Book Reviews

Bioorganometallics. Edited by Gerard Jaouen. Wiley-VCH, Weinheim, Germany. 2006. xviii + 444 pp. 17.5 × 25 cm. ISBN 352730990x. $170.00.

Bioorganometallics provides a timely update to an important emerging subfield of bioinorganic chemistry. The subtitle (Biomolecules, Labeling, Medicine) indicates the themes that are developed in this 12-chapter volume. The text is well-illustrated and covers all the key areas. Each chapter provides comprehensive citations to pertinent literature through 2004. There is no obvious rationale to the ordering of the chapters, although each stands well on its own as an independent contribution.

Chapter 1 provides a clear historical perspective on the development of the field, highlighting key breakthroughs and discoveries and providing a backdrop for the organometallic chemistry that underlies the remaining chapters. Chapter 2 summarizes the structural and functional chemistry underlying the anticancer activity of ruthenium arene complexes, while chapter 3 outlines methods for directing therapeutically relevant organometallics to target sites, as well as accounting for their individual modes of action. Chapter 4 introduces radiopharmaceuticals, reviewing strategies for the preparation of technetium complexes by way of organometallic chemistry and the use of organometallic derivatives of technetium in imaging. This chapter also provides a useful discussion of organometallic chemistry in water. Chapter 5 reviews methodologies for the coupling of organometallics to peptide nucleic acid polymers, while chapter 6 provides a complementary discussion of strategies for labeling proteins with organometallics as well as a variety of applications in crystallography, microscopy, immunology, and fluorescent markers. Chapter 7 provides an interesting discussion of organometallic bioprobes as sensors, probes of structure, and genetic screening methods. Chapter 8 complements chapter 4 by discussing the use of organometallic complexes for development of nonisotopic immunoassays where an antigen-coupled organometallic complex is used to generate antibodies sensitive to the structure of that antigen. Chapter 9 provides a short description of the use of ferrocenyl oligonucleotides, in particular to detect genes or other DNA fragments by way of electrochemical analysis. Chapter 10 returns to the theme of organometallic pharmaceuticals, engineered around organometallic siderophore hosts that can recognize a variety of guests including amino acids, nucleobases, cell-surface receptors, and monovalent cations and anions. Chapter 11 makes the strongest connection with traditional bioinorganic subject matter, reviewing the structural and mechanistic chemistry of metalloenzymes that mediate organometallic-type reactions, as well as some others where the connection is less clear. Chapter 12 provides a complementary perspective with a discussion of synthetic models for metalloenzymes that mediate bioorganometallic chemistry.

A strength of this text lies in the diversity of topics that are covered in such a succinct fashion. It will appeal to a broad spectrum of coordination chemists (organometallic to bioinorganic) as well as biochemists and molecular and cellular biologists needing a primer in this area. The price of the text is reasonable for a general review volume. It should find a place on all library shelves and will no doubt be a routine reference text for specialists in this field.

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Drug Discovery. A History. By Walter Sneader. John Wiley & Sons Ltd., West Sussex, England. 2005. x + 468 pp. 17 × 24.5 cm. ISBN 0471899801 (Paperback). $65.00.

This book will provide all interested in scientific historical writings a fascinating journey through drug discovery from prehistoric time to the present day. Dr. Sneader's writing style keeps the reader intently interested, not an easy task for a subject of this kind. The author claims that the book was written for the general reader, but it contains information and chemistry sufficiently detailed and advanced to appeal to medicinal chemists. This reviewer envisions an elective course at the professional or introductory graduate level built around this text.

The book is divided into three parts. Part 1, The Legacy of the Past, comprises eight chapters addressing the history of drugs or preparations used in the treatment of pain and disease, from the prehistoric period through the Greek, Roman, and Arab worlds to the early chemical medicines involving inorganic and organometallic compounds. This part concludes with a chapter, Systematic Medicine, that traces the development and use of anesthetic molecules in surgical anesthesia. Part 2, Drugs from Naturally Occurring Prototypes, comprises 17 chapters describing some of the most clinically significant advances in drug discovery and covering the period from the late 18th century to the mid-20th century. The first of three specific subsections covers phytochemicals, and the first chapter (entitled Alkaloids) discusses the discovery and isolation of medicinally active substances from plants, beginning in the early 19th century with the isolation of morphine. The author discusses the isolation and evaluation of other therapeutically important alkaloids including quinine, atropine, cocaine, Vinca alkaloids, and camptothecin. Although the discussions are relatively brief, the author's style presents the stories in an interesting and relatively complete fashion.

The next chapter covers nonalkaloid plant substances including salicin, digitalis glycosides, dicoumarol, tetrahydrocannabinol, and paclitaxel. Next is a chapter discussing analogues of plant products and other compounds derived from them. This chapter expands upon the transition from the early drug discovery process to analogue development and the early drug design process.

The second section in Part 2 contains chapters on biochemical substances including neurohormones, peptide, sex, and adrenocortical hormones, prostaglandins, hormone analogues, vitamins, antimetabolites, and blood and biological products. The first chapter in this section provides a brief discussion of the origins of hormone therapy in the late 19th century. Organotherapy is introduced in this chapter and traces the development of thyroxine.

The next chapter in this section addresses the discovery and development of neurohormones. Beginning with the isolation and purification of epinephrine, the author extends the discussion to include norepinephrine, tyramine, dopamine, and the development of levodopa. The chapter concludes with the discovery of histamine, acetylcholine, 5-hydroxytryptamine, and GABA.

The discovery and clinical development of peptide hormones are the subject of the next chapter, beginning with the discovery and clinical development of insulin, followed by a brief reference to the discovery of glucagon. Discussion of the pituitary hormones completes the chapter.

Chapter 15 (entitled Sex Hormones) begins with a short introduction to the organotherapy approach to hormone replacement therapy (HRT) in the late 19th century. The isolation of estrogens from ovarian extracts and from urine collected at the onset of pregnancy is described. The further separation of the estrogens into estrone, estriol, and estradiol prototypes is also presented, as is the discovery of progesterone and the discovery and isolation of androsterone and testosterone. The discovery of the adrenal cortex hormones is presented in the next chapter.

Prostaglandins are covered in a very brief chapter that traces the isolation of prostaglandins E, F2α, and E2.

Chapter 18 describes the studies of analogues of the hormonal substances presented in the previous chapters. The development of orally active progesterone analogues, the resulting oral contraceptive products, and progesterone antagonists is also presented. Analogues of testosterone as anabolic agents and the discovery of drugs for benign prostatic hyperplasia are presented as well.

Chapter 18 also contains a section devoted to the development of orally active, topical, and inhaled cortisone analogues. Other major topics in this chapter include the development of H2 receptor antagonists, 5-HT analogues as both anti-inflammatory agents, and serotonin agonists and antagonists. The chapter closes with brief discussions of the development of methyldopa and analogues of GABA and prostaglandin.

The Biochemicals Section closes with three chapters entitled Vitamins, Antimetabolites, and Blood and Biological Products. The chapter on vitamins opens with a brief description of early experiments conducted in animals and proceeds to discuss the discovery of the individual water-soluble and fat-soluble vitamins.

Antimetabolites are introduced through a discussion of the development of folicacid analogues and the design of purine analogues. Pyrimidine antimetabolites and other analogues are discussed in detail, and there follows a section on modified nucleosides, which in turn leads into a discussion on the historical development of drugs used in the treatment of HIV/AIDS including HIV protease inhibitors.

The chapter entitled Blood and Biological Products begins with the discovery of an anticoagulant compound from liver extracts and describes the development of heparin. Other blood-related topics include alteplase, aprotinin, epoetin, and colony-stimulating factors. Interferons are discussed briefly. A discussion of bile acids precedes an analysis of hypocholesterolemic drugs derived from dehydrocholic acid. The author discusses the development of antidiabetic drugs. This chapter closes with the history of the development angiotensin converting enzyme (ACE) inhibitors.

The third section of Part 2 is Drugs from Micro-organisms and contains four chapters entitled Antibiotics, Antibiotic Analogs, Pharmacodynamic Agents from Micro-organisms, and Analogs of Pharmacodynamic Agents from Fungi. The antibiotics chapter begins with brief discussions of pyocyanase and tyrothricin, then moves to a discussion of fungal antibiotics and an account of the discovery and development of penicillins. This is followed first by discussions of aminoglycosides. The tetracyclines, the macrolides, and polyene antibiotics are also mentioned. The chapter closes with the discovery of the cytotoxic antibiotics. Chapter 23 describes the development of analogues of the classes of antibiotics covered in the previous chapter.

The last two chapters in this section are entitled Pharmacodynamic Agents from Micro-organisms (Chapter 24) and Analogs of Pharmacodynamic Agents from Fungi (Chapter 25).

Part 3 of the book addresses synthetic drugs. The discussion covers the discovery of aspirin and the development of aspirin analogues. Hypnotic agents are traced from chloral hydrate through barbiturates to the various anticonvulsant agents.

The next chapter discusses drugs obtained from screening dyes and the development of antimalarial/antiprotozoal agents. The antibacterial sulfonamides are also covered, along with other drugs derived from sulfonamides.The development of antituberculosis drugs and related antidepressant/MAO inhibitors is discussed as well. This chapter closes with drugs developed as gastric proton pump inhibitors and the aminosalicylates used in bowel disorders.

Chapter 28, entitled Drugs Originating from the Screening of Organic Chemicals, is devoted to the discovery of drug prototypes through screening and their development into therapeutic agents. This chapter is categorized by pharmacological class and focuses on classical antihistamines, antipsychotic agents, anxiolytic drugs, tricyclic antidepressants, selective serotonin reuptake inhibitors, nonsteroidal anti-inflammatory drugs (including COX-1 and COX-2 inhibitors), and angiotensin II antagonists.

Chapter 29 is a short presentation entitled Drugs Discovered through Serendipitous Observations Involving Humans. The chapter focuses on the organonitrates, lidocaine, and the organophosphate anticholinesterases. Chapter 30 is entitled Drugs Discovered through Serendipity in the Laboratory. The author relates the laboratory discovery of penicillin. Other drugs described include acetanilide, oxazolidine-2,4-diones, alkylating drugs that have antitumor activity, and valproic acid.

The final chapter is Concluding Remarks in which the author points to the importance of protecting the ability of the pharmaceutical industry to continue to do the research and development required to produce more effective and specifically targeted drugs for the treatment of disease.

The text is well written and well illustrated with chemical structures throughout. Every chapter is thoroughly referenced. The book is an excellent bibliographic resource for those interested in the background papers that serve as the foundation for discovery of specific drug entities. The index is very complete. This is a book that belongs in the personal library of every medicinal chemist, pharmacist, and all others interested in drug discovery and the historical basis of medicinal chemistry.

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Annual Review of Pharmacology and Toxicology. Volume 46. Edited by Arthur K. Cho, Terrence F. Blaschke, Paul A. Insel, and Horace H. Loh. Annual Reviews Inc., Palo Alto, CA. 2006. x + 548 pp. 15.5 × 23.5 cm. ISBN 0-8243-0446-2. $80.00.

This book is the 46th volume of this review series. A variety of timely topics are covered in 17 reviews, written by experts working in their respective fields. The reviews cover a broad range of individual topics in pharmacology and toxicology. Each will be of great value ito medicinal chemists working in fields directly related to the topics covered. Select reviews likely to be of most direct interest to medicinal chemists in specific fields of drug discovery include (1) Peroxisome Proliferator-Activated Receptors; How Their Effects on Macrophages Can Lead to the Development of a New Drug Therapy against Atherosclerosis; (2) Cannabinoid Receptors as Therapeutic Targets; (3) Accessory Proteins for G Proteins: Partners in Signaling; (4) The Proteasome and Proteasome Inhibitors in Cancer Therapy; (5) Regulation of Platelet Functions by P2 Receptors; (6) Molecular Mechanism of 7TM Receptor Activation—A Global Toggle Switch Model.

All reviews are well written and informative. The subject index is thorough. Citations for most reviews are extensive and up to date. This book contains a short but useful list of reviews in other annual review publications that are related to topics in this volume. The present volume is a welcome addition to this long-standing series, providing concise summaries of advances in pharmacology and toxicology. It is notable that this book is located online at http://pharmtox.annualreviews.org. In addition, additional Annual Reviews series are located at www.annualreviews.org.

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Modern Biopharmaceuticals. Design, Development, and Optimization. Volumes 1−4. Edited by Jörg Knäblein. Wiley/VCH Verlag, Weinheim, Germany. 2005. cxxxviii + 1886 pp. 17.5 × 24.5 cm. ISBN 3527331184. $535.00.

This series of four volumes is an ambitious attempt to define the current state of biopharmaceuticals. Perhaps the biggest challenge with such a series is to define what is meant by the term and where the boundaries are with "traditional pharmaceuticals". In the introduction, Gary Walsh defines biopharmaceuticals as "protein or nucleic acid based pharmaceuticals used for therapeutic or in vivo diagnostic purposes and produced by means other than direct extraction from a nonengineered biological source". This defines the boundaries in Dr. Walsh's contribution, but the entire four-volume set with 186 contributing authors is not encumbered by this definition. Topics run the gamut, from overviews of protein based and nucleic acid based therapeutics and therapeutic candidates to cell therapy, diagnostics, pharmacogenomics, analytical techniques, regulatory approval issues for pharmaceuticals, and drug delivery. It is a strikingly ambitious attempt to define and describe a burgeoning field of exciting research and development at the interface of science and commerce.

Individual contributions are somewhat variable in their scope and utility to a general reader, but such a series is likely to be a fine addition to library shelves in academic and corporate libraries. For the uninitiated in the field, this four-volume set will be somewhat overwhelming except for selected chapters. The 100+ pages of introductory materials before the first chapter include short vignettes about virtually every contributor and topic. All in all, this is an impressive snapshot of the field.

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G Protein-Coupled Receptors as Drug Targets: Analysis of Activation and Constitutive Activity. Methods and Principles in Medicinal Chemistry. Vol. 24. Edited by Roland Seifert and Thomas Wieland. Wiley-VCH, Weinheim, Germany. 2005. xxvii + 275 pp. 17.5 × 24.5 cm. ISBN 3527308199. $170.00.

The current installment of the Methods and Principles in Medicinal Chemistry series is a comprehensive treatment of the theory, study, and therapeutic applications of constitutive activity, a fundamental, underappreciated principle of G-protein-coupled receptor function. Although originally perceived as a simple ligand-operated on/off switch for activating cellular G-proteins, G-protein-coupled receptors (GPCRs) are now understood to possess varying degrees of ligand-independent or constitutive activity. In compiling G Protein-Coupled Receptors as Drug Targets: Analysis of Activation and Constitutive Activity, editors Roland Seifert and Thomas Wieland have assembled an international cast of experts to weigh in on diverse topics related to constitutive receptor activity in an accessible format.

The first half of the book gives detailed reviews of the structural, biochemical, and physiological basis for and implications of constitutive GPCR activity, beginning with an accessible description of mechanistic and mathematical models for inverse agonists and constitutive activation. Structural determinants that affect constitutive GPCR activity are reviewed, including splice forms, naturally occurring mutants, and G-protein coupling. Potential pathological roles for aberrant constitutive activity, as well as the potential therapeutic use of inverse agonists, are also presented in this section. The basic concepts section of the book ends with a thorough discussion of techniques commonly used to define constitutive GPCR activity, including thoughtful analysis of the limitations of the approaches.

The second half of this book examines the constitutive activity of various GPCR systems in greater depth, in most cases including structural, chemical, pharmacological, and physiological aspects and implications. Highlighted systems include α and β adrenergic receptors, muscarinic acetylcholine receptors, histamine receptors, serotonin receptors, and chemokine receptors.

The chapters of this book were designed to stand alone as sovereign units such that they can be read à la carte. This is helpful for use as a quick reference, although it does lead to some redundancy (each chapter has an introduction to basic concepts) and a few inconsistencies. However, extensive cross-referencing between chapters helps to tie together concepts and make the book more cohesive. In summary, this book is an excellent review of the body of evidence describing constitutive GPCR activity. It is of general interest to pharmacologists, structural biologists, biochemists, and medicinal chemists with an interest in GPCR signaling pathways and as such would be

a good addition to personal or departmental libraries of many basic scientists.

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St. John's Wort and Its Active Principles in Depression and Anxiety. Edited by W. E. Muller. Birkhäuser Verlag, Basel, Switzerland. 2005. viii + 188 pp. 17 × 24 cm. ISBN 10: 3-7643-6160-3. 126.26 Euro.

This book is a part of the series Milestones in Drug Therapy, edited by Michael J. Parnham and Jacques Bruinvels. There is a total of 13 chapters, written by 20 investigators actively involved in research on St. John's wort. Most of the authors are from Germany (eight), but some are from Austria (one), Italy (four), United Kingdom (one), Sweden (three), and Switzerland (two). This is not surprising because St. John's wort has been widely used as an antidepressant for over 500 years in Europe. Muller provides a short but well-written historical overview in the introductory chapter and suggests that, with the most recent work that has been done on this age old remedy, clinical use of the extracts of St. John's wort for the treatment of depression is a success story. His suggestion is that patients are more comfortable in accepting this natural herbal remedy as the initial treatment for their problem and might be more willing to accept continued treatment with chemical antidepressants in case such a need is clinically determined.

The chapter on phytochemistry provides a good account of the structures of various chemical constituents of St. John's wort and suggests which of these may be responsible for the antidepressant and other types of activities. Physicochemical properties of various chemical entities have been given. The authors also provide information on how to analyze various chemical entities that are present in clinically used preparations and how to standardize them by using certain marker compounds. A brief discussion of the analytical methods, including application of LC/ESI−MS/MS is given at the end of the chapter.

Receptor binding studies that can provide information on the relative affinities of various chemical entities for different receptors, as an objective but easier and faster method to characterize the mechanism of action, suggestive of therapeutic applications, are presented in the next chapter. The authors are careful in suggesting that data from the in vitro receptor binding studies have often been overinterpreted particularly because in vitro studies do not take into account the in vivo pharmacokinetic data. The authors suggest that the central nervous system effects of St. John's wort extracts are not due to direct interactions of its major chemical constituents, hypericin and hyperforin, with the receptors or neurotransmitter transporters, since concentrations of these chemicals necessary to produce significant in vitro interactions with the receptors and transporters far exceed those found in the brain after pharmacologically effective doses of the extracts have been administered.

In the next chapter, which is probably the most up-to-date of all the chapters in this monograph, the authors conclude that the preclinical studies with hyperforin and adhyperforin indicate that they are unselective inhibitors of 5-HT, dopamine, norepinephrine, GABA, and L-glutamate uptake. On the basis of the data available, inhibition of Na^+-dependent neurotransporter mechanisms due to the intracellular elevation of $[Na^+]$ is suggested by these authors as the principle mechanism. However, one should be careful in accepting this as the in vivo mechanism of action because such a fundamental change in the $[Na^+]$ would drastically alter many other cellular functions. Additional effects of these compounds on $[Ca^{2+}]$, on vesicular uptake, and on vesicular release of monoamines further complicate the issue of the mechanisms of action of St. John's wort as a clinically effective antidepressant. Although appropriate illustrations have been included in this chapter, Figure 1 (p. 32) illustrating the mechanisms of action of St. John's wort extract has an error in showing NE as being stored in the vesicles of a 5-HT synapse.

From the results obtained by using both in vitro and ex vivo neurochemical techniques, the authors of this chapter essentially draw the same conclusion that the mechanisms of action of St. John's wort extract and of heperforin are more complex than those of SSRIs, NSRIs, and MAOIs. The conclusion drawn by the authors of this chapter is that St. John's wort extracts and hyperforin show effectiveness in animal models of depression. The test systems used include the forced swimming test, escape deficit test, and the stress disruption of sustained appetitive behavior test.

Evaluation of preclinical antidepressant activity of isolated constituents of the St. John's wort extracts is the theme of the next chapter. After reviewing relevant evidence, the authors conclude that at present only a few constituents of St. John's wort extracts have been isolated and studied for their pharmacological activity. The pharmacological effects of single constituents differ when studied alone compared to the mixture of various constituents administered together. Thus, a clinically effective extract is more than its individual constituents.

The next chapter deals with the effects of St. John's wort extracts and of hyperforin on rat models of anxiety, depression, and cognitive functions as well as their effects on the central cholinergic neurotransmission. The author concludes that the activity profiles of St. John's wort extracts and of hyperforin are unlike those of known antidepressants and psychoactive agents. Effectiveness against nicotine withdrawal, causing reduction in alcohol intake, memory consolidation, and facilitation of learning ability, stimulation of AcCh release, and modulation of amyloid processing (in vitro) are some of the activities that might form the basis of use of St. John's wort extracts in other clinical conditions.

Pharmacokinetics of hyperforin, hypericin, and pseudohypericin and other chemical constituents after administration of St. John's wort extracts and evaluation of bioequivalency is addressed in the next chapter. The advantages of studies conducted in biorelevant media, compared to those conducted in compedial media, for dissolution testing are discussed and emphasized. This chapter provides very useful information on pharmacokinetics of active ingredients and the bioequivalency of clinically used extracts.

Clinical efficacy in short-term and long-term studies is discussed in the next chapter. It is emphasized that St. John's wort extracts show a favorable side effects profile, and the usefulness of meta analysis to establish the validity of data obtained from various clinical trials is discussed. The author concludes that after more than 20 years of clinical studies, usefulness of St. John's Wort extracts in the treatment of mild-to-moderate depression is well established. The author suggests

that St. John's wort extracts are effective in somatoform disorders also.

The next chapter provides important information on side effects and drug interactions. Although it was suggested for many years that St. John's wort extracts are devoid of any side effects, more objective work and surveillance have established that they produce several types of side effects and that these extracts cause significant pharmacokinetic drug interactions involving cyclosporin, dicoumarol types of oral anticoagulants, antiviral agents, and anticancer agents.

The last chapter deals with the release of hormones such as ACTH, corticotrophin releasing factor, cortisol, prolactin, melatonin, growth hormone, and others. It has been suggested that the central neurotransmitter function is involved in the release of hormones. If St. John's wort is producing its antidepressant effects by its action on the central neurotransmitter function, then one can study the hormonal changes induced by St. John's wort as a way to understand the mechanism of its antidepressant effect. This line of reasoning is interesting to follow, but the results presented do not give a clear understanding of the relationship between the two effects.

In conclusion, it is clear to this reviewer that this book presents an excellent account of experimental as well as clinical research that has been done on St. John's wort. Not only have the authors been successful in presenting up-to-date information on many important topics but they have successfully discussed the pros and cons of many conclusions. Bibliographies for each chapter are up to date. It is recommended that all those who are involved in clinical as well as in experimental work on St. John's wort should keep a copy of this book as a ready reference. The editor of this book should be congratulated for his efforts.

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