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Book Review

Natural Products. Drug Discovery and Therapeutic Medicine Edited by Lixin Zhang and Arnold L. Demain. Humana Press, Totowa, NJ. 2005. xiv + 384 pp. 18.5 × 26 cm. ISBN 1-58829-383-1. $135.00.

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This book presents a timely review of basic and applied aspects of natural products, with a particular emphasis on those of microbial origin. The book is divided into five parts. Part I is written by the editors and discusses fundamental aspects related to natural-product-based drug discovery, with emphasis on microbial antibodies. The editors stress the need to combine the wide diversity of natural product discovery with modern technologies such as high-throughput screening, integrative and systems biology, combinatorial biosynthesis, and combinatorial chemistry to provide future pharmaceutical success. Part II contains five chapters that cover strategies for drug discovery from microbial natural products, including integrated approaches, automated HPLC analyses, genetic metabolite manipulation, genomics/bioinformatics, and strain improvement by gene shuffling engineering. Part III discusses specific groups of drugs. The first chapter provides an overview of anticancer drugs from prokaryotes, plants, and marine sources. The next two chapters specifically cover taxoids/vinca alkaloids and terpenoids as therapeutic agents. The fourth chapter in Part III discusses the current status of traditional Chinese medicine in the pharmaceutical industry. Part III ends with a chapter on the history, clinical use, and mechanism of action of the antileukemic arsenic trioxide. Part IV discusses new methods for access to both microbial diversity for small-molecule discovery and the genomes of uncultivated microbes for novel natural products. Part V contains three chapters dealing with specific sources of new plant and microbial natural products: marine actinomycetes, rain forest endophytes, and traditional Ecuadorian medicine.

The editors have brought together noted experts in various fields of natural products to explore the history and wide diversity of natural products, to detail integrative approaches and methodologies in the discovery of bioactive products, and to discuss specific groups and sources of natural products. They emphasize that a successful past and present certainly inspire a bright future for therapeutic discovery from natural products.

In summary, this book will be an important addition to the library of practicing medicinal, organic, and natural products chemists who are involved in drug discovery, development, and therapeutic uses.

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Name Reactions and Reagents in Organic Synthesis. Second Edition. By Bradford P. Mundy, Michael G. Ellerd, and Frank G. Favaloro, Jr. Wiley-Interscience, Hoboken, NJ. 2005. xv + 882 pp. 16 × 24 cm. ISBN 0-471-22854-0. $89.95.

This compendium of organic chemistry name reactions and reagents ushers the 1988 first edition into the contemporary laboratory. Countless references are given to 2004 literature and, on occasion, to 2005 literature! Reactions are formatted in an outline fashion, first giving a general depiction followed by proposed mechanism(s). Then salient features of the chemistry are succinctly noted, and finally examples are given. The comprehensive name reaction section occupies most of the book. The reagents section offers a more selective listing, and most entries reference the Encyclopedia of Reagents for Organic Synthesis of 1995. However, this section meaningfully contributes to the field by updating the application of these reagents to post-1995 chemical literature.

The reaction mechanisms proposed for each name reaction offer uncommonly explicit step-by-step detail, facilitating the prediction of how general each reaction may be. Very few reaction intermediates are taken for granted, and molecular orbital theory is accorded its place. The strict accounting of atoms, ions, and electrons in the illustrated mechanisms, in addition to a tutorial-like but unobtrusive punctuation with chemical termi nology, provides excellent theory for advanced chemistry students. Name Reactions and Reagents in Organic Synthesis serves equally well as a key reference for the professional chemist.

The name reactions are systematically cross-referenced and consolidated by reaction type. Though there is little text in this structure-intensive book, important concepts regarding asymmetric induction depart from the outline format. Molecular stereoviews utilize only traditional conventions. The two pages assigned to solvents in the reagents section should have been omitted or expanded to at least include fundamental chemical properties. The index does not include a classification of reactions by type of compound synthesized.

Name Reactions and Reagents in Organic Synthesis compiles and organizes the most significant organic synthesis advances to date, and presents these in such a definitive mechanistic context that this book belongs in all academic and research environments engaged in organic chemistry.

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Frontiers in Medicinal Chemistry. Volume 2. Edited by Atta-ur-Rahman and Allen B. Reitz. Bentham Science Publishers, Ltd., Hilversum, The Netherlands. 2005. xii + 606 pp. ISBN 90-77527-01-X. $130.00.

This series is a further addition to the existing four major comprehensive multivolume medicinal chemistry review compendia (*Annual Reviews in Medicinal Chem-*

istry, "*Burger*", *Progress in Medicinal Chemistry*, and *Comprehensive Medicinal Chemistry*) and to the more than half-dozen books on drug design that have appeared in the past few years. It is the second volume of *Frontiers in Medicinal Chemistry*, a series that, according to its stated "Aims and Scope", is "devoted to the review of ... all areas of medicinal chemistry." The present volume, as described in a prefatory editorial, is "a collection of 26 updated articles ... previously published in the top medicinal chemical journals ... divided according to disease groups."

Written by 70 authors from academic and industrial laboratories in the U.S., the EC, Australia, Israel, Korea, Switzerland, and Taiwan, the reviews consider infectious diseases (Chapter 2), cardiovascular diseases (Chapter 1), CNS disorders (Chapter 4), endocrine disorders (Chapter 4), oncology (Chapter 5), other targets and new approaches (Chapter 4), and enabling technologies (Chapter 5). Although a detailed consideration of this wealth of information is beyond the scope of the present review, I found the chapters on PPAR science by Shearer and Hoekstra, farnesyl transferase inhibitors by Dinsmore and Bell, and NKT cell targets for autoimmune disease by Wilson and Van Kaer to be of special interest. The book is moderately priced considering its size. It is well written and edited and attractively printed and produced by the publisher, and the 20-page index makes it easy to find topics of interest. The chapters are well documented with timely references; the discussion of the neurobiology of nitric oxide by Contestable and coauthors is supported by more than 500 references.

Although this volume would appear to have numerous attractive features of ostensible interest both to individual readers and to institutional libraries, one has to wonder whether there is meaningful justification for the existence of this type of publication. All of these reviews have been previously published, and their citation information and abstracts can be identified and retrieved online through Medline. Likewise, full texts of all of the reviews can be retrieved online through infotrieve.com and downloaded for a $12 service fee and a cost of $50, identical to the Copyright Clearance Center charge for all photocopies made from the volume itself. Under these circumstances, institutions and individuals alike will have to decide whether the acquisition of a recycled collection is appropriate in an era of increasing information costs.

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Organic Reaction Mechanisms. 2000. Edited by A. C. Knipe. John Wiley & Sons, Ltd., Chichester, West Sussex, England. 2004. ix + 667 pp. 15.5 × 23.5 cm. ISBN 0-470-85439-1. $565.00.

The current volume represents the 36th addition to this series since its inception. This contribution summarizes original high-quality research related to the study of organic reaction mechanisms from the literature dated from December 1999 to December 2000. The chapters include reactions of aldehydes and ketones, acids (e.g., carboxylic, phosphoric, and sulfonic), radical reactions, oxidation and reduction, carbenes and nitrenes, nucleophilic and electrophilic aromatic substitutions, carbocations, carbanions, nucleophilic and electrophilic aliphatic substitutions, elimination reactions, polar addition, and cycloaddition reactions. Nineteen expert investigators have contributed to the current volume. This is a highly comprehensive compilation of the literature, consisting of 15 chapters covering several organic reaction mechanisms. However, some notable exceptions are evident (e.g., photochemical reactions, biosynthesis, electrochemistry, organometallic chemistry, surface chemistry, and heterogeneous catalysis) because it has been appropriately acknowledged that these topics are adequately reviewed in other specialized publications, and therefore, inclusion in this publication would have been redundant. In addition, the editor (A. C. Knipe, University of Ulster, Northern Ireland) has impressively reviewed and ensured that relevant literature was allocated to the appropriate chapter and not reiterated. Also, besides the normal table of contents for the entire volume, each individual chapter possessed its own summary of contents to allow the rapid location of specific topics of interest by the reader. In addition, the volume editor has highlighted organic reaction mechanisms that result in diastereomeric/enantiomeric products, with the appropriate notations in the margins. Finally, it was highly impressive and helpful that the volume editor provided a complete author index for every article that was referenced in the volume, allowing specific researchers to be rapidly identified.

The editor has done an exceptional job of providing an in-depth comprehensive compilation of published research on organic reaction mechanisms for December 1999 to December 2000. Presently, with the availability of on-line databases (e.g., SciFinder, Beilstein, etc.) it may be argued that this detracts from the significance of the current collection, since utilizing available on-line databases for identification of approaches for the preparation of individual compounds or necessary synthetic transformations has been highly effective. However, with these search engines the identification of literature relevant for individual organic reaction mechanisms and their effect on specific synthetic strategies can be cumbersome. Therefore, this volume is an important contribution to the knowledge base of organic chemistry via a mechanistic approach. In addition, the tremendous amount of information and expert analysis provided makes this a valuable reference source, especially since subscription fees for commercially available databases can be prohibitive for some companies and academic concerns.

Overall, the contributing authors have provided well-written and expert reviews on their individual topics. A couple of the chapters (e.g., Chapters 7 and 8) were somewhat limited (only 10 pages and approximately 50 references). However, Chapter 15, which reviewed molecular rearrangements, was extremely detailed and complete, with 125 pages and almost 500 relevant references all compiled by one contributor. All of the chapters were carefully detailed with illustrations that assist in conveying the reaction mechanisms and were integrated well with the corresponding text.

It is obvious that this volume would be prohibitively expensive for an individual researcher's collection, but

such a comprehensive compilation of the literature is recommended for institutional libraries as a valuable reference source. This publication would be especially encouraged if previous volumes are already in the research organization's possession.

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Chemoinformatics in Drug Discovery. Methods and Principles in Medicinal Chemistry. Volume 23. Edited by R. Mannhold, H. Kubinyi, and G. Folkers. Wiley-VCH Verlag GmbH, Weinheim, Germany. 2005. xxii + 493 pp. 17 × 25 cm. ISBN 3-5273-0753-2. $185.00.

This is a well-written, up-to-date, and practical book for medicinal chemists and computational chemists working in drug discovery. It will give medicinal chemists a feel for how chemoinformatics methods may help their projects and help computational chemists and other practitioners to place their current methodologies into a larger context. The book is well referenced, with many 2003 and 2004 references. Typographical errors are few. There is a good subject index but no author index.

A broad definition of chemoinformatics is taken, encompassing the disciplines of structure-based design, pharmacophore design and discovery, molecular similarity, and QSAR. Theory and methods are well reviewed; several chapters refer to the recent advance by Oprea and others in characterizing "leadlike" vs "druglike" structures and the advantages of focusing on the former. But equally as valuable are the real-world examples of use of these techniques in projects at most major pharmaceutical laboratories, as well as in academia and research institutes.

The book begins with a personal view from a pioneer in computational approaches to drug discovery, Garland Marshall, and ends with a recounting of Donald Abraham's successful discovery of almost-drugs (submitted for FDA approval) in an academic setting. In between are a four-chapter section on virtual screening, three chapters on hit and lead discovery, four chapters on databases and libraries, and four chapters on applications. Following are some highlights of individual chapters.

Garland Marshall nicely shows the importance of chemoinformatics by estimating (in some detail) that the patent for enalaprilate ACE inhibitors encompasses over 59 trillion structures! Clearly, a project chemist could benefit from computational tools in choosing which of these may be active or worth synthesizing.

In the virtual screening section, Tudor Oprea discusses where drug discovery may have gone wrong and offers a practical discussion of chemoinformatics-based drug discovery strategies. Michael Hann et al. discuss GlaxoSmithKline's treatment of virtual (possible), tangible (commercially available or synthetically accessible), and real (in hand) chemical samples to find drug leads. Michael Rarey et al. give a wide-ranging view of algorithmic engines in virtual screening, effectively categorizing and describing algorithms for molecular docking, structural alignment, molecular similarity, and pharmacophore mapping (only occasionally resorting to equations) and showing advantages and disadvantages of each method. This wide-ranging review (56 pages, 298 references) concludes with an impressive number of prospective studies, generating micromolar or submicromolar leads in each case cited. Finally, Dragos Horvath et al. apply pharmacophore-based virtual screening to Cox2 activity in order to illustrate strengths and weaknesses of this approach.

The hit and lead discovery section features a chapter on Wyeth's complex approach to screening selection, and examples of its success by McFayden et al.; a very nice review of molecular diversity methods for designing discovery and focused libraries by Cavallaro et al.; and a discussion by Ho of a software package, RACHEL, for optimizing weak-binding lead compounds in an automated, combinatorial fashion.

The databases and libraries section features WOMBAT (World of Molecular Bioactivity), an annotated database of chemical structures and biological activities by Oprea et al.; and Metaphonic's Cabinet, a federated collection of databases of chemical structures, biological activities, protein−ligand interactions, metabolic pathways, and other interesting information, all available for integrated search strategies over the Web. Kenny and Sadowski describe Astra-Zeneca's tools for dealing with practical issues of protonation, formal charges, tautomerism, and nitrogen inversion to improve database search results, and Savchuk et al. recount their rational design of GPCR-specific combinatorial libraries.

In the chemoinformatics applications section, Maggiora et al. describe tools used at Pharmacia and precursor companies for selecting commercially available compounds to expand and complement an in-house sample collection. Baringhaus and Matter review methods for simultaneously optimizing affinity, selectivity, and pharmacokinetics of leads, and recount successful uses of these approaches by Aventis and others. Goodnow et al. nicely enumerate the tools and issues relating to hit-to-lead projects and recount Roche's experience with their integrated methods, called RADDAR (Roche adaptive drug design and refinement). Finally, Alex Tropsha demonstrates how QSAR models with variable selection can be used for virtual screening of chemical databases and virtual libraries, provided that the QSAR model is properly validated and used within its applicability domain by methods recounted here.

What comes across most clearly in this book is that lead discovery and optimization remain brutally challenging endeavors, resulting in failure much more often than in success; and that the chemoinformatics methods described herein, and the insights resulting from their application, can provide a leg up in bringing a drug discovery project to a successful conclusion.

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