Synthesis and Antifungal Activity of New 1-Vinylimidazoles

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Carbonyl compounds I were subjected to an imidazole transfer reaction with *N,N'*-sulfinyldiimidazole or *N,N'*-carbonyldiimidazole to obtain the diimidazole II and the monoimidazole III. Various 1-vinylimidazoles IV, derived from *o*-hydroxyacetophenones by imidazole transfer reaction, were alkylated to furnish the title compounds V. The structure–activity relationships of these 1-vinylimidazole compounds V are described.

Substances containing the imidazole (triazole) nucleus have been synthesized because they display antifungal activity. In recent years, we found a new imidazole transfer reaction using *N,N'*-sulfinyldiimidazole or *N,N'*-carbonyldiimidazole, which gives the diimidazole II and the monoimidazole III from carbonyl compounds I.[1,2] Our interest in further use of this reaction in organic synthesis led us to investigate the synthesis of antifungal imidazoles. One of the compounds synthesized by the imidazole transfer reaction, croconazole, was studied in detail, and its synthesis and antifungal activity were described in a previous report.[1b]

The present paper discusses the synthesis and the structure–activity relationships of various 1-vinylimidazoles V.

Chemistry

Various carbonyl compounds I underwent facile imidazole transfer reaction with *N,N'*-sulfinyldiimidazole to give the diimidazole II and monoimidazole III (Table I, Scheme I). Among them, *o*-hydroxyacetophenones afforded the 1-vinylimidazoles IV in good yield.[1a,3] Treatment of IV with alkyl halides in the presence of sodium hydride in dimethylformamide gave the target ethers V (Table II).

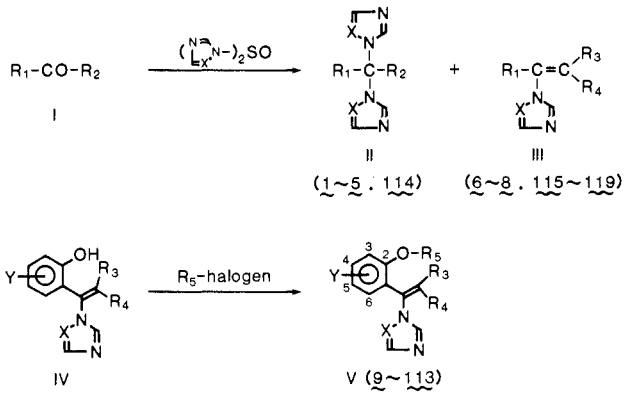
When R_3 and R_4 in IV are different substituents, two geometrical isomers are obtained. The determination of the geometrical isomer of IV was done by X-ray analysis (Figure 1) or comparison of the NMR spectra. Namely, *o*-hydroxypropiophenone (I, R_1 = *o*-hydroxyphenyl, R_2 = Et) was treated with *N,N'*-sulfinyldiimidazole to obtain a mixture of geometrical isomers IV (*E* form, trans form of imidazole and methyl groups, X = CH, Y = H, R_3 = Me, R_4 = H; *Z* form, cis form of imidazole and methyl groups, X = CH, Y = H, R_3 = H, R_4 = Me), which were separated by silica gel column chromatography and then treated with *p*-chlorobenzyl bromide to obtain the benzyl ethers V (*E* form, **60**, and *Z* form, **61**, respectively). The structure of the *E* isomer (**60**, trans form of imidazole and methyl groups) was defined from the crystal structure by X-ray diffraction (Figure 1). This *E* isomer (IV, X = CH, Y = H, R_3 = Me, R_4 = H) can be distinguished from the *Z* isomer (IV, X = CH, Y = H, R_3 = H, R_4 = Me) by the characteristic vinyl and methyl proton signals in the ^{1}H NMR spectra. Comparison of the ^{1}H NMR spectra of the *E* and *Z* isomers showed that the proton signals of the vinyl and the methyl groups of the *E* isomer (methyl proton, δ 1.60; vinyl proton, δ 6.07) were shifted to lower field than those of the *Z* isomer (methyl proton, δ 1.68; vinyl proton, δ 6.28) (Experimental Section). This relationship led to distinction among the geometrical isomers of compounds **100–109**, which have various aminomethyl groups.

The antifungal activities were compared by replacing the oxygen atom of the ether of V with a nitrogen or sulfur atom. The 1-vinylimidazole (III, R_1 = *o*-aminophenyl, R_3 = R_4 = H)[1a] prepared from *o*-aminoacetophenone with *N,N'*-sulfinyldiimidazole was treated with trifluoroacetic anhydride to obtain the trifluoroacetamide, which was alkylated with *p*-chlorobenzyl bromide in the presence of potassium carbonate to obtain the benzylamino compound **116**. Deprotection by hydrolysis with dilute sodium hydroxide afforded the target compound **117**.

Treatment of 2-acetylthiophenol with 4-chlorobenzyl bromide in the presence of potassium carbonate in acetone gave 2-[(4-chlorobenzyl)thio]acetophenone, which was treated with *N,N'*-sulfinyldiimidazole[5] to obtain the target compound **118** (Scheme II).

Compounds **100–109**, which have an aminomethyl group in R_3 or R_4 of V, were prepared by the following methods (Scheme III). *o*-Hydroxyacetophenones were treated with dimethylamine hydrochloride (or morpholine hydrochloride) in the presence of paraformaldehyde in ethanolic hydrochloric acid (standard Mannich reaction) to obtain the aminoethyl ketones VI. If necessary, the dimethylamino group in these compounds was converted to the anilino compound VII by heating with *N*-methylaniline in ethanol. The above ketones VI and VII underwent an imidazole transfer reaction with *N,N'*-sulfinyldiimidazole to give the 1-vinylimidazoles IV, which have the aminomethyl or morpholinomethyl group in R_3 or R_4. These 1-vinylimidazoles IV were treated with alkyl halides to

Scheme I



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‡Division of Physical Chemistry.
§Division of Microbiology.

(1) (a) Ogata, M.; Matsumoto, H.; Kida, S.; Shimizu, S. *Tetrahedron Lett.* **1979**, 5011. (b) Ogata, M.; Matsumoto, H.; Hamada, Y.; Takehara, M.; Tawara, K. *J. Med. Chem.* **1983**, *26*, 768. (c) Ogata, M.; Matsumoto, H. *Synth. Commun.* **1980**, *10*, 559. (d) Ogata, M.; Matsumoto, H. *Synth. Commun.* **1980**, *10*, 733.
(2) Ogata, M. *Shionogi Kenyusho Nenpo* **1986**, *36*, 1.
(3) Ogata, M.; Matsumoto, H.; Takahashi, K.; Shimizu, S.; Kida, S.; Ueda, M.; Kimoto, S.; Haruna, M. *J. Med. Chem.* **1984**, *27*, 1142.
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(5) Ogata, M.; Matsumoto, H.; Takahashi, K.; Shimizu, S.; Kida, S.; Murabayashi, A.; Shiro, M.; Tawara, K. *J. Med. Chem.* **1987**, *30*, 1054.

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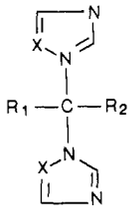
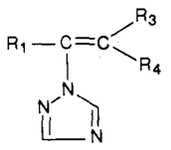
Table I



II(1-5, 114)

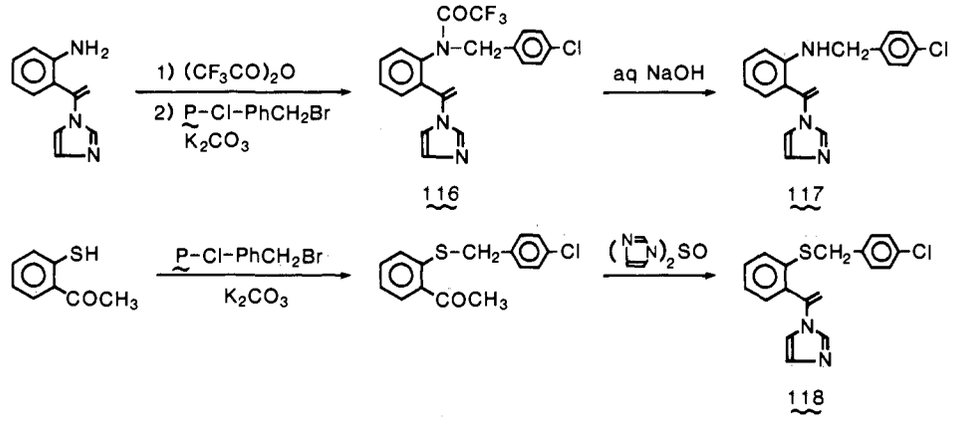


III(6-8, 115-119)

no.	X	R_1	R_2	R_3	R_4	recrystn solvent[c] (mp, °C)	yield, %	formula[d]	MIC,[e,5,6] μg/mL C.a.	MIC,[e,5,6] μg/mL A.f.	MIC,[e,5,6] μg/mL T.a.	MEC,[f,5] μg/mL
1	CH	Me	Me	–	–	A/I (103–106)	3	$C_9H_{12}N_4$	>100	>100	>100	
2	CH	Ph	H	–	–	A/I (98–99)	30	$C_{13}H_{12}N_4$	>100	>100	>100	
3	CH	Ph	Me	–	–	A/I (141–143)	37	$C_{14}H_{14}N_4$	>100	>100	>100	
4	CH	4-ClC_6H_4	Me	–	–	A/I (126–127.5)	26	$C_{14}H_{13}ClN_4$	>100	>100	>100	
5	CH	Ph	Ph	–	–	A/I (189–191)	32	$C_{19}H_{16}N_4$	>100	>100	0.8	
6	CH	Me	–	H	H	M/E (132–134)	2	$C_6H_8N_2 \cdot C_6H_3N_3O_7$				
7	CH	Ph	–	H	H	M/E (113–115.5)	12	$C_{11}H_{10}N_2 \cdot C_6H_3N_3O_7$	>100	>100	100	>20
8	CH	4-ClC_6H_4	–	H	H	M/E (146–149)	13	$C_{11}H_9ClN_2 \cdot C_6H_3N_3O_7$	100	100	25	>20
114	CH	3-(CP-O)C_6H_4[a]	Me	–	–	A/E (130–131.5)	18	$C_{21}H_{19}ClN_4O$	>100	>100	12.5	
115	CH	3-(CP-O)C_6H_4	–	H	H	(oil)	20	$C_{18}H_{15}ClN_2O \cdot {}^1/_2H_2O$	50	12.5	1.6	5
116	CH	2-[N(CP)(TF)]C_6H_4[b]	–	H	H	I (101–101.5)	17	$C_{20}H_{25}ClF_3N_3O$	1.6	50	1.6	20
117	CH	2-[NH(CP)]C_6H_4	–	H	H	A (147–148)	36	$C_{18}H_{16}ClN_3$	>100	>100	>100	
118	CH	2-[S(CP)]C_6H_4	–	H	H	M/E (153–163)	12	$C_{18}H_{15}ClN_2S \cdot HCl$	50	0.8	0.1	
119	CH	2-OHC_6H_4	–	H	H	P(152.5–154.5)	75	$C_{11}H_{10}N_2O$				

[a] CP: 4-$ClC_6H_4CH_2$. [b] TF: CF_3CO. [c] AcOEt, A; *i*-Pr_2O, I; MeOH, M; Et_2O, E; *i*-PrOH, P. [d] All compounds were analyzed for C, H, and N and, where present, Cl, F, and S, and results were withint 0.4% of the calculated values. [e] Lowest value in experiments duplicated. *C.a.* = *Candida albicans*, *A.f.* = *Aspergillus fumigatus*, *T.a.* = *Trichophyton asteroides*. [f] Lowest values in experiments duplicated. For pseudomycelium formation of *Candida albicans*.

Scheme II



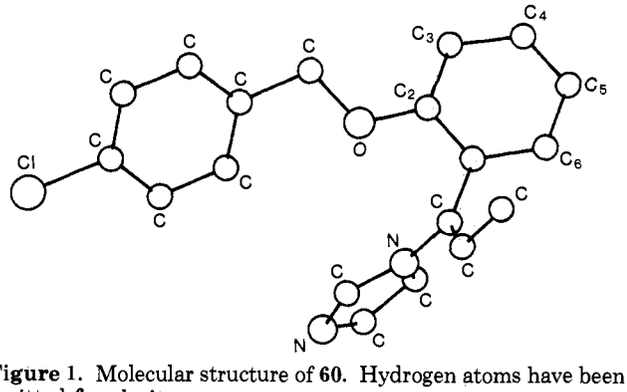


Figure 1. Molecular structure of **60**. Hydrogen atoms have been omitted for clarity.

obtain the target compounds V in the usual manner.

Results and Discussion

1-Vinylimidazoles II–V were tested for fungistatic activity (MIC) against three species of fungi and inhibitory effect (MEC) on pseudomycelium formation of *Candida albicans* according to a method described earlier.[5] The test results are summarized in Tables I and II. Most of the compounds that belonged to type V showed good fungistatic activity. Compounds II–IV were weakly active or inactive. Among compounds V, **25**, **27**, **30**, **32**, **60**, **61**, **67**, **73**, and **93** were chosen as candidates for broad-spectrum imidazole antimycotics. Their fungistatic activities were evaluated by the agar dilution method and compared with that of clotrimazole.

The agar dilution test was conducted on Sabouraud's glucose agar, with inocula[6] of 1×10^6 cells/mL of yeast (two strains) or 1×10^6 conidia/mL of dermatophyte (four strains). The comparative test results are given in Table III. These 1-vinylimidazole candidates inhibited the *Trichophyton* species at MIC values of 0.4–1.6 μg/mL and *Candida albicans* at 6.3–12.5 μg/mL. Clotrimazole caused inhibition at 0.4–0.8 μg/mL and at 6.3–12.5 μg/mL, respectively. Compound **27**[1b] was found to be the most active

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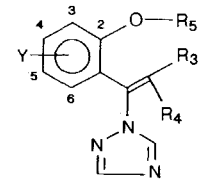
Table II



V(9-113)

no.	X	Y	R_3	R_4	R_5	recrystn solvent[c] (mp °C)	yield, %	formula[d]	MIC,[e,5,6] μg/mL C.a.	A.f.	T.a.	MEC,[f,5] μg/mL
9	CH	H	H	H	Me	M/A (190–195)	41	$C_{12}H_{12}N_2O$·HCl	>100	12.5	1.6	
10	CH	5-Cl	H	H	Me	M/A (239 dec)	78	$C_{12}H_{11}ClN_2O$·HCl	>100	3.1	0.4	
11	CH	H	H	H	Et	M/A (159–162)	66	$C_{13}H_{14}N_2O$·HCl·$^1/_2H_2O$	>100	3.1	0.4	
12	CH	4-Cl	H	H	Me	M/A (193–196)	87	$C_{12}H_{11}N_3O$·HCl·$^1/_2H_2O$	>100	100	25	
13	CH	H	H	H	*n*-Pr	M/A (146–148)	79	$C_{14}H_{16}N_2O$·HCl·$^1/_2H_2O$	100	1.6	0.1	
14	CH	5-Cl	H	H	*n*-Pr	M/A (178–181)	75	$C_{14}H_{15}ClN_2O$·HCl	25	0.8	0.1	
15	CH	5-Cl	H	H	*i*-Pr	M/A (127–128)	66	$C_{14}H_{15}ClN_2O$·$(COOH)_2$	50	0.8	0.1	5
16	CH	H	H	H	*n*-Bu	(oil)	84	$C_{15}H_{18}N_2O$	25	1.6	50	
17	CH	5-Cl	H	H	*n*-Bu	M/A (121.5–122.5)	81	$C_{15}H_{17}ClN_2O$·$(COOH)_2$	25	0.4	0.2	
18	CH	5-Cl	H	H	*i*-Bu	M/A (101–103)	70	$C_{17}H_{19}ClN_2O_5$·$(COOH)_2$	50	0.8	0.1	1.25
19	CH	H	H	H	*i*-Bu	M/A (97–98)	58	$C_{17}H_{20}N_2O_5$·$^4/_5H_2O$	100	1.6	0.1	0.63
20	CH	H	H	H	*i*-Am	A (103–104)	59	$C_{20}H_{26}N_2O_5$	25	0.4	0.1	0.63
21	CH	H	H	H	$PhCH_2$	M/A (154–156)	46	$C_{18}H_{16}N_2O$·HCl	12.5	3.1	0.2	
22	CH	H	H	H	4-$MeC_6H_4CH_2$	M/A (180–183)	49	$C_{19}H_{18}N_2O$·HCl·$^1/_{10}H_2O$	3.1	3.1	0.1	
23	CH	H	H	H	4-$NO_2C_6H_4CH_2$	A/I (94–95.5)	24	$C_{18}H_{15}N_3O_3$	12.5	6.2	0.1	
24	CH	H	H	H	4-$MeOC_6H_4CH_2$	(oil)	99	$C_{19}H_{18}N_2O_2$	25.0	6.2	0.1	
25	CH	H	H	H	4-$ClC_6H_4CH_2$	M/A (180.5–181)	51	$C_{18}H_{15}ClN_2O$·HCl	6.2	3.1	0.1	
26	CH	H	H	H	4-$EtC_6H_4CH_2$	M/A (138–147)	7	$C_{20}H_{20}N_2O$·HCl	12.5	25.0	0.1	
27	CH	H	H	H	3-$ClC_6H_4CH_2$	A/N (148.5–150)	82	$C_{18}H_{15}ClN_2O$·HCl	3.1	3.1	0.1	
28	CH	H	H	H	2,4-$Cl_2C_6H_3CH_2$	M/A (161–163)	67	$C_{18}H_{14}Cl_2N_2O$·HCl	50	1.6	0.1	
29	CH	H	H	H	3,4-$Cl_2C_6H_3CH_2$	M/A (172–174)	60	$C_{18}H_{14}Cl_2N_2O$·HCl	25	3.1	0.1	
30	CH	5-Cl	H	H	4-$ClC_6H_4CH_2$	M/A (188–190)	44	$C_{18}H_{14}Cl_2N_2O$·HCl	12.5	3.1	0.1	
31	CH	3,5-Cl_2	H	H	$PhCH_2$	M/A (170–172)	49	$C_{18}H_{14}Cl_2N_2O$·HCl	>100	>100	3.1	
32	CH	5-Cl	H	H	$PhCH_2$	M/A (174–175)	81	$C_{18}H_{15}ClN_2O$·HCl	6.2	3.1	0.1	
33	CH	H	H	H	4-*i*-$PrC_6H_4CH_2$	(oil)	80	$C_{21}H_{22}N_2O$	25	3.1	3.1	
34	CH	5-Cl	H	H	4-$MeC_6H_4CH_2$	M/A (180–183)	48	$C_{19}H_{18}N_2O$·HCl·$^1/_{10}H_2O$	25	1.6	0.8	
35	CH	H	H	H	2-$ClC_6H_4CH_2$	A/I (69.5–70.5)	36	$C_{18}H_{15}ClN_2O$	6.2	0.8	0.1	
36	CH	3,6-Cl_2	H	H	4-$ClC_6H_4CH_2$	N (127–129)	45	$C_{18}H_{13}Cl_3N_2O$·$(COOH)_2$	>100	>100	12.5	
37	CH	5-Cl	H	H	4-$COOMeC_6H_4CH_2$	A/I (100–101)	63	$C_{20}H_{17}ClN_2O_3$	25	6.2	0.1	
38	CH	H	H	H	4-$ClC_6H_4O(CH_2)_2$	M/A (140–142)	12	$C_{19}H_{17}ClN_2O_2$·HCl	50	1.6	0.1	
39	CH	H	H	H	4-$ClC_6H_4O(CH_2)_3$	(oil)	74	$C_{20}H_{19}ClN_2O_2$	12.5	12.5	0.1	
40	CH	H	H	H	$Ph(CH_2)_3$	(oil)	67	$C_{20}H_{20}N_2O$	12.5	3.1	0.1	
41	CH	H	H	H	4-$ClC_6H_4S(CH_2)_3$	M/A (138–140)	62	$C_{20}H_{19}ClN_2OS$·HCl	25	3.1	0.1	
42	CH	5-Cl	H	H	$Ph(CH_2)_2$	M/A (136–138)	23	$C_{19}H_{17}ClN_2O$·$(COOH)_2$	50	6.3	0.1	
43	CH	H	H	H	4-$ClC_6H_4(CH_2)_2$	M/A (102.5–103.5)	20	$C_{19}H_{17}ClN_2O$·$(COOH)_2$	25	0.4	0.1	1.25
44	CH	H	H	H	2,4-$Cl_2C_6H_4(CH_2)_2$	M/A (126–127)	7	$C_{19}H_{16}Cl_2N_2O$·$(COOH)_2$	25	0.4	0.1	
45	CH	H	H	H	4-$ClC_6H_4(CH_2)_3$	M/A (116–118)	17	$C_{20}H_{19}ClN_2O(COOH)_2$	12.5	0.8	0.2	
46	CH	5-Cl	H	H	$Ph(CH_2)_3$	M/A (126–127)	43	$C_{20}H_{19}ClN_2O$·$(COOH)_2$	50	1.6	0.2	
47	CH	H	H	H	$PhO(CH_2)_2$	M/A (158–160)	54	$C_{19}H_{18}N_2O_2$·HCl	50	12.5	0.1	
48	CH	H	H	H	$Ph(CH_2)_2$	M/A (100.5–102)	43	$C_{19}H_{18}N_2O$·$(COOH)_2$	12.5	0.4	0.1	1.25
49	CH	H	H	H	4-$ClC_6H_4CH(Me)$	M/A (110–113)	71	$C_{19}H_{17}ClN_2O$·$(COOH)_2$	3.1	6.2	0.1	
50	CH	H	H	H	PhCH(Me)	N (172.5–174.5)	35	$C_{19}H_{18}N_2O$·HCl	25	6.2	0.1	

51	CH	5-Cl	H	H	PhCH(Me)	N (74–75)	45	$C_{19}H_{17}ClN_2O\cdot HCl\cdot H_2O$	25	6.2	0.1		
52	CH	H	H	H	PhCH(Et)	N/E (130–132)	19	$C_{20}H_{20}N_2O\cdot(COOH)_2$	6.2	3.1	0.1		
53	CH	5-Cl	H	H	PhCH(Et)	(oil)	58	$C_{20}H_{19}ClN_2O$	>100	12.5	0.1		
54	CH	H	H	H	4-$MeOC_6H_4CH$(Me)	(oil)	6	$C_{20}H_{20}N_2O_2\cdot{}^3/_{10}CH_2Cl_2$	12.5	12.5	0.4		
55	CH	H	H	H	PhCH(*n*-Pr)	A (105–107)	49	$C_{21}H_{22}N_2O\cdot(COOH)_2$	12.5	12.5	0.4		
56	CH	H	H	H	3-ClC_6H_4CH(Me)	N/E (97–98)	35	$C_{19}H_{17}ClN_2O\cdot(COOH)_2$	6.2	12.5	0.4		
57	CH	5-Cl	H	H	3-ClC_6H_4CH(Me)	N/E (115–117)	37	$C_{19}H_{16}Cl_2N_2O\cdot(COOH)_2$	6.2	12.5	0.1		
58	CH	5-Cl	H	H	PhCH(*n*-Pr)	(oil)	63	$C_{21}H_{21}ClN_2O$	>100	>100	0.8		
59	CH	5-Cl	H	H	4-ClC_6H_4CH(Me)	M/A (179.5–180)	44	$C_{19}H_{16}Cl_2N_2O\cdot HCl$	12.5	12.5	0.1		
60	CH	H	Me	H	4-$ClC_6H_4CH_2$	M/A (185–187)	59	$C_{19}H_{17}ClN_2O\cdot HCl$	6.2	3.1	0.1		
61	CH	H	H	Me	4-$ClC_6H_4CH_2$	M/A (170–178)	55	$C_{19}H_{17}ClN_2O\cdot HCl$	6.2	3.1	0.1		
62	CH	5-Cl	H	Ph	Me	M/A (118–118.5)	92	$C_{18}H_{15}ClN_2O$	12.5	25	6.2	>20	
63	CH	H	Me, H[a]		2,4-$Cl_2C_6H_3CH_2$	M/A (177–178)	45	$C_{19}H_{16}Cl_2N_2O\cdot HCl$	12.5	0.1	6.2		
64	CH	5-Cl	Me, H[a]		$PhCH_2$	M/A (132–134)	37	$C_{19}H_{17}ClN_2O\cdot HCl$	6.2	3.1	0.2		
65	CH	5-Cl	Me, H[a]		4-$ClC_6H_4CH_2$	M/A (211–212)	68	$C_{19}H_{16}Cl_2N_2O\cdot HCl$	3.1	0.8	0.8		
66	CH	5-Cl	Me, H[a]		2,4-$Cl_2C_6H_3CH_2$	M/A (170–174)	60	$C_{19}H_{15}Cl_3N_2O\cdot HCl$	12.5	0.4	1.6		
67	CH	H	Me, H[a]		3,4-$Cl_2C_6H_3CH_2$	M/A (156–158)	63	$C_{19}H_{16}Cl_2N_2O\cdot HCl$	6.2	0.4	0.1		
68	CH	H	Me, H[a]		3-$ClC_6H_4CH_2$	(oil)	71	$C_{19}H_{17}ClN_2O$	6.2	1.6	3.1		
69	CH	4-Cl	H	H	4-$ClC_6H_4CH_2$	A/E (132–133)	61	$C_{18}H_{14}Cl_2N_2O$	>100	>100	>100		
70	CH	3,5-Cl_2	H	H	4-$ClC_6H_4CH_2$	M/E (155–165)	56	$C_{18}H_{13}Cl_3N_2O\cdot HCl$	>100	>100	6.2		
71	CH	5-Cl	Me	Me	4-$ClC_6H_4CH_2$	M/A (201–203)	49	$C_{20}H_{18}Cl_2N_2O\cdot HCl$	6.2	6.2	0.2		
72	CH	H	Me	H	3-ClC_6H_4CH(Me)	(oil)	99	$C_{20}H_{19}ClN_2O_2$	3.1	1.6	0.1		
73	CH	H	Me	Me	4-$ClC_6H_4CH_2$	M/A (137–138)	61	$C_{20}H_{19}ClN_2O\cdot HCl$	3.1	6.2	0.1		
74	CH	5-Cl	Me	Me	3,4-$Cl_2C_6H_3CH_2$	M/A (193–194)	66	$C_{20}H_{17}Cl_3N_2O\cdot HCl$	12.5	6.2	3.1		
75	CH	H	Me	Me	$PhCH_2$	(oil)	53	$C_{20}H_{20}N_2O$	25	12.5	1.6		
76	CH	H	Me	Me	2,4-$Cl_2C_6H_3CH_2$	I (100–102)	36	$C_{20}H_{18}Cl_2N_2O$	12.5	1.6	3.1		
77	CH	H	Me	Me	4-$ClC_6H_4O(CH_2)_3$	(oil)	87	$C_{22}H_{23}ClN_2O_2\cdot{}^1/_3H_2O$	12.5	6.2	1.6		
78	CH	5-Cl	Me	Me	4-$ClC_6H_4O(CH_2)_3$	(oil)	82	$C_{22}H_{22}Cl_2N_2O_2\cdot{}^1/_3H_2O$	>100	>100	3.1		
79	CH	H	Me	Me	$PhO(CH_2)_3$	I(76–78)	45	$C_{21}H_{22}N_2O_2$	25	6.2	3.1		
80	CH	H	Me	Me	3-$ClC_6H_4CH_2$	I/T (62.5–64)	60	$C_{20}H_{19}ClN_2O$	12.5	3.1	3.1		
81	CH	H	Me	Me	4-$MeC_6H_4CH_2$	I/T (58–60)	29	$C_{21}H_{22}N_2O$	25	6.2	3.1		
82	CH	5-Cl	Me	Me	4-$MeC_6H_4CH_2$	I (106–108)	47	$C_{21}H_{22}ClN_2O$	25	12.5	1.6		
83	CH	H	Me	Me	$Ph(CH_2)_2$	M/A (138.5–139.5)	28	$C_{21}H_{22}N_2O\cdot(COOH)_2$	50	0.8	0.1		
84	CH	H	Me	Me	$Ph(CH_2)_3$	M/A (121–122)	79	$C_{22}H_{24}N_2O\cdot(COOH)_2$	25	1.6	0.2		
85	CH	H	Me	Me	*n*-Pr	M/A (136–137)	64	$C_{18}H_{22}N_2O_5$	12.5	0.8	0.2	0.31	
86	CH	5-Cl	Me	H	*n*-Pr	M/A (125–126)	70	$C_{15}H_{17}ClN_2O\cdot(COOH)_2\cdot{}^3/_4H_2O$	25	1.6	0.1	0.63	
87	CH	5-Cl	H	Me	*n*-Pr	M/A (125–126)	80	$C_{15}H_{17}ClN_2O\cdot(COOH)_2$	25	6.3	0.1	0.63	
88	CH	5-Cl	Me	Me	*n*-Pr	A (95–97)	64	$C_{16}H_{19}ClN_2O\cdot(COOH)_2\cdot{}^1/_2H_2O$	25	6.3	0.2	0.31	
89	CH	H	Me	Me	*t*-Bu-CH_2	M/A (110–115)	43	$C_{18}H_{24}N_2O\cdot(COOH)_2\cdot{}^3/_4H_2O$	25	6.3	0.1	0.31	
90	CH	H	Me	Me	*n*-Bu	M/A (121–123)	82	$C_{17}H_{22}N_2O\cdot(COOH)_2$	50	1.6	0.1	0.31	
91	CH	5-Cl	H	H	2-ClTh-3-CH_2	M/A (159–161.5)	62	$C_{16}H_{12}Cl_2N_2OS\cdot HCl$	25	6.2	0.1		
92	CH	H	H	H	Th-3-CH_2	M/A (139–142)	30	$C_{16}H_{14}N_2OS\cdot HCl$	50	3.1	0.1		
93	CH	H	H	H	2-ClTh-3-CH_2	M/A (165–172)	59	$C_{16}H_{13}ClN_2OS\cdot HCl$	6.2	1.6	0.1	0.8	
94	CH	3,5-Cl_2	H	H	2-ClTh-3-CH_2	M/A (150–153.5)	46	$C_{16}H_{11}Cl_3N_2OS\cdot HCl$	>100	50	3.1		
95	CH	3,5-Cl_2	H	H	Th-3-CH_2	M/A (170–171)	43	$C_{16}H_{12}Cl_2N_2OS\cdot HCl$	>100	100	6.2		
96	CH	5-Cl	H	H	Th-3-CH(Me)	(oil)	40	$C_{17}H_{15}ClN_2OS$	12.5	3.1	0.1		
97	CH	5-Cl	Et, H[a]		4-$ClC_6H_4CH_2$	M/A (220–222)	57	$C_{20}H_{18}Cl_2N_2O$	6.2	0.8	0.4		
98	CH	5-Cl	Et, H[a]		2,4-$Cl_2C_6H_3CH_2$	M/A (166–167)	58	$C_{20}H_{17}Cl_3N_2O\cdot HCl$	12.5	0.8	0.2		
99	CH	5-Cl	Et, H[a]		$PhCH_2$	M/A (158.5–159.5)	36	$C_{20}H_{19}ClN_2O\text{-}HCl$	6.2	1.6	1.6		
100	CH	H	$(Me)_2NCH_2$	H	*i*-Bu	M/A (130–132)	61	$C_{18}H_{25}N_3O\cdot 2(COOH)_2\cdot H_2O$	>100	>100	6.3	0.16	
101	CH	H	$(Me)_2NCH_2$	H	*n*-Pr	M/A (141 dec)	63	$C_{17}H_{23}N_3O\cdot 2(COOH)_2\cdot{}^1/_6H_2O$	>100	>100	12.5	0.31	
102	CH	H	Me	$(Me)_2NCH_2$	*i*-Bu	M/A (175 dec)	63	$C_{19}H_{27}N_3O\cdot 2(COOH)_2$	>100	>100	0.8	0.63	
103	CH	H	$(Me)_2NCH_2$	H	4-$ClC_6H_4CH_2$	M/A (170 dec)	37	$C_{21}H_{22}ClN_3O\cdot{}^3/_2(COOH)_2$	>100	>100	1.6	1.25	
104	CH	H	$(Me)_2NCH_2$	Me	*i*-Bu	M (191 dec)	61	$C_{19}H_{27}N_3O\cdot 2(COOH)_2\cdot H_2O$	>100	>100	25	1.25	
105	CH	H	H	$(Me)_2NCH_2$	*i*-Bu	M (193 dec)	47	$C_{18}H_{25}N_3O\cdot{}^5/_2(COOH)_2$	>100	>100	>100	5	
106	CH	H	MO-CH_2[b]	H	*i*-Bu	M/A (153.5 dec)	27	$C_{20}H_{27}N_3O_2\cdot{}^5/_2(COOH)_2$	>100	>100	6.3	2.5	
107	CH	H	H	PhN(Me)CH_2	*i*-Bu	A (121–122)	58	$C_{23}H_{27}N_3O\cdot(COOH)_2$	12.5	6.3	0.1	5	

Table II (Continued)

no.	X	Y	R_3	R_4	R_5	recrystn solvent[c] (mp °C)	yield, %	formula[d]	MIC,[e,5,6] μg/mL C.a.	A.f.	T.a.	MEC,[f,5] μg/mL
108	CH	5-Cl	$(Me)_2NCH_2$	H	*i*-Bu	M/E (162–163 dec)	58	$C_{18}H_{24}ClN_3O\cdot 2(COOH)_2\cdot{}^1/_2H_2O$	>100	>100	0.8	2.5
109	N	5-Cl	$(Me)_2NCH_2$	H	*i*-Bu	M/E (190–192)	63	$C_{17}H_{23}ClN_4O\cdot(COOH)_2$	>100	>100	12.5	0.31
110	N	5-Cl	H	H	*i*-Am	M/I (111–114)	45	$C_{15}H_{18}ClN_3O\cdot(COOH)_2$	>100	>100	0.8	20
111	N	5-Cl	Et	Et	Me	I/T (73–74)	57	$C_{15}H_{18}ClN_3O$	100	100	0.8	1.25
112	N	5-Cl	Et	Et	*i*-Am	I/T (69–70)	83	$C_{17}H_{22}ClN_3O$	>100	>100	0.8	1.25
113	N	5-Cl	Et	Et	4-$ClC_6H_4CH_2$	A/I (129–130)	86	$C_{21}H_{21}Cl_2N_3O$	>100	>100	>100	20

[a] A mixture of *E* and *Z* isomers. [b] MO: morpholine. [c] MeOH, M; AcOEt, A; *i*-Pr_2O, I; CH_3CN, N; petroleum ether, T; Et_2O, E. [d] All compounds were analyzed for C, H, and N and, where present, Cl, F, and S, and results were within 0.4% of the calculated values. [e] Lowest value in experiments duplicated. *C.a.* = *Candida albicans*, *A.f.* = *Aspergillus fumigatus*, *T.a.* = *Trichophyton asteroides*. [f] Lowest value in experiments duplicated. For pseudomycelium formation of *Candida albicans*.

agent, and its antifungal activity was comparable to that of clotrimazole.

These antimycotic candidates were also examined for their protection against the systemic murine model of candidiasis, but they were all inactive by oral or parenteral administrations. Previously, we reported[5] that the imidazolyl and triazolyl propranolone compounds display a strong inhibitory effect on the pseudomycelium formation of *C. albicans* and at the same time these compounds exhibited good oral efficacies against the murine candidiasis. Since some of the compound V in this study also displayed a strong inhibitory effect on the pseudomycelium formation, as shown in Table II, there is still a possibility that these morpholigically effective 1-vinylimidazoles may be active against murine candidiasis by oral administration.

Finally, we examined the influence of chemical modification on the antifungal activity. Although compounds **9–20**, in which R_5 of V is a C_1–C_5 alkyl group, show moderate activity, the aralkyl groups (**21–99**) in R_5 are much more active than the alkyl groups. The monochlorobenzyl group seems to be the best substituent (**25**, **27**, **30**, **60**, **61**, **68**, **72**, **73**). As for the chlorine substituent Y in V, 3-Cl (**31**, **36**, **70**, **94**, **95**) and 4-Cl (**69**) cause loss of activity, while with 5-Cl (**30**), some activity is retained. The effect of isomerization about the olefin bond in V was tested by the preparation of **60** and **61**. No difference in activity was observed. The R_3 and R_4 groups, which have the basic nitrogen atom, produce a negative effect on the activity (**100–109**).

Replacement of the ether group in **25** by the amino group causes loss of activity (**117**), but some activity is retained by the trifluoroacetamide (**116**). Replacement of the ether group in **25** by the thioether group produces a negative effect (**118**).

Transfer of the 4-chlorobenzyl ether group to the 3-position (**115**) from the 2-position in **25** also resulted in a negative effect.

Experimental Section

Melting points were determined in a Büchi capillary melting point apparatus and are uncorrected. NMR spectra were obtained with a Varian T-60 or EM-390 spectrometer. A Hitachi 260-10 spectrophotometer was used to obtain IR spectra. Elemental analyses were performed by the Analytical Department of Shionogi Research Laboratories. Where analyses are indicated only by symbols of the elements, analytical results obtained for these elements were within ±0.4% of the theoretical values.

4-Chloro(1,1-di-1*H*-imidazol-1-ylethyl)benzene (4) and 1-[1-(4-Chlorophenyl)vinyl]-1*H*-imidazole (8). Imidazole (7.93 g, 116.5 mmol) was mixed with dry CH_2Cl_2 (40 mL), to which $SOCl_2$ (3.46 g, 19.4 mmol) was added with stirring and ice cooling. The mixture was stirred for 5 min, and *p*-chloroacetophenone (3 g, 19.4 mmol) was added. The mixture was stirred at room temperature for 96 h, then neutralized with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_8O_4, and evaporated to remove the solvent. The residue was chromatographed on silica gel. The fractions eluted with 2% $MeOH/CH_2Cl_2$ gave **8** as an oil (picrate, 1.13 g, mp 146–149 °C, from MeOH/AcOEt, 13%): NMR (Me_2SO) δ 5.87 (1 H, d, *J* = 2 Hz, =CH*H*), 6.03 (1 H, d, *J* = 2 Hz, =C*H*H), 7.50–9.47 (9 H, m, aromatic), 11.90 (1 H, br s, $\equiv NH^+$). Anal. ($C_{11}H_9ClN_2\cdot C_6H_3N_3O_7$) C, H, Cl, N.

The fractions eluted with 5% $MeOH/CH_2Cl_2$ gave **4** (1.38 g, mp 126–127.5 °C, from AcOEt/*i*-Pr_2O, 26%): NMR ($CDCl_3$) δ 2.60 (3 H, s, Me), 6.80–7.47 (10 H, m, aromatic). Anal. ($C_{14}H_{13}ClN_4$) C, H, Cl, N.

The other compounds **1–3**, **5–7**, **114**, and **115** were prepared from the appropriate carbonyl compounds in a similar manner (Table I).

1-[1-(2-Methoxyphenyl)vinyl]-1*H*-imidazole Hydrochloride (9). To a solution of **119**[1b,3] (1 g, 5.4 mmol) and dry DMF (5 mL) was added NaH (60% dispersion in oil, 322 mg, 8 mmol).

Scheme III

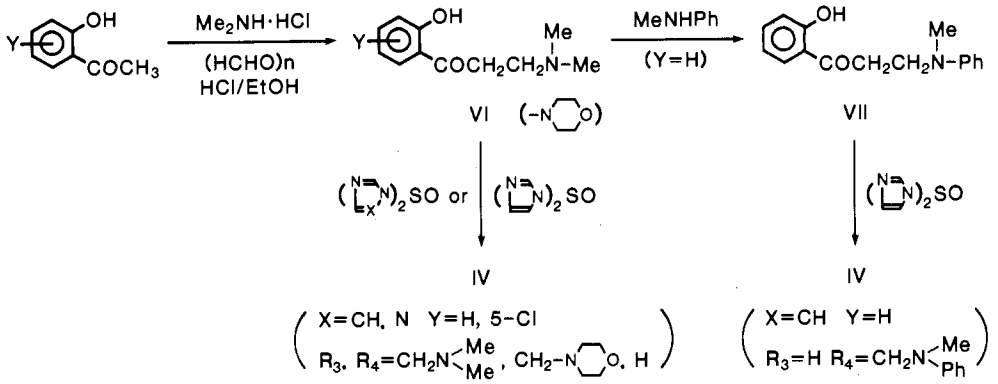


Table III. In Vitro Antifungal Activity of 1-Vinylimidazoles and Clotrimazole as Measured on Sabouraud's Glucose Agar

	MIC,[a] μg/mL					
compd	*T.m.*[b] IFO 5809	*T.m.* IFO 5810	*T.r.*[b] IFO 5467	*T.r.* IFO 5807	*C.a.*[b] IFO 1060	*C.a.* IFO 1388
25	1.6	0.8	0.8	0.8	6.3	12.5
27	0.8	0.8	0.4	0.4	6.3	12.5
30	1.6	1.6	0.8	0.8	12.5	12.5
32	1.6	1.6	1.6	0.8	12.5	12.5
60	0.8	0.8	0.8	0.8	12.5	12.5
61	1.6	0.8	0.8	1.6	12.5	12.5
67	0.8	0.8	0.8	0.8	6.3	12.5
73	1.6	0.8	1.6	0.8	12.5	12.5
93	1.6	0.8	0.4	0.8	12.5	12.5
clotrimazole	0.8	0.4	0.8	0.8	6.3	12.5

[a] Lowest value in experiments duplicated. [b] *T.m.* = *Trichophyton mentagrophytes*, *T.r.* = *Trichophyton rubrum*, *C.a.* = *Candida albicans*.

After the mixture had been stirred at room temperature for 5 min, MeI (1.14 g, 8 mmol) was added. The mixture was stirred at room temperature for 10 min, poured into ice water, and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (elution with 3% MeOH/CH_2Cl_2) to obtain the free base of **9** (853 mg, oil, 79%). A solution of the above free base in Et_2O was treated with 8% HCl/EtOH to give its hydrochloride **9** (520 mg, 41%, mp 190–195 °C, from MeOH/AcOEt): NMR (Me_2SO-d_6) δ 3.63 (3 H, s, OMe), 5.53 (1 H, d, J = 2 Hz, =C*H*H), 5.93 (1 H, d, J = 2 Hz, =CH*H*), 6.87–7.77 (7 H, m, aromatic), 9.27 (1 H, m, ≡NH$^+$). Anal. ($C_{12}H_{12}N_2O$·HCl) C, H, Cl, N.

The other compounds **10**–**113** were prepared in a similar manner, and the synthesis of the starting 1-vinylimidazoles IV was described in ref 1b and 3 (Table I).

(*E* and *Z*)-1-[1-(2-Hydroxyphenyl)-2-methylvinyl]-1*H*-imidazole (IV, *E* Form, X = CH, Y = H, R_3 = Me, R_4 = H and *Z* Form, X = CH, Y = H, R_3 = H, R_4 = Me). Imidazole (8.16 g, 119.9 mmol) was mixed with dry CH_2Cl_2 (41 mL), to which $SOCl_2$ (3.57 g, 30 mmol) was added dropwise with stirring and ice cooling. After the mixture had been stirred for 5 min, *o*-hydroxypropiophenone (3 g, 20 mmol) was added dropwise at room temperature with stirring. After 15 min, the mixture was diluted with H_2O and extracted with CH_2Cl_2. The extract was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on silica gel and eluted with 2% MeOH/CH_2Cl_2 to obtain IV (*Z* isomer, X = CH, Y = H, R_3 = H, R_4 = CH_3) (242 mg, mp 199.5–201.5 °C, from MeOH, 6%): NMR (Me_2SO-d_6) δ 1.68 (3 H, d, J = 7 Hz, Me), 6.28 (1 H, q, J = 7 Hz, =C*H*Me), 6.72–7.58 (7 H, m, aromatic), 9.82 (1 H, s, OH). Anal. ($C_{12}H_{12}N_2O$) C, H, N.

The fractions eluted with 3% MeOH/CH_2Cl_2 gave IV (*E* isomer, X = CH, Y = H, R_3 = Me, R_4 = H) (703 mg, mp 187–190 °C, from MeOH, 18%): NMR (Me_2SO-d_6) δ 1.60 (3 H, d, J = 7 Hz, Me), 6.07 (1 H, q, J = 7 Hz, =C*H*Me), 6.37–7.57 (7 H, m, aromatic), 9.77 (1 H, s, OH). Anal. ($C_{12}H_{12}N_2O$) C, H, N.

These compounds IV (*Z* and *E* isomers) were converted to **60** and **61** with *p*-chlorobenzyl bromide as follows, respectively.

1-[1-[4-[(Chlorobenzyl)oxy]phenyl]-2-methylvinyl]-1*H*-imidazole Hydrochloride (60). To a solution of the above IV (*E* isomer, X = CH, Y = H, R_3 = Me, R_4 = H, mp 187–190 °C, 400 mg, 2 mmol) and dry DMF (4 mL) was added NaH (60% dispersion in oil, 122 mg, 3 mmol). After the mixture had been stirred at room temperature for 5 min, *p*-chlorobenzyl bromide (616 mg, 3 mmol) was added. The mixture was stirred at room temperature for 15 min, poured into ice water, and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel (elution with 2% MeOH/CH_2Cl_2) to obtain the free base of **60**. A solution of the above free base in AcOEt was treated with HCl to give its hydrochloride **60** (425 mg, 59%, mp 185–187 °C, from MeOH/AcOEt): NMR (Me_2SO-d_6) δ 1.68 (3 H, d, J = 7 Hz, Me), 5.03 (2 H, s, CH_2), 6.47 (1 H, q, J = 7 Hz, =CH), 7.05–7.70 (11 H, m, aromatic, imidazole), 9.20 (1 H, s, ≡NH$^+$). Anal. ($C_{19}H_{17}ClN_2O$·HCl) C, H, Cl, N.

Compound **61** was prepared in a similar manner.

X-ray Results. Crystal Data. 60: $C_{19}H_{17}ClN_2O$·HCl, triclinic, space group $P\bar{1}$, a = 9.437 (1) Å, b = 12.499 (2) Å, c = 8.745 (1) Å, α = 96.91 (1)°, β = 114.55 (1)°, γ = 77.77 (1)°, Z = 2. The structure was solved by direct methods and refined by a block-diagonal least-squares technique. R = 0.101 excluding the hydrogen atoms (Figure 1).

3-(Dimethylamino)-2′-hydroxypropiophenone Hydrochloride (VI, Y = H). A mixture of *o*-hydroxyacetophenone (20 g, 147 mmol), dimethylamine hydrochloride (18.2 g, 223 mmol), paraformaldehyde (8.82 g, 294 mmol), and concentrated HCl (0.83 mL) in EtOH (66 mL) was refluxed for 5.5 h. After cooling in ice bath, the resulting precipitates were collected and washed with cold EtOH to give 14.1 g of VI, Y = H (mp 172–173 °C, from EtOH, 42%). Anal. ($C_{11}H_{16}ClNO_2$) C, H, Cl, N.

(*E* and *Z*)-1-[1-(2-Hydroxyphenyl)-2-[(dimethylamino)-methyl]vinyl]-1*H*-imidazole (IV, *E* Form, X = CH, Y = H, R_3 = CH_2NMe_2, R_4 = H and *Z* Form, X = Ch, Y = H, R_3 = H, R_4 = CH_2NMe_2). To a stirred solution of imidazole (2.11 g, 31 mmol) and dry CH_2Cl_2 (21 mL) was added dropwise $SOCl_2$ (924 mg, 7.77 mmol) with ice cooling. After the mixture had been stirred for 5 min, 3-(dimethylamino)-2′-hydroxypropiophenone (1 g, 5.17 mmol) was added at room temperature. After the reaction mixture had been stirred for 30 min, it was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on alumina. The fractions eluted

with 3% MeOH/CH_2Cl_2 gave (*E*)-IV (527 mg, mp 96.5–98.5 °C, from AcOEt/*i*-Pr_2O, 42%): NMR ($CDCl_3$) δ 2.33 (6 H, s, 2 × Me), 2.98 (2 H, d, *J* = 8.1 Hz, CH_2), 6.05 (1 H, t, *J* = 8.1 Hz, =CH), 6.81–7.56 (7 H, m, aromatic), 8.68–9.71 (1 H, br, s, OH). Anal. ($C_{14}H_{17}N_3O$) C, H, N.

The fractions eluted with 5% MeOH/CH_2Cl_2 gave (*Z*)-IV (70 mg, mp 170–171 °C, from AcOEt, 6%): NMR ($CDCl_3$) δ 2.34 (6 H, s, 2 × Me), 3.03 (2 H, d, *J* = 7.2 Hz, CH_2), 6.46 (1 H, t, *J* = 7.2 Hz, =CH), 6.70–7.63 (7 H, m, aromatic), 8.09–9.21 (1 H, br s, OH). Anal. ($C_{14}H_{17}N_3O$) C, H, N.

2′-Hydroxy-3-(*N*-methylanilino)propiophenone (VII) (Y = H). A mixture of VI (Y = H, 3 g, 13.1 mmol) and *N*-methylaniline (1.41 g, 13.1 mmol) in 30% H_2O/EtOH (30 mL) was refluxed for 4 h. The solvent was evaporated, and the residue was poured into aqueous NaOH. The mixture was extracted with Et_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with benzene gave VII (Y = H, 1.23 g, as an oil, 37%): NMR ($CDCl_3$) δ 2.93 (3 H, s, CH_3), 3.03–3.36 (2 H, m, CH_2), 3.64–3.98 (2 H, m, CH_2), 6.54–7.87 (9 H, m, aromatic), 12.31 (1 H, s, OH).

(*E* and *Z*)-1-[1-(2-Hydroxyphenyl)-2-[(*N*-methylanilino)methyl]vinyl]-1*H*-imidazole [IV, *E* Form, X = CH, Y = H, R_3 = $CH_2N(Me)Ph$, R_4 = H and *Z* Form, X = CH, Y = H, R_3 = H, R_4 = $CH_2N(Me)Ph$]. To a stirred solution of imidazole (1.74 g, 25.6 mmol) and dry CH_2Cl_2 (17.4 mL) was added dropwise $SOCl_2$ (762 mg, 6.4 mmol) with ice cooling. After the mixture had been stirred for 5 min, VII (Y = H, 1.09 g, 4.3 mmol) in CH_2Cl_2 (2 mL) was added at room temperature. After the reaction mixture had been stirred for 30 min, it was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated to give the oil. NMR ($CDCl_3$) E/Z ratio = 3/7. *E* form: δ 2.86 (0.3 × 3 H, s, Me), 3.81 (0.3 × 2 H, d, *J* = 6.8 Hz, CH_2), 5.88 (0.3 × 1 H, t, *J* = 6.8 Hz, =CH), 6.50–7.56 (0.3 × 12 H, m, aromatic), 8.75 (0.3 × 1 H, br s, OH). *Z* form, 2.86 (0.7 × 3 H, s, Me), 3.88 (0.3 × 2 H, d, *J* = 6.8 Hz, CH_2), 5.95 (0.7 × 1 H, t, *J* = 6.8 Hz, =CH), 6.50–7.56 (0.7 × 12 H, m, aromatic), 8.75 (0.7 × 1 H, br s, OH).

The above residual oil was chromatographed on silica gel. The fractions eluted with 5% MeOH/CH_2Cl_2 gave (*Z*)-IV [X = CH, Y = H, R_3 = H, R_4 = $CH_2N(Me)Ph$, 857 mg, 66%, mp 153–154 °C, from MeOH/AcOEt]. NMR ($CDCl_3$) *Z* forms: δ 2.85 (3 H, s, Me), 3.91 (2 H, d, *J* = 6.8 Hz, CH_2), 5.93 (1 H, t, *J* = 6.8 Hz, =CH), 6.56–7.53 (12 H, m, aromatic), 9.32 (1 H, br s, OH). The *E* form of IV [X = CH, Y = H, R_3 = $CH_2N(Me)Ph$, R_4 = H] isomerized to the *Z* form of IV [X = CH, Y = H, R_3 = H, R_4 = $CH_2N(Me)Ph$] by silica gel chromatography. Anal. ($C_{19}H_{19}N_3O$) C, H, N.

1-[1-[2-[(4-Chlorobenzyl)amino]phenyl]vinyl]-1*H*-imidazole (117). To a solution of 1-[1-(2-aminophenyl)vinyl]-1*H*-imidazole[1a] (1.51 g, 8.2 mmol) and dry CH_2Cl_2 (30 mL) was added trifluoroacetic anhydride (5.1 g, 24.3 mmol) with ice cooling. After the mixture had been stirred for 10 min, it was added to aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was crystallized from MeOH/AcOEt to give the trifluoroacetamide (600 mg, mp 168–169 °C, 26%): NMR (Me_2SO-d_6) δ 5.07 (1 H, d, *J* = 2 Hz, =C*H*H), 5.60 (1 H, d, *J* = 2 Hz, =CH*H*), 6.93–7.53 (7 H, m, aromatic), 11.03 (1 H, br s, NH).

A solution of the above acetamide (570 mg, 2 mmol), K_2CO_3 (560 mg, 4.1 mmol), and 4-chlorobenzyl bromide (624 mg, 3 mmol) in dry acetone (20 mL) was refluxed for 16 h. The reaction mixture was evaporated, added to aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 1% MeOH/CH_2Cl_2 gave **116** (614 mg, mp 101–101.5 °C, 75%, after washing with *i*-Pr_2O: NMR δ 3.88 (1 H, d, *J* = 15 Hz, CH*H*), 5.22 (1 H, d, *J* = 15 Hz, C*H*H), 5.27 (1 H, d, *J* = 2 Hz, =C*H*H), 5.77 (1 H, d, *J* = 2 Hz, =CH*H*), 7.07–7.77 (11 H, m, aromatic). Anal. ($C_{20}H_{25}ClF_3N_3O$) C, H, Cl, F, N.

A solution of **116** (547 mg, 1.3 mmol) and 10% NaOH (3 mL) in dioxane (6 mL) was refluxed for 3 h. The reaction mixture was diluted with H_2O and extracted with Et_2O. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 50% AcOEt/benzene gave the target **117** (150 mg, mp 147–148 °C, 36%, from AcOEt): NMR ($CDCl_3$) δ 4.23 (3 H, br s, CH_2NH), 5.10 (1 H, d, *J* = 2 Hz, =C*H*H), 5.50 (1 H, d, *J* = 2 Hz, =CH*H*), 6.53–7.53 (11 H, m, aromatic). Anal. ($C_{18}H_{16}ClN_3$) C, H, Cl, N.

1-[1-[2-[(4-Chlorobenzyl)thio]phenyl]vinyl]-1*H*-imidazole (118). A solution of 4-chlorobenzyl bromide (4.05 g. 19.7 mmol), 2-mercaptoacetophenone (1.5 g, 9.9 mmol), and powdered K_2CO_3 (2.73 g, 19.8 mmol) in dry acetone (30 mL) was refluxed for 16 h. The reaction mixture was evaporated, added to H_2O, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 1% MeOH/CH_2Cl_2 gave 2-[(4-chlorobenzyl)thio]acetophenone [I, R_1 = 2-(4-ClC_6H_4-CH_2S)C_6H_4, R_2 = CH_3, 2.18 g, mp 126–128 °C, 80%, after washing with *i*-Pr_2O]: IR (Nujol) 1670 cm^{-1}. Anal. ($C_{15}H_{13}ClOS$) C, H, Cl, S.

$SOCl_2$ (1.29 g, 10.8 mmol) was added to a mixture of imidazole (2.95 g, 43.3 mmol) and dry CH_2Cl_2 (15 mL) at room temperature. After 5 min, the above acetophenone (2 g, 7.2 mmol) was added at room temperature. After 70 h of stirring, the mixture was washed with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried (Na_2SO_4), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with CH_2Cl_2 gave the starting acetophenone (750 mg, 37.5%). The fractions eluted with 2% MeOH/CH_2Cl_2 gave the free base (oil) of the target **118**. HCl salt (**118**) (310 mg, mp 153–163 °C, 12%, from MeOH/Et_2O): NMR (Me_2SO-d_6) δ 4.20 (2 H, s, CH_2Ph), 5.47 (1 H, d, *J* = 2 Hz, =CH*H*), 6.13 (1 H, d, *J* = 2 Hz, =C*H*H), 7.30–7.77 (11 H, m, aromatic), 9.20 (1 H, br s, $=NH^+$). Anal. ($C_{18}H_{15}ClN_2S$·HCl) C, H, Cl, N, S.

Fungistatic Activity. All the compounds were tested for fungistatic activity against *Candida albicans*, *Aspergillus fumigatus*, and *Trichophyton asteroides*. MIC values were determined by a microtiter dilution system[6] combined with PS-microtiter plates (Labortechnik) and Micom Auto Diluter SPR2 (Sanko), using final inocula[6] of 1 × 10^5 cells (yeast) or 1 × 10^5 conidia (mold and dermatophyte) per milliliter of Sabouraud's glucose broth.

Inhibitory Effect on Pseudomycelium Formation of *Candida albicans*. *C. albicans* KE-2 (an isolate from a clinical specimen) was prepared in its final inoculum to be 1 × 10^6 yeast cells/mL of EMEM supplemented with 20% calf serum. The test compounds were treated with the microtiter dilution system in the same was as for evaluation of MICs. After incubation, morphological features of the fungal growth in each well were examined by a microscope following Giemsa staining (5% in phosphate buffer solution). Minimal effective concentration (MEC, μg/mL) was defined as the lowest concentration of compound that prevented typical pseudomycelium formation.

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