Researches on Antibacterial and Antifungal Agents, XII[1]:

Analogues of Bifonazole with Two Imidazole Moieties and Related Azoles

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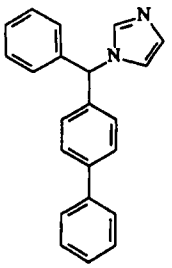
Analogues of bifonazole bearing two imidazole rings and other related azoles have been synthesized and tested as antifungal agents against *Candida albicans* and *Candida spp.*. Only a slight part of the antifungal power of the parent drug is retained by some derivatives as evinced by the comparison of new compounds with bifonazole, miconazole, and ketoconazole.

Antibakterielle und antimykotische Verbindungen, 12. Mitt.[1]: Bifonazol-Analoge mit zwei Imidazol-Gruppen und verwandte Azole

Bifonazol-Analoge mit zwei Imidazolringen und andere verwandte Azole wurden synthetisiert und auf antimykotische Wirksamkeit gegen *Candida albicans* und *Candida ssp.* geprüft. - Ein Vergleich der neuen Verbindungen mit Bifonazol, Miconazol und Ketoconazol zeigt, daß einige der neuen Derivate wirksam sind, aber schwächer wirken als die Bezugssubstanzen.

Our previous studies[1,2] led us to observe that replacement of the biphenyl portion by the 4-(1H-pyrrol-1-yl)phenyl moiety retained the potent antifungal activities of bifonazole (**1**)[3] in compounds **2a-c** (Fig. 1).



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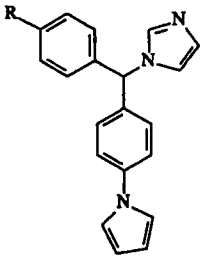


2a R = H
2b R = Cl
2c R = CH_3

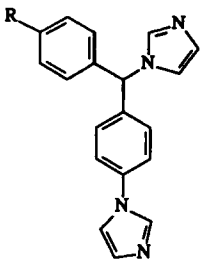
Fig. 1

Furthermore, we observed that the presence of the imidazole ring was crucial for antifungal activities of **2a-c**. In fact, analogues of **2** having the imidazole ring replaced by other azoles or by heteroalicyclic rings lack on the whole antimicrobial activities.

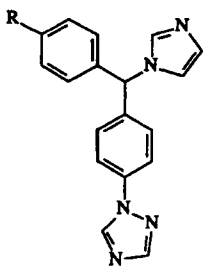
As a part of this program we decided to study the influence on antifungal activities produced by the replacement of pyrrole with the imidazole ring in the molecule of derivatives **2**. We expected bifonazole analogues bearing two imidazole rings to be much more potent than compounds **1** and **2**. This idea was supported by recent studies on new useful antifungal agents having two triazole rings attached to an aryl propanol chain[4].

The new derivatives we prepared and tested as antifungal agents are represented by the general formula **3**. Triazole [**4**] and tetrazole [**5** and **6**] analogues of **3** were also prepared in order to better define the structure-activity relationships of the new bifonazole-like compounds here reported (Fig 2).

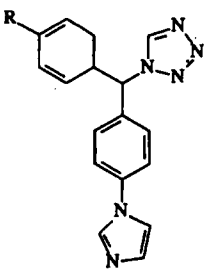
During development of the synthesis pathway leading to **3-6** some intermediate carbinols were transformed into the



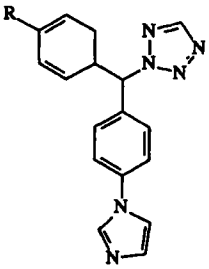
3a R = H
3b R = Cl
3c R = CH_3



4a R = H
4b R = Cl
4c R = CH_3



5a R = H
5b R = Cl
5c R = CH_3



6a R = H
6b R = Cl
6c R = CH_3

Fig. 2

benzyl ethers **7** and **8**, strictly related to econazole (**9a**) and miconazole (**9b**), two clinically important antifungal agents[5] (Fig. 3).

Chemistry

As described in Scheme 1 the known[6,7] fluorobenzophenones **10** were reacted with imidazole. The obtained 4-(1H-imidazol-1-yl)benzophenones **11** were reduced to the related carbinols **12**. Reaction of **12** with $SOCl_2$ afforded the

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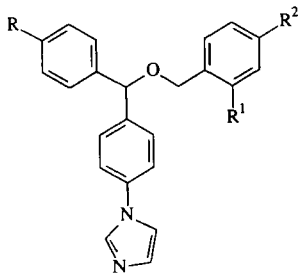

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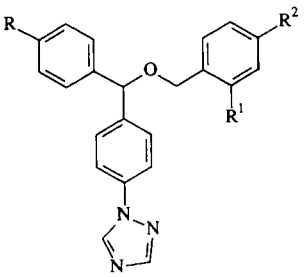
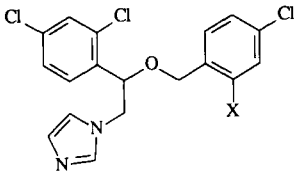


8

7,8	R	R^1	R^2	7,8	R	R^1	R^2	7,8	R	R^1	R^2
a)	H	H	H	d)	Cl	H	H	g)	CH_3	H	H
b)	H	H	Cl	e)	Cl	H	Cl	h)	CH_3	H	Cl
c)	H	Cl	Cl	f)	Cl	Cl	Cl	i)	CH_3	Cl	Cl



9a X = H
9b X = Cl

Fig. 3

crude chloroderivatives hydrochlorides **13**, which were transformed as such into the required bis-imidazole derivatives **3** by reaction with imidazole. Analogous reaction of **13** with tetrazole led to the isomeric derivatives **5** and **6**. Carbinols **12** reacted with the appropriate arylmethyl chlorides to give the ethers **7**.

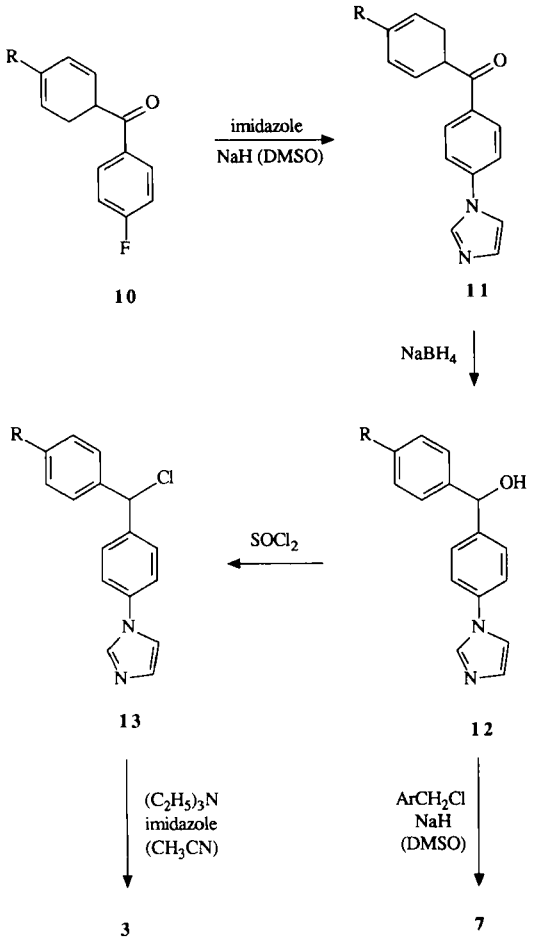
Reaction of **10** with triazole afforded a mixture of ketones **14** and **15**, **14** being predominant. Reduction of **14** furnished the carbinols **16**. These alcohols were transformed into the ethers **8** and into the imidazole-triazole derivatives **4**, respectively, by etherification with the proper benzyl chloride and by treatment with 1,1'-sulfinyl diimidazole (Scheme 2).

Microbiological Part

Materials and Methods

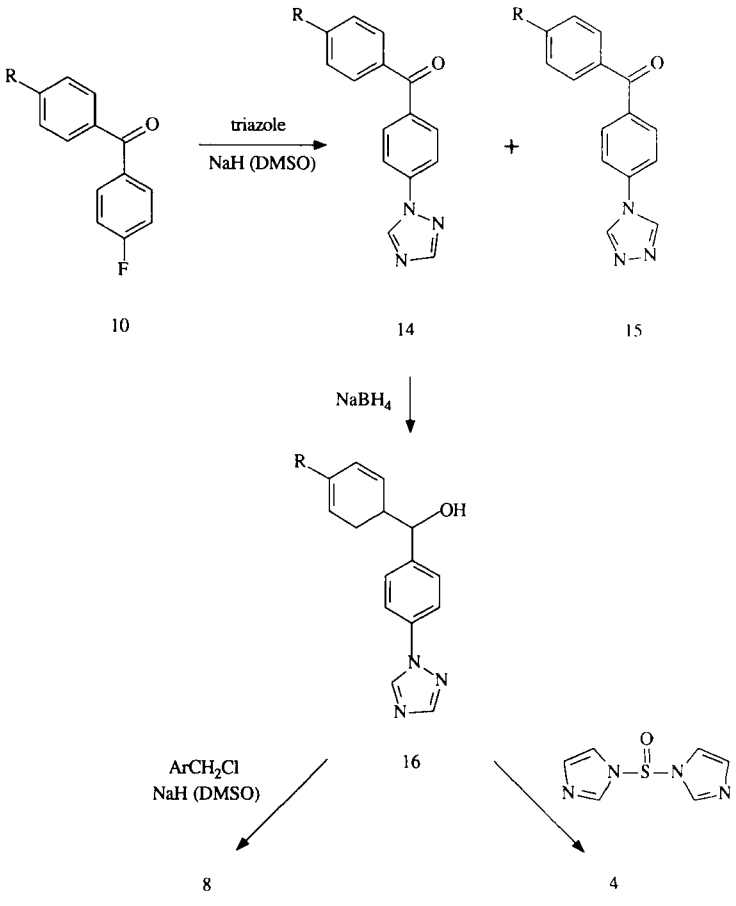
Derivatives **3-8** were tested for antimycotic activities against *Candida albicans* and *Candida* spp.. The antimycotic potency was evaluated by means of the minimal inhibitory concentration (MIC) using the serial dilution test in a liquid nutrient medium.

MIC was defined as the lowest concentration of test substance at which there was no macroscopic colonial growth in comparison with a blank experiment after the preset incubation time. For the preparation of the dilution series 5 mg



10 **11** **12** **13** **3** **7**

Scheme 1



10 14 15 16 8 4

Scheme 2

Table 1: Antimycotic activities of derivatives **3-8** at pH 7.2 against 31 strains of *Candida albicans* and 7 strains of *Candida* spp. (1 *C. glabrata*, 1 *C. tropicalis*, 2 *C. krusei*, 1 *C. pseudotropicalis*, 1 *C. guilliermondii*, 1 *C. parapsilosis*).

Tested substance	*Candida albicans* (31)		Fungi (no of strains tested)	*Candida* spp. (7)		
	R%	X	Range	R%	X	Range
Miconazole	0	3.23	<0.2 - 25	0	0.66	<0.2 - 1.56
Ketoconazole	0	18.84	<0.2 - 200	0	1.61	<0.2 - 6.25
Bifonazole	10	8.90	0.2 - >200	0	9.07	<0.2 - 25
3a**	13	63.88	25 - <200	57	33.73	0.4 - >200
3b**	0	89.51	25 - >200	57	76.04	3.12 - >200
3c**	6	113.79	100 - >200	71	15.62	6.25 - >200
4a**	52	144.27	1.56 - >200	71	2.34	1.56 - >200
4b**	0	49.79	6.25 - 200	43	64.26	0.8 - >200
4c**	94	25	25 - >200	86	0.2	0.2 - >200
5a*	87	200	200 - >200	71	0.98	0.4 - >200
5b*	97	100	100 - >200	71	14.06	3.12 - >200
5c*	94	200	200 - >200	86	6.25	6.25 - >200
6a***	97	100	100 - >200	71	4.68	3.12 - >200
6b*	65	120.59	1.56 - >200	43	106.45	0.8 - >200
6c***	68	170.15	1.56 - >200	57	66.73	0.2 - >200
7a*	81	151.04	6.25 - >200	86	0.8	0.8 - >200
7b	100		>200	100		>200
7c	98	200	200 - >200	86	50	50 - >200
7d*	90	133.33	100 - >200	71	0.3	0.2 - >200
7e*	97	200	200 - >200	71	106.25	12.5 - >200
7f*	87	125	50 - >200	86	100	100 - >200
7g*	94	150	100 - >200	57	76.04	3.12 - >200
7h*	84	130	25 - >200	86	25	25 - >200
7i*	97	200	200 - >200	86	50	50 - >200
8a	97	100	100 - >200	100		>200
8b*	94	103.12	6.25 - >200	86	0.8	0.8 - >200
8c*	97	200	200 - >200	86	6.25	6.25 - >200
8d	94	200	200 - >200	100		>200
8e*	97	200	200 - >200	86	50	50 - >200
8f	100		>200	100		>200
8g	94	25	25 - >200	86	0.2	0.2 - >200
8h*	77	178.57	25 - >200	86	100	100 - >200
8i*	94	200	200 - >200	100		>200

*mononitrate; **dinitrate; ***sulfate

of active ingredient were 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 0.2 to 200 µg/ml. Blanks were prepared in the test medium with the above reported quantities of water and DMSO.

Bifonazole, ketoconazole and miconazole were used as standard controls. Mean MIC values X (C_{max} at least 200 µg/ml) and R% were calculated as reported[2,3]. Strains with MIC > 200µg/ml were regarded as resistant (R).

All the tested microorganisms were preliminarly incubated at 37°C on *Sabouraud* (BBL) dextrose broth. The incubation time was 18 h. Antimicrobial tests were performed on *Mueller-Hinton* (BBL) agar using inocula of 10^3/ml of fungi. Readings of MICs were taken after 36 h incubation at 37°C.

Experiments were carried out using lots of *Candida albicans* and *Candida* spp. freshly isolated from hospitalized patients. The specimens used were: 31 strains of *Candida albicans* and 7 strains of *Candida spp.* (1 *C. glabrata*, 1 *C. tropicalis*, 2 *C. Krusei*, 1 *C. pseudotropicalis*, 1 *C. guilliermondii* and 1 *C. parapsilosis*). Antimicotic activities were evaluated at pH 7.2 (Tab. 1) and at pH 5.8 (Tab. 2).

Results and discussion

As shown by the data of Table 1 (test at pH 7.2) the most potent derivatives (R% = 0) against *Candida albicans* are compounds **4b** and **3b**. However, they did not retain their good activity when screened against *Candida* spp.. Against *Candida albicans* they were found to be superior to bifonazole (**1**) as regard to resistant strains, but their MIC media values (X) were significantly inferior, resulting bifonazole (X = 8.90) > **4b** (X = 49.79) > **3b** (X = 89.51).

Derivatives containing two imidazole rings [**3a-c**] were found in general superior to all other test compounds. Replacement of one imidazole ring with other azoles (triazole, tetrazole) or with chloro(dichloro)benzyloxy moieties

Table 2: Antimycotic activities of derivatives **3-8** at pH 5.8 against 31 strains *Candida albicans* and 7 strains of *Candida* spp. (1 *C. glabrata*, 1 *C. tropicalis*, 2 *C. krusei*, 1 *C. pseudotropicalis*, 1 *C. guilliermondii*, 1 *C. parapsilosis*).

Tested substance	Fungi (n° of strains tested)					
	Candida albicans (31)			*Candida* spp. (7)		
	R%	X	Range	R%	X	Range
Miconazole	0	5.4	0.8 - 12.5	0	3.2	0.4 - 12.5
Ketoconazole	0	35.25	0.2 - 50	0	21.57	0.2 - 50
Bifonazole	0	6.3	0.8 - 6.25	0	10.7	3.12 - 25
3a**	97	200	200 - >200	100		>200
3b**	71	188.88	100 - >200	86	100	100 - >200
3c**	90	200	200 - >200	100		>200
4a**	84	61.33	0.4 - >200	100		>200
4b**	6	40.90	<0.2 - >200	43	131.25	25 - >200
4c**	77	121.42	25 - >200	71	150	100 - >200
5a*	100		>200	100		>200
5b*	100		>200	100		>200
5c*	100		>200	100		>200
6a***	97	200	200 - >200	100		>200
6b*	16	178.84	50 - >200	57	200	200 - >200
6d***	61	118.8	0.2 - >200	71	200	200 - >200
7a*	0	70.46	3.12 - 200	0	139.28	25 - 200
7b	90	137.5	12.5 - >200	100		>200
7c	97	200	200 - >200	100		>200
7d*	55	71.12	0.4 - >200	71	200	200 - >200
7e*	74	58.59	6.25 - >200	86	200	200 - >200
7f*	58	192.30	100 - >200	86	200	200 - >200
7g*	87	87.5	25 - >200	100		>200
7h*	97	12.5	12.5 - 200	100		>200
7i*	68	83.14	0.2 - >200	86	25	25 - >200
8a	77	114.73	3.12 - >200	100		>200
8b*	84	100	100 - >200	100		>200
8c*	81	69.27	3.12 - >200	86	200	200 - >200
8d	94	200	200 - >200	100		>200
8e*	81	12	50 - >200	100		>200
8f	94	200	200 - >200	100		>200
8g	100		>200	100		>200
8h*	65	46.48	0.4 - >200	86	50	5 - >200
8i*	87	131.25	25 - >200	100		>200

*mononitrate; **dinitrate; ***sulfate

abated heavily the antifungal activity in the test compounds, with the only exception for **4b**.

As regard to the relative potency, the bis-imidazoles **3a-c** were more active than the imidazole-triazoles **4a** and **4c**, the latter compounds being comparable in potency to the imidazole-tetrazoles **5a-c** and **6a-c**.

The substituent R at the benzene ring markedly influenced the antifungal activity, which was decreasing in the order Cl > CH_3 > H. A clear example in this sense was furnished by the derivatives **3a-c**, being **3b** (R = Cl) (R% = 0; X = 89.51) superior in activity to **3c** (R = CH_3) (R% = 6; X = 113.79) and this in turn to compound **3a** (R = H) (R% = 13; X = 63.88). Only few exceptions to this rule were observed.

It is noteworthy that some derivatives, e.g. **7a**, were enhancing their activities when the test was performed at pH 5.8. In these conditions decrease of activity was observed for derivatives **4b** and **3b** as revealed by comparing their R% values at pH 7.2 with those obtained at pH 5.8.

In comparison with bifonazole we can observe that all test derivatives were inferior as antifungal agents, much more than the pyrrole related isosteres **2a-c** described in our previous works[1,2].

Again, none of the ethers here described [**7a-i**] and [**8a-i**] was comparable to miconazole either in the imidazole serie [**7a-i**] or in the triazole one [**8a-i**] at pH 7.2. Derivative **7a** exceptionally showed R% = 0 against *Candida albicans* and *Candida* spp., but X values were too high when compared with those of controls (miconazole, ketoconazole and bifonazole).

We can, therefore, conclude that replacement of the pyrrole moiety in **2a-c** with other azoles leads to less active compounds.

Furthermore, we confirmed our previous remark[2] that the presence of the imidazole ring in derivatives **1** and **2a-c** is curcial for antifungal power. In fact, the activity was dramatically abated when a replacement of imidazole by the

Table 3: Preparative and Analytical Data

Nr.	Yield (%)[a]	Formula (mol.weight)	M.p.(°C) Solvent	Analysis (%): Found / Calcd.				
				C	H	N	Cl	S
3a[b]	38	$C_{19}H_{18}N_6O_6$	169-172	53.40	4.22	19.60	-	-
		(426.38)	dry ethanol	53.52	4.26	19.71	-	-
3b[b]	29	$C_{19}H_{17}ClN_6O_6$	160-164	49.79	3.72	18.23	7.52	-
		(460.83)	dry ethanol	49.51	3.71	18.23	7.69	-
3c[b]	30	$C_{20}H_{20}N_6O_6$	115-120 (c)	54.32	4.62	18.78	-	-
		(440.41)		54.54	4.58	19.08	-	-
4a[b]	38	$C_{18}H_{17}N_7O_6$	153-155	50.68	4.40	22.62	-	-
		(427.37)	dry ethanol	50.58	4.01	22.94	-	-
4b[b]	36	$C_{18}H_{16}ClN_7O_6$	77-80	46.52	3.68	21.48	7.42	-
		(461.82)	dry ethanol/$(C_2H_5)_2O$	46.81	3.49	21.23	7.67	-
4c[b]	53	$C_{19}H_{19}N_7O_6$	90-95	51.96	4.55	22.36	-	-
		(441.40)	dry ethanol/$(C_2H_5)_2O$	51.70	4.34	22.21	-	-
5a[d]	27	$C_{17}H_{15}N_7O_3$	141-144	56.11	4.13	26.71	-	-
		(365.34)	dry ethanol	55.88	4.13	26.83	-	-
5b[d]	25	$C_{17}H_{14}ClN_7O_3$	173-175	51.20	3.68	24.56	8.67	-
		(399.79)	dry ethanol	51.06	3.52	24.52	8.86	-
5c[d]	27	$C_{18}H_{17}N_7O_3$	170-173	56.73	4.44	25.64	-	-
		(379.37)	dry ethanol	56.98	4.52	25.85	-	-
6a[e]	26	$C_{17}H_{16}N_6O_4S$	124-127	50.68	3.95	20.78	-	8.10
		(441.41)	dry ethanol	50.98	4.02	20.99	-	8.00
6b[d]	24	$C_{17}H_{14}ClN_7O_3$	140-143	51.32	3.55	24.40	8.99	-
		(399.79)	dry ethanol	51.06	3.52	24.52	8.86	-
6c[e]	27	$C_{18}H_{18}N_6O_4S$	120-125	51.90	4.67	19.98	-	7.48
		(414.44)	dry ethanol	52.16	4.38	20.28	-	7.73
7a[d]	83	$C_{23}H_{21}N_3O_4$	148-151	68.19	5.29	10.40	-	-
		(403.42)	dry ethanol	68.47	5.25	10.42	-	-
7b	72	$C_{23}H_{19}ClN_2O$	72-74	73.51	4.99	7.59	9.68	-
		(374.85)	cyclohexane	73.69	5.11	7.47	9.45	-
7c	74	$C_{23}H_{18}Cl_2N_2O$	72-73	67.45	4.35	6.82	17.28	-
		(409.30)	cyclohexane	67.48	4.43	6.84	17.32	-
7d[d]	69	$C_{23}H_{20}ClN_3O_4$	118-121	62.78	4.46	9.43	8.12	-
		(437.87)	dry ethanol/$(C_2H_5)_2O$	63.08	4.60	9.59	8.09	-
7e[d]	79	$C_{23}H_{19}Cl_2N_3O_4$	139-141	58.36	3.97	8.73	15.07	-
		(472.32)	dry ethanol/$(C_2H_5)_2O$	58.48	4.05	8.89	15.01	-
7f[d]	80	$C_{23}H_{18}Cl_3N_3O_4$	163-165	54.31	3.48	8.05	20.91	-
		(506.77)	dry ethanol	54.50	3.58	8.29	20.99	-
7g[d]	79	$C_{24}H_{23}N_3O_4$	129-131	68.76	5.60	9.99	-	-
		(417.45)	dry ethanol/$(C_2H_5)_2O$	69.05	5.55	10.07	-	-
7h[d]	69	$C_{24}H_{22}ClN_3O_4$	157-159	63.53	4.86	9.29	8.14	-
		(451.91)	dry ethanol/$(C_2H_5)_2O$	63.78	4.90	9.30	7.84	-
7i[d]	96	$C_{24}H_{21}Cl_2N_3O_4$	157-160	59.07	4.30	8.35	14.57	-
		(486.34)	dry ethanol	59.26	4.35	8.64	14.58	-
8a	78	$C_{22}H_{19}N_3O$	103-104	77.16	5.60	12.48	-	-
		(341.40)	cyclohexane	77.39	5.61	12.31	-	-
8b[d]	72	$C_{22}H_{19}ClN_4O_4$	140-141	59.94	4.20	12.53	8.36	-
		(438.86)	dry ethanol	60.20	4.36	12.76	8.07	-
8c[d]	85	$C_{22}H_{18}Cl_2N_4O_4$	123-124	55.81	3.75	11.68	15.17	-
		(473.31)	dry ethanol	55.82	3.83	11.83	14.98	-
8d	80	$C_{22}H_{18}ClN_3O$	137-138	70.25	4.80	11.13	9.58	-
		(375.84)	benzene/cyclohexane	70.30	4.82	11.18	9.43	-
8e[d]	76	$C_{22}H_{18}Cl_2N_4O_4$	111-112	55.77	3.83	11.68	14.79	-
		(473.31)	dry ethanol/$(i\text{-}C_3H_7)_2O$	55.82	3.83	11.83	14.98	-

Table 3: follows

8f[d]	72	$C_{22}H_{17}Cl_3N_4O_4$	133-134	51.96	3.44	10.23	20.96	-
		(507.75)	dry ethanol/$(i\text{-}C_3H_7)_2O$	52.03	3.73	11.03	20.94	-
8g	73	$C_{23}H_{21}N_3O$	122-124	77.54	5.97	11.89	-	-
		(355.42)	cyclohexane	77.42	5.96	11.82	-	-
8h[d]	69	$C_{23}H_{21}ClN_4O_4$	110-111	61.29	4.69	12.62	7.60	-
		(452.88)	dry ethanol	60.99	4.67	12.37	7.82	-
8i[d]	77	$C_{23}H_{20}Cl_2N_4O_4$	126-127	56.86	4.16	11.47	14.68	-
		(487.43)	dry ethanol	56.67	4.13	11.49	14.54	-
11a	94	$C_{16}H_{12}N_2O$	113-114	77.15	4.74	11.52	-	-
		(248.27)	toluene/n-hexane	77.40	4.87	11.28	-	-
11b	89	$C_{16}H_{11}ClN_2O$	161-165	67.74	3.82	10.09	12.48	-
		(282.72)	DMF/water	67.96	3.92	9.90	12.54	-
11c	93	$C_{17}H_{14}N_2O$	157-159	77.64	5.34	10.59	-	-
		(262.30)	DMF/water	77.84	5.38	10.68	-	-
12a	89	$C_{16}H_{14}N_2O$	130-133	76.58	5.76	11.32	-	-
		(250.29)	toluene	76.78	5.64	11.19	-	-
12b	56	$C_{16}H_{13}ClN_2O$	148-150	67.68	4.56	9.73	12.60	-
		(284.73)	toluene/ligroin	67.48	4.60	9.83	12.45	-
12c	72	$C_{17}H_{16}N_2O$	131-133	77.24	6.15	10.54	-	-
		(264.31)	toluene/ligroin	77.25	6.10	10.60	-	-
13a	99	$C_{16}H_{14}Cl_2N_2$ (305.20)	151-155 (c)					
13b	99	$C_{16}H_{13}Cl_3N_2$ (339.65)	190-195 (c)					
13c	99	$C_{17}H_{16}Cl_2N_2$ (319.22)	192-195 (c)					
14a	81	$C_{15}H_{11}N_3O$	128-130	72.46	4.41	17.05	-	-
		(249.26)	ethanol	72.27	4.45	16.86	-	-
14b	81	$C_{15}H_{10}ClN_3O$	193-196	63.50	3.47	14.91	12.74	-
		(283.71)	ethanol	63.49	3.55	14.81	12.49	-
14c	87	$C_{16}H_{13}N_3O$	139-142	72.94	4.90	16.20	-	
		(263.29)	toluene	72.98	4.98	15.96	-	-
15a	6	$C_{15}H_{11}N_3O$	189-192	72.55	4.43	16.71	-	-
		(249.26)	ethanol	72.27	4.45	16.86	-	-
15b	3	$C_{15}H_{10}ClN_3O$	234-237	63.68	3.56	14.56	12.65	-
		(283.71)	DMF/water	63.49	3.55	14.81	12.49	-
15c	8	$C_{16}H_{13}N_3O$	213-216	72.77	4.97	16.08	-	-
		(263.29)	ethanol	72.98	4.98	15.96	-	-
16a	94	$C_{15}H_{13}N_3O$	90-92	71.49	5.34	16.53	-	-
		(251.28)	toluene/ligroin	71.69	5.21	16.72	-	-
16b	82	$C_{15}H_{12}ClN_3O$	134-136	62.80	4.12	14.58	12.49	-
		(285.72)	toluene/petroleum ether	63.05	4.23	14.70	12.40	-
16c	83	$C_{16}H_{15}N_3O$	119-120	72.28	5.73	15.58	-	-
		(265.30)	toluene/petroleum ether	72.43	5.70	15.84	-	-

(a) free base; (b) dinitrate; (c) only washed with dry ethyl ether; (d) mononitrate; (e) sulfate

tetrazole or arylmethyloxy moiety was carried out in our series (derivatives **5a-c** — **8a-c**).

Occasionally, some antifungal activities were evinced for **6c** against *C. guilliermondii* and *C. pseudotropicalis*; these MIC were comparable to those of controls (MIC > 0.2 μg/ml).

Compound **4b**, showing a good activity also at pH 5.8, can be considered the most important among all tested compounds.

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Chemical Experimental Part

M.p.: Electrothermal IA6304 (uncorr.). - IR-spectra (nujol mulls): Perkin Elmer 297. - ^{1}H-NMR-spectra: Varian EM-390 (90 MHz, TMS) - ^{13}C-NMR-spectra: Varian XL-300 MHz. - Column chromatography: silica gel Merck (70-230 mesh) and alumina Merck (70-230 mesh). - TLC: Stratocrom SIF Carlo Erba (silica gel precoated plates with fluorescent indicator) and Stratocrom ALF Carlo Erba (aluminium oxide precoated plates with fluorescent indicator). - Microanalyses: Laboratories of Prof. A. Pietrogrande, University of Padova (Italy). - Organic extracts were dried over anhydrous Na_2SO_4. - Evaporation of solvents under reduced pressure. - Chemical and physical data of compounds **4-8** and **11-16** are reported in Tables 3-5.

Table 4: ^{1}H-NMR Data ($CDCl_3$) of Derivatives **3-8**

Nr.	δ
3a	6.60 (s, 1H, CH [a]), 6.88 (m, 1H, H-C5-imidazole [a]), 6.98-7.72 (m, 13H), 7.90 (m, 1H, H-C2-arylimidazole [b])
3b	6.60 (s, 1H, CH [a]), 6.88 (m, 1H, H-C5-imidazole [a]), 7.00-7.57 (m, 12H), 7.92 (m, 1H, H-C2-arylimidazole [b])
3c	2.32 (s, 3H), 6.53 (s, 1H, CH [a]), 6.87 (m, 1H, H-C5-imidazole [a]), 6.98-7.52 (m, 12H), 7.87 (m, 1H, H-C2-arylimidazole [b])
4a	6.63 (s, 1H, CH [a]), 6.90 (m, 1H, H-C5-imidazole [a]), 7.07-7.60 (m, 9H), 7.70-7.87 (m, 2H), 8.17 (s, 1H, H-C3-triazole [b]), 8.63 (s, 1H, H-C5-triazole [b])
4b	6.60 (s, 1H, CH [a]), 6.88 (s, 1H, H-C5-imidazole [a]), 7.03-7.53 (m, 8H), 7.73-7.87 (m, 2H), 8.15 (s, 1H, H-C3-triazole [b]), 8.65 (s, 1H, H-C5-triazole [b])
4c	2.33 (s, 3H), 6.57 (s, 1H, CH [a]), 6.88 (m, 1H, H-C5-imidazole [a]), 7.00-7.55 (m, 8H), 7.68-7.88 (m, 2H), 8.15 (s, 1H, H-C3-triazole [b]), 8.65 (s, 1H, H-C5-triazole [b])
5a	7.16-7.59 (m, 12H), 7.92 (s, 1H, H-C2-arylimidazole [b]), 8.62 (s, 1H, H-C5-tetrazole)
5b	7.12-7.72 (m, 11H), 7.93 (s, 1H, H-C2-arylimidazole [b]), 8.68 (s, 1H, H-C5-tetrazole)
5c	2.35 (s, 3H), 7.05-7.58 (m, 11H), 7.90 (s, 1H, H-C2-arylimidazole [b]), 8.63 (s, 1H, H-C5-tetrazole)
6a	7.22-7.55 (m, 12H), 7.90 (s, 1H, H-C2-arylimidazole [b]), 8.65 (s, 1H, H-C4-tetrazole)
6b	7.18-7.51 (m, 11H), 7.92 (s, 1H, H-C2-arylimidazole [b]), 8.65 (s, 1H, H-C4-tetrazole)
6c	2.33 (s, 3H), 7.18-7.48 (m, 11H), 7.90 (s, 1H, H-C2-arylimidazole [b]), 8.62 (s, 1H, H-C4-tetrazole)
7a	4.57 (s, 2H), 5.50 (s, 1H), 7.15-7.70 (m, 16H), 7.87 (s, 1H, H-C2-arylimidazole [b])
7b	4.50 (s, 2H), 5.47 (s, 1H), 7.15-7.67 (m, 15H), 7.83 (s, 1H, H-C2-arylimidazole [b])
7c	4.62 (s, 2H), 5.53 (s, 1H), 7.15-7.77 (m, 14H), 7.83 (s, 1H, H-C2-arylimidazole [b])
7d	4.58 (s, 2H), 5.49 (s, 1H), 7.22-7.72 (m, 15H), 7.93 (s, 1H, H-C2-arylimidazole [b])
7e	4.52 (s, 2H), 5.45 (s, 1H), 7.12-7.65 (m, 14H), 7.88 (s, 1H, H-C2-arylimidazole [b])
7f	4.59 (s, 2H), 5.50 (s, 1H), 7.18-7.67 (m, 13H), 7.87 (s, 1H, H-C2-arylimidazole [b])
7g	2.29 (s, 3H), 4.55 (s, 2H), 5.46 (s, 1H), 7.18-7.65 (m, 15H), 7.84 (s, 1H, H-C2-arylimidazole [b])
7h	2.28 (s, 3H), 4.48 (s, 2H), 5.41 (s, 1H), 7.06-7.61 (m, 14H), 7.82 (s, 1H, H-C2-arylimidazole [b])
7i	2.27 (s, 3H), 4.58 (s, 2H), 5.48 (s, 1H), 7.07-7.63 (m, 13H), 7.85 (s, 1H, H-C2-arylimidazole [b])
8a	4.57 (s, 2H), 5.51 (s, 1H), 7.25-7.82 (m, 14H), 8.16 (s, 1H, H-C3-triazole [b]), 8.57 (s, 1H, H-C5-triazole [b])
8b	4.53 (s, 2H), 5.50 (s, 1H), 7.32-7.82 (m, 13H), 8.17 (s, 1H, H-C3-triazole [b]), 8.59 (s, 1H, H-C5-triazole [b])
8c	4.62 (s, 2H), 5.56 (s, 1H), 7.23-7.81 (m, 12H), 8.16 (s, 1H, H-C3-triazole [b]), 8.61 (s, 1H, H-C5-triazole [b])
8d	4.57 (s, 2H), 5.47 (s, 1H), 7.28-7.80 (m, 13H), 8.15 (s, 1H, H-C3-triazole [b]), 8.57 (s, 1H, H-C5-triazole [b])
8e	4.51 (s, 2H), 5.46 (s, 1H), 7.23-7.83 (m, 12H), 8.16 (s, 1H, H-C3-triazole [b]), 8.60 (s, 1H, H-C5-triazole [b])
8f	4.60 (s, 2H), 5.52 (s, 1H), 7.23-7.83 (m, 11H), 8.14 (s, 1H, H-C3-triazole [b]), 8.60 (s, 1H, H-C5-triazole [b])
8g	2.30 (s, 3H), 4.55 (s, 2H), 5.45 (s, 1H), 7.05-7.83 (m, 13H), 8.12 (s, 1H, H-C3-triazole [b]), 8.54 (s, 1H, H-C5-triazole [b])
8h	2.32 (s, 3H), 4.51 (s, 2H), 5.45 (s, 1H), 7.12-7.82 (m, 12H), 8.13 (s, 1H, H-C3-triazole [b]), 8.49 (s, 1H, H-C5-triazole [b])
8i	2.32 (s, 3H), 4.58 (s, 2H), 5.51 (s, 1H), 7.12-7.78 (m, 11H), 8.14 (s, 1H, H-C3-triazole [b]), 8.57 (s, 1H, H-C5-triazole [b])

[a] ^{1}H-NMR of N-diphenylmethylazoles [8]; [b] ^{1}NMR of N-arylazoles [9].

Table 5: ^{13}C Chemical Shifts[a] of Tetrazole in Compounds **5c**, **6c**, 1-Methyl-1,2,3,4-tetrazole[b] and 1-Methyl-1,2,3,5-tetrazole[b]

Compd.	Solvent	C-5	C-4
5c	Chloroform	142.7	
1-Methyl-1,2,3,4-tetrazole	Dioxane	144.2	
6c	Chloroform		153.1
1-Methyl-1,2,3,5-tetrazole	Dioxane		153.4

[a] In parts per million relative to tetramethylsilane; [b] ^{13}C Magnetic Resonance Studies of Azoles [10].

Reaction between fluoroketones **10** *and azoles: synthesis of derivatives* **11**, **14**, *and* **15**

A solution of 4'-substituted-4-fluorobenzophenones **10** (0.10 mol) and imidazole (or triazole) (0.15 mol) in anhydrous DMSO (240 ml) was slowly dropped into a well stirred suspension of NaH (80% in white oil) (0.12 mol) in the same solvent (70 ml). The mixture was heated at 100°C for 17 h.

After cooling, water (1 l) was added and the mixture was treated firstly with ethyl acetate. In the case of imidazole derivatives N-HCl was added until pH 2. The org. extracts were discarded and the aqueous solution was made basic by solid Na_2CO_3 under stirring. The precipitate was collected, washed with water and recrystallized from the appropriate solvent to give **11**. In the preparation of triazole derivatives the ethyl acetate extracts were washed with saturated NaCl solution and, after evaporation of the solvent, chromatographed on silica gel column (ethyl acetate), to give firstly derivatives **14** and then the isomeric azoles **15**.

$NaBH_4$ reduction of ketones **11** *and* **14**: *synthesis of* **12** *and* **16**

A mixture of ketone **11** or **14** (0.1 mol) and $NaBH_4$ (0.1 mol) in THF (320 ml) containing 7 ml of H_2O was heated at reflux for 1 h. After cooling water (80 ml) was added under stirring and the solution was evaporated to

a small volume. Extraction with ethyl acetate and subsequent evaporation of the solvent from the dried solution furnished a residue which was chromatographed on a silica gel column (ethyl acetate) to give **12** or **16**, respectively.

Preparation of crude chloroderivatives **13** *(hydrochlorides)*

A solution of 0.1 mol of carbinols **12** in $SOCl_2$ (125 ml) was refluxed overnight and then evaporated to dryness. Trituration of the residue with anhydrous Et_2O gave **13** as highly hygroscopic hydrochlorides, which were used for the next reaction as such.

General procedures for alkylation of azoles and carbinols

A) Synthesis of derivatives **3**, **5**, *and* **6**

Chloroderivatives **13** (hydrochlorides) (0.01 mol) were added to a solution of the proper azole (0.01 mol) and triethylamine (0.02 mol) in acetonitrile. The mixture was refluxed for 24 h, then concentrated to a small volume, diluted with chloroform and washed with saturated NaCl solution. The org. layer was dried and evaporated to give a residue, which was chromatographed on alumina [$CHCl_3$ for **3a** and **3b**; $CHCl_3$-ethyl acetate (2:1) for **3c**] or silica gel [ethyl acetate for derivatives **5** (second eluates) and **6** (first eluates)].

B) Synthesis of derivatives **7** *and* **8**

A suspension of NaH (80% in white oil) (0.08 mol) and the proper carbinol (**12** or **16**) (0.08 mol) in a mixture of anhydrous THF (38 ml) - DMSO (2 ml) was refluxed for 30 min. After cooling the appropriate arylmethyl chloride (0.08 mol) was added and the mixture refluxed for 1.5 h. Treatment with crushed ice and extraction with Et_2O followed by evaporation of the dried ethereal solution furnished a residue which was purified by passing through a silica gel column (ethyl acetate). Evaporation of the eluates gave **7** or **8**, respectively.

Transformation of carbinols **16** *into derivatives* **4**

$SOCl_2$ (0.016 mol) was dropped while stiring into a cooled solution of imidazole (0.064 mol) in anhydrous acetonitrile (65 ml). After stirring for further 1 h the precipitate was removed by suction and the solution was dropped into a stirred solution of the proper carbinol **16** (0.016 mol) in acetonitrile (100 ml). Stirring was continued for 24 h at room temp., then the solvent was removed. The residue was treated with saturated NaCl solution and $CHCl_3$. After shaking, the org. layer was removed, dried and evaporated to give crude **4**. Purification by chromatography on a silica gel column (ethyl acetate) gave analytically pure **4**.

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