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F75 SSY726, a New Triazole Antifungal Agent: *in vitro* and *in vivo* Evaluation. K. YOKOYAMA*, L. WANG, and M. MIYAJI. Research Center for Pathogenic Fungi and Microbial Toxicoses, Chiba University, Chiba, and A. IWASA. Research Laboratories, SS Pharmaceutical Co., Ltd., Narita, and Y. Ikeda. Research Laboratories, Yoshitomi Pharmaceutical Industries, Ltd., Fukuoka, Japan.

The *in vitro* and *in vivo* antifungal activity of SSY726, a new antifungal agent, was compared with that of fluconazole (FLCZ) against *Candida* spp., *Cryptococcus neoformans*, and *Aspergillus* spp.. Minimum inhibitory concentration (MIC) was determined to estimate the *in vitro* activity by the twofold agar dilution method. The MIC ranges were as follows: SSY726, 0.5 - 4 μg/ml; FLCZ, 0.5 - 8 with synthetic amino acid medium for fungal (SAAMF), SSY726, 128 - >512; FLCZ, 512 - >512 with RPMI-1640 MOPS medium (RPMI) against *C.albicans* (30 strains). SSY726, 4 - 256 μg/ml; FLCZ, 4 - 256 with RPMI against *C.neoformans* (30 strains). SSY726, 32 - >512 μg/ml; FLCZ, 128 - >512 with SAAMF against *A.fumigatus* (30 strains).

The *in vivo* activity was measured following one time on day 0 (in *Candida* and *Cryptococcus* models) or once a day on five successive days (in *Aspergillus* models) injection of the agent into 5-week old, ICR male mice. The efficacy was determined by the dose of agent necessary to achieve a certain T/C (treated group/control group) ratio of survival days. In the candidosis model, 0.313 mg/kg of SSY726 or 5 mg/kg of FLCZ was required to achieve 300 % of T/C ratio, respectively. In the cryptococcosis model, 5 mg/kg of SSY726 or 20 mg/kg of FLCZ achieved 122 % of T/C. In the aspergillosis model, no significant difference in efficacy was detected between these two agents. Our study suggests that the *in vivo* efficacy of SSY726 is higher than that of FLCZ against *Candida* and *Cryptococcus*.

F76 Efficacy of SSY726 on Systemic Candidosis and Cryptococcosis in Neutropenic Mice. M. MATSUMOTO*, T. ASAOKA, and A. IWASA. Research Laboratories, SS Pharmaceutical Co., Ltd., Narita, and Y. IKADA, K. YAMAMOTO, and F. HIRAYAMA. Research Laboratories, Yoshitomi Pharmacetical Industries, Ltd., Fukuoka, Japan.

SSY726:(R)-(-)-3-methyl-3-methylsulfonyl-1-(1*H*-1, 2, 4 - triazol - 1-yl) 2-[4-(trifluoromethyl)phenyl]butan-2-ol is a new triazole antifungal agent. Its *in vivo* efficacies on the basis of prolongation of survival were tested in comparison with those of fluconazole (FLCZ). SSY726 showed more potent activity than FLCZ with a single i.v. treatment on systemic candidosis (*C.albicans* IFM 40009) and cryptococcosis (*C.neoformans* TIMM 1855) in mice. In normal mice, minimum effective doses were 0.313 mg/kg of SSY726 and 1.25 mg/kg of FLCZ on candidosis, and 20 mg/kg of SSY726 and over 20 mg/kg of FLCZ on cryptococcosis. In neutropenic mice (cyclophosphamide 100 mg/kg i.p. treated: Cy), they were 0.313 mg/kg of SSY726 and 5 mg/kg of FLCZ on candidosis, and 1.25 mg/kg of SSY726 and 20 mg/kg of FLCZ on cryptococcosis. In 5-fluorouracil treated mice (150 mg/kg i.p.), they were 0.313 mg/kg of SSY726 and 5 mg/kg of FLCZ on candidosis. SSY726 efficacy was also compared to that of FLCZ after repeated treatments. In normal mice, i.v. treatment of SSY726 every two days or daily doses of 1.25 mg/kg for eight days showed an equivalent effect to that of i.v. daily treatment of 5 mg/kg FLCZ for eight days. In neutropenic mice (Cy), i.v. treatment of SSY726 every four days doses of 1.25 mg/kg for eight days showed an equivalent effect to that of i.v. daily treatment of 5 mg/kg FLCZ for eight days. Thus, SSY726 was more effective than FLCZ in the systemic infection with *C.albicans* and *C.neoformans*, especially in neutropenic mice.

F77 Anticryptococcal Activity of SSY726, a New Triazole Antifungal Agent, in a Murine Pulmonary Infection Model. Y. IKEDA*, K. YAMAMOTO, and F. HIRAYAMA. Research Laboratories, Yoshitomi Pharmaceutical Industries, LTD., Fukuoka. M. MATSUMOTO, T. ASAOKA, and A. IWASA, Central Research Laboratories, SS Pharmaceutical Co., LTD., Chiba, Japan.

SSY726, a new triazole antifungal agent, was evaluated for anticryptococcal activity in normal or neutropenic mice. The leukopenic mice with cyclophosphamide (CY, 100 mg/kg, i.p.), 5-fluorouracil (5-FU, 150 mg/kg, i.p.) or prednisolone (PDN, 50 mg/kg, s.c.), and normal mice were inoculated intranasally with 1.7 - 3.0 x 10^5 cells of *Cryptococcus neoformans* TIMM 1855. Intravenous treatment with SSY726 or fluconazole (FLCZ) was initiated 1 hour after the challenge, and was followed by once daily, every two days or every four days for 8 days. Therapeutic effect was estimated by the reduction of viable cell counts (CFU) in lungs at day 10 after the infection. In once daily for eight successive days injection, SSY726 significantly reduced CFU in lungs at a dose of 0.31 mg/kg/day in CY- and 5-FU-treated mice, and at a dose of 5 mg/kg/day in normal and PDN-treated mice. FLCZ reduced CFU in lungs at a dose of 5 mg/kg/day and 20 mg/kg/day in CY- and 5-FU-treated mice, respectively, but did not up to 80 mg/kg/day in normal and PDN-treated mice. Every four days treatment with 5 mg/kg/day of SSY726 (total dose: 10 mg/kg) showed the effect comparable to once daily for eight successive days treatment with 20 mg/kg/day of FLCZ (total dose: 160 mg/kg) in CY-treated mice. These results suggest that SSY726 is more effective than FLCZ in the therapy of pulmonary cryptococcosis in compromised humans.

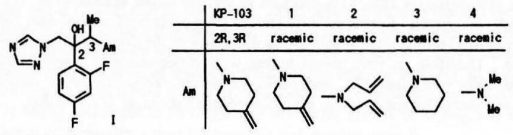
F78 **KP-103, a Novel Topical Antifungal Triazole: Structure-Activity Relationships of Azolylamine Derivatives.** H.OGURA*, H.KOBAYASHI, K.NAGAI, T.NISHIDA, T.NAITO, Y.TATSUMI, M.YOKOO and T.ARIKA. Kaken Pharm. Co., LTD., Kyoto, Japan.

In a search for an antifungal agent, we have prepared a variety of new azolylamine derivatives with general formula (I) and measured in vitro activity. MIC values (μg/ml) were shown below.

Fungi	KP-103	1	2	3	4	CTZ	Media[a]
C. albicans KC-03	<0.025	<0.025	<0.025	0.05	0.2	0.025	A
Cr. neoformans KC-201	0.05	0.2	0.1	0.78	6.25	0.2	B
A. fumigatus KA-01	0.2	0.2	1.56	1.56	50.0	0.78	B
T. mentagrophytes KD-04	0.39	0.78	1.56	3.13	25.0	0.39	B

[a] A; SAAMF broth. B; sabouraud dextrose agar.

We found that the cyclic amine having methylene group at the 3 position is necessary for a broad antifungal spectrum and a potent activity. KP-103 which has a (2R,3R)-absolute configuration and a 4-methylenepiperidine moiety, showed the most potent activity and significantly lower MIC values than clotrimazole(CTZ).



Am = substituted amino group

F79 ***In Vitro* Activity of KP-103, a Novel Topical Antifungal Triazole.** Y. TATSUMI*, M. YOKOO, T. ARIKA, H. OGURA, K. NAGAI, and T. NAITO. Kaken Pharmaceutical Co. Ltd., Kyoto, Japan, H. YAMAGUCHI, Teikyo Univ., Tokyo, Japan.

The *in vitro* activity of KP-103, a triazole having 4-methylenepiperidine moiety at the C-3 position, was compared with that of clotrimazole (CTZ), neticonazole (NCZ), lanoconazole (LCZ), and butenafine (BTF) against pathogenic fungi. MIC_{80} values (μg/ml) were shown below.

Fungi (No. of strains)	KP-103	CTZ	NCZ	LCZ	BTF	Media[a]
C. albicans (44)	0.002	0.0313	0.0625	0.25	>8.0	A
M. furfur (6)	0.025	6.25	3.13	0.78	12.5	C
Aspergillus spp.(15)	0.0625	2.0	0.25	0.002	0.25	A
T. rubrum (39)	0.125	0.5	0.25	0.0078	0.0078	B
T. mentagrophytes (28)	0.25	0.25	0.25	0.0313	0.0156	B

[a] A, 0.2M MOPS-buffered RPMI 1640, pH 7.0; B, Sabouraud dextrose broth; C, medium C (Faergemann J et al. Ata Derm. Venereol. Suppl 86: 1-23, 1979).

KP-103 was the most active against *C. albicans* and *M. furfur* among the tested drugs. Its activity against *Trichophyton* spp. was almost equal to that of CTZ and NCZ, but was weaker than that of LCZ and BTF.

Anti-*T. mentagrophytes* activities of the reference drugs were reduced by the addition of human serum and horny materials as reported, while that of KP-103 was not affected. Furthermore, Anti-*T. mentagropytes* activity of KP-103 on the stripped human horny layer was equal to that of LCZ and BTF. These results reflected *in vivo* efficacies.

In summary, KP-103 has a broad antifungal spectrum and could keep a high activity in the horny layer where fungi reside.

F80 **Therapeutic Efficacy of KP-103, a Novel Topical Antifungal Triazole, on Experimental Superficial Mycosis.** Y. TATSUMI*, M. YOKOO, T. ARIKA, H. OGURA, K. NAGAI, and T. NAITO. Kaken Pharmaceutical Co. Ltd., Kyoto, Japan, H. YAMAGUCHI, Teikyo Univ., Tokyo, Japan.

The therapeutic efficacy of KP-103 on dermatomycosis models in guinea pig was compared with that of neticonazloe (NCZ), lanoconazole (LCZ), butenafine (BTF), and clotrimazole (CTZ). One % solution of each drug was topically applied once a day. Two days after last application, skin blocks or homogenates were cultured. Rate of complete cure was expressed by the percentage of mycologically cured animals in infected animals (n=10).

Mycosis models	Treatment duration (days)	Rate of complete cure (%)				
		KP-103	NCZ	LCZ	BTF	CTZ
Tinea corporsis	10	100	10	90	100	N.D.
Tinea pedis	10	100	30	100	100	N.D.
Interdigital *tinea pedis*	10	100	40	100	100	N.D.
Skin *candidiasis*	3	80	0	0	N.D.	0

The efficacy of KP-103 on dermatophytosis models was superior to that of NCZ and almost equal to that of LCZ and BTF. KP-103 was effective on skin candidiasis, while the other drugs were not. To clarify the duration of retention time of the drug in skin after topical application, the prophylactic effect of KP-103 on dermatophytosis model was examined. KP-103 exerted prophylactic effect with 90% cure rate at application of 48h before infection.

In summary, the excellent efficacy of KP-103 on dermatophytosis and skin candidiasis may be attributed to its high activity and long time retention in the horny layer.

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