Foye's Principles of Medicinal Chemistry

FIFTH EDITION

Foye's Principles of Medicinal Chemistry

Fifth Edition

David A. Williams, Ph.D.
Professor of Chemistry
Massachusetts College of Pharmacy and Health Sciences
Boston, Massachusetts

Thomas L. Lemke, Ph.D.
Associate Dean for Professional Programs and
Professor of Medicinal Chemistry
College of Pharmacy
University of Houston
Houston, Texas

LIPPINCOTT WILLIAMS & WILKINS
A **Wolters Kluwer** Company
Philadelphia • Baltimore • New York • London
Buenos Aires • Hong Kong • Sydney • Tokyo

Editor: David Troy
Managing Editor: Matt Hauber
Marketing Manager: Anne Smith
Production Editor: Christina Remsberg
Designer: Armen Kojoyian
Compositor: Graphic World
Printer: Quebecor World-Dubuque

351 West Camden Street
Baltimore, MD 21201

530 Walnut Street
Philadelphia, PA 19106

Printed in the United States of America

First Edition, 1974

Library of Congress Cataloging-in-Publication Data
Williams, David A., 1938-
Foye's principles of medicinal chemistry/David A. Williams, Thomas L. Lemke.—5th ed.
p. cm.
Includes index.
ISBN 0-683-30737-1
1. Pharmaceutical chemistry. I. Title: Principles of medicinal chemistry. II. Lemke, Thomas L. III. Title.

RS403 .P75 2002
616.07'56–dc21 2001050327

To purchase additional copies of this book, call our customer service department at **(800)638-3030** or fax orders to **(301)824-7390**. International customers should call **(301)714-2324**.

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.

03 04 05
3 4 5 6 7 8 9 10

2. Drug Design and Relationship of Functional Groups to Pharmacologic Activity

JAMES KNITTEL AND ROBIN ZAVOD

Medicinal chemistry is the discipline concerned with determining the influence of chemical structure on biological activity. As such, it is therefore necessary for the medicinal chemist to understand not only the mechanism by which a drug exerts its effect, but also the physicochemical properties of the molecule. The term "physicochemical properties" refers to the influence of the organic functional groups present within a molecule on its acid/base properties, water solubility, partition coefficient, crystal structure, stereochemistry etc. All of these properties influence the absorption, distribution, metabolism and excretion (ADME) of the molecule. In order to design better medicinal agents the medicinal chemist needs to understand the relative contributions that each functional group makes to the overall physical chemical properties of the molecule. Studies of this type involve modification of the molecule in a systematic fashion and determination of how these changes affect biological activity. Such studies are referred to as studies of structure-activity relationships i.e., what structural features of the molecule contribute to, or take away from, the desired biological activity of the molecule of interest.

Because of the fundamental nature of its subject matter, this chapter includes numerous case studies throughout (as boxes) and at the end. In addition, a list of study questions at the end of—and unique to—this chapter provides further self-study material on the subject of drug design.

INTRODUCTION

Chemical compounds, usually derived from plants, have been used by humans for thousands of years to alleviate pain, diarrhea, infection and various other maladies. Until the 19th century these "remedies" were primarily crude preparations of plant material whose constituents were unknown and the nature of the active principal (if any) was also unknown. The revolution in synthetic organic chemistry during the 19th century produced a concerted effort toward identification of the structures of the active constituents of these naturally derived medicinals and synthesis of what were hoped to be more efficacious agents. By determining the molecular structures of the active components of these complex mixtures it was thought that a better understanding of how these components worked could be elucidated.

Relationship Between Molecular Structure and Biologic Activity

Early studies of the relationship between chemical structure and biologic activity were conducted by Crum-Brown and Fraser (1) in 1869. They showed that many compounds containing tertiary amine groups became muscle relaxants when converted to quaternary ammonium compounds. Compounds with widely differing pharmacological properties such as, strychnine (a convulsant), morphine (an analgesic), nicotine (deterrent, insecticide), and atropine (anticholinergic), all could be converted to muscle relaxants with properties similar to tubocurarine when methylated (Fig. 2.1). Crum-Brown and Fraser therefore concluded that muscle relaxant activity required a quaternary ammonium group within the chemical structure. This initial hypothesis was later disproven by the discovery of the natural neurotransmitter and activator of muscle contraction, acetylcholine (Fig. 2.2). Even though Crum-Brown and Fraser's initial hypothesis concerning chemical structure and muscle relaxation was proven to be incorrect, it demonstrated the concept that molecular structure does influence the biological activity of chemical compounds.

With the discovery by Crum-Brown and Fraser that quaternary ammonium groups could produce compounds with muscle relaxant properties scientists began looking

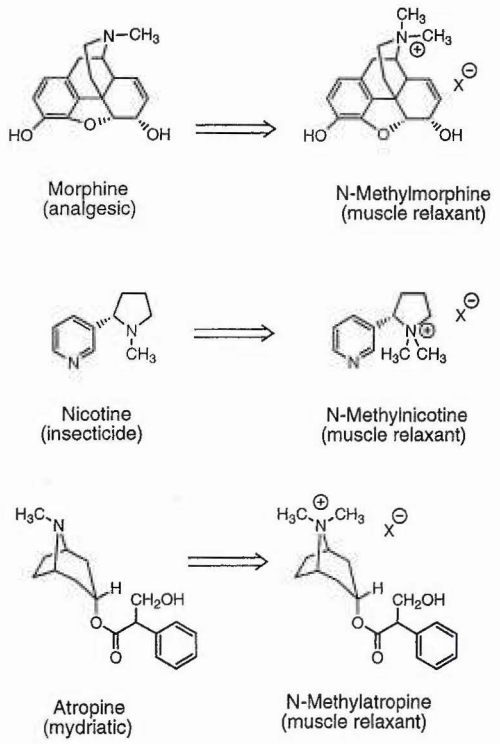


Fig. 2.1. Effects of methylation on biologic activity.

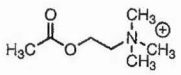


Fig. 2.2. Acetylcholine, a neurotransmitter and muscle relaxant.

for other organic functional groups that would produce specific biologic responses. The thinking at this period of time was that specific chemical groups, or nuclei (rings), were responsible for specific biologic effects. This lead to the postulate, which took some time to disprove, that "one chemical group gives one biological action." (2) Even after the discovery of acetylcholine by Loewi and Navrati (3) which effectively dispensed with Crum-Brown and Fraser's concept of all quaternary ammonium compounds being muscle relaxants, this was still considered dogma and took a long time to replace.

Selectivity of Drug Action and Drug Receptors

Though the structures of many drugs or xenobiotics were known at the turn of the century, or at least the composition of functional groups, it was still a mystery as to how these compounds exerted their effects. Utilizing his observations regarding the staining behavior of microorganisms, Ehrlich developed the concept of drug receptors (4). He postulated that certain "side chains" on the surfaces of cells were "complementary" to the dyes (or drug), thereby allowing the two substances to combine. In the case of antimicrobial compounds, this combining of the chemical to the "side chains" produced a toxic effect. This concept effectively was the first description of what later became know as the receptor hypothesis for explaining the biological action of chemical compounds. Ehrlich also discussed selectivity of drug action via the concept of a "magic bullet" for compounds that would eradicate disease states without producing undue harm to the organism being treated (i.e., the patient). This concept was later modified by Albert (5) and is generally referred to as "selective toxicity." Utilizing this concept Ehrlich developed organic arsenicals that were toxic to trypanosomes as a result of their irreversible reaction with mercapto groups present on vital proteins within the organism. The formation of As-S bonds resulted in death to the target organism. However, it was soon learned that these compounds were not only toxic to the target organism, but also to the host once certain blood levels of arsenic were achieved.

The "paradox" that resulted after the discovery of acetylcholine of how one chemical group can produce two different biologic effects, i.e., muscle relaxation and muscle contraction, was explained by Ing (6) using the actions of acetylcholine and tubocurarine as his examples. Ing hypothesized that both acetylcholine and tubocurarine act at the same receptor but that one molecule fits to the receptor in a more complementary manner and "activates" it, causing muscle contraction. Just how this activation occurs was not elaborated upon. The larger molecule, tubocurarine, simple occupies part of the receptor and prevents acetylcholine, the smaller molecule, from occupying the receptor. With both molecules the quaternary ammonium functional group is a common structural feature and interacts with the same region of the receptor. If one closely examines the structures of other compounds that have opposing effects on the same pharmacologic system, this appears to be a common theme: Molecules that block the effects of natural neurotransmitters (antagonists) are generally larger in size than the native compound. Both compounds share common structural features, however, thus providing support to the concept that the structure of a molecule, its composition and arrangement of chemical functional groups, determines the type of pharmacologic effect that it possesses (i.e., structure-activity relationship). Thus, compounds that are muscle relaxants acting via the cholinergic nervous system will possess a quaternary ammonium or protonated tertiary ammonium group and will be larger than acetylcholine. Structure-activity relationships (SARs) are the underlying principle of medicinal chemistry. Similar molecules exert similar biological actions in a qualitative sense. A corollary to this is that structural elements (functional groups) within a molecule most often contribute in an additive manner to the physicochemical properties of a molecule and therefore its biological action. One need only peruse the structures of drug molecules in a particular pharmacologic class to become convinced of this (e.g., histamine H_1 antagonists; histamine H_2 antagonists; β-adrenergic antagonists; etc.). The objective of the medicinal chemist in his/her quest for better medicinal agents (drugs) is to discover what functional groups within a specific structure are important for its pharmacologic activity, and how can these groups be modified to produce more potent, selective and safer compounds.

An example of how different functional groups can yield compounds with similar physicochemical properties is shown with sulfanilamide antibiotics. In Figure 2.3 the structures of sulfanilamide and p-aminobenzoic acid (PABA) are shown. In 1940, Woods (7) demonstrated that PABA was capable of reversing the antibacterial action of sulfanilamide (and other sulfonamides antibacterials) and that both PABA and sulfanilamide had similar steric and electronic properties. Both compounds contain acidic func-

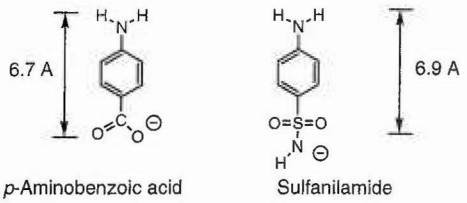


Fig. 2.3. Ionized forms of PABA and sulfanilamide. Comparison of distance between amine and ionized acids of each compound. Note how closely sulfanilamide resembles PABA.

tional groups with PABA containing an aromatic carboxylic acid and sulfanilamide an aromatic sulfonamide. When ionized at physiological pH both compounds have a similar electronic configuration and the distance between the ionized acid and the weakly basic amino group is also very similar. It should therefore be no surprise that sulfanilamide acts as an antagonist to PABA metabolism in bacteria.

PHYSICOCHEMICAL PROPERTIES OF DRUGS

Acid/Base Properties

The human body is composed of 70–75% water, which amounts to approximately 55 liters of water for a 160 lb (55 kg) individual. For an average drug molecule with a molecular weight of 200 g/mol and a dose of 20 mg this leads to a concentration of $\sim 2 \times 10^{-6}$ M solution. When considering the solution behavior of a drug within the body we are therefore dealing with a dilute solution. For dilute solutions the Brönsted-Lowry (8) acid/base theory is most appropriate for explaining and predicting acid/base behavior. This is a very important concept in medicinal chemistry since the acid/base properties of drug molecules directly affect absorption, excretion and compatibility with other drugs in solution. According to the Brönsted-Lowry Theory an acid is any substance capable of yielding a proton (H^+) and a base is any substance capable of accepting a proton. When an acid gives up a proton to a base it is converted to its *conjugate base.* Similarly, when a base accepts a proton it is converted to its *conjugate acid* form (Equations 2.1 and 2.2).

Eq. 2.1 $CH_3COOH + H_2O \rightleftharpoons CH_3COO^{\ominus} + H_3O^{\oplus}$

Acid	Base	Conjugate base	Conjugate acid
(acetic acid)	(water)	(acetate)	(hydronium)

Eq. 2.2 $CH_3NH_2 + H_2O \rightleftharpoons CH_3NH_3^{\oplus} + {}^{\ominus}OH$

Base	Acid	Conjugate Acid	Conjugate base
(methylamine)	(water)	(methylammonium)	(hydroxide)

Note that when an acid loses its proton it is left with an extra pair of electrons that are no longer neutralized by the proton. This is the *ionized* form of the acid and is now very water soluble due to the charge. Since the acid has lost its proton it is often also referred to as having undergone dissociation. There are many different organic functional groups that behave as acids and these are listed in Table 2.1. It is important that the student learn to recognize these functional groups and their relative acid strengths. This will help the student to predict absorption, distribution, excretion and potential incompatibilities between drugs.

When a base is converted to its conjugate acid form it too becomes ionized. However, in this instance it becomes positively charged due to the presence of the extra proton. Most basic drugs are usually derived from primary, secondary and tertiary amines. Other organic functional groups that act as bases are shown in Table 2.2. Again the student should familiarize himself with these functional groups and be able to readily recognize them by name and relative strengths.

Organic functional groups that are neither capable of giving up a proton, nor accepting a proton are considered to be neutral (or nonelectrolytes) with respect to their acid/base properties. Common functional groups of this type are shown in Table 2.3. In the case of quaternary ammonium compounds the molecule is not electrically neutral even though it is neither acidic nor basic. Additional reading on the acid/base behavior of the functional groups listed in Tables 2.1–2.3 can be found in Remington (9) and Lemke (10).

A molecule may contain multiple functional groups and therefore possess both acid and base properties. For example, ciprofloxacin (Fig. 2.4) a quinolone antibiotic, contains a secondary alkyl amine and a carboxylic acid. Depending upon the pH of the solution (or tissue) this molecule will either accept a proton, yield a proton or both. Thus it can be a base, acid or amphoteric (both acid and base) in its properties. Figure 2.5 shows the acid/base behavior of ciprofloxacin at two different locations of the gastro-intestinal tract. Note that at a given pH value (e.g., pH of 1.0–3.5) only one of the functional groups (the alkylamine) is ionized. In order to be able to make this prediction one has to understand the relative acid/base strength of acids and bases. Thus, one needs to be able to know which acid or base within a molecule containing multiple functional groups is the strongest and which is the weakest. The concept of pK_a not only indicates the relative acid/base strength of organic functional groups, but it also allows one to calculate, for a given pH, exactly how much of the molecule is in the ionized and unionized form.

Relative Acid Strength (pK_a)

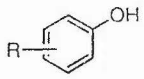
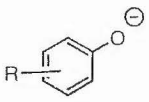
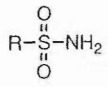
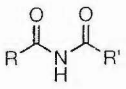
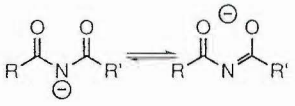
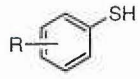
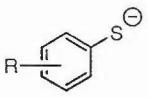
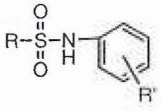
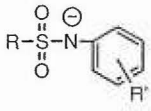
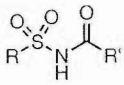
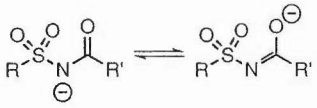
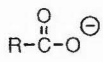
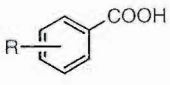
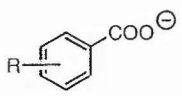
Strong acids and bases completely dissociate or accept a proton in aqueous solution to produce their respective conjugate bases and acids. For example, mineral acids such as HCl or bases such as NaOH undergo complete dissociation in water with the equilibrium shifted completely to the right side as shown in equations 2.3 and 2.4:

Eq. 2.3 $HCl + H_2O \longrightarrow Cl^{\ominus} + H_3O^{\oplus}$

Eq. 2.4 $NaOH + H_2O \longrightarrow Na^{\oplus} + OH^{\ominus} + H_2O$

However, acids and bases of intermediate or weak strength incompletely dissociate or accept a proton and the equilibrium lies somewhere in between. The equilibrium is such that all possible species may exist. Note that in equations 2.3 and 2.4 water is acting as a base in one instance and as an acid in the other. Water is amphoteric, it may act as an acid or a base depending upon the conditions. Because we are always dealing with a dilute aqueous solution the strongest base that can be present is OH^- and the strongest acid H_3O^+. This is known as the leveling ef-

Table 2.1. Common Acidic Organic Functional Groups and Their Ionized (Conjugate Base) Forms

Acids	pKa			Conjugate Base
Phenol	9–11			Phenolate
Sulfonamide	9–10			Sulfonamidate
Imide	9–10			Imidate
Alkylthiol	10–11			Thiolate
Thiophenol	9–10			Thiophenolate
N-Arylsulfonamide	6–7			N-Arylsulfonamidate
Sulfonimide	5–6			Sulfonimidate
Alkylcarboxylic acid	5–6			Alkylcarboxylate
Arylcarboxylic acid	4–5			Arylcarboxylate
Sulfonic acid	0–1			Sulfonate

Acid strength usually increases as one moves down the table.

Table 2.2. Common Basic Organic Functional Groups and Their Ionized (Conjugate Acid) Forms

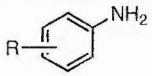
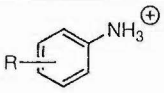
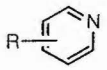
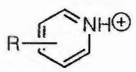
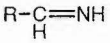
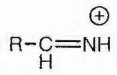
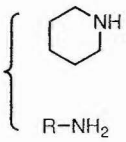
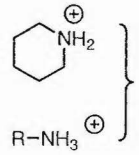
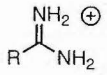
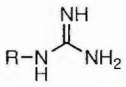
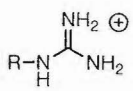
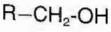
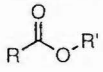
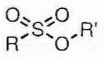
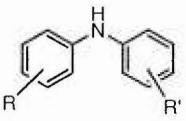
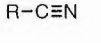
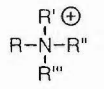
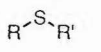
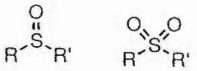
Base	pKa			Conjugate Acid
Arylamine	4–5			Arylammonium
Aromatic amine	5–6			Aromatic ammonium
Imine	3–4			Iminium
Alkylamines	10–11 9–10			Alkylammonium
Amidine	10–11			Amidinium
Guanidine	10–11			Guanidinium

Table 2.3. Common Organic Functional Groups That Are Considered Neutral Under Physiologic Conditions

			
Alkyl alcohol	Ether	Ester	Sulfonic acid ester
			
Amide	Diarylamine	Nitrile	Quaternary ammonium
			
Amine oxide	Ketone & Aldehyde	Thioether	Sulfoxide Sulfone

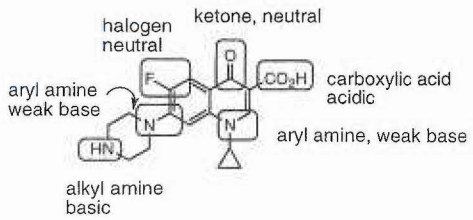


Fig. 2.4. Chemical structure of ciprofloxacin showing the various organic functional groups.

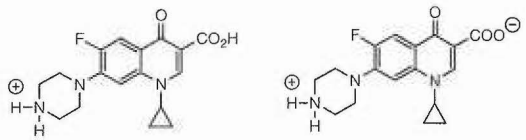


Fig. 2.5. Predominate forms of ciprofloxacin at two different locations within the gastrointestinal tract.

fect of water. Thus, some organic functional groups that are considered acids or bases with respect to their chemical reactivity do not behave as such under physiological conditions in aqueous solution. For example, alkyl alcohols such as ethyl alcohol, are not sufficiently acidic to undergo ionization to a significant extent in aqueous solution. Water is not sufficiently basic to remove the proton from the alcohol to form the ethoxide ion (Equation 2.5).

Eq. 2.5 $CH_3CH_2OH + H_2O \rightleftharpoons CH_3CH_2O^{\ominus} + H_3O^{\oplus}$

Predicting the Degree of Ionization of a Molecule

From general principles it is possible to predict if a molecule is going to be ionized or unionized at a given pH simply by knowing if the functional groups present on the molecule are acid or basic. However, in order to be able to quantitatively predict the degree of ionization of a molecule one must know the pK_a values of the acid and basic functional groups present and the pH of the environment to which the compound will be exposed. The Henderson-Hassalbach equation (Equation 2.6) can be used to calculate the percent ionization of a compound at a given pH. This equation was used to calculate the major forms of ciprofloxacin in Figure 2.5.

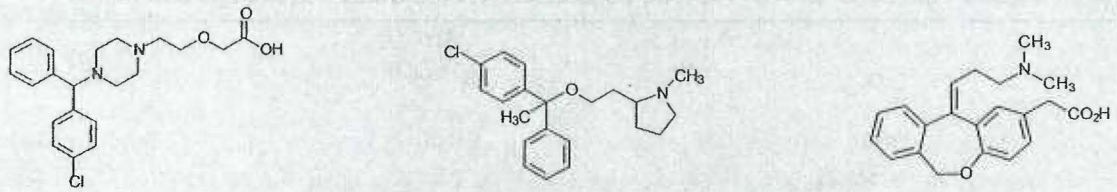
Eq. 2.6 $$pK_a = pH + \log \frac{[\text{acid form}]}{[\text{base form}]}$$

The key to understanding the use of the Henderson-Hassalbach equation for calculating percent ionization is to realize that this equation relates a constant, pK_a, to the ratio of acid form to base form of the drug. Since pK_a is a constant for any given molecule, then the ratio of acid to base will determine the pH of the solution. Conversely, a given pH determines the ratio of acid to base. A sample calculation is shown in Figure 2.6 for the sedative hypnotic amobarbital.

When dealing with a base, the student must recognize that the conjugate acid form is the ionized form of the drug. Thus, as one should expect, a base behaves in a manner opposite to that of an acid. Figure 2.7 shows the calculated percent ionization for the decongestant

Absorption/Acid-Base Case

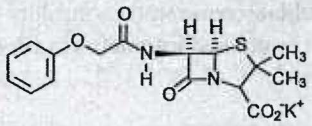
A long distance truck driver comes into the pharmacy complaining of seasonal allergies. He asks you to recommend an agent that will act as an antihistamine, but will not cause drowsiness. He regularly takes TUMs for indigestion because of the bad food that he eats while he is on the road.



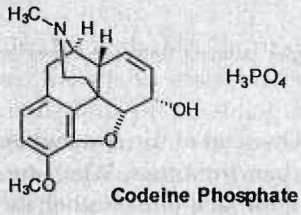
1. Identify the functional groups present in Zyrtec and Tavist and evaluate the effect of each functional group on the ability of the drug to cross lipophilic membranes (e.g., blood brain barrier). Based on your assessment of each agent's ability to cross the blood brain barrier (and therefore potentially cause drowsiness), provide a rationale for whether the truck driver should be taking Zyrtec, or Tavist.
2. Patanol is sold as an aqueous solution of the hydrochloride salt. Modify the structure above to show the appropriate salt form of this agent. This agent is applied to the eye to relieve itching associated with allergies. Describe why this agent is soluble in water and what properties make it able to be absorbed into the membranes that surround the eye.
3. Consider the structural features of Zyrtec and Tavist. In which compartment will each of these two drugs be best absorbed? (stomach, pH = 1 or intestine, pH = 7.5).
4. TUMs neutralizes stomach acid (pH of stomach = 3.5). Based on your answer to question #3, determine whether the truck driver will get the full antihistaminergic effect if he takes his antihistamine at the same time as he takes his TUMs. Provide a rationale for your answer.

Acid Base Chemistry/Compatibility Cases

The IV technician in the hospital pharmacy gets an order for a patient that includes the two drugs drawn below. She is unsure if she can mix the two drugs together in the same IV bag and isn't sure how water-soluble either of the agents are.

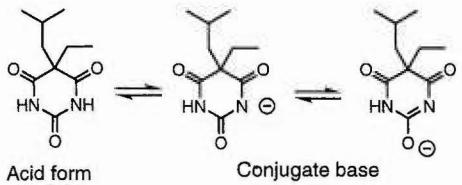


Penicillin V Potassium



Codeine Phosphate

1. Penicillin V potassium is drawn in its salt form, whereas codeine phosphate is not. Modify the structure above to show the salt form of codeine phosphate. Determine the acid/base character of the functional groups in the two molecules drawn above, as well as the salt form of codeine phosphate.
2. As originally drawn above, which of these two agents is more water-soluble? Provide a rationale for your selection that includes appropriate structural properties. Is the salt form of codeine phosphate more or less water soluble than the free base form of the drug? Provide a rationale for your answer based on the structural properties of the salt form of codeine phosphate.
3. What is the chemical consequence of mixing aqueous solutions of each drug in the same IV bag? Provide a rationale that includes an acid/base assessment.



Acid form
pK_a 8.0

Conjugate base

Question: At a pH of 7.4, what is the percent ionization of amobarbital?

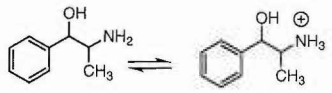
Answer: $8.0 = 7.4 + \log \frac{[\text{acid}]}{[\text{base}]}$

$0.6 = \log \frac{[\text{acid}]}{[\text{base}]}$

$10^{6} = \frac{[\text{acid}]}{[\text{base}]} = \frac{0.25}{1}$

$\%\ \text{acid form} = \frac{0.25 \times 100}{1.25} = 80\%$

Fig. 2.6. Calculation of % ionization of amobarbital. Calculation indicates that 20% of the molecules are in the acid (or protonated) form, leaving 80% in the conjugate base (ionized) form.



Base form

Conjugate acid form
pK_a 9.4

Question: What is the percent ionization of phenylpropanolamine at pH 7.4?

Answer: $9.4 = 7.4 + \log \frac{[\text{acid}]}{[\text{base}]}$

$2.0 = \log \frac{[\text{acid}]}{[\text{base}]}$

$10^{2} = \frac{[\text{acid}]}{[\text{base}]} = \frac{100}{1}$

$\%\ \text{acid form} = \frac{100}{101} \times 100 = 99\%$

Fig. 2.7. Calculation of % ionization of phenylpropanolamine. Calculation indicates that 99% of the molecules are in the acid form which is the same as % ionization.

phenylpropanolamine. It is very important to recognize that for a base, the pK_a refers to the conjugate acid or ionized form of the compound. To thoroughly comprehend this relationship, the student should calculate the percent ionization of an acid and a base at different pH values.

Water Solubility of Drugs

The solubility of a drug molecule in water greatly affects the routes of administration available and its absorption, distribution and elimination. Two key concepts to keep in mind when considering the water (or fat) solubility of a molecule are the hydrogen bond forming potential of the functional groups present in the molecule and the ionization of functional groups.

Hydrogen Bonds

Each functional group capable of donating or accepting a hydrogen bond will contribute to the overall water solubility of the compound. Hence, such functional groups will increase the hydrophilic (water loving) nature of the molecule. Conversely, functional groups that cannot form hydrogen bonds will not enhance hydrophilicity, and will actually contribute to the hydrophobicity (water hating) of the molecule. Hydrogen bonds are a special case of what are generally referred to as dipole-dipole bonds. Dipoles result from unequal sharing of electrons between atoms within a covalent bond. This unequal sharing of electrons results when two atoms involved in a covalent bond have significantly different electronegativities. As a result, partial ionic character develops between the two atoms, produc-

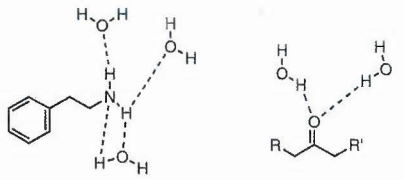
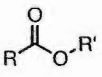


Fig. 2.8. Examples of hydrogen bonding between water and hypothetical drug molecules.

ing a permanent dipole: One end of the covalent bond has higher electron density than the other. When two molecules containing dipoles approach one another they align such that the negative end of one dipole is electrostatically attracted to the positive end of the other. When the positive end of the dipole is a hydrogen atom, this interaction is referred to as a *hydrogen bond* (or H-bond). Thus, for a hydrogen bond to occur at least one dipole must contain an electropositive hydrogen. The hydrogen atom must be involved in a covalent bond with an electronegative atom such as oxygen (O), nitrogen (N), sulfur (S) or selenium (Se). Of these four elements only O and N contribute significantly to the dipole and we will therefore only concern ourselves with the hydrogen bonding capability of OH and NH groups. This is only in reference to functional groups that "donate" hydrogen bonds.

Even though the energy involved for each hydrogen bond is small, 1–10 kcal/mol/bond, it is the additive nature of multiple hydrogen bonds that contributes to water solubility. We will see in Chapter 4 that this same bonding interaction is also important in drug-receptor interactions. Figure 2.8 shows several possible hydrogen bond types that may occur with different organic functional groups and water. As a general rule, the more hydrogen bonds that are possible, the greater the water solubility of the molecule. Table 2.4 lists several common organic functional groups and the number of potential hydrogen bonds for each. This table does not take into account the possibility of *intramolecular* hydrogen bonds that could form. Each intramolecular hydrogen bond would decrease water solubility (and increase lipid solubility) since one less interaction with solvent occurs.

Table 2.4. Common Organic Functional Groups and Their Hydrogen-Bonding Potential

Functional Groups	Number of Potential H-bonds
R–OH	3
	2
$R–NH_2$	3
	2
	1
	4

Ionization

In addition to the hydrogen bonding capability of a molecule, another type of bonding interaction plays an important role in determining water solubility: Ion-Dipole bonding. This type of bonding comes into play when one deals with organic salts. Ion-dipole bonds develop between either a cation or anion and a formal dipole such as water. A cation, having a deficiency in electron density, will be attracted to regions of high electron density. When dealing with water, this would be the two lone pairs of electrons associated with the oxygen atom. An anion will associate with regions of low electron density or the positive end of the dipole. In the case of water as solvent, this would be the hydrogen atoms (Fig. 2.9).

Not all organic salts are necessarily very water soluble. In order to associate with enough water molecules to become soluble, the salt must be highly dissociable; i.e., the cation and anion must be able to separate and each interact with water molecules. Highly dissociable salts are those formed from strong acids with strong bases, weak acids with strong bases and strong acids with weak bases. Strong acids are hydrochloric, sulfuric, nitric, perchloric and phosphoric acid. All other acids are considered to be weak. Sodium hydroxide and potassium hydroxide are considered to be strong bases, with all other bases classified as weak. Thus the salt of a carboxylic acid and alkylamine is a salt of a weak acid and weak base respectively, and therefore does not dissociate appreciable. This salt would not be very water soluble. Some examples of common organic salts used in pharmaceutical preparations are provided in Figure 2.10.

When dealing with the water solubility of ionized molecules one must also consider the possibility of intramolecular ionic bonding. Compounds with ionizable functional groups that produce opposite charges have the potential to interact with each other rather than water molecules. When this occurs such compounds often become very insoluble in water. A classic example is the amino acid tyrosine (Fig. 2.11). Tyrosine contains three very polar functional groups with two of these (the alkylamine and carboxylic acid) being capable of ionization, depending on the pH of the solution. The phenolic hy-

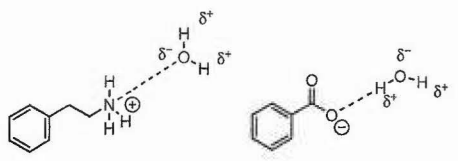


Fig. 2.9. Examples of ion-dipole bonds.

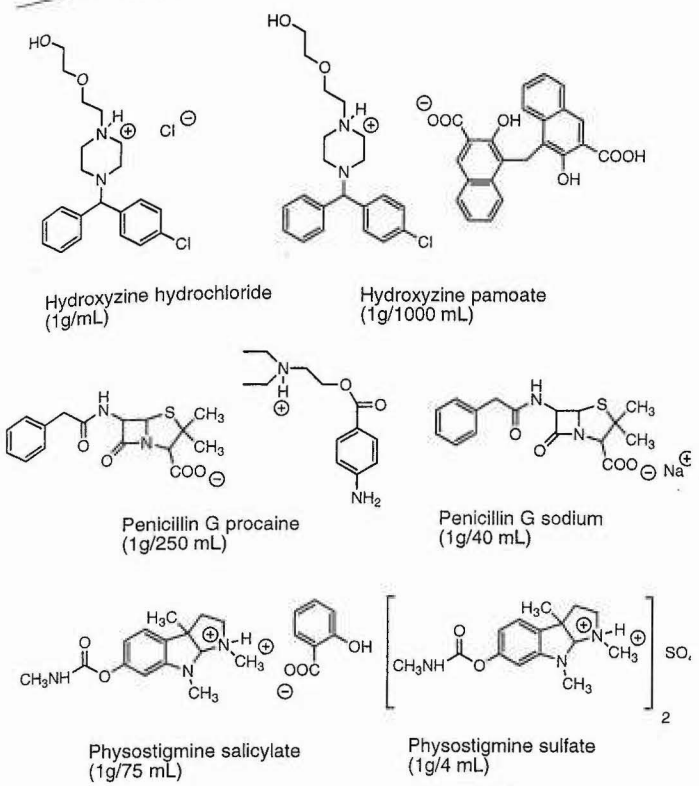
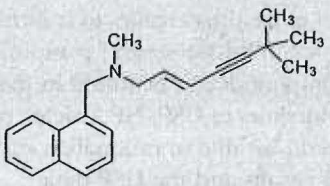


Fig. 2.10. Water solubilities of different salt forms of selective drugs.

Absorption/Binding Interactions Case

A 24-year-old male comes into the pharmacy and asks you for a recommendation for a treatment for the itching and burning he has recently noticed on both feet. He indicates that he would prefer a cream rather than a spray or a powder. Your recommendation to this patient is to use Lamisil, a very effective topical antifungal agent that is sold over the counter.



Terbinafine (Lamisil)

1. Identify the structural characteristics and the corresponding properties that make terbinafine an agent that can be utilized topically.
2. The biological target for drug action for terbinafine is squalene epoxidase. Consider each of the structural features of this antifungal agent and describe the type of interactions that the drug will have with the target for drug action. Which amino acids are likely to be present in the active site of this enzyme?

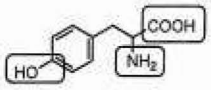


Fig. 2.11. Functional groups present in tyrosine, their hydrogen-bonding potential, and pK_a values.

droxyl is also ionizable, but it doesn't contribute under the conditions most often encountered in pharmaceutical formulations or physiologic conditions. Because of the presence of three very polar functional groups (two of them being ionizable) one would therefore expect tyrosine to be very soluble in water, yet its solubility is only 0.45 g/1000ml. Since the basic alkylamine (pK_a 9.1, for the conjugate acid) and the carboxylic acid (pKa 2.2) can react with one another a zwitterionic molecule is formed. The two charged groups are sufficiently close to allow a strong ion-ion bond to form, thereby keeping each of these groups from forming ion-dipole bonds with the surrounding water molecules. The lack of interaction of the ions with the water dipoles results in a molecule that is very insoluble (Fig. 2.12). Not all zwitterions or multiply charged molecules show this behavior. Only those containing ionized functional groups that are close enough to interact to form an ion-ion bond will be poorly soluble. The greater the separation between charges, the more highly water soluble the molecule will be.

Predicting Water Solubility: Empiric Approach

Lemke (10) has developed an empirical approach to predicting water solubility of molecules based upon the carbon solubilizing potential of several organic functional groups. If the solubilizing potential of the functional groups exceeds the total number of carbon atoms present, then the molecule is considered to be water soluble. Otherwise, it is insoluble. Functional groups that can interact either through intramolecular hydrogen bonds or ion-ion interactions will decrease the solubilizing potential of each group. It is difficult to quantitate how much such interactions will take away from water solubility, but recognizing these interactions will allow one to explain anomalous results.

Table 2.5 shows the water solubilizing potential for several organic functional groups common to many drugs. Since most drug molecules contain more than one functional group (i.e., are polyfunctional) the second column in the table will be used most often. A couple examples for predicting water solubility will be used to demonstrate Lemke's method. Anileridine (Fig. 2.13) is a narcotic analgesic containing three organic functional groups that contribute to water solubility: an aromatic amine (very weak base), a terti-

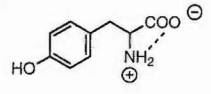
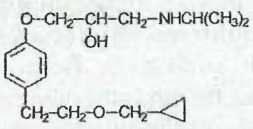


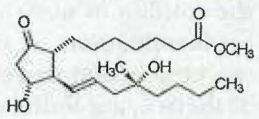
Fig. 2.12. Zwitterion form of tyrosine showing ion-ion bond.

Binding Interactions

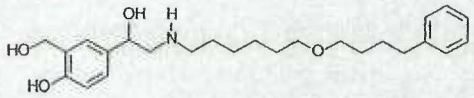
Each of these drug molecules interacts with a different biological target and elicits a unique pharmacologic response. For each of the three molecules, list the types of binding interactions that are possible with a target for drug action. For each type of binding interaction, provide one example of an amino acid that could participate in that interaction.



Betaxolol (Betoptic)



Misoprostol (Cytotec)



Salmeterol (Serevent)

Example: Binding Interaction: Van der Waals Amino Acid: leucine

Table 2.5. Water-solubilizing Potential of Organic Functional Groups When Present in a Mono- or Polyfunctional Molecule

Functional Group	Monofunction Molecule	Polyfunctional Molecule
Alcohol	5 to 6 carbons	3 to 4 carbons
Phenol	6 to 7 carbons	3 to 4 carbons
Ether	4 to 5 carbons	2 carbons
Aldehyde	4 to 5 carbons	2 carbons
Ketone	5 to 6 carbons	2 carbons
Amine	6 to 7 carbons	3 carbons
Carboxylic acid	5 to 6 carbons	3 carbons
Ester	6 carbons	3 carbons
Amide	6 carbons	2 to 3 carbons
Urea, carbonate, carbamate		2 carbons

Water solubility is defined as >1% solubility (9).

ary alkylamine (weak base) and an ester (neutral). There are a total of 21 carbon atoms in the molecule with a solubilizing potential from the three functional groups of 9 carbon atoms. Since the solubilizing potential of the functional groups is less than the total number of carbons present, the prediction would be that anileridine is insoluble in water. This is indeed the case, for its solubility is reported in the U.S. Pharmacopeia (USP) as >1g/10,000ml or <0.01%. However, when the hydrochloride salt of anileridine is considered, not only do the three functional groups contribute a solubilizing potential of 9 carbons, but the positive charge of the alkylammonium also contributes to its ionization. Lemke estimates that each charge on a molecule (cationic or anionic) contributes a solubilizing potential of 20–30 carbons. Thus, the solubilizing potential for these groups in anileridine hydrochloride is 29–39 carbons, which is more than the total number of carbon atoms in the molecule. The compound would therefore be soluble in water, and it is to the extent of 0.2g/ml or 20%. Problem 6 at the end of the chapter provides more opportunity to utilize this approach to predict water solubility for several compounds. Solubility data for these compounds can be found in the USP (USP 24 Approximate Solubilities of USP/NF Articles, pp 2299–2304). The student should be able to rationalize any discrepancies between his/her results and the USP data.

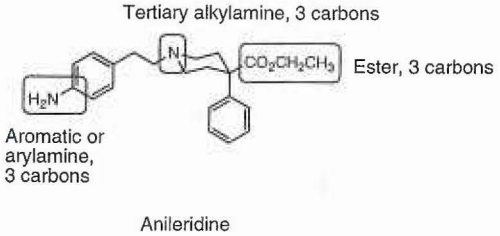


Fig. 2.13. Identification of functional groups in anileridine.

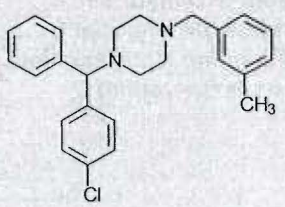
Predicting Water Solubility: Analytical Approach

Another method for predicting water solubility involves calculating an approximate logP, or log of the partition coefficient for a molecule. This approach is based on an approximation method developed by Cates (11) and discussed in Lemke (10). In this approach, one sums the hydrophobic or hydrophilic properties of each functional group present in the molecule. Before we can calculate logP values, we must first digress to a brief explanation of the concept of partition coefficient.

Water/Lipid Solubility Case

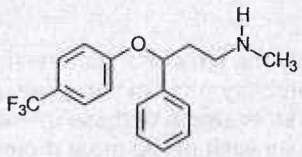
When you look at any drug molecule there are a number of functional groups that are present that contribute to the properties of that drug molecule. Identify the types of functional groups present in each molecule and to which physical properties (water/lipid solubility) each contributes.

1. Structural Feature Physical Property



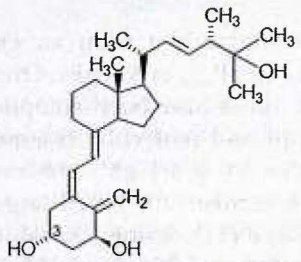
Meclizine
(Antivert)

2. Structural Feature Physical Property



Fluoxetine
(Prozac)

3. Structural Feature Physical Property



1, 25-dihydroxy Vit D_2

In its simplest form the partition coefficient, P, refers to the ratio of the concentrations of drug in octanol to that of water. Octanol is used to mimic the amphiphilic nature of lipid since it has a polar head group (primary alcohol) and a long hydrocarbon chain, or tail, such as that of fatty acids which make up part of a lipid membrane. Since P is logarithmically related to free energy (12) it is generally expressed as logP, and is therefore the sum of the hydrophobic and hydrophilic characteristics of the organic functional groups making up the structure of the molecule. Thus, logP is a measure of the solubility characteristics of the entire molecule. Because each organic functional group contained within the molecule contributes to the overall hydrophobic/hydrophilic nature of the molecule, a hydrophobic/hydrophilic value (the hydrophobic substituent constant, π) can be assigned to each organic functional group. Equation 2.7 defines this relationship.

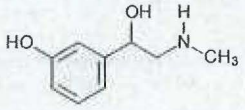
Eq. 2.7 $$\text{LogP} = \Sigma\pi \text{ (fragments)}$$

When calculating logP from hydrophobic substituent constants the sum is usually referred to as $\text{logP}_{\text{calc}}$ or

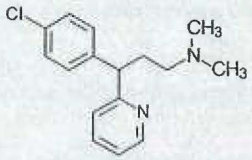
Binding Interactions/Solubility Case

JK presents a prescription for her daughter (6 months old) for Donatussin Drops. She wants to know if this medication will have an effect on her daughter's alertness.

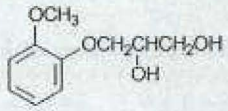
Components of Donatussin:
Phenylephrine (decongestant)
Chlorpheniramine (antihistamine)
Guaifenesin (expectorant)



Phenylephrine



Chlorpheniramine



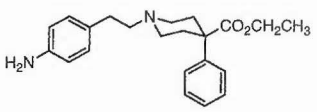
Guaifenesin

1. Identify the structural features/functional groups of phenylephrine and guaifenesin that contribute to improved water solubility (medication given as drops). List the type(s) of interactions that these groups have with water and draw an example of these interactions (with appropriate labels) below.
2. Evaluate each of the three molecules and determine if each molecule contains any functional groups that will allow the drug to cross the blood brain barrier and have an effect on this child's alertness (create a list of relevant functional groups. for each molecule). Based on your evaluation, which agent is likely to have the most significant effect? Identify what property is necessary for these agents to cross this biological membrane.
3. Identify the binding interactions that chlorpheniramine and guaifenesin could have with their respective targets for drug action. Be sure to identify which functional groups will participate in each of these binding interactions.

ClogP to distinguish it from an experimentally determined value ($logP_{meas}$ or MlogP). Over the years extensive tables of π values have been compiled for organic functional groups and molecular fragments (see references 12–15). Table 2.6 is a highly abbreviated summary of π values from Lemke (10) based largely upon the manuscript by Cates (11). Using the values in this table, it is possible to obtain a fairly reasonable estimate of the water solubility of many organic compounds. As an example we will once again use the narcotic analgesic anileridine to demonstrate the calculation of logP. This compound has a total of 21 carbon atoms, some aliphatic and some aromatic. We therefore need to separate these since aromatic carbon atoms, due to delocalized p orbitals for the sp^2 hybridized atoms, are more polar than aliphatic carbons. The compound also contains one tertiary alkylamine, one aromatic amine and an ester. Note that when dealing with esters and amides the oxygen, nitrogen and ester/amide carbon are counted in this π value. The remaining aliphatic carbons are then counted. Figure 2.14 summa-

Table 2.6. Hydrophilic-lipophilic Values (π V) for Organic Fragments (9)

Fragments	π Value
C (aliphatic)	+0.5
Phenyl	+2.0
Cl	+0.5
O_2NO	+0.2
IMHB	+0.65
S	0.0
O = C–O (carboxyl)	−0.7
O = C–N (amide, imide)	−0.7
O (hydroxyl, phenol, ether)	−1.0
N (amine)	−1.0
O_2N (aliphatic)	−0.85
O_2N (aromatic)	−0.28



Fragments	π
2 amines	−2.0
9 aliphatic carbons	+4.5
2 phenyl rings	+4.0
1 ester	−0.7
logP	+5.8

Fig. 2.14. Calculation of logP for anileridine.

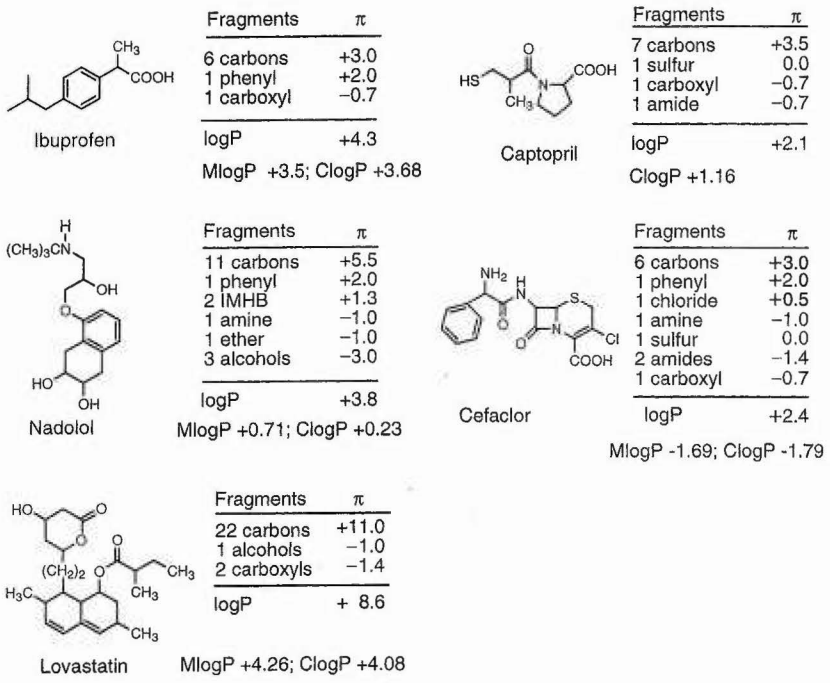


Fig. 2.15. ClogP calculations for selected compounds.

Questions We Can Now Answer About Any Drug Molecule

Based on your knowledge of acid/base chemistry, from where will this drug primarily be absorbed?
What is the solubility of the drug in the stomach, plasma, or in an aqueous IV?
What are the possible interactions that the drug could have with its respective target for drug action?
What is the compatibility of the drug if mixed with other drugs?
How should this drug be delivered? Is it stable in stomach acid?

rizes the logP calculation for anileridine. The calculation gives a ClogP value for anileridine of +5.8. Water solubility as defined by the USP is solubility of greater than 3.3%, which equates to an approximate logP of +0.5. Values less than +0.5 are therefore considered to be water soluble, and those greater than +0.5 are water insoluble. According to our calculation, anileridine would be predicted to be insoluble in water. This calculation agrees with the more empiric procedure discussed earlier. Other sample calculations are shown in Figure 2.15 and several problems are provided at the end of this chapter. In Figure 2.15, MlogP values (when available) and ClogP values obtained from the program MaclogP (16) are included for comparison purposes. Even though the π values used from Table 2.6 are not as extensive as those used in the computer program, there is good general agreement with most of these compounds with respect to their solubility (or insolubility) in water.

Predicting the percent ionization or water solubility of a molecule should not be viewed only as an exercise in arithmetic, but also as a way to understand the solution behavior of molecules, especially when dealing with admixtures and differences among molecules in their pharmacokinetics. The ionization state of a molecule not only influences its water solubility, but also its ability to traverse membranes and therefore its ability to be absorbed. Serum protein binding, and therefore the amount of free drug available for receptor binding, is also greatly influenced by the ionization state and the hydrophilic/hydrophobic nature of the molecule.

STEREOCHEMISTRY AND DRUG ACTION

The physicochemical properties of a drug molecule are not only dependent upon what functional groups are present in the molecule, but also the spatial arrangement of these groups. This becomes an especially important factor when a molecule is subjected to an asymmetric environment such as the human body. Since proteins and other biological macromolecules are asymmetric in nature, how a particular drug molecule interacts with these macromolecules is determined by the three-dimensional orientation of the organic functional groups present. If crucial functional groups are not occupying the proper spatial region surrounding the molecule, then productive bonding interactions with the biological macromolecule (or receptor) will not be possible, thereby potentially negating the desired

Learning the Lingo: Drug Molecule Evaluation

Analysis of Individual Functional Groups:
- Name of Functional Group
- Shape of Functional Group
- Hydrophobic vs. Hydrophilic Character
- Polar vs. Nonpolar Character
- Acidic vs. Basic (pKa) Character
- Binding Interactions
- Chemical/Enzymatic Stability

Analysis of the Whole Drug Molecule:
- Looking for Functional Group Balance: Water Solubility and Absorption
- Ionization Issues: Effect on Solubility and Absorption
- Drug Combinations: Acid/Base Interactions
- Drug Interactions with BiologicalTarget: Good Fit or Not?
- Stability and Bioavailability: Route of Administration

pharmacologic effect. However, if these functional groups are in the proper three-dimensional orientation, the drug can produce a very strong interaction with its receptor. It is therefore very important for the medicinal chemist responsible for developing a new molecular entity for therapeutic use to understand not only what functional groups are responsible for the drug's activity, but also what three-dimensional orientation of these groups is also needed.

Enantiomers

Approximately one in every four drugs currently on the market can be considered to be a mixture. That is, these compounds are combinations of isomers. Yet for many of these compounds the biological activity may reside in only one isomer or at least predominate in one isomer. The majority of these isomeric mixtures are what are referred to as racemic mixtures (racemates). These are compounds, usually synthetic, that contain equal amounts of both possible enantiomers, or optical isomers. Enantiomers are isomers whose three-dimensional arrangement of atoms results in nonsuperimposable mirror images. These compounds have identical physical chemical properties except for their ability to rotate the plane of polarized light in opposite directions with equal magnitude. Enantiomers are also referred to as chiral compounds, antipodes or enantiomorphs. When introduced into an asymmetric, or chiral, environment, such as the human body, enantiomers will display different physical chemical properties producing significant differences in their pharmacokinetic and pharmacodynamic behavior. Such differences can result in adverse side effects or toxicity due to one of the isomers or the isomers may exhibit significant differences in absorption (especially active transport), serum protein binding and metabolism. With the latter one isomer may be converted into a toxic substance or may influence the metabolism of another drug. To further discuss the influence of stereochemistry on drug action, some of the basic concepts of stereochemistry need to be reviewed.

Stereochemical Definitions

Organic compounds can exist as isomers, compounds with the same number and kinds of atoms, but with different bonding arrangements. The arrangement of bonds within a molecule that provides it with a particular three-dimensional shape is referred to as the *configuration* of the molecule. Differences in configuration result in compounds with differing physicochemical properties such as solubility, melting point, or boiling point, just to name a few. For example, the empirical formula C_2H_6O can describe at least two different compounds: dimethyl ether (CH_3OCH_3) or ethyl alcohol (CH_3CH_2OH). The former has a boiling point of −23.6°C (i.e., it is a gas), whereas the latter has a boiling point of 78.5°C. Numerous other examples of isomers exist in which the empirical formula can describe two or more compounds with different physical and chemical properties (see problem 8 at the end of the chapter).

Diastereomers

Stereoisomers are compounds containing the same number and kinds of atoms, the same arrangement of bonds, but different three-dimensional structures i.e., they only differ in the three-dimensional arrangements of atoms in space. Stereoisomers are subdivided into two types: enantiomers and diastereoisomers. As indicated earlier, enantiomers are compounds whose three-dimensional arrangement of atoms is such that they are nonsuperimposable mirror images. Diastereoisomers are all stereoisomeric compounds that are not enantiomers. Thus, the term diastereoisomer includes compounds containing double bonds as well as ring systems. Unlike enantiomers, diastereoisomers exhibit different physical and chemical properties, including melting point, boiling point, solubility and chromatographic behavior. These differences in physical chemical properties allow for the separation of diastereoisomers from mixtures utilizing standard chemical separation techniques such as column chromatography or crystallization. Enantiomers cannot be separated using such techniques unless a chiral environment is provided or they are converted to diastereoisomers (e.g., salt formation with another enantiomer). Examples of enantiomers and diastereoisomers are provided in Figure 2.16.

Designation of Stereoisomers and Nomenclature

At first enantiomers were distinguished by their ability to rotate the plane of polarized light. Isomers rotating light to the right, or clockwise direction, were designated as dextrorotatory and this was indicated by a (+)-sign before the chemical name (e.g., (+)-amphetamine or dextroamphetamine). The opposite designation, levorotatory or (−)-, was given to compounds which rotated the plane of polarized light to the left or counterclockwise. The letters d- and l- were formerly used to indicate (+)- and (−)- respectively. A racemate (racemic mixture), i.e., a 1:1 mixture of enantiomers, is indicated by (±)-before the compound name. The student should be made aware that

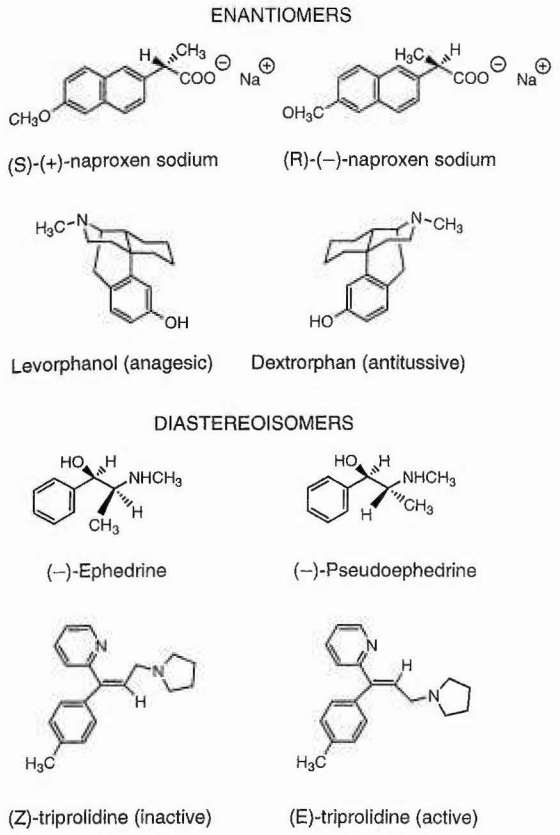
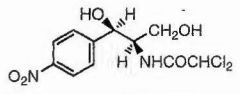


Fig. 2.16. Examples of stereoisomers.

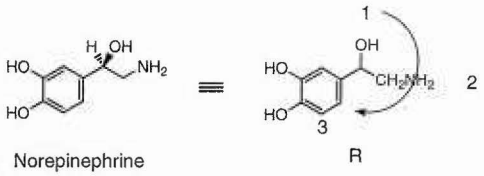
this method of nomenclature is based upon a physical property of the molecule and does not provide any information concerning the *absolute configuration* or three-dimensional arrangement of atoms around the chiral center. Since the rotation of plane polarized light is a physical property, both the magnitude and direction of rotation can vary depending upon the conditions used. Thus, temperature, solvent and concentration of the substance are only three factors that need to be considered. A good example of this is the antibiotic chloramphenicol. There are



two chiral centers in this molecule resulting in four possible stereoisomers. The isomer shown is dextrorotatory when its optical rotation is measured in ethanol, but levorotatory in ethyl acetate. It is obvious that the simple measurement of a physical property such as rotation of the plane of polarized light is not sufficient for the assignment of the absolute configuration of a molecule.

Fisher and Rosanoff in the late 19th century developed a system of nomenclature based upon the structure of glyceraldehyde (Fig. 2.17). Since there were no known methods for determining the absolute three dimensional arrangement of atoms in space at that time, the two isomers of glyceraldehyde were arbitrarily assigned the designation of D-(+)- and L-(−). It wasn't until the 1950s that the absolute configurations were determined and it was found that Fisher had fortuitously guessed correctly. Assignments of configuration to other molecules were done based upon their relationship to D- or L-glyceraldehyde via synthesis irrespective of the observed direction of rotation of plane polarized light. Thus, via chemical degradation, it was possible to determine that (+)-glucose, (−)-2–deoxyribose and (−)-fructose had the same terminal configuration as D-(+)-glyceraldehyde and were therefore given the D-absolute configuration. Amino acids were assigned based upon their relationship to D-(+)- and L-(−)-serine (Fig. 2.17). Unfortunately, this system becomes very cumbersome with molecules containing more than one chiral center.

In 1956 Cahn, Ingold and Prelog devised a system of nomenclature for stereoisomers referred to as the Sequence Rule System (or CIP system). With this system, atoms attached to a chiral center are ranked according to their atomic number. Highest priority is given to the atom with highest atomic number and subsequent atoms are ranked accordingly from highest to lowest. When a decision cannot be made regarding priority, e.g., two atoms with the same atomic number attached to the chiral center, the process continues to the next atom until a decision can be made. The molecule is then viewed from the side opposite the lowest priority atom and the priority sequence from highest to lowest is determined. If the sequence is to the right, or clockwise, the chiral center is designated as the R absolute configuration. When the priority sequence is to the left, or counterclockwise, the designation is S. An example of this is seen in the neurotransmitter norepinephrine.



Degradation studies demonstrated that (−)-norepinephrine is related to D-(−)-mandelic acid and was therefore given the D-designation using the Fisher system. With the CIP system norepinephrine is assigned the R absolute configuration.

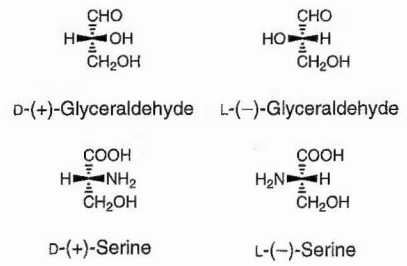


Fig. 2.17. Relationship of optical isomers of serine to D and L glyceraldehyde.

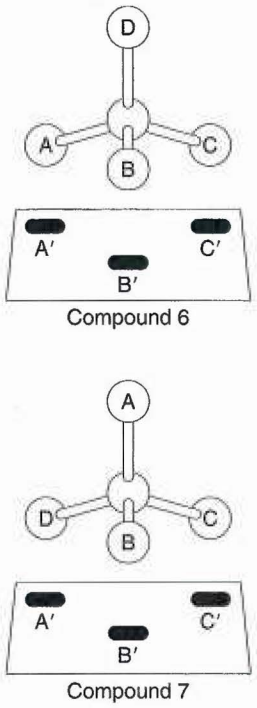
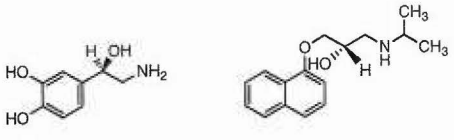


Fig. 2.18. Optical isomers. Only in compound 6 do the functional groups A, B, and C align with the corresponding sites of binding on the asymmetric surface.

The student should note that the CIP system of nomenclature uses a set of arbitrary rules and therefore should be viewed as a system that keeps track of absolute configuration only. There are many instances where two molecules may have different absolute configurations as designated by the CIP system, but the same relative orientation of the functional groups relevant for biological activity. A case in point is the absolute configuration of the nonselective alpha-adrenogenic antagonist propranolol as compared to norepinephrine. Because of the ether oxygen, the priority sequence of the functional groups about the chiral center results in the assignment of the (S)-absolute configuration for the more active enantiomer of propranolol. However, close inspection of both (R)-norepinephrine and (S)-propranolol shows that the hydroxy group, basic amine and aromatic rings of both compounds occupy the same regions in 3D space.



(R)-Norepinephrine (S)-Propranolol

Stereochemistry and Biologic Activity

Easson-Stedman Hypothesis

In 1886 Piutti (17) reported different physiologic actions for the enantiomers of asparagine, with (+)-asparagine having a sweet taste and (−)-asparagine bland.

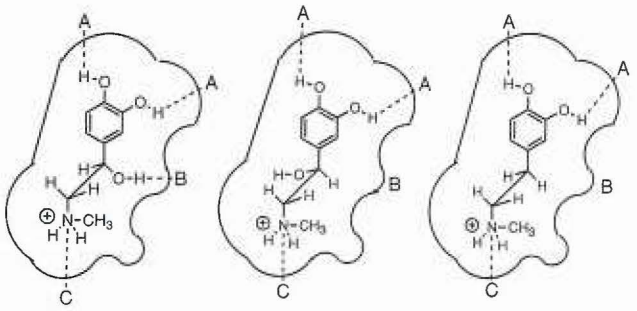


Fig. 2.19. Drug receptor interation of (R)- (−)-epinephrine, (S)-(+)-epinephrine, and N-methyldopamine.

This was one of the earliest observations that enantiomers can exhibit differences in biological action. In 1933, Easson and Stedman (18) reasoned that differences in biological activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor. They postulated that such interactions require a minimum of a three-point fit to the receptor. This is demonstrated in Figure 2.18 for two hypothetical enantiomers. In Figure 2.18, A, B, and C represent hypothetical functional groups that can interact with complementary sites on the hypothetical receptor surface, represented by A′, B′ and C′. Only one enantiomer is capable of attaining the correct orientation enabling all three functional groups to fit their respective sites on the receptor surface. The lack of achieving the same interactions with the other enantiomer explains its reduced biological activity since it is unable to properly fit the receptor and therefore cannot "trigger" the appropriate change in the receptor conformation. The Easson-Stedman Hypothesis states that the more potent enantiomer must be involved in a minimum of three intermolecular interactions with the receptor surface and the less potent enantiomer only interacts with two sites. This can be illustrated by looking at the differences in vasopressor activity of (R)-(−)-epinephrine, (S)-(+)-epinephrine and the achiral N-methyldopamine (Fig. 2.19). With (R)-(−)-epinephrine, the three points of interaction with the receptor site are the substituted aromatic ring, β-hydroxyl group and the protonated secondary ammonium group. All three functional groups interact with their com-

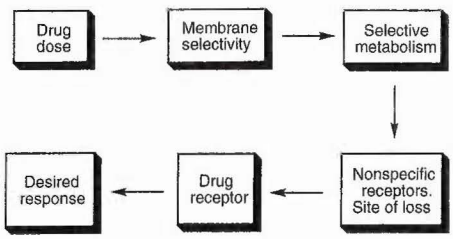


Fig. 2.20. Selective phases to which opitcal isomers may be subjected before biologic response.

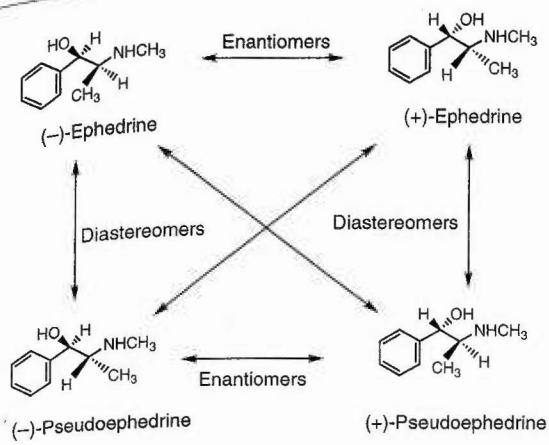


Fig. 2.21. Relationship between the diastereomers of ephedrine and pseudoephedrine.

plementary binding sites on the receptor surface producing the necessary interactions that stimulate the receptor. With (S)-(+)-epinephrine only two interactions are possible (the protonated secondary ammonium and the substituted aromatic ring). The β-hydroxyl group occupies the wrong region of space and therefore cannot interact properly with the receptor. N-methyldopamine can achieve the same interactions with the receptor as (S)-(+)-epinephrine and it is therefore not suprising that its vasopressor response is the same as (S)-(+)-epinephrine and less than (R)-(−)-epinephrine.

Not all stereoselectivity seen with enantiomers can be attributed to differences in reactivity at the receptor site. Differences in biological activity can also be due to differences in the ability of each enantiomer to reach the receptor site. Since the biological system encountered by the drug is asymmetric, each enantiomer may experience selective penetration of membranes, metabolism, absorption at sites of loss (e.g., adipose tissue) or excretion. Figure 2.20 shows the selective phases enantiomers may encounter prior to reaching the receptor. Not all of these processes may be encountered by a particular enantiomer, but such processes may provide enough of an influence to cause one enantiomer to produce a significantly better pharmacologic effect than the other. Conversely, such processes may also contribute to untoward effects of a particular enantiomer. The student must continually keep in mind that not all pharmacologic effects of a drug are necessarily beneficial to the patient and differences in pharmacologic action among stereoisomers provide excellent examples of this concept.

Diastereomers

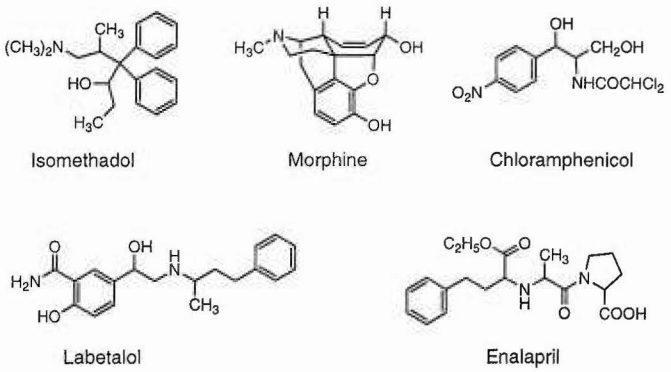
As mentioned earlier, diastereoisomers are compounds that are non-superimposable, non-mirror image isomers. Such compounds can result from the presence of more than one chiral center in the molecule, double bonds or ring systems. These isomers have different physical and chemical properties and thus differences in biological activity between such isomers can often be attributed to these properties.

Compounds containing more than one chiral center are probably the most common type of diastereoisomer used as drugs. The classic example of compounds of this type is the diastereoisomers ephedrine and pseudoephedrine (see Fig. 2.21). When a molecule contains two chiral centers there can be up to four possible stereoisomers consisting of two sets of enantiomeric pairs. For each enantiomeric pair there is inversion of both chiral centers, while the difference between diastereomers is inversion of only one chiral center (problem 9 at the end of the chapter helps illustrate this point). Figure 2.22 shows several examples of other compounds that contain two or more chiral centers and therefore are diastereoisomeric (problem 10 at the end of the chapter).

Restricted bond rotation due to carbon-carbon double bonds (alkenes or olefins) and similar systems such as C=N (imines) can produce stereoisomers. These are also referred to as geometric isomers, although they are more properly diastereoisomers. In compounds of this type substituents can be oriented on the same side or opposite sides of the double bond. The alkene 2–butene is a simple example of this.

cis or Z isomer trans or E isomer

With 2-butene it is readily apparent that the methyl groups may be on the same side or opposite sides of the double bond. When they are on the same side the molecule is defined as the cis- or Z-isomer (from the German zusammen or "together"); when they are on opposite sides the designation is trans- or E- (from the German entgegen or "opposite"). With simple compounds such as 2-butene it is easy to determine which groups in the molecule are cis or trans to one another. However, this becomes more difficult to determine with more complex structures where it is less obvious which substituents should be referred to



Isomethadol Morphine Chloramphenicol

Labetalol Enalapril

Fig. 2.22. Examples of chiral drugs with two or more asymmetric centers.

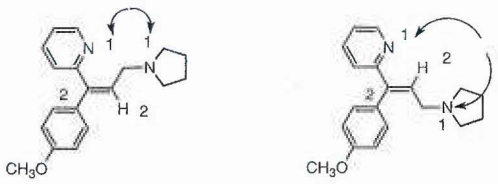


Fig. 2.23. Geometric isomers of triprolidine.

when naming the compound. In 1968 Blackwood et al. (19) proposed a system for the assignment of "absolute" configuration with respect to double bonds. Using the CIP sequence rules, each of the two substituents attached to the carbon atoms comprising the double bond are assigned a priority of 1 or 2 depending upon the atomic number of the atom attached to the double bond. When two substituents of higher priority are on the same side of the double bond, this isomer is given the designation of cis or Z. When the substituents are on opposite sides, the designation is trans or E. The histamine H_1-receptor antagonist, triprolidine, (Fig. 2.23) is a good example for demonstrating how this nomenclature system works. The E-isomer of triprolidine is more active both in vitro and in vivo, indicating that the distance between the pyridine and pyrrolidine rings is critical for binding to the receptor.

Diastereoisomers (as well as enantiomers) can also be found in cyclic compounds. For example, the cyclic alkane 1,2-dimethylcyclohexane can exist as *cis/trans* diastereoisomers and the *trans* isomer can also exist as an enantiomeric pair. In Figure 2.24 each of the trans-enantiomorphs are depicted in the two possible chair conformations for the cyclohexane ring. Cyclohexane rings can exhibit significant conformational freedom that allows for the possibility of conformational isomers. Isomers of this type will be discussed in the next section. When two or more rings share a common bond (e.g., decalin) rotation around the bonds is even more restricted, preventing even ring "flipping" (conformationally rigid) from occurring thereby producing diastereoisomers and enantiomers.

In the case of the two-ring system of decalin, the rings can join together at the common bond either in the trans or cis configuration as shown. Steroids, a class of medicinally important compounds consisting of four fused rings (three cyclohexane, 1 cyclopentane), exhibit significantly different biological activity when the first two cyclohexane rings are fused into different configurations referred to as the 5α or 5β-isomers (Fig. 2.25). The α-designation indicates that the substituent in the 5-position is below the "plane" of the ring system while the β-designation refers to the substituent being above this plane. What appears to be a very minor change in orientation for the substituent results in a very drastic change in the three-dimensional shape of the molecule and in its biological activity. Figure 2.25 shows the diastereoisomers 5α-cholestane and 5β-cholestane as examples. The chemistry and pharmacology of steroids will be discussed in more detail in Chapters 28 and 29.

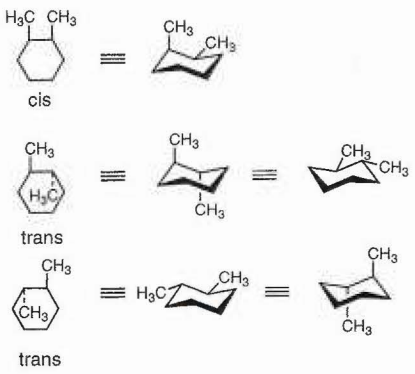


Fig. 2.24. Diastereomers of 1,2-dimethylcyclohexane.

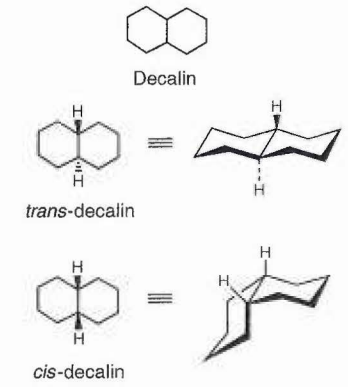


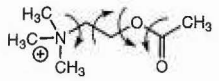
Fig. 2.25. The 5α and 5β conformations of the steriod nucleus cholestane.

Conformational Isomerism

With conformational isomerism we are dealing with a dynamic process, that is, isomerization takes place via rotation about one or more single bonds. Such bond rotation results in non-identical spatial arrangement of atoms in a molecule. Changes in spatial orientation of atoms due to bond rotation results in different *conformations* (or rotameters) whereas conversion of one enantiomer into another (or diastereoisomer) requires the breaking of bonds which has a much higher energy requirement than single bond rotation.

The neurotransmitter acetylcholine can be used to demonstrate the concept of conformational isomers.

Each single bond within this molecule is capable of undergoing rotation, and at room temperature such rotations



Acetylcholine

readily occur. Even though rotation around single bonds was shown by Kemp and Pitzer in 1936 (20) not to be free, but to have a energy barrier, this barrier is sufficiently low that at room temperature acetylcholine exists in many interconvertible conformations (see Chapter 10). Close observation reveals that rotation around the central C2–C3 bond produces the greatest spatial rearrangement of atoms than rotation around any other bond within the molecule. In fact, several rotatable bonds in acetylcholine produce redundant structures because all of the atoms attached to one end of some bonds are identical, resulting in no change in spatial arrangement of atoms (e.g., methyl groups). When viewed along the C2–C3 bond, acetylcholine can be depicted in the sawhorse or Newman projections as shown in Figure 2.26. When the ester and trimethylammonium group are 180° apart the molecule is said to be in the anti or staggered conformation (or anti or staggered rotamer). This conformation allows for maximum separation of the functional groups and is therefore considered to be the energetically most stable conformation. Other conformations are possibly more stable if factors other than steric interactions come into play; e.g., intramolecular hydrogen bonds. Rotation of one end of the C2–C3 bond by 120° or 240° results in the two gauche or skew conformations shown in Figure 2.26. These are considered to be less stable than the anti-conformer, although some studies suggest that an electrostatic attraction between the electron poor trimethylammonium and electron rich ester oxygen stabilizes this conformation. Rotation by 60°, 180° and 240° produce conformations where all of the atoms overlap or what are referred to as eclipsed conformations. These are the least stable conformers.

An interesting observation can be made with the two gauche conformers shown in Figure 2.26. These conformers are not distinct molecules and only exist for a transient period of time at room temperature. However, if these could be "frozen" into the conformations shown, they would be nonsuperimposable mirror images or enantiomers. Thus, a compound that is achiral, such as acetylcholine, can exhibit prochirality if certain conformational isomers can be formed. It is quite possible that such a situation could exist when acetylcholine binds to one of its receptors. Studies have suggested that the gauche conformation is the form that binds to the nicotinic receptor while the anti form (which is achiral) binds to the muscarinic receptor.

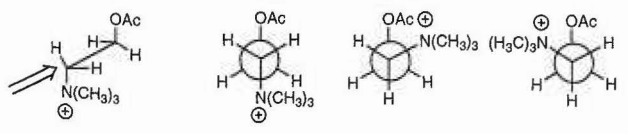


Fig. 2.26. Anti and gauche conformations of acetylcholine.

DRUG DESIGN: DISCOVERY AND STRUCTURAL MODIFICATION OF LEAD COMPOUNDS

Natural Product Screening

Perhaps the most difficult aspect of drug discovery for the medicinal chemist is that of lead discovery. Until the late 19th century the development of new chemical entities for medicinal purposes was primarily achieved through the use of natural products derived primarily from plant sources. As the colonial powers of Europe discovered new lands in the Western Hemisphere and colonized Asia, the Europeans learned of remedies derived from herbs for many ailments from the indigenous peoples of the newly discovered lands. Salicylic acid was isolated from the bark of willow trees after learning that Native Americans brewed the bark to treat inflammatory ailments. Further development of this lead compound by the Bayer Corporation of Germany resulted in acetylsalicylic acid or aspirin, the first non-steroidal anti-inflammatory agent. Teas obtained by brewing Cinchona bark were used by South American natives to treat chills and fever. Further study in Europe led to the isolation of quinine and quinidine, which were subsequently used to treat malaria and arrhythmias respectively. Following leads such as these chemists of the late 19th and early 20th centuries began to seek new medicinals from plant sources and to assay them for many types of pharmacologic actions. This approach to drug discovery is often referred to as natural product screening. With this approach compounds were isolated from natural sources based upon information obtained from indigenous peoples in many parts of the world. Until the mid-1970s this was one of the major approaches to obtaining new chemical entities as leads for new drugs. Unfortunately, this approach declined in favor of more rational approaches to drug design that developed during that period (see below). Recently, due to heightened awareness of the fragility of ecosystems on this planet, especially the rainforests, there has been a resurgence of screening products from plants before they become extinct. A new field of pharmacology, called ethnopharmacology, has emerged as a result. Ethnopharmacology is the term used to for the discipline of identifying potential natural product sources with medicinal products based upon native lore.

Compounds isolated from natural sources are usually tested in bioassays for the ailment that the plant material has been described to treat. Sometimes this may require several bioassays because the plant has been reported to be effective against several ailments. Often the treatment of different ailments requires different methods of preparation (e.g., brewing, chewing, direct application to wounds, etc.) or different parts of the same plant (e.g., roots, stem,

leaves, flowers, sap etc.). Each method of administration or part of the plant may involve different chemical compounds to produce the desired outcome. One can readily see that isolation of active constituents from plants that may be useful as medicinals is not a simple process and a number of variables are involved that may influence the amount of active compound or compounds that may influence the pharmacologic activity of the extract.

Random Screening of Synthetic Organic Compounds

This approach to discovering new chemical structures for a particular biological action began in the 1930s after the discovery of the sulfonamide class of antibacterials. Thousands of compounds and their synthetic intermediates were assayed in search of new structures that possessed antibacterial activity. All compounds available to the investigator (natural products, synthetic compounds), regardless of structure, were tested in the assays available at the time. This approach was also applied in the 1960s and 1970s in an effort to find agents that were effective against cancer. Some groups did not limit themselves to a particular biological activity, but tested compounds in a wide variety of assays. This approach was a precursor to what is now referred to as high throughput screening assays. This involves the bioassay of thousands of compounds in hundreds to thousands of bioassays simultaneously. This only became possible with the advent of computer controlled robotic systems for the assays and combinatorial chemistry techniques. These will be discussed further below.

What is crucial for random screening to be successful is a good bioassay system for the pharmacologic action of interest. Unfortunately, this means of lead discovery is very inefficient because no rational approach is taken to what compounds are to be tested to find new lead structures. Random screening eventually gave way to dedicated screening and rational design techniques.

Targeted Dedicated Screening and Rational Drug Design

This approach is more or less random in nature and involves greater knowledge of the therapeutic targets and some actual design based on physicochemical properties. Testing is usually with one or two models (e.g., specific receptor systems or enzymes) based on the therapeutic target. The design aspect often involves molecular modeling and the use of quantitative structure-activity relationships (QSAR) to better define the physicochemical properties that are crucial for biological activity. The drawback of these approaches is that they are better for developing a lead compound rather than discovery of the lead compound.

New Drug Discovery via Drug Metabolism Studies

New compounds have been "discovered" by investigating the metabolism of compounds that already are clinical candidates or, in rare instances, compounds that are already on the market. Metabolites of known compounds are isolated and then assayed for biological effects either on the same target system or a broader screen of several other target systems. The latter will be more useful if the metabolite being studied is a chemical structure that has been radically altered from the parent molecule through some unusual rearrangement reaction. More often the metabolite is not radically different from the parent molecule and therefore would be expected to have similar pharmacologic effects. The advantage is that a metabolite may possess better pharmacokinetic properties such as a longer duration of action, better absorption orally, or less toxicity with fewer side effects (e.g., terfenadine and its antihistaminic metabolite, fexofenadine). The sulfonamide antibacterial agents were discovered in this way. The azo dye prontosil was found to have antibacterial action in vitro only. It was soon discovered that this compound required reduction of the diazo group to produce 4-aminobenzene sulfonamide (Fig. 2.27) which was found to act as an antagonist to p-aminobenzoic acid, a crucial component in microbial metabolism.

New Drug Discovery via Observation of Side Effects

An astute clinician or pharmacologist may detect a side effect in a patient or animal model that could lead, upon further development, to a new therapeutic use for a particular chemical structure. Further development may even lead to an entirely new chemical class. This discovery of new lead compounds has occurred several times and will be discussed below.

One of the more interesting cases of drug development is that of the phenothiazine antipsychotics. These compounds can be traced back to the first histamine H_1-receptor antagonists developed in the 1930s. Bovet in 1937 (21) was the first to recognize that it should be possible to antagonize the effects of histamine and thereby treat allergic reactions. He tested compounds that were known to act on the autonomic nervous system and eventually discovered that benzodioxanes (Fig. 2.28) were capable of significant antagonism of the effects of histamine. In attempts to improve the antihist-

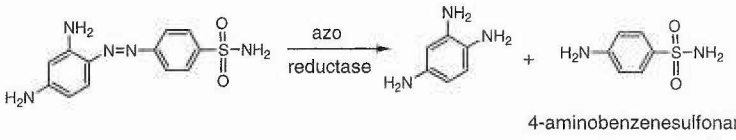


Fig. 2.27. Metabolic conversion of prontosil to 4-aminobenzenesulfonamide.

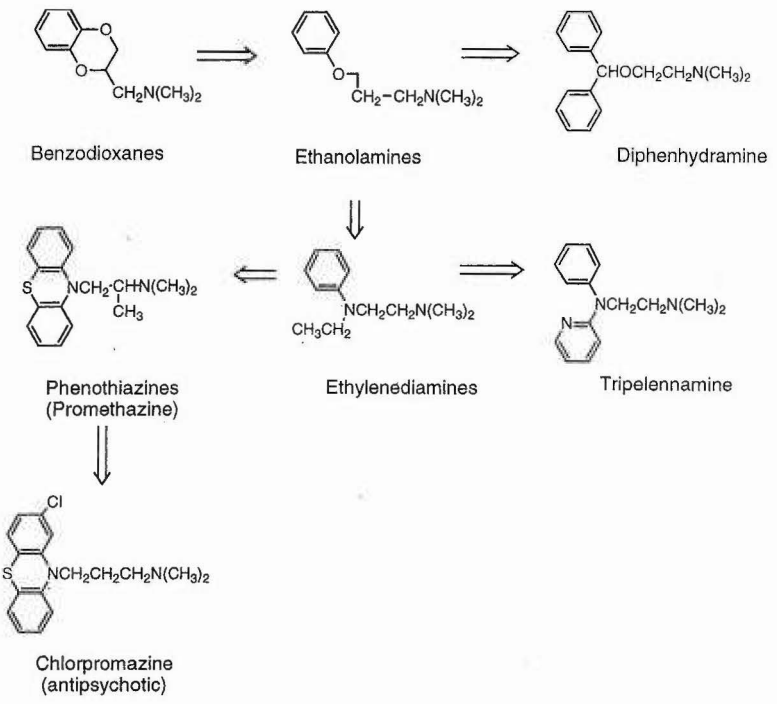


Fig. 2.28. Develpoment of phenothiazine-type antipsychotic drugs.

aminic action of the benzodioxanes it was discovered that ethanolamines also provided significant antihistaminic activity. Further development of this class ended up going in two directions. One approach led to the development of the diphenhydramine class of antihistamines and is represented by the first clinically useful H_1-receptor antagonist developed in the United States, diphenhydramine (Fig. 2.28). The other approach led to the ethylenediamine class represented by tripelennamine (Fig. 2.28).

Incorporation of the aromatic rings of the ethylenediamines into the tricyclic phenothiazine structure produced compounds (e.g., promethazine) with good antihistaminic action and relatively strong sedative properties. At first these compounds were found to not only be useful as antihistamines, but their very strong sedative properties lead to their use as potentiating agents for anesthesia (22). Further development to increase the sedative properties of the phenothiazines resulted in the development of chlorpromazine in 1950 (23).

Chlorpromazine was found to produce a tendency for sleep, but unlike the prior phenothiazines it also produced a disinterest in surroundings in patients and, with patients suffering psychiatric disorders, an ameliorative effect on the psychosis as well as relief of anxiety and agitation. These observations suggested that chlorpromazine had potential for the treatment of psychiatric disorders. Thus, what started out as attempts to improve antihistaminic activity, ultimately resulted in an entirely new class of chemical entity useful in an unrelated disorder (24).

Another example of how new chemical entities can be derived from compounds with unrelated biological effects is that of the development of the K^+ channel agonist diazoxide (Fig. 2.29). This compound was developed as the result of the observation that the thiazide diuretics such as chlorothiazide not only had a diuretic component due to inhibition of sodium absorption in the distal convoluted tubule but also a direct effect on the renal vasculature. Structural modification to enhance this direct effect led to the development of diazoxide and related K^+ channel agonists for the treatment of hypertension.

REFINEMENT OF THE LEAD STRUCTURE

Determination of the Pharmacophore

Once a lead compound has been discovered for a particular therapeutic use, the next step is to determine the pharmacophore for this compound. The pharmacophore of a drug molecule is that portion of the molecule containing the essential organic functional groups that directly interact with the receptor active site and therefore confers upon the molecule the biologic activity of interest. Since drug receptor interactions are very specific, the pharmacophore may constitute a small portion of the molecule. It has been found on several occasions that what seem to be very complex molecules can often be reduced to simpler structures with retention of the desired biological action. A well known example of this is the narcotic analgesic morphine. Morphine is a tetracyclic compound with five chiral centers. Not only would simplification of the structure possibly provide molecules with fewer side effects, but a reduction in the number of chiral centers would also greatly simplify the synthesis of morphine derivatives and thereby decrease cost. Figure 2.30 shows

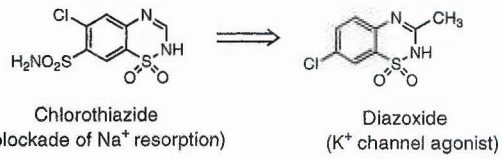


Fig. 2.29. Structural similarity of chlorothiazide, a diuretic, and diazoxide an antihypertensive that acts via opening of K^+ channels.

how the morphine structure has been simplified in the search for compounds with fewer deleterious side effects such as respiratory depression and addiction potential. Within each class there are analogs that are less potent, equipotent and with potencies many times that of morphine. It can be readily seen from the figure that the pharmacophore of morphine must consist of a tertiary alkylamine that is at least four atoms away from an aromatic ring. A more detailed discussion of the chemistry and pharmacology of morphine can be found in Chapter 19.

Alterations in Alkyl Chains: Chain Length, Branching, Rings

Alterations in alkyl chains such as increasing or decreasing chain length, branching and changing ring size can have profound effects on the potency and pharmacologic activity of the molecule. Simply changing the length of an alkyl chain by one CH_2 unit or branching the chain will alter the lipophilic character of the molecule and therefore its absorption, distribution and excretion properties. If the alkyl chain is directly involved in the receptor interaction, then chain length and branching can alter the binding characteristics. Molecules that are conformationally flexible may become less flexible if branching is introduced at a key position of an alkyl chain. Changes in conformation will affect the spatial relationship of functional groups in the molecule, thereby influencing receptor binding. Changes as small as one CH_2 unit may seem trivial at first, but in many instances such small changes are important aspects in the design of analogs.

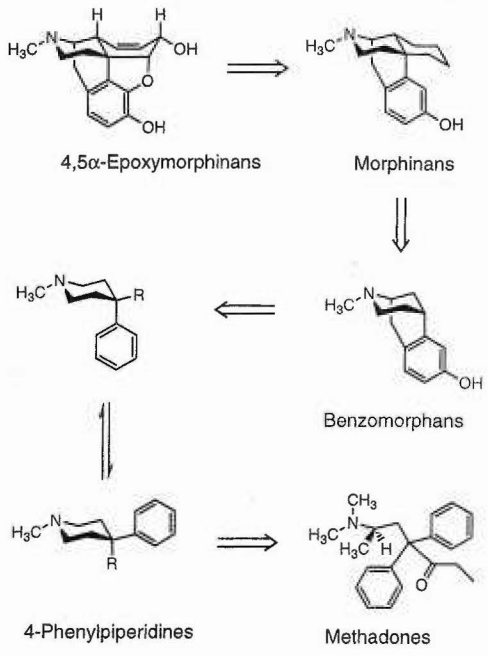
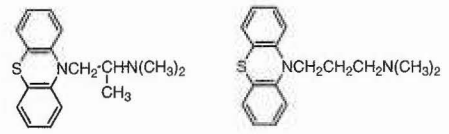


Fig. 2.30. Morphine pharmacophore and its relationship to analgesic derivatives.

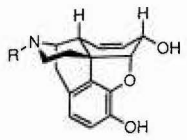
An example where simply increasing hydrocarbon chain length has significant effects not only on potency but also the agonist or antagonist action of a molecule is seen with a series of N-alkyl morphine analogs (Fig. 2.31). In this series, going from R = CH_3 (morphine) to R = $CH_2CH_2CH_3$ (N-propylnormorphine) produces a pronounced decrease in agonist activity and an increase in antagonist activity. When R = $CH_2CH_2CH_2CH_3$ (N-butylnormorphine) the compound is totally devoid of agonist or antagonist activity: i.e., the compound is inactive. However, further increases in chain length (R = $CH_2CH_2CH_2CH_2CH_3$ and R = $CH_2CH_2CH_2CH_2CH_2CH_3$) produce compounds with increasing potency as agonists. When R is β-phenylethyl the compound is a full agonist with a potency approximately 14× that of morphine (25,26).

Branching of alkyl chains can also produce drastic changes in potency and pharmacologic activity. If the mechanism of action is closely related to the lipophilicity of the molecule, then branching of a hydrocarbon chain will result in a less lipophilic compound and significantly altered biological effect. This decrease in lipophilicity as the result of hydrocarbon chain branching results from the chain becoming more compact and therefore produces less disruption of the H-bonding network of water. If the hydrocarbon chain is directly involved in receptor interactions, then branching can produce major changes in pharmacologic activity. For example, consider the phenothiazines promethazine and promazine:



The primary pharmacologic activity of promethazine is that of an antihistamine, whereas promazine is an antipsychotic. The only difference between the two is the alkylamine side chain. In the case of promethazine it contains a isopropylamine side chain while promazine has a n-propylamine. In this case the small change of one carbon atom from a branched to a linear hydrocarbon radically alters the pharmacologic activity.

Position isomers of substituents on aromatic rings may also possess different pharmacologic properties. Substituents on aromatic rings can alter the electron distribution throughout the ring which in turn can affect how the ring interacts with the receptor. Ring substituents may also influence the conformation of a flexible molecule, especially if they are located ortho to flexible side chains and



R	Pharmacologic activity
$-CH_3$	Analgesic (morphine)
$-CH_2CH_3$	Opioid agonist activity decreased
$-CH_2CH_2CH_3$	Opioid antagonist activity increased
$-CH_2CH_2CH_2CH_3$	Inactive as opioid agonist or antagonist
$-CH_2CH_2CH_2CH_2CH_3$, $-CH_2CH_2CH_2CH_2CH_2CH_3$	Opioid antagonist activity increased
$-CH_2CH_2$ 	14X potency of morphine

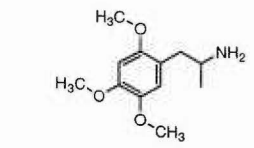
Fig. 2.31. Effect of alkyl chain length on activity of morphine.

can participate in steric or electronic intramolecular interactions (e.g., hydrogen, ion-dipole or ion-ion bonds). Ring substituents influence the conformations of adjacent substituents via steric interactions and may significantly affect receptor interactions. The observation that aromatic methoxy groups ortho to two other substituents take on a conformation perpendicular to the plane of the aromatic ring in hallucinogenic phenylalkylamines was used to explain the lack of hallucinogenic activity in these compounds (Fig. 2.32) by Knittel and Makriyannis (27).

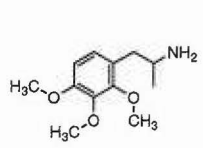
FUNCTIONAL GROUP MODIFICATION: ISOSTERISM AND BIOISOSTERISM

Isosterism

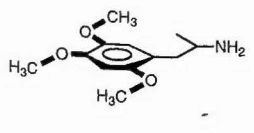
When a lead compound is first discovered for a particular disease state, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate. These may include undesirable side effects, physicochemical properties that limit bioavailability and adverse metabolic or excretion properties. These undesirable properties could be due to specific functional groups present in the molecule. The medicinal chemist therefore must modify the compound to reduce or elimi-



Potent hallucinogen



Inactive



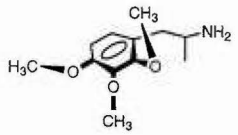


Fig. 2.32. Effect of positional isomers on structural conformation and biologic acitivity.

Table 2.7. Comparison of Physical Properties of N_2O and CO_2

Property	N_2O	CO_2
Viscosity at 20°C	148×10^{-6}	148×10^{-6}
Density of liquid at +10°C	0.856	0.858
Refractive index of liquid, D line 16°C	1.193	1.190
Dielectric constant of liquid at 0°C	1.593	1.582
Solubility in alcohol at 15°C	3.250	3.130

nate these undesirable features without losing the desired biological activity. Replacement or modification of functional groups with other groups having similar properties is known as isosteric or bioisosteric replacement.

In 1919, Langmuir first developed the concept of chemical isosterism to describe the similarities in physical properties among atoms, functional groups, radicals, and molecules (28,29). The similarities among atoms described by Langmuir primarily resulted from the fact that these atoms contained the same number of valence electrons and came from the same columns within the periodic table. This concept was limited to elements in adjacent rows and columns, inorganic molecules, ions and small organic molecules such as diazomethane and ketene. Table 2.7 shows a comparison of the physical properties of N_2O and CO_2 to illustrate Langmuir's concept.

To account for similarities between groups with the same number of valence electrons but different numbers of atoms, Grimm (30) developed his hydride displacement law. However, this is not a "law" in the strict sense, but more of an illustration of similar physical properties among closely related functional groups. Table 2.8 presents an example of hydride displacement. Descending diagonally from left to right in the table H atoms are progressively added to maintain the same number of valence electrons for each group of atoms within a column. Within each column the groups are considered to be "pseudoatoms" with respect to one another. Thus, NH_2 is considered to be isosteric to OH, etc. This early view of isosterism did not consider the actual location, motion, and resonance of electrons within the orbitals of these functional group replacements. Careful observation of this table reveals that some groups do share similar physical and chemical properties, but others have very different properties despite having the same number of valence electrons. For example, OH and NH_2 do share similar hydrogen bonding properties and should therefore be interchangeable if that is the only criterion necessary. But, the NH_2 group is basic whereas the OH is neutral. Hence, at

Table 2.8. Grimm's Hydride Displacement "Law"

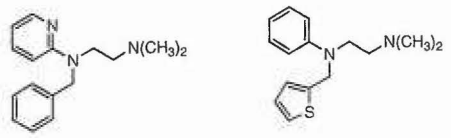
C	N	O	F	Ne
	CH	NH	OH	FH
		CH_2	NH_2	OH_2
			CH_3	NH_3

physiological pH the NH_2 group would impart a positive charge to the molecule. If OH is being substituted by NH_2 the additional positive charge could have a significant effect on the overall physico-chemical properties of the molecule in which it is being introduced. The difference in physical chemical properties of the CH_3 group relative to the OH and NH_2 groups is even greater. In addition to basicity and acidity, this "law" fails to take into account other important physical chemical parameters such as electronegativity, polarizability, bond angles, size, shape of molecular orbitals, electron density, and partition coefficients which all contribute significantly to the overall physicochemical properties of a molecule.

Instead of considering only partial structures Hinsberg (31) applied the concept of isosterism to entire molecules. He developed the concept of "ring equivalents"; groups that can be exchanged for one another in aromatic ring systems without drastic changes in physical chemical properties relative to the parent structure. Benzene, thiophene and pyridine illustrate this concept (Fig. 2.33). A −CH=CH- group in benzene is replaced by the divalent sulfur, -S-, in thiophene and a −CH= is replaced by the trivalent −N= to give pyridine. The physical properties of benzene and thiophene are very similar. For example, the boiling point of benzene is 81.1°C and that of thiophene is 84.4°C (at 760 mmHg). Pyridine, however, deviates with a boiling point of 115–116°C. Hinsberg therefore concluded that divalent sulfur (-S- or thioether) must resemble −C=C- in shape and these groups were considered to be isosteric. Note that hydrogen atoms are ignored in this comparison. Today this isosteric relationship is seen in many drugs, e.g., H_1-receptor antagonists (Fig. 2.33).

Bioisosterism

It is difficult to relate biological properties to physicochemical properties of individual atoms, functional groups or entire molecules because many physical and chemical parameters are involved simultaneously and are therefore difficult to quantitate. Simple relationships as described above often do not hold up across the many types of biological systems seen with medicinal agents. That is, what may work as an isosteric replacement in one biological system (or a given drug receptor) may not in another. Because of this it was necessary to introduce the term "bioisosterism" to describe functional groups related in structure and having similar biological effects. Friedman introduced the term bioisosterism and defined it as: "Bioisosteres are (functional) groups or molecules that have chemical and physical similarities producing broadly similar biological properties." (32) Recently Burger expanded this definition to take into account biochemical views of biological activity: "Bioisosteres are compounds or groups that possess near equal molecular shapes and volumes, approximately the same distribution of electrons, and which exhibit similar physical properties such as hydrophobicity. Bioisosteric compounds affect the same biochemically associated systems as agonist or antagonists and thereby produce biological properties that are related to each other." (33) The key point is that the same pharmacologic target is influenced by bioisoteres as agonists or antagonists. What may work as a bioisosteric group in one biological system (or receptor) may not have similar effects on another.



Tripelennamine Methaphenilene

Fig. 2.33. Isosteric substitution of thiophene for benzene and benzene for pyridine.

Classical and Nonclassical Bioisosteres

Bioisosteric groups can be subdivided into two categories: Classical and nonclassical bioisosteres. Functional groups that satisfy the original conditions of Langmuir and Grimm are referred to as classical bioisosteres. Nonclassical bioisosteres do not obey steric and electronic definitions of classical bioisoteres and do not necessarily have the same number of atoms as the substituent they replace. A wider set of compounds and functional groups are encompassed by nonclassical bioisoteres which produce, at the molecular level, qualitatively similar agonist or antagonist responses. In animals, many hormones, neurotransmitters etc. with very similar structures and biological actions can be classified as bioisosteres. An example would be the insulins isolated from various mammalian species. Even though these insulins may differ by several amino acid residues, they still produce the same biological effects. If this did not occur, the use of insulin to treat diabetes would have had to wait another 60 years for recombinant DNA technology to allow production of human insulin.

What may be a successful bioisosteric replacement for a given molecule interacting with a particular receptor in one instance, quite often has no effect or abolishes biological activity in another system. Thus, the use of bioisosteric replacement (classical or nonclassical) in drug design is highly dependent upon the biological system being investigated. No hard and fast rules exist to determine what bioisosteric replacement is going to work with a given molecule, although as the following tables and examples demonstrate, some generalizations have been possible. However, the medicinal chemist still must rely on experience and intuition in order to decide the best approach to be used when applying this strategy.

Table 2.9. Classical Bioisosteres (Groups Within the Row Can Replace Each Other)

Monovalent bioisosteres
F, H
OH, NH
F, OH, NH or CH_3 for H
SH, OH
Cl, Br, CF_3

Divalent bioisosteres
–C=S, –C=O, –C=NH, –C=C–

Trivalent atoms or groups
–C=, –N=
H
–P=, –As=

Tetrasubstituted atoms

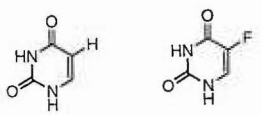
Ring equivalents

Each category of bioisostere can be further subdivided as shown below, and examples are provided in Table 2.9:

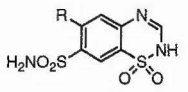
I. Classical Bioisosteres
   A. Monovalent atoms and groups
   B. Divalent atoms and groups
   C. Trivalent atoms and groups
   D. Tetrasubstituted atoms
   E. Ring equivalents
II. Nonclassical Bioisoteres
   A. Exchangeable groups
   B. Rings versus noncyclic structure

Classical Bioisoteres

Substitution of hydrogen by fluorine is one of the most common monovalent isosteric replacements. Sterically hydrogen and fluorine are quite similar with their van der Waal's radii being 1.2 and 1.35 Å, respectively. Since fluorine is the most electronegative element in the periodic table, any differences in biological activity resulting from replacement of hydrogen with fluorine can be attributed to this property. A classical example of hydrogen replacement by fluorine is development of the antineoplastic agent 5-fluorouracil from uracil.



Another example is shown in Figure 2.34 where the chlorine of chlorothiazide has been replaced with



R =	Cl	Br	CF_3
σ	+0.23	+0.23	+0.54
π	+0.71	+0.86	+0.88
E_s	−0.97	−1.16	−2.40

Fig. 2.34. Isosteric replacement of Cl in thiazide diuretics. Comparison of physical chemical properties of the substituents.

bromine and a trifluoromethyl group. For each of the substitutions the electronic (σ, where σ^+ is electron withdrawing; σ^- electron donating) and hydrophobic (π) properties of each group are maintained relatively constant while the size of each group varies significantly as indicated by the Taft steric parameter (E_s).

Figure 2.35 shows an example of classical isosteric substitution of an amino for hydroxyl group in folic acid. The amino group is capable of mimicking the tautomeric forms of folic acid and providing the appropriate hydrogen bonds to the enzyme active site.

A tetravalent bioisosteric replacement study was done by Grisar et al. (33) with a series of α-tocopherol analogues (Fig. 2.36). α-Tocopherol has been shown to scavenge lipoperoxyl and superoxide radicals and to accumulate in heart tissue. This is thought to be part of its mechanism of action for reducing cardiac damage due to myocardial infarction. All of the bioisosteric analogues were found to produce similar biological activity.

Nonclassical Bioisoteres

As mentioned earlier, nonclassical bioisosteres are replacements of functional groups not defined by classical definitions. Some of these groups though mimic spatial arrangements, electronic properties or some other physicochemical property of the molecule or functional group crit-

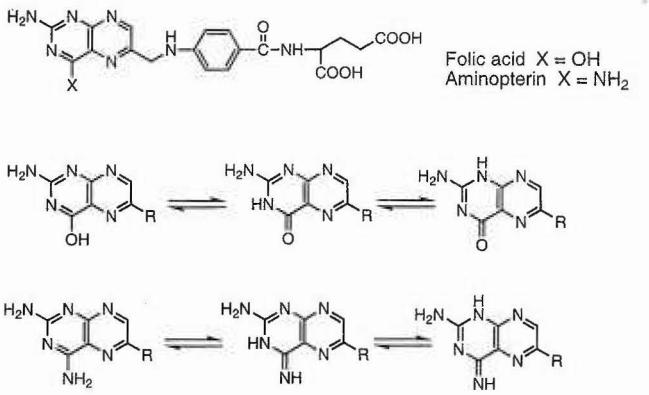


Fig. 2.35. Isosteric replacement of OH by NH_2 in folic acid and possible tautomers of folic acid and aminopterin.

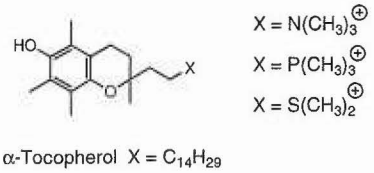


Fig. 2.36. Tetravalent bioisoseres of α-tocopherol.

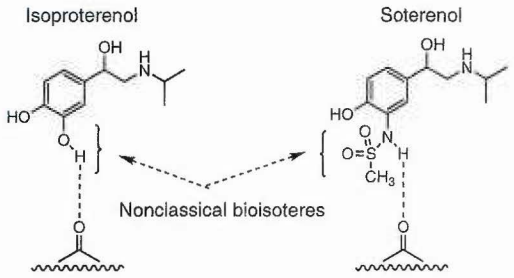


Fig. 2.38. Bioisosteric replacement of m-OH of isoproterenol with a sulfonamido group and similar hydrogen bonding capacity to a possible drug receptor.

ical for biological activity. One example is the use of a double bond to position essential functional groups into a particular spatial configuration critical for activity. This is shown with the naturally occurring hormone estradiol and the synthetic analog diethylstilbestrol in Figure 2.37. The trans isomer of diethylstilbestrol has approximately the same potency as estradiol while the cis isomer is only one-fourteenth as active. In the trans configuration the phenolic hydroxy groups mimic the correct orientation of the phenol and alcohol in estradiol (34,35). This is not possible with the cis isomer and more flexible analogs (Fig. 2.37) have little or no activity (36,37).

Another example of a nonclassical replacement is that of a sulfonamide group for a phenol in catecholamines (Fig. 2.38). With this example steric factors appear to have less influence on receptor binding than acidity and hydrogen bonding potential of the functional group on the aromatic ring. Both the phenolic hydroxyl of isoproterenol and the acidic proton of the arylsulfonamide have nearly the same pK_a values of approximately 10 (38). Both groups are weakly acidic and capable of losing a proton and interacting with the receptor as anions or participating as hydrogen bond donors at the receptor as shown in Figure 2.38). Since the replacement is not susceptible to metabolism by catechol O-methyltransferase, this replacement also has the added advantage of increasing the duration of action and making the compound orally active. Other examples of successful bioisosteric replacements are shown in Table 2.10 and a more detailed description of the role of biosisosterism can be found in the review by Patani and LaVoie (39).

SUMMARY

Medicinal chemistry involves the discovery of new chemical entities for the treatment of disease and the systematic study of the structure activity relationships of these compounds. Such studies provide the basis for development of better medicinal agents from lead compounds found via random screening, systematic screening and rational design. The role of the medicinal chemist is that of increasing the potency and duration of action of newly discovered compounds as well as decreasing adverse side effects. Without a thorough understanding of the physical chemical properties of the organic functional groups that comprise any given structure the task would be impossible.

For the pharmacist it is also important to understand the physical and chemical properties of the medicinal agents that he/she is dispensing. Not only will such knowledge help the practicing pharmacist to better understand the clinical properties of these compounds, but also to anticipate the properties of new agents that appear on the market. An understanding of the chemical properties of the molecule will allow the pharmacist to anticipate formulation problems (especially IV admixtures) as well as potential adverse interactions with other drugs as the result of serum protein binding and metabolism.

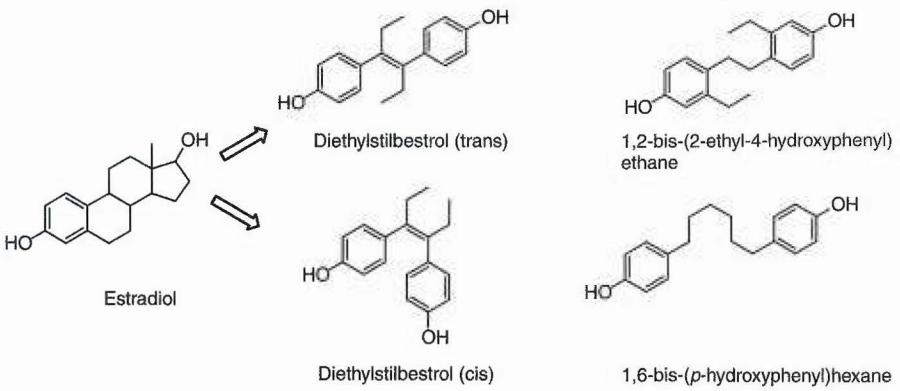
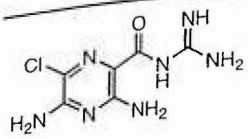
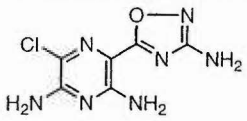
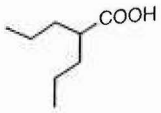
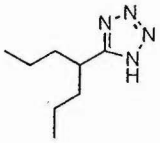
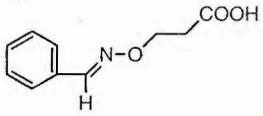
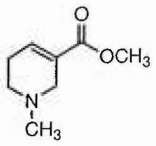
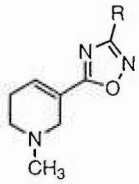
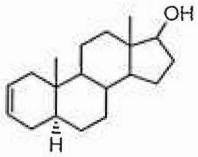
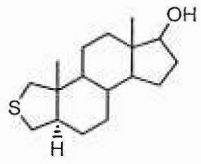
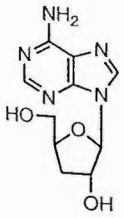
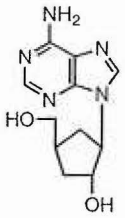
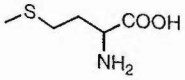
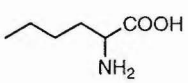


Fig. 2.37. Noncyclic analogs of estradiol.

Table 2.10. Nonclassical Bioisosteric Replacements

Compound	Bioisosteric Replacement	Reference
		40
		41
		42
		43
		44
		45
		46

Problems

The following problems are provided for additional study:

1. Calculate the percent ionization of amobarbital at pH 2.0, 5.5 and 8.0. What trend is seen?
2. Calculate the percent ionization of phenylpropanolamine at pH 2.0, 5.5 and 8.0. Compare these results with those obtained in Problem 1.
3. Calculate the percent ionization of sulfacetamide in the stomach, duodenum and ileum. Draw the structure of the predominate form of the drug in each tissue.
4. Referring to Figure 2.15, redraw each compound in its ionized form.
5. For the organic functional groups listed in Table 2.4, name each functional group and redraw them showing all potential hydrogen bonds with water.
6. Using the empiric method of Lemke, predict the water solubility for each of the following molecules. Note: Water solubility is defined as >1% solubility.

Aspirin	Carphenazine Maleate
Chlordiazepoxide	Codeine
Codeine Phosphate	Cyproheptadine Hydrochloride
Haloperidol	Phenytoin

7. Calculate the logP value for each of the following: Aspirin, Carphenazine, Codeine, Cyproheptadine, Haloperidol, Chlordiazepoxide, Phenytoin.
8. Using the Merck Index, find the chemical structures for the following empirical formulae. List as many physical chemical properties as possible for each compound and compare them within each group of isomers.

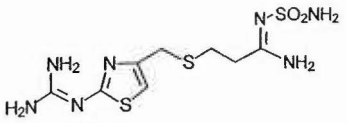
   $C_4H_{10}O_2$ C_5H_8O
   $C_5H_{11}O_2$ $C_7H_7NO_2$ $C_8H_8O_2$
   $C_{12}H_{17}NO_3$
   $C_{20}H_{30}O_2$
9. Using the Cahn-Ingold-Prelog rules, assign the absolute configuration to each chiral center of ephedrine and pseudoephedrine (Figure 2.21).
10. For the compounds shown in Figure 2.22 indicate, using an *, where the chiral centers are in each molecule.
11. Draw each possible stereoisomer for chloramphenicol and enalapril. Assign the absolute stereochemistry to each chiral center.
12. I. Draw the Newman projection along the CH_3-N bond of acetylcholine in the staggered conformation. Rotate the bond 120° and 240°. Are these rotameters conformational isomers? Explain why or why not.
    II. Repeat the above exercise with the N1–C2 bond of acetylcholine.
13. Draw the three most stable rotameters of norepinephrine. Of these rotameters, is there the possibility of an intramolecular interaction that would stabilize what would normally be considered to be an unstable rotameter? Explain.

CASE STUDY

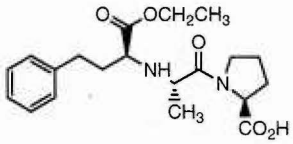
Victoria F. Roche and S. William Zito

JO, a 57-year-old male executive, arrives at the pharmacy from his annual physical with refills for his blood pressure medications (Enalapril and Amlopidine) and a new prescription for Pepcid. He wants to know if he can take all three medications at the same time.

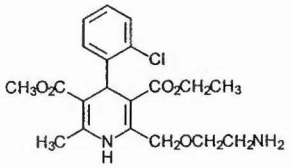
1. *Complete the table below considering all three of the drug molecules.*



Famotidine
(Pepcid)



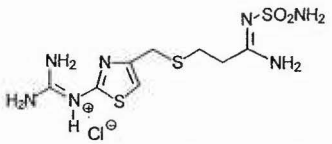
Enalapril
(Vasotec)



Amlopidine
(Norvasc)

	Amine/Guanidine	Ketone	Carboxylic Acid	Amide
Which drug(s) contain this functional group?				
Hydrophobic or hydrophilic in character?				
Acidic, basic, or neutral as drawn				
Types of interactions possible with target for drug action				
Is this group a H-bond donor, H-bond acceptor, both or neither?				

2. *Pepcid (famotidine; pKa = 10.5) is sold as a hydrochloride salt. Is the molecule as drawn acidic, basic or neutral? Given that Pepcid decreases the secretion of acid into the lumen of the stomach (stomach pH = 3.5 in presence of Pepcid), will Pepcid be ionized or unionized in the stomach?*



Famotidine hydrochloride

3. *Considering the structural features of enalapril and amlodipine, determine the ionization state of each of these agents in the stomach (pH = 1) in the absence of Pepcid and in the presence of Pepcid (pH = 3.5). Use pKa = 9 for all aliphatic amines and pKa = 3 for all carboxylic acids.*

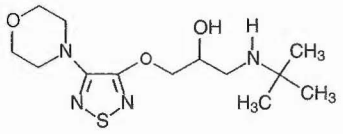
4. *Would you recommend that this patient take all three of these medications at the same time? Provide a brief rationale for your recommendation.*

5. *Enalapril is not administered as the active drug. It is readily hydrolyzed in the stomach to the active drug. Draw all of the products of hydrolysis.*

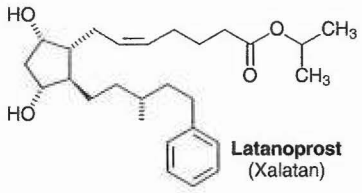
CASE STUDY

Acid/Base Chemistry, Solubility and Absorption Case

Timoptic and Xalatan are agents that are used in the treatment of glaucoma. They are both dispensed as aqueous eye drops and the target for drug action for both drugs is a receptor in the eye.



Timolol
(Timoptic)



Latanoprost
(Xalatan)

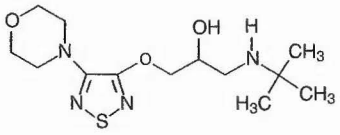
1. *What is the acid/base character of Lantanoprost as drawn?*

   Circle One: ACID BASE NEUTRAL

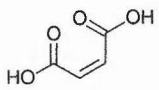
2. *What is the acid/base character of Timolol as drawn?*

   Circle One: ACID BASE NEUTRAL

3. *Timolol is actually formulated as a water-soluble salt of maleic acid. Modify the structure below to show the salt form (ionized form) of timolol. Clearly identify the acid/base character of the salt form of this drug.*



Timolol
(Timoptic)



Maleic Acid

4. *Which of the functional groups in each of these drug molecules enhance the water solubility of these drugs?*

5. *Which of these two agents would you expect to be more hydrophobic and therefore more readily absorbed into the eye? Provide a structural rationale for your answer.*

6. *One of these agents is readily hydrolyzed and cannot be delivered orally. Which agent is unstable? Draw the products of hydrolysis.*

REFERENCES

1. Crum-Brown A, Fraser TR. Trans. Roy. Soc. Edinburgh 1869;25: 151.
2. Loewi O, Navrati E. Plugers Arch. Ges. Physiol. Menshen Tiere 1926;214: 689.
3. Ariëns EJ. A General Introduction to the Field of Drug Discovery. In: Ariëns EJ, ed. Drug Design, New York, Academic Press, 1971;1: 1–270.
4. Ehrlich P. In: Himmelweit F, ed. Collected Papers of Paul Ehrlich, London, Pergamon, 1957.
5. Albert A. The Long Search for Valid Structure-Action Relationships in Drugs. J. Med. Chem. 1982;25: 1–5.
6. Ing HR. Physiol. Rev. 1936;16: 527.
7. Woods DD. Br. J. Exp. Pathol. 1940;21: 74.
8. Piutti A. Compt. Red. 1886; 103: 134–138.
9. Shinkai JH, Gennaro AR. Organic Pharmaceutical Chemistry. In: Gennaro AR, ed. Remington's Pharmaceutical Sciences, Easton, Mack Publishing Company, 1990; 356–378.
10. Lemke TL. Review of Organic Functional Groups: Introduction to Medicinal Organic Chemistry. 3rd ed. Philadelphia: Lea & Febiger, 1992.
11. Cates, LA. Calculation of Drug Solubilities by Pharmacy Students. Amer. J. Pharm. Ed. 1981;45; 11–13.
12. Fujita T. The Extrathermodynamic Approach to Drug Design. In: Hansch C, ed. Comprehensive Medicinal Chemsitry, New York, Pergamon Press, 1990; 4: 497–560.
13. Tute MS. Principles and Practice of Hansch Analysis: A Guide to Structure-Activity Correlation for the Medicinal Chemist. In: Harper NJ, Simons AB, eds. Advances in Drug Research, London, Academic Press, 1971; 6: 1–77.
14. Hansch C, Leo A. Substituent Constants for Correlation Analysis in Chemistry and Biology. New York: John Wiley, 1979.
15. Hansch C, Leo A. Exploring QSAR: Hydrophobic, Electronic and Steric Constants, Washington, D.C.: American Chemical Society, 1995.
16. MacLogP v2.0.0, BioByte Corp., Claremont, CA
17. Pruitti A. Compt. Red. 1886; 103: 134–138.
18. Easson LH, Stedman E. Studies on the Relationship Between Chemical Constitution and Physiological Action. V. Molecular Dissymmetry and Physiological Activity. Biochem. J. 1933; 27: 1257.
19. Blackwood JE, Gladys CL, Loening KL, et al. J. Amer. Chem. Soc. 1968; 90: 509–510.
20. Kemp JD, Pitzer KS. Hindered Rotation of the Methyl Groups in Ethane. J. Chem. Phys. 1936; 4: 749.
21. Bovet D. C.R. Soc. Biol. (Paris). 1937; 124: 547.
22. Laboit H, et al. Presse Med. 1952; 60: 206.
23. Charpentier P, et al. C.R. Acad. Sci. (Paris). 1952; 325: 59.
24. Delay J, et al. Ann. Med. Psychol. (Paris). 1952; 110: 112.
25. McCawley EL, Hart ER, Marsh DF. J. Amer. Chem. Soc. 1941; 63: 314.
26. Clark RL, Pessolano AA, Weijlard J, et al. J. Amer. Chem. Soc. 1953; 75: 4964.
27. Knittel JJ, Makriyannis A. Studies on Phenethylamine Hallucinogens. 2. Conformations of Arylmethoxyl Groups Using 13C NMR. J. Med. Chem. 1981; 24: 906–909.
28. Langmuir I. J. Amer. Chem. Soc. 1919; 41: 868.
29. Langmuir I. J. Amer. Chem. Soc. 1919; 41: 1543.
30. Grimm HG. Z Elekrochemie. 1925; 31: 474.
31. Hinsberg O. J. Prakt. Chem. 1916; 93: 302.
32. Friedman HL. Symposium on Chemical-Biological Correlation. Natl. Acad. Sci. Natl. Res. Council, publ. No. 206, Washington, D.C., 1951, p. 295.
33. Burger A. Isosterism and Bioisosterism in Drug Design. Progress in Drug Research. 1991; 37: 288–371.
34. Grisar JM, Marciniak G, Bolkenius FN, et al. Cardioselective Ammonium, Phosphonium and Sulfonium Analogues of α-Tocopherol and Ascorbic Acid That Inhibit in Vitro and ex Vivo Lipid Peroxidation and Scavange Superoxide Radicals. J. Med. Chem. 1995; 38: 2880–2886.
35. Dodds EC, et al. Nature 1938; 141:247.
36. Walton E, Brownlee G. Nature 1943; 151; 305.
37. Blanchard EW, et al. Endocrinology. 1943; 32: 307.
38. Baker BR. J. Amer. Chem. Soc. 1943; 65: 1572.
39. Larsen AA, Gould WA, Roth HR, et al. Sulfonanilides. II. Analogs of Catecholamines. J. Med. Chem. 1967; 10: 462–472.
40. Patani GA, LaVoie EJ. Bioisosterism: A Rational Approach in Drug Design. Chem. Rev. 1996; 96: 3147–3176.
41. Watthey JWH, Desai M, Rutledge R, et al. J. Med. Chem. 1980; 23: 690.
42. Krause JL. Pharmacol. Res. Comm. 1983; 15: 119.
43. Macchia B, Balsamo A, Lapucci A, et al. Molecular Design, Synthesis and Anti-inflammatory Activity of a Series of β-Aminoxyproionic Acids. J. Med. Chem. 1990; 33: 1423–1430.
44. Street LJ, Baker R, Book T, et al. Synthesis and Biological Activity of 1,2,4-oxadiazole Derivatives: Highly Potent and Efficacious Agonists for Cortical Muscarinic Receptors. J. Med. Chem. 1990; 33: 2690–2697.
45. Wolff Me, Zanati G. J. Med. Chem. 1969; 12: 629.
46. Schaeffer HJ, et al. J. Pharm. Sci. 1964; 53: 1368.
47. Sawyer TK, Sanfilippo PJ, Hruby VJ, et al. 4-Norleucine, 7-D-phenylalanine-α-melanocyte-stimulating hormone: A Highly Potent α-Melanotropin with Ultralong Biological Activity. Proc. Natl. Acad. Sci. USA.1980; 77: 5754–5758.