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EDITORIAL

Standards for Computational Methods in Drug Design and Discovery: Simplified Guidance for Authors and Reviewers

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Part I: Policy Statement

Computational methods are integral to modern drug discovery and development. However, manuscripts that apply these approaches superficially or without methodological rigor undermine scientific progress. *Drug Design, Development and Therapy* will therefore only consider computational studies that are transparent, reproducible, validated and biologically meaningful.

- 2D-QSAR studies will be rejected immediately.
- Predictions of bioactivities, ADMET, pharmacokinetics, or toxicity without experimental or external validation will be rejected.
- Black-box applications of computational servers or uncritical pipelines will not be accepted.
- Docking, virtual screening, molecular dynamics (MD), quantum mechanics/molecular mechanics (QM/MM), artificial intelligence and machine learning (AI/ML), and free energy approaches must be conducted and reported according to established best practices.

Submissions not meeting these minimal requirements will not be sent for review.

Part II: Detailed Guidelines

QSAR and Molecular Modeling

2D-QSAR studies are obsolete and unacceptable. 3D-QSAR or more advanced models are permissible if applied to sufficiently large datasets, with rigorous alignment justification, proper cross-validation, and interpretable mechanistic insights.[1] Molecular modeling may generate structural hypotheses but must not be overstated or presented as equivalent to experimental methods. Authors must highlight the *model character* of such work. Misrepresentation through selective omission or manipulative depictions will not be tolerated.

Docking and Virtual Screening

Docking studies are welcome when rationalizing structure–activity relationships or providing mechanistic support for experimental findings.[2,3] Docking scores must not be reported as absolute binding energies. Binding site preparation, protonation states,

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tautomerization (e.g., histidine residues), and docking parameters must be fully described.[4,5] Benchmarking of docking protocols or scoring functions—including ML scoring functions—is encouraged if robust metrics and clear recommendations are provided.[6] Virtual screening campaigns must include experimental validation of proposed hits; unvalidated hit lists will not be accepted.

Artificial Intelligence and Machine Learning

The journal encourages the responsible use of AI/ML. Generative models for *de novo* drug design must be supported by preliminary experimental testing or confirmatory in silico validation such as MD simulations. Development of new ML models or scoring functions is welcome if trained on curated datasets, validated on independent sets, and evaluated with accepted performance metrics. Black-box models without interpretability or benchmarking will not be considered.[7]

MD and MM-PBSA/GBSA

MD simulations can provide insights into protein flexibility and ligand binding, but submissions based on single, short, or poorly prepared trajectories will be rejected. Best practices include initiating runs from high-quality structures, assigning correct protonation states, including relevant cofactors, ensuring production timescales are adequate, and using multiple replicas – if possible – to assess reproducibility.[8] MM-PBSA/GBSA calculations may be used only for relative comparisons within consistent protocols and must be based on equilibrated ensembles. Considering absolute free energies of MM-PBSA/GBSA or single post-docking snapshot calculations is unacceptable.[9] It is essential to consider what types of movements or structural changes are realistically observable on the timescale of the dynamics simulation. When interpreting the results of MD simulations any kind of bias, particularly unconscious bias, must be avoided at all costs. Video files with a meaningful graphical representation of major findings should be submitted as supplementary data or as part of the actual manuscript.

QM-Methods (HF, Post-HF, DFT, Semiempirical Methods) and QM/MM

QM and QM/MM calculations are valuable when appropriately and thoroughly applied. Authors must justify the choice of theory level, functional, and basis set, ideally benchmarking against higher-level methods. Reports of meaningless QM-derived descriptors (e.g., isolated orbital energies) will be rejected. FMO analysis (including depictions of HOMO/LUMOs) will only be tolerated, if it properly illustrates reactivities or reaction mechanisms with a suitable experimental basis. Depictions of molecular electrostatic potentials (MEPs) can be used to illustrate specific electrostatic features of molecular interactions, particularly when comparing similar compounds. However, they are not acceptable without proper justification and discussion. We encourage the use of QM methods for acceptable applications, such as evaluating protonation states, pKa values, conformational energy analysis, solvation energies, and key interactions in ligand–target complexes.[10]

Free Energy Methods

Free energy perturbation (FEP) and related alchemical methods are increasingly considered best-in-class for predicting relative binding affinities. These approaches will be accepted when system preparation, sampling, convergence analysis, and benchmarking against experimental data are rigorously documented. Submissions without error analysis or correlation to experiment will not be considered.[11]

Prospective Considerations for "Beyond Rule of Five (bRo5)" Modalities

The bRo5 space (MW > 500 Da) primarily includes macrocycles, constrained peptides, bulky natural products (e.g., paclitaxel, cyclosporine, etc.), and emerging proximity-based therapeutics such as PROTACs and other hetero-bifunctional agents designed to form ternary complexes for gain- or loss-of-function outcomes. In certain cases, it also encompasses molecular glue-like natural products with large molecular footprints (e.g., rapamycin). Owing to their size, conformational flexibility, chameleonicity, and multi-protein binding modes, these molecules often challenge conventional in silico methods.

Key considerations include:

- Adopting bRo5-tailored descriptors and ML models as conventional QSARs is unreliable in this chemical regimen.[12–14]
- Avoid over-interpreting single docking poses or raw docking scores, as they can be particularly misleading for highly flexible chemotypes such as macrocyclic and hetero-bifunctional ligands.[15–17]
- Avoid off-the-shelf (default) scoring functions as they may often fail; instead, calibrate or adapt scoring functions to capture the complexity of ternary systems.[15,18]
- Employ enhanced sampling methods (e.g., metadynamics, TTMD, etc.) to adequately explore conformational ensembles and transition states.[19]
- Use free energy methods (MM-GBSA, MM-PBSA) with caution; they may be useful for relative rankings but require wise interpretation with bRo5 compounds.[20,21]

Part III: Reject vs Best Practices Checklist

Immediate Rejection if Manuscripts Contain:

- Predictions of bioactivities, ADMET, pharmacokinetics, or toxicity without validation.
- 2D-QSAR studies or unvalidated QSAR models.
- Black-box computational servers or uncritical pipelines.
- Docking studies reporting raw scores as binding energies or lacking methodological transparency.
- Virtual screening recommending hits without experimental validation.
- AI/ML models without proper interpretability, benchmarking, or independent test sets.
- MD studies with single, short trajectories, poor setup, or overinterpretation.
- MD studies selectively highlighting certain frames or expected outcomes.
- MD studies including videos/graphics as decorative add-ons with no scientific value.
- MM-PBSA/GBSA based on single snapshots or reported as absolute values.
- QM/MM studies presenting meaningless QM-derived properties.
- FMO analysis presented as standalone explanations of activity or potency without mechanistic or experimental backing.
- MEPs used as decorative or speculative with no interpretation.
- FEP studies lacking convergence checks, error estimates, or experimental correlation.

Best Practices Required for Consideration:

- Use 3D-QSAR/advanced models with rigorous validation and interpretable insights.
- Employ molecular modeling strictly as hypothesis generation or rationalization, with accurate 3D depictions.
- For docking/VS: disclose preparation parameters, benchmark against known ligands, and validate hits experimentally.
- For benchmarking: provide robust metrics and clear recommendations.
- For AI/ML: justify algorithm choice, train on curated datasets, validate independently, ensure proper interpretability.
- For MD: use high-quality starting structures, correct protonation/tautomer states, sufficient timescales, and multiple replicas if possible. Use objective, reproducible analyses and provide videos that illustrate major findings, not cosmetic motions.
- For MM-PBSA/GBSA: apply only to equilibrated ensembles, clearly stating snapshot protocols.
- For QM/QM-MM: justify method choice, benchmark where possible, focus on biologically relevant properties.
- For FMO analysis: link to specific reactivity hypotheses with supporting experimental or mechanistic discussion.
- For HOMO/LUMO illustrations: they must serve an explanatory purpose.
- For MEPs: illustrate well-defined electrostatic features rationalizing site-specific interactions in a ligand–target complex.
- For FEP: apply rigorous sampling, convergence analysis, and experimental benchmarking.

Disclosure

Frank M. Boeckler is the Editor-in-Chief of *Drug Design, Development and Therapy*. Tamer M. Ibrahim and Muzammal Hussain are Associate Editors of *Drug Design, Development and Therapy*. The authors declare that they have no other competing interests in this work.

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