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BOOK REVIEWS

Carbohydrates in Drug Design By Z. J. Witczak and K. A. Nieforth, Eds., Marcel Dekker Inc. New York, 1997, ix + 703pp, \$175.00. ISBN 0-8247-9982-8.

The role of carbohydrates in life processes has been recognized increasingly over the last years. The translation of the recent progress in glycobiology into successful concepts in pharmaceutical research is, however, a slow process, and this book may be of help! The *design* of a drug is certainly a difficult task and requires a good knowledge of the target molecule, usually the X-ray structure of a protein; for most of the projects discussed in this volume, however, this degree of knowledge has not been reached yet.

The editors have managed to attract expert authors from four continents to give their view on various topics of carbohydrate chemistry with pharmaceutical relevance. Z. Witczak, one of the editors, starts off with an introductory chapter concisely reviewing the use of carbohydrates as drug targets in various indications - an excellent appetizer for the chapters to follow. In their chapter on "Sialic Acid Analogues as Potential Antimicrobial Agents" M. von Itzstein and M. J. Kiefel describe, besides a good amount of the chemistry of sialic acids, a true example of drug design: the development of an antiviral sialic acid derivative based on the X-ray structure of influenza virus sialidase, which is also represented on the book cover as an attractive eye-catcher. Above compound is in advanced clinical trials against influenza and shows good promise - a hot topic in drug research, indeed! R. Roy goes on with a chapter on the use of sialoside mimetics as selectin antagonists, including glycopeptide mimetics and pharmacophore approaches, good examples of carbohydrate medicinal chemistry. The principle of multivalent binding is pointed out, and sLe^x conjugates and dendrimer and cluster approaches are described. It is hoped that these compounds might be applied against influenza virus infections. The late A. Hasegawa and M. Kiso elaborate the synthesis of sLe^x oligosaccharides and analogues and sulfatide and analogues including binding data with selectins.

In chapter 5, M. Witvrouw, C. Pannecouque, and E. de Clercq describe polysulfated compounds as potential antiviral drugs and particularly anti-HIV agents. Sulfated poly- and oligosaccharides and sulfated modified cyclodextrins are reviewed covering chemistry as well as biological and clinical data in a well-equilibrated way.

S. Alban follows upon sulfated carbohydrates with anticoagulant and antithrombotic properties: heparin, low-molecular weight heparins, other glycosaminoglycans and sulfated oligosaccharides, but also synthetic carbohydrate derivatives of lower molecular weight are discussed including the clinical fate of these preparations. Chapter 7 by R. J. Linhardt and T. Toida unfortunately shows considerable overlap with the preceding one, and a focus on the title 'new analogue' of heparin oligosaccharides would have been desirable; a new paragraph is on activities of heparin other than anticoagulation.

S. Ozaki and L. Lei highlight chemoenzymatic methods (enzymatic esterification or hydrolysis) for the preparation of optically active inositol derivatives which play a role as second messengers, and K. S. Bruzik guides us well through the complicated field of receptor-mediated activation of phosphatidylinositol-specific phospholipase. Some medicinal chemistry on the basis of the three-dimensional structure of (bacterial) PI-PLC is explained. Inhibitors are predicted to find an application in cancer, inflammation, and non-insulin dependent diabetes mellitus.

Chapter 10 by S. Ogawa deals with carba-sugars as building blocks of natural products such as aminocyclitol antibiotics and glycohydrolase inhibitors as well as structurally related synthetic inhibitors. The following chapter by L. van den Broek nicely complements the preceding one and focuses on the aspect that azasugars might be used as anti-HIV drugs based on the inhibition of α -glucosidase I.

AZT and analogues are marketed drugs against HIV due to the inhibition of reverse transcriptase. The late S. Czernecki and J. M. Valery report on synthetic modifications of pyrimidine nucleosides at the carbohydrate moiety in chapter 12. J. W. Beach concentrates on the chemistry of those analogues in which the crucial 3'-position of the nucleoside has not been deoxygenated but replaced by a heteroatom.

Chapter 14 by W. Priebe and R. Perez-Soler is on anticancer anthracyclines related to doxorubicin and daunorubicin: the authors focus on modifications at the carbohydrate part to overcome the phenomenon of multidrug resistance; structure-activity relation based hypotheses led to the clinical testing of a new member of the family of anthracycline topoisomerase inhibitors. Chapter 15 by O. Achmatowicz and B. Szechner deals with the clinically employed antibiotic lincomycin which acts through a specific blockade of a ribosomal peptidyl transferase; the authors explain the chemistry of the interesting eight carbon sugar moiety as well as derivatives and analogues. In the last chapter A. Misaki and M. Kakuta report on fungal (1 \rightarrow 3)- β -glucans that are used as immunostimulants in cancer therapy in Japan.

In summary, this book gives a wealth of information and close to 2000 references to go into more details. Very helpful is the index of keywords to find rapid access to specific topics. Overall this highly valuable collection of reviews in the field of pharmaceutically relevant carbohydrate chemistry and biology is a pleasure to read and will attract a wide range of industrial as well as academic scientists and motivated graduate students.

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The Carbohydrate Bioengineering Meeting at Elsinore, Denmark, represented a significant gathering of carbohydrate biotechnologists, largely from European laboratories, with notable presence also of others invited from distinguished research centers throughout the world. Each of the twenty-eight chapters is of long lasting value. The first chapter by Prof. Nathan Sharon, "Glycans of glycoconjugates as modulatory and recognition molecules" is a keynote to the significance of much that follows in subsequent chapters. Since in Sharon's concepts the glycans, whether bound to protein or lipids, serve as recognition determinants in molecule-cell or cell-cell interactions, the next three chapters give details of these glycans by modern NMR analyses for their structure and dynamics (van Halbeek), linkage sequences by mass spectrometry (Nilsson), and sensitive enzyme electrode for determining sugar concentrations (Spener).

Subsequent chapters consider key carbohydrate hydrolytic enzyme activities from a mechanistic point of view, protein expression of cloned genes, and potential industrial scale-up of fermentation enzymes for commercial applications. Examples (by no means exhaustive of all the chapters) are carbohydrate binding to the *E. coli* maltodextrin phosphorylase (P. Drucekes); the chitinolytic system of a *Streptomyces* (H. Schrempf); the binding cleft of *Bacillus* 1,3-1,4- β -D-glucan-4-glucanohydrolases (*A. Planas*); and thiooligosaccharides as probes for catalytic active sites of glycanases (H. Driguez). Particular emphasis was paid to cellulolytic enzymes with statements pointing to the future of these hydrolytic tools in industrial saccharification processes in more than six chapters. The potential of cloned cellulases is also made evident in these cellulase chapters. An intriguing cellulase paper was that of Simi Ali on targeted expression of microbial cellulases in non-ruminant transgenic animals, which would then be capable of using structural carbohydrates such as cellulose and xylan as a dietary source.

A chapter that was particularly interesting in the light of Nathan Sharon's overview on the significance of glycans was that of Welinder and Tams on effects of glycosylation on protein folding, stability, and solubility in chemically modified or engineered plant and fungal peroxidases. The physical stability of these proteins, made from a series of recombinant glyco-forms of *C. cinereus* and then expressed in transformed *A. oryzae*, was measured thermodynamically on the peroxidases as heat denaturation and changes in absorbance at 402nm. Another experimentally very well conceived and presented chapter was that of Baptista and coworkers on electrostatic studies of carbohydrate active enzymes. This work probed charged or titratable residues residing on the protein surface of amylases as well as prediction of consequences of protein engineering on *Acetobacter xylinum*. Illustrations of three dimensional structures of these enzyme active sites in color photographs are remarkable models for understanding these catalytic mechanisms.

The mechanism and action of glucansucrases by John Robyt is a unique monograph of original research. The diversity of enzymes involved in such dextran-synthesizing systems is unified by these explanations of Robyt. The reader is alerted to the considerable substance of the work in this chapter. Another interesting variation on the enzymic conversion of sucrose to a glucan is the chapter by Remaud-Simeon on studies of recombinant amylosucrase, which makes only a slightly branched amylose-type product.

In terms of carbohydrate bioengineering a final chapter need be given attention because of its direction to multiple component agricultural waste utilization through application of cloned monocomponent carbohydrases for modification of plant materials. In this paper Kofod and coworkers from Novo-Nordisk show how they developed and applied several plant cell wall degrading enzymes through cloning, and how these enzymes can be used to degrade plant cell wall polysaccharides into potentially utilizable fiber or fermentation energy source. This work is particularly interesting because new recombinant organisms are able to take the products of, e.g., arabinoxylans or rhamnogalacturonans to more easily transformed substrates in fermentations.

The volume *Carbohydrate Bioengineering* is necessarily a polyglot of information and diversity of subject matter. Although the editors S.B. Peterson, B. Svensson, and S. Pedersen have done a commendable job of making sure that each chapter is highly organized and understandable, from chapter to chapter there are often great shifts of emphasis. The effect has been for me as a reader to study each of the chapters over a longer period of time because the attention span required for the whole book is so broad. On the other hand each of these chapters, without exception, is a worthwhile contribution to the field of carbohydrate developments in the enormously growing collection of knowledge about their scientific role in the makeup of living things, medicine, agriculture, and industrial materials. Consequently, this volume will remain a permanently valuable primary reference source for each of the subjects expertly presented in its pages.

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