Book Reviews

Combinatorial Library Design and Evaluation. Edited by Arup K. Ghose and Vellarkad N. Viswanadhan. Marcel Dekker Inc., New York. 2001. xv + 631 pp. 16 × 23.5 cm. ISBN 0-8247-0487-8. $195.00.

Combinatorial chemistry is an integral component of the modern medicinal chemist's drug discovery toolbox that has evolved rapidly since 1990. Initially, generation of libraries containing the greatest number of compounds was the preferred approach, but it is now accepted that all libraries and compounds are not created 'equal'. This book deals with the principles, software tools, and applications in drug discovery and is an excellent introduction to the appropriate design and evaluation of combinatorial chemistry libraries.

The book is organized in four parts and contains 20 chapters contributed by scientists from academia and industry. Part I describes the concepts of combinatorial library design and strategies for implementation, issues relating to library design, and the importance of clearly understanding the purpose of the library, be it to expand the diversity of a screening library, to find a lead for a specific target, or to improve an existing lead.

Part II (Chapters 2−7) describes the principles used in the design of combinatorial libraries covering such topics as phamacophore modeling, QSAR/3D-QSAR and fast continuum electrostatic methods for structure-based ligand docking, and how to develop and use appropriate scoring functions to evaluate the library. All the presently used techniques are represented and well-described although some chapters are mathematically 'heavy', an approach that may well present a challenge for traditional medicinal chemists.

Part III (Chapters 8−15) describes the current methods and software tools used in combinatorial library design with particular emphasis on druglikeness and its use in both the library design and as a filter in data mining. Chapter 8, in particular, provides a very useful step-by-step guide for identifying factors to be evaluated when designing the most appropriate combinatorial library.

Part IV (Chapters 16−20) illustrates some applications of the principles and methods described in the earlier chapters and introduces some of the algorithms used effectively, especially genetic algorithm directed lead generation and other machine-learning techniques. Also, the need to integrate the design and synthesis of the library in order to ensure the most cost-effective combinatorial library is appropriately emphasized.

Overall, the book is a very fine attempt to provide chemists with a guide to the power and the pitfalls of combinatorial chemistry libraries. It provides a wealth of excellent reference material and is an essential addition to the library of medicinal chemistry departments both in academia and industry, but I believe that the most enthusiastic audience will be the chemists in computer modeling departments rather than the medicinal bench chemists—who will still look to their computational colleagues, or their own experience and intuition, to provide the answer to 'which compound will be the best drug'.

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The Nitro Group in Organic Synthesis. By Noboru Ono. Wiley-VCH, New York. 2001. xvi + 372 pp. 16 × 24 cm. ISBN 0-471-31611-3. $130.00.

This book is another in the "Organic Nitro Series" that has been produced under Henry Feuer as Managing Editor for Wiley-VCH. Since the book is an addition to a series, it is not intended to be comprehensive regarding the chemistry of nitro organic compounds. Rather, the emphasis is on recent advances in organic synthesis utilizing nitro compounds. There is a particular emphasis on new methods of synthesis of organic nitro compounds that use environmentally friendly methods for nitration (highlighted in Chapter 2). Recent developments that have established aliphatic nitro compounds as important synthetic intermediates are also highlighted, especially those where stereoselective transformations are possible, e.g., stereoselective Henry reactions and asymmetric Michael additions. There is also a focus on use of nitroalkenes as heterodienes in tandem [4 + 2]/[3 + 2] cycloadditions and radical denitration. More conventional reactions involving organic nitro compounds are included, but they are treated with less emphasis.

The book is composed of 10 chapters. Chapter 1 is a brief introduction. Chapter 2 describes synthetic methods. Chapters 3−9 descibe reactions that utilize organic nitro compounds as key components: the nitro-aldol (Henry) reaction; Michael addition; alkylation, acylation, and halogenation of nitro compounds; conversion of nitro compounds into other compounds; substitution and elimination of NO_2 in $R-NO_2$; cycloaddition chemistry of nitro compounds; and nucleophilic aromatic displacement. Chapters 9 and 10 concentrate on synthesis of heterocyclic compounds—in which strategy is very valuable, especially with regard to electron-rich ring systems such as pyrroles and indoles.

The structures and reactions in the book are clearly drawn and are an asset to the narratives. Literature citations are extensive, and they provide a significant resource for ready access to the primary literature. This book is a valuable addition to institutional libraries and to the personal library of those scientists who are

actively engaged in organic synthesis. This book is highly recommended.

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Chiral Intermediates. Edited by Cynthia A. Challener. Ashgate Publishing, Burlington, VT. 2001. xxiii + 804 pp. 18 × 25 cm. ISBN 0-5660-8412-0. $295.00.

The heart of this book is an alphabetical tabulation of over 4700 commercially available chiral intermediates, with each entry accompanied by a structure, a formula, and a listing of suppliers. Additional information (for example, alternate or formal names, CAS registry numbers, melting point, and specific rotation) is provided for some compounds. The tabulation is followed by a useful list of manufacturers and suppliers of chiral intermediates and an index of compound names/synonyms. The book begins with four short chapters (just over 100 pages) introducing chiral chemistry. Chapter 1, "Overview of Chirality", is set at a very basic level. Chapter 2 contains a very brief description of some of the factors encouraging use of chiral intermediates. The third chapter provides an overview of typical sources of chiral intermediates (the chiral pool, resolutions, and asymmetric syntheses), while the fourth chapter provides selected examples of methodology for preparation or isolation of chiral compounds. Although references are current (many through 1999 and a few through 2000), a substantial number are to four books listed as "further reading".

It is difficult to visualize the niche that this book will occupy. The first four chapters do not provide sufficient depth to recommend this book as an introduction to preparation or isolation of chiral intermediates. While the extensive tabulation of chiral intermediates could be useful in terms of serendipitous discovery, the overall utility is questionable in light of the ready availability of structure-driven databases.

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Methods in Enzymology. Volume 340. Drug—Nucleic Acid Interactions. Edited by Jonathan B. Chaires and Michael J. Waring. Academic Press, New York. 2001. xxxiv + 705 pp. 16 × 23.5 cm. ISBN 0-12-182241-9. $129.95.

This volume is packed with timely reviews of methods for investigating the interactions of small molecules with DNA and RNA. The first 14 chapters (Section I. Biophysical Approaches) cover tools such as NMR, X-ray crystallography, molecular modeling, scanning force microscopy, surface plasmon resonance, and calorimetry. Section II, covering chemical and molecular biological approaches, includes chapters on covalent drug—DNA interactions, footprinting, and design and synthesis of DNA-targeting agents. The last five chapters are not quite so easily categorized. There is one on targeting telomerase, one on high-throughput engineering of sequence-specific zinc fingers, one on topoisomerase inhibitors, one on HIV-1 integrase assays, and one on the use of Xenopus egg extracts to study effects of DNA-binding drugs on chromatin assembly, nuclear assembly, and DNA replication.

Most of the chapters would be better described as "reviews", but a few recapture the "methods" style of the original volumes. For example, the chapter "Drug Interactions with Nucleosomes and Chromatin" has step-by-step procedures for isolation of chromatin and nucleosome core particles from chicken blood, as well as protocols for binding isotherms, footprinting, sedimentation analysis, and circular dichroism analysis.

Some chapters show the biases of their authors. The NMR, X-ray, and molecular modeling chapters, for example, deal only with DNA; the surface plasmon resonance chapter deals only with RNA.

This volume will be of considerable value to those interested in the interactions of small molecules with nucleic acids.

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Goodman and Gilman's The Pharmacological Basis of Therapeutics. 10th Edition. Edited by J. G. Hardman, L. E. Limbird, and A. G. Gilman. McGraw Hill, New York. 2001. xxvii + 2148 pp. 21 × 26 cm. ISBN 0-07-1354469-7. $125.00.

The first edition of this text was released some 60 years ago, and it reinforced pharmacology as a unique discipline. This 10th edition synthesizes and integrates the last five years of revolutionary advances in the biomedical sciences into a contemporary best-practices of pharmacotherapy. It also witnesses the passing of the last namesake, Alfred G. Gilman. The foremost intent of this rich resource is to elevate the "push button physician" to the level of the discerning clinician. The book offers the foundation for informed drug individualization: "Each therapeutic encounter must be considered an experiment with a hypothesis that can be tested."

The chapter-by-chapter book layout follows that of the ninth edition. While the depth of references for each chapter is variable, an appropriate inclusion of late-breaking primary literature punctuates each. The first

five chapters address general principles of pharmacology, and these are followed by 61 chapters assigned to drug classes. An excellent complement of figures helps simplify an advanced understanding of pharmacodynamic mechanisms. The text closes with two chapters on toxicology, followed by a 100 page compendium of pharmacokinetic parameters.

The introductory pharmacokinetics chapter would benefit from a more comprehensive overview of metabolic drug interactions, transporter dynamics, and pharmacogenomics, all supported by summary tables. Discussion of bioavailability should more clearly address extent and rate of absorption, as specified by the FDA. The index, though quite extensive, occasionally omits significant terms found in the text, e.g., ion trapping, enterohepatic recycling, arylhydrocarbon receptor, flavanoids, β-carbolines, and "fractional availability".

"Goodman and Gilman" remains an indispensable reference and text for the medicinal chemist.

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