Book Reviews

Chemoinformatics, Concepts, Methods, and Tools for Drug Discovery. Edited by Jurgen Bajorath. Humana Press Inc., Totowa, NJ. 2004. xiii + 524 pp. 15.5 × 23.5 cm. ISBN 1-588-29-261-4. $125.00.

High-throughput screening (HTS) and combinatorial chemistry produce mountains of data. Inevitably, to find the "needles in the haystack", informatics was developed, and "all the information resources that a scientist needs to optimize the properties of a ligand to become a drug" (Brown 1998) is a practical definition of chemoinformatics. Rather than set a theme and develop it, the editor elected to focus on authors who have made contributions to the field and provided them a great degree of freedom in choosing their topics. Consequently, each of the individual chapters can be read instructively in isolation.

The first two chapters describe the theoretical basis of the concepts of molecular diversity and similarity. Chapters 3−5 describe a Web-based chemoinformatics system for drug discovery and its practical application to HTS. Chapter 5 outlines various strategies for the identification and generation of informative compound sets. These chapters especially are valuable for the nonexpert medicinal chemist and are full of practical information.

Chapters 6−11 focus on the derivation and use of "descriptors" used in QSAR and include questions to ask when performing a QSAR study and determining screening strategies. Chapters discussing methods of partitioning libraries to design sets of compounds for screening and the design of combinatorial chemistry libraries for a given target class with the problems of chirality and conformational flexibility and the development of novel scoring methods are included. The chapter on the prediction of druglike properties and the development of computational models to predict CYP liabilities is of particular interest in drug discovery with its critical need to be able to predict metabolic stability/liability as early as possible.

Overall, the book is a fine attempt to provide medicinal chemists with a "how-to" guide to chemoinformatics and how to use it in drug discovery and contains informative chapters on topics that are difficult to find elsewhere. The book provides a wealth of excellent reference material and is a worthwhile addition to the library of most computational chemists and to medicinal chemists, especially those chapters that deal with the practical aspects of drug discovery.

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Annual Review of Pharmacology and Toxicology. Volume 44. Edited by Arthur K. Cho, Terrence F. Blaschke, Paul A. Insel, and Horace H. Loh. Annual Reviews, Palo Alto, CA. 2004. viii + 647 pp. 15.5 × 23.5 cm. ISBN 0-8243-04.44-6. $74.00.

This book is another in the long-running, high-quality series. It consists of 23 reviews written by individual authors or groups of authors on a wide variety of topics of current interest. The volume also includes a subject index and a cumulative index of contributing authors (Vols. 40−44) and a cumulative index of chapter titles (Vols. 40−44).

All of the chapters are interesting and important. However, several chapters were of particular interest to this reviewer: (1) Predicting Human Drug Glucuronidation Parameters: Application of in Vitro and in Silico Modeling Approaches, (2) ErbB Receptors: Directing Key Signaling Networks throughout Life, (3) Novel Angiogenic Signaling Pathways and Vascular Targets, (4) DARPP-32: An Integrator of Neurotransmission, (5) "β-Adrenergic Receptors and Regulation of Energy Expenditure: A Family Affair, (6) The Role of Calpain in Oncotic Cell Death, (7) CRF and CRF Receptors: Role in Stress Responsivity and Other Behaviors, and (8) Membrane Trafficking of G-Protein-Coupled Receptors. There are also two chapters on pharmacokinetics/pharmacodynamics that are of general interest: (i) The Integration of Pharmacokinetics and Pharmacodynamics: Understanding Dose-Response and (ii) Sex Differences in Pharmacokinetics and Pharmacodynamics. It could be said that there is something for everyone in this volume.

This book is certainly to be recommended as an addition to the series in library collections. Individual medicinal chemists may also want this book in their personal collections, particularly for the chapters that discuss detailed studies of the mechanism of drug action and the functioning of many neurotransmitter systems. The chapters are extensively referenced, and thus, they provide substantial resources and entrances to the primary literature. This book is definitely a fine effort on the part of the authors and the editors.

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Molecular Biology in Medicinal Chemistry. Edited by Th. Dingermann, D. Steinhilber, and G. Folkers. Wiley-VCH, Weinheim, Germany. 2004. xxi + 413 pp. 17.5 × 24.5 cm. ISBN 3527304312. $195.00.

Molecular biology has left an indelible mark on medicinal chemistry. The way in which chemists discover and optimize leads is heavily dependent on the use of modem molecular techniques to clone and overexpress protein targets as well as to screen for biological activity. This volume approaches the subject of medicinal chemistry from a fundamentally different point of view, emphasizing the importance of molecular biology in the drug discovery process.

The authors have elected to organize the book in four parts, each composed of several detailed chapters. The first part discusses the identification of molecular targets using high-throughput assays based on gene expression, antibody technology, and highly sensitive fluorescence and bioluminescence techniques. This section also provides an introduction to the development and use of knock-out mice and other transgenic organisms. Part 2 begins with a chapter devoted to biotransformations and the use of enzymes to conduct stereoselective synthesis. There follows a detailed discussion of nucleic acid drugs, such as antisense, and includes newer subjects such as RNAi. Part 3 is composed of chapters devoted to important separation techniques, such as affinity chromatography and chiral separations, then it leads into a discussion of protein crystalization, NMR in drug discovery, and isotopic labeling of proteins for NMR studies. Finally, Part 4 is organized into three chapters that provide detailed discussions concerning pharmacogenomics and toxicology.

In all, the book touches on some of the trendiest subjects that interface to form the frontier of modem medicinal chemistry. The chapters are written in sufficient detail to go well beyond the scope of an undergraduate text, and perhaps they are most appropriate for graduate students in need of breadth of coverage and terminology. This text would also be highly recommended for established medicinal chemists in need of an introductory or refresher course in the many applications of molecular biology in medicinal chemistry.

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Protein Crystallograpy in Drug Discovery. Edited by Robert E. Babine and Sherin S. Abdel-Meguid. Wiley-VCH Velag GmbH & Co., Weinheim, Germany. 2004. xvi +262 pp. 17 × 25 cm. ISBN 3527306781. $175.00.

Protein Crystallography in Drug Discovery is Volume 20 in the series "Methods and Principles in Medicinal Chemistry", edited by R. Mannhold, H. Kubinyi, and G. Folkers. The aim of this volume is to "... provide a forward looking overview of the use of protein crystallography in drug discovery". The volume is organized on the lines of what you might find at a modern symposium on drug discovery or in a session at a crystallography meeting in that there are chapters that are concerned with case studies, as well as contributions describing emerging methodologies. A number of the chapters are very well written and would serve as an excellent introduction to their subjects.

The first part of the volume deals with the case studies of a wide range of accessible drug discovery targets, including chapters on nuclear hormones, kinases, the proteasome, the ribosome, cathepsin K, and Cdk4. The central two chapters are concerned with biotechnology-based approaches, that of the use of a generalized method for studying serine proteases involving the protein ecotin, and the formation of "orthogonal ligand−receptor pairs" to design either small molecules or mutant proteins. The final chapters are methodological, discussing techniques for engineering proteins to enable crystallization and subsequent structure-based design, with a chapter describing the use of high-throughput techniques to identify lead compounds and accelerate the development of clinical candidates. The final chapter deals with the emerging field of microcrystallization, a topic of much interest to pharmaceutical companies who may need to produce reliable supplies of protein crystals from a wide variety of sources.

The quality of the individual chapters of this volume is high, and each of the contributors is to be commended for their efforts. In particular, the chapter by Adams, Veal, and Shewchuk dealing with kinases and their emerging role as targets for therapeutic intervention is not only well written but is a very nice introduction to the structural biology of this important enzyme class. Anyone who is attempting to become familiar with the kinases would be well served by a read of this chapter. In addition, Hansen's chapter on how ribosome antibiotics interact with their target is a fine introduction to this complicated subject.

The dedication of an entire volume in a series on medicinal chemistry may signal the "coming of age" of both protein crystallography and structural biology as tools for drug discovery. However, since there is not an agreed upon methodology for the use of these techniques, it is clear that this field will continue to evolve and mature. If there is a disappointment in this volume in this series on medicinal chemistry, it is that there is not a unifying concept or process presented that describes their use in structure-based drug design. Given the state of the art, however, it could be that there actually is not a single proscribed manner with which to use these tools in drug discovery.

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