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3D-QSAR study of insecticidal neonicotinoid compounds based on 3-way partial least squares model

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Abstract

A choice of an active conformer and the corresponding alignment rule is an important problem for determining the success of 3D-QSAR study. For flexible molecules, this problem is the most difficult one and construction of the method with appropriate chemometric tools has been required. Recently, Bro [J. Chemom., 10, 1996, 47–61] has proposed a trilinear PLS algorithm as the trilinear extension of standard bilinear PLS in the field of analytical chemistry. Bro's 3-way PLS method seems to be suitable to the 3D-QSAR problem but only few attempts have so far been made at the subject. The object of this study is to investigate the ability of Bro's 3-way PLS method for solving the conformer/alignment problem in 3D-QSAR study. The structure-activity data of insecticidal neonicotinoid compounds were used as a test example. The 3-way arrays were constructed from eight sample vectors and eight electrostatic similarity matrices derived from eight combinations of conformers and alignment rules. The correlation between the 3-way arrays and the insecticidal activity vector was investigated by Bro's 3-way PLS method. The 3-way PLS model with three significant components was obtained, and from its PLS loading the best combination of conformer and alignment rule could be selected.

Keywords: 3D-QSAR; Insecticidal neonicotinoid compounds; 3-Way partial least squares model

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1. Introduction

Quantitative structure-activity relationship (QSAR) is an important tool to keep the number of synthesized and tested compounds at a minimum in the process of development of new drugs [1]. The purpose of QSAR is to obtain the quantitative correlation of molecular structure with biological activity and to predict the biological activities for novel compounds. QSAR should help to characterize those structural features that are responsible for biological activity and the information is crucial for drug design. The various QSAR methods that can be applied are rather different, depending on whether 3-dimensional (3D) structure of the receptor is known or not. In the latter case, which frequently occurs, any quantitative correlation has to be focused on relative differences of structural features (descriptors) within a series of compounds [2].

The work of Hansch and Fujita [3] provided the first formalism for deriving the QSAR model which could be used to predict a biological activity from the structural descriptors. Although this method using multiple linear regression (MLR) has been of general use, there are a number of practical problems in the application to a data set of interest. A major limitation is that the descriptors are derived from 2-dimensional (2D) structure. The 2D descriptors are those based on experimentally derived octanol/water partition coefficients to model the hydrophobic effect, Hammett substituent constants to model electronic effects, and a wide range of descriptors, from molecular weights to complex topological indices, to model steric interactions [4]. In general, the drug–receptor interaction has to be described by 3D intermolecular forces [5], and the 2D descriptors are insufficient to explain a complex structure-activity data.

In recent years, the growth of computational chemistry has brought so-called 3D-QSAR study with molecular and atom-based descriptors [6]. The 3D-QSAR study includes the descriptors derived from individual atomic partial charges, HOMO/LUMO energies, and molecular fields such as comparative molecular field analysis (CoMFA)[7], etc. With these types of descriptors, one can easily end up with a data matrix consisting of a large number of descriptors. Multivariate statistical techniques have to be adopted with those many descriptors. MLR causes severe problems in that case because of chance correlation and multicollinearity among descriptors [8]. Techniques such as principal component analysis (PCA), principal component regression (PCR), and partial least squares regression (PLS), which identify a small number of latent variables that can explain biological activity, have been increasingly applied [9,10].

When analyzing a structure-activity data to generate the 3D-QSAR model, flexible molecules are the most difficult to be treated [11]. A choice of an active conformer and the corresponding alignment rule has to be undertaken, either in accordance with available experimental data or based on hypothetical assumptions. Thus, one of the key steps in the 3D-QSAR methodology is selection of the active conformer for each compound in the series, followed by the molecular alignment rule. The success of 3D-QSAR study is dependent on both selections.

In order to define the alignment rule for flexible molecules, one can use a variety of methods. If crystallographic data are available, the field-fit alignment procedure may be applied based on the crystal structure as a template molecule. The field-fit procedure minimizes the root-mean squares (RMS) difference between a fixed template field and the corresponding field of the molecules being aligned by adjusting atomic coordinates. This procedure has been extensively discussed in conjunction with alignment issues and applied to some data set [12,13]. When no structural data are available, the computational procedure using the conformational and cluster analysis may keep in finding the molecular alignment rule. In this procedure, low energy conformers of each molecule are generated and the best match between various molecules is selected from all possible combinations of conformers based on some fitting criteria. Active

analog approach (AAA) [14] and molecular shape analysis (MSA) [15] are the representative techniques belonging to the computational procedure.

The fundamental problem of the above mentioned methods, especially when crystallographic data are not available, is that the proposed solution is merely derived from the geometrical comparison among conformers. Because the result is not statistically examined with the structure-activity data, the correlation obtained from the proposed alignment rule may be spurious.

In a recent report, a novel chemometric approach for the 3D-QSAR problem was proposed and applied to a set of flexible DHFR inhibitors by Dunn et al. [16]. In their approach, the 3-way arrays were constructed from samples, conformers and alignments of DHFR inhibitors and the active conformer and alignment rule were predicted from the factor decomposition of the 3-way arrays using the 3-way PLS method. This approach was useful to suggest a new direction for the 3D-QSAR study, but unfortunately, the algorithm used as the 3-way PLS method (hereafter, denoted as Wold's method [17]) was not a trilinear PLS algorithm based on the basic property of PLS, namely maximum covariance between scores and activity in a trilinear sense. Wold's method is a kind of intermediate between the truly trilinear PLS and standard bilinear PLS because it unfolds the 3-way arrays to the 2-way matrix and uses the bilinear PLS algorithm. Recently, Bro has proposed a trilinear PLS algorithm as the trilinear extension of standard bilinear PLS [18]. He has applied this algorithm to the analytical problems and discussed its advantages compared with the unfolding method in view of fewer parameters and simplicity of the model. Bro's 3-way PLS method seems to be suitable to the 3D-QSAR problem but only few attempts have so far been made at the subject [19,20].

The object of this study is to investigate the ability of Bro's 3-way PLS method for solving the conformer/alignment problem in 3D-QSAR study. The structure-activity data of insecticidal neonicotinoid compounds were used as a test example [21]. At the beginning, four possible conformers on each compound were generated from the X-ray crystal structure of imidacloprid as a template compound and two alignment rules were considered to weight the pyridine and imidazolidine-like moiety as the pharmacophoric points of molecules. Electrostatic similarity index between all pairs of molecules based on the Carbo formula was used as structural descriptor [22]. Based on these definitions, the 3-way arrays were constructed from eight sample vector and eight electrostatic similarity matrices derived from eight combinations of conformers and alignment rules. The correlation between the 3-way arrays and the insecticidal activity vector was investigated by Bro's 3-way PLS method. The 3-way PLS model with three significant components was obtained to explain the insecticidal activity well. Finally, from the PLS loading and subsequently calculated scoring function, the best combination of conformer and alignment rule could be selected and its combination gave the standard (bilinear) PLS model with high internal predictivity.

2. Materials and methods

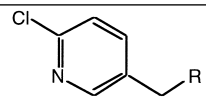
2.1. Data set

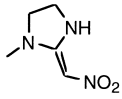
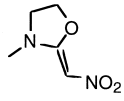
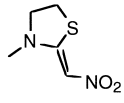
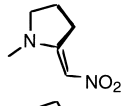
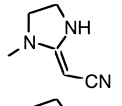
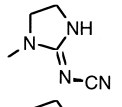
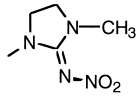
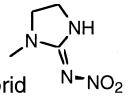
Eight neonicotinoid compounds with insecticidal activity were used in the 3D-QSAR study. The insecticidal activity was expressed as the logarithm of the reciprocal value of binding constant (K_i) against the nicotinic acetylcholine (ACh) receptor derived from the head of honey bee. The chemical structures and insecticidal activities of neonicotinoid compounds are shown in Table 1. The structure-activity data were taken from the study by Sukekawa and Nakayama [21]. Some compounds were removed from the data set because they did not have the imidazolidine-like moiety necessary for the alignment.

2.2. Molecular modelling

The conformational profiles of neonicotinoid compounds are defined by two torsion angles α and β (Fig. 1). Four possible conformers of imidacloprid were generated from its X-ray crystal structure [23]. Conformer 1 (C1) is identical to the X-ray crystal structure and the values of two torsion angles are defined to be zeros ($\alpha = 0$, $\beta = 0$). Conformer 2 (C2) is generated by rotating the first torsion angle of C1 conformer by 180-degrees ($\alpha = 180$, $\beta = 0$). Conformer 3 (C3) is generated by rotating the second

Table 1
Observed and calculated insecticidal activity for nicotinic acetylcholine receptor



No.	R	obs[a]	cal1[b]	cal2[c]
1		7.67	6.94	6.94
2		6.51	6.75	6.90
3		6.94	6.36	6.78
4		6.45	7.02	6.93
5		4.75	4.77	4.85
6		5.16	5.18	5.16
7		3.79	3.30	3.91
8 imidacloprid		5.81	6.15	5.67

[a]Observed activity.
[b]Calculated activity by 3-way PLS model.
[c]Calculated activity by standard PLS model.

torsion angle of C1 conformer by 180-degrees ($\alpha = 0$, $\beta = 180$). Conformer 4 (C4) is generated by rotating both torsion angles of C1 conformer by 180-degrees ($\alpha = 180$, $\beta = 180$). These conformers represent the possible relative configurations between the pyridine and imidazolidine-like moieties and the rational framework behind this conformer definition is fully described in the study of Okazawa et al. [24]. Four conformers of all compounds other than imidacloprid were constructed from the corresponding four conformers of imidacloprid by the standard fragment library in the molecular modelling software SPARTAN [25] implemented on the Silicon Graphics Workstation. Finally, to avoid the steric clash, all conformers were energy-minimized by the semi-empirical molecular orbital calculation with the AM1 method in SPARTAN.

Two alignment rules were considered in this 3D-QSAR study (Fig. 1). The first alignment focuses on the pyridine moiety and the second one focuses on the

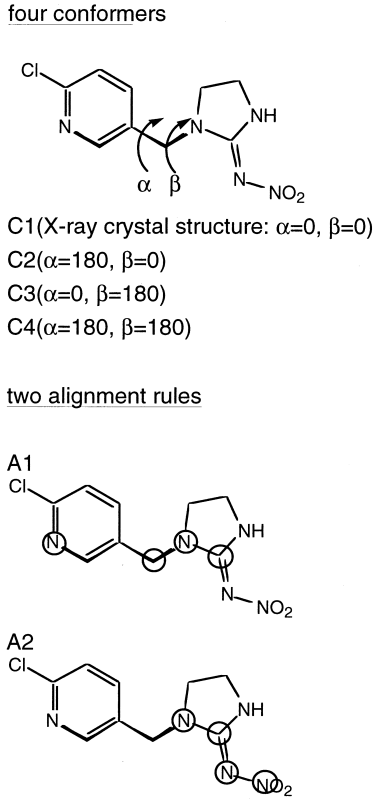


Fig. 1. Definition of conformers and alignment rules.

imidazolidine-like moiety of the molecule. The fitting atomic points for alignment were marked by a circle in Fig. 1. This alignment definition corresponds to the two binding modes proposed by Kagabu [23]. Four conformers of all compounds were superimposed on the corresponding ones of imidacloprid by the two alignment rules and then eight combinations of conformers and alignment rules were defined.

2.3. Structural descriptors

Electrostatic similarity index between all pairs of molecules was used as structural descriptors [22]. By comparing each molecule to every other in a series, the N by N similarity matrix is formed which provides a numerical representation of how all the molecules correlate. The electrostatic similarity index based on the Carbo formula C_{AB} is calculated from the electrostatic properties P_A and P_B of the two molecules being compared.

$$C_{AB} = \sum P_A \cdot P_B / \left(\sum P_A^2\right)^{1/2} \cdot \left(\sum P_B^2\right)^{1/2} \quad (1)$$

The numerator measures a property overlap while the denominator normalizes the similarity index. In this study, molecular electrostatic potential (MEP) was used as the electrostatic property P. MEP at the arbitrary position r ($P(r)$) is computed according to the following equation:

$$P(r) = \sum_{i=1}^{na} q_i / |r - r_i| \quad (2)$$

Here q_i is the point charge on atom i and r_i is its position and na is the number of atoms in the molecule. MEP is evaluated at the grid points around the two molecules using the point charge obtained from the AM1 method. In order to avoid singularities at the atomic nuclei, evaluation is restricted to grid points outside the van der Waals volume of the molecules. The resulting MEP values are then used to evaluate the electrostatic similarity index numerically. A symmetric N by N similarity matrix created from all pairs of molecules was calculated by the ASP (automated similarity package) program [26] implemented on a personal computer.

As a result, the eight by eight similarity matrix was generated from eight samples and then the 3-way arrays were constructed by collecting the eight similarity matrices (sheets) derived from the eight combinations of conformers and alignment rules (Fig. 2).

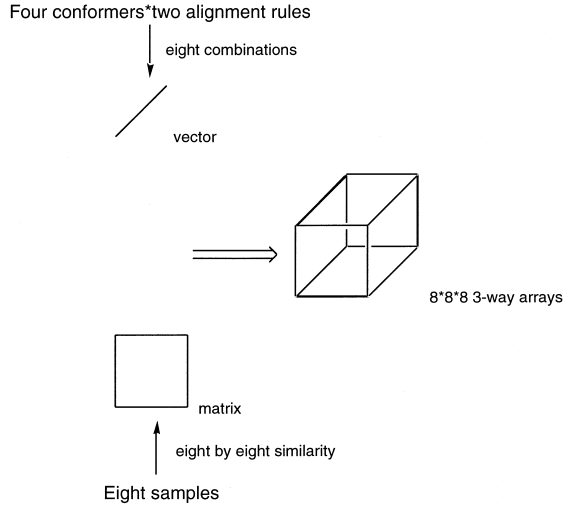


Fig. 2. 3-Way arrays for 3D-QSAR study.

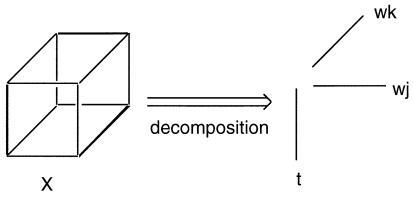


Fig. 3. Schematic illustration of 3-way PLS algorithm.

2.4. 3-Way PLS

The correlation between the 3-way arrays and the insecticidal activity vector was investigated by Bro's 3-way PLS method [18]. The goal of the method is to make a decomposition of the 3-way arrays into a set of triads. A triad consists of one score vector $\boldsymbol{t}$ and two weight vectors, the vector one in the second mode called $\boldsymbol{wj}$ and in the third mode called $\boldsymbol{wk}$ (Fig. 3). The model of X is given by the equation:

$$X = \sum_{h=1}^{A} \boldsymbol{t}_h \otimes \boldsymbol{wj}_h \otimes \boldsymbol{wk}_h + E \quad (3)$$

$$\boldsymbol{y} = \sum_{h=1}^{A} \boldsymbol{t}_h \cdot q_h + f \quad (4)$$

where X and $\boldsymbol{y}$ are the 3-way arrays and insecticidal activity vector, respectively. Symbol Z is the Kronecker product. E and f are the model residuals of X and $\boldsymbol{y}$. A is the number of components determined by a cross-validation experiment (see Section 3). The score $\boldsymbol{t}$ is expressed by X and two weight vectors $\boldsymbol{wk}$ and $\boldsymbol{wj}$.

$$\boldsymbol{t} = X(\boldsymbol{wk} \otimes \boldsymbol{wj}) \quad (5)$$

The weight vectors $\boldsymbol{wj}$ and $\boldsymbol{wk}$ should give the score $\boldsymbol{t}$ that simultaneously satisfies two conditions: (i) the score $\boldsymbol{t}$ is highly correlated with the dependent variable $\boldsymbol{y}$; (ii) the score $\boldsymbol{t}$ models the variance among the independent variables X as much as possible. By the simple algebraic manipulations, the problem of finding the vector $\boldsymbol{wj}$ and $\boldsymbol{wk}$ leads to a singular value decomposition (SVD) of $\mathbf{Z}$ [18]. The matrix $\mathbf{Z}$ is a J by K matrix with the jk'th element being the inner product of $\boldsymbol{y}$ and the column obtained by fixing the second and third mode of X at $\boldsymbol{j}$ and k, respectively. The 3-way PLS analysis was carried out using the MATLAB program [27] implemented on the Power Macintosh computer. The source code of the 3-way PLS method is available from World Wide Web (http://newton.foodsci.kvl.dk/foodtech).

3. Results and discussion

3.1. 3-way PLS analysis

In PLS, determination of the optimum number of components is an important factor to obtain a predictive PLS model [9,10]. For this purpose, a cross-validation experiment was performed, monitoring the internal predictivity of the model at each component [28]. The optimum number of components was assumed to be one which gives the highest internal predictivity of the PLS model in the cross-validation experiment. A squared predictive correlation coefficient Q^2 with the leave-one-out procedure was used as the index of the internal predictivity. Q^2 is defined as follows:

$$Q^2 = 1 - \sum_{i=1}^{n} (\boldsymbol{y}_{i,\mathrm{obs}} - \boldsymbol{y}_{i,\mathrm{pred}})^2 / \sum_{i=1}^{n} (\boldsymbol{y}_{i,\mathrm{obs}} - \boldsymbol{y}_{\mathrm{ave}})^2 \quad (6)$$

where $y_{i,\mathrm{obs}}$ and $y_{i,\mathrm{pred}}$ are the observed and predicted activity for sample i, respectively. y_{ave} is the averaged activity and n is the number of samples. Table 2 shows the Q^2 value for each component after centering the insecticidal activity vector $\boldsymbol{y}$ and electrostatic similarity 3-way arrays X. The values of the explained variance of X and $\boldsymbol{y}$ are also listed in Table 2. The cross-validation experiment indicates that three is the optimal number of components ($A = 3$). The calculated insecticidal activity given by the 3-way PLS model with three components is shown in Table 1.

In order to select the best conformer/alignment combination from a statistical point of view, the PLS loading of the second weight vector $\boldsymbol{wk}$ was examined. The loading represents how much each conformer/alignment combination contributes to a component of the model. The loading values of the 3-way PLS model up to three components are shown in

Table 2
Results of 3-way PLS analysis

Component	1	2	3	4	5
Explained variance of X	0.542	0.841	0.903	0.916	0.933
Explained variance of $\boldsymbol{y}$	0.792	0.884	0.956	0.974	0.998
Q^{2a}	0.597	0.791	0.855	0.803	0.829

[a] Squared predictive correlation coefficient.

Table 3
Loading of second weight vector and scoring function

Component	1	2	3	F_s[a]
C1A1[b]	0.378	0.289	0.360	0.352
C1A2	0.388	0.423	0.278	0.366
C2A1	0.292	0.291	0.472	0.292
C2A2	0.356	0.386	0.355	0.343
C3A1	0.367	0.283	0.312	0.339
C3A2	0.387	0.427	0.242	0.363
C4A1	0.280	0.284	0.433	0.279
C4A2	0.363	0.402	0.319	0.347

[a]Scoring function.
[b]Combinations of conformer/alignment.
For the definitions, see Fig. 1.

Table 3. From the table, no clear by dominant combination for the insecticidal activity is observed. Therefore, for ranking the set of conformer/alignment combination numerically, a scoring function (F_s) incorporating the partial explained variance and loading of second weight vector was computed according to the previous 3-way PLS analysis [16]:

$$F_s = \sum_{h=1}^{3} \mathrm{pv}_h \cdot \boldsymbol{wk}_h \qquad (7)$$

where pv_h and $\boldsymbol{wk}_h$ are the partial explained variance of $\boldsymbol{y}$ and loading value of the second weight vector at the h-th component, respectively. The F_s value of each combination is shown in Table 3. As Table 3 indicates, the combination (C1A2) gives the highest scoring function among eight combinations. Thus, the 3-way PLS analysis supports the X-ray crystal structure and binding mode 2 as the conformer and alignment rule of imidacloprid. This result should be validated with the direct biochemical experiments. For example, the complex structure of ACh receptor and imidacloprid are decided by the X-ray crystallography or high resolution NMR. However, since such experiments have not been reported so far, the predicted conformer/alignment combination (C1A2) is assumed to be a good candidate and the standard PLS analysis was performed for the 3D-QSAR study.

3.2. Standard PLS analysis

For the best conformer/alignment combination (C1A2), the standard PLS method was applied [9,10]. The insecticidal activity and corresponding similarity matrix were mean centered before the standard PLS analysis. A three-component PLS model was derived by the cross-validation experiment based on the Q^2 value. The insecticidal activity calculated by the standard PLS model equation is shown in Table 1. Converting the score $\boldsymbol{t}$ to the original structural descriptors according to the previous study [29], the following QSAR equation (MLR-like equation) with the mean centered descriptors was obtained.

$$\begin{aligned}\log(1/K_i) = {} & 2.045 * C_{1j} + 1.935 * C_{2j} \\ & + 1.697 * C_{3j} + 1.765 * C_{4j} \\ & + 0.695 * C_{5j} + 0.519 * C_{6j} \\ & - 1.610 * C_{7j} + 0.254 * C_{8j}\end{aligned}$$

$$n = 8, A = 3,$$

$$R^2 = 0.913, Q^2 = 0.800 \qquad (8)$$

where n, A, R^2, and Q^2 are the number of samples, the number of components, the squared correlation coefficient, and the cross-validated r-squared value, respectively. C is the Carbo similarity index whose definition is described in Section 2.3. The sign of regression parameters in the MLR-like model equation indicates that the most active molecules should in their electrostatic properties be similar to compound 1 and dissimilar to compound 7. This is indeed the real structure-activity result. Compound 1 has the highest activity while compound 7 has the lowest activity in the data set. This easy-to-understand interpretation is the advantage of the similarity approach [30].

As a supplement, the standard PLS method was applied to the remaining seven combinations and their Q^2 values were calculated. The calculated Q^2 values are listed in Table 4. The Q^2 values of seven

Table 4
Results of standard PLS analysis

	A[a]	R^2[b]	Q^2[c]
C1A1[d]	4	0.955	0.782
C1A2	3	0.913	0.800
C2A1	4	0.933	0.471
C2A2	5	0.985	0.700
C3A1	4	0.949	0.738
C3A2	3	0.903	0.763
C4A1	2	0.761	0.395
C4A2	5	0.982	0.685

[a]Number of components.
[b]Squared correlation coefficient.
[c]Squared predictive correlation coefficient.
[d]Combinations of conformer/alignment.
For the definitions, see Fig. 1.

combinations were inferior to that of the best combination (C1A2). This suggests that the 3-way PLS method may give a potential solution to the conformer/alignment problem in 3D-QSAR study although the general utility could not be guaranteed by this preliminary study.

4. Conclusion

This paper demonstrates that the 3-way PLS method with Bro's trilinear algorithm may give a potential solution to the conformer/alignment problem in 3D-QSAR study. From the loading vector of the obtained 3-way PLS model, the best conformer and alignment rule of neonicotinoid compounds could be selected from the chemometric point of view. The best combination gave the standard PLS model with high internal predictivity and the insecticidal activities were fully explained.

The advantage of Bro's 3-way PLS method, compared to the unfolding methods such as Wold's method, is twofold. Bro's method is much more parsimonious. This means the model is simple and easier to interpret because the model uses fewer parameters. Moreover, the model is potentially less prone to noise, because the information across all modes is used for the decomposition.

Bro's 3-way PLS method should be applied to other types of 3D-QSAR study. Especially, selection of the best conformer/alignment combination is also a critical problem in CoMFA and this matter will be investigated in our future report.

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