Antifungal Agents. 9. 3-Aryl-4-[α-(1*H*-imidazol-1-yl)arylmethyl]pyrroles: A New Class of Potent Anti-*Candida* Agents

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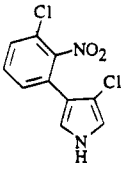
Received November 28, 1994®

A new class of potent antifungal agents, namely, 3-aryl-4-[α-(1*H*-imidazol-1-yl)arylmethyl]-pyrroles, is described. These compounds are related to bifonazole and pyrrolnitrin, two compounds belonging to the class of antimycotic drugs. The synthesis of the title pyrroles has been performed starting from 1,3-diaryl-2-propen-1-ones, which were reacted with tosylmethyl isocyanide to give 3-aroyl-4-arylpyrroles. Reduction of the resulting compounds by lithium aluminum hydride furnished the related alcohols, which were treated with 1,1′-carbonyldiimidazole to afford the required imidazole derivatives. Forty-four new pyrroles which incorporate an (arylmethyl)imidazole moiety in the 3-arylpyrrole structure were prepared by the above procedure and tested *in vitro* against *Candida albicans* and *Candida* spp. Among test compounds, 10 were found to be highly active against *C. albicans*. The most active derivative (**27**) was twice as potent (MIC_{90}) as bifonazole, and its activity was 4 times greater than those of miconazole and ketoconazole. The other nine compounds showed antifungal activity of the same order of that of bifonazole and were ca. 2 times as active as miconazole and ketoconazole. Derivatives **21** and **27** tested *in vivo* against *C. albicans* A_{170} were shown to be highly effective in rabbit skin candidosis. Pharmacological studies on compounds **27** and other related pyrroles (**19**, **35**, **36**, **38**, **39**, and **49**) are in progress to select one of them as a potential candidate for clinical experiments.

Introduction

After the discovery of pyrrolnitrin **1**[1] in 1965, a great amount of work was directed toward the synthesis of pyrrole derivatives with the aim to obtain new efficacious antifungal agents.[2–8] Despite the large number of pyrroles synthesized by Japanese researchers, none of the new derivatives were found to be as potent as pyrrolnitrin, which still remains the sole pyrrole introduced in the medical practice of fungal diseases. Pyrrolnitrin is marketed in Japan as Pyroace and in Italy as Micutrin for topical application in fungal diseases of the skin.



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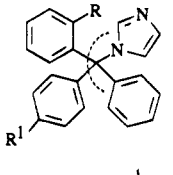
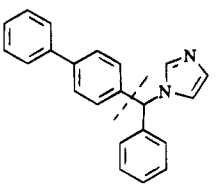


2 R = Cl; R^1 = H
3 R = R^1 = F



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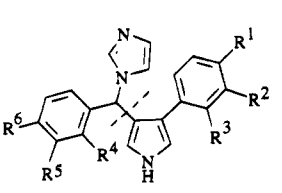

5-42

More recently the chemistry of azole derivatives received impetus when compounds containing imidazole and triazole rings were found to have potent antifungal activity. Miconazole and related derivatives together with ketoconazole and bifonazole belong to the class of imidazoles; fluconazole, itraconazole, and terconazole are the most important drugs of the triazole family.[9–12]

During our search for new antifungal agents, we decided to prepare derivatives containing both the pyrrole and the imidazole nucleus in order to have in a single structure the chemical features of pyrrole antibiotics and antifungal imidazole drugs. We anticipated that the presence of the imidazole pharmacophoric group would lead to pyrroles with antifungal activity as potent as that possessed by miconazole and other clinically used azoles.

Because of the fundamental role played by the 1-benzylimidazole moiety in some highly active imidazoles, such as clotrimazole (**2**),[13] flutrimazole (**3**),[14] and bifonazole (**4**),[15] we synthesized a new class of pyrroles, **5–42**, which contains the 3-arylpyrrole moiety linked to the 1-benzylimidazole portion. Such derivatives resemble the structure of the above-cited drugs and are expected to be highly active against pathogenic fungi.

As substituents we chose atoms or groups which were found to be capable of enhancing the antifungal activity, such as halogens (chloro and fluoro), nitro, and some biaryl moieties. In fact, in our previous studies[16–20] on antifungal agents related to bifonazole, we found that 4-biphenyl, 4-(1-pyrryl)phenyl, and naphthyl (1- and 2-) moieties could be reciprocally exchanged without loss of activity. We therefore prepared derivatives **43–49** in an attempt to enhance the antimycotic potency and to understand the structure–activity relationships of the new pyrroles reported in the present work.

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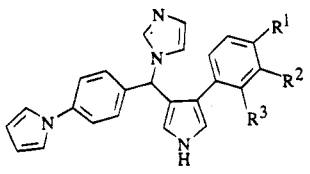
® Abstract published in *Advance ACS Abstracts*, August 15, 1995.

0022-2623/95/1838-4223$09.00/0

Table 1. Chemical and Physical Data of Derivatives **5–49**

no.	R^1	R^2	R^3	R^4	R^5	R^6	formula[a]	yield, %	mp, °C	crystlztn[b] from	reaction time
5	H	H	H	H	H	H	$C_{20}H_{17}N_3$	94	170–171	A	2 h
6	H	H	H	H	H	Cl	$C_{20}H_{16}ClN_3$	67	174–175	B	17 h
7	H	H	H	H	H	F	$C_{20}H_{16}FN_3$	78	159–160	B	1 h 45 min
8	H	H	H	H	H	CH_3	$C_{21}H_{19}N_3$	27	168–169	A	2 h
9	H	H	H	H	H	NO_2	$C_{20}H_{16}N_4O_2$	65	187–189	C	4 h
10	H	H	H	H	H	NH_2	$C_{20}H_{18}N_4$	100	86–88	C	
11	H	H	H	Cl	H	Cl	$C_{20}H_{15}Cl_2N_3$	48	141–143	A	16 h
12	H	H	H	H	Cl	Cl	$C_{20}H_{15}Cl_2N_3$	64	oil		3 h 45 min
13	H	H	Cl	H	H	H	$C_{20}H_{16}ClN_3$	35	161–163	C	1 h 10 min
14	H	H	Cl	H	H	Cl	$C_{20}H_{15}Cl_2N_3$	48	212–214	C	15 h
15	H	H	Cl	H	H	F	$C_{20}H_{15}ClFN_3$	34	199–201	C	40 min
16	H	H	Cl	H	H	CH_3	$C_{21}H_{18}ClN_3$	19	215–217	C	1 h 30 min
17	H	H	Cl	H	H	NO_2	$C_{20}H_{15}ClN_4O_2$	87	180–182	C	1 h 10 min
18	H	H	Cl	H	H	NH_2	$C_{20}H_{17}ClN_4$	36	oil		
19	H	H	Cl	Cl	H	Cl	$C_{20}H_{14}Cl_3N_3$	31	156–158	B	50 min
20	H	H	Cl	H	Cl	Cl	$C_{20}H_{14}Cl_3N_3$	60	163–165	B	1 h
21	Cl	H	H	H	H	H	$C_{20}H_{16}ClN_3$	71	218–219	C	2 h
22	Cl	H	H	H	H	Cl	$C_{20}H_{15}Cl_2N_3$	82	225–226	C	1 h
23	Cl	H	H	H	H	F	$C_{20}H_{15}ClFN_3$	60	189–190	C	15 h
24	Cl	H	H	H	H	CH_3	$C_{21}H_{18}ClN_3$	50	229–231	C	40 min
25	Cl	H	H	H	H	NO_2	$C_{20}H_{15}ClN_4O_2$	24	208–209	C	2 h
26	Cl	H	H	H	H	NH_2	$C_{20}H_{17}ClN_4$	51	114–115	B	
27	Cl	H	H	Cl	H	Cl	$C_{20}H_{14}Cl_3N_3$	26	220–221	C	1 h
28	Cl	H	H	H	Cl	Cl	$C_{20}H_{14}Cl_3N_3$	60	125–126	C	2 h
29	Cl	H	Cl	H	H	H	$C_{20}H_{15}Cl_2N_3$	89	213–215	C	1 h 40 min
30	Cl	H	Cl	H	H	Cl	$C_{20}H_{14}Cl_3N_3$	53	220 dec	C	15 h
31	Cl	H	Cl	H	H	F	$C_{20}H_{14}Cl_2FN_3$	78	218–220	C	2 h 50 min
32	Cl	H	Cl	H	H	CH_3	$C_{21}H_{17}Cl_2N_3$	88	224–226	C	15 h
33	Cl	H	Cl	H	H	NO_2	$C_{20}H_{14}Cl_2N_4O_2$	100	190 dec	C	1 h
34	Cl	H	Cl	Cl	H	Cl	$C_{20}H_{13}Cl_4N_3$	45	178–180	A	2 h
35	Cl	H	Cl	H	Cl	Cl	$C_{20}H_{13}Cl_4N_3$	40	212–214	C	1 h
36	Cl	Cl	H	H	H	H	$C_{20}H_{15}Cl_2N_3$	71	140–142	C	1 h 20 min
37	Cl	Cl	H	H	H	Cl	$C_{20}H_{14}Cl_3N_3$	71	199–201	C	1 h 30 min
38	Cl	Cl	H	H	H	F	$C_{20}H_{14}Cl_2FN_3$	35	191–193	C	50 min
39	Cl	Cl	H	H	H	CH_3	$C_{21}H_{17}Cl_2N_3$	64	147–149	C	1 h 30 min
40	Cl	Cl	H	H	H	NO_2	$C_{20}H_{14}Cl_2N_4O_2$	66	79–81	C	1 h
41	Cl	Cl	H	Cl	H	Cl	$C_{20}H_{13}Cl_4N_3$	75	182–184	C	1 h
42	Cl	Cl	H	H	Cl	Cl	$C_{20}H_{13}Cl_4N_3$	56	208–210	C	1 h 20 min
43	H	H	H				$C_{24}H_{20}N_4$	32	174–176	C	2 h 30 min
44	H	H	Cl				$C_{24}H_{19}ClN_4$	39	221–223	C	1 h 40 min
45	Cl	H	H				$C_{24}H_{19}ClN_4$	54	125 dec	C	45 min
46	Cl	H	Cl				$C_{24}H_{18}Cl_2N_4$	27	247–249	C	1 h
47	Cl	Cl	H				$C_{24}H_{18}Cl_2N_4$	60	193–195	C	1 h 15 min
48							$C_{26}H_{20}ClN_3$	100	229–230	D	1 h 30 min
49							$C_{24}H_{18}ClN_3$	53	225–226	B	15 h

[a] All compounds were analyzed for C, H, N, and, when present, Cl and F; analytical results are within ±4% of the theoretical values. [b] A = benzene; B = benzene–cyclohexane; C = ethanol; D = *N*,*N*-dimethylformamide.



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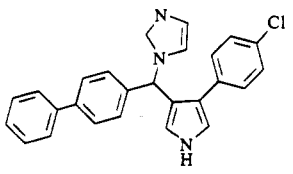

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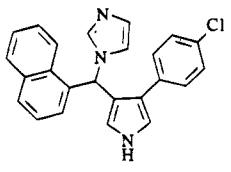

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Chemistry

Derivatives **5–42** were synthesized starting from 3-aroyl-4-arylpyrroles **65–99**, which were obtained by reacting toluene-4-sulfonylmethyl isocyanide (TosMIC)[21,22] with the appropriate 1,3-diaryl-2-propen-1-ones, including the new propenones **50–59** (Table 2), in anhydrous DMSO–Et_2O mixture in the presence of sodium hydride. Compounds **50–59** and the known analogues employed as starting material in the above reaction were prepared according to procedures reported in the literature.[23–39]

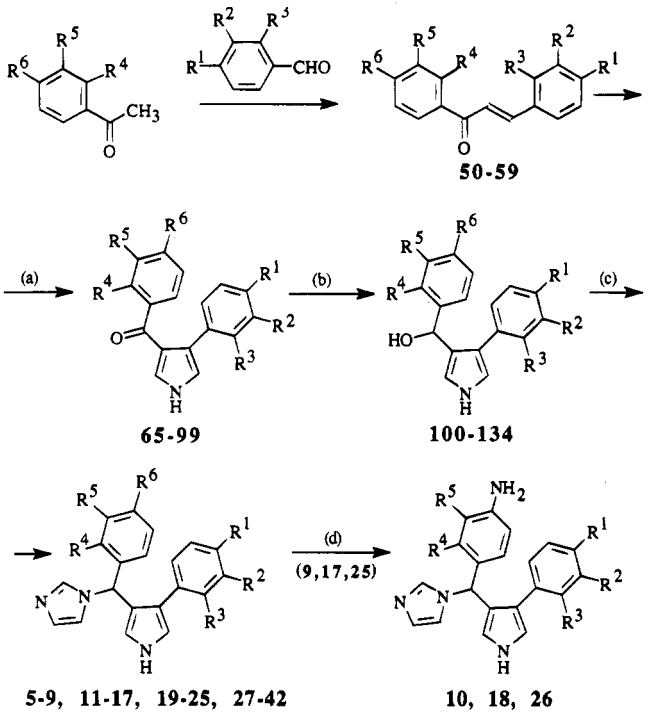
Reduction of **65–99** by lithium aluminum hydride furnished the corresponding alcohols **100–134**, which were then reacted with 1,1′-carbonyldiimidazole (CDI)

Table 2. Chemical and Physical Data of Derivatives **50–64**

no.	R^1	R^2	R^3	R^4	R^5	R^6	formula[a]	yield, %	mp, °C
50	H	H	Cl	Cl	H	Cl	$C_{15}H_9Cl_3O$	50	97–99
51	H	H	Cl	H	Cl	Cl	$C_{15}H_9Cl_3O$	59	105–107
52	Cl	H	Cl	H	H	F	$C_{15}H_9Cl_2FO$	56	111–113
53	Cl	H	Cl	H	H	NO_2	$C_{15}H_9Cl_2NO_3$	53	152–154
54	Cl	H	Cl	H	Cl	Cl	$C_{15}H_8Cl_4O$	48	129–130
55	Cl	Cl	H	H	H	F	$C_{15}H_9Cl_2FO$	63	135–136
56	Cl	Cl	H	H	H	CH_3	$C_{16}H_{12}Cl_2O$	58	137–139
57	Cl	Cl	H	H	H	NO_2	$C_{15}H_9Cl_2NO_3$	20	134–136
58	Cl	Cl	H	Cl	H	Cl	$C_{15}H_8Cl_4O$	31	155–157
59	Cl	Cl	H	H	Cl	Cl	$C_{15}H_8Cl_4O$	21	157–159
60	H	H	H	H	H	1-pyrryl	$C_{19}H_{15}NO$	88	156–158
61	H	H	Cl	H	H	1-pyrryl	$C_{19}H_{14}ClNO$	51	118–120
62	Cl	H	H	H	H	1-pyrryl	$C_{19}H_{14}ClNO$	34	229–231
63	Cl	H	Cl	H	H	1-pyrryl	$C_{19}H_{13}Cl_2NO$	100	133–135
64	Cl	Cl	H	H	H	1-pyrryl	$C_{19}H_{13}Cl_2NO$	90	191–193

[a] All compounds were analyzed for C, H, N, and, when present, Cl and F; analytical results are within ±4% of the theoretical values.

Scheme 1[a]

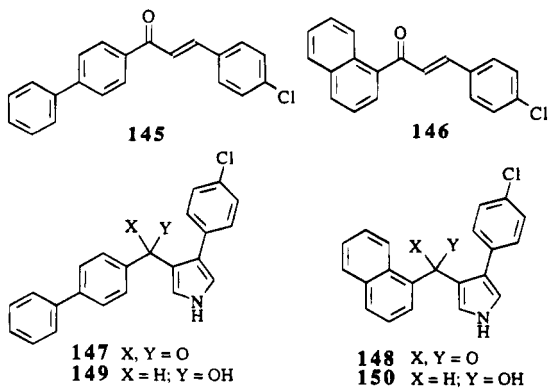


[a] (a) Tosylmethyl isocyanide (TosMIC), NaH, DMSO, Et_2O; (b) $LiAlH_4$, THF; (c) 1,1′-carbonyldiimidazole (CDI), MeCN; (d) H_2, Pd/C, AcOEt.

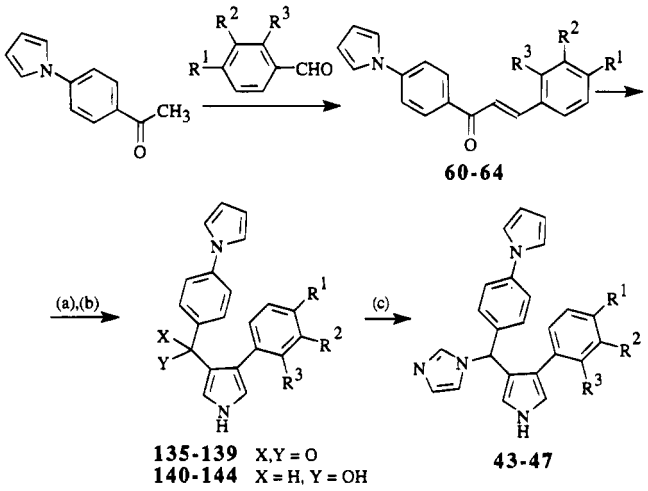
to afford the required imidazoles **5**–**9**, **11**–**17**, **19**–**25**, and **27**–**42** (Scheme 1). Catalytic hydrogenation of nitro derivatives **9**, **17**, and **25** with hydrogen in presence of 5% palladium on charcoal furnished amino derivatives **10**, **18**, and **26**. Attempts to transform these compounds into the related pyrroles **43**–**47** via the Clauson–Kaas procedure were unsuccessful.

Compounds **43**–**47** were obtained as reported above using as starting materials the calchones **60**–**64**, which were prepared by condensation of the known methyl 4-(1*H*-pyrrol-1-yl)phenyl ketone[40] with the proper aryl aldehyde. Treatment with TosMIC followed by lithium aluminum hydride reduction and reaction with CDI gave compounds **135**–**144** and **43**–**47**, respectively (Scheme 2).

Naphthyl and biphenyl derivatives **48** and **49** were obtained from ketones **145**[38] and **146**,[39] which were transformed into pyrroles **147** and **148** by treatment with TosMIC. The latter derivatives were reduced to the corresponding carbinols **149** and **150**, which were condensed with CDI to afford the required imidazoles **48** and **49**.



Scheme 2[a]



[a] (a) TosMIC, NaH, DMSO, Et_2O; (b) $LiAlH_4$, THF; (c) CDI, MeCN.

Microbiological Results and Discussion

***In Vitro* Anti-*Candida* Activities.** The results of the *in vitro* antifungal activities of imidazoles **5**–**49** against 40 strains of *Candida albicans* and 12 strains of *Candida* spp. (three *Candida lipolytica*, three *Candida krusei*, two *Candida glabrata*, and four *Candida tropicalis*) at pH 7.2 and 5.8 are reported in Tables 6 and 7, respectively. Data refer to MIC mean values (MIC), MIC_{90}, MIC_{50}, *R*% (percentage of resistant species at 256 μg/mL), and MIC range. With some few exception, MIC_{50} and MIC values parallel the related MIC_{90} data, which were chosen for a preliminar comparison between these new derivatives and reference drugs (miconazole, ketoconazole, and bifonazole). When a more detailed comparative analysis was required for a better understanding of structure–activity relationships, the use of geometric mean MICs was preferred. Antifungal experiments were carried out at the pH which reproduced in the growth medium the systemic physiological conditions (pH 7.2) and the mild acid conditions of the skin in topical application (pH 5.8).

Activity against *C. albicans*. Like the controls, at pH 7.2 the majority of the test derivatives inhibited all the strains of *C. albicans* used for the antifungal assays. On the basis of MIC_{90} values of **5**–**49** against *C. albicans*, compond **27** was found to be ca. 2 and 4 times more active than bifonazole and ketoconazole or miconazole, respectively. Eleven derivatives (**14**, **19**, **21**, **29**, **32**, **34**, **36**, **38**, **39**, **41**, and **49**) were as potent as bifonazole and 2 times as active as miconazole and ketoconazole. The good activity (MIC_{90} values) for compounds **27** and **39** (MIC_{90} = 8 μg/mL) and **19**, **29**–**32**, **35**, **37**, and **41** (MIC_{90} = 16 μg/mL) against *C. albicans* was verified at pH 5.8. The last eight derivatives were as potent as bifonazole (MIC_{90} = 16 μg/mL) and 2 times as active as miconazole and ketoconazole (MIC_{90} = 32 μg/mL). Activity equal to miconazole and ketoconazole was exhibited in our experiments by several other test derivatives.

A comparison of MIC data (Table 6) of nitro derivatives **9**, **17**, **25**, **33**, and **40** at pH 7.2 shows that introduction of chlorine atoms at the phenyl bonded at position 3 of the pyrrole ring leads to compounds with decreased activity (from 5.18 to 312 μg/mL). On the contrary, with compounds bearing a methyl as the

Table 3. Chemical and Physical Data of Derivatives **65–99**, **135–139**, **147**, and **148**

no.	R^1	R^2	R^3	R^4	R^5	R^6	formula[a]	yield, %	mp, °C	crystlztn[b] from	reaction time, min	purifictn[c] method
65	H	H	H	H	H	H	$C_{17}H_{13}NO$[d]					
66	H	H	H	H	H	Cl	$C_{17}H_{12}ClNO$	39	228–230	A	5	A
67	H	H	H	H	H	F	$C_{17}H_{12}FNO$	44	239–240	B	5	A
68	H	H	H	H	H	CH_3	$C_{18}H_{15}NO$	47	234–236	A	5	A
69	H	H	H	H	H	NO_2	$C_{17}H_{12}N_2O_3$	28	200–202	A	30	C
70	H	H	H	Cl	H	Cl	$C_{17}H_{11}Cl_2NO$	65	282–284	B	5	A
71	H	H	H	H	Cl	Cl	$C_{17}H_{11}Cl_2NO$	12	191–193	A	5	C
72	H	H	Cl	H	H	H	$C_{17}H_{12}ClNO$	53	288–290	A	5	A
73	H	H	Cl	H	H	Cl	$C_{17}H_{11}Cl_2NO$	35	236–238	B	5	A
74	H	H	Cl	H	H	F	$C_{17}H_{11}ClFNO$	50	280–282	A	5	A
75	H	H	Cl	H	H	CH_3	$C_{18}H_{14}ClNO$	33	238–240	C	15	A
76	H	H	Cl	H	H	NO_2	$C_{17}H_{11}ClN_2O_3$	29	290–292	C	30	C
77	H	H	Cl	Cl	H	Cl	$C_{17}H_{10}Cl_3NO$	48	189–191	C	5	D
78	H	H	Cl	H	Cl	Cl	$C_{17}H_{10}Cl_3NO$	100	229–231	A	5	C
79	Cl	H	H	H	H	H	$C_{17}H_{12}ClNO$	50	232–234	A	5	A
80	Cl	H	H	H	H	Cl	$C_{17}H_{11}Cl_2NO$	40	272–273	A	30	A
81	Cl	H	H	H	H	F	$C_{17}H_{11}ClFNO$	34	262–263	A	5	A
82	Cl	H	H	H	H	CH_3	$C_{18}H_{14}ClNO$	41	275–276	B	5	A
83	Cl	H	H	H	H	NO_2	$C_{17}H_{11}ClN_2O_3$	65	299–300	A	5	B
84	Cl	H	H	Cl	H	Cl	$C_{17}H_{10}Cl_3NO$	41	244–245	B	5	D
85	Cl	H	H	H	Cl	Cl	$C_{17}H_{10}Cl_3NO$	48	266–267	A	5	C
86	Cl	H	Cl	H	H	H	$C_{17}H_{11}Cl_2NO$	53	227–229	A	30	A
87	Cl	H	Cl	H	H	Cl	$C_{17}H_{10}Cl_3NO$	99	212–214	A	5	D
88	Cl	H	Cl	H	H	F	$C_{17}H_{10}Cl_2FNO$	48	214–216	A	10	A
89	Cl	H	Cl	H	H	CH_3	$C_{18}H_{13}Cl_2NO$	49	210–212	A	20	A
90	Cl	H	Cl	H	H	NO_2	$C_{17}H_{10}Cl_2N_2O_3$	65	216–218	A	45	C
91	Cl	H	Cl	Cl	H	Cl	$C_{17}H_9Cl_4NO$	23	216–218	A	10	A
92	Cl	H	Cl	H	Cl	Cl	$C_{17}H_9Cl_4NO$	58	198–200	A	20	A
93	Cl	Cl	H	H	H	H	$C_{17}H_{11}Cl_2NO$	37	204–206	A	5	A
94	Cl	Cl	H	H	H	Cl	$C_{17}H_{10}Cl_3NO$	56	206–208	A	5	A
95	Cl	Cl	H	H	H	F	$C_{17}H_{10}Cl_2FNO$	48	220–222	A	5	A
96	Cl	Cl	H	H	H	CH_3	$C_{18}H_{13}Cl_2NO$	52	224 dec	A	5	A
97	Cl	Cl	H	H	H	NO_2	$C_{17}H_{10}Cl_2N_2O_3$	31	214–216	A	30	C
98	Cl	Cl	H	Cl	H	Cl	$C_{17}H_9Cl_4NO$	45	202–204	C	5	D
99	Cl	Cl	H	H	Cl	Cl	$C_{17}H_9Cl_4NO$	38	187–189	C	5	D
135	H	H	H				$C_{21}H_{16}N_2O$	23	122–124	B	30	C
136	H	H	Cl				$C_{21}H_{15}ClN_2O$	54	218–220	A	5	B
137	Cl	H	H				$C_{21}H_{15}ClN_2O$	93	300–301	B	5	B
138	Cl	H	Cl				$C_{21}H_{14}Cl_2N_2O$	33	212–214	A	20	C
139	Cl	Cl	H				$C_{21}H_{14}Cl_2N_2O$	57	210–212	A	25	B
147							$C_{23}H_{16}ClNO$	54	288–290	B	5	A
148							$C_{21}H_{14}ClNO$	52	266–268	B	5	A

[a] All compounds were analyzed for C, H, N, and, when present, Cl and F; analytical results are within ±4% of the theoretical values. [b] A = *N*,*N*-dimethylformamide–water; B = *N*,*N*-dimethylformamide; C = ethanol. [c] A: recrystallized after filtration. B: chromatographed after filtration. C: recrystallized after extraction. D: chromatographed after extraction. [d] From literature.[43]

substituent (**8**, **16**, **24**, **32**, and **39**), the introduction of more than one atom of chlorine either retained or improved the antifungal activity, the highest potency being displayed by the 3,4-dichloro-substituted derivative **39**.

Generally, 4-(1-pyrryl)phenyl derivatives were of low activity (**45–47**) with the exception of **43** and **44**, which were moderately active.

At pH 5.8 the most active compound was still **27**, which was 2 times as active as bifonazole and exhibited an antifungal activity 4 times greater than ketoconazole and miconazole. In some cases (compare MIC values of compounds **30**, **34–36**, and **48** at both the pHs) the antifungal activity against *C. albicans* increased remarkably when pH of test medium shifted from 7.2 to 5.8.

The activity of compound **5**, characterized by the absence of substituents, increased strongly when more than one halogen was introduced in its structure. The chloro derivatives were more active than the fluoro counterparts in the dihalo derivative series.

Substitution in the phenyl of the benzylimidazole portion by chlorine (compounds **6**, **11**, and **12**) or fluorine (compound **7**) atoms did not affect significantly the antifungal potency of **5**. On the contrary, derivatives bearing a chloro atom either at the 4-position or at the 2-position of the phenyl linked at the 3-position of the pyrrole ring were found to be either highly active (compound **21**) or significantly active (**13**, **14**, **16**, **22–24**, **44**, and **49**, at either pH 7.2 or 5.8) depending on the nature of the substituent introduced on the phenyl portion of the benzylimidazole moiety.

Among monochloro derivatives, compound **21** shared the best activity, 3 times superior to that of the *o*-chloro analogue **13**. Generally, introduction of substituents other than chlorine at the *para* position of the phenyl ring of the benzyl portion of derivatives **13** and **21** resulted in a reduction of activity (compare at pH 7.2 **13** and **21** with derivatives **15**, **17**, **18**, and **48** and, respectively, **22–26** and **45**, with the sole exceptions of **14** and **16**).

A naphthyl group (compound **49**) could replace the phenyl ring of **21** without loss of activity, whereas a strong decrease in activity occurred when 4-biphenyl (compound **48**) and 4-(1-pyrryl)phenyl (compound **45**) moieties replaced the phenyl (Table 6).

When the chlorine of **21** was moved to the *ortho* position, a slight or a very strong decrease of activity was observed either in the isomer **13** or in its substituted derivatives (**13–20** and **44**).

Table 4. Chemical and Physical Data of Derivatives **100–134**, **140–144**, **149**, and **150**

no.	R^1	R^2	R^3	R^4	R^5	R^6	formula[a]	yield, %	hydride/ketone ratio	reaction time
100	H	H	H	H	H	H	$C_{17}H_{15}NO$	82	3.0	9 h
101	H	H	H	H	H	Cl	$C_{17}H_{14}ClNO$	100	2.0	3 h
102	H	H	H	H	H	F	$C_{17}H_{14}FNO$	100	1.8	2 h 30 min
103	H	H	H	H	H	CH_3	$C_{18}H_{17}NO$	100	2.0	4 h
104	H	H	H	H	H	NO_2	$C_{17}H_{14}N_2O_3$	100	1.1	15 h
105	H	H	H	Cl	H	Cl	$C_{17}H_{13}Cl_2NO$	42	2.0	5 h
106	H	H	H	H	Cl	Cl	$C_{17}H_{13}Cl_2NO$	100	2.0	6 h 20 min
107	H	H	Cl	H	H	H	$C_{17}H_{14}ClNO$	100	3.3	6 h
108	H	H	Cl	H	H	Cl	$C_{17}H_{13}Cl_2NO$	100	2.8	5 h 30 min
109	H	H	Cl	H	H	F	$C_{17}H_{13}ClFNO$	29	3.8	7 h
110	H	H	Cl	H	H	CH_3	$C_{18}H_{16}ClNO$	65	5.5	20 h
111	H	H	Cl	H	H	NO_2	$C_{17}H_{13}ClN_2O_3$	100	1.6	18 h
112	H	H	Cl	Cl	H	Cl	$C_{17}H_{12}Cl_3NO$	100	3.8	6 h
113	H	H	Cl	H	Cl	Cl	$C_{17}H_{12}Cl_3NO$	100	1.7	2 h
114	Cl	H	H	H	H	H	$C_{17}H_{14}ClNO$	98	3.0	5 h
115	Cl	H	H	H	H	Cl	$C_{17}H_{13}Cl_2NO$	96	1.4	30 min
116	Cl	H	H	H	H	F	$C_{17}H_{13}ClFNO$	100	1.4	2 h
117	Cl	H	H	H	H	CH_3	$C_{18}H_{16}ClNO$	100	2.0	3 h 45 min
118	Cl	H	H	H	H	NO_2	$C_{17}H_{13}ClN_2O_3$	65	2.0	2 h 40 min
119	Cl	H	H	Cl	H	Cl	$C_{17}H_{12}Cl_3NO$	100	1.4	2 h
120	Cl	H	H	H	Cl	Cl	$C_{17}H_{12}Cl_3NO$	100	1.4	3 h
121	Cl	H	Cl	H	H	H	$C_{17}H_{13}Cl_2NO$	100	2.8	5 h
122	Cl	H	Cl	H	H	Cl	$C_{17}H_{12}Cl_3NO$	42	4.9	5 h 20 min
123	Cl	H	Cl	H	H	F	$C_{17}H_{12}Cl_2FNO$	100	4.0	5 h 40 min
124	Cl	H	Cl	H	H	CH_3	$C_{18}H_{15}Cl_2NO$	100	4.2	5 h 45 min
125	Cl	H	Cl	H	H	NO_2	$C_{17}H_{12}Cl_2N_2O_3$	100	1.7	15 h
126	Cl	H	Cl	Cl	H	Cl	$C_{17}H_{11}Cl_4NO$	96	2.0	5 h
127	Cl	H	Cl	H	Cl	Cl	$C_{17}H_{11}Cl_4NO$	81	1.4	1 h 30 min
128	Cl	Cl	H	H	H	H	$C_{17}H_{13}Cl_2NO$	100	1.7	2 h 10 min
129	Cl	Cl	H	H	H	Cl	$C_{17}H_{12}Cl_3NO$	95	1.4	1 h 20 min
130	Cl	Cl	H	H	H	F	$C_{17}H_{12}Cl_2FNO$	100	1.7	2 h
131	Cl	Cl	H	H	H	CH_3	$C_{18}H_{15}Cl_2NO$	100	2.2	3 h
132	Cl	Cl	H	H	H	NO_2	$C_{17}H_{12}Cl_2N_2O_3$	100	1.7	15 h
133	Cl	Cl	H	Cl	H	Cl	$C_{17}H_{11}Cl_4NO$	100	2.2	3 h 30 min
134	Cl	Cl	H	H	Cl	Cl	$C_{17}H_{11}Cl_4NO$	100	1.1	1 h 30 min
140	H	H	H				$C_{21}H_{18}N_2O$	100	1.4	1 h 30 min
141	H	H	Cl				$C_{21}H_{17}ClN_2O$	100	1.6	2 h
142	Cl	H	H				$C_{21}H_{17}ClN_2O$	100	1.5	2 h 30 min
143	Cl	H	Cl				$C_{21}H_{16}Cl_2N_2O$	99	1.7	3 h
144	Cl	Cl	H				$C_{21}H_{16}Cl_2N_2O$	100	1.7	1 h 45 min
149							$C_{23}H_{18}ClNO$	96	1.4	30 min
150							$C_{21}H_{16}ClNO$	81	3.9	4 h

[a] All compounds were oils, and elemental analyses were performed on chromatographically pure samples; C, H, N, and, when present, Cl and F were analyzed, and analytical results are within ±4% of the theoretical values.

Among dihalo derivatives, the activity (MIC values of Table 6 were considered) decreased in the order: **29**, **39** > **14**, **36** > **22**, **23**, **32** > **12**, **15**, **33** > **11**, **40**, **46**, **47**. The best activity was observed with chlorine atoms bonded to the phenyl of the 3-phenylpyrrole portion or to both the phenyl rings. Antifungal activity was influenced by the position of halogens on the phenyl ring (compare **11**, **12**, **29**, and **36**), and introduction of substituents other than chlorine affected strongly the potency of new derivatives (compare compounds bearing methyl and nitro groups as substituents). The presence of the 4-(1-pyrryl)phenyl moiety (compounds **46** and **47**) decreased the good activity of derivatives **29** and **36**.

Generally, the tetrachloro derivatives were less active than trichloro and dichloro compounds, with few exceptions.

Activity against *Candida* spp. (three *C. lipolytica*, three *C. krusei*, two *C. glabrata*, and four *C. tropicalis*). In comparison to the controls, several of the compounds **5–49** displayed good activity in the *in vitro* assays developed at either pH 7.2 or 5.8 (Tables 6 and 7) against *Candida* spp.

At pH 7.2 two compounds (**14** and **36**) showed the same MIC_{90} as bifonazole (MIC_{90} = 16 μg/mL), and 11 pyrroles (**16**, **19**, **22**, **24**, **29**, **31**, **35**, **38**, **39**, **41**, and **49**) were as active as miconazole and ketoconazole (MIC_{90} = 32 μg/mL).

If MIC geometric mean is used for comparison, trichloro derivative **27**, the most active against *C. albicans*, is found to be about 8, 5, and 14 times less potent than ketoconazole, miconazole, and bifonazole, respectively. On the contrary, four dichloro derivatives, **36**, **14**, **29**, and **39**, show MIC values (ranging from 11.4 to 17.5 μg/mL) near to that of miconazole (13 μg/mL).

In terms of MIC data, eight derivatives (**19**, **27**, **30**, **32**, **35**, **38**, **39**, and **49**) are as active as miconazole and ketoconazole in the assays performed at pH 5.8, thus confirming the good microbiological profile of derivatives **19**, **35**, **38**, **39**, and **49** at both experimental pHs.

***In Vivo* Anti-*Candida* Activity.** Since *in vitro* susceptibility results, especially with the azole antifungal agents, are known to have variable correlation with clinical efficacy,[41] we decided to evaluate the *in vivo* activity of two chlorine derivatives, namely, monochloro derivative **21** and dichloro derivative **27**, chosen as representative members of this novel class of antifungal agents from those showing activity in the *in vitro* assays. Data of topical efficacy of these derivatives in experimental cutaneous candidosis produced by *C. albicans* A_{170} strain in albino female rabbits are reported in Table

Table 5. IR and ^1H NMR Spectra of Derivatives **5–49**

no.	IR, cm^{-1}	^1H NMR ($CDCl_3$), δ
5	3110 (NH)	6.43–6.55 (2H, m, CH, Cα-H pyrrole), 6.83–7.33 (12H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.48 (1H, s, C_2-H imidazole), 11.23 (1H, bs, NH)
6	3110 (NH)	6.46 (1H, m, Cα-H pyrrole), 6.85 (1H, s, CH), 6.92–7.47 (12H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.62 (1H, s, C_2-H imidazole), 11.26 (1H, bs, NH)
7	3120 (NH)	6.45 (1H, m, Cα-H pyrrole), 6.88–7.38 (13H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.68 (1H, s, C_2-H imidazole), 11.32 (1H, bs, NH)
8	3100 (NH)	2.28 (3H, s, CH_3), 6.44 (1H, m, Cα-H pyrrole), 6.76–7.41 (13H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.68 (1H, s, C_2-H imidazole), 11.26 (1H, bs, NH)
9	3050 (NH)	6.50 (1H, m, Cα-H pyrrole), 7.00–7.57 (11H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.73 (1H, s, C_2-H imidazole), 8.23–8.40 (2H, m, benzene H near nitro group), 11.33 ppm (1H, bs, NH)
10	3380, 3340, 3200 (NH, NH_2)	3.85 (2H, bs, NH_2), 6.40 (1H, m, Cα-H pyrrole), 6.50–7.48 (13H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.67 (1H, s, C_2-H imidazole), 8.40 (1H, bs, NH)
11	3120 (NH)	6.35 (1H, m, Cα-H pyrrole), 6.65–7.65 (13H, m, CH, Cα-H pyrrole, imidazole and benzene H), 10.95 ppm (1H, bs, NH)
12	3150 (NH)	6.30–8.07 (14H, m, CH, Cα-H pyrrole, imidazole and benzene H), 11.37 (1H, bs, NH)
13	3080 (NH)	6.43–6.61 (2H, m, CH, Cα-H pyrrole), 6.83–7.56 (13H, m, Cα-H pyrrole, imidazole and benzene H), 11.29 (1H, bs, NH)
14	3080 (NH)	6.52–6.65 (2H, m, CH, Cα-H pyrrole), 6.87–7.58 (12H, m, Cα-H pyrrole, imidazole and benzene H), 11.32 (1H, bs, NH)
15	3050 (NH)	6.43–6.63 (2H, m, CH, Cα-H pyrrole), 6.85–7.57 (12H, m, Cα-H pyrrole, imidazole and benzene H), 11.27 (1H, bs, NH)
16	3040 (NH)	2.27 (3H, s, CH_3), 6.43–6.55 (2H, m, CH, Cα-H pyrrole), 6.83–7.33 (11H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.48 (1H, s, C_2-H imidazole), 11.23 (1H, bs, NH)
17	3040 (NH)	6.58 (1H, m, Cα-H pyrrole), 6.75–7.65 (11H, m, CH, Cα-H pyrrole, imidazole and benzene H), 8.20–8.37 (2H, m, benzene H near nitro group), 11.38 (1H, bs, NH)
18	3380, 3320, 3200 (NH, NH_2)	3.63 (2H, bs, NH_2), 6.33–7.55 (14H, m, CH, pyrrole, imidazole and benzene H), 8.12 (1H, bs, NH)
19	3060 (NH)	6.44 (1H, m, Cα-H pyrrole), 6.82–7.62 (12H, m, CH, Cα-pyrrole, imidazole and benzene H), 11.32 (1H, bs, NH)
20	3040 (NH)	6.58–7.70 (13H, m, CH, pyrrole, imidazole and benzene H), 11.33 (1H, bs, NH)
21	3110 (NH)	6.46 (1H, m, Cα-H pyrrole), 6.85 (1H, s, CH), 6.92–7.47 (12H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.62 (1H, s, C_2-H imidazole), 11.26 (1H, bs, NH)
22	3050 (NH)	6.42 (1H, m, Cα-H pyrrole), 6.88–7.42 (12H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.65 (1H, s, C_2-H imidazole), 11.32 (1H, bs, NH)
23	3080 (NH)	6.42 (1H, m, Cα-H pyrrole), 6.92–7.42 (12H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.63 (1H, s, C_2-H imidazole), 11.30 (1H, bs, NH)
24	3060 (NH)	2.27 (3H, s, CH_3), 6.42 (1H, m, Cα-H pyrrole), 6.77–7.32 (12H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.58 (1H, s, C_2-H imidazole), 11.25 (1H, bs, NH)
25	3100 (NH)	6.45 (1H, m, Cα-H pyrrole), 6.95–7.52 (10H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.68 (1H, s, C_2-H imidazole), 8.18–8.35 (2H, m, benzene H near nitro group), 11.38 (1H, bs, NH)
26	3380, 3300, 3160 (NH, NH_2)	3.78 (2H, bs, NH_2), 6.50–7.58 (14H, m, CH, pyrrole, imidazole and benzene H), 10.82 (1H, bs, NH)
27	3080 (NH)	6.42 (1H, m, Cα-H pyrrole), 6.85–7.75 (12H, m, CH, pyrrole, imidazole and benzene H), 11.37 (1H, bs, NH)
28	3080 (NH)	6.48–7.73 (13H, m, CH, pyrrole, imidazole and benzene H), 11.35 (1H, bs, NH)
29	3050 (NH)	6.45 (1H, m, Cα-H pyrrole), 6.62 (1H, s, CH), 6.85–7.40 (11H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.52 (1H, s, C_2-H imidazole), 11.35 (1H, bs, NH)
30	3040 (NH)	6.48 (1H, m, Cα-H pyrrole), 6.62 (1H, s, CH), 6.82–7.58 (11H, m, Cα-H pyrrole, imidazole and benzene H), 11.35 (1H, bs, NH)
31	3050 (NH)	6.47 (1H, m, Cα-H pyrrole), 6.63 (1H, s, CH), 6.82–7.35 (11H, m, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.52 (1H, s, C_2-H imidazole), 11.33 (1H, bs, NH)
32	3070 (NH)	2.27 (3H, s, CH_3), 6.42–6.60 (2H, m, CH, Cα-H pyrrole), 6.82–7.57 (12H, m, Cα-H pyrrole, imidazole and benzene H), 11.28 (1H, bs, NH)
33	3050 (NH)	6.55 (1H, m, Cα-H pyrrole), 6.77–7.63 (10H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.68 (1H, s, C_2-H imidazole), 8.20–8.35 (2H, m, benzene H near nitro group), 11.40 (1H, bs, NH)
34	3060 (NH)	6.43 (1H, m, Cα-H pyrrole), 6.78–7.65 (11H, m, CH, Cα-H pyrrole, imidazole and benzene H), 11.35 (1H, bs, NH)
35	3070 (NH)	6.55–7.68 (12H, m, CH, pyrrole, imidazole and benzene H), 11.40 (1H, bs, NH)
36	3080 (NH)	6.38 (1H, m, Cα-H pyrrole), 6.92–7.55 (12H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.65 (1H, s, C_2-H imidazole), 11.37 (1H, bs, NH)
37	3100 (NH)	6.42 (1H, m, Cα-H pyrrole), 6.93–7.57 (11H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.65 (1H, s, C_2-H imidazole), 11.42 (1H, bs, NH)
38	3050 (NH)	6.38 (1H, m, Cα-H pyrrole), 6.93–7.53 (11H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.63 (1H, s, C_2-H imidazole), 11.38 (1H, bs, NH)
39	3160 (NH)	2.26 (3H, s, CH_3), 6.35 (1H, m, Cα-H pyrrole), 6.84–7.52 (11H, m, CH, Cα-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.62 (1H, s, C_2-H imidazole), 11.36 (1H, bs, NH)
40	3080 (NH)	6.45 (1H, m, C_α-H pyrrole), 6.98–7.60 (10H, m, CH, C_α-H pyrrole, C_4- and C_5-H imidazole, benzene H), 7.72 (1H, s, C_2-H imidazole), 8.23–8.38 (2H, m, benzene H near nitro group), 11.48 (1H, bs, NH)
41	3100 (NH)	6.42 (1H, m, C_α-H pyrrole), 6.87–7.72 (11H, m, CH, C_α-H pyrrole, imidazole and benzene H), 11.42 (1H, bs, NH)
42	3060 (NH)	6.42–7.72 (12H, m, CH, pyrrole, imidazole and benzene H), 11.45 (1H, bs, NH)
43	3120 (NH)	6.25 (2H, m, C_β-H pyrrole of 4-pyrrylphenyl group), 6.50–7.73 (17H, m, CH, pyrrole, imidazole and benzene H), 11.30 (1H, bs, NH)
44	3050 (NH)	6.27 (2H, m, C_β-H pyrrole of 4-pyrrylphenyl group), 6.63–7.70 (16H, m, CH, Cα-H pyrrole of 4-pyrrylphenyl group, Cα-H pyrrole, imidazole and benzene H), 11.32 (1H, bs, NH)
45	3060 (NH)	6.27 (2H, m, C_β-H pyrrole of 4-pyrrylphenyl group), 6.48 (1H, m, C_α-H pyrrole), 6.90–7.73 (15H, m, CH, pyrrole, imidazole and benzene H), 11.33 (1H, bs, NH)
46	3050 (NH)	6.21 (2H, m, C_β-H pyrrole of 4-pyrrylphenyl group), 6.50–7.80 (15H, m, CH, pyrrole, imidazole and benzene H), 11.38 (1H, bs, NH)
47	3050 (NH)	6.25 (2H, m, C_β-H pyrrole of 4-pyrrylphenyl group), 6.45 (1H, m, C_α-H pyrrole), 6.95–7.75 (14H, m, CH, pyrrole, imidazole and benzene H), 11.43 (1H, bs, NH)
48	3040 (NH)	6.42 (1H, m, C_α-H pyrrole), 6.82–7.77 (18H, m, CH, C_α-H pyrrole, imidazole and benzene H), 11.25 (1H, bs, NH)
49	3100 (NH)	6.27 (1H, m, C_α-H pyrrole), 6.90–8.10 (16H, m, CH, C_α-H pyrrole, imidazole and benzene H), 11.27 (1H, bs, NH)

8. The *in vivo* anti-*Candida* activity was evaluated in comparison with a reference group treated with a 1% bifonazole lotion and a control group treated with the vehicles only.

All tested lotions demonstrated clear antifungal activity, although to different degrees. The lesions recorded during the 4 days following the initial treatment showed a marked clinical improvement (a rapid decrease in the

Table 6. *In Vitro* Antifungal Activites of Imidazole Derivatives against *C. albicans* and *Candida* spp. (three *C. krusei*, three *C. lipolytica*, two *C. glabrata*, and four *C. tropicalis*) at pH 7.2

	fungi (no. of tested strains)									
	C. albicans (40)					*Candida* spp. (12)				
tested substance	*R*%	MIC, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL	*R*%	MIC, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL
5	2.7	≥35.4	32	64	2–>256	75	≥396	>256	>256	16–>256
6	0	21.3	8	128	2–128	0	40	32	128	4–128
7	0	55.1	32	64	8–128	0	74.5	64	128	4–128
8	0	48.4	32	64	8–128	0	51.6	64	64	8–64
9	0	5.18	8	64	2–128	20	≥192.1	256	256	8–>256
10	0	161.8	128	256	16–256	80	≥331	256	>256	64–>256
11	100	>256	>256	>256	>256	100	>256	>256	>256	>256
12	0	41.9	16	64	4–256	20	191.3	128	256	8–>256
13	0	19.2	16	32	4–32	0	22.6	32	64	8–64
14	0	9.1	8	16	4–16	0	15	16	16	2–32
15	0	36.45	32	64	2–128	0	107.2	64	256	16–256
16	0	13.2	4	64	0.5	0	30.1	32	32	4–32
17	15	≥91.62	32	256	4–>256	30	≥200	64	>256	8–>256
18	0	131.2	64	256	4–256	50	≥221.6	256	256	2–>256
19	0	7.3	4	16	0.5–32	0	21.8	32	32	2–32
20	0	12.7	16	32	2–32	0	36.2	32	64	2–64
21	0	6.4	2	16	0.5–32	0	46.5	32	128	1–128
22	0	16.3	16	32	8–32	0	21.3	16	32	8–32
23	0	19.2	16	32	2–64	0	31.8	32	64	2–64
24	0	18.9	16	32	4–32	0	23.1	16	32	16–32
25	0	≥91.8	32	64	2–>256	10	≥91.8	32	64	2–>256
26	0	98.2	64	128	32–128	0	183.7	128	128	64–128
27	0	3.6	2	8	0.5–16	0	61	32	128	1–128
28	0	19.34	2	64	0.25–128	10	91.3	64	64	0.5–128
29	0	5.4	2	16	0.25–16	0	16.6	16	32	4–32
30	5	≥66.38	8	256	1–>256	40	≥212	64	>256	0.5–>256
31	0	10.4	8	32	0.5–32	0	20.9	16	32	2–32
32	0	13.1	8	16	4–32	50	≥224.2	256	>256	2–>256
33	0	38.5	32	64	2–64	30	≥206.6	256	>256	2–>256
34	0	20.6	8	16	2–256	0	101.1	256	256	1–256
35	0	19.6	16	32	8–64	0	21.3	16	32	8–32
36	0	≥10.9	8	16	0.5–32	0	11.4	16	16	0.25–16
37	0	9.6	4	16	2–32	0	39.2	32	64	8–64
38	0	7.2	4	16	2–16	0	26.6	32	32	2–64
39	0	5.8	4	16	0.5–16	0	17.5	16	32	2–32
40	50	≥312	256	>256	0.25–>256	100	>256	>256	>256	>256
41	0	5.8	2	16	1–16	0	38.2	32	32	4–32
42	0	13.96	8	32	0.5–128	50	≥309	>256	>256	1–>256
43	0	37.3	16	32	4–64	0	42.1	32	64	32–64
44	0	25.3	8	64	4–256	0	24.1	16	64	2–64
45	20	≥121.3	64	256	4–>256	50	≥229.3	256	256	4–>256
46	100	>256	>256	>256	>256	100	>256	>256	>256	>256
47	50	≥289.1	128	>256	1–>256	80	≥438.4	>256	>256	32–>256
48	40	≥150	64	256	1–>256	60	≥352.1	>256	>256	2–>256
49	0	10.1	1	16	0.5–128	0	29	16	32	1–128
ketoconazole	0	8.3	2	32	0.5–64	0	8.1	4	32	0.5–16
miconazole	0	6.1	2	32	0.25–32	0	13	16	32	0.5–32
bifonazole	0	4.1	4	16	2–16	0	4.5	4	16	2–16

inflammation status and in the diameter of lesions) as was demonstrated by the daily observation of the treated animals and through the microbiological control performed by cultivation of cutaneous specimens taken from the infected areas. The results reported in Table 8 show the progressive recovery of the infected areas treated with the test lotions. After 12 days from assessed infection (48 h from inoculum), all the animals treated with azoles **21** and **27** were cleared of the *C. albicans* infection following the application of 1% of active ingredient, whereas incomplete recovery was observed in the controls. Ten (83%) and seven (58.3%) of 12 animals treated with azoles **21** and **27** were cured on day 18 after the beginning of treatment.

Conclusion

The susceptibility of 40 clinical isolates of *C. albicans* to the new pyrroles at 256 μg/mL was determined and expressed as *R*% (percent of resistant strains). Among 44 derivatives tested at pH 7.2, only two (**11** and **46**) showed $R = 100\%$, and for eight compounds (**5**, **17**, **25**, **30**, **40**, **45**, **47**, and **48**), more *R* were ranging from 2.7% to 50%. Like the controls (bifonazole, miconazole, and ketoconazole), the remaining derivatives at 256 μg/mL inhibited all of the clinical isolates employed in the experiments. The absence of strains resistant to these derivatives is expressed by $R\% = 0$.

In terms of MIC_{90} values, the most active of the test compounds was the trichloro derivative **27**, which was found to be 2 times as active as derivatives **14**, **19**, **21**, **29**, **32**, **34**, **36**, **38**, **39**, **41**, and **49** and bifonazole and 4 times more active than miconazole and ketoconazole.

The fact that the 1-naphthyl can replace the 2,4-dichlorophenyl moiety without any decrease in activity (compare MIC_{50} and MIC_{90} values of **19**, **27**, and **41** with

Table 7. *In Vitro* Antifungal Activities of Imidazole Derivatives against *C. albicans* and *Candida* spp. (three *C. krusei*, three *C. lipolytica*, two *C. glabrata*, and four *C. tropicalis*) at pH 5.8

	fungi (no. of tested strains)									
	C. albicans (40)					*Candida* spp. (12)				
tested substance	*R*%	MIC, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL	*R*%	MIC, μg/mL	MIC_{50}, μg/mL	MIC_{90}, μg/mL	range, μg/mL
5	0	53.9	32	128	8–128	0	88	128	128	8–128
6	0	47.3	32	64	2–128	0	51.4	64	64	2–64
7	0	71.2	64	128	8–128	0	99.5	64	128	64–256
8	0	133.3	64	256	8–128	0	71	64	256	32–128
9	0	56.7	8	128	2–128	0	182.8	128	≥256	128–256
10	0	142.4	128	256	16–256	80	≥327	256	≥256	64–>256
11	100	>256	>256	>256	>256	100	>256	>256	>256	>256
12	0	38.6	16	64	4–256	0	114.4	64	64	8–256
13	0	43.8	32	64	4–32	0	78.2	64	32	64–128
14	0	18.7	16	32	4–16	0	30.2	32	64	16–32
15	0	48.3	32	64	2–128	0	71.1	64	64	64–128
16	0	35.4	32	64	0.5	0	41.7	32	64	1–128
17	0	≥50.7	32	64	4–>256	0	48.4	64	64	32–64
18	0	100.4	64	256	4–256	50	201	256	256	2–256
19	0	5.19	4	16	0.5–32	0	13.7	16	16	2–32
20	0	13.8	8	32	2–32	0	24.8	32	32	8–32
21	0	12.8	16	32	0.5–32	0	44.4	32	32	8–32
22	0	12.3	8	32	8–32	0	20.2	16	32	0.25–32
23	0	15.4	8	32	2–64	0	26.6	32	32	2–32
24	0	12.3	16	32	4–32	0	20.4	16	32	8–32
25	0	≥60.12	16	64	2–>256	60	≥355	>256	>256	32–>256
26	0	42.8	32	128	32–128	0	82.5	128	128	4–128
27	0	3.94	2	8	0.5–16	0	14.4	16	32	8–32
28	0	14.4	4	64	0.25–128	0	32.2	32	64	2–64
29	0	8.4	4	16	0.25–16	0	23.5	32	32	4–32
30	0	≥6.8	4	256	1–>256	0	13.7	16	16	4–16
31	0	7.8	2	32	0.5–32	0	21.5	16	32	16–32
32	0	7.9	8	16	4–32	0	16.4	16	32	4–32
33	0	22.9	16	64	2–64	0	30.2	32	32	8–64
34	0	7.4	2	16	2–256	0	23.4	32	32	1–32
35	0	7.2	2	32	8–64	0	14.2	16	16	4–32
36	0	7.2	8	16	0.5–32	0	19.1	16	32	4–32
37	0	8.9	4	16	2–32	0	30.2	32	64	4–64
38	0	7.2	4	16	2–16	0	16.4	16	32	4–32
39	0	7.9	4	16	0.5–16	0	14.2	16	16	8–32
40	50	≥283	256	>256	0.25–>256	100	>256	>256	>256	>256
41	0	5.9	2	16	1–16	0	27.7	32	32	2–32
42	0	9.2	8	32	0.5–128	50	≥328	256	>256	2–>256
43	0	30.4	16	32	4–64	0	40	32	64	32–64
44	0	20.5	8	64	4–256	0	30.2	32	32	16–64
45	16	≥119.2	64	256	4–>256	40	≥156.1	64	>256	16–>256
46	0	33.7	16	64	0.5–128	0	19.5	16	32	8–32
47	40	≥264.2	128	>256	1–>256	100	>256	>256	>256	>256
48	0	≥26.5	8	256	1–>256	0	28.4	32	128	4–128
49	0	11.22	4	16	0.5–128	0	16.6	8	32	2–64
ketoconazole	0	8.6	0.5	32	<0.5–64	0	16.9	4	32	<0.25–64
miconazole	0	5.9	0.5	32	<0.25–32	0	13	2	32	1–32
bifonazole	0	3.72	4	16	2–16	0	7.5	8	8	4–8

those of **49** at both pHs) supported the supposition that highly lipophilic groups are needed for better antifungal activity.

However, the highest degree of lipophilicity does not correlate with the greatest activity. In fact, highly lipophilic substances such as the tetrachloro derivatives **34**, **35**, **41**, and **42** were found to be generally inferior in antifungal activity to the less lipophilic di- and trichloro derivatives, with the trichloro derivative **27** being the most active.

Compound **27** appears to be highly selective in inhibiting the activity of *C. albicans* at either pH 7.2 (MIC = 3.6 μg/mL) or 5.8 (MIC = 3.94 μg/mL), whereas its action was less against *Candida* spp., being practically inactive at pH 7.2 (MIC = 61 μg/mL) and moderately active at pH 5.8 (MIC = 14.4 μg/mL) when compared to controls.

At pH 5.8 compound **39**, which bears two chloro atoms at positions 3 and 4 of the phenyl ring bonded to the pyrrole ring and a methyl group at the 4-position of the phenyl of the benzylimidazole moiety, was found to exert potent inhibition against both *C. albicans* and *Candida* spp.

It is noteworthy that in terms of MIC (Table 6, assay against *C. albicans*) four compounds range from 4.1 (bifonazole) to 6.1 (miconazole) μg/mL values. With the exception of **9**, which contains a nitro group, the pyrroles **29**, **39**, and **41** all contain from two to four chlorine atoms. Generally, the number of chloro atoms rather than their position is the major determinant for antifungal activity. The sole exception was monochloro derivative **21**, which against *C. albicans* at pH 7.2 was as potent (MIC = 6.4 μg/mL) as miconazole (MIC = 6.1 μg/mL).

From the active derivatives, **21** and **27** were chosen to evaluate *in vivo* antifungal activity against *C. albicans*. These compounds have been shown to be highly effective *in vivo* in the rabbit skin candidosis (topical

Table 8. Topical Efficacy of Derivatives **21** and **27** and Bifonazole in Experimental Cutaneous Candidiasis (*C. albicans* A_{170}) in White Male Rabbits[a]

compd	conctn, %	cure rate at day postinfection, no. (% of animals)		
		6	10	18
21	1	4/12 (33)	6/12 (50)	10/12 (83)
27	1	1/12 (8)	3/12 (25)	7/12 (58.6)
bifonazole	1	3/12 (25)	5/12 (41.6)	9/12 (75)
drug vehicle		0	2/12 (16.6)	3/12 (25)

[a] Negative cultures from treated areas. Treatment twice daily on 15 consecutive days starting 48 h after inoculation (0.3 mL of a 1% solution/treatment).

treatment twice daily for 18 days starting 2 days after inoculation). A good mycological cure rate (83% and 58.3% for **21** and **27**, respectively) was observed for both the test substances on day 18 from assessed infection following the application of 1% solution of active ingredient.

In conclusion, 3-aryl-4-[α-(1*H*-imidazol-1-yl)arylmethyl]pyrroles are a novel class of antifungal agents endowed with potent anti-*Candida* activity. Pharmacological studies are actually in progress to select a potential clinical candidate among the most active derivatives.

Experimental Section

Chemistry. Melting points (Electrothermal IA6304 apparatus) are uncorrected. IR spectra (Nujol mulls) were obtained on a Perkin-Elmer 1310 spectrophotometer. ^{1}H NMR spectra were recorded with a Varian EM-390 (90 MHz) spectrometer using tetramethylsilane as internal reference standard; DMF-d_7 ($CDCl_3$ for derivatives **10** and **18**) was used as solvent. Column chromatographies were performed on an alumina column (Merck; 70–230 mesh). Stratocrom ALF Carlo Erba (aluminum oxide-precoated plates with fluorescent indicator) was used in TLC. Developed plates were visualized by UV light. Organic solutions were dried over anhydrous sodium sulfate. Concentration of solutions after reactions and extractions involved the use of a rotary evaporator (Büchi) operating at reduced pressure (ca. 20 bar). Elemental analyses were performed by laboratories of Prof. A. Pietrogrande, University of Padova, Italy; analytical results are within ±0.4% of theoretical values. All compound were analyzed for C, H, N, and, when present, Cl and F.

1,3-Diaryl-2-propen-1-ones. These compounds were prepared according to standard procedures.[23-39] Chemical and physical data of propenones **50–64** are reported in Table 1. Compounds **50–56** and **58–64** were recrystallized from ethanol, and compound **57** was recrystallized from DMF.

Aryl 4-Aryl-1*H*-pyrrol-3-yl Ketones 65–99 and 135–139. A solution of the proper 1,3-diaryl-2-propen-1-one (25 mmol) and TosMIC (25 mmol) in anhydrous DMSO–Et_2O mixture (50:120 mL) was added, by dropping, to a well-stirred suspension of sodium hydride (NaH) (120 mmol, 4.8 g of 60% suspension in white oil) in anhydrous Et_2O (50 mL). When addition stopped, the mixture was stirred at room temperature for 5–45 min and then treated with water (250 mL). Crystalline precipitates were filtered and recrystallized from suitable solvent (method A) or chromatographed (method B). In the other cases the reaction mixture was extracted with ethyl acetate. The organic extracts were collected, washed with brine, and dried. Removal of the solvent gave a residue, which was purified by column chromatography eluting with ethyl acetate (method C) or recrystallized from suitable solvent (method D).

Aryl(4-aryl-1*H*-pyrrol-3-yl)carbinols 100–134 and 140–144. Ketone (20 mmol) was added in small portions onto a well-stirred suspension of $LiAlH_4$ in anhydrous THF (140 mL) cooled to 0 °C. After addition the mixture was stirred at room temperature and then carefully treated with crushed ice. The inorganic precipitate was removed, and the solution was concentrated and shaken with chloroform. The organic solution was washed with brine, dried, and evaporated. Crude carbinols were used for the next reaction without further purification with the exception of derivatives **107**, **108**, **113**, and **119**, which were previously purified by passing through an alumina column (chloroform as eluent).

4-Aryl-3-[aryl(1*H*-imidazol-1-yl)methyl]-1*H*-pyrroles 5–49. A solution of the proper carbinol (30 mmol) and 1,1′-carbonyldiimidazole (4.4 mequiv, 1.1 mequiv for the preparation of **6**, **11**, **23**, **30**, and **32**) in anhydrous acetonitrile (500 mL) was stirred at room temperature (for reaction times, see Table 1). The solvent was removed, and the residue was dissolved in ethyl acetate. The organic solution was washed with brine and dried. Removal of the solvent afforded imidazole derivatives which were purified by column chromatography (Al_2O_3/EtOAc).

4-Aryl-3-[(4-aminophenyl)(1*H*-imidazol-1-yl)methyl]-1*H*-pyrroles 10, 18, and 26. The nitro derivative **9**, **17**, or **25** (5.5 mmol) dissolved in ethyl acetate (200 mL) was hydrogenated in the presence of 10% palladium on charcoal (240 mg) as a catalyst for 2 h in a Parr apparatus at 45 °C at an initial pressure of 4 atm. The catalyst was then filtered off, and the filtrate was evaporated to furnish the amino derivative **10**, **18**, or **26**, which was purified by passing through an alumina column (ethyl acetate as eluent). Treatment of amino derivatives **10**, **18**, and **26** with 2,5-dimethoxytetrahydrofuran according to the Clauson–Kaas method[42] failed to afford the related pyrroles. Then, bispyrroles **43–47** were prepared starting from methyl 4-(1*H*-pyrrol-1-yl)phenyl ketone.

Micology. Anti-*Candida in Vitro* Assays. Derivatives **5–49** were tested for antimycotic activities against *C. albicans* and *Candida* spp. The antifungal potency was evaluated by means of the minimal inhibitory concentration (MIC) using the serial dilution test in a liquid nutrient medium. MIC was defined as the lowest concentration of test substance at which there was no visible growth in comparison with a blank experiment after the preset incubation time. For the preparation of the dilution series, 5 mg of substance was dissolved in DMSO (1 mL) and the solution was treated on shaking with distilled water (9 mL). Further progressive double dilutions with test medium furnished the required concentrations in the range from 0.25 to 256 mg/mL; in some cases dissolution was completed by addition of a few drops of diluted hydrochloric acid. Blanks were prepared in the test medium with the above-reported quantities of water and DMSO, without adding test substance.

Bifonazole, miconazole, and ketoconazole were used as standard controls. Data of mean MIC values (MIC), MIC_{50}, and MIC_{90} together with percent of resistant strains (R%, MIC > 256 μg/mL) in the assayed MIC ranges are reported in Tables 6 and 7.

All tested microorganisms were preliminarily incubated at 37 °C for 18 h on Sabouraud (BBL) dextrose broth and then added to media containing the antimycotic agent. Antimicrobial tests were performed on Sabouraud broth (Difco) using inocula of 10^3/mL of fungi. Readings of MICs were taken at 24 h of growth at 37 °C.

MIC values were calculated by the expression $MIC = \Sigma MIC_i / s_t$, where MIC_i is the minimal inhibitory concentration values of all strains at the used concentration C_i and s_t is the total number of strains. MIC_{50} and MIC_{90} refer to MIC for 50% and 90% of strains, respectively.

Strains with MIC > 256 μg/mL are regarded as resistant (R) and are expressed as percentage by the equation $R\% = N_t - N_s/N_t \times 100$, where N_t is the total number of tested strains and N_s is the number of sensitive strains.

Experiments were carried out at both pH 7.2 and 5.8 employing two different lots of *C. albicans* and *Candida* spp. freshly isolated from hospitalized patients (strains were identified using standard methods). The specimens used were 40 strains of *C. albicans* and 12 strains of *Candida* spp. (three *C. lipolytica*, three *C. krusei*, two *C. glabrata*, and four *C. tropicalis*).

Anti-*Candida in Vivo* Assays. The activity of derivatives **21** and **27** against skin infections with *C. albicans* was evaluated in comparison with bifonazole, used as standard reference. For this purpose 0.5 g of test compound was dissolved in a mixture of poly(ethylene glycol) (36.25 mL), ethanol (11.25 mL), and dimethyl sulfoxide (2.5 mL). The 1% lotion was then used for topical application on the infected area of the animals. For the *in vivo* assays, *C. albicans* A_{170}, a human clinical pathogenic isolate obtained from the bile of a hospitalized female patient, 33 years old, suffering from a pancreas tumor, was used. Identification of the strain was carried out by standard procedures, and its growing was accomplished in Sabouraud agar (Difco, Detroit, MI) at 37 °C for 48 h. Growth from the above culture was washed with water and suspended in sterile 5% glucose solution. For the experiments, the cell suspensions were controlled by direct count in a Burke camera and diluted until the required concentration was reached.

Twelve male New Zealand white rabbits weighing 2.0 ± 0.2 kg were housed in separated cages, maintained in an aerated environment at 22 °C, lighted daily for 14 h (light period 5 a.m.−9 p.m.), and nourished with suitable fodder supplied by Ditta Morini (Modena, Italy), following National Institute of Health guidelines on care and use of laboratory animals. Before treatment, the hair was shorn from the backs of albino rabbits with electric clippers (Aesculap, Germany) and six areas of the skin ca. 3 cm^2, each in two rows, were scarified by sandpaper type 60. These abraded portions of the skin were then infected with 0.3 mL of a suspension of *C. albicans* containing ca. 0.6×10^6 infective blastocells of the A_{170} strain; 48 h after the challenge, an inflammatory state ensued in each treated area of animals. The topical treatment with 0.4 mL of 1% lotion containing the test derivative was applied twice daily on 15 consecutive days beginning 48 h after *C. albicans* inoculation. The activity of test derivatives was assessed in comparison with a reference group treated with a 1% lotion of bifonazole and a control group treated with the vehicles only. During the treatment with the lotions, the evolutions of the lesions were evaluated daily (degree of inflammation, diameter of lesions). Evaluation of activity was performed on days 6, 10, and 18. Yeasts were removed from scales, transferred to Sabouraud agar, and incubated for cfu evaluation. Animals were considered to be cured when attempts to reisolate *C. albicans* after a 4 day incubation at 37 °C failed.

Acknowledgment. This research was supported by financial aid from the Foundation "Istituto Pasteur-Fondazione Cenci Bolognetti", Università di Roma "La Sapienza". Italian MURST and CNR are also acknowledged for partial support.

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JM940793Y