

FOYE'S Principles of Medicinal Chemistry

SIXTH EDITION

Edited By

THOMAS L. LEMKE, PHD

*Professor Emeritus
College of Pharmacy
University of Houston
Houston, Texas*

DAVID A. WILLIAMS, PHD

*Professor Emeritus of Chemistry
Massachusetts College of Pharmacy and
Health Sciences
Boston, Massachusetts*

Assistant Editors

VICTORIA F. ROCHE, PHD

*Senior Associate Dean
School of Pharmacy and Health Professions
Creighton University
Omaha, Nebraska*

S. WILLIAM ZITO, PHD

*Professor of Pharmaceutical Sciences
College of Pharmacy and
Allied Health Professions
St. John's University
Jamaica, New York*



Wolters Kluwer | Lippincott Williams & Wilkins

Health

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

Acquisitions Editor: David Troy
Managing Editor: Meredith Brittain
Marketing Manager: Christen Murphy
Production Editor: Hearthside Publishing Services
Designer: Sunflower Publishing Services
Graphic Artist: Nicole Williams
Compositor: Aptara

Cover image courtesy of Wavefunction, Inc. The ribbon display (green and red) is tyrosine kinase. The "active site" for tyrosine kinase is shown as tube display with a mesh-style electrostatic potential map (a charge distribution map), with the drug imatinib shown in the "active site" with a solid-color style electrostatic potential map (where the colors toward red depict negative potential; colors toward blue depict positive potentials; and colors such as yellow, orange, green, and violet depict intermediate values). Imatinib (a 2-phenyl amino pyrimidine derivative, a.k.a. CGP57148B, STI571 or Gleevec®) is a selective inhibitor of several tyrosine kinases that binds to the ATP-binding pocket of tyrosine kinase and blocks the activities of Abl, c-kit, and PDGFR. It is used for treating chronic myelogenous leukemia (CML), gastrointestinal stromal tumors (GISTs), and a number of other malignancies.

Sixth Edition

Copyright © 2008, 2002, 1995, 1989, 1981, 1974
Lippincott Williams & Wilkins, a Wolters Kluwer business.

351 West Camden Street
Baltimore, MD 21201

530 Walnut Street
Philadelphia, PA 19106

Printed in the USA

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 website at lww.com (products and services).

9 8 7 6 5 4 3 2 1

Library of Congress Cataloging-in-Publication Data

Foye's principles of medicinal chemistry / edited by Thomas L. Lemke . . . [et al.]. — 6th ed.
p. ; cm.

Includes bibliographical references and index.

ISBN 978-0-7817-6879-5

I. Pharmaceutical chemistry. I. Foye, William O. II. Lemke, Thomas L.

III. Title: Principles of medicinal chemistry.

[DNLM: 1. Chemistry, Pharmaceutical. QV 744 F7962 2008]

RS403.P75 2008

616.07'56—dc22

2007026228

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.

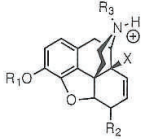
The authors, editors, and publisher have exerted every effort to ensure that drug selection and dosage set forth in this text are in accordance with the current recommendations and practice at the time of publication. However, in view of ongoing research, changes in government regulations, and the constant 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 health care 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.

Table 24.3. Marketed Drugs that are Derivatives of Morphine



| Generic name | R ₁ | R ₂ | R ₃ | X | Other |
|-------------------|-----------------|----------------|--------------------------------------|----|--------------------|
| (-)-Morphine | H | OH | -CH ₃ | H | None |
| (-)-Codeine | CH ₃ | OH | -CH ₃ | H | None |
| (-)-Hydromorphone | H | Keto | -CH ₃ | H | No 7,8-double bond |
| (-)-Oxymorphone | H | Keto | -CH ₃ | OH | No 7,8-double bond |
| (-)-Hydrocodone | CH ₃ | Keto | -CH ₃ | H | No 7,8-double bond |
| (-)-Oxycodone | CH ₃ | Keto | -CH ₃ | OH | No 7,8-double bond |
| (-)-Nalbuphine | H | OH | -H ₂ C-cBu | H | No 7,8-double bond |
| (-)-Naloxone | H | Keto | -CH ₂ -CH=CH ₂ | OH | No 7,8-double bond |
| (-)-Naltrexone | H | Keto | -H ₂ C-cPr | OH | No 7,8-double bond |

dose of morphine is usually 60 mg, followed by maintenance doses of 20 to 30 mg every 4 hours. Addiction to clinically used morphine by the oral route generally is not a problem.

Overdoses of morphine, as well as all μ agonists in this section, can be effectively reversed with naloxone.

(-)-Codeine Phosphate

Codeine is used extensively to treat moderate to mild pain. Codeine is a weak μ agonist, but approximately 10% of an oral dose (30–60 mg) is metabolized to morphine (see the section on metabolism in this chapter), which contributes significantly to its analgesic effect. The plasma half-life of codeine after oral dose is 3.5 hours. The dose of codeine needed to produce analgesia after parenteral dose causes releases of histamine sufficient to produce hypotension, pruritus, and other allergic responses. Thus, administration of codeine by parenteral route is not recommended.

(-)-Hydromorphone Hydrochloride (Dilaudid)

Hydromorphone is a potent μ agonist (eight times greater than morphine) that is used to treat severe pain. It is available in intramuscular, intravenous, subcutaneous, oral, and rectal dosage forms. Like all strong μ agonists, hydromorphone is addicting and is a Schedule II drug. Hydromorphone has an oral:parenteral potency ratio of 5:1. The plasma half-lives after parenteral and oral dosage are 2.5 and 4 hours, respectively.

(-)-Oxymorphone Hydrochloride (Numorphan)

Oxymorphone is a potent μ agonist (10 times greater than morphine) that is used to treat severe pain. It is used by intramuscular, subcutaneous, intravenous, and rectal routes of administration. The intramuscular dose of oxymorphone (1 mg) has a half-life of 3 to 4 hours. It is a

Schedule II drug. Oxymorphone, because of its 14-hydroxy group, has low antitussive activity.

(-)-Levorphanol Bitartrate (Levo-Dromoran)

Levorphanol is a potent μ agonist (approximately sixfold greater than morphine), and its uses, side effects, and physical dependence liability are like those of oxymorphone or hydromorphone. Levorphanol is available in oral, subcutaneous, and intravenous dosage forms. The oral dose of levorphanol is approximately twice the parenteral dose. This drug is unique among the μ agonists in that its analgesic duration of action is 4 to 6 hours, whereas its clearance half-life is 11.4 hours. Thus, effective analgesic doses of this agent can lead to a buildup of the drug in the body and result in excessive sedation.

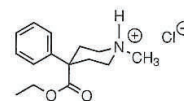
(-)-Hydrocodone Bitartrate (Lortab, Vicodin in Combinations with Acetaminophen)

Hydrocodone is a Schedule III drug that is used to treat moderate pain. It is used mostly by the oral route (5-mg tablets and solutions) in combination with acetaminophen. The compound has good oral bioavailability and is metabolized in a manner similar to codeine.

(-)-Oxycodone Hydrochloride (Roxicodone, Oxycotin Sustained Release; and Percocet, Percodan, Tylox; in Combinations)

Oxycodone is about equipotent with morphine, but because of the 3-OCH group, it has a much lower oral:parenteral dose ratio. Thus, oxycodone is used orally to treat severe to moderate pain. It is a Schedule II drug as a single agent and when combined in strong analgesic mixtures. Oxycodone has a plasma half-life of approximately 4 hours and requires dosing every 4 to 6 hours. Metabolism of this agent is comparable to that of codeine.

Meperidine Hydrochloride (Demerol)



Meperidine is a μ agonist with approximately one-tenth the potency of morphine after intramuscular dose. Meperidine produces the analgesia, respiratory depression, and euphoria caused by other μ opioid agonists, but it causes less constipation and does not inhibit cough. When given orally, meperidine has 40 to 60% bioavailability because of significant first-pass metabolism. Because of the limited bioavailability, it is one-third as potent after an oral dose compared to a parenteral dose.

Meperidine has received extensive use in obstetrics because of its rapid onset and short duration of action. When it is given intravenously in small (25-mg) doses during delivery, the respiratory depression in the newborn child is minimized. Meperidine is used as an analgesic