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Original paper

Research on anti-bacterial and anti-fungal agents II. Synthesis and anti-fungal activity of new(*1H*-imidazol-1-ylmethyl)-benzenamine derivatives*

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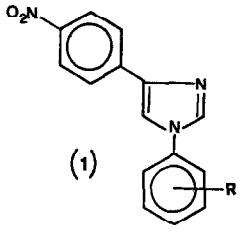
Summary — The synthesis and *in vivo* and *in vitro* anti-fungal activities of new (*1H*-imidazol-1-ylmethyl)benzenamine derivatives are reported. Anti-microbial data in comparison with miconazole show that many compounds exhibit an interesting anti-mycotic activity.

Résumé — **Recherche sur des agents anti-bactériens et anti-fongiques II. Synthèse et activité anti-fongique de nouveaux dérivés de la (*1H*-imidazolyl-1 méthyl)-benzénamine.** *On a préparé de nouveaux dérivés de la (*1H*-imidazol-1-ylméthyl)-benzénamine. Leur activité comme fongicides* in vivo *et* in vitro *est présentée. De nombreux dérivés ont montré une bonne activité parfois comparable à celle du miconazole.*

imidazole anti-fungal agents / anti-fungal activity / (*1H*-imidazol-1-ylmethyl)benzenamine derivatives

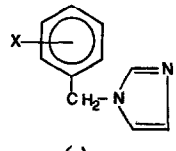
Introduction

In our previous work concerning compounds containing an imidazole ring, we reported the synthesis and the anti-microbial activity of compounds with general structure **1** and **2** [1, 2].



(1)

R = 4 Cl; 4 CH_3; 4 OCH_3; 2 OCH_3; 3,5 CH_3; 4 $COOC_2H_5$; 4 COOH; 4 CH_3; H



(2)

a) X = 2 NH_2; 2 N=CH-Ph_5; 2 NH-CH_2-Ph_5

b) X = 4 NH_2; 4 N=CH-Ph_5; 4 NH-CH_2-Ph_5

Encouraged by the observed *in vitro* anti-fungal activity of compounds **3**—**7**, we decided to extend our synthesis program to compounds with the general structure **2**, which was further supported by data, published by other authors such as Zirngibl [3] Godefroi [4, 5] and Strehlke and Kessler [6—10]. Strehlke in particular showed that *N*-(2,4-dichlorobenzyl)-2-(1-imidazolyl)aniline and *N*-(2,4-dichlorobenzyl)-4-(1-imidazolyl)aniline had interesting anti-fungal activities.

First of all, we wanted to study the structure—activity relationships based upon the following three fundamental parameters: 1) the introduction of an unsubstituted imidazole nucleus not directly connected with the phenyl ring; 2) the presence of an amine group on the phenyl ring in *ortho*, *meta* and *para* positions; 3) the introduction of suitable substituents on the amine group in accordance with the published data and our previous research on pyrrolnitrin analogues [11—13].

Herein, we report the synthesis and the anti-fungal *in vitro* activities of the *3*-(*1H*-imidazol-1-ylmethyl)-benzenamine derivatives **8**—**11** and of the *2*-, *3*- and *4*-(*1H*-imidazol-1-ylmethyl)benzenamides **12**, **13** and **15**. We also report the anti-fungal *in vivo* activities of some *meta* derivatives which showed good activity *in vitro*. Finally, we report the anti-fungal *in vivo* activity of **3** in order to compare the active isomeric compounds **3** and **9**.

Chemistry

Synthetic pathways for the title compounds are illustrated in Scheme 1. *3*-(*1H*-imidazol-1-ylmethyl)benzenamine **9** was used as the starting material. The preparation of **9**

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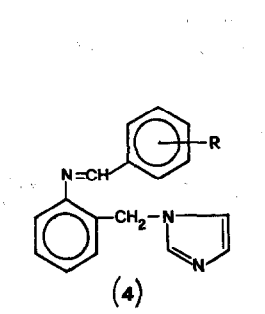
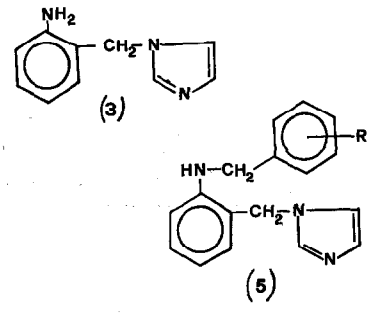
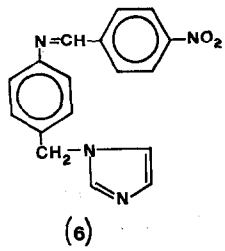
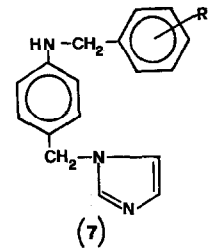


R= 4 NO_2; 4 Cl; 3 NO_2; 2,4 Cl



R= 4 NO_2; 2 Cl; 2,4 Cl

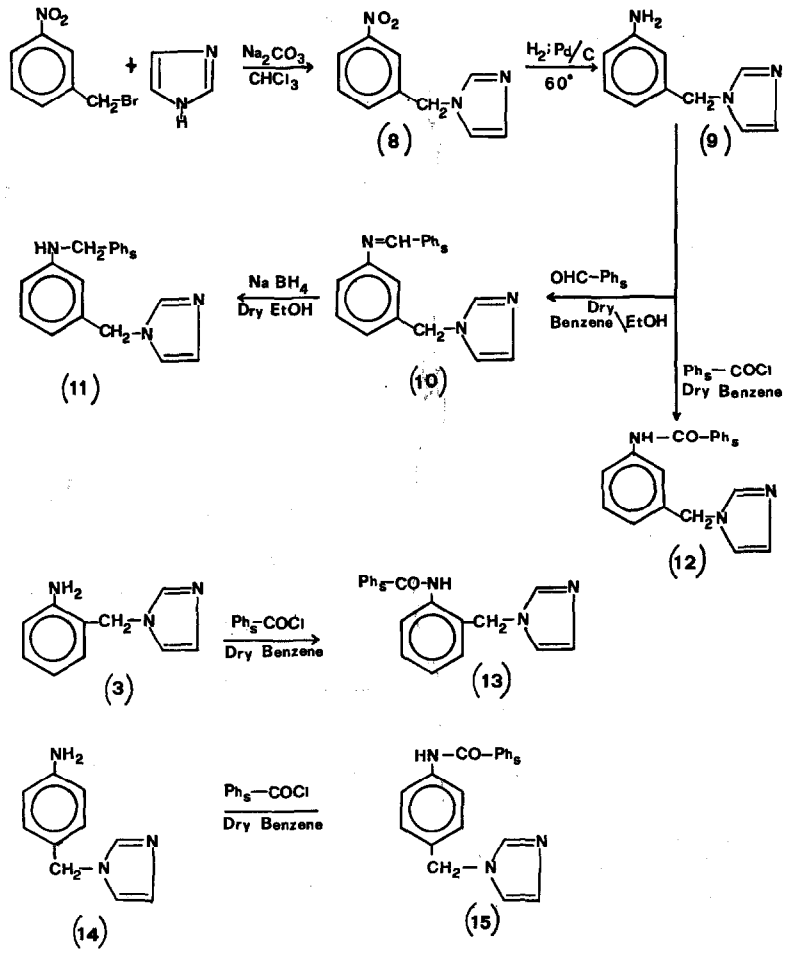




R= 2 Cl ; 4 Cl

was accomplished by catalytic hydrogenation on (Pd/C, 10%) of 1-(3-nitrobenzyl)imidazole **8** which was obtained from the reaction between 3-nitrobenzyl bromide and imidazole in dry chloroform in the presence of sodium carbonate. The reaction between *3*-(*1H*-imidazol-1-ylmethyl)-benzenamine **9** and the appropriate benzaldehydes afforded the Schiff bases **10**, which were further reduced with sodium borohydride in dry ethanol to the corresponding amines **11**. From the reaction between appropriate acid chlorides and *3*-(*1H*-imidazol-1-ylmethyl)benzenamine **9**, the amides **12** were obtained in quite good yield. Compounds **13** and **15** were prepared in the same way from the corresponding aniline derivatives, which were prepared as previously reported [2].

The structure of derivatives **8**—**13** was confirmed by elemental analyses and spectral data. The IR, NMR and Mass spectra are in agreement with the proposed structures. Compounds **10** and **11**, in particular, showed the NMR chemical shifts and a characteristic fragmentation in agreement with the previously reported values for the corresponding *2*- or *4*-(*1H*-imidazol-1-ylmethyl)benzenamine derivatives [2].



Scheme 1.

Results and Discussion

In vitro *activity*

The results of the anti-fungal screening are listed in Tables I—IV. Compounds **10g, 10h, 10i, 15o** and **9** exhibited some activity against *Candida albicans* while **13e** and **10h** showed activity against *Candida sp.* **11a, 11f** and **11h** were more active against *Candida albicans* and *Candida sp.* Among the tested derivatives, the most active compound was **13o** which approached miconazole. The remaining compounds showed poor anti-fungal activity.

In vivo *activity*

The results of the anti-fungal screening are reported in Table V. Lesions treated with **3** disappeared after 4 days of treatment. On the 8th day, all compounds except **13o** showed a positive effect compared to the placebo. On the contrary, areas treated with compound **13o** and placebo were nearly similar after 10 days of therapy.

From data reported here, the following conclusions can be drawn: 1) *in vivo* and *in vitro* activities are not in agreement; 2) the most active derivative *in vivo*, **3**, was *in vitro* ($R\% = 24$, $n\bar{X} = 134.5$, range conc. 25—200 μg/ml against *C. albicans*; $R\% = 89$, $n\bar{X} = 25$, range conc. 25—200 μg/ml against *C. sp.* [2]) less active than compound **13o** (the most active *in vitro*) which was *in vivo* practically inactive; 3) the above and previous [2] anti-microbial data allow us to confirm that the order of anti-fungal activity for the (*1H*-imidazol-1-ylmethyl)benzenamine derivatives is *ortho* > *meta* > *para*. This is in contrast with literature data reported by Strehlke with reference to *N*-(2,4-dichlorobenzyl-2-(1-imidazolyl)-aniline and *N*-(2,4-dichlorobenzyl)-4-(1-imidazolyl)aniline, but in agreement with the observations pointed out by Strehlke with reference to 2-, 3- or 4-(1-imidazolyl-methyl)-phenols which can be considered as isosteric compounds of the (*1H*-imidazol-1-ylmethyl)benzenamine derivatives; 4) all derivatives **12, 13** and **15** were considered inactive except **13o** which *in vitro* showed nearly the same activity as miconazole; 5) the compounds **10** were found to be less active than the corresponding amino derivatives 11.

Table I. Anti-mycotic activity of miconazole and compounds **15a—o** against 25 strains of *Candida albicans* and 7 strains of *Candida sp.*[a] at pH 7.2.

Compound	*Candida albicans*			*Candida sp.*		
	$R\%$	$n\bar{X}$	range (μg/ml)	$R\%$	$n\bar{X}$	range (μg/ml)
Miconazole		1.15	<0.2—3.12		0.97	<0.2—1.56
15a	76	158.33	50—>200	100		>200
15b	72	91.96	3.12—>200	100		>200
15c	80	160	100—>200	100		>200
15d	84	150	100—>200	100		>200
15e	64	100.52	1.56—>200	71	200	200—>200
15f	88	200	200—>200	100		>200
15g	76	83.33	25—>200	100		>200
15h	76	142.18	3.12—>200	86	50	50—>200
15i	68	143.75	50—>200	100		>200
15l	72	109.37	3.12—>200	86	200	200—>200
15m	88	200	200—>200	100		>200
15n	80	125	25—>200	100		>200
15o	44	126.45	1.56—>200	100		>200

[a]2 strains of *C. parapsilosis*, 1 of *C. utilis*, 1 of *C. wiswanathii*, 1 of *C. guilliermondii*, 1 of *C. kruzei* and 1 of *C. pseudotropicalis*.

Table II. Anti-mycotic activity of miconazole and compounds **13a—o** against 13 strains of *Candida albicans* and 7 strains of *Candida sp.*[a] at pH 7.2.

Compound	*Candida albicans*			*Candida sp.*		
	$R\%$	$n\bar{X}$	range (μg/ml)	$R\%$	$n\bar{X}$	range (μg/ml)
Miconazole		2.3	<0.2—6.25		0.5	<0.2—0.8
13a	69	125	100—>200	86	200	200—>200
13b	69	87.52	<0.2—>200	43	137.5	50—>200
13c	85	150	100—>200	71	100	100—>200
13d	85	50	50—>200	86	100	100—>200
13e	30	156.25	6.25—>200		173.21	12.5—200
13f	69	150	100—>200	71	106.25	12.5—>200
13g	61	122.66	0.8—>200	71	112.5	25—>200
13h	69	112.5	25—>200	86	200	200—>200
13i	69	156.25	25—>200	43	115.62	12.5—>200
13m	54	71.90	0.2—>200	100		>200
13n	77	67.77	0.2—>200	86	100	100—>200
13o		11.23	0.8—50		13.61	1.56—25
13l	77	166.6	100—>200	100		>200

[a]2 strains of *C. parapsilosis*, 1 of *C. utilis*, 1 of *C. wiswanathii*, 1 of *C. guilliermondii*, 1 of *C. kruzei* and 1 of *C. pseudotropicalis*.

Table III. Anti-mycotic activity of miconazole and compounds **12a—o** against 27 strains of *Candaida albicans* and 8 strains of *Candida sp.*[a] at pH 7.2.

Compound	*Candida albicans*			*Candida sp.*		
	$R\%$	$n\bar{X}$	range (μg/ml)	$R\%$	$n\bar{X}$	range (μg/ml)
Miconazole		5.38	<0.2—12.5		0.50	<0.2—1.50
12a	89	116.66	50—>200	100		>200
12b	96	200	200—>200	100		>200
12c	93	200	200—>200	100		>200
12d	85	200	200—>200	62.5	166.66	100—>200
12e	78	166.66	100—>200	50	175	100—>200
12f	78	158.33	50—>200	62.5	133.33	100—>200
12g	85	118.75	25—>200	100		>200
12h	89	133.33	200—>200	37.5	200	200—>200
12i	85	100	50—>200	75	200	200—>200
12l	85	175	100—>200	87.5	200	200—>200
12m	78	133.33	50—>200	75	125	50—>200
12n	14	145.31	6.25—>200	25	166.66	100—>200
12o	96	100	100—>200	100		>200

[a]3 strains of *C. parapsilosis*, 1 of *C. kruzei*, 1 of *C. wiswanathii*, 1 of *C. pseudotropicalis*, 1 of *C. rugosa* and 1 of *C. guilliermondii*.

Table IV. Anti-mycotic activity of miconazole and compounds **8, 9, 10a—i, 11a—i**, against 15 strains of *Candida albicans* and 6 strains of *Candida sp.*[a] at pH 7.2.

Compound	*Candida albicans*			*Candida sp.*		
	$R\%$	$n\bar{X}$	range (μg/ml)	$R\%$	$n\bar{X}$	range (μg/ml)
Miconazole		5.45	<0.2—12.5		0.55	<0.2—1.56
8	53	96.42	6.25—>200	75	100	100—>200
9	7	134.97	3.12—>200		200	>200
10a	66	137.5	25—>200	75	25	25—>200
10b	40	90.97	6.25—>200	75	3.12	3.12—>200
10c	33	150.62	6.25—>200	75	0.4	0.4—>200
10d	28	140.31	3.12—>200	25	150	50—>200
10e	73	165	25—>200	75	50	50—>200
10f	20	130.72	6.25—>200	25	134.37	3.12—>200
10g		82.18	1.56—200	25	100.52	1.56—>200
10h	7	88.56	0.8—>200		153.12	12.5—200
10i	7	84.59	3.12—>200	25	108.33	25—>200
11a		81.5	3.12—>200		82.5	12.5—>200
11b	28	125	50—>200	50	125	50—>200
11c	40	155.55	100—>200	75	100	100—>200
11d	47	115.87	0.4—>200	25	141.66	25—>200
11e	87	125	50—>200	100		>200
11f		156.57	12.5—200		130	50—200
11g	47	112.5	25—>200	25	134.37	3.12—>200
11h		41.83	0.4—200		150	50—200
11i	85	75	50—200	100		>200

[a]1 strain each of *C. parapsilosis, C. guilliermondii, C. kruzei, C. lypolytica, C. rugosa* and *C. macedoniensis.*

Table V. Protective action on epidermic lesions in rabbits infected with strains of *Candida Albicans 6.*

Day	Placebo	Miconazole	**3**	**9**	**11a**	**11f**	**11h**	**13o**
2	100	100	100	100	100	100	100	100
3	100	100	80	100	100	100	100	100
4	100	100	40	100	100	100	100	100
5	100	100	—	100	100	100	100	100
6	100	90	—	90	90	90	90	100
7	100	80	—	80	80	80	80	90
8	100	65	—	65	65	65	65	90
9	100	25	—	25	25	25	25	85
10	100	—	—	—	—	—	—	85

Values are shown in decreasing order (as a percentage of number of controls) of diameter of lesions in comparison with placebo.

Experimental protocols

Chemistry

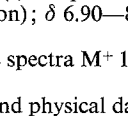
Melting points uncorrected were taken on a Fisher—Johns apparatus. Infrared spectra (nujol mulls) were run on a Perkin—Elmer spectrophotometer 297. The NMR spectra were recorded on a Varian EM 390 (90 MHz) spectrometer, using deuterochloroform as the solvent and TMS as the internal standard. Mass spectra were obtained with a Hewlett—Packard HP 5980A spectrometer operating at 70 eV. All compounds were analyzed for C, H, N and, when present, Cl, Br, F. The analyzed values were within $\pm$0.4 of the calculated values. Elemental analyses were performed by A. Pietrogrande, Padova, Italy. Merck aluminum oxide (II—III, according to Brockmann) was used for chromatographic purification.

1-(3-Nitrobenzyl)imidazole ***8***

A suspension of imidazole (13.6 g, 0.2 mol), 3-nitrobenzyl bromide

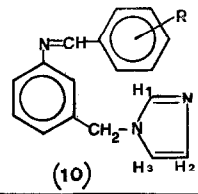
(Aldrich) (43.2 g, 0.2 mol) and sodium carbonate (21.2 g, 0.2 mol) in 200 ml of dry chloroform was heated at reflux for 6 h with stirring. The solid was filtered and subsequently the organic layer was washed with water and evaporated. The oily residue was dissolved in 1 M HCl and the acid layer was extracted with chloroform which was discarded. The acid layer was made alkaline (pH 10) with sodium carbonate. The resulting precipitate was filtered and dissolved in chloroform. The organic layer was washed with water and dried (Na_2SO_4). The evaporation of the solvent gave a solid (70% yield) which, after crystallization from CCl_4, melted at 95—97°C (lit. 88—89°C from ethylacetate) [15] IR: 1520 and 1340 cm^{-1} (ν NO_2).

3-*(1H-Imidazol-1-ylmethyl)benzenamine* **9**
A solution of 1-(3-nitrobenzyl)imidazole **8** (17.9 g, 0.088 mol) in 150 ml of ethylacetate was hydrogenated at 60°C (1 atm.) in the presence of 400 mg of 10% palladium on charcoal. When the theoretical amount of H_2 had been taken up the mixture was filtered in order to remove the catalyst and the filtrate was evaporated under reduced pressure to give a solid residue (80% yield) which was crystallized from ethylether (mp: 73—75°C). IR: 3460 and 3420 cm^{-1} (ν NH_2).

Preparation of Schiff bases **10**
To a solution of 0.007 mol of the appropriate benzaldehyde and 0.0066 mol of **9** in 100 ml of dry ethanol were added 50 ml of dry benzene and two drops of glacial acetic acid. The mixture was heated at reflux for 24 h. The water formed during the reaction was eliminated by a Dean—Stark apparatus containing anhydrous sodium sulfate. Evaporation of the solvent gave a residue which was crystallized from suitable solvent. NMR $CDCl_3$: δ 5.36—5.40 (s, —CH_2—Im); δ 6.90—6.94 (s, H_3 proton); δ 7.16—7.23 (s, H_2 proton); δ 7.70—7.79 (s, H_1 proton); δ 6.90—8.60 (m, Ar protons); δ 8.80—8.90 (s, —CH=N—). Mass spectra M^+ 100% = M-67 (67 = MW of N ). Chemical and physical data for compounds **10** are reported in Table VI.

N-*(Benzyl)-3-(1H-imidazol-1-ylmethyl)benzenamine* **11**
A solution of $NaBH_4$ (0.009 mol) in 20 ml of dry ethanol was added dropwise at room temperature to a stirred solution of 0.003 mol of appropriate Schiff bases **10** in 20 ml of dry ethanol. Thereupon the mixture was heated with stirring for 2 h at reflux and subsequently evaporated under reduced pressure. The residue was treated with water and chloroform. The organic layer was separated, washed with water, dried on anhydrous sodium sulfate and evaporated. The residue was dissolved in ethylacetate and passed on an aluminum oxide column (⌀ = 2 cm; h = 50 cm). The ethylacetate eluates were discarded then elution was carried out with ethanol. Evaporation of ethanol eluates afforded a solid which was crystallized from suitable solvent. IR: 3420 cm^{-1} (ν NH). NMR $CDCl_3$: δ 4.20—4.31 (d, J = 6 cps, —CH_2—NH—); δ 5.00—5.20 (s, —CH_2—Im); δ 6.00—6.41 (t, J = 6 cps, —CH_2—NH—); δ 6.50—6.75 (s, H_3 proton); δ 6.90—7.25 (s, H_2 proton); δ 7.65—7.78 (s, H_1 proton); δ 6.30—7.70 (m, Ar protons). Mass spectra M^+ 100% = M-172 (172 = MW of HN—Ph—CH_2—Im). Chemical and physical data for compound **11** are reported in Table VII.

Table VI.

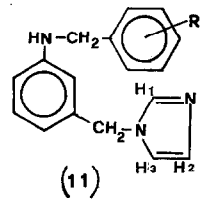


(10)

Compd.	R	Yield %	Recryst. solvent	mp °C	Formula
10a	2-Cl	50	—	[a]	$C_{17}H_{14}N_3Cl$
10b	4-NO_2	65	benzene	147—149	$C_{17}H_{14}N_4O_2$
10c	3,4,5-OCH_3	50	benzene	135—138	$C_{20}H_{21}N_3O_3$
10d	4-$N(CH_3)_2$	40	benzene	160—163	$C_{19}H_{20}N_4$
10e	4-$NHCOCH_3$	50	ethylacetate	159—160	$C_{19}H_{18}N_4O$
10f	2,4-Cl	60	cyclohexane	119—120	$C_{17}H_{13}N_3Cl_2$
10g	3-NO_2	45	benzene—light petr.	91—92	$C_{17}H_{14}N_4O_2$
10h	4-Cl	50	cyclohexane	109—111	$C_{17}H_{14}N_3Cl$
10i	2-NO_2	50	benzene—light petr.	92—93	$C_{17}H_{14}N_4O_2$

[a]bp: 153°C/0.035 mm Hg.

Table VII.



(11)

Compd.	R	Yield %	Recryst. solvent	mp °C	Formula
11a	2-Cl	40	cyclohexane	85—86	$C_{17}H_{16}N_3Cl$
11b	4-NO_2	50	benzene—light petr.	104—106	$C_{17}H_{16}N_4O_2$
11c	3,4,5-OCH_3	40	benzene—cyclohexane	115—116	$C_{20}H_{23}N_3O_3$
11d	4-$N(CH_3)_2$	40	cyclohexane	100—102	$C_{19}H_{22}N_4$
11e	4-$NHCOCH_3$	50	benzene	178—180	$C_{19}H_{20}N_4O$
11f	2,4-Cl	50	cyclohexane	100—104	$C_{17}H_{15}N_3Cl_2$
11g	3-NO_2	50	benzene	176—178	$C_{17}H_{16}N_4O_2$
11h	4-Cl	60	cyclohexane	107—109	$C_{17}H_{16}N_3Cl$
11i	2-NO_2	40	cyclohexane	38—40	$C_{17}H_{16}N_4O_2$

(1H-Imidazol-1-ylmethyl)benzenamides ***12, 13 and 15***

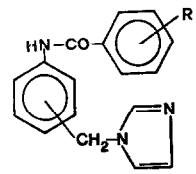
A solution of the appropriate acid chloride (0.012 mol) in 20 ml of dry benzene was dropped slowly into a well-stirred solution of the appropriate (*1H*-imidazol-1-ylmethyl)benzenamine derivatives **3**, **9**, or **14** (0.012 mol) and triethylamine (0.012 mol) in 60 ml of dry benzene at room temperature, then the solution was heated at reflux for 18 h. The solvent was removed under reduced pressure and the solid was washed with water and the residual precipitate was collected on a filter and washed with water and with light petroleum. Finally the crude solid was crystallized from suitable solvent. IR: 3400 cm^{-1} (broad) (ν NH); 1680—1640 cm^{-1} (ν CO). Chemical and physical data for compounds **12**, **13** and **15** are reported in Table VIII.

Microbiological assays

In vitro *activity*

Derivatives **8**, **9**, **10a—i**, **11a—i**, **12a—o**, **13a—o** and **15a—o** were tested against various strains of *Candida albicans* and various strains of different *Candida sp.* Miconazole was used as the reference compound. The minimum inhibitory concentration (*MIC*) was determined using the method of progressive double dilution in solid media [14]. Data were recorded after 36 h of incubation at 37°C. Test substances for the experiments were dissolved in dimethyl sulfoxide (DMSO) (5 mg/ml); further dilution in the test medium furnished the required concentration ranging from 0.1 to 200 μg/ml. The cultures were obtained on Sabouraud (B.B.L.) after 18 h of incubation at 37°C. Tests were carried out using Sabouraud agar (B.B.L.); inocula were 10^3 for *Candida*. Medium *MIC* values $n\overline{X}$ (C_{max} at least 200 μg/ml) were calculated by the equation: $n\overline{X} = \Sigma i(s_i \cdot c_i)/s_t$; where s_i is the numbe of sensitive strains at the given concentration c_i and s_t is the whole number of sensitive strains. Strains with *MIC* > 200 μg/ml are regarded as resistant (*R*) and are expressed in percentage by the equation: $R(\%) = (N_t - N_s)/N_t \times 100$; where N_t is the whole number of tested strains and N_s is the number of sensitive strains. The following species of fungi and their different strains isolated from various clinical specimens were tested: 80 *Candida albicans* strains, 8 *Candida parapsilosis* strains, 2 *Candida utilis* strains, 3 *Candida wiswanathii* strains, 4 *Candida guilliermondii* strains, 4 *Candida kruzei* strains, 3 *Candida pseudo-*

Table VIII.



Compd.	R	—CH_2—Im	Yield %	Recryst. solvent	mp °C	Formula
13a	2-NO_2, 4-Cl	*ortho*	50	ethanol—water (1:1)	156—158	$C_{17}H_{13}N_4O_3Cl$
13b	3-NO_2	*ortho*	60	methanol	199—201	$C_{17}H_{14}N_4O_3$
13c	4-NO_2	*ortho*	50	water	209—210	$C_{17}H_{14}N_4O_3$
13d	2-Cl	*ortho*	80	acetone	168—170	$C_{17}H_{14}N_3OCl$
13e	3-Cl	*ortho*	80	acetone	161—162	$C_{17}H_{14}N_3OCl$
13f	4-Cl	*ortho*	80	methanol	170—172	$C_{17}H_{14}N_3OCl$
13g	2,4-Cl	*ortho*	80	acetone	168—169	$C_{17}H_{13}N_3OCl_2$
13h	4-F	*ortho*	80	chloroform	180—181	$C_{17}H_{14}N_3OF$
13i	4-Br	*ortho*	80	methanol	200—202	$C_{17}H_{14}N_3OBr$
13l	H	*ortho*	50	acetone	141—142	$C_{17}H_{15}N_3O$
13m	3,4,5-OCH_3	*ortho*	50	benzene	165—168	$C_{20}H_{21}N_3O_4$
13n	2,4-NO_2	*ortho*	40	acetone	170—172	$C_{17}H_{13}N_5O_5$
13o	3,5—NO_2	*ortho*	40	acetone	194—196	$C_{17}H_{13}N_5O_5$
12a	2-NO_2, 4-Cl	*meta*	55	ethanol	123—125	$C_{17}H_{13}N_4O_3Cl$
12b	3-NO_2	*meta*	40	ethanol	153—154	$C_{17}H_{14}N_4O_3$
12c	4-NO_2	*meta*	40	ethanol	220—221	$C_{17}H_{14}N_4O_3$
12d	2-Cl	*meta*	40	ethanol	175—177	$C_{17}H_{14}N_3OCl$
12e	3-Cl	*meta*	45	ethanol—water (1:1)	169—170	$C_{17}H_{14}N_3OCl$
12f	4-Cl	*meta*	50	ethanol	190—191	$C_{17}H_{14}N_3OCl$
12g	2,4-Cl	*meta*	40	ethanol—water (1:1)	157—159	$C_{17}H_{13}N_3OCl_2$
12h	4-F	*meta*	50	ethanol—water (1:1)	160—162	$C_{17}H_{14}N_3OF$
12i	4-Br	*meta*	50	ethanol—water (1:1)	200—202	$C_{17}H_{14}N_3OBr$
12l	H	*meta*	45	ethanol—water (1:1)	169—170	$C_{17}H_{15}N_3O$
12m	3,4,5-OCH_3	*meta*	30	ethanol—water (1:1)	135—136	$C_{20}H_{21}N_3O_4$
12n	2,4-NO_2	*meta*	50	ethanol—water (1:1)	229—232	$C_{17}H_{13}N_5O_5$
12o	3,5-NO_2	*meta*	70	ethanol—water (1:1)	231—232	$C_{17}H_{13}N_5O_5$
15a	2-NO_2, 4-Cl	*para*	60	ethanol	142—143	$C_{17}H_{13}N_4O_3Cl$
15b	3-NO_2	*para*	70	ethanol	222—224	$C_{17}H_{14}N_4O_3$
15c	4-NO_2	*para*	50	methanol	245—247	$C_{17}H_{14}N_4O_3$
15d	2-Cl	*para*	40	ethanol	206—208	$C_{17}H_{14}N_3OCl$
15e	3-Cl	*para*	80	ethanol	188—189	$C_{17}H_{14}N_3OCl$
15f	4-Cl	*para*	50	ethanol—water (1:1)	256—258	$C_{17}H_{14}N_3OCl$
15g	2,4-Cl	*para*	50	ethanol	248—249	$C_{17}H_{13}N_3OCl_2$
15h	4-F	*para*	70	ethanol	232—233	$C_{17}H_{14}N_3OF$
15i	4-Br	*para*	80	ethanol	251—252	$C_{17}H_{14}N_3OBr$
15l	H	*para*	60	methanol	198—200	$C_{17}H_{15}N_3O$
15m	3,4,5-OCH_3	*para*	50	methanol	235—236	$C_{20}H_{21}N_3O_4$
15n	2,4-NO_2	*para*	80	ethanol—water (1:1)	235—238	$C_{17}H_{13}N_5O_5$
15o	3,5-NO_2	*para*	80	ethanol—water (1:1)	280—283	$C_{17}H_{13}N_5O_5$

tropicalis strains, 2 *Candida rugosa* strains, 1 *Candida lypolytica* strain and 1 *Candida macedoniensis* strain.

In vivo *activity*

Six male New Zeland albino rabbits (1.8—2.0 kg) were used. Eight area abrasions (1 cm^2/each) for placebo, miconazole and 6 test compounds (**3, 9, 13o, 11a, 11f** and **11h**) were prepared on the back sheared with an electric razor (Aesculap rasant) with glass—paper (no. 3) and then infected with strains of *Candida albicans 6*. 24 h after inoculation, the infected areas were topically treated with a solution (50 μg/ml) of the compounds **3, 9, 13o, 11a, 11f, 11h,** miconazole and placebo supplemented with 0.5% benzyl alcohol in water. The animals were treated topically every 12 h for 10 consecutive days. The diameter and area of the lesions were determined once daily, according to the method proposed by Simonetti [16] and expressed as a percentage value in comparison with the placebo.

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