Substrates activity with purine nucleoside phosphorylase (calf spleen, Sigma) was tested as described by Stoeckler and coworkers[58] using analytical HPLC.

Registry No. 2, 107796-00-9; 5, 107796-01-0; 6, 6129-68-6; 7, 6067-31-8; 8, 88293-57-6; 9, 107712-09-4; 10, 107796-02-1; 11, 14631-20-0; 12, 107712-10-7; 13, 6027-65-2; 14, 87-42-3; 15, 107712-11-8; 16, 107712-12-9; 17, 107712-13-0; 18, 107712-14-1; 19, 5451-40-1; 20, 107712-15-2; 21, 107712-16-3; 22, 107712-17-4; 23, 107712-18-5; 24, 107712-19-6; 25, 107712-20-9; 26, 107712-21-0; 27, 107712-22-1; 28, 107712-23-2; 29, 107712-24-3; 30, 107712-25-4; 2,4-bis(trimethylsilyl)uracil, 10457-14-4; 1,5-anhydro-2-deoxy-3,4,6-tris-*O*-(4-nitrobenzoyl)-D-*ribo*-hex-1-enitol, 107796-03-2; bis-*O*-(trimethylsilyl)-*N*-acetylcytosine, 107712-26-5; adenosine deaminase, 9026-93-1.

(58) Stoeckler, J. D.; Cambor, C.; Parks, R. E., Jr. *Biochemistry* **1980**, *19*, 102.

Synthesis and Oral Antifungal Activity of Novel Azolylpropanolones and Related Compounds

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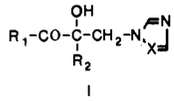
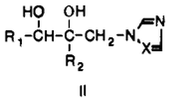
To find orally active antifungal agents, novel imidazolyl- and 1,2,4-triazolylpropanolones I and related compounds II–IV were synthesized. Compounds I were derived from ketones V (method A), α-diketone IX (method B), α-hydroxy ketones X (method C), α-chloro ketone XII (method D), and enones VI (method E). Diols II, synthesized from I with $NaBH_4$, were cyclized to five-membered cyclic compounds III by using *N,N'*-carbonyldiimidazole, thionyl chloride, *N,N'*-(thiocarbonyl)diimidazole, bromochloromethane, 2,2-dimethoxypropane, and cyclohexanone dimethyl ketal. Diols IV were synthesized from I by Grignard reaction (method F), hydroxymethylation of X (method G), and reaction of ketones XXI with 1-[(trimethylsilyl)methyl]-1,2,4-triazole (method H). Compounds I–IV were examined for their antifungal activities in vitro by evaluation of broth dilution MIC values against three species of fungi and the inhibitory effect on pseudomycelium of *Candida albicans*, and they were examined for oral efficacy in vivo against subacute systemic candidiasis in mice and superficial dermatophytosis in guinea pigs. Compounds **2**, **12**, **38**, **39**, and **92** exhibited strong oral antifungal activity. An asymmetric synthesis and the structure–activity relationships of the compounds examined are discussed.

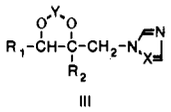
With the advent of ketoconazole,[1] the synthesis of orally active and broad-spectrum antimycotic azoles has been explored actively in recent years.[2] Nevertheless, there is still a need for more potent and better antimycotic drugs. In recent years, (*R,S*)-1-(2,4-dichlorophenyl)-1-(4-fluorophenyl)-2-(1,2,4-triazol-1-yl)ethanol, ICI 153066,[3] was reported to show oral antifungal activity. Therefore our interest was directed to the synthesis of azolylpropanolones and related compounds with the partial structure of ICI 153066. Here we report the synthesis and antifungal properties of new orally active antifungal agents I–IV.[4,5]



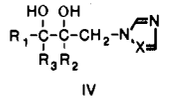
I



II



III



IV

X : CH, N
Y : CO, SO, CS, CH_2, cyclohexyl
R_1, R_2, R_3 : alkyl, aryl

Chemistry

The synthetic routes (A–E) to the target compounds I are illustrated in Scheme I (Table I). The starting ketones V reacted with *N,N,N',N'*-tetramethyldiaminomethane in acetic anhydride to give the conjugated ketones VI,[6] which were oxidized to the epoxy ketones VII with hydrogen peroxide in aqueous NaOH. Compounds VII were then treated with 1,2,4-triazole in the presence of NaH in DMF to obtain a mixture of the desired compounds I and the isomeric 1,2,4-triazol-4-yl derivatives VIII as minor byproducts (method A). The triazole isomers I and VIII were separable by chromatography. The structure assignment was made by NMR chemical shift of the triazole ring protons.

Reaction of the α-diketones IX with diazomethane gave the oxiranes VII,[7] which were then treated with 1,2,4-triazole in the presence of NaH in DMF to give a mixture of I and VIII (method B).

Hydroxymethylation of the α-hydroxy ketones X with paraformaldehyde in the presence of $KHCO_3$ afforded the primary alcohols, which were treated with *p*-TsCl to give the tosylate XI. Compound XI was transformed with triethylamine to obtain I and VIII (method C).

Treatment of V with SO_2Cl_2 gave the chloro compounds XII, which were then treated with paraformaldehyde and

† Division of Organic Chemistry.
‡ Division of Physical Chemistry.
§ Division of Microbiology.

(1) Heeres, J.; Van Cutsem, J. *J. Med. Chem.* **1981**, *24*, 1360.
(2) Gravestock, M. B.; Ryley, J. F. In *Annual Reports in Medicinal Chemistry*; Bailey, D. M., Ed.; Academic: Orlando, 1984; p 127 and references cited therein.
(3) Ryley, J. F.; Willson, R. G. *Proceedings, 22nd ICAAC*, Miami Beach, FL, 4–6 Oct. 1982; Abstract 477.
(4) (a) Walter, K.; Elmer, S. Eur. Pat. Appl. 0114567. (b) John Martin, C.; Paul Anthony, W.; Michael Barry, G. Eur. Pat. Appl. 0114487; *Chem. Abstr.* **1984**, *101*, 2305540*j*.
(5) (a) Ogata, M.; Matsumoto, H.; Tawara, K. Japan Unexamined Pat. Publn. No. 59 155365, 1984. (b) Ogata, M.; Matsumoto, H.; Tawara, K. Jpn. Unexamined Pat. Publn. No. 59 167573, 1984. (c) Ogata, M.; Matsumoto, H.; Tawara, K. Jpn. Unexamined Pat. Publn. No. 59 199680, 1984. (d) Ogata, M.; Matsumoto, H.; Kida, S.; Tawara, K. Jpn. Unexamined Pat. Publn. No. 60 25990, 1985.
(6) Takahashi, K.; Shimizu, S.; Ogata, M. *Synth. Commun.*, in press.
(7) Siegel, H.; Wittmann, H. *Monatsh. Chem.* **1982**, *113*(8/9), 1005.

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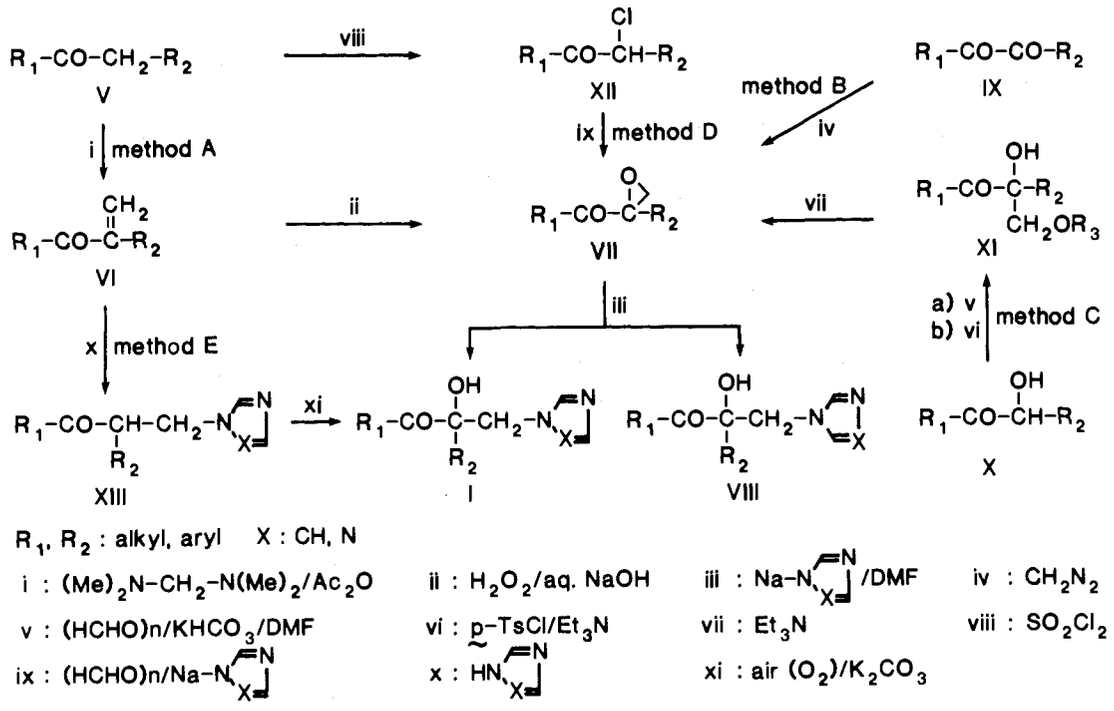
Scheme I



sodium 1,2,4-triazole to give the mixture of I and VIII (method D).

The reaction of VI with 1,2,4-triazole gave the triazolyl ketones XIII[6] as the sole product, which was subsequently oxidized with air in the presence of K_2CO_3 to give I (method E). This method prevented the production of the undesired isomers VIII. In order to compare the antifungal activities of the two optical isomers of **2**, (*R*)-(−)- and (*S*)-(+)-1,2-bis(2,4-dichlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one (**83** and **84**) were synthesized as depicted in Scheme II. The starting conjugated ketone **77** was reduced to the allyl alcohol **78** with $NaBH_4/CeCl_3$ or diisobutylaluminum hydride (DIBAH). Compound **78** was oxidized enantioselectively with (+)-diisopropyl-L-tartrate [(+)-L-DIPT], Ti(O-*i*-Pr)$_4$ and *tert*-butyl hydroperoxide (TBHP) by the Sharpless method[8a-c] to obtain the epoxy alcohol **79** and the allyl alcohol **80**. A similar procedure using (−)-D-DIPT, Ti(O-*i*-Pr)$_4$ and TBHP was carried out with **78** to obtain the epoxy alcohol **81** and the allyl alcohol **82**. The enantiomeric epoxy alcohols **79** and **81** were oxidized with pyridinium chlorochromate (PCC) and then treated with sodium 1,2,4-triazole in DMF to obtain the desired levorotory and dextrorotatory triazolylpropiophenone **83** and **84**, respectively.

The absolute configuration of the potent isomer **83** was determined by X-ray analysis of the *p*-bromobenzoate **85**, and the analysis established that the absolute configuration of **83** is (*R*)-(−) and that of **84** is (*S*)-(+) (Figure 1).

Next, we attempted the synthesis of the other antifungal imidazolyl- and 1,2,4-triazolylpropanols II–IV from I. Ketols I were reduced with $NaBH_4$ to obtain two diastereomeric diols II; one of the pair was the major product (Scheme III, Tables II and III). To confirm the configuration of the diastereomer, diols II (**108**) (major product) and II (**109**) (minor product) derived from ketol I (**24**) were

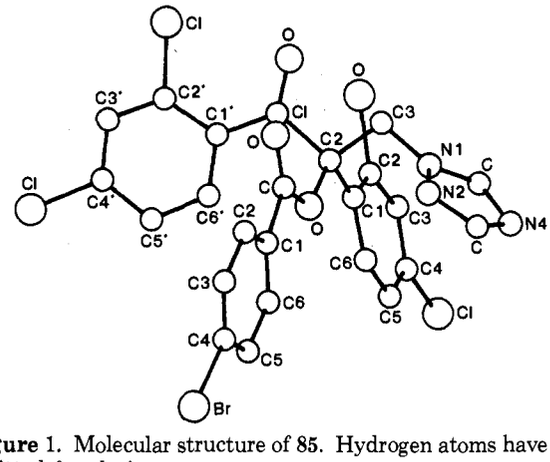


Figure 1. Molecular structure of **85**. Hydrogen atoms have been omitted for clarity.

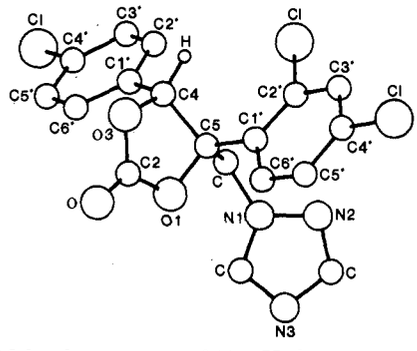
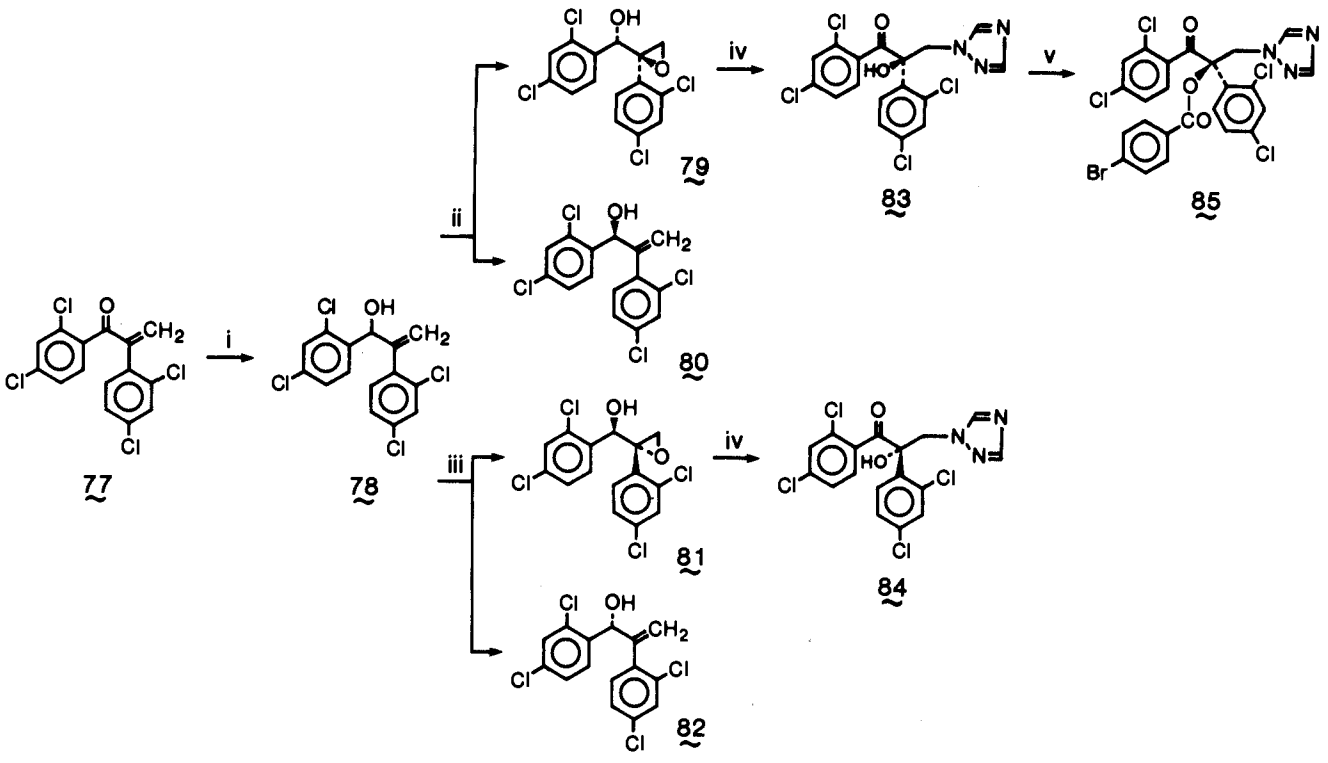


Figure 2. Molecular structure of **115**. Hydrogen atoms have been omitted for clarity.

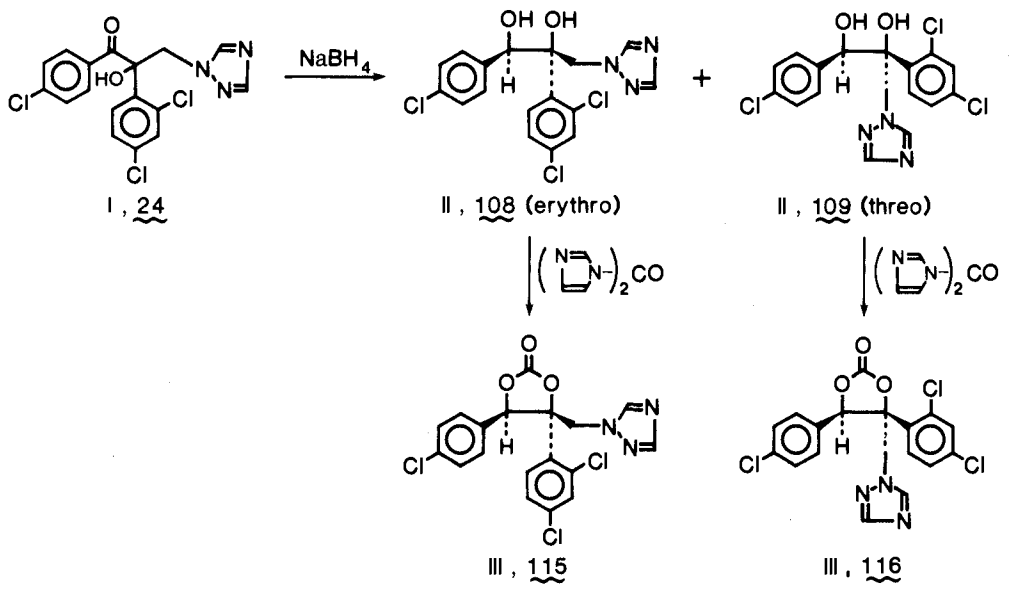
treated with *N*,*N*′-carbonyldiimidazole, and 2-oxo-1,3-dioxolanes III (**115**) and III (**116**) were obtained, respectively. X-ray analysis of **115** demonstrated that both chlorosubstituted-phenyl nuclei were of the trans configuration (Figure 2). This indicated the configuration of **108** (major product) to be the erythro form and that of **109** (minor product) to be the threo form. The major product diol can be distinguished from the minor one by the characteristic methylene proton signals in the NMR spectra. Namely,

(8) (a) Katsuki, T.; Sharpless, K. B. *J. Am. Chem. Soc.* **1980**, *102*, 5974. (b) The enantiomeric excess was determined by ^{1}H NMR on the corresponding epoxy acetate in the presence of Eu(hfbc)$_3$ by conversion to MTPA ester. Dale, J. P.; Dull, P. L.; Mosher, H. S. *J. Org. Chem.* **1969**, *34*, 2543. (c) Pffenninger, A. *Synthesis* **1986**, *2*, 89.

Scheme II



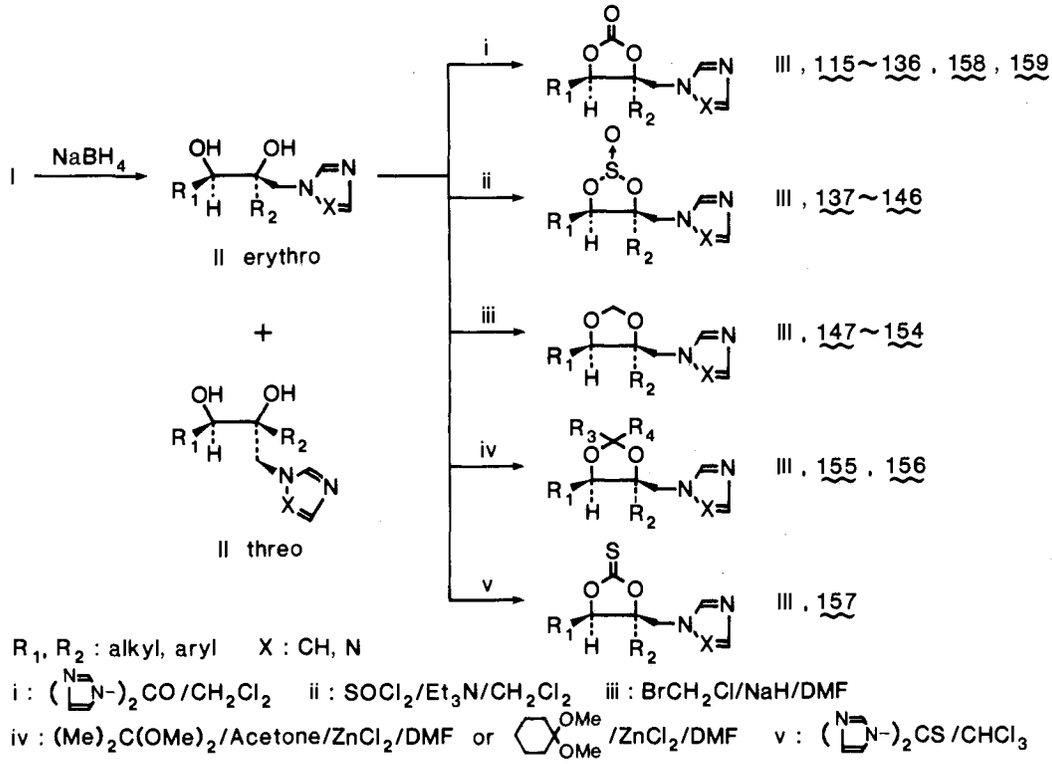
Scheme III



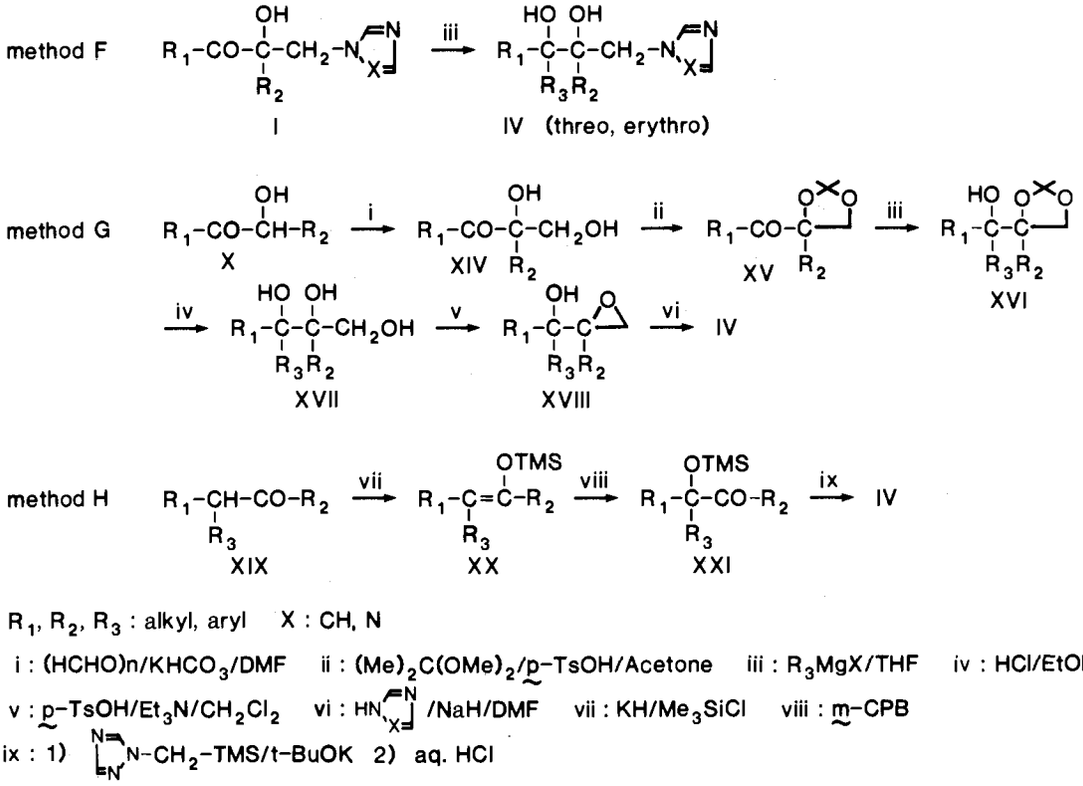
the NMR spectrum of the diol (major product) had a large chemical shift difference between the geminal methylene proton signals while that of the other diol (minor product) was small. Because of the relatively poor biological activity of the threo diol (minor product) compared to the erythro diol (major product), the isolation of threo diol was not made except for **89**, **101**, **104**, **107**, and **109** (Table III). To obtain the other potential antifungal compounds, these erythro diols II were cyclized to five-membered cyclic compounds III by various methods (Scheme IV).

The target diols IV were prepared by methods F, G, and H (Scheme V). Compounds IV were obtained from I using excess Grignard reagent R_3MgX (method F). The α-hydroxy ketones X were hydroxymethylated with paraformaldehyde/$KHCO_3$ in DMF to give the diols XIV. The diol groups of XIV were protected by 2,2-dimethoxypropane to obtain the dimethyl ketals XV, which were subjected to Grignard reaction with R_3MgX to obtain the alcohols XVI. Compounds XVI were deprotected with dilute HCl, giving the triols XVII, which were treated with *p*-TsCl/Et_3N to obtain the epoxy alcohols XVIII. Compounds XVIII were treated with sodium imidazole or 1,2,4-triazole in DMF to obtain the target diols IV (method G). Trimethylsilyl enol ether XX was derived from ketone XIX by KH/TMSCl treatment and then was oxidized to ketone XXI with *m*-chloroperbenzoic acid. Compound XXI[9] was

Scheme IV



Scheme V



treated with 1-[(trimethylsilyl)methyl]-1,2,4-triazole[10]/*t*-BuOK and then hydrolyzed with HCl to obtain the target diol IV (method H).

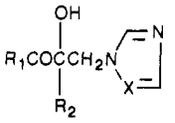
The configuration of the two diastereomeric diols IV (threo, erythro) was deduced from comparison of the NMR spectra, as accomplished for II.

Biological Results and Discussion

The in vitro and in vivo antifungal activities of imidazolyl- and triazolylpropanolones I and related compounds II–IV are summarized in Table VI. All the compounds were evaluated in vitro on the basis of their MIC values against three species of fungi and MEC values for inhibition of pseudomycelium formation of *Candida albicans*, and they were examined in vivo on the basis of the ther-

(9) Rubottom, G. M.; Vazquez, M. A.; Pelegrina, D. R. *Tetrahedron Lett.* 1974, 4319.
(10) (a) Shimizu, S.; Ogata, M. *Heterocycles* **1986**, *24*, 237. (b) Shimizu, S.; Ogata, M. *J. Org. Chem.* **1986**, *51*, 3897.

Table I



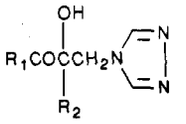
I (1-65)

no.	R_1	R_2	X	method	recrystn solvent	mp, °C	yield,[a] %	formula	anal.
1	Ph	Ph	N	B	MeOH/AcOEt	175–177	13	$C_{17}H_{15}N_3O_2$	C, H, N
2	2,4-Cl_2Ph	2,4-Cl_2Ph	N	A	AcOEt/(*i*-Pr)$_2$O	167–168	24	$C_{17}H_{11}Cl_4N_3O_2$	C, H, Cl, N
3	4-ClPh	4-ClPh	N	B	AcOEt/(*i*-Pr)$_2$O	102–104	13	$C_{17}H_{13}Cl_2N_3O_2$, Me_2NCHO	C, H, Cl N
4	4-MeOPh	4-MeOPh	N	B	AcOEt/(*i*-Pr)$_2$O	134–135	11	$C_{19}H_{19}N_3O_4$	C, H, N
5	4-MePh	4-MePh	N	B	AcOEt/(*i*-Pr)$_2$O	123–124	5	$C_{19}H_{19}N_3O_2$	C, H, Cl, N
6	4-FPh	2,4-Cl_2Ph	N	B	MeOH/AcOEt	200–201	21	$C_{17}H_{12}Cl_2FN_3O_2$	C, H, Cl, F, N
7	2-ClPh	2-ClPh	N	B	(*i*-Pr)$_2$O	172.5–174	18	$C_{17}H_{13}Cl_2N_3O_2$	C, H, Cl, N
8	3-ClPh	3-ClPh	N	B	AcOEt/(*i*-Pr)$_2$O	117–118	4	$C_{17}H_{13}Cl_2N_3O_2$	C, H, Cl, N
9	4-FPh	4-FPh	N	B	AcOEt/(*i*-Pr)$_2$O	143–144	19	$C_{17}H_{13}FN_3O_2$	C, H, F, N
10	2-MeOPh	2-MeOPh	N	B	AcOEt/Et_2O	149–150	6	$C_{19}H_{19}N_3O_4$	C, H, N
11	2,4-Cl_2Ph	4-ClPh	N	D	AcOEt/(*i*-Pr)$_2$O	92–95	18	$C_{17}H_{12}Cl_3N_3O_2$	C, H, Cl, N
12	isopropyl	2,4-Cl_2Ph	N	A	AcOEt/(*i*-Pr)$_2$O	163.5–165	46	$C_{14}H_{15}Cl_2N_3O_2$	C, H, Cl, N
13	isopropyl	4-ClPh	N	A	(*i*-Pr)$_2$O	80–81	5	$C_{14}H_{16}ClN_3O_2$	C, H, Cl, N
14	2-MePh	2-MePh	N	B	(*i*-Pr)$_2$O	101–102	11	$C_{19}H_{19}N_3O_2$	C, H, N
15	2-ClPh	Ph	N	B	AcOEt/(*i*-Pr)$_2$O	95–96	18	$C_{17}H_{14}ClN_3O_2$	C, H, Cl, N
16	2-ClPh	4-ClPh	N	B	AcOEt/(*i*-Pr)$_2$O	156–157	41	$C_{17}H_{13}Cl_2N_3O_2$	C, H, Cl, N
17	2-ClPh	4-FPh	N	B	AcOEt/(*i*-Pr)$_2$O	123–125	9	$C_{17}H_{13}ClFN_3O_2$	C, H, Cl, F, N
18	4-ClPh	2-ClPh	N	B	MeOH/AcOEt	179–180	5	$C_{19}H_{13}N_3O_2 \cdot {}^1/_2AcOEt$	C, H, Cl, N
19	4-FPh	2-ClPh	N	A	AcOEt	175–177	24	$C_{17}H_{13}ClFN_3O_2$	C, H, Cl, F, N
20	Ph	2-ClPh	N	B	AcOEt/(*i*-Pr)$_2$O	172–173	14	$C_{17}H_{14}ClN_3O_2$	C, H, Cl, N
21	4-MePh	2-ClPh	N	B	AcOEt/(*i*-Pr)$_2$O	141–143	18	$C_{18}H_{16}ClN_3O_2 \cdot {}^1/_2AcOEt$	C, H, Cl, N
22	2-ClPh	2,4-Cl_2Ph	N	A	AcOEt	162–163	8	$C_{17}H_{12}Cl_3N_3O_2$	C, H, Cl, N
23	2,4-Cl_2Ph	2-ClPh	N	A	AcOEt	153–154	39	$C_{17}H_{12}Cl_3N_3O_2 \cdot {}^3/_5AcOEt$	C, H, Cl, N
24	4-ClPh	2,4-Cl_2Ph	N	A	AcOEt	198–199	11	$C_{17}H_{12}Cl_2N_3O_2 \cdot {}^1/_{10}AcOEt$	C, H, Cl, N
25	*n*-butyl	2,4-Cl_2Ph	N	A	CH_2Cl_2/Et_2O	113–114	23	$C_{15}H_{17}Cl_2N_3O_2$	C, H, Cl, N
26	Ph	2,4-Cl_2Ph	N	A	MeOH	192–193	25	$C_{17}H_{13}Cl_2N_3O_2$	C, H, Cl, N
27	2-FPh	2,4-Cl_2Ph	N	A	AcOEt/(*i*-Pr)$_2$O	96–97	10	$C_{17}H_{22}Cl_2FN_3O_2 \cdot AcOEt \cdot {}^1/_2H_2O$	C, H, Cl, F, N
28	Me	2,4-Cl_2Ph	N	A	AcOEt	181–183	35	$C_{12}H_{11}Cl_2N_3O_2$	C, H, Cl, N
29	Et	2,4-Cl_2Ph	N	A	MeOH/AcOEt	205–208	29	$C_{13}H_{13}Cl_2N_3O_2$	C, H, Cl, N
30	*n*-propyl	2,4-Cl_2Ph	N	A	AcOEt	145–146	59	$C_{14}H_{15}Cl_2N_3O_2$	C, H, Cl, N
31	*tert*-butyl	2,4-Cl_2Ph	N	A	AcOEt/(*i*-Pr)$_2$O	148.5–150	29	$C_{15}H_{17}Cl_2N_3O_2$	C, H, Cl, N
32	isobutyl	2,4-Cl_2Ph	N	A	(*i*-Pr)$_2$O	132–133	10	$C_{15}H_{17}Cl_2N_3O_2$	C, H, Cl, N
33	cyclopentyl	2,4-Cl_2Ph	N	A	AcOEt/(*i*-Pr)$_2$O	168.5–170.5	19	$C_{16}H_{17}Cl_2N_3O_2$	C, H, Cl, N
34	*n*-propyl	4-ClPh	N	A	AcOEt/(*i*-Pr)$_2$O	112–113	15	$C_{14}H_{16}ClN_3O_2$	C, H, Cl, N
35	*n*-propyl	2-ClPh	N	A	AcOEt/(*i*-Pr)$_2$O	124–125	12	$C_{14}H_{16}ClN_3O_2$	C, H, Cl, N
36	isopropyl	4-ClPh	N	A	MeOH	197 dec	27	$C_{14}H_{16}ClN_3O_2 \cdot (COOH)_2$	C, H, Cl, N
37	isobutyl	4-ClPh	N	A	MeOH	183–185 dec	6	$C_{15}H_{18}ClN_3O_2 \cdot (COOH)_2$	C, H, Cl, N
38	2,4-Cl_2Ph	4-FPh	N	A	AcOEt/(*i*-Pr)$_2$O	93–95	14	$C_{17}H_{12}Cl_3N_3O_2$	C, H, Cl, N
39	isopropyl	4-ClPh	N	A	(*i*-Pr)$_2$O	80–81	8	$C_{14}H_{16}ClN_3O_2$	C, H, Cl, N
40	4-FPh	4-ClPh	N	A	AcOEt/(*i*-Pr)$_2$O	121–122	19	$C_{17}H_{13}ClFN_3O_2$	C, H, Cl, F, N
41	2-furyl	2-furyl	N	B	AcOEt(*i*-Pr)$_2$O	154–155	29	$C_{13}H_{11}N_3O_4$	C, H, N
42	2-pyridyl	2-pyridyl	N	B	AcOEt	145.5–147	11	$C_{15}H_{13}N_5O_2$	C, H, N
43	2,4-Cl_2Ph	benzyl	N	A	AcOEt/(*i*-Pr)$_2$O	110–111	34	$C_{18}H_{15}Cl_2N_3O_2$	C, H, Cl, N
44	4-ClPh	isopropyl	N	A	AcOEt/(*i*-Pr)$_2$O	96.5–97.5	17	$C_{14}H_{16}ClN_3O_2$	C, H, Cl, N
45	4-ClPh	*n*-propyl	N	A	MeOH/AcOEt	169–170	15	$C_{14}H_{16}ClN_3O_2 \cdot (COOH)_2$	C, H, Cl, N
46	2,4-Cl_2Ph	*n*-butyl	N	A	AcOEt/(*i*-Pr)$_2$O	117–118	38	$C_{15}H_{17}Cl_2N_3O_2 \cdot (COOH)_2$	C, H, Cl, N
47	4-ClPh	*n*-amyl	N	A	AcOEt	169–171 dec	32	$C_{16}H_{20}ClN_3O_2 \cdot (COOH)_2$	C, H, Cl, N
48	2,4-Cl_2Ph	*n*-propyl	N	A	AcOEt/(*i*-Pr)$_2$O	150–151 dec	27	$C_{14}H_{15}Cl_2N_3O_2 \cdot (COOH)_2$	C, H, Cl, N
49	2,4-Cl_2Ph	Et	N	A	AcOEt/(*i*-Pr)$_2$O	104–106	42	$C_{13}H_{13}Cl_2N_3O_2$	C, H, Cl, N
50	4-ClPh	cyclopentyl	N	A	AcOEt/(*i*-Pr)$_2$O	126–128 dec	4	$C_{16}H_{18}ClN_3O_2 \cdot {}^3/_2(COOH)_2$	C, H, Cl, N
51	2-ClPh	*n*-butyl	N	A	MeOH/(*i*-Pr)$_2$O	151–153 dec	30	$C_{15}H_{18}ClN_3O_2 \cdot (COOH)_2$	C, H, Cl, N
52	4-ClPh	cyclohexyl	N	A	AcOEt/(*i*-Pr)$_2$O	150–152 dec	10	$C_{17}H_{20}ClN_3O_2 \cdot {}^3/_2(COOH)_2$	C, H, Cl, N
53	4-ClPh	isobutyl	N	A	AcOEt	115–117 dec	12	$C_{15}H_{18}ClN_3O_2 \cdot (COOH)_2$	C, H, Cl, N
54	4-ClPh	*n*-butyl	N	A	acetone/*n*-hexane	102–103	26	$C_{15}H_{18}ClN_3O_2$	C, H, Cl, N
55	4-ClPh	4-ClPh	CH	B	AcOEt	220–221	5	$C_{18}H_{14}Cl_2N_2O_2$	C, H, Cl, N
56	2-ClPh	2-ClPh	CH	B	EtOH	232–234	19	$C_{18}H_{14}Cl_2N_2O_2$	C, H, Cl, N
57	isopropyl	4-ClPh	CH	A	MeOH/AcOEt	184–186	13	$C_{15}H_{17}ClN_2O_2$	C, H, Cl, N
58	4-FPh	2,4-Cl_2Ph	CH	A	MeOH	233–235	20	$C_{18}H_{13}Cl_2FN_2O_2$	C, H, Cl, F, N
59	*n*-butyl	2,4-Cl_2Ph	CH	A	MeOH	189–191	11	$C_{16}H_{18}Cl_2N_2O_2$	C, H, Cl, N
60	2-thienyl	4-ClPh	CH	A	MeOH/$CHCl_3$	239 dec	43	$C_{16}H_{13}ClN_2O_2S$	C, H, Cl, N, S
61	2,4-ClPh	4-ClPh	CH	A	MeOH/AcOEt	161–162	13	$C_{18}H_{13}Cl_3N_2O_2$	C, H, Cl, N
62	isopropyl	2,4-Cl_2Ph	CH	A	MeOH/AcOEt	246 dec	21	$C_{15}H_{16}Cl_2N_2O_2$	C, H, Cl, N
63	4-ClPh	2,4-Cl_2Ph	CH	A	MeOH	255–257	12	$C_{18}H_{13}Cl_3N_2O_2$	C, H, Cl, N
64	Ph	2,4-Cl_2Ph	CH	A	MeOH	253–254	17	$C_{18}H_{14}Cl_2N_2O_2$	C, H, Cl, N
65	2,4-Cl_2Ph	2,4-Cl_2Ph	CH	A	AcOEt/DMF	164–166	22	$C_{18}H_{12}Cl_4N_2O_2 \cdot {}^1/_5AcOEt \cdot {}^1/_2H_2O$	C, H, Cl, N

[a] Method A: overall yield from V to I. Method B: overall yield from IX to I. Method C: overall yield from X to I.

apeutic effect on the subacute systemic murine model of candidiasis. The compounds in general were highly active against *Trichophyton asteroides* but slightly active or inactive (up to 100 μg/mL) against both *C. albicans* and

Table II

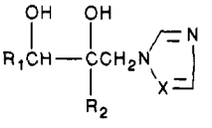


VIII (66-76)

no.	R_1	R_2	method	recrystn solvent	mp, °C	yield,[a] %	formula	anal.
66	Ph	Ph	B	AcOEt	261–263	4	$C_{17}H_{15}N_3O_2$	C, H, N
67	2,4-Cl_2Ph	2,4-Cl_2Ph	A	AcOEt	137 dec	4	$C_{17}H_{11}Cl_4N_3O_2 \cdot {}^1/_2H_2O \cdot {}^1/_3AcOEt$	C, H, Cl, N
68	4-ClPh	4-ClPh	B	AcOEt/(i-Pr)$_2$O	232–233	7	$C_{17}H_{13}Cl_2N_3O_2$	C, H, Cl, N
69	4-MeOPh	4-MeOPh	B	AcOEt	142–144 dec	6	$C_{19}H_{19}N_3O_4 \cdot {}^1/_2AcOEt$	C, H, N
70	4-FPh	2,4-Cl_2Ph	B	MeOH/AcOEt	>260	3	$C_{17}H_{12}Cl_2FN_3O_2$	C, H, Cl, F, N
71	3-ClPh	3-ClPh	B	AcOEt	204–205	2	$C_{17}H_{13}Cl_2N_3O_2$	C, H, Cl, N
72	4-FPh	4-FPh	B	MeOH/AcOEt	241–242	9	$C_{17}H_{13}F_2N_3O_2 \cdot MeOH$	C, H, F, N
73	2,4-Cl_2Ph	4-ClPh	C	AcOEt	219–221	7	$C_{17}H_{12}Cl_3N_3O_2 \cdot {}^1/_5AcOEt$	C, H, Cl, N
74	isopropyl	2,4-Cl_2Ph	A	AcOEt	>250	4	$C_{14}H_{15}Cl_2N_3O_2$	C, H, Cl, N
75	4-FPh	2-ClPh	A	MeOH/AcOEt	258–260	4	$C_{17}H_{13}ClFN_3O_2$	C, H, Cl, F, N
76	Et	2,4-Cl_2Ph	A	MeOH/AcOEt	238–240	4	$C_{13}H_{13}Cl_2N_3O_2$	C, H, Cl, N

[a] Method A: overall yield from V to VIII. Method B: overall yield from IX to VIII. Method C: overall yield from X to VIII.

Table III



II (86-114)

no.	R_1	R_2	X	recrystn solvent	mp, °C	yield, %	configuration[a]	formula	anal.
86	Ph	Ph	N	AcOEt/(i-Pr)$_2$O	189–191	10	E	$C_{17}H_{17}N_3O_2 \cdot {}^1/_{10}H_2O$	C, H, N
87	2,4-Cl_2Ph	2,4-Cl_2Ph	N	AcOEt/(i-Pr)$_2$O	214–217	64	E	$C_{17}H_{13}Cl_4N_3O_2 \cdot {}^1/_5AcOEt$	C, H, Cl, N
88	4-ClPh	4-ClPh	N	AcOEt/(i-Pr)$_2$O	168–170	87	E	$C_{17}H_{15}Cl_2N_3O_2$	C, H, Cl, N
89	4-ClPh	4-ClPh	N	AcOEt/(i-Pr)$_2$O	161–162	1	T	$C_{17}H_{15}Cl_2N_3O_2$	C, H, Cl, N
90	4-MeOPh	4-MeOPh	N	AcOEt/(i-Pr)$_2$O	82.5–83.5	40	E	$C_{19}H_{21}N_3O_4 \cdot {}^1/_2AcOEt$	C, H, N
91	4-MePh	4-MePh	N	AcOEt/(i-Pr)$_2$O	166	44	E	$C_{19}H_{21}N_3O_2$	C, H, N
92	4-FPh	2,4-Cl_2Ph	N	AcOEt/(i-Pr)$_2$O	180–181	70	E	$C_{17}H_{14}Cl_2FN_3O_2$	C, H, Cl, F, N
93	2-ClPh	2-ClPh	N	MeOH	207.5–209.5	48	E	$C_{17}H_{15}Cl_2N_3O_2$	C, H, Cl, N
94	3-ClPh	3-ClPh	N	(i-Pr)$_2$O	64–66	23	E	$C_{17}H_{15}Cl_2N_3O_2 \cdot {}^1/_2AcOEt \cdot {}^1/_2H_2O$	C, H, Cl, N
95	4-FPh	4-FPh	N	AcOEt/(i-Pr)$_2$O	170–172	75	E	$C_{17}H_{15}F_2N_3O_2$	C, H, F, N
96	2-MeOPh	2-MeOPh	N	(Et)$_2$O	197–199	15	E	$C_{19}H_{21}N_3O_4 \cdot {}^1/_2AcOEt \cdot {}^1/_{10}H_2O$	C, H, N
97	2-ClPh	Ph	N	AcOEt	247–250	48	E	$C_{17}H_{15}Cl_2N_3O_2$	C, H, Cl, N
98	2-ClPh	4-FPh	N	MeOH/AcOEt	222–225	33	E	$C_{17}H_{15}ClFN_3O_2$	C, H, Cl, F, N
99	n-propyl	2,4-Cl_2Ph	N	AcOEt	170–172	20	E	$C_{14}H_{17}Cl_2N_3O_2$	C, H, Cl, N
100	isopropyl	4-ClPh	N	AcOEt/(i-Pr)$_2$O	110–111	28	E	$C_{14}H_{18}ClN_3O_2$	C, H, Cl, N
101	isopropyl	4-ClPh	N	AcOEt/(i-Pr)$_2$O	149–151	18	T	$C_{14}H_{18}ClN_3O_2$	C, H, Cl, N
102	2,4-Cl_2Ph	4-FPh	N	AcOEt/(i-Pr)$_2$O	166–167.5	80	E	$C_{17}H_{14}Cl_2FN_3O_2$	C, H, Cl, N
103	4-FPh	4-ClPh	N	AcOEt	164–166	64	E	$C_{17}H_{15}ClFN_3O_2$	C, H, Cl, F, N
104	4-FPh	4-ClPh	N	AcOEt/(i-Pr)$_2$O	162–164	6	T	$C_{17}H_{15}ClFN_3O_2$	C, H, Cl, F, N
105	4-FPh	2,4-Cl_2Ph	N	MeOH/AcOEt	228–230	4	E	$C_{17}H_{14}Cl_2FN_3O_2$	C, H, Cl, F, N
106	n-propyl	4-ClPh	N	AcOEt/(i-Pr)$_2$O	96–97	70	E	$C_{14}H_{18}ClN_3O_2$	C, H, Cl, N
107	n-propyl	4-ClPh	N	AcOEt/(i-Pr)$_2$O	146–147	13	T	$C_{14}H_{18}ClN_3O_2$	C, H, Cl, N
108	4-ClPh	2,4-Cl_2Ph	N	MeOH/CH_3CN	184–186	60	E	$C_{17}H_{14}Cl_3N_3O_2$	C, H, Cl, N
109	4-ClPh	2,4-Cl_2Ph	N	MeOH	228–230	3	T	$C_{17}H_{14}Cl_3N_3O_2$	C, H, Cl, N
110	2,4-Cl_2Ph	4-ClPh	N	MeOH/AcOEt	221–223	33	E	$C_{17}H_{14}Cl_3N_3O_2$	C, H, Cl, N
111	isopropyl	2,4-Cl_2Ph	N	AcOEt/(i-Pr)$_2$O	139.4–141	28	E	$C_{14}H_{17}Cl_2N_2O_2$	C, H, Cl, N
112	4-ClPh	4-ClPh	CH	AcOEt	114–117	28	E	$C_{18}H_{16}Cl_2N_2O_2 \cdot {}^1/_2AcOEt$	C, H, Cl, N
113	2-ClPh	2-ClPh	CH	MeOH	250–251	35	E	$C_{18}H_{16}Cl_2N_2O_2$	C, H, Cl, N
114	2,4-Cl_2Ph	2,4-Cl_2Ph	CH	AcOEt/Et_2O	220–230	37	E	$C_{18}H_{14}Cl_4N_2O_2$	C, H, Cl, N

[a] E: erythro form (**86–114**). T: threo form (**89**, **100**, **103**, **109**).

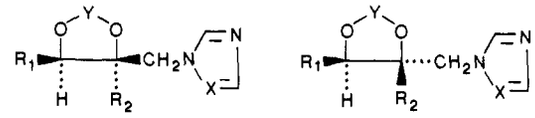
Aspergillus fumigatus. A considerable number of the compounds exhibited a high inhibitory effect on pseudomycelium formation of the yeast.

Compounds **2**, **11–13**, **19**, **22–24**, **27**, **31**, **36**, **38**, **39**, **83**, **92**, **117**, **120**, **131**, **140**, **153**, **162**, and **197** showed good oral efficacy against the murine model of candidiasis. They also displayed a high inhibitory effect on the pseudomycelium formation (MECs ranging from 0.02 to 2.5 μg/mL), in spite of their poor fungistatic activity (MICs ranging from 50 to >100 μg/mL).

Compounds **2**, **12**, **38**, and **92** were selected as the most interesting candidates for orally active antifungal agents. The results of comparative in vitro and in vivo studies of ketoconazole and our selected compounds are given in Table VII. Ketoconazole and compounds **39** and **92** displayed essentially similar in vitro activities with compounds **2**, **12**, and **38** showing lower activity against *A. fumigatus*. Compound **39** was about twice as effective as ketoconazole against the model of candidiasis. Meanwhile, compound **2** was much more effective than ketoconazole against guinea pig dermatophytosis. Others were similar (compounds **12** and **92**) to ketoconazole or more toxic (compounds **38** and **39**).

The lower fungistatic activity of our selected compounds

Table IV



III (115-159)

no.[a]	R_1	R_2	X	Y	recrystn solvent	mp, °C	yield, %	formula	anal.
115	4-ClPh	2,4-Cl_2Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	178–179	86	$C_{18}H_{12}Cl_3N_3O_3$	C, H, Cl, N
116[b]	4-ClPh	2,4-Cl_2Ph	N	CO		foam	47	$C_{18}H_{12}Cl_3N_3O_3$	C, H, Cl, N
117	4-FPh	2,4-Cl_2Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	191–192	79	$C_{18}H_{12}Cl_2FN_3O_3$	C, H, Cl, F, N
118	Ph	2,4-Cl_2Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	138–139	34	$C_{18}H_{13}Cl_2N_3O_3$	C, H, Cl, N
119	Ph	2-ClPh	N	CO	AcOEt/MeOH	220–222	20	$C_{18}H_{14}ClN_3O_3$	C, H, Cl, N
120	2,4-Cl_2Ph	4-ClPh	N	CO	AcOEt	162–163	78	$C_{18}H_{12}Cl_3N_3O_3$	C, H, Cl, N
121	2,4-Cl_2Ph	2,4-Cl_2Ph	N	CO	MeOH	222–223	64	$C_{18}H_{11}Cl_4N_3O_3$	C, H, Cl, N
122	2-ClPh	2-ClPh	N	CO	MeOH	234–235	93	$C_{18}H_{13}Cl_2N_3O_3$	C, H, Cl, N
123	4-FPh	4-FPh	N	CO	AcOEt/MeOH	81–82	68	$C_{18}H_{13}F_2N_3O_3 \cdot {}^1/_2(i\text{-Pr})_2O$	C, H, F, N
124	4-ClPh	4-ClPh	N	CO	AcOEt/(*i*-Pr)$_2$O	155–156	70	$C_{18}H_{13}Cl_2N_3O_3$	C, H, Cl, N
125	3-ClPh	3-ClPh	N	CO	AcOEt/(*i*-Pr)$_2$O	148.5–149.5	58	$C_{18}H_{13}Cl_2N_3O_3$	C, H, Cl, N
126	4-MePh	4-MePh	N	CO	AcOEt/(*i*-Pr)$_2$O	139–140	80	$C_{20}H_{19}N_3O_3$	C, H, N
127	4-MePh	2-ClPh	N	CO	AcOEt	195–196	26	$C_{19}H_{16}ClN_3O_3$	C, H, Cl, N
128	2,4-Cl_2Ph	Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	145–146	64	$C_{18}H_{13}Cl_2N_3O_3$	C, H, Cl, N
129	4-ClPh	2,4-Cl_2Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	178–179	86	$C_{18}H_{12}Cl_3N_3O_3$	C, H, Cl, N
130	4-ClPh	2,4-Cl_2Ph	N	CO	MeOH/AcOEt	238–239	51	$C_{19}H_{13}Cl_3N_2O_3$	C, H, Cl, N
131	isopropyl	2,4-Cl_2Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	150–150.5	52	$C_{15}H_{15}Cl_2N_3O_3$	C, H, Cl, N
132	*n*-propyl	2,4-Cl_2Ph	N	CO	AcOEt/(*i*-Pr)$_2$O	179–180	71	$C_{15}H_{15}Cl_2N_3O_3$	C, H, Cl, N
133	*n*-propyl	4-ClPh	N	CO	AcOEt/(*i*-Pr)$_2$O	121–122	69	$C_{15}H_{16}ClN_2O_3$	C, H, Cl, N
134	isopropyl	4-ClPh	N	CO	AcOEt/(*i*-Pr)$_2$O	104–105	52	$C_{15}H_{16}ClN_3O_3$	C, H, Cl, N
135[b]	isopropyl	4-ClPh	N	CO	AcOEt/MeOH	200–201	82	$C_{15}H_{16}ClN_3O_3$	C, H, Cl, N
136	*n*-butyl	2,4-Cl_2Ph	N	CO	(*i*-Pr)$_2$O	137–138	42	$C_{16}H_{17}Cl_2N_3O_3$	C, H, Cl, N
137	4-FPh	2,4-Cl_2Ph	N	SO	AcOEt/(*i*-Pr)$_2$O	170–171	35	$C_{17}H_{12}Cl_2FN_3O_3S$	C, H, Cl, F, N, S
138	4-FPh	2,4-Cl_2Ph	N	SO	MeOH	237–239	30	$C_{17}H_{12}Cl_2FN_3O_3S$	C, H, Cl, F, N, S
139	2,4-Cl_2Ph	4-ClPh	N	SO	AcOEt/(*i*-Pr)$_2$O	163.5–164.5	19	$C_{17}H_{12}Cl_3N_3O_3S$	C, H, Cl, N, S
140	2,4-Cl_2Ph	4-ClPh	N	SO	AcOEt/(*i*-Pr)$_2$O	108–109	28	$C_{17}H_{12}Cl_3N_3O_3S$	C, H, Cl, N, S
141	Ph	2,4-Cl_2Ph	N	SO	AcOEt	179–180	27	$C_{17}H_{13}Cl_2N_3O_3S$	C, H, Cl, N, S
142	Ph	2,4-Cl_2Ph	N	SO	AcOEt	231–233	16	$C_{17}H_{13}Cl_2N_3O_3S$	C, H, Cl, N, S
143	4-ClPh	2,4-Cl_2Ph	N	SO	AcOEt/(*i*-Pr)$_2$O	187–188	40	$C_{17}H_{12}Cl_3N_3O_3S$	C, H, Cl, N, S
144	4-ClPh	2,4-Cl_2Ph	N	SO	AcOEt	235–235	35	$C_{17}H_{12}Cl_3N_3O_3S$	C, H, Cl, N, S
145	isopropyl	4-ClPh	N	SO	AcOEt/(*i*-Pr)$_2$O	157–158	23	$C_{14}H_{16}ClN_3O_3S$	C, H, Cl, N
146	isopropyl	4-ClPh	N	SO	AcOEt/(*i*-Pr)$_2$O	120–121	20	$C_{14}H_{16}ClN_3O_3S$	C, H, Cl, N, S
147	2,4-Cl_2Ph	4-ClPh	N	CH_2	AcOEt	201–203	54	$C_{18}H_{14}Cl_3N_3O_2$	C, H, Cl, N
148	4-FPh	2,4-Cl_2Ph	N	CH_2	AcOEt/(*i*-Pr)$_2$O	153–155	67	$C_{18}H_{14}Cl_2FN_3O_2$	C, H, Cl, N
149	Ph	2,4-Cl_2Ph	N	CH_2	AcOEt/(*i*-Pr)$_2$O	137–138	40	$C_{18}H_{15}Cl_2N_3O_2$	C, H, Cl, N
150	2,4-Cl_2Ph	Ph	N	CH_2	AcOEt/(*i*-Pr)$_2$O	146–147	82	$C_{18}H_{15}Cl_2N_3O_2$	C, H, Cl, N
151	4-FPh	4-ClPh	N	CH_2	AcOEt/(*i*-Pr)$_2$O	130–131	63	$C_{18}H_{15}ClFN_3O_2$	C, H, Cl, F, N
152	4-ClPh	2,4-Cl_2Ph	N	CH_2	AcOEt/(*i*-Pr)$_2$O	144–145	52	$C_{19}H_{15}Cl_3N_2O_2$	C, H, Cl, N
153	isopropyl	4-ClPh	N	CH_2	AcOEt/petroleum ether	90–92	74	$C_{15}H_{18}ClN_3O_2$	C, H, Cl, N
154	isopropyl	4-ClPh	N	CH_2	Et_2O	139–140	37	$C_{15}H_{18}ClN_3O_2$	C, H, Cl, N
155	2,4-Cl_2Ph	4-ClPh	N	$C(CH_2)_5$	(*i*-Pr)$_2$O	141–142	20	$C_{20}H_{18}Cl_3N_3O_2$	C, H, Cl, N
156	2,4-Cl_2Ph	4-ClPh	N	$C(Me)_2$	AcOEt	180–181 dec	35	$C_{23}H_{22}Cl_3N_3O_2 \cdot (COOH)_2$	C, H, Cl, N
157	4-FPh	2,4-Cl_2Ph	N	CS	AcOEt/(*i*-Pr)$_2$O	169–170	65	$C_{18}H_{12}Cl_2FN_3O_2S$	C, H, Cl, F, N, S
158	4-FPh	2,4-Cl_2Ph	CH	CO	AcOEt	209–212	77	$C_{19}H_{13}Cl_2FN_2O_3$	C, H, Cl, F, N
159	Ph	2,4-Cl_2Ph	CH	CO	AcOEt	230–232	82	$C_{19}H_{14}Cl_2N_2O_3$	C, H, Cl, N

[a] R_1, R_2: trans configuration unless otherwise noted. [b] R_1, R_2: cis configuration (116, 135).

against *C. albicans* in vitro corresponded poorly with their good therapeutic effect in vivo. Conversely, the in vitro morphological test results (inhibitory effect on the pseudomycelium formation) correlated comparatively well to the in vivo oral efficacy. Polka et al.[11] also reported that the correlation between in vitro and in vivo responses of *C. albicans* isolates was very poor for orally administered ketoconazole.

Our selected compounds were comparable to ketoconazole, which inhibits pseudomycelium formation of *C. albicans* at low concentrations.[12-18] These findings on in vitro and in vivo antifungal activities of triazolylpropiophenones against *C. albicans* led us to agree with Borgers,[14] who noted that in vitro results obtained with *C. albicans* cultured on EMEM correspond more closely to the in vivo potency of the imidazole antimycotics than to results obtained in other culture media.

Structure–Activity Relationships

The substituents on phenyl groups (R_1 and R_2) in I such as chlorine and fluorine atoms (2, 11, 19, 22–24, 27, 28) led

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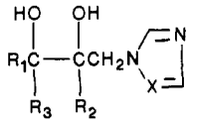
Table V



IV (160-198)

no.	R_1	R_2	R_3	X	method	recrystn solvent	mp, °C	yield,[a] %	config[b]	formula	anal.
160	4-FPh	4-FPh	Me	N	F	Et_2O/*n*-hexane	163–164	27	E	$C_{18}H_{17}F_2N_3O_2$	C, H, F, N
160	4-FPh	4-FPh	Me	N	G	Et_2O/*n*-hexane	163–164	24	E	$C_{18}H_{17}F_2N_3O_2$	C, H, F, N
161	4-FPh	4-FPh	Me	N	F	Et_2O/*n*-hexane	170–171	12	T	$C_{18}H_{17}F_2N_3O_2 \cdot (COOH)_2 \cdot {}^1/_2H_2O$	C, H, F, N
161	4-FPh	4-FPh	Me	N	G	Et_2O/*n*-hexane	170–171	50	T	$C_{18}H_{17}F_2N_3O_2 \cdot (COOH)_2$	C, H, F, N
162	4-FPh	4-ClPh	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	155–156	22	E	$C_{18}H_{17}ClFN_3O_2$	C, H, Cl, F, N
163	4-FPh	4-ClPh	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	154–155	22	T	$C_{18}H_{17}ClFN_3O_2$	C, H, Cl, F, N
164	4-FPh	4-FPh	Ph	N	F	AcOEt/$(i\text{-Pr})_2O$	189–191	29	E	$C_{23}H_{19}F_2N_3O_2$	C, H, F, N
165	4-FPh	4-FPh	Ph	N	F	MeOH/$(i\text{-Pr})_2O$	100–102	12	T	$C_{23}H_{19}F_2N_3O_2 \cdot (COOH)_2 \cdot (i\text{-Pr})_2O$	C, H, F, N
166	Ph	2,4-Cl_2Ph	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	125–126	44	E	$C_{18}H_{17}Cl_2N_3O_2$	C, H, Cl, N
167	Ph	2,4-Cl_2Ph	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	91–92	12	T	$C_{18}H_{17}Cl_2N_3O_2 \cdot {}^1/_5(i\text{-Pr})_2O$	C, H, Cl, N
168	isopropyl	2,4-Cl_2Ph	Me	N	F	$(i\text{-Pr})_2O$	127–128	16	E	$C_{15}H_{19}Cl_2N_3O_2$	C, H, Cl, N
169	isopropyl	2,4-Cl_2Ph	Me	N	F	AcOEt	148–149	21	T	$C_{15}H_{19}Cl_2N_3O_2$	C, H, Cl, N
170	4-FPh	4-ClPh	Et	N	F	AcOEt/$(i\text{-Pr})_2O$	169–171	36	E	$C_{19}H_{19}ClFN_3O_2$	C, H, Cl, F, N
171	4-FPh	4-ClPh	Et	N	F	AcOEt/$(i\text{-Pr})_2O$	154–155	8	T	$C_{19}H_{19}ClFN_3O_2$	C, H, Cl, F, N
172	4-ClPh	isopropyl	Me	N	F	AcOEt	137–138	22	E	$C_{15}H_{20}ClN_3O_2$	C, H, Cl, N
173	4-FPh	2,4-Cl_2Ph	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	156–157	50	E	$C_{18}H_{16}Cl_2FN_3O_2$	C, H, Cl, F, N
174	4-FPh	2,4-Cl_2Ph	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	137–139	15	T	$C_{18}H_{16}Cl_2FN_3O_2$	C, H, Cl, F, N
175	4-ClPh	2,4-Cl_2Ph	Me	N	F	$(i\text{-Pr})_2O$/petroleum ether	158–159	68	E	$C_{18}H_{16}Cl_3N_3O_2$	C, H, Cl, N
176	4-ClPh	2,4-Cl_2Ph	Me	N	F	$(i\text{-Pr})_2O$/petroleum ether	142–144	16	T	$C_{18}H_{16}Cl_3N_3O_2$	C, H, Cl, N
177	isopropyl	Ph	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	138.5–139.5	11	E	$C_{13}H_{17}N_3O_2$	C, H, N
178	4-FPh	2,4-Cl_2Ph	2-thienyl	N	F	AcOEt/$(i\text{-Pr})_2O$	185–186	53	E	$C_{21}H_{16}Cl_2FN_3O_2S$	C, H, Cl, F, N, S
179	2,4-Cl_2Ph	4-ClPh	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	92–93	20	E	$C_{18}H_{16}Cl_3N_3O_2 \cdot {}^1/_2(i\text{-Pr})_2O$	C, H, Cl, N
180	4-ClPh	4-FPh	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	211.5–213.5	59	E	$C_{19}H_{18}ClFN_2O_2$	C, H, Cl, F, N
181	4-FPh	2-ClPh	Me	N	F	$(i\text{-Pr})_2O$/petroleum ether	91–92	33	E	$C_{18}H_{17}ClFN_3O_2 \cdot {}^1/_{10}(i\text{-Pr})_2O$	C, H, Cl, F, N
182	4-FPh	2-ClPh	Me	N	F	$(i\text{-Pr})_2O$	127–128	8	T	$C_{18}H_{17}ClFN_3O_2$	C, H, Cl, F, N
183	4-FPh	2-ClPh	Me	CH	F	AcOEt/$(i\text{-Pr})_2O$	144–145	38	E	$C_{19}H_{18}ClFN_2O_2$	C, H, Cl, F, N
184	4-FPh	4-ClPh	Me	CH	F	AcOEt/$(i\text{-Pr})_2O$	177–178	33	E	$C_{19}H_{18}ClFN_2O_2$	C, H, Cl, F, N
185	4-ClPh	4-FPh	Me	CH	F	*i*-PrOH	225–227	14	T	$C_{19}H_{18}ClFN_2O_2$	C, H, Cl, F, N
186	4-ClPh	isopropyl	4-ClPh	N	F	AcOEt/$(i\text{-Pr})_2O$	166–168	89	E	$C_{20}H_{21}ClN_3O_2 \cdot {}^1/_2H_2O$	C, H, Cl, N
187	Ph	2,4-Cl_2Ph	*n*-Bu	N	F	MeOH/AcOEt	176–177	31	E	$C_{21}H_{23}Cl_2N_3O_2$	C, H, Cl, N
188	4-FPh	2-ClPh	*n*-Bu	N	F	AcOEt/petroleum ether	134–136	21	E	$C_{21}H_{23}ClFN_3O_2$	C, H, Cl, F, N
189	4-FPh	2-ClPh	*n*-Bu	N	F	$(i\text{-Pr})_2O$/petroleum ether	108–109	6	T	$C_{21}H_{23}ClFN_3O_2$	C, H, Cl, F, N
190	4-ClPh	*n*-butyl	Me	N	F	AcOEt/$(i\text{-Pr})_2O$	151–153	49	E	$C_{16}H_{22}ClN_3O_2$	C, H, Cl, N
191	4-ClPh	*n*-butyl	Me	N	F	AcOEt	142–144	49	T	$C_{16}H_{22}ClN_3O_2$	C, H, Cl, N
192	4-ClPh	4-ClPh	Me	CH	F	MeOH/Et_2O	156–158	68	E	$C_{19}H_{18}Cl_2N_2O_2$	C, H, Cl, N
193	4-ClPh	4-ClPh	Me	N	F	MeOH/Et_2O	137–139	46	E	$C_{20}H_{19}Cl_2N_3O_6$	C, H, Cl, N
194	4-ClPh	4-ClPh	Me	N	F	MeOH/Et_2O	160–162	29	T	$C_{20}H_{19}Cl_2N_3O_6$	C, H, Cl, N
195	4-FPh	4-ClPh	4-$ClPhCH_2$	N	F	AcOEt/$(i\text{-Pr})_2O$	161–162	37	E	$C_{24}H_{20}Cl_2FN_3O_2 \cdot {}^1/_2AcOEt$	C, H, Cl, F, N
196	Ph	2,4-Cl_2Ph	4-$ClPhCH_2$	N	F	MeOH	211–213	29	E	$C_{24}H_{20}Cl_3N_3O_2$	C, H, Cl, N
197	4-FPh	4-ClPh	*n*-propyl	N	F	AcOEt/$(i\text{-Pr})_2O$	160–161	19	E	$C_{20}H_{21}ClFN_3O_2$	C, H, Cl, F, N
198	Me	Ph	Me	N	H	AcOEt/$(i\text{-Pr})_2O$	138.5–139.5	11		$C_{13}H_{17}N_3O_2$	C, H, N

[a] Yield based on the last step. [b] E: erythro. T: threo.

to in vitro and in vivo activity. Replacement of the halogen by hydrogen, methyl, and methoxy groups produces negative effects (**1**, **4**, **5**, **10**, **14**, **15**, **20**, **21**, **26**). Replacement of the phenyl group in R_2 of I by an alkyl group (**43**–**53**) causes loss of in vitro and in vivo activity, with the retaining of some activity in R_1. The size of the alkyl group in R_1 plays an important role in the high activity in vivo. Namely, methyl, ethyl, *n*-propyl, isobutyl, and cyclopentyl

Table VI. In Vitro and in Vivo Antifungal Activities of Triazole Derivatives

no.	in vitro MIC, μg/mL *C.a.*[c]	*A.f.*[c]	*T.a.*[c]	MEC, μg/mL[a]	in vivo, no. of survivors/total infected (%)[b]	no.	in vitro MIC, μg/mL *C.a.*[c]	*A.f.*[c]	*T.a.*[c]	MEC, μg/mL[a]	in vivo, no. of survivors/total infected (%)[b]
1	>100	>100	12.5	>20	0/8 (0)	83	>100	>100	0.1	0.08	8/8 (100)
2	50	>100	0.1	0.16	7/8 (87.5)	84	50	>100	0.1	1.25	1/8 (12.5)
3	50	100	0.39	20		86	>100	>100	25	>20	
4	>100	>100	12.5	>20		87	100	>100	0.1	0.08	6/8 (75)
5	>100	>100	1.56	20		88	50	>100	0.39	1.25	
6	>100	>100	0.1	1.25	2/8 (25)	89	50	>100	12.5	20	
7	50	50	0.1	0.08	2/8 (25)	90	>100	>100	25	>20	
8	>100	>100	3.13	>20		91	>100	>100	1.6	2.5	
9	100	>100	0.79	10		92	50	25	0.1	0.08	8/8 (100)
10	>100	>100	12.5	>20		93	100	6.3	0.1	0.08	2/8 (25)
11	100	>100	0.1	0.31	8/8 (100)	94	>100	>100	3.1	>20	
12	100	100	0.1	0.04	8/8 (100)	95	>100	>100	1.6	10	
13	>100	12.5	0.1	0.08	7/8 (87.5)	96	>100	>100	3.1	10	
14	>100	>100	3.1	5.0	0/8 (0)	97	>100	>100	0.8	>20	
15	>100	>100	1.6	>20		98	>100	>100	0.8	10	0/8 (100)
16	>100	>100	0.4	>20	0/8 (0)	99	>100	50	0.1	0.04	
17	100	>100	0.4	10	0/8 (0)	100	>100	>100	0.8	0.16	
18	>100	>100	0.8	10		101	>100	>100	6.3	0.63	
19	100	>100	1.6	2.5	8/8 (100)	102	>100	>100	0.1	0.31	
20	>100	>100	1.6	2.5		103	>100	>100	0.8	0.31	
21	>100	>100	0.8	2.5	1/8 (12.5)	104	50	>100	6.3	2.5	
22	>100	>100	0.1	0.04	8/8 (100)	105	>100	>100	25	5	
23	100	100	0.1	0.31	7/8 (87.5)	106	>100	>100	1.6	0.16	
24	>100	>100	0.1	1.25	7/8 (87.5)	107	>100	>100	6.3	0.16	
25	50	>100	0.1	0.04	2/8 (25)	108	>100	25	0.1	0.04	
26	>100	>100	0.1	1.25	0/8 (0)	109	100	>100	12.5	20	
27	100	>100	0.1	0.04	7/8 (87.5)	110	100	>100	0.1	0.31	
28	>100	50	0.2	0.04	2/8 (25)	111	>100	50	0.1	0.04	
29	100	100	0.1	0.04	2/8 (25)	112	>100	>100	50	>20	
30	50	50	0.1	0.04	4/8 (50)	113	>100	100	0.4	1.25	4/8 (50)
31	>100	>100	0.1	0.04	7/8 (87.5)	114	50	100	0.1	1.25	3/8 (37.5)
32	100	100	0.1	0.02	0/8 (0)	115	>100	>100	0.2	0.04	
33	50	>100	0.1	0.02	0/8 (0)	116	>100	>100	25	>20	
34	100	12.5	0.1	0.08	0/8 (0)	117	50	>100	0.1	0.63	7/8 (87.5)
35	>100	100	0.8	0.04		118	100	>100	0.16	0.16	0/8 (0)
36	100	12.5	0.1	0.04	7/8 (87.5)	119	>100	>100	6.3	0.31	
37	100	50	0.1	0.04	0/8 (0)	120	50	>100	0.1	0.63	8/8 (100)
38	100	>100	0.1	0.31	8/8 (100)	121	>100	>100	0.1	0.16	0/8 (0)
39	>100	12.5	0.1	0.08	7/8 (87.5)	122	>100	>100	12.5	0.31	0/8 (0)
40	100	>100	0.8	1.25		123	>100	>100	3.1	2.5	
41	>100	>100	100	>20		124	50	>100	0.8	1.25	
42	>100	>100	>100	>20		125	100	>100	6.3	>20	
43	>100	>100	1.6	5		126	>100	>100	3.1	1.25	
44	>100	100	0.2	0.63		127	>100	>100	3.1	0.63	
45	>100	50	0.8	0.31		128	>100	>100	0.4	1.25	
46	100	50	0.1	0.31		129	>100	>100	0.2	0.04	
47	100	>100	0.2	0.63		130	>100	>100	0.1	0.08	
48	>100	50	0.4	1.25	1/8 (12.5)	131	100	>100	3.1	0.63	8/8 (100)
49	>100	>100	1.6	20		132	100	>100	1.6	0.16	
50	100	50	0.1	0.16	1/8 (12.5)	133	>100	>100	1.6	0.31	
51	>100	50	0.4	0.63		134	>100	>100	1.6	0.31	
52	>100	50	0.8	0.08	0/8 (0)	135	>100	>100	6.3	0.63	
53	>100	>100	0.8	0.31		136	>100	>100	0.2	0.63	
54	100	100	0.2	0.31	2/8 (25)	137	>100	50	0.1	0.04	4/8 (50)
55	100	>100	0.1	20		138	>100	>100	0.1	0.04	0/8 (0)
56	100	100	0.1	2.5	2/8 (25)	139	100	>100	0.1	0.08	5/8 (62.5)
57	>100	25	0.2	0.08	2/8 (25)	140	100	>100	0.1	0.02	7/8 (87.5)
58	>100	>100	0.1	1.25		141	>100	50	0.1	0.04	
59	>100	>100	0.1	0.04	0/8 (0)	142	>100	>100	0.1	0.08	
60	>100	>100	0.8	5		143	50	25	0.1	0.16	
61	25	25	0.1	2.5	0/8 (0)	144	>100	>100	0.1	0.02	
62	>100	>100	0.1	0.04	1/8 (12.5)	145	>100	>100	0.4	0.16	
63	>100	>100	0.1	2.5	0/8 (0)	146	>100	>100	0.4	0.16	
64	>100	>100	0.1	0.63	0/8 (0)	147	>100	>100	0.1	0.31	0/8 (0)
65	50	25	0.1	5	1/8 (12.5)	148	>100	>100	0.1	0.31	
66	>100	>100	>100	>20		149	>100	12.5	0.2	0.08	
67	>100	>100	25	>20		150	>100	12.5	0.2	0.63	
68	>100	>100	50	>20		151	>100	>100	0.2	0.63	
69	>100	>100	50	2.5		152	50	0.2	0.1	0.02	
70	>100	>100	>100	>20		153	>100	100	0.2	0.04	7/8 (87.5)
72	>100	>100	>100	>20		154	>100	100	0.4	0.04	
73	>100	>100	>100	>20		155	>100	>100	0.1	5	0/8 (0)
74	>100	>100	50	2.5		156	>100	>100	>100	>20	
75	>100	>100	>100	>20		157	100	>100	3.1	10	

Table VI (Continued)

no.	in vitro MIC, μg/mL C.a.[c]	A.f.[c]	T.a.[c]	MEC, μg/mL[a]	in vivo, no. of survivors/total infected (%)[b]	no.	in vitro MIC, μg/mL C.a.[c]	A.f.[c]	T.a.[c]	MEC, μg/mL[a]	in vivo, no. of survivors/total infected (%)[b]
158	100	50	0.2	0.16		**179**	100	50	0.1	1.25	
159	100	20	0.1	0.16		**180**	>100	>100	0.4	2.5	
160	>100	25	0.1	0.16	2/8 (25)	**181**	>100	6.3	0.1	1.25	
161	>100	100	0.2	2.5		**182**	>100	12.5	0.1	2.5	
162	>100	100	0.1	0.08	8/8 (100)	**183**	>100	100	0.1	1.25	
163	100	>100	0.2	0.63		**184**	>100	>100	0.4	2.5	
164	>100	>100	>100	>20		**185**	>100	>100	1.6	10	
165	>100	>100	25	>20		**186**	>100	>100	6.3	>20	
166	>100	12.5	0.1	0.04		**187**	>100	>100	0.2	2.5	
167	50	25	0.1	0.08		**188**	>100	>100	0.2	2.5	
168	>100	25	0.1	0.04		**189**	>100	50	0.4	20	
169	>100	50	0.1	0.08		**190**	>100	50	0.8	2.5	
170	>100	25	0.1	0.04		**191**	>100	>100	0.6	1.25	
171	>100	>100	0.1	0.16		**192**	>100	>100	0.8	1.25	
172	>100	50	1.6	5		**193**	100	50	0.1	0.36	
173	>100	25	0.1	0.31		**194**	50	>100	0.8	2.5	
174	100	50	0.1	0.31		**195**	>100	>100	>100	20	
175	>100	25	0.1	0.31		**196**	>100	>100	50	20	
176	50	50	0.1	0.63		**197**	>100	>100	0.2	0.31	7/8 (87.5)
177	>100	>100	6.3	10		**198**	>100	>100	6.3	>20	
178	>100	>100	0.8	5							

[a] For pseudomycelium formation of *C. albicans*. [b] Terminated at day 15 after infection. [c] Abbreviations: *C.a.* = *Candida albicans*; *A.f.* = *Aspergillus fumigatus*; *T.a.* = *Trichophyton asteroides*.

Table VII. In Vitro and in Vivo Antifungal Activities of Ketoconazole and Selected Triazole Derivatives

compd	in vitro fungistatic act.: MIC, μg/mL C.a.[a]	A.f.[a]	T.a.[a]	in vitro inhibn for pseudomycelium formation of C.a.: MEC, μg/mL	in vivo murine candidiasis dose range, mg/kg	ED_{50},[b,c] mg/kg	in vivo guinea pig dermatophytosis dose, mg/kg	skin sections yielding negative culture, no./total (%)
2	50	100	0.1	0.16	12.5–100	32.3 (14.9–62.6)	40	27/48[e] (56.3)[g]
12	100	100	0.1	0.04	12.5–100	22.6 (0.9–47.7)	40	7/48[e] (14.6)
38	100	>100	0.1	0.31	12.5–100	20.2 (9.7–31.0)	40	died[f]
39	>100	12.5	0.1	0.08	12.5–100	14.7 (4.9–22.0)[d]	40	died[f]
92	50	25	0.1	0.08	12.5–100	25.6 (3.8–55.1)	40	11/48[e] (22.9)
KCZ	100	12.5	0.1	0.08	12.5–100	32.8 (21.2–49.8)	40	8/48[e] (16.7)
							no drug	2/48[e] (4.2)

[a] Abbreviations: *C.a.* = *Candida albicans*; *A.f.* = *Aspergillus fumigatus*; *T.a.* = *Trichophyton asteroides*. [b] Determined at day 15 after infection. [c] Presumed by logit analysis with 95% confidence. [d] Significantly different from the value of KCZ (relative potency of 39 to KCZ by parallel line assay using logit transformation = 2.5684 (1.2579–5.2443)). [e] Six skin sections cut out from each treated site. [f] Death by toxicity. [g] Significantly different from the values of KCZ, 12 and 92 (Fisher's exact probability, $P < 0.01$).

groups (**25, 28–30, 32–34, 37**) are particularly active in vitro but not in vivo, whereas the isopropyl group (**12, 39**) shows high activity in vitro and in vivo. The isopropyl group seems to be the best among the alkyl groups tried so far in R_1.

Replacement of the triazole nucleus by the imidazole nucleus causes loss of in vitro and in vivo activities (**55–65**).

In the partial common structure of orally active antifungal azolylethanols (Bay n-7133,[19] ICI 153066,[3] SM 4470,[20] UK 49858[21]), the tertiary 1-phenyl azolylethanol structure seems to be the pharmacophore for oral antifungal activity. Therefore, the steric correlation around the asymmetric center carbon atom attached to the hydroxy and azolylmethyl groups seems to play an important role. Support for this point of view comes from the comparison of in vivo and MEC activity in the racemic compound with its optically active one. **83** (*R*-(−)) is much more active than **84** (*S*-(+)), and their racemate **2** is less active than **83** (*R*-(−)) but still much more active than **84** (*S*-(+)) in both in vitro and in vivo activities.[22]

Antifungal compounds containing the imidazole or the 1,2,4-triazole ring system are known to block the 14α-demethylation reaction in ergosterol biosynthesis in fungi, which is a cytochrome P-450 enzyme system.[23a,b] Thus, antifungals that are active inhibitors should bind to cytochrome P-450. Computer graphics[23a] shows how optical antipodes could interfere with ergosterol biosynthesis. To our knowledge, only a small amount of data is available on the relationship between optical antipodes and antifungal activities in numerous antifungal agents.[24]

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(20) Okuda, T.; Ichise, K.; Tanio, T.; Saji, I. *Proceedings, 23rd ICAAC*, Las Vegas, 24–26 Oct. 1983; Abstract 265B.
(21) Fromtling, R. A. *Drugs Future* **1985**, *10*(12), 982.
(22) The superiority of the *R*-(−) isomer has also been found with other azole derivatives of the same general structure. U.S. Patent 4526983; *Chem. Abstr.* **1986**, *104*, 5872m. Jpn. Patent 58203973; *Chem. Abstr.* **1984**, *100*, 139112q. Ger. Patent 3425848; *Chem. Abstr.* **1986**, *105*, 42818q. Ger. Patent 3440118.
(23) (a) See ref 15. (b) Heeres, J. In *Medicinal Chemistry: The Role of Organic Chemistry*; Roberts, S. M., Price, B. J., Eds.; Academic: Orlando, 1985; p 249 and references cited therein.
(24) Sugavanam, B. *Pestic. Sci.* **1984**, *15*, 296.

For diastereomeric diols II and III, the erythro form is much more active than the threo form (**88, 89; 100, 101; 104, 105; 106, 107; 108, 109**).

Although we stated that the presence of the tertiary 1-phenyl azolylethanol structure seems to be essential for oral antifungal activity, several five-membered 1,3-dioxa compounds III (Y = CH_2, CO, SO), which have no hydroxy group, show potent in vitro and in vivo activity (**117, 120, 131, 137, 139, 140**). The 1,3-dioxa structure is also found in ketoconazole,[1] itraconazole,[25] and related compounds. These results indicate that, like the tertiary 1-phenyl azolylethanol structure, the five-membered 1,3-dioxa structure is also an important pharmacophore for oral antifungal activity.

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 spectrometer. Elemental analyses were performed by the analytical department of Shionogi Research Laboratories and are within ±0.4% of the calculated values.

2-(2,4-Dichlorophenyl)-2-hydroxy-4-methyl-1-(1*H*-1,2,4-triazol-1-yl)pentan-3-one (12) and 2-(2,4-Dichlorophenyl)-2-hydroxy-4-methyl-1-(4*H*-1,2,4-triazol-4-yl)pentan-3-one (74) (Method A). To a solution of 2,4-dichlorobenzyl isopropyl ketone (3.6 g, 15.6 mmol) in acetic anhydride (2.4 g, 23.5 mmol) was added portionwise *N,N,N',N'*-tetramethyldiaminomethane (2.4 g, 23.5 mmol) with stirring at room temperature. After 15 min at room temperature, the mixture was diluted with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with CH_2Cl_2 were collected to obtain VI (R_1 = isopropyl, R_2 = 2,4-dichlorophenyl, 3.1 g) as an oil. ^1H NMR ($CDCl_3$): δ 5.85 (1 H, s, C=CH), 6.37 (1 H, s, C=CH). To a solution of the above product VI (3.1 g, 12.8 mmol) in acetone (16 mL) and 10% aqueous NaOH (0.63 mL, 12.8 mmol) was added 30% H_2O_2 (4.34 g, 38.2 mmol) dropwise with stirring at room temperature. After 30 min at room temperature, the mixture was mixed with ice water and aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with CH_2Cl_2 were collected to obtain VII (R_1 = isopropyl, R_2 = 2,4-dichlorophenyl, 3.1 g) as an oil. ^1H NMR ($CDCl_3$): δ 3.07 (1 H, d, J = 5.0 Hz, oxirane), 3.47 (1 H, d, J = 5.0 Hz, oxirane). To a solution of 1,2,4-triazole (1.24 g, 18 mmol) in DMF (15.5 mL) was added 50% NaH (dispersion in mineral oil, 172 mg, 3.6 mmol) at room temperature. After the solution was stirred at room temperature for 5 min, the above oxirane VII (R_1 = isopropyl, R_2 = 2,4-dichlorophenyl, 3.1 g, 12 mmol) was added, and the mixture was stirred at 50 °C for 17 h. The reaction mixture was poured into ice water and extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on a column of silica gel. The fractions eluted with 2% MeOH/CH_2Cl_2 were collected to obtain **12** [1.8 g, mp 163.5–165 °C, from AcOEt/(i-Pr)$_2$O, overall yield 46%].

The fractions eluted with 7% MeOH/CH_2Cl_2 were collected to obtain **74** (150 mg, mp >250 °C, overall yield 4%, from AcOEt). **12** ^1H NMR (Me_2SO-d_6): δ 0.87 (3 H, d, J = 7 Hz, CH_3), 1.08 (3 H, d, J = 7 Hz, CH_3), 2.70 (1 H, m, CH), 4.68 (1 H, d, J = 14 Hz, CH*H*), 5.13 (1 H, d, J = 14 Hz, C*H*H), 7.08 (1 H, s, OH), 7.25–7.47 (3 H, m, aromatic), 7.55 (1 H, s, triazole), 8.12 (1 H, s, triazole). Anal. ($C_{14}H_{15}Cl_2N_3O_2$) C, H, Cl, N. **74** ^1H NMR (Me_2SO-d_6): δ 0.85 (3 H, d, J = 7 Hz, CH_3), 1.03 (3 H, d, J = 7 Hz, CH_3), 2.63 (1 H, m, CH), 4.53 (1 H, d, J = 14 Hz, CH*H*), 4.95 (1 H, d, J = 14 Hz, C*H*H), 7.22 (1 H, s, OH), 7.97 (2 H, s, triazole), 7.35–9.60 (3 H, m, aromatic). Anal. ($C_{14}H_{15}Cl_2N_3O_2$) C, H, Cl, N.

The other compounds I and VIII in method A were prepared in a similar manner.

4'-Chloro-2-(4-chlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propiophenone (3) and 4'-Chloro-2-(4-chlorophenyl)-2-hydroxy-3-(4*H*-1,2,4-triazol-4-yl)propiophenone (68) (Method B). An ethereal solution of diazomethane prepared from *N*-(nitrosomethyl)urea (5.54 g, 53.7 mmol) and aqueous KOH (86% KOH, 15.1 g, 231 mmol) was added to a solution of 4,4'-dichlorobenzil (5 g, 1.8 mmol) in dioxane (50 mL). After the solution was stirred at room temperature for 16 h, the reaction mixture was concentrated in vacuo to give VII (R_1 = R_2 = 4-chlorophenyl) as an oil. This product was dissolved in DMF (50 mL) and added to a mixture of 1,2,4-triazole (1.9 g, 27.5 mmol), NaH (50% dispersion in mineral oil, 1.3 g, 27.1 mmol), and DMF (19 mL). After the solution was stirred at 50 °C for 20 min, the reaction mixture was mixed with ice water and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The fractions eluted with 2% MeOH/CH_2Cl_2 were collected to obtain **3** [1 g, mp 102–104 °C, overall yield 13%, from AcOEt/(i-Pr)$_2$O]. The fractions eluted with 7% MeOH/CH_2Cl_2 were collected to obtain **68** (420 mg, mp 232–233 °C, from MeOH/AcOEt, overall yield 7%). **3** ^1H NMR (Me_2SO-d_6): δ 4.33 (1 H, d, J = 14 Hz, CH*H*), 5.00 (1 H, d, J = 14 Hz, CH*H*), 6.18 (1 H, s, OH), 7.10–7.97 (10 H, m, aromatic, triazole). Anal. ($C_{17}H_{13}Cl_2N_3O_2$) C, H, Cl, N. **68** ^1H NMR (Me_2SO-d_6): δ 4.70 (2 H, s, CH_2), 7.35–8.00 (11 H, m, aromatic, triazole, OH). Anal. ($C_{17}H_{13}Cl_2N_3O_2$) C, H, Cl, N.

The other compounds in method B were prepared in a similar manner.

2-(2,4-Dichlorobenzoyl)-2-(2,4-dichlorophenyl)oxirane (VII, R_1 = R_2 = 2,4-Dichlorophenyl) (Method A). To 9.2 g (0.09 mol) of *N,N,N',N'*-tetramethyldiaminomethane was added 25 g (0.075 mol) of 2-(2,4-dichlorophenyl)-2',4'-dichloroacetophenone (V, R_1 = R_2 = 2,4-dichlorophenyl). Then 9.2 g (0.09 mol) of Ac_2O was added to the mixture was stirring at 50 °C. After 30 min at 50 °C, the mixture was mixed with ice water and extracted with AcOEt. The organic layer was washed with dilute HCl, aqueous $NaHCO_3$, and H_2O, dried over Na_2SO_4, and evaporated. The residue was washed with petroleum ether to give 17.1 g (66%, mp 62–62 °C) of VI (R_1 = R_2 = 2,4-dichlorophenyl). ^1H NMR ($CDCl_3$): δ 6.12 (1 H, s, vinyl H), 6.22 (1 H, s, vinyl H), 7.27–7.57 (6 H, m, aromatic). Anal. ($C_{15}H_8Cl_4O$) C, H, Cl.

To a mixture of the above product VI (17 g, 0.049 mol), DMF (85 mL), and aqueous 20% NaOH (4.9 mmol) was added 30% H_2O_2 (8.1 g, *0.07* mol) dropwise with stirring at 24 °C. After the addition, the mixture was stirred for 30 min at room temperature. The reaction mixture was mixed with ice water and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give VII (R_1 = R_2 = 2,4-dichlorophenyl) (15.6 g, mp 79–81 °C, 88%, after washing with petroleum ether, 69 mL). ^1H NMR ($CDCl_3$): δ 3.15 (1 H, d, J = 15 Hz, oxirane), 3.33 (1 H, d, J = 15 Hz, oxirane), 7.10–7.50 (6 H, m, aromatic). IR (Nujol): 1705 cm^{-1}. Anal. ($C_{15}H_8Cl_4O_2$) C, H, Cl.

2-(2,4-Dichlorobenzoyl)-2-(2,4-dichlorophenyl)oxirane (VII, R_1 = R_2 = 2,4-Dichlorophenyl) (Method C). A mixture of 2,2',4,4'-tetrachlorobenzoin (X, R_1 = R_2 = 2,4-dichlorophenyl, 3.0 g, 8.6 mmol), 80% paraformaldehyde (857 mg, 20.2 mmol), and $KHCO_3$ (1.287 g, 12.9 mmol) in 80% aqueous DMF (14 mL) was stirred under N_2 atmosphere for 5 h at room temperature. The reaction mixture was diluted with aqueous NaCl and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with benzene were collected to obtain the starting material (X, 60 mg, 2%). The fractions eluted with Et_2O were collected to obtain XI (R_1 = R_2 = 2,4-dichlorophenyl, R_3 = H, 3.46 g, mp 59–60 °C, 95%, after washing with Et_2O/n-hexane). ^1H NMR ($CDCl_3$): δ 3.33 (1 H, s, OH), 3.40 (1 H, dd, J = 10 Hz and 18 Hz, CH*H*OH), 4.28 (1 H, dd, J = 10 Hz and 18 Hz, C*H*HOH), 5.0 (1 H, s, OH). Anal. ($C_{15}H_{10}Cl_4O_3 \cdot {}^1/_2$ n-hexane) C, H.

A mixture of the above product (XI, R_1 = R_2 = 2,4-dichlorophenyl, R_3 = H, 3.80 g, 9 mmol) and p-TsCl (2.10 g, 11 mmol) in pyridine (10 mL) was stirred at room temperature for 15 h. The reaction mixture was diluted with 5% K_2CO_3 and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give XI (R_1 = R_2 = 2,4-dichlorophenyl, R_3 = p-CH_3PhSO_2, 4.32 g, mp 148–150 °C, 90%, after washing with Et_2O/n-hexane). ^1H NMR ($CDCl_3$): δ 2.43 (3 H, s, CH_3), 4.82 (2 H, dd, J = 11 Hz, CH_2O), 4.80 (1 H, br s, OH), 6.9–8.7

(25) Heeres, J.; Backx, L. J. J.; Van Cutsem, J. *J. Med. Chem.* **1984**, *27*, 894.

(10 H, m, aromatic). Anal. ($C_{22}H_{16}Cl_4O_5S$) C, H, Cl, S.

A mixture of the above product XI (R_1 = R_2 = 2,4-dichlorophenyl, R_3 = p-CH_3PhSO_2, 1.0 g, 1.87 mmol) and Et_2N (0.78 mL, 5.62 mmol) in CH_2Cl_2 (3 mL) was stirred at 50 °C for 1 h. The reaction mixture was evaporated, diluted with 5% K_2CO_3, and extracted with benzene. The organic layer was washed with H_2O and evaporated. The residue was chromatographed on silica gel. The fractions eluted with $CHCl_3$ gave VII (R_1 = R_2 = 2,4-dichlorophenyl, 660 mg, mp 80–81 °C, 97%, after washing with Et_2O/*n*-hexane). This compound was identical with authentic sample described in method A in comparison with IR and NMR spectra.

2-(4-Chlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)-2′,4′-dichloropropiophenone (11) and 2-(4-Chlorophenyl)-2-hydroxy-3-(4*H*-1,2,4-triazol-4-yl)-2′,4′-dichloropropiophenone (73) (Method D). A mixture of 2-(4-chlorophenyl)-2′,4′-dichloroacetophenone (2.9 g, 9.7 mmol) and sulfuryl chloride (4 g, 29.6 mmol) was stirred at 70 °C for 1 h. The reaction mixture was poured into ice water and aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 50% benzene/*n*-hexane gave XII (R_1 = 4-chlorophenyl, R_2 = 2,4-dichlorophenyl, 2.5 g) as an oil. ^1H NMR ($CDCl_3$): δ 6.08 (1 H, s, ClCH).

To a stirred solution of 1,2,4-triazole (620 mg, 9 mmol) and NaH (50% dispersion in mineral oil, 430 mg, 9 mmol) in Me_2SO (5 mL) was added 80% paraformaldehyde (340 mg, 9 mmol) with ice cooling in nitrogen atmosphere. Then a solution of the above product XII (2.5 g, 7.5 mmol) in Me_2SO (5 mL) was added to the above reaction mixture with stirring at room temperature. After 40 h at room temperature with stirring, the reaction mixture was poured into ice water and extracted with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 2% MeOH/CH_2Cl_2 were collected to obtain 11 [690 mg, mp 92–95 °C, overall yield 18%, from AcOEt/(i-Pr)$_2$O]. The fractions eluted with 7% MeOH/CH_2Cl_2 were collected to obtain **73** (280 mg, mp 219–221 °C, from AcOEt, overall yield 7%).

2-(2,4-Dichlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)-2′,4′-dichloropropiophenone (2) (Method E). A mixture of 2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)-2′,4′-dichloropropiophenone (XIII, R_1 = R_2 = 2,4-dichlorophenyl,[4] 1.0 g, 2.41 mmol), K_2CO_3 (1.0 g, 7.25 mmol), and DMF (8 mL) was stirred vigorously at room temperature for 5 h under an atmospheric pressure of dry air. The reaction mixture was diluted with CH_2Cl_2 and washed with H_2O. The organic layer was dried over Na_2SO_4 and evaporated to leave a solid, which was chromatographed on silica gel. Elution with 5% MeOH/CH_2Cl_2 yielded **2** (351 mg, 34%), which was identical with the authentic sample prepared by method A in comparison with IR and and NMR spectra. ^1H NMR ($CDCl_3$): δ 4.93 (1 H, d, J = 14 Hz, C*H*H), 5.23 (1 H, d, J = 14 Hz, CH*H*), 6.63 (1 H, s, OH), 6.90–7.16 (6 H, m, aromatic), 7.87 (1 H, s, triazole), 7.90 (1 H, s, triazole).

(*RS*)-1,2-Bis(2,4-dichlorophenyl)prop-2-en-1-ol (78). (a) $NaBH_4$ (659 mg, 17.3 mmol) was added to a cooled solution (0–5 °C) of the enone **77** (6.00 g, 17.3 mmol) and $CeCl_3 \cdot 7H_2O$ (6.46 g, 17.3 mmol) in MeOH (412 mL) over 30 min. The mixture was evaporated, and the residue was extracted with CH_2Cl_2. The organic layer was washed with brine, dried over Na_2SO_4, and evaporated to leave an oil, which was chromatographed on silica gel. Elution with 5% AcOEt/*n*-hexane gave **78** (3.50 g, 58%) as a colorless oil. IR (film): 3550 and 1580 cm^{-1}. ^1H NMR ($CDCl_3$): δ 7.41–6.86 (6 H, m, aromatic), 5.98 (1 H, d, J = 6 Hz, C*H*OH), 5.55 and 5.10 (each 1 H, each d, J = 1 Hz, C=CH_2), and 2.42 (1 H, d, J = 6 Hz, CHO*H*, exchanged with D_2O). Anal. ($C_{15}H_{10}Cl_4O$) C, H, Cl.

(b) i-Bu_2AlH (1.0 M solution in hexane, 2 mL) was added to a stirred solution of the enone **77** (692 mg, 2 mmol) in CH_2Cl_2 (4 mL) at −78 °C. After 3 h of stirring at −78 °C, aqueous NH_4Cl solution (2 mL) was added and temperature was raised to 25 °C. Layers were separated, and the organic layer was dried over Na_2SO_4 and evaporated. The residue was purified with silica gel chromatography (5% AcOEt/*n*-hexane) to yield **78** (303 mg, 44%) as a colorless oil, which was identical with the material described in method A.

(*R*)-(−)-1,2-Bis(2,4-dichlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one (83). (+)-Diisopropyl L-tartrate (1.17 g, 5 mmol) was added to a stirred solution of Ti(O-i-Pr)$_4$ (1.42 g, 5 mmol) in CH_2Cl_2 (20 mL) at −20 °C. The allylic alcohol **78** (1.75 g, 5 mmol) in CH_2Cl_2 (10 mL) was added to the mixture. After 5 min, *tert*-butyl hydroperoxide (4.0 M solution of 1,1-dichloroethane, 0.625 mL, 2.5 mmol) was added, and the mixture was kept at −20 °C for 15 h. H_2O was added, and the resulting emulsion was filtered through a pad of Celite. The organic layer was separated, dried over Na_2SO_4, and evaporated, and the residue was chromatographed on silica gel. Elution with 5% AcOEt/*n*-hexane afforded **(*S*)-1,2-bis(2,4-dichlorophenyl)prop-2-en-1-ol (80)** (743 mg, 42%) as a colorless oil, $[\alpha]^{25}_D$ −8.2° (c 1.02, $CHCl_3$) (90% ee),[8b] whose IR and NMR spectra were superimposable with those of the racemic **78**. Further elution with the same solvent gave **(1*S*,2*R*)-1,2-bis(2,4-dichlorophenyl)-2,3-epoxypropan-1-ol (79)** (688 mg, 38%) as a colorless oil, $[\alpha]^{22}_D$ −76.3° (c 1.01, $CHCl_3$) (84% ee).[6b] ^1H NMR ($CDCl_3$): δ 7.60–7.00 (6 H, m, aromatic), 5.64 (1 H, d, J = 3 Hz, C*H*OH), 3.00 and 2.72 (each 1 H, each d, J = 4.5 Hz, CH_2), and 2.70 (1 H, d, J = 3 Hz, OH).

A mixture of the epoxy alcohol **79** (500 mg, 1.37 mmol) and PCC (600 mg, 2.78 mmol) in CH_2Cl_2 (10 mL) was stirred at room temperature for 18 h. Et_2O (10 mL) was added to the mixture, and the solution was filtered through a column of silica gel to give the epoxy ketone (485 mg, 98%), which was used in the next step without further purification. A solution of the epoxy ketone in DMF (2 mL) was added to a stirred mixture of 1,2,4-triazole (143 mg, 2.07 mmol) and NaH (50% dispersion in mineral oil, 66 mg, 1.38 mmol) in DMF (2 mL) and stirred at 60 °C for 4 h.

The mixture was dissolved in CH_2Cl_2, and the organic layer was washed with aqueous NH_4Cl solution, dried over Na_2SO_4, and evaproated. The residue was chromatographed on silica gel with 10% MeOH/CH_2Cl_2 as the eluent, yielding **83** (352 mg, 59%): mp 111–113 °C (from Et_2O); $[\alpha]^{25}_D$ −212.7° (c 1.003, $CHCl_3$). Anal. ($C_{17}H_{11}Cl_4N_3O_2 \cdot {}^1/_4Et_2O$) C, H, Cl, N.

(*S*)-(+)-1,2-Bis(2,4-dichlorophenyl)-2-hydroxy-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one (84). A procedure similar to that described above for **83** was carried out. Thus, asymmetric epoxidation of the allylic alcohol **78** (1.75 g, 5 mmol) using (−)-diisopropyl-D-tartrate gave **(1*R*,2*S*)-1,2-bis(2,4-dichlorophenyl)-2,3-epoxypropan-1-ol (81)** (755 mg, 41%) as a colorless oil, $[\alpha]^{22}_D$ +69.7° (c 1.033, $CHCl_3$) (84% ee).[6b] PCC oxidation of **81** (500 mg, 1.37 mmol) followed by reaction of the resulting epoxy ketone with the sodium salt of 1,2,4-triazole yielded **84** (287 mg, 48% from **80**): mp 111–113 °C (from Et_2O); $[\alpha]^{25}_D$ +206.4° (c 1.006, $CHCl_3$). Anal. ($C_{17}H_{11}Cl_4N_3O_2 \cdot {}^1/_4Et_2O$) C, H, Cl, N.

(*R*)-(−)-1,2-Bis(2,4-dichlorophenyl)-2-[(4-bromobenzoyl)oxy]-3-(1*H*-1,2,4-triazol-1-yl)propan-1-one (85). To a stirred solution of **83** (90 mg, 0.21 mmol) in CH_2Cl_2 (6 mL) were added Et_3N (32 mg, 0.32 mmol) and 4-(dimethylamino)pyridine (6 mg, 0.05 mmol) at room temperature. 4-Bromobenzoic anhydride (150 mg, 0.39 mmol) was added to the mixture at room temperature. After 16 h, the mixture was diluted with aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 20% AcOEt/benzene were collected to obtain **85** [45 mg, mp 143–145 °C, from Et_2O/(i-Pr)$_2$O, 35%]. ^1H NMR ($CDCl_3$): δ 5.60 (2 H, s, CH_2), 6.88–7.83 (12 H, m, aromatic and triazole). $[\alpha]^{23}_D$ −59.7° (c 1.050, $CHCl_3$). Anal. ($C_{24}H_{14}BrCl_4N_3O_3$) C, H, Br, Cl, N.

X-ray Analysis of 85. Crystals obtained from a benzene solution are solvated by benzene with a 1:1 molecular ratio. Crystal data: $C_{24}H_{14}BrCl_4N_3O_3 \cdot C_6H_6$, fw = 692.2, orthorhombic, space group $P2_12_12_1$, a = 16.517 (3), b = 23.708 (4), c = 7.813 (1) Å, V = 3059.4 (8) Å^3, Z = 4, D_x = 1.503 g cm^{-3}.

The structure was solved by the heavy-atom method and refined by the block-diagonal least-squares technique to R = 0.081 (excluding H atoms) for 2284 reflections of 3040 unique ones measured in the range of $\theta \leq 25°$, using Mo $K\alpha$ radiation. The absolute configuration was determined by the anomalous-dispersion method, with differences between the intensities of Bijvoet pairs ($\Delta f'$) = −0.374 and $\Delta f''$ = 2.456 for Br).

1-(4-Chlorophenyl)-2-(2,4-dichlorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propylene Glycol (108, 109). To a solution of **24** (7 g, 17.6 mmol) in EtOH (35 mL) was added $NaBH_4$ (700 mg, 18.5 mmol), and the mixture was stirred for 1 h at room tem-

perature. The reaction mixture was acidified with 6 N HCl, basified with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 5% MeOH/CH_2Cl_2 were collected to obtain **108** (4.2 g, mp 184–186 °C, from MeOH/CH_2Cl_2, 60%). ^1H NMR (Me_2SO-d_6) δ 3.73 (1 H, d, J = 15 Hz, C*H*H), 5.22 (1 H, d, J = 15 Hz, CH*H*), 5.57 (1 H, d, J = 4.5 Hz, C*H*OH), 5.82 (1 H, d, J = 4.5 Hz, OH), 5.83 (1 H, s, OH), 7.13–7.50 (7 H, m, aromatic), 7.55 (1 H, s, triazole), 8.08 (1 H, s, triazole). Anal. ($C_{18}H_{12}Cl_3N_3O_3$) C, H, Cl, N.

The fractions eluted with 10% MeOH/CH_2Cl_2 were collected to obtain **109** (192 mg, mp 228–230 °C, from MeOH, 3%). ^1H NMR (Me_2SO-d_6): δ 4.87 (1 H, d, J = 15 Hz, CH*H*), 5.45 (1 H, d, J = 15 Hz, CH*H*), 5.62 (1 H, d, J = 4.5 Hz, C*H*OH), 5.97 (1 H, s, OH), 6.32 (1 H, d, J = 4.5 Hz, OH), 6.97–7.43 (7 H, m, aromatic), 7.58 (1 H, s, triazole), 8.35 (1 H, s, triazole). Anal. ($C_{18}H_{12}Cl_3N_3O_3$) C, H, Cl, N.

The other glycols (**86–114**) were prepared in a similar manner.

4-(2,4-Dichlorophenyl)-5-(4-chlorophenyl)-2-oxo-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane (115). To a solution of **108** (600 mg, 1.5 mmol) in $CHCl_3$ (12 mL) was added *N,N'*-carbonyldiimidazole (610 mg, 3.76 mmol), and the mixture was refluxed for 1 h. The reaction mixture was added to ice water, acidified with 6 N HCl, basified with aqueous $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with water, dried over Na_2SO_4, and evaporated. The resulting residue was chromatographed on a column of silica gel. The fractions eluted with 2% MeOH/CH_2Cl_2 were collected to obtain **115** [550 mg, mp 178–179 °C, from AcOEt/(*i*-Pr)$_2$O, 86%]. IR (Nujol): 1810 cm^{-1}. Anal. ($C_{18}H_{12}Cl_3N_3O_3$) C, H, Cl, N.

The other 1,3-dioxolanes (**116–136, 158,** and **159**) were prepared in a similar manner.

X-ray Results. Crystal data, compound 115: recrystallization from dioxane, mp 184–186 °C, $C_{18}H_{12}Cl_3N_3O_3 \cdot {}^1/_2C_4H_8O_2$, triclinic, space group $P\bar{1}$, a = 9.885 (2), b = 12.467 (2), c = 8.917 (1) Å, α = 104.81 (1)°, β = 100.99 (2)°, γ = 85.44 (2)°. The unit cell contains two molecules and one dioxane molecule. On refinement (all H atoms included) the conventional R value converged to R = 0.045 for 2954 reflections.

4-(2,4-Dichlorophenyl)-5-(4-chlorophenyl)-2-oxo-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane (116). To a solution of **109** (100 mg, 0.25 mmol) in CH_2Cl_2 (10 mL) was added *N,N'*-carbonyldiimidazole (130 mg, 0.8 mmol), and the mixture was refluxed for 1 h. The reaction mixture was treated as above. The resulting residue was chromatographed on a column of silica gel. The fractions eluted with 50% benzene/AcOEt were collected to obtain **116** (50 mg, foam, 47%). IR ($CHCl_3$): 1815 cm^{-1}. Anal. ($C_{18}H_{12}Cl_3N_3O_3$) C, H, Cl, N.

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3,2-dioxathiolane 2-Oxide (139, 140). To a solution of **108** (1.7 g, 4.26 mmol) and Et_3N (646 mg, 6.4 mmol) in $CHCl_3$ (17 mL) was added $SOCl_2$ (760 mg, 6.4 mmol) in $CHCl_3$ (3 mL), and the mixture was stirred for 30 min at room temperature. To the reaction mixture was added aqueous $NaHCO_3$, and the mixture was extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The resulting residue was chromatographed on a column of silica gel. The fractions eluted with 20% AcOEt/benzene were collected to obtain **139** [366 mg, mp 163.5–164.5 °C, from AcOEt/(*i*-Pr)$_2$O, 19%]. Anal. ($C_{17}H_{12}Cl_3N_3O_3S$) C, H, Cl, N, S.

The fractions eluted with 20% AcOEt/benzene and AcOEt were collected to obtain **140** [522 mg, mp 108–109 °C, from AcOEt/(*i*-Pr)$_2$O, 28%]. Anal. ($C_{17}H_{12}Cl_2N_3O_3S$) C, H, Cl, N, S.

The other 1,3,2-dioxathiolane 2-oxides (**137–146**) were prepared in a similar manner.

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane (147). To a solution of **109** (500 mg, 1.25 mmol) in DMF (5 mL) was added NaH (180 mg, 3.75 mmol, 50% dispersion in mineral oil) with stirring at room temperature. After 5 min, bromochloromethane (490 mg, 3.78 mmol) was added, and the mixture was heated at 50 °C for 1 h. The reaction mixture was mixed with ice water and shaken with Et_2O. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on a column of silica gel. The fractions eluted with 3% MeOH/CH_2Cl_2 were collected to obtain **147** (280 mg, mp 201–203 °C, from AcOEt, 54%). Anal. ($C_{18}H_{14}Cl_3N_3O_2$) C, H, Cl, N.

The other 1,3-dioxolanes (**148–154**) were prepared in a similar manner.

4-(4-Chlorophenyl)-5-(2,4-dichlorophenyl)-2,2-dimethyl-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane (155). To a mixture of **110** (500 mg, 1.25 mmol), acetone (20 mL), and DMF (1 mL) was added 2,2-dimethoxypropane (2 mL), *p*-toluenesulfonic acid (100 mg), and $ZnCl_2$ (50 mg), and the mixture was refluxed for 68 h. The reaction mixture was mixed with aqueous $NaHCO_3$ and shaken with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to remove the solvent. The residue was chromatographed on a column of silica gel. The fractions eluted with 50% benzene/AcOEt were collected to obtain **155** [110 mg, mp 141–142 °C, 20% after washing with (*i*-Pr)$_2$O]. Anal. ($C_{20}H_{18}Cl_3N_3O_2$) C, H, Cl, N.

Compound **156** was prepared in a similar manner.

4-(2,4-Dichlorophenyl)-5-(4-fluorophenyl)-2-thioxo-4-[(1*H*-1,2,4-triazol-1-yl)methyl]-1,3-dioxolane (157). To a solution of **92** (500 mg, 1.3 mmol) in $CHCl_3$ (10 mL) was added *N,N'*-(thiocarbonyl)diimidazole (700 mg, 3.9 mmol), and the mixture was refluxed for 1 h. The reaction mixture was added to ice/water and extracted with $CHCl_3$. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The resulting residue was chromatographed on a column of silica gel. The fractions eluted with 20% AcOEt/benzene were collected to obtain **157** [360 mg, mp 169–170 °C, from AcOEt/(*i*-Pr)$_2$O, 64.9%]. Anal. ($C_{18}H_{12}Cl_2FN_3O_2S$) C, H, Cl, F, N, S.

1-(4-Fluorophenyl)-1-methyl-2-(4-fluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propylene Glycol (160, 161) (Method F). Compound **9** (4 g, 12.1 mmol) in dry THF (80 mL) was added to methylmagnesium bromide in Et_2O (80 mL) prepared from magnesium (1.18 g, 49.2 mmol) and methyl iodide (7 g, 49.3 mmol), and the mixture was stirred for 1 h at room temperature. The mixture was poured into ice water and extracted with AcOEt. The organic layer was washed with H_2O and dried over Na_2SO_4. After evaporation of organic solvent, the residue was chromatographed on a silica gel column (lobar column). The fractions eluted with 33% benzene/AcOEt were collected to obtain **160** (1.15 g, mp 163–164 °C, from Et_2O/*n*-hexane, 28%). ^1H NMR ($CDCl_3$): δ 1.43 (3 H, s, CH_3), 2.60 (1 H, s, OH), 4.82 (1 H, s, OH), 4.02 (1 H, d, J = 15 Hz, CH*H*), 4.92 (1 H, d, J = 15 Hz, C*H*H), 6.70–7.70 (10 H, m, aromatic and triazole). Anal. ($C_{18}H_{17}F_2N_3O_2$) C, H, F, N.

The fractions eluted with AcOEt were collected to obtain **161** (640 mg, mp 170–171 °C, from Et_2O/*n*-hexane, 12%). ^1H NMR ($CDCl_3$): δ 1.50 (3 H, s, CH_3), 3.57 (1 H, s, OH), 4.45 (1 H, d, J = 15 Hz, CH*H*), 4.83 (1 H, d, J = 15 Hz, C*H*H), 5.40 (1 H, s, OH), 6.60–7.67 (10 H, m, aromatic and triazole). Anal. ($C_{18}H_{17}F_2N_3O_2 \cdot C_2H_2O_4 \cdot {}^1/_2H_2O$) C, H, F, N.

The other compounds (method F) listed in Table V were prepared in a similar manner.

1-(4-Fluorophenyl)-1-methyl-2-(4-fluorophenyl)-3-(1*H*-1,2,4-triazol-1-yl)propylene Glycol (160, 161) (Method G). To a solution of 4,4'-difluorobenzoin (X; R_1 = R_2 = 4-FPh, 1.50 g, 6.1 mmol) in DMF (7 mL) was added a mixture of 80% paraformaldehyde (0.68 g, 18 mmol) and $KHCO_3$ (0.91 g, 9.1 mmol) with stirring at room temperature under nitrogen atmosphere. After 1 h, the mixture was diluted with H_2O and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with 2% MeOH/$CHCl_3$ were collected to obtain XIV (R_1 = R_2 = 4-FPh, 1.68 g) as an oil. IR (film): 3450 and 1660 cm^{-1}. ^1H NMR ($CDCl_3$): δ 2.65 (1 H, dd, J = 9 Hz and 12 Hz, CHO*H*), 3.48 (1 H, dd, J = 12 Hz and 18 Hz, CH*H*), 4.43 (1 H, dd, J = 9 Hz and 12 Hz, CH*H*), 4.50 (1 H, s, OH).

A mixture of the above XIV (R_1 = R_2 = 4-FPh, 1.68 g, 5.3 mmol), 2,2-dimethoxypropane (1.0 mL, 7.1 mmol), and *p*-TsOH (60 mg) in acetone (14 mL) was refluxed for 30 min. The reaction mixture was evaporated, diluted with 5% K_2CO_3, and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated to give XV (R_1 = R_2 = 4-FPh, 1.87 g) as an oil. IR (film): 1680 cm^{-1}.

A mixture of the above product XV (R_1 = R_2 = 4-FPh, 1.86 g, 5.8 mmol) in dry THF (30 mL) was added to methylmagnesium bromide (12 mL of 1 mmol/mL THF solution, 1.7 mmol), and the mixture was refluxed for 2 h. The reaction mixture was poured into ice water and extracted with $CHCl_3$. The organic layer was washed with H_2O and dried over Na_2SO_4. After evaporation of organic solvent, the residue was chromatographed on a silica gel column. The fractions eluted with 2% MeOH/$CHCl_3$ were collected to obtain XVI as a mixture of diastereomers (ratio 2/1) (R_1 = R_2 = 4-FPh, 1.85 g) as an oil. IR (film): 3450 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.10 (3 H, s, CH_3) and 1.16 (3 H, s, CH_3) (ratio 2/1), 1.30 (3 H, s, CH_3) and 1.43 (3 H, s, CH_3) (ratio 2/1), 1.50 (3 H, s, CH_3) and 1.56 (3 H, s, CH_3) (ratio 2/1), 2.56 (3 H, s, OH) and 2.70 (3 H, s, OH) (ratio 2/1), 3.93 (1 H, d, J = 9 Hz, CH*H*) and 4.16 (1 H, d, J = 9 Hz, CH*H*) (ratio 2/1), 4.65 (1 H, d, J = 9 Hz, CH*H*) and 4.46 (1 H, d, J = 9 Hz, CH*H*) (ratio 2/1).

A mixture of the above product XVI (R_1 = R_2 = 4-FPh, 1.85 g) and 1 N HCl (2.5 mL) in MeOH (20 mL) was refluxed for 4 h. After evaporation of the solvent, the residue was diluted with H_2O and extracted with $CHCl_3$. The organic solvent was washed with H_2O, dried over Na_2SO_4, and evaporated to obtain XVII (R_1 = R_2 = 4-FPh, 1.65 g) as an oil.

A mixture of the above product XVII (1.62 g, 5.5 mmol), Et_3N (3.8 mL, 27.5 mmol), and p-TsCl (1.15 g, 6 mmol) in CH_2Cl_2 (12 mL) was refluxed for 2 h. After evaporation of organic solvent, the residue was diluted with 5% K_2CO_3 and extracted with benzene. The organic layer was washed with H_2O and evaporated. The residue was chromatographed on a column of silica gel. The fractions eluted with $CHCl_3$ were collected to obtain XVIII (R_1 = R_2 = 4-FPh, 904 mg) as an oil. IR (film): 3460 cm^{-1}. ^1H NMR ($CDCl_3$): δ 1.55 (3 H, s, CH_3) and 1.60 (3 H, s, CH_3) (ratio 2/1), 2.63 (1 H, d, J = 5 Hz, CH*H*) and 2.73 (1 H, d, J = 5 Hz, CH*H*) (ratio 2/1), 3.53 (1 H, d, J = 5 Hz, CH*H*) and 3.21 (1 H, d, J = 5 Hz, CH*H*), 2.72 (1 H, s, OH) and 2.90 (1 H, s, OH) (ratio 2/1).

A solution of the above product XVIII (R_1 = R_2 = 4-FPh, 875 mg, 3.2 mmol) in DMF (10 mL) was added to a stirred mixture of 1,2,4-triazole (328 mg, 4.8 mmol) and NaH (60% dispersion in mineral oil, 38 mg, 1 mmol) in DMF (5 mL) and stirred at room temperature for 24 h. The mixture was poured into ice water and extracted with benzene. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on a silica gel column. The fractions eluted with 50% AcOEt/benzene were collected to obtain IV (R_1 = R_2 = 4-FPh, **160**, erythro) (265 mg, mp 163–164 °C, from Et_2O/n-hexane, 24%). ^1H NMR ($CDCl_3$): δ 1.40 (3 H, s, CH_3), 2.95 (1 H, br s, OH), 4.05 (1 H, d, J = 15 Hz, CHH), 4.93 (1 H, d, J = 15 Hz, CH*H*), 4.84 (1 H, s, OH), 6.8–7.7 (10 H, m, triazole and aromatic). Anal. ($C_{18}H_{17}F_2N_3O_2$) C, H, F, N.

The fractions eluted with 50% AcOEt/benzene were collected to obtain IV (R_1 = R_2 = 4-FPh, **161**, threo) (545 mg, mp 170–171 °C, from Et_2O/n-hexane, 50%). ^1H NMR ($CDCl_3$): δ 1.50 (3 H, s, CH_3), 3.53 (1 H, br s, OH), 4.52 (1 H, d, J = 15 Hz, CH*H*), 4.83 (1 H, d, J = 15 Hz, CH), 5.43 (1 H, s, OH), 6.7–7.68 (10 H, triazole and aromatic). Anal. ($C_{18}H_{17}F_2N_3O_2$) C, H, F, N.

1,1-Dimethyl-2-phenyl-3-(1*H*-1,2,4-triazol-1-yl)propylene Glycol (198) (Method H). Compound XXI (R_1 = R_3 = Me, R_2 = Ph) was prepared according to the procedure of Rubottom et al.[9] [bp 140 °C (25 mm) (lit. bp 119–121 °C (6 mm))]. To a solution of XXI (R_1 = R_3 = Me, R_2 = Ph) (500 mg, 2.1 mmol) and 1-[(trimethylsilyl)methyl]-1,2,4-triazole[8] (394 mg, 2.5 mmol) in dry THF (4 mL) was added t-BuOK (285 mg, 2.5 mmol) under nitrogen atmosphere at −20 °C. After the mixture was stirred for 2 h, 6 N HCl (3 mL) was added and stirring continued for 15 h at room temperature. The reaction mixture was poured into aqueous $NaHCO_3$ and extracted with CH_2Cl_2. The organic layer was washed with H_2O, dried over Na_2SO_4, and evaporated. The residue was chromatographed on silica gel. The fractions eluted with 10% MeOH/CH_2Cl_2 gave IV (R_1 = R_2 = Me, R_3 = Ph, **198**) [59 mg, mp 138.5–139.5 °C, from AcOEt/(i-Pr)$_2$O, 11%]. ^1H NMR ($CDCl_3$): δ 1.16 (3 H, s, Me), 1.29 (3 H, s, Me), 2.75 (1 H, s, OH), 4.72 (1 H, d, J = 15 Hz, CH*H*), 4.85 (1 H, s, OH), 4.90 (1 H, d, J = 15 Hz, CH=H), 7.06–7.82 (7 H, m, aromatic and triazole). Anal. ($C_{13}H_{17}N_3O_2$) C, H, N.

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[26] combined with PS microtiter plates (Labortechnik) and Micom autodiluter SPR2 (sanko), using final inocula[26] of 1×10^5 cells (yeast) or 1×10^5 conidia (mold and dermatophyte)/mL 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 way 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.

Systemic Infections with *Candida albicans* in Mice. Jcl-ICR female mice, weighing 20–22 g, were used as experimental animals. Usually, 5×10^5 yeast cells of *C. albicans* KE-2 were injected into a tail vein to produce a subacute systemic model killing 100% of untreated animals within 10 days. For the preliminary therapeutic test, 50 mg/kg oral dose of each compound was administered to eight infected mice once daily for 5 consecutive days, from day 0 (immediately after the challenge) to day 4. Oral efficacy was evaluated by the survival rate of mice at day 15. Some of the active compounds selected from the preliminary test were administered in multiple doses ranging from 6.25 to 100 mg/kg (groups of 10 mice each). The ED_{50} values were determined by the logit analysis method at day 15. Ketoconazole was administered in the same doses and its ED_{50} compared with those of our selected compounds.

Superficial Infections with *Trichophyton asteroides* in Guinea Pigs. The compounds recognized to be effective against systemic candidiasis in mice were tested for their therapeutic effect on experimental dermatophytosis[27] in guinea pigs. Each 40 mg/kg oral dose of the compounds and ketoconazole was administered to four infected animals (having two lesion sites each) once daily for 10 consecutive days, from day 3 to day 12. Oral efficacies were made in terms of the rate of appearance of negative cultures from infected skin sections.

Acknowledgment. We thank N. Sunagawa, K. Kanazawa, and K. Ito for their excellent technical assistance.

Registry No. (±)-**1**, 107658-57-1; (±)-**2**, 107658-58-2; (±)-**3**, 107741-23-1; (±)-**4**, 107658-59-3; (±)-**5**, 107658-60-6; (±)-**6**, 107658-61-7; (±)-**7**, 107658-62-8; (±)-**8**, 107658-63-9; (±)-**9**, 107658-64-0; (±)-**10**, 107658-65-1; (±)-**11**, 107658-66-2; (±)-**12**, 107658-67-3; (±)-**13**, 107658-68-4; (±)-**14**, 107658-69-5; (±)-**15**, 107658-70-8; (±)-**16**, 107658-71-9; (±)-**17**, 107658-72-0; (±)-**18**, 107658-73-1; (±)-**19**, 107658-74-2; (±)-**20**, 107658-75-3; (±)-**21**, 107658-76-4; (±)-**22**, 107658-77-5; (±)-**23**, 107658-78-6; (±)-**24**, 107741-24-2; (±)-**25**, 107658-79-7; (±)-**26**, 107658-80-0; (±)-**27**, 107658-81-1; (±)-**28**, 107658-82-2; (±)-**29**, 107658-83-3; (±)-**30**, 107658-84-4; (±)-**31**, 107658-85-5; (±)-**32**, 107658-86-6; (±)-**33**, 107658-87-7; (±)-**34**, 107658-88-8; (±)-**35**, 107658-89-9; (±)-**36**, 107658-90-2; (±)-**36** (free base), 107658-68-4; (±)-**37**, 107658-92-4; (±)-**37** (free base), 107658-91-3; (±)-**38**, 107658-93-5; (±)-**40**, 107658-94-6; (±)-**41**, 107658-95-7; (±)-**42**, 107658-96-8; (±)-**43**, 107658-97-9; (±)-**44**, 107658-98-0; (±)-**45**, 107659-00-7; (±)-**45** (free base), 107658-99-1; (±)-**46**, 107659-02-9; (±)-**47**, 107659-04-1; (±)-**47** (free base), 107659-03-0; (±)-**48**, 107659-06-3; (±)-**48** (free base), 107659-05-2; (±)-**49**, 107659-07-4; (±)-**50**, 107659-09-6; (±)-**50** (free base), 107659-08-5; (±)-**51**, 107659-11-0; (±)-**51** (free base), 107659-10-9; (±)-**52**, 107659-13-2; (±)-**52** (free base), 107659-12-1; (±)-**53**, 107659-15-4; (±)-**53** (free base), 107659-14-3; (±)-**54**, 107659-16-5; (±)-**55**, 107659-17-6; (±)-**56**, 107659-18-7; (±)-**57**, 107659-19-8; (±)-**58**, 107659-20-1; (±)-**59**, 107659-21-2; (±)-**60**, 107659-22-3; (±)-**61**, 107659-23-4; (±)-**62**, 107659-24-5; (±)-**63**, 107659-25-6; (±)-**64**, 107659-26-7; (±)-**65**, 107659-27-8; (±)-**66**, 107659-28-9; (±)-**67**, 107659-29-0; (±)-**68**, 107659-30-3; (±)-**69**, 107659-31-4; (±)-**70**, 107659-32-5; (±)-**71**, 107659-33-6; (±)-**72**,

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Synthesis and Structure-Activity Studies of Corticosteroid 17-Heterocyclic Aromatic Esters. 1. 9α,11β-Dichloro Series

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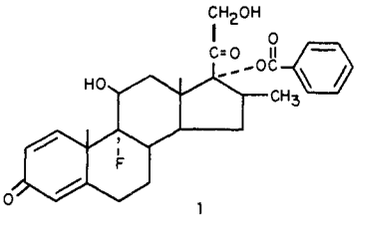
The preparation and topical antiinflammatory potencies of a series of 9α,11β-dichloro-16-methyl corticosteroid 17-heteroaryl carboxylates are described. The 17-acyl group was introduced to the 9α,11β-dichloro 21-acetate by direct acylation with the appropriate heteroaryl carbonyl chloride in the presence of 4-(dimethylamino)pyridine. Alternatively, the 21-functionalized 17-hydroxy $\Delta^{9(11)}$ compound was acylated at 17, followed by C-ring chlorination. The most extensively studied heterocyclic acyl functionality was the 2-furoyl, but the 3-furoyl, and 2- and 3-thenoyl derivatives were also investigated. Antiinflammatory potencies were measured in mice by a 5-day modification of the Tonelli croton oil ear assay. The most potent topical antiinflammatory compounds were 17-heteroaryl esters in the 16α-methyl series where the 21-substituent was chloro or fluoro. Thus **2p** [21-chloro 17-(2′-furoate)] was 8 times as potent as betamethasone valerate, while **2s** [21-fluoro 17-(2′-furoate)], **2r** [21-chloro 17-(2′-thenoate)], and **2v** [6α-fluoro 21-chloro 17-(2′-furoate)] were 3 times as potent as betamethasone valerate.

This paper describes a new class of corticosteroids with high topical antiinflammatory potencies.[1] Some of the compounds described in this paper have shown higher topical antiinflammatory potencies than any other topical corticosteroid tested in our laboratories.

This class of corticosteroids consists of aromatic heterocyclic ester derivatives of the 17-hydroxy function of the side chain. These include furoyl, thenoyl, and pyrrolylcarbonyl esters. The corticosteroids reported here are 9α,11β-dichloro compounds, while the 11-oxygenated analogues will be described elsewhere.

Corticosteroid 17-benzoates have demonstrated substantial topical antiinflammatory potency.[2,3] In particular, betamethasone 17-benzoate (1) has been used in clinical practice for a long time. We anticipated that similar esters



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of furan-, thiophene-, and pyrrolecarboxylic acids would exhibit topical antiinflammatory activity. Accordingly, a variety of these esters were synthesized. The results of

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