Studies on Antiallergic Agents. II.[1] Quantitative Structure–Activity Relationships of Novel 6-Substituted *N*-(1*H*-Tetrazol-5-yl)-2-pyrazinecarboxamides

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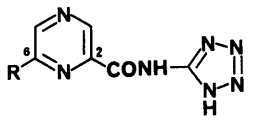
The effect of structural modifications of 6-substituted *N*-(1*H*-tetrazol-5-yl)-2-pyrazinecarboxamides on their antiallergic activity was analyzed quantitatively by means of the Hansch–Fujita method. The activity of these compounds was correlated with hydrophobic (π) and steric (molecular refractivity and STERIMOL B_1) effects of the 6-substituent on the pyrazine ring. The 6-substituents with a length greater than *n*-propylamino possess an extra effect enhancing the activity. Moreover, the activity increased progressively from 6-non-amino *via* alkylamino- to dialkylamino-substituted compounds, other factors being equal. This could be attributable to an electronic effect of substituents. Electron-donating small and yet symmetric substituents with high hydrophobicity longer than *n*-propylamino seemed to be favorable to the activity. By compromising these contradictory requirements, small dialkylamino (including cyclic amino) groups were decided to be the most favorable substituents. This analysis was in agreement with the observation that the most effective compounds were the 6-dimethylamino (I-27) and 6-(1-pyrrolidinyl) (I-34) derivatives.

Keywords quantitative structure–activity relationship; Hansch–Fujita analysis; antiallergic agent; *N*-(1*H*-tetrazol-5-yl)-2-pyrazinecarboxamide; allergic histamine release; pyrazinecarboxamide

As a part of our studies on antiallergic agents, a number of novel pyrazine derivatives have been synthesized and their inhibitory activity on allergic histamine release has been examined.[1] The *N*-(1*H*-tetrazol-5-yl)carbamoyl group at the 2-position and a 6-amino derivative, especially the 6-dimethylamino or 6-(1-pyrrolidinyl) group, as the 6-substituent have been found to be most favorable to the activity.[1]

Attempting to understand the physicochemical background of the effects of the 6-substituent of *N*-(1*H*-tetrazol-5-yl)-2-pyrazinecarboxamides (I) on the activity, we have examined the structure–activity relationships quantitatively for a number of variously 6-substituted derivatives using physicochemical substituent parameters and regression analysis.[2]



I

R = H, alkyl, halogen, alkoxy alkylamino, dialkylamino

Chart 1

Synthesis Some 6-substituted *N*-(1*H*-tetrazol-5-yl)-2-pyrazinecarboxamides (I) were newly synthesized in a manner similar to that described previously.[1] Compounds with R = H (I-1), Me (I-2) and Cl (I-3) were prepared by the condensation of the mixed anhydride of the corresponding carboxylic acid with 5-amino-1*H*-tetrazole (method A), while those having R = alkoxy (I-4—7) and amino (I-8—41) were obtained by the condensation of I-3 with corresponding alcoholates and amines, respectively, (method B), as shown in Chart 2.

The physicochemical properties of compounds I are summarized in Table I.

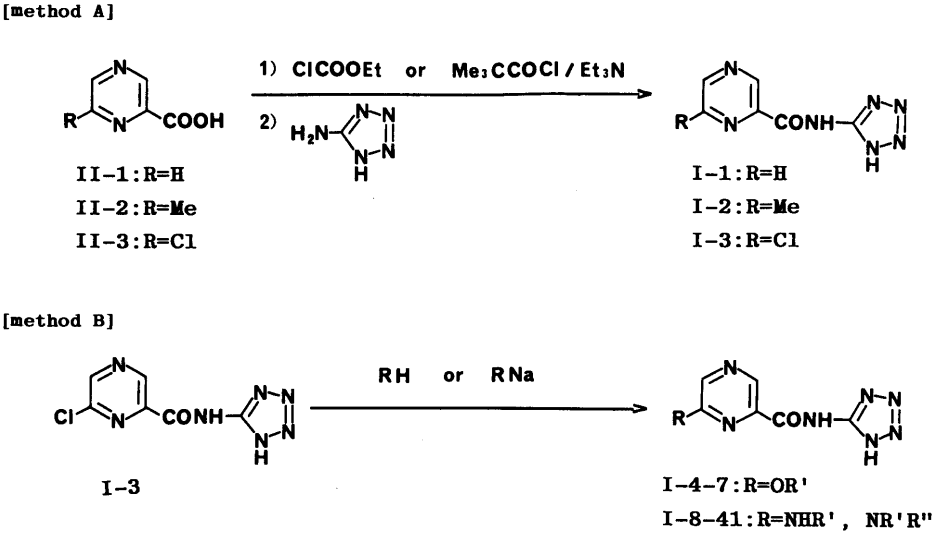
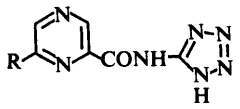


Chart 2

TABLE I. Physicochemical and Pharmacological Data for 6-Substituted *N*-(1*H*-Tetrazol-5-yl)-2-pyrazinecarboxamides (I)



I

Compd. No.	R	Yield (%) (Method)	Salt	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	AHR[a] IC_{50} (M)
1[b]	H	89 (A)	Free	295—298 (dec.) (DMSO)	$C_6H_5N_7O$	37.70 (37.87	2.64 2.36	51.29 51.32)	4.2×10^{-7}
2[b]	Me	69 (A)	Free	268—273 (dec.) (DMF–EtOH)	$C_7H_7N_7O$	40.98 (41.02	3.44 3.75	47.79 47.54)	1.0×10^{-7}
3[b]	Cl	75 (A)	Free	263—268.5 (dec.) (DMSO–MeOH)	$C_6H_4ClN_7O$	31.94 (32.03	1.79 1.70	43.46 43.68)	1.6×10^{-7}
4[b]	OMe	75 (B)	Free	258—262 (dec.) (DMF–EtOH)	$C_7H_7N_7O_2$	38.01 (38.05	3.19 3.55	44.33 44.00)	1.1×10^{-7}
5	OEt	59 (B)	Free	255—256 (dec.) (DMSO–MeOH)	$C_8H_9N_7O_2$	40.85 (41.01	3.86 4.22	41.69 41.98)	3.2×10^{-7}
6	O-*n*-Pr	45 (B)	Free	232—234 (dec.) (DMF–EtOH)	$C_9H_{11}N_7O_2$	43.37 (43.26	4.45 4.49	39.34 39.53)	4.8×10^{-7}
7	OPh	60 (B)	Free	271—272 (dec.) (DMF–EtOH)	$C_{12}H_9N_7O_2$	50.89 (50.99	3.20 3.49	34.62 34.31)	1.2×10^{-6}
8[b]	NHMe	71 (B)	Free	260 (dec.) (DMSO–MeOH)	$C_7H_8N_8O$	38.18 (38.16	3.66 3.85	50.89 51.14)	2.5×10^{-9}
9[b]	NHEt	71 (B)	Free	272—273.5 (dec.) (DMSO–MeOH)	$C_8H_{10}N_8O$	41.02 (40.95	4.30 4.45	47.84 47.99)	4.0×10^{-9}
10[b]	NH-*n*-Pr	73 (B)	Free	278—279.5 (dec.) (DMSO–MeOH)	$C_9H_{12}N_8O$	43.54 (43.42	4.87 5.23	45.14 44.91)	2.1×10^{-8}
11[b]	NH-iso-Pr	55 (B)	Free	272—274 (dec.) (DMSO–MeOH)	$C_9H_{12}N_8O$	43.54 (43.51	4.87 5.00	45.14 45.49)	1.3×10^{-8}
12	NH-cyclo-Pr	55 (B)	Free	272—280 (dec.) (DMSO–EtOH)	$C_9H_{10}N_8O$	43.90 (44.01	4.09 4.20	45.51 45.70)	1.0×10^{-8}
13[b]	NH-*n*-Bu	76 (B)	Free	269—272 (dec.) (DMF–EtOH)	$C_{10}H_{14}N_8O$	45.80 (45.65	5.38 5.53	42.72 42.83)	3.0×10^{-9}
14[b]	NH-iso-Bu	80 (B)	Free	265—275 (dec.) (DMF–EtOH)	$C_{10}H_{14}N_8O$	45.80 (45.77	5.38 5.38	42.72 42.82)	1.7×10^{-8}
15[b]	NH-*sec*-Bu	49 (B)	Free	265—269 (dec.) (DMF–EtOH)	$C_{10}H_{14}N_8O$	45.80 (45.54	5.38 5.36	42.72 42.49)	9.2×10^{-8}
16[b]	NH-*tert*-Bu	41 (B)	Free	263—273 (dec.) (DMF–EtOH)	$C_{10}H_{14}N_8O$	45.80 (45.39	5.38 5.35	42.72 42.76)	1.3×10^{-7}
17[b]	NH-*n*-Hex	67 (B)	Free	263—267 (dec.) (DMF–EtOH)	$C_{12}H_{18}N_8O$	49.64 (49.54	6.25 6.26	38.60 38.48)	2.5×10^{-9}
18	NH-cyclo-Hex	65 (B)	Free	287—291 (dec.) (DMSO–EtOH)	$C_{12}H_{16}N_8O$	49.99 (49.99	5.59 5.76	38.87 38.88)	7.8×10^{-9}
19[b]	NH-*n*-Oct	86 (B)	Free	268—272 (dec.) (DMF–EtOH)	$C_{14}H_{22}N_8O$	52.82 (52.54	6.96 6.79	35.19 35.24)	3.0×10^{-9}
20[b]	NH-*n*-Dec	87 (B)	Free	263—267 (dec.) (DMF–EtOH)	$C_{16}H_{26}N_8O$	55.47 (55.34	7.56 7.45	32.34 32.44)	3.4×10^{-8}
21[b]	NH-*n*-Dodec	58 (B)	Free	250—259 (dec.) (DMSO–EtOH)	$C_{18}H_{30}N_8O$	57.73 (57.85	8.07 8.09	29.92 29.92)	3.3×10^{-7}
22	$NHCH_2Ph$	55 (B)	Free	268—270 (dec.) (DMF–EtOH)	$C_{13}H_{12}N_8O$	52.70 (52.39	4.08 4.31	37.82 37.77)	1.8×10^{-8}
23	$NH(CH_2)_2OH$	74 (B)	Free	291—293 (dec.) (DMSO–MeOH)	$C_8H_{10}N_8O_2$	38.40 (38.43	4.03 3.84	44.78 44.74)	3.4×10^{-8}
24	$NH(CH_2)_3OH$	66 (B)	Free	278—280 (dec.) (DMF–EtOH)	$C_9H_{12}N_8O_2$	40.91 (40.97	4.58 4.79	42.40 42.22)	1.6×10^{-8}
25	$NH(CH_2)_2OMe$	74 (B)	Free	268.5—270 (DMF–H_2O)	$C_9H_{12}N_8O_2$	40.91 (40.63	4.58 4.48	42.40 42.31)	5.0×10^{-8}
26	$NH(CH_2)_2NH_2$	78 (B)	HCl	295—297 (dec.) (H_2O)	$C_8H_{11}N_9O$ ·HCl·1/2 H_2O	32.60 (32.84	4.45 4.41	42.78 42.69)	3.8×10^{-7}
27[b]	NMe_2	74 (B)	Free	267—269 (dec.) (DMSO–MeOH)	$C_8H_{10}N_8O$	41.02 (40.95	4.30 4.63	47.84 47.83)	4.7×10^{-10}
28[b]	N(Me)Et	72 (B)	Free	224—226 (DMF–EtOH)	$C_9H_{12}N_8O$	43.54 (43.42	4.87 4.81	45.14 45.49)	1.8×10^{-9}
29[b]	N(Me)*n*-Pr	69 (B)	Free	243—245 (DMF–EtOH)	$C_{10}H_{14}N_8O$	45.80 (45.79	5.38 5.41	42.72 43.02)	2.9×10^{-9}
30[b]	N(Me)*n*-Bu	83 (B)	Free	204.5—205.5 (EtOH)	$C_{11}H_{16}N_8O$	47.82 (47.76	5.84 5.98	40.55 40.31)	9.7×10^{-10}

TABLE I. (continued)

Compd. No.	R	Yield (%) (Method)	Salt	mp (°C) (Recrystn. solvent)	Formula	Analysis (%) Calcd (Found) C	H	N	AHR[a] IC_{50} (M)
31[b]	N(Me)*n*-Hex	81 (B)	Free	192.5—193.5 (EtOH)	$C_{13}H_{20}N_8O$	51.30 (51.16	6.62 6.44	36.82 36.78)	4.2×10^{-9}
32	N(Me)CH_2Ph	68 (B)	Free	230—232 (DMF–EtOH)	$C_{14}H_{14}N_8O$	54.19 (54.52	4.55 4.62	36.11 36.36)	8.6×10^{-8}
33[b]	NEt_2	57 (B)	Free	217—218 (DMSO–MeOH)	$C_{10}H_{14}N_8O$	45.80 (45.57	5.38 5.67	42.72 42.84)	1.5×10^{-8}
34[b]	1-Pyrrolidinyl	84 (B)	Free	288—294 (dec.) (DMSO)	$C_{10}H_{12}N_8O$	46.15 (46.17	4.65 4.59	43.05 42.75)	4.6×10^{-10}
35[b]	1-Piperidinyl	72 (B)	Free	247—250 (dec.) (DMSO–MeOH)	$C_{11}H_{14}N_8O$	48.17 (48.12	5.14 5.38	40.85 40.93)	5.6×10^{-9}
36[b]	4-Morpholinyl	75 (B)	Free	276—278 (dec.) (DMSO–MeOH)	$C_{10}H_{12}N_8O_2$	43.48 (43.47	4.38 4.56	40.56 40.70)	3.6×10^{-8}
37	1-(3-OH)piperidinyl	64 (B)	Free	257—259 (dec.) (DMSO–MeOH)	$C_{11}H_{14}N_8O_2$	45.51 (45.41	4.86 5.16	38.60 38.42)	1.5×10^{-8}
38	1-(4-OH)piperidinyl	69 (B)	Free	259.5—261 (dec.) (DMSO–MeOH)	$C_{11}H_{14}N_8O_2$	45.51 (45.35	4.86 5.15	38.60 38.57)	2.4×10^{-8}
39[b]	1-Piperazinyl	60 (B)	Free	>300 (10% NaOH–10% HCl)	$C_{10}H_{13}N_9O\cdot1/2H_2O$	42.25 (41.90	4.96 4.89	44.34 44.23)	1.5×10^{-7}
40	1-(4-Me)piperazinyl	66 (B)	HCl	246—250 (dec.) (DMSO–MeOH)	$C_{11}H_{15}N_9O\cdot HCl\cdot H_2O$	38.43 (38.62	5.28 5.15	36.67 36.71)	3.6×10^{-8}
41	1-(4-Et)piperazinyl	68 (B)	HCl	230—243 (dec.) (DMSO–MeOH)	$C_{12}H_{17}N_9O\cdot HCl$	42.42 (42.59	5.34 5.55	37.10 36.83)	2.7×10^{-7}

a) Inhibitory effect on allergic histamine release from rat PEC. Each value represents the mean of 2 to 6 experiments. *b*) Ref. 1.

Results and Discussion

Pharmacological data of the compounds I are given in Table I. Inhibitory activity on allergic histamine release was tested in rat peritoneal exudate cells and is shown as the IC_{50} (concentration producing 50% inhibition of histamine release) value.

First, we analyzed the pIC_{50} ($-\log IC_{50}$) values of secondary amino compounds (I-8—26) using single parameters. No single parameter gave a satisfactory correlation with the activity. As shown in Fig. 1, in which the pIC_{50} value is plotted *versus* MR[3] (molecular refractivity), however, compounds with 6-NHR′ substituents (R′=alkyl) having R′ groups longer than *n*-propyl exhibited an activity more potent than their isomers having an equivalent ΔMR value. For the sake of simplicity, MR was used as values relative to that of H: $\Delta MR(X)=MR(X)-MR(H)$ and was multiplied by 0.1 to place it on a scale similar those of the other parameters. Moreover, if such hydrophilic groups as OH, NH_2 and –O– were included in the R′ chain, the activity was lower than expected from the ΔMR value of the whole substituent. There seemed to be three factors contributing to the variations in the activity: one is the bulk of all the substituents represented by ΔMR, the second is the activity enhancing factor assignable to substituents NHR′ where R′ is longer than *n*-propyl, and the third is the hydrophobicity expressible by π.

After examining parameters available for rationalizing the second effect, we found that an indicator variable I which takes the value of unity for substituents (NHR′) where R′ is longer than *n*-propyl, irrespective of whether the R′ is alkyl or oxyalkyl, is most relevant when ΔMR and π are used simultaneously. Thus, Eq. 3 (Table II) was formulated for 19 secondary amino compounds. The stepwise development of Eq. 3 is shown in Table II. The π value used here is that

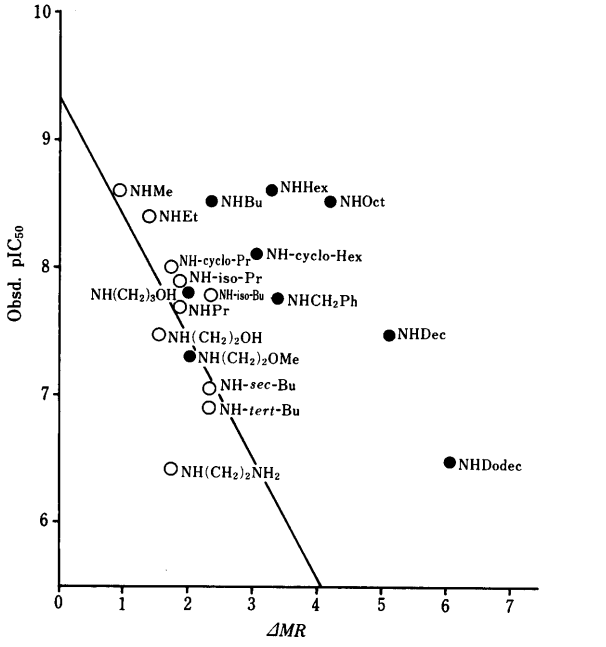


Fig. 1. Plots of IC_{50} *versus* ΔMR

○, compound with NHR′ substituents where R′ is shorter than *n*-Bu; ●, compound with NHR′ substituents where R′ is longer than *n*-Pr.

for monosubstituted pyrazines.[4] The I term would indicate that an extra binding interaction with a specific moiety of the receptor site occurs with increasing the length of the substituent R′ beyond propyl. The situation of Eq. 3 is illustrated in Fig. 2.

In the next analysis, we tried to incorporate tertiary amino compounds (I-27—41). In Fig. 2 illustrating Eq. 3, 15 tertiary amino compounds were also included. Almost

all tertiary amino compounds deviated upward from the regression line, and cyclic amino compounds exhibited greater deviations.

By employing a second indicator variable *I*(*tert*-N) which takes the value of unity for tertiary amino compounds and ΔB_1[5] (the STERIMOL width parameter) in addition to ΔMR, π and *I*, Eq. 8 (Table III) of a good quality was derived. B_1 represents the minimum width of substituents from the axis connecting the α-atom of substituents to the rest of the molecule. For the sake of simplicity, B_1 was

TABLE II. Development of the Correlation Equations for the Antiallergic Activity of Compounds (I-8—26)

Eq. No.	ΔMR	π	*I*	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F_{l,n-m-1}{}^{d)}$
1	−0.12			8.04	19	0.23	0.68	0.98
	(0.26)[e]			(0.75)				
2	−0.77	0.53		8.69	19	0.63	0.56	8.94
	(0.50)	(0.38)		(0.77)				
3	−1.22	0.67	1.09	9.08	19	0.87	0.37	21.48[f]
	(0.40)	(0.26)	(0.50)	(0.55)				

a) Number of compounds used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Observed *F* value; *l*, the number of additional parameter terms; m, the number of total parameter terms. Theoretical *F* values are $F_{1,17:\alpha=0.05}=4.45$ for Eq. 1, $F_{1,16:\alpha=0.05}=4.49$ for Eq. 2 and $F_{1,15:\alpha=0.05}=4.54$ for Eq. 3. *e*) Figures in parentheses are 95% confidence intervals. *f*) $F_{3,15}=15.05$, $F_{3,15:\alpha=0.05}=3.29$.

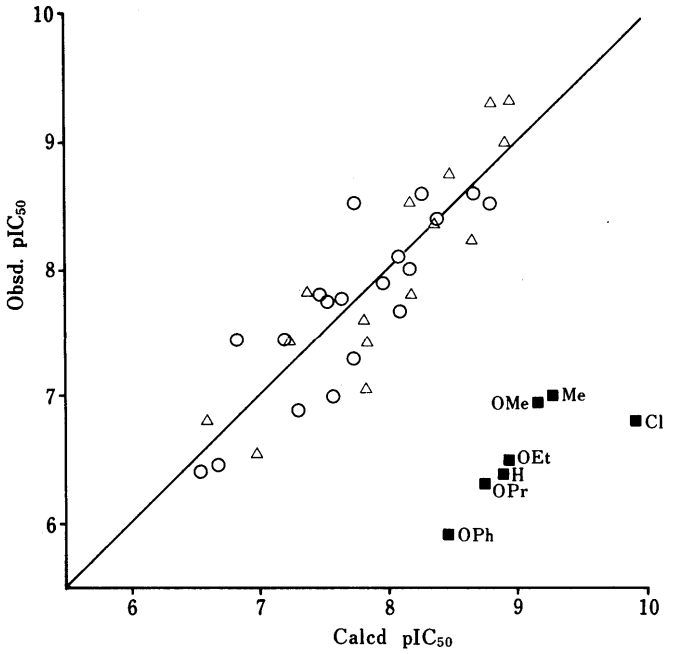


Fig. 3. Plots of Observed IC_{50} *versus* Calculated Value from Eq. 8

○, secondary amino compound; △, tertiary amino compound; ■, non-amino compound.

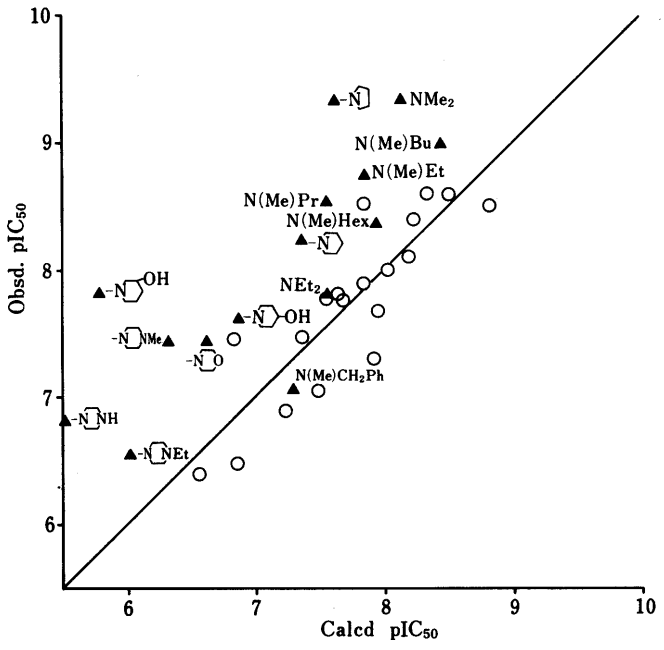


Fig. 2. Plots of Observed IC_{50} *versus* Calculated Value from Eq. 3

○, secondary amino compound; ▲, tertiary amino compound.

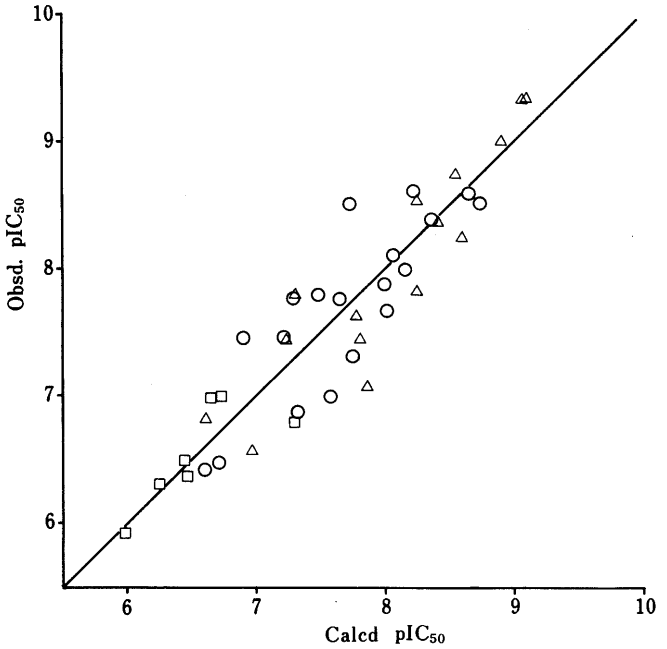


Fig. 4. Plots of Observed IC_{50} *versus* Calculated Value from Eq. 14

○, secondary amino compound; △, tertiary amino compound; □, non-amino compound.

TABLE III. Development of the Correlation Equations for the Antiallergic Activity of Compounds (I-8—41)

Eq. No.	ΔMR	π	ΔB_1	*I*	*I*(*tert*-N)	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F_{l,n-m-1}{}^{d)}$
4	−0.23 (0.25)[e]					8.46 (0.71)	34	0.31	0.75	3.52
5	−0.66 (0.30)	0.41 (0.21)				8.90 (0.62)	34	0.64	0.61	16.72
6	−0.90 (0.33)	0.62 (0.25)	1.26 (0.98)			8.57 (0.63)	34	0.72	0.56	6.82
7	−1.39 (0.36)	0.79 (0.22)	1.96 (0.87)	0.95 (0.47)		8.81 (0.52)	34	0.84	0.45	17.02
8	−1.34 (0.32)	0.75 (0.20)	1.23 (0.92)	0.94 (0.42)	0.53 (0.37)	8.89 (0.47)	34	0.88	0.40	8.82[f]

a) Number of compounds used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Observed *F* value; *l*, the number of additional parameter terms; *m*, the number of total parameter terms. Theoretical *F* values are $F_{1,32:\alpha=0.05}=4.15$ for Eq. 4, $F_{1,31:\alpha=0.05}=4.16$ for Eq. 5, $F_{1,30:\alpha=0.05}=4.17$ for Eq. 6, $F_{1,29:\alpha=0.05}=4.18$ for Eq. 7, and $F_{1,28:\alpha=0.05}=4.20$ for Eq. 8. *e*) Figures in parentheses are 95% confidence intervals. *f*) $F_{5,28}=18.90$, $F_{5,28:\alpha=0.05}=2.56$.

TABLE IV. Development of the Correlation Equations for the Antiallergic Activity of Compounds (I-1—41)

Eq. No.	I(N)	ΔMR	π	ΔB_1	I	I(*tert*-N)	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F_{l,n-m-1}{}^{d)}$
9	1.30 (0.61)[e]						6.55 (0.56)	41	0.57	0.73	18.46
10	1.69 (0.68)	−0.24 (0.22)					6.79 (0.57)	41	0.63	0.69	5.02
11	2.19 (0.60)	−0.66 (0.26)	0.41 (0.19)				6.72 (0.47)	41	0.78	0.57	19.48
12	2.31 (0.57)	−0.86 (0.28)	0.58 (0.22)	1.07 (0.80)			6.30 (0.54)	41	0.82	0.53	7.32
13	2.63 (0.51)	−1.28 (0.32)	0.72 (0.20)	1.60 (0.73)	0.86 (0.44)		6.23 (0.46)	41	0.88	0.44	15.81
14	2.44 (0.45)	−1.28 (0.28)	0.71 (0.17)	1.00 (0.72)	0.88 (0.38)	0.58 (0.33)	6.47 (0.42)	41	0.91	0.38	12.42[f]

a) Number of compounds used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Observed F value; l, the number of additional parameter terms; m, the number of total parameter terms. Theoretical F values are $F_{1,39:\alpha=0.05}=4.09$ for Eq. 9, $F_{1,38:\alpha=0.05}=4.10$ for Eq. 10, $F_{1,37:\alpha=0.05}=4.10$ for Eq. 11, $F_{1,36:\alpha=0.05}=4.11$ for Eq. 12, $F_{1,35:\alpha=0.05}=4.12$ for Eq. 13 and $F_{1,34:\alpha=0.05}=4.13$ for Eq. 14. *e*) Figures in parentheses are 95% confidence intervals. *f*) $F_{6,34}=28.76$, $F_{6,34:\alpha=0.05}=2.38$.

employed as the value relative to that of H: $\Delta B_1(\mathrm{X})=B_1(\mathrm{X})-B_1(\mathrm{H})$. The stepwise development of Eq. 8 for 34 compounds is shown in Table III. The situation is summarized in Fig. 3.

Finally, the analysis including compounds with non-amino substituents (I-1—7) was attempted. As shown in Fig. 3, the activity of these compounds was considerably low. By considering a third indicator variable I(N) which takes the value of unity for secondary as well as tertiary amino compounds, Eq. 14 (Table IV) was formulated, the situation being illustrated in Fig. 4. The stepwise development of Eq. 14 justified statistically for a total of 41 derivatives is shown in Table IV, and the physicochemical parameters of each substituent used in this analysis are listed in Table V. As summarized in Table VI, the intercorrelation between the independent variables for 41 derivatives is shown to be insignificant.

The magnitude of the indicator variable terms, I(*tert*-N) and I(N), in Eq. 14 indicates that the activity is progressively increased in the order of non-amino, secondary amino and tertiary amino compounds, the effect from the non-amino to the secondary amino compounds being more important. This seemed to be due to the electronic effect of the substituents. Among electronic parameters examined, we found that the σ_I[6] and σ_R^+[6] were well able to replace the I(*tert*-N) and I(N) terms, as shown in Eq. 15, although the quality of the correlation was slightly poorer than that of Eq. 14.

$$\begin{aligned}\mathrm{pIC_{50}} = &-1.18\Delta MR + 0.58\pi + 1.71\Delta B_1 + 0.84I - 2.68\sigma_I \\ &(0.35)\quad (0.21)\quad (0.82)\quad (0.47)\quad (1.66) \\ &-2.90\sigma_R^+ + 5.82 \\ &(0.68)\quad (0.69) \\ &(n=41,\ r=0.86,\ s=0.48,\ F_{6,34}=16.61)\end{aligned} \tag{15}$$

The parameters σ_I and σ_R^+ stand for inductive and resonance components of electronic effects, respectively. The σ_R^+ parameter represents the resonance effect of substituents on the electron deficient center including a through-resonance effect. The pyrazinecarboxamide is highly electron-withdrawing. The significant contribution of the negative σ_R^+ term could be justified since the amino substituents could exhibit an electron-donating through-resonance effect on the ring. The coefficient of the σ_I and σ_R^+ terms are practically equivalent indicating that the two terms can be combined as the σ^+ term. The σ_I and σ_R^+ values are listed in Table V.

Equations 14 and 15 show that electron-donating (*e.g.* dialkylamino) substituents with high hydrophobicity as well as with small overall bulk but large minimum width, and possessing a chain length longer than the *n*-propylamino group, are favorable to the activity. These requirements are difficult to satisfy simultaneously. Thus, by considering the weight of each term, small dialkylamino substituents, including cyclic amino groups, were thought to be most favorable to the activity, as was experimentally observed in the dimethylamino (I-27) and 1-pyrrolidinyl (I-34) derivatives.

In the above analyses, the π values of substituents were either those given by Yamagami *et al.*[4] for monosubstituted pyrazines or those calculated according to the additive-constitutive nature of log P. The details of the calculation method are given in the experimental section. As listed in Table VII, the π values of hydrogen-bonding pyrazine substituents such as alkoxy and amino are considerably higher than the corresponding values for monosubstituted benzenes. This is due to the higher electron-withdrawing effects of the pyrazine ring affecting the relative solvation with partitioning solvents of alkoxy and amino groups. With the use of π values from monosubstituted benzenes Eq. 14′ was obtained, which is only slightly poorer than Eq. 14.

$$\begin{aligned}\mathrm{pIC_{50}} = &-1.13\Delta MR + 0.63\pi(\mathrm{benzene}) + 1.03\Delta B_1 + 0.77I \\ &(0.29)\quad (0.18)\quad (0.82)\quad (0.41) \\ &+0.43I(\textit{tert}\text{-N}) + 2.77I(\mathrm{N}) + 6.76 \\ &(0.37)\quad (0.56)\quad (0.44) \\ &(n=41,\ r=0.89,\ s=0.42,\ F_{6,34}=22.52)\end{aligned} \tag{14′}$$

This was not unexpected since the substituents used here were mostly OR′, NHR′ and NR′R′ (R′ or R′: alkyl and substituted alkyl) where the π(pyrazine) value is almost parallel with the π(benzene) value, the former being 1.0—1.5 log unit higher than the latter. If pyrazines to which substituents of various electron-withdrawing properties are attached directly were to be analyzed, the use of the π(pyrazine) value should give much better results statistically as well as physicochemically.

Recent structure–activity studies of allergic agents have shown that an extended planar (or quasi-planar) aromatic system within which an acidic function is located in close proximity to a carbonyl group is one of the most important

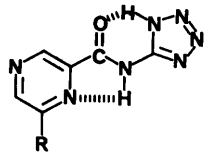
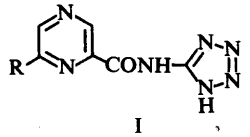


Chart 3

TABLE V. Antiallergic Activity and Physicochemical Parameters of Compounds (I)



I

Compd. No.	R	ΔMR[a]	π[b]	ΔB_1[c]	I[d]	I(*tert*-N)[e]	I(N)[f]	σ_I[g]	σ_R^+[g]	pIC$_{50}$ Obsd.[h]	Eq. 3 Calcd (Δ)[i]	Eq. 8 Calcd (Δ)[i]	Eq. 14 Calcd (Δ)[i]
1	H	0.000[j]	0.00[k]	0.00	0.00	0.00	0.00	0.00	0.00	6.38			6.47 (−0.09)
2	Me	0.462[j]	0.47[k]	0.52	0.00	0.00	0.00	−0.01	−0.13[l]	7.00			6.73 (0.27)
3	Cl	0.500[j]	0.96[k]	0.80	0.00	0.00	0.00	0.47	−0.21	6.80			7.32 (−0.52)
4	OMe	0.684[j]	0.99[k]	0.35	0.00	0.00	0.00	0.30	−0.66	6.96			6.65 (0.31)
5	OEt	1.144[j]	1.54[k]	0.35	0.00	0.00	0.00	0.28	−0.65	6.50			6.45 (0.05)
6	O-*n*-Pr	1.603[j]	2.09	0.35	0.00	0.00	0.00	0.28	−0.65[m]	6.32			6.26 (0.06)
7	OPh	2.665[j]	2.39	0.35	1.00	0.00	0.00	0.40	−0.65[m]	5.92			5.99 (−0.07)
8	NHMe	0.930[j]	0.82[k]	0.35	0.00	0.00	1.00	0.13	−1.16	8.60	8.50 (0.10)	8.69 (−0.09)	8.66 (−0.06)
9	NHEt	1.395[j]	1.25	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	8.40	8.22 (0.18)	8.39 (0.01)	8.37 (0.03)
10	NH-*n*-Pr	1.860	1.69	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	7.68	7.95 (−0.27)	8.09 (−0.41)	8.08 (−0.40)
11	NH-iso-Pr	1.860	1.52	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	7.89	7.83 (0.06)	7.96 (−0.07)	7.96 (−0.07)
12	NH-cyclo-Pr	1.718	1.54	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	8.00	8.02 (−0.02)	8.17 (−0.17)	8.16 (−0.16)
13	NH-*n*-Bu	2.323	2.21	0.35	1.00	0.00	1.00	0.13[n]	−1.16[n]	8.52	8.82 (−0.30)	8.80 (−0.28)	8.74 (−0.22)
14	NH-iso-Bu	2.323[o]	1.92	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	7.77	7.54 (0.23)	7.64 (0.13)	7.65 (0.12)
15	NH-*sec*-Bu	2.323[o]	1.82	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	7.04	7.47 (−0.43)	7.57 (−0.53)	7.58 (−0.54)
16	NH-*tert*-Bu	2.323[o]	1.46	0.35	0.00	0.00	1.00	0.13[n]	−1.16[n]	6.89	7.23 (−0.34)	7.30 (−0.41)	7.32 (−0.43)
17	NH-*n*-Hex	3.253	3.17	0.35	1.00	0.00	1.00	0.13[n]	−1.16[n]	8.60	8.33 (0.27)	8.27 (0.33)	8.23 (0.37)
18	NH-cyclo-Hex	3.034	2.55	0.35	1.00	0.00	1.00	0.13[n]	−1.16[n]	8.11	8.18 (−0.07)	8.10 (0.01)	8.07 (0.04)
19	NH-*n*-Oct	4.183	4.13	0.35	1.00	0.00	1.00	0.13[n]	−1.16[n]	8.52	7.84 (0.68)	7.74 (0.78)	7.72 (0.08)
20	NH-*n*-Dec	5.113	5.09	0.35[p]	1.00	0.00	1.00	0.13[n]	−1.16[n]	7.47	7.35 (0.12)	7.21 (0.26)	7.22 (0.25)
21	NH-*n*-Dodec	6.043	6.05	0.35	1.00	0.00	1.00	0.13[n]	−1.16[n]	6.48	6.86 (−0.38)	6.68 (−0.20)	6.71 (−0.23)
22	$NHCH_2Ph$	3.370[j]	2.41	0.35	1.00	0.00	1.00	0.13[n]	−1.16[n]	7.75	7.68 (0.07)	7.54 (0.21)	7.54 (0.21)
23	$NH(CH_2)_2OH$	1.549	−0.55	0.35	0.00	0.00	1.00	0.38[q]	−1.16[n]	7.47	6.83 (0.64)	6.83 (0.64)	6.88 (0.59)
24	$NH(CH_2)_3OH$	2.014	−0.11	0.35[p]	1.00	0.00	1.00	0.13[n]	−1.16[n]	7.80	7.64 (0.16)	7.47 (0.33)	7.48 (0.32)
25	$NH(CH_2)_2OMe$	2.033	0.27	0.35[p]	1.00	0.00	1.00	0.38[q]	−1.16[n]	7.30	7.87 (−0.57)	7.73 (−0.43)	7.73 (−0.43)
26	$NH(CH_2)_2NH_2$	1.739	−0.60	0.35[p]	0.00	0.00	1.00	0.28[r]	−1.16[n]	6.42	6.56 (−0.14)	6.54 (−0.12)	6.60 (−0.18)
27	NMe_2	1.452[j]	1.19[k]	0.35	0.00	1.00	1.00	0.17	−1.22	9.33		8.80 (0.53)	8.83 (0.50)
28	N(Me)Et	1.917	1.62	0.35	0.00	1.00	1.00	0.17[s]	−1.22[s]	8.75		8.50 (0.25)	8.54 (0.21)
29	N(Me)*n*-Pr	2.383	2.06	0.35[p]	0.00	1.00	1.00	0.17[s]	−1.22[s]	8.54		8.20 (0.34)	8.25 (0.29)
30	N(Me)*n*-Bu	2.846	2.58	0.35[p]	1.00	1.00	1.00	0.17[s]	−1.22[s]	9.01		8.91 (0.10)	8.91 (0.10)
31	N(Me)*n*-Hex	3.777	3.54	0.35[p]	1.00	1.00	1.00	0.17[s]	−1.22[s]	8.38		8.37 (0.01)	8.40 (−0.02)
32	$N(Me)CH_2Ph$	3.888	2.78	0.49[p]	1.00	1.00	1.00	0.17[s]	−1.22[s]	7.07		7.83 (−0.76)	7.86 (−0.79)
33	NEt_2	2.382[j]	2.05	0.35	0.00	1.00	1.00	0.17[s]	−1.22[s]	7.82		8.19 (−0.37)	8.25 (−0.43)
34	1-Pyrrolidinyl	2.176	1.75	0.90	0.00	1.00	1.00	0.17[s]	−1.22[s]	9.34		8.92 (0.42)	8.85 (0.49)
35	1-Piperidinyl	2.643[j]	2.22	0.91	0.00	1.00	1.00	0.17[s]	−1.22[s]	8.25		8.66 (−0.41)	8.60 (−0.35)
36	4-Morpholinyl	2.354[j]	0.60	0.91[p]	0.00	1.00	1.00	0.38[t]	−1.22[s]	7.44		7.83 (−0.39)	7.81 (−0.37)
37	1-(3-OH)piperidinyl	2.825	0.20	1.30[p]	0.00	1.00	1.00	0.38[q]	−1.22[s]	7.82		7.38 (0.44)	7.31 (0.51)
38	1-(4-OH)piperidinyl	2.825	0.20	0.89[p]	1.00	1.00	1.00	0.17[s]	−1.22[s]	7.62		7.81 (−0.19)	7.78 (−0.16)
39	1-Piperazinyl	2.720	−0.38	0.91	0.00	1.00	1.00	0.28[u]	−1.22[s]	6.82		6.61 (0.21)	6.64 (0.18)
40	1-(4-Me)piperazinyl	3.182	0.05	0.90[p]	1.00	1.00	1.00	0.28[r]	−1.22[s]	7.44		7.23 (0.21)	7.22 (0.22)
41	1-(4-Et)piperazinyl	3.647	0.47	0.94[p]	1.00	1.00	1.00	0.28[r]	−1.22[s]	6.57		6.97 (−0.40)	6.97 (−0.40)

a) Each value was calculated according to the equations in the experimental section, unless otherwise noted. All values were scaled by 0.1 and used as values relative to that of H. *b*) Each value was calculated according to the equations in the experimental section, unless otherwise noted. *c*) Each value was taken from a brochure distributed by Dr. A. Verloop, unless otherwise noted. All values were used as values relative to that of H. *d*) Indicator variable which takes the value of unity for compounds with a longer substituent than *n*-propylamino group and zero for others. *e*) Indicator variable which takes the value of unity for tertiary amino compounds and zero for others. *f*) Indicator variable which takes the value of unity for amino compounds and zero for others. *g*) Taken from ref. 6 unless otherwise noted. *h*) pIC$_{50}$ value of inhibitory activity of allergic histamine release from rat peritoneal exudate cells. *i*) Δ, the difference between observed and calculated values. *j*) Taken from ref. 3. *k*) Taken from ref. 4. *l*) Taken as being equivalent to the value of *tert*-Bu in ref. 6. *m*) Taken as being equivalent to the value of OEt. *n*) Taken as being equivalent to the value of NHMe. *o*) Taken as being equivalent to the value of NHBu. *p*) Calculated by means of the STERIMOL Program presented by Dr. A. Verloop. *q*) Taken as being equivalent to the value of 4-morpholinyl. *r*) Taken as being equivalent to the value of 1-piperazinyl. *s*) Taken as being equivalent to the value of NMe_2. *t*) Estimated from the equation $\sigma_I = \sigma_p - \sigma_R$. σ_p(4-morpholinyl) = −0.50 was taken from ref. 7 and σ_R(4-morpholinyl) = −0.88 was taken as being equivalent to the value of NMe_2 in ref. 6. *u*) Estimated from the equation σ_I(1-piperazinyl) = [σ_I(1-piperidinyl) + σ_I(4-morpholinyl)]/2, because of pK_a(piperazine) ≒ [pK_a(piperidine) + pK_a(morpholine)]/2.

requirements for the activity.[8] Considering the role of hydrogen bonding in stabilizing the planar conformation, such a structure as shown in Chart 3 could be most plausible for compound I.

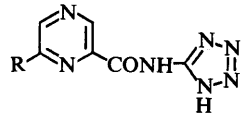
There could be a hydrophobic cavity of a limited size on a hypothetical receptor corresponding to the R-substituent at the 6-position of the pyrazine ring. The electron-donating effect represented by the negative σ terms of 6-substituents in Eq. 15 acts on the 1-N atom of the pyrazine ring as well as on the carbonyl group so that the planar structure required for the activity can is favored.

In summary, the present quantitative analysis of the

TABLE VI. Correlation Coefficient Matrix (r) for the Parameters of Eq. 14

	I(N)	ΔMR	π	ΔB_1	I	I(*tert*-N)
I(N)	1.00					
ΔMR	0.52	1.00				
π	0.13	0.69	1.00			
ΔB_1	0.16	0.15	0.31	1.00		
I	0.23	0.68	0.42	0.05	1.00	
I(*tert*-N)	0.35	0.23	0.12	0.60	0.02	1.00

TABLE VII. π Value for Monosubstituted Pyrazines and Benzenes



I

Compd. No.	R	π[a]	π (benzene)[b]
1	H	0.00	0.00
2	Me	0.47	0.56
3	Cl	0.96	0.71
4	OMe	0.99	−0.02
5	OEt	1.54	0.38
6	O-*n*-Pr	2.09	1.05
7	OPh	2.39	2.08
8	NHMe	0.82	−0.47
9	NHEt	1.25	0.08
10	NH-*n*-Pr	1.69	0.40[c]
11	NH-iso-Pr	1.52	0.23[c]
12	NH-cyclo-Pr	1.54	0.25[c]
13	NH-*n*-Bu	2.21	0.92[c]
14	NH-iso-Bu	1.92	0.63[c]
15	NH-*sec*-Bu	1.82	0.53[c]
16	NH-*tert*-Bu	1.46	0.17[c]
17	NH-*n*-Hex	3.17	1.88[c]
18	NH-cyclo-Hex	2.55	1.26[c]
19	NH-*n*-Oct	4.13	2.84[c]
20	NH-*n*-Dec	5.09	3.80[c]
21	NH-*n*-Dodec	6.05	4.76[c]
22	$NHCH_2Ph$	2.41	1.00
23	$NH(CH_2)_2OH$	−0.55	−1.72[c]
24	$NH(CH_2)_3OH$	−0.11	−1.40[c]
25	$NH(CH_2)_2OMe$	0.27	−0.90[c]
26	$NH(CH_2)_2NH_2$	−0.60	−1.77[c]
27	NMe_2	1.19	0.18
28	N(Me)Et	1.62	0.61[c]
29	N(Me)*n*-Pr	2.06	1.05[c]
30	N(Me)*n*-Bu	2.58	1.57[c]
31	N(Me)*n*-Hex	3.54	2.53[c]
32	$N(Me)CH_2Ph$	2.78	1.77[c]
33	NEt_2	2.05	1.18
34	1-Pyrrolidinyl	1.75	0.74[c]
35	1-Piperidinyl	2.22	0.85
36	4-Morpholinyl	0.60	−0.77[c]
37	1-(3-OH)piperidinyl	0.20	−1.17[c]
38	1-(4-OH)piperidinyl	0.20	−1.17[c]
39	1-Piperazinyl	−0.38	−1.75[c]
40	1-(4-Me)piperazinyl	0.05	−1.32[c]
41	1-(4-Et)piperazinyl	0.47	−0.90[c]

a) The π value for monosubstituted pyrazines. References and methods for estimation are shown in Table V and the experimental section. *b*) The π value for monosubstituted benzenes. Taken from ref. 7 unless otherwise noted. *c*) The value was calculated by a similar method to that used for pyrazines (see the experimental section).

effect of substituents at the 6-position of antiallergic *N*-(1*H*-tetrazol-5-yl)-2-pyrazinecarboxamide seems adequate to allow us to identify the most effective structural features for the activity so as to give a physicochemical basis to the selection of the most favorable candidate compounds for further clinical development as antiallergic drugs.

Experimental

Compounds The preparation of most compounds was previously described.[1] The others were similarly prepared. The physicochemical data of all compounds are summarized in Table I.

Antiallergic Activity Pharmacological measurement of the immunoglobulin E (IgE)-mediated histamine release from rat peritoneal exudate cells was described previously.[1] The pharmacological data of all compounds are summarized in Table I.

Calculations of Substituent Parameters, *MR* and π **1. Steric Parameter *MR*** The *MR* values of substituents other than those presented in ref. 3 were estimated from the following Eq. 16—25.

$$MR(\text{NH-}n\text{-Pr or NH-iso-Pr}) = MR(\text{NHEt})^{3)} + [MR(\text{NHEt}) - MR(\text{NHMe})^{3)}] \quad (16)$$

$$MR(\text{NH-cyclo-Pr or NH-cyclo-Hex}) = MR(\text{NHMe})^{3)} + [MR(\text{cyclo-Pr or cyclo-Hex})^{3)} - MR(\text{Me})^{3)}] \quad (17)$$

$$MR(\text{NH-}n\text{-Hex, NH-}n\text{-Oct, NH-}n\text{-Dec or NH-}n\text{-Dodec}) = MR(\text{NH-}n\text{-Bu})^{3)} + (m-4) \times [MR(\text{NHEt}) - MR(\text{NHMe})] \quad (18)$$

In Eq. 18, m is the number of carbon atoms.

$$MR[\text{NH}(\text{CH}_2)_2\text{OH, NH}(\text{CH}_2)_2\text{OMe or NH}(\text{CH}_2)_2\text{NH}_2] = MR(\text{NHMe}) + [MR(\text{CH}_2)_2\text{OH, } (\text{CH}_2)_2\text{OMe or } (\text{CH}_2)_2\text{NH}_2]^{7)} - MR(\text{Me})] \quad (19)$$

$$MR[\text{NH}(\text{CH}_2)_3\text{OH}] = MR[\text{NH}(\text{CH}_2)_2\text{OH}] + [MR(\text{Et})^{3)} - MR(\text{Me})] \quad (20)$$

$$MR[\text{N(Me)Et, N(Me)}n\text{-Pr, N(Me)}n\text{-Bu, N(Me)}n\text{-Hex or N(Me)CH}_2\text{Ph}] = MR(\text{NMe}_2)^{3)} + [MR(\text{Et, }n\text{-Pr, }n\text{-Bu, }n\text{-Hex or CH}_2\text{Ph})^{3)} - MR(\text{Me})] \quad (21)$$

$$MR(\text{1-pyrrolidinyl}) = MR(\text{1-piperidinyl})^{3)} + [MR(\text{cyclo-Pent})^{3)} - MR(\text{cyclo-Hex})^{3)}] \quad (22)$$

$$MR(\text{3- or 4-hydroxy-1-piperidinyl}) = MR(\text{1-piperidinyl}) + [MR(\text{OH})^{3)} - MR(\text{H})^{3)}] \quad (23)$$

$$MR(\text{1-piperazinyl}) = MR(\text{1-piperidinyl}) + [MR(\text{1-piperidinyl}) - MR(\text{cyclo-Hex})] \quad (24)$$

$$MR(\text{4-methyl- or 4-ethylpiperazinyl}) = MR(\text{1-piperazinyl}) + [MR(\text{Me or Et}) - MR(\text{H})] \quad (25)$$

2. Hydrophobic Parameter π The π value used here is that for monosubstituted pyrazines. The π values of the substituents other than those presented in ref. 4 were estimated in from the following equations.

NHEt, NH-*n*-Pr, NH-iso-Pr, NH-*n*-Bu, NH-iso-Bu, NH-*sec*-Bu, NH-*tert*-Bu, NH-*n*-Hex, NH-cyclo-Hex, $NHCH_2Ph$, N(Me)Et, N(Me)*n*-Pr, N(Me)*n*-Bu, N(Me)*n*-Hex, $N(Me)CH_2Ph$, NEt_2, 1-Pyrrolidinyl and 1-Piperidinyl Groups: As described in ref. 9, the logarithm of the partition coefficient (log P) of amines ($NR_1R_2R_3$) can be estimated from Eq. 26.

$$\log P = 0.962\pi + 4.034\sigma_1 + 0.270[E_s'^c(R_1) + E_s'^c(R_2)] - 1.251 \quad (26)$$

$$[E_s'^c(R_1) \geqq E_s'^c(R_2) \geqq E_s'^c(R_3)]$$

In Eq. 26, π and σ_1 are, respectively, the sum of the hydrophobic π values for aliphatic groups and the inductive electronic σ_1 values, and $E_s'^c(R_i)$ is a modified steric constant derived from the Dubois E_s' value considering the branching effect of N-substituents. On the basis of the assumption that the most bulky substituent R_3 is pyrazinyl in Eq. 26, the log P of NR_1R_2-substituted pyrazine is given by the following Eq. 27.

$$\log P(\text{NR}_1\text{R}_2/\text{subst. pyrazine}) = 0.962[\pi(R_1) + \pi(R_2) + \pi(\text{pyrazinyl})] + 4.034[\sigma_I(R_1) + \sigma_I(R_2) + \sigma_I(\text{pyrazinyl})] + 0.270[E_s'^c(R_1) + E_s'^c(R_2)] - 1.251 \quad (27)$$

If the π value of a substituent ($NR_1'R_2'$) on the pyrazine has been observed, the unknown π value of the substituent (NR_1R_2) can be estimated from Eq. 28.

$$\pi(\text{NR}_1\text{R}_2/\text{pyrazine}) = \pi(\text{NR}_1'\text{R}_2'/\text{pyrazine}) + [\log P(\text{NR}_1\text{R}_2/\text{subst. pyrazine})$$

$$= -\log P(NR_1'R_2'/\text{subst. pyrazine})]$$
$$= \pi(NR_1'R_2'/\text{pyrazine}) + 0.962[\pi(R_1) + \pi(R_2) - \pi(R_1') - \pi(R_2')] + 4.034[\sigma_I(R_1) + \sigma_I(R_2) - \sigma_I(R_1') - \sigma_I(R_2')] + 0.270[E_s^c(R_1) + E_s^c(R_2) - E_s^c(R_1') - E_s^c(R_2')] \quad (28)$$

For substituents in secondary and tertiary amino compounds, NHMe and NMe_2 groups whose π values are known[4] were used as the standard $NR_1'R_2'$, respectively, to give the calculated π value from Eq. 28.

NH-cyclo-Pr Group: Eq. 29 was used.

$$\pi(\text{NH-cyclo-Pr/pyrazine}) = \pi(\text{NHMe/pyrazine})^{4)} + [\pi(\text{cyclo-Pr/aliphatic})^{10)} - \pi(\text{Me/aliphatic})^{10)}] \quad (29)$$

NH-*n*-Oct, NH-*n*-Dec and NH-*n*-Dodec Groups: The π values were estimated from Eq. 30, where m is the number of carbon atoms.

$$\pi(\text{NH-}n\text{-Oct, NH-}n\text{-Dec or NH-}n\text{-Dodec/pyrazine}) = \pi(\text{NH-}n\text{-Hex/pyrazine}) + (m-6)/2 \times [\pi(\text{NH-}n\text{-Hex/pyrazine}) - \pi(\text{NH-}n\text{-Bu/pyrazine})] \quad (30)$$

$NH(CH_2)_2OH$, $NH(CH_2)_2OMe$ and $NH(CH_2)_2NH_2$ Groups: Equation 31 was used.

$$\pi[NH(CH_2)_2OH, NH(CH_2)_2OMe \text{ or } NH(CH_2)NH_2/\text{pyrazine}] = \pi(\text{NHEt/pyrazine}) + \pi(\text{OH, OMe or } NH_2/\text{aliphatic})^{11)} \quad (31)$$

$NH(CH_2)_3OH$: Equation 32 was used.

$$\pi[NH(CH_2)_3OH/\text{pyrazine}] = \pi(\text{NH-}n\text{-Pr/pyrazine}) + \pi(\text{OH/aliphatic}) \quad (32)$$

4-Morpholinyl Group: From Eq. 33.

$$\pi(\text{4-morpholinyl/pyrazine}) = \pi(\text{1-piperidinyl/pyrazine}) + [[\log P(\text{4-phenylmorpholine})^{12)} - \log P(\text{benzene})^{12)}] - \pi(\text{1-piperidinyl/benzene})]^{7)} \quad (33)$$

3- and 4-Hydroxypiperidinyl Groups: From Eq. 34.

$$\pi(\text{3- or 4-hydroxypiperidinyl/pyrazine}) = \pi(\text{1-piperidinyl/pyrazine}) + \pi(\text{OH/aliphatic}) + F_{GBR} \quad (34)$$

F_{GBR} represents the group branch factor.[13]

1-Piperazinyl Group: From Eq. 35.

$$\pi(\text{1-piperazinyl/pyrazine}) = \pi(\text{1-piperidinyl/pyrazine}) + [\log P(\text{piperidine})^{12)} - \log P(\text{cyclo-hexane})^{12)}] \quad (35)$$

4-Methyl- and 4-Ethylpiperazinyl Groups: Through a process similar to that used to derive Eq. 28, Eq. 36 for 4-alkylpiperazinyl group was formulated, where R_1 is Me or Et.

$$\pi(\text{4-}R_1\text{-1-piperazinyl/pyrazine}) = \pi(\text{1-piperazinyl/pyrazine}) + 0.962[\pi(R_1)] + 4.034[\sigma_I(R_1)] + 0.270[E_s^c(R_1) - E_s^c(H)] \quad (36)$$

O-*n*-Pr Group: From Eq. 37.

$$\pi(\text{O-}n\text{-Pr/pyrazine}) = \pi(\text{OEt/pyrazine})^{4)} + [\pi(\text{OEt/pyrazine}) - \pi(\text{OMe/pyrazine})^{4)}] \quad (37)$$

OPh Group: As described in ref. 14, the π value of substituents on the pyridine ring can be estimated using that on the benzene ring from Eq. 38.

$$\pi(\text{X/pyridine}) = 0.935\pi(\text{X/benzene}) + 0.162\sigma_x^0 \quad (38)$$

In Eq. 38, π(X/pyridine) and π(X/benzene)[15] are the π values of the substituent X in monosubstituted pyridine and benzene, respectively, and σ_x^0 is a "σ" value applicable to cases where the reaction center is insulated from direct conjugation with the substituent X.[16] Moreover, the π value of substituents on the pyrazine ring can be calculated from Eq. 39.[17]

$$\pi(\text{X/pyrazine}) = 1.120\pi(\text{X/pyridine}) + 0.717\sigma_x^0(meta) + 0.375\rho_x(meta) + 0.027 \quad (39)$$

In Eq. 39, π(X/pyridine) and σ_x^0 have the same meanings as in Eq. 38, π(X/pyrazine) is the π value of the substituent X in monosubstituted pyrazine, and ρ_x is the susceptibility constant of substituent X for the relative solvation to the electronic effect of the 4-nitrogen at the pyridine ring.[17]

According to Eqs. 38 and 39, the π value of OPh was estimated.

Acknowledgement We wish to express our gratitude to Mr. J. Sakaguchi and Mr. E. Iwasa, Central Research Laboratories, Hokuriku Seiyaku Co., Ltd., for skillful assistance in the correlation analyses and to the staff of the Central Research Laboratories, Hokuriku Seiyaku Co., Ltd., for their cooperation in the biological and analytical examinations.

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