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# Advances of Quantum Chemistry Methods in Pharmaceutical Researches

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**Abstract**

Quantum chemistry, a branch of theoretical chemistry, applies quantum mechanics and quantum field theory for chemical researches. In recent years, quantum chemistry calculation methods have been increasingly used in all aspects of drug research field and provided many new methods, tools and ideas for the development of new drug design. This article introduced the fundamental principle and calculation methods of quantum chemistry. The progress of quantum chemistry methods applied in different areas of pharmaceutical research was reviewed, and its application in medicine researches was also prospected.

## 1 Introduction

Quantum chemistry (QM) is a branch of theoretical chemistry, which applies quantum mechanics and quantum field theory for chemical research study. One of the applications of quantum chemistry is to obtain descriptions of the electronic behavior of atoms and molecules as pertaining to their reactivity, which can be used to analyze the "structure-activity relationships" of compounds and that's often just what pharmacologist needed eagerly [1-5]. QM lies on the border between chemistry and physics, and significant contributions have been made by scientists from both fields. It has a strong and active overlap with the field of atomic physics and molecular physics, as well as physical chemistry.

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In the field of drug research, quantum chemistry methods could be able to help to achieve the optimization of drug molecules conformation, conduct 3D QSAR analysis, explain the mechanism of drug action at the molecular level and predict drug *in vivo* metabolism and side effects, thereby allowing designing new molecules and predicting the activity of them at a more precise level of atoms and functional groups [6].

In recent years, as computer technology improves and structural and functional information of biological macromolecules, such as protein and nucleic acid, enriches, as well as the continual emergence of new methods, quantum chemistry calculation methods have been increasingly used in all aspects of drug research field and provides many new methods, tools and ideas for the development of new drug design. This paper reviews the recent application and development of QM in molecular conformation analysis, pharmacodynamics, pharmacokinetics, and toxicology in drug research.

## 2 Basic Principles and Computational Methods of Quantum Chemistry （QM） [1-3, 7].

Quantum chemistry is an important method in the study of molecular structure and properties. In the seventh decade of last century, in pace with Heisenberg putting forward the Uncertainty Principle and Matrix Mechanics, Schrodinger introducing the Wave Equation, Dirac proposing the equation with relativity, the objects of physics study transferred from the macro field into micro field, which marked the establishment of the quantum mechanical system. Subsequently, scientists began to apply the quantum mechanics to treat chemical issues, for example, Heitler-London approach quantum mechanics to investigate Hydrogen atom and Hydrogen molecular. With the rapid emergence and widely spread of computer technology, easy-to-programmed quantum chemistry methods have been effectively used around the world.

The first step in solving a quantum chemical problem is usually solving the Schrödinger equation (or Dirac equation in relativistic quantum chemistry) with the electronic molecular Hamiltonian. This is called determining the '"electronic structure"' of the molecule. It can be said that the electronic structure of a molecule or crystal implies essentially its chemical properties. An exact solution for the Schrödinger equation can only be obtained for the hydrogen atom. Since all other atomic or molecular systems, their Schrödinger equations cannot be solved exactly and so approximate solutions must be sought.

The solution methods consist of ab initio methods, semi-empirical methods and density functional methods (DFT).

### *2.1 Semi-empirical Methods*

Semi-empirical quantum chemistry methods are based on the Hartree-Fock formalism, but make many approximations and obtain some parameters from empirical data. They are very important in computational chemistry since treating large molecules where the full Hartree-Fock method without the approximations is too expensive. The use of empirical parameters appears to allow some inclusion of electron correlation effects into the methods.

Although not close enough in theory, such treatment improves the calculation speed greatly, almost 100 times faster than *ab initio* calculation method; it requires smaller disk space and less computer memory synchronously, either. Therefore, the semi-empirical calculation method could be used for larger molecular systems; despite some calculation accuracy sacrificed.

### *2.2 Ab initio Methods*

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*Ab initio* quantum chemistry methods are computational chemistry methods, according to variation principle and calculus of variations, while based on non-relativistic approximation, Born-Oppenheimer approximation and the Hartree-Fock approximation, that solve the HF equation strictly.

Therefore, except for a few physical constants (such as Plank constant, velocity of light, charge and mass of electrons and nuclei ), there is no need of any experimental information and new approximation; all calculations are based on Principles of Quantum Mechanics, that means they are much more strictly and precisely than the Semi-empirical Methods.

In general, semi-empirical methods can only provide qualitative descriptions of system; only when the parameters of the system are suitable to study the case, can it provides accurate quantitative molecular descriptions. Yet, because there is no experimental data to determine the parameters, *ab initio* methods can be applied to a greater extent and provide accurate descriptions of systems, while the cost of calculation increases significantly.

### *2.3 Density Functional Methods*

Density functional theory (DFT) is a quantum mechanical theory used in physics and chemistry to investigate the electronic structure (principally the ground state) of many-body systems, in particular atoms, molecules, and the condensed phases. With this theory, the properties of a many-electron system can be determined by using functional, i.e. Functions of another function, which in this case are the spatially dependent electron density. DFT is among the most popular and versatile methods available in condensed-matter physics, computational physics, and computational chemistry.

In many cases the results of DFT calculations for solid-state systems agreed quite satisfactorily with experimental data. Also, the computational costs were relatively low when compared to traditional ways which were based on the complicated many-electron wave function, such as Hartree-Fock theory and its descendants. However, DFT was not considered accurate enough for calculations in quantum chemistry until the 1990s, when the approximations used in the theory were greatly refined to better model the exchange and correlation interactions. DFT is now a leading method for electronic structure calculations in chemistry and solid-state physics.

In addition, as involving a number of biological macromolecules (such as proteins, nucleic acids, etc.) with great molecular weight, complex structure and flexible structure, it is difficult to use the method with high-precision calculation subject to its calculation speed. In the last decade combined quantum mechanic/molecular mechanic (QM/MM) methods have been applied to a large variety of chemical problems. QM / MM combine the advantages of both quantum mechanic method and molecular mechanic method, as well as some strongpoint of molecular dynamics (MD). In a QM / MM model, the studying system would be divided into two parts, namely the part of quantum mechanics (QM) and the part of molecular mechanics (MM), while there is an interaction zone between them. In the calculation process, the active part of the system would be treated with QM methods and correspondingly the rest with MM methods. Thus, when dealing with complex systems, it can not only reach the fastest calculating speed, but also achieve a high enough accuracy in the key areas [8-15].

In short, the various theoretical calculations have their own features in the long course of development. The researchers should select an appropriate method based on the characteristics of the research system, in order to find out the most

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economical way to get the most accurate results.

## 3 Progress of QM in Molecular Modeling and Spectra Analysis

Before carrying out theoretical simulation, how to determine the actual molecular conformation, including conformations of small molecule compounds and biological macromolecules, is the first problem we face. In general, structures of drug molecules are complex and usually possess several chiral centers therein; meanwhile the different conformations may have completely different biological activities. Furthermore, most of biological molecules *in vivo*, such as proteins and nucleic acids, are macromolecules which have many intra-and intermolecular chemical bonds *Van der Waals* force (like hydrogen bonds and disulfide bonds). This means that drug molecular structure identification is very difficult.

The main methods of traditional compounds structural identification involve chemical (organic structure identification) and physical methods (spectroscopy). Quantum chemistry calculation introduced a new means for identification of the compounds; on the other hand, it provides a useful theoretical help for the physical methods, involving nuclear magnetic resonance (NMR) [18-20], mass spectrum (MS) [21-23], infrared spectrum (IR), Raman scattering [24-25], ultraviolet spectrum (UV) [26] and X-ray diffraction spectra.

### *3.1 Utilization on Molecular Conformation Analysis and Seeking of Biological Active Sites*

Mouse epidermal growth factor (mEGF) is a single-chain polypeptide with 53 amino acid residues contained three intermolecular disulfide bonds in it [27-29]. FENG-Yu Li etc. used semi-empirical method to study the structures and properties of 16 different mEGF molecules under gas and solvent condition. The results under the gas condition showed that the section makes the greatest contribution to the highest occupied molecular orbital (HOMO) of the mEGF molecules constitutes of residues on the carbon terminal and the lowest unoccupied molecular orbital (LUMO) is mainly distributed on the disulfide bonds. This indicates that the disulfide bonds and C-terminal amino acid residues are very essential for biological activity of mEGFs. In solvent condition, the position of LUMO and HOMO is almost free from solvent effect's influence. In the solvents with relatively large dielectric constant, the formation heat and average polarizability of mEGF molecules lowed and dipole moment enhanced. In addition, the study of the location of hydrogen bonds confirmed that B loop region is important to biological activity and structural stability for mEGF molecules. The researchers concluded that amino acid residues of N-terminal and C-terminal parts are critical for the stability of mEGF molecular structure and may be related to the linking direction of EGF to its receptor [30]。

### *3.2 Theoretical Study on Spectra Analysis*

Vibration spectroscopy is of one of the important ways to study the molecular structure, while research on the characteristic bands is a powerful tool for identifying chemical groups. The fundamental frequencies of molecules are required not only to distinguish vibrational partition function in thermodynamics but also to interpret doubling frequency, beat frequency and so on. Therefore, to study the fundamental vibration frequency of molecular is therefore a principle in vibration spectrum analysis [24-26].

Bu-yi Xu etc. obtained IR and Raman spectra of 2 - (toluene -4 - Sulphonyl amino) - benzoic acid with geometry optimization and frequency calculations using DFT methods. Results showed

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that: the carbonyl group, the nitrogen atom in the sulphonyl amino and the benzene ring formed different modes of large π bond, and the two benzene rings were not in the same plane due to steric effect and conjugative effect. When using the DFT method with the first excited state electronic transition energy, it was acquired that the maximum absorption wavelength of 312.7nm (near the ultraviolet region) is consistent with the experimental measured value of 307nm in diazomethane [31-32].

Shu Zhang etc. conducted a theoretical study of three kinds of commonly used carbamate pesticides and obtained their fluorescence spectra. The computational data showed little difference with that from experiment. Each of the three types of molecule has a strong co-planarity respectively for the ultra-conjugated system; with the addition of electron donor, fluorescence wavelength increased and spectral redshifted. Moreover, the addition of alkyl molecular had little effect on the fluorescence spectra, while it did an obvious impact on the molecular fluorescence spectroscopy when amine group was added [33-34].

Chemical shifts obtained by NMR contain numerous of information of molecular structure and intramolecular interactions. In drug research, NMR could be applied in structural confirmation of drug molecules, detection of drug purity, and analysis of drug metabolism, etc. Therefore, the importance of chemical shifts is self-evident. However, when using NMR analysis to resolve complex chemical structure, attribution of chemical shift peak is often very difficult; then the introduction of theoretical methods to solve these problems would be helpful [18-20].

Shinji Suzuki utilized DFT methods to investigate the 13C chemical shifts of glucose, cellobiose and native cellulose, the impact of molecular conformational change and the formation of hydrogen bonds on chemical shifts, especially [35-37]. The linear relationship between the chemical shift of the $C_6$ carbon and the torsion angle around the $C_6$- $O_6$ bond in the $CH_2OH$ side group, which was previously obtained in experiments, is successfully reproduced for β-D-glucose. Furthermore, it is found that when intramolecular hydrogen bonding, about γ-hydrogen atom on the β-glucose's side chain ( — OH), formed, C5 chemical shift values downfield; to the contrary, no significant effects as different intramolecular and intermolecular hydrogen bondings forming between neighboring glucose residues on the chemical shifts of the respective carbons [38].

As the correlation exists between structure of organic molecules and their MS fragmentation patterns, mass spectrometry makes a powerful tool for structure analysis of compounds ever since its creation. Because most of MS fragmentation is decomposition reaction of single molecular ion, research and clarification of features and mechanisms of different types of fragmentation has become a hotspot problem in present mass spectrometry research [21-23].

In the report of Yan Liang etc., the fragmentation pathway of kaempferol, a kind of flavonoids compounds, was theoretically studied by means of DFT methods [39-41]. The structures of all the fragment ions and the corresponding bond dissociation energies (BDEs) were analyzed. Based on the comparison with the calculated BDEs，the structure and the origin of each fragment ion were determined and the whole fragmentation pathway was deduced. The calculating results show that the fragment ions of kaempferol mainly formed by the cleavage of the C ring．And the BDE of fragment ion at m／z 210．7 is the lowest，while the BDE of fragment ion at m／z 1 50．7 is the highest，suggesting that the former is evidently easier to form from the parent ion，and the latter is comparatively more difficult to form [42].

The application of quantitative structure -

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retention relationship (QSRR) method is of great importance for exploring the variation pattern between molecular structure and its chromatographic retention behavior, which means that it can help to predict the relationship between their physical and chemical properties and retention characteristics, choose reasonable separation conditions and make further elaboration of retention mechanism [43-46].

Hongying Du etc. predicted the retention time of several peptide compounds on the reverse liquid chromatography (RPLC) on the basis of QSRR method. In the calculation, descriptors were obtained by semi-empirical methods and nonlinear QSRR model was established radial basis function neural network (RBFNN) and Projection Pursuit Regression (PPR). The non-cross-validation coefficients of training sets in RBFNN and PPR R2 were 0.9787 and 0.9881, respectively, and corresponding RMSE root mean square errors were 0.5666 and 0.4207. The practice proves that the computed result of both models and the empirical datum basically tallies [46].

## 4 Progress of QM in Pharmacodynamics

Most of the drugs for clinical application are structure-specific ones. The biological activity of these compounds is mainly due to their ability to form three-dimensional complex with specific receptors (biological macromolecule) in the body as a result of the specificity of chemical structure. Therefore, it would be impacted by chemical reactivity of drugs, molecular shape and size, chemical configuration and functional group of compounds, electronic effect (conjugation and the inductive effect), and even the possible situation of drug-receptor binding [47]. By means of calculating characteristics (both drug and receptor) mentioned above with QM methods, it would be available that acquiring pharmacophore Modeling of compounds, comprehending drug-receptor bonding type, computing interaction energy, exploring catalytic mechanism of enzymes, and interpreting structure-activity relationships of drugs.

### *4.1 Theoretical Study on the Antimalarial Mechanism of Artemisinin*

Artemisinin, extracted from Artemisia annua, is one of sesquiterpene lactones drugs which had peroxide groups. It is mainly considered that the antimalarial role of these compounds belongs to oxidizing mechanism: when peroxide radical disrupted, the molecules unfold or denature and typically lose biological activity. Experiments show that the reaction of heme and artemisinin leading to production of free radicals is the principal step of the antimalarial effects with these drugs [48-50].

Lingbo Qu etc. verified this suppose by calculations. Four kinds of artemisinin compounds were geometry optimized at B3LYP/6-31G（d）level, and their reaction mechanism with iron porphyrin was investigated at HF/STO-3G level. The results showed that it is synchronized that Fe-N bond broken and Fe-O bond formed, consistent with the findings of molecular docking, which confirmed the hypothesis that heme iron approached O13 atom in the artemisinin molecule and then 1-5 hydrogen migration reaction occurred to yield bioactive free radicals [51-52].

### *4.2 Investigation on Mechanism of Action Organometallic Anticancer Drugs*

In recent years, results of plentiful studies showed that some metal complexes, with a planar square or octahedral shape, possessed high antitumor activity. However, because of its negative performance in clinical applications, such as short of targeted selectivity and oral activity deficiency, researchers attempted to explore structure-activity

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relationship of these drugs and reveal their anticancer mechanisms, so as to find new anti-tumor drugs with high targeted selectivity and low toxicity. A series of studies have been carried out on this topic all over the world[53-54].

Studies of the geometrical and electrical configuration of the composite compound of the dinuclear platinum compound [{trans-PtCI($NH_3$)$_2$}$_2$ (μ-$NH_2$($CH_2$) $NH_2$)]$^{2+}$ and the 12-mer duplex d(ATATG*TACATAT)·d(ATATG*TACATAT) were performed by using the MM and QM methods by Sulan Huang etc. The investigating result showed that the coordinate bonds between Pt of the dinuclear platinum composite compound and two N7's of guanines in the DNA duplex are the most important interaction and hydrogen bond interactions are critical factors influenced the configuration of the composite compound. Based on the calculation results, they claimed that little distortion of DNA binding the di-nuclear platinum complex may result in a significantly diferent antitumor activity from cis-platin [55-56].

Previous experimental studies revealed that cisplatin binding to adjacent guanine and adenine is sensitive to nucleobase sequence. Whereas AG 1,2-intrastrand cross-links are commonly observed, the analogous GA adducts are seldom known [57-59]. The bifunctional binding of the anticancer drug cis-platin to two adjacent nucleobases in DNA is modeled using density functional theory by Y. Mantri etc. Monofunctional and bifunctional cis-platin adducts were generated and the transition states that connect them were located for the dinucleotides d(pApG) and d(pGpA), assuming that initial platination takes place at the guanine site. The study focused on understanding this directional preference by constructing a full reaction profile using quantum chemical simulation methods. Results revealed a significant kinetic preference for formation of the AG over the GA adduct: the activation free energies of ~23 kcal/mol for AG and ~32 kcal/mol for GA suggested that bifunctional closure was ~6 orders of magnitude faster for AG than for GA. Responsible for the stabilization of the transition state that afforded the AG adduct was a strong hydrogen bond between one of the ammine ligands of cisplatin and the 5' phosphate group of the DNA backbone; while this interaction was absent in the transition state that lead to the GA adduct, because the right-handed helix of the DNA backbone places the phosphate out of reach for the ammine ligand. A detailed analysis of the energies and structures of the bifunctional adducts revealed that the observed AG 1,2-intrastrand cross-link adducts were more reasonable compared to GA ones [60].

Jincan Chen etc. investigated the hydrolysis of a potential antitumor Ru(III) complex trans-[$Ru^{III}Cl_4$（2-$NH_2$-5-Me-STz）$_2$] using DFT methods combined with the conductor-like polarizable calculation model (CPCM). The structural characteristics and detailed energy profiles for the hydrolysis processes of this complex were obtained. For the first hydrolysis step, complex 1 had an activation energy of 92.9 kJ·mol-1 in solution and this was similar to that of the reported Ru(III) complex trans-[$Ru^{III}Cl_4$（2-$NH_2$-5-Me-Tz）$_2$] (96.3 kJ·mol-1) and was in good agreement with experimental results. For the second hydrolysis step, the formation of cis-diaqua products was found to be thermodynamically preferred over the trans isomers. Similar to the hydrolysis action mechanism of cis-platin, a “cis effect” was present wherein the cis-diaqua products preferred binding to pertinent biomolecular targets. Therefore, cis-diaqua products could be expected to be important precursors for biological actions. These theoretical results should help in understanding the action mechanism of these potential Ru(III) drugs with pertinent biomolecular targets [61].

### *4.3 Analysis of enzyme activity*

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Acetylcholinesterase (AChE, EC 3.1.1.7) is a hydrolytic enzyme that belongs to the serine hydrolase family. It plays important roles during the course of signal transmission at cholinergic synapses [62]. The principal biological role of acetylcholinesterase is the termination of impulse transmissions by rapidly hydrolyzing the neurotransmitter, acetylcholine (ACh). Dysfunctions of AChE or other components of cholinergic synapses are involved in several human diseases, including myasthenia gravis, glaucoma, Alzheimer's and Parkinson's Diseases. As a result, AChE has become an important target for rational drug design [63-64].

Generally, the catalytic triad in AChE consisting of Ser203(200), His447(440) and Glu334(327) was believed to be essential to hydrolysis. However, recent experimental mutagenesis studies have brought new challenges to all the above proposed reaction mechanisms. $TFK^+$(m-(N,N,N-trimethy-lammonio) trifluoroacetophenone (TMTFA)), a common inhibitor to AChE, can still react with the mouse AChE (mAChE), even with the replacement of His447 by a hydrophobic Ile. In contrast, its neutral analog, $TFK^0$, shows no apparent binding activity to H447I mutant, while it shows slightly reduced binding to the wild-type mAChE as compared to $TFK^+$.

The reaction mechanisms of two inhibitor $TFK^+$ and $TFK^0$ binding to H447I mutant mouse acetylcholinesterase (mAChE) have been investigated by Y.H.Cheng etc. using a combined QM/MM approach and classical molecular dynamics (MD) simulations. $TFK^+$ binding to the H447I mutant may proceed with a different reaction mechanism from the wild type. A water molecule took over the role of His447 and participates in the bond breaking and forming as a "charge relayer". Unlike in the wild-type mAChE case, Glu334, a conserved residue from the catalytic triad, acted as a catalytic base in the reaction. The calculated energy barrier for this reaction was about 8 kcal/mol. These predictions awaited experimental verification. In the case of the neutral ligand $TFK^0$, however, multiple MD simulations on the $TFK^0$/H447I complex revealed that none of the water molecules can be retained in the active site as a "catalytic" water. Taken together computational studies confirmed that $TFK^0$ was almost inactive in the H447I mutant, and also provided detailed mechanistic insights into the experimental observations [65].

PTPs (protein tyrosine phosphatases) are fundamental enzymes for cell signalling and have been linked to the pathogenesis of several diseases, including cancers [66]. Hence, PTPs are potential drug targets and inhibitors that have been designed as possible therapeutic agents for Type II diabetes and obesity [67,68]. Free-energy profiles, obtained by computer simulations of catalysis by a dual-specificity PTP, were shown in G. M. Arantes etc. study and were used to shed light on the catalytic mechanism. Reactions of alkyl and aryl substrates, with different protonation states and PTP active-site mutations, were simulated. Results showed the PTP substrate reacted as a bi-anion, with an ionized nucleophile，which was still a matter of debate in the literature. The inactivity of Cys→Ser active-site mutants was also not fully understood. It was shown that mutants were inactive because the serine nucleophile was protonated. Results also clarified the interpretation of experimental data, particularly kinetic isotope effects [69].

## 5. Progress of QM in Pharmacokinetics

When certain dose of the drug entered into the body, the amount and rate of drugs absorbed into the blood circulation are the inherent characteristics of drugs, which makes up the disposal and application of the body for drugs together with drug

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—protein binding degree, the amount and rate of metabolic transformation, metabolism properties, excretion manners and so on. Research on these *in vivo* process of drugs above could predict the pharmacokinetic processes of drug molecules and guide the structural modification of leading compound to achieving reasonable dynamic quality and avoiding the inappropriate losses caused by pharmacokinetics nature [70-71].

### *5.1 Investigation on Absorption of Drugs in vivo.*

$_P$Ka value of compounds plays a significant role in drug absorption: absorption amount improves as compound $_P$Ka value decreases [72]. Through the unremitting efforts of chemists, a variety of theoretical models have been produced at present, and the accuracy of some models is considerable high compared with the experimental results.

J. Pratuangdejkul etc. used quantum mechanics calculations to predict the two pKa's of 5-hydrotryptamine (5-HT). Proton dissociation reaction succeeded to predict the experimental $_P$Ka 1 corresponding to ionization of the protonated amine group but failed for pKa2 corresponding to ionization of the 5-hydroxyl group. For $_P$Ka 2, a cluster-continuum model including three water molecules in the first hydration shell around 5-hydroxyl and 5-hydroxide groups enabled researchers to reproduce the experimental pKa2 value. Furthermore, they demonstrated that specific conformations of acid/base pair of 5-HT was critical to predict accurately the experimental pKa's of the flexible 5-HT molecule [73].

### *5.2 Theoretical Study on Distribution of Drug*

In most cases, the pharmacological effects of drugs would become effective only by entering into the tissues or organs from the blood circulation. For example, drugs affected on central nervous system (CNS) should be distributed to the nerve center. The blood-brain barrier (BBB) is a separation of circulating blood and cerebrospinal fluid (CSF) in the CNS. It occurs along all capillaries and consists of tight junctions around the capillaries that do not exist in normal circulation. Endothelial cells restrict the diffusion of microscopic objects (e.g. bacteria) and large or hydrophilic molecules into the CSF, while allowing the diffusion of small hydrophobic molecules ($O_2$, hormones, $CO_2$). Cells of the barrier actively transport metabolic products such as glucose across the barrier with specific proteins [74,75].

Xiaolei Ma built up a theoretical model of organic compounds for the prediction of the activity of small molecules through the blood-brain barrier (BBB). A training set of 37 structurally diverse compounds was used to construct QSAR models while intermolecular and intramolecular solute descriptors were calculated using MM, QM, MD stimulations and so on. Significant QSAR models (R=0.955, s=0.232) of the BBB penetration of organic compounds were constructed. BBB penetration was found to depend upon the polar surface area, the octanol / water partition coefficient, Balaban Index, the strength of a small molecule to combine with the membrane-water complex, and the changeability of the structure of a solute-mem-brane-water complex. The results indicated that the distribution of organic molecules through BBB was not only influenced by organic solutes themselves, but also related to the properties of the solute-membrane-water complex, that was, interactions of the molecule with the phospholipids-rich regions of cellular membranes [76].

### **5.3 Analysis of the Relationships between Compound structures and Biological Transformation**

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Cytochromes P450 (CYPs) constitute one of the most important families of enzymes involved in the metabolism of drugs and their pharmacological and toxicological effects [77].

Hydroxylations of octane and lauric acid by Cytochrome P450-BM3 (CYP102A1) wild-type [77,78] and three active site mutants—F87A, L188Q/A74G, and F87V/L188Q/A74G—were rationalized using a combination of substrate orientation from docking, substrate binding statistics from molecular dynamics simulations, and barrier energies for hydrogen atom abstraction from quantum mechanical calculations by K.A.Feenstra etc.. Wild-type BM3 typically hydroxylated medium- to long-chain fatty acids on subterminal but not the terminal positions. The known carboxylic anchoring site Y51/R47 for lauric acid, and hydrophobic interactions and steric exclusion, mainly by F87, for octane as well as lauric acid, played a critical role in the binding modes of the substrates. Electrostatic interactions between the protein and the substrate strongly modulated the substrate's regiodependent activation barriers. A combination of the binding statistics and the activation barriers of hydrogen-atom abstraction in the substrates is proposed to determine the product formation. It is concluded that the combination of substrate binding statistics and hydrogen–atom abstraction barrier energies is a valuable tool to rationalize substrate binding and product formation and constitutes an important step toward prediction of product ratios [79].

In research work of T. Scior etc., the postulated transition of Bis-Maltolato-OxoVanadium(IV) (BMOV) from its inactive trans- into its cis-aquo-BMOV isomeric form in solution was simulated by means of computational molecular modeling. The rotational barrier was calculated with DFT method. The results are consistent with reports on the putative molecular mechanism of BMOV triggering the insulin-like cellular response (insulin mimetic) as a potent inhibitor of the protein tyrosine phosphatase-1B (PTP-1B) [81,82]. Initially, trans-BMOV was present in its solid dosage formed but in aqueous solution, and during oral administration, it was readily converted into a mixture of “open-type” and “closed-type” complexes of cis-aquo-BMOV under equilibrium conditions. However, in the same measure as the “closed-type” complex bound to the cytosolic PTP-1B, it disappeared from solution, and the equilibrium shifted towards the “closed-type” species. In full accordance, the computed binding mode of cis-BMOV was energetically favored over sterically hindered trans-BMOV [80].

Bacterial resistance to antibiotics is an increasingly serious problem in clinical drug treatment [83]. Modelling of the first step of the deacylation reaction of benzylpenicllin in the E. coli TEM1 β-lactamase with QM / MM methods showed that a mechanism in which Glu166 acts as the base to deprotonate a conserved water molecule was both energetically and structurally consistented with experimental data [84]; the results may assist the design of new antibiotics and β-lactamase inhibitors [85].

### 5.4 Research on in vivo Elimination process of drug molecule

Omeprazole is a substituted benzimidazole which suppresses gastric-acid secretion by means of H+, K+-ATPase inhibition [86]. It is an optically active drug with the sulfur of the sulfoxide being the chiral center. This pro-drug can be easily converted into its respective sulfenamide at low pH [87]. Racemization barrier and Decomposition reaction behavior of omeprazole has been studied by A.T.Bruni etc. in relation to racemization barrier and decomposition reaction. Quantum chemistry coupled to PCA chemometric method were used to find all minimum energy structures.

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Conformational analysis and calculation of racemization barriers were carried out by PM3 semiempirical method. The average racemization energy barrier for all minimum energy structures (43.56 kcal*mol-1) can be related to the velocity constant in Eyring's equation. The enormous half-life time at 100°C ($9.04*10^4$ years) indicates that the process cannot be observed in human time scale. On the other hand, the difference of free energy change ($\Delta(\Delta G)$ =-266.78 kcal* $mol^{-1}$) for the decomposition reaction showed that the process is favorable to the sulfenamide formation. The highly negative $\Delta(\Delta G)$ obtained for the decomposition reaction showed that this process was extremely exothermic. This result explained why omeprazole decomposes and does not racemize [88].

## 6 Progress of QM in Drug Toxicology Research

Drug side effects is integrated performance of a complex process, but fundamentally, the cause of this effect can be considered as the interaction between the drug molecules and biological molecules in the body. Studies on toxicological properties of drugs by QM method would contribute to designing and synthesizing of compounds, understanding drug action mechanism and mode, providing the theoretical basis for reasonable and effective drug research [71,72].

Conjugated Type-2 alkenes, such as acrylamide (ACR), are soft electrophiles that produce neurotoxicity by forming adducts with soft nucleophilic sulfhydryl groups on proteins [89-91]. Soft–soft inter-actions are governed by frontier molecular orbital characteristics and can be defined by quantum mechanical parameters such as softness (σ) and chemical potential (μ). The neurotoxic potency of ACR is likely related to the rate of adduct formation, which is reflected in values of σ. Correspondingly, differences in μ, the ability of a nucleophile to transfer electrons to an electrophile, could determine protein targets of these chemicals. Here, σ and μ were calculated for a series of structurally similar Type-2 alkenes and their potential sulfhydryl targets. M. LoPachin etc. calculated structures of conjugated Type-2 alkenes compounds and σ and μ of their potential sulfhydryl receptor through a series of studies. The result suggested that the neurotoxicity of ACR and its conjugated alkene analogs was related to electrophilic softness and that the thiolate state of cysteine residues was the corresponding adduct target.

Du Juan etc. used QM methods to describe the quantificational relationship between structures and cytotoxicitives of 33 flavonoe derivatives against HIV. 14 quantum chemical descriptors had been calculated. A total of 5 important descriptors had been selected by stepwise regression analysis (SRA). A leave-one out cross- validation method was used to select the number of latent variables for the building of the QSAR models by principal component regression (PCR) and partial least square regression (PLS) method respectively. The cross-validation squared correlation coefficients RCV2 were 0.70 for PCR and 0.74 for PLS, showing that both of these two models had good prediction ability and the PLS model was superior to the PCR model. The QSAR model showed that the effects of the five desciptors, and directs the investigation of the flavonoids with low toxicity [92].

## 7 Conclusion and Outlook

In summary, the parameters calculated by quantum chemistry methods are closely linked with the molecular properties, which can be used to explain drug action principle and the interaction

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between macromolecules in biological systems, and even has successfully set out a number of relationships between chemical structures and the biological activity.

However, experimental studies could not be replaced completely by means of computational chemistry methods; the most effective results could only be produced by complement with both sides. At the same time, due to defect on the level of computer technology and the imperfect quantum chemical calculation method itself, some results restricted the applications of quantum chemistry in drug research for lack of accuracy, lack of precision and long term computing cycle.

Quantum chemistry is undeniable that it has brought some new ideas, tools and methods for drug research, which implies providing a reliable guide, saving research resources and eliminating a lot of blind experiments. Quantum chemistry method will become a powerful tool and a solid basis for new drug research.

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