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Pyrimidine Derivatives. V.[1] Structure–Activity Studies of Antihypertensive Quinazoline Derivatives Using the Adaptive Least-Squares Method

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The structure–activity relationships of thirty 2-(4-cinnamoyl-1-piperazinyl)-6,7-dimethoxy-4-quinazolinamine derivatives for antihypertensive activity were analyzed by the adaptive least-squares (ALS) method. When the retention index (ΔRI) obtained from a C-18 reversed-phase column high-pressure liquid chromatography system was used as a lipophilic parameter, the discriminant equation $L = -1.022\Delta RI - 2.560\Sigma\sigma^{Ph} - 1.966I^{Ph}(2\text{-OR}) + 0.799$ gave the best prediction, where L is the discriminant score, $\Sigma\sigma^{Ph}$ is the sum of the Hammett substituent constants of the substituents on the phenyl group and $I^{Ph}(2\text{-OR})$ is an indicator variable assigned a value of 1 for the presence of 2-alkoxy groups on the phenyl group. The effects of the lipophilicity and electronic character of substituents on the activity are discussed.

Keywords——pattern recognition; adaptive least-squares method; quantitative structure activity relationship; antihypertensive; 4-quinazolinamine; HPLC system; hydrophobic parameter

Prazosin,[3] 6,7-dimethoxy-2-(4-(2-furoyl)-1-piperazinyl)-4-quinazolinamine hydrochloride, has an excellent antihypertensive effect resulting from a peripheral α-adrenergic blockade and is available for the treatment of hypertension. Some compounds structurally related to prazosin, such as trimazosin.[4] E-643,[5] tiodazosin,[6] and terazosin,[7] have also been reported to show hypotensive activity. In a previous paper,[1] we reported the synthesis of various 2-(4-acryloyl-1-piperazinyl)-6,7-dimethoxy-4-quinazolinamine derivatives (Fig. 1) and determined their antihypertensive activities. When structure–activity relationships of the derivatives were considered, the electronic effect of the substituents on R^2 when R^2 was the phenyl group appeared important with respect to the activity, and some other factors were also presumed to influence the activity.

This paper describes the analysis of the structure–activity relationships of these derivatives for hypotensive activity using the adaptive least-squares (ALS) method[8] recently developed by Moriguchi *et al.* The ALS system, which is a nonparametric pattern classifier, has been devised (a) to formulate a quantitative structure–activity relationship in a single mathematical equation irrespective of the number of activity classes and (b) to categorize structural patterns into multiple ordered classes by means of the equation. The equation, called the discriminant function, is formulated by a feedback adaptation procedure in a single linear form as in Eq. 1.

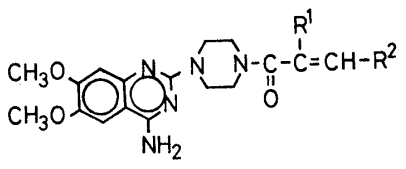

Fig. 1.

R^1 is H or Me. R^2 is a substituted phenyl, furyl, or thienyl group; see Table I.

$$L=w_0+w_1x_1+w_2x_2+\cdots+w_px_p \quad (1)$$

where L is the discriminant score for the classification, x_k ($k=1, 2, \cdots, p$) is the k th descriptor for the structure, and w_k ($k=0, 1, \cdots, p$) is the weight coefficient. The value of w_k is determined by the least-squares adaptation[8] using the starting score, a_j ($j=1, 2, \cdots, m$ in the m-group case; see the method section), and the correction term, $C_i(t)$ (see the method section).

In the parametrization of structural features for the ALS study, we examined lipophilic constants (retention index (ΔRI), $\Sigma\pi$), electronic parameters ($\Sigma\sigma$, ΣF, ΣR), steric factors (Es, MR), and various indicator variables for common structural features as descriptors. The retention index (ΔRI)[9] was determined by using a C-18 reversed-phase high-pressure liquid chromatography (LC) system. A good correlation with the biological activity was obtained when a descriptor set including the retention index was used.

Method

Activity Class——Thirty 2-(4-acryloyl-1-piperazinyl)-6,7-dimethoxy-4-quinazolinamines (**1**—**30**) were classified into 4 groups based on the dosage and the maximum rate of fall of blood pressure ($\Delta H/H_0$; ΔH is the maximum fall of the mean blood pressure (mmHg), and H_0 is the initial mean blood pressure (mmHg)) as shown in Table I.

Descriptor Variables——The descriptors used in the ALS analysis are lipophilic factors ($\Sigma\pi$, $\Sigma\pi^2$, ΔRI, ΔRI^2), electronic factors ($\Sigma\sigma^{Ph}$, ΣF^{Ph}, ΣR^{Ph}), steric factors ($Es^{Ph(o)}$, $MR^{Ph(o)}$), and indicator variables (I^{Ph}(2-OR), $I(R^1)$, I^t, I^f, $I^{t,f}$(Cl), HB). The $\Sigma\pi$ values are the sum of the Hansch aromatic standard substiuent constants[10] of the substituents on R^2 when R^2 is a phenyl group. When R^2 is a thienyl or furyl group, $\Sigma\pi$ values are the sum of the Hansch π constants of the substituents on R^2 and the π (Th or Fu) which is defined by the following equation; π(Th or Fu)= log P(ThH or FuH) − log P(PhH). For compounds **18**, **22**, and **29**, the π(Me; R^1) value calculated by the method of Leo[11] is used. The values of ΔRI are 1/100 of the retention index I proposed by Baker *et al.*,[9] and are determined by the use of a reversed-phase high-pressure LC system. The $\Sigma\pi$ and ΔRI values of compound **24** are defined as 0. The $\Sigma\sigma^{Ph}$ values show the sum of the Hammett substituent constants[10] of the substituents on R^2 when R^2 is a phenyl group; in the case of an *ortho*-substituent, the values of *para*-substituent constants were used.[12] The ΣF^{Ph} and ΣR^{Ph} values are the sum of the Swain–Lupton substituent constants[10] of the substituents on R^2 when R^2 is a phenyl group; the positional weighting factors of Williams and Norrington are used.[13] $Es^{Ph(o)}$ and $MR^{Ph(o)}$ are the Taft–Kutter–Hansch steric substituent constants[14] and molecular refractions[11] of *ortho*-substituents on R^2, respectively, when R^2 is a phenyl group. The indicator variable, I^{Ph}(2-OR), is assigned a value of 1 for the presence of 2-alkoxy groups on R^2 when R^2 is a phenyl group. The variable $I(R^1)$ is assigned a value of 1 when R^1 is a methyl group. When R^2 is a thienyl or furyl group, the variable I^t or I^f is assigned a value of 1, respectively. The variable $I^{t,f}$(Cl) is assigned a value of 1 for the presence of a chloro-substituent on R^2 when R^2 is a thienyl or a furyl group. The HB value is assigned a value of 1 for the presence of a hydrogen-bonding substituent.[15] The descriptors used finally are shown in Table II. Table III shows the squared correlation matrix of the descriptors.

ALS Calculation——The calculation was performed according to the method of Moriguchi.[8] The starting score a_j ($j=1, 2, \cdots, m$), and the cutting point, b_j ($j=1, 2, \cdots, m-1$), where assumed in the same manner as previously described [8a] (Eq. 2 and Eq. 3).

$$a_j=2\left(2\sum_{i=1}^{j-1} n_i+n_j\right)\Big/n-2 \quad (2)$$

$$b_j=(a_j+a_{j+1})/2 \quad (3)$$

TABLE I. Classification of Antihypertensive Activity

Class	Dose (mg/kg *p.o.*)	Activity (%)	No. of compd.
1	10	$\Delta H/H_0<15$	11
2	10	$15\leqq\Delta H/H_0$	5
	(or 3	$10\leqq\Delta H/H_0$)	
3	3	$15\leqq\Delta H/H_0$	9
	(or 10	$20\leqq\Delta H/H_0$)	
4	1	$15\leqq\Delta H/H_0$	5

TABLE II. Antihypertensive Activity and Physicochemical Descriptors

No.	R^1	R^2 [a]	Act.[obs.]	ΔRI [b]	$\Sigma\pi$ [c]	$\Sigma\sigma^{Ph}$	I^{Ph}(2-OR)	$I(R^2)$	I^t	I^f	HB
1	H	4-IsoPrPH	1	2.36	1.53	−0.15	0	0	0	0	0
2	H	2-MeOPh	1	0.49	−0.02	−0.27	1	0	0	0	1
3	H	2-EtOPh	1	1.18	0.38	−0.24	1	0	0	0	1
4	H	3,5-DiMeOPh	1	0.56	−0.04	0.24	0	0	0	0	1
5	H	3-NO_2Ph	1	0.03	−0.28	0.71	0	0	0	0	1
6	H	3,4-DiClPh	1	2.19	1.42	0.60	0	0	0	0	0
7	H	3-CF_3Ph	1	1.17	0.88	0.43	0	0	0	0	0
8	H	3-MeOPh	1	0.28	−0.02	0.12	0	0	0	0	1
9	H	4-ClPh	1	1.01	0.71	0.23	0	0	0	0	0
10	H	4-BrPh	1	1.26	0.86	0.23	0	0	0	0	0
11	H	5-Cl-2-Th	1	0.89	0.39[d]	0.00	0	0	1	0	0
12	H	3-MePh	2	1.01	0.56	−0.07	0	0	0	0	0
13	H	4-MePh	2	0.95	0.56	−0.17	0	0	0	0	0
14	H	4-IsoPrOPh	2	1.53	0.82[e]	−0.45	0	0	0	0	1
15	H	2,3,4-TriMeOPh	2	−0.09	−0.06	−0.42	1	0	0	0	1
16	H	5-Me-2-Th	2	0.69	0.24[d]	0.00	0	0	1	0	0
17	H	2-MePh	3	0.83	0.56	−0.17	0	0	0	0	0
18	Me	Ph	3	0.20	0.54[f]	0.00	0	1	0	0	0
19	H	3-Fu	3	−1.29	−0.79[g]	0.00	0	0	0	1	1
20	H	5-Me-2-Fu	3	0.04	−0.23[g]	0.00	0	0	0	1	1
21	H	5-Cl-2-Fu	3	0.51	−0.08[g]	0.00	0	0	0	1	1
22	Me	2-Th	3	−0.13	0.22[d,f]	0.00	0	1	1	0	0
23	H	3-Me-2-Th	3	0.48	0.24[d]	0.00	0	0	1	0	0
24	H	Ph	3	0.00	0.00	0.00	0	0	0	0	0
25	H	2-Th	3	−0.36	−0.32[d]	0.00	0	0	1	0	0
26	H	4-MeOPh	4	0.19	−0.02	−0.27	0	0	0	0	1
27	H	4-EtOPh	4	0.92	0.38	−0.24	0	0	0	0	1
28	H	2-Fu	4	−0.84	−0.79[g]	0.00	0	0	0	1	1
29	Me	2-Fu	4	−0.71	−0.25[f,g]	0.00	0	1	0	1	1
30	H	3-Th	4	−0.61	−0.32[d]	0.00	0	0	1	0	0

a) Ph=phenyl, Th=thienyl, Fu=furyl.
b) The ΔRI of compound **24** was defined as 0.
c) The sum of standard aromatic substituent constants (ref. 10); The $\Sigma\pi$ of compound **24** was defined as 0.
d) $\pi(Th)=\log P(ThH)-\log P(PhH)=1.81-2.13=-0.32$.
e) $\pi(isoPrO)=\pi(EtO)-f(H)+f(Me)+F_{gBr}=0.82$.
f) $\pi(Me;R^1)=f(\rangle N(CO)\text{-}C(Me)=CHR^2)-f(\rangle N(CO)\text{-}CH=CHR^2)=f(Me)+f(CH)+F_b-f(CH_2)=0.54$.
g) $\pi(Fu)=\log P(FuH)-\log P(PhH)=1.34-2.13=-0.79$.

TABLE III. Squared Cross-Correlation Matrix of Descriptor Variables

	ΔRI	$\Sigma\pi$	$\Sigma\sigma^{Ph}$	I^{Ph}(2-OR)	$I(R^2)$	I^t	I^f	HB
ΔRI	1.000							
$\Sigma\pi$	0.868	1.000						
$\Sigma\sigma^{Ph}$	0.004	0.008	1.000					
I^{Ph}(2-OR)	0.000	0.006	0.167	1.000				
$I(R^2)$	0.081	0.001	0.000	0.012	1.000			
I^t	0.040	0.021	0.000	0.027	0.012	1.000		
I^f	0.267	0.297	0.000	0.022	0.022	0.049	1.000	
HB	0.111	0.279	0.052	0.127	0.008	0.219	0.229	1.000

where n is the number of whole substances, and n_i and n_j refer to the size of groups i and j, respectively. With the whole data set of 30 compounds in this study, the starting score a_j and cutting point b_j are as follows; $a_1=-1.267$, $a_2=-0.200$, $a_3=0.733$, $a_4=1.667$, $b_1=-0.733$, $b_2=0.267$, and $b_3=1.200$. The correction term, $C_i(t)$, for substance i at the tth iteration is given by Eq. 4,[8b]

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

where $\delta_i(t)$ is the deviation defined by Eq. 5.

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

In Eq. 5, $L_i(t)$ is the discriminant score for substance i at the tth iteration, and b_k is the cutting point (nearer to $L_i(t)$) for the observed class for substance i. The adaptive iteration was performed 20 times,[8b] and the best discriminant function was selected. As the criteria of the best discrimination, the Spearman rank correlation coefficient with many ties,[16] R_S, and the ε value[8] were used.

Computation——All computations were performed with a UNIVAC 1100/81, and all of the ALS programs used were written in ASCII FORTRAN. The original ALS programs from Moriguchi were written in JIS FORTRAN.

Measurement of Retention Indices——Chromatographic Conditions: A 3.9 mm i.d × 30 cm C_{18} reversed-phase column (μ-Bondapak C_{18}, Waters Associates Inc.) of 10 μm particle size was used for the study. The mobile-phase was prepared from 3.3 g of K_2HPO_4, 4.2 g of KH_2PO_4, 2.8 l of CH_3OH, and 1.2 l of H_2O, and its flow rate was 1.5 ml/min. The pH value of the mobile phase was 7.0 before the addition of CH_3OH. A Waters model 6000 pump, U6K injector, and model 440 detector (254 nm) were used.

Materials: The 2-alkanones (C_6-C_{11}) were obtained from Tokyo Kasei Kogyo Co., Ltd., and 2-decanone from Aldrich Chemical Co., Inc. The quinazolinamine derivatives were synthesized in our laboratory.[1]

Measurement of Retention Indices: The retention index (RI) of a given 2-alkanone standard is by definition equal to the number of carbons in the compound. Thus, 2-butanone was assigned a value of 4. The retention index of a given drug or other test compound was calculated from the observed capacity factor for the drug (k_D'), the capacity factor for a 2-alkanone standard eluted just before the test compound (k_N'), and that for the homologue having one more carbon atom (k'_{N+1}) using Eq. 7.

$$RI=I/100=\frac{\log k'_D-\log k'_N}{\log k'_{N+1}-\log k'_N}+N \quad (7)$$

where I is the retention index defined by Baker *et al.*[9] The RI value of compund **24**, which is taken as the reference in the ALS calculation, was found to be 7.93.

Results and Discussion

Factors essential to the structure–activity correlation were selected from many kinds of descriptors such as lipophilic, electronic, and steric factors and other indicator variables based on the contribution index (CI) defined in Eq. 8.

$$CI=w_k\times s_k \quad (8)$$

TABLE IV. Results of the ALS Recognition and Prediction

No.	Obs.	Recognition			Prediction			No.	Obs.	Recognition			Prediction		
		Eq. 9	Eq. 10	Eq. 11	Eq. 9	Eq. 10	Eq. 11			Eq. 9	Eq. 10	Eq. 11	Eq. 9	Eq. 10	Eq. 11
1	1	1	1	1	1	1	1	**16**	2	2	2	2	2	2	2
2	1	1	1	1	1	1	2	**17**	3	3	3	3	2	3	2
3	1	1	1	1	1	1	1	**18**	3	3	3	3	3	3	3
4	1	1	2	2	2	2	2	**19**	3	4	4	4	4	4	4
5	1	1	1	1	1	1	1	**20**	3	3	3	3	3	3	3
6	1	1	1	1	1	1	1	**21**	3	3	3	3	2	2	3
7	1	1	1	1	1	1	1	**22**	3	3	3	3	3	3	3
8	1	2	2	2	2	2	2	**23**	3	3	3	2	2	2	2
9	1	1	1	1	1	1	1	**24**	3	3	3	3	3	3	3
10	1	1	1	1	1	1	1	**25**	3	3	3	3	3	3	3
11	1	2	2	2	2	2	2	**26**	4	4	4	4	3	4	3
12	2	2	2	2	2	2	2	**27**	4	3	3	3	3	3	3
13	2	2	2	3	2	3	3	**28**	4	4	4	4	4	4	3
14	2	3	3	3	3	3	3	**29**	4	4	4	4	4	4	4
15	2	2	2	2	2	2	2	**30**	4	4	4	3	4	4	3

TABLE V. Contribution Index of the Descriptors for Eq. 9, Eq. 10, and Eq. 11

ΔRI	$\Sigma\pi$	$\Sigma\sigma^{Ph}$	I^{Ph}(2-OR)	$I(R^2)$	I^t	I^f	Eq.
0.721		0.820	0.590		0.073	0.106	9
0.837		0.652	0.589				10
	0.591	0.717	0.631	0.239			11

where w_k is the weight coefficient (Eq. 1) and s_k is the standard deviation. In the descriptor selection, full consideration was given to avoiding possible chance correlation. The best discriminant function using five descriptors is expressed in Eq. 9, which was derived from iteration 15, and where n stands for the number of compounds, n_{mis} is the number misclassified, the figure in parentheses after the value of n_{mis} is the number misclassified into the next class but one, and p is the percentage of correct interpretations. The calculated classes are listed in Table IV.

$$L = -0.880\Delta RI - 3.217\Sigma\sigma^{Ph} - 1.969I^{Ph}(2-OR) + 0.183I^t + 0.285I^f + 0.524 \quad (9)$$

$$n=30,\quad n_{mis}=5(0),\quad p=0.833,\quad \varepsilon=0.557,\quad R_S=0.939$$

On the basis of Eq. 9, more hydrophilic properties of the molecules are required to improve the activity. When R^2 is a phenyl group, electron-donating character is favorable for the activity; however, the presence of an alkoxy group at the *ortho* position produced a decrease in the activity. To clarify the physicochemical meaning of the indicator variable I^{Ph}(2-OR), it is necessary to examine additional derivatives having an *ortho*-substituted phenyl group as R^2.

As to the variables I^t and I^f, the presence of thienyl and furyl groups seems to be preferable to that of a phenyl group; however, the contribution indices of I^t and I^f prove that their contributions to the activity are much less than those of ΔRI, $\Sigma\sigma^{Ph}$, and I^{Ph}(2-OR), as shown in Table V. Then, by using the descriptors other than I^t and I^f, Eq. 10 was obtained at iteration 18.

$$L = -1.022\Delta RI - 2.560\Sigma\sigma^{Ph} - 1.966I^{Ph}(2-OR) + 0.799 \quad (10)$$

$$n=30,\quad n_{mis}=6(0),\quad p=0.800,\quad \varepsilon=0.495,\quad R_S=0.930$$

In Eq. 10, 80% of the compounds were correctly classified. The R_S value, 0.930, is similar to the value of 0.939 in Eq. 9, and shows good predictive success. This finding suggests that ΔRI, $\Sigma\sigma^{Ph}$, and I^{Ph}(2-OR) are significant factors in relation to the activity.

By using $\Sigma\pi$ values instead of ΔRI values as lipophilic factors, Eq. 11 was obtained as the best discriminant function at iteration 9.

$$L = -1.088\Sigma\pi - 2.811\Sigma\sigma^{Ph} - 2.105I^{Ph}(2-OR) + 0.797I(R^1) + 0.431 \quad (11)$$

$$n=30,\quad n_{mis}=9(0),\quad p=0.700,\quad \varepsilon=0.493,\quad R_S=0.855$$

The recognition success was 70%. The classfication results obtained with Eq. 11 were inferior to those from both Eq. 9 and Eq. 10. The descriptors $\Sigma\pi(\Delta RI)$, $\Sigma\sigma^{Ph}$, and I^{Ph}(2-OR) in Eq. 11 were used in common with Eq. 10, whereas $I(R^1)$ had to be newly added. The variable $I(R^1)$ in Eq. 11 seems to correspond to a correction term of the calculated $\Sigma\pi$ value. This is because, in the regression line of $\Sigma\pi$ *vs.* ΔRI, the deviations of compounds **18**, **22**, and **29**, where R^1 is a methyl group, were much greater than those of other compounds.

To confirm the validity of the ALS results, the leave-one-out technique was applied to the

TABLE VI. The Correlation of π and ΔRI

$$\Sigma\pi = a + b\Delta RI + cHB + dI(R^1)$$

$a^{a)}$	$b^{a)}$	$c^{a)}$	$d^{a)}$	n	r	s	Eq.
−0.07 (±1.37)	0.62 (±0.09)			30	0.932	0.197	12
−0.15 (±1.13)	0.75 (±0.12)			11[b)]	0.977	0.107	13
0 (±1.18)	0.66 (±0.09)	−0.22 (±0.13)		11[b)]	0.992	0.062	14
0.08 (±2.40)	0.56 (±0.08)	−0.27 (±0.13)		30	0.961	0.080	15
0 (±2.03)	0.61 (±0.06)	−0.22 (±0.09)	0.37 (±0.15)	30	0.980	0.058	16

a) Figures in parentheses are 95% confidence limits.
b) Compounds **1**, **5**, **7**—**10**, **12**, **13**, **24**, **26**, and **27**.

ALS analysis. The descriptor set in Eq. 10 gave the best predictive results, when n_{mis} was 9(0). These results indicated the significance of lipophilic character and electronic factors, and are shown in Table IV.

The equation using retention index gave a better correlation to biological activity than that using $\Sigma\pi$ values in this study. Baker *et al.* have contended that a C-18 reversed-phase high-pressure LC system might be a better model for biological interactions than the direct octanol–water partitioning model.[9] From our results, we cannot determine whether the LC system is a better model or not, because the $\Sigma\pi$ values in this study were not actually measured. Therefore, the correlation between the $\Sigma\pi$ and ΔRI values was examined, and Eqs. 12—16 shown in Table VI were derived from the data in Table II.

First, the $\Sigma\pi$ values of the selected eleven compounds where R^1 is a hydrogen atom and R^2 is a *m*- or *p*-mono-substituted cinnamoyl group were correlated with the ΔRI values in Eq. 13. Equation 13 gave a better relation that Eq. 12 where the data set of 30 derivatives was used. As to the eleven compounds, an excellent correlation was obtained by using the ΔRI value and indicator variable *HB*, which is assigned a value of 1 when a substituent of the cinnamoyl group has hydrogen-bonding activity, in Eq. 14 (r is 0.992). Then, we evaluated the relation of the $\Sigma\pi$ values of all 30 compounds by using *HB* and ΔRI, and obtained Eq. 15. The *HB* value in Eq. 15 is assigned a value of 1 in the case where R^2 is a furyl group besides the above described assignment in Eq. 14. Moreover, the addition of the $I(R^1)$ value to the ΔRI and *HB* value afforded an improved Eq. 16, where r is 0.980. These findings suggest that the difference between $\Sigma\pi$ and ΔRI is related to the character of the organic phase in the partition process. That is, the organic layer in the C-18 reversed-phase LC system seems to be more hydrocarbon-like than octanol-like. The indicator variable $I(R^1)$ is considered to express a steric effect on the neighboring amido group for lipophilicity, that is, $I(R^1)$ may be the correction term for the calculated $\pi(Me; R^1)$ value.

Based on these considerations, we examined the correlation between the biological activity and the structure by using the *HB* value in addition to the descriptors in Eq. 11. Unfortunately, we could not obtain a better correlation than Eq. 11. The reasons why the addition of the *HB* value did not improve the correlation are considered to be as follows; the $\Sigma\pi$ value is a calculated one in contrast with the ΔRI value (actually measured), and in the structure–activity relation the contribution of the *HB* value to $\Sigma\pi$ was smaller than that of the *HB* value to ΔRI, so the addition of the *HB* value resulted only in an increase of descriptors without any improvement. As to the propriety of the lipophilic parameter, it is difficult to discuss this because the biological response in this study, which was classified based on doses and activity, does not strictly satisfy the free-energy relation.

In conclusion, the structure–activity relationships of 2-(4-acryloyl-1-piperazinyl)-6,7-dimethoxy-4-quinazolinamine derivatives with antihypertensive activity were successfully analyzed by the ALS method. The descriptor set of ΔRI, $\Sigma\sigma^{Ph}$, and I^{Ph}(2-OR) gave the best

predictions. The results indicate the significance of lipophilicity and the electron donating effect of substituents on R^2. At the same time, we found advantages in the use of the retention index as a lipophilic parameter. Based on the indications obtained by the structure–activity studies, a series of compounds predicted to have more potent hypotensive activity was synthesized, and one of these is under further investigation for clinical use.

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