Book Reviews

Fundamentals of Early Clinical Drug Development. From Synthesis Design to Formulation. Edited by A. F. Abdel-Magid and Stéphane Caron. John Wiley & Sons, New York. 2006. xv + 323 pp. 16 × 24 cm. ISBN 0-471-69278-6. $99.95.

The volume originated from a process chemistry symposium organized jointly in 2003 by the Organic and Medicinal Chemistry Divisions of the American Chemical Society, but its scope extends beyond the bounds of that symposium to review many other aspects of drug development. There are 15 chapters, including 6 on recent advances in synthetic process chemistry and 9 on other aspects of early drug development. Ample illustrations and well-selected references enhance the value of most of the chapters. The balance is good between real process chemistry, which does not make an appearance until 100 fascinating pages of synthetic organic and medicinal chemistry have gone by, and pharmaceutical development, the discussion of which begins a further 115 pages later. Chapters are written by the great and the good of the U.S. pharmaceutical industry and give a lot of insight into how synthetic problems are tackled in order to provide a viable commercial synthesis and why it is sometimes not possible to make a suitable formulation despite best efforts. Edward Grabowski opens with a reflection on his many years at Merck in an ever-changing industry and gives valuable insights into several drug development processes, including the failures. Case studies of synthesis optimization, including several that involved varying degrees of difficulty with asymmetry, provide a rich source of material for the medicinal and organic chemist. There are excellent chapters on intellectual property, laying out in a simple way what is and is not patentable, on outsourcing as a guide for the unwary, on automation and the changing face of process research, and on the synthesis and use of radioisotopes in pharmaceutical development. Large-scale synthesis is given an engineering perspective. The problems of drug formulation are well addressed in chapters covering selection of drug forms, strategies to achieve the appropriate particle size of active pharmaceutical ingredients, and challenges in turning drug substance into drug product.

The book will give a lot of pleasure and information to the medicinal chemist, the synthetic organic chemist, and anyone involved in taking a drug candidate to the stage of pharmaceutical formulation. One small gripe, however, is that I opened it on a false premise, expecting that it would address the issues of early clinical development in the sense of phase I and early phase II studies in healthy human volunteers and patients, respectively. In fact, the major clause of the title is entirely misleading, and the essence of the book lies in the small print of the minor clause. Nowhere is clinical development, early or late, a subject for discussion. Nevertheless, a jolly good read despite my misgivings.

Roger M. Pinder

Pharma Consultant
5 Monkgate Cloisters
York YO31 7HY, U.K.

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Combinatorial Chemistry: From Theory to Application. Second Revised Edition. Edited by Willi Bannwarth and Berthold Hinzen. Wiley/VCH, Weinheim, Germany. 2006. xxii+ 629 pp. 15.5 × 24.5 cm. ISBN 3527306935. $205.00

This book is the 26th volume in a series of valuable specialized monographs on topics pertaining to drug discovery. Following the development of combinatorial chemistry around 1985, for many years the field was sharply divided between the solid-phase vs the solution-phase advocates. To many observers both groups seemed either to ignore the other or to strive to prove their own superiority by highlighting the limitations and disadvantages of the other approach. Also, there was a tremendous amount of hype that created the expectation that combinatorial chemistry would provide much needed drugs solely because of the vast numbers of compounds that could be generated. Fortunately, in recent years the two competing technologies have become far more mature and complementary. Combinatorial chemistry is now recognized as being one more valuable tool for modern medicinal chemists in their endeavors to discover and develop new drugs, and it also has applications in many other areas beyond pharmaceutical research.

This book is part of a highly regarded, well-established series, and it is updated from the original 2000 version, with significant new additions. The volume editors have provided a nice balance of chapters covering aspects of both technologies, and the contributing authors come from both academia and industry.

This volume still is weighted toward solid-phase organic synthesis with increasing development of different chemistries being adapted to solid-phase synthesis. However, Chapter 1 is a comprehensive description of the purification principles in high-speed solution-phase synthesis, long recognized as the major hurdle in the solution-phase approach, with the goal of automating such procedures. Chapter 2 describes the wide variety of available linkers and approaches in solid-phase organic synthesis. Chapters 3−5 describe various types of bond-forming reactions including some involving many common heterocycles. Chapters 6−8 cover the presently available reagent preparation encoding strategies and automation, while chapter 9 describes a variety of computer-assisted approaches to library design, a particularly important area because the field has progressed from simply a random numbers generating technology to one of smaller focused libraries for specific purposes.

Chapter 10 provides a comprehensive description of the complementary technology of high-throughput screening assays and the various types that are appropriate together with their advantages and applicability of each type of assay. The appendix provides a very useful set of Web sites and chemoinformatics resources applicable to combinatorial chemistry that are essential, as modern scientists recognize that the Internet is an invaluable tool for us all.

I found the highlighted specific and detailed experimental procedures that are in each chapter and cover all aspects of the combinatorial chemistry technologies particularly helpful. Individual chapters provide ample useful illustrative examples and up-to-date appropriate literature references. This volume is an excellent addition to the series, and it will become a standard reference text for chemists, particularly those involved in drug discovery.

In such an excellent book it is a pity that the foreword by the editors is so full of obvious typographical errors that appear to have been introduced in the editing process.

Jan W. F. Wasley

Simpharma LLC
1, Stone Fence Lane
Guilford, Connecticut 06437

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Microwave Assisted Organic Synthesis. Edited by Jason P. Tierney and Pelle Lidstrom. Blackwell Publishing, Oxford, U.K. 2005. xi + 280 pp. 18 × 21 cm. ISBN 0-8493-2371-1. £89.50.

The editors have put together excellent overviews and surveys of the field of microwave-assisted organic synthesis, incorporating both theoretical and experimental aspects. The book comprises nine chapters written by an international team of leading experts, mainly from academia. The clear advantage of microwave-assisted synthesis over conventional heating methods in terms of phenomenal increases in reaction rates and significant improvements in product yields and purity is evident throughout the book. References cited cover the literature up to 2003 in all but one chapter where a few 2004 references are included.

Chapter 1 gives a brief introduction to the beginnings of microwave-assisted heating and a discussion of the theoretical aspects and covers the phenomenon of microwave dielectric heating and the characteristics of materials, such as solvents, that determine the degree of interaction with microwave radiation and the magnitude of thermal energy generated. For the most part the chapter is well written, but the tables could have done with a little more coordination. It is also unclear how some of the values in the tables relate to the loss tangents equation in the text. This notwithstanding, the chapter is instructive.

Chapter 2 considers the use of microwave-assisted heating in dramatically accelerating the rates of transition metal catalyzed synthetic reactions. A very good survey is presented covering primarily palladium-catalyzed couplings involving C−C and C−N bond formation. A brief coverage of applications to $Mo(CO)_6$ catalysis of asymmetric allylic alkylations and carbonylative couplings is also added, as is a subsection on carbonylative coupling with dimethylformamide as a CO releasing agent. The chapter is well written, but it left out comparative data that would give the reader a clear sense of the degree of superiority of the microwave-assisted reaction to the conventional one.

Chapter 3 covers the use of microwave heating in heterocyclic syntheses, giving an overview of recent uses of microwave synthesis in the construction of heteroaromatic systems, starting with five-membered rings containing one heteroatom and covering common heteroaromatic systems, including fused systems with one or more bridge nitrogens. A wide variety of examples is given, and once again the remarkable reaction rate and yield increases are highlighted. The increasing use of solvent-free reactions in microwave-assisted synthesis is also featured in the chapter.

Chapter 4 reviews microwave-assisted reduction reactions. The preference for nonvolatile sources of hydrogen is pointed out with several examples. The use of solid supports in lieu of solvents in facilitating microwave-assisted reductions is discussed. The increasing use of microwave heating in the preparation of some catalysts, not only for the speed with which they are obtained but also for better catalytic activity, is also covered. Examples are also given to illustrate the enabling power of microwave heating for difficult reductions.

Chapter 5 covers the application of microwave heating to the speeding up of multicomponent one-pot reactions. After a short introductory terminology/definitions section, various important multicomponent name reactions such as Hansch, Bignelli, Ugi, and Kindler reactions, Gewald synthesis, and Mannich and Pauson−Khand reactions are discussed. This is followed by an extended discussion of miscellaneous multicomponent reactions used to prepare a variety of nitrogen heterocycles.

Chapter 6 covers the integration of microwave flash heating with polymer-supported synthesis. The first part of the chapter focuses, inter alia, on microwave heating, heat distribution, reacting species transport or diffusion properties, and solvent characteristics. The effects of microwave heating on polymer swelling and its effects on reactant and product interactions with the support are also discussed. After a brief consideration of the use of microwave heating for polymer drying, the authors present examples of polymer-supported reactions, including reductive aminations, nitro aldol reactions, alkylations, Wittig reactions, acylations, and Heck reactions, as well as a whole variety of reactions used to prepare specific compounds, and applications in enzyme catalyzed synthesis. The use of microwave-assisted heating in catch and release chemistry is also discussed, as well as applications in high-throughput compound library synthesis.

Chapter 7 is related somewhat to Chapter 6 in that it considers microwave-assisted reactions with solid-supported reagents. Unlike Chapter 6, this chapter is focused on solid-phase synthesis where reagents are linked to polymeric material. Appropriate equipment is also briefly discussed, which is then followed by numerous examples of a wide variety solid-phase reactions.

Chapter 8 deals with quantitative aspects of increases in reaction rates associated with microwave-assisted synthesis. The author provides quantitative comparisons of times required to conduct the reactions in the conventional way with the times it takes to conduct the same reactions under standardized conditions. Tables are provided of the comparisons, but the tables are not self-explanatory.

The final chapter is concerned with scale-up issues in microwave-assisted organic synthesis. In addition to scale-up, safety issues are also discussed.

Starting with Chapter 1, the controversy as to whether there are nonthermal effects of microwave energy interaction with reaction components that contribute to the dramatic increases in rates and course of reactions is raised often. The consensus appears to be that there has not been enough experimentation to make firm conclusions in this regard.

Overall, this is a well-written, concise book on this fledgling but fast growing field of microwave-assisted organic synthesis. The book does a good job of showcasing the enormous potential (waiting to be harnessed) of microwave-assisted synthesis. There are overlaps in coverage among some of chapters, but they do not detract from the utility of the book. The book is replete with many good examples of the reactions to which microwave heating has been successfully applied, and the chapters are well referenced. The book also includes a useful index. It will be an important addition to the few books on this relatively new aspect

of modern organic synthesis. Students of organic chemistry should find it useful as well.

John K. Buolamwini

Department of Pharmaceutical Sciences
College of Pharmacy
University of Tennessee Health Science Center
847 Monroe Avenue
Memphis, Tennessee 38163

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Computer Applications in Pharmaceutical Research and Development. Edited by Sean Ekins. John Wiley & Sons, Inc., Hoboken, NJ. 2006. xix + 805 pp. 16 × 24 cm. ISBN 0-471-73779-8. $125.00.

This book is an addition to the "Wiley Series in Drug Discovery and Development", edited by Binghe Wang. The volume is rather broad, encompassing multiple research, development, management and information technology applications, and considerations relating to computers in the pharmaceutical research and development (PR&D) enterprise. The book has been divided into eight parts, beginning with a general overview (three chapters) that sets the tone for the remainder of the book. The first of these chapters, by Boyd and Marsh, reminds us how far we have come, with amusing anecdotes of the early days of computer-aided drug discovery (CADD). Chapters on computers in preclinical development and statistical modeling in PR&D complete Part I. Part II is entitled "Understanding Diseases: Mining Complex Systems for Knowledge" and contains an interesting chapter on mining historical herbal texts for bioactive leads by Buenz along with nice chapters on putting the real impact of bioinformatics on preclinical drug and vaccine development in greater context and an overview of systems (biology and pharmacology) approaches for PR&D.

The five chapters of Part III are about handling of scientific information and how that can (or should) enhance productivity. Information management topics, from multiple perspectives, are the core of these chapters. A timely chapter describing implementation of electronic laboratory notebooks in PR&D by Nehme and Scoffin is included. In Part IV the more usual topics in a book of this nature are covered, i.e., "Computers in Drug Discovery". However, the six chapters of Part IV are more focused on PR&D and less on academic issues. The consistent theme is the need to enhance commercial value of discoveries through, above all, accuracy and validation of computer methods. Part IV also contains a comprehensive, very readable, and well-referenced summary of computer-aided design success stories by Kubinyi. Part V contains five well-written chapters on computers applied to preclinical development, covering issues from metabolism, toxicity, disposition, and PK/PD to trial design.

Part VI (two chapters) is concerned with economic issues in decision making for PR&D. Part VII focuses on computer issues related to clinical development, including a chapter by Weinberg on regulatory concerns, particularly by the U.S. Food and Drug Administration, for computer systems.

Last, Part VIII is entitled "Further Applications and Future Development". This is more than a catchall of leftover topics, but it includes chapters on pharmaceutical formulation, intellectual property protection of innovative uses of computers in PR&D, ethics of computing, and expert systems for contextual hyperlinking, and it concludes with a visionary chapter on the future of PR&D computing.

In summary, this is a well-put-together volume with a lot of very interesting and timely information to convey. The breadth of topics it handles is large, and this could be perceived as a fault; but I believe that all topics are handled at an appropriate level. Many in the PR&D enterprise could learn from this text and broaden their own perspective. It would be a nice addition to individual, academic, and industrial libraries.

Glen E. Kellogg

Department of Medicinal Chemistry
School of Pharmacy
Virginia Commonwealth University
Richmond, Virginia 23298-0540

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Organic Synthesis. State of the Art 2003−2005. By Douglas F. Taber. John Wiley and Sons, Inc., Hoboken, New Jersey. 2006. ix + 216 pp. 16 × 24.5 cm. ISBN 0-470-05331-3. $99.95.

This book is a compilation of 103 Organic Chemistry Highlights columns posted on the Internet (http://www.organic-chemistry.org) in 2004 and 2005. For the reader unfamiliar with the Internet-published Organic Chemistry Highlights columns, each column is a brief overview or summary of developments in a particular area of organic synthesis up to the time of posting. As such, this book affords a useful platform for these weekly highlights by providing a single hardcopy compilation with subject/transformation and senior author indexes. This book will certainly be of interest to chemists looking for a portable overview of highlights in organic transformations reported in 2003−2005. The summaries are brief, and they direct the reader to primary literature references. The book is somewhat less functional than the Web-based versions of the summaries where direct links to the online journal articles are provided. The timely significance of the Highlights columns is also somewhat lost with hardcopy publication of brief summaries for transformations published up to nearly 4 years ago. For all readers of *Journal of Medicinal Chemistry* involved in the synthesis of bioactive molecules, the weekly Internet posting of Organic Chemistry Highlights is certainly suggested reading. The hardcopy compilation of past highlights represented in this book is likely of most interest to the dedicated scholar of synthetic chemistry and to students, as an excellent survey of modern synthetic transformations. Advantages and disadvantages of online versus hardcopy access to these past columns are left to individual readers and their personal choice.

Robert J. Kerns

Division of Medicinal and Natural Products Chemistry
College of Pharmacy
University of Iowa
Iowa City, Iowa 52242

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