Book Reviews

Bioorganic Chemistry: Peptides and Proteins. Edited by Sidney M. Hecht. Oxford University Press, New York. 1998. x + 532 pp. 17 × 24.5 cm. ISBN 0-19-508468-3. $75.00.

This book is the second in a series of texts on the subject of bioorganic chemistry written for organic chemistry graduate students. The chapters are contributed by experts in their fields and largely meet the expectations of the intended audience with overviews of topics ranging from the basics of peptide structure and synthesis to catalytic antibodies and peptidomimetics. Most chapters begin with introductory information and progress to informative case studies and detailed examples drawn from the individual chapters authors' research. The balance between text and research review differs with the individual chapters, but most should be able to satisfy readers of all levels and backgrounds. The text has a considerable number of references through 1997, but the chapters are not comprehensive reviews. Overall, the topics are chosen well, and the book is an excellent introduction to the field.

The first chapter (Axley) presents a general overview of peptides and proteins at an elementary level, unfortunately with little connection to the remaining chapters. Hruby and Meyer give a concise, up-to-date summary of peptide synthesis in Chapter 2 that leads nicely into the following review (Fitzgerald and Kent) in which the chemical ligation method for synthesizing proteins from smaller peptide precursors is described. Shively's review in Chapter 4 discusses the structural analysis of proteins via Edman degradation, chromatographic methods, and mass spectrometry. Chapters on protein structure follow (Carter and Liu, Rizo, Gierasch) and are illustrated with several relevant case studies. The lack of color figures could undermine the value of these chapters, but the authors and editor have chosen excellent gray-scale images that adequately show the points made in the text.

The theme of structural chemistry is continued in Chapter 7 (Massiah, Blake, and Summers) with specific examples of the zinc finger motif. Chapter 8 (Gertl) probes enzyme-catalyzed proton-transfer reactions. Chapter 9 (Loida, Hernan, and Sligar) concentrates on PCR and cassette methods for site-directed mutagenesis with a focus on techniques while including examples from the authors' work. The structural aspects of antibody catalysis are described in Chapter 10 (Hilvert, MacBeath, and Shin) with a focus on chorismate mutase. Peptide hormones are the topic of the next chapter by Spatola told from the perspective of drug discovery. Chapter 12 (Nakanishi and Kahn) continues the discussion of peptidomimetics, providing a brief overview of amide bond surrogates and a selective review of secondary structure mimetics that reflects the authors' perspectives. Chapter 13 (Yang and Russell) provides a broad introduction to the utilization of enzymes in organic syntheses, but references extend only through the early 1990s. The final chapter (Tirrell, Tirrell, Mason, and Fournier) discusses the design of de novo protein structures in materials applications.

In summary, *Bioorganic Chemistry: Peptides and Proteins* is well-written and very informative. Graduate students in organic chemistry in addition to industrial researchers will find it a good introduction to the field.

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Metal Ions in Biological Systems. Volume 25. Iron Transport in Microorganisms, Plants, and Animals. Edited by A. Sigel and H. Sigel. Marcel Dekker, Inc., New York. 1998. xlii + 775 pp. 16 × 23.5 cm. ISBN 0-8247-9984-4. $250.00.

This latest addition to *Metal Ions in Biological Systems* maintains the high quality of this series. Despite having over 700 pages, the book attempts to cover so many topics that the depth of coverage is still limited. Readers will nonetheless find the book quite valuable as a general reference for iron uptake and storage in microbial and mammalian systems. The references for most of the chapters appear to provide reasonably good coverage of the literature through 1996, with a scattering of 1997 citations. Its value as a general reference source is enhanced by a very extensive subject index. This reviewer would recommend it for personal purchase by researchers in the area of iron biochemistry were it not for the high price. Fortunately, this series is maintained by most libraries, so the book will be widely available.

Although the book is not formally divided into subsections, most of the chapters fall into one of two broad categories. Six of the early chapters, representing about 40% of the book, are devoted to siderophores and microbial iron uptake. Two of these chapters cover siderophore structure and basic iron chelation chemistry. In one chapter Albretch-Gary and Crumbliss provide an excellent review of the usual topics such as types of chelating functional groups, ferric−siderophore stability constants, spectroscopic characterization of siderophore complexes, metal complexation kinetics, and iron−siderophore redox chemistry. The second chapter by Schranzer and Libman focuses more narrowly on results from that laboratory on the preorganization of the siderophore molecules. Three other chapters are organized by the type of organism: bacteria, fungi, and human pathogens. The last chapter in this group is devoted to siderophore receptors. Compared with older reviews on microbial iron uptake, there is less emphasis on kinetic studies of iron uptake with isotopic labels and more discussion of the molecular biology of iron uptake, the role of ferrous ion as a regulatory element in iron uptake, and the energy transduction processes that

drive receptor-mediated siderophore uptake. These chapters also provide a more limited description of iron uptake pathways that do not involve siderophores, such as uptake of heme and ferric citrate.

A second major grouping of six chapters, representing about 30% of the book, focuses on the proteins involved in mammalian iron transport and storage: ferritin, transferrin, and the transferrin receptor. There are three very complementary chapters on ferritin. One chapter by Harrison et al. focuses heavily on crystallographic studies of the protein structure, while a second chapter by Chasteen puts more emphasis on iron binding and oxidation. Both of these chapters include some discussion of bacterioferritin. The third chapter by Powell is devoted exclusively to mineralization and iron core formation, with an interesting discussion of the edge effects associated with the very small iron cores. There are also chapters on transferrin and the transferrin receptor and on the iron responsive element on mRNA's and the genetic control of iron uptake. The final chapter in this group by Crichton and Ward covers the broad topic of iron homeostasis and serves as a nice summary of much of the material covered in the other chapters in this group.

This book also attempts to cover iron transport and storage in plants. Thus there are chapters on the role of both microbial and plant siderophores in plant iron uptake and on plant ferritin. However, the coverage of iron metabolism in plants is not that extensive and somewhat fragmented. Other than a general discussion of the role of proteins and siderophores in limiting the iron available to pathogenic organisms and one chapter on clinical iron chelators, there is not much coverage of clinical issues.

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Progress in Medicinal Chemistry. Volume 35. Edited by G. P. Ellis, D. K. Luscombe, and A. W. Oxford. Elsevier Science B.V., Amsterdam, The Netherlands. 1998. vii + 270 pp. 14.5 × 21 cm. ISBN 0-444-82909-1. $198.50.

This book is the latest volume in this well-established medicinal chemistry review series. Chapters in this volume include: Modern View of Vitamin D_3 and its Medicinal Uses by M. J. Beckman and H. F. DeLuca (56 pages, 410 references), Neurokinin Receptor Antagonists by C. J. Swain (24 pages, 75 references), Opioid Receptor Antagonists by H. Schmidhammer (49 pages, 207 references), Mechanisms of Bacterial Resistance to Antibiotics and Biocides by A. D. Russell (64 pages, 326 references), and Towards Cannabinoid Drugs - Revisited by R. Mechoulam, L. Hanus, and E. Fride (44 pages, 202 references). The first three chapters cite references up to and including 1996, the last two, 1998. The volume contains a 6-page subject index.

The chapter on vitamin D_3 includes a detailed description of its biosynthesis, metabolism, and current understanding of mechanism of action, followed by a discussion of the therapeutic uses of vitamin D_3 and its analogues. In the last section of the chapter, the authors discuss the potential of vitamin D_3 analogues in the treatment of cancer and immune-related diseases.

The next chapter reveals the therapeutic potential and structural diversity of the many high-affinity neurokinin (NK) receptor antagonists. The authors classify the antagonists as NK_1, NK_2, or NK_3 receptor-selective or as dual NK_1/NK_2 receptor-selective. In the body of the text, useful comparative quantitative receptor affinity and pharmacological data are presented.

The chapter on opioid receptor antagonists begins with a description of receptor antagonism and universal opioid receptor antagonists. The remainder is divided into three sections: μ-opioid, κ-opioid, and δ-opioid receptor-selective antagonists. In each of the three sections, opioid antagonists are classified as peptide or non-peptide and, within these subheadings, as competitive or irreversible/long-acting. Binding affinity and receptor selectivity data are presented in 11 tables. Concise descriptions of the synthesis of the opioid antagonists are presented throughout the text.

The chapter on antibiotic resistance begins with some definitions and in turn discusses the mechanisms of intrinsic resistance, mechanisms of acquired resistance, pathogenic-resistant Gram-positive bacteria, mechanisms of multidrug resistance in Gram-negative bacteria, linked antibiotic-biocide resistance, and overcoming bacterial resistance. The use of drug combinations as a strategy to overcome bacterial drug resistance is only briefly mentioned, and the stereochemistry for some of the structures is not indicated. Despite these minor flaws, this chapter presents some well-organized information on this important topic.

The chapter on cannabinoid drugs describes cannabinoid receptors and the SAR of both the classical cannabinoids and the endogenous ligands, anandamide and 2-arachidonoyl glycerol. This is followed by a discussion of the medicinal properties of the cannabinoids which includes a discussion of the recently discovered oleamide and its potential in the treatment of sleep disorders. An interesting perspective is also provided on the ongoing debate over "medical marijuana."

The quality of the volume is very good. This book will likely be quite useful not only to those familiar with the topics presented but also to those who wish to learn more about these subjects.

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Integration of Pharmaceutical Discovery and Development: Case Histories. Edited by Ronald T. Borchardt, Roger M. Freidinger, Tomi K. Sawyer, and Philip L. Smith. Plenum Press, New York. 1998. xxix + 607 pp. 16 × 23 cm. ISBN 0-306-45743-1. $125.00.

In the past few years, an almost bewildering array of novel drug discovery technologies has appeared. The genomic revolution, combinatorial chemistry, and the availability of high-speed computers and associated software, to name only a few of the latest tools, have combined to provide a panoply of new approaches for drug discovery. But the importance of factors other than ligand−target affinity is sometimes seriously underestimated in drug discovery. Of equal, if not greater, importance to potency are issues of absorption, distribution, metabolism, and excretion (ADME). These questions are normally faced during the *development* phase of the R&D process. But as more is understood about these processes, the possibility of specifically maximizing drug activity through rational structural changes designed to enhance absorption and distribution to the site of action, while favorably influencing metabolism and excretion, is increasingly feasible. Thus, a closer integration of discovery and development in pharmaceutical R&D is clearly desirable, and this timely and important book takes an excellent approach to exploring the implications of this challenge.

Written almost exclusively by industrial scientists from "big-pharma", the volume comprises 25 case histories that describe, with varying degrees of success, both the discovery and the development issues encountered in bringing agents from discovery to market. Experiences with renin inhibitors, angiotensin II antagonists, thrombin inhibitors, and endothelin receptor antagonists comprise the first five chapters in the book. These reports are followed by case histories that consider LHRH agonists and antagonists, as well as somatostatin agonists. The discussions of the development of agonist drugs are of special interest inasmuch as the medicinal chemical theories underlying agonist design are still almost nonexistent. Further lessons are drawn from antiviral projects, prodrug development, and the development of topically active carbonic anhydrase inhibitors for the treatment of glaucoma.

The importance of the search for orally active drugs is considered again and again in these case histories. Important factors for enhancing this property were found to be aqueous solubility and relatively low molecular weight to minimize biliary excretion. The use of Caco-2 cells to study intestinal absorption is discussed in several places.

Pharmaceutical development in an era of cost containment brings on a new set of challenges for new products. One important factor is the price of production, considered in discussions of large-scale synthesis. Another is the choice of medical indication, examined by Doherty and Uprichard in their interesting discourse on endothelin antagonists. The development of new antihypertensive agents had little appeal, given the availability of cheap but effective generic diuretics and ACE inhbitors that cost the patient only $0.10−0.20/day. Additionally, the expense of lengthy clinical studies to determine outcomes of antihypertensive therapy mandated an examination of other indications for clinical studies of endothelin antagonists.

There is a wealth of interesting and important information for the medicinal chemist in this reasonably priced, well-produced book. A welcome addition would have been a chapter that classifies and summarizes the issues and answers discussed in the individual chapters.

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