Book Reviews

Protein Structure: A Practical Approach. Edited by T. E. Creighton, Editor. IRL Press, New York. 1997. xxiii + 383 pp. 15.5 x 23.5 cm. ISBN 0-19-963618-4. $55.00 (pbk).

Protein Function: A Practical Approach. Edited by T. E. Creighton, Editor. IRL Press, New York. 1997. xxi + 334 pp. 15.5 x 23.5 cm. ISBN 0-19-963615-4. $55.00 (pbk).

The second editions of *Protein Structure: A Practical Approach* and *Protein Function: A Practical Approach* are the new additions to the extensive *The Practical Approach* series by IRL Press. Dr. Creighton, a well-known protein chemist and expert in protein folding, has continued as editor for both of these texts. The focus is clearly on the experimental: these are "how to" books for modern protein chemistry, and they cover over 20 different experimental methodologies, both standard and state-of-the-art. What differentiates these texts from a *Methods in Enzymology* collection of techniques is the depth and comprehensiveness of each chapter. For many, these texts will be excellent training and reference guides for graduate students, postdoctoral scientists, and the practiced experimentalist who wishes to pick up new techniques: the explanations of the basic methodologies are concise yet clearly written for the nonspecialist; step-by-step experimental protocols are detailed and easily followed; in-depth discussions of data interpretation are provided; and plenty of background references are given. For others, particularly those engaged in collaborations with "specialists", the texts will provide a reasonably thorough introduction and background into several techniques, such as mass spectrometry and two-dimensional peptide mapping, to help create an informed nonspecialist.

In *Protein Structure: A Practical Approach*, Chapter 1 deals with perhaps the most common (and most abused) technique in biochemistry: molecular weight determination by sodium dodecyl sulfate polyacrylamide electrophoresis (SDS−PAGE). The authors created a reference on the basic techniques of SDS−PAGE that I can recommend to all my students. Moreover, this chapter lays the technical ground work for many of the electrophoretic methods described in many of the other chapters, particularly for Chapters 6 (Counting Integral Numbers of Residues by Chemical Modification), 5 (Peptide Mapping), and 8 (Analysis of Protein Conformation by Gel Electrophoresis). Chapter 2 covers the basics of analyzing protein structure by mass spectrometry which in turn dovetails nicely with Chapters 4 (Identification of Common Post-Translation Modifications), 5 (Peptide Mapping), and 7 (Disulfide Bonds between Cysteine Residues). The characterizations of the protein surface using immunological techniques are nicely covered by Chapters 3 (Immunological Detection of Proteins of Known Sequence) and 13 (Immunochemical Analysis of Protein Conformation). The use of spectroscopic methods to elucidate a protein's physical characteristics are covered in Chapters 10 (How To Determine the Molar Absorption Coefficient of a Protein), 11 (Optical Spectroscopy To Characterize Protein Conformation and Conformational Changes), and 12 (Measuring the Conformational Stability of a Protein).

The least useful chapters for providing "how to" information on experimental design and practice are Chapters 9 and 14, but for clearly different reasons. Chapter 9 (Hydrodynamic Properties of Proteins) tries to cover the characterization of proteins by analytical size-exclusion chromatography, dynamic light scattering, and analytical ultracentrifugation, all in one chapter. Because of the breadth of the material they discuss, the authors cannot give the methods anything more than passing introductions and discussions, which they did well given the limited space. However, this makes the experimental protocols they provide much less useful. The ready availability of these analytical techniques to today's researchers demands almost separate chapters for each technique. Chapter 14 (Stabilization of Protein Structure by Solvents), on the other hand, provides no experimental protocols or discussions of experimental design. While this chapter is purely an article on the solvation and stabilization of proteins by different solvents and cosolutes, it nonetheless is an excellent data resource for the protein chemist.

Protein Function: A Practical Approach is oddly titled, as only half of the chapters deal purely with the functional behavior of proteins. Rather, the text deals more specifically with methods to address structure−function relationships in proteins, where the term "structure" refers either to a protein or to a putative ligand. Thus, *Protein Function: A Practical Approach* complements *Protein Structure: A Practical Approach* with some minor overlap. Chapters 1 (Identifying Proteins for Proteome Studies: A Two-Dimensional Gel Electrophoresis Approach), 5 (Ligand Blotting), and 8 (Analysis of Sequence-Specific DNA-Binding Proteins) again show the versatility and power of electrophoresis as a general analytical tool that can be combined with other techniques, whether they be computational, immunological, or chemical. Chapters 6 (Affinity Labeling), 7 (Chemical Cross-Linking and Protein Function), 8 (Analysis of Sequence-Specific DNA-Binding Proteins), and 10 (Chemical Modification) deal *in depth* with the use of chemical probes to explore structure−function relationships in protein and DNA. Chapter 4 (Ligand Binding) covers the determination of the thermodynamic parameters for ligand binding to receptors using such diverse techniques as filter assays, centrifugation, equilibrium dialysis, titration calorimetry, and surface plasmon resonance; the discussion of measuring the kinetic parameters is, however, quite brief. Chapters 2 (Expressing Cloned Genes in *E. coli*) and 9 (Purification of Sequence-Specific DNA-Binding Proteins by Affinity Chromatography) do not address specifically aspects of protein function but, nonetheless, cover what are now important ancillary techniques in modern protein chemistry laboratories. Along this line, I missed complementary chapters on other useful molecular biology techniques, such as alanine or cysteine scanning and combinatorial phage display, which are powerful

new tools for biochemistry and protein chemistry. Finally, Chapter 3 (Folding Proteins) is a little out of place yet deals nicely with the technical aspects of monitoring protein folding as well as indirectly addressing the problems that arise in protein overexpression systems (Chapter 2).

In summary, *Protein Structure: A Practical Approach* and *Protein Function: A Practical Approach* are complementary texts which should be considered almost companion volumes. The authors are experts in their fields, and many have substantial international reputations as experimentalists. *Protein Structure: A Practical Approach* and *Protein Function: A Practical Approach* could be improved by a better organization within and between the two texts. Nonetheless, they are reference texts which should end up as well-thumbed volumes on any laboratory bookshelf.

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Guanidino Compounds in Biology and Medicine: 2. Edited by P. De Deyn, B. Mareseau, I. A. Quneshi, and A. Mori. John Libbey & Company Limited, London. 1997. 405 pp. 19.5 × 24.5 cm. ISBN 0-81696-543-4. £66.00.

This book contains selected papers from the Fourth International Symposium on Guanidino Compounds in Biology and Medicine held in Montreal, Canada, in September 1994. Like the previous volume in this series (reviewed in *Journal of Medicinal Chemistry* **1993**, *36*, 2241), this work focuses on the biochemical rather than the pharmacological role of guanidine-containing compounds. Thus the book comprises eight sections each relating to specific aspects of metabolic processes involving guanidino compounds, especially arginine. The first section, which is likely to be of greatest interest to the readers of *Journal of Medicinal Chemistry*, contains several short papers on the arginine−nitric oxide pathway and its possible role in various clinical disorders. The work presented, and particularly the SAR data on neuronal nitric oxide synthase inhibitors, is a useful addition to the medicinal chemical literature. Other sections deal with hyperarginemia/arginase and the creatine−creatinine biosynthesis pathway and its physiological and clinical importance. There are also sections devoted to the metabolism of guanidino compounds and their involvement in renal failure, liver failure, and diabetes. An additional section includes discussion of electrophysiological and neurochemical studies, and the final section relates to guanidino compounds in microorgansism, plants, and invertebrata.

This book adds to the wealth of data supporting the importance of guanidino compounds in biological processes. In addition to its obvious interest to specialists in the areas covered, this book is well-worth perusal by medicinal chemists and others with an interest in the chemistry and biology of guanidines. It is a useful addition to library shelves in academia or industry.

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Antiviral Chemotherapy. By Richard Challand and Robert J. Young. In **Biochemical and Medicinal Chemistry Series**. Series Editor John Mann. Spektrum Academic Publishers, Oxford, and University Science Books, Sausolito. 1997. viii + 128 pp. 19 × 24.5 cm. ISBN 1-901217-03-5. $28.50 (pbk).

Antiviral Chemotherapy is the fourth offering in a series of text books tailored to provide advanced undergraduate students in the biological sciences with concise accounts of subjects where both chemistry and biology converge but which are inadequately covered in standard texts. After a general introduction to the structure of viruses and a brief description of viruses that infect humans, Chapters 3 and 4 provide the reader with a basic understanding of assay design and a summary of the major biochemical targets that have proven to be clinically useful sites for intervention in the replication cycle of many pathogenic viruses. Reflective of their preeminent role in the development of effective antiviral chemotherapeutics, Chapter 5 is devoted to a discussion of nucleoside analogues, providing a mechanistic understanding of the design and mode of action of this important class of drug. With this background, the reader is well-prepared for the remaining chapters which focus attention on drugs that are used to treat specific viral infections, beginning with the herpes virus family and following with individual discussions of HIV, hepatitis, and respiratory infections. The appendices include a useful list of the viruses known to be responsible for disease in humans and a compilation of the structures of all the marketed and late-stage antiviral therapeutics. The book concludes with a glossary of terms used in the text and a list of references to general textbooks as well as reviews and articles in both the primary and secondary literature that will be of interest to those who seek a more detailed and deeper discussion of the major topics covered.

Written by two medicinal chemists from the former Wellcome Research Laboratories at Beckenham in the United Kingdom, *Antiviral Chemotherapy* succeeds in its mission. The book provides an excellent and succinct introduction to the history of the discovery and development of antiviral chemotherapeutics and describes all of the current clinically useful agents. The information is organized in a logical fashion and presented in a readable and engaging manner, with the liberal use of figures and structures that illustrate and enhance the discussion. All of the major discoveries are dealt with, and the text briefly covers several emerging opportunities for drug discovery that remain of contemporary interest.

There are several errors, fundamental in nature, that will be readily apparent to those more familiar with the

subject matter and which detract from the overall value of the text. The authors' use and definition of the terms monocistronic and polycistronic are incorrect and confusing, and the description of an ELISA assay is not the experimental design more commonly employed. The structure of the nonpeptidic HIV protease inhibitor U-96988 is in error, and the influenza M_2 ion channel is not accurately or overtly represented in the depiction of the virus, surprising given the focus of subsequent discussion on amantadine and the historical importance of this agent. The contention that integration of the HIV genome into the host cell chromosome is not essential for viral replication is clearly incorrect and seems to have been carried over from the description of HBV. In addition, ribavirin is not, as stated, a natural product.

Despite these shortcomings, *Antiviral Chemotherapy* is a useful text that is modestly priced and should appeal not only to its target audience but also to those individuals embarking on a career in the pharmaceutical industry.

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Introduction to Medicinal Chemistry: How Drugs Act and Why. Alex Gringauz. Wiley−VCH, Inc., New York. 1997. xiii + 721 pp. 18.5 × 26 cm. ISBN 0-471-18545-0. $89.95.

"This book is intended to be useful, indeed necessary, to students pursing a career in the health sciences...the pharmacy student...will find this book invaluable. * * * It is anticipated that this publication will also be used at the early graduate training level..." states Alex Gringauz in his preface to this volume, explaining that "(t)his book is not intended for the medicinal chemistry practitioner...". But in spite of this, the promotional material provided by the publisher on the back cover indicates "(i)t will be extremely useful...for research scientists entering the pharmaceutical industry."

The book consists of 15 chapters that discuss basic considerations and mechanisms of drug activity, drug metabolism, antineoplastics, analgesics, antimocrobials, cholinergic and adrenergic agonists and antagonists, cardiovascular drugs, CNS drugs, antiulcer drugs, local anesthetics, steroids, and new developments. These divisions result in some strange bedfellows: both thyromimetic drugs and insulin mimetics appear in the chapters devoted to cardiovascular drugs.

The exposition is at once subject to both the advantages and disadvantages of a single-author text. On the one hand, a single author can uniquely provide a unified treatment of an entire field. But on the other, it is extraordinarily difficult for a single author to be successful in the present case given that medicinal chemistry today is a broad, complex, and rapidly changing field. These difficulties become painfully apparent in the case of the references to the chapters, which tend to be quite old—for example, no later than 1989 in the chapter on anticancer drugs—or even nonexistent—for example, in the case of the chapter on drug metabolism. It is not only the references but also the text itself that are out of date in places. For example, the crucially important topic of G-protein-coupled receptors is absent altogether in the discussion of receptors in the chapter on the mechanism of drug action.

Except for a huge number of structural formulas, the volume is almost devoid of illustrations, and the few that are presented, for example, in the chapters on cholinergics and CNS drugs, are amatueurish line drawings. Most of the formulas have been (badly) drafted, rather than set in type. In my mind these are all serious defects in a book intended for students.

We live in a competitive world, and this book will have to compete against other texts, notably Foye's *Principles of Medicinal Chemistry* (4th edition, 1995), available at a similar price. Even though it is now 2 years old, Foye's is a far better book. It is written by a panel of experts, represents current knowledge, has large numbers of useful references, is beautifully illustrated, and is produced using clear, typeset formulas.

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Annual Reports in Combinatorial Chemistry and Molecule Diversity, Volume 1. Edited by Walter H. Moos, Michael R. Pavia, Andrew D. Ellington, and Brian K. Kay. ESCOM Publishers, Leiden, The Netherlands. 1997. xiii + 354 pp. 17 × 24.5 cm. ISBN 90-72199-23.5. $97.00.

This volume is the first of a new annual review series that will follow progress in the exploding field of combinatorial chemistry. The book has chapters written by 33 different authors who are experts in the fields surveyed. Combinatorial chemistry and molecular diversity are emerging disciplines, and this volume does an excellent job of bringing the reader up to date. The book is divided into three major sections: Combinatorial Chemistry, Combinatorial Biology and Evolution, and Informatics and Related Topics. All together, there are 1464 references in 20 different chapters. There is a fairly extensive subject index, but its coverage is not uniform. The keyword indexes for the biological topics seem to be thorough, whereas the indexes for the chemical topics are less so. There are, for example, no index terms for biphenyl scaffolds, the Mitsunobu reaction, or the Suzuki reaction, even though these topics are detailed in several chapters. In addition, some index terms are odd, such as Microsoft Windows and fuzzy. Overall, however the volume is packed with good information.

Each major section is launched with excellent overviews, following which chapters continue with more focused topics. The first chapter in Section I, by Kiely (Houghten Pharmaceuticals), describes techniques for

mixture synthesis, emphasizing non-peptide approaches. Many of the methods discussed in this chapter have their roots at the beginning of combinatorial chemistry, such as Houghten's tea-bags, Geyson's pins, or Furka's split-mix method. Kiely maintains that deconvolution of mixtures "remains a robust and highly useful" method, and he provides three answers to the question, "Why mixtures?" First, current robotic synthesis of single compounds can not keep up with high-throughput screening. Second, the use of mixtures to find individual pure active compounds is well-precedented (cf. natural products). Finally, sometimes the biological target is in short supply, and it is desirable to minimize the number of assays. The second chapter, by Sarshar and Mjalli (Ontogen Corp.), reviews various techniques for synthesis of individual pure compounds—"singles." The next chapter, by Hall (Sphinx Pharmaceuticals), provides an overview of advances in solid-phase synthesis. He describes the state of the art and mentions the fact that most reactions are carried out on only two solid supports—cross-linked polystyrene (Merrifield resin) or Tentagel (a PEG-modified polystyrene). He discusses the use of linkers and describes solid-phase variants of many well-known name reactions. The chapter by Sucholeiki (Sphinx) details selection of commercially available solid supports and provides much useful data on physical properties of resin materials, including swelling and loading. Next, Coe and Storer (Glaxo) discuss solution-phase synthesis of compounds such as methods that employ soluble polymeric supports, dendrimeric solution-phase arrays, and other techniques. Mention is also made of the latest novel method—flourous-phase synthesis. The next chapter, by Fitch (Affymax), reports on analytical chemistry of combinatorial library synthesis. While product cleavage and off-bead analysis are widely used, measurement of yields by gravimetric methods is recommended by Fitch, based on experience at Affymax. The chapter also reports examples of on-bead spectroscopic methods such as IR, NMR, and ^{13}C NMR. A survey of the great advances in LC/MS techniques leads to a warning: "...there is no excuse for not fully characterizing compounds made by parallel synthesis". The assumption in this statement by Fitch is that mass spectrometry actually provides full compound characterization. It is widely known that this is not the case. In the next chapter, Dewitt (Diversomer Technologies) surveys the field of automated synthesis. Finally, the chapter by Patel (Versicor) discusses actual applications of combinatorial chemistry in drug discovery. Patel surveys both synthesis and screening and leaves the impression that diverse chemistry provides promising biological results.

The second major section is titled Combinatorial Biology and Evolution. The five chapters in this section provide an interesting collection of reviews on the more biological approaches to combinatorial chemistry. The first chapter, by Levitan (Santa Fe Institute), discusses both biological strategies for molecular diversity and information theory, as well as concepts underlying the application of such techniques to discovery. This is followed by a chapter by Schuster (Universitat Wien and Santa Fe Institute) that reviews the principles of evolutionary biotechnology. The following chapter by Ellington (Indiana University) continues with an excellent description of biological approaches to molecular evolution. The concept of "fitness landscape" for evolution and in vitro selection is very nicely described. The relationship of genetic diversity (random synthesis of DNA) and methods for the selection of compounds are examined; molecules that bind suitably to a receptor are allowed to "breed", for example, by PCR, which can amplify by a factor of 1 000 000 the desired molecule in a single generation. The next chapter, by Lam (Selectide), describes the solid-phase synthesis of peptide libraries by split-mix techniques. This topic examines a subject which truly is the roots of combinatorial chemistry. Lam makes a good case that the future for synthetic peptides is still bright, since many natural ligands are peptides. The final chapter in this section is an excellent review of phage display. Collins (Braunschweig) describes phage display in the context of the concepts of molecular diversity. He clearly presents the technique in comparison to organic chemistry methods. Collins describes the presentation of millions of ligands on the surface of a bacteriophage, the use of affinity selection techniques (called "panning") to concentrate the best specific binding clones, and finally sequencing of the consensus motifs and even model building to provide insights on the final structure. This chapter is long (52 pages with 255 references) and is quite comprehensive.

The final section, Informatics and Related Topics, is a collection of seven diverse topics: databases, high-throughput screening, deconvolution methods, combinatorial patent strategies, combinatorial business alliances, the promise of combinatorial chemistry, and a compendium of 643 solid-phase synthesis references. While these sections are not as detailed or comprehensive as those of parts I and II, they are filled with interesting tidbits. The penultimate chapter of the section is called Combinatorial Chemistry—Promise Fulfilled? This chapter is a teaser for the next volume of this series. The author claims: "The future versions of this section will provide the answer to this question."

In conclusion, this review volume is very worthwhile for all practitioners of molecular diversity: chemists, biologists, theoreticians, and even business types. One's first impression is that Volume 1 may be the best of the series. It will be interesting to see if the editors can continue to maintain such a meaty series. It may be largely determined by the efforts of scientists around the world who are discovering, developing, and publishing new advances in the fields of combinatorial chemistry and molecular diversity. In conclusion, I recommend this book to everyone with an interest in combinatorial chemistry and molecular diversity.

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Purinergic Approaches in Experimental Therapeutics. Edited by Kenneth A. Jacobson and Michael F. Jarvis. Wiley-Liss, New York. 1997. xiv + 581 pp. 16 × 24 cm. ISBN 0-47114071-6. $89.95.

Research in the area of purine and pyrimidine nucleosides and nucleotides in this decade has entered a new phase due to the increase in understanding of the adenosine (P1) receptors and several known and new nucleotide (P2) receptors, partially through cloning and expression. This book is a collection of articles summarizing the most recent understanding of various facets of purinergic research by some of the leading researchers in the field. A total of 28 articles are distributed into four parts in the book. Seven of these cover historical perspective, molecular pharmacology, and medicinal chemistry of nucleosides, nucleotides, and their receptors. The remaining articles cover a variety of physiological and therapeutic implications of activation or inhibition of the P1 and P2 receptors. Although the subject matter of a number of articles in the book is covered in review articles published in the literature, this book compiles these and several other important articles with up-to-date references on purinergic research and serves as a guidebook of the most recent understanding and bibliography in this field of research.

The article on historical perspective provides a brief overview of the research findings on P1 and P2 receptors and their ligands. An excellent summary of the receptor cloning and pharmacology of the P1 receptors and the role of adenosine as an inhibitor of excitotoxic neurotransmitters and in ischemia, inflammation, asthma, epilepsy, and nociception is provided with the most current literature references (Chapters 2, 8, 15−17, 19, and 25). Unlike the research on P1 receptors, that on P2 is relatively new, and therefore, fewer sources provide a collection of research articles on the topic. This book is one of a couple of sources available today on the topic of nucleotide receptors and their function. The structure and function of P2Y receptors is nicely summarized; however, that on P2X is missing (it has been described partially in the article on ATP in Brain Function). The potential role of P2 receptor modulating agents in the treatment of thrombosis, diabetes, and cancer is described clearly (Chapters 11, 13, and 28), while that on complications of the respiratory system (Chapter 18) is less-focused. The chapters on the medicinal chemistry of agents that modulate the P1 and P2 receptors and levels of adenosine are succinct, yet rich in bibliography.

The index has been written thoroughly and was found to be very useful in accessing subject matters quickly. Although the book is slightly expensive, it is a useful addition to one's collection of sources providing valuable information, summary, and bibliography.

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