Synthesis and Structure-Activity Relationship of New Piperidinyl and Piperazinyl Derivatives as Antiallergics

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A series of piperazinebenzothiazoles **3-5**, piperazinebenzimidazoles **6-12**, piperidinobenzothiazoles **14-45**, piperidinobenzoxazoles **46-52** and piperidinobenzimidazoles **53-129** has been synthesized and their antiallergic activity evaluated by means of the passive cutaneous anaphylaxis (PCA) assay. Structure-activity relationships are discussed and related to classical antihistaminics. Piperidino derivatives with an aryl group linked to the nitrogen atom by an ethyl chain are the most active compounds, with $ID_{50} < 1$ mg/kg po. Some of these compounds are more potent antiallergics than astemizole and terfenadine.

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Introduction.

Incidence of allergic diseases is high among human population, particularly in developed countries [1] and, according to recent reviews, the severity of some of these disorders is increasing [2]. Classical H_1-antihistaminic compounds have been useful tools, since 1942, for treating symptomatology of allergy.

The principal limitations for the use of classical H_1-antihistaminics are their action on the central nervous system, that cause depressive effects such as sedation, hypnosis, etc. [3], as well as some peripheral side effects that may be due to their anticholinergic properties [4].

In recent years a considerable research effort has been dedicated to the discovery and introduction into clinical medicine of several new compounds that have been reported to be devoid of CNS effects while retaining a high efficacy as antihistaminics. Until the late 1970s most of H_1-antihistaminics could be represented by the general formula in Figure 1, where a tertiary amino moiety was linked to two aromatic groups by a three units chain (-X-CH_2-CH_2-); X might be a carbon (*e.g.* chlorpheniramine), an oxygen (*e.g.* diphenydramine), or a nitrogen (*e.g.* chlorcyclizine), and the two aryl groups might be bridged to form tricyclic derivatives [5,6].

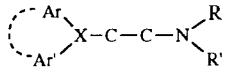
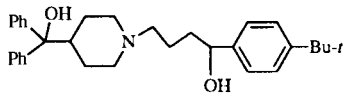


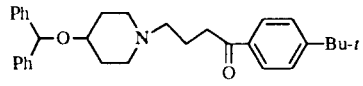
Figure 1

Some of the most recent antihistaminics, as terfenadine [7] and ebastine [8], are structurally related to classical antihistaminics while others, as astemizole [9] and KB-2413 [10], present some relevant differences in their structures, the principal being the presence of a 1*H*-benzimidazole unit linked to the tertiary amino group. On the other hand, both compounds have a common structural feature: they have a nitrogen atom linking the benzimidazole moiety to the characteristic ethylamino group. As it has been aforementioned, the presence of a nitrogen linking the lipophylic diaryl unit to the alkylamino group was not necessary in classical antihistaminics (X = N in Figure 1) for activity.

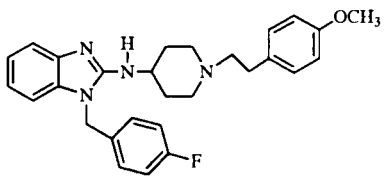
Chart 1



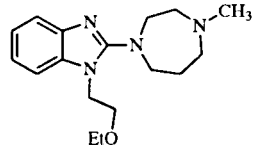
Terfenadine



Ebastine



Astemizole



KB-2413

In order to find new more potent antiallergic agents, as well as to elucidate the exact role of the nitrogen atom-linkage, we have prepared a novel series of compounds in which different benzo heterocyclic systems are attached to an alkylamino radical through a carbon (Y = CH) or a nitrogen atom (Y = N) (Figure 2).

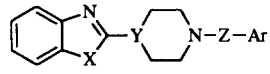


Figure 2

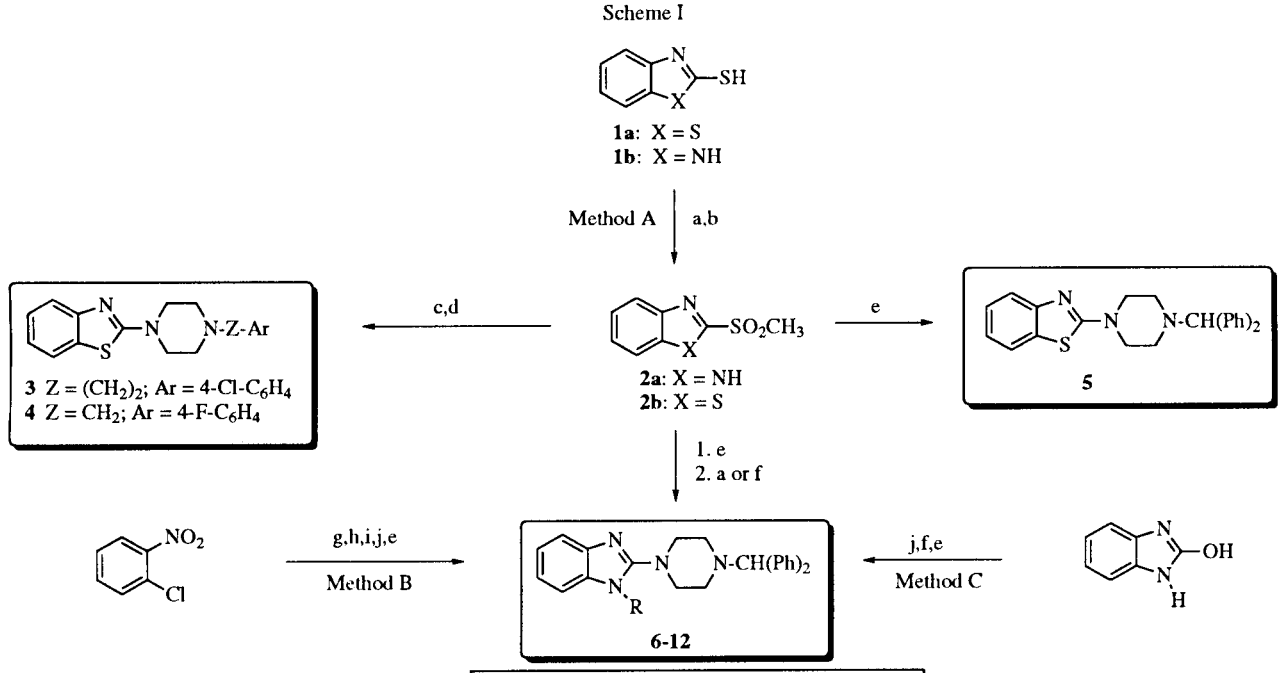
The present paper deals with the synthesis and antiallergic activity evaluation of novel benzo heterocyclic piperidine and piperazine derivatives. The structure-activity relationship of these compounds is also discussed.

Some of the evaluated compounds have shown to be more potent antiallergic compounds than astemizole and terfenadine in the PCA test and have been selected for further studies.

Chemistry.

Compounds listed in Tables I-III were prepared by the synthetic methods outlined in Schemes I and II. Piperazinebenzothiazoles were obtained by method A in Scheme I. Mercaptobenzothiazole **1b** was converted to 2-methylsulfonylbenzothiazole by standard reactions [11]. The methylsulfonyl group was easily displaced in a nucleophilic substitution reaction by diphenylmethylpiperazine to afford **5** or by piperazine to form 2-piperazinebenzothiazole which was subsequently alkylated to give **3** and **4**. Three different methods were employed to synthesize piperazinebenzimidazoles **6-12** as depicted in Scheme I. The 2-(4-diphenylmethyl)-1-piperazinyl-1*H*-benzimidazole, obtained by method A, was treated with sodium hydride and then alkylated with the appropriate substrate to give **6-8**. Compounds **9-11** were prepared by method B

Scheme I



Compound	R	Method
6	CH_3	(A,a)
7	CH_2CO_2Et	(A,f) or (C)
8	CH_2-C_6H_4(4-Cl)	(A,f)
9	$CH(Me)CH_2OCH_3$	(B)
10	$(CH_2)_3OCH_3$	(B)
11	$(CH_2)_2OCH_3$	(B)
12	$CH_2C_6H_5$	(C)

Reagents. (a) NaH, CH_3I; (b) $KMnO_4$, AcOH; (c) piperazine, 5 eq., 130°C; (d) HalZAr, Na_2CO_3, DMF; (e) 4-(diphenylmethyl)piperazine; (f) NaH, RHal, 60°C; (g) RNH_2, heat; (h) Zn, OH^-; (i) urea, 150°C, 1 hour; (j) $POCl_3$, 120°C.

Table I

Physical Data and Inhibitory Dose in PCA of Piperazine Derivatives

Compound No.	X	Z	Ar	mp, °C	Recrystallization solvent [a]	Formula [b]	Rat PCA Test ID_{50} mg/kg po >50
3	S	$(CH_2)_2$	4-ClC_6H_4	131-133	A	$C_{19}H_{20}ClN_3S$	x
4	S	CH_2	4-FC_6H_4	143-145	C	$C_{18}H_{18}FN_3S$	x
5	S	CHC_6H_5	C_6H_5	163-165	A	$C_{24}H_{23}N_3S$	x
6	NMe	"	"	123-125	A	$C_{25}H_{26}N_4$•HFu [c]	x
7	NCH_2CO_2Et	"	"	125-126 dec	B	$C_{28}H_{30}N_4O_2$•HFu [c]	x
8	$NCH_2C_6H_5$(4F)	"	"	170-172	F	$C_{31}H_{29}FN_4$	x
9	$NCH(Me)CH_2OCH_3$	"	"	192-194	D	$C_{28}H_{32}N_4O$•HFu [c]	x
10	$N(CH_2)_3OCH_2CH_3$	"	"	160-162 dec	D	$C_{29}H_{34}N_4O$•HFu [c]	x
11	$N(CH_2)_2OCH_3$	"	"	195-197 dec	F	$C_{27}H_{30}N_4O$•HFu [c]	x
12	$NCH_2C_6H_5$	"	"	157-159	E	$C_{31}H_{30}N_4$	x

[a] A, 2-propanol; B, acetone; C, ethanol; D, 2-propanol/water; E, 2-(1-methylethoxy)propane/ethanol; F, ethanol/water. [b] Analytical results were within 0.4% of the theoretical values. [c] Hydrogen fumarate.

Table II

Physical Data and Inhibitory Dose in PCA of Piperidinobenzothiazoles and Piperidinobenzoxazoles

Compound No.	X	Z	Ar	mp, °C	Recrystallization solvent [a]	Formula [b]	Rat PCA Test ID_{50} mg/kg po <1	1-5	5-25	25-50	>50
14	S	$(CH_2)_2$	C_6H_5	73-75	D	$C_{20}H_{22}N_2S$			X		
15	S	"	4-ClC_6H_4	102-104	A	$C_{20}H_{21}ClN_2S$			X		
16	S	"	4-FC_6H_4	87-89	D	$C_{20}H_{21}FN_2S$			X		
17	S	"	4-$OCH_3C_6H_4$	92-93	A	$C_{21}H_{24}N_2OS$					X
18	S	"	2-ClC_6H_4	91-93	A	$C_{20}H_{21}ClN_2S$		X			
19	S	"	4-MeC_6H_4	193-195 dec	C	$C_{21}H_{24}N_2S$					X
20	S	"	4-$NO_2C_6H_4$	149-151	C	$C_{20}H_{21}N_3O_2S$					X
21	S	"	4-$(Me)_2NC_6H_4$	128-130	A	$C_{22}H_{27}N_3S$				X	
22	S	"	3-MeC_6H_4	58-60	C	$C_{21}H_{24}N_2S$	X				
23	S	"	3-$OCH_3C_6H_4$	108-110	C	$C_{21}H_{24}N_2OS$					X
24	S	"	3-ClC_6H_4	61-63	G	$C_{20}H_{21}ClN_2S$			X		
25	S	"	3-$CF_3C_6H_4$	75-77	G	$C_{21}H_{21}F_3N_2S$			X		
26	S	"	3-$NO_2C_6H_4$	224-226 dec	A	$C_{20}H_{21}N_3O_2S$				X	
27	S	"	3-OHC_6H_4	175-180	C	$C_{20}H_{22}N_2OS$					X
28	S	"	2-FC_6H_4	87-89	C	$C_{20}H_{21}FN_2S$					X
29	S	"	4-OHC_6H_4	201-204	C	$C_{20}H_{22}N_2OS$					X
30	S	CH_2CO	4-ClC_6H_4	120-122	F	$C_{20}H_{19}ClN_2OS$					X
31	S	$CH_2CH(OH)$	4-ClC_6H_4	138-140	F	$C_{20}H_{21}ClN_2OS$					X
32	S	$(CH_2)_2O$	4-BrC_6H_4	82-83	C	$C_{20}H_{21}BrN_2OS$					X
33	S	$(CH_2)_3$	C_6H_5	192-194	A	$C_{21}H_{24}N_2S$•HFu [c]					X
34	S	$CH_2CH(CH_3)$	"	77-79	C	$C_{21}H_{24}N_2S$				X	
35	S	$CH(CH_3)CH_2$	"	68-70	C	$C_{21}H_{24}N_2S$					X
36	S	$CH(C_6H_5)$	"	145-147	C	$C_{25}H_{24}N_2S$					X
37	S	$(CH_2)_3CO$	4-FC_6H_4	101-103	A	$C_{22}H_{23}FN_2OS$			X		
38	S	CH_2	4-*t*-BuC_6H_4	117-119	C	$C_{23}H_{28}N_2S$			X		
39	S	"	3-ClC_6H_4	62-64	F	$C_{19}H_{19}ClN_2S$					X
40	S	"	4-ClC_6H_4	101-103	A	$C_{19}H_{19}ClN_2S$					X
41	S	"	3-$OCH_3C_6H_4$	61-63	C	$C_{20}H_{22}N_2OS$					X
42	S	"	3-CNC_6H_4	75-78	F	$C_{20}H_{19}N_3S$					X
43	S	"	4-$NO_2C_6H_4$	136-138	C	$C_{19}H_{19}N_3O_2S$					X
44	S	$CH(CH_3)$	C_6H_5	81-83	C	$C_{20}H_{22}N_2S$•HFu [c]					X
45	S	CH(Et)	"	105-107	C	$C_{21}H_{24}N_2S$				X	
46	O	$(CH_2)_2$	4-ClC_6H_4	108-110	C	$C_{20}H_{21}ClN_2O$					X
47	O	"	4-FC_6H_4	93-95	D	$C_{20}H_{21}FN_2O$					X
48	O	"	4-$OCH_3C_6H_4$	86-88	F	$C_{21}H_{24}N_2O_2$					X
49	O	$CH(C_6H_5)$	C_6H_5	107-109	C	$C_{25}H_{24}N_2O$					X
50	O	$(CH_2)_3CO$	4-FC_6H_4	198-200	C	$C_{22}H_{23}FN_2O_2$•HCl [d]				X	
51	O	CH_2	4-ClC_6H_4	106-107	A	$C_{19}H_{19}ClN_2O$					X
52	O	$(CH_2)_3CO$	4-*t*-BuC_6H_4	235-236	C	$C_{26}H_{32}N_2O_2$•HCl [d]				X	

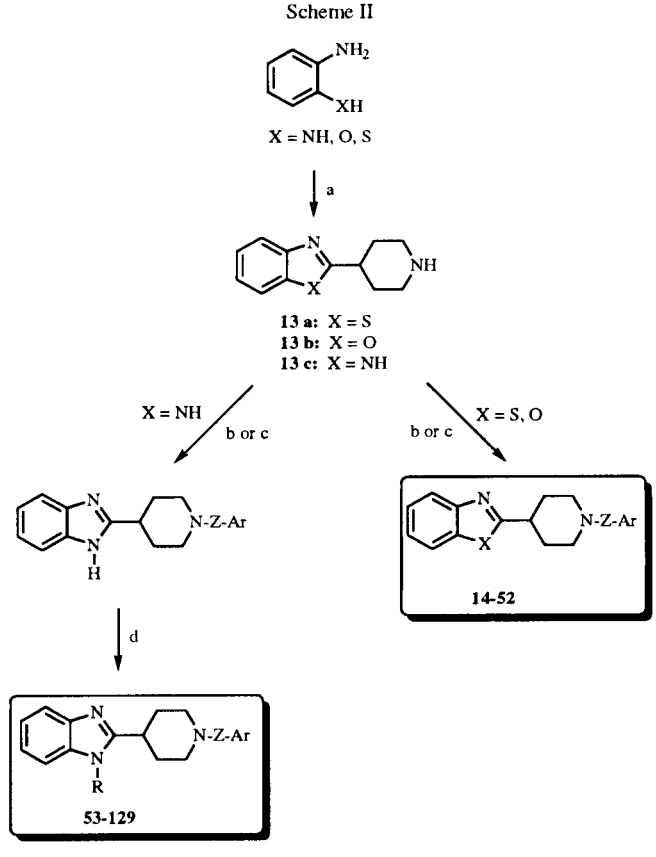
[a] A, 2-propanol; C, ethanol; D, 2-propanol/water; F, ethanol/water; G, hexane. [b] Analytical results were within ± 0.4% of the theoretical values. [c] Hydrogen fumarate. [d] Hydrochloride.

according to the following sequence of reactions: 2-chloronitrobenzene was coupled with a primary alcoxyalkylamine and then reduced to the diamino compound which was treated with urea to give the *N*-substituted-2-hydroxybenzimidazole; conversion to the 2-chloroderivative by phosphorus oxychloride and substitution of the chlorine atom by diphenylmethylpiperazine afforded compounds **9-11** in good yields. Method C allowed us to prepare compounds **7** and **12** by alkylation of 2-chlorobenzimidazole and subsequent amination with diphenylmethylpiperazine. As 2-chlorobenzimidazole was not commercially available it had to be prepared by a convenient modification of the method of Harrison [12]. The synthesis of piperidinylbenzothiazoles **14-45** in Table II was accomplished by *N*-alkylation of 2-(4-piperidinyl)-benzothiazole **13a** obtained by cyclocondensation of piperidine-4-carboxylic acid with 2-aminothiophenol in the presence of polyphosphoric acid as outlined in Scheme II. Bromo derivatives or the corresponding tosylates were used as alkylating agents. When not commercially available, the bromo derivatives were prepared from the corresponding alcohols according to the method of Wiley [13]. Piperidinobenzoxazoles **46-52** were prepared in a similar way starting from 2-aminophenol. The hydroxyethyl compound **31** was obtained by reduction of the carbonyl derivative **30** with sodium borohydride in methanol. When 2-(4-piperidinyl)benzothiazole was reacted with 4-chloro-1-(4-fluorophenyl)-1-butanone, **37** was formed in poor yield; this inconvenience was overcome by the previous protection of the carbonyl group as its ethylenglycol acetal. The same process was used in the preparation of **50** and **52**. Piperidinobenzimidazoles **55-129** were obtained from 2-(4-piperidinyl)-1*H*-benzimidazole **13c** through two consecutive alkylation reactions; first, **13c** was selectively alkylated on the piperidine nitrogen atom under weakly basic conditions as confirmed by ir and nmr spectroscopy; subsequent treatment with sodium hydride and an alkyl halide or an alkyl sulfonate at moderate temperature afforded the desired compounds in good yields. Compounds obtained as oils were converted into crystalline salts by reaction with appropriate acids and recrystallized for characterization.

Results and Discussion.

The new piperidine and piperazine derivatives were evaluated for their antiallergic activity using the rat PCA assay. The compounds were administered orally 1 hour before antigenic challenge and compared with astemizole and terfenadine, two well known antiallergic compounds. The effect of the nature of the Y group on biological activity was first examined. All the prepared piperazines were inactives in the PCA assay, with values of ID_{50} >50 mg/kg (Table I). Substitution of the nitrogen atom linked to the heterocyclic group by a carbon atom (Y = CH in Figure 2) enhanced antiallergic activity in benzothiazoles (compare compounds **3** and **15**) as well as in benzimidazoles (compare compounds **5** and **8** with **36** and **56**) thus corroborating our initial hypothesis that a nitrogen linkage between the alkylamino chain and the benzo heterocycle was not necessary for antiallergic activity. Next, the nature of the Z group was studied. Maximal activity was found when Z was an ethyl group. Replacement of the ethyl group by a methyl or substituted methyl group led to a decrease in the activity (see compounds **15, 40, 44,** and **45**); in the same way the replacement of the ethyl group by a propyl (**33**) or oxyethyl group (**32**) led to a considerable decay in antiallergic activity. A similar effect was observed when the ethyl group was oxidized to an hydroxyethyl (**31**) or a methylcarbonyl group (**30**). Different methyl-branched ethyl derivatives did not show an increase in the activity (see compounds **34, 35,** and **127**).

Scheme II



Reagents. (a) 4-piperidinecarboxylic acid, PPA, 180°C; (b) K_2CO_3, DMF; (c) Na_2CO_3, NaI, CH_3CN; (d) HNa

With regard to the different assayed benzo heterocycles, the observed order of activity was: benzoxazole < benzothiazole < benzimidazole. The series of the 4-fluorophenylethyl derivatives are a clear example of this order.

Table III

Physical Data and Inhibitory Dose in PCA of Piperidinobenzimidazoles

Compound No.	R	Z	Ar	mp, °C	Recrystallization solvent [a]	Formula [b]	Rat PCA Test ID_{50} mg/kg po			
							<1	1-5	5-25	>25
53	H	$(CH_2)_2$	4-ClC_6H_4	230-231 dec	F	$C_{20}H_{22}ClN_3$				X
54	H	"	4-$OCH_3C_6H_4$	222-223 dec	F	$C_{20}H_{25}N_3O$				X
55	CH_3	$CH(C_6H_5)$	C_6H_5	158-160	D	$C_{26}H_{27}N_3$				X
56	$CH_2C_6H_4$(4F)	"	C_6H_5	162-164	A	$C_{32}H_{30}NFN_3$			X	
57	$(CH_2)_2$(4-morpholinyl)	CH_2	4-*t*-BuC_6H_4	183-185 dec	C	$C_{29}H_{40}N_4O$				X
58	$(CH_2)_2OCH_3$	"	4-FC_6H_4	176-178	A	$C_{22}H_{26}FN_3O$•HFu [c]			X	
59	CH_3	"	"	155-156	F	$C_{20}H_{22}FN_3$				X
60	$(CH_2)_2OEt$	"	"	155-157	C	$C_{23}H_{28}FN_3O$•HFu [c]			X	
61	CH_2CO_2Et	"	"	191-193	A	$C_{23}H_{26}FN_3O_2$•HFu [c]				X
62	$(CH_2)_2OMe$	"	3-FC_6H_4	194-196	A	$C_{22}H_{26}FN_3O$•HFu [c]			X	
63	$(CH_2)_2OEt$	"	"	172-174	C	$C_{23}H_{28}FN_3O$•HFu [c]			X	
64	"	"	2-ClC_6H_4	150-152 dec	C	$C_{23}H_{28}ClN_3O$•HFu [c]			X	
65	$(CH_2)_2OCHMe_2$	"	"	198-201	C	$C_{24}H_{30}ClN_3O$•HFu [c]			X	
66	$CH_2C_6H_4$(4Cl)	"	"	220-222	A	$C_{26}H_{25}Cl_2N_3$•HFu [c]			X	
67	$(CH_2)_2OEt$	"	3-ClC_6H_4	184-186	C	$C_{23}H_{28}ClN_3O$•HFu [c]			X	
68	$(CH_2)_2$(4-morpholinyl)	"	"	199-201	C	$C_{25}H_{31}ClN_4O$				X
69	$CH_2C_6H_4$(4Cl)	"	"	221-223 dec	C	$C_{26}H_{25}Cl_2N_3$•HFu [c]				X
70	$(CH_2)_2OMe$	"	4-ClC_6H_4	89-91	G	$C_{22}H_{26}ClN_3O$			X	
71	$(CH_2)_2OEt$	"	"	150-152	C	$C_{23}H_{28}ClN_3O$•HFu [c]			X	
72	$(CH_2)_2OCHMe_2$	"	"	102-104	C	$C_{24}H_{30}ClN_3O$•HFu [c]			X	
73	$(CH_2)_3OEt$	"	"	63-65 dec	B	$C_{24}H_{30}ClN_3O$•HFu [c]				X
74	$CH_2C_6H_4$(4Cl)	"	"	205-207 dec	C	$C_{26}H_{25}Cl_2N_3$•HFu [c]			X	
75	$(CH_2)_2OCHMe_2$	"	3-MeC_6H_4	201-203	C	$C_{25}H_{23}N_3O$•HFu [c]	X			
76	$CH_2C_6H_4$(4Cl)	"	"	131-133	G	$C_{27}H_{28}ClN_3$				X
77	$(CH_2)_2OMe$	"	2-$CF_3C_6H_4$	174-176	B	$C_{23}H_{26}F_3N_3O$•HFu [c]			X	
78	$(CH_2)_2OEt$	"	"	155-157	C	$C_{24}H_{28}F_3N_3O$•HFu [c]			X	
79	"	"	3-$CF_3C_6H_4$	195-197	C	$C_{24}H_{28}F_3N_3O$•HFu [c]			X	
80	$(CH_2)_2OCHMe_2$	"	"	205-207	C	$C_{25}H_{30}F_3N_3O$•HFu [c]				X
81	$(CH_2)_2OMe$	"	4-$OCH_3C_6H_4$	179-181	C	$C_{23}H_{29}N_3O_2$•HFu [c]			X	
82	$(CH_2)_2OCHMe_2$	"	"	205-208	C	$C_{25}H_{33}N_3O_2$•HFu [c]			X	
83	$(CH_2)_2OMe$	"	3-$OCH_3C_6H_4$	162-164	A	$C_{23}H_{29}N_3O_2$•HFu [c]			X	
84	$(CH_2)_2OCHMe_2$	"	"	205-210	C	$C_{25}H_{33}N_3O_2$•HFu [c]			X	
85	"	"	4-CNC_6H_4	194-195	C	$C_{25}H_{30}N_4O$•HFu [c]			X	
86	"	"	4-MeC_6H_4	110-111	G	$C_{25}H_{33}N_3O$		X		
87	$(CH_2)_2OEt$	"	"	92-93	G	$C_{24}H_{31}N_3O$	X			
88	$(CH_2)_2OEt$	$(CH_2)_2$	C_6H_5	104-106	C	$C_{24}H_{31}N_3O$		X		
89	$(CH_2)_2OCHMe_2$	"	"	96-98	G	$C_{25}H_{33}N_3O$			X	
90	$CH_2C_6H_4$(4F)	"	4-ClC_6H_4	153-155	G	$C_{27}H_{27}ClFN_3O$		X		
91	$(CH_2)_2OMe$	"	"	155-157	F	$C_{23}H_{28}ClN_3O$			X	
92	$(CH_2)_2OEt$	"	"	116-118	F	$C_{24}H_{30}ClN_3O$		X		
93	$(CH_2)_2OCHMe_2$	"	"	105-107	G	$C_{25}H_{32}ClN_3O$		X		
94	$(CH_2)_3OEt$	"	"	111-113	E	$C_{25}H_{32}ClN_3O$			X	
95	$(CH_2)_2$(2-dioxolanyl)	"	"	171-173	G	$C_{24}H_{28}ClN_3O_2$				X
96	$CH_2C_6H_4$(4F)	"	4-FC_6H_4	138-140	G	$C_{27}H_{27}F_2N_3$				X
97	$(CH_2)_2OMe$	"	"	129-131	F	$C_{23}H_{28}FN_3O$			X	
98	$(CH_2)_2OEt$	$(CH_2)_2$	4-FC_6H_4	91-93 dec	F	$C_{24}H_{30}FN_3O$		X		
99	$(CH_2)_2OCHMe_2$	"	"	78-81	F	$C_{25}H_{32}FN_3O$			X	
100	CH_3	"	4-$OCH_3C_6H_4$	128-131	C	$C_{22}H_{27}N_3O$				X
101	$CH_2C_6H_4$(4F)	"	"	128-130	A	$C_{28}H_{30}FN_3O$	X			
102	$(CH_2)_2OMe$	"	"	114-116	C	$C_{24}H_{31}N_3O_2$		X		
103	$(CH_2)_2OEt$	"	"	183-185	A	$C_{25}H_{33}N_3O_2$	X			
104	$(CH_2)_2OCHMe_2$	"	"	201-203	A	$C_{26}H_{35}N_3O_2$•HFu [c]	X			
105	$(CH_2)_3OEt$	"	"	178-180	A	$C_{26}H_{35}N_3O_2$•HFu [c]				X
106	$(CH_2)_2OEt$	"	4-MeC_6H_4	205-207	C	$C_{25}H_{33}N_3O$	X			
107	$(CH_2)_2OCHMe_2$	"	"	78-80	G	$C_{26}H_{35}N_3O$	X			
108	$(CH_2)_2OMe$	"	4-$(Me)_2NC_6H_4$	92-94	G	$C_{25}H_{54}N_4O$		X		
109	$(CH_2)_2OCHMe_2$	"	"	98-100	C	$C_{27}H_{38}N_4O$		X		
110	$(CH_2)_2OCHMe_2$	"	3-MeC_6H_4	191-193	C	$C_{24}H_{31}N_3O$•HFu [c]			X	
111	$(CH_2)_2OEt$	"	"	177-179	C	$C_{25}H_{33}N_3O$	X			
112	$(CH_2)_2OCHMe_2$	"	"	215-217	C	$C_{26}H_{35}N_3O$•HFu [c]	X			

Table III (continued)

Compound No.	R	Z	Ar	mp, °C	Recrystallization solvent [a]	Formula [b]	Rat PCA Test ID_{50} mg/kg po <1	1-5	5-25	>25
113	$(CH_2)_2$(4-morpholinyl)	"	"	200-202	A	$C_{27}H_{36}N_4O$•HFu [c]			X	
114	$(CH_2)_2OMe$	"	3-$OCH_3C_6H_4$	189-192	C	$C_{24}H_{31}N_3O_2$•HFu [c]			X	
115	"	"	3-ClC_6H_4	191-193	C	$C_{23}H_{28}ClN_3O$•HFu [c]				X
116	$(CH_2)_2OEt$	"	3-$CF_3C_6H_4$	183-186 dec	C	$C_{25}H_{30}F_3N_3O$•HFu [c]			X	
117	$(CH_2)_2OEt$	"	3-$NO_2C_6H_4$	200-202	C	$C_{24}H_{30}N_4O_3$•HFu [c]		X		
118	$(CH_2)_2OCHMe_2$	"	"	195-197	C	$C_{25}H_{32}N_4O_3$•HFu [c]	X			
119	$(CH_2)_2OMe$	"	2-MeC_6H_4	209-211 dec	C	$C_{24}H_{31}N_3O$•HFu [c]			X	
120	$(CH_2)_2OEt$	"	"	189-191 dec	C	$C_{25}H_{33}N_3O$•HFu [c]			X	
121	$(CH_2)_2OEt$	"	2-$CF_3C_6H_4$	168-170 dec	C	$C_{25}H_{30}F_3N_3O$•HFu [c]			X	
122	$(CH_2)_2OCHMe_2$	"	"	211-213 dec	C	$C_{26}H_{32}F_3N_3O$•HFu [c]			X	
123	$(CH_2)_2OEt$	"	2-FC_6H_4	99-101 dec	G	$C_{24}H_{30}FN_3O$		X		
124	$(CH_2)_2OEt$	"	2-$OCH_3C_6H_4$	183-185 dec	C	$C_{25}H_{33}N_3O_2$•HFu [c]		X		
125	$(CH_2)_2OCHMe_2$	"	"	215-216 dec	C	$C_{26}H_{35}N_3O_2$•HFu [c]		X		
126	$(CH_2)_2OMe$	"	4-OHC_6H_4	217-218 dec	C	$C_{23}H_{29}N_3O_2$			X	
127	$(CH_2)_2OCHMe_2$	$CH_2CH(Me)$	C_6H_5	181-183	A	$C_{26}H_{35}N_3O$•HFu [c]				X
128	$(CH_2)_2OEt$	$(CH_2)_2$	2-thienyl	167-169	A	$C_{22}H_{29}N_3OS$			X	
129	$(CH_2)_2OCHMe_2$	"	"	205-207	C	$C_{23}H_{31}N_3OS$			X	
Astemizole								X		
Terfenadine								X		

[a] A, 2-propanol; B, acetone; C, ethanol; D, 2-propanol/water; E, 2-(1-methylethoxy)propane/ethanol; F, ethanol/water; G, hexane. [b] Analytical results were within ± 0.4% of the theoretical values. [c] Hydrogen fumarate.

Table IV

Compound No.	Molecular Formula	mol wt	Elemental Analysis (Calcd./Found) C	H	N
14	$C_{20}H_{22}N_2S$	322.46	74.49 / 74.80	6.88 / 6.87	8.69 / 8.72
15	$C_{20}H_{21}ClN_2S$	356.91	67.30 / 67.53	5.93 / 5.89	7.85 / 7.87
16	$C_{20}H_{21}FN_2S$	340.45	70.55 / 70.75	6.22 / 6.26	8.23 / 8.19
18	$C_{20}H_{21}ClN_2S$	356.91	67.30 / 67.13	5.93 / 5.95	7.85 / 7.88
19	$C_{21}H_{24}N_2S$	336.48	74.95 / 74.88	7.19 / 7.17	8.33 / 8.30
20	$C_{20}H_{21}N_3O_2S$	367.45	65.37 / 65.51	5.76 / 5.78	11.44 / 11.40
21	$C_{22}H_{27}N_3S$	365.52	72.29 / 72.40	7.45 / 7.43	11.49 / 11.45
22	$C_{21}H_{24}N_2S$	336.48	74.95 / 74.86	7.19 / 7.20	8.33 / 8.35
23	$C_{21}H_{24}N_2OS$	352.48	71.55 / 71.75	6.86 / 6.88	7.95 / 7.97
24	$C_{20}H_{21}ClN_2S$	356.91	67.30 / 67.38	5.93 / 5.95	7.80 / 7.86
25	$C_{21}H_{21}F_3N_2S$	390.46	64.59 / 64.43	5.42 / 5.40	7.18 / 7.17
26	$C_{20}H_{21}N_3O_2S$	367.45	65.37 / 65.19	5.76 / 5.74	11.44 / 11.48
27	$C_{20}H_{22}N_2OS$	338.46	70.97 / 71.05	6.55 / 6.53	8.28 / 8.26
28	$C_{20}H_{21}FN_2S$	340.45	70.55 / 70.69	6.22 / 6.21	8.23 / 8.21
29	$C_{20}H_{22}N_2OS$	338.46	70.97 / 71.11	6.55 / 6.54	8.28 / 8.29
30	$C_{20}H_{19}ClN_2OS$	370.89	64.76 / 64.73	5.16 / 5.18	7.55 / 7.52
32	$C_{20}H_{21}BrN_2OS$	417.36	57.55 / 57.61	5.07 / 5.05	6.71 / 6.72
33	$C_{25}H_{28}N_2O_4S$	452.55	66.35 / 66.19	6.24 / 6.26	6.19 / 6.17
35	$C_{21}H_{24}N_2S$	336.48	74.95 / 74.85	7.19 / 7.25	8.33 / 8.30
36	$C_{25}H_{24}N_2S$	384.52	78.03 / 78.20	6.29 / 6.28	7.29 / 7.25
37	$C_{22}H_{23}FN_2OS$	382.48	69.08 / 69.17	6.06 / 6.08	7.33 / 7.31
38	$C_{23}H_{28}N_2S$	364.53	75.78 / 75.87	7.74 / 7.77	7.69 / 7.68
39	$C_{19}H_{19}ClN_2S$	342.88	66.55 / 66.42	5.59 / 5.60	8.17 / 8.15
40	$C_{19}H_{19}ClN_2S$	342.88	66.55 / 66.40	5.59 / 5.57	8.17 / 8.13
41	$C_{20}H_{22}N_2OS$	338.46	70.97 / 70.85	6.55 / 6.57	8.28 / 8.31
42	$C_{20}H_{19}N_3S$	333.43	72.04 / 72.15	5.74 / 5.75	12.60 / 12.57
43	$C_{19}H_{19}N_3O_2S$	353.42	64.57 / 64.70	5.42 / 5.45	11.89 / 11.87
44	$C_{24}H_{26}N_2O_4S$	438.53	65.73 / 65.61	5.98 / 6.00	6.39 / 6.38
45	$C_{21}H_{24}N_2S$	336.48	74.95 / 74.87	7.19 / 7.17	8.33 / 8.36
46	$C_{20}H_{21}ClN_2O$	340.84	70.47 / 70.60	6.21 / 6.20	8.22 / 8.20
47	$C_{20}H_{21}FN_2O$	324.39	74.05 / 74.22	6.52 / 6.51	8.63 / 8.66
49	$C_{25}H_{24}N_2O$	368.46	81.49 / 81.32	6.57 / 6.59	7.60 / 7.56
50	$C_{22}H_{24}ClFN_2O_2$	402.08	65.58 / 65.66	6.00 / 6.02	6.95 / 6.90

Table IV (continued)

Compound No.	Molecular Formula	mol wt	Elemental Analysis (Calcd./Found) C	H	N
51	$C_{19}H_{19}ClN_2O$	326.81	69.82 / 69.71	5.86 / 5.85	8.57 / 8.58
53	$C_{20}H_{22}ClN_3$	339.85	70.68 / 70.72	6.53 / 6.51	12.36 / 12.40
54	$C_{21}H_{25}N_3O$	335.43	75.19 / 75.03	7.51 / 7.48	12.53 / 12.57
55	$C_{26}H_{27}N_3$	381.50	81.85 / 81.70	7.13 / 7.10	11.01 / 11.04
56	$C_{32}H_{30}N_3$	475.58	81.23 / 81.30	6.35 / 6.33	8.83 / 8.86
57	$C_{29}H_{40}N_4O$	462.64	75.28 / 75.32	8.72 / 8.74	12.11 / 12.07
59	$C_{20}H_{22}FN_3$	323.40	74.27 / 74.03	6.85 / 6.86	12.99 / 13.03
60	$C_{27}H_{32}FN_3O_5$	497.55	65.17 / 65.34	6.48 / 6.55	8.45 / 8.39
61	$C_{27}H_{30}FN_3O_6$	511.53	63.39 / 63.31	5.91 / 5.87	8.21 / 8.20
62	$C_{26}H_{30}FN_3O_5$	483.52	64.58 / 64.49	6.25 / 6.24	8.69 / 8.70
63	$C_{27}H_{32}FN_3O_5$	497.55	65.17 / 65.08	6.48 / 6.46	8.45 / 8.42
64	$C_{27}H_{32}ClN_3O_5$	514.00	63.09 / 63.29	6.28 / 6.32	8.17 / 8.21
65	$C_{28}H_{34}ClN_3O_5$	528.02	63.69 / 63.61	6.49 / 6.50	7.96 / 7.93
66	$C_{30}H_{29}Cl_2N_3O_4$	566.46	63.61 / 63.86	5.16 / 5.15	7.42 / 7.39
67	$C_{27}H_{32}ClN_3O_5$	514.00	63.09 / 63.12	6.28 / 6.26	8.17 / 8.15
68	$C_{25}H_{31}ClN_4O$	438.98	68.40 / 68.31	7.12 / 7.08	12.76 / 12.79
69	$C_{30}H_{29}Cl_2N_3O_4$	566.46	63.61 / 63.48	5.16 / 5.19	7.42 / 7.41
70	$C_{22}H_{26}ClN_3O$	383.90	68.82 / 68.97	6.83 / 6.79	10.95 / 10.99
71	$C_{27}H_{32}ClN_3O_5$	514.00	63.09 / 63.18	6.28 / 6.32	8.17 / 8.15
72	$C_{28}H_{34}ClN_3O_5$	528.02	63.69 / 63.78	6.49 / 6.50	7.96 / 7.93
73	$C_{28}H_{34}ClN_3O_5$	528.02	63.09 / 62.94	6.49 / 6.48	7.96 / 7.94
74	$C_{30}H_{29}Cl_2N_3O_4$	566.46	63.61 / 63.72	5.16 / 5.14	7.42 / 7.38
75	$C_{29}H_{37}N_3O_5$	507.61	68.61 / 68.05	7.35 / 7.36	8.28 / 8.30
76	$C_{27}H_{28}ClN_3$	429.96	75.42 / 75.47	6.56 / 6.60	9.77 / 9.82
77	$C_{27}H_{30}F_3N_3O_5$	533.53	60.78 / 60.70	5.67 / 5.68	7.88 / 7.85
78	$C_{28}H_{32}F_3N_3O_5$	547.56	61.41 / 61.23	5.89 / 5.91	7.67 / 7.70
79	$C_{28}H_{32}F_3N_3O_5$	547.56	61.41 / 61.47	5.89 / 5.90	7.67 / 7.63
80	$C_{29}H_{34}F_3N_3O_5$	561.58	62.02 / 61.95	6.10 / 6.06	7.48 / 7.46
81	$C_{27}H_{33}N_3O_6$	495.55	65.44 / 65.49	6.71 / 6.73	8.48 / 8.45
82	$C_{29}H_{37}N_3O_6$	523.61	66.52 / 66.60	7.12 / 7.11	8.03 / 8.00
83	$C_{27}H_{33}N_3O_6$	495.55	65.44 / 65.51	6.71 / 6.67	8.48 / 8.51
84	$C_{29}H_{37}N_3O_6$	523.61	66.52 / 66.43	7.12 / 7.10	8.03 / 8.07
85	$C_{29}H_{34}N_4O_5$	518.59	67.16 / 67.04	6.61 / 6.65	10.80 / 10.77
86	$C_{25}H_{33}N_3O$	391.53	76.69 / 76.64	8.49 / 8.48	10.73 / 10.70
87	$C_{24}H_{31}N_3O$	377.51	76.35 / 76.38	8.28 / 8.26	11.13 / 11.15
88	$C_{24}H_{31}N_3O$	377.51	76.35 / 76.39	8.28 / 8.32	11.13 / 11.17
89	$C_{25}H_{33}N_3O$	391.53	76.69 / 76.53	8.49 / 8.53	10.73 / 10.70
90	$C_{27}H_{27}ClFN_3O$	463.96	69.89 / 69.70	5.87 / 5.88	9.06 / 9.03
91	$C_{23}H_{28}ClN_3O$	397.92	69.42 / 69.31	7.09 / 7.12	10.56 / 10.58
92	$C_{24}H_{30}ClN_3O$	411.95	69.97 / 69.88	7.34 / 7.32	10.20 / 10.16
93	$C_{25}H_{32}ClN_3O$	425.98	70.48 / 70.37	7.57 / 7.54	9.86 / 9.85
94	$C_{25}H_{32}ClN_3O$	425.98	70.48 / 70.38	7.57 / 7.62	9.86 / 9.90
95	$C_{24}H_{28}ClN_3O_2$	425.93	67.67 / 67.91	6.63 / 6.65	9.87 / 9.82
96	$C_{27}H_{27}F_2N_3$	431.51	75.15 / 75.22	6.31 / 6.35	9.74 / 9.71
97	$C_{23}H_{28}FN_3O$	381.47	72.41 / 72.33	7.40 / 7.42	11.02 / 11.00
98	$C_{24}H_{30}FN_3O$	395.50	72.88 / 72.93	7.65 / 7.68	10.62 / 10.66
99	$C_{25}H_{32}FN_3O$	409.53	73.32 / 72.38	8.12 / 8.15	10.26 / 10.31
100	$C_{22}H_{27}N_3O$	349.46	75.61 / 75.58	7.79 / 7.80	12.02 / 12.08
101	$C_{28}H_{30}FN_3O$	443.54	75.82 / 75.83	6.82 / 6.87	9.47 / 9.45
102	$C_{24}H_{31}N_3O_2$	393.51	73.25 / 73.21	7.94 / 7.97	10.68 / 10.62
103	$C_{25}H_{33}N_3O_2$	407.53	73.68 / 73.59	8.16 / 8.13	10.31 / 10.34
104	$C_{30}H_{39}N_3O_6$	537.63	67.02 / 67.09	7.31 / 7.29	7.82 / 7.85
105	$C_{30}H_{39}N_3O_6$	537.63	67.02 / 67.07	7.31 / 7.28	7.82 / 7.84
106	$C_{25}H_{33}N_3O$	591.53	76.69 / 76.63	8.49 / 8.52	10.73 / 10.77
107	$C_{26}H_{35}N_3O$	405.56	76.99 / 70.93	8.70 / 8.73	10.36 / 10.39
108	$C_{25}H_{34}N_4O$	406.55	73.85 / 73.88	8.43 / 8.47	13.78 / 13.75
109	$C_{27}H_{38}N_4O$	434.62	74.61 / 74.65	8.81 / 8.77	12.89 / 12.88
110	$C_{28}H_{35}N_3O_5$	493.58	68.13 / 68.08	7.15 / 7.18	8.51 / 8.54
111	$C_{29}H_{37}N_3O_5$	507.61	68.61 / 68.73	7.35 / 7.37	8.28 / 8.25
112	$C_{30}H_{39}N_3O_5$	521.63	69.07 / 68.93	7.54 / 7.59	8.06 / 8.11
113	$C_{31}H_{40}N_4O_5$	548.66	67.86 / 67.88	7.35 / 7.34	10.21 / 10.18
114	$C_{28}H_{35}N_3O_6$	509.58	65.99 / 66.05	6.92 / 6.88	8.25 / 8.24
115	$C_{27}H_{32}ClN_3O_5$	514.00	63.09 / 63.01	6.28 / 6.24	8.17 / 8.13

Table IV (continued)

Compound No.	Molecular Formula	mol wt	Elemental Analysis (Calcd./Found) C	H	N
116	$C_{29}H_{34}F_3N_3O_5$	561.58	62.02 / 62.08	6.10 / 6.11	7.48 / 7.45
117	$C_{28}H_{34}N_4O_7$	538.58	62.44 / 62.77	6.36 / 6.32	10.40 / 10.45
118	$C_{29}H_{36}N_4O_7$	552.61	63.03 / 63.01	6.57 / 6.55	10.14 / 10.18
119	$C_{28}H_{35}N_3O_5$	493.58	68.13 / 68.19	7.15 / 7.11	8.51 / 8.46
120	$C_{29}H_{37}N_3O_5$	507.61	68.61 / 68.70	7.35 / 7.37	8.28 / 8.26
121	$C_{25}H_{34}F_3N_3O_5$	513.54	58.47 / 58.41	6.67 / 6.63	8.18 / 8.15
122	$C_{30}H_{36}F_3N_3O_5$	575.61	62.59 / 62.66	6.30 / 6.34	7.30 / 7.35
123	$C_{24}H_{30}FN_3O$	395.50	72.88 / 72.81	7.65 / 7.68	10.62 / 10.61
124	$C_{29}H_{37}N_3O_6$	523.61	66.52 / 66.73	7.12 / 7.08	8.03 / 8.08
125	$C_{30}H_{39}N_3O_6$	537.63	67.02 / 67.11	7.31 / 7.30	7.82 / 7.77
126	$C_{23}H_{29}N_3O_2$	379.48	72.79 / 72.70	7.70 / 7.65	11.07 / 11.11
127	$C_{30}H_{39}N_3O_5$	521.63	69.07 / 69.13	7.54 / 7.57	8.06 / 8.03
128	$C_{22}H_{29}N_3OS$	383.55	68.89 / 68.77	7.62 / 7.66	10.96 / 10.93
129	$C_{23}H_{31}N_3OS$	397.58	69.48 / 69.58	7.87 / 7.91	10.58 / 10.55

Thus, the benzoxazole **47** was inactive (X = 0, ID_{50} >50 mg/kg) and the benzothiazole **16** was moderately active (X = S, ID_{50} between 5 and 25 mg/kg) whereas the benzimidazole derivatives **96** and **97** presented a high degree of activity (X = NR, ID_{50} between 1 and 5 mg/kg). Among the benzimidazole derivatives, maximal activity was found when the R group linked to the heterocyclic nitrogen was an alcoxyethyl group (-CH_2CH_2OR'). Ten out of eleven compounds of the series with ID_{50} lesser than 1 mg/kg hold this structural feature, being the ethyl and isopropyl derivatives slightly more active than the methyl ones (see compounds **91, 92, 93,** and **102, 103, 104**). Replacement of the alkoxyethyl group by an alkoxypropyl group caused a decrease (**94**) or a marked fall (**73, 105**) in activity.

Although no clear SARs were observed among the differently-substituted phenyl compounds prepared, it seems that electron donating substituents on the meta and para position of the benzene ring, such as 3-Me (**110, 75**), 4-Me (**87**) and 4-OMe (**103**) enhance activity whereas ortho substitution tends to slightly diminish it, probably due to steric reasons.

Conclusions.

In accordance with the SAR study of the synthesized compounds, maximum oral activity is present when the following structural requirements are fulfilled: 1. Presence of a piperidine ring linked at its 4 position to a benzo heterocycle; substitution of the piperidine ring by a piperazine causes the disappearance of the antiallergic activity. 2. A phenylethyl group attached to the nitrogen of the piperidine; replacement of the phenylethyl by a phenylmethyl or phenylpropyl group reduces the activity. 3. Electron-donating substituents in positions 3 and 4 of the benzene ring of the phenylethyl group. 4. A benzimidazole substituted at the 1 position by an alcoxyethyl group.

Several of the compounds tested were found to have more potent antiallergic activitiy than astemizole and terfenadine, and have been selected for further studies.

EXPERIMENTAL

All starting materials were obtained from commercial sources. When necessary, solvents were purified and/or dried by standard procedures [14]. During work up, organic extracts were routinely dried over anhydrous magnesium sulfate and concentrated to dryness by using a rotary evaporator under reduced pressure. All melting points were determined on a Büchi SMP-20 melting point apparatus and are uncorrected. Nuclear magnetic resonance spectra were obtained on either a Hitachi Perkin-Elmer R-24B spectrometer or a Bruker 200 AC spectrometer. Unless otherwise indicated, nmr spectra were run in deuteriochloroform solution with tetramethylsilane as an internal standard. Chemical shifts are reported in ppm downfield from tetramethylsilane. Mass spectra were recorded on a Hewlett-Packard 5930 A spectrometer. Infrared spectra were recorded on a Perkin Elmer 1310 spectrophotometer. Flash chromatography was performed with Kieselgel 60 (230-240 mesh) supplied by E. Merck. All compounds were checked for purity by hplc (Nucleosil C_{18} column, 100 x 4.6 mm i.d., 5-μm, acetonitrile gradients in *p*H 6.0 ammonium acetate buffer, uv detection).

General Procedure for Preparing Compounds **2a-2b**.

To a slurry of 4.80 g (0.1 mole) of hexane-washed sodium hydride (50% in oil) in dimethylformamide (150 ml) at 0°, a solution of 2-mercapto-1*H*-benzimidazole or 2-mercaptobenzothiazole (0.1 mole) in dimethylformamide (100 ml) was added dropwise. The mixture was allowed to stir for a period of 20 minutes at 0° and another 30 minutes at room temperature. Then the mixture was cooled again to 0°, treated with a cold solution of iodomethane (6.2 ml, 100 mmoles) in dimethylformamide (50 ml), and allowed to stir for 1 hour at room temperature. The mixture was concentrated and the residue dissolved in ether, washed successively with water and brine, and dried. After removal of solvents was obtained an oil which was dissolved in acetic acid (200 ml). Then a solution of potassium permanganate

(27.30 g, 172 mmoles) in water (260 ml) was slowly added over the acetic solution at 25° and the mixture stirred at 25° for 2 hours, treated with saturated sodium bisulfite solution (25 ml) and brought to *p*H 8 with ammonium hydroxide and extracted with ethyl acetate. The organic solution was washed successively with water and brine, dried, and concentrated.

2-Methylsulfonyl-1*H*-benzimidazole (**2a**).

This compound was obtained from 2-mercapto-1*H*-benzimidazole as an oil (16.46 g, 84%); ^{1}H nmr (DMSO d_6): δ 3.4 (s, 3H), 7.1-7.9 (m, 5H).

Anal. Calcd. for $C_8H_8N_2O_2S$: C, 48.97; H, 4.11; N, 14.28. Found: C, 49.53; H, 4.21; N, 13.96.

2-Methylsulfonylbenzothiazole (**2b**).

This compound was obtained from 2-mercaptobenzothiazole as an oil (15.07 g, 70%); ^{1}H nmr (deuteriochloroform): δ 3.4 (s, 3H), 7.3-8.1 (m, 4H).

Anal. Calcd. for $C_8H_7NO_2S_2$: C, 45.05; H, 3.31; N, 6.57. Found: C, 45.09; H, 3.28; N, 6.60.

General Procedure for Preparing Compounds **3-4**.

A mixture of 2-methylsulfonylbenzothiazole (10.65 g, 50 mmoles) and piperazine (43.00 g, 0.5 mole) was heated at reflux for 4 hours; the mixture was cooled and dissolved in dichloromethane, washed with water, dried and concentrated. The residue (9.30 g) was redissolved in dimethylformamide (50 ml) and added to a mixture of a substituted alkylhalide (50 mmoles) and potassium carbonate (6.12 g, 45 mmoles) in dimetylformamide (60 ml). The mixture was heated at 70° for 16 hours and then cooled, poored into cold water, and extracted with dichloromethane. The organic extract was washed with water, dried, and concentrated.

2-[4-[2-(4-Chlorophenyl)ethyl]piperazin-1-yl]benzothiazole (**3**).

This compound was obtained from 1-(2-bromoethyl)-4-chlorobenzene as a solid which was recrystallized from 2-propanol yielding 12.50 g (70%), mp 131-133°; ^{1}H nmr (deuteriochloroform): δ 2.4-2.8 (m, 8H), 3.4-3.8 (m, 4H), 6.9-7.7 (m, 8H,)

Anal. Calcd. for $C_{19}H_{20}ClN_3S$: C, 63.76; H, 5.63; N, 11.74. Found: C, 63.48; H, 5.65; N, 11.72.

2-[4-[4-Fluorophenylmethyl]piperazin-1-yl]benzothiazole (**4**).

This compound was obtained from 1-chloromethyl-4-fluorobenzene as a solid which was recrystallized from ethanol to yield 12.76 g (78%), mp 143-145°; ^{1}H nmr (deuteriochloroform): δ 2.4-2.7 (m, 4H), 3.5 (s, 2H), 3.5-3.8 (m, 4H); ^{13}C nmr (deuteriochloroform): δ 46.6, 50.4, 60.3, 112.9, 113.9, 117.2, 119.6, 124.1, 128.5, 129.1, 131.6, 132.0, 151.1, 154.5, 166.5, 166.9; ms: m/z 327 (M^+, 25), 218 (3), 177 (47), 163 (67), 135 (10), 109 (100), 56 (11).

Anal. Calcd. for $C_{18}H_{18}FN_3S$: C, 66.03; H, 5.54; N, 12.83: Found: C, 65.93; H, 5.58; N, 12.79.

2-[4-(Diphenylmethyl)piperazin-1-yl]benzothiazole (**5**).

A solution of 2-methylsulfonylbenzothiazole (**2b**) (10.65 g, 50 mmoles) and 1-(diphenylmethyl)piperazine (12.60 g, 50 mmoles) in acetonitrile (100 ml) was refluxed for 20 hours. The mixture was concentrated and the residue recrystallized from 2-propanol to give 16.30 g (85%) of **5** as a white solid, mp 163-165°; ^{1}H nmr (deuteriochloroform): δ 2.2-2.6 (t, 4H), 3.3-3.7 (t, 4H), 4.1 (s, 1H), 6.8-7.6 (m, 14H); ^{13}C nmr (deuteriochloroform): δ 47.0, 49.5, 74.3, 117.2, 119.1, 119.4, 124.1, 126.0, 126.4, 127.1, 129.3, 140.6, 151.4, 167.1; ms: m/z 385 (M^+, 19), 222 (21), 208 (44), 168 (14), 167 (100), 165 (27), 163 (29), 152 (16), 56 (23).

Anal. Calcd. for $C_{24}H_{23}N_3$ S: C, 74.77; H, 6.01; N, 10.90. Found: C, 74.53; H, 6.03; N, 10.89.

2-[4-(Diphenylmethyl)piperazin-1-yl]-1-methyl-1*H*-benzimidazole (**6**).

A solution of 2-methylsulfonyl-1*H*-benzimidazole (**2a**) (1.96 g, 10 mmoles) and 1-(diphenylmethyl)piperazine (11.95 g, 50 mmoles) in acetonitrile (50 ml) was refluxed for 48 hours. The mixture was concentrated and the residue dissolved in ethyl acetate, washed successively with water and brine, dried, and concentrated. The residue was dissolved in dimethylformamide (10 ml) and added to an ice-bath cooled slurry of 0.48 g (10 mmoles) of hexane-washed sodium hydride (50% in oil) in dimethylformamide (10 ml). The mixture was stirred at 0° for 20 minutes and at 25° for 30 minutes. The reaction was cooled again at 0° and treated with a cold solution of iodomethane (0.62 ml, 10 mmoles) in dimethylformamide (5 ml) and then stirred at 25° for 12 hours. The mixture was concentrated and poured into cold water to yield a solid that was filtered off and dried. The solid was treated with fumaric acid (0.80 g) in warm 2-propanol (15 ml) to give 3.25 g (65%) of **6** as white crystals, mp 123-125°; ^{1}H nmr (DMSO d_6): δ 2.4-2.6 (t, 4H), 3.2-3.3 (t, 4H), 3.4 (s, 3H), 4.3 (s, 1H), 6.8 (s, 2H), 7.0-7.4 (m, 13H), 7.4-7.5 (m, 1H), 8.7 (s, 1H); ^{13}C nmr (DMSO d_6): δ 30.3, 50.2, 51.3, 75.9, 108.1, 117.6, 121.0, 121.6, 126.9, 127.8, 128.4, 135.4, 140.9, 142.1, 157.6; ms: m/z 382 (M^+, 9), 236 (3), 215 (7), 208 (10), 174 (8), 167 (40), 160 (100), 147 (18).

Anal. Calcd. for $C_{29}H_{30}N_4O_4$: C, 69.86; H, 6.07; N, 11.24. Found: C, 70.15; H, 6.06; N, 11.21.

General Procedure for Preparing Compounds **7-8**.

A solution of 2-methylsulfonyl-1*H*-benzimidazole (**2a**) (1.96 g, 10 mmoles) and 1-(diphenylmethyl)piperazine (11.95 g, 50 mmoles) in acetonitrile (50 ml) was refluxed for 48 hours. The mixture was concentrated, dissolved in ethyl acetate, washed successively with water and brine, dried, and concentrated. The residue was dissolved in dimethylformamide (10 ml) and added to an ice-bath cooled slurry of 0.48 g (10 mmoles) of hexane-washed sodium hydride (50% in oil) in dimethylformamide (10 ml). The mixture was stirred at 0° for 20 minutes and at 25° for 30 minutes and then treated with a solution of an alkyl halide (10 mmoles) in dimethylformamide (10 ml). The mixture was heated at 80° for 20 hours, cooled, and poured into ice-water (200 ml) to yield a solid which was subjected to flash chromatography (chloroform).

Ethyl [2-(4-(Diphenylmethyl)piperazin-1-yl)-1*H*-benzimidazol-1-yl]acetate (**7**).

This compound was obtained from ethylchloroacetate as a solid which was recrystallized from acetone to yield 4.16 g (73%), mp 125-126° dec; ir (potassium bromide): ν CO 1750 cm^{-1}; ^{1}H nmr (deuteriochloroform): δ 1.1-1.4 (t, 3H), 2.4-2.8 (m, 4H), 3.2-3.5 (m, 4H), 3.9-4.4 (q, 2H), 4.3 (s, 1H), 4.6 (s, 2H), 6.9-7.6 (m, 14H).

Anal. Calcd. for $C_{32}H_{34}N_4O_6$: C, 67.35; H, 6.01; N, 9.82. Found: C, 67.58; H, 5.98; N, 9.83.

2-[4-(Diphenylmethyl)piperazin-1-yl]-1-(4-fluorophenyl)-methyl-1*H*-benzimidazole (**8**).

This compound was obtained from 1-chloromethyl-4-fluorobenzene as a solid which was recrystallized from ethanol/water (1:1) to yield 3.28 g (69%) of **8** as white crystals, mp 170-172°; ^{1}H nmr (deuteriochloroform): δ 2.4-2.5 (m, 4H), 3.2-3.3 (m, 4H), 4.2 (s, 1H), 5.0 (s, 2H), 6.7-7.6 (m, 18H); ^{13}C nmr (deuteriochloroform): δ 46.7, 50.6, 51.3, 75.8, 108.9, 115.5, 115.8, 118.0, 121.2, 121.8, 126.8, 127.4, 127.5, 127.7, 128.3, 131.7, 131.7, 135.1, 141.5, 142.0, 157.9, 160.2, 163.5; ms: m/z 476 (M^+, 11), 295 (14), 269 (16), 254 (73), 241 (24), 208 (13), 167 (66), 109 (100).

Anal. Calcd. for $C_{31}H_{29}FN_4$: C, 78.12; H, 6.13; N, 11.75. Found: C, 77.85; H, 6.11; N, 11.71.

General Procedure for Preparing Compounds **9-11**.

A mixture of 2-nitrochlorobenzene (13.16 g, 83.6 mmoles) and RNH_2 (230 mmoles) was refluxed for 24 hours and then cooled and diluted with ethyl acetate (100 ml). The organic solution was washed with water, dried, and concentrated. The crude residue was dissolved in ethanol (100 ml) and added over 2*N* sodium hydroxide solution (100 ml). The mixture was vigorously stirred and gently boiled and then zinc dust (45.10 g, 0.69 mole) was added in several portions, frequently enough to keep the solution boiling. After the addition was completed, the mixture was filtered off and the filtrate was poured into water (100 ml) and extracted with ethyl acetate. The organic solution was washed successively with water and brine, dried, and concentrated to give a *N*-substituted-1,2-benzenediamine. This diamine was added over urea (4.50 g, 75 mmoles) and the mixture heated at 150° for 1 hour. To the cooled mixture 1.5*N* sodium hydroxide solution (200 ml) was added. The reaction mixture was stirred for 2 hours and then filtered off. The filtrate was treated with 10% hydrochloric acid until *p*H 5 and the solid thus obtained was filtered off and dried to yield a 2-hydroxy-1*H*-benzimidazole. Phosphorus oxychloride (17 ml, 200 mmoles) was added to the previously obtained benzimidazole and the mixture heated in a sealed tube at 120° for 2 hours and then allowed to cool to room temperature. The cooled mixture was poured into ice-cold water, neutralized with ammonium hydroxide solution, extracted with ethyl acetate, washed with water, dried, and concentrated. The residue was added over diphenylmethylpiperazine (35.02 g, 139 mmoles) and the mixture heated in a sealed tube at 120° for 48 hours. The mixture was cooled, dissolved in chloroform, and washed successively with water, 5% hydrochloric acid, water again, and dried. The chloroformic solution was concentrated and the residue was subjected to flash chromatography (hexane/ethyl acetate 1:1).

2-[4-(Diphenylmethyl)piperazin-1-yl]-1-(1-methyl-2-methoxy)-ethyl-1*H*-benzimidazole (**9**).

This compound was obtained from 1-methoxy-2-propanamine as an oil which was transformed into its hydrogen fumarate and recrystallized from 2-propanol/water (1:1) to yield 13.07 g (55%), mp 192-194°; ^{1}H nmr (deuteriochloroform): δ 1.4-1.6 (d, 3H), 2.4-2.7 (m, 4H), 3.1-3.4 (m, 4H), 3.2 (s, 3H), 3.7 (d, 2H), 4.2 (s, 1H), 4.3-4.7 (m, 1H), 6.8-7.5 (m, 14H).

Anal. Calcd. for $C_{32}H_{36}N_4O_5$: C, 69.04; H, 6.52; N, 10.06. Found: C, 69.43; H, 6.49; N, 10.03.

2-[4-(Diphenylmethyl)piperazin-1-yl]-1-(3-methoxypropyl)-1*H*-benzimidazole (**10**).

This compound was obtained from 3-methoxypropanamine as an oil which was transformed into its hydrogen fumarate and recrystallized from 2-propanol/water (1:1) to yield 22.42 g (47%), mp 160-162° dec; ^{1}H nmr (DMSO d_6): δ 0.8-1.2 (t, 3H), 1.8-2.1 (m, 2H), 2.3-2.6 (m, 4H), 3.0-3.8 (m, 8H), 3.8-4.1 (t, 2H), 4.3 (s, 1H), 6.1 (s, 2H), 6.7 (s, 2H), 7.0-7.6 (m, 14H).

Anal. Calcd. for $C_{33}H_{38}N_4O_5$: C, 69.45; H, 6.71; N, 9.82. Found: C, 69.48; H, 6.70; N, 9.85.

2-[4-(Diphenylmethyl)piperazin-1-yl]-1-(2-methoxyethyl)-1*H*-benzimidazole (**11**).

This compound was obtained from 2-methoxyetanamine as an oil which was transformed into its hydrogen fumarate and recrystallized from ethanol/water (1:1) to yield 14.51 g (32%), mp 195-197° dec; ^{1}H nmr (DMSO d_6): δ 2.3-2.8 (m, 4H), 3.1 (s, 3H), 3.0-3.4 (m, 4H), 3.5-3.8 (t, 2H), 3.8-4.2 (t, 2H), 4.3 (s, 1H), 6.7 (s, 2H), 7.0-7.6 (m, 14H), 10.1 (s, 2H).

Anal. Calcd. for $C_{31}H_{34}N_4O_5$: C, 68.61; H, 6.32; N, 10.33. Found: C, 69.05; H, 6.28; N, 10.37.

1-Benzyl-2-[4-(diphenylmethyl)piperazin-1-yl]-1*H*-benzimidazole (**12**).

To a slurry of 0.48 g (10 mmoles) of hexane-washed sodium hydride (50% in oil) in dimethylformamide (15 ml), 2-chlorobenzimidazole (1.52 g, 10 mmoles) was added at 0°. The mixture was stirred at 0° for 20 minutes and at 25° for 30 minutes, and then benzylbromide (1.18 ml, 10 mmoles) was added. The mixture was heated at 80° for 16 hours, allowed to cool and poured into water yielding a solid that was filtered off, washed and dried. The dry product was added to 1-(diphenylmethyl)piperazine (2.52 g, 10 mmoles) and heated at 150° for 15 minutes. The mixture was allowed to cool to room temperature and 10% sodium hydroxide solution (20 ml) was added. The solution was extracted with chloroform, washed with water, dried, and concentrated to give a solid which was recrystallized from 2-(1-methylethoxy)propane/ethanol to give **12** as white crystals (3.10 g, 67%), mp 157-159°; ^{1}H nmr (deuteriochloroform): δ 2.3-2.7 (m, 4H), 3.1-3.4 (m, 4H), 4.25 (s, 1H), 5.1 (s, 2H), 6.9-7.7 (m, 19H).

Anal. Calcd. for $C_{31}H_{30}N_4$: C, 81.18; H, 6.59; N. 12.21. Found: C, 80.93; H, 6.62; N. 12.19.

General Procedure for Preparing Compounds **13a, 13b** and **13c**.

To a solution of 4-piperidinecarboxylic acid (12.90 g, 0.1 mole) in polyphosphoric acid (50.00 g), 0.1 mole of a 2-aminosubstituted benzene was added. The mixture was heated at 180° for 2 hours, allowed to cool, poured into water, and filtered off. The filtrate was treated with 50% potassium hydroxide solution until *p*H 12 and the precipitate filtered off, washed with water until pH 7, and dried.

2-(4-Piperidinyl)benzothiazole (**13a**).

This compound was obtained from 2-aminothiophenol as a solid, (19.60 g, 90%), mp 102-104°; ^{1}H nmr (DMSO d_6): δ 1.3 (s, 1H), 1.5-2.3 (m, 4H), 2.5-3.2 (m, 5H), 7.0-7.4 (m, 2H), 7.5-7.9 (m, 2H).

Anal. Calcd. for $C_{12}H_{14}N_2S$: C, 66.02; H, 6.46; N, 12.83. Found: C, 66.18; H, 6.39; N, 12.90.

2-(4-Piperidinyl)benzoxazole (**13b**).

This compound was obtained from 2-aminophenol as a solid, (18.78 g, 93%); ^{1}H nmr (deuteriochloroform): δ 1.6-2.4 (m, 4H), 2.4 (s, 1H), 2.5-3.4 (m, 5H), 7.1-7.8 (m, 4H).

Anal. Calcd. for $C_{12}H_{14}N_2O$: C, 71.26; H, 6.98; N, 13.85. Found: C, 71.53; H, 7.13; N, 13.59.

2-(4-Piperidinyl)-1*H*-benzimidazole (**13c**).

This compound was obtained from 1,2-diaminobenzene as a solid, (17.08 g, 85%), mp >200° ; ^{1}H nmr (DMSO d_6): δ 1.6-1.8 (m, 2H), 1.8-2.0 (m, 2H), 2.4-2.6 (m, 3H), 2.8-3.1 (m, 3H), 7.0-7.1 (m, 2H), 7.3-7.5 (m, 2H) ; ^{13}C nmr (DMSO d_6): δ 31.5, 36.6, 45.8, 121.0, 128.1, 128.9, 158.4.

Anal. Calcd. for $C_{12}H_{15}N_3$: C, 71.61; H, 7.51; N, 20.88. Found: C, 71.83; H, 7.39; N, 21.12.

General Procedure for Preparing Benzothiazoles **14-30** and **32-36**.

These compounds were prepared using indistinctly both procedures described below for **17** and **34**.

2-[1-(4-Methoxyphenyl)ethyl)piperidin-4-yl)]benzothiazole (**17**).

To a suspension of 1-(2-bromoethyl)-4-methoxybenzene (2.14 g, 10 mmoles) and potassium carbonate (1.38 g, 10 mmoles) in dimethylformamide (25 ml), 2.18 g (10 mmoles) of **13a** were added. The mixture was heated at 80° for 16 hours and then allowed to cool and poured into water (100 ml). The precipitated product was filtered off, washed with water and dried. Recrystallization from 2-propanol gave **17** as white crystals (2.90 g, 83%): mp 92-93°; ^{1}H nmr (deuteriochloroform): δ 1.7-1.9 (m, 2H), 1.9-2.2 (m, 4H), 2.4 (dd, 2H), 2.6 (dd, 2H), 2.9-3.0 (m, 3H), 3.6 (s, 3H), 6.7 (d, 2H), 6.9 (d, 2H), 7.1 (t, 1H), 7.3 (t, 1H), 7.7 (d, 1H), 7.8 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 32.1, 32.4, 41.1, 52.9, 54.7, 60.4, 113.4, 121.1, 122.2, 124.2, 125.4, 129.1, 131.9, 134.2, 152.6, 157.5, 175.5; ms: m/z 352 (M^+) 231 (100), 188 (13), 96 (34).

Anal. Calcd. for $C_{21}H_{24}N_2OS$: C, 71.55; H, 6.86; N, 7.95. Found: C, 71.68; H, 6.86; N, 7.95.

2-[1-(2-Phenylpropyl)piperidin-4-yl]benzothiazole (**34**).

To a solution of 2-phenyl-1-propanol (2.72 g, 20 mmoles) in pyridine (20 ml) at 5°, *p*-toluenesulfonyl chloride (4.76 g, 25 mmoles) was added. The solution was stirred at 5° for 30 minutes and at 25° for 2 hours and then poured into ice-water. The solution was treated with 20% hydrochloric acid until *p*H 6 and extracted with chloroform. The extract was washed successively with water, 5% sodium hydrogen carbonate solution and water again, dried, and concentrated *in vacuo*. The residue was dissolved in dimethylformamide (30 ml) and added to a suspension of **13a** (4.36 g, 20 mmoles) and potassium carbonate (2.76 g, 20 mmoles) in dimethylformamide (20 ml). The solution was heated at 70° for 8 hours, allowed to cool, poured into water, and extracted with ether. The ethereal extract was washed with water, dried and concentrated. The residue was purified by flash chromatography (hexane/ethyl acetate, 8:2) to yield **34** (3.91 g, 58%). An analytical sample was obtained by recrystallization from ethanol: mp 77-79°; ^{1}H nmr (deuteriochloroform): δ 1.2-1.4 (d, 3H), 1.6-2.3 (m, 6H), 2.3-2.6 (d, 2H), 2.7-3.2 (m, 4H), 7.1-8.0 (m, 9H).

Anal. Calcd. for $C_{21}H_{24}N_2S$: C, 74.95; H, 7.19; N, 8.33. Found: C, 75.05; H, 7.23; N, 8.30.

General Procedure for Preparing Benzothiazoles **38-45** and Benzoxazoles **46-49** and **51**.

These compounds were prepared using the general method described below for **48**.

2-[1-(2-(4-Methoxyphenyl)ethyl)piperidin-4-yl]benzoxazol (**48**).

To a suspension of 1-(2-bromoethyl)-4-methoxybenzene (2.14 g, 10 mmoles), sodium carbonate (1.06 g, 10 mmoles) and sodium iodide (1.49 g, 10 mmoles) in acetonitrile (30 ml), 2.02 g (10 mmoles) of **13b** were added. The mixture was heated at 80° for 24 hours and then poured into water (100 ml). The precipitated product was filtered off, washed with water, dried and recrystallized from ethanol/water (1:1) to yield 2.45 g (73%) of **48**, mp 86-88°; ^{1}H nmr (deuteriochloroform): δ 1.7-2.1 (m, 6H), 2.4-2.5 (t, 2H), 2.6-2.7 (t, 2H), 2.6-2.7 (m, 1H), 2.8-2.9 (m, 2H), 3.6 (s, 3H), 6.6 (d, 2H), 6.9 (d, 2H), 7.1 (m, 2H), 7.3 (m, 1H), 7.5 (m, 1H); ^{13}C nmr (deuteriochloroform): δ 29.1, 32.3, 35.5, 52.5, 54.6, 60.4, 109.8, 113.3, 119.2, 123.5, 123.9, 129.1, 131.9, 140.8, 150.1, 157.5, 168.6; ms: m/z 336 (M^+, 5), 215 (100), 172 (11), 146 (3), 121 (3), 96 (29), 42 (4).

Anal. Calcd. for $C_{21}H_{24}N_2O_2$: C, 74.97; H, 7.19; N, 8.33. Found: C, 75.09; H, 7.21; N, 8.34.

2-[1-(2-(2-(4-Chlorophenyl)-2-hydroxyethyl)piperidin-4-yl]benzothiazole (**31**).

To a solution of potassium hydroxide (2.00 g) in methanol (40 ml), a solution of **30** (4.60 g, 12.4 mmoles) in tetrahydrofurane (60 ml) was added. Sodium borohydride (0.5 g) was slowly added for a period of 30 minutes and the reaction mixture was stirred at room temperature overnight. Then, water was added (10 ml) and the solution concentrated. The residue was recrystallized from ethanol/water (1:1) to give **31** (4.10 g, 87%), mp 138-140°; ^{1}H nmr (deuteriochloroform): δ 1.8-2.0 (m, 2H), 2.0-2.1 (m, 2H), 2.2-2.5 (m, 4H), 2.8 (d, 1H), 2.9-3.1 (m, 1H), 3.1 (d, 1H), 4.0-4.1 (bs, 1H), 4.6-4.7 (dd, 1H), 7.1-7.3 (m, 6H), 7.3-7.4 (t, 1H), 7.7 (d, 1H), 7.9 (d, 1H); ^{13}C nmr (deuteriochloroform): δ 32.0, 32.3, 40.9, 51.4, 54.5, 65.9, 68.0, 121.3, 122.3, 124.5, 125.7, 126.9, 128.2, 132.8, 134.5, 140.9, 153.0, 175.4.

Anal. Calcd. for $C_{20}H_{21}ClN_2OS$: C, 64.41; H, 5.68; N, 7.51. Found: C, 64.81; H, 5.67; N, 7.50.

General Procedure for Preparing Compounds **37, 50** and **52**.

The procedure described below for **52** was also used for the preparation of **37** and **50**.

4-[4-(2-Benzoxazolyl)piperidin-1-yl]-1-(4-tercbutylphenyl)-1-butanone (**52**).

A mixture of 4-chloro-1-(4-tercbutylphenyl)-1-butanone (9.16 g, 38 mmoles), ethyleneglycol (8.45 g, 136 mmoles) and *p*-toluensulfonic acid monohydrate (0.05 g, 0.26 mmoles) in toluene (30 ml) was refluxed in a Dean-Stark apparatus for 16 hours. The solution was washed successively with 5% sodium hydrogen carbonate solution and water, dried, and concentrated. The residue was dissolved in acetonitrile (40 ml) and added to a suspension of **13b** (7.07 g, 35 mmoles), sodium carbonate (3.66 g, 35 mmoles) and sodium iodide (5.18 g, 35 mmoles) in acetonitrile (60 ml). The mixture was refluxed for 72 hours and then cooled and poured into 5% hydrochloric acid (250 ml). The precipitate was filtered off and dissolved in 25% hydrochloric acid (250 ml) and tetrahydrofurane (20 ml). The solution was refluxed for 30 minutes, concentrated, and the residue recrystallized from ethanol to yield **52** as its hydrochloride (8.00 g, 57%), mp 235-236°; ^{1}H nmr (DMSO d_6): δ 1.3 (s, 9H), 2.0-2.2 (m, 6H), 2.5 (m, 3H), 2.8-2.9 (m, 1H), 2.9-3.0 (m, 1H), 3.1-3.2 (m, 4H), 3.6-3.7 (m, 1H), 6.7 (t, 1H), 6.8-7.0 (m, 2H), 7.5 (d, 2H), 7.7 (d, 1H), 7.9 (d, 2H); ^{13}C nmr (DMSO d_6): δ 16.1, 24.1, 28.9, 32.9, 33.0, 37.9, 49.4, 53.8, 113.8, 116.9, 123.3, 123.5, 124.2, 125.8, 126.0, 131.9, 145.9, 154.4, 170.1, 195.9; ir (potassium bromide): ν CO, 1660 cm^{-1}.

Anal. Calcd. for $C_{26}H_{33}ClN_2O_2$: C, 70.81; H, 7.54; N, 6.35. Found: C, 71.13; H, 7.50; N, 6.38.

General Procedure for Preparing Piperidinobenzimidazoles **53-129**.

These compounds were prepared using the method described below for **58**.

2-[1-(4-Fluorophenylmethyl)piperidin-4-yl]-1-(2-methoxyethyl)-1*H*-benzimidazole (**58**).

To a suspension of **13c** (4.02 g, 20 mmoles) and potassium carbonate (2.76 g, 20 mmoles) in dimethylformamide (20 ml), 4-fluorobenzyl chloride (2.88 g, 20 mmoles) was added. The mixture was heated at 80° for 16 hours and then allowed to cool and poured into ice-cooled water (300 ml). The precipitate was filtered off, washed with water, and dried. The dry solid was dissolved in dimethylformamide (40 ml) and added to a stirred slurry of hexane-washed sodium hydride (0.96 g, 20 mmoles) in dimethylformamide (40 ml) at 0°. The mixture was stirred at 0° for 20 minutes and at 25° for 30 minutes and then treated with a solution of 2-chloroethyl methyl ether (1.88 g, 20 mmoles) in dimethylformamide (10 ml). The mixture was heated at 60° for 8 hours, allowed to cool, poured into water, and extracted with ether. The ethereal extract was washed with water, dried, and concentrated. The residue was subjected to flash chromatography (chloroform/methanol, 95:5) to give **58** as an oil which crystallized as the hydrogen fumarate from 2-propanol (6.91 g, 72%), mp 176-178°; ^{1}H nmr (DMSO d_6): δ 1.9-2.0 (m, 4H), 3.0-3.1 (m, 2H), 3.1 (s, 3H), 3.2-3.3 (m, 1H), 3.3-3.5 (m, 2H), 3.6-3.7 (t, 2H), 4.3-4.4 (t, 2H), 7.1-7.3 (m, 4H), 7.3-7.4 (m, 3H), 7.4-7.6 (m, 1H); ^{13}C nmr (D_2O): δ 26.2, 30.3, 33.3, 45.9, 53.9, 61.0, 72.5, 113.4, 118.5, 119.8, 125.9, 127.1, 135.9, 137.8, 142.0, 158.7, 164.3, 167.6; ms: m/z 367 (M^+, 5), 258 (47), 203 (100), 109 (33).

Anal. Calcd. for $C_{26}H_{30}FlN_3O_5$: C, 64.58; H, 6.25; N, 8.69. Found: C, 64.49; H, 6.20; N, 8.69.

Pharmacology.

Antiallergic activity was investigated in IgE-dependent PCA in rats. The anti-ovalbumin reaginic serum was produced by Mota's method [15]. Male Wistar rats weighing about 200 g received 0.1 ml/rat ip of killed *Bortedella pertussis* suspension and 10 mg/kg ip of ovalbumin. Fourteen days later the rats were anesthetized and exsanguinated by jugular puncture. The obtained serum was pooled and stored at -20°. PCA was induced in male rats weighing about 150-200 g by the technique described by Brocklehurst [16]. Shaved rats were sensitized at dorsal sites (2/rat) by intradermal injection of 0.1 ml of an appropriate dilution (from 4-fold to 16-fold) of antiserum in 0.9% sodium chloride solution, 1 hour after drug administration. After a latency period of 48 hours, 25 mg/kg of ovalbumin and 25 mg/kg of Evans blue in 0.9% sodium chloride solution, were injected into the caudal vein. Thirty minutes after antigen challenge, the rats were sacrificed (CO_2) and the skin of each wheal was removed, placed in 5 ml of formamide, and heated at 50-60° for 48 hours. The intensity of the extracted dye was measured by spectrophotometry at 620 nm. ID_{50} ranges were estimated depending on the obtained results with the orally administered doses (initial dose: 50 mg/kg po).

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