Methods and Principles in Medicinal Chemistry

Edited by Jarkko Rautio

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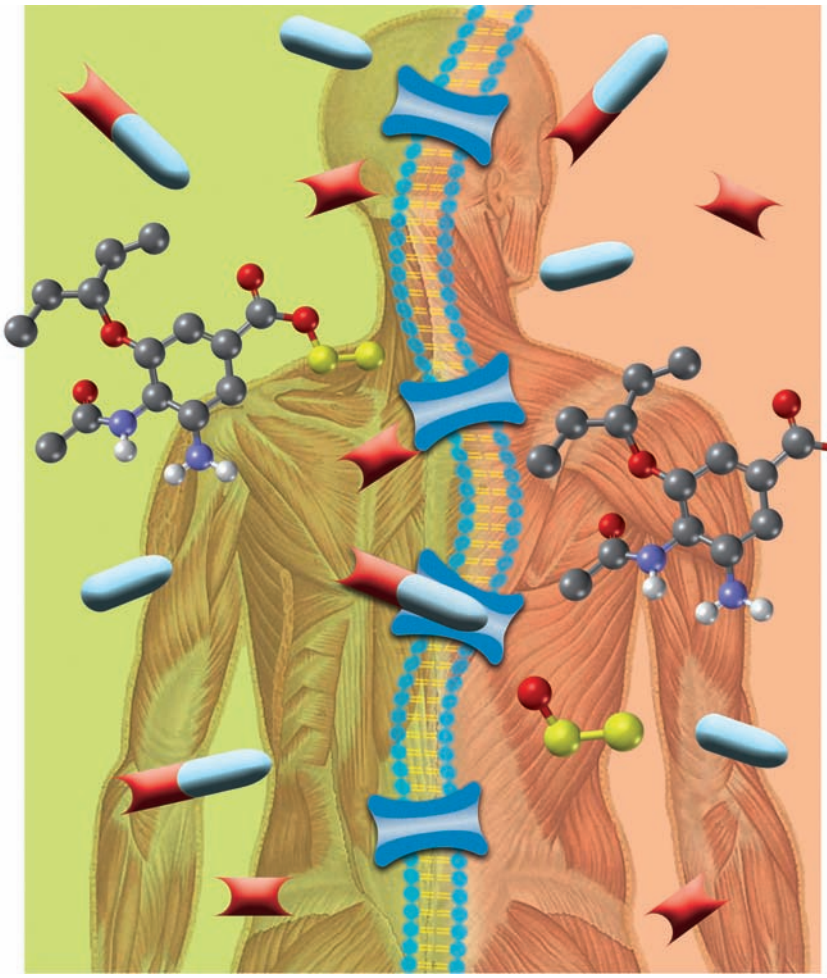
Prodrugs and Targeted Delivery

Towards Better ADME Properties



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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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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.

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.

October 2010 *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

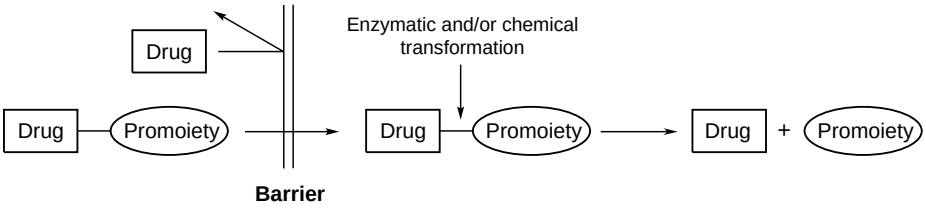

Figure 1.1 Simplified representation of the prodrug concept. The drug–promoiety molecule is the prodrug that is typically inactive pharmacologically. In broad terms, the barrier can be thought of as any biological liability for a parent drug that prevents optimal (bio)pharmaceutical or pharmacokinetic 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