Journal of Medicinal Chemistry
Editorial

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Computational Medicinal Chemistry

Approximately one-third of current submissions to the *Journal of Medicinal Chemistry* (Journal) report computational work of varying weight and complexity. To ensure a high level of consistency in evaluating computational studies, the Journal extends and further refines the current requirements and acceptance criteria for computational manuscripts (specified in the January 2010 revision of the Guidelines for Authors, sections 2.3.5 and 2.3.6.). These revisions especially focus on combined experimental and computational studies, given the large number of submissions that fall into this category.

1. Predictive Use of Computational Methods

The submission of manuscripts that report the prospective computational design and experimental evaluation of new chemical entities is highly encouraged. Applications of modeling and computational chemistry methods including, among others, pharmacophore and 3D-QSAR modeling or molecular dynamics simulations are only considered by the Journal in combination with original experimental data that utilize or assess computational predictions.

Virtual screening studies must adhere to the significance criteria for combined experimental and computational studies as detailed in the editorial on "Computational Studies, Virtual Screening, and Theoretical Molecular Models" in the January 14, 2010, issue of the Journal. In addition, for virtual screens that produce compound rankings, the total number of compounds that were screened and the ranks of identified hits before application of any further manual or other subjective selection steps must be provided as Supporting Information. Complex virtual screening protocols are not per se validated by identifying a few active compounds. In such cases, evidence must be provided that much simpler approaches would not have yielded comparable results (e.g., 2D similarity or substructure searching). Moreover, the experimental findings must be significant. As an example, identifying weakly potent ATP-site directed protein kinase inhibitors through virtual screening is no longer considered a significant advance in this maturing field because of the availability of many known potent inhibitors acting by this mechanism.

2. Retrospective Use of Computational Methods

A large number of manuscripts submitted to the Journal report experimental studies with additional computational elements that are purely retrospective in nature. The Journal will accept reports of retrospective computational work only under a number of conditions. Both authors and referees should use the following criteria to assess the relevance of such studies for the Journal:

- Computational work must lead to clearly stated messages, either in the form of improved understanding of the experimental work or in the form of well-defined experimentally testable hypotheses.
- Models and hypothetical statements must be clearly distinguished from experimental observations both in the text and in figure captions.
- Computational methods must be described in sufficient detail for the reader to reproduce the results.
- Computational methods must be thoughtfully selected and not used uncritically. It should be explained why the applied method is an appropriate choice and why it was chosen over similar methods, if they exist. Calculation results, in particular those of automated modeling software, must be critically examined.
- Conclusions from modeling must be drawn with an appropriate amount of caution, under consideration of all assumptions made, and within the accuracy limitations of the applied computational methods.
- The overall amount of space (text and figures) devoted to retrospective computational work must be proportionate to its significance.

The prediction of compound binding modes by docking is currently the single most frequent computational application submitted to the Journal. The larger the number of assumptions relied upon, the lower the reliability of a modeled binding mode and thus its value for the readers of the Journal. Models derived by minor modifications of known X-ray structures are often reliable, whereas binding modes suggested on the basis of a protein homology model are usually speculative. To be considered for publication in the Journal, all binding mode predictions must be well-founded. In the absence of supporting structural information, authors should demonstrate that putative binding modes are consistent with structure−activity relationships for a series of analogues.

In the absence of target structural information, QSAR, pseudoreceptor, or machine learning models are occasionally applied to retrospectively analyze biological activities observed in the context of experimental SAR studies. Such modeling studies do not conform to the acceptance criteria of the Journal and are not considered unless the models are used in a predictive fashion or illustrate a point of central relevance.

3. Computational Data Analysis

The Journal encourages the submission of manuscripts presenting analyses of publicly available databases or data sets that provide unexpected or provocative insights into topical problems and advance medicinal chemistry knowledge. Such investigations must be based on large data sets rather than small series of compounds. Furthermore, benchmark investigations such as comparisons of virtual screening algorithms are only considered if they provide particularly clear and generally relevant conclusions that

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set new standards in the field. In such cases, general relevance must be clearly stated and put into scientific context.

These criteria are effective with the publication of this editorial and will be part of the January 2011 revision of the Scope and Editorial Policy of the Journal. We look forward to the continued submission of high-quality computational studies that further advance the medicinal chemistry field.

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