Quantitative Structure–Activity Relationships of H_1-Antihistaminic Benzimidazole Derivatives[1)]

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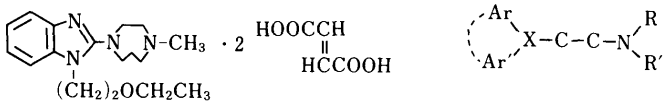
The quantitative structure–activity relationships (QSAR) of 2-(4-substituted-1-piperazinyl)benzimidazole derivatives for antihistaminic activity were examined. Taking into consideration the specific conformations of some derivatives, a significant correlation was obtained using Verloop's STERIMOL parameters B_3 and L of the substituent at the 1-position of the benzimidazole nucleus. The results indicated that the derivatives having a substituent with a small breadth and an appropriate length at the 1-position showed potent activity. From the results, a model of the binding site is proposed. The QSAR of side effects (anticholinergic activity and central nervous system depressive effect) were also examined and the results showed that a sterically small substituent at the 1-position was required to decrease side effects.

Keywords quantitative structure–activity relationship; regression analysis; adaptive least-squares calculation; benzimidazole; H_1-antihistaminic activity; side effect; anticholinergic activity; central nervous system depressive effect

Antihistaminics (H_1-antagonists) are useful for treating the symptoms of allergic reactions, including seasonal hay-fever, allergic rhinitis, conjunctivitis, *etc.*, but side effects occur commonly with all classical antihistaminics. Those seen most often are dry mouth (anticholinergic activity) and central nervous system (CNS) depressive effects such as sedation, hypnosis, *etc.* With the aim of developing an effective antihistaminic drug with minimal side effects, extensive studies have been carried out.[2)] We have already reported the synthesis and H_1-antihistaminic activity of a series of benzimidazole derivatives.[3)] After examination of the pharmacological[4)] and toxicological properties of these compounds, 1-(2-ethoxyethyl)-2-(hexahydro-4-methyl-1*H*-1,4-diazepin-1-yl)-1*H*-benzimidazole difumarate (KG-2413) was selected as the most promising compound, and is now under clinical trial.

KG-2413 is considered to be a unique compound in terms of its chemical structure, which has only a single aromatic unit (=benzimidazole nucleus) linked through a chain to a basic nitrogen; the classical antihistaminics generally comprise a double aromatic unit linked through a chain to a basic tertiary amino group[5)] as shown in structure I.



KG-2413 I

Chart 1

The unique structures of KG-2413 and related compounds prompted us to attempt quantitative structure–activity relationship (QSAR) analyses with the aim of providing a basis for the design of better antihistaminics.

Results and Discussion

Antihistaminic Activity Initially, we tried to analyze benzimidazole derivatives (**1**—**7**) (II; $m=2$), where R^2 is a methyl group and R^1 is a straight-chain alkyl group. A qualitative study suggested that the number of carbon atoms (NA) in the substituent R^1 seems to correlate with the potency. This relation can be formulated according to Eq. 1.

$$\log 1/IC_{50} = -0.075(\pm 0.056)NA^2 + 0.730(\pm 0.648)NA + 5.581(\pm 1.653) \quad (1)$$
$$n=7,\ r=0.893,\ s=0.448,\ F=7.88$$

In Eq. 1 the number in parentheses is the 95% confidence interval, n is the number of data points used in deriving the equation, r is the correlation coefficient, s is the standard deviation and F is the F-ratio between the variances of calculated and observed activities. The result indicates that the activity is parabolically related to NA, and the optimum NA is calculated to be 5. The hydrophobic effect and the steric effect are parallel to the number of methylenes in a straight-chain alkyl group, so NA was used as a temporary parameter.

In the second stage, the compounds with various substituents at the 1-position of the benzimidazole nucleus (**1**—**30**) were subjected to analysis. The analysis excluding seven compounds (**8**—**11**, **16**, **19** and **29**) gave Eq. 2, where NA means the number of atoms other than hydrogen in the substituent R^1.

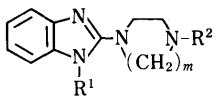
$$\log 1/IC_{50} = -0.079(\pm 0.033)NA^2 + 0.875(\pm 0.397)NA + 5.155(\pm 1.165) \quad (2)$$
$$n=23,\ r=0.754,\ s=0.480,\ F=13.16$$

This equation is essentially the same as Eq. 1. From Eq. 2 it is confirmed that the effect of R^1 on the activity depends only on NA (the number of atoms in the substituent R^1), not on the kind of atoms or bonds, so in this case the parameter NA seems to be a kind of steric parameter. Among the compounds omitted from the calculation, six compounds (**8**—**11**, **16** and **19**) exhibit about 1.5 log unit lower activity and one compound (**29**) exhibits about 1.5 log unit higher activity than predicted from Eq. 2.

The reasons why the observed activities of these seven compounds markedly deviate from the calculated ones from Eq. 2 are considered to be as follows. In the case of compounds **8**—**11**, the large width of the substituent R^1 may weaken the interaction between the molecule and the histamine H_1-receptor. The low activities of compounds **16** and **19** may be ascribed to the folding of the substituent R^1 as observed in 1-(3-phenoxypropyl)uracil.[6)] The phenoxyethyl group of compound **29** seems to fit the cavity of the receptor better than expected from Eq. 2.

If these considerations are correct, the antihistaminic

TABLE I. Structural Features and Antihistaminic Activities of Benzimidazoles (II)

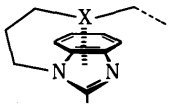


II

Compd. No.	m	R^1	R^2	B_3[a]	L[a]	I[b]	log 1/IC_{50}	
							Obs.	Calcd[c]
1	2	CH_3	CH_3	1.90	3.00	0	6.50	5.75
2	2	$(CH_2)_2CH_3$	CH_3	1.90	5.05	0	6.42	7.13
3	2	$(CH_2)_3CH_3$	CH_3	1.90	6.17	0	7.30	7.55
4	2	$(CH_2)_4CH_3$	CH_3	1.90	7.11	0	7.72	7.71
5	2	$(CH_2)_5CH_3$	CH_3	1.90	8.22	0	7.59	7.67
6	2	$(CH_2)_6CH_3$	CH_3	1.90	9.16	0	6.82	7.46
7	2	$(CH_2)_9CH_3$	CH_3	1.90	12.33	0	5.38	5.47
8	2	$(CH_2)_2CH(CH_3)_2$	CH_3	2.76	6.17	0	5.85	6.51
9	2	$CH(CH_3)(CH_2)_2CH_3$	CH_3	3.66	6.17	0	5.85	5.43
10	2	$CH_2CH(CH_3)(CH_2)_2CH_3$	CH_3	3.18	7.11	0	5.82	6.17
11	2	Ph	CH_3	3.11[d]	6.28[d]	0	6.12	6.12
12	2	CH_2Ph	CH_3	1.90[e]	5.91[e]	0	7.77	7.47
13	2	$(CH_2)_2Ph$	CH_3	1.90[e]	8.41[e]	0	7.62	7.64
14	2	$CH_2S(CH_2)_2CH_3$	CH_3	1.90	7.59	0	7.17	7.72
15	2	$(CH_2)_2SCH_2CH_3$	CH_3	1.90	7.29	0	7.72	7.72
16	2	$(CH_2)_3SCH_2CH_3$	CH_3	2.97[f]	5.86[f]	0	6.28	6.25
17	2	$CH_2O(CH_2)_2CH_3$	CH_3	1.90	6.95	0	7.75	7.69
18	2	$(CH_2)_2OCH_2CH_3$	CH_3	1.90	6.97	0	8.00	7.69
19	2	$(CH_2)_3OCH_3$	CH_3	2.84[f]	5.38[f]	0	6.06	6.25
20	2	$(CH_2)_2NHCH_2CH_3$	CH_3	3.03	6.68	0	6.54	6.30
21	2	$(CH_2)_2OH$	CH_3	1.90	4.79	0	6.39	7.00
22	2	$(CH_2)_2OCH_3$	CH_3	1.90	6.03	0	7.89	7.51
23	2	$(CH_2)_2OCH=CH_2$	CH_3	1.90	7.09	0	8.00	7.70
24	2	$(CH_2)_2O(CH_2)_2OH$	CH_3	1.90	7.95	0	7.37	7.70
25	2	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	1.90	8.10	0	7.70	7.69
26	2	$(CH_2)_2OCH_2CH=CH_2$	CH_3	1.90	8.32	0	7.77	7.66
27	2	$(CH_2)_2OCH_2C\equiv CH$	CH_3	1.90	8.73	0	7.92	7.58
28	2	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	1.90	9.04	0	7.42	7.49
29	2	$(CH_2)_2OPh$	CH_3	1.90[e]	7.85[e]	0	8.16	7.71
30	2	$(CH_2)_2OCH_2Ph$	CH_3	1.90[e]	10.33[e]	0	6.37	6.95
31	2	$(CH_2)_2OCH_2CH_3$	H	1.90	6.97	0	7.96	7.69
32	2	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	1.90	6.97	0	7.75	7.69
33	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	1.90	6.97	0	7.80	7.69
34	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_3CH_3$	1.90	6.97	0	7.82	7.69
35	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_4CH_3$	1.90	6.97	0	7.52	7.69
36	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_5CH_3$	1.90	6.97	0	8.06	7.69
37	2	$(CH_2)_2OCH_2CH_3$	CH_2Ph	1.90	6.97	0	7.57	7.69
38	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2Ph$	1.90	6.97	0	7.51	7.69
39	3	$(CH_2)_2OCH_2CH_3$	H	1.90	6.97	1	7.60	7.99
40	3	$(CH_2)_2OCH_2CH_3$	CH_3	1.90	6.97	1	8.21	7.99
41	3	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	1.90	6.97	1	7.80	7.99
42	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	1.90	6.97	1	8.08	7.99
43	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_3CH_3$	1.90	6.97	1	8.08	7.99
44	3	$(CH_2)_2OCH_2CH_3$	$(CH_2)_4CH_3$	1.90	6.97	1	8.13	7.99
45	3	$(CH_2)_2OCH_2CH_3$	CH_2Ph	1.90	6.97	1	7.82	7.99
46	3	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	1.90	8.10	1	7.80	7.99
47	3	$(CH_2)_2OCH_2CH=CH_2$	CH_3	1.90	8.32	1	8.00	7.96
48	3	$(CH_2)_2OCH_2C\equiv CH$	CH_3	1.90	8.73	1	8.00	7.88
49	3	$(CH_2)_2O(CH_2)_3CH_3$	CH_3	1.90	9.04	1	8.00	7.79
50	3	$(CH_2)_2OPh$	CH_3	1.90[e]	7.85[e]	1	8.04	8.01

a) The STERIMOL parameters for the substituent R^1 calculated from ref. 7. *b*) Indicator variable which takes the value of one for 2-(homopiperazino)benzimidazoles (II, $m=3$) and zero for others. *c*) From Eq. 6. *d*) Calculated by assuming that the phenyl ring is coplanar with the benzimidazole ring. *e*) Calculated by assuming that the phenyl ring in the substituent R^1 is perpendicular to the benzimidazole ring. *f*) Calculated by assuming that 3-(ethylthio)propyl and 3-(methoxy)propyl groups fold onto the benzimidazole ring.

activities are expected to be explained by steric parameters which represent the width and the length of the substituent R^1 in a specific conformation. So an analysis including these seven compounds was performed using Verloop's STERIMOL parameters.[7] In calculating the parameters, the following conformations are considered. Namely, the phenyl group (compound **11**) is coplanar with the benzimidazole ring; the 3-(ethylthio)propyl and 3-(methoxy)-



X=O or S

Fig. 1. Folding of Alkyl Chain

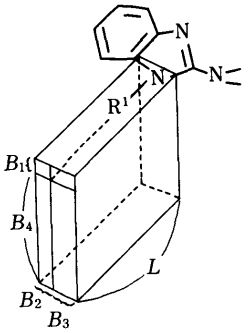


Fig. 2. Relation between STERIMOL Parameters B_1—B_4 and L

propyl groups of compounds **16** and **19** fold onto the benzimidazole ring (Fig. 1); and the phenyl ring of compounds **12**, **13**, **29** and **30** is perpendicular to the benzimidazole ring.

Taking into consideration these specific conformations, a good correlation was obtained as shown in Eq. 3.

$$\log 1/IC_{50} = -1.173(\pm 0.321)B_3 + 1.413(\pm 0.369)L - 0.096(\pm 0.025)L^2 + 4.686(\pm 1.401) \quad (3)$$
$$n=30,\ r=0.891,\ s=0.397,\ F=33.32$$

In Eq. 3, B_3 means a width parameter and L means a length parameter of the substituent R^1 as defined by Verloop *et al.*[7] In this series, B_1 and B_4 of the substituent R^1 except for the phenyl group are all in opposite directions. Therefore, the relation between B_1–B_4 and L of the substituent R^1 (except for R^1 = Ph) is represented as shown in Fig. 2. In the case of the phenyl group, B_1 and B_2 are opposite, so B_1, B_3 and L are in the same directions as those of other substituents. Equation 3 indicates that a small value of the second largest width B_3 and an appropriate length of the substituent R^1 are required for high activity. The use of the largest width parameter B_4 did not give a significantly better result.

Next, compounds **31**—**50**, in which R^2 is hydrogen or an alkyl group and m is two or three, in addition to the above 30 compounds were considered. In this case a good correlation was also obtained as shown in Eq. 4 using the same parameter as in Eq. 3.

$$\log 1/IC_{50} = -1.265(\pm 0.267)B_3 + 1.541(\pm 0.301)L - 0.104(\pm 0.020)L^2 + 4.480(\pm 1.219) \quad (4)$$
$$n=50,\ r=0.894,\ s=0.356,\ F=61.06$$

When R^1 is an ethoxyethyl group, homopiperazine derivatives (**39**—**45**) tend to exhibit slightly higher activity than the corresponding piperazine derivatives (**18**, **31**—**38**). This may be because the positively charged homopiperazine nitrogen is situated closer to the anionic site of the receptor than piperazine nitrogen. So re-analysis was performed using the indicator variable I for homopiperazine derivatives (**39**—**49**) to afford an improved Eq. 5.

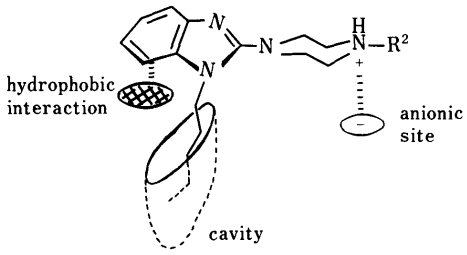


Fig. 3. A Model of the Binding Site

$$\log 1/IC_{50} = -1.194(\pm 0.252)B_3 + 1.440(\pm 0.287)L - 0.098(\pm 0.019)L^2 + 0.338(\pm 0.231)I + 4.643(\pm 1.135) \quad (5)$$
$$n=50,\ r=0.912,\ s=0.329,\ F=55.63$$

Equation 5 indicates that a smaller value of the second largest width B_3, which is perpendicular to the largest width B_4, and an appropriate length ($L \fallingdotseq 7.3$) of the substituent R^1 are required to improve the activity. Namely, the substituent with a small breadth and an appropriate length is favorable for high activity. Equation 5 also indicates that the substituent R^2 at the piperazine or homopiperazine 4-position has little effect on the activity, and homopiperazine derivatives ($I=1$) are favorable for high activity.

From the above results, a model of the binding site is proposed as shown in Fig. 3. It includes an anionic site which interacts electronically with the positively charged piperazine or homopiperazine nitrogen atom. There is also a slit-shaped cavity, which is perpendicular to the site which interacts with the benzimidazole ring. The role of the benzimidazole moiety does not appear explicitly in the equations, but there may be a hydrophobic interaction between the benzimidazole moiety and the receptor as proposed by Rekker *et al.*[8]

Generally, the classical H_1-antagonists have a tertiary amino group such as piperidine, ethylenediamine, piperazine or homopiperazine, and these are thought to be bioisosteres. Based on the concept of bioisosterism, the benzimidazole derivatives with various substituents at the 2-position were designed (III, type A—D). The synthesis and antihistaminic activity of these compounds were already reported.[9] These compounds (**51**—**82**) are summarized in Table II.

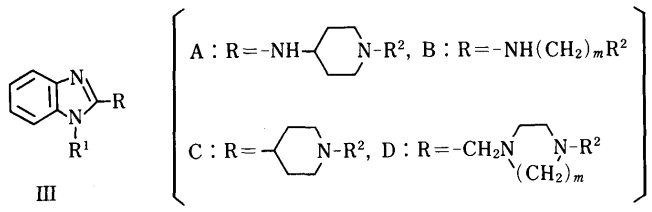
All 82 compounds were subjected to analysis and a similar result to Eq. 5 was obtained, as shown in Eq. 6.

$$\log 1/IC_{50} = -1.202(\pm 0.234)B_3 + 1.458(\pm 0.260)L - 0.097(\pm 0.018)L^2 + 0.299(\pm 0.202)I + 4.528(\pm 1.081) \quad (6)$$
$$n=82,\ r=0.875,\ s=0.321,\ F=62.71$$

The parameters in Eq. 6 have already been defined. Equation 6 is essentially the same as Eq. 5, so the antihistaminic activity of the additionally prepared compounds (**51**—**82**) was correctly predicted by Eq. 5. They may interact with the same histamine H_1-receptor, as exemplified in Fig. 3.

Anticholinergic Activity As described above, side effects related to the anticholinergic activity of many of the antihistaminics are common. Rekker *et al.*[10] suggested a complementarity between anticholinergic activity and antihistaminic activity in the various series of diphenhydramine

TABLE II. Structural Features and Antihistaminic Activities of Benzimidazoles (III)



III

Compd. No.	Type	m	R^1	R^2	B_3[a]	L[a]	I[b]	log 1/IC$_{50}$	
								Obs.	Calcd[c]
51	A	—	$(CH_2)_2OCH_2CH_3$	CH_3	1.90	6.97	0	7.75	7.69
52	A	—	$(CH_2)_2OCH_2CH=CH_2$	CH_3	1.90	8.32	0	7.85	7.66
53	A	—	$(CH_2)_2OPh$	CH_3	1.90[e]	7.85[e]	0	6.89	7.71
54	A	—	$(CH_2)_2OCH_2CH_3$	CH_2Ph	1.90	6.97	0	7.18	7.69
55	A	—	$(CH_2)_2OCH_2CH_3$	H	1.90	6.97	0	7.70	7.69
56	B	2	$(CH_2)_2OCH_2CH_3$	$N(CH_3)_2$	1.90	6.97	0	7.89	7.69
57	B	2	$(CH_2)_2OCH_2CH_3$	$N(CH_2CH_3)_2$	1.90	6.97	0	7.36	7.69
58	B	2	$(CH_2)_2OCH_2CH_3$	Pyrrolidino	1.90	6.97	0	8.06	7.69
59	B	3	$(CH_2)_2OCH_2CH_3$	$N(CH_3)_2$	1.90	6.97	0	7.59	7.69
60	B	3	$(CH_2)_2OCH_2CH_3$	$N(CH_2CH_3)_2$	1.90	6.97	0	7.23	7.69
61	C	—	$(CH_2)_2OCH_2CH_3$	CH_3	1.90	6.97	0	7.77	7.69
62	C	—	$(CH_2)_2OCH_2CH=CH_2$	CH_3	1.90	8.32	0	7.96	7.66
63	C	—	$(CH_2)_2OCH_2C\equiv CH$	CH_3	1.90	8.73	0	7.92	7.58
64	C	—	$(CH_2)_2OPh$	CH_3	1.90[e]	7.85[e]	0	7.72	7.71
65	C	—	$(CH_2)_2OCH_2CH_3$	H	1.90	6.97	0	7.92	7.69
66	C	—	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	1.90	6.97	0	7.82	7.69
67	D	2	$(CH_2)_2OCH_2CH_3$	CH_3	1.90	6.97	0	7.68	7.69
68	D	2	$(CH_2)_2OCH=CH_2$	CH_3	1.90	7.09	0	7.70	7.70
69	D	2	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	1.90	8.10	0	7.80	7.69
70	D	2	$(CH_2)_2OCH_2CH=CH_2$	CH_3	1.90	8.32	0	8.02	7.66
71	D	2	$(CH_2)_2OCH_2C\equiv CH$	CH_3	1.90	8.73	0	7.92	7.58
72	D	2	$(CH_2)_2OCH_2CH_3$	H	1.90	6.97	0	7.62	7.69
73	D	2	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	1.90	6.97	0	7.68	7.69
74	D	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2CH_3$	1.90	6.97	0	7.47	7.69
75	D	2	$(CH_2)_2OCH_2CH_3$	$(CH_2)_2OH$	1.90	6.97	0	7.08	7.69
76	D	3	$(CH_2)_2OCH_2CH_3$	CH_3	1.90	6.97	0	7.85	7.69
77	D	3	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	1.90	8.10	0	7.75	7.69
78	D	3	$(CH_2)_2OCH_2CH=CH_2$	CH_3	1.90	8.32	0	8.04	7.66
79	D	3	$(CH_2)_2OCH_2C\equiv CH$	CH_3	1.90	8.73	0	8.04	7.58
80	D	3	$(CH_2)_2OPh$	CH_3	1.90[e]	7.85[e]	0	7.70	7.71
81	D	3	$(CH_2)_2OCH_2CH_3$	H	1.90	6.97	0	7.70	7.69
82	D	3	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	1.90	6.97	0	8.00	7.69

a—*c*) and *e*) see footnotes in Table I.

derivatives. Namely, they suggested that anticholinergic activity tends to increase as a result of ring substitutions which lower antihistaminic activity, while it is decreased by substitutions increasing antihistaminic activity.

Anticholinergic activity was examined for twelve compounds (**18**, **25**—**27**, **29**, **31**, **32**, **40**, **46**—**48** and **50**), which exhibited potent antihistaminic activity *in vivo* as well as *in vitro* (Table III).

As shown in Table III, anticholinergic activities of these compounds are negligible, being about 3 to 4 log unit lower than the antihistaminic activities.

For this reason, the QSAR of anticholinergic activity seems hardly worth analyzing. But, in order to elucidate the factors which correlate with the activity, the analysis was performed to give Eq. 7 as the best equation.

$$\log 1/IC_{50} = 0.287(\pm 0.198)B_4 + 0.725(\pm 0.405)I + 2.411(\pm 1.103) \quad (7)$$

$$n=12,\ r=0.879,\ s=0.304,\ F=15.37$$

In Eq. 7 B_4 means the STERIMOL parameter of the substituent R^1 and I means an indicator variable defined above. Equation 7 indicates that lower values of the largest width B_4 of the substituent R^1 and piperazine moiety are required to decrease anticholinergic activity. In this case the difference of the antihistaminic activities among these twelve compounds is so small that complementarity between antihistaminic activity and anticholinergic activity could not be observed.

CNS Depressive Effect The most common side effect of many antihistaminics is hypnotic-sedative (CNS depressive effect), resulting in daytime drowsiness, lack of concentration, diminished mental acuity and impairment of the handling of machinery and the driving of vehicles.

We evaluated the CNS depressive effect of above twelve benzimidazole derivatives in terms of the potentiating effect on hexobarbital-induced sleep in mice, and examined the structure–activity relationships (Table III).

For such discrete data, regression analysis is not ap-

TABLE III. Anticholinergic and CNS Depressive Effects of Benzimidazoles (II)

Compd. No.	m	R^1	R^2	B_4[a]	$MR/10$[b]	I[c]	Anticholinergic act. $\log 1/IC_{50}$			CNS depressive effect		
							Obs.	Calcd[d]	Δ[e]	Obs.	Recog.[f]	Pred.[g]
18	2	$(CH_2)_2OCH_2CH_3$	CH_3	4.82	2.136	0	3.59	3.80	0.21	+	−	−
25	2	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	5.75	2.602	0	4.76	4.06	0.70	+	+	+
26	2	$(CH_2)_2OCH_2CH=CH_2$	CH_3	5.92	2.555	0	3.99	4.11	0.12	+	+	+
27	2	$(CH_2)_2OCH_2C\equiv CH$	CH_3	4.38	2.526	0	3.82	3.67	0.15	+	+	+
29	2	$(CH_2)_2OPh$	CH_3	7.42[h]	3.684	0	4.35	4.54	0.19	+	+	+
31	2	$(CH_2)_2OCH_2CH_3$	H	4.82	2.136	0	3.67	3.80	0.13	−	−	−
32	2	$(CH_2)_2OCH_2CH_3$	CH_2CH_3	4.82	2.136	0	3.60	3.80	0.20	−	−	−
40	3	$(CH_2)_2OCH_2CH_3$	CH_3	4.82	2.136	1	4.51	4.52	0.01	−	−	−
46	3	$(CH_2)_2O(CH_2)_2CH_3$	CH_3	5.75	2.602	1	5.12	4.79	0.33	+	+	−
47	3	$(CH_2)_2OCH_2CH=CH_2$	CH_3	5.92	2.555	1	4.60	4.84	0.24	−	−	−
48	3	$(CH_2)_2OCH_2C\equiv CH$	CH_3	4.38	2.526	1	4.32	4.40	0.08	−	−	−
50	3	$(CH_2)_2OPh$	CH_3	7.42[h]	3.684	1	5.26	5.27	0.01	+	+	+

a) The STERIMOL parameter calculated from ref. 7. *b*) MR value for the substituent R^1 calculated from ref. 12. *c*) Indicator variable which takes the value of one for homopiperazine derivatives and zero for others. *d*) From Eq. 7. *e*) Absolute difference between observed and calculated values for anticholinergic activity. *f*) Recognition from Eq. 8. *g*) Prediction using the leave-one-out technique. *h*) See footnote *e*) in Table I.

propriate. The ALS method[11] was thought to be more appropriate to analyze our data. The best discriminant function is expressed in Eq. 8, which was derived from iteration 17, and where Y is the discriminant score for the classification, MR[12] is a steric parameter of the substituent at the 1-position of the benzimidazole nucleus, I is an indicator variable defined above, n is the number of compounds, n_{mis} is the number misclassified, t is Student's t value calculated at $t=R_s[(n-2)/(1-R_s^2)]^{1/2}$ and p is the level of significance.

$$Y=1.061(MR/10)-0.431I-2.458 \quad (8)$$

$$n=12,\ R_s=0.845,\ \varepsilon=0.830,\ n_{mis}=1,\ t=5.00,\ p<0.001$$

In Eq. 8, 92% of the compounds were correctly classified. To confirm the validity of the ALS result, the leave-one-out technique was applied and the predictive result classified 83% of the compounds correctly. The results are summarized in Table III.

Equation 8 suggests that a sterically smaller substituent such as an ethoxyethyl group and a homopiperazine moiety at the 1- and 2-position of the benzimidazole nucleus, respectively, decrease the CNS side effect.

Conclusion

The structure–activity relationships of benzimidazole derivatives with antihistaminic activity were successfully analyzed by regression analysis using Verloop's STERIMOL parameters B_3 and L with consideration of specific conformations. The results indicated that the derivatives having a substituent with a small breadth and an appropriate length at the 1-position of the benzimidazole nucleus were favorable for high activity. On the basis of the results, a model of the binding site was proposed. Moreover, the results of the QSAR analyses of side effects indicated that a sterically small substituent at the 1-position of the benzimidazole nucleus was required to decrease side effects.

The results obtained in this study should be helpful in designing new types of potent antihistaminics with minimal side effects.

Experimental

Materials All the compounds examined in this study are summarized in Tables I and II. The preparation of them was previously described.[3,9]

Antihistaminic Activity Antihistaminic activity of the compounds was reported previously.[3,9] The IC_{50} values (M) evaluated in isolated ileum from guinea pigs were used as the index of antihistaminic activity.

Anticholinergic Activity The IC_{50} values (M) were evaluated using 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 °C). The contractile responses to acetylcholine (5.5×10^{-7} M) were measured with an isotonic transducer (TD-112S, Nihon Koden, Tokyo, Japan). Each test compound was added to the organ bath 5 min before the addition of acetylcholine. IC_{50} (M) values of the test compounds were calculated by the probit method[13] and were used as the index of anticholinergic activity.

CNS Depressive Effect This effect was evaluated in terms of the potentiating effect on hexobarbital-induced sleep in mice. Each test compound (200 mg/kg) was administered orally to groups of five mice, fasted for 20—24 h, 30 min prior to the intraperitoneal administration of 50 mg/kg of hexobarbital. Sleeping time was considered to be the interval between loss and recovery of an effective righting reflex. A compound which statistically significantly potentiated the effect of hexobarbital-induced sleep was classified as "positive", otherwise it was classified as "negative".

Regression Analysis A regression analysis was carried out to investigate the relationship between the various parameters of the substituents R^1 and R^2 of the benzimidazole nucleus and antihistaminic activity. This analysis was also applied to anticholinergic activity.

Adaptive Least-Squares (ALS) Calculation The ALS method of Moriguchi *et al.*[11] (ALS 81) was applied to investigate the relationship between the parameters of the substituent R^1 at the 1-position of the benzimidazole nucleus and CNS depressive effect. The adaptive iteration was performed 20 times, and the best discriminant function was selected. As the criteria of the best discrimination, the Spearman rank correlation coefficient with many ties, R_s, and the ε value[11] were used.

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References and Notes

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