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Short communication

Studies on anti-*Candida* agents with a pyrrole moiety. Synthesis and microbiological activity of some 3-aminomethyl-1,5-diaryl-2-methyl-pyrrole derivatives

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Summary — The synthesis and anti-*Candida* activity of some 3-aminomethyl-1,5-diaryl-2-methyl-pyrrole derivatives are reported. Some derivatives show a rather strong anti-*Candida* activity. On the basis of experimental results, microbiological activity of 1,5-diarylpyrroles appears to be mainly related to aminic nitrogen lone pair availability of C3 substituent of the pyrrole nucleus. The C5 and N1 substituents play an important role in modulating biological activity. Some structure–activity relationships are proposed.

pyrrole / anti-*Candida* agent / *N*-methylpiperazine / pyrrolidine / dimethylamine / imidazole / structure–activity relationship

Introduction

In our previous papers [1–5], we investigated the antimicrobial activity against *Candida* strains of several [(1-alkyl), (1-aryl) and (1-arylalkyl)]-3-carboxamido-2-methyl-pyrrole derivatives **1**. The evaluation of antimicrobial data of the proposed compounds allowed us to point out that only *N*-methylpiperazinamide **7c** showed a remarkable activity. These results are in agreement with the antimycotic properties of some 1 substituted 4-methylpiperazines, as reported by Chinn *et al* [6], and with the observation that the piperazine nucleus is included in several antifungal derivatives such as fluorene-9-carboxamides **2**, ketoconazole **3**, terconazole **4**, itraconazole **5** and in some antibacterial quinolones **6** (fig 1).

Since we suppose the activity of our structures is mainly related to non-bonded electrons of nitrogen on C3 substituent, in the present paper we describe the synthesis and the anti-*Candida* activity of the compounds **20–29**, related to the previously reported 4-methyl-piperazinamides **7c** [1–4], the compounds **30–39** and **40–45** (fig 2), containing a basic nitrogen atom not included in a piperazine nucleus, and the compounds **58–63** and **64–65** (fig 2) with a less avail-

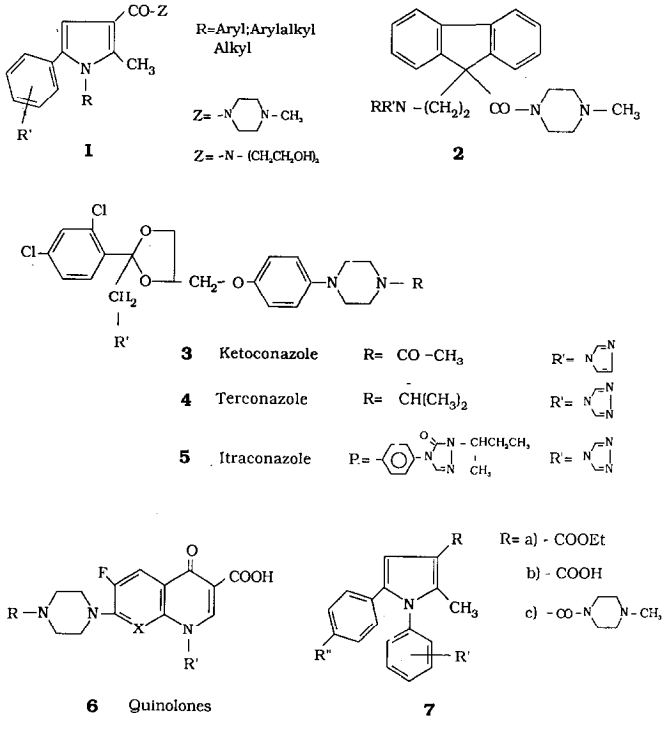

Fig 1.

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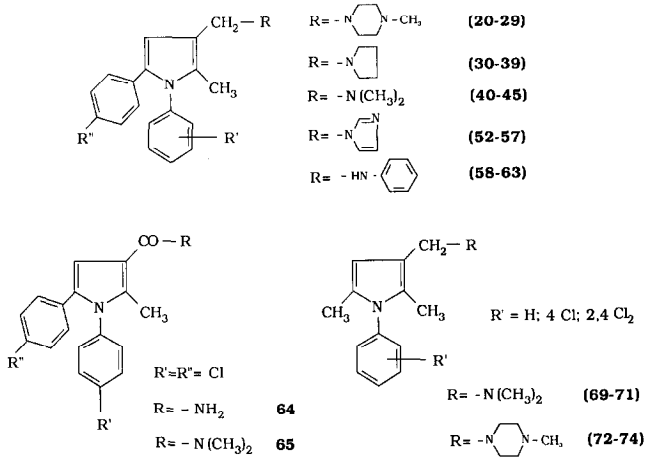


Fig 2.

able nitrogen lone pair. Since the activity of azole antifungal agents is strictly related to the non-bonded electrons of nitrogen atom on the azole ring, we propose also some C3 imidazolylmethyl derivatives **52–57** to investigate the effectiveness of this nucleus comparing their anti-*Candida* activity to that of the corresponding aliphatic amines **20–45**.

We chose the C5 4Cl-phenyl substitution and 4 Cl and 2, 4 Cl_2 as N1 phenyl substituents because this set of substituents appears to be the most sensitive to C3 substitutions in terms of biological activity, based on previous QSAR analysis [7]. As reference we synthesized similar compounds with unsubstituted N1 and C5 phenyl rings.

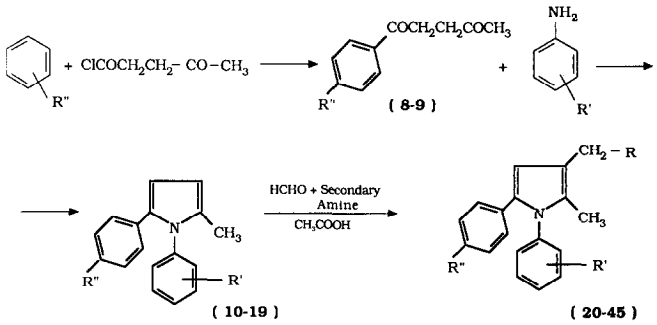
In piperazinyl (**20–29**) and pyrrolidinyl (**30–39**) series, we also considered the N1 4NO_2 and 4F phenyl to examine a wide set of substituents.

Finally, to define the structure–activity relationships of our molecules further we carried out the synthesis of a set of 1-aryl-2,5-dimethyl-3-dimethylaminomethyl **69–71** or (4-methylpiperazin-1-ylmethyl)-pyrroles **72–74** and assessed their biological activity in the same experimental system.

Chemistry

Synthetic pathways to obtain 3-aminomethyl-1,5-diaryl-2-methyl-pyrroles **20–45** and **52–63** are reported in scheme 1.

Phenacylacetone **8** and 4-chlorophenacylacetone **9** have been used as starting material and prepared according to Buchanan [8] and Stetter [9]. 1,5-Diaryl-2-methyl pyrroles **10–19**, obtained in excellent yields by reacting a suitable arylamine with **8** or **9**, were successfully transformed into the related 3-aminomethyl derivatives **20–45** by Mannich reactions.



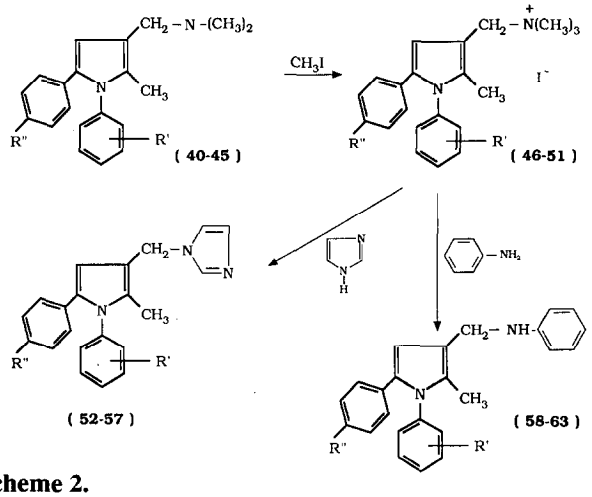
Scheme 1.

3-Dimethylaminomethyl derivatives **40–45** were transformed into the corresponding ammonium salts **46–51** by reacting with methyliodide. 3-(1H-imidazolyl-methyl) derivatives **52–57** and related 3-phenylaminomethyl pyrroles **58–63** were obtained by reacting ammonium salts **46–51** with aniline or imidazole. 1-Aryl-2,5-dimethyl-pyrroles **66—68** (scheme 3), prepared from acetonylacetone and the appropriate aniline [10, 11] were easily converted into the related 3-(dimethylamino methyl) derivatives **69–71** [11, 12] or into the 3-(4-methylpiperazin-1-ylmethyl) derivatives **72–74** by a Mannich reaction.

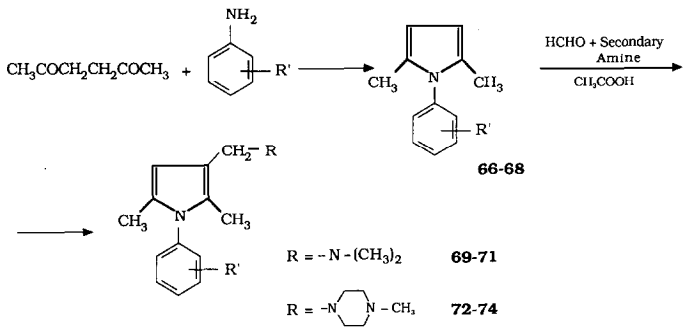
The amido derivatives **64–65** were synthesized as previously reported [1].

Microbiological assays

The minimum inhibitory concentration (MIC) for each strain of *Candida* or bacteria was determined using the method of progressive double dilutions in



Scheme 2.



Scheme 3.

solid media [13]. The mean MIC value was calculated according to [14] by using the following formula:

$$n\bar{X} = \Sigma i\ (Si \cdot Ci)/St$$

where *Si* is the number of sensitive strains at the used concentration *Ci* and *St* is the whole number of sensitive strains.

The test substances were dissolved in DMSO (5 mg/ml) as mother solution; further dilution in the medium furnished the required concentration generally ranging from 0.1 to 400 µg/ml.

Anti-Candida tests

Derivatives **10–45** and **52–74** were tested for their *in vitro* anti-fungal activity against *Candida albicans* and *Candida* sp. Pyrrolnitrin and miconazole were used as positive controls. The cultures were obtained on Sabouraud (BBL) after 18 h incubation at 37°C and Sabouraud agar (BBL) was used to carry out the tests. Each plate was inoculated with 10^3 *Candida* cells. The following species of fungi, isolated from various clinical specimens, were tested: 20 *Candida albicans*; 1 *C stellatoidea*; 1 *C guillermondi*; 1 *C parapsilosis*; 1 *C krusei*; 1 *C tropicalis*. Data were recorded after 36 h incubation at 37°C.

Results

Anti-Candida activity

Compounds **10–19** are inactive against all tested *Candida* strains. Activities of compounds **10–45** are reported in tables I and III; activities of compounds **52–63**, **64–65** and **69–74** are reported in tables II and IV.

To facilitate the biological activity comparison we report in table V the relative activity (Ar) of some imidazolylmethyl (A), dimethylaminomethyl (B), pyrrolidinylmethyl (C), 4-methylpiperazin-1-ylmethyl (D) derivatives and the previously synthesized related C3 4-methylpiperazinamides (E) [1, 2, 4]. (Ar = $MIC_{compound}/MIC_{pyrrolnitrin}$ (MIC values expressed as mol/l).)

Discussion

As far as the activity against *Candida albicans* of the pyrroles **10–19**, **20–45**, **52–63** and **69–74** is concerned (cf table I, II and V) several points are to be considered:

– The 1,5-diaryl-2-methyl-pyrroles **10–19**, as well as the related esters and acids **7a**, **b** [1–3, 4] are inactive;

– By comparing anti-*Candida* data concerning the piperazinyl and piperazinamido derivatives (cf table V), it appears that the higher lone pair availability of the 1 nitrogen atom of 4-methylpiperazine nucleus improves spectrum amplitude while causing a slight decrease of MIC values;

– The 4-methylpiperazinyl derivatives **20–29** show a slightly higher activity than that of the corresponding pyrrolidinyl derivatives **30–39**;

– With respect to C3 substituents, the dimethylaminomethyl derivatives **40–45** exhibit the best biological action among all tested compounds;

– With respect to the dimethylaminomethyl derivatives **40–45**, the imidazolylmethyl ones, **52–57**, show a slightly decreased activity;

– All phenylaminomethyl derivatives **58–63** and dimethylamides **64–65** are inactive;

– With respect to C5 and N1 substituents, C5 4Cl phenyl and N1 4Cl and/or 2, $4Cl_2$ phenyl substituted derivatives show the highest microbiological activity. When the NO_2 group is present on N1 substituent, anti-*Candida* activity falls drastically;

– A chlorine atom on *para* position of C5 phenyl substituent strongly increases the biological activity as compared to C5 unsubstituted phenyl derivatives;

– 2,5-dimethyl derivatives **69–74**, except N1 2, $4Cl_2$ derivative **74** possessing a weak activity, are inactive;

From these considerations, it appears that anti-*Candida* activity is not related to the piperazine nucleus but is associated with the presence of a nitrogen atom lone pair on C3 substituent. Indeed, the imidazolylmethyl **52–57** and dimethylaminomethyl **40–45** derivatives show a comparable activity and this is in agreement with the hypothesis proposed by Mailman *et al*, that antifungal activity is frequently related to potential ligands as a nitrogen atom with sp^2 or sp^3 non-bonded sterically accessible electrons [15]. The inactivity of compounds **64–65** and **58–63**, presenting amidic tautomerism and a partial involvement of a lone pair of aminic nitrogen with π electrons of a benzene ring, also supports this hypothesis.

Table I. Antimycotic activity of compounds **10–45** against 20 strains of *Candida albicans* at pH 7.2.

Compound	*R'*	*R''*	*R%*	*Candida albicans*			
				nX (μg/ml)	*Range (μg/ml)*	*St dev*	*nX (mmol/l)*
10–19			100	> 200	200–> 200		
20	4Cl	Cl	0	57.3	6.25–200	22.3	0.1384
21	2, $4Cl_2$	Cl	0	50.1	6.25–100	7.4	0.1118
22	H	Cl	0	64.4	12.5–100	31.4	0.1699
23	4F	Cl	0	45.3	0.4–100	35.7	0.1141
24	$4NO_2$	Cl	54	100	50–400	54.7	0.2358
25	4Cl	H	0	159.5	25–200	73.4	0.4208
26	2, $4Cl_2$	H	0	43.5	3.12–100	29.6	0.1050
27	$4NO_2$	H	0	255	25–400	129	0.6556
28	4F	H	0	168	12.5–400	142	0.4634
29	H	H	0	200	200	0	0.5797
30	4Cl	Cl	0	59.8	3.12–100	45.3	0.1555
31	2, $4Cl_2$	Cl	0	70.2	12.5–200	56.5	0.1675
32	H	Cl	0	61.7	3.12–100	27.7	0.1764
33	4F	Cl	0	107.2	6.25–200	82.9	0.2913
34	$4NO_2$	Cl	0	100.9	25–200	83.2	0.2554
35	4Cl	H	0	104.8	12.5–200	82.8	0.2994
36	2, $4Cl_2$	H	0	50	25–100	25	0.1299
37	H	H	0	126.9	50–200	63.3	0.4016
38	4F	H	0	113.4	25–200	67	0.3395
39	$4NO_2$	H	0	219	50–400	138.6	0.6072
40	4Cl	Cl	0	27.8	12.5–100	24.0	0.0776
41	2, $4Cl_2$	Cl	0	61.0	6.25–100	45.1	0.1552
42	H	Cl	0	38.4	25–50	12.9	0.1185
43	4Cl	H	0	51.9	0.4–100	40.1	0.1602
44	2, $4Cl_2$	H	0	16.3	12.5–25	6.0	0.0455
45	H	H	0	69.8	25–100	30.1	0.2415
Pyrrolnitrin			0	20.7	3.12–25	7.3	0.0805
Miconazole			0	5.87	0.2–6.25	7.6	0.0142

Table II. Antimycotic activity of compounds **52–65** and **69–74** against 20 strains of *Candida albicans* at pH 7.2.

Compound	*R'*	*R''*	*R%*	*Candida albicans*			
				nX (μg/ml)	*Range (μg/ml)*	*St dev*	*nX (mmol/l)*
52	4Cl	Cl	0	34.0	6.25–100	32.5	0.0892
53	2, $4Cl_2$	Cl	0	53.4	12.5–100	29.1	0.1287
54	H	Cl	0	50.7	12.5–100	33.7	0.1465
55	4Cl	H	0	84.1	25–200	54.1	0.2431
56	2, $4Cl_2$	H	0	36.6	12.5–50	10.1	0.0946
57	H	H	0	81.8	50–100	15.3	0.6220
58–63			100	> 200	200–> 200	–	–
64–65			100	> 200	200–> 200	–	–
69	H	b[a]	100	> 200	200–> 200	–	–
70	4Cl	b	75	200	200–> 200	–	–
71	2, $4Cl_2$	b	25	32.8	12.5–200		0.1249
72	H	b	100	> 200	200–> 200		
73	4Cl	b	90	200	200–> 200		
74	2, $4Cl_2$	b	50	155	50–> 200		
Pyrrolnitrin			0	18.5	3.12–25	8.29	0.0720
Miconazole			0	3.98	0.2–25	3.79	0.0096

[a]b, C5 substituent = CH_3

Table III. Antimycotic activity of compounds **10–45** against five strains of *Candida* sp at pH 7.2. (MIC expressed in μg/ml).

Compound	*R'*	*R''*	*α*[a]	*β*[b]	*Γ*[c]	*δ*[d]	*ε*[e]
10–19			> 200	> 200	> 200	> 200	> 200
20	4Cl	Cl	25	50	50	50	1.25
21	2, $4Cl_2$	Cl	3.12	25	25	6.25	1.56
22	H	Cl	25	100	100	50	3.12
23	4F	Cl	12.5	50	100	100	0.8
24	$4NO_2$	Cl	50	> 400	100	> 400	25
25	4Cl	H	200	200	200	200	6.25
26	2, $4Cl_2$	H	25	50	100	100	0.4
27	$4NO_2$	H	200	200	200	400	100
28	4F	H	100	200	200	400	125
29	H	H	200	200	200	400	100
30	4Cl	Cl	12.5	100	50	100	25
31	2, $4Cl_2$	Cl	12.5	200	100	200	25
32	H	Cl	50	400	400	400	0.8
33	4F	Cl	25	200	25	200	25
34	$4NO_2$	Cl	25	200	50	100	3.12
35	4Cl	H	50	200	200	200	12.5
36	2, $4Cl_2$	H	25	100	100	200	25
37	H	H	50	200	200	400	50
38	4F	H	50	200	50	400	100
39	$4NO_2$	H	50	400	400	400	0.8
40	4Cl	Cl	6.25	25	50	25	12.5
41	2, $4Cl_2$	Cl	12.5	100	100	100	6.25
42	H	Cl	25	50	50	50	25
43	4Cl	H	25	100	100	100	25
44	2, $4Cl_2$	H	6.25	25	12.5	25	12.5
45	H	H	25	25	100	100	100
Pyrrolnitrin			25	12.5	25	25	1.56
Miconazole			6.25	3.12	12.5	3.12	< 0.4

[a]*α* = 1 *C stellatoidea*; [b]*β* = 1 *C Tropicalis*; [c]*Γ* = 1 *C guillermondi*; [d]*δ* = 1 *C parapsilosis*; [e]*ε* = 1 *C krusei*

Table IV. Antimycotic activity of compounds **52–65** and **69–74** against five strains of *Candida* sp at pH 7.2. (MIC expressed in μg/ml).

Compound	*R'*	*R''*	*α*[a]	*β*[b]	*Γ*[c]	*δ*[d]	*ε*[e]
52	4Cl	Cl	12.5	50	25	200	6.25
53	2, $4Cl_2$	Cl	12.5	12.5	25	100	6.25
54	H	Cl	12.5	50	100	200	0.8
55	4Cl	H	25	100	200	200	50
56	2, $4Cl_2$	H	6.25	25	25	25	6.25
57	H	H	12.5	50	50	100	6.25
58–63			> 200	> 200	> 200	> 200	> 200
64–65			> 200	> 200	> 200	> 200	> 200
69	H	b[f]	> 200	100	100	> 200	100
70	4Cl	b	> 200	200	> 200	100	25
71	2, $4Cl_2$	b	> 200	200	> 200	100	50
72	H	b	50	> 200	> 200	> 200	50
73	4Cl	b	100	200	100	> 200	50
74	2, $4Cl_2$	b	50	> 200	50	> 200	12.5
Pyrrolnitrin			12.5	25	25	25	6.25
Miconazole			3.12	3.12	6.25	12.5	3.12

[a]*α* = 1 *C stellatoidea*; [b]*β* = 1 *C tropicalis*; [c]*Γ* = 1 *C guillermondi*; [d]*δ* = 1 *C parapsilosis*; [e]*ε* = 1 *C krusei*; [f]b, C5 substituent = CH_3

Table V. Comparative activity of some C3 substituted 1,5-diarylpyrroles against *Candida albicans*.

			C3 Substituents									
	R'	*R''*	*A*[c]		*B*[d]		*C*[e]		*D*[f]		*E*[g]	
			R%[a]	*Ar*[b]	*R%*	*Ar*	*R%*	*Ar*	*R%*	*Ar*	*R%*	*Ar*
a	4Cl	Cl	0	1.1	0	0.9	0	1.9	0	1.7	0	1.1
b	$2,4Cl_2$	Cl	0	1.6	0	1.9	0	2.1	0	1.4	0	1.3
c	H	Cl	0	1.8	0	1.5	0	2.2	0	2.1	36	8.4
d	4Cl	H	0	3.0	0	2.0	0	3.7	0	5.2	8	5.5
e	$2,4Cl_2$	H	0	1.2	0	0.6	0	1.6	0	1.3	4	1.8
f	H	H	0	7.7	0	3.0	0	5.0	0	7.2	–	–

[a]R% = percentage of resistant strains; [b]Ar = $MIC_{compound}/MIC_{pyrrolnitrin}$ (MIC values expressed as mol/l); [c]A = imidazolylmethyl; [d]B = dimethylaminomethyl; [e]C = pyrrolidinylmethyl; [f]D = 4-methylpiperazinylmethyl; [g]E = 4-methylpiperazinamide

The diminished activity of pyrrolidinyl derivatives is probably also related to steric hindrance of the cyclic alkylic chain. On the contrary the *N*-methylpiperazinyl derivatives **20–29** show a comparable activity with the dimethylaminomethyl ones **40–45**, presumably because the lone pair of the 4-nitrogen atom of the piperazinyl group is very accessible. Moreover, the availability of this lone pair is a reasonable explanation of the piperazinamido derivatives activity compared to inactivity of compounds **64–65**.

Finally, the absence of activity of the 1-aryl-2,5-dimethyl-3-dimethylaminomethyl **69–71** or (4-methylpiperazin-1-yl-methyl)-pyrroles **72–74**, supports the hypothesis that the C5 position of the pyrrole nucleus needs an aromatic substitution to be active. On the basis of the present results we can conclude that anti-*Candida* activity of our compounds is strictly connected to N1 and C5 aryl substitution with the concomitant presence of a nitrogen atom with an available non-hindered lone pair on the C3 pyrrole position.

Experimental protocols

Chemistry

Melting points, taken on a Kofler apparatus, are uncorrected. 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. All compounds were analysed for C, H, N and, when present, Cl and F. The analysed values were within ± 0.4 of the calculated values. Elemental analyses were performed by A Pietrogrande, Padova, Italy. Merck aluminium oxide (II–III, according to Brockmann) was used for chromatographic purification. Chemical and physical data of compounds **10–74** are reported in table VI.

*1,5-Diaryl-2-methyl pyrroles **10–19***

A solution of appropriate arylacylacetone (5.7 mmol) **8**, **9** and a suitable aniline (5.9 mmol) with a catalytic amount of aniline hydrobromide (0.1 g) in 50 ml of dry ethanol was heated to reflux for 3 h (5 h using 2,4 dichloroaniline). The solvent was evaporated under reduced pressure and the residue was purified using a Al_2O_3/cyclohexane chromatographic column. The first fractions were discarded and the central ones were evaporated to afford a pure solid. NMR $CDCl_3$: δ 1.9–2.1 (s, 3H(CH_3 pyrrole)); δ 6.15–6.20 (m, 1H(H_3 pyrrole)); 6.30–6.35 (d, 1H, J = 3 cps (H_4 pyrrole)).

*1,5-Diaryl-2-methyl-3-(4-methylpiperazin-1-ylmethyl)pyrroles **20–29***

A mixture of 0.21 ml (3.3 mmol) of HCHO 40% water solution and 0.4 ml (3.3 mmol) of *N*-methylpiperazine in 2 ml of glacial acetic acid was slowly added dropwise to a solution of suitable pyrrole **10–19** (3.3 mmol) in glacial acetic acid and left overnight at room temperature. The solution was poured onto crushed ice and made alkaline (pH 12) with sodium hydroxide. The reaction product was extracted with chloroform and the organic layer was washed with water and dried over sodium sulfate. The residue from evaporation of the solvent was purified with $Al_2O_3/CHCl_3$ chromatography. The first fractions were discarded and the central ones were evaporated to afford a pure solid. NMR $CDCl_3$: δ 2.1 (s, 3H(CH_3 pyrrole)); δ 2.25 (s, 3H(N-CH_3)); δ 2.35–2.6 (m, 8H(piperazine methylene protons)); δ 3.4–3.45 (s, 2H (pyrroleCH_2piperazine)); 6.35–6.40 (s, 1H (H_4 pyrrole)).

*1,5-Diaryl-2-methyl-3-(pyrrolidin-1-ylmethyl)pyrroles **30–39***

These compounds were synthesized as previously reported for **20–29**. NMR $CDCl_3$: δ 1.7–1.85 and 2.4–2.55 (m, 8H(*pyrrolidine* protons)); δ 1.95–2.05 (s, 3H(CH_3 pyrrole)); δ 3.4–3.5 (s, 2H(CH_2-pyrrolidine)); δ 6.4–6.5 (s, 1H(H_4 pyrrole)).

*1,5-Diaryl-3-(dimethylaminomethyl)-2-methyl-pyrroles **40–45***

These compounds were synthesized as previously reported for **20–29**. NMR $CDCl_3$: δ 1.95–2.05 (s, 3H(CH_3 pyrrole)); δ 2.25 (s, 6H(N-(CH_3)$_2$)); δ 3.3–3.4 (s, 2H(CH_2-N-(CH_3)$_2$)); δ 6.35–6.45 (s, 1H(H_4 pyrrole)).

*1,5-Diaryl-2-methyl-3-(trimethyl ammonium methyl)pyrrole iodides **46–51***

1.8 g of methyl iodide (12.8 mmol) was added dropwise to a solution of appropriate 1,5-diaryl-3-(dimethylamino-methyl)-2-methyl-pyrrole **40–45** (12.1 mmol) in 15 ml of dry ethanol. The resulting precipitate (30–40% yield) was filtered off and washed with the minimum amount of dry ethanol and with diethyl ether. These compounds were employed without further purification.

Table VI. Chemical and physical data of compounds **10–74**.

Compd	*R'*	*R''*	*Y%*	*mp°C*	*Formula*
10	4Cl	Cl	58	123–5	$C_{17}H_{13}NCl_2$
11	2, 4Cl_2	Cl	60	131–3	$C_{17}H_{12}NCl_3$
12	H	Cl	62	126–9	$C_{17}H_{14}NCl$
13	4F	Cl	80	125–7	$C_{17}H_{13}NClF$
14	4NO_2	Cl	42	142–6	$C_{17}H_{13}N_2O_2Cl$
15	4Cl	H	72	130–1	$C_{17}H_{14}NCl$
16	2, 4Cl_2	H	51	135–7	$C_{17}H_{13}NCl_2$
17	H	H	47	123–5	$C_{17}H_{15}N$
18	4F	H	63	130–2	$C_{17}H_{14}NF$
19	4NO_2	H	36	133–5	$C_{17}H_{14}N_2O_2$
20	4Cl	Cl	61	197–8	$C_{23}H_{25}N_3Cl_2$
21	2, 4Cl_2	Cl	56	130–2	$C_{23}H_{24}N_3Cl_3$
22	H	Cl	61	192–4	$C_{23}H_{26}N_3Cl$
23	4F	Cl	43	163–5	$C_{23}H_{25}N_3ClF$
24	4NO_2	Cl	34	205–7	$C_{23}H_{25}N_4O_2Cl$
25	4Cl	H	58	164–5	$C_{23}H_{26}N_3Cl$
26	2, 4Cl_2	H	32	95–8	$C_{23}H_{25}N_3Cl_2$
27	H	H	40	107–9	$C_{23}H_{27}N_3$
28	4F	H	44	140–2	$C_{23}H_{26}N_3F$
29	4NO_2	H	55	178–9	$C_{23}H_{26}N_4O_2$
30	4Cl	Cl	40	135–8	$C_{22}H_{22}N_2Cl_2$
31	2, 4Cl_2	Cl	44	115–9	$C_{22}H_{21}N_2Cl_3$
32	H	Cl	43	158–9	$C_{22}H_{23}N_2Cl$
33	4F	Cl	35	137–9	$C_{22}H_{22}N_2ClF$
34	4NO_2	Cl	48	154–9	$C_{22}H_{22}N_3O_2Cl$
35	4Cl	H	35	131–3	$C_{22}H_{23}N_2Cl$
36	2, 4Cl_2	H	30	103–6	$C_{22}H_{22}N_2Cl_2$
37	H	H	55	73–4	$C_{22}H_{24}N_2$
38	4F	H	70	96–9	$C_{22}H_{23}N_2F$
39	4NO_2	H	53	196–9	$C_{22}H_{23}N_3O_2$
40	4Cl	Cl	73	131–3	$C_{20}H_{20}N_2Cl_2$
41[a]	2, 4Cl_2	Cl	80	252–3	$C_{20}H_{20}N_2Cl_4$
42	H	Cl	77	141–2	$C_{20}H_{21}N_2Cl$
43	4Cl	H	70	116–7	$C_{20}H_{21}N_2Cl_1$
44	2, 4Cl_2	H	47	116–8	$C_{20}H_{20}N_2Cl_2$
45	H	H	80	88–9	$C_{20}H_{22}N_2$
46	4Cl	Cl	h		
47	2, 4Cl_2	Cl	h		
48	H	Cl	h		
49	4Cl	H	h		
50	2, 4Cl_2	H	h		
51	H	H	h		

Table VI. *Continued*

Compd	*R'*	*R''*	*Y%*	*mp°C*	*Formula*
52	4Cl	Cl	45	107–9	$C_{24}H_{20}N_2Cl_2$
53	2, 4Cl_2	Cl	45	144–5	$C_{24}H_{19}N_2Cl_3$
54	H	Cl	50	132–3	$C_{24}H_{21}N_2Cl$
55	4Cl	H	65	132–3	$C_{24}H_{21}N_2Cl$
56[a]	2, 4Cl_2	H	40	178–9	$C_{24}H_{21}N_2Cl_3$
57	H	H	40	113–5	$C_{24}H_{22}N_2$
58	4Cl	Cl	25	143–4	$C_{21}H_{17}N_3Cl_2$
59	2, 4Cl_2	Cl	30	75–6	$C_{21}H_{16}N_3Cl_3$
60	H	Cl	20	120–2	$C_{21}H_{18}N_3Cl$
61	4Cl	H	22	126–8	$C_{21}H_{18}N_3Cl$
62	2, 4Cl_2	H	20	148–9	$C_{21}H_{17}N_3Cl_2$
63	H	H	35	152–3	$C_{21}H_{19}N_3$
64	4Cl	Cl	65	208–9	$C_{18}H_{14}N_2OCl_2$
65	4 Cl	Cl	72	185–7	$C_{20}H_{18}N_2OCl_2$
66	H	i	e		$C_{12}H_{13}N$
67	4Cl	i	f		$C_{12}H_{12}NCl$
68	2, 4Cl_2	i		b	$C_{12}H_{11}NCl_2$
69	H	i	g		$C_{15}H_{20}N_2$
70	4Cl	i	f		$C_{15}H_{19}N_2Cl$
71	2, 4Cl_2	i		c	$C_{15}H_{18}N_2Cl_2$
72	H	i		70–2	$C_{18}H_{25}N_3$
73	4Cl	i		94–5	$C_{18}H_{24}N_3Cl$
74	2, 4Cl_2	i		d	$C_{18}H_{23}N_3Cl_2$

[a]Analyzed as hydrochloride; [b]bp 97–9°C/0.08 mmHg; [c]bp 123°C/0.1 mmHg; [d]bp 153°C/0.09 mmHg; [e]see [9]; [f]see [10]; [g]see [11]; [h]uncharacterized compounds; [i]C5 substituent = CH_3

1,5-Diaryl-2-methyl-3-(phenylaminomethyl)pyrroles ***58–63***

A solution of appropriate **46–51** (1.4 mmol) and of aniline (7.35 mmol) in DMSO was stirred and heated at 100°C for 4 h. Water was added to the reaction mixture and the product taken out in ethyl acetate. Organic layer, dried on Na_2SO_4 and evaporated under reduced pressure, gave a residue which was chromatographed on Al_2O_3/benzene. The first fractions were discarded and the central ones were evaporated to afford a solid. NMR $CDCl_3$: δ 2.05 (s, 3H(CH_3 pyrrole)); δ 4.20 (s, 2H(CH_2-NH-Ar)); δ 6.50(s, 1H(H_4 pyrrole)); IR 3400 cm^{-1} (NH).

1,5-Diaryl-3-(imidazol-1-ylmethyl)-2-methyl-pyrroles ***52–57***

A solution of appropriate **46–51** (1.4 mmol) and imidazole (7.35 mmol) in DMSO was stirred and heated at 100°C for 4 h. Water was added to the reaction mixture and the product taken out in ethyl acetate. Organic layer dried on Na_2SO_4 evaporated under reduced pressure, gave a residue which was chromato-

graphed on $Al_2O_3/CHCl_3$. The first fractions were discarded and the central ones were evaporated to afford a solid. NMR $CDCl_3$: δ 2.0 (s, 3H(CH_3 pyrrole)); δ 4.85–4.95 (s, 2H(CH_2-Im)); δ 6.25–6.30 (s, 1H(H_4 pyrrole)).

1-(2,4-dichlorophenyl)-2,5-dimethyl-pyrrole ***68***
Acetonylacetone (1 mmol), 2,4-dichloroaniline (1 mmol) and 1 ml of acetic acid in 50 ml of benzene and 5 ml of dry ethanol was heated at reflux for 5 h and the water formed during the reaction was eliminated by a Dean-Stark apparatus. Organic layer was washed with water and dried over sodium sulfate. Benzene was evaporated under reduced pressure and residue-purified using Al_2O_3/cyclohexane chromatography. NMR $CDCl_3$: δ 1.95 (s, 6H(CH_3 pyrrole)); δ 5.9 (s, 2H(H_3, H_4 pyrrole)); δ 7.15–7.6 (m, 3H(*Ar* protons)).

1-(2,4-dichlorophenyl)-2,5-dimethyl-3-(dimethylaminomethyl)-pyrrole ***71***
0.21 ml (3.3 mmol) of HCHO 40% water solution and 0.70 ml (3.3 mmol) of dimethylamine 40% in 2 ml of glacial acetic acid were added dropwise to a solution of pyrrole **68** (3.3 mmol) in glacial acetic acid. The mixture was heated at 50°C for 1 h. The solution was poured onto crushed ice and made alkaline (pH 12) with sodium hydroxide. The reaction product was extracted with chloroform and the organic layer was washed with water and dried over sodium sulfate. The residue from evaporation of the solvent was chromatographed on $Al_2O_3/CHCl_3$. The first fractions were discarded and the central ones were evaporated to afford a solid. NMR $CDCl_3$: δ 1.95 (s, 6H(CH_3 pyrrole)); δ 2.30 (s, 6H(N-$(CH_3)_2$)); δ 3.40 (s, 2H(CH_2-N-$(CH_3)_2$)); δ 6.0 (s, 1H(H_4 pyrrole)); 7.2–7.7 (m, 3H(*Ar* protons)).

1-Aryl-2,5-dimethyl-3(4-methylpiperazin-lylmethyl)pyrroles ***72–74***
These compounds were obtained as previously described for compound **71**. NMR $CDCl_3$: δ 1.8–1.9 (s, 6H(CH_3 pyrrole)); δ 2.25–2.30 (s, 3H(N-CH_3); δ 2.3–2.5 (m, 8H(piperazine protons); δ 3.35 (s, 2H(CH_2-piperazine); δ 5.9–6.0 (s, 1H(H_4 pyrrole)).

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