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Book Review

Enzyme Inhibition in Drug Discovery and Development. The Good and the Bad. Edited by Chuang Lu and Albert P. Li. John Wiley & Sons, Inc., Hoboken, NJ. 2010. xiii + 854 pp. 16 × 24 cm. ISBN 978-0-470-28174-1. $175.00.

Out of the approximate 3000 druggable proteins in humans, enzymes represent a large and diverse class of proteins exploited in drug discovery and development. It is no surprise that the identification and development of unique small molecule enzyme inhibitors, through systematic medicinal chemistry and pharmacological efforts, continue to grow. However, inhibitor selectivity, potency, and efficacy (the good) must be leveraged in the context of inhibitor off-target consequences (the bad). This textbook offers a discourse on the positive and negative aspects of enzyme inhibition that comprise 23 chapters with 50 contributing authors (mostly from scientists in the pharmaceutical sector), with special attention paid to ADME and drug metabolism and pharmacokinetics (DMPK). Each chapter contains timely references to the literature and includes a reasonable blend of figures and tables (black and white). Also included are eight pages of color figures located in the center of the textbook.

The book is divided into three main parts plus a comprehensive index. Part 1 (Drug Discovery Approaches and Technologies, six chapters) provides an overview of the drug discovery process with a special emphasis on small molecule enzyme inhibitors. Bioanalytical technologies, safety biomarkers, and applied pharmacokinetics are covered. Part II (Inhibition of the Drug Metabolizing Enzymes—The Undesirable Inhibition, twelve chapters) focuses on the consequences of drug action with respect to cytochrome P450 inhibition, induction, and degradation and also contains specialized chapters devoted to transferases, esterases, and the polymorphisms of drug transporters. Part III (Inhibition of the Drug Target Enzymes—The Desirable Inhibition, five chapters) includes three chapters dealing with non-enzyme targets (GPCRs, ion channels, transcription factors) and two chapters on enzyme targets. Part III of the book would have benefited from the inclusion of additional chapters dedicated to other select classes of enzymes/inhibitors or molecular modeling and computational strategies in the design and development of enzyme inhibitors.

There are several prominent chapters that demand special consideration. Chapter 5 provides a clear and concise overview of ADME processes and outlines the applications, assumptions, and limitations of in vitro−in vivo correlations, CYP phenotyping, and in vitro drug−drug interaction studies. It is also the only chapter that covers the critical issues of mechanism-based inhibition and reactive intermediates. Chapter 10 reviews the value of in vitro hepatic systems in characterizing drug inhibition potential of new chemical entities and provides a nice overview of experimental design protocols and alternatives. Chapter 11 is also noteworthy in its coverage of the important area of CYP450 degradation and turnover.

Overall, the textbook meets its objective in examining the practical aspects of enzyme inhibition, framed within the context of DMPK, and it represents an excellent undertaking by the editors and contributing authors. Scientists in academia (faculty and graduate students) should consider adding this textbook to their personal library, since it provides a unique window of authoritative knowledge from an industrial perspective and illustrates the challenges, rewards, and penalties associated with enzyme inhibition.

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