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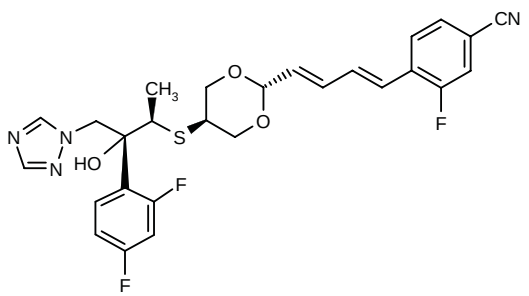
CCC: 0377-8282/2003

CS-758

Antifungal
Lanosterol 14α-Demethylase Inhibitor

R-120758

trans-4-[4-[5-[2(*R*)-(2,4-Difluorophenyl)-2-hydroxy-1(*R*)-methyl-3-(1*H*-1,2,4-triazol-1-yl)propylsulfanyl]-1,3-dioxan-2-yl]-1(*E*),3(*E*)-butadienyl]-3-fluorobenzonitrile



$C_{27}H_{25}F_3N_4O_3S$
Mol wt: 542.5795
CAS: 329744-44-7
EN: 293411

Abstract

Due to the increase in incidence of opportunistic nosocomial fungal infections over the past years and the risk they pose to immunocompromised individuals, the search for potent broad spectrum antimycotics remains a research priority. Triazole agents emerged as a standard therapy for fungal infections with agents such as fluconazole and itraconazole exhibiting broad spectrum activity and improved safety profiles over other antifungal compounds. One novel triazole to emerge which shows considerable clinical promise is the oral azole CS-758 (R-120758). The agent has shown excellent activity *in vitro* and *in vivo* against clinically important fungal organisms such as *Candida albicans*, *Candida neoformans*, *Aspergillus fumigatus* and *Aspergillus flavus*. CS-758 was chosen for further development as an oral antifungal and is currently undergoing early-stage clinical trials in the U.S.

Synthesis

Bromination of 3-fluoro-4-methylbenzonitrile (I) using *N*-bromosuccinimide, AIBN and light in 1,2-dichloroethane affords the benzyl bromide (II) (1, 2), which is converted into phosphonate (III) by heating with triethyl phosphite (1-4). Horner-Emmons condensation of phosphonate (III) with the monoprotected fumaraldehyde (IV) by means of either *t*-BuOK (1) or BuLi (2-4) in THF produces the diene acetal (V), which is then hydrolyzed to aldehyde (VI) with aqueous HCl (1-4). Scheme 1.

Heating of tosylate (VII) with sodium thioacetate in DMF (5, 6) gives *S*-(*trans*-2-phenyl-1,3-dioxan-5-yl)thioacetate (IX), which is converted into thioether (X) by reaction with the chiral epoxide (IX) by means of NaOMe in EtOH (1) or NaOMe:MeOH in DMF (5, 6). Hydrolysis of the acetal function of (X) with HCl in H_2O/toluene yields the diol (XI) (1, 5, 6), which is finally coupled with aldehyde (VI) by means of *p*-toluenesulfonic acid monohydrate in THF (1-4). Scheme 2.

The known chiral epoxide (IX) can be synthesized by several different ways shown in the following:

1) 2(*S*)-Acetoxypropionic acid (XII) is treated first with oxalyl chloride in DMF/CH_2Cl_2, and then the resultant acyl chloride is submitted to a Friedel-Crafts reaction with 1,3-difluorobenzene (XIII) by means of $AlCl_3$ to provide a 1:1 mixture of α(*S*)-acetoxypropiophenone (XIV) and α(*S*)-hydroxy-propiophenone (XV). This mixture is treated with H_2SO_4 in MeOH to give the pure alcohol (XV). Tosylation of alcohol (XV) with *p*-toluenesulfonyl chloride in pyridine furnishes tosylate (XVI), which is converted into α(*R*)-hydroxypropiophenone (XVII) by an S_N2 displacement reaction with LiOH in DMF/H_2O. Reaction of the hydroxy group of (XVII) with 2,3-dihydropyran (XVIII) and pyridinium *p*-toluenesulfonate (PPTS) in CH_2Cl_2 gives the protected compound (XIX), which is converted into the silyl alcohol (XXI) by a Grignard reaction with (chloromethyl)dimethylisopropoxysilane (XX) in the presence of Mg and a small amount of MeI. Oxidative desilylation of (XXI) by means of $NaHCO_3$ and H_2O_2 in THF/MeOH, followed by hydrolysis with TsOH in MeOH, affords the triol (XXII), which is then mesylated with methanesulfonyl chloride in pyridine to provide the dimesylate (XXIII). Finally, nucleofilic substitution of one mesylate group of (XXIII) with 1*H*-1,2,4-triazole (XXIV) by means of NaH in

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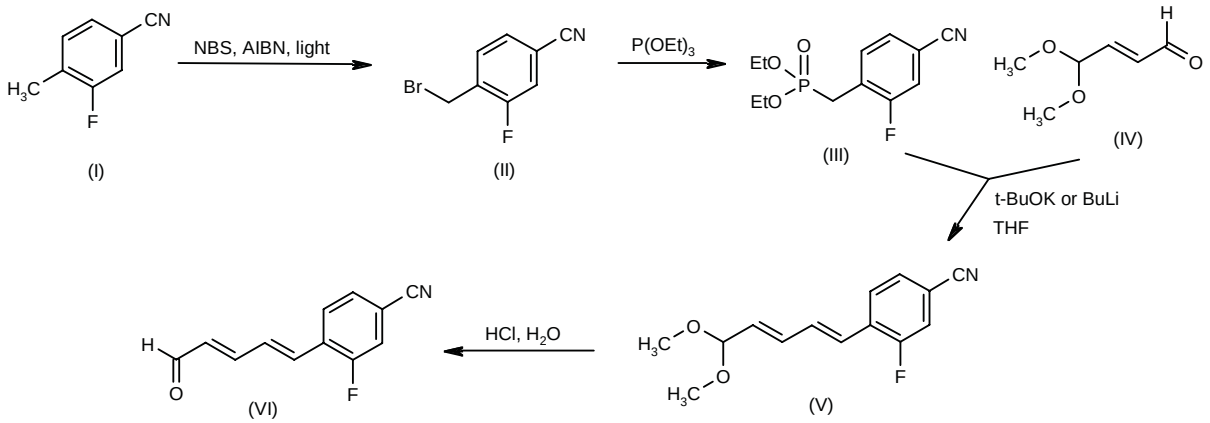
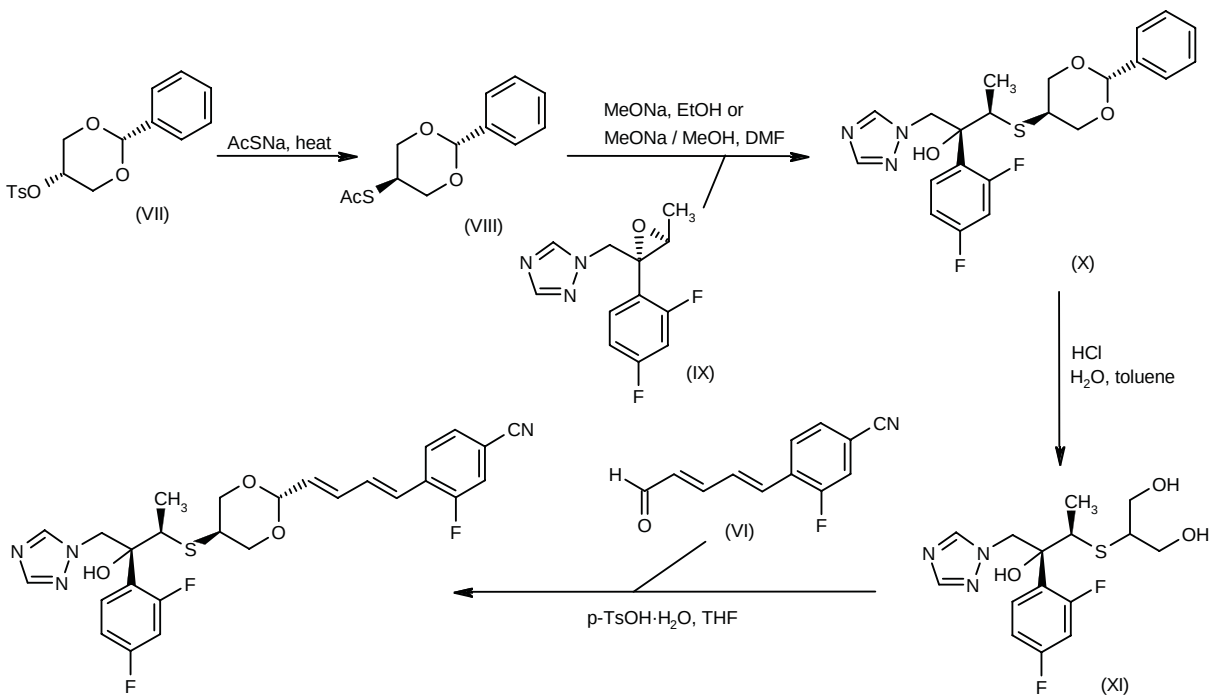
Scheme 1: Synthesis of Intermediate (VI)



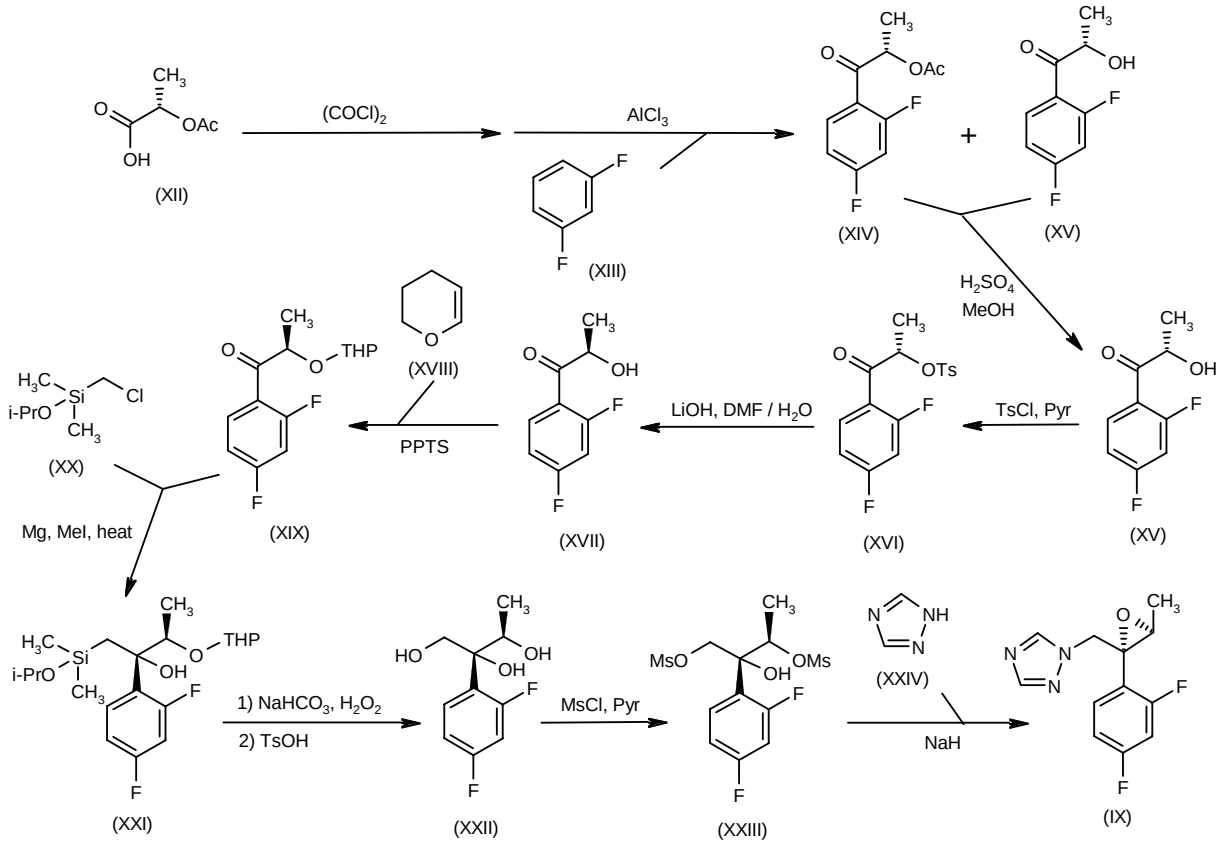
Scheme 2: Synthesis of CS-758



DMF with concomitant epoxide formation affords the desired intermediate (IX) (7). Scheme 3.

2) Propiophenone derivative (XXV) – prepared according to a procedure similar to that described for compound (XIX) – is subjected to a Grignard reaction with (chloromethyl)trimethylsilane (XXVI) and Mg in ether to give the silyl alcohol (XXVII), which by treatment with *p*-toluenesulfonic acid in MeOH undergoes β-elimination and deprotection to yield the allylic alcohol (XXVIII). Epoxidation of (XXVIII) with *tert*-butyl hydroperoxide and catalytic oxyvanadium acetylacetonate gives the epoxyalcohol (XXIX), which is subjected to a Mitsunobu reaction with benzoic acid (XXX) by means of DEAD and PPh_3 in THF to provide benzoate (XXXI). Solvolysis of compound (XXXI) in MeOH with catalytic NaOMe yields the epoxyalcohol (XXXII), which is mesylated with

Scheme 3: Synthesis of Intermediate (IX)



methanesulfonyl chloride and triethylamine in CH_2Cl_2 to afford the protected alcohol (XXXIII). Finally, treatment of compound (XXXIII) with 1*H*-1,2,4-triazole (XXIV) and NaH in DMF affords the desired intermediate (IX) (7). Scheme 4.

Introduction

The incidence of opportunistic nosocomial fungal infections is on the rise, posing a life-threatening risk to immunocompromised individuals such as AIDS patients, patients undergoing chemotherapy, patients in intensive care units and recipients of organ transplants. *Candida albicans* is the organism most frequently associated with mucosal and hematogenously disseminated mycosis, although other *Candida* spp. such as *Candida glabrata*, *Candida tropicalis* and *Candida krusei* and *Aspergillus* spp. and *Cryptococcus neoformans* have emerged as clinically significant pathogens (8-11).

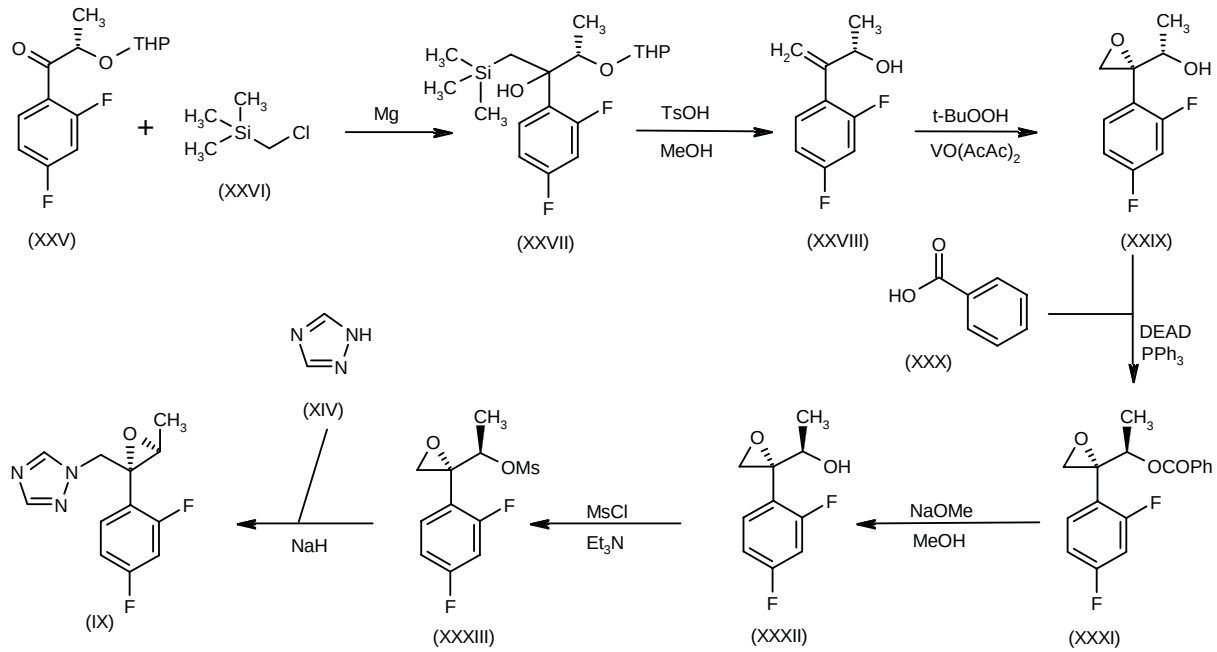
Triazole agents have emerged as a standard therapy for fungal infections. Triazole antimycotics such as fluconazole and itraconazole possess broad spectrum activity and exhibit improved safety profiles over compounds such as flucytosine and amphotericin B. Thus, the search for novel triazoles with increased antifungal activity is ongoing due to the superior efficacy and safety of these agents (11-13).

One agent to emerge which shows considerable clinical promise is CS-758 (R-120758). The oral active dioxane-triazole has shown excellent activity *in vitro* and *in vivo* against clinically important fungal organisms such as *C. albicans*, *C. neoformans*, *Aspergillus fumigatus* and *Aspergillus flavus* and was chosen for further development as an oral antifungal agent.

Pharmacological Actions

CS-758 has exhibited potent *in vitro* activity against *C. albicans* (SANK51486; MIC = 0.008 μg/ml or less), *C. neoformans* (TIMM1855; MIC = 0.016 μg/ml), *A. fumigatus* (SANK10569; MIC = 0.063 μg/ml) and *A. flavus* (SANK18497; MIC = 0.25 μg/ml). CS-758 was more potent *in vitro* than fluconazole and itraconazole (MICs, respectively) against *C. albicans* (SANK18497: 0.008 or

Scheme 4: Synthesis of Intermediate (IX)



less *vs.* 0.25 and 0.031 μg/ml; TIMM3164: 0.063 *vs.* >4 and 0.25 μg/ml; ATCC24433: 0.016 *vs.* 0.5 and 0.125 μg/ml), *Candida parapsilosis* (ATCC90018: 0.016 *vs.* 0.5 and 0.125 μg/ml), *Candida guilliermondii* (4 strains: 0.03-0.06 *vs.* 2-4 and 0.25-0.5 μg/ml), *C. krusei* (ATCC6258: 0.25 *vs.* >4 and 0.5 μg/ml), *Candida kefyr* (3 strains: 0.008 or less *vs.* 0.25-1 and 0.06 μg/ml), *C. tropicalis* (ATCC750: 0.25 *vs.* 2 and 0.5 μg/ml), *Trichosporon asahii* (6 strains: 0.03 *vs.* 4-8 and 0.25-0.5 μg/ml), *C. neoformans* (TIMM1855: 0.016 *vs.* > 4 and 0.25 μg/ml), *A. fumigatus* (ATCC26430 and SANK10569: 0.063 *vs.* >4 and 0.25 μg/ml) and *A. flavus* (SANK18497: 0.25 *vs.* >4 and 0.5 μg/ml). CS-758 displayed good activity (MIC = 0.016-0.5 μg/ml) against 7 *C. albicans* strains with low susceptibility to fluconazole (MIC = 4-32 μg/ml) and was also more potent than amphotericin B against *C. albicans* (139 strains: 0.008/0.008 or less *vs.* 0.5 μg/ml), *C. parapsilosis* (29 strains: 0.016 *vs.* 0.25 μg/ml), *C. guilliermondii* (4 strains: 0.03-0.06 *vs.* 0.12-1 μg/ml), *C. kefyr* (3 strains: 0.008 or less *vs.* 0.25 μg/ml), *C. krusei* (15 strains: 0.25 *vs.* 1 μg/ml), *C. tropicalis* (43 strains: 0.016 *vs.* 0.25 μg/ml), *T. asahii* (6 strains: 0.03 *vs.* 0.12-2 μg/ml), *C. neoformans* (22 strains: 0.008 or less *vs.* 0.25 μg/ml), *A. fumigatus* (29 strains: 0.063 *vs.* 2 μg/ml) and *A. flavus* (19 strains: 0.063 *vs.* 2 μg/ml). The activity of all agents examined was comparable against strains of *C. glabrata* (1, 2, 14, 15).

Further examination of the *in vitro* activity of CS-758 against 21 clinical isolates of *C. neoformans* revealed the MIC_{90}s for the agent (0.008 μg/ml) to be 2048-, 16-, 32- and 16-fold lower than those obtained for fluconazole, itraconazole, voriconazole and posaconazole, respectively (16, 17).

CS-758 was also shown to be more potent than over 250 clinical fungal isolates including 150 systemic fungi, 12 zygomycetes, 48 hyalohyphomycetes, 25 phaeohyphomycetes and 15 dermatophytes. MICs obtained for CS-758 were lower than those obtained for fluconazole, itraconazole and amphotericin B. For example, the geometric mean MIC for CS-758 against the hyalohyphomycetes *Paecilomyces lilacinus* and *Fusarium* spp. was 0.5 μg/ml as compared to 101.6, 4.2 and 4.5 μg/ml for fluconazole, itraconazole and amphotericin B, respectively. Similarly, the MIC_{90} for CS-758 against resistant *Scedosporium* spp. was 0.29 μg/ml as compared to 35.9, 2 and 11.3 μg/ml obtained for the respective comparison agents. CS-758 also showed superior activity against systemic fungi such as *Coccidioides immitis*, *Histoplasma capsulatum* and *Blastomyces dermatitidis* (MIC_{90} = 0.007 *vs.* 10, 0.06 and 0.2 μg/ml, for the respective agents) (18).

An *in vitro* study using microsomes from fluconazole-resistant and -susceptible *C. albicans* clinical isolates examined the mechanism of resistance of organisms to CS-758 and itraconazole. The IC_{50} values for the inhibition of the synthesis of ergosterol from [^{14}C]-mevalonic acid for both agents against isolates that were resistant to either one or both agents (MIC = 1 and 4 μg/ml for CS-758 and itraconazole, respectively) were ~0.003-0.004 μg/ml. Results suggest that the 14α-demethylases of resistant *C. albicans* isolates are highly susceptible to

CS-758 and itraconazole, possibly indicating that efflux pumps rather than 14α-demethylase mediate resistance to these agents (19).

In an *in vivo* study using a murine systemic infection model, CS-758 (once daily p.o. for 10 days) dose-dependently delayed mortality of mice infected i.v. with *C. albicans*, *A. fumigatus*, *A. flavus* and *C. neoformans* (ED_{50}s = 0.41-5 mg/kg for all infections). The agent showed efficacy similar to fluconazole (ED_{50} = 0.41 and 0.43 mg/kg, respectively) but was ~100-fold more potent than itraconazole (ED_{50} = >6.3 mg/kg) against *C. albicans* infection. The ED_{50} value of 2.38 mg/kg against *A. fumigatus* infections was about 55- and 38-fold lower than values obtained for fluconazole and itraconazole, respectively. CS-758 was also 16- and 30-fold more potent that fluconazole and itraconazole, respectively, against *C. neoformans* infections and 16-fold more potent than either agent against *A. flavus* infections (14, 20).

The efficacy of CS-758 (2 and 10 mg/kg p.o.) was demonstrated and compared to fluconazole and itraconazole in an *in vivo* study using a murine experimental oropharyngeal candidiasis model. In this model, immunosuppressed (cortisone acetate treatment) ddY mice were inoculated in the oral cavity with *C. albicans* (SANK51486) and treated 3 days later once daily for 2 days. Both CS-758 and fluconazole (2 and 10 mg/kg p.o.) significantly reduced viable cell numbers in the oral cavity, although the effects of CS-758 were greater; differences in oral cavity fungal burden reductions between the agents were 0.9 and 0.6 $\log_{10}$ CFU/g of tissue for the respective doses. Itraconazole had no significant effects at either dose. Relapse of infection occurred after treatment with both CS-758 and fluconazole, although it was slower in CS-758-treated animals so that viable cells increased only 1.1 $\log_{10}$ CFU/g of tissue as compared to 2.7 $\log_{10}$ CFU/g of tissue in fluconazole-treated animals (21).

CS-758 was also effective in a similar model that involved oropharyngeal candidiasis due to 5 strains of fluconazole-resistant (fluconazole MICs = 1, 8, 16, 32 and 64 μg/ml) *C. albicans*. While only the 10 and 50 mg/kg doses of fluconazole had significant effects in reducing oral cavity viable cell numbers at 5 days postinoculation in animals infected with strains with fluconazole MICs of 1-16 μg/ml, and 50 mg/kg fluconazole was effective against infections caused by strains with a fluconazole MIC of 32 μg/ml, CS-578 dose-dependently reduced viable cell numbers of all strains (22, 23).

The *in vivo* efficacy of CS-758 (2.5, 5 and 10 mg/kg p.o. once daily for 7 days starting 24 h postinoculation) was compared to fluconazole (80 mg/kg p.o.), itraconazole (10 and 80 mg/kg p.o.) and amphotericin B (1.25, 2.5 and 5 mg/kg i.p.) in a study using an experimental murine model of invasive aspergillosis (*A. fumigatus* TIMM1776) in immunosuppressed DBA/2 mice. Survival was significantly prolonged on day 10 postinoculation in animals treated with 10 mg/kg CS-758 (88% survival), 80 mg/kg itraconazole (13% survival) and 5 mg/kg amphotericin B (50% survival); fluconazole was not effective in this model. The minimum steady-state plasma concentration of CS-758 following once-daily administration of 10 mg/kg for 7 days was 0.30 μg/ml (24).

In an *in vivo* study using ddY mice inoculated with *C. neoformans* (TIMM0362) i.v. (*i.e.*, systemic infection) or intratracheally (*i.e.*, pulmonary infection), all doses of CS-758 (0.4, 2 and 10 mg/kg p.o. once daily for 3 days starting 24 h postinoculation) significantly decreased viable cell counts in the brain (systemic infection model) at 4 days postinfection, while the 2 highest doses significantly reduced viable cell counts in the lung (pulmonary infection model). In the systemic infection model, although fluconazole reduced viable cell counts in the brain at doses of 2 and 10 mg/kg, itraconazole had no effects even at the highest 10 mg/kg dose. However, neither fluconazole nor itraconazole were effective in the pulmonary infection model at any of the doses tested (17).

CS-758 (10 mg/kg p.o. once daily for 7 days) was shown to have superior efficacy over fluconazole (10 mg/kg p.o.) against experimental fatal cryptococcosis (*C. neoformans* YC-11) in BALB/c mice. Survival of mice treated with CS-758 was significantly prolonged (33.3 days) as compared to controls (19.8 days) and fluconazole-treated animals (25.1 days). In addition, fungal burden in the lungs was significantly less in CS-758-treated animals as compared to controls and animals treated with fluconazole; viable cell number in the brain was comparably reduced by both antifungals as compared to controls (25).

Pharmacokinetics and Metabolism

The pharmacokinetics of CS-758 were examined in rats and monkeys. After i.v. administration (2 mg/kg dissolved in 13.3% hydroxylpropyl-β-cyclodextrin) to animals the plasma concentrations of the agent decreased biexponentionally with elimination half-life values of 4.7 and 3.6 h obtained in rats and monkeys, respectively. Further examination of the pharmacokinetics and metabolism of CS-758 (5 mg/kg p.o. or 2 mg/kg i.v.) in monkeys revealed that C_{max} values of 0.85 μg/ml were achieved at about 3 h after oral dosing. Following i.v. dosing in monkeys, the total body clearance and distribution volume at steady state were 7.7 ml/min/kg and 2.3 l/kg, respectively. There was extensive tissue distribution observed after treatment with [^{14}C]-CS-758 (2 mg/kg i.v.) with the highest levels observed in the adrenal glands followed by the liver, fat, kidneys, lungs, skin, muscle, plasma and brain at 8 h postdosing. Levels of radioactivity in the lungs and skin were more then 3 times that detected in plasma while levels in brain were 0.8 times less. The parent compound in addition to sulfoxides, an amide and some unidentified metabolites were observed in rat plasma; small amounts of the unchanged compound and its metabolites were identified in feces although these were barely detectable in urine. *In vitro* experiments using monkey and human liver microsomes found that the agent was metabolized to the sulfoxides and the amide.

Table I: Pharmacokinetic data for CS-758 (26-28).

Dose	Parameter	Unit	Mean value
Monkeys			
2 mg/kg i.v.	$AUC_{0-\infty}$	µg·h/ml	3.7-4.6
	Cl	l/h/kg	0.5
	FR_{0-336}	%	57.6
	$t_{1/2}$	h	3.6-4.6
	UR_{0-336}	%	25
	V_{ss}	l/kg	2.2-2.3
5 mg/kg p.o.	$AUC_{0-\infty}$	µg·h/ml	11.4
	C_{max}	µg/ml	0.9
	F	%	99.6
	FR_{0-336}	%	57.6
	$t_{1/2}$	h	15.5
	t_{max}	h	3.5
	UR_{0-336}	%	22.8
Rats			
2 mg/kg i.v.	$AUC_{0-\infty}$	µg·h/ml	2.9
	Cl	l/h/kg	0.7
	FR_{0-336}	%	77.6
	$t_{1/2}$	h	4.7
	UR_{0-336}	%	19.3
	V_{ss}	l/kg	3.83
5 mg/kg p.o.	$AUC_{0-\infty}$	µg·h/ml	13.2
	C_{max}	µg/ml	0.9
	F	%	98.3
	$t_{1/2}$	h	6.5
	t_{max}	h	3

AUC, area under the curve; Cl, clearance; FR, fecal recovery; $t_{1/2}$, half-life; UR, urinary recovery; V_{ss}, volume of distribution; F, bioavailability; t_{max}, time to peak concentrations; C_{max}, peak concentrations

The majority of radioactivity was recovered in feces after i.v. administration, indicating that biliary excretion was involved. Disposition of CS-758 was similar following oral or i.v. administration (Table I) (26-28).

Toxicity

The safety of single doses (up to 2000 mg/kg p.o.) and multiple doses (30, 100, 300 and 1000 mg/kg/day p.o. for 14 days) of CS-758 was examined in rats and/or dogs and monkeys. A single dose of even the highest CS-758 dose was not lethal in rats, dogs and monkeys of either sex. Multiple dosing did not alter general signs, body weight, urinalysis, blood chemistry, hepatic enzyme induction or necropsy findings. However, after dosing with 100 mg/kg, female rats had a lower hemoglobin concentration, a lower mean blood cell volume and higher reticulocyte counts as compared to males. In addition, in some animals treated with doses above 300 mg/kg, histological examination revealed hypertrophy of the zona fasciculata and reticularis cells in the adrenal glands. Therefore, the nontoxic dose was concluded to be 300 mg/kg p.o. Genotoxicity studies were also performed with no genotoxic signs detected after dosing with CS-758. It was concluded that CS-758 was highly tolerable as compared to other marketed triazoles (29).

Clinical Studies

CS-758 is currently undergoing early-stage clinical trials in the U.S. (30).

Source

Sankyo Co., Ltd. (JP); licensed to Fujisawa Pharmaceutical Co., Ltd. (JP).

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