

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.

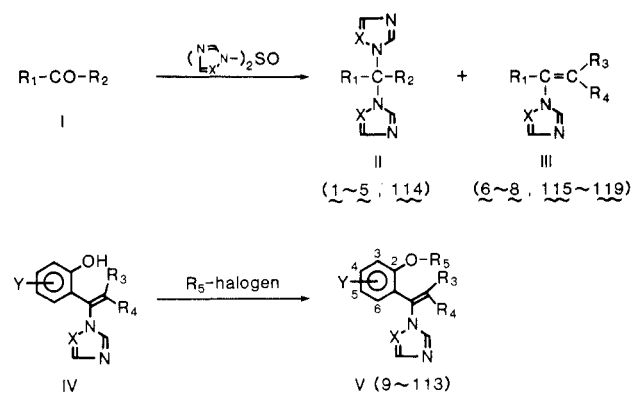
Chemistry

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 R₃ and R₄ 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, R₁ = *o*-hydroxyphenyl, R₂ = 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, R₃ = Me, R₄ = H; *Z* form, cis form of imidazole and methyl groups, X = CH, Y = H, R₃ = H, R₄ = 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, R₃ = Me, R₄ = H) can be distinguished from the *Z* isomer (IV, X = CH, Y = H, R₃ = H, R₄ = Me) by the characteristic vinyl and methyl proton signals in the ¹H NMR spectra. Comparison of the ¹H 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

Scheme I



atom. The 1-vinylimidazole (III, R₁ = *o*-aminophenyl, R₃ = R₄ = 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'*-sulfinyldiimidazole⁵ to obtain the target compound 118 (Scheme II).

Compounds 100-109, which have an aminomethyl group in R₃ or R₄ 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 amino-methyl or morpholinomethyl group in R₃ or R₄. These 1-vinylimidazoles IV were treated with alkyl halides to

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- (4) Ogata, M.; Matsumoto, H.; Shimizu, S. *Heterocycles* 1980, 14, 955.
- (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,6} µg/mL | | | MEC, ^{f,5} µg/mL |
|-----|----|---------------------------------------------------------|----------------|----------------|----------------|-------------------------------------------|----------|--------------------------------------------------------------------------------------------------------------|---------------------------|------|------|------------------------------|
| | | | | | | | | | C.a. | A.f. | T.a. | |
| 1 | CH | Me | Me | - | - | A/I (103-106) | 3 | C ₉ H 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 ₆ H 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 ₆ H ₅ N ₂ ·C ₆ H ₃ N ₃ O ₇ | | | | |
| 7 | CH | Ph | - | H | H | M/E (113-115.5) | 12 | C ₁₁ H ₁₀ N ₂ ·C ₆ H ₃ N ₃ O ₇ | >100 | >100 | 100 | >20 |
| 8 | CH | 4-ClC ₆ H ₄ | - | H | H | M/E (146-149) | 13 | C ₁₁ H ₉ ClN ₂ ·C ₆ H ₃ N ₃ O ₇ | 100 | 100 | 25 | >20 |
| 114 | CH | 3-(CP-O)C ₆ H ₄ ^a | Me | - | - | A/E (130-131.5) | 18 | C ₂₁ H ₁₉ ClN ₄ O | >100 | >100 | 12.5 | |
| 115 | CH | 3-(CP-O)C ₆ H ₄ | - | H | H | (oil) | 20 | C ₁₈ H ₁₅ ClN ₂ O ^{1/2} ·H ₂ O | 50 | 12.5 | 1.6 | 5 |
| 116 | CH | 2-[N(CP)(TF)]C ₆ H ₄ ^b | - | H | H | I (101-101.5) | 17 | C ₂₀ H ₂₅ ClF ₃ N ₃ O | 1.6 | 50 | 1.6 | 20 |
| 117 | CH | 2-[NH(CP)]C ₆ H ₄ | - | H | H | A (147-148) | 36 | C ₁₈ H ₁₆ ClN ₃ | >100 | >100 | >100 | |
| 118 | CH | 2-[S(CP)]C ₆ H ₄ | - | H | H | M/E (153-163) | 12 | C ₁₈ H ₁₅ ClN ₂ S·HCl | 50 | 0.8 | 0.1 | |
| 119 | CH | 2-OHC ₆ H ₄ | - | H | H | P (152.5-154.5) | 75 | C ₁₁ H ₁₀ N ₂ O | | | | |

^a CP: 4-ClC₆H₄CH₂. ^b TF: CF₃CO. ^c AcOEt, A; *i*-Pr₂O, I; MeOH, M; Et₂O, E; *i*-PrOH, P. ^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 values in experiments duplicated. For pseudomycelium formation of *Candida albicans*.

Scheme II

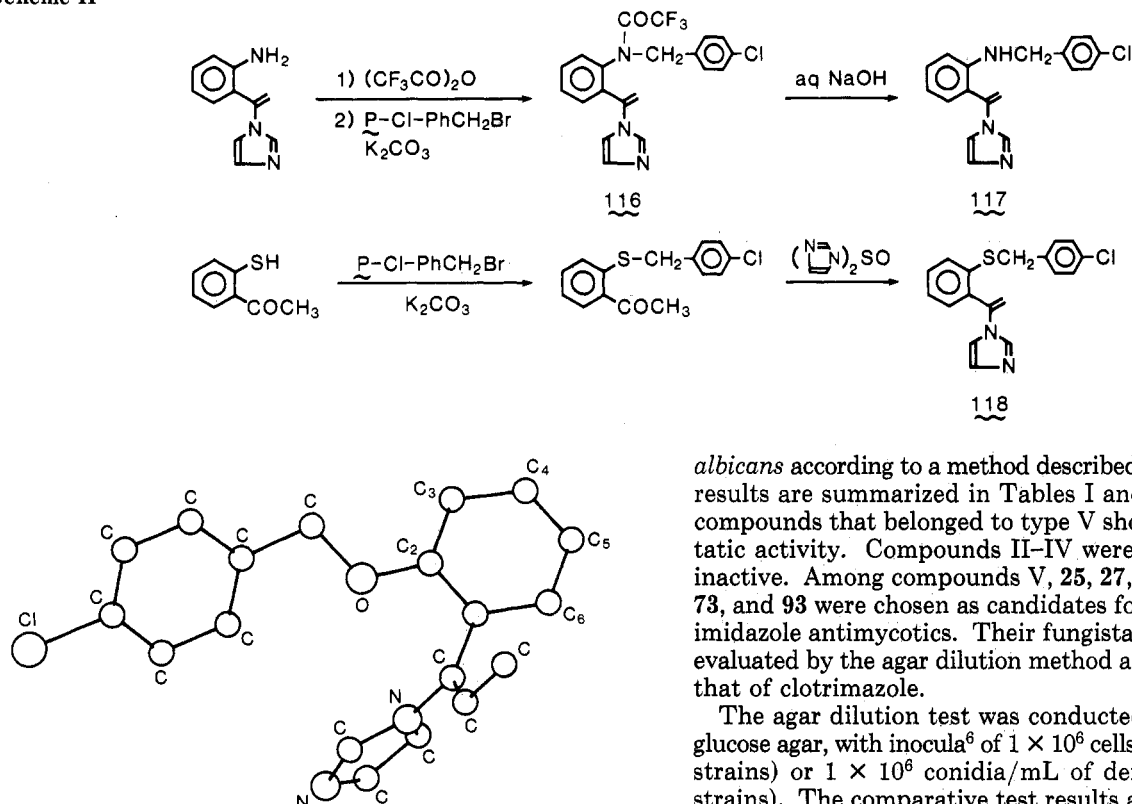


Figure 1. Molecular structure of 60. Hydrogen atoms have been omitted for clarity.

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*

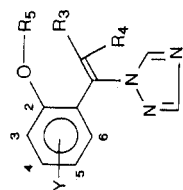
albicans according to a method described earlier.⁵ The test results are summarized in Tables I and II. Most of the compounds that belonged to type V showed good fungistatic activity. Compounds II-IV were weakly active or inactive. Among compounds V, 25, 27, 30, 32, 60, 61, 67, 73, and 93 were chosen 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 inocula⁶ 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

| no. | X | Y | R ₃ | R ₄ | R ₅ | recrystn solvent ^c (mp °C) | yield, % | formula ^d | MIC, ^{e,6} µg/mL | | MEC, ^{f,5} µg/mL |
|-----|----|---------------------|----------------|----------------|-----------------------------------------------------------------------------------|------------------------------------------|-------------|--------------------------------------------------------------------------------------|---------------------------|------|------------------------------|
| | | | | | | | | | C.a. | A.f. | T.a. |
| 9 | CH | H | H | H | Me | M/A (190–195) | 41 | C ₁₂ H ₁₁ N ₂ O·HCl | >100 | 12.5 | 1.6 |
| 10 | CH | 5-Cl | H | H | Me | M/A (239 dec) | 78 | C ₁₂ H ₁₁ N ₂ O·HCl | >100 | 3.1 | 0.4 |
| 11 | CH | H | H | H | Et | M/A (159–162) | 66 | C ₁₃ H ₁₄ N ₂ O·HCl·1/2H ₂ O | >100 | 3.1 | 0.4 |
| 12 | CH | 4-Cl | H | H | Me | M/A (193–196) | 87 | C ₁₂ H ₁₁ N ₂ O·HCl·1/2H ₂ O | >100 | 100 | 25 |
| 13 | CH | H | H | H | n-Pr | M/A (146–148) | 79 | C ₁₄ H ₁₆ N ₂ O·HCl·1/3H ₂ O | 100 | 1.6 | 0.1 |
| 14 | CH | 5-Cl | H | H | n-Pr | M/A (178–181) | 75 | C ₁₄ H ₁₆ N ₂ O·HCl | 25 | 0.8 | 0.1 |
| 15 | CH | 5-Cl | H | H | i-Pr | M/A (127–128) | 66 | C ₁₄ H ₁₅ ClN ₂ O·(COOH) ₂ | 50 | 0.8 | 0.1 |
| 16 | CH | H | H | H | n-Bu | (oil) | 84 | C ₁₅ H ₁₈ N ₂ O | 25 | 1.6 | 50 |
| 17 | CH | 5-Cl | H | H | n-Bu | M/A (121.5–122.5) | 81 | C ₁₅ H ₁₇ ClN ₂ O·(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 ₂ O ₅ ·(COOH) ₂ | 50 | 0.8 | 0.1 |
| 19 | CH | H | H | H | i-Bu | M/A (97–98) | 58 | C ₁₇ H ₂₀ N ₂ O ₅ ·4/5H ₂ O | 100 | 1.6 | 0.1 |
| 20 | CH | H | H | H | i-Am | A (103–104) | 59 | C ₂₀ H ₂₆ N ₂ O ₅ | 25 | 0.4 | 0.1 |
| 21 | CH | H | H | H | PhCH ₂ | M/A (154–156) | 46 | C ₁₈ H ₁₆ N ₂ O·HCl | 12.5 | 3.1 | 0.2 |
| 22 | CH | H | H | H | 4-MeC ₆ H ₄ CH ₂ | M/A (180–183) | 49 | C ₁₉ H ₁₈ N ₂ O·HCl·1/10H ₂ O | 3.1 | 3.1 | 0.1 |
| 23 | CH | H | H | H | 4-NO ₂ C ₆ H ₄ CH ₂ | A/1 (94–95.5) | 24 | C ₁₈ H ₁₅ N ₃ O ₃ | 12.5 | 6.2 | 0.1 |
| 24 | CH | H | H | H | 4-MeOC ₆ H ₄ CH ₂ | (oil) | 99 | C ₁₉ H ₁₈ N ₂ O ₃ | 25.0 | 6.2 | 0.1 |
| 25 | CH | H | H | H | 4-ClC ₆ H ₄ CH ₂ | M/A (180.5–181) | 51 | C ₁₈ H ₁₅ ClN ₂ O·HCl | 6.2 | 3.1 | 0.1 |
| 26 | CH | H | H | H | 4-EtC ₆ H ₄ CH ₂ | M/A (138–147) | 7 | C ₂₀ H ₂₆ N ₂ O·HCl | 12.5 | 25.0 | 0.1 |
| 27 | CH | H | H | H | 3-ClC ₆ H ₄ CH ₂ | A/N (148.5–150) | 82 | C ₁₈ H ₁₅ ClN ₂ O·HCl | 3.1 | 3.1 | 0.1 |
| 28 | CH | H | H | H | 2,4-Cl ₂ C ₆ H ₃ CH ₂ | M/A (161–163) | 67 | C ₁₈ H ₁₄ Cl ₂ N ₂ O·HCl | 50 | 1.6 | 0.1 |
| 29 | CH | H | H | H | 3,4-Cl ₂ C ₆ H ₃ CH ₂ | M/A (172–174) | 60 | C ₁₈ H ₁₄ Cl ₂ N ₂ O·HCl | 25 | 3.1 | 0.1 |
| 30 | CH | 5-Cl | H | H | 4-ClC ₆ H ₄ CH ₂ | M/A (188–190) | 44 | C ₁₈ H ₁₄ Cl ₂ N ₂ O·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 ₂ N ₂ O·HCl | >100 | >100 | 3.1 |
| 32 | CH | 5-Cl | H | H | PhCH ₂ | M/A (174–175) | 81 | C ₁₈ H ₁₅ ClN ₂ O·HCl | 6.2 | 3.1 | 0.1 |
| 33 | CH | H | H | H | 4-i-PrC ₆ H ₄ CH ₂ | (oil) | 80 | C ₂₁ H ₂₂ N ₂ O | 25 | 3.1 | 3.1 |
| 34 | CH | 5-Cl | H | H | 4-MeC ₆ H ₄ CH ₂ | M/A (180–183) | 48 | C ₁₉ H ₁₈ N ₂ O·HCl·1/10H ₂ O | 25 | 1.6 | 0.8 |
| 35 | CH | H | H | H | 2-ClC ₆ H ₄ CH ₂ | A/1 (69.5–70.5) | 36 | C ₁₈ H ₁₅ ClN ₂ O | 6.2 | 0.8 | 0.1 |
| 36 | CH | 3,6-Cl ₂ | H | H | 4-ClC ₆ H ₄ CH ₂ | N (127–129) | 45 | C ₁₈ H ₁₃ Cl ₃ N ₂ O·(COOH) ₂ | >100 | >100 | 12.5 |
| 37 | CH | 5-Cl | H | H | 4-COOMeC ₆ H ₄ CH ₂ | A/1 (100–101) | 63 | C ₂₀ H ₁₇ ClN ₂ O ₃ | 25 | 6.2 | 0.1 |
| 38 | CH | H | H | H | 4-ClC ₆ H ₄ O(CH ₂) ₂ | M/A (140–142) | 12 | C ₁₉ H ₁₇ ClN ₂ O ₂ ·HCl | 50 | 1.6 | 0.1 |
| 39 | CH | H | H | H | 4-ClC ₆ H ₄ O(CH ₂) ₃ | (oil) | 74 | C ₁₉ H ₁₇ ClN ₂ O ₂ | 12.5 | 12.5 | 0.1 |
| 40 | CH | H | H | H | Ph(CH ₂) ₃ | (oil) | 67 | C ₂₀ H ₂₀ N ₂ O | 12.5 | 3.1 | 0.1 |
| 41 | CH | H | H | H | 4-ClC ₆ H ₄ S(CH ₂) ₃ | M/A (138–140) | 62 | C ₂₀ H ₁₉ ClN ₂ OS·HCl | 25 | 3.1 | 0.1 |
| 42 | CH | 5-Cl | H | H | Ph(CH ₂) ₃ | M/A (136–138) | 23 | C ₁₉ H ₁₇ ClN ₂ O·(COOH) ₂ | 50 | 6.3 | 0.1 |
| 43 | CH | H | H | H | 4-ClC ₆ H ₄ (CH ₂) ₂ | M/A (102.5–103.5) | 20 | C ₁₉ H ₁₇ ClN ₂ O·(COOH) ₂ | 25 | 0.4 | 0.1 |
| 44 | CH | H | H | H | 2,4-Cl ₂ C ₆ H ₃ (CH ₂) ₂ | M/A (126–127) | 7 | C ₁₉ H ₁₆ Cl ₂ N ₂ O·(COOH) ₂ | 25 | 0.4 | 0.1 |
| 45 | CH | H | H | H | 4-ClC ₆ H ₄ (CH ₂) ₃ | M/A (116–118) | 17 | C ₂₀ H ₁₉ ClN ₂ O·(COOH) ₂ | 12.5 | 0.8 | 0.2 |
| 46 | CH | 5-Cl | H | H | PhO(CH ₂) ₃ | M/A (126–127) | 43 | C ₂₀ H ₁₉ ClN ₂ O·(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 ₂ O ₂ ·HCl | 50 | 12.5 | 0.1 |
| 48 | CH | H | H | H | Ph(CH ₂) ₃ | M/A (100.5–102) | 43 | C ₁₉ H ₁₈ N ₂ O·(COOH) ₂ | 12.5 | 0.4 | 0.1 |
| 49 | CH | H | H | H | 4-ClC ₆ H ₄ CH(Me) | M/A (110–113) | 71 | C ₁₉ H ₁₇ ClN ₂ O·(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 ₂ O·HCl | 25 | 6.2 | 0.1 |



V(9–113)

| | | | | | | | | | | | | | |
|-----|----|---------------------|------------------------------------|----|----|--------------------------------------------------------------------|-------------------|----|----------------------------------------------------------|------|------|------|------|
| 51 | CH | 5-Cl | H | 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 | H | PhCH(Et) | N/E (130-132) | 19 | $C_{30}H_{20}N_2O \cdot (COOH)_2$ | 6.2 | 3.1 | 0.1 | |
| 53 | CH | 5-Cl | H | H | H | PhCH(Et) | (oil) | 58 | $C_{30}H_{19}ClN_2O$ | >100 | 12.5 | 0.1 | |
| 54 | CH | H | H | H | H | 4-MeOC ₆ H ₄ CH(Me) | (oil) | 6 | $C_{30}H_{20}N_2O_3 / 10 \cdot CH_2Cl_2$ | 12.5 | 12.5 | 0.4 | |
| 55 | CH | H | H | H | H | PhCH(n-Pr) | A (105-107) | 49 | $C_{30}H_{22}N_2O \cdot (COOH)_2$ | 12.5 | 12.5 | 0.4 | |
| 56 | CH | H | H | H | H | 3-ClC ₆ H ₄ CH(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 | H | 3-ClC ₆ H ₄ CH(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 | H | PhCH(n-Pr) | (oil) | 63 | $C_{21}H_{21}ClN_2O$ | >100 | >100 | 0.8 | |
| 59 | CH | 5-Cl | H | H | H | 4-ClC ₆ H ₄ CH(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 | H | 4-ClC ₆ H ₄ CH ₂ | M/A (185-187) | 59 | $C_{19}H_{17}ClN_2O \cdot HCl$ | 6.2 | 3.1 | 0.1 | |
| 61 | CH | H | Me | H | H | 4-ClC ₆ H ₄ CH 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 | H | H | Me | M/A (118-118.5) | 92 | $C_{18}H_{15}ClN_2O$ | 12.5 | 25 | 6.2 | |
| 63 | CH | H | Me, H ^a | Ph | | 2,4-Cl ₂ C ₆ H ₃ CH 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 ₆ H ₄ CH 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 ₂ C ₆ H ₃ CH 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 ₂ C ₆ H ₃ CH 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 ₆ H ₄ CH ₂ | (oil) | 71 | $C_{19}H_{17}ClN_2O$ | 6.2 | 1.6 | 3.1 | |
| 69 | CH | 4-Cl | H | H | H | 4-ClC ₆ H ₄ CH ₂ | A/E (132-133) | 61 | $C_{18}H_{14}Cl_2N_2O$ | >100 | >100 | >100 | |
| 70 | CH | 3,5-Cl ₂ | H | H | H | 4-ClC ₆ H ₄ CH 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 | Me | 4-ClC ₆ H ₄ CH ₂ | M/A (201-203) | 49 | $C_{30}H_{18}Cl_2N_2O \cdot HCl$ | 6.2 | 6.2 | 0.2 | |
| 72 | CH | H | Me | Me | Me | 3-ClC ₆ H ₄ CH(Me) | (oil) | 99 | $C_{30}H_{19}ClN_2O_2$ | 3.1 | 1.6 | 0.1 | |
| 73 | CH | H | Me | Me | Me | 4-ClC ₆ H ₄ CH ₂ | M/A (137-138) | 61 | $C_{30}H_{19}ClN_2O \cdot HCl$ | 3.1 | 6.2 | 0.1 | |
| 74 | CH | 5-Cl | Me | Me | Me | 3,4-Cl ₂ C ₆ H ₃ CH ₂ | M/A (193-194) | 66 | $C_{30}H_{17}Cl_3N_2O \cdot HCl$ | 12.5 | 6.2 | 3.1 | |
| 75 | CH | H | Me | Me | Me | PhCH ₂ | (oil) | 53 | $C_{30}H_{20}N_2O$ | 25 | 12.5 | 1.6 | |
| 76 | CH | H | Me | Me | Me | 2,4-Cl ₂ C ₆ H ₃ CH ₂ | I (100-102) | 36 | $C_{30}H_{18}Cl_2N_2O$ | 12.5 | 1.6 | 3.1 | |
| 77 | CH | H | Me | Me | Me | 4-ClC ₆ H ₄ O(CH ₂) ₃ | (oil) | 87 | $C_{22}H_{23}ClN_2O_2 \cdot 1/3 \cdot H_2O$ | 12.5 | 6.2 | 1.6 | |
| 78 | CH | 5-Cl | Me | Me | Me | 4-ClC ₆ H ₄ O(CH ₂) ₃ | I/T (62.5-64) | 82 | $C_{22}H_{22}Cl_2N_2O_2 \cdot 1/3 \cdot H_2O$ | >100 | >100 | 3.1 | |
| 79 | CH | H | Me | Me | Me | PhO(CH ₂) ₃ | I/T (58-60) | 45 | $C_{31}H_{22}N_2O_2$ | 25 | 6.2 | 3.1 | |
| 80 | CH | H | Me | Me | Me | 3-ClC ₆ H ₄ CH ₂ | I/T (106-108) | 60 | $C_{30}H_{19}ClN_2O$ | 12.5 | 3.1 | 3.1 | |
| 81 | CH | H | Me | Me | Me | 4-MeC ₆ H ₄ CH ₂ | M/A (138.5-139.5) | 29 | $C_{31}H_{22}ClN_2O$ | 25 | 6.2 | 3.1 | |
| 82 | CH | 5-Cl | Me | Me | Me | Ph(CH ₂) ₂ | M/A (121-122) | 47 | $C_{31}H_{22}ClN_2O$ | 25 | 12.5 | 1.6 | |
| 83 | CH | H | Me | Me | Me | Ph(CH ₂) ₃ | M/A (136-137) | 28 | $C_{31}H_{22}N_2O \cdot (COOH)_2$ | 50 | 0.8 | 0.1 | |
| 84 | CH | H | Me | Me | Me | n-Pr | M/A (125-126) | 79 | $C_{32}H_{24}N_2O \cdot (COOH)_2$ | 25 | 1.6 | 0.2 | |
| 85 | CH | H | Me | Me | Me | n-Pr | M/A (125-126) | 64 | $C_{18}H_{22}N_2O_5$ | 12.5 | 0.8 | 0.2 | 0.31 |
| 86 | CH | 5-Cl | Me | H | H | n-Pr | A (95-97) | 70 | $C_{15}H_{17}ClN_2O \cdot (COOH)_2$ | 25 | 1.6 | 0.1 | 0.63 |
| 87 | CH | 5-Cl | Me | Me | Me | n-Pr | M/A (110-115) | 80 | $C_{15}H_{17}ClN_2O \cdot (COOH)_2$ | 25 | 6.3 | 0.1 | 0.63 |
| 88 | CH | 5-Cl | Me | Me | Me | n-Pr | M/A (121-123) | 64 | $C_{16}H_{19}ClN_2O \cdot (COOH)_2 \cdot 1/2 \cdot H_2O$ | 25 | 6.3 | 0.2 | 0.31 |
| 89 | CH | H | Me | Me | Me | n-Bu | M/A (159-161.5) | 43 | $C_{18}H_{24}N_2O \cdot (COOH)_2 \cdot 3/4 \cdot H_2O$ | 25 | 6.3 | 0.1 | 0.31 |
| 90 | CH | H | Me | Me | Me | n-Bu | M/A (139-142) | 82 | $C_{16}H_{12}Cl_2N_2O \cdot HCl$ | 25 | 6.2 | 0.1 | |
| 91 | CH | 5-Cl | H | H | H | 2-ClTh-3-CH ₂ | M/A (165-172) | 62 | $C_{16}H_{14}N_2OS \cdot HCl$ | 50 | 3.1 | 0.1 | |
| 92 | CH | H | H | H | H | Th-3-CH ₂ | M/A (150-153.5) | 30 | $C_{16}H_{13}Cl_2N_2OS \cdot HCl$ | 6.2 | 1.6 | 0.1 | 0.8 |
| 93 | CH | H | H | H | H | 2-ClTh-3-CH ₂ | M/A (170-171) | 59 | $C_{16}H_{11}Cl_3N_2OS \cdot HCl$ | >100 | 50 | 3.1 | |
| 94 | CH | 3,5-Cl ₂ | H | H | H | Th-3-CH ₂ | (oil) | 46 | $C_{16}H_{12}Cl_2N_2OS \cdot HCl$ | >100 | 100 | 6.2 | |
| 95 | CH | 3,5-Cl ₂ | H | H | H | Th-3-CH ₂ | M/A (220-222) | 43 | $C_{17}H_{15}ClN_2OS$ | 12.5 | 3.1 | 0.1 | |
| 96 | CH | 5-Cl | H | H | H | Th-3-CH(Me) | M/A (166-167) | 40 | $C_{30}H_{18}Cl_2N_2O$ | 6.2 | 0.8 | 0.4 | |
| 97 | CH | 5-Cl | Et, H ^a | | | 4-ClC ₆ H ₄ CH ₂ | M/A (158.5-159.5) | 57 | $C_{30}H_{17}Cl_3N_2O \cdot HCl$ | 12.5 | 0.8 | 0.2 | |
| 98 | CH | 5-Cl | Et, H ^a | | | 2,4-Cl ₂ C ₆ H ₃ CH ₂ | M/A (130-132) | 58 | $C_{30}H_{19}ClN_2O \cdot HCl$ | 6.2 | 1.6 | 1.6 | |
| 99 | CH | 5-Cl | Et, H ^a | | | PhCH ₂ | M/A (141 dec) | 36 | $C_{17}H_{23}N_3O \cdot 2(COOH)_2 \cdot 1/6 \cdot H_2O$ | >100 | >100 | 6.3 | 0.16 |
| 100 | CH | H | (Me) ₂ NCH ₂ | H | H | i-Bu | M/A (175 dec) | 61 | $C_{17}H_{23}N_3O \cdot 2(COOH)_2 \cdot 1/2 \cdot H_2O$ | >100 | >100 | 12.5 | 0.31 |
| 101 | CH | H | (Me) ₂ NCH ₂ | H | H | i-Bu | M/A (170 dec) | 63 | $C_{21}H_{22}ClN_3O_3 \cdot 1/2 \cdot (COOH)_2$ | >100 | >100 | 0.8 | 0.63 |
| 102 | CH | H | Me | | | 4-ClC ₆ H ₄ CH ₂ | M (191 dec) | 37 | $C_{19}H_{25}N_3O_5 \cdot 1/2 \cdot (COOH)_2$ | >100 | >100 | 1.6 | 1.25 |
| 103 | CH | H | (Me) ₂ NCH ₂ | H | H | i-Bu | M (193 dec) | 61 | $C_{30}H_{27}N_3O_5 \cdot 1/2 \cdot (COOH)_2$ | >100 | >100 | 25 | 5 |
| 104 | CH | H | (Me) ₂ NCH ₂ | Me | | i-Bu | A (121-122) | 47 | $C_{33}H_{27}N_3O \cdot (COOH)_2$ | >100 | >100 | 6.3 | 2.5 |
| 105 | CH | H | MeO-CH ₂ ^b | H | H | i-Bu | | 27 | | 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 | | | MFC, ^{f,5} μg/mL |
|-----|----|------|------------------------------------|----------------|---------------------------------------------------|------------------------------------------|-------------|---------------------------------------------------------------------------------------------------------|-----------------------------|------|------|---------------------------|
| | | | | | | | | | C.a. | A.f. | T.a. | |
| 108 | CH | 5-Cl | (Me) ₂ NCH ₂ | H | i-Bu | M/E (162–163 dec) | 58 | C ₁₈ H ₂₄ CIN ₃ O-2(COOH) ₂ ¹ /2H ₂ O | >100 | >100 | 0.8 | 2.5 |
| 109 | N | 5-Cl | (Me) ₂ NCH ₂ | H | i-Bu | M/E (190–192) | 63 | C ₁₇ H ₂₃ CIN ₃ O-(COOH) ₂ | >100 | >100 | 12.5 | 0.31 |
| 110 | N | 5-Cl | H | H | i-Am | M/I (111–114) | 45 | C ₁₆ H ₁₈ CIN ₃ O-(COOH) ₂ | >100 | >100 | 0.8 | 20 |
| 111 | N | 5-Cl | Et | Et | Me | I/T (73–74) | 57 | C ₁₅ H ₁₈ CIN ₃ O | 100 | 100 | 0.8 | 1.25 |
| 112 | N | 5-Cl | Et | Et | i-Am | I/T (69–70) | 83 | C ₁₇ H ₂₂ CIN ₃ O | >100 | >100 | 0.8 | 1.25 |
| 113 | N | 5-Cl | Et | Et | 4-ClC ₆ H ₄ CH ₂ | A/I (129–130) | 86 | C ₂₁ H ₂₁ Cl ₂ N ₃ O | >100 | >100 | >100 | 20 |

^a A mixture of *E* and *Z* isomers. ^b MeOH, M; AcOEt, A; *i*-Pr₂O, I; CH₃CN, N; petroleum ether, T; Et₂O, 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 reported⁵ 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 morphologically 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 R₅ of V is a C₁–C₅ alkyl group, show moderate activity, the aralkyl groups (21–99) in R₅ 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 R₃ and R₄ 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 CH₂Cl₂ (40 mL), to which SOCl₂ (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 NaHCO₃, and extracted with CH₂Cl₂. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was chromatographed on silica gel. The fractions eluted with 2% MeOH/CH₂Cl₂ gave 8 as an oil (picrate, 1.13 g, mp 146–149 °C, from MeOH/AcOEt, 13%): NMR (Me₂SO) δ 5.87 (1 H, d, *J* = 2 Hz, =CHH), 6.03 (1 H, d, *J* = 2 Hz, =CHH), 7.50–9.47 (9 H, m, aromatic), 11.90 (1 H, br s, =NH⁺). Anal. (C₁₁H₉CIN₂·C₆H₃N₃O₇) C, H, Cl, N.

The fractions eluted with 5% MeOH/CH₂Cl₂ gave 4 (1.38 g, mp 126–127.5 °C, from AcOEt/*i*-Pr₂O, 26%): NMR (CDCl₃) δ 2.60 (3 H, s, Me), 6.80–7.47 (10 H, m, aromatic). Anal. (C₁₄H₁₃CIN₄) 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

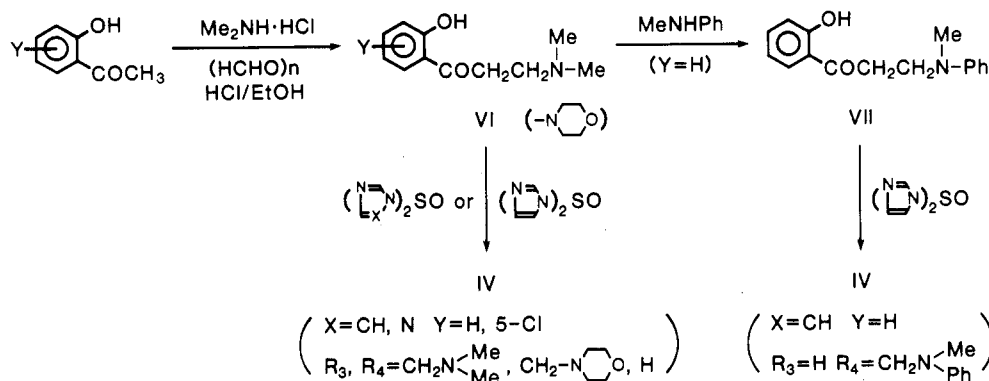


Table III. In Vitro Antifungal Activity of 1-Vinylimidazoles and Clotrimazole as Measured on Sabouraud's Glucose Agar

| compd | MIC, ^a $\mu\text{g/mL}$ | | | | | |
|--------------|--------------------------------------|-------------------------|--------------------------------------|-------------------------|--------------------------------------|-------------------------|
| | <i>T.m.</i> ^b IFO 5809 | <i>T.m.</i> IFO 5810 | <i>T.r.</i> ^b IFO 5467 | <i>T.r.</i> IFO 5807 | <i>C.a.</i> ^b IFO 1060 | <i>C.a.</i> 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 |

^aLowest 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 Et₂O. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel (elution with 3% MeOH/CH₂Cl₂) to obtain the free base of 9 (853 mg, oil, 79%). A solution of the above free base in Et₂O was treated with 8% HCl/EtOH to give its hydrochloride 9 (520 mg, 41%, mp 190–195 °C, from MeOH/AcOEt): NMR (Me₂SO-*d*₆) δ 3.63 (3 H, s, OMe), 5.53 (1 H, d, *J* = 2 Hz, =CHH), 5.93 (1 H, d, *J* = 2 Hz, =CHH), 6.87–7.77 (7 H, m, aromatic), 9.27 (1 H, m, =NH⁺). Anal. (C₁₂H₁₂N₂O·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, R₃ = Me, R₄ = H and *Z* Form, X = CH, Y = H, R₃ = H, R₄ = Me). Imidazole (8.16 g, 119.9 mmol) was mixed with dry CH₂Cl₂ (41 mL), to which SOCl₂ (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 H₂O and extracted with CH₂Cl₂. The extract was washed with H₂O, dried over Na₂SO₄, and evaporated to remove the solvent. The residue was chromatographed on silica gel and eluted with 2% MeOH/CH₂Cl₂ to obtain IV (*Z* isomer, X = CH, Y = H, R₃ = H, R₄ = CH₃) (242 mg, mp 199.5–201.5 °C, from MeOH, 6%): NMR (Me₂SO-*d*₆) δ 1.68 (3 H, d, *J* = 7 Hz, Me), 6.28 (1 H, q, *J* = 7 Hz, =CHMe), 6.72–7.58 (7 H, m, aromatic), 9.82 (1 H, s, OH). Anal. (C₁₂H₁₂N₂O) C, H, N.

The fractions eluted with 3% MeOH/CH₂Cl₂ gave IV (*E* isomer, X = CH, Y = H, R₃ = Me, R₄ = H) (703 mg, mp 187–190 °C, from MeOH, 18%): NMR (Me₂SO-*d*₆) δ 1.60 (3 H, d, *J* = 7 Hz, Me), 6.07 (1 H, q, *J* = 7 Hz, =CHMe), 6.37–7.57 (7 H, m, aromatic), 9.77 (1 H, s, OH). Anal. (C₁₂H₁₂N₂O) 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, R₃ = Me, R₄ = 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 Et₂O. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel (elution with 2% MeOH/CH₂Cl₂) 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 (Me₂SO-*d*₆) δ 1.68 (3 H, d, *J* = 7 Hz, Me), 5.03 (2 H, s, CH₂), 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. (C₁₉H₁₇ClN₂O·HCl) C, H, Cl, N.

Compound 61 was prepared in a similar manner.

X-ray Results. Crystal Data. 60: C₁₉H₁₇ClN₂O·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. (C₁₁H₁₆ClNO₂) 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, R₃ = CH₂NMe₂, R₄ = H and *Z* Form, X = CH, Y = H, R₃ = H, R₄ = CH₂NMe₂). To a stirred solution of imidazole (2.11 g, 31 mmol) and dry CH₂Cl₂ (21 mL) was added dropwise SOCl₂ (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 NaHCO₃ and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was chromatographed on alumina. The fractions eluted

with 3% MeOH/CH₂Cl₂ gave (E)-IV (527 mg, mp 96.5–98.5 °C, from AcOEt/*i*-Pr₂O, 42%): NMR (CDCl₃) δ 2.33 (6 H, s, 2 × Me), 2.98 (2 H, d, *J* = 8.1 Hz, CH₂), 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. (C₁₄H₁₇N₃O) C, H, N.

The fractions eluted with 5% MeOH/CH₂Cl₂ gave (Z)-IV (70 mg, mp 170–171 °C, from AcOEt, 6%): NMR (CDCl₃) δ 2.34 (6 H, s, 2 × Me), 3.03 (2 H, d, *J* = 7.2 Hz, CH₂), 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. (C₁₄H₁₇N₃O) C, H, N.

2-Hydroxy-3-(*N*-methylanilino)propiofenone (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% H₂O/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 Et₂O, dried (Na₂SO₄), 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 (CDCl₃) δ 2.93 (3 H, s, CH₃), 3.03–3.36 (2 H, m, CH₂), 3.64–3.98 (2 H, m, CH₂), 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, R₃ = CH₂N(Me)Ph, R₄ = H and Z Form, X = CH, Y = H, R₃ = H, R₄ = CH₂N(Me)Ph]. To a stirred solution of imidazole (1.74 g, 25.6 mmol) and dry CH₂Cl₂ (17.4 mL) was added dropwise SOCl₂ (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 CH₂Cl₂ (2 mL) was added at room temperature. After the reaction mixture had been stirred for 30 min, it was poured into aqueous NaHCO₃ and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated to give the oil. NMR (CDCl₃) *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, CH₂), 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, CH₂), 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/CH₂Cl₂ gave (Z)-IV [X = CH, Y = H, R₃ = H, R₄ = CH₂N(Me)Ph, 857 mg, 66%, mp 153–154 °C, from MeOH/AcOEt]. NMR (CDCl₃) *Z* forms: δ 2.85 (3 H, s, Me), 3.91 (2 H, d, *J* = 6.8 Hz, CH₂), 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, R₃ = CH₂N(Me)Ph, R₄ = H] isomerized to the *Z* form of IV [X = CH, Y = H, R₃ = H, R₄ = CH₂N(Me)Ph] by silica gel chromatography. Anal. (C₁₉H₁₉N₃O) 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 CH₂Cl₂ (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 NaHCO₃ and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was crystallized from MeOH/AcOEt to give the trifluoroacetamide (600 mg, mp 168–169 °C, 26%): NMR (Me₂SO-*d*₆) δ 5.07 (1 H, d, *J* = 2 Hz, =CHH), 5.60 (1 H, d, *J* = 2 Hz, =CHH), 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), K₂CO₃ (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 NaHCO₃, and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel.

The fractions eluted with 1% MeOH/CH₂Cl₂ gave 116 (614 mg, mp 101–101.5 °C, 75%, after washing with *i*-Pr₂O): NMR δ 3.88 (1 H, d, *J* = 15 Hz, CHH), 5.22 (1 H, d, *J* = 15 Hz, CHH), 5.27 (1 H, d, *J* = 2 Hz, =CHH), 5.77 (1 H, d, *J* = 2 Hz, =CHH), 7.07–7.77 (11 H, m, aromatic). Anal. (C₂₀H₂₅ClF₃N₃O) 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 H₂O and extracted with Et₂O. The organic layer was washed with H₂O, dried (Na₂SO₄), 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 (CDCl₃) δ 4.23 (3 H, br s, CH₂NH), 5.10 (1 H, d, *J* = 2 Hz, =CHH), 5.50 (1 H, d, *J* = 2 Hz, =CHH), 6.53–7.53 (11 H, m, aromatic). Anal. (C₁₈H₁₈ClN₃) 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 K₂CO₃ (2.73 g, 19.8 mmol) in dry acetone (30 mL) was refluxed for 16 h. The reaction mixture was evaporated, added to H₂O, and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 1% MeOH/CH₂Cl₂ gave 2-[(4-chlorobenzyl)thio]acetophenone [I, R₁ = 2-(4-ClC₆H₄-CH₂S)C₆H₄, R₂ = CH₃, 2.18 g, mp 126–128 °C, 80%, after washing with *i*-Pr₂O]: IR (Nujol) 1670 cm⁻¹. Anal. (C₁₅H₁₃ClOS) C, H, Cl, S.

SOCl₂ (1.29 g, 10.8 mmol) was added to a mixture of imidazole (2.95 g, 43.3 mmol) and dry CH₂Cl₂ (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 NaHCO₃ and extracted with CH₂Cl₂. The organic layer was washed with H₂O, dried (Na₂SO₄), and evaporated. The residue was chromatographed on silica gel. The fractions eluted with CH₂Cl₂ gave the starting acetophenone (750 mg, 37.5%). The fractions eluted with 2% MeOH/CH₂Cl₂ gave the free base (oil) of the target 118. HCl salt (118) (310 mg, mp 153–163 °C, 12%, from MeOH/Et₂O): NMR (Me₂SO-*d*₆) δ 4.20 (2 H, s, CH₂Ph), 5.47 (1 H, d, *J* = 2 Hz, =CHH), 6.13 (1 H, d, *J* = 2 Hz, =CHH), 7.30–7.77 (11 H, m, aromatic), 9.20 (1 H, br s, =NH⁺). Anal. (C₁₈H₁₅ClN₂S·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 system⁶ combined with PS-microtiter plates (Labortechnik) and Micom Auto Diluter SPR2 (Sanko), using final inocula⁶ of 1 × 10⁵ cells (yeast) or 1 × 10⁵ 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 × 10⁶ yeast cells/mL of EMEM supplemented with 20% calf serum. The test compounds were treated with the microtiter dilution system in the same way 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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