

Book Reviews

Structure-Based Ligand Design. Klaus Gubernator and Hans-Joachim Böhm, Eds. John Wiley & Sons Inc., 605 Third Ave., New York, NY 10158-0012, 1998. xiv, 153 pp., illustrations. \$135.00.

"Structure-based Ligand Design" is a relatively short book (147 pages excluding subject index) that provides a very good introduction to a rapidly advancing area of importance for drug development. The book is appropriate for scientists with backgrounds in chemistry, biology, or the pharmaceutical sciences. It would be most useful for someone who plans to do research in drug development and is seeking a basic overview of recent developments in structure-based drug design. This book provides an excellent introduction to structure-based drug design. However, the book is aptly named "Structure-based Ligand Design," because, as is clearly pointed out in the text, there is a significant gap between designing a tight binding ligand and obtaining a molecule with appropriate parameters for uptake, delivery to the biological target, and eventual elimination.

The book is divided into nine chapters. Chapter 1, "Rational Design of Bioactive Molecules," by K. Gubernator and H. J. Baron provides a good overview of structure-based ligand design and relates it to the more difficult task of drug development. Chapters 2 and 3 provide accounts of structure-based drug design within a historical perspective. It is possible from reading these chapters to gain an appreciation of how difficult it is to accomplish structure-based ligand design with minimal structural information. The authors provide considerable insight into the complexities of structure-based ligand design. To work at the forefront in this area requires substantial resources and a team of experts.

Chapters 4–7 cover a number of examples where structure-based ligand design has played a significant role in the development of new high affinity ligands. Chapter 4 offers little that can not be found elsewhere in the book, unless the reader has a special interest in zinc endoproteases. The most interesting chapters were those that provide a thorough analysis of mechanism of action and correlate this to protein structure, and then relate both to inhibitor design. The best examples of this approach were Chapter 5, "Structure-Based Design of Potent Beta-Lactamase Inhibitors," and Chapter 6 "Inhibition of Sialidase." Chapter 8 provides a deeper insight into the computational/modeling problem. Hans-Joachim Böhm outlines development of the computer program LUDI, which provides a means for data base searching and ligand construction. Section 8.3, "Computational Methods to Predict Ligand Binding Affinities," was an interesting introduction to the problems that have yet to be solved in the structure-based ligand design area. Chapter 8 is the only section of the book with much discussion of computational techniques. For readers who would like more extensive information about computer-based ligand design, I recommend volume 11 (1997) of the series "Reviews in Computational Chemistry," edited by K.B. Lipkowitz and D.R. Boyd, published by Wiley-VCH. Chapter 1, "Recent Advances in Ligand Design Methods" and Chapter 2, "Current Issues in De Novo Molecular Design," outline the computational problems and solutions associated with ligand design.

Chapter 9, "The Future of Structure-Based Design: A Worthy Precept," has little to add to what was already said in earlier chapters, but does nicely summarize the state-of-the-art. The kinds of problems that one must consider in translating ligand design to drug design are discussed here as well as in a number of earlier chapters. The limitations of current methodology are generally well delineated throughout the book.

The figures in this volume were not always very clear. For example Fig. 8a, Chapter 5 looked as if it had been printed on a worn dot matrix printer. This was true for a number of other figures as well. Some of the characters are virtually unreadable. The figures in Chapter 4 appeared to be copies of slides taken from an out-of-focus computer monitor. In most of the chapters, many of the figures, especially the protein structures were too small (typically 6 cm × 4 cm). It was not always possible to see the details discussed in the accompanying text. Many of the graphics are in stereo, but because of the small size it was difficult to view the stereo images, even with a VCH Reflecting Stereoscope™. I found it far more effective to log on to the Protein Data Bank (PDB) (<http://www.pdb.bnl.gov/>), find the protein in question (not always easy since there may be many different structures for some extensively studied proteins), and then explore the structure using the tools available on the PDB site. The latest version of MDL's Chime (see instructions for downloading version 2.0 at the PDB site) allows extensive manipulation of the structure and provides one the opportunity to visualize the protein-ligand interactions in a way that is simply not possible through a book.

One is left with the impression that the successful design and development of drug molecules more and more resembles the design and construction of a new generation of Boeing airliner. Structure-based drug design, along with other rapidly developing experimental and theoretical methods for predicting biological properties, and *in vivo* systems for rapidly evaluating the behavior of potential drug molecules in animal models by mapping protein expression, may one day provide the means for unequivocal prediction of putative drug efficacy before human testing is even initiated. "Structure-based Ligand Design" is a great place to start if you wish to understand one important component of the upcoming revolution in drug development.

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Alfred Benzon Symposium 43 Peptide and Protein Drug Delivery. Sven Frøkjær, Lona Christrup, Povl Krosgaard-Larsen, Eds. Munksgaard, 35 Nørre Søgade, P.O. Box 2148, DK-1016 Copenhagen K, Denmark. 484 pp. illustrations. no price listed.

This book contains the proceedings of the 43rd Alfred Benzon Symposium on Peptide and Protein Delivery, which

was held in Copenhagen on August 17–21, 1997. Because many peptides and proteins are complex high molecular weight molecules, which are labile, and charged, their delivery into the body at levels which are therapeutically effective is a major challenge. The book deals with several aspects of this interdisciplinary field of research. After introductory chapters on the structure, biochemistry and function of biomembranes, one section deals specifically with the transport of peptides through biomembranes, with emphasis on transport through the epithelial cells lining the gastro-intestinal tract and the endothelial cells lining the capillaries in the blood-brain barrier. Subsequently different routes of administration (i.e., oral, pulmonary, nasal, and transdermal delivery) are discussed. Three separate sections of the book focus on the formulation of peptides and proteins with emphasis on respectively physicochemical, chemical and pharmaceutical aspects. The final chapters deal with targeting/site specific delivery and possible alternatives to peptide and protein drugs.

All chapters in this book are written by leading scientists in the field of drug delivery and the overall quality is high. Of particular interest are the extensive lists of references in each of the chapters and the summaries of the discussions following each of the presentations. Such a book provides an accurate overview of the current status of research in the area of protein and peptide delivery.

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Confocal Microscopy: Methods and Protocols. (Methods in Molecular Biology, Volume 22). Humana Press, 999 Riverview Drive, Suite 208, Totowa, NJ 07512, 1999. xi, 446 pp., illustrations. \$99.50.

The 24 chapters of this book contain 440 pages of detailed methods in the area of confocal microscopy. The book is written for the scientist with little experience in the methodology of confocal microscopy and no desire or need to become an "expert". In fact, the book makes no attempt to provide the user with an encyclopedia of the technology. What this book does very successfully achieve is to provide the user with detailed methodology of how to prepare materials to create the images which are usually the endpoint for most uses of this technology.

The first 3 and last 4 chapters discuss the use of the technology in general. Chapters 1-3 give an introduction into the technology of confocal microscopy which provides the reader with a broad overview of how confocal microscopes work and what can be done with them. Additional practical discussions of general operational hints and useful information on fluorescent probes complete this introductory section. The last 4 chapters discuss some of the issues of dimensionality and visualization which impact data presentation.

The core of this book (17 chapters) discusses quite specific methods essentially in a "cookbook" style, where in lies the

real value of this book. While understanding the technology is important, from a user perspective it is the really practical advice from other users that makes successful confocal microscopy. Several chapters deal with studies of embryos including *Drosophila*, *C. elegans*, *Danio rerio* (Zebrafish) and *Xenopus laevis*. One chapter discusses plant images and five chapters deal with the complex issues of live cell imaging. In particular, the chapter devoted to live-cell imaging using GFP deserves mention. This chapter is really very comprehensive with an excellent description of GFP and its particular application in confocal imaging, detailed methods, and a really complete reference list. I think that there would be few people with access to a confocal microscope who could not successfully achieve good results using GFP if they studied this chapter first.

Confocal microscopy is not a new technique - it's been around for a long while. However, assuming instruments are well managed and operated, 90% of the eventual result depends on material preparation. This book contains a set of chapters that provide minute detail and that are written by scientists who do these studies on an everyday basis. They know both the pitfalls to avoid and the tricks to employ for good sample preparation which facilitates high-quality imaging. That's what makes having this book well worth while.

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Targeting of Drugs 6. Strategies for Stealth Therapeutic Systems. Gregory Gregoriadis and Brenda McCormack, Eds. Plenum Publishing Corporation, 233 Spring St., New York, NY 10013, 1998. ix, 302 pp., illustrations. \$105.00.

Another book edited by Gregory Gregoriadis and another success. This time, with Brenda McCormack, they published the new, 6th issue of The NATO Advanced Studies Institute series "Targeting of Drugs", summarizing the papers presented in 1997 at the traditional Cape Sounion Symposium (which was, by the way, initiated by Gregory himself). This last Symposium was called "Targeting of Drugs: Strategies for Stealth Therapeutic Systems", and, subsequently, the papers relate mainly to this popular topic.

One can ask, why do we need another book on the subject already reflected in many good books and special journal issues? Wouldn't such a book present just another set of well known data reworded slightly to meet the minimum novelty requirements? No, this is absolutely not the case. The book I am writing about is very different in the sense that it reflects well the Symposium atmosphere, i.e., it does not provide a set of academic reviews of well established areas. It rather preserves a nice taste of free discussion on topics many of which are still on the cutting edge.

Traditionally, the main attention in stealth pharmacology is devoted to liposomal carriers, since these particles were at the epicenter of the majority of studies and discussion on long-circulating pharmaceuticals. Gregoriadis and McCormack could not escape this fact, and stealth liposomology still takes the major part of the book (15 of 24 Chapters). However, the editors

widely opened the doors for all other possible pharmaceutical strategies involving long-circulating drugs and drug carriers. Earlier, I also attempted to bring together scientists working in different areas of Stealth therapeutics in a Special Issue of *Advanced Drug Delivery Reviews* (Vol. 16, 1995). But we certainly see now a big step ahead not only in the number of papers, but also in the depth of research and understanding.

To be fair, I have to say that even the more traditional "liposomal" portion of the book contains a lot of new and challenging data. Such as an excellent paper by the late Demetrios Papahadjopoulos on steric stabilization of liposome-DNA complexes, or the paper by Bill Phillips on the use of PEG-liposomes for imaging applications. Already, we even can see the data questioning the general statement that PEG-liposomes are always better for drug delivery purposes than conventional liposomes. Scherphof and co-authors clearly demonstrated that sometimes it is not the case. (By the way, we came to a similar conclusion in our paper on factors influencing the target accumulation of PEG-coated immunoliposomes (Torchilin et al., *Biochim. Biophys. Acta*, 1279: 75-83, 1996), which probably somehow escaped the authors' attention.)

The non-liposomal portion of the book is very diverse and informative. This ranges from the analysis of interactions between blood components and artificial surfaces (K. Caldwell) to new steric protectors, such as polysialic acids (G. Gregoriadis and co-authors) and poloxamines (S. Moghimi); and from new soluble polymeric carriers (P. Ferruti and co-authors) to long-circulating nanoparticles (papers by J. Kreuter, M. Peracchia, and co-authors, R. Gref and co-authors).

While Reading the book, I at times felt sorry for the Symposium participants - to be in a place like Cape Sounion and to have so much good science to listen to instead of laying on the beach! This is a real price for real knowledge! Therefore, let me finish with what I said at the very beginning - another book by Gregory and Brenda and another success.

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Carbohydrate Mimics. Concepts and Methods. Yves Chapleur, Ed. John Wiley & Sons, Inc. 605 Third Avenue, New York, NY 10158-0012, 1998. xxviii, 604 pp., illustrations. \$190.00.

Carbohydrate Mimics is a collection of 29 short review chapters originating from two conferences held on the subject in 1995 (France) and 1996 (Italy). Carbohydrate mimics/mimetics are generally thought of as analogs of naturally occurring carbohydrates in which one of the two oxygen atoms of an acetal moiety, i.e., either the glycosidic oxygen atom or the ring oxygen atom has been replaced with a carbon, nitrogen, or sulfur atom. Other analogs, viz., analogs of carbohydrate sulfates and phosphates, are also covered in the book. For the most part, the compounds covered are C-glycosyl compounds or so-called "azasugars", i.e., carbohydrates in which the ring

oxygen atom has been replaced with a -NH or -NR group. They are generally analogs of biologically active compounds or of substrates of enzymes involved in important physiological processes. Frequently these compounds are designed to block recognition signals or to inhibit carbohydrate processing enzymes in order to impact such biological processes as cancer/tumor growth, immune/inflammatory responses, and viral and bacterial growth. Two chapters deal with shapes of the mimics. The remainder cover either (1) design of, and synthetic strategies for, analogs of specific compounds or classes of compounds or (2) application of a specific approach to synthesis of analogs.

Glycobiology as a field has grown dramatically over the past 3 decades as the biological importance of carbohydrates and glycoconjugates has been revealed. This has led to determination of structures of important compounds, synthetic strategies for those compounds, and synthetic strategies for analogs/mimics. During the same period, structures of other compounds with potent biological activities have been determined and synthesized using carbohydrates as chiral synthons; examples are the marine cyclic ethers. The synthetic approaches are the subject of this book. A growing number, but relatively few, chemists have been involved with this chemistry. Many of the leaders, especially those from Europe, are contributors to this collection.

There have been previous reviews on C-glycosyl compounds and "azasugars" and a book on the former subject. However, this is a useful overview of the field of carbohydrate mimics. It is a reference book, rather than a book to be read from cover to cover, in part because there is no obvious order to the chapters. Because of that, the index will be most useful. Chapters are relatively free of errors. Some problems with nomenclature were noticed, e.g., use of designations such as β -D-mannose.

The book is a useful source of information and reference on this important subject. It is recommended to all interested in synthetic strategies for carbohydrate mimics.

Books Received

Analysis

Fractals in Chemistry. Walter G. Rothschild. John Wiley & Sons Inc., 605 Third Ave., New York, NY 10158-0012, 1998. x, 231 pp., illustrations. \$69.95.

GC/MS. A Practical User's Guide. Marvin McMaster and Christopher McMaster. John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, 1998. xi, 167 pp., illustrations. \$59.95.

Receptor Binding Techniques volume 106. Mary Keen, Editor, The Humana Press, 999 Riverview Drive, Suite 208, Totowa, New Jersey 07512, x, 283 pp., illustrations, \$79.50.

Biomaterials

Biorelated Polymers and Gels. Controlled Release and Applications in Biomedical Engineering. Teruo Okano, Ed. Academic Press, 525 B Street, Suite 1900, San Diego, CA 92101, 1998. xvi, 257 pp., illustrations. \$95.00.

Biopolymers at Interfaces. Surfactant Science Series volume 75. Martin Malmsten, Ed. Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016. ix, 645 pp. illustrations. no price listed.

Organic/Inorganic Hybrid Materials. Richard M. Laine, Clément Sanchez, C. Jeffrey Brinker, Emmanuel Giannelis, Eds. Materials Research Society, 506 Keystone Drive, Warrendale, PA 15086, 1998. xi, 415 pp., illustrations. \$81.00.

Nanostructured Powders and Their Industrial Application. Materials Research Society, 506 Keystone Drive, Warrendale, PA 15086, 1998. xi, 316 pp., illustrations. \$55.00 (member) and \$63.00 (nonmember).

Porous and Cellular Materials for Structural Applications. Daniel S. Schwartz, Donald S. Shih, Anthony G. Evans, and Haydn N. G. Wadley, Eds. Materials Research Society, 506 Keystone Drive, Warrendale, PA 15086, 1998. xi, 324 pp., illustrations. \$79.00.

Cancer Therapy

Antiangiogenic Agents in Cancer Therapy. Beverly A. Teicher, Ed. Humana Press, 999 Riverview Drive, Suite 208, Totowa, NJ 07512, 1999. xi, 450 pp., illustrations. \$145.00.

Antifolate Drugs in Cancer Therapy. Ann L. Jackman, Ed., The Humana Press, 999 Riverview Drive, Suite 208, Totowa, New Jersey 07512, 1999. x, 456 pp., illustrations. \$145.00.

Computational Chemistry

Reviews in Computational Chemistry, Volume 12. Kenny B. Lipowitz and Donald B. Boyd, Eds., John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, 1998. xiii, 403 pp., illustrations. \$120.00.

Microscopic Simulation of Interfacial Phenomena in Solids and Liquids. Simon R. Phillpot, Paul D. Bristowe, David G. Stroud, and John R. Smith, Eds. Materials Research Society, 506 Keystone Drive, Warrendale, PA 15086, 1998. xiii, 410 pp., illustrations. \$71.00.

Drugs and Chemicals

Peptidomimetics Protocols. Wieslaw M. Kazmierski, Ed. Humana Press, 999 Riverview Dr., Suite 208, Totowa, NJ 07512, 1999. xxx, 549 pp. illustrations. \$89.50.

On the Pill. Elizabeth Siegel Watkins. John Hopkins University Press, 2715 N. Charles St., Baltimore, MD 21218-4319, 1998. viii, 183 pp., illustrations. \$25.95.

Access to Experimental Drugs in Terminal Illness-Ethical Issues. Udo Schüklenk, Pharmaceutical Products Press, an imprint of The Haworth Press, Inc., 10 Alice Street, Binghamton, NY 13904-1580, 1998. x, 228 pp. \$49.95 (5+ copies \$29.95).

Medicinal Plants of the World Chemical Constituents, Traditional and Modern Medicinal Uses. Ivan A. Ross, Humana Press, 999 Riverview Drive, Suite 208, Totowa, New Jersey 07512. xi, 415 pp., illustrations. \$99.50.

1001 Chemicals in Everyday Products, second edition. Grace Ross Lewis, John Wiley & Sons, Inc. 605 Third Avenue, New York, NY 10158-0012, x, 308 pp., \$29.95

Immunology

Atlas of Immunology. Julius M. Cruse and Robert E. Lewis. CRC Press LLC, 2000 Corporate Blvd. N.W., Boca Raton, FL 33431, 1999. ix, 451 pp., illustrations. \$69.95.

(The *Atlas of Immunology* is designed to provide a pictorial reference and serve as a primary resource for the most up-to-date and thorough illustrated treatise available in the complex science of immunology. This book contains more than 1,000 illustrations and depicts essentially every concept of importance in understanding the subject matter of immunology—from Preface).

Molecular and Cellular Basis of Inflammation. Humana Press, 999 Riverview Drive, Suite 208, Totowa, NJ 07512, 1999. xii, 338 pp., illustrations. \$125.00.

Molecular Biology and Biotechnology

Pichia Protocols. David R. Higgins and James M. Cregg, Eds. Humana Press, 999 Riverview Dr., Suite 208, Totowa, NJ 07512, 1998. xi, 270 pp. illustrations. \$74.50.

Integration of Pharmaceutical Discovery and Development. Case Histories. Ronald T. Borchardt, Roger M. Freidinger, Tomi K. Sawyer, and Philip L. Smith, Eds. Plenum Publishing Corporation, 233 Spring St., New York, NY 10013-1578, 1998. xxix, 607 pp., illustrations. \$125.00.

Organic Reactions

Named Organic Reactions. Thomas Laue and Andreas Plagens. John Wiley & Sons, Inc. 605 Third Avenue, New York, NY 10158-0012, x, 288 pp., illustrations. \$69.95.

The CH/π Interaction. Evidence, Nature, and Consequences. Motohiro Nishio, Minoru Hirota, and Yoji Umezawa. John Wiley & Sons, Inc., 605 Third Avenue, New York, NY 10158-0012, 1998. xiii, 217 pp., illustrations. \$90.00.

(The CH/π bond is the weakest among the hydrogen bonds, but has been found in a variety of substances to play important roles in their physical, chemical, and biological properties — from Preface).

Organic Reactions. Vol. 53. Leo A. Paquette, Editor-in-Chief. John Wiley & Sons, Inc. 605 Third Avenue, New York, NY 10158-0012, 1998. vii, 654 pp., illustrations. \$95.00.

Pharmacy Practice

Non-Prescription (OTC) Medications Tables and Algorithms of Methods for Counseling the Patient. A Handbook for Pharmacists, Pharmacy Students and Consumers. Augustine S. Aruna. Whittier Publications, Inc., 20 West Park Avenue, Long Beach, NY 11561, 1995. 106 pp. Paper. \$23.50.

Handbook of Basic Pharmacokinetics . . . including Clinical Applications. 5th Edn. Wolfgang A. Ritschel and Gregory L. Kearns. American Pharmaceutical Association, 2215 Constitution Avenue, NW, Washington, DC 20037-2985, 1999. xiv, 563 pp., illustrations. Paper. \$49.00.

Statistical Experimental Design

Pharmaceutical Experimental Design Drugs and the Pharmaceutical Sciences, volume 92. Garreth A. Lewis, Didier Mathieu, and Roger Phan-Tan-Luu, Eds. Marcel Dekker, Inc., 270 Madison Avenue, New York, NY 10016, 1999. vi, 489 pp., illustrations, \$175.00.

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