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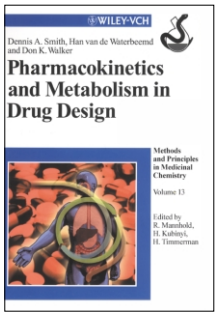

Pharmacokinetics and Metabolism in Drug Design

(Volume 13 in the *Methods and Principles in Medicinal Chemistry* series), Denis A. Smith *et al.*, edited by Mannhold, R. *et al.*, Wiley-Vch, 2001, Price €85, 149 pages, ISBN 3-527-30197-6

In recent years, the pharmaceutical industry has come to realize that new medicines must have optimal pharmacokinetic (PK) and metabolic properties if they are to be successful. Too often in the past, potent and selective molecules failed in the clinic because of inappropriate PK and metabolic characteristics, which in turn led to unacceptable dosage regimes or unexpected safety problems. As a result, lead optimization programs in drug discovery now incorporate Drug Metabolism and Pharmacokinetic (DMPK) screens to enhance the prospects of a candidate drug having all the properties that will enable it to succeed in the clinic. DMPK experts are integral members of those discovery teams, guiding the path of synthetic chemistry. This involves close dialogue between the DMPK scientists and the medicinal chemists, which is most fruitful if the chemists have a broad understanding of DMPK issues. *Pharmacokinetics and Metabolism in Drug Design* will provide the medicinal chemist with that understanding. The authors, all senior scientists within Pfizer (Sandwich, UK), have drawn on their extensive experience to provide a review of the current state of DMPK knowledge that will be, in the words of the editors, 'of great value to many medicinal chemists'.

The book comprises 10 chapters, each outlining a specific DMPK topic. All chapters make liberal use of examples, enabling the reader to put the concepts into context, and an extensive bibliography for further reading. The first chapter focusses on physicochemistry as the foundation of a molecule's DMPK properties. This theme runs throughout the book and provides an important focus for the synthetic chemist to consider during lead optimization. The DMPK consequences of molecular change are clearly highlighted. The subsequent four chapters provide a basic introduction to pharmacokinetics, which is addressed from a conceptual viewpoint, leading the reader through the meaning of each parameter and its importance to the overall disposition of a molecule. Excessive mathematics is avoided, making the text accessible to the target readership who will not, by definition, be specialist pharmacokineticists. The many topics covered include the relevance of half-life to clinical dosage interval and the importance of plasma protein binding in determining free (active) drug concentrations. The authors also raise the relatively new topic of membrane transporters and their importance when considering drug disposition.

Chapters 6–8 focus on renal and metabolic clearance, with some toxicological consequences highlighted. The relevance of how physicochemical properties impact on renal clearance is covered in detail and there is a thorough review of our current knowledge of drug metabolism. The SARs of the important P450 isozymes, 2D6, 2C9 and 3A4, are discussed, as well as conjugating enzymes and the often forgotten esterases. The toxicology chapter summarizes the potential toxicity issues that can arise as a result of specific metabolic pathways, all of which are well illustrated with many real examples.

Later in the book, Chapter 9 introduces the topic of inter-species scaling. During drug discovery, animal pharmacokinetics are studied in the expectation that they are relevant to the human population. This chapter reviews the methods used to relate preclinical data to humans, highlighting the difficulties and providing some recommendations.

The final chapter provides a brief overview of the research tools that the DMPK scientist has at his or her disposal to enable appropriate data to be generated with a throughput that meets the demands of the rapid synthetic chemistry techniques now common in drug discovery.

A book of this size, covering such a wide range of topics, must by necessity be brief. However, the flow of some of the chapters is interrupted by the resulting cross-referencing between chapters. Also, the relationship between some sections within a chapter could have been more intuitive. An introduction to each chapter would have made it an easier read. However, it does provide an excellent summary of the DMPK topics that the chemist should be aware of, and if the reader wants a more detailed understanding of DMPK they should consult the many references quoted in the book, or indeed their DMPK colleagues. The authors are successful in providing a valuable summary of the state of DMPK knowledge and its application in the industrial environment and we would recommend the book to medicinal chemists involved in lead optimization.

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