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Novel Phenoxyalkylamine Derivatives. III.[1] Quantitative Structure–Activity Relationships of Ca^{2+}-Antagonistic α-Alkyl-α-[(phenoxypropylamino)propyl]-3,4,5-trimethoxybenzeneacetonitrile Derivatives

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The effects of structural modifications of α-alkyl-α-[(phenoxypropylamino)propyl]-3,4,5-trimethoxybenzeneacetonitrile derivatives on their Ca^{2+}-antagonistic activity were analyzed quantitatively by means of the Hansch–Fujita method. The effect of the alkyl substituent at the α-quaternary carbon atom was rationalized by a parabolic function of either steric parameter MR or ΔB_5, where the optimal value is $MR = 1.83$ or $\Delta B_5 = 3.04$. For substituents on the benzene ring (B ring) at the phenoxy moiety, an electron-releasing substituent with about $\pi = 0$ seemed to be most favorable to the activity. The correlations with the local steric and hydrophobic parameters, ΔB_5^{para} and π_{para}, of the *para* substituent of the B ring showed that a substituent with small width and high hydrophobicity is favorable in enhancing activity, leading to the conclusion that hydrogen is the most preferable *para* substituent. The most effective compound (**24**) examined in this study has an *m*-OMe group on the B ring and an iso-Pr group at the quaternary carbon atom. This observation was in agreement with the present analyses.

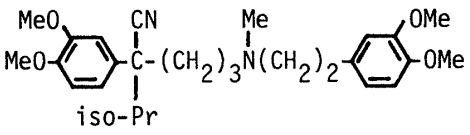
Keywords——quantitative structure–activity relationship; Hansch–Fujita analysis; phenoxyalkylamine; α-alkyl-α-[(phenoxypropylamino)propyl]-3,4,5-trimethoxybenzeneacetonitrile; Ca^{2+}-antagonistic activity

As a part of our studies on cardiovascular agents, we designed and synthesized a number of novel phenoxyalkylamine derivatives (I) as verapamil analogs.[1,2] As expected, they showed various degrees of Ca^{2+}-antagonistic activity and also exhibited α-blocking activity. It was found that the conditions of $m = n = 3$ and $R_1 = Me$ were suitable for Ca^{2+}-antagonistic activity, while those of $m = 3$, $n = 2$ and $R_1 = H$ were favorable for α-blocking activity.[2] Further structural modifications showed that the *N*-Me derivatives where $m = n = 3$, $R_2 = 3,4,5\text{-}(OMe)_3$, $R_3 =$ iso-Pr and R_4 is one of *m*-OMe, $3,5\text{-}(OMe)_2$, $3,5\text{-}Me_2$ or $3,4,5\text{-}(OMe)_3$ exhibited high Ca^{2+}-antagonistic activities.[1]

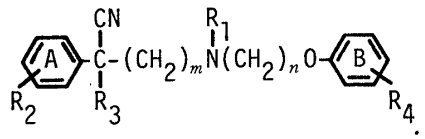
Attempting to understand the physicochemical background of the effects of substituents R_3 and R_4 on the Ca^{2+}-antagonism, we have examined their structure–activity relationships quantitatively for each series of R_3-substituted (II) and R_4-substituted compounds (III) using physicochemical substituent parameters and regression analyses.[3] We report here that the Ca^{2+}-antagonistic potency of these series of compounds is determined by the hydrophobic, electronic and steric effects of substituents R_3 and R_4.

Materials and Methods

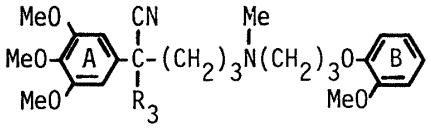
Compounds——All compounds examined in this study are summarized in Tables I and II. The preparation of



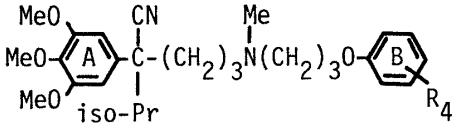
verapamil



I



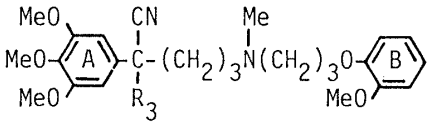
II



III

Chart 1

TABLE I. Ca^{2+}-Antagonistic Activity and Physicochemical Parameters of R_3-Substituted Compounds (II)



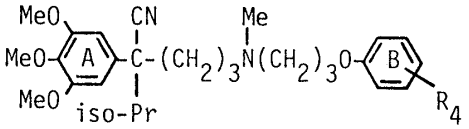
No.	R_3	$\pi^{a)}$	$MR^{b)}$	$\Delta B_5{}^{c)}$	$I^{d)}$	pA_2					
						Obsd.$^{e)}$	Eq. 2		Eq. 5		Eq. 7	
							Calcd.	$(\Delta)^{f)}$	Calcd.	$(\Delta)^{f)}$	Calcd.	$(\Delta)^{f)}$
1	H	0.00	0.103	0.00	0.00	5.56	5.72	(−0.16)	5.83	(−0.27)	5.73	(−0.17)
2	Me	0.54	0.565	1.04	0.00	6.76	6.66	(0.10)	6.61	(0.15)	6.67	(0.09)
3	Et	1.08	1.030	2.17	0.00	7.44	7.32	(0.12)	7.15	(0.29)	7.32	(0.12)
4	*n*-Pr	1.62	1.496	2.49	0.00	7.79	7.68	(0.11)	7.43	(0.36)	7.68	(0.11)
5	iso-Pr	1.49	1.498	2.17	0.00	8.05	7.68	(0.37)	7.43	(0.62)	7.68	(0.37)
6	*n*-Bu	2.16	1.959	3.54	0.00	7.21	7.74	(−0.53)	7.47	(−0.26)	7.74	(−0.53)
7	iso-Bu	2.03	1.959$^{g)}$	3.45	0.00	7.53	7.74	(−0.21)	7.47	(0.06)	7.74	(−0.21)
8	*n*-Hex	3.24	2.890$^{h)}$	4.96	0.00	7.46	6.97	(0.49)	6.79	(0.67)	6.97	(0.49)
9	*n*-Oct	4.32$^{i)}$	3.820$^{h)}$	6.39	0.00	5.06	5.03	(0.03)	5.11	(−0.05)	5.03	(0.03)
10$^{j)}$	*n*-Dodecyl	6.48$^{i)}$	5.680$^{h)}$	9.27	0.00	5.33						
11	Benzyl	2.22	3.001	5.02	0.00	6.48	6.80	(−0.32)	6.64	(−0.16)	6.80	(−0.32)
12	$(CH_2)_2OMe$	−0.04$^{k)}$	1.671$^{l)}$	3.49	1.00	6.80			7.48	(−0.68)	6.77	(0.03)
13	$(CH_2)_2OEt$	0.22$^{k)}$	2.136$^{l)}$	3.81	1.00	6.68			7.42	(−0.74)	6.71	(−0.03)

a) From ref. 4 unless otherwise noted. *b*) Scaled by 0.1 and from ref. 8 unless otherwise noted. *c*) Calculated from the B_5 values cited from a brochure distributed by Dr. A. Verloop. *d*) Indicator variable which takes the value of one for alkoxyalkyl groups and zero for others. *e*) pA_2 values in the KCl depolarized guinea-pig taenia coli. *f*) Δ, the difference between observed and calculated values. *g*) Taken as being equivalent to the value of *n*-Bu. *h*) Estimated from the equation MR(*n*-Hex, *n*-Oct or *n*-Dodecyl) = MR(*n*-Pent) + 4.65 × (*n* − 5). *n* is the number of carbon atoms. *i*) Estimated from the equation π(*n*-Oct or *n*-Dodecyl) = π(*n*-Hex) + 0.54 × (*n* − 6). *n* is the number of carbon atoms. *j*) Omitted from the calculation. *k*) Estimated from the equation $\pi[(CH_2)_2OMe \text{ or } (CH_2)_2OEt] = \pi(n\text{-Bu or } n\text{-Pent}) - f(-CH_2-) + f(-O-)$. $f(-CH_2-) = 0.66$ and $f(-O-) = -1.54$ (**12**), −1.82 (**13**) are hydrophobic fragment constants of $-CH_2-$ and $-O-$, respectively, taken from ref. 10. *l*) Estimated from the equation $MR[(CH_2)_2OMe \text{ or } (CH_2)_2OEt] = MR\ (CH_2OMe) + 4.65 \times (n-2)$. *n* is the number of carbon atoms.

most compounds was previously described.[1,2] The others (**11**—**13**) were similarly prepared. The structures were confirmed by mass (MS), nuclear magnetic resonance (NMR) and infrared (IR) spectroscopic studies and by elemental analyses. The melting point (mp) of **11** as the hydrochloride was 160.5—162.0 °C and the refractive indexes (n_D^{25}) of **12** and **13** were 1.532 and 1.534, respectively.

Ca^{2+}-Antagonistic Activity——Pharmacological procedures using KCl-depolarized guinea-pig taenia coli were

TABLE II. Ca^{2+}-Antagonistic Activity and Physicochemical Parameters of R_4-Substituted Compounds (III)



No.	R_4	$\pi^{a)}$	$\sigma^{0\,b)}$	$F_{ortho}{}^{c)}$	$\Delta B_5{}^{d)}$ *para*	$\pi^{a)}$ *para*	pA_2 Obsd.$^{e)}$	pA_2 Eq. 9 Calcd. (Δ)$^{f)}$	pA_2 Eq. 14 Calcd. (Δ)$^{f)}$
14	H	0.00	0.00	0.00	0.00	0.00	8.19	8.04 (0.15)	8.50 (−0.31)
15	*o*-Me	0.52	−0.12	−0.04	0.00	0.00	8.31	7.95 (0.36)	8.50 (−0.19)
16	*o*-*n*-Pr	1.43	−0.13$^{g)}$	−0.06	0.00	0.00	7.79	7.35 (0.44)	7.83 (−0.04)
5	*o*-OMe	−0.08	−0.16	0.26	0.00	0.00	8.05	8.04 (0.01)	8.16 (−0.11)
17	*o*-OEt	0.30	−0.14	0.22	0.00	0.00	8.10	8.01 (0.09)	8.18 (−0.08)
18	*o*-F	0.21	0.17	0.43	0.00	0.00	7.95	8.03 (−0.08)	7.78 (0.17)
19	*o*-Cl	0.77	0.27	0.41	0.00	0.00	7.69	7.84 (−0.15)	7.56 (0.13)
20	*o*-NO_2	0.03	0.82	0.67	0.00	0.00	7.26	8.04 (−0.78)	7.20 (0.06)
21	*o*-NH_2	−1.35	−0.38	0.02	0.00	0.00	8.15	7.42 (0.73)	7.89 (0.26)
22	*m*-Me	0.54	−0.07	0.00	0.00	0.00	8.48	7.94 (0.54)	8.41 (0.07)
23	*m*-*tert*-Bu	1.85	−0.07	0.00	0.00	0.00	6.88	6.88 (0.00)	7.17 (−0.29)
24	*m*-OMe	0.03	0.06	0.00	0.00	0.00	9.00	8.04 (0.96)	8.48 (0.52)
25	*m*-F	0.26	0.35	0.00	0.00	0.00	8.29	8.02 (0.27)	8.35 (−0.06)
26	*m*-Cl	0.79	0.37	0.00	0.00	0.00	8.36	7.83 (0.53)	8.12 (0.24)
27	*m*-NO_2	−0.03	0.70	0.00	0.00	0.00	8.17	8.04 (0.13)	8.25 (−0.08)
28	*m*-NH_2	−1.14	−0.14	0.00	0.00	0.00	8.13	7.60 (0.53)	8.04 (0.09)
29	*m*-CF_3	0.98	0.47	0.00	0.00	0.00	8.06	7.71 (0.35)	7.96 (0.10)
30	*m*-CH_2OH	−0.91	0.00$^{g)}$	0.00	0.00	0.00	8.11	7.76 (0.35)	8.17 (−0.06)
31	*p*-Me	0.52	−0.12	0.00	1.04	0.52	7.61	7.95 (−0.34)	8.05 (−0.44)
32	*p*-*n*-Pr	1.43	−0.13$^{g)}$	0.00	2.49	1.43	6.88	7.35 (−0.47)	6.90 (−0.02)
33	*p*-*tert*-Bu	1.82	−0.17	0.00	2.17	1.82	6.88	6.91 (−0.03)	6.79 (0.09)
34	*p*-OMe	−0.08	−0.16	0.00	2.07	−0.08	7.64	8.04 (−0.40)	7.27 (0.37)
35	*p*-F	0.21	0.17	0.00	0.35	0.21	8.02	8.03 (−0.01)	8.31 (−0.29)
36	*p*-Cl	0.77	0.27	0.00	0.80	0.77	7.73	7.84 (−0.11)	8.04 (−0.31)
37	*p*-NO_2	0.03	0.82	0.00	1.44	0.03	7.39	8.04 (−0.65)	7.36 (0.03)
38	*p*-NH_2	−1.35	−0.38	0.00	0.97	−1.35	6.50	7.42 (−0.92)	6.71 (−0.21)
39	*p*-CN	−0.30	0.69	0.00	0.60	−0.30	7.64	8.01 (−0.37)	7.72 (−0.08)
40	*p*-CH_2OH	−1.00	0.05$^{g)}$	0.00	1.70	−1.00	6.56	7.70 (−1.14)	6.60 (−0.04)
41	2,3-$(OMe)_2$	−0.05$^{h)}$	−0.10$^{h)}$	0.26	0.00	0.00	8.23		8.14 (0.09)
42	2,4-Me_2	1.04$^{h)}$	−0.24$^{h)}$	−0.04	1.04	0.52	7.97		7.83 (0.14)
43	2,5-Me_2	1.06$^{h)}$	−0.19$^{h)}$	−0.04	0.00	0.00	8.68		8.18 (0.50)
44	2,6-$(OMe)_2$	−0.16$^{h)}$	−0.32$^{h)}$	0.52$^{h)}$	0.00	0.00	7.57		7.82 (−0.25)
45$^{i)}$	3,5-$(OMe)_2$	0.06$^{h)}$	0.12$^{h)}$	0.00	0.00	0.00	10.20$^{j)}$		8.46
46$^{i)}$	3,5-Me_2	1.08$^{h)}$	−0.14$^{h)}$	0.00	0.00	0.00	9.53$^{j)}$		8.09
47$^{i)}$	3,4,5-$(OMe)_3$	−0.02$^{h)}$	−0.04$^{h)}$	0.00	2.07	−0.08	9.32$^{j)}$		7.24

a) Estimated from Eq. 1 cited from ref. 5. *b*) Taken from ref. 11 unless otherwise noted. *c*) Taken from ref. 7. *d*) Calculated from the B_5 values cited from a brochure distributed by Dr. A. Verloop. *e*) pA_2 values in the KCl depolarized guinea-pig taenia coli unless otherwise noted. *f*) Δ, the difference between observed and calculated values. *g*) Estimated from the values for related substituents. *h*) Values are the sum of the values for substituents. *i*) Omitted from the calculation. *j*) pA_2 values in the KCl depolarized rabbit thoracic aorta.

described previously.[2] Because the 3,5-$(OMe)_2$ (**45**) 3,5-Me_2 (**46**) and 3,4,5-$(OMe)_3$ (**47**) derivatives of III showed a non-competitive inhibition of Ca^{2+} influx in this test system, their activities in terms of pA_2 were measured with rabbit thoracic aorta, and the data were not included in the analysis.

Substituent Parameters——As the hydrophobic parameter for R_3, the π values[4] for aliphatic groups were used. For R_4, the π values for substituted anisoles estimated from Eq. 1[5] were used.

$$\pi(\text{X/subst. anisoles}) = 0.924\pi_x + 0.272\sigma_x^0 - 0.193\rho_x(para) + 0.037 \quad (1)$$

In this equation, π_x is the π value of the substituent X in monosubstituted benzenes, and σ_x^0 is a "σ" value applicable to cases where the reaction center is insulated from direct conjugation with the substituent X.[6] The σ_x^0 term takes care of the electronic effect of substituent X on solvation with 1-octanol relative to that on hydration at the alkoxy oxygen. ρ_x is the susceptibility constant of substituent X for the relative solvation to the electronic effect of the OMe group. The ρ_x term represents a backward electronic effect of alkoxy groups on the variable substituent X. For non-hydrogen bonding substituents, $\rho_x = 0$. This term is applicable only when the substituent is at the *para* position. The π value of the *ortho* substituent was approximated by that of the corresponding *para* substituent.

As the parameter of the electronic effect of R_4 on the activity, the σ^0 value was used. For *ortho* substituents, $\sigma^0(para)$ value and the Swain–Lupton–Hansch F[7] value were used for the "ordinary" electronic effect and the "proximity" electronic factor, respectively.

As the steric substituent parameters, MR[8] and ΔB_5 were used. MR was multiplied by 0.1 to place it on a scale similar to those of the other parameters. B_5[9] is one of the STERIMOL parameters for each substituent and represents the maximum width (in Å) from the axis connecting the α atom of the substituent to the rest of the molecule. ΔB_5 is the value relative to that of H.

For R_4 polysubstituted derivatives, the $\sum\sigma^0$ and $\sum\pi$ values summed up for component substituents were used along with position-specific parameters.

Results and Discussion

The Effect of Substituent R_3

The activities of the compounds where R_3 is either hydrogen (**1**) or an alkyl group (**2**—**9**, **11**) listed in Table I were analyzed. The result indicated that the activity expressed in terms of pA_2 was parabolically related to either one of the steric parameters MR and ΔB_5 much better than to the hydrophobic parameter π, as shown in Eqs. 2—4 in Table III. In these equations compound **10** was omitted from the calculation because of its pronounced deviation from the correlations. The reason is not clear, but an extra binding interaction with another receptor site may arise with increasing length of the R_3 chain. The good correlation with not only MR but also ΔB_5 is due to a high colinearity between these steric parameters.

The analyses including additional compounds with alkoxyalkyl groups (**12**, **13**) were also performed by using the same parameters as above, giving poorer correlations with MR and ΔB_5 shown by Eqs. 5 and 6. By a closer examination of the differences between observed and calculated activity values, the activity of the alkoxyalkyl derivatives was found to deviate to

TABLE III. Correlation Equations for the Ca^{2+}-Antagonistic Activity of R_3-Substituted Compounds (II)

Eq. No.	MR^2	MR	$\Delta B_5{}^2$	ΔB_5	π^2	π	I	Const.	$n^{a)}$	$r^{b)}$	$s^{c)}$	$F^{d)}$
2	−0.68 (0.21)[e)]	2.49 (0.85)						5.47 (0.75)	10	0.95	0.35	31.17
3			−0.23 (0.08)	1.40 (0.51)				5.61 (0.76)	10	0.94	0.37	27.22
4					−0.45 (0.24)	1.76 (1.08)		5.82 (1.07)	10	0.86	0.56	10.32
5	−0.58 (0.27)	2.08 (1.08)						5.62 (1.00)	12	0.86	0.50	12.90
6			−0.20 (0.09)	1.18 (0.60)				5.76 (0.94)	12	0.87	0.49	13.65
7	−0.68 (0.19)	2.49 (0.78)					−0.97 (0.63)	5.48 (0.68)	12	0.95	0.33	23.89
8			−0.23 (0.07)	1.40 (0.47)			−0.89 (0.67)	5.61 (0.69)	12	0.94	0.35	20.92

a) Number of compounds used for correlations. *b*) Correlation coefficient. *c*) Standard deviation. *d*) Observed F value. Theoretical F values are: $F_{2,7;\alpha=0.05} = 4.74$ for Eqs. 2—4, $F_{2,9;\alpha=0.05} = 4.26$ for Eqs. 5, 6 and $F_{3,8;\alpha=0.05} = 4.07$ for 7, 8. *e*) Figures in parentheses are 95% confidence intervals.

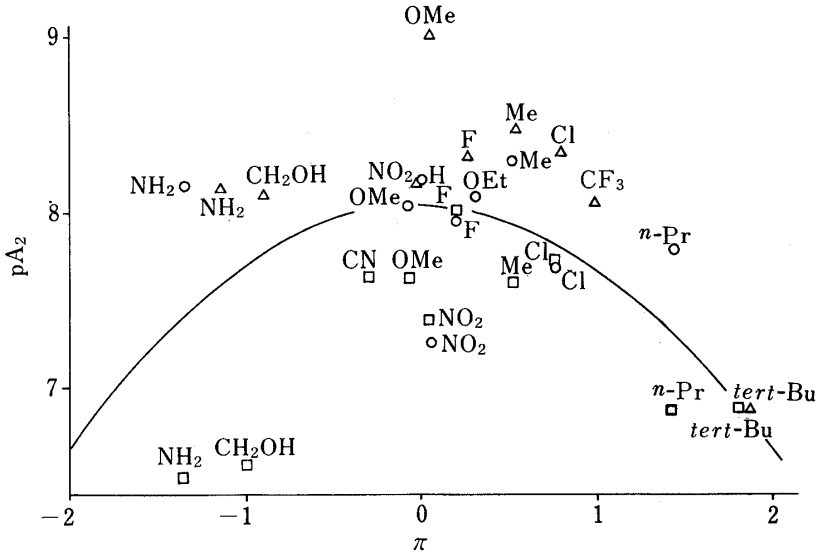


Fig. 1. Plots of pA_2 *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative.

the negative side from the calculated value much more than the others. By considering an indicator variable I which takes the value of one for alkoxyalkyl derivatives, Eqs. 7 and 8 were derived. With π^2, π and the I variable, the correlation was not reasonable (data not shown).

The result indicates that the steric size of the substituents R_3, rather than the hydrophobicity seems to contribute to the activity. The lone pair electrons may play a role in the activity of alkoxyalkyl derivatives.

The Effect of Substituent R_4

The pA_2 values of unsubstituted (**14**) and monosubstituted compounds (**5**, **15**—**40**) were analyzed using single parameters. The results indicated that the activity was correlated best by a quadratic equation of hydrophobic parameter π as shown in Eq. 9 in Table IV, although the quality of correlation was not satisfactory. The situation is illustrated in Fig. 1. In elaborating the correlation, attention was paid to the fact that the activities of *para*-substituted derivatives in most cases fall below the parabola as compared with those of the corresponding *meta*-substituted isomers, irrespective of the hydrophobicity and/or electron-withdrawing property of the substituents. This suggests that a steric effect specific to *para* substituents is unfavorable to the activity. It was also noticed that electron-withdrawing substituents such as NO_2 and halogen at the *ortho* position lower the activity to a greater extent than at the *meta* or *para* position. This is probably due to a proximity electron-withdrawing effect detrimental to the activity. Participation of other position-specific effects was anticipated. For instance, hydrophilic substituents such as NH_2 and CH_2OH at the *para* position are undoubtedly more unfavorable to the activity than hydrophobic substituents such as *n*-Pr and *tert*-Bu. Various combinations of electronic, steric and hydrophobic parameters at each substituent position were therefore examined.

Since *meta*-substituted derivatives showed activity higher than the parabola, being approximately aligned along another parabola, and the scatters seemed to be inversely related with the electron-withdrawing property of substituents, participation of "ordinary" electronic effects of substituents at *ortho*, *meta* and *para* positions in addition to the quadratic correlation with π was examined as shown in Fig. 2. The coefficient, 0.38, of the σ^0 term added to pA_2 on the ordinate was selected so that the plot for the *meta* derivatives was at least aligned as well as possible, as shown by the solid line. The plot for *ortho*- and *para*-substituted

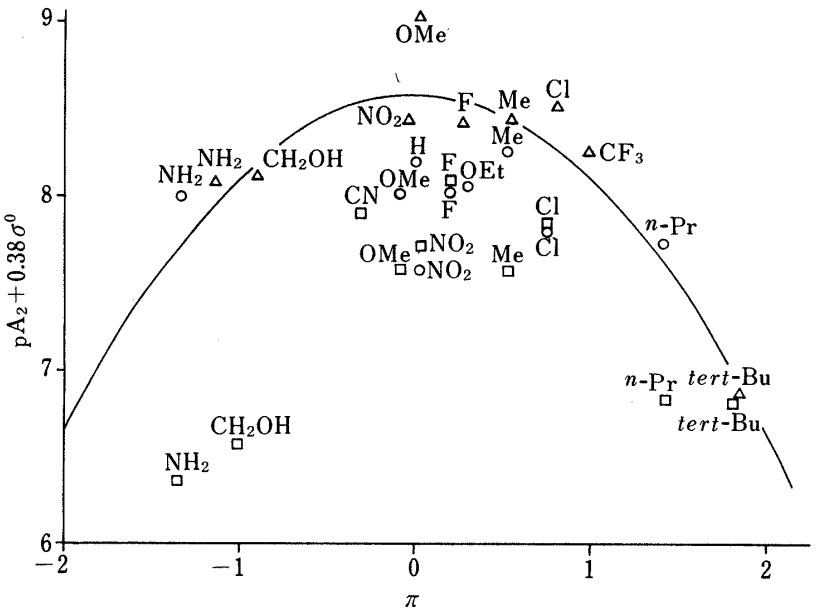


Fig. 2. Plots of Sum of pA_2 and $0.38\sigma^0$ *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative.

TABLE IV. Developments of the Correlation Equations for the Ca^{2+}-Antagonistic Activity of R_4-Substituted Compounds (III)

Eq. No.	$\pi^{2\,a)}$	ΔB_5^{para}	π_{para}	F_{ortho}	σ^0	Const.	$n^{b)}$	$r^{c)}$	$s^{d)}$	$F^{e)}$
9	−0.34					8.04	28	0.56	0.51	11.74
	(0.20)$^{f)}$					(0.25)				
10	−0.24	−0.43				8.17	28	0.77	0.40	17.90
	(0.17)	(0.21)				(0.21)				
11	−0.29	−0.51	0.39			8.22	28	0.84	0.35	19.26
	(0.15)	(0.19)	(0.26)			(0.19)				
12	−0.35	−0.58	0.43	−1.40		8.39	28	0.92	0.26	31.14
	(0.11)	(0.15)	(0.20)	(0.64)		(0.16)				
13	−0.40	−0.58	0.45	−1.28	−0.35	8.46	28	0.93	0.24	30.54
	(0.11)	(0.14)	(0.18)	(0.60)	(0.32)	(0.16)				
14	−0.39	−0.60	0.46	−1.50	−0.35	8.50	32	0.92	0.25	29.68
	(0.12)	(0.14)	(0.19)	(0.55)	(0.30)	(0.16)				

a) In Eqs. 9—14 the linear term of π is insignificant. *b*) Number of compounds used for correlations. *c*) Correlation coefficient. *d*) Standard deviation. *e*) Observed F value. Theoretical F values are: $F_{1,26;\alpha=0.05}=4.23$ for Eq. 9: $F_{2,25;\alpha=0.05}=3.39$ for Eq. 10, $F_{3,24;\alpha=0.05}=3.01$ for Eq. 11, $F_{4,23;\alpha=0.05}=2.80$ for Eq. 12, $F_{5,22;\alpha=0.05}=2.66$ for Eq. 13 and $F_{5,26;\alpha=0.05}=2.59$ for Eq. 14. *f*) Figures in parentheses are 95% confidence intervals.

derivatives in Fig. 2 generally deviated downward.

By considering the proximity electronic F term for the *ortho* substituents and the position-specific hydrophobic π and steric ΔB_5 terms for the *para* substituents, Eq. 13 was finally derived. The stepwise development of Eq. 13 justified statistically for twenty-eight monosubstituted derivatives is shown in Table IV. The addition of the σ^0 term next to the π^2 term was statistically insignificant, as reflected in the rather inadequate overall correlation in Fig. 2.

In Eq. 14 and Fig. 3, four disubstituted compounds were also included. The quality of the correlation of Eq. 14 was satisfactory. Equations 13 and 14 were practically identical. The fact that the behavior of disubstituted compounds conformed to that of the monosubstituted

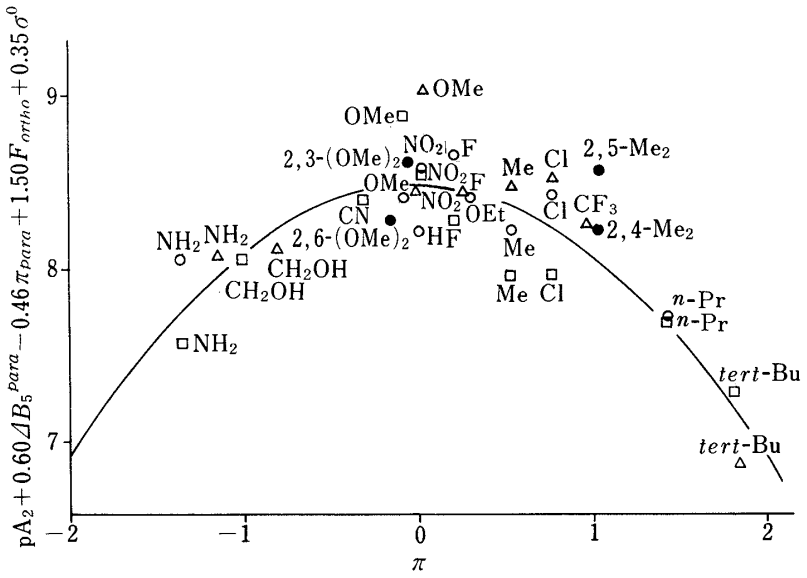


Fig. 3. Plots of Sum of pA_2, $0.60\Delta B_5^{para}$, $-0.46\pi_{para}$, $1.50F_{ortho}$ and $0.35\sigma^0$ *versus* Hydrophobic Parameter π

○, *ortho*-substituted derivative; △, *meta*-substituted derivative; □, *para*-substituted derivative; ●, disubstituted derivative.

TABLE V. Correlation Coefficient Matrix for the Parameters of Eq. 14

	π^2	σ^0	F_{ortho}	ΔB_5^{para}	π_{para}
π^2	1.00				
σ^0	0.40	1.00			
F_{ortho}	0.34	0.16	1.00		
ΔB_5^{para}	0.31	0.10	0.29	1.00	
π_{para}	0.29	0.06	0.07	0.37	1.00

derivatives indicates that the effect of substituents is almost additive.

The hydrophobicity of substituents seems to exert dual effects. One is the effect on the transport process expressed by the π (or $\sum\pi$) value, independent of position, corresponding to the toal hydrophobicity of the molecule. The other is an additional effect only for the *para* substituents perhaps participating in the position-specific hydrophobic interaction at the receptor site.

As summarized in Table V, the intercorrelation between independent variables for thirty-two compounds was shown to be insignificant.

The above result shows that electron-donating substituents whose π values are close to zero are favorable to the activity. It also indicates that a small and yet hydrophobic *para* substituent is needed for high activity. Since these two requirements for the *para* substituent are difficult to satisfy simultaneously, hydrogen was chosen as the most suitable *para* substituent.

The most favorable substitution patterns expected from Eq. 14 are those with lower alkoxy groups at *ortho* and/or *meta* positions, as was experimentally observed with the *m*-OMe derivative (**24**). The biological data of the 3,5-$(OMe)_2$ (**45**) and 3,4,5-$(OMe)_3$ (**47**) derivatives cannot be compared directly with those of the other compounds, because of the difference in the test systems. However, very high activities of **45** and **47** are not inconsistent with the present analyses.

In summary, the present quantitative analyses of the effects of substituents at the quaternary carbon atom and the B ring are considered to give reliable correlation equations which allow us to identify the most effective structural features for the Ca^{2+}-antagonistic activity. Further studies of substituent effects at other positions are in progress.

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