Book Reviews

Carbohydrate-Based Drug Discovery, Volumes 1 and 2. Edited by Chi-Huey Wong (Scripps Research Institute). Wiley-VCH, New York. 2003. xxxii + 459 (1) pp; xxiv + 486 (2) pp. 7 × 10.5 in. $295.00. ISBN 3-527-30632-3.

As little as 15 years ago, the role of carbohydrates in biologically relevant processes was highly underappreciated, let alone associated with the discovery of novel therapeutics. Today the situation is radically different, with the recognition that cellular glycans—in particular those covalently attached to proteins and lipids—rival in importance their protein and nucleic acid counterparts. Since cells use carbohydrate structures to communicate, attach, move, infect, and metastasize, it is no wonder that drug discovery research would model strategies to modulate or inhibit these processes based on the structures themselves. These two volumes constitute a very successful attempt to decipher the current state-of-the-art in this burgeoning field.

The volumes are loosely clustered into subject categories dealing with the preparation and characterization of saccharides in general, interspersed with case studies of specific carbohydrate structures or families that have been directly evaluated as drug candidates. Volume 1 opens, not surprisingly, with several chapters on synthetic methodology that set the stage for the production of actual therapeutic agents. Chapters 1−3 take us through general methodology with an emphasis on glycosylation chemistry, the synthesis of complex carbohydrates (a chapter wholly devoted to ganglioside oligosaccharides), and a comprehensive and excellent tour of the chemistry of sialic acid from de novo synthesis to the engineering of novel analogues. Chapter 4 succinctly describes the state-of-the-art in solid phase synthesis of various glycans with references to biologically relevant molecules. Chapter 5 seems to represent a very brief "bridge" between Chapters 4 and 6, in which the author communicates a technique that combines the use of water-soluble polymers and immobilized glycosyltransferases as a biomimetic glycan synthesis system. The enzymatic synthesis of oligosaccharides is described in Chapter 6, covering very useful technologies from various labs (including the authors'). This leads to the chemistry and biology of glycopeptides, a very relevant subject well documented in Chapter 7, with a section on the use of synthetic glycopeptides in cancer immunotherapy. A fascinating and elegant case study of the synthesis of an important antibiotic containing a highly complex carbohydrate portion, everninomicin, follows in Chapter 8, and Chapter 9 describes the pangs and successes in the synthesis of asparagine-linked glycans. Chapter 10 continues with more details of the biochemistry of N-linked glycosylation, outlining examples of synthetic inhibitors of this pathway. Two chapters by the Kishi group follow. The first takes on the conformational analysis of C- versus O-linked glycosides, an area that this group pioneered, and the second describes a drug discovery effort toward the development of synthetic analogues of lipid A, the bacterial-based toxin responsible for life-threatening sepsis. Chapters 13 and 14 continue with one of the "original" applications of carbohydrate therapeutics, namely, vaccine design, and deal with polysialic acid vaccines and primarily cancer vaccines, respectively. Both first- and second-generation vaccines, i.e., purified immunogens and synthetic neoglycoconjugates, are covered by both authors. The volume concludes with a discussion of the biochemistry and therapeutic potentials of the glycosaminoglycans (GAGs), another structural family involved in several critical disease-related signaling pathways. The discussions cover heparin, hyaluronan, chondroitin sulfate, and others, while the final chapter deals specifically with a small synthetic heparin analogue as a potential antithrombotic.

Volume 2 continues in a different vein, concentrating initially on the structural analysis of relevant glycans from various animals and tissues with excellent reviews on sequencing, EI mass spectrometry of aminoglycosides, high-pH anion exchange chromatography of a P-selectin antagonist, and analytical techniques for GAG characterization. Multivalency is covered next with a thorough technical as well as practical review, followed by more examples of synthetic multivalent ligands designed to specifically inhibit biological processes. The next chapter tackles the subject of glycosyltransferase inhibitors, an extremely important area of carbohydrate drug discovery that serves to unravel biochemical pathways and possibly prevent various diseases. The structure−activity relationships of amino glycoside−RNA interactions are nicely discussed, followed by what may be of keen interest to the readership of this Journal—the function of the sugars in glycosylated natural products. This field was also once underappreciated, but has recently come to prominence by the work on molecules such as bleomycin, vancomycin, and erythromycin. Novel enzymatic mechanisms in the in vivo production of unusual sugars are covered next. These can be very important in bacterial and viral immunity. Glycolipids are then discussed in a chapter on the determination of functional saccharides from neoglycolipids, which is followed by a contrasting view that considers the role of the lipid portion of the glycoconjugate in membrane organization and function of entire glycolipid molecules. There is a chapter on small molecule inhibitors of sulfotransferases, a field in which great strides have been made in just a few years. Cancer metastasis is treated next, concentrating on the role of Lewis antigens and selectins in tumor progression and dissemination and the role carbohydrate mimics may have in slowing this process. The next chapter aptly discusses *N*-acetylneuraminic acid analogues as anti-influenza agents (the author's group was the main player in the discovery and development of the anti-influenza agent Relenza). Two short reviews outline efforts to discover modified sugars as therapeutic agents. The first describes sialic acid derivatives and the second deals with glycosylated phospholipids as potential antiproliferative agents. An interesting chapter on glycoside "primers" follows. This concept is based on the addition and cellular uptake of simple glycosides with hydrophobic aglycones that serve to affectively divert the standard endogenous glycan processing pathways toward the utilization of the added glycoside for the biosynthesis of unusual sugar chains. This "priming" may be useful in probing glycosyltransferase mechanisms as well as the treatment of various diseases. The volume concludes with an offering by the editor on efforts

to develop new antibiotics based on exploiting various biosynthetic pathways in bacteria that can be inhibited by sugar analogues. This is described in the context of a one-pot programmable oligosaccharide synthesis system developed in the author's group. This is a major advance in the rapid preparation and therapeutic evaluation of oligosaccharides.

As is evident from the above description, these volumes are a must for those interested in almost any aspect of carbohydrate chemistry and biochemistry as it relates to drug design. The editor has done an admirable job in assembling experts in the field to contribute to the volumes. There seem to be no major errors in content, and omissions from the field are few. The volumes are written for the more advanced readers, with adequate referencing and a welcome use of "interim summaries" of specific sections in some chapters to orient the reader for the subsequent discussion. While not all natural product chemists may be equally thrilled by this area of therapeutics, they nonetheless will have a reference to all major areas of carbohydrate drug design with this set on their shelves.

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Handbook of Plant Biotechnology, Volumes 1 & 2. Edited by P. Christou (Fraunhofer Institute of Molecular Biology and Applied Ecology) and H. Klee (University of Florida). John Wiley & Sons, Ltd., Chichester, UK. 2004. xxvii + 1420 pp. 19 × 25 cm. $695. ISBN 0-471-85199-X.

This two-volume handbook is an ambitious effort by two well-recognized editors, assisted by 145 expert authors contributing a total of 69 chapters, to cover every possible aspect of biotechnology, from classical genetics and breeding to the business and international impact of biotechnology. Each section of the handbook is introduced in lay terms by an authority in the field, and many chapters are concluded with a view into the future, a necessity in a field moving at a very fast pace. The editors provide useful appendices, including current products derived from plant biotechnology and key patents in the field. In a work of this magnitude, redundancy between chapters is unavoidable, but the editors have managed to keep repetition and errors to a minimum. While some of the longest chapters provide selected technical directions that could be of use to the experimentalist, most of the sections provide accurate and current overviews of specific topics or techniques, with appropriate references to more specialized publications.

Efforts to integrate plant biotechnology into a single publication have been tried before. In my view, however, few have succeeded in this endeavor in the way this handbook does. This very comprehensive repertoire of scientific disciplines, as the editors attempt to define plant biotechnology, is both the main strength and weakness of this handbook. It is difficult to identify the ideal readership for this work. The high, yet easily justifiable price of the handbook makes it prohibitive as a textbook for the increasing number of courses taking the global view of plant biotechnology offered here. However, the handbook would provide a powerful reference for professors and instructors teaching plant biotechnology, as well as a convenient source of references for scientists working in any of the multiple disciplines covered here. In summary, although this handbook is not openly targeted to natural product specialists, with only two chapters focusing directly on plant natural products and plant metabolic engineering, it contains information that will certainly be of use to anybody with an interest in the multiple applications of plants for biotechnology.

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Promoting Civility in Pharmacy Education. Edited by Bruce A. Berger (Auburn University). The Haworth Press, Inc., Binghamton, NY. 2003. 122 pp. 6 × 8.5 in. $19.95 (soft); $34.95 (hard). ISBN 0-7890-21201-8.

Edited by Dr. Bruce Berger, who has written and published extensively on this subject, this book focuses on promoting civility in pharmacy education. Incivility is a speech or action that is disrespectful or rude. Dr. Berger believes all incivilities can be prevented or eliminated and that they occur most frequently when people are stressed. They occur with faculty as well as students. In this book a number of contributing authors provide a variety of perspectives for all kinds of situations that may arise in the classroom, and most importantly the book is about preventing and managing incivilities in different settings.

Dr. Berger provides the introductory chapter as well as a chapter dealing with civility in large classrooms. Dr. Brian Crabtree addresses civility in the small classroom or small group setting. Drs. Diane Beck, Janelle Krueger, and Debbie Byrd have a chapter on experiential learning, transitioning of students from civility to professionalism. Dr. Dana Hammer has written a chapter on this subject as well. Dr. Donna West describes her experience as a new faculty member dealing with civility issues. Dr. Heidi Anderson-Harper explores boundary violations and faculty groups that are vulnerable to incivilities. Finally, Dr. Holly Mason describes the situation as it pertains to graduate education.

All of these chapters are well written and provide tremendous insight into an ever-growing problem in education in general and especially in a pharmacy setting. There are excellent examples of what to do and not do, and how to best handle these situations—what works and what does not.

The book will primarily appeal to faculty members teaching in a school or college of pharmacy since many of the chapters deal specifically with unique aspects of pharmacy education. However, anyone dealing with undergraduate education would benefit from reading these chapters. This book would also be a very valuable resource in dealing with civility issues in graduate education as well. The cost of this paperback is very reasonable and would

be a great resource for all faculty members. This reviewer recommends it highly, especially for new faculty members.

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Biosynthesis in Insects. By E. David Morgan (Keele University). Royal Society of Chemistry, Cambridge, UK. 2004. xiv + 208 pp. 6 × 9 in. £34.95. ISBN 0-85404-691-7.

Over the past 40 years, the field of chemical ecology has uncovered a huge variety of compounds that play essential roles in the behavior and life cycles of insects. The question of how these compounds are formed becomes a useful predictive tool when structure elucidation must be carried out on submilligram amounts of material. This intriguing volume was written as a textbook for a postgraduate course on the biosynthetic origins of insect chemicals, complete with questions at the end of each chapter, and it introduces its subject so clearly that an advanced undergraduate should easily master the material. The chemical structures are clearly drawn, and there is a section of excellent color photographs of insects exemplifying some of the more striking examples discussed in the book.

There are chapters introducing basic concepts and definitions of natural product structure, the study of biosynthetic pathways, and a detailed explanation of specific enzymes and coenzymes and their particular chemical activities. Additionally, there is a chapter describing the various biosynthetic methods, ranging from traditional radiolabeling to stable isotope incorporation using the power of modern NMR and mass spectroscopy.

There are two chapters dealing with the formation of fatty acids and polyketide acetogenins found in insects, since they are ubiquitous and serve as precursors to many other kinds of compounds. The discussions are wide-ranging, showing the origins of such compounds as pheromonal hydrocarbons, beetle alkaloids, and green leaf volatiles from the fatty acids and of aromatic coumarins and volatile cyclic ketal pheromones from the acetogenins.

The last four chapters are the heart of the book, covering terpenes, higher terpenes and sterols, aromatic compounds, and alkaloids. Each of these chapters begins with a detailed section on biosynthesis, followed by sections concerning compounds of increasing complexity within the class. For example in the chapter on aromatic compounds, after a presentation of the shikimic acid pathway, the sections that follow are phenyl-C_3 compounds, aromatic amines, phenols, quinines, and last a large section on complex insect pigments, melanin, aphins, pterins, tetrapyrroles, ommochromes, etc. Finally, there is a chapter presenting the present state of knowledge of the interesting plant compounds that are sequestered by insects.

Biosynthesis in Insects is intended by design to be a textbook rather than a scholarly review, but anyone conversant with modern literature search technology can easily find the relevant original literature. What makes this book exceptional are the fascinating examples presented in each chapter. The presentation of this material sparks an interest in the subject far beyond what would be expected of a review of insect natural products. This rare quality is what is so necessary in higher education to nurture a new generation of biochemists, chemists, and chemical ecologists.

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Drugs, From Discovery to Approval. By Rick Ng (Biopharmaceutical Manufacturing Technology Centre, Singapore). Wiley-Liss, New York. 2004. xii +355 pp. 6 × 9 $^1/_2$ in. $59.95. ISBN 0-471-60150-0.

This is an affordable and well-written book that presents a clear, step-by-step overview of the entire process. Using simple language, this comprehensive guide introduces basic concepts and describes disease target selection and the discovery processes for both small and large molecule drugs. Subsequent chapters explain preclinical studies, clinical trials, regulatory issues, good manufacturing practices (GMPs), and perspectives on the future.

The book is written for professionals in the pharmaceutical industry and others who wish to study the "big picture" of the drug development process. The industry is constantly hiring specialists and requiring them to adapt quickly to a cross-functional environment, and this book goes some way to providing very useful tools. Coverage includes representative examples of drug mechanisms in action; introductory approaches in emerging technology of antisense, gene therapy, and cloning and stem cells; a helpful listing of current FDA and European guidelines; and a special section on regulatory authorities and processes in Japan and China.

This book is suitable also at the graduate level. Students specializing in popular disciplines such as molecular biology and medicinal chemistry, hoping to make careers in the industry, are not generally exposed to the background and tools needed to deal with the challenges downstream from early discoveries and the decisions required for drug development. The chapters follow a logical sequence and are well referenced. There are well-chosen diagrams and tables as support material, with illustrations throughout. If there is one small criticism, the figures used in the book are uneven and in several places are either too small or unclear.

The author presents an appropriate balance between the drug development process for both small and large molecules. There are different techniques and approaches required to find a lead molecule successfully. The author points to the importance of NMR and X-ray crystallography with explanations and examples, but short-changes the enormous impact of mass spectrometry. Rapid advances have been made in large measure based on complex structure determination, protein sequence and identification, use of photoaffinity labeling, and drug metabolism studies, to name but a few contributions in part due to advances in mass spectrometric instrumentation and detection.

Readers of this Journal might question the author's choice of the term "irrational approach" to drug discovery

and its relationship to screening natural products. Irrational approach is defined in the book as the historical method of discovering and developing drugs through empirical observations of pharmacological effects from screening of many natural products. Yet this approach has yielded most drugs available today, by successfully screening microbial products (especially bacteria and fungi), and the plethora of new compounds emerging from these programs is a testament to that endeavor. Targeted biological screens were used for both synthetic and natural compounds, with considerable success, microbe-derived compounds more so than plant- or marine-derived compounds (with taxol and vincristine being exceptions).

In contrast, the "rational approach" requires three-dimensional knowledge of the biological target structure involved in the disease, and drugs are designed to interact and elicit a biological response. In describing this approach, including combinatorial approaches, as "an emerging field", one can only suppose the author has done the math and realizes that huge efforts have yielded as yet little reward.

In a chapter on future trends, the author anticipates a continuing role of traditional medicine through application of scientific methodologies and controls that could be applied also to development of dietary supplements. Also, one day drugs will be tailor-made for individuals and adapted to each person's genetic makeup. In this way drugs will be used optimally and adverse effects reduced and possibly eliminated.

In conclusion, statistics show that out of five thousand compounds with initial promise, five will go into human clinical trials, and only one will become an approved drug. This tiny fraction illustrates the enormous complexities involved in bringing a drug to market, a process that brings together scientific research, medical ethics, business, and various regulatory agencies. In addition to strongly recommending this book to all scientists wishing to learn more about the drug discovery and development process, I believe it might also make good bedtime reading for company CEOs wanting to keep up with how their dollars are spent and how much scientific, technical, and regulatory effort is really needed to bring a drug successfully to market.

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