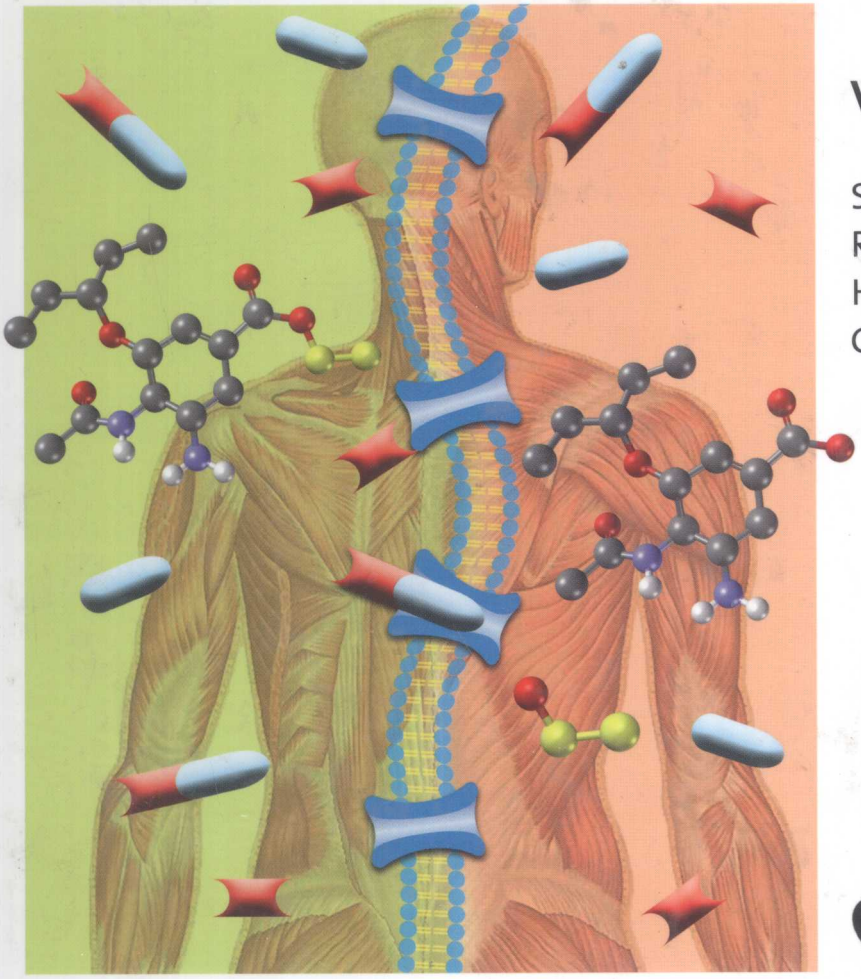
Methods and Principles in Medicinal Chemistry

Edited by Jarkko Rautio

WILEY-VCH

Prodrugs and Targeted Delivery

Towards Better ADME Properties



Volume 47

Series Editors:
R. Mannhold,
H. Kubinyi,
G. Folkers

Edited by
Jarkko Rautio

Prodrugs and Targeted Delivery

Towards Better ADME Properties

WILEY-VCH Verlag GmbH & Co. KGaA

Series Editors

Prof. Dr. Raimund Mannhold
Molecular Drug Research Group
Heinrich-Heine-Universität
Universitätsstrasse 1
40225 Düsseldorf
Germany
mannhold@uni-duesseldorf.de

Prof. Dr. Hugo Kubinyi
Donnersbergstrasse 9
67256 Weisenheim am Sand
Germany
kubinyi@t-online.de

Prof. Dr. Gerd Folkers
Collegium Helveticum
STW/ETH Zurich
8092 Zurich
Switzerland
folkers@collegium.ethz.ch

Volume Editor

Prof. Dr. Jarkko Rautio
University of Eastern Finland
School of Pharmacy
Yliopistonranta 1
70211 Kuopio
Finland

Cover Description

Prodrugs are bioreversible derivatives of drug molecules that can address ADME issues ("backbone") and must undergo an enzymatic and/or chemical transformation *in vivo* to release the pharmacologically active parent drug. A representative prodrug is oseltamivir (Tamiflu®).
(Laskowski anatomy taken with courtesy of the U.S. National Library of Medicine)

Library of Congress Card No.: applied for

British Library Cataloguing-in-Publication Data
A catalogue record for this book is available from the British Library.

Bibliographic information published by the Deutsche Nationalbibliothek
The Deutsche Nationalbibliothek lists this publication in the Deutsche Nationalbibliografie; detailed bibliographic data are available on the Internet at http://dnb.d-nb.de.

Typesetting Thomson Digital, Noida, India
Printing and Binding betz-druck GmbH, Darmstadt
Cover Design Grafik-Design Schulz, Fußgönheim

Printed in the Federal Republic of Germany
Printed on acid-free paper

ISBN: 978-3-527-32603-7

List of Contributors

Jane P.F. Bai
US Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Science
Office of Clinical Pharmacology
10903 New Hampshire, Ave.
Silver Spring
MD 20993
USA

Eyal H. Barash
Barash Law LLC
3000 Kent Avenue
West Lafayette
IN 47906
USA

Ujjwal Chakraborty
University of Kentucky
Department of Chemistry
Lexington
KY 40536-0082
USA

Peter A. Crooks
University of Kentucky
College of Pharmacy
Department of Pharmaceutical Sciences
Lexington
KY 40536-0082
USA

Harpreet K. Dhooper
University of Kentucky
Department of Chemistry
Lexington
KY 40536-0082
USA

Paul W. Erhardt
The University of Toledo College of Pharmacy
Center for Drug Design and Development
Toledo
OH
USA

Ripal Gaudana
University of Missouri-Kansas City
School of Pharmacy
Division of Pharmaceutical Sciences
Kansas City
MO
USA

Prodrugs and Targeted Delivery: Towards Better ADME Properties. Edited by Jarkko Rautio

ISBN: 978-3-527-32603-7

Victor R. Guarino
Bristol-Myers Squibb
Pharmaceutical Candidate
Optimization
Princeton
NJ 08543
USA

Douglas Hedley
Institute of Cancer Research
CRC Centre for Cancer Therapeutics
15 Cotswold Road
Sutton
Surrey SM2 5NG
UK

Kristiina Huttunen
University of Eastern Finland
School of Pharmacy
Yliopistonranta 1
FI-70211 Kuopio
Finland

Jwala Jwala
University of Missouri-Kansas City
School of Pharmacy
Division of Pharmaceutical Sciences
Kansas City
MO
USA

Deep Kwatra
University of Missouri-Kansas City
School of Pharmacy
Division of Pharmaceutical Sciences
Kansas City
MO
USA

Krista Laine
University of Eastern Finland
School of Pharmacy
Yliopistonranta 1
FI-70211 Kuopio
Finland

Lawrence L. Lesko
US Food and Drug Administration
Center for Drug Evaluation and
Research
Office of Translational Science
Office of Clinical Pharmacology
10903 New Hampshire, Ave.
Silver Spring
MD 20993
USA

Paul R. Lockman
Texas Tech University Health Sciences
Center
Department of Pharmaceutical Sciences
1406 Coulter
Amarillo
TX 79106
USA

Susruta Majumdar
Memorial Sloan
Kettering Cancer Center
Laboratory of Chemistry, Pharmacology,
and Neuroscience
1275 York Avenue
New York
NY 10021
USA

Ashim K. Mitra
University of Missouri-Kansas City
School of Pharmacy
Division of Pharmaceutical Sciences
Kansas City
MO
USA

Majid Y. Moridani
Texas Tech University
Health Sciences Center
Amarillo
TX 79106
USA

Gabriel Negoita-Giras
Institute of Cancer Research
CRC Centre for Cancer Therapeutics
15 Cotswold Road
Sutton
Surrey SM2 5NG
UK

Dan Niculescu-Duvaz
Institute of Cancer Research
CRC Centre for Cancer Therapeutics
15 Cotswold Road
Sutton
Surrey SM2 5NG
UK

John P. O'Donnell
Pfizer Global Research and
Development
Department of Antibacterials Research
Eastern Point Road
Groton
CT 06340
USA

Mike Pacanowski
US Food and Drug Administration
Center for Drug Evaluation and
Research
Office of Translational Science
Office of Clinical Pharmacology
10903 New Hampshire, Ave.
Silver Spring
MD 20993
USA

Atiqur Rahman
US Food and Drug Administration
Center for Drug Evaluation and
Research
Office of Translational Science
Office of Clinical Pharmacology
10903 New Hampshire, Ave.
Silver Spring
MD 20993
USA

Jarkko Rautio
University of Eastern Finland
School of Pharmacy
Yliopistonranta 1
FI-70211 Kuopio
Finland

Michael D. Reese
The University of Toledo College of
Pharmacy
Center for Drug Design and
Development
Toledo
OH
USA

Kenneth Sloan
University of Florida
Department of Medicinal Chemistry
1600 SW Archer Road P6-20
Gainesville
FL 32610
USA

Quentin R. Smith
Texas Tech University
Health Sciences Center
Department of Pharmaceutical Sciences
1406 Coulter
Amarillo
TX 79106
USA

Caroline J. Springer
Institute of Cancer Research
CRC Centre for Cancer Therapeutics
15 Cotswold Road
Sutton
Surrey SM2 5NG
UK

Ravi Vaishya
University of Missouri-Kansas City
School of Pharmacy
Division of Pharmaceutical Sciences
Kansas City
MO
USA

Scott C. Wasdo
University of Florida
Department of Anesthesiology
1600 SW Archer Road M5-16
Gainesville
FL 32610
USA

Mark S. Warren
XenoPort, Inc.
3410 Central Expressway
Santa Clara
CA 95051
USA

Preface

Historically, biological screening of new compounds was performed in animals. Application by the enteral route automatically provided a first overview on bioavailability and biological half-life. Nowadays, lead structure search and optimization are dominated by *in vitro* screening systems. Correspondingly, problems in compound liberation, oral absorption, organ distribution, metabolism, and excretion (LADME) are often observed at a relatively late stage. The problems may already result either from inappropriate lead structure selection or from unidirectional affinity optimization, without sufficient consideration for solubility, permeation properties, and metabolic stability. However, there are many options to rescue a preclinical candidate with such problems. Liberation can be enhanced by increasing the solubility via the formation of polar derivatives, for example, phosphates, reduction of carbonyl to hydroxyl groups, or introduction of polar, most often basic residues, where they do not negatively interfere with binding. Absorption can be enhanced by making the compound more lipophilic in first line by the conversion of acids into esters. Distribution can be influenced by using transporters, for example, for the blood–brain barrier penetration of L-DOPA, or by designing compounds that are preferentially metabolized in a certain organ or tumor, for example, omeprazole or capecitabine. Metabolism can be easily controlled by avoiding or introducing metabolically labile groups.

Prodrugs are inactive or less active drug analogues or derivatives that have better physicochemical or pharmacokinetic properties than their parent drugs. They are more or less specifically metabolized to the active form of the drug. There are manifold reasons for the development of a prodrug. In most cases, prodrugs are designed for a drug that is not sufficiently bioavailable. Other reasons are that the drug does not permeate the blood–brain barrier, the drug has poor solubility or taste, the drug has no sufficient chemical stability, or the drug has no sufficient organ or cell specificity. Soft drugs (sometimes also called antedrugs) are drugs with very short half-life or without systemic activity. Some esters of corticosteroid carboxylic acids are topically active; after dermal absorption, they are metabolically degraded to inactive analogues, in this manner avoiding systemic side effects. Targeted drugs are drugs or prodrugs that exert their biological action only in certain organs or cells.

Prodrugs and Targeted Delivery: Towards Better ADME Properties. Edited by Jarkko Rautio

ISBN: 978-3-527-32603-7

We are very grateful to Jarkko Rautio, who assembled a team of leading experts to discuss all these concepts. In a comprehensive manner, strategies are presented to rescue a drug candidate with insufficient ADME properties. For this purpose, the book is well suited both for all practitioners in medicinal chemistry and for graduate students who want to learn about rational concepts of lead structure optimization. We are also grateful to Frank Weinreich and Nicola Oberbeckmann-Winter for their ongoing support and enthusiasm for our book series, *Methods and Principles in Medicinal Chemistry*, of which this book is another highlight.

October 2010

Raimund Mannhold, Düsseldorf
Hugo Kubinyi, Weisenheim am Sand
Gerd Folkers, Zurich

A Personal Foreword

The prodrug concept, as first introduced by Adrian Albert in the 1950s, defines a prodrug as a pharmacologically inactive agent that undergoes an enzymatic and/or chemical transformation *in vivo* to a therapeutically active drug. Prodrug strategies have traditionally been used to address ADMET (absorption, distribution, metabolism, excretion, and toxicity) properties and risks of marketed drugs or as a tool in late-stage problem solving for drug development candidates. However, prodrugs are now increasingly being integrated into early drug discovery. Indeed, the successful application of prodrug strategies over the past two decades has significantly increased the percentage of drugs approved as prodrugs to an eye-catching 10%. In addition, the percentage of prodrugs among the world's top-selling drugs is particularly high, including blockbusters such as all the proton pump inhibitor "prazoles," the antiplatelet agent clopidogrel, and the hypercholesterolemia drugs simvastatin and fenofibrate, to name a few.

The success of prodrugs can also be seen in the literature. Books, book chapters, and numerous research and review articles have been published in recent years, with the compilation of the prodrug two-volume book in 2007 by AAPS Press/Springer and edited by Professor Valentino Stella *et al.* certainly providing the most comprehensive overview of early and current prodrug strategies. So why do we need a new book on prodrugs so soon? The idea of this new prodrug book was mulled over by several prodrug enthusiasts, and it soon became obvious that there are topics that are not really addressed in the existing works. Moreover, I think the more perspectives we can explore on strategies suitable for a prodrug approach, or when they should not be pursued, the better off we will be scientifically. Thus, with some trepidation regarding content, especially trying to avoid extensive redundancy, the task was indeed found worth rewarding and invigorating.

This volume of *Methods and Principles in Medicinal Chemistry* contains various strategies for prodrug design and highlights many examples of prodrugs that either have been launched or are undergoing experimental assessment. Part One begins with a historical overview and is followed by approaches of prodrug design and the concepts of prodrug patentability. Part Two focuses on the ADMET issues that can be addressed by prodrugs, ranging from permeability and solubility to targeting. In Part

Prodrugs and Targeted Delivery: Towards Better ADME Properties. Edited by Jarkko Rautio

ISBN: 978-3-527-32603-7

Three, the emphasis is on codrugs, which consist of two active drugs incorporated into a single chemical entity, and soft drugs, which in contrast to prodrugs are designed to undergo inactivation after their biotransformation. Both prodrugs and soft drugs rely upon biotransformation to dictate their course of activation and are worth discussing in the same context. Part Four is devoted to preclinical and clinical considerations for prodrugs providing a discovery screening strategy for evaluation of prodrugs and pharmacogenetic focus for prodrugs.

I want to express my sincere gratitude to all authors for their excellent efforts and cooperation. It has been a pleasure for me to be involved with all of these high-profile prodrug enthusiasts. I also want to acknowledge the people at Wiley-VCH, namely, Dr Nicola Oberbeckmann-Winter for her tireless support in the production of this book and Dr Hugo Kubinyi for his valuable advice on its content. I truly hope that this book will stimulate multidisciplinary teams of medicinal chemists, biologists, and other scientists in drug design and development process to consider a prodrug approach as a rational tool in drug discovery that will ultimately lead to better drugs.

October 2010 *Jarkko Rautio*, Kuopio

Contents

Prodrugs and Targeted Delivery: Towards Better ADME Properties. Edited by Jarkko Rautio

ISBN: 978-3-527-32603-7