Prodrugs
Biotechnology: Pharmaceutical Aspects

Ronald T. Borchardt and C. Russell Middaugh, Series Editors

Volume I: Pharmaceutical Profiling in Drug Discovery for Lead Selection

Volume II: Lyophilization of Biopharmaceuticals
H.R. Constantino, M.J. Pikal

Volume III: Methods for Structural Analysis of Protein Pharmaceuticals
W. Jiskoot, D.J.A. Crommelin

Volume IV: Optimizing the “Drug-Like” Properties of Leads in Drug Discovery

Volume V: Prodrugs: Challenges and Rewards, Parts 1 and 2
Prodrugs: Challenges and Rewards

Part 1
Preface

This book is a collaborative effort by the editors and many authors and coauthors to address the need for an update on the challenges and rewards of using prodrugs to effect better drug delivery. In the middle of the last century, Adrian Albert was the first to use the terms “pro-drug” and “pro-agent” in both an early paper and various editions of his book “Selective Toxicity” (see the first chapter for more details). It was clear from these early publications that the terms described bioreversible chemical derivatives of medicinal agents used to effect better activity, delivery, formulation, or targeting to tissues. Albert recognized that while many molecules might be effective at the cellular level, the properties that made them useful were not necessarily those that allowed their formulation, delivery, or targeting.

The astute reader will recognize that this concept is as applicable now as it was in the 1950s. At present we use terms such as “drugability” or the need for “drug-like” properties to describe the requirement to incorporate these properties so that the complex synthetic molecules of today can be clinically tested and potentially commercialized. In the mid-1980s, with the advent of molecular biology and the availability of pure protein targets, many new chemical entities were found to be effective at the molecular/receptor level but ineffective as molecules of commercial value. Maximizing binding often led to molecules so chemically constrained that drug-like properties could no longer be built in without significantly compromising activity. Some have referred to this as the “high affinity trap.” Of necessity, this began to change. The papers and talks given by C.A. Lipinski and his collaborators made medicinal chemists aware that high throughput screening for drug-like properties should be performed in parallel with molecular/receptor screens so that leads and, ultimately, drug candidates had a better chance of clinical success.

Therefore, in the two parts of this book, we attempt to present the current status of the prodrug concept and its many applications and to highlight its many successes in overcoming the formulation and delivery of problematic drugs. Dictated by the quantity of material, this book is divided into two parts.

The first part is composed of chapters that address the ability of prodrugs to overcome biopharmaceutical challenges resulting from poor permeability of polar drug entities, poor aqueous solubility of oral and parenteral drugs, inadequate targeting of the drug to the brain or particular diseased tissues, etc. This part was specifically directed to teams responsible for the design and delivery of problematic drugs in which the flaw in the parent drug was clearly identified and a prodrug solution sought. Approved and marketed prodrug examples as well as experimental and research concepts are presented.
The second part begins with a series of chapters describing a functional group approach to prodrugs designed more for synthetic medicinal chemists. What type of prodrug can be used to modify functional groups x, y and z? Some functional groups are not covered because they have had little attention paid to them, or because we, as editors, had to draw the line somewhere. The next series of chapters is directed to organizational groups responsible for issues such as toxicology and product development, namely, preclinical and clinical considerations. Finally, the last series of chapters consists of 25 case studies of marketed prodrugs. These represent some of the more successful examples of the prodrug approach from which one might learn and apply to future strategic endeavors in the development of prodrug candidates.

We had intended to supply a list of prodrugs that are currently in clinical trials, but found that in many cases the structures were not available or companies were reluctant to provide publishable information. A search of the topic “prodrugs in clinical trials” in one of the major search engines resulted in 92,000 hits. Of course, these include many redundancies, and many of the older citations are no longer relevant. Nevertheless, one would conclude from this cursory search that prodrugs continue to be a fertile area of research. This is also borne out by the large number of patents on the subject. There are a number of small pharmaceutical/biotech companies dedicated to using prodrugs for the delivery of older but problematic drugs as well as to developing broad-based prodrug technologies that can be applied to new and future drugs. At least one major pharma company has started a prodrug group within their R&D structure. As further evidence of the interest in prodrugs, the American Association of Pharmaceutical Scientists (AAPS) recently started a prodrug focus group. There is no question that the use of prodrugs will be considered earlier and with greater frequency in solving challenges to the delivery of problematic drugs.

Our goal, therefore, in editing and contributing to this book is to provide sufficient examples and supporting literature to introduce this topic to the novice as well as to help the professional in the design of prodrugs. We hope our enthusiasm for this topic is obvious and infective with a full recognition of the challenges and rewards that prodrugs can bring.

Valentino J. Stella, Ph.D.

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