SYNTHESIS AND ANTIHISTAMINIC H_1 ACTIVITY OF 1,2,5(6)-TRISUBSTITUTED BENZIMIDAZOLES

Hakan Göker, *[a] Gülgün Ayhan-Kılcıgil,[a] Meral Tunçbilek,[a] Canan Kus,[a] Rahmiye Ertan,[a] Engin Kendi,[b] Süheyla Özbey,[b] Mercé Fort,[c] Celia Garcia,[c] and Antonio J. Farré [c]

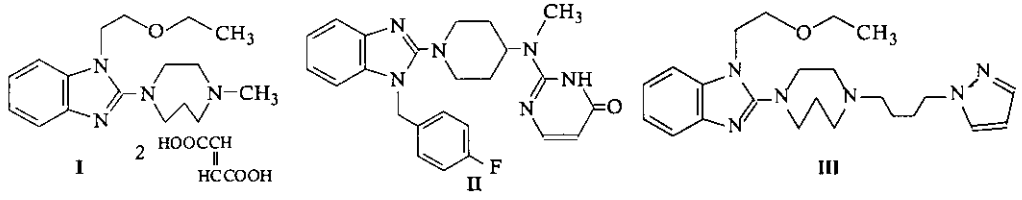
[a]Ankara University, Faculty of Pharmacy, Department of Pharmaceutical Chemistry, 06100-Tandogan, Ankara, Turkey [b]Hacettepe University, Department of Engineering Physics, Beytepe 06532, Ankara, Turkey [c]Department of Pharmacology, Laboratorios Dr. Esteve, S.A., Avda. Mare de Déu de Montserrat, 221, 08041-Barcelona , Spain

Abstract - A number of benzimidazoles, having several substituents on the azole and benzene nuclei and C-2 (methylamino, ethylenediamine, morpholine, piperazine and piperidine) were prepared. Regioselective synthesis was designed for the N^1-alkyl substituted benzimidazoles **(14-15)**. X-Ray structure analysis of **(14)** was also revealed. Compounds were evaluated for their *in vitro* H_1-antihistaminic activity in the isolated guinea-pig ileum method. The compound **(11)** exhibits best activity.

Classical H_1--antihistaminic compounds have been useful for the treatment of allergic diseases. Unfortunately, because of their depressive effects such as sedation and hypnosis on the central nervous system and peripheral side effects there is a limitation for the use of them.[1] During the last decade considerable efforts have been spent for discovering a new antihistaminic agent with minimum CNS effects while retaining a potent antihistaminic activity. It is getting more important day by day, because of the increasing ratio of the allergic disease particularly in developed countries.[2] In previous studies[3,4] we reported the synthesis and biological evaluation of 1,2,5(6)-trisubstituted benzimidazoles as an antimicrobial agents. Continuing our interest in this field, we found some papers concerning the synthesis and structure activity relationships of 2-(4-substituted 1-piperazinyl)benzimidazoles, which have potent H_1-antihistaminic activity.[5,6] Among the synthesized compounds, 1-(2-ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole (KB-2413) **(I)** was 39 times more potent than *chlorpheniramine maleate* in H_1-antihistaminic activity *in vivo* launched in Japan in 1994, for the treatment of allergic rhinitis and urticaria, named as *Emedastine Difumarate.*[7]

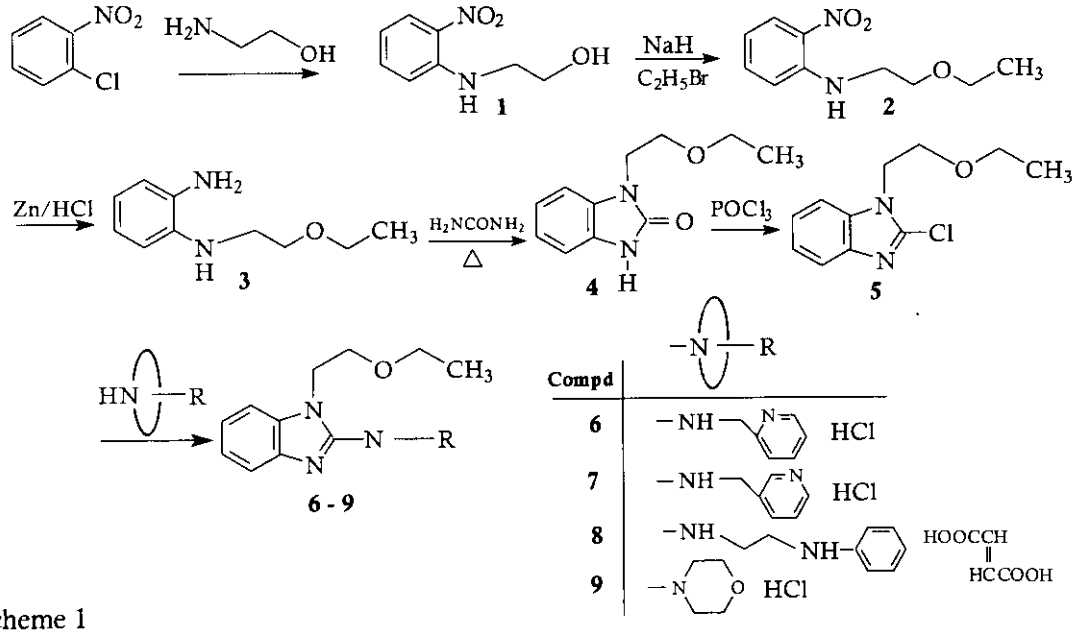
Furthermore *Mizolastine*[8] **(II)** and *Astemizole*[9] (on the market) were discovered as a potent histamine H_1 receptor antagonist. In another study,[10] a new series of benzimidazoles as H_1-antihistaminic agents were synthesized and according to their structure-activity relationships, the best antihistaminic activity required the presence of a homopiperazinyl benzimidazole system and an unsubstituted pyrazole ring **(III)**.

These findings prompted us to synthesize new analogues of benzimidazole derivatives in order to develop new antiallergic agents. The most active compound **(11)** has been selected for the further pharmacological studies.



Synthesis

The target 2-amino-1-ethoxyethyl-N^1-substituted 1*H*-benzimidazole were prepared by the reaction outlined in Scheme 1. The reaction of *o*-chloronitrobenzene with ethanolamine and its alkylation with ethyl bromide gave the intermediates **(1)** and **(2)**, respectively. Reduction of the nitro group afforded the *o*-phenylenediamine derivative **(3)**, which tended to cyclize to **4**, with urea and heat. Treatment of **4** with $POCl_3$ gave **5**, and substitution of this compound at the position 2 with several amine derivatives afforded **6-9**. By the similar reactions compound **(11-15)** were



Scheme 1

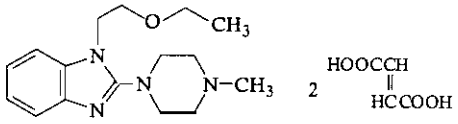
prepared (Scheme 2). The reaction of 2-chlorobenzimidazole with 1-(2-hydroxyethyl)piperazine gave **16** and alkylation of this compound with the appropriate alkylating agent afforded **(17-21)**. It was noteworthy that the reactions involving the isopropyl bromide and *m*-chlorobenzyl bromide afforded just alkylated imidazole derivatives **(18)** and **(21)**, respectively, even after a much longer reaction time.

Single crystal X-Ray diffraction studies were performed on **14.** Final atomic coordinates and selected bond distances, bond angles and torsion angles are contained in Tables 1 and 2. ORTEP (C. K. Johnson, ORTEP II. Report ORNL-5138. Oak Ridge National Laboratory, Tennessee, 1976) drawing of the compound showing the molecular conformation and atom-labelling scheme is depicted in Figure 1. As expected, the benzimidazole system is planer [maximum deviation -0.019(4) Å for C2]. The Cl atom attached to C5 lies -0.011(2) Å from the best-plane of the benzimidazole ring system. The benzene ring at N1 is also planer and makes an angle of 92.7(1)° with the plane through the complete benzimidazole ring system ; the F and C10 atoms lie almost in the phenyl ring plane with the greatest deviation being 0.095(6) Å for C10. The torsion angles C2-N1-C10-C11 and N3-C2-N2-C20 are -120.8(5) and 109.1(6)°, respectively. The piperazine ring shows the typical chair conformation, the N2 and N4 atoms lie 0.688(4) and -0.675(4) Å, respectively, from the least-square plane defined by the remaining four atoms of the piperazine ring. The dihedral angle between the best planes of the benzimidazole and the piperazine ring is 44.8(2) Å.

Results and discussion

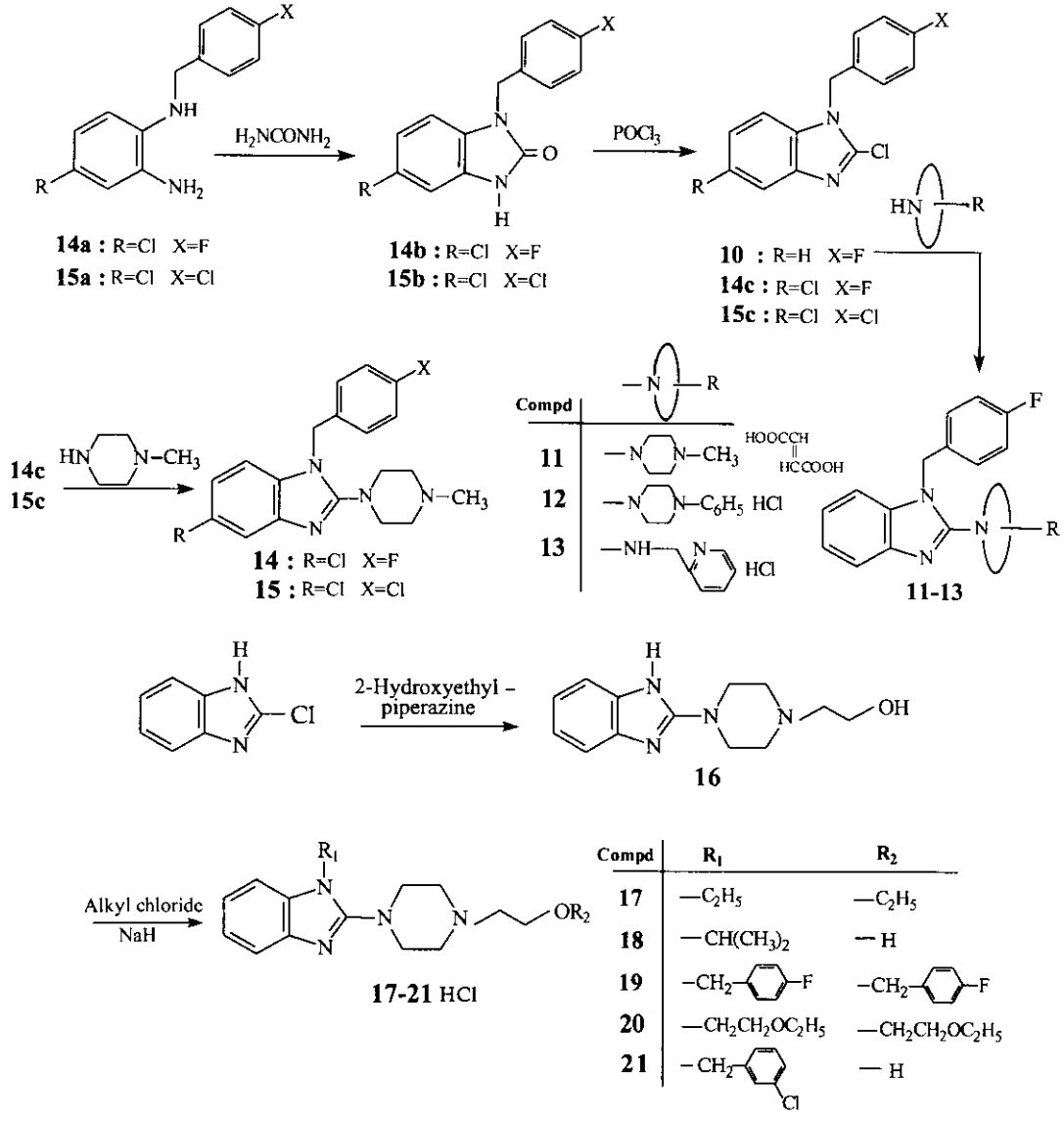
Compounds **(6-9,11-15,17,18,20** and **21)** were evaluated for their *in vitro* H_1-antihistaminic activity in the isolated guinea-pig ileum method.

All the synthesized compounds inhibited histamine-induced contractions of the isolated guinea-pig ileum in a competitive manner at the lower concentrations of histamine. Some of the compounds inhibited the histamine induced contractions, at the highest concentractions of histamine, in a noncompetitive manner. The corresponding pA_2 and pD'_2 values were calculated. However, the obtained results show that none of the synthesized compounds was found to be as active as the reference compound, 1-(2-ethoxyethyl)-2-(4-methyl-1-piperazinyl)benzimidazole **(IV)**,[5] with a pA_2 of 9.40. The compound **(11)** was the most active compound, with a pA_2 of 8.83, followed by the compounds **(15)** and **(14)** (pA_2 7.12 and 6.78, respectively). According to these results, it appears that when the benzimidazole nucleus having a *p*-fluorobenzyl group at the N1 atom [compound **(11)**], instead the 2-ethoxyethyl group, which has the reference compound **(IV)**, the antihistaminic activity was slightly reduced. The additional substitution with a Cl at the 5 position of benzimidazole compounds **(15)** and **(14)**, provokes an additional decrease in the antihistaminic activity.



IV

The (2-ethoxyethyloxy)ethyl group at the 4 position of the piperazinyl group [compound **(20)**] instead the methyl [reference **(IV)**] also seems to cause a reduction in the antihistaminic activity (pA_2 = 6.92) at the same range than the compounds **(14)** and **(15)**. The rest of substitutions induces clear decreases in the antihistaminic activity.



Scheme 2

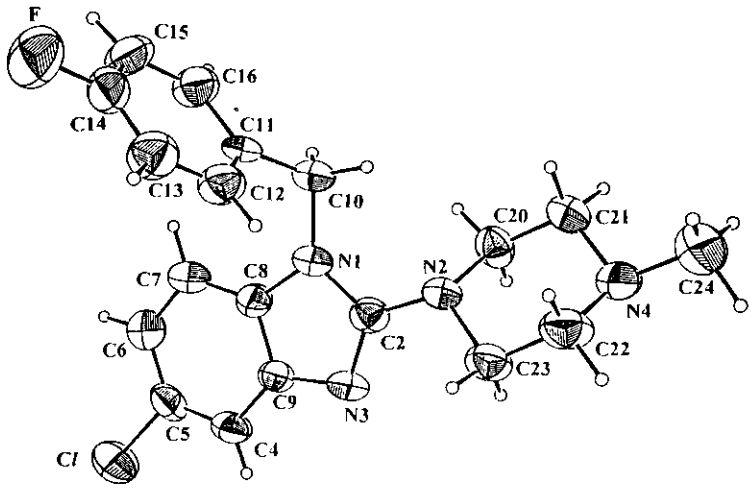


Figure 1. Numbering scheme with thermal ellipsoids drawn at the 50% probability level of compound **(14)**. H atoms are shown as small circles with arbitrary radii.

Table 1. Fractional atomic coordinates and equivalent displacement parameters of non-hydrogen atoms for compound **(14)**.

$$B_{eq} = (8\pi^2/3) \sum_i \sum_j U_{ij} a_i^* a_j^* a_i a_j$$

	x/a	Y/b	z/c	B(Å^2)
Cl	0.0669 (3)	0.0728 (1)	0.6500 (1)	6.32 (5)
F	-0.3802 (6)	-0.2655 (3)	0.2439 (3)	6.9 (1)
N1	-0.3384 (6)	-0.3907 (3)	0.7574 (3)	3.3 (1)
N2	-0.2337 (6)	-0.5863 (3)	0.8786 (3)	3.2 (1)
N3	-0.0544 (6)	-0.3967 (3)	0.8331 (3)	3.5 (1)
N4	-0.2778 (7)	-0.8355 (4)	1.0525 (3)	4.0 (1)
C2	-0.2051 (8)	-0.4614 (4)	0.8258 (4)	3.1 (1)
C4	0.0146 (9)	-0.1714 (4)	0.7463 (4)	3.9 (1)
C5	-0.0631 (9)	-0.0639 (4)	0.6787 (4)	4.1 (2)
C6	-0.2416 (9)	-0.0567 (5)	0.6323 (4)	4.5 (2)
C7	-0.3490 (9)	-0.1624 (4)	0.6532 (4)	4.3 (2)
C8	-0.2713 (9)	-0.2716 (4)	0.7196 (4)	3.4 (1)
C9	-0.0925 (8)	-0.2771 (4)	0.7667 (4)	3.2 (1)
C10	-0.5093 (8)	-0.4323 (5)	0.7228 (4)	4.0 (2)
C11	-0.4715 (8)	-0.3815 (4)	0.5931 (4)	3.3 (1)
C12	-0.2763 (9)	-0.3978 (4)	0.5271 (4)	4.4 (2)
C13	-0.2446 (9)	-0.3582 (5)	0.4097 (4)	4.8 (2)
C14	-0.4077 (9)	-0.3036 (5)	0.3597 (4)	4.2 (2)
C15	-0.6019 (9)	-0.2841 (5)	0.4199 (4)	4.8 (2)
C16	-0.6320 (9)	-0.3240 (5)	0.5379 (4)	4.4 (2)
C20	-0.4358 (8)	-0.6384 (4)	0.9762 (4)	3.8 (2)
C21	-0.4651 (8)	-0.7726 (4)	1.0145 (4)	3.9 (2)
C22	-0.0801 (9)	-0.7836 (5)	0.9565 (5)	4.9 (2)
C23	-0.0436 (8)	-0.6488 (4)	0.9172 (5)	4.2 (2)
C24	-0.310 (1)	-0.9649 (5)	1.0938 (5)	6.0 (2)

Table 2. Selected geometric parameters of compound **(14)**.

Cl - C5	1.755 (6)	C2 - N1 - C8	106.8 (5)	C2 - N1 - C10 - C11	-120.8 (5)
F - C14	1.359 (6)	C2 - N1 - C10	127.1 (4)	C8 - N1 - C10 - C11	54.2 (7)
N1 - C2	1.366 (6)	C8 - N1 - C10	125.9 (4)	C20 - N2 - C2 - N1	-71.1 (6)
N1 - C8	1.374 (6)	C2 - N2 - C20	114.5 (4)	C20 - N2 - C2 - N3	109.1 (6)
N1 - C10	1.467 (8)	C2 - N2 - C23	114.3 (4)	C23 - N2 - C2 - N1	161.7 (4)
N2 - C2	1.375 (6)	C20 - N2 - C23	109.4 (3)	C23 - N2 - C2 - N3	-18.2 (7)
N2 - C20	1.491 (5)	C2 - N3 - C9	104.9 (4)	C23 - N2 - C20 - C21	-58.6 (5)
N2 - C23	1.458 (6)	C21 - N4 - C22	108.9 (3)	C20 - N2 - C23 - C22	58.9 (5)
N3 - C2	1.322 (8)	C21 - N4 - C24	111.5 (5)	C22 - N4 - C21 - C20	-59.2 (6)
N3 - C9	1.378 (6)	C22 - N4 - C24	111.3 (4)	C21 - N4 - C22 - C23	58.9 (6)
N4 - C21	1.442 (7)	N1 - C2 - N2	120.8 (5)	N1 - C10 - C11 - C12	56.1 (7)
N4 - C22	1.462 (6)	N1 - C2 - N3	112.8 (4)	N1 - C10 - C11 - C16	-127.5 (6)
N4 - C24	1.444 (7)	N2 - C2 - N3	126.4 (4)	N2 - C20 - C21 - N4	59.3 (5)
C13 - C14	1.341 (8)	Cl - C5 - C4	118.6 (5)	N4 - C22 - C23 - N2	-59.7 (6)
C14 - C15	1.359 (8)	N1 - C10 - C11	113.6 (4)		
		F - C14 - C13	119.4 (5)		
		F - C14 - C15	117.8 (5)		

Table 3. Antihistaminic H_1 activity in the isolated guinea pig ileum of the synthesized compounds

Compound No	Range of Doses [M]	pA_2	pD'_2	n
IV(Reference)	1^{-9} M - 3^{-8} M	9.40	7.26	4
6	3^{-6} M - 3^{-5} M	4.76	-	3
7	3^{-6} M - 3^{-5} M	5.44	-	2
8	3^{-6} M - 3^{-5} M	4.99	4.73	5
9	3^{-6} M - 3^{-5} M	5.66	-	3
11	3^{-9} M - 1^{-6} M	8.83	5.97	4
12	3^{-7} M - 3^{-6} M	6.37	4.89	4
13	3^{-6} M - 3^{-5} M	6.55	4.53	2
14	3^{-7} M - 3^{-6} M	6.78	5.38	4
15	1^{-7} M - 3^{-6} M	7.12	4.97	5
17	1^{-6} M - 1^{-5} M	5.32	-	1
18	3^{-6} M - 3^{-5} M	5.07	-	3
20	1^{-7} M - 3^{-5} M	6.92	-	4
21	3^{-7} M - 3^{-6} M	-	5.19	1

EXPERIMENTAL

Mps were measured with a capillary melting point apparatus (Buchi SMP-20) and are uncorrected. The ^{1}H-NMR spectra were recorded on a Bruker AC 80, Bruker AC 200, Bruker AM 300 or Bruker DPX 400 spectrometers, in DMSO-d_6 unless otherwise stated, δ scale (ppm) from internal standart TMS. Chemical shifts are given as δ values (ppm). MS spectra were taken on JEOL-JMS 01SG-2, VG Analytical 70-250S and Kratos MS-9/50 (low resolution) spectrometers by

using EI (70 eV) or CI (NH_3). Elemental analyses were performed by TUBITAK (Instrumental Analyse Lab., Ankara) on a Leco CHNS-O 932 analyzer. Column chromatography was accomplished on silica gel 60 (40-63 μm particle size, Merck). Compounds **(4** and **5),**[5] **(11),**[11] **(14a),**[3] **(15a-15c),**[4] 5-chloro-benzimidazol-2-one,[12] 2-chloro-1*H*-benzimidazole,[13] 2-[4-(β-hydroxyethyl)piperazin-1-yl]-1*H*-benzimidazole **(16),**[14] mp 218°C, ref. mp 217-219°C were synthesized according to the literature. The HCl salts of the bases were prepared by bubbling dry HCl gas in a C_2H_5OH - ether solution of the base, unless otherwise stated.

N-(β-Hydroxyethyl)-o-nitroaniline **(1)** : A mixture of *o*-nitrochlorobenzene (10 g, 63 mmol) and ethanolamine (11 g, 180 mmol) was heated with stirring at 100°C for 3 h. After cooling, water was added, and red colored precipitate was collected to yield 11 g (95.2 %) of **1,** mp 71°C; mp wasn't changed after recrystallization from C_2H_5OH.

N-(β-Ethoxyethyl)-o-nitroaniline **(2)** : A mixture of **1** (10 g, 55 mmol), ethyl bromide (12 g, 110 mmol) and NaH (3.33 g, 83 mmol, 60% dispersion in mineral oil) in DMF (20 mL) was stirred at 30-35°C until the starting material was used up. The reaction mixture was diluted with C_2H_5OAc, washed with saturated NaCl solution, dried over Na_2SO_4 and evaporated *in vacuo*. The resulting brown colored oil (6.4 g , 55.5 %) was used for further steps without distillation.

N-(β-Ethoxyethyl)-o-phenylenediamine **(3)** : It was prepared according to the literature method,[5] but herein, Zn/HCl was used instead of Zn/NaOH.

2-Amino-1-(2-ethoxyethyl)-N-[(2-pyridinyl)methyl]-1H-benzimidazole **(6)** : A mixture of **5** (0.82 g, 3.65 mmol) and 2-aminomethylpyridine (2.3 g, 21.3 mmol) was stirred at 110°C for 5 h. 1N NaOH (15 mL) was added and the mixture was extracted with C_2H_5OAc. The extract was washed with water, dried over Na_2SO_4 and evaporated. The residue was chromatographed with $CHCl_3$: CH_3OH (15:0.5) ; 0.62 g (57.3%) ; mp 85-87°C, 228-230°C (HCl salt) ; ^{1}H-NMR(300 MHz) : δ 1.04 (t, 3H, J=7 Hz), 3.45(q, 2H, J=7 Hz), 3.67(t, 2H, J=6.5 Hz), 4.24(t, 2H, J=5 Hz), 4.68(d, 2H, J=5 Hz), 6.96(m, 2H, J=7 Hz), 7.30(m, 4H), 7.40(d, 1H, J=8 Hz), 7.73(t,1H, J=8 Hz), 8.51(d,1H, J=5 Hz) ; MS : m/z 296.2($M^{+\cdot}$, 22.7), 252.3(20.1), 224.2(100), 146(39), 118(15.2), 92.9(20). *Anal.* Calcd for $C_{17}H_{20}N_4O$. 0.2 CH_3OH : C, 68.23 ; H, 6.90 ; N, 18.50. Found : C, 68.32 ; H, 6.44 ; N, 18.30.

2-Amino-1-(2-ethoxyethyl)-N-[(3-pyridinyl)methyl]-1H-benzimidazole **(7)** : It was prepared and purified in

analogy to **6** starting from **5** (0.89 g, 3.9 mmol) and 3-aminomethylpyridine (2 g, 18.51 mmol) ; 0.5 g (46.3 %) ; mp 112°C; 234°C (HCl salt) ; ^{1}H-NMR (300 MHz) : δ 6.98(m, 2H), 7.13(t, 1H, J=6 Hz), 7.18(m, 2H), 7.33(m, 1H), 7.78(dt, 1H, J_o=8 Hz, J_m=1 Hz), 8.47(dd, 1H, J_o=5 Hz, J_m=1.5 Hz), 8.59(d, 1H, J_o=1.5 Hz) , other protons are same with **6** ; MS : m/z 296.2($M^{+\cdot}$, 100), 251.2(46.7), 237.1(64.3), 224.1(53.4), 208(11.7), 158(13), 146(11.4), 133(16.9), 118 (42.7), 91.9(77.2). *Anal.* Calcd for $C_{17}H_{20}N_4O$: C, 68.88 ; H, 6.81 ; N, 18.90. Found : C, 68.89 ; H, 6.99 ; N, 18.40.

2-Amino-1-(2-ethoxyethyl)-N-(2-phenylaminoethyl)-1H-benzimidazole **(8)** : It was prepared and purified in analogy to **6**, starting from **5** (0.82 g, 3.65 mmol) and *N*-phenylethylenediamine (1.46 g, 10.7 mmol), at 60°C, for 7 h, as hydrogen fumarate ; 0.55 g (34.24%) ; mp 140-141°C (from C_2H_5OH) ; ^{1}H-NMR (300 MHz) : δ 1.02(t, 3H, J=7 Hz), 3.27(t, 2H, J=7 Hz), 3.40(q, 2H, J=7 Hz), 3.60(4H), 4.14(t, 2H, J=5 Hz), 6.62(m, 3H), 6.81-7.32(m, 8H) ; MS : m/z 324.16($M^{+\cdot}$,11.2), 218.2(100), 206.2(74.09), 174(13.92), 161(12.97), 146(15.42), 133.1(54.28), 97.9(19.04). *Anal.* Calcd for $C_{19}H_{24}N_4O$. $C_4H_4O_4$: C, 62.70 ; H, 6.41 ; N,12.72. Found : C, 62.90 ; H,6.41 ; N,12.67.

1-(2-Ethoxyethyl)-2-(1-morpholino)-1H-benzimidazole **(9)** : It was prepared in analogy to **6** (without column chromatography), starting from **5** (0.89 g, 3.95 mmol) and morpholine (0.5 g, 5.74 mmol) at 120°C for 4 h, as HCl salt (recrystallized from absolute C_2H_5OH), very hygroscopic, 0.62 g (50.4%) ; mp 162°C ; ^{1}H-NMR (300 MHz) : δ 0.99(t, 3H, J=7 Hz), 3.40(q, 2H, J=7 Hz), 3.69(t, 4H, J=5 Hz), 3.78(t, 6H, J=5 Hz), 4.42(q, 2H, J=5 Hz), 7.37(m, 2H), 7.56(m, 1H), 7.73(m, 1H) ; MS : m/z 275.1($M^{+\cdot}$, 55), 218.1(100), 203.1(24.8), 173.1(20.5), 158.2(27.7), 146.1(52), 133(50), 118(43), 69(42.8), 57.2(65). *Anal.* Calcd for $C_{15}H_{21}N_3O_2$. HCl . 0.5 H_2O : C, 56.16 ; H, 7.17 ; N, 13.10. Found : C, 56.45 ; H, 6.99 ; N,13.20.

2-Chloro-1-(p-fluorobenzyl)-1H-benzimidazole **(10)** : A mixture of 2-chlorobenzimidazole (1 g , 6.56 mmol), *p*-fluorobenzyl bromide (1.52 g, 8.03 mmol) and NaH (60 %, in oil, 0.35 g, 8.75 mmol) in DMF (15 mL) was stirred at 60°C for 0.5 h. The reaction mixture was poured into water and extracted with C_2H_5OAc. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed (C_2H_5OAc : hexane, 5 :10, v/v), as colorless crystals, 1.1 g (61.8%), mp 77-79°C ; ^{1}H-NMR (80 MHz, $CDCl_3$) : δ 5.25(s, 2H), 6.71-7.83 (m, 8H) ; MS : m/z 260($M^{+\cdot}$, 23.2), 262(7.8), 109(100). *Anal.* Calcd for $C_{14}H_{10}N_2ClF$: C, 64.60 ; H, 3.88; N,10.77. Found : C, 64.85 ; H, 3.85 ; N, 10.74. (lit.,[15]).

1-(p-Fluorobenzyl)-2-(4-phenyl-1-piperazinyl)-1H-benzimidazole **(12)** : It was prepared in analogy to **6**,

starting from **10** (0.9 g, 3.45 mmol) and *N*-phenylpiperazine (1.12 g, 6.9 mmol), at 120°C, for 9 h. The mixture of C_2H_5OAc : hexane (10 : 3, v/v) was used for column chromatography, 0.55 g (41.43%), mp 136°C ; ^{1}H-NMR (80 MHz, $CDCl_3$) : δ 2.82-3.50(8H), 5.29(s, 2H), 6.71-7.72(m, 13H, aromat.) ; MS : m/z 386(M^+, 3.6), 277(2.7), 254(34.5), 241(15.7), 144(5.6), 109(100). HCl salt of **12** was prepared with a few drops of conc. HCl acid in C_2H_5OH and crystallised by adding ether, mp 155-156°C. *Anal.* Calcd for $C_{24}H_{23}N_4F$: C, 74.57; H, 6.00 ; N, 14.50. Found : C, 74.36 ; H, 6.04 ; N, 14.50.

2-Amino-1-(p-fluorobenzyl)-N-[(2-pyridinyl)methyl]-1H-benzimidazole **(13)** : It was prepared in analogy to **6**, starting from **10** (0.69 g, 2.65 mmol) and 2-aminomethylpyridine (0.57 g, 5.29 mmol), at 120°C, for 10 h. The mixture was chromatographed with C_2H_5OAc : hexane (10 : 5, v/v), 0.42 g (47.76 %), mp 133°C; ^{1}H-NMR (80 MHz, $CDCl_3$) : δ 4.68(d, 2H, J=6.4 Hz), 5.2(s, 2H), 5.85(br s, 1H), 6.81-7.31(10H), 7.73(ddd, 1H, J_o=9 Hz, J_m=1 Hz), 8.51(dd, 1H, J_o=9.5 Hz, J_m=1 Hz) ; MS : m/z 332(55.2), 254(11.6), 223(100), 119(10.4), 109(82.7). HCl salt of **13** was prepared with conc. HCl acid, in C_2H_5OH : ether, mp 272°C. *Anal.* Calcd for $C_{20}H_{17}N_4F.2H_2O$: C, 65.20; H, 5.75 ; N, 15.20. Found : C, 65.10 ; H, 5.85 ; N, 15.30.

5-Chloro-1-(p-fluorophenylmethyl)-2(1H)-benzimidazolone **(14b)** : A mixture of **14a** (0.7 g, 2.8 mmol) and urea (1 g, 16.67 mmol) was heated at 150°C for 5 h. Water was added, precipitate was collected and recrystallized from toluene to yield 0.5 g (64.9%) of **14b,** as colorless crystals, mp 204° C (lit., [16] 202-204° C).

2,5-Dichloro-1-(p-fluorophenylmethyl)-1H-benzimidazole **(14c)** : A mixture of **14b** (1 g, 3.6 mmol) and $POCl_3$ (14 mL, 150 mmol) was refluxed with stirring for 7 h and dry HCl gas was passed through the refluxing liquid during the first 4 h, then $POCl_3$ was evaporated, reaction mixture was poured into ice-cold water, 4N NaOH was added and the mixture was extracted with C_2H_5OAc. The extract was washed with water, dried over Na_2SO_4 and evaporated. Recrystallization of the mixture from C_2H_5OAc : n-hexane (% 50, v/v) gave **14c**, 0.54 g (50.9 %), mp 165°C (lit., [16] 164-167°C).

5-Chloro-1-(p-fluorophenylmethyl)-2-(4-methylpiperazin-1-yl)-1H-benzimidazole **(14)** : A mixture of **14c** (0.5 g, 1.7 mmol) and *N*-methylpiperazine (0.2 g, 2 mmol) in DMF (0.5 mL) was heated for 8 h at 110°C, water was added and the mixture was extracted with C_2H_5OAc. The extract was washed water, dried over Na_2SO_4 and evaporated. The residue was chromatographed ($CHCl_3$: isopropanol 10 : 1, v/v) to give **14** in 42 % yield (0.255 g), colorless crystals, mp 161°C , 245°C (HCl salt) ;

^{1}H-NMR (200 MHz, $CDCl_3$) : δ 2.51(s, 3H), 2.82(br s, 4H), 3.49(br s, 4H), 5.16(s, 2H), 6.96(d, 1H, J=8.5 Hz), 7.03-7.22 (5H), 7.59(d, 1H, J_m=1.5 Hz) ; MS : m/z 358($M^{+\cdot}$, 31.5), 360(M+2,10.5), 302(17.5), 304(5.8), 289 (68), 291(23.3), 277(100), 179(17), 181(6.2), 152(27), 154(8.5), 110(80), 83(52.5), 71(72.5). *Anal.* Calcd for $C_{19}H_{20}N_4ClF$: C, 63.66 ; H, 5.63 ; N, 15.60. Found : C, 63.34 ; H, 5.51 ; N, 15.30.

5-Chloro-1-(p-chlorophenylmethyl)-2-(4-methylpiperazin-1-yl)-1H-benzimidazole **(15)** : It was prepared in analogy to **14**, starting from **15c** (0.25 g, 0.8 mmol) and *N*-methylpiperazine (0.3 g, 3 mmol) in 20.5 % yield, (0.062 g), mp 150°C, 296-298°C (HCl salt). ^{1}H-NMR : δ (400 MHz, $CDCl_3$) : δ 2.41(s, 3H), 2.62(t, 4H, J=4.6 Hz), 3.4(t, 4H, J=4.5 Hz), 5.15(s, 2H), 6.86(d, J=8 Hz, 1H), 7.15(m, 4H), 7.35(d, 1H, J=8 Hz), 7.62(1H) . *Anal.* Calcd for $C_{19}H_{20}N_4Cl_2$: C, 60.95 ; H, 5.39 ; N, 14.97. Found C, 60.47; H, 5.32 ; N, 14.74.

2-[4-(β-Ethoxyethyl)piperazin-1-yl]-1-ethyl-1H-benzimidazole **(17)** : A mixture of **16** (0.5 g, 2.03 mmol), ethyl bromide (0.6 mL, 8 mmol) and NaH (60%, in oil, 0.2 g, 5 mmol) in DMF (2 mL) was stirred at 60°C, for 5.5 h. The reaction mixture was poured into water and extracted with C_2H_5OAc. The extract was washed with water, dried over Na_2SO_4 and concentrated *in vacuo*. The residue was chromatographed ($CHCl_3$: acetone : ammonium hydroxide (25%), 5 : 18 : 1, v/v). Oily product was crystallized from the CH_3OH : ether, as HCl salt, 0.25 g 32.9%, mp 238°C; ^{1}H-NMR (300 MHz) : δ 1.18(t, 3H, J=7 Hz), 1.45(t, 3H, J=7 Hz), 3.41(t, 2H, J=5 Hz), 3.50(q, 2H, J=7 Hz), 3.71(br s, 4H), 3.85(t, 2H, J=6.5 Hz), 4.05(br s, 4H), 4.27(q, 2H, J=7 Hz), 7.42(m, 2H), 7.62(dd, 1H, J_o=8 Hz, J_m=2 Hz), 7.75(dd, 1H, J_o= 8 Hz, J_m=2 Hz), 11.9(br s, H^+) ; MS : m/z 302($M^{+\cdot}$,41), 273(8), 256 (32), 243 (15), 188(62), 174(100), 161(87), 146(32), 133(38), 118(58). *Anal.* Calcd for $C_{17}H_{26}N_4O$. 2HCl . 0.1 H_2O : C, 54.14; H, 7.48 ; N, 14.86. Found : C, 53.96 ; H, 7.31 ; N, 14.81.

2-[4-(β-Hydroxyethyl)piperazin-1-yl]-1-isopropyl-1H-benzimidazole **(18)** : It was prepared in analogy to **17** starting from **16** (0.75 g, 3.04 mmol), isopropyl bromide (1.11 g, 9 mmol) and NaH (60 %, in oil, 0.3 g, 7.5 mmol) in DMF (3 mL) for 48 h at rt. The residue was chromatographed ($CHCl_3$: isopropanol : dimethylamine 20 : 1 : 0.3, v/v) and oily product was crystallized from the C_2H_5OH : ether, as HCl salt, in 23 % yield (0.25 g), mp 223°C; ^{1}H-NMR (300 MHz) : δ 1.62(d, 6H, J=7 Hz), 3.31-3.91 (12H), 4.65(m, 1H), 7.40(m, 2H), 7.65(dd, 1H, J_o=8 Hz, J_m=2 Hz), 7.9(dd, 1H, J_o=8 Hz, J_m=2 Hz), 11.3(br s, 1H) ; MS : m/z 289(M+1, 12.5), 271(6), 258(11), 203(25), 188(100), 175(85), 160(18), 146(92), 133(46), 118(42). CI(NH_3) : 289 (M+1, 100). *Anal.* Calcd for $C_{16}H_{24}N_4O$. 2HCl .

0.6 H_2O : C, 51.64 ; H, 7.31 ; N, 15.06. Found : C, 51.61 ; H, 6.89 ; N, 15.06 .

1-(p-Fluorobenzyl)-2-[4-(2-(p-fluorobenzyloxy)ethyl)piperazin-1-yl]-1H-benzimidazole **(19)** : A mixture of compound **(16)** (0.5 g, 2.03 mmol), *p*-fluorobenzyl bromide (1.54 g, 8.15 mmol) and NaH (60 %, in oil, 0.2 g, 5 mmol) in DMF (2 mL) was stirred for 4 h at 60°C. Water was added and the mixture was extracted with C_2H_5OAc, then evaporated. Oily base product was crystallized from the CH_3OH : ether, to give **19**, in 29 % yield (0.315 g), as HCl salt, mp 165-169°C ; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 3.55-3.81 and 4.11(m, 10H), 4.20(t, 2H, J=5 Hz), 5.35(s, 2H), 5.42(s, 2H), 6.90-7.42(m, 9H), 7.60(dd, 1H, J_o=7 Hz, J_m=1 Hz), 7.7(m, 2H) ; MS : m/z 462(M^+,2), 353(2.2), 336(3), 254(32), 241(27), 146(5), 109(100) ; CI(NH_3) : 463 (M+1, 80) . *Anal.* Calcd for $C_{27}H_{28}N_4OF_2$. 2HCl : C, 60.65 ; H, 5.66. Found : C, 61.09 ; H, 5.66 .

(2-Ethoxyethyl)-2-[4-(2-ethoxyethyloxy)ethyl)piperazin-1-yl]-1H-benzimidazole **(20)** : It was prepared in analogy to **19** starting from **16** (0.3 g, 1.22 mmol), ethoxyethyl bromide (0.54 g, 3.5 mmol) and NaH (60 %, in oil, 0.2 g, 5 mmol) in DMF (1 mL) for 24 h and 48 h, at 65°C and rt, respectively. The residue was recrystallized from acetone : ether to give **20**, in 17 % yield (0.1 g), as HCl salt, mp 140-142°C ; ^{1}H-NMR (300 MHz, $CDCl_3$) : δ 1.10(t, 3H, J=7Hz), 1.21(t, 3H, J=7Hz), 3.41-4.50 (24H), 7.35(m, 3H), 7.75(d, 1H, J=8 Hz) ; MS : m/z 391(M+1, 18), 300(41), 232(43), 218(100), 205(86), 161(82), 133(84). *Anal.* Calcd for $C_{21}H_{34}N_4O_3$. 2HCl . 1.2 H_2O : C, 52.00 ; H, 7.97 ; N, 11.56. Found : C, 51.90 ; H, 7. 45 ; N, 11.78.

1-(3-Chlorobenzyl)-2-[4-(β-hydroxyethyl)piperazin-1-yl]-1H-benzimidazole **(21)** : It was prepared in analogy to **19** starting from **16** (0.3 g, 1.22 mmol), 3-chlorobenzyl chloride (0.635 g, 3.09 mmol) and NaH (60 %, in oil, 0.2 g, 5 mmol) in DMF (1 mL) for 14 h. The residue was recrystallized from C_2H_5OH : ether to give **21**, in 21.6 % yield (0.124 g), as HCl salt, mp 230°C ; ^{1}H-NMR (80 MHz, DMSO-d_6 +$CDCl_3$) : δ 3.41-4.30(12H), 4.65(s, 2H), 7.13-7.55(m, 8H) ; MS : m/z 370(M^+, 4.87), 372(1.9), 270(2.6), 272(0.84), 259(0.58), 257(1.4), 245(2.5), 228(12.8), 215(10.3), 160(21.8), 146(100), 133(30.2), 125(17.2). *Anal.* Calcd for $C_{20}H_{23}N_4OCl$. 2 HCl . 1.5 H_2O : C, 51.06 ; H, 5.95 ; N, 11.91. Found: C, 51.11; H, 5.8 ; N, 11.70.

X-Ray Crystallography for **14**

Crystal data : $C_{19}H_{20}N_4ClF$, M_r=358.85, triclinic, space group P1, a=6.274(1), b=12.38(1), c=13.340(2)Å, α=62.80(1), β=75.61(1), γ=86.82(1)°, V=890.7(3)Å^3, Z=2, D_c=1.338 gcm^{-3},

$\lambda(MoK_\alpha)$=1.71073Å, μ=0.23mm^{-1}, T=293 K. Intensity data were measured on Enraf-Nonius CAD4 diffractometer using graphite monochromated MoK_α radiation and the ω-2θ scan technique up to $2\theta_{max}$=47.1°. Reflections measured 2904, unique 2625, observed 1131[I>2σ(I)]. The structure was solved by direct methods using SIR in MolEN[17] and refined on F by full-matrix least-squares. All H atoms were geometrically located 0.95 Å from their parent atoms and included using a riding model; displacement parameters were fixed at $1.3U_{eq}$ of the parent atom. The refinement converged at R=0.0541 and R=0.0513 for 1131 reflections and 232 parameters. Excursions in difference Fourier map between 0.20(5) and -0.41(5) eÅ^{-3}.

Biological method : Inhibition of Histamine-induced contraction of guinea-pig ileum.
This test was performed according to the method of Magnus.[18] Male Dunkin-Hartley guinea-pigs (bw 250-450 g), fasted overnight, were used. Animals were stunned, the abdomen was opened, and 3 cm long ileum sections were cut off. The sections were placed in a petri dish containing Tyrode's solution at 37°C and continuously bubbled with carbogen. The ileum fragments were washed with Tyrode's solution and then transferred to an organ bath. Ileum isotonic contractions were measured using a HP 7DCDT-1000 transducer and Letica polygraph-400 analogical recorder. The initial load was 1 g. The organ was immersed in Tyrode's solution at 37°C, continuously bubbled with carbogen, and the stabilization period was 30 min. Dose-response curves to histamine were sequential, the exposure times were 20 s, the interval between doses was 2 min. The contraction curves in absence or presence (15 min incubation) of the test compounds were recorded. The contraction response was expressed as % of the histamine maximal response. The activities of the antagonists are expressed as pA2, values for competitive antagonism (negative logarithm of the molar concentration of antagonist which causes a shift of agonist activity by a factor of 2) calculated following the Schild plot method,[19,20] or pD'2 values for noncompetitive antagonism (negative logarithm of the molar concentration of antagonist which causes a depression to 50% of the maximum response of agonist), calculated according to Van Rossum .[21]

REFERENCES

1. D.T. Witiak and R.C. Cavestri, Burger's Medicinal Chemistry, Vol III, John Wiley & Sons, New York, 1981, p. 553.
2. A. Orjales, M. Bordell, and V. Rubio, *J. Heterocycl. Chem.*, 1995, **32**, 707.
3. H. Göker, C. Kus, and U. Abbasoglu, *Arch. Pharm (Weinheim).*, 1995, **328**, 425 .
4. C. Kus, H. Göker, G. Ayhan, R. Ertan, N. Altanlar, and A. Akin, *Farmaco*, 1996, **51**, 413.

5. R. Iemura, T. Kawashima, T. Fukuda, K. Ito, and G. Tsukamoto , *J. Med. Chem.*, 1986, **29**, 1178.
6. R. Iemura, T. Kawashima, T. Fukuda, K. Ito, and G. Tsukamoto, *J. Heterocycl. Chem.*, 1987, **24**, 31.
7. X. M. Cheng., *Ann. Reports in Med. Chem.*, 1994, **29**, 336.
8. J. Benavides, H. Schoemaker, C. Dana, Y. Claustre, M. Delahaye, M. Prouteau, P. Manoury, J. Allen, B. Scatton, S. Z. Langer, and S. Arbilla. *Arzneim.-Forsch./Drug Res.*, 1995, **45**, 551.
9. A. Wauquier, and C. J. E. Niemegeers, *Eur. J. Pharmacol.*, 1981, **72**, 245.
10. M. R. Cuberes, M. Contijoch, C. Calvet, J. Alegre, J. R. Quintana, and J. Frigola, *Chem. Pharm. Bull.*, 1989, **45**, 1287.
11. S. Özbey, E. Kendi, H. Göker, and M. Tunçbilek. *J. Chem. Crystallogr.*, 1998, **28**, 461.
12. W. B. Wright, *J. Heterocycl. Chem.*, 1965, **1-2**, 41.
13. D. Harrison, J. T. Ralph and A. C. B. Smith, *J. Chem. Soc.*, 1963, 2930.
14. T. Kodama, A. Takai, M. Nakabayashi, I. Watanabe, H. Sadaki, T. Kodama, N. Abe, and A. Kurukawa, Japan Kokai Patent 126,682 (1975) (*Chem. Abstr.*, 1976, **84**, 44060h).
15. M. V. Suryanarayana, S. Venkataraman, M. S. Reddy, B. P. Reddy, C. S. P. Sastry, and G. L. D. Krupadanam, *Talanta* , 1993, **40**, 1357 .
16. P. Manoury, J. Binet, G. Defosse, and E. Dewitte, Fr. Demande FR, 2,637,595 (*Chem. Abstr.*, 1990, **113**, 191389t).
17. C. K. Fair, MolEN. An Interactive Intelligent System for Crystal Structure Analysis. Enraf-Nonius, Delft, The Netherlands, 1990.
18. R. Magnus. Pflügers. *Arch. Ges. Physiol.*, 1904, **102**, 123.
19. H. O. Schild *Br. J. Pharmacol.*, 1947, **2**, 189.
20. O. Arunlakshana, and H. O. Schild, *Br. J. Pharmacol.*, 1959, **14**, 48.
21. J. M. Van Rossum, and F. G. Van der Brink, *Arch. Int. Pharmacodyn.*, 1963, **143**, 299.

Received, 12th April, 1999