

SUBSTITUTED BENZIMIDAZOLES. Part I.
SYNTHESIS AND PROPERTIES OF SOME 2-ARYL-5-FLUORO-
6-(4-METHYL-1-PIPERAZINYL)-1H-BENZIMIDAZOLES

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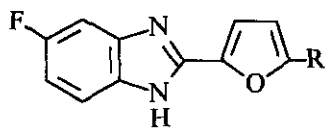
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Abstract — 2-Aryl-5-fluoro-6-(4-methyl-1-piperazinyl)benzimidazoles (**8a-k**) were synthesized for bioassay *via* interaction of 4-fluoro-5-(4-methyl-1-piperazinyl)-1,2-diaminobenzene (**6**) with the appropriate aldehyde. The intermediate Schiff bases (**7a-k**) were isolated and converted, thermally in nitrobenzene, to the respective heterocycles (**8a-k**). However, none of the tested model compounds (**8c-e**) showed any significant *in vitro* activity against *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Aspergillus parasiticus* and *Candida albicans* at concentration $\leq 100 \mu\text{g} / \text{ml}$.

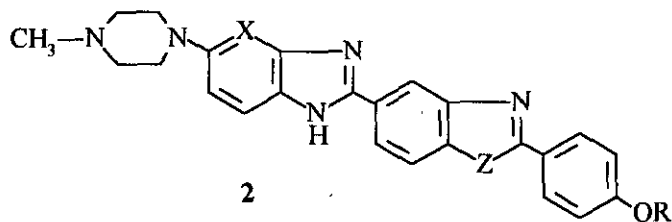
INTRODUCTION

Several benzimidazole derivatives exhibit remarkable bio-activity, and are commercially available pharmaceuticals.^{1,2} Thus, benzimidazoles represent the only class of truly low-dose broad-spectrum anthelmintics with a high therapeutic index.³ A number of benzimidazoles are anti-tumorial agents,⁴ while others show activity against fungi.¹ A limited number of benzimidazoles carrying fluorine or 1-piperazinyl moiety as ring substituents are known in the literature. Compound (**1**) was reported to exhibit a marked *in vitro* and *in vivo* activity against Gram positive bacteria and different mycetes such as *C. albicans* and *Cryptococcus neoformans*.⁵ The 5(6)-(4-methyl-1-piperazinyl)

derivative (**2a**) (Hoechst 33258) is a DNA binding fluorochrome used in chromosome staining,⁶ and compounds (**2b,c**) are recently described⁷ as analogs of **2a**. Also, the 2-(4-substituted 1-piperaziny)benzimidazole derivatives (**3**) have been reported to exhibit antihistaminic activity.⁸

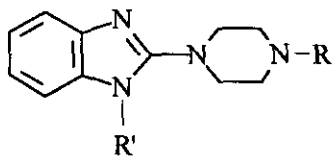


1 (R: H, NO₂)



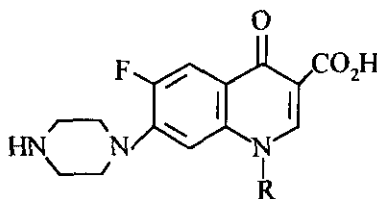
2

	R	Z	X
2a	H	NH	CH
2b	CH ₃	O	CH
2c	CH ₃	O	N



3

(e.g. R = CH₃; R' = CH₂CH₂OC₂H₅)



4

a : R = Δ

b : R = NHCH₃

However, benzimidazoles incorporating both fluorine and piperazine substituents at the 5- and 6- positions are hitherto undescribed in the literature. Such substituents might together enhance and / or modify the bioactivity of the derivatized benzimidazoles. This is inferred from the fact that the presence of both fluorine and piperazine as substituents in the 4-quinolone nucleus led to considerable enhancement of the antibacterial potency of the second generation "fluoroquinolones",⁹ such as ciprofloxacin (**4a**)¹⁰ and amifloxacin (**4b**).¹¹ Therefore, the present work aims at obtaining a selected set of 2-aryl (and heteroaryl)-5(6)-fluoro-6(5)-(4-methyl-1-piperaziny)benzimidazoles (**8a-k**, Scheme 1) for bioassay.

Benzimidazoles normally undergo, in solution, very rapid proton transfer between N-1 and N-3 of the imidazole ring at room temperature¹² (*cf.* tautomeric equilibrium **8A** \rightleftharpoons **8B** / Scheme 1). Throughout the paper, when we refer to this ambiguous tautomeric mixture, we shall use the system employing the lowest numbers (i.e tautomeric form **8A**) regardless of the form adopted in the crystal. Herein we describe the synthesis and properties of compounds (**8a-k**).

SYNTHESIS

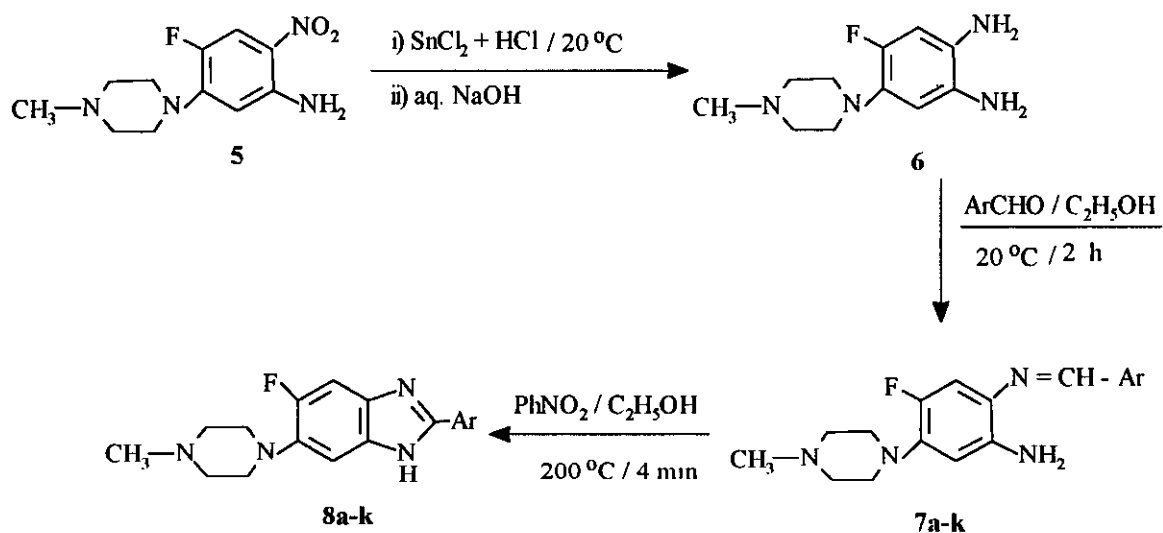
The target benzimidazoles (**8a-k**) were prepared by the reaction of 4-fluoro-5-(4-methyl-1-piperazinyl)-1,2-diaminobenzene (**6**) with the appropriate aryl (or heteroaryl) aldehyde. This reaction proceeds *via* the initial formation of the corresponding Schiff bases (**7a-k**) as shown in Scheme 1. The latter acyclic intermediates are stable yellow solids that were converted into the corresponding heterocycles (**8a-k**) in a subsequent oxidative cyclization step *via* heating in nitrobenzene at 200 °C. The reaction conditions employed here are similar to those reported^{1,13} for preparing related 2-arylbenzimidazoles; the solvent nitrobenzene acts also as an oxidant.^{7,14} The generality of this convenient route, namely the condensation of *o*-phenylenediamines with aromatic aldehydes, toward the synthesis of 2-arylbenzimidazoles has been documented,^{1,2} and isolation of the intermediate Schiff bases has also been realized.^{1,13}

The required diamine (**6**) is obtained by reduction of 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**5**) with stannous chloride in concentrated hydrochloric acid (Scheme I); the conditions adopted here involve modifications to those reported¹⁵ for the reduction of related *o*-nitroanilines into *o*-phenylenediamines. The steps involved in the preparation of the *o*-nitroaniline precursor (**5**) have been previously described.¹⁶⁻¹⁸ Physical and analytical data for the new compounds (**6-8**) are shown in Table 1.

MASS SPECTRA

(i) Compounds (**8a-k**). The mass spectra of these compounds show the correct molecular ions $[M]^+$ as expected from their molecular formulas. The molecular ions and the major fragment ions, observed in the mass spectra of these compounds, are shown in Table 2.

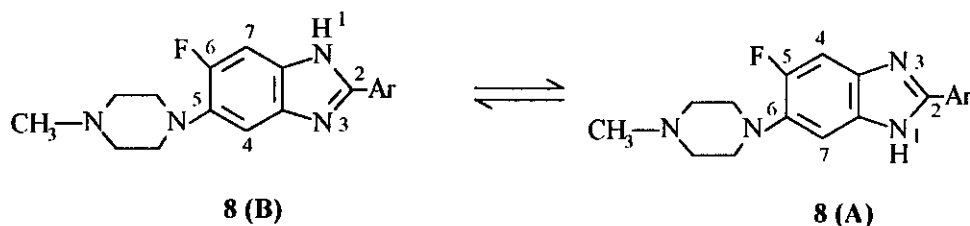
Scheme I



Compounds (7 and 8)

No.	a	b	c	d	e	f
Ar			-C ₆ H ₅	C ₆ H ₄ F (<i>m</i>)	-C ₆ H ₄ F (<i>p</i>)	-C ₆ H ₄ Cl (<i>m</i>)

No.	g	h	i	j	k
Ar	-C ₆ H ₄ Cl (<i>p</i>)	-C ₆ H ₄ Br (<i>m</i>)	-C ₆ H ₄ Br (<i>p</i>)	-C ₆ H ₄ OCH ₃ (<i>p</i>)	-C ₆ H ₄ CH ₃ (<i>p</i>)



The main fragmentation pathways are displayed in Scheme II. The fragment ions at M-15, M-44, and M-71 (ion A), observed in all mass spectra, are obviously formed through bond rupture of the piperazine moiety. Fragment ion (B), at M-99, arises due to elimination of the piperazine moiety from the molecular ions. This cation (B) then eliminates ArCN

Table 1. Physical and Analytical Data for Compounds (6, 7a-c,g and 8a-k)

Compd No	Yield (%)	mp(°C)	Molecular Formula	[M] ⁺	% Analysis ^a		
					(Calcd ^a C	/ H	Found) N
6	51	96-97	C ₁₁ H ₁₇ N ₄ F	224	58.91	7.64	24.98
					59.16	7.39	25.01
6. 1HCl	96	188-189 (decomp.)	C ₁₁ H ₁₈ N ₄ FCI	260	50.67	6.96	21.49
					50.53	6.91	21.57
7 a	71	154	C ₁₆ H ₁₉ N ₄ OF	302	63.56	6.33	18.53
					63.32	6.34	18.36
7 b	53	170	C ₁₆ H ₁₉ N ₄ FS	318	60.35	6.01	17.60
					60.29	5.75	17.48
7 c	83	179	C ₁₈ H ₂₁ N ₄ F	312	69.21	6.78	17.93
					69.05	6.66	17.81
7 g	77	185	C ₁₈ H ₂₀ N ₄ FCI	346/348	62.33	5.81	16.15
					62.09	5.58	16.07
8 a	57	210-211	C ₁₆ H ₁₇ N ₄ OF	300	60.37	6.01	17.60
					60.27	5.60	17.52
8 b	61	140-141	C ₁₆ H ₁₇ N ₄ FS	316	57.67	5.69	16.67
					57.33	5.73	16.59
8 c	82	208-209	C ₁₈ H ₁₉ N ₄ F	310	65.89	6.44	17.06
					65.70	6.63	17.14
8 d	72	214-215	C ₁₈ H ₁₈ N ₄ F ₂	328	62.42	5.82	16.17
					62.74	6.03	16.34
8 e	63	216-217	C ₁₈ H ₁₈ N ₄ F ₂	328	62.42	5.82	16.17
					62.19	5.98	16.24
8 f	71	213-214	C ₁₈ H ₁₈ N ₄ FCI	344/346	59.59	5.56	15.44
					59.54	5.72	15.47
8 g	75	220-221	C ₁₈ H ₁₈ N ₄ FCI	344/346	59.59	5.56	15.44
					59.26	5.69	15.24

Table 1 (continued)

8 h	61	199-200	C ₁₈ H ₁₈ N ₄ FBr	388/390	53.08 52.97	4.95 5.17	13.76 13.93
8 i	50	223-224	C ₁₈ H ₁₈ N ₄ FBr	388/390	53.08 52.82	4.95 5.04	13.70 13.87
8 j	56	200-201	C ₁₈ H ₂₁ N ₄ OF	340	63.67 63.93	6.47 6.59	15.63 15.81
8 k	52	192-193	C ₁₉ H ₂₁ N ₄ F	324	66.65 66.28	6.77 6.86	16.36 16.40

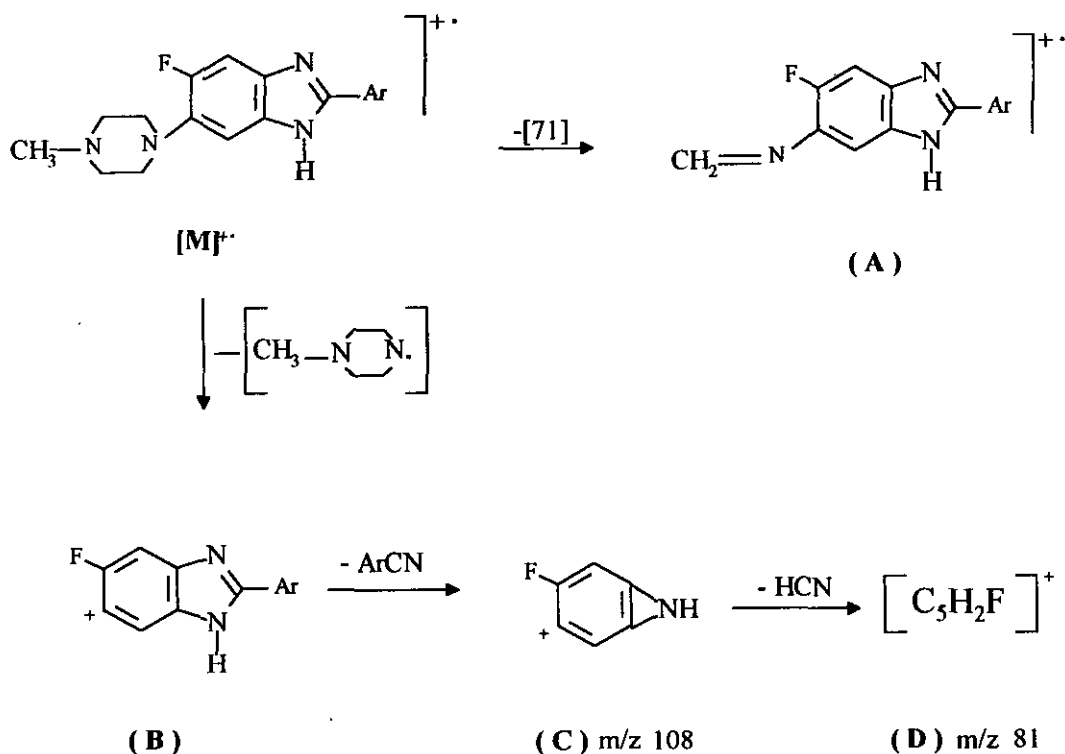
^a All compounds (**8a-k**) are monohydrates; calcd % elements is based on [mol. Formula. 1H₂O].

molecule giving fragment (C), at *m/z* 108. The latter ion then undergoes subsequent loss of HCN leading to fragment (D) at *m/z* 81. This mode of fragmentation is characteristic of 2-arylbenzimidazoles.¹⁹ The base peak at *m/z* 43 (100%), and another significant peak at *m/z* 71 correspond to the ions $\text{CH}_3\text{---}\overset{+}{\text{N}}\text{=CH}_2$ and $(\text{CH}_3)_2\text{---}\overset{+}{\text{N}}\text{---CH=CH}_2$, respectively. Both ions arise from two bond rupture of the piperazine moiety.

(ii) Compounds (**7a-c,g**). The mass spectra of these Schiff bases show the correct molecular ions, as suggested by their molecular formulas; the molecular ions and the major fragment ions, observed in their mass spectra, are shown in Table 3. The main fragmentation pathways are displayed in Scheme III. The spectra exhibit the molecular ions [M]⁺ as the base peak in most cases which eliminates [Ar]⁺ to give fragment ion (A) at *m/z* 235. An intense peak, ion (B) at *m/z* 164, is observed in all compounds and is formed via the loss of (CH₃)₂ - N - CH = CH₂ (mass 71) from ion (A). Ejection of the piperazinyll moiety from ion (A) produces ion (C) at *m/z* 136, which undergoes successive loss of two molecules of HCN to give ions (D) and (E), respectively.

(iii) Compound (**6**). The mass spectrum of this compound is in agreement with the assigned structure, and shows the correct molecular ion [M]⁺ (100 %) suggested by its molecular formula. The molecular ion undergoes stepwise-ejection of the piperazinyll moiety to produce ions at *m/z* 209 (4 %), 180 (5 %), 153 (60 %) and 125 (14 %).

Scheme II

¹H-NMR SPECTRA

(i) Compound (6). The spectrum of this compound shows a broad exchangeable singlet at δ 3.3 ppm (4H) which corresponds to the N-1 and N-2 protons. The aromatic protons H-3 (adjacent to the fluorine atom) and H-6 appear as two doublets (due to coupling with the fluorine atom) at δ 6.5 and δ 6.4 ppm, respectively. The H-3 proton is more deshielded and shows a larger $J_{\text{H-F}}$ value (13 Hz) than H-6 ($J_{\text{H-F}} = 8$ Hz). The N-4' methyl protons appear as a singlet at δ 2.4 ppm. The methylene protons of the piperazine moiety appear as two broad triplets centered at δ 3.0 ppm (C_2'/C_6') and δ 2.6 ppm (C_3'/C_5').

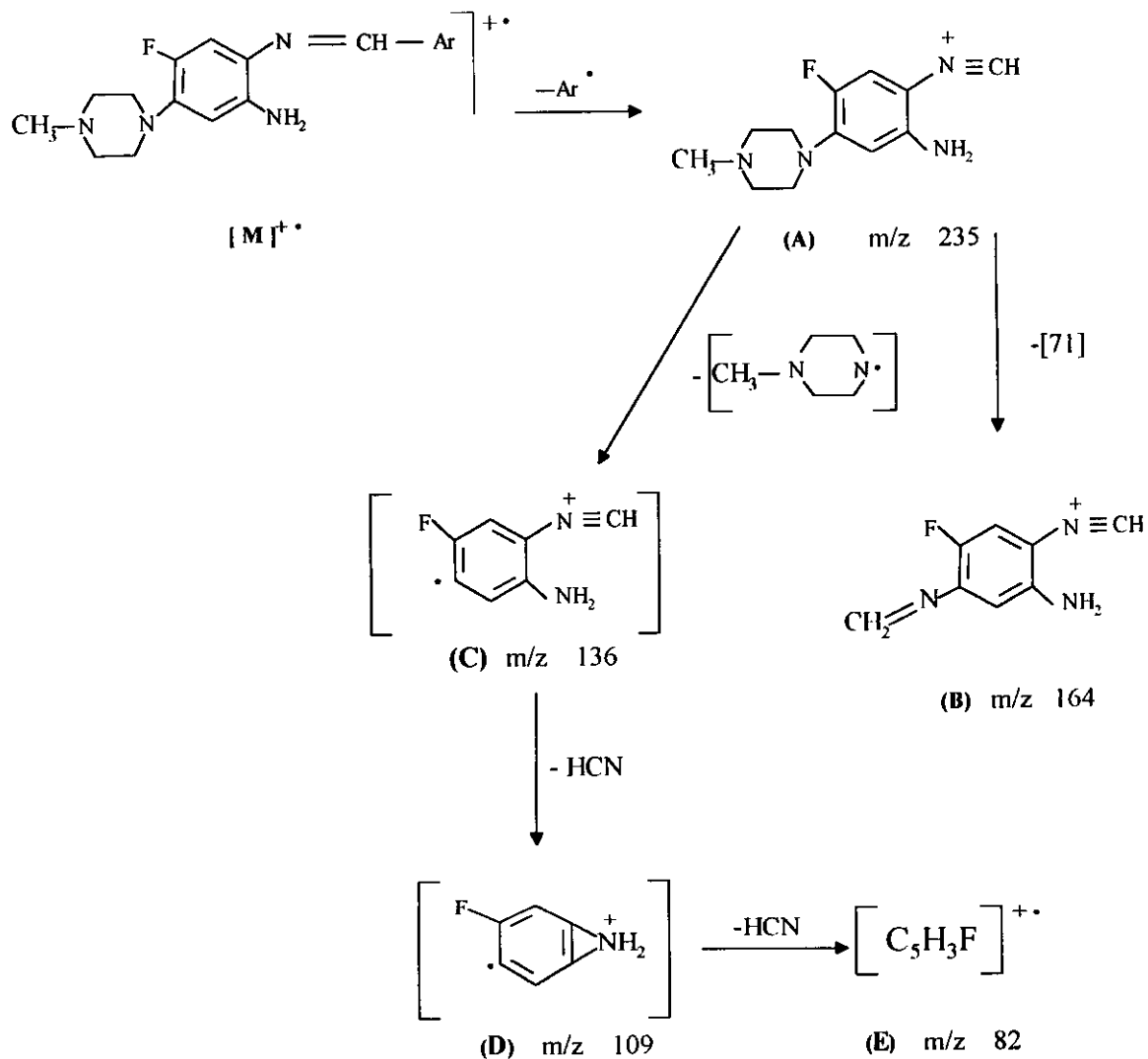
(ii) Compounds (7a-c,g). The ¹H-nmr spectra of these compounds are in agreement with their suggested structures. The chemical shift values and coupling constants are given in

Table 2. The m/z Values and % Relative Intensities (given in parenthesis) of the Principle Fragment Ions in the Mass Spectra of Compounds (8a-k)

Compd No	$[M]^{+}$	(A)	(B)	(C)	(D)	$\text{CH}_3-\overset{\text{CH}=\text{CH}_2}{\underset{\text{CH}_3}{\text{N}^+}}$	$\text{CH}_3-\overset{+}{\text{N}}=\text{CH}_2$
8 a	300 (100)	229 (36)	201 (7)	108 (5)	81 (5)	71 (28)	43 (53)
8 b	316 (100)	245 (39)	217 (8)	108 (6)	81 (5)	71 (43)	43 (65)
8 c	310 (76)	239 (41)	211 (8)	108 (9)	81 (6)	71 (60)	43 (100)
8 d	328 (72)	257 (37)	229 (7)	108 (9)	81 (6)	71 (57)	43 (100)
37 e	328 (62)	257 (27)	229 (5)	108 (8)	81 (14)	71 (40)	43 (100)
8 f	344 (50)	273 (27)	245 (6)	108 (8)	81 (7)	71 (61)	43 (100)
8 g	344 (41)	273 (17)	245 (4)	108 (8)	81 (6)	71 (52)	43 (100)
8 h	388 (34)	317 (16)	289 (2)	108 (7)	81 (6)	71 (60)	43 (100)
8 i	388 (32)	317 (15)	289 (2)	108 (9)	81 (5)	71 (53)	43 (100)
8 j	340 (98)	269 (42)	241 (3)	108 (4)	81 (3)	71 (60)	43 (100)
8 k	324 (80)	253 (42)	225 (8)	108 (8)	81 (4)	71 (61)	43 (100)

Table 4. The aromatic H-6 proton resonates at about δ 6.4 ppm (1H, d, $J_{\text{H-F}} = 7$ Hz) which is almost invariant to its position (δ 6.4 ppm) in the 1,2-diaminobenzene precursor (6). In contrast, the signal belonging to the aromatic H-3 proton in these Schiff bases appears at about δ 6.9 ppm (1H, d, $J_{\text{H-F}} = 13$ Hz) and is thus shifted downfield as compared to its

Scheme III



position (δ 6.5 ppm) in 1,2-diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**6**). This sizable shift might be attributed to the condensation of the aldehyde with the 1,2-diaminobenzene (**6**) at position 2. This situation brings the H-3 proton under the anisotropic effect of the azomethine (C=N) π -bond, resulting in the observed downfield shift. The methine proton appears as a singlet around δ 8.2-8.6 ppm. The exchangeable broad singlet, which appears around 4.2 ppm (2H), is assigned to the N-1 protons. The N-methyl protons appear as sharp singlet at δ 2.36 ppm, while the methylene protons of the piperazine moiety

Table 3 . The m/z Values and % Relative Intensities (given in parenthesis) of the Principle Fragment Ions in the Mass Spectra of Compounds (7a - c,g).

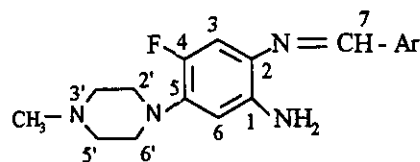
Compd No	[M] ⁺	(A)	(B)	(C)	(D)	(E)	$\text{CH}_3\text{-N}^+\text{(CH=CH}_2\text{)CH}_3$	$\text{CH}_3\text{-N}^+=\text{CH}_2$
7 a	302 (100)	235 (1)	164 (12)	136 (5)	109 (4)	82 (2)	71 (41)	43 (96)
7 b	318 (100)	235 (5)	164 (20)	136 (7)	109 (6)	82 (3)	71 (36)	43 (93)
7 c	312 (75)	235 (20)	164 (31)	136 (9)	109 (4)	82 (2)	71 (30)	43 (100)
7 g	346 (100)	235 (47)	164 (80)	136 (20)	109 (8)	82 (3)	71 (41)	43 (87)

appear as two broadened triplets at δ 3.1 (C_{2'} / C_{6'}) and δ 2.6 ppm (C_{3'} / C_{5'}). The spectrum of compound (7g) shows two doublets (AB system) at δ 7.4 ppm (J = 8 Hz), and at δ 7.8 ppm (J = 8 Hz), a pattern characteristic of the *para*-substituted phenyl ring protons.

(iii) Compounds (8). The ¹H-nmr spectra of these compounds are consistent with their proposed structures. The aromatic protons (H-4 and H-7) appear as two doublets around δ 7.4 (J_{H-F} 12 Hz) and δ 7.2 ppm (J_{H-F} 7 Hz), respectively, while those at C-2 appear in the range of δ 6.5, and δ 8.0 ppm. The N-4' methyl protons appear as sharp singlet around δ 2.3 ppm, while the methylene protons of the piperazine moiety appear as two broadened triplets around δ 2.5 (C_{3'} / C_{5'}) and δ 3.0 ppm (C_{2'}/C_{6'}). The exchangeable imidazole N-H proton appears as a broad singlet at *ca.* δ 12.2 ppm (for solutions of model compounds (8c, g, k) in DMSO-d₆). The chemical shift values and coupling constants for representative compounds of this series are given in Table 5.

BIOASSAY

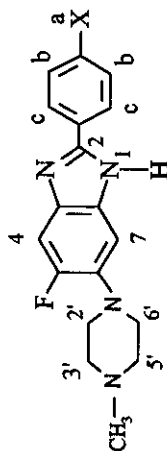
The following model compounds : 4-Flouro-5-(4-methy-1-piperaziny)-1,2-diaminobenzene (6), and 2-aryl-5- fluoro-6-(4-methyl-1-piperaziny)benzimidazoles (8c-e) were tested *in vitro*, in the form of their hydrochloride salts in aqueous solutions, against *E. coli*,

Table 4. The Chemical Shift Values (δ) and Coupling Constants of the Different Protons of Representative Compounds (7a - c, g).

Comp d No	Ar	N ₁ -H ₂	C ₇ -H	C ₃ -H (J _{H₃-F})	C ₆ -H (J _{H₆-F})	C _{2'} -H / ^e C _{6'} -H	C _{3'} -H / ^e C _{5'} -H	N-CH ₃	Ar - protons
7 a		4.21 (s)	8.25 (s)	6.87 (d) (J=13.5 Hz)	6.34 (d) (J=8.3 Hz)	3.12 (4H)	2.60 (4H)	2.36 (s)	6.54 (1H, dd, J = 3.5, 1.8 Hz) 6.91 (1H, dd, J = 3.4, 0.5 Hz) 7.58 (1H, dd, J = 1.8, 0.6 Hz)
7 b		4.20 (s)	8.55 (s)	6.91 (d) (J=13.6 Hz)	6.34 (d) (J=8.3 Hz)	3.12 (4H)	2.60 (4H)	2.36 (s)	7.10 (1H, dd, J = 3.7, 5.0 Hz) 7.40 (2H, m)
7 c		4.24 (s)	8.46 (s)	6.94 (d) (J=13.6 Hz)	6.37 (d) (J=8.3 Hz)	3.12 (4H)	2.60 (4H)	2.36 (s)	7.40 (3H, m) 7.90 (2H, m)
7 g		4.22 (s)	8.41 (s)	6.93 (d) (J=13.6 Hz)	6.35 (d) (J=8.3 Hz)	3.12 (4H)	2.60 (4H)	2.36 (s)	7.30 (2H, d, J = 8.0 Hz) 7.40 (2H, d, J = 8.0 Hz)

^e These signals appear as broad triplets.

Table 5. The Chemical Shift Values (δ) and Coupling Constants of the Different Protons of Representative Compounds (8c, e, g, i, j).



Compd. No	x	H-a	H-b	H-c	H-4 (J_{H_4-F})	H-7 (J_{H_7-F})	C _{2'} -H/e C _{6'} -H	C _{3'} -H/e C _{5'} -H	N-CH ₃
8c	H	7.47 (3H, m)		8.14 (2H, d, J = 7.3 Hz)	7.53 (d) (J=12.5 Hz)	7.20 (d) (J=7.0 Hz)	3.03 (4H)	2.53 (4H)	2.26 (3H, s)
8e	F	-	7.38 (2H, m)	8.16 (2H, m)	7.39 (d) (J=13.1 Hz)	7.16 (d) (J=7.1 Hz)	3.01 (4H)	2.53 (4H)	2.26 (3H, s)
8g	Cl	-	7.59 (2H, d, J = 8.8 Hz)	8.12 (2H, d, J = 8.8 Hz)	7.37 (d) (J=12.5 Hz)	7.16 (d) (J=6.7 Hz)	3.02 (4H)	2.52 (4H)	2.26 (3H, s)
8i	Br	-	7.73 (2H, d, J = 8.5 Hz)	8.02 (2H, d, J = 8.5 Hz)	7.37 (d) (J=12.4 Hz)	7.16 (d) (J=7.1 Hz)	3.04 (4H)	2.55 (4H)	2.28 (3H, s)
8j	OCH ₃	3.84 (3H, s)	7.10 (2H, d, J = 8.9 Hz)	8.05 (2H, d, J = 8.9 Hz)	7.36 (d) (J=12.3 Hz)	7.15 (d) (J=7.0 Hz)	3.00 (4H)	2.54 (4H)	2.27 (3H, s)

^e These signals appear as broad triplets.

S. aureus, *A. parasiticus* and *C. albicans*. The *in vitro* antibacterial activity was evaluated by the minimal inhibitory concentration (MIC) technique according to the macrodilution method.²⁰ However, none of the above compounds showed any significant activity at concentrations $\leq 100 \mu\text{g/ml}$.

The benzimidazole derivatives (**8a-k**) are being tested for possible anthelmintic / antihistaminic activity, and the results (if any) will be communicated separately.

EXPERIMENTAL

3-Chloro-4-fluoroaniline and *N*-methylpiperazine, used in this study, were purchased from Janssen Chimica. The benzaldehydes and hetero-aldehydes, used in this work, were commercial samples. The 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**5**), required in the present work, is prepared from 3-chloro-4-fluoroaniline by a sequence of steps involving acylation, nitration and deacylation,^{16,17} followed by piperazinylation,^{17,18} according to published procedures.

Melting points were measured on an electrothermal Mel-Temp. apparatus, and are uncorrected. ¹H-Nmr spectra were recorded on a Bruker WM-200 spectrometer, for solutions in CDCl₃ [compounds (**7**)] and in DMSO-d₆ + CD₃OD (3 : 1 v/v) [compounds (**8**)], with TMS as an internal reference. Electron impact (EI) mass spectra were obtained using a Finnigan MAT 731 spectrometer at 70 eV. Elemental analyses were carried out by M. H. W. Laboratories, Phoenix, Arizona, U. S. A.

1,2-Diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (6)

To a solution of 4-fluoro-5-(4-methyl-1-piperazinyl)-2-nitroaniline (**5**) (5.0 g, 20 mmol) in conc. HCl (100 ml) was slowly added stannous chloride (22.44 g, 0.12 mol) at room temperature during 10 min. Stirring was continued for additional 2 h. The reaction mixture was then cooled (ice-water bath) and treated gradually with concentrated solution of sodium hydroxide (40%) until the solution is strongly alkaline. The resulting aqueous mixture was extracted with chloroform (2×80 ml). The organic layer was separated, filtered and concentrated *in vacuo*. The resulting yellow solid was collected by suction filtration and crystallized from chloroform / pet. ether (bp 40-60 °C). Yield 2.3 g (51%); mp 96-97 °C.

The title 1,2-diaminobenzene (**6**), was converted to its hydrochloride salt as follows : HCl gas was allowed to bubble into a solution of 1,2-diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**6**) (3 g, 13 mmol) in anhydrous ether (30 ml) for 5 min. The resulting precipitate was collected, washed with anhydrous ether (5 ml) and recrystallized from methanol / ether. Yield 3.2 g (96%); mp 188-189 °C (decomp.).

1-Amino-2-arylideneamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzenes (7a-k)

General procedure. To a stirred solution of 1,2-diamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**6**) (1.1 g, 5 mmol) in absolute ethanol (10 ml) was added dropwise, the appropriate arylaldehyde (5 mmol) at room temperature. Stirring was continued for an additional hour. The resulting precipitate was collected and recrystallized from ethanol to give the corresponding Schiff base (key intermediates for the next step).

2-Aryl-5-fluoro-6-(4-methyl-1-piperazinyl)-1H-benzimidazoles (8a-k)

A solution of the particular 1-amino-2-arylideneamino-4-fluoro-5-(4-methyl-1-piperazinyl)benzene (**7a-k**), prepared above, in absolute ethanol (5 ml) and nitrobenzene (10 ml) was heated at 80-90 °C until most of ethanol was evaporated; the temperature was then raised to about 200 °C and maintained for 3 to 5 min. The reaction mixture was cooled, and allowed to stand overnight at room temperature. The resulting precipitate was collected, washed with ether and recrystallized from CHCl₃ / pet. ether (bp 40-60 °C) to give the title compounds (**8a-k**).

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