Book Reviews

Analytical Methods in Combinatorial Chemistry. By Bing Yan. Technomic Publishing Company, Inc., Lancaster, PA. 2000. xv + 268 pp. 15.5 × 23.5 cm. ISBN 1-56676-809-8. $199.95.

This book is the first comprehensive treatise covering all aspects of the complex problem of analysis of combinatorial chemistry libraries. The focus of the book is primarily on the application of analytical methods to solid-phase organic synthesis. However, since in many cases the analysis phase is frequently conducted in solution following cleavage from the resin support, the majority of the methods are also applicable to solution-based combinatorial chemistry libraries. The book is organized into nine chapters. Chapter 1 outlines the history and development of combinatorial chemistry and the analytical challenges that this technology presents. Chapter 2 discusses the features of resin supports and illustrates how their physical properties have a direct impact on the design of the library, optimization of reaction conditions, and synthetic schemes. Chapters 3−5 deal with various aspects of reaction optimization, with each chapter being devoted to the use of a specific type of analytical method, e.g., FTIR, MS, NMR, and other spectroscopic methods. Chapter 6 deals with the issue of quality control, which is a particular challenge in combinatorial chemistry, since the biological screening of minimally purified libraries causes significant problems. Chapters 7 and 8 focus on the basic driver for combinatorial chemistry, namely the selection and subsequent optimization of active lead compounds from the combinatorial chemistry libraries. The author also critiques the present method of selecting/optimizing "*hit*" compounds where in vitro potency is the prime criterion, and the "hit" is then manipulated to provide satisfactory drug-like properties. In contrast, compounds that are expected to have drug-like properties but are only moderately active in vitro are seldom considered for optimization. Chapter 9 provides a glimpse into the immediate and long term challenges for the area, particularly the incompatibility between parallel synthesis and serial analysis and purification, and emphasizes that a major breakthrough is needed in the coming years to resolve this basic problem. Overall, I found the book to be well written and very readable. I particularly liked the inclusion of tables, directly comparing the advantages and limitations of each analytical method. This reviewer also applauds the organization of each chapter which follows the general format of background, description of technique(s), examples, and summary. The book is well referenced with current material and it will be a very useful source for chemists involved in combinatorial chemistry as well for those proposing to enter the field.

The material presented in the book should stimulate research to solve some of the major challenges that are well defined by the author, and it should also provoke questions about the wisdom of current lead selection/optimization practices. The book is an essential addition to the library of anyone wishing to obtain a good overall review of the field of combinatorial chemistry and of its evolution and future development.

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Antimalarial Chemotherapy: Mechanisms of Action, Resistance, and New Directions in Drug Discovery. Edited by P. J. Rosenthal. Humana Press, Totowa, NJ. 2001. xi + 396 pp. 18 × 26 cm. ISBN 0-89603-670-7. $135.00.

With contributions from 41 different authors, this book provides a welcome collection of short reviews covering numerous topics in antimalarial chemotherapy. After a perusal of the coauthor list, one immediately makes the unsettling observation that only one of the coauthors is employed in the pharmaceutical industry, although this does not materially compromise the utility of the book. For most of the book chapters, the primary literature through 1999 seems to be covered, although in a few, one or two 2000 references are cited. The volume includes a 12-page index.

The book begins with a short introductory chapter followed by a brief chapter on the history of antimalarial drugs. Chapters on transport and trafficking in *Plasmodium*-infected red cells, the *Plasmodium* food vacuole, and antimalarial drug resistance from a clinical and public health perspective comprise the remainder of the "Introduction" section of the book. The second section of the book, "Established Antimalarial Drugs and Compounds Under Clinical Development", begins with fairly extensive chapters on 4-aminoquinolines/quinolinemethanols and 8-aminoquinolines. The up-to-date coverage of the 8-aminoquinolines is timely, considering the recent discovery and development of tafenoquine. Next we find a welcome review of quinoline resistance which, in part, reconciles the often disparate primary literature on this subject. The final two chapters in the section cover the antifolates and semisynthetic artemisinins. The third section of the book, "New Compounds, New Approaches, and New Targets", begins with chapters on novel quinolines and trioxane/endoperoxide antimalarials, followed by a chapter on antibiotics and the plasmodial plastid organelle as a potential drug target. The next chapter presents some intriguing observations on antimetabolite antimalarial drug design. Chapters on iron chelators, protease inhibitors, inhibitors of phospholipid metabolism, and new malaria

chemotherapy based on parasite-induced transport pathways complete this final section of the book.

Although certain drug classes such as antimalarial 4-aminoquinolines and artemesinins/peroxides (particularly the latter) are more fully covered in numerous recent reviews, the editor has made good his intention that "this book will offer a useful review for those who study malaria and, more importantly, an entry point into antimalarial chemotherapy for those new in the field."

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The Story of Taxol. Nature and Politics in the Pursuit of an Anti-Cancer Drug. By Jordan Goodman and Vivien Walsh. Cambridge University Press, Cambridge, U.K. 2001. xiii + 282 pp. 15.5 × 23.5 cm. ISBN 0-521-56123-X. $27.95.

This book details the convoluted, torturous, and controversial path from the National Cancer Institute's early experiences with a variety of natural products with anti-cancer potential that led to the collection of samples of the Pacific yew tree, *Taxus brevifolia*, by Arthur Barclay on August 21, 1962, to the discovery that a component, taxol, of this tree had clinically useful activity against several kinds of cancer, and finally to the Food and Drug Administration's approval of the marketing of taxol as an anti-cancer drug on December 29, 1992. Under the terms of the Waxman-Hatch Act, Bristol-Myers Squibb was granted five years of exclusive marketing rights to the drug. As of 1998, taxol was the best-selling anti-cancer drug ever with worldwide sales of $1.2 billion. It has revolutionized the treatment options for advanced forms of breast and ovarian cancers and some types of leukemia, and it shows promise for treating AIDS-related Kaposi's sarcoma.

Each step in taxol's journey from the forest to its current utility in the treatment of cancer has been fraught with exceptionally difficult challenges. These challenges have been addressed by botanists, biologists, chemists, pharmacists, clinicians, and others. All have contributed greatly to the success of this product. United States governmental agencies, particularly the National Cancer Institute (NCI), provided the initiative for the whole process and managed and funded the first 30 years of taxol's research and development. Certainly, they deserve major credit for this success story. The establishment in 1955 of the Cancer Chemotherapy National Service Center (CCNSC) within the NCI in response to the United States Congress' directive "to explore the feasibility of an engineered, directed extramural research program in the chemotherapy of acute leukemia" was an early critical juncture that enabled the collection and screening of a large number of plant extracts and triggered the whole process that led to the discovery of this major drug product.

Each step in the biological development of taxol from the initial screening of plant extracts for antitumor activity, to establishment of its unique mechanism of action, to its screening in specially bred nude mice infected with human cancers, to recognition of its clinical effectiveness required a "leap of faith" and considerable funding. Even final recognition of taxol's effectiveness in treating patients with refractory ovarian cancer suggested a response rate of less than 20%. The chemistry of taxol was equally demanding; it is a complex molecule with seven asymmetric centers. Although several groups have achieved total synthesis of the molecule, semisynthesis devised by similarly challenging chemistry is presently employed for large-scale preparation. Until the mid-1990s, however, extraction and purification of taxol with about 0.01% isolation from the bark of the Pacific yew served as the main source for its development. Thus, supply was a major obstacle. Further, the tree is especially slow-growing, and it is destroyed when the bark is removed. This led to major concerns, especially to environmental activists, about the consequence of the removal of large numbers of trees from the forests and also of its resultant impact on the spotted owl. The American public was overwhelmed with news reports about this exciting new drug and its effect on the ecology. The formulation of taxol, which is insoluble in water and biological fluids, in a form suitable for administration presented its special challenge. The transfer of the drug from government to private industry has presented its own set of controversy and problems. Even the naming of taxol has been controversial. Wall had given this name to the bioactive compound from the bark of *Taxus brevifolia* in 1967. Nevertheless, the Patent and Trademark Office approved taxol as the registered trade name, hence taxol became Taxol®, and paclitaxel was approved as the generic name.

The book is very clearly written, and it is extremely well referenced. It has a complete list of references following each section and concludes with cumulative author and subject indexes. The authors have presented *The Story of Taxol* by a method referred to as actor-network theory. This has enabled them to organize a large amount of material, oral and verbal, published and unpublished, in a comprehensible and fascinating manner. The entire history of taxol has been researched with exceptional thoroughness. In many cases, this has enabled presentation of the thinking and motivations of the major players in the story of this drug product. The overall result is a truly captivating one. I found the book entertaining, enjoyable, and educational reading from cover to cover. I recommend it for all, especially those concerned with drug research and development.

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New Trends in Synthetic Medicinal Chemistry. Methods and Principles in Medicinal Chemistry, Volume 7. Edited by Fulvio Gaultieri. Wiley-VCH, Weinheim, Federal Republic of Germany. 2000. xvi + 354 pp. 17 × 24.5 cm. ISBN 3-527-29799-5. DM 248.00.

As the seventh addition to this eight-volume set, this book breaks with the computational medicinal chemistry tradition of the other seven volumes and presents medicinal chemistry in its purest form: synthetic medicinal chemistry. The volume contains a balanced collection of contributions from academic and industry experts covering new trends in synthetic chemistry relevant to drug synthesis.

The book opens with an introduction from the editor, highlighting the chemistry addressed in the forthcoming contributions. The next chapter on series design in synthetic chemistry falls more within the realm of computational methods; this topic has already been handled in some of the other volumes in this series, but was probably included here for reasons of completeness. The main message of the chapter is that the familiar Craig plots have been computationalized and that this should be of interest to synthetic medicinal chemists. The third and fourth chapters deal with combinatorial chemistry on solid phases, and they overlap to some extent in their content. Nevertheless, they provide a good overview of solid-phase methods. Lacking is a discussion of the use of homogeneous multicomponent synthesis in combinatorial chemistry. The next chapter on stereoselective synthesis begins with an introduction to the classification system selective, followed by a very useful series of examples of how these methods have been set to work in the synthesis of enantiomerically pure drugs. The next chapter deals with the relevant topic of enantiomeric separation, and it provides an excellent overview of current methods employed in the resolution of enantiomeric mixtures. Chapter 7 details biocatalytic reactions in the synthesis of drug intermediates; not only is it a well-developed overview of the field but it also provides lists of enzyme sources and suppliers. The last two chapters deal with synthetic methods for glycosides and oligonucleotides, two topics which have recently undergone a renaissance of activity. The chapter on glycosidation reactions provides practical synthetic examples, but no mention is made of the recent advances in solid-phase synthesis. The last contribution is an outstanding review of the chemistry of antisense oligonucleotides, with 466 references to both classic and recent work.

As is usual for this series, the book is well edited, and the reaction schemes and figures are professionally presented. However, the 4+ page subject index is only marginally adequate. Chapter literature citations are generally up-to-date to 1998 and are numerous (1300+ in all). The strength of this volume lies not in the most recent citations but rather in the completeness with which most of the topics have been handled; the chapters aim to present a solid, in-depth review of each area. The book should be well received by both graduate students and scientists who wish to orient themselves in one of the fields covered in the volume. The book is a very worthwhile contribution and can be recommended for the libraries of all medicinal chemists.

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High Throughput Synthesis. Principles and Practice. Edited by Irving Sucholeiki. Marcel Dekker, New York. 2001. xxi + 366 pp. 15.5 × 23.5 cm. ISBN 0-8247-0256-5. $175.00.

Combinatorial chemistry and high throughput synthesis have, in recent years, become standard techniques utilized by medicinal chemists in the pharmaceutical industry. However, the majority of the books on these subjects do not cover the practical aspects of the methods used in the synthetic manipulations. In most cases, these texts are compilations of potential scaffolds for further modification. This book, on the other hand, is a practical guide to the subject. The book is organized into four sections: (i) theory and methods in solid phase synthesis; (ii) high throughput synthesis in drug discovery; (iii) high throughput synthesis of new materials and catalysts; and (iv) new directions in high throughput synthesis.

The first section covers the historical development of solid supported organic synthesis from Merrifield to the present. It also addresses the characteristics of various supports: porosity, loading capacity, and swelling properties in common solvents. This is followed by analytical techniques used to determine the progress of a reaction on solid support. The next section begins with an introductory chapter which explores the development of high throughput synthesis in the pharmaceutical industry over the past decade. This is followed by chapters on producing compound libraries for biological screening, purification strategies, and automation of the synthetic process. Throughout these chapters, "case studies" are presented. These are practical experimental procedures used as teaching examples. These case studies are very useful, and they accomplish the editor's stated goal of producing a cookbook for combinatorial synthesis. The third section covers the application of combinatorial/high throughput concepts to dielectrics, ferroelectrics, and catalyst development. This section also includes case studies as teaching tools to increase the reader's understanding of the material. In the fourth and final part, newer techniques which are under current development are presented. These include the potential of "lab on a chip" technology and chemical synthesis chips, chemical and biological sensors, and the use of magnetic separation and ultrasonic mixing in high throughput synthesis.

This is an extremely useful text which should be in every library. The text is an excellent reference for the

practitioner, and it will be a welcome addition to graduate courses on the subject.

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From Bench to Market: The Evolution of Chemical Synthesis. By Walter Cabri and Romano Di Fabio. Oxford University Press, New York. 2000. xvi + 266 pp. 19 × 24.5 cm. ISBN 0-19-850383-0. $24.95.

Pharmaceutical development in an era of cost containment brings on new challenges. One is the price of production of generic and proprietary products using large-scale syntheses. Another is the array of synthetic schemes that are permitted or, alternatively, blocked by the existence of patents.

Cabri and Di Fabio attempt to address these issues in this volume, but they are only partially successful in doing so. Comprising 11 chapters, the book begins with a consideration of modern process research and development. Four chapters on individual antibiotics and one chapter each on an NSAID, an angiotensin II antagonist, an antiviral, and an antineoplastic follow. Each chapter begins with an introduction and a brief discussion of mechanism of action before launching into the merits and drawbacks of various synthetic routes to each product. But the highly detailed, narrowly focused consideration of production processes for only a few individual classes of NCE's, as well as the extensive treatment of their patent issues, suggest that the authors obtained this information for their own specific interests, rather than for the purposes of a volume directed to a general audience. To that extent, the book is insufficiently general and, therefore, less valuable as "essential reading for graduate and undergraduate chemists intending to work in the pharmaceutical industry" as claimed by the publishers. A further problem is the tendency of the authors to editorialize regarding the legitimacy of the cited patents: "(t)his purification procedure is 'the trick' that the industrial producers did not disclose in their patents and publications" (p 177). Inasmuch as failure to disclose "best mode" is grounds for patent invalidation, this is a serious charge, indeed. Nevertheless, the emphasis on patents does make this volume of interest to chemists, patent attorneys, and patent agents who are engaged in "design around" strategies to circumvent proprietary synthetic procedures.

Despite the reservations noted above, there is interesting information in this reasonably priced, well-produced book. A welcome addition would have been a chapter that classifies and summarizes the chemical group transformations discussed in the individual chapters.

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Annual Review of Pharmacology and Toxicology. Volume 41. Edited by Arthur K. Cho, Terrance F. Blaschke, Paul A. Insel, and Horace H. Loh. Annual Reviews, Palo Alto, CA. 2001. vii + 934 pp. 15.5 × 24 cm. ISBN 0-8243-0441-1. $65.00.

Identification of compounds that exhibit useful pharmacological and toxicological activity in order to discover drugs is the purpose of medicinal chemistry. An intelligent approach to drug discovery requires a detailed understanding of the biology of the systems being treated, as well as of the behavior of the potential drug and its metabolites in the body. This Annual Review series provides up-to-date reviews of specific topics of current interest. Volume 41 consists of 33 well-written articles ranging from topics such as "Metabolism of Fluorine-Containing Drugs" and "The Basic and Clinical Pharmacology of Nonpeptide Vasopressin Receptor Antagonists" to "Use of Biomarkers and Surrogate Endpoints in Drug Development and Regulatory Decision Making: Criteria, Validation, Strategies" and "Drug Treatment Effects on Disease Progression". Each of the articles includes extensive references to the recent literature, and the book has a reasonable subject index. It also has a useful index of chapter titles for volumes 37−41 of the series, arranged by topic. Although an individual might not be inclined to purchase this book despite its very modest price, every library connected with drug research should include this Annual Review series. This series is one of the prime places for becoming and remaining current in a specific research area. In addition, the articles are short enough (20−30 pages) so that they may be browsed, just to extend general knowledge of current drug research.

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