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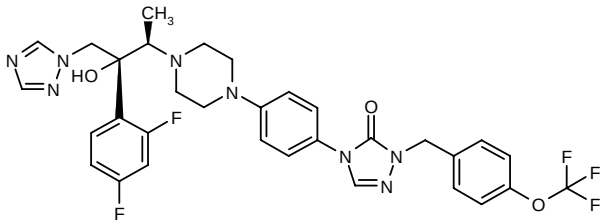
Syn-2869

Antifungal

4-[4-[4-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-1-piperazinyl]phenyl]-2-[4-(trifluoromethoxy)benzyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one



$C_{32}H_{31}F_5N_8O_3$ Mol wt: 670.6399

CAS: 210562-98-4

EN: 268123

Synthesis*

The synthesis of Syn-2869 has been performed by two related ways: (1, 2).

1) The reaction of 1-(4-nitrophenyl)piperazine (I) with *tert*-butyl dicarbonate (II) and triethylamine in dichloromethane gives 4-(4-nitrophenyl)piperazine-1-carboxylic acid *tert*-butyl ester (III), which is reduced with H_2 over Pd/C, yielding the corresponding 4-amino compound (IV). The reaction of (IV) with phenyl chloroformate (V) and triethylamine in dichloromethane affords the carbamate (VI), which by reaction with hydrazine is converted into the semicarbazide (VII). The cyclization of (VII) with formamidine (VIII) and triethylamine in hot 2-methoxy-ethanol affords the triazolone (IX), which is condensed with 4-(trifluoromethoxy)benzyl bromide (X) by means of Cs_2CO_3 in DMF, giving the disubstituted triazolone (XI). The deprotection, elimination of the *tert*-butoxycarbonyl group, of (XI) with HCl yields the monosubstituted piperazine (XII), which is finally condensed with (2*R*,3*S*)-oxirane (XIII) by means of $LiClO_4$ in refluxing acetonitrile. Scheme 1.

2) The addition of 1-(4-nitrophenyl)piperazine (I) to the chiral oxirane (XIII) as before gives the disubstituted piperazine (XIV), which is hydrogenated with H_2 over Pd/C in ethyl acetate, yielding the anilino derivative (XV). The acylation of (XV) with phenyl chloroformate (V) and triethylamine in dichloromethane affords the carbamate (XVI), which is treated with hydrazine to give the semicarbazide (XVII). The cyclization of (XVII) with formamidine (VIII) as before affords the triazolone (XVIII), which is finally condensed with 4-(trifluoromethoxy)benzyl bromide (X) by means of Cs_2CO_3 in DMF. Scheme 2.

Description

Colorless solid, m.p. 175-7 °C (1).

Introduction

Life-threatening systemic fungal infections continue to be a significant problem in health care today (3-13). In particular, patients who become immunocompromised by diabetes, prolonged steroid therapy, organ transplantation antirejection therapy, the acquired immune deficiency syndrome (AIDS) or other physiologically or immunologically compromising syndromes, are especially susceptible to opportunistic fungal infections. Species of *Candida* and *Aspergillus*, and *Cryptococcus neoformans* are among the most common fungi causing potential fatal, secondary fungal infections in this group of patients. Studies have documented that, during the last 20 years, the incidence of sepsis caused by *Candida* species has increased significantly in debilitated and immunocompromised patients (6, 10).

In addition, the emergence of fluconazole-resistant isolates of pathogenic yeasts (14-22), particularly in HIV-positive and AIDS patients, and the general refractory nature of treating fungal infections caused by *Aspergillus* species (23-27), are growing concerns among infectious disease specialists. The precise incidence of infections caused by *Aspergillus* species is difficult to determine due to a lack of accurate, reliable diagnostic methodologies and poor antemortem diagnosis (8). The majority of *Aspergillus* infections in AIDS patients occur in late stage disease when immune cell functions are minimal. Impaired neutrophil and macrophage function is related to increased infection rates with *Aspergillus* species. The

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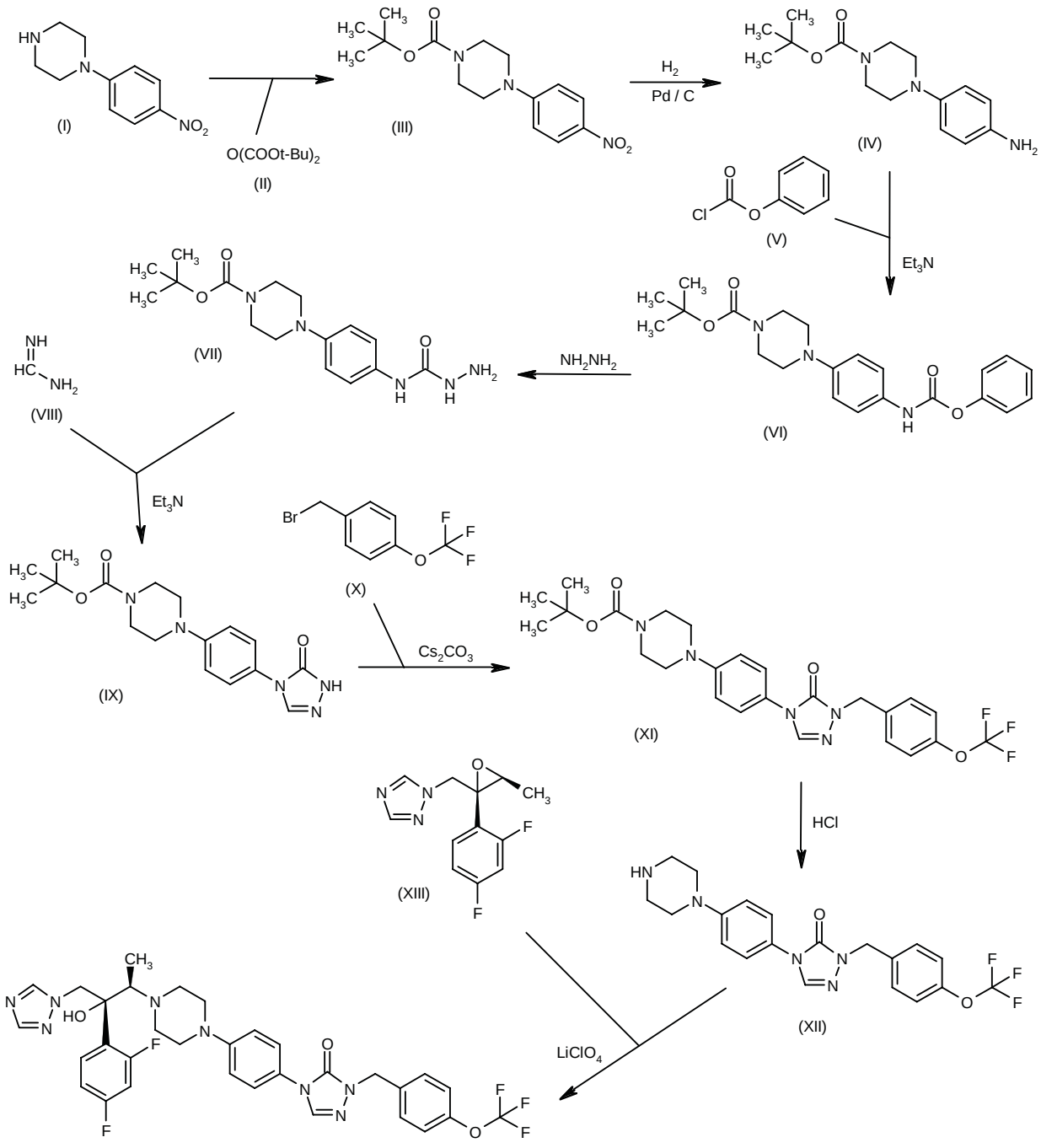
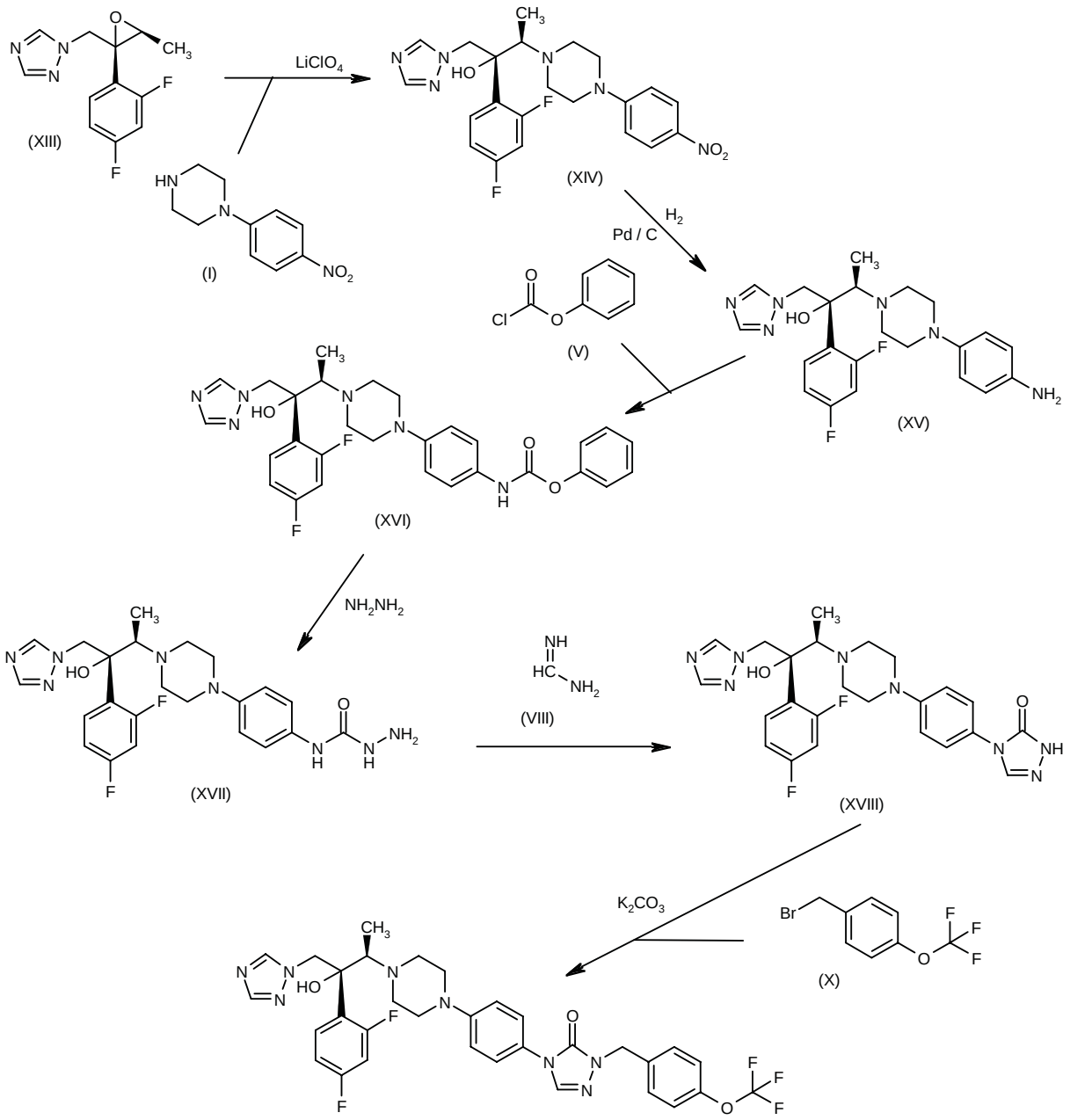
Scheme 1: Synthesis of Syn-2869



most common species of *Aspergillus* causing disease in AIDS patients are *A. fumigatus* (83%), *A. flavus* (9%), *A. niger* (5%) and *A. terreus* (3%) (19).

Fluconazole is the current drug of choice for the treatment of severe infections caused by *Candida* species and *C. neoformans* (28-31). However, fluconazole has only weak activity against isolates of *Aspergillus* species (minimum inhibitory concentration (MIC) values of 400 μg/ml), since the drug has low potency (IC_{50} = 4.8 μM) against lanosterol 14α-demethylase, the target enzyme in the fungus (31). Itraconazole, another triazole antifungal compound, generally is more active than fluconazole in the treatment of aspergillosis (31), but its activity in the clinic remains mixed.

Scheme 2: Synthesis of Syn-2869



Despite the therapeutic success of fluconazole and itraconazole, there remains a significant need for improved antifungal compounds which have potent, broad spectrum antifungal activity and minimal potential for development of resistance among target fungi. In addition, a compound with potent activity against *Aspergillus* would be a significant advance in antifungal chemotherapy.

Syn-2869 is a new, orally active antifungal triazole derivative that has broad spectrum and potent activity against a variety of pathogenic fungi both *in vitro* and *in vivo* (2, 32-38). Most significant is the potent activity of Syn-2869 against species of *Aspergillus*. This compound is among the most recent antifungal triazole derivatives being investigated as potential candidates for development.

Table I: In vitro *antifungal activity of Syn2869, Syn2836, Syn2903 and Syn2921 compared to fluconazole, itraconazole and amphotericin B against selected yeast-like and filamentous fungi.*

	Geometric Mean MIC Values (μg/ml)						
Organism (No. Isolates)	Syn2869	Syn2836	Syn2903	Syn2921	Amphotericin B	Fluconazole	Itraconazole
Candida albicans (Flu-susceptible) (10)	0.16	0.16	0.16	0.19	0.35	0.29	0.03
Candida albicans (Flu-resistant) (10)	0.93	1.52	1.15	0.76	0.25	111.43	0.75
Candida glabrata (10)	2.64	2.64	1.74	1.41	0.57	12.13	0.87
Candida tropicalis (10)	0.93	1.0	2.30	3.25	0.25	2.14	0.20
Candida parapsilosis (10)	0.13	0.18	0.17	0.17	0.12	0.71	0.05
Candida spp. (10)	0.19	0.31	0.33	0.14	0.20	10.56	0.15
Cryptococcus neoformans (10)	0.13	0.13	0.13	0.13	0.22	3.48	0.14
Aspergillus fumigatus (10)	0.5	0.62	0.71	0.66	0.76	128.0	0.27
Aspergillus flavus (5)	0.29	0.22	0.29	0.57	2.0	128.0	0.11
Aspergillus terreus (3)	0.31	0.25	0.25	0.31	3.17	101.59	0.10
Aspergillus niger (2)	1.41	1.0	1.0	2.0	0.71	128.0	0.35

This report summarizes the available published information on the *in vitro*, experimental *in vivo* and experimental pharmacokinetic data of this new triazole antifungal compound.

Structure-Activity Relationships

Abel *et al.* (2) reported on the synthesis and structure-activity relationships of a new series of antifungal azole compounds. The objectives of the program were to develop a novel antifungal triazole with: 1) broad spectrum activity (*Candida*, *Aspergillus*, *Cryptococcus*), 2) activity against systemic fungal infections, 3) flexible route of administration and 4) favorable pharmacokinetic profile (preferably once-daily dosing in humans). The chemistry team focused on a series of 2-(2,4-difluoro-3-(4-(substituted piperazin-1-yl)-1-(1,2,4-triazol-1-yl)butanols. Systematic modification on the piperazine moiety resulted in a series of compounds with potent *in vitro* and *in vivo* antifungal activity. The investigators defined the following parameters in their SAR studies. Absolute stereochemistry at the C-2 and C-3 positions strongly affects antifungal activity. The (2*R*,3*R*)-configuration is the main structural element that contributes to antifungal activity. Introduction of lipophilic groups, such as alkyl and benzyl groups on triazolone, increases antifungal activity. The presence of a 2-substituted (2*H*-1,2,4-triazol-3-one-4-yl)phenyl group on the piperazine ring is critical for *in vivo* activity. Hydroxyl and carboxylic esters containing alkyl groups reduce antifungal activity. Based on structure-activity relationship data, Syn-2869 was selected for further evaluation as a primary development candidate.

In Vitro *Activity*

Fothergill *et al.* (32) studied the *in vitro* antifungal activity of four new triazole antifungal compounds (Syn-2836, Syn-2869, Syn-2903 and Syn-2921; SynPhar/Taiho) in comparison to amphotericin B, fluconazole and itraconazole. Using the National Committee for Clinical Laboratory Standards (NCCLS) M-27A method for *in vitro* susceptibility testing, these compounds were compared for activity against a panel of 90 clinical yeast and filamentous fungal isolates. A modified NCCLS macrobroth method was used for testing the filamentous fungi. Isolates tested included *Candida albicans* (susceptible and resistant to fluconazole), *C. glabrata*, *C. tropicalis*, other *Candida* species, *C. neoformans*, *A. fumigatus*, *A. flavus*, *A. terreus* and *A. niger*. The MIC values were defined as the lowest concentration of drug that resulted in an 80% reduction in turbidity as compared to a drug-free control for the azoles, and no visible growth as compared to the drug-free control for amphotericin B.

The panel of Syn-azoles had potent *in vitro* activity against both fluconazole-susceptible and fluconazole-resistant isolates of *C. albicans* (Table I). The geometric mean MIC values for the Syn-azoles, fluconazole and itraconazole against fluconazole-susceptible *C. albicans* were 0.16-0.19, 0.29 and 0.03 μg/ml, respectively. The geometric mean MIC values for the Syn-azoles, fluconazole and itraconazole against fluconazole-resistant *C. albicans* were 0.76-1.52, 111.43 and 0.75 μg/ml, respectively. These data demonstrate a remarkable lack of cross-resistance of fluconazole with the Syn-azoles and itraconazole. The Syn-azoles also had potent *in vitro* activity against the filamentous aspergilli (Table I). The geometric mean MIC values for the Syn-azoles, fluconazole and itraconazole against *A. fumigatus* were 0.5-0.7, 128 and 0.27 μg/ml, respectively. This study demonstrates that the new series of triazole antifungal compounds has *in vitro* antifungal activity comparable to that of itraconazole and generally greater than that observed with fluconazole. Activity of all antifungal compounds

tested was weakest against isolates of *C. glabrata*. Further studies with this new series of azole compounds are warranted and will be of interest.

Gibb and van den Elzen (33) studied the *in vitro* antifungal activity of Syn-2869 as compared to fluconazole and itraconazole against 139 yeast isolates from normally sterile sites in a hospital setting. Of the 139 isolates, 68 were from blood cultures, 27 from peritoneal fluids, 7 from cerebrospinal fluid and the remaining 37 from other tissue and fluid sources. The NCCLS M27-T method for *in vitro* susceptibility testing of yeasts was used. Syn-2869 was solubilized in DMSO. Among the 139 isolates tested, 83 were *C. albicans*, 18 were *C. glabrata* and 38 were *Candida* species. Against this panel of *Candida* organisms, the MIC_{90}s in μg/ml for Syn-2869, itraconazole and fluconazole were, respectively: *C. albicans* –0.06, ≤ 0.03, 0.25; *C. glabrata* –4, 4, ≥64; *Candida* species –0.25, 0.5, ≥64. The fluconazole MICs were high in the *Candida* species group due to several isolates of *C. parapsilosis*, which were resistant to fluconazole. In addition, the MICs for *C. glabrata* were high for all three azoles tested. Overall, Syn-2869 had *in vitro* antifungal activity that was comparable to that of itraconazole and superior to that of fluconazole. Seven isolates of *C. tropicalis* or *C. paratropicalis* had MICs of 64 μg/ml against fluconazole. Five of these isolates were susceptible to itraconazole with MICs of 0.03-0.06 μg/ml. The MICs of Syn-2869 against these isolates ranged from 0.0125-0.25 μg/ml. The highest MIC values for all drugs tested were against *C. glabrata*. Among the 83 *C. albicans* isolates, all strains were susceptible to fluconazole with MIC values < 8.0 μg/ml; itraconazole was fully active against all but four isolates which demonstrated dose-dependent susceptibility to the drug. All *C. albicans* isolates were susceptible to Syn-2869, with MIC values of ≤ 0.125 μg/ml. Further studies are needed to elucidate the full spectrum of *in vitro* antifungal activity of this new azole compound.

Salama *et al*. (34) studied the *in vitro* activity of Syn-2869 against clinical isolates of yeasts and dermatophytes. The investigators tested a panel of 240 clinical isolates of the pathogenic yeasts *C. albicans*, *C. tropicalis*, *C. kefyr*, *C. guilliermondii*, *C. krusei*, *Torulopsis* (*Candida*) *glabrata*, *C. neoformans*, the filamentous fungi *A. fumigatus*, *A. flavus*, *A. niger*, and the dermatophytes *Trichophyton rubrum*, *T. mentagrophytes* and *Microsporum canis*. The *in vitro* MIC_{90}s and range of MICs in μg/ml, respectively, for Syn-2869 were: *C. albicans* (0.09; < 0.048-0.39), *C. tropicalis*; 0.19; < 0.048-0.19), *C. kefyr* (0.19; 0.048-0.19), *C. guilliermondii* (0.39; 0.09-0.39), *C. krusei* (0.19; < 0.09-0.19), *T. glabrata* (0.78; < 0.048-0.19). *C. neoformans* (0.19; < 0.048-0.19), the filamentous fungi *A. fumigatus* (0.19; < 0.048-0.19), *A. flavus* (0.39; < 0.048-0.39), *A. niger* (0.19; 0.09-0.39), and the dermatophytes *T. rubrum* (< 0.048), *T. mentagrophytes* (< 0.048; < 0.048-0.78) and *M. canis* (< 0.048). Overall, the MIC data for Syn-2869 were comparable to those obtained with itraconazole and amphotericin B and were superior to those obtained with fluconazole.

A time-kill study with an isolate of *C. albicans* indicated that Syn-2869 is fungistatic, generally characteristic of azole compounds, and that the kinetics of antifungal activity are comparable to that of itraconazole and fluconazole (34). The antifungal activity of Syn-2869 was stable at a pH range of 3.0-7.0 and a temperature range of 30-37 °C.

Table II: In vitro *antifungal activity of Syn2869 compared to itraconazole and amphotericin B against selected moulds (filamentous fungi).*

Organism	Antifungal Compound	MIC_{90} (μg/ml)
Sporothrix schenckii	Syn2869	>16.0
	Itraconazole	4.0
	Amphotericin B	4.0
Absidia corymbifera	Syn2869	0.5
	Itraconazole	0.5
	Amphotericin B	0.25
Cladophialophora bantiana	Syn2869	0.125
	Itraconazole	0.125
	Amphotericin B	0.5
Exophiala dermatitidis	Syn 2869	0.5
	Itraconazole	0.5
	Amphotericin B	1.0
Fonsecaea pedrosoi	Syn2869	0.25
	Itraconazole	0.25
	Amphotericin B	1.0
Fusarium solani	Syn2869	>16.0
	Itraconazole	>16.0
	Amphotericin B	2.0
Scedosporium apiospermum	Syn2869	1.0
	Itraconazole	4.0
	Amphotericin B	8.0
Phialophora parasitica	Syn2869	0.5
	Itraconazole	2.0
	Amphotericin B	2.0

Johnson *et al*. (35) studied the *in vitro* antifungal activity of Syn-2869 against emerging and less common mould pathogens. The NCCLS M27-T method was used to test the *in vitro* susceptibility of 100 pathogenic moulds (filamentous fungi) to Syn-2869, itraconazole and amphotericin B. The fungi tested comprised 10 strains each of *Absidia corymbifera*, *Cladophialophora bantiana*, *Exophiala dermatitidis*, *Fonsecaea pedrosoi*, *Fusarium solani*, *Phialophora parasitica*, *Scedosporium apiospermum* and *Sporothrix schenckii*, and 5 strains each of *C. carionii*, *Ramichloridium mackenziei*, *S. prolificans* and *Scopulariopsis brevicaulis*. Overall, Syn-2869 was comparable to itraconazole in activity against these mould pathogens (Table II). Syn-2869 and itraconazole were more active than amphotericin B against the dematiaceous (dark or brown fungi) moulds (*Cladophialophora*, *Exophiala*, *Fonsecaea* and *Ramichloridium* species). Syn-2869 was the most active compound against *F. pedrosoi* and *P. parasitica* and the least active against

Table III: Experimental pharmacokinetics of Syn2869 in mice, rats and rabbits.

Animal Model	C_{max} (μg/ml)	AUC (μg.h/ml)	T_{max} (h)	Plasma Half-Life (h)	Plasma Clearance (ml/min/kg)
Mice	6.29	61.48	1.60	3.74	24.5
Rats	0.55	4.75	2.00	6.24	176.62
Rabbits	1.30	10.59	1.66	5.73	87.7

S. schenckii. Syn-2869 and itraconazole were poorly active (MIC = 16 μg/ml) against the hyaline fungi (*Fusarium*, *Scedosporium* and *Scopulariopsis* species). Amphotericin B had only moderate activity (MICs = 1-> 16 μg/ml) against these pathogens. This study demonstrated that Syn-2869 has broad spectrum *in vitro* activity against a wide range of pathogenic moulds.

In Vivo *Activity*

Salama *et al.* (36) studied the *in vivo* activity of Syn-2869 in experimental systemic infections of *T. glabrata* and *C. neoformans* infections in cyclophosphamide-treated immunosuppressed mice. Mice were infected intravenously with either *T. glabrata* or *C. neoformans*. One hour after infection the mice were treated orally with a single dose of either Syn-2869 or itraconazole at doses ranging from 11.25-90 mg/kg. Activity was assessed as mean survival over a 10-day period compared to infected, untreated control mice. In the *T. glabrata* infection model, Syn-2869 was more active than itraconazole in prolonging mean survival in mice at the lower doses of 11.25 and 22.5 mg/kg. At the higher doses of 45 and 90 mg/kg, Syn-2869 and itraconazole were comparable in prolonging mean survival. In the *C. neoformans* infection model, Syn-2869 and itraconazole were comparable in prolonged mean survival at all doses tested. Syn-2869 reduced organ burdens of yeast approximately 1 log more than itraconazole. Neither drug sterilized target organs, indicative of the fungistatic nature of these triazole compounds; however, reduction of colony-forming units in tissue was drug-concentration dependent.

Furukawa *et al*. (37) studied the *in vivo* antifungal activity of Syn-2869 in murine models of pulmonary aspergillosis and systemic infections of cryptococcosis and candidiasis. In the pulmonary aspergillosis model, X-ray irradiated immunocompromised mice were infected intranasally with a strain of *A. fumigatus*. Mice were treated orally for 3 successive days with 50 mg/kg of either Syn-2869 or itraconazole. Mean survival was calculated over a 22-day period. Compared to infected, untreated control mice, the Syn-2869-treated mice had prolonged survival of 104%, which was superior to the itraconazole-treated mice, which had prolonged survival of 42%. Syn-2869 and itraconazole both reduced organ burden of fungi during the experiment but did not eradicate the aspergilli.

In experimental systemic infections of candidiasis and cryptococcosis in immunocompromised mice, Syn-2869 was comparable to itraconazole in prolonging mean survival and in reducing colony-forming units of yeast isolated from target organs (37). Following a single oral dose (50 mg/kg) of Syn-2869 or itraconazole, Syn-2869 achieved higher tissue concentrations in the lungs than itraconazole. This observation may be significant in the clinic and will require further testing with regard to the treatment of pulmonary fungal infections.

Experimental Pharmacokinetics

Khan *et al*. (38) studied the pharmacokinetics and oral bioavailability of Syn-2869 compared to itraconazole in mice, rats and rabbits. A single oral dose (50 mg/kg) of Syn-2869 was administered to mice, rats and rabbits and the pharmacokinetic values were calculated. The data are summarized in Table III. Bioavailability of Syn-2869 ranged from 14.75% in rats to 60% in mice; itraconazole had a bioavailability of 23% in the mouse. These studies indicated that Syn-2869 has a propensity for the lung. The AUCs (over the test time period) in mouse lungs were 128.5 and 39.5 μg.h/g tissue for Syn-2869 and itraconazole, respectively. The higher tissue to plasma ratio of Syn-2869 contributed to its superior activity compared to itraconazole in experimental animal models of pulmonary fungal infections. Overall, the data support further study of Syn-2869 in the clinic.

Conclusions

Syn-2869 represents the latest development lead in the triazole class of antifungal compounds. This agent has potent *in vitro* activity against a variety of pathogenic yeasts (*Candida* species, *C. neoformans*) and filamentous fungi (*A. fumigatus*, *A. flavus* and *A. niger*), as well as a wide variety of mould pathogens, including dermatophytes. Syn-2869 also has potent experimental *in vivo* activity against *C. albicans*, *C. glabrata*, *C. neoformans* and *A. fumigatus*. This compound has favorable experimental pharmacokinetics which, in early testing, suggest that the compound may be 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 to determine whether it may be a candidate for further

development as a novel antifungal agent. The *in vitro*, experimental *in vivo* and experimental pharmacokinetic data summarized in this overview support the further development of Syn-2869.

Manufacturers

SynPhar Laboratories, Inc. (CA); Taiho Pharmaceutical Co., Inc. (JP).

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