The ORGANIC CHEMISTRY of DRUG DESIGN and DRUG ACTION

Richard B. Silverman

The Organic Chemistry of Drug Design and Drug Action

Richard B. Silverman
Department of Chemistry
Northwestern University
Evanston, Illinois

沈阳药学院图书
750208
Y750208

Academic Press, Inc.
Harcourt Brace Jovanovich, Publishers
San Diego New York Boston London Sydney Tokyo Toronto

This book is printed on acid-free paper. ♾

Copyright © 1992 by ACADEMIC PRESS, INC.
All Rights Reserved.
No part of this publication may be reproduced or transmitted in any form or by any means, electronic or mechanical, including photocopy, recording, or any information storage and retrieval system, without permission in writing from the publisher.

Academic Press, Inc.
1250 Sixth Avenue, San Diego, California 92101-4311

United Kingdom Edition published by
Academic Press Limited
24–28 Oval Road, London NW1 7DX

Library of Congress Cataloging-in-Publication Data

Silverman, Richard B.
The organic chemistry of drug design and drug action / Richard B. Silverman.
p. cm.
Includes index.
ISBN 0-12-643730-0 (hardcover)
1. Pharmaceutical chemistry. 2. Bioorganic chemistry.
3. Molecular pharmacology. 4. Drugs--Design. I. Title.
[DNLM: 1. Chemistry, Organic. 2. Chemistry, Pharmaceutical.
3. Drug Design. 4. Pharmacokinetics. QV 744 S587o]
RS403.S55 1992
615'.19--dc20
DNLM/DLC
for Library of Congress

91-47041
CIP

PRINTED IN THE UNITED STATES OF AMERICA
92 93 94 95 96 97 HA 9 8 7 6 5 4 3 2 1

To Mom and the memory of Dad,
for their warmth, their humor, their ethics, their inspiration,
but mostly for their genes.

Preface

From 1985 to 1989 I taught a one-semester course in medicinal chemistry to senior undergraduates and first-year graduate students majoring in chemistry or biochemistry. Standard medicinal chemistry courses are generally organized by classes of drugs with the emphasis on descriptions of their biological and pharmacological effects. I thought that there was a need to teach a course based on the organic chemical aspects of medicinal chemistry. It was apparent then, as it still is today, that there is no text that concentrates exclusively on the organic chemistry of drug design, drug development, and drug action. This book has evolved to fill that important gap and, because of the emphasis on the mechanistic organic chemistry of these biologically important reactions, it also can serve as a text for advanced bioorganic chemistry. (However, if the reader is interested in learning about a specific class of drugs, its biochemistry, pharmacology, and physiology, he or she is advised to look elsewhere for that information.)

Organic chemical principles and reactions vital to drug design and drug action are the emphasis of this text and clinically important drugs are used as examples. Therefore, only one (or at most a few) representative examples of drugs that exemplify a particular principle are given; no attempt is made to be comprehensive in any area. When more than one example is given, it generally is used to demonstrate different chemistry. It is assumed that the reader has taken a one-year course in organic chemistry that included the bioorganic components—amino acids, proteins, and carbohydrates—and is familiar with organic structures and basic organic reaction mechanisms. Only the chemistry and biochemistry background information pertinent to understanding the material in this text is discussed. Related background topics are briefly discussed or are referenced in the general readings section at the end of each chapter.

Depending on the depth of coverage that is desired, this text could be used for a one-semester or a full-year course. The references cited could be ignored in a shorter course or could be assigned for more detailed discussion in an intensive or full-year course. Additionally, not all sections need to be covered, particularly when multiple examples of a particular principle are

此为试读，需要完整PDF请访问：www.ertongbook.com

described. The instructor can select those examples that may be of most interest to the class.

It is my intent that the reader, whether a student or a scientist interested in entering the field of medicinal chemistry, will learn to take a rational physical organic chemical approach to drug design and drug development and to appreciate the chemistry of drug action. This knowledge is of utmost importance to understand how drugs function at the molecular level. The principles are the same regardless of the particular receptor or enzyme involved. Once the fundamentals of drug design and drug action are understood, these concepts can be applied to understand the many classes of drugs described in classical medicinal chemistry texts. This basic understanding can be the foundation for future elucidation of drug action or the rational discovery of new drugs that utilize organic chemical phenomena.

I am very grateful to Carol Slingo for single-handedly typing the entire manuscript and to Cindy Colvin, Eric Lightcap, Katie Bichler, Yury Zelechonok, Cheryl Chamberlain, Ting Su, Zhaozhong Ding, Jon Woo, Xingliang Lu, and Bill Hawe for the computer-generation of all of the structures, schemes, figures, and tables (except where they were reproduced directly with permission). Any errors found in the artwork, however, are the result of my editing oversights.

Evanston, Illinois
November, 1991

Richard B. Silverman

Contents

Chapter 5
Enzyme Inhibition and Inactivation

Chapter 7
Drug Metabolism

此为试读，需要完整PDF请访问: www.ertongbook.com

Chapter 8
Prodrugs and Drug Delivery Systems

CHAPTER 1

Introduction

I. Medicinal Chemistry Folklore

Medicinal chemistry is the science that deals with the discovery or design of new therapeutic chemicals and their development into useful medicines. It may involve synthesis of new compounds, investigations of the relationships between the structure of natural and/or synthetic compounds and their biological activities, elucidations of their interactions with receptors of various kinds, including enzymes and DNA, the determination of their absorption, transport, and distribution properties, and studies of the metabolic transformations of these chemicals into other chemicals.

Medicinal chemistry, in its crudest sense, has been practiced for several thousand years. Man has searched for cures of illnesses by chewing herbs, berries, roots, and barks. Some of these early clinical trials were quite successful; however, not until the last 100–150 years has knowledge of the active constituents of these natural sources been known. The earliest written records of the Chinese, Indian, South American, and Mediterranean cultures described the therapeutic effects of various plant concoctions.[1–3]

Two of the earliest medicines were described about 5100 years ago by the Chinese Emperor Shen Nung in his book of herbs called *Pentsao*.[4] One of these is *Ch'ang Shan*, the root *Dichroa febrifuga*, which was prescribed for fevers. This plant contains alkaloids which are used in the treatment of malaria today. Another plant called *Ma Huang* (now known as *Ephedra sinica*) was used as a heart stimulant, a diaphoretic agent (perspiration producer), and to allay coughing. It contains ephedrine, a drug that raises the blood pressure and relieves bronchial spasms. Theophrastus in the third century B.C. mentioned opium poppy juice as an analgetic, and in the tenth century A.D. Rhazes (Persia) introduced opium pills for coughs, mental disorders, aches, and pains. The opium poppy *Papaver somniferum* contains morphine, a potent analgetic, and codeine, prescribed today as a cough suppressant. The Orientals and the Greeks used henbane, which contains scopolamine (truth serum), as a sleep inducer. Inca mail runners and silver miners in the high Andean mountains chewed coca leaves (cocaine) as a stimulant and euphoric. The antihypertensive drug reserpine was extracted by ancient Hindus from the snakelike root of the *Rauwolfia serpentina* plant and used to treat hypertension, insomnia, and insanity. Alexander of Tralles in the sixth century A.D. recommended the autumn crocus (*Colchicum autumnale*) for relief of pain of the joints, and it was used by Avicenna (eleventh century Persia) and by Baron Anton von Störck (1763) for the treatment of gout. Benjamin Franklin heard about this medicine and brought it to America. The active principle in this plant is the alkaloid colchicine, which is used today to treat gout.

In 1633 a monk named Calancha, who accompanied the Spanish Conquistadors to Central and South America, introduced one of the greatest herbal medicines to Europe upon his return. The South American Indians would extract the bark of *Cinchona* trees and use it for chills and fevers; the Europeans used it for the same and for malaria. In 1820 the active constituent was isolated and later determined to be quinine, an antimalarial drug.

Modern therapeutics is considered to have begun with an extract of the foxglove plant, which was cited by Welsh physicians in 1250, named by Fuchsius in 1542, and introduced for the treatment of dropsy (now congestive heart failure) in 1785 by Withering.[2,5] The active constituents are secondary glycosides from *Digitalis purpurea* (the foxglove plant) and *Digitalis lanata*, namely, digitoxin and digoxin, respectively, both important drugs for the treatment of heart failure. Today, digitalis, which refers to all of the cardiac glycosides, is still manufactured by extraction of foxglove and related plants.

II. Discovery of New Drugs

If the approach to drug discovery continued as in ancient times, few diseases would be treatable today. Natural products make up a small percentage of drugs on the current market. Typically, when a natural product is found to be active, it is chemically modified in order to improve its properties. As a result of advances made in synthesis and separation methods and in biochemical techniques since the late 1940s, a more rational approach to drug discovery has been possible, namely, one which involves the element of design. In Chapter 2 a discussion is presented regarding how drugs are discovered and chemically modified in order to improve or change their medicinal properties.

References

1. Bauer, W. W. 1969. "Potions, Remedies and Old Wives' Tales." Doubleday, New York.
2. Withering, W. 1785. "An Account of the Foxglove and Some of Its Medicinal Uses: With Practical Remarks on Dropsy and Other Diseases." C. G. J. Robinson and J. Robinson, London; reprinted in *Med Class.* **2,** 305 (1937).

3a. Sneader, W. 1985. "Drug Discovery: The Evolution of Modern Medicines." Wiley, Chichester.

3b. Margotta, R. 1968. "An Illustrated History of Medicine." Paul Hamlyn, Middlesex, England.

4. Chen, K. K. 1925. *J. Am. Pharm. Assoc.* **14,** 189.
5. Burger, A. 1980. *In* "Burger's Medicinal Chemistry" (Wolff, M. E., ed.), 4th Ed., Part I, Chap. 1. Wiley, New York.

General References

The following references are excellent sources of material for this entire book.

Journals

Annual Reports in Medicinal Chemistry. Academic Press, San Diego, California.
Biochemical Pharmacology. Pergamon, New York.
Journal of Medicinal Chemistry. American Chemical Society, Washington, D.C.
Medicinal Research Reviews. Wiley, New York.
Molecular Pharmacology. Academic Press. San Diego, California.
Progress in Medicinal Chemistry. Elsevier/North-Holland, Amsterdam.
Progress in Drug Research. Birkäuser, Basel.

Books

Albert, A. 1985. "Selective Toxicity," 7th Ed. Chapman & Hall, London.
Ariëns, E. J., ed. 1971–1980. "Drug Design," Vols. 1–10. Academic Press, New York.
Budavari, S., ed. 1989. "The Merck Index," 11th Ed. Merck & Co., Rahway, New Jersey.
Burger, A. 1983. "A Guide to the Chemical Basis of Drug Design." Wiley, New York.
Foye, W. O. 1989. "Principles of Medicinal Chemistry," 3rd Ed. Lea & Febiger, Philadelphia, Pennsylvania.
Gilman, A. L., Goodman, L. S., Rall, T. W., and Murad, F. 1985. "Goodman and Gilman's The Pharmacological Basis of Therapeutics," 7th Ed. Macmillan, New York.
Hansch, C., Emmett, J. C., Kennewell, P. D., Ramsden, C. A., Sammes, P. G., and Taylor, J. B., eds. 1990. "Comprehensive Medicinal Chemistry," Vols. 1–6. Pergamon, Oxford.
Korolkovas, A. 1988. "Essentials of Medicinal Chemistry," 2nd Ed. Wiley, New York.
Wolff, M. E., ed. 1979–1981. "Burger's Medicinal Chemistry," 4th Ed., Parts 1–3. Wiley, New York.

CHAPTER 2

Drug Discovery, Design, and Development

I. Drug Discovery

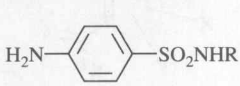
In general, clinically used drugs are not discovered. What is more likely discovered is known as a *lead* compound. The lead is a prototype compound that has the desired biological or pharmacological activity, but may have many other undesirable characteristics, for example, high toxicity, other biological activities, insolubility, or metabolism problems. The structure of the lead compound is then modified by synthesis to amplify the desired activity and to minimize or eliminate the unwanted properties. Prior to an elaboration of approaches to lead discovery and lead modification, two of the rare drugs discovered without a lead are discussed.

A. Drug Discovery without a Lead

1. Penicillins

In 1928 Alexander Fleming noticed a green mold growing in a culture of *Staphylococcus aureus*, and where the two had converged, the bacteria were lysed.[1] This led to the discovery of penicillin, which was produced by the mold. It may be thought that this observation was made by other scientists who just ignored it, and, therefore, Fleming was unique for following up on it. However, this is not the case. Fleming tried many times to rediscover this phenomenon without success; it was his colleague, Dr. Ronald Hare,[2,3] who was able to reproduce the observation. It only occurred the first time because a combination of unlikely events all took place simultaneously. Hare found that very special conditions were required to produce the phenomenon initially observed by Fleming. The culture dish inoculated by Fleming must have become accidentally and simultaneously contaminated with the mold spore. Instead of placing the dish in the refrigerator or incubator when he went on vacation as is normally done, Fleming inadvertently left it on his lab bench. When he returned the following month, he noticed the lysed bacteria. Ordinarily, penicillin does not lyse these bacteria; it prevents them from developing, but it has no effect if added after the bacteria have developed. However, while Fleming was on vacation (July to August) the weather was unseasonably cold, and this provided the particular temperature required for the mold and the staphylococci to grow slowly and produce the lysis. Another extraordinary circumstance was that the particular strain of the mold on Fleming's culture was a relatively good penicillin producer, although most strains of that mold (*Penicillium*) produce no penicillin at all. The mold presumably came from the laboratory just below Fleming's where research on molds was going on at the time.

Although Fleming suggested that penicillin could be useful as a topical antiseptic, he was not successful in producing penicillin in a form suitable to treat infections. Nothing more was done until Sir Howard Florey at Oxford University reinvestigated the possibility of producing penicillin in a useful form. In 1940 he succeeded in producing penicillin that could be administered topically and systemically,[4] but the full extent of the value of penicillin was not revealed until the late 1940s.[5] Two reasons for the delay in the universal utilization of penicillin were the emergence of the sulfonamide antibacterials (sulfa drugs, **2.1**; see Chapter 5, Section IV,B,1) in 1935 and the outbreak of World War II. The pharmacology, production, and clinical application of penicillin were not revealed until after the war so that this wonder drug would



2.1

此为试读，需要完整PDF请访问：www.ertongbook.com