90 versus 91.4% cures, respectively) in the therapy of the superficial fungal infections. In a study involving vaginal candidiasis in 51 patients, efficacy of single-dose oxiconazole (600-mg vaginal tablet) versus a 3-day course of econazole (150-mg ovule daily) was evaluated. Identical cure rates of 92% were obtained with both drugs (109). The only reported side effect was vaginal burning following application of either drug in a few of the patients. In a comparative study of 144 patients with dermatomycoses and tinea versicolor, oxiconazole applied once daily was compared with oxiconazole applied twice daily. The data demonstrated no significant differences in the efficacy of the therapies; thus, once-daily applications of oxiconazole may be a suitable therapeutic regimen (334).

Sulconazole

Sulconazole is an imidazole derivative developed by Syntex Research as a topical antifungal agent for the treatment of dermatomycoses, pityriasis versicolor, and cutaneous candidiasis.

In vitro activity. Sulconazole has broad-spectrum antifungal activity. It is active against dermatophytes and yeastlike fungi, including *C. albicans*, as well as gram-positive bacteria (351). Its mode of action is not well defined, but in one study it inhibited macromolecular synthesis in the order ribonucleic acid > deoxyribonucleic acid > protein > mannan (344). RIF values for *Candida* species, *Aspergillus* species, and dermatophytes were 69, 71, and 12%, respectively (208). These values suggest that sulconazole is very active against dermatophytes, but only moderately active against *Candida* and *Aspergillus* species. Against resting cells of *C. parapsilosis* sulconazole exerted direct physicochemical damage to the fungus at a concentration of 3.8×10^{-5} M (16). In addition, against early logarithmic phase cells of *C. albicans*, sulconazole was fungicidal at a concentration of 2×10^{-5} M (18). These data support the premise that sulconazole is capable of producing direct fungal cell membrane damage.

Experimental in vivo activity. In a model of experimental trichophytosis in guinea pigs, sulconazole was comparable to miconazole at a variety of dosage schedules and cream formulations (352). In other experimental guinea pig dermatophyte and mouse vaginal candidiasis models, sulconazole was comparable to miconazole (L. Tanenbaum, C. Anderson, M. Chaplin, R. Jones, T. Matthews, and K. Walker, Program Abstr. 19th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 148, 1979). Sulconazole also penetrated full thickness skin 4 to 8 times more effectively than miconazole (Tanenbaum et al., 19th ICAAC). Using radiolabeled sulconazole 1.0% cream on rats with intact or damaged skin, Fujihara et al. (96) demonstrated that some drug was absorbed. Radioactivity in tissues and organs of rats with damaged skin was three to five times higher than that in rats with normal skin. Radioactivity in both groups was high in the skin area on which the drug had been applied, moderate in adrenals, liver, kidneys, and lung, and very low in the spleen, brain, blood, and muscle. Absorption of radioactivity from intact skin and damaged skin was 6 and 14%, respectively.

Clinical studies. Clinical trials of sulconazole have been limited to superficial fungal infections, i.e., tinea versicolor, and dermatophytoses. In one such study, which was multicenter, double-blind, randomized, and parallel, 181 patients with tinea versicolor were treated with either 1.0% sulconazole or 2.0% miconazole (295) applied twice daily for 3 weeks. Mycological cures were obtained in 93 and 87% of the patients treated with sulconazole and miconazole, respectively. Complete healing of lesions was observed in 89 and 82% of the patients, respectively. No serious side effects were recorded with either compound. In another comparative study, this time in 96 patients with either tinea pedis or tinea cruris/corporis, the same azoles were compared in the same dosage schedule (296). The compounds were administered twice a day for 3 weeks. Sulconazole was comparable to miconazole in producing mycological cures and in the rate of relapse, but it was superior to miconazole in producing fewer side effects. An additional clinical study comparing sulconazole with miconazole in the treatment of dermatophytoses showed that sulconazole was significantly superior to miconazole in providing a more rapid onset of clinical improvement, particularly in cases of tinea pedis (105). Statistically significant differences favoring sulconazole were observed for erythema, scaling, and overall clinical improvement.

Sulconazole has been compared to econazole in the treatment of dermatophytoses as well. In a double-blind, parallel study of 34 patients, the 1.0% creams of both agents were applied twice daily for 4 weeks (167). Sulconazole was comparable to econazole in producing mycological cures. More importantly, however, none of the patients (0 of 18) treated with sulconazole had relapsed 6 weeks after the completion of therapy, whereas 3 of the 16 patients that had been successfully treated with econazole had relapsed. This low relapse rate for sulconazole had been observed in an earlier comparative study with clotrimazole, a study in which sulconazole was shown to be statistically significantly more effective than clotrimazole in the treatment of dermatophytoses (168). In another study, simultaneous use of sulconazole 1.0% cream on infected skin and sulconazole powder around the adjacent body and clothing completely cleared inflammation in 14 patients with dermatophytic infections (232). The results were comparable to those obtained with econazole 1.0% cream and econazole powder. Thus, several clinical trials have demonstrated that sulconazole is an effective agent for the therapy of dermatophytic and other superficial fungal infections.

Tioconazole

Tioconazole is a 1-substituted imidazole derivative synthesized and developed by Pfizer U.K. (Sandwich, England). Tioconazole has broad-spectrum in vitro inhibitory activity against a variety of pathogenic yeasts, dermatophytes, and *Aspergillus* species (152), as well as activity against some chlamydia, trichomonads, and gram-positive bacteria (53). It is indicated for the topical therapy of superficial dermatophytic and yeast infections of the skin and for vaginal candidiasis. In the United States, tioconazole has been approved for over the counter use in the treatment of skin and nail infections due to dermatophytes and yeasts, including those infections complicated by gram-positive organisms (Sochynsky and Hardcastle (ed.), Pharma Projects, p. a 301, May 1986).

In vitro activity and mode of action. In in vitro studies, tioconazole was fourfold more active than miconazole against *Candida* species and was more potent than miconazole against isolates of *Cryptococcus neoformans*, *Torulopsis glabrata*, and several species of dermatophytes; tiocona-

zole was comparable to miconazole against *Aspergillus* species (145). In vitro studies by Odds and co-workers (201, 202) and Lefler and Stevens (174) also demonstrated the broad-spectrum activity of tioconazole in comparison to other azole derivative antifungal drugs.

The mode of action of tioconazole is unclear, but it lowered ATP concentrations in cells of *C. albicans* (7,203) and inhibited sterol C-14 demethylation in *Candida* species (231). Both of these parameters suggest direct membrane damage to the yeast cells by the drug. In one study, tioconazole was shown to have an intermediate effect on the suppression of new hyphal growth of *C. albicans*; it was comparable to ketoconazole in this assay (205). A number of other studies have shown tioconazole to have potent fungicidal activity, however. Beggs (17) demonstrated that tioconazole at a concentration of 3.8×10^{-5} M caused a rapid 2- to 3-log reduction in viable yeast cells of late-lag, logarithmic-phase, or stationary-phase *C. albicans* and *C. parapsilosis*. This fungicidal activity appeared to be pH dependent and did not occur under moderate acidic conditions (19). Thus, tioconazole demonstrated a growth phase-independent fungicidal action, an activity quite desirable in clinical situations.

Experimental in vivo activity. Tioconazole has proven effective in the treatment of experimental animal infections. Tioconazole was more effective than miconazole in the treatment of systemic *C. albicans* infection in mice following oral, i.v., or subcutaneous administration of the drugs (152). In a murine model of vaginal candidiasis, tioconazole 2.0% cream was slightly more effective than miconazole 2.0% cream in producing mycological cures (185). Tioconazole 1.0 and 2.0% creams were comparable to miconazole 2.0% cream in the treatment of experimental dermatomycoses in guinea pigs (185). In general, pharmacologic studies in animals have shown tioconazole to be well tolerated with minimal systemic exposure following topical application (185). One exception is a report by Latrille et al. (169), who reported that tioconazole administered orally to pregnant rats at 100 mg/kg per day affected parturition and was associated with modification of progesterone and 17β-estradiol serum levels; the data have questionable relevance to humans, however.

Pharmacokinetics. Pharmacokinetic studies in humans have shown tioconazole to be only minimally absorbed following either cutaneous (121) or vaginal (8, 121, 142) application. For example, the mean plasma concentration of tioconazole 8 h following insertion of a 300-mg ovule in the vagina was 21.2 ng/ml; no drug was detected 24 h after insertion. The mean vaginal concentration of tioconazole was 21.4 mg/liter 24 h after insertion, and drug remained detectable in seven and two of nine patients after 48 and 72 h, respectively. These data support once-a-day administration of this drug.

Clinical studies. In a number of open and comparative clinical trials, tioconazole was effective for the treatment of dermatophytic infections and cutaneous and vaginal candidiasis. A recent comprehensive review of these clinical trials was published by Clissold and Heel (53); thus, only a few of the evaluations will be discussed in this report. Kashin et al. (154) studied more than 200 patients with dermatophytic infections and noted that tioconazole 1.0% cream administered once daily was just as effective in producing mycological cures (85 to 95%) as drug administered twice daily. In another study involving more than 1,000 patients with a variety of superficial fungal infections, tioconazole was compared with miconazole, clotrimazole, and econazole and all were found to be of equal efficacy in reducing symptoms and producing mycological cures (211). Hay et al. (123) demonstrated that a special 28% tioconazole formulation, suitable for application to nails, caused clinical improvement in 11 patients, some improvement in 5 patients, and no improvement in 5 patients, all of whom had nail infections caused by a variety of fungal species. None of the patients had responded to therapy with ketoconazole or griseofulvin. Further clinical trials are needed to determine the role of tioconazole in the treatment of nail infections.

Tioconazole is effective in reducing symptoms and producing mycological cures of vaginal candidiasis. Non-relapse cure rates of 85% were reported in a study following 3-, 6-, or 14-day administration of tioconazole (100-mg pessary or 5 g of 2.0% cream); cure rates of 96% were reported following single-dose treatment with tioconazole (300-mg pessary or 6.0% ointment) (131). In several other studies tioconazole has been comparable or superior to econazole, clotrimazole, and miconazole for treatment of vaginal candidiasis (53). In one such study, tioconazole administered topically once or twice was superior to ketoconazole administered orally once daily for 5 days in producing mycological cures in both short-term (75 versus 30% for tioconazole and ketoconazole, respectively) and long-term (90 versus 70% for tioconazole and ketoconazole, respectively) follow-up evaluations (244).

ANTIFUNGAL IMIDAZOLES UNDER DEVELOPMENT

Newer antifungal imidazole derivatives are being developed by several companies. Most of these compounds are in very early development and little information is available. Although this chemical group is well represented with numerous clinically useful drugs, the search for more effective, safer, and preferably orally active azole derivatives continues. The need for improved antifungal chemotherapy remains; the imidazoles presently under development may eventually meet that need. Chemical structures, proposed routes of administration, and proposed clinical uses of these compounds are listed in Table 3.

Aliconazole

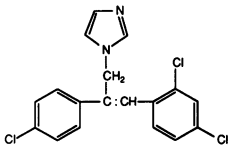
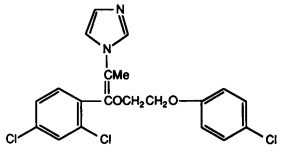
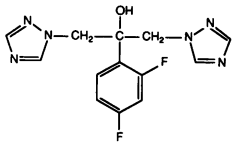
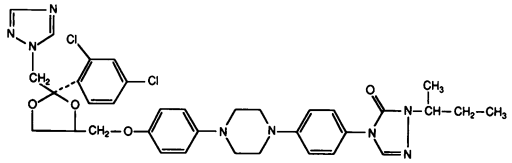
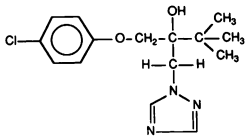
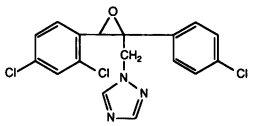
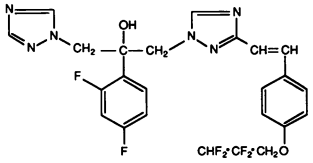
Aliconazole is an antifungal imidazole derivative being developed by Knoll Pharmaceuticals (Whippany, N.J.). The compound is in phase III clinical trials for the determination of efficacy in the topical treatment of cutaneous fungal infections (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 640, May 1987).

Omoconazole

Omoconazole (CM 8282) is an antifungal imidazole derivative that is being developed as a topical antifungal agent by Siegfried AG (301). This compound is in phase II clinical trials to evaluate its effectiveness for treating dermatological fungal infections (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 1171, May 1987).

In vitro, this drug is comparable in activity to clotrimazole, econazole, isoconazole, ketoconazole, miconazole, and tioconazole against a panel of 55 recent clinical isolates of yeasts (196). Omoconazole was the second most active drug; tioconazole was the most active and ketoconazole was the least active in this agar dilution assay. Further studies are in progress.

TABLE 3. Generic name, developer, chemical structure, proposed route(s) of administration, and proposed clinical uses of imidazole and triazole antifungal derivatives currently under development

Generic name (developer)	Chemical structure	Proposed route(s) of administration	Proposed clinical uses
Imidazoles			
Aliconazole (Knoll)		Topical	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Omoconazole (Siegfried AG)		Topical	Superficial fungal infections, including dermatomycoses, tinea versicolor, and cutaneous and vaginal candidiasis
Triazoles			
Fluconazole (Pfizer U.K.)		Oral Topical	Superficial and systemic fungal infections, including tinea versicolor, dermatomycoses, cutaneous, vaginal, and systemic candidiasis; special indication for fungal meningitis
Itraconazole (Janssen)		Oral Topical (?)	Superficial and systemic fungal infections, including tinea versicolor, dermatomycoses, cutaneous, vaginal, and systemic candidiasis and systemic aspergillosis, sporotrichosis, and chromomycosis
Vibunazole (Bayer AG)		Oral Topical	Superficial and systemic fungal infections, including tinea versicolor, dermatomycoses, cutaneous, vaginal, and systemic candidiasis and systemic aspergillosis
Alteconazole (Knoll)		Oral Topical	Superficial and systemic mycoses
ICI 195,739 (Imperial Chemical Industries)		Oral Topical	Superficial and systemic mycoses

ANTIFUNGAL TRIAZOLES AVAILABLE FOR CLINICAL USE AND UNDER DEVELOPMENT

Antifungal triazole derivatives presently under development represent a much needed advance in the field of antifungal chemotherapy. They are the second major chemical group of antifungal azole derivatives. In general, the triazole group appears to have a broader spectrum of antifungal activity and reduced toxicity when compared with the imidazole antifungal drugs. To date, terconazole is the only triazole marketed for clinical use against fungal infections, and its uses are limited. The two leading triazole candidates under development are fluconazole and itraconazole. Both of these compounds are active orally and appear to have broader spectra of activity and less toxicity than ketoconazole. Other triazoles reviewed in this section are in earlier phases of development; therefore, it is difficult to estimate their potential value as antifungal drugs at this time. Chemical structures, proposed routes of administration, and proposed clinical uses of these compounds are listed in Table 3; terconazole, a marketed compound, is listed in Table 2.

Terconazole

Terconazole is a novel triazole ketal that was synthesized by Janssen Pharmaceutica (129). This compound represents the first triazole antifungal drug marketed for human use. Terconazole is undergoing phase II clinical trials in the United States. Terconazole is available as a 0.8% vaginal cream and pessaries and is indicated for the treatment of vaginal candidiasis (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 596, May 1987).

In vitro activity. Terconazole has broad-spectrum antifungal activity in vitro. In one study, 89% of dermatophytes, 100% of *Cryptococcus neoformans* isolates, and 60% of *Candida* species were completely or significantly inhibited by terconazole at a concentration of 10 μg/ml; in vitro activity was dependent on the medium used for the assays, however. Terconazole prevented the transformation of *C. albicans* cells into the pseudohyphal phase in vitro (322). Tolman et al. (304) demonstrated that terconazole had a broad range of in vitro antifungal activity, but that the potency varied against isolates of *C. albicans* and *Candida* species. These investigators also noted that the anticandidal potency of terconazole was enhanced when the drug was added to yeast cells undergoing mycelial formation. In an assay to test for the suppression of intracellular ATP synthesis, terconazole had no effect. Other tested triazoles also had no effect in this assay (202).

Experimental in vivo activity. Terconazole is effective in the treatment of a variety of dermatomycoses and candidiasis in experimental animal models (129, 322). In a guinea pig model, treatment with 0.5% terconazole yielded 100% cures against infection caused by *T. mentagrophytes*, and treatment with 1.0% terconazole yielded complete cures against infection caused by *M. canis*. In an experimental model of rat vaginal candidiasis, terconazole administered twice daily for 3 days as 1.0 and 0.5% creams produced cure rates of 97 and 76%, respectively. In these studies, terconazole also was effective in the treatment of experimental skin candidiasis (322).

Terconazole has been shown to have moderate activity following oral administration in experimental vaginal and skin candidiasis and in experimental dermatomycoses (322). Terconazole administered orally at 10 mg/kg cured 50% of rats with experimental vaginal candidiasis; oral administration at 40 mg/kg cured 67% of animals with experimental *M. canis* infection. Ketoconazole was superior to terconazole in each of these experiments.

Clinical studies. Although clinical studies with terconazole are limited, summary reports of several phase II clinical trials have been published in a special supplement of the journal *Gynäkolische Rundschau* (vol. 25, Suppl. 1) in 1985. These studies demonstrated the efficacy and tolerability of terconazole in the treatment of vaginal candidiasis. One double-blind study demonstrated that 0.4% terconazole cream was comparable to 1.0% clotrimazole cream in the topical treatment of vaginal candidiasis in a group of 39 pregnant and 40 nonpregnant patients (242). The compound was well tolerated and no serious side effects were reported. The relapse rates of the terconazole- and clotrimazole-treated groups were 10.3 and 17.9%, respectively. A study of similar design also demonstrated the comparable activity of terconazole cream and clotrimazole cream in the treatment of vaginal candidiasis (67). In a study of 60 patients with vaginal candidiasis, terconazole (80 mg) vaginal tablets were compared with clotrimazole (200 mg) tablets each administered once daily for 3 days or a terconazole (240 mg) tablet administered once followed by 2 days of placebo tablets (160). At 1 week after treatment, all groups had >90% cure rates. However, by 3 weeks after treatment, patients in whom terconazole had been administered once daily for 3 days had significantly greater cure rates (94%) than those receiving either the terconazole single-dose (55%) or clotrimazole three-dose (65%) therapy.

Thus, terconazole represents the triazole group of azole derivatives that is active topically against vaginal candidiasis and dermatomycoses. Although its activity is limited, this drug represents the first of a chemical class of compounds that have great promise for improved antifungal therapy.

Fluconazole

Fluconazole (UK-49,858) is an orally active triazole antifungal agent under development by Pfizer U.K. This compound has a high degree of systemic bioavailability and is being developed for once-daily oral, i.v., and topical use against systemic and superficial fungal infections (130). Phase III clinical trials in the United States are in progress, with favorable results reported to date on the treatment of several systemic fungal infections, including the successful treatment of cryptococcal meningitis in compromised patients. Fluconazole also has been reported to be active in the treatment of vaginal and cutaneous candidiasis as well as superficial fungal infections (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 917, May 1987).

In vitro activity. In general, the measurement of in vitro antifungal activity of azole derivatives is difficult in that such studies with these chemical compounds often produce irregular and diverse data that are difficult to interpret. Tests with fluconazole do not appear to produce clinically useful in vitro data under many experimental conditions; in vitro susceptibility data seldom predict in vivo efficacy. However, a few reports of in vitro activity of fluconazole have appeared in the literature. Rogers and Galgiani (243) reported that, at physiologic pH, fluconazole was 16-fold less active than ketoconazole against 35 isolates of *C. albicans* as assayed with a synthetic broth dilution susceptibility test. Marriott and Richardson (186) also noted that fluconazole was less active than ketoconazole and amphotericin B against yeasts and filamentous fungi when tested in both liquid and solid medium assays. These investigators observed that fluconazole was more active at pH 7 to 7.5 than at lower pH values when an agar dilution assay was used. Fluconazole activity was not affected by pH, however, in liquid medium assays with *C. albicans*. The reasons for these observations are unclear, but may reflect sequestration of the drug in the agar matrix. Fluconazole was active against *Candida* species and *Cryptococcus neoformans*, less active against dermatophytes, and inactive against *Aspergillus* species (186). Viability studies of three isolates of *Candida* species exposed to fluconazole demonstrated that the drug was fungistatic and not fungicidal whether tested against the yeast in stationary or early logarithmic phase (144). The fungistatic data of fluconazole were comparable to that of ketoconazole, vibunazole, and ICI 153,066.

Odds et al. (204) examined the in vitro antifungal activity of fluconazole by using four different test systems: relative inhibition factors, agar dilution susceptibility assay, effect of drug on hyphal formation of *C. albicans*, and effect of drug on ATP content of *C. albicans* spheroplasts. Fluconazole was poorly active in each of the assays, and it was less active than ketoconazole and other azole derivatives tested. In other studies, fluconazole was relatively inactive in vitro

against organisms causing phaeohyphomycoses (72) and against *Histoplasma capsulatum* (226). The generally poor in vitro activity of fluconazole, however, did not correlate with its high in vivo activity in experimental animal models of several mycoses (see below).

Experimental in vivo activity. Although fluconazole would not appear to be a useful antifungal agent if evaluated on the basis of in vitro data alone, in vivo activity of the drug appears to be quite good. Fluconazole, administered orally, is active in the treatment of a variety of systemic and superficial fungal infections, including fungal meningitis (110, 307). In one study of the efficacy of fluconazole in the treatment of experimental cryptococcal meningitis, the triazole was comparable to ketoconazole and amphotericin B in controlling cryptococcosis in mice following intransal and i.v. infection (213). Moreover, fluconazole was superior to ketoconazole and comparable to amphotericin B in controlling intracerebrally administered yeast cells of *Cryptococcus neoformans* in the same model. In a study by Troke et al. (309) fluconazole was 5- to 20-fold more active than ketoconazole in the treatment of experimental intracranial and pulmonary cryptococcosis in mice, but fluconazole was less active than amphotericin B in this study. Perfect et al. (216) compared fluconazole and itraconazole in a rabbit model of cryptococcal meningitis. Both compounds were effective in controlling the disease. In a study of experimental coccidioidal meningitis, Graybill et al. (115) treated mice that had been challenged intracerebrally with endospores of *Coccidioides immitis* with fluconazole, ketoconazole, or amphotericin B. Each drug prolonged survival of the mice and reduced the colony-forming units of fungus in brain. Mice treated orally with high-dose fluconazole, however, had a longer mean survival time than mice treated with ketoconazole; again, amphotericin B was the most effective drug.

Fluconazole also is effective in the treatment of experimental histoplasmosis and blastomycosis. Using a quantitative spleen culture technique, Polak and Dixon (226) demonstrated that fluconazole was fungicidal for cells of *H. capsulatum* in an experimental mouse model of systemic disease. In a study of experimental histoplasmosis in AKR and C57BL/6 mice, fluconazole had lower toxicity than amphotericin B with therapeutic indices of 4.3 (AKR) and 7.1 (C57BL/6) versus 2.0 for amphotericin B (161). Orally administered fluconazole was comparable in activity to amphotericin B administered intraperitoneally in the two mouse strains used in this study. In another study, daily doses (subcutaneous) of 25 and 50 mg of fluconazole per kg for 21 days in mice with experimental pulmonary blastomycosis produced 30 and 100% survival, respectively (182). Amphotericin B at 1 mg/kg per day produced 100% survival. Fluconazole failed to clear the fungus from the lungs, while amphotericin B eradicated the fungus from 66% of the survivors.

Fluconazole is active in the treatment of experimental candidiasis as well. In normal and immunosuppressed mice, fluconazole administered for 10 days was found to be significantly more active than ketoconazole against systemic infections with *C. albicans* (308). In normal mice, fluconazole administered for 30 days prolonged survival of infected mice for >90 days, and up to 60% of the animals had no detectable *C. albicans* cells in their kidneys. In immunosuppressed mice with intestinal candidiasis, feces were culture negative in >90% of the mice 3 days after treatment as compared to 62 and 23% of animals treated with amphotericin B and ketoconazole, respectively. In another study, rats infected with *C. albicans* had prolonged survival times following treatment with fluconazole, although the in vitro data were not suggestive of protection (243). Fluconazole was 20-fold more active in vivo than ketoconazole. Of importance in this study was the observation that cross-resistance between ketoconazole and fluconazole existed in vitro and in vivo with isolates of *C. albicans*. Richardson et al. (236) demonstrated that fluconazole was more effective than ketoconazole in the treatment of experimental systemic and vaginal candidiasis in mice. More recently, fluconazole was shown to penetrate into rabbit eye tissue more readily than ketoconazole or itraconazole (253). Fluconazole was effective in reducing the numbers of *C. albicans* in experimental hematogenous endophthalmitis when therapy was initiated within 24 h of infection; only ketoconazole was effective when the initiation of therapy was delayed for 7 days.

Data on the efficacy of fluconazole in the treatment of experimental aspergillosis are contradictory. In a report by Troke et al. (309), fluconazole was 5- to 20-fold more active than ketoconazole in the treatment of experimental aspergillosis in mice. Effective dose 50% endpoints ranged from 5 to 50 mg/kg against isolates of *A. fumigatus* and *Aspergillus flavus*; amphotericin B remained the most active compound in these tests (307, 309). To the contrary, Graybill (110) reported that fluconazole (up to 50 mg/kg) did not protect mice with experimental aspergillosis. Further data are required to clarify the role of fluconazole in the treatment of aspergillosis.

Although the studies are not numerous, fluconazole also has been shown to be active in the treatment of experimental tinea versicolor (307) and dermatomycoses (236, 307). In the dermatomycoses models, fluconazole was shown to be 5 to 10 times more active than ketoconazole (307).

Pharmacokinetics. In rabbits, fluconazole crossed the blood-brain barrier easily at 1 order of magnitude greater than that observed with other azole derivatives, i.e., ketoconazole, vibunazole, and itraconazole (215, 216). Fluconazole is distinctive for its excellent cerebrospinal fluid penetration. A recent pharmacokinetic study demonstrated an excellent cerebrospinal fluid to serum penetration after a single 6-mg/kg i.v. dose (C. A. Arndt, T. J. Walsh, C. L. McCully, F. M. Balis, P. A. Pizzo, and D. G. Poplack, J. Infect. Dis., in press). Scientists at Pfizer U.K. have developed a sensitive gas chromatographic technique for the detection of fluconazole in plasma and urine samples (34, 342). Using this technique, they determined that after oral and i.v. administration of fluconazole to mice, rats, dogs, and humans, bioavailability was almost complete in each species (34, 146). Peak plasma concentrations of fluconazole normalized to a 1-mg/kg oral dose were 0.7, 0.6, 1.1, and 1.4 μg/ml in mice, rats, dogs, and humans, respectively, with volume of distribution of 1.1 liters/kg in mice and 0.7 liter/kg in humans. Radiolabeled [^{14}C]fluconazole administered i.v. to mice was shown to distribute evenly in all body tissues, including the central nervous system and gastrointestinal tract. Plasma protein binding ranged from 11 to 12%, and elimination half-lives were 4.8, 4.0, 14, and 22 h in mice, rats, dogs, and humans, respectively. Renal clearance was the major route of elimination, with 70% of unchanged drug excreted in the urine of all species.

Thus, fluconazole has a pharmacokinetic profile unlike any other antifungal azole derivative. Its low molecular weight, low affinity for plasma binding, and water solubility make it readily absorbable following oral or i.v. administration, and there is no evidence for first-pass metabolism. In human studies, the bioavailability of fluconazole is linear

with oral dose, another parameter that sets this drug apart from the other antifungal azole derivatives. The long half-life of fluconazole (up to 25 h in humans) also makes this drug a prime candidate for once-daily therapy of susceptible fungal infections (34).

Clinical studies. Fluconazole is undergoing phase II and III clinical trials in several countries. Many of these data are being evaluated and analyzed at present. The clinical trial data reviewed here all were published recently in the proceedings of an antifungal telesymposium (92).

Fluconazole was evaluated in a two-center, noncomparative, open study of 43 patients with superficial mycotic infections, e.g., dermatomycoses, candidiasis, or tinea versicolor (197). Fluconazole was administered orally at 50 mg once daily for a varied number of days. All patients were clinically cured or substantially improved by the end of therapy, which ranged from 9 to 42 days; relapse of the treated infection(s) was uncommon. Fluconazole was most effective in the treatment of intertrigenous candidiasis, with 100% cure rates in 14 patients and a mean therapy duration of 9 days.

The remaining clinical studies of fluconazole reported to date all concern the treatment of infections due to *Candida* species. Brammer and Lees (33) have made an interim analysis of a multicenter study designed to evaluate the efficacy of oral fluconazole (150-mg single dose) as compared with intravaginally administered clotrimazole (200 mg daily for 3 consecutive days) tablets in the treatment of vaginal candidiasis. Both drugs performed well in week 1 of the study, producing mycological cures in >80% of the patients. At the 5- to 7-week follow-up examinations, however, fluconazole had produced 73% clinical and mycological cures as compared with 64% for the clotrimazole-treated group. Although there is not a striking difference between the two groups, the single-dose oral therapy of fluconazole is more desirable than the 3-day intravaginal course of clotrimazole therapy.

Two studies on the efficacy of fluconazole in the treatment of oropharyngeal candidiasis in compromised patients have been reported (78, 189). In one noncomparative study, fluconazole (50 mg) was administered orally once daily to a group of 63 patients with oropharyngeal candidiasis, 55 of whom tested positive for the human immunodeficiency virus antibody (78). Daily therapy ranged from 5 to 20 days and was followed by alternate-day maintenance therapy. The symptoms resolved in 37 of the treated patients within 1 week. Eradication or significant reduction in oral yeasts was observed in all treated patients during the study. No adverse reactions or minor side effects were noted. The penetration of fluconazole into the cerebrospinal fluid will likely allow its use in chronic, suppressive therapy of cryptococcal meningoencephalitis in human immunodeficiency virus patients. A recent report of a successfully treated case (76) documents this possible therapeutic use. In a noncomparative study, the efficacy of fluconazole in the treatment of oropharyngeal candidiasis in cancer patients was evaluated (189). Clinical resolution of oral candidiasis was obtained in 28 (90%) of the patients; however, negative cultures were obtained in only 16 (53%). These data are similar to those obtained in other studies with ketoconazole at a dose of 600 mg daily. Neutropenic patients were not able to eradicate the fungus following fluconazole therapy. Thus, fluconazole was effective at 50 mg/day in controlling oral candidiasis in cancer patients, but higher daily doses must be evaluated to determine whether eradication of the infecting fungus can be accomplished.

In general, fluconazole is effective for treating superficial fungal infections, including vaginal candidiasis, and for controlling oral candidiasis in compromised patients. Higher doses of fluconazole need to be evaluated in multicenter, comparative clinical trials to make more relevant decisions regarding the potential use of fluconazole in the clinic.

Toxicity and adverse reactions. In the experimental and clinical studies reported to date, fluconazole appears to be a well-tolerated, relatively nontoxic compound. In spite of the compound's solubility in water and ready penetration of even an uninflamed blood-brain barrier, fluconazole has not been reported to cause unusual or undesirable central nervous system side effects or other significant side effects. Tachibana et al. (292) summarized the known toxicological properties of fluconazole. It was less toxic than ketoconazole in several assays, including liver enzyme induction, inhibition of steroid biosynthesis, induction of fetal malformations, and teratological effects. It was not mutagenic. The authors concluded that the lesser toxicity of fluconazole in the animal models studied, in combination with its potent antifungal activity, suggests that fluconazole may have a higher margin of safety than ketoconazole.

Shaw et al. (270) summarized the effect of fluconazole on cytochrome P-450-mediated sterol synthesis and metabolism. Fluconazole had activity comparable to that of ketoconazole in the inhibition of fungal C-14 demethylase, i.e., inhibition of ergosterol synthesis. Fluconazole was significantly less potent than ketoconazole, however, in the inhibition of the mammalian enzyme, i.e., as assayed in rat liver. Studies in humans demonstrated that fluconazole, administered chronically at a therapeutic dose level, did not affect plasma testosterone concentrations or the pharmacokinetics of coadministered antipyrine or oral contraceptives. In addition, fluconazole was a more specific inhibitor of the fungal cytochrome P-450 versus mammalian cytochrome P-450-mediated reactions, including those involved in steroid biosynthesis (cholesterol, testosterone, estrogen) and drug metabolism, than other antifungal azole derivatives studied, including ketoconazole. From these data, the authors concluded that the drug would have a superior therapeutic ratio in comparison with other antifungal azole derivatives.

Itraconazole

Itraconazole (R 51,211) is an orally active triazole antifungal agent under development by Janssen Pharmaceutica (128). This agent is in phase III clinical trials in the United States for the treatment of gynecological and dermatophytic fungal infections. Phase III clinical trials for the treatment of a variety of fungal infections are in progress in Belgium, Canada, and The Netherlands. Itraconazole is being developed as an alternative to ketoconazole therapy (111). In comparison to ketoconazole, its potential advantages include less toxicity, better pharmacokinetics, and broader spectrum of antifungal activity, particularly activity in aspergillosis and sporotrichosis. Experimental and clinical data on itraconazole have been summarized recently in the proceedings of an antifungal telesymposium (92).

In vitro activity. Itraconazole was compared with ketoconazole, vibunazole, and a morpholine antifungal (Ro 14-4767/002) for in vitro antifungal activity, using an agar dilution assay. Itraconazole was found to be the most active agent against isolates of *H. capsulatum*, *A. fumigatus*, *A. flavus*, *Blastomyces dermatitidis*, and *Cryptococcus neoformans* (80). Van Cutsem et al. (320) summarized the in vitro activity of itraconazole against 2,813 strains of fungi. They

demonstrated that itraconazole had potent, broad-spectrum antifungal activity. RIF values for itraconazole against isolates of *Candida* species, *Aspergillus* species, and dermatophytes all were superior to those of ketoconazole, indicating that itraconazole may be a more active compound (208). In one study, itraconazole was 100 times more potent than ketoconazole in inhibiting the growth of *A. fumigatus* and *Aspergillus niger* (184). Itraconazole totally inhibited the growth of *A. fumigatus* within 24 h at a concentration of 5×10^{-8} M; ketoconazole exerted the same activity at 5×10^{-6} M. Moreover, itraconazole induced irreversible structural damage to a variety of fungi; the antifungal activity was dependent upon the species tested, the time of incubation, and morphogenetic form of the fungus tested (30). Irreversible structural damage due to itraconazole was achieved at concentrations comparable to that required for ketoconazole (*C. albicans* and *C. neoformans*), at concentrations 10- to 100-fold lower (*Pityrosporum ovale*, *T. rubrum*, *Paracoccidioides brasiliensis*), or at concentrations 100-fold lower (*A. fumigatus*). Itraconazole also has been shown to be synergistic in vitro with 5-fluorocytosine against isolates of *A. fumigatus* and *A. flavus* (156).

Experimental in vivo activity. Itraconazole is a potent agent for the oral and parenteral treatment of a wide variety of experimental systemic and superficial fungal infections. Van Cutsem et al. (319, 320) summarized several "in house" studies of the efficacy of itraconazole in animal models of fungal infections. Overall, it was more active than ketoconazole in treating most of the experimental infections. At doses four to eight times lower than ketoconazole, itraconazole had similar activity in the treatment of experimental dermatophytoses and both superficial and systemic candidiasis. Disseminated dermatophytoses were treated more effectively with itraconazole than with ketoconazole. Itraconazole administered orally or parenterally was equally effective in treating experimental systemic candidiasis. Topically administered itraconazole was more effective than griseofulvin in the treatment of experimental dermatophytoses and cutaneous candidiasis. Of prime significance were the observations that orally administered itraconazole was effective in the treatment of experimental aspergillosis, meningeal cryptococcosis, generalized cryptococcosis, histoplasmosis, and sporotrichosis. The drug's activity against aspergillosis, sporotrichosis, and meningeal cryptococcosis is noteworthy, as successful treatment of these diseases would represent an expanded panel of activity in comparison to ketoconazole.

Van Cutsem et al. (321) first reported the activity of itraconazole against experimental aspergillosis. Oral administration of itraconazole to mice with experimental acute, systemic aspergillosis prolonged the survival of the animals and cleared the fungus from the organs of 6 of 30 of the mice. Graybill and Ahrens (111) confirmed the observations of Van Cutsem et al. (321) in a mouse model. These investigators noted, however, that amphotericin B was more effective than itraconazole in prolonging survival in infected/treated mice. They also noted that itraconazole was effective in prolonging survival only after infection was initiated by the i.v. route; the drug was not effective in treating the mice following intranasal infection with *A. fumigatus*. Finally, itraconazole was effective in reducing colony-forming units of the fungus in the kidneys of mice with experimental renal aspergillosis (2).

Itraconazole is effective in the treatment of experimental vaginal candidiasis in rats (279) and systemic candidiasis in guinea pigs (316) and rats (353). In vaginal candidiasis, itraconazole was superior to ketoconazole at all doses ranging from 1.0 to 7.5 mg/kg. Moreover, a single 25-mg/kg dose was as effective as five daily 5-mg/kg doses, suggesting that this drug may be useful for once-daily, short-term therapy. In studies in guinea pigs and rats, systemic candidiasis was suppressed by itraconazole administered once daily orally at a concentration of 2.5 mg/kg or less.

Pharmacokinetics. Summaries of the pharmacokinetic studies of itraconazole in animals and humans recently have been published by Heykants et al. (133) and Van Cauteren et al. (314). Itraconazole is an extremely weak base, lipophilic, and soluble only in a few solvent systems. Following oral dosing, it was characterized by good absorption, extensive tissue distribution with tissue concentrations several times higher than in plasma, a relatively long elimination half-life (up to 24 h in humans), and biotransformation to several antifungally inactive metabolites (133, 341). Penetration across the blood-brain barrier was minimal (215). In comparison to ketoconazole, itraconazole was 20 times higher in volume of distribution and it had a 35-fold-longer elimination half-life, whereas its clearance via urine and feces was twice lower. Itraconazole is not excreted as unchanged drug in the urine, and metabolites that are not antifungally active have been found in the urine and bile. These data suggest that the parent compound is the active component (133).

Itraconazole binds strongly to plasma proteins, i.e., 99.8%, mainly to albumin. Studies have shown that, even though plasma concentrations of itraconazole are low (<1.0 μg/ml), tissue concentrations of the drug are severalfold higher and bioavailability is good. Preliminary studies suggested that no dose adjustments of itraconazole are required in patients with renal or hepatic insufficiency (133). The long half-life and pronounced steady state of this drug suggest that once-daily administration will be sufficient therapy for most fungal infections. The poor penetration of the drug to the brain suggests that itraconazole will not be effective for the treatment of fungal meningitis.

Clinical studies. Itraconazole is an effective agent in the treatment of superficial and systemic fungal infections. Several of the clinical trials that have been completed were reported in a special issue of *Reviews of Infectious Diseases* (January-February 1987, vol. 9, Suppl. 1). The reader is referred to this special issue for more complete information. Only a brief overview will be presented here.

Cauwenbergh and De Doncker (49, 50) have estimated that more than 5,000 patients have been treated or are presently undergoing therapy with itraconazole. Overall, itraconazole has proven to be most effective against cases of paracoccidioidomycosis (95% effective), blastomycosis (91%), sporotrichosis (86%), noninvasive aspergillosis (83%), and histoplasmosis (81%). Mean durations of therapy ranged from 1 to 22 months at daily concentrations of 50 to 400 mg of drug. Itraconazole was least active against invasive aspergillosis (62%), meningeal cryptococcosis (50%), and aspergilloma (44%).

In specific studies, Negroni et al. (199) reported clinical cures or improvements in all of 25 patients with paracoccidioidomycosis who had been treated orally with itraconazole at 50 mg/day for 6 months. Twelve of 17 patients with histoplasmosis who had received 100 mg of itraconazole once daily were clinically cured. Four patients improved and one did not respond. Restrepo et al. (235) reported that itraconazole administered orally at 100 mg/day for 6 months was as effective as ketoconazole in producing clinical improvements and cures among the 16 patients treated. No adverse reactions were noted. Borelli (29) reported that

itraconazole was effective in the treatment of patients with paracoccidioidomycosis, sporotrichosis, and chromomycosis caused by *Cladosporium carrionii*. Improvement in mycetoma caused by *Madurella grisea* also was obtained. Similarly, encouraging data on the activity of itraconazole in the treatment of aspergillosis, blastomycosis, candidiasis (systemic and mucocutaneous), chromomycosis, coccidioidomycosis, and sporotrichosis have been reported by several investigators (77, 100, 170, 217). In one study of particular interest, itraconazole was found to be more active than ketoconazole in the antifungal prophylaxis of patients with severe granulocytopenia (306). Itraconazole was particularly active in preventing infections due to *Aspergillus* species.

Itraconazole also is active in the treatment of superficial fungal infections, including dermatomycoses (66, 122, 200, 214, 252) tinea versicolor (68, 81, 214, 252), cutaneous and oral candidiasis (122, 252), and vaginal candidiasis (45, 251, 252). In general, itraconazole was well tolerated, although reports of minor side effects such as nausea, headache, diarrhea, and fatigue were reported in a small percentage of the patients. In cases of dermatomycoses, 2 weeks of therapy produced substantial clinical improvement or cures in large percentages of the patients; 4 weeks of therapy improved clinical responses further. Daily oral doses of 50 mg of itraconazole were not adequate for the treatment of superficial mycoses in one study (252). Daily doses of 100 mg of itraconazole appeared to be a more effective therapeutic regimen.

Itraconazole is effective in the treatment of tinea versicolor (81, 194) and in causing ultrastructural changes in *Malassezia furfur* (98), the etiologic agent of tinea versicolor. In one study, cure rates of 95 and 75% were obtained in patient groups that had received oral itraconazole for 5 consecutive days at doses of 200 and 100 mg, respectively (81). Another study also demonstrated the efficacy of itraconazole administered once or twice daily at 100 mg per dose in producing clinical cures in patients with tinea versicolor (194). Skin samples were culture negative by day 18 of the study.

In the treatment of vaginal candidiasis, itraconazole produced clinical cures, but the percent cures (55 to 75%) were less than those reported for topical antifungal agents (80 to 90%) (251). Further studies will be required to determine the optimal dose and length of therapy in the oral treatment of vaginal candidiasis.

Most of these studies were open and noncomparative (in relation to other drugs) in design. Comparative studies will have to be done to evaluate properly the clinical efficacy of using an orally administered drug for the treatment of superficial (cutaneous, oral, or vaginal) fungal infections.

Toxicity and adverse reactions. Summaries of the toxicity and adverse reactions of itraconazole recently have been reviewed by De Coster et al. (64), Van Cauteren et al. (314), and Vanden Bossche et al. (326, 327). Subchronic toxicity studies in experimental animals demonstrated that the potential target organs for toxicity are the gastrointestinal tract, the mononuclear phagocytizing system, and the adrenals, although the activity observed was less than that seen with ketoconazole (313, 314). Repeated oral dosing in animals at 10 mg/kg did not produce any significant toxic effects; dosing at higher levels produced dose-dependent toxic effects. Itraconazole was not mutagenic. Embryotoxicity and teratogenicity studies in rats demonstrated that itraconazole at 10 mg/kg was not toxic. However, at 40 and 160 mg/kg dose-dependent maternal toxicity was observed; this was associated with embryotoxic and teratogenic effects as well. In rabbits, no dose effects at concentrations up to 80 mg/kg were observed (313, 314). Thus, itraconazole appears to be a relatively well-tolerated drug in laboratory animals at concentrations that are therapeutically useful. Evidence for toxicity at concentrations severalfold above therapeutic concentrations has been observed.

The effects of itraconazole on the pituitary-testicular-adrenal axis have been studied extensively (64, 326, 327). Daily administration of itraconazole at 100 mg for 1 month in human volunteers revealed that basal or luteinizing hormone-releasing hormone-stimulated plasma prolactin, follicle-stimulating hormone, and luteinizing hormone concentrations were not affected. Also unaffected in both human and animal studies were basal or adrenocorticotropin-stimulated glucocorticoid production or mineralocorticoids. These investigators also noted no changes in plasma androgens in animal models, human volunteers, and human patients (64). Thus, unlike ketoconazole, itraconazole does not appear to be associated with changes in pituitary-testicular-adrenal function.

Vanden Bossche et al. (326, 327) determined that itraconazole is a highly selective inhibitor of cytochrome P-450-dependent ergosterol biosynthesis. These authors hypothesized that itraconazole has a high affinity for the apoprotein of fungal cytochrome P-450 involved in the C-14 demethylation of lanosterol. The affinity is sufficiently greater than that of ketoconazole; thus, itraconazole has the distinct advantage of not significantly affecting mammalian steroid biosynthesis. Thus, itraconazole is far more selective for fungal enzymes than for mammalian enzymes. This characteristic in combination with the improved potency and broader spectrum of antifungal activity make itraconazole an antifungal compound with an improved margin of safety and efficacy in comparison to ketoconazole.

Vibunazole

Vibunazole (BAY-n-7133) is an antifungal triazole derivative with oral and topical activity that is under development by Bayer AG (M. Plempel, Pharma Rep. no. 9492, Bayer AG Institute for Chemotherapy, Wuppertal, Federal Republic of Germany, 1980). Vibunazole is presently undergoing phase III clinical trials in the Federal Republic of Germany and phase I clinical trials in Belgium and The Netherlands (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m 302, May 1986).

In vitro activity. Vibunazole has broad-spectrum antifungal activity in vitro. Recent studies have demonstrated that the spectrum of vibunazole was comparable to those of ketoconazole and miconazole (93–95). Vibunazole demonstrated activity against *Fusarium* species, but lacked clinically significant activity against isolates of *Aspergillus* species, *S. schenckii*, and *Scopulariopsis* species (94, 95). Yamaguchi et al. (346) also noted broad-spectrum activity with MICs against most pathogenic yeasts and fungi ranging from 0.04 to 10 μg/ml in an agar dilution assay; these investigators also noted that vibunazole had poor or no activity against *Aspergillus* species, *Zygomycetes* species, and *S. schenckii*. In another in vitro study, vibunazole was found to be the least active of four antifungal drugs tested against a panel of pathogenic yeasts and filamentous fungi, including dermatophytes (266). In vitro activity of vibunazole, as with many of the antifungal azole derivatives, is affected by media constituents and pH (139, 346). RIF values for isolates of *Candida* species, *Aspergillus* species, and dermatophytes were 59, 56, and 24%, respectively (208), suggesting that this compound has potential activity in vivo.

Vibunazole appears to be fungistatic (20, 137). Using a two-step cultivation technique, Rumler et al. (247) demonstrated that vibunazole, as well as several other antifungal agents, required less than 1 h of contact time with fungal cells to inhibit growth. Thus, the concentration of vibunazole in the infected area may be more significant clinically than the plasma levels of the compound.

Pharmacokinetics. Studies in a variety of experimental animals have shown that vibunazole is absorbed following oral administration (237). Mice administered vibunazole orally at a concentration of 25 mg/kg had peak plasma levels of 14 to 16 mg/liter, with a first-dose half-life of 4.7 h. However, plasma half-life decreased to 1.2 h after the fifth dose, suggesting enzyme induction by the drug. Enzyme induction following multiple dosing was demonstrated in beagle dogs, but not rhesus monkeys. In dogs, absolute bioavailability of vibunazole was 70%. Vibunazole, as well as ketoconazole, penetrates the blood-brain barrier poorly in experimental rabbits; inflamed meninges did not enhance the penetration of vibunazole into the cerebrospinal fluid (215). Thus, vibunazole may not be an effective drug for the treatment of fungal meningitis.

In humans, plasma concentrations of vibunazole following oral administration of a 400-mg tablet denoted a one-compartment, open model with first-order absorption (329). The mean peak plasma concentration was 2.76 μg/ml, with an elimination half-life of 2 h 22 min.

Experimental in vivo activity. In a number of experimental animal models of fungal infections, vibunazole was an effective therapeutic agent. Of particular interest are two reports that vibunazole was effective in the treatment of experimental aspergillosis (2, 113). In one study of systemic aspergillosis following i.v. or intranasal inoculation, vibunazole prolonged the survival of infected, treated mice and reduced the number of colony-forming units of *A. fumigatus* from lungs; ketoconazole was not efficacious in this model (113). In a model of experimental renal aspergillosis, vibunazole was effective in reducing colony-forming units in affected kidneys; itraconazole and amphotericin B also were effective, while ketoconazole, miconazole, and 5-fluorocytosine were ineffective (2).

The efficacy of vibunazole against other experimental systemic fungal infections also has been tested. In an experimental model of coccidioidomycosis in mice, vibunazole was as active as ketoconazole in controlling colony-forming units in cultured organs following 30 days of i.v. administration (138). Both drugs were fungistatic in this model. However, Levine (177) noted that vibunazole was not as effective as ketoconazole in the treatment of experimental acute, disseminated, or chronic coccidioidomycosis in mice. In an experimental model of murine blastomycosis, vibunazole was less effective than ketoconazole, amphotericin B, ICI 153,066, and *N*-D-ornithylamphotericin methyl ester in the treatment of the pulmonary/systemic infection (173). In an experimental mouse model of cryptococcosis, vibunazole was effective, but less active than ketoconazole and ICI 153,066 in prolonging survival and reducing colony-forming units of evaluated tissues (112). In an experimental model of systemic paracoccidioidomycosis, vibunazole was less active than ketoconazole and other antifungal drugs in controlling this acute, disseminated infection (172). Plempel (219) determined that vibunazole was as effective or more effective than ketoconazole in the oral treatment of experimental systemic infections of *A. fumigatus*, *C. albicans*, and *Cryptococcus neoformans*. However, Lefler and Stevens (175) observed that vibunazole administered orally twice daily for 1 month was not effective in the treatment of experimental systemic candidiasis in mice. The authors suggested that the pharmacokinetics of this dose regimen may not have been suitable for effective therapy. In an experimental rat model of vaginal candidiasis, vibunazole was shown to have the least efficacy in comparison to ketoconazole and another experimental imidazole, BAY-l-9139 (278). However, Plempel (219) observed good activity with vibunazole in the parenteral treatment of experimental systemic candidiasis in the mouse and in the topical treatment of experimental trichophytosis in guinea pigs.

The experimental data on vibunazole are varied, some studies showing good activity and others demonstrating poor activity against a variety of systemic and superficial fungal infections. The most significant data come from studies that demonstrate the potency of vibunazole against experimental aspergillosis following oral administration. This fungal infection is refractory to most currently available antifungal drugs. Reports on the clinical trials are pending. Until those data are made available, the future of vibunazole remains uncertain.

Alteconazole

Alteconazole (LU-40797) is a triazole that is under development by Knoll Pharmaceuticals as both an orally and topically active antifungal drug. The compound is presently in the pharmacology phase of development. MICs were reported to be 2.0, <0.125, and 1.0 μg/ml against *Microsporum ferruginium*, *C. albicans*, and *Mucor pusilis*, respectively. In mice, alteconazole administered orally for 4 days at 100 mg/kg produced greater antifungal activity than the reference compounds assayed; the fungal infection and reference compounds were not listed. In a rat model of experimental vaginal candidiasis, alteconazole was active following both oral and topical administration. If development continues, alteconazole may be indicated in the treatment of superficial mycoses, dermatomycoses, and systemic mycoses (Sochynsky and Hardcastle [ed.], Pharma Projects, p. m641, May 1987).

ICI 195,739

ICI 195,739 (Imperial Chemical Industries, Alderly Park, England) is a recently discovered, novel 3'-tetrafluoropropoxy styryl-substituted bis-triazole tertiary alcohol that has potent antifungal activity in experimental animal models following oral administration (R. A. Fromtling, Drugs Future, in press).

Pharmacokinetics and mode of action. In a pharmacokinetic study in BALB/cBYJ male mice, a single dose of ICI 195,739 at 50 mg administered orally produced peak serum concentrations of 17.5 μg/ml at 12 h postdosing, with a half-life of 48 h. Daily dosing produced a steady state by day 21, with peak serum concentrations of 21 μg/ml at 8 h postdosing, a trough of 19.5 μg/ml, and a serum half-life greatly in excess of 48 h (R. M. Tucker, E. Brummer, L. Hanson, and D. Stevens, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 779, 1987).

ICI 195,739 reduces ergosterol biosynthesis by inhibiting sterol C-14 demethylation, resulting in the accumulation of methylated sterols (K. Barrett-Bee, J. Lees, J. Campbell, P. Pinder, and L. Newboult, First Int. Conf. Drug Res. Immunol. Infect. Dis. Antifungal Drugs: Synthesis, Preclin. Clin. Eval., abstr. no. 17, 1987; K. Barrett-Bee, J. Lees, J. Campbell, P. Pinder, and L. Newboult, Proc. N.Y. Acad.

Sci., in press). This is similar to other antifungal azole derivatives; however, the inhibition of ergosterol synthesis by ICI 195,739 occurs at drug concentrations that are much less than those that induce a reduction in cholesterol biosynthesis, suggesting that this compound will not adversely affect mammalian enzyme systems. Inhibition is of type II binding and is noncompetitive in regard to substrate. ICI 195,739 penetrates whole cells of *C. albicans* much more effectively than either ketoconazole or fluconazole. Due to this apparent absence of a permeability barrier to the compound, ketoconazole-resistant fungi (when resistance is due to reduced uptake of drug by the fungus) are more susceptible to ICI 195,739. ICI 195,739 also is a poor inhibitor of human placental aromatase and other human steroid biosynthetic enzymes; thus, this compound may have an improved safety profile in regard to alterations in human steroid synthesis pathways (Barrett-Bee et al., in press).

Experimental in vivo activity. ICI 195,739 is active against experimental *B. dermatitidis* infection in mice (Tucker et al., 27th ICAAC). Among five isolates of *B. dermatitidis*, the in vitro MICs were ≤0.125 and 0.25 μg/ml for three and two isolates, respectively. The in vitro minimum fungicidal concentrations were ≤0.125, 0.25, and 0.5 μg/ml for two, one, and two isolates, respectively (Tucker et al., 27th ICAAC). Three days after an intranasal inoculation of *B. dermatitidis* yeast cells, ICI 195,739 was administered orally once daily for 21 days at doses of 2, 10, 50, and 100 mg/kg per day. Ketoconazole was administered orally twice daily in doses up to 100 mg/kg per day. Sixty days after infection, all infected mice were alive in the groups treated with ICI 195,739 at doses of 10, 50, and 100 mg/kg per day; the fungus had been eliminated from all mice in the 50- and 100-mg/kg per day groups and in 9 of 10 mice in the 10-mg/kg per day group. Thus, ICI 195,739 is fungicidal against *B. dermatitidis* both in vitro and in vivo; the drug was ≥50 times more active in vivo than ketoconazole (Tucker et al., 27th ICAAC). This is the first azole derivative to have produced biocure in this model.

ICI 195,739 is more potent than ketoconazole, itraconazole, and fluconazole in the treatment of experimental intestinal candidiasis in infant mice. Daily oral doses of ICI 195,739 at 0.5 mg/kg eliminated *C. albicans* from the gut of infant mice at the same rate as ketoconazole, itraconazole, and fluconazole at doses of 250, 5, and 2.5 mg/kg, respectively (J. F. Ryley, S. McGregor, and R. G. Wilson, First Int. Conf. Drug Res. Immunol. Infect. Dis. Antifungal Drugs: Synthesis, Preclin. Clin. Eval., abstr. no. 22, 1987; J. F. Ryley, S. McGregor, and R. G. Wilson, Proc. N.Y. Acad. Sci., in press; J. F. Ryley, S. McGregor, and R. G. Wilson, Program Abstr. 27th Intersci. Conf. Antimicrob. Agents Chemother., abstr. no. 978, 1987).

ICI 195,739, dosed once daily for 5 days at 1.0 mg/kg cured vaginal candidiasis in mouse and rat models. Minimum dose levels for other drugs were as follows: ketoconazole, 25 mg/kg in mice and 10 mg/kg in rats; itraconazole, 25 mg/kg in mice and 1.0 mg/kg in rats; fluconazole, 2.5 mg/kg in mice and 1.0 mg/kg in rats (Ryley et al., 27th ICAAC). The data suggest that ICI 195,739 may be suitable for single-dose therapy in the treatment of vaginal candidiasis. ICI 195,739 was more active than ketoconazole, fluconazole, and amphotericin B in prolonging life in a mouse model of systemic candidiasis. Daily oral dosing ranged from 3 to 90 days. Relapses of infection occurred, however, when ICI 195,739 dosing was discontinued after 30 days, but not after 90 days (Ryley et al., in press; Ryley et al., 27th ICAAC), suggesting that this compound may be fungistatic under certain experimental conditions. ICI 195,739 also prolonged survival of mice experimentally infected with isolates of *Cryptococcus neoformans* and *A. fumigatus* (Ryley et al., in press; Ryley et al., 27th ICAAC). Following daily oral dosing for 21 days, ICI 195,739 was more active than fluconazole and amphotericin B in prolonging survival of mice infected with *Cryptococcus neoformans*; ICI 195,739 at 25 and 50 mg/kg was more active than fluconazole at 100 mg/kg; ICI 195,739 at 50 mg/kg was more active than amphotericin B at 6 mg/kg. In experimental aspergillosis, ICI 195,739 at 10, 25, and 50 mg/kg was more active than ketoconazole at 100 mg/kg and amphotericin B at 6 mg/kg in prolonging survival of mice treated daily for 21 days. ICI 195,739 at 50 mg/kg was marginally more active than fluconazole at 100 mg/kg in this model.

ICI 195,739 is more effective than ketoconazole, itraconazole, fluconazole, griseofulvin, and terbinafine in controlling dermatophytic infections caused by *Trichophyton quinckeanum* in mice and *T. mentagrophytes* in guinea pigs. Minimum treatment doses (milligrams per kilogram, six doses) of ICI 195,739 against *T. quinckeanum* infection were 5 to 25 times lower than those of ketoconazole, itraconazole, and fluconazole (Ryley et al., 27th ICAAC). Against *T. mentagrophytes* infections, ICI 195,739 at 5 mg/kg satisfactorily controlled the infection; comparable control was obtained with ketoconazole at 100 mg/kg, fluconazole at 25 mg/kg, and griseofulvin or terbinafine at 10 to 25 mg/kg. A topical formulation containing 0.3% ICI 195,739 was comparable to proprietary formulations containing 1 to 2% of active antifungal compound in the treatment of dermatophytic infections.

In addition to antifungal activity, ICI 195,739 also has potent activity against experimental *Trypanosoma cruzi* infection in mice (Ryley et al., 27th ICAAC). Daily oral doses of 10 and 100 mg of ICI 195,739 per kg administered on days 10 to 45 after infection prevented mortality and yielded cures in 18 of 19 and in 18 of 18 mice, respectively. In mice, ICI 195,739 is slightly active against *Plasmodium berghei* infection but inactive against infections caused by *Trypanosoma rhodesiense*, *Trypanosoma congolense*, or *Trypanosoma vivax*. No data are available on the activity of ICI 195,739 against bacteria.

In conclusion, ICI 195,739 is a new triazole antifungal compound with broad-spectrum activity and potency. In experimental models of superficial and systemic fungal infections it is superior to antifungal azole derivatives presently available on the market or under development. The relative potency of this compound in experimental animal studies suggests that a daily dose of 10 to 50 mg/day in humans may prove to be efficaceous in the treatment of a wide variety of fungal infections (Ryley et al., in press).

PROPOSED MODES OF ACTION OF ANTIFUNGAL AZOLE DERIVATIVES

The elucidation of the mode(s) and site(s) of action of antifungal azole derivatives has been and continues to be an active and rapidly progressing area of investigation. At present, the specific ways in which the antifungal imidazoles and triazoles affect fungal cells have not been characterized. There is a growing body of evidence that the primary mode of action of these antifungal drugs is the inhibition of ergosterol biosynthesis in the cytoplasmic membrane of fungi, resulting in the accumulation of lanosterol or other sterol intermediates (25, 290, 325). Vanden Bossche and co-workers (325–327) and other investigators (186, 270) have demonstrated with a number of antifungal azole derivatives

that these compounds affect cytochrome P-450 involved in the 14α-demethylation of lanosterol. Fluconazole and itraconazole are more selective for the fungal cytochrome P-450 isozymes than is ketoconazole; thus, mammalian physiology is less seriously disturbed by the newer triazoles as compared to the imidazole ketoconazole. Inhibition of ergosterol biosynthesis leads to disorganization of the fungal plasma membrane. Several studies have demonstrated that plasma membrane physiology and function are adversely affected by relatively low concentrations of azole derivatives that lead to changes in permeability and transport function (325). Membrane damage subsequently leads to metabolic imbalances that result in the inhibition of fungal cell growth or eventual death of the cell or both. This primary antifungal activity of inhibition of cell membrane biosynthesis tends to be a fungistatic rather than a fungicidal action. In general, antifungal azole derivatives require some host immune response to complete the elimination of the invading fungus. This fungistatic activity is one reason why most azole derivatives require long terms of therapy for treatment of the more severe systemic infections and do not work well in immunocompromised patients.

Less well understood are the secondary effects of the antifungal azole derivatives. Varied test conditions by different groups of investigators have produced confusing data concerning the fungistatic versus fungicidal activity in this class of antifungal drugs (173, 289, 290). Sud and Feingold (289, 290) demonstrated that both miconazole and clotrimazole exerted direct physicochemical cell membrane damage on yeast cells that was a lethal event; interestingly, ketoconazole did not demonstrate lethal activity in this assay. Studies by Cope (54) and Beggs (15) both demonstrated direct damage to fungal cell membranes as measured by the release of potassium ions from cells of *C. albicans* and *C. parapsilosis* exposed to high concentrations of miconazole. Bifonazole also has been reported to exert direct cell membrane damage to cells of *C. albicans* and *Torulopsis glabrata* (11).

Antifungal azole derivatives also may affect fungal respiration. Sud and Feingold (290) discovered that the fungistatic potentials of miconazole and clotrimazole were abrogated in reduced oxygen tensions. Miconazole also has been shown to adversely affect cytochrome and peroxidase activity in cells of *C. albicans* and *Saccharomyces cerevisiae* (69). Ketoconazole blocks the transport of electrons in the respiratory chain of *C. albicans* (273, 311).

The data published to date suggest that there are at least two distinct mechanisms of azole derivative antifungal action (21). The first mechanism is physicochemical: this is dependent on the growth phase of the fungus, requires high concentrations of drug, is a fungicidal event, and is not common to all azole derivatives. The second mechanism is metabolic: this activity occurs at lower concentrations of drug, is a fungistatic event, and is generally common to all azole derivatives. Clinically, most antifungal azole derivatives are fungistatic drugs; reports of fungicidal activity are largely from in vitro studies that do not correlate well with clinical reality.

In conclusion, much remains to be learned about the mode(s) and site(s) of action of the antifungal azole derivatives. Serious questions presently are under investigation by a number of research groups. One subject that requires additional investigation is the emergence of azole-resistant fungal isolates (249). The mechanisms that lead to this resistance must be elucidated. Definitive answers should be forthcoming.

CONCLUSION

This overview puts into perspective many of the antifungal azole derivatives that have been marketed for clinical use and those that presently are under development and evaluation. There is no question that new, safer, and more effective antifungal drugs are needed to satisfy the increasing needs of patients afflicted with fungal infections. Ketoconazole has been the standard for a number of years among the azole derivatives, but the triazoles fluconazole and itraconazole may be superior antifungal compounds in that they are more potent and less toxic and have a broader spectrum of activity. These two compounds may represent the next major step forward in the development of more potent antifungal drugs. A moderate selection of topically active antifungal azole derivatives also is available for use, and new ones are presently being developed and evaluated.

In essence, we cannot continue to rely on antifungal drugs developed years or decades ago; we must continue to search for newer, safer, more effective chemotherapeutic agents. Some of the compounds described in this overview may contribute to the slow, but steady evolution of improved antifungal drugs.

ACKNOWLEDGMENTS

I am greatly indebted to Allyson Houck and Susan Bach of Merck Information Services for their comprehensive literature searches.

LITERATURE CITED

1. **Abruzzo, G. K., D. M. Giltinan, T. P. Capizzi, and R. A. Fromtling.** 1986. Influence of six antifungal agents on the chemiluminescence response of mouse spleen cells. Antimicrob. Agents Chemother. **29**:602–607.
2. **Ackerbauer, H., J. G. Meingassner, and H. Mieth.** 1985. Experimentelle renale Infektionen der Maus mit *Aspergillus fumigatus*: ein chemotherapeutisches Modell einer Organmykose. Mykosen **28**:244–250.
3. **Ainsworth, G. C.** 1956. Agostino Bassi, 1773–1856. Nature (London) **177**:255–257.
4. **Alexander, J., J. Cornelissen, L. Debrabandere, H. L. Timmermans, E. Vandeputte, A. Van Waes, and E. Van Waes-Van de Velde.** 1972. Miconazole (R 14899) in the treatment of vaginal candidosis. A multicentre trial in gynaecological practice. Eur. J. Obstet. Gynecol. **2**:65–70.
5. **Alford, R. H., and B. B. Cartwright.** 1983. Comparison of ketoconazole and amphotericin B in interference with thymidine uptake by and blastogenesis of lymphocytes stimulated with *Histoplasma capsulatum* antigens. Antimicrob. Agents Chemother. **24**:575–578.
6. **Amery, W. K., R. De Coster, and I. Caers.** 1986. Ketoconazole: from an antimycotic to a drug for prostate cancer. Drug Dev. Res. **8**:299–307.
7. **Ansehn, S., and L. Nilsson.** 1984. Direct membrane-damaging effect of ketoconazole and tioconazole on *Candida albicans* demonstrated by bioluminescent assay of ATP. Antimicrob. Agents Chemother. **26**:22–25.
8. **Artner, J., and G. Fuchs.** 1983. Open studies of the efficacy, tolerance, systemic absorption and vaginal persistence following single application of tioconazole ointment in the treatment of patients with vaginal candidiasis. Gynäkol. Rundsch. **23**(Suppl. 1):12–19.
9. **Athow-Frost, T. A., K. Freeman, T. A. Mann, R. Marks, D. Vollum, and A. F. Warin.** 1986. Clinical evaluation of fenticonazole cream in cutaneous fungal infections: a comparison with miconazole cream. Curr. Med. Res. Opin. **10**:107–116.
10. **Balbi, C., M. D'Ajello, and G. C. Balbi.** 1986. Treatment with ketoconazole in diabetic patients with vaginal candidiasis. Drugs Exp. Clin. Res. **12**:413–414.
11. **Barug, D., and C. De Groot.** 1983. Microscopic studies of *Candida albicans* and *Torulopsis glabrata* after *in vitro* treat-

ment with bifonazole. Arneim. Forsch. 33:538–545.
12. **Barug, D., C. De Groot, and R. A. Samson.** 1987. Morphology and ultrastructure of *Candida albicans* after *in vitro* treatment with bifonazole, p. 353–368. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
13. **Bastide, M., S. Jouvert, and M. J. Bastide.** 1982. A comparison of the effects of several antifungal imidazole derivatives and polyenes on *Candida albicans*: an ultrastructural study by scanning electron microscopy. Can. J. Microbiol. 28:1119–1126.
14. **Baxter, J. G., C. Brass, J. L. Schentag, and R. L. Slaughter.** 1986. Pharmacokinetics of ketoconazole administered intravenously to dogs and orally as tablet and solution to humans and dogs. J. Pharm. Sci. 75:443–447.
15. **Beggs, W. H.** 1983. Comparison of miconazole- and ketoconazole-induced release of K^+ from *Candida* species. J. Antimicrob. Chemother. 11:381–383.
16. **Beggs, W. H.** 1983. The effects of antifungal imidazoles on resting cells of *Candida parapsilosis*. IRCS Med. Sci. 11:677.
17. **Beggs, W. H.** 1984. Fungicidal activity of tioconazole in relation to growth phase of *Candida albicans* and *Candida parapsilosis*. Antimicrob. Agents Chemother. 26:699–701.
18. **Beggs, W. H.** 1985. Influence of growth phase on the susceptibility of *Candida albicans* to butoconazole, oxiconazole and sulconazole. J. Antimicrob. Chemother. 16:397–399.
19. **Beggs, W. H.** 1987. Rapid fungicidal action of tioconazole and miconazole. Mycopathologia 97:187–188.
20. **Beggs, W. H., and C. E. Hughes.** 1986. Irrelevance of growth phase with respect to the Bay n 7133 and ICI 153,066 susceptibilities of *Candida albicans*. Diagn. Microb. Infect. Dis. 4:83–86.
21. **Beggs, W. H., and C. E. Hughes.** 1987. Exploitation of the direct cell damaging action of antifungal azoles. Diagn. Microb. Infect. Dis. 6:1–3.
22. **Benijts, G., M. Vignalli, and S. Stettendorf.** 1980. Three-day therapy of vaginal candidiasis with clotrimazole vaginal tablets and econazole ovules: a multicentre comparative study. Curr. Med. Res. Opin. 7:55–61.
23. **Bennett, J. E.** 1981. Miconazole in cryptococcosis and systemic candidiasis: a word of caution. Ann. Intern. Med. 94: 708–709.
24. **Berg, D., K.-H. Büchel, M. Plempel, and E. Regel.** 1987. Biochemical characteristics of bifonazole, p. 313–334. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
25. **Berg, D., E. Regel, H. E. Harenberg, and M. Plempel.** 1984. Bifonazole and clotrimazole. Their mode of action and the possible reason for the fungicidal behavior of bifonazole. Arneim. Forsch. 34:139–146.
26. **Bergan, T., and M. Vangdal.** 1983. *In vitro* activity of antifungal agents against yeast species. Chemotherapy (Basel) 29:104–110.
27. **Best, T. R., J. K. Jenkins, F. Y. Murphy, S. A. Nicks, K. L. Bussel, and D. L. Vesely.** 1987. Persistent adrenal insufficiency secondary to low-dose ketoconazole therapy. Am. J. Med. 82:676–680.
28. **Boelaert, J., R. Daneels, J. Van Landuyt, and J. Symoens.** 1976. Miconazole plasma levels in healthy subjects and in patients with impaired renal function, p. 165–169. *In* J. D. Williams and A. M. Geddes (ed.), Chemotherapy, vol. 6. Plenum Publishing Corp., New York.
29. **Borelli, D.** 1987. A clinical trial of itraconazole in the treatment of deep mycoses and leishmaniasis. Rev. Infect. Dis. 9(Suppl. 1):64–70.
30. **Borgers, M., and M.-A. Van de Ven.** 1987. Degenerative changes in fungi after itraconazole treatment. Rev. Infect. Dis. 9(Suppl. 1):33–42.
31. **Botter, A. A.** 1971. Topical treatment of nail and skin infections with miconazole, a new, broad-spectrum antimycotic. Mykosen 14:187–191.
32. **Bradbeer, C. S., S. R. Mayhew, and D. Barlow.** 1985. Butoconazole and miconazole in treating vaginal candidiasis. Genitourin. Med. 61:270–272.
33. **Brammer, K. W., and L. J. Lees.** 1987. Single dose oral fluconazole in the treatment of vulvovaginal candidiasis: an interim analysis of a comparative study versus three-day intravaginal clotrimazole tablets, p. 151–156. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
34. **Brammer, K. W., and M. H. Tarbit.** 1987. A review of the pharmacokinetics of fluconazole (UK-49,858) in laboratory animals and man, p. 141–149. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
35. **Brass, C., J. N. Galgiani, T. F. Blaschke, R. Defelice, R. A. O'Reilly, and D. A. Stevens.** 1982. Disposition of ketoconazole, an oral antifungal, in humans. Antimicrob. Agents Chemother. 21:151–158.
36. **Brewster, E., P. M. Preti, R. Ruffmann, and J. Studd.** 1986. Effect of fenticonazole in vaginal candidiasis. A double-blind clinical trial versus clotrimazole. J. Int. Med. Res. 14:306–310.
37. **Brown, D., Jr., M. R. Henzl, M. E. LePage, L.-L. Tsao, A. E. Izu, K. A. M. Walker, G. D. Adamson, and W. Droegmuller.** 1986. Butoconazole vaginal cream in the treatment of vulvovaginal candidiasis. Comparison with miconazole nitrate and placebo. J. Reprod. Med. 31(Suppl.):1045–1048.
38. **Brown, D., Jr., J. V. Standard, D. G. Adamson, and M. R. Henzl.** 1985. Butoconazole vaginal inserts for vulvovaginal candidiasis: comparison to clotrimazole. Adv. Ther. 2:60–64.
39. **Brown, R., and E. L. Hazen.** 1949. Activation of antifungal extracts of actinomycetes by ultrafiltration through gradocol membranes. Soc. Exp. Biol. Med. 71:454–457.
40. **Brugmans, J. P., D. C. Thienpont, I. van Wijngaarden, O. F. Vanparijs, V. L. Schulmans, and H. L. Lauwers.** 1971. Mebendazole in enterobiasis. J. Am. Med. Assoc. 217:313–316.
41. **Büchel, K.-H., W. Draber, E. Regel, and M. Plempel.** 1972. Synthesis and properties of clotrimazole and other antimycotic 1-triphenyl-methyl imidazoles. Drugs Germ. 15:79–94.
42. **Bullock, W. E., and G. S. Deepe.** 1983. Medical mycology in crisis. J. Lab. Clin. Med. 102:685–693.
43. **Burgess, M. A., and G. P. Bodey.** 1972. Clotrimazole (Bay b 5097): in vitro and clinical pharmacological studies. Antimicrob. Agents Chemother. 2:423–426.
44. **Cacciaglia, G. B., A. J. Tenczar, and I. O. Kanat.** 1984. A review of the literature of ketoconazole therapy in the treatment of tinea pedis and onychomycosis. J. Foot Surg. 23:420–423.
45. **Calderon-Marquez, J. J.** 1987. Itraconazole in the treatment of vaginal candidosis and the effect of treatment of the sexual partner. Rev. Infect. Dis. 9(Suppl. 1):143–145.
46. **Cartwright, R. Y.** 1974. Clotrimazole in the treatment of acute and 'resistant' vaginal candidiasis. Postgrad. Med. J. 50 (Suppl.):90–92.
47. **Cartwright, R. Y.** 1976. Oral clotrimazole in the treatment of fungal infection, p. 183–187. *In* J. D. Williams and A. M. Geddes (ed.), Chemotherapy, vol 6. Plenum Publishing Corp., New York.
48. **Cauwenbergh, G.** 1986. Prophylaxis of mycotic infections in immunocompromised patients: a review of 27 reports and publications. Drugs Exp. Clin. Res. 12:419–427.
49. **Cauwenbergh, G., and P. De Doncker.** 1986. Itraconazole (R 51 211): a clinical review of its antimycotic activity in dermatology, gynecology, and internal medicine. Drug Dev. Res. 8:317–323.
50. **Cauwenbergh, G., and P. De Doncker.** 1987. The clinical use of itraconazole in superficial and deep mycoses, p. 273–284. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
51. **Chandler, F. W.** 1985. Pathology of mycoses in patients with the acquired immunodeficiency syndrome (AIDS), p. 1–23. *In* M. R. McGinnis (ed.), Current topics in medical mycology, vol. 1. Springer-Verlag, New York.

52. **Clayton, Y. M., and B. L. Connor.** 1973. Comparison of clotrimazole cream, Whitfield's ointment and nystatin ointment for the topical treatment of ringworm infections, pityriasis versicolor, erythrasma and candidiasis. Br. J. Dermatol. **89**:297–303.
53. **Clissold, S. P., and R. C. Heel.** 1986. Tioconazole. A review of its antimicrobial activity and therapeutic use in superficial mycoses. Drugs **31**:29–51.
54. **Cope, J.** 1980. Mode of action of miconazole on *Candida albicans*: effect on growth, viability and K^+ release. J. Gen. Microbiol. **119**:245–251.
55. **Corrado, M. L., M. Kramer, M. Cummings, and R. H. Eng.** 1982. Susceptibility of dematiaceous fungi to amphotericin B, miconazole, ketoconazole, flucytosine and rifampin alone and in combination. Sabouraudia **20**:109–113.
56. **Costa, A. L.** 1982. *In vitro* antimycotic activity of fenticonazole (Rec 15/1476). Mykosen **25**:47–52.
57. **Costa, A. L., A. Valenti, and M. Veronese.** 1984. Study of the morphofunctional alterations produced by fenticonazole on strains of *Candida albicans*, using the scanning electron microscope (S.E.M.). Mykosen **27**:29–35.
58. **Cullen, S. I., and M. K. Cullen.** 1987. Ketoconazole and griseofulvin in the treatment of toenail dermatophyte onychomycosis. Curr. Ther. Res. **41**:24–29.
59. **Cullen, S. I., I. H. Rex, and E. G. Thorne.** 1984. A comparison of a new antifungal agent, 1 percent econazole nitrate (Spectazole^R) cream versus 1 percent clotrimazole cream in the treatment of intertriginous candidosis. Curr. Ther. Res. **35**: 606–609.
60. **Cusumano, V., A. L. Costa, and M. Veronese.** 1985. Evaluation of the antifungal activity of fenticonazole on strains of *Candida albicans* on cellular lines. Mykosen **28**:238–243.
61. **Daneshmend, T. K.** 1986. Systemic absorption of miconazole from the vagina. J. Antimicrob. Chemother. **18**:507–511.
62. **Daneshmend, T. K., D. W. Warnock, M. D. Ene, E. M. Johnson, M. R. Potten, M. D. Richardson, and P. J. Williamson.** 1984. Influence of food on the pharmacokinetics of ketoconazole. Antimicrob. Agents Chemother. **25**:1–3.
63. **D'Arcy, P. F., and E. M. Scott.** 1978. Antifungal agents. Prog. Drug Res. **22**:93–147.
64. **De Coster, R., D. Beerens, C. Haelterman, and R. Doolaege.** 1987. Effects of itraconazole on the pituitary-testicular-adrenal axis: an overview of preclinical and clinical studies, p. 251–261. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
65. **DeFelice, R., D. G. Johnson, and J. N. Galgiani.** 1981. Gynecomastia with ketoconazole. Antimicrob. Agents Chemother. **19**:1073–1074.
66. **Degreef, H., K. Marien, H. De Veylder, K. Duprez, A. Borghys, and L. Verhoeve.** 1987. Itraconazole in the treatment of dermatophytoses: a comparison of two daily doses. Rev. Infect. Dis. **9**(Suppl. 1):104–108.
67. **Del Palacio-Hernanz, A., F. Sanz-Sanz, and A. Rodriquez-Noriega.** 1984. Double-blind investigation of R-42470 (terconazole cream 0.4%) and clotrimazole (cream 1%) for the topical treatment of mycotic vaginitis. Chemioterapia **3**:192–195.
68. **Del Palacio-Hernanz, A., S. D. Vincente, F. M. Ramos, and A. R.-N. Belaustegui.** 1987. Randomized comparative clinical trial of itraconazole and selenium sulfide shampoo for the treatment of pityriasis versicolor. Rev. Infect. Dis. **9**(Suppl. 1): 134–138.
69. **De Nollin, S., H. Van Belle, F. Goossens, F. Thone, and M. Borgers.** 1977. Cytochemical and biochemical studies of yeast after in vitro exposure to miconazole. Antimicrob. Agents Chemother. **11**:500–513.
70. **Diepernik, H., and J. Moller.** 1982. Ketoconazole and cyclosporin. Lancet **ii**:1217.
71. **Dismukes, W. E., A. M. Stamm, J. R. Graybill, P. C. Craven, D. A. Stevens, R. L. Stiller, G. A. Sarosi, G. Medoff, C. R. Gregg, H. A. Gallis, B. T. Fields, Jr., R. L. Marier, T. M. Kerkering, L. G. Kaplowitz, G. Cloud, C. Bowles, and S. Shadomy.** 1983. Treatment of systemic mycoses with ketoconazole: emphasis on toxicity and clinical response in 52 patients. Ann. Intern. Med. **98**:13–20.
72. **Dixon, D. M., and A. Polak.** 1987. *In vitro* and *in vivo* drug studies with three agents of central nervous system phaeohyphomycosis. Chemotherapy (Basel) **33**:129–140.
73. **Dixon, D. M., S. Shadomy, H. J. Shadomy, A. Espinel-Ingroff, and T. M. Kerkering.** 1978. Comparison of the *in vitro* antifungal activities of miconazole and a new imidazole, R41,400. J. Infect. Dis. **138**:245–248.
74. **Droegemueller, W., D. G. Adamson, D. Brown, L. Cibley, F. Fleury, M. E. LePage, and M. R. Henzl.** 1984. Three-day treatment with butoconazole nitrate for vulvovaginal candidiasis. Obstet. Gynecol. Scand. **64**:530–534.
75. **Duarte, P. A., C. C. Chow, F. Simmons, and J. Ruskin.** 1984. Fatal hepatitis associated with ketoconazole therapy. Arch. Intern. Med. **144**:1069–1070.
76. **Dupont, B., and E. Drouhet.** 1987. Cryptococcal meningitis and fluconazole. Ann. Intern. Med. **106**:778.
77. **Dupont, B., and E. Drouhet.** 1987. Early experience with itraconazole *in vitro* and in patients: pharmacokinetic studies and clinical results. Rev. Infect. Dis. **9**(Suppl. 1):71–76.
78. **Dupont, B., and E. Drouhet.** 1987. Fluconazole in the management of oropharyngeal candidiasis in a predominantly HIV antibody-positive group of patients, p. 163–168. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
79. **Espinel-Ingroff, A., S. Shadomy, and J. F. Fisher.** 1977. Bioassay for miconazole. Antimicrob. Agents Chemother. **11**:365–368.
80. **Espinel-Ingroff, A., S. Shadomy, and R. J. Gebhardt.** 1984. In vitro studies with R 51,211 (Itraconazole). Antimicrob. Agents Chemother. **26**:5–9.
81. **Estrada, R. A.** 1987. Itraconazole in pityriasis versicolor. Rev. Infect. Dis. **9**(Suppl. 1):128–130.
82. **Fainstein, V., G. P. Bodey, L. Elting, A. Maksymiuk, M. Keating, and K. B. McCredie.** 1987. Amphotericin B or ketoconazole therapy of fungal infections in neutropenic cancer patients. Antimicrob. Agents Chemother. **31**:11–15.
83. **Farkas, B., and N. Simon.** 1984. Ergebnisse einer Vergleichsstudie mit einem oral und einem lokal zu applizierenden Antimykoticum bei Vaginalmykosen. Mykosen **27**:554–561.
84. **Feldman, D.** 1986. Ketoconazole and other imidazole derivatives as inhibitors of steroidogenesis. Endocr. Rev. **7**:409–420.
85. **Ferguson, R. M., D. E. R. Sutherland, R. L. Simmons, and J. S. Najaria.** Ketoconazole, cyclosporin metabolism, and renal transplantation. Lancet **ii**:882–883.
86. **Finzi, A., A. Fioroni, P. M. Preti, and M. Mounari.** 1986. A double-blind evaluation of fenticonazole cream 2 percent and clotrimazole cream 1 percent in dermatomycoses. Mykosen **29**:41–44.
87. **Fraser, D. W., J. I. Ward, L. Ajello, and B. D. Plikaytis.** 1979. Aspergillosis and other systemic mycoses—the growing problem. J. Am. Med. Assoc. **242**:1631–1635.
88. **Fredriksson, T.** 1979. Treatment of dermatomycoses with topical econazole and clotrimazole. Curr. Ther. Res. **25**:590–594.
89. **Fromtling, R. A.** 1984. Imidazoles as medically important antifungal agents: an overview. Drugs Today **20**:325–349.
90. **Fromtling, R. A.** 1985. Bifonazole (Mycospor^R)—an update. Drugs Today **21**:401–404.
91. **Fromtling, R. A.** 1986. Butoconazole: a new antifungal agent. Review of recent work. Drugs Today **22**:261–263.
92. **Fromtling, R. A. (ed.).** 1987. Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
93. **Fromtling, R. A., G. K. Abruzzo, and G. S. Bulmer.** 1986. *Cryptococcus neoformans*: comparisons of *in vitro* antifungal susceptibilities of serotypes AD and BC. Mycopathologia **94**:27–30.
94. **Fromtling, R. A., H.-P. Yu, and S. Shadomy.** 1983. *In-vitro* inhibitory activities of 2 new orally absorbable imidazole derivatives: Bay n 7133 and Bay l 9139. Sabouraudia **21**:179–185.

95. **Fromtling, R. A., H.-P. Yu, and S. Shadomy.** 1984. *In vitro* antifungal activities of Bay N 7133 and Bay L 9139, two new orally absorbed antifungal imidazole derivatives, against pathogenic yeasts. Mycopathologia **86**:45–50.
96. **Fujihara, M., K. Hirakoso, and S. Harigaya.** 1984. Pharmacokinetics of sulconazole nitrate. (1). Fate in rats after application to the skin. Pharmacometrics **28**:145–154.
97. **Galgiani, J. N.** 1983. Ketoconazole in the treatment of coccidioidomycosis. Drugs **26**:355–363.
98. **Galimberti, R. L., I. Villalba, S. Galarza, A. Raimondi, and V. Flores.** 1987. Itraconazole in pityriasis versicolor: ultrastructural changes in *Malassezia furfur* produced during treatment. Rev. Infect. Dis. **9**(Suppl. 1):134–138.
99. **Gan, V. N., M. Petruska, and C. M. Ginsburg.** 1987. Epidemiology and treatment of tinea capitis: ketoconazole vs. griseofulvin. Pediatr. Infect. Dis. J. **6**:46–49.
100. **Ganer, A., E. Arathoon, and D. A. Stevens.** 1987. Initial experience in therapy for progressive mycoses with itraconazole, the first clinically studied triazole. Rev. Infect. Dis. **9**(Suppl. 1):77–86.
101. **Gastaldi, A.** 1985. Treatment of vaginal candidiasis with fenticonazole and miconazole. Curr. Ther. Res. **35**:489–493.
102. **Gebhart, R. J., A. Espinel-Ingroff, and S. Shadomy.** 1984. *In vitro* susceptibility studies with oxiconazole (Ro 13-8996). Chemotherapy (Basel) **30**:244–247.
103. **Georgopapadakou, N. H., B. A. Dix, S. A. Smith, J. Freudenberger, and P. T. Funke.** 1987. Effect of antifungal agents on lipid biosynthesis and membrane integrity in *Candida albicans*. Antimicrob. Agents Chemother. **31**:46–51.
104. **Gip, L.** 1984. Comparison of oxiconazole (Ro 13-8996) and econazole in dermatomycoses. Mykosen **27**:295–302.
105. **Gip, L., and S. Forsstrom.** 1983. A double-blind parallel study of sulconazole nitrate 1% cream compared with miconazole 2% cream in dermatophytoses. Mykosen **26**:231–241.
106. **Gisslen, H., K. Hersle, H. Mobacken, and P. Nordin.** 1977. Topical treatment of dermatomycoses and tinea versicolor with econazole cream 1% (Parvaryl). Curr. Ther. Res. **21**:681–684.
107. **Godefroi, E. F., J. Heeres, J. Van Cutsem, and P. A. J. Janssen.** 1969. The preparation and antimycotic properties of derivatives of 1-phenethylimidazole. J. Med. Chem. **12**:784–791.
108. **Goffe, B. S.** 1987. Response of tinea corporis/cruris and tinea versicolor to once-a-day topical treatment with bifonazole cream—a safety and efficacy study, p. 423–429. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
109. **Gouveia, D. C., and C. Jones da Silva.** 1984. Oxiconazole in the treatment of vaginal candidiasis: single dose versus 3-day treatment with econazole. Pharmatherapeutica **3**:682–685.
110. **Graybill, J. R.** 1987. Fluconazole efficacy in animal models of mycotic diseases, p. 113–124. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
111. **Graybill, J. R., and J. Ahrens.** 1985. Itraconazole treatment of murine aspergillosis. Sabouraudia: J. Med. Vet. Mycol. **23**:219–223.
112. **Graybill, J. R., S. R. Kaster, and D. J. Drutz.** 1983. Comparative activities of Bay n7133, ICI 153,066, and ketoconazole in murine cryptococcosis. Antimicrob. Agents Chemother. **24**: 829–834.
113. **Graybill, J. R., S. R. Kaster, and D. J. Drutz.** 1983. Treatment of experimental murine aspergillosis with Bay n7133. J. Infect. Dis. **148**:898–906.
114. **Graybill, J. R., and H. B. Levine.** 1978. Successful treatment of cryptococcal meningitis with intraventricular miconazole. Arch. Intern. Med. **138**:814–816.
115. **Graybill, J. R., S. H. Sun, and J. Ahrens.** 1986. Treatment of murine coccidioidal meningitis with fluconazole (UK-49,858). J. Med. Vet. Mycol. **24**:113–119.
116. **Green, C. A., P. M. Farr, and S. Shuster.** 1987. Treatment of seborrhoeic dermatitis with ketoconazole. II. Response of seborrhoeic dermatitis of the face, scalp and trunk to topical ketoconazole. Br. J. Dermatol. **116**:217–221.
117. **Greene, N. B., R. P. Baughman, C. K. Kim, and G. A. Roselle.** 1985. Failure of ketoconazole in an immunosuppressed patient with pulmonary blastomycosis. Chest **88**:640–641.
118. **Grigoriu, D., and A. Grigoriu.** 1983. Double-blind comparison of the efficacy, toleration and safety of tioconazole base 1% and econazole nitrate 1% creams in the treatment of patients with fungal infections of the skin or erythrasma. Dermatology **166**(Suppl. 1):8–13.
119. **Guaschino, S., G. Michelone, E. Stola, G. Lombardi, A. Spinillo, and P. Viale.** 1986. Mycotic vaginitis in pregnancy: a double evaluation of the susceptibility to the main antimycotic drugs of isolated species. Biol. Res. Preg. **7**:20–22.
120. **Hansen, R. M., N. Reinerio, P. G. Sohnle, R. A. Abrams, P. S. Ritch, J. A. Libnoch, and T. Anderson.** 1987. Ketoconazole in the prevention of candidiasis in patients with cancer. A prospective, randomized, controlled, double-blind study. Arch. Intern. Med. **147**:710–712.
121. **Hay, R. J.** 1983. A medical review of tioconazole and other antifungal imidazoles, p. 43–64. *In* R. Rieth (ed.), A comprehensive guide to the therapeutic use of tioconazole. Pharma Libri, Chicago.
122. **Hay, R. J., and Y. M. Clayton.** 1987. Treatment of chronic dermatophytosis and chronic oral candidosis with itraconazole. Rev. Infect. Dis. **9**(Suppl. 1):114–118.
123. **Hay, R. J., R. M. Mackie, and Y. M. Clayton.** 1985. Tioconazole nail solution—an open study of its efficacy in onychomycosis. Clin. Exp. Dermatol. **10**:111–115.
124. **Hector, R. F., and P. C. Braun.** 1987. The effect of bifonazole on chitin synthesis in *Candida albicans*, p. 369–382. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
125. **Heel, R. C., R. N. Brogden, A. Carmine, P. A. Morley, T. M. Speight, and G. S. Avery.** 1982. Ketoconazole: a review of its therapeutic efficacy in superficial and systemic fungal infections. Drugs **23**:1–36.
126. **Heel, R. C., R. N. Brogden, G. E. Parkes, T. M. Speight, and G. S. Avery.** 1980. Miconazole: a preliminary review of its therapeutic efficacy in systemic fungal infections. Drugs **19**: 7–30.
127. **Heeres, J., L. J. J. Backx, J. H. Mostmans, and J. Van Cutsem.** 1979. Antimycotic imidazoles. 4. Synthesis and antifungal activity of ketoconazole, a new potent orally active broad-spectrum antifungal agent. J. Med. Chem. **22**:1003–1005.
128. **Heeres, J., L. J. J. Backx, and J. Van Cutsem.** 1984. Antimycotic azoles. 7. Synthesis and antifungal properties of a series of novel triazol-3-ones. J. Med. Chem. **27**:894–900.
129. **Heeres, J., R. Hendrickx, and J. Van Cutsem.** 1983. Antimycotic imidazoles. 6. Synthesis and antifungal properties of terconazole, a novel triazole ketal. J. Med. Chem. **26**:611–613.
130. **Henderson, J. T.** 1987. Fluconazole—a significant advance in the management of human fungal disease, p. 77–79. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
131. **Henderson, J. T., W. Neilson, A. B. Wilson, and S. Jevons.** 1983. Tioconazole in the treatment of vaginal candidiasis. Gynäkol. Rundsch. **23**(Suppl. 1):42–60.
132. **Herrling, S., H. Sous, W. Krüppe, G. Osterloh, and H. Mückter.** 1959. Experimentelle Untersuchungen über eine neue gegen Pilze wirksame Verbindung. Arneim. Forsch. **9**:489–494.
133. **Heykants, J., M. Michiels, W. Meuldermans, J. Monbaliu, K. Lavrijsen, A. Van Peer, J. C. Levron, R. Woestenborghs, and G. Cauwenbergh.** 1987. The pharmacokinetics of itraconazole in animals and man: an overview, p. 223–249. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
134. **Higashi, Y., M. Omura, K. Suzuki, H. Inano, and H. Oshima.**

1987. Ketoconazole as a possible universal inhibitor of cytochrome P-450 dependent enzymes: its mode of inhibition. Endocrinol. Jpn. **34**:105–115.
135. **Hiratani, T., and H. Yamaguchi.** 1985. Mode of action of oxiconazole nitrate toward *Candida albicans*. Chemotherapy (Tokyo) **33**:215–226.
136. **Hoeprich, P. D., and E. Goldstein.** 1974. Miconazole therapy for coccidioidomycosis. J. Am. Med. Assoc. **230**:1153–1157.
137. **Hoeprich, P. D., and J. M. Merry.** 1984. In vitro activities of two new antifungal azoles. Antimicrob. Agents Chemother. **25**:339–341.
138. **Hoeprich, P. D., and J. M. Merry.** 1985. Activity of BAY n 7133 and BAY I 9139 *in vitro* and in experimental murine coccidioidomycosis. Eur. J. Clin. Microbiol. **4**:400–403.
139. **Hoeprich, P. D., and J. M. Merry.** 1986. Influence of culture medium on susceptibility testing with BAY n 7133 and ketoconazole. J. Clin. Microbiol. **24**:269–271.
140. **Höffken, G., H. Lode, and H.-J. Kessler.** 1983. Einfluss von Doxycyclin und Isoconazolnitrat auf die intestinale Pilzflora des Menschen. Arneim. Forsch. **33**:273–276.
141. **Holt, R. J., and R. L. Neumann.** 1972. Laboratory assessment of the antimycotic drug clotrimazole. J. Clin. Pathol. **25**:1089–1097.
142. **Houang, E. T., and A. G. Lawrence.** 1985. Systemic absorption and persistence of tioconazole in vaginal fluid after insertion of a single 300-mg tioconazole ovule. Antimicrob. Agents Chemother. **27**:964–965.
143. **Huang, Y.-C., J. L. Colaizzi, R. H. Bierman, R. Woestenborghs, and J. Heykants.** 1986. Pharmacokinetics and dose proportionality of ketoconazole in normal volunteers. Antimicrob. Agents Chemother. **30**:206–210.
144. **Hughes, C. E., and W. H. Beggs.** 1987. Action of fluconazole (UK-49,858) in relation to other systemic antifungal agents. J. Antimicrob. Chemother. **19**:171–174.
145. **Hume, A. L., and T. M. Kerkering.** 1983. Ketoconazole (Nizoral, Janssen Pharmaceutica, Inc.). Drug Intell. Clin. Pharm. **17**:169–173.
146. **Humphrey, M. J., S. Jervons, and M. H. Tarbit.** 1985. Pharmacokinetic evaluation of UK-49,858, a metabolically stable triazole antifungal drug, in animals and humans. Antimicrob. Agents Chemother. **28**:648–653.
147. **Hussain-Qadri, S. M. H., D. J. Flourney, S. G. M. Qadri, and E. G. Ramirez.** 1986. Susceptibility of clinical isolates of yeasts to antifungal agents. Mycopathologia **95**:183–187.
148. **Ishibashi, Y., and Y. Matsumoto.** 1985. Intravenous miconazole therapy for experimental keratomycosis in rabbits. Sabouraudia: J. Med. Vet. Mycol. **23**:55–61.
149. **Jacobson, J. B., A. J. Hajman, J. Wiese, P. Gandrup, and S. Forsström.** 1985. A new vaginal antifungal agent—butoconazole nitrate. Acta Obstet. Gynecol. Scand. **64**:241–244.
150. **Janssen, P. A. J., and J. E. Symoens.** 1983. Hepatic reactions during ketoconazole treatment. Am. J. Med. **74**(Suppl. 1B): 80–85.
151. **Jerchel, D., H. Fischer, and M. Fracht.** 1952. Zur Darstellung der Benzimidazole. Liebigs Ann. Chem. **575**:162–173.
152. **Jervons, S., G. E. Gymer, K. W. Brammer, D. A. Cox, and M. R. G. Lemming.** 1979. Antifungal activity of tioconazole (UK-20,349), a new imidazole derivative. Antimicrob. Agents Chemother. **15**:597–602.
153. **Jordan, W. M., G. P. Bodey, V. Rodriguez, S. J. Ketchel, and J. Henney.** 1979. Miconazole therapy for treatment of fungal infections in cancer patients. Antimicrob. Agents Chemother. **16**:792–797.
154. **Kashin, P., M. C. Phyfferoen, and D. L. Gibbs.** 1985. A comparative study of once versus twice daily treatment of superficial dermatophyte and yeast infections with tioconazole (1%) cream. J. Int. Med. Res. **13**:85–95.
155. **Katz, M. E., and P. A. Cassileth.** 1977. Disseminated candidiasis in a patient with acute leukemia. Successful treatment with miconazole. J. Am. Med. Assoc. **237**:1124–1125.
156. **Kerkering, T. M., and A. Espinel-Ingroff.** 1987. *In vitro* synergistic activity of itraconazole and 5-fluorocytosine against *Aspergillus fumigatus* and *Aspergillus flavus*, p. 61–70. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
157. **Kessler, H.-J.** 1979. Mikrobiologische Untersuchungen mit Isoconazolnitrat, einem Breitspektrum-Antimykoticum aus der Gruppe der Imidazol-Derivative. Arneim. Forsch. **29**: 1344–1351.
158. **Kessler, H.-J., D. Haude, and C. Schöbel.** 1979. Tierexperimentelle Prüfung des neuen Breitspektrum-Antimykoticum Isoconazolnitrat. Arneim. Forsch. **29**:1352–1357.
159. **Kirkpatrick, C. H., and D. W. Alling.** 1978. Treatment of chronic oral candidiasis with clotrimazole troches. N. Engl. Med. J. **299**:1201–1203.
160. **Kjaeldgaard, A.** 1986. Comparison of terconazole and clotrimazole vaginal tablets in the treatment of vulvovaginal candidosis. Pharmatherapeutica **4**:525–531.
161. **Kobayashi, G. S., S. Travis, and G. Medoff.** 1986. Comparison of the in vitro and in vivo activity of the bis-triazole derivative UK-49,858 with that of amphotericin B against *Histoplasma capsulatum*. Antimicrob. Agents Chemother. **29**:660–662.
162. **Koch, H.** 1983. Ketoconazole: broad spectrum antifungal agent. Pharma Int. Engl. Ed. **4**:151–152.
163. **Kokoschka, E. M., G. Miebauer, M. Mounari, and P. M. Preti.** 1986. Treatment of dermatomycoses with topical fenticonazole and econazole. Mykosen **29**:45–50.
164. **Kowal, J.** 1983. The effect of ketoconazole on steriodogenesis in cultured mouse adrenal cortex tumor cells. Endocrinology **112**:1541–1543.
165. **Kraemer, F. B., and A. Pont.** 1986. Inhibition of cholesterol synthesis by ketoconazole. Am. J. Med. **80**:616–622.
166. **Lake-Bakaar, G., P. J. Scheuer, and S. Sherlock.** 1987. Hepatic reactions associated with ketoconazole in the United Kingdom. Br. Med. J. **294**:419–422.
167. **Lassus, A., and S. Forsström.** 1984. A double-blind parallel study comparing sulconazole with econazole in the treatment of dermatophytoses. Mykosen **27**:592–598.
168. **Lassus, A., O. Salo, and S. Forsström.** 1983. A double-blind, parallel study of sulconazole nitrate 1% cream compared with clotrimazole 1% cream in dermatophytoses. Br. J. Dermatol. **108**:195–198.
169. **Latrille, F., J. Perraud, J. Stadler, A. M. Monro, and B. Ch. J. Sutter.** 1987. Effects of tioconazole on parturition and serum levels of 17β-oestradiol, progesterone, LH and PRL in the rat. Biochem. Pharmacol. **36**:1119–1124.
170. **Lavalle, P., P. Suchil, F. De Ovando, and S. Reynoso.** 1987. Itraconazole for deep mycoses: preliminary experience in Mexico. Rev. Infect. Dis. **9**(Suppl. 1):64–70.
171. **Lavrijsen, K., J. Van Houdt, D. Thijs. W. Meuldermans, and J. Heykants.** 1986. Induction potential of antifungals containing an imidazole or triazole moiety. Biochem. Pharmacol. **35**: 1867–1878.
172. **Lefler, E., E. Brummer, J. G. McEwen, G. L. Hoyos, A. Restrepo, and D. A. Stevens.** 1985. Study of current and new drugs in a murine model of acute paracoccidioidomycosis. Am. J. Trop. Med. Hyg. **34**:134–140.
173. **Lefler, E., E. Brummer, A. M. Perlman, and D. A. Stevens.** 1985. Activities of the modified polyene *N*-D-ornithyl amphotericin methyl ester and the azoles ICI 153,066, Bay n 7133, and Bay I 9139 compared with those of amphotericin B and ketoconazole in the therapy of experimental blastomycosis. Antimicrob. Agents Chemother. **27**:363–366.
174. **Lefler, E., and D. A. Stevens.** 1984. Inhibition and killing of *Candida albicans* in vitro by five imidazoles in clinical use. Antimicrob. Agents Chemother. **25**:450–454.
175. **Lefler, E., and D. A. Stevens.** 1985. New azole compounds: vibunazole (Bay n7133) and Bay I9139, compared with ketoconazole in the therapy of systemic candidosis and in pharmacokinetic studies, in mice. J. Antimicrob. Chemother. **15**: 69–75.
176. **Levine, H. B.** 1976. R34000, a dioxolane imidazole in the therapy for experimental coccidioidomycosis. Chest **70**:755–759.
177. **Levine, H. B.** 1984. A direct comparison of oral treatments with

BAY-n-7133, BAY-l-9139 and ketoconazole in experimental murine coccidioidomycosis. Sabouraudia: J. Med. Vet. Mycol. **22**:37–46.

178. **Levine, H. B., D. A. Stevens, J. M. Cobb, and A. E. Gebhardt.** 1975. Miconazole in coccidioidomycosis. I. Assays of activity in mice and *in vitro*. J. Infect. Dis. **132**:407–414.
179. **Lewis, J. H., H. J. Zimmerman, G. D. Benson, and K. G. Ishak.** 1984. Hepatic injury associated with ketoconazole therapy: analysis of 33 cases. Gastroenterology **86**:503–513.
180. **Loose, D. S., P. B. Kan, M. A. Hirst, R. A. Marcus, and D. Feldman.** 1983. Ketoconazole blocks adrenal steroidogenesis by inhibiting cytochrome p450-dependent enzymes. J. Clin. Invest. **71**:1495–1499.
181. **Lutwick, L. I., M. W. Rytel, J. P. Yañez, J. N. Galgiani, and D. A. Stevens.** 1979. Deep infections from *Petriellidium boydii* treated with miconazole. J. Am. Med. Assoc. **241**:271–272.
182. **Lyman, C. A., A. M. Sugar, and R. D. Diamond.** 1986. Comparative activities of UK-49,858 and amphotericin B against *Blastomyces dermatitidis* infections in mice. Antimicrob. Agents Chemother. **29**:161–162.
183. **Marcano, C., and M. Feo.** 1983. Eficacia del econazol en embarazadas con candidiasis vulvo-vaginal. Mycopathologia **81**:65–70.
184. **Marichal, P., J. Gorrens, and H. Van den Bossche.** 1984. The action of itraconazole and ketoconazole on growth and sterol synthesis in *Aspergillus fumigatus* and *Aspergillus niger*. Sabouraudia: J. Med. Vet. Mycol. **22**:13–21.
185. **Marriott, M. S., J. R. C. Baird, K. W. Brammer, J. K. Faulkner, G. Halliwell, S. Jevons, and M. H. Tarbit.** 1983. Tioconazole, a new imidazole-antifungal agent for the treatment of dermatomycoses. Antifungal and pharmacologic properties. Dermatology **116**(Suppl. 1):1–7.
186. **Marriott, M. S., and K. Richardson.** 1987. The discovery and mode of action of fluconazole, p. 81–92. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
187. **Matthews, T.** 1986. Butoconazole. Pharmacologic considerations, chemistry and microbiology. J. Reprod. Med. **31**:655–657.
188. **Mazabrey, D., J. Nadal, J-P. Seguela, and M.-D. Linas.** 1985. Scanning and transmission electron microscopy: study of effects of econazole on *Microsporum canis*. Mycopathologia **91**:151–157.
189. **Meunier, F., J. Gerain, R. Snoeck, F. Libotte, C. Lambert, and A. M. Ceuppens.** 1987. Fluconazole therapy of oropharyngeal candidiasis in cancer patients, p. 169–174. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
190. **Meunier-Carpentier, F., M. Cruciani, and J. Klastersky.** 1983. Oral prophylaxis with miconazole or ketoconazole of invasive fungal disease in neutropenic cancer patients. Eur. J. Cancer Clin. Oncol. **19**:43–48.
191. **Mixich, G., and K. Thiele.** 1979. Ein Beitrag zur stereospezifischen Synthese von antimykotisch wirksamen Imidazolyloximäthern. Oxiconazol-nitrat (Sgd 301-76), ein neues Breitbandantimykotikum. Arneim. Forsch. **29**:1510–1513.
192. **Mobacken, H., and S. Moberg.** 1986. Ketoconazole treatment of 13 patients with chronic mucocutaneous candidiasis. A prospective 3-year trial. Dermatologica **173**:229–236.
193. **Mora, R. G., D. L. Greer, and H. W. Jolly, Jr.** 1987. Prospective analysis of the response of tinea versicolor to topical application of bifonazole 1% cream, p. 415–421. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
194. **Morales-Doria, M.** 1987. Pityriasis versicolor: efficacy of two five-day regimens of itraconazole. Rev. Infect. Dis. **9**(Suppl. 1):131–133.
195. **Morita, T., and Y. Nozawa.** 1985. Effects of antifungal agents on ergosterol biosynthesis in *Candida albicans* and *Trichophyton mentagrophytes*: differential inhibitory sites of naphthiomate and miconazole. J. Invest. Dermatol. **85**:434–437.
196. **Mosse, M., M. P. Alric, M. Berceaux, N. Fourcine, and A. Salhi.** 1986. Etude comparative de l'activité fongistatique *in vitro* de l'omoconazole et de six autres imidazolés sur les levures. Pathol. Biol. **34**:684–687.
197. **Naeyaert, J. M., J. de Bersaques, C. de Cuypers, P. Hindryckx, H. van Landuyt, and B. Gordts.** 1987. Fluconazole (UK-49,858): a novel oral antifungal, in the treatment of fungal skin infections. Results of an open study in 43 patients, p. 157–161. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
198. **National Institute of Allergy and Infectious Diseases Mycoses Study Group.** 1985. Treatment of blastomycosis and histoplasmosis with ketoconazole. Results of a prospective randomized clinical trial. Ann. Intern. Med. **103**:861–872.
199. **Negroni, R., O. Palmieri, K. Koren, I. N. Tiraboschi, and R. L. Galimberti.** 1987. Oral treatment of paracoccidioidomycosis and histoplasmosis with itraconazole in humans. Rev. Infect. Dis. **9**(Suppl. 1):47–50.
200. **Nuijten, S. T. M., and J. L. Schuller.** 1987. Itraconazole in the treatment of tinea corporis: a pilot study. Rev. Infect. Dis. **9**(Suppl. 1):119–120.
201. **Odds, F. C.** 1980. Laboratory evaluation of antifungal agents: A comparative study of five imidazole derivatives of clinical importance. J. Antimicrob. Chemother. **6**:749–761.
202. **Odds, F. C., A. B. Abbott, G. Pye, and P. F. Troke.** 1986. Improved method for estimation of azole antifungal inhibitory concentrations against *Candida* species, based on azole/antibiotic interactions. J. Med. Vet. Mycol. **24**:305–311.
203. **Odds, F. C., S. L. Cheesman, and A. B. Abbott.** 1985. Suppression of ATP in *Candida albicans* by imidazole and derivative antifungal agents. Sabouraudia: J. Med. Vet. Mycol. **23**:415–424.
204. **Odds, F. C., S. L. Cheesman, and A. B. Abbott.** 1986. Antifungal effects of fluconazole (UK 49,858), a new triazole antifungal, *in vitro*. J. Antimicrob. Chemother. **18**:473–478.
205. **Odds, F. C., A. Cockayne, J. Hayward, and A. B. Abbott.** 1985. Effects of imidazole- and triazole-derivative antifungal compounds on the growth and morphological development of *Candida albicans* hyphae. J. Gen. Microbiol. **131**:2581–2589.
206. **Odds, F. C., and F. MacDonald.** 1981. Persistence of miconazole in vaginal secretions after single applications. Implications for the treatment of vaginal candidosis. Br. J. Vener. Dis. **57**:400–401.
207. **Odds, F. C., L. J. R. Milne. J. C. Gentles, and E. H. Ball.** 1980. The activity *in vitro* and *in vivo* of a new imidazole antifungal, ketoconazole. J. Antimicrob. Chemother. **6**:97–104.
208. **Odds, F. C., C. E. Webster, and A. B. Abbott.** 1984. Antifungal relative inhibition factors: BAY l-9139, bifonazole, butoconazole, isoconazole, itraconazole (R 51211), oxiconazole, Ro 14-4767/002, sulconazole, terconazole and vibunazole (BAY n-7133) compared *in vitro* with nine established antifungal agents. J. Antimicrob. Chemother. **14**:105–114.
209. **Ogata, M., H. Matsumoto, Y. Hamada, M. Takehara, and K. Tawara.** 1983. 1-[1-[2-[(3-chlorobenzyl) oxy] phenyl] vinyl]-1H-imidazole hydrochloride, a new potent antifungal agent. J. Med. Chem. **26**:768–770.
210. **Oij, E. O., and Y. M. Clayton.** 1981. The role of econazole in the management of oculomycosis. Int. Ophthalmol. **4**:137–142.
211. **O'Neill East, M., J. T. Henderson, and S. Jevons.** 1983. Tioconazole in the treatment of fungal infections of the skin. Dermatologica **166**(Suppl. 1):20–33.
212. **Osumi, M., N. Yamada, J. Okada, H. Yamaguchi, T. Hiratani, and M. Plempel.** 1983. The effect of bifonazole on the structure of *Trichophyton*. Arneim. Forsch. **33**:1484–1491.
213. **Palou de Fernandez, E., M. M. Patino, J. R. Graybill, and M. H. Tarbit.** 1986. Treatment of cryptococcal meningitis in mice with fluconazole. J. Antimicrob. Chemother. **18**:261–270.
214. **Panconesi, E., and E. Difonzo.** 1987. Treatment of dermatophytoses and pityriasis versicolor with itraconazole. Rev. Infect. Dis. **9**(Suppl. 1):109–113.
215. **Perfect, J. R., and D. T. Durack.** 1985. Penetration of imidazoles and triazoles into cerebrospinal fluid of rabbits. J. Antimicrob. Chemother. **16**:81–86.

216. **Perfect, J. R., D. V. Savani, and D. T. Durack.** 1986. Comparison of itraconazole and fluconazole in treatment of cryptococcal meningitis and *Candida* pyelonephritis in rabbits. Antimicrob. Agents Chemother. **29**:579–583.
217. **Phillips, P., R. Fetchick, I. Weisman, S. Foshee, and J. R. Graybill.** 1987. Tolerance to and efficacy of itraconazole in treatment of systemic mycoses: preliminary results. Rev. Infect. Dis. **9**(Suppl. 1):87–93.
218. **Plempel, M.** 1982. On the action kinetics of clotrimazole. Chemotherapy (Basel) **28**(Suppl. 1):22–31.
219. **Plempel, M.** 1984. Antimycotic activity of BAY N 7133 in animal experiments. J. Antimicrob. Chemother. **13**:447–463.
220. **Plempel, M., and K. Bartmann.** 1972. Experimental studies on the antimycotic action of clotrimazole (Canesten) *in vitro* and after local application *in vivo*. Drugs Germ. **15**:103–120.
221. **Plempel, M., K. Bartmann, K.-H. Büchel, and E. Regel.** 1969. Experimentelle Befunde über ein neues oral wirksames Antimykoticum mit breiten Wirkungsspecktrum. Dtsch. Med. Wochenschr. **94**:1356–1364.
222. **Plempel, M., D. Berg, and J. Abbink.** 1987. Antimycotic characteristics of bifonazole, p. 287–312. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
223. **Plempel, M., E. Regel, and K.-H. Büchel.** 1983. Antimycotic efficacy of bifonazole *in vitro* and *in vivo*. Arneim. Forsch. **33**:517–524.
224. **Polak, A.** 1982. Oxiconazole, a new imidazole derivative. Arneim. Forsch. **32**:17–24.
225. **Polak, A.** 1984. Antifungal activity of four antifungal drugs in the cutaneous retention time test. Sabouraudia: J. Med. Vet. Mycol. **22**:501–503.
226. **Polak, A., and D. M. Dixon.** 1987. Fungistatic and fungicidal effects of amphotericin B, ketoconazole and fluconazole (UK 49,858) against *Histoplasma capsulatum in vitro* and *in vivo*. Mykosen **30**:186–194.
227. **Polak, A., H. J. Scholer, and M. Wall.** 1982. Combination therapy of experimental candidiasis, cryptococcosis and aspergillosis in mice. Chemotherapy (Basel) **28**:461–479.
228. **Polak-Wyss, A., H. Lengsfeld, and G. Oesterhelt.** 1985. Effect of oxiconazole and Ro 14-4767/002 on sterol pattern in *Candida albicans*. Sabouraudia: J. Med. Vet. Mycol. **23**:433–442.
229. **Pont, A., P. L. Williams, D. S. Loose, D. Feldman, R. E. Reitz, C. Bochra, and D. A. Stevens.** 1982. Ketoconazole blocks adrenal steroid synthesis. Ann. Intern. Med. **97**:370–372.
230. **Preusser, H. J., and H. Rostek.** 1978. Econazole effects on *Trichophyton rubrum* and *Candida albicans*. Electron microscopic and cytochemical studies. Mykosen **21**(Suppl. 1): 314–321.
231. **Pye, G. W., and M. S. Marriott.** 1982. Inhibition of sterol C14 demethylation by imidazole-containing antifungals. Sabouraudia **20**:325–329.
232. **Qadripur, S.-A.** 1984. Double-blind parallel comparison of sulconazole nitrate, 1% cream and powder, with econazole, 1% cream and powder, in the treatment of cutaneous dermatophytoses. Curr. Ther. Res. **35**:753–758.
233. **Rajfer, J., S. C. Sikka, F. Rivera, and D. J. Handelsman.** 1986. Mechanism of inhibition of human testicular steroidogenesis by oral ketoconazole. J. Clin. Endocrinol. Metab. **63**:1193–1198.
234. **Reingold, A. L., X. Dong Lu, B. D. Plikaytis, and L. Ajello.** 1986. Systemic mycoses in the United States, 1980–1982. J. Med. Vet. Mycol. **24**:433–436.
235. **Restrepo, A., I. Gomez, J. Robledo, M. M. Patino, and L. E. Cano.** 1987. Itraconazole in the treatment of paracoccidioidomycosis: a preliminary report. Rev. Infect. Dis. **9**(Suppl. 1): 51–56.
236. **Richardson, K., K. W. Brammer, M. S. Marriott, and P. F. Troke.** 1985. Activity of UK-49,858, a bis-triazole derivative, against experimental infections with *Candida albicans* and *Trichophyton mentagrophytes*. Antimicrob. Agents Chemother. **27**:832–835.
237. **Ritter, W., and M. Plempel.** 1984. Pharmacokinetics of the oral triazole antimycotic vibunazole in animals. J. Antimicrob. Chemother. **14**:243–252.
238. **Ritter, W., and H.-M. Siefert.** 1987. Biological disposition and percutaneous absorption of bifonazole in animals and man, p. 383–405. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
239. **Ritter, W., S. Stettendorf, and H. Weber.** 1982. Pharmacokinetics of bifonazole and their clinical implications, p. 48–53. *In* H. Urabe, N. Zaias, and S. Stettendorf (ed.), International Antifungal Symposium: Bifonazole. Excerpta Medica, Amsterdam.
240. **Roberts, D. T., B. Adriaans, and J. C. Gentles.** 1985. A comparative study of once daily bifonazole cream versus twice daily miconazole cream in the treatment on tinea pedis. Mykosen **28**:550–552.
241. **Robinson, H. J., H. F. Phares, and O. E. Graessle.** 1964. Antimycotic properties of thiabendazole. J. Invest. Dermatol. **42**:479–482.
242. **Rodriquez-Noriega, A., A. Palacio-Hernanz, F. Sanz-Sanz, S. Reyes, A. Bartlett-Coma, and M. Bris-Orche.** 1984. Double-blind investigation of R-42470 (terconazole cream 0.4%) and clotrimazole (cream 1%) for the topical treatment of mycotic vaginitis, p. 61/28-61/30. *In* K. H. Spitzy and K. Karrer (ed.), Proceedings of the 13th International Congress of Chemotherapy, vol. 6. Antivirals, antimycotics and experimental infections. Verlag H. Egermann, Vienna.
243. **Rogers, T. E., and J. N. Galgiani.** 1986. Activity of fluconazole (UK 49,858) and ketoconazole against *Candida albicans* in vitro and in vivo. Antimicrob. Agents Chemother. **30**:418–422.
244. **Rohde-Werner, H.** 1984. Topical tioconazole versus systemic ketoconazole treatment of vaginal candidiasis. J. Int. Med. Res. **12**:298–302.
245. **Rohwedder, J. J., and G. Archer.** 1976. Pulmonary sporotrichosis: Treatment with miconazole. Am. Rev. Respir. Dis. **114**: 403–406.
246. **Rumler, W., and S. Heins.** 1983. Konzentrations-Kontakzeit-Beziehungen bei der Wirkung von Clotrimazol auf *Candida albicans*. Mykosen **26**:293–297.
247. **Rumler, W., S. Heins, and J. Heins.** 1984. Relations between the concentration and the contact-time in the antifungal activity of 5-fluorocytosine, bifonazole and BAY N7133 to *Candida albicans*. Mykosen **27**:436–442.
248. **Rutgeerts, L., and H. Verhaegen.** 1977. Intravenous miconazole in the treatment of chronic esophageal candidiasis. Gastroenterology **72**:316–318.
249. **Ryley, J. F., R. G. Wilson, and K. Barrett-Bee.** 1984. Azole resistance in *Candida albicans*. Sabouraudia: J. Med. Vet. Mycol. **22**:53–63.
250. **Santen, R. J., H. Van den Bossche, J. Symoens, J. Brugmans, and R. DeCoster.** 1983. Site of action of low dose ketoconazole on androgen biosynthesis in men. J. Clin. Endocrinol. Metab. **57**:732–736.
251. **Sanz, F. S., and A. Del Palacio Hernanz.** 1987. Randomized comparative trial of three regimens of itraconazole for treatment of vaginal mycoses. Rev. Infect. Dis. **9**(Suppl. 1):139–142.
252. **Saúl, A., A. Bonifáz, and I. Arias.** 1987. Itraconazole in the treatment of superficial mycoses: an open trial of 40 cases. Rev. Infect. Dis. **9**(Suppl. 1):100–103.
253. **Savani, D. V., J. R. Perfect, L. M. Cobo, and D. T. Durack.** 1987. Penetration of new azole compounds into the eye and efficacy in experimental *Candida* endophthalmitis. Antimicrob. Agents Chemother. **31**:6–10.
254. **Schaffner, A., and P. G. Frick.** 1985. The effect of ketoconazole on amphotericin B in a model of disseminated aspergillosis. J. Infect. Dis. **151**:902–910.
255. **Schär, G., F. H. Kayser, and M. C. Dupont.** 1976. Antimicrobial activity of econazole and miconazole *in vitro* and in experimental candidiasis and aspergillosis. Chemotherapy (Basel) **22**:211–220.
256. **Schlüter, G.** 1982. Toxicology of bifonazole, p. 37–40. *In* H. Urabe, N. Zaias, and S. Stettendorf (ed.), International Antifungal Symposium: Bifonazole. Excerpta Medica, Amsterdam.

257. **Schurmeyer, T., and E. Nieschlag.** 1984. Effect of ketoconazole and other imidazole fungicides on testosterone biosynthesis. Acta Endocrinol. **105**:275–280.
258. **Scott, E. M., S. P. Gorman, and S. J. McGrath.** 1985. Inhibition of hyphal development in *Trichophyton mentagrophytes* arthroconidia by ketoconazole and miconazole. J. Antimicrob. Chemother. **15**:405–415.
259. **Scott, E. M., S. P. Gorman, J. S. Millership, and L. R. Wright.** 1986. Effect of miconazole and clotrimazole on K^+ release and inhibition of ergosterol biosynthesis in *Trichophyton mentagrophytes* and related ultrastructural observations. J. Antimicrob. Chemother. **17**:423–432.
260. **Scudamore, J., and P. Tooley.** 1983. The treatment of recurrent vaginal candidosis in general practice with the orally active antifungal agent ketoconazole. Curr. Ther. Res. **33**:917–920.
261. **Seeliger, H. P. R.** 1958. Pilzemmende Wirkung eines neuen Benzimidazol Derivatives. Mykosen **1**:162–171.
262. **Shadomy, S.** 1971. In vitro antifungal activity of clotrimazole (Bay b 5097). Infect. Immun. **4**:143–148.
263. **Shadomy, S.** 1971. In vivo studies with bay b 5097, p. 169–174. Antimicrob. Agents Chemother. 1970.
264. **Shadomy, S., D. M. Dixon, and R. May.** 1982. A comparison of bifonazole (Bay H 4502) with clotrimazole *in vitro*. Sabouraudia **20**:313–323.
265. **Shadomy, S., D. M. Dixon, R. May, and B. L. Shadomy.** 1982. *In vitro* and *in vivo* activity of bifonazole, p. 18–28. *In* H. Urabe, N. Zaias, and S. Stettendorf (ed.), International Antifungal Symposium: Bifonazole. Excerpta Medica, Amsterdam.
266. **Shadomy, S., A. Espinel-Ingroff, and T. M. Kerkering.** 1984. *In vitro* studies with four new antifungal agents: BAY n 7133, bifonazole (BAY h 4502), ICI 153,066 and Ro 14-4767/002. Sabouraudia: J. Med. Vet. Mycol. **22**:7–15.
267. **Shadomy, S., A. Espinel-Ingroff, T. A. Tartaglione, W. E. Dismukes, and the NIAID Mycoses Study Group.** 1986. Treatment of systemic mycoses with ketoconazole: studies of ketoconazole serum levels. Mykosen **29**:195–209.
268. **Shadomy, S., and L. Paxton.** 1976. *In vitro* studies with miconazole and miconazole nitrate, p. 171–178. *In* J. D. Williams and A. M. Geddes (eds.), Chemotherapy, vol. 6. Plenum Publishing Corp., New York.
269. **Shadomy, S., S. C. White, H.-P. Yu, W. E. Dismukes, and the NIAID Mycoses Study Group.** 1985. Treatment of systemic mycoses with ketoconazole: *in vitro* susceptibilities of clinical isolates of systemic and pathogenic fungi to ketoconazole. J. Infect. Dis. **152**:1249–1256.
270. **Shaw, J. T. B., M. H. Tarbit, and P. F. Troke.** 1987. Cytochrome P-450 mediated sterol synthesis and metabolism: differences in sensitivity to fluconazole and other azoles, p. 125–139. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
271. **Shepard, J. H., and R. L. Simmons.** 1986. Cyclosporin-ketoconazole: a potentially dangerous drug interaction. Clin. Pharmacol. **6**:468.
272. **Shepp, D. H., A. Klosterman, M. S. Siegel, and J. D. Meyers.** 1985. Comparative trial of ketoconazole and nystatin for prevention of fungal infection in neutropenic patients treated in a protective environment. J. Infect. Dis. **152**:1257–1263.
273. **Shigematsu, M. L., J. Uno, and T. Arai.** 1982. Effect of ketoconazole on isolated mitochondria from *Candida albicans*. Antimicrob. Agents Chemother. **21**:919–924.
274. **Slotman, G. J., and K. W. Buchard.** 1987. Ketoconazole prevents *Candida* sepsis in critically ill surgical patients. Arch. Surg. **122**:147–151.
275. **Smith, E. B., and E. Tschen.** 1987. Treatment of interdigital tinea pedis and tinea versicolor with bifonazole 1% solution applied once-daily, p. 407–414. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
276. **Smith, J., J. Hows, P. Donnelly, A. Baughan, J. Goldman, and E. C. Gordon-Smith.** 1983. Interaction of cyclosporin A and ketoconazole. Exp. Hematol. **11**(Suppl. 13):176–178.
277. **Sobel, J. D.** 1986. Recurrent vulvovaginal candidiasis. A prospective study of the efficacy of maintenance ketoconazole therapy. N. Engl. J. Med. **315**:1455–1458.
278. **Sobel, J. D., and G. Muller.** 1983. Comparison of ketoconazole, Bay N7133, and Bay L9139 in the treatment of experimental vaginal candidiasis. Antimicrob. Agents Chemother. **24**:434–436.
279. **Sobel, J. D., and D. Muller.** 1984. Comparison of itraconazole and ketoconazole in the treatment of experimental candidal vaginitis. Antimicrob. Agents Chemother. **26**:266–267.
280. **Sonino, N.** 1986. The endocrine effects of ketoconazole. J. Endocrinol. Invest. **9**:341–347.
281. **Sonino, N.** 1987. The use of ketoconazole as an inhibitor of steroid production. N. Engl. J. Med. **317**:812–818.
282. **Stenderup, A., and H. Schoenheyder.** 1984. Mycoses complicating AIDS. Microbiol. Sci. **1**:219–223.
283. **Stettendorf, S., and J. Sommer.** 1982. Local and systemic tolerance of bifonazole following topical application, p. 60–63. *In* H. Urabe, N. Zaias, and S. Stettendorf (ed.), International Antifungal Symposium: Bifonazole. Excerpta Medica, Amsterdam.
284. **Stevens, D. A.** 1977. Miconazole in the treatment of systemic fungal infections. Am. Rev. Respir. Dis. **116**:801–806.
285. **Stevens, D. A.** 1983. Miconazole in the treatment of coccidioidomycosis. Drugs **26**:347–354.
286. **Stevens, D. A., H. B. Levine, and S. C. Deresinski.** 1976. Miconazole in coccidioidomycosis. II. Therapeutic and pharmacologic studies in man. Am. J. Med. **60**:191–202.
287. **Stüttgen, G., and E. Bauer.** 1982. Bioavailability, skin- and nail penetration of topically applied antimycotics. Mykosen **25**: 74–80.
288. **Stüttgen, G., and E. Bauer.** 1985. Permeation von markiertem Oxiconazol. Vergleich der autoradiographischen mit der Horizontal-schnitt-Technik an menschlisher Haut. Mykosen **28**: 138–147.
289. **Sud, I. J., and D. S. Feingold.** 1981. Heterogeneity of action mechanisms among antimycotic imidazoles. Antimicrob. Agents Chemother. **20**:71–74.
290. **Sud, I. J., and D. S. Feingold.** 1981. Mechanisms of action of the antimycotic imidazoles. J. Invest. Dermatol. **76**:438–441.
291. **Sung, J. P., J. G. Grendahl, and H. B. Levine.** 1977. Intravenous and intrathecal miconazole therapy for systemic mycoses. West. Med. J. **126**:5–13.
292. **Tachibana, M., Y. Noguchi, and A. M. Monro.** 1987. Toxicology of fluconazole in experimental animals, p. 93–102. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
293. **Takechi, M., and M. Harada.** 1984. Antigenicity of 1-[1-[o-(m-chloro-benzyloxy) phenyl] vinyl]-1H-imidazole hydrochloride (710674-S) in the guinea pig. Pharmacometrics **28**:893–899.
294. **Talbot, M. D., and R. C. Spencer.** 1983. Oral ketoconazole in the treatment of vaginal candidosis. Curr. Ther. Res. **34**:746–749.
295. **Tannenbaum, L., C. Anderson, M. J. Rosenberg, and W. Akers.** 1984. 1% Sulconazole cream v 2% miconazole cream in the treatment of tinea versicolor. Arch. Dermatol. **120**:216–219.
296. **Tannenbaum, L., C. Anderson, M. J. Rosenberg, W. Howard, W. McDaniel, A. Neimanis, M. E. Ryan, and R. Perez.** 1982. Sulconazole nitrate 1.0 percent cream: a comparison with miconazole in the treatment of tinea pedis and tinea cruris/corporis. Cutis **30**:105–118.
297. **Täuber, U.** 1987. Availability of isoconazole in human skin after dermal application as free base and as nitrate *in vitro*. Arneim. Forsch. **37**:461–463.
298. **Täuber, U., P. Rach, and U. Lachnit.** 1984. Persistence of isoconazole in vaginal secretion after single application. Mykosen **27**:97–101.
299. **Taylor, F. R., R. J. Rodriques, and L. W. Parks.** 1983. Relationship between antifungal activity and inhibition of sterol biosynthesis in miconazole, clotrimazole, and 15-azasterol. Antimicrob. Agents Chemother. **23**:515–521.
300. **Tettenborn, D.** 1974. Toxicity of clotrimazole. Postgrad. Med.

J. **50**(Suppl. 1):17–20.
301. **Thiele, K., L. Zirngibl, M. H. Pfenniger, M. Egli, and M. Dobler.** 1987. Antimykotish wirksame Imidazolyl-alkene: Synthese und Rontgenstrukturanalyse von Omoconazol. Helv. Chim. Acta **70**:441–444.
302. **Thienpont, D., J. Van Cutsem, F. Van Gervan, J. Heeres, and P. A. J. Janssen.** 1979. Ketoconazole—a new broad spectrum orally active antimycotic. Experientia **35**:606–607.
303. **Thienpont, D., J. Van Cutsem, J. M. Van Nueten, C. J. E. Niemegeers, and R. Marsboom.** 1975. Biological and toxicological properties of econazole, a broad-spectrum antimycotic. Arneim. Forsch. **25**:224–230.
304. **Tolman, E. L., D. M. Isaacson, M. E. Rosenthale, J. L. McGuire, J. Van Cutsem, M. Borgers, and H. Van den Bossche.** 1986. Anticandidal activities of terconazole, a broad-spectrum antimycotic. Antimicrob. Agents Chemother. **29**:986–991.
305. **Trachtenberg, J.** 1984. Ketoconazole therapy in advanced prostatic cancer. J. Urol. **132**:61–63.
306. **Tricot, G., E. Joosten, M. A. Boogaerts, J. Vande Pitte, and G. Cauwenbergh.** 1987. Ketoconazole vs. itraconazole for antifungal prophylaxis in patients with severe granulocytopenia: preliminary results of two nonrandomized studies. Rev. Infect. Dis. **9**(Suppl. 1):94–99.
307. **Troke, P. F.** 1987. Efficacy of fluconazole in animal models of superficial and opportunistic systemic fungal infection, p. 103–112. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
308. **Troke, P. F., R. J. Andrews, K. W. Brammer, M. S. Marriott, and K. Richardson.** 1985. Efficacy of UK-49,858 (fluconazole) against *Candida albicans* experimental infections in mice. Antimicrob. Agents Chemother. **28**:815–818.
309. **Troke, P. F., R. J. Andrews, M. S. Marriott, and K. Richardson.** 1987. Efficacy of fluconazole (UK-49,858) against experimental aspergillosis and cryptococcosis in mice. J. Antimicrob. Chemother. **19**:663–670.
310. **Ueda, A. K., M. Franco, S. A. Fabio, and F. R. Prestes.** 1987. Ketoconazole in the treatment of experimental murine paracoccidioidomycosis. Mycopathologia **98**:27–34.
311. **Uno, J., M. L. Shigematsu, and T. Arai.** 1982. Primary site of action of ketoconazole on *Candida albicans*. Antimicrob. Agents Chemother. **21**:912–918.
312. **Utz, J. P.** 1980. Chemotherapy for the systemic mycoses: the prelude to ketoconazole. Rev. Infect. Dis. **2**:625–632.
313. **Van Cauteren, H., W. Coussement, J. Vandenberghe, V. Herin, P. Vanparys, and R. Marsboom.** 1987. The toxicological properties of itraconazole, p. 263–271. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
314. **Van Cauteren, H., J. Heykants, R. De Coster, and G. Cauwenbergh.** 1987. Itraconazole: pharmacologic studies in animals and humans. Rev. Infect. Dis. **9**(Suppl. 1):43–46.
315. **Van Cutsem, J.** 1983. The antifungal activity of ketoconazole. Am. J. Med. **74**(Suppl. 1B):9–15.
316. **Van Cutsem, J., J. Fransen, and P. A. J. Janssen.** 1987. Therapeutic efficacy of itraconazole in systemic candidosis in guinea pigs. Chemotherapy (Basel) **33**:52–60.
317. **Van Cutsem, J., J. Fransen, F. Van Gervan, and P. A. J. Janssen.** 1985. Oral treatment with ketoconazole in systemic candidosis of guinea-pigs: microbiology, hematology and histopathology. Sabouraudia: J. Med. Vet. Mycol. **23**:189–198.
318. **Van Cutsem, J., and F. Van Gerven.** 1986. The *in vivo* antifungal activity of broad-spectrum azoles. Drug Dev. Res. **8**:309–316.
319. **Van Cutsem, J., F. Van Gervan, and P. A. J. Janssen.** 1987. Activity of orally, topically, and parenterally administered itraconazole in the treatment of superficial and deep mycoses: animal models. Rev. Infect. Dis. **9**(Suppl. 1):15–32.
320. **Van Cutsem, J., F. Van Gervan, and P. A. J. Janssen.** 1987. The *in vitro* and *in vivo* antifungal activity of itraconazole, p. 177–192. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
321. **Van Cutsem, J., F. Van Gervan, M.-A. Van de Ven, M. Borgers, and P. A. J. Janssen.** 1984. Itraconazole, a new triazole that is orally active in aspergillosis. Antimicrob. Agents Chemother. **26**:527–534.
322. **Van Cutsem, J., F. Van Gerven, R. Zaman, and P. A. J. Janssen.** 1983. Terconazole—a new, broad-spectrum antifungal. Chemotherapy (Basel) **29**:322–331.
323. **Van Cutsem, J. M., and D. Thienpont.** 1972. Miconazole, a broad-spectrum antimycotic agent with antibacterial activity. Chemotherapy (Basel) **17**:392–404.
324. **Vanden Bossche, H.** 1974. Biochemical effects of miconazole on fungi. Biochem. Pharmacol. **23**:887–899.
325. **Vanden Bossche, H.** 1985. Biochemical targets for antifungal azole derivatives: hypothesis on the mode of action, p. 313–351. *In* M. R. McGinnis (ed.), Current topics in medical mycology, vol. 1. Springer-Verlag, New York.
326. **Vanden Bossche, H.** 1987. Itraconazole: a selective inhibitor of the cytochrome P-450 dependent ergosterol biosynthesis, p. 207–221. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
327. **Vanden Bossche, H., D. Bellens, W. Cools, J. Gorrens, P. Marichal, H. Verhoeven, G. Willemsens, R. De Coster, D. Beerens, C. Haelterman, M.-C. Coene, W. Lauwers, and L. Le Jeune.** 1986. Cytochrome P-450: target for itraconazole. Drug Dev. Res. **8**:287–298.
328. **Van Dyck, W. A., Jr.** 1986. A comparative study of butoconazole, miconazole and placebo. J. Reprod. Med. **31**(Suppl): 662–663.
329. **Van Gulpen, C., O. Kelder, H. Mattie, J. W. M. van der Meer, and J. van't Wout.** 1985. Pharmacokinetics of vibunazole (BAY n 7133) administered orally to healthy subjects. J. Antimicrob. Chemother. **16**:75–79.
330. **Van Rensburg, C. E. J., R. Anderson, G. Joone, M. F. van der Merwe, and H. A. Eftychis.** 1983. The effects of ketoconazole on cellular and humoral immune functions. J. Antimicrob. Chemother. **11**:49–55.
331. **Veronese, M., D. Barzaghi, and A. Bertoncini.** 1981. Antifungal activity of fenticonazole in experimental dermatomycosis and candidiasis. Arneim. Forsch. **31**:2137–2139.
332. **Veronese, M., M. Salvaterra, and D. Barzaghi.** 1981. Fenticonazole, a new imidazole derivative with antibacterial and antifungal activity. Arneim. Forsch. **31**:2133–2137.
333. **Wade, T. R., H. E. Jones, and J. J. Chanda.** 1979. Intravenous miconazole therapy of mycotic infection. Arch. Intern. Med. **139**:784–786.
334. **Wagner, W.** 1986. Comparison of clinical efficacy and tolerability of oxiconazole one dose vs. two doses daily. Mykosen **29**:280–284.
335. **Walker, K. A. M., A. C. Braemer, S. Hitt, R. E. Jones, and T. R. Matthews.** 1978. 1-[4-(4-Chlorophenyl)-2-(2,6-dichlorophenylthio)-n-butyl]-1-H-imidazole nitrate, a new potent antifungal agent. J. Med. Chem. **21**:840–843.
336. **Walther, M.** 1982. Feldstudie die Einmaltherapie von Vaginalmykosen mit Isoconazolnitrat. Praxis **71**:152–156.
337. **Weber, H., K. Patzschke, A. Casale, J. Castro, R. Galimberti, R. Gutman, W. Maul, W. Ritter, R. Rohwedder, and L. Wegner.** 1982. Pharmacokinetic investigations on bifonazole after topical application, p. 41–47. *In* H. Urabe, N. Zaias, and S. Stettendorf (ed.), International Antifungal Symposium: Bifonazole. Excerpta Medica, Amsterdam.
338. **Weisberg, M.** 1986. Treatment of vaginal candidiasis in pregnant women. Clin. Ther. **8**:563–567.
339. **Weuta, H.** 1976. Clinical studies with clotrimazole: pharmacokinetics, efficacy, tolerance, p. 179–182. *In* J. D. Williams and A. M. Geddes (ed.), Chemotherapy, vol. 6, Plenum Publishing Corp., New York.
340. **Wishart, J. M., and P. W. Gould.** 1981. Econazole treatment of fungal infections: an open trial. N. Z. Med. J. **94**:226–227.
341. **Woestenborghs, R., W. Lorreyne, and J. Heykants.** 1987. Determination of itraconazole in plasma and animal tissues by high performance liquid chromatography. J. Chromatogr. **413**: 332–337.

342. **Wood, P. R., and M. H. Tarbit.** 1986. Gas chromatographic method for the determination of fluconazole, a novel antifungal agent, in human plasma and urine. J. Chromatogr. **383**:179–186.
343. **Woolley, D. W.** 1944. Some biological effects produced by benzimidazole and their reversal by purines. J. Biol. Chem. **152**:225–232.
344. **Yamaguchi, T., T. Hiratani, and K. Iwata.** 1983. Studies on the mode of action of a new imidazole antimycotic sulconazole. Shinkin To Shinkinsho **24**:253–262.
345. **Yamaguchi, T., T. Hiratani, and M. Plempel.** 1983. *In vitro* studies of a new imidazole antimycotic, bifonazole, in comparison with clotrimazole and miconazole. Arneim. Forsch. **33**: 546–551.
346. **Yamaguchi, T., T. Hiratani, and M. Plempel.** 1983. *In vitro* studies of a new oral azole antimycotic, BAY N 7133. J. Antimicrob. Chemother. **11**:135–149.
347. **Yamaguchi, T., T. Hiratani, and K. Uchida.** 1987. The *in vitro* activity and evaluation of bifonazole, p. 335–352. *In* R. A. Fromtling (ed.), Recent trends in the discovery, development and evaluation of antifungal agents. J. R. Prous Publishers, Barcelona.
348. **Yamaguchi, T., and K. Iwata.** 1979. Effect of two imidazole antimycotics, clotrimazole and miconazole, on amino acid transport in *Candida albicans*. Sabouraudia **17**:311–322.
349. **Yamamoto, K., K. Hirose, A. Matsushita, M. Ueda, Y. Ozaki, M. Doteuchi, M. Nakamura, A. Akahori, and S. Narita.** 1984. General pharmacology of 1-[1-[2-[(3-chlorobenzyl) oxy] phenyl] vinyl]-1H-imidazole hydrochloride (710674-S), a new antifungal agent. Pharmacometrics **27**:533–562.
350. **Yap, B.-S., and G. P. Bodey.** 1979. Oropharyngeal candidiasis treated with a troche form of clotrimazole. Arch. Intern. Med. **139**:656–657.
351. **Yoshida, H., O. Kasuga, and T. Yamaguchi.** 1984. Studies on antifungal activities of sulconazole. 1. *In vitro* antimicrobial activity. Chemotherapy (Tokyo) **32**:477–484.
352. **Yoshida, H., O. Kasuga, T. Yamaguchi, S. Oshima, and H. Iwasaki.** 1984. Studies on antifungal activities of sulconazole. 2. Therapeutic effect of the cream formulation on experimental *Trichophyton mentagrophytes* infection of guinea pig. Chemotherapy (Tokyo) **32**:485–489.
353. **Yozwiak, M L., and J. N. Galgiani.** 1987. Itraconazole treatment of experimental systemic candidiasis in male rats. J. Med. Vet. Mycol. **25**:125–126.