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Strategies Rooted in Quantum Mechanics for Drug Discovery: Keeping Pace with Novel Hurdles in Pharmaceutical Design

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ABSTRACT

The exploration of vastly enlarged chemical spaces, consisting of practical libraries with billions of achievable synthetic compounds, presents thrilling possibilities for drug development while also testing the limits of computational tools in selecting the top prospects. This particularly impacts quantum mechanics (QM) techniques, which offer highly precise chemical insights but are confined to smaller molecular scales. Central to numerous research initiatives is the balance between retaining precision and minimizing computational expense, as seen in advanced algorithms and novel computing methodologies. Developing customized QM-derived physics-based force fields, along with integrating QM approaches with machine learning—bolstered by high-performance computing infrastructure—will greatly expand the utility of these methods in drug research. The hurdle is significant, yet extraordinary breakthroughs are certain, marking the beginning of a groundbreaking period in the discipline.

Keywords: Strategies, Quantum mechanics, Pharmaceutical, Chemical spaces

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Introduction

Methods based on electronic structure theory offer a powerful and flexible framework for investigating chemical reactivity within biological macromolecular systems. The quantum mechanical (QM) cluster approach and the hybrid multiscale quantum mechanics/molecular mechanics (QM/MM) methodology have revealed the key elements responsible for the remarkable catalytic power of enzymes [1-4]. In addition to elucidating reaction pathways, these techniques have been applied to diverse challenges, including the rational design of covalent inhibitors, the enzyme-mediated or photoinduced activation of prodrugs, and the directed modification of enzymatic function [5, 6].

Over recent decades, QM methodologies have increasingly influenced the field of drug discovery. Initially constrained by high computational demands to the study of small molecules, their broader adoption in structure-based drug design has been facilitated by innovative algorithmic developments—including integration with machine learning (ML)—as well as substantial improvements in hardware capabilities. For an in-depth overview of progress in refined QM/MM protocols and the rise of quantum machine learning (QML), the reader is referred to the review by Manathunga *et al*. [7]. A recent comparative evaluation of the strengths of QM/MM approaches versus conventional computational drug design tools is also available [8].

The present contribution seeks to highlight key developments from the last few years in the use of QM-based techniques for characterizing biologically active compounds, guiding structure-based optimization from initial hits to lead candidates, and pinpointing structural determinants of bioactivity **(Figure 1).**

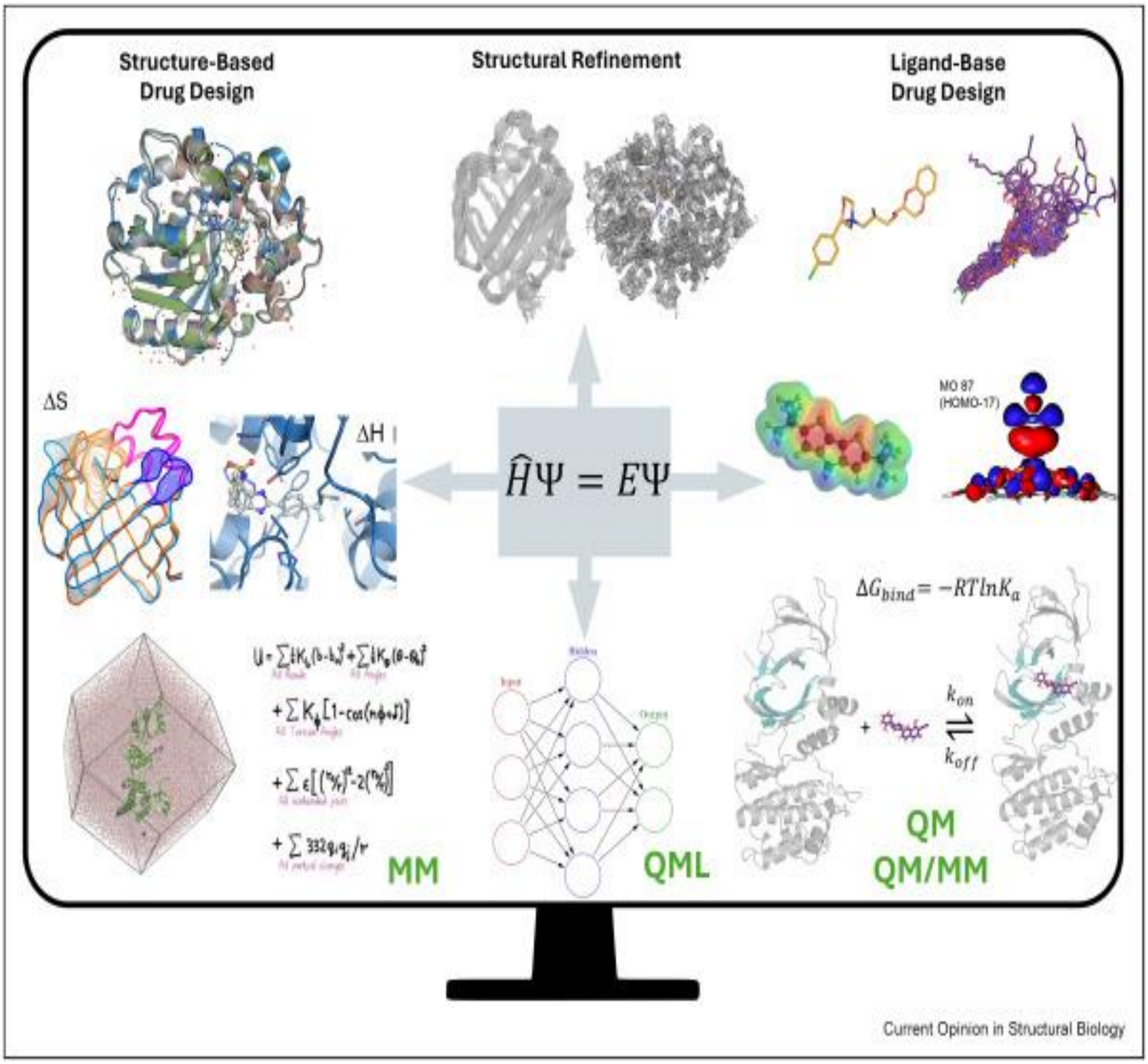

Figure 1. Illustration depicting the growing integration of QM-based approaches into computational drug design, driven by advancements in semiempirical QM and hybrid QM/MM methodologies, specialized QM-derived physics-based force fields, and the synergy between QM and machine learning techniques.

Conformational sampling of ligands

Evaluating the torsional preferences of small molecules and pinpointing low-energy rotamers play a crucial role in defining the physicochemical characteristics of drug candidates and explaining their biological effects [9]. Similarly, producing realistic ensembles of accessible conformers helps in recognizing the bioactive conformation, constructing pharmacophore hypotheses, and supporting the selection of reference structures for 3D ligand-based virtual screening [10, 11]. Moreover, examining conformational distributions across different solvent conditions is essential for forecasting the solubility and membrane permeability of “chameleonic” molecules that fall outside the traditional rule-of-5 boundaries [12].

Although significant progress has been made in refining molecular mechanics (MM) force fields, their precision remains hampered by limitations in the torsional potential functional form and incomplete parametrization [13]. These shortcomings restrict the reliability of MM approaches for thoroughly mapping the conformational landscapes of diverse compounds, particularly those featuring unconventional chemical scaffolds [14, 15]. Nonetheless, the pursuit of comprehensive, high-accuracy force fields remains a vibrant research field, exemplified by the XFF force field, which was parameterized using an extensive collection of functional groups and corresponding QM-derived energies [16].

In this landscape, QM-based techniques stand out as a dependable alternative for accurately determining conformational preferences in organic and bioorganic systems. This is demonstrated by the thorough studies conducted by Rulíšek and colleagues on di- and tripeptides, where DFT calculations combined with implicit solvation models were employed to elucidate preferences for protein secondary structure motifs [17, 18]. Another notable application involves the use of QM/MM simulations to investigate atropisomerism in PI3Kδ inhibitors [19].

A major breakthrough has come from the creation of efficient, purpose-built software tools for ligand conformational exploration. A prominent example is the freely available CREST (Conformer-Rotamer Ensemble Sampling Tool) program, which automates the generation of conformers for drug-like molecules using the semiempirical extended tight-binding (xTB) method, while also accounting for configurational entropy and solvation contributions [20, 21]. Boz and Stein applied this tool to study how ligand flexibility affects binding to synthetic macrocyclic receptors [22]. The binding free energies derived from CREST-based QM sampling yielded an average error of approximately 3 kcal/mol compared to experimental values. This performance was further validated against higher-level meta-GGA PW6B95 calculations with the COSMO-RS solvation model on TPSS-D3(COSMO)-optimized structures, which achieved an error of about 2 kcal/mol.

Efforts have also focused on leveraging machine learning models trained on high-quality QM reference data. For instance, Liu *et al*. [23] introduced Auto3D, a Python tool designed to generate stereoisomer-specific conformational ensembles for small molecules. Auto3D relies on the ANI-2xt neural network potential, trained to reproduce DFT-level energies and forces using a dataset enriched with tautomers. In a similar vein, TorsionNet represents a dedicated deep learning approach for rapid and precise prediction of dihedral energy profiles in small molecules [24]. Trained on a large dataset of 1.2 million DFT torsional scan points from diverse chemical fragments, the model achieves a root-mean-square deviation of 1.3 kcal/mol relative to DFT benchmarks. TorsionNet offers an efficient way to navigate complex potential energy surfaces of flexible compounds, though its accuracy may diminish for structures containing chemical features underrepresented in the training data.

A different hybrid approach is embodied in the QDπ model [25], which integrates a rapid third-order density-functional tight-binding method (DFTB3/3OB) with a deep learning correction trained against ωB97X/6-31G* reference calculations. This framework not only provides a reliable mapping of conformational energy landscapes but also consistently handles variations in charge, protonation, and spin states.

Lastly, Das *et al*. [26] described an ab initio pipeline for predicting collisional cross sections (CCS) from ion mobility-mass spectrometry experiments on small molecules. The protocol progressively refines candidate structures through a combination of MM, machine learning potentials, clustering, and QM optimizations. In a follow-up study [27], the same group benchmarked conformational ensembles produced by Auto3D, CREST, and traditional force field methods (Balloon and ETKDG). Auto3D excelled in locating global energy minima, whereas CREST demonstrated superior accuracy in reproducing experimental CCS values.

Refinement of experimental binding poses

Accurately determining the ligand's orientation and conformation within the binding site is essential for the effectiveness of medicinal chemistry efforts. Quantum mechanical (QM) and hybrid QM/MM approaches are particularly effective for optimizing the ligand's geometry under the influence of the protein's electrostatic environment, thereby enhancing the precision of intramolecular parameters and protein–ligand intermolecular contacts. To keep the discussion concise, we highlight two representative cases: the QM/MM-based identification of the correct binding mode for the O-arylcarbamate inhibitor URB524 in fatty acid amide hydrolase, which successfully distinguished between two plausible poses [28], and the detailed mechanistic insight into covalent adduct formation between dipeptidyl nitriles and cruzain [29].

QM and QM/MM techniques have emerged as robust tools for supporting structural refinement by comparing computed physicochemical properties with experimental data, thereby allowing reliable differentiation between authentic binding poses and incorrect decoys. This strategy has been applied in several recent investigations.

Standard crystallographic refinement of protein–ligand complexes relies on stereochemical restraints and empirical energy terms to ensure proper ligand fitting within the electron density map. Borbulevych *et al.* [30] incorporated a QM/MM framework to improve the refinement of a carefully curated collection of structures from the community structure–activity resource database, with particular emphasis on correctly assigning ligand tautomer and protomer states. More recently, the Quantum Mechanical Restraints (QMR) protocol has been introduced to directly optimize ligand geometry during macromolecular crystallographic refinement [31]. In this method, the ligand's structure is refined in the context of the binding pocket, accounting for interactions with nearby amino acid residues and solvent molecules to identify local energy minima. Application of QMR to over 1700 protein–ligand complexes demonstrated that these quantum-derived restraints produce ligand geometries that better conform to the surrounding protein environment than traditional empirical restraints, especially in providing reliable torsional constraints for highly flexible ligands.

The automated fragmentation QM/MM (AF-QM/MM) approach has proven to be a powerful and efficient tool for predicting protein–ligand binding structures using NMR-derived data [32]. This method automatically partitions the ligand and/or the binding pocket into capped fragments, enabling DFT-level calculations of NMR chemical shifts that incorporate electrostatic polarization from the surrounding solvent. The resulting ligand-induced perturbations in 1H chemical shifts are then integrated with docking scores to improve pose ranking. Building on this, AF-QM/MM has facilitated the development of the empirical HECSP scoring function, which offers a rapid and precise prediction of proton chemical shift changes in the protein upon ligand binding [33]. The methodology has recently been extended to ligands in membrane proteins, as demonstrated by Zhang *et al.* [34], who examined how local environmental factors—such as inter-protomer contacts, phospholipid composition, and solvation—affect the 15N and 13C chemical shifts of retinal in the light-driven sodium-pumping rhodopsin 2.

Conversely, direct comparison of experimental NMR chemical shifts with those calculated via QM/MM from crystal structures has revealed inconsistencies, particularly for ligand protons engaged in hydrogen-bonding networks. These differences underscore the limitations of relying on a static single conformation to represent the dynamic solution-state behavior of protein–ligand complexes. In this context, Platzer *et al.* have illustrated that QM/MM molecular dynamics simulations can generate structural ensembles that, when used to refine the starting X-ray co-crystal structure, yield significantly improved agreement with observed ligand chemical shifts [35].

Prediction of binding affinity

One of the most significant hurdles in drug discovery remains the precise computation of the binding free energy between a ligand and its biological target. Given that binding affinity serves as a fundamental pillar in structure-based drug design, there is ongoing enthusiasm for creating reliable and precise physics-based approaches suitable for pharmaceutical applications. Various quantum mechanical (QM) techniques have been utilized, spanning from semiempirical QM, through density functional theory (DFT), up to rigorous coupled-cluster methods [36].

Cavasotto and Aucar [37] demonstrated that a QM-derived scoring function integrating PM7-based ligand–protein interactions with adjustments for solvation and entropy terms substantially outperformed conventional docking in virtual high-throughput screening across 10 diverse targets. More recently, Pecina *et al.* introduced SQM2.20 [38], an advanced semiempirical QM scoring function building on the earlier SQM/COSMO framework [39]. This scoring metric incorporates gas-phase interaction energies computed at the PM6-D3H4X level, solvation free energy changes upon complexation, ligand conformational contributions, proton transfer free energies between ligand and buffer, and the entropic penalty from loss of ligand flexibility upon binding. Evaluations are performed on a truncated system of approximately 2000 atoms, including all residues within 10 Å of superimposed ligands for each protein, with typical computation times of about 20 minutes per protein–ligand complex.

Alternative approaches have emerged within the linear response approximation framework. Leveraging the “divide-and-conquer” fragment molecular orbital (FMO) method, SophosQM [40] estimates ligand–target interactions by summing pairwise energies between the ligand and protein fragments, while non-enthalpic terms are approximated via the octanol/water partition coefficient (logP). Binding affinity is then modeled through multilinear regression incorporating interaction energy and logP, with coefficients calibrated against experimental affinities for congeneric series. This assumes conserved binding modes without major pocket rearrangements. A similar linear combination of FMO-derived interaction and ligand deformation energies with solvation terms forms the basis of FMOScore, successfully applied in lead optimization for Src homology-2-containing protein tyrosine phosphatase 2 [41]. The QMH-L method [42] uses a single MM-preoptimized target–ligand complex (including bridging water molecules) to estimate binding free energy by combining QM fragment interaction energies with a ligand molecular size descriptor as a proxy for entropy. Applications to protein complexes with small molecules and peptides demonstrate a favorable balance of accuracy, scope, and computational demand.

QM/MM methodologies can also refine binding free energies obtained from classical simulations via the "indirect" correction approach, applying QM/MM energy adjustments selectively at key thermodynamic endpoints. This avoids the high cost of full QM/MM free energy perturbations while addressing classical force field shortcomings, assuming adequate configurational sampling overlap between MM and QM/MM descriptions. A recent investigation explored force-matching techniques for predicting binding free energies of several narcotics in the SAMPL blind challenge [43].

The high computational demands of QM and QM/MM have driven exploration of complementary strategies, including (i) specialized force fields and (ii) machine learning models for affinity prediction.

The ARROW force field [44] exemplifies the first category, designed to overcome limitations in conventional force fields regarding electrostatics, exchange repulsion, many-body effects, and parameter transferability. ARROW employs multipolar electrostatics and anisotropic polarization, with all parameters derived solely from high-level QM references—such as MP2/aug-cc-pVQZ for monomers and MP2/complete-basis-set extrapolations for amino acid–fragment and water dimers. Nonbonded terms include multipolar electrostatics and exchange-repulsion, spherical dispersion (C6/C8), and induced dipole many-body polarization. An updated variant incorporates short-range neural network corrections to intermolecular energies [45].

Another force field enhancement strategy involves the Minimal Basis Iterative Stockholder approach, as implemented by González *et al.* [46] and Macaya *et al.* [47], which derives atomic charges and Lennard-Jones parameters from the polarized electron density of the ligand across multiple bound and unbound configurations.

Rizzi *et al.* [48] developed targeted free energy perturbation to bridge inexpensive MM reference potentials to high-level QM targets. A neural network learns a mapping to improve phase-space overlap between distributions, using sparse QM energy and gradient evaluations. Application to 22 ligands yielded excellent agreement with reference benchmarks.

In QM-informed machine learning, Isert *et al.* [49] employed critical points (CPs) of electron density as descriptors of protein–ligand interactions. Models were trained on GFN2-xTB CPs combined with a linearized Poisson–Boltzmann solvation model. Predictive performance was moderate compared to established benchmarks, possibly limited by the semiempirical QM level, CP representation, or omission of ligand strain and entropic effects.

Beyond equilibrium binding affinity, predicting ligand dissociation rate constants (k_off)—and thus residence time—has gained attention, as it critically influences drug efficacy [50]. Ahmad *et al.* [51] reviewed advances in simulation methods for k_off, highlighting massively parallel DFT-QM/MM with machine learning enhancements to capture electronic polarizability and charge transfer in unbinding pathways. Here, we focus on QMrebind by Ojha *et al.* [52], integrated into the SEEKR2 framework for kinetics estimation via multistate MD simulations. QMrebind refits ligand partial charges in the bound state using QM calculations to generate system-specific force fields. Improved parameters enhanced accuracy for host–guest systems and Hsp90–inhibitor complexes.

Molecular determinants of bioactivity

Elucidating the structural and chemical attributes that govern a ligand's bioactivity profile—encompassing both pharmacodynamics and pharmacokinetics—is crucial for guiding the rational development of drug candidates.

Quantum mechanical (QM) approaches enable the detailed investigation of specific non-covalent interactions that classical molecular mechanics (MM) force fields struggle to describe accurately, including halogen bonding [53, 54], polarized CH/π, CH/n, and XH/π contacts [55], as well as amide–π or alkene–π stacking in peptides [56, 57]. The shortcomings of MM descriptions are particularly evident in coordination to metal ions [58]. Furthermore, QM-computed reactivity indices for covalent inhibitors have proven valuable in structure–activity relationship analyses [59].

Additional work has focused on overcoming limitations in traditional molecular descriptors, thereby enhancing similarity-based, pharmacophore-driven, and docking-guided virtual screenings [60]. For example, in a similarity search for analogues of remdesivir targeting the SARS-CoV-2 RNA-dependent RNA polymerase, COSMO-RS σ-profiles—generated from QM(B3LYP/DNP)/MM-optimized structures—facilitated effective compound prioritization [61]. In a recent virtual screening effort against soluble epoxide hydrolase, 3D hydrophobic descriptors derived from QM continuum solvation models significantly improved the ranking of top docking hits

[62, 63]. QM fragment molecular orbital (FMO) analyses have also identified key interaction hotspots at protein–protein interfaces, providing insights for designing modulators of such complexes [64].

QM cluster calculations at the GFN2-xTB level have been employed to evaluate bioisosteric substitutions, offering a means to fine-tune ligand properties related to potency, bioavailability, and metabolic stability [65]. In a related application, COSMO-RS-derived QM descriptors guided bioisosteric modifications to enhance passive permeability in a series of protein arginine methyltransferase 5 inhibitors [66]. Notably, these studies identified hydrogen-bond acceptor strength as a critical factor influencing membrane transport.

While machine learning (ML) holds great promise across drug design, progress is hindered by the scarcity of large, high-quality curated datasets. To address this, the openly available Quantum-Mechanical Properties of Drug-like Molecules (Q-Mugs) dataset [67] was created, containing GFN2-xTB QM properties for over 665,000 compounds sourced from ChEMBL. Similarly, Merck & Co. released QM9-extended [68], featuring 153,716 drug-relevant molecules with B3LYP/6-31G(2df,p) properties tailored for ADME predictions. Isert *et al.* [69] assembled an internal dataset to train ML models for octanol/water partition coefficient prediction, where the message-passing neural network Chemprop [70] achieved the lowest mean absolute error of 0.34 log units.

Conclusion

High-throughput experimental screening remains the primary method for discovering new small molecules capable of modulating target biology [71]. The rapid expansion of explorable chemical space—now encompassing billions of synthesizable compounds—offers tremendous potential to uncover hits with innovative scaffolds, reduced bias toward naturally occurring structures, and superior complementarity to target binding pockets [72]. Yet, this vast scale also strains the ability of computational tools to effectively rank and select optimal candidates without introducing systematic biases in library evaluation [73].

In this landscape, the future impact of QM-based methods in drug design will hinge on parallel advances in algorithms and computing infrastructure. Three prominent trends are evident: (i) the creation of precise yet efficient semiempirical techniques alongside refined multiscale QM/MM protocols, (ii) the design of specialized QM-informed physics-based force fields capable of faithfully capturing intricate intermolecular networks, and (iii) the development of QM-enhanced machine learning frameworks. On the hardware front, emerging supercomputing platforms [74, 75] and, in particular, quantum computing technologies [76, 77]—despite needing substantial code adaptation—promise transformative gains in quantum chemical simulations. Collectively, the recent surge in methodological innovations, combined with powerful new computational resources, points to a dynamic and promising transformation in the role of quantum chemistry within drug discovery.

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