Synthesis of Benzimidazole Derivatives as Potential H_1-Antihistaminic Agents

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Several types of benzimidazole derivatives were prepared and were screened for H_1-antihistaminic activity. Most of the compounds showed potent antihistaminic activity *in vitro*. Among them 2-[(1-piperazinyl)methyl]-benzimidazoles **14** and 2-[(1-homopiperazinyl)methyl]benzimidazoles **15** exhibited potent activity also *in vivo*.

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In the previous paper [1], we reported the synthesis and H_1-antihistaminic activity of 2-(4-substituted-1-piperazinyl)benzimidazoles. The results of the study revealed that compounds **1** and **2** exhibited potent H_1-antihistaminic activity *in vitro* and *in vivo*. Moreover, it turned out that the presence of a 2-alkoxyethyl group at the 1-position of benzimidazole nucleus played an important role for the occurence of potent H_1-antihistaminic activity, especially *in vivo*. Among them 1-(2-ethoxyethyl)-2-(4-methyl-1-homopiperazinyl)benzimidazole (**2a**: $R^1 = CH_2CH_3$, $R^2 = CH_3$; KB-2413) was selected for clinical evaluation. Its activity *in vivo* was 39 times more potent than that of chlorpheniramine (**3**), which is one of the potent H_1-antihistaminic agents.

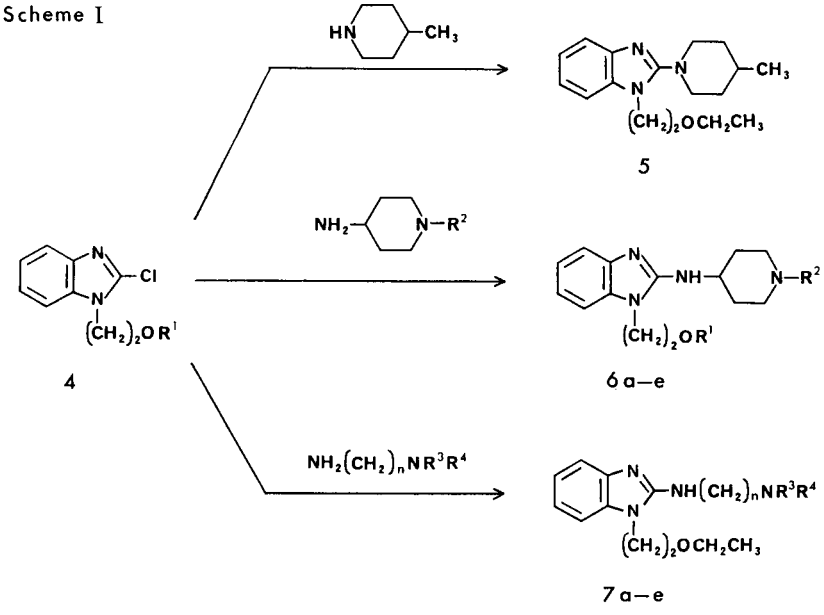
The novel structures of compounds **1** and **2** as well as their potent H_1-antihistaminic activities prompted us to synthesize new types of benzimidazole derivatives in order to explore new antiallergic agents.

We now wish to report the synthesis and H_1-antihistaminic activity of several types of benzimidazole derivatives. The synthetic routes are outlined in Scheme I.

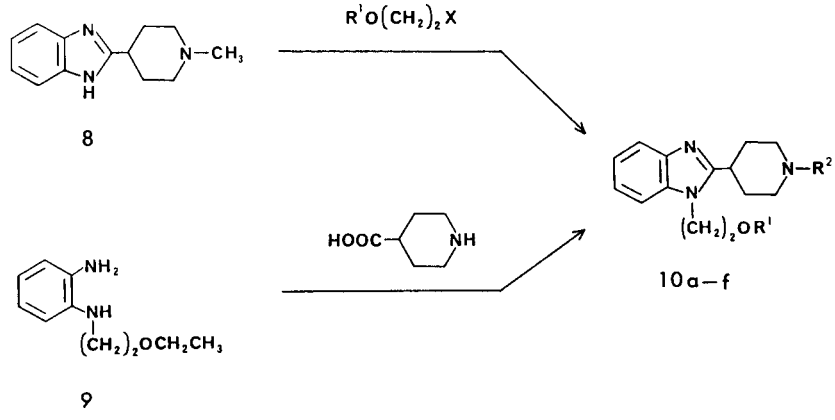
1-Substituted-2-chlorobenzimidazoles **4** [1], prepared from alkylation of 2-chlorobenzimidazole or from chlorination of 1-substituted-2-benzimidazolone derivatives, were treated with 4-methylpiperidine, appropriate 4-aminopiperidines [2a,b] of alkylenediamines to afford 2-(4-methylpiperidino)benzimidazole **5**, 2-aminobenzimidazoles **6a-d** or **7a-e**, respectively. 2-[(4-Piperidinyl)amino]benzimidazole **6e** was obtained from hydrogenolysis of 2-[(1-benzyl-4-piperidinyl)amino]benzimidazole **6d**.

1-Substituted-2-chlorobenzimidazoles **4** [1], prepared from alkylation of 2-chlorobenzimidazole or from chlorination of 1-substituted-2-benzimidazolone derivatives, were treated with 4-methylpiperidine, appropriate 4-aminopiperidines [2a,b] or alkylenediamines to afford 2-(4-methylpiperidino)benzimidazole **5**, 2-aminobenzimidazoles **6a-d**

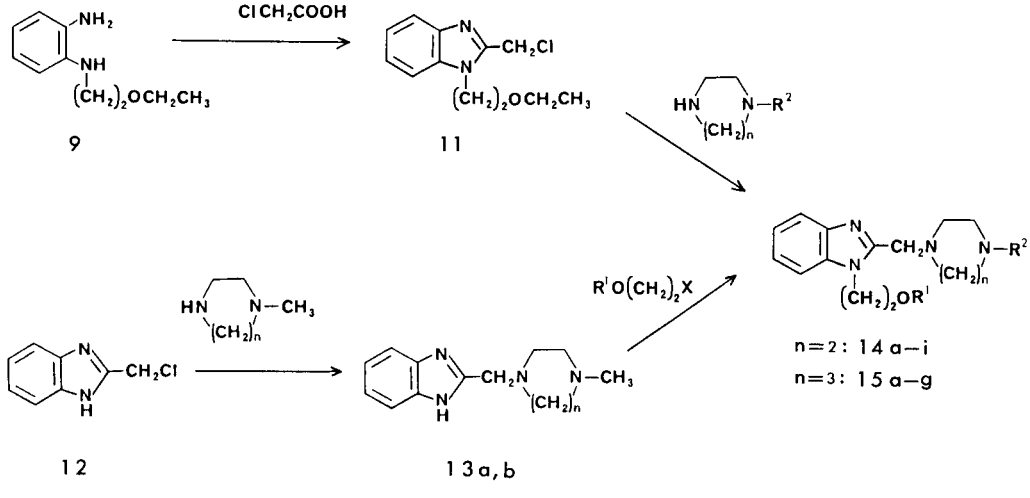
Scheme I



Scheme I



Scheme I



or **7a-e**, respectively. 2-[(4-Piperidinyl)amino]benzimidazole **6e** was obtained from hydrogenolysis of 2-[(1-benzyl-4-piperidinyl)amino]benzimidazole **6d**.

1-(2-Ethoxyethyl)-2-[(1-piperazinyl)methyl]benzimidazoles **14a,f,i** were prepared from the reaction of 2-chloromethyl-1-(2-ethoxyethyl)benzimidazole (**11**), prepared by treatment of compound **9** with chloroacetic acid, with appropriate piperazines. 1-Substituted-2-[(4-methyl-1-piperazinyl)methyl]benzimidazoles **14b-e** were prepared from 2-chloromethylbenzimidazole (**12**) [4], by treatment of *N*-methylpiperazine, followed by alkylation with 2-alkoxyethyl halides. Compounds **14g,h** were obtained from the alkylation of **14f**.

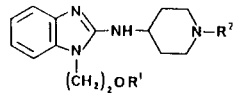
Homopiperazine derivatives **15a-g** were prepared in the same manner as the syntheses of piperazine derivatives **14a-i**.

Compounds listed in Tables I-IV and **5** were tested for H_1-antihistaminic activity *in vitro* (guinea pig ileum) and *in vivo* (histamine-induced mortality in guinea pigs). The results are presented in Table V.

In the *in vitro* test all the compounds, except compound **5**, exhibit potent antihistaminic activity, whose activities are comparable to that of KB-2413 (**2a**) and chlorpheniramine maleate (**3**). The comparison of the activities between compounds **10a-f** and **5** reveals that the nitrogen atom of piperidine ring in compounds **10a-f**, not in compound **5**, is important for the occurrence of H_1-antihistaminic activity. This fact suggests that the nitrogen atom at the 4-position of (homo)piperazine in compounds **1** and **2** is prerequisite for the occurrence of activity.

Table I

Preparation of *N*-(4-Piperidinyl)-1*H*-benzimidazol-2-amines

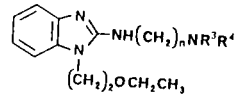


Compound	R^1	R^2	Yield [a] (%)	Mp [b] (°C)	Formula [c]	Analysis (%) Calcd. (Found) C	H	N
6a	CH_2CH_3	CH_3	59	211-214	$C_{17}H_{26}N_4O \cdot 2C_4H_4O_4$	56.17 (56.16	6.41 6.53	10.48 10.60)
6b	$CH_2CH=CH_2$	CH_3	42	191-197	$C_{18}H_{26}N_4O \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$	57.94 (57.95	6.68 6.71	11.26 11.26)
6c	Ph	CH_3	46	225-226.5	$C_{21}H_{26}N_4O \cdot 2C_4H_4O_4$	59.79 (59.81	5.88 5.88	9.62 9.56)
6d	CH_2CH_3	CH_2Ph	49	197.5-199.5	$C_{23}H_{30}N_4O \cdot 2C_4H_4O_4$	60.97 (61.09	6.27 6.30	9.17 9.20)
6e	CH_2CH_3	H	52	185-187	$C_{16}H_{24}N_4O \cdot 2C_4H_4O_4$	55.38 (55.03	6.20 6.28	10.76 10.79)

[a] Yield of free base. [b] Recrystallization solvent: ethanol for **6a,b,d,e**; ethanol/methanol for **6c**. [c] $C_4H_4O_4$: hydrogen fumarate.

Table II

Preparation of *N*-(Dialkylaminoalkyl)-1*H*-benzimidazol-2-amines



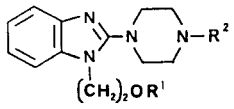
Compound	n	NR^3R^4	Yield [a] (%)	Mp [b] (°C)	Formula [c]	Analysis (%) Calcd. (Found) C	H	N
7a	2	$N(CH_3)_2$	50	124.5-125.5	$C_{15}H_{24}N_4O \cdot 2C_4H_4O_4$	54.32 (54.24	6.34 6.23	11.02 10.99)
7b	2	$N(CH_2CH_3)_2$	68	113.5-116	$C_{17}H_{28}N_4O \cdot 2C_4H_4O_4$	55.96 (56.16	6.76 6.80	10.44 10.55)
7c	2	pyrrolidino	60	129.5-131	$C_{17}H_{26}N_4O \cdot 2C_4H_4O_4$	56.17 (56.15	6.41 6.41	10.48 10.64)
7d	3	$N(CH_3)_2$	60	143-144	$C_{16}H_{26}N_4O \cdot 2C_4H_4O_4$	55.16 (55.16	6.56 6.57	10.72 10.81)
7e	3	$N(CH_2CH_3)_2$	68	129-130.5	$C_{18}H_{30}N_4O \cdot 2C_4H_4O_4$	56.72 (56.87	6.96 7.10	10.18 10.26)

[a] Yield of free base. [b] Recrystallization solvent: ethanol/ethyl acetate. [c] $C_4H_4O_4$: hydrogen maleate.

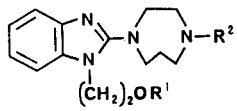
In the *in vivo* (po) test only the compounds possessing (1-piperazinyl)methyl group (**14**) or (1-homopiperazinyl)-methyl group (**15**) at the 2-position of the benzimidazole nucleus show considerably potent activity, whose activities are comparable to that of KB-2413 (**2a**).

These results seem to indicate that the pharmacokinetic profiles, such as absorption, distribution or metabolism, of compounds **14** and **15** are superior to those of compounds **6**, **7**, or **10**.

Most compounds that are effective at low dose levels in antagonizing histamine at H_1 receptor sites may be described by the general structure **16**, which comprize a

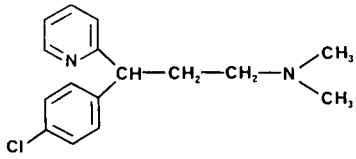


1



2

2a ($R^1 = CH_2CH_3$, $R^2 = CH_3$)



3

(chlorpheniramine)

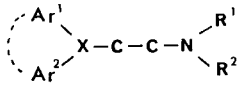


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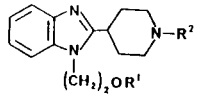
Table III

Preparation of 2-(4-Piperidinyl)-1*H*-benzimidazoles



Compound	R^1	R^2	Yield [a] (%)	Mp [b] (°C)	Formula [c]	Analysis (%) Calcd. (Found) C	H	N
10a	CH_2CH_3	CH_3	50	181-183	$C_{17}H_{25}N_3O \cdot C_4H_4O_4 \cdot 0.5H_2O$	61.14 (60.72)	7.33 7.16	10.19 9.80)
10b	$CH_2CH=CH_2$	CH_3	70	171.5-173	$C_{18}H_{25}N_3O \cdot 1.5C_4H_4O_4$	60.88 (60.62	6.60 6.68	8.87 8.81)
10c	$CH_2C\equiv CH$	CH_3	84	174-176	$C_{18}H_{23}N_3O \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$	59.99 (60.36	6.29 6.27	8.74 8.65)
10d	Ph	CH_3	61	184.5-187	$C_{21}H_{25}N_3O \cdot 1.5C_4H_4O_4$	63.64 (63.12	6.13 6.33	8.25 8.08)
10e	CH_2CH_3	H	5	173.5-175	$C_{16}H_{23}N_3O \cdot 1.5C_4H_4O_4$	59.05 (58.97	6.53 6.64	9.39 9.34)
10f	CH_2CH_3	CH_2CH_3	78	184-186	$C_{18}H_{27}N_3O \cdot 1.5C_4H_4O_4$	60.61 (60.58	7.00 7.14	8.84 8.79)

[a] Yield of free base. [b] Recrystallization solvent: ethanol/ethyl acetate. [c] $C_4H_4O_4$: hydrogen fumarate.

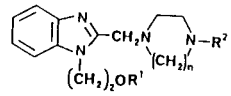
double-aromatic unit linked through a chain to a basic tertiary amino group [5,6]. Therefore compounds **14** and **15** together with **1** and **2** are of interest because they provide only a single aromatic unit (= benzimidazole nucleus) linked through a chain to a basic nitrogen.

EXPERIMENTAL

Melting points were taken on a capillary melting point apparatus (Yamato MR-21) and are uncorrected. The structures of all compounds were supported by their ir (Shimadzu IR-440) and ^{1}H-nmr (Hitachi R-24A) spectra. Elemental analyses were performed by the Analtyical Department of Kyoto University or Kanebo Research Center.

Table IV

Preparation of 2-[(1-Piperazinyl)methyl]-1*H*-benzimidazoles



Compound	n	R^1	R^2	Yield [a] (%)	Mp [b] (°C)	Formula [c]	Analysis (%) Calcd. (Found) C	H	N
14a	2	CH_2CH_3	CH_3	97	155-160	$C_{17}H_{26}N_4O \cdot C_4H_4O_4 \cdot 0.5H_2O$	59.00 (59.27	7.31 7.29	13.11 13.01)
14b	2	$CH=CH_2$	CH_3	56	65.5-67.5	$C_{17}H_{24}N_4O$	67.97 (68.11	8.05 8.04	18.65 18.61)
14c	2	$(CH_2)_2CH_3$	CH_3	89	160.5-161.5	$C_{18}H_{28}N_4O \cdot 2C_4H_4O_4$	56.92 (56.84	6.61 6.56	10.21 10.23)
14d	2	$CH_2CH=CH_2$	CH_3	55	166 dec	$C_{18}H_{26}N_4O \cdot C_4H_4O_4 \cdot 1.5H_2O$	57.75 (57.21	7.27 7.12	12.25 12.14)
14e	2	$CH_2C\equiv CH$	CH_3	29	159.5-163	$C_{18}H_{24}N_4O \cdot C_4H_4O_4 \cdot 0.5H_2O$	60.40 (60.40	6.68 6.43	12.81 12.33)
14f	2	CH_2CH_3	H	93	158.5 dec	$C_{16}H_{24}N_4O \cdot C_4H_4O_4 \cdot H_2O$	56.86 (56.49	7.16 7.01	13.26 13.15)
14g	2	CH_2CH_3	CH_2CH_3	92	182-183	$C_{18}H_{28}N_4O \cdot 1.5C_4H_4O_4$	58.76 (58.80	6.99 7.00	11.42 11.36)
14h	2	CH_2CH_3	$(CH_2)_2CH_3$	84	178.5-180	$C_{19}H_{30}N_4O \cdot 1.5C_4H_4O_4$	59.51 (59.54	7.19 7.35	11.10 11.14)
14i	2	CH_2CH_3	$(CH_2)_2OH$	98	160-160.5	$C_{18}H_{28}N_4O_2 \cdot 1.5C_4H_4O_4$	56.91 (56.86	6.76 6.91	11.06 11.00)
15a	3	CH_2CH_3	CH_3	70	119-121.5	$C_{18}H_{28}N_4O \cdot 1.5C_4H_4O_4 \cdot 0.5H_2O$	57.70 (57.63	7.06 7.13	11.22 11.30)
15b	3	$(CH_2)_2CH_3$	CH_3	28	132.5-134.5	$C_{19}H_{30}N_4O \cdot 1.5C_4H_4O_4$	59.51 (59.41	7.19 7.21	11.10 11.11)
15c	3	$CH_2CH=CH_2$	CH_3	39	125.5-128	$C_{19}H_{28}N_4O \cdot 1.5C_4H_4O_4$	59.75 (59.76	6.82 6.88	11.15 11.12)
15d	3	$CH_2C\equiv CH$	CH_3	45	133-136	$C_{19}H_{26}N_4O \cdot 1.5C_4H_4O_4$	59.99 (59.98	6.44 6.52	11.19 11.36)
15e	3	Ph	CH_3	62	140.5-142.5	$C_{22}H_{28}N_4O \cdot 1.5C_4H_4O_4$	62.44 (62.40	6.36 6.39	10.40 10.32)
15f	3	CH_2CH_3	H	66	151-152	$C_{17}H_{26}N_4O \cdot 1.5C_4H_4O_4$	57.97 (58.24	6.77 6.97	11.76 11.82)
15g	3	CH_2CH_3	CH_2CH_3	67	129-134	$C_{19}H_{30}N_4O \cdot 1.5C_4H_4O_4$	59.51 (59.47	7.19 7.19	11.10 11.18)

[a] Yield of free base. [b] Recrystallization solvent: ethanol for **14a,d,f-i,15g**; ethanol/ethyl acetate for **14c,e,15a-f**; ether/hexane for **14b**. [c] $C_4H_4O_4$: hydrogen fumarate.

1-(2-Ethoxyethyl)-2-(4-methylpiperidino)-1*H*-benzimidazole (**5**).

A mixture of 3.0 g (13 mmoles) of 2-chloro-1-(2-ethoxyethyl)-1*H*-benzimidazole [1] and 3.0 g (30 mmoles) of 4-methylpiperidine was stirred at 120° for 2 hours. To the reaction mixture was added 30 ml of 1*N* sodium hydroxide and the mixture was extracted with ethyl acetate. After evaporation to dryness, the residue was chromatographed on silica gel with hexane/chloroform (1:1) to give 2.9 g (76%) of **5**, which crystallized as the hydrogen fumarate. Recrystallization from ethanol/ethyl acetate gave colorless columns, mp 132-133.5°.

Anal. Calcd. for $C_{17}H_{25}N_3O \cdot C_4H_4O_4$: C, 62.51; H, 7.24; N, 10.41. Found: C, 62.50; H, 7.33; N, 10.26.

N-(4-Piperidinyl)-1*H*-benzimidazole-2-amines **6a-d**.

Reaction of 10 mmoles of the 2-chloro-1*H*-benzimidazoles (**4**) [1] with 20 mmoles of 1-alkyl-4-aminopiperidine [2a,b] as described for **5** afforded the desired products, which crystallized as the hydrogen fumarate (Table I).

Table V

H_1-Antihistaminic Activity *In Vitro* and *In Vivo* [a]

Compound	*in vitro*: IC_{50}, M	*in vivo*: ED_{50}, mg/kg
5	$>3.0\times10^{-6}$	NT [b]
6a	1.8×10^{-8}	0.012
6b	1.4×10^{-8}	0.047
6c	1.3×10^{-7}	>0.10
6d	6.6×10^{-8}	>0.050
6e	2.0×10^{-8}	>0.050
7a	1.3×10^{-8}	>0.025
7b	4.4×10^{-8}	>0.050
7c	8.6×10^{-9}	>0.050
7d	2.6×10^{-8}	>0.050
7e	5.9×10^{-8}	>0.10
10a	1.7×10^{-8}	0.014
10b	1.1×10^{-8}	>0.10
10c	1.2×10^{-8}	0.017
10d	1.9×10^{-8}	>0.050
10e	1.2×10^{-8}	0.046
10f	1.5×10^{-8}	>0.050
14a	2.1×10^{-8}	0.0026
14b	2.0×10^{-8}	0.0071
14c	1.6×10^{-8}	0.0059
14d	9.6×10^{-9}	0.0059
14e	1.2×10^{-8}	0.0023
14f	2.4×10^{-8}	0.0033
14g	2.1×10^{-8}	0.0067
14h	3.4×10^{-8}	0.0095
14i	8.3×10^{-8}	0.0040
15a	1.4×10^{-8}	0.0092
15b	1.8×10^{-8}	0.056
15c	9.2×10^{-9}	0.021
15d	9.1×10^{-9}	0.017
15e	2.0×10^{-8}	>0.050
15f	2.0×10^{-8}	0.014
15g	9.9×10^{-9}	0.028
2a	6.1×10^{-9}	0.0044
3	1.2×10^{-8}	0.17

[a] See experimental. [b] NT: not tested.

1-(2-Ethoxyethyl)-*N*-(4-piperidinyl)-1*H*-benzimidazol-2-amine (**6e**).

A solution of 3.0 g (7.9 mmoles) of **6d** in isopropyl alcohol (15 ml) and water (10 ml) was hydrogenolized over 0.6 g of 10% palladium on carbon at 60° (50 psi) for 11 hours. After removal of the catalyst and evaporation to dryness, the residue was crystallized as the hydrogen fumarate (Table I).

N-(Dialkylaminoalkyl)-1-(2-ethoxyethyl)-1*H*-benzimidazol-2-amines **7a-e**.

Compounds **7a-e** were prepared in the same manner as the synthesis of compound **5**. The products obtained were crystallized as the hydrogen maleate (Table II).

2-(4-Piperidinyl)-1*H*-benzimidazoles **10a-d**.

A mixture of 10 mmoles of 2-(1-methyl-4-piperidinyl)-1*H*-benzimidazole (**8**) [3a,b], 15 mmoles of 2-alkoxyethyl halide and 15 mmoles of sodium hydride in 30 ml of *N,N*-dimethylformamide was stirred at 60° for 2-5 hours. The reaction mixture was poured into 70 ml of water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with chloroform/methanol (20:1) furnished **10a-d**, which crystallized as the hydrogen fumarate (Table III).

1-(2-Ethoxyethyl)-2-(4-piperidinyl)-1*H*-benzimidazole (**10e**).

A solution of 14.3 g (79 mmoles) of *N*-(2-ethoxyethyl)-*o*-phenylenediamine (**9**) [1], 11.0 g (85 mmoles) of 4-piperidinecarboxylic acid in 160 ml of 6*N* hydrochloric acid was refluxed for 15 hours. The reaction mixture was made basic with 6*N* sodium hydroxide and was extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with chloroform/methanol (5:1) gave 1.1 g (5%) of **10e** as a brown liquid, which crystallized as the hydrogen fumarate (Table III).

1-(2-Ethoxyethyl)-2-(1-ethyl-4-piperidinyl)-1*H*-benzimidazole (**10f**).

A mixture of 1.4 g (5.1 mmoles) of **10e**, 0.94 g (6.0 mmoles) of ethyl iodide, 0.83 g (6.0 mmoles) of potassium carbonate and 20 ml of ethanol was stirred at 70° for 3 hours. The reaction mixture was filtered and the filtrate was evaporated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with chloroform/methanol (20:1) furnished 1.2 g (78%) of **10f** as a pale brown liquid, which crystallized as the hydrogen fumarate (Table III).

2-Chloromethyl-1-(2-ethoxyethyl)-1*H*-benzimidazole (**11**).

A solution of 6.0 g (33 mmoles) of **9**, 4.5 g (48 mmoles) of chloroacetic acid in 4*N* hydrochloric acid was refluxed for 4 hours. After cooling, the reaction mixture was neutralized with ammonia water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was column chromatographed on silica gel with cyclohexane/ethyl acetate (3:1) to give a pale yellow solid. Recrystallization from methanol/water gave 3.75 g (47%) of **11** as colorless columns, mp 75.5-77°.

Anal. Calcd. for $C_{12}H_{15}ClN_2O$: C, 60.38; H, 6.33; N, 11.73. Found: C, 60.45; H, 6.33; N, 11.78.

2-[(4-Methyl-1-piperazinyl)methyl]-1*H*-benzimidazole (**13a**).

To a stirred solution of 15 g (150 mmoles) of *N*-methylpiperazine in 70 ml of ethanol at 60° was added dropwise a solution of 10 g (60 mmoles) of 2-chloromethyl-1*H*-benzimidazole (**12**) [4] in 100 ml of ethanol and 25 ml of *N,N*-dimethylformamide. After 2 hours, the reaction mixture was concentrated *in vacuo*. To the residue were added 50 ml of saturated sodium chloride solution and 40 ml of 4*N* sodium hydroxide, and the mixture was extracted with chloroform. The extract was washed with saturated sodium chloride solution, dried over magnesium sulfate and concentrated *in vacuo*. The solid obtained was recrystallized from ethyl acetate to give 4.24 g (31%) of **13a** as pale yellow needles, mp 179-183°.

Anal. Calcd. for $C_{13}H_{18}N_4$: C, 67.80; H, 7.88; N, 24.33. Found: C, 67.79; H, 8.08; N, 24.28.

2-[(Hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)methyl]-1*H*-benzimidazole (**13b**).

Reaction of 15 g (130 mmoles) of *N*-methylhomopiperazine and 10 g (60 mmoles) of 2-chloromethyl-1*H*-benzimidazole as described for **13a** afforded 3.81 g (26%) of **13b** as pale yellow prisms (toluene), mp 152-155°.

Anal. Calcd. for $C_{14}H_{20}N_4$: C, 68.82; H, 8.25; N, 22.93. Found: C, 68.48; H, 8.57; N, 22.68.

1-(2-Ethoxyethyl)-2-[(1-piperazinyl)methyl]-1*H*-benzimidazoles **14a,f,i**.

To a stirred solution of 20-100 mmoles of piperazine derivatives in 50-100 ml of dioxane at 50° was added dropwise a solution of 10 mmoles of **11** in 50 ml of dioxane. After 2 hours, the reaction mixture was concen-

trated *in vacuo*. To the residue were added 30 ml of chloroform and 30 ml of saturated sodium chloride solution. The chloroform layer was separated, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with chloroform/methanol gave **14a,f,i** which crystallized as the hydrogen fumarate (Table IV).

2-[(4-Methyl-1-piperazinyl)methyl]-1*H*-benzimidazoles **14b-e**.

A mixture of 15 mmoles of **13a**, 21 mmoles of 2-alkoxyethyl halide and 20 mmoles of sodium hydride in 30 ml of *N,N*-dimethylformamide was stirred at 60° for 2 hours. The reaction mixture was poured into water and extracted with ethyl acetate. The extract was washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with chloroform/methanol (20:1) gave **14b-e**. Compounds **14c-e** were crystallized as the hydrogen fumarate (Table IV).

2-[(4-Alkyl-1-piperazinyl)methyl]-1*H*-benzimidazoles **14g,h**.

A mixture of 10 mmoles of **14f**, 12 mmoles of alkyl halide, 12 mmoles of potassium carbonate and 30 ml of ethanol was refluxed for 3 hours. The reaction mixture was concentrated *in vacuo*. To the residue were added water and ethyl acetate. The organic layer was separated, washed with water, dried over magnesium sulfate and concentrated *in vacuo*. The residue was purified by column chromatography on silica gel. Elution with chloroform/methanol (20:1) gave **14g,h**, which crystallized as the hydrogen fumarate (Table IV).

1-(2-Ethoxyethyl)-2-[(hexahydro-1*H*-1,4-diazepin-1-yl)methyl]-1*H*-benzimidazoles **15a,f**.

Compounds **15a,f** were prepared in the same manner as the synthesis of **14a,f,i**. The products obtained were crystallized as the hydrogen fumarate (Table IV).

2-[(Hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)methyl]-1*H*-benzimidazoles **15b-e**.

Compounds **15b-e** were prepared in the same manner as the synthesis of **14b-e**. The products obtained were crystallized as the hydrogen fumarate (Table IV).

1-(2-Ethoxyethyl)-2-[(hexahydro-4-ethyl-1*H*-1,4-diazepin-1-yl)methyl]-1*H*-benzimidazole (**15g**).

Reaction of 3.4 g (11 mmoles) of **15a** with 2.2 g (14 mmoles) of ethyl iodide as described for **14g,h** afforded 2.5 g (67%) of **15g**, which crystallized as the hydrogen fumarate (Table IV).

H_1-Antihistaminic Activity: Contraction of Isolated Ileum from Guinea Pigs Induced by Histamine (*in vitro*).

A study of the interaction with histamine was carried out with isolated ileum from guinea pigs according to the usual method. The segments (1 cm) of ileum were suspended in an organ bath containing Tyrode solution (ventilation, 32°). The contractile responses to histamine (5.4×10^{-7} mol/l) were measured with an isotonic transducer (TD-112S, Nihon Koden, Tokyo, Japan). Each test compound was added in the organ bath 5 minutes before the addition of histamine. IC_{50} values of the test compounds were calculated by the probit method [7].

Histamine-Induced Mortality in Guinea Pigs (*in vivo*).

Histamine-induced mortality in guinea pigs was performed according to the method of Labell and Tislow [8]. Groups of six to ten animals (250-350 g) were fasted for 20-24 hours. Each test compound was administered orally, and 1 hour later, histamine (1.1 mg/kg) was injected iv. The number of animals dying within 1 hour of the injection of histamine was recorded. ED_{50} values of the test compounds were calculated by the probit method [7].

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