Drug Development and Industrial Pharmacy, 32:399–400, 2006

ISSN: 0363-9045 print / 1520-5762 online
DOI: 10.1080/03639040500519466

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Book Review

Evaluation of Enzyme Inhibitors in Drug Discovery; Robert A. Copeland, John Wiley and Sons, Hoboken, New Jersey, Hardcover (271 pages), ISBN: 0-471-68696-4

Numerous texts are available that discuss the kinetics of enzyme catalysis and inhibition, often providing a mathematical treatment of the subject matter rather than using a conceptual approach. Although enzyme inhibition and the associated kinetics are fully described in these texts, specific drugs are generally used only to illustrate the various types of inhibition. Furthermore, the relationship between the evaluation of enzyme inhibitors and the drug discovery process is seldom discussed. Thus, the text *Evaluation of Enzyme Inhibitors in Drug Discovery* fills a significant gap by providing a complete guide to evaluating enzyme inhibitors in the generation and optimization of potential therapeutic agents.

This book is written to provide chemists and pharmacologists in industry and academia with a means to learn about and implement techniques that can be applied to the latest techniques in modern drug discovery. In eight chapters, this book provides the reader with a concise description of enzyme structure, energetics, catalysis, and inhibition. At the beginning of each chapter, a set of key learning points are included that describe the focus of the section. I found these learning points to be so general that they did not adequately outline the topics to be covered. Each chapter includes a set of references that range from classic, historical references to recently published manuscripts. Three appendices are included that provide additional practical information of interest to anyone involved in inhibitor drug discovery.

Chapter 1 sets the stage with a brief review of basic biochemical principles pertaining to enzyme structure and dynamics, as well as a rationale for the discovery of enzyme inhibitors as potential therapeutic agents. A number of examples of successful drugs that act through enzyme inhibition were included, and more than half of the chapter described the rationale for the discovery of new inhibitors. Chapter 2 extends the treatment of basic principles through a discussion of enzyme reaction mechanisms, including transition state theory, bonding forces, types of catalysis and steady state kinetics. Chapter 3 provides a standard description of inhibition kinetics by inhibition type, including graphical considerations. However, a portion of the chapter deals with topics unique to drug discovery such as inhibitor modality, target selectivity, and lead optimization. The remaining chapters of this text depart from a traditional description of enzyme kinetics and inhibition in favor of a discussion of inhibitor evaluation in drug discovery. Chapter 4 provides an excellent description of the use of enzyme inhibitor evaluation in library screening and touches on topics such as hit criteria, initial rates determinations, balanced assay conditions, and hit validation and progression.

Chapter 5 continues by discussing lead optimization and structure/activity relationships for reversible enzyme inhibitors. Techniques for determining reversibility, affinity, and modality are followed by a section describing methods to relate enzyme inhibition to cellular effects. Chapters 6 and 7 are devoted to slow-binding inhibitors and tight-binding inhibitors, respectively, and fully describe the unique kinetic and mechanistic considerations, as well as graphical techniques and assay procedures used to characterize such inhibitors. Chapter 8 is dedicated to irreversible enzyme inactivators, including affinity labels and mechanism-based inhibitors. Criteria for determining irreversibility are described, as well as kinetic experiments unique to this type of inhibitor (determination of Ki, partition ratio, etc.).

In summary, *Evaluation of Enzyme Inhibitors in Drug Discovery* represents a unique reference source that combines traditional discussions of enzymes, catalysis,

and inhibition with an extremely useful description of techniques useful in the discovery of potential drugs from libraries of potential inhibitors molecules. This book will be of great value to anyone involved in drug discovery research in the area of enzyme inhibition, whether in academia or the pharmaceutical industry. The book would also be useful as a text for a graduate level course in enzyme kinetics and drug discovery. The modest price of this book makes it a valuable addition to the library of individual investigators, as well as a must for any reference collection.

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