Book Reviews

Drug Metabolism in Drug Design and Development. Edited by Donglu Zhang, Minshe Zhu, and W. Griffith Humphreys. Wiley-Interscience, Hoboken, NJ. 2008. xxi + 609 pp. 16 × 24 cm. ISBN 047173313x. $110.00.

This book should be read by anyone interested in drug metabolism in drug development. It is divided into four sections, each of which will appeal scientists with different levels of expertise in the field. The first section would be an appropriate introduction to drug metabolism for new graduate students interested in the pharmaceutical sciences. The second section provides important information for anyone who wants to understand the role of drug metabolism in the context of developing new drugs. Sections 3 and 4 provide enough details to be interesting to anyone practicing in the area of small molecule characterization and doing drug metabolism.

Section 1 provides a nice overview of drug metabolism and drug metabolizing enzymes. The first three chapters provide an overview of phase I and phase II enzymes and of the importance of drug metabolism in drug design and development. This is followed by a chapter on enzyme kinetics, including atypical kinetics, and different types of inhibition. This is a very nice overview of the kinetics of enzymatic systems, with good references. Metabolic drug−drug interactions, induction, in vitro/in vivo concerns are covered in the next chapter. This is followed by an introduction to transporters with a helpful table of transporter-based drug−drug interactions. An interesting section covers strengths and weaknesses of different in vitro high throughput transporter assays. This chapter is very thorough with a large number of references. The last chapter in this part gives an overview of regulatory considerations, the FDA regulations and guidelines relating to drug metabolism. The section on the pitfalls of relying on in vitro data to predict in vivo outcome makes for interesting reading, and the discussion about toxicity testing for major metabolites is also thought-provoking. This chapter provides a number of references that deal with the complex regulatory aspects of drug metabolism.

Section 2 is entitled "Role of Drug Metabolism in the Pharmaceutical Industry". It is divided into the roles of drug metabolism in drug discovery and in drug development. The many benefits of including drug metabolism in drug discovery are discussed in the first chapter, and this is a "must read" for synthetic medicinal chemists. A discussion of accounting (or not) for free fraction in in vitro/in vivo correlations provides interesting food for thought on how errors cancel in these types of correlations. Reactive metabolites are also discussed in some detail here. The next chapter discusses the role of drug metabolism in the development phase and mainly focuses on in vivo drug metabolism, pharmacokinetic studies, and metabolite safety.

Section 3 gives an overview of analytical techniques in drug metabolism with the first chapter giving a detailed description of radiochromatography techniques. This is followed by HPLC/MS methods in the next chapter. This chapter has a useful introduction to ionization methods and different mass spectrometers, followed by the applications to metabolite identification. Some helpful tables are included that summarize the different masses and mass changes that can be used to identify different metabolic pathways. Overall, this chapter is very thorough and provides a large amount of background information for anyone interested in small molecule mass spectrometry. This is followed by a chapter that covers metabolite identification by NMR.

The final section of the book (part IV) gives very detailed experimental protocols for common experiments in drug metabolism. Topics covered include metabolic rates, assessment of bioactivation, reaction phenotyping, in vitro inhibition of P450 enzymes, 3A4 induction, and animal studies.

Overall, I highly recommend this book to anyone interested in drug metabolism. It suffers from not having any detailed discussion of in silicio methods in drug metabolism/design and has a number of typographical errors in the references and figures. However, it does provide a good overview of the common practices used in drug metabolism. Graduate students, pharmacologists, and medicinal chemists will all appreciate the introductory and overview chapters that provide a number of good references that will provide more details. Anyone working in drug metabolism will be interested in the detailed protocols and experimental methods provided later in the book.

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Iminosugars: From Synthesis to Therapeutic Applications. Edited by Philippe Compain and Olivier R. Martin. John Wiley and Sons, Ltd., Chichester, U.K.2008. xiv + 467 pp. 17.5 × 25.5 cm. ISBN 352731699x. $200.00.

Iminosugars are carbohydrate analogues that possess a nitrogen at the position usually occupied by the endocyclic oxygen. This family of compounds was first conceived and prepared in the mid-1960s, and soon thereafter, examples such as the antibiotic nojirimycin were isolated from natural sources. With so many exciting discoveries in the field over the past decade, this book is a timely and successful discussion of an intriguing class of compounds now moving from the laboratory to the clinical setting.

The book comprises 14 chapters contributed by 30 active and internationally recognized investigators in the area. With such a large and varied subject it is always a challenge to produce a cohesive volume, but editors Compain and Martin have done a good job in this regard. After a Foreward by chemist Stephen Hanessian, one of the earlier investigators of iminosugars, the book begins with a Preface and Chapter 1 by the editors themselves. They relate that since the discovery of these compounds 40 years ago a first renaissance of interest in them occurred in the mid-1970s when their profound biological activity was initially noted. The editors contend that we are now in yet a second renaissance of iminosugar excitement fueled by new synthetic methods for their construction and expanding medicinal applications. Chapter 2 deals with structure, activity, and applications of naturally occurring iminosugars, many of which are polyhydroxylated pyrrolidine and piperidine alkaloids. Likely, even more diverse natural product iminosugars await eventual discovery.

Chapters 3−5 next address the issue of the preparing these challenging compounds. Chapter 3 nicely summarizes the general synthetic strategies to assemble monocyclic, bicyclic, and iminosugar conjugate forms of this compound class. The references appear to be timely, with a number of them as recent as 2006. The remaining book chapters are devoted to the specific applications of iminosugars as enzyme inhibitors, antiviral drugs, and cancer chemotherapeutic agents. To a degree, Chapter 13 is somewhat repetitive, but it does provide a good overview of the large range of iminosugar medicinal applications, especially from a clinical perspective. The final chapter of the volume is extremely valuable. It is a lengthy, tabular compilation of more than 600 iminosugars arranged in increasing structural complexity, correlating these compounds with their biological activities, as well as numerous literature references. The book concludes with a comprehensive key word index.

Given the recent resurgence of interest in this class of compounds, the text is a welcome review of the area. The overall quality of this multiauthor work is very good, and the chapters are readable with many pertinent references to the original literature. The volume will definitely find a useful place in university libraries as well as both academic and industrial groups engaged in carbohydrate synthesis and drug discovery.

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Drug Discovery and Development. Volume 2. Drug Development. Edited by Mukund S. Chorghade. John Wiley & Sons, Hoboken, NJ. 2007. xvii + 381 pp. 18 × 26 cm. ISBN 978-0-471-39847-6. $99.95.

This is the second book of a two-volume set. The first was reviewed here some 20 months ago. According to their prefaces, the volumes are not an encyclopedia but they are "envisioned to be an advanced-level monograph with appeal to active researchers and investigators in drug discovery and development" and a text for a course in pharmaceutical chemistry.

Of 15 chapters (Chapters 17−31, numbered sequentially starting from Volume 1) written by nearly 30 authors from academic and industrial laboratories in the U.S., EU, and India, one-third discuss subjects in drug *discovery* rather than drug *development*. An examination of bioactive molecules in medicinal plants (Taneja and Qazi) is useful for a presentation of their structures and of an outline of some experimental techniques but not for outrageous assertions regarding their therapeutic utility ("herbal medicine: the best possible route to health care"). Ley et al. give an excellent, well-documented description of the multistep application of supported reagents, scavengers, and catch-and-release techniques to the synthesis of natural products and structurally related libraries. The discovery and SAR of insulin sensitizers are presented by Lohray and Lohray. Sharma and Krishna discuss synthetic routes to C-glycosides, after wrongly asserting that carbohydrates were thought to have "no signifiicant biological function" up to 1969 (ignoring the determination of the structures of streptomycin [1947], puromycin [1953], and digitoxin [1962]). In "Library Quality Metrics", Wife and Tijhuis consider (without documentation) chemical strategies to enhance the quality and biological relevance of chemical libraries, particularly with reference to ADME properties that they cite as being responsible for 40% of clinical failures. These are old data; by 2000 industry efforts had reduced ADME attrition to 10%, whereas efficacy and toxicology had become the major obstacles, accounting jointly for 50% of attrition (Kola and Landis, 2004). Nor do these authors refer to standard chemical diversity metrics such as Tanimoto similarity calculations.

In the development-oriented contributions, P. Pollak ably documents outsourcing in drug manufacture: its rationale and requirements, its increasing magnitude, its facility requirements, and its scheduling and contractual characteristics. S. Kulkarni cogently reviews process chemistry regulatory requirements, discussing such approaches as emission control and green chemistry and closing with an example of their application to aromatic nitro compounds for pesticide synthesis. Extensive analyses of process scale-up issues are presented in Chapters 23, 27, 29, and 30, each of which ends with a variety of API (active pharmaceutical ingredient) case studies. Developments relating to chiral catalysis and enantioselective synthesis, topics of growing current technical and intellectual property importance, are explored in Chapters 20 and 21. The subject of polymorphs and salts of API materials is broadly considered in Chapter 24 by Pandey et al. As I know from recent experience as a consultant, the properties of polymorphs and salts of API materials can have major effects on their intellectual property status, a matter that is not widely appreciated. A concise but important treatment of the principles and practice of clinical drug development by Scott outlines the ethical and regulatory aspects of preclinical development and clinical development.

Less comprehensive than its title suggests, this monograph focuses on chemical aspects of drug development, but it ignores or gives short shrift to other drug development activities such as formulation, drug metabolism, safety pharmacology, toxicology, pharmacokinetics, toxicokinetics, genotoxicity, and project management. The book is reasonably priced, well-written, and produced. It includes a relatively brief seven-page index, and it may be considered for acquisition by both industrial and academic libraries.

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