reacted with piperazine (0.31 g, 3.60 mmol). The HF acceptor was omitted. The product was washed with Et_2O, cold CH_3OH, and Et_2O. The yield of **13** was 0.26 g (81.3%); mp 233 °C dec; ^1H NMR(TFA) δ 1.60–1.78 (m, 2 H), 1.88–2.08 (m, 2 H), 3.57–3.85 (m, 4 H), 3.90–4.10 (m, 4 H), 4.65 (s, 2 H), 8.07 (d, J = 11.4 Hz, 1 H), 8.97 (s, 1 H); IR (KBr) 3435, 1726, 1620 cm^{-1}; MS, m/z 360 (M^+ + 1, base); HPLC 99.3%. Anal. ($C_{18}H_{18}FN_3O_4 \cdot 1.13H_2O \cdot 0.14HF$) C, H, N, F.

10′-[3-[(Ethylamino)methyl]-1-pyrrolidinyl]-9′-fluoro-7′-oxospiro[cyclopropane-1,3′(2′*H*)-[7*H*]pyrido[1,2,3-*de*][1,4]benzoxazine]-6′-carboxylic Acid (15). As described above, **12b** (0.27 g, 0.92 mmol) was reacted with *N*-ethyl-3-pyrrolidinemethanamine, (0.17 g, 1.32 mmol) and Et_3N (0.10 g, 0.99 mmol). The product was washed with CH_3CN and Et_2O to give crude **15** (0.32 g, 86%). A portion of crude **15** (0.24 g) was purified as follows: The solid was suspended in H_2O, and 1 N NaOH was added to give a solution (pH 11.6). This solution was filtered, and the pH was adjusted to 1 with 1 N HCl. The solution was lyophilized to a gum, which crystallized from hot isopropyl alcohol to give 0.20 g of pure **15**: mp 254 °C dec; ^1H NMR (TFA) δ 1.27–2.30 (m, 7 H) 2.34–2.70 (m, 1 H), 2.72–3.00 (m, 1 H), 3.23–3.93 (m, 6 H), 4.15–5.30 (m, 5 H), 7.15 (br s, 1 H), 8.23 (br s, 1 H), 9.17 (br s, 1 H); IR (KBr) 3435, 1733, 1619 (cm^{-1}); MS, m/z 402 (M^+1), 58 (base); HPLC (98.8%). Anal. ($C_{21}H_{24}FN_3O_4 \cdot 1.3HCl \cdot 1.25H_2O$) C, H, Cl; N: calcd, 8.90; found, 8.45.

10′-[3-[(Dimethylamino)methyl]-1-pyrrolidinyl]-9′-fluoro-7′-oxospiro[cyclopropane-1,3′(2′*H*)-[7*H*]pyrido-[1,2,3-*de*][1,4]benzoxazine]-6′-carboxylic Acid (14). As described above, **12b** (0.40 g, 1.36 mmol) was reacted with *N,N*-methyl-3-pyrrolidinemethanamine (0.19 g, 1.48 mmol) and 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) (0.23 g, 1.51 mmol). No solids were formed upon cooling, and the reaction mixture was evaporated to a gum. This gum was triturated with Et_2O to give a solid, which was collected by filtration, suspended in H_2O, and basified with 1 N NaOH, and the resulting solution (pH 12) was extracted four times with Et_2O. The pH of the aqueous layer was adjusted to 7 and extracted five times with $CHCl_3$. The combined $CHCl_3$ extracts were dried, filtered, and evaporated to give **14** as a solid: 0.31 g (56%); mp 193–197 °C; ^1H NMR ($CDCl_3$) δ 1.16–1.42 (m, 2 H), 1.45–1.87 (m, 3 H), 1.98–2.20 (m, 1 H), 2.22–2.67 (m, 9 H), 3.43–3.98 (m, 4 H), 4.22 (ab q, J = 11.6 Hz, 1 H), 4.26 (ab q, J = 11.6 Hz, 1 H), 7.66 (d, J = 13.9 Hz, 1 H), 8.28 (s, 1 H); IR (KBr) 3443, 1724, 1620 cm^{-1}; MS, m/z 401 (M), 58 (base); HPLC 98.7%. Anal. ($C_{21}H_{24}FN_3O_4 \cdot 0.05CHCl_3$) C, H, N, F.

Registry No. **5a**, 1559-02-0; **5b**, 3697-66-3; **6**, 107259-05-2; **7**, 107017-73-2; **8**, 115652-52-3; **9**, 111630-16-1; **10**, 115652-53-4; **11**, 113211-50-0; **12a**, 115652-51-2; **12b**, 113211-52-2; **13**, 113211-55-5; **14**, 115652-54-5; **15**, 113211-56-6; **16**, 82419-52-1; **17**, 91196-82-6; **18**, 115652-55-6; piperazine, 110-85-0; *N,N*-dimethyl-3-pyrrolidinemethanamine, 99724-17-1; *N*-ethyl-3-pyrrolidinemethanamine, 91187-83-6.

Studies on Antifungal Agents. 23. Novel Substituted 3,5-Diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-alkylisoxazolidine Derivatives

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The synthesis and antifungal activity of a novel series of substituted 3,5-diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-alkylisoxazolidine derivatives (**15–30**) are described. The synthesis of the title compounds was accomplished via a 1,3-dipolar cycloaddition reaction of α-substituted ketonitrones with appropriate styrene precursors. The compounds when tested in vitro in solid agar cultures exerted a very potent antifungal activity against a wide variety of yeast and systemic mycoses and dermatophytes, especially *Trichophyton* and *Microsporum* sp., *Epidermophyton floccosum* and *Candida stellatoidea*. The in vitro activity against *Aspergillus fumigatus* and *Candida albicans* was moderate to potent. Overall, the two bis(4-chlorophenyl) analogues **18** and **19** were the most potent in vitro compounds, showing MIC values ranging between 0.2 and 7.0 μg/mL, as compared to 0.2–20.0 μg/mL for ketoconazole, which was used as the positive standard in all assays. When tested in vivo in the rat vaginal candidiasis model, derivative **18**, although showing significant antifungal activity when compared to controls, was less effective than ketoconazole. The title 3,5-substituted isoxazolidine compounds represent a novel class of potent antifungal agents.

Over the past 2 decades or so, the frequency of systemic fungal infections in man has increased dramatically. Undoubtedly, the population most susceptible to such infections are immunocompromized patients,[1-6] especially those with hematologic malignancies (such as leukemia), acquired immune deficiency syndrome (AIDS),[7] and patients undergoing cancer chemotherapy and organ transplantation. Although *Candida* species continue to be the major patogenic fungi in immunocompromized patients, the number of other fungal infections (cryptococcosis,[8] aspergillosis,[8] zygomycosis,[8] coccidioidomycosis,[9-11] paracoccidioidomycosis,[12] and chromoblastomycosis[13]) have become increasingly worrisome.

Since its discovery in 1953,[14] and after a quarter of a century of continuing clinical use, the polyene antibiotic amphotericin B is still the drug of choice in the treatment of serious systemic fungal infections.[5,15-18] Although amphotericin B exerts an excellent activity against most pathogenic fungi, along with an impressive lack of native or developed resistance, its poor solubility in water at

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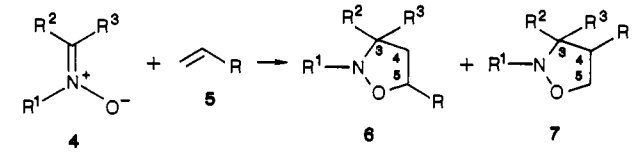
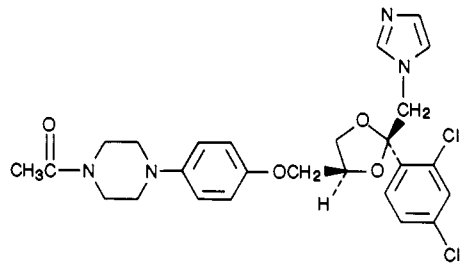
physiologic pH levels, physicochemical instability,[19] and most formidable toxicity have turned into serious drawbacks that continue to hamper its use in the clinic.[18,20]

Since the advent to the clinic of the first antifungal imidazoles, clotrimazole,[23] miconazole, and econazole,[24] several other azole derivatives, most notably ketoconazole (1),[5,11,12,25-29] have been successfully developed and marketed as antifungal agents. Ketoconazole was the first orally active antifungal agent that was effective against a broad array of systemic and superficial fungal infections.[28] Recently, two new azole derivatives, itraconazole (2)[9,13,30,31] and fluconazole (3),[32-35] have been introduced into clinical trials. These newer drugs are claimed to be free of the major side effects of ketoconazole (especially hepatotoxicity[28]) and to possess a better pharmacokinetic profile.[36] However, like ketoconazole, they are fungistatic, rather than fungicidal agents. The N-substituted azole drugs are known to interfere with the cytochrome P_{450} dependent 14α-demethylation of lanosterol or 24-methylenedihydrolanosterol, a key step in the biosynthesis of ergosterol, which is the main sterol in the vast majority of yeasts and fungi.[37,38]

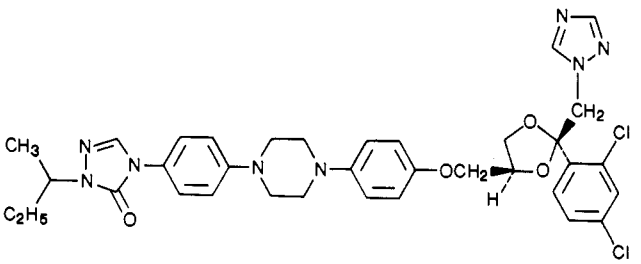
Scheme I



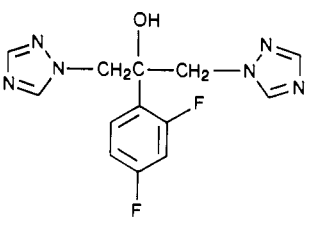
4 5 6 7



1



2



3

In addition to azole derivatives, a number of antifungal agents having chemical structures other than azoles have recently been introduced to the clinic. Thus, amorolfine, a morpholine derivative, is reported to show high efficacy against experimental trichophytosis and vaginal candidiasis and is currently in clinical evaluation as topical antimycotic.[39] Amorolfine was shown to inhibit the fungal sterol

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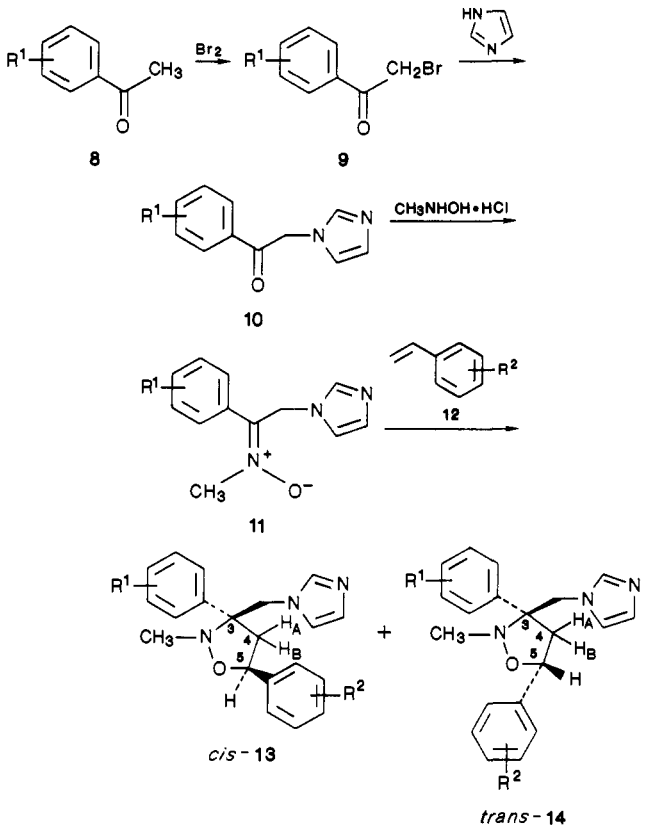
Scheme II



biosynthesis that changed the membrane permeability and induced abnormal chitin deposition leading to growth abnormalities in fungi.[40] Two novel allylamine agents, naftifine and terbinafine, have also shown promising antifungal activity by inhibiting the microsomal squalene epoxidase in a specific and reversible manner.[41-46]

In spite of the introduction of several novel antifungal agents, the number of available drugs with sufficient efficacy to treat an increasing array of life-treatening systemic mycoses remains rather limited. There still exists a great need for a more potent and broad-spectrum antimycotic agent with fungicidal properties and reduced side effects.[10,36]

In previous studies,[47,48] we have described the application of 1,3-dipolar cycloaddition reactions to the synthesis of biologically active compounds. We recognized an opportunity to apply our knowledge of 1,3-dipolar species to the synthesis of novel antifungal agents and initiated the synthesis of a series of 3,5-substituted isoxazolidine compounds through the 1,3-dipolar cycloaddition reaction of α-substituted ketonitrones and styrene derivatives. The resulting 5-phenylisoxazolidines were expected to differ in their chemical and antifungal properties from the known azole antimycotics, thus providing valuable information of a new generation of antifungal agents.

The present paper represents part of our studies in this direction.[49]

Table I. ^{1}H NMR Coupling Constants (J) for Cis and Trans Diastereomeric Isoxazolidines (in Hertz)

compd	$J(H_5-H_{4A})$	$J(H_5-H_{4B})$	$\Delta[J(H_5-H_{4B}) - J(H_5-H_{4A})]$
cis-18	4.7	10.3	5.6
trans-28	8.8	8.8	0
cis-31	5.4	9.5	4.1
trans-32	7.7	9.1	1.4

Chemistry

When nitrones (4) undergo a 1,3-dipolar cycloaddition reaction with monosubstituted olefins (5), the resulting product most often represents a mixture of the corresponding isoxazolidines 6 and 7 (Scheme I).[50] Similar to the Diels–Alder reaction, the 1,3-dipolar cycloaddition reaction is thought to have a concerted mechanism that may be formally treated as an allowed [π^4s + π^2s] process via frontier molecular orbital theory. The regio- and stereospecificity of the reaction is highly dependent on the structures of the nitrone and the dienophile and involves both electronic and steric factors.[50,51]

The synthesis of the title 3,5-diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines is depicted in Scheme II. An initial bromination of the appropriate acetophenones 8, followed by reaction of the resulting bromo derivatives 9 with imidazole furnished the corresponding 2-(1*H*-imidazol-1-yl)-1-phenylethanones 10.[52] The latter were converted into the nitrone intermediates 11 by treatment with *N*-methylhydroxylamine hydrochloride under mild conditions. The 1,3-dipolar cycloaddition reaction of 2-(1*H*-imidazol-1-yl)-*N*-methyl-1-phenylethanimine *N*-oxides 11 with appropriate styrene derivatives (12) yielded in a regiospecific manner a cis/trans mixture of diastereomers 13 and 14. In this case the 4-substituted products 7 are excluded on the basis of both steric and electronic factors.[50,51,53] Of the two diastereomers, the cis products 13 were the predominant components of the mixtures. The cis and trans diastereomers were conven-

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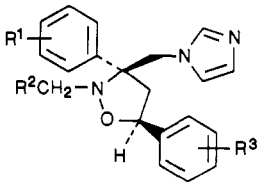
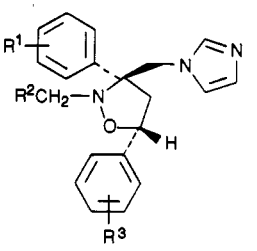
(51) The regiospecificity of the 1,3-dipolar cycloaddition reaction involving monosubstituted olefins is usually dominated by HOMO–LUMO (highest occupied molecular orbital–lowest unoccupied molecular orbital) interactions.[58,59] Thus, electron-rich olefins will give exclusively the 5-substituted isoxazolidines, whereas electron-poor olefins can give the 5- or 4-substituted product or a mixture of both.
(52) The 2-(1*H*-imidazol-1-yl)-1-(substituted phenyl)ethanones 10 were prepared by modified procedures of the method of Godefroi et al. (Godefroi, E. F.; Heeres, J.; Van Cutsem, J.; Janssen, P. A. J. *J. Med. Chem.* **1969**, *12*, 784). In addition to the 2-bromo-1-(substituted phenyl)ethanones, a number of the corresponding 2-chloroethanones have been also utilized in the synthesis of 10.
(53) The presence of a sterically demanding α-substitution pattern in nitrones 11 [3-phenyl-3-(1*H*-imidazol-1-ylmethyl)], coupled with the bulky phenyl group of styrenes 12, will make highly unlikely the formation of 4-substituted isoxazolidines 7, since in 7 the phenyl group (R = phenyl) is situated next to a quarternary carbon carrying the 3-phenyl-3-(1*H*-imidazol-1-ylmethyl) unit.

Table II. Substituted 3,5-Diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidines and Related Derivatives



cis-15-25



trans-26-30

compd	R^1	R^2	R^3	mp, °C	recrystn solvent	yield, %	formula	anal.
15	H	H	H	97–99	ether	25.5	$C_{20}H_{21}N_3O$	C, H, N
16	H	H	3,4-$(OCH_3)_2$	136–144[a]	2-propanol	54.5[a]	$C_{22}H_{26}ClN_3O_3$	
17	4-Cl	H	H	159–163	ethyl acetate	61.0	$C_{20}H_{20}ClN_3O$	C, H, Cl, N
18	4-Cl	H	4-Cl	137.5–139.5	ethyl acetate	68.0	$C_{20}H_{19}Cl_2N_3O$	C, H, Cl, N
19	4-Cl	H	2-Cl	129–132	ethyl acetate	48.0	$C_{20}H_{19}Cl_2N_3O$	C, H, Cl, N
20	4-Cl	H	4-CH_3	135.5–137	ethyl acetate	47.0	$C_{21}H_{22}ClN_3O$	C, H, Cl, N
21	4-Cl	H	2,6-Cl_2	64–66[b]	2-propanol	3.0	$C_{23}H_{26}Cl_3N_3O_2$	C, H, Cl, N
22	4-F	H	H	130–132	ethyl acetate	60.0	$C_{20}H_{20}FN_3O$	C, H, F, N
23	4-OCH_3	H	4-OCH_3	117–120	ethyl acetate	32.0	$C_{22}H_{25}N_3O_3$	C, H, N
24	4-Cl	$C_6H_4OCH_3$-4	H	162–167	ethyl acetate–hexane (1:1)	28.0	$C_{27}H_{26}ClN_3O_2$	C, H, Cl, N
25	4-F	C_6H_5	H	162–164	ethyl acetate	48.0	$C_{26}H_{24}FN_3O$	C, H, F, N
26	H	H	H	200–202	methanol	5.0	$C_{20}H_{21}N_3O$	C, H, N
27	4-Cl	H	H	124–127	ethyl acetate	11.0	$C_{20}H_{20}ClN_3O$	
28	4-Cl	H	4-Cl	137–140	ethyl acetate	9.5	$C_{20}H_{19}Cl_2N_3O$	C, H, Cl, N
29	4-Cl	H	4-CH_3	129	ethyl acetate	4.0	$C_{21}H_{22}ClN_3O$	C, H, Cl, N
30	4-Cl	H	2,6-Cl_2	159–161	ethyl acetate	6.4	$C_{20}H_{18}Cl_3N_3O$	C, H, N

[a] As the monohydrochloride salt. [b] As 1:1 complex with 2-propanol.

Table III. In Vitro Antifungal Activity of Substituted 3,5-Diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-alkylisoxazolidines (Measured as the Minimum Inhibitory Concentration (MIC), μg/mL)

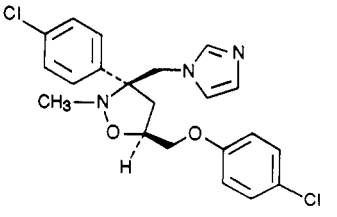
compd	*T. a.*[a]	*T. r.*[b]	*T. t.*[c]	*T. s.*[d]	*E. f.*[e]	*M. a.*[f]	*M. c.*[g]	*A. f.*[h]	*C. a.*[i]	*C. s.*[j]
15	0.7	2.0	0.7	7.0	7.0	20.0	7.0	70.0	70.0	7.0
17	<0.2	0.7	0.7	2.0	0.7	7.0	2.0	70.0	20.0	7.0
18	<0.2	0.7	<0.2	0.7	<0.2	2.0	2.0	7.0	7.0	2.0
19	<0.2	0.7	<0.2	0.7	<0.2	2.0	2.0	7.0	7.0	0.7
20	0.7	2.0	0.7	2.0	0.7	7.0	7.0	70.0	7.0	0.7
21	7.0	0.7	0.7	7.0	0.7	20.0	2.0	2.0	7.0	7.0
22		2.0						20.0	70.0	
23	20.0	20.0	20.0	70.0	7.0	70.0	20.0	>70.0	70.0	20.0
25		0.7						>70.0	20.0	
29	2.0	2.0	2.0	2.0	2.0	20.0	7.0	70.0	20.0	0.7
30	7.0	0.7	0.7	7.0	0.7	20.0	2.0	7.0	7.0	7.0
ketoconazole	2.0	0.7	<0.2	0.7	<0.2	7.0	2.0	7.0	20.0	20.0

[a] *T. m.* = *Trichophyton mentagrophytes* ATCC 9533. [b] *T. r.* = *Trichophyton rubrum* ATCC 18762. [c] *T. t.* = *Trichophyton tonsurans* ATCC 9085. [d] *T. s.* = *Trichophyton schoenleinii* ATCC 22775. [e] *E. f.* = *Epidermophyton floccosum* ATCC E-18397. [f] *M. a.* = *Microsporum audouinii* ATCC 9079. [g] *M. c.* = *Microsporum canis* ATCC 44459. [h] *A. f.* = *Aspergillus fumigatus* ATCC 28212. [i] *C. a.* = *Candida albicans* ATCC 10259. [j] *C. s.* = *Candida stellatoidea* ATCC 36232.

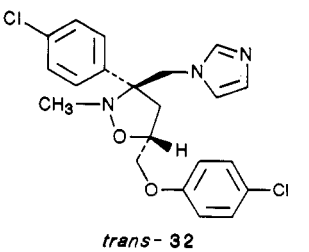
iently separated by flash chromatography on neutral silica gel.

The two *N*-benzyl analogues **24** and **25** were obtained by similar procedures by using *N*-benzylhydroxylamine in place of *N*-methylhydroxylamine hydrochloride.

The stereochemistry of the two asymmetric centers of the *cis*- and *trans*-isoxazolidines **13** and **14**, respectively, was determined by ^{1}H NMR spectroscopy. Thus, for the cis analogues **13** (e.g. **18**) the difference (Δ) between the coupling constants *J* of H_{4A} and H_{4B} protons and the H_5 proton was 5.6 Hz, whereas no difference (Δ = 0) was observed for the corresponding coupling constants of the trans diastereomers **14** (e.g. **28**) (Table I). Similar correlations between the coupling constants *J* of the structurally related *cis*- and *trans*-isoxazolidines **31** and **32**, respectively, have been observed on a previous occasion.[54] As with the case of *cis*-**18**, the Δ value for *cis*-**31** (4.1 Hz) is considerably higher than the Δ = 1.4 Hz observed for the trans diastereomer **32** (Table I). An X-ray crystal-structure determination of *cis*-**31** was undertaken to define unambiguously the structure of both cis and trans diastereomers.[55]



cis-31



trans-32

The stereochemical assignment of all remaining *cis*- and *trans*-isoxazolidine derivatives was defined by ^{1}H NMR spectroscopy according to the *J* and Δ values of *cis*-**18** and *trans*-**28** (see the Experimental Section for details).

(54) Mullen, G. B.; Swift, P. A.; Maryniak, D. M.; Allen, S. D.; Mitchell, J. T.; Kinsolving, C. R.; Georgiev, V. St. *Helv. Chim. Acta* **1988**, *71*, 718.

(55) Carroll, P. J.; Mullen, G. B.; Georgiev, V. St. *Acta Crystallogr., Sect. C: Cryst. Struct. Commun.*, in press.

Table IV. Oral Antifungal Activity of Compound *cis*-18 and Ketoconazole in the Rat Vaginal Candidiasis Model

compd	days postinfections with *C. albicans* SOB FM-391 (in $\log_{10}$)[b]					
	1	2	3	4	7	8
cis-18[a]	4.7	4.0	3.6	3.4	3.3	1.8
ketoconazole[a]	5.0	1.5	0.3	0.0	0.0	0.0
controls	5.1	5.0	5.1	5.0	4.5	3.8

[a] Drug was administered orally at 20 mg/kg. [b] $\log_{10}$ is the number of *C. albicans* organisms per milliliter of lavage fluid.

All compounds synthesized during the present study are listed in Table II.

Results and Discussion

All results of the testing for antifungal activity are summarized in Table III. The in vitro antifungal activity was assayed in solid agar tests performed in 24-well tissue culture plates and was measured as the minimum inhibitory concentration (MIC) value. Substitution was varied at both phenyl rings and the nitrogen at the isoxazolidine ring.

As seen from Table III, the majority of the tested 3,5-diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-alkylisoxazolidines **15–30** displayed excellent activity against dermatophytes (*Trichophyton* and *Microsporum* species and *Epidermophyton floccosum*) and *Candida stellatoidea*. The antifungal activity against *Candida albicans* was moderate to potent. When tested against *Aspergillus fumigatus*, only several derivatives (**18**, **19**, **21**, and **30**) showed potent activity.

Introduction of chlorine substituent(s) into one or both phenyl rings proved to be very beneficial for activity. Thus, compounds **18** and **19** showed excellent MIC values against all fungi ranging between 0.2 and 7.0 μg/mL. By comparison, the corresponding values for the standard drug ketoconazole were 0.2–20.0 μg/mL. The superior in vitro activity of **18** and **19** is especially noticeable in the case of *Candida* sp. Substituting the chlorine of the C-3 phenyl ring with either fluorine (**22** and **25**) or methoxy group (**23**) resulted in a significant decrease in activity, especially in the case of the bis(4-methoxyphenyl) derivative **23**. The *N*-benzyl analogue **25**, while retaining a potent activity against dermatophytes (*Trichophyton rubrum*), was considerably less effective against *A. fumigatus* and only moderately active against *C. albicans*.

The stereochemical relationship of compounds **15–25** is one in which the 3-(1*H*-imidazol-1-ylmethyl) substituent is positioned cis to the 5-phenyl ring. The same stereochemistry is also present in ketoconazole (**1**) about the dioxolane ring. One might expect that the minor trans diastereomers **26–30** would show some difference in the degree and/or nature of in vitro antifungal activity.[56] Although, in general, the trans analogues **26–30** were slightly less effective than their cis counterparts **15–25**, the activity of **26–30** against both dermatophyte and yeast systemic fungi was still from moderate to potent.

The *cis*-bis(4-chlorophenyl)imidazole analogue **18** displayed the best overall in vitro activity among all of the compounds tested, with MIC values ranging between 0.2 and 7.0 μg/mL. Compound **18** was tested further for oral in vivo antifungal activity in the rat vaginal candidiasis model and compared to ketoconazole (Table IV). As seen from the table, ketoconazole induced a rapid reduction of the infection by day 2 with complete eradication on day 7. By comparison, *cis*-**18** caused a more gradual reduction of the infection with time. Although still considerably potent when compared to controls, analogue **18** was less effective in vivo than ketoconazole.

In summary, the title substituted 3,5-diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-alkylisoxazolidines **15–30** represent a novel class of potent antifungal agents. Their synthesis was accomplished by 1,3-dipolar cycloaddition reaction of α-substituted ketonitrones and appropriate styrene precursors that resulted in the formation of both cis and trans diastereomers in a regiospecific manner. While in vitro antifungal activity was evident throughout the series, in general, compounds having chlorine substituent(s) in either or both phenyl rings displayed the most potent activity. Compounds **18** and **19** were shown to be more effective in vitro antifungal agents than ketoconazole, especially against *T. mentagrophytes*, *M. audouinii* and *Candida* sp. However, when compared to ketoconazole, the in vivo antifungal activity of analogue **18**, although still significant, was less effective.[57]

Experimental Section

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. The infrared (IR) spectra were obtained on a Nicolet MX-1 FT spectrometer as KBr disks. The proton nuclear magnetic resonance (^{1}H NMR) spectra were taken on a Varian EM-360A (60 MHz) spectrometer with tetramethylsilane as an internal standard; the 200-MHz ^{1}H NMR spectra were recorded on a Bruker-IBM 200 SY Fourier transform spectrometer with the same internal standard. All spectra were consistent with the assigned structures. Elemental analyses were within the acceptable limits of 0.4% of theory.

3,5-Bis(4-chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine. A solution of 29.98 g (0.120 mol) of 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)-*N*-methylethanimine *N*-oxide (**11**; R^1 = 4-Cl) and 25.41 g (0.183 mol) of 4-chlorostyrene (**12**; R^2 = 4-Cl) in 500 mL of toluene was refluxed for 48 h under a nitrogen atmosphere. Upon being cooled to ambient temperature, the solution was extracted with water (3 × 150 mL). The organic layer was dried ($MgSO_4$) and concentrated under reduced pressure to give a solid residue, which was crystallized from ether, yielding 25.16 g (54%) of the cis diastereomer **18**, mp 137.5–139.5 °C (ethyl acetate). IR (KBr): 2970 (m), 2892 (w), 1595 (w), 1570 (w), 1507 (s), 1492 (s), 1466 (m), 1451 (m), 1401 (m), 1280 (m), 1231 (m), 1095 (s), 1077 (m), 1038 (m), 1011 (m), 930 (m), 904 (m), 860 (m), 828 (s), 750 (m), 725 (m), and 666 (m) cm^{-1}. ^{1}H NMR (200 MHz, $CDCl_3$): δ 2.42 (dd, 1 H, J = 4.7, 12.7 Hz, H_{4A}), 2.59 (s, 3 H, NCH_3), 3.19 (dd, 1 H, J = 10.3, 12.7 Hz, H_{4B}), 4.00 (d, 1 H, J = 14.1 Hz, *H*CHN), 4.29 (d, 1 H, J = 14.1 Hz, HC*H*N), 5.62 (dd, 1 H, J = 4.7, 10.3 Hz, OCH), 6.10 (s, 1 H), 6.60 (s, 1 H), 6.79 (s, 1 H), 7.02 (d, 2 H, J = 8.6 Hz), 7.31 (d, 2 H, J = 8.6 Hz), 7.41 (s, 4 H). Anal. Calcd for $C_{20}H_{19}Cl_2N_3O$: C, 61.87; H, 4.93; N, 10.82. Found: C, 61.73; H, 4.99; N, 10.81.

The mother liquor was concentrated to dryness, and the resulting oily residue was flash chromatographed on neutral silica gel with ethyl acetate as the eluent to provide an additional amount (6.52 g, 14%) of *cis*-**18** and 4.25 g (9.5%) of the trans diastereomer **28**, mp 137–140 °C (ethyl acetate). IR (KBr): 3110 (w), 2986 (w), 2972 (w), 1648 (w), 1505 (m), 1493 (s), 1455 (m), 1404 (m), 1279 (m), 1228 (m), 1105 (m), 1092 (s), 1079 (m), 1021

(56) So far we have not been able to find any reference in the literature indicating that the trans diastereomer of ketoconazole has been isolated and/or tested for antifungal activity.

(57) For Part 22 of the series "Studies on Antifungal Agents", see ref 54.

(58) Sims, J.; Houk, K. N. *J. Am. Chem. Soc.* **1973**, *95*, 5798.
(59) Houk, K. N.; Bimanand, A.; Mukherjee, D.; Sims, J.; Chang, Y.-M.; Kaufman, D. C.; Domelsmith, L. N. *Heterocycles* **1977**, *7*, 293.

(m), 1014 (m), 913 (m), 900 (m), 830 (m), 816 (m), 743 (m), and 660 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.46 (s, 3 H, NCH_3), 2.70 (dd, 1 H, J = 8.8, 12.7 Hz, H_{4A}), 2.86 (dd, 1 H, J = 8.8, 12.7 Hz, H_{4B}), 4.30 (d, 1 H, J = 14.3 Hz, *H*CHN), 4.41 (d, 1 H, J = 14.3 Hz, HC*H*N), 5.40 (t, 1 H, J = 8.8 Hz, OCH), 6.50 (s, 1 H), 6.94 (s, 1 H), 7.05 (d, 2 H, J = 7.7 Hz), 7.08 (s, 1 H), 7.26–7.33 (m, 6 H). Anal. Calcd for $C_{20}H_{19}Cl_2N_3O$: C, 61.87; H, 4.93; Cl, 18.26; N, 10.82. Found: C, 61.91; H, 4.76; Cl, 18.35; N, 10.70.

The following 3,5-diphenylisoxazolidine derivatives were prepared by procedures similar to that for the synthesis of *cis*-18 and *trans*-28 (yield, mp, IR, and ^1H NMR spectral analysis given).

3,5-Diphenyl-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine. ***cis*-15**: 25.5%, mp 97–99 °C (ether). IR (KBr): 3063 (m), 3032 (m), 2989 (m), 2880 (m), 1638 (w), 1605 (m), 1587 (w), 1504 (s), 1470 (m), 1447 (s), 1382 (m), 1350 (m), 1282 (m), 1232 (s), 1110 (m), 1075 (s), 1030 (m), 931 (m), 904 (m), 820 (m), 748 (s), 700 (s), and 662 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.46 (dd, 1 H, J = 4.4, 12.9 Hz, H_{4A}), 2.62 (s, 3 H, NCH_3), 3.23 (ddd, 1 H, J = 1.2, 10.4, 12.9 Hz, H_{4B}), 4.14 (d, 1 H, J = 14.0 Hz, *H*CHN), 4.31 (dd, 1 H, J = 1.2, 14.0 Hz, HC*H*N), 5.71 (dd, 1 H, J = 4.4, 10.4 Hz, OCH), 5.90 (d, 1 H, J = 1.0 Hz), 6.42 (s, 1 H), 6.72 (d, 1 H, J = 1.0 Hz), 7.10–7.52 (m, 10 H). Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.14; H, 6.71; N, 13.14. *trans*-**26**: 5%, mp 200–202 °C (methanol). IR (KBr): 3110 (w), 3060 (w), 3028 (w), 2985 (w), 2890 (w), 1600 (m), 1580 (w), 1510 (m), 1495 (m), 1443 (m), 1360 (m), 1281 (m), 1241 (m), 1108 (m), 1076 (m), 1030 (m), 1021 (m), 912 (m), 833 (s), 759 (m), 741 (s), 707 (s), and 662 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.54 (s, 3 H, NCH_3), 3.3 (dd, 1 H, J = 9.3, 13.3 Hz, H_{4A}), 3.17 (dd, 1 H, J = 7.9, 13.3 Hz, H_{4B}), 4.39 (d, 1 H, J = 14.0 Hz, *H*CHN), 4.80 (d, 1 H, J = 14.0 Hz, HC*H*N), 5.60 (t, 1 H, J = 8.5 Hz, OCH), 6.88–7.01 (m, 3 H), 7.26–7.41 (m, 9 H), 8.43 (s, 1 H). Anal. Calcd for $C_{20}H_{21}N_3O$: C, 75.21; H, 6.63; N, 13.16. Found: C, 75.07; H, 6.73; N, 13.12.

***cis*-3-(1*H*-Imidazol-1-ylmethyl)-5-(3,4-dimethoxyphenyl)-2-methyl-3-phenylisoxazolidine (16).** Monohydrochloride salt, 54.5%, mp 136–144 °C (2-propanol). IR (KBr): 3138 (w), 2960 (w), 2800–2300 (br w, NH^+), 1648 (m), 1630 (m), 1519 (s), 1465 (m), 1448 (m), 1290 (m), 1272 (m), 1256 (s), 1240 (m), 1161 (m), 1134 (m), 1030 (m), 823 (m), 763 (m), and 701 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.60 (dd, 1 H, J = 5.0, 13.2 Hz, H_{4A}), 2.64 (s, 3 H, NCH_3), 3.35 (dd, 1 H, J = 9.4, 13.2 Hz, H_{4B}), 3.91 (s, 3 H, OCH_3), 3.93 (s, 3 H, OCH_3), 3.94 (d, 1 H, J = 13.2 Hz, *H*CHN), 4.57 (d, 1 H, J = 13.2 Hz, HC*H*N), 5.69 (dd, 1 H, J = 5.0, 9.4 Hz, OCH), 6.62 (t, 1 H, J = 1.0 Hz), 6.86–7.04 (m, 5 H), 7.20 (t, 1 H, J = 1.0 Hz), 7.27–7.36 (m, 4 H, 3× arom + NH^+), 7.94 (s, 1 H).

3-(4-Chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-phenylisoxazolidine. ***cis*-17**: 61%, mp 159–163 °C (ethyl acetate). IR (KBr): 2995 (w), 2963 (w), 2890 (w), 1600 (w), 1503 (m), 1493 (s), 1460 (m), 1398 (m), 1285 (m), 1231 (m), 1095 (s), 1077 (m), 1013 (m), 858 (m), 816 (s), 745 (s), and 664 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.47 (dd, 1 H, J = 4.6, 12.7 Hz, H_{4A}), 2.61 (s, 3 H, NCH_3), 3.19 (dd, 1 H, J = 10.3, 12.7 Hz, H_{4B}), 4.08 (d, 1 H, J = 14.1 Hz, *H*CHN), 4.30 (d, 1 H, J = 14.1 Hz, HC*H*N), 5.69 (dd, 1 H, J = 4.6, 10.3 Hz, OCH), 6.02 (d, 1 H, J = 1.0 Hz), 6.53 (s, 1 H), 6.77 (d, 1 H, J = 1.0 Hz), 7.03 (d, 2 H, J = 6.5 Hz), 7.27–7.50 (m, 7 H). Anal. Calcd for $C_{20}H_{20}ClN_3O$: C, 67.89; H, 5.70; Cl, 10.02; N, 11.88. Found: C, 67.78; H, 5.80; Cl, 9.94; N, 11.83. *trans*-**27**: 11%, mp 124–127 °C (ethyl acetate).

***cis*-5-(2-Chlorophenyl)-3-(4-chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine (19)**: 48%, mp 129–132 °C (ethyl acetate). IR (KBr): 3060 (w), 2990 (w), 2961 (w), 1596 (w), 1572 (w), 1505 (s), 1493 (s), 1472 (m), 1442 (m), 1281 (m), 1234 (m), 1090 (m), 1077 (s), 1038 (m), 1012 (m), 937 (m), 821 (s), 757 (s), 732 (m), 710 (m), and 660 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.32 (dd, 1 H, J = 4.8, 13.2 Hz, H_{4A}), 2.62 (s, 3 H, NCH_3), 3.34 (dd, 1 H, J = 10.2, 13.2 Hz, H_{4B}), 4.03 (d, 1 H, J = 14.1 Hz, *H*CHN), 4.31 (d, 1 H, J = 14.1 Hz, HC*H*N), 5.76 (dd, 1 H, J = 4.8, 10.2 Hz, OCH), 6.06 (d, 1 H, 1.0 Hz), 6.59 (s, 1 H), 6.78 (d, 1 H, J = 1.0 Hz), 7.03 (d, 2 H, J = 8.6 Hz), 7.26–7.48 (m, 5 H), 7.76–7.81 (m, 1 H). Anal. Calcd for $C_{20}H_{19}Cl_2N_3O$: C, 61.87; H, 4.93; N, 10.82. Found: C, 61.77; H, 5.00; N, 10.77.

3-(4-Chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-(4-methylphenyl)isoxazolidine. ***cis*-20**: 47%, mp 135.5–137 °C (ethyl acetate). IR (KBr): 3097 (m), 3054 (m), 2998 (m), 2970 (m), 2920 (m), 2897 (m), 1509 (s), 1493 (s), 1468 (m), 1450 (m), 1282 (m), 1230 (s), 1095 (s), 1076 (s), 1038 (m), 1012 (m), 901 (m), 858 (m), 827 (s), 753 (m), 724 (m), and 667 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.38 (s, 3 H, $ArCH_3$), 2.44 (dd, 1 H, J = 5.0, 12.7 Hz, H_{4A}), 2.59 (s, 3 H, NCH_3), 3.14 (dd, 1 H, J = 9.9, 12.7 Hz, H_{4B}), 4.07 (d, 1 H, J = 14.3 Hz, *H*CHN), 4.29 (d, 1 H, J = 14.3 Hz, HC*H*N), 5.65 (dd, 1 H, J = 5.0, 9.9 Hz, OCH), 6.04 (s, 1 H), 6.55 (s, 1 H), 6.77 (s, 1 H), 7.02 (d, 2 H, J = 8.8 Hz), 7.23 (d, 2 H, J = 8.8 Hz), 7.30 (d, 2 H, J = 8.8 Hz), 7.34 (d, 2 H, J = 8.8 Hz). Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; Cl, 9.64; N, 11.42. Found: C, 68.40; H, 6.10; Cl, 9.67; N, 11.26. *trans*-**29**: 4%, mp 129 °C (ethyl acetate). IR (KBr): 3105 (w), 3006 (w), 2975 (m), 2920 (w), 2885 (m), 1594 (w), 1505 (s), 1494 (s), 1452 (m), 1400 (m), 1280 (m), 1234 (m), 1110 (m), 1097 (m), 1078 (s), 1025 (m), 1016 (m), 915 (m), 906 (m), 840 (m), 821 (s), 813 (s), 751 (m), and 664 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.34 (s, 3 H, $ArCH_3$), 2.47 (s, 3 H, NCH_3), 2.73 (dd, 1 H, J = 9.4, 13.8 Hz, H_{4A}), 2.86 (dd, 1 H, J = 8.3, 13.8 Hz, H_{4B}), 4.31 (d, 1 H, J = 15.4 Hz, *H*CHN), 4.42 (d, 1 H, J = 15.4 Hz, HC*H*N), 5.39 (t, 1 H, J = 8.8 Hz, OCH), 6.50 (s, 1 H), 6.94 (s, 1 H), 7.04–7.34 (m, 9 H). Anal. Calcd for $C_{21}H_{22}ClN_3O$: C, 68.56; H, 6.03; Cl, 9.64; N, 11.42. Found: C, 68.67; H, 6.14; Cl, 10.06; N, 11.44.

3-(4-Chlorophenyl)-5-(2,6-dichlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine. ***cis*-21**: 1:1 complex with 2-propanol, 3%, mp 64–66 °C (2-propanol). IR (KBr): 3300–3150 (br w, OH), 2961 (m), 1580 (m), 1562 (m), 1496 (s), 1438 (s), 1232 (m), 1113 (m), 1094 (m), 1078 (m), 1010 (m), 816 (m), 786 (m), 771 (s), 745 (m), and 658 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 1.21 (d, 6 H, J = 6.1 Hz), 1.85 (br s, 1 H, OH), 2.71 (s, 3 H, NCH_3), 2.71 (dd, 1 H, J = 6.7, 12.7 Hz, H_{4A}), 3.07 (dd, 1 H, J = 10.9, 12.7 Hz, H_{4B}), 4.10 (septet, 1 H, J = 6.1 Hz), 4.46 (d, 1 H, J = 14.9 Hz, *H*CHN), 4.54 (d, 1 H, J = 14.9 Hz, HC*H*N), 5.82 (dd, 1 H, J = 6.7, 10.9 Hz, OCH), 6.66 (d, 1 H, J = 1.0 Hz), 6.96 (s, 1 H), 7.11–7.35 (m, 8 H). Anal. Calcd for $C_{23}H_{26}Cl_3N_3O_2$: C, 57.21; H, 5.43; Cl, 22.03; N, 8.70. Found: C, 57.20; H, 5.40; Cl, 22.12; N, 8.74. *trans*-**30**: 6.4%, mp 159–161 °C (ethyl acetate). IR (KBr): 3092 (m), 2985 (m), 1584 (m), 1562 (m), 1490 (m), 1442 (m), 1425 (m), 1230 (s), 1094 (s), 1079 (s), 1013 (m), 905 (m), 833 (m), 823 (s), 775 (s), 771 (s), 760 (m), 725 (m), and 663 (s) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.51 (dd, 1 H, J = 7.5, 13.2 Hz, H_{4A}), 2.71 (s, 3 H, NCH_3), 3.33 (dd, 1 H, J = 9.3, 13.2 Hz, H_{4B}), 3.99 (d, 1 H, J = 14.0 Hz, *H*CHN), 4.15 (d, 1 H, J = 14.0 Hz, HC*H*N), 6.17 (dd, 1 H, J = 7.5, 9.3 Hz, OCH), 6.50 (s, 1 H), 6.98 (s, 1 H), 7.11 (s, 1 H), 7.20–7.56 (m, 7 H). Anal. Calcd for $C_{20}H_{18}Cl_3N_3O$: C, 56.82; H, 4.29; N, 9.94. Found: C, 56.90; H, 4.50; N, 9.73.

***cis*-3-(4-Fluorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methyl-5-phenylisoxazolidine (22).** 60%, mp 130–132 °C (ethyl acetate). IR (KBr): 3098 (w), 3065 (w), 3028 (w), 2992 (w), 2970 (w), 1650 (m), 1635 (m), 1602 (m), 1508 (s), 1442 (s), 1410 (m), 1326 (m), 1285 (m), 1232 (s), 1226 (s), 1077 (m), 1041 (m), 1012 (m), 908 (m), 860 (m), 831 (m), 821 (m), 746 (m), 701 (s), and 665 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.48 (dd, 1 H, J = 4.4, 12.7 Hz, H_{4A}), 2.61 (s, 3 H, NCH_3), 3.21 (dd, 1 H, J = 10.4, 12.7 Hz, H_{4B}), 4.09 (d, 1 H, J = 14.3 Hz, *H*CHN), 4.30 (d, 1 H, J = 14.3 Hz, HC*H*N), 5.70 (dd, 1 H, J = 4.4, 10.4 Hz, OCH), 5.98 (s, 1 H), 6.50 (s, 1 H), 6.76 (s, 1 H), 6.99–7.50 (m, 9 H). Anal. Calcd for $C_{20}H_{20}FN_3O$: C, 71.20; H, 5.97; F, 5.63; N, 12.45. Found: C, 71.33; H, 6.52; F, 5.64; N, 12.46.

***cis*-3,5-Bis(4-methoxyphenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-methylisoxazolidine (23).** 32%, mp 117–120 °C (ethyl acetate). IR (KBr): 2992 (w), 2970 (m), 2961 (m), 2934 (m), 2837 (w), 1612 (m), 1514 (s), 1462 (m), 1439 (m), 1301 (m), 1253 (s), 1232 (m), 1180 (s), 1047 (m), 1033 (m), 904 (m), 834 (m), 823 (m), and 663 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.38 (dd, 1 H, J = 4.4, 13.2 Hz, H_{4A}), 2.59 (s, 3 H, NCH_3), 3.13 (dd, 1 H, J = 9.9, 13.2 Hz, H_{4B}), 3.81 (s, 3 H, OCH_3), 3.83 (s, 3 H, OCH_3), 4.13 (d, 1 H, J = 14.3 Hz, *H*CHN), 4.25 (d, 1 H, J = 14.3 Hz, HC*H*N), 5.64 (dd, 1 H, J = 4.4, 9.9 Hz, OCH), 5.98 (s, 1 H), 6.49 (s, 1 H), 6.74 (s, 1 H), 6.86 (d, 2 H, J = 8.8 Hz), 6.96 (d, 2 H, J = 8.3 Hz), 7.03 (d, 2 H, J = 8.8 Hz), 7.38 (d, 2 H, J = 8.3 Hz). Anal. Calcd for $C_{22}H_{25}N_3O_3$: C, 69.64; H, 6.64; N, 11.07. Found: C, 69.57; H, 6.85; N, 10.88.

***cis*-3-(4-Chlorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-2-[(4-methoxyphenyl)methyl]-5-phenylisoxazolidine (24)**: 28%,

mp 162–167 °C (ethyl acetate–hexane, 1:1). IR (KBr): 3132 (w), 2930 (w), 2905 (w), 2830 (w), 1609 (m), 1582 (w), 1513 (s), 1492 (m), 1452 (m), 1250 (s), 1235 (m), 1175 (m), 1095 (m), 1077 (m), 1038 (m), 1012 (m), 820 (m), 745 (s), and 698 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.54 (dd, 1 H, J = 5.0, 12.7 Hz, H_{4A}), 3.24 (dd, 1 H, J = 10.4, 12.7 Hz, H_{4B}), 3.61 (d, 1 H, J = 13.8 Hz, Ar *H*CHN), 3.78 (d, 1 H, J = 13.8 Hz, Ar HC*H*N), 3.80 (s, 3 H, OCH_3), 4.10 (d, 1 H, J = 13.8 Hz, *H*CHN), 4.36 (d, 1 H, J = 13.8 Hz, HC*H*N), 5.75 (dd, 1 H, J = 5.0, 10.4 Hz, OCH), 6.03 (s, 1 H), 6.55 (s, 1 H), 6.78 (s, 1 H), 6.88 (d, 2 H, J = 8.8 Hz), 7.11 (d, 2 H, J = 8.8 Hz), 7.24–7.47 (m, 9 H). Anal. Calcd for $C_{27}H_{26}ClN_3O_2$: C, 70.50; H, 5.70; Cl, 7.71; N, 9.14. Found: C, 70.40; H, 5.80; Cl, 8.13; N, 9.14.

***cis*-3-(4-Fluorophenyl)-3-(1*H*-imidazol-1-ylmethyl)-5-phenyl-2-(phenylmethyl)isoxazolidine (25)**: 48%, mp 162–164 °C (ethyl acetate). IR (KBr): 3095 (m), 2848 (m), 1678 (m), 1585 (m), 1505 (s), 1490 (s), 1438 (m), 1277 (m), 1223 (s), 1150 (m), 1102 (m), 1067 (m), 1031 (m), 1018 (m), 1003 (m), 897 (m), 850 (m), 818 (m), 738 (m), 725 (m), 697 (s), and 660 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 2.56 (dd, 1 H, J = 5.0, 13.2 Hz, H_{4A}), 3.26 (dd, 1 H, J = 10.4, 13.2 Hz, H_{4B}), 3.67 (d, 1 H, J = 14.3 Hz, Ar *H*CHN), 3.86 (d, 1 H, J = 14.3 Hz, Ar HC*H*N), 4.11 (d, 1 H, J = 13.8 Hz, *H*CHN), 4.37 (d, 1 H, J = 13.8 Hz, HC*H*N), 5.76 (dd, 1 H, J = 5.0, 10.4 Hz, OCH), 6.02 (s, 1 H), 6.42 (s, 1 H), 6.77 (s, 1 H), 7.00–7.48 (m, 14 H). Anal. Calcd for $C_{26}H_{24}FN_3O$: C, 75.52; H, 5.85; F, 4.59; N, 10.16. Found: C, 75.50; H, 6.04; F, 4.74; N, 10.05.

General Procedure for the Preparation of α-Substituted Ketonitrones 11. A suspension of 35.54 g (0.191 mol) of 2-(1*H*-imidazol-1-yl)-1-phenylethanone (**10**; R^1 = H), 20.63 g (0.247 mol) of *N*-methylhydroxylamine hydrochloride, and 40.60 g (0.494 mol) of sodium acetate in 400 mL of ethanol was stirred for 48 h at ambient temperature under a nitrogen atmosphere. The reaction mixture was poured into 500 mL of water, basified with sodium bicarbonate, and extracted with chloroform (4 × 200 mL). The combined organic extract was dried ($MgSO_4$) and concentrated under reduced pressure. Addition of ether resulted in the precipitation of a yellow solid, which was recrystallized from ethyl acetate to furnish 29.82 g (72.6%) of 2-(1*H*-imidazol-1-yl)-*N*-methyl-1-phenylethanimine *N*-oxide (**11**; R^1 = H) as white needles, mp 126–128 °C. IR (KBr): 1587 (m), 1507 (m), 1289 (m), 1246 (s, NO), 1102 (m), 1078 (m), 962 (m), 831 (m), 771 (s), 699 (m), and 677 (m) cm^{-1}. ^1H NMR (200 MHz, $CDCl_3$): δ 3.59 (s, 3 H, NCH_3), 5.25 (s, 2 H, NCH_2), 6.80 (s, 1 H), 6.89 (s, 1 H), 6.97–7.02 (m, 2 H), 7.31–7.38 (m, 4 H). Anal. Calcd for $C_{12}H_{13}N_3O$: C, 66.96; H, 6.09; N, 19.52. Found: C, 66.74; H, 6.18; N, 19.38.

All remaining nitrone precursors **11** were prepared by procedures similar to that of **11** (R^1 = H).

In Vitro Assay for Antifungal Activity. The antifungal activity was assayed in vitro in solid agar tests performed in 24-well tissue culture plates. The test medium was prepared by diluting the test compound 10-fold into Antibiotic Medium 3 + 2% agar. The testing was performed by using either a four-point (70, 20, 2, and 2 μg/mL) or six-point (70, 20, 7, 2, 0.7, and 0.2 μg/mL) dilution scheme with ketoconazole being used as a control in all assays. All test organisms were grown on Potato Flake Agar at 26 °C. *C. albicans* was grown overnight, *A. fumigatus* was grown for approximately 1 week, and *T. rubrum* was grown for approximately 2 weeks. The cells were either removed from the plates with a sterile cotton swab and suspended in sterile water (*C. albicans*, *A. fumigatus*) or washed from the surface of the plate with sterile water and diluted in sterile water (*T. rubrum*). The actual cell counts were performed with a hemacytometer, and the suspensions were diluted to 1 × 10^4 cells/mL. The test and control plates were inoculated with 0.05 mL of the fungal suspension and were incubated at 26 °C until visible growth in the compound-free control plates was evident. The minimum inhibitory concentration (MIC) values were interpreted as the lowest dilution at which no visible growth occured.

Rat Vaginal Candidiasis Assay. Groups of eight Sprague–Dawley ovariectomized female rats (weighing 170–230 g) were used in the assay. Pseudoestrus was initiated by subcutaneous injection of 0.5 mg of estradiol valerate (Delestrogen Squibb, Princeton, NJ) (diluted in sesame oil to a final concentration of 5 mg/mL). The animals were maintained in pseudoestrus by weekly injection of estradiol valerate. Clinical isolates of *C. albicans* SOB FM-391 were cultured in Sabouraud dextrose agar, and isolated colonies were picked from the surface of the plate, placed in 50 mL of Sabouraud's dextrose broth, and allowed to grow for 22 h on a clinical rotator at room temperature. One-milliliter aliquots of the broth culture were transfered into 5-mL falcon tubes and frozen at −20 °C. When needed, the aliquots of *C. albicans* were each placed in a 50-mL flask containing 10 mL of 1% phytone-peptone and 1% glucose broth, and the flasks were then placed on a clinical rotator for 36 h at room temperature. After removal of the supernatant (by centrifuging for 10 min), the residual pellet was resuspended in RPMI Tissue Culture Media (R-3505, Sigma) plus 100 units/mL of Penicillin G (PEN-NA, Sigma) and 100 μg/mL of streptomycin sulfate (S-6501, Sigma) (designated $RPMI^+$). This stock was quantitated by hemacytometer to make an inoculum containing 1 × 10^8 organisms/mL.

On the day of infection (4 days after the initial estradiol application) the animals were tranquilized by ip injection of 10 mg of ketamine hydrochloride. The anesthetized animals were then suspended head down, and a dry cotton swab was inserted into the vagina to dilate it. Following dilation, 0.1 mL of the inoculum was inserted into the vagina by using a tuberculin syringe with a 1-cm length of butterfly tubing attached. Animals were challenged with 1 × 10^7 organisms in 0.1 mL of $RPMI^+$. The test compound was applied at concentrations of 5.0, 2.0, and 0.5 mg/mL in 1% (carboxymethyl)cellulose. All rats were dosed twice daily with a 18 gauge 2-in. ball ended feeding needle. The rats were treated for 7 days starting 24 h after the infection. Ketoconazole was used as the positive standard in all assays.

The quantitation of the candidal infection was performed as follows. The animal being sampled was anesthetized with 10 mg of ketamine hydrochloride (ip), and a sterile swab, dampened in sterile PBS and wrung out, was inserted into the vagina and twisted several times before removal. The swab was then swirled in 0.3 mL of sterile PBS in a 5-mL falcon tube and wrung out. The suspensions were diluted 10-fold in sterile PBS; 0.1 mL of each dilution (10^1, 10^2, etc.) was then placed on a SDA plate by spreading the lavage fluid evenly using alcohol-flamed bent glass rod until the plates were dry. The plates were incubated at 24–26 °C for 48 h, and plates containing 15–150 colonies were counted. The number of organisms is reported as the $\log_{10}$ (the number of *C. albicans* organisms/mL of lavage fluid).

Registry No. **10** (R' = H), 24155-34-8; **10** (R' = 4-Cl), 24155-32-6; **10** (R' = 4-F), 24155-33-7; **10** (R' = 4-OMe), 46720-41-6; **11** (R' = H), 113944-26-6; **11** (R' = 4-Cl), 113944-25-5; **11** (R' = 4-F), 113944-27-7; **11** (R' = 4-OMe), 114372-91-7; **12** (R^2 = H), 100-42-5; **12** (R^2 = 3,4-$(OMe)_2$), 6380-23-0; **12** (R^2 = 4-Cl), 1073-67-2; **12** (R^2 = 2-Cl), 2039-87-4; **12** (R^2 = 4-Me), 622-97-9; **12** (R^2 = 2,6-Cl_2), 28469-92-3; **12** (R^2 = 4-OMe), 637-69-4; **15**, 113614-46-3; **16**, 113614-60-1; **16**·HCl, 115797-07-4; **17**, 113614-48-5; **18**, 113614-50-9; **19**, 113614-52-1; **20**, 113614-56-5; **21**, 113614-54-3; **22**, 113614-58-7; **23**, 113614-44-1; **24**, 115797-08-5; **25**, 115797-09-6; **26**, 113614-47-4; **27**, 113614-49-6; **28**, 113614-51-0; **29**, 113614-57-6; **30**, 113614-55-4; CH_3NHOH·HCl, 4229-44-1; *p*-$MeOC_6H_4NHOH$·HCl, 115797-10-9; PhNHOH·HCl, 22755-09-5; 1-(4-chlorophenyl)-2-(1*H*-imidazol-1-yl)-*N*-(4-methoxybenzyl)-ethanimine *N*-oxide, 115797-11-0; 1-(4-fluorophenyl)-2-(1*H*-imidazol-1-yl)-*N*-benzylethanimine *N*-oxide, 114371-20-9.