

Application of the Novel Molecular Alignment Method Using the Hopfield Neural Network to 3D-QSAR

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Recently, we investigated and proposed the novel molecular alignment method with the Hopfield Neural Network (HNN). Molecules are represented by four kinds of chemical properties (hydrophobic group, hydrogen-bonding acceptor, hydrogen-bonding donor, and hydrogen-bonding donor/acceptor), and then those properties between two molecules correspond to each other using HNN. The 12 pairs of enzyme–inhibitors were used for validation, and our method could successfully reproduce the real molecular alignments obtained from X-ray crystallography. In this paper, we apply the molecular alignment method to three-dimensional quantitative structure–activity relationship (3D-QSAR) analysis. The two data sets (human epidermal growth factor receptor-2 inhibitors and cyclooxygenase-2 inhibitors) were investigated to validate our method. As a result, the robust and predictive 3D-QSAR models were successfully obtained in both data sets.

INTRODUCTION

Comparative Molecular Field Analysis (CoMFA)¹ has been widely used as a powerful 3D-QSAR (Quantitative Structure–Activity Relationship) tool in the field of medicinal chemistry. In CoMFA, steric and electrostatic field variables are calculated with a probe atom at intersections of three-dimensional lattice around the compound using Lennard-Jones and Coulomb potentials. Then the statistical model is constructed between their field variables and biological activities of molecules. Usually the PLS (Partial Least Squares) method is used as a regression method. The results of CoMFA can be easily understood by drawing contour plots of regression coefficients of a PLS model.

CoMFA is frequently used as a standard QSAR technique, but some problems still remain. Molecular alignment is one of the key problems in QSAR study. In the CoMFA and most other 3D-QSAR techniques, proper alignment between molecules is necessary. Since molecular alignment is an important factor in 3D-QSAR analysis, a variety of methodologies have been proposed^{2–7} and reviewed by Lemmen and Lengauer.⁸ We also proposed the new method that can solve the conformation/alignment problem using 4-way PLS formulation.^{2,3} Possible 3D conformations of all molecules are generated by conformational analysis, and they are characterized by field variables of CoMFA with some possible alignment rules. Then 4-way array for 4-way PLS analysis is created according to the similarity measure, and conformations largely contributing to the inhibitory activity are selected as an active conformer by regression coefficients of the 4-way PLS model. To demonstrate the general utility, the data set of glucose analogue inhibitors of glycogen phosphorylase² and benzodiazepine analogue inhibitors of cholecystokinin³ were used as test samples.

Recently, we investigated and proposed the novel molecular alignment method with the Hopfield Neural Network (HNN).⁹ This alignment method is based on the methodology which solves the pattern-matching problem developed by Doucet et al.¹⁰ Molecules are represented by four kinds of chemical properties (hydrophobic group, hydrogen-bonding acceptor, hydrogen-bonding donor, and hydrogen-bonding donor/acceptor), and then those properties between two molecules correspond to each other using HNN. In the previous paper,⁹ the 12 pairs of enzyme–inhibitors were used for validation, and our method could successfully reproduce the real molecular alignments obtained from X-ray crystallography. In this paper, we apply the molecular alignment method to three-dimensional quantitative structure–activity relationship (3D-QSAR) analysis. The two data sets (human epidermal growth factor receptor-2 inhibitors and cyclooxygenase-2 inhibitors) were investigated to validate our method. The robust and predictive CoMFA models could be successfully obtained in both data sets.

METHOD

Novel Alignment Method using HNN. Molecules are represented by four kinds of chemical properties (hydrophobic group, hydrogen-bonding acceptor, hydrogen-bonding donor, and hydrogen-bonding donor/acceptor), and then those properties between two molecules correspond to each other using HNN. This scheme is a natural extension of the pattern-matching method which was introduced by Doucet et al.¹⁰ The details of the alignment method were explained in our previous paper.⁹

The definitions of chemical properties used in this study are listed below. The definitions are cited from ref 4. Users of the alignment method can change these flexible definitions depending on the alignment problem to be solved.

(1) Hydrophobic group (HY): (A) aromatic ring of a phenyl, naphthalene, pyridine, thiophene, etc.; (B) an aliphatic chain with alkyl chain of three atoms or more; and (C) trifluoromethyl.

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2. Hydrogen-bonding donor (HD): the nitrogen atom accompanying a hydrogen atom, such as an amine, amide, amidine, or guanidine.

3. Hydrogen-bonding acceptor (HA): the oxygen atom of a carbonyl, sulfone, phosphone, ester, ether, etc.

4. Hydrogen-bonding donor/acceptor (HDA): (A) the oxygen atom of a hydroxyl group and (B) the sulfur atom of a thiol group.

Hopfield Neural Network. The pattern matching problem with chemical properties is a combinatorial optimization problem, and it is said to be a NP-hard problem. If the number of chemical properties is huge, calculations cannot be finished within a practical time. To overcome this problem, HNN was used as an optimization tool. HNN was proposed by Hopfield and Tank,¹¹ and it was applied to the NP-complete problem such as the Traveling Salesman Problem for proving its capability of optimization.¹² Neurons arranged in a single layer have values of 1 or 0. Each neuron is connected to each other in a symmetrical manner. First, values of all neurons are randomly initialized (i.e. about half of neurons are set 1, and the others are set 0), and then each neuron is iteratively updated according to Hebb's rule

$$\sum_j W_{ij} S_j - \theta_i > 0: S_i = 1$$

$$\leq 0: S_i = 0 \quad (1)$$

where θ_i is the threshold value, and S_i is the state of the neuron i , and W_{ij} is the weight value between the neurons i and j . As a result of this iteration, the energy value of the HNN system is minimized. The energy value of the HNN system is calculated by the following energy function:

$$E = -\frac{1}{2} \sum_i \sum_{j \neq i} W_{ij} S_i S_j + \sum_i \theta_i S_i \quad (2)$$

This energy function is the general form of the HNN system. Values of W_{ij} and θ_i are automatically determined by comparing the HNN system with each problem to be solved.

The energy function used in this study is described below. The energy function consists of five terms.

$$\text{Energy} = \sum_i^5 T_i \quad (3)$$

The first two terms are

$$T_1 + T_2 = \sum_{il} \sum_{jl}^{mn} S_{il} S_{jl} [A \delta_{lj} (1 - \delta_{ij}) + B \delta_{ij} (1 - \delta_{lj})] \quad (4)$$

where m and n are the numbers of chemical properties assigned to molecules A and B. S_{il} is the state of the neuron placed (i, l). δ_{ij} is the Kronecker delta function that returns 1 if i is equal to j and returns 0 otherwise. As a result of the minimization of these terms, each chemical property of the molecule corresponds to at most one chemical property of the other molecule.

The third one

$$T_3 = C[\min(m, n) - \sum_{il}^{mn} S_{il}] \quad (5)$$

Table 1. Scores between Chemical Properties

| | HY | HD | HA | HDA |
|-----|-----|-----|-----|-----|
| HY | -3 | Inf | Inf | Inf |
| HD | Inf | -2 | Inf | -1 |
| HA | Inf | Inf | -2 | -1 |
| HDA | Inf | -1 | -1 | -1 |

maximizes the number of correspondence of chemical properties.

The fourth one

$$T_4 = D[\sum_{il} \sum_{jl}^{mn} S_{il} S_{jl} (1 - \delta_{ij})(1 - \delta_{lj}) |d_A(ij) - d_B(lj)|] \quad (6)$$

evaluates the difference in distance between corresponding chemical properties.

The fifth one

$$T_5 = E[\sum_{il}^{mn} S_{il} P(i, l)] \quad (7)$$

evaluates the consistency of each kind of chemical property. The definition of the score matrix P is shown in Table 1. If the kind of chemical property is different, the infinite value is added to the energy value. These values are cited from ref 4. The definition of the energy function described above is based on the previous definition by Doucet et al.,¹⁰ and the chemical meaning of each term is explained in the reference paper. A, B, C, D, and E are constants to adjust the weight of each term. These coefficients are determined depending on the purpose of molecular alignment or the number of chemical properties and so on. The ratio of coefficients used in this study is decided by empirical trials:

$$A:B:C:D:E = 4:4:8:1:1 \quad (8)$$

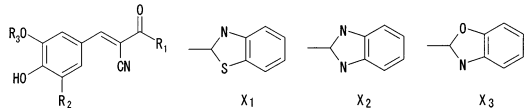
The results of HNN depend on initial condition and cannot always find the global minimum. Therefore, multiple calculations of HNN are necessary to avoid local minimum. In this study, the learning of HNN was carried out 100 times with a different initial state at each pair of conformers. The result that gave the minimum energy was adopted as the final molecular alignment.

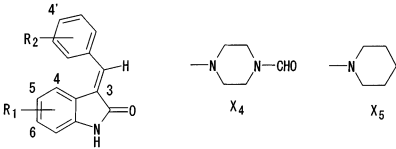
Data Set. In this paper, as an application of the novel alignment method, the CoMFA studies for the two data sets are reported. The first data set is the series of 27 inhibitors of human epidermal growth factor receptor-2 (HER2).¹³ And the second one is the series of 54 inhibitors of cyclooxygenase-2 (COX-2).¹⁴ The pIC_{50} values are used as biological activities in both data sets. The chemical structures and their activities are shown in Tables 2 and 3.

RESULTS AND DISCUSSION

Data Set of HER2 Inhibitors. The 27 HER2 inhibitors can be divided into two groups after their chemical structures. The first group is the benzylidene malononitrile family (compounds 1–19), and the second one is the 3-substituted indoline-2-ones family (compounds 20–27). Compounds 13 and 21 were used to represent each family in accordance with ref 13, and conformational analysis was carried out for compounds 13 and 21. Each structure was built from the fragment library of SPARTAN,¹⁵ and conformations were

Table 2. HER2 Inhibitors and Their Activities

|  | | | | |
|--|--|---|----------------|-------------------|
| no. | R ₁ | R ₂ | R ₃ | pIC ₅₀ |
| 1 | -NH-Ph | -H | -H | 4.35 |
| 2 | -NH-CH ₂ -Ph | -H | -H | 4.92 |
| 3 | -NH-(CH ₂) ₂ -Ph | -H | -H | 5.03 |
| 4 | -NH-(CH ₂) ₃ -Ph | -H | -H | 4.48 |
| 5 | -NH-(CH ₂) ₄ -Ph | -H | -H | 4.66 |
| 6 | -Ph | -H | -H | 4.70 |
| 7 | -NH-CH ₂ -(4'-OH)-Ph | -H | -H | 5.54 |
| 8 | -NH-(4'-Cl)-Ph | -H | -H | 4.21 |
| 9 | -NH-(2',4'-di-OMe)-Ph | -H | -H | 4.70 |
| 10 | -NH-(2',6'-di-Me)-Ph | -H | -H | 4.36 |
| 11 | -NH-(2',4',6'-tri-Me)-Ph | -H | -H | 4.68 |
| 12 | -NH-cyclo-C ₆ H ₁₁ | -H | -H | 4.72 |
| 13 | -NH ₂ | -CH ₂ -S-Ph | -Me | 6.89 |
| 14 | -NH ₂ | -CH ₂ -S-(2'-COOH)-Ph | -Me | 6.35 |
| 15 | -NH ₂ | -CH ₂ -S-(4'-Me)-Ph | -Me | 5.78 |
| 16 | -NH ₂ | -CH ₂ -S-CH ₂ -Ph | -Me | 6.70 |
| 17 | -NH ₂ | -CH ₂ -S-X ₁ | -Me | 6.46 |
| 18 | -NH ₂ | -CH ₂ -S-X ₂ | -Me | 5.82 |
| 19 | -NH ₂ | -CH ₂ -S-X ₃ | -Me | 5.21 |

|  | | | |
|--|----------------|-----------------------------------|-------------------|
| no. | R ₁ | R ₂ | pIC ₅₀ |
| 20 | H | 4'-X ₄ | 4.04 |
| 21 | H | 4'-X ₅ | 4.03 |
| 22 | H | 3',5'-di-CMe ₃ ,4'-OH | 4.19 |
| 23 | 5-Cl | 3',5'-di-CHMe ₂ ,4'-OH | 5.09 |
| 24 | H | 3'-CMe ₃ ,4'-OMe,5'-Br | 4.72 |
| 25 | H | 4'-CHMe ₂ | 4.77 |
| 26 | H | 3',5'-di-CHMe ₂ ,4'-OH | 5.15 |
| 27 | H | 3'-CHMe ₂ ,4'-OMe | 4.88 |

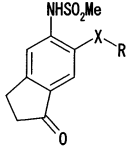
generated with the "systematic" option in SPARTAN. Geometry optimizations were carried out using molecular mechanics (SYBYL) with no solvent. As a result, the number of conformers of compounds 13 and 21 were 50 and 8, respectively. Many alignment rules between compounds 13 and 21 were obtained from HNN, and the best one that has the minimum energy value of HNN was selected as molecular alignment. The correspondence of chemical properties of compounds 13 and 21 is shown in Figure 1, and the molecular alignment is shown in Figure 2. The other compounds were built from the selected conformers of compounds 13 and 21. The molecular alignment of all compounds is shown in Figure 3.

Then the CoMFA model was constructed with conformations and molecular alignment shown in Figure 3. As a result, the robust PLS model could be obtained. The number of components was two, the value of R^2 was 0.805, and the value of Q^2 is 0.701. The standard error of estimation was 0.18, and the standard error of cross-validated prediction was 0.40, respectively. The contour plots of the regression coefficients are shown in Figure 4. In the figure the red regions represent coefficient of plus value and the blue regions represent minus value, respectively. In the steric contour plot, the red regions exist around the R₂ position of

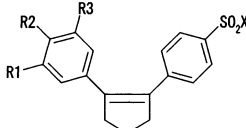
compounds 1–19. Indeed, compounds that have high activities (13–19) have a bulky group at the R₂ position, and the other compounds (1–12) have no substituent at the R₂ position. The blue region near the R₁ position indicates that the bulky group decreases the binding affinity. For example, compounds 1–12 have a bulky group at the R₁ site, but compounds 13–19 have only a small amide group. In the electrostatic contour plot, the red regions exist near the R₁ position and the blue region exists near the R₂ position, respectively. Indeed, for compounds that have high activities (13–19), R₁ is an amino group and compounds 1–12 have more electrostatically negative substituents. Similarly, the carbon atoms are placed around the blue region for compounds 13–19, and hydrogen atoms are placed there for compounds 1–12. From these observations, it can be said that a sufficient CoMFA model was constructed.

Data Set of COX-2 Inhibitors. The 54 COX-2 inhibitors were divided into three groups after their chemical structures. The first group contains compounds 1–11, 39–43, and 48, the second group contains compounds 12–37, 44–47, and 49–54, and last one is compound 38. For the first two groups, compounds 11 and 37 were used to represent each group in accordance with ref 14. Then conformational analysis of each template structure was carried out as in the

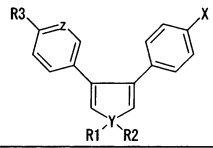
Table 3. COX-2 Inhibitors and Activities



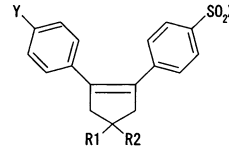
| Compounds | X | R | Activity (pIC ₅₀) |
|-----------|-----------------|------------------------|-------------------------------|
| 1 | S | 3-MePh | 5.0 |
| 2 | O | 4-MeSPh | 7.0 |
| 3 | O | cyclohexyl | 7.3 |
| 4 | SO ₂ | 2,4-F ₂ Ph | 5.0 |
| 5 | NH | 2,4-F ₂ Ph | 6.0 |
| 6 | CH ₂ | 2,4-F ₂ Ph | 6.7 |
| 7 | O | cyclopentyl | 6.0 |
| 8 | S | 3-FPh | 5.0 |
| 9 | S | 4-FPh | 6.0 |
| 10 | S | 2,6-F ₂ Ph | 7.0 |
| 11 | O | 2,4-Cl ₂ Ph | 8.1 |



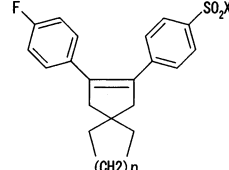
| | R ₁ | R ₂ | R ₃ | X | |
|----|----------------|-----------------|----------------|-----------------|-----|
| 12 | H | F | H | Me | 7.6 |
| 13 | H | CF ₃ | F | Me | 6.1 |
| 14 | H | F | H | NH ₂ | 8.2 |



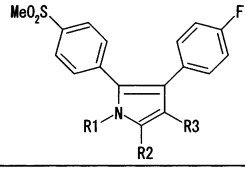
| | R ₁ | R ₂ | R ₃ | X | Y | Z | |
|----|----------------|----------------|----------------|---------------------------------|---|----|-----|
| 15 | Me | Me | F | SO ₂ Me | C | CH | 7.3 |
| 16 | Me | Me | F | SO ₂ NH ₂ | C | CH | 8.5 |
| 17 | - | - | F | SO ₂ Me | S | N | 6.7 |
| 18 | - | - | OMe | OMe | S | CH | 6.1 |



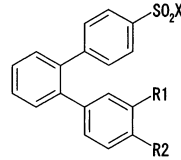
| | R ₁ | R ₂ | X | Y | |
|----|----------------|----------------|-----------------|----|-----|
| 19 | H | H | Me | F | 7.6 |
| 20 | H | H | NH ₂ | Cl | 8.5 |
| 21 | Me | Me | Me | F | 7.8 |
| 22 | H | H | NH ₂ | F | 8.2 |



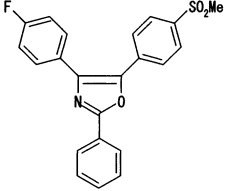
| | N | X | |
|----|---|-----------------|-----|
| 23 | 0 | Me | 8.1 |
| 24 | 1 | Me | 8.4 |
| 25 | 0 | NH ₂ | 8.5 |
| 26 | 1 | NH ₂ | 8.7 |



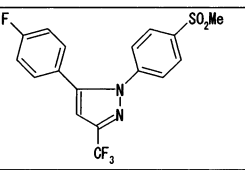
| | R ₁ | R ₂ | R ₃ | |
|----|----------------|----------------|----------------|-----|
| 27 | COMe | Br | H | 3.5 |
| 28 | Me | Cl | Cl | 4.6 |
| 29 | H | H | H | 4.9 |
| 30 | Me | H | H | 4.7 |
| 31 | H | SCN | H | 4.1 |



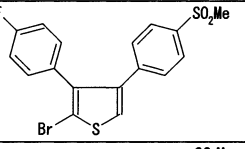
| | X | R ₁ | R ₂ | |
|----|-----------------|----------------|----------------|-----|
| 32 | Me | H | Cl | 6.9 |
| 33 | NH ₂ | Cl | OMe | 7.7 |



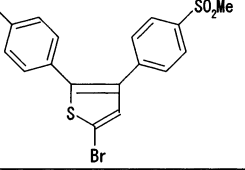
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|----|--|--|--|-----|
| 34 | | | | 7.4 |
|----|--|--|--|-----|



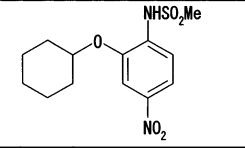
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|----|--|--|--|-----|
| 35 | | | | 7.3 |
|----|--|--|--|-----|



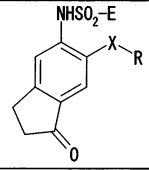
| | | | | |
|----|--|--|--|-----|
| 36 | | | | 7.0 |
|----|--|--|--|-----|



| | | | | |
|----|--|--|--|-----|
| 37 | | | | 8.0 |
|----|--|--|--|-----|

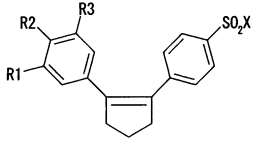
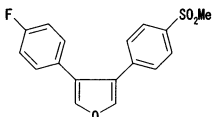
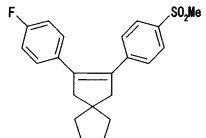
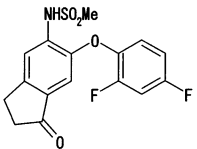
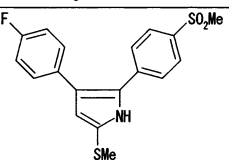
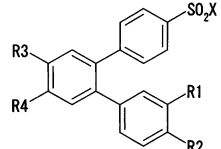


| | | | | |
|----|--|--|--|-----|
| 38 | | | | 5.4 |
|----|--|--|--|-----|



| | X | E | R | |
|----|---|----|-----------------------|-----|
| 39 | S | Me | 2,4-F ₂ Ph | 7.6 |
| 40 | S | Me | cyclohexyl | 7.3 |
| 41 | S | Et | 2,4-F ₂ Ph | 5.0 |
| 42 | S | Me | 4-i-PrPh | 5.0 |
| 43 | S | Me | 4-CO ₂ HPh | 5.0 |

Table 3. (Continued)

| | | | | | |
|---|-----------------|----------------|----------------|----------------|----------------|
|  | | | | | |
| | R ₁ | R ₂ | R ₃ | X | |
| 44 | H | Cl | H | Me | 8.5 |
| 45 | Cl | OMe | Cl | Me | 7.8 |
|  | | | | | |
| 46 | | | | | 5.7 |
|  | | | | | |
| 47 | | | | | 7.2 |
|  | | | | | |
| 48 | | | | | 7.3 |
|  | | | | | |
| 49 | | | | | 4.5 |
|  | | | | | |
| | X | R ₁ | R ₂ | R ₃ | R ₄ |
| 50 | Me | H | F | H | H |
| 51 | NH ₂ | F | OMe | H | H |
| 52 | Me | H | F | F | F |
| 53 | Me | H | F | Cl | Cl |
| 54 | Me | Cl | OMe | H | H |

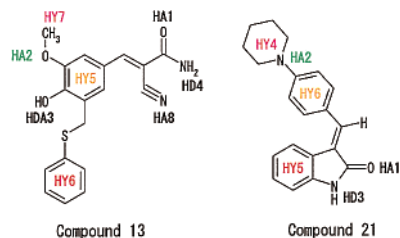


Figure 1. Correspondence of chemical properties.

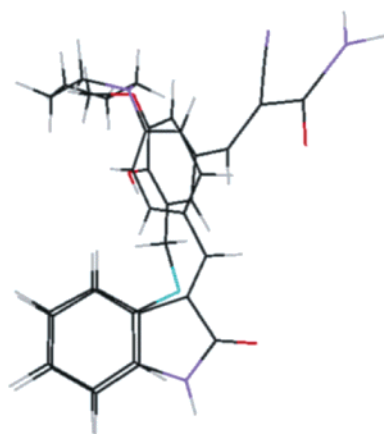


Figure 2. Alignment of compounds 13 and 21.

case of HER2. Each structure was built from the fragment library of SPARTAN, and possible conformations were generated with "systematic" option. Geometry optimizations were carried out using molecular mechanics (SYBYL) with no solvent. As a result, the number of conformers for compounds 11, 37, and 38 were 57, 21, and 47, respectively. Then two independent searches for the alignment rule (compounds 11 and 38 and compounds 37 and 38) were carried out using HNN, and the alignment rule that has the common conformation for compound 38 was selected as the best one. The correspondence of chemical properties is shown

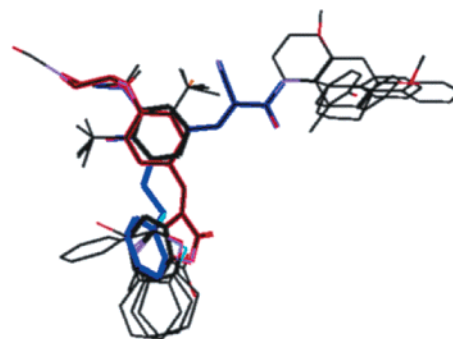


Figure 3. Alignment of all compounds with compounds 13 (blue) and 21 (red).

in Figure 5, and the molecular alignment is shown in Figure 6.

The CoMFA model was constructed with the selected conformations and molecular alignment. To remove outliers and improve model performance, the PLS regression models were separately constructed for groups 11 and 37. The CoMFA model for group 11 had one latent component with $R^2 = 0.518$ and $Q^2 = 0.205$. The CoMFA model for group 37 had three latent components with $R^2 = 0.907$ and $Q^2 = 0.617$. The difference between calculated activity and experimental activity was calculated at each compound, and the compound that has a larger error than 1.5 was presumed as an outlier. From this preliminary analysis, compound 39 (group 11) and compounds 13, 27, 34, and 54 (group 37) were eliminated as outliers. The final CoMFA model was constructed with the remaining 49 compounds, and it had four latent variables with $R^2 = 0.922$ and $Q^2 = 0.653$. The standard error of estimation was 0.36, and the standard error of cross-validated prediction was 0.77, respectively. Since the values of R^2 and Q^2 are large enough, it can be said that the model is robust and predictive. Figure 7 contains the contour plots of the regression coefficients of the final CoMFA model with reference compounds 11 and 37. The four red regions in the steric contour plot (a) around R_1 and R_2 indicate that bulky substituents increase activity. Com-

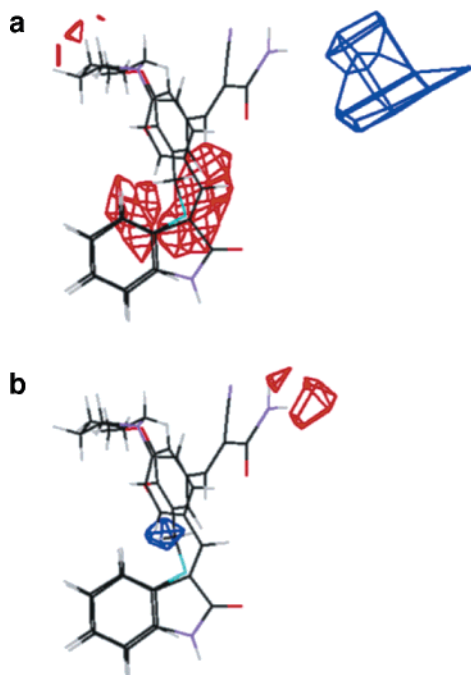


Figure 4. Contour plots of the CoMFA model: (a) steric and (b) electrostatic.

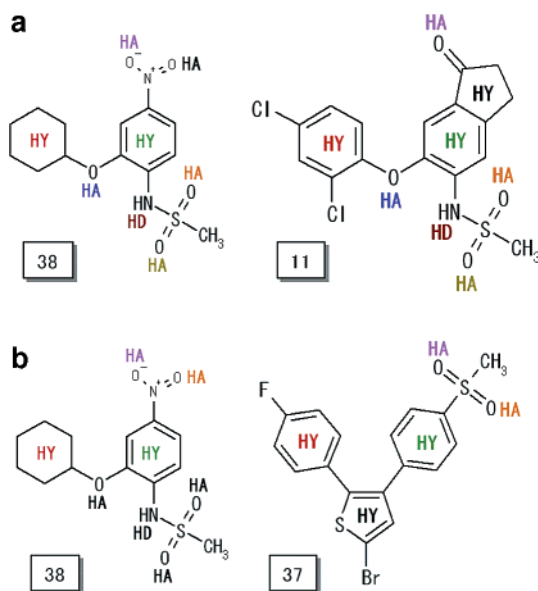


Figure 5. Correspondence of chemical properties: (a) compounds 38 and 11 and (b) compounds 38 and 37.

pounds 15, 16, 21, and 47 have a bulky group around these regions and actually have high activities. Figure 7(b) contains the contour plot for the electrostatic field variables. The blue region around the oxygen atom in a five-membered ring of compound 34 indicates that a heteroatom such as oxygen or nitrogen is favorable for activity. Red regions near sulfonic acid of compound 25 indicate that sulfone amide is favorable for activity.

CONCLUSION

In this paper, we apply the novel molecular alignment method using HNN to 3D-QSAR. To validate our method, the two data sets of HER2 and COX-2 inhibitors were investigated. Although each data set consists of molecules that have different chemical skeletons, proper alignment

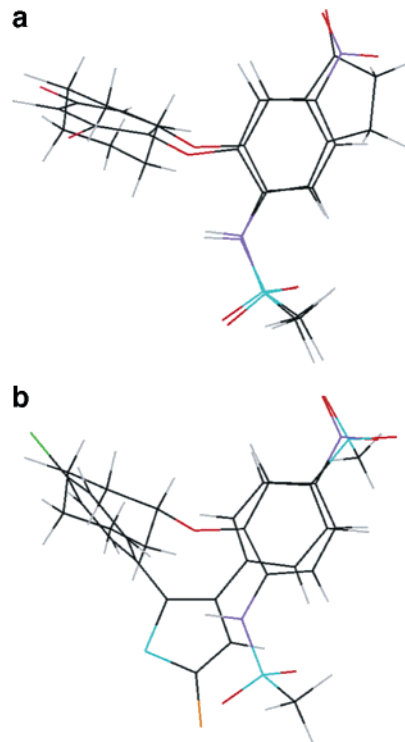


Figure 6. Alignments of active conformers: (a) compounds 38 and 11 and (b) compounds 38 and 37.

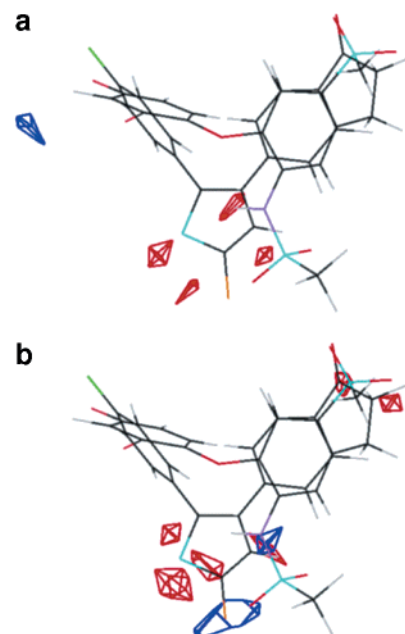


Figure 7. Contour plots of the CoMFA model: (a) steric and (b) electrostatic.

could be obtained. As a result of molecular alignment and subsequent QSAR study, the robust and predictive CoMFA models were obtained for both data sets. These models nicely represent the important regions for biological activity, and ideas for further chemical modifications could be easily generated.

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