Chapter 2

Drug Design and Relationship of Functional Groups to Pharmacologic Activity

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Abbreviations

HCl, hydrochloric acid
IV, intravenous
MW, molecular weight
NaOH, sodium hydroxide
PABA, *p*-aminobenzoic acid
QSAR, quantitative structure–activity relationship
SAR, structure–activity relationship
USP, U.S. Pharmacopeia

Medicinal chemistry is an interdisciplinary science at the intersection of organic chemistry, biochemistry (bioorganic chemistry), computational chemistry, pharmacology, pharmacognosy, molecular biology, and physical chemistry. This branch of chemistry is involved with the identification, design, synthesis, and development of new drugs that are safe and suitable for therapeutic use in humans and pets. It also includes the study of marketed drugs, their biologic properties, and their quantitative structure–activity relationships (QSARs).

Medicinal chemistry studies how chemical structure influences biologic activity. As such, it is necessary to understand not only the mechanism by which a drug exerts its effect, but also how the molecular and physicochemical properties of the molecule influence the drug's pharmacokinetics (absorption, distribution, metabolism, toxicity, and elimination) and pharmacodynamics (what the drug does to the body). The term "physicochemical properties" refers to how the functional groups present within a molecule influence its acid–base properties, water solubility, partition coefficient, crystal structure, stereochemistry, and ability to interact with biologic systems, such as enzyme active sites (Chapter 8) and receptor sites (Chapter 3). To design better medicinal agents, the relative contribution that each functional group (i.e., pharmacophore) makes to the overall physicochemical properties of the molecule must be evaluated. Studies of this type involve modification of the molecule in a systematic fashion followed by a determination of how these changes affect biologic activity. Such studies are referred to as structure–activity relationships (SARs)—that is, the relationship of how structural features of the molecule contribute to, or take away from, the desired biologic activity.

Because of the foundational nature of the content of this chapter, there are numerous case studies presented throughout the chapter (as boxes), as well as at the end. In addition, a list of study questions at the conclusion of—and unique to—this chapter provides further self-study material related to the subject of medicinal chemistry/drug design.

INTRODUCTION

Chemical compounds, usually derived from plants and other natural sources, 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 of unknown constitution. 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 demonstrated that many compounds containing tertiary amine groups exhibited activity as muscle relaxants when converted to quaternary ammonium compounds. Molecules with widely differing pharmacologic properties, such as strychnine (a convulsant), morphine (an analgesic), nicotine (a deterrent, insecticide), and atropine (an anticholinergic), could be converted to muscle relaxants with properties similar to those of tubocurarine when methylated (Fig. 2.1). Crum-Brown and Fraser therefore concluded that muscle relaxant activity required the presence of a quaternary ammonium group within the 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 that related chemical structure with action as a muscle relaxant was incorrect, it demonstrated the concept that molecular structure influences the biologic activity of chemical entities and that alterations in structure produce changes in biologic action.

With the discovery by Crum-Brown and Fraser that quaternary ammonium groups could produce molecules with muscle relaxant properties, scientists began to look for other functional groups that produce specific biologic responses. At this time, it was thought that specific chemical groups, or nuclei (rings), were responsible for specific biologic effects. This led to the postulate, that 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 to be dogma and took a long time to refute.

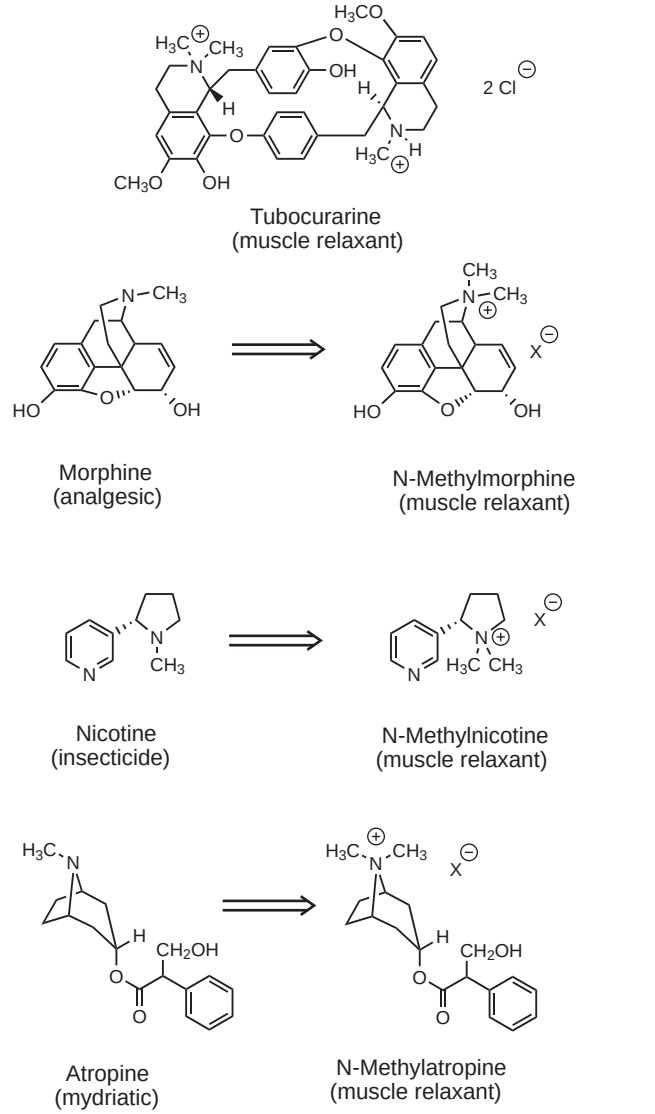


FIGURE 2.1 Effects of methylation on biologic activity.

SELECTIVITY OF DRUG ACTION AND DRUG RECEPTORS

Although the structures of many drugs or xenobiotics, or at least their functional group composition, were known at the start of the 20th century, how these compounds exerted their effects was still a mystery. Using his observations with regard to the staining behavior of microorganisms, Ehrlich (4) developed the concept of drug receptors. He postulated that certain "side chains" on the surfaces of cells were "complementary" to the dyes (or drug) and suggested that the two could therefore interact with one another. In the case of antimicrobial compounds, interaction of the chemical with the cell surface "side chains" produced a toxic effect. This concept was the first description of what later became known as the receptor hypothesis for explaining the biologic action of chemical entities. Ehrlich also discussed selectivity

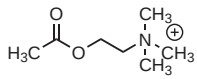


FIGURE 2.2 Acetylcholine, a neurotransmitter and muscle relaxant.

of drug action via the concept of a "magic bullet." He suggested that this selectivity permitted eradication of disease states without significant harm coming to the organism being treated (i.e., the patient). This was later modified by Albert (5) and today is referred to as "selective toxicity." An example of poor selectivity was demonstrated when Ehrlich developed organic arsenicals that were toxic to trypanosomes as a result of their irreversible reaction with thiol groups (-SH) on vital proteins. The formation of As–S bonds resulted in death to the target organism. Unfortunately these compounds were toxic not only 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—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 (see also Chapter 9). 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. (Ing did not elaborate just how this activation occurred.) The blocking effect of the larger molecule, tubocurarine, could be explained by its occupation of part of the receptor, thereby preventing acetylcholine, the smaller molecule, from interacting with 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 molecules with opposing effects on the same pharmacologic system, this appears to be a common theme: Molecules that block the effects of natural neurotransmitters, such as norepinephrine, histamine, dopamine, or serotonin for example are called antagonists and, are usually larger in size than the native compound, which is not the case for antagonists of peptide neurotransmitters and hormones such as cholecystokinin, melanocortin, or substance P. Antagonists to these peptide molecules are usually smaller in size. However, regardless of the type of neurotransmitter (biogenic amine or peptide), both agonists and antagonists share common structural features with the neurotransmitter that they influence. This provides support to the concept that the structure of a molecule, its composition and arrangement of functional groups, determines the type of pharmacologic effect that it possesses (i.e., SAR). For example, compounds that are muscle relaxants that act via the cholinergic nervous system possess a quaternary ammonium or protonated tertiary ammonium group and are larger than acetylcholine (compare acetylcholine in Fig. 2.2 with tubocurarine in Fig. 2.1).

SARs are the underlying principle of medicinal chemistry. Similar molecules exert similar biologic 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, to its biologic action. One need only peruse the structures of drug molecules in a particular pharmacologic class to become convinced (e.g., histamine H_1 antagonists, histamine H_2 antagonists, β-adrenergic antagonists). In the quest for better medicinal agents (drugs), it must be determined which functional groups within a specific structure are important for its pharmacologic activity and how these groups can be modified to produce more potent, more selective, and safer compounds.

An example of how different functional groups can yield chemical entities with similar physicochemical properties is demonstrated by the sulfanilamide antibiotics. In Figure 2.3, the structures of sulfanilamide and *p*-aminobenzoic acid (PABA) are shown. In 1940, Woods (7) demonstrated that PABA reverses the antibacterial action of sulfanilamide (and other sulfonamide-based antibacterials) and that both PABA and sulfanilamide have similar steric and electronic properties. Both molecules contain acidic functional groups, with PABA containing an aromatic carboxylic acid and sulfanilamide an aromatic sulfonamide. When ionized at physiologic 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 be no surprise that sulfanilamide acts as an antagonist to PABA metabolism in bacteria.

Biologic Targets for Drug Action

In order for drug molecules to exhibit their pharmacologic activity, they must interact with a biologic target, typically a receptor, enzyme, nucleic acid, or excitable membrane or other biopolymer. These interactions occur between the functional groups found in the drug molecule and those found within each biologic target. The relative fit of each drug molecule with its target is a function of a number of physicochemical properties including acid–base chemistry and related ionization, functional group shape and size, and three-dimensional spatial orientation. The quality of this "fit" has a direct impact on the biologic response produced. In this chapter, functional group characteristics are discussed as a means to better understand overall drug molecule absorption, distribution, metabolism, and excretion, as well as potential interaction with a biologic target.

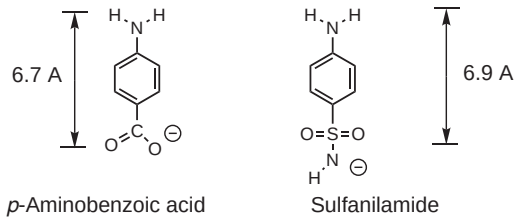


FIGURE 2.3 Ionized forms of *p*-aminobenzoic acid (PABA) and sulfanilamide, with comparison of the distance between amine and ionized acids of each compound. Note how closely sulfanilamide resembles PABA.

PHYSICOCHEMICAL PROPERTIES OF DRUGS

Acid–Base Properties

The human body is 70 to 75% water, which amounts to approximately 51 to 55 L of water for a 160-lb (73-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 solution concentration of approximately 2×10^{-6} M (2 μM). When considering the solution behavior of a drug within the body, we are dealing with a dilute solution, for which the Brönsted-Lowry (8) acid–base theory is most appropriate to explain and predict acid–base behavior. This is a very important concept in medicinal chemistry, because the acid–base properties of drug molecules have a direct effect on 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" (Eqs. 2.1 and 2.2):

Eq. 2.1

$$\underset{\text{Acid (acetic acid)}}{CH_3COOH} + \underset{\text{Base (water)}}{H_2O} \rightleftharpoons \underset{\text{Conjugate Base (acetate)}}{CH_3COO^{\ominus}} + \underset{\text{Conjugate Acid (hydronium ion)}}{H_3O^{\oplus}}$$

Eq. 2.2

$$\underset{\text{Base (methylamine)}}{CH_3NH_2} + \underset{\text{Acid (water)}}{H_2O} \rightleftharpoons \underset{\text{Conjugate Acid (methylammionium ion)}}{CH_3NH_3^{\oplus}} + \underset{\text{Conjugate Base (hydroxide ion)}}{{}^{\ominus}OH}$$

Note that when an acidic functional group loses its proton (often referred to as having undergone "dissociation"), it is left with an extra electron and becomes negatively charged. This is the "ionized" form of the acid. The ability of the ionized functional group to participate in an ion-dipole interaction with water (see the Water Solubility of Drugs section) enhances its water solubility. Many functional groups behave as acids (Table 2.1). The ability to recognize these functional groups and their relative acid strengths helps to predict absorption, distribution, excretion, and potential incompatibilities between drugs.

When a basic functional group is converted to the corresponding conjugate acid, it too becomes ionized. In this instance, however, the functional group becomes positively charged due to the extra proton. Most drugs that contain basic functional groups contain primary, secondary, and tertiary amines or imino amines, such as guanidines and amidines. Other functional groups that are basic are shown in Table 2.2. As with the acidic groups, it is important to become familiar with these functional groups and their relative strengths.

Functional groups that cannot give up or accept a proton are considered to be "neutral" (or "nonelectrolytes") with respect to their acid–base properties. Common

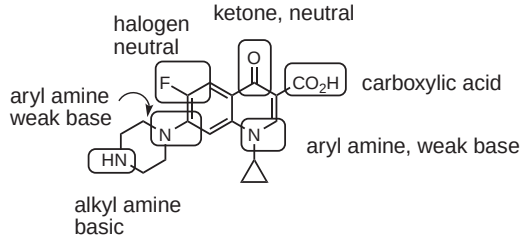
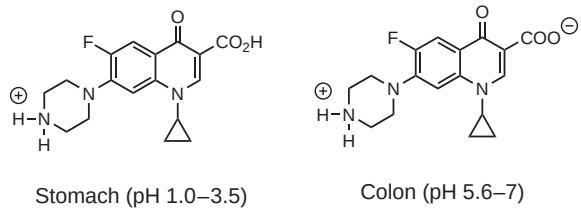


FIGURE 2.4 Chemical structure of ciprofloxacin showing the various organic functional groups.

neutral functional groups are shown in Table 2.3. Quaternary ammonium compounds are neither acidic nor basic and are not electrically neutral. Additional information about the acid–base properties of the functional groups listed in Tables 2.1 through 2.3 can be found in Gennaro (9) and Lemke (10). Review of functional groups and their acid–base properties can also be found at www.duq.edu/pharmacy/faculty/harrold/basic-concepts-in-medicinal-chemistry.cfm.

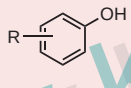
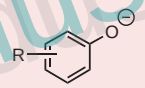
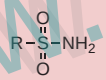
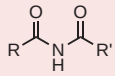
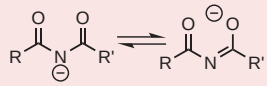
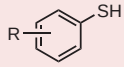
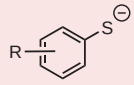
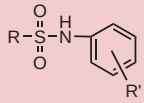
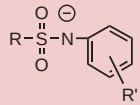
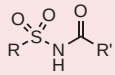
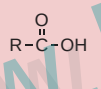
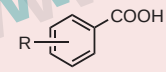
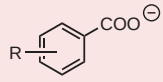
A molecule can contain multiple functional groups with acid–base properties and, therefore, can possess both acidic and basic character. For example, ciprofloxacin (Fig. 2.4), a fluoroquinolone antibacterial agent, contains a secondary alkylamine, two tertiary arylamines (aniline-like amines), and a carboxylic acid. The two arylamines are weakly basic and, therefore, do not contribute significantly to the acid–base properties of ciprofloxacin under physiologic conditions. Depending on the pH of the physiologic environment, this molecule will either accept a proton (secondary alkylamine), donate a proton (carboxylic acid), or both. Thus, it is described as amphoteric (both acidic and basic) in nature. Figure 2.5 shows the acid–base behavior of ciprofloxacin in two different environments. Note that at a given pH (e.g., pH 1.0 to 3.5), only one of the functional groups (the alkylamine) is significantly ionized. To be able to make this prediction, an appreciation for the relative acid–base strength of both the acidic and basic functional groups is required. Thus, one needs to know which acidic or basic functional group within a molecule containing multiple functional groups is the strongest and which acidic or basic functional group is the weakest. The concept of pK_a not only describes relative acid–base strength of functional groups,



Stomach (pH 1.0–3.5) Colon (pH 5.6–7)

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

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)	R–SH		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 increases as one moves down the table.

but also allows one to calculate, for a given pH, the relative percentages of the ionized and un-ionized forms of the drug. As stated earlier, this helps to predict relative water solubility, absorption, and excretion for a given compound.

Relative Acid Strength (pK_a)

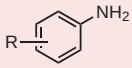
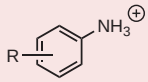
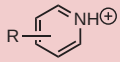
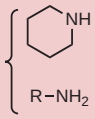
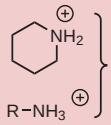
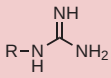
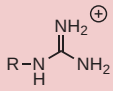
Strong acids and bases completely donate (dissociate) or accept a proton in aqueous solution to produce their respective conjugate bases and acids. For example, mineral acids, such as hydrochloric acid (HCl), or bases, such as sodium hydroxide (NaOH), undergo 100% dissociation in water, with the equilibrium between the ionized and un-ionized forms shifted completely to the right (ionized), as shown in Equations 2.3 and 2.4:

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

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

Acids and bases of intermediate or weak strength, however, incompletely donate (dissociate) or accept a proton, and the equilibrium between the ionized and un-ionized forms lies somewhere in the middle, such that all possible species can exist at any given time. Note that in Equations 2.3 and 2.4, water acts as a base in one instance and as an acid in the other. Water is therefore *amphoteric*—that is, it can act as an acid or a base, depending on the prevailing pH of the solution. From a physiologic perspective, drug molecules are always present as a dilute aqueous solution. The strongest base

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

Base (pKa)			Conjugate Acid
Arylamine (9-11)			Arylammonium
Aromatic amine (5-6)			Aromatic ammonium
Imine (3-4)			Iminium
Alkylamines (2° - 10-11) (1° - 9-10)			Alkylammonium
Amidine (10-11)			Amidinium
Guanidine (12-13)			Guanidinium

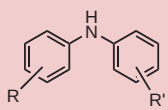
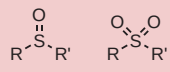
that is present is OH^-, and the strongest acid is H_3O^+. This is known as the "leveling effect" of water. Thus, some functional groups that have acidic or basic character do not behave as such under physiologic conditions in aqueous solution. For example, alkyl alcohols, such as ethyl alcohol, are not sufficiently acidic to become significantly ionized in an aqueous solution at a physiologically pH. Water is not sufficiently basic to remove the proton from ethyl alcohol to form the ethoxide ion (Eq. 2.5). Therefore, under physiologic conditions, alcohols are neutral with respect to acid–base properties:

Eq. 2.5 $$CH_3CH_2OH + H_2 \not\rightleftharpoons CH_3CH_2O^- + H_3O^{\oplus}$$

Predicting the Degree of Ionization of a Molecule

By knowing if there are acidic and/or basic functional groups present in a molecule, one can predict

TABLE 2.3 Common Organic Functional Groups That are Considered Neutral Under Physiologic Conditions

$R–CH_2–OH$			
Alkyl alcohol	Ether	Ester	Sulfonic acid ester
		R–C≡N	
Amide	Diarylamine	Nitrile	Quaternary ammonium
			
Amine oxide	Ketone & Aldehyde	Thioether	Sulfoxide Sulfone

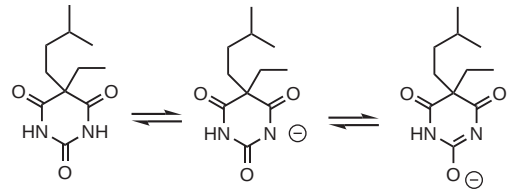
whether a molecule is going to be predominantly ionized or un-ionized at a given pH. To be able to quantitatively predict the degree of ionization of a molecule, the pK_a values of each of the acidic and basic functional groups present and the pH of the environment in which the molecule will be located must be known. The magnitude of the pK_a value is a measure of relative acid or base strength, and the Henderson-Hasselbalch equation (Eq. 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 Fig. 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-Hasselbalch equation for calculating percent ionization is to realize that this equation relates a constant, pK_a, to the ratio of the acidic form of a functional group to its conjugate base form (and conversely, the conjugate acid form to its base). Because pK_a is a constant for any given functional group, the ratio of acid to conjugate base (or conjugate acid to base) will determine the pH of the solution. A sample calculation is shown in Figure 2.6 for the sedative hypnotic amobarbital.

When dealing with a basic functional group, one must recognize the conjugate acid represents the ionized form of the functional group. Figure 2.7 shows the calculated percent ionization for the decongestant phenylpropanolamine. It is very important to understand that for a base, the pK_a refers to the conjugate acid or ionized form of the compound. To thoroughly comprehend this relationship, calculate the percent ionization of an acidic functional group and a basic functional group at different pH values and carefully observe the trend.



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

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

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

$$10^{0.6} = \frac{[\text{acid}]}{[\text{base}]} = \frac{3.98}{1}$$

$$\% \text{ acid form} = \frac{3.98 \times 100}{4.98} = 79.9\%$$

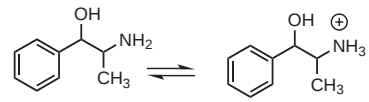
FIGURE 2.6 Calculation of percent ionization of amobarbital. Calculation indicates that 80% of the molecules are in the acid (or protonated) form, leaving 20% in the conjugate base (ionized) form.

Water Solubility of Drugs

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

Hydrogen Bonds

Each functional group capable of donating or accepting a hydrogen bond contributes to the overall water solubility of the compound and increases the hydrophilic (water-loving) nature of the molecule. Conversely, functional groups that cannot form hydrogen bonds do not enhance hydrophilicity and will contribute to the hydrophobic (water-fearing) nature of the molecule. Hydrogen bonds are a special case of what are usually referred to as dipole–dipole interactions. A permanent dipole occurs as a result of an unequal sharing of electrons between the two atoms within a covalent bond. This unequal sharing of electrons only occurs when these two atoms have significantly different electronegativities. When a permanent dipole is present, a partial charge is associated



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

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

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

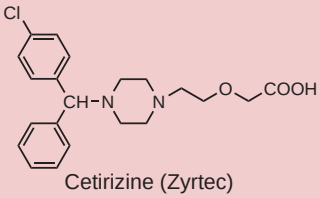
$$10^{2} = \frac{[\text{acid}]}{[\text{base}]} = \frac{100}{1}$$

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

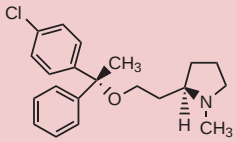
FIGURE 2.7 Calculation of percent ionization of phenylpropanolamine. Calculation indicates that 99% of the molecules are in the acid form, which is the same as the percent ionization.

ABSORPTION/ACID–BASE CASE

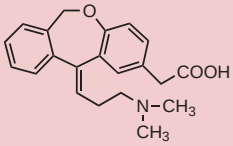
A long-distance truck driver comes into the pharmacy complaining of seasonal allergies. He asks you to recommend an agent that will act as an antihistamine but that will not cause drowsiness. He regularly takes TUMS for indigestion due to the bad food that he eats while on the road.



Cetirizine (Zyrtec)



Clemastine (Tavist)

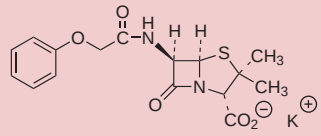


Olopatadine (Patanol)

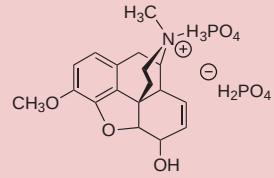
1. Identify the functional groups present in Zyrtec and Tavist, and evaluate the effect of each functional group on the ability of the drug to cross lipophilic membranes (e.g., blood–brain barrier). Based on your assessment of each agent's ability to cross the blood–brain barrier (and, therefore, potentially 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 present in the box 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 (stomach [pH 1] or intestine [pH 6 to 7]) will each of these two drugs be best absorbed?
4. TUMS neutralizes stomach acid to pH 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 that he takes his TUMS. Provide a rationale for your answer.

ACID–BASE CHEMISTRY/COMPATIBILITY CASES

The intravenous (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 is not certain how water soluble the agents are.



Penicillin V Potassium



Codine 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.

with each of these atoms along a single bond (one atom has a partial negative charge, and one atom has a partial positive charge). The atom with a partial negative charge has higher electron density than the other atom. When two functional groups that contain one or more permanent 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 bonding interaction to occur, at least one functional group must contain a dipole with an electropositive hydrogen. The hydrogen atom must be covalently bound to an electronegative atom, such as oxygen (O), nitrogen (N), sulfur (S), or selenium (Se). Of these four elements, only oxygen and nitrogen atoms contribute significantly to the dipole, and we will therefore concern ourselves only with the hydrogen-bonding capability (specifically as hydrogen bond donors) of functional groups that contain a bond between oxygen and hydrogen atoms (e.g., alcohols) and functional groups that contain a bond between nitrogen and hydrogen atoms (e.g., primary and secondary amines and amides) (e.g., NH and CONH groups).

Even though the energy associated with each hydrogen bond is small (1 to 10 kcal/mol/bond), it is the additive nature of multiple hydrogen bonds that contributes to the overall water solubility of a given drug molecule. This type of interaction is also important in the interaction between a drug and its biologic target (e.g., receptor). Figure 2.8 shows several types of hydrogen bonding interactions that can occur with a couple of functional groups and water. As a general rule, the more hydrogen

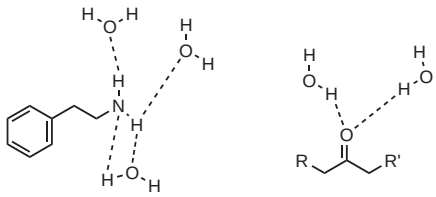


FIGURE 2.8 Examples of hydrogen bonding between water and hypothetical drug molecules.

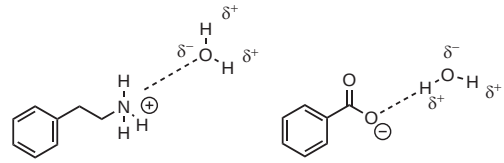


FIGURE 2.9 Examples of ion–dipole interactions.

bonds that are possible between a drug molecule and water, the greater the water solubility of the molecule. Table 2.4 lists several common functional groups and the number of hydrogen bonds in which they can potentially participate. Note that this table does not take into account the possibility of intramolecular hydrogen bond formation. Each intramolecular hydrogen bond decreases water solubility (and increases lipid solubility) because there is one less interaction possible with water.

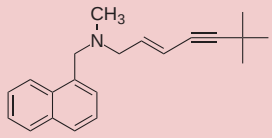
Ionization

In addition to the hydrogen-bonding capacity of a molecule, another type of interaction plays an important role in determining water solubility: the ion–dipole interaction. This type of interaction can occur with organic salts. Ion–dipole interactions occur between either a cation and the partially negatively charged atom found in a permanent dipole (e.g., the oxygen atom in water) or an anion and the partially positively charged atom found in a permanent dipole (e.g., the hydrogen atoms in water) (Fig. 2.9).

Organic salts are composed of a drug molecule in its ionized form and an oppositely charged counterion. For example, the salt of a carboxylic acid is composed of the carboxylate anion (ionized form of the functional group) and a positively charged ion (e.g., Na^+) and the salt of a secondary amine is composed of the ammonium cation (ionized form of the functional group and a negatively charged ion; e.g., Cl^-). Not all organic salts are very water soluble. To associate with enough water molecules to become soluble, the salt must be highly dissociable; in other words, the cation and anion must be able to separate and interact independently with water molecules. Highly dissociable salts are those formed from strong acids with strong bases (e.g., sodium chloride), weak acids with strong bases (e.g., sodium phenobarbital), or strong acids with weak bases (e.g., atropine sulfate). Examples of strong acids (strong acids are 100% ionized in water [i.e., no ionization constants or pK_a values of <1]) include the hydrohalic (hydrochloric, hydrobromic, and hydrofluoric), sulfuric, nitric, and perchloric acids. All other acids (e.g., phosphoric, tartaric, acetic, and other organic acids, and phenols) are partially ionized with pK_a values from 1 to 14 and are, therefore, considered to be moderate or weak acids. Hydroxides of sodium, potassium, and

ABSORPTION/BINDING INTERACTIONS CASE

A 24-year-old man comes into the pharmacy and asks you to recommend 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 (terbinafine), 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 used topically.
2. The biologic target of 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?

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
	2

calcium are strong bases because they are 100% ionized, whereas other bases, such as amines, are of moderate or weak strength. The salt formed by a carboxylic acid with an alkylamine is the salt of a weak acid and weak base, respectively. This salt does not dissociate appreciably and cannot significantly contribute to the overall water solubility of a given drug molecule. In general, low molecular weight salts are water soluble, and high molecular weight salts are water insoluble. Examples of common organic salts used in pharmaceutical preparations are provided in Figure 2.10.

The extent to which ionized molecules are soluble in water is also dependent on the presence of intramolecular ionic interactions. Molecules with ionizable functional groups of opposite charges have the potential to interact with each other rather than with water molecules. When this occurs, these molecules often become water insoluble. A classic example is the amino acid tyrosine (Fig. 2.11). Tyrosine contains three very polar functional groups, two of which are ionizable (the alkylamine and carboxylic acid) depending on the pH of the environment.

The phenolic hydroxyl group is also ionizable (pK_a 9 to 10); however, it does not contribute significantly to the ionization of tyrosine under pharmaceutically or physiologically relevant conditions (<1% ionized at pH 7). Because of the presence of three very polar functional groups (two of them being ionizable), one would expect tyrosine to be very soluble in water, yet its solubility is

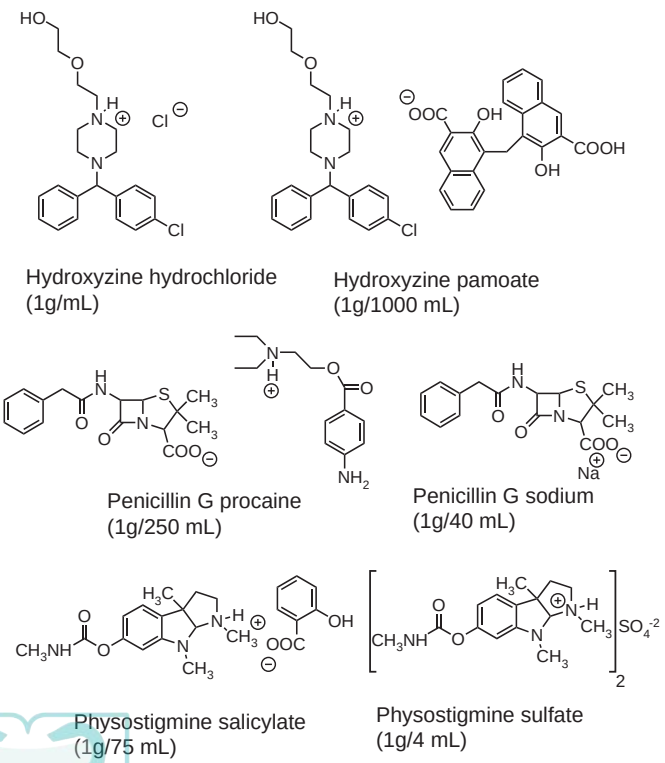


FIGURE 2.10 Water solubilities of different salt forms of selective drugs.

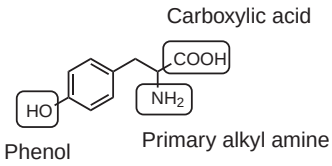


FIGURE 2.11 Organic functional groups in tyrosine (see text for pK_a values).

only 0.45 g/1,000 mL. The basic alkylamine (pK_a 9.1 for the conjugate acid) and the carboxylic acid (pK_a 2.2) are both ionized at physiologic pH, and a zwitterionic molecule results. These two charged groups are sufficiently close that a strong ion–ion interaction occurs, thereby keeping each group from participating in ion–dipole interactions with surrounding water molecules. This lack of interaction between the ions and the dipoles found in water results in a molecule that is very water insoluble (Fig. 2.12). Not all zwitterions or multiply charged molecules demonstrate this behavior; only those that contain ionized functional groups close enough for an ionic interaction to occur will be poorly soluble. Generally, the greater the separation between charges, the more highly water soluble one anticipates the molecule will be. This is only true, however, up to a certain number of carbon atoms. This will be discussed in more detail later.

Predicting Water Solubility: The Empirical Approach

Lemke (10) developed an empiric approach to predicting the water solubility of molecules based on the carbon-solubilizing potential of several functional groups. In his approach, 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 considered to be water insoluble. Participation in intramolecular hydrogen bonding or ionic interactions decreases the solubilizing potential of a given functional group. It is difficult to quantitate how much such interactions will decrease a molecule's overall water solubility.

Table 2.5 shows the water-solubilizing potential for several functional groups common to many drugs. Because most drug molecules contain more than one functional group (i.e., are polyfunctional), the second column in the table will be of more utility. To demonstrate Lemke's method, consider the structure of anileridine. Anileridine (Fig. 2.13) is an opioid analgesic that contains three functional groups that contribute to water

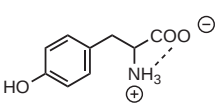
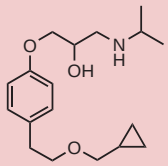


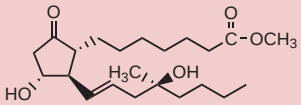
FIGURE 2.12 Zwitterionic form of tyrosine showing ion–ion bond.

BINDING INTERACTIONS CASE

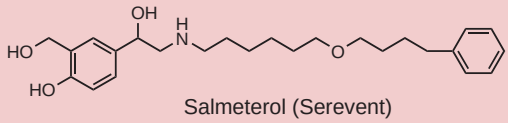
Each of these drug molecules interacts with a different biologic target and elicits a unique pharmacologic response. For each of the three molecules, list the types of interactions that are possible with a biologic target. For each type of interaction, provide one example of an amino acid that could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



Betaxolol (Betoptic)



Misoprostol (Cytotec)



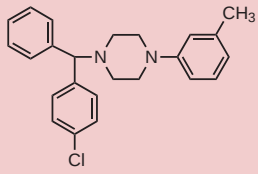
Salmeterol (Serevent)

Example: Binding interaction: Van der Waals
Amino acid: Leucine

WATER/LIPID SOLUBILITY CASE

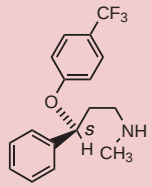
When you look at any drug molecule, there are a number of functional groups present that contribute to the properties of that drug molecule. Identify the types of functional groups in each molecule and to which physical properties (water/lipid solubility) each contributes.

1. Structural feature Physical property



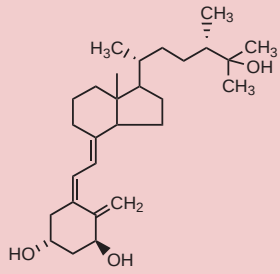
Meclizine (Antivert)

2. Structural feature Physical property



Fluoxetine (Prozac)

3. Structural feature Physical property



1,25-Dihydroxy Vit D_2

solubility: an aromatic amine (very weak base), a tertiary alkylamine (weak base), and an ester (neutral). There are a total of 21 carbon atoms in the molecule and a solubilizing potential from the three functional groups of nine carbon atoms. Since the solubilizing potential of the functional groups is less than the total number of carbons that are present, it is predicted that anileridine is insoluble in water. This is, indeed, the case: The solubility of anileridine is reported in the U.S. Pharmacopeia (USP) as 1 g/10,000 mL, or 0.01%. Now consider the hydrochloride salt of anileridine. Not only do the three functional groups contribute a solubilizing potential of nine carbon atoms, the positive charge of the alkylammonium contributes also to its water solubility. Lemke (10) estimates that each ionized functional group (cationic or anionic) found within a drug molecule contributes a solubilizing potential of 20 to 30 carbon atoms. Thus, the solubilizing potential for all of the functional groups in anileridine hydrochloride is 29 to 39 carbon atoms, which is more than the total number of carbon atoms in the molecule. This salt should therefore be soluble in water, and it is (to the extent of 0.2 g/mL, or 20%).

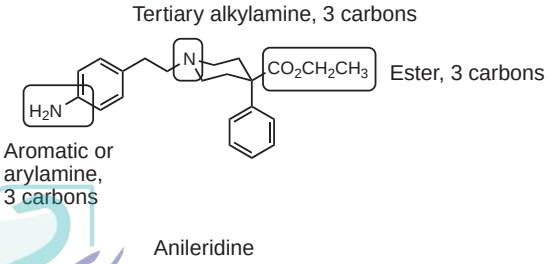
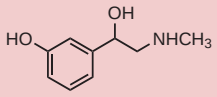


FIGURE 2.13 Identification of functional groups in anileridine.

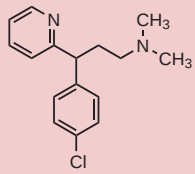
INTERACTIONS/SOLUBILITY CASE

J.K. presents a prescription for her 6-month-old daughter for Donatussin Drops. She wants to know if this medication will have an effect on her daughter's alertness.

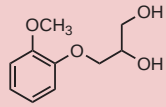
Components of Donatussin:
Phenylephrine (decongestant)
Chlorpheniramine (antihistamine)
Guaifenesin (expectorant)



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).
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 biologic 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.

Problem 6, found at the end of the chapter, provides an additional opportunity to use this approach to predict water solubility. Solubility data for these drug molecules can be found in the USP. In most instances, discrepancies between approximate and actual water solubilities can be rationalized by careful inspection of the chemical structure.

Predicting Water Solubility: Analytical/Quantitative Approach

Another method for predicting water solubility involves calculation of 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, a brief explanation of the concept of partition coefficient is necessary.

TABLE 2.5 Water-solubilizing Potential of Organic Functional Groups 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 greater than 1% solubility (9).

Eq. 2.7 $$P = C_{oct}/C_{water}$$

In its simplest form, the partition coefficient, P, refers to the ratio of drug concentration in octanol (C_{oct}) to that in water (C_{water}) (Eq. 2.7). Octanol is used to mimic the amphiphilic nature of lipid, because it has a polar head group (primary alcohol) and a long hydrocarbon chain, or tail, similar to the fatty acid tail that makes up part of a lipid membrane. Because P is logarithmically related to free energy (12), P is generally expressed as logP and is, therefore, the sum of the hydrophobic and hydrophilic characteristics of the functional groups that make up the structure of the molecule. Thus, logP is a measure of the lipid/water solubility characteristics of the entire molecule. Because each functional group contained within the molecule contributes to the overall hydrophilic/hydrophobic character of the molecule, a hydrophilic/hydrophobic value (the hydrophobic substituent constant, π) can be assigned to each functional group. Equation 2.8 defines this relationship:

Eq. 2.8 $$\text{LogP} = \Sigma\pi \text{ (fragments)}$$

When calculating logP from hydrophobic substituent constants, the sum is usually referred to as logP_{calc} or ClogP [for software sources to calculate ClogP, see (16)] to distinguish it from an experimentally determined value (MlogP or logP_{meas}). Over the years, extensive tables

of π values have been compiled for organic functional groups and molecular fragments (12–15). Table 2.6 is a highly abbreviated summary of π values from Lemke (10), based largely on the manuscript by Cates (11). Using the values in this table, a fairly reasonable estimate for the water solubility of many organic compounds (shown as logP) can be determined.

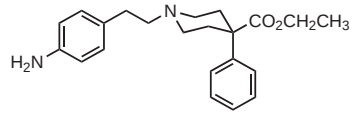
Again we will consider the structure of the opioid analgesic anileridine to demonstrate the calculation of logP (Fig. 2.13). This compound has a total of 22 carbon atoms, some aliphatic and some aromatic. We need to distinguish between the aliphatic and aromatic carbon atoms because the delocalized π orbitals for the sp^2 hybridized aromatic carbon atoms make them more polar than aliphatic carbons. The compound also contains one tertiary alkylamine, one aromatic or aryl amine, and one ester. Evaluation of esters and amides requires that the oxygen, nitrogen, and ester/amide carbon atoms are counted in this π value. The remaining aliphatic carbons are then counted. Figure 2.14 summarizes the logP calculation for anileridine. The calculation gives a ClogP value for anileridine of +4.8. Water solubility as defined by the USP is solubility greater than 3.3%, which equates to an approximate logP of +0.5. LogP values less than +0.5 are therefore considered to be water soluble, and those greater than +0.5 are considered to be 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 (16) are included for comparison purposes (see Appendix A for additional ClogP values). Even though the π values from Table 2.6 are not as extensive as those in the computer program, there is good general agreement with most of these compounds with respect to their solubility (or insolubility) in water. In addition, other programs besides ClogP are available to predict logP values; some of these programs are available on the Internet. One must keep in mind that due to the assumptions made in these programs, they cannot produce results that are in total agreement with measured values or other prediction programs. ClogP values calculated from ACDLogP (16) are generally more accurate. Other programs for calculating logP values, such as Molinspiration (17) and Interactive Analysis (18), use different methods and assumptions and, therefore, do not always agree with ClogP predictions or experimentally determined values. This is not to say that the latter two programs do not give accurate results. Often, one or all of the programs will have reasonable agreement with measured values, but greater disagreement tends to occur as the number of functional groups in the molecule that participate as hydrogen-bond acceptor and/or hydrogen-bond donor groups increases. This increases the likelihood that intramolecular interactions will occur—something that is not always taken into account with these programs.

TABLE 2.6 Hydrophilic-lipophilic Values (πV) for Organic Fragments (10)

Functional Group	π value (aliphatic)	π value (aromatic)
H		0.00
Alkane	0.50	0.56 (CH_3); 1.02 (CH_2CH_3)
Alkene		0.82
C_6H_5 (phenyl)	2.15	1.96
Br, Cl, F, I	0.60; 0.39; −0.17; 1.00	0.86; 0.71; 0.14; 1.12
NO_2	−0.85	−0.28
NH_2 (primary amine)	−1.19	−1.23
NHR (secondary amine)	−0.67	0.47
NR_2 (tertiary amine)	−0.30	0.18
-NHC=OR (amide)	−0.97	
SC_6H_5	2.32	
OH	−1.12	−0.67
OCH_3		−0.02
-OC=OR (ester)	−0.27	−0.64
CHO (aldehyde)		−0.65
$C{=}OCH_3$ (ketone)		−0.55
CO_2H		−0.32
SO_2NH_2 (sulfonamide)		−1.82

The ability to predict the percent ionization or water solubility of a molecule should not be viewed as an exercise in arithmetic, but rather as a way to understand the solution behavior of molecules, especially as it relates to admixtures and the pharmacokinetic differences among molecules. The ionization state of a molecule not only influences its water solubility, but also its ability to traverse



Fragments	π
1 primary alkylamine	-1.23
1 teriary alkylamine	-0.30
9 aliphatic carbons	+4.5
2 phenyl rings	+4.30
1 ester	-0.27
logP	+7.0

FIGURE 2.14 Calculation of logP for anileridine.

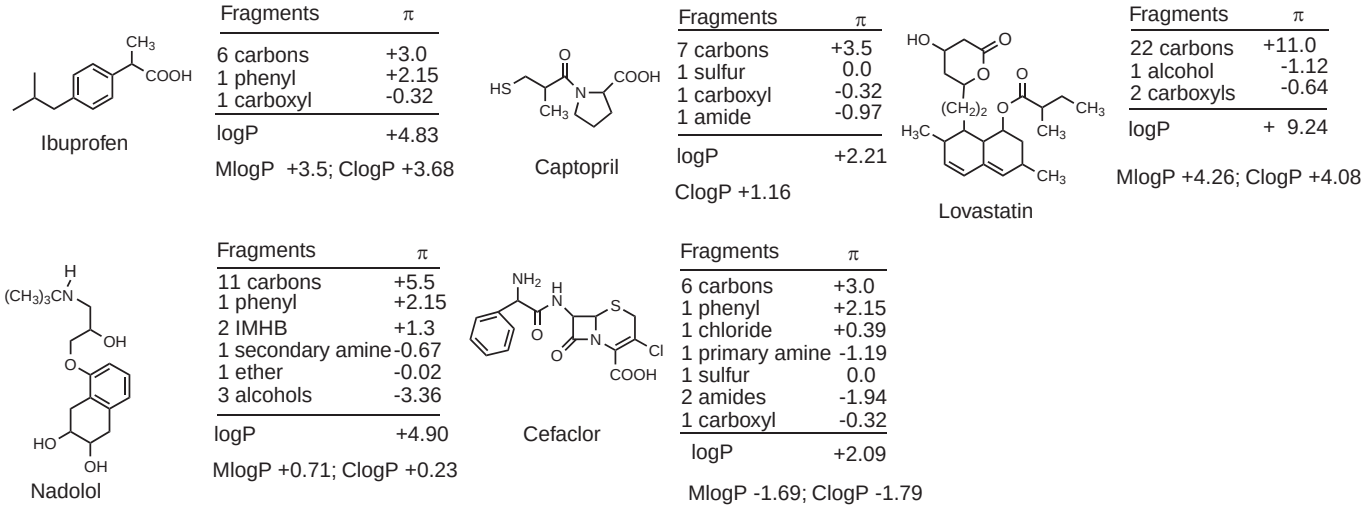


FIGURE 2.15 ClogP calculations for selected compounds.

membranes and, therefore, its ability to be absorbed. The distribution of the drug and its ability to bind to proteins other than its target are also greatly influenced by the ionization state and the hydrophilic/hydrophobic nature of the molecule.

STEREOCHEMISTRY AND DRUG ACTION

Stereoisomers are molecules that contain the same number and kinds of atoms, the same arrangement of bonds, but different three-dimensional structures; in other words, they only differ in the three-dimensional arrangement of atoms in space. There are two types of stereoisomers: enantiomers and diastereoisomers. Enantiomers are pairs of molecules for which the three-dimensional arrangement of atoms represents nonsuperimposable mirror images. Diastereoisomers represent all of the other stereoisomeric compounds that are not enantiomers. Thus, the term "diastereoisomer" includes compounds that contain double bonds (geometric isomers) and ring systems. Unlike enantiomers, diastereoisomers exhibit different physicochemical properties, including, but not limited to, melting point, boiling point, solubility, and chromatographic behavior. These differences in physicochemical properties allow the separation of individual diastereoisomers from mixtures with the use of standard chemical separation techniques, such as column chromatography or crystallization. Enantiomers cannot be separated using such techniques unless a chiral environment is provided or if they are first converted to diastereoisomers (e.g., salt formation with another enantiomer). Examples of enantiomers and diastereoisomers are provided in Figure 2.16.

The physicochemical properties of a drug molecule are dependent not only on what functional groups are present in the molecule but also on the spatial arrangement of these groups. This becomes an especially important factor when the environment that a molecule is in is asymmetric, such as the human body. Proteins and other biologic targets are asymmetric in nature. How a particular drug molecule interacts with these macromolecules is determined by the three-dimensional orientation of the functional groups present. If critical functional groups in the drug molecule do not occupy the proper spatial region, then productive interactions with the biologic target will not be possible. As a result, it is possible that the desired pharmacologic activity will not be achieved. If, however, the functional groups within a drug molecule are located in the proper three-dimensional orientation, then the drug can participate in multiple key interactions with its biologic target. It is important to understand not only which functional groups contribute to the pharmacologic activity of a drug, but also the importance of the three-dimensional nature of these functional groups in predicting drug potency and potential side effects.

Approximately one in every four drugs currently on the market is some type of isomeric mixture. For many of these drugs, the biologic activity can only reside in one isomer (or at least predominate in one isomer). The majority of these isomeric mixtures are termed "racemic mixtures" (or "racemates"). A racemic mixture is comprised of equal amounts of both of the possible drug enantiomers. As mentioned earlier in this chapter, when enantiomers are introduced into an asymmetric, or chiral, environment, such as the human body, they display different physicochemical properties. This can lead to significant differences in their pharmacokinetic and pharmacodynamic behavior, resulting in adverse side effects or toxicity. For example, the individual isomers in a racemic mixture can exhibit significant differences in absorption (especially active transport), serum protein binding, and metabolism. As it relates to drug metabolism, it is certainly possible that only one of the

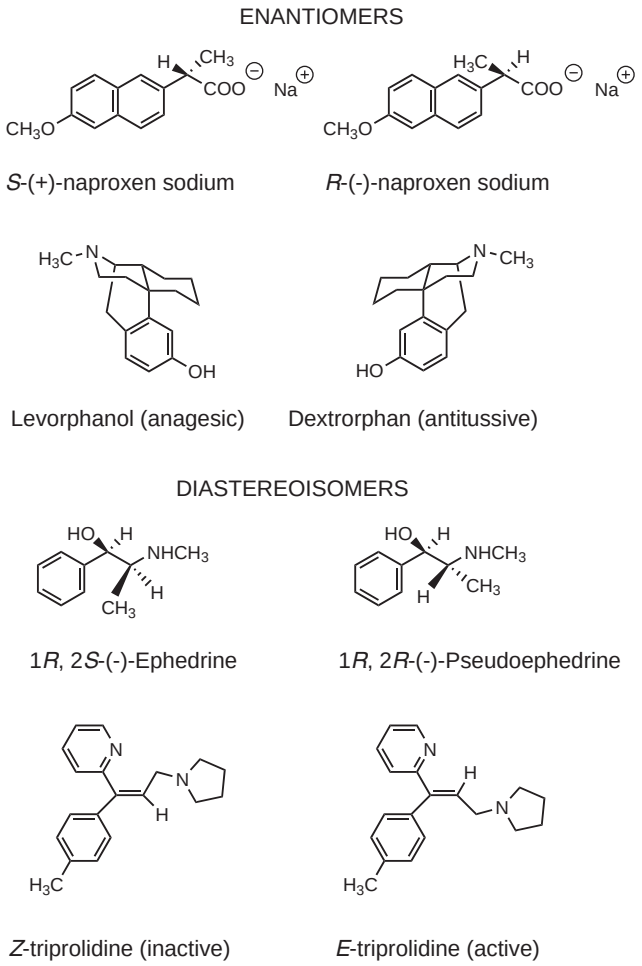


FIGURE 2.16 Examples of stereoisomers.

isomers can be converted into a toxic substance or can influence the metabolism of another drug (Chapter 4). Since stereochemistry can have a profound effect on both the pharmacokinetic and pharmacodynamic properties of a drug, it is important to review the foundational concepts

Stereochemical Definitions

Designation of Absolute Configuration

At first, enantiomers were distinguished by their ability to rotate the plane of polarized light. Isomers that rotate the plane of polarized light to the right, or in a clockwise direction, were designated as dextrorotatory, indicated by a (+)- sign before the chemical name [e.g., (+)-amphetamine or dextroamphetamine]. The opposite designation, levorotatory or (−)-, was assigned to molecules that rotate the plane of polarized light to the left, or in a counterclockwise direction. The letters *d*- and *l*- were formerly used to indicate (+)- and (−)-, respectively. A racemate (racemic mixture)—that is, a 1:1 mixture of enantiomers—is indicated by placement of a (±)- before the compound name. This nomenclature is based on a

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 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?

physical property of the molecule and does not describe the absolute configuration or three-dimensional arrangement of atoms around the chiral center.

In the late 19th century, Fisher and Rosanoff developed a system of nomenclature based on the structure of glyceraldehyde (Fig. 2.17). Since there were no methods at that time to determine the absolute three-dimensional arrangement of atoms in space, the two isomers of glyceraldehyde were arbitrarily assigned the designation of D-(+)- and L-(−). It was not until the 1950s that the absolute configurations of these molecules were determined (Fisher had fortuitously guessed correctly). The configurations of other molecules were then assigned based on their relationship to D- or L-glyceraldehyde via synthetic methods or chemical degradation. Thus, via chemical degradation, it was possible to determine that (+)-glucose, (−)-2–deoxyribose, and (−)-fructose had the same terminal configuration as D-(+)-glyceraldehyde and, therefore, were assigned the D-absolute configuration. Amino acid configurations were assigned based on their relationship to D-(+)- and L-(−)-serine (Fig. 2.17). Unfortunately, this system becomes very cumbersome with molecules that contain more than one chiral center.

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 (pK_a) 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 biologic target: good fit or not?
Stability and bioavailability: route of administration

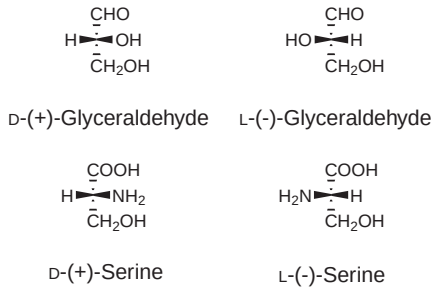
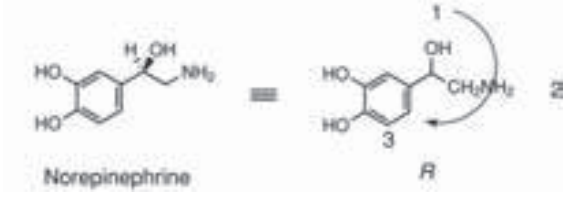


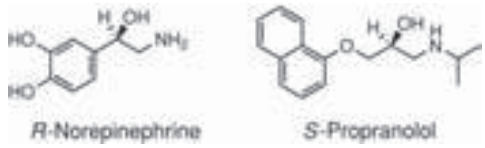
FIGURE 2.17 Relationship of optical isomers of serine to D- and L-glyceraldehyde.

In 1956, a new system of stereochemical nomenclature was introduced by Cahn et al. (19) and is known as the Sequence Rule or CIP system. With this system, atoms attached to a chiral center are ranked based on their atomic number. Highest priority is given to the atom with the highest atomic number, and subsequent atoms are ranked accordingly, from highest to lowest. When a decision cannot be made in the assignment of priority—for example, two atoms with the same atomic number attached to the chiral center—this evaluation extends to the next atom until a priority can be established. When the molecule is then viewed from the side opposite to the lowest-priority atom, the priority sequence from highest to lowest can then be determined. If the priority sequence proceeds to the right, or in a clockwise direction, the chiral center is designated with an *R*-absolute configuration. The designation is *S* when the priority sequence proceeds to the left, or in a counterclockwise direction. An example of this is seen in the neurotransmitter norepinephrine.



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

It should be noted that the CIP nomenclature system uses a set of arbitrary rules and, therefore, should be viewed as a system that tracks absolute configuration only. In many instances, two molecules can have different absolute configurations as designated by the CIP system, but the same relative orientation of the functional groups relevant for biologic activity. An example of this is demonstrated when the absolute configuration of the nonselective β-adrenergic antagonist propranolol is compared to norepinephrine. Because of the presence of the ether oxygen atom, 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. Close inspection of both *R*-norepinephrine and *S*-propranolol, however, shows that the hydroxy group, basic amine, and aromatic rings of both compounds occupy the same regions in three-dimensional space.



Stereochemistry and Biologic Activity

Easson-Stedman Hypothesis

In 1886, Piutti (20) reported different physiologic actions for the enantiomers of asparagine, with (+)-asparagine having a sweet taste and (−)-asparagine a bland one. This was one of the earliest observations that enantiomers can exhibit differences in biologic action. In 1933, Easson and Stedman (21) reasoned that differences in biologic 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, the letters 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

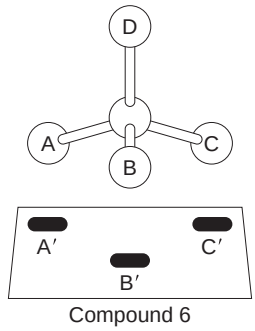


FIGURE 2.18 Optical isomers. Only in compound 6 do the functional groups A, B, and C align with the corresponding sites of binding on the asymmetric surface.

one enantiomer is capable of attaining the correct special orientation to enable all three functional groups to interact with their respective sites on the receptor surface. The inability of the other enantiomer to achieve the same number of interactions with the hypothetical receptor surface explains its reduced biologic activity. The Easson-Stedman Hypothesis states that the more potent enantiomer must be involved in a minimum of three intermolecular interactions with the surface of the biologic target and that 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 complementary sites on the receptor surface, resulting in receptor stimulation (in this case). With *S*-(+)-epinephrine, only two interactions are possible (the protonated secondary ammonium and the substituted aromatic ring). The β-hydroxyl group is located in the wrong place in space and, therefore, cannot interact properly with the receptor. *N*-methyldopamine can achieve the same interactions with the receptor as *S*-(+)-epinephrine; therefore, it is not surprising that its vasopressor response is the same as that of *S*-(+)-epinephrine and less than that of *R*-(−)-epinephrine.

Not all stereoselectivity seen with enantiomers can be attributed to differences in the ability of the drug molecule to interact with its biologic target. Differences in biologic activity can also result from differences in the ability of each enantiomer to reach the biologic target. Because the biologic system encountered by the drug is asymmetric, each enantiomer can experience selective penetration into membranes, metabolism, absorption at sites of loss (e.g., adipose tissue), and/or excretion. Figure 2.20 shows various phases that enantiomers can encounter before reaching the biologic target. An enantiomer cannot encounter stereoselective environments at each of these points; however, enantioselectivity at any

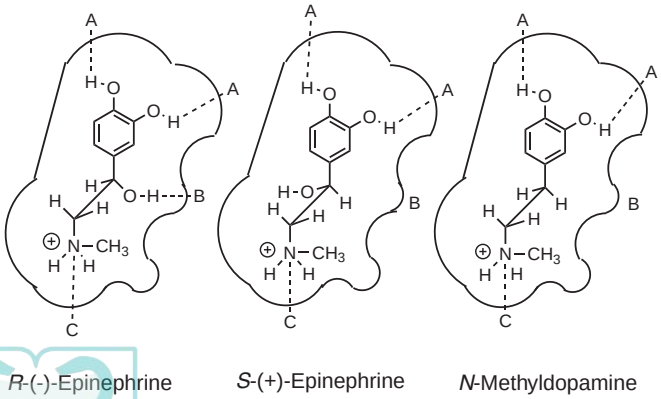


FIGURE 2.19 Drug receptor interaction of *R*-(−)-epinephrine, *S*-(+)-epinephrine, and *N*-methyldopamine.

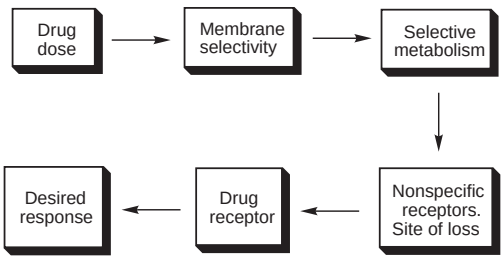


FIGURE 2.20 Selective phases to which optical isomers can be subjected before biologic response.

point can provide enough of an influence to cause one enantiomer to produce a significantly better pharmacologic effect than the other. Conversely, such processes can also contribute to untoward effects of a particular enantiomer. Differences in pharmacologic action among stereoisomers provides an excellent example of how not all pharmacologic effects of a drug are necessarily beneficial to the patient. Although there is no regulatory prohibition on the development of racemic agents, it is reasonable that single enantiomer drugs will become the overwhelming therapeutic choice in the future.

Diastereomers

As mentioned earlier, diastereoisomers are molecules that are nonsuperimposable, non–mirror images. This type of isomer can result from the presence of more than one chiral center in the molecule, double bonds, or ring systems. These isomers have different physicochemical properties, and as a result, it is possible that they can have differences in biologic activity.

Molecules that contain more than one chiral center probably are the most common type of drug-based diastereoisomers. Classic examples are the diastereoisomers ephedrine and pseudoephedrine (Fig. 2.21). When a molecule contains two chiral centers, there can be as

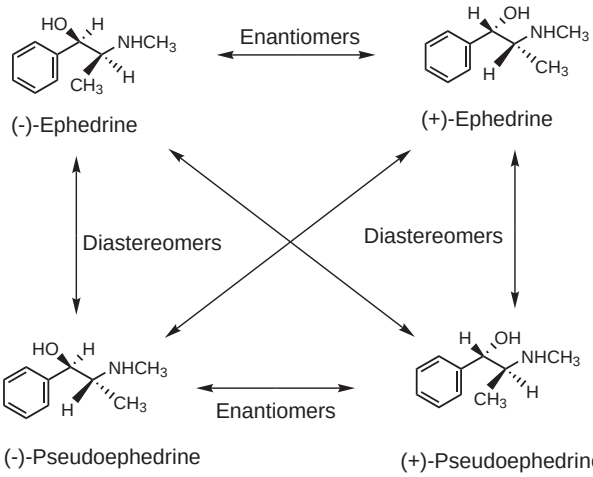


FIGURE 2.21 Relationship between the diastereomers of ephedrine and pseudoephedrine.

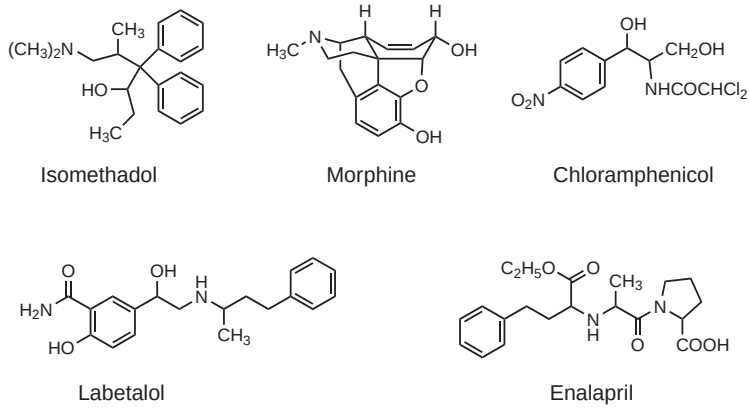


FIGURE 2.22 Examples of chiral drugs with two or more asymmetric centers.

many as four possible stereoisomers consisting of two sets of enantiomeric pairs. When considering an enantiomeric pair of molecules, there is inversion of both chiral centers. In diastereomers, there is inversion of only one chiral center. (Problem 9 at the end of this chapter helps to illustrate this point.) Figure 2.22 shows several examples that contain two or more chiral centers and, therefore, are diastereoisomeric (see Problem 10 at the end of this chapter).

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

With 2-butene, it is readily apparent that the methyl groups can be on the same or on 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*, meaning "together"); when they are on opposite sides, the designation is *trans*- or *E*- (from the German *entgegen*, meaning "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. This becomes more difficult to determine, however, with more complex structures, where it is less obvious which substituents should be referred to when naming the compound. In 1968, Blackwood et al. (22) 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 on 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 molecules. 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 is depicted in the two possible chair conformations for the cyclohexane ring. Since cyclohexane rings can exhibit significant conformational freedom, this 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. This prevents ring "flipping" from occurring, and as a result, diastereoisomers and enantiomers are generated.

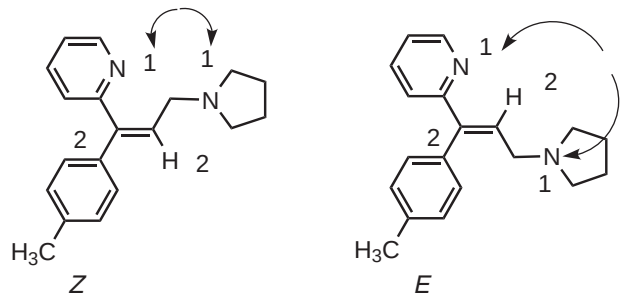


FIGURE 2.23 Geometric isomers of triprolidine.

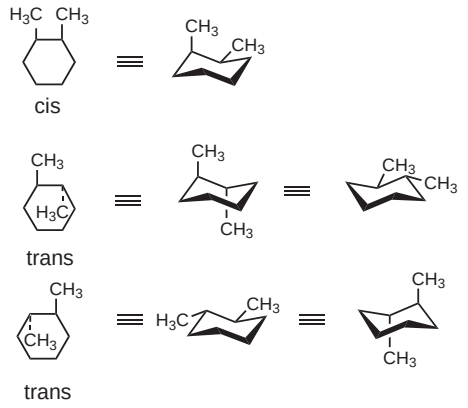
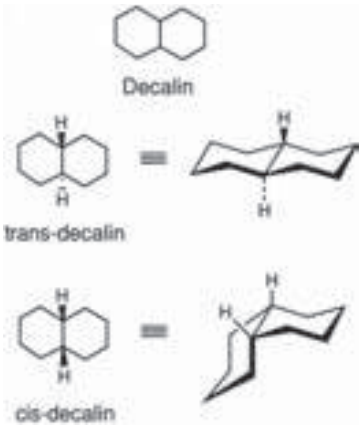


FIGURE 2.24 Diastereomers of 1,2-dimethylcyclohexane.



In the case of decalin, a two-ring system, the rings are fused together via a common bond in either the *trans* or *cis* configuration as shown. Steroids, a class of medicinally important compounds that consist of four fused rings (three cyclohexanes and one cyclopentane), exhibit significantly different biologic 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 hydrogen atom in the 5-position is below the "plane" of the ring system; the β-designation refers to the hydrogen atom 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 biologic 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 (Adrenocorticoids), 40 (Men's Health: Androgens), and 41 (Women's Health: Estrogens and Progestins).

Conformational Isomerism

Conformational isomerism takes place via rotation about one or more single bonds. Such bond rotation results in nonidentical spatial arrangement of atoms in a molecule. This type of isomerism does not require much energy because no bonds are broken. In the conversion of one enantiomer into another (or diastereoisomer), bonds are broken, which requires significantly more energy. The neurotransmitter acetylcholine can be used to demonstrate the concept of conformational isomers.

Each single bond within the acetylcholine molecule is capable of undergoing rotation, and at room temperature, such rotations readily occur. Rotation around single bonds Cα–Cβ bond of acetylcholine was shown by Kemp and Pitzer (23) in 1936 not to be free but, rather, to have an energy barrier, which is sufficiently low that at room temperature acetylcholine exists in many interconvertible conformations (see Chapter 9). Rotation around the central Cα–Cβ bond produces the greatest spatial rearrangement of atoms compared to rotation around any other bond. Since the atoms at the end of some of the bonds within acetylcholine are identical, rotation about several of these bonds produces redundant structures when viewed along the Cα–Cβ bond, and acetylcholine can be depicted in

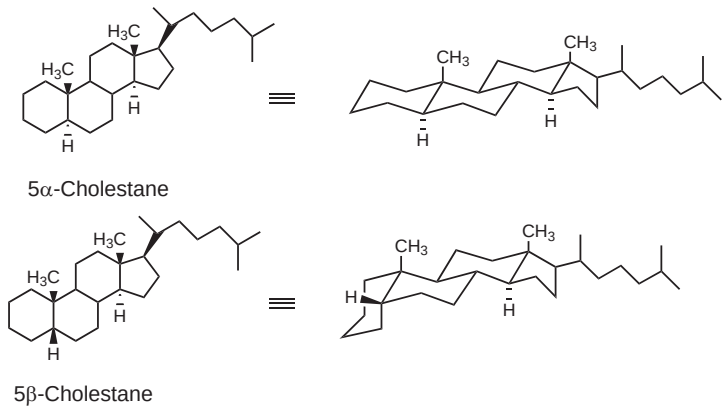


FIGURE 2.25 The 5α and 5β conformations of the steroid nucleus cholestane.

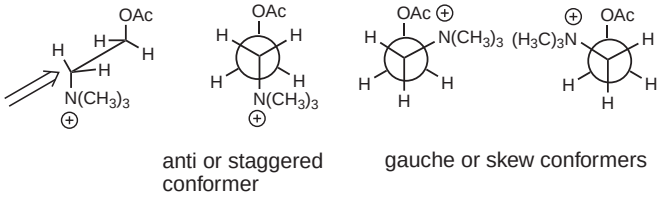


FIGURE 2.26 Anti and gauche conformations of acetylcholine.

the sawhorse or Newman projections, as shown in Figure 2.26. When the ester and trimethylammonium groups are 180° apart, the molecule is said to be in the anti, or staggered, conformation (or conformer or rotamer). This conformation allows maximum separation of the functional groups and is the most stable conformation energetically. It is possible that other conformations are more stable if factors other than steric interactions are considered (e.g., intramolecular hydrogen bonds). Rotation of one end of the Cα–Cβ bond by 120° or 240° results in the two gauche, or skew, conformations shown in Figure 2.26. These are less stable than the anti conformer, although some studies suggest that an electrostatic attraction between the electron-poor trimethylammonium and electron-rich ester oxygen atom stabilizes this conformation. Rotation by 60°, 180°, and 240° produces the least stable conformations in which all of the atoms overlap, what are referred to as eclipsed conformations.

DRUG DESIGN: DISCOVERY AND STRUCTURAL MODIFICATION OF LEAD COMPOUNDS

Process of Drug Discovery

The process of drug discovery begins with the identification of new, previously undiscovered, biologically active compounds, often called "hits," which are typically found by screening many compounds for the desired biologic properties. We will next explore the various approaches used to identify "hits" and to convert these "hits" into "lead" compounds and, subsequently, into drug candidates suitable for clinical trials. Sources of "hits" can originate from natural sources, such as plants, animals, or fungi; from synthetic chemical libraries, such as those created through combinatorial chemistry or historic chemical compound collections; from chemical and biologic intuition from years of chemical–biologic training; from targeted/rational drug design; or from computational modeling of a target site such as an enzyme. Chemical or functional group modifications of the "hits" are performed in order to improve the pharmacologic, toxicologic, physiochemical, and pharmacokinetic properties of a "hit" compound into a "lead" compound. The lead compound to be optimized should be of a known chemical structure and possess a known mechanism of action, including knowledge of its functional groups (pharmacophoric groups) that are recognized by the receptor/active site and are responsible for that molecule's affinity at the targeted receptor site. "Lead optimization" is the process whereby modifications of the functional groups of the lead compound are carried out in order to improve its recognition, affinity, and binding geometries of the pharmacophoric groups for the targeted site (a receptor or enzyme); its pharmacokinetics; or its reactivity and stability toward metabolic degradation. The final step of the drug discovery process involves rendering the lead compound into a drug candidate that is safe and suitable for use in human clinical trials, including the preparation of a suitable drug formulation.

Natural Product Screening

Perhaps the most difficult aspect of drug discovery is that of lead discovery. Until the late 19th century, the development of new chemical entities for medicinal purposes was achieved primarily through the use of natural products, generally derived from plant sources (see Chapter 1). As the colonial powers of Europe discovered new lands in the Western Hemisphere and colonized Asia, the Europeans learned from the indigenous peoples of the newly discovered lands of remedies for many ailments derived from herbs. Salicylic acid was isolated from the bark of willow trees after learning that Native Americans brewed the bark to treat inflammatory ailments. Structural optimization of this lead compound (salicylic acid) by the Bayer Corporation of Germany resulted in acetylsalicylic acid, or aspirin, the first nonsteroidal anti-inflammatory agent. South American natives used a tea obtained by brewing Cinchona bark to treat chills and fever. Further study in Europe led to the isolation of quinine and quinidine, which subsequently were used to treat malaria and cardiac arrhythmias, respectively. Following "leads" from folklore medicine, 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." Before the mid-1970s, this was one of the major approaches to obtaining new chemical entities as "leads" for new drugs. Unfortunately, this approach fell out of favor and was replaced with the rational approaches to drug design developed during that period (see next section). Heightened awareness of the fragility of ecosystems, especially the rainforests, has fueled a resurgence of screening products from plants before they become extinct. A new field of pharmacology, called "ethnopharmacology," which is the discipline of identifying potential natural product sources with medicinal properties based on native lore, has emerged as a result.

Compounds isolated from natural sources are usually tested in one or more bioassays for the ailment(s) that the plant material has been purported to treat. Interestingly, the treatment of different ailments can require different methods of preparation (e.g., brewing, chewing, or direct application to wounds) or different parts of the same plant (e.g., roots, stem, leaves, flowers, or sap). As it turns out, each method of administration or part of the plant used can produce one or more different chemical compounds that are necessary to generate the desired outcome.

Drug Discovery via Random Screening of Synthetic Organic Compounds

The random screening of synthetic organic compounds approach to the discovery of new chemical entities for a particular biologic action began in the 1930s, after the discovery of the sulfonamide class of antibacterials. All compounds available to the investigator (natural products, synthetic molecules), regardless of structure, were tested in the pharmacologic assays available at the time. This random screening 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 their assays to identify a particular type of biologic activity but, rather, tested compounds in a wide variety of assays. This large-scale screening approach of drug "leads" is referred to as high-throughput screening, which involves the simultaneous bioassay of thousands of compounds in hundreds to thousands of bioassays. These types of bioassays became possible with the advent of computer-controlled robotic systems for the assays and combinatorial chemistry techniques for the synthesis of large numbers of compounds in small (milligram) quantities. This type of random screening eventually gave way to targeted dedicated screening and rational design techniques.

Drug Discovery from Targeted Dedicated Screening and Rational Drug Design

Rational drug design is a more focused approach that uses greater knowledge (structural information) about the drug receptor (targets) or one of its natural ligands as a basis to design, identify, or create drug "leads." Testing is usually done with one or two models (e.g., specific receptor systems or enzymes) based on the therapeutic target. The drug design component often involves molecular modeling and the use of quantitative structure–activity relationships (QSARs) to better define the physicochemical properties and the pharmacophoric groups that are essential for biologic activity. The development of QSARs relies on the ability to examine multiple relationships between physical properties and biologic activities. In classic QSAR (e.g., Hansch-type analysis), an equation defines biologic activity as a linear free-energy relationship between physicochemical and/or structural properties. It permits evaluation of the nature of interaction forces between a drug and its biological target, as well as the ability to predict activity in molecules. These approaches are better for the development of a lead compound into a drug candidate than for the discovery of a lead compound.

Drug Discovery via Drug Metabolism Studies

New drug entities have been "discovered" as drug leads through investigation of the metabolism of drug molecules that already are clinical candidates or, in some instances, are already on the market. In this method, metabolites of known drug entities are isolated and assayed for biologic activity using either the same target system or broader screen target systems. The broader screening systems are more useful if the metabolite under evaluation is a chemical structure that was radically altered from the parent molecule through some unusual metabolic rearrangement reaction. In most cases, the metabolite is not radically different from the parent molecule and, therefore, would be expected to exhibit similar pharmacologic effects. One advantage of evaluating this type of drug candidate is that a metabolite can possess better pharmacokinetic properties, such as a longer duration of action, better oral absorption, or less toxicity with fewer side effects (e.g., terfenadine and its antihistaminic hydroxylated metabolite, fexofenadine). As it turns out, the sulfonamide antibacterial agents were discovered in this way. The azo dye Prontosil was found to have only antibacterial action in vivo. It was soon discovered that this compound required metabolic activation via reduction of the diazo group to produce the active metabolite 4-aminobenzene sulfonamide (Fig. 2.27). The sulfonamide mimics the physicochemical properties of PABA, a crucial component in microbial metabolism. It is no surprise that the sulfonamide acts as a competitive inhibitor of the enzyme for which PABA is a substrate.

Drug Discovery from the Observation of Side Effects

An astute clinician or pharmacologist can detect a side effect in a patient or animal model that could lead, on further development, to a new therapeutic use for a particular chemical entity. Discovery of new lead compounds via exploitation of side-effect profiles of existing agents is discussed below.

One of the more interesting drug development scenarios is that of the phenothiazine antipsychotics (see Chapter 14). Molecules with this type of biologic activity can be traced back to the first histamine H_1-receptor antagonists developed in the 1930s. In 1937, Bovet and Staub (24) were the first to recognize that it should be possible to antagonize the effects of histamine and, thereby, treat allergic reactions. They tested compounds that were known to act on the autonomic nervous system and, eventually, discovered that benzodioxanes (Fig. 2.28) significantly antagonized the effects of histamine. During an attempt

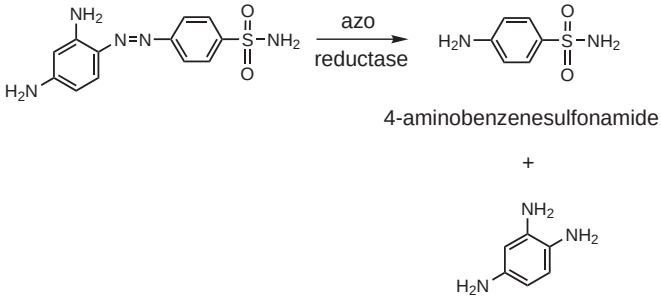


FIGURE 2.27 Metabolic conversion of prontosil to 4-aminobenzenesulfonamide.

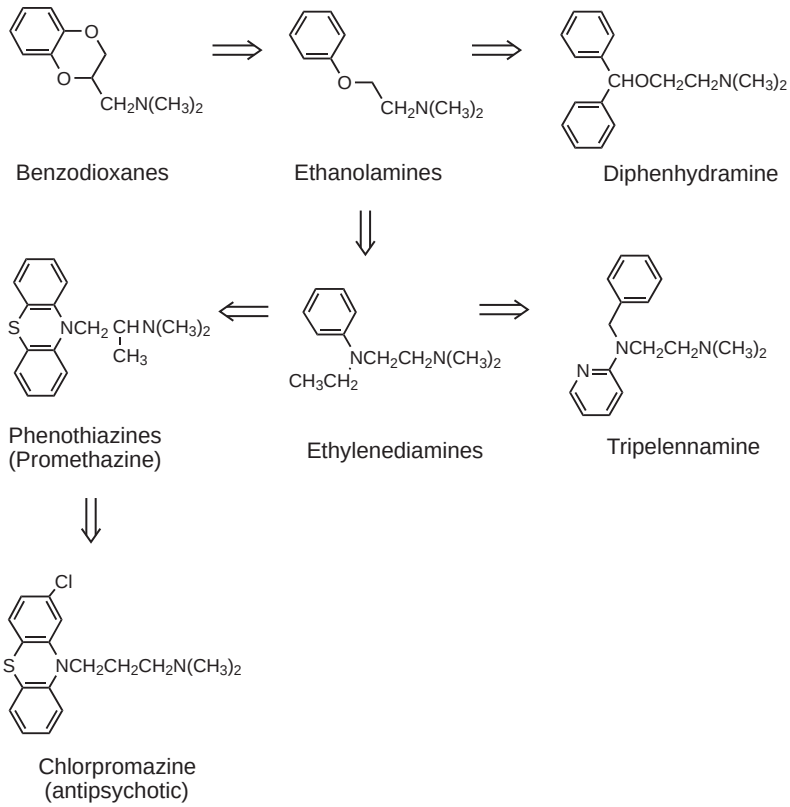


FIGURE 2.28 Development of phenothiazine-type antipsychotic drugs.

to improve the antihistaminergic action of the benzodioxanes, it was discovered that phenyl substituted ethanolamines also demonstrated significant antihistaminergic activity. Further development of this class generated two different classes of antihistamines, the diphenhydramine class of antihistamines represented by diphenhydramine (Fig. 2.28) and the ethylenediamine class, represented by tripelennamine (Fig. 2.28) (see also Chapter 32).

Incorporation of the aromatic rings of the ethylenediamines into the rigid and planar tricyclic phenothiazine structure produced molecules (e.g., promethazine) with good antihistaminergic action and relatively strong sedative properties (see also Chapter 32). At first, these compounds were found to be useful as antihistamines, but their very strong sedative properties led to their use as potentiating agents for anesthesia (25). Further development to increase the sedative properties of the phenothiazines resulted in the development of chlorpromazine in 1950 (26).

Chlorpromazine was found to produce a tendency for sleep, but unlike the antihistamine phenothiazines, it also produced a disinterest in patients with regard to their surroundings (i.e., tranquilizing effects). In patients with psychiatric disorders, an ameliorative effect on the psychosis and a relief of anxiety and agitation were noted. These observations suggested that chlorpromazine had potential for the treatment of psychiatric disorders. Thus, what started out as an attempt to improve antihistaminergic activity ultimately resulted in an entirely new class of chemical entities useful in the treatment of an unrelated disorder (27).

Another example of how new chemical entities can be derived from biologically unrelated molecules is illustrated by the development of the potassium channel agonist diazoxide (Fig. 2.29). This molecule was developed as a result of the observation that the thiazide diuretics, such as chlorothiazide, not only exhibited diuretic activity, due to inhibition of sodium absorption in the distal convoluted tubule, but also demonstrated a direct effect on the renal vasculature. Structural modification to enhance this direct effect led to the development of diazoxide and related potassium channel agonists for the treatment of hypertension (see Chapter 28).

Refinement of the Lead Structure

Determination of the Pharmacophore

Once a "hit" compound has been discovered for a particular therapeutic use, the next step is to identify the pharmacophoric groups. The pharmacophore of a drug molecule

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

is that portion of the molecule that contains the essential functional group(s) that directly bind with the active site of the biologic target to produce the desired biologic activity. Because drug–target interactions can be very specific (think of a lock [receptor] and key [drug] relationship), the pharmacophore can constitute a small portion of the molecule. In many cases, a very structurally complex molecule can be "stripped down" to a simpler structure with retention of the pharmacophoric groups while maintaining the desired biologic action. An example of this is the opioid analgesic morphine, a tetracyclic compound with five chiral centers. Not only would structure simplification possibly provide molecules with fewer side effects, but a reduction in the number of chiral centers would greatly simplify the synthesis of morphine derivatives. Figure 2.30 shows how the morphine structure has been simplified in the search for molecules with fewer deleterious side effects, such as respiratory depression and addiction potential. Within each class are analogues that are less potent, equipotent, and many times more potent than morphine. As shown in the figure, the pharmacophore of morphine consists 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 20.

Alterations in Alkyl Chains: Chain Length, Branching, and Rings

An increase or decrease in the length of an alkyl chain (homologation), branching, and alteration of ring size can have a profound effect on the potency and pharmacologic activity of the molecule. A change in the length of an alkyl chain by one CH_2 unit or branch alters the lipophilic character of the molecule and, therefore, its properties of absorption, distribution, and excretion. If the alkyl chain is directly involved in an interaction with the biologic target, then this type of alteration can influence the quality of those interactions. Molecules that are conformationally flexible can become less flexible if branching is introduced at a key position of an alkyl chain or the alkyl chain is incorporated into a ring equivalent. Changes in conformation can alter the spatial relationship between the pharmacophoric (functional) groups in the molecule and thereby influence interactions with the biologic target. Small structural changes are important to consider in the design of structural analogues.

An example that demonstrates how an increase in hydrocarbon chain length has significant effects not only on potency, but also on drug action (agonist vs. antagonist) is provided by a series of *N*-alkyl morphine analogues (Fig. 2.31). In this series, homologation of 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 further homologated by one methylene unit R=$CH_2CH_2CH_2CH_3$ (*N*-butylnormorphine), the resulting analog is totally devoid of agonist or antagonist activity (i.e., the compound is inactive). Additional 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-fold that of morphine (28,29).

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 hydrocarbon chain branching will result in a less lipophilic compound and a significant alteration in

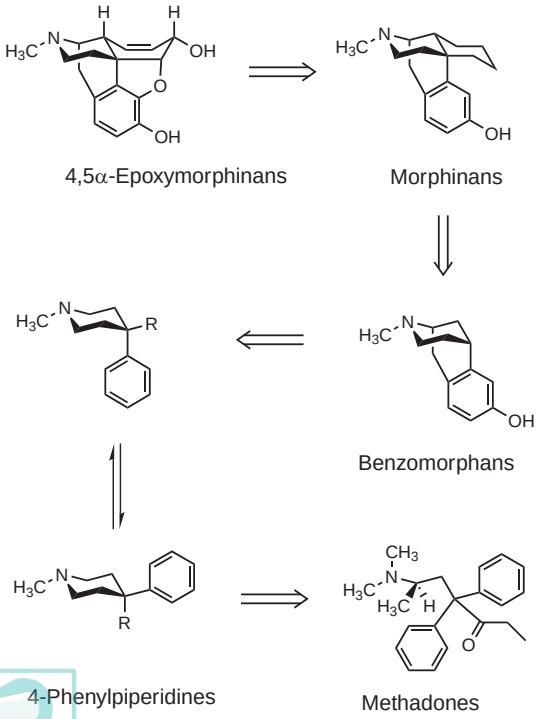
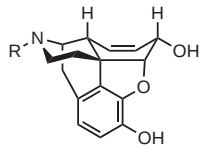


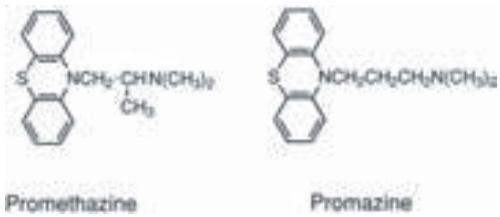
FIGURE 2.30 Morphine pharmacophore and its relationship to analgesic derivatives.



R	Pharmacological 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
$-CH_2CH_2CH_2CH_2CH_3$	Opioid antagonist activity increased
$-CH_2CH_2CH_2CH_2CH_2CH_3$	
$-CH_2CH_2-C_6H_5$	14X potency of morphine

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

biologic effect. This decrease in lipophilicity is a result of the alkyl chain becoming more compact and causes less disruption of the hydrogen-bonding network of water. If the hydrocarbon chain is directly involved in interactions with its biologic target, 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 molecules is the alkylamine side chain. In the case of promethazine, there is an isopropylamine side chain, whereas promazine contains an *n*-propylamine. In this case, simple modification of one carbon atom from a branched to a linear hydrocarbon radically alters the pharmacologic activity.

Positional isomers of aromatic ring substituents can also possess different pharmacologic properties. Substituents on aromatic rings can alter the electron distribution throughout the ring, which, in turn, can influence how the ring interacts with the biologic target. Aromatic ring substituents can also influence the conformation of the flexible portion of a molecule, especially if the substituents are located ortho to the same carbon attached to the flexible side chain. Ring substituents influence the conformations of adjacent substituents via steric interactions and can significantly alter interactions with the biologic target.

Functional Group Modification: Bioisosterism

Bioisosterism

When a lead compound is first discovered, it often lacks the required potency and pharmacokinetic properties suitable for making it a viable clinical candidate. These can include undesirable side effects, physicochemical properties, other factors that affect oral bioavailability (see also Chapter 3), and adverse metabolic or excretion properties. These undesirable properties are often the result of the presence of specific pharmacophoric (functional) groups in the molecule. Successful modification of the compound to reduce or eliminate these undesirable features without losing the desired biologic activity is the goal. Replacement or modification of specific pharmacophoric (functional) groups with other groups having similar properties is known as "isosteric replacement" or "bioisosteric replacement."

In 1919, Langmuir (30,31) first developed the concept of chemical isosterism to describe the similarities in physical properties among atoms, functional groups, radicals, and molecules. The similarities among atoms described by Langmuir resulted primarily 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 of isosterism 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.

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

To account for similarities between functional groups with the same number of valence electrons but different numbers of atoms, Grimm (32) developed his hydride displacement law. This is not a "law" in the strict sense but, rather, more an illustration of similar physical properties among closely related functional groups. Table 2.8 presents an example of Grimm's hydride displacement. Descending diagonally from left to right in the table, hydrogen atoms are progressively added to maintain the same number of valence electrons for each group of atoms within a column (thus the term "hydride"). Within each column, the groups are considered to be "pseudoatoms" with respect to each another. Thus, NH_2 is considered to be isosteric to OH, and so on. 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 physicochemical properties, but others have very different properties, despite having the same number of valence electrons. For example, OH and NH_2 share similar hydrogen-bonding properties and, therefore, should be interchangeable if that is the only important criterion. The NH_2 group is basic, whereas the OH is neutral. Hence, at physiologic pH, the NH_2 group exists in

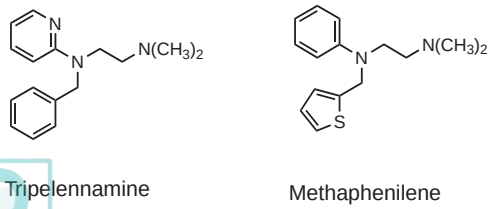
TABLE 2.8 Grimm's Hydride Displacement "Law"

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

its protonated or conjugate acid form and the molecule becomes positively charged. If OH is being replaced by NH_2, the additional positive charge could have a significant effect on the overall physicochemical properties of the molecule in which it is being introduced. The difference in physicochemical properties of the CH_3 group relative to the OH and NH_2 groups is even greater. In addition to acid–base character, this "law" fails to take into account other important physicochemical parameters, such as electronegativity, polarizability, bond angles, size, shape of molecular orbitals, electron density, and partition coefficients, all of which contribute significantly to the overall physicochemical properties of a molecule.

Instead of considering only partial structures, Hinsberg (33) applied the concept of isosterism to entire molecules. He developed the concept of "ring equivalents"—that is, functional groups that can be exchanged for one another in aromatic ring systems without drastic changes in physicochemical properties relative to the parent structure. Benzene, thiophene, and pyridine illustrate this concept (Fig. 2.32). 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 mm Hg). Pyridine, however, deviates, with a boiling point of 115 to 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. 2.32).

It is difficult to relate biologic properties to physicochemical properties of individual atoms, functional groups, or entire molecules, because many physicochemical parameters are involved simultaneously and, therefore, are difficult to quantitate. Simple relationships as described earlier often do not hold up across the many types of biologic systems seen with medicinal agents. That is, what can work as an isosteric replacement in one biologic system can not work in another. Because of this, it was necessary to introduce the term "bioisosterism" to describe functional groups related in structure that have similar biologic effects. Friedman (34) introduced the term bioisosterism and defined it as follows: "Bioisosteres are (functional) groups or molecules that have chemical and physical similarities producing broadly similar biological properties."



Tripelennamine Methaphenilene

FIGURE 2.32 Isosteric substitution of thiophene for benzene and benzene for pyridine.

Burger (35) 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."

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 bioisosteres and do not necessarily have the same number of atoms as the functional group that they replace. A wider set of compounds and functional groups are encompassed by nonclassical bioisosteres that produce, at the molecular level, qualitatively similar agonist or antagonist action. In animals, many hormones and neurotransmitters with very similar structures and biologic actions can be classified as bioisosteres. An example is the insulins isolated from various mammalian species. Even though these insulins can differ by several amino acid residues, they still produce the same biologic 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.)

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

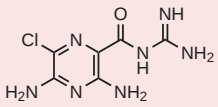
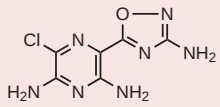
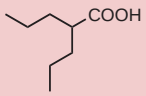
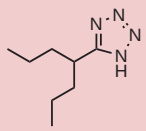
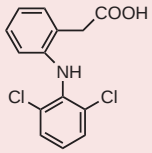
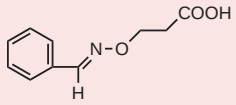
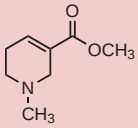
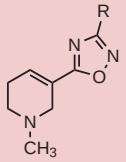
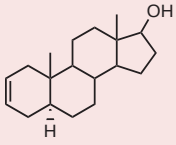
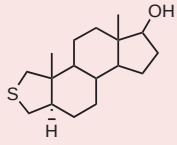
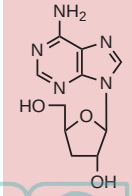
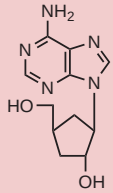
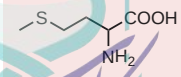
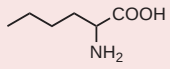
Monovalent bioisosteres F, H OH, NH F, OH, NH or CH_3 for H SH, OH Cl, Br, CF_3
Divalent bioisosteres: —C=S, —C=O, —C=NH, —C=C—
Trivalent atoms or groups: —C(H)=, —N= —P=, —As=
Tetrasubstituted atoms: $-\overset{\oplus}{N}<$, $>C<$, $-\overset{\oplus}{P}<$, $-\overset{\oplus}{As}<$
Ring equivalents:

What can be a successful bioisosteric replacement for a given molecule that interacts with a particular biologic target quite has often no effect or abolishes biologic activity in another. Thus, the use of bioisosteric replacement (classical or nonclassical) in the design of new chemical entities (drug discovery) is highly dependent on the biologic system under investigation. No hard-and-fast rules exist to determine which bioisosteric replacement is going to work with a given molecule, although as the following tables and examples demonstrate, some generalizations are possible. Each category of bioisostere can be further subdivided as shown below, and examples are provided in Tables 2.9 and 2.10:

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 bioisosteres
- A. Exchangeable groups
- B. Rings versus noncyclic structure

TABLE 2.10 Nonclassical Bioisosteric Replacements

Compounds	Bioisosteric Replacement	References
		40
		41
		42
		43
		44
		45
		46

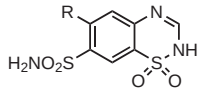
CLASSICAL BIOISOSTERES Substitution of hydrogen with fluorine is a common monovalent isosteric replacement. Sterically, hydrogen and fluorine are quite similar, with their van der Waals' radii measuring 1.2 and 1.35 Å, respectively. Because fluorine is the most electronegative element in the periodic table, any differences in biologic activity resulting from replacement of hydrogen with fluorine can be attributed to this property.

A classic example of hydrogen replacement by fluorine is development of the antineoplastic agent 5-fluorouracil from uracil. Another example is shown in Figure 2.33, in which the chlorine of chlorothiazide has been replaced with bromine or a trifluoromethyl group. For each of the substitutions, the electronic (σ, where σ^+ is electron withdrawing and σ^- is electron donating) and hydrophobic (π) properties of each group are maintained relatively constant, but the size of each group varies significantly, as indicated by the Taft steric parameter (E_s).

Figure 2.34 shows an example of classical isosteric substitution of an amino group for a 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. (36) with a series of α-tocopherol analogues (Fig. 2.35). 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 to reduce cardiac damage resulting from myocardial infarction. All of the bioisosteric analogues were found to produce similar biologic activity.

NONCLASSICAL BIOISOSTERES As mentioned earlier, nonclassical bioisosteres are replacements of functional groups



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

FIGURE 2.33 Isosteric replacement of chlorine in thiazide diuretics. Comparison of physicochemical properties of the substituents.

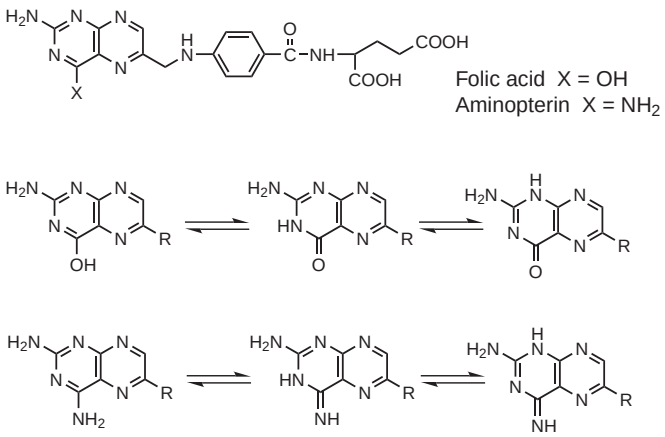


FIGURE 2.34 Isosteric replacement of OH by NH_2 in folic acid and possible tautomers of folic acid and aminopterin.

not defined by classical definitions. Some of these groups, however, mimic spatial arrangements, electronic properties, or some other physicochemical property of the molecule or functional group critical for biologic 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 in Figure 2.36 with the naturally occurring hormone estradiol and the synthetic analogue diethylstilbestrol. The *trans* isomer of diethylstilbestrol has approximately the same potency as estradiol, whereas 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 (37,38). This is not possible with the *cis* isomer, and more flexible analogues (Fig. 2.36) have little or no activity (39,40).

Another example of a nonclassical replacement is that of a sulfonamide group for a phenol in catecholamines (Fig. 2.37). 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 (~10) (41). Both groups are weakly acidic and capable of losing a proton and interacting with the biologic target as anions (Fig. 2.37). Because the replacement is not susceptible to metabolism by catechol *O*-methyltransferase, it has also the added advantage of increasing the duration of action and making the compound orally active. Other

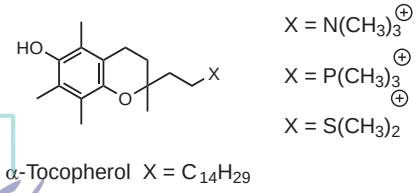


FIGURE 2.35 Tetravalent bioisosteres of α-tocopherol.

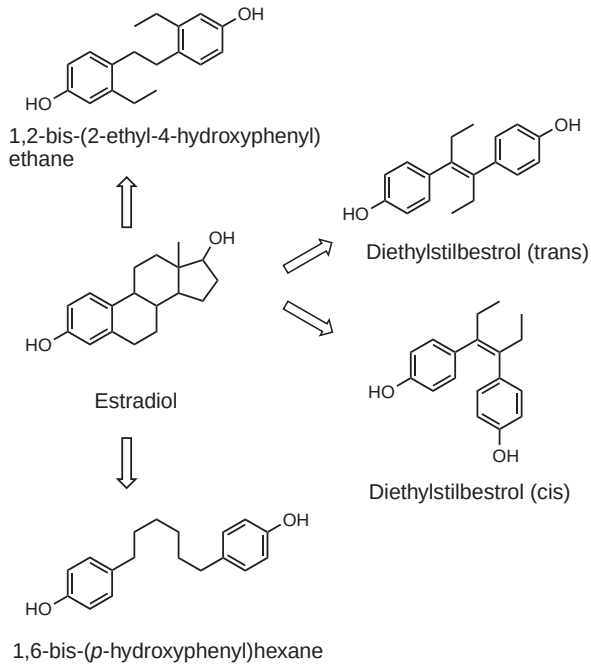


FIGURE 2.36 Noncyclic analogs of estradiol.

examples of successful bioisosteric replacements are shown in Table 2.10, and a more detailed description of the role of bioisosterism can be found in the review by Patani and LaVoie (42).

PEPTIDE AND PROTEIN DRUGS

Not all drugs are small molecules as described thus far. Some very important therapeutic agents are peptidic in nature (e.g., insulin, calcitonin) and, due to their physical chemical properties, generally cannot be delivered orally and must be administered parenterally. Peptides and proteins are very similar in that they are made up of units, or residues, of amino acids that are linked by amide bonds, also referred to as peptide bonds. There is no definitive number of amino acid residues that delineates a peptide from a protein. However, the term peptide refers generally to molecules that contain 15 to

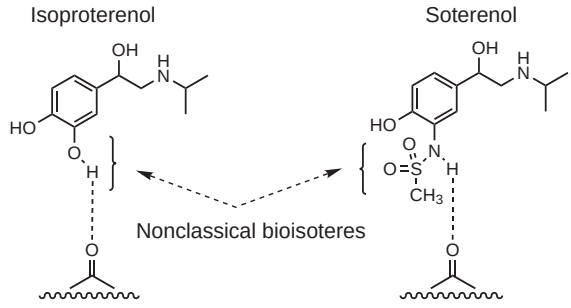
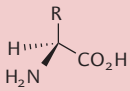
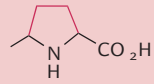
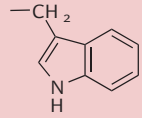
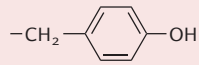
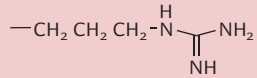
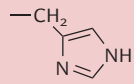


FIGURE 2.37 Bioisosteric replacement of m-OH of isoproterenol with a sulfonamido group and similar hydrogen-bonding capacity to a possible drug receptor.

50 amino acids. Molecules composed of more than 50 residues are generally referred to as proteins.

There are 20 naturally occurring amino acids that serve as the building blocks for both peptide and protein drugs (Table 2.11). Each amino acid contains a common functional group "backbone" that includes a basic amine attached to the α-carbon of an acidic carboxylic acid. The α-carbon for each amino acid is substituted with a unique side chain. The amino acid side chains contribute significantly to the physical chemical properties of

TABLE 2.11 The Twenty Natural Occurring Amino Acids

Name		General Structure		
	3 Letter code	Single Letter code	Structure R =	pKa of side chain
Glycine	Gly	G	-H	none
Alanine	Ala	A	$-CH_3$	none
Valine	Val	V	$-CH(CH_3)_2$	none
Isoleucine	Ile	I	$-CH(CH_3)CH_2CH_3$	none
Leucine	Leu	L	$-CH_2CH(CH_3)_2$	none
Proline	Pro	P	 (side chain highligted)	none
Phenylalanine	Phe	F	$-CH_2-C_6H_5$	none
Tryptophan	Trp	W		none
Methionine	Met	M	$-CH_2CH_2SCH_3$	none
Cysteine	Cys	C	$-CH_2SH$	(acidic) ~8
Serine	Ser	S	$-CH_2OH$	none
Threonine	Thr	T	$-CH(CH_3)OH$	none
Tyrosine	Tyr	Y		(acidic) ~10
Arginine	Arg	R		(basic) ~12.5
Lysine	Lys	K	$-CH_2CH_2CH_2NH_2$	(basic) ~10.5
Histidine	His	H		(basic) ~6
Asparagine	Asn	N	$-CH_2CONH_2$	none
Glutamine	Gln	Q	$-CH_2CH_2CONH_2$	none
Aspartic Acid	Asp	D	$-CH_2COOH$	(acidic) ~3.8
Glutamic Acid	Glu	E	$-CH_2CH_2COOH$	(acidic) ~4

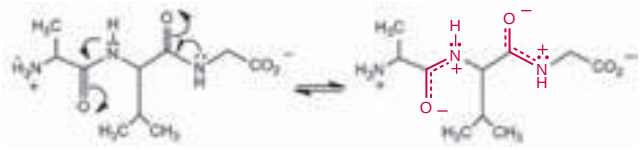


FIGURE 2.38 A tripeptide, Ala-Val-Gly, indicating the planarity of the peptide bonds caused by the restricted rotation around the amide bond.

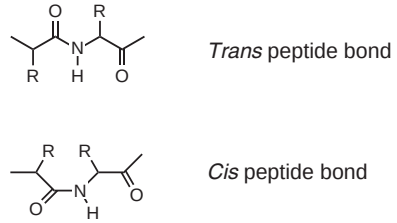


FIGURE 2.39 *Cis*/*trans* peptide bond configuration.

the peptide that is formed from a unique sequence of amino acids.

As previously mentioned, the amino acid residues are linked by amide bonds, as shown in Figure 2.38. Each carboxylic acid forms an amide bond with the amine group of the next amino acid in the sequence. As with other amide bonds, conjugation between the lone pair of electrons on the nitrogen atom and the adjacent carbonyl group results in the amide bond having partial double-bond character due to a resonance structure as shown in Figure 2.38. This property has two major consequences: 1) the amide bond is therefore co-planar; and 2) there is restricted rotation around the C–N bond (Fig. 2.38). Because of this restricted rotation, there are two conformations possible, *cis* and *trans* (Fig 2.39). The *trans*-conformation is lower in energy due to fewer steric interactions (similar to that found with a carbon–carbon double bond) and is favored. When proline is one of the amino acid residues, the *cis*-conformation can be favored as a result of the amine group being part of a pyrrolidine ring. For this reason, the presence of proline in peptides and proteins is associated with a "kink" or bend in the overall conformation of the peptide chain.

Physical Chemical Properties of Peptides

Since the α-amine and α-carboxylic acid of each amino acid are involved in the peptide backbone (except at each terminus of the chain), the basic and acidic nature of these functional groups does not contribute to the overall physical chemical properties of the molecule. The functional groups found within the amino acid side chains are what are integral to the physicochemical properties of the peptide or protein and represent important points of interaction with the corresponding biologic target. Examination of Table 2.11 shows that the functional groups found within the amino acid side chains can be basic (e.g., amine, guanidine, imidazole), acidic (e.g., carboxylic acid, phenol, thiol), neutral (e.g., thioether, amide), or hydrocarbon (e.g., alkyl, aromatic rings) in nature. All of the functional groups found in amino acid side chains were discussed previously as components of small-molecule drugs. The primary differences in physical chemical properties between peptides and small molecules are due to their large size (molecular weight [MW]) and, as a result, the sheer number of different side chains (i.e., functional groups) present in a given structure. As might be expected, the types and number of functional groups present in the side chains dictate how much more or less polar the peptide is compared to a small-molecule drug. It is certainly plausible that peptide-based drugs will not have optimal logP values for passive absorption across membranes and, given their large MW, will not readily cross membranes (see also Chapter 3).

Metabolism/Degradation of Peptide and Protein Drugs

Peptides and proteins are metabolized extensively by enzymes in the gastrointestinal tract, blood, interstitial fluid, vascular bed, and cell membranes, which results in very poor oral absorption and a short half-life for these molecules. The primary route of metabolism of peptides and proteins involves hydrolysis of the peptide bonds that link the amino acids by enzymes called peptidases. Some of these peptidases exhibit specificity for certain amino acid sequences or have specificity for either the amino or carboxyl terminus of the peptide (exopeptidase). For example, carboxypeptidases cleave off one C-terminal residue, dipeptidyl carboxypeptidases cleave dipeptides from the C terminus, aminopeptidases cleave off one N-terminal residue, and amidases (endopeptidases) cleave internal peptide bonds. There are also peptidase subclasses that exhibit specificity for certain amino acid sequences within the peptide or at either of the termini. Some peptidases (e.g., dipeptidyl peptidase IV) have been found to catalyze the degradation of naturally occurring peptides (e.g., GLP-1) (Fig. 2.40) (see also Chapter 37).

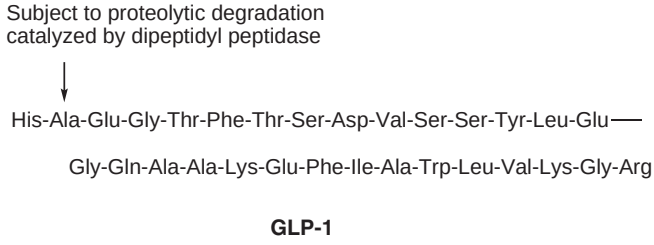


FIGURE 2.40 GLP-1 degradation by dipeptidyl peptidase IV.

SUMMARY

Medicinal chemistry involves the discovery of new chemical entities and the systematic study of the SARs of these compounds for disease state management. Such studies provide the basis for development of better and therapeutically safer medicinal agents from lead compounds found from natural sources, random screening, systematic screening, and focused rational design. Drug design goals include increasing the potency and duration of action of newly discovered compounds and decreasing adverse side effects.

For the pharmacist, it is also important to understand how the physicochemical properties influence the pharmacokinetic properties of the medicinal agents being dispensed. Such knowledge will help the pharmacist not only to better understand the clinical properties of these compounds but also to anticipate the properties of newly marketed agents. 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.

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:

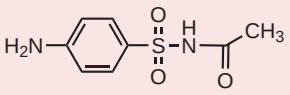
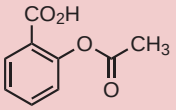
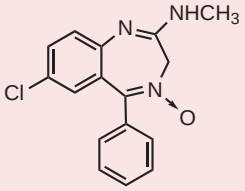
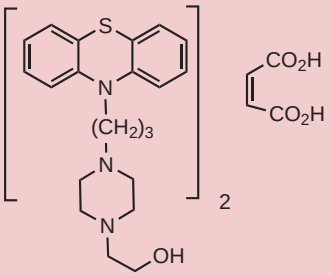
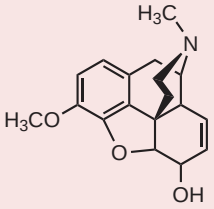
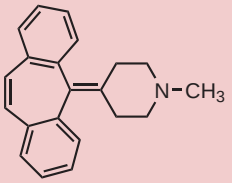
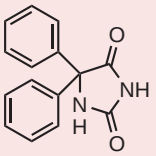
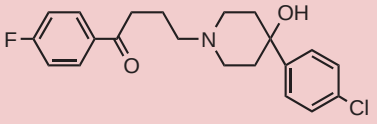
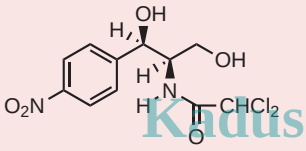
Aspirin	Carphenazine
Codeine	Cyproheptadine
Haloperidol	Chlordiazepoxide
Phenytoin	

8. Using the Merck Index or other source, find the chemical structures for the following empirical formulae. List as many physicochemical 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 (Fig. 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 normally would be considered an unstable rotameter? Explain.

TABLE 2.12 Drug Structures not Included in Text for Problems at End of Chapter 2

Problem #	Drug Name	Drug structure
3	Sulfacetamide	
6 + 7	Aspirin	
6 + 7	Chlordiazepoxide	
6 + 7	Carphenazine maleate	
6 + 7	Codeine	
6 + 7	Cyproheptadine	
6 + 7	Phenytoin	
6 + 7	Haloperidol	
11	Chloramphenicol	

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