Structure–Activity Relationships of 1,3-Benzoxazole-4-carbonitriles as Novel Antifungal Agents with Potent *in Vivo* Efficacy

Jun-ichi Kuroyanagi,*[,a] Kazuo Kanai,[a] Takao Horiuchi,[a] Hiroshi Takeshita,[a] Shozo Kobayashi,[b] Issei Achiwa,[a] Kumi Yoshida,[c] Koichi Nakamura,[d] and Katsuhiro Kawakami[a]

[a] *Lead Discovery & Optimization Research Laboratories II, Daiichi Sankyo Co., Ltd.;* [c] *Biological Research Laboratories, Daiichi Sankyo Co., Ltd.; 1–16–13 Kitakasai, Edogawa-ku, Tokyo 134–8630, Japan:* [b] *Lead Discovery & Optimization Research Laboratories I, Daiichi Sankyo Co., Ltd.; and* [d] *Drug Metabolism & Pharmacokinetics Research Laboratories, Daiichi Sankyo Co., Ltd.; 1–2–58 Hiromachi, Shinagawa-ku, Tokyo 140–8710, Japan.*

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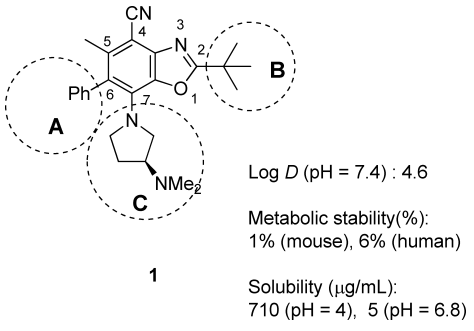
A series of 1,3-benzoxazole-4-carbonitriles was synthesized and evaluated for its antifungal activity, solubility, and metabolic stability. Among those compounds, 4-cyano-*N*,*N*,5-trimethyl-7-[(3*S*)-3-methyl-3-(methylamino)pyrrolidin-1-yl]-6-phenyl-1,3-benzoxazole-2-carboxamide (16b) exhibited potent *in vitro* activity against *Candida* species, higher water solubility, and improved metabolic stability compared to lead compound 1. Compound 16b showed potent *in vivo* efficacy against mice *Candida* infection models and good bioavailability in rats.

Key words 1,3-benzoxazole-4-carbonitrile; antifungal agent; physicochemical property; *in vivo* efficacy; bioavailability

Increased incidence of invasive mycoses is often related to the growing use of broad-spectrum antibiotics, immunosuppressive agents, anti-cancer, and anti-AIDS drugs.[1—3] Although antifungal agents, such as polyenes, azoles, and candins, have shown potent efficacy against *Candida* species (spp.) in the treatment of systemic fungal infections, currently available drugs could not satisfy the increasing requirement for antifungal therapy in complex patient populations. This is because of the unfavorable properties, such as side effects, a narrow spectrum, and drug resistance.[4—10] These unresolved issues have caused a high rate of mortality and the spread of antifungal drug resistance. Therefore, new antifungal agents with a novel mode of action have been urgently required to open the possibility of a novel therapeutic approach.

We have reported the discovery of new antifungal agents possessing 1,3-benzoxazole-4-carbonitrile skeleton with a novel mode of action inhibiting the synthesis of β-1,6-glucan, which was known to play a key role in cellular growth and proliferation of *Candida* spp.[11] Among those 1,3-benzoxazole analogs, compound **1** showed potent antifungal activity against *Candida* spp. However, *in vivo* efficacy of **1** has not been observed in mice *Candida albicans* infection models. We considered the lack of *in vivo* efficacy of our compound was mainly due to its poor physicochemical properties such as high lipophilicity, low metabolic stability, and poor water solubility at pH 6.8 as shown in Fig. 1. Therefore, we embarked on an exploration of the structure–activity relationships (SARs) of its peripheral analogs, as well as improvement of their physicochemical properties.



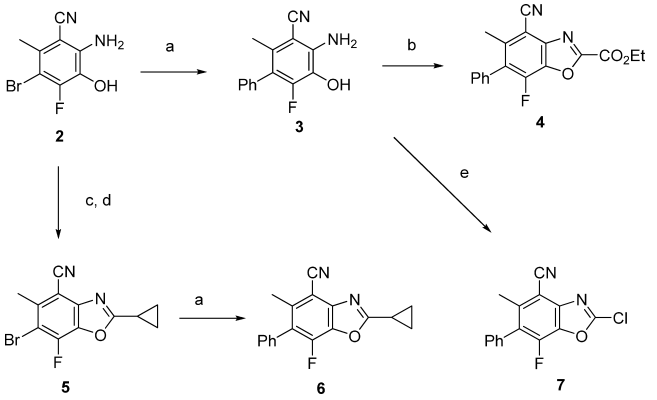
1

Fig. 1. Structure of **1**

Initial SARs of this type of antifungal agent suggested that the cyano group at the 4-position and the methyl group at the 5-position are indispensable for potent antifungal activity.[11,12] To develop SARs studies, we subdivided lead structure **1** into three sections: (A) phenyl ring, (B) aliphatic group, and (C) amino substituent. Each structural moiety was modified independently to clarify its function.

Herein, we would like to report the SARs and physicochemical properties of 1,3-benzoxazole analogs focusing on the relationship between physicochemical properties and *in vivo* activities in mice infection models.

Chemistry Various 1,3-benzoxazole-4-carbonitrile derivatives were synthesized from intermediates **4**—**7**, which were prepared from useful hexa-substituted benzenes **2** and **3** as starting materials.[11] Compound **3** was converted to 1,3-benzoxazole intermediates **4** and **7** possessing ethoxycarbonyl or chloro group at the 2-position. 2-Cyclopropane derivative **5** was synthesized directly from **2**, and then con-



Reagents and conditions: (a) $PhB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane-H_2O, 91%; (b) triethoxyacetic acid ethyl ester, 96%; (c) cyclopropanecarboxylic acid chloride, *i*-Pr_2NEt, CH_2Cl_2; (d) *p*-TsOH, xylene, 80% (two steps); (e) $EtOCS_2K$, pyridine; $SOCl_2$, 100%.

Chart 1. Synthesis of 1,3-Benzoxazole-4-carbonitrile Intermediates

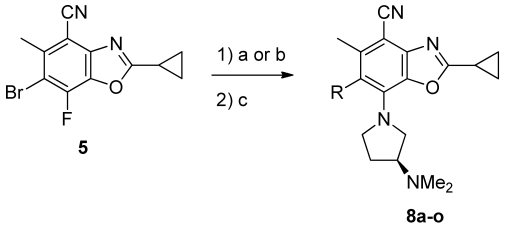
* To whom correspondence should be addressed. e-mail: kuroyanagi.junichi.d5@daiichisankyo.co.jp

verted to intermediate **6** (Chart 1).

To evaluate the effect of substituents at the 6-position, compounds **8a**—**o** were synthesized in a similar way. Cross-coupling reaction[13,14] at the 6-position, followed by incorporation of (3*S*)-3-(dimethylamino)pyrrolidine into the 7-position afforded 6-functionalized analogs **8a**—**o** (Chart 2).

To figure out the effects of substituents at the 2-position, compounds **9** and **11**—**14** were designed and synthesized. Analogs **9**, **11a**, and **11b**, bearing 2-carboxylate or amide moieties, were prepared from 2-ethoxycarbonyl intermediate **4** as shown in Chart 3. Aryl and heteroaryl groups were introduced to intermediates **3** or **7** by condensation reaction or cross coupling reaction to give 2-substituted analogs **12a**—**f**. Compounds **12g**—**j** bearing a C–N bond at the 2-position were also prepared from **7** with corresponding amines (Chart 4). Further steps were required to obtain 2-oxopyrrolidin-1-yl analog **14** as shown in Chart 5.

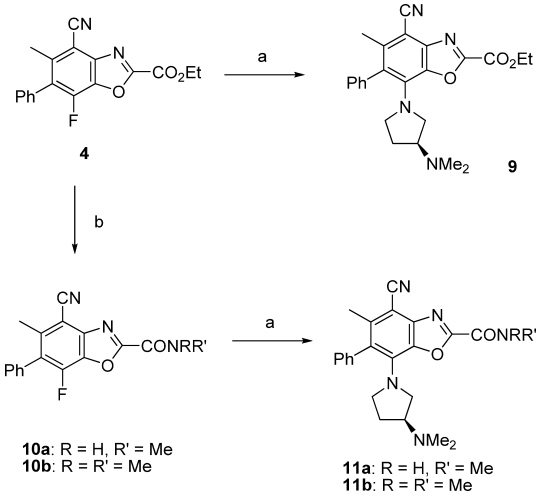
As outlined in Chart 6, intermediates **6** and **10b** were selected and converted to amines **15a**—**e** and **16a**—**c** by the same manner described in Chart 2. To obtain **16b** and **16c**, optically active 3-amino-3-methylpyrrolidines **20** and **23** were prepared as substituents at the 7-position (Chart 7).



8a R = Ph
8b R = Pyridin-2-yl
8c R = Pyridin-4-yl
8d R = 1-Me-1*H*-pyrrol-2-yl
8e R = 2-Furyl
8f R = 2-Thienyl
8g R = 3-Thienyl
8h R = Vinyl
8i R = 2-F-Ph
8j R = 3-F-Ph
8k R = 4-F-Ph
8l R = 3-NH_2-Ph
8m R = 3-(CH_2OH)-Ph
8n R = 3-OMe-Ph
8o R = 3-CN-Ph

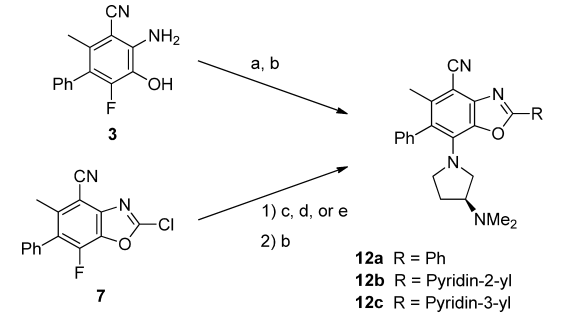
Reagents and conditions: (a) *n*-Bu_3SnR, $Pd(PPh_3)_2Cl_2$, 2,6-di-*tert*-butylcresol, toluene; (b) $RB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane; (c) (3*S*)-3-(dimethylamino)pyrrolidine, Et_3N, DMSO.

Chart 2. Synthesis of 6-Substituted 1,3-Benzoxazole-4-carbonitriles



Reagents and conditions: (a) (3*S*)-3-(dimethylamino)pyrrolidine, Et_3N, DMSO; (b) amine, Me_3Al, CH_2Cl_2.

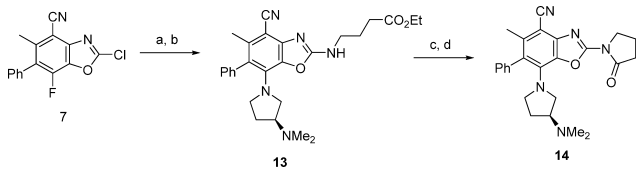
Chart 3. Synthesis of 2-Substituted 1,3-Benzoxazole-4-carbonitriles



12a R = Ph
12b R = Pyridin-2-yl
12c R = Pyridin-3-yl
12d R = Pyridin-4-yl
12e R = 1-Me-1*H*-pyrrol-2-yl
12f R = 2-Furyl
12g R = NHMe
12h R = NMe_2
12i R = NEt_2
12j R = Pyrrolidin-1-yl

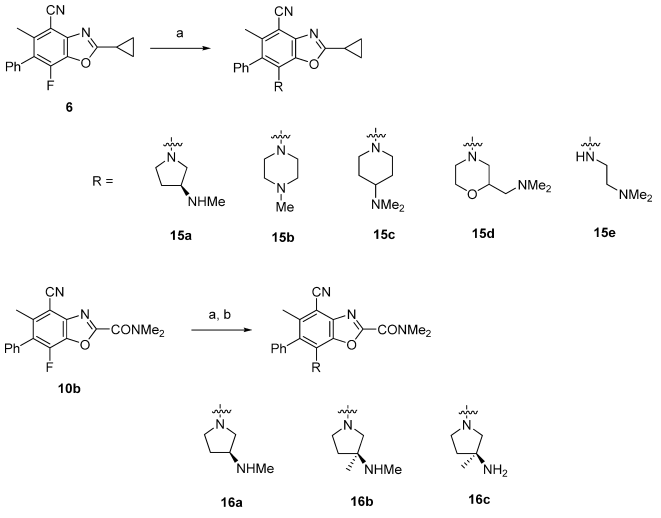
Reagents and conditions: (a) RCOCl, Et_3N; PPTS, Xylene; (b) (3*S*)-3-(dimethylamino)pyrrolidine, Et_3N, DMSO; (c) $RB(OH)_2$, $Pd(PPh_3)_4$, K_3PO_4, 1,4-dioxane; (d) *n*-Bu_3SnR, $Pd(PPh_3)_2Cl_2$, 2,6-di-*tert*-butylcresol, toluene; (e) amine, Et_3N, CH_2Cl_2.

Chart 4. Synthesis of 2-Substituted 1,3-Benzoxazole-4-carbonitriles **12a**—**j**



Reagents and conditions: (a) $H_2N(CH_2)_3CO_2Et$, iPr_2NEt, CH_2Cl_2, 99%; (b) (3*S*)-3-(dimethylamino)pyrrolidine, Et_3N, DMSO, 49%; (c) 1 M NaOH aq., EtOH, 69%; (d) $SOCl_2$, CH_2Cl_2; Pyridine, 62%.

Chart 5. Synthesis of 2-(2-Oxopyrrolidin-1-yl) Derivative **14**



Reagents and conditions: (a) diamine, Et_3N, DMSO (b) TFA, CH_2Cl_2.

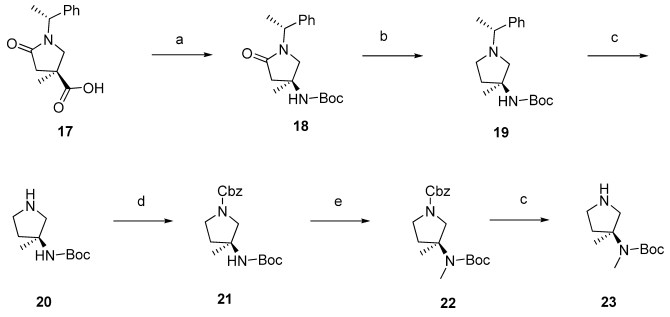
Chart 6. Synthesis of 7-Substituted 1,3-Benzoxazole-4-carbonitriles **15** and **16**

Results and Discussion

Prepared 1,3-benzoxazoles **8**—**9**, **11**—**12**, and **14**—**16**, as well as **1** and fluconazole (FLCZ) as positive control agents were evaluated for their *in vitro* antifungal activity against FLCZ-susceptible *Candida albicans* ATCC 90028 (*C. albicans-s*), FLCZ-resistant *Candida albicans* ATCC MYA-573 (*C. albicans-r*), *Candida glabrata* ATCC 48435 (*C. glabrata*), *Candida tropicalis* ATCC 44508 (*C. tropicalis*), and *Candida krusei* ATCC 44507 (*C. krusei*). Minimum inhibitory concentration MIC-1 (the lowest drug concentration showing 80% growth inhibition compared to the control without drug) was determined for each compound by using the microdilution method previously described.[11)]

MIC-1s of the 6-substituted compounds **8a**—**o** were summarized in Table 1. Phenyl derivative **8a**[11)] showed high and broad activity against *Candida* spp. with MIC-1 ranging from 0.032 to 0.125 μg/ml, while the corresponding pyridin-2-yl **8b** and pyridin-4-yl **8c** demonstrated MIC-1 ranging from 1 to >4 μg/ml, respectively. Among the five-membered heteroaromatic derivatives, thienyl derivatives **8f** and **8g** showed a broad range of activity with MIC-1s ranging from 0.032 to 0.5 μg/ml. Vinyl derivative **8h** was less active than **8a**. These results indicate that the phenyl group is considered to be the best substituent at the 6-position showing potent antifungal activity. To investigate substituent effects on the phenyl group, we prepared various substituted phenyl derivatives **8i**—**o**. Although 2- and 4-fluorophenyl derivatives **8i** and **8k** had only a moderate effect, corresponding 3-fluorophenyl analog **8j** was found to be as potent as **8a**. Replacing the 3-fluoro group with polar functionalities was not well tolerated, resulting in a two- to five-fold decrease in antifungal activities against *C. albicans* (derivatives **8l**—**o**). These results indicated that substituents on the benzene ring at the 6-position had no profound effect on antifungal activity in comparison to the unsubstituted analog **8a**.

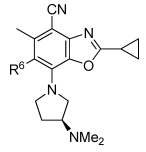
Substituents at the 2-position influenced the antifungal activity as shown in Table 2. Among the 2-carbonyl derivatives, dimethylcarbamoyl analog **11b** demonstrated potent growth inhibition against *Candida* spp., which suggested that polar groups were tolerated for antifungal activity as well as aliphatic substituents such as *tert*-butyl and cyclopropyl group. On the other hand, when the cyclopropyl group in **8a** was replaced by phenyl group, the inhibitory activity decreased significantly (**12a**). Interestingly, pyridin-2-yl analog **12b** exhibited moderate inhibition against *C. albicans* (FLCZ-susceptible and -resistant) and *C. glabrata* (MIC-1=0.25, 0.25, 0.032 μg/ml, respectively), while correspon-



Reagents and conditions: (a) diphenylphosphoryl azide, Et_3N, toluene; *t*BuOH, 60%; (b) BH_3·THF, THF, 85%; (c) H_2, 20% $Pd(OH)_2$, EtOH; (d) CbzCl, $NaHCO_3$, Et_2O–H_2O, 100%; (e) MeI, NaH, DMF, 88%.

Chart 7. Synthesis of Pyrrolidine Derivatives **20** and **23**

Table 1. *In Vitro* Activity of Compounds **8a**—**o**

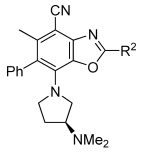


8a-o

Compd.	R^6	MIC-1 (μg/ml)[a)]				
		C. albicans-s[b)] ATCC 90028	*C. albicans-r*[c)] ATCC MYA-573	*C. glabrata* ATCC 48435	*C. tropicalis* ATCC 44508	*C. krusei* ATCC 44507
8a	Ph	0.063	0.063	0.032	0.032	0.125
8b	Pyridin-2-yl	4	4	1	2	>4
8c	Pyridin-4-yl	>4	>4	>4	>4	>4
8d	1-Me-1*H*-pyrrol-2-yl	0.5	1	0.5	0.25	0.5
8e	2-Furyl	2	2	0.25	0.5	2
8f	2-Thienyl	0.25	0.25	0.063	0.063	0.25
8g	3-Thienyl	0.25	0.25	0.032	0.063	0.5
8h	Vinyl	2	2	0.25	0.5	1
8i	2-F-Ph	0.25	0.25	0.063	0.125	0.5
8j	3-F-Ph	0.063	0.125	0.032	≤0.016	0.063
8k	4-F-Ph	16	16	2	4	>16
8l	3-NH_2-Ph	2	4	1	1	2
8m	3-(CH_2OH)-Ph	0.5	1	0.25	0.25	0.25
8n	3-OMe-Ph	0.25	0.5	0.125	0.125	0.25
8o	3-CN-Ph	0.25	0.5	0.25	0.125	0.25
1	—	0.063	0.125	0.063	0.032	2
FLCZ	—	0.25	>128	16	0.5	32

a) MIC-1s (in micrograms per milliliter) were determined by using the microdilution method. *b*) FLCZ-susceptible *C. albicans*. *c*) FLCZ-resistant *C. albicans*.

Table 2. *In Vitro* Activity of Compounds **9**, **11**, **12**, and **14**



9, 11, 12, 14

Compd.	R^2	MIC-1 (μg/ml)[a]				
		C. albicans-s[b] ATCC 90028	*C. albicans*-r[c] ATCC MYA-573	*C. glabrata* ATCC 48435	*C. tropicalis* ATCC 44508	*C. krusei* ATCC 44507
9	CO_2Et	>4	>4	0.125	1	>4
11a	CONHMe	0.25	0.25	0.032	0.063	1
11b	$CONMe_2$	0.063	0.063	0.016	0.016	0.125
12a	Ph	>4	>4	1	2	>4
12b	Pyridin-2-yl	0.25	0.25	0.032	0.125	>4
12c	Pyridin-3-yl	2	1	0.125	0.25	>16
12d	Pyridin-4-yl	>16	16	8	8	>16
12e	1-Me-1*H*-pyrrol-2-yl	0.25	0.125	0.063	0.063	4
12f	2-Furyl	0.25	0.25	0.032	0.063	>4
12g	NHMe	0.25	0.25	0.063	0.063	0.125
12h	NMe_2	0.125	0.5	0.063	0.063	1
12i	NEt_2	0.125	0.25	0.032	0.063	0.25
12j	Pyrrolidin-1-yl	1	1	0.125	0.25	>4
14	2-Oxo-pyrrolidin-1-yl	0.25	0.5	0.063	0.125	4
1	*tert*-Butyl	0.063	0.125	0.063	0.032	2
FLCZ	—	0.25	>128	16	0.5	32

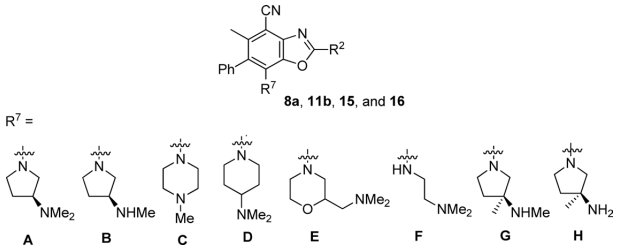
a) MIC-1s (in micrograms per milliliter) were determined by using the microdilution method. *b*) FLCZ-susceptible *C. albicans*. *c*) FLCZ-resistant *C. albicans*.

ding pyridin-3-yl and pyridin-4-yl derivatives **12c** and **12d** resulted in a loss of activity. Five-membered heteroaromatic analogs **12e** and **12f** showed activity similar to the pyridin-2-yl analog **12b**. Alkylamino analogs **12g**—**i** showed moderate activities, while pyrrolidin-1-yl **12j** had only a small effect. Interestingly, 2-oxopyrrolidin-1-yl analog **14** exhibited enhanced activity, which indicates that the carbonyl group at this position has significant effect. These facts imply that the small aliphatic groups with carbon atoms up to four, such as *tert*-butyl and cyclopropyl, or polar functionalities with a particular combination of carbon, nitrogen, and oxygen atoms, such as alkylcarbamoyl, alkylamino, and 2-oxopyrrolidon-1-yl seem to be favorable.

In the view of antifungal activities summarized in Tables 1 and 2, we focused on the basic functionality at the 7-position for further optimization by means of 2-cyclopropyl and 2-$CONMe_2$ analogs **8a** and **11b** (Table 3). Six-membered heterocycles and ethylenediamine structure at the 7-position resulted in diminished or complete loss of *in vitro* activity, whereas pyrrolidine groups showed high potency. Based on the hypothesis that the methyl group in the (dimethylamino)-pyrrolidinyl analog **8a** was easily metabolized to a corresponding mono-methyl derivative, we prepared mono-methyl **15a**. Unfortunately, replacement of NMe_2 into NHMe diminished antifungal activities. Similar results were obtained when 2-dimethylcarbamoyl **16a** was evaluated. *N*-Demethylation of the terminal amine at the 7-positon resulted in a slight loss of *in vitro* potency, suggesting that the basic center such as NHMe and NH_2 was not appropriate for antifungal activity. We considered the loss of activity was caused by the existence of proton on the nitrogen atom, which might interfere with the binding of the amine center to the appropriate binding pocket or interaction with another binding site. However, we anticipated that the conversion of the NMe_2 group into the NHMe structure could improve aqueous solubility and metabolic stability. To make full use of the physicochemically profitable moiety, we decided to retain the NHMe and to seek other ways of enhancing *in vitro* activity. Therefore, we designed 3-methyl-3-(methylamino)pyrrolidin-1-yl to cover the unfavorable N–H moiety by the incorporation of 3-methyl group adjacent to the NHMe group. As a result, (3*S*)-3-methyl-3-(methylamino)pyrrolidin-1-yl analog **16b** demonstrated potent activity against *Candida* spp. including *C. krusei* in spite of the existence of NHMe moiety on the pyrrolidine ring. These results suggest that a slight modification of 3-aminopyrrolidin-1-yl group at the 7-position influences *in vitro* activity including both the potency and the spectrum.

To investigate the relationship between the structure and physicochemical properties of the obtained compounds, we chose potent antifungal analogs **8j**, **15a**, **16a**, and **16b**. Their lipophilicity, water solubility, and metabolic stability were summarized in Table 4. The initial focus of the optimization program was aimed at modifications of amine at the 7-position designed to increase the metabolic stability. Although antifungal activity was decreased, water solubility at pH 6.8 and metabolic stability were significantly improved by replacing (dimethylamino)pyrrolidin-1-yl with (methylamino)-pyrrolidin-1-yl at the 7-position. For example, water solubilities of **8j** and **15a** at pH 6.8 were 17 and 610 μg/ml, whereas metabolic stabilities of **8j** and **15a** for mouse microsomes were 4 and 70%, respectively. It is well known that dimethylamino structure NMe_2 is easily metabolized and that low lipophilicity could improve physicochemical property. Thus,

Table 3. *In Vitro* Activity of Compounds **15** and **16**



Compd.	R^2	R^7	MIC-1 (μg/ml)[a]				
			C. albicans-s[b] ATCC 90028	*C. albicans-r*[c] ATCC MYA-573	*C. glabrata* ATCC 48435	*C. tropicalis* ATCC 44508	*C. krusei* ATCC 44507
8a	Cyclopropyl	A	0.063	0.063	0.032	0.032	0.125
15a	Cyclopropyl	B	0.25	0.25	0.063	0.125	1
15b	Cyclopropyl	C	>16	>16	>16	>16	>16
15c	Cyclopropyl	D	>16	>16	>16	>16	>16
15d	Cyclopropyl	E	>16	>16	>16	>16	>16
15e	Cyclopropyl	F	16	8	4	4	8
11b	$CONMe_2$	A	0.063	0.063	0.016	0.016	0.125
16a	$CONMe_2$	B	0.25	0.25	0.032	0.063	2
16b	$CONMe_2$	G	0.063	0.063	0.016	0.032	0.25
16c	$CONMe_2$	H	0.5	0.5	0.063	0.125	8
1	*tert*-Butyl	A	0.063	0.125	0.063	0.032	2
FLCZ	—	—	0.25	>128	16	0.5	32

a) MIC-1s (in micrograms per milliliter) were determined by using the microdilution method. *b*) FLCZ-susceptible *C. albicans*. *c*) FLCZ-resistant *C. albicans*.

Table 4. Physicochemical Properties of Selected Compounds

Compd.	MIC-1 (μg/ml) *C. albicans-s* ATCC 90028	Log D[a] (pH=7.4)	Solubility (μg/ml)[b]		Metabolic stability (% remaining)[c]		
			pH 4	pH 6.8	Mouse	Rat	Human
8j	0.063	3.9	780	17	4	0	7
15a	0.25	2.9	610	610	70	45	55
16a	0.25	1.9	760	690	66	87	80
16b	0.063	2	820	810	100	76	71
1	0.063	4.6	710	5	1	NT[d]	6

a) Log D values were determined from the partition coefficient for 1-octanol/phosphate buffer saline (PBS) at pH 7.4. *b*) Water solubility was measured at pH 4 and 6.8. *c*) Metabolic stability for mouse, rat, and human microsomes. *d*) Not tested.

we considered the improvement of the physicochemical properties of our products was caused by the modification of the terminal alkylamino moiety at the 7-position and the consequent reduced lipophilicity. The second approach was the introduction of $CONMe_2$ at the 2-position as a low lipophilic moiety. Log D value was decreased by the introduction of the $CONMe_2$ group at the 2-position (Log D=2.9 and 1.9 for **15a** and **16a**, respectively). Water solubility and metabolic stability of **16a** were somewhat improved compared to the 2-cyclopropyl analog **15a**. Surprisingly, compound **16b** demonstrated the most potent antifungal activity and improved physicochemical properties. Although **16b** possessed an additional methyl group on the pyrrolidin-1-yl at the 7-position, the Log D value was similar to that of demethyl analog **16a** (Log D=1.9 and 2 for **16a** and **16b**, respectively). Based on the results obtained above, the $CONMe_2$ group at the 2-position and the (3*S*)-3-methyl-3-(methylamino)pyrrolidin-1-yl group at the 7-position were regarded as effective in both physicochemical properties and antifungal activity.

The most potent antifungal agents **8j** and **16b** were selected as test compounds for acute systemic infection models in mice to evaluate the relationship between physicochemical properties and *in vivo* efficacy. Each compound was subcutaneously administrated at a dose of 20 and 40 mg/kg at 0 and 6 h after infection of *C. albicans* ATCC 90028. The *in vivo* efficacy was evaluated by survival rates 8 d after infection. As a result, no effect was observed for **8j** at a dose of 20 mg/kg, whereas slightly prolonged survival days were observed at a dose of 40 mg/kg (Fig. 2). On the other hand, **16b** demonstrated apparently enhanced *in vivo* efficacy compared to **8j** in a dose-dependent manner, indicated by a survival rate of 90% at the end of day eight (Fig. 3). These results suggest that the *in vivo* efficacies of our compounds are strongly influenced by their physicochemical properties.

Potent *in vitro* activities against *C. grabrata* and *C. krusei* were regarded as another attractive feature of our compounds, whereas reference compound FLCZ showed little potency against those *Candida* spp. In acute systemic infection models in mice infected with *C. glabrata*, **16b** demonstrated excellent efficacy indicated by 100% survival at a

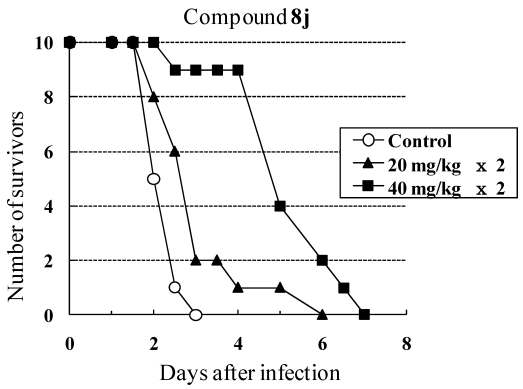


Fig. 2. *In Vivo* Efficacy of **8j** by Subcutaneous Infusion in a Model of *C. albicans* ATCC 90028 in Mice

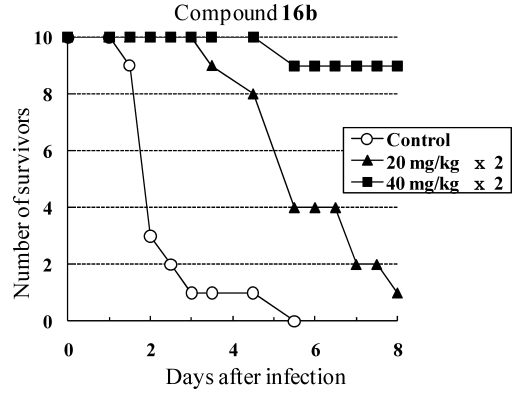


Fig. 3. *In Vivo* Efficacy of **16b** by Subcutaneous Infusion in a Model of *C. albicans* ATCC 90028 in Mice

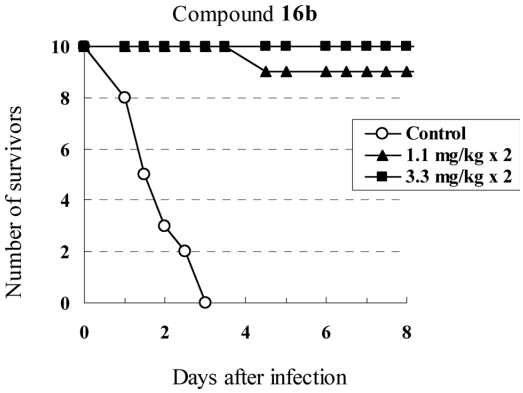


Fig. 4. *In Vivo* Efficacy of **16b** by Subcutaneous Infusion in a Model of *C. glabrata* ATCC 48435 in Mice

Table 5. Pharmacokinetic Parameters of **16b** in Mice and Rats

Species	Administration	Dose (mg/kg)	*AUC* (ng·h/ml)	$T_{1/2}$ (h)	BA[c] (%)
Mice	s.c.	10	5578[a]	2.9	
Rats	i.v.	5	1311[b]	3.2	
	p.o.	5	647[b]	4.8	68

a) $AUC_{0-24\,h}$. *b*) $AUC_{0-6\,h}$. *c*) Bioavailability calculated from the *AUC* ratio.

dose of 3.3 mg/kg in eight days after infection (Fig. 4).

Pharmacokinetic profiles of **16b** were investigated for mice and rats as shown in Table 5. It was noteworthy that a bioavailability of **16b** in rats was evaluated as 68% suggesting the possibility of **16b** as an orally and intravenously active agent. Thus, we anticipated that **16b** could be administrated both intravenously and orally in clinical therapy.

Conclusion

In summary, we have discovered a series of 1,3-benzoxazole-4-carbonitrile derivatives with potent activity against *Candida* spp. Of these, **16b** exhibited potent *in vitro* activity, water solubility, and improved metabolic stability as a potential preclinical candidate. Combination of antifungal activities and physicochemical properties was accomplished by introducing the hydrophilic $CONMe_2$ and the metabolically stable (3*S*)-3-methyl-3-(methylamino)pyrrolidin-1-yl groups at the 2- and 7-positions, respectively. Compound **16b** demonstrated potent *in vivo* efficacy against mice *Candida* infection models and good bioavailability in rats.

Experimental

Chemistry Unless otherwise noted, materials were obtained from commercial suppliers and used without further purification. Melting points were taken on a Yanako MP-500D melting point apparatus and are uncorrected. Optical rotations were measured in a 0.5-dm cell at 25 °C at 589 nm with a HORIBA SEPA-300 polarimeter. ^{1}H-NMR spectra were determined on a JEOL JNM-EX400 spectrometer. ^{13}C-NMR spectra were determined on a JEOL JNM-ECP500 spectrometer. Chemical shifts are reported in parts per million relative to tetramethylsilane as an internal standard. Significant ^{1}H-NMR data are tabulated in the following order: number of protons, multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad), and coupling constant(s) in hertz. Infrared (IR) spectra were obtained on a HORIBA FT-720 spectrometer or a JASCO FT/IR-6100 typeA. High-resolution mass spectra were obtained on a JEOL JMS-700 mass spectrometer under electron impact ionization conditions (EI), electron spray ionization conditions (ESI) or fast atom bombardment ionization conditions (FAB). Column chromatography refers to flash column chromatography conducted on Merck silica gel 60, 230—400 mesh ASTM. Thin-layer chromatography (TLC) was performed with Merck silica gel 60 F_{254} TLC plates, and compound visualization was effected with a 5% solution of molybdophosphoric acid in ethanol, UV-lamp, iodine, or Wako Ninhydrin Spray.

Ethyl 4-Cyano-7-fluoro-5-methyl-6-phenyl-1,3-benzoxazole-2-carboxylate (4) A mixture of **3**[11] (5.0 g, 20.64 mmol) and ethyl triethoxyacetate (18.2 g, 82.6 mmol) was stirred at 100 °C for 23 h. *n*-Hexane was added and the resulting precipitate was collected by filtration to afford the title compound (6.39 g, 96%) as a pale brown solid. mp: 159—161 °C. HR-MS (EI) *m/z*: 324.0908 (Calcd for $C_{18}H_{13}FN_2O_3$ 324.0911). ^{1}H-NMR ($CDCl_3$) δ: 1.52 (3H, t, J=7.1 Hz), 2.48 (3H, s), 4.60 (2H, q, J=7.12 Hz), 7.25—7.29 (2H, m), 7.48—7.56 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 14.1, 19.6 (d, J=1.9 Hz), 64.0, 102.1 (d, J=4.8 Hz), 113.9, 129.0 (2C), 129.0, 129.6 (2C), 130.6 (d, J=13.4 Hz), 131.8, 137.1 (d, J=13.4 Hz), 142.4 (d, J=1.9 Hz), 143.8 (d, J=2.9 Hz), 145.9, 147.9, 155.0 (d, J=76.8 Hz). IR (ATR): 2229, 1740, 1547, 1475, 1288, 1182, 1157, 1124, 1011, 849, 779, 727, 702 cm^{-1}. *Anal.* Calcd for $C_{18}H_{13}FN_2O_3 \cdot 0.25H_2O$: C, 65.75; H, 4.14; N, 8.52; F, 5.78. Found: C, 65.99; H, 3.96; N, 8.57; F, 5.78.

6-Bromo-2-cyclopropyl-7-fluoro-5-methyl-1,3-benzoxazole-4-carbonitrile (5) To a solution of **2**[11] (7.86 g, 32.1 mmol) and *N*,*N*-diisopropylethylamine (19.5 ml, 112 mmol) in AcOEt (300 ml) was added cyclopropanecarbonyl chloride (4.4 ml, 48.1 mmol) at 0 °C and the mixture was stirred for 16 h at room temperature. AcOEt was added and the organic layer was washed with water and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. To a solution of the residue in toluene (80 ml) was added *p*-toluenesulfonic acid monohydrate (1.60 g), and the mixture was refluxed for 19 h. After cooling to room temperature, the mixture was diluted with AcOEt and filtrated. The precipitate was recrystallized from AcOEt to give the title compound (6.02 g, 80%) as a pale red solid. mp: 164—168 °C. MS (ESI) *m/z*: 295, 297 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.27—1.34 (2H, m), 1.38—1.42 (2H, m), 2.25—2.32 (1H, m), 2.73 (3H, s). ^{13}C-NMR (DMSO-d_6) δ: 8.9, 10.5 (2C), 21.3, 98.3, 106.9 (d, J=17.3 Hz), 114.2, 135.5 (d, J=10.6 Hz), 139.3, 145.1 (d, J=196.7 Hz), 146.3, 172.5. IR (ATR): 3057, 2230, 1625, 1567, 1317, 1131, 1034 cm^{-1}. *Anal.* Calcd for $C_{12}H_8BrFN_2O$: C, 48.84; H, 2.73; N, 9.49; F, 6.44. Found: C, 49.02; H, 2.75; N, 9.57; F,

6.55.

2-Cyclopropyl-7-fluoro-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (6) A mixture of **5** (300 mg, 1.02 mmol), phenylboronic acid (256 mg, 2.03 mmol), potassium phosphate tribasic (432 mg, 2.03 mmol), and tetrakis(triphenylphosphine)palladium(0) (118 mg, 0.10 mmol) in 1,4-dioxane (6 ml) was stirred at 100 °C for 17 h under nitrogen atmosphere. The mixture was cooled to room temperature. Satd NH_4Cl aq. was added and the resultant mixture was extracted with AcOEt. The obtained organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=8/1, v/v to afford the title compound (275 mg, 92%) as a white solid. MS (ESI) *m/z*: 293 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.26—2.01 (2H, m), 2.38—2.42 (2H, m), 2.28—2.34 (1H, m), 2.40 (3H, s), 7.21—7.26 (2H, m), 7.42—7.51 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 9.5, 10.4 (2C), 19.1 (d, J=1.9 Hz), 99.1 (d, J=3.8 Hz), 115.0, 126.8 (d, J=14.4 Hz), 128.5, 128.8 (2C), 130.0 (2C), 132.7, 136.1 (d, J=13.4 Hz), 139.3, 146.3 (d, J=3.8 Hz), 146.3 (d, J=258.2 Hz), 172.0. IR (ATR): 2221, 1562, 1412, 1321, 1122, 1026, 722 cm^{-1}. *Anal.* Calcd for $C_{18}H_{13}FN_2O$: C, 73.96; H, 4.48; N, 9.58; F, 6.50. Found: C, 73.65; H, 4.47; N, 9.54; F, 6.23.

2-Chloro-7-fluoro-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (7) A mixture of **3** (500 mg, 2.06 mmol) and ethylxantic acid potassium salt (1.00 g, 6.24 mmol) in pyridine (25 ml) was refluxed for 3 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved with AcOEt. The organic layer was washed with 1 M HCl aq., water, and brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. A mixture of the residue and thionyl chloride (12 ml) was stirred for 1 h at 70 °C. The reaction mixture was concentrated *in vacuo* and diluted with CH_2Cl_2. The organic layer was washed with 1 M NaOH aq., water, and brine, and then dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2 to afford the title compound (560 mg, 95%) as a yellow solid. mp: 120—122 °C. MS (ESI) *m/z*: 287, 289 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 2.44 (3H, s), 7.20—7.27 (2H, m), 7.45—7.54 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 19.4 (d, J=2.3 Hz), 100.1 (d, J=3.8 Hz), 114.0, 128.6 (d, J=13.8 Hz), 128.9, 128.9 (2C), 129.7 (2C), 131.9, 137.4 (d, J=13.8 Hz), 141.0 (d, J=2.3 Hz), 145.9 (d, J=259.8 Hz), 144.7 (d, J=3.1 Hz), 153.9. IR (ATR): 2232, 1632, 1517, 1116 cm^{-1}. *Anal.* Calcd for $C_{15}H_8ClFN_2O$: C, 62.84; H, 2.81; N, 9.77; Cl, 12.37, F, 6.63. Found: C, 62.61; H, 2.81; N, 9.78; Cl, 12.56; F, 6.73.

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (8a) To a solution of **6** (70 mg, 0.24 mmol) in dimethyl sulfoxide (DMSO) (2 ml) were added triethylamine (50 μl, 0.36 mmol) and (3*S*)-3-(dimethylamino)pyrrolidine (40 μl, 0.31 mmol), and then the mixture was stirred at 90 °C for 14.5 h. AcOEt was added and the mixture was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH=97/3, v/v to afford the title compound (64 mg, 69%) as a white solid. MS (ESI) *m/z*: 387 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—2.30 (4H, m), 1.55—1.67 (1H, m), 1.90—1.98 (1H, m), 2.14 (6H, s), 2.17 (3H, s), 2.24 (1H, ddd, J=5.1, 8.5, 13.0 Hz), 2.48—2.57 (1H, m), 2.94 (1H, t, J=9.3 Hz), 3.22—3.39 (3H, m), 7.10 (1H, d, J=7.6 Hz), 7.23 (1H, d, J=7.6 Hz), 7.31—7.42 (3H, m). ^{13}C-NMR ($CDCl_3$) δ: 9.4 (2C), 9.6, 20.1, 30.3, 44.1 (2C), 50.9, 56.3, 65.4, 91.6, 117.2, 125.9, 127.4, 128.2, 128.6, 131.0, 131.5, 136.5, 139.2, 139.5, 139.6, 144.2, 169.4. IR (ATR): 2206, 1585, 1560, 1466, 1152, 712, 702 cm^{-1}. *Anal.* Calcd for $C_{24}H_{26}N_4O\cdot0.25H_2O$: C, 73.72; H, 6.83; N, 14.33. Found: C, 74.08; H, 6.76; N, 14.35. $[\alpha]_D^{25}$ +97.2 (c=0.746, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-pyridin-2-yl-1,3-benzoxazole-4-carbonitrile (8b) A mixture of **5** (200 mg, 0.68 mmol), 2-(tributylstannyl)pyridine (299 mg, 0.81 mmol), 2,6-di-*tert*-butyl-4-methylphenol (2 mg), and bis(triphenylphosphine)palladium(II) dichloride (24 mg, 0.03 mmol) in toluene (4 ml) was refluxed for 17 h. The reaction mixture was filtered, and the filtrate was concentrated *in vacuo*. The residue was roughly purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=3/1, v/v to afford 2-cyclopropyl-7-fluoro-5-methyl-6-pyridin-2-yl-1,3-benzoxazole-4-carbonitrile (184 mg) as a pale yellow oil. A mixture of the oil obtained above (184 mg), triethylamine (219 μl, 1.56 mmol), and (3*S*)-(dimethylamino)pyrrolidine (103 μl, 0.81 mmol) in DMSO (3.7 ml) was stirred at 90 °C for 15 h. AcOEt was added, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH=97/3, v/v. The obtained crude product was recrystallized from Et_2O to afford the title compound (108 mg, 41%) as a pale brown solid. mp: 150—151 °C. MS (ESI) *m/z*: 388 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.12—1.31 (4H, m), 1.58—1.66 (1H, m), 1.95 (1H, br s), 2.12 (6H, s), 2.16 (3H, s), 2.19—2.30 (1H, m), 2.51 (1H, br s), 2.60—3.00 (1H, m), 3.29—3.47 (3H, m), 7.27 (2H, ddd, J=0.7, 4.9, 7.3 Hz), 7.73 (1H, t, J=7.0 Hz), 8.71 (1H, d, J=4.2 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.4, 9.5, 9.6, 19.3, 30.7, 44.3 (2C), 51.0, 56.8, 65.4, 91.4, 117.0, 122.3, 124.0, 126.8, 127.4, 136.6, 139.0, 139.9, 144.6, 149.4, 158.9, 169.7. IR (ATR): 2204, 1583, 1473 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}N_5O$: C, 71.29; H, 6.50; N, 18.07. Found: C, 71.26; H, 6.48; N, 17.98. $[\alpha]_D^{25}$ +70.9 (c=1.07, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-pyridin-4-yl-1,3-benzoxazole-4-carbonitrile (8c) Following the procedure as described for **8b**, the title compound was prepared in 45% (2 steps) from **5** and 4-(tributylstannyl)pyridine as a white solid. mp: 160—161 °C. MS (ESI) *m/z*: 388 $(M+1)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.16—1.26 (4H, m), 1.49—1.59 (1H, m), 1.85—1.92 (1H, m), 2.01 (6H, s), 2.09 (3H, s), 2.28—2.35 (1H, m), 2.51—2.60 (1H, m), 2.84 (1H, dd, J=8.0, 9.5 Hz), 3.00—3.35 (3H, m), 7.21 (1H, br s), 7.35 (1H, br s), 8.63 (2H, d, J=5.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.4, 9.7, 9.8, 20.0, 30.3, 44.2 (2C), 51.3, 56.6, 65.3, 92.4, 116.7, 123.2, 126.2, 126.6, 136.2, 138.3, 139.7, 144.7, 148.4, 149.7, 150.3, 170.0. IR (ATR): 2206, 1587, 1405 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}N_5O\cdot0.5H_2O$: C, 69.67; H, 6.61; N, 17.66. Found: C, 70.05; H, 6.46; N, 17.62. $[\alpha]_D^{25}$ +79.2 (c=1.01, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-(1-methyl-1*H*-pyrrol-2-yl)-1,3-benzoxazole-4-carbonitrile (8d) Following the procedure as described for **8b**, the title compound was prepared in 40% (2 steps) from **5** and 1-methyl-2-(tributylstannyl)pyrrole as a white solid. mp: 127—128 °C. MS (ESI) *m/z*: 390 $(M+1)^+$. ^{1}H-NMR (DMSO-d_6) δ: 1.15—1.24 (4H, m), 1.53—1.62 (1H, m), 1.87—1.95 (1H, m), 2.05 (1H, s), 2.06 (3H, s), 2.07 (3H, s), 2.12 (1H, s), 2.26—2.33 (1H, m), 2.52—2.57 (1H, m), 2.65 (0.5H, dd, J=7.8, 10.0 Hz), 2.95 (0.5H, dd, J=7.8, 10.2 Hz), 3.07—3.12 (1H, m), 3.15—3.20 (1H, m), 3.21 (1.5H, s), 3.28 (1.5H, s), 3.31—3.40 (1.5H, m), 3.49—3.56 (0.5H, m), 5.87 (0.5H, dd, J=2.0, 3.7 Hz), 5.95 (0.5H, dd, J=2.0, 3.7 Hz), 6.08 (0.5H, t, J=2.9 Hz), 6.10 (0.5H, t, J=2.9 Hz), 6.81 (0.5H, dd, J=2.2, 2.7 Hz), 6.85 (0.5H, t, J=1.7, 2.4 Hz). IR (ATR): 2206, 1608, 1468 cm^{-1}. *Anal.* Calcd for $C_{23}H_{27}N_5O$: C, 70.92; H, 6.99; N, 17.98. Found: C, 70.80; H, 7.00; N, 17.95. $[\alpha]_D^{25}$ +106 (c=1.01, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-6-(2-furyl)-5-methyl-1,3-benzoxazole-4-carbonitrile (8e) Following the procedure as described for **8b**, the title compound was prepared in 29% (2 steps) from **5** and 2-(tributylstannyl)furan as a white solid. mp: 158—159 °C. HR-MS (ESI) *m/z*: 377.1936 (Calcd for $C_{22}H_{24}N_4O_2$+H 377.1978). ^{1}H-NMR (DMSO-d_6) δ: 1.12—1.26 (4H, m), 1.64—1.75 (1H, m), 2.02—2.07 (1H, m), 2.20 (6H, s), 2.22 (3H, s), 2.20—2.25 (1H, m), 2.55—2.57 (1H, m), 3.05 (1H, t, J=9.4 Hz), 3.38 (1H, dd, J=7.3, 10.3 Hz), 3.46 (1H, td, J=5.9, 10.7 Hz), 3.56 (1H, dd, J=8.8, 10.3 Hz), 6.23 (1H, d, J=3.2 Hz), 6.48 (1H, dd, J=2.0, 3.2 Hz), 7.53 (1H, s). IR (ATR): 2208, 1606, 1583, 1473, 1149 cm^{-1}. $[\alpha]_D^{25}$ +93.6 (c=0.10, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-(2-thienyl)-1,3-benzoxazole-4-carbonitrile (8f) Following the procedure as described for **8b**, the title compound was prepared in 78% (2 steps) from **5** and 2-(tributylstannyl)thiophene as a pale brown solid. MS (ESI) *m/z*: 393 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.30 (4H, m), 1.60—1.71 (1H, m), 1.96—2.03 (1H, m), 2.18 (6H, s), 2.19—2.28 (1H, m), 2.29 (3H, s), 2.51—2.60 (1H, m), 3.08 (1H, t, J=9.5 Hz), 3.39 (1H, dt, J=6.6, 10.5 Hz), 3.44—3.73 (2H, m), 6.88 (1H, dd, J=1.2, 3.4 Hz), 7.07 (1H, dd, J=3.4, 5.1 Hz), 7.40 (1H, dd, J=1.2, 5.1 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.4, 9.5, 9.6, 20.0, 30.4, 44.3 (2C), 50.7, 55.8, 65.3, 91.5, 116.6, 117.0, 126.8, 127.0, 129.7, 138.0, 139.3, 140.1, 141.6, 144.7, 169.7. IR (ATR): 2206, 1604, 1585, 1556, 1468, 1437, 1392, 1362, 1176, 1151, 852, 706 cm^{-1}. *Anal.* Calcd for $C_{22}H_{24}N_4OS\cdot0.25H_2O$: C, 66.55; H, 6.22; N, 14.11; S, 8.08. Found: C, 66.66; H, 6.08; N, 14.18; S, 8.25. $[\alpha]_D^{25}$ +93.4 (c=1.02, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-(3-thienyl)-1,3-benzoxazole-4-carbonitrile (8g) Following the procedure as described for **6** and **8a**, the title compound was prepared in 42% (2 steps) from **5** and thiophene-3-boronic acid as a pale brown solid. MS (ESI) *m/z*: 393 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.30 (4H, m), 1.58—1.69 (1H, m), 1.95—2.02 (1H, m), 2.17 (6H, s), 2.20—2.27 (1H, m), 2.22 (3H, s), 2.49—2.57 (1H, m), 2.99 (1H, dd, J=7.8, 8.5 Hz), 3.30—3.39 (2H, m), 3.42 (1H, dt, J=3.0, 8.5 Hz), 6.96 (1H, d, J=4.8 Hz), 7.05 (1H, br s), 7.38 (1H, dd, J=2.9, 4.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.4, 9.4, 9.6, 19.9, 30.3, 44.1 (2C), 50.7, 55.7, 65.3, 91.4, 117.1, 119.8, 124.9, 125.4, 130.7, 137.1, 139.1, 139.3, 140.1, 144.3, 169.5. IR (ATR): 2206, 1604, 1585, 1560, 1469, 1442, 1365, 1174, 1151 cm^{-1}. *Anal.* Calcd for $C_{22}H_{24}N_4OS\cdot0.25H_2O$: C, 66.55; H, 6.22; N, 14.11; S, 8.08. Found: C, 66.55; H, 6.07; N, 14.17; S, 8.11. $[\alpha]_D^{25}$ +92.0 (c=1.03, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-vinyl-1,3-benzoxazole-4-carbonitrile (8h) Following the procedure as described for **8b**, the title compound was prepared in 78% (2 steps) from **5** and tributyl(vinyl)tin as a white solid. MS (ESI) *m/z*: 337 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.29 (4H, m), 1.76—1.87 (1H, m), 2.13—2.26 (2H, m), 2.28 (6H, s), 2.47 (3H, s), 2.70—2.79 (1H, m), 3.52—3.61 (2H, m), 3.67 (1H, t, *J*=8.6 Hz), 3.89 (1H, dt, *J*=6.6, 10.0 Hz), 5.14 (1H, dd, *J*=1.8, 17.8 Hz), 5.58 (1H, dd, *J*=1.8, 11.2 Hz), 6.68 (1H, dd, *J*=11.2, 17.8 Hz). ^{13}C-NMR ($CDCl_3$) δ: 9.4, 9.5, 9.6, 19.7, 30.6, 44.4 (2C), 51.5, 57.2, 65.8, 92.6, 117.0, 120.1, 123.7, 134.7, 136.7, 138.7, 140.0, 143.8, 169.5. IR (ATR): 2210, 1604, 1587, 1560, 1468, 1363, 1192, 1155 cm^{-1}. *Anal.* Calcd for $C_{20}H_{24}N_4O$: C, 71.40; H, 7.19; N, 16.65. Found: C, 71.16; H, 7.20; N, 16.45. $[\alpha]_D^{25}$ +85.9 (*c*=1.03, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-6-(2-fluorophenyl)-5-methyl-1,3-benzoxazole-4-carbonitrile (8i) Following the procedure as described for **6** and **8a**, the title compound was prepared in 58% (2 steps) from **5** and 2-fluorophenylboronic acid as a white solid. MS (ESI) *m/z*: 405 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.30 (4H, m), 1.56—1.71 (1H, m), 1.90—2.03 (1H, m), 2.14 (3.6H, s), 2.15 (2.4H, s), 2.19 (3H, s), 2.20—2.29 (1H, m), 2.47—2.61 (1H, m), 2.91 (0.6H, t, *J*=9.0 Hz), 3.04 (0.4H, t, *J*=9.0 Hz), 3.26—3.44 (3H, m), 7.03—7.24 (3H, m), 7.34—7.41 (1H, m). IR (ATR): 2204, 1606, 1587, 1558, 1470, 1446, 756 cm^{-1}. *Anal.* Calcd for $C_{24}H_{25}FN_4O$: C, 71.27; H, 6.23; N, 13.85. Found: C, 71.11; H, 6.20; N, 13.66. $[\alpha]_D^{25}$ +82.1 (*c*=1.02, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-6-(3-fluorophenyl)-5-methyl-1,3-benzoxazole-4-carbonitrile (8j) Following the procedure as described for **6** and **8a**, the title compound was prepared in 58% (2 steps) from **5** and 3-fluorophenylboronic acid as a white solid. MS (ESI) *m/z*: 405 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.18—1.31 (4H, m), 1.57—1.67 (1H, m), 1.92—2.00 (1H, m), 2.15 (3H, s), 2.15 (3H, s), 2.18 (1.5H, s), 2.19 (1.5H, s), 2.20—2.27 (1H, m), 2.49—2.58 (1H, m), 2.99 (0.5H, t, *J*=9.0 Hz), 3.02 (0.5H, t, *J*=9.0 Hz), 3.21—3.40 (3H, m), 6.84 (0.5H, ddd, *J*=1.5, 2.4, 9.5 Hz), 6.91 (0.5H, dt, *J*=1.5, 7.6 Hz), 6.97 (0.5H, ddd, *J*=1.5, 2.4, 9.5 Hz), 7.03—7.09 (1.5H, m), 7.33—7.41 (1H, m). IR (ATR): 2202, 1608, 1589, 1562, 1470, 1446, 1365, 1192, 779 cm^{-1}. *Anal.* Calcd for $C_{24}H_{25}FN_4O$: C, 71.27; H, 6.23; N, 13.85. Found: C, 70.93; H, 6.21; N, 13.66. $[\alpha]_D^{25}$ +93.0 (*c*=1.01, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-6-(4-fluorophenyl)-5-methyl-1,3-benzoxazole-4-carbonitrile (8k) Following the procedure as described for **6** and **8a**, the title compound was prepared in 71% (2 steps) from **5** and 4-fluorophenylboronic acid as a white solid. MS (ESI) *m/z*: 405 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.31 (4H, m), 1.56—1.66 (1H, m), 1.92—2.00 (1H, m), 2.15 (6H, s), 2.17 (3H, s), 2.20—2.28 (1H, m), 2.47—2.56 (1H, m), 3.00 (1H, t, *J*=9.3 Hz), 3.21—3.36 (3H, m), 7.06—7.14 (3H, m), 7.19—7.23 (1H, m). IR (ATR): 2210, 1587, 1564, 1510, 1471, 1404, 1365, 1306, 1217, 1161, 1026, 951, 841 cm^{-1}. *Anal.* Calcd for $C_{24}H_{25}FN_4O$: C, 71.27; H, 6.23; N, 13.85. Found: C, 71.01; H, 6.24; N, 13.78. $[\alpha]_D^{25}$ +93.2 (*c*=1.02, $CHCl_3$).

6-(3-Aminophenyl)-2-cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-1,3-benzoxazole-4-carbonitrile (8l) Following the procedure as described for **6** and **8a**, the title compound was prepared in 94% (2 steps) from **5** and 3-aminophenylboronic acid as a white solid. MS (ESI) *m/z*: 402 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.30 (4H, m), 1.57—1.68 (1H, m), 1.89—2.01 (1H, m), 2.16 (3H, s), 2.17 (3H, s), 2.20 (1.5H, s), 2.22 (1.5H, s), 2.18—2.28 (1H, m), 2.49—2.59 (1H, m), 3.06 (0.5H, t, *J*=9.3 Hz), 3.14 (0.5H, t, *J*=9.3 Hz), 3.26 (0.5H, dt, *J*=6.6, 10.3 Hz), 3.31—3.46 (2.5H, m), 3.50—4.00 (2H, br), 6.42 (0.5H, t, *J*=2.2 Hz), 6.50 (0.5H, d, *J*=7.6 Hz), 6.54 (0.5H, t, *J*=2.2 Hz), 6.62 (0.5H, d, *J*=7.6 Hz), 6.64—6.68 (1H, m), 7.16 (1H, q, *J*=7.6 Hz). IR (ATR): 3365, 2204, 1587, 1560, 468, 1448, 1396, 1362, 1308, 1159, 868 cm^{-1}. *Anal.* Calcd for $C_{24}H_{27}N_5O \cdot 0.25H_2O$: C, 71.00; H, 6.83; N, 17.25. Found: C, 70.88; H, 6.81; N, 16.88. $[\alpha]_D^{25}$ +90.5 (*c*=1.01, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-6-[3-(hydroxymethyl)phenyl]-5-methyl-1,3-benzoxazole-4-carbonitrile (8m) Following the procedure as described for **6** and **8a**, the title compound was prepared in 83% (2 steps) from **5** and 3-(hydroxymethyl)phenylboronic acid as a pale brown solid. MS (ESI) *m/z*: 417 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.33 (4H, m), 1.54—1.67 (1H, m), 1.85—2.05 (1H, m), 2.03 (3H, s), 2.13 (1.8H, s), 2.19 (1.2H, s), 2.20—2.28 (1H, m), 2.24 (1.2H, s), 2.30—2.90 (1H, br), 2.40—2.60 (2H, m), 2.62 (0.8H, s), 2.94—3.03 (1H, m), 3.14—3.26 (0.6H, m), 3.36 (0.4H, dd, *J*=6.8, 9.8 Hz), 3.47—3.57 (1H, m), 4.62 (0.6H, d, *J*=12.7 Hz), 4.66 (0.6H, d, *J*=12.7 Hz), 4.71 (0.8H, s), 7.04 (0.4H, d, *J*=7.1 Hz), 7.16 (0.6H, d, *J*=7.1 Hz), 7.24 (0.6H, s), 7.26 (0.4H, s), 7.33—7.43 (2H, m). IR (ATR): 3340, 2210, 1606, 1587, 1560, 1468, 1398, 1363, 1155, 1030 cm^{-1}. *Anal.* Calcd for $C_{25}H_{28}N_4O_2 \cdot 0.5H_2O$: C, 70.56; H, 6.87; N, 13.17. Found: C, 70.25; H, 6.77; N, 12.91. $[\alpha]_D^{25}$ +82.6 (*c*=1.02, $CHCl_3$).

2-Cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-6-(3-methoxyphenyl)-5-methyl-1,3-benzoxazole-4-carbonitrile (8n) Following the procedure as described for **6** and **8a**, the title compound was prepared in 47% (2 steps) from **5** and 3-methoxyphenylboronic acid as a white solid. MS (ESI) *m/z*: 417 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.16—1.30 (4H, m), 1.57—1.69 (1H, m), 1.91—2.00 (1H, m), 2.16 (3H, s), 2.17 (3H, s), 2.18 (1.5H, s), 2.20 (1.5H, s), 2.20—2.28 (1H, m), 2.50—2.60 (1H, m), 3.04 (0.5H, t, *J*=9.0 Hz), 3.07 (0.5H, t, *J*=9.0 Hz), 3.21—3.42 (3H, m), 3.80 (1.5H, s), 3.82 (1.5H, s), 6.65 (0.5H, t, *J*=2.0 Hz), 6.71 (0.5H, d, *J*=7.6 Hz), 6.79 (0.5H, t, *J*=2.0 Hz), 6.84 (0.5H, d, *J*=7.6 Hz), 6.87—6.91 (1H, m), 7.29 (0.5H, d, *J*=8.5 Hz), 7.33 (0.5H, d, *J*=8.5 Hz). IR (ATR): 2204, 1608, 1585, 1562, 1466, 1363, 1309, 1240, 1198, 1159, 1041, 800, 777, 746, 700 cm^{-1}. *Anal.* Calcd for $C_{25}H_{28}N_4O_2 \cdot 0.25H_2O$: C, 71.32; H, 6.82; N, 13.31. Found: C, 71.28; H, 6.77; N, 13.11. $[\alpha]_D^{25}$ +84.5 (*c*=1.04, $CHCl_3$).

6-(3-Cyanophenyl)-2-cyclopropyl-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-1,3-benzoxazole-4-carbonitrile (8o) Following the procedure as described for **6** and **8a**, the title compound was prepared in 23% (2 steps) from **5** and 3-cyanophenylboronic acid as a white solid. MS (ESI) *m/z*: 412 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.20—1.33 (4H, m), 1.58—1.69 (1H, m), 1.92—2.02 (1H, m), 2.14 (1.5H, s), 2.14 (1.5H, s), 2.15 (3H, s), 2.16 (3H, s), 2.21—2.28 (1H, m), 2.50—2.61 (1H, m), 2.92 (0.5H, t, *J*=9.0 Hz), 3.01 (0.5H, t, *J*=9.0 Hz), 3.15 (0.5H, dt, *J*=6.6, 10.0 Hz), 3.21—3.39 (2.5H, m), 7.42 (0.5H, dt, *J*=1.2, 7.8 Hz), 7.45 (0.5H, s), 7.53—7.62 (2H, m), 7.68 (0.5H, d, *J*=9.0 Hz), 7.68 (0.5H, d, *J*=9.0 Hz). IR (ATR): 2210, 1606, 1587, 1560, 1470, 1415, 1365, 1273, 1157, 1047, 1028, 874, 818, 756 cm^{-1}. *Anal.* Calcd for $C_{25}H_{25}N_5O \cdot 0.5H_2O$: C, 71.41; H, 6.23; N, 16.65. Found: C, 71.43; H, 6.03; N, 16.36. $[\alpha]_D^{25}$ +81.0 (*c*=1.04, $CHCl_3$).

Ethyl 4-Cyano-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazole-2-carboxylate (9) To a solution of **4** (200 mg, 0.62 mmol) and triethylamine (112 μl, 0.62 mmol) in DMSO (12 ml) was added (3*S*)-3-(dimethylamino)pyrrolidine (94 μl, 0.74 mmol) in DMSO (2 ml) at 150 °C, and then the mixture was stirred at 150 °C for 1 h. The mixture was combined with AcOEt and water, extracted with AcOEt, and the organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC plates eluting with $CHCl_3$/MeOH=49/1, v/v to afford the title compound (17.5 mg, 7%) as a yellow solid. mp: 65—68 °C. MS (ESI) *m/z*: 419 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.48 (3H, t, *J*=7.1 Hz), 1.59—1.70 (1H, m), 1.97—2.05 (1H, m), 2.12 (6H, s), 2.22 (3H, s), 2.49—2.57 (1H, m), 2.91 (1H, t, *J*=10.0 Hz), 3.31 (1H, dd, *J*=7.1, 10.0 Hz), 3.50—3.58 (2H, m), 4.55 (2H, q, *J*=7.1 Hz), 7.11—7.15 (1H, m), 7.26—7.29 (1H, m), 7.36—7.46 (3H, m). IR (ATR): 2208, 1739, 1603, 1471, 1392, 1369, 1304, 1261, 1174 1149 cm^{-1}. *Anal.* Calcd for $C_{24}H_{26}N_4O_3 \cdot 0.25H_2O$: C, 68.15; H, 6.31; N, 13.25. Found: C, 68.18; H, 6.15; N, 13.02. $[\alpha]_D^{25}$ +97.2 (*c*=1.04, $CHCl_3$).

4-Cyano-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-*N*,5-dimethyl-6-phenyl-1,3-benzoxazole-2-carboxamide (11a) To a solution of methylamine hydrochloride (125 mg, 1.85 mmol) in CH_2Cl_2 (2 ml) was added trimethylaluminum (1.03 M solution in *n*-hexane) (1.80 ml, 1.85 mmol), and the mixture was stirred for 40 min at room temperature. A solution of **4** (200 mg, 617 μmol) in CH_2Cl_2 (2 ml) was added and the reaction mixture was stirred for 63 h at room temperature. The mixture was cooled in an ice bath and 1 M HCl was added. After stirring at room temperature, the mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH=100/1, v/v to afford 4-cyano-7-fluoro-*N*,5-dimethyl-6-phenyl-1,3-benzoxazole-2-carboxamide **10a** (122 mg, 64%) as a yellow solid. Following the procedure as described for **9**, the title compound was prepared in 12% from the solid obtained above as a yellow solid. mp: 214—216 °C. HR-MS (ESI) *m/z*: 404.2055 (Calcd for $C_{23}H_{25}N_5O_2$+H 404.2087). ^{1}H-NMR ($CDCl_3$) δ: 1.53—1.68 (1H, m), 1.96—2.05 (1H, m), 2.10 (6H, s), 2.21 (3H, s), 2.44—2.56 (1H, m), 2.73—2.83 (1H, m), 3.07 (1.5H, s), 3.08 (1.5H, s), 3.19—3.27 (1H, m), 3.58—3.73 (2H, m), 7.11—7.15 (1H, m), 7.23—7.27 (1H, m), 7.34—7.47 (4H, m). IR (ATR): 2206, 1655, 1595, 1475, 1456, 1394, 1369, 1309, 1151 cm^{-1}. $[\alpha]_D^{25}$ +93.1 (*c*=0.145, $CHCl_3$).

4-Cyano-7-fluoro-*N*,*N*,5-trimethyl-6-phenyl-1,3-benzoxazole-2-carboxamide (10b) Following the procedure as described for **10a**, the title compound was prepared in 67% from **4** and dimethylamine hydrochloride as a white solid. mp: 170—172 °C. MS (ESI) *m/z*: 324 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 2.47 (3H, s), 3.23 (3H, s), 3.54 (3H, s), 7.24—7.28 (2H, m), 7.46—7.55 (3H, m). IR (ATR): 2229, 1658, 1477, 1400, 1255, 1130,

1099 cm^{-1}.

4-Cyano-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-*N*,*N*,5-trimethyl-6-phenyl-1,3-benzoxazole-2-carboxamide (11b) Following the procedure as described for **9**, the title compound was prepared in 21% from **10b** as a pale brown solid. mp: 139—142 °C. MS (ESI) *m*/*z*: 418 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.55—1.68 (1H, m), 1.91—2.02 (1H, m), 2.09 (6H, s), 2.22 (3H, s), 2.43—2.55 (1H, m), 2.73—2.81 (1H, m), 3.16—3.26 (1H, m), 3.20 (3H, s), 3.51—3.68 (2H, m), 3.55 (3H, s), 7.10—7.15 (1H, m), 7.24—7.27 (1H, m), 7.34—7.45 (3H, m). IR (ATR): 2206, 1651, 1603, 1473, 1441, 1396, 1365, 1112 cm^{-1}. *Anal.* Calcd for $C_{24}H_{27}N_5O_2\cdot 0.25H_2O$: C, 68.31; H, 6.57; N, 16.60. Found: C, 68.43; H, 6.49; N, 16.37. $[\alpha]_D^{25}$ +84.4 (*c*=0.736, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-2,6-diphenyl-1,3-benzoxazole-4-carbonitrile (12a) A mixture of **7** (200 mg, 0.70 mmol), phenylboronic acid (171 mg, 1.40 mmol), tetrakis(triphenylphosphine)palladium(0) (81 mg, 0.07 mmol), and potassium phosphate (297 mg, 1.40 mmol) in 1,4-dioxane (20 ml) was refluxed for 1 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=6/1, v/v to afford 7-fluoro-5-methyl-2,6-diphenyl-1,3-benzoxazole-4-carbonitrile (161 mg, 70%) as a pale yellow solid. mp: >270 °C. MS(ESI) *m*/*z*: 329 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 2.45 (3H, s), 7.28—7.34 (2H, m), 7.45—7.62 (6H, m), 7.71—7.78 (1H, m), 8.30—8.35 (1H, m).

A mixture of the carbonitrile (156 mg, 0.475 mmol), triethylamine (150 μl), and (3*S*)-(dimethylamino)pyrrolidine (90 μl, 0.71 mmol) in DMSO (6 ml) was stirred at 130 °C for 3 h. The reaction mixture was concentrated *in vacuo*, diluted with $CHCl_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC plates eluting with $CHCl_3$/MeOH=9/1, v/v. The obtained crude product was recrystallized from EtOH/*i*-Pr_2O to afford the title compound (63 mg, 31%) as a pale yellow solid. mp: 205—214 °C. MS (EI) *m*/*z*: 422 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.63—1.74 (1H, m), 1.97—2.08 (1H, m), 2.17 (6H, s), 2.22 (3H, s), 2.57 (1H, br s), 3.07 (1H, t, *J*=8.4 Hz), 3.39—3.54 (3H, m), 7.15 (1H, d, *J*=8.0 Hz), 7.26—7.30 (1H, m), 7.35—7.47 (3H, m), 7.51—7.58 (3H, m), 8.24 (2H, dd, *J*=1.6, 7.6 Hz). IR (ATR): 2206, 1598, 1550, 1466, 1365, 1200 cm^{-1}. *Anal.* Calcd for $C_{27}H_{26}N_4O\cdot 0.25H_2O$: C, 75.94; H, 6.25; N, 13.12. Found: C, 75.72; H, 6.08; N, 12.94. $[\alpha]_D^{25}$ +103.8 (*c*=1.01, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-2-pyridin-2-yl-1,3-benzoxazole-4-carbonitrile (12b) To a suspension of picolinic acid (271 mg, 2.2 mmol) in CH_2Cl_2 (7 ml) were added oxalyl chloride (262 μl, 3 mmol) and catalytic *N*,*N*-dimethylformamide (DMF) at 0 °C, and then the resulting mixture was stirred for 20 min at room temperature. *N*,*N*-diisopropylethylamine (697 μl, 4 mmol) and **3** (485 mg, 2.0 mmol) were added and the mixture was stirred for 2 h. The reaction mixture was diluted with $CHCl_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. To a solution of the residue in xylene (20 ml) was added catalytic *p*-toluenesulfonic acid monohydrate, and then the mixture was refluxed for 12 h. The mixture was diluted with $CHCl_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was roughly purified by silica gel column chromatography eluting with $CHCl_3$/MeOH=98/2, v/v to afford 7-fluoro-5-methyl-6-phenyl-2-pyridin-2-yl-1,3-benzoxazole-4-carbonitrile.

A mixture of the carbonitrile, (3*S*)-3-(dimethylamino)pyrrolidine (129 μl, 1.02 mmol), and triethylamine (150 μl) in DMSO (8 ml) was stirred at 100 °C for 3 h. The reaction mixture was concentrated *in vacuo*, diluted with $CHCl_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with $CHCl_3$/MeOH=9/1, v/v. The obtained crude product was recrystallized from EtOH/*i*-Pr_2O to afford the title compound (190 mg, 22%) as a yellow solid. mp: 227—233 °C. MS (ESI) *m*/*z*: 424 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.73 (1H, m), 2.02—2.10 (1H, m), 2.13 (6H, s), 2.24 (3H, s), 2.50—2.62 (1H, m), 2.85—2.93 (1H, m), 3.30 (1H, dd, *J*=7.2, 9.6 Hz), 3.60—3.74 (2H, m), 7.13—7.17 (1H, m), 7.26—7.30 (1H, m), 7.35—7.49 (4H, m), 7.89 (1H, dt, *J*=2.0, 7.6 Hz), 8.40 (1H, d, *J*=8.0 Hz), 8.79—8.81 (1H, m). IR (ATR): 2206, 1604, 1581, 1458, 1435, 1367 cm^{-1}. *Anal.* Calcd for $C_{26}H_{25}N_5O\cdot 0.75H_2O$: C, 71.46; H, 6.11; N, 16.02. Found: C, 71.70; H, 5.87; N, 15.75. $[\alpha]_D^{25}$ +113.2 (*c*=1.01, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-2-pyridin-3-yl-1,3-benzoxazole-4-carbonitrile (12c) Following the procedure as described for **12b**, the title compound was prepared in 60% (3 steps) from **3** and nicotinoyl chloride hydrochloride as a yellow solid. mp: 192—194 °C. MS (ESI) *m*/*z*: 424 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.72 (1H, m), 1.97—2.06 (1H, m), 2.16 (6H, s), 2.23 (3H, s), 2.50—2.60 (1H, m), 3.02 (1H, t, *J*=9.2 Hz), 3.37—3.56 (3H, m), 7.13—7.17 (1H, m), 7.26—7.30 (1H, m), 7.34—7.51 (4H, m), 8.56 (1H, dt, *J*=8.1, 1.7 Hz), 8.79 (1H, dd, *J*=4.9, 1.7 Hz), 9.41 (1H, dd, *J*=2.2, 0.7 Hz). IR (ATR): 2968, 2945, 2868, 2823, 2777, 2206, 1593, 1549, 1471, 1446, 1396, 1367, 1302, 1277, 1192, 1163, 1091, 1059, 1014, 935, 862, 820, 789, 723 cm^{-1}. *Anal.* Calcd for $C_{26}H_{25}N_5O$: C, 73.74; H, 5.95; N, 16.54. Found: C, 73.54; H, 5.92; N, 16.44. $[\alpha]_D^{25}$ +111.7 (*c*=1.01, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-2-pyridin-4-yl-1,3-benzoxazole-4-carbonitrile (12d) Following the procedure as described for **12b**, the title compound was prepared in 21% (3 steps) from **3** and isonicotinoyl chloride hydrochloride as a yellow solid. mp: 227—229 °C. MS (ESI) *m*/*z*: 424 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.60—1.72 (1H, m), 1.98—2.06 (1H, m), 2.16 (6H, s), 2.24 (3H, s), 2.50—2.61 (1H, m), 3.04 (1H, t, *J*=9.2 Hz), 3.36—3.48 (2H, m), 3.49—3.56 (1H, m), 7.13—7.16 (1H, m), 7.26—7.29 (1H, m), 7.35—7.46 (3H, m), 8.07 (2H, dd, *J*=4.4, 1.7 Hz), 8.83 (2H, dd, *J*=4.4, 1.7 Hz). IR (ATR): 3051, 2947, 2868, 2821, 2773, 2210, 1595, 1541, 1469, 1441, 1396, 1365, 1302, 1271, 1196, 1155, 1095, 1057, 989, 939, 862, 831, 783, 702 cm^{-1}. *Anal.* Calcd for $C_{26}H_{25}N_5O$: C, 73.74; H, 5.95; N, 16.54. Found: C, 73.73; H, 5.92; N, 16.55. $[\alpha]_D^{25}$ +115.3 (*c*=1.05, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-2-(1-methyl-1*H*-pyrrol-2-yl)-6-phenyl-1,3-benzoxazole-4-carbonitrile (12e) A mixture of **7** (200 mg, 0.70 mmol), 1-methyl-2-(tributylstannyl)pyrrole (389 mg, 1.05 mmol), 2,6-di-*tert*-butyl-4-methylphenol (2 mg), and bis(triphenylphosphine)palladium(II) dichloride (49 mg, 0.07 mmol) in toluene (20 ml) was refluxed for 3 h. The reaction mixture was filtered and the filtrate was concentrated *in vacuo*. The residue was roughly purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=5/1, v/v to afford 7-fluoro-5-methyl-2-(1-methyl-1*H*-pyrrol-2-yl)-6-phenyl-1,3-benzoxazole-4-carbonitrile (50 mg) as a pale yellow oil. A mixture of the carbonitrile, triethylamine (100 μl), and (3*S*)-(dimethylamino)pyrrolidine (53 μl, 0.42 mmol) in DMSO (2 ml) was stirred at 110 °C for 3.5 h. The reaction mixture was concentrated *in vacuo*, diluted with $CHCl_3$, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC plates eluting with $CHCl_3$/MeOH=9/1, v/v. The obtained crude product was recrystallized from EtOH/*i*-Pr_2O to afford the title compound (24 mg, 6%) as a white solid. mp: 188—191 °C. MS (EI) *m*/*z*: 425 (M^+). ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.67 (1H, m), 1.93—2.01 (1H, m), 2.15 (6H, s), 2.21 (3H, s), 2.53 (1H, br s), 3.01 (1H, t, *J*=8.8 Hz), 3.30—3.47 (3H, m), 4.19 (3H, s), 6.24 (1H, dd, *J*=2.8, 4.0 Hz), 6.89 (1H, t, *J*=2.0 Hz), 6.99 (1H, dd, *J*=2.0, 4.0 Hz), 7.14 (1H, d, *J*=7.2 Hz), 7.25—7.29 (1H, m), 7.35—7.45 (3H, m). IR (ATR): 2206, 1616, 1589, 1565, 1457, 1400, 1361, 1090 cm^{-1}. *Anal.* Calcd for $C_{26}H_{27}N_5O\cdot 0.5H_2O$: C, 71.87; H, 6.49; N, 16.12. Found: C, 72.12; H, 6.30; N, 16.22. $[\alpha]_D^{25}$ +121.9 (*c*=0.421, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-2-(2-furyl)-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (12f) Following the procedure as described for **12b**, the title compound was prepared in 28% (3 steps) from **3** and 2-furoyl chloride as a white solid. MS (ESI) *m*/*z*: 413 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.59—1.70 (1H, m), 1.95—2.03 (1H, m), 2.15 (6H, s), 2.20 (3H, s), 2.50—2.60 (1H, m), 2.98 (1H, t, *J*=9.3 Hz), 3.33—3.51 (3H, m), 6.63 (1H, dd, *J*=1.7, 3.4 Hz), 7.14 (1H, d, *J*=7.1 Hz), 7.27 (1H, d, *J*=7.1 Hz), 7.31 (1H, d, *J*=3.4 Hz), 7.33—7.45 (3H, m), 7.67 (1H, d, *J*=1.7 Hz). IR (ATR): 3597, 2202, 1595, 1442, 1363, 1302, 746, 727, 708 cm^{-1}. *Anal.* Calcd for $C_{25}H_{24}N_4O_2\cdot 1.0H_2O$: C, 69.75; H, 6.09; N, 13.01. Found: C, 70.10; H, 5.99; N, 12.90. $[\alpha]_D^{25}$ +82.9 (*c*=0.336, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-2-(methylamino)-6-phenyl-1,3-benzoxazole-4-carbonitrile (12g) To a solution of **7** (0.20 g, 0.70 mmol) in CH_2Cl_2 (10 ml) were added *N*,*N*-diisopropylethylamine (0.15 ml, 0.88 mmol) and methylamine (2 M in tetrahydrofuran (THF), 0.50 ml, 1.00 mmol), and the mixture was heated at 60 °C for 3 h in a sealed tube. The reaction mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was roughly purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH=50/1, v/v to afford 7-fluoro-5-methyl-2-(methylamino)-6-phenyl-1,3-benzoxazole-4-carbonitrile (170 mg). A mixture of the carbonitrile (170 mg), triethylamine (0.17 ml, 1.23 mmol), and (3*S*)-3-(dimethylamino)pyrrolidine (0.16 ml, 1.26 mmol) in DMSO (5 ml) was heated at 150 °C for 4 h in a sealed tube. The mixture was diluted with CH_2Cl_2, washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with CH_2Cl_2/MeOH=10/1, v/v to afford the title compound (68.3 mg, 26%) as a pale yellow solid. mp: 212—214 °C. MS (ESI) *m*/*z*: 376 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.65 (1H, m), 1.85—2.00 (1H, m), 2.13 (6H, s), 2.16 (3H, s), 2.50—2.60 (1H, m), 2.90—3.00 (1H, m), 3.15—3.25 (4H, m), 3.25—

3.35 (2H, m), 7.12 (1H, d, J=7.3 Hz), 7.20—7.25 (1H, m), 7.30—7.45 (4H, m). *Anal.* Calcd for $C_{22}H_{25}N_5O$: C, 70.38; H, 6.71; N, 18.65. Found: C, 69.98; H, 6.73; N, 18.39. $[\alpha]_D^{25}$ +118 (c=0.791, $CHCl_3$).

2-(Dimethylamino)-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (12h) Following the procedure as described for **12g**, the title compound was prepared in 29% (2 steps) from **7** and dimethylamine as a pale yellow solid. MS (ESI) m/z: 390 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.65 (1H, m), 1.85—1.95 (1H, m), 2.12 (6H, s), 2.15 (3H, s), 2.45—2.60 (1H, m), 2.90—3.00 (1H, m), 3.10—3.35 (3H, m), 3.22 (6H, s), 7.10—7.15 (1H, m), 7.20—7.25 (1H, m), 7.30—7.40 (3H, m). *Anal.* Calcd for $C_{23}H_{27}N_5O \cdot 0.25H_2O$: C, 70.11; H, 7.03; N, 17.77. Found: C, 70.36; H, 6.94; N, 17.83. $[\alpha]_D^{25}$ +100.5 (c=0.989, $CHCl_3$).

2-(Diethylamino)-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (12i) Following the procedure as described for **12g**, the title compound was prepared in 53% (2 steps) from **7** and diethylamine as a brown solid. MS (ESI) m/z: 418 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.28 (6H, t, J=7.1 Hz), 1.50—1.61 (1H, m), 1.85—1.95 (1H, m), 2.13 (6H, s), 2.14 (3H, s), 2.45—2.55 (1H, m), 2.96 (1H, t, J=9.0 Hz), 3.11 (1H, dt, J=6.9, 10.0 Hz), 3.24 (1H, t, J=8.3 Hz), 3.33 (1H, dt, J=7.1, 9.0 Hz), 3.55—3.67 (4H, m), 7.11 (1H, d, J=7.3 Hz), 7.23 (1H, d, J=7.3 Hz), 7.28—7.40 (3H, m). IR (ATR): 2208, 1633, 1599, 1560 cm^{-1}. *Anal.* Calcd for $C_{25}H_{31}N_5O \cdot 0.25H_2O$: C, 71.15; H, 7.52; N, 16.59. Found: C, 71.09; H, 7.51; N, 16.40. $[\alpha]_D^{25}$ +97.8 (c=1.01, $CHCl_3$).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-2-pyrrolidin-1-yl-1,3-benzoxazole-4-carbonitrile (12j) Following the procedure as described for **12g**, the title compound was prepared in 28% (2 steps) from **7** and pyrrolidine as a pale yellow solid. MS (ESI) m/z: 416 $(M+H)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.50—1.65 (1H, m), 1.85—1.95 (1H, m), 2.00—2.10 (4H, m), 2.13 (6H, s), 2.15 (3H, s), 2.45—2.60 (1H, m), 2.95—3.05 (1H, m), 3.10—3.20 (1H, m), 3.20—3.35 (2H, m), 3.60—3.75 (4H, m), 7.11 (1H, d, J=7.3 Hz), 7.22 (1H, d, J=7.6 Hz), 7.25—7.40 (3H, m). *Anal.* Calcd for $C_{25}H_{29}N_5O \cdot 0.25\ H_2O$: C, 71.49; H, 7.08; N, 16.67. Found: C, 71.58; H, 7.06; N, 16.47. $[\alpha]_D^{25}$ +97.2 (c=1.05, $CHCl_3$).

Ethyl 4-({4-Cyano-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazol-2-yl}amino)butanoate (13) To a solution of **7** (213 mg, 0.743 mmol) in CH_2Cl_2 (7 ml) were added ethyl 4-aminobutyrate hydrochloride (149 mg, 0.892 mmol) and *N*,*N*-diisopropylamine (303 μl, 1.78 mmol) at 0 °C, and then the mixture was stirred at room temperature for 15 h. The mixture was concentrated *in vacuo* and diluted with AcOEt. The mixture was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=1/1, v/v to afford ethyl 4-({4-cyano-7-fluoro-5-methyl-6-phenyl-1,3-benzoxazol-2-yl}amino)butanoate (279 mg, 99%) as a white solid.

Following the procedure as described for **12g**, the title compound was prepared in 49% from the solid obtained above as a brown oil. MS (ESI) m/z: 476 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.26 (3H, t, J=7.1 Hz), 1.49—1.61 (1H, m), 1.86—1.95 (1H, m), 1.98—2.07 (2H, m), 2.13 (6H, s), 2.15 (3H, s), 2.43—2.49 (2H, m), 2.49—2.58 (1H, m), 2.87—2.96 (1H, m), 3.14—3.29 (3H, m), 3.60 (2H, q, J=6.5 Hz), 4.15 (2H, q, J=7.2 Hz), 5.72 (1H, br s), 7.09—7.13 (1H, m), 7.21—7.41 (4H, m).

7-[(3*S*)-3-(Dimethylamino)pyrrolidin-1-yl]-5-methyl-2-(2-oxopyrrolidin-1-yl)-6-phenyl-1,3-benzoxazole-4-carbonitrile (14) To a solution of **13** (170 mg, 0.357 mmol) in EtOH (3.5 ml) was added 1 M NaOH aq. (536 μl, 0.536 mmol) and the mixture was stirred at room temperature for 15 h. The mixture was cooled in an ice bath and 1 M HCl aq. (536 μl, 0.536 mmol) was added. The mixture was concentrated *in vacuo*. The residue was purified by preparative TLC plates eluting with $CHCl_3$/MeOH=5/1, v/v to afford 4-({4-Cyano-7-[(3*S*)-3-(dimethylamino)pyrrolidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazol-2-yl}amino)butanoic acid (110 mg, 69%) as a pale brown foam.

To a solution of the foam (90.0 mg, 0.201 mmol) in CH_2Cl_2 (2 ml) was added thionyl chloride (43.5 μl, 0.603 mmol) and the mixture was stirred at room temperature for 1 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved with pyridine (2 ml). After stirred at 70 °C for 1 h, the mixture was concentrated *in vacuo*, diluted with $CHCl_3$, and washed with brine. The organic layer was dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by preparative TLC plates eluting with $CHCl_3$/MeOH=10/1, v/v to afford the title compound (54 mg, 62%) as a white solid. mp: 196—198 °C. MS (ESI) m/z: 430 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.51—1.66 (1H, m), 1.91—2.01 (1H, m), 2.13 (6H, s), 2.18 (3H, s), 2.22—2.32 (2H, m), 2.45—2.55 (1H, m), 2.67 (2H, t, J=8.1 Hz), 2.94 (1H, t, J=9.4 Hz), 3.31—3.44 (3H, m), 4.19 (2H, t, J=7.2 Hz), 7.12 (1H, d, J=7.1 Hz), 7.23—7.28 (1H, m), 7.31—7.43 (3H, m). IR (ATR): 2974, 2952, 2871, 2821, 2773, 2210, 1743, 1593, 1552, 1468, 1441, 1408, 1389, 1363, 1304, 1248, 1186, 1155, 1063, 1005, 935, 918, 837 cm^{-1}. *Anal.* Calcd for $C_{25}H_{27}N_5O_2 \cdot 0.25H_2O$: C, 69.18; H, 6.39; N, 16.14. Found: C, 69.14; H, 6.24; N, 16.04. $[\alpha]_D^{25}$ +92.3 (c=1.03, $CHCl_3$).

2-Cyclopropyl-5-methyl-7-[(3*S*)-3-(methylamino)pyrrolidin-1-yl]-6-phenyl-1,3-benzoxazole-4-carbonitrile (15a) Following the procedure as described for **8a**, the title compound was prepared in 63% from **6** and (3*S*)-3-(methylamino)pyrrolidine as a white solid. MS (ESI) m/z: 373 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.17—1.30 (4H, m), 1.59 (1H, dq, J=6.6, 6.6 Hz), 1.87—1.96 (1H, m), 2.17 (3H, s), 2.20—2.27 (1H, m), 2.32 (3H, s), 2.92 (1H, dd, J=5.1, 10.0 Hz), 3.07 (1H, dq, J=5.1, 5.1 Hz), 3.20—3.27 (2H, m), 3.32—3.38 (1H, m), 7.16—7.20 (2H, m), 7.32—7.42 (3H, m). IR (ATR): 3346, 2200, 1608, 1587, 1562, 1465, 1438, 1365, 1340, 1302 cm^{-1}. *Anal.* Calcd for $C_{23}H_{24}N_4O \cdot 0.25H_2O$: C, 73.28; H, 6.55; N, 14.86. Found: C, 73.46; H, 6.43; N, 14.68. $[\alpha]_D^{25}$ +6.91 (c=1.02, $CHCl_3$).

2-Cyclopropyl-5-methyl-7-(4-methylpiperazin-1-yl)-6-phenyl-1,3-benzoxazole-4-carbonitrile (15b) Following the procedure as described for **8a**, the title compound was prepared in 7% from **6** and 1-methylpiperazine as a brown solid. mp: 176—178 °C. MS (FAB) m/z: 373 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.18—1.34 (4H, m), 2.10—2.30 (11H, m), 3.04—3.11 (4H, m), 7.16—7.20 (2H, m), 7.33—7.47 (3H, m). IR (ATR): 3627, 3016, 2931, 2841, 2794, 2744, 2684, 2218, 1608, 1593, 1564, 1448, 1400, 1375, 1294, 1267, 1227, 1194, 1153, 1099, 1072, 1036, 1007, 974, 951 cm^{-1}. *Anal.* Calcd for $C_{23}H_{24}N_4O \cdot 0.25H_2O$: C, 73.28; H, 6.55; N, 14.86. Found: C, 73.30; H, 6.41; N, 14.52.

2-Cyclopropyl-7-[4-(dimethylamino)piperidin-1-yl]-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (15c) Following the procedure as described for **8a**, the title compound was prepared in 50% from **6** and 4-(dimethylamino)piperidine as a white solid. mp: 157—159 °C. MS (ESI) m/z: 401 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.08—1.17 (2H, m), 1.21—1.34 (4H, m), 1.50—1.70 (2H, m), 2.07—2.17 (1H, m), 2.22 (6H, s), 2.22—2.28 (1H, m), 2.28 (3H, s), 2.81—2.90 (2H, m), 3.22—3.30 (2H, m), 7.17—7.20 (2H, m), 7.32—7.37 (1H, m), 7.42—7.46 (2H, m). IR (ATR): 2945, 2821, 2771, 2218, 1608, 1593, 1564, 1458, 1398, 1377, 1296, 1240, 1194, 1134, 1099, 1059, 1030, 951, 877, 814 cm^{-1}. *Anal.* Calcd for $C_{25}H_{28}N_4O \cdot 0.25H_2O$: C, 74.14; H, 7.09; N, 13.83. Found: C, 73.81; H, 7.04; N, 13.54.

2-Cyclopropyl-7-{2-[(dimethylamino)methyl]morpholin-4-yl}-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (15d) Following the procedure as described for **8a**, the title compound was prepared in 23% from **6** and *N*,*N*-dimethyl(morpholin-2-yl)methanamine as a brown solid. mp: 135—137 °C. MS (FAB) m/z: 417 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.21—1.34 (4H, m), 1.93 (1H, dd, J=4.5, 12.6 Hz), 2.14 (6H, s), 2.21—2.36 (2H, m), 2.29 (3H, s), 2.70 (1H, dd, J=9.9, 12.1 Hz), 2.92—2.99 (1H, m), 3.04 (1H, dt, J=2.2, 12.2 Hz), 3.13 (1H, td, J=2.9, 11.6 Hz), 3.20—3.28 (1H, m), 3.34 (1H, td, J=2.6, 11.1 Hz), 3.69—3.75 (1H, m), 7.17—7.23 (2H, m), 7.33—7.47 (3H, m). IR (ATR): 2943, 2856, 2821, 2769, 2216, 1608, 1593, 1444, 1400, 1354, 1290, 1277, 1252, 1196, 1140, 1105, 1065, 1041, 989, 949, 887, 845, 781 cm^{-1}. *Anal.* Calcd for $C_{25}H_{28}N_4O_2$: C, 72.09; H, 6.78; N, 13.45. Found: C, 71.81; H, 6.73; N, 13.46.

2-Cyclopropyl-7-{[2-(dimethylamino)ethyl]amino}-5-methyl-6-phenyl-1,3-benzoxazole-4-carbonitrile (15e) Following the procedure as described for **8a**, the title compound was prepared in 25% from **6** and *N*,*N*-dimethylethylenediamine as a white solid. MS (FAB) m/z: 361 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.15—1.32 (4H, m), 2.08 (6H, s), 2.19 (3H, s), 2.21—2.28 (1H, m), 2.30—2.40 (2H, m), 3.48—3.59 (2H, m), 4.38—4.48 (1H, m), 7.12—7.17 (2H, m), 7.38—7.44 (1H, m), 7.45—7.53 (2H, m). IR (ATR): 3369, 3057, 2979, 2945, 2862, 2823, 2785, 2210, 1616, 1566, 1506, 1487, 1450, 1410, 1362, 1304, 1252, 1200, 1144, 1113, 1061, 960, 872 cm^{-1}. *Anal.* Calcd for $C_{22}H_{24}N_4O \cdot 0.25H_2O$: C, 72.40; H, 6.77; N, 15.35. Found: C, 72.28; H, 6.62; N, 15.09.

4-Cyano-*N*,*N*,5-trimethyl-7-[(3*S*)-3-(methylamino)pyrrolidin-1-yl]-6-phenyl-1,3-benzoxazole-2-carboxamide (16a) Following the procedure as described for **9**, the title compound was prepared in 34% from **10b** and (3*S*)-3-(methylamino)pyrrolidine as a pale yellow solid. mp: 148—151 °C. MS (ESI) m/z: 404 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.58—1.67 (1H, m), 1.86—1.96 (1H, m), 2.22 (3H, s), 2.31 (3H, s), 2.94—2.98 (1H, m), 3.05—3.12 (1H, m), 3.20 (3H, s), 3.28—3.33 (1H, m), 3.52—3.36 (2H, m), 3.56 (3H, s), 7.18—7.20 (2H, m), 7.35—7.44 (3H, m). IR (ATR): 2208, 1652, 1602, 1467, 1438, 1396, 1365, 1111, 704 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}N_5O_2 \cdot 0.25H_2O$: C, 67.71; H, 6.30; N, 17.17. Found: C, 67.59; H, 6.23; N, 16.84. $[\alpha]_D^{25}$ −7.77 (c=1.02, $CHCl_3$).

4-Cyano-*N*,*N*,5-trimethyl-7-[(3*S*)-3-methyl-3-(methylamino)pyrrolidin-1-yl]-6-phenyl-1,3-benzoxazole-2-carboxamide (16b) To a solution of **10b** (400 mg, 1.24 mmol) in DMSO (6 ml) were added **23** (318 mg,

1.48 mmol) and triethylamine (241 μl, 1.73 mmol) in DMSO (1 ml) at 150 °C, and then the mixture was stirred at 150 °C for 30 min. The mixture was concentrated *in vacuo*, diluted with AcOEt. The mixture was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was roughly purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=1/2, v/v to afford the crude Boc-**16b** as a yellow foam. To a solution of the crude foam in CH_2Cl_2 (3 ml) was added trifluoracetic acid (6 ml) at 0 °C and the mixture was stirred at room temperature for 5 h. The mixture was concentrated *in vacuo* and neutralized with satd $NaHCO_3$ aq. The mixture was extracted with $CHCl_3$ and the organic layer was concentrated *in vacuo*. The residue was purified by preparative TLC plates eluting with $CHCl_3$/MeOH=10/1, v/v to afford the compound (109 mg, 21%) as a pale yellow solid. mp: 172—174 °C. MS (ESI) *m/z*: 418 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.13 (3H, s), 1.55—1.85 (2H, m), 2.23 (3H, s), 2.27 (3H, s), 3.07 (1H, d, *J*=10.50 Hz), 3.20 (3H, s), 3.18—3.40 (3H, m), 3.55 (3H, s), 7.16—7.46 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 20.4, 22.1, 29.7, 36.5, 36.5, 39.0, 50.6, 60.0, 62.5, 92.4, 116.8, 127.4, 127.7, 128.5, 128.5, 131.0, 131.1, 137.7, 139.3, 139.6, 141.3, 142.2, 155.6, 157.0. IR (ATR): 3319, 2962, 2929, 2856, 2798, 2212, 1655, 1604, 1577, 1471, 1442, 1396, 1367, 1308, 1259, 1201, 1153, 1111, 1070, 1016, 970, 916, 785 cm^{-1}. *Anal.* Calcd for $C_{24}H_{27}N_5O_2\cdot 0.5H_2O$: C, 67.59; H, 6.62; N, 16.42. Found: C, 67.72; H, 6.46; N, 16.24. $[\alpha]_D^{25}$ +13.5 (*c*=1.04, $CHCl_3$).

7-[(3*S*)-3-Amino-3-methylpyrrolidin-1-yl]-4-cyano-*N*,*N*,5-trimethyl-6-phenyl-1,3-benzoxazole-2-carboxamide (16c) Following the procedure as described for **16b**, the title compound was prepared in 41% from **10b** and **20** as a pale yellow solid. mp: 202—204 °C. MS (ESI) *m/z*: 404 $(M+1)^+$. ^{1}H-NMR ($CDCl_3$) δ: 1.16 (3H, s), 1.51—1.71 (2H, m), 2.23 (3H, s), 3.20 (3H, s), 3.12—3.33 (4H, m), 3.56 (3H, s), 7.14—7.46 (5H, m). IR (ATR): 2956, 2931, 2871, 2212, 1720, 1655, 1604, 1577, 1473, 1444, 1396, 1367, 1306, 1259, 1203, 1153, 1111, 1070, 1016, 970, 904, 866, 831 cm^{-1}. *Anal.* Calcd for $C_{23}H_{25}N_5O_2\cdot 0.25H_2O$: C, 67.71; H, 6.30; N, 17.17. Found: C, 67.67; H, 6.14; N, 16.90. $[\alpha]_D^{25}$ −17.6 (*c*=1.02, $CHCl_3$).

***tert*-Butyl {(3*S*)-3-Methyl-5-oxo-1-[(1*R*)-1-phenylethyl]pyrrolidin-3-yl}carbamate (18)** To a stirred solution of (3*S*)-3-methyl-5-oxo-1-[(1*R*)-1-phenylethyl]pyrrolidine-3-carboxylic acid (**17**)[15] (652 mg, 2.64 mmol) in toluene (20 ml) were added triethylamine (735 μl, 5.27 mmol) and diphenylphosphoryl azide (739 μl, 3.43 mmol), and the mixture was stirred for 30 min at room temperature. After being refluxed for 3 h, 2-methyl-2-propanol (20 ml) was added and the mixture was refluxed for 11 h. The reaction mixture was concentrated *in vacuo* and the residue was dissolved with AcOEt. The organic layer was washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The residue was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=2/1 to 1//4, v/v to afford the title compound (500 mg, 60%) as a colorless oil. HR-MS (ESI) *m/z*: 319.2011 (Calcd for $C_{18}H_{26}N_2O_3$+H 319.2022). ^{1}H-NMR ($CDCl_3$) δ: 1.35 (9H, s), 1.47 (3H, s), 1.51 (3H, d, *J*=7.08 Hz), 2.43 (1H, d, *J*=16.60 Hz), 2.66 (1H, d, *J*=16.60 Hz), 3.20—3.33 (2H, m), 4.54 (1H, s), 5.51 (1H, q, *J*=7.08 Hz), 7.24—7.35 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 16.2, 25.2, 28.3 (3C), 45.7, 48.7, 52.9, 53.7, 79.8, 127.0 (2C), 127.5, 128.6 (2C), 139.8, 154.4, 171.5. IR (ATR): 3319, 2976, 2935, 2881, 1672, 1603, 1522, 1496, 1448, 1425, 1366, 1313, 1277, 1252, 1167, 1066, 1032, 1016, 931, 874, 785 cm^{-1}. $[\alpha]_D^{25}$ +68.0 (*c*=1.06, $CHCl_3$).

***tert*-Butyl {(3*S*)-3-Methyl-1-[(1*R*)-1-phenylethyl]pyrrolidin-3-yl}carbamate (19)** To a solution of **18** (500 mg, 1.57 mmol) in THF (15 ml) was added boran–THF complex (1.2 mol/l in THF, 3.93 ml, 4.71 mmol) at 0 °C and the mixture was stirred at room temperature for 17 h. EtOH (12 ml), triethylamine (4 ml), and water (4 ml) were added, and then the resultant mixture was refluxed for 3 h. The mixture was concentrated *in vacuo*, diluted with AcOEt and water, and extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=2/1 to 1/2, v/v to give the title compound (406 mg, 85%) as a colorless oil. HR-MS (ESI) *m/z*: 305.2213 (Calcd for $C_{18}H_{28}N_2O_2$+H 305.2229). ^{1}H-NMR ($CDCl_3$) δ: 1.33 (3H, d, *J*=6.59 Hz), 1.43 (3H, s), 1.43 (9H, s), 1.75—1.86 (1H, m), 1.95—2.06 (1H, m), 2.41 (1H, d, *J*=9.52 Hz), 2.51—2.67 (2H, m), 2.67—2.77 (1H, m), 3.25 (1H, q, *J*=6.59 Hz), 4.68 (1H, s), 7.19—7.33 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 23.0, 26.6, 28.5 (3C), 38.9, 51.6, 58.2, 65.1, 65.5, 78.0, 126.8, 127.1 (2C), 128.3 (2C), 145.4, 155.0. IR (ATR): 3356, 2972, 2931, 2871, 2787, 1697, 1604, 1493, 1452, 1390, 1365, 1277, 1250, 1165, 1068, 1032, 964, 872 cm^{-1}. $[\alpha]_D^{25}$ +46.2 (*c*=1.10, $CHCl_3$).

***tert*-Butyl [(3*S*)-3-Methylpyrrolidin-3-yl]carbamate (20)** To a solution of **19** (406 mg, 1.33 mmol) in 1,4-dioxane (13 ml) was added palladium hydroxide (20 wt% Pd on carbon) (100 mg) and the mixture was stirred for 5 h under hydrogen atmosphere at 50 °C. The mixture was filtered and concentrated *in vacuo* to give the title compound (266 mg, 100%) as a colorless oil. HR-MS (ESI) *m/z*: 201.1564 (Calcd for $C_{10}H_{20}N_2O_2$+H 201.1603). ^{1}H-NMR ($CDCl_3$) δ: 1.41 (3H, s), 1.44 (9H, s), 1.69—1.78 (1H, m), 1.89—2.07 (2H, m), 2.72 (1H, d, *J*=11.47 Hz), 2.88—2.99 (1H, m), 3.04—3.21 (2H, m), 4.59 (1H, br s). ^{13}C-NMR ($CDCl_3$) δ: 24.8, 28.5 (3C), 40.2, 45.3, 59.2, 60.0, 79.2, 154.8. IR (ATR): 3340, 3195, 2974, 2931, 2871, 1693, 1523, 1446, 1365, 1279, 1252, 1169, 1066, 985, 947, 874, 783 cm^{-1}. $[\alpha]_D^{25}$ −1.29 (*c*=1.03, $CHCl_3$).

Benzyl (3*S*)-3-[(*tert*-Butoxycarbonyl)amino]-3-methylpyrrolidine-1-carboxylate (21) To a solution of **20** (240 mg, 1.20 mmol) in Et_2O (12 ml) were added satd $NaHCO_3$ aq. (12 ml) and benzyl chloroformate (222 μl, 1.56 mmol), and the mixture was stirred for 16 h at room temperature. The mixture was extracted with AcOEt and the obtained organic layer was washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=2/1, v/v to give the title compound (400 mg, 100%) as a colorless oil. HR-MS (ESI) *m/z*: 335.1970 (Calcd for $C_{18}H_{26}N_2O_4$+H 335.1971). ^{1}H-NMR ($CDCl_3$) δ: 1.41—1.45 (12H, m), 1.76—1.84 (1H, m), 2.16—2.41 (1H, m), 3.34 (1H, d, *J*=11.5 Hz), 3.44—3.55 (2H, m), 3.56—3.69 (1H, m), 4.46—4.52 (1H, m), 5.12 (2H, s), 7.26—7.36 (5H, m). ^{13}C-NMR ($CDCl_3$) δ: 23.5, 28.5 (3C), 36.9, 44.5, 57.0, 57.8, 65.4, 66.9, 79.7, 127.9 (2C), 128.0, 128.5 (2C), 137.1, 154.7. IR (ATR): 3344, 2974, 2885, 1689, 1522, 1498, 1446, 1419, 1390, 1363, 1344, 1271, 1254, 1169, 1101, 1076, 1022, 953, 876, 768 cm^{-1}. $[\alpha]_D^{25}$ +29.9 (*c*=1.02, $CHCl_3$).

Benzyl (3*S*)-3-[(*tert*-Butoxycarbonyl)(methyl)amino]-3-methylpyrrolidine-1-carboxylate (22) To a solution of **21** (400 mg, 1.20 mmol) and methyl iodide (112 μl, 1.79 mmol) in DMF (12 ml) was added sodium hydride (55%, 62.6 mg, 1.44 mmol) at 0 °C, and the mixture was stirred at 0 °C for 2 h. To a reaction mixture was added 10% citric acid aq., and the mixture was extracted with AcOEt. The organic layers were washed with brine, dried over Na_2SO_4, and concentrated *in vacuo*. The crude product was purified by silica gel column chromatography eluting with *n*-hexane/AcOEt=2/1 to 1/4, v/v to afford the title compound (367 mg, 88%) as a colorless oil. HR-MS (ESI) *m/z*: 349.2163 (Calcd for $C_{19}H_{28}N_2O_4$+H 349.2127). ^{1}H-NMR ($CDCl_3$) δ: 1.29 (3H, s), 1.45 (9H, s), 1.97—2.20 (2H, m), 2.84 (3H, s), 3.34 (1H, td, *J*=6.9, 10.9 Hz), 3.47 (1H, d, *J*=11.5 Hz), 3.56 (1H, br s), 3.81—3.92 (1H, m), 5.09—5.17 (2H, m), 7.25—7.36 (5H, m). ^{13}C-NMR (DMSO-d_6) δ: 19.9, 28.1 (3C), 31.4, 37.0, 43.5, 57.8, 62.0, 65.9, 79.2, 127.3 (2C), 127.7, 128.3 (2C), 137.2, 154.0, 155.0. IR (ATR): 2974, 2885, 1689, 1454, 1417, 1363, 1342, 1232, 1169, 1144, 1099, 1003, 966, 883, 825 cm^{-1}. $[\alpha]_D^{25}$ −2.39 (*c*=1.14, $CHCl_3$).

***tert*-Butyl Methyl[(3*S*)-3-methylpyrrolidin-3-yl]carbamate (23)** Following the procedure as described for **20**, the title compound was prepared in 100% from **22** as a colorless oil. HR-MS (ESI) *m/z*: 215.1750 (Calcd for $C_{11}H_{22}N_2O_2$+H 215.1760). ^{1}H-NMR ($CDCl_3$) δ: 1.28 (3H, s), 1.46 (9H, s), 1.77—1.94 (1H, m), 2.02—2.11 (1H, m), 2.87 (3H, s), 2.92—3.09 (3H, m), 3.16 (1H, d, *J*=11.47 Hz). ^{13}C-NMR ($CDCl_3$) δ: 21.4, 28.5 (3C), 32.4, 40.0, 45.1, 59.6, 64.6, 79.7, 156.1. IR (ATR): 2974, 2931, 2873, 1687, 1541, 1477, 1419, 1363, 1252, 1171, 1130, 1039, 1011, 935, 879, 812, 775 cm^{-1}. $[\alpha]_D^{25}$ −1.04 (*c*=1.20, $CHCl_3$).

***In Vitro* Antifungal Activity** MIC-1 (the lowest drug concentration showing 80% growth inhibition compared to the control without drug) was evaluated by the serial dilution methods in 96-well microtest plates using YPD [1% yeast extract (Difco, Detroit, MI, U.S.A.), 2% peptone (Difco, Detroit, MI, U.S.A.), and 20% glucose] as the medium.[11] Test organisms were purchased from the American Type Culture Collection (Rockville, MD, U.S.A.), the Institute for Fermentation Osaka (Osaka, Japan), or Teikyo Institute of Medical Micology (Tokyo, Japan). Initial cell densities (1×10^3—1×10^4 cells/ml) and incubation times (18—72 h) were decided for each strain in consideration of their growth speed. The fungi were incubated at 37 °C. Follwing incubation, OD_{600} was measured with a Wallac 1420 ARVOsx multi-label counter (Wallac, Tokyo, Japan) and MIC-1s were calculated. Compounds were tested at different concentrations ranging from 0.016 to 128 μg/ml.

Distribution Coefficient (Log *D*) The distribution coefficients (Log *D*) were determined by the shake-flask method. Four hundred micromolar of compound solution of each compound in a 2 ml *n*-octanol–2 ml PBS solution was placed on a shaker for 30 min at pH 7.4. After centrifuging each solution separately at 3000 rpm for 10 min, an LC/MS method was used to assay each layer. The LC/MS system consisted of an 1100 Series LC/MSD (Agilent) and an X Terra® MSC18 column (30×3.0 mm, 3.5 μm) (Waters). The mobile phase was a 10 mM ammonium acetate buffer (pH 4.5)/0.05% (v/v) acetic acid mixture in acetonitrile with a gradient condition (95/5—

10/90). Analyst software program (version 1.4, Applied BioSystems) was used to calculate the Log *D*.

Metabolic Stability Compounds (final 1 μM) were incubated with liver microsomes (mouse, rat, and human) in sodium phosphate buffer (pH 7.4) for 30 min at 37 °C. The microsomal protein concentration in the assay was 0.1 mg/ml for mice and rats or 0.5 mg/ml for humans. Reaction was started by the addition of NADPH at 37 °C and stopped by the addition of MeOH after 30 min. After centrifuging each solution separately at 3500 rpm for 10 min at 4 °C, the corresponding loss of parent compound was determined by LC/MS/MS.

***In Vivo* Efficacy** Six-week-old female Crlj : CD1 (ICR) mice (Charles River Japan) were immunosuppressed by cyclophosphamide, and then infected with *C. albicans* ATCC 90028 (1.2×10^5 CFU/mouse) or *C. glabrata* ATCC 48435 (1.7×10^8 CFU/mouse). Compounds were subcutaneously administrated at a dose of 1.1, 3.3, 20, and 40 mg/kg in 0 and 6 h after infection. Survival rates were observed for 8 d.

Pharmacokinetic Studies on Mice Six-week-old female Crlj : CD1 (ICR) mice (Charles River Japan) were used. The test compound was dissolved in 1% lactic acid and 5% glucose solution, and the solution was administrated subcutaneously at a dose of 10 mg/kg. At 0.083, 0.25, 0.5, 1, 2, 4, 6, and 24 h after treatment, peripheral blood (600 μl) was collected from axillary vein. Blood samples were centrifuged ($5000\times\boldsymbol{g}$, 10 min, 4 °C) and the supernatant was collected. The plasma samples were subsequently stored at −20 °C until analysis. The concentrations of the compounds were determined by liquid chromatography/positive electrospray ionization tandem mass spectrometry (LC/ESI-MS/MS), comprised of an Alliance 2695 HPLC (Waters), SunFire C18 column (30×2.1 mm, 3.5 μm) (Waters), and Quattro Ultima (Micromass). The mobile phase consisted of 10 mM ammonium formate in water (A) and acetonitrile (B). The initial condition was set at 10% of B. Then B (%) was increased linearly to 95% from 0.35 to 0.40 min and maintained to 3.4 min and then brought back to the initial concentration linearly from 3.4 to 3.5 min and maintained to 5.2 min. The flow rate was 0.4 ml/min. The *AUC* and $T_{1/2}$ were estimated by noncompartment method using the WinNonlin Software program (version 1.13.1, Pharsight, Mountain View, CA, U.S.A.).

Pharmacokinetic Studies on Rats Six-week-old female Sprague-Dawley rats (SLC Japan) were used. The test compound was dissolved in 1% lactic acid and 5% glucose solution, and the solution was intravenously or orally administrated at a dose of 5 mg/kg. Peripheral blood (0.4 ml) was collected from jugular vein at 0.083, 0.25, 0.5, 1, 2, 4, and 6 h after administration. Blood samples were centrifuged ($5000\times\boldsymbol{g}$, 10 min, 4 °C) and the supernatant was collected. The plasma samples were subsequently stored at −20 °C until analysis. These samples were analyzed according to the pharmacokinetic studies on mice.

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