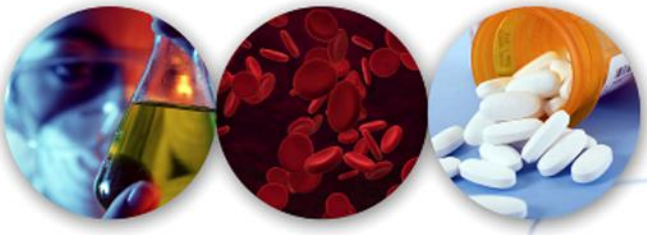
Drug-like Properties: Concepts, Structure Design and Methods

from ADME to Toxicity Optimization



metabolism • solubility • pharmacokinetics
permeability • CYP inhibition
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Edward H. Kerns and Li Di

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Contents

Preface

Drug research is a fulfilling career, because new drugs can improve human health, quality of life, and life span. For scientists dedicated to drug research, it can also be a supremely challenging mission, owing to the numerous attributes that must be simultaneously optimized to arrive at an efficacious drug-like compound. ADME/Tox (absorption, distribution, metabolism, elimination, toxicity) is one of these challenges. Of the thousands of novel compounds that a drug discovery project team invents and that bind to the therapeutic target, typically only a fraction of these have sufficient ADME/Tox properties to become a drug product. This book is devoted to providing you, the drug research scientist or student, with an introduction to ADME/Tox property concepts, structure design, and methodology to help you succeed with these challenges.

Chemists will be aided by the case studies, structure-property relationships, and structure modification strategies in this book. These assist in diagnosing the substructures of a lead structure that are not drug-like and suggest ideas for ADME/Tox structure design. Overviews of property methods provide the background needed to accurately interpret and apply the data for informed decisions. For ADME/Tox scientists, insights on property assays assist with selecting methods and generating data that impacts projects.

Biologists/pharmacologists will benefit from an increased understanding of ADME/Tox concepts. This is especially important, because in recent years the application of property data has expanded from optimizing *in vivo* pharmacokinetics and safety to biological assays. Low solubility, chemical instability, and low permeability can greatly affect bioassay data. Equipped with this understanding, biologists are better able to optimize bioassays and include property affects in data interpretation.

Accordingly, understanding ADME/Tox is important for all drug researchers, owing to its increasing importance in advancing high quality candidates to clinical studies and the processes of drug discovery. ADME/Tox properties are a crucial aspect of clinical candidate quality. If the properties are weak, the candidate will have a high risk of failure or be less desirable as a drug product. ADME/Tox has become integrated in the drug discovery process and is a tremendous asset in guiding selection and optimization of precious leads. This book is a tool and resource for scientists engaged in, or preparing for, the selection and optimization process. The authors wish you success in creating the pharmaceuticals of the future that will benefit all people.

In preparing this book, the authors had the support and counsel of many drug research colleagues. The leadership of Magid Abou-Gharbia, Guy T. Carter, and Oliver J. McConnell of Wyeth Research, Chemical and Screening Sciences are greatly appreciated. The careful manuscript review and feedback by Christopher P. Miller was highly beneficial. The thoughtful comments of several anonymous reviewers are greatly appreciated. LD thanks

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Dedication

Ed Kerns dedicates this book to:
William, Virginia, Nancy, Chrissy, and Patrick: for your love and support.

Li Di dedicates this book to:
My parents: I am infinitely in debt to you.
My sisters, Ning and Qing: for being my best friends.
My children, Kevin and Sophia: I am very proud of you.