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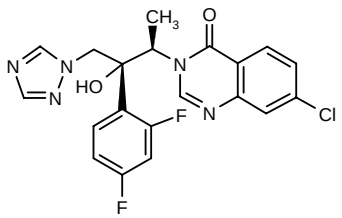
Albaconazole

Prop INN

Antifungal

UR-9825

(1*R*,2*R*)-7-Chloro-3-[2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]quinazolin-4(3*H*)-one



$C_{20}H_{16}ClF_2N_5O_2$

Mol wt: 431.833

CAS: 187949-02-6

EN: 248978

Abstract

The search for novel, potent broad-spectrum oral antifungal agents continues to be a research priority due to the increase in incidence of opportunistic fungal infections over the past 15 years. Azoles are attractive antimycotics with agents such as fluconazole and itraconazole exhibiting broad-spectrum activity and improved safety profiles over other antifungal compounds. One such novel azole to emerge which shows considerable clinical promise is albaconazole (UR-9825). The orally active azole has shown excellent activity *in vitro*, with MIC values lower than or comparable to those obtained for fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole. The agent was also active against fluconazole-resistant *Candida* spp., non-*albicans Candida* strains, *Cryptococcus neoformans*, filamentous fungi (*e.g.*, *Aspergillus* spp., *Trichophyton* spp., *Microsporum* spp.), *Scedosporium*, other life-threatening molds including amphotericin B-resistant strains and the parasite *Trypanosoma cruzi*. Moreover, the agent was markedly active *in vivo* in animal models of candidiasis, aspergillosis, cryptococcosis, scedosporiosis and trypanosomiasis. Albaconazole has been shown to be rapidly absorbed in humans with excellent cardiovascular safety and tolerability profiles obtained. The agent is scheduled to begin phase II clinical trials in vulvovaginal candidiasis later this year.

Synthesis*

Albaconazole can be prepared by two different ways:

1) Condensation of the chiral oxazolidinone (I) with 2,4-difluorophenacyl bromide (II) by means of NaHMDS in THF/Et_2O gives the chiral oxirane (III), which is treated with LiOH and H_2O_2 to eliminate the chiral auxiliary, yielding the carboxylic acid (IV). Opening the oxirane ring of (IV) with 1,2,4-triazole (V) and NaH in hot DMF results in the chiral hydroxyacid (VI), which is submitted to Curtius rearrangement by means of DPPA in hot pyridine to provide the chiral oxazolidinone (VII). Cleavage of the oxazolidinone ring of compound (VII) by means of refluxing aqueous HCl affords the chiral aminoalcohol (VIII) (1), which is condensed with 2-amino-4-chlorobenzoic acid (IX) by means of DCC and HOBt to yield the corresponding amide (X). Finally, this compound is cyclized by reaction with triethyl orthoformate in hot dioxane/NMP (2, 3). Scheme 1.

2) Condensation of (*R*)-lactic acid (XI) with morpholine (XII) gives the corresponding morpholide (XIII), which is protected at the hydroxyl position with dihydropyran (XIV) to yield the tetrahydropyranyl ether (XV). The Grignard reaction of (XV) with 2,4-difluorophenylmagnesium bromide (XVI) affords the chiral 1-propanone (XVII), which by a Corey's diastereoselective epoxidation with trimethylsulfoxonium iodide is converted into the oxirane (XVIII). Opening the oxirane ring of (XVIII) by means of 1,2,4-triazole (V) and NaH provides the tertiary alcohol (XIX), which is treated with pyridine *p*-toluenesulfonate to give the deprotected diol (XX) as a (2*R*,3*R*) and (2*R*,3*S*) 4:1 diastereomeric mixture, from which the desired (2*R*,3*R*)-isomer (XXI) is isolated by crystallization. Reaction of compound (XXI) with Ms-Cl and TEA, followed by cyclization with NaOMe, yields the oxirane (XXII) (4), which is finally condensed with 7-chloroquinazolin-4(3*H*)-one (XXIII) – obtained by condensation of 2-amino-4-chlorobenzamide (XXIV) with triethyl orthoformate in hot dioxane/NMP – by means of K_2CO_3 in hot NMP (5). Scheme 2.

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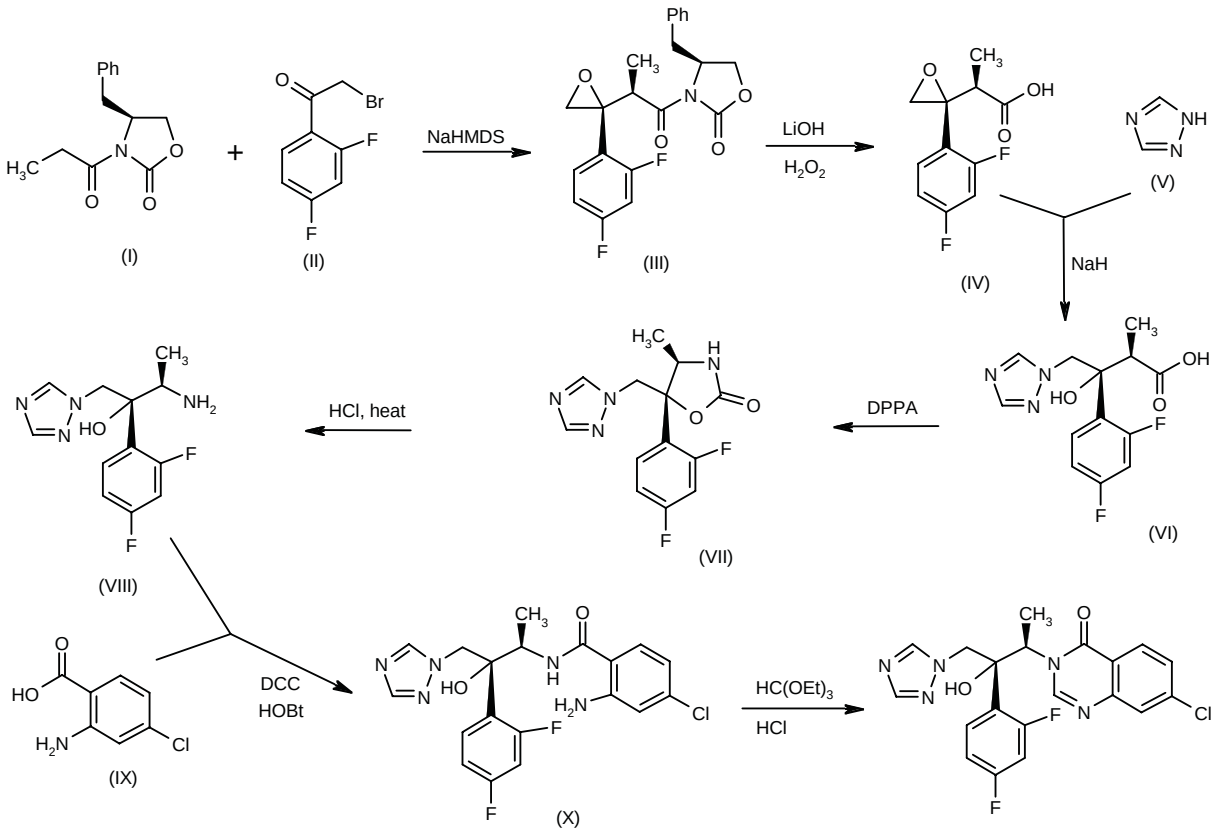
Scheme 1: Synthesis of Albaconazole



Introduction

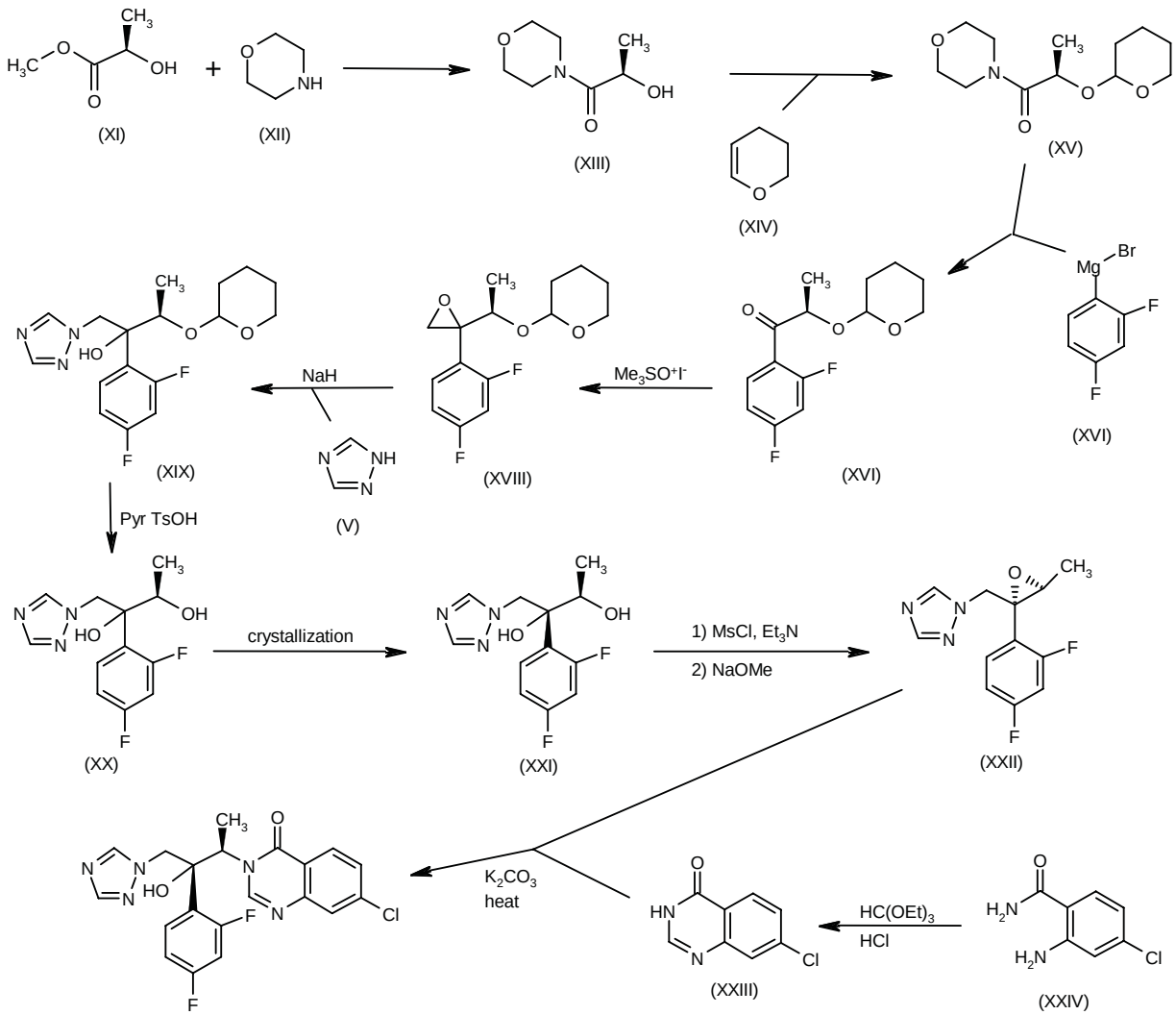
Systemic mycosis has become a major clinical concern and research priority due to the increase in the incidence of opportunistic fungal infections over the past 15 years. This type of infection can be a life-threatening condition for immunocompromised individuals such as HIV-infected and cancer patients, patients in intensive care units and recipients of organ transplants. *Candida* spp. in particular are commonly found in intensive care units, with *Candida albicans* the most frequently isolated strain associated with mucosal and hematogenously disseminated mycosis. An increase has also been observed in the incidence of non-*albicans* infections such as those caused by *Candida glabrata*, *Candida tropicalis* and *Candida krusei*, and *Aspergillus* spp., *Histoplasma capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis*, *Scedosporium prolificans* and *Cryptococcus neoformans* have emerged as clinically significant pathogens (6-12).

There are numerous antifungal agents currently available. However, they are frequently associated with adverse events, resistance development and/or poor bioavailability (13, 14). Thus, the search for novel antifungals displaying increased efficacy and tolerability remains of paramount importance.

Azoles in particular, such as fluconazole, itraconazole and voriconazole, have demonstrated considerable promise as effective antimycotics. They exhibit broad-spectrum activity and improved safety profiles over compounds such as flucytosine and amphotericin B. Due to the superior efficacy of these agents, the search for novel triazoles with increased antifungal activity is ongoing (12, 15, 16).

One agent to emerge which shows considerable clinical promise is albaconazole. The orally active azole has displayed excellent activity *in vitro* against clinically important fungal organisms such as *Candida albicans*, non-*albicans Candida* strains, *Cryptococcus neoformans*, *Aspergillus fumigatus* and *A. flavus* and the parasite *Trypanosoma cruzi*. The MIC values obtained for the agent were lower than or comparable to those obtained for fluconazole, itraconazole, voriconazole, posaconazole and ravuconazole. Moreover, albaconazole displayed potent *in vivo* activity in animal models of candidiasis, aspergillosis, cryptococcosis, scedosporiosis and

Scheme 2: Synthesis of Albaconazole



trypanosomiasis. Albaconazole was therefore chosen for further development as an oral antifungal agent.

Antifungal Activity

In vitro *studies*

The *in vitro* activity of albaconazole was examined using the broth microdilution method and compared to activities of fluconazole, itraconazole and voriconazole against 97 strains of yeast including fluconazole-resistant strains and filamentous fungi. The MIC values obtained for albaconazole against all yeast species tested were slightly higher than voriconazole and superior to the values obtained for itraconazole and fluconazole. The geometric mean MICs (μg/ml) for albaconazole *versus* voriconazole, fluconazole and itraconazole (respectively) were: 0.03 *vs.* 0.11, 1.07 and 0.87 for *C. albicans*; 0.32 *vs.* 0.36, 9.36 and 2.20 for *C. glabrata*; 0.01 *vs.* 0.09, 5.66 and 0.71 for *C. guilliermondii*; 0.01 *vs.* 0.02, 0.77, and 0.25 for *C. parapsilosis*; 0.07 *vs.* 0.17, 3.62 and 0.82 for *C. tropicalis*; 0.01 *vs.* 0.04, 2.00, 0.31 for *Cryptococcus neoformans*; and 0.05 *vs.* 0.10, 2.83 and 0.50 for *Trichosporum cutaneum*. Albaconazole also displayed activity and was superior to voriconazole and itraconazole (respectively) against fluconazole-resistant (MICs > 32 μg/ml) *C. albicans* (geometric mean MIC = 5.66 *vs.* 17.96 and >32 μg/ml for 6 strains), *C. glabrata* (2.83 *vs.* 2 and >32 μg/ml for 2 strains), *C. krusei* (0.25 *vs.* 0.50 and 1 μg/ml for 3 strains) and *C. tropicalis* (0.28 *vs.* 0.80 and 8 μg/ml for 2 strains) (data on file, Uriach).

An *in vitro* study using a broth microdilution method compared the antifungal activity of albaconazole with fluconazole and itraconazole against 283 clinical isolates of *Candida* spp. Albaconazole was superior to fluconazole and itraconazole ($MIC_{50/90}$ μg/ml, respectively) against isolates of *C. albicans* (0.0002/0.0002 or less, 0.2/4 and 0.03/0.25), *C. parapsilosis* (0.0002/0.0002 or less, 1/2 and 0.03/0.06), *C. guilliermondii* (0.0002/0.0002 or less, 8/8 and 0.5/0.5), *C. tropicalis* (0.0002 or less/0.03, 0.5/8 and 0.06/0.12), *C. glabrata* (0.06/0.12, 8/32 and 0.5/1) and *C. krusei* (0.015/0.06, 32/64 and 0.25/0.25) (18, 19).

Similar results were obtained when the activity of albaconazole was compared to fluconazole and itraconazole against 100 bloodstream yeast strains of *C. albicans*, *C. parapsilosis*, *C. glabrata*, *C. tropicalis*, *C. krusei*, *C. kefyr*, *C. guilliermondii*, *C. dubliniensis*, *C. lusitaniea*, *Cryptococcus neoformans*, *Trichosporon mucoides* and *Rhodoootorula rubra* isolated from blood cultures of symptomatic patients with deep fungal infections. The geometric mean MIC values for albaconazole against all strains were lower (less than 0.06 μg/ml for all strains except *C. glabrata* [0.28 μg/ml] and *C. krusei* [0.08 μg/ml]) than those obtained for fluconazole and itraconazole in all cases (20).

Albaconazole was more active than voriconazole, ravuconazole and posaconazole against *C. albicans* (74 isolates), *C. glabrata* (47 isolates), *C. guilliermondii* (8 isolates), *C. krusei* (5 isolates), *C. parapsilosis* (10 isolates) and *C. tropicalis* (14 isolates) strains of which the majority were isolated from patients with *Candida* vulvovaginitis. The geometric mean MIC for albaconazole was 0.039 μg/ml as compared to 0.060, 0.065 and 0.267 μg/ml obtained for ravuconazole, voriconazole and posaconazole, respectively (data on file, Uriach).

Several studies have demonstrated the excellent activity of albaconazole against filamentous fungi.

Albaconazole displayed excellent activity against 190 clinical *A. fumigatus* isolates cultured between 1945 and 1998 in the Netherlands. The geometric mean MICs obtained for albaconazole, itraconazole, voriconazole, terbinafine, amphotericin B and LY-303366 (anidulafungin) were 0.16, 1, 0.17, 1.72, 2 and 0.12 μg/ml, respectively. In this study, 3 isolates that were moderately resistant (MIC = > 32 μg/ml) to itraconazole were susceptible to both albaconazole and voriconazole (21).

The activity of albaconazole (geometric MIC = 0.31 μg/ml) was comparable to voriconazole (geometric mean MIC = 0.29 μg/ml) and itraconazole (geometric mean MIC = 0.41 μg/ml) and superior to fluconazole (geometric mean MIC = 22.63 μg/ml) against 30 strains of filamentous fungi including *Absidia corymbifera*, *Alternaria* sp., *Aspergillus* spp., *Beauveria* sp., *Cladosporium* sp., *Drechslera* sp., *Emmonsia parva*, *Fusarium* sp., *Microsporum* spp., *Sporotrix* sp., *Trichophyton* spp., *Ulocladium* sp. and *Wangiella dermatiditis* (data on file, Uriach).

Albaconazole was superior to amphotericin B against 77 strains of clinically important filamentous fungi (*A. fumigatus*, *A. flavus*, *A. niger*, *Paecilomyces* spp., *Chaetomium globosum* and *Scytalidium* spp.) *in vitro*, with MICs in the range of 0.1-2 μg/ml for all isolates tested except *Fusarium solani* and *Scitadilium lignicola* (> 16 μg/ml *vs.* 2 for amphotericin B for both strains) (22, 23).

Albaconazole displayed excellent *in vitro* activity against 508 strains of dermatophytes (*Epidermophyton floccosum*, *Microsporum* spp., *Trichophyton* spp.; MIC_{90} = 0.25 μg/ml for all strains). Comparable activity was observed for voriconazole, clotrimazole and terbinafine (MIC_{90} = 0.25, 0.25 and 0.06 μg/m, respectively). Albaconazole was more potent than miconazole (MIC_{90} = 0.5 μg/ml), itraconazole (MIC_{90} = 0.5 μg/ml), ketoconazole (MIC_{90} = 1 μg/ml), amphotericin B (MIC_{90} = 1 μg/ml), furvina (MIC_{90} = > 16 μg/ml) and fluconazole (MIC_{90} = 32 μg/ml) (23).

Albaconazole also showed *in vitro* activity against *Scedosporium* spp. and *Malassezia* spp. (*M. furfur*, *M. pachydermatis*, *M. sympodialis*, *M. slooffiae*). In contrast to amphotericin B, ketoconazole, itraconazole and nystatin, which were ineffective against *Scedosporium apiospermum* (11 strains; geometric mean MICs = 4 to 13 μg/ml) and *S. prolificans* (33 strains; geometric mean MICs = 6.5 to 15 μg/ml), albaconazole (MIC = 1 μg/ml), posaconazole (MIC = 0.08 μg/ml), ravuconazole (MIC = 0.125 μg/ml) and voriconazole (0.06 μg/ml) displayed activity against *S. apiospermum*. Albaconazole (MIC = 0.35 μg/ml) and voriconazole (1.83 μg/ml) were the only agents active against *S. prolificans* (24). Albaconazole was very active against all 40 strains of *Malassezia* isolates examined (MIC = 0.06 μg/ml or less for all strains). MIC values for ketoconazole, itraconazole and voriconazole were 0.03 or less, 0.03 or less to 6 and 0.03 or less to 12 μg/ml, respectively. All strains were resistant to 5-fluorocytosine (MIC > 64 μg/ml) and the MICs for fluconazole ranged from 0.25-4 μg/ml (25).

Results from an *in vitro* study demonstrated the excellent activity of albaconazole against *T. cruzi*. The MIC for the agent was 33-fold lower than that obtained for ketoconazole. Moreover, the MIC for albaconazole against the intracellular amastigote was even lower (10 nM) and comparable to that obtained for ketoconazole. Further examination of the effects of albaconazole revealed that at the MIC, growth arrest correlated with a depletion of the parasite's 4,14-desmethyl endogenous sterols which were replaced by methylated sterols. Thus, the mechanism of action of albaconazole against this parasite was concluded to involve inhibition of C14α demethylase. In addition, analysis of growth-arrested epimastigotes showed significant increases in phosphatidylethanolamine and phosphatidylserine and reductions in phosphatidylcholine (26).

In vivo *studies*

The antifungal efficacy of albaconazole was demonstrated *in vivo* in animal models of candidiasis, aspergillosis, cryptococcosis, trypanosomiasis and scedosporiosis.

Albaconazole was effective in both rat and rabbit models of systemic candidiasis (*C. albicans*). In rats, both albaconazole and fluconazole at an oral dose of 5 mg/kg b.i.d. (for 5 days) significantly decreased kidney fungal burden as compared to placebo (1.18 ± 0.63 and 1.17 ± 0.44 $\log_{10}$ cfu/g, respectively, *vs.* 7.19 ± 0.20 $\log_{10}$ cfu/g in placebo) on day 40. Similarly, in rabbits, both albaconazole (0.5, 2.5, 12.5 and 20 mg/kg once daily p.o. for 7 days starting 4 h before infection) and fluconazole (12.5 and 20 mg/kg once daily p.o. for 7 days) significantly reduced fungal burden in the kidney and lung as compared to controls. Albaconazole at a dose of 12.5 mg/kg was significantly more effective in reducing kidney and lung fungal burden than an equivalent dose of fluconazole (27).

A study using a rat model of aspergillosis (*A. fumigatus* CECT 2071) demonstrated that albaconazole (1, 5, 25 and 50 mg/kg p.o. starting 6 h before infection, 1 h postinfection and continued b.i.d. for 6 days) dose-dependently reduced hepatic fungal burden. A dose of 50 mg/kg was more effective than amphotericin B (2 mg/kg i.v. starting 6 h before infection, 1 h postinfection and continued for once daily for 6 days) in that it completely eradicated fungus from the liver (27).

In a study using a rabbit model of systemic cryptococcosis (*C. neoformans*), albaconazole and fluconazole significantly decreased fungal burden (5 mg/kg once daily for 19 days, 20 mg/kg once daily p.o. for 22 days and 80 mg/kg once daily for 14 days starting 4 days postinfection) in aspirated cerebral spinal fluid (CSF). Comparative drug concentrations between serum and CSF suggested a CSF penetration from serum of 15% by day 7 when using 80 mg/kg therapy (28).

The efficacy of albaconazole (15, 25 and 50 mg/kg p.o. starting 24 h postinfection and continuing for 9 days) on increasing survival rates and reducing fungal burden was examined in a study using a rabbit model of scedosporiosis (*S. prolificans*) and amphotericin B (0.8 mg/kg/day i.v.) as a comparison agent. All animals treated with 50 mg/kg albaconazole survived until the end of the study period as compared to only 50% treated with 25 mg/kg albaconazole or with amphotericin B; albaconazole at a dose of 15 mg/kg did not increase survival rates. At the end of the study period, all albaconazole-treated animals regardless of the dose had a complete eradication in the spleen, liver and lung and greater reductions in fungal burden in the brain and kidney as compared to amphotericin B-treated animals and controls (29).

Preliminary results from an ongoing study using a dog model of trypanosomiasis (*T. cruzi* strains: Berenice-78, susceptible to benznidazole or Y strain, partially susceptible to benznidazole) indicate that treatment with albaconazole (1.5 mg/kg for 90 days) cured all animals infected with the Y strain; albaconazole was not effective in animals infected with the Berenice-78 strain. In contrast, benznidazole cured all animals regardless of the strain used for infection. However, results still suggest that albaconazole may be an option for the treatment of Chagas' disease (30).

Safety studies

The effects of albaconazole on the cardiovascular, respiratory, central nervous, gastrointestinal and renal systems and on behavior were examined in mice, rats and rabbits (data on file, Uriach).

Albaconazole displayed a favorable safety profile. The agent had no affinity for adenosine, α- and β-adrenergic, dopamine, cholinergic histamine, serotonin, opiate, GABA and NMDA receptors but was shown to inhibit the 5-HT_{1B} receptor subtype in the rat cerebral cortex by 50%. Mild flaccidity or muscle relaxation was observed in mice with doses of 250 and 1250 mg/kg p.o. and reduced motor activity was seen in mice at the high dose of 1250 mg/kg. In rats, some ulcerogenic activity and a reduction in urinary potassium excretion was detected but only at a high dose of 1250 mg/kg p.o.

Ethanol- and hexobarbital-induced sleeping time was dose-dependently increased by oral albaconazole (50, 250 and 1250 mg/kg); increases in ethanol-induced sleep time were significant only at the highest dose while doses of 260 and 1250 mg/kg produced significant increases in barbiturate-induced sleeping time.

Albaconazole (i.v.) had no detectable effect on cardiovascular (including ECGs), respiratory or hemodynamic parameters in dogs (31). In addition, studies *in vitro* showed that albaconazole had no effects on action potential duration in isolated Purkinje fibers and negligible inhibition of the HERG channel transfected in HEK 293 cells.

Toxicity studies

Albaconazole was shown to have very low toxicity in acute toxicity studies conducted in rodents. The LD_{50} value for albaconazole obtained for rats and mice of both sexes in acute toxicity studies was greater than 2000 mg/kg p.o. A 13-week oral toxicity study with a 4-week recovery period is currently under way (data on file, Uriach).

Very low toxicity was noted in 4-week oral toxicity studies in rats (3, 30 and 300 mg/kg/day p.o.), dogs (0.5, 2 and 8 mg/kg/day) and cynomolgus monkeys (3, 21 and 150 mg/kg/day p.o.). Increases in liver weight were observed in all treated animals and histopathological examination revealed that the liver is the main target organ for the agent. In dogs and monkeys, dose-dependent decreases in total cholesterol levels were observed with treatment. Treatment of dogs with the two highest doses was associated with an increase in prothrombin time in both sexes and an increase in alkaline phosphatase levels in females; dogs treated with the highest dose had signs of multifocal necrosis of the gastric mucosa and sinusoidal hepatic and gastrointestinal tract congestion with a sanguinolent content.

Two 4-week toxicity studies were conducted in monkeys. In the first dose-finding study, that included a 13- and 15-day recovery period for animals administered 50 and 150 mg/kg, all albaconazole doses were associated

with reductions in erythrocyte count, hemoglobin and hematocrit levels for both sexes, with recovery to baseline levels only observed in animals treated with the 10 mg/kg dose. The 2 monkeys administered the 150 mg/kg dose displayed increased GPT levels (also noted in a male treated with the 50 mg/kg dose), reductions in phosphorus, albumin and total cholesterol; the slight increases in total cholesterol levels returned to baseline during the recovery period. The highest dose was associated with increased liver and adrenal weights, although no histopathological changes were noted in the adrenals, liver and kidneys.

In the second 4-week toxicity study which included a 2-week recovery period, no alterations in ECG (including the QTc interval), ocular or urinary parameters were observed and any changes in hematological parameters seen were not attributed to treatment. However, 2 of the 10 monkeys treated with 150 mg/kg suffered from emesis and cutaneous lesions and died or were sacrificed before the end of treatment; 5 animals from this group developed acanthotic interstitial dermatitis. The high dose was also associated with a decrease in total cholesterol levels, HDL cholesterol, albumin and albumin/globulin ratios and an increase in ALT/GPT serum levels. Multifocal hepatocytic necrosis with the presence of Councilman bodies and hepatocytic vacuolization was observed as well as fatty changes in the fascicular cortical area of the adrenals in animals treated with 150 mg/kg. The 21 mg/kg dose was also associated with an increase in ALT/GPT levels and a decrease in total serum cholesterol levels. Centrilobular hepatocytic steatosis was noted in these animals and alterations in the adrenals; no cutaneous lesions or emesis was seen in this dose group. The lowest 3 mg/kg dose was associated with only slight increases in serum ALT/GPT levels. All alterations observed with the 21 and 150 mg/kg doses resolved or showed signs of recovery at the end of the recovery period. A 13-week oral toxicity study in monkeys including a 4-week recovery period is currently under way (data on file, Uriach).

Albaconazole did not show mutagenicity in the Ames test or clastogenic effects in the micronucleus test *in vivo* in mice or *in vitro* after metaphase chromosome aberration analysis in human lymphocytes (data on file, Uriach).

Teratology studies were conducted in both rats (10, 65 and 400 mg/kg/day p.o. from day 6-17 of pregnancy) and rabbits (4, 20 and 80 mg/kg/day p.o. from days 6 to 18 of pregnancy). The no observable adverse effects level (NOAEL) in rats for embryo-fetal development was 10 mg/kg/day. In rabbits, the NOAELs for pregnant females and fetuses were determined to be 20 and 4 mg/kg/day, respectively (data on file, Uriach).

Pharmacokinetics and Metabolism

The pharmacokinetics of single-dose albaconazole were determined in mice, rats, rabbits, dogs, monkeys and humans. In animals, half-life values for the agent ranged from 1 h in mice to almost 60 h in dogs. The absolute oral bioavailability was 100% in rats and dogs and 50-57% in monkeys (data on file, Uriach).

The terminal $t_{1/2}$, t_{max}, C_{max} and $AUC_{0-\infty}$ values for albaconazole (20 mg/kg p.o.) in mice were 1.1 h, 0.5 h, 2.8 μg/ml and 8.7 μg·h/ml, respectively.

In rats, i.v. albaconazole (15 mg/kg) presented a terminal $t_{1/2}$ value of 2.96 h. The calculated volume of distribution and plasma clearance were 2.4 l/kg and 0.57 l/kg·h, respectively. A C_{max} of 3.2 μg/ml was achieved at 4 h postdosing. The absolute oral bioavailability was more than 100% and no unchanged compound was detected in urine after oral administration at 3 mg/kg. The $AUC_{0-\infty}$ values for males and females were 7.1 and 6.4 μgEq·h/ml, respectively, following oral dosing and 9.5 and 10.2 μgEq·h/ml, respectively, after i.v. dosing. The $t_{1/2}$ value for oral administration was 5.5 h in females and 7.2 h hours in males; following i.v. dosing, these values were 7.4 and 10.8 h, respectively.

The distribution and excretion of single-dose [^{14}C]-albaconazole (3 mg/kg p.o. 60 μCi/kg) were examined in rats. The agent was absorbed rapidly with plasma levels peaking at 1 h postdosing. Absorption of radioactivity appeared to more rapid and more extensive in female as compared to male rats, although plasma $t_{1/2}$ values were similar for both. Radioactivity was widely distributed throughout the body. The highest concentrations were detected in systemic organs at about 1 h postdosing. The gastrointestinal tract was found to have the highest concentration of radioactivity and up to 10% of the administered dose was found in the liver. High levels of radioactivity were also noted in perirenal fat, brown fat and the adrenal glands in both males and females and in the mammary glands of females. Biliary excretion was suggested to be involved in the metabolism of the agent since there was a low level (less than 3%) of radioactivity detected in urine. Radioactivity was mainly excreted in feces (88.5 and 93.3% of the dose detected after i.v. and p.o. dosing respectively) in both males and females. Excretion patterns were similar after i.v. administration of the agent (3 mg/kg). Results from specific biliary excretion studies performed in rats treated with a 3 mg/kg kg oral dose of [^{14}C]-albaconazole indicated that 90% or more of the dose of radioactivity was recovered in bile and that there was the possibility of involvement of an enterohepatic cycle.

A pharmacokinetic study in rabbits reported terminal $t_{1/2}$, C_{max} and $AUC_{0-\infty}$ values for single-dose albaconazole (20 mg/kg p.o.) of 8.6 ± 0.8 h, 5.1 ± 1.8 μg/ml (at 0.5 and 24 h postdosing) and 111.4 ± 14.8 μg·h/ml, respectively.

The pharmacokinetics of single-dose albaconazole (15 mg/kg i.v. and p.o.) were examined in male beagle dogs. The terminal $t_{1/2}$ value was 59.6 ± 3.2 h after i.v. dosing and 51.2 ± 5.5 h after oral dosing. The volume of distribution after i.v. dosing was 6.1 ± 1.4 l/kg and maximum plasma concentrations of 2.6 ± 0.24 μg/ml were seen between 4 and 24 h postdosing. The absolute oral bioavailability was 100.7 ± 1.2%.

The pharmacokinetics of albaconazole were examined in male and female cynomolgus monkeys receiving a single oral dose (3 mg/kg) followed by a washout period and a subsequent i.v. bolus (1 mg/kg). The AUC values obtained for oral and i.v. dosing (males/females) were 7.4 ± 1.0/8.1 ± 1.8 μg·h/ml and 4.3 ± 0.7/5.4 ± 0.09 μg·h/ml, respectively. C_{max} and t_{max} values after oral dosing (males/females) were 0.82 ± 0.2/0.68 ± 0.1 μg/ml and 27 ± 1.2/1.7 ± 0.6 h, respectively. The $t_{1/2}$, clearance and volume of distribution values after an i.v. bolus (males/females) were 11 ±12.6/13.6 ± 4.2 h, 187.7 ± 17.1/175 ± 15.7 ml/h and 3 ± 0.7/3.5 ± 1.3 l, respectively.

The absorption, distribution and excretion of oral and i.v. [^{14}C]-albaconazole (3 mg/kg; 20 μCi/kg) were examined in cynomolgus monkeys. Values for maximum plasma radioactivity, t_{max}, $AUC_{0-\infty}$, $t_{1/2}$ and volume of distribution after oral administration were 1.1 μgEq·h/ml, 1.8 h, 37.2 μgEq·h/ml, 53.2 h and 5.2 l/kg, respectively. $AUC_{0-\infty}$, $t_{1/2}$ and volume of distribution values after i.v. administration were 15.4 μgEq·h/ml, 45.4 h and 4.3 l/kg, respectively. The total body clearance value was 0.07 l/kg.h. The agent was predominantly eliminated in feces, where 64.1% of the radioactivity was recovered after oral and i.v. administration; 17.6% of the radioactivity was recovered in urine and 3.3% recovered during the washout period.

A study examining the metabolism of albaconazole in vitro by incubating hepatocytes from rat, dog and monkey with [^{14}C]-albaconazole (1, 2 and 3 μM), identified 5 metabolites. In human hepatocytes, the 5 metabolites appeared later (48 h) as compared to other species following incubation with 2 and 3 μM albaconazole (data on file, Uriach).

In vitro experiments using pooled human liver microsomes showed that [^{14}C]-albaconazole (1-20 μM for 4 h) was dose-dependently metabolized to a single metabolite. Metabolism was catalyzed by cytochrome P450 (CYP) 3A4/5. K_m and V_{max} values were 3.1 μM and 125 pmol/h/mg protein, respectively, and the calculated intrinsic clearance and hepatic extraction coefficient were 0.65 ml/min/kg and 0.13%, respectively (32). Further investigation of the interactions of albaconazole with CYPs as compared to other antifungal agents obtained IC_{50} values for the inhibition of [^{14}C]-testosterone metabolism (*i.e.*, CYP3A4 activity) for fluconazole, voriconazole and albaconazole of 98.7, 45.9 and 12.4 μM, respectively. Results from another *in vitro* study using rat microsomes compared the inhibitory activity of antifungals in inhibiting testosterone metabolism with the following order of potency obtained: ketoconazole = posaconazole > ravuconazole = albaconazole > voriconazole > fluconazole. Albaconazole was also shown to be a relatively weak inhibitor of CYP2C8/9/10 and CYP2D6. It was concluded that only its interaction with CYP3A4 has the potential to cause drug-drug interactions (data on file, Uriach).

The effect of albaconazole (3, 21 and 150 mg/kg p.o. for 4 weeks) on hepatic CYPs was examined in male and female cynomolgus monkeys. Examination of liver samples revealed that treatment with the 21 and 150 mg/kg doses induced CYP1A, CYP2B, CYP2E and CYP3A; the lowest dose had no effect on the CYPs measured. Induction of CYPs with the two highest doses was reversed during a 2-week period when the drug was withdrawn (data on file, Uriach).

Clinical Studies

The absorption, metabolism, pharmacokinetics and excretion of [^{14}C]-albaconazole (80 mg in a 50 ml oral solution; about 67 μCi) were examined in a phase I, open-label study involving 6 healthy male volunteers. Results suggest that the agent was safe and well tolerated. No serious adverse events or changes in vital signs or ECG or laboratory parameters were observed. A total of 25 adverse events were reported, of which the most common was headache (9 cases). Radioactivity was absorbed rapidly with a t_{max} of 0.75 h obtained. The C_{max} values for radioactivity in plasma and whole blood were 1.1 ± 0.3 and 0.63 ± 0.2 μgEq/ml, respectively, and the mean $t_{1/2}$ values for radioactivity in plasma and whole blood were 63 and 71.2 h, respectively. AUCt values were 46.4 ± 6.5 and 23.3 ± 3.4 μgEq·h/ml in plasma and whole blood, respectively, and the AUC values were 50 ± 8.6 and 30.2 ± 4.3 μgEq·h/ml, respectively. Very little binding of radioactivity to red blood cells was noted. *In vitro* experiments showed that binding of [^{14}C]-albaconazole to plasma proteins was not dose-dependent and was 96-97%.

In this study, albaconazole was shown to be rapidly absorbed and well distributed to tissues, with biexponential decay and a long half-life of 55.3 h. Radioactivity was mainly excreted in feces (55.8 ± 11.2% of the dose during 0-336 h) with 29.9 ± 10.9% recovered in urine. At 3 h postdosing, the unchanged compound was the major component detected in plasma together with very low concentrations of 4 minor metabolites The unchanged compound and 2 metabolites, a sulphate and glucuronide of a single hydroxylated albaconazole derivative, were detected in urine samples (32).

The safety, tolerability and pharmacokinetics of an oral solution of albaconazole have been studied in a total of 48 healthy volunteers participating in 2 double-blind, randomized, placebo-controlled studies. Subjects were administered either single (80, 160, 240 or 320 mg) or multiple (80 or 160 mg/day for 14 days) doses in an oral solution formulation. Good tolerance was reported. The most frequent adverse event was mild to moderate headache (12%). High drug exposure was detected after both single and multiple doses. After single doses, peak plasma levels increased proportionally with dose (mean C_{max} = 0.94, 1.84, 3.24 and 3.60 μg/ml, respectively), but the increase in $AUC_{0-\infty}$ (15.1, 35.5, 60.8 and 95.3 μg·h/ml, respectively) was greater than proportional. Albaconazole was characterized by little intersubject variability in pharmacokinetic parameters, rapid absorption (mean t_{max} = 1 h) and prolonged, dose-dependent elimination ($t_{1/2}$ = 55-93 h). Plasma accumulation appeared to occur after

repeated administration of high doses of the agent (33). The study continues with additional single doses of 400, 600 and 800 mg (data on file, Uriach).

An open-label, nonrandomized study in 24 healthy male subjects examined the interaction of albaconazole (80 mg capsule p.o.) with CYP3A4 using simvastatin (40 mg p.o.) as a marker for enzyme activity. Subjects were given a single oral simvastatin dose followed by a 2-day washout period after which they received oral albaconazole followed by simvastatin 2 h later; multiple dosing was initiated on day 5 and continued for 13 days. No serious adverse events or clinically significant changes in vital signs or ECG parameters were observed. The most common adverse events were headache (2 cases), abdominal pain (2 cases) and myalgia (2 cases). Single- and multiple-dose albaconazole increased plasma simvastatin and hydroxyacid simvastatin levels so that C_{max} and AUC values for the 2 latter compounds were increased 5- to 7-fold; the t_{max} (2 h) and $t_{1/2}$ values (8-16 h) of simvastatin were not altered by albaconazole. The interactions observed for albaconazole were comparable to and less than those observed for ravuconazole and itraconazole, respectively. Because there was a significant reduction in simvastatin total clearance and volume of distribution with albaconazole coadministration, it was suggested that the mechanism of interaction involves metabolic (*e.g.*, inhibition of CYP3A4) and drug distribution components (data on file, Uriach).

Albaconazole was concluded to have a good cardiac safety profile. Analysis of a total of 2,872 ECGs collected from 4 phase I trials involving over 126 volunteers administered albaconazole (n = 103; 5-400 mg) or placebo (n = 23) revealed that only 3 volunteers had a slight increase (> 60 ms) in QTcB (QT interval adjusted using Bazett's formula) from baseline after receiving albaconazole doses of 5 mg on day 1 (74.1 ms), 20 mg on day 16 (64.4 ms) and 40 mg on day 1 (61.8 ms). One subject given placebo also experienced an increase in QTcB from baseline on day 16 at 4 (67.5 ms) and 8 h (75 ms) and on day 20 (82.8 ms). However, when a QTcF (adjusted Fridericia's formula) was applied, no relevant changes in QT, QTcB and QTcF from baseline were detected. Absolute QT, QTcB and QTcF were all lower than 500 ms (31).

A phase II study in vulvovaginal candidiasis administering a single dose of an oral solution containing albaconazole is planned to start in late 2003.

Source

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