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Computer-Aided Drug Design for Undergraduates

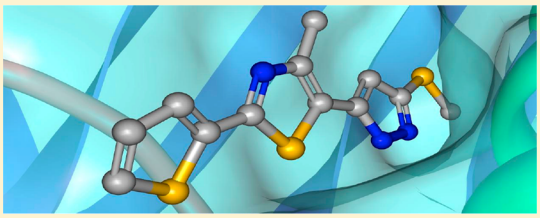
Dean J. Tantillo,*[,†] Justin B. Siegel,[†,‡] Carla M. Saunders,[†] Teresa A. Palazzo,[†] Phillip P. Painter,[†] Terrence E. O'Brien,[†] Nicole N. Nuñez,[†] Dustin H. Nouri,[†] Michael W. Lodewyk,[†] Brandi M. Hudson,[†] Stephanie R. Hare,[†] and Rebecca L. Davis[†]

[†]Department of Chemistry, University of California—Davis, Davis, California 95616, United States

[‡]Department of Biochemistry & Molecular Medicine, Genome Center, University of California—Davis, Davis, California 95616, United States

Supporting Information

ABSTRACT: A series of computational laboratory experiments aimed at teaching students principles of rational drug design are described and evaluated. These experiments range from an introduction to viewing protein−ligand complexes to optimizing geometries of potential drugs with quantum chemistry and automated docking. Student feedback indicates that such a course increased their appreciation for the roles of chemists in the drug discovery−development process.



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INTRODUCTION

Recently, Cherkasov and co-workers published a paper on "Best Practices of Computer-Aided Drug Discovery (CADD)".[1] Inspired, in part, by the realization that most of the recommended best practices have been incorporated in an upper-division undergraduate course on CADD methods developed at the University of California—Davis (UC Davis), we decided to share details on this course so that others can benefit from our experiences. Because various groups in the pharmaceutical industry have argued for a greater emphasis on structure-guided drug design and involvement in projects that stress the development of problem-solving skills,[2] such a course appears to be timely.

The aim of this course, Pharmaceutical Chemistry 2, is to introduce students to strategies for rational drug design (some of which they have seen in Pharmaceutical Chemistry 1, vide infra) and provide them with hands-on experience with CADD[3] software and web-based resources used by practicing drug designers. The course involves a series of laboratory exercises, short lectures and discussions[4] on special topics, and a drug-design project. Each of these is described below and additional details (e.g., current versions of laboratory guidelines and grading rubrics) are provided as Supporting Information. Over the past decade when Pharmaceutical Chemistry 2 has been offered and continually revised, several reports on specific computer-based laboratory exercises related to those described below have been disclosed,[5] including a report of a related but different approach to an integrated, multilab computer-aided-drug-design course.[6]

Pharmaceutical Chemistry 2 is the second course in a multicourse sequence required for undergraduate majors in our Pharmaceutical Chemistry degree program.[7] This course has been offered since 2007, including seven offerings abroad as part of UC Davis's Pharmaceutical Chemistry in Taipei Quarter Abroad Program.[8] The domestic version of this course has involved class sizes ranging from approximately 20 to 150 students, with a single section never exceeding 40 students, whereas the quarter-abroad version has involved class sizes ranging from approximately 10 to 30 students. For the latter, some students were undergraduates from UC Davis and other UC campuses, and some students were graduate students studying at Academia Sinica Taipei (AST). All domestic students are required to have completed Pharmaceutical Chemistry 1, a lecture-style course that introduces the principles of medicinal chemistry, before taking Pharmaceutical Chemistry 2; this is not a requirement for AST students, although having previous experience with introductory medicinal chemistry is strongly recommended. Before 2014, Pharmaceutical Chemistry 2 included weekly guest lectures from academic and industrial chemists working on medicinal- or pharmaceutical-chemistry-related projects, but this seminar series is now offered as a separate course, Case Studies in Pharmaceutical Chemistry.

LABORATORY EXERCISES

The laboratory exercises used in Pharmaceutical Chemistry 2 have been consistently revised and expanded since the course's inception. These exercises are modular, each having been designed to require a once per week 3 h laboratory period run by one or two instructors (see the Supporting Information for

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additional details) and only some requiring specific information from earlier exercises (prelaboratory practice with the software has not been implemented but is recommended when feasible). Consequently, particular exercises can be deleted, modified, or replaced depending on available lab time, student background, and instructor preference. Courses have been run using as few as four of these exercises: A, B, D, and E, the core exercises for taking on a drug-design project. The exercises developed so far, in the order in which they are usually implemented, are as follows (see the Supporting Information for details).

Exercise A: Visualizing and Analyzing Receptor Structures

In this exercise, students are introduced to tools for visualizing proteins, common targets for (potential) drugs. First, students are introduced to the protein data bank (PDB) and explore the data available there.[9] Currently, students are then introduced to the PyMOL visualization software,[10] although past iterations of this laboratory have made use of visualization software accessible directly through the PDB website.[11] This laboratory exercise addresses best practice #1 from Cherkasov and co-workers: "Study your target, gain deep knowledge of its biology and corresponding experimental assays."[1] Laboratory exercises similar to the one described here have been reported,[5a] one of which describes an excellent exercise that involves a more in-depth examination of the manner in which X-ray crystal structures are solved.[5b]

As an extension of our protein-visualization exercises, students may also be exposed to a detailed analysis of binding sites, with an emphasis on regions that are either structurally conserved or unique in the specific protein of interest. These analyses are achieved by using a combination of BLAST (for homologue identification and alignment)[12] and Jalview (for conservation analysis)[13] to identify conserved and unique sites within the protein being analyzed. This activity has broad implications in drug design, as portions of the binding site that are unique can be utilized to impart specificity toward an organism of interest. However, sites that have been observed to change over time are also susceptible to mutations that confer resistance. Therefore, students are taught to think about the problem their molecule is trying to solve and must evaluate if drug resistance or organism specificity is of greater importance and how these factors affect their molecular-design choices. The bioinformatics portion of this lab generally takes less than 1 h; the majority of the 3 h lab is spent utilizing PyMOL and Jalview to analyze unique and conserved regions of a binding site.

Exercise B: Optimizing the Geometries of Drug Candidates

In this exercise, students are introduced to quantum-chemistry software for optimizing the geometries (and electronic structures) of small-molecule drug candidates. Methods are employed that have been validated in terms of providing reasonable geometries for the specific molecules described in the laboratory manual and in terms of computing time appropriate for a 3 h lab period. Other more involved quantum-chemical methods could be implemented if resources are available. Although the laboratory manual describes the use of specific software, any computational quantum-chemistry program could be used.[14] Appendices to this lab on examining molecular-charge distributions are also provided for instructors with interests in this area and access to appropriate laboratory time (see the Supporting Information).

Exercise C: Prediction of Molecular Properties

In this exercise, students are introduced to software that predicts relevant ADME/Tox properties[15] using empirical means. Through Pharmaceutical Chemistry 1 and the lecture and discussion sessions associated with Pharmaceutical Chemistry 2 (vide infra), students will have been introduced to the connections between absorption, distribution, metabolism, excretion, and toxicity; in this exercise, they are shown that such properties can be predicted using informatics-based approaches. Although such methods are qualitative at best, they do allow particularly problematic structures to be ruled out early in the drug-design process on the basis of issues such as poor solubility and expected toxicity. Again, although specific software is described in the laboratory manual, many other options exist.[16] This laboratory exercise addresses the first part of best practice #7 from Cherkasov and co-workers (free-energy-perturbation (FEP) calculations are not feasible given the time and resources currently available): "Utilize ADMET predictions and FEP for better lead optimization recommendations."[1] In some implementations of the course, this exercise was omitted in favor of requiring students to predict ADME/Tox properties using only their chemical knowledge and intuition.

Exercise D: Comparing Structures and Generating Conformations

In this exercise, students are introduced to two types of software: (1) a program that compares the shapes of drug candidates in the absence of a target, so that structures that differ dramatically from known binders can be rapidly discounted and (2) a program that generates libraries of conformations for potential drugs. Although such libraries are generated here specifically for use in a subsequent exercise on automated docking (vide infra), they also reveal the degree of flexibility of potential drugs, the implications of which for binding efficiency and off-target effects can then be discussed. This exercise provides an opportunity to stress that in some contexts, one needs libraries of energetically accessible conformations, whereas in other contexts, one needs fully optimized conformations; as stated in a recent review, "Conformer generation therefore needs to be conducted in a fashion relevant to the manner in which the conformers generated will be consumed."[17]

Exercise E: Automated Docking

In this exercise, students are introduced to software for docking small-molecule drug candidates into binding sites of protein targets. Again, although specific software is described in the laboratory manual, many other options exist, some of which have been described previously in the context of laboratory exercises for courses.[5c,d] Cherkasov and co-workers' best practice #2 suggests, "Validate your screening tools and prepare your molecular databases thoroughly. Use diverse methods of virtual screening, multiple docking programs, utilize both ligand- and structure-based approaches, and employ consensus scoring."[1] We agree with this advice and recommend that instructors point out the merits of using multiple programs and consensus scoring, even though neither is implemented in the laboratory exercise because of time constraints. Cherkasov and co-workers' best practice #4 suggests, "Analyze and visually inspect generated docking poses, use your chemical intuition to create testable binding hypotheses."[1] This point is stressed during the laboratory

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exercise. Extensions of this exercise could involve the implementation of haptic interfaces.[18]

Exercise F: Isosteric Replacements

In this exercise, students are introduced to software that generates isosteric replacements for particular functional groups, a means of generating drug candidates with new scaffolds without, hopefully, harming binding or physical properties. The importance of covering related structural space for patent protection is emphasized; specifically, how "all" structurally reasonable molecules, not just the best molecule, need to be protected in order to convince a company to invest hundreds of millions of dollars to move a drug candidate through clinical trials.

Exercise G: Homology Modeling

As genomic sequencing has become widely accessible at low cost, the number of known protein sequences now outnumber the number of known protein structures by more than 1000 to 1.[9,19] Therefore, although ideally there is a known structure of the protein of interest, it is common nowadays that one may know the sequence of the protein but not its three-dimensional structure. Sequence analysis provides insight into regions of an active site that can be targeted for new drug−receptor interactions. When looking for a broad-spectrum drug or a molecule that will be difficult for the protein to evade, interactions with amino acids that are highly conserved should be targeted. However, when looking for organism specificity, amino acids that are unique (i.e., highly variable with low conservation) within a protein's active site should be targeted. In short, students are shown that high versus low conservation is not good or bad, but is simply a feature that can be assessed and utilized to increase specificity or decrease susceptibility to resistance. Students are introduced in this exercise to template-based homology modeling through the online server SWISS-MODEL.[20] Students are introduced to the process of using a protein sequence to predict a three-dimensional model. That the resulting structure is only a predicted model is emphasized, and students are shown how to analyze for regions of the protein where the predictions are of low-confidence. Students then utilize the model to conduct docking studies (vide supra).

Exercise H: Prediction of NMR Chemical Shifts

In this exercise, students are shown how quantum chemistry can be used to predict ^{1}H and ^{13}C NMR chemical shifts. The implications for deducing the correct structures of synthetic compounds (e.g., lead compounds), drug metabolites, and natural products as potential drugs are highlighted. This exercise was described in a previous report.[21]

SPECIAL TOPICS FOR LECTURE AND DISCUSSION

In addition to the laboratory exercises described above, Pharmaceutical Chemistry 2 instructors generally guide a short lecture or discussion session at the beginning of each laboratory period. In some cases, these sessions provide theoretical background for the techniques that will be used in that day's exercise, but in other cases, they are discussions of special topics that go beyond subject matter generally encountered previously in undergraduate organic-, medicinal-, or pharmaceutical-chemistry courses. Topics previously discussed in this format include: (a) frontier molecular-orbital arguments to rationalize and predict conformational preferences (an excellent overview of conformational preferences for pharmaceuticals has been provided by Stahl and co-workers[22]), (b) the importance of often-overlooked intramolecular interactions for docking experiments,[23] and (c) kinetic isotope effects applied to the regulation of drug metabolism[24] (a fantastic visualization of kinetic isotope effects has been provided by O'Leary and co-workers[25]). Other potential topics that could readily be connected to laboratory experiments (and have been suggested by previous Pharmaceutical Chemistry 2 instructors) include prodrugs, drug cocktails, nonprotein targets, quantum-chemical applications (e.g., enzyme mechanisms and metabolism), molecular-dynamics simulations to reveal protein motions, allostery, ensemble docking, and natural products as drugs.[26]

DRUG-DESIGN PROJECT

A major component of Pharmaceutical Chemistry 2 is a drug-design project. A recently implemented prompt for this assignment states:

> *Imagine that you want to make a new drug. Where do you start? One place that many laboratories start is with computer modeling. The final project in this class is centered around this idea—that you are a researcher looking to find a new drug for a disease of your choice and, like any researcher, you must provide justification for why your drug is potentially better than existing drugs or drug candidates... You will find a protein which has a ligand bound in its active site and design two (or more) new small molecules that are "better" than the one found in the active site. Here, "better" means either (a) having a better docking score without introducing problematic ADME/Tox properties, or (b) having improved predicted ADME/Tox properties without disrupting binding... You must turn in a final report in which you explain in detail why you think that your proposed drug candidates show promise. Your argument must be supported by computational evidence that you obtain yourself. In your final report, you must clearly describe the methods and results of calculations you have carried out in search of support for your proposed molecule(s) being promising leads. You should describe your level of confidence in these results, i.e., which results do you feel are most reliable and which are more tentative? Your report will be graded on the quality of the arguments you make, i.e., the quality and quantity of evidence you provide in support of your argument from both the primary literature on your biological target and your computations. You need to make a strong argument, but you should NOT hide any evidence that might suggest problems with your proposed drug candidate—a balanced argument that provides a reasonable assessment of the likelihood of success is what we are after! A description of the failures and successes you encounter during the process of finding viable drug candidates is most appreciated. While brainstorming for potential drug candidates, you should keep in mind Lipinski's rules, things that affect ADME/Tox properties, and things that might make your drug candidate selective for your target over other possible targets. For this project, you do not need to concern yourself with the difficulty of synthesizing the drug candidate you propose, although you should not invent new functional groups!*

This project is generally implemented in phases. First, early in the quarter or semester, even before all laboratory exercises are completed, a short proposal from each student on the drug family they intend to target is collected (note that the project could also be carried out by groups of students). Although this

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proposal is graded (see the Supporting Information for a rubric), the purpose of the assignment is to prevent procrastination and to give students feedback on the appropriateness of their drug family given the computational techniques available to them for completing the project. Second, students give oral presentations summarizing their results. Again, although it is graded (see the Supporting Information for a rubric), this experience not only allows students to practice speaking about scientific results but also allows them to receive feedback before turning in their final reports. These presentations should be scheduled, if possible, before the final laboratory session so that students can implement the feedback they receive. Although there are difficulties associated with having oral presentations when class sizes grow large, anecdotal experience suggests that this activity is beneficial. The number of sessions required to complete the project can vary, depending on the number of analogues an instructor expects students to design and test and the level of detail an instructor expects in the analysis of results. Third, as described above, each student writes and turns in a report that details not only their results but the implications of these results and the logic used by the student throughout the project (see the Supporting Information for a rubric). Students thus address aspects of best practices #3 and #6 from Cherkasov and co-workers:[1]

> *Analyze your inactives, build cheminformatics models distinguishing them from your hits. Build QSAR models to rank your hits and use them to re-iterate your CADD pipeline; adhere to best QSAR practices... Analyze your confirmed hits, search for analogues, explore chemical space around them, and assess synthetic feasibility of possible derivatives.*

Unfortunately, best practice #5 from Cherkasov and co-workers, "Work closely with experimentalists during all stages of the project, learn from negative results, and fine-tune your CADD pipeline based on the wet lab outputs,"[1] is not possible in this course, although the spirit of collaboration between theoreticians and experimentalists is frequently highlighted.

STUDENT FEEDBACK

In the Spring 2018 incarnation of Pharmaceutical Chemistry 2 in the Quarter Abroad Program discussed above, pre- and postcourse surveys (online, anonymous, 11−13 responses for each survey) were administered (all data available in the Supporting Information). Although the number of students surveyed is small, qualitative conclusions can be drawn, which will inform future assessments. Survey data are included in the Supporting Information. As a measure of changes to student perceptions about the drug-design process, the following question was posed both before and after the course: "Based on your current perception/knowledge, rank the following in terms of their influence (in general) on the design of the specific molecular structures of drug candidates (1 = most influence, 10 = least influence)," with the following choices: medical doctors, company executives, legislators, biologists, marketing staff, synthetic organic chemists, patients, robots, and process chemists. One aim of the course as implemented was to showcase the dominant role of synthetic organic and process chemists in the drug-design process. The precourse mean rankings for these groups were 3.0 and 4.4, respectively, whereas the postcourse mean rankings for these groups were 2.8 and 2.6, respectively. Thus, recognition of the influence of both groups increased by the end of the course, slightly for synthetic chemists and dramatically for process chemists. Recognition of the influence of biologists also increased (from 4.7 to 3.8).

The following free-response questions were also included in both surveys:

(a) What roles do enzymes play in the human body?
(b) What is meant by a "drug target"?
(c) What is a "binding site" and what is its role in small molecule drug design?
(d) What types of interactions can be present between a drug and a drug target?
(e) What characteristics of a drug affect its potency?
(f) What characteristics of a drug affect its toxicity?
(g) What properties would make a compound a bad drug candidate for a particular disease?
(h) Assume that you have identified an enzyme whose inhibition would reduce the severity of a particular disease. What information about the enzyme would you need to design a drug for the disease?
(i) What properties of (potential) drugs can be predicted using computer modeling?

As assessed by at least two coauthors in each case, the contents of the answers to some questions (a, d, e, and h) were found to be similar in the pre- and postcourse surveys, thereby providing no evidence of changes in student perceptions as a result of the course, and answers to question (g) were so variable as to prevent us from drawing meaningful conclusions.

For question (b), the postcourse responses included many more references to proteins, receptors, and enzymes, that is, *molecules*, than did the precourse responses, which included more references to "locations" or biological structures such as tissues and organs.

For question (c), postcourse responses consistently included references to locations on proteins, receptors, and enzymes, whereas precourse responses included more references to locations within biological structures and parts of drugs rather than targets.

For questions (f) and (g), postcourse responses consistently included references to structural features of drug molecules, whereas precourse surveys generally referred to bulk or macroscopic properties, such as half-life, dosage, and solubility. Although the term "off-target" appeared in multiple precourse responses, connections of this concept to features of drug molecules was not evident. Both molecular and bulk properties are no doubt important in drug design, but we note here that students appear to have shifted their focus during the course. Future incarnations of the course will aim to make sure that this shift is not coupled to a loss of appreciation for bulk properties.

For question (i), pre- and postcourse responses were similar, although several precourse responders explicitly stated that they were "not sure".

Overall, it appears, on the basis of this anecdotal data and other discussions with students, that completing Pharmaceutical Chemistry 2 led to a greater recognition of the importance of structural features of both small molecules and receptor molecules in drug design.

OUTLOOK

A series of computer-based exercises is described that can be readily implemented in courses covering medicinal- and pharmaceutical-chemistry content, such as standalone CADD

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courses like Pharmaceutical Chemistry 2, courses on medicinal chemistry that are predominantly lecture-based, or even introductory or advanced organic-chemistry courses.[27]

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available on the ACS Publications website at DOI: 10.1021/acs.jchemed.8b00712.

Feedback-survey data (PDF)
Feedback-survey results for 2017 (XLSX)
Feedback-survey results for 2018 (XLSX)
Project overview and description (PDF)
Grading rubrics (PDF)
Lab manual for spring 2018 in Taiwan (PDF)
Lab manual for spring 2018 at UC Davis (PDF)
Alternative experiment A handout (PDF)

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: djtantillo@ucdavis.edu.

ORCID

Dean J. Tantillo: 0000-0002-2992-8844
Carla M. Saunders: 0000-0001-6699-2848
Terrence E. O'Brien: 0000-0002-5621-5065
Brandi M. Hudson: 0000-0003-2288-9157

Notes

The authors declare no competing financial interest.

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