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Antivertigo Agents. V.[1] Quantitative Structure–Activity Relationships of 6-[2-(4-Aryl-1-piperazinyl)ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines

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The quantitative structure–activity relationships (QSAR) between the molecular structures and antivertigo activities of 6-[2-(4-aryl-1-piperazinyl)ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines were investigated. The effects of the *ortho*-, *meta*-, and *para*-substituents on the phenyl ring of the arylpiperazine moiety were examined by means of regression analysis using various physicochemical parameters related to these substituents. The results showed that only the parameters concerning the *ortho*-substituent were statistically significant. Namely, the relative activity depended on both F_{ortho} (Swain–Lupton field effect constant of the *ortho*-substituent) and I (indicator variable for the presence of an *ortho*-alkoxy group and an *ortho*-dimethylamino group). Thus, regression analysis for only the *ortho*-substituted compounds was examined and afforded a result similar to that described above. Further, the net atomic charge calculated by the molecular orbital method besides free energy-related substituent parameters was used as electronic parameters of the *ortho*-substituents on the phenyl ring for this QSAR analysis. For the *ortho*-substituted compounds alone, the potency correlated well with the net atomic charge on the first atom of the *ortho*-substituent (Q_{ortho}), while the correlation for all the compounds (*ortho*-, *meta*-, and *para*-substituents) was slightly lower than that for the *ortho*-substituted compounds alone. It was found that increase in the negative net atomic charge on the first atom of the *ortho*-position increased the relative activity. The correlation between Q_{ortho}, and F_{ortho} and I was examined and the role of I is discussed in connection with hydrogen bond-forming ability. The interaction between the arylpiperazine moiety in the compound and a putative receptor is discussed based on the QSAR analysis.

Keywords——antivertigo activity; quantitative structure–activity relationship; molecular orbital calculation; 1-arylpiperazine; hydrogen-bond

We have previously reported[1] the synthesis and antivertigo activity of 6-[ω-(4-aryl-1-piperazinyl)alkyl]-5,6,7,8-tetrahydro-1,6-naphthyridines. Among these compounds, 2-{2-[4-(2-ethoxyphenyl)-1-piperazinyl]ethyl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine (NK 422, **28**) was found to be more potent than betahistine and diphenidol. Some chemical modifications of these derivatives reveraled preliminary structure–activity relationships. The position and nature of substituents on the phenyl ring in the arylpiperazine moiety greatly affected the activity. Thus, our interest was focussed on the role of the arylpiperazine moiety in the activity. Some *ortho*-substituted derivatives (especially those with 2-fluoro, 2-chloro, 2-methoxy, and 2-methylthio groups) were more potent than the corresponding 3- or 4-congeners, suggesting that the effects of *ortho*-substituents on the antivertigo activity should be more fully evaluated.

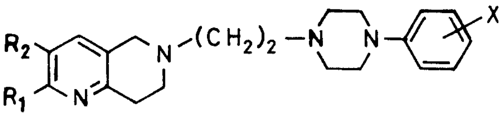


Chart 1

From these points of view, the effects of the *ortho*-substituents on the phenyl ring on the activity were investigated by evaluating quantitative structure–activity relationships (QSAR) based on a variety of physicochemical parameters such as π, E_s^{ortho}, σ, F_{ortho}, I, and I_R. The net atomic charges for *ortho*-substituents on the phenyl ring were calculated by a molecular orbital method, as well as σ and F_{ortho}, and applied to this QSAR analysis. The results are presented here.

Materials and Methods

Chemistry——All melting points and boiling points are uncorrected. The structures of all compounds were supported by the infrared (IR), proton nuclear magnetic resonance (^{1}H-NMR), and mass spectra (MS). IR spectra were measured with a JASCO IR-G spectrometer. ^{1}H-NMR spectra were recorded on a JEOL JNM-PMX 60 spectrometer using Me_4Si as an internal standard. MS were determined with a Shimadzu GCMS-7000 spectrometer.

Synthesis of 6-[2-(4-aryl-1-piperazinyl)ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines used in this study has been previously reported[1] except for compounds **21**, **25**, **29**, **30**, and **31**.

Typical Example: 2-{2-[4-(2-Methylthiophenyl)-1-piperazinyl]ethyl}-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]-naphthyridine Difumarate (29)——A solution of 2-(2-chloroethyl)-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridine·2HCl (4.9 g, 15 mmol), 1-(2-methylthiophenyl)piperazine·HCl (3.7 g, 15 mmol), and Et_3N (7.6 g, 75 mmol) in EtOH (70 ml) was refluxed for 2 h. The reaction mixture was evaporated *in vacuo* to give the residue, which was partitioned between toluene and H_2O. The toluene layer was separated, dried over K_2CO_3, and then evaporated *in vacuo* to give the residue. This residue was chromatographed on a SiO_2 column using AcOEt : Et_3N = 8 : 1 (v/v) as an eluent to give the free base of **29** (4.8 g, 76%) as a liquid. IR (neat): 2920, 1440, 1125 cm^{-1}. ^{1}H-NMR ($CDCl_3$) δ: 1.6—2.0 (4H, m, C_7 and C_8-H), 2.41 (3H, s, SCH_3), 2.5—3.3 (20H, m, aliphatic H), 3.60 (2H, s, C_1-H), 6.95 (1H, s, C_{10}-H), 7.06 (4H, s, phenyl H). MS *m/z* (rel. intensity): 422 (M^+, 4.3), 221 (100), 207 (8.5), 201 (69.6), 70 (20.1). This free base was converted to the salt **29** by treatment with fumaric acid in acetone.

Compounds **21**, **25**, **30**, and **31** were prepared by a similar method. Table I lists yields, melting points, recrystallization solvents, and values of elementary analyses of the salts.

Antivertigo Activity——The antivertigo activities of compounds were evaluated by their ability to inhibit spontaneous nystagmus in cats, according to our previous report,[1] and the activities were expressed as ID_{30} (μmol/kg, *i.v.*). The activities of compounds used in this study have previously been reported, except for compounds **21**, **25**, **29**, **30**, and **31**.

Molecular Orbital Calculation——The net atomic charges of 1-arylpiperazines were calculated by the CNDO/2 (complete neglect of differential overlap) method.[2] This method was selected because it has been employed for calculations of net atomic charges of an enormous variety of compounds and because its strengths and weaknesses are fairly well known.[3]

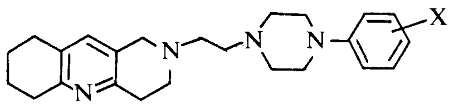
The input data on the geometries used for CNDO/2 calculations were examined by using the MNDO (modified neglect of diatomic overlap)[4] and PCILO (perturbative configuration interaction using localized orbitals) methods.[5]

Firstly, we tried to estimate the most stable conformation by the MNDO method, which has recently been employed in studies on the geometrical structures of various organic compounds. The MNDO calculation indicated that the phenyl ring was perpendicular to the piperazine ring in all the compounds calculated here. In contrast to these calculated results, the dihedral angle τ was estimated to be about 40° from the X-ray data[6] of the (2-methoxyphenyl)piperazine moiety in fluanisone (1-(4-flurophenyl)-4-[4-(2-methoxyphenyl)-1-piperazinyl]-1-butanone), where τ is the angle between the plane of the phenyl ring and the plane perpendicular to the one containing N(7), C(1), and N(10), as shown in Fig. 1. This discrepancy implied that the MNDO method may not be approprite for the conformational study with respect to τ of 1-arylpiperazines in this series.

On the other hand, Tollenaere *et al.*[7] calculated the conformational behavior of 1-(2-methoxyphenyl)-4-methylpiperazine by the PCILO method, which has successfully been applied to conformational studies of a wide variety of drugs,[8] and reported that the τ value of the most stable conformer calculated by the PCILO method was in good agreement with the corresponding experimental τ value of fluanisone obtained from the X-ray analysis.

Thus, the PCILO method was used for a conformational study of τ of 1-arylpiperazines. The starting geometries were taken from the geometries optimized by the MNDO method at $\tau=0$ and 90°, respectively, considering the reorganization of geometry accompanying the rotation around the central C(1)–N(7) bond. The calculations were carried out with 10° increments in τ. The arithmetic mean energy between the Kekulé structures of the phenyl ring

TABLE I. 2-[2-(4-Aryl-1-piperazinyl)ethyl]-1,2,3,4,6,7,8,9-octahydrobenzo[*b*][1,6]naphthyridines



·difumarate

Comp. No.	X	Yield (%)[a]	mp (°C)	Recrystn. solvent	Formula	Analysis (%) Calcd (Found) C	H	N
21	2-F	55	211—212	MeOH-EtOH	$C_{24}H_{31}FN_4\cdot$ $2C_4H_4O_4$	61.34 (61.71	6.27 6.44	8.94 9.25)
25	2-NMe$_2$	75	218—221 (dec.)	MeOH-EtOH	$C_{26}H_{37}N_5\cdot$ $2C_4H_4O_4$	62.65 (62.37	6.96 6.86	10.75 10.48)
29	2-SMe	31	215—221 (dec.)	CH_3COCH_3-MeOH	$C_{25}H_{34}N_4S\cdot$ $2C_4H_4O_4$	60.52 (60.89	6.47 6.70	8.56 8.95)
30	3-SMe	34	212—214 (dec.)	MeOH	$C_{25}H_{34}N_4S\cdot$ $2C_4H_4O_4$	60.52 (60.76	6.47 6.40	8.56 8.81)
31	4-SMe	38	212—215 (dec.)	MeOH	$C_{25}H_{34}N_4S\cdot$ $2C_4H_4O_4$	60.52 (60.37	6.47 6.58	8.56 8.84)

a) The yield is based on the free base.

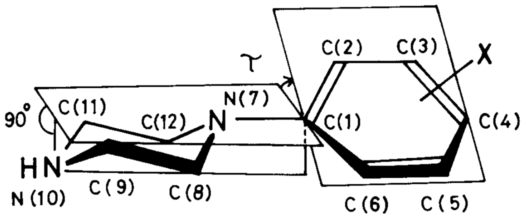


Fig. 1. The Geometries of 1-Arylpiperazines

The dihedral angle τ was defined as the angle between the plane of the phenyl group and the plane containing N(7) and C(1), which is perpendicular to the plane containing C(1), N(7), and N(10). This angle τ is positive for clockwise rotation of the plane of the phenyl group around the N(7)–C(1) bond axis, when looking from N(7) to C(1). In a conformer with a τ value of 0°, the phenyl group is virtually parallel to the plane containing C(8), C(9), and C(12) or C(8), C(11), and C(12), and the lone-pair electrons of N(7) conjugate with the π-orbitals of the phenyl group.

was adopted as the conformational energy, taking into account the delocalization of π-electrons in the phenyl ring. Of the two conformational energy values calculated by using the two starting geometries for a compound, the lower value was adopted as the final conformational energy.

The τ values of the most stable conformation estimated by the PCILO calculations are shown in Table II for all the 1-(substituted phenyl)piperazines calculated here. The geometries of the conformations with these τ values were used as the input ones for CNDO/2 calculations on the net atomic charges.

The net atomic charges on the significant atoms, namely Q_{ortho} and Q_N are listed in Table II. Q_{ortho} and Q_N denote the net atomic charges on the first atom of the *ortho*-substituent or on the hydrogen atom bonded to C(2), and on N(7), respectively. The net atomic charges for 1-(2-methoxyphenyl)piperazines were employed for convenience as the charges for 1-(2-ethoxy-, 2-propoxy-, and 2-butoxyphenyl)piperazines.

The molecular orbital calculations were performed on a VAX-11/750 computer.

Regression Analysis——A regression analysis was carried out to investigate the relationships between the various parameters of the substituents on the phenyl ring in 6-[2-(4-aryl-1-piperazinyl)ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines and the antivertigo activities.

In order to analyze the effects of the *ortho*-substituents on the same basis as those of the *meta*- or *para*-substituents on the phenyl ring, we employed Eq. 1 proposed by Fujita *et al.*[9]

$$\log k_{ortho,meta,para} = \rho\sigma_{ortho,meta,para} + \delta E_s^{ortho} + fF_{ortho} + C \qquad (1)$$

Where $k_{ortho,meta,para}$ is either the rate or equilibrium constant, σ_{meta} or σ_{para} is used as the Hammett constant[10] of a *meta*- or *para*-substituent on the phenyl ring, and $\sigma_{ortho}=\sigma_{para}$. E_s^{ortho} is the Taft–Kutter Hansch steric effect constant[11] of the *ortho*-substituent. F_{ortho} is the Swain–Lupton field effect constant[10] of the *ortho*-substituent. We also used an indicator variable I, which takes a value of 1 for *ortho*-alkoxy and -dimethylamino groups and otherwise takes as value of 0.

Therefore, the structure–activity relationships for 6-[2-(4-aryl-1-piperazinyl)ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines were examined by fitting the various parameters of the substituents to Eq. 2, where π is the lipophilicity[10] of the substituent on the phenyl ring. The term I_R is an indicator variable for the presence of the 2,3-

Table II. Dihedral Angles (τ)[a] between the Piperazine and the Phenyl Rings, and the Net Atomic Charges[b] on N(7) (Q_N) and the Atoms (Q_{ortho}) at the *Ortho* Position for the Most Stable Conformation

X[a]	τ (°) for the most stable conformation	Net atomic charge	
		Q_N	Q_{ortho}
H	30	−0.1564	0.0010
2-F	30	−0.1451	−0.1981
4-F	30	−0.1551	0.0068
2-Cl	50	−0.1539	−0.1684
3-Cl	30	−0.1551	0.0203
4-Cl	30	−0.1545	0.0083
2-Me	60	−0.1638	−0.0028
3-Me	30	−0.1574	−0.0001
4-Me	0	−0.1510	−0.0020
2-NMe$_2$	40	−0.1531	−0.1563
2-OMe	30	−0.1459	−0.2074
3-OMe	30	−0.1577	0.0179
4-OMe	30	−0.1557	0.0028
2-SMe	50	−0.1559	−0.1304
3-SMe	30	−0.1556	0.0081
4-SMe	30	−0.1561	0.0041
2-Me, 4-Cl	90	−0.1675	−0.0036
2-Me, 5-Cl	90	−0.1668	−0.0042
2, 5-di-Me	60	−0.1637	−0.0012
2, 6-di-Me	90	−0.1736	−0.0024
2, 5-di-OMe	30	−0.1474	−0.2080

a) See Fig. 1. *b*) The net atomic charges were calculated by the CNDO/2 method (see Materials and Methods).

tetramethylene group at the 5,6,7,8-tetrahydro-1,6-naphthyridine ring, and takes a value of 1 for the tetramethylene group and otherwise takes a value of 0; *a*, *b*, *d*, *f*, ρ, and δ are susceptibility constants and *C* is a constant.

$$\log 1/\mathrm{ID}_{30} = a\pi + \rho\sigma_{ortho,meta,para} + \delta E_s^{ortho} + fF_{ortho} + bI + dI_R + C \tag{2}$$

As for the regression analysis using quantum chemical indices, Q_{ortho} and Q_N calculated by the CNDO/2 method described above were used instead of σ_{ortho} and F_{ortho} in Eq. 2 as electronic parameters of the 4-arylpiperazine moiety.

In the regression analysis, *n* is the number of compounds used, *r* is the correlation coefficient, *s* is the standard deviation, and *F* is the *F* ratio between the variances of calculated and observed activities.

Results and Discussion

All equations obtained by regression analysis from all combinations of the parameters π, E_s^{ortho}, σ, F_{ortho}, *I*, and I_R as shown in Table III were examined. The equations justified at the 99% level by the *t*-test on each term were as follows:

$$\log 1/\mathrm{ID}_{30} = 3.592(\pm 0.994)F_{ortho} - 1.619(\pm 0.162) \tag{3}$$

$$(n=31,\ s=0.379,\ r=0.808,\ F^1_{29}=54.647)$$

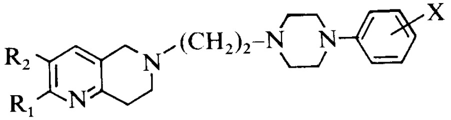
$$\log 1/\mathrm{ID}_{30} = 1.169(\pm 0.307)I - 1.620(\pm 0.156) \tag{4}$$

$$(n=31,\ s=0.365,\ r=0.823,\ F^1_{29}=60.742)$$

$$\log 1/\mathrm{ID}_{30} = 2.199(\pm 0.863)F_{ortho} + 0.753(\pm 0.276)I - 1.697(\pm 0.117) \tag{5}$$

$$(n=31,\ s=0.265,\ r=0.914,\ F^2_{28}=71.476)$$

TABLE III. Antivertigo Activities and Parameters of 6-[2-(4-Aryl-1-piperazinyl)-ethyl]-5,6,7,8-tetrahydro-1,6-naphthyridines Used for Derivation of Eqs. 5 and 6



									log 1/ID$_{30}$				
										Eq. 5		Eq. 6	
Compd. No.	R$_1$–R$_2$	X	I_R a)	I b)	E_s^{ortho} c)	$\sum\pi$ d)	$\sum\sigma$ d)	F_{ortho} d)	Obsd. e)	Calcd. f)	Δ g)	Calcd. h)	Δ i)
1	H	H	0	0	0.00	0.00	0.00	0.00	−1.899	−1.697	0.202	−1.746	0.153
2	H	4-F	0	0	0.00	0.14	0.06	0.00	−1.885	−1.697	0.188		
3	H	2-Cl	0	0	−0.97	0.71	0.23	0.41	−0.748	−0.795	0.047	−0.806	0.058
4	H	3-Cl	0	0	0.00	0.71	0.37	0.00	−1.619	−1.697	0.078		
5	H	4-Cl	0	0	0.00	0.71	0.23	0.00	−1.350	−1.697	0.347		
6	H	2-Me	0	0	−1.24	0.56	−0.17	−0.04	−1.918	−1.785	0.133	−1.838	0.080
7	H	3-Me	0	0	0.00	0.56	−0.07	0.00	−1.990	−1.697	0.293		
8	H	4-Me	0	0	0.00	0.56	−0.17	0.00	−1.961	−1.697	0.264		
9	H	2-OMe	0	1	−0.55	−0.02	−0.27	0.26	−0.491	−0.372	0.120	−0.368	0.123
10	H	3-OMe	0	0	0.00	−0.02	0.12	0.00	−1.182	−1.697	0.515		
11	H	4-OMe	0	0	0.00	−0.02	−0.27	0.00	−1.241	−1.697	0.456		
12	H	2-OEt	0	1	−0.55	0.38	−0.24	0.22	−0.342	−0.460	0.118	−0.460	0.118
13	H	2-OC$_3$H$_7$	0	1	−0.55	1.05	−0.25	0.22	−0.146	−0.460	0.314	−0.460	0.314
14	H	2-OC$_4$H$_9$	0	1	−0.55	1.72	−0.32	0.25	−0.255	−0.394	0.139	−0.391	0.136
15	H	4-Cl, 2-Me	0	0	−1.24	1.27	0.06	−0.04	−1.957	−1.785	0.172	−1.838	0.119
16	H	5-Cl, 2-Me	0	0	−1.24	1.27	0.20	−0.04	−1.651	−1.785	0.134	−1.838	0.187
17	H	2,5-di-Me	0	0	−1.24	1.12	−0.24	−0.04	−1.740	−1.785	0.045	−1.838	0.098
18	H	2,6-di-Me	0	0	−1.24	1.12	−0.34	−0.04	−1.772	−1.785	0.013	−1.838	0.066
19	H	2,5-di-OMe	0	1	−0.55	−0.04	−0.15	0.26	−0.929	−0.372	0.558	−0.368	0.561
20	(CH$_2$)$_4$	H	1	0	0.00	0.00	0.00	0.00	−1.849	−1.697	0.152	−1.746	0.103
21	(CH$_2$)$_4$	2-F	1	0	−0.46	0.14	0.06	0.43	−0.875 j)	−0.751	0.124	−0.760	0.115
22	(CH$_2$)$_4$	3-Cl	1	0	0.00	0.71	0.37	0.00	−1.869	−1.697	0.172		
23	(CH$_2$)$_4$	4-Cl	1	0	0.00	0.71	0.23	0.00	−1.873	−1.697	0.176		
24	(CH$_2$)$_4$	2-Me	1	0	−1.24	0.56	−0.17	−0.04	−1.791	−1.785	0.006	−1.838	0.047
25	(CH$_2$)$_4$	2-NMe$_2$	1	1	−0.61	0.18	−0.83	0.10	−1.000 j)	−0.723	0.277	−0.735	0.265
26	(CH$_2$)$_4$	2-OMe	1	1	−0.55	−0.02	−0.27	0.26	−0.301	−0.372	0.071	−0.368	0.067
27	(CH$_2$)$_4$	4-OMe	1	0	0.00	−0.02	−0.27	0.00	−1.185	−1.697	0.512		
28	(CH$_2$)$_4$	2-OEt	1	1	−0.55	0.38	−0.24	0.22	−0.146	−0.460	0.314	−0.460	0.314
29	(CH$_2$)$_4$	2-SMe	1	0	−1.07	0.61	0.00	0.20	−1.176 j)	−1.257	0.081	−1.288	0.112
30	(CH$_2$)$_4$	3-SMe	1	0	0.00	0.61	0.15	0.00	−1.881 j)	−1.697	0.184		
31	(CH$_2$)$_4$	4-SMe	1	0	0.00	0.61	0.00	0.00	−1.851 j)	−1.697	0.154		

a) Indicator variable for the presence of a tetramethylene group in R$_1$–R$_2$ (see Materials and Methods). *b*) Indicator variable for the presence of the *ortho*-alkoxy group and the *ortho*-dimethylamino group (see Materials and Methods). *c*) From ref. 11. *d*) From ref. 10. *e*) From ref. 1*a* unless otherwise noted. *f*) Calculated from Eq. 5. *g*) Absolute difference between observed and calculated values (|Δ log 1/ID$_{30}$|). *h*) Calculated from Eq. 6. *i*) Absolute difference between observed and calculated values (|Δ log 1/ID$_{30}$|). *j*) The value was based on the experiments in this report (see Materials and Methods).

TABLE IV. Squared Correlation Matrix for Variables of Eqs. 3—5, 8, and 12

	I_R	I	E_s^{ortho}	π	σ	F_{ortho}	Q_N	Q_{ortho}
I_R	1.000							
I	0.000	1.000						
E_s^{ortho}	0.022	0.013	1.000					
π	0.069	0.008	0.212	1.000				
σ	0.001	0.354	0.073	0.021	1.000			
F_{ortho}	0.006	0.349	0.020	0.022	0.026	1.000		
Q_N	0.026	0.447	0.178	0.132	0.024	0.537	1.000	
Q_{ortho}	0.003	0.711	0.067	0.008	0.191	0.837	0.526	1.000

The two single-variable equations, Eqs. 3 and 4, of the parameters comprising Eq. 5 showed high correlation coefficients ($r=0.808$ and 0.823, respectively). Although the squared correlation between the F_{ortho} and I terms relatively high, as shown in Table IV. Eq. 5 involving the two parameters was selected as the best equation with the highest correlation coefficient ($r=0.914$). Although the regression analysis covered all the compounds, involving *ortho*-, *meta*-, and *para*-substituents, the two parameters (F_{ortho} and I) in Eq. 5 relate only to the *ortho*-substituents. In addition, the compounds with large deviations between the log $1/ID_{30}$ values calculated from Eq. 5 and the observed ones were **10**, **11**, **19**, and **27**. All these compounds possessed a *meta*- or *para*-alkoxy group, as shown in Table III.

Thus, regression analysis was carried out by using only the *ortho*-substituted compounds. Equation 6 was obtained as the best equation; it contains the F_{ortho} and I terms, like Eq. 5. As we had expected the correlation coefficient of Eq. 6 was better than that of Eq. 5. The coefficients of these parameters in both Eqs. 5 and 6 were essentially identical. The calculated log $1/ID_{30}$ values from Eq. 6 for the *ortho*-substituted compounds agreed well with the observed ones except for the 2,5-dimethoxy group (**19**), as shown in Table III.

$$\log 1/\mathrm{ID}_{30}=2.294(\pm 0.770)F_{ortho}+0.782(\pm 0.245)I-1.746(\pm 0.151) \qquad (6)$$

$$(n=19,\ s=0.219,\ r=0.954,\ F_{16}^{2}=81.356)$$

It has been assumed that the effect of the substituents at the *ortho* position can be described by E_s, σ, and F according to the method of Fujita *et al.*[9] However, only the F_{ortho} term among these three parameters was found to be statistically significant in this series. Besides this term, the indicator variable I was also a significant parameter, although the real situation may well be more complicated. Other parameters such as π, σ, E_s^{ortho}, and I_R were statistically insignificant on the basis of Eqs. 5 and 6. The coefficient of F_{ortho} in Eq. 6 is positive, indicating that the introduction of a substituent with a large F value (such as chloro or fluoro) at the *ortho*-position on the phenyl ring leads to an increase in the activity. The coefficient of I is positive, indicating that the introduction of an alkoxy group or a dimethylamino group at the *ortho*-position leads to an increase in the activity.

The results obtained above suggest that an electronic factor involving the *ortho*-substituents may be closely related to the appearance of the activity. On the other hand, quantum chemical indices such as net atomic charges, *etc.*, have been successfully used in QSAR analysis.[12] Thus, we attempted to apply net atomic charges as quantum chemical indices for QSAR analysis in this series. Namely, since N(7) and the first atom of the substituent or the hydrogen atom bonded to the *ortho*-position on the phenyl ring were considered to be the crucial atoms of the 4-arylpiperazine moiety, the net atomic charges Q_{ortho} and Q_N were calculated by the CNDO/2 method. The regression analysis using parameters such as π, E_s^{ortho}, I, I_R, Q_{ortho}, and Q_N was carried out. Equation 7 was selected as the best

TABLE V. The Calculated Values from Eqs. 7, 8, 11, and 12

Compd. No.	log 1/ID$_{30}$							
	Eq. 7		Eq. 8		Eq. 11		Eq. 12	
	Calcd.	$\Delta^{a)}$	Calcd.	$\Delta^{a)}$	Calcd.	$\Delta^{a)}$	Calcd.	$\Delta^{a)}$
1	−1.859	0.040	−1.708	0.191	−1.203	0.696	−1.405	0.494
2			−1.742	0.143			−1.322	0.563
3	−0.724	0.024	−0.712	0.036	−1.041	0.293	−1.246	0.498
4			−1.822	0.203			−1.322	0.297
5			−1.751	0.401			−1.284	0.066
6	−1.834	0.084	−1.686	0.232	−1.684	0.234	−1.875	0.044
7			−1.702	0.288			−1.468	0.522
8			−1.691	0.270			−1.062	0.899
9	−0.463	0.028	−0.482	0.009	−0.521	0.030	−0.738	0.247
10			−1.808	0.626			−1.487	0.305
11			−1.719	0.478			−1.360	0.119
12	−0.463	0.121	−0.482	0.140	−0.521	0.179	−0.738	0.396
13	−0.463	0.317	−0.482	0.336	−0.521	0.375	−0.738	0.592
14	−0.463	0.208	−0.482	0.227	−0.521	0.266	−0.738	0.483
15	−1.828	0.129	−1.681	0.276	−1.924	0.033	−2.109	0.152
16	−1.824	0.173	−1.678	0.027	−1.879	0.228	−2.065	0.414
17	−1.844	0.104	−1.695	0.045	−1.677	0.063	−1.868	0.128
18	−1.836	0.064	−1.688	0.084	−2.321	0.549	−2.497	0.725
19	−0.459	0.470	−0.479	0.450	−0.618	0.311	−0.833	0.096
20	−1.859	0.010	−1.708	0.141	−1.203	0.646	−1.405	0.444
21	−0.525	0.350	−0.537	0.338	−0.469	0.406	−0.687	0.188
22			−1.822	0.047			−1.322	0.547
23			−1.751	0.122			−1.284	0.589
24	−1.834	0.043	−1.686	0.105	−1.684	0.107	−1.875	0.084
25	−0.805	0.195	−0.783	0.217	−0.989	0.011	−1.195	0.195
26	−0.463	0.162	−0.482	0.181	−0.521	0.220	−0.738	0.437
27			−1.719	0.534			−1.360	0.175
28	−0.463	0.317	−0.482	0.336	−0.521	0.375	−0.738	0.592
29	−0.979	0.197	−0.935	0.241	−1.171	0.006	−1.373	0.197
30			−1.750	0.131			−1.354	0.527
31			−1.727	0.124			−1.386	0.465

a) Absolute difference between observed (see Table III) and calculated values ($|\Delta \log 1/\mathrm{ID}_{30}|$).

equation for only the *ortho*-substituted compounds. Equation 7 showed a significant F value, ($F^{1}_{17\,(\alpha=0.001)}=15.722$), although the value of the correlation coefficient in Eq. 7 was equal to that in Eq. 6.

$$\log 1/\mathrm{ID}_{30} = -6.702(\pm 1.803)Q_{ortho} - 1.852(\pm 0.159) \qquad (7)$$

$$(n=19,\ s=0.214,\ r=0.954,\ F^{1}_{17}=170.367)$$

The adoption of the net atomic charges for the *ortho*-substituted compounds provided a significant and simple correlation between the molecular structures of the 4-arylpiperazine moieties and the antivertigo activities. The log 1/ID$_{30}$ values calculated from Eq. 7, like those from Eq. 6, were in good agreement with those observed except for compound **19**, as shown in Table V. This finding indicated that the net atomic charges on the first atom of the substituent for *ortho*-substituted compounds might play an important role in the appearance of the activity.

Table VI. Squared Correlation Matrix for Variables of Eqs. 6—8

	I_R	I	E_s^{ortho}	π	σ	F_{ortho}	Q_N	Q_{ortho}
I_R	1.000							
I	0.000	1.000						
E_s^{ortho}	0.050	0.179	1.000					
π	0.207	0.041	0.352	1.000				
σ	0.030	0.378	0.012	0.010	1.000			
F_{ortho}	0.022	0.225	0.146	0.076	0.004	1.000		
Q_N	0.048	0.562	0.474	0.189	0.038	0.682	1.000	
Q_{ortho}	0.019	0.637	0.165	0.062	0.072	0.808	0.821	1.000

In connection with the *ortho*-substituted compounds, regression analysis for all the compounds containing *ortho*-, *meta*-, and *para*-substituents was similarly carried out. Equation 8 was selected as the best equation. The coefficient of the Q_{ortho} term and the constant term in Eq. 8 tended to be similar to those in Eq. 7. Equation 8 showed a significant F value ($F^1_{29\,(\alpha=0.001)}=13.391$), although the correlation coefficient ($r=0.899$) of Eq. 8 was lower than that for only the *ortho*-substituted compounds.

$$\log 1/\mathrm{ID}_{30} = -5.884(\pm 1.087)Q_{ortho} - 1.702(\pm 0.125) \qquad (8)$$

$$(n=31,\ s=0.281,\ r=0.899,\ F^1_{29}=122.473)$$

The Q_{ortho} parameter in Eqs. 7 and 8 might statistically be considered to represent a factor of both the F_{ortho} and I terms in Eqs. 5 and 6, respectively. Thus, the correlations between the Q_{ortho} term in Eqs. 7 and 8, and the F_{ortho} and I terms in Eqs. 5 and 6 were examined by regression analysis to give Eqs. 9 and 10, respectively. As we had expected, both Eqs. 9 and 10 suggested that I was closely related to an electronic factor of the substituent. In addition, it is known[13] that alkoxy and dimethylamino groups have hydrogen bond-forming ability and that the capability of hydrogen bond formation is closely related[14] to electrostatic potential. Thus, the indicator variable I might be considered to reflect the ability to form hydrogen bonds.

$$Q_{ortho} = -0.418(\pm 0.095)F_{ortho} - 0.082(\pm 0.031)I - 0.024(\pm(0.018) \qquad (9)$$

$$(n=19,\ s=0.027,\ r=0.967,\ F^2_{16}=115.371)$$

$$Q_{ortho} = -0.435(\pm 0.049)F_{ortho} - 0.101(\pm 0.016)I - 0.003(\pm 0.007) \qquad (10)$$

$$(n=31,\ s=0.015,\ r=0.989,\ F^2_{28}=601.817)$$

Since the F_{ortho} term has been assumed to represent a proximity effect[9] of the *ortho*-substituent to N(7) in the 4-phenylpiperazine moiety, regression analysis using Q_N as well as Q_{ortho} was also examined. Equations 11 and 12 containing the Q_N term, corresponding to Eqs. 7 and 8, respectively, were derived. The correlation coefficients of Eqs. 11 and 12 were considerably less than those of Eqs. 7 and 8, respectively, although Eqs. 11 and 12 were statistically significant. Both Eqs. 11 and 12 indicated that a decrease in the negative charges on N(7) increased the activity. It was considered that a physicochemical interpretation of Eqs. 11 and 12 was consistent with the results derived from Eqs. 7 and 8, because the decrease in negative charge on N(7) might be due to the electron-withdrawing effect of the *ortho*-substituent.

$$\log 1/\mathrm{ID}_{30} = 64.979(\pm 18.961)Q_N + 8.960(\pm 2.942) \qquad (11)$$

$$(n=19,\ s=0.352,\ r=0.869,\ F^1_{17}=52.284)$$

$$\log 1/\mathrm{ID}_{30} = 63.489(\pm 22.844)Q_{\mathrm{N}} + 8.525(\pm 3.545) \qquad (12)$$

$$(n = 31,\ s = 0.442,\ r = 0.726,\ F^{1}_{29} = 32.304)$$

Although the negative charge of the nitrogen atom may, in general, be considered to interact with an electron-deficient site of a certain molecule or a putative receptor, the role of N(7) in the arylpiperazine moiety may be different from that of a usual nitrogen atom. For example, in the case of the 2-alkoxy compounds, which show high potency, it is possible that the oxygen atom of the alkoxy group at the *ortho*-position rather than N(7) may interact with a putative receptor.

In conclusion, regression analysis using various parameters with respect to the 4-arylpiperazine moiety revealed that F_{ortho} and I of the *ortho*-substituent were determining parameters for the appearance of the activity. In this series, the Q_{ortho} term was found to express a factor of both the F_{ortho} and I terms. Furthermore, it was suggested that the oxygen atom of the alkoxyl group at the *ortho*-position rather than N(7) in the 4-aryl-1-piperazine moiety might enhance the activity by interaction with a putative receptor.

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