Book Reviews

Combinatorial Library Methods and Protocols. Edited by Lisa Bellavance English. Humana Press, Totowa, NJ. 2002. xi + 383 pp. 16 × 23.5 cm. ISBN 0-86093-980-3. $99.50.

Over the past 10−12 years, combinatorial chemistry has evolved from the initial concept of the generation of libraries containing the greatest number of compounds to one in which combinatorial libraries address different needs and to the realization that "a combinatorial library only brings value when screened". This book deals with the methods and protocols involved with the design, synthesis, quality control, and screening of combinatorial libraries produced primarily by solid-phase synthesis, and it is an excellent "how to" book for the appropriate design and evaluation of combinatorial chemistry libraries.

The book contains 21 chapters, contributed by scientists mainly from industry. Part I (Chapters 1−12) describes the concepts of combinatorial library synthesis and control with particular emphasis on quality control, preparation of encoded combinatorial libraries, tools for parallel solid-phase synthesis, and finally automated structure verification of small-molecule libraries.

Part II (Chapters 13−16) focuses on the critical issues of library purification and screening, covering such topics as the resolution of racemic mixtures, the development of libraries for the extraction of metal ions, and automated purification techniques. In addition, the merits and limitations of both on-bead and solution based screening approaches are discussed.

Part III (Chapters 17−21) describes the current methods and software tools used in combinatorial library design, with particular emphasis on druglikeness, and it includes such germane topics as virtual combinatorial library design and reagent-based vs product-based combinatorial strategies. This section highlights the importance of clearly understanding the purpose of the library, be it to expand the diversity of a screening library or to find a lead for a specific target or to improve an existing lead.

Overall, the book is a fine attempt to provide chemists with a "how to" guide to the design, construction, and use of combinatorial libraries, at least as far as solid-phase synthesis is concerned. Unfortunately, little or no mention is made of the use of solution-based combinatorial library methodologies, a technique with some significant advantages in terms of versatility but also having its own unique challenges. The book is well written and I particularly like the inclusion of the practical protocols that are included in most chapters. In addition, the book contains informative chapters on topics that are difficult to find elsewhere, specifically simple tools for parallel synthesis and the chapter on the use of host−guest chemistry to design artificial receptors using dynamic combinatorial chemistry methods. The book provides a wealth of excellent reference material and it is a worthwhile addition to the library of most medicinal chemists. However, I believe that the most enthusiastic audience will be those already committed to the solid-phase synthetic approach to combinatorial libraries.

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Medicinal Chemistry: Principles and Practice. Second Edition. Edited by F. D. King. The Royal Society of Chemistry, Cambridge, U.K. 2002. xxii + 450 pp. 15.5 × 23.5 cm. ISBN 0-85404-631-3(PB). £39.50.

This is an excellent book with many useful insights for the medicinal chemist engaged in drug discovery/development. As expected in a book of 20 chapters written by 28 different authors, there is some overlap of topic coverage but not enough to detract significantly from the high quality of the book. Of the 28 authors, 25 are from the pharmaceutical industry, primarily from GlaxoSmithKline; the remainder are from academia. There is a thorough list of abbreviations and five appendices with useful information such as a list of receptor agonists/antagonists and conversion tables helpful for the medicinal chemist. The structures are well-drawn, and in only one chapter (Chapter 3) are drug trade names used without the corresponding generic names. For most of the book chapters, the primary literature through 2001 is covered. The volume includes a seven-page index.

The title of the book chapters are the following: Drug−Receptor Interactions, An Introduction to Ion Channels, Intracellular Targets, Enzyme Inhibitors, Biological Evaluation of Novel Compounds, Pharmacokinetics, Drug Metabolism, Toxicology in the Drug Discovery Process, Chemical Development, Physicochemical Properties, Quantitative Structure−Activity Relationships, Computational Chemistry and Target Structure, Patent Medicine, An Introduction to Molecular Biology, Strategy and Tactics in Drug Discovery, Combinatorial Chemistry: Tools for the Medicinal Chemist, The Identification of Selective 5-HT_{2C} Receptor Antagonists: A New Approach to the Treatment of Depression and Anxiety, The Identification of the HIV Protease Inhibitor Saquinavir, The Discovery of Vioxx (Rofecoxib), and NK1 Receptor Antagonists.

The chapter titles give a reasonable idea of the content of the book. In the first chapter, there is a compact but sophisticated discussion of the mathematics of drug−receptor interactions. In the chapter "Biological Evaluation of Novel Compounds", one could argue that it might be prudent first to evaluate a lead compound in an animal model to establish proof-of-concept before one undertakes pharmacokinetic/metabolic studies. In the chapter on computational chemistry, the author rightly points out the commonly overestimated contribution of hydrogen bonds to ligand−receptor interac-

tions. Although certain topics such as molecular biology, combinatorial chemistry, pharmacokinetics, and pharmaceutical patents, particularly the first two, are adequately covered in numerous recent reviews, the chapters on pharmacokinetics and pharmaceutical patents are really well done and are most useful for someone unfamiliar with these topics. In future editions of the book, one would welcome an expansion of the excellent chapter on development chemistry. As indicated by their titles, the last four chapters in the book provide a number of illustrative case examples of successful drug design and development.

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