QSPR Study on the Binding Constants of Coumarins and Human Serum Albumin

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Three-dimensional holographic vector of atomic interaction field (3D-HoVAIF) was used to describe the chemical structures of 20 coumarins and it was employed to the quantitative structure property relationship studies between the binding constants of coumarins and human serum albumin. Here the quantitative structure property relationship model was built by multiple linear regression and partial least square regression. The stability and prediction ability of the established model were strictly examined by leave-one-out cross-validation and external validation. Meanwhile, the model of built pointed out hydrophobic interaction is important especially the hydrophobic interaction between H atoms and sp^3 -hybridized O atoms (sp^3O) is in favour of the binding constants. Furthermore, the satisfactory results showed that 3D-HoVAIF could preferably express the structure information of the coumarins.

Key Words: Coumarin, Binding constants, Three-dimensional holographic vector of atomic interaction field, QSPR.

INTRODUCTION

Human serum albumin (HSA) is the most abundant protein in plasma, which is a single peptide chain protein consisting 585 amino acid residues, molecular weight 66500. It is the major storage and transport protein for numerous endogenous and exogenous compounds and is also capable of binding an extraordinarily diverse range of metabolites, drugs and organic compounds. Coumarins drugs are commonly used drugs, many of which exhibit useful pharmaceutical activity, such as anti-bacterial, antithrombotic, anti-inflammatory and antitumor properties¹⁻⁴. In order to make the drugs putting into the body pharmacodynamic effect, the drugs have to reach receptor sites through the storage and transport of plasma. The remarkable binding capacity of drugs and human serum albumin has a significant impact for pharmacodynamics and pharmacokinetics. While the binding constant is an important parameter measuring the binding strength, so, construction of quantitative correlation between the molecular structure and the binding constants of coumarins and human serum albumin has an important significance to research drug screening and prediction of protein interactions. This has stimulated a great deal of research on the nature of the drug binding capacity and sites. The quantitative structure-property relationship (QSPR) is a well-established technique for estimation of the physico-chemical properties of a compound based on the descriptors derived from the molecular structure. It is widely used in all

kinds of fields, such as the prediction of gas chromatographic relative retention times, drug activity designing and screening, etc.^{5,6}. To date, many researches about coumarins and protein interaction are mainly focused on experimental and theoretical research is relatively small⁷⁻¹³. In this paper, the relation between binding constants of coumarins drugs and human serum albumin molecules were investigated utilizing three-dimensional holographic vector of atomic interaction field (3D-HoVAIF) as the descriptor, with the help of multiple stepwise linear regression, the QSPR model on human serum albumin (HSA) was established. Meanwhile, the influence of molecular structure on the binding was also discussed. The model could predict the binding constants of coumarins and human serum albumin with satisfactory results. The paper provides a new way for the structures characterization of coumarins and derivative and determine which group will help the binding by virtue of their different parameters, the binding of coumarins to human serum albumin shows a relationship with electrostatic and hydrophobic interaction of coumarins molecules, which is useful for the design and screening of medicines.

EXPERIMENTAL

Here 20 coumarins are studied (Table-1), whose molecular structures and the binding constants taken from reference^{4,13-16}. The binding constants of the 20 samples were gained in the mimic physiological condition at room temperature, together with a wide concentration range of 1.0×10^{-6} – 5.0×10^{-4} mol L⁻¹.

[illegible]

big bulkness of alkyl chain will cause steric hindrance. The hydrophobic interaction between H atoms and sp^3 -hybridized O atoms (sp^3 O) is in favour of the binding constants. On the other hand, the electrostatic interaction between sp^2 -hybridized C atoms (sp^2 C) and halogen atoms (F) is also propitious to binding. For the compounds, the influence mainly reflected in the fourth substituent group. The larger electronegativity substituent group can reduce the electron density between the third and fourth C atoms, resulting in the higher molecular conjugation and lower energy and make the binding be tight. Fig. 1 showed plots of calculated binding constant ($\log K$) against experimental $\log K$ values of all samples. From Fig. 1, it can be seen that almost all samples are uniformly distributed around diagonal, not obviously exceptional point has selected.

Fig. 1. Plot of $\log K$ calculated vs. experimental value by MLR model

Partial least square model: Partial least square (PLS) is a novel multivariate data analysis method, can solve many important problems which can not be solved by common multiple regression analysis method. Such as avoiding the harmful effects of multicollinearity and being capable of building the models when the number of observations is less than the number of variables, etc. In this work, PLS was performed in Simca-P 10.0 and the PLS latent variable number for each original variable matrix in PLS was determined by default standards. The selected three variables by SMR were then modeled by PLS, which the two principal components explained 89.1% and 77.2% variance of Y and cross-validation variance of Y, respectively. Fig. 2 presents different loading contributions of 3 variables to the first two principal components. V_{27} and V_{112} had prominent contributions to PC1 loadings well correlative to Y variables, while V_{27} had prominent contributions to PC2. Meanwhile, dependent variable is further away from PC1 than PC2, this indicated that PC1 had prominent contributions to dependent variable. Besides, variable importance of projection (VIP) index of original variables is presented in Fig. 3. The most contributive top V_{112} indicated an intimate relationship between $\log K$ and hydrophobic interaction. The plot of $\log K$ calculated by PLS model versus those experimental is shown in Fig. 4.

Finally, in order to further verification the reliability of 3D-HoVAIF model, the whole data set was divided into two

Fig. 2. Loading contributions of original variables to the top two principal components

Fig. 3. Plot for variable importance of projection

Fig. 4. Plot of $\log K$ calculated vs. experimental value by PLS model

subsets. In Table-1, the binding constants were rearranged from large to small. The tenth and twentieth sample were chosen to create a test set and the remaining 18 samples were regarded as the training set. Then, 18 training samples were utilized to construct the QSPR model. The other 2 samples were utilized to validate the external prediction power of the model developed.

Consequently, a 3-variable MLR model was constructed for the training set with its $R^2_{\text{cum}} = 0.894$, $Q^2_{\text{LOO}} = 0.841$ and RMSE 0.324. The constructed model was then utilized to predict the test set, with the result of $Q^2_{\text{ext}} = 0.919$. All of these depict the model has favorable simulative for internal samples and predictive ability for external samples.

Conclusion

In this paper, the descriptor-3D-HoVAIF derived solely from chemical structures and easily obtained, involving classical electric, steric and hydrophobic interactions. Furthermore, the obtained model with obvious physicochemical meaning. From QSPR model, it can be concluded that hydrophobic interaction is more important than electrostatic interaction. Moreover, it can be seen that the log K of binding constant is high positively correlated with hydrophobic and electrostatic interaction. In other words, hydrophobic groups will promote the binding constants. Thus it is suggested the 3D-HoVAIF descriptor behaves quite well in structural characterization ability and will be extremely useful in QSAR studies. Mean while, these descriptors have been applied in the QSAR/QSPR studies on many complicated molecular systems, such as steroids and anti HIV drugs, etc.²²⁻²⁵.

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