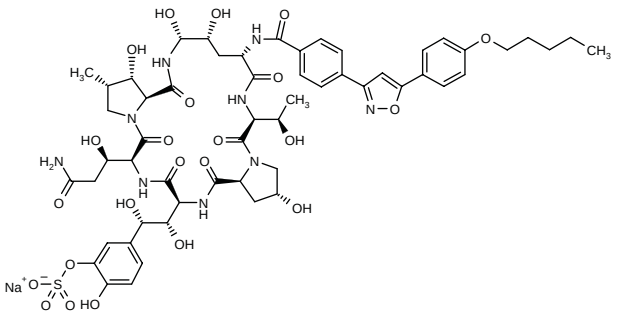
Drugs of the Future 1998, 23(12): 1273-1278

CCC: 0377-8282/98

FK-463

Antifungal

(3*S*,6*S*,9*S*,11*R*,15*S*,18*S*,20*R*,21*R*,24*S*,25*R*,26*S*)-3-[3-Amino-1(*R*)-hydroxy-3-oxopropyl]-6-[1(S),2(*S*)-dihydroxy-2-(4-hydroxy-3-sulfooxyphenyl)ethyl]-11,20,21,25-tetrahydroxy-15-[1(*R*)-hydroxyethyl]-26-methyl-18-[4-[5-[4-(pentyloxy)phenyl]isoxazol-3-yl]benzamido]-1,4,7,13,16,22-hexaazatricyclo[22.3.0.0$^{9.13}$]heptacosane-2,5,8,14,17,23-hexaone sodium salt



$C_{56}H_{70}N_9O_{23}S.Na$ Mol wt: 1292.265

CAS: 208538-73-2
CAS: 179165-70-9 (undefined stereochemistry)

EN: 263634
EN: 267240 (undefined stereochemistry)

Synthesis*

The synthesis of FK-463 can be performed as follows: Scheme 1.

The enzymatic deacylation of FR-901379 with *Streptomyces anulatas* No. 4811, *S. anulatas* No. 8703, *Streptomyces* strain No. 6907 or *A. utahensis* IFO13244 gives the deacylated lipopeptide FR-179642 (1), which is then reacylated with 1-[4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoyl]benzotriazole 3-oxide (VI) by means of dimethylaminopyridine (DMAP) in DMF (2).

The acylating compound (VI) can be obtained as follows: The cyclization of 4-pentyloxyphenylacetylene (I) with 4-(hydroxyiminomethyl)benzoic acid methyl ester (II) by means of triethylamine in hot THF gives 4-[5-(4-pentyloxyphenyl)isoxazol-3-yl]benzoic acid methyl ester (III), which is hydrolyzed with NaOH in hot THF/water yielding the corresponding free acid (IV). Finally, this compound is condensed with 1-hydroxybenzotriazole (V) by means of 1-ethyl-3-[3-(dimethylamino)propyl]carbodiimide (EDMCD) in dichloromethane (2).

Introduction

The emergence in the clinic of fluconazole-resistant isolates of pathogenic yeasts, particularly in HIV-positive and AIDS patients, as well as organ transplant patients, is a growing concern among infectious disease specialists (3-11). There is an important need for improved antifungal compounds which have potent, broad spectrum antifungal activity and minimal potential for development of resistance among target fungi. The development of antifungal compounds which are not members of the azole chemical class also represents an important advancement in the field of antifungal chemotherapy.

A novel target in fungi is the cell wall constituent 1,3-β-D-glucan. Echinocandin compounds have been shown to have potent and focused activity against this critical backbone structure of fungal cell walls (12). Investigational compounds in this novel class of antifungal agents include cilofungin (13), LY-303366 (14), L-733,560 (15) and MK-0991 (16-19). LY-303366 and MK-0991 currently are being evaluated for safety and antifungal efficacy in clinical trials.

FK-463 is a novel, water-soluble echinocandin-like lipopeptide that is in development by Fujisawa Pharmaceutical Company (1, 20). FK-463 has broad spectrum and potent activity against a variety of pathogenic fungi both *in vitro* and *in vivo*. Preclinical testing is in progress and phase I clinical trials have been initiated.

This report summarizes the available published information of the *in vitro*, experimental *in vivo*, experimental pharmacokinetics and initial phase I clinical trial data of this new echinocandin antifungal.

Development Strategies

The first publication on this series of echinocandin-like lipopeptide antifungal compounds was by Iwamoto *et al.*

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Scheme 1: Synthesis of FK-463

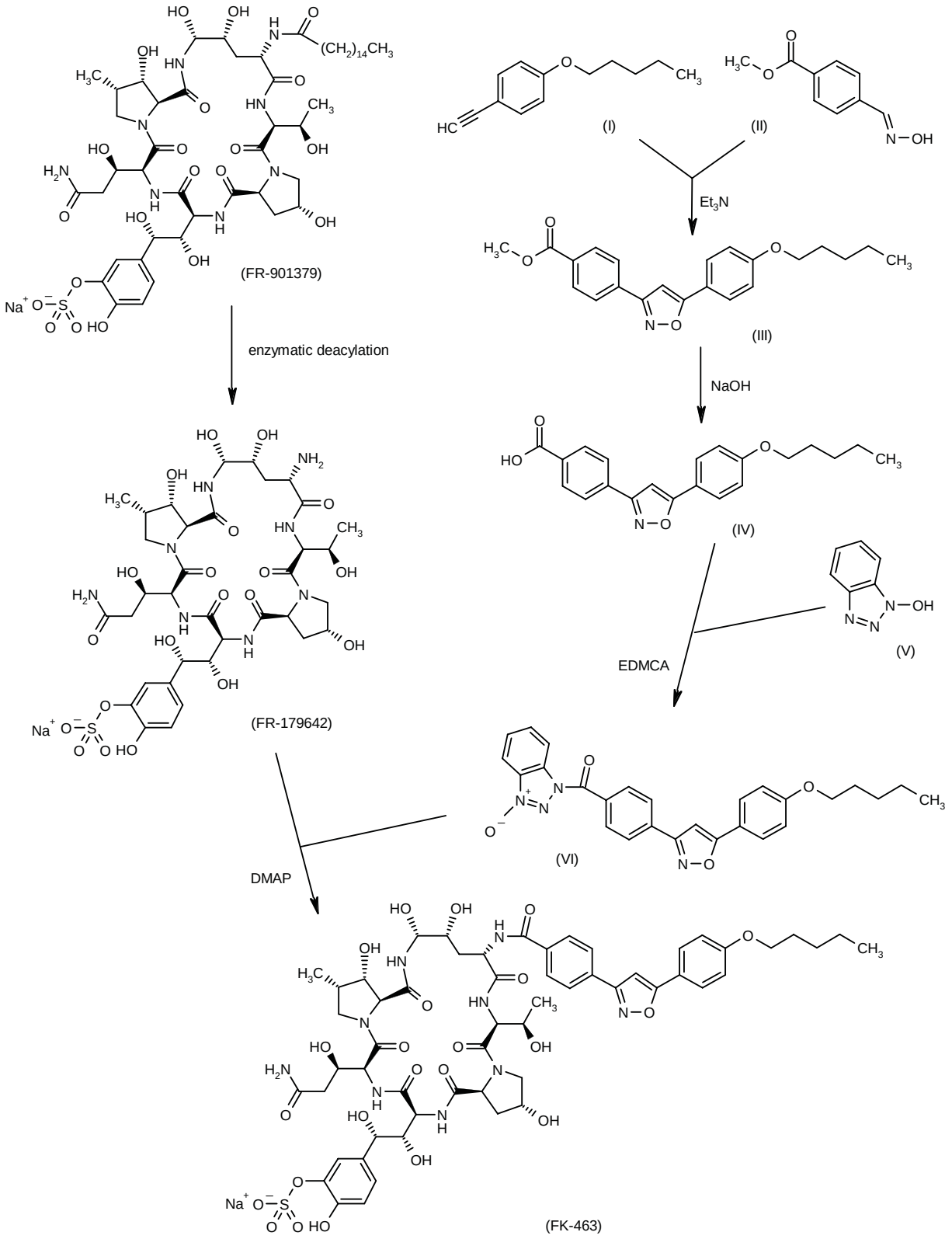

Table I: In vitro *antifungal activity of FK-463 compared to fluconazole, itraconazole and amphotericin B against selected fungi.*

Organism (No. of isolates)	Compound	MIC range (μg/ml)	MIC_{90} (μg/ml)
Candida albicans (37)	FK-463	≤ 0.0039-0.0156	0.0156
	Fluconazole	0.125-4.0	0.5
	Itraconazole	0.0156-0.25	0.0313
	Amphotericin B	0.25-1.0	0.5
Candida albicans (4)	FK-463	0.0156-0.0313	0.0313
(fluconazole-resistant)	Fluconazole	16->64	>64.0
	Itraconazole	0.5->8	>8.0
	Amphotericin B	0.25-0.5	0.5
Candida glabrata (20)	FK-463	0.0078-0.0156	0.0156
	Fluconazole	4->64	64.0
	Itraconazole	0.5->8	8.0
	Amphotericin B	0.0625-1.0	1.0
Candida krusei (11)	FK-463	0.125-0.25	0.125
	Fluconazole	16-64	64.0
	Itraconazole	0.25-1.0	1.0
	Amphotericin B	0.5-1.0	1.0
Cryptococcus neoformans (5)	FK-463	>64	>64.0
	Fluconazole	1.0-8	8.0
	Itraconazole	0.01313-0.5	0.5
	Amphotericin B	0.25-0.5	0.5
Aspergillus fumigatus (29)	FK-463	0.0078-0.0313	0.0156
	Fluconazole	8->64	>64.0
	Itraconazole	0.0156-1.0	0.5
	Amphotericin B	0.125-1.0	32.0
Aspergillus flavus (13)	FK-463	0.0078-0.0156	0.0156
	Fluconazole	8->64	>64.0
	Itraconazole	0.125-0.5	0.5
	Amphotericin B	0.5-1.0	1.0

(20) in 1993. They reported on the isolation of FR-901379, a novel antibiotic isolated from the culture broth of *Coleophoma empredi* strain F11899. This early study demonstrated that FR-901379 is a water-soluble, lipopeptide-like echinocandin with a sulfonate. The IC_{50} of FR-901379 was 0.7 mcg/ml against 1,3-β-D-glucan synthase in *Candida albicans*; the IC_{50} for echinocandin B in this assay was 2.6 μg/ml. The IC_{50}s for FR-901379 against *C. albicans* strain FP633 and *Aspergillus fumigatus* strain FD050 were 0.025 and 1.9 μg/ml, respectively, demonstrating potent *in vitro* antifungal activity against a pathogenic yeast and filamentous fungus. This compound and related derivatives had potent activity against experimental infections in mice caused by *C. albicans*, *A. fumigatus* and *Pneumocystis carinii*. The ED_{50} of FR-901379 in a mouse model of systemic candidiasis was 2.7 mg/kg. Prophylactic treatment of an experimental murine model of *P. carinii* eradicated cysts in the lung of infected treated mice. These early studies of this new series of antifungal compounds led to the further evaluation of FR-901379 and derivatives.

In lipopeptide antibiotics, the acyl side chain has an important role in both antimicrobial and toxicological activity. FR-901379, a selective inhibitor of 1,3-β-D-glucan synthase in fungi, was used as a key intermediate in the development of new echinocandin antifungal compounds. Ueda *et al*. (1) developed a screen for detecting a lipopeptide acylase that would remove the acyl side chain (palmitoyl) from FR-901379. They determined that three isolates of *Streptomyces adulates* produced the desired enzyme in the culture broths. The acylase was closely associated with the mycelia of *Streptomyces* strain No. 6907, which was selected as the bioreactor. The investigators characterized the acylases in order to optimize their use for the development of new echinocandin antifungal compounds. For the primary acylases, the optimum pH range was 8-9 and the optimum temperature was 50 °C. Acylase activity was maximized in the presence of 10% methanol. The K_m and V_{max} values of the lipopeptide acylase for FR-901379 deacylation were 257 μM and 14.3 U/mg-protein, respectively. Sequencing of amino acid chains of the acylases revealed that these were novel acylases. These acylases were studied for their ability to bioconvert FR-901379 to FR-179642, an essential intermediate for the semisynthetic development of lipopeptide antifungal compounds, including FK-463.

In Vitro Activity

Maki *et al*. (21) studied the *in vitro* antifungal activity of FK-463 in comparison to amphotericin B, fluconazole and itraconazole using the National Committee for Clinical Laboratory Standards (NCCLS) M27-A method. Against isolates of *C. albicans*, FK-463 had minimum inhibitory concentrations (MICs) ranging from ≤ 0.0039-2.0 μg/ml. Against isolates of *A. fumigatus*, FK-463 had MICs ranging from ≤ 0.0039-0.0313 μg/ml. The MICs obtained with FK-463 were more potent than those obtained with the other antifungal compounds tested, including amphotericin B (Table I). FK-463 was active against azole-resistant isolates of *C. albicans*. In addition,

Table II: The activity of FK-463 in reducing colony forming units of Candida albicans *from the kidneys in an experimental model of systemic candidiasis.*

Compound	Dose (mg(kg)	Log_{10} CFU/kidney
Control at 0 h	-	3.35 ± 0.04
Control at 24 h	-	4.93 ± 0.04
FK-463	1.0	1.73 ± 0.07
	0.5	2.62 ± 0.14
	0.25	4.20 ± 0.05
Amphotericin B	1.0	2.35 ± 0.07
	0.5	2.98 ± 0.08
	0.25	3.5 ± 0.11
Fluconazole	4.0	3.86 ± 0.05

there was no cross-resistance with the azole antifungals. The fungicidal activity of FK-463 against *C. albicans* was determined to be equal to or more than 0.0156 μg/ml during a 24-h test period. The antifungal activity was not affected by type or pH of the medium used in the assay or inoculum size, but the presence of human serum albumin did reduce *in vitro* antifungal activity, suggesting some protein binding. The minimum fungicidal concentrations (MFCs) for FK-463 against *C. albicans* was within a 2-fold difference with the MICs. FK-463 was fungistatic against isolates of *A. fumigatus*.

Target kinetics studies confirmed that FK-463 inhibited 1,3-β-D-glucan synthase in the membrane fraction of *C. albicans* and *A. fumigatus*. There was no evidence for inhibition of fungal proteins or nucleic acids.

As has been observed with other echinocandin antifungal compounds, FK-463 had no *in vitro* activity against isolates of encapsulated yeast *Cryptococcus neoformans*, the dimorphic pathogen *Trichosporon cutaneum* or the filamentous fungus *Fusarium solani*. Thus, FK-463 has potent but limited spectrum of *in vitro* antifungal activity as has been observed with other echinocandin compounds (13-19). Additional studies indicated that FK-463 had a low potential for inducing development of resistance.

Experimental *In Vivo* Activity

Matsumoto *et al.* (22) studied the activity of FK-463 compared to that of fluconazole and amphotericin B in an experimental murine model of systemic candidiasis. Cyclophosphamide was used to produce a state of immunosuppression in the experimental mice. Following intravenous infection with an isolate of *C. albicans*, the compounds were administered intravenously once daily for 4 days. ED_{50}s were calculated at 15 days and were 0.28-0.45, 0.13-0.23 and 4.0-14.9 mg/kg for FK-463, amphotericin B and fluconazole, respectively. FK-463 also was the most active compound in reducing the number of colony forming units (CFUs) of *C. albicans* isolated from the kidneys of mice at the conclusion of the study period (Table II). These data demonstrate that a single intravenous treatment of FK-463 at doses of 0.5 mg/kg or higher significantly reduced the counts of yeast from the kidneys as compared to untreated control mice. The efficacy measured by CFUs from kidneys showed FK-463 to be superior in activity to amphotericin B and fluconazole (only suppressive effect at a dose of 4 mg/kg).

The investigators also studied the activity of FK-463 in comparison to fluconazole and amphotericin B in models of systemic candidiasis caused by other *Candida* species, including *C. tropicalis*, *C. glabrata*, *C. parapsilosis* and *C. krusei*. In cyclophosphamide immunosuppressed mice, the ED_{50}s for FK-463, fluconazole and amphotericin B against *C. tropicalis* infection were 0.28, 3.71 and 0.09 mg/kg, respectively. The ED_{50}s for FK-463, fluconazole and amphotericin B against *C. glabrata* infection were 0.30, 6.27 and 0.11 mg/kg, respectively. The ED_{50}s for FK-463, fluconazole and amphotericin B against *C. parapsilosis* infection were 1.00, 10.9 and 0.057 mg/kg, respectively, and against *C. krusei* were 0.77, 9.52 and 0.26 mg/kg, respectively. These data demonstrate that FK-463 has potent *in vivo* activity against experimental infections caused by this range of *Candida* species.

Wakai *et al.* (23) studied the activity of FK-463 compared to that of fluconazole and amphotericin B in an experimental murine model of pulmonary aspergillosis. Cyclophosphamide was used to produce a state of immunosuppression in experimental ICR mice; mice were infected intranasally to produce a lung-based aspergillosis. Three isolates of *A. fumigatus* were used in this model. The ED_{50}s (range) were 0.26-0.51, 0.26-0.46 and > 20 mg/kg for FK-463, amphotericin B and fluconazole, respectively, demonstrating that FK-463 was comparable in activity to amphotericin B and superior to fluconazole in this model. FK-463 was the most active compound in reducing the number of CFUs of *A. fumigatus* isolated from the lungs of mice at the conclusion of the study period. A significant reduction in fungal cells was observed at plasma concentrations ranging from 0.55-0.80 μg/ml. This study indicates that FK-463 is active in an animal model against isolates of *A. fumigatus* and further experimental studies are warranted.

Pharmacokinetics

Suzuki *et al.* (24) studied the pharmacokinetics of FK-463 in experimental animals. FK-463 was administered as an intravenous bolus to mice, rats and dogs at doses of 0.32, 1.0 and 3.2 mg/kg or via a 1-h intravenous infusion at a dose of 1.0 mg/kg. Following bolus injection the plasma concentration of drug decreased in a biphasic manner. After administration of FK-463 the pharmacokinetics were linear in each animal model studied. Key pharmacokinetic parameters are summarized in Table III. There were no important differences in pharmacokinetics characteristics between bolus and infusion routes of administration in rats and dogs. FK-463 had strong serum

Table III: Experimental pharmacokinetics of FK-463.

Animal model	AUC range (μg.h/ml)	Plasma half-life (h)	Clearance (ml/min/kg)	Volume distribution (l/kg)
Mice	4.9-5.4	5.34-5.71	0.92-1.01	0.38-0.49
Rats	3.3-48.3	3.96-5.05	1.04-1.50	0.42-0.56
Dogs	7.2-84.8	4.24-5.43	0.59-0.78	0.23-0.25

Table IV: Pharmacokinetic parameters of FK-463 in normal human volunteers following daily single intravenous doses of compound.

Day	C_{max} (μg/ml)	AUC (μg.h/ml)	Plasma half-life (h)	Clearance (ml/kg)	Total clearance (ml/min/kg)
1	1.91 ± 0.20	18.8 ± 2.5	-	-	-
4	2.39 ± 0.28	27.9 ± 4.5	-	-	-
7	2.46 ± 0.27	29.6 ± 4.6	14.6 ± 1.5	14.3 ± 1.9	0.222 ± 0.027

protein binding in all animal species tested: 99.80, 99.73 and 99.75% in mice, rats and dogs, respectively. Following administration of an intravenous bolus of [^{14}C]-labeled FK-463 in rats and dogs, 14.4 and 15.2% of radioactivity was recovered in urine, respectively, with 83.5 and 83.8% recovered in feces, respectively. In bile duct cannulated rats, radioactivity recovered in urine, feces and bile was 13.2, 8.3 and 43.9%, respectively. Unchanged drug was minimally excreted in these tests. The pharmacokinetic data support further investigational studies with FK-463.

Clinical Studies

Azuma *et al.* (25) conducted a phase I clinical trial in healthy adult male subjects. In a single-dose study, FK-463 was administered intravenously over a 2-h period at doses of 2.5, 5, 12.5, 25 or 50 mg. FK-463 was generally well-tolerated, although several adverse events of mild severity were noted by the investigators. At 5 and 12.5 mg, 1 patient at each dose level had an increase in percent eosinophils. At 12.5 mg, 1 patient experienced binaural tinnitus, and at 25 mg, 1 subject experienced mild redness in the upper limbs and body. Both events were considered to be only remotely related to study drug as no other clinical symptoms were observed at the same or higher doses. At the 50 mg dose, occult blood and urine sediment were noted. These adverse events were considered mild and remotely related to study drug. The AUC and C_{max} values increased in a dose-proportional manner. The mean plasma terminal half-life was calculated as 14.6 h. Key pharmacokinetic parameters of this study are summarized in Table IV.

In a multiple-dose study, subjects were administered 25 mg of FK-463 as a 1-h infusion. A total of 7 daily doses were administered with 6 subjects receiving drug and 3 a saline placebo. Plasma concentrations of the compound in this study were characterized by a linear, two-compartment model with first-order input. Steady-state plasma concentrations were attained at 4 days. FK-463 was generally well tolerated in this study, with the only adverse events being increases in blood urea nitrogen values, which were mild and only remotely related to study drug. Further clinical study of this novel echinocandin antifungal compound is proceeding.

Conclusions

FK-463 represents the latest lead in a novel chemical class of echinocandin-like lipopeptide antifungal compounds. This agent has potent *in vitro* and experimental *in vivo* activity against a variety of pathogenic *Candida* species (yeasts) and *A. fumigatus* (filamentous fungus). This compound has favorable experimental pharmacokinetics and a unique mode of action, which makes it active against fungal isolates that are resistant to established antifungal agents, particularly the triazole agent fluconazole. This new lead compound is undergoing extensive preclinical evaluation in Japan to determine whether it may be a candidate for further development as a novel, antifungal agent. Single-dose and initial multiple-dose phase I studies in normal human volunteers have been completed with the compound being generally well tolerated.

FK-463 has advanced to phase II clinical trials (26).

Manufacturer

Fujisawa Pharm. Co., Ltd. (JP).

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