Asian Journal of Chemistry; Vol. 26, No. 18 (2014), 5917-5922

ASIAN JOURNAL OF CHEMISTRY

http://dx.doi.org/10.14233/ajchem.2014.18490

REVIEW

Trend of Multi-Scale QSAR in Drug Design†

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Received: 22 July 2014; *Accepted*: 22 August 2014; *Published online*: 1 September 2014; AJC-15822

Quantitative structure-activity relationship (QSAR) is a common method for drug designing. The classification methods of conventional QSAR often consider the dimensions of research measures or the variety of biological activity. The research objects of traditional QSAR are always at the mesoscopic-scale. With the multi-scale development of drug, different strategies of QSAR should be adopted based on the characteristics of an object at a specific scale, which gradually caused the multi-scale development of QSAR in recent years. In this paper, a new classification method of multi-scale QSAR was presented and the existing six QSAR technologies were classified into three scales.Wherein, atom-based QSAR belongs to micro-scale, fragment-based QSAR and small molecular-based QSAR belong to mesoscopic-scale, while macroscopic-scale includes macromolecule-based QSAR, multi-target-based QSAR and cell-based QSAR.This paper hackles the basic concept, historical origins, mature technologies and recent research results of each multi-scale QSAR methods. Generally speaking, multi-scale QSAR is more applicable to QSAR model in today's trends of drug design. And the new research ideas for further development of QSAR are presented in this review.

Keywords: QSAR, Multi-scale, Atom, Fragment, Multi-target, Cell.

INTRODUCTION

Quantitative structure-activity relationship (QSAR) indicates the relationship between structural property and biological activity of compounds, which are widely used in the field of pharmacy, materials science, agronomy, environment, *etc.*[1,2]. The basic construction procedures of QSAR model include four important steps.Firstly, as the structural description of the training set compounds is recorded, this structural information and relative biological activity are used to construct correlation function model by suitable algorithm. Afterwards, statistical methods are applied for internal validation of the model. Finally, the test set is used for external test of the model. Reliable QSAR model should be satisfied with the requirement of internal validation and external validation[3,4]. The main purpose of QSAR model is to predict the activity of compounds, guide compound design and optimize leads.

Classification of QSAR methodologies: Different classification methods of QSAR were presented to make the study more reliable and credible. The two main methods, introduced as following, have been widely accepted by QSAR researchers.

The first classification method is based on the different dimensions of molecular features, which is also called multi-dimensional QSAR including 2D-QSAR, 3D-QSAR, 4D-QSAR and so on. Physicochemical properties and 2D structure descriptors are always calculated as structural features for 2D-QSAR models construction. The molecular features for 3D-QSAR models are based on the non-covalent force field around the specific conformation of the compound. Based on 3D-QSAR principle, 4D-QSAR, 5D-QSAR and 6D-QSAR add structural properties, respectively to make QSAR model more coincident with the true active mode of molecules, such as the whole molecular conformations of ligands, influence of ligand-receptor interactions and solvation[5,6]. The development of multi-dimensional molecular features is a rewarding process, by which the QSAR models can be more reliable and more effective. However, the study of the 2D-QSAR and 3D-QSAR are widely engaged by many researchers, comparing with 4D-QSAR to 6D-QSAR which are reported by a few researchers.

The second classification method is based on the different species of predictive activities. Generalized QSAR also includes quantitative structure-property relationships (QSPR), quantitative structure-toxicity relationship (QSTR), quantitative

†Presented at iCBEB2014

structure-spectrum relationship (QSSR), *etc.*[7-9]. The expansion of the classification makes QSAR widely used in multi-disciplinary. But sometimes, the compound study on the physicochemical properties, toxicity and spectral properties is directly categorized as QSAR by part of the researchers[10].

In addition, there are also other classification methods. Based on correlation analysis, QSAR models can be divided into linear models and non-linear models[11,12]. Besides, QSAR models are also classified as receptor-dependent QSAR and receptor-independent QSAR depending on whether considering the molecule-receptor binding way[5]. According to these two kinds of classification methods, certain specific characteristic of building model is only considered. However, if QSAR is only divided into two types, it will be unsuitable to systematically induce principles and methods, because of the diversity and complexity of QSAR.

Multi-scale QSAR: Nowadays, there are many great challenges for QSAR. Not only the predictive defects of it are found, but also a variety of advanced molecular modeling methods and up-to-date experimental techniques have been presented[13,14]. In order to cope with these challenges, a new trend of QSAR development is discussed in this paper, which is named as multi-scale QSAR.

Multi-scale QSAR refers to the use of different simulation methods to investigate three scales of research objects, which include micro-scale simulation, mesoscopic-scales imulation and macroscopic-scale simulation[15-17]. Different QSAR models are built in different scales based on the various computing precision of research objects. From the perspective of QSAR model building process, multi-scale research objects refer to the structural description of the training set. The applications of multi-scale research objects in the process of building QSAR model are presented in Fig. 1, wherein the main research aim of multi-scale QSAR is small molecules and macromolecules. Different methods for molecules can be selected at three scales, namely micro, mesoscopic and macroscopic scale. Moreover biological activities of multi-scale QSAR are also expanded from the traditional binding affinity to various fields, which play a vital role for the development of multi-scale QSAR, as multi-scale QSAR need to describe molecules under specific conditions as much as possible. Also, compared to no target and single target, the study of multi-scale QSAR pays continuing attention to multi-target areas. Therefore, innovation of modeling algorithms is an important research field for multi-scale QSAR.

Quantum chemical methods can be used for accurate calculation in micro-scale simulation, like atom-based QSAR[18]. Molecular force field methods are often used in mesoscopic-scale simulation, including fragment-based QSAR and small molecular-based QSAR. Macroscopic-scale simulation usually carries on coarse-grained study, including macromolecule-based QSAR, multi-target-based QSAR and cell-based QSAR. With multi-scale progress of drug development, molecules predicted and designed at different scales are a new research direction of QSAR technology[19]. The purpose of the development trend of multi-scale QSAR is to expand the usefulness of QSAR, which provides a more effective guide for drug design and expands a predicted range of QSAR. So it is true that multi-scale QSAR is also called purpose-oriented methods. Meanwhile, this classification method more methodically summa-

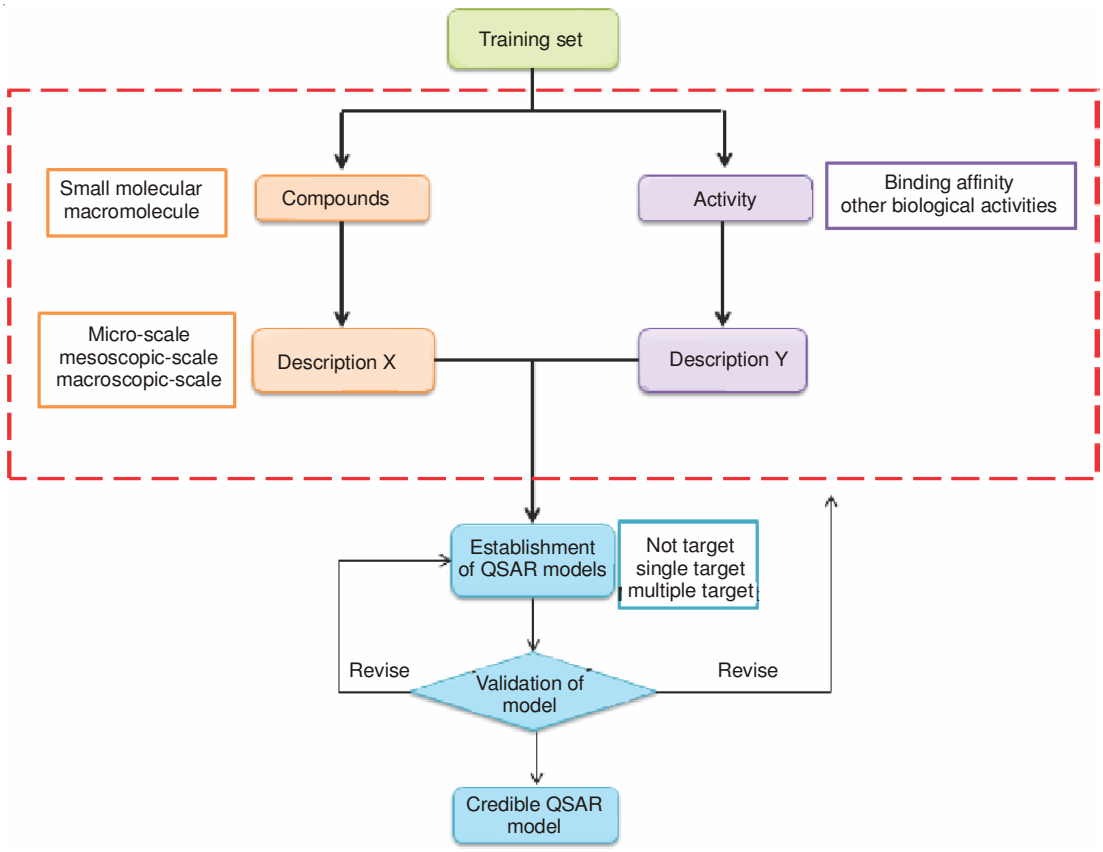

Fig. 1. Applications of multi-scale research objects in the process of building QSAR model

rizes QSAR, which can effectively include all existing QSAR methods. Multi-scale QSAR has also pointed out the direction and guided the progress of QSAR technology.In this review, the advantages, basic concept, historical origins, mature technology and recent research results of each scale modeling methods of QSAR are all discussed in this passage.

Atom-based QSAR: Atom-based QSAR is a method of the description of compounds structure in atomic scale and the construction of according QSAR model. Atom-based QSAR was studied for long time and has been applied in 2D-QSAR and 3D-QSAR. It originated from atom-based physicochemical properties in 1991 and atom-based template alignment in 1999[20,21]. 2D-atom-based QSAR was enlightened by atom-based physicochemical properties. It was until 2005 that the first atom-based indices, atom-based quadratic indices, was presented[22]. Afterward, other atom-based indices have been proposed, including atom-based 3D-chiral quadratic indices[23], atom-based bilinear indices[24], *etc.*

3D atom-based QSAR was enlightened by atom-based template alignment approach. Then RMS fitting atom-based QSAR[25], pharmacophore-based alignment QSAR and 3D atom-based QSAR were gradually proposed[26]. In essence, 3D atom-based QSAR is a creation of overlap way. Since the traditional template-based alignment might be affected by human factors which may cause problems in objectivity and accuracy of the model, pharmacophore-based alignment and docking-based alignment emerged. But still, some problems exist in pharmacophore-based alignment, like the expression of steric. Also, that was the reason for the atom-based alignment was developed. 3D atom-based QSAR is a combination of pharmacophore and 3D-QSAR methods. Pharmacophore method is based on the characteristics of interaction, which can effectively find reasonable pharmacophore features, while 3D-QSAR is based on the inherent feature of the molecules which can represent some features that pharmacophore cannot represent, like the ligand's possible steric clashes with the receptor.

PHASE was used in drug design by Dixon *et al*.[26], wherein a molecule was treated as a set of overlapping of the van der Waals spheres. Each sphere was encoded by rules for describing the basic characteristics of chemical structure. The model of superimposed training set of molecules was placed into a regular grid of cube and each cube was allocated zero or more "bits" to accommodate different types of atoms. This representation presented binary-valued occupation patterns, which could be known as independent variables. In their studies, 3D atom-based QSAR model of human dihydrofolate reductase (hDHFR) inhibitors was constructed by PHASE. Favorable or unfavorable region and pharmacophore were visualized. Also, model presented a reasonably good correlation in train set and test set. Compared with the predictive rate of active compound calculated by Catalyst/HypoGenQSAR models (67 %), PHASE model was proved to be higher rate (74 %). Nowadays, PHASE is widely used in drug design as mature 3D atom-based QSAR technique[27,28]. The use of atom-based QSAR can be more beneficial to the development of new drugs, which is aimed at exacting the contour map to atom to facilitate further drug design.

Fragment-based QSAR: In recent years, fragment-based QSAR is highly appreciated by researchers. Researchers hope to define the impact of molecular fragments on active compounds. So, to some extent, predicting the activity of molecular fragments is more significant than forecasting the activity of the whole molecule.The origin of fragment-based QSAR can be traced back to 1964, when the Free-Wilson QSAR was proposed[29].

Fragment-based QSAR includes 2D-QSAR and 3D-QSAR. The most typical 2D fragment-based QSAR is fragment-based QSAR (FB-QSAR), which is presented by Song and Clark[30]. Two-dimensional molecular descriptors are used in FB-QSAR to describe the structure of the compound, including physical and chemical parameters of compounds and heavy index of fragments[31]. There are also some other 2D-fragment-based QSAR methods, including Hologram QSAR (HQSAR), fragment-similarity based QSAR (FS-QSAR) and so on. Therefore, 2D fragment-based QSAR has been widely used as an important measure in fragment-based drug design[32].

Typical 3D fragment-based QSAR is Topomer CoMFA, which is an extension of the traditional CoMFA and is first reported by Cramer[33]. A Topomer is a bioisosteric shape of fragment. The rotatable key of molecules is cut into two or more fragments.Based on the theory that the same Topomer have the same biological activity, CoMFA columns are generated by cycles and computations for further analysis. Auto-alignment is the biggest feature of Topomer CoMFA, which can avoid the subjectivity of overlapping and generate more reliable QSAR models. Meanwhile, compared with traditional CoMFA, Topomer CoMFA is more rapid and efficient to regress automatically. Besides, virtual screening can also be performed by Topomer search[34]. In a word, Topomer CoMFA is a good technical method used in the transition of skeleton and substitute of the R-groups, which can providedrug design with wealthy structures[35].

Small molecular-based QSAR: Small molecular-based QSAR, as the most classical QSAR, is one of the receptor-independent QSAR. Research of QSAR was carried on in the early years. The presentation of Hansch method in 1964 was known as the beginning of small molecular-based QSAR[36]. In terms of 2D-QSAR, the structural index and physico-chemical parameters of the molecules was considered as the independent variable, regardless of the three-dimensional structure of the compounds. Additionally, the proposed comparative molecular field analysis (CoMFA), a 3D-QSAR method, was known as the second leap to small molecular-based QSAR in 1988[37]. In terms of 3D-QSAR, the conformation of the molecule in three-dimensional space was contained. As CoMFA is proposed, small molecular-based QSAR comes into a period of rapid development. Then, a large number of 3D-QSAR methods have been proposed, including k-Nearest Neighbor Molecular Field Analysis (kNN-MFA),self-organizing molecular field analysis (SoMFA), comparative molecular similarity indices analysis (CoMSIA), *etc.*[12,38].

3D-QSAR, which was regarded as the basic method of model generation, has directly led the proposed concept of multi-dimensional QSAR. Accordingly, in 4D-QSAR, all conformations of molecules were taken into account rather than a single conformation[39]. 5D-QSAR builds a virtual receptor analog, considering the interaction between ligand and virtual receptor[40]. Besides, in 6D-QSAR, solvation is added so as to

simulate true molecular mode of action[41,42]. Despite the differences, the multi-dimensional QSARs derived from the same origin. It can be considered as a great progress from 2D-QSAR to 3D-QSAR; however,it is not an obvious leap from three to six dimensions.Small molecular-based QSAR belongs to receptor-independent QSAR and actual receptor molecules were not used in the research, which is a defect to the development of drug design based on target. This is a big limitation but also an essential advantage of QSAR. After all, not all of the targetshave been or can be separated[43].

Macromolecule-based QSAR: Macromolecule-based QSAR is a QSAR model of protein and nucleic acid. To introduce macromolecule-based QSAR, the first problem is to describe the structure of macromolecule. But it is difficult for description of the structure of the entire macromolecules, because of the sequence complexity and conformation diversity of macromolecule. As early as the 1980s, researchers have constructed peptide QSAR model based on the position and physico-chemical properties of amino acids in the primary sequence[44,45]. Further, description of macromolecules was generally characterized by sequence parameters, physicochemical descriptor and so on by subsequent researchers. Quantitative sequence-activity models (QSAM) are typical methods of building relationships between the sequence and the activity of macromolecule[46,47]. With further research, more methods of describing macromolecules have been proposed. Three typical methods are listed as follows:the first is slicing macromolecule into fragments to characterize, like amino acid-based peptide prediction (AABPP). The second is the overall characterization of macromolecules through the network descriptors, which is called network-QSAR. The third is to describe the part of the macromolecular structure, not expect to get the whole scheme, like biomacromolecule QSAR (BioQSAR).

AABPP is a macromolecules study method based on characterizing macromolecular fragments. It is not a macromolecule-based QSAR in the strict sense, but more similar to the fragment-based QSAR. Characterization of macromolecules depends on structure descriptors and weight descriptors of the amino acid fragment[48,49]. In contrast,the network-QSAR and bioQSAR, which are recently proposed, is to predict the activity of macromolecules from a holistic perspective.

The basic principle of network-QSAR is to use network descriptors to describe the structure of the molecules and construct model,wherein protein molecules are described through lattice network descriptors and amino acids are expressed numerically. Sequence and structure of associated proteins and non-associated proteins are described by network. Network descriptors are formed to describe related proteins and non-related proteins. Network-QSAR model is established by classification discriminant model, so as to determine whether sealed proteins are objective proteins or not [50].

Zhou *et al.*[51] presented BioQSAR to infer the biological functions of structure-available macromolecule. 144 affinity-known complexes were used to construct models. Firstly, the binding surface of the protein and ligand is determined. Then five varieties of descriptors are used to describe the interaction of the ligand with the receptor, including constitutional descriptors, contacting descriptors, geometrical descriptors, physicochemical descriptors and non-bonded descriptors. Finally, linear and nonlinear machine learning protocols are used to build the models. In their studies, three BioQSAR models were built and the model built by Genetic algorithm-Gaussian process (GA-GP) showed the best statistical results. Compared with conventional methods, BioQSAR has a better ability to predict and interpret the binding affinity between proteins.

Multi-target-based QSAR: There are two significant drawbacks presented in Traditional QSAR methodologies, which are small training set and single-target study. Multi-target-based QSAR (mt-QSAR) can be more effective to solve these problems[52]. Multi-target-based QSARbecomes more prevalent in recent years and the basic principle is to use the joint model to predict multi-target effects on drug molecules. Gonza'lez-Diaz *et al.*[53] and Prado-Prado *et al.*[54] have made important contributions to multi-target-based QSAR.

Mt-QSAR is one of 2D-QSAR methods. To be more specific, the basic principle to build mt-QSAR is broadly divided into the following steps: Initially, molecular structure is described by molecular descriptors. Then the active and non-active compounds are used to build single target discriminant model. Next, various single target models are combined to form mt-QSAR by non-linear Artificial Neural Networks (ANNs) or Linear Discriminant Analysis (LDA)[55]. In recent years, more algorithms are used to construct mt-QSAR, such as Moving Average Analysis (MAA), Linear Neural Network (LNN) and multiple linear regressions (MLR)[56,57]. The advantage of multi-target-based QSAR is the ability to build biological networks relied on multi-target. Then multi-target drugs are developed through taking advantage of the principles of systems biology and network pharmacology research. Multi-target-based QSAR model can also predict multiple biological entity activities of drug molecules,including protein, partition system, tissue, microorganism and so on.

Speck-Planche *et al.*[58] established two multi-target-based QSAR models aimed at seven HIV-related proteins and used these models to obtain relevant functional fragment for multi-target molecules design. 745 compounds which contained 150 non-active compounds were described by fragment-based descriptors or global 2D descriptors, wherein the model built by fragment-based descriptors was presented in this equation:

$$A_{HIV-IP} = a_0 + \sum_k b_k D_k + \sum_k c_k avgD_k + \sum_k d_k dif\,D_k k \quad (1)$$

This is the kernel function of the mt-QSAR. A_{HIV-IP} is a score to discriminate the activity against one protein. D_k means the different fragment-based descriptor. Besides, avg D_k and dif D_k are average and deviation values, respectively. These parameters were used to describe that ligands were, respectively matched with seven proteins. The a_0 is the const, while b_k, c_k and d_k are the coefficients of the variables. Moreover,both LDA and ANN could be used to form QSAR model, but ANN model was proved to be a better statistical quality than LDA. Meanwhile, active fragments were used to design and predict multi-target drug, six molecules were theoretically designed to inhibit seven protein related HIV.

Cell-based QSAR: Cell-based QSAR is an innovative way to describe the essence of biological activity. The traditional methods of describing the activities merely rely on experimental data on the activity of one target or cell. But

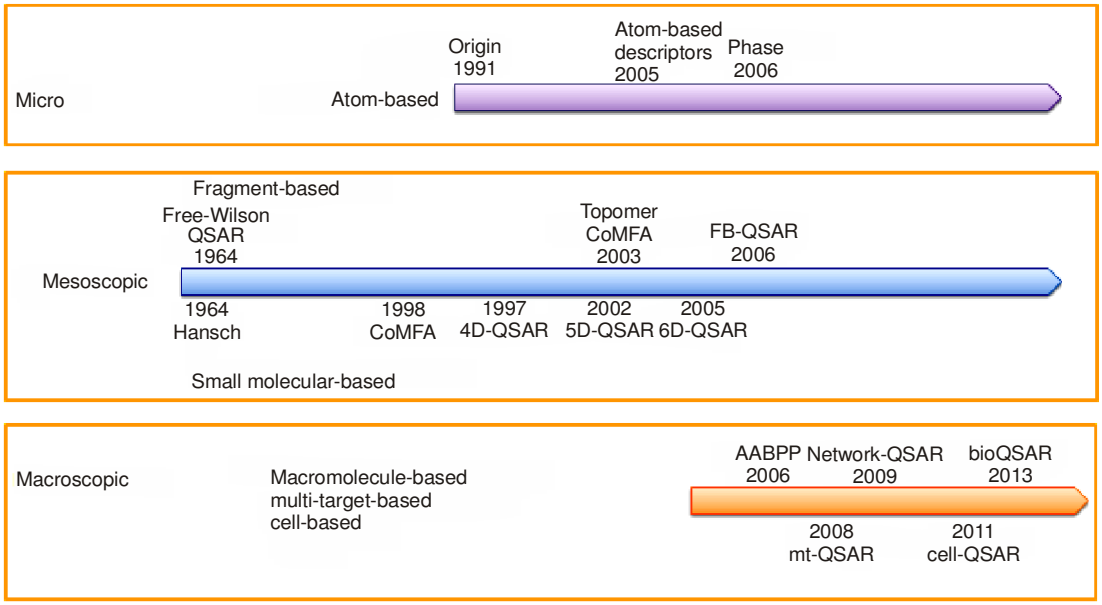

Fig. 2. History of multi-scale QSAR

sometimes, it is difficult for biological macromolecules to be separated and to obtain the binding affinity. Even if the binding affinity could be obtained, it cannot successfully express the mode of action of drugs *in vivo*. For reasons given above, the application of QSAR is limited. Therefore, in order to describe active mode of drugs *in vivo* more veritably, cell-based QSAR was raised in 2011[59,60].

The basic principle of cell-based QSAR is that disposition values can be added to the traditional binding affinity. So a description of the biological activity is used to describe drug molecules. The eqn. 2 was used to build the relationship for cell-based QSAR.

$$\log\left(\frac{1}{EC_{50}}\right) = \log(K) + \log[DF(p,t)] \quad (2)$$

In terms of the equation, log K is an MSMM-CoMFA expression for the receptor binding and the remaining terms (log DF) describe disposition function. Cell-based QSAR was successfully used to study the antifilarial activities of antimycin analogues[61]. Compared to the models of traditional CoMFA method, DF was a necessary part to ensure reliably predictive abilities. Disposition is a function to describe the distribution way of the molecular inside the cell. The advantage of cell-based QSAR is more actually to describe the distribution of drug molecules inside the cells, which revises the binding affinity. Although cell-based QSAR method is not fully mature, it is still an essential direction for the innovation of QSAR.

In this paper, multi-scale QSAR is classified into three scales, which involves six methods. Atom-based QSAR belongs to micro-scale simulation. Fragment-based QSAR and small molecular-based QSAR are classed as mesoscopic-scale simulation. Macroscopic-scale simulation includes macromolecule-based QSAR, multi-target-based QSAR and cell-based QSAR. The history of multi-scale QSAR is illustrated in Fig. 2.

2D-QSAR methods are known as one of the most mature QSAR methods, including almost all scales of QSAR. If QSAR model can be established by integrated application of multi-scales descriptors, a better prediction results will be obtained. 3D-QSAR method is to simulate molecules in three-dimensional space and mainly used in microscale and mesoscopic scale currently. Although the application of 3D-QSAR is not widespread, it may exert positive influence over future research in the macroscopic scale.

In micro and mesoscopic scales, the application of molecular simulation method provides more intuitive mode to study molecular structure and biological activity. However, in macroscopic scales, statistical calculation method can make research more convenient. Nowadays, a QSAR study with the combination of both approaches has become the new direction of current research.

Currently, QSAR plays a vital role in the development of pharmacy, materials science and agronomy. Multi-scale QSAR has become a trend to the development of QSAR, which will continue to meet the trend of drug development. Due to technical limitations, the study of macromolecular scales is not yet applied to 3D-QSAR studies, which also limits the widespread application of QSAR technology to some extent. When macromolecule can be calculated at macroscopic scale by 3D-QSAR, the third leap of QSAR will be reached.

ACKNOWLEDGEMENTS

Authors would like to acknowledge the financial support by the National Natural Science Foundation of China (No. 81173522) and the National Undergraduate Innovative Training Project (No. 201310026069).

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