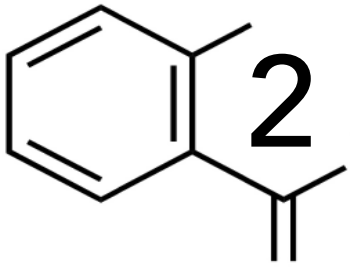


2

Functional Group Characteristics and Roles

INTRODUCTION

This chapter is written with the assumption that the reader has a basic knowledge of organic chemistry and is at least familiar with the terminology used to describe the parts of an organic molecule. The goals of this chapter are to define the term *functional group,* review the major chemical properties or characteristics inherent to any given functional group, relate these chemical properties or characteristics to the discipline of medicinal chemistry, and to provide some initial examples of how these properties or characteristics are important for drug action.

Subsequent chapters provide detailed information with regard to the ionization of acidic and basic functional groups, the roles of water and lipid soluble functional groups, the types of chemical interactions possible between functional groups and their biological targets, the specific routes of metabolism associated with specific functional groups, and how functional groups can be altered to provide a therapeutic benefit.

LEARNING OBJECTIVES

After completing this chapter, students will be able to:

1. Identify the individual functional groups that comprise the structure of a given drug molecule.
2. Explain the general purpose of functional groups and provide specific examples of how functional groups affect drug activity.
3. Analyze the electronic, solubility, and steric effects that an individual functional group can impart to a specific drug molecule.

4. Explain how a specific functional group can serve different purposes on different drug molecules and how the importance of a specific functional group can vary among different drug molecules based on the influence of the adjacent functional groups.
5. Explain how functional groups can affect therapeutic outcomes.
6. Identify the key chemical properties of the functional groups present in amino acids and proteins.

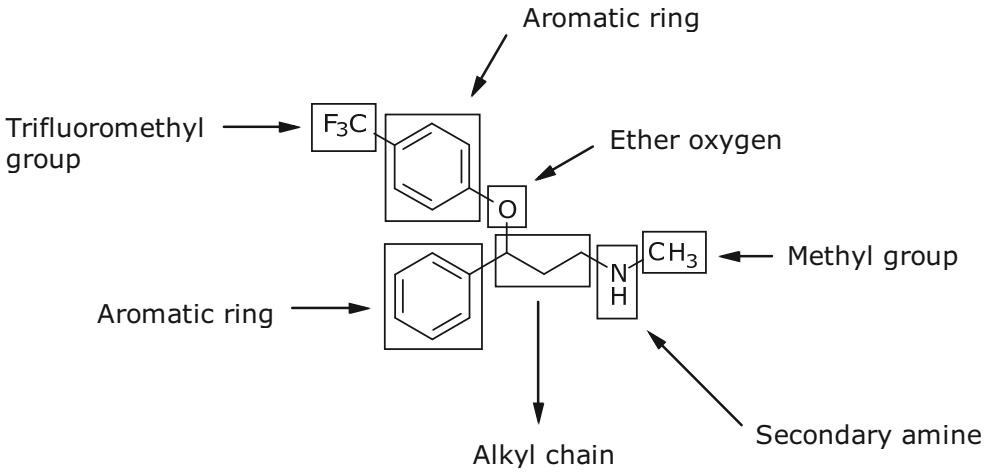
WHAT IS A FUNCTIONAL GROUP?

Prior to answering this question, let us begin with two objects for which everyone is familiar, an automobile and a refrigerator. Each of these machines consists of hundreds of interrelated parts that are essential for specific functions. Some of these functions are absolute requirements, while others are desired but not considered required. As an example, let's consider the wheels. This part of the automobile is essential to allow it to move quickly and smoothly over hundreds and thousands of miles. In contrast, the wheels found on most modern refrigerators are helpful in moving it a few feet for cleaning purposes or perhaps to remodel a kitchen, however they are not considered essential. A refrigerator without wheels is still fully functional and it is still possible to move it, either using a dolly or by a couple of people pushing it. On the other hand, an automobile without wheels is no longer functional. **Table 2-1** outlines some additional comparisons between these objects. The key point of this initial example is to emphasize that these familiar objects have different uses and functions, contain both similar and different parts, and that the relative need of a given specific part varies depending upon the object. Some parts, such as a power source, are essential for almost all machines, while others, such as a mirror or a horn, are not.

Table 2-1. A comparison of the specific requirements for selected parts of an automobile and a refrigerator

Part	Automobile	Refrigerator
Power source	Essential. Requires gasoline, electricity or a hybrid.	Essential. Requires electricity.
Doors	Essential. Required to enter and exit the vehicle.	Essential. Required to access food and keep items at proper temperature.
Windows	Essential. Required to see the road, pedestrians, traffic signs, etc. Power windows are somewhat standard, but really not required.	Not needed.
Thermostat and coolant system	Essential. Required to ensure the engine does not overheat.	Essential. Required to keep food and drinks at desired temperature.
Lights	Essential. Required for nighttime driving and signaling stops and turns.	Highly desired but not essential.

Similar to automobiles, refrigerators, and other machines, drug molecules consist of various components known as functional groups. This is exemplified by fluoxetine, an antidepressant that selectivity blocks the reuptake of serotonin. This drug is comprised of seven parts or seven specific functional groups.



Definitions

Pharmacokinetic effects have been generally defined as those that explain what the body does to the drug, whereas pharmacodynamics effects have been generally defined as those that explain what the drug does to the body. More specifically, pharmacokinetic effects include the absorption, distribution, metabolism, and elimination (ADME) of a drug molecule, while pharmacodynamic effects include the intensity, duration, and mechanism of action of that same drug molecule. Intrinsic within a pharmacodynamic effect is the ability of the drug molecule to interact with its biological target. Biological targets can be organized into four general categories (receptors, enzymes, nucleic acids, and excitable membranes/other biopolymers) and are typically composed of proteins or nucleic acids.

From a medicinal chemistry perspective, functional groups provide specific properties and behaviors that allow drug molecules to exert their desired pharmacodynamic and pharmacokinetic effects. For a given drug molecule they play a significant role in the:

- overall water/lipid solubility
- route of administration
- ability to interact with specific biological targets
- mechanism of action
- route of metabolism and elimination

- duration of action
- suitability for a specific therapeutic situation
- tendency to cause adverse effects or drug interactions

An Exclusive Interview with Some Functional Groups

It is a rare occasion when a functional group will grant an interview; however, the following five functional groups have agreed to talk with Tongue-In-Cheek Productions. Functional groups A–C reside within the structure of enalaprilat, an angiotensin converting enzyme inhibitor that is used to treat hypertension and other cardiovascular diseases; while functional groups D and E residue within the structure of terbutaline, a selective β_2 agonist that is indicated for the treatment of asthma and chronic obstructive pulmonary disease (COPD). Here are their responses to the question, "What's your job?"

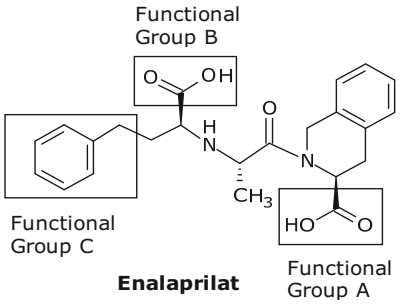
Functional Group A: "I provide the initial ionic bond that allows this drug to interact with its target enzyme."

Functional Group B: "I interact with a zinc atom involved in normal substrate catalysis."

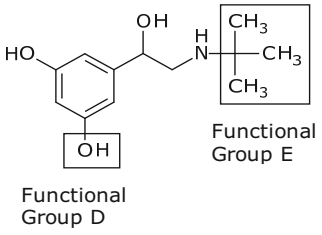
Functional Group C: "I interact with a hydrophobic site and greatly enhance binding."

Functional Group D: "I moved one carbon away from the other OH group in order to decrease the metabolism of our molecule. I also help to provide selective β_2 action."

Functional Group E: "I provide selectivity for receptors located in the pulmonary system that helps to decrease unwanted side effects."



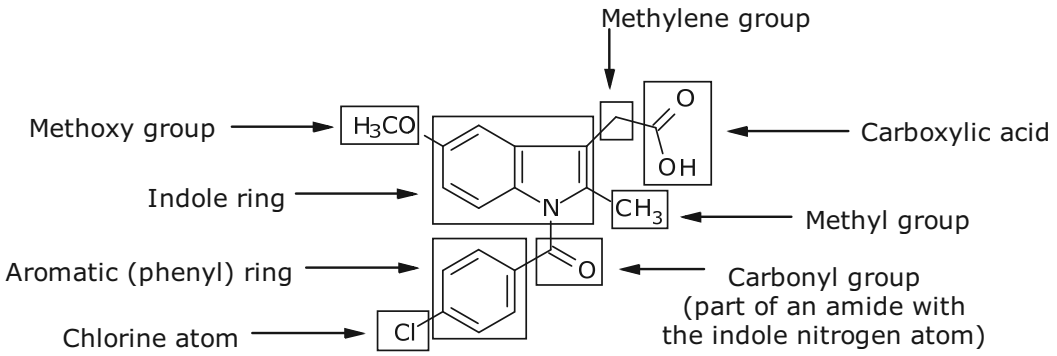
Enalaprilat



Terbutaline

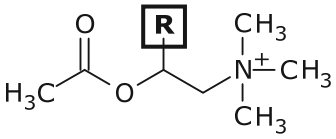
Hopefully, these testimonials will help you understand why the term *functional groups* is used to describe the pieces or parts of a drug molecule. The key point here is that each individual group within a drug molecule can serve to provide one or more specific roles, tasks, or functions. As evidenced by functional groups A and B, the same functional group—a carboxylic acid in this case—can serve different roles depending upon its location within the structure of the drug molecule.

When examining drug molecules, there are three overriding concepts that you should always consider. First, every atom within the structure of a drug molecule is part of a specific functional group. This was shown above with fluoxetine. An additional example of this concept is shown below using the nonsteroidal anti-inflammatory agent, indomethacin.

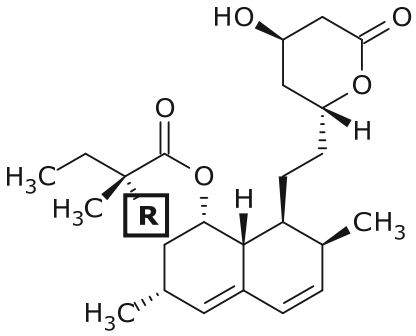


Indomethacin

Second, within any given drug molecule or class of drug molecules, some functional groups will be more important than others. This will vary among drug molecules and drug classes. As an example, consider the presence or absence of a simple methyl group. As shown in **Figure 2-1**, bethanechol and simvastatin have an additional methyl group as compared to acetylcholine and lovastatin, respectively. The methyl group in bethanchol offers several advantages for bethanechol over acetylcholine as acetylcholine non-selectively interacts with both muscarinic and nicotinic receptors, is rapidly metabolized by acetylcholinesterase, and is not orally active. The additional methyl group in bethanechol allows it to selectively interact with muscarinic receptors and prevents its degradation by acetylcholinesterase, thus allowing it to be administered as an oral tablet. In comparison, while the additional methyl group in simvastatin does enhance its overall activity as compared to lovastatin, both drugs can produce very similar actions in lowering plasma cholesterol levels. Other pharmacological and pharmaceutical properties of these two drugs are essentially identical. Thus, while the methyl group in bethanechol is essential for its activity, duration and route of administration, the methyl group in simvastatin, in comparison, is of much less importance.



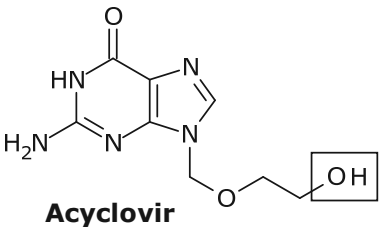
Acetylcholine: R = H
Bethanecol: R = CH_3



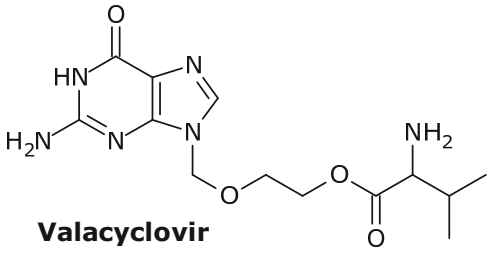
Lovastatin: R = H
Simvastatin: R = CH_3

Figure 2-1. A comparison of the relative importance of an extra methyl group.

Third, it is possible to alter functional groups to enhance activity, increase absorption, decrease adverse effects, or provide other therapeutic benefits. An example of this can be seen with acyclovir (**Figure 2-2**). Acyclovir demonstrates very poor oral absorption. Alteration of the highlighted hydroxyl group to a valine ester provides a significant increase in oral absorption. An additional example is seen with terbutaline in Tongue-In-Cheek's "An Exclusive Interview with Some Functional Groups." The movement of an aromatic hydroxyl group (Functional Group D) from one carbon atom to another led to the enhanced duration and increased selectivity observed with terbutaline.



Acyclovir



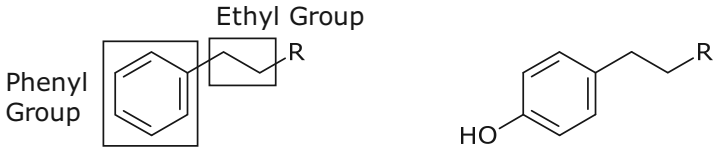
Valacyclovir

Figure 2-2. Acyclovir and valcyclovir.

CHEMICAL PROPERTIES OF FUNCTIONAL GROUPS

There are three major chemical properties that need to be considered for every functional group. Each functional group has an electronic effect, a solubility effect, and a steric effect that needs to be considered when evaluating the overall pharmacodynamic and pharmacokinetic properties of any given drug molecule. Prior to proceeding, there are two key points to keep in mind. First of all, the addition of a single functional group to a given molecule will affect the overall electronics, solubility, and steric dimensions of that molecule. It is impossible for a functional group to alter only one of these

properties. As an example, consider a drug molecule that contains an unsubstituted phenylethyl group. The addition of a *para* hydroxyl group will influence the electron density of the phenyl ring through its ability to interact with the aromatic electrons.



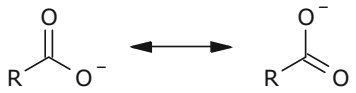
Additionally, the ability of this hydroxyl group to form hydrogen bonds will increase the water solubility of the compound. Finally, since the hydroxyl group is larger than the original hydrogen atom, its addition changes the overall steric dimensions of the compound. The specifics of all of these changes will be subsequently addressed; however, the key point here is that a single functional group can affect the overall electronic, solubility, and steric profile of a drug molecule. The second key point is that the overall effect of a given functional group depends upon all of the other functional groups surrounding it or attached to it. As will be discussed in the next section, the presence or absence of adjacent functional groups can drastically affect the chemical properties of a specific functional group.

Electronic Effects

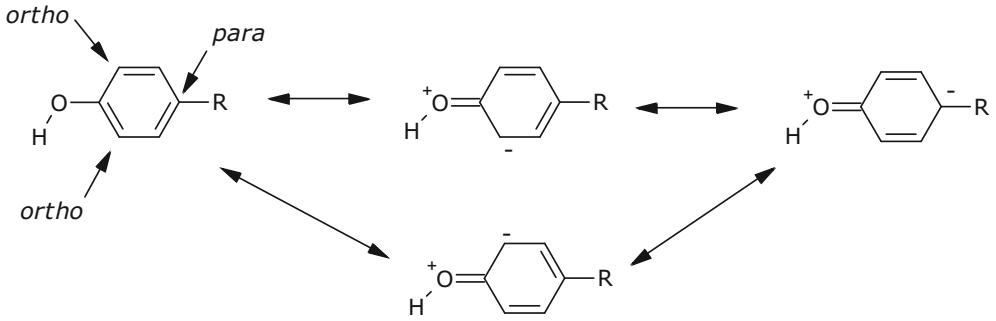
The electronic effect of a functional group is measured by its ability to either donate its electrons to adjacent atoms or functional groups or to pull or withdraw electrons away from adjacent atoms or functional groups. There are two main components that comprise the overall electronic effect of a functional group, its ability to participate in resonance and its intrinsic inductive effects. Let us examine each of these components separately.

Resonance occurs when electrons are shared among a group of atoms that have adjacent double bonds and lone pairs of electrons. Since the electrons are being equally shared, the overall structure is actually a hybrid of all of the possible resonance structures. Examples of resonance structures can be seen in **Figure 2-3**. As seen with the carboxylic acid, resonance structures can exist within a functional group. In this example, the negative charge is being equally shared across the two oxygen atoms. The ability to allow a positive or negative charge to be shared among multiple atoms is extremely important since it enhances the acidity or basicity of specific functional groups. This will be discussed in more detail in Chapter 3. Resonance structures can also occur when a functional group donates or withdraws electrons from adjacent groups. An aromatic hydroxyl group, also known as a phenol, can share its electrons with the adjacent aromatic ring. In this case, the oxygen donates its electrons to the aromatic ring. As illustrated by the resonance structures, the negative charge can be equally

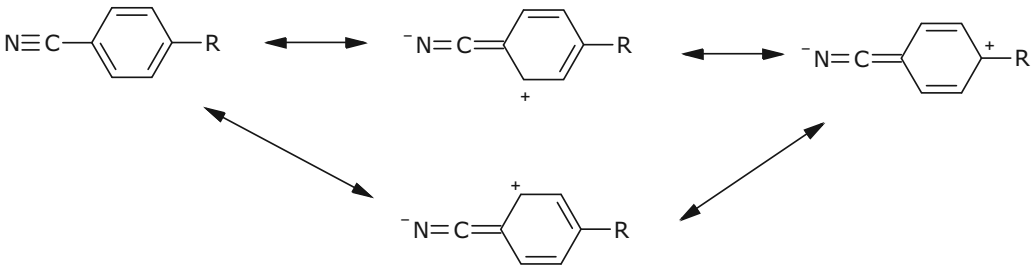
shared by the three aromatic carbon atoms either *ortho* or *para* to the phenolic group. In contrast to a phenolic group, a nitrile group will withdraw or remove electrons from the aromatic ring. In this case, the nitrile group acquires a negative charge, and the aromatic ring acquires a positive charge. Similar to the phenolic group, the positive charge can be equally shared among the aromatic carbons *ortho* or *para* to the nitrile.



Resonance structures
of a carboxylic acid



Resonance structures of an
aromatic hydroxyl group



Resonance structures of an
aromatic nitrile group

Figure 2-3. Examples of resonance structures.

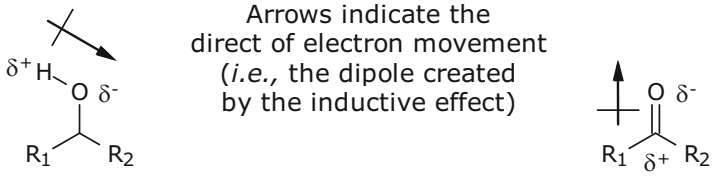
The intrinsic inductive character or nature of an atom or functional group depends upon its overall electronegativity, a chemical property that defines the ability of an atom or functional group to attract electrons towards itself and away from other atoms or functional groups. The larger the electronegativity the greater ability of an atom or functional group to attract electrons. The electronegativity values for atoms com-

monly seen in drug molecules are shown in **Table 2-2**. There are a few key points to remember when looking at this table.

1. Fluorine, oxygen, chlorine, and nitrogen have the highest electronegativities, respectively, among all of the atoms in the periodic table.
2. With the sole exception of fluorine, oxygen will inductively attract electrons from all other atoms.
3. Oxygen, nitrogen, and all four halogens (i.e., F, Cl, Br, and I) will inductively attract electrons from carbon.
4. Carbon will inductively attract electrons from hydrogen.
5. The above inductive effects (due to differences in electronegativity) will create a partial charge separation between the atoms comprising a functional group. This partial charge separation results in a dipole. Two examples of dipoles are shown below. These dipoles are very important in enhancing water solubility (discussed later in this chapter) and allow a drug molecule to interact with its biological target (discussed in depth in Chapter 6).

Table 2-2. Electronegativity Values for Atoms Commonly Seen in Drug Molecules

Atom	Electronegativity Value
F	3.98
O	3.44
Cl	3.16
N	3.04
Br	2.96
I	2.66
S	2.58
C	2.55
H	2.20
P	2.19



As previously mentioned, the presence or absence of adjacent functional groups can affect the chemical properties of a given functional group. Let us revisit the phenylethyl group to see how an adjacent phenyl ring can affect the overall electronic effect

of a hydroxyl group. **Figure 2-4** shows the original phenylethyl group along with two analogs, one that contains an aromatic hydroxyl group and one that contains an aliphatic (i.e., non-aromatic) hydroxyl group. As discussed above and shown in Figure 2-3, the aromatic hydroxyl group of Analog A is involved in resonance with the adjacent aromatic ring. This ability to form multiple resonance structures overrides the inductive effect of the oxygen atom and allows this functional group to act as an electron donating group. In contrast, the aliphatic hydroxyl group of Analog B cannot participate in resonance. Thus, its electronic effect is solely the result of its inductive effect. Since oxygen is more electronegative than carbon, an aliphatic hydroxyl group acts as an electron withdrawing group.

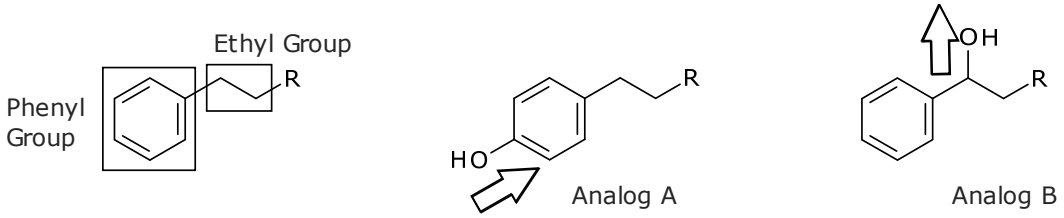


Figure 2-4. Varying electronic effects of a hydroxyl group based upon adjacent functional groups. The arrows represent the flow of electrons.

Electron Donating Functional Groups

The most commonly seen electron donating groups are shown in **Figure 2-5**. A few key points need to be made here. First, negatively charged functional groups, such as a carboxylic acid, can donate electrons through induction. This is also true for the other acidic functional groups that will be discussed in Chapter 3. Second, functional groups that contain a lone pair of electrons, such as a hydroxyl group, an aromatic amine, an aromatic thiol, or a methoxy group, can donate electrons into a phenyl or aromatic ring system as previously discussed. Finally, alkyl groups, such as a methyl group or an ethyl group can serve as electron donating groups through induction.

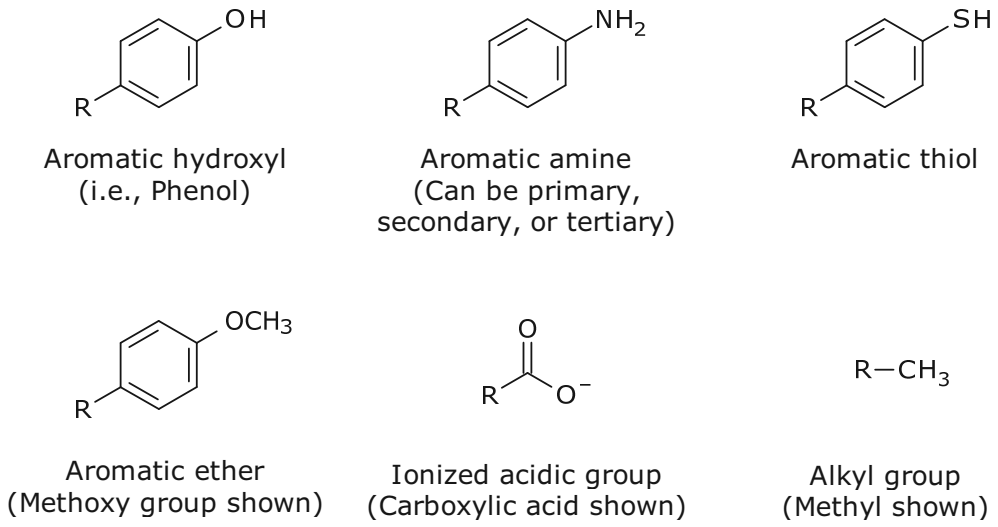
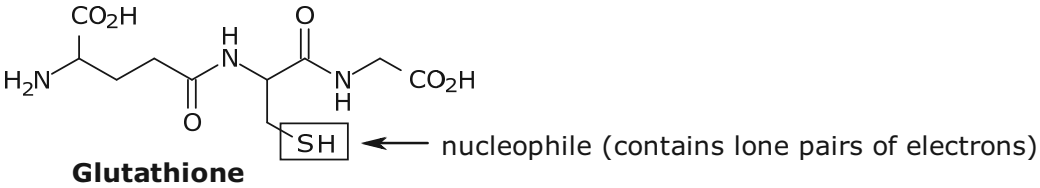


Figure 2-5. Common electron donating groups.

Some of the electron donating groups mentioned previously can also serve as nucleophilic functional groups. As the name implies, a nucleophilic group (i.e., a nucleophile) is "nucleus loving" and thus attracted to the positive charge present in the nucleus of an atom. Nucleophilic groups contain either a negative charge or a lone pair of electrons that can be used to form a covalent bond with a biological target, drug molecule or endogenous compound. Nucleophilic functional groups are involved in the formation of hydrogen bonds, as well as with the irreversible bonds formed in the mechanisms of alkylating agents, a select number of drug molecules, and a few endogenous compounds (e.g., the sulfhydryl group found on glutathione). As will be discussed in Chapter 8, this sulfhydryl group is very important in the inactivation of highly reactive intermediates.



Glutathione

Electron Withdrawing Functional Groups

The most commonly seen electron withdrawing groups are shown in Figure 2-6. Similar to electron donating groups, there are a few key points to remember. First, halogens, a trifluoromethyl group, as well as positively charged functional groups, such as an ionized amine, will pull or withdraw electrons through induction. Second, when hydroxyl groups, sulfhydryl groups, and ether groups are not adjacent to either

an aromatic ring or a double bond system, they act as electron withdrawing groups as a result of their inductive effects. Finally, all of the other groups shown in **Figure 2-6** can withdraw electrons through either ***resonance*** or ***induction***. Adjacent functional groups, as well as the presence or absence of direct attachment to an aromatic ring, will determine the relative involvement of these two processes.

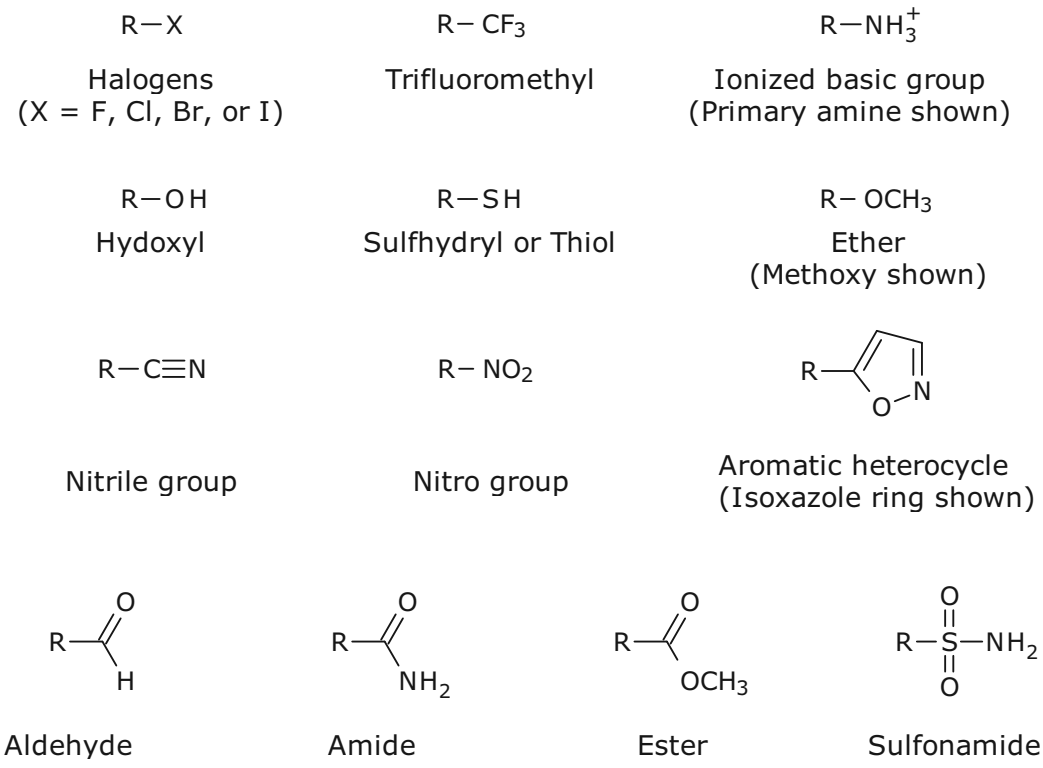
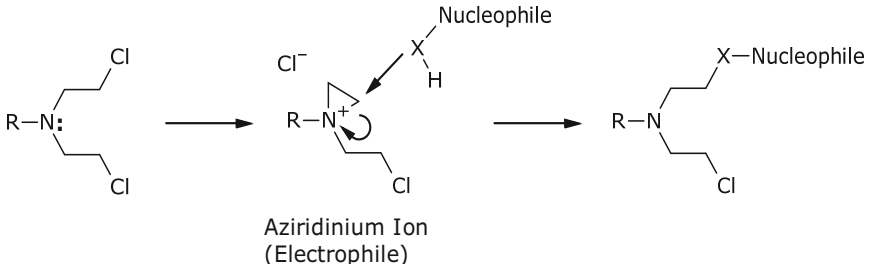


Figure 2-6. Common electron withdrawing groups.

As opposed to electron donating groups that can serve as nucleophiles, some electron withdrawing groups can also serve as electrophilic functional groups. As the name implies, an electrophilic group (i.e., an electrophile) is "electron loving." Thus, examples of electrophilic functional groups are those that contain positive charges or a good leaving group, such as a halogen or an ester. As alluded to previously, a nucleophilic functional group can attack an electrophilic functional group in order to form a covalent bond. An example of this is shown with the nitrogen mustards. This class of antineoplastic drugs forms an aziridinium intermediate as part of its mechanism. This positively charged, three-membered ring is highly ***electrophilic*** and quickly forms a covalent bond with a ***nucleophile***.



To close out this section, let us examine a specific situation where an electron withdrawing group bestows a therapeutic benefit. Penicillin G and penicillin V are naturally occurring penicillins; however, the oral bioavailability of penicillin V is superior to that seen in penicillin G. As seen in **Figure 2-7**, the only structural difference between penicillin G and penicillin V is the presence of an ether oxygen atom in penicillin V. Before proceeding, let us evaluate this ether oxygen atom. As previously discussed, the oxygen atom of an ether can be either electron donating (via resonance) or electron withdrawing (via induction). In the case of penicillin V, it is both. The ether oxygen can donate electrons to the adjacent aromatic ring via resonance and withdraw electrons via induction from the adjacent methylene carbon and the other atoms attached to this methylene unit. This results in an overall electron flow that withdraws electrons from the right side of the drug molecule and donates them into the phenyl ring as illustrated in Figure 2-7. It is this electron flow, specifically the electron withdrawing effect, that allows penicillin V to have a better oral bioavailability than penicillin G.

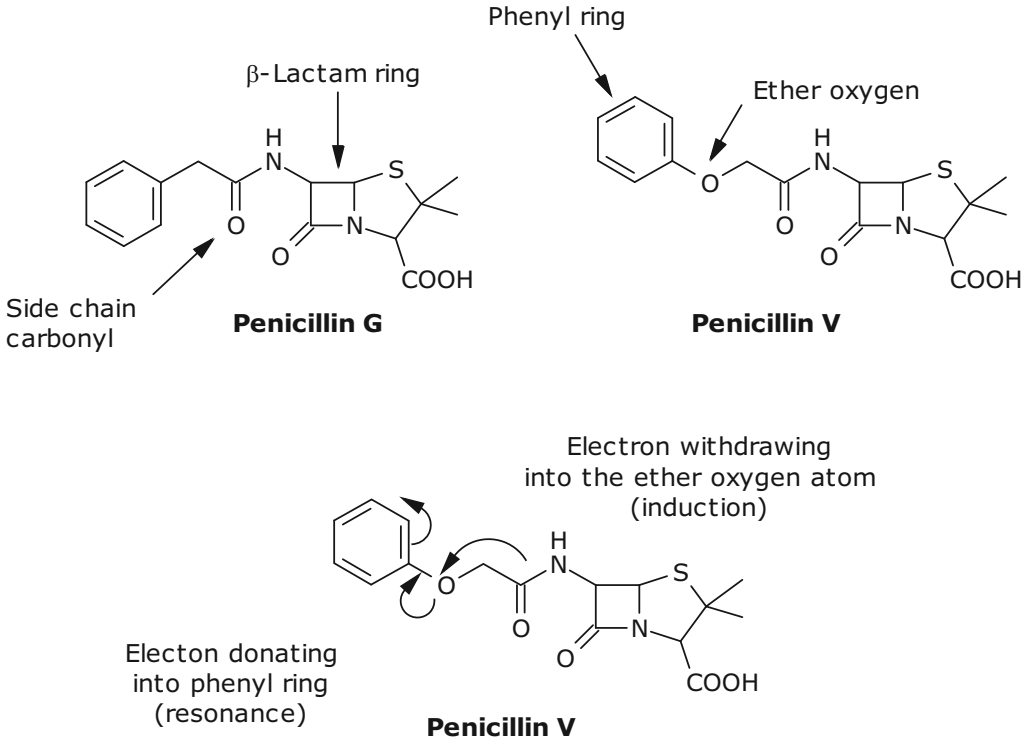
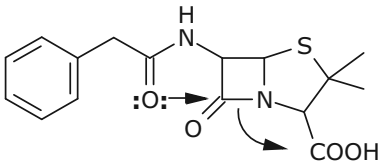
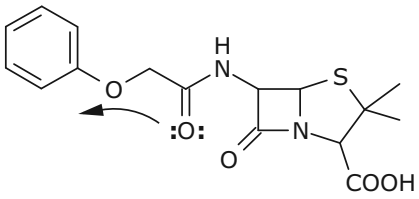


Figure 2-7. Electron flow of penicillin G and penicillin V.

In the acidic environment of the stomach, penicillin G undergoes significant acid-catalyzed degradation. The key mechanistic step involves the lone pair of electrons present on the side chain carbonyl group. In an acidic environment, these electrons attack the carbonyl carbon of the β-lactam ring. The ultimate effect is destruction of the β-lactam ring in the stomach and inactivation of penicillin G. In contrast, the presence of the ether oxygen, withdraws the lone pair of electrons from the side chain carbonyl as discussed above. This decreases the availability of the lone pair of electrons to attack the carbonyl carbon of the β-lactam ring, thus allowing penicillin V to be much more stable in the acid environment of the stomach. From a therapeutic standpoint, both of these drugs have a similar spectrum of antibiotic activity; however, penicillin V can be used orally, while penicillin G must be administered either intravenously (IV) or intramuscularly (IM).



Electon flow in an acidic environment for **Penicillin G**



Electon flow in an acidic environment for **Penicillin V**

Solubility Effects

The overall water and/or lipid solubility of a drug molecule affects its route(s) of administration, distribution within the body, metabolism, duration of action, and route(s) of elimination. This overall solubility is a composite sum of the contributions of each functional group present within the drug structure. The primary purpose of this section is to identify those functional groups that confer water solubility and those that confer lipid solubility. Similar to electronic effects, the overall solubility contribution of a specific functional group can vary depending upon adjacent groups. Further explanations with respect to the importance of water and lipid solubility, partition coefficients, the ability to analyze a drug molecule and identify its water soluble and lipid soluble components, the need for a balance between water and lipid solubility, the advantages of increasing either water or lipid solubility, and common strategies to alter solubility in a desired direction are discussed in detail in Chapter 5.

Water Soluble Functional Groups

Functional groups that enhance the water solubility of a drug molecule are often referred to as hydrophilic functional groups. The two major properties that contribute to the water solubility of a functional group are its ability to ionize and/or its ability to form hydrogen bonds. Let us examine each of these properties separately. Acidic and basic functional groups are capable of ionization and can become negatively or positively charged, respectively. A permanently charged quaternary ammonium group can also provide a positive charge; however, this functional group is only seen in a small number

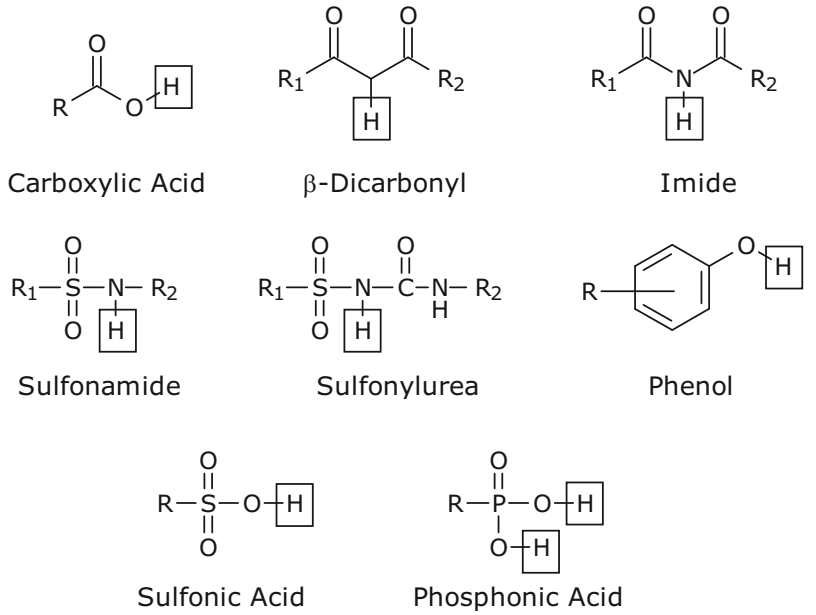


Figure 2-8. Common acidic functional groups (acidic hydrogen atoms have been highlighted).

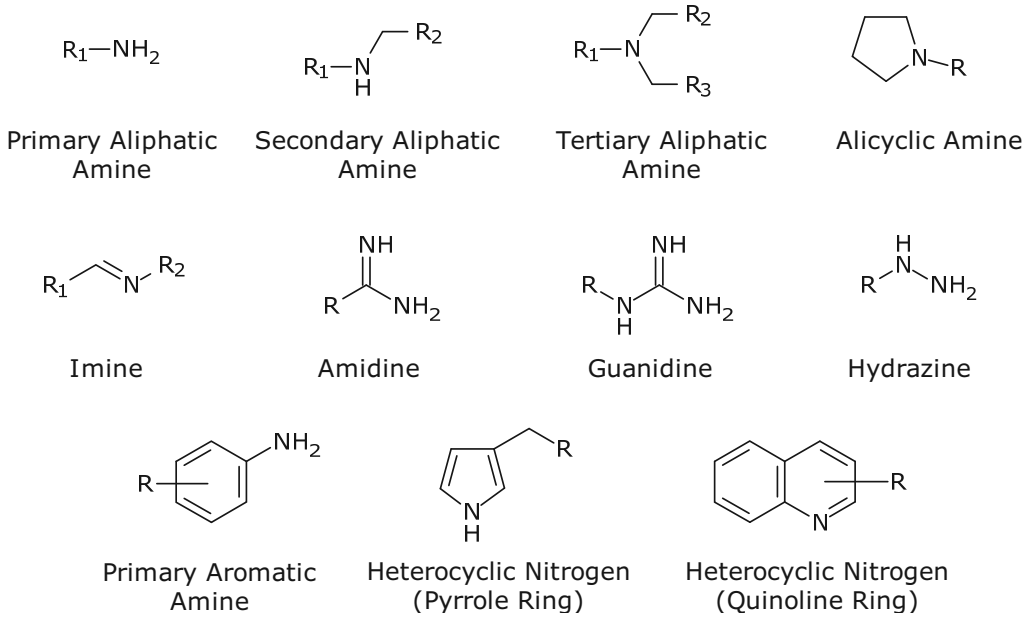
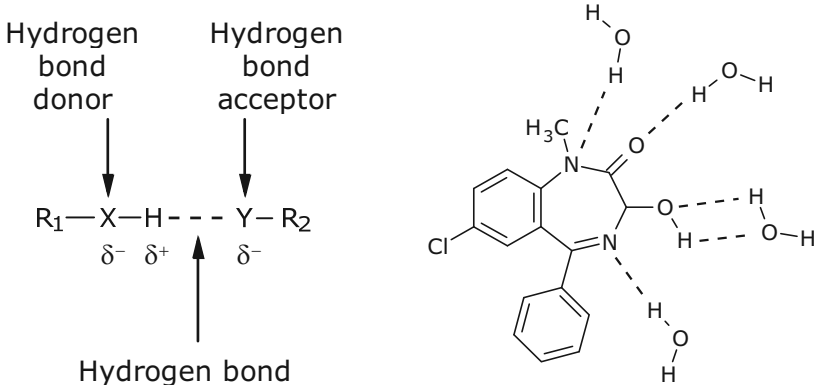


Figure 2-9. Common basic functional groups.

of drug molecules. Functional group ionization imparts an increase in the water solubility of a drug molecule. As such, it is important that you are able to identify acidic and basic functional groups. The most common acidic and basic functional groups are shown in **Figures 2-8** and **2-9**, respectively. Chapter 3 provides a more detailed explanation of the acidic and basic nature of these groups, as well as several additional functional groups.

A hydrogen bond is a specialized type of interaction between two dipoles (i.e., a dipole-dipole interaction), and occurs whenever a hydrogen atom is able to serve as a bridge between two electronegative atoms. In this type of bond, the hydrogen atom is covalently bound to one atom and non-covalently bound to the other. A general representation of a hydrogen bond is shown below. The atom that is covalently bound to the hydrogen atom is known as the hydrogen bond donor, and the atom that is non-covalently bound to the hydrogen atom is known as the hydrogen bond acceptor. Thus, in the representation above, atom X is the hydrogen bond donor and Y is the hydrogen bond acceptor. In general, oxygen and nitrogen are the most common hydrogen bond donors and acceptors. A water molecule can act as both a hydrogen bond donor and an acceptor as shown below. Thus, functional groups that are capable of forming hydrogen bonds can form these types of bonds with water and increase water solubility. Functional groups capable of forming hydrogen bonds are shown in **Figure 2-10**.

As will be discussed further in Chapter 6, hydrogen bonds are also very important for the interactions between a drug and its biological target.

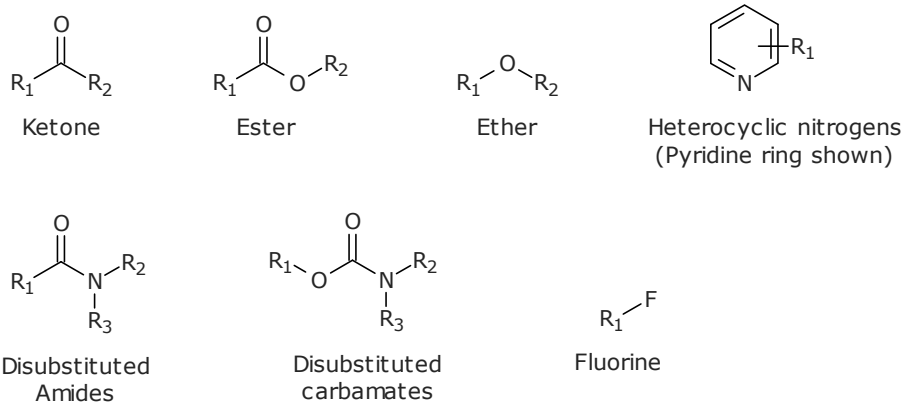


Lipid Soluble Functional Groups

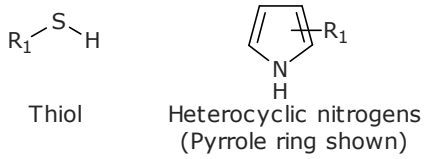
Functional groups that enhance the lipid solubility of a drug molecule are often referred to as hydrophobic or lipophilic functional groups. Functional groups that lack the ability to either ionize or form hydrogen bonds tend to impart a measure of lipid solubility to a drug molecule. Common lipid soluble functional groups are shown in **Figure 2-11** and include unsubstituted aromatic rings, alkyl groups (aka aliphatic side chains), unsaturated carbon rings (aka alicyclic rings), and halogens.

Fluorine is not included in the list of halogens because its effects on solubility can vary. As shown in Figure 2-10, fluorine can act as a hydrogen bond acceptor and enhance water solubility; however, the substitution of a hydrogen atom with a fluorine atom often slightly enhances the lipid solubility of a drug molecule. Esters and ethers can be viewed as lipid soluble functional groups depending upon the atoms or groups attached to them. The easiest way to explain this is by way of an example. Let

Hydrogen Bond Acceptors



Hydrogen Bond Donors



Hydrogen Bond Acceptors and Donors

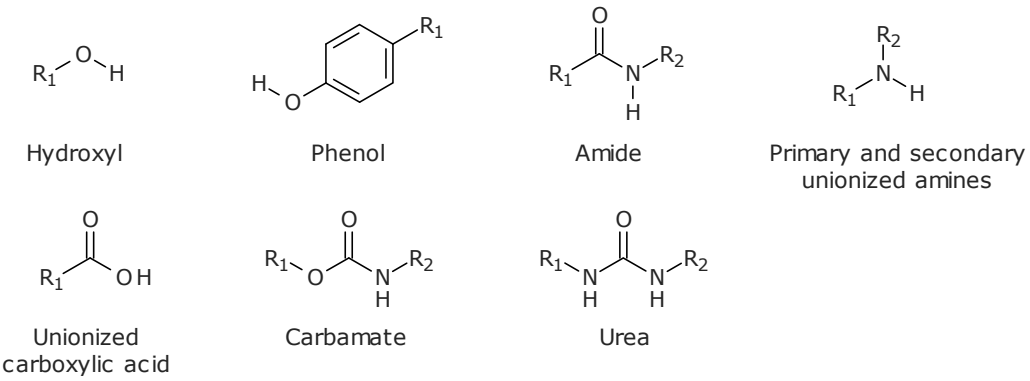
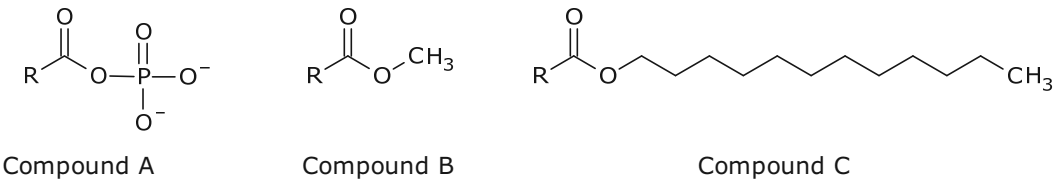


Figure 2-10. Functional groups capable of hydrogen bonds.

us consider the three esters shown below with the assumption that the "R" group is identical for all of the compounds.



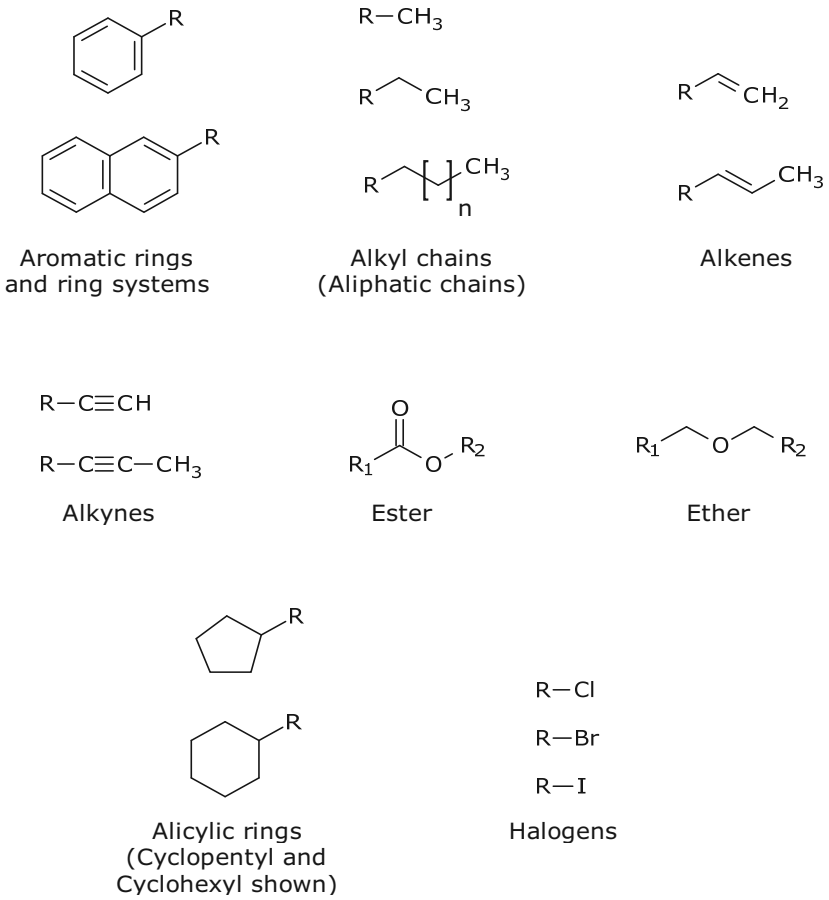


Figure 2-11. Lipid soluble functional groups.

The phosphate ester seen in compound A is clearly water soluble as it contains an ionized functional group. In contrast, compounds B and C contain methyl and dodecenoyl esters, respectively. The oxygen atoms present in these latter two compounds are still capable of forming hydrogen bonds and contributing to the overall water solubility; however, the large alkyl chain in compound C makes the ester, as a whole, a lipid soluble functional group. Compound B contains the smallest possible alkyl ester and lies somewhere in the middle. In general, when viewing an ester and evaluating its overall water/lipid solubility, you need to consider both the CO_2 portion as well as what is connected to it. The same is true for ether functional groups.

Steric Effects

Each functional group has a finite size or steric dimension that contributes to the overall conformation or three-dimensional shape of a given drug molecule. Obviously, some functional groups are larger and more bulky than others, and it is impossible for two atoms or functional groups to occupy the same space. Additionally the size and shape of each functional group must be able to be accommodated for by the binding sites

present at its biological target. The addition of functional groups to a drug molecule based primarily upon their steric effects can provide a number of therapeutic benefits for a drug molecule including:

- increased selectivity for its biological target
- enhanced binding interactions with its biological target
- favorable alteration of its rate of metabolism

Increased Selectivity

We have already seen one example of this with acetylcholine and bethanechol (Figure 2-1). While acetylcholine non-selectively interacts with both muscarinic and nicotinic receptors, the addition of a methyl group to the beta carbon of acetylcholine provides bethanechol, an analog that is selective for muscarinic receptors. The selectivity results from the fact that the muscarinic receptor has additional space that can accommodate an extra methyl group at this position, whereas the nicotinic receptor does not.

An additional example can be seen with β-adrenergic agonists and antagonists. In addition to a number of other physiological effects, agonist activity at β_1 receptors produces contraction of vascular and cardiac smooth, whereas agonist action at β_2 receptors produces bronchial smooth muscle relaxation. Therefore, antagonists at the β_1 receptor are useful in the treatment of hypertension and other cardiovascular disorders, while agonists at the β_2 receptor are useful in the treatment of asthma and chronic obstructive pulmonary disease (COPD). Non-selective β antagonists can cause unwanted adverse drug reactions due to their ability to constrict bronchial smooth muscle and exacerbate asthma and COPD. On the other hand, non-selective β agonists can cause unwanted adverse drug reactions due to their ability to constrict vascular and cardiac smooth muscle. Similar to the example with acetylcholine and bethanechol, selectivity between β_1 and β_2 receptors can be achieved by the presence or absence of a methyl group. Shown in **Figure 2-12** are the structures of atenolol, a selective β_1 receptor antagonist, and albuterol, a selective β_2 receptor agonist.

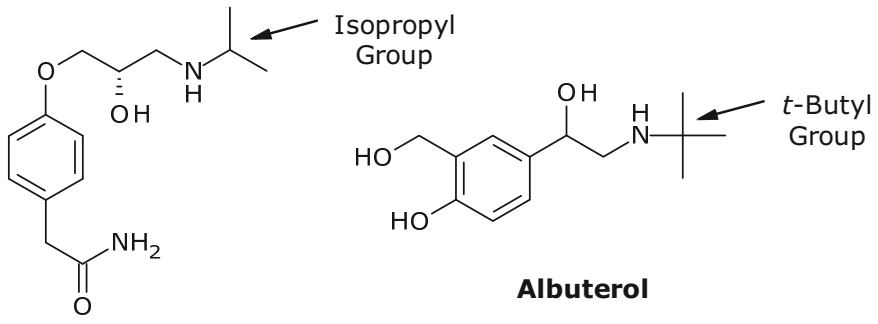


Figure 2-12. Atenolol and albuterol.

While there are a number of structural features responsible for this selectivity, let us focus on the size of the alkyl group on the secondary amine. The presence of the additional methyl group seen in the t-butyl group of albuterol is very important for selective interaction with the β_2 receptor. In contrast, the absence of this methyl group in the isopropyl group of atenolol allows it to be more selective for β_1 receptors.

Enhanced Binding Interactions

The interaction between a drug molecule and its biological target relies upon the ability of the drug molecule to adopt a conformation that is complimentary to the three-dimensional shape of the biological target. Some drugs have a considerable amount of flexibility and can orient their functional groups in a variety of different conformations. The energy released when a drug molecule begins to interact with its biological target can be used to allow it to rotate about its single bonds to adopt the specific conformation required by the biological target. However, if the energy required to adopt the proper conformation is similar to or exceeds the energy released through the binding interaction, then the overall binding affinity of the drug for its biological target can be significantly diminished. This can lead to a decrease in the overall potency of the drug and the need to administer higher doses.

One way to enhance the interaction of a drug with its biological target is to decrease the conformational flexibility and essentially lock the drug in its active conformation. This concept will be discussed in more detail in Chapter 7; however, one way to accomplish this is by adding adjacent functional groups that sterically hinder the rotation of specific bonds. An example of this can be seen in the comparison of diclofenac and fenoprofen, two non-steroidal anti-inflammatory drugs (NSAIDs). Both of these drugs exert their mechanism of action by inhibiting the enzyme cyclooxygenase. As illustrated in **Figure 2-13**, both drugs interact with cyclooxygenase through three key interactions.

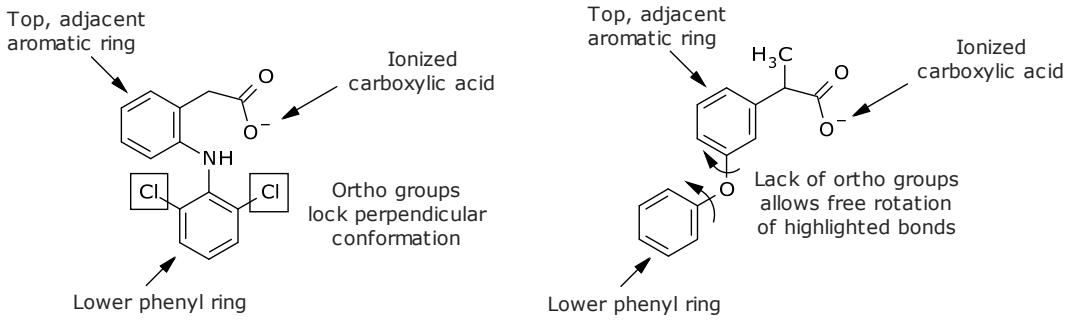
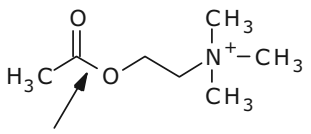


Figure 2-13. A comparison of diclofenac and fenoprofen interactions with cyclooxygenase.

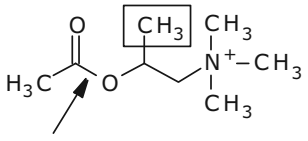
The negatively charged carboxylic acid forms an ionic bond with a positively charged cation within the enzyme. The top or adjacent aromatic ring interacts with a hydrophobic pocket within the enzyme, and the lower phenyl ring interacts with a second hydrophobic pocket within the enzyme. A key component of this binding interaction is that the lower phenyl ring binds perpendicular to the top aromatic ring. The key difference between these two drugs is that the structure of diclofenac contains two ortho chloro groups. These two functional groups sterically lock diclofenac in its required active conformation. In comparison, the lower ring of fenoprofen is unsubstituted which allows for free rotation about the indicated bonds. While fenoprofen can still interact with cyclooxygenase, it requires energy to adopt the required active conformation. As such, its affinity for cyclooxygenase is less than that observed for diclofenac. From a therapeutic perspective, this difference can be seen in the normal doses used for these two agents. The normal dose of diclofenac is 50 mg BID or TID, while the normal dose of fenoprofen is 400 to 600 mg TID or QID. While there are a number of factors that contribute to the dosing of these to drugs, the steric effect seen in diclofenac definitely plays a key role.

Alteration of Metabolism

Similar to the interaction between a drug and its biological target, the metabolism of a drug molecule requires it to interact with the active site of the enzyme that catalyzes its metabolism. Steric hindrance is a common strategy used to block or slow a specific metabolic pathway. In this approach, additional atoms are added adjacent to the functional group undergoing metabolism in order to block the interaction of the drug molecule with the enzyme carrying out the metabolic transformation. In many cases, these additional atoms need not be very large. Returning back to our example of acetylcholine and bethanechol (Figure 2-1), the additional methyl group seen on bethanechol prevents the enzyme acetylcholinesterase from cleaving the ester bond.



Acetylcholine: Ester hydrolysis occurs very rapidly



Bethanechol: Highlighted adjacent methyl group blocks hydrolysis

Another example of this concept can be seen with the cephalosporin class of antibacterial agents (Figure 2-14). This class of drug molecules requires an intact β-lactam ring in order to exert their antibacterial action. Some bacteria can produce β-lactamase, an enzyme that catalyzes the hydrolysis of this ring and thereby inactivates the cephalosporin. Cephalosporins, such as cephalexin, that can be inactivated in this manner are known as β-lactamase sensitive. This inactivation can be blocked

by placing functional groups adjacent to the β-lactam bond. As seen in **Figure 2-14**, the methoxy group of cefoxitin produces steric hindrance and permits the drug to be resistant to the actions of β-lactamase.

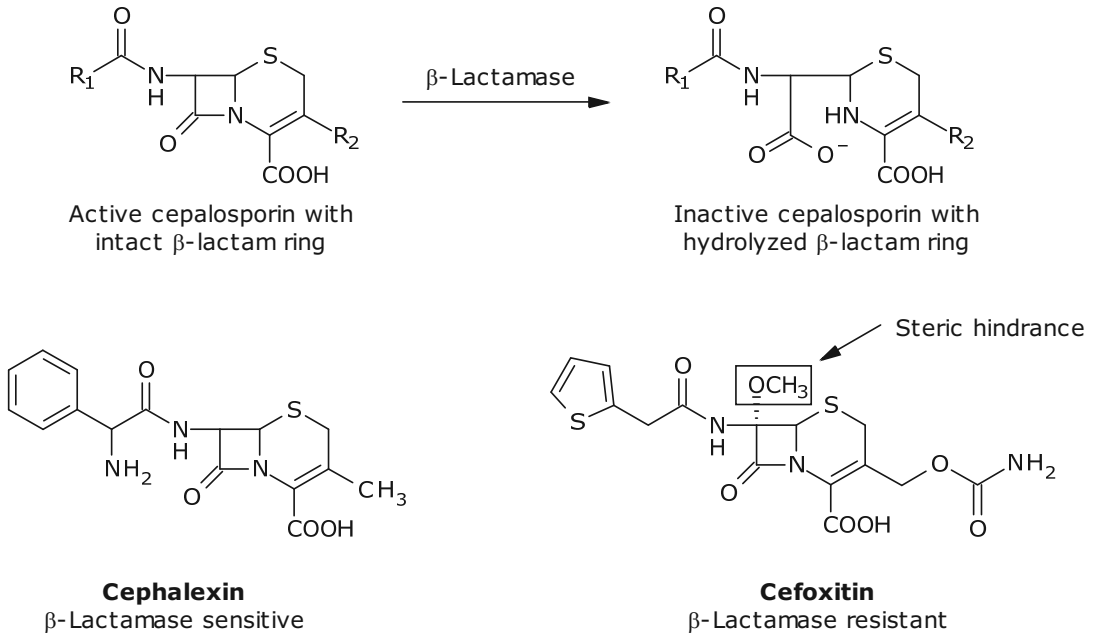


Figure 2-14. The role of steric hindrance in inhibiting β-lactam destruction by β-lactamase.

FINAL CONSIDERATIONS FOR FUNCTIONAL GROUPS ON DRUG MOLECULES

There are three key points that need to be emphasized with regard to the concepts and examples discussed previously. First, the same functional group can provide different effects on different drug molecules. We have already seen this in several of the prior examples. The addition of a simple methyl group can result in a number of therapeutic benefits depending upon the drug molecule and the location of the methyl group. It can increase the selectivity of a drug for one biological target over another. This was seen in earlier discussions of bethanechol compared to acetylcholine (Figure 2-1) and atenolol compared to albuterol (Figure 2-12). Addition of a methyl group can also increase the potency of a drug. This was previously discussed in the comparison of lovastatin to simvastatin (Figure 2-1). An additional example can be seen in the comparison of morphine with its N-desmethyl metabolite. The N-methyl group naturally present on morphine enhances its potency approximately four fold as compared to N-desmethylmorphine (**Figure 2-15**). Finally, the addition of a methyl group can sterically block metabolism and thus increase the duration of action of a specific drug molecule. This was described previously in the addition of the methyl group to ace-

tylcholine. An additional example of this concept is demonstrated when comparing testosterone with methyltestosterone (Figure 2-15). Testosterone is a naturally occurring androgenic hormone; however, it cannot be taken orally due to rapid oxidation of the C_{17} hydroxyl group to an inactive ketone. Addition of a methyl group at the C_{17} position converts the secondary hydroxyl group into a tertiary hydroxyl group. This blocks oxidative metabolism and allows methyltestosterone to be administered orally.

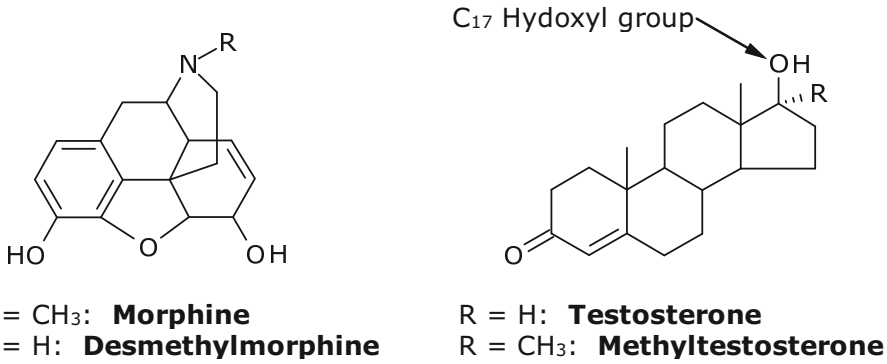
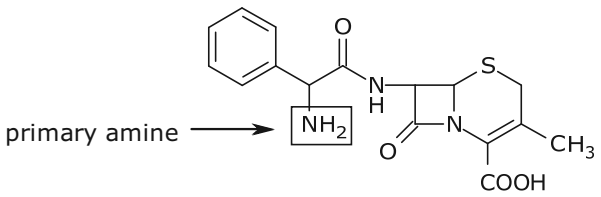


Figure 2-15. Morphine and methyltestosterone: the advantages of an additional methyl group.

Second, a single functional group may sometimes serve two distinct purposes. Examples of this can be found in three of the drugs already discussed in this chapter. The methyl group of bethanechol serves to both increase selectivity and prevent metabolism. The two *ortho* chloro groups present on the lower phenyl ring of diclofenac (Figure 2-13) provide steric hindrance and lock diclofenac in its active conformation. Additionally, due to their electron withdrawing properties, these halogens deactivate this ring from oxidative metabolism and allow it to have a longer duration of action than fenoprofen. Finally, the primary amine of cephalexin provides acid stability of the β-lactam ring and enhances its ability to enter gram negative bacteria. In the acidic environment of the stomach, this primary amine will be protonated and will act as an electron withdrawing group. Similar to the ether oxygen of penicillin V (Figure 2-7), this electronic effect will prevent the acid catalyzed destruction of the β-lactam ring. Additionally, this primary amine will be primarily ionized at all physiologically relevant pH environments. This enhances the water solubility of cephalexin and better allows it to be transported by porins, the hydrophilic protein channels that allow access of antibiotics to gram negative bacteria.



Cephalexin

Finally, it is important to reemphasize that the properties of a functional group can be altered by adjacent functional groups. Examples of this were presented earlier with the discussion of electronic effects, so let us look at one final example that involves solubility. Tetracycline and doxycycline (**Figure 2-16**) have the same molecular formula ($C_{22}H_{24}N_2O_8$) and are chemically identical with the exception that tetracycline contains a C_6 hydroxyl group, whereas doxycycline contains a C_5 hydroxyl group.

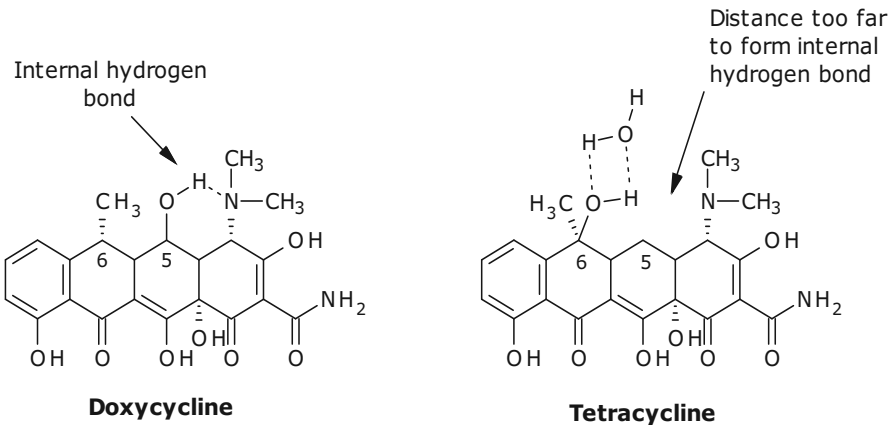


Figure 2-16. Tetracycline and doxycycline.

Despite their structural similarities, doxycycline is much less water soluble than tetracycline. As shown in Figure 2-16, the C_5 hydroxyl group of doxycycline is able to form an internal hydrogen bond with the adjacent tertiary amine. This decreases the ability of this hydroxyl group to form hydrogen bonds with water and also decreases the ability of the amine to ionize since its lone pair of electrons is involved in this internal hydrogen bond. In tetracycline, the hydroxyl group is no longer adjacent to the tertiary amine and is therefore not able to form hydrogen bonds with it. As such, it is much more available to form hydrogen bonds with water, and the lone pair of electrons of the tertiary amine is much more available to interact with a proton to become ionized. Thus, the position of this hydroxyl group, as well as the presence or absence of an adjacent functional group, plays an important role in its chemical properties. From a therapeutic perspective this minor change in the position of a single functional group results in a number of benefits. The decrease in water solubility seen in doxycycline allows it to have better oral absorption, enhanced penetration into bacteria, and a longer duration of action.

A REVIEW OF FUNCTIONAL GROUPS PRESENT ON AMINO ACIDS

As initially mentioned in Chapter 1, amino acids serve as the building blocks for a small number of peptide based drug molecules. Amino acids also serve a much larger

Summary of Key Points to Consider When Evaluating Functional Groups

1. Every atom within the structure of a drug molecule is part of a specific functional group.
2. The importance of a given functional group will vary among drug molecules and drug classes.
    a. A specific functional group can produce different effects on different drug molecules.
    b. It is possible for a single functional group to serve more than one distinct purpose on a single drug molecule.
3. Each functional group has an electronic effect, a solubility effect, and a steric effect.
    a. It is impossible for a functional group to alter only one of these properties without affecting the others.
    b. The relative importance of these three properties will vary depending upon the functional group.
    c. The overall electronic effect of a given functional group depends on both its ability to participate in resonance delocalization and its intrinsic inductive effect.
    d. Some electron donating groups can also act as nucleophiles, whereas some electron withdrawing groups can also act as electrophiles.
    e. The two key properties that contribute to the water solubility of a functional group are its ability to ionize and its ability to participate in hydrogen bonding interactions.
    f. Each functional group has a finite size or steric dimension that contributes to the overall conformation of a given drug molecule.
4. The overall effect of a given functional group is dependent upon other adjacent or surrounding functional groups.
5. Functional groups can be altered to provide specific therapeutic benefits.

role as the building blocks for proteins and enzymes. Among a plethora of other functions, proteins and enzymes serve as biological targets for drug molecules. As such, it is important to review the functional groups present on the twenty naturally occurring amino acids, as well as the functional groups present on commonly modified amino acids. A more in-depth discussion of drug binding interactions between drug molecules and their biological targets is provided in Chapter 6. The primary goal here is to identify the key chemical properties of the functional groups present in amino acids

and therefore in proteins. Similar to functional groups present on a drug molecule, the functional groups present on amino acids have electronic, solubility, and steric effects. The primary difference is that unlike drug molecules, the functional groups present on the amino acids of a protein or enzyme can't be changed. In many of the examples discussed in this chapter, we examined the advantages that could be gained by adding, removing, or altering a functional group. Since these types of alterations do not occur with the amino acids present in proteins and enzymes, this section has been intentionally placed at the end of the chapter.

As shown in **Figure** 2-17, each amino acid contains a primary amine, a carboxylic acid, and a side chain at the α-carbon. While this section focuses primarily on the functional groups present on the side chains, let us briefly examine the amines and carboxylic acids of amino acids. These functional groups are used to form amide bonds, or peptide bonds. A protein therefore consists of one or more peptide chains that contain numerous amide bonds, a primary amine at one end, and a carboxylic acid at the other end. These ionizable groups are often masked as amides and esters in order to avoid degradation by endogenous exopeptidases. The multiple amides that comprise the peptide backbone are polar functional groups and are extremely important for forming internal hydrogen bonds. Once the three-dimensional conformation of the peptide has been established, the functional groups present on the side chains are able to interact with drug molecules or other endogenous moieties.

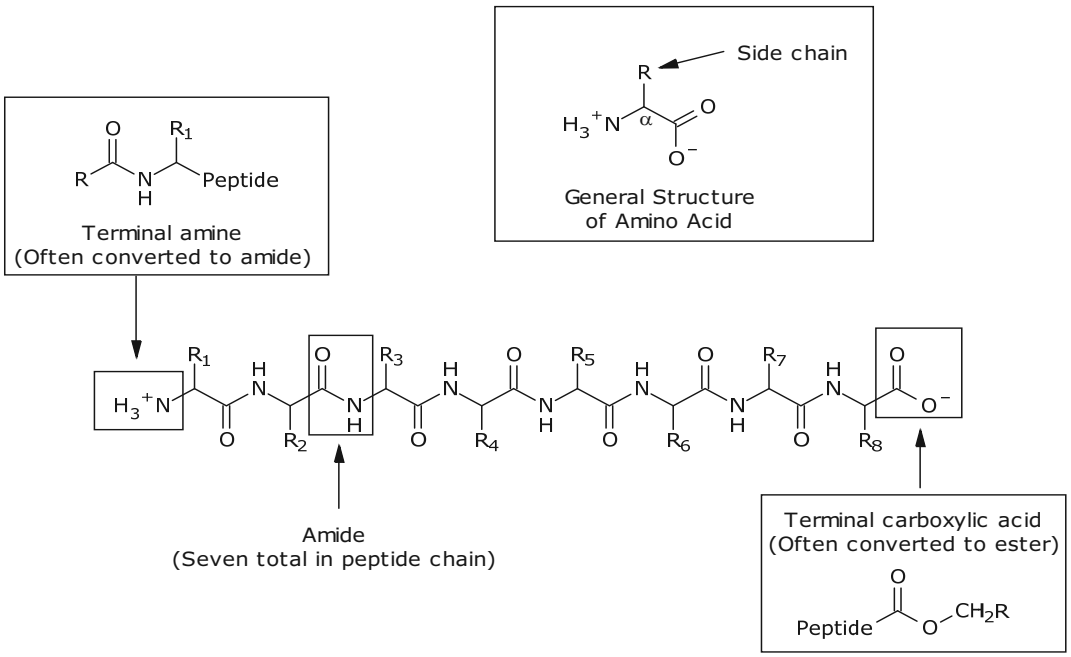
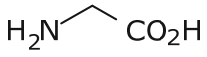


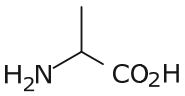
Figure 2-17. General structures of amino acids and peptide chains.

Glycine is the smallest and simplest of all of the amino acids. Its side chain is a hydrogen atom; although some texts view glycine has having no side chain. It is essentially neutral in terms of electronic or solubility effects. From a steric perspective, it really has no steric hindrance and conveys flexibility to a peptide chain. Please note that for glycine and all of the other amino acids to follow, the primary amine and the carboxylic acid are intentionally drawn in their unionized forms since they are normally involved in the formation of a peptide bond.

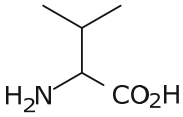


Glycine

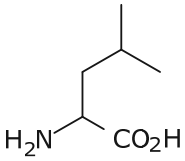
Alanine, valine, leucine, and isoleucine all contain aliphatic, lipid soluble, hydrocarbon side chains and have varying steric bulk. The side chains on these amino acids are most important for forming lipid soluble pockets within a protein or enzyme and interacting with other hydrocarbon chains on drug molecules or endogenous compounds. Additionally, the varying steric bulk on these amino acids can either block or allow access to certain portions of a protein depending upon which amino acid is present.



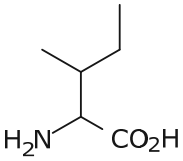
Alanine



Valine

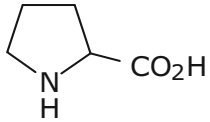


Leucine



Isoleucine

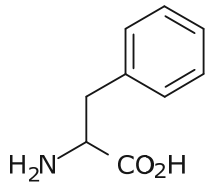
Proline is unique from all of the other naturally occurring amino acids in that it contains a secondary amine. Similar to the previous four amino acids, proline has a lipid soluble, hydrocarbon side chain. The key difference is that the side chain forms an alicyclic ring with the nitrogen atom. The most important feature of proline is that the alicyclic ring produces a significant steric affect that causes protein chains to kink or bend. In addition, due to the alicyclic ring, natural human proteases cannot cleave peptide bonds that include a proline amino acid.



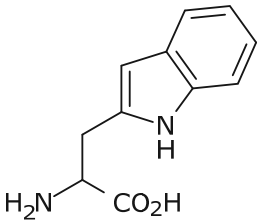
Proline

Phenylalanine and tryptophan contain aromatic rings and similar to the aliphatic and alicyclic amino acids are lipid soluble. Due to the aromaticity of both rings, these functional groups have a greater electronic nature and can interact with aromatic rings present on drug molecules. A key difference between these two amino acids is the

presence of the nitrogen atom in the bicyclic indole ring of tryptophan. This nitrogen is not basic due to the fact that its lone pair of non-bonding electrons is required for the aromaticity of the bicyclic ring. This donation of electrons causes the indole ring of tryptophan to be more electron rich than the phenyl ring of phenylalanine. Additionally, the nitrogen atom in the indole ring can act as a hydrogen bond donor and therefore can participate in hydrogen bonds. The phenyl ring of phenylalanine cannot do this. From a steric perspective, both rings are larger than the side chains of the above aliphatic or alicyclic amino acids.

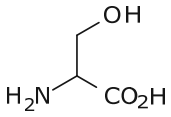


Phenylalanine

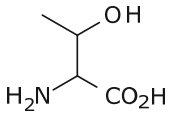


Tryptophan

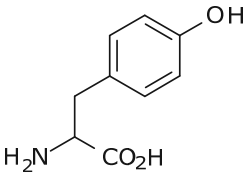
Serine, threonine, and tyrosine all contain hydroxyl groups within their side chains. These functional groups are very important due to their ability to form hydrogen bonds as both hydrogen bond donors and acceptors with water, as well as with other functional groups present within drug molecules. Both serine and threonine are classified as water soluble uncharged amino acids. Tyrosine is often classified as an aromatic amino acid along with phenylalanine and tryptophan; however, it is included here due to its phenolic hydroxyl group. It is more water soluble than the phenyl ring of phenylalanine. Additionally, the hydroxyl groups of all three of these amino acids are nucleophiles and are important for specific mechanisms in biochemical pathways and for the mechanisms of action of some drug molecules. Due to their nucleophilic nature, these functional groups are often phosphorylated as part of a regulatory mechanism or are added to increase the number of negative charges associated with the protein or enzyme. An example of this is seen with phosphoserine.



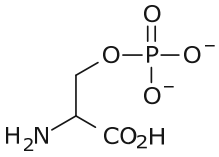
Serine



Threonine



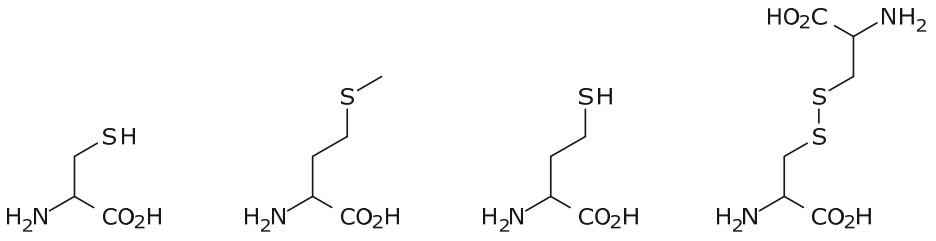
Tyrosine



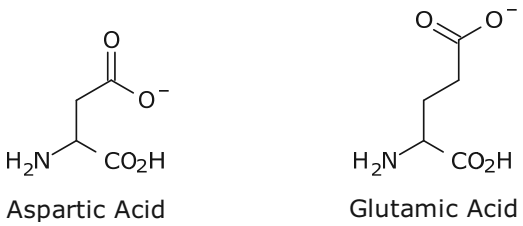
Phosphoserine

Cysteine and homocysteine are very similar to serine. Cysteine is one of the twenty naturally occurring amino acids, whereas homocysteine is a precursor to methionine and is involved in several biochemical pathways. Both of these are water soluble un-

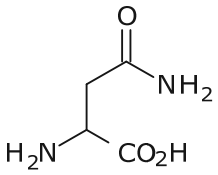
charged amino acids; however, their ability to form hydrogen bonds is weaker than that observed with serine, threonine, and tyrosine. They are also very nucleophilic. The ability of cysteine to form disulfide bonds is essential for the three-dimensional conformation of a number of peptides and proteins. Methionine, which contains a thioether in its side chain, is much less reactive and is often grouped along with alanine, valine, leucine, and isoleucine as a lipid soluble amino acid. It is included here because of its relationship to cysteine and homocysteine.



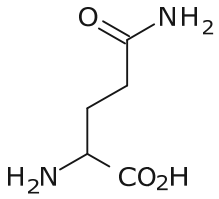
As the names imply, aspartic acid and glutamic acid are the two naturally occurring acidic amino acids. These carboxylic acids will be primarily ionized in most physiological environments, with the stomach being the primary exception. These functional groups are water soluble and provide negative charges for ionic interactions with positively charged functional groups or metal ions. The only difference between these two amino acids is the additional methylene carbon present in glutamic acid. Thus from a steric perspective, glutamic acid has somewhat more steric bulk than does aspartic acid. Similar to the terminal carboxylic acid shown in Figure 2-17, these amino acids can be esterified to remove their ability to be ionized and decrease their overall water solubility.



Asparagine and glutamine are the amide analogs of aspartic acid and glutamic acid, respectively. These amino acids are similar to serine, cysteine, and threonine in that their side chains are water soluble and not able to be ionized. The amide groups can serve as hydrogen bond donors and acceptors. Since the lone pair of non-bonding electrons on the amide nitrogen are involved in resonance with carbonyl group, they are not very nucleophilic.

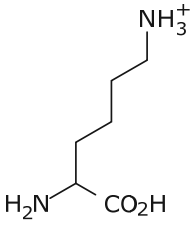


Asparagine

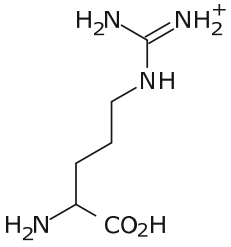


Glutamine

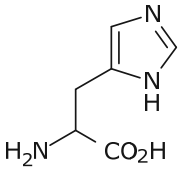
Finally, lysine, arginine, and histidine are the three naturally occurring basic amino acids. The relative basicities of these functional groups is discussed in more detail in the next chapter; however, both lysine and arginine are primarily ionized in all physiological environments and can provide positive charges for ionic interactions with negatively charged functional groups. Histidine is less basic than either lysine or arginine and is primarily unionized in most physiologically relevant environments. Histidine can act as either a hydrogen bond donor or a hydrogen bond acceptor. The functional groups on all three amino acids enhance water solubility. The primary amine of lysine can be methylated to form a quaternary amine, trimethyllysine. This provides a permanent positive charge within a protein.



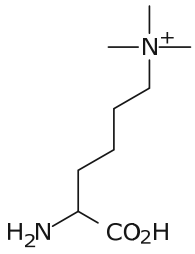
Lysine



Arginine



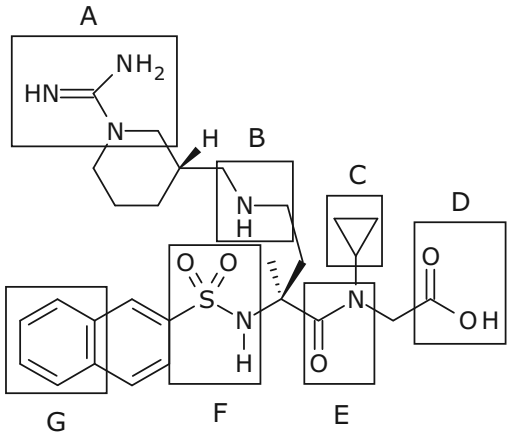
Histidine



Trimethyllysine

REVIEW QUESTIONS

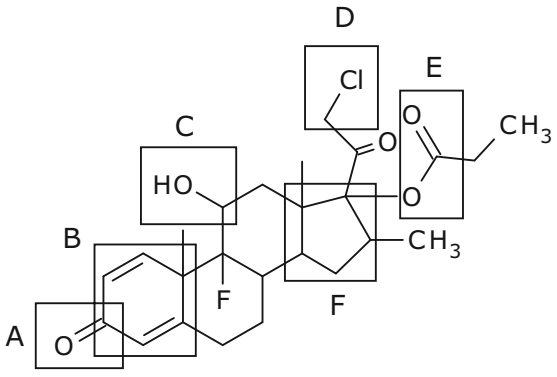
1. For the structure of napsagatran, name all of the boxed functional groups in the grid below.



Napsagatran

Box	Functional Group Name
A	
B	
C	
D	
E	
F	
G	

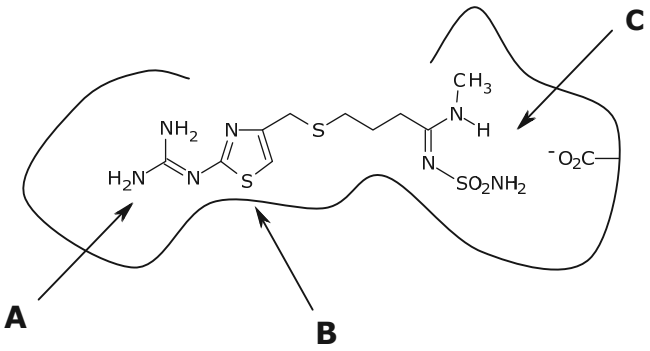
2. For the structure of clobetasol, name all of the boxed functional groups in the grid below.



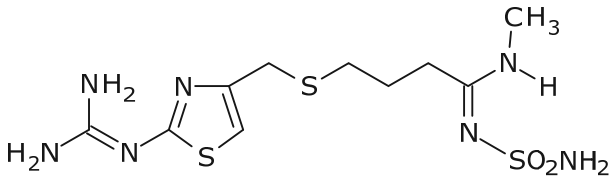
Clobetasol

Box	Functional Group Name
A	
B	
C	
D	
E	
F	

3. The structural features found within H_2 receptor antagonists include a basic functional group that is protonated at physiological pH (A), an aromatic ring (B) and a terminal non-basic polar functional group (C) that is separated from the aromatic ring by the equivalent of a four-carbon chain. The terminal non-basic polar functional group participates in a key ion-dipole interaction with an ionized carboxylic acid found in the binding region within the H_2 receptor.



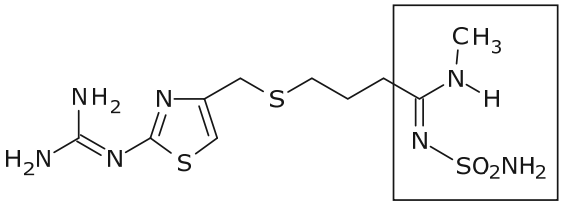
A. Identify all of the functional groups that are present in the structure of famotidine.



Famotidine (Pepcid)

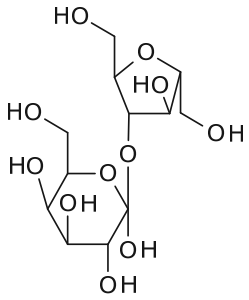
B. Guanidines and amidines that are substituted with electron withdrawing groups have significantly decreased basicity compared to unsubstituted guanidines (pKa ~ 12.5) and amidines (pKa ~ 9) and are unprotonated (unionized) at physiological pH. Name the two electron withdrawing functional groups found within famotidine.

C. The boxed functional group (show below) participates in a key ion-dipole interaction with an ionized carboxylic acid group found in the H_2 receptor binding region. Provide a brief rationale why this functional group is not protonated (ionized) at physiological pH.



Famotidine (Pepcid)

4. JB, a 47-year-old mother of three children under the age of eight, has experienced prolonged periods of constipation after the birth of her last child 3 years ago. She has changed her diet to include more fiber and has increased her fluid intake as recommended by her physician. There does not appear to be any correlation between what she eats and the length of time she experiences constipation. She does stay away from foods that are binding, including bananas, rice, and apples. Her physician suggests that she try taking Enulose®, and if that doesn't work, he may recommend glycerin suppositories.



Lactulose (Enulose)

A. Consider the structure of Enulose® drawn above when completing the grid below.

Name of Three Oxygen Containing Functional Groups	Hydrophilic and/or Hydrophobic	Contribution to Water Solubility and/or Lipid Solubility	Hydrogen Bond Acceptor, Donor, Both or Neither

B. Enulose® is supplied as an aqueous solution of lactulose 10 mg/15 mL and is typically administered three or four times daily (30–45 mL/dose). Based on your functional group evaluation on the previous page, provide a structural rationale for why Enulose® can be formulated as an aqueous solution.

C. Mechanistically, lactulose is classified as an osmotic laxative, which means that it is able to draw water into the intestine to help soften the stool. Based on your functional group evaluation on the previous page, provide a structural rationale for why Enulose® is able to draw water into the intestine.

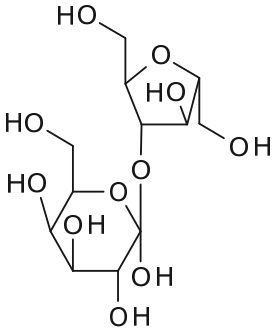
D. Using the structure below, show (and label) examples of the following interactions.

a. Drug/water interaction: drug = hydrogen bond acceptor; water = hydrogen bond donor

b. Drug/water interaction: drug = hydrogen bond donor; water = hydrogen bond acceptor

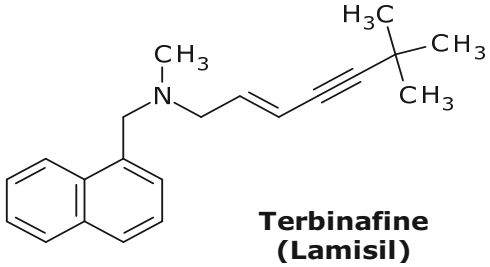
c. Drug/water interactions: dipole/dipole interaction

Note: When appropriate, be sure to draw in the correct arrow and partial charges.



Lactulose (Enulose)

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



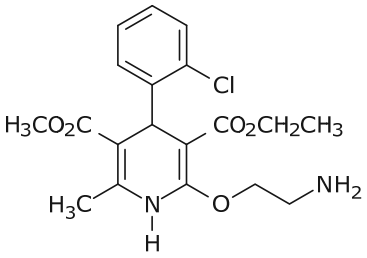
Terbinafine (Lamisil)

A. Identify all of the structural features present in terbinafine and complete the grid below.

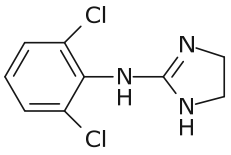
Name of Functional Group	Hydrophilic and/or Hydrophobic	Contribution to Water Solubility and/or Lipid Solubility

B. Using the information that you provided in the grid in the previous question, provide a structural rationale for why terbinafine is an agent that can be applied topically. (Hint: Agents that are administered topically must absorb into the hydrophobic components of the skin in order to be effective.)

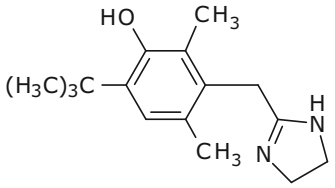
6. Binding interactions with a biological target can be significantly impacted by the presence or absence of functional groups that dictate a molecule's shape. In each of these molecules, functional groups in the *ortho* position of the aromatic rings force the two ring systems to be perpendicular to one another. Circle the functional groups that influence the shape of each of these molecules.



Amlodipine

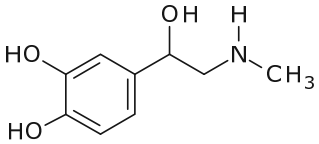


Clonidine

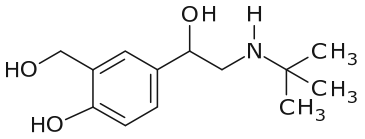


Oxymetazoline

7. Specificity for a biological target can be significantly impacted by the presence or absence of functional groups that alter the size of a molecule. Epinephrine is a non-selective agonist at α and β receptors. Determine which functional group in albuterol causes it to have β receptor selectivity and identify if the functional group represents a change in electronic or steric factors.

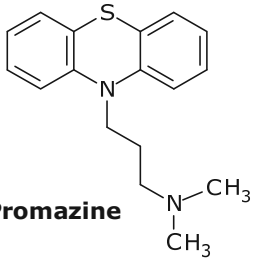


Epinephrine

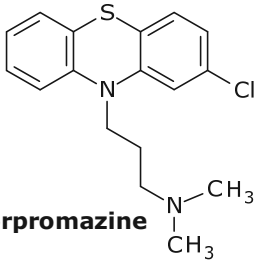


Albuterol

8. The addition of one functional group can significantly alter the biological activity that a molecule exhibits. In this case, the presence of a chloro substituent allows for dopaminergic action. Determine whether or not this change in biological activity is a result of a steric or electronic effect and provide a rationale for your answer.

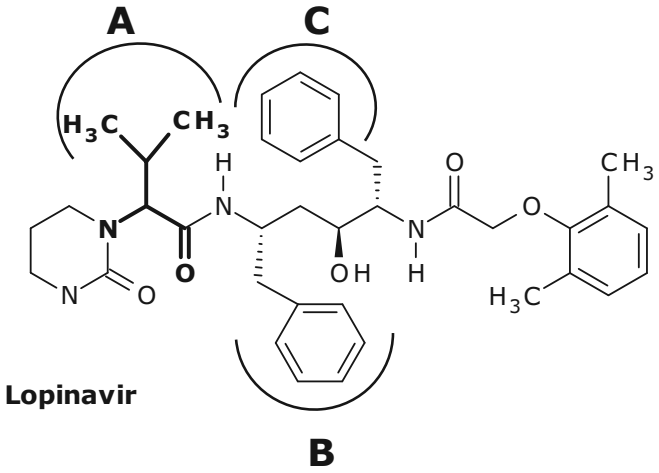


Promazine



Chlorpromazine

9. Lopinavir is an HIV protease inhibitor. Structurally, this drug is considered a peptidomimetic, in that it resembles (at least in part), the peptide substrate for the protease. In the presence of this agent, HIV protease is unable to cleave the *gag-pol* polypeptide into its functional proteins during viral assembly and budding.



Lopinavir

A. Consider the portion of the molecule designated as "A" (You will notice that the atoms and bonds of this portion of the molecule have been bolded for you.) Which amino acid is this? How do you anticipate that the side chain of this amino acid will contribute to solubility and absorption of this drug?

B. Consider the portions of the molecule designated as "B" and "C," while the normal peptide bond sequence has been slightly changed, the side chains are unaltered. Which amino acid do these portions resemble? How do you anticipate that the side chain of this amino acid interacts with the biological target?