Book Reviews

Software Program Title: Molecular Conceptor Drug Design Courseware. Version 1.02. By Claude Cohen. Synergix Ltd., Jerusalem, Israel. August, 2002. CD-ROM (plus HASP key, table of contents, and installation guide). ISBN 965-90508-0-1. $4900 (commercial), $2900 (academic).

This CD-ROM has the following system requirements: 350 MHz (minimum) Intel Pentium processor, Windows 98/Me/2000/XP, 64 MB of free RAM, 430 MB available disk space, 24-bit color monitor with 1023 × 768 resolution (runs much less satisfactorily on an 800 × 600 monitor).

In my experience, medicinal chemists have varying attitudes about the usefulness of computer-aided drug design and discovery technologies. Some, especially ones with a computational bent, learn as much as they can and manage to apply the methods productively to their research problems; in fact, a number of professional computational chemists started their careers as bench chemists. Others are unsure what such methods can do for them or have unrealistic expectations and are disappointed in the results.

There are a number of computer programs for molecular modeling and computations that are geared toward direct use by the medicinal chemists, but they are far less prevalent than the ubiquitous 2D structure drawing programs. If practicing medicinal chemists gained greater knowledge of these techniques, one would expect many more productive applications, but convenient, practical training in computational chemistry is hard to come by, even in many colleges and universities. Molecular Conceptor Drug Design Courseware may help to fill this gap. Molecular Conceptor consists of 4 volumes, 18 chapters, about 1500 pages, and over 1200 3D illustrations and is the equivalent of a 50 h course. It uses cartoons, animation, and a great many pharmaceutical discovery examples to impart the concepts and strategies of computer-aided drug design. Yet, despite making the subject accessible and entertaining, it does not "dumb down" or oversimplify the examples. The courseware reflects the experience and expertise of Dr. Claude Cohen, one of the pioneers of CADD.

Molecular Conceptor is not keyed to any particular molecular modeling software. It only requires installation of the (included) Discovery Studio Viewer Active-X control to permit interactive manipulation of the example molecular structures, alignments, surfaces, and enzyme complexes. The software requires insertion of the included HASP key in a USB port; the mechanism worked perfectly on two machines I tried it on, under Windows 98 and Windows XP. For those wishing to try before buying, a demo version containing several sections is available for download from the website.

After an introductory section on how drug discovery and development are carried out (useful to the nonspecialist), there is a thorough review of the molecular basis of drug design. Topics include potential energy surfaces, conformational analysis including common errors made with minimization, molecular dynamics, etc. Preferred conformations of various acyclic, cyclic, and heterosystems are then shown.

The next volume covers strategies and principles in drug design. It introduces the concepts of rational drug design, elaborates on the two major approaches, (pharmacophore-based and receptor-base design), advocates applying both methods in parallel, and reviews some of the limitations and successes of these approaches.

There follows a major volume on pharmacophore-based drug design, which consists of three sections: analysis, design, and examples. (Pharmacophores here are 3D patterns of molecular functionality that are associated with the biological action of a small molecule.) The first section explains the basis of the method, covers application strategies, and shows examples. The second section gives four strategies for pharmacophore-based molecular design—chemical modification of leads, 3D database searching, de novo design, and manual design—with examples of each. Finally, numerous examples of applications to actual drug discovery projects, and resulting project contributions, are reviewed. The ACE inhibitor and β-lactam antibiotics cases strike me as particularly instructive.

The next volume provides an equally extensive discussion of receptor-based drug design. (Receptors here are 3D biomolecular structures, usually proteins, containing sites where bioactive molecules bind to exert their action.) Again, there are three sections: analysis, design, and examples. First, the technique and its variations are introduced, with discussion of receptor and ligand flexibility, role of solvent, prediction of binding modes, etc. Then are discussed practical strategies for designing ligands for receptor sites, termed the "8 Golden Rules". Next, the four methods of analog design, database searching, de novo design, and manual design are presented, and the "success story" of HIV protease inhibitor design is given. The last section gives many real examples of application. For the several systems I am most familiar with, I found the presentations remarkably on-target.

The last volume, Topics in Design, consists of a chapter on molecular graphics and another on peptidomimetics that discusses the challenge of designing nonpeptide mimics of bioactive peptides, with many real-world examples.

The stars of this collection of material are the many real examples, with countless manipulatable 3D views of molecules, alignments, and complexes—thoughtfully laid out and annotated to clearly make important points. The program also features a search engine, to jump to the (screen) page that introduces a requested topic, and "bookmarking" capability to easily return to specific pages. Finally, there is an extensive list of references for the drug discovery examples.

I found the option of having the text read out loud by the computer disconcerting partly because some of the technical terms were not pronounced in the usual way; but others may prefer hearing the unfamiliar words. Occasional misspellings detracted slightly from the

presentation, but I found the scientific concepts to be remarkably error-free. Regular upgrades, with corrections and additional topics, are promised.

While the software is fairly expensive, the prodigious number of examples and the obvious effort put into optimal presentation of the concepts and the structure views no doubt justify the premium price. There is a networked version available at higher cost.

I think that most pharmaceutical laboratories would want at least one copy, for self-education of interested medicinal chemists and as a useful refresher course for their computational chemists, who often know some areas of their discipline better than others. It also is ideal for university chemistry departments, where interested honors students could select one of the referenced examples for more in-depth study. Finally, university chemistry professors might consider introducing some of the material into their organic, medicinal, and pharmaceutical chemistry courses where these inspired examples are sure to fire the imagination of students.

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Alkaloids. Nature's Curse or Blessing?. By Manfred Hesse. Wiley-VCH, Weinheim, Germany. 2002. xii + 413 pp. 22 × 23.5 cm. ISBN 3906390241. $115.00.

This English translation of a book originally published in German comprises 11 chapters: Introduction; Classification of Alkaloids; Structure Elucidation of Alkaloids; Artifacts; Chiroptical Properties of Alkaloids; Alkaloid Synthesis; Alkaloids and Chemotaxonomy; Aspects of Alkaloid Biogenesis; Biological Significance of Alkaloids; Historical Aspects of Alkaloid Chemistry; and Active Principles from Selected Alkaloid Sources and Their Cultural and Historical Significance. It is impossible to categorize this unusual book. Printed on heavy, "slick" stock, nicely and attractively bound, and lavishly supplemented with colored photographs and other artwork, it is almost a "coffee table" volume. Interspersed with well-written and informative examples of most aspects of alkaloid chemistry (classification, structure elucidation, stereochemistry, synthesis, chemotaxonomy, biogenesis) are discussions of botany, anthropological considerations, and history of science. This reviewer is unable to understand the significance of the title; it does not seem to reflect the contents of the book.

The book contains a little bit of just about everything related to the topic of "alkaloids". It is not a textbook, a review monograph, or an account of original research. It appears to be a true "labor of love" by the author. The English translation is written in a lively style that is a pleasure to read. This reviewer must confess that he could not put the book down, and I suspect that most medicinal chemists would find it an appealing choice for pleasure reading. In this sense, it is highly recommended.

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