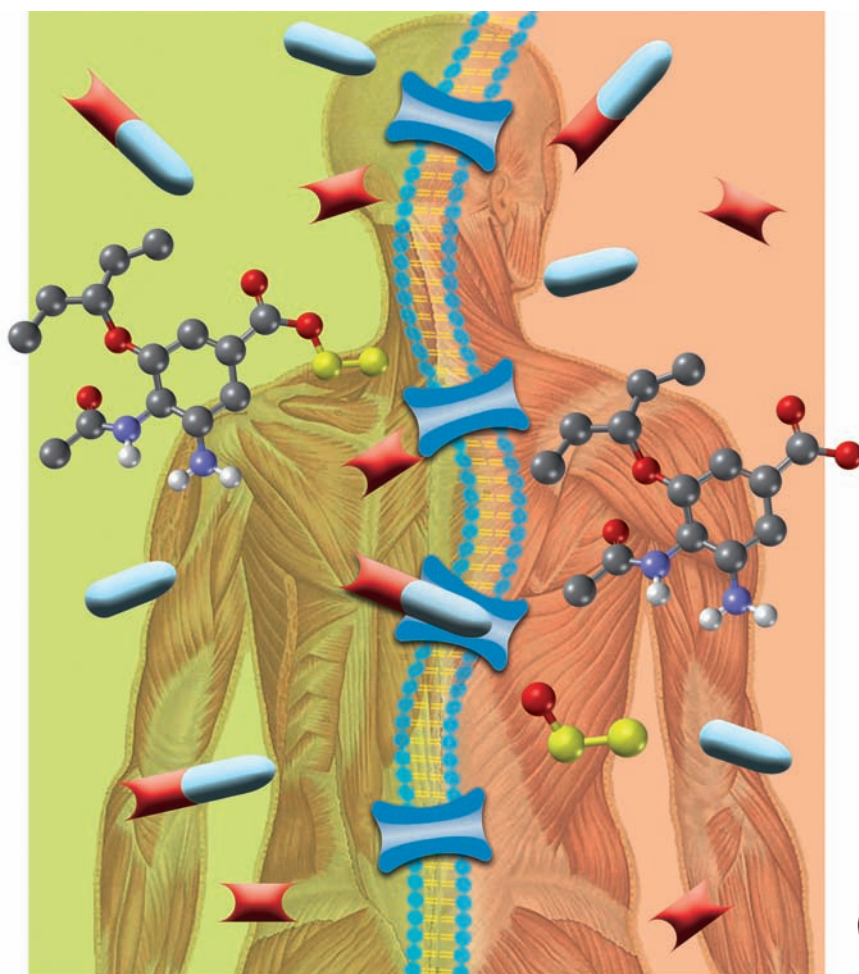


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Prodrugs and Targeted Delivery

Towards Better ADME Properties



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Prodrugs and Targeted Delivery

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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)

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Contents

List of Contributors	XVII
Preface	XXI
A Personal Foreword	XXIII

Part One Prodrug Design and Intellectual Property 1

1	Prodrug Strategies in Drug Design	3
	<i>Jarkko Rautio</i>	
1.1	Prodrug Concept	3
1.2	Basics of Prodrug Design	4
1.3	Rationale for Prodrug Design	5
1.3.1	Overcoming Formulation and Administration Problems	6
1.3.2	Overcoming Absorption Barriers	8
1.3.3	Overcoming Distribution Problems	9
1.3.4	Overcoming Metabolism and Excretion Problems	10
1.3.5	Overcoming Toxicity Problems	10
1.3.6	Life Cycle Management	13
1.4	History of Prodrug Design	14
1.5	Recently Marketed Prodrugs	17
1.5.1	Prodrug Prevalence	17
1.5.2	Recent Prodrug Approvals	17
1.6	Concluding Remarks	25
	References	26
2	The Molecular Design of Prodrugs by Functional Group	31
	<i>Victor R. Guarino</i>	
2.1	Introduction	31
2.2	The Prodrug Concept and Basics of Design	32
2.3	Common Functional Group Approaches in Prodrug Design	34

2.3.1	Aliphatic and Aromatic Alcohols	34
2.3.1.1	Phosphate Monoesters	35
2.3.1.2	Simple Acyl Esters	37
2.3.1.3	Amino Acid Esters	38
2.3.1.4	Other Ester-Based Approaches	39
2.3.2	Carboxylic Acids	40
2.3.2.1	Alkyl Esters	41
2.3.2.2	Aminoalkyl Esters	42
2.3.2.3	Spacer Groups to Alleviate Steric Hindrance	42
2.3.3	Imides, Amides, and Other NH Acids	43
2.3.3.1	Imide-Type NH Acids	44
2.3.3.2	Amide-Type NH Acids	44
2.3.3.3	Sulfonamide NH Acids	48
2.3.4	Phosphates, Phosphonates, and Phosphinates	49
2.3.4.1	Simple Alkyl and Aryl Esters	49
2.3.4.2	Acyloxyalkyl and Alkoxy-carbonyloxyalkyl Esters	50
2.3.4.3	Aryl Phospho(n/r)amidates and Phospho(n/r)diamides	51
2.3.4.4	HepDirect Technology	53
2.3.5	Amines and Benzamidines	53
2.3.5.1	N-Acyloxyalkoxycarbonyl Prodrugs	54
2.3.5.2	N-Mannich Bases	55
2.3.5.3	N-Acyloxyalkyl and N-Phosphoryloxyalkyl Prodrugs of Tertiary Amines	55
2.3.5.4	N-Hydroxy and Other Modifications for Benzamidines	56
2.4	Conclusions	56
	References	57

3 Intellectual Property Primer on Pharmaceutical Patents with a Special Emphasis on Prodrugs and Metabolites

Eyal H. Barash

3.1	Introduction	61
3.2	Patents and FDA Approval Process	61
3.3	Obtaining a Patent	65
3.3.1	Utility	66
3.3.2	Novelty	67
3.3.3	Nonobviousness	71
3.4	Conclusion	78

Part Two Prodrugs Addressing ADMET Issues

4 Increasing Lipophilicity for Oral Drug Delivery

Majid Y. Moridani

4.1	Introduction	81
4.2	pK_a , Degree of Ionization, Partition Coefficient, and Distribution Coefficient	81

4.3	Prodrug Strategies to Enhance Lipid Solubility	85
4.4	Prodrug Examples for Antibiotics	87
4.4.1	Bacampicillin	87
4.4.2	Carindacillin	88
4.4.3	Cefditoren Pivoxil	89
4.4.4	Cefuroxime Axetil	90
4.4.5	Cefpodoxime Proxetil	91
4.5	Antiviral Related Prodrugs	92
4.5.1	Oseltamivir	92
4.5.2	Famciclovir	92
4.5.3	Adefovir Dipivoxil	93
4.5.4	Tenofovir Disoproxil	94
4.6	Cardiovascular Related Prodrugs	95
4.6.1	Enalapril	95
4.6.2	Fosinopril	96
4.6.3	Olmesartan Medoxomil	97
4.7	Lipophilic Prodrugs of Benzamidine Drugs	98
4.7.1	Ximelagatran	98
4.7.2	Dabigatran Etxilate	99
4.8	Miscellaneous Examples	100
4.8.1	Capecitabine	100
4.8.2	Mycophenolate Mofetil	101
4.8.3	Misoprostol	102
4.8.4	Additional Examples	102
4.9	Summary and Conclusion	104
	References	106
5	Modulating Solubility Through Prodrugs for Oral and IV Drug Delivery	111
	<i>Victor R. Guarino</i>	
5.1	Introduction	111
5.2	Basics of Solubility and Oral/IV Drug Delivery	112
5.2.1	Some Basic Fundamentals of Solubility	112
5.2.2	Some General Comments on IV Drug Delivery	114
5.2.3	Some General Comments on Oral Drug Delivery	116
5.3	Prodrug Applications for Enhanced Aqueous Solubility	117
5.3.1	Prodrug Concept	117
5.3.2	Examples of Prodrugs to Enhance Aqueous Solubility for IV Administration	118
5.3.2.1	Fosphenytoin	118
5.3.2.2	Fospropofol	119
5.3.2.3	Parecoxib	120
5.3.2.4	Irinotecan	120
5.3.3	Prodrugs to Enhance Aqueous Solubility for Oral Administration	121
5.3.3.1	Fosamprenavir	121

5.3.3.2	Valganciclovir	122
5.4	Challenges with Solubilizing Prodrugs of Insoluble Drugs	123
5.4.1	Challenges with Solubilizing Prodrug Strategies for IV Administration	123
5.4.2	Challenges with Solubilizing Prodrug Strategies for Oral Administration	124
5.5	Additional Applications of Prodrugs for Modulating Solubility	125
5.5.1	Alleviating pH-Dependent Oral Bioavailability of Weakly Basic Drugs	126
5.5.2	Aligning pH-Solubility and pH-Stability Relationships for IV Products	126
5.5.3	Modulating Solubility in Negative Direction	127
5.6	Parallel Exploration of Analogues and Prodrugs in Drug Discovery (Commentary)	128
5.7	Conclusions	129
	References	129
6	Prodrugs Designed to Target Transporters for Oral Drug Delivery	133
	<i>Mark S. Warren and Jarkko Rautio</i>	
6.1	Introduction	133
6.2	Serendipity: An Actively Transported Prodrug	133
6.3	Requirements for Actively Transported Prodrugs	135
6.4	Peptide Transporters: PEPT1 and PEPT2	135
6.5	Monocarboxylate Transporters	140
6.6	Bile Acid Transporters	143
6.7	Conclusions	147
	References	147
7	Topical and Transdermal Delivery Using Prodrugs: Mechanism of Enhancement	153
	<i>Kenneth Sloan, Scott C. Wasdo, and Susruta Majumdar</i>	
7.1	Introduction	153
7.2	Arrangement of Water in the Stratum Corneum	155
7.3	A New Model for Diffusion Through the Stratum Corneum: The Biphasic Solubility Model	156
7.4	Equations for Quantifying Effects of Solubility on Diffusion Through the Stratum Corneum	158
7.4.1	The Roberts–Sloan Equation When the Vehicle is Water	159
7.4.2	The Roberts–Sloan Equation When the Vehicle is a Lipid	160
7.4.3	The Series/Parallel Equation When the Vehicle is a Lipid	161
7.5	Design of Prodrugs for Topical and Transdermal Delivery Based on the Biphasic Solubility Model	162
7.5.1	5-Fluorouracil Prodrugs	164
7.5.1.1	N-Acyl 5-FU Prodrugs	165
7.5.1.2	N-Soft Alkyl 5-FU Prodrugs	166

7.5.2	Acetaminophen (APAP) Prodrugs	167
7.5.2.1	O-Acyl APAP Prodrugs	168
7.5.2.2	O-Soft Alkyl APAP Prodrugs	170
7.5.3	S-Soft Alkyl Prodrugs of 6-Mercaptopurine	170
7.5.3.1	Effect of Vehicles on Topical and Transdermal Delivery	171
7.6	Comparison of Human and Mouse Skin Experiments	172
7.7	Summary	174
	References	175

8 Ocular Delivery Using Prodrugs 181

Deep Kwatra, Ravi Vaishya, Ripal Gaudana, Jwala Jwala, and Ashim K. Mitra

8.1	Introduction	181
8.2	Criteria for an Ideal Ophthalmic Prodrug	181
8.3	Anatomy and Physiology of the Eye	182
8.3.1	Anterior Chamber	183
8.3.2	Posterior Chamber	183
8.4	Barriers to Ocular Drug Delivery	184
8.4.1	Tear Film	184
8.4.2	Corneal Epithelium	184
8.4.3	Aqueous Humor and BAB	184
8.4.4	Conjunctiva	184
8.4.5	Blood–Retinal Barrier	185
8.5	Influx and Efflux Transporters on the Eye	185
8.6	Transporter-Targeted Prodrug Approach	186
8.6.1	Acyclovir	186
8.6.2	Ganciclovir	188
8.6.3	Quinidine	188
8.7	Drug Disposition in Ocular Delivery	189
8.8	Effect of Physiochemical Factors on Drug Disposition in Eye	190
8.9	Prodrug Strategy to Improve Ocular Bioavailability (Nontransporter-Targeted Approach)	192
8.9.1	Epinephrine	192
8.9.2	Phenylephrine	192
8.9.3	Pilocarpine	193
8.9.4	Timolol	195
8.9.5	Prostaglandin F _{2α}	197
8.10	Recent Patents and Marketed Ocular Prodrugs	198
8.11	Novel Formulation Approaches for Sustained Delivery of Prodrugs	201
8.12	Conclusion	201
	References	202

9 Reducing Presystemic Drug Metabolism 207

Majid Y. Moridani

9.1	Introduction	207
-----	--------------	-----

9.2	Presystemic Metabolic Barriers	209
9.2.1	Esterases	209
9.2.2	Cytochrome P450 Enzymes	212
9.2.3	Phase II Drug Metabolizing Enzymes	214
9.2.4	Peptidases	215
9.2.5	Other Oxidative Metabolizing Enzymes	216
9.3	Prodrug Approaches to Reduce Presystemic Drug Metabolism	217
9.4	Targeting Colon	220
9.5	Targeting Lymphatic Route	221
9.6	Conclusion	225
	References	226

10 Enzyme-Activated Prodrug Strategies for Site-Selective Drug Delivery 231

Krista Laine and Kristiina Huttunen

10.1	Introduction	231
10.2	General Requirements for Enzyme-Activated Targeted Prodrug Strategy	232
10.3	Examples of Targeted Prodrug Strategies	232
10.3.1	Tumor-Selective Prodrugs	232
10.3.1.1	Prodrugs Activated by Hypoxia-Associated Reductive Enzymes	233
10.3.1.2	Prodrugs Activated by Glutathione S-Transferase	236
10.3.1.3	Prodrugs Activated by Thymidine Phosphorylase	237
10.3.2	Organ-Selective Prodrugs	239
10.3.2.1	Liver-Targeted Prodrugs	239
10.3.2.2	Kidney-Targeted Prodrugs	242
10.3.2.3	Colon-Targeted Prodrugs	243
10.3.3	Virus-Selective Prodrugs	244
10.4	Summary	245
	References	246

11 Prodrug Approaches for Central Nervous System Delivery 253

Quentin R. Smith and Paul R. Lockman

11.1	Blood–Brain Barrier in CNS Drug Development	253
11.2	Prodrug Strategies	255
11.3	Prodrug Strategies Based Upon BBB Nutrient Transporters	257
11.4	Prodrug Strategies Based Upon BBB Receptors	263
11.5	CNS Prodrug Summary	264
	References	266

12 Directed Enzyme Prodrug Therapies 271

Dan Niculescu-Duvaz, Gabriel Negoita-Giras, Ion Niculescu-Duvaz, Douglas Hedley, and Caroline J. Springer

12.1	Introduction	271
12.2	Theoretical Background of DEPT	271

12.2.1	ADEPT and Other Enzyme–Conjugates Approaches	272
12.2.2	LIDEPT	273
12.2.3	GDEPT and Other Gene Delivery Approaches	273
12.2.4	BDEPT	275
12.3	Comparison of ADEPT and GDEPT	275
12.4	Enzymes in ADEPT and GDEPT	278
12.5	Design of Prodrugs	282
12.5.1	Mechanisms of Prodrug Activation	282
12.5.1.1	Electronic Switch	282
12.5.1.2	Cell Exclusion	285
12.5.1.3	Blockage of the Pharmacophore	285
12.5.1.4	Conversion to Substrate for Endogenous Enzymes	287
12.5.1.5	Formation of a Reactive Moiety	287
12.5.1.6	Formation of a Second Interactive Group	288
12.5.2	Enzymatic Reactions Activating the Prodrug. The Trigger	288
12.5.2.1	Reactions Catalyzed by Hydrolases: Hydrolytic Cleavage	289
12.5.2.2	Activation by Nucleotide Phosphorylation	290
12.5.2.3	Activation by Reductases	290
12.5.2.4	Activation by Oxidases	291
12.5.2.5	(Deoxy)Ribosyl Transfer	291
12.5.3	The Linker. Self-Immolative Prodrugs	292
12.5.3.1	Self-Immolative Prodrugs Fragmenting by Elimination	293
12.5.3.2	Linker–Drug Connection	293
12.5.3.3	Self-Immolative Prodrugs Fragmenting Following Cyclization	296
12.6	Strategies Used for the Improvement of DEPT Systems	296
12.6.1	Improvement of the Prodrug	296
12.6.1.1	Cytotoxicity Differential	297
12.6.1.2	Stability of Prodrugs	298
12.6.1.3	Cytotoxicity and Mechanism of Action of the Released Drug	299
12.6.1.4	Stability of the Released Drug	299
12.6.1.5	Resistance (Prodrug Related)	300
12.6.1.6	Kinetics of Activation	300
12.6.1.7	Physicochemical Properties	302
12.6.1.8	Pharmacokinetics	303
12.6.1.9	Specificity of Enzyme Activation	304
12.6.2	Improving the Enzymes	304
12.6.3	The Multigene Approach	305
12.6.4	Enhancing the Immune Response	307
12.7	Biological Data for ADEPT and GDEPT	307
12.7.1	Bacteria	308
12.7.2	Viruses	308
12.7.3	Adenoviral Vectors	308
12.7.4	Pox Viral Vectors	309
12.7.5	Adeno-Associated Viral Vectors	309

12.7.6	Retroviral Vectors	309
12.7.7	Lentiviral Vectors	310
12.7.8	Measles Viral Vectors	310
12.7.9	Herpes Simplex Viral Vectors	311
12.7.10	Neural Stem Cells/Progenitor Cells	311
12.7.11	Liposomes	311
12.7.12	ADEPT Vectors	312
12.7.13	Vectors for Prodrugs	312
12.7.14	Clinical Studies	316
12.8	Conclusions	316
	References	318

Part Three Codrugs and Soft Drugs 345

13	Improving the Use of Drug Combinations Through the Codrug Approach	347
	<i>Peter A. Crooks, Harpreet K. Dhooper, and Ujjwal Chakraborty</i>	
13.1	Codrugs and Codrug Strategy	347
13.2	Ideal Codrug Characteristics	348
13.3	Examples of Marketed Codrugs	349
13.4	Topical Codrug Therapy for the Treatment of Ophthalmic Diseases	351
13.4.1	Codrugs for the Treatment of Diabetic Retinopathy	351
13.4.2	Codrugs Containing Corticosteroids for Proliferative Vitreoretinopathy	353
13.4.3	Codrugs Containing Nonsteroidal Anti-Inflammatory Agents for Treatment of Proliferative Vitreoretinopathy	355
13.4.4	Codrugs Containing Ethacrynic Acid for Treatment of Elevated Intraocular Pressure	356
13.5	Codrugs for Transdermal Delivery	357
13.5.1	Codrugs for the Treatment of Alcohol Abuse and Tobacco Dependence	357
13.5.2	Duplex Codrugs of Naltrexone for Transdermal Delivery	362
13.5.3	Codrugs Containing α -Tocopherol for Skin Hydration	362
13.6	Codrugs of L-DOPA for the Treatment of Parkinson's Disease	363
13.6.1	L-DOPA Codrugs that Incorporate Inhibitors of L-DOPA Metabolism	363
13.6.2	L-DOPA-Antioxidant Codrugs	364
13.7	Analgesic Codrugs Containing Nonsteroidal Anti-Inflammatory Agents	367
13.7.1	Flurbiprofen-Histamine H ₂ Antagonist Codrugs	367
13.7.2	NSAID-Acetaminophen Codrugs	368
13.7.3	Naproxen-Propyphenazone Codrugs	370
13.7.4	Flurbiprofen-Amino Acid Codrugs	371
13.7.5	NSAID-Chlorzoxazone Codrugs	372

- 13.7.6 Acetaminophen–Chlorzoxazone Codrug 373
- 13.8 Analgesic Codrugs of Opioids and Cannabinoids 373
- 13.9 Codrugs Containing Anti-HIV Drugs 375
- 13.9.1 AZT–Retinoic Acid Codrug 377
- References 378

14 Soft Drugs 385

Paul W. Erhardt and Michael D. Reese

- 14.1 Introduction 385
 - 14.1.1 Definition 385
 - 14.1.2 Prototypical Agent 386
 - 14.1.2.1 Backdrop 386
 - 14.1.2.2 Clinical Challenge 386
 - 14.1.2.3 Pharmacological Target 388
 - 14.1.2.4 Pharmacology, Human Pharmacokinetic Profile, and Clinical Deployment 389
- 14.2 Indications 390
 - 14.2.1 A Huge Potential 391
 - 14.2.2 “To Market, To Market” 392
- 14.3 Design Considerations 396
 - 14.3.1 General Requirements 396
 - 14.3.2 Enzymatic Aspects 397
 - 14.3.3 Chemical Structural Aspects 397
- 14.4 Case Study: The Discovery of Esmolol 400
 - 14.4.1 Internal Esters 400
 - 14.4.2 External Esters 402
 - 14.4.3 “Square Pegs and Round Holes” 402
 - 14.4.4 Surrogate Scaffolds for Testing Purposes and a “Glimmer of Hope” 403
 - 14.4.5 A “Goldilocks” Compound Called Esmolol 404
 - 14.4.6 “Esmolol Stat” 406
 - 14.4.7 Case Study Summary and Some Take-Home Lessons for Today 407
 - 14.4.7.1 Compound Libraries 407
 - 14.4.7.2 Biological Testing 408
 - 14.4.7.3 SAR 408
- 14.5 Summary 408
- References 409

Part Four Preclinical and Clinical Consideration for Prodrugs 415

15 Pharmacokinetic and Biopharmaceutical Considerations in Prodrug Discovery and Development 417

John P. O'Donnell

- 15.1 Introduction 417

15.2	Understanding Pharmacokinetic/Pharmacodynamic Relationships	417
15.3	Pharmacokinetics	418
15.4	Tools for the Prodrug Scientist	421
15.4.1	Bioanalytical Assay Development	421
15.4.2	Use of Radiolabel	422
15.5	Enzymes Involved with Prodrug Conversion	423
15.5.1	Carboxylesterases	423
15.5.2	Alkaline Phosphatase	426
15.5.3	Cytochrome P450	428
15.6	Use of the Caco-2 System for Permeability and Active Transport Evaluation	428
15.7	XP13512: Improving PK Performance by Targeting Active Transport	432
15.8	Prodrug Absorption: Transport/Metabolic Conversion Interplay	434
15.8.1	Pivampicillin	434
15.8.2	Valacyclovir	436
15.9	Preabsorptive Degradation	438
15.9.1	Cephalosporin Prodrugs	438
15.9.2	Sulopenem Prodrugs PF-00398899, PF-03709270, and PF-04064900	439
15.10	Biopharmaceutical-Based PK Modeling for Prodrug Design	440
15.11	Conclusions	447
	References	447

16 The Impact of Pharmacogenetics on the Clinical Outcomes of Prodrugs 453

Jane P.F. Bai, Mike Pacanowski, Atiqur Rahman, and Lawrence L. Lesko

16.1	Introduction	453
16.2	Clopidogrel and CYP2C19	454
16.2.1	Summary	457
16.3	Codeine and CYP2D6	457
16.3.1	Summary	460
16.4	Tamoxifen and CYP2D6	460
16.4.1	Summary	463
16.5	Fluorouracil Prodrugs and Carboxylesterase	464
16.5.1	Capecitabine and Carboxylesterase	465
16.5.1.1	Summary	467
16.5.2	Tegafur and CYP2A6	467
16.5.2.1	Summary	468
16.6	Irinotecan and Carboxylesterase 2	468
16.6.1	Summary	469
16.7	Others	470

16.7.1	ACE Inhibitors and CES	470
16.7.2	Cyclophosphamide and CYP2B6/CYP2C19	470
16.7.2.1	Summary	471
16.8	Drug Development Implication	471
16.9	Conclusions	473
	References	473
	Index	483

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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 antedugs) 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.

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

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.

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Jarkko Rautio, Kuopio

Part One

Prodrug Design and Intellectual Property

1

Prodrug Strategies in Drug Design

Jarkko Rautio

1.1

Prodrug Concept

Prodrugs are bioreversible derivatives of pharmacologically active agents that must undergo an enzymatic and/or chemical transformation *in vivo* to release the active parent drug, which can then elicit its desired pharmacological effect [1–4]. According to this strict definition, active agents whose metabolites contribute to a pharmacological response and salts of active drugs, which have sometimes mistakenly been referred to as prodrugs, are not considered to be prodrugs. In most cases, prodrugs are simple chemical derivatives that are one or two chemical or enzymatic steps away from the active parent drug. Some prodrugs lack an obvious carrier or promoiety, but result from a molecular modification of the active drug itself *in vivo*. Such a modification can be, for example, a metabolic oxidation or reduction that generates a new and active compound. These prodrugs are usually referred to as “bioprecursor prodrugs.” In some cases, a prodrug may consist of two pharmacologically active drugs that are coupled together in a single molecule, so that each drug acts as a promoiety for the other. Such derivatives are called “codrugs” [5]. Finally, “soft drugs,” which are often confused with prodrugs, also find applications in tissue targeting. In contrast to prodrugs, soft drugs are active drugs as such but are designed to transform into an inactive form *in vivo* after achieving their therapeutic effect [6]. The prodrug concept is illustrated in Figure 1.1.

Prodrugs have been classified according to several criteria; these being, for example, based on therapeutic categories, or based on categories of chemical linkages between the parent drug and the promoiety, or based on mechanism of action of a prodrug. A recently proposed more systematic approach categorizes prodrugs on the basis of their two cellular sites of conversion: intracellular (e.g., antiviral nucleoside analogues and statins) and extracellular be it in digestive fluids or the systemic circulation (e.g., valganciclovir, fosamprenavir, and antibody-, gene-, or virus-directed enzyme prodrugs) [7, 8]. Both types can be further categorized into subtypes depending on whether or not the intracellular converting location is also the site of therapeutic action, or the conversion occurs in the gastrointestinal fluids or

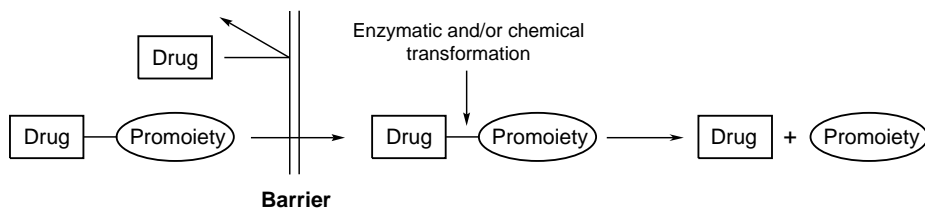


Figure 1.1 Simplified representation of the prodrug concept. The drug–promoiety molecule is the prodrug that is typically inactive pharmacologically. In broad terms, the barrier can be thought of as any biological liability for

a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic performance. This barrier must be overcome in order to achieve a marketable drug.

systemic circulation. From a regulatory perspective, this new classification system will certainly help in the understanding of a prodrug's pharmacokinetics and safety.

1.2

Basics of Prodrug Design

The design of an appropriate prodrug structure should be considered in the early stages of preclinical development, bearing in mind that prodrugs may alter the tissue distribution, efficacy, and even the toxicity of the parent drug. Although designing a prodrug so as to include all important factors in one molecule is admittedly very challenging, it can still be more feasible than searching for an entirely new therapeutic agent that has the desired properties. Moreover, the prodrug approach can enable the selection of a suitable drug candidate faster. The main factors that should be carefully considered when designing a prodrug structure are as follows:

- Which functional groups on the parent drug are amenable to chemical derivatization?
- Chemical modifications made to the parent drug must be reversible and allow the prodrug to be converted back into the parent drug by an *in vivo* chemical and/or enzymatic reaction.
- The promoiety should be safe and rapidly excreted from the body. The choice of promoiety and relative safety should be considered with respect to the disease state, the dose, and the duration of therapy.
- The absorption, distribution, metabolism, and excretion (ADME) properties of parent drug and prodrug require a comprehensive understanding.
- Possible degradation by-products can affect both chemical and physical stability that lead to the formation of new degradation products.

Arguably, the most common approaches for prodrug design are aimed at prodrugs undergoing metabolic bioconversion to the active parent molecule by functionally prominent and diversity-tolerant hydrolase enzymes such as peptidases, phosphatases, and, especially, carboxylesterases [9]. Because they are distributed throughout