Antifungal Agents, II[1]:

Synthesis and Antifungal Activities of Aryl-1*H*-pyrrol-2-yl-1*H*-imidazol-1-yl-methane Derivatives with Unsaturated Chains

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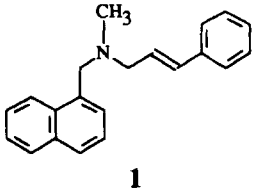
The synthesis and antifungal activities of aryl-1*H*-pyrrol-2-yl-1*H*-imidazol-1-yl-methanes having allyl, crotyl, and acrylate chains linked to the *N*-pyrrole atom and substituted at phenyl ring by Cl, F, CH_3, and NO_2 groups are reported. *In vitro* tests against *Candida albicans* and *Candida spp.* showed 2,4-dichlorophenyl-1-allyl-1*H*-pyrrol-2-yl-1*H*-imidazol-1-yl-methane to be the most potent derivative with activities comparable to those of ketoconazole and slightly inferior to those of bifonazole and miconazole. Some structure-activity relationships are discussed.

Synthese und antimykotische Wirkung von Aryl-1*H*-pyrrol-1*H*-imidazol-1-yl-methan-Derivaten mit ungesättigten Seitenketten

Herstellung und antimykotische Eigenschaften der Titelverbindungen mit Allyl-, Crotyl- und Acrylat-Gruppen am Pyrrol-N-Atom und Cl-, F-, CH_3- und NO_2-substituierten Phenylgruppen werden beschrieben. *In vitro* tests gegen *Candida albicans* und *Candida* ssp. zeigten, daß 2,4-Dichlorphenyl-1-allyl-1*H*-pyrrol-1-yl-1*H*-imidazol-1-yl-methan die wirksamste Verbindung ist. Ihre Wirkung ist mit der von Ketoconazol vergleichbar und etwas schwächer als die von Bifonazol und Miconazol. Einige Struktur-Wirkungsbeziehungen werden diskutiert.

Antifungal agents containing unsaturated chains have received great attention after the discovery of naftifine (**1**), a new lead compound among modern classes investigated as potential chemotherapeutic substances against fungal diseases. Naftifine is actually marketed in some countries and terbinaftine (**2**), a new improved derivative of the allylamine series, is under clinical development. Both derivatives are characterized by the presence of an unsaturated chain in their structure, which was found to be essential for their antimicrobial power[2-4].



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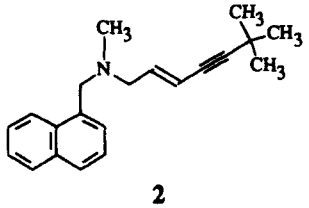
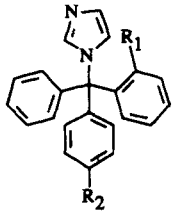
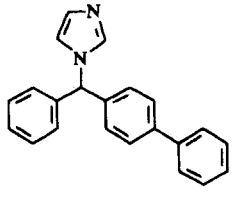


2

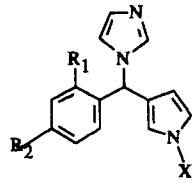
Pursuing our studies[5-11] on pyrrole antimycotics related to clotrimazole (**3**), flutrimazole (**4**), and bifonazole (**5**), we decided to synthesize derivatives of aryl-1*H*-pyrrol-2-yl-1*H*-imidazol-1-yl-methane containing an unsaturated chain linked to the N-atom of the pyrrole ring. The new compounds which share structural features with compounds **1-5** are represented by the general formula **6**. The substituents at the phenyl ring were chosen in the range from electron-releasing to electron-withdrawing groups, with particular reference to chlorine and fluorine. These halogens were capable to enhance the antifungal potency in the imidazole and triazole series, as demonstrated by the high activity shown by clotrimazole, flutrimazole, fluconazole, miconazole, ketoconazole and other analogues.



3 R_1 = H; R_2 = Cl Clotrimazole
4 R_1 = R_2 = F Flutrimazole



5 Bifonazole



R_1 = H, Cl
R_2 = H, Cl, F, CH_3, NO_2
X = H, allyl, crotyl and methoxycarbonylvinyl

6

The antifungal activities of derivatives **6** were tested *in vitro* against *Candida albicans* and *Candida spp.* in comparison with miconazole, bifonazole and ketoconazole, three potent commercially available antimycotic drugs.

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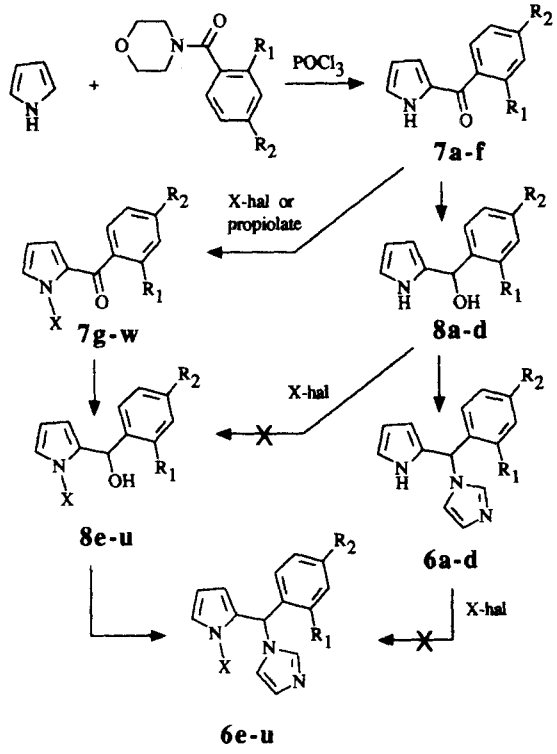
Chemistry

The synthesis of derivatives **6** is depicted in Scheme 1. - Reaction of pyrrole with the proper 4-aroylmorpholine (*Vilsmeier-Haack*) afforded the aroyl-1*H*-pyrrol-2-yl ketones **7a-f**, some of which were reduced to the corresponding carbinols **8a-d** by $NaBH_4$.



R_1 = H, Cl; R_2 = H, Cl, F, CH_3, NO_2, 2,4-Cl_2; X = allyl, crotyl, methoxycarbonylvinyl

Scheme 1

Treatment of **8a-d** with 1,1'-carbonyldiimidazole (CDI) afforded the imidazoles **6a-d**. Attempt to alkylate **6a-d** at the pyrrole-N with allyl bromide/K_2CO_3 was unsuccessful. Therefore, the title imidazoles **6e-u** were prepared starting from ketones **7a-f** which were alkylated to afford compounds **7g-w** which were reduced by $NaBH_4$ to carbinols **8e-u**. These on treatment with CDI afforded the required imidazoles **6e-u**.

Alkylation of **8a-d** to achieve the corresponding alcohols **8e-j** by reaction with allyl bromide/K_2CO_3 failed, whereas alkylation of ketones **7a-f** was easily performed with allyl bromide, crotyl bromide, and by methyl propiolate.

Microbiological Part

Materials and Methods

Derivatives **6a-u** were tested *in vitro* 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 tested 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 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 0.25 to 256 µg/ml. Blanks were prepared with the above reported quantities of water and DMSO.

Bifonazole, miconazole, and ketoconazole were used as standard controls. Mean MIC values nX (C_{max} at least 256 µg/ml) and R% were calculated as reported[5-11]. MIC_{50} and MIC_{90} refer to MIC for 50% and 90% of strains, respectively. Strains with MIC > 256 µg/ml were regarded as resistant (R) and were expressed in percent (%).

All tested microorganisms were preliminarily incubated at 37°C for 18 h on *Sabouraud* (BBL) dextrose broth. The microorganisms were added to media containing the antimycotic agents. Experiments were carried out in *Sabouraud* broth (Difco) at pH 7.2 and 5.8 using inocula of 10^3/ml of fungi. The MICs were determined after 24 h of growth at 37°C.

Candida albicans and *Candida* spp. freshly isolated from hospitalized patients (strains were identified using standard methods). The specimens used were: 40 strains of *Candida albicans* and 12 strains of *Candida spp.* (3 *C. guilliermondii*, 3 *C. lipolytica*, 3 *C. krusei*, and 3 *C. parapsilosis*).

Results and Discussion

The results of the *in vitro* screening of **6a-u** measured at pH 7.2 and pH 5.8 are reported in Tables 4 and 5. Data refer to R%, nX, MIC_{50}, and MIC_{90} values in comparison with those of miconazole, bifonazole and ketoconazole.

At pH 7.2 compounds **6f**, **6j**, **6l**, **6p**, and **6u**, like the control substances, show no resistant strains against *Candida albicans*. The same result, with the exception of compound **6f**, was observed for these derivatives at pH 7.2 against *Candida* spp. Various strains were resistant to all other test compounds.

Data of Table 4 indicate that the most potent compound is the dichloro derivative **6j** which is as potent as ketoconazole and twice less potent than bifonazole and miconazole against either *Candida albicans* or *Candida* spp. Derivatives **6f**, **6l**, **6p**, and **6u** are from four to sixteen times less potent than controls and their activity is decreasing in the order **6p** > **6u**, **6l** > **6f**.

As evinced from data of Table 5 the antifungal powers of derivatives **6** at pH 5.8 are very similar to those observed at pH 7.2. Again derivative **6j** is the most potent test compound, although its potencies were slightly inferior to those of ketoconazole.

Some interesting relationships between chemical structure of compounds **6** and their activities can be drawn from these data.

Chlorine markedly influenced the antifungal activity. A clear example in this sense is furnished by the reciprocal comparison of data of compounds **6a,e,k,q**, **6b,f,l,r** and **6d,j,p,u**. In fact, introduction of Cl at C-4 of the phenyl ring increased the antifungal activity, which became the highest for the 2,4-dichloro derivatives. Replacement of chlorine with fluorine led to less potent derivatives (**6g,m,s**). Similar behaviour was observed when methyl and nitro groups replaced chlorine at C-4 of the phenyl ring.

We can, therefore, state that substituents at the phenyl ring were strongly affecting the antifungal activity, which was decreasing in the order 2,4-Cl_2>4-Cl>4-NO_2>4-F>4-CH_3, 4-H.

A large increase in activity was observed when an unsaturated chain was introduced at the pyrrole-N. The best activity was shown by derivatives bearing the allyl side chain. The high activity observed was retained when crotyl replaced the allyl chain, whereas derivatives with the β-acrylate portion and those deprived of an unsaturated chain were scarcely and/or totally inactive, respectively.

In conclusion, derivatives **6j** and **6p**, which contain 2,4-dichlorophenyl and 1-allyl-1*H*-pyrrol-2-yl or 1-crotyl-1*H*-pyrrol-2-yl moieties, are the most active among the derivatives **6a-u**. Their activities against *Candida albicans* and *Candida spp.* are comparable or slightly inferior to those of ketoconazole and from two to four times inferior to those of miconazole and bifonazole.

Attempts to introduce the unsaturated chains of naftifine and terbinaftine at the *N*-pyrrole position are in progress.

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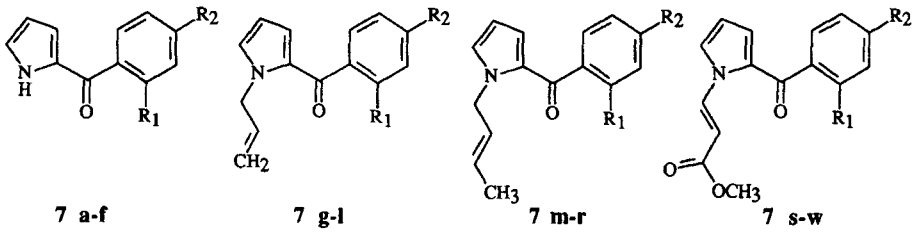
Table 1: Chemical and Physical Data of Derivatives 7



7 a-f **7 g-l** **7 m-r** **7 s-w**

Compd.	R_1	R_2	Yield (%)	Formula (Mol. weight)	MP (°C) Solvent	Analysis (%): Calcd.				
						C	H	N	Cl	F
7a	H	H	100	$C_{11}H_9NO$	78-79	77.17	5.30	8.18		
				171.20	*n*-hexane	77.01	5.27	8.22		
7b	H	Cl	77	$C_{11}H_8ClNO$	117-8	64.25	3.92	6.81	17.24	
				205.65	*n*-hexane	64.19	3.88	6.75	17.31	
7c	H	F	74	$C_{11}H_8FNO$	106-7	69.84	4.26	7.40		10.04
				189.19	*n*-hexane	69.89	4.27	7.33		10.00
7d	H	CH_3	44	$C_{12}H_{11}NO$	118-9	77.81	5.99	7.56		
				185.20	*n*-hexane	77.75	5.91	7.59		
7e	H	NO_2	80	$C_{11}H_8N_2O_3$	166-8	61.11	3.73	12.96		
				216.20	cyclohexane/benzene	61.20	3.77	12.89		
7f	Cl	Cl	22	$C_{11}H_7Cl_2NO$	120-1	55.03	2.94	5.83	29.53	
				240.09	*n*-hexane/benzene	55.12	2.99	5.77	29.60	
7g	H	H	100	$C_{14}H_{13}NO$	oil	79.59	6.20	6.63		
				211.27		79.49	6.16	6.70		
7h	H	Cl	85	$C_{14}H_{12}ClNO$	oil	68.44	4.92	5.70	14.43	
				245.71		68.39	4.91	5.73	14.39	
7i	H	F	75	$C_{14}H_{12}FNO$	oil	73.35	5.28	6.11		8.29
				229.26		73.27	5.22	6.15		8.33
7j	H	CH_3	60	$C_{15}H_{15}NO$	oil	79.97	6.71	6.22		
				225.29		79.90	6.65	6.29		
7k	H	NO_2	92	$C_{14}H_{12}N_2O_3$	89-90	65.62	4.72	10.93		
				256.26	cyclohexane	65.70	4.76	10.87		
7l	Cl	Cl	100	$C_{14}H_{11}Cl_2NO$	110 (dec.)	60.02	3.96	5.00	25.31	
				280.16	cyclohexane	60.11	3.96	4.99	25.27	
7m	H	H	100	$C_{15}H_{15}NO$	oil	79.97	6.71	6.22		
				225.29		79.89	6.69	6.26		
7n	H	Cl	100	$C_{15}H_{14}ClNO$	oil	69.37	5.43	5.39	13.65	
				259.74		69.29	5.39	5.42	13.72	
7o	H	F	90	$C_{15}H_{14}FNO$	oil	74.06	5.80	5.76		7.81
				243.28		73.98	5.71	5.80		7.73
7p	H	CH_3	85	$C_{16}H_{17}NO$	oil	80.30	7.16	5.85		
				239.32		80.37	7.18	5.78		
7q	H	NO_2	100	$C_{15}H_{14}N_2O_3$	oil	66.66	5.22	10.36		
				270.29		66.71	5.25	10.31		
7r	Cl	Cl	100	$C_{15}H_{13}Cl_2NO$	oil	61.24	4.45	4.76	24.10	
				294.18		61.18	4.39	4.80	24.15	
7s	H	H	100	$C_{15}H_{13}NO_3$	oil	70.58	5.13	5.49		
				255.26		70.65	5.20	5.41		
7t	H	Cl	71	$C_{15}H_{12}ClNO_3$	122-3	62.19	4.17	4.83	12.24	
				289.72	cyclohexane	62.13	4.16	4.87	12.27	
7u	H	F	100	$C_{15}H_{13}FNO_3$	141-2	65.93	4.43	5.13		6.95
				273.27	cyclohexane/benzene	65.99	4.47	5.09		6.90
7v	H	CH_3	64	$C_{16}H_{15}NO_3$	119-20	71.36	5.61	5.20		
				269.30	cyclohexane	71.35	5.60	5.19		
7w	Cl	Cl	100	$C_{15}H_{11}Cl_2NO_3$	oil	55.58	3.42	4.32	21.87	
				324.17		55.61	3.44	4.31	21.81	

Experimental Part

M.p.: Büchi 530 (uncorr.).- IR-spectra (nujol mulls): Perkin Elmer 1310.- ^{1}H-NMR-spectra: Varian EM-390 (90 mHz, TMS).- 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 (Al_2O_3 precoated plates with fluorescent indicator).- Microanalyses: Laboratories of Prof. A. Pietrogrande, University of Padova (Italy).- Org. extracts were dried over Na_2SO_4.- Evaporation of solvents under reduced pressure.- Chemical and physical data of compounds **7a-w**, **8a-u**, and **6a-u**: Tables 1-3.

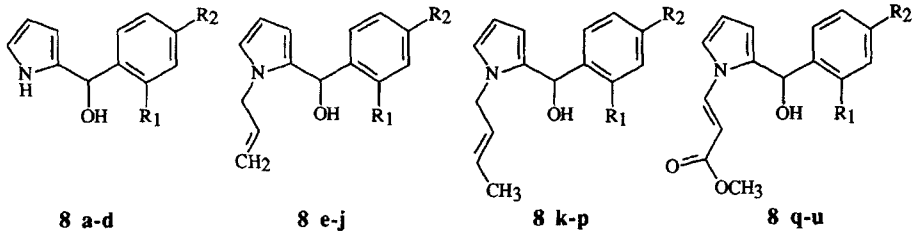
Preparation of 4-morpholinamides[12]

Morpholides were prepared in high yield by treatment of the appropriate acid chloride in CH_2Cl_2 with two equivalents of morpholine and were recrystallized from *n*-hexane/cyclohexane.

Aryl-1H-pyrrol-2-yl ketones **7a-f**[13]

The appropriate amide was dissolved in $POCl_3$ (0.2 ml/mmole of amide), and the solution, protected from moisture, was stirred at room temp. until the formation of the complex was complete. A 0.2 M solution of pyrrole (1 equivalent relative to amide) in anhydrous 1,2-dichloroethane

Table 2: Chemical and Physical Data of Derivatives **8**



8 a-d **8 e-j** **8 k-p** **8 q-u**

Compd.	R_1	R_2	Yield (%)	Formula (Mol. weight)	MP (°C) Solvent	Analysis: Calcd. / Found	C	H	N	Cl	F
8a	H	H	100	$C_{11}H_{11}NO_3$ 173.22	oil		76.28	6.40	8.09		
							76.19	6.38	8.13		
8b	H	Cl	100	$C_{11}H_{10}ClNO_3$ 207.66	oil		63.62	4.85	6.74	17.07	
							63.55	4.80	6.77	17.15	
8c	H	NO_2	100	$C_{11}H_{10}N_2O_3$ 218.21	112-3 cyclohexane		60.55	4.62	12.84		
							60.66	4.66	12.79		
8d	Cl	Cl	100	$C_{11}H_9Cl_2NO$ 242.11	oil		54.57	3.75	5.79	29.29	
							54.70	3.77	5.71	29.20	
8e	H	H	100	$C_{14}H_{15}NO$ 213.18	oil		78.84	7.09	6.57		
							78.91	7.11	6.50		
8f	H	Cl	100	$C_{14}H_{14}ClNO$ 247.73	71-72 *n*-hexane		67.88	5.70	5.65	14.31	
							67.95	5.79	5.58	14.27	
8g	H	F	100	$C_{14}H_{14}FNO$ 231.27	63-64 *n*-hexane		72.71	6.10	6.06		8.21
							72.81	6.12	6.03		8.17
8h	H	CH_3	100	$C_{15}H_{17}NO$ 227.31	oil		79.26	7.54	6.16		
							79.33	7.58	6.11		
8i	H	NO_2	100	$C_{14}H_{14}N_2O_3$ 258.28	oil		65.11	5.46	10.85		
							65.25	5.50	10.80		
8j	Cl	Cl	100	$C_{14}H_{13}Cl_2NO$ 282.17	oil		59.59	4.64	4.96	25.13	
							59.66	4.67	4.96	25.10	
8k	H	H	100	$C_{15}H_{17}NO$ 227.31	70-71 *n*-hexane		79.26	7.54	6.16		
							79.30	7.55	6.12		
8l	H	Cl	100	$C_{15}H_{16}ClNO$ 261.75	91-92 *n*-hexane		68.83	6.16	5.35	13.54	
							68.84	6.16	5.34	13.57	
8m	H	F	100	$C_{15}H_{16}FNO$ 245.30	90-91 *n*-hexane		73.45	6.57	5.71		7.74
							73.53	6.61	5.67		7.69
8n	H	CH_3	86	$C_{16}H_{18}NO$ 240.33	oil		79.97	7.55	5.83		
							80.00	7.57	5.82		
8o	H	NO_2	100	$C_{15}H_{16}N_2O_3$ 272.31	oil		66.16	5.92	10.29		
							66.11	5.89	10.31		
8p	Cl	Cl	100	$C_{15}H_{15}Cl_2NO$ 296.20	oil		60.83	5.10	4.73	23.94	
							60.88	5.11	4.70	23.90	
8q	H	H	100	$C_{15}H_{15}NO_3$ 257.29	116-7 cyclohexane		70.02	5.88	5.44		
							70.00	5.87	5.45		
8r	H	Cl	86	$C_{15}H_{14}ClNO_3$ 291.74	116-7 cyclohexane		61.76	4.84	4.80	12.15	
							61.79	4.87	4.82	12.09	
8s	H	F	100	$C_{15}H_{14}FNO_3$ 275.28	118-20 cyclohexane		65.45	5.13	5.09		6.90
							65.49	5.15	5.00		6.88
8t	H	CH_3	100	$C_{16}H_{17}NO_3$ 271.32	99-101 cyclohexane		70.83	6.32	5.16		
							70.83	6.35	5.14		
8u	Cl	Cl	100	$C_{15}H_{13}Cl_2NO_3$ 326.18	173-4 cyclohexane/benzene		55.24	4.02	4.29	21.74	
							55.31	4.09	4.26	21.71	

was added in one batch to the syrupy complex. After thorough mixing the homogeneous solution was allowed to stand until the azafulvene formation was complete. The mixture was poured into 10% aqueous Na_2CO_3 (25 ml/ml $POCl_3$) and stirred at room temp. for 2 h. The product was isolated from the 1,2-dichloroethane layer and recrystallized from suitable solvent (Table 1).

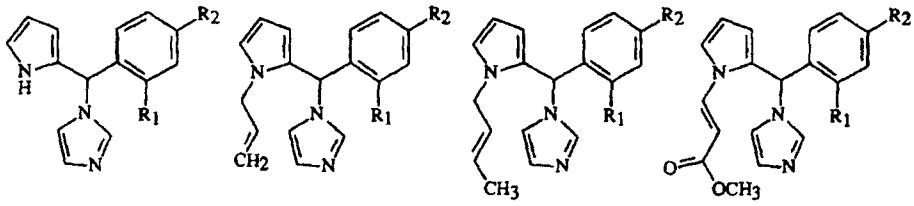
Aryl-1-allyl-1H-pyrrol-2-yl ketones and aryl-1-crotyl-1H-pyrrol-2-yl ketones **7g-r**

A mixture of the proper 2-acylpyrrole (5.0 mmole), K_2CO_3 (10.0 mmole), 18-crown-6 (0.38 mmole), and the appropriate alkyl bromide (10.0 mmole) in anhydrous acetone (100 ml) was stirred at reflux for 24 h. After cooling, the mixture was filtered and the solvent was evaporated. The crude residue was chromatographed (alumina/$CHCl_3$) to give pure **7g-r**.

Aryl-1-methoxycarbonylvinyl-1H-pyrrol-2-yl ketones **7s-w**

A mixture of the proper 2-acylpyrrole (7.5 mmole), methylpropiolate (7.5 mmole) and tetrabutylammonium fluoride (0.38 mmole) in anhydrous THF (100 ml) was stirred at room temp. for 2 h. The mixture was diluted with H_2O (100 ml) and concentrated. The aqueous residue was extracted with $CHCl_3$ (3 x 50 ml) and the org. layers were washed with brine (3 x 50 ml), dried and evaporated. Solid substances were recrystallized from suitable solvents and oils were purified by column chromatography (SiO_2/$CHCl_3$).

Table 3: Chemical and Physical Data of Derivatives **6**



6 a-d **6 e-j** **6 k-p** **6 q-u**

Compd.	R_1	R_2	Formula (Mol. weight)	Yield (%)	MP (°C) Solvent	Analysis (%): Calcd. / Found C	H	N	Cl	F
6a	H	H	$C_{14}H_{12}N_3$ (233.28)	43	125-7 *n*-hexane-benzene	75.31 75.13	5.87 6.00	18.82 18.66		
6b	H	Cl	$C_{14}H_{12}ClN_3$ (257.72)	50	146-7 *n*-hexane-benzene	65.25 65.41	4.69 4.76	16.30 16.08	13.76 13.75	
6c	H	NO_2	$C_{14}H_{12}N_4O_2$ (268.28)	33	140-2	62.68 62.42	4.51 4.43	11.93 12.36		
6d	Cl	Cl	$C_{14}H_{11}Cl_2N_3$ (292.17)	40	164-7 pet. ether-diet. ether	57.55 57.82	3.79 3.93	14.38 14.13	24.27 24.12	
6e	H	H	$C_{17}H_{17}N_3$ (263.35)	100	oil	77.54 77.38	6.51 6.48	15.96 16.14		
6f	H	Cl	$C_{17}H_{16}ClN_3$ (297.79)	71	99-100 pet. ether-*n*-hexane	68.57 68.00	5.42 5.58	14.11 14.25	11.91 11.17	
6g	H	F	$C_{17}H_{16}FN_3$ (281.34)	60	oil	72.58 72.41	5.73 5.69	14.94 15.07		6.75 6.83
6h	H	CH_3	$C_{18}H_{19}N_3$ (277.37)	62	oil	77.95 77.78	6.90 6.85	15.15 15.37		
6i	H	NO_2	$C_{17}H_{16}N_4O_2$ (308.34)	86	oil	66.22 66.15	5.23 5.19	10.38 10.52		
6j	Cl	Cl	$C_{17}H_{15}Cl_2N_3$ (332.24)	86	oil	61.46 61.71	4.55 4.63	12.65 12.67	21.34 20.99	
6k	H	H	$C_{18}H_{19}N_3$ (277.37)	100	oil	77.95 78.30	6.90 6.93	15.15 14.77		
6l	H	Cl	$C_{18}H_{18}ClN_3$ (311.82)	84	oil	69.34 69.68	5.82 5.85	13.48 13.41	11.37 11.06	
6m	H	F	$C_{18}H_{18}FN_3$ (295.36)	77	oil	73.20 73.01	6.14 6.03	14.23 14.31		6.43 6.65
6n	H	CH_3	$C_{19}H_{21}N_3$ 291.40) *	75	oil	78.32 78.12	7.26 7.19	14.42 14.69		
6o	H	NO_2	$C_{18}H_{18}N_4O_2$ (322.37)	75	oil	67.07 66.99	5.63 5.61	9.93 10.07		
6p	Cl	Cl	$C_{18}H_{17}Cl_2N_3$ (346.26)	75	oil	62.44 62.50	4.95 4.99	12.14 11.96	20.48 20.55	
6q	H	H	$C_{18}H_{17}N_3O_2$ (307.36)	70	oil	70.34 70.55	5.58 5.67	13.67 13.72		
6r	H	Cl	$C_{18}H_{16}ClN_3O_2$ (341.09)	50	oil	63.33 63.41	4.73 4.75	12.32 12.35	10.25 10.21	
6s	H	F	$C_{18}H_{16}FN_3O_2$ (325.35)	90	oil	66.43 66.57	4.96 5.01	12.92 12.85		5.84 5.67
6t	H	CH_3	$C_{19}H_{19}N_3O_2$ (321.38)	86	oil	71.01 70.88	5.96 5.82	13.07 13.00		
6u	Cl	Cl	$C_{18}H_{15}Cl_2N_3O_2$ (377.25)	90	149-52 diet. ether-benzene	57.46 57.59	4.02 4.11	11.17 11.33	18.85 18.81	

Table 4: Antimycotic Activity of Derivatives **6** at pH 7.2[a]

Tested substance	Fungi (n° of tested strain)									
	Candida albicans (40)					*Candida* spp (12)[b]				
	R%	$n\bar{X}$	MIC_{50}	MIC_{90}	Range	R%	$n\bar{X}$	MIC_{50}	MIC_{90}	Range
6a	100	>256				100	>256			
6b	100	>256				100	>256			
6c	100	>256				100	>256			
6d	9.5	97.53	64	128	32->256	50	152	64	256	64->256
6e	100	>256				100	>256			
6f	0	52.5	32	64	16-64	16.6	116.3	16	64	16->256
6g	26.19	196.95	128	>256	64->256	50	225	64	256	64->256
6h	100	>256				100	>256			
6i	12.5	77.65	32	128	16->256	75	200	256	256	32->256
6j	0	5.17	4	8	1-8	0	12.1	8	8	4-32
6k	35	219.2	128	>256	64->256	90	371	>256	256	64->256
6l	0	40.95	32	64	4-128	0	28.70	32	64	32-128
6m	19.04	123.42	128	256	16->256	50	231	64	256	64->256
6n	100	>256				100	>256			
6o	12.5	65.2	32	128	8-256	75	184	64	128	32->256
6p	0	10.35	8	32	1-32	0	16.8	4	16	4-64
6q	14.2	131.4	64	256	32->256	50	345.6	256	>256	64->256
6r	52.3	163.04	128	256	32->256	66.6	202.6	256	256	64->256
6s	25	169	128	>256	8->256	50	229.1	64	256	64->256
6t	20	103.6	32	>256	16->256	75	264	256	>256	32->256
6u	0	46.8	16	64	16-128	0	41.6	16	128	16-128
Ketoconazole	0	7.9	2	4	0.25-32	0	10.9	8	16	2-32
Miconazole	0	2.9	2	4	0.25-16	0	5.9	4	8	1-8
Bifonazole	0	3.1	1	4	1-16	0	4.5	1	8	0.5-8

[a] The *in vitro* activities are expressed as the minimum inhibitory concentration (MIC) in µg/ml. R%: percentage of resistant strains; MIC_{50} and MIC_{90}: MIC for 50% and 90% of strain, respectively.
[b] Respectively, 3 *C. guilliermondii*, 3 *C. lipolytica*, 3 *C. krusei*, and 3 *C. parapsilosis*.

Table 5: Antimycotic Activity of Derivatives **6** at pH 5.8[a]

Tested substance	Fungi (n° of tested strain)									
	Candida albicans (40)					*Candida* spp (12)[b]				
	R%	$n\bar{X}$	MIC_{50}	MIC_{90}	Range	R%	$n\bar{X}$	MIC_{50}	MIC_{90}	Range
6a	100	>256				100	>256			
7b	100	>256				100	>256			
7c	100	>256				100	>256			
7d	10.7	114.1	64	128	32->256	50	161	64	256	64->256
7e	100	>256				100	>256			
7f	0	48.5	32	64	16-128	20	121.4	16	64	16->256
7g	31.2	202.1	128	>256	64->256	50	261.5	64	256	64->256
7h	100	>256				100	>256			
7i	14.9	81.2	32	128	16->256	75	213.5	256	256	32->256
7j	0	9.3	4	16	2-32	0	15.3	8	16	4-32
7k	38	230.2	128	>256	64->256	90	359	256	>256	64->256
7l	0	41.5	32	64	8-128	0	31.3	32	64	16-128
7m	21.3	133.4	128	256	16->256	50	287.1	128	256	128->256
7n	100	>256				100	>256			
7o	15.2	71.1	32	128	16-256	75	190.1	64	128	64->256
7p	0	15.8	8	32	4-32	0	17.8	8	16	4-64
7q	16.1	14.01	64	256	32->256	50	341.3	256	>256	64->256
7r	50	149.1	128	256	32-256	66.6	231.5	256	256	64->256
7s	28.3	181.2	128	256	16->256	50	221.7	64	256	64->256
7t	21.9	141.7	32	>256	32->256	75	274	256	>256	32->256
7u	0	48.1	16	64	16-128	0	50.1	32	128	6-128
Ketoconazole	0	4.5	4	16	0.25-16	0	10.9	2	32	2-32
Miconazole	0	3.9	2	4	0.25-16	0	3.1	1	4	0.25-8
Bifonazole	0	3.6	2	4	0.5-16	0	6.5	2	8	0.5-8

[a] The *in vitro* activities are expressed as the minimum inhibitory concentration (MIC) in µg/ml. R%: percentage of resistant strains; MIC_{50} and MIC_{90}: MIC for 50% and 90% of strains, respectively.
[b] Respectively, 3 *C. guilliermondii*, 3 *C. lipolytica*, 3 *C. krusei*, and 3 *C. parapsilosis*.

Table 6: ^{1}H-NMR Data of derivatives **6**

Compd	solvent	^{1}H-NMR (δ)
6a	$CDCl_3$	5.90 (m, 1H, H-C4 pyrrole), 6.15 (m, 1H, H-C3 pyrrole), 6.63 (s, 1H, =CH-), 6.80-6.93 (m, 2H, pirrole and imidazole), 6.97-7.63(m, 7H, benzene and other imidazole), 10.38 (s, broad, 1H, NH).
6b	$CDCl_3$	5.90 (m, 1H, H-C4 pyrrole), 6.19 (m, 1H, H-C3 pyrrole), 6.47 (s, 1H, =CH-), 6.73-6.97 (m, 2H, pirrole and imidazole), 6.97-7.23(m, 4H, benzene and other imidazole), 7.37 (d, 2H, other benzene), 10.43 (s, broad, 1H, NH).
6c	DMF-d_7	5.89 (m, 1H, H-C4 pyrrole), 6.07 (m, 1H, H-C3 pyrrole), 6.91 (m, 1H, H-C5 pirrole), 7.04 (m, 2H, imidazole), 7.13 (s, 1H, =CH-), 7.36 (d, 2H, benzene), 7.67 (s, 1H, H-C2 imidazole), 8.30 (d, 2H, other benzene), 11.33 (s, broad,1H, NH).
6d	DMF-d_7	5.73 (m, 1H, H-C4 pyrrole), 6.07 (m, 1H, H-C3 pyrrole), 6.77-7.20 (m, 5H, H-C5 pirrole, =CH- and imidazole), 7.37-7.73 (m, 3H, benzene), 11.25 (s, broad,1H).
6e	CCl_4	4.24 (m, 2H, CH_2=CH-CH_2-), 4.93 (dd, J=16.5 Hz, 1H, CH_2=CH-CH_2-), 5.15 (dd, J=10.5 Hz, CH_2=CH-CH_2-), 5.60 (m, 1H, H-C4 pyrrole), 5.66-5.95 (m, 1H, CH_2=CH-CH_2-), 5.98 (m, 1H, H-C3 pyrrole), 6.43 (s, 1H, =CH-), 6.52 (m, 1H, H-C5 pyrrole), 6.72 (d, broad, 1H, imidazole), 6.88-7.42 (m, 7H, other imidazole and benzene).
6f	CCl_4	4.27 (m, 2H, CH_2=CH-CH_2-), 4.77-5.20 (m, 2H, CH_2=CH-CH_2-), 5.72 (m, 1H, H-C4 pyrrole), 5.76-6.05 (m, 1H, CH_2=CH-CH_2-), 6.11 (m, 1H, H-C3 pyrrole), 6.47 (s, 1H, =CH-), 6.72 (m, 1H, H-C5 pyrrole), 6.88-7.42 (m, 8H, imidazole and benzene).
6g	CCl_4	4.24 (m, 2H, CH_2=CH-CH_2-), 4.91 (dd, J=16.5 Hz, 1H, CH_2=CH-CH_2-), 5.16 (dd, J=10.5 Hz, CH_2=CH-CH_2-), 5.57 (m, 1H, H-C4 pyrrole), 5.65-5.92 (m, 1H, CH_2=CH-CH_2-), 5.98 (m, 1H, H-C3 pyrrole), 6.40 (s, 1H, =CH-), 6.62 (m, 1H, H-C5 pyrrole), 6.70 (d, broad, 1H, imidazole), 6.90-7.07 (m, 5H, imidazole and benzene), 7.17 (s, 1H, imidazole).
6h	CCl_4	2.33 (s, 3H, CH_3-ph), 4.22 (m, 2H, CH_2=CH-CH_2-), 4.77-5.30 (m, 2H, CH_2=CH-CH_2-), 5.53-6.07(m, 3H, CH_2=CH-CH_2-, H-C4 and H-C3 pyrrole), 6.38(s, 1H, =CH-), 6.52-6.76 (m, 2H, H-C5 pyrrole and imidazole), 6.80-7.30 (m, 6H, other imidazole and benzene).
6i	CCl_4	4.32 (m, 2H, CH_2=CH-CH_2-), 4.92 (dd, J=16.5 Hz, 1H, CH_2=CH-CH_2-), 5.15 (dd, J=10.5 Hz, CH_2=CH-CH_2-), 5.56 (m, 1H, H-C4 pyrrole), 5.62-5.95 (m, 1H, CH_2=CH-CH_2-), 6.01 (m, 1H, H-C3 pyrrole), 6.58-6.82 (m, 3H, H-C5 pyrrole and imidazole), 6.97 (s, 1H, =CH-), 7.18 (d, 2H, benzene), 7.42 (s, 1H, H-C2 imidazole), 8.16 (d, 2H, other benzene).
6j	CCl_4	4.27 (m, 2H, CH_2=CH-CH_2-), 5.00 (dd, J=16.5 Hz, 1H, CH_2=CH-CH_2-), 5.14 (dd, J=10.5 Hz, CH_2=CH-CH_2-), 5.54 (m, 1H, H-C4 pyrrole), 5.60-5.93 (m, 1H, CH_2=CH-CH_2-), 6.00 (m, 1H, H-C3 pyrrole), 6.60-6.80 (m, 4H, =CH-, H-C5 pyrrole and imidazole), 6.95 (s, 1H, H-C2 imidazole), 7.15-7.33 (m, 2H, H-C5 H-C6 benzene) 7.43 (d, 1H, benzene).
6k	CCl_4	1.73 (m, 3H, CH_3-CH=CH-CH_2-), 4.26 (m, 2H, =CH-CH_2-), 5.38-5.67 (m, 3H, CH_3-CH=CH-CH_2- and H-C4 pyrrole), 5.97 (m, 1H, H-C3 pyrrole), 6.47 (s, 1H, =CH-), 6.62 (m, 1H, H-C5 pyrrole), 6.73 (d, broad, 1H, imidazole), 6.92-7.63 (m, 7H, other imidazole and benzene).
6l	CCl_4	1.67 (m, 3H, CH_3-CH=CH-CH_2-), 4.23 (m, 2H, CH_2=CH-CH_2-), 5.27-5.73 (m, 3H, CH_3-CH=CH-CH_2- and H-C4 pyrrole), 5.97 (m, 1H, H-C3 pyrrole), 6.33-7.50 (m, 9H, =CH-, H-C5 pyrrole, imidazole and benzene).
6n	CCl_4	1.60 (m, 3H, CH_3-CH=CH-CH_2-), 4.24 (m, 2H, =CH-CH_2-), 5.32-5.67 (m, 3H, CH_3-CH=CH-CH_2- and H-C4 pyrrole), 5.87 (m, 1H, H-C3 pyrrole), 6.43 (s, 1H, =CH-), 6.52 (m, 1H, H-C5 pyrrole), 6.68 (d, broad, 1H, imidazole), 6.87-7.08 (m, 5H, imidazole and benzene), 7.17 (s, 1H, imidazole).
6o	CCl_4	1.63 (m, 3H, CH_3-CH=CH-CH_2-), 2.32 (s, 3H, CH_3-ph), 4.13 (m, 2H, =CH-CH_2-), 5.07-5.63 (m, 3H, CH_3-CH=CH-CH_2- and H-C4 pyrrole), 5.92 (m, 1H, H-C3 pyrrole), 6.38 (s, 1H, =CH-), 6.57 (m, 1H, H-C5 pyrrole), 6.67 (s, broad, 1H, imidazole), 6.77-7.10 (m, 6H, other imidazole and benzene).
6p	CCl_4	1.64 (m, 3H, CH_3-CH=CH-CH_2-), 4.33 (m, 2H, =CH-CH_2-), 5.32-5.67 (m, 3H, CH_3-CH=CH-CH_2- and H-C4 pyrrole), 5.97 (m, 1H, H-C3 pyrrole), 6.60-6.83 (m, 3H, H-C5 pyrrole and imidazole), 6.97 (s, 1H, =CH-), 7.05-7.40 (m, 3H, H-C2 imidazole and benzene), 8.14 (d, 2H, other benzene).
6q	CCl_4	1.55 (m, 3H, CH_3-CH=CH-CH_2-), 4.27 (m, 2H, =CH-CH_2-), 5.33-5.60 (m, 3H, CH_3-CH=CH-CH_2- and H-C4 pyrrole), 5.97 (m, 1H, H-C3 pyrrole), 6.57-6.80 (m, 4H, =CH-, H-C5 pyrrole and imidazole), 6.95 (s, 1H, H-C2 imidazole), 7.18 (d, broad, 1H, H-C5 benzene), 7.23 (dd, 1H, H-C6 benzene), 7.45 (d, 1H, H-C3 benzene).
6r	$CDCl_3$	3.70 (s, 3H, CH_3-OCO), 5.81 (m, 1H, H-C4 pyrrole), 5.87 (d, J=15 Hz, 1H, CO-CH=CH-N), 6.27 (m, 1H, H-C3 pyrrole), 6.67 (s, 1H, =CH-), 6.86 (d, broad, 1H, imidazole), 6.94-7.53 (m, 8H, H-C5 pyrrole, imidazole and benzene), 7.74 (d, 1H, CO-CH=CH-N).
6s	CCl_4	3.58 (s, 3H, CH_3-OCO), 5.72 (m, 1H, H-C4 pyrrole), 5.78 (d, J=15 Hz, 1H, CO-CH=CH-N), 6.17 (m, 1H, H-C3 pyrrole), 6.67-7.50 (m, 9H, =CH-, H-C5 pyrrole, imidazole and benzene), 7.68 (d, J=15 Hz, 1H, CO-CH=CH-N).
6t	$CDCl_3$	3.58 (s, 3H, CH_3-OCO), 5.69 (m, 1H, H-C4 pyrrole), 5.75 (d, J=15 Hz, 1H, CO-CH=CH-N), 6.17 (m, 1H, H-C3 pyrrole), 6.67-7.23 (m, 9H, =CH-, H-C5 pyrrole, imidazole and benzene), 7.32 (s, 1H, H-C2 imidazole), 7.68 (d, J=15 Hz, 1H, CO-CH=CH-N).
6u	CCl_4	2.35 (s, 3H, CH_3-ph), 3.62 (s, 3H, CH_3-OCO), 5.72 (m, 1H, H-C4 pyrrole), 5.77 (d, J=15 Hz, 1H, CO-CH=CH-N), 6.16 (m, 1H, H-C3 pyrrole), 6.67-7.40 (m, 9H, =CH-, H-C5 pyrrole, imidazole and benzene), 7.66 (d, J=15 Hz, 1H, CO-CH=CH-N).
6w	$CDCl_3$	3.72 (s, 3H, CH_3-OCO), 5.11 (d, J=15 Hz, 1H, CO-CH=CH-N), 6.17-7.83 (m, 10H, =CH-, H-C5 pyrrole, imidazole and benzene), 8.00 (d, J=15 Hz, 1H, CO-CH=CH-N).

Carbinols **8a-u**

A mixture of the appropriate ketone **7** (5.0 mmole) and $NaBH_4$ (10.0 mmole) in methanol (50 ml) was stirred at room temp. for 2 h. The mixture was diluted with H_2O (50 ml) and concentrated. Extraction with $CHCl_3$ (3 x 50 ml) and evaporation of the solvent from the dried solution furnished a residue which was recrystallized from suitable solvent or chromatographed ($SiO_2/CHCl_3$).

Imidazoles **6a-u**

A mixture of the appropriate carbinol **8** and 1,1-carbonyldiimidazole (10% excess) in anhydrous acetonitrile was stirred at room temp. for 2 h. The mixture was diluted with H_2O and concentrated. Extraction with ethyl acetate and evaporation of the solvent furnished a residue which was chromatographed (alumina/$CHCl_3$) to give pure **6**.

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