

Quantum mechanics implementation in drug-design workflows: does it really help?

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Abstract: The pharmaceutical industry is progressively operating in an era where development costs are constantly under pressure, higher percentages of drugs are demanded, and the drug-discovery process is a trial-and-error run. The profit that flows in with the discovery of new drugs has always been the motivation for the industry to keep up the pace and keep abreast with the endless demand for medicines. The process of finding a molecule that binds to the target protein using *in silico* tools has made computational chemistry a valuable tool in drug discovery in both academic research and pharmaceutical industry. However, the complexity of many protein–ligand interactions challenges the accuracy and efficiency of the commonly used empirical methods. The usefulness of quantum mechanics (QM) in drug–protein interaction cannot be overemphasized; however, this approach has little significance in some empirical methods. In this review, we discuss recent developments in, and application of, QM to medically relevant biomolecules. We critically discuss the different types of QM-based methods and their proposed application to incorporating them into drug-design and -discovery workflows while trying to answer a critical question: are QM-based methods of real help in drug-design and -discovery research and industry?

Keywords: quantum mechanics, drug discovery, drug design, molecular mechanics, molecular dynamics, *in silico* tools

Introduction

Drug discovery plays an important role in the growth of any pharmaceutical company and society, as newer and safer drugs are launched in the market with the sole objective of improving the therapeutic value and safety of drugs. The pharmaceutical industry has consistently shown that it can discover and develop innovative medicines for a wide range of diseases.¹

Drug research, as it is called today, began when chemistry had reached the peak of its career, allowing chemical principles and theories to be applied to problems outside the scope of chemistry, and when pharmacology became an independent scientific discipline on its own. By 1870, some of the important foundations of chemistry theory had been laid.^{2,3} In the twentieth century, biochemistry had remarkable influence on drug research in numerous ways (Table 1). It was during this period that the concept of targeting enzymes and designing drugs as inhibitors came into existence.⁴ However, the current drug-discovery process is very time consuming and expensive and can take up to 12–16 years of exhaustive research, huge financial investment, and clinical trials before a molecule can be recognized as a drug (Figure 1).⁵

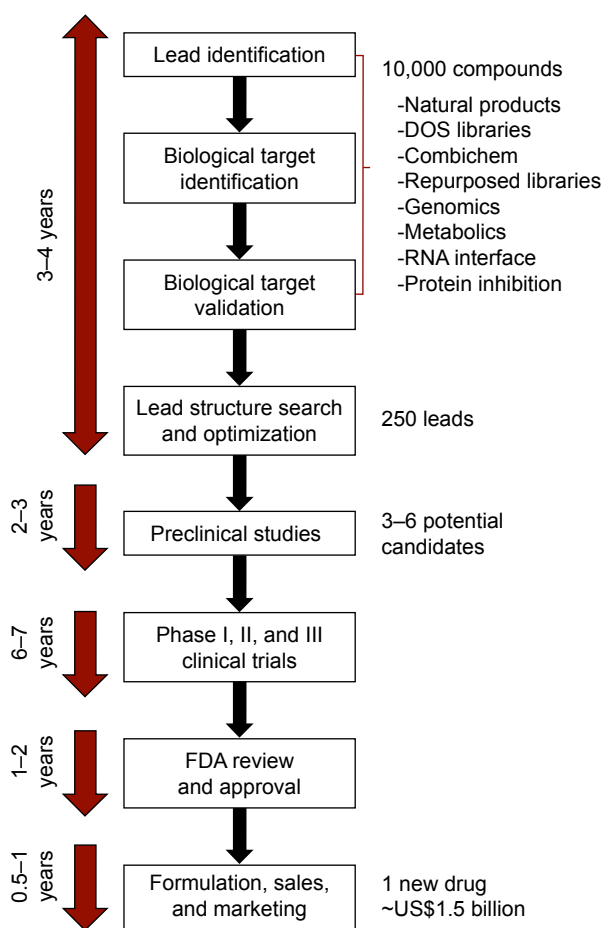
Despite the diverse research and development (R&D) approaches adopted by pharmaceutical companies, the attrition rate is inadmissibly high. One of the factors contributing to the high attrition rates is an active compound with unacceptable

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Table 1 Some of the important discoveries in medicine in the last two centuries

	Year of discovery	Drug name	Category
1	1806	Morphine	Hypnotic agent
2	1899	Aspirin	Analgesic and antipyretic agent
3	1922	Insulin	Antidiabetic agent
4	1928	Penicillin	Antibiotic
5	1960	Chlordiazepoxide	Tranquilizer
6	1971	L-Dopa	Anti-Parkinson agent
7	1987	Artemisinin	Antimalaria agent
8	1998	Sildenafil	Erectile dysfunctional treatment
9	1999	Celecoxib, rofecoxib	Selective COX-2 inhibitors
10	1999	Zanamivir, oseltamivir	Anti-influenza drugs
11	2001	Imatinib	Leukemia treatment

absorption, distribution, metabolism, excretion, and toxicity (ADMET) adverse effects that thus needs to be withdrawn from development. This factor represents approximately 50% of all costly failures in drug development,⁶ and it has become widely appreciated that these areas should be considered as early as possible in the drug-discovery process.^{7,8} It is evident

**Figure 1** Flowchart of drug-discovery and -development process.

Abbreviations: DOS, diversity-oriented synthesis; combiChem, combinatorial chemistry; FDA, Food and Drug Administration (US).

that the pitfall in the current drug-discovery process urges an unconventional approach, which would not only truncate the R&D time but also reduce the cost involved.⁹

The process of finding a molecule that binds to the target protein has now moved from the laboratory to the computer.¹⁰ Years ago, drug design (DD) substantially extended its range of applications from target identification to clinical trials.¹¹ Computer-generated models, which serve as good predictive models for the evaluation of biological activities, have had numerous successes predicting the possible structures of biological targets, thus reducing fruitless effort using nuclear magnetic resonance and spectroscopy-structure elucidations.¹² With *in silico* tools, it is possible to accelerate the drug-discovery process by modeling the most relevant ADMET properties.¹² A molecule could be too toxic, too quickly eliminated from the body, possess fast metabolic reaction, unstable, too challenging to synthesize in large volume, or too expensive to produce. Therefore, many promising compounds will regrettably have to be rejected once they are found to show unacceptable adverse effects in humans. Furthermore, compared to the status a decade ago, protein structure-based DD is swiftly gathering energy, and results have shown a remarkable increase in the structural knowledge of medically relevant proteins through various methods,¹³⁻¹⁸ as well as computer-aided programs. The large number of structural studies on medically relevant proteins suggests that the structure of a potential drug target is treasurable knowledge for any pharmaceutical company, not only for lead discovery and lead optimization but also in the later stages of drug development, where such concerns as toxicity, bioavailability, and binding modes of potential drug candidates to the target protein are extremely important.

A drug reveals its action when it binds to its biological target (enzyme, nucleic acid, or antibody), typically receptors. Receptors possess the active sites for the binding of a drug. Therefore, it is important to know the structure of the target, in order to design a good drug and identify an accurate binding site. In DD, predicting drug-receptor interactions involves the development of pharmacophore-based and molecular docking/scoring techniques. However, some biologically relevant biomolecules lack X-ray crystal structures. To resolve this, homology modeling has been implemented,¹⁹ and modeled proteins behave somewhat like the real proteins in their native biological environment when simulated.²⁰ Recently, many computer-assisted models have been developed, and several thousand candidates are being screened for various activities using these models. The methods of choice for activity

screening using these models are computer programs that superimpose molecules with flexible alignment to develop pharmacophoric patterns and/or quantitative structure–activity relationships (QSARs), dock molecules to the receptor or a pseudoreceptor, or construct new drugs within a predefined active site.^{21,22} Different molecular properties (eg, electrostatic, steric, and hydrophobic) and hydrogen bond-acceptor and donor fields have been used to achieve this purpose.²³ Computational studies of biological targets allow the study of their structure, function, and dynamics at molecular and atomic levels. The entire process is about the simulation of the biological targets using quantum mechanics (QM) calculation, which is based on the principles of chemistry and physics.

In this review, we discuss how the implementation of QM methods in academic and pharmaceutical companies' research can be a useful tool in the elucidation of drug–target interactions, which will help DD and drug development with respect to accuracy, time, and cost.

Computer-aided drug-design (CADD) approaches

CADD is aimed at improving the development and efficacy of drugs using modern computational tools that are fast and

cost-effective compared to conventional methods.^{24–26} The development of drugs that bind to specific targets has been recognized by the pharmaceutical industry as an important foundation that provides it with the necessary return on investment to invest in further R&D, leading to a discovery-and-development cycle.²⁷ Broadly speaking, DD is divided into two areas: structure-based DD (SBDD) and ligand-based DD (Figure 2).

The CADD approach has been applied to various successful drugs, some of which are in use in the market. Examples include imatinib²⁸ and nilotinib.²⁹ Several other targets include ER,^{30,31} EGFR,^{32,33} PKC β_2 ,³⁴ and BCR-Abl.³⁵ A biomolecular system can be simulated using molecular mechanics (MM), QM, or a hybrid method (QM/MM), depending on the research problem to be answered.

Molecular mechanics

MM is commonly applied in large systems to calculate molecular structures and relative potential energies of a molecular conformation or atom arrangement.^{36–38} The electrons in the studied system are not explicitly considered, but instead each atom – specifically, the atomic nucleus and the associated electrons – is treated as a single particle. The exclusion of electrons in MM is justified on the basis

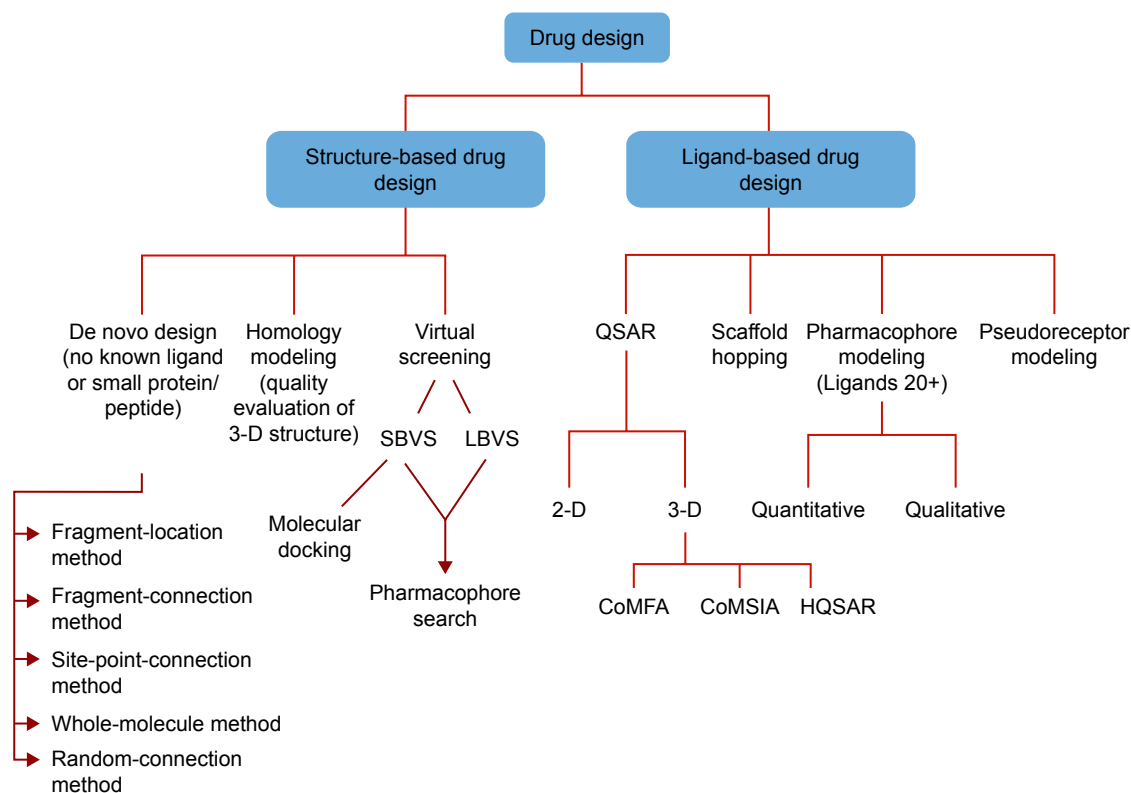


Figure 2 Different *in silico* tools used in drug design.

Abbreviations: QSAR, quantitative structure–activity relationship; SBVS, structure-based virtual screening; LBVS, ligand-based virtual screening; CoMFA, comparative molecular field analysis; CoMSIA, comparative molecular similarity index analysis; HQSAR, hologram quantitative structure–activity relationship.

of Born–Oppenheimer approximation,³⁹ which states that electronic and nuclear motions can be uncoupled from each other and considered separately. Energy differences between conformations are significant in such calculations, rather than absolute values of potential energies.

MM can simply be viewed as a ball-and-spring model of atoms and molecules with classical forces between them.⁴⁰ Such forces are accounted by potential energy functions with respect to such structural features as bond length, bond angles, and torsional angles. Potential energy functions are equipped with parameters designed to reproduce experimental properties.³⁷ The MM or rather the total potential energy of a molecule is described as the sum of bond-stretching energy (E_{str}), bond angle-bending energy (E_{bend}), torsion energy (E_{tor}), and energy of interactions among unbound atoms (E_{nb}). Energy contributions of the latter constitute van der Waals and electrostatic interactions:

$$E_{\text{tot}} = E_{\text{str}} + E_{\text{bend}} + E_{\text{tor}} + E_{\text{vdw}} + E_{\text{elec}}$$

$$E_{\text{tot}} = \sum_{\text{bonds}} k_r (r - r_{\text{eq}})^2 + \sum_{\text{angles}} k_\theta (\theta - \theta_{\text{eq}})^2$$

$$+ \sum_{\text{dihedrals}} \frac{V_n}{2} [1 + \cos(n\phi - r)] + \sum_{i < j} \left[\frac{A_{ij}}{r_{ij}^{12}} - \frac{B_{ij}}{r_{ij}^6} + \frac{q_i q_j}{\epsilon r_{ij}} \right]$$

where E_{tot} is total potential energy, stretch terms refer to E_{str} , bend terms refer to bond angle-bending energy E_{bend} , torsional terms refer to E_{tor} or twisting energy, and unbound interactions are van der Waals forces and electrostatic forces between atoms that are not chemically bonded. Energy contributions from special treatment of hydrogen bonding and stretch–bend coupling interactions may also be seen in MM.

Quantum mechanics

The QM method treats molecules as collections of nuclei and electrons without any reference to “chemical bonds”. QM is important in understanding the behavior of systems at the atomic level. QM methods apply the laws of QM to approximate the wave function and to solve the Schrödinger equation.^{36,41} The solution to the Schrödinger equation is in terms of the motions of electrons, which in turn lead directly to molecular structure and energy among other observables, as well as to information about bonding. However, the Schrödinger equation cannot actually be solved for any but a one-electron system (the hydrogen atom), and approximations need to be made. According to QM, an electron bound to an atom cannot possess any arbitrary energy or occupy any position in space. These characteristics can be

determined by solving the time-independent Schrödinger equation:^{42,43}

$$H = T + V$$

where H is the Hamiltonian operator (sum of kinetic energy), T the potential energy, and V the operator. H can also be defined as:

$$H = \left[-\frac{\hbar^2}{8\pi^2} \sum_i \frac{1}{m_j} \left(\frac{\partial^2}{\partial x^2} + \frac{\partial^2}{\partial y^2} + \frac{\partial^2}{\partial z^2} \right) \right] + \sum_i \sum_{j < i} \left(\frac{e_i e_j}{r_{ij}} \right)$$

QM methods include ab initio⁴⁴ density functional theory (DFT)^{45–47} and semiempirical calculations.^{48–50} For more accurate QM calculations, electron correlation methods, namely, CCSDT and MP2, etc, are necessary.⁴⁶ DFT methods conduct calculations by electron correlation approximation.^{46,47,51} These methods can be employed to calculate crucial properties of a system such as vibrational frequencies, equilibrium molecular structure, dipole moments and free energy of reaction, which cannot be achieved by experimental methods.³⁶ They also help to identify the activated complex when applied to reacting chemical species and therefore in the identification of a reaction pathway. Since the Schrödinger equation cannot be solved for complex molecular systems, semiempirical ab initio DFT methods were developed to approximate the precise QM solution to the problem.^{36,46,52} QM models are the most accurate, but also the most expensive methods in terms of time and computational resources, and are thus applied on small systems.

Classical mechanics or QM – which to choose?

Classical mechanics, also called MM, is the alternative to QM when chemical reactions do not need to be considered in a simulation. MM does not start from an “exact theory” (the Schrödinger equation), but rather describes molecules in terms of “bonded atoms”, which have been distorted from some idealized geometry due to unbound van der Waals and Columbic interactions. Though MM does not solve the Schrödinger equation for electron motions, it requires an explicit description of chemical bonding and lots of information about the structures of molecules. It is the use and extent of this information that distinguishes different MM models.^{53–56} While many of the details of mechanical and biochemical interactions in enzymes are currently unclear, MM can rely on force fields with fixed parameters to provide better understanding of conformational analysis between

conformers,⁵⁷ mechanical deformation of DNA, RNA, and proteins, and changes in cellular structure, response, and function.⁵⁸ This understanding can offer new prognoses of diseases, as MM calculations are used to provide qualitative descriptions of molecular interactions.

QM has been said to succeed outstandingly in the area where MM failed. In contrast to QM, MM ignores electrons, fails to illustrate reality, and also computes the energy of a system as only a function of the nuclear positions. Generally, QM incorporates four phenomena for which MM cannot justify. These include quantization of some physical properties, quantum entanglement, the principle of uncertainty, and wave-particle duality. QM is applied in the determination of interactions between possible drugs and enzyme active sites.^{59–65} It is slow but accurate with respect to DD. In spite of the advantages of MM, it has some setbacks, such as inappropriate parameterization, inability to predict chemical reactions, or explain bond breaking/formation.^{66–70}

QM in CADD arena

In answering research questions, computational chemists have a vast selection of methodologies at their disposal. The key tools available belong to six all-encompassing classes: molecular dynamic (MD) simulation, MM, QM, ab initio calculations, DFT, and semiempirical calculations. MM can be used to study very large molecules, because other QM methods, such as semiempirical calculations, ab initio, and DFT are relatively slow and would exhaust computational resources. However, MM methods are unable to address interactions between the ligand and the receptor in metal-containing systems.

Such algorithms as hybrid QM/MM, which combine QM and MM, have been developed to limit issues brought about by the individual application of these methods.^{71–74} QM methods are the most accurate, but also computationally expensive and time-consuming calculations.⁷⁵ QM calculations are employed in semiempirical methods (eg, AM1, PM3) only for valence electrons in the system, whereas for other electrons and atomic nuclei behavior of other atoms, approximations are made.⁷⁵ Combined QM-MM methods provide the accuracy of a QM description with low computational cost of MM.^{71,76} Even though QM-MM may not be applicable in every SBDD project, the majority of important systems cannot be well addressed by any other computational methods. QM-MM is thus the crucial component in computational drug discovery.

Five key facets are imperative in planning a QM-MM calculation on an enzyme: choice of the QM method, choice of

Table 2 Accuracy of different quantum mechanics methods

	Accuracy	Maximum atoms
Semiempirical	Low	2,000
Hartree–Fock and density functional	Medium	500
Perturbation and variation methods	High	50
Coupled cluster	Very high	20

MM force field, segregation of the system into QM and MM regions, simulation type (eg, MD simulation or calculation of potential energy profiles), and whether advanced conformational sampling will be performed. The choice of QM method is crucial. A plethora of different QM methods exists, ranging from fast, semiempirical methods (eg, AM1, PM3, SCC-DFTB; low accuracy and maximum of 2,000 atoms) to more accurate but more computationally expensive Hartree–Fock and density-functional (eg, B3LYP; medium accuracy and maximum of 500 atoms), and molecular orbital ab initio (eg, MP2, coupled cluster; very high accuracy and maximum of 20 atoms) methods. Not all methods are applicable to all systems, for reasons of accuracy, practicality, or lack of parameters (eg, for semiempirical methods) (Table 2). Generally, but not always, improved accuracy comes at the price of increased calculation expenses.

Typical applications of QM in DD include calculation of energies and structure optimization of ligand and/or protein–ligand complexes,⁷⁷ especially for docking studies to obtain the correct binding mode of a ligand.⁷⁸ QM-MM methods have shown promise for their accurate predictions when employed in the calculation of binding energies; however, this approach still requires further sampling of ligand–target conformations through MD simulations.⁷⁹ QM methods have proved useful in the study of some target proteins, including HIV1 integrase,⁷⁷ trypsin,⁷⁸ West Nile virus NS3 serine protease, HIV1PR, and CDK2.⁷⁹

The use of supercomputing to calculate QM has been attributed to expensive calculations for small systems. However, the use of Hadoop⁸⁰ could make QM faster and more scalable and efficient. Hadoop could allow for better cluster utilization as well to accommodate larger jobs, which will help QM, as it needs more computational resources to run calculations for larger systems.

Recent QM developments in drug discovery

Tangible advances in the use of QM to solve relevant pharmaceutical problems have been seen in the last decade, eg, the use of the hybrid QM-MM approach to determine the free-energy

landscape of the enzymatic reaction mechanism.^{81,82} The next step in the evolution of drug discovery is the routine use of QM in all levels of *in silico* DD.

SBDD is an important factor in the drug-discovery process, and designs more potent molecules with few alterations made, ie, derivatives of “lead” molecules.^{83–86} *In silico* tools can be used to design molecules to investigate existing protein–ligand interactions, as well as explore the active site for any supplementary hydrophilic or hydrophobic interactions that can increase binding affinity.^{87–89} The use of *in silico* tools allows the testing of a theory in a short time frame, using high-throughput empirical methods. However, there are concerns regarding the accuracy of these methods, particularly in the area of docking and scoring^{90–93} and QSAR.^{94,95}

The *in silico* approach is fast and environmentally friendly, but it does not replace experimentation. Regardless, failures encountered in the pharmaceutical industry at the drug-discovery stage can be attributed to a number of factors that are not limited to wrong force-field parameters, especially for metals,⁹⁶ disregard for protein flexibility^{97,98} or domain of applicability,⁹⁹ or nonrigorous validation of the QSAR model.^{100,101}

QM, a method used to replicate an experimental work accurately, proffers a potential solution to the failures mentioned.^{88,102} Increasingly, QM-MM methods are being applied to enzymes that are drug targets, often with the aim of providing information for DD.^{103–115} Examples include the HIV1-replication enzymes: reverse transcriptase, protease, and integrase. The reaction mechanisms of these enzymes have been studied using the QM-MM approach.^{116–126} Other examples are G-protein-coupled receptors,^{127–129} 5-HT₄ receptors,^{130,131} design and evaluation of a novel class of FKBP12 ligands,^{132,133} and novel inhibitors of human DHFR.^{134–136} The number of accidental discoveries in drug history is also legion.^{83,137–141} Another development in DD research is the hybrid QM-MM method, developed to improve the accuracy of biomolecular simulations,^{71–75} QM docking, QM virtual screening, and QM-QSAR.^{142,143} The QM approach has been successfully applied in drug discovery in pharmaceutical companies, eg, in the combination of artificial intelligence and cloud computing to search molecular entities and aid in the design of novel drugs.¹⁴⁴

QM in DD research: time vs accuracy

In spite of growing computational resources, simulations of complex biosystems at the atomic/molecular level remain a challenge. The application of QM is limited to relatively

small systems (Table 2). On the other hand, MM methods can treat millions of atoms or more. The hybrid QM-MM method, which combines the accuracy of QM descriptions with the low computational cost of MM modeling, and other QM-based methods (QM docking, QM virtual screening, QM-QSAR) can thus offer a promising solution to the computational challenge in DD. In addition, a recent article implicitly explained that the need for suitable computational approaches or tools could enhance success rates in the drug-discovery process.¹⁴⁵

QM/MM docking method

The process of docking involves the correct prediction of ligand conformation and orientation within a targeted binding site, while scoring predicts the binding free energy of a complex formation.¹⁴⁶ There are numerous molecular docking programs,¹⁴⁷ such as Dock,¹⁴⁸ AutoDock,¹⁴⁹ Gold,¹⁵⁰ Flexx,¹⁵¹ Glide,^{152,153} ICM,¹⁴⁷ PhDock,¹⁵⁴ and Surflex.¹⁵⁴ However, some problems have been reported in docking,^{155,156} which could be due to either posing or scoring. Each docking program is ideal for precise docking problems;¹⁵⁷ however, combining different computational methods can improve the reliability and accuracy of results.¹⁵⁸ QM is specifically useful in DD when the interaction of the drug involves a chemical reaction. As such, implementation of QM docking would systematically improve the accuracy of description of enzyme–ligand interactions, as well as binding affinity. Limitations in scoring functions are being increasingly exposed, particularly as more challenging and electronically complex pockets are being probed, eg, systems with metals.¹⁵⁹ Cho et al¹⁶⁰ obtained ligand atomic charges using a QM-MM calculation. Calculations indicated generally improved poses after docking. The ability of QM-MM docking has been further evaluated in other studies to predict the poses of metalloproteins.^{161,162} Another study¹⁶³ employed full QM calculation rather than QM-MM calculations to obtain partial charges for the ligand and receptor. Therefore, there appears to be evidence that QM-based models provide scoring functions that can improve the quality of predicted docking poses for challenging receptors.

QM virtual screening method

Virtual screening has become a powerful tool in the drug-discovery process to search for novel compounds with desired properties.^{164,165} This method has found its application in screening of combinatorial chemistry, genomics, protein, and peptide libraries.¹⁶⁶ Virtual screening involves the docking of selected lead molecules against a specific biological target.

This is followed by a scoring function.¹⁶⁷ Virtual screening, which can be ligand-based^{168,169} or structure-based,^{168,170,171} screens the library by applying Lipinski's rule of five before further evaluation.¹⁷² Pharmaceutical companies rely on this method when searching for new novel compounds. Considering today's computational resources, several million compounds can be screened in a few days on supercomputers, and QM could be used to evaluate binding for further drug development.

QM-QSAR method

QSAR is a mathematical representation that attempts to correlate a set of compounds with dependent variables (activity values, eg, K_i , EC_{50} , ED_{50} , IC_{50}) and a set of independent variables called descriptors.¹⁷³ There are various statistical models that are used to derive a QSAR equation,¹⁷⁴⁻¹⁷⁶ and a QSAR model can be 2-D, 3-D, or 4-D.¹⁷⁷⁻¹⁷⁹ Using the QSAR method, predicted chemical structures that possess good activity values need only be synthesized.¹⁸⁰⁻¹⁸² QM-QSAR uses QM methods to develop quantum-based QSAR models.¹⁸³ Studies have provided details of QM-based descriptors used in QSAR programs, such as Codessa-, AM1-, and DFT-based descriptors, to understand the relationship between physico-chemical properties and their descriptors.¹⁸⁴⁻¹⁸⁶

QM implementation in the pharmaceutical industry: time vs accuracy

As the ADMET properties of a drug determine its activity, the development of a new drug with reasonable ADMET makes drug discovery a more difficult and challenging process in the pharmaceutical industry. The pharmaceutical industry is

progressively operating in an era where development costs are constantly under pressure, higher percentages of drugs are demanded, and the drug-discovery process is a trial-and-error run. The profits that flow in with the discovery of new drugs have always been the motivation for the industry to keep up the pace and keep abreast with the endless demand for medicines.^{187,188}

In recent years, the use of CADD to simulate drug-receptor interactions has made rational DD feasible and cost-effective. *in silico* tools, such as docking, virtual screening, QSAR, molecular simulation, MM, and QM, use their respective mathematical equation to predict rapidly the binding affinities of a large library of compounds, as well as analyze homolytic or heterolytic fission/fusion before undergoing chemical (synthesis) and biological (activity) evaluation as a novel compound.

However, more attention should be paid to the way pharmaceutical companies use *in silico* tools. While docking, virtual screening, QSAR, and MM manage computational resources and allow rapid scans of large libraries, the accuracy of the results is in question when it comes to experimental data correlation. Compared to those used in pharmaceutical companies, there are more efficient methods, but the cost with respect to computer time/resources is high when one has to scan a really large library of compounds. Therefore, using a combination of QM to parameterize the molecules and MM to describe and solvate the protein, a more accurate understanding of binding affinity and protein-molecule interaction could be gained (Figure 3). If this method was implemented in pharmaceutical companies' R&D, it would give correct binding affinities and free binding energy using different ligand geometries in QM-MM energy calculations.

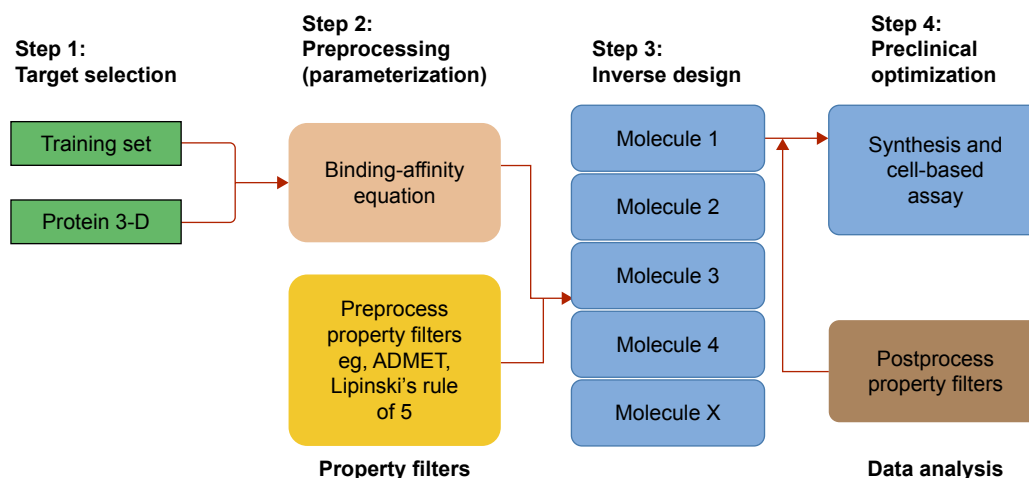


Figure 3 Implementation of QM in pharmaceutical companies' drug design workflow.

Abbreviations: ADMET, absorption, distribution, metabolism, excretion, toxicity; QM, quantum mechanics.

Table 3 Description of various QM-based methods

Approaches	Description	References
QM-MM MD	The hybrid QM-MM method is a molecular simulation approach that combines the accuracy of QM to treat the region of the system where the chemical process takes place and the speed of MM to the rest of the system, thus allowing for the study of chemical processes in large systems. This approach has been applied to target proteins, such as human acetylcholinesterase, ¹⁶⁸ heme peroxidases, metallo- β -lactamases, α -synuclein, ligase ribozymes, ¹⁶⁹ and trypsin. ¹⁷⁰	171–181, 199–204
QM-MM docking	The accuracy of electric charges plays an important role in protein–ligand docking, which is why QM-MM calculations are incorporated into docking procedures. Fixed charges of ligands obtained from force-field parameterization are replaced by QM-MM calculations in the protein–ligand complex, treating only the ligand as the quantum region. This approach has been applied to target proteins, including F-actin, ⁹³ protein kinases, ¹²⁶ and metalloproteins. ¹⁸²	171, 183–189, 205–210
QM-QSAR	QSAR models combined with QM-MM allow the prediction of drug ADMET and give reliable information on how the modification of a compound affects or improves pharmacokinetic/ pharmacological profiles. QM-QSAR has been applied to such targets as ACE ¹⁹⁰ and cytochrome P450. ¹⁹¹	86, 192, 193, 211–213
QM-VS	The QM-VS approach provides unprecedented accuracy in structure-based binding-energy calculations that enable application of QM methodologies to noncovalent interactions in systems as large as protein–ligand complexes and conformational ensembles. This method bridges the gap between the high accuracy of QM and high-volume computations (VS) in drug research and has been applied to such targets as HIV1 integrase ¹⁹⁴ and butyrylcholinesterase. ¹⁹⁵	195–198, 214–219

Abbreviations: QM, quantum mechanics; MM, molecular mechanics; MD, molecular dynamics; QSAR, quantitative structure–activity relationship; ADMET, absorption, distribution, metabolism, excretion, toxicity; VS, virtual screening.

Furthermore, using QSAR to predict the activity of an existent molecule may lead to remarkable savings with respect to development time and cost (Table 3).

Probably, most pharmaceutical companies today follow common technology processes for discovering drugs. These include cloning and expression of human receptors and enzymes using high-throughput, automated screening and the application of combinatorial chemistry.¹⁸⁹ The field of combinatorial chemistry is in constant evolution. We believe that pharmaceutical companies rarely use accurate DD tools, eg, QM, in their DD, owing to the fast pace of their work. The use of QM is not limited to creating a computational model of a drug, but can also be applied to proteins, DNA, carbohydrates, and lipids, as well as solvent molecules that are involved in drug transportation, binding, and signaling.

Future perspectives

The application of QM-based approaches in guiding SBDD is not new. QM has featured in some medicinally relevant chemistry calculations in providing informative descriptors for QSAR and 3-D conformation for ligands. QM methods offer the ability to provide an accurate representation of ligands and proteins where MM parameterization struggles. QM approaches hold promise in addressing pharmacological problems on the time scale demanded by drug-discovery research. After ups and downs in the perception of CADD and perhaps some overhyping of its promises in drug development, it could be said that CADD is becoming a routinely used component of drug discovery.

Currently, sophisticated CADD tools are typically applied by modeling experts, but are increasingly spreading to the desktops of medicinal chemists as well. Ligand poses predicted from docking to receptors, such as metalloproteins, have been shown to resemble experiments more closely when partial charges are derived from QM or QM-MM calculations. The use of QM and QM-MM approaches in computation of protein–ligand binding affinities has met with mixed success. However, the QM-MM approach appears to be of most benefit for low-resolution X-ray structures, where an incorrectly assigned ligand structure due to its MM force field is more likely. Studies demonstrate that the use of accurate charges, in many cases, leads to improvement in docking accuracy in a wide range of Protein Data Bank complexes. The principal uncertainty at this point is whether this improved performance in docking can be noticed in other *in silico* methods.

In this review, we have discussed how the implementation of QM-based methods could help the drug-discovery and DD process in the pharmaceutical industry. This review outlines the major roles played by QM in the DD workflow and its importance in the drug-discovery process to avoid “dead-end” lead compounds. This method could have strong impact in future drug development, because of the endless demand for new drugs and the short time frame pharmaceutical companies have in developing them. Pharmaceutical companies have to reach a compromise between accuracy and productivity by applying QM in their research. The selection of the most appropriate method (MM, QM, or QM-MM)

during drug development is of extreme importance. QM should be applied to “lead” compounds to provide insight into the free-energy landscape. Most importantly, before embarking on CADD, it is appropriate to evaluate the diversity and demand of accuracy of molecules to be designed in the project, which in turn dictates the most appropriate approach to select. It is also possible to reparameterize approximate methods in order to improve the accuracy of results in specific reactions that require numerous energy evaluations. A number of studies have sought to incorporate QM and QM-MM into their approaches for calculating ligand–receptor binding affinities. These approaches show promising results, but require further development to be broadly applicable. Finally, QM methods have proved valuable in quantitative analysis of the energetics of ligand deformation on binding. Although computation of binding energies remain a challenging and evolving area, current QM approaches could offer detailed information on the nature and relative strengths of complex active-site interaction, which is valuable in molecular design. It is likely that QM will become a more prominent tool in the repertoire of the computational medicinal chemist. Therefore, modern QM approaches will play a more direct role in informing and streamlining the drug-discovery process. The insight gained from this review could serve as a cornerstone for medicinal chemists, industry R&D and clinicians. This could provide better understanding of the in silico tools in drug design and development with improved ADMET, pharmacokinetics and the timely assessment of property profiles.

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Disclosure

The authors report no conflicts of interest in this work.

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