Optically Active Antifungal Azoles. X.[1] Synthesis and Antifungal Activity of *N*-[4-(Azolyl)phenyl]- and *N*-[4-(Azolylmethyl)phenyl]-*N′*-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-azolones

Tomoyuki KITAZAKI,[b] Takashi ICHIKAWA,*[,a] Akihiro TASAKA,[b] Hiroshi HOSONO,[b] Yoshihiro MATSUSHITA,[a] Ryogo HAYASHI,[c] Kenji OKONOGI,[d] and Katsumi ITOH[a]

Discovery Research Laboratories V,[a] Pharmaceutical Discovery Research Division; Medicinal Chemistry Research Laboratories,[b] Pharmacology Research Laboratories II[c] and Research Management Department,[d] Pharmaceutical Research Division: Takeda Chemical Industries, Ltd., 17–85, Jusohonmachi 2-chome, Yodogawa-ku, Osaka 532–8686, Japan. Received July 3, 2000; accepted August 28, 2000

New optically active antifungal azoles, *N*-[4-(azolyl)phenyl]- and *N*-[4-(azolylmethyl)phenyl]-*N′*-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]azolones (1, 2, 3), were prepared in a stereocontrolled manner. Compounds 1—3 showed strong antifungal activity against *Candida albicans in vitro*. Among them, the imidazolidinones 3 showed a broad antifungal spectrum *in vitro* as well as potent *in vivo* activity against candidiasis and aspergillosis in mice. The imidazolidinones (3i, j, k) having 1*H*-1,2,3-triazol-1-yl, 2*H*-2-tetrazolyl and 1*H*-1-tetrazolyl moieties were found to exert strong protective effect against aspergillosis.

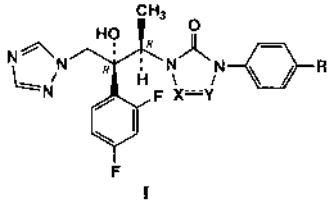
Key words optically active antifungal azole; 1,2,3-trisubstituted-2-butanol; triazolone; imidazolone; imidazolidinone; stereocontrolled synthesis; antifungal activity

Over the past two decades, the incidence of systemic fungal infections has been increasing due to an increase in the number of immunocompromised hosts. Patients undergoing organ transplants, anticancer chemotherapy or long-term treatment with antimicrobial agents and patients with AIDS are immunosuppressed and susceptible to life threating systemic fungal infections such as candidiasis, cryptococcosis and aspergillosis. Orally active antifungal azoles, fluconazole and itraconazole, which are strong inhibitors of lanosterol 14α-demethylase (cytochrome $P450_{14DM}$), have been widely used in antifungal chemotherapy. However, the development of resistance to currently available antifungal azoles in *Candida* spp. as well as clinical failures in the treatment of fungal infections have been reported in recent years.[2] Furthermore, invasive aspergillosis still remains resistant to antifungal chemotherapy, although injectable amphotericin B has been used for this purpose. Therefore, there is still the medical need for new and more effective antifungal agents with a broad antifungal spectrum.

In the course of our search for therapeutically useful antifungal azoles, we designed optically active azolone-based triazole derivatives depicted by the general formula I (Chart 1).[3f,h] We previously described the stereocontrolled synthesis of the three types of azolones; triazolones (Ia),[3f] imidazolones (Ib)[3h] and imidazolidinones (Ic)[3h] bearing a phenyl group substituted with the metabolically stable fluorine-containing groups. These azolones revealed strong growth inhibitory activity against *Candida albicans* (*C. albicans*) *in vitro* as well as potent protective effects against candidiasis in mice. From these azolones, 2-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2,2,3,3-tetrafluoropropoxy)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (TAK-187)[3g] was selected as a candidate for clinical trials. Furthermore, we recently reported that the imidazolidinones (Ic) bearing tetrafluoroethoxy- and tetrafluoropropoxyphenyl groups at the nitrogen atom exert strong *in vitro* antifungal activity against not only yeasts such as *C. albicans* and *Cryptococcus neoformans* (*C. neoformans*), but also against molds such as *Aspergillus fumigatus* (*A. fumigatus*).[3h]

As an extension of our study on the azolone-based antifungal triazoles, we planned to modify the physicochemical properties of this series of derivatives in order to improve the *in vitro* and the *in vivo* antifungal activities. For this purpose, we chose five-membered aromatic heterocycles (Az: azoles), *i.e.*, thiazole, oxazole, 1,2,3-triazole, pyrazole, imidazole, 1,2,4-triazole and tetrazole, as the substituent R in place of the fluoroalkoxy group in Ia—c and designed *N*-[4-(azolyl)-phenyl]- and *N*-[4-(azolylmethyl)phenyl]-*N′*-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]azolones (**1**—**3**) depicted in Chart 2. Compounds **1**—**3** were expected to have potent antifungal activity because of their structural similarity to I, although they possess a variety of Az structures.

In this paper, we describe the synthesis of the triazolones (**1a**—**j**), the imidazolones (**2a**—**k**) and the imidazolidinones (**3e**—**k**) bearing a phenyl group substituted with 2-methyl-4-thiazolyl (**a**), 2-methyl-4-oxazolyl (**b**), 2*H*-1,2,3-triazol-2-ylmethyl (**c**), 1*H*-1,2,3-triazol-1-ylmethyl (**d**), 1*H*-1-pyrazolyl (**e**), 1*H*-1-imidazolyl (**f**), 1*H*-1,2,4-triazol-1-yl (**g**), 2*H*-1,2,3-triazol-2-yl (**h**), 1*H*-1,2,3-triazol-1-yl (**i**), 2*H*-2-tetrazolyl (**j**)



I

a: X, Y = N, CH
(TAK-187: X = N, Y = CH, R = $OCH_2CF_2CF_2H$)
b: X = Y = CH
c: X = Y = CH_2
R = $OCH_2CF_2CF_2H$, OCF_2CF_2H

Chart 1

* To whom correspondence should be addressed. e-mail: Ichikawa_Takashi@takeda.co.jp

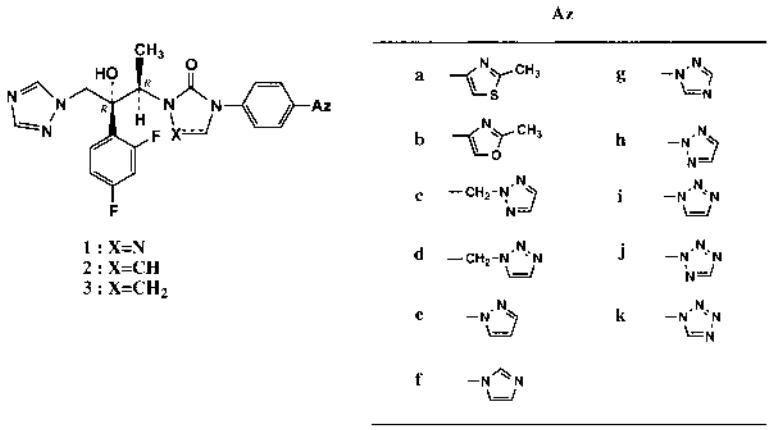


Chart 2

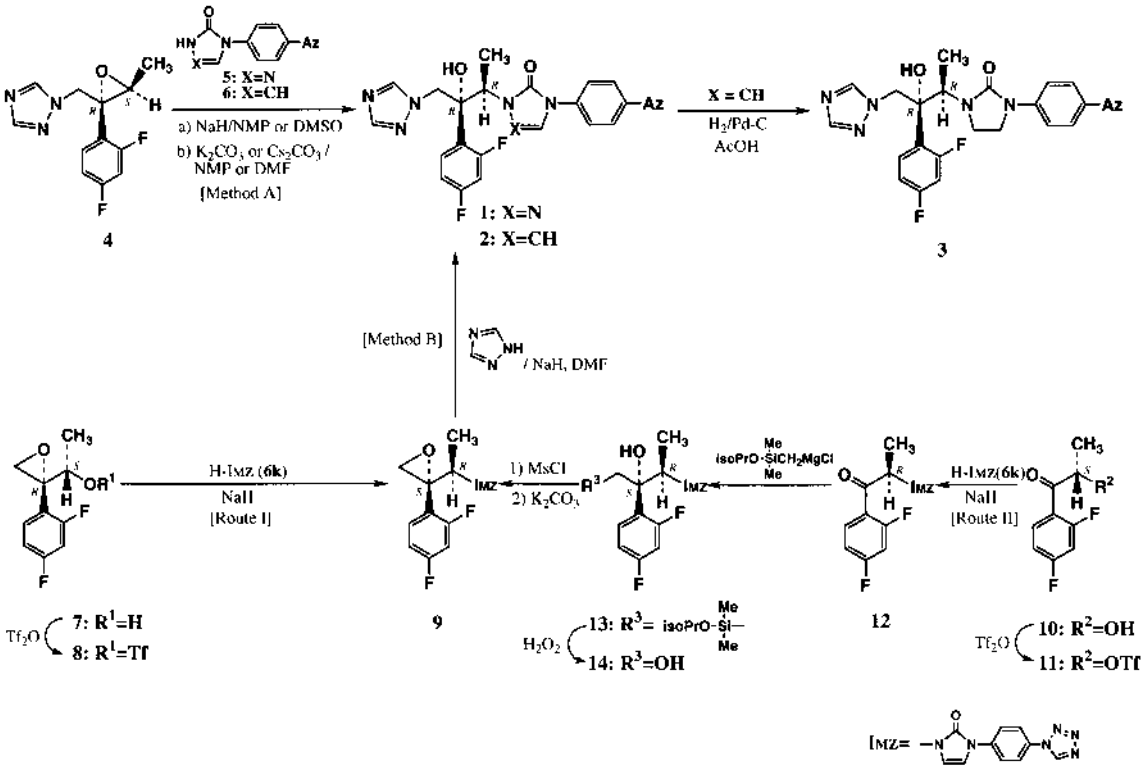


Chart 3

and 1*H*-1-tetrazolyl (**k**) groups, as well as their antifungal activities *in vitro* and *in vivo*.

Chemistry We previously established the route for the stereocontrolled synthesis of (2*R*,3*S*)-2-(2,4-difluorophenyl)-3-methyl-2-(1*H*-1,2,4-triazol-1-yl)methyloxirane (**4**),[3a] (1*S*)-1-[(2*R*)-2-(2,4-difluorophenyl)-2-oxiranyl]ethanol (**7**)[3f,g,h] and (2*S*)-2′,4′-difluoro-2-hydroxypropiophenone (**10**)[1] starting from the esters of (*R*)- or (*S*)-lactic acid. Compounds **4**, **7** and **10** were the key synthetic intermediates for the preparation of a variety of optically active antifungal azoles with the 1,2,3-trisubstituted 2-butanol skeleton.[3] We exploited these synthetic intermediates for the preparation of the newly designed triazolone (**1**), imidazolone (**2**) and imidazolidinone (**3**) derivatives shown in Chart 2. The synthetic route for the new azolones is illustrated in Chart 3.

The oxirane **4** was allowed to react with *N*-(4-substituted phenyl)-triazolones (**5a**—**j**: Table 2) and -imidazolones (**6a**—**j**: Table 3) in the presence of base [sodium hydride (NaH), potassium carbonate (K_2CO_3) or cesium carbonate (Cs_2CO_3)] in aprotic polar solvent [dimethylsulfoxide (DMSO), *N*-methyl-2-pyrrolidone (NMP) or *N*,*N*-dimethylformamide (DMF)]. The corresponding triazolones (**1a**—**j**: Table 1) and imidazolones (**2a**—**j**: Table 1) were obtained in 9—41% isolated yields [Method A]. In the case of the synthesis of the 1-[4-(1*H*-1-tetrazolyl)phenyl]-2(1*H*,3*H*)-imidazolone derivative (**2k**: Table 1), the oxiranylethanol (**7**) was used as the starting material [Route I]. Compound **7** was converted to the triflate **8** by treatment with trifluoromethansulfonic anhydride (Tf_2O) in the presence of diisopropylethylamine ($isoPr_2NEt$) and then allowed to react with the sodium salt of 1-[4-(1*H*-1-tetrazolyl)phenyl]-2(1*H*,3*H*)-imidazolone (H-IMZ, **6k**) to obtain the *SN*2 reaction product **9**.[4] Consider-

able decomposition of the triflate was observed during the course of the reaction and the isolated yield of **9** was low (7.7% based on **6k**). The oxirane **9** was reacted with 1*H*-1,2,4-triazole in the presence of NaH in DMF to give the imidazolone derivative **2k** in 63% yield [Method B]. The preparation of the precursor **9** for the synthesis of **2k** was carried out by an alternative route starting from the hydroxypropiophenone **10** [Route II]. Compound **10** was converted to the triflate **11**, and the resulting triflate **11** was then allowed to react with the sodium salt of **6k** at −20—−30 °C in a mixture of tetrahydrofuran (THF) and NMP (2 : 3, v/v) to give the propiophenone **12**. Compound **12** was reacted with (dimethylisopropoxysilyl)methylmagnesium chloride [iso-PrOSi(Me_2)CH_2MgCl][5] in THF to obtain the silylalcohol **13** in 20% isolated yield. Oxidative desilylation of **13** with hydrogen peroxide (H_2O_2)[5] in the presence of sodium bicarbonate ($NaHCO_3$) afforded the (1*R*,2*S*)-diol **14** in 79% yield, which was then converted to the corresponding mesylate by treatment with methanesulfonyl chloride (MsCl). Subsequent oxirane ring formation with K_2CO_3 afforded **9** in 62% isolated yield. Compound **9** prepared by this route was identical to that obtained by Route I.

The imidazolidinones **3e**—**k** (Table 1) were prepared from the corresponding imidazolones (**2e**—**k**) by catalytic hydrogenation on palladium on carbon (Pd–C) in acetic acid (AcOH). The structural confirmation of these triazolone, imidazolone and imidazolidinone derivatives (**1**—**3**) was done by assignment of the analytical results shown in Table 1.

The triazolones **5** and the imidazolones **6**, which were used in the above synthesis, were prepared by the methods shown in Chart 4.

4-Substituted nitrobenzenes (**17c**—**k**)[7] were synthesized from 4-chloromethylnitrobenzene (**15**) or 4-fluoronitrobenzene (**16**) by displacement reaction with the commercially available azoles (H-Az). In the case of the reaction of **15** and **16** with 1*H*-1,2,3-triazole or 1*H*-tetrazole, mixtures of the substitution position isomers (**17c**, **d**; **17h**, **i** and **17j**, **k**) at the azole nitrogen atom were obtained. Compounds **17c**, **d** and **17h**, **i** were separated into each isomer by crystallization and/or silica gel column chromatography. The substitution position on the 1,2,3-triazole moiety in these two regioisomers (**17c**, **d** and **17h**, **i**) was determined by ^{1}H-NMR measurement; the two nonequivalent protons of the 1*H*-1,2,3-triazole moiety in **17d** and **17i** appeared as two singlets and as two doublets, respectively, while the two equivalent protons in **17c** and **17h** appeared as one singlet. The nitrobenzenes (**17c**—**i**) were reduced to the corresponding anilines (**18c**—**i**) by catalytic hydrogenation or with hydrazine hydrate ($N_2H_4 \cdot H_2O$)–ferric chloride ($FeCl_3$). The mixture of 4-tetrazolylnitrobenzenes (**17j**, **k**) was submitted to the next reduction step without separation and the resulting isomeric 4-tetrazolyl anilines **18j** and **18k**[8] were separated. The anilines containing thiazole and oxazole moieties, **18a** and **18b**, were prepared by catalytic hydrogenation with Pd–C from the corresponding 4-nitrobenzenes (**17a**,[9] **b**[10]). All anilines (**18a**—**k**) were allowed to react with phenyl chloroformate (PhO-COCl) to afford the phenyl carbamates **19a**—**k**. The phenyl carbamates **19a**—**j** were converted to the corresponding 2-(4-substituted phenyl)-3(2*H*,4*H*)-1,2,4-triazolones **5a**—**j** (Table 2) by treatment with $N_2H_4 \cdot H_2O$ affording the semicarbazides **20a**—**j** followed by cyclization with formamidine acetate (HN=CH−$NH_2 \cdot$AcOH). The 1-(4-substituted phenyl)-2(1*H*,3*H*)-imidazolones (**6a**—**k**: Table 3) were prepared from the corresponding phenylcarbamates **19a**—**k** *via* two reaction steps: conversion of **19a**—**k** to the ureas **21a**—**k** by treatment with 2,2-diethoxyethylamine [$(EtO)_2CHCH_2NH_2$] and the subsequent cyclization with hydrochloric acid (HCl).

Antifungal Activities *In vitro* antifungal activities of the triazolone, imidazolone and imidazolidinone derivatives (**1**—**3**) against *C. albicans* TA are shown in Table 1. The *in vitro* assay using *C. albicans* TA was carried out by an agar-dilution method on RPMI 1640 medium under 20% CO_2.[11] The *in vitro* activity is expressed as the minimum inhibitory concentration (*MIC*, μg/ml). Compounds **1**—**3**, except **1d**, **2d** which showed moderate activity (*MIC*, 0.13—0.5 μg/ml) comparable to fluconazole, had strong growth-inhibitory activity against *C. albicans* TA in agar-dilution assay (*MIC*, $<$0.001—0.03 μg/ml). In particular, the imidazolidinone derivatives **3** mostly showed lower *MIC* values for *C. albicans* TA compared with those of the corresponding triazolone and imidazolone derivatives (**1** and **2**). The order of inhibitory potency was the imidazolidinones (**3**) $\geq$ the imidazolones (**2**) $\geq$the triazolones (**1**).

Selected compounds **3e**, **g**, **i**—**k**, which had potent activity against *C. albicans* TA, were evaluated for their *in vitro* antifungal spectrum against *C. albicans* (TIMM1756, TIMM1850), *C. neoformans* (TIMM1740, TIMM1855) and *A. fumigatus* (437, TIMM1728, IFO6344), and for *in vivo* activity against *C. albicans* and *A. fumigatus* in mice. The results are shown in Table 4. The *MIC* values for yeast type fungi such as *C. albicans* and *C. neoformans* were determined by an agar-dilution method on RPMI 1640 medium under 20% CO_2, and *MIC* values for *A. fumigatus* were measured using the same medium but under air. *C. albicans* TA infected mice and *A. fumigatus* 437 infected neutropenic mice were used for the *in vivo* assay. In the *in vivo* assay against *C. albicans* TA, the test compounds were administered orally once immediately after infection. On the other hand, in the case of the *in vivo* assay against *A. fumigatus* 437, the test compounds were administered orally, once on the day of infection and twice daily on the following 2 d. The *in vivo* activity is expressed in terms of ED_{50} (mg/kg, the dose of the test compound which allows 50% survival of the infected mice).

In the *in vitro* assay with two strains of *C. albicans*, TIMM1756 and TIMM1850, the selected imidazolidinone derivatives (**3e**, **g**, **i**—**k**) showed low *MIC* values of $\leq$0.001—0.016 μg/ml, which were lower than those of fluconazole and itraconazole. Moreover, these compounds had strong inhibitory activity against *C. neoformans* (TIMM1740, TIMM1855: *MIC*, 0.016—0.13 μg/ml) as well as against *A. fumigatus* (437, TIMM1728, IFO6344: *MIC*, 0.25—1 μg/ml). These potencies are superior to those of fluconazole and are comparable to itraconazole. In the *in vivo* assay, compounds **3g**, **i**—**k** were found to have strong protective effects against candidiasis. The activity (ED_{50}, 0.18—0.89 mg/kg) against *C. albicans* TA infection in mice was comparable with that of fluconazole (ED_{50}, 0.22—0.35 mg/kg), although **3e** showed higher ED_{50} value (2.0 mg/kg).[13] Furthermore, compounds **3e**, **g**, **i**—**k** showed potent therapeutic effects against aspergillosis (ED_{50}, 4.4—17.7 mg/kg) in neutropenic mice. In particular, compounds **3i**, **j**, **k** showed lower ED_{50}

Table 1. Physicochemical Properties and *In Vitro* Antifungal Activity of *N*-[4-(Azolyl)phenyl]- and *N*-[4-(Azolylmethyl)phenyl]-*N*′-[(1*R*,2*R*)-2-(2,4-difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]azolones (**1**—**3**)

Compd.	Yield[a] (%) [Solv. /Base][b]	mp (°C) (Solv.)[c]	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (KBr) cm^{-1}	$[\alpha]_D$ {°C} MeOH	*MIC* (μg/ml)[d] *C. albicans* TA[e]
1a	25 [DMF /K_2CO_3]	195—197 (EA-IPE)	$C_{24}H_{21}F_2N_7O_2S$ 56.57 (56.42)	4.15 (4.19)	19.24 (19.11)	1.31 (3H, d, *J*=7 Hz), 2.79 (3H, s), 4.37 (1H, d, *J*=14 Hz), 5.04 (1H, d, *J*=14 Hz), 5.11 (1H, q, *J*=7 Hz), 5.47 (1H, s), 6.77—6.90 (2H, m), 7.39 (1H, s), 7.50—7.70 (4H, m), 7.85—8.05 (4H, m)	3468, 1698, 1559, 1503, 1395, 1273	−21.0° {20} (1.0)	0.002
1b	33 [DMF-MP /K_2CO_3]	166—168 (EA-IPE)	$C_{24}H_{21}F_2N_7O_3$ 58.42 (58.11)	4.29 (4.43)	19.87 (19.67)	1.31 (3H, d, *J*=7 Hz), 2.54 (3H, s), 4.36 (1H, d, *J*=14 Hz), 5.04 (1H, d, *J*=14 Hz), 5.10 (1H, q, *J*=7 Hz), 5.47 (1H, s), 6.77—6.88 (2H, m), 7.51—7.69 (4H, m), 7.85 (1H, s), 7.86 (2H, d, *J*=8 Hz), 7.88 (1H, s), 7.96 (1H, s)	1314, 1705, 1559, 1510, 1431, 1395	−22.0° {20} (1.1)	0.004
1c	18 [NMP /NaH]	142—143 (EA-IPE)	$C_{23}H_{21}F_2N_9O_2$ 55.98 (55.87)	4.29 (4.18)	25.55 (25.42)	1.29 (3H, d, *J*=7 Hz), 4.34 (1H, d, *J*=14.4 Hz), 5.02 (1H, d, *J*=14.4 Hz), 5.08 (1H, q, *J*=7 Hz), 5.44 (1H, s), 5.66 (2H, s), 6.73—6.87 (2H, m), 7.46 (2H, d, *J*=8.6 Hz), 7.50—7.62 (1H, m), 7.58 (2H, d, *J*=8.6 Hz), 7.66 (2H, s), 7.68 (1H, s), 7.78 (1H, s), 7.94 (1H, s)	3532, 1678, 1618, 1563, 1518, 1503	−25.1° {20} (1.2)	0.03
1d	24 [DMF /K_2CO_3]	168—169 (AC-EA)	$C_{23}H_{21}F_2N_9O_2$ 55.98 (55.82)	4.29 (4.44)	25.55 (25.49)	1.30 (3H, d, *J*=7 Hz), 4.36 (1H, d, *J*=14 Hz), 5.00 (1H, d, *J*=14 Hz), 5.08 (1H, q, *J*=7 Hz), 5.41 (1H, s), 5.63 (2H, s), 6.75—6.90 (2H, m), 7.40—7.64 (6H, m), 7.69 (1H, s), 7.76 (1H, s),7.80 (1H, s), 7.94 (1H, s)	3517, 1682, 1563, 1520, 1503, 1400	−23.4° {20} (1.1)	0.5
1e	19 [NMP /NaH]	210—212 (EA-IPE)	$C_{23}H_{20}F_2N_8O_2$ 57.94 (57.47)	4.21 (4.17)	23.42 (23.45)	1.32 (3H, d, *J*=7 Hz), 4.38 (1H, d, *J*=14.4 Hz), 5.05 (1H, d, *J*=14.4 Hz), 5.11 (1H, q, *J*=7 Hz), 5.45 (1H, s), 6.52—6.54 (1H, m), 6.76—6.90 (2H, m), 7.50—7.65 (1H, m), 7.65—7.93 (7H, m), 7.96 (1H, s), 7.98 (1H, d, *J*=2.6 Hz)	3340, 1695, 1560, 1522, 1500, 1384	−24.5° {20} (0.4)	0.002
1f	21 [NMP /NaH]	Amorphous powder	$C_{23}H_{20}F_2N_8O_2 \cdot 1/2H_2O$ 56.94 (56.73)	4.34 (4.34)	22.99 (22.71)	1.32 (3H, d, *J*=7 Hz), 4.40 (1H, d, *J*=14 Hz), 5.03 (1H, d, *J*=14 Hz), 5.11 (1H, q, *J*=7 Hz), 5.42 (1H, s), 6.73—6.88 (2H, m), 7.26 (1H, s), 7.33 (1H, s), 7.51—7.65 (1H, m), 7.57 (1H, d, *J*=9 Hz), 7.71 (1H, s), 7.76 (2H, d, *J*=9 Hz), 7.86 (1H, s), 7.91 (1H, s), 7.95 (1H, s)	3400, 1700, 1612, 1554, 1521, 1498	−21.1° {20} (1.0)	0.016
1g	28 [DMSO /NaH]	182—184 (DCM -EE)	$C_{22}H_{19}F_2N_9O_2$ 55.11 (55.05)	3.99 (4.01)	26.29 (26.14)	1.32 (3H, d, *J*=7 Hz), 4.40 (1H, d, *J*=14.4 Hz), 5.03 (1H, d, *J*=14.4 Hz), 5.11 (1H, q, *J*=7 Hz), 5.41 (1H, s), 6.75—6.90 (2H, m), 7.50—7.65 (1H, m), 7.69 (1H, s), 7.79 (2H, d, *J*=9 Hz), 7.88 (2H, d, *J*=9 Hz), 7.92 (1H, s), 7.96 (1H, s), 8.14 (1H, s), 8.65 (1H, s)	1714, 1618, 1556, 1527, 1394	−23.4° {20} (1.0)	0.03
1h	34 [DMSO /NaH]	213—215 (EA-IPE)	$C_{22}H_{19}F_2N_9O_2$ 55.11 (54.97)	3.99 (3.96)	26.29 (26.29)	1.32 (3H, d, *J*=7 Hz), 4.38(1H, d, *J*=14.2 Hz), 5.04 (1H, d, *J*=14.2 Hz), 5.11 (1H, q, *J*=7 Hz), 5.42 (1H, s), 6.75—6.90 (2H, m), 7.50—7.64 (1H, m), 7.69 (1H, s), 7.74 (2H, d, *J*=9 Hz), 7.85 (2H, s), 7.86 (1H, s), 7.95 (1H, s), 8.25 (2H, d, *J*=9 Hz)	1697, 1623, 1602, 1564, 1519, 1510	−23.1° {20} (0.4)	<0.016
1i	14 [DMSO /NaH]	219—220 (DCM-IPE)	$C_{22}H_{19}F_2N_9O_2$ 55.11 (54.91)	3.99 (3.97)	26.29 (26.26)	1.32 (3H, d, *J*=7 Hz), 4.40 (1H, d, *J*=14.2 Hz), 5.03 (1H, d, *J*=14.2 Hz), 5.10 (1H, q, *J*=7 Hz), 5.38 (1H, s), 6.75—6.90 (2H, m), 7.50—7.65 (1H, m), 7.70 (1H, s), 7.82 (2H, d, *J*=9 Hz), 7.88 (1H, s), 7.90 (1H, s), 7.94 (2H, d, *J*= 9 Hz), 7.94 (1H, s), 8.05 (1H, s)	1700, 1975, 1618, 1556, 1527, 1502	−23.8° {20} (1.0)	0.03
1j	9 [NMP /NaH]	165—166 (ME-W)	$C_{21}H_{18}F_2N_{10}O_2$ 52.50 (52.36)	3.78 (3.85)	29.15 (29.02)	1.33 (3H, d, *J*=7 Hz), 4.40 (1H, d, *J*=14 Hz), 5.04 (1H, d, *J*=14 Hz), 5.11 (1H, q, *J*=7 Hz), 5.37 (1H, s), 6.77—6.88 (2H, m), 7.52—7.64 (1H, m), 7.71 (1H, s), 7.87 (2H, d, *J*= 9Hz), 7.92 (1H, s), 7.95 (1H, s), 8.34 (2H, d, *J*=9 Hz), 8.71 (1H, s)	3420, 1700, 1618, 1562, 1517, 1502	−22.2° {20} (1.0)	0.002
2a	13 [NMP /NaH]	147—149 (EA-IPE)	$C_{25}H_{22}F_2N_6O_2S$ 59.05 (59.01)	4.36 (4.46)	16.53 (16.48)	1.21 (3H, d, *J*=7 Hz), 2.78 (3H, s), 4.22 (1H, d, *J*=14 Hz), 4.98 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14 Hz), 5.60 (1H, br), 6.70—6.85 (4H, m), 7.33 (1H, s), 7.40—7.55 (1H, m), 7.69—8.00 (6H, m)	3411, 1655, 1615, 1635, 1501, 1427	−13.0° {20} (1.2)	0.004
2b	41 [NMP /NaH]	110—111 (EA-IPE)	$C_{25}H_{22}F_2N_6O_3$ 60.97 (60.69)	4.50 (4.56)	17.06 (17.05)	1.21 (3H, d, *J*=7 Hz), 2.53 (3H, s), 4.21 (1H, d, *J*=14 Hz), 4.97 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14 Hz), 5.60 (1H, br), 6.69—6.86 (4H, m), 7.42—7.55 (1H, m), 7.69 (2H, d, *J*=9 Hz), 7.73 (1H, s), 7.80 (2H, d, *J*=9 Hz), 7.84 (1H, s), 7.86 (1H, s)	3137, 1672, 1617, 1588, 1503, 1429, 1395	−15.3° {20} (1.2)	≤0.001
2c	30 [NMP /NaH]	Amorphous powder	$C_{24}H_{22}F_2N_8O_2 \cdot 1/2H_2O$ 57.48 (57.48)	4.62 (4.54)	22.34 (22.31)	1.19 (3H, d, *J*=7 Hz), 4.17 (1H, d, *J*=14.4 Hz), 4.95 (1H, q, *J*=7 Hz), 5.09 (1H, d, *J*=14.4 Hz), 5.55 (1H, br), 5.63 (2H, s), 6.63 (1H, d, *J*=3.2 Hz), 6.70—6.86 (3H, m), 7.40—7.55 (1H, m), 7.42 (2H, d, *J*=8.6 Hz), 7.64 (2H, s), 7.64 (2H, d, *J*=8.6Hz), 7.73 (1H, s), 7.85 (1H, s)	3405, 1686, 1615, 1520, 1431, 1254	−17.5° {20} (1.2)	0.016
2d	30 [NMP /NaH]	Amorphous powder	$C_{24}H_{22}F_2N_8O_2 \cdot 1/2H_2O$ 57.48 (57.71)	4.62 (4.55)	22.34 (22.22)	1.20 (3H, d, *J*=7Hz), 4.19 (1H, d, *J*=14Hz), 4.97 (1H, q, *J*=7Hz), 5.09 (1H, d, *J*=14Hz), 5.55 (1H, br), 5.59 (2H, s), 6.65 (1H, d, *J*=3.2Hz), 6.75—6.90 (3H, m), 7.35—7.55 (4H, m), 7.66—7.75 (4H, m), 7.84 (1H, s)	3382, 3125, 1684, 1615, 1520, 1501, 1431, 1254	−16.9° {20} (1.1)	0.13

Table 1. (continued)

Compd.	Yield[a] (%) [Solv. /Base][b]	mp (°C) (Solv.)[c]	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (KBr) cm^{-1}	$[\alpha]_D$ {°C} MeOH	*MIC* (μg/ml)[d] *C. albicans* TA[e]
2e	32 [NMP /NaH]	100—110 (AC-EE-IPE)	$C_{24}H_{21}F_2N_7O_2$ 60.37 (60.29)	4.43 (4.42)	20.53 (20.50)	1.21 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14.4 Hz), 4.98 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14.4 Hz), 5.56 (1H, br), 6.47—6.54 (1H, m), 6.68—6.88 (4H, m), 7.40—7.56 (1H, m), 7.70—7.85 (6H, m), 7.85 (1H, s), 7.94 (1H, d, *J*=2.4 Hz)	3320, 1660, 1615, 1510, 1430, 1390	−16.0° {20} (1.0)	0.004
2f	24 [NMP /NaH]	Amorphous powder	$C_{24}H_{21}F_2N_7O_2 \cdot 1/2H_2O$ 59.25 (59.13)	4.56 (4.42)	20.15 (19.96)	1.21 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14 Hz), 5.00 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14 Hz), 5.56 (1H, br), 6.70 (1H, d, *J*=3 Hz), 6.76—6.86 (3H, m), 7.23 (1H, s), 7.30 (1H, s), 7.42—7.54 (1H, m), 7.49 (2H, d, *J*=8 Hz), 7.75 (1H, s), 7.78 (1H, s), 7.84 (2H, d, *J*=8 Hz), 7.86 (1H, s)	3400, 1685, 1612, 1521, 1498, 1428	−15.7° {20} (1.0)	0.004
2g	22 [DMF /Cs_2CO_3]	Amorphous powder	$C_{23}H_{20}F_2N_8O_2 \cdot 1/2H_2O$ 56.67 (56.88)	4.34 (4.67)	22.99 (22.61)	1.21 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14.2 Hz), 5.01 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14.2 Hz), 5.50 (1H, br), 6.72 (1H, d, *J*=3.2 Hz), 6.73—6.90 (2H, m), 6.83 (1H, d, *J*=3.2 Hz), 7.40—7.55 (1H, m), 7.75 (1H, s), 7.78 (2H, d, *J*=9.4 Hz), 7.86 (1H, s), 7.86 (2H, d, *J*=9.4Hz), 8.13 (1H, s), 8.59 (1H, s)	3400, 3118, 1683, 1616, 1527, 1500	−15.0° {20} (1.0)	<0.016
2h	29 [NMP /NaH]	182—185 (ME-W)	$C_{23}H_{20}F_2N_8O_2$ 57.74 (57.67)	4.21 (4.20)	23.42 (23.59)	1.22 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14.4 Hz), 4.99 (1H, q, *J*=7 Hz), 5.01 (1H, d, *J*=14.4 Hz), 5.13 (1H, br), 6.70—6.88 (4H, m), 7.40—7.56 (1H, m), 7.75 (1H, s), 7.81 (2H, d, *J*=9.2 Hz), 7.84 (2H, s), 7.86 (1H, s), 8.18 (2H, d, *J*=9.2 Hz)	3328, 1664, 1614, 1519, 1430, 1384	−17.4° {20} (1.0)	<0.008
2i	38 [NMP /NaH]	178—181 (AC-EA-IPE)	$C_{23}H_{20}F_2N_8O_2$ 57.74 (57.46)	4.21 (4.25)	23.42 (23.30)	1.22 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14.4 Hz), 5.01 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14.4 Hz), 5.38 (1H, br), 6.70—6.88 (4H, m), 7.40—7.55 (1H, m), 7.76 (1H, s), 7.80—7.93 (6H, m), 8.03 (1H, s)	1691, 1656, 1619, 1527, 1502, 1430	−16.0° {20} (1.0)	<0.008
2j	17 [NMP /NaH]	135—137 (ME-W)	$C_{22}H_{19}F_2N_9O_2 \cdot 1/2H_2O$ 54.10 (53.89)	4.13 (4.18)	25.81 (25.82)	1.21 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14 Hz), 5.02 (1H, q, *J*=7 Hz), 5.12 (1H, d, *J*=14 Hz), 5.49 (1H, br), 6.75 (3H, d, *J*=3 Hz), 6.75—6.85 (2H, m), 6.85 (1H, d, *J*=3 Hz), 7.42—7.54 (1H, m), 7.76 (1H, s), 7.85 (1H, s), 7.93 (2H, d, *J*=9 Hz), 8.25 (2H, d, *J*=9 Hz), 8.68 (1H, s)	3400, 3120, 1691, 1670, 1611, 1518, 1500, 1426	−14.3° {20} (1.0)	0.002
2k	63	198—200 (EA)	$C_{22}H_{19}F_2N_9O_2$ 55.11 (54.92)	3.99 (4.04)	26.29 (26.05)	1.21 (3H, d, *J*=7 Hz), 4.22 (1H, d, *J*=14 Hz), 5.03 (1H, q, *J*=7 Hz), 5.13 (1H, d, *J*=14 Hz), 5.45 (1H, br), 6.74—6.88 (4H, m), 7.42—7.55 (1H, m), 7.77 (1H, s), 7.82 (2H, d, *J*=9 Hz), 7.86 (1H, s), 7.96 (2H, d, *J*=9 Hz), 9.06 (1H, s)	3420, 3115, 1678, 1610, 1520, 1498, 1422	−15.6° {20} (0.40)	0.008
3e	73	142—144 (EE-IPE)	$C_{24}H_{23}F_2N_7O_2$ 60.12 (60.02)	4.83 (4.95)	20.45 (20.34)	1.08 (3H, d, *J*=7 Hz), 3.68—4.10 (4H, m), 4.53 (1H, d, *J*=14.2 Hz), 4.55—4.75 (1H, m), 5.12 (1H, d, *J*=14.2 Hz), 5.45 (1H, br), 6.46—6.48 (1H, m), 6.70—6.85 (2H, m), 7.35—7.50 (1H, m), 7.60—7.75 (5H, m), 7.76 (1H, s), 7.88 (1H, s), 7.90 (1H, d, *J*=2.6 Hz)	3130, 1690, 1660, 1520, 1500, 1420	−60.5° {20} (1.0)	0.002
3f	63	Amorphous powder	$C_{24}H_{23}F_2N_7O_2 \cdot H_2O$ 59.01 (58.87)	4.95 (4.86)	20.07 (19.93)	1.08 (3H, d, *J*=7 Hz), 3.70—4.08 (4H, m), 4.52 (1H, d, *J*=14 Hz), 4.55—4.76 (1H, m), 5.11 (1H, d, *J*=14 Hz), 5.40 (1H, br), 6.73—6.84 (2H, m), 7.20 (1H, s), 7.26 (1H, s), 7.36—7.50 (1H, m), 7.39 (2H, d, *J*=9 Hz), 7.69 (2H, d, *J*=9 Hz), 7.76 (1H, s), 7.82 (1H, s), 7.87 (1H, s)	3400, 1690, 1610, 1519, 1492, 1480	−58.4° {20} (1.0)	0.004
3g	74	205—206 (EA-IPE)	$C_{23}H_{22}F_2N_8O_2$ 57.50 (57.46)	4.62 (4.47)	23.32 (23.19)	1.08 (3H, d, *J*=7.2 Hz), 3.68—4.18 (4H, m), 4.52 (1H, d, *J*=14 Hz), 4.58—4.80 (1H, m), 5.12 (1H, d, *J*=14 Hz), 5.38 (1H, br), 6.70—6.86 (2H, m), 7.35—7.50 (1H, m), 7.66 (2H, dt, *J*=9.4 Hz, 2.4 Hz), 7.75 (2H, dt, *J*=9.4 Hz, 2.4 Hz), 7.77 (1H, s), 7.87 (1H, s), 8.11 (1H, s), 8.53 (1H, s)	3390, 3106, 1677, 1614, 1523, 1484	−60.2° {20} (1.0)	≤0.001
3h	87	196—197 (EA-IPE)	$C_{23}H_{22}F_2N_8O_2$ 57.50 (57.42)	4.62 (4.54)	23.32 (23.25)	1.08 (3H, d, *J*=7.4 Hz), 3.68—4.12 (4H, m), 4.53 (1H, d, *J*=14 Hz), 4.58—4.76 (1H, m), 5.13 (1H, d, *J*=14 Hz), 5.42 (1H, br), 6.70—6.85 (2H, m), 7.36—7.50 (1H, m), 7.71 (2H, d, *J*=9 Hz), 7.76 (1H, s), 7.81 (2H, s), 7.87 (1H, s), 8.07 (2H, d, *J*=9 Hz)	3426, 1687, 1658, 1616, 1517, 1484	−61.6° {20} (1.0)	<0.008
3i	86	193—195 (ET-IPE)	$C_{23}H_{22}F_2N_8O_2$ 57.50 (57.38)	4.62 (4.59)	23.32 (23.41)	1.08 (3H, d, *J*=7 Hz), 3.70—4.14 (4H, m), 4.52 (1H, d, *J*=14.2 Hz), 4.60—4.78 (1H, m), 5.12 (1H, d, *J*=14.2 Hz), 5.38 (1H, br), 6.70—6.86 (2H, m), 7.35—7.50 (1H, m), 7.68—7.82 (4H, m), 7.77 (1H, s), 7.86 (2H, s), 7.97 (1H, s)	1697, 1664, 1618, 1527, 1502, 1427	−61.6° {20} (1.0)	0.008
3j	66	165—166 (EA-IPE)	$C_{22}H_{21}F_2N_9O_2$ 54.88 (54.62)	4.40 (4.55)	26.18 (26.19)	1.08 (3H, d, *J*=7 Hz), 3.69—3.81 (1H, m), 3.94—4.10 (3H, m), 4.52 (1H, d, *J*=14 Hz), 4.62—4.80 (1H, m), 5.13 (1H, d, *J*=14 Hz), 5.25—5.50 (1H, br), 6.72—6.84 (2H, m), 7.36—7.49 (1H, m), 7.77 (1H, s), 7.80 (2H, d, *J*=9 Hz), 7.86 (1H, s), 8.13 (2H, d, *J*=9Hz), 8.64 (1H, s)	3420, 1695, 1610, 1518, 1500, 1482	−61.1° {20} (1.0)	≤0.001

Table 1. (continued)

Compd.	Yield[a] (%) [Solv. /Base][b]	mp (°C) (Solv.)[c]	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in $CDCl_3$) δ	IR (KBr) cm^{-1}	$[\alpha]_D$ {°C} MeOH	*MIC* (μg/ml)[d] *C. albicans* TA[e]
3k	48	211—213 (ET)	$C_{22}H_{21}F_2N_9O_2$ 54.88 (54.79)	4.40 (4.42)	26.18 (26.00)	1.08 (3H, d, J=7 Hz), 3.69—4.14 (4H, m), 4.52 (1H, d, J=14 Hz), 4.65—4.80 (1H, m), 5.12 (1H, d, J=14 Hz), 5.35 (1H, br), 6.74—6.84 (2H, m), 7.36—7.49 (1H, m), 7.68 (2H, d, J=9 Hz), 7.77 (1H, s), 7.82 (2H, d, J=9 Hz), 7.87 (1H, s), 8.98 (1H, s)	3400, 3120, 1680, 1610, 1520, 1498, 1480	−60.6° {20} (1.0)	0.002
Fluconazole									0.13

a) **1a**—**j**, **2a**—**j**: yields based on the oxirane (**4**); **2k**: yields from the oxirane (**9**); **3e**—**k**: yields from the imidazolones (**2**). *b*) Reaction solvent: NMP, *N*-methyl-2-pyrrolidone; DMSO, dimethylsulfoxide; DMF, *N*,*N*-dimethylformamide. *c*) Recrystallization solvent: DCM, dichloromethane; EE, diethyl ether; EA, ethyl acetate; IPE, diisopropyl ether; ME, methanol; W, water; AC, acetone; H, hexane; ET, ethanol. *d*) Medium: RPMI 1640 containing 1.0% agar. *e*) Determined under 20% CO_2.

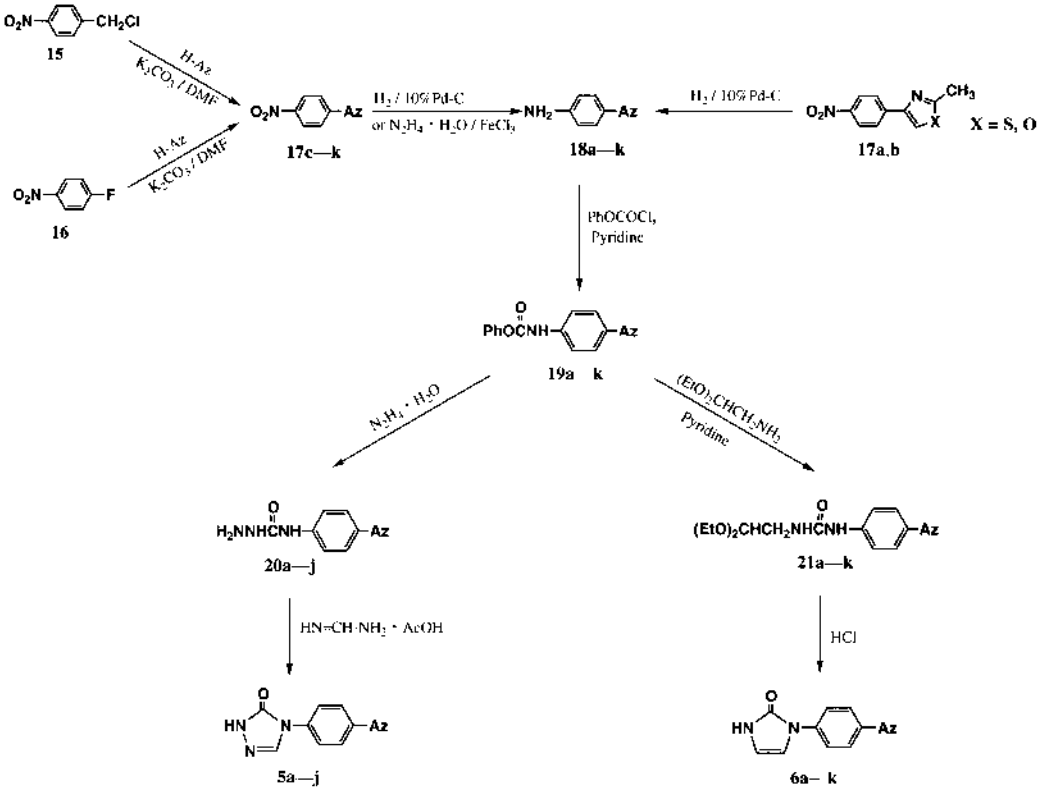


Chart 4

values (*ca*. 4 mg/kg) than that of itraconazole.

In conclusion, we found that the optically active imidazolidinone derivatives (**3**) showed potent *in vitro* antifungal activity against not only yeasts such as *C. albicans* and *C. neoformans* but also against molds such as *A. fumigatus*. It was particularly noteworthy that the imidazolidinones having 1*H*-1,2,3-triazol-1-yl, 2*H*-2-tetrazolyl and 1*H*-1-tetrazolyl moieties, **3i**, **j**, **k**, exhibited excellent therapeutic effects against candidiasis as well as aspergillosis. Further biological evaluations of this series of derivatives are in progress.

Experimental

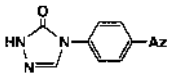
Melting points were determined using a Yanagimoto melting point apparatus and are uncorrected. IR spectra were measured with a JASCO IR-810 spectrometer. ^{1}H-NMR spectra were recorded on a Varian Gemini-200 spectrometer with tetramethylsilane as an internal standard. The following abbreviations are used: s=singlet, d=doublet, t=triplet, q=quartet, m=multiplet, br=broad. The secondary ion mass spectra (SI-MS) were measured with a Hitachi M-80A mass spectrometer. The optical rotations were recorded with a JASCO DIP-181 or DIP-370 digital polarimeter.

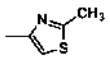
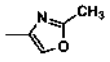
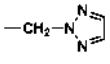
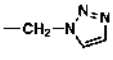
Reactions were carried out at room temperature unless otherwise noted and followed by TLC on Silica gel 60 F_{254} precoated TLC plates (E. Merck) or by HPLC using an octadecyl silica (ODS) column (A-303, 4.6 mm i.d.× 250 mm, YMC Co., Ltd.). Standard work-up procedures were as follows. The reaction mixture was partitioned between the indicated solvent and water. Organic extracts were combined and washed in the indicated order using the following aqueous solutions; water, 1 N aqueous sodium hydroxide solution (1 N NaOH), 5% aqueous $NaHCO_3$ solution (aqueous $NaHCO_3$), 1 N HCl and saturated sodium chloride (NaCl) solution (brine). Extracts were dried over anhydrous magnesium sulfate ($MgSO_4$), filtered and evaporated *in vacuo*.

Chromatographic separations were carried out on Silica gel 60 (0.063—0.200 mm, E. Merck) using the indicated eluents.

2-(4-Nitrobenzyl)-2*H*-1,2,3-triazole (17c) and 1-(4-Nitrobenzyl)-1*H*-1,2,3-triazole (17d) A mixture of **15** (24.6 g, 143 mmol), 1*H*-1,2,3-triazole (10.9 g, 157 mmol), K_2CO_3 (65 g, 471 mmol) and DMF (150 ml) was stirred for 3 h. The whole was poured into ice-water and worked up (AcOEt; water). The residue was crystallized from ethyl acetate (AcOEt)–diisopropyl ether

Table 2. 4-(4-Substituted phenyl)-3(2*H*, 4*H*)-1,2,4-triazolones (**5**)



5	Az	Yield (%)	mp (°C) (Solv.)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in DMSO-d_6) δ {IR (KBr) cm^{-1}}
5a		54	282—284 (ME-EA)	$C_{12}H_{10}N_4OS$	55.80 (55.63	3.90 4.01	21.69 21.39)	2.72 (3H, s), 7.77 (2H, d, J=9 Hz), 7.97 (1H, s), 8.05 (2H, d, J=9 Hz), 8.42 (1H, s), 11.99 (1H, br) {3102, 1705, 1568, 1535, 1508, 1227}
5b		70	280—283 (DMF-W)	$C_{12}H_{10}N_4O_2$	59.50 (59.08	4.16 4.23	23.13 22.71)	2.48 (3H, s), 7.75 (2H, d, J=8.4Hz), 7.87 (2H, d, J=8.4Hz), 8.41 (1H, s), 5.51 (1H, s), 12.0 (1H, br) {—[b]}
5c		49	201—205 (ME)	$C_{11}H_{10}N_6O$	54.54 (54.44	4.16 4.23	34.69 34.96)	5.69 (2H, s), 7.38 (2H, d, J=8.4 Hz), 7.68 (2H, d, J=8.4 Hz), 7.81 (1H, s), 8.34 (1H, s), 11.98 (1H, br) {3090, 1719, 1572, 1522, 1435, 1221}
5d		76	250—252 (ME)	$C_{11}H_{10}N_6O$	54.54 (54.47	4.16 4.36	34.69 34.47)	5.67 (2H, s), 7.44 (2H, d, J=8.8 Hz), 7.70 (2H, d, J=8.8 Hz), 7.75 (1H, s), 8.21 (1H, s), 8.36 (1H, s), 11.99 (1H, br) {3137, 1717, 1559, 1518, 1439, 1385}
5e		64	269—270 (DMF)	$C_{11}H_9N_5O$	58.15 (58.01	3.99 4.10	30.82 30.74)	6.58 (1H, t, J=2 Hz), 7.78 (1H, d, J=1.6 Hz), 7.84 (2H, d, J=9 Hz), 7.98 (2H, d, J=9 Hz), 8.44 (1H, s), 8.60 (1H, d, J=2 Hz) {3144, 1717, 1559, 1532, 1397, 1339}
5f		46	284—286 (DMF-W)	$C_{11}H_9N_5O$	58.15 (57.97	3.99 3.99	30.82 30.77)	7.13 (1H, s), 7.79 (1H, s), 7.80 (2H, d, J=9 Hz), 7.87 (2H, d, J=9 Hz), 8.31 (1H, s), 8.46 (1H, s), 12.1 (1H, br) {3112, 1709, 1530, 1435, 1350, 1316}
5g		40	>300 (DMF-W)	$C_{10}H_8N_6O$	52.63 (52.66	3.53 3.58	36.83 36.79)	7.91 (2H, d, J=9.4 Hz), 8.00 (2H, d, J=9.4 Hz), 8.25 (1H, s), 8.46 (1H, s), 9.33 (1H, s) {3123, 1717, 1561, 1532, 1426, 1279}
5h		54	281—283 (DMF-W)	$C_{10}H_8N_6O$	52.63 (52.34	3.53 3.69	36.83 36.55)	7.92 (2H, d, J=9 Hz), 8.14 (2H, d, J=9 Hz), 8.14 (2H, s), 8.46 (1H, s) {3185, 1732, 1559, 1520, 1416, 1373}
5i		58	>300 (EA)	$C_{10}H_8N_6O$	52.63 (52.16	3.53 3.72	36.83 36.39)	7.96 (2H, d, J=9 Hz), 7.98 (1H, s), 8.06 (2H, d, J=9 Hz), 8.49 (1H, s), 8.87 (1H, d, J=1 Hz) {3115, 1694, 1603, 1559, 1522, 1362}
5j		63	245—248 (dec.) (DMF-W)	$C_9H_7N_7O$	SIMS (MH^+): 230			8.06 (2H, d, J=9 Hz), 8.25 (2H, d, J=9 Hz), 8.55 (1H, s), 9.28 (1H, s), 12.2 (1H, br) {—}

a) Recrystallization solvent: DMF, *N*,*N*-dimethylformamide; W, water; EA, ethyl acetate; ME, methanol. *b*) Not measured.

(isoPr$_2$O) to give **17d** (9.65 g, 33.2%) as pale yellow needles. The mother liquor was concentrated *in vacuo* and the residue was purified by silica gel column chromatography (hexane–AcOEt, 2 : 1→AcOEt, v/v). The compound in the first eluted fraction was crystallized from AcOEt–isoPr$_2$O to give **17c** (10.1 g, 37%). The compound in the second eluted fraction was crystallized from AcOEt–isoPr$_2$O to give an additional amount of **17d** (4.9 g, 16.8%). **17c**[7c]: mp 112—114 °C. ^{1}H-NMR ($CDCl_3$) δ: 5.73 (2H, s), 7.43 (2H, d, J=8.8 Hz), 7.69 (2H, s), 8.22 (2H, d, J=8.8 Hz). **17d**[7c]: ^{1}H-NMR ($CDCl_3$) δ: 5.70 (2H, s), 7.40 (2H, d, J=8.6 Hz), 7.57 (1H, s), 7.79 (1H, s), 8.24 (2H, d, J=8.6 Hz).

General Procedure for the Preparation of *N*-(Nitrophenyl)azoles (17e—k) A mixture of **16** (1 eq), H-Az (1—1.5 eq), K_2CO_3 (1—2 eq) in DMF was stirred at 70—80 °C for 3—10 h. The whole was poured into ice-water. The precipitate was collected by filtration and purified by silica gel column chromatography or by recrystallization.

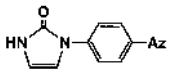
Compounds **17h** and **17i**, which were the substitution position isomers, were separated by silica gel column chromatography [dichloromethane (CH_2Cl_2)→CH_2Cl_2–acetone, 8 : 1, v/v] and crystallized from CH_2Cl_2–isoPr$_2$O. The mixture of **17j** and **17k** was used for the next step without separation.

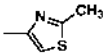
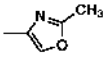
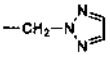
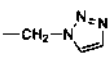
17e[7a,b] (96%): mp 172—173 °C (recrystallized from DMF–water). *Anal*. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 56.97; H, 3.57; N, 22.17. ^{1}H-NMR ($CDCl_3$) δ: 6.57 (1H, t, J=2 Hz), 7.81 (1H, d, J=2 Hz), 7.90 (2H, dt, J=9.2 Hz, 2 Hz), 8.05 (1H, d, J=2 Hz), 8.36 (2H, dt, J=9.2 Hz, 2 Hz). **17f**[7a,b] (98%): mp 204—206 °C (recrystallized from DMF–water). *Anal*. Calcd for $C_9H_7N_3O_2$: C, 57.14; H, 3.73; N, 22.21. Found: C, 57.18; H, 3.69; N, 22.26. ^{1}H-NMR ($CDCl_3$) δ: 7.29 (1H, s), 7.39 (1H, s), 7.60 (2H, d, J=9.1 Hz), 8.00 (1H, s), 8.40 (2H, d, J=9.1 Hz). **17g**[7a—c] (83%): mp 198—199 °C (recrystallized from AcOEt–isoPr$_2$O). *Anal*. Calcd for $C_8H_6F_4N_2O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.73; H, 3.19; N, 29.31. ^{1}H-NMR ($CDCl_3$) δ: 7.93 (2H, dt, J=9.4 Hz, 2.4 Hz), 8.05 (1H, s), 8.18 (1H, s), 8.43 (2H, dt, J=9.4 Hz, 2.4 Hz). **17h**[14] (22%): mp 183—184 °C (recrystallized from CH_2Cl_2–isoPr$_2$O). *Anal*. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.76; H, 3.19; N, 29.51. ^{1}H-NMR ($CDCl_3$) δ: 7.90 (2H, s), 8.28 (2H, dt, J=9.4 Hz, 2.4 Hz), 8.38 (2H, dt, J=9.4 Hz, 2.4 Hz). **17i**[15](50%): mp 205—206 °C (recrystallized from CH_2Cl_2–isoPr$_2$O). *Anal*. Calcd for $C_8H_6N_4O_2$: C, 50.53; H, 3.18; N, 29.46. Found: C, 50.30; H, 2.94; N, 29.41. ^{1}H-NMR ($CDCl_3$) δ: 7.92 (1H, d, J=1.4 Hz), 8.00 (2H, dt, J=9 Hz, 2.4 Hz), 8.13 (1H, d, J=1.4 Hz), 8.44 (2H, dt, J=9 Hz, 2.4 Hz).

1-(4-Aminophenyl)-1*H*-1,2,4-triazole (18g) A solution of **17g** (20 g) in ethanol (EtOH, 760 ml) was hydrogenated over 10% Pd–C (50% wet, 3.0 g) under atmospheric pressure. After absorption of hydrogen stopped, the catalyst was removed by filtration and the filtrate was concentrated *in vacuo*. The residue was crystallized from AcOEt to give **18g**[16a,b] (15.9 g, 94%) as a colorless crystalline powder. mp 138—139 °C. ^{1}H-NMR ($CDCl_3$) δ: 3.85 (2H, bs), 6.76 (2H, dt, J=8.8 Hz, 2.2 Hz), 7.40 (2H, dt, J=8.8 Hz, 2.2 Hz), 8.05 (1H, s), 8.39 (1H, s). *Anal*. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.12; H, 4.97; N, 34.93.

The anilines (**18a**—**f**, **h**, **i**) were prepared from the corresponding 4-substituted nitrobenzenes (**17a**—**f**, **h**, **i**) by the same method as described above. **18a**[17] (86%): ^{1}H-NMR ($CDCl_3$) δ: 2.75 (3H, s), 3.74 (2H, br s), 6.71 (2H, dt, J=8.4 Hz, 2.6 Hz), 7.10 (1H, s), 7.68 (2H, dt, J=8.4 Hz, 2.6 Hz). **18b**[18] (quant.): ^{1}H-NMR ($CDCl_3$) δ: 2.50 (3H, s), 5.48 (2H, br s), 6.71 (2H, dt, J=8.6 Hz, 2.4 Hz), 7.49 (2H, dt, J=8.6 Hz, 2.4 Hz), 7.67 (1H, s). **18c** (96%): ^{1}H-NMR ($CDCl_3$) δ: 3.70 (2H, br s), 5.48 (2H, s), 6.64 (2H, d, J=8.4 Hz), 7.16 (2H, d, J=8.4 Hz), 7.60 (2H, s). 18d (98%): ^{1}H-NMR ($CDCl_3$) δ: 3.77 (2H, br s), 5.43 (2H, s), 6.66 (2H, d, J=7.4 Hz), 7.10 (2H, d, J=7.4 Hz), 7.42 (1H, s), 7.68(1H,s). **18e**[16a,b] (97%): ^{1}H-NMR ($CDCl_3$) δ: 3.74 (2H, br s), 6.38—6.45 (1H, m), 6.75 (2H, dt, J=7.4 Hz, 1.4 Hz), 7.45 (2H, dt, J=7.4 Hz, 1.4 Hz), 7.67 (1H, s), 7.75—7.80 (1H, m). **18f**[16a,b] (73%): mp 145—146 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 5.29 (2H, s), 6.65 (2H, d, J=8.8 Hz), 7.03 (1H, s), 7.23 (2H, d, J=8.8 Hz), 7.49 (1H, s), 7.97 (1H, s). **18h**[16a] (quant.): mp 50—51 °C (recrystallized from AcOEt–hexane). ^{1}H-NMR ($CDCl_3$) δ: 3.80 (2H, br s), 6.76 (2H, dt, J=7.1 Hz, 1.6

Table 3. 1-(4-Substituted phenyl)-2(2*H*, 3*H*)-imidazolones (**6**)



6	Az	Yield (%)	mp (°C) (Solv.)[a]	Formula	Analysis (%) Calcd (Found) C	H	N	^{1}H-NMR (in DMSO-d_6) δ {IR (KBr) cm^{-1}}
6a		60	206—208 (EA-ME)	$C_{13}H_{11}N_3OS \cdot 1/2H_2O$	58.63 (59.12	4.54 4.95	15.78 15.38)	2.73 (3H, s), 6.60 (1H, t, *J*=2.6 Hz), 7.00 (1H, t, *J*=2.6 Hz), 7.80 (2H, d, *J*=8.8 Hz), 7.89 (1H, s), 7.98 (2H, d, *J*=8.8 Hz), 10.34 (1H, br) {3146, 1674, 1534, 1505, 1429, 1310}
6b		73	216—218 (ME-W)	$C_{13}H_{11}N_3O_2$	64.72 (64.56	4.60 4.84	17.40 17.28)	2.47 (3H, s), 6.60 (1H, t, *J*=2.8 Hz), 7.00 (1H, t, *J*=2.8 Hz), 7.79 (4H, s), 8.45 (1H, s), 10.30 (1H, br) {—[b]}
6c		81	190—191 (ME)	$C_{12}H_{11}N_5O$	59.74 (59.65	4.60 4.63	29.03 29.00)	5.66 (2H, s), 6.55—6.64 (1H, m), 6.90—7.00 (1H, m), 7.33 (2H, d, *J*=8.6 Hz), 7.70 (2H, d, *J*=8.6 Hz), 7.81 (2H, s), 10.32 (1H, br) {3164, 1686, 1520, 1433, 1410, 1339}
6d		82	213—215 (ME)	$C_{12}H_{11}N_5O$	59.74 (59.64	4.60 4.74	29.03 28.93)	5.63 (2H, s), 6.57—6.60 (1H, m), 6.93—6.96 (1H, m), 7.37 (2H, d, *J*=8.6 Hz), 7.73 (2H, d, *J*=8.6 Hz), 7.75 (1H, s), 8.20 (1H, s), 10.33 (1H, br) {3129, 1699, 1520, 1429, 1314, 1219}
6e		98	239—240 (ME-W)	$C_{12}H_{10}N_4O$	63.71 (63.45	4.46 4.51	24.76 24.77)	6.55 (1H, t, *J*=2.5 Hz), 6.62 (1H, t, *J*=2.5 Hz), 7.02 (1H, t, *J*=2 Hz), 7.75 (1H, d, *J*=1.6 Hz), 7.88 (4H, br s), 8.50 (1H, d, *J*=2 Hz) {3142, 1678, 1526, 1429, 1393, 1323}
6f		57	210—211 (ME-W)	$C_{12}H_{10}N_4O$	SIMS (MH^+): 227			6.65 (1H, t, *J*=3 Hz), 7.09 (1H, t, *J*=3 Hz), 7.54 (1H, s), 7.80 (2H, d, *J*=9 Hz), 7.97 (2H, d, *J*=9 Hz), 8.06 (1H, s), 9.07 (1H, s), 10.5 (1H, br) {3094, 1709, 1686, 1526, 1424, 1310}
6g		92	294—296 (ME-W)	$C_{11}H_9N_5O$	58.15 (57.91	3.99 3.85	30.83 30.56)	6.65 (1H, t, *J*=2.8 Hz), 7.08 (1H, dd, *J*=2.8 Hz, 2 Hz), 7.91 (2H, d, *J*=9.6 Hz), 7.97 (2H, d, *J*=9.6 Hz), 8.25 (1H, s), 9.33 (1H, s), 10.42 (1H, br) {3142, 1682, 1518, 1429, 1304, 1238}
6h		85	>300 (ME-W)	$C_{11}H_9N_5O$	58.15 (57.80	3.99 4.01	30.83 30.68)	6.64 (1H, t, *J*=2.8 Hz), 7.05 (1H, t, *J*=2.8 Hz), 7.95 (2H, d, *J*=9.4 Hz), 8.07 (2H, d, *J*=9.4 Hz), 8.11 (2H, s) {3135, 1703, 1520, 1439, 1414, 1325}
6i		86	255—257 (dec.) (ME-W)	$C_{11}H_9N_5O$	58.15 (58.01	3.99 3.85	30.83 30.82)	6.65 (1H, t, *J*=2.8 Hz), 7.09 (1H, t, *J*=2.8 Hz), 7.90—8.03 (5H, m), 8.83 (1H, d, *J*=1 Hz) {3140, 1690, 1524, 1310, 1231, 1038}
6j		62	235—240 (dec.) (DMF)	$C_{10}H_8N_6O$	52.63 (52.34	3.53 3.57	36.83 36.65)	6.69 (1H, d, *J*=3 Hz), 7.13 (1H, d, *J*=3 Hz), 8.09 (2H, d, *J*=9 Hz), 8.17 (2H, d, *J*=9 Hz), 9.25 (1H, s), 10.5 (1H, br) {3144, 1705, 1607, 1516, 1422, 1310}
6k		79	251—255 (dec.) (DMF)	$C_{10}H_8N_6O$	52.63 (52.33	3.53 3.70	36.83 36.46)	6.67 (1H, s), 7.12 (1H, s), 7.96 (2H, d, *J*=9 Hz), 8.06 (2H, d, *J*=9 Hz), 10.1 (1H, s), 10.5 (1H, br) {3283, 1713, 1694, 2 1524, 1395, 1221}

a) Recrystallization solvent: DMF, *N*,*N*-dimethylformamide; W, water; EA, ethyl acetate; ME, methanol. *b*) Not measured.

Table 4. Antifungal Activity of Compound **3**

Compd.	*MIC* (μg/ml)[a] *C. albicans*[b] TIMM1756	*C. albicans*[b] TIMM1850	*C. neoformans*[b] TIMM1740	*C. neoformans*[b] TIMM1855	*A. fumigatus*[c] 437	*A. fumigatus*[c] TIMM1728	*A. fumigatus*[c] IFO6344	ED_{50} (mg/kg) *p.o.*[d] *C. albicans* TA	ED_{50} (mg/kg) *p.o.*[d] *A. fumigatus* 437
3e	0.004	0.004	0.016	0.06	0.5	0.25	0.25	2.0	17.7
3g	0.002	≤0.001	0.06	0.13	1	0.5	1	0.32	8.84
3i	0.016	0.016	0.13	0.13	0.5	0.5	0.5	0.71	4.42
3j	0.004	0.002	0.03	0.06	0.5	0.25	0.25	0.18	4.8
3k	0.008	0.004	0.03	0.06	1	0.5	0.5	0.89	4.4
Fluconazole	0.5	0.25	4	8	>64	>64	>64	0.22—0.35[e]	179[e]
Itraconazole	0.03	0.016	0.06	0.13	0.5	0.5	0.25	5.2[f]	19[f]

a) Medium: RPMI 1640 containing 1.0% agar. *b*) Determined under 20% CO_2. *c*) Determined under air. *d*) Administered in the form of a 0.5% carboxymethylcellulose (CMC) suspension except fluconazole and itraconazole. *e*) Administered as an aquenous solution. *f*) Administered as a 2-hydroxypropyl β-cyclodextrin solution.[12]

Hz), 7.75 (2H, s), 7.84 (2H, dt, *J*=7.1 Hz, 1.6 Hz). *Anal*. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 59.77; H, 4.95; N, 34.87. **18i**[16a] (96%): mp 121—122 °C (recrystallized from AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 3.93 (2H, br s), 6.77 (2H, dt, *J*=9 Hz, 2.2 Hz), 7.48 (2H, dt, *J*=9 Hz, 2.2 Hz), 7.81 (1H, s), 7.87 (1H, s). *Anal*. Calcd for $C_8H_8N_4$: C, 59.99; H, 5.03; N, 34.98. Found: C, 60.02; H, 5.08; N, 34.66.

2-(4-Aminophenyl)-2*H*-tetrazole (18j) and 1-(4-Aminophenyl)-1*H*-tetrazole (18k) A mixture of **16** (50.4 g, 357 mmol), 1*H*-tetrazole (25 g, 357 mmol), K_2CO_3 (50 g, 357 mmol), and DMF (350 ml) was stirred at 70—75 °C for 10 h. The mixture was cooled and poured into water (2.5 l). The resulting precipitate was collected by filtration and washed with water (500 ml) to give a mixture of **17j** and **17k** as a pale yellow wet solid. $N_2H_4 \cdot H_2O$

Table 5. Phenyl(4-Substituted phenyl)carbamates (**19**), 4-(4-Substituted phenyl)semicarbazides (**20**) and *N*-(2,2-Diethoxyethyl)-*N'*-(4-substituted phenyl)ureas (**21**)

Compd.	Yield (%)	mp (°C) (Solv.)[a]	Analysis (%) Calcd (Found)	^{1}H-NMR (in DMSO-d_6) δ
			C H N	
19a	94	—[b]	$C_{17}H_{14}N_2O_2S$ 65.79 4.55 9.03 (—)	2.77 (3H, s), 7.02 (1H, br), 7.18—7.26 (4H, m), 7.28—7.53 (4H, m), 7.68 (2H, d, J=8.4 Hz) (in $CDCl_3$)
19b	56	181—183 (EA-H)	$C_{17}H_{14}N_2O_3$ 69.38 4.79 9.52 (—)	2.51 (3H, s), 7.04 (1H, br), 7.18—7.28 (3H, m), 7.37—7.51 (4H, m), 7.69 (2H, d, J=8.6 Hz), 7.78 (1H, s) (in $CDCl_3$)
19c	95	161—162 (EA-IPE)	$C_{16}H_{14}N_4O_2$ 65.30 4.79 19.04 (—)	5.58 (2H, s), 6.98 (1H, br), 7.13—7.50 (9H, m), 7.63 (2H, s) (in $CDCl_3$)
19d	91	—	$C_{16}H_{14}N_4O_2$ 65.30 4.79 19.04 (—-)	5.54 (2H, s), 7.10 (1H, br), 7.15—7.55 (10H, m), 7.72 (1H, s) (in $CDCl_3$)
19e	95	174—176 (EA-IPE)	$C_{16}H_{13}N_3O_2$ 68.81 4.69 15.04 (69.05 4.40 15.18)	6.53 (1H, t, J=2.4 Hz), 7.23—7.49 (5H, m), 7.63 (2H, d, J=9 Hz), 7.72 (1H, d J=2.4 Hz),7.80 (2H, d, J=9 Hz), 8.42 (1H, d, J=2.4 Hz), 10.38 (1H, br)
19f	98	158—160 (EA)	$C_{16}H_{13}N_3O_2$ 68.81 4.69 15.04 (68.62 4.83 14.94)	7.18—7.32 (4H, m), 7.42—7.46 (2H, m), 7.65 (4H, s), 7.74 (1H, s), 8.33 (1H, s), 10.5 (1H, s)
19g	96	157—160 (EA-IPE)	$C_{15}H_{12}N_4O_2$ 64.28 4.31 19.98 (64.24 4.31 19.95)	7.24—7.49 (5H, m), 7.68 (2H, d, J=9 Hz), 7.82 (2H, d, J=9 Hz), 8.22 (1H, s), 9.22 (1H, s), 10.48 (1H, br)
19h	90	143—144 (DCM-IPE)	$C_{15}H_{12}N_4O_2$ 64.28 4.31 19.98 (64.09 4.29 19.99)	7.22—7.49 (5H, m), 7.70 (2H, d, J=9 Hz), 8.00 (2H, d, J=9 Hz), 8.09 (2H, s), 10.49 (1H, br)
19i	97	195—200 (EA)	$C_{15}H_{12}N_4O_2$ 64.28 4.31 19.98 (64.38 4.32 20.02)	7.24—7.49 (5H, m), 7.72 (2H, d, J=9 Hz), 7.88 (2H, d, J=9 Hz), 7.96 (1H, s), 8.76 (1H, s), 10.53 (1H, br)
19j	89	164—165 (EA-IPE)	$C_{14}H_{11}N_5O_2$ 59.78 3.94 24.90 (59.64 4.03 24.84)	7.26—7.33 (3H, m), 7.43—7.51 (2H, m), 7.81 (2H, d, J=9 Hz), 8.10 (2H, d, J=9 Hz), 9.21 (1H, s), 10.7 (1H, s)
19k	88	186—189 (EA)	$C_{14}H_{11}N_5O_2$ 59.78 3.94 24.90 (59.56 3.99 24.89)	7.25—7.34 (3H, m), 7.42—7.50 (2H, m), 7.77 (2H, d, J=9 Hz), 7.89 (2H, d, J=9 Hz), 10.0 (1H, s), 10.6 (1H, s)
20a	84	—	$C_{11}H_{12}N_4O_S$ 53.21 4.87 22.56 (—)	2.70 (3H, s), 4.35 (2H, br), 7.42 (1H, br), 7.69 (2H, d, J=8.4 Hz), 7.72 (1H, s), 7.80 (2H, d, J= 8.4 Hz), 8.71(1H, br)
20b	92	251—253 (ET-W)	$C_{11}H_{12}N_4O_2$ 56.89 5.21 24.12 (—)	2.45 (3H, s), 4.38 (2H, br), 7.47 (1H, br), 7.59 (4H, s), 8.32 (1H, s), 8.72 (1H, br s)
20c	98	243—244 (ET)	$C_{10}H_{12}N_6O$ 51.72 5.21 36.19 (—)	4.33 (2H, br), 5.54 (2H, s), 7.16 (2H, d, J=8.4 Hz), 7.40 (1H, br), 7.49 (2H, d, J=8.4 Hz), 7.78 (2H, s), 8.65 (1H, br s)
20d	97	—	$C_{10}H_{12}N_6O$ 51.72 5.21 36.19 (—)	4.33 (2H, br), 5.51 (2H, s), 7.20 (2H, d, J=8.6 Hz), 7.42 (1H, br), 7.51 (2H, d, J=8.6 Hz), 7.71 (1H, d, J=1 Hz), 8.12 (1H, d, J=1 Hz), 8.67 (1H, br s)
20e	95	259—261 (ET)	$C_{10}H_{11}N_5O$ 55.29 5.10 32.24 (55.26 4.88 32.31)	4.37 (2H, br), 6.49 (1H, t, J=2.4 Hz), 7.47 (1H, br), 7.61—7.71(5H,m), 8.36 (1H, d, J= 2.4 Hz), 8.77 (1H, br)
20f	78	202—203 (ET-W)	$C_{10}H_{11}N_5O$ 55.29 5.10 32.24 (55.05 5.08 32.23)	4.41 (2H, br), 7.09 (1H, s), 7.50 (2H, d, J=9 Hz), 7.52 (1H, s), 7.65 (1H, s), 7.69 (2H, d, J= 9 Hz), 8.15 (1H, s), 8.85 (1H, s)
20g	95	228—232 (ET)	$C_9H_{10}N_6O$ 49.54 4.62 38.51 (49.72 4.49 38.41)	4.42 (2H, br), 7.54 (1H, br), 7.72 (4H, br), 8.18 (1H, s), 8.89 (1H, s), 9.16 (1H, s)
20h	96	275—277 (ET)	$C_9H_{10}N_6O$ 49.54 4.62 38.51 (49.67 4.48 38.47)	4.39 (2H, br), 7.53 (1H, br), 7.73 (2H, d, J=9 Hz), 7.88 (2H, d, J=9 Hz), 8.04 (2H, s), 8.88 (1H, br)
20i	98	225—234 (ET)	$C_9H_{10}N_6O$ 49.54 4.62 38.51 (49.73 4.64 38.74)	4.40 (2H, br), 7.55 (1H, br), 7.76 (4H, br), 7.92 (1H, s), 8.70 (1H, s), 8.92 (1H, s)
20j	98	203—210 (dec.) (ET-W)	$C_8H_9N_7O$ 43.83 4.14 44.73 (43.75 4.25 44.85)	4.42 (2H, br), 7.62 (1H, br), 7.84 (2H, d, J=9 Hz), 7.97 (2H, d, J=9 Hz), 9.06 (1H, s), 9.18 (1H, s)
21a	[This compound was used for the next step without purification.]			

Table 5. (continued)

Compd.	Yield (%)	mp (°C) (Solv.)[a]	Analysis (%) Calcd (Found) C H N	^{1}H-NMR (in DMSO-d_6) δ
21b	88	124—126 (ET-IPE)	$C_{18}H_{25}N_3O_4$ 62.23 7.25 12.10 (—)	1.15 (6H, t, J=7 Hz), 2.44 (3H, s), 3.19 (2H, t, J=6 Hz), 3.42—3.72 (4H, m), 4.50 (1H, t, J=6 Hz), 6.15 (1H, t, J=6 Hz), 7.42 (2H, d, J=8.6 Hz), 7.60 (2H, d, J=8.6 Hz), 8.31 (1H, s), 7.70 (1H, s)
21c	91	111—112 (IPE-H)	$C_{17}H_{25}N_5O_3$ 58.77 7.25 20.16 (—)	1.21 (6H, t, J=7 Hz), 3.30—3.80 (6H, m), 4.53 (1H, t, J=5 Hz), 5.13 (1H, br), 5.55 (2H, s), 6.93 (1H, br), 7.20—7.30 (4H, m), 7.62 (2H, s) (in $CDCl_3$)
21d	98	89—91 (IPE)	$C_{17}H_{25}N_5O_3$ 58.77 7.25 20.16 (—)	1.21 (6H, t, J=7 Hz), 3.34—3.80 (7H, m), 4.55 (1H, t, J=5 Hz), 5.47 (1H, br), 5.48 (2H, s), 7.15 (2H, d, J=8.6 Hz), 7.32 (2H, d, J=8.6 Hz), 7.40 (1H, br), 7.49 (1H, s), 7.71 (1H, s) (in $CDCl_3$)
21e	97	132—133 (IPE)	$C_{16}H_{22}N_4O_3$ 60.36 6.96 15.08 (60.28 6.88 17.68)	1.15 (6H, t, J=7 Hz), 3.20 (2H, t, J=5.4 Hz), 3.35—3.68 (4H, m), 4.51 (1H, t, J=5.4 Hz), 6.14 (1H, t, J=5.4 Hz), 6.48 (1H, t, J=2.4 Hz), 7.50 (2H, d, J=9 Hz), 7.66—7.71 (3H, m), 8.36 (1H, d, J=2.4 Hz), 8.74 (1H, br)
21f	82	148—151 (ET-IPE)	$C_{16}H_{22}N_4O_3 \cdot 1/2H_2O$ 58.70 7.08 17.11 (58.31 6.77 16.81)	1.15 (6H, t, J=7 Hz), 3.20 (2H, t, J=6 Hz), 3.43—3.70 (4H, m), 4.51 (1H, t, J=6 Hz), 6.21 (1H, t, J=6 Hz), 7.08 (1H, s), 7.51 (4H,s), 7.63 (1H, s), 8.13 (1H, s), 8.85 (1H, s)
21g	94	139—140 (IPE-PE)	$C_{15}H_{21}N_5O_3$ 56.41 6.63 21.93 (56.36 6.68 21.95)	1.25 (6H, t, J=7.2 Hz), 3.43 (2H, t, J=5 Hz), 3.52—3.85 (4H, m), 4.57 (1H, t, J=5 Hz), 5.08—5.18 (1H, m), 7.16 (1H, br), 7.49 (2H, d, J=9.4 Hz), 7.57 (2H, d, J=9 Hz), 8.08 (1H, s), 8.48 (1H, s) ($CDCl_3$)
21h	84	175—176 (IPE-H)	$C_{15}H_{21}N_5O_3$ 56.41 6.63 21.93 (56.10 6.41 21.85)	1.15 (6H, t, J=7 Hz), 3.21 (2H, t, J=5 Hz), 3.30—3.69 (4H, m), 4.52 (1H, t, J=5 Hz), 6.16—6.21 (1H, m), 7.57 (2H, d, J=9 Hz), 7.89 (2H, d, J=9 Hz), 8.05 (1H, s), 8.86 (1H, s)
21i	95	194—196 (ET)	$C_{15}H_{21}N_5O_3$ 56.41 6.63 21.93 (56.59 6.58 22.02)	1.15 (6H, t, J=7 Hz), 3.21 (2H, t, J=5 Hz), 3.30—3.74 (4H, m), 4.52 (1H, t, J=5 Hz), 6.15—6.28 (1H, m), 7.58 (2H, d, J=9 Hz), 7.74 (2H, d, J=9 Hz), 7.91 (1H, s), 7.87 (1H, s), 8.89 (1H, s) (in $CDCl_3$).
21j	92	116—117 (ET-IPE)	$C_{14}H_{20}N_6O_3$ 52.49 6.29 26.23 (52.37 6.34 26.26)	1.15 (6H, t, J=7 Hz), 3.23 (2H, t, J=6 Hz), 3.47—3.73 (4H, m), 4.53 (1H, t, J=6 Hz), 6.26 (1H, t, J=6 Hz), 7.67 (2H, d, J=9 Hz), 7.97 (2H, d, J=9 Hz), 9.03 (1H, s), 9.18 (1H, s)
21k	99	169—170 (ET-IPE)	$C_{14}H_{20}N_6O_3$ 52.49 6.29 26.23 (52.46 6.19 26.32)	1.15 (6H, t, J=7 Hz), 3.22 (2H, t, J=6 Hz), 3.40—3.70 (4H, m), 4.52 (1H, t, J=6 Hz), 6.25 (1H, t, J=6 Hz), 7.64 (2H, d, J=9 Hz), 7.75 (2H, d, J=9 Hz), 8.98 (1H, s), 9.18 (1H, s)

a) Recrystallization solvent: IPE, diisopropyl ether; DCM, dichloromethane; W, water; EA, ethyl acetate; ME, methanol; PE, peteroleum ether; H, hexane. *b*) Not measured.

(27 g, 539 mmol) was added dropwise over a period of 15 min at 50 °C to a stirred mixture of the wet solid (**17j** and **17k**), $FeCl_3$ (0.33 g), activated carbon (3.3 g), methanol (MeOH, 280 ml) and THF (420 ml). The resulting mixture was refluxed with stirring for 10 h and cooled. The activated carbon was filtered off and washed with MeOH (200 ml). The filtrate and the washing were combined and evaporated *in vacuo*. The residue was purified by column chromatography on silica gel (THF–hexane, 2 : 3→THF–hexane–AcOEt, 1 : 1 : 1, v/v). The first eluted fraction was evaporated *in vacuo* and the residue was crystallized from hexane to give **18j** (14.5 g, 25% based on **16**) as a pale yellow crystalline powder. The second eluted fraction was evaporated *in vacuo* and the residue was crystallized from $isoPr_2O$ to give **18k** (25.3 g, 44% based on **16**) as a pale yellow crystalline powder. **18j**[16a]: mp 124—125 °C (recrystallized from AcOEt–$isoPr_2O$). ^{1}H-NMR (DMSO-d_6) δ: 5.76 (2H, s), 6.76 (2H, d, J=8.8 Hz), 7.74 (2H, d, J=8.8 Hz), 9.08 (1H, s). *Anal*. Calcd for $C_7H_7N_5$: C, 52.17; H, 4.38; N, 43.45. Found: C, 52.01; H, 4.44; N, 43.41. **18k**[16a]: mp 142—143 °C (recrystallized from AcOEt–$isoPr_2O$). ^{1}H-NMR (DMSO-d_6) δ: 5.65 (2H, s), 6.73 (2H, d, J=8.8 Hz), 7.48 (2H, d, J=8.8 Hz), 9.83 (1H, s). *Anal*. Calcd for $C_7H_7N_5$: C, 52.17; H, 4.38; N, 43.45. Found: C, 51.88; H, 4.38; N, 43.62.

Phenyl 4-(1*H*-1,2,4-Triazol-1-yl)phenylcarbamate (19g: Table 5) PhOCOCl (14.6 g, 93.5 mmol) was added dropwise to a stirred mixture of **18g** (13.6 g, 85 mmol), pyridine (7.4 g, 93.5 mmol) and CH_2Cl_2 (200 ml) at 0 °C. After having been stirred for 30 min, the mixture was washed (water, brine) and concentrated *in vacuo*. The deposited crystals were collected by filtration and washed with AcOEt–$isoPr_2O$ to give **19g**[19] (22.8 g, 96%) as pale yellow crystals.

The phenyl carbamates (**19a**—**f**, **h**—**k**: Table 5) were prepared from the corresponding 4-substituted anilines (**18a**—**f**, **h**—**k**) by the same method as described above.

4-[4-(1*H*-1,2,4-Triazol-1-yl)phenyl]semicarbazide (20g: Table 5) A mixture of **19g** (22.8 g, 81.4 mmol), $N_2H_4 \cdot H_2O$ (8.14 g, 163 mmol) and EtOH (150 ml) was stirred at 80 °C for 1 h. After having been cooled, the precipitate was collected by filtration and washed with cooled EtOH to give **20g** (16.8 g, 95%) as colorless crystals.

The semicarbazides (**20a**—**f**, **h**—**j**: Table 5) were prepared from the corresponding phenyl carbamates (**19a**—**f**, **h**—**j**) by the same method as described above.

1-(2,2-Diethoxyethyl)-3-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]urea (21g: Table 5) A mixture of **19g** (13 g), pyridine (3.67 g) and $(EtO)_2CHCH_2NH_2$ (7.4 g) was heated at 50 °C for 3 h. After having been cooled, the precipitate was collected by filtration and washed with a mixture of $isoPr_2O$–petroleum ether (1 : 1, v/v; 100 ml×2) to give **21g** (14.5 g, 94%) as a colorless crystalline powder.

The ureas (**21a**—**f**, **h**—**k**: Table 5) were prepared from the corresponding phenyl carbamates (**19a**—**f**, **h**—**k**) by the same method as described above.

4-(1*H*-1,2,4-Triazol-1-yl)phenyl-3(2*H*,4*H*)-1,2,4-triazolone (5g: Table 2) A mixture of $HN{=}CH{-}NH_2 \cdot AcOH$ (19 g, 183 mmol), **20g** (8 g, 36.6 mmol) and DMF (200 ml) was stirred for 2 h. AcOH (19 g, 183 mmol) was added, and the resulting mixture was heated at 80 °C for 9 h. The whole was evaporated *in vacuo*, and the residue was poured into water. The precipitate was collected by filtration and recrystallized from DMF–water to give **5g** (3.34 g, 40%) as colorless needles.

The triazolones **5a**—**f**, **h**—**j** (Table 2) were prepared from the corresponding semicarbazides (**20a**—**f**, **h**—**j**) by the same method as described above.

1-[4-(1*H*-1,2,4-Triazol-1yl)phenyl]-2-(1*H*,3*H*)-imidazolone (6g: Table 3) Compound **21g** (14.5 g, 43.5 mmol) was dissolved in a mixture of MeOH (214 ml) and water (85 ml), and then 0.48 N HCl (104 ml) was added to the solution. The mixture was stirred for 14 h, and the resulting precipitate was collected by filtration to give **6g** (9.01 g, 92%) as a colorless crystalline powder.

The imidazolones **6a**—**f**, **h**—**k** (Table 3) were prepared from the corresponding carbamates (**19a**—**f**, **h**—**k**) by the same method as described above.

2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(2-methyl-4-oxazolyl)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (1b: Table 1) A mixture of **4** (0.5 g), **5b** (0.56 g), K_2CO_3 (powder:

1.38 g), NMP (5 ml) and DMF (4 ml) was stirred at 90 °C for 2 h. After having been cooled, the whole was worked up (AcOEt; water, 0.5 N NaOH, 1 N HCl, brine). The residue was purified by silica gel column chromatography (AcOEt→AcOEt–MeOH, 9 : 1, v/v) to give **1b** (0.33 g, 33%) as a colorless crystalline powder.

2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(1*H*-1,2,3-triazol-1-ylmethyl)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (1d: Table 1) A mixture of **4** (1.25 g, 5.0 mmol), **5d** (1.44 g, 6.0 mmol), K_2CO_3 (powder: 3.0 g, 21 mmol) and DMF (60 ml) was heated at 80 °C with stirring for 26 h. After having been cooled, the mixture was filtered to remove the insoluble substance. The filtrate was concentrated *in vacuo* and AcOEt (300 ml) was added. The resulting precipitate was filtered off, and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography (AcOEt–MeOH, 20 : 1, v/v) to give **1d** (0.6 g, 24%) as a colorless crystalline powder.

The reaction of **4** with **5a** was carried out by the same method as described above to obtain **1a** (Table 1).

2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(1*H*-1-imidazolyl)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (1f: Table 1) NaH (70% oil dispersion, 150 mg, 4.5 mmol) was added to a mixture of **5f** (1140 mg, 5 mmol) and NMP (30 ml). The mixture was stirred for 1.5 h, and then **4** (1000 mg, 4.0 mmol) was added. The resulting mixture was stirred at 80 °C for 19 h under an argon atmosphere. After having been cooled, the whole was worked up (AcOEt; water). The residue was purified by silica gel column chromatography [AcOEt–MeOH, 4 : 1, v/v] to give **1f** (400 mg, 21%) as a colorless amorphous powder.

The reaction of **4** with **5c**, **e**, **j** was carried out by the same method as described above to obtain the corresponding triazolone derivatives (**1c**, **e**, **j**: Table 1).

2-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-4-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-3(2*H*,4*H*)-1,2,4-triazolone (1g: Table 1) A mixture of NaH (70% oil dispersion, 160 mg, 4.0 mmol) and DMSO (40 ml) was stirred at 80 °C for 30 min. Compound **5g** (910 mg, 4 mmol) was added, and the mixture was stirred for 5 min. Next, compound **4** (1000 mg, 4.0 mmol) was added and the resulting mixture was stirred at 80 °C for 24 h under an argon atmosphere. After having been cooled, the whole was worked up (AcOEt; water, brine). The residue was purified by silica gel column chromatography (CH_2Cl_2–MeOH, 10 : 1, v/v) to give **1g** (540 mg, 28%) as a colorless crystalline powder.

The reaction of **4** with **5h** and **5i** was carried out by the same method as described above to obtain the corresponding triazolone derivatives (**1h**, **i**: Table 1)

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-2(1*H*,3*H*)-imidazolone (2g: Table 1) A mixture of **4** (2.5 g), **6a** (2.72 g), Cs_2CO_3 (powder: 9.7 g) and DMF (150 ml) was stirred at 80 °C for 9.5 h. After having been cooled, the whole was worked up (AcOEt; water, 0.5 N NaOH, 1 N HCl, brine). The residue was purified by silica gel column chromatography (AcOEt–acetone, 2 : 1, v/v) to give **2g** (1.03 g, 22%) as a pale yellow amorphous powder.

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(1*H*-1,2,3-triazol-1-yl)phenyl]-2(1*H*,3*H*)-imidazolone (2i: Table 1) Compound **4** (2.51 g) was allowed to react with **6i** (2.72 g) in the presence of NaH (70% oil dispersion, 0.4 g) in a manner similar to that described for the synthesis of **1f**, and the product was purified by silica gel column chromatography (AcOEt→AcOEt–acetone, 5 : 1, v/v) followed by crystallization from acetone–AcOEt–isoPr$_2$O to give **2i** (1.82 g, 38%) as a pale yellow crystalline powder.

The reaction of **4** with **6a**—**f**, **h**, **j** was carried out in the same manner as described above to obtain the corresponding imidazolone derivatives (**2a**—**f**, **h**, **j**: Table 1).

1-[(1*R*,2*S*)-2-(2,4-Difluorophenyl)-2,3-epoxy-1-methylpropyl]-3-[4-(1*H*-1-tetrazolyl)phenyl]-2(1*H*,3*H*)-imidazolone (9) Route I: Tf_2O (0.49 ml) was added dropwise to a stirred solution of **7**[3f,g] (1.20 g) and isoPr$_2$NEt (1.15 ml) in CH_2Cl_2 (26 ml) over a period of 5 min at −78 °C under a nitrogen atmosphere. The resulting mixture was stirred for 20 min at −78 °C and then for 15 min at −20 °C. The mixture was diluted with hexane (26 ml), and the whole was evaporated to about 9 ml *in vacuo* at −10°C. The residue was submitted to flash chromatography on silica gel (CH_2Cl_2-hexane, 1 : 1, v/v). The eluates containing the triflate **8**[3e—h] were combined and concentrated to about 20 ml. This solution was added to a stirred mixture of **6k** (0.94 g), NaH (72% in oil, 0.126 g), DMF (20 ml), DMSO (10 ml) and THF (10 ml) at −30 °C. The resulting mixture was stirred at −30 °C for 20 min and at 0 °C for further 40 min. The whole was worked up (AcOEt; water, brine) and the residue was purified by chromatography on silica gel (hexane–AcOEt, 1 : 3, v/v) to give **9** (0.13 g, 7.7% based on **6k**) as a colorless crystalline powder. mp 205—207 °C (recrystallized from hexane–AcOEt). ^{1}H-NMR ($CDCl_3$) δ: 1.39 (3H, d, J=7.2 Hz), 2.74 (1H, d, J=4.6 Hz), 2.83 (1H, d, J=4.6 Hz), 5.10 (1H, q, J=7.2 Hz), 6.53 (1H, d, J=3.2 Hz), 6.67 (1H, d, J=3.2 Hz), 6.83—6.96 (2H, m), 7.40—7.48 (1H, m), 7.79 (2H, d, J=9 Hz), 7.95 (2H, d, J=9 Hz), 9.03 (1H, s). SIMS (MH^+): 411. IR (KBr): 3080, 1678, 1615, 1520, 1500, 1420 cm^{-1}. $[\alpha]_D^{25}$=−22.6° (c=0.36, MeOH).

Route II: A mixture of **6k** (23.1 g), NaH (72% in oil, 3.3 g) and NMP (300 ml) was stirred for 1 h. The resulting solution was cooled in an ice bath and added dropwise to a solution of **11**[3h] (32.3 g) in THF (200 ml) over a period of 20 min at −30 °C under a nitrogen atmosphere. After having been stirred for 30 min at −20 °C, the whole was worked up (AcOEt; water, 1 N HCl, brine). The residue was purified by silica gel column chromatography (hexane–AcOEt–AcOH, 1 : 2 : 0.03→1 : 3 : 0.04, v/v) and crystallized from AcOEt to give **12** (13.8 g, 34%) as a colorless crystalline powder. mp 140—141 °C. *Anal*. Calcd for $C_{19}H_{14}F_2N_6O_2$: C, 57.58; H, 3.56; N, 21.20. Found: C, 57.40; H, 3.58; N, 21.03. ^{1}H-NMR ($CDCl_3$) δ:1.66 (3H, d, J=7.2 Hz), 5.77 (1H, q, J=7.2 Hz), 6.66 (1H, d, J=3.2 Hz), 6.73 (1H, d, J=3.2 Hz), 6.88—7.05 (2H, m), 7.76 (2H, d, J=8.8 Hz), 7.90 (2H, d, J=8.8 Hz), 7.95—8.07 (1H, m), 8.99 (1H, s). $[\alpha]_D^{25}$=+11.8° (c=1.0, THF).

A mixture of isoPrOSi(Me$_2$)CH$_2$Cl (8.34 g), magnesium (Mg, turnings, 1.22 g) and THF (50 ml) was refluxed. After having been cooled, the mixture was diluted with THF (12.5 ml) to obtain a 0.8 M solution of the Grignard reagent. This 0.8 M solution (6.31 ml) was added dropwise to a solution of **12** (1.00 g) in THF (20 ml) over a period of 5 min at −5 °C. The resulting mixture was stirred for 3 h at −5 °C and diluted with a cooled saturated aqueous solution of ammonium chloride (aq. NH_4Cl, 20 ml) and ice water (20 ml). The whole was worked up (AcOEt; brine) and the residue was purified by silica gel column chromatography (hexane–AcOEt, 3 : 1→2 : 1, v/v). The product was recrystallized from isoPr$_2$O–hexane (1 : 2, v/v, 15 ml) to obtain **13** (0.27 g, 20%) as colorless needles. mp 124–135 °C. *Anal*. Calcd for $C_{24}H_{30}F_2N_6O_3Si$: C, 56.80; H, 5.72; N, 15.90. Found: C, 56.48; H, 5.79; N, 15.00. ^{1}H-NMR (DMSO-d_6) δ: −0.27 (3H, s), −0.26 (3H, s), 0.96—1.07 (10H, m), 1.57 (1H, d, J=17 Hz), 3.81 (1H, quintet, J=6 Hz), 4.70 (1H, q, J=7 Hz), 5.27 (1H, br s), 6.89 (1H, d, J=3 Hz), 7.13—7.30 (2H, m), 7.28 (1H, d, J=3 Hz), 7.65—7.78 (1H, m), 8.02 (2H, d, J=9 Hz), 8.12 (2H, d, J=9 Hz), 10.13 (1H, s). IR (KBr): 1670, 1610, 1520, 1500 cm^{-1}.

A 30% aqueous solution of H_2O_2 (3.86 ml) and $NaHCO_3$ (0.32 g) were added to a solution of **13** (2.00 g) in MeOH–THF (1 : 1, v/v, 20 ml). The mixture was heated for 3 h at 50 °C. After having been cooled, the whole was worked up [AcOEt; water, aqueous solution of sodium thiosulfate ($Na_2S_2O_3$), brine]. The residue was purified by silica gel column chromatography (hexane–AcOEt, 1 : 2→1 : 3, v/v), and crystallized from isoPr$_2$O to give **14** (1.28 g, 79%) as a colorless crystalline powder. mp 204—210 °C. *Anal*. Calcd for $C_{20}H_{18}F_2N_6O_3$: C, 56.07; H, 4.24; N, 19.62. Found: C, 55.73; H, 4.30; N, 19.05. ^{1}H-NMR ($CDCl_3$) δ: 1.27 (3H, d, J=7 Hz), 2.35 (1H, t, J=6 Hz), 3.80 (1H, dd, J=12 Hz, 6 Hz), 3.97 (1H, dd, J=12 Hz, 6 Hz), 4.40—4.65 (1H, br), 4.86 (1H, q, J=7 Hz), 6.61 (1H, d, J=3.2 Hz), 6.70 (1H, d, J=3.2 Hz), 6.79—7.00 (2H, m), 7.69—7.83 (1H, m), 7.80 (1H, d, J=9 Hz), 7.94 (2H, d, J=9 Hz), 9.01 (1H, s).

MsCl (0.39 ml) and triethylamine (Et_3N, 0.51 g) were added dropwise to a mixture of **14** (1.31 g), AcOEt (10 ml) and THF (50 ml) at 0 °C. After having been stirred at 0 °C for 30 min, the whole was worked up (AcOEt; water, brine). The residue was dissolved in DMF (15 ml). K_2CO_3 (0.70 g) was added to the solution, and the mixture was heated at 40 °C for 1 h. After having been cooled, the whole was worked up (AcOEt–THF; aq. NH_3Cl, brine). The residue was purified by silica gel column chromatography (hexane–AcOEt, 1 : 1→2 : 3, v/v) and crystallized from AcOEt–Et$_2$O to give **9** (0.78 g, 62%) as a colorless crystalline powder, which was identical with the authentic sample prepared above.

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(1*H*-1-tetrazolyl)phenyl]-2(1*H*,3*H*)-imidazolone (2k: Table 1) Method B: 1*H*-1,2,4-Triazole (42 mg) was added to a stirred mixture of NaH (72% in oil, 17 mg) and DMF (3 ml) at 0 °C, and the mixture was stirred for 40 min. A solution of **9** (0.205 g) in DMF (2 ml) was added and the resulting mixture was stirred for 6 h at 50 °C. The whole was worked up (AcOEt; water, brine) and the residue was chromatographed on silica gel (AcOEt) to give **2k** (0.15 g, 63%).

1-[(1*R*,2*R*)-2-(2,4-Difluorophenyl)-2-hydroxy-1-methyl-3-(1*H*-1,2,4-triazol-1-yl)propyl]-3-[4-(1*H*-1,2,4-triazol-1-yl)phenyl]-2-imidazolidinone (3g: Table 1) A solution of **2g** (0.5 g) in AcOH (25 ml) was hydrogenated over 10% Pd–C (0.2 g) under atmospheric pressure for 3 h and then at 50 °C

for a further 3 h. The catalyst was removed by filtration, and the filtrate was concentrated *in vacuo*. The residue was purified by chromatography on silica gel (AcOEt–acetone, 5 : 1→2 : 1, v/v) to give **3g** (0.37 g, 74%) as a colorless crystalline powder.

Catalytic hydrogenation of **2e**, **f**, **h**—**k** was carried out by the same method as described above to obtain the corresponding imidazolidinones (**3e**, **f**, **h**—**k**: Table 1).

Antifungal Activity *In vitro* antifungal activities against *C. albicans* and *C. neoformans* were measured by the following method: *MIC*s were determined by an agar dilution method using RPMI-1640 medium (Gibco BRL, Grand Island, N.Y.). A double concentration of RPMI-1640 medium was prepared with 0.3 M morpholinepropanesulfonic acid (MOPS; Dojindo, Tokyo, Japan) buffer (pH 7.0), sterilized by filtration through a membrane filter (pore size, 0.45 μm), and mixed with an equal volume of 2.0% agar (Wako, Osaka, Japan) which had been autoclaved at 121 °C for 15 min and kept at 55 °C. The agar medium (9.9 ml) was then poured into petri dishes containing 0.1 ml of serial dilutions of antifungal agents dissolved in DMSO (Wako) and allowed to solidify. About 10^3 CFU of fungal cells suspended in saline was inoculated with a multiple inoculator (Sakuma, Tokyo, Japan) onto the agar plates prepared as described above. The plates were then incubated in a CO_2 incubator at 35 °C for 20 h. After the *MIC*s for *C. albicans* were determined, the plates were incubated in a CO_2 incubator for an additional 48 h to determine the *MIC* for *C. neoformans*. The *MIC* was defined as the lowest concentration of antifungal agent giving no visible growth or causing almost complete inhibition of growth.

In vitro antifungal activity against *A. fumigatus* was measured by the following method: *MIC*s were determined by an agar dilution method using RPMI-1640 medium. A double concentration of RPMI-1640 medium was prepared with 0.3 M MOPS buffer (pH 7.0), sterilized by filtration through a membrane filter (pore size, 0.45 μm), and mixed with an equal volume of 2.0% agar which had been autoclaved at 121 °C for 15 min and kept at 55 °C. The agar medium (9.9 ml) was then poured into petri dishes containing 0.1 ml of serial dilutions of antifungal agents dissolved in DMSO and allowed to solidify. About 10^3 CFU of fungal cells suspended in saline was inoculated with a multiple inoculator onto the agar plates prepared as described above. The plates were then incubated in an ordinary incubator at 35 °C for 20 h. The *MIC* was defined as the lowest concentration of antifungal agent giving no visible growth.

ED_{50} values of the compounds against candidiasis were determined by the method described in our preceding report.[3a)]

In vivo antifungal activity against *A. fumigatus* was measured by the following method: six-week-old CDF_1 female mice were infected intravenously with 2×10^4—5×10^4 CFU of *A. fumigatus* 437 per mouse 4 d after the intraperitoneal administration of 200 mg/kg of cyclophosphamide. The test compound was administered orally (*p.o.*) 4 h after infection and twice daily on the following 2 d. ED_{50} values were calculated by the method of Reed and Muench[20)] from survival rates on day 10 after infection.

Acknowledgments We thank Dr. S. Kishimoto and Dr. A. Miyake for their encouragement throughout this work. We also thank Ms. J. Obita, Ms. N. Kitamoto and Mr. T. Yoshida for the biological assays.

References and Notes

1) Part IX: Kitazaki T., Tasaka A., Hosono H., Matsushita Y., Itoh K., *Chem. Pharm. Bull*., **47**, 360—368 (1999).
2) *a*) Odd F. C., *J. Antimicrob. Chemother*., **31**, 463—471 (1993); *b*) Hitchcock C. A., *Biochem. Soc. Trans*., **21**, 10—39 (1993); *c*) Johnson E. M., Warnock D. W., Luker J., Porter S. R., *J. Antimicrob. Chemother*., **35**, 103—114 (1995); *d*) Rex J. H., Rinaldi M. G., Pfallar M. A., *Antimicrob. Agents Chemother*., **39**, 1—8 (1995).
3) *a*) Tasaka A., Tamura N., Matsushita Y., Teranishi K., Hayashi R., Okonogi K., Itoh K., *Chem. Pharm. Bull*., **41**, 1035—1042 (1993); *b*) Tasaka A., Tamura N., Matsushita Y., Hayashi R., Okonogi K., Itoh K., *ibid*., **41**, 1043—1048 (1993); *c*) Tasaka A., Teranishi K., Matsushita Y., Tamura N., Hayashi R., Okonogi K., Itoh K., *ibid*., **42**, 85—94 (1994). *d*) Tasaka A., Tamura N., Matsushita Y., Kitazaki T., Hayashi R., Okonogi K., Itoh K., *ibid*., **43**, 432—440 (1995); *e*) Tasaka A., Tsuchimori N., Kitazaki T., Hiroe K., Hayashi R., Okonogi K., Itoh K., *ibid*., **43**, 441—449 (1995); *f*) Kitazaki T., Tamura N., Tasaka A., Matsushita Y., Hayashi R., Okonogi K., Itoh K., *ibid*., **44**, 314—327 (1996); *g*) Tasaka A., Kitazaki T., Tsuchimori N., Matsushita Y., Hayashi R., Okonogi K., Itoh K., *ibid*., **45**, 321—326 (1997); *h*) Kitazaki T., Tasaka A., Matsushita Y., Hosono H., Hayashi R., Okonogi K., Itoh K., *ibid.*, **47**, 351—359 (1999).
4) The formation of a byproduct was observed by TLC analysis of the reaction mixture. The byproduct was assumed to be the *O*-substituted isomer (the 2-imidazolyloxy derivative) since this type of isomer was isolated as the byproduct in the synthesis of Ib.[3h)]
5) It has been reported that reaction of a Grignard's reagent and a propiophenone derivative (**12**) proceeds with high stereoselectivity to give a single diastereomer.[1,6)]
6) *a*) Tamao K., Ishida N., *Tetrahedron Lett*., **25**, 4245—4248 (1984); *b*) Konosu T., Tajima Y., Takeda N., Miyaoka T., Kasahara M., Yasuda H., Oida S., *Chem. Pharm. Bull*., **38**, 2476—2486 (1990); *c*) Konosu T., Miyaoka T., Tajima Y., Oida S., *ibid*., **39**, 2241—2246 (1991).
7) *a*) Macky M. F., Trautino G. J., Wilshire J. F. K., *Aust. J. Chem*., **46**, 417—425 (1993); *b*) Cerrada M. L., Elguero J., Fuente J. de la, Pardo C., Ramos M., *Synth. Commun*., **23**, 1949—1952 (1993). *c*) Street L. J., Baker R., Davey W. B., Guiblin A. R., Jelley R. A., Reeve A. J., Routledge H., Sternfeld F., Watt A. P., Beer M. S., Middlemiss D. N., Noble A. J., Stanton J. A., Scholey K., Hargreaves R. J., Sohal B., Graham M. I., Matassa V. G., *J. Med. Chem*., **38**, 1799—1810 (1995).
8) The substitution positions on the tetrazole moieties in these two regioisomers, **18j** and **18k**, were tentatively assigned to be at the 2- and 1-positions, respectively, based on the chemical shift of the proton attached to the tetrazole nuclei in the ^{1}H-NMR spectrum. The proton on the 1-substituted-1*H*-tetrazole derivative appeared at higher magnetic field than that of the corresponding proton of the 2-substituted-2*H*-tetrazole derivative without exception in our previous studies.[3d,e,f)] The structure of **18k** was unequivocally confirmed by direct comparison with an authentic sample which was obtained from **17k** prepared *via* an alternative route [Gaponik P. N., Karuvai V. P., Grigor'ev Yu. V., *Chem. Heterocycl. Compd*., **21**, 1255—1258 (1985)].
9) *a*) Das B. B., Rout M. K., *J. Indian Chen. Soc*., **34**, 505—508 (1957); *b*) Behera G. B., Ka J. N., Acharya R. C., Rout M. K., *J. Org. Chem*., **38**, 2164—2166 (1973).
10) Hammar W. J., Rustad M. A., *J. Heterocycl. Chem*., **18**, 885—888 (1981).
11) The agar dilution method for *in vitro* susceptibility testing of antifungal agents under 20% CO_2 was developed in our laboratories: Yoshida T., Jono K., Okonogi K., *Antimicrob. Agents Chemother*., **41**, 1349—1351 (1997).
12) Hostetler J. S., Hanson L. H., Stevens D. A., *Antimicrob. Agents Chemother*., **36**, 477—480 (1992).
13) A discrepancy between the *in vitro* potency and the *in vivo* activity has often been observed in azole antifungals : Troke P. F., Marriott M. S., Richardson K., Tarbit M. H., *Ann. N. Y. Acad. Sci*., **544**, 248—293 (1988).
14) Jonas A., Pechmann H. v., *Justus Liebigs Ann. Chem*., **262**, 292 (1891).
15) Michael A., Luehn F., Higbee H. H., *Amer. Chem. J*., **20**, 377 (1898).
16) *a*) Bouchet P., Coquelet C., Elquero J., *J. Chem. Soc. Perkin Trans. 2*, **1974**, 449—451; *b*) Elguro J., Gil M., Iza N., Pardo C., Ramos M., *Appl. Spectrosc*., **49**, 1111—1119 (1995).
17) Kulkarni B. S., Fernandez B. S., Patel M. R., Bellare R. A., Deliwala C. V., *J. Pharm. Sci*., **58**, 852—857 (1969).
18) Smithkline Beecham PLC, UK, PCT Int. Appl., WO 9850358 A1 (1998) [*Chem. Abstr*., **130**, 13915 (1998)].
19) Farbenfabriken Bayer A. G., ZA 6901244 (1969) [*Chem. Abstr*., **72**, 100715*s* (1970)].
20) Reed L. J., Muench H., *Am. J. Hyg*., **27**, 493 (1938).