Wilson and Gisvold's
Textbook of

Organic Medicinal and Pharmaceutical Chemistry

Twelfth Edition

John M. Beale, Jr. ◆ John H. Block

Wolters Kluwer Health | Lippincott Williams & Wilkins

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ORGANIC MEDICINAL AND PHARMACEUTICAL CHEMISTRY

TWELFTH EDITION

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Wolters Kluwer Health | Lippincott Williams & Wilkins
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

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

351 West Camden Street
Baltimore, MD 21201

530 Walnut Street
Philadelphia, PA 19106

Printed in The People's Republic of China

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

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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 (*Organic Chemistry in Pharmacy*)	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

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CHAPTER 1

Introduction

JOHN M. BEALE, JR. AND JOHN H. BLOCK

The discipline of medicinal chemistry is devoted to the discovery and development of new agents for treating diseases. Most of this activity is directed to new natural or synthetic organic compounds. Paralleling the development of medicinal agents has come a better understanding of the chemistry of the receptor. The latter has been greatly facilitated by low-cost computers running software that calculates molecular properties and structure and pictures it using high-resolution graphics. Development of organic compounds has grown beyond traditional synthetic methods. It now includes the exciting field of biotechnology using the cell's biochemistry to synthesize new compounds. Techniques ranging from recombinant DNA and site-directed mutagenesis to fusion of cell lines have greatly broadened the possibilities for new entities that treat disease. The pharmacist now dispenses modified human insulins that provide more convenient dosing schedules, cell-stimulating factors that have changed the dosing regimens for chemotherapy, humanized monoclonal antibodies that target specific tissues, and fused receptors that intercept immune cell–generated cytokines.

This 12th edition of *Wilson and Gisvold's Textbook of Organic Medicinal and Pharmaceutical Chemistry* continues the philosophy of presenting the scientific basis of medicinal chemistry originally established by Professors Charles Wilson and Ole Gisvold, describing the many aspects of organic medicinals: how they are discovered, how they act, and how they developed into clinical agents. The process of establishing a new pharmaceutical is exceedingly complex and involves the talents of people from various disciplines, including chemistry, biochemistry, molecular biology, physiology, pharmacology, pharmaceutics, and medicine. Medicinal chemistry, itself, is concerned mainly with the organic, analytical, and biochemical aspects of this process, but the chemist must interact productively with those in other disciplines. Thus, medicinal chemistry occupies a strategic position at the interface of chemistry and biology. All of the principles discussed in this book are based on fundamental organic chemistry, physical chemistry, and biochemistry. To provide an understanding of the principles of medicinal chemistry, it is necessary to consider the physicochemical properties used to develop new pharmacologically active compounds and their mechanisms of action, the drug's metabolism, including possible biological activities of the metabolites, the importance of stereochemistry in drug design, and the methods used to determine what "space" a drug occupies.

The earliest drug discoveries were made by random sampling of higher plants. Some of this sampling, although based on anecdotal evidence, led to the use of such crude plant drugs as opium, belladonna, and ephedrine that have been important for centuries. With the accidental discovery of penicillin came the screening of microorganisms and the large number of antibiotics from bacterial and fungal sources. Many of these antibiotics provided the prototypical structure that the medicinal chemist modified to obtain antibacterial drugs with better therapeutic profiles. With the changes in federal legislation reducing the efficacy requirement for "nutriceutical," the public increasingly is using so-called nontraditional or alternative medicinals that are sold over the counter, many outside of traditional pharmacy distribution channels. It is important for the pharmacist and the public to understand the rigor that is required for prescription-only and Food and Drug Administration (FDA)-approved nonprescription products to be approved relative to the nontraditional products. It is also important for all people in the healthcare field and the public to realize that whether these nontraditional products are effective as claimed or not, many of the alternate medicines contain pharmacologically active agents that can potentiate or interfere with physician-prescribed therapy.

Hundreds of thousands of new organic chemicals are prepared annually throughout the world, and many of them are entered into pharmacological screens to determine whether they have useful biological activity. This process of random screening has been considered inefficient, but it has resulted in the identification of new lead compounds whose structures have been optimized to produce clinical agents. Sometimes, a lead develops by careful observation of the pharmacological behavior of an existing drug. The discovery that amantadine protects and treats early influenza A came from a general screen for antiviral agents. The use of amantadine in long-term care facilities showed that it also could be used to treat parkinsonian disorders. More recently, automated high-throughput screening systems utilizing cell culture systems with linked enzyme assays and receptor molecules derived from gene cloning have greatly increased the efficiency of random screening. It is now practical to screen enormous libraries of peptides and nucleic acids obtained from combinatorial chemistry procedures.

Rational design, the opposite approach to high-volume screening, is also flourishing. Statistical methods based on the correlation of physicochemical properties with biological potency are used to explain and optimize biological activity. Significant advances in x-ray crystallography and nuclear magnetic resonance have made it possible to obtain detailed representations of enzymes and other drug receptors. The techniques of molecular graphics and computational

chemistry have provided novel chemical structures that have led to new drugs with potent medicinal activities. Development of human immunodeficiency virus (HIV) protease inhibitors and angiotensin-converting enzyme (ACE) inhibitors came from an understanding of the geometry and chemical character of the respective enzyme's active site. Even if the receptor structure is not known in detail, rational approaches based on the physicochemical properties of lead compounds can provide new drugs. For example, the development of cimetidine involved a careful study of the changes in antagonism of H_2-histamine receptors induced by varying the physical properties of structures based on histamine.

As you proceed through the chapters, think of what problem the medicinal chemist is trying to solve. Why were certain structures selected? What modifications were made to produce more focused activity or reduce adverse reactions or produce better pharmaceutical properties? Was the prototypical molecule discovered from random screens, or did the medicinal chemist have a structural concept of the receptor or an understanding of the disease process that must be interrupted?

CHAPTER 2

Drug Design Strategies

JOHN H. BLOCK

CHAPTER OVERVIEW

Modern drug design as compared with the classical approach—*let's make a change on an existing compound or synthesize a new structure and see what happens*—continues to evolve rapidly as an approach to solving a drug design problem. The combination of increasing power and decreasing cost of desktop computing has had a major impact on solving drug design problems. Although drug design increasingly is based on modern computational chemical techniques, it also uses sophisticated knowledge of disease mechanisms and receptor properties. A good understanding of how the drug is transported into the body, distributed throughout the body compartments, metabolically altered by the liver and other organs, and excreted from the patient is required, along with the structural characteristics of the receptor. Acid–base chemistry is used to aid in formulation and biodistribution. Structural attributes and substituent patterns responsible for optimum pharmacological activity can often be predicted by statistical techniques such as regression analysis. Computerized conformational analysis permits the medicinal chemist to predict the drug's three-dimensional (3D) shape that is *seen* by the receptor. With the isolation and structural determination of specific receptors and the availability of computer software that can estimate the 3D shape of the receptor, it is possible to design molecules that will show an optimum fit to the receptor.

DRUG DISTRIBUTION

A drug is a chemical molecule. Following introduction into the body, a drug must pass through many barriers, survive alternate sites of attachment and storage, and avoid significant metabolic destruction before it reaches the site of action, usually a receptor on or in a cell (Fig. 2.1). At the receptor, the following equilibrium (Rx. 2.1) usually holds:

$$\text{Drug} + \text{Receptor} \rightleftharpoons \text{Drug-Receptor Complex} \downarrow \text{Pharmacologic Response} \qquad \text{(Rx. 2.1)}$$

The ideal drug molecule will show favorable binding characteristics to the receptor, and the equilibrium will lie to the right. At the same time, the drug will be expected to dissociate from the receptor and reenter the systemic circulation to be excreted. Major exceptions include the alkylating agents used in cancer chemotherapy (see Chapter 10), a few inhibitors of the enzyme acetylcholinesterase (see Chapter 17), suicide inhibitors of monoamine oxidase (see Chapter 16), and the aromatase inhibitors 4-hydroxyandrostenedione and exemestane (see Chapter 25). These pharmacological agents form covalent bonds with the receptor, usually an enzyme's active site. In these cases, the cell must destroy the receptor or enzyme, or, in the case of the alkylating agents, the cell would be replaced, ideally with a normal cell. In other words, the usual use of drugs in medical treatment calls for the drug's effect to last for a finite period of time. Then, if it is to be repeated, the drug will be administered again. If the patient does not tolerate the drug well, it is even more important that the agent dissociate from the receptor and be excreted from the body.

Oral Administration

An examination of the *obstacle course* (Fig. 2.1) faced by the drug will give a better understanding of what is involved in developing a commercially feasible product. Assume that the drug is administered orally. The drug must go into solution to pass through the gastrointestinal mucosa. Even drugs administered as true solutions may not remain in solution as they enter the acidic stomach and then pass into the alkaline intestinal tract. (This is explained further in the discussion on acid–base chemistry.) The ability of the drug to dissolve is governed by several factors, including its chemical structure, variation in particle size and particle surface area, nature of the crystal form, type of tablet coating, and type of tablet matrix. By varying the dosage form and physical characteristics of the drug, it is possible to have a drug dissolve quickly or slowly, with the latter being the situation for many of the sustained-action products. An example is orally administered sodium phenytoin, with which variation of both the crystal form and tablet adjuvants can significantly alter the bioavailability of this drug widely used in the treatment of epilepsy.

Chemical modification is also used to a limited extent to facilitate a drug reaching its desired target (see Chapter 3). An example is olsalazine, used in the treatment of ulcerative colitis. This drug is a dimer of the pharmacologically active mesalamine (5-aminosalicylic acid). The latter is not effective orally because it is metabolized to inactive forms before reaching the colon. The dimeric form passes

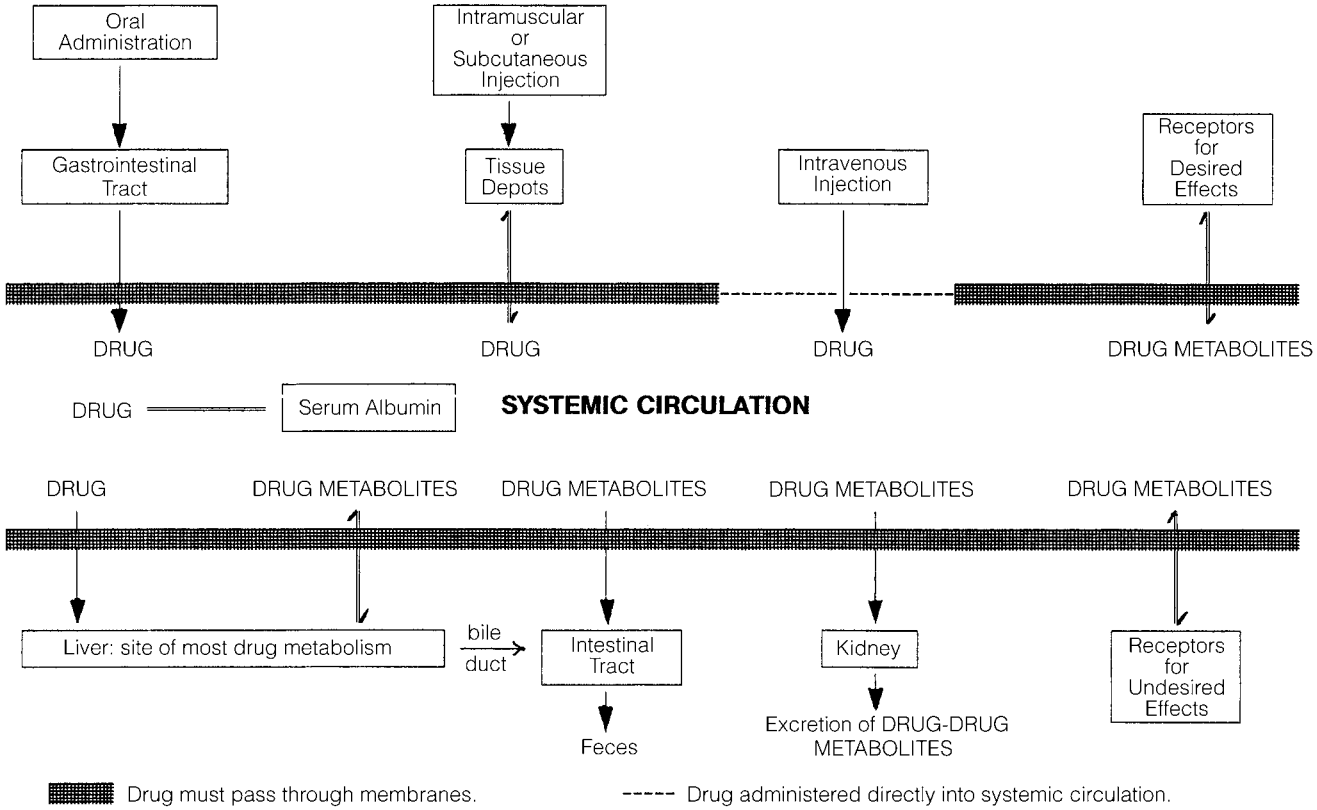
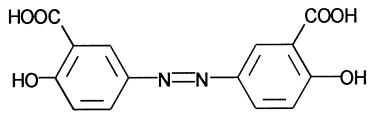
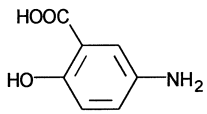


Figure 2.1 • Summary of drug distribution.

through a significant portion of the intestinal tract before being cleaved by the intestinal bacteria to two equivalents of mesalamine.



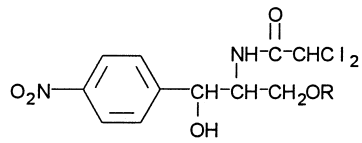
Olsalazine



Mesalamine

As illustrated by olsalazine, any compound passing through the gastrointestinal tract will encounter a large number and variety of digestive and bacterial enzymes, which, in theory, can degrade the drug molecule. In practice, a new drug entity under investigation will likely be dropped from further consideration if it cannot survive in the intestinal tract or its oral bioavailability is low, necessitating parenteral dosage forms only. An exception would be a drug for which there is no effective alternative or which is more effective than existing products and can be administered by an alternate route, including parenteral, buccal, or transdermal.

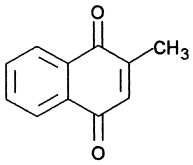
In contrast, these same digestive enzymes can be used to advantage. Chloramphenicol is water soluble enough (2.5 mg/mL) to come in contact with the taste receptors on the tongue, producing an unpalatable bitterness. To mask this intense bitter taste, the palmitic acid moiety is added as an ester of chloramphenicol's primary alcohol. This reduces the parent drug's water solubility (1.05 mg/mL), enough so that it can be formulated as a suspension that passes over the bitter taste receptors on the tongue. Once in the intestinal tract, the ester linkage is hydrolyzed by the digestive esterases to the active antibiotic chloramphenicol and the very common dietary fatty acid palmitic acid.



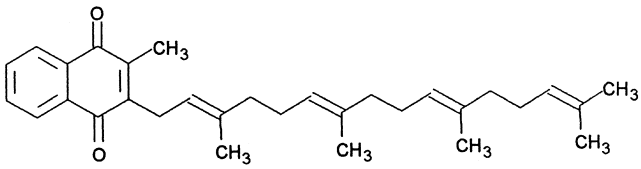
Chloramphenicol: R = H

Chloramphenicol Palmitate: R = $CO(CH_2)_{14}CH_3$

Olsalazine and chloramphenicol palmitate are examples of *prodrugs*. Most prodrugs are compounds that are inactive in their native form but are easily metabolized to the active agent. Olsalazine and chloramphenicol palmitate are examples of prodrugs that are cleaved to smaller compounds, one of which is the active drug. Others are metabolic precursors to the active form. An example of this type of prodrug is menadione, a simple naphthoquinone that is converted in the liver to phytonadione (vitamin $K_{2(20)}$).

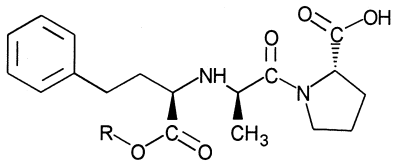


Menadione



Phytonadione (Vitamin $K_{2(20)}$)

Occasionally, the prodrug approach is used to enhance the absorption of a drug that is poorly absorbed from the gastrointestinal tract. Enalapril is the ethyl ester of enalaprilic acid, an active inhibitor of angiotensin-converting enzyme (ACE). The ester prodrug is much more readily absorbed orally than the pharmacologically active carboxylic acid.



Enalapril: R = C_2H_5

Enalaprilic Acid: R = H

Unless the drug is intended to act locally in the gastrointestinal tract, it will have to pass through the gastrointestinal mucosal barrier into venous circulation to reach the site of the receptor. The drug's route involves distribution or partitioning between the aqueous environment of the gastrointestinal tract, the lipid bilayer cell membrane of the mucosal cells, possibly the aqueous interior of the mucosal cells, the lipid bilayer membranes on the venous side of the gastrointestinal tract, and the aqueous environment of venous circulation. Some very lipid-soluble drugs may follow the route of dietary lipids by becoming part of the mixed micelles, incorporating into the chylomicrons in the mucosal cells into the lymph ducts, servicing the intestines, and finally entering venous circulation via the thoracic duct.

The drug's passage through the mucosal cells can be passive or active. As is discussed later in this chapter, the lipid membranes are very complex with a highly ordered structure. Part of this membrane is a series of channels or tunnels that form, disappear, and reform. There are receptors that move compounds into the cell by a process called *pinocytosis*. Drugs that resemble a normal metabolic precursor or intermediate may be actively transported into the cell by the same system that transports the endogenous compound. On the other hand, most drug molecules are too large to enter the cell by an active transport mechanism through the passages. The latter, many times, pass into the patient's circulatory system by passive diffusion.

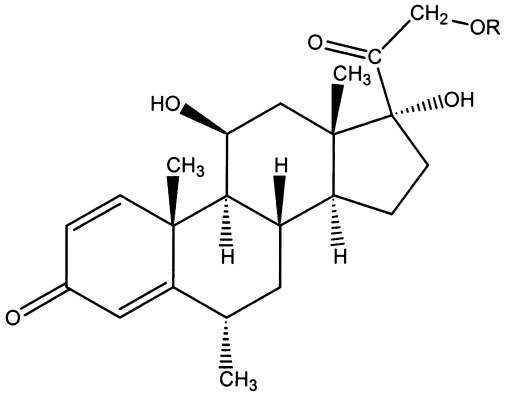
Parenteral Administration

Many times, there will be therapeutic advantages in bypassing the intestinal barrier by using parenteral (injectable) dosage forms. This is common in patients who, because of illness, cannot tolerate or are incapable of accepting drugs orally. Some drugs are so rapidly and completely metabolized to inactive products in the liver (first-pass effect) that oral administration is precluded. But that does not mean that the drug administered by injection is not confronted by obstacles (Fig. 2.1). Intravenous administration places the drug directly into the circulatory system, where it will be rapidly distributed throughout the body, including tissue depots and the liver, where most biotransformations occur (see later in this chapter), in addition to the receptors. Subcutaneous and intramuscular injections slow distribution of the drug, because it must diffuse from the site of injection into systemic circulation.

It is possible to inject the drug directly into specific organs or areas of the body. Intraspinal and intracerebral routes will place the drug directly into the spinal fluid or brain, respectively. This bypasses a specialized epithelial tissue, the blood-brain barrier, which protects the brain from exposure to a large number of metabolites and chemicals. The blood-brain barrier is composed of membranes of tightly joined epithelial cells lining the cerebral capillaries. The net result is that the brain is not exposed to the same variety of compounds that other organs are. Local anesthetics are examples of administration of a drug directly onto the desired nerve. A spinal block is a form of anesthesia performed by injecting a local anesthetic directly into the spinal cord at a specific location to block transmission along specific neurons.

Most of the injections a patient will experience in a lifetime will be subcutaneous or intramuscular. These parenteral routes produce a depot in the tissues (Fig. 2.1), from which the drug must reach the blood or lymph. Once in systemic circulation, the drug will undergo the same distributive phenomena as orally and intravenously administered agents before reaching the target receptor. In general, the same factors that control the drug's passage through the gastrointestinal mucosa will also determine the rate of movement out of the tissue depot.

The prodrug approach described previously can also be used to alter the solubility characteristics, which, in turn, can increase the flexibility in formulating dosage forms. The solubility of methylprednisolone can be altered from essentially water-insoluble methylprednisolone acetate to slightly water-insoluble methylprednisolone to water-soluble methylprednisolone sodium succinate. The water-soluble sodium hemisuccinate salt is used in oral, intravenous, and intramuscular dosage forms. Methylprednisolone itself is normally found in tablets. The acetate ester is found in topical ointments and sterile aqueous suspensions for intramuscular injection. Both the succinate and acetate esters are hydrolyzed to the active methylprednisolone by the patient's own systemic hydrolytic enzymes (esterases).



Methylprednisolone: R = H

Methylprednisolone Acetate: R = $C(=O)CH_3$

Methylprednisolone Sodium Succinate: R = $C(=O)CH_2CH_2COO^-$ Na^+

Another example of how prodrug design can significantly alter biodistribution and biological half-life is illustrated by two drugs based on the retinoic acid structure used systemically to treat psoriasis, a nonmalignant hyperplasia. Etretinate has a 120-day *terminal* half-life after 6 months of therapy. In contrast, the active metabolite, acitretin, has a 33- to 96-hour *terminal* half-life. Both drugs are potentially teratogenic. Women of childbearing age must sign statements that they are aware of the risks and usually are administered a pregnancy test before a prescription is issued. Acitretin, with its shorter half-life, is recommended for a woman who would like to become pregnant, because it can clear her body within a reasonable time frame. When effective, etretinate can keep a patient clear of psoriasis lesions for several months.

Protein Binding

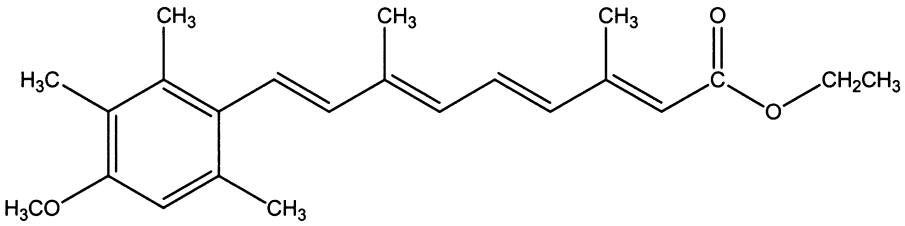
Once the drug enters the systemic circulation (Fig. 2.1), it can undergo several events. It may stay in solution, but many drugs will be bound to the serum proteins, usually albumin (Rx. 2.2). Thus, a new equilibrium must be considered. Depending on the equilibrium constant, the drug can remain in systemic circulation bound to albumin for a considerable period and not be available to the sites of biotransformation, the pharmacological receptors, and excretion.

Drug + Albumin $\rightleftharpoons$ Drug-Albumin Complex (Rx. 2.2)

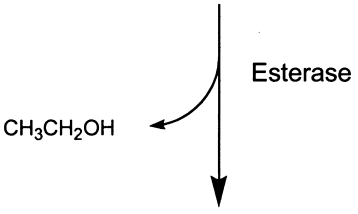
Protein binding can have a profound effect on the drug's effective solubility, biodistribution, half-life in the body, and interaction with other drugs. A drug with such poor water solubility that therapeutic concentrations of the unbound (active) drug normally cannot be maintained still can be a very effective agent. The albumin–drug complex acts as a reservoir by providing large enough concentrations of free drug to cause a pharmacological response at the receptor.

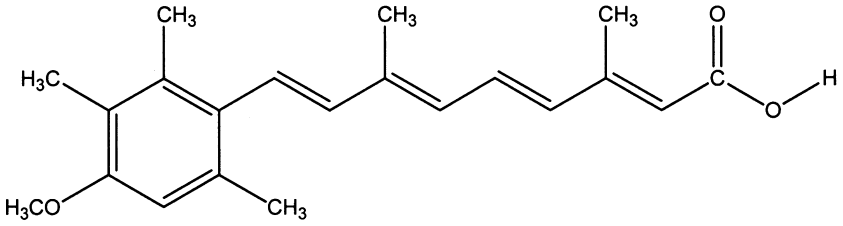
Protein binding may also limit access to certain body compartments. The placenta is able to block passage of proteins from maternal to fetal circulation. Thus, drugs that normally would be expected to cross the placental barrier and possibly harm the fetus are retained in the maternal circulation, bound to the mother's serum proteins.

Protein binding also can prolong the drug's duration of action. The drug–protein complex is too large to pass through the renal glomerular membranes, preventing rapid excretion of the drug. Protein binding limits the amount of drug available for biotransformation (see later in this chapter and Chapter 3) and for interaction with specific receptor sites. For

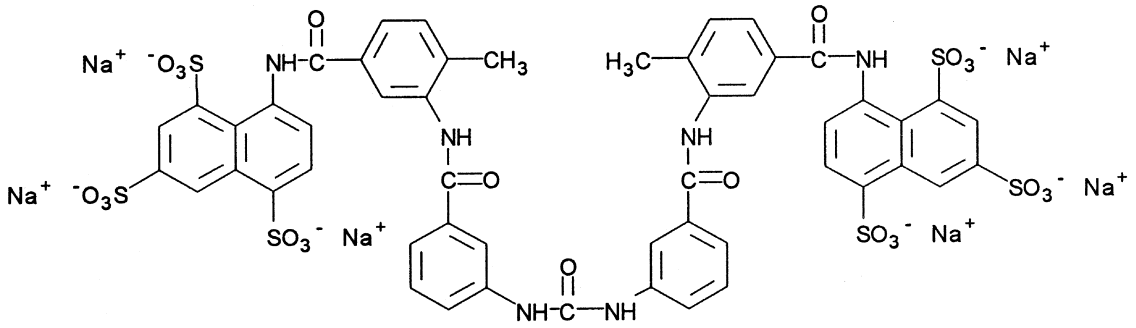


Etretinate





Acitretin



Suramin Sodium

example, the large, polar trypanocide suramin remains in the body in the protein-bound form for as long as 3 months ($t_{1/2}$ = 50 days). The maintenance dose for this drug is based on weekly administration. At first, this might seem to be an advantage to the patient. It can be, but it also means that, should the patient have serious adverse reactions, a significant length of time will be required before the concentration of drug falls below toxic levels.

The drug–protein binding phenomenon can lead to some clinically significant drug–drug interactions that result when one drug displaces another from the binding site on albumin. A large number of drugs can displace the anticoagulant warfarin from its albumin-binding sites. This increases the effective concentration of warfarin at the receptor, leading to an increased prothrombin time (increased time for clot formation) and potential hemorrhage.

Tissue Depots

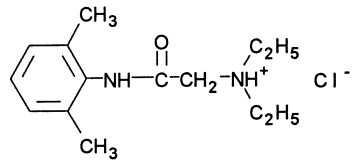
The drug can also be stored in tissue depots. Neutral fat constitutes some 20% to 50% of body weight and constitutes a depot of considerable importance. The more lipophilic the drug, the more likely it will concentrate in these pharmacologically inert depots. The ultra–short-acting, lipophilic barbiturate thiopental's concentration rapidly decreases below its effective concentration following administration. It *disappears* into tissue protein, redistributes into body fat, and then slowly diffuses back out of the tissue depots but in concentrations too low for a pharmacological response. Thus, only the initially administered thiopental is present in high enough concentrations to combine with its receptors. The remaining thiopental diffuses out of the tissue depots into systemic circulation in concentrations too small to be effective (Fig. 2.1), is metabolized in the liver, and is excreted.

In general, structural changes in the barbiturate series (see Chapter 12) that favor partitioning into the lipid tissue stores decrease duration of action but increase central nervous system (CNS) depression. Conversely, the barbiturates with the slowest onset of action and longest duration of action contain the more polar side chains. This latter group of barbiturates both enters and leaves the CNS more slowly than the more lipophilic thiopental.

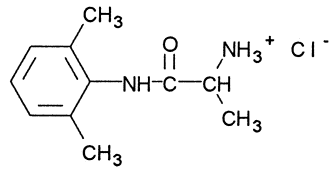
Drug Metabolism

All substances in the circulatory system, including drugs, metabolites, and nutrients, will pass through the liver. Most molecules absorbed from the gastrointestinal tract enter the portal vein and are initially transported to the liver. A significant proportion of a drug will partition or be transported into the hepatocyte, where it may be metabolized by hepatic enzymes to inactive chemicals during the initial trip through the liver, by what is known as the first-pass effect (see Chapter 3).

Lidocaine is a classic example of the significance of the first-pass effect. Over 60% of this local anesthetic antiarrhythmic agent is metabolized during its initial passage through the liver, resulting in it being impractical to administer orally. When used for cardiac arrhythmias, it is administered intravenously. This rapid metabolism of lidocaine is used to advantage when stabilizing a patient with cardiac arrhythmias. Should too much lidocaine be administered intravenously, toxic responses will tend to decrease because of rapid biotransformation to inactive metabolites. An understanding of the metabolic labile site on lidocaine led to the development of the primary amine analog tocainide. In contrast to lidocaine's half-life of less than 2 hours, tocainide's half-life is approximately 15 hours, with 40% of the drug excreted unchanged. The development of orally active antiarrhythmic agents is discussed in more detail in Chapter 19.



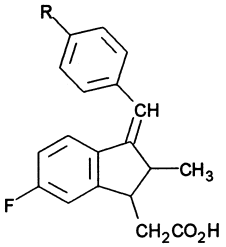
Lidocaine



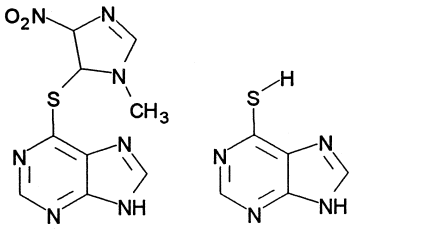
Tocainide

A study of the metabolic fate of a drug is required for all new drug products. Often it is found that the metabolites are also active. Sometimes the metabolite is the pharmacologically active molecule. These drug metabolites can provide leads for additional investigations of potentially new products. Examples of an inactive parent drug that is converted to an active metabolite include the nonsteroidal anti-inflammatory agent sulindac being reduced to the active sulfide metabolite, the immunosuppressant azathioprine being cleaved to the purine antimetabolite 6-mercaptopurine, and purine and pyrimidine antimetabolites and antiviral

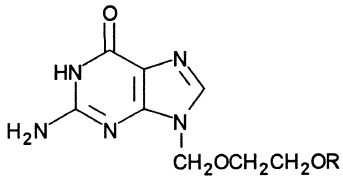
agents being conjugated to their nucleotide form (acyclovir phosphorylated to acyclovir triphosphate). Often both the parent drug and its metabolite are active, which has led to additional commercial products, instead of just one being marketed. About 75% to 80% of phenacetin (now withdrawn from the U.S. market) is converted to acetaminophen. In the tricyclic antidepressant series (see Chapter 12), imipramine and amitriptyline are *N*-demethylated to desipramine and nortriptyline, respectively. All four compounds have been marketed in the United States. Drug metabolism is discussed more fully in Chapter 3.



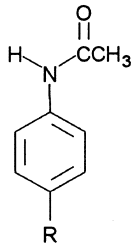
Sulindac: R = $CH_3S(=O)$
Active Sulfide Metabolite: R = CH_3S



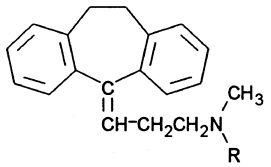
Azathioprine 6-Mercaptopurine



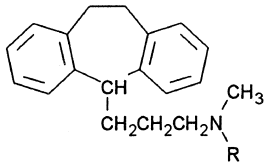
Acyclovir: R = H
Acyclovir triphosphate: R = O-P-O-P-O-P



Phenacetin: R = OC_2H_5
Acetaminophen: R = OH



Amitriptyline: R = CH_3
Nortriptyline: R = H



Imipramine: R = CH_3
Desipramine: R = H

Although a drug's metabolism can be a source of frustration for the medicinal chemist, pharmacist, and physician and lead to inconvenience and compliance problems with the patient, it is fortunate that the body has the ability to metabolize foreign molecules (xenobiotics). Otherwise, many of these substances could remain in the body for years. This has been the complaint against certain lipophilic chemical pollutants, including the once very popular insecticide dichlorodiphenyltrichloroethane (DDT). After entering the body, these chemicals reside in body tissues, slowly diffusing out of the depots and potentially harming the individual on a chronic basis for several years. They can also reside in tissues of commercial food animals that have been slaughtered before the drug has *washed out* of the body.

Excretion

The main route of excretion of a drug and its metabolites is through the kidney. For some drugs, enterohepatic circulation (Fig. 2.1), in which the drug reenters the intestinal tract from the liver through the bile duct, can be an important part of the agent's distribution in the body and route of excretion. Either the drug or drug metabolite can reenter systemic circulation by passing once again through the intestinal mucosa. A portion of either also may be excreted in the feces. Nursing mothers must be concerned, because drugs and their metabolites can be excreted in human milk and be ingested by the nursing infant.

One should keep a sense of perspective when learning about drug metabolism. As explained in Chapter 3, drug metabolism can be conceptualized as occurring in two stages or phases. Intermediate metabolites that are pharmacologically active usually are produced by phase I reactions. The products from the phase I chemistry are converted into inactive, usually water-soluble end products by phase II reactions. The latter, commonly called *conjugation* reactions, can be thought of as synthetic reactions that involve addition of water-soluble substituents. In human drug metabolism, the main conjugation reactions add glucuronic acid, sulfate, or glutathione. Obviously, drugs that are bound to serum protein or show favorable partitioning into tissue depots are going to be metabolized and excreted more slowly for the reasons discussed previously.

This does not mean that drugs that remain in the body for longer periods of time can be administered in lower doses or be taken fewer times per day by the patient. Several variables determine dosing regimens, of which the affinity of the drug for the receptor is crucial. Reexamine Reaction 2.1 and Figure 2.1. If the equilibrium does not favor formation of the drug–receptor complex, higher and usually more frequent doses must be administered. Further, if partitioning into tissue stores or metabolic degradation and/or excretion is favored, it will take more of the drug and usually more frequent administration to maintain therapeutic concentrations at the receptor.

The Receptor

With the possible exception of general anesthetics (see Chapter 22), the working model for a pharmacological response consists of a drug binding to a specific receptor. Many drug receptors are the same as those used by endogenously produced ligands. Cholinergic agents interact with the same receptors as the neurotransmitter acetylcholine.

Synthetic corticosteroids bind to the same receptors as cortisone and hydrocortisone. Often, receptors for the same ligand are found in various tissues throughout the body. The nonsteroidal anti-inflammatory agents (see Chapter 26) inhibit the prostaglandin-forming enzyme cyclooxygenase, which is found in nearly every tissue. This class of drugs has a long list of side effects with many patient complaints. Note in Figure 2.1 that, depending on which receptors contain bound drug, there may be desired or undesired effects. This is because various receptors with similar structural requirements are found in several organs and tissues. Thus, the nonsteroidal anti-inflammatory drugs combine with the desired cyclooxygenase receptors at the site of the inflammation and the undesired cyclooxygenase receptors in the gastrointestinal mucosa, causing severe discomfort and sometimes ulceration. One of the *second-generation* antihistamines, fexofenadine, is claimed to cause less sedation because it does not readily penetrate the blood-brain barrier. The rationale is that less of this antihistamine is available for the receptors in the CNS, which are responsible for the sedation response characteristic of antihistamines. In contrast, some antihistamines are used for their CNS depressant activity because a significant proportion of the administered dose is crossing the blood-brain barrier relative to binding to the histamine H_1 receptors in the periphery.

Although it is normal to think of side effects as undesirable, they sometimes can be beneficial and lead to new products. The successful development of oral hypoglycemic agents used in the treatment of diabetes began when it was found that certain sulfonamides had a hypoglycemic effect. Nevertheless, a real problem in drug therapy is patient compliance in taking the drug as directed. Drugs that cause serious problems and discomfort tend to be avoided by patients.

At this point, let us assume that the drug has entered the systemic circulation (Fig. 2.1), passed through the lipid barriers, and is now going to make contact with the receptor. As illustrated in Reaction 2.1, this is an equilibrium process. A good ability to fit the receptor favors binding and the desired pharmacological response. In contrast, a poor fit favors the reverse reaction. With only a small amount of drug bound to the receptor, there will be a much smaller pharmacological effect. If the amount of drug bound to the receptor is too small, there may be no discernible response. Many variables contribute to a drug's binding to the receptor. These include the structural class, the 3D shape of the molecule, and the types of chemical bonding involved in the binding of the drug to the receptor.

Most drugs that belong to the same pharmacological class have certain structural features in common. The barbiturates act on specific CNS receptors, causing depressant effects; hydantoins act on CNS receptors, producing an anticonvulsant response; benzodiazepines combine with the γ-aminobutyric acid (GABA) receptors, with resulting anxiolytic activity; steroids can be divided into such classes as corticosteroids, anabolic steroids, progestogens, and estrogens, each acting on specific receptors; nonsteroidal anti-inflammatory agents inhibit enzymes required for the prostaglandin cascade; penicillins and cephalosporins inhibit enzymes required to construct the bacterial cell wall; and tetracyclines act on bacterial ribosomes.

With the isolation and characterization of receptors becoming a common occurrence, it is hard to realize that the concept of receptors began as a postulate. It had been realized early that molecules with certain structural features would elucidate a specific biological response. Very slight changes in structure could cause significant changes in biological activity. These structural variations could increase or decrease activity or change an agonist into an antagonist. This early and fundamentally correct interpretation called for the drug (ligand) to fit onto some surface (the receptor) that had fairly strict structural requirements for proper binding of the drug. The initial receptor model was based on a rigid lock-and-key concept, with the drug (key) fitting into a receptor (lock). It has been used to explain why certain structural attributes produce a predictable pharmacological action. This model still is useful, although one must realize that both the drug and the receptor can have considerable flexibility. Molecular graphics, using programs that calculate the preferred conformations of drug and receptor, show that the receptor can undergo an adjustment in 3D structure when the drug makes contact. Using space-age language, the drug *docks* with the receptor.

More complex receptors now are being isolated, characterized, and cloned. The first receptors to be isolated and characterized were the reactive and regulatory sites on enzymes. Acetylcholinesterase, dihydrofolate reductase, angiotensin, and human immunodeficiency virus (HIV) protease-converting enzyme are examples of enzymes whose active sites (the receptors) have been modeled. Most drug receptors probably are receptors for natural ligands used to regulate cellular biochemistry and function and to communicate between cells. Receptors include a relatively small region of a macromolecule, which may be an isolatable enzyme, a structural and functional component of a cell membrane, or a specific intracellular substance such as a protein or nucleic acid. Specific regions of these macromolecules are visualized as being oriented in space in a manner that permits their functional groups to interact with the complementary functional groups of the drug. This interaction initiates changes in structure and function of the macromolecule, which lead ultimately to the observable biological response. The concept of spatially oriented functional areas forming a receptor leads directly to specific structural requirements for functional groups of a drug, which must complement the receptor.

It now is possible to isolate membrane-bound receptors, although it still is difficult to elucidate their structural chemistry, because once separated from the cell membranes, these receptors may lose their native shape. This is because the membrane is required to hold the receptor in its correct tertiary structure. One method of receptor isolation is affinity chromatography. In this technique, a ligand, often an altered drug molecule known to combine with the receptor, is attached to a chromatographic support phase. A solution containing the desired receptor is passed over this column. The receptor will combine with the ligand. It is common to add a chemically reactive grouping to the drug, resulting in the receptor and drug covalently binding with each other. The drug–receptor complex is washed from the column and then characterized further.

A more recent technique uses recombinant DNA. The gene for the receptor is located and cloned. It is transferred into a bacterium, yeast, or animal, which then produces the receptor in large enough quantities to permit further study. Sometimes it is possible to determine the DNA sequence of the cloned gene. By using the genetic code for amino acids, the amino acid sequence of the protein component of the receptor can be determined, and the receptor then modeled,

producing an estimated 3D shape. The model for the receptor becomes the template for designing new ligands. Genome mapping has greatly increased the information on receptors. Besides the human genome, the genetic composition of viruses, bacteria, fungi, and parasites has increased the possible sites for drugs to act. The new field of proteomics studies the proteins produced by structural genes.

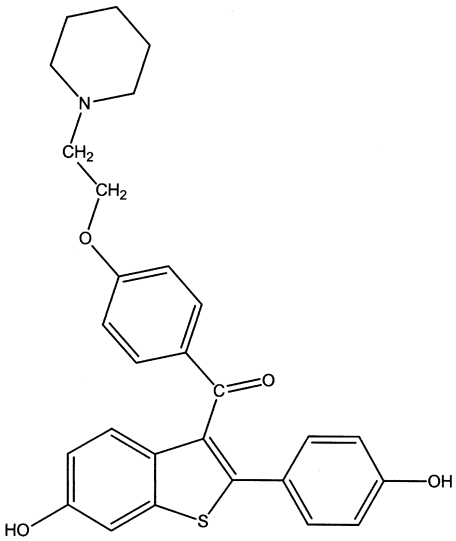
The earlier discussion in this chapter emphasizes that the cell membrane is a highly organized, dynamic structure that interacts with small molecules in specific ways; its focus is on the lipid bilayer component of this complex structure. The receptor components of the membranes appear to be mainly protein. They constitute a highly organized, intertwined region of the cell membrane. The same type of molecular specificity seen in such proteins as enzymes and antibodies is also a property of drug receptors. The nature of the amide link in proteins provides a unique opportunity for the formation of multiple internal hydrogen bonds, as well as internal formation of hydrophobic, van der Waals, and ionic bonds by side chain groups, leading to such organized structures as the α-helix, which contains about four amino acid residues for each turn of the helix. An organized protein structure would hold the amino acid side chains at relatively fixed positions in space and available for specific interactions with a small molecule.

Proteins can potentially adopt many different conformations in space without breaking their covalent amide linkages. They may shift from highly coiled structures to partially disorganized structures, with parts of the molecule existing in *random chain* or *folded sheet* structures, contingent on the environment. In the monolayer of a cell membrane, the interaction of a small foreign molecule with an organized protein may lead to a significant change in the structural and physical properties of the membrane. Such changes could well be the initiating events in the tissue or organ response to a drug, such as the ion-translocation effects produced by interaction of acetylcholine and the cholinergic receptor.

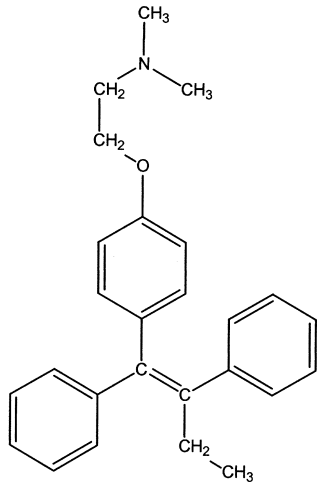
The large body of information now available on relationships between chemical structure and biological activity strongly supports the concept of flexible receptors. The fit of drugs onto or into macromolecules is rarely an all-or-none process as pictured by the earlier lock-and-key concept of a receptor. Rather, the binding or partial insertion of groups of moderate size onto or into a macromolecular pouch appears to be a continuous process, at least over a limited range, as indicated by the frequently occurring regular increase and decrease in biological activity as one ascends a homologous series of drugs. A range of productive associations between drug and receptor may be pictured, which leads to agonist responses, such as those produced by cholinergic and adrenergic drugs. Similarly, strong associations may lead to unproductive changes in the configuration of the macromolecule, leading to an antagonistic or blocking response, such as that produced by anticholinergic agents and HIV protease inhibitors. Although the fundamental structural unit of the drug receptor is generally considered to be protein, it may be supplemented by its associations with other units, such as mucopolysaccharides and nucleic acids.

Humans (and mammals in general) are very complex organisms that have developed specialized organ systems. It is not surprising that receptors are not distributed equally throughout the body. It now is realized that, depending on the organ in which it is located, the same receptor class may behave differently. This can be advantageous by focusing drug therapy on a specific organ system, but it can also cause adverse drug responses because the drug is exerting two different responses based on the location of the receptors. An example is the selective estrogen receptor modulators (SERMs). They cannot be classified simply as agonists or antagonists. Rather, they can be considered variable agonists and antagonists. Their selectivity is very complex because it depends on the organ in which the receptor is located.

This complexity can be illustrated with tamoxifen and raloxifene (Fig. 2.2). Tamoxifen is used for estrogen-sensitive breast cancer and for reducing bone loss from osteoporosis. Unfortunately, prolonged treatment increases the risk of endometrial cancer because of the response from the uterine estrogen receptors. Thus, tamoxifen is an estrogen antagonist in the mammary gland and an agonist in the uterus and bone. In contrast, raloxifene does not appear to have much agonist property in the uterus but, like tamoxifen, is an antagonist in the breast and agonist in the bone.



Raloxifene



Tamoxifen

Figure 2.2 ● Selective SERMs.

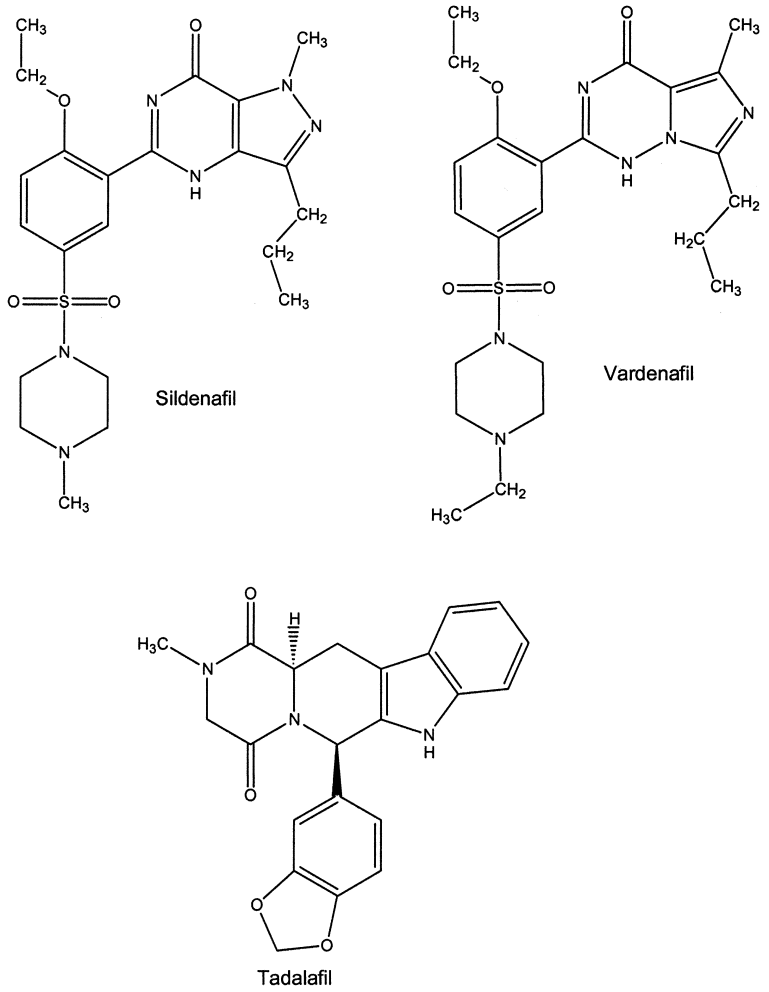


Figure 2.3 ● Examples of phosphodiesterase type 5 inhibitors.

There are a wide variety of phosphodiesterases throughout the body. These enzymes hydrolyze the cyclic phosphate esters of adenosine monophosphate (cAMP) and guanosine monophosphate (cGMP). Although the substrates for this family of enzymes are cAMP and cGMP, there are differences in the active sites. Figure 2.3 illustrates three drugs used to treat erectile dysfunction (sildenafil, tadalafil, and vardenafil). These three take advantage of the differences in active site structural requirements between phosphodiesterase type 5 and the other phosphodiesterases. They have an important role in maintaining a desired lifestyle: treatment of erectile dysfunction caused by various medical conditions. The drugs approved for this indication were discovered by accident. The goal was to develop a newer treatment of angina. The approach was to develop phosphodiesterase inhibitors that would prolong the activity of cGMP. The end result was drugs that were not effective inhibitors of the phosphodiesterase that would treat angina, but were effective inhibitors of the one found in the corpus cavernosum. The vasodilation in this organ results in penile erection.

Summary

One of the goals is to design drugs that will interact with receptors at specific tissues. There are several ways to do this, including (a) altering the molecule, which, in turn, can change the biodistribution; (b) searching for structures that show increased specificity for the target receptor that will produce the desired pharmacological response while decreasing the affinity for undesired receptors that produce adverse responses; and (c) the still experimental approach of attaching the drug to a monoclonal antibody (see Chapter 5) that will bind to a specific tissue antigenic for the antibody. Biodistribution can be altered by changing the drug's solubility, enhancing its ability to resist being metabolized (usually in the liver), altering the formulation or physical characteristics of the drug, and changing the route of administration. If a drug molecule can be designed so that its binding to the desired receptor is enhanced relative to the undesired receptor and biodistribution remains favorable, smaller doses of the drug can be administered. This, in turn, reduces the amount of drug available for binding to those receptors responsible for its adverse effects.

The medicinal chemist is confronted with several challenges in designing a bioactive molecule. A good fit to a specific receptor is desirable, but the drug would normally be expected to dissociate from the receptor eventually. The specificity for the receptor would minimize side effects. The drug would be expected to clear the body within a reasonable time. Its rate of metabolic degradation should allow reasonable dosing schedules and, ideally, oral administration. Many times, the drug chosen for commercial sales has been selected from hundreds of compounds that have been screened. It usually is a compromise product that meets a medical need while demonstrating good patient acceptance.