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Benzylpiperazine Derivatives. V.¹⁾ Quantitative Structure–Activity Relationships of 1-Benzyl-4-diphenylmethylpiperazine Derivatives for Cerebral Vasodilating Activity

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The quantitative structure–activity relationships of 1-benzyl-4-diphenylmethylpiperazines for cerebral vasodilating activity and duration of action were examined. The analyses indicate that increase of the electron density on the benzylic nitrogen atom and the introduction of sterically small substituents at the *para* position of the diphenylmethyl moiety bring about strong interactions of the molecule with the active site and result in high potency as well as prolonged action.

Keywords—quantitative structure–activity relationship; regression analysis; adaptive least-squares calculation; benzylpiperazine; cerebral vasodilator; action duration

In the course of our search for novel cerebral vasodilators, we have synthesized a series of 1-benzyl-4-diphenylmethylpiperazine derivatives (I) and tested them for vertebral blood flow-increasing activity in anesthetized dogs.¹⁾ From the standpoint of stronger activity as well as longer-lasting effect than papaverine, 1-[bis(4-fluorophenyl)methyl]-4-(2,3,4-trimethoxybenzyl)piperazine dihydrochloride (**16**: KB-2796) was selected for clinical evaluation. A consideration of structure–activity relationships suggested that bulky substituents on the diphenylmethyl moiety decrease the activity. Other factors are also presumed to influence the potency as well as the duration of action. These results prompted us to attempt a quantitative structure–activity relationship analysis with the aim of providing a basis for the design of better cerebral vasodilators.

Chart 1

Method

Cerebral Vasodilating Activity—The cerebral vasodilating activities (CVA) of the compounds reported previously¹⁾ were expressed in terms of the ratio of the maximum change of blood flow in vertebral arteries after intravenous administration of the test compound at 1 mg/kg to that in the case of papaverine at the same dose. For either the extrathermodynamic or the *de novo* method, the potency of compounds should be properly expressed on a molar basis. Therefore, the relative potencies (log RP) of the compounds were estimated as reported previously.²⁾ The dose–response curves of two potent derivatives (**10** and **16**) had been determined. The log(dose)–response plots of these analogs gave parallel lines.³⁾ Therefore the dose–response curves for a series of analogs were assumed to be parallel lines having a slope estimated as the mean of those for the two compounds (= 1.36). This assumption may be expressed in equation form:

$$\log(\text{dose}) = a_x + b \text{ response}_x \quad (1)$$

TABLE I. Cerebral Vasodilating Activities and Parameters of 1-Benzyl-4-diphenylmethylpiperazines Used for Derivation of Eqs. 6—19

Compd. No.	X	Y	Z	$\Sigma\sigma^a)$	$MR^b)$	log RP Duration	
						Obs.	Obs.
1	4-OAc	H	H	(0.31)	1.03	6.54	1
2	4-Cl	H	H	(0.23)	1.03	6.43	0
3	4-F	H	H	(0.06)	1.03	6.49	0
4	H	H	H	0	1.03	6.48	0
5	4-NHAc	H	H	0	1.03	6.53	0
6	3,4,5-(OMe) ₃	H	H	-0.03	1.03	6.57	0
7	3,4-(OMe) ₂	H	H	-0.15	1.03	6.52	0
8	4-Me	H	H	-0.17	1.03	6.79	1
9	3,4-OCH ₂ O	H	H	-0.32	1.03	6.67	0
10	4-OH	H	H	-0.37	1.03	7.01	0
11	2,3,4-(OMe) ₃	H	H	-0.42	1.03	7.32	0
12	2,4-(OMe) ₂	H	H	-0.54	1.03	7.06	1
13	2,4,6-(OMe) ₃	H	H	-0.81	1.03	7.67	0 ^{c)}
14	4-NH ₂	H	H	-0.66	1.03	6.79 ^{d)}	0
15	4-NMe ₂	H	H	-0.83	1.03	6.64 ^{d)}	1
16	2,3,4-(OMe) ₃	F	F	-0.42	0.92	7.41	1
17	2,3,4-(OMe) ₃	Me	Me	-0.42	5.65	7.17	0
18	2,3,4-(OMe) ₃	Cl	Cl	-0.42	6.03	6.66	0
19	2,3,4-(OMe) ₃	OMe	OMe	-0.42	7.87	6.31	0
20	2,3,4-(OMe) ₃	F	H	-0.42	1.03	7.17	1
21	2,3,4-(OMe) ₃	Me	H	-0.42	5.65	6.41	0
22	2,3,4-(OMe) ₃	Cl	H	-0.42	6.03	6.73	1
23	2,3,4-(OMe) ₃	OMe	H	-0.42	7.87	6.13	0
24	3,4,5-(OMe) ₃	F	F	-0.03	0.92	6.56	0
25	2,4,6-(OMe) ₃	F	F	-0.81	0.92	7.18	0 ^{c)}
26	2,4-(OMe) ₂	F	F	-0.54	0.92	7.18	1
27	3,4-OCH ₂ O	F	F	-0.32	0.92	6.66	0
28	4-OH	F	F	-0.37	0.92	6.79	1
29	H	F	F	0	0.92	6.46	0
30	4-Me	F	F	-0.17	0.92	6.50	1
31	4-NMe ₂	F	F	-0.83	0.92	7.31	1
32	4-OAc	F	F	(0.31)	0.92	6.60	0
33	2,4,6-(OMe) ₃	F	H	-0.81	1.03	7.00	0 ^{c)}
34	2,4-(OMe) ₂	F	H	-0.54	1.03	7.04	1
35	3,4,5-(OMe) ₃	F	H	-0.03	1.03	6.61	0
36	3,4-OCH ₂ O	F	H	-0.32	1.03	6.47	0
37	4-NMe ₂	F	H	-0.83	1.03	7.13	1

a) In Eqs. 13—19 $\Sigma\sigma=0$ was used when $\Sigma\sigma>0$. b) MR stands for the larger value of MR_Y and MR_Z . c) Not included in the calculation. d) Not included in the correlation.

in which x refers to the analog x , and b is the slope of the log(dose)–response curve ($=1.36$). The value of interest for the structure–activity analysis is the negative logarithm of the dose required to produce a given response. From Eq. 1 it may be seen that at constant response and constant slope b , the logarithm of the dose of x is proportional to the value of $-a_x$; i.e., $-a_x$ is the relative potency. The relative potencies of the compounds were calculated by using Eq. 2.

$$\log RP = -\log(\text{dose}) + 1.36CVA \quad (2)$$

Parameters—The classical physicochemical parameters of this type of analysis have been used, such as the π of Hansch for lipophilic effects, the MR for steric ones and the σ of Hammett for electronic effects. The values are taken from the literature.⁴⁾

Regression Analysis—A regression analysis was carried out to investigate the relationships between the various parameters of the substituents (X, Y and Z) in 1-benzyl-4-diphenylmethylpiperazines and the cerebral vasodilating activities.

Adaptive Least-Squares (ALS) Calculation—The ALS method of Moriguchi *et al.*⁵⁾ (ALS 81) was applied to investigate the relationships between the various parameters of the substituents (X, Y and Z) in 1-benzyl-4-diphenylmethylpiperazines and the duration of action.

The ALS method, which is a nonparametric pattern classification method, has been devised to categorize multidimensional structural patterns into multiple ordered classes by means of a single equation. The equation (discriminant function) is formulated by a feedback procedure in a linear form, as in Eq. 3.

$$Y = w_0 + w_1x_1 + w_2x_2 + \cdots + w_px_p \quad (3)$$

where Y is the discriminant score for the classification, x_k ($k = 1, 2, \dots, p$) is the k th descriptor for the structure, and w_k ($k = 0, 1, 2, \dots, p$) is the weight coefficient. The value of w_k is determined by the least-squares adaptation using the starting score, a_j ($j = 1, 2, \dots, m$ in the m -group case) and the correction term, $C_i(t)$, for misclassified substance i at the t -th iteration, which is given by Eq. 4

$$C_i(t) = 0.1/(\delta_i(t) + 0.45)^2 + 0.1 \quad (4)$$

where δ is the deviation defined by Eq. 5.

$$\delta_i(t) = |Y_i(t) - b_k| \quad (5)$$

In Eq. 5, b_k is the cutting point (nearer to $Y_i(t)$). With the data set of 34 compounds in this study, the starting score and the cutting point are as follows, $a_1 = -0.765$, $a_2 = 1.235$, $b_1 = 0.235$. The adaptive iteration was performed 10 times, and the best discriminant function was selected. As the criteria of the best discrimination, the Spearman rank correlation coefficient with many ties, R_s , and the ε value⁵⁾ were used.

Results and Discussion

Initially, the relationships between structure and cerebral vasodilating activity (log RP) were examined by regression analysis.

With compounds that have no substituents on the diphenylmethyl moiety (**1**—**15**), $\sum\sigma$ seemed to correlate with the potency, when two analogs (**14** and **15**) were excluded (Fig. 1). This relation can be formulated as Eq. 6.

$$\log RP = -1.083(\pm 0.370)\sum\sigma + 6.591 \quad (6)$$

$$n = 13, \quad r = 0.889, \quad s = 0.184, \quad F = 41.42$$

In Eq. 6 the number in parentheses is the 95% confidence interval, n is the number of data points used in deriving the equation, r is the correlation coefficient, s is the standard deviation and F is the F -ratio between the variance of calculated and observed activities.

Figure 1 shows that the potency seems to be constant in the range of $\sum\sigma > 0$, so these compounds were re-analyzed using $\sum\sigma = 0$ when $\sum\sigma > 0$ to give Eq. 7.

$$\log RP = -1.388(\pm 0.340)\sum\sigma + 6.475 \quad (7)$$

$$n = 13, \quad r = 0.938, \quad s = 0.139, \quad F = 80.73$$

Next, 1-[bis(fluorophenyl)methyl]piperazine derivatives (**16**, **24**—**32**) were considered, and Eq. 8 was obtained as the best equation.

$$\log RP = -0.806(\pm 0.502)\sum\sigma + 6.609 \quad (8)$$

$$n = 10, \quad r = 0.794, \quad s = 0.235, \quad F = 13.71$$

Re-analysis of these compounds using $\sum\sigma = 0$ when $\sum\sigma > 0$ gave Eq. 9.

Fig. 1

$$\log RP = -0.994(\pm 0.517)\Sigma\sigma + 6.518 \quad (9)$$

$$n=10, \quad r=0.842, \quad s=0.208, \quad F=19.63$$

Addition of a steric factor and/or lipophilic factor to Eqs. 6—9 did not give a significantly better results. These results suggest that the electron-donating effect of the substituent on the benzyl moiety is predominantly important for high activity.

In terms of the polar substituent constant of Taft (σ^*),⁶⁾ the electron withdrawing power is the following order: diphenylmethyl ($\sigma^*=0.405$) > benzyl ($\sigma^*=0.215$) > methyl ($\sigma^*=0$). The benzylic nitrogen atom is more basic in our compounds and the electron-donating group on the benzyl moiety increases the basicity. The second dissociation constants (pK_{a2}) of our molecules are expected to be slightly lower than that of 1-diphenylmethyl-4-methylpiperazine ($pK_{a1}=2.5$ and $pK_{a2}=7.9$)⁷⁾ owing to the electron-withdrawing groups on the benzyl moiety. In such a case, there would be no diprotonated species and little of the monoprotonated species in blood, which is controlled to nearly neutral pH. The reason why Eqs. 7 and 9 gave better results than Eqs. 6 and 8, respectively, may be as follows: the monoprotonated species, which increases in amount with increase of basicity of the benzylic nitrogen atom, is important for high activity, and the mechanism of action may be slightly different between the monoprotonated species and the free base.

A bulky substituent on the diphenylmethyl moiety seems to decrease the potencies of the compounds in which X=2,3,4-tri-OMe (11, 16—23). This tendency can be formulated in Eq. 10.

$$\log RP = -0.143(\pm 0.070)MR + 7.480 \quad (10)$$

$$n=9, \quad r=0.876, \quad s=0.243, \quad F=22.99$$

In Eq. 10, MR stands for the larger value between MR_Y and MR_Z . Analyses using Verloop's steric parameters (L , B_4)⁸⁾ gave similar results (Eqs. 11 and 12).

$$\log RP = -0.631(\pm 0.326)B_4 + 8.010 \quad (11)$$

$$n=9, \quad r=0.864, \quad s=0.253, \quad F=20.78$$

$$\log RP = -0.618(\pm 0.338)L + 8.762 \quad (12)$$

$$n=9, \quad r=0.853, \quad s=0.263, \quad F=18.72$$

Addition of an electronic factor and/or a lipophilic factor to Eqs. 10—12 did not give a significantly better result. Next, 35 compounds were subjected to the analysis (14 and 15 were excluded again) and Eqs. 13—15 were obtained.

$$\log RP = -0.996(\pm 0.285)\Sigma\sigma - 0.073(\pm 0.036)MR + 6.593 \quad (13)$$

$$n=35, \quad r=0.809, \quad s=0.220, \quad F=30.27$$

$$\log RP = -1.064(\pm 0.272)\Sigma\sigma - 0.371(\pm 0.157)B_4 + 6.939 \quad (14)$$

$$n=35, \quad r=0.831, \quad s=0.208, \quad F=35.91$$

TABLE II. Results of the Regression Analysis and the ALS Recognition and Prediction

Compd. No.	Potency log RP		Duration Recognition				Prediction		
	Obs.	Eq. 13	Obs.	Eq. 17	Eq. 18	Eq. 19	Eq. 17	Eq. 18	Eq. 19
1	6.54	6.52	1	0	0	0	0	0	0
2	6.43	6.52	0	0	0	0	0	0	0
3	6.49	6.52	0	0	0	0	0	0	0
4	6.48	6.52	0	0	0	0	0	0	0
5	6.53	6.52	0	0	0	0	0	0	0
6	6.57	6.55	0	0	0	0	0	0	0
7	6.52	6.67	0	0	0	0	0	0	0
8	6.79	6.69	1	0	0	0	0	0	0
9	6.67	6.84	0	0	0	0	0	1	0
10	7.01	6.89	0	0	1	0	1	1	1
11	7.32	6.94	0	1	1	1	1	1	1
12	7.06	7.06	1	1	1	1	1	1	1
13	7.67	7.33	0 ^{a)}	—	—	—	—	—	—
14	6.79 ^{b)}	—	0	1	1	1	1	1	1
15	6.64 ^{b)}	—	1	1	1	1	1	1	1
16	7.41	6.95	1	1	1	1	1	1	1
17	7.17	6.60	0	0	0	0	0	0	0
18	6.66	6.57	0	0	0	0	0	0	0
19	6.31	6.44	0	0	0	0	0	0	0
20	7.17	6.94	1	1	1	1	1	1	1
21	6.41	6.60	0	0	0	0	0	0	0
22	6.73	6.57	1	0	0	0	0	0	0
23	6.13	6.44	0	0	0	0	0	0	0
24	6.56	6.56	0	0	0	0	0	0	0
25	7.18	7.33	0 ^{a)}	—	—	—	—	—	—
26	7.18	7.07	1	1	1	1	1	1	1
27	6.66	6.85	0	0	0	0	0	0	0
28	6.79	6.90	1	1	0	0	1	1	1
29	6.46	6.53	0	0	0	0	0	0	0
30	6.50	6.70	1	0	0	0	0	0	0
31	7.31	7.35	1	1	1	1	1	1	1
32	6.60	6.53	0	0	0	0	0	0	0
33	7.00	7.33	0 ^{a)}	—	—	—	—	—	—
34	7.04	7.06	1	1	1	1	1	1	1
35	6.61	6.55	0	0	0	0	0	0	0
36	6.47	6.84	0	0	1	0	0	0	0
37	7.13	7.35	1	1	1	1	1	1	1

a) Not included in the calculation. b) Not included in the correlation.

TABLE III. Correlation Matrix of Variables Used in Eqs. 13—15

	$\Sigma\sigma$	MR	B_4	L
$\Sigma\sigma$	1.000			
MR	-0.138	1.000		
B_4	-0.274	0.834	1.000	
L	-0.226	0.898	0.944	1.000

$$\log RP = -1.087(\pm 0.286)\Sigma\sigma - 0.315(\pm 0.146)L + 7.235 \quad (15)$$

$$n=35, \quad r=0.818, \quad s=0.215, \quad F=32.42$$

The correlation coefficient is not so high. There seem to be several reasons for this: the range of potency is very narrow, the slope of log(dose)–response curve (=1.36) is too steep, introducing error in measuring the potency, and the mechanisms of action of all compounds were assumed to be the same, even though, some exhibit prolonged action and others do not. The calculated potencies using Eq. 13 are summarized in Table II.

Next, the relationships between structure and duration of action were examined. For such discrete data, regression analysis is not appropriate. The ALS method was thought to be more appropriate to analyze our data. From the data, the compounds of stronger potency appeared to exhibit long-lasting effects. The ALS analysis between potency and duration of all 37 compounds gave unsatisfactory results ($n_{\text{mis}}=11$, $Rs=0.317$, $t=1.977$, $p>0.05$). However, when the compounds which have a 2,4,6-tri-OMe group on the benzyl moiety (**13**, **25** and **33**) were excluded, a highly significant result was obtained (Eq. 16).

$$Y = 0.532 \log RP - 3.340 \quad (16)$$

$$n=34, \quad Rs=0.571, \quad \varepsilon=0.921, \quad n_{\text{mis}}=7, \quad t=3.93, \quad p<0.001$$

Equation 16 was obtained after 9 iterative calculations. A possible justification for the exclusion is that the conformations of **13**, **25** and **33** may be different from the others because of the di-*ortho* substituents on the benzyl moiety.

Relative potency (log RP) was explained well with $\Sigma\sigma$ and a steric parameter (Eqs. 13—15), so analysis using these parameters instead of log RP was performed to give Eqs. 17—19.

$$Y = -1.774\Sigma\sigma - 0.128MR - 0.302 \quad (17)$$

$$n=34, \quad Rs=0.620, \quad \varepsilon=0.773, \quad n_{\text{mis}}=6, \quad t=4.47, \quad p<0.001$$

$$Y = -2.175\Sigma\sigma - 0.512B_4 - 0.044 \quad (18)$$

$$n=34, \quad Rs=0.491, \quad \varepsilon=0.734, \quad n_{\text{mis}}=8, \quad t=3.18, \quad p<0.01$$

$$Y = -1.031\Sigma\sigma - 0.055L - 0.051 \quad (19)$$

$$n=34, \quad Rs=0.555, \quad \varepsilon=0.868, \quad n_{\text{mis}}=7, \quad t=3.77, \quad p<0.001$$

In Eqs. 17—19, 82, 76 and 79% of the compounds were correctly classified, respectively. To confirm the validity of the ALS results, the leave-one-out technique was applied and the predictive results classified 76—79% of the compounds correctly. The results are summarized in Table II.

Duration of action of a drug depends on various factors such as elimination, distribution and in some cases the biological activity of the metabolites. However, Eqs. 13—16 and 17—19 suggest that increase of the electron density on the benzylic nitrogen atom and the introduction of a sterically small substituent at the *para* position on the diphenylmethyl moiety bring about

Fig. 2. A Model of the Active Site

strong interactions of the compound with the active site, resulting in strong potency as well as prolonged action. The mechanism of action of our compounds is likely to be a direct calcium-antagonistic action on vascular smooth muscle.¹⁾ These results suggest that a compound with strong cerebral vasodilating activity has a strong affinity for the active site; such a compound may bind too tightly to be easily washed out by the blood flow, so that it would show a long-lasting action, while opposite considerations would apply to a compound with weak activity.

From the above results, a model of the active site is proposed as shown in Fig. 2. The putative active site may be like a hydrophobic pocket, and there is an anionic site which interacts electrostatically with the positively charged benzylic nitrogen atom. The effect of the diphenylmethyl moiety does not appear explicitly in the equations, but the introduction of a diphenylmethyl moiety resulted in a high activity compared to the activity of trimetazidine. Thus, there may be a strong hydrophobic interaction between the diphenylmethyl moiety and the wall of the pocket. The depth of the pocket from the anionic site is limited, leading to steric repulsion, which lowers the binding interaction, with the bulky substituents Y and Z. The lead development based on these assumptions will be reported separately.

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