Synthesis and Antifungal Activities of (2*R*,3*R*)-2-Aryl-1-azolyl-3-(substituted amino)-2-butanol Derivatives as Topical Antifungal Agents

Hironobu OGURA,* Haruhito KOBAYASHI, Kiyoshi NAGAI, Tokiko NISHIDA, Takanobu NAITO, Yoshiyuki TATSUMI, Mamoru YOKOO, and Tadashi ARIKA

Development Research Laboratories, Kaken Pharmaceutical Co., Ltd., 14, Shinomiya Minamikawara-cho, Yamashina-ku, Kyoto 607–8042, Japan. Received May 10, 1999; accepted July 20, 1999

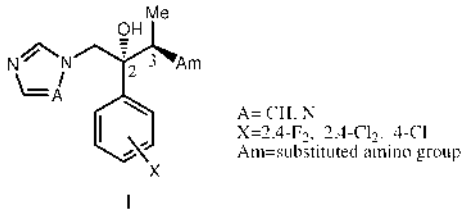
2-Aryl-1-azolyl-3-(substituted amino)-2-butanol derivatives I were prepared by ring-opening reaction of epoxides II with excess amine, and their antifungal activities were evaluated as topical agents. Azolyl-cyclic amine derivatives with a methylene group showed extremely strong activity with a broad spectrum *in vitro*. In general, anti-*Trichophyton mentagrophytes* activities of most of the topical antifungal agents are substantially reduced by addition of keratin (a major constituent of the keratinized tissue). However, the triazole derivative (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol ((−)-40, KP-103) showed very little deactivation by addition of keratin. This biological characteristic of triazole derivative (−)-40 resulted in excellent therapeutic efficacy on dermatophytosis superior to that of the corresponding imidazole derivative ((−)-41).

Key words KP-103; topical antifungal agents; 4-methylenepiperidine; 1,2,4-triazole; structure–activity relationship

Many kinds of topical antifungal agents have been developed and are available as commercial products. These agents are classified into a number of groups, *i.e.* allylamines, benzylamines, imidazoles, thiocarbamates and morpholines, which exhibit quite different biological properties. Benzylamines and allylamines show strong antifungal activities against dermatophytes such as *Trichophyton mentagrophytes*, but show weak activity against yeast-like fungi such as *Candida albicans*. Thiocarbamates and morpholines show very weak effects against yeast-like fungi and *Aspergillus* spp., respectively. Imidazoles have moderate antifungal activities, but their activity and spectra are wider than those of the other groups. These agents are used for the treatment of dermatomycosis, but relapse of infection is often observed after therapy. Therefore, there it is still necessary to develop new topical antifungal agents with broad spectrum, strong *in vitro* antifungal activity and excellent therapeutic efficacy.

For this purpose, we focused our attention on triazole derivatives. Similarly to imidazoles, triazoles have been shown to inhibit the conversion of lanosterol to ergosterol,[1] which is an important constituent of the fungal cell membrane. Although a large number of triazole derivatives have been synthesized, only two triazole drugs (fluconazole,[2] itraconazole[3]) have been developed commercially for treatment of systemic fungal infection, but they can not be used topically. Among the triazoles currently under development, the sulfonyl derivative SM-8668[4] (Chart 1, active enantiomer has a (2*R*,3*R*)-absolute configuration), showed the strongest and broadest spectrum antifungal activity, and was used as the reference drug in the present study. We replaced the sulfonyl group at the 3-position of SM-8668 with a substituted amino group.

Here, we describe the preparation of 2-aryl-1-azolyl-3-(substituted amino)-2-butanol derivatives I, which we called "azolylamine derivatives," and the antifungal activities of I



I

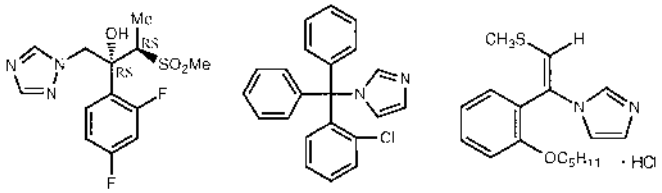


Chart 1

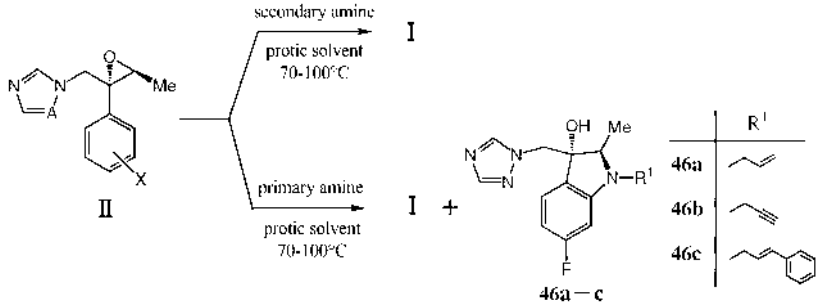


Chart 2

* To whom correspondence should be addressed.

against several species of fungi in comparison with those of clotrimazole and neticonazole[5] (Chart 1). Furthermore, we evaluated the differences between triazole and imidazole derivatives to determine the usefulness of triazole as a topical agent.

Chemistry The azolylamine derivatives I (**2**—**43**, Table 1) were prepared by ring-opening reaction of epoxides II with excess amine on heating at 70—100 °C (Chart 2). This reaction proceeded more smoothly with the addition of a protic solvent such as water or alcohol in comparison with that in the presence of only nonprotic solvents. However, when primary amines were used for ring-opening reaction of 2,4-difluorophenyl-epoxide II (X=2,4-F_2), indoline derivatives[6] (**46a**—**c**) were obtained together with the desired compounds (**10**, **13**, **18**). The epoxides II were prepared as described.[4a,4c,7] With the exception of commercially available

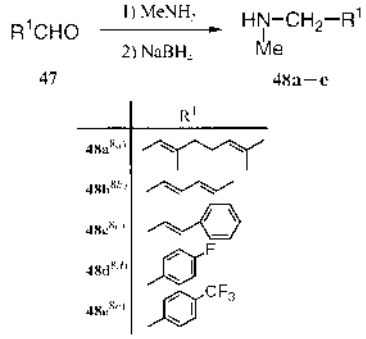
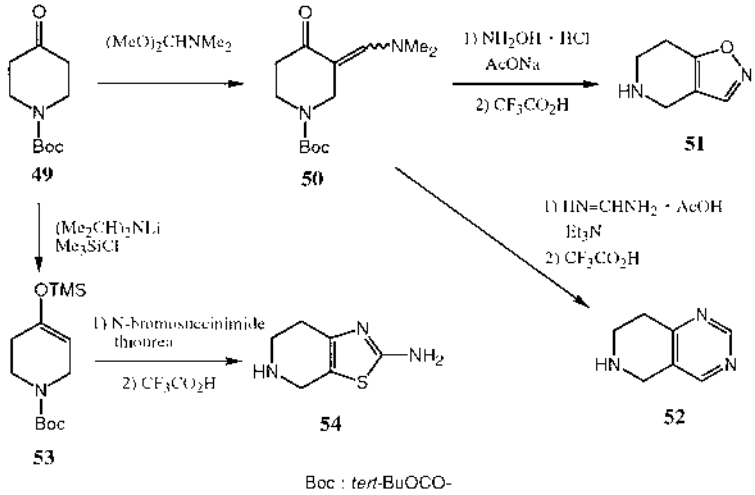
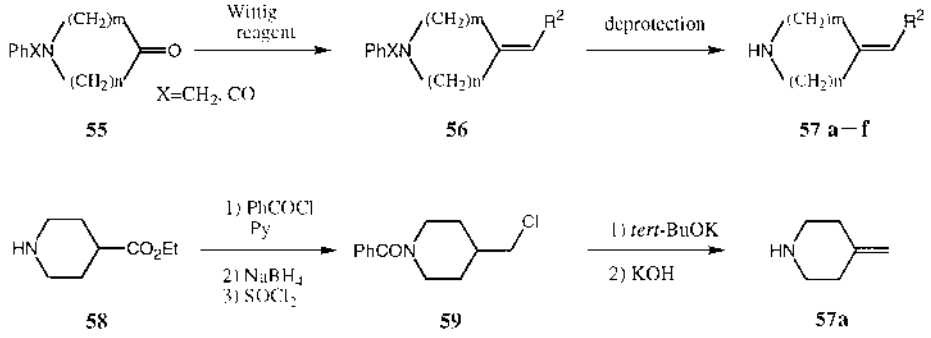


Chart 3



Boc : *tert*-BuOCO-

Chart 4



	m	n	R^2
57a	2	2	H
57b	2	2	Me
57c	2	2	$CH=CH_2$
57d	2	2	Ph
57e	3	1	H
57f	2	1	H

Chart 5

Table 1. MICs (μg/ml) of Azolylamine Derivatives

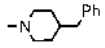
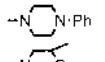
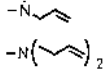
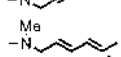
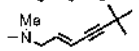
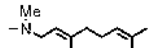
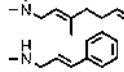
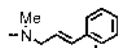
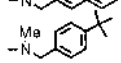
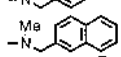
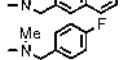
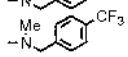
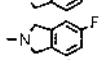
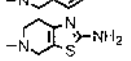
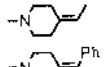
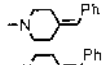
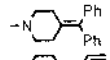
Compd.[a]	X	A	Am	Config.	MIC (μg/ml)[b]			
					C. a. (KC-03)	*Cr. n.* (KC-201)	*A. fu.* (KA-01)	*T. m.* (KD-04)
1[c]	2,4-F_2	N	$-NH_2$	(2*R**,3*R**)	25.0	>100	>100	>100
2	2,4-F_2	N	$-N(Me)_2$	(2*R**,3*R**)	0.2	6.25	50.0	25.0
3	2,4-F_2	N		(2*R**,3*R**)	0.2	12.5	50.0	25.0
4	2,4-F_2	N		(2*R**,3*R**)	0.05	0.78	1.56	3.13
5	2,4-F_2	N		(2*R**,3*R**)	0.1	0.78	1.56	1.56
6	2,4-F_2	N		(2*R**,3*R**)	0.1	0.39	1.56	3.13
7	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.1	0.78	1.56
8	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.1	0.39	1.56
9	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.78	3.13	3.13
10	2,4-F_2	N		(2*R**,3*R**)	0.05	3.13	100	50.0
11	2,4-F_2	N		(2*R**,3*R**)	0.025	0.78	3.13	6.25
12	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.1	1.56	1.56
13	2,4-F_2	N		(2*R**,3*R**)	0.025	3.13	50.0	12.5
14	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.39	0.78	0.78
15	2,4-F_2	N		(2*R**,3*R**)	0.025	0.39	3.13	0.78
16	2,4-F_2	N		(2*R**,3*R**)	0.05	0.39	6.25	1.56
17	2,4-F_2	N		(2*R**,3*R**)	0.05	0.1	12.5	6.25
18	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.78	6.25	6.25
19	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.1	1.56	0.39
20	2,4-F_2	N		(2*R**,3*R**)	0.025	0.2	25.0	0.78
21	2,4-F_2	N		(2*R**,3*R**)	0.05	0.2	>100	6.25
22	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.2	1.56	0.39
23	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.1	0.78	1.56
24	2,4-F_2	N		(2*R**,3*R**)	0.2	0.78	12.5	6.25
25	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.2	0.39	1.56
26	2,4-F_2	N		(2*R**,3*R**)	0.05	0.1	0.39	1.56
27	2,4-F_2	N		(2*R**,3*R**)	0.2	6.25	1.56	3.13
28	2,4-F_2	N		(2*R**,3*R**)	0.78	6.25	25.0	25.0
29	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.39	1.56	0.78
30	2,4-F_2	N		(2*R**,3*R**)	0.78	3.13	12.5	12.5
31	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.78	0.78	1.56
32	2,4-F_2	CH		(2*R**,3*R**)	0.05	1.56	6.25	1.56
33	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.1	0.39	0.78
34	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.05	0.39	0.78
(−)-**35**	2,4-F_2	N		(2*R*,3*R*)	<0.025	0.78	>100	>100
(−)-**36**	2,4-F_2	N		(2*R*,3*R*)	<0.025	0.1	0.2	0.39
(−)-**37**	2,4-F_2	N		(2*R*,3*R*)	<0.025	0.1	0.2	0.2

Table 1. (continued)

Compd.[a]	X	A	Am	Config.	MIC (μg/ml)[b]			
					C. a. (KC-03)	*Cr. n.* (KC-201)	*A. fu.* (KA-01)	*T. m.* (KD-04)
(−)-**38**	2,4-F_2	N		(2*R*,3*R*)	0.1	0.39	0.78	0.78
(−)-**39**	2,4-F_2	N		(2*R*,3*R*)	<0.025	0.39	0.39	0.78
40	2,4-F_2	N		(2*R**,3*R**)	<0.025	0.2	0.2	0.78
(−)-**40**	2,4-F_2	N		(2*R*,3*R*)	<0.025	0.05	0.2	0.39
(+)-**40**	2,4-F_2	N		(2*S*,3*S*)	0.39	1.56	>100	100
41	2,4-F_2	CH		(2*R**,3*R**)	<0.025	0.05	0.2	0.39
(−)-**41**	2,4-F_2	CH		(2*R*,3*R*)	<0.025	≦0.025	0.1	0.39
42	2,4-Cl_2	N		(2*R**,3*R**)	0.025	0.2	0.39	0.78
43	4-Cl	N		(2*R**,3*R**)	<0.025	0.2	6.25	3.13
44	Clotrimazole				≦0.025	0.2	0.78	0.39

a) All compounds except (−)-**35**, (−)-**36**, (−)-**37**, (−)-**38**, (−)-**39**, (−)-**40**, (+)-**40** and (−)-**41** were racemic. *b*) Abbreviations: *C. a.*, *Candida albicans*; *Cr. n.*, *Cryptococcus neoformans*; *A. fu.*, *Aspergillus fumigatus*; *T. m.*, *Trichophyton mentagrophytes*. *c*) Compound **1** was prepared as described.[7a]

amines, most of the amines used in this study were prepared using the reported methods. For example, *N*-methyl secondary amines such as **48a**—**e**[8] were prepared by reductive alkylation[8e] (Chart 3). Heteroaromatic cyclic amines such as **51**, **52**[9] and **54**[10] were prepared from *N*-(*tert*-butoxycarbonyl)piperidone (**49**) in three steps (Chart 4). Cyclic amines[11] with a methylene group or substituted methylene group (**57a**—**f**) were prepared from *N*-protected ketones (**55**) by the Wittig reaction and subsequent deprotection. 4-Methylenepiperidine (**57a**) was also prepared from *N*-benzoyl-4-chloromethyl piperidine (**59**)[12] by an elimination reaction and subsequent deprotection.

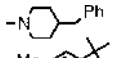
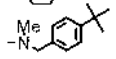
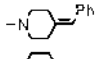
Antifungal Activity The azolylamine derivatives I (**1**—**43**) obtained as described above were examined for their *in vitro* activities against *Candida albicans*, *Cryptococcus neoformans*, *Aspergillus fumigatus* and *Trichophyton mentagrophytes* in comparison with those of clotrimazole, and the minimum inhibitory concentrations (MICs) are shown in Table 1.

Many of these compounds showed excellent *in vitro* antifungal activities. Their activities were generally exceptionally high against *C. albicans* and good against the others. The tertiary amine derivatives (**11**, **12**, **14**, **19**) had higher activities than the corresponding secondary amine derivatives (**10**, **13**, **18**). In particular, cyclic amine derivatives (**33**—**43**) with a methylene group or a substituted methylene group showed the strongest activities. With the exception of (−)-**35**, only this class showed MIC values of $<1.0\,\mu$g/ml against all fungi. Among a series of 4-methylenepiperidine derivatives (**40**—**43**), (2*R*,3*R*)-(−)-**40** was 16- to 32-fold more active than the (2*S*,3*S*)-enantiomer (+)-**40** against *C. albicans* and *C. neoformans*, and (+)-**40** showed no significant activity against *A. fumigatus* or *T. mentagrophytes*. The imidazole derivative ((−)-**41**) showed similar activity to the triazole derivative ((−)-**40**) against these fungi. The 2,4-Cl_2 derivative (**42**) showed similar activity to the 2,4-F_2 derivative (**40**), whereas the 4-Cl derivative (**43**) was less active than **40** and **42** against *A. fumigatus* and *T. mentagrophytes*. In the *in vitro* assay, the cyclic amine derivatives with a methylene group showed strong activities, which were equivalent or superior to that of clotrimazole. However, we could not decide on one candidate for development based only on MIC values.

We next examined the effects of keratin (human hair) on anti-*T. mentagrophytes* activity. In general, the activities of most topical antifungal agents are greatly reduced by adsorption to keratin,[13] which is a major constituent of the keratinized tissue where fungi reside. MICs of some of these derivatives were determined by the microdilution method using Sabouraud dextrose broth (SDB) and saline containing 5% human hair (Table 2). The anti-*T. mentagrophytes* activities of the reference drugs clotrimazole and neticonazole were markedly reduced (32-fold) by addition of human hair, but the activities of methylenepiperidine derivatives (**33**, **34**, **40**, **41**) were less affected (2—8-fold). The order of deactivation for the substituent adjacent to the double bond of these derivatives (**33**, **34**, **40**) was as follows: Ph (**34**)>Me (**33**)>H (**40**). This order suggested that addition of a lipophilic substituent on the double bond reduced the activity. Furthermore, we found that the imidazole derivatives (**32**, **41**) were more markedly deactivated than corresponding triazole derivatives (**31**, **40**). These results indicated that 4-methylenepiperidino triazole derivative (**40**) had low affinity to keratin and could retain a high level of activity in the keratinized tissue.[14]

To clarify the difference between the triazole derivative ((−)-**40**) and the imidazole derivative ((−)-**41**), we evaluated their therapeutic efficacy in the guinea pig model of *Tinea corporis* infection (Fig. 1). Topical treatment was started 3 or 4 d after infection and continued for 10 d by once-a-day application. The *T. mentagrophytes* KD-04 strain used in this study has a strong virulence to invade the hair follicles[15] and can invade the hair follicles deeply on 4 d after infection compared with on 3 d after infection. Triazole derivative ((−)-**40**) showed high efficacy against *Tinea corporis* both days after infection. On the other hand, imidazole derivative

Table 2. Effect of Human Hair on *anti-T. mentagrophytes* Activity of Azolylamine Derivatives

Compd.	A	Am	MIC (μg/ml)		Saline containing 5% hair / SDB
			SDB	Saline containing 5% hair	
7	N		0.78	6.25	×8
20	N		1.56	50	×32
25	N		0.78	6.25	×8
26	N		0.39	12.5	×32
31	N		0.78	3.13	×4
32	CH		3.13	100	×32
33	N		0.39	1.56	×4
34	N		0.39	3.13	×8
40	N		0.2	0.39	×2
41	CH		0.2	1.56	×8
44		Clotrimazole	0.39	12.5	×32
45		Neticonazole	0.2	6.25	×32

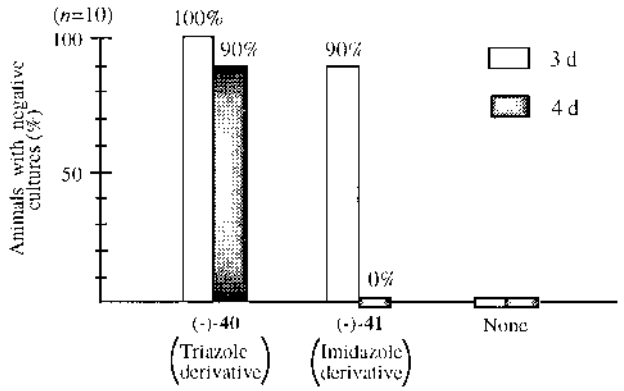


Fig. 1. Therapeutic Efficacy of 1.0% Solution of Triazole Derivative (−)-**40** or Imidazole Derivative (−)-**41** in the Guinea Pig Model of *Tinea corporis* Infection

Topical treatments were started 3 or 4 d after infection and were continued for 10 d by application of once-a-day.

((−)-**41**) showed high efficacy on day 3 postinfection but the efficacy was extremely low on day 4 postinfection. These results suggested that triazole derivative ((−)-**40**) showed better penetration into the hair follicles than imidazole derivative ((−)-**41**) and the triazole group in (−)-**40** was necessary for its property. We confirmed that (−)-**40** penetrates easily into the skin by the transfollicular route in addition to transepidermal route from the distribution pattern in the skin of guinea pigs 24 h after application of the 1% ^{14}C-labelled drug (data not shown). Lipophilic compounds generally penetrate well into the skin through both the epidermis and hair follicles.[16] The 1-octanol/water partition coefficients of (−)-**40** and (−)-**41** at pH 5 were 287.6 and 103.7, respectively, and (−)-**40** was more lipophilic than (−)-**41**. This data supported the better penetration of triazole derivative ((−)-**40**) into the skin than the imidazole derivative ((−)-**41**).

In conclusion, many of the azolylamine derivatives prepared in this study exhibited excellent antifungal activities. Among these, triazole derivative ((−)-**40**, KP-103), which had a 4-methylenepiperidine moiety, was found to have a broad antifungal spectrum and showed excellent therapeutic efficacy. The excellent efficacy may be attributable to good penetration and low reduction of the activity in the skin in addition to its antifungal activity.

Experimental

Chemistry Melting points were determined on a Yanagimoto melting point apparatus without correction. IR spectra were measured on a Shimadzu FTIR4200 spectrometer. ^{1}H-NMR and ^{19}F-NMR spectra were recorded on a JEOL JNM-EX270 spectrometer using tetramethylsilane and trifluoroacetic acid as respective internal standards. The following abbreviations were used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. Mass spectra (MS) were obtained on a JEOL JMS-HX110A mass spectrometer. The optical rotations were determined on a Perkin-Elmer 241 spectrometer. Elemental analysis was performed with a Yanaco MT-5 CHN CORDER. Thin-layer chromatography (TLC) was performed on Silica gel 60 F_{254} precoated TLC plates, with a thickness of 0.25 mm (E. Merck). Column chromatography was performed on Silica gel 60 (0.063—0.200 mm, E. Merck).

(2*R*,3*R*)-2-Aryl-3-(substituted amino)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanols As a typical example, the preparation of (2*R*,3*R*)-2-(2,4-difluorophenyl)-3-(4-methylenepiperidino)-1-(1*H*-1,2,4-triazol-1-yl)-2-butanol ((−)-**40**) is described. A mixture of (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-methyl-2-[(1*H*-1,2,4-triazol-1-yl)methyl]oxirane (II, A=N, X=2,4-F_2) (0.25 g, 1 mmol), 4-methylenepiperidine (0.97 g, 10 mmol), EtOH (3 ml) and water (3 ml) was stirred at 85 °C for 24 h. After cooling, the mixture was partitioned between AcOEt (20 ml) and water (20 ml). The organic layer was washed with brine, dried over $MgSO_4$ and concentrated *in vacuo*. The residue (*ca*. 0.4 g) was chromatographed on silica gel (8 g, AcOEt : *n*-hexane=1 : 5→1 : 3, v/v). The product was recrystallized from hexane to obtain (−)-**40** (0.19 g, 54% yield from epoxide II) as colorless crystals. Other azolylamine derivatives were prepared in the same manner by ring-opening reaction of the epoxides II with the corresponding amine. Spectroscopic data and results of elementary analysis of these derivatives are shown in Table 3.

Susceptibility Testing Procedures *Candida albicans*: MICs were determined by the microdilution method using synthetic amino acid medium fungal (SAAMF). The fungal cells were suspended in saline with 0.05%

Table 3. Physical Data for Azolylamine Derivatives and Related Compounds

Compd.	Yield[a] (%)	mp (°C)[b] Optical rotation	^{1}H-NMR (in $CDCl_3$) δ	IR (cm^{-1}) (KBr)	Formula	Analysis (%) or FAB-MS Calcd (Found)		
						C	H	N
2	21	177—178	0.93 (3H, dd, J=7, 3 Hz), 2.22 (6H, s), 2.88 (1H, q, J=7 Hz), 4.76 (1H, d, J=14 Hz), 4.85 (1H, d, J=14 Hz), 5.45 (1H, s), 6.65—6.85 (2H, m), 7.4—7.6 (1H, m), 7.77 (1H, s), 8.01 (1H, s)	3300, 1620, 1500, 1270, 1140	$C_{14}H_{18}F_2N_4O$	56.75 (56.78)	6.12 6.11	18.91 18.94)
3	81	79—80	0.93 (3H, dd, J=7, 3 Hz), 1.6—1.8 (4H, m), 2.5—2.65 (4H, m), 3.19 (1H, q, J=7 Hz), 4.77 (1H, d, J=15 Hz), 4.84 (1H, d, J=15 Hz), 6.7—6.85 (2H, m), 7.4—7.55 (1H, m), 7.77 (1H, s), 8.02 (1H, s)	3300, 1640, 1500, 1280, 1140	$C_{16}H_{20}F_2N_4O$	59.62 (59.24)	6.25 6.26	17.38 17.52)
4	60	83—85	1.00 (3H, dd, J=7, 3 Hz), 1.3—1.6 (6H, m), 2.15—2.35 (2H, m), 2.4—2.6 (2H, m), 2.76 (1H, q, J=7 Hz), 4 .74 (1H, d , J=15 Hz), 4.83 (1H, d, J=15 Hz), 5.81 (1H, br s), 6.7—6.85 (2H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 8.08 (1H, s)	3300, 2950, 1620, 1500, 1280, 1140	$C_{17}H_{22}F_2N_4O$	60.70 (61.03 (61.03	6.59 6.56 6.56	16.66 17.00) 17.00)
5	90	88—89	1.02 (3H, dd, J=7, 4 Hz), 1.4—1.8 (8H, m), 2.3—2.5 (2H, m), 2.55—2.7 (2H, m), 2.88 (1H, q, J=J=7 Hz), 4.74 (1H, d, J=15 Hz), 4.84 (1H, d, J=15 Hz), 5.84 (1H, br s), 6.7—6.85 (2H, m), 7.5—7.6 (1H, m), 7.79 (1H, s), 8.07 (1H, s)	3300, 2900, 1620, 1500, 1280, 1140	$C_{18}H_{24}F_2N_4O$	61.70 (61.86	6.90 6.86	15.99 16.27)
6	59	126—128	0.9 (3H, d, J=6 Hz), 1.00 (3H, dd, J=7, 3 Hz), 1.0—1.8 (5H, m), 2.00 (1H, dt, J=12, 2 Hz), 2.4—2.6 (3H, m), 2.79 (1H, q, J=7 Hz), 4.73 (1H, d, J=15 Hz), 4.82 (1H, d, J=15 Hz), 5.77 (1H, br s), 6.7—6.85 (2H, m), 7.45—7.6 (1H, m), 7.79 (1H, s), 8.07 (1H, s)	3250, 2900, 1620, 1500, 1280, 1140	$C_{18}H_{24}F_2N_4O$	61.70 (62.07	6.90 6.88	15.99 16.31)
7	51	108—109	0.97 (3H, dd, J=7, 3 Hz), 1.05—1.7 (5H, m), 1.9—2.05 (1H, m), 2.4—2.65 (5H, m), 2.80 (1H, q, J=7 Hz), 4.73 (1H, d, J=15 Hz), 4.82 (1H, d, J=15 Hz), 5.69 (1H, br s), 6.65—6.85 (2H, m), 7.05—7.35 (5H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 8.06 (1H, s)	3420, 2920, 1620, 1500, 1270, 1140	$C_{24}H_{28}F_2N_4O$	67.59 (66.35	6.62 6.88	13.14 12.77)
8	40	165—166	0.99 (3H, dd, J=7, 2 Hz), 2.5—2.65 (2H, m), 2.9—3.05 (3H, m), 3.1—3.25 (4H, m), 4.84 (1H, d, J=15 Hz), 4.94 (1H, d, J=15 Hz), 5.21 (1H, br s), 6.7—6.95 (5H, m), 7.2—7.3 (2H, m), 7.4—7.55 (1H, m), 7.79 (1H, s), 7.97 (1H, s)	3600, 1620, 1500, 1240, 1140	$C_{22}H_{25}F_2N_5O$	63.91 (63.84	6.09 6.08	16.94 17.01)
9	44	Oil	0.92 (3H, dd, J=7, 2 Hz), 1.12 (3H, d, J=6 Hz), 1.15 (3H, d, J=6 Hz), 1.98 (1H, dd, J=12, 10 Hz), 2.25—2.5 (2H, m), 2.8—2.95 (2H, m), 3.55—3.8 (2H, m), 4.82 (1H, d, J=15 Hz), 4.92 (1H, d, J=15 Hz), 5.13 (1H, s), 6.65—6.8 (2H, m), 7.4—7.5 (1H, m), 7.78 (1H, s), 7.95 (1H, s)	3400, 3000, 1620, 1500, 1140 (neat)	$C_{18}H_{24}F_2N_4O_2$	367 (M^++1), 298, 142		
10	64	65—66	0.92 (3H, d, J=7 Hz), 3.10 (1H, dq, J=7, 2 Hz), 3.20 (1H, dd, J=14, 6 Hz), 3.44 (1H, dd, J=14, 6 Hz), 4.76 (1H, d, J=14 Hz), 4.9 (1H, s), 4.92 (1H, d, J=14 Hz), 5.13 (1H, d, J=10 Hz), 5.21 (1H, dd, J=17, 2 Hz), 5.8—6.0 (1H, m), 6.75—6.85 (2H, m), 7.3—7.45 (1H, m), 7.76 (1H, s), 7.92 (1H, s)	3300, 1620, 1500, 1140	$C_{15}H_{18}F_2N_4O$	58.43 (58.54	5.88 5.82	18.17 18.18)
11	46	61—62	0.93 (3H, dd, J=7, 3 Hz), 2.20 (3H, s), 2.85 (1H, dd, J=14, 8 Hz), 3.00 (1H, q, J=7 Hz), 3.17 (1H, dd, J=14, 5 Hz), 4.75 (1H, d, J=15 Hz), 4.87 (1H, d, J=15 Hz), 5.11 (1H, d, J=10 Hz), 5.13 (1H, dd, J=17, 1 Hz), 5.43 (1H, s), 5.7—5.85 (1H, m), 6.65—6.85 (2H, m), 7.45—7.6 (1H, m), 7.77 (1H, s), 8.00 (1H, s)	3200, 1620, 1500, 1275, 1140	$C_{16}H_{20}F_2N_4O$	59.62 (59.64	6.25 6.39	17.38 17.37)
12	55	85—86	0.92 (3H, dd, J=7, 2 Hz), 2.78 (2H, dd, J=14, 8 Hz), 3.13 (1H, q, J=7 Hz), 3.35 (2H, br d, J=14 Hz), 4.72 (1H, d, J=15 Hz), 4.90 (1H, d, J=15 Hz), 5.12 (2H, d, J=10 Hz), 5.15 (1H, s), 5.20 (2H, d, J=16 Hz), 5.7—5.9 (2H, m), 6.65—6.85 (2H, m), 7.4—7.55 (1H, m), 7.77 (1H, s), 7.97 (1H, s)	3200, 1620, 1500, 1280, 1140	$C_{18}H_{22}F_2N_4O$	62.06 (62.06	6.36 6.37	16.08 16.04)
13	36	Oil	0.94 (3H, d, J=7 Hz), 2.26 (1H, t, J=2 Hz), 3.31 (1H, dq, J=7, 2 Hz), 3.49 (1H, dd, J=17, 2 Hz), 3.57 (1H, dd, J=17, 2 Hz), 4.7 (1H, br s), 4.79 (1H, d, J=14 Hz), 4.91 (1H, d , J=14 Hz), 6.7—6.8 (2H, m), 7.3—7.45 (1H, m), 7.76 (1H, s), 7.88 (1H, s)	3300, 1620, 1500, 1270, 1140 (neat)	$C_{15}H_{16}F_2N_4O$	307 (M^++1), 238, 82		
14	1	Oil	0.91 (3H, dd, J=7, 2 Hz), 2.25 (1H, t, J=2 Hz), 2.39 (3H, s), 3.2—3.3 (2H, m), 3.47 (1H, dd, J=17, 2 Hz), 4.84 (1H, d, J=15 Hz), 4.90 (1H, d, J=15 Hz), 6.65—6.8 (2H, m), 7.4—7.5 (1H, m), 7.77 (1H, s), 7.93 (1H, s)	3400, 1620, 1500, 1270, 1140 (neat)	$C_{16}H_{18}F_2N_4O$	321 (M^++1), 252, 96		
15	50	69—71	0.93 (3H, dd, J=7, 3 Hz), 1.77 (3H, d, J=6 Hz), 2.17 (3H, s), 2.86 (1H, dd, J=14, 7 Hz), 3.00 (1H, q, J=7 Hz), 3.16 (1H, dd, J=14, 5 Hz), 4.74 (1H, d, J=15 Hz), 4.85 (1H, d, J=15 Hz), 5.4—5.75 (2H, m), 5.95—6.15 (2H, m), 6.65—6.85 (2H, m), 7.45—7.6 (1H, m), 7.76 (1H, s), 8.01 (1H, s)	3400, 1620, 1500, 1280, 1140	$C_{19}H_{24}F_2N_4O$	62.97 (62.92	6.67 6.63	15.46 15.47)
16	37	67—70	0.91 (3H, dd, J=7, 2 Hz), 1.26 (9H, s), 2.23 (3H, s), 2.86 (1H, dd, J=14, 7 Hz), 3.01 (1H, q, J=7 Hz), 3.30 (1H, dd, J=14, 6 Hz), 4.79 (1H, d, J=15 Hz), 4.85 (1H, d, J=15 Hz), 5.23 (1H, s), 5.61 (1H, d, J=16 Hz), 5.99 (1H, ddd, J=16, 7, 6 Hz), 6.65—6.8 (2H, m), 7.4—7.55 (1H, m), 7.77 (1H, s), 7.97 (1H, s)	3300, 2950, 1640, 1500, 270, 1140	$C_{22}H_{28}F_2N_4O$	65.65 (65.53	7.01 7.12	13.92 13.90)
17	54	71—75	0.96 (3H, dd, J=7, 2 Hz), 1.5—1.8 (9H, m), 1.95—2.2 (7H, m), 2.85—3.05 (3H, m), 4.72 (1H, d, J=15 Hz), 4.85 (1H, d, J=15 Hz), 5.05—5.2 (2H, m), 5.5 (1H, br s), 6.65—6.85 (2H, m), 7.45—7.6 (1H, m), 7.77 (1H, s), 8.02 (1H, s)	3400, 2950, 1620, 1500, 1280, 1140	$C_{23}H_{32}F_2N_4O$	66.01 (66.09	7.71 7.66	13.39 13.33)

Table 3. (continued)

Compd.	Yield[a] (%)	mp (°C)[b] Optical rotation	^{1}H-NMR (in $CDCl_3$) δ	IR (cm^{-1}) (KBr)	Formula	Analysis (%) or FAB-MS Calcd (Found)		
						C	H	N
18	11	Oil	0.95 (3H, d, J=7 Hz), 3.16 (1H, q, J=7 Hz), 3.36 (1H, dd, J=14, 6 Hz), 3.59 (1H, dd, J=14, 6 Hz), 4.77 (1H, d, J=14 Hz), 4.9 (1H, br s), 4.95 (1H, d, J=14 Hz), 6.2—6.35 (1H, m), 6.56 (1H, br d, J=16 Hz), 6.65—6.8 (2H, m), 7.2—7.45 (6H, m), 7.44 (1H, s), 7.91 (1H, s)	3300, 1620, 1500, 1270, 1140 (neat)	$C_{21}H_{22}F_2N_4O$	385 (M^++1), 316,160,117		
19	32	90—91	0.96 (3H, dd, J=7, 3 Hz), 2.27 (3H, s), 2.95—3.45 (3H, m), 4.79 (1H, d, J=15 Hz), 4.89 (1H, d, J=15 Hz), 5.34 (1H, s), 6.1—6.25 (1H, m), 6.49 (1H, br d, J=16 Hz), 6.65—6.85 (2H, m), 7.2—7.4 (5H, m), 7.45—7.55 (1H, m), 7.72 (1H, s), 7.97 (1H, s)	3400, 1620, 1500, 1270, 1140	$C_{22}H_{24}F_2N_4O$	66.32 (66.55	6.07 6.07	14.06 14.11)
20	85	98—100	0.97 (3H, dd, J=7, 2 Hz), 1.34 (9H, s), 2.25 (3H, s), 3.09 (1H, q, J=7 Hz), 3.38 (1H, d, J=13 Hz), 3.76 (1H, d, J=13 Hz), 4.72 (1H, d, J=15 Hz), 4.91 (1H, d, J=15 Hz), 5.27 (1H, s), 6.6—6.8 (2H, m), 7.24 (2H, d, J=8 Hz), 7.36 (2H, d, J=8 Hz), 7.4—7.55 (1H, m), 7.75 (1H, s), 7.89 (1H, s)	3400, 2950, 1620, 1500, 1280, 1140	$C_{24}H_{30}F_2N_4O$	67.27 (67.65	7.06 7.31	13.07 12.81)
21	83	132—134	0.99 (3H, dd, J=7, 2 Hz), 2.46 (3H, s), 3.12 (1H, q, J=7 Hz), 3.81 (1H, d, J=13 Hz), 4.09 (1H, d, J=15 Hz), 4.21 (1H, d, J=13 Hz), 4.66 (1H, d, J=15 Hz), 4.91 (1H, s), 6.5—6.75 (2H, m), 7.3—7.6 (6H, m), 7.66 (1H, s), 7.8—7.9 (2H, m), 8.15—8.2 (1H, m)	3400, 1620, 1500, 1280, 1140	$C_{24}H_{24}F_2N_4O$	68.23 (68.60	5.73 5.79	13.26 13.46)
22	40	125—126	0.95 (3H, dd, J=7, 2 Hz), 2.28 (3H, s), 3.09 (1H, q, J=7 Hz), 3.39 (1H, d, J=13 Hz), 3.78 (1H, d, J=13 Hz), 4.70 (1H, d, J=15 Hz), 4.92 (1H, d, J=15 Hz), 5.16 (1H, s), 6.6—6.8 (2H, m), 7.0—7.1 (2H, m), 7.25—7.35 (2H, m), 7.4—7.5 (1H, m), 7.75 (1H, s), 7.87 (1H, s)	3200, 1620, 1510, 1220, 1140	$C_{20}H_{21}F_3N_4O$	61.53 (61.65	5.42 5.31	14.35 14.42)
23	7	109—110	0.96 (3H, d, J=7 Hz), 2.33 (3H, s), 3.14 (1H, q, J=7 Hz), 3.48 (1H, d, J=14 Hz), 4.00 (1H, d, J=14 Hz), 4.80 (1H, d, J=14 Hz), 4.96 (1H, d, J=14 Hz), 5.08 (1H, s), 6.6—6.8 (2H, m), 7.4—7.5 (3H, m), 7.61 (2H, d, J=8 Hz), 7.75 (1H, s), 7.87 (1H, s)	3300, 1620, 1500, 1330, 1140	$C_{21}H_{21}F_5N_4O$	57.27 (57.25	4.81 4.78	12.72 12.93)
24	34	103—105	0.85 (3H, dd, J=7, 1 Hz), 2.45 (3H, s), 2.49 (1H, dd, J=14, 3 Hz), 2.97 (1H, dd, J=14, 5 Hz), 3.15 (1H, q, J=7 Hz), 3.9—4.15 (4H, m), 4.78 (1H, d, J=15 Hz), 4.95—5.05 (2H, m), 5.11 (1H, s), 6.7—6.8 (2H, m), 7.35—7.5 (1H, m), 7.73 (1H, s), 7.89 (1H, s)	3300, 1620, 1500, 1280, 1210, 1140	$C_{17}H_{22}F_2N_4O_3$	55.43 (55.56	6.02 5.99	15.21 15.47)
25	24	156—158	0.98 (3H, dd, J=7, 2 Hz), 3.46 (1H, q, J=7 Hz), 4.16 (4H, br s), 4.93 (3H, br s), 6.7—6.85 (2H, m), 7.22 (4H, s), 7.4—7.55 (1H, m), 7.78 (1H, s), 7.91 (1H, s)	3200, 1620, 1500, 1275, 1140	$C_{20}H_{20}F_2N_4O$	64.85 (64.47	5.44 5.37	15.13 15.12)
26	16	170—172	0.95 (3H, dd, J=7, 1 Hz), 3.45 (1H, q, J=7 Hz), 4.10 (2H, d, J=16 Hz), 4.18 (2H, d, J=16 Hz), 4.85—5.0 (3H, m), 6.6—6.8 (2H, m), 6.85—6.95 (2H, m), 7.1—7.2 (1H, m), 7.4—7.5 (1H, m), 7.77 (1H, s), 7.88 (1H, s)	3500, 1620, 1500, 1275, 1140	$C_{20}H_{19}F_3N_4O$	61.85 (61.48	4.93 4.84	14.43 14.49)
27	49	157—159	1.05 (3H, dd, J=7, 2 Hz) 2.45—2.6 (1H m) 2.7—3.15 (4H m), 3.63 (1H, d, J=15 Hz), 3.94 (1H, d, J=15 Hz), 4.82 (1H, d, J=15 Hz), 4.92 (1H, d, J=15 Hz), 5.32 (1H, s), 6.7—6.85 (2H, m), 6.95—7.05 (1H, m), 7.05—7.2 (3H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 7.97 (1H, s)	3400, 1620, 1500, 1275, 1140	$C_{21}H_{22}F_2N_4O$	65.61 (65.79	5.77 5.82	14.57 14.52)
28	8	Oil	1.01 (3H, dd, J=7, 1 Hz), 2.5—2.7 (3H, m), 3.05—3.2 (2H, m), 3.52 (1H, d, J=14 Hz), 3.81 (1H, d, J=14 Hz), 4.84 (1H, d, J=14 Hz), 4.92 (1H, d, J=14 Hz), 5.2 (1H, br s), 6.65—6.85 (2H, m), 7.4—7.55 (1H, m), 7.77 (1H,s), 7.96 (1H, s)	3300, 1620, 1500, 1270, 1140 (neat)	$C_{18}H_{20}F_2N_6OS$	407 (M^++1)		
29	35	172—174	0.99 (3H, dd, J=7, 1 Hz), 2.55—2.7 (1H, m), 2.8—3.0 (2H, m), 3.21 (1H, q, J=7 Hz), 3.3—3.45 (1H, d, J=14 Hz), 3.95 (1H, d, J=14 Hz), 4.87 (1H, s), 5.05 (1H, br s) 6.65—6.85 (2H, m), 7.4—7.5 (1H, m), 7.77 (1H, s), 7.88 (1H, s), 8.12 (1H, s)	3600, 1620, 1500, 1140, 1100	$C_{18}H_{19}F_2N_5O_2$	57.59 (57.70	5.10 5.13	18.66 18.71)
30	30	202—204	1.01 (3H, dd, J=7, 1 Hz), 2.7—2.85 (1H, m), 2.95—3.1 (2H, m), 3.27 (1H, q, J=7 Hz), 3.35—3.5 (1H, m), 3.72 (1H, d, J=15 Hz), 4.13 (1H, d, J=15 Hz), 4.89 (1H, s), 5.05 (1H, br s), 6.65—6.85 (2H, m), 7.4—7.55 (1H, m), 7.77 (1H, s), 7.87 (1H, s), 8.41 (1H, s), 8.98 (1H, s)	3600, 1500, 1275, 1140	$C_{19}H_{20}F_2N_6O$	59.06 (58.74	5.22 5.31	21.75 21.42)
31	69	90—92	1.01 (3H, dd, J=7, 3 Hz), 1.9—2.4 (3H, m), 2.65—2.8 (1H, m), 2.8—3.0 (2H, m), 3.1—3.3 (1H, m), 4.79 (1H, d, J=15 Hz), 4.88 (1H, d, J=15 Hz), 5.50 (1H, s), 5.63 (1H, dd, J=10, 2 Hz), 5.72 (1H, ddd, J=10, 4, 2 Hz), 6.65—6.85 (2H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 8.03 (1H, s)	3300, 1620, 1500, 1275, 1140	$C_{17}H_{20}F_2N_4O$	61.07 (61.14	6.03 5.94	16.76 16.72)
32	6	Oil	1.09 (3H, dd, J=7, 5 Hz), 1.85—2.2 (2H, m), 2.2—2.3 (2H, m), 2.74 (1H, q, J=7 Hz), 2.89 (1H, br d, J=17 Hz), 3.05 (1H, br d, J=17 Hz), 4.34 (1H, d, J=14 Hz), 4.54 (1H, d, J=14 Hz), 5.6 (1H, br d, J=10 Hz), 5.72 (1H, br d, J=10 Hz), 6.65—6.9 (3H, m), 6.94 (1H, s), 7.47 (1H, s), 7.5—7.65 (1H, m)	3400, 2900, 1620, 1500, 1270, 1140 (neat)	$C_{18}H_{21}F_2N_3O$	334 (M^++1)		
33	31	115—117	0.97 (3H, dd, J=7, 3 Hz), 1.56 (3H, d, J=7 Hz), 2.1—2.5 (6H, m), 2.5—2.8 (2H, m), 2.87 (1H, q, J=7 Hz), 4.79 (1H, d, J=15 Hz), 4.88 (1H, d, J=15 Hz), 5.17 (1H, q, J=7 Hz), 5.62 (1H, s), 6.7—6.9 (2H, m), 7.5—7.6 (1H, m), 7.79 (1H, s), 8.05 (1H, s)	3300, 2920, 1620, 1510, 1280, 1145	$C_{19}H_{24}F_2N_4O$	62.97 (62.98	6.67 6.58	15.46 15.56)

Table 3. (continued)

Compd.	Yield[a] (%)	mp (°C)[b] Optical rotation	^{1}H-NMR (in $CDCl_3$) δ	IR (cm^{-1}) (KBr)	Formula	Analysis (%) or FAB-MS Calcd (Found)		
						C	H	N
34	68	75—78	0.96 (3H, dd, J=7, 3 Hz), 2.2—2.85 (8H, m), 2.91 (1H, q, J=7 Hz), 4.82 (1H, d, J=15 Hz), 4.91 (1H, d, J=15 Hz), 5.50 (1H, s), 6.26 (1H, s), 6.65—6.85 (2H, m), 7.1—7.35 (5H, m), 7.45—7.6 (1H, m), 7.79 (1H, s), 8.03 (1H, s)	3400, 2920, 1620, 1500, 1270, 1140	$C_{24}H_{26}F_2N_4O$	67.91 (67.87	6.17 6.56	13.20 12.82)
(2*R*,3*R*)-(−)-**35**	62	Oil $[\alpha]_D^{26}$ −53.3° (c=1.00, MeOH)	1.00 (3H, dd, J=7, 3 Hz), 2.2—2.5 (6H, m), 2.6—2.75 (2H, m), 2.89 (1H, q, J=7 Hz), 4.79 (1H, d, J=15 Hz), 4.88 (1H, d, J=15 Hz), 6.65—6.85 (2H, m), 7.05—7.35 10H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 8.05 (1H, s)	3400, 1620, 1500, 1270, 1140 (neat)	$C_{30}H_{30}F_2N_4O$	501 (M^++1), 432, 276		
(2*R*,3*R*)-(−)-**36**	14	Oil $[\alpha]_D^{27}$ −40.7° (c=1.00, MeOH)	0.95 (3H, dd, J=7, 3 Hz), 2.1—2.5 (6H, m), 2.6—2.8 (2H, m), 2.91 (1H, q, J=7 Hz), 4.77 (1H, d, J=15 Hz), 4.87 (1H, d, J=15 Hz), 5.01 (1H, dd, J=10, 2 Hz), 5.13 (1H, dd, J=17, 2 Hz), 5.52 (1H, br s), 5.82 (1H, d, J=11 Hz), 6.55 (1H, ddd, J=17, 11, 10 Hz), 6.65—6.85 (2H, m), 7.45—7.6 (1H, m), 7.79 (1H, s), 8.02 (1H, s)	3400, 2950, 1620, 1500, 1270, 1140 (neat)	$C_{20}H_{24}F_2N_4O$	375 (M^++1), 306, 150		
(2*R*,3*R*)-(−)-**37**	24	82—83 $[\alpha]_D^{26}$ −68.6° (c=1.00, MeOH)	0.99 (3H, dd, J=7, 3 Hz), 1.2—2.15 (6H, m), 2.5—2.75 (3H, m), 2.83 (1H, q, J=7 Hz), 4.75 (1H, d, J=15 Hz), 4.84 (1H, d, J=15 Hz), 4.94 (1H, dd, J=11, 1 Hz), 4.98 (1H, ddd, J=17, 2, 1 Hz), 5.60 (1H, s), 5.77 (1H, ddd, J=17, 11, 7 Hz), 6.7—6.85 (2H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 8.05 (1H, s)	3150, 2920, 1620, 1500, 1270, 1140	$C_{19}H_{24}F_2N_4O$	62.97 (62.99	6.67 6.62	15.46 15.63)
(2*R*,3*R*)-(−)-**38**	34	Oil $[\alpha]_D^{26}$ −70.4° (c=1.00, MeOH)	1.02 (3H, dd, J=7, 3 Hz), 1.5—1.8 (2H, m), 2.0—2.2 (2H, m), 2.3—2.45 (1H, m), 2.6—2.9 (3H, m), 3.05 (1H, d, J=12 Hz), 4.65 (1H, s), 4.70 (1H, s), 4.75 (1H, d, J=15 Hz), 4.83 (1H, d, J=15 Hz), 5.53 (1H, s), 6.7—6.85 (2H, m), 7.45—7.6 (1H, m), 7.78 (1H, s), 8.04 (1H, s)	3400, 2950, 1620, 1500, 1270, 1140 (neat)	$C_{18}H_{22}F_2N_4O$	349 (M^++1), 280, 124		
(2*R*,3*R*)-(−)-**39**	40	55—56 $[\alpha]_D^{24}$ −109.3° (c=1.00, $CHCl_3$)	0.90 (3H, dd, J=7, 2 Hz), 2.35—2.5 (2H, m), 2.7—2.9 (2H, m), 3.2—3.4 (3H, m), 4.81 (1H, d, J=15 Hz), 4.89 (2H, d, J=2 Hz), 4.90 (1H, d, J=15 Hz), 6.7—6.85 (2H, m), 7.4—7.55 (1H, m), 7.77 (1H, s), 7.95 (1H, s)	3400, 1620, 1500, 1270, 1140	$C_{17}H_{20}F_2N_4O$	61.07 (60.75	6.03 6.03	16.76 16.67)
40	60	85—86	0.96 (3H, dd, J=7, 3 Hz), 2.1—2.5 (6H, m), 2.6—2.8 (2H, m), 2.91 (1H, q, J=7 Hz), 4.64 (2H, s), 4.80 (1H, d, J=15 Hz), 4.89 (1H, d, J=15 Hz), 5.47 (1H, br s), 6.65—6.85 (2H, m), 7.45—7.55 (1H, m), 7.79 (1H, s), 8.03 (1H, s)	3200, 2940, 1620, 1500, 1280, 1140	$C_{18}H_{22}F_2N_4O$	62.06 (62.12	6.36 6.33	16.08 16.08)
(2*R*,3*R*)-(−)-**40**	54	86—87 $[\alpha]_D^{24}$ −95.0° (c=1.00, $CHCl_3$)	Identical with that of **40** ^{19}F-NMR −30.74 (dd, J=20, 9 Hz), −37.2～−37.35 (m)[c]		$C_{18}H_{22}F_2N_4O$	62.06 (62.05	6.36 6.37	16.08 16.04)
(2*S*,3*S*)-(+)-**40**	55	86—87 $[\alpha]_D^{24}$ +93.7° (c=1.00, $CHCl_3$)	Identical with that of **40**		$C_{18}H_{22}F_2N_4O$	62.06 (61.94	6.36 6.65	16.08 16.00)
41	50	Amorphous powder	1.03 (3H, dd, J=7, 5 Hz), 2.2—2.4 (8H, m), 2.77 (1H, q, J=7 Hz), 4.35 (1H, d, J=14 Hz), 4.54 (1H, d, J=14 Hz), 4.64 (2H, s), 6.7—6.8 (3H, m), 6.92 (1H, s), 7.45 (1H, s), 7.5—7.6 (1H, m)	3400, 1640, 1500, 1270, 1140	$C_{19}H_{23}F_2N_3O$	65.69 (65.67	6.67 6.68	12.10 12.09)
(2*R*,3*R*)-(−)-**41**	28	137—138 $[\alpha]_D^{24}$ −40.8° (c=1.00, $CHCl_3$)	Identical with that of **41**		$C_{19}H_{23}F_2N_3O$	65.69 (65.78	6.67 6.57	12.10 12.09)
42	13	109—111	0.80 (3H, d, J=7 Hz), 2.2—2.4 (4H, m), 2.4—2.6 (2H, m), 2.9—3.1 (2H, m), 3.55 (1H, q, J=7 Hz), 4.66 (2H, s), 4.83 (1H, d, J=15 Hz), 4.91 (1H, s), 5.52 (1H, d, J=15 Hz), 7.09 (1H, dd, J=9, 2 Hz), 7.27 (1H, d, J=2 Hz), 7.56 (1H, d, J=9 Hz), 7.74 (1H, s), 7.93 (1H, s)	3300, 2950, 1650, 1520, 1280, 1030	$C_{18}H_{22}Cl_2N_4O$	56.70 (56.91	5.82 5.83	14.69 14.64)
43	61	85—87	1.07 (3H, d, J=7 Hz), 2.0—2.25 (6H, m), 2.25—2.4 (2H, m), 2.55 (1H, q, J=7 Hz), 4.41 (1H, d, J=14 Hz), 4.61 (2H, s), 4.70 (1H, d, J=14 Hz), 5.80 (1H, s), 7.25—7.45 (4H, m), 7.84 (1H, s), 8.17 (1H, s)	3300, 2950, 1640, 1140	$C_{18}H_{23}ClN_4O$	62.33 (62.38	6.68 6.70	16.15 16.07)
46a	30	137—140	1.34 (3H, d, J=7 Hz), 3.55—3.7 (2H, m), 3.90 (1H, dd, J=16, 4 Hz), 4.19 (1H, d, J=14 Hz), 4.37 (1H, d, J=14 Hz), 4.52 (1H, s), 5.23 (1H, d, J=11 Hz), 5.28 (1H, dd, J=17, 1 Hz), 5.7—5.9 (1H, m), 5.95—6.05 (1H, m), 6.15—6.35 (2H, m), 7.83 (1H, s), 8.02 (1H, s)	3150, 1620, 1500, 1130	$C_{15}H_{17}FN_4O$	62.49 (62.53	5.94 5.99	19.43 19.43)
46b	20	143—144	1.38 (3H, d, J=7 Hz), 2.12 (1H, t, J=2 Hz), 3.69 (1H, q, J=7 Hz), 3.84 (1H, dd, J=18, 2 Hz), 4.08 (1H, dd, J=18, 2 Hz), 4.17 (1H, d, J=14 Hz), 4.38 (1H, d, J=14 Hz), 4.53 (1H, s), 6.0—6.1 (1H, m), 6.25—6.45 (2H, m), 7.82 (1H, s), 8.01 (1H, s)	3300, 1620, 1490, 1130	$C_{15}H_{15}FN_4O$	62.93 (63.00	5.28 5.27	19.57 19.40)
46c	40	170—173	1.38 (3H, d, J=7 Hz), 3.68 (1H, q, J=7 Hz), 3.79 (1H, dd, J=16, 8 Hz), 4.08 (1H, ddd, J=16, 5, 2 Hz), 4.20 (1H, d, J=14 Hz), 4.37 (1H, d, J=14 Hz), 4.50 (1H, s), 6.01 (1H, dd, J=8, 5 Hz), 6.1—6.3 (2H, m), 6.36 (1H, dd, J=10, 2 Hz), 6.62 (1H, d, J=16 Hz), 7.2—7.4 (5H, m), 7.84 (1H, s), 8.02 (1H, s)	3200, 1620, 1495, 1130	$C_{21}H_{21}FN_4O$	69.21 (69.02	5.81 5.90	15.37 15.03)

a) Yield based on epoxide. *b*) These compounds were recrystallized from AcOEt–hexane. *c*) DMSO-d_6 was used as the solvent.

Tween 80 to provide a cell concentration of 1×10^3 cells/ml. Aliquots of 300 μl of the fungal suspension were dispensed into the wells of 96-well microdilution plates containing 3 μl of twofold serial drug dilutions (final inoculumn size; 1×10^3 cells/ml) followed by incubation at 35 °C for 2 d.

Other Fungi: MICs were determined by the agar dilution method. The fungal cells were suspended in saline with 0.05% Tween 80 to provide a cell concentration of 1×10^6 cells/ml. Aliquots of 5 μl of the suspension were spotted on plates of Sabouraud dextrose agar (SDA) containing twofold serial drug dilutions (final inoculumn size; 5×10^3 cells/spot) followed by incubation at 30 °C for 2 d for *A. fumigatus* and *C. neoformans* or 7 d for *T. mentagrophytes*.

MICs were defined as the lowest drug concentrations that inhibited visible growth.

Effects of Hair on anti-*T. mentagrophytes* Activity MICs of *T. mentagrophytes* were determined by the microdilution method using SDB and saline containing 5% human hair.

Guinea Pig *Tinea corporis* Infection Model Animals: Male Hartley guinea pigs (350—500 g) were divided into groups of 10 animals.

Organisms: A microconidial suspension of *T. mentagrophytes* KD-04 (0.1 ml, 10^6 cells) was applied to membrane filters, placed on plates of brain heart infusion agar, and cultured in the presence of 17% carbon dioxide for 7 d at 30 °C. The arthrospores were suspended in saline containing 0.05% Tween 80. The resultant suspension was homogenized with a glass homogenizer and adjusted to give 10^7 arthrospores per ml by counting with a hemacytometer.

Infection (*Tinea corporis*): Skin infection was induced by the method of Sakai *et al.*[17] Hair was plucked by hand from an area (2.5×2.5 cm) on the back of guinea pigs and the skin was lightly abraded with sandpaper. Each locus was inoculated with a suspension of *T. mentagrophytes* arthrospores (0.1 ml, 10^6 conidia).

Treatment: Each guinea pig was topically treated with 0.2 ml of 1.0% solution of (−)-**40** or (−)-**41**, formulated in polyethylene glycol 400–ethanol (75 : 25; v/v). Once-a-day treatment with drug was started on day 3 or 4 postinfection and was continued for 10 d.

Evaluation: Two days after the last treatment, all animals were sacrificed, and ten skin blocks were obtained from treated sites. Each block was implanted onto a Sabouraud glucose agar plate containing 1000 μg of cycloheximide per ml, 50 μg of chloramphenicol per ml, 100 μg of gentamocin per ml, and 50 μg of 5-fluorocytosine per ml followed by incubation at 30 °C for 10 d. The skin blocks yielding fungal growth were regarded as culture-positive, and treated sites with no culture-positive skin blocks were considered to be negative.

References and Notes

1) *a*) Bossche H. V., Willemsens G., Cools W., Lauwers W. F., Jeune L. le, *Chem. Biol. Interact.*, **21**, 59—78 (1978); *b*) Bossche H. V., Willemsens G., Cools W., Cornelissen F., Lauwers W. F., Cutsem J. M. V., *Antimicrob. Agents Chemother.*, **17**, 922—928 (1980); *c*) Poulos T. L., Howord A. J., *Biochemistry*, **26**, 8165—8174 (1987).
2) *a*) Richardson K., Brammer K. W., Marriott M. S., Troke P. F., *Antimicrob. Agents Chemother.*, **27**, 832—835 (1985); *b*) Richardson K., Cooper K., Marriott M. S., Tarbit M. H., Troke P. F., Whittle P. J., *Ann. N. Y. Acad. Sci.*, **544**, 12—31 (1988); *c*) Washton H., *Diagn. Microbiol. Infec. Dis.*, **12**, 229S (1989).
3) Heeres J., Backx L. J. J., Cutsem Van J., *J. Med. Chem.*, **27**, 894—900 (1984).
4) *a*) Saji I., Tamoto K., Tanio T., Okuda T., Atsumi T., Abstracts of Papers, The 8th Symposium on Medicinal Chemistry, Osaka, Nov. 1986, pp. 9—12; *b*) Saji I., Ohashi N., Tamoto K., Tanio T., Okuda T., Atsumi T., Abstracts of Papers, The 28th Interscience Conference on Antimicrobial Agents and Chemotherapy, Los Angeles, Oct. 1988, p. 140; *c*) Saji I., Tamoto K., Tanaka Y., Miyauchi H., Fujimoto K., Ohashi N., *Bull. Chem. Soc. Jpn.*, **67**, 1427—143 (1994).
5) *a*) Maebashi K., Hiratani T., Asagi Y., Yamaguchi H., *Jpn. J. Med. Mycol.*, **31**, 343—354 (1990); *b*) Asaoka T., Kawahara R., Iwasa A., *Chemotherapy*, **38**, 753—768 (1990); *c*) *Idem, ibid.*, **38**, 769—779 (1990).
6) Similar by-products have been reported in the literature: Konosu T., Tajima Y., Takeda N., Miyaoka T., Kasahara M., Yasuda H., Oida S., *Chem. Pharm. Bull.*, **39**, 2581—2589 (1991).
7) *a*) Konosu T., Tajima Y., Takeda N., Miyaoka T., Kasahara M., Yasuda H., Oida S., *Chem. Pharm. Bull.*, **38**, 2476—2486 (1990); *b*) Konosu T., Miyaoka T., Tajima Y., Oida S., *ibid.*, **39**, 2241—2246 (1991); *c*) Tasaka A., Tamura N., Matsushita Y., Teranishi K., Hayashi R., Okonogi K., Itoh K., *ibid.*, **41**, 1035—1042 (1993).
8) *a*) Doyle M. P., Kalinin A. V., *J. Org. Chem.*, **61**, 2179—2184 (1996); *b*) Ferles M., Kocian O., Silhankova A., *Collect. Czech. Chem. Commun.*, **39**, 3532—3537 (1974); *c*) Williams C. H., Lawson J., Backwell F. R. C., *Biochem. J.*, **256**, 911—915 (1988); *d*) Neidigh K. A., Avery M. A., Williamson J. S., Bhattacharyya S., *J. Chem. Soc., Perkin Trans. 1*, **1998,** 2527—2532; *e*) Meindl W. R., Von Angerer E., Schonenberger H., Ruckdeschel G., *J. Med. Chem.*, **27**, 1111—1118 (1984).
9) Kaken Pharma Co., Ltd., Japan. Kokai Tokkyo Koho JP 06073056 (1994) [*Chem. Abstr.*, **121**, 157661*f* (1994)].
10) Pfizer Inc., U. S. Patent US 5037834 (1991) [*Chem. Abstr.*, **116**, 59210*k* (1992)].
11) *a*) Mimura M., Hayashida M., Nomiyama K., Ikegami S., Iida Y., Tamura M., Hiyama Y., Ohishi Y., *Chem. Pharm. Bull.*, **41**, 1971—1986 (1993); *b*) Kaken Pharma Co., Ltd., WO 9426734 (1994) [*Chem. Abstr.*, **123**, 55887*h* (1995)].
12) Soai K., Oyamada H., Takase M., Ookawa A., *Bull. Chem. Soc. Jpn.*, **57**, 1948—1953 (1984).
13) Arika T., Hase T., Yokoo M., *Nishinihon Hifuka* (*Nishinihon J. Dermatol.*), **52**, 545—549 (1990).
14) Tatsumi Y., Yokoo M., Arika T., Ogura H., Nagai K., Naito T., Abstracts of Papers, The 36th Interscience Conference on Antimicrobial Agents and Chemotherapy, New Orleans, LA, Sep. 1996, p. 113.
15) Arika T., Hase T., Yokoo M., *Antimicrob. Agents Chemther.*, **37**, 363—365 (1993).
16) Takahashi H., Ishii T., Tanabe K., Ikeda H., Yamamoto K., *Jpn. J. Dermatol.*, **85**, 517—524 (1975).
17) Sakai S., Kada T., Saito G., Muraoka N., Takahashi Y., *J. Sci. Res. Inst.*, **46**, 113—117 (1952).