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Antimycotic Azoles. 7. Synthesis and Antifungal Properties of a Series of Novel Triazol-3-ones

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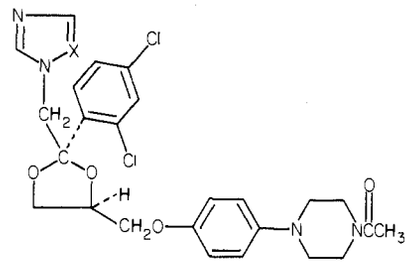
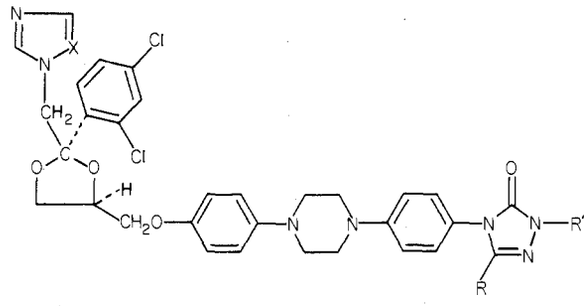
A series of novel triazol-3-ones have been synthesized, and their in vitro and in vivo antifungal properties are reported. Compound 68 (itraconazole), which displays a pronounced oral activity against vaginal candidosis in rats and against microsporosis in guinea pigs, has been selected for clinical evaluation.

With the advent of ketoconazole (Ia), which was dis-



Ia, X = CH (ketoconazole)
b, X = N



IIa, X = CH
b, X = N

covered approximately 30 years after the development of the first orally active broad-spectrum antibiotics, the first oral broad-spectrum antimycotic became available for medical practice. This introduction may be considered a milestone in the treatment of fungal diseases with azoles. The in vitro spectrum of ketoconazole covers a wide variety of yeasts, dermatophytes, and other fungi.[1,2] Its potential in the therapy of dermatomycoses, candidosis of the mouth and the vagina, systemic candidosis, chronic mucocutaneous candidosis and candiduria, as well as of deep and subcutaneous mycoses by dimorphic and other fungi has extensively been reviewed.[1-5]

Notwithstanding the promising results obtained in the oral treatment of mycoses with ketoconazole and the convenience for the patient, there still is a need for more potent and better antimycotic drugs. The present paper deals with the synthesis and antifungal properties of the title compounds IIa,b, and some of them fulfill these criteria in animal models.

Chemistry. The synthesis, starting from *cis*-[2-(2,4-dichlorophenyl)-2-(1*H*-imidazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl methanesulfonate (**1a**)[6] and *cis*-[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methyl methanesulfonate (**1b**),[7] is outlined in Scheme I.

Ketoconazole (**3a**) and the corresponding triazole analogue **3b** were prepared from **1a,b** and **2** according to the method described in a previous paper.[6] These compounds were deacylated at reflux temperature with NaOH in *n*-BuOH to the piperazines **4a** and **4b**, respectively. Both compounds, as well as 1-(4-methoxyphenyl)piperazine (**5**) were arylated with 1-chloro-4-nitrobenzene to the corresponding nitroaryl compounds **6a–c**. Catalytic reduction with 5% Pt/C afforded the anilino derivatives **7a–c**, which were acylated with phenyl chloroformate to the phenyl carbamates **8a–c**. Conversion of these carbamates with hydrazine hydrate at reflux temperature yielded the semicarbazides **9a–c**, which were cyclized to the triazol-3-ones IIIa–c. Alkylation of these triazol-3-ones with alkyl bromides or with dimethyl sulfate gave the target compounds IIa,b (method A) and IIc, respectively. Phenols IId were prepared by demethylation with a 48% HBr solution of compounds IIc. Methanesulfonates **1a,b** in a suspension of NaH (50% dispersion in mineral oil) were coupled either with the sodium salt of phenols IId, generated in situ from IId, to give IIa,b (method B) or with compound **2** to give **3a,b**.

Biological Methods. The title compounds were tested against a large number of microorganisms. Preliminary in vitro experiments were conducted according to the method described by Godefroi[8] with the fungi *Microsporum canis* (*M.c.*), *Trichophyton mentagrophytes* (*T.m.*), *Trichophyton rubrum* (*T.r.*), *Phialophora verrucosa* (*Ph.v.*), *Cryptococcus neoformans* (*Cr.n.*), *Candida tropicalis* (*C.tr.*), *Candida albicans* (*C.a.*), *Mucor* sp. (*Muc.*), *Aspergillus fumigatus* (*A.f.*), *Sporothrix schenckii* (*Sp.s*), and *Saprolegnia* sp. (*Sapr.*). In vivo, the compounds were tested in experimental vaginal candidosis in rats[6] and in experimental microsporosis.[9] For oral treatment, the compounds were formulated in polyethylene glycol (PEG) 200. In vaginal candidosis, the animals were treated therapeutically (treatment starting 3 days after infection) o.d. for 3 consecutive days with doses ranging from 0.63 to 10 mg/kg. Vaginal candidosis in ovarectomized and hysterectomized Wistar rats, kept in pseudopregnancy by weekly injections of 0.1 mg of oestradiol undecylate, was induced by infection with 8×10^5 cells of *C. albicans* (strain B 2630) Experimental microsporosis was treated prophylactically (treatment starting the day of infection

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(4) Graybill, J. R., *Am. J. Med.* **1983**, *74*(1B).
(5) Symoens, J.; Cauwenberg, G., to be published in *Prog. Drug. Res.*
(6) Heeres, J.; Backx, L. J. J.; Mostmans, J. H.; Van Cutsem, J. *J. Med. Chem.* **1979**, *22*, 1003.
(7) Heeres, J.; Hendrickx, R.; Van Cutsem, J. *J. Med. Chem.* **1983**, *26*, 611.
(8) Godefroi, E. F.; Van Cutsem, J.; Van der Eycken, C. H. M.; Janssen, P. A. J. *J. Med. Chem.* **1967**, *10*, 1160.
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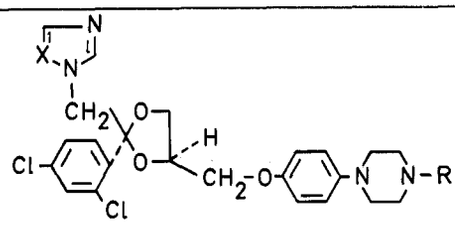
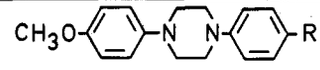
Table I



Compd.	X	R	M.p. °C	Formula	Cryst. solv.	Mr	Yield	Anal.[a]
3a[c]	CH	-C(=O)CH$_3$	146	$C_{26}H_{28}Cl_2N_4O_4$	MIK		59	
3b	N	-C(=O)CH$_3$	176.4	$C_{25}H_{27}Cl_2N_5O_4$	MIK / *i*-Pr_2O	532.42	58	C, H, N
4a	CH	-H	171.7	$C_{24}H_{26}Cl_2N_4O_3$	MIK	489.39	71	C, H, N
4b	N	-H	130.6	$C_{23}H_{25}Cl_2N_5O_3$	*i*-Pr_2O	490.38	79	C, H, N
6a	CH	-C$_6$H$_4$-NO$_2$	181	$C_{30}H_{29}Cl_2N_5O_5$	*n*-BuOH	610.48	54	C, H, N
6b	N	-C$_6$H$_4$-NO$_2$	167.8	$C_{29}H_{28}Cl_2N_6O_5$	*n*-BuOH	611.47	50	Cl, N
7a	CH	-C$_6$H$_4$-NH$_2$	174.4	$C_{30}H_{31}Cl_2N_5O_3$	*i*-PrOH	580.50	97	Cl, N
7b	N	-C$_6$H$_4$-NH$_2$	186.8	$C_{29}H_{30}Cl_2N_6O_3$	*n*-BuOH	581.49	80	Cl, N
8a	CH	-C$_6$H$_4$-NHC(=O)O-Ø	198.8	$C_{37}H_{35}Cl_2N_5O_5$	dioxane	700.60	82	C, H, N
8b	N	-C$_6$H$_4$-NHC(=O)O-Ø	203.1	$C_{36}H_{34}Cl_2N_6O_5$		701.61	86	C, H, N
9a	CH	-C$_6$H$_4$-NHC(=O)NHNH$_2$	225.9	$C_{31}H_{33}Cl_2N_7O_4$		638.53	98	C, H, N
9b	N	-C$_6$H$_4$-NHC(=O)NHNH$_2$	199.7	$C_{30}H_{32}Cl_2N_8O_4$		639.54	99	N

[a] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values. [b] MIK = $CH_3C(=O)CH_2CH(CH_3)_2$. [c] Reference 5.

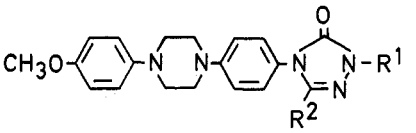
Table II



Compd.	R	M.p. °C	Formula	Cryst. solv.	Mr	Yield	Anal.[a]
6c	-NO$_2$	195.1	$C_{17}H_{19}N_3O_3$	dioxane	313.35	67	N
7c	-NH$_2$	191.8	$C_{17}H_{21}N_3O$	*n*-BuOH	283.36	74	C, H, N
8c	-NHC(=O)O-Ø	204.5	$C_{24}H_{25}N_3O_3$	*n*-BuOH	403.46	61	N
9c	-NHC(=O)NHNH$_2$	>300	$C_{18}H_{23}N_5O_2$	DMF	341.40	63	N

[a] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values.

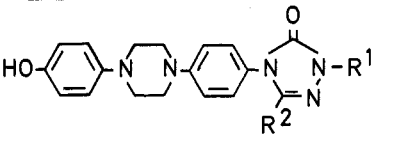
Table III



Compd.	R^1	R^2	m.p.	Formula	Crystn. solv.	Mr.	Yield	Anal.[a]
10	H	H	>300	$C_{19}H_{21}N_5O_2$	DMF	351.40	28	C,H,N
11	CH_3	H	245.2	$C_{20}H_{23}N_5O_2$	dioxane	365.42	35	N
12	C_2H_5	H	210.2	$C_{21}H_{25}N_5O_2$	*n*-BuOH	379.45	44	C,H,N
13	*n*-C_3H_7	H		$C_{22}H_{27}N_5O_2$	*n*-BuOH	393.48	65	—[b]
14	*i*-C_3H_7	H	209.5	$C_{22}H_{27}N_5O_2$	*n*-BuOH	393.48	47	C,H,N
15	*n*-C_4H_9	H	171.6	$C_{23}H_{29}N_5O_2$	*n*-BuOH	407.51	61	C,H,N
16	*i*-C_4H_9	H	203.0	$C_{23}H_{29}N_5O_2$	*n*-BuOH	407.51	57	N
17	H	CH_3	298.4	$C_{20}H_{23}N_5O_2$	dioxane	365.42	34	C,H
18	CH_3	CH_3	196.7	$C_{21}H_{25}N_5O_2$	*n*-BuOH	379.45	31	C,H,N
19	C_2H_5	CH_3	179.8	$C_{22}H_{27}N_5O_2$	*i*-PrOH	393.48	80	C,H,N
20	*n*-C_3H_7	CH_3	144.5	$C_{23}H_{29}N_5O_2$	*i*-PrOH	407.50	83	C,H,N
21	*i*-C_3H_7	CH_3	192.7	$C_{23}H_{29}N_5O_2$	*i*-PrOH	407.50	51	C,H,N
22	*n*-C_4H_9	CH_3	150.1	$C_{24}H_{31}N_5O_2$	*i*-PrOH	421.54	59	N
23	*i*-C_4H_9	CH_3	139.0	$C_{24}H_{31}N_5O_2$	*i*-PrOH	421.54	53	C,H,N

[a] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values. [b] Product was used without further purification.

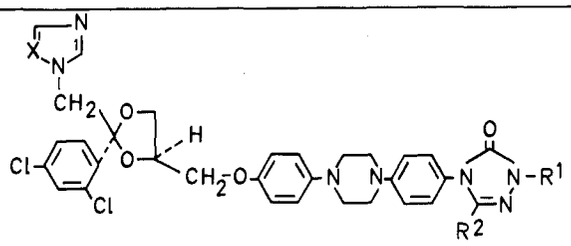
Table IV



Compd.	R^1	R^2	m.p. °C	Formula	Crystn. solv.	Mr.	Yield	Anal.[a]
24	CH_3	H	>260	$C_{19}H_{21}N_5O_2$	DMF	351.40	96	—[b]
25	C_2H_5	H	217	$C_{20}H_{23}N_5O_2$	DMF	365.42	95	C,H,N
26	*n*-C_3H_7	H		$C_{21}H_{25}N_5O_2$	DMF	379.45	83	—[b]
27	*i*-C_3H_7	H	208.4	$C_{21}H_{25}N_5O_2$	DMF	379.45	86	C,H,N
28	*n*-C_4H_9	H	221.6	$C_{22}H_{27}N_5O_2$	*i*-PrOH	393.49	69	N
29	*i*-C_4H_9	H	211.4	$C_{22}H_{27}N_5O_2$	*i*-PrOH	393.49	38	C,H,N
30	CH_3	CH_3	>260	$C_{20}H_{23}N_5O_2$	DMF	365.42	96	C,H,N
31	C_2H_5	CH_3	287.8	$C_{21}H_{25}N_5O_2$	DMF	379.45	92	C,H,N
32	*n*-C_3H_7	CH_3	258.2	$C_{22}H_{27}N_5O_2$	*i*-PrOH	393.49	88	C,H,N
33	*i*-C_3H_7	CH_3	251.3	$C_{22}H_{27}N_5O_2$	*n*-BuOH	393.49	100	C,H,N
34	*n*-C_4H_9	CH_3	262.0	$C_{23}H_{29}N_5O_2$	*n*-BuOH	407.51	84	C,H,N
35	*i*-C_4H_9	CH_3	268.7	$C_{23}H_{29}N_5O_2$	*i*-PrOH	407.51	89	C,H,N

[a] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values. [b] Products were used without further purification.

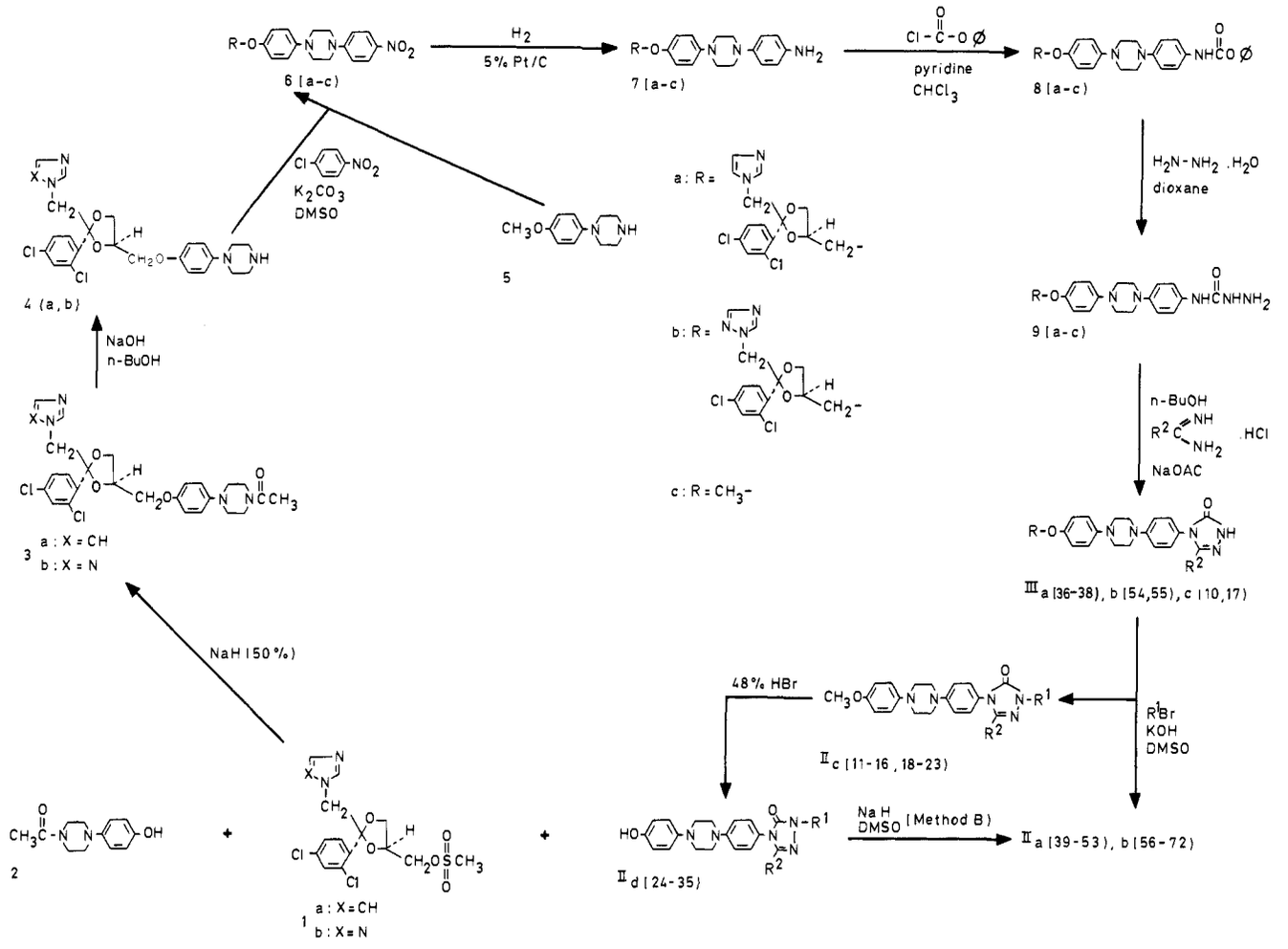
Table V



Compd.	Stereochem.	X	R^1	R^2	m.p.°C	Formula	Crystn. solv.	Mr.	Yield	Method	Anal.[a]
36	cis	CH	H	H	255.0	$C_{32}H_{31}Cl_2N_7O_4$	*n*-BuOH	648.53	30	-	N
37	cis	CH	H	CH_3	295.7	$C_{33}H_{33}Cl_2N_7O_4 \cdot {}^1/_2 C_3H_8O$	*i*-PrOH	692.62	44	-	C[c],H,N[c],Cl
38	cis	CH	H	C_2H_5	275.6	$C_{34}H_{35}Cl_2N_7O_4$	*n*-BuOH	676.58	26	-	N
39	cis	CH	CH_3	H	212.8	$C_{33}H_{33}Cl_2N_7O_4$	*n*-BuOH	662.55	44	B	C,H,N
40	cis	CH	CH_3	CH_3	147.3	$C_{34}H_{35}Cl_2N_7O_4$	MIK	676.58	74	B	Cl,N
41	cis	CH	C_2H_5	H	204.7	$C_{34}H_{35}Cl_2N_7O_4$	*n*-BuOH	676.58	53	B	C,H,N
42	cis	CH	C_2H_5	CH_3	135.5	$C_{35}H_{37}Cl_2N_7O_4 \cdot H_2O$ [d]	*i*-PrOH	708.63	51	B	C,H,N
43	cis	CH	*n*-C_3H_7	H	185.7	$C_{35}H_{37}Cl_2N_7O_4$	MIK	690.61	51	B	C,H,N
44	cis	CH	*n*-C_3H_7	CH_3	153.9	$C_{36}H_{39}Cl_2N_7O_4 \cdot H_2O$ [e]	*n*-BuOH	722.67	61	B	N,C[e],H
45	cis	CH	*n*-C_3H_7	C_2H_5	170.4	$C_{37}H_{41}Cl_2N_7O_4$	MIK / *i*-Pr_2O	718.68	70	B	C,H,N
46	cis	CH	*i*-C_3H_7	H	222.1	$C_{35}H_{37}Cl_2N_7O_4$	MIK	690.61	37	A	C,H,N
47	cis	CH	*i*-C_3H_7	CH_3	146.1	$C_{36}H_{39}Cl_2N_7O_4 \cdot H_2O$ [f]	MIK / *i*-Pr_2O	722.67	71	A	C,H,N
48	cis	CH	*n*-C_4H_9	H	199.2	$C_{36}H_{39}Cl_2N_7O_4$	MIK	704.65	45	A	C,H,N
49	cis	CH	*n*-C_4H_9	CH_3	172.6	$C_{37}H_{41}Cl_2N_7O_4$	$PhCH_3$ / *i*-Pr_2O	718.68	70	A	Cl,N
50	cis	CH	*i*-C_4H_9	H	195.0	$C_{36}H_{39}Cl_2N_7O_4$	MIK	704.65	35	B	C,H,N
51	cis	CH	*i*-C_4H_9	CH_3	150.3	$C_{37}H_{41}Cl_2N_7O_4$	MIK	718.68	23	A	N
52	cis	CH	$CH_2CH{=}CH_2$	H	181.3	$C_{35}H_{35}Cl_2N_7O_4$	MIK	688.61	49	A	C,H,N
53	cis	CH	*s*-C_4H_9	H	170.7	$C_{36}H_{39}Cl_2N_7O_4$	MIK	704.65	74	-	C,H,N
54	cis	N	H	H	254.4	$C_{31}H_{30}Cl_2N_8O_4$	DMF / *i*-Pr_2O	652.31	62	-	C,H,N
55	cis	N	H	CH_3	212.4	$C_{32}H_{32}Cl_2N_8O_4 \cdot {}^1/_2 C_2H_6O$ [g]	EtOH	686.59	38	-	Cl,C[g],H,N
56	cis	N	CH_3	H	212.8	$C_{32}H_{32}Cl_2N_8O_4$	*n*-BuOH	663.55	42	B	C,H,N
57	cis	N	CH_3	CH_3	161.9	$C_{33}H_{34}Cl_2N_8O_4 \cdot H_2O$ [h]	MIK	695.60	71	B	Cl
58	cis	N	C_2H_5	H	184.4	$C_{33}H_{34}Cl_2N_8O_4$	*n*-BuOH	677.57	74	B	C,H,N
59	cis	N	C_2H_5	CH_3	178.3	$C_{34}H_{36}Cl_2N_8O_4$	*n*-BuOH	691.60	71	B	N,Cl
60	cis	N	*n*-C_3H_7	H	176.3	$C_{34}H_{36}Cl_2N_8O_4$	MIK	691.60	53	B	N,Cl
61	cis	N	*n*-C_3H_7	CH_3	165.5	$C_{35}H_{38}Cl_2N_8O_4 \cdot H_2O$ [i]	*n*-BuOH	723.64	52	B	C,H,N
62	cis	N	*i*-C_3H_7	H	200.4	$C_{34}H_{36}Cl_2N_8O_4$	MIK	691.62	64	B	Cl,N
63	cis	N	*i*-C_3H_7	CH_3	158.6	$C_{35}H_{38}Cl_2N_8O_4 \cdot H_2O$ [j]	MIK	723.66	68	B	Cl,N,C[j],H
64	cis	N	*n*-C_4H_9	H	180.5	$C_{35}H_{38}Cl_2N_8O_4$	*n*-BuOH	705.62	70	B	C,H,N
65	cis	N	$(CH_3)_2CHCH_2$-	CH_3	140.0	$C_{36}H_{40}Cl_2N_8O_4$	MIK	719.67	50	B	C,H,N
66	cis	N	$(CH_3)_2CHCH_2$-	H	155.8	$C_{35}H_{38}Cl_2N_8O_4$	MIK	705.62	54	B	C,H,N
67	cis	N	$-CH_2CH{=}CH_2$	H	159.2	$C_{34}H_{34}Cl_2N_8O_4$	$PhCH_3$	689.60	54	A	Cl
68	cis	N	*s*-C_4H_9	H	166.2	$C_{35}H_{38}Cl_2N_8O_4$	$PhCH_3$	705.64	46	A	C,H,N
69	cis	N	$(CH_3)_2CHCH_2CH_2$-	H	183.4	$C_{36}H_{40}Cl_2N_8O_4$	$PhCH_3$	719.67	68	A	C,H,N
70	cis	N		H	197.3	$C_{36}H_{38}Cl_2N_8O_4$	$PhCH_3$	717.66	43	A	C,H,N
71	cis	N	$-CH_2$-	H	174.5	$C_{35}H_{36}Cl_2N_8O_4$	MIK	703.63	40	A	N,Cl
72	cis	N	*s*-C_4H_9	CH_3	146.1	$C_{36}H_{40}Cl_2N_8O_4$	MIK / *i*-Pr_2O	719.67	68	A	C,H,Cl

[a] Unless otherwise stated, the analyses are within ±0.4% of the theoretical values. [b] MIK = $CH_3C(=O)CH_2CH(CH_3)_2$. [c] C = calcd, 59.82; found, 58.80. N: calcd, 14.80; found, 14.16. [d] NMR for H_2O δ 1.86. [e] C: calcd, 59.84; found, 59.16; NMR for H_2O δ 1.86. [f] NMR for H_2O δ 1.82. [g] C: calcd, 57.73; found, 56.81; NMR for C_2H_5OH δ 1.20 (CH_3), 3.71 (CH_2). [h] NMR for H_2O δ 1.84. [i] NMR for H_2O δ 1.75. [j] C: calcd, 58.09; found, 58.64. NMR for H_2O δ 1.75.

Scheme I



or the day before) o.d. for 14 consecutive days with doses ranging from 1.25 to 20 mg/kg. Experimental microsporosis was induced in guinea pigs by artificial infection on the back with *M. canis*. Substances showing more than a 50% cure rate were tested at lower doses.

Results and Discussion

The test results are summarized in Table VI. The in vitro results represent the lowest dose levels for total inhibition of growth. Compared with the title compounds, ketoconazole demonstrates the highest in vitro activity and is also clearly more active than its triazole analogue. The low in vitro activity of the triazol-3-ones may be associated with their low solubility in the test medium. Compound **68**, when tested in Me_2SO solution in Sabouraud broth at pH 7.4, was active against dermatophytes at concentrations ranging from 0.1 to 1 μg/mL and against *Candida* spp., *Cr. neoformans*, *A. fumigatus*, *S. schenckii*, and *Ph. verrucosa* at 0.1 μg/mL.[10] Some compounds (**39**, **53**, **58**, and **67**) appear to be active at rather low concentrations (1–10 μg/mL) against dermatophytes, such as *T. rubrum*, *T. mentagrophytes*, and yeasts, such as *Cr. neoformans* and *C. tropicalis*. It is striking that even at 100 μg/mL none of the tested compounds showed significant activity against *Mucor* sp., and only one compound (**40**) showed significant activity against *M. canis*. Three compounds (**39**, **40**, and **53**) inhibit the growth of *A. fumigatus* at 100 μg/mL.

Compound **67** was active against *T. mentagrophytes*, *T. rubrum*, *Cr. neoformans*, and *C. tropicalis* and was the only compound that had an inhibitory effect on the growth of *S. schenckii* at 100 μg/mL. By comparison, it can be concluded that in vitro and in vivo activity are very poorly correlated. Although none of the triazol-3-ones displays any in vitro activity against *M. canis* at 100 μg/mL, when tested under the conditions described, several compounds (**39**, **47**, **62** and **66–68**) demonstrated significant oral activity against experimental microsporosis, even at low doses (2.5 mg/kg). None of the nonalkylated triazol-3-ones was found to be active in established vaginal candidosis and microsporosis at the indicated doses. N-Alkylation has a pronounced enhancing effect on in vivo activity. In the prophylactic experiments against vaginal candidosis as well as against microsporosis, it was seen that nonalkylated triazol-3-ones were less potent than the alkylated analogues.[11] Moreover, the in vivo results prove that it is favorable to substitute a triazole ring for the imidazole moiety (**46** < **62** and **53** < **68**). Introduction of a methyl group in the 5-position of the triazol-3-one ring (R^2) tends to decrease the oral activity, in particular in microsporosis (**66** > **65** and **62** > **63**, and **68** > **72**). No definite conclusions can be drawn concerning the influence of alkyl chain variation (R^1) on biological activity in the imidazole derivatives, since the gained in vivo results are too heterogeneous. Only minor effects on activity in vaginal candidosis have been observed after elongation of the alkyl chain (R^1) from methyl to *n*-propyl (**56**, **58**, and **60**) in the

(10) Van Cutsem, J.; Van Gerven, F.; Zaman, R.; Heeres, J; Janssen, P. A. J. 13th International Congress of Chemotherapy, Vienna, Aug 28–Sept 2, 1983.

(11) Van Cutsem J., unpublished results.

Table VI. In Vitro and in Vivo Antifungal Activity

Compd.	IN VITRO [a]											IN VIVO [b]							
												VAGINAL CANDIDOSIS IN RATS				MICROSPOROSIS GUINEA PIGS			
												DOSE (mg/kg)				DOSE (mg/kg)			
	M. c.	T.m.	T.r.	Ph.v.	Cr.n.	C.tr.	C.a.	Muc.	A.f.	Sp.s.	Sapr.	10	2.5	1.25	0.63	20	10	2.5	1.25
36	>100	100	>100	>100	>100	100	>100	>100	>100	>100	>100		0/2						
37	>100	10	10	>100	100	10	100	>100	>100	>100	>100						0/2		
38	>100	>100	>100	>100	>100	100	100	>100	>100	>100	>100							0/2	
39	>100	1	1	>100	1	1	>100	>100	100	>100	100	5/6	4/11	3/12	0/4		4/4	2/6	0/6
40	100	10	100	>100	>100	>100	100	>100	100	>100	>100	3/4	0/2			2/2	0/2		
41	>100	100	10	>100	>100	100	100	>100	>100	>100	>100		0/2						
42	>100	100	>100	>100	>100	100	>100	>100	>100	>100	>100		0/2					0/2	
43	>100	100	100	>100	>100	>100	>100	>100	>100	>100	>100	4/4	0/2						
44	>100	>100	>100	>100	>100	100	100	>100	>100	>100	>100		0/2						
45	>100	10	100	>100	>100	10	100	>100	>100	>100	>100		1/2				1/4		
46	>100	100	100	>100	>100	100	100	>100	>100	>100	>100		0/2				2/4	0/2	
47	>100	100	>100	>100	>100	1	100	>100	>100	>100	>100		1/6				5/6	1/6	0/6
48	>100	100	10	>100	>100	100	100	>100	>100	>100	>100		4/6	0/2					
49	>100	10	10	>100	100	1	100	>100	>100	>100	>100		4/8	1/6	0/4		4/6	0/6	0/2
50	>100	100	>100	>100	>100	>100	100	>100	>100	>100	>100		1/2				0/2		
51	>100	100	100	>100	100	100	>100	>100	>100	>100	>100		2/4				2/2	0/2	
52	>100	10	1	>100	>100	10	100	>100	>100	>100	>100		0/2				1/2	0/2	
53	>100	1	1	100	10	1	>100	>100	100	>100	>100		1/2				1/2	2/4	
54	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100						0/2		
55	>100	10	100	100	100	1	>100	>100	>100	>100	>100						0/2		
56	>100	1	10	100	100	10	100	>100	>100	>100	>100	2/2	4/6	5/6	4/8		1/8	0/2	0/2
57	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	1/2	1/2			0/2			
58	>100	1	1	>100	10	1	100	>100	>100	>100	>100	10/12	13/15	16/18	4/12		4/8	3/10	0/8
59	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100	>100		9/10	1/4	1/6		0/4		
60	>100	100	1	>100	100	100	>100	>100	>100	>100	>100	6/6	9/10	9/10	3/10		1/8	0/5	0/6
61	>100	1	>100	>100	100	100	100	>100	>100	>100	>100		1/4		0/2				
62	>100	100	>100	>100	>100	>100	>100	>100	>100	>100	>100	5/6	20/24	12/22	2/12		6/6	7/12	2/6
63	>100	100	>100	>100	>100	10	>100	>100	>100	>100	>100		1/2				0/2		
64	>100	100	>100	>100	>100	>100	>100	>100	>100	>100	>100		0/2				1/6		
65	>100	10	>100	>100	100	1	100	>100	>100	>100	>100		6/6	6/6	4/11		2/6	0/8	0/8
66	>100	10	10	>100	100	10	100	>100	>100	>100	>100		7/10	7/10	4/10		2/2	5/8	3/6
67	>100	1	10	>100	10	1	>100	>100	>100	100	>100		3/6	1/2	1/6		2/2	4/6	0/4
68	>100	10	10	>100	100	100	>100	>100	>100	>100	>100	12/12	29/34	13/33	7/40		6/6	11/12	12/15
69	>100	100	>100	>100	>100	>100	100	>100	>100	>100	>100		0/2				1/2		
70	>100	100	>100	>100	>100	>100	>100	>100	>100	>100	>100		1/2				2/2	0/2	
71	>100	10	10	100	>100	>100	100	>100	>100	>100	>100		1/2				2/2	0/2	
72	>100	100	>100	>100	>100	>100	10	>100	>100	>100	>100		2/2		0/2		2/2	0/2	
3b	100	1	10	100	10	>100	>100	>100	>100	100	10	1/2	0/2			0/2			
3a	100	1	1	10	10	10	100	>100	100	10	10	173/181	2/8	0/12		30/30	4/34	0/14	

[a] Lowest level of total inhibition (micrograms per milliliter). [b] Ratio of animals cured/animals infected.

triazoles, whereas the *n*-butyl derivative (**64**) is devoid of activity.

Replacement of the *n*-propyl (**60**) by an allyl chain (**67**) tends to decrease the activity against vaginal candidosis, but, on the other hand, an important increase in activity against microsporosis is noticed. Branching of the alkyl chain gives rise to a dramatic increase of activity against vaginal candidosis, as well as against microsporosis (**62**, **66**, and **68**). Introduction of a cyclopropylmethyl group (**71**) for isobutyl (**66**) leads to a decreased activity in both in-

fection models. Based on the results,[10] also gained from other animal models, one compound [**68**, (itraconazole, proposed international nonproprietary name)] has been selected for clinical studies.

Experimental Section

Melting points are measured with a Mettler FP_1 melting point apparatus and are uncorrected. New compounds were routinely checked for their structure by UV and/or IR and NMR spectrometry (UV, Hewlett-Packard HP-8450; IR, Perkin-Elmer 580B; NMR, Brucker WP 200).

***cis*-1-Acetyl-4-[4-[[2-(2,4-dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (3b).** To a suspension of NaH (50% dispersion) (37.0 g, 0.772 mol) in Me_2SO (1500 mL) was added compound **2** (168.0 g, 0.772 mol). After the solution was stirred for 1 h, **1b** (286.0 g, 0.7 mol) was added, and stirring was continued for 5 h at 80 °C. The reaction mixture was cooled, and water was added. After extraction with CH_2Cl_2, the organic layer was dried ($MgSO_4$) and evaporated to afford an oily residue, which was crystallized from 4-methyl-2-pentanone to give **3b** (240.0 g, 64%), mp 176.4 °C. Anal. ($C_{22}H_{27}Cl_2N_5O_4$) C, H, N.

***cis*-1-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]piperazine (4b).** A solution of **3b** (240.0 g, 0.450 mol) and NaOH pellets (22.0 g, 0.54 mol) in *n*-BuOH (1000 mL) was refluxed with stirring overnight. The reaction mixture was cooled, whereupon water was added. The mixture was subsequently extracted with $CHCl_3$; the organic layer was dried ($MgSO_4$) and evaporated in vacuo. The solid residue was crystallized from 4-methyl-2-pentanone/isopropyl ether to give **4b** (156.0 g, 70%), mp 130.6 °C. Anal. ($C_{23}H_{25}Cl_2N_5O_3$) C, H, N.

***cis*-1-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-4-(4-nitrophenyl)piperazine (6b).** A solution of **4b** (150.0 g, 0.306 mol) and 1-chloro-4-nitrobenzene (56.0 g, 0.356 mol) in Me_2SO (400 mL) was stirred overnight at 120 °C in the presence of K_2CO_3 (22.4 g, 0.160 mol). The reaction mixture was cooled and diluted with water. The crystallized product was filtered and taken up in $CHCl_3$. The solution was dried ($MgSO_4$) and evaporated in vacuo, yielding **6b** (180.0 g, 96%), mp 165.0 °C. Recrystallization from *n*-BuOH afforded an analytical sample, mp 167.8 °C. Anal. ($C_{29}H_{28}Cl_2N_6O_5$) C, H, N.

***cis*-4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]benzenamine (7b).** A solution of **6b** (175.0 g, 0.286 mol) in $MeOCH_2CH_2OH$ (1000 mL) was hydrogenated at 50 °C in the presence of a solution of thiophene (4%) in MeOH (1 mL) with 5% Pt/C (2.0 g) as the catalyst. When hydrogen uptake was complete, the mixture was heated to reflux, and, subsequently, the catalyst was filtered off. While the mixture was cooling, the product crystallized and then filtered off to give **7b** (134.4 g, 81%), mp 180.0 °C. Recrystallization from *n*-BuOH afforded an analytical sample, mp 186.8 °C. Anal. ($C_{29}H_{30}Cl_2N_6O_3$) C, H, N.

***cis*-Phenyl [4-[4-[4-[[2-(2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]carbamate (8b).** To a solution of **7b** (129.0 g, 0.222 mol) in $CHCl_3$ (1000 mL) and pyridine (300 mL) was added dropwise over a period of 15 min phenyl chloroformate (36.3 g, 0.232 mol). The reaction mixture was stirred for 3 h, and subsequently, H_2O and petroleum ether were added. The product crystallized and was filtered off. The crystals were subsequently washed with H_2O, *i*-PrOH, and finally with isopropyl ether to give, after drying, **8b** (133.0 g, 86%), mp 203.0 °C. Anal. ($C_{36}H_{34}Cl_2N_6O_5$) C, H. N.

***cis*-*N*-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]hydrazinecarboxamide (9b).** Hydrazine hydrate (50.0 g, 1.0 mol) and **8b** (130.0 g, 0.185 mol) in 500 mL of dioxane were stirred and refluxed for 3 h. Subsequently, the reaction mixture was poured into H_2O, whereupon the product crystallized. The crystalline solid was filtered, washed with H_2O and *i*-PrOH, and dried to give **9b** (170.0 g, 99%), mp 199.7 °C. Anal. ($C_{30}H_{32}Cl_2N_8O_4$) C, H, N.

***cis*-4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-3*H*-1,2,4-triazol-3-one (10b).** Formamidine acetate (83.2 g, 0.800 mol) and **9b** (115.0 g, 0.179 mol) in DMF (300 mL) were stirred at 130 °C for 3 h. The product crystallized on dilution with water. The solid was filtered off and recrystallized from DMF/*i*-Pr_2O, yielding **10b** (72.0 g, 62%), mp 254.4 °C. Anal. ($C_{31}H_{30}Cl_2N_8O_4$) C, H, N.

***cis*-4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperizinyl]phenyl]-2,4-dihydro-2-(1-methylpropyl)-3*H*-1,2,4-triazol-3-one (68).** To a suspension of KOH powder (0.7 g, 0.01 mol) and **10b** (5.0 g, 0.0077 mol) in Me_2SO (100 mL) was added 2-bromobutane (1.23 g, 0.009 mol). Stirring was continued for 14 h, whereupon the reaction mixture was diluted with water. Extracting with $CHCl_3$, drying ($MgSO_4$), and evaporating in vacuo afforded a solid,which was chromatographed on silica with $CHCl_3/CH_3OH$ (98:2) as the eluent. The pure compound was recrystallized from toluene to give **68** (2.5 g, 46%), mp 166.2 °C. Anal. ($C_{35}H_{38}Cl_2N_8O_4$) C, H, N.

2,4-Dihydro-4-[4-[4-(4-hydroxyphenyl)-1-piperazinyl]phenyl]-2-(1-methylethyl)-3*H*-1,2,4-triazol-3-one (27). A mixture of **14** (4.7 g, 0.012 mol) and 48% HBr solution (50 mL) was refluxed overnight. The reaction mixture was cooled, whereupon a product crystallized. The solid was filtered off and dissolved in a water/MeOH mixture (50:50). After neutralization of the solution with $NaHCO_3$, the product was extracted with $CHCl_3$ (500 mL). The organic layer was dried ($MgSO_4$) and evaporated to afford a residue, which was crystallized from DMF to give **27** (3.9 g, 86%), mp 208.4 °C. Anal. ($C_{21}H_{25}N_5O_2$) C, H, N.

***cis*-4-[4-[4-[4-[[2-(2,4-Dichlorophenyl)-2-(1*H*-1,2,4-triazol-1-ylmethyl)-1,3-dioxolan-4-yl]methoxy]phenyl]-1-piperazinyl]phenyl]-2,4-dihydro-2-(1-methylethyl)-3*H*-1,2,4-triazol-3-one (62).** To a suspension of NaH (50% dispersion in mineral oil) (0.4 g, 0.0083 mol) in dry Me_2SO (100 mL) was added **27** (3.0 g, 0.0079 mol). after the solution was stirred at 50 °C for 1 h, **1b** (3.2 g, 0.0079 mol) was added, and stirring at 100 °C was continued for 3 h. After dilution with water, the mixture was extracted with CH_2Cl_2; the organic layer was washed with water, dried ($MgSO_4$), and evaporated in vacuo to leave a solid residue. Purification on silica with $CHCl_3/CH_3OH$ (98:2) as the eluent, followed by recrystallization from 4-methyl-2-pentanone, gave **62** (3.5 g, 64%), mp 200.4 °C. Anal. ($C_{34}H_{36}Cl_2N_8O_4$) Cl, N.

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