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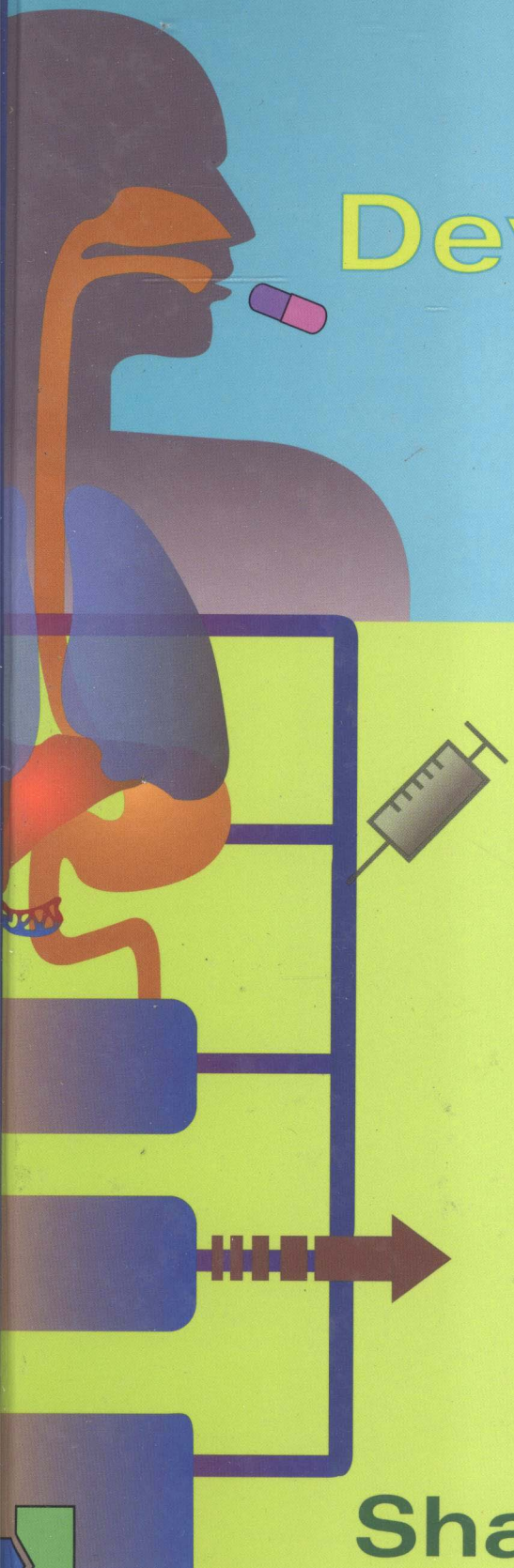
Preclinical Development Handbook



ADME and Biopharmaceutical Properties

Edited by

Shayne Cox Gad

PRECLINICAL DEVELOPMENT HANDBOOK

ADME and Biopharmaceutical Properties

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PREFACE

This *Preclinical Development Handbook: ADME and Biopharmaceutical Properties* continues and extends the objective behind the entire *Handbook* series: an attempt to achieve a through overview of the current and leading-edge nonclinical approaches to evaluating the pharmacokinetic and pharmacodynamic aspects of new molecular entity development for therapeutics. The 38 chapters cover the full range of approaches to understanding how new molecules are absorbed and distributed in model systems, have their biologic effects, and then are metabolized and excreted. Such evaluations provide the fundamental basis for making decisions as to the possibility and means of pursuing clinical development of such moieties. Better performance in this aspect of the new drug development process is one of the essential keys to both shortening and increasing the chance of success in developing new drugs.

The volume is unique in that it seeks to cover the entire range of available approaches to understanding the performance of a new molecular entity in as broad a manner as possible while not limiting itself to a superficial overview. Thanks to the persistent efforts of Mindy Myers and Gladys Mok, these 38 chapters, which are written by leading practitioners in each of these areas, provide coverage of the primary approaches to the problems of understanding the mechanisms that operate in *in vivo* systems to transfer a drug to its site of action and out.

I hope that this newest addition to our scientific banquet is satisfying and useful to all those practitioners working in or entering the field.

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MODELING AND INFORMATICS IN DRUG DESIGN

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Preclinical Development Handbook: ADME and Biopharmaceutical Properties,
edited by Shayne Cox Gad

1.1 INTRODUCTION

Modeling and informatics have become indispensable components of rational drug design (Fig. 1.1). For the last few years, chemical analysis through molecular modeling has been very prominent in computer-aided drug design (CADD). But currently modeling and informatics are contributing in tandem toward CADD. Modeling in drug design has two facets: modeling on the basis of knowledge of the drugs/leads/ligands often referred to as ligand-based design and modeling based on the structure of macromolecules often referred to as receptor-based modeling (or structure-based modeling). Computer-aided drug design is a topic of medicinal chemistry, and before venturing into this exercise one must employ computational chemistry methods to understand the properties of chemical species, on the one hand, and employ computational biology techniques to understand the properties of biomolecules on the other. Information technology is playing a major role in decision making in pharmaceutical sciences. Storage, retrieval, and analysis of data of chemicals/biochemicals of therapeutic interest are major components of pharmacoinformatics. Quite

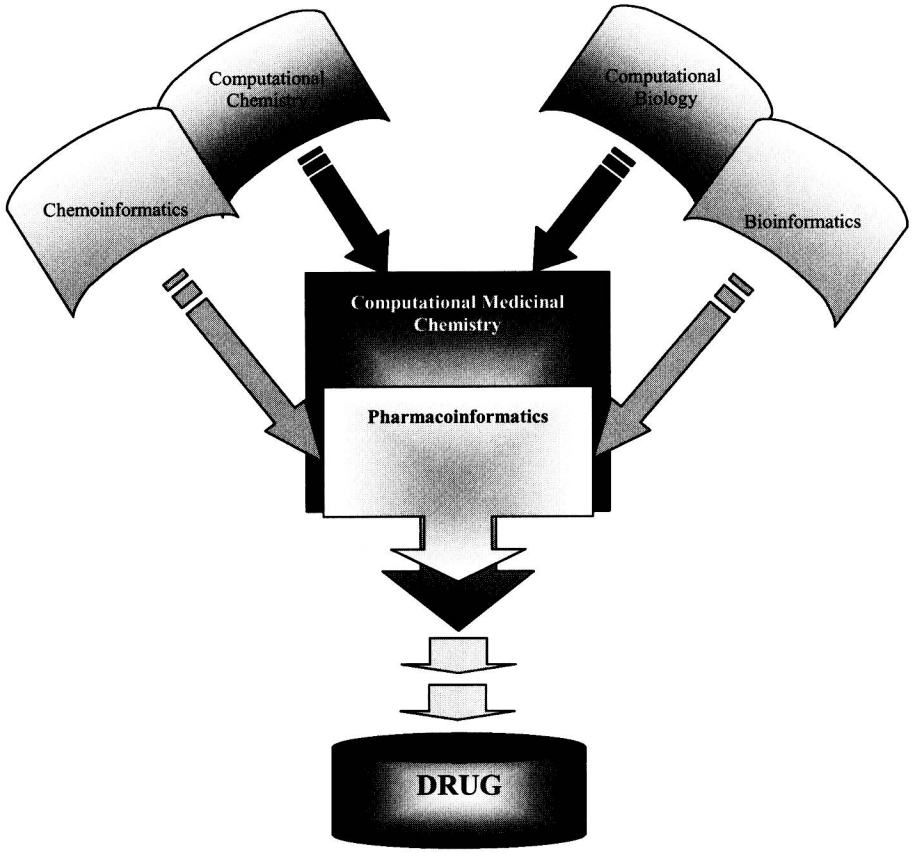

FIGURE 1.1 A schematic diagram showing a flowchart of activities in computer aided drug development. The figure shows that the contributions from modeling methods and informatics methods toward the drug development are parallel and in fact not really distinguishable.

often, the efforts based on modeling and informatics get thoroughly integrated with each other, as in the case of virtual screening exercises. In this chapter, the molecular modeling methods that are in vogue in the fields of (1) computational chemistry, (2) computational biology, (3) computational medicinal chemistry, and (4) pharmacoinformatics are presented and the resources available in these fields are discussed.

1.2 COMPUTATIONAL CHEMISTRY

Two-dimensional (2D) structure drawing and three-dimensional (3D) structure building are the important primary steps in computational chemistry for which several molecular visualization packages are available. The most popular of these are ChemDraw Ultra and Chem3D Pro, which are a part of the ChemOffice suite of software packages [1]. ACD/ChemSketch [2], MolSuite [3], and many more of this kind are other programs for the same purpose. Refinement has to be carried out on all the drawings and 3D structures so as to improve the chemical accuracy of the structure on the computer screen. Structure refinement based on heuristic rules/cleanup procedures is a part of all these software packages. However, chemical accuracy of the 3D structures still remains poor even after cleanup. Further refinement can be carried out by performing energy minimization using either molecular mechanical or quantum chemical procedures. By using these methods, the energy of a molecule can be estimated in any given state. Following this, with the help of first and second derivatives of energy, it can be ascertained whether the given computational state of the molecules belongs to a chemically acceptable state or not. During this process, the molecular geometry gets modified to a more appropriate, chemically meaningful state – the entire procedure is known as geometry optimization. The geometry optimized 3D structure is suitable for property estimation, descriptor calculation, conformational analysis, and finally for drug design exercise [4–6].

1.2.1 Ab Initio Quantum Chemical Methods

Every molecule possesses internal energy (U), for the estimation of which quantum chemical calculations are suitable. Quantum chemical calculations involve rigorous mathematical derivations and attempt to solve the Schrödinger equation, which in its simplest form may be written as

$$H\Psi = E\Psi \tag{1.1}$$

$$\hat{H}_{\text{el}} = \sum\left(-\frac{1}{2}\nabla_i^2\right) - \sum_i\sum_a \frac{Z_a}{|r_i - d_a|} + \frac{1}{2}\sum_i\sum_{j\neq i}\frac{1}{|r_i - r_j|} + \frac{1}{2}\sum_a\sum_{b\neq a}\frac{Z_a Z_b}{|d_a - d_b|} \tag{1.2}$$

where ψ represents the wavefunction, E represents energy, ∇ represents the kinetic energy operator for electrons, r_i defines the vector position of electron i with vector components in Bohr radii, Z_a is the charge of fixed nucleus a in units of the elementary charge, and d_a is the vector position of nucleus a with vector components in Bohr radii.