

BURGER'S MEDICINAL CHEMISTRY AND DRUG DISCOVERY

Fifth Edition

Volume I: Principles and Practice

Edited by

Manfred E. Wolff

ImmunoPharmaceutics, Inc.
San Diego, California



A WILEY-INTERSCIENCE PUBLICATION

JOHN WILEY & SONS, Inc., New York · Chichester · Brisbane · Toronto · Singapore

Apotex v. Auspex
IPR2021-01507

Apotex Ex. 1021



Notice Concerning Trademark or Patent Rights.

The listing or discussion in this book of any drug in respect to which patent or trademark rights may exist shall not be deemed, and is not intended as a grant of, or authority to exercise, or an infringement of, any right or privilege protected by such patent or trademark.

This text is printed on acid-free paper.

Copyright © 1995 by John Wiley & Sons, Inc.

All rights reserved. Published simultaneously in Canada.

Reproduction or translation of any part of this work beyond that permitted by Section 107 or 108 of the 1976 United States Copyright Act without the permission of the copyright owner is unlawful. Requests for permission or further information should be addressed to the Permissions Department, John Wiley & Sons, 605 Third Avenue, New York, NY 10158-0012.

Library of Congress Cataloging in Publication Data:

Burger, Alfred, 1905-
 [Medicinal chemistry]
 Burger's medicinal chemistry and drug discovery. -- 5th ed. /
 edited by Manfred E. Wolff.
 p. cm.
 "A Wiley-Interscience publication."
 Contents: v. 1. Principles and practice
 Includes bibliographical references and index.
 ISBN 0-471-57556-9
 1. Pharmaceutical chemistry. I. Wolff, Manfred E. II. Title.
 III. Title: Medicinal chemistry and drug discovery.
 RS403.B8 1994
 615'.19--dc20

94-12687

Printed in the United States of America

10 9 8 7 6 5 4 3 2 1

Apotex Ex. 1021

CHAPTER SIX

Drug Metabolism

BERNARD TESTA

Institut de Chimie Thérapeutique, Ecole de
Pharmacie, Université de Lausanne
Lausanne, Switzerland

CONTENTS

- 1 Introduction, 130
 - 1.1 Definitions and concepts, 131
 - 1.2 Types of metabolic reactions affecting xenobiotics, 131
 - 1.3 Specificities and selectivities in xenobiotic metabolism, 132
 - 1.4 Pharmacodynamic consequences of xenobiotic metabolism, 133
 - 1.5 Biological factors affecting drug metabolism, 133
- 2 Functionalization Reactions, 134
 - 2.1 Introduction, 134
 - 2.2 Enzymes catalyzing functionalization reactions, 134
 - 2.2.1 Oxidoreductases, 134
 - 2.2.2 Hydrolases, 137
 - 2.3 Oxidation and reduction of carbon atoms, 137
 - 2.3.1 sp^3 -Carbon atoms, 137
 - 2.3.2 sp^2 - and sp -Carbon atoms, 140
 - 2.4 Oxidation and reduction of nitrogen atoms, 141
 - 2.5 Oxidation and reduction of sulfur and other atoms, 143
 - 2.6 Oxidative cleavage reactions, 146
 - 2.7 Hydration and hydrolysis, 147
- 3 Conjugation Reactions, 147
 - 3.1 Introduction, 147
 - 3.2 Methylation, 148
 - 3.2.1 Introduction, 148
 - 3.2.2 Methylation reactions, 148
 - 3.3 Sulfation, 150
 - 3.3.1 Introduction, 150
 - 3.3.2 Sulfation reactions, 150
 - 3.4 Glucuronidation and glucosidation, 152

129

Apotex Ex. 1021

Burger's Medicinal Chemistry and Drug Discovery,
Fifth Edition, Volume 1: Principles and Practice,
Edited by Manfred E. Wolff.
ISBN 0-471-57556-9 © 1995 John Wiley & Sons, Inc.

- 3.4.1 Introduction, 152
- 3.4.2 Glucuronidation reactions, 152
- 3.4.3 Glucosidation reactions, 156
- 3.5 Acetylation and acylation, 156
 - 3.5.1 Acetylation reactions, 156
 - 3.5.2 Other acylation reactions, 157
- 3.6 Conjugation with coenzyme A and subsequent reactions, 158
 - 3.6.1 Conjugation with coenzyme A, 158
 - 3.6.2 Formation of amino acid conjugates, 159
 - 3.6.3 Formation of hybrid lipids and sterol esters, 160
 - 3.6.4 Chiral inversion of arylpropionic acids, 161
 - 3.6.5 β -Oxidation and 2-carbon chain elongation, 161
- 3.7 Conjugation and redox reactions of glutathione, 163
 - 3.7.1 Introduction, 163
 - 3.7.2 Glutathione reactions, 164
- 3.8 Other conjugation reactions, 167
- 4 The Significance of Drug Metabolism in Medicinal Chemistry, 168
 - 4.1 Structure-metabolism relationships, 168
 - 4.1.1 Metabolic schemes, 168
 - 4.1.2 The influence of configurational factors, 170
 - 4.1.3 Quantitative structure-metabolism relationships: the influence of electronic factors and lipophilicity, 170
 - 4.2 Metabolism and drug design, 171
 - 4.2.1 Modulation of drug metabolism by structural variations, 171
 - 4.2.2 Principles of prodrug design, 172
 - 4.2.3 Examples of prodrugs and chemical delivery systems, 174
 - 4.3 The concept of toxophoric groups, 177
- 5 Concluding Remarks, 178

1 INTRODUCTION

Xenobiotic metabolism, which includes drug metabolism, has become an important pharmacological science with particular relevance to biology, therapeutics, and toxicology. Drug metabolism also is of great importance in medicinal chemistry, because it influences in qualitative, quantitative, and kinetic terms the deactivation, activation, detoxication, and toxication of the vast majority of drugs. As a result, medi-

nal chemists engaged in drug discovery (lead finding and optimization) must be able to integrate metabolic considerations into drug design. To do so, however, requires a fair or even good knowledge of xenobiotic metabolism.

This chapter presents knowledge and understanding rather than encyclopedic information. Readers wanting to go further in the study of xenobiotic metabolism should consult available references (1-3).

1.1 Definitions and Concepts

Drugs are but one category of the many xenobiotics (Table 6.1) that enter the body but have no nutritional or physiological value. The study of the disposition (or fate) of xenobiotics in living systems includes the consideration of their absorption into the organism, how and where they are distributed and stored, the chemical and biochemical transformations they may undergo, and how and by what route(s) they are finally excreted and returned to the environment. The word metabolism has acquired two meanings: it is synonymous with (1) disposition (i.e., the sum of the processes affecting the fate of a chemical substance in the body) and (2) biotransformation as understood in this chapter (5).

In pharmacology, one speaks of pharmacodynamic effects to indicate what a drug does to the body and pharmacokinetic effects to indicate what the body does to a drug; these two aspects of the behavior of xenobiotics are strongly interdependent. Pharmacokinetic effects will obviously have a decisive influence on the intensity and duration of pharmacodynamic effects, while metabolism will generate new chemical entities (metabolites) that may have distinct pharmacodynamic properties of their own. Conversely, by its own phar-

macodynamic effects, a compound may affect the state of the organism (e.g., hemodynamic changes and enzyme activities) and hence its capacity to handle xenobiotics. Only a systemic approach can help one appreciate the global nature of this interdependence (6).

1.2 Types of Metabolic Reactions Affecting Xenobiotics

A first discrimination that can be made among metabolic reactions is based on the nature of their catalysts. Reactions of xenobiotic metabolism, like other biochemical reactions, are catalyzed by enzymes. However, while the vast majority of reactions of xenobiotic metabolism are indeed enzymatic ones, some nonenzymatic reactions are also well documented. This is due to the fact that a variety of xenobiotics have been found to be labile enough to react nonenzymatically under biological conditions of pH and temperature (7). But there is more. In a normal enzymatic reaction, metabolic intermediates exist en route to the product(s) and do not leave the catalytic site. However, many exceptions to this rule are known: the metabolic intermediate leaves the active site and reacts with water, an endogenous molecule or macromole-

Table 6.1 Major Categories of Xenobiotics^a

Drugs
Food constituents devoid of physiological roles
Food additives (preservatives, coloring and flavoring agents, antioxidants, etc.)
Chemicals of leisure, pleasure, and abuse (ethanol, coffee and tobacco constituents, hallucinogens, etc.)
Agrochemicals (fertilizers, insecticides, herbicides, etc.)
Industrial and technical chemicals (solvents, dyes, monomers, polymers, etc.)
Pollutants of natural origin (radon, sulfur dioxide, hydrocarbons, etc.)
Pollutants produced by microbial contamination (e.g., aflatoxins)
Pollutants produced by physical or chemical transformation of natural compounds (polycyclic aromatic hydrocarbons from burning, Maillard reaction products from heating, etc.)

^aModified from Ref. 4.

Apotex Ex. 1021

Explore Litigation Insights

Docket Alarm provides insights to develop a more informed litigation strategy and the peace of mind of knowing you're on top of things.

Real-Time Litigation Alerts



Keep your litigation team up-to-date with **real-time alerts** and advanced team management tools built for the enterprise, all while greatly reducing PACER spend.

Our comprehensive service means we can handle Federal, State, and Administrative courts across the country.

Advanced Docket Research



With over 230 million records, Docket Alarm's cloud-native docket research platform finds what other services can't. Coverage includes Federal, State, plus PTAB, TTAB, ITC and NLRB decisions, all in one place.

Identify arguments that have been successful in the past with full text, pinpoint searching. Link to case law cited within any court document via Fastcase.

Analytics At Your Fingertips



Learn what happened the last time a particular judge, opposing counsel or company faced cases similar to yours.

Advanced out-of-the-box PTAB and TTAB analytics are always at your fingertips.

API

Docket Alarm offers a powerful API (application programming interface) to developers that want to integrate case filings into their apps.

LAW FIRMS

Build custom dashboards for your attorneys and clients with live data direct from the court.

Automate many repetitive legal tasks like conflict checks, document management, and marketing.

FINANCIAL INSTITUTIONS

Litigation and bankruptcy checks for companies and debtors.

E-DISCOVERY AND LEGAL VENDORS

Sync your system to PACER to automate legal marketing.