Nonlinear Partial Least Squares Modeling of Phenyl Alkylamines with the Monoamine Oxidase Inhibitory Activities

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The nonlinear partial least squares (PLS) method is a nonlinear version of PLS. In this approach, a quadratic inner relation is used instead of the linear inner relation in PLS. Since the quadratic inner relation can be extended to a general form, it is said that the nonlinear PLS method has a high potential for nonlinear modelling. However, few applications of the method have been appeared in quantitative structure−activity relationships (QSAR) studies, because the mathematical descriptions underlying the algorithm were not so clear. In this paper, we have carried out the QSAR analysis of four monoamine oxidase (MAO) inhibitory activities using the nonlinear PLS method. The *in vitro* and *in vivo* MAO inhibitory activities were analyzed separately. From the PLS loadings, the structural requirements could be estimated and the utility of the nonlinear PLS method was demonstrated.

INTRODUCTION

An important task in a quantitative structure−activity relationships (QSAR) is to model a relationship between the chemical structures and biological activities. The established QSAR model provides a valuable aid in rationalizing the essential structural features of compounds and optimizing the activities.[1]

The ordinary least squares (OLS) method called the Hansch−Fujita approach[2] has been widely used as a statistical method in QSAR. However, it has no ability to give a robust model in the cases where the structural descriptors describing the chemical structures are correlated, and the number of compounds with the activities is smaller than the number of structural descriptors.[3]

The partial least squares (PLS) method developed by Wold et al. is a versatile statistical method.[4] PLS finds some components on which to perform a regression. These components are chosen to simultaneously satisfy two conditions: (i) that they are highly correlated with the dependent variables and (ii) that they model as much of the variance among the independent variables as possible. Since a dimension of each component is one, the problems of correlation and limited compounds can be circumvented. Applications of the PLS method in QSAR have been much increased, and many successful PLS models have been obtained.[5,6]

Although the PLS method is useful, its major restriction is that only linear relation can be extracted from the data. Since many structure−activity data are inherently nonlinear in nature, it is desirable to have a flexible method which can model any nonlinear relations.

There has been a considerable interest in the artificial neural networks (ANN) for nonlinear modelling.[7,8] The ANN method can model any data, but prediction of the model is not so high unless the structure of networks and learning rule are carefully examined. Another shortcoming of the ANN method is that the interpretation of the model is complicated although some attempts solving the problem have been made.[9,10]

Recently, Wold et al. have proposed the nonlinear PLS method as a nonlinear version of PLS.[11] In their approach, a quadratic inner relation is used instead of the linear inner relation in PLS. Since the quadratic inner relation can be extended to a general form by a smooth spline function,[12] it is said that the nonlinear PLS method has a high potential for nonlinear modelling. Unfortunately, the mathematical descriptions underlying the algorithm were not so clear, and few applications of the nonlinear PLS method have been appeared in QSAR studies.

In this paper, we have carried out the QSAR analysis of four monoamine oxidase (MAO) inhibitory activities using the nonlinear PLS method with the quadratic inner relation. Principal component analysis (PCA) was used in order to see similarities and differences among four MAO biological activities. Two groups of biological activities were detected from PCA, and each group corresponds to the *in vitro* and *in vivo* MAO inhibitory activities, respectively. The two groups were analyzed separately by the nonlinear PLS method. Both models could well explain the variance of the MAO inhibitory activities with high internal predictivity. From the PLS loadings, the structural requirements could be estimated, and the utility of the method was demonstrated.

MATERIAL AND METHODS

Data Set. Twenty phenyl alkylamines with the MAO inhibitory activities were used as a data set. The data set has been shown to have a nonlinearity by Norinder et al.,[13] and it is a suitable example for the nonlinear PLS analysis. The chemical structures and MAO inhibitory activities of phenyl alkylamines were shown in Table 1. The activity values were taken from the study by Norinder et al.[13] The compounds without full inhibitory activities were not in-

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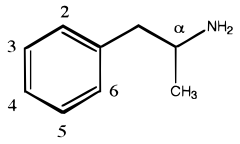
Table 1. Chemical Structures and Observed MAO Inhibitory Activities of Phenyl Alkylamines



no.	name	structure			MAO inhibitory activities in vitro[a]	NA[b]	DA[c]	5-HT[d]
1	FLA-299		4-$CHMe_2$		4.90	4.57	3.52	4.48
2	FLA-289		4-NMe_2		5.43	5.60	5.47	5.60
3	FLA-558	2-F	4-NMe_2		5.92	6.35	5.96	6.35
4	FLA-314	2-Cl	4-NMe_2		6.68	5.62	5.52	5.66
5	FLA-405	2-Br	4-NMe_2		6.66	5.38	5.10	5.47
6	FLA-336	2-Me	4-NMe_2		5.57	5.42	5.26	5.64
7	AMIFLAMINE(+)	2-Me	4-NMe_2		6.10	5.70	5.48	5.96
8	FLA-336(−)	2-Me	4-NMe_2		5.52	5.10	4.57	5.07
9	FLA-365	2-Cl	4-NMe_2	6-Cl	7.89	5.32	5.42	5.46
10	FLA-463	2-Cl	4-NMe_2	α-Me	5.92	5.00	4.92	5.07
11	FLA-717	2-Me	4-NMe_2	α-Me	4.92	4.44	4.68	5.10
12	FLA-384	3-Me	4-NMe_2		5.10	4.46	4.24	5.12
13	NBF-003(+)	2-Me	4-NMe_2	5-Br	5.96	5.00	4.92	4.82
14	FLA-727		4-NHMe		6.26	5.89	5.60	6.15
15	FLA-788(+)	2-Me	4-NHMe		6.89	5.68	5.43	6.10
16	NBF-008(+)	2-Me	4-NHMe	5-Br	7.05	5.10	4.98	5.12
17	FLA-334		4-NH_2		5.14	4.82	5.07	4.30
18	FLA-668	2-Me	4-NH_2		5.80	5.30	4.46	4.82
19	FLA-668(−)	2-Me	4-NH_2		5.12	4.58	4.00	4.57
20	NBF-021(+)	2-Me	4-NH_2	5-Br	6.10	4.70	4.46	4.55

[a] The *in vitro* MAO inhibitory activity. [b] The *in vivo* MAO inhibitory activity inside noradrenergic neuron. [c] The *in vivo* MAO inhibitory activity inside dopaminergic neuron. [d] The *in vivo* MAO inhibitory activity inside serotonergic neuron.

cluded in the data set in order to see the relation among biological activities using PCA.

There are four biological activities in the data set. The first biological activity is the *in vitro* MAO inhibitory activity. The second, third, and fourth biological activities are the *in vivo* MAO inhibitory activities inside noradrenergic (NA), dopaminergic (DA), and serotonergic (5-HT) neurons of the rat brain, respectively. The *in vitro* MAO inhibitory activity is defined as the potency of a given compound to inhibit a MAO-selective substrate in the mitochondrial preparation of the rat brain.[14] The activity was expressed as the negative logarithm of the 50% inhibitory concentration (pIC_{50}). The *in vivo* MAO inhibitory activities within specific neurons are determined using a special technique, which utilizes selective inhibitors of the neural uptake mechanism for the transmitter amines (noradrenaline, dopamine, and serotonine).[14] The activity was given as the negative logarithm of the 50% effective dose (pED_{50}).

Structural Descriptors. The structural descriptors describing each chemical structure of phenyl alkylamines is represented by a 29 dimensional vector x as the one used in the study of Norinder et al.[13]

$$x = (\sigma_m(o), \sigma_p(o), F(o), R(o), \pi(o), MR(o), L(o), B_1(o), B_5(o), \sigma_m(m), \sigma_p(m), F(m), R(m), \pi(m), MR(m), L(m), B_1(m), B_5(m), \sigma_m(p), \sigma_p(p), F(p), R(p), \pi(p), MR(p), L(p), B_1(p), B_5(p), I_{Me}, I_S) \quad (1)$$

The vector x consists of nine physico-chemical parameters (σ_m, σ_p, F, R, π, MR, L, B_1, and B_5) for substituents at ortho (o), meta (m), and para (p) positions on the aromatic ring and two additional indicator variables (I_{Me} and I_S) in the aliphatic side chain of phenyl alkylamines. σ_m and σ_p are the Hammett σ constants at meta and para positions. F and R are the Swain−Lupton field and resonance descriptors. π is the Hansch aromatic fragment constant. MR is the molecular refractivity. L, B_1, and B_5 are the Verloop sterimol parameters. I_{Me} is the indicator variable, which is equal to one when the substituent at α position is a methyl group and zero for a hydrogen. I_S is the indicator variable treating the stereochemistry at α position ($I_S = 1$ for *S*-configuration, $I_S = -1$ for *R*-configuration, and $I_S = 0$ for racemates). The values of nine physico-chemical parameters of substituents taken from the compiling tables[15,16] were shown in Table 2. Since it is hard to differentiate between the two ortho and two meta positions on the aromatic ring, the sum of variables for each of these two pairs of positions was used in this case.

Nonlinear PLS Method. The relationship between the MAO inhibitory activities and structural descriptors was analyzed using the nonlinear PLS method. A detailed description and algorithm of the method have been given in the Wold's paper.[11] Minimum introduction of the method will be described below.

The nonlinear PLS model is derived in a principal component-like manner as that of the PLS model. The independent variables (X) and dependent variables (Y) are individually decomposed into a loading and a score vector (outer relation). The X block contains the structural descriptors and Y block contains the biological variables. The outer relation for the X and Y blocks are

$$X = \bar{X} + \sum_{h=1}^{A} t_h p_h^T + E \quad (2)$$

$$Y = \bar{Y} + \sum_{h=1}^{A} u_h q_h^T + F \quad (3)$$

where $\bar{X}$ and $\bar{Y}$ are the corresponding mean value matrices; p_h^T and q_h^T are the transpose of loading vectors for the X and Y blocks in the hth component, respectively; and E and F are the model residual matrices of X and Y, respectively. A is the optimum number of components for the nonlinear PLS model determined by the cross-validation technique.[17] Two scores t_h and u_h in hth component are correlated through an inner relation,

$$u_h = c_0 + c_1 t_h + c_2 t_h^2 \quad (4)$$

where c_0, c_1, and c_2 represent the coefficients in the quadratic form. If both the quadratic coefficient (c_2) and constant (c_0) are equal to zero, the inner relation becomes a linear one in the PLS model. It is said that the nonlinear PLS model minimizes the residuals E and F and maximizes the correlation of two scores t_h and u_h in the quadratic form.

The nonlinear PLS analysis was performed using a program[18] developed in our laboratory and run on a Silicon Graphics workstation. The program was written in FORTRAN language according to the Wold's algorithm[11] with a minor correction.[19]

RESULTS

PCA of Four Biological Activities. PCA was used in order to see similarities and differences among four MAO

Table 2. The Physico-Chemical Parameters Describing Substituents on the Aromatic Ring of Phenyl Alkylamines

no.	substituent	σ_m[a]	σ_p[a]	F[a]	R[a]	π[a]	MR[a]	L[b]	B_1[b]	B_5[b]
1	H	0.00	0.00	0.00	0.00	0.00	1.03	2.06	1.00	1.00
2	F	0.34	0.06	0.43	−0.34	0.14	0.92	2.65	1.35	1.35
3	Cl	0.37	0.23	0.41	−0.15	0.71	6.03	3.52	1.80	1.80
4	Br	0.39	0.23	0.44	−0.17	0.86	8.88	3.82	1.95	1.95
5	Me	−0.07	−0.17	−0.04	−0.13	0.56	5.65	2.87	1.52	2.04
6	$CHMe_2$	−0.07	−0.15	−0.05	−0.10	1.53	14.96	4.11	1.90	3.17
7	NMe_2	−0.15	−0.83	0.10	−0.92	0.18	15.55	3.53	1.35	2.56
8	NHMe	−0.30	−0.84	−0.11	−0.74	−0.47	10.33	3.53	1.35	3.08
9	NH_2	−0.16	−0.66	0.02	−0.68	−1.23	5.42	2.78	1.35	1.97

[a] The value was taken from ref 15. [b] The value was taken from ref 16.

Table 3. Observed and Calculated MAO Inhibitory Activities by the Nonlinear PLS Models

	in vitro		NA		DA		5-HT	
no.	obsd[a]	calcd[b]	obsd[a]	calcd[b]	obsd[a]	calcd[b]	obsd[a]	calcd[b]
1	4.90	4.90	4.57	4.36	3.52	3.94	4.48	4.31
2	5.43	5.34	5.60	5.62	5.47	5.46	5.60	5.75
3	5.92	5.92	6.35	6.18	5.96	6.12	6.35	6.38
4	6.68	6.68	5.62	5.55	5.52	5.37	5.66	5.67
5	6.66	6.66	5.38	5.36	5.10	5.,14	5.47	5.45
6	5.57	5.73	5.42	5.37	5.26	5.16	5.64	5.47
7	6.10	6.06	5.70	5.69	5.48	5.54	5.96	5.83
8	5.52	5.40	5.10	5.08	4.57	4.81	5.07	5.14
9	7.89	7.89	5.32	5.48	5.42	5.29	5.46	5.59
10	5.92	5.92	5.00	5.02	4.92	4.74	5.07	5.06
11	4.92	4.92	4.44	4.87	4.68	4.56	5.10	4.90
12	5.10	5.10	4.46	4.71	4.24	4.36	5.12	4.71
13	5.96	6.05	5.00	5.01	4.92	4.72	4.82	5.05
14	6.26	6.29	5.89	5.77	5.60	5.63	6.15	5.91
15	6.89	6.96	5.68	5.84	5.43	5.72	6.10	6.00
16	7.05	6.95	5.10	5.12	4.98	4.86	5.12	5.18
17	5.14	5.20	4.82	4.97	5.07	4.68	4.30	5.01
18	5.80	5.59	5.30	4.78	4.46	4.45	4.82	4.79
19	5.12	5.26	4.58	4.56	4.00	4.18	4.57	4.54
20	6.10	6.10	4.70	4.69	4.46	4.34	4.55	4.69

[a] The observed MAO inhibitory activity. [b] The calculated MAO inhibitory activity by the nonlinear PLS model.

biological activities in a biological variable space. PCA is a useful method for extracting some condensed principal components from the variation of variables in the data.[20] By examination of the loading plot of principal components, it is possible to evaluate the relations between variables. The cross-validation criterion[17] is applied to obtain the optimum number of components of PCA. PCA was carried out using the Unscrambler software package developed by Martens on an IBM PS/2 microcomputer.[21]

PCA of four biological activities gave two significantly components. Two components of PCA explained 83.7% and 82.1% of the total variance in the conventional and cross-validated steps, respectively. The loading plot of second against first principal component indicastes that four biological activities are clustered in two groups. The first group is the biological variable 1, and the second group is the biological variable 2, 3, and 4. The two groups correspond to the *in vitro* and *in vivo* MAO inhibitory activities, and this correspondence implicitly validates PCA of four MAO inhibitory activities.

The two groups of biological activities (the *in vitro* and *in vivo* MAO inhibitory activities) were analyzed separately, as described below.

Nonlinear PLS Model for *in Vitro* MAO Inhibitory Activity. The *in vitro* MAO activity and structural descriptor matrix were autoscaled to unit variance prior to the nonlinear PLS analysis. A one-component nonlinear PLS model was obtained by the cross-validation technique.[17] The model gave the R^2 values of 0.988 and Q^2 values of 0.861. R^2 is the squared conventional correlation coefficient, and Q^2 is the squared cross-validated one. The observed and calculated *in vitro* MAO inhibitory activity given by the nonlinear PLS model was shown in Table 3.

The coefficients of the nonlinear PLS model (c_0, c_1, and c_2) are 0.026, 1.025, and −0.028, respectively.[22] Because the quadratic coefficients (c_2) almost equals zero, the relation between the *in vitro* MAO inhibitory activity and structural descriptors is considered to be linear. The PLS plot of the *y*-score (u) against the *x*-score (t) for the first component also reveals a linear relation as shown in Figure 1.

Nonlinear PLS Model for *in Vivo* MAO Inhibitory Activities. In analogy with the *in vitro* MAO activity, the nonlinear PLS model was developed for three *in vivo* MAO inhibitory activities. A one-component nonlinear PLS model was obtained, giving the average R^2 values of 0.872 and Q^2 values of 0.561. The R^2 values for each of three biological activities (NA, DA, and 5-HT) are 0.863, 0.897, and 0.855, respectively. The corresponding Q^2 values are 0.576, 0.511, and 0.595. The observed and calculated *in vivo* MAO inhibitory activities given by the nonlinear PLS model were shown in Table 3.

The coefficients of the nonlinear PLS model (c_0, c_1, and c_2) are −0.153, 2.262, and 0.309, respectively.[23] There is a weak nonlinearity between the *in vivo* MAO inhibitory

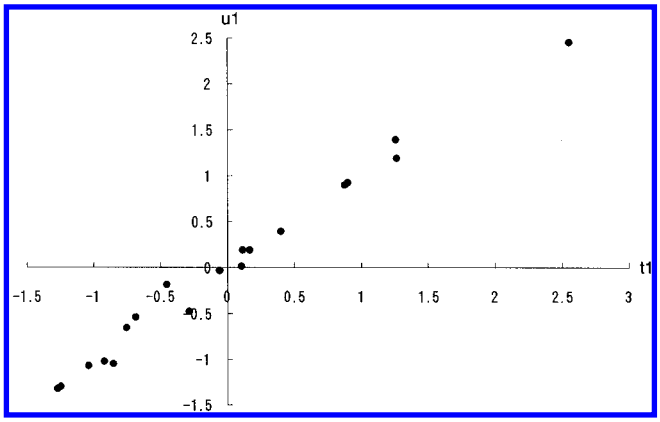


Figure 1. The PLS plot of the *y*-score (*u*) against *x*-score (*t*) for the first component of the nonlinear PLS model for *in vitro* MAO inhibitory activity.

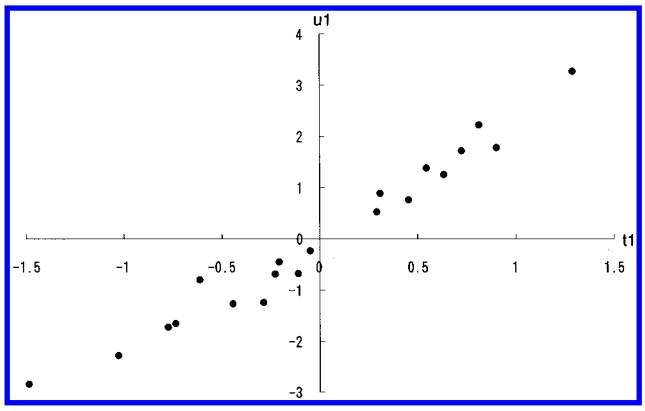


Figure 2. The PLS plot of the *y*-score (*u*) against *x*-score (*t*) for the first component of the nonlinear PLS model for *in vivo* MAO inhibitory activities.

activities and structural descriptors. The PLS plot of two scores (*u*, *t*) for the first component was shown in Figure 2.

DISCUSSIONS

The PLS loadings of two nonlinear PLS models were shown in Table 4. The loadings show how much the structural descriptors contribute to a component of the model.[20] A large loading value means that the structural descriptor is important in the model, and a small loading value means that it is only a minor contribution to the model. Hence, the structural requirements for the MAO inhibitory activities can be estimated from the PLS loadings. The structural descriptors with the loading values greater than ±0.3 were considered to be important ones in the model from a statistical point of view.[24]

First, the structural requirements for the *in vitro* MAO inhibitory activity were estimated. The all structural descriptors at ortho positions are significantly important. From the sign of the loading values, the activity is favored by large, electron-withdrawing and hydrophobic substituents at ortho positions. The descriptors related to the meta positions are not significant, and the structural requirements are not so clear. The electronic nature are important at para positions. The activity is increased when the electron-donating substituents are incorporated into the para positions. The *S*-stereochemistry is needed at α position for the activity from the loading value of the indicator variable.

Finally, the structural requirements for the *in vivo* MAO inhibitory activities were considered. The activities are favored by the electron-withdrawing substituents at ortho positions. The substituents at meta positions are limited to the ones with a small steric size. The large and electron-donating substituents are an advantage for the activity at para positions.

Table 4. Values of First Loading in the Nonlinear PLS Models

no.	variable	*in vitro* model p_1	*in vivo* model p_1
1	σ_m(o)	0.592	0.479
2	σ_p(o)	0.484	0.356
3	F(o)	0.607	0.503
4	R(o)	−0.552	−0.557
5	π(o)	0.687	0.163
6	MR(o)	0.640	0.083
7	L(o)	0.733	0.289
8	B_1(o)	0.724	0.270
9	B_5(o)	0.537	0.074
10	σ_m(m)	0.247	−0.249
11	σ_p(m)	0.296	−0.123
12	F(m)	0.236	−0.269
13	R(m)	−0.101	0.418
14	π(m)	0.120	−0.405
15	MR(m)	0.130	−0.397
16	L(m)	0.155	−0.360
17	B_1(m)	0.137	−0.391
18	B_5(m)	0.050	−0.445
19	σ_m(p)	−0.474	−0.585
20	σ_p(p)	−0.416	−0.933
21	F(p)	−0.174	0.113
22	R(p)	−0.277	−0.805
23	π(p)	−0.055	0.104
24	MR(p)	0.082	0.471
25	L(p)	0.125	0.337
26	B_1(p)	−0.305	−0.670
27	B_5(p)	0.255	0.630
28	I_{Me}	−0.228	−0.213
29	I_s	0.406	0.294

CONCLUSIONS

The four MAO inhibitory activities which have been shown to have nonlinearity were selected as the illustration. The *in vitro* and *in vivo* MAO inhibitory activities were analyzed separately. Two successful models have been obtained, and the structural requirements for the MAO inhibitory activities could be estimated from the PLS loadings.

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