Natural Born Killers

Natural Compounds as Drugs, Volumes I and II

Edited by *Frank Petersen* and *René Amstutz*.

Birkhäuser Verlag, Basel 2008. Volume I: XII + 377 pp., hardcover €189.00.—ISBN 978-3-7643-8098-4; Volume II: X + 427 pp., hardcover €189.00.—ISBN 978-3-7643-8594-1

Over the last decade, the pharmaceutical sector has largely turned its back on natural product-based drug discovery programs. This fall from grace for natural products can be linked to the advent of automated high-throughput screening and synthesis techniques, beside which the traditional "find-and-grind" approach to natural product isolation appeared out-dated and "dirty". However, these technological advances have failed to improve the basic metrics of drug discovery, and their adaptation to natural product-based drug discovery programs, as detailed in Natural Compounds as Drugs, may well signal a revival for "Mother Nature's chemistry".

These companion volumes are the most recent additions to the Progress in Drug Research series and cover a broad range of topics that transcend conventional divisions in natural product research. Both volumes contain nine chapters written by experts from academia and industry, and are extensively referenced and easily navigated through the table of contents and keyword index. Thematically, Volume I focuses on natural product drugs and drug candidates, evolution and diversification of secondary metabolites, biodiversity and chemical diversity, and recent developments in the screening and production of secondary metabolites. Volume II covers complex natural product synthesis and new approaches to expand and explore the natural product structural space or identify modes of action. Volume II concludes with a series of monographs that chronicle the development of several naturally occurring compounds into drugs or drug candidates.

Volume I starts off with a well-organized chapter aptly titled "Mother nature's gifts to diseases of man", which reviews natural product drugs in current use and those in Phase II/III clinical trials or undergoing drug registration (accurate to October 2006) sub-divided by disease class. This review clearly highlights the historical and continued significance of natural compounds in drug discovery and sets a theme for both Volumes I and II: *the future is bright for natural products!* While the following chapter focuses on plant-derived drug candidates and contains some duplicate information, a more detailed description of the most promising lead compounds is offered along with a useful discussion of large-scale production methods and the successes and failings of the Convention on Biological Diversity. The following two thought-provoking chapters discuss the diversification of secondary metabolite production from an evolutionary standpoint or with respect to biodiversity. Both chapters include intriguing discussions on the ecological roles of secondary metabolites as well as the importance of understanding these roles in directing the selection of organisms for screening. These chapters also set the stage for an excellent review on high-impact technologies for natural product screening that includes a useful summary of pitfalls commonly encountered in screening campaigns along with some practical solutions. In addition, advances in mass spectrometry and NMR spectroscopy applicable to the rapid dereplication of natural product hits are summarized. This chapter is a valuable source of references and practical tips for practitioners in the field. The next chapter focuses on the virtual screening of natural products with an emphasis on integrated screening strategies designed to improve the quantity and quality of hits identified in screening campaigns. The final two chapters in Volume I discuss methods designed to enhance the production of secondary metabolites by microbes or plant cell cultures for the pharmaceutical sector and are excellent resources for those involved in process development.

The second volume of Natural Compounds as Drugs starts with a survey on the activation of silent gene clusters through genetic engineering as a means to produce new secondary metabolites, which is followed by an extensive and highly detailed review on the biological activity and synthesis of the macrocyclic pipecolic acid natural products FK506, antascomicins and rapamycin. Where appropriate, mechanistic discussions are included and each synthesis is critically analyzed with an emphasis placed on overall yield and convergence. This authoritative review includes over 450 references and close to 120 very well-organized schemes depicting what are certain to be classics in synthesis. The subsequent chapter details efforts in natural product-inspired diversity-oriented synthesis (including a step-by-step approach to library production) and is followed by a very interesting analysis of more than 130 000 natural product structures using cheminformatics. This study compares and contrasts the most common structural scaffolds and substituents found in natural products with those found in common organic molecules and drugs, highlighting accessible areas of structural space that have been underexplored.

The final review surveys recent developments in the exciting area of chemical genetics profiling that permit prioritization of crude extracts or rapid deconvolution of target pathways. Volume II concludes with four chapters compiled by industry experts that detail natural product-based (epothilones, artemisinin, FK228) or inspired (fingolimod) drug discovery programs. Each chapter provides an overview of the development process from crude extract to clinical trials, including discussions on discovery, mechanism of action, medicinal chemistry and large-scale production. For example, the final chapter (artemisinin) provides, in great detail (e.g. color photographs of artemisinin crystals of varying purity and a HPLC chromatogram of crude artemisinin), a behind the scenes look at the challenges encountered and overcome in developing an agriculturally produced drug substance and the global effort required to deliver over 100 million artemisinin-based combination therapies to African countries as part of the Roll Back Malaria initiative. These chapters provide tremendous insight into the drug discovery process, and are an excellent conclusion to this two-volume tour de force in natural product chemistry.

Together, Volumes I and II provide a detailed and up-to-date look at the state of the art and evolving practices in natural product-based drug discovery and highlight the bright future for natural compounds as drugs. The figures and schemes are clear, and through an excellent choice and organization of reviews, the editors accomplish their stated goals in demonstrating how natural products can be integrated into modern drug discovery programs and the incredible potential for natural compounds as drugs. Although the combined cost of these volumes may preclude their use as graduate-level textbooks, both volumes would be excellent resource material for a senior undergraduate or graduate course in natural products or drug discovery, or for faculty, students and industry professionals engaged in natural product research.

Dr. Robert A. Britton
Simon Fraser University (Canada)
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Essential Concepts in Toxicogenomics (Methods in Molecular Biology Series)

Edited by *Donna L. Mendrick* and *William B. Mattes.*

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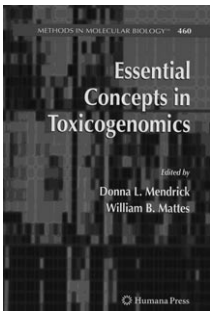

Toxicogenomics has now been with us for more than 10 years. It was first heralded as representing a "sea change" in the toxicological sciences, and there was considerable optimism that the ability to simultaneously interrogate toxicant-induced changes in many thousands of genes—or even the entire genome—would transform predictive and mechanistic toxicology overnight. After that first flush of enthusiasm had been tempered by experience, there was a period of consolidation and of re-evaluation of how best this technology might be deployed in the interests of toxicology. This period was characterised by the realisation that it is not always easy to translate data into knowledge—and that the problem is even greater when it is possible to generate vast amounts of data. In recent years, toxicogenomics has come of age—or at least is coming of age—and this excellent and very readable book reflects that growing maturity and the increasing utility of "omics" technologies.

The book is comprised of 12 separate chapters with many leading lights in the discipline as contributing authors. The book opens with an excellent piece by one of the editors (Donna Mendrick) that effectively and concisely sets the scene for the remainder of the volume. Thereafter all the key elements—theoretical and practical—that are required for the successful design, conduct and interpretation of toxicogenomic investigations are discussed in some detail. Included are considerations of the application of toxicogenomics to mechanistic toxicology and predictive testing, the identification of novel biomarkers, and preclinical drug development. Importantly, and in addition to coverage of these discrete scientific applications, there are extremely thoughtful and valuable chapters that examine, among other issues, the role of statistics in toxicogenomics, quality control, the use of and need for bioinformatics and gene annotation, the work of public consortia in toxicogenomics, and—in the concluding chapter—a regulatory perspective in the context of drug development.

Overall, this is an excellent book that will be of interest to all those who practice toxicology, and particularly those using microarray analyses. This reader would perhaps have liked to have heard a little more about some of the regulatory issues that are posed by the increasing use of toxicogenomics, but that is a minor quibble, and not one that prevents me from recommending this book unreservedly.

Prof. Ian Kimber
University of Manchester (UK)

New Antibiotic Targets

Edited by *W. Scott Champley.*

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Much has been written about the alarming rate at which pathogenic bacteria are becoming resistant to available antibiotics and the resulting clinical consequences and economic impact on the healthcare system. Whereas antibiotic resistance was once largely confined to hospitals and long-term care facilities, resistance has emerged in community settings and has escalated into one of the most pressing global public health concerns. Resistance is an unavoidable side effect of antibiotic use and this fact fuels the search for new antibiotic targets and novel therapeutic agents to treat drug-resistant organisms and emerging infectious diseases. *New Antibiotic Targets* is an attempt to assemble a broad selection of detailed methods for antibacterial

