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BOOK REVIEWS

Hydrolysis in Drug and Prodrug Metabolism: Chemistry, Biochemistry, and Enzymology. By Bernard Testa (University of Lausanne, Switzerland) and Joachim M. Mayer (deceased). Verlag Helvetica Chimica Acta: Zurich and Wiley-VCH GmbH & Co. KGaA: Weinheim, Germany. 2003. xx + 780 pp. $215.00. ISBN 3-906390-25-X.

This book provides an outstanding and comprehensive review of metabolic reactions catalyzed by hydrolytic enzymes (esterases, amidases, and epoxide hydrolases) and their role in the biotransformation of xenobiotic substrates. As indicated in the preface, what was originally conceived as a single chapter grew, out of necessity, into a thorough treatise covering all aspects of these versatile and essential enzymes, including nomenclature, catalytic mechanisms, substrate specificities, and the critical roles that these enzymes play in terminating drug action and bioactivating prodrugs.

The initial section of the book focuses on issues of nomenclature for the enzymes involved and the importance of these enzymes in the design of prodrugs to overcome barriers to a drug's usefulness. The specific challenges associated with the design of prodrugs are well articulated, and numerous examples of success stories in the design of prodrugs are presented throughout the volume. Schemes for classifying peptidases and esterases are thoroughly addressed in this section, and their cellular localization, tissue, and physiological roles are discussed. A comprehensive and detailed discussion of the catalytic mechanisms of the various subclasses of hydrolases as well as other enzymes that exhibit "hydrolase-like" activities is also given.

The second section addresses the enzymatic hydrolysis of amides, including acyclic amides, lactams, and peptides, with an emphasis on the relation between hydrolysis and substrate structure for amide-cleaving enzymes. Of particular interest is the treatment of β-lactam antibiotics (e.g., penicillins and cephalosporins) and their role in inactivating the hydrolytic transpeptidases involved in the synthesis of cell walls as their primary mechanism of antibiotic action and as the basis for selectivity against bacteria (versus human cells). The role of microbial β-lactamases in conferring resistance to antibiotics by their ability to destroy (hydrolyze) the β-lactam pharmacophore is also discussed. This logically leads to a discussion of the design of mechanism-based inhibitors of these protective β-lactamases in order to reestablish sensitivity of the pathogen to the parent β-lactam antibiotics. It is clear from the authors' comprehensive presentation of these related topics that a continued understanding of the evolving nature of these enzymes is essential in this escalating "cat-and-mouse" game associated with the development of resistance to antibiotics and our response in terms of drug design.

Hydrolysis of esters, including carboxylic acid esters and esters of inorganic acids, is the topic of the third section of the volume, with major emphasis on the role of carboxylic acid esters as the most commonly used functionality in the design of prodrugs. The authors provide excellent examples of the development of quantitative structure−metabolism relationships to help predict structural features that will yield optimized properties for prodrugs, for example, lipophilicity, contribution of steric and electronic factors, acceptable rates of hydrolysis to yield the active drug, etc. Examples of esters of inorganic acids that are addressed include the organic nitrates and nitrites used in the treatment of coronary artery disease and the organophosphates that are important as insecticides, plasticizers, and warfare agents.

The final section of the book addresses the hydration of epoxides, including the important role of epoxide hydrolases in endobiotic biosynthesis and the conversion of arene oxides to dihydrodiols. The latter area is of tremendous toxicological significance, and the authors provide a thorough discussion of the role of these enzymes in "toxification reactions" resulting from the production of diol-epoxides from polycyclic aromatic hydrocarbons and subsequent interactions with macromolecules.

The authors indicate in the introductory chapter that an objective of this book is to correct the comparative "neglect" afforded the role of hydrolytic reactions in metabolism compared to other types of biotransformations that have garnered more attention. This outstanding volume has accomplished that objective and much more. To quote from the last chapter, "...those who take the global view of the work presented here cannot fail to be impressed by the simultaneous unity and diversity of hydrolytic reactions."

Patrick J. Davis, *University of Texas, Austin*

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