

*Wilson and Gisvold's
Textbook of*

ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY

T W E L F T H E D I T I O N

Edited by

John M. Beale, Jr., PhD

Associate Professor of Medicinal Chemistry
Division of Basic and Pharmaceutical Sciences
St. Louis College of Pharmacy
Saint Louis, Missouri



John H. Block, PhD, RPh

Professor Emeritus, Medicinal Chemistry
Department of Pharmaceutical Sciences
College of Pharmacy
Oregon State University
Corvallis, Oregon



Wolters Kluwer | Lippincott Williams & Wilkins
Health

Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Editor: David B. Troy
Product Manager: Meredith L. Brittain
Vendor Manager: Kevin Johnson
Designer: Holly McLaughlin
Compositor: Absolute Service, Inc./Maryland Composition

12th Edition

Copyright © 2011 by Lippincott Williams & Wilkins, a Wolters Kluwer business.

First Edition, 1949	Fifth Edition, 1966	Ninth Edition, 1991
Second Edition, 1954	Sixth Edition, 1971	Tenth Edition, 1998
Third Edition, 1956	Seventh Edition, 1977	Eleventh Edition, 2004
Fourth Edition, 1962	Eighth Edition, 1982	

351 West Camden Street Baltimore, MD 21201	530 Walnut Street Philadelphia, PA 19106
---	---

Printed in The People's Republic of China

All rights reserved. This book is protected by copyright. No part of this book may be reproduced or transmitted in any form or by any means, including as photocopies or scanned-in or other electronic copies, or utilized by any information storage and retrieval system without written permission from the copyright owner, except for brief quotations embodied in critical articles and reviews. Materials appearing in this book prepared by individuals as part of their official duties as U.S. government employees are not covered by the above-mentioned copyright. To request permission, please contact Lippincott Williams & Wilkins at 530 Walnut Street, Philadelphia, PA 19106, via email at permissions@lww.com, or via Web site at <http://www.lww.com> (products and services).

9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

Wilson and Gisvold's textbook of organic medicinal and pharmaceutical chemistry. — 12th ed. / edited by John M. Beale, Jr., John H. Block.

p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-7817-7929-6

1. Pharmaceutical chemistry. 2. Chemistry, Organic. I. Wilson, Charles Owens, 1911- II. Beale, John Marlowe. III. Block, John H. IV. Title: Textbook of organic medicinal and pharmaceutical chemistry.

[DNLM: 1. Chemistry, Pharmaceutical. 2. Chemistry, Organic. QV 744 W754 2011]

RS403.T43 2011

615'.19—dc22

2009043714

DISCLAIMER

Care has been taken to confirm the accuracy of the information present and to describe generally accepted practices. However, the authors, editors, and publisher are not responsible for errors or omissions or for any consequences from application of the information in this book and make no warranty, expressed or implied, with respect to the currency, completeness, or accuracy of the contents of the publication. Application of this information in a particular situation remains the professional responsibility of the practitioner; the clinical treatments described and recommended may not be considered absolute and universal recommendations.

The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant flow of information relating to drug therapy and drug reactions, the reader is urged to check the package insert for each drug for any change in indications and dosage and for added warnings and precautions. This is particularly important when the recommended agent is a new or infrequently employed drug.

Some drugs and medical devices presented in this publication have Food and Drug Administration (FDA) clearance for limited use in restricted research settings. It is the responsibility of the healthcare provider to ascertain the FDA status of each drug or device planned for use in their clinical practice.

To purchase additional copies of this book, call our customer service department at (800) 638-3030 or fax orders to (301) 223-2320. International customers should call (301) 223-2300.

Visit Lippincott Williams & Wilkins on the Internet: <http://www.lww.com>. Lippincott Williams & Wilkins customer service representatives are available from 8:30 am to 6:00 pm, EST.

The 12th Edition of Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry is dedicated to the memory of Robert F. Doerge.

Robert F. Doerge
1915–2006

Robert Doerge—pharmacist, medicinal chemist, and educator—experienced the Depression and served in the Civilian Conservation Corp in Sheridan, AR. Dr. Doerge received his B.S. in pharmacy in 1943 and his PhD in pharmaceutical chemistry, both from the University of Minnesota in 1949. The latter was under the direction of Dr. Charles O. Wilson, who, with Dr. Ole Gisvold, started this well-respected medicinal chemistry textbook. Dr. Doerge began his professional career as an assistant professor in the University of Texas-Austin School of Pharmacy before becoming a research chemist with the former Smith Kline and French Laboratories in Philadelphia. Beginning in 1960, he returned to academia as professor and chair of the pharmaceutical chemistry department in Oregon State University's College of Pharmacy. Prior to his retirement as professor emeritus in 1981, he was the assistant dean.

Dr. Doerge's initial publications were on the topic of synthesis of anticonvulsants. At Smith Kline and French, his work included publications on vitamin stability, and at Oregon State University, his papers focused on the heterocyclic phenylindolizines. Dr. Doerge was a volunteer abstractor for *Chemical Abstracts*. As an educator, Dr. Doerge was an author of chapters in *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, coeditor of the 6th and 7th editions, and editor of the 8th edition. His skill and dedication in the classroom were recognized by the students and university with several teaching awards.

We certainly miss this fine gentleman who put the students first and advanced the teaching of medicinal chemistry as a chapter author, coeditor, and editor of the Wilson and Gisvold textbook series.

John H. Block

PREFACE

For 6 decades, *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* has been a standard in the literature of medicinal chemistry. Generations of students and faculty have depended on this textbook not only for undergraduate courses in medicinal chemistry but also as a supplement for graduate studies. Moreover, students in other health sciences have found certain chapters useful. The current editors and authors worked on the 12th edition with the objective of continuing the tradition of a modern textbook for undergraduate students and also for graduate students who need a general review of medicinal chemistry. Because the chapters include a blend of chemical and pharmacological principles necessary for understanding structure–activity relationships and molecular mechanisms of drug action, the book should be useful in supporting courses in medicinal chemistry and in complementing pharmacology courses.

ABOUT THE 12TH EDITION

The 12th edition follows in the footsteps of the 11th edition by reflecting the dynamic changes occurring in medicinal chemistry. With increased knowledge of the disease process and the identification of the key steps in the biochemical process, the chapters have been updated, expanded, and reorganized. At the same time, to streamline the presentation of the content, some topics were combined into existing chapters. For example, Chapter 2, “Drug Design Strategies,” incorporates material from 11th edition Chapters 2, 3, and 28, and Chapter 3, “Metabolic Changes of Drugs and Related Organic Compounds,” includes the content from 11th edition Chapter 5, “Prodrugs and Drug Latentiation.” In addition, with the newer drugs that have entered the pharmaceutical armamentarium since publication of the 11th edition, coverage of the following topics has been expanded in the 12th edition: Central Dopaminergic Signaling Agents (Chapter 13), Anticonvulsants (Chapter 14), Hormone-Related Disorders: Nonsteroidal Therapies (Chapter 20), Agents Treating Bone Disorders (Chapter 21), and Anesthetics (Chapter 22).

New features of the 12th edition include a chapter overview at the beginning of each chapter to introduce material to be covered in the chapter and review questions at the end of each chapter to reinforce concepts learned in the chapter (answers to these questions are available to students on the book's companion Web site; see next section).

ADDITIONAL RESOURCES

Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry, 12th Edition, includes additional resources for both instructors and students that are available on the book's companion Web site at <http://www.thePoint.lww.com/Beale12e>.

Instructors

Approved adopting instructors will be given access to the following additional resources:

- Image bank of all the figures and tables in the book

Students

Students who have purchased *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 12th Edition, have access to the following additional resources:

- The answers to the review questions found in the book

In addition, purchasers of the text can access the searchable Full Text On-line by going to the *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry*, 12th Edition, Web site at <http://www.thePoint.lww.com/Beale12e>. See the inside front cover of this text for more details, including the passcode you will need to gain access to the Web site.

ACKNOWLEDGMENTS

The editors welcome the new contributors to the 12th edition: Jeffrey J. Christoff, A. Michael Crider, Carolyn J. Friel, Ronald A. Hill, Shengquan Liu, Matthias C. Lu, Marcello J. Nieto, and Kenneth A. Witt. The editors extend thanks to all of the authors who have cooperated in the preparation of the current edition. Collectively, the authors represent many years of teaching and research experience in medicinal chemistry. Their chapters include summaries of current research trends that lead the reader to the original literature. Documentation and references continue to be an important feature of the book.

We continue to be indebted to Professors Charles O. Wilson and Ole Gisvold, the originators of the book and editors of five editions, Professor Robert Doerge, who joined Professors Wilson and Gisvold for the 6th and 7th editions and single-handedly edited the 8th edition, and Professors Jaime Delgado and William Remers, who edited the 9th and 10th editions. They and the authors have contributed significantly to the education of countless pharmacists, medicinal chemists, and other pharmaceutical scientists.

*John M. Beale, Jr.
John H. Block*

1st	1949	Wilson and Gisvold (<i>Organic Chemistry in Pharmacy</i>)	6th	1971	Wilson, Gisvold, and Doerge
2nd	1954	Wilson and Gisvold	7th	1977	Wilson, Gisvold, and Doerge
3rd	1956	Wilson	8th	1982	Doerge
4th	1962	Wilson and Gisvold	9th	1991	Delgado and Remers
5th	1966	Wilson	10th	1998	Delgado and Remers
			11th	2004	Block and Beale

CONTRIBUTORS

John M. Beale, Jr., PhD

Associate Professor of Medicinal
Chemistry
Division of Basic and Pharmaceutical
Sciences
St. Louis College of Pharmacy
Saint Louis, Missouri

John H. Block, PhD, RPh

Professor Emeritus, Medicinal
Chemistry
Department of Pharmaceutical
Sciences
College of Pharmacy
Oregon State University
Corvallis, Oregon

Jeffrey J. Christoff, PhD, RPh

Professor
Department of Pharmaceutical
and Biomedical Sciences
College of Pharmacy, Ohio Northern
University
Ada, Ohio

C. Randall Clark, PhD

Professor
Department of Pharmaceutical
Sciences
Auburn University School of
Pharmacy
Auburn, Alabama

A. Michael Crider, PhD

Chair and Professor
Department of Pharmaceutical
Sciences
Southern Illinois University
Edwardsville
Edwardsville, Illinois

Horace G. Cutler, PhD

Senior Research Professor
College of Pharmacy and Health
Sciences
Mercer University
Atlanta, Georgia

Stephen J. Cutler

Chair and Professor
Department of Medicinal Chemistry
University of Mississippi
Oxford, Mississippi

Michael J. Deimling, RPh, PhD

Department of Pharmaceutical
Sciences
School of Pharmacy
Georgia Campus—Philadelphia
College of Osteopathic Medicine
Suwanee, Georgia

Jack DeRuiter, MS, PhD

Professor
Department of Pharmaceutical
Sciences
Auburn University School of
Pharmacy
Auburn, Alabama

Carolyn J. Friel, RPh, PhD

Associate Professor of Medicinal
Chemistry
Department of Pharmaceutical
Sciences
Massachusetts College of Pharmacy
and Health Sciences—Worcester
Worcester, Massachusetts

Ronald A. Hill, PhD

Associate Professor
Department of Basic Pharmaceutical
Sciences
The University of Louisiana at
Monroe
Monroe, Louisiana

Thomas J. Holmes, Jr., PhD

Professor
Department of Pharmaceutical
Sciences
Campbell University College of
Pharmacy and the Health Sciences
Buies Creek, New Carolina

M. O. Faruk Khan, BPharm, MPharm, PhD

Assistant Professor of Medicinal
Chemistry
Department of Pharmaceutical
Sciences
Southwestern Oklahoma State
University College of Pharmacy
Weatherford, Oklahoma

Matthias C. Lu, PhD

Professor and Assistant Head for
Curricular Affairs
Department of Medicinal Chemistry
and Pharmacognosy
College of Pharmacy, University of
Illinois at Chicago
Chicago, Illinois

Shengquan Liu, PhD

Assistant Professor
Department of Medicinal Chemistry
Touro University—California
Vallejo, California

Marcello J. Nieto, PhD

Assistant Professor
Department of Pharmaceutical
Sciences
Southern Illinois University
Edwardsville, Illinois

Gustavo R. Ortega, RPh, PhD

Professor Emeritus
Department of Pharmaceutical
Sciences
Southwestern Oklahoma State
University College of Pharmacy
Weatherford, Oklahoma

Philip J. Proteau, PhD

Associate Professor of Medicinal
Chemistry
Department of Pharmaceutical
Sciences
Oregon State University College of
Pharmacy
Corvallis, Oregon

Forrest T. Smith, PhD

Associate Professor
Department of Pharmaceutical
Sciences
Auburn University School of
Pharmacy
Auburn, Alabama

Kenneth A. Witt, PhD

Assistant Professor
Department of Pharmaceutical
Sciences
Southern Illinois University
Edwardsville
Edwardsville, Illinois

CONTENTS

<i>Preface</i>	iv
<i>Contributors</i>	vi

CHAPTER 1	
<i>Introduction</i>	1
<i>John M. Beale, Jr. and John H. Block</i>	

CHAPTER 2	
<i>Drug Design Strategies</i>	3
<i>John H. Block</i>	
Drug Distribution	3
Acid-Base Properties	12
Computer-Aided Drug Design: Early Methods . . .	17
Computer-Aided Drug Design: Newer Methods . .	25
Selected Web Pages	40

CHAPTER 3	
<i>Metabolic Changes of Drugs and Related Organic Compounds</i>	43
<i>Stephen J. Cutler and John H. Block</i>	
General Pathways of Drug Metabolism	43
Sites of Drug Biotransformation	45
Role of Cytochrome P450 Monooxygenases in Oxidative Biotransformations	45
Oxidative Reactions	47
Reductive Reactions	78
Hydrolytic Reactions	86
Phase II or Conjugation Reactions	88
Factors Affecting Drug Metabolism	104

CHAPTER 4	
<i>Biotechnology and Drug Discovery</i>	119
<i>John M. Beale, Jr.</i>	
Biotechnology and Pharmaceutical Care	119
Literature of Biotechnology	119
Biotechnology and New Drug Development . . .	119
The Biotechnology of Recombinant DNA	121
Some Types of Cloning	126
Expression of Cloned DNA	127
Manipulation of DNA Sequence Information . . .	127
New Biological Targets for Drug Development . .	128
Novel Drug-Screening Strategies	129
Processing of the Recombinant Protein	131
Pharmaceuticals of Recombinant DNA-Produced Agents	131
Delivery and Pharmacokinetics of Biotechnology Products	134
Recombinant Drug Products	134
The Interleukins	141
Enzymes	142
Vaccines	145
Preparation of Antibodies	146
Genomics	150

Antisense Technology	152
Gene Therapy	153
Afterword	153

CHAPTER 5	
<i>Immunobiologicals</i>	156
<i>John M. Beale, Jr.</i>	
Cells of the Immune System	156
Immunity	159
Acquisition of Immunity	165
New Vaccine Technologies: Adjuvant Technology	174
New Vaccine Technologies: Nucleic Acid Vaccines	177

CHAPTER 6	
<i>Anti-infective Agents</i>	179
<i>John M. Beale, Jr.</i>	
Evaluation of the Effectiveness of a Sterilant . . .	180
Alcohols and Related Compounds	181
Phenols and Their Derivatives	183
Oxidizing Agents	185
Halogen-Containing Compounds	185
Cationic Surfactants	186
Dyes	188
Mercury Compounds (Mercurials)	189
Preservatives	190
Antifungal Agents	191
Synthetic Antibacterial Agents	206
Antiprotozoal Agents	220
Anthelmintics	224
Antiscabious and Antipedicular Agents	227
Antibacterial Sulfonamides	228
Dihydrofolate Reductase Inhibitors	239
Sulfones	239

CHAPTER 7	
<i>Antimalarials</i>	242
<i>John H. Block</i>	
Stimulation of Antimalarial Research by War . . .	245
Cinchona Alkaloids	245

CHAPTER 8	
<i>Antibacterial Antibiotics</i>	258
<i>John M. Beale, Jr.</i>	
Historical Background	258
Current Status	259
Commercial Production	259
Spectrum of Activity	259
Mechanisms of Action	259
Chemical Classification	260
Microbial Resistance	260
β -Lactam Antibiotics	260

The Penicillins	261
β -Lactamase Inhibitors	274
Cephalosporins	278
Monobactams	293
Aminoglycosides	294
Tetracyclines	301
Macrolides	308
Lincomycins	313
Polypeptides	315
Unclassified Antibiotics	320
Newer Antibiotics	324
New Directions in Antibiotic Discovery	326

CHAPTER 9

Antiviral Agents 330*John M. Beale, Jr.*

The Classification and Biochemistry of Viruses	330
Classification of Viruses	330
Targets for the Prevention of Viral Infections—Chemoprophylaxis	331
The Infectious Process for a Virus	333
Nucleoside Antimetabolites: Inhibiting Viral Replication	339
Newer Agents for the Treatment of HIV Infection	346

CHAPTER 10

Antineoplastic Agents 355*Forrest T. Smith and C. Randall Clark*

Introduction	355
Drug Classes	358
Antimetabolites	372
Antibiotics and Natural Products	383
Protein Kinase Inhibitors	400
Miscellaneous Compounds	406

CHAPTER 11

Agents for Diagnostic Imaging 413*Jeffrey J. Christoff*

Radiopharmaceuticals	413
Contrast Agents	430

CHAPTER 12

Central Nervous System Depressants 443*Shengquan Liu*

Anxiolytic, Sedative, and Hypnotic Agents	443
Antipsychotics	457
Acknowledgment	469

CHAPTER 13

Central Dopaminergic Signaling Agents 471*A. Michael Crider, Marcelo J. Nieto, and Kenneth A. Witt*

Dopamine	471
Parkinson Disease	473

Antipsychotic Drugs	478
Future Directions	488

CHAPTER 14

Anticonvulsants 491*Matthias C. Lu*

Disease States Requiring Anticonvulsant Therapy	491
Mechanisms of Action of Anticonvulsants	492
Clinically Important Anticonvulsants	494
Future Development of Antiepileptic Drugs	501

CHAPTER 15

Central Nervous System Stimulants 504*John M. Beale, Jr.*

Analeptics	504
Methylxanthines	505
Central Sympathomimetic Agents (Psychomotor Stimulants)	506
Antidepressants	509
Miscellaneous CNS-Acting Drugs	515

CHAPTER 16

Adrenergic Agents 519*Shengquan Liu*

Adrenergic Neurotransmitters	519
Adrenergic Receptors	524
Drugs Affecting Adrenergic Neurotransmission	528
Sympathomimetic Agents	531
Adrenergic Receptor Antagonists (Blockers)	545
Acknowledgment	554

CHAPTER 17

Cholinergic Drugs and Related Agents 558*Stephen J. Cutler*

Cholinergic Receptors	559
Cholinergic Neurochemistry	563
Cholinergic Agonists	564
Cholinergic Receptor Antagonists	567
Cholinergic Blocking Agents	581
Parasympathetic Postganglionic Blocking Agents	583
Solanaceous Alkaloids and Analogs	584
Synthetic Cholinergic Blocking Agents	588
Ganglionic Blocking Agents	596
Neuromuscular Blocking Agents	599

CHAPTER 18

Drugs Acting on the Renal System . . 607*Stephen J. Cutler*

Renin–Angiotensin System Inhibitors	609
ACE-Inhibitor Prodrugs	610
Angiotensin Antagonists	612

Angiotensin II Blockers	613
Renin Inhibitors	614
Alosterone Antagonists	615

CHAPTER 19

Cardiovascular Agents 617*Stephen J. Cutler*

Antianginal Agents and Vasodilators	617
Antiarrhythmic Drugs	629
Antihypertensive Agents	637
Antihyperlipidemic Agents	647
Anticoagulants	654
Synthetic Hypoglycemic Agents	658
Thyroid Hormones	663
Antithyroid Drugs	663

CHAPTER 20

**Hormone-Related Disorders:
Nonsteroidal Therapies 666***Ronald A. Hill*

Disorders of Glucose Metabolism: Diabetes and the Metabolic Syndrome	666
Gonadotropins, Gonadotropin-Releasing Hormone, and GnRH Receptor Agonists and Antagonists	695
Concluding Remarks	701

CHAPTER 21

Agents Treating Bone Disorders 705*John H. Block*

Diseases of Bone Tissue Utilizing Approved Drug Therapies	705
Drugs Used to Treat Diseases of the Bone	706
Hormone Therapy	708
Future Directions	710

CHAPTER 22

Anesthetics 711*Carolyn J. Friel*

The Inhaled General Anesthetics	711
The Injectable General Anesthetics	716
The Local Anesthetics	718
Local Anesthetic Monographs, Individual Products Including Adverse Reactions	725

CHAPTER 23

**Histamine and Antihistaminic
Agents 733***Jack DeRuiter*

Histamine Chemistry	733
Histamine as a Chemical Messenger	733
Antihistamines	737
Inhibition of Histamine Release: Mast Cell Stabilizers	757

Recent Antihistamine Developments: the "Dual-Acting" Antihistamines	759
Histamine H ₂ -Antagonists	760
Histamine H ₃ - and H ₄ -Receptor Ligands	773

CHAPTER 24

Analgesics 776*Carolyn J. Friel and Matthias C. Lu*

Pain and Pain Management	776
Opioids	777
Drug Monographs	782
Nonsteroidal Anti-inflammatory Drugs	792
Disease-Modifying Antirheumatic Drugs	806
Drugs Used in the Management of Gout and Hyperuricemia	809
Triptans	811

CHAPTER 25

**Steroid Hormones and
Therapeutically Related
Compounds 819***Philip J. Proteau*

Steroid Nomenclature, Stereochemistry, and Numbering	819
Steroid Biosynthesis	819
Chemical and Physical Properties of Steroids	822
Changes to Modify Pharmacokinetic Properties of Steroids	822
Steroid Hormone Receptors	823
Gonadotropin-Releasing Hormone and Gonadotropins	826
Sex Hormones	827
Chemical Contraceptive Agents	841
Androgens	847
Adrenal Cortex Hormones	853
Neurosteroids	864
Acknowledgment	864

CHAPTER 26

**Prostaglandins, Leukotrienes,
and Essential Fatty Acids 868***Thomas J. Holmes, Jr.*

Essential Fatty Acids	868
History of Eicosanoid Discovery	868
Eicosanoid Biosynthesis	869
Drug Action Mediated by Eicosanoids	872
COX-2 Inhibitors	872
Design of Eicosanoid Drugs	872
Eicosanoid Receptors	875
Commercially Available Essential Fatty Acid Supplements	875
Eicosanoids Approved for Human Clinical Use	876
Prostaglandins for Ophthalmic Use	878
Veterinary Uses of Prostanoids	878
Eicosanoids in Clinical Development for Human Treatment	879

CHAPTER 27

Proteins, Enzymes, and Peptide Hormones 880

Stephen J. Cutler and Horace G. Cutler

Protein Hydrolysates	880
Amino Acid Solutions	881
Proteins and Proteinlike Compounds	881
Enzymes	885
Hormones	890
Blood Proteins	906
Impact of Biotechnology on the Development and Commercial Production of Proteins and Peptides as Pharmaceutical Products	907
Biotechnology-Derived Pharmaceutical Products	909

CHAPTER 28

Vitamins 915

Michael J. Deimling, M. O. Faruk Khan, and Gustavo R. Ortega

Introduction	915
Fat-Soluble Vitamins	917
Water-Soluble Vitamins	935

CHAPTER 29

An Introduction to the Medicinal Chemistry of Herbs 961

John M. Beale, Jr.

Historical Aspects	961
What Is an Herb?	962
Herbal Purity and Standardization	962
An Herb Is a Drug	962
Types of Herbs	963

APPENDIX

Calculated Log P, Log D, and pK_a . . 976

Index 984