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"Gh. Asachi" Technical University of Iasi, Romania

Book review

METHODS AND PRINCIPLES IN MEDICINAL CHEMISTRY
Pharmacokinetics and Metabolism in Drug Design

Dennis A. Smith, Han van de Waterbeemd, Don K. Walker, vol.31,
Series Editors: R. Mannhold, H. Kubinyi, G. Folkers, Second edition,
WILEY-VCH, Verlag GmbH & Co. KgaA, Weinheim,
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The volume *Pharmacokinetics and Metabolism in Drug Design* from the prestigious series *Methods and Principles in Medicinal Chemistry* is dedicated to providing both the fundamental and state-of-the-art knowledge in drug discovery and drug development, and in particular to the impacts of the science of drug metabolism and pharmacokinetics on medicinal chemistry.

The book extending over 187 pages, and consisting of ten chapters is an outstanding work meant to give medicinal chemists an as much as possible understanding about the drugs they are creating.

Chapter 1 entitled *Physicochemistry* gives information on the membrane barriers of the body, which a drug should cross, and defines according to IUPAC recommendation the hydrophobicity and lipophylicity of the molecules. Special attention is given to the partition (*P* or *log P*) and distribution (*D* or log *D*) coefficients as measures of lipophilicity, the limitations on the use of 1-octanol, which is the most widely used model for a biological membrane, the hydrogen bonding involved in the uptake of drugs, the impacts of the molecular size and shape of a molecule in the oral absorption of a drug, and to the modern alternative lipophylicity scales. Computational approaches of lipophilicity, membrane systems designed to study drug behavior and concepts such as dissolution, solubility and ionization (pK_a) are also part of the subjects included in this chapter.

The main topics covering the pharmacokinetics of drugs, which reefers to the study of the time course of a drug within the body incorporating the processes of absorption, distribution, metabolism and excretion (*ADME*), are to be found in Chapter 2. Herein problems related to volume distribution, clearance, half-time, and infusion in intravenous administration as well as particularities of oral administration, unbound drug and drug action are also discussed.

Chapters 3 and 4 are devoted to the specific aspects of the absorption of the drugs in the body and their distribution, respectively. Topics such as: dissolution, membrane transfer of a drug, distribution of drugs across the membranes of the body and drugs access to the target, brain penetration, volume and duration of distribution are thoroughly discussed.

The clearance processes, the role of transport proteins in drug clearance as well as the role of lipophilicity in drug clearance are among the topics that are given consideration in Chapter 5.

Being given the fact that clearance of drug normally occurs from the kidneys and liver, the following two chapters are dealing with renal clearance and metabolic (hepatic) clearance, respectively.

Great attention is given to the toxicity of the drugs in Chapter 8. The three main types of toxicity: pharmacophore-induced toxicity, structure-related toxicity and metabolism-induced toxicity along with several metabolites (e.g. epoxides, benzoquinone, nitrenium and iminium ions, hydroxylamines, thiophene ring, chloroquinolines) responsible for various toxic effects are very carefully analyzed. Toxicity prediction (computational toxicology) and toxicogenomics, which are new approaches to drug toxicity understanding, are also taken into consideration.

Chapter 9, *Inter-Species Scaling*, reveals the objectives of the modern principal aim of pharmacokinetic studies which, within the drug discovery setting, have to be able to estimate the likely pharmacokinetic behavior of a new chemical entity in man. This chapter considers in some depth the allometric scaling (body size of the drug molecule) which is considered to be the main responsible for the inter-species variation in pharmacokinetic properties. Additionally, the consequences of allometric scaling on volume distribution, clearance and metabolism are also reviewed.

The last chapter, *High(er) Throughput ADME Studies*, introduces the new approaches to medicinal chemistry such as parallel synthesis and combinatorial chemistry strategies, and refinement of high-throughput screening in biology place drug discovery at a crossroad.

All information contained in this volume, along the updated references given for each chapter offer a rich scientific support for all scientists, academics and students interested in enhancing their knowledge of the impacts of pharmacokinetics and metabolism over a very fascinating scientific topic such the design of drug is.

Adina Dumitrascu
Department of Organic and Biochemical Engineering
Faculty of Chemical Engineering
Technical University Iasi, Romania