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Integrated Teaching of Structure-Based Drug Design and Biopharmaceutics: A Computer-Based Approach

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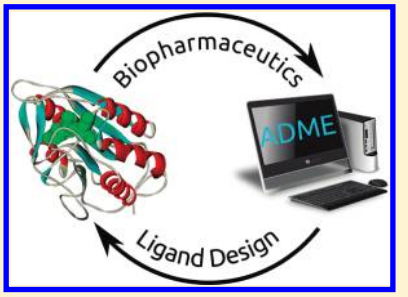
ABSTRACT: Rational drug design requires expertise in structural biology, medicinal chemistry, physiology, and related fields. In teaching structure-based drug design, it is important to develop an understanding of the need for early recognition of molecules with "drug-like" properties as a key component. That is, it is not merely sufficient to teach students how to design an effective inhibitor for a particular protein; instead, it is important to convey the need for simultaneous consideration of biopharmaceutical properties that will optimize the chances of the inhibitor becoming a drug. These are advanced concepts, but they can be addressed through computer-based methods. Here, an educational approach using a case study is described in which students "design" a potential drug through use of software, most of which is Web-based and freely available.



KEYWORDS: Graduate Education/Research, Upper-Division Undergraduate, Chemoinformatics, Interdisciplinary/Multidisciplinary, Computer-Based Learning, Internet/Web-Based Learning, Computational Chemistry, Drugs/Pharmaceuticals

Of the approximately 100,000 proteins in the human proteome, only about 500 are currently targeted by one of the approximately 40,000 drugs approved worldwide.[1] This suggests that there is considerable scope for identification of new targets and for the design and discovery of new drugs. On the other hand, the current average failure rate for drugs in clinical trials is 81%.[2] A lack of efficacy causes 30% of these failures, and concerns with toxicological and clinical safety account for another 30%.[3] Failure in the later stages of drug development is very expensive, particularly if a potential drug reaches phase II or III clinical trials before problems emerge. On average, companies are spending $27 million per year to advance drugs through clinical trials, at a total cost to market of over $1 billion.[4] Emergence of safety issues postapproval can have major costs of recall and legal fees, as demonstrated by the voluntary recall by Merck of Vioxx (rofecoxib) in 2004; this event has been estimated to have a cost of $9 billion in foregone profits and $5 billion in future litigation costs.[5]

These issues emphasize the importance of identification of molecules that are likely to reach the market at the early stage of drug discovery. In 1991, the industry observed a failure rate of 40% due to bioavailability and pharmacokinetic issues,[3] but incorporation of ADME (absorption, distribution, metabolism, and excretion) principles earlier in the drug development process to eliminate weak candidates has reduced failures for these reasons to 10%.[6] This approach has been facilitated by development of theoretical methods for prediction of "drug-like" properties of small molecules over the last 20 years. These have ranged from the simple, but effective and widely accepted, Lipinski "rule of five"[7] to sophisticated algorithms for prediction of ADME properties.[8,9] Input to these algorithms has been facilitated by use of text-based molecular representation through the powerful SMILES approach.[10]

Structure-based drug design against protein targets has been facilitated by the growing number of protein structures. There are currently 71,516 structures in the RCSB Protein Databank (March 1, 2011).[11] However, not all these proteins are targets for drug design. The number of "druggable" proteins (those that may be targets for drugs) was first addressed in 2002 by Hopkins and Groom,[12] with an upper estimate of 1500, and more recent reviews[13,14] suggest that this number remains valid. In 2006, Overington et al.[1] identified 1357 unique drugs that targeted 266 human proteins from examination of the FDA Orange Book[15] and the CDER Web site.[16] Thus, many druggable proteins have not been targeted. A goal of structure-based drug design[17] is to use structures of these proteins, or homology models derived from related proteins, to identify lead compounds computationally. The main method is molecular docking,[18,19] in which an attempt is made to locate molecules in a binding site using stereochemical and energetic considerations, with various simplifying assumptions depending on the required throughput.

This background presents a challenge for teaching of drug design at all educational levels. In 2006, Wild and Wiggins reviewed the development of educational initiatives and degree programs in chemoinformatics, in response to the growing availability of computer resources for storage and evaluation of molecular information.[20] Prior to this, Carvalho et al. had presented an interesting molecular modeling approach to active learning of structure−activity relationships and drug action, with a focus on enzyme mechanism and ligand fitting in an active site.[21] Cohen et al. have described strategies for teaching chemoinformatics and modeling in combination using commercial software

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(Molecular Conceptor), with a target audience of professional medicinal chemists.[22] At an earlier stage in the educational process, Gledhill et al. described a fascinating broad-based software approach that allows preuniversity students to perform hands-on drug design with Web-based distributed software.[23] Satyanarayanajois pointed out the importance of structural visualization for promoting understanding of basic principles in medicinal chemistry and biochemistry among professional pharmacy (Pharm.D.) students,[24] and Manallack et al. have described a detailed teaching strategy using molecular modeling, with a focus on GPCR targeting.[25]

Appreciation of the science of structure-based drug design requires familiarity with structural biology, thermodynamics, molecular association, stereochemistry, and computational methods; while appreciation of the biopharmaceutical properties of drugs (these are also commonly referred to as "ADME properties", but "biopharmaceutical properties" is used in this article because the focus is mainly on properties that influence absorption) requires an understanding of cell biology, physiology, preclinical formulation, and physical organic chemistry. The subject of structure-based drug design is only properly understood in the context of an integrated approach: this is a key in commercial drug design and it is also required in teaching of drug design. Here, a computational approach using Web-based software is shown to be effective for this purpose.

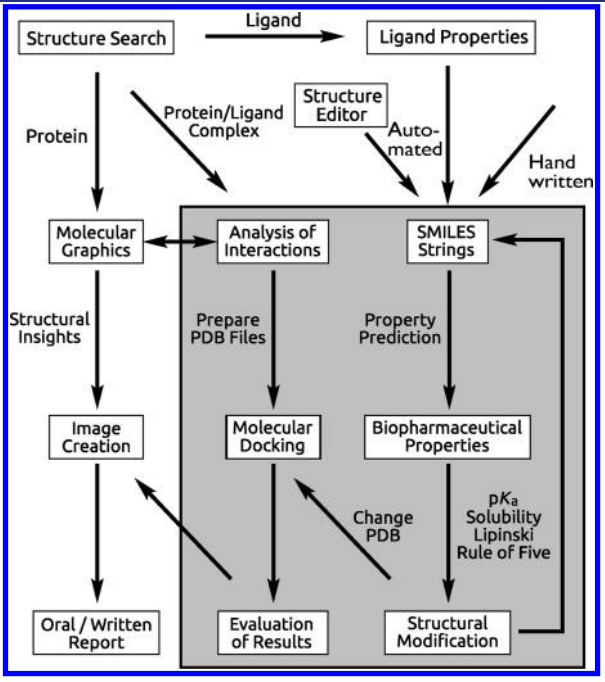

Figure 1. Flow of activities in the course. Each box in the shaded area corresponds to Web sites listed in Table 1. Each arrow indicates a hands-on activity in the course. The nonshaded area indicates related content that is not described in detail in this article.

COURSE DESIGN

Background

The key elements in the course are shown in Figure 1. The integration of molecular design (docking) and evaluation of biopharmaceutical properties are the primary focus of this article, as shown in the shaded part of Figure 1. Each box in the figure corresponds to a course element that can be taught in 2−4 h, with variation in the level of details. A list of URLs of Web sites associated with each course element is shown in Table 1 and the corresponding expected learning outcomes are described in Table 2. Each element is discussed in the sections below. To illustrate the teaching approach, the example of the complex of caspase-3 bound to the modified peptide inhibitor acetyl-Asp-Val-Ala-Asp-fluoromethyl ketone[26] (at the time of publication of this structure, caspase-3 was referred to as CPP32) is used. This complex provides the basis for a good example of structure-based drug design, molecular docking, and modifications to improve biopharmaceutical properties. The choice of caspase-3 was made for illustration only in this article. However, this enzyme has a well established role in apoptosis in neuronal cells and there is also emerging evidence for nonapoptotic roles of caspase-3 in neurogenesis.[27] Therefore, caspase-3 may be a potential therapeutic target.

Structure Search

The protein−ligand complex (PDB ID: 1CP3) was downloaded from the RCSB Protein Databank.[11] The procedure provides an opportunity to illustrate searching strategies on this

Table 1. URLs and Names of Web Sites Used in the Course

Course Activity[a]	Web site Name (Google Keyword Search)[b]	URL[c]
Structure Search	RCSB Protein Databank	http://www.pdb.org/pdb/home/home.do
Molecular Graphics	Accelrys Discovery Studio	http://accelrys.com/products/discovery-studio/
Analysis of Interactions	—[d]	http://ligin.weizmann.ac.il/cgi-bin/lpccsu/V_LpcCsu.cgi?PDB_ID=1CP3&Viz=Jmol&LpcCsu=LPC& [structure-specific entry][d]
Molecular Docking	MEDock Server	http://medock.csbb.ntu.edu.tw/
	Dundee PRODRG	http://davapc1.bioch.dundee.ac.uk/prodrg/[e]
SMILES Strings	Daylight SMILES	http://www.daylight.com/dayhtml/doc/theory/theory.smiles.html
Biopharmaceutical Properties	Molinspiration	http://www.molinspiration.com/
	Sparc Calculator	http://archemcalc.com/sparc/
	ALOGPS 2.1	http://www.vcclab.org/lab/alogps/
Ligand Properties	PubChem	http://pubchem.ncbi.nlm.nih.gov/
Structure Editor	SMILES Translator	http://cactus.nci.nih.gov/translate/

[a] The terms in this column corresponds to a box in Figure 1. Some entries have multiple Web sites. [b] Searching using Google (http://www.google.com/) with this phrase will locate the Web site in the first few matches (as checked in Aug 2011). [c] All URLs were accessible as of Aug 2011. [d] Accessed from RCSB Protein Databank: > Links > Analysis of Ligand-Protein Contacts (LPC). [e] Alternatively, Open Babel can be used (downloaded at http://openbabel.org/wiki/Main_Page).

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Table 2. Learning Outcomes

Course Activity[a]	Expected Outcome
Structure Search	Students are able to navigate the PDB Web site, locate a suitable protein−ligand complex, and retrieve a PDB file.
Molecular Graphics	Students understand how to open pdb files, understand the contents, manipulate a structure on the computer screen, use distance/angle tools, highlight and change atom representations, and save molecules as images, SMILES, and native formats (preserving markup).
Analysis of Interactions	Students can use the PDB Web site to identify interacting atoms and measure distances between atoms. Students can identify hydrogen bonds, hydrophobic pockets, and salt bridges formed between ligand and protein.
Molecular Docking	Students understand the process of ligand−protein docking, can extract the ligand from a ligand−protein complex pdb file, and can create pdbq files for the ligand. Students can dock a ligand to a target protein and evaluate the results for conservation of key protein−ligand interactions.
SMILES Strings	Students can convert a structure from an image to a SMILES representation and vice versa using computational tools. Students can write a simple SMILES string and modify a computer-generated SMILES string.
Biopharmaceutical Properties	Students understand the dependence of biopharmaceutical properties on molecular structure and how to influence these properties by molecular modification. Students can use Web sites for calculating key biopharmaceutical data, including pK_a, solubility, Log *P*, Log *D*, and bioavailability.
Ligand Properties	Students are familiar with PubChem as a starting point for evaluation of ligand properties.
Structure Editor	Students can use molecular editors to introduce changes into a ligand, which can then be converted into appropriate formats (SMILES) for input into other Web sites.

[a] The terms in this column corresponds to a box in Figure 1.

Web site and explore the many features and links for geometrical analysis. One such feature permits an analysis of the protein−ligand contacts (Table 1). This is used simultaneously with molecular graphics display of the complex to develop an understanding of the manner in which the ligand interacts with the protein. Identification of key interactions is required so that subsequent modifications can be made while attempting to retain key contacts. For this example, the approach is complemented by the use of a figure from the original publication, in which the contacts are described.[26] This provides a "reason" for the students to look at the literature, because there is value in the simplified published figure.

Analysis of Interactions (Molecular Graphics)

An important element in the course is the use of molecular graphics. This can be done relatively simply using just a few instructions within a graphics package such as Accelrys Discovery Studio (Table 1). This package is simple and intuitive to use and permits basic visualization of the protein and ligand and identification of ligand−protein interactions. If time permits in a particular course, a further module is added to teach molecular graphics in more detail, with more emphasis on protein structure (Figure 1). However, for a drug design course, the focus is placed on molecular association. The most effective approach is to require students to measure interactions between the ligand and the protein, which provides an understanding of contacts based on hydrogen bonding, electrostatics, and hydrophobic association. Preparation of images with coloring of key amino acids involved in the ligand interaction is also required. These activities provide a basis for modification of the ligand later in the course.

Molecular Docking

The MEDock server[28] is used as a docking platform. This Web site has the major advantage of simplicity for teaching initial principles of docking. There are alternatives, as discussed below, but the MEDock has the correct combination of efficacy and simplicity. Preparation of input "pdbq" files for input into the MEDock server is achieved using the Dundee PRODRG Web site (Table 1) after saving initial pdb files for the ligand and the protein in DS Viewer. The conversion to pdbq format also permits further discussion of molecular representation in computational chemistry because this format contains connectivity information. This is a useful educational issue because this aspect of molecular display is "hidden" behind the interface of modern molecular graphics packages. The pdbq file also includes charges, which permits a discussion of an important element of molecular association. In addition, the Dundee PRODRG server is limited to pdb files of only 300 atoms, and therefore the protein must be reduced to only the amino acids that are important for ligand binding. This is not a disadvantage in an educational context: in contrast, this requirement enhances understanding of the ligand−protein association through graphics visualization and reference to the literature.

For the docking, the ligand taken from the X-ray structure and a set of key amino acids are initially used. Rigid docking is performed for simplicity, but lecture content given in association with the docking can emphasize modern methods that allow flexibility in the ligand and protein. However, the educational goal is better served by reducing the complexity and obtaining a good answer (albeit in a somewhat idealized context) to show the students that this methodology does work. The effectiveness of this simple method is shown by comparison of the ligand geometry in the X-ray structure (Figure 2A) with the docked version of the ligand (Figure 2B). By performing the entire docking procedure, the students obtain a key skill that they can use for further docking of modified molecules, as described below.

Several points of clarification are required regarding the docking exercise. Docking was performed with a rigid conformation for the ligand (the X-ray conformation) and the protein, and this biases the results. This is clearly stated in teaching the class and it is emphasized that modern molecular docking is increasingly performed with flexible ligands and partly flexible receptors. It is also stressed that the results of the docking exercise require experimental validation; that is, they only provide a starting point for drug discovery. Regarding the choice of the caspase-3 complex for this exercise, this is used only as an example to illustrate the approach of ligand design and not because caspase-3 is currently a particularly important drug target. Also noted is that the chosen

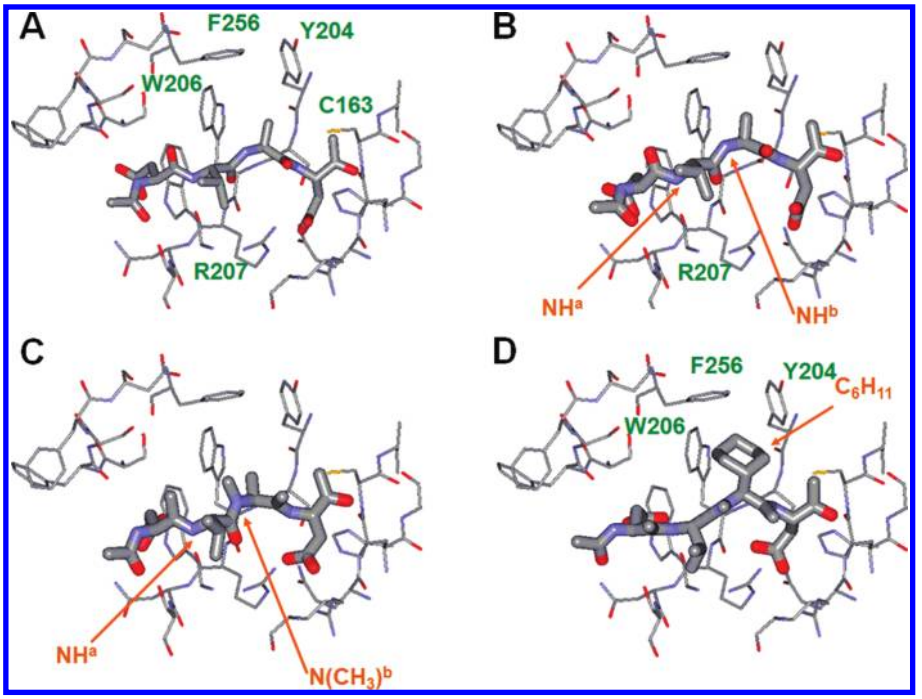

Figure 2. (A) X-ray structure of acetyl-Asp-Val-Ala-Asp-fluoromethyl ketone binding to caspase-3.[26] Only a few residues of the protein are shown. The fluorine atom of the ligand has been displaced by covalent bond formation of the ligand with Cys-163. (B) Docked version of the original ligand, showing hydrogen bond formation for NH^a and the absence of an interaction of NH^b. (C) Docked version of a ligand with N-methylation at NH^b (i.e., $N(CH_3)^b$) and replacement of two carbonyl groups with C═C bonds. (D) Docked version of a ligand with a cyclohexane (C_6H_{11}) added to the ligand in (C) to fill a hydrophobic site formed by W206, F256, and Y204. Hydrogen atoms are omitted in all images for clarity.

complex has a covalent bond between the enzyme and ligand (Figure 2). Therefore, docking was performed with a ligand that excluded the fluorine atom of the fluoromethyl group because this atom is displaced when the molecule reacts with the enzyme.

SMILES Strings

SMILES (simplified molecular input line entry specification) strings[10] are representations of molecular structure that are used as text input for software for conversion into two- or three-dimensional structure or for calculation of molecular parameters. In reverse, SMILES strings can be generated from three-dimensional structure using molecular graphics programs such as DS Viewer. Thus, a SMILES string provides an excellent medium for navigation among a variety of software. More importantly in an educational context, writing of a SMILES string requires a careful consideration of the chemistry of a molecule, including bond types, charge, and chirality.

Initially, the writing of SMILES strings is taught from first principles (i.e., handwritten strings) to increase the understanding of molecular structure and bond connectivity. However, the students are encouraged to use Web sites such as PubChem (Table 1), which provides a wealth of ligand information, including the SMILES string, and is directly accessible from the RSCB database. The use of sites for interconversion of SMILES strings to molecular structure and vice versa, including the SMILES translator site (Table 1), are also encouraged. Ultimately, the goal in teaching the background of the SMILES string is to show the students the value of this representation for navigation through computational chemistry and biopharmaceutical Web sites.

Biopharmaceutical Properties

The second part of the integrated approach is to examine the biopharmaceutical properties of the original ligand and modified ligands. Having established strategies for obtaining a SMILES string, these strings are used in several Web sites to obtain properties associated with Lipinski rules, solubility, ionization (pK_a), potential degradation, metabolism, active transport, and bioavailability. The extent of this approach depends on the available time in the course. For a relatively basic approach, using the Molinspiration Web site (Table 1) is favored because this site is simple to use and provides a straightforward overview of the Lipinski properties of a molecule. This Web site can be accessed with a SMILES string or through simple structure building using an intuitive molecular editor.

Snapshots from the Molinspiration Web site output for the original ligand are shown in Figure 3B, based on input of the SMILES string in Figure 3A(i). These kind of results provide an excellent basis for understanding the biopharmaceutical issues associated with ligand design. Most of the properties violate the Lipinski rules, including the very negative LogP (miLogP), and the related high numbers of hydrogen bond acceptors (nON) and donors (nOHNH). This provides a good basis for discussion of the likely difficulty of oral delivery of this agent, based on its probable poor absorption properties. In addition, the number of rotatable bonds (nrotb) is high, and this allows discussion of potential affinity problems and the need to build in rigidity in the molecular structure. Further analysis of the molecule is possible using other Web sites (Table 1), such as the ALOGPS 2.1 site for calculation of solubility and the SPARC site for evaluation of ionization and other properties, and through discussion of potential in vivo degradation (because the molecule is peptidic). However, the Molinspiration site provides sufficient detail for discussion in an introductory course.

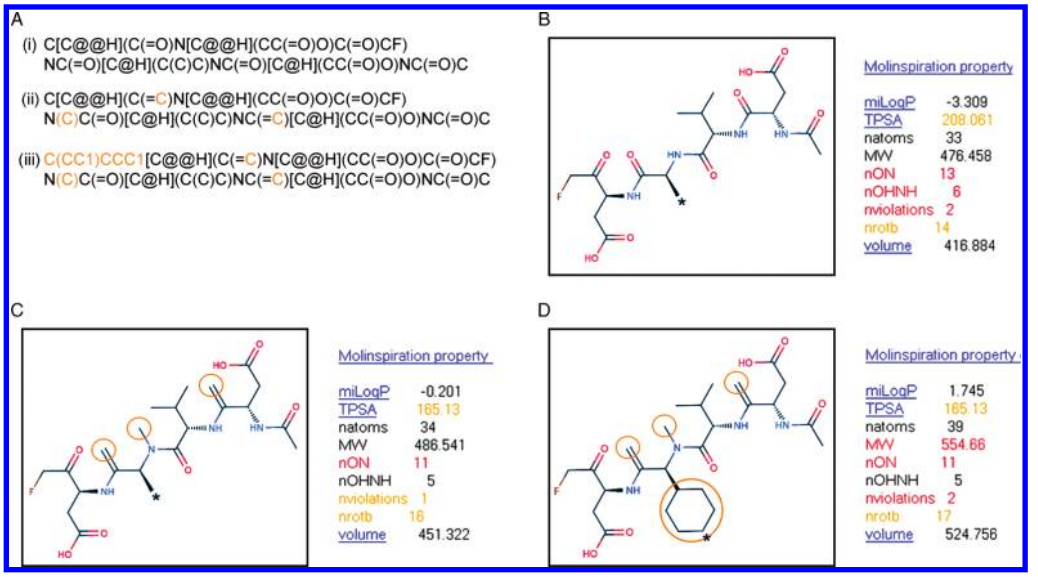

Figure 3. (A) SMILES strings of (i) the original ligand in Figure 2A,B, (ii) the modified ligand in Figure 2C, and (iii) the modified ligand in Figure 2D. Modifications to the SMILES string of the original ligand are shown in orange. (B–D) Molinspiration output showing biopharmaceutical properties for the three ligands. The asterisk on each ligand (not present in the Molinspiration output) indicates the C atom at the start of the respective SMILES string. Each ligand was redrawn from the Molinspiration output to produce a similar orientation. Changes from the original ligand (B) are indicated by orange circles in (C) and (D) and correspond to the changes in the SMILES strings shown in orange in (A).

Structural Modification and Evaluation of Results

At this stage, the students have developed the requisite methodological skills and have sufficient knowledge of a particular protein–ligand complex to permit modification of the original ligand, with the goal of improving the biopharmaceutical properties while maintaining the binding affinity of the modified ligand. They have an understanding of molecular graphics, basic docking skills, the ability to write and modify SMILES strings, and an appreciation of favorable biopharmaceutical properties. They are now ready to integrate these activities in an exercise that mirrors the drug design process at the research and development level.

To illustrate this procedure, two modifications of the original ligand based on evaluation of the original complex (Figure 2A) or the similar docked version of this complex (Figure 2B) are used. An aspect of the binding is the use of one peptide bond N–H in the ligand (NH^a in Figure 2B) to form a hydrogen bond to the backbone carbonyl group of R207, while in contrast, a second ligand N–H (NH^b in Figure 2B) appears unimportant in the ligand–protein interaction. This suggests that N-methylation of this peptide bond may be allowable from a binding perspective, while also improving the biopharmaceutical properties (reducing the hydrophilicity). This change (and isosteric replacement of two carbonyl groups in the ligand with alkenes) was implemented through modification of the ligand in DS Viewer. The resulting PDB file was processed and docked using MEDock (Figure 2C). The SMILES string for the new ligand (Figure 3A(ii)) was obtained by modification of the original SMILES string, and then used in Molinspiration to compute the biopharmaceutical profile (Figure 3C).

This exercise provides a valuable learning experience and is accomplished by the students in a relatively short period of time. The results are "real" and relatively easily interpretable. It is clear that the key interactions of the original ligand with the protein have been maintained in the docking of the modified ligand (Figure 2C) (these interactions can be quantified), whereas some of the problematic Lipinski properties have been improved. This can be developed further. For example, a hydrophobic site formed by W206, F256, and Y204 seems to be present in the ligand binding site, and it is possible that this could be exploited by addition of a large hydrophobic group to the ligand (a cyclohexane is used in this example). Further docking and evaluation of biopharmaceutical properties gives the results shown in Figures 2D and 3D, respectively.

Additional Teaching Elements

The choice of a given complex can be made such that key principles can be illustrated through the procedure of design and biopharmaceutical evaluation. In addition, the use of a particular structure allows other principles related to the structure to be discussed. For the caspase 3–Ac-DVAD-fmk complex, a brief background discussion of the caspase cascade in apoptosis is provided. Discussion of a "suicide inhibitor", given the formation of the covalent bond to Cys-163 in the protein, is also possible This discussion requires presentation of the basic catalytic mechanism of a cysteine protease, and how this mechanism is exploited in the design of the inhibitor. These important principles become clearer and perhaps of more interest to the student because they have become acquainted with the protein and the inhibitor. Clearly, these teachable opportunities will vary from complex to complex, but an interesting background presentation should be possible for each complex.

■ DISCUSSION

The approach described above can be used in several teaching contexts. Variants of the approach have been used in short intensive courses (7 h per day over 5 days) or in semester-long courses. In the first setting, the material is taught through short lectures (typically of about 30 min) followed by directed computational exercises. These exercises work best in small groups of students (three or four) and with floating assistance from the lecturer and assistants. Given the relatively short time

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availability, there is a need to move the exercises forward and ensure that each student or group is moving at the same pace.

The course has also been taught at the introductory graduate level over a semester. The material does not differ, but the problem is given to the students as a case study, in which there may also be an additional element to mimic an industrial setting. This can involve assignment of an enzyme class, with a small group of students asked to research this enzyme class, determine its relevance to disease, and then identify a target (with a solved X-ray structure) prior to engaging in the activities described above. This clearly requires much more time, but the case study can be performed as an out-of-class assignment while the lectures in the course provide background on the methods. In this setting, it is also possible to include several student presentations of the findings.

The procedure can also be presented as a lecture or demonstration without significant hands-on work by students. This includes an introduction of basic principles and discussion of some of the more detailed ideas associated with the complex. A class time of 6 to 8 h is needed for this approach. Some preparation would also be required, particularly for building and running the files for docking. This approach may be appropriate for a graduate-level course in which drug design is one of several components and could be given by a single lecturer. It has the disadvantage of not allowing students to use the software and is also limited by the focus on one complex only. However, the approach may still be more effective in inspiring student thinking, compared to a purely didactic description of the principles of drug design.

An important element of this article is that the course (in any of the above settings) can be performed entirely with free and Internet-based applications. The availability of such extensive and effective software is a remarkably positive aspect of the Internet and a testament to the generosity of the authors of this software. This availability also permits the course to be mobile both geographically and in a computer platform-independent manner. More sophisticated software applications are available and may be appropriate in some educational settings. However, these require greater technical understanding and more time for adequate interpretation of results. For example, Autodock Vina[29] is an open-source molecular docking program that provides a platform-independent method for docking ligands to target molecules. The interface to Autodock Vina is intuitive and the steps required to obtain docking results can be taught through a video tutorial. Autodock Vina provides greater flexibility and customization than is afforded with MEDock. Having several programs that accomplish the same goals with different depths allows educators to tailor the curriculum to the audience or time constraint.

The curriculum could also be supplemented with commercial programs for functions that are not adequately filled by open-source software. ACD Labs ADME suite[30] can be used to predict the probability of a ligand being a substrate for cytochrome P450 metabolism and *P*-glycoprotein efflux. GastroPlus from Simulations Plus[9] can be used to predict absorption and bioavailability of molecules and establish a direct relationship between structure and in vivo drug performance. These programs allow students to appreciate cutting edge ADME prediction methods. Rational modification of the structure can be achieved with feedback on whether a change was positive based on drug absorption profiles that include many factors influencing bioavailability. This is valuable for extending the course to a more sophisticated discussion of drug design and delivery, but clearly requires more time and a wider series of lectures on issues such as drug metabolism and transport. Other related areas can also be included in the course, at the discretion of the lecturer and within the time available. In particular, more discussion of structural biology can be included as an additional module (Figure 1), with a focus on protein and DNA structure. A further possibility is extension of the drug design element of the class to include discussion of QSAR and pharmacophore methods, perhaps based on the results obtained from the docking exercise.

The main concern in developing new modules as extensions of the drug design focus is to maintain the hands-on computational approach. This may be the most important aspect of the course. First, the computational approach is helpful in overcoming difficulties with language, if the class contains students with a first language that differs from that of the instructor. The course has been taught in several international settings and the effectiveness of the computer-based approach is evident. Only this anecdotal experience is presented and there seems to be an absence of academic literature addressing this issue. After performing a few exercises in docking, SMILES string development, and interaction with key Web sites, students become proficient in the techniques. The methods are no longer a barrier to obtaining output. The output also has a sense of "belonging" to the student because the design of the new ligand was based on individual or group-based ideas. The end point is understandable and achievable, and this produces a greater desire to learn and recognize the creativity of the science behind the drug-design process. This is a key to developing future scientists who will be effective in this area and may be able to reverse the current trend in the decline of blockbuster drugs emerging from the pharmaceutical industry.[31]

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