APP

ANSWERS TO CHAPTER QUESTIONS

CHAPTER 2

STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

1. Answers provided in table below.

	Functional Group Name	Contribution to Water and/or Lipid Solubility
A	Halogen (chlorine atom)	Lipid Solubility
B	Alicyclic ring, alkyl ring, cycloalkane	Lipid Solubility
C	Tertiary amine (piperazine)	Water Solubility
D	Heterocyclic ring system (pyrrolopyridine)	Hydrocarbons: Lipid Solubility Nitrogen atoms: Water Solubility
E	Aromatic ring; phenyl ring; aromatic hydrocarbon	Lipid Solubility
F	Sulfonamide	Water Solubility
G	Secondary aromatic amine/aniline	Water Solubility
H	Ether	Hydrocarbons: Lipid Solubility Oxygen atom: Water Solubility

2. The sulfonamide and tertiary amine will be primarily ionized in most physiological environments and can participate in ion-dipole interactions (as the ion) with water. In the event that they are unionized, they could participate in hydrogen bonding interactions with water. The nitrogen atoms of the heterocyclic ring system, as well as the secondary aromatic amine, and the oxygen atom of the ether will not be appreciably ionized, but can participate in hydrogen bonding interactions with water. Thus, all of these functional groups contribute to the water solubility of venetoclax. The halogen as well as the hydrocarbon chains and rings are not able to ionize or form hydrogen bonds with water and thus contribute to the lipid solubility of venetoclax.

3. Answers provided in table below.

	Electron Donating or Withdrawing	Resonance or Induction
A	Electron Withdrawing	Induction
B	Both	Donates electrons into the aromatic ring through resonance. Withdraws electrons from adjacent methylene groups through induction.
C	Electron Donating	Resonance
D	Electron Withdrawing	Induction (from aromatic ring) Resonance (from ionized sulfonamide)
E	Electron Withdrawing	Resonance

Checkpoint Drug 2: Elamipretide

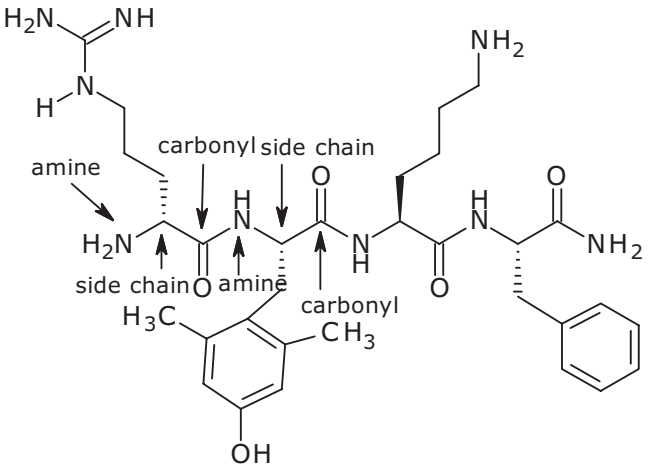
1. Answers provided in the grid below.

	Name of Functional Group	Character: Hydrophobic, Hydrophilic, or both	Function: Contribute to Solubility or Absorption
A	Guanidine	Hydrophobic (R) Hydrophilic ($H_2NCNHNH$)	Absorption (R) Solubility ($H_2NCNHNH$)
B	Primary amine	Hydrophobic (R) Hydrophilic (NH_2)	Absorption (R) Solubility (NH_2)
C	Amide	Hydrophobic (R) Hydrophilic ($C{=}ONH_2$)	Absorption (R) Solubility ($C{=}ONH_2$)
D	Aromatic hydrocarbon; aromatic ring; phenyl ring	Hydrophobic (R)	Absorption (R)
E	Phenol	Hydrophobic (R) Hydrophilic (OH)	Absorption (R) Solubility (OH)

R = carbon scaffolding

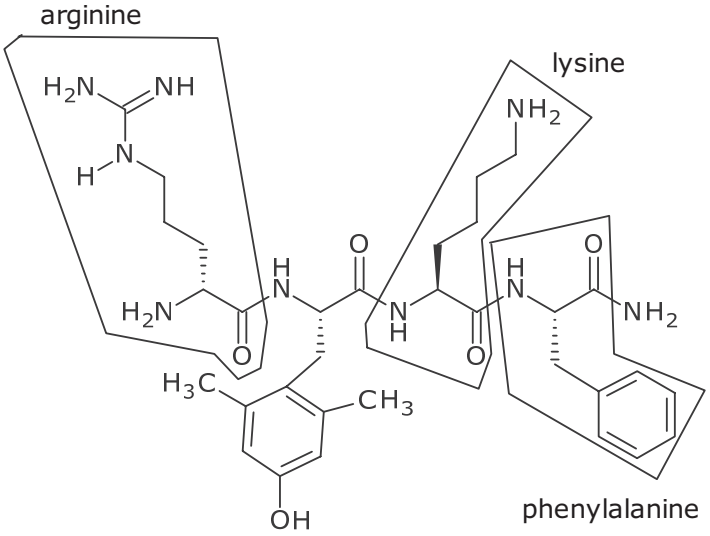
2. **Part A:** Every amino acid has an amine (basic), a unique side chain, and a carboxylic acid (acidic). As building blocks of proteins, the amine and carboxylic acid of adjacent amino acids are linked to form an amide or peptide linkage (neutral).

   Part B: As building blocks of endogenous proteins or peptidomimetic drugs, the amine and carboxylic acid of adjacent amino acids are linked to form a peptide bond (amide = neutral). The easiest way to read these kinds of molecules is to look for the pattern "amine-side chain-carbonyl" (representing one amino acid) and to completely ignore the fact that the amine and adjacent carboxylic acid are really an amide. In the diagram below, the "amine-side chain-carbonyl" pattern for the first two amino acids/amino acid derivatives is shown.



Using this pattern, the first amino acid in the sequence is the amino acid arginine, the second amino acid is a derivative of tyrosine, the third amino acid is lysine, and the fourth amino acid is phenylalanine.

Part C: The portions of the molecule that represent arginine, lysine, and phenylalanine have been boxed.



Part D: The second amino acid is a derivative of tyrosine.

3. Answers provided in the grid below.

	Name of Amino Acid or Amino Acid Derivative	Amino Acid Side Chain Evaluation: Hydrophobic, Hydrophilic, or Both	Amino Acid Side Chain Evaluation: Acidic, Basic, Neutral	Amino Acid Side Chain Evaluation: Nucleophilic, Electrophilic, NA
1	Arginine	Hydrophilic ($NHC{=}NHNH_2$) Hydrophobic (R)	Basic	NA
2	Tyrosine derivative	Hydrophilic (OH) Hydrophobic (R)	Acidic	Nucleophilic
3	Lysine	Hydrophilic (NH_2) Hydrophobic (R)	Basic	Nucleophilic
4	Phenylalanine	Hydrophobic	Neutral	NA

R = carbon scaffolding.

REVIEW QUESTIONS

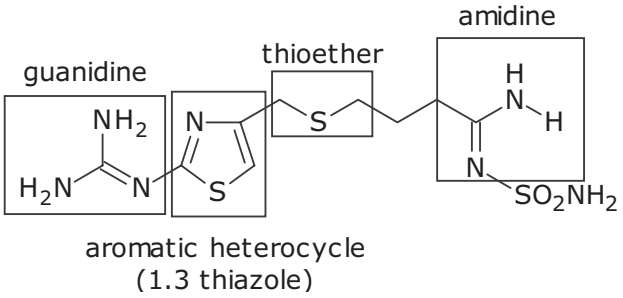
1. Answers provided in the grid below.

Box	Functional Group Name
A	Guanidine
B	Secondary amine
C	Cycloalkane (cyclopropane)
D	Carboxylic acid
E	Amide
F	Sulfonamide
G	Aromatic hydrocarbon (or aromatic ring)

2. Answers provided in the grid below.

Box	Functional Group Name
A	Ketone
B	Cycloalkene (cyclohexadiene)
C	Secondary alcohol
D	Aliphatic halogen
E	Ester
F	Cycloalkane

3. **Part A:** Functional groups are identified in the structure shown below.



Part B: The aromatic heterocycle (1,3 thiazole) and the sulfonamide are both electron withdrawing groups and will significantly decrease the magnitude of the pK_a values for both the guanidine and amidine. The experimentally measured pK_a values for the guanidine and the amidine are in the range of 6.7–6.9.

Part C: The amidine is not protonated at physiological pH because the sulfonamide is an electron withdrawing group and will pull (or withdraw) electrons from the amidine through induction. This will decrease the ability of the amidine to attract protons (H^+); therefore, its basicity will decrease.

The experimentally measured pK_a values for famotidine are all in the range of 6.7 and 6.9. The amidine, guanidine, and aromatic heterocycle are all basic in character. At pH = 7.4, the pH > pK_a for these functional groups and, therefore, the basic functional groups are predominantly unionized in this pH environment.

4. **Part A:** Answers provided in 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**
Primary alcohol	Hydrophilic (OH) Hydrophobic (R)	Water solubility (OH) Lipid solubility (R)	Hydrogen bond acceptor and donor
Secondary alcohol	Hydrophilic (OH) Hydrophobic (R)	Water solubility (OH) Lipid solubility (R)	Hydrogen bond acceptor and donor
Ether	Hydrophilic (O) Hydrophobic (R)	Water solubility (O) Lipid solubility (R)	Hydrogen bond acceptor

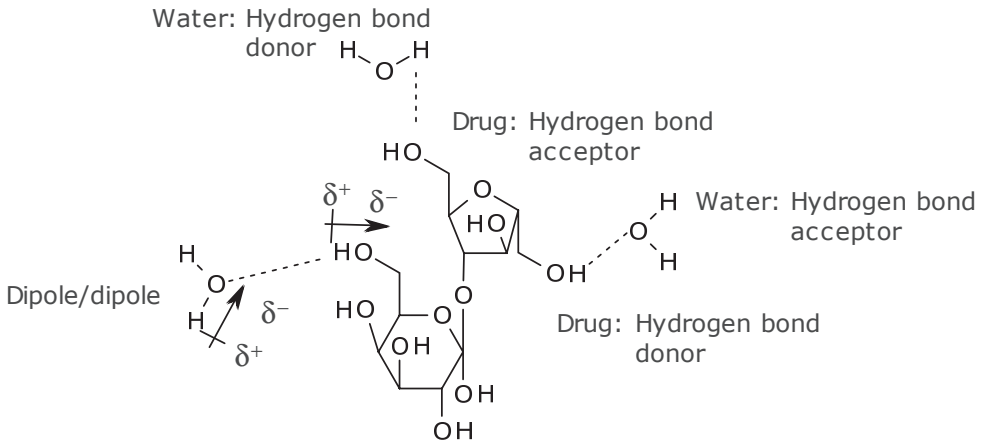
R = carbon scaffolding.

Part B: The primary and secondary alcohols, as well as the ethers, all have hydrophilic character. The alcohols (primary and secondary) are able to interact with water as both hydrogen bond acceptor and donors, which means that they make a sizable contribution to the water solubility of lactulose. The ethers are able to interact with water as a hydrogen bond acceptor only and, therefore, make somewhat less of a contribution to water solubility as compared to the alcohols.

Part C: The primary and secondary alcohols, as well as the ethers all have hydrophilic character. The alcohols (primary and secondary) are able to interact with water as both hydrogen bond acceptors and donors, which means that they will be able to attract and interact with water. The ethers are able to interact with water as a hydrogen bond acceptor only and, therefore, make somewhat less of a contribution to the drug's ability to attract and interact with water.

One mechanism to relieve constipation is to increase the water content of the stool so as to make it easier to eliminate. Lactulose achieves this by attracting and interacting with water with its seven OH groups and two ethers.

Part D: Answer provided in figure below.



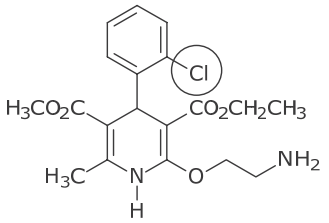
5. **Part A:** Answers provided in the grid below.

Name of Functional Group	Hydrophilic and/or Hydrophobic	Contribution to Water Solubility and/or Lipid Solubility
Aromatic hydrocarbon	Hydrophobic	Lipid solubility
Aliphatic alkane (branched)	Hydrophobic	Lipid solubility
Tertiary amine	Hydrophobic (R) Hydrophilic (N atom)	Lipid solubility (R) Water solubility (N atom)

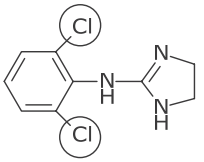
R = carbon scaffolding.

Part B: Butenafine has several functional groups (aromatic hydrocarbons, branched aliphatic alkane) that are hydrophobic in character and contribute significantly to lipid solubility and drug absorption. These features contribute to the ability of the drug to easily absorb into the skin, which has considerable lipid character.

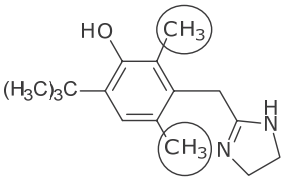
6. Functional groups that influence the shape of each molecule have been circled.



Amlodipine



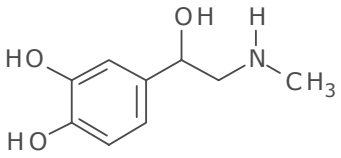
Clonidine



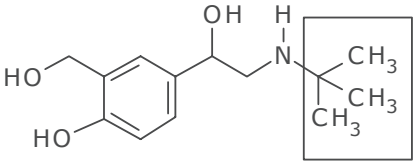
Oxymetazoline

7. Functional group and explanation provided below.

Change in steric factor



Epinephrine



Albuterol

8. The only structural difference between these two molecules is the presence of a tertiary amine in the parent drug and an *N*-methylated secondary amine in the active metabolite. The parent drug (with the tertiary amine) selectively inhibits the reuptake of serotonin. The active metabolite (desmethyl metabolite) selectively inhibits the reuptake of norepinephrine. This change in the number of methyl substituents represents a change in the steric character of the molecule.

9. **Part A:** The portion of the molecule designated as "A" is the amino acid valine. The side chain of this amino acid is hydrophobic in character and will improve the ability of the drug to be absorbed across lipophilic membranes. This characteristic will decrease the water solubility of the drug.

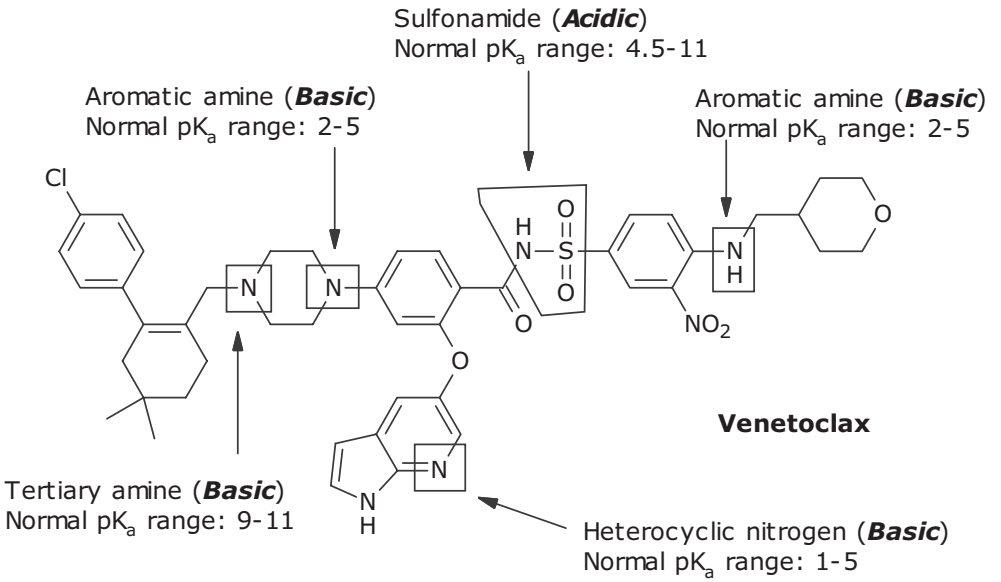
   Part B: The portions of the molecule designated as "B" and "C" resemble the side chain of the amino acid phenylalanine. The side chain of this amino acid is hydrophobic in character and will interact with hydrophobic regions present within the biological target. The most likely interactions would be with the side chains of the aromatic amino acids phenylalanine, tyrosine, or tryptophan; however, it could also interact with the side chains of the aliphatic amino acids, alanine, valine, leucine, or isoleucine. The ritonavir side chains "B" and "C" can also participate in π-π stacking interactions with the side chains of phenylalanine, tyrosine, tryptophan, and histidine present within the biological target. It is also possible for these side chains to participate in cation-π interactions with lysine and arginine that are ionized at physiological pH.

CHAPTER 3

STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

1. Acidic and basic functional groups along with normal pK_a ranges are shown below.



Venetoclax

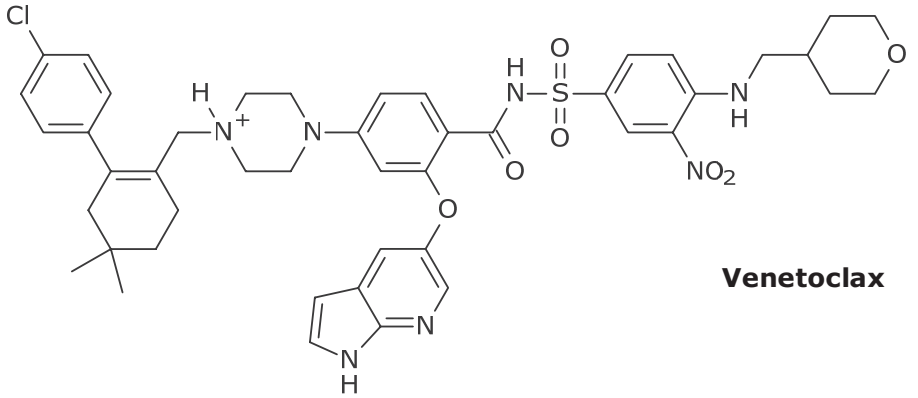
2. Venetoclax is an amphoteric drug because its structure contains both acidic and basic functional groups.

3. There are two main factors that contribute to the enhanced acidity of the sulfonamide functional group. First, this functional group is directly attached to a carbonyl group. Similar to sulfonylureas, this adjacent carbonyl enhances the acidity of the sulfonamide through resonance stabilization of the negative charge. Once the proton leaves, the resulting negative charge can be equally delocalized to all three adjacent oxygen atoms. Second, the nitro group on the adjacent aromatic ring can withdraw electrons from the aromatic ring through resonance. This decreases the electron density of the aromatic ring and causes an inductive effect that withdraws electrons from the adjacent sulfonamide. The overall effect of this nitro group is somewhat decreased due to the ability of the aromatic amine to donate electrons through resonance into this same aromatic ring. Since the electron withdrawing properties of the nitro group are stronger than the electron donating properties of the aromatic amine, the net result is an electron withdrawing effect that enhances the acidity of the sulfonamide group.

4. Five-membered rings that contain a single nitrogen atom are not basic because the lone pair of electrons on the nitrogen atom is involved in the aromaticity or resonance delocalization of the ring and unavailable for binding to a proton. The presence of a second nitrogen atom within the five-membered ring enhances basicity as discussed in the chapter; however, in this case, the second nitrogen

atom is in the six-membered pyridine ring. This nitrogen atom is basic because the lone pair of electrons on the nitrogen atom is oriented perpendicular to the plane of the aromatic π electrons. Thus, the lone pair of electrons are involved in the aromaticity of the ring and are available to bind to a proton.

5. The ionized form of the tertiary amine is shown below.



Venetoclax

Checkpoint Drug 2: Elamipretide

1. Answers provided in the grid below.

	Name of Functional Group	Character: Acidic, Basic, Neutral	pK_a Value or Range (NA is acceptable)
A	Guanidine	Basic	12.5*
B	Primary amine	Basic	9–11
C	Amide	Neutral	NA
D	Phenol	Acidic	9–10

*The pK_a range for guanidine can dip as low as 6, especially if the functional group is attached to one or more electron withdrawing groups, as found in the H_2 antagonist class of drugs.

2. Functional group C is an amide. The carbonyl carbon is electron poor due to the electronegativity of the adjacent oxygen atom and the resulting dipole. This carbon atom looks to its neighbor nitrogen atom for electron density. The neighboring nitrogen atom has a non-bonding pair of electrons that is available (via resonance) to donate electron density to the electron deficient carbon atom. Because this non-bonding pair of electrons is busy helping the neighbor electron deficient carbon atom, it is unavailable to participate as a proton acceptor (base). By way of reminder, the electronegative oxygen atom has two pairs of non-bonding electrons, but these electrons are held too tightly to the nucleus of the oxygen atom to participate as a proton acceptor (base). As a result, amides are neutral in character.

3. The ionization states and acid/base character are provided below.

	Stomach (pH=1) Ionized, Unionized, NA	Acid/Base Character at pH=1	Intestine (pH=8) Ionized, Unionized, NA	Acid/Base Character at pH=8	Urine (pH=5) Ionized, Unionized, NA	Acid/Base Character at pH=5
A	Ionized	Acidic	Ionized	Acidic	Ionized	Acidic
B	Ionized	Acidic	Ionized	Acidic	Ionized	Acidic
C	NA	Neutral	NA	Neutral	NA	Neutral
D	Unionized	Acidic	Unionized	Acidic	Unionized	Acidic

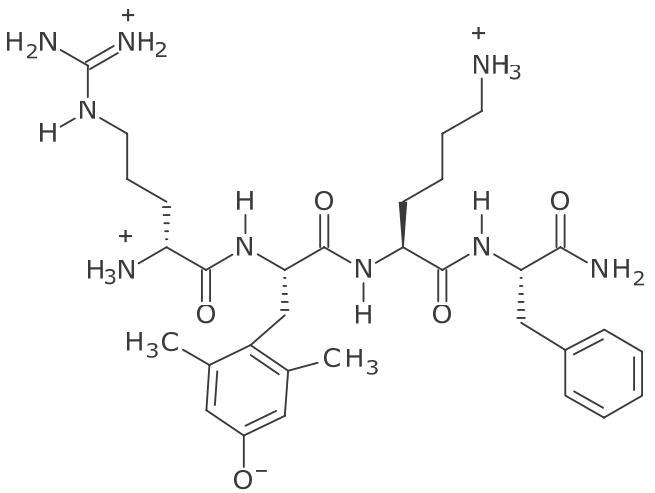
Functional group A (guanidine) is basic in character with a pK_a = ~12.5. It will be ionized in all three physiological locations because the environmental pH<pK_a of the functional group. In its ionized form, a guanidine is a proton donor (acidic).

Functional group B (primary amine) is basic in character with a pK_a range = 9–11. It will be ionized in all three physiological locations because the environmental pH<pK_a of the functional group. In its ionized form, a primary amine is a proton donor (acidic).

Functional group C (amide) is neutral in character. It is not an ionizable functional group, so NA should be placed in the grid.

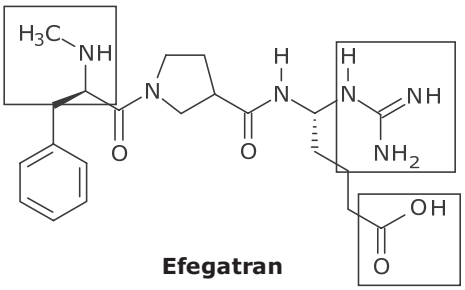
Functional group D (phenol) is acidic in character with a pK_a = 9–10. It will be unionized in all three physiological locations because the environmental pH<pK_a of the functional group. In its unionized form, a phenol is a proton donor (acidic).

4. The guanidine of arginine, the primary amine of lysine, and the phenol of the tyrosine derivative are all ionizable. Don't forget that this peptide-based drug has an amino- and a carboxy terminus!!! In this case, the carboxy terminus carboxylic acid has been masked as an amide, but the amino terminus primary amine is still present and is ionizable.

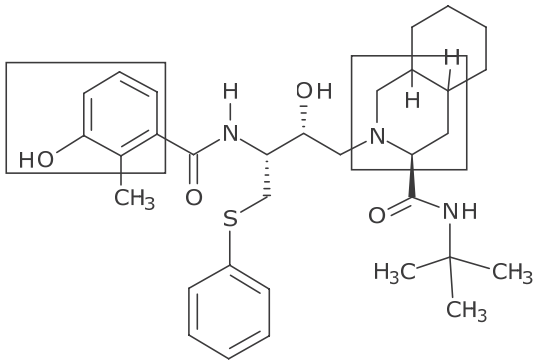


REVIEW QUESTIONS

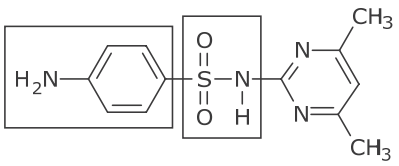
1. Acidic and basic functional groups are identified below.



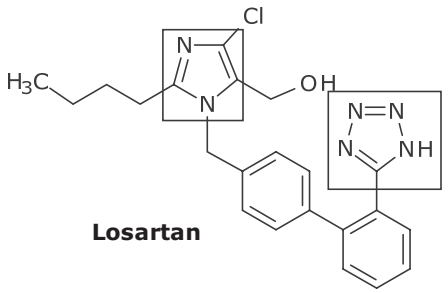
Efegatran



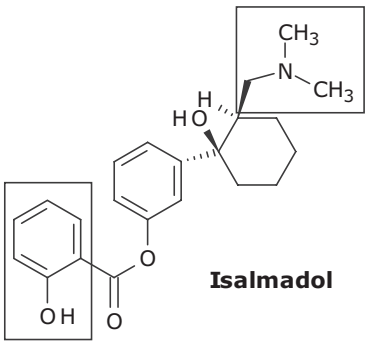
Nelfinavir



Sulfamethazine



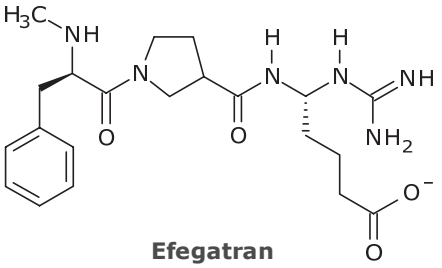
Losartan



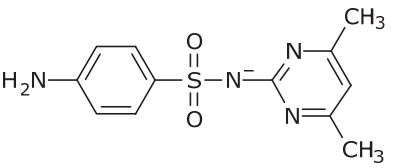
Isalmadol

Drug Name	Acidic Functional Groups	Basic Functional Groups
Efegatran	Carboxylic acid	Secondary amine Guanidine
Nelfinavir	Phenol	Tertiary amine (piperidine)
Sulfamethazine	Sulfonamide	Aniline
Losartan	Tetrazole	Imidazole
Isalmadol	Phenol	Tertiary amine

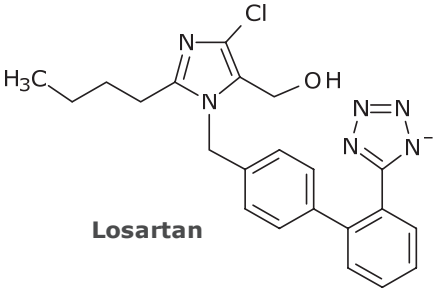
2. Acidic functional groups have been modified to show the ionized form.



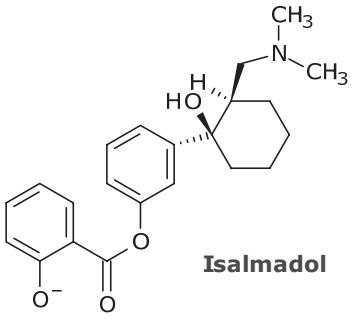
Efegatran



Sulfamethazine

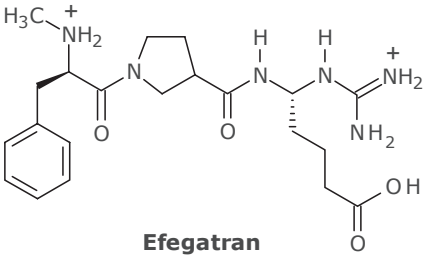


Losartan

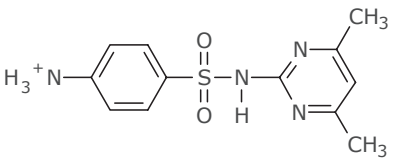


Isalmadol

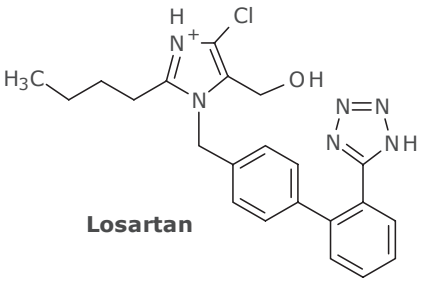
3. Basic functional groups have been modified to show the ionized form.



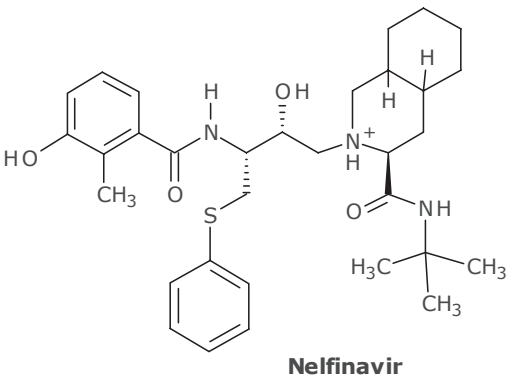
Efegatran



Sulfamethazine



Losartan



Nelfinavir

4. Functional groups that are acidic when they are in their ionized form are identified below.

Efegatran	Sulfamethazine	Nelfinavir	Losartan	Isalmadol
Secondary amine	Aniline	Tertiary amine (piperidine)	Imidazole	Tertiary amine
Guanidine				

Functional groups that are basic when they are in their ionized form are identified below.

Efegatran	Sulfamethazine	Nelfinavir	Losartan	Isalmadol
Carboxylic acid	Sulfonamide	Phenol	Tetrazole	Phenol

5. Amphoteric: contains at least one acidic and at least one basic functional group. All of the drugs in Question #1 are amphoteric in nature.

6. Answers provided in the grid below.

Drug	Name of Functional Group(s)	Approximate pK_a Value(s)	Acidic, Basic, or Amphoteric
Bromocriptine	Heterocycle (tertiary amine)	pK_a = 9–11	Basic
Imipenem	Carboxylic acid Amidine	pK_a = 2.5–5 pK_a = 10–11	Amphoteric
Physostigmine	Heterocycle (tertiary amine) Aniline	pK_a = 9–11 pK_a = 2–5	Basic

7. **Part A:** Colesevelam contains a neutral quaternary ammonium salt as a component of the polymer. It also contains ionizable functional groups (primary amine, secondary amine) both of which are basic in character. Evaluating the entire polymeric structure, colesevelam is considered basic in character. Because colesevelam will dissociate into ions in solution, it is therefore classified as an electrolyte.

   Part B: Drugs that contain one or more functional groups that are anionic (negatively charged) when in an environment of pH ~8 will exchange for the chloride ion in the polymer. The drug will then be associated with the polymer and be eliminated via a fecal route. This results in less drug available to be absorbed into the body (also less bile acids being removed). This will likely reduce the therapeutic effectiveness of the drug because a portion of the dose was removed by the polymer.

   Part C: Repaglinide (carboxylic acid), gliclazide (sulfonylurea), ciprofloxacin (carboxylic acid), and irbesartan (tetrazole) are all likely to be anionic at pH ~8 and therefore will be sequestered by the polymeric drug.

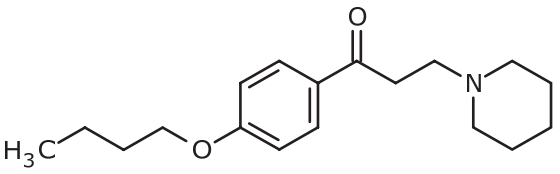
8. **Part A:** Ionizable functional groups are listed in the table below.

	Acidic Functional Groups	**Basic Functional Groups**
Repaglinide	Carboxylic acid	Aniline
Gliclazide	Sulfonylurea	Heterocycle (tertiary amine)
Ciprofloxacin	Carboxylic acid	Aniline Heterocycle (tertiary amine)
Irbesartan	Tetrazole	Imine

Part B: The acidic and/or basic character of each drug molecule is provided below.

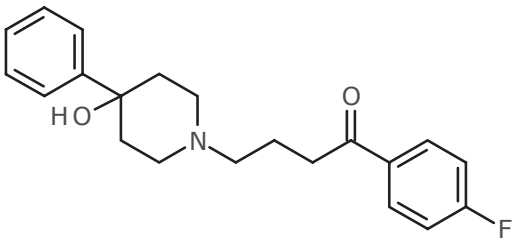
	Acidic Character, Basic Character, or Both Acidic and Basic Character
Repaglinide	Acidic and Basic Character
Gliclazide	Acidic and Basic Character
Ciprofloxacin	Acidic and Basic Character
Irbesartan	Acidic and Basic Character

9. The acidic, basic, or amphoteric character of the four drugs is provided below.



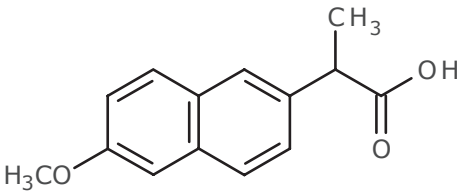
Dyclonine

Basic drug molecule (heterocycle – tertiary amine)



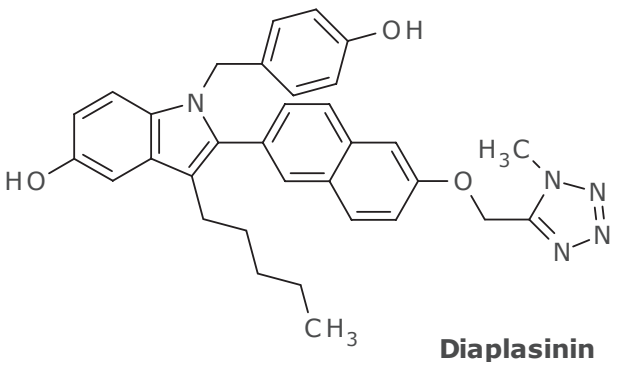
Haloperidol

Basic drug molecule (heterocycle – tertiary amine)



Naproxen

Acidic drug molecule (carboxylic acid)



Diaplasinin

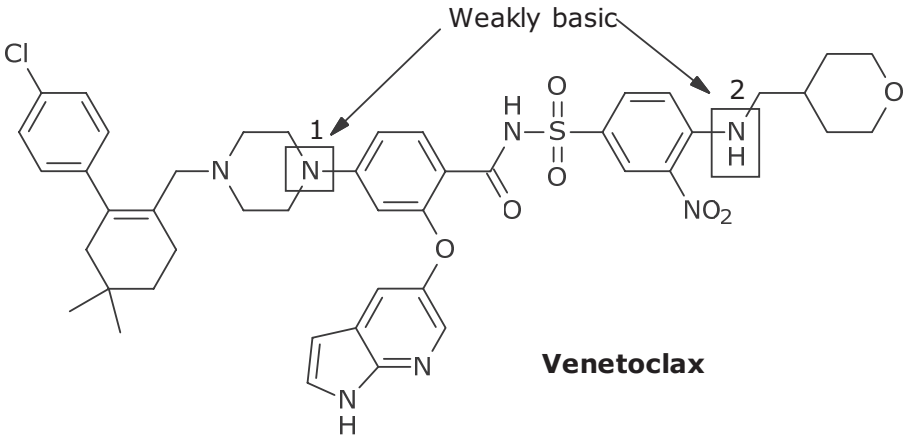
Acidic drug molecule (phenols)

CHAPTER 4

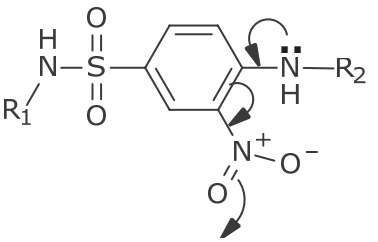
STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

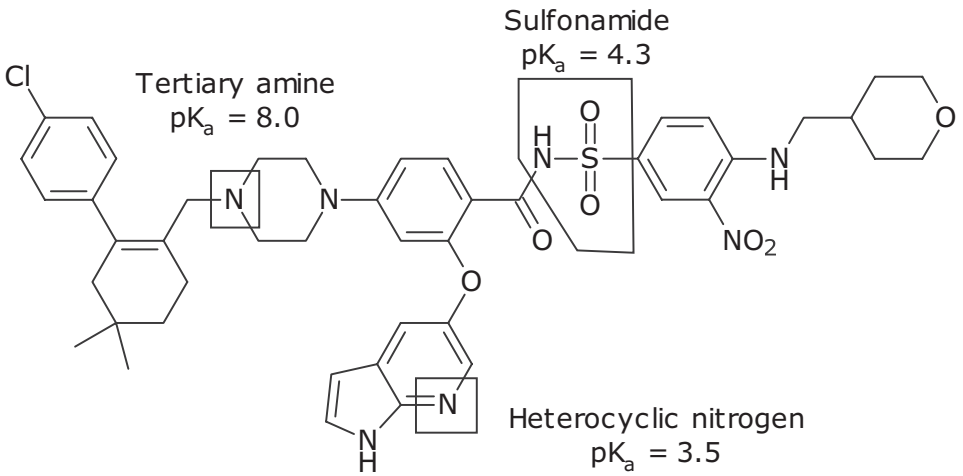
1. **Part A:**The two aromatic amines are weakly basic due to the presence of other electron withdrawing groups attached to their respective phenyl rings. As discussed in Chapter 3, aromatic amines are much less basic than aliphatic or alicyclic amines due to their ability to donate electrons into the aromatic ring through resonance. This donating ability can be either enhanced or hindered due to the presence of other functional groups. For aromatic amine 1, the *para* carbonyl on the aromatic ring is electron withdrawing, mostly through inductive effects, and enhances the flow of electrons away from the nitrogen and further decreases its basicity. Additionally, the *meta* ether oxygen atom may play a role. While both the aromatic amine and the ether oxygen can donate electrons into the aromatic ring, the oxygen atom is more electronegative than the nitrogen atom and thus withdraws electrons from the nitrogen atom via induction. Both of these effects decrease the availability of the lone pair of electrons and thus the basicity of aromatic amine 1.



For aromatic amine 2, the *ortho* nitro group is electron withdrawing in character and will greatly decrease the basicity of the amine through resonance delocalization as shown below.



Part B: The normal pK_a range for a tertiary amine is 9–11. Given this piece of information, the pK_a of 8.0 should be assigned to this basic functional group. The lower basicity may be due to steric hindrance or adjacent functional groups. This leaves the heterocyclic nitrogen atom (***basic***) and the sulfonamide (***acidic***) and the pK_a values of 3.5 and 4.3. The normal pK_a range for a sulfonamide is 4.5–11, and the normal pK_a range for heterocyclic nitrogen atoms is 1–5. While both of these pK_a values fall with the normal range for heterocyclic nitrogen atoms, the pK_a value of 3.5 belongs to the heterocyclic nitrogen atom. This is because the pK_a value of 4.3 is only slightly lower than the normal range for sulfonamides, while the pK_a value of 3.5 is too far outside this range. A full explanation of the pK_a value for the sulfonamide can be found in the answers for Chapter 3.



2. **Part A:** The tertiary amine and the heterocyclic nitrogen will be primarily ionized, and the sulfonamide will be primarily unionized.

   Part B: The tertiary amine and the sulfonamide will be primarily ionized, and the heterocyclic nitrogen will be primarily unionized.

   Part C: The tertiary amine and the sulfonamide will be primarily ionized, and the heterocyclic nitrogen will be primarily unionized.

3. **Part A:** To use the Rule of Nines, the difference between the pH and the pK_a must be an integer (i.e., 1, 2, 3). In evaluating the above nine scenarios, there is only one scenario that meets this criteria, ***the sulfonamide at a urine pH of 5.3***. For this sulfonamide, the absolute value between the pH and the pK_a is equal to 1; thus, there is a 90:10 ratio. Because the sulfonamide (pK_a = 4.3) is acidic, it will be primarily ionized in a basic environment (pH = 5.3). We can then use this ratio to determine that it will be 90% ionized.

   Part B: There are two methods that allow the Rule of Nines to approximate the percent to which a functional group is ionized even if the difference between the pH and the pK_a ***is not*** an integer. The first method is to round either the pH of the environment or the pK_a of the functional group so that there is an integral difference. Using the tertiary amine, absolute value between the pH and the pK_a is approximately equal to 6; thus, there is an approximate ratio of 99.9999:0.0001. Because the tertiary amine (pK_a = 8.0) is basic, it will be primarily ionized in an acidic environment (pH = 1.8). We can then use this ratio to determine that it will be approximately 99.9999% ionized. The second method is to establish a range. Using sulfonamide, the absolute value between the pH and the pK_a is 2.5. Since the sulfonamide (pK_a = 4.3) is acidic, it will be primarily unionized in an acidic environment (pH = 1.8). If the absolute value was 2, then 99% would be unionized, and if the absolute value was 3, then 99.9% would be unionized. Since the absolute value lies between 2 and 3, then we can conclude that the percent to which the sulfonamide is unionized is somewhere between 99% and 99.9%.

4. **Part A:** As determined in question 1B, the pK_a of 4.3 belongs to the acidic sulfonamide functional group, thus the ionized form is the Base Form and the unionized form is the Acid Form.

$$pH = pK_a + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$3.1 = 4.3 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-1.2 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.063 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.063}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or unionized) form, there is 0.063 molecule that contains the functional group in the base (or ionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.063 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} - 1.063 \text{ total molecules}$$

$$\text{Base form} = \text{Ionized form and Acid form} = \text{Unionized form}$$

$$\text{Percent in Unionized Form} = \frac{1 \text{ Molecule in Unionized Form}}{1.063 \text{ Total Molecules}} \times 100\% = 94.1\%$$

$$\text{Percent in Ionized Form} = \frac{0.063 \text{ Molecule in Unionized Form}}{1.063 \text{ Total Molecules}} \times 100\% = 5.9\%$$

The question asks for the percent that will be ionized, so the correct answer is 5.9%.

Part B: As determined in question 1B, the pK_a of 8.0 belongs to the basic tertiary amine functional group, thus the ionized form is the Acid Form and the unionized form is the Base Form.

$$pH = pK_a + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$7.3 = 8.0 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-0.7 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.20 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.20}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or ionized) form, there is 0.20 molecule that contains the functional group in the base (or unionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.20 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} - 1.20 \text{ total molecules}$$

$$\text{Base form} = \text{Unionized form and Acid form} = \text{Ionized form}$$

$$\text{Percent in Unionized Form} = \frac{0.20 \text{ Molecule in Unionized Form}}{1.20 \text{ Total Molecules}} \times 100\% = 16.7\%$$

$$\text{Percent in Ionized Form} = \frac{1.0 \text{ Molecule in Unionized Form}}{1.2 \text{ Total Molecules}} \times 100\% = 83.3\%$$

The question asks for the percent that will be ionized, so the correct answer is 83.3%.

Part C: As determined in Question 1B, the pK_a of 3.5 belongs to the basic heterocyclic nitrogen atom, thus the ionized form is the Acid Form and the unionized form is the Base Form. The functional group is 30% ionized. This means that for every 100 molecules of venetoclax, 30 of them will have an ionized heterocyclic nitrogen atom, and 70 will have an unionized heterocyclic nitrogen atom. Thus, the [Base Form]/[Acid Form] ratio is 70:30. Using this ratio and the given pK_a, the pH can be determined.

$$\mathrm{pH} = \mathrm{pK_a} + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$\mathrm{pH} = 3.5 + \log \frac{70}{30}$$

$$\mathrm{pH} = 3.5 + \log 2.3$$

$$\mathrm{pH} = 3.5 + 0.36$$

$$\mathrm{pH} = 3.86$$

Checkpoint Drug 2: Elamipretide

1. Answer provided in table below.

	Name of Functional Group	**Character: Acidic, Basic, Neutral**	**pK_a Value or Range**
A	Guanidine (arginine side chain)	Basic	~12.5
B	Primary amine (lysine side chain)	Basic	~10.5
C	Phenol (modified tyrosine side chain)	Acidic	~10.5
D	Primary amine (peptide backbone)	Basic	~10.5

2. To determine the extent to which a functional group is ionized in a given physiological environment (qualitatively or quantitatively), you must know several facts and must select how to set the problem up. You will need to know the pK_a of the functional group and the pH of the environment (facts) and then, in order to set the problem up, you must know whether the functional group is acidic or basic.

   For example, using the Henderson-Hasselbalch equation to solve the problem qualitatively, you must be able to identify the base form (ionized form for acids; unionized form for bases) and the acid form (unionized form for acids; ionized form for bases) of the drug molecule. When using qualitative methods, remember that when $pH < pK_a$ (for acids), the functional group is predominantly unionized; but, when $pH < pK_a$ (for bases), the functional group is predominantly ionized.

3. Answers provided in the tables below.

	Name of Functional Group	Character: Acidic, Basic, Neutral	pK_a Value or Range	Primarily Ionized (>50%) Primarily Unionized (<50%) pH = 2
A	Guanidine (arginine side chain)	Basic	~12.5	Primarily ionized
B	Primary amine (lysine side chain)	Basic	~10.5	Primarily ionized
C	Phenol (modified tyrosine side chain)	Acidic	~10.5	Primarily unionized
D	Primary amine (amino terminus)	Basic	~10.5	Primarily ionized

	Name of Functional Group	Character: Acidic, Basic, Neutral	pK_a Value or Range	Primarily Ionized (>50%) Primarily Unionized (<50%) pH=5
A	Guanidine (arginine side chain)	Basic	~12.5	Primarily ionized
B	Primary amine (lysine side chain)	Basic	~10.5	Primarily ionized
C	Phenol (modified tyrosine side chain)	Acidic	~10.5	Primarily unionized
D	Primary amine (amino terminus)	Basic	~10.5	Primarily ionized

	Name of Functional Group	Character: Acidic, Basic, Neutral	pK_a Value or Range	Primarily Ionized (>50%) Primarily Unionized (<50%) pH=7.4
A	Guanidine (arginine side chain)	Basic	~12.5	Primarily ionized
B	Primary amine (lysine side chain)	Basic	~10.5	Primarily ionized
C	Phenol (modified tyrosine side chain)	Acidic	~10.5	Primarily unionized
D	Primary amine (amino terminus)	Basic	~10.5	Primarily ionized

Functional group A (guanidine) is basic in character with a pK_a =~12.5. It will be primarily ionized in all three physiological locations because the environmental $pH<pK_a$ of the functional group. In its ionized form, a guanidine is a proton donor (acidic).

Functional group B (primary amine) is basic in character with a pK_a =~10.5. It will be primarily ionized in all three physiological locations because the environmental $pH<pK_a$ of the functional group. In its ionized form, a primary amine is a proton donor (acidic).

Functional group C (phenol) is acidic in character with a pK_a =~10.5. It will be primarily unionized in all three physiological locations because the environmental $pH<pK_a$ of the functional group. In its ionized form, a phenol is a proton acceptor (basic).

Functional Group D (amino terminus primary amine) is basic in character with a pK_a =~10.5. It will be primarily ionized in all three physiological locations because the environmental $pH<pK_a$ of the functional group. In its ionized form, a primary amine is a proton donor (acidic).

4. Answers provided in the tables below.

	Name of Functional Group	Character: Acidic, Basic, Neutral	pK_a Value or Range	Percent Ionized pH=5.4
A	Guanidine (arginine side chain)	Basic	~12.5	99.9999921%
B	Primary amine (lysine side chain)	Basic	~10.5	99.99921%
C	Phenol (modified tyrosine side chain)	Acidic	~10.5	0.00079%
D	Primary amine (amino terminus)	Basic	~10.5	99.99921%

	Name of Functional Group	Character: Acidic, Basic, Neutral	pK_a Value or Range	Percent Ionized pH=8.5
A	Guanidine (arginine side chain)	Basic	~12.5	99.99%
B	Primary amine (lysine side chain)	Basic	~10.5	99.01%
C	Phenol (modified tyrosine side chain)	Acidic	~10.5	0.99%
D	Primary amine (amino terminus)	Basic	~10.5	99.01%

Part A: pH = 5.4

For the guanidine functional group at pH=5.4:

$$\mathrm{pH} = \mathrm{pK_a} + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$5.4 = 12.5 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-7.1 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.000000079 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.000000079}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or ionized) form, there is 0.000000079 molecule that contains the functional group in the base (or unionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.000000079 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} = 1.000000079 \text{ total molecules}$$

$$\text{Base form} = \text{Unionized form and Acid form} = \text{Ionized form}$$

$$\text{Percent in Unionized Form} = \frac{0.000000079 \text{ Molecule in Unionized Form}}{1.000000079 \text{ Total Molecules}} \times 100\% = 0.0000079\%$$

$$\text{Percent in Ionized Form} = \frac{1.0 \text{ Molecule in Ionized Form}}{1.000000079 \text{ Total Molecules}} \times 100\% = 99.9999921\%$$

The question asks for the percent that will be ionized, so the correct answer is 99.9999921%.

For both primary amine functional groups at pH=5.4:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$5.4 = 10.5 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-5.1 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.0000079 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.0000079}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or ionized) form, there is 0.0000079 molecule that contains the functional group in the base (or unionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.0000079 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} = 1.0000079 \text{ total molecules}$$

$$\text{Base form} = \text{Unionized form and Acid form} = \text{Ionized form}$$

$$\text{Percent in Unionized Form} = \frac{0.0000079 \text{ Molecule in Unionized Form}}{1.0000079 \text{ Total Molecules}} \times 100\% = 0.00079\%$$

$$\text{Percent in Ionized Form} = \frac{1.0 \text{ Molecule in Ionized Form}}{1.0000079 \text{ Total Molecules}} \times 100\% = 99.99921\%$$

The question asks for the percent that will be ionized, so the correct answer is 99.99921%.

For the phenol functional group at pH=5.4:

$$\log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$5.4 = 10.5 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-5.1 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.0000079 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.0000079}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or unionized) form, there is 0.0000079 molecule that contains the functional group in the base (or ionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.0000079 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} = 1.0000079 \text{ total molecules}$$

$$\text{Base form} = \text{Ionized form and Acid form} = \text{Unionized form}$$

$$\text{Percent in Ionized Form} = \frac{0.0000079 \text{ Molecule in Unionized Form}}{1.0000079 \text{ Total Molecules}} \times 100\% = 0.00079\%$$

$$\text{Percent in Unionized Form} = \frac{1.0 \text{ Molecule in Ionized Form}}{1.0000079 \text{ Total Molecules}} \times 100\% = 99.99921\%$$

The question asks for the percent that will be ionized, so the correct answer is 0.00079%.

Part B: pH = 8.5

For the guanidine functional group at pH=8.5

$$\text{pH} = \text{pK}_a + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$8.5 = 12.5 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-4 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.0001 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.0001}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or ionized) form, there is 0.0001 molecule that contains the functional group in the base (or unionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.0001 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} = 1.0001 \text{ total molecules}$$

$$\text{Base form} = \text{Unionized form and Acid form} = \text{Ionized form}$$

$$\text{Percent in Unionized Form} = \frac{0.0001 \text{ Molecule in Unionized Form}}{1.0001 \text{ Total Molecules}} \times 100\% = 0.009999\%$$

$$\text{Percent in Ionized Form} = \frac{1.0 \text{ Molecule in Ionized Form}}{1.0001 \text{ Total Molecules}} \times 100\% = 99.99\%$$

The question asks for the percent that will be ionized, so the correct answer is 99.99%.

For both primary amine functional groups at pH=8.5:

$$\text{pH} = \text{pK}_a + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$8.5 = 10.5 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-2 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.01 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.01}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or ionized) form, there is 0.01 molecule that contains the functional group in the base (or unionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.01 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} = 1.01 \text{ total molecules}$$

$$\text{Base form} = \text{Unionized form and Acid form} = \text{Ionized form}$$

$$\text{Percent in Unionized Form} = \frac{0.01 \text{ Molecule in Unionized Form}}{1.01 \text{ Total Molecules}} \times 100\% = 0.99\%$$

$$\text{Percent in Ionized Form} = \frac{1.0 \text{ Molecule in Ionized Form}}{1.01 \text{ Total Molecules}} \times 100\% = 99.01\%$$

The question asks for the percent that will be ionized, so the correct answer is 99.01% .

For the phenol functional group at pH=8.5:

$$\log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$8.5 = 10.5 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-2 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.01 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.01}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or unionized) form, there is 0.01 molecule that contains the functional group in the base (or ionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.01 \text{ molecule in base form} + 1.0 \text{ molecule in acid form} = 1.01 \text{ total molecules}$$

$$\text{Base form} = \text{Ionized form and Acid form} = \text{Unionized form}$$

$$\text{Percent in Ionized Form} = \frac{0.01 \text{ Molecule in Unionized Form}}{1.01 \text{ Total Molecules}} \times 100\% = 0.99\%$$

$$\text{Percent in Unionized Form} = \frac{1.0 \text{ Molecule in Ionized Form}}{1.01 \text{ Total Molecules}} \times 100\% = 99.001\%$$

The question asks for the percent that will be ionized, so the correct answer is 0.99%.

REVIEW QUESTIONS

1. Answers provided in the grid below.

Drug (pK_a value)	**Name of Functional Group**	**Acidic/Basic**
Acetaminophen (9.7)	Phenol	Acidic
Naproxen (4.2)	Carboxylic acid	Acidic
Baclofen (5.4)	Carboxylic acid	Acidic
Baclofen (9.5)	Primary amine	Basic
Dyclonine (8.2)	Tertiary amine (piperidine)	Basic

2. The acidic, basic, or neutral environments are provided below.

Saliva (pH = 6.4)	**Stomach (pH = 2)**	**Duodenum (pH = 5.4)**	**Plasma (pH = 7.4)**	**Urine (pH = 5.7)**
Acidic	Acidic	Acidic	Basic (nearly neutral)	Acidic

3. Predominant ionization states are provided below.

Drug (pK_a value)	**Saliva (pH = 6.4)**	**Stomach (pH = 2)**	**Duodenum (pH = 5.4)**	**Plasma (pH = 7.4)**
Acetaminophen (9.7)	Unionized	Unionized	Unionized	Unionized
Naproxen (4.2)	Ionized	Unionized	Ionized	Ionized
Baclofen (5.4)	Ionized	Unionized	50% ionized/50% unionized	Ionized
Baclofen (9.5)	Ionized	Ionized	Ionized	Ionized
Dyclonine (8.2)	Ionized	Ionized	Ionized	Ionized

4. Baclofen contains an acidic functional group (carboxylic acid; pK_a 5.4), and it will be predominantly ionized when the environmental pH > pK_a. As stated in the chapter text, the Rule of Nines can be used in lieu of the Henderson-Hasselbalch equation if the difference between the pH and pK_a is an integer, as it is in this scenario. Using this rule we can calculate the approximate percent ionization in each of these environments (duodenum pH = 5.4; saliva pH = 6.4; plasma pH = 7.4) by simply determining the magnitude of the difference between the pH and pK_a. In the duodenum, the pH = pK_a and, therefore, 50% of the carboxylic acid will be ionized at any given time and 50% will be unionized. In the saliva, the difference between the pH and the pK_a values is 1; therefore, 90% of the carboxylic acid functional groups will be ionized and 10% will be unionized. In the plasma, the difference between the pH and the pK_a values is 2; therefore, 99% of the carboxylic acid functional groups will be ionized and 1% will be unionized.

5. **Part A:** Qualitative Approach (predominantly ionized or unionized?)

   Naproxen contains a carboxylic acid (acidic; pK_a = 5.4) in an environment pH = 7.4. For acids, if pH > pK_a, then the functional group is predominantly ionized.

   Dyclonine contains a tertiary amine (piperidine) (basic; pK_a = 8.2) in an environment pH = 7.4. For basic functional groups, if the pH < pK_a, then the functional group is predominantly ionized.

   Part B: Quantitative Approach (% ionized and % unionized?)

   Answer for the Acidic Functional Group (Naproxen):

   The form of the Henderson-Hasselbalch equation used for acidic functional groups is shown below.

$$\mathrm{pH} = \mathrm{pK_a} + \log\frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]} \quad \text{or} \quad \mathrm{pH} = \mathrm{pK_a} + \log\frac{[\text{Basic Form}]}{[\text{Acidic Form}]}$$

   When using this equation to determine whether the functional group is predominantly ionized or unionized, we need to know the pK_a of the functional group (carboxylic acid in naproxen pK_a = 4.2) and the pH of the environment (plasma pH = 7.4).

$$7.4 = 4.2 + \log\frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

$$3.2 = \log\frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

   The fact that the number on the left is positive indicates that the carboxylic acid is predominantly in its unprotonated (basic, ionized) form at pH = 7.4.

   To determine the percentage of ionized and unionized drug in the plasma, we need to calculate the antilog of both sides of this equation. In this case the antilog of 3.2 is 1585. This means that for every one molecule that is protonated (unionized carboxylic acid), there are 1585 molecules that are unprotonated (ionized carboxylic acid).

Calculation of the percentage of ionized drug and unionized drug at pH = 7.4 requires one additional step.

1585 molecules in ionized form + 1.0 molecule in unionized form = 1586 total molecules

$$\text{Percent of Molecules in Ionized Form} = \frac{1585 \text{ Molecules in Ionized Form}}{1586 \text{ Total Molecules}} \times 100\% = 99.93\%$$

$$\text{Percent of Molecules in Unionized Form} = \frac{1585 \text{ Molecules in Unionized Form}}{1586 \text{ Total Molecules}} \times 100\% = 0.06\%$$

Answer for the Basic Functional Group (Dyclonine):

The form of the Henderson-Hasselbalch equation used for basic functional groups is show below.

$$\text{pH} = \text{pK}_a + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

When using this equation to determine whether the functional group is predominantly ionized or unionized, we need to know the pK_a of the functional group (tertiary amine in dyclonine pK_a = 8.2) and the pH of the environment (plasma pH = 7.4).

$$7.4 = 8.2 + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

$$-0.8 = \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

The fact that the number on the left is negative indicates that the tertiary amine is predominantly in its protonated (acidic, ionized) form at pH = 7.4.

To determine the percentage of ionized and unionized drug in the plasma, we need to calculate the antilog of both sides of the equation. In this case, the antilog of -0.8 is 0.16. This means that for every one molecule that is protonated (ionized tertiary amine) there are 0.16 molecules that are unprotonated (unionized tertiary amine).

Calculation of the percentage of ionized drug and unionized drug at pH = 7.4 requires one additional step.

1 molecule in ionized form + 0.16 molecule in unionized form = 1.16 total molecules

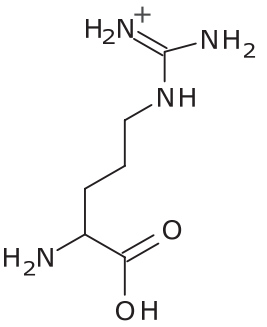
$$\text{Percent of Molecules in Unionized Form} = \frac{0.16 \text{ Molecule in Unionized Form}}{1.16 \text{ Total Molecules}} \times 100\% = 13.7\%$$

$$\text{Percent of Molecules in Ionized Form} = \frac{1 \text{ Molecule in Ionized Form}}{1.16 \text{ Total Molecules}} \times 100\% = 86.3\%$$

6. Based on ionization only (which allows for ion-dipole interactions with water), acetaminophen is the only one of the four drugs that is unionized in the plasma. Although this molecule can participate in other types of interactions with water (e.g., H-bonding), it cannot participate in ion-dipole interactions because it is not ionized in that environment.

   Based on ionization only (which allows for ion-dipole interactions with water), baclofen is the only one of the four drugs that has two ionized functional groups in the plasma. This molecule will be able to interact with water via both the ionized primary amine and the ionized carboxylic acid.

7. In order to determine if a drug can participate in an ionic interaction with the ionized arginine residue found within the active site of COX-1, we first need to determine what the ionized form of arginine looks like at pH = 7.4. Using the Henderson-Hasselbalch equation to determine if this functional group is predominantly ionized in the plasma (pH = 7.4), we learn that 99.9991% of the molecules of arginine will be ionized in that environment (see structure of ionized arginine side chain below).



   For a drug to participate in an ionic interaction with the side chain of this arginine residue, it must contain a functional group that is negatively charged in the same environment. Because we have already determined that naproxen will be predominantly ionized at pH = 7.4 (via the carboxylic acid), it stands to reason that naproxen can participate in this critical ionic interaction with the ionized arginine residue.

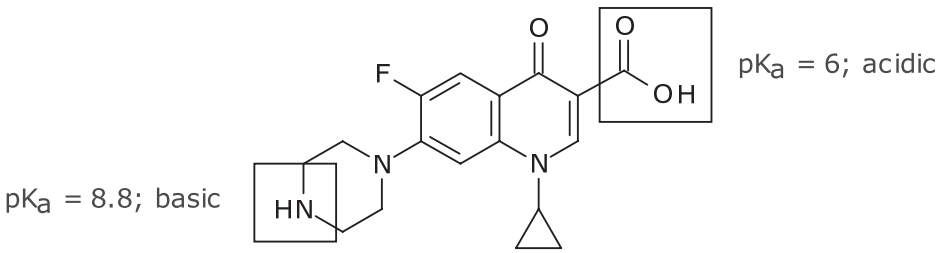
   Dyclonine contains a basic tertiary amine (piperidine) and when ionized will be positively charged. As we determined in Question #5, dyclonine will be 86.3% ionized in this environment (pH = 7.4). Since an ionic interaction requires that an ion pair form between one negatively and one positively charged functional group, it stands to reason that the positively charged tertiary amine (piperidine) in dyclonine cannot participate in an ionic interaction with the positively charged side chain of the arginine residue.

8. Acidic and basic functional groups are identified below.

Functional Group Name	Acidic or Basic	Saliva (pH = 6.4)	Stomach (pH = 2)	Duodenum (pH = 5.4)	Plasma (pH = 7.4)	Urine (pH = 5.7)
Tertiary amine (piperidine)	Basic (pK_a=9-11)	Ionized	Ionized	Ionized	Ionized	Ionized
Carboxylic acid	Acidic (pK_a=2.5-5)	Ionized	Unionized	Ionized	Ionized	Ionized

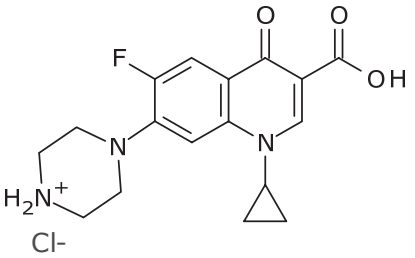
There are no physiological environments in which fexofenadine is predominantly in its unionized form. In order for the drug to be absorbed via passive diffusion, we can see that in the stomach the carboxylic acid will primarily be in its unionized form; however, only a very, very small fraction of the tertiary amine (piperidine) will be in its unionized form in that environment at any given time. We know that an equilibrium exists between the unionized and ionized form of the drug and that the equilibrium will be re-established as the unionized drug is absorbed, so we might anticipate that little by little fexofenadine will be absorbed from the stomach.

9. **Part A:** Acidic and basic functional groups and their respective pK_a values are shown below.



Ciprofloxacin

Part B: The hydrochloride salt form of the drug is ionized (amine is in its protonated form) and, therefore, is capable of participating in an ion-dipole interaction with water. This enhances the solubility of the drug in an aqueous solution.



Part C:

Answer for Acidic Functional Group (Carboxylic Acid)

The form of the Henderson-Hasselbalch equation used for acidic functional groups is shown below.

$$\text{pH} = \text{pK}_a + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]} \quad \text{or} \quad \text{pH} = \text{pK}_a + \log \frac{[\text{Basic form}]}{[\text{Acidic}]}$$

When using this equation to determine whether the functional group is predominantly ionized or unionized, we need to know the pK_a of the functional group (carboxylic acid in ciprofloxacin $pK_a = 6$) and the pH of the environment (formulation pH = 5).

$$5 = 6 + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

$$-1 = \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

The fact that the number on the left is negative indicates that the carboxylic acid is predominantly in its protonated (acidic, unionized) form at pH = 5.

To determine the percentage of ionized and unionized drug in the formulation, we need to calculate the antilog of both sides of this equation. In this case, the antilog of −1 is 0.1. This means that for every one molecule that is protonated (unionized carboxylic acid; acidic) there is 0.1 molecule that is unprotonated (ionized carboxylic acid; basic).

Calculation of the percentage of ionized drug and unionized drug at pH = 5 requires one additional step.

$$0.1 \text{ molecule in ionized form} + 1.0 \text{ molecule in unionized form} = 1.1 \text{ total molecules}$$

$$\text{Percent of Molecules in Ionized Form} = \frac{0.1 \text{ Molecule in Ionized Form}}{1.1 \text{ Total Molecules}} \times 100\% = 9.09\%$$

$$\text{Percent of Molecules in Unionized Form} = \frac{1 \text{ Molecule in Unionized Form}}{1.1 \text{ Total Molecules}} \times 100\% = 90.9\%$$

Answer for Basic Functional Group (Secondary Amine/Piperazine)

The form of the Henderson-Hasselbalch equation used for basic functional groups is show below.

$$\text{pH} = \text{pH}_a + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

When using this equation to determine whether the functional group is predominantly ionized or unionized, we need to know the pK_a of the functional group (secondary amine in ciprofloxacin pK_a = 8.8) and the pH of the environment (formulation pH = 5).

$$5 = 8.8 + \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

$$-3.8 = \log \frac{[\text{Unprotonated Form}]}{[\text{Protonated Form}]}$$

The fact that the number on the left is negative indicates that the secondary amine is predominantly in its protonated (acidic, ionized) form at pH = 5.

To determine the percentage of ionized and unionized drug in the formulation, we need to calculate the antilog of both sides of the equation. In this case, the antilog of −3.8 is 0.000158. This means that for every one molecule that is protonated (ionized secondary amine), there are 0.000158 molecules that are unprotonated (unionized secondary amine).

Calculation of the percentage of ionized drug and unionized drug at pH = 5 requires one additional step.

$$1 \text{ molecule in ionized form} + 0.000158 \text{ molecule in unionized form} = 1.000158 \text{ total molecules}$$

$$\text{Percent of Molecules in Unionized Form} = \frac{0.000158 \text{ Molecule in Unionized Form}}{1.000158 \text{ Total Molecules}} \times 100\% = 0.016\%$$

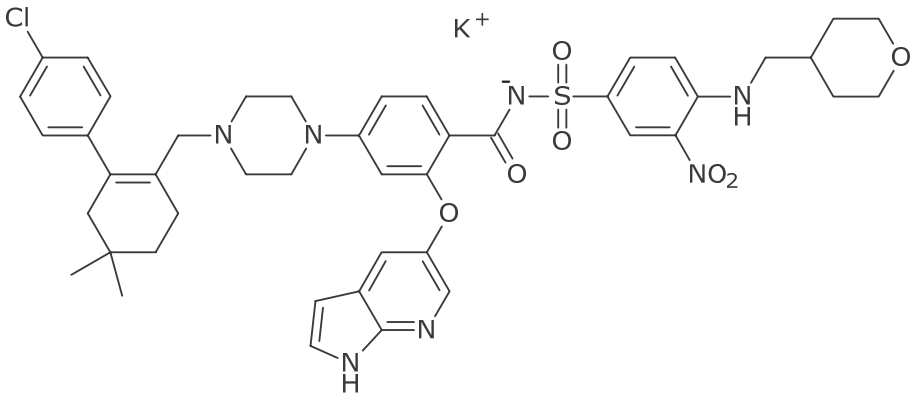
$$\text{Percent of Molecules in Ionized Form} = \frac{1 \text{ Molecule in Ionized Form}}{1.000158 \text{ Total Molecules}} \times 100\% = 99.98\%$$

CHAPTER 5

STRUCTURE ANALYSIS CHECKPOINT

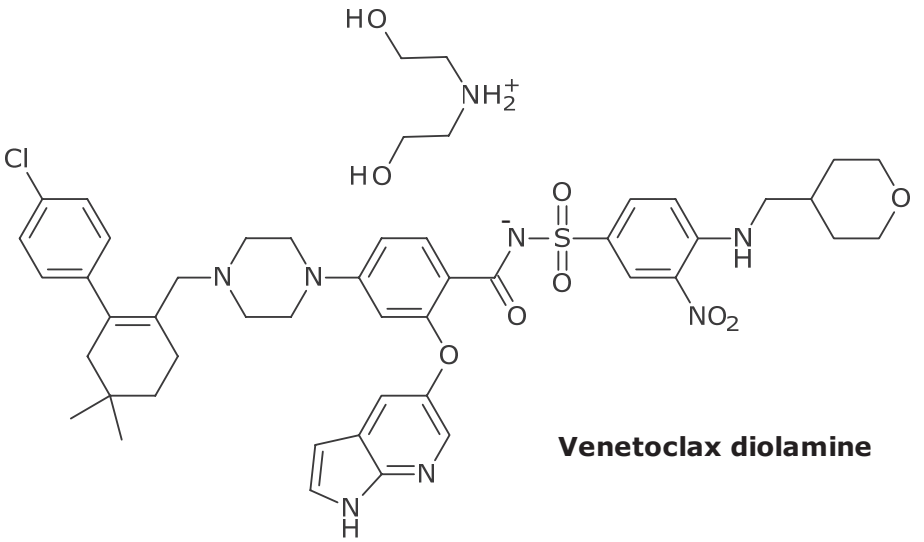
Checkpoint Drug 1: Venetoclax

1. The potassium salt of venetoclax is shown below.



Part A: In Chapter 3, we identified five ionizable functional groups. Four of these five functional groups are basic, while one is acidic. In order to form a salt, it is necessary to combine an acid and a base in a solution. In this case, an inorganic potassium salt was formed, so it can be concluded that the potassium ion came from KOH, a strong inorganic molecule. The addition of KOH to a solution containing venetoclax will cause a significant increase in the pH of the solution. All four basic functional groups will be primarily unionized, while the acidic sulfonamide will be primarily ionized. Under these conditions, the negatively charged sulfonamide will react with the positively charged potassium to form the salt shown in the answer to question 1.

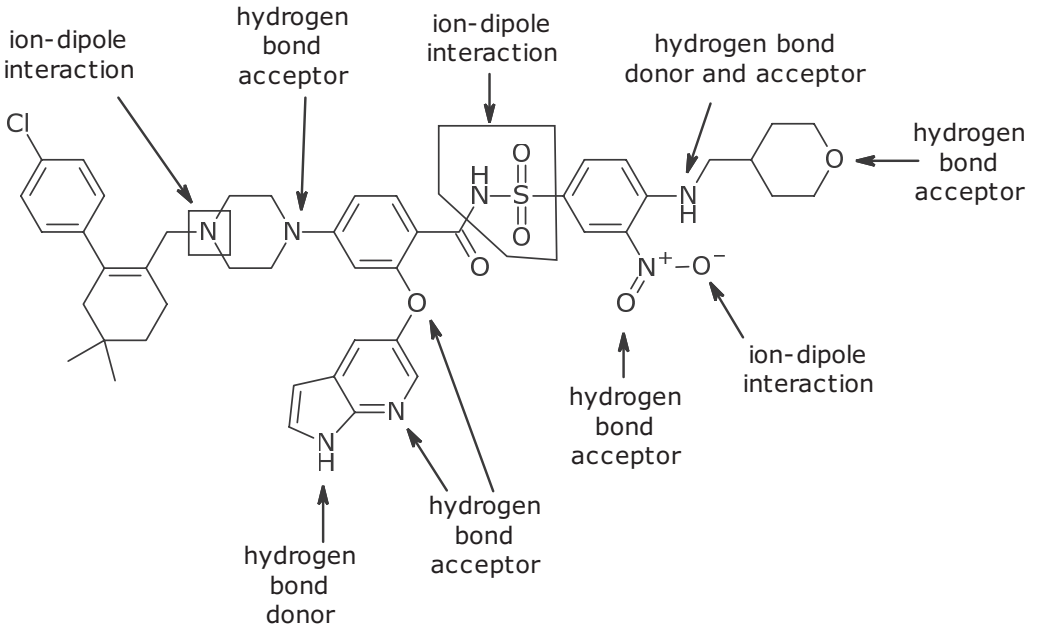
Part B: Shown below is a diolamine salt of venetoclax. Another base that could be used to make a salt with the sulfonamide is tromethamine



Venetoclax diolamine

Part C: Water-soluble organic salts are able to provide enhanced solvation and dissolution as compared to inorganic salts. The inorganic potassium ion is able to form ion-dipole bonds with water (as the ion). This is also true with the nitrogen atom of diolamine salt; however, the two hydroxyl groups allow additional hydrogen bonds with water, thus further enhancing water solubility beyond what is possible with the potassium salt.

2. The structure of venetoclax contains a large number of functional groups that can form hydrogen bonds or ion-dipole interactions with water. These have been highlighted below. Please note that the tertiary amine and the sulfonamide (boxed) will be primarily ionized in the pH of the small intestine and would participate in ion-dipole interactions with water. These functional groups provide sufficient water solubility for venetoclax to dissolve in the gastrointestinal (GI) tract. The remaining functional groups (aromatic and alicyclic rings, alkyl chains, and halogens) provide sufficient lipid solubility to allow venetoclax to traverse the GI membrane once it is dissolved.



3. As compared to the original structure of venetoclax, the addition of a hydroxyl group enhances water solubility due to the fact that this functional group can form hydrogen bonds with water. Additionally, the addition of a hydroxyl group allows for the formation of water- and lipid-soluble ester prodrugs. As discussed in the Chapter, esterases are ubiquitous throughout the human body, allowing the release of the active drug in the liver, the blood stream, the GI tract, or the target tissue.

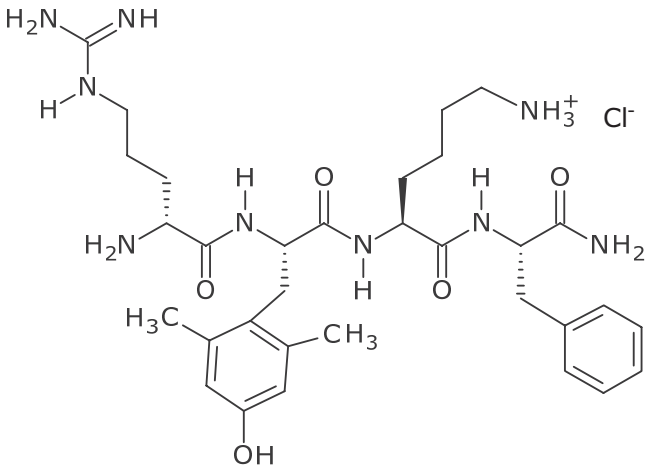
4. The chlorine group is lipid soluble; therefore, removing it and replacing it with a hydrogen atom would decrease the overall lipid solubility, or increase the overall water solubility, of venetoclax. Additionally, because the chlorine group is electron withdrawing through induction, the aromatic ring would no longer be electron deficient. This could affect charge transfer interactions and other interactions between the aromatic ring and its biological target. A full explanation of these types of interactions is provided in the next chapter. Additionally, electron withdrawing groups on aromatic rings decrease the metabolic oxidation of the ring. This will be discussed in Chapter 8. Finally, since a hydrogen atom is smaller than a chlorine atom, the *para* position of this aromatic ring would be less sterically hindered.

Checkpoint Drug 2: Elamipretide

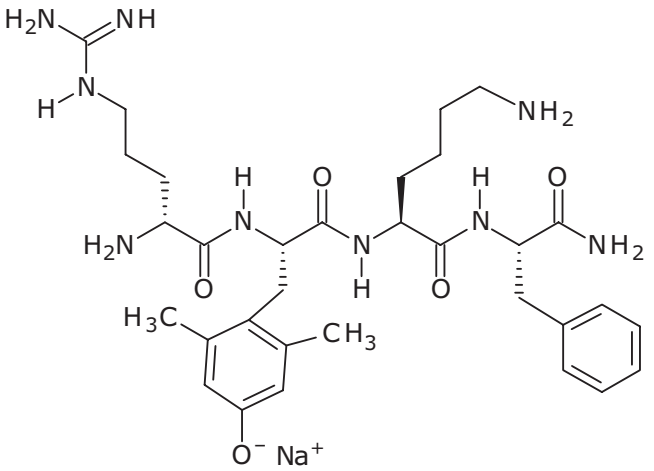
1. **Part A:** Elamipretide can be formulated as a sodium or potassium salt (phenol) or as a hydrochloride or hydrobromide salt (guanidine and primary amine).

   Part B:

   The hydrochloride salt of the primary amine of lysine is shown below.



The sodium salt of the phenol is shown below.



Part C: When comparing the sodium salt of elamipretide with the parent drug, it is important to note that the sodium salt will allow for an ion-dipole interaction with water that will enhance the overall hydrophilic character of the drug molecule. This will enhance water solubility and therefore improve distribution in the plasma. This will also translate into better solubility and dissolution of the sodium salt of the drug when compared to the parent drug.

2. Elamipretide is a molecule that is significantly ionized across a range of pH values. The likelihood of it being water soluble at pH = 7.4 for IV administration is fairly good. If you are concerned that the substituted phenol and the aromatic hydrocarbon represent significant enough hydrophobic character to warrant formation of a water-soluble organic salt, then consider formulation as a tartrate salt (in Figure 5-3 there are other examples). Because elamipretide contains several basic function groups (guanidine and two primary amines), it is possible to formulate the drug as a lactate salt.

3. **Part A:** We know that the smaller the value of log P the more water soluble the drug molecule is. In this case cLog P = 0.3677 for elamipretide and the cLogP values for the HMGCoA reductase inhibitors are all larger than this value (although rosuvastatin isn't significantly larger!!). That means that elamipretide is likely to be significantly more water soluble than the HMGCoA reductase inhibitors.

   Part B: The structure evaluation conducted in Chapter 2 revealed that there is significant hydrophilic character present in elamipretide (phenol [OH], primary amines, guanidine, amides). This supports the small cLogP value that indicates that elamipretide is water soluble.

   Part C: There are several structural modifications that could be made to increase the lipophilic character of elamipretide. A lipid-soluble salt (e.g., stearate) could be formed with the basic functional groups. A lipid-soluble ester prodrug (e.g.,

benzoate) of the phenol could be developed. Converting the amino terminus (primary amine) to an acetamide or other lipophilic amide is another option, but only if this primary amine isn't involved in a critical ionic interaction or ion-dipole interaction (as the ionic component) with the biological target.

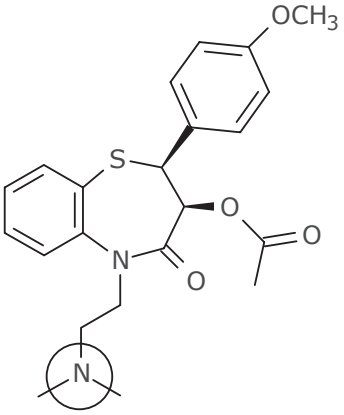
4. **Part A:** As mentioned in the answer to Question 3C, the amino terminus primary amine group can be converted to a lipophilic amide to improve lipid solubility of the drug molecule (provided that key ionic and/or ion-dipole interactions with the amine are not required). This type of transformation also protects the molecule from degradation from aminopeptidases, since the enzyme would no longer recognize the drug molecule as a potential substrate. [*Note*—if the other primary amine (side chain of lysine) was converted into a lipophilic amide, the drug molecule would become more lipid soluble, but would still remain subject to degradation via aminopeptidases.]

   The one problem with this strategy is that amidases are not as ubiquitous as esterases, and there is the potential that the amide would not undergo bioactivation (hydrolysis) to form an appreciable amount of the component carboxylic acid and amine (parent drug). My earlier warning about the types of interactions that are required with this primary amine determine whether or not the amide would represent a prodrug. *Remember*—a prodrug must be able to be metabolically cleaved to produce the active drug!!!

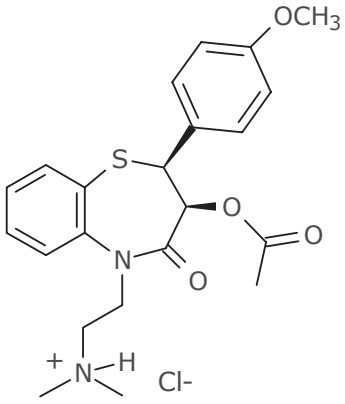
   Part B: Lipid-soluble ester prodrugs enhance the overall lipid solubility of the drug molecule and, therefore, improve absorption across lipophilic members (e.g., GI wall, skin, cell membranes). This will cause an increase in cLog P to reflect less water solubility and more lipid solubility. This improved solubility will enhance oral bioavailability. These types of prodrugs can also be used in depot-based formulations, which increases the duration of action of the product administered.

REVIEW QUESTIONS

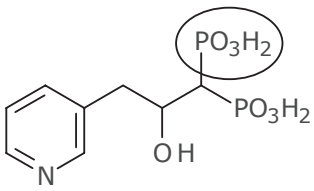
1. **Parts A and B:** Functional groups required to form salts have been circled and modified below.



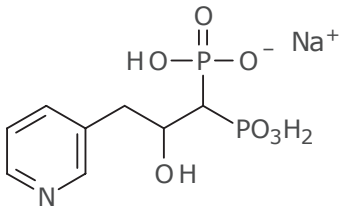
Diltiazem



Diltiazem hydrochloride



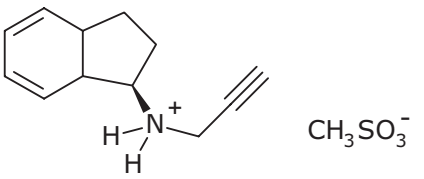
Risedronate



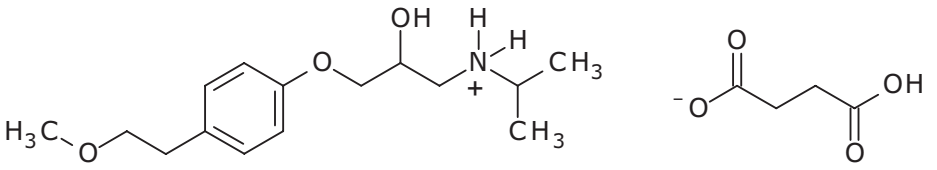
Risedronate sodium
(Note that the sodium salt can be formed with either phosphate)

Part C: The salts formed are both inorganic salts.

2. Rasagiline mesylate and metoprolol mesylate are examples of organic salts. Each drug has been modified below to represent the form present at pH = 7.4.



Rasagiline mesylate



Metoprolol succinate

3. **Part A:** Answers are provided in the grid below.

Name of Functional Group	Hydrophilic and/or Hydrophobic	Acidic, Basic, or Neutral	Contribution to Aqueous Solubility and/or Absorption
Ether(s)	Hydrophilic (O) Hydrophobic (R)	Neutral	Aqueous solubility (O) Absorption (R)
Aromatic hydrocarbon	Hydrophobic	Neutral	Absorption
Tertiary amine	Hydrophilic (N) Hydrophobic (R)	Basic (ionized at pH = 7.4)	Aqueous solubility (N) Absorption (R)
Cycloalkene	Hydrophobic	Neutral	Absorption
Secondary alcohol	Hydrophilic (OH) Hydrophobic (R)	Neutral	Aqueous solubility (OH) Absorption (R)

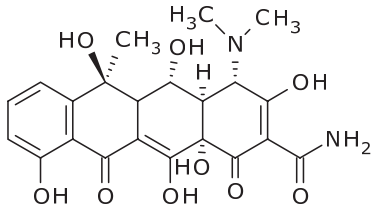
R = carbon scaffolding.

Part B:

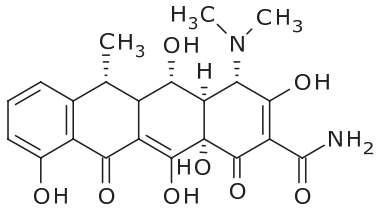
Galatamine has a balance between functional groups that are hydrophobic (aromatic hydrocarbon, cycloalkene) and can contribute to the ability of the drug to be absorbed/cross lipophilic membranes and groups that are hydrophilic (ether, secondary alcohol, ionized tertiary amine) that will allow for dissolution/solubility in the aqueous contents of the stomach.

Part C: Galantamine hydrobromide is more hydrophilic due to the presence of an ionized functional group that can participate in strong ion-dipole interactions with water.

4. Log P = –1 can be translated to mean for every one molecule that partitions into the organic phase, there are 10 molecules that partition into the aqueous phase. The more negative the value of log P, the more water soluble the drug is. When you compare the log P values for oxytetracycline and doxycycline, you can see that the number is becoming more positive, meaning the drug is becoming less water soluble. If you analyze the functional group composition of each of these tetracyclines, you will see that doxycycline contains one less hydroxyl group and therefore is likely to be slightly less hydrophilic than oxytetracycline.



Oxytetracycline (log P= -1.12)



Doxycycline (log P= -0.02)

5. **Part A:** The structure evaluation is provided in the grid below.

Name of Functional Group	Hydrophilic and/or Hydrophobic	Acidic, Basic, or Neutral	Contribution to Aqueous Solubility and/or Absorption
ACITRETIN			
Aromatic Hydrocarbon	Hydrophobic	Neutral	Absorption
Alkene	Hydrophobic	Neutral	Absorption
Carboxylic acid	Hydrophilic (COOH) Hydrophobic (R)	Acidic	Aqueous Solubility (COOH) Absorption (R)
CALCIPOTRIOL			
Cycloalkane	Hydrophobic	Neutral	Absorption
Alkene	Hydrophobic	Neutral	Absorption
Secondary alcohol(s)	Hydrophilic (OH) Hydrophobic (R)	Acidic	Aqueous Solubility (OH) Absorption (R)
TAZAROTENE			
Aromatic hydrocarbon	Hydrophobic	Neutral	Absorption
Alkyne	Hydrophobic	Neutral	Absorption
Azine (pyridine)	Hydrophilic (N) Hydrophobic (R)	Basic	Aqueous Solubility (N) Absorption (R)
Ester	Hydrophilic (COO) Hydrophobic (R)	Neutral	Aqueous Solubility (COO) Absorption (R)
Thiane (cyclic thioether)	Hydrophobic	Neutral	Absorption

R = carbon scaffolding.

Part B: Psoriasis is an autoimmune disease characterized by areas of inflammation and excessive skin production. In the affected areas, skin accumulates rapidly and forms plaques that are commonly silvery-white in color. Although typically associated with the skin, in 10–15% of patients psoriasis can cause inflammation in the joints as well (psoriatic arthritis). Topical application of a medication to treat these plaques will allow for local treatment of only the affected areas and hopefully prevent unnecessary systemic distribution.

Calcipotriol contains functional groups that are hydrophobic in character (cycloalkane, alkene) that will contribute to absorption of the drug into the affected skin and plaques. Tazarotene contains functional groups that are hydrophobic in character (aromatic hydrocarbon, alkyne, thiane) that will contribute to absorption of the drug into the affected skin and plaques.

Part C: Acitretin contains a mixture of hydrophilic (carboxylic acid, ionized at most physiological pHs) and hydrophobic functional groups (aromatic hydrocarbon, alkenes). This provides sufficient hydrophobic/hydrophilic balance to allow the drug to be solubilized in the aqueous contents of the GI tract and then absorbed across the lipophilic membrane of the GI tract.

Part D: Tazarotene contains functional groups that are hydrophobic in character (aromatic hydrocarbon, alkyne, thiane) that will contribute to absorption of the drug into the affected skin and plaques. Given that this agent has systemic side effects, one can assume that this agent is able to cross the skin and enter systemic circulation. The hydrophilic azine and ester contribute to the ability of the drug to be solubilized in the plasma.

6. **Part A:** The structure evaluation is provided in the grid below

Functional Group Name	Hydrophilic and/or Hydrophobic	Contribution to Aqueous Solubility and/or Absorption
NAFTIFINE (MARKETED AS HCL SALT)		
Aromatic hydrocarbon	Hydrophobic	Absorption
Tertiary amine (basic, ionized at most physiological pHs)	Hydrophilic (N) Hydrophobic (R)	Aqueous solubility (N) Absorption (R)
Alkene	Hydrophobic	Absorption
UNDECYLENIC ACID (MARKETED AS CALCIUM SALT [POWDER] OR ZINC SALT [CREAM])		
Alkene	Hydrophobic	Absorption
Alkane	Hydrophobic	Absorption
Carboxylic acid (acidic, ionized at most physiological pHs)	Hydrophilic (COOH) Hydrophobic (R)	Aqueous solubility (COOH) Absorption (R)
FLUCONAZOLE		
Halogenated aromatic hydrocarbon	Hydrophobic (R)	Absorption (R)
1,2,4 Triazole	Hydrophilic (Ns) Hydrophobic (R)	Aqueous solubility (Ns) Absorption (R)
Tertiary alcohol	Hydrophilic (OH) Hydrophobic (R)	Aqueous solubility (OH) Absorption (R)

N = nitrogen atoms; R = carbon scaffolding.

Part B: Naftifine and undecylenic acid contain several functional groups (e.g., aromatic hydrocarbon, alkene, aliphatic alkane) that contribute to the hydrophobic character of these molecules. Because they are predominantly hydrophobic in character, this allows for enhanced absorption across lipophilic membranes.

The therapeutic goal for these patients is to treat a fungal infection that is localized on their feet; therefore, medication does not need to be administered systemically. In order to be effective, the medication used must be able to penetrate both the skin and the fungal cell wall, both of which have a hydrophobic component associated with them.

Part C: For a drug to be given orally it must have hydrophilic character to allow for solubility in the aqueous contents of the stomach and hydrophobic character to allow for absorption across the lipophilic membranes of the GI tract. A balance in these two types of structural characteristics is necessary for a drug to be administered orally.

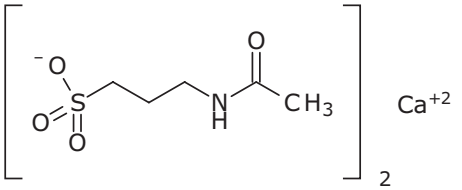
In fluconazole there is a halogenated aromatic hydrocarbon present. This functional group is hydrophobic and will contribute to drug absorption. The heteroatoms in the 1,2,4 triazole rings are hydrophilic in character, as is the tertiary alcohol. These three functional groups contribute significantly to the water solubility of this agent.

Part D: This agent contains ethers (several) and other oxygen containing functional groups (ketones), all of which can interact with water via H-bonding (as H-bond acceptors). This suggests that this agent has more hydrophilic character than the antifungal agents (used topically) discussed above. Although there is a halogenated aromatic hydrocarbon (chloro substituent) and a cycloalkene present that will contribute to the hydrophobic character of the drug, this agent is poorly absorbed across lipophilic membranes and is not utilized topically to treat fungal infections.

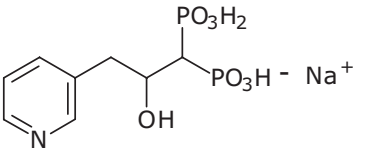
7. **Part A**: Hydrocortisone sodium succinate is a water-soluble organic ester. This increases the hydrophilic character of hydrocortisone sufficiently to become water soluble enough to be administered IM or IV. The strategy utilized to allow hydrocortisone to be administered IM or IV was via formation of a water-soluble organic ester.

   Part B: Hydrocortisone valerate is hydrophobic ester of hydrocortisone. This structural change further increases the hydrophobic character of hydrocortisone and decreases its aqueous solubility. Without sufficient balance between hydrophilic and hydrophobic character, this agent is unlikely to be sufficiently bioavailable if administered via an oral route and will not be soluble enough to allow for IM or IV administration.

8. Both of these agents are very hydrophilic in character (acamprosate calcium: sulfonate salt, amide; risedronate sodium: bisphosphonate, secondary alcohol, pyridine) and are likely to be very water soluble. As a result, their elimination pathway is unlikely to include the need for Phase I or Phase II metabolic transformations.



Acamprosate calcium

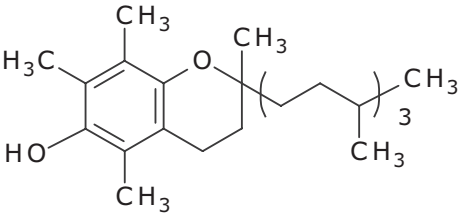


Risedronate sodium

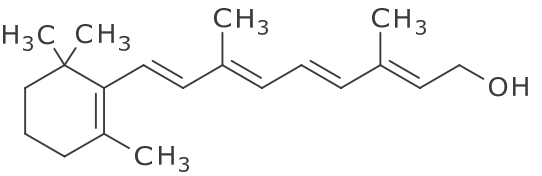
9. The acidic or basic character of each drug is shown below.

Fentanyl citrate	Fentanyl is basic.
Diphenhydramine hydrochloride	Diphenhydramine is basic.
Fenoprofen calcium	Fenoprofen is acidic.
Morphine sulfate	Morphine is basic.
Clevidipine butyrate	Clevidipine is basic.
Miconazole nitrate	Miconazole is basic.
Pravastatin sodium	Cromolyn is acidic.
Diclofenac potassium	Diclofenac is acidic

10. Both vitamin E and vitamin A (in the form of retinol) are used in the management of skin conditions, including acne, wound healing, and the effects of aging.



Vitamin E



Vitamin A

Part A: We know that the partition coefficient of a drug molecule is defined as the ratio of the solubility of the unionized drug in an organic solvent to the solubility of the same unionized drug in an aqueous environment. Log P = 1 can be translated to mean for every 10 molecules that partition into the organic phase, there is 1 molecule that partitions into the aqueous phase. The more positive the value of log P, the more lipid soluble the drug is. In this case, both vitamin A and vitamin E have cLogP values that are much larger than one, which means that they

are very hydrophobic in character. Administration of a drug molecule (or in this case a vitamin) via the skin requires that the drug/vitamin possess considerable hydrophobic character in order for it to be absorbed into and potentially across the lipophilic skin.

Part B:

1. Vitamin E contains an ionizable phenol functional group. This group can be converted into an inorganic salt (e.g., potassium salt) that can participate in an ion-dipole interaction with water and therefore enhance the aqueous solubility of the vitamin. Vitamin E could also be modified to form a water-soluble organic salt (e.g., a tromethamine salt). Again, the ionized drug can participate in an ion-dipole interaction with water and, therefore, enhances the aqueous solubility of the vitamin.

2. Vitamin A does not contain an ionizable functional group, so it cannot form inorganic salts or a water-soluble organic salt. It can, however, be formulated as a water-soluble prodrug (e.g., sodium succinate ester) that can be metabolically cleaved to the parent vitamin. In this case, the inactive vitamin prodrug is able to participate in the ion-dipole interactions with water to improve the water solubility of the prodrug, and then metabolic hydrolysis will release the less aqueous soluble vitamin. Another option is to oxidize the primary alcohol to the corresponding carboxylic acid and then form an inorganic salt that will confer additional aqueous solubility. In this scenario, the carboxylic acid form of the vitamin represents one of the active forms of the vitamin and represents most of the activity of vitamin A.

CHAPTER 6

STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

1. Answers provided in the table below.

	Functional Group	Types of Binding Interactions	Amino Acids Capable of Forming Specific Binding Interaction
A	Halogenated phenyl ring (or aromatic ring)	(1) van der Waals; Hydrophobic (2) π-π Stacking (3) Charge Transfer (as electron poor aromatic ring) (4) Cation-π Interactions	(1) Tyr, Phe, Trp (better interaction)*; Val, Leu, Ile, Met, Ala (2) Tyr, Phe, Trp (3) Tyr, Trp (4) Lys, Arg, His**
B	Tertiary amine	(1) Ionic (2) Ion-Dipole (as the Ion)	(1) Asp, Glu (2) Ser, Thr, Tyr, Cys, Asn, Gln
C	Sulfonamide***	(1) Ionic (2) Ion-Dipole (as the Ion)	(1) Lys, Arg, His** (2) Ser, Thr, Tyr, Cys, Asn, Gln, Trp, His**
D	Heterocyclic non-aromatic ring (ether containing alicyclic ring)	*Ether oxygen* (1) Ion-Dipole (as the Dipole) (2) Dipole-Dipole (3) Hydrogen Bond (Acceptor) *Hydrocarbon ring* van der Waals; Hydrophobic	 (1) Lys, Arg, His** (2) Asn, Gln (3) Ser, Thr, Tyr, Trp, Cys, Asn, Gln, His** Val, Leu, Ile, Met, Ala (better interaction)*; Tyr, Phe, Trp

*Stronger van der Waals interactions occur when aromatic rings interact with aromatic rings and when aliphatic rings and chains interact with aliphatic rings and chains; however, all of the listed amino acids could possibly interact with the indicated functional groups.

**The side chain of histidine is primarily unionized at a pH =7.4. The small fraction that is ionized could participate in a cation-π interaction or an ionic bond, while the unionized fraction can serve as a dipole in an ion-dipole interaction or as a hydrogen bond donor or acceptor.

***The carbonyl group has been included in the box because it provides additional resonance delocalization of the negative charge of the sulfonamide (see Chapter 3 Questions/Answers).

2. Answers provided in the table below.

	Functional Group	**Types of Binding Interactions**	**Possible with DNA (Yes or No) and Why or Why Not.**
A	Halogenated phenyl ring (or aromatic ring)	(1) van der Waals; Hydrophobic	(1) *Yes*, the purine and pyrimidine rings have a dipole, so dipole-induced dipole interactions are possible. Hydrophobic interactions are less likely due to the normal stacking of DNA bases (i.e., less displacement of water).
		(2) π-π Stacking	(2) *Yes*, this could occur with the purine and pyrimidine bases.
		(3) Charge Transfer (as electron poor aromatic ring	(3) *Yes*, this could occur with the purine and pyrimidine bases.
		(4) Cation-π Interactions	(4) *No*, positive charges are not normally present in DNA
B	Tertiary amine	(1) Ionic	(1) *Yes*, ionic bonds could form with the phosphate groups of DNA.
		(2) Ion-Dipole (as the Ion)	(2) *Yes*, this could occur with dipoles present in the purine and pyrimidine bases as well as the deoxyribose sugar.
C	Sulfonamide	(1) Ionic	(1) *No*, positive charges are not normally present in DNA.
		(2) Ion-Dipole (as the Ion)	(2) *Yes*, this could occur with dipoles present in the purine and pyrimidine bases as well as the deoxyribose sugar.
D	Heterocyclic non-aromatic ring (ether-containing alicyclic ring)	*Ether oxygen* (1) Ion-Dipole (as the Dipole)	(1) *Yes*, this could occur with dipoles present in the purine and pyrimidine bases as well as the deoxyribose sugar.
		(2) Dipole-Dipole	(2) *Unlikely*, but could occur with partially positive carbon atoms in the purine and pyrimidine bases
		(3) Hydrogen Bond (Acceptor)	(3) *Yes*, hydrogen bond donors exist in purine and pyrimidine rings as well as the deoxyribose sugar.
		Hydrocarbon ring van der Waals; Hydrophobic	*No*, these interactions generally occur with alicylic rings and chains, not the heterocylic bases in DNA.

2. Yes, it is possible for venetoclax to form covalent bonds with proteins, enzymes, and other biomolecules; however, the probability of this occurring is somewhat low. None of the functional groups present within the structure of venetoclax are inherently highly reactive; thus, alkylation, acylation, or phosphorylation reactions would not be expected to occur. It is, however, possible for one or more of these functional groups to be metabolically transformed to a more highly reactive intermediate similar to the rearrangement reactions discussed in the chapter. If this were to occur, then a covalent bond could be formed.

Checkpoint Drug 2: Elamipretide

1. Answers provided in the table below.

	Functional Group Name	**Interactions Possible (as drawn)**	**Interactions Possible (at pH=7.4)**	**Amino Acid Whose Side Chain Can Interact with the Functional Group at pH=7.4**
A	Guanidine	1. Hydrogen bonding (acceptor and donor)	1. Ionic	1. Glu, Asp
		2. Ion-dipole (as the dipole)	2. Ion-dipole (as the ion)	2. Ser, Thr, Tyr, Cys, Gln, Asn
B	Primary amine	1. Hydrogen bonding (acceptor and donor)	1. Ionic	1. Glu, Asp
		2. Ion-dipole (as the dipole)	2. Ion-dipole (as the ion)	2. Ser, Thr, Tyr, Cys, Gln, Asn
C	Amide	1. Hydrogen bonding (acceptor and donor)	1. Hydrogen bonding (acceptor and donor)	1. Ser, Thr, Met, Tyr, Cys, Gln, Asn, Trp, His
		2. Ion-dipole (as the dipole)	2. Ion-dipole (as the dipole)	2. Glu, Asp, Lys, Arg
D	Phenol	1. Hydrogen bonding (acceptor and donor)	1. Hydrogen bonding (acceptor and donor)	1. Ser, Thr, Met, Tyr, Cy, Gln, Asn, Trp, His
		2. Ion-dipole (as the dipole)	2. Ion-dipole (as the dipole)	2. Glu, Asp, Lys, Arg

2. Answers provided in the table below.

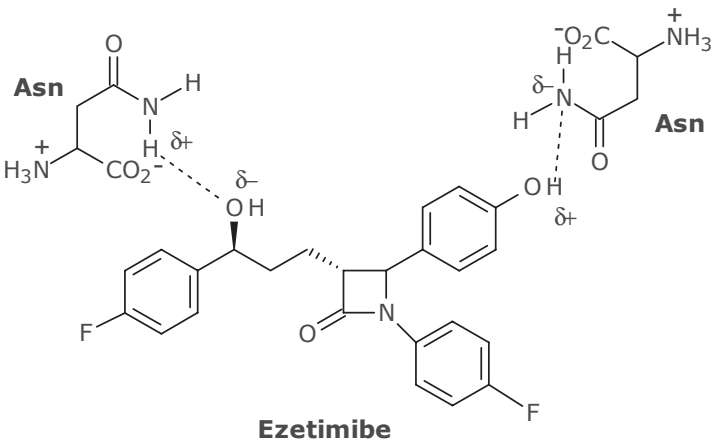
Interaction Type	**Functional Groups**
Cation-π	D
Ionic	A, B
Chelation	A, B
van der Waals	D
Ion-dipole (as the dipole)	C, D

REVIEW QUESTIONS

1. Answers provided in the table below.

Name of Functional Group	Acidic, Basic, or Neutral (As Drawn)	Ionized, Unionized or not Ionizable (at pH = 7.4)	Hydrogen Bond Acceptor, Donor, Both, or Neither (at pH = 7.4)	Amino Acids Whose Side Chain Can Interact with the Functional Group via Hydrogen Bonding (at pH = 7.4). None Is a Possible Answer.
Amide	Neutral	Not ionizable	Both	Serine, Threonine, Tyrosine, Cysteine, Asparagine, Glutamine, Tryptophan, Histidine, Methionine
Phenol	Acidic	Unionized	Both	Serine, Threonine, Tyrosine, Cysteine, Asparagine, Glutamine, Tryptophan, Histidine, Methionine
Secondary Alcohol	Neutral	Not ionizable	Both	Serine, Threonine, Tyrosine, Cysteine, Asparagine, Glutamine, Tryptophan, Histidine, Methionine
Secondary Amine	Basic	Ionized	Neither	None
Ether	Neutral	Not ionizable	Acceptor	Serine, Threonine, Tyrosine, Cysteine, Asparagine, Glutamine, Tryptophan, Histidine

2. Hydrogen bonding interactions with the hydroxyl groups are shown below.



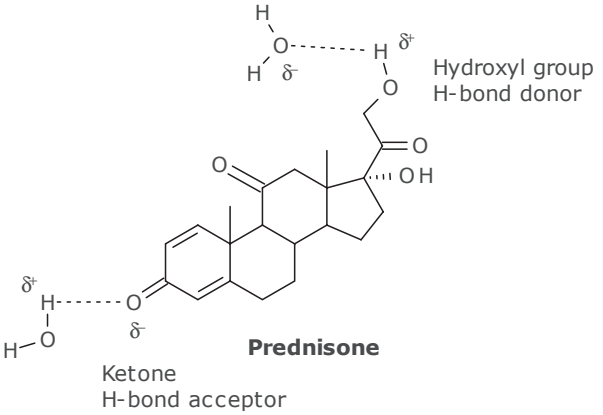
3. Possible interactions are provided in the grid below.

Name of Functional Group	Acidic, Basic, Neutral (As Drawn)	H-bond Acceptor, Donor, Both, or Neither (at pH = 7.4)	Interaction Possible with Serine (at pH = 7.4)	Interaction Possible with Glutamic Acid (at pH = 7.4)	Interaction Possible with Lysine (at pH = 7.4)	Interaction Possible with Tryptophan (at pH = 7.4)
ERTAPENEM						
Amide (mono substituted)	Neutral	Both	Hydrogen bonding; dipole-dipole	Ion dipole Drug = dipole	Ion dipole Drug = dipole	Hydrogen bonding; dipole-dipole
Amide (Lactam)	Neutral	Acceptor only	Hydrogen bonding; dipole-dipole	Ion-dipole Drug = dipole	Ion-dipole Drug = dipole	Hydrogen bonding; dipole-dipole
Carboxylic acid	Acidic pK_a 2.5–5	Neither (ionized)	Ion-dipole Drug = ion	None	Ionic	Ion-dipole Drug = ion
Secondary alcohol	Neutral	Both	Hydrogen bonding; dipole-dipole	Ion-dipole Drug = dipole	Ion-dipole Drug = dipole	Hydrogen bonding; dipole-dipole
Thioether	Neutral	Acceptor only	Hydrogen bonding	None	None	Hydrogen bonding; Hydrophobic interaction
Secondary amine (pyrrolidine)	Basic pK_a 9–11	Neither (ionized)	Ion-dipole Drug = Ion	Ionic	None	Ion dipole Drug = ion; Cation-π interaction
Aromatic hydrocarbon	Neutral	Neither	None	None	Cation-π interaction	Hydrophobic interaction; π-π stacking

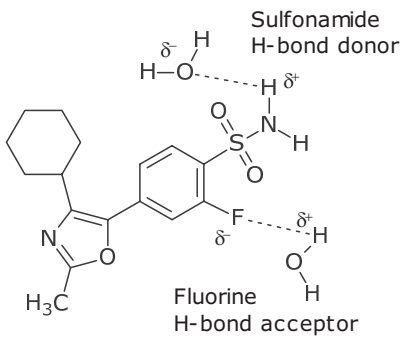
4. Answers provided in the table below.

Name of Functional Group	Acidic, Basic, or Neutral	Hydrogen Bond Acceptor, Donor, Both, or Neither	Interaction Possible with the Estrogen Receptor (assume pH=7.4)	Name of One Amino Acid That Can Participate in the Interaction Identified in the Previous Column with the Functional Group (assume pH = 7.4)
Tertiary Amine	Basic	Acceptor	Ion-dipole (Drug = ion)	Ser, Thr, Tyr, Cys, Asn, Gln, His, Trp (as dipole)
			Ionic	Asp, Glu
			Cation-π interaction	Phe, Tyr, Trp
Ether	Neutral	Acceptor	Hydrogen Bonding (Acceptor) Dipole-Dipole	Ser, Thr, Tyr, Cys, Asn, Gln, His
			Ion-dipole (Drug = dipole)	Lys, Arg, Asp, Glu
Alkene	Neutral	Neither	Hydrophobic	Val, Leu, Ile, Phe, Met, Tyr, Trp
Halogenated Aliphatic Hydrocarbon	Neutral	Neither	Hydrophobic	Val, Leu, Ile, Phe, Tyr, Met, Trp
Aromatic Hydrocarbon	Neutral	Neither	Hydrophobic; π-π stacking	Phe, Tyr, Trp, His (unionized form)
			Cation-π interaction	Lys, Arg, His (ionized form)

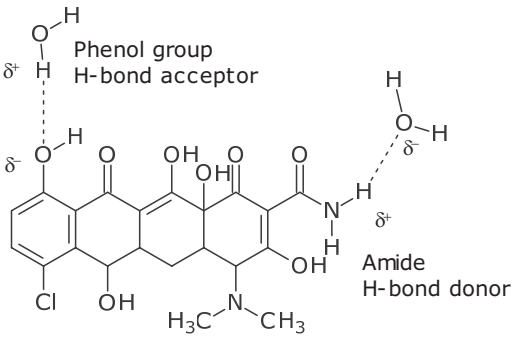
5. Some sample interactions are shown below. Please note that prednisone and demeclocycline contain additional hydroxyl groups and carbonyl groups that could undergo similar types of hydrogen bonds.



Prednisone



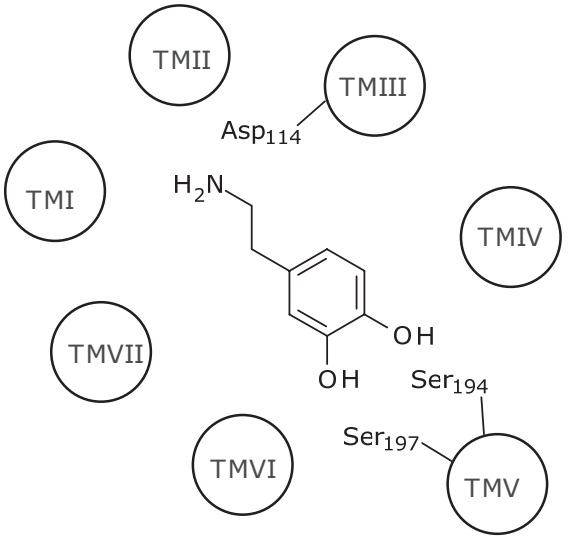
Tolvaptan



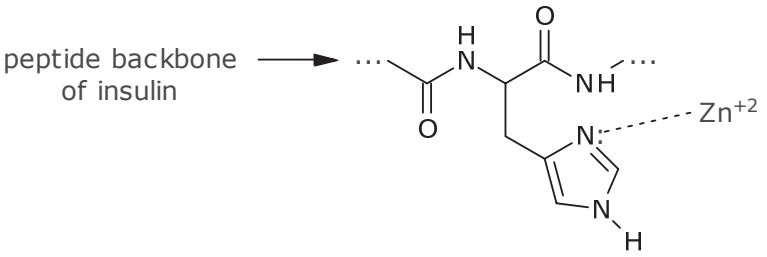
Demeclocycline

6. **Part A:** An ionic interaction occurs between the ionized carboxylic acid found in the side chain of aspartic acid and the ionized primary amine found in the structure of dopamine.

   Part B: The serine hydroxyl group is a neutral functional group and is not ionizable in any physiological environment. The catechol is acidic in character and at physiological pH (pH=7.4) the pH < pK_a and the catechol will be unionized. Both of these functional groups are able to participate in hydrogen bonding or dipole-dipole interactions.



7. The positively charged zinc atom complexes with the lone pair of electrons on the imidazole ring. Although the zinc atom can also complex with an amide carbonyl found on the peptide backbone of insulin, it is much more likely to complex with the histidine side chain because this side chain is less sterically hindered and thus more available.



8. Answers provided in the table below.

Amino Acid Side Chain	Possible Binding Interactions with Cetirizine
Box 1 Glutamine	*Unionized amines:* Dipole-dipole; hydrogen bonding (amino acid side chain = donor or acceptor) *Ionized amines:* Ion-dipole (drug = ion);
Box 2 Tyrosine	Hydrophobic interactions; π-π interactions; van der Waals *Unionized amine:* Dipole-dipole; hydrogen bonding (amino acid side chain is the donor) *Ionized amine:* Ion-dipole (drug = ion); Cation-π interaction
Box 3 Serine or Threonine	*Unionized carboxylic acid:* Dipole-dipole; hydrogen bonding (drug = donor or acceptor) *Ionized carboxylic acid:* Ion dipole (drug = ion)
Box 4 Arginine or Lysine	*Ionized arginine (or lysine) and carboxylic acid:* ionic *Ionized arginine (or lysine):* ion-dipole (with the ether) (amino acid side chain = ion)

9. The dihydropyridine ring system found in the center of this molecule is largely hydrophobic in character; however, it is unlikely to participate in van der Waals or hydrophobic bonding interactions. There are five substituents attached to the five carbons associated with this ring system. Three of the substituents are polar in nature (two esters and an ether) and, although hydrophobic, the halogenated aromatic hydrocarbon represents significant steric hindrance.

   Formation of van der Waals interactions requires that the dihydropyridine is in close proximity with another hydrophobic functional group. The halogenated aromatic hydrocarbon is likely to create sufficient steric hindrance to prevent this type of interaction to occur.

   The polar nature of the three dihydropyridine substituents will likely interfere with the formation of hydrophobic bonding interactions. As stated in the chapter, when there is a polar region within a drug molecule, it is unlikely that the biological target will contain complementary nonpolar functional groups.

10. Answers provided in the table below.

	Distance Requirement (r = Distance Between Functional Groups)	**Strength of Interaction**
Ionic	$1/r$	5–10 kcal/mol (strong)
Ion-dipole	$1/r^2$ (functional groups need to be closer together than in an ionic interaction)	4–5 kcal/mol
Dipole-dipole and hydrogen bonding	$1/r^3$ (functional groups need to be closer together than in an ion-dipole interaction)	1–7 kcal/mol (intermediate) (hydrogen bonding 3–4 kcal/mol)
van der Waals and hydrophobic interactions	$1/r^4$–$1/r^6$ (functional groups need to be closer together than in a dipole-dipole interaction)	0.5–1 kcal/mol (weak)

11. Drug molecules that covalently bind to their biological targets demonstrate enhanced selectivity for their targets and a prolonged duration of action. Let's look at each of these properties individually. The enhancement in selectivity is primarily achieved via the use of prodrugs that are converted to reactive intermediates (active drug) in close proximity to their biological targets. Proximity of the reactive intermediate and the biological target is important to maximize so as to avoid unnecessary misadventures between the reactive intermediate and other proteins present. In fact, it should be noted that those drugs that bind covalently that are not prodrugs and therefore do not require in vivo bioactivation, are generally no more selective than analogous drugs that interact via noncovalent means. Although drugs that form a covalent bond with their biological target do have a longer duration of action than drug molecules that participate in noncovalent interactions, it is important to be cautious when championing this property. It should be no surprise that the effects of covalently bound drugs are not as readily reversed (if at all!) as those associated with drugs that participate in noncovalent interactions; however, there is a possibility that the overall duration of drug action may be too long for the desired therapeutic effect (representing a potential disadvantage).

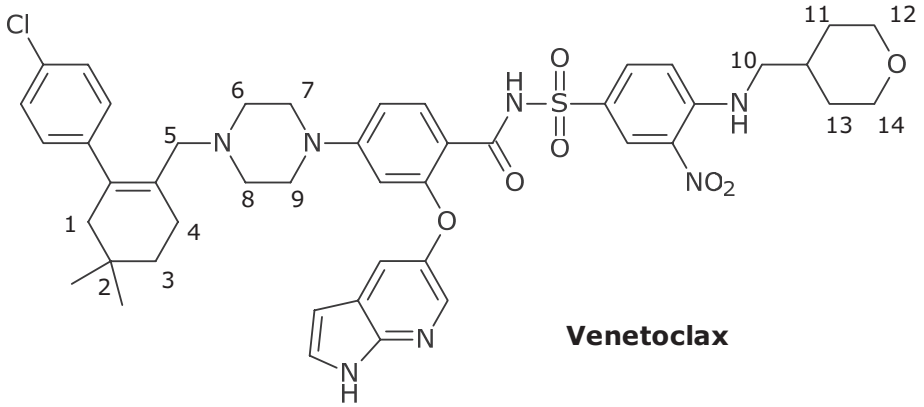
As you might expect, the possibility for drug misadventure, as mentioned previously, represents the major disadvantage associated with drugs that form covalent bonds with their biological targets. Because the active form of the drug is highly reactive, the potential for the drug to react with a nearby protein can be significant. As a result, special preparation and administration guidelines may need to be in place to ensure that drug activation occurs in close proximity to the desired biological target.

CHAPTER 7

STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

1. The structure of venetoclax does not contain any chiral centers; however, there are 14 potential prochiral centers. These have been identified below. With the exception of prochiral center 2, the metabolic addition of a functional group to any of these carbon atoms would result in a chiral center. For prochiral center 2, the addition of a functional group to either of the adjacent methyl groups would create a chiral center. At this point, we are only looking at ***potential*** prochiral centers. In Chapter 8, after we have discussed all of the metabolic pathways, we will revisit this question to see which of these potential prochiral centers can actually be converted to a chiral center.



Venetoclax

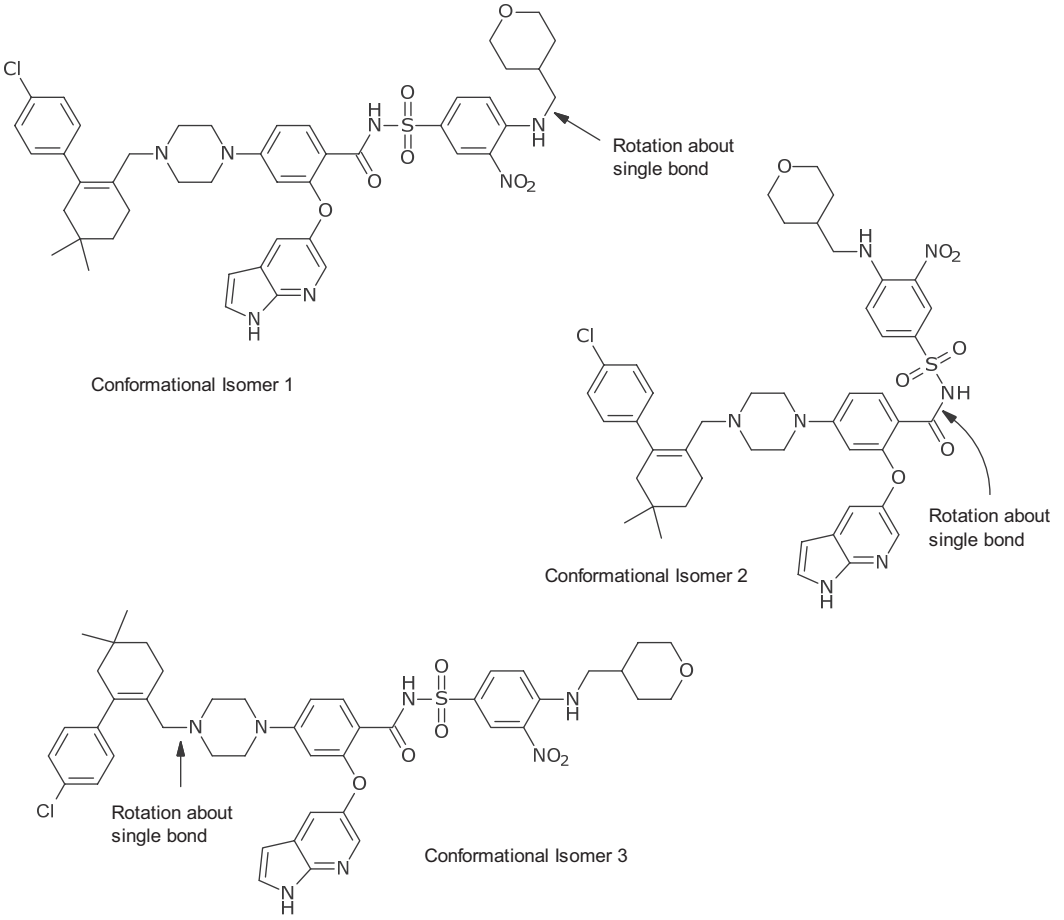
2. **Part A:** No. Drug molecules need to have at least one chiral center in order to have enantiomers. The structure of venetoclax does not contain any chiral centers, so it is not possible for it to have enantiomers.

   Part B: No. Drug molecules need to have at least two chiral centers in order to have diastereomers. The structure of venetoclax does not contain any chiral centers, so it is not possible for it to have diastereomers.

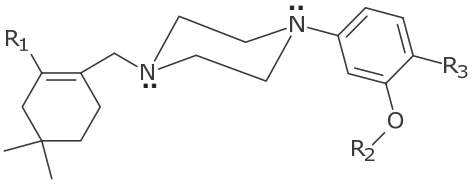
   Part C: No. Geometric isomers are a specialized type of diastereomers that occur due to the presence of an alicyclic ring or a double bond. The structure of venetoclax does contain two alicyclic rings; however, as mentioned above, neither of these contains a chiral center. The cyclohexene ring that is attached to the *para*-chlorophenyl ring does contain a double bond; however, due to the geometry and rigidity of a six-membered ring, it is not able to have *cis* and *trans* isomers. In order to have geometric isomers, the double bond needs to be in an aliphatic chain and not a ring.

   Part D: Yes. Conformational isomers result from the rotation of single bonds with a drug molecule. Since the structure of venetoclax contains numerous single bonds that can undergo free rotation, it is possible for venetoclax to have multiple conformational isomers.

3. Shown below are three conformational isomers of venetoclax. Although all of these conformational isomers are possible, conformational isomer 2 requires rotation of a bond involved in the resonance stabilization of the sulfonamide and may be less likely than the other two.

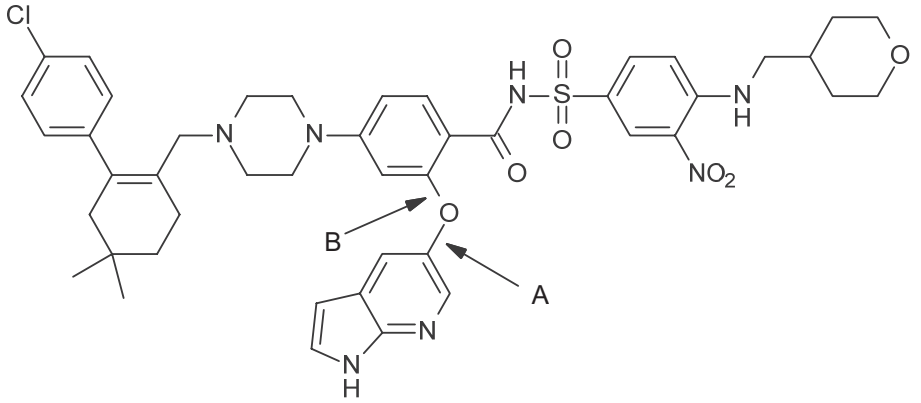


4. Cyclohexane and other six-membered, nonaromatic, heterocyclic ring systems (i.e., a piperazine ring) can adopt either a chair or boat conformation. Of these two options, chair conformations are preferred due to lower steric hindrance (or repulsion) and the presence of staggered bonds (as compared to eclipsed bonds seen in boat formations). Similar to chair-chair inversion seen with cyclohexane, the ability of nitrogen atoms to undergo inversion of their lone-pair of electrons allows for the minimization of steric hindrance (or repulsion) and the maximization of attractive forces. In the case of venetoclax, the nitrogen atoms in the piperazine ring are attached to aromatic and alicyclic rings. Due to steric reasons, these groups should be oriented such that they both occupy equatorial positions as shown below.



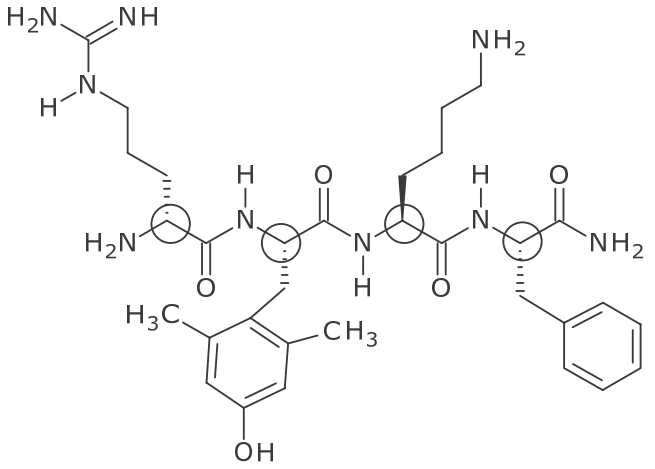
Predicted preferred conformation

5. The pyrrolopyridine ring can assume a variety of conformational orientations relative to its adjacent aromatic ring and the *meta* piperazine ring and the *ortho* side chain attached to this ring. The pyrrolopyridine ring can rotate about two bonds indicated in the structure below. Due to the rigidity and distance of the piperazine ring, it would not be expected to influence the conformation of the pyrrolopyridine ring. Rotation about bond A would allow the pyrrolopyridine ring to lie parallel to the adjacent aromatic ring, perpendicular to the adjacent aromatic ring, and any intermediate orientation. There are minimal steric factors affecting this rotation. Rotation about bond B would allow similar orientations; however, rotations approaching 135–180° would cause increasingly significant steric interactions with the *ortho* side chain and would not be favored. In terms of bond B, the orientation shown below of the pyrrolopyridine with respect to the *ortho* side chain provides the least steric hindrance.



Checkpoint Drug 2: Elamipretide

1. There are four chiral carbons present in elamipretide.



Elamipretide

2. For the arginine component of elamipretide, there are three additional prochiral carbons.

   For the tyrosine derivative component of elamipretide, there is one additional prochiral carbon.

   For the lysine component of elamipretide, there are four additional prochiral carbons.

   For the phenylalanine component of elamipretide, there is one additional prochiral carbon.

3. **Part A:** Enantiomers must contain at least one chiral carbon. Elamipretide contains four chiral carbons. In order to produce an *enantiomer* of elamipretide (SSRS = configuration as drawn), all of the chiral carbons would need to be in their opposite configuration (RRSR).

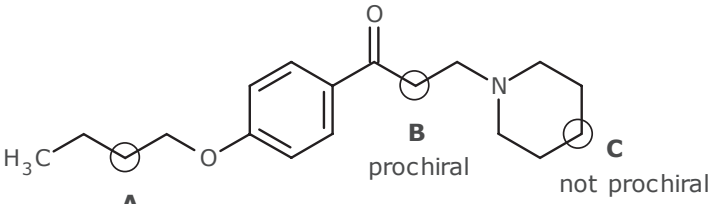
   Part B: In order for a molecule to have diastereomers, it must contain at least two chiral carbons. Elamipretide contains four chiral carbons. In order to produce a *diastereomer* of elamipretide (SSRS = configuration as drawn), at least one of the chiral carbons must be in its opposite configuration (RSRS). There are many, many diastereomers possible for elamipretide!!!

4. Geometric isomers are *not* possible for elamipretide because it does not contain a double bond or alicyclic ring system.

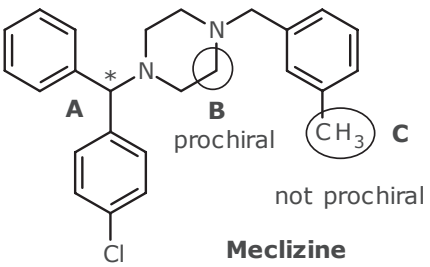
5. Because elamipretide contains numerous rotatable single bonds, not only at the ends of the molecule but in the middle of the molecule, it is considered conformationally flexible. In addition, it does not contain any double bonds or rigid ring systems.

REVIEW QUESTIONS

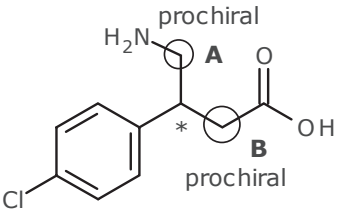
1. Chiral carbon atoms are identified below with asterisks. Circled carbon atoms are identified below as being prochiral or not prochiral.



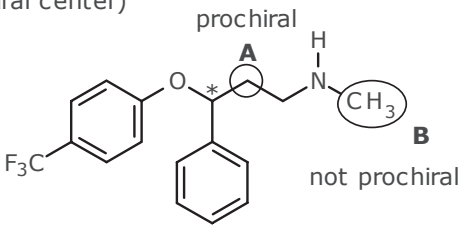
Dyclonine
(Does not have a chiral center)



Meclizine
(Has one chiral center)



Baclofen
(Has one chiral center)



Fluoxetine
(Has one chiral center)

2. *Priority #1:* substituted amine

   Priority #2: CH_2-halogenated aromatic hydrocarbon

   Priority #3: methyl group

   Priority #4: hydrogen atom

   The *R* enantiomer is drawn.

3. *Similar properties:* molecular weight, infrared (IR) and nuclear magnetic resonance (NMR) spectral properties, log P values, water/lipid solubility balance, dissolution rates, pK_a values of the amine group, and the percent ionization at any given pH value.

   Different property: direction that the molecule rotates plane polarized light.

4. Correct matches are shown below.

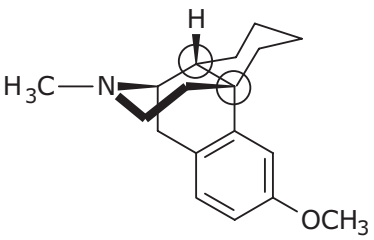
(+)/(-) matches with	Direction that enantiomer rotates plane polarized light
	Dextrorotatory/levorotatory
d/l matches with	Direction that enantiomer rotates plane polarized light
	Dextrorotatory/levorotatory
D/L matches with	Absolute configuration
	Steric arrangement of atoms about a chiral carbon
R/S matches with	Absolute configuration
	Steric arrangement of atoms about a chiral carbon

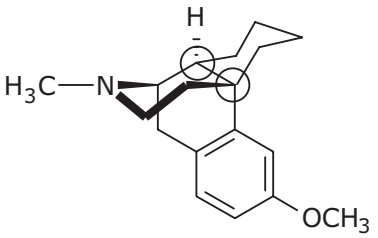
5. **Part A:** Only one (+)/(-) designation that indicates the net rotation of plane polarized light.

   Part B: Yes, it can have an enantiomer (non-superimposable mirror image), a diastereomer (non-superimposable non-mirror image), and conformational isomers (non-superimposable isomers that differ due to free rotation of atoms about single bonds). There is not enough information provided to determine if a geometric isomer is possible (e.g., no information related to presence of rings or double bonds).

6. The *R* enantiomer is drawn. It is possible that the two biological targets (reuptake transporters) have stereochemical differences for their interaction requirements. For example, in the *R* enantiomer the aromatic ring is pointed behind the plane of the paper where there is a suitably large hydrophobic pocket present in the serotonin-related biological target. In the *S* enantiomer, this aromatic ring is pointed in front of the plane of the paper (opposite side as *R* enantiomer), where there may be a suitably large hydrophobic pocket present in the norepinephrine-related biological target.

7. Chiral centers have been circled below.





Similarities to enantiomers:	Same molecular formula, not superimposable
Differences from enantiomers:	Not mirror images, different chemical and physical properties may have different pharmacological activities.

   At least one of the stereocenters has not changed configuration between the two structures; therefore, these two isomers are diastereomers.

8. Priority of the double bond substituents using the CIP system are listed below.

Priority #1:	Ether side chain with primary amine
Priority #2:	Nonbonding electrons on nitrogen atom
Priority #1′:	Substituted aromatic hydrocarbon
Priority #2′:	Methyl ether side chain

Because the two #1 priorities are on opposite sides of the double bond, therefore the structure above is drawn as the *trans* (*E*) isomer.

9. Tranexamic acid is a conformationally restricted analog of aminocaproic acid. The primary amine and the carboxylic acid are both located in equatorial positions, but on opposite sides of the cyclohexyl ring. The equatorial position is favored in order to avoid 1,3 diaxial effects. The two substituents on the cyclohexyl ring are *trans* to one another (opposite sides of the ring).

   The cyclohexyl ring system is a conformationally restricted isomer of the very flexible aminocaproic acid. The value of this restriction is that the two substituents (primary amine and carboxylic acid) are now fixed in a particular location in space relative to one another. This allows for improved interactions with the lysine receptor (requires less binding energy) and a decrease in the likelihood of misadventures with other biological targets (increase in specificity for desired biological target, decrease in adverse events).

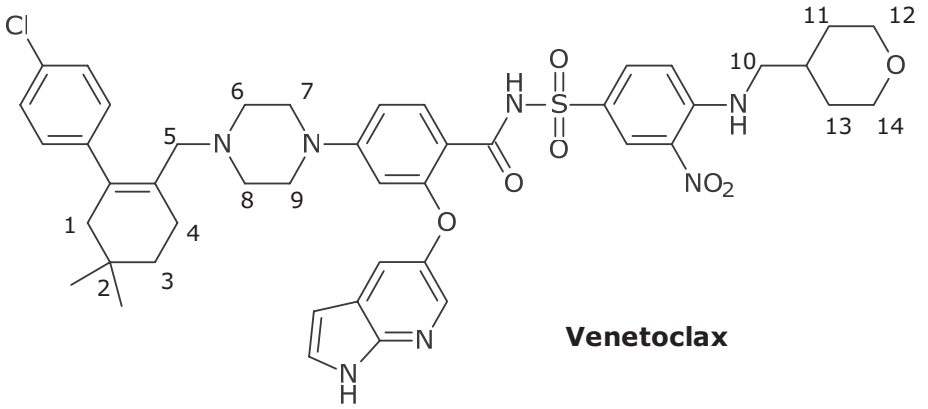
10. The 5α-androstane steroid is flatter in shape than the 5β-androstane. In the 5α isomer, the circled hydrogen atom and the methyl group (bold) are oriented *trans* to one another (located on opposite sides of the fused ring system). This permits the fused cyclohexane rings to remain elongated or flattened in shape. In the 5β isomer, the circled hydrogen atom and the methyl group (bold) are oriented *cis* to one another (located on the same side of the ring system). In this case, the steroid rings adopt a cupped shape. The mineralocorticoid receptor interacts best with receptor agonists that are flatter in shape, and it is expected that the 5α isomer would be the best "fit" for this receptor.

CHAPTER 8

STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

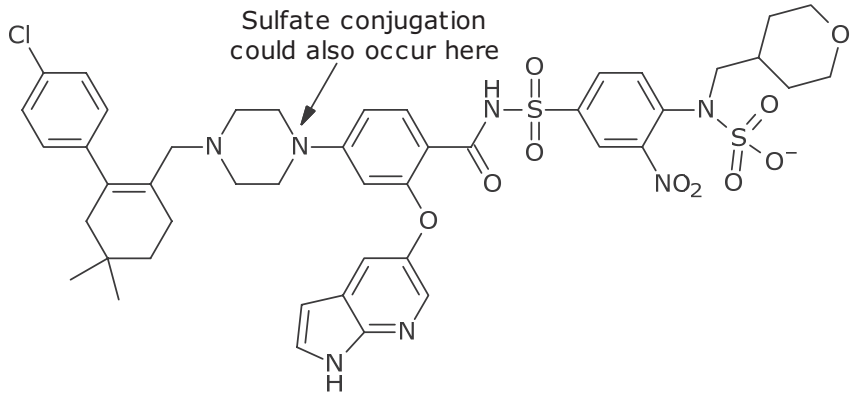
1. Shown below is the answer provided in Chapter 7. Of the 14 potential prochiral centers, only four of these (1–4) are valid. Carbon atoms 1 and 4 are allylic carbon atoms and can undergo allylic oxidation that would make these carbon atoms chiral. Either one of the methyl groups attached to carbon atom 2 can undergo ω oxidation, thus making carbon atom 2 chiral. Alicyclic rings can be oxidized at C_3 and C_4 positions. Carbon atom 3 resides at either the C_3 position relative to carbon atom 5 or the C_4 position relative to the *para*-chlorophenyl ring. Oxidation of this carbon atom would create a chiral center; however, the probability of this metabolic transformation is decreased due to steric hindrance by the adjacent dimethyl substitution. Oxidation at carbon atoms 5–10 can occur during the process of oxidative *N*-dealkylation. While the initial oxidation of these carbon atoms produces a chiral center, the resulting carbinolamine is unstable and readily forms an aldehyde. The same is true with carbon atoms 12 and 14 as they can be involved with oxidative *O*-dealkylation. Oxidation at carbon atoms 11 and 13 is highly unlikely. As mentioned above, alicyclic rings can be oxidized, but this normally occurs at the C_3 and C_4 positions of a cyclohexane ring and not at the carbon atoms adjacent to the aliphatic chain.



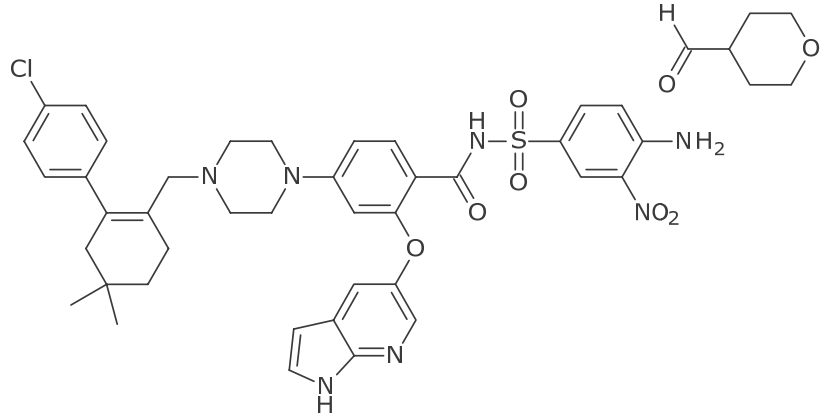
Venetoclax

2. **Metabolic Pathway A: No.** Benzylic oxidation is a ***Phase I*** metabolic transformation that requires an aliphatic carbon atom that is directly attached to an aromatic ring. While the structure of venetoclax contains four aromatic rings, only two of these are directly attached to an aliphatic carbon. Neither of these aliphatic carbon atoms have a hydrogen atom attached and thus cannot be oxidized

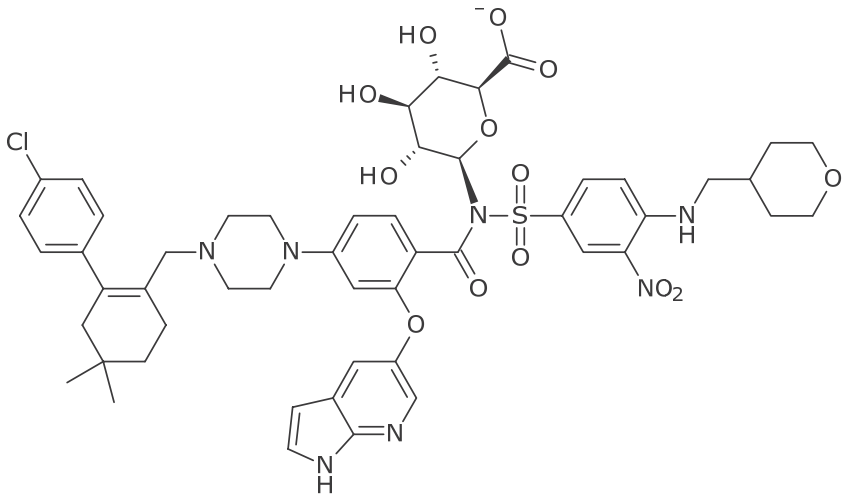
   Metabolic Pathway B: Yes. Sulfate conjugation is a ***Phase II*** metabolic transformation. Sulfate conjugation can occur with aromatic amines. The structure of venetoclax contains two aromatic amines.



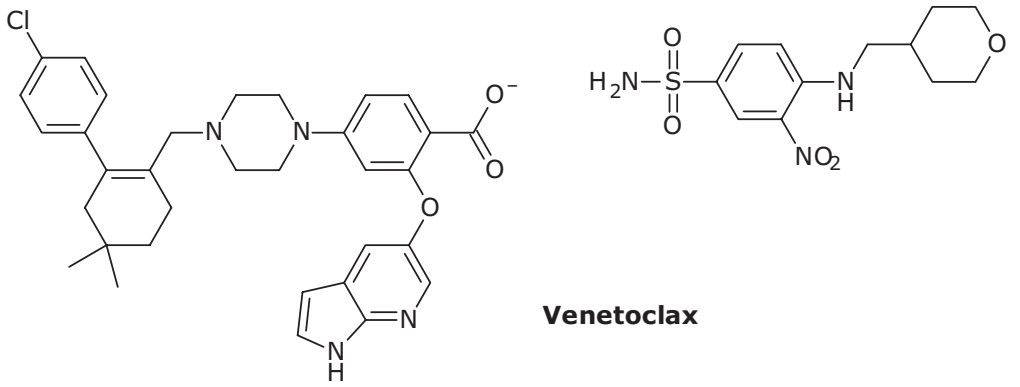
Metabolic Pathway C: Yes. Oxidative *N*-dealkylation is a ***Phase I*** metabolic transformation. As discussed in Question 1, venetoclax has six possible oxidative *N*-dealkylation sites. The metabolite shown below results from oxidation at the least sterically hindered (or most accessible) site.



Metabolic Pathway D: Yes. Glucuronic conjugation is a ***Phase II*** metabolic transformation. Glucuronide conjugation can occur with the sulfonamide (shown), the tertiary amine, and the two aromatic amines. It should be noted that due to steric hindrance and the electron withdrawing properties of the nitro group, glucuronide conjugation of venetoclax is a minor metabolic pathway.



Metabolic Pathway E: Yes. Hydrolysis is a ***Phase I*** metabolic transformation. The bond between the benzyl carbonyl and the sulfonamide can be hydrolyzed.



Venetoclax

Metabolic Pathway F: No. Alkene oxidation is a ***Phase I*** metabolic transformation that can occur with nonaromatic carbon-carbon double bonds. Although the structure of venetoclax contains a double bond in the cyclohexene ring, neither carbon atom involved in this double bond bears a hydrogen atom. Thus, this metabolism cannot occur.

3. All three of these phenyl rings are either electronically deactivated and/or sterically hindered, thus minimizing the probability that they would undergo aromatic oxidation. The *para*-chloro phenyl ring is very accessible to metabolism; however, the electron withdrawing chloro group deactivates the ring. The aromatic ring in the middle of the molecule is attached to both electron withdrawing groups (the carbonyl) and electron donating groups (the ether oxygen and the aromatic amine); however, due to its position in the molecule and the size of the rings and chains to which it is attached, it is not very accessible to metabolizing enzymes. It is thus highly unlikely that aromatic oxidation would occur here at this aromatic ring. Similarly, the aromatic ring with the nitro group is highly sterically hindered and not very accessible. Additionally, the nitro group is a very strong electron withdrawing group and will electronically deactivate the ring from aromatic oxidation.

4. There are two sites of metabolic transformation, the nitro group and the tetrahydropyran ring (i.e., the oxygen containing alicylic ring). The nitro group is first reduced to a primary aromatic amine. This is followed by acetylation. The tetrahydropyran ring first undergoes oxidative *O*-dealkylation to give a primary hydroxyl group and an aldehyde. The aldehyde is further oxidized by ALDH enzymes to a carboxylic acid. The carboxylic acid then undergoes amino acid conjugation to yield the final metabolic product.

Checkpoint Drug 2: Elamipretide

1. The cLogP for elamipretide is 0.3677 which indicates significant water solubility (the amount of hydrophilic character of guanidine, primary amines, phenol, and multiple amides is greater than the hydrophobic character of phenol, aromatic hydrocarbon). The ability of the guanidine and two primary amines to be predominantly ionized in most physiological environments contributes to the overall water solubility of elamipretide. Because renal elimination requires a drug to be highly water soluble, it is likely that elamipretide can be eliminated without the need for Phase I or Phase II metabolic transformation.

2. **No,** a Phase I transformation does not need to occur prior to a Phase II transformation. The primary amine can directly undergo a Phase II acetylation transformation. The phenol can directly undergo a phase II POMT catalyzed *O*-methylation, as well as Phase II sulfation and glucuronidation transformations.

3. *Primary amine (amino terminus):* oxidative deamination; *N*-oxidation

   Primary amine (lysine): oxidative deamination; *N*-oxidation

   Phenol: benzylic oxidation of CH_3; benzylic oxidation of CH_2 (prochiral carbon); aromatic hydroxylation (*ortho, para*)

   Aromatic hydrocarbon: benzylic oxidation of CH_2 (prochiral carbon); aromatic hydroxylation (*ortho, para*)

   Amide: amide hydrolysis

4. This prodrug must undergo the following metabolic transformations to become the active drug:

   Primary amine (amino terminus): amide hydrolysis

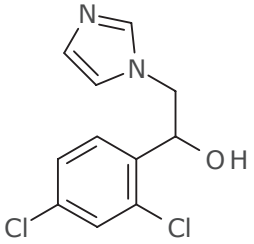
   Phenol: oxidative-*O*-dealkylation

REVIEW QUESTIONS

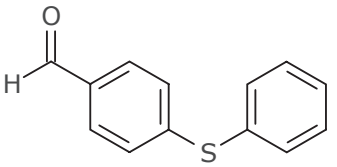
1. **Part A:** *Para* and *ortho* aromatic hydroxylation; oxidative *O*-dealkylation; *N*-oxidation (imidazole, minor pathway).

   Part B: The typical products of *S*-dealkylation are either a thiol and an aldehyde or a thiol and a ketone. In fenticonazole, the sulfur atom is bound to carbon atoms that are components of aromatic hydrocarbons. These carbons do not have a hydrogen atom attached to them and therefore cannot undergo oxidation to form a ketone.

Part C: The pairs of structures drawn below represent the products of oxidative *O*-dealkylation. For this particular ether, oxidative *O*-dealkylation can occur on either side of the oxygen atom.

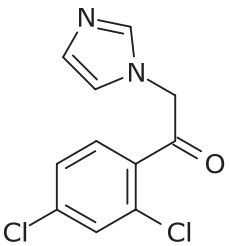


Secondary alcohol

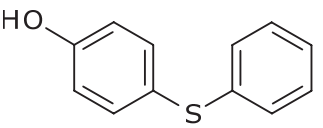


Aldehyde

OR



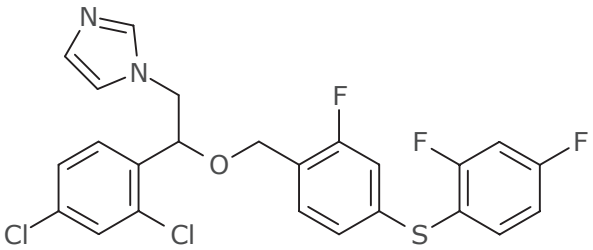
Ketone



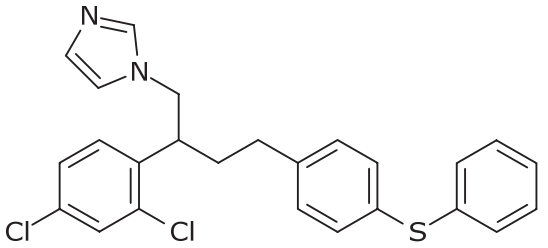
Phenol

Part D: First, consider the answers you provided for possible Phase I metabolic transformations; then, determine how you could modify the structure of fenticonazole to prevent *para* and/or *ortho* aromatic hydroxylation or oxidative *O*-dealkylation.

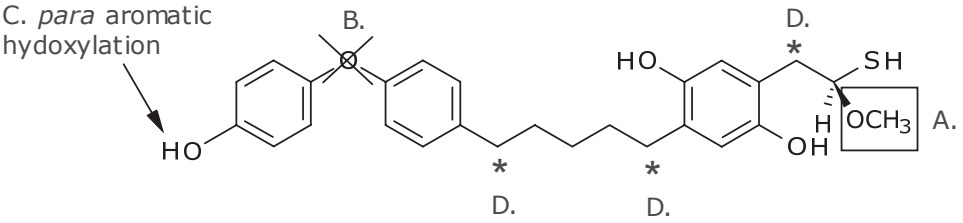
The addition of fluoro substituents in the *ortho* and *para* positions (several examples, but not all possibilities are shown below) can limit Phase I metabolic transformation of this molecule into a more water-soluble analog (that is easily eliminated). Fluoro substituents are electron withdrawing in character and will deactivate the aromatic ring toward metabolic aromatic hydroxylation similar to that observed with the chloro substituent found in diazepam (Figure 8-5).



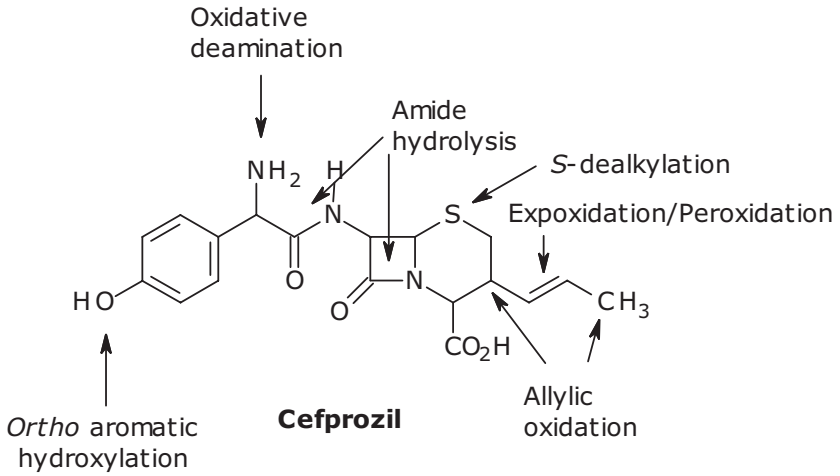
Replacement of the ether oxygen with a methylene (CH_2) group will prevent Phase I metabolic transformation (oxidative *O*-dealkylation) of this molecule into a more water-soluble analog (that is easily eliminated).



2. The typical products of oxidative *O*-dealkylation are either an alcohol and an aldehyde or an alcohol and a ketone. Like we saw with the thioether in fenticonazole, the oxygen atom of the ether functional group that is crossed out is bound to carbon atoms that are components of aromatic hydrocarbons. These carbons do not have a hydrogen atom attached to them and therefore cannot undergo oxidation.



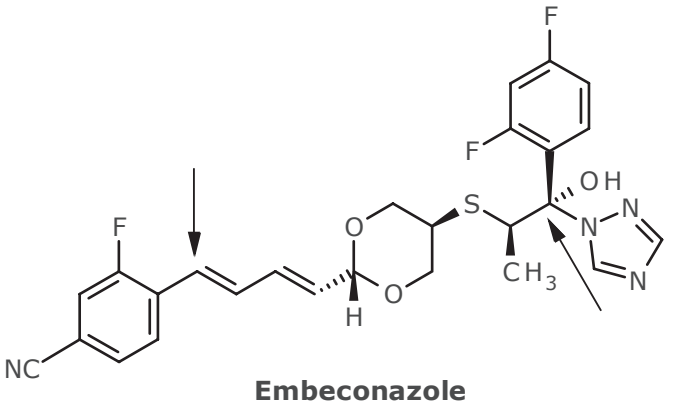
3. All possible Phase I metabolic transformations are provided below.



Names of Phase I Transformations Possible:

Aromatic hydroxylation (*ortho*)
Oxidative deamination
Amide hydrolysis
S-dealkylation
Epoxidation/peroxidation
Allylic oxidation

4. There are two aromatic rings in the molecule and potentially two benzylic carbons (see arrows). One benzylic carbon already has a hydroxyl substituent, and the other is part of a double bond. Neither can undergo benzylic oxidation as neither carbon bears a requisite hydrogen atom.

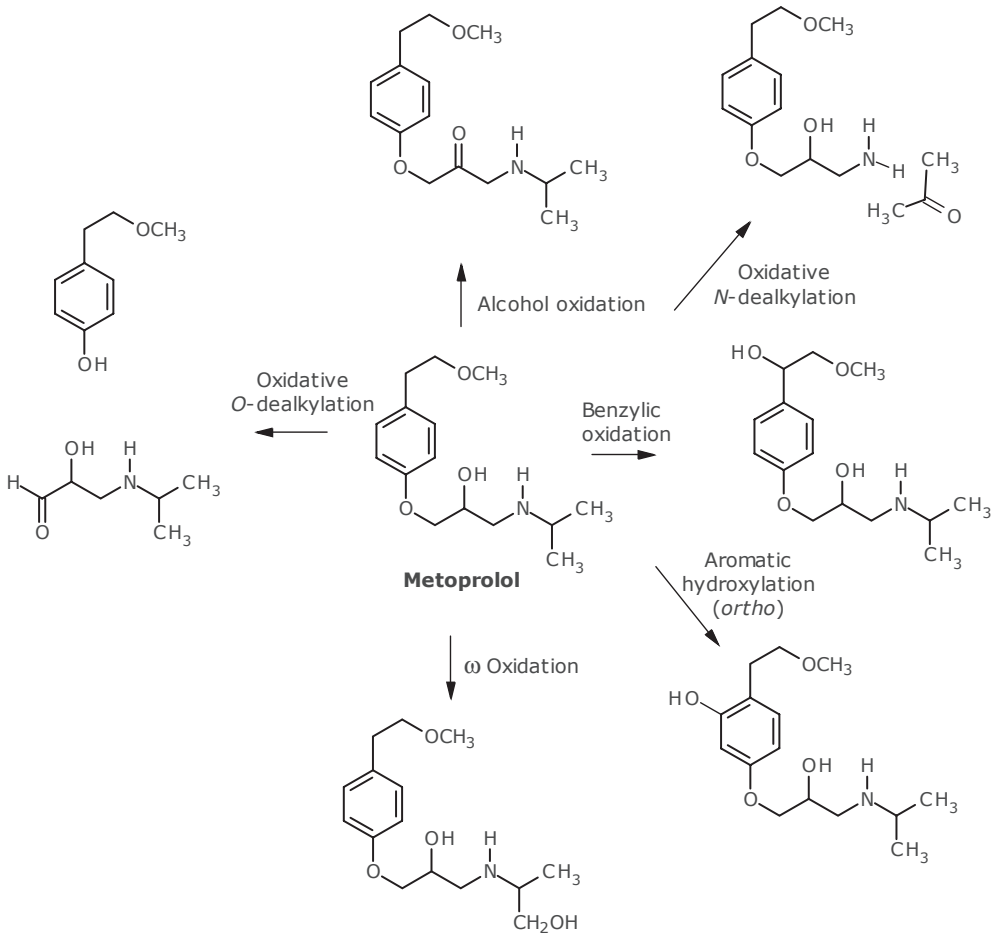


Embeconazole

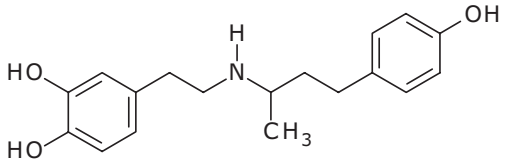
5. *Amide:* Amide hydrolysis (Phase I) followed by acetylation (Phase II)
   Ether: Oxidative *O*-dealkylation (Phase I) followed by sulfation (Phase II)
   Secondary alcohol: Alcohol oxidation (Phase I)
   Phenol: Aromatic hydroxylation (*ortho, para*) (Phase I)

6. Possible Phase I metabolic transformations of metoprolol are listed and shown below:

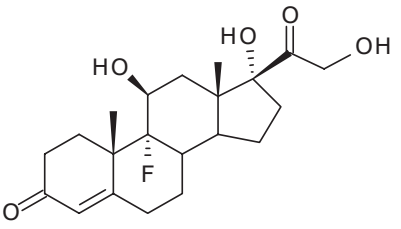
   Alcohol oxidation
   Benzylic oxidation
   Oxidative *O*-dealkylation (methyl ether and phenyl ether)
   Oxidative *N*-dealkylation
   ω/ω-1 oxidation
   Aromatic hydroxylation (*ortho*)



7. Lists of all Phase I and Phase II metabolic transformation for each drug are provided below.

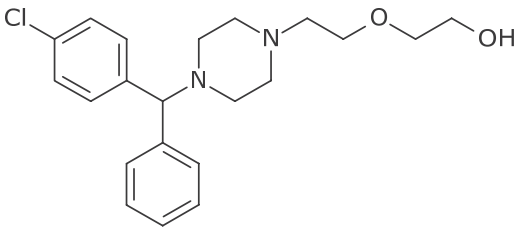


Dobutamine

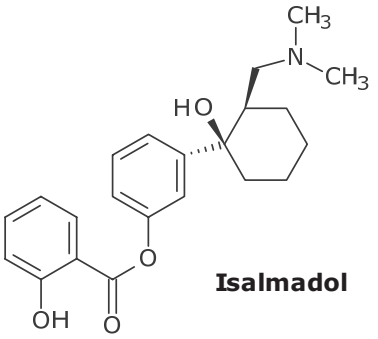


Fludrocortisone

Dobutamine	**Fludrocortisone**
Aromatic hydroxylation (*ortho*, *para*)	Allylic oxidation
Oxidative *N*-dealkylation	Alcohol oxidation (secondary)
Benzylic oxidation	Reduction
Phase II: COMT catalyzed *O*-methylation; POMT catalyzed *O*-methylation; sulfation; glucuronidation	Phase II: Glucuronidation

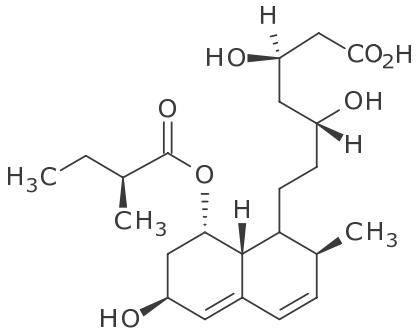


Hydroxyzine

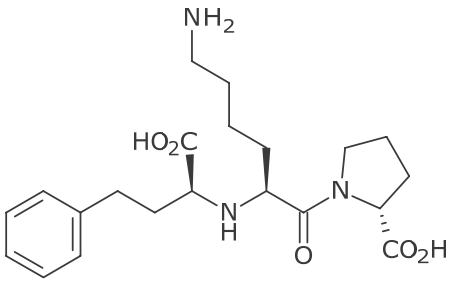


Isalmadol

Hydroxyzine	Isalmodol
Aromatic hydroxylation (*ortho, para*)	Aromatic hydroxylation (*ortho, para*)
Oxidative *N*-dealkylation	Ester hydrolysis
N-oxidation	Oxidative *N*-dealkylation
Oxidative *O*-dealkylation	*N*-oxidation
Alcohol oxidation	Phase II: POMT catalyzed *O*-methylation; sulfation; glucuronidation
Phase II: Glucuronidation	

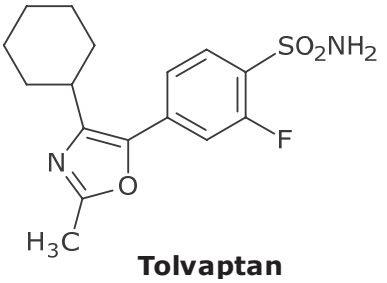


Pravastatin



Lisinopril

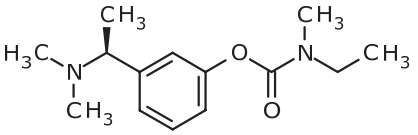
Pravastatin	Lisinopril
ω/ω-1 oxidation	Aromatic hydroxylation (*ortho, para*)
Ester hydrolysis	Benzylic oxidation
Allylic oxidation	Amide hydrolysis
Epoxidation/peroxidation	Oxidative deamination
Alcohol oxidation	Oxidative *N*-dealkylation
Phase II: Amino acid conjugation; glucuronidation	Phase II: Acetylation; glucuronidation; amino acid conjugation



Tolvaptan

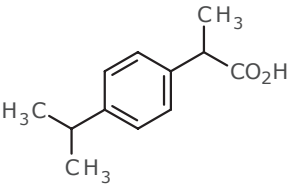
Tolvaptan
ω/ω-1 oxidation
Benzylic oxidation (of 1,3-oxazole)
Aromatic hydroxylation (*ortho, para*)
Phase II: only after Phase I transformation (e.g., sulfation)

8. Answers for each drug molecule are shown below.



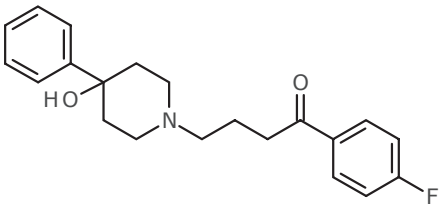
Rivastigmine

(B) = True



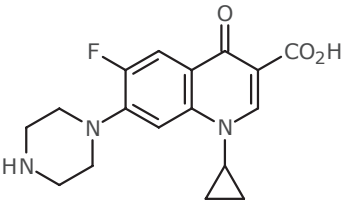
Ibuprofen

(A) Glucuronidation; amino acid conjugation



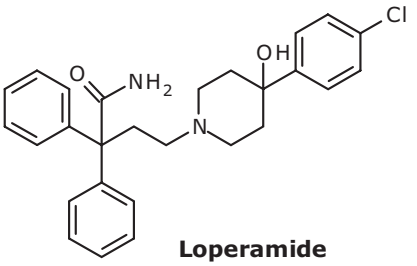
Haloperidol

(B) = True; Tertiary alcohol too sterically hindered to undergo glucuronidation



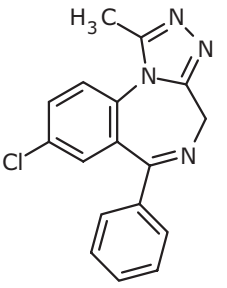
Ciprofloxacin

(A) Glucuronidation; amino acid conjugation



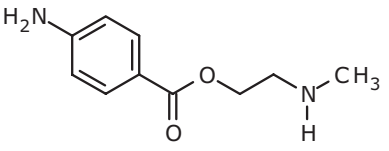
Loperamide

(B) = True; Tertiary alcohol too sterically hindered to undergo glucuronidation



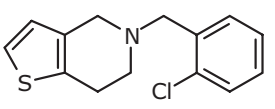
Alprazolam

(B) = True



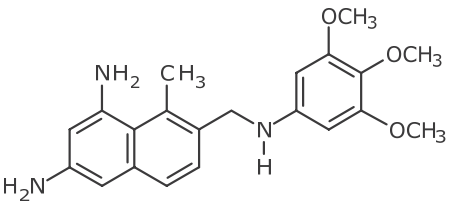
Procainamide

(A) Glucuronidation; acetylation



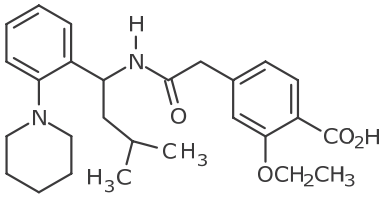
Ticlopidine

(B) = True



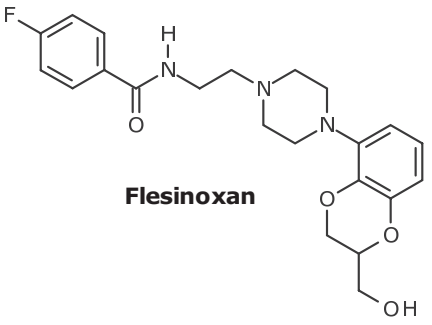
Trimetrexate

(A) Glucuronidation (aniline nitrogen)



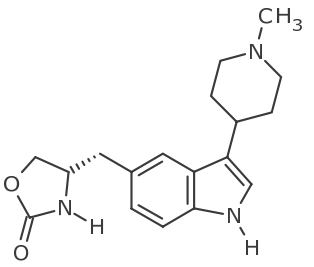
Repaglinide

(A) Glucuronidation; amino acid conjugation



Flesinoxan

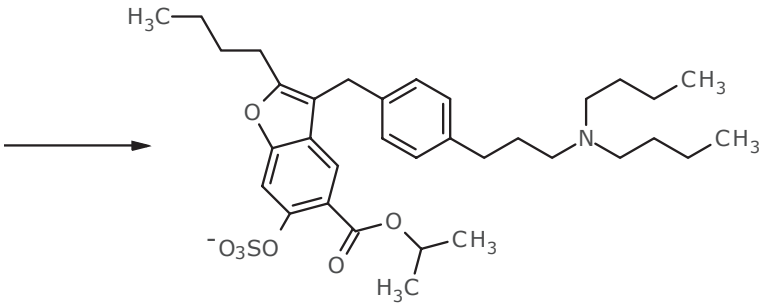
(A) Glucuronidation of primary alcohol



Zolmitriptan

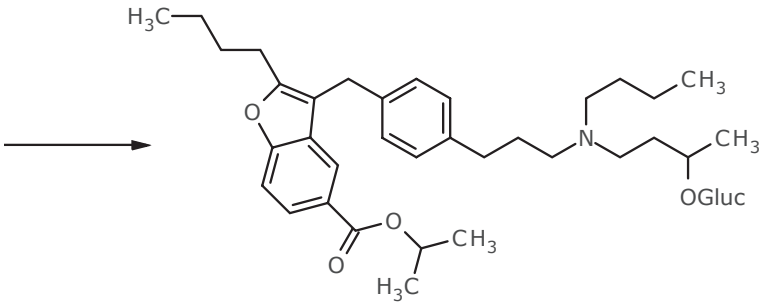
(B) = True

9. Phase I and Phase II metabolic transformations for celivaronum are identified below.



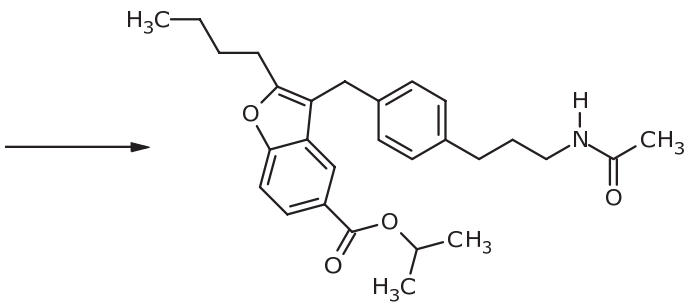
Aromatic hydroxylation (*ortho*) (Phase I)

Sulfate conjugation (Phase II)



Omega-1 oxidation (Phase I)

Glucuronic acid conjugation (Phase II)



Oxidative *N*-dealkylation (Phase I)

Oxidative *N*-dealkylation (Phase I)

Acetylation (Phase II)

CHAPTER 9

STRUCTURE ANALYSIS CHECKPOINT

Checkpoint Drug 1: Venetoclax

1. The alteration of functional groups on the aromatic ring can change the solubility of the drug molecule, the electronics of the aromatic ring, and/or the overall steric size of the aromatic ring and drug molecule. In examining the six functional groups and the activity profile, the difference in steric size does not explain the activity profile. The NO_2 and CN groups enhanced activity, while the OCH_3, a functional group of similar size, caused an elimination of activity. The same is true with solubility. While the OH and OCH_3 groups are more water soluble than the original chloro group, the CH_3 has similar solubility to the chloro group. All three of these functional groups caused either a decrease or elimination of activity. Thus, the changes in activity must be due to the electronic differences in the functional group. The original Cl group is electron withdrawing due to induction. Replacement with functional groups that are electron withdrawing due to induction—the F group—retain activity, while replacement with functional groups that are electron withdrawing through resonance—the NO_2 or CN groups—enhance activity. As discussed in Chapter 2, the ability to donate or withdraw electrons through resonance is stronger than the ability to donate or withdraw electrons through induction. The CH_3, OH, and OCH_3 all decrease or eliminate activity. All of these functional groups are electron donating, the CH_3 through induction, and the OH and OCH_3 through resonance. *Given all of this information, the following SAR statements can be made:*
   - Electron withdrawing functional groups on this aromatic ring enhance activity, while electron donating groups detract from activity.
   - Those functional groups that withdraw electrons through resonance enhance the activity to a greater extent than those that can only withdraw electrons through induction.
   - Functional groups that can donate electrons through resonance eliminate activity.

2. The original pyrrolopyrimidine bicyclic ring can interact with its biological target through hydrogen bonds, van der Waals interactions, π-π stacking, and cation-π interactions. In evaluating these four analogs, the major difference among them is their ability to form specific types of hydrogen bonds. The pyrrole nitrogen (i.e., the one in the five-membered ring) acts as a hydrogen bond donor, while the pyrimidine nitrogen (i.e., the one in the six-membered ring) acts as a hydrogen bond acceptor. The only analog to retain activity is Analog B. This bicyclic indole ring retains the nitrogen atom that can act as a hydrogen bond donor. Please note that the location/position of the hydrogen bond donor is the same. Analog D also has a nitrogen atom that can act as a hydrogen bond donor; however, due to the fact that the pyrrolopyrimidine is now attached to the rest of the molecule via a different carbon atom, this hydrogen bond donor is located or positioned differently. As such, the strength of the hydrogen bond to the biological target

is not as strong leading to the 10-fold loss in activity. Analogs A and C lack a hydrogen bond donor in the aromatic ring and are thus inactive. Given this information, the following SAR statement can be made:

- The pyrrolopyridine ring provides a key hydrogen bond (as the donor) to its biological target. This bicyclic ring can be altered as long as the position of the hydrogen bond donor is unaltered.

3. Replacing the ether oxygen atom with a secondary amine will enhance the water solubility of venetoclax. The ether oxygen atom can form hydrogen bonds with water (as the acceptor); however, the secondary amine will be primarily ionized at physiological pH and thus be able to form ion-dipole interactions with water (as the ion). An ion-dipole bond enhances water solubility to greater extent than a hydrogen bond. Additionally, the presence of an ionized amine would allow this isostere of venetoclax to participate in ionic or ion-dipole bonds with its biological target. This is assuming that complementary functional groups are present on the biological target. The presence of an ionized amine could also cause a decrease in the overall binding activity. The tetrahydropyran ring may reside in a hydrophobic pocket with the most important interactions occurring via van der Waals interactions with the carbon atoms. If this is true, then the presence of an ionized secondary amine may decrease drug binding and activity. Given that "O" and "NH" are pseudoatoms and classical isosteres, it would be expected that these groups would be similar in size and thus not alter activity due to steric reasons. The same is true for the methylene carbon.

   Replacing the ether oxygen with a methylene group will decrease water solubility and increase lipid solubility of the drug. As mentioned above, the ether oxygen atom can form hydrogen bonds with water, while the methylene group cannot. In terms of receptor binding, if the ether oxygen was essential in forming a hydrogen bond (as the acceptor) with its biological target, then this isosteric substitution could decrease the activity of this analog. Conversely, if the tetrahydropyran ring resides in a hydrophobic pocket, this isosteric replacement could enhance van der Waals interactions with its biological target.

4. The answer is "NO" with the key word being "easily." The easiest way to convert a drug molecule to a more water- or lipid-soluble prodrug is to form an ester as these functional groups can be easily hydrolyzed back to the active drug at various locations within the body. In order to form an ester, the structure of the drug must contain either a carboxylic acid or a hydroxyl group that is easily accessible to esterase enzymes. Because neither of these functional groups is present within the structure of venetoclax, it cannot be easily converted to a prodrug. For the sake of completeness, it should be noted that it is theoretically possible to make a prodrug from the sulfonamide functional group; however, this would create a sterically hindered site that may be difficult to access by metabolizing/activating enzymes.

Checkpoint Drug 2: Elamipretide

1. Possible binding interactions are provided in the table below.

	Amino Terminus	**Carboxy Terminus**
SS-31 (elamipretide)	Ionic Ion dipole Cation-π Chelation	Cation-π π-π stacking Hydrophobic H-bonding Ion-dipole (dipole)
SS-02	Ionic Ion-dipole (ion) Ion-dipole (dipole) Cation-π H-bonding π-π stacking Hydrophobic	Ionic Ion-dipole (ion) Ion-dipole (dipole) H-bonding Cation-π Chelation
SS-20	Ionic Ion-dipole (ion) Cation-π π-π stacking Hydrophobic	Ionic Ion-dipole (ion) Ion-dipole (dipole) H-bonding Cation-π Chelation

SS-02 is the only analog that can participate in H-bonding and ion-dipole (as the dipole) at the amino terminus (via the phenol OH) at physiological pH. These types of interactions might be important for μ receptor activation.

2. At physiological pH the basic functional groups (guanidine and primary amine) found within elamipretide and the two analogs will be ionized and able to interaction via an ionic interaction with a phosphate head. In all three molecules, the two amino acids with basic side chains are always separated by one amino acid and are therefore always in the same proximity to one another.

3. In elamipretide and in SS-20, the tyrosine derivative is located between the amino acids with the basic side chains. In SS-02 the phenylalanine residue is located between the amino acids with the basic side chains. The basic side chains are required for an important electrostatic interaction with the phosphate head found within cardiolipin. It is possible that cardiolipin also requires a particular type of interaction (ion-dipole, H-bonding, or dipole-dipole) between these two basic amino acids for optimal binding. If this is the case, then SS-02 would not have the right type of functionality to participate in this important interaction (ion-dipole, H-bonding, or dipole-dipole) with cardiolipin.

4. **Part A:** There are several reasons why a lipophilic ester prodrug might be valuable including improving bioavailability and the related absorption across lipophilic membranes. Prodrugs also protect drug molecules from metabolic and/or enzymatic degradation, as well as may prevent metabolic transformations that lead to rapid drug elimination.

   Part B: This prodrug form of elamipretide contains amides at both the amino- and carboxy terminus. Amino- and carboxypeptidases require their substrates to contain either a primary amine or carboxylic acid (respectively). In order to fool these enzymes, these functional groups can be "protected" or "masked" as amides. Once the primary amine and/or carboxylic acid is modified to be an amide (prodrug), then the amino- and carboxypeptidases no longer recognize the drug as a substrate, thus extending the half-life of the drug. Since amides are relatively easily cleaved to the corresponding carboxylic acid and amine (Phase I metabolic transformation catalyzed by amidases), they serve as valuable prodrugs.

REVIEW QUESTIONS

1. **Part A,** Insulin #1: Inactive—three disulfide bonds must be present to allow insulin to adopt the correct conformation. In this scenario the amino and carboxy terminal amino acid residues are identical to that found in endogenous insulin; however, if the amino acids at the amino or carboxy termini of the A chain are different than that found in the endogenous hormone, then the key receptor interactions may not occur and the corresponding analog would be biologically inactive.

   Part B, Insulin #2: Inactive—only six amino acids can be removed from the amino terminus of the B chain and still retain biological activity. In this case 10 amino acids are missing from the amino terminus of the B chain.

   Part C, Insulin #3: Inactive—there is a good chance that this insulin analog will be inactive due to the number of *D*-amino acids present. The change in stereochemistry in so many locations will more than likely not only change the shape of the insulin molecule (amino acid side chains may not be located in the right place in space to allow for the appropriate secondary and ternary structural features to form), but also may influence how many amino acids can interact with the insulin receptor.

2. Glipizide contains an acidic sulfonylurea functional group, whereas repaglinide contains an acidic carboxylic acid functional group. This molecular modification is an example of the use of a non-classical bioisostere. There are several other molecular modifications that you might have identified, including shortening the hydrocarbon chain between the arylsulfonylurea and the amide functional groups, reversal of the placement of the amide carbonyl group, and replacement of an aromatic heterocycle with an aromatic hydrocarbon.

3. Insulin lispro contains a proline residue as part of its primary structure; however, it is in closer proximity to the carboxy terminus as a result of a structural exchange of the Lys_{29} with the Pro_{28}. You might imagine that the size of the "hook" is now smaller (only one amino acid in length) and that the likelihood of insulin dimerization will decrease. This is in fact exactly what happens!!! As a result of this structural modification there is more monomer present in the formulation and the time that it takes for the insulin dimer present to dissociate into two monomers is likely to be shorter than that required for Humulin R.

   Insulin aspart does not contain a proline residue as part of its primary structure. This means that there is no "hook" present within the carboxy terminus of the B chain of this insulin analog. This means that this analog will not dimerize and will only need to dissociate from the insulin stabilizer present in the formation (which is true for all insulin formulations) in order to be an active drug. This will take less time and, therefore, the onset and duration of action is shorter than Humulin R.

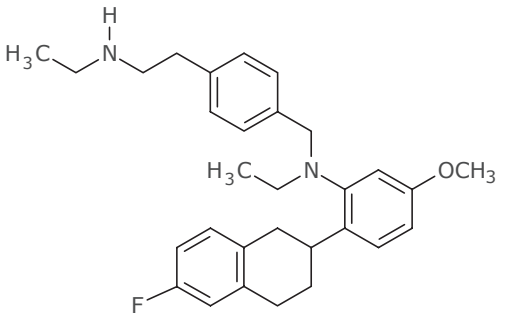
   Note: Although insulin glulisine is also considered an ultra-short acting insulin, the rationale for this has nothing to do with the primary structure (Pro_{28} is present), but rather has to do with the type of insulin stabilizer used in the formulation.

4. Tazarotene is formulated as a topical agent in the treatment of several skin disorders. For this drug to penetrate the affected skin, it must be highly hydrophobic in character. Although the carboxylic acid is important for biological activity, it is very hydrophilic and limits the ability of the drug to be appropriately formulated for topical use. Formation of the ethyl ester significantly decreases the hydrophilic character of this functional group and, therefore, not only improves the overall characteristics from a formulation perspective, but also improves the ability of the drug to penetrate the skin.

5. For many years ciprofloxacin represented the gold standard to which other fluoroquinolones were compared. Thousands of analogs were synthesized, with only a handful exhibiting equal or better action against gram-negative pathogens. When looking at the analog series A–D, there is a progressive addition of hydrocarbon character associated with the N atom substituent. Once this substituent contains more than three carbons, there is a complete loss of biological activity. One could surmise that the interaction between the drug and its biological target allows for a finite amount of hydrophobicity/bulk in this location, and once this hydrophobic space is exceeded, the interaction of the drug with the biological target suffers significantly.

6. **Analog A:** Replace phenol OH with F.

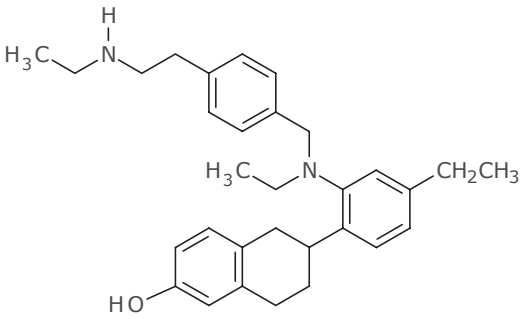
   This decreases the potential for Phase I catechol formation and Phase II sulfation, glucuronidation, and *O*-methylation catalyzed by POMT.



Analog A

Analog B: Replace oxygen atom in methyl ether substituent with a methylene unit (CH_2).

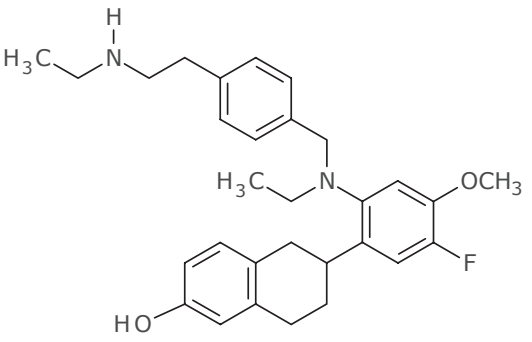
This decreases the potential for Phase I oxidative *O*-dealkylation (potentially followed by Phase II sulfation, glucuronidation, and *O*-methylation catalyzed by POMT).



Analog B

Analog C: Insert fluoro substituent *ortho* to the methyl ether substituent.

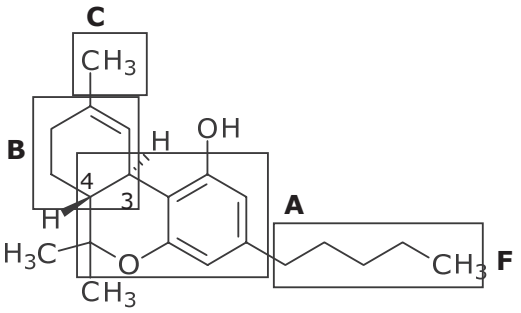
This decreases the potential for Phase I aromatic hydroxylation (potentially followed by Phase II sulfation, glucuronidation, and *O*-methylation catalyzed by POMT).



Analog C

There are a number of other functional groups that can undergo metabolic transformation (e.g., oxidative *N*-dealkylation of the secondary or tertiary amines; benzylic oxidation of the carbon atoms attached to aromatic hydrocarbon); however, isosteric modification is not available. In these cases, other strategies can be employed (e.g., steric hindrance) to limit the potential for metabolic transformation at these sites.

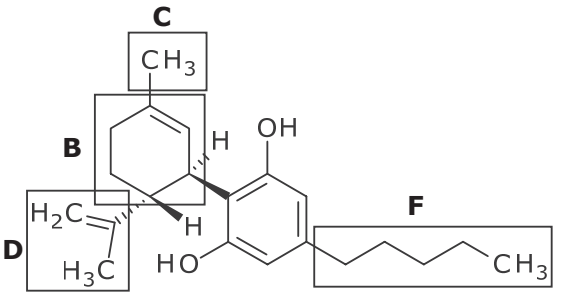
7. **Part A:** Each of the structural requirements has been boxed and labeled.



Tetrahydrocannabinol

D: not a requirement; not present
E: not a requirement; not present

Part B: This analog meets nearly all of the structural requirements to have cannabinoid activity. Unfortunately, it does not contain the benzopyran ring system and, therefore, is devoid of cannabinoid activity. Based on what we learned in Chapter 7, the benzopyran ring system likely provides much needed conformational restriction to allow for the correct spatial orientation of the rest of the functional groups. This conformational restriction permits the functional groups to optimally interact with the cannabinoid receptor.



Tetrahydrocannabinol analog

A: Required; not present
E: Not required; not present

CHAPTER 10

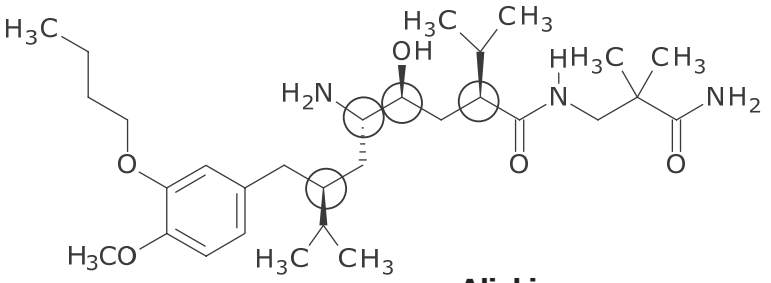
Aliskiren

1. Functional group names and other information provided below.

	Name of Functional Group	**Character** Hydrophilic and/or Hydrophobic	**Character** Acidic, Basic, or Neutral Provide pK_a When Relevant	**Function** Contribute to Aqueous Solubility and/or Contribute to Absorption.	**Function** Interaction(s) Possible with Biological Target at Physiological pH=7.4	**Function** Amino Acids That Can Interact with the Functional Group via Ion–Dipole Interactions at pH=7.4. *None* Is Acceptable.
A	Ether	Hydrophilic (O) Hydrophobic (R)	Neutral	Solubility (O) Absorption (R)	H-bonding (A) Dipole–dipole Ion–dipole (as the dipole)	Lys, Arg
B	Aromatic hydrocarbon	Hydrophobic	Neutral	Absorption	Hydrophobic van der Waals π-π stacking Cation-π	None
C	Aliphatic alkane	Hydrophobic	Neutral	Absorption	Hydrophobic van der Waals	None
D	Primary amine	Hydrophilic (NH_2) Hydrophobic (R)	Basic pK_a ~9–11	Solubility (NH_2) Absorption (R)	Ion–dipole (as the ion) Ionic	Ser, Thr, Cys, Tyr, Asn, Gln, His, Trp
E	Secondary alcohol	Hydrophilic (OH) Hydrophobic (R)	Neutral	Solubility (OH) Absorption (R)	H-bonding (A + D) Dipole–dipole Ion–dipole (as the dipole)	Asp, Glu, Lys, Arg
F	Amide	Hydrophilic ($CONH_2$) Hydrophobic (R)	Neutral	Solubility ($CONH_2$) Absorption (R)	H-bonding (A) Dipole–dipole Ion–dipole (as the dipole)	Asp, Glu, Lys, Arg

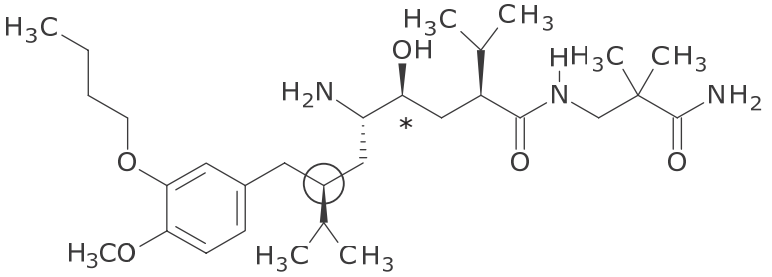
R = carbon scaffolding.

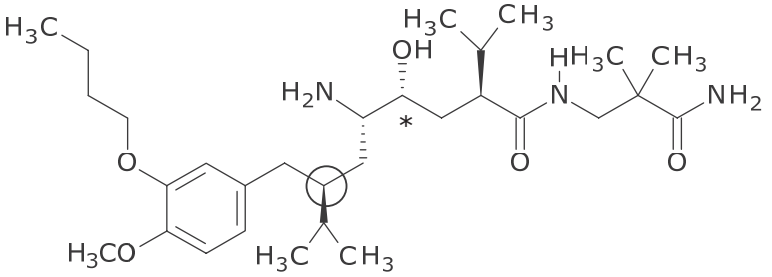
2. Chiral carbon atoms have been circled.



Aliskiren

If there are two or more chiral carbon atoms, then it is possible for the drug to have diastereomeric forms. In the case of aliskiren, there are four chiral carbon atoms; therefore, there are a lot of potential diastereomeric forms. ***A quick reminder on how to determine if a pair of isomers is diastereomeric***—if one chiral carbon is held constant (e.g., *R*-isomer) and you vary at least one additional chiral carbon, then the pair of isomers will be diastereomeric to one another. In the example below, the chiral center that is circled is held constant and the (*) chiral center is varied. The pair of isomers drawn are diastereomers.





For geometric isomers to be possible there must be restricted rotation around a carbon–carbon bond (e.g., presence of a double bond or alicyclic ring). Evaluation of aliskiren reveals the absence of double bonds and alicyclic rings; therefore, geometric isomers cannot exist.

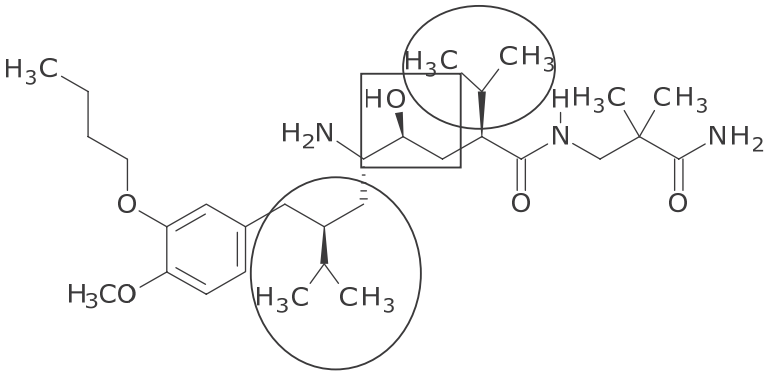
3. Oral bioavailability is dependent on the drug's ability to dissolve in the aqueous contents of the gastrointestinal (GI) tract and its ability to cross the lipid bilayer membrane. The hydrophilic character of the drug promotes aqueous solubility. Evaluation of the entire molecule (not just the boxed functional groups) for hydrophilic character reveals two ethers, two amides, a primary amine (in its ionized form), and a secondary alcohol that will contribute meaningfully to the hydrophilic character of the drug. (***NOTE:*** the drug is sold as a hemifumarate salt that further increases the overall water solubility of the drug). The hydrophobic character of the drug promotes absorption across the lipid bilayer. Evaluation of the entire molecule (not just the boxed functional groups) for hydrophobic character reveals an aromatic hydrocarbon, a lipophilic ether, and several aliphatic alkanes. The drug is formulated as a water-soluble salt and has ample hydrophilic character. Unfortunately, it does not have sufficient hydrophobic character to allow for meaningful absorption.

4. Metabolic transformations and identification of oxidative or non-oxidative provided below.

	Name of Metabolic Transformation	**Oxidative or Non-oxidative**
A	Oxidative *O*-dealkylation	Oxidative
B	Alcohol oxidation	Oxidative
C	Oxidative deamination	Oxidative
D	Oxidative *O*-dealkylation*	Oxidative
E	Amide hydrolysis*	Non-oxidative

*This metabolite has been identified as one of the two primary metabolites produced.

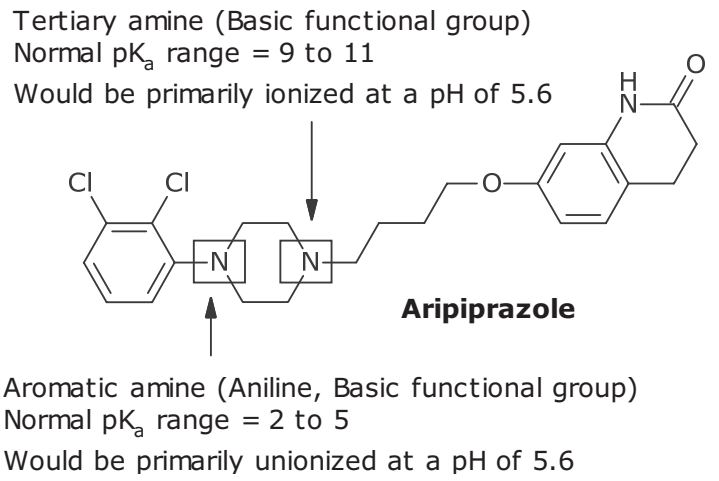
5. Functional groups mimicking Leu and Val are circled. The non-hydrolyzable hydroxyethylene group is boxed.



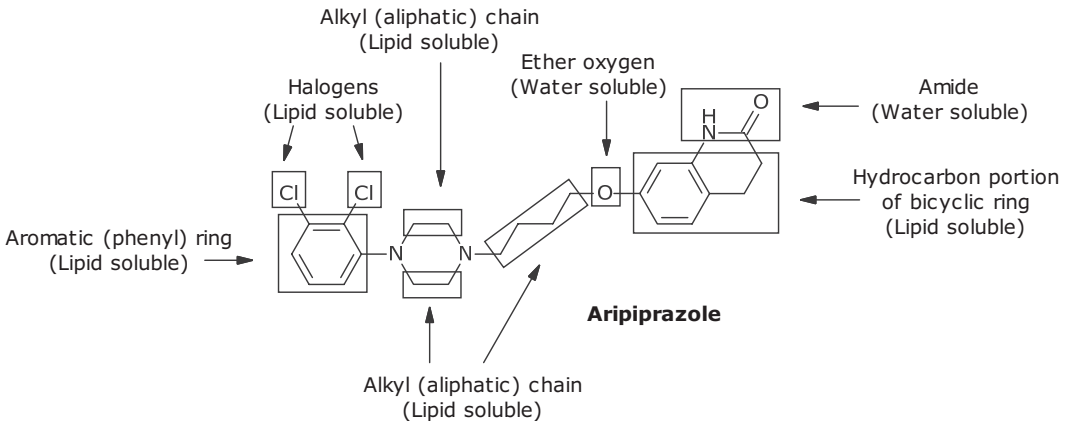
6. It is important to first determine whether these drugs are basic, acidic, or amphoteric in nature. Based on a structural evaluation of the entire aliskiren molecule (not just the boxed functional groups), there is one basic functional group (primary amine) and no acidic functional groups present. The same evaluation for amlodipine yields identification of two basic functional groups (primary amine and dihydropyridine ring) and no acidic functional groups. Based on this evaluation, both drugs are basic, and both would be bound to α_1-acid glycoprotein (plasma protein). It is important to remember that plasma protein binding interactions are likely to happen when a drug is >90% plasma protein bound. Given the extent to which amlodipine is plasma protein bound, it is highly likely that a plasma protein binding interaction will occur when aliskiren displaces amlodipine from the glycoprotein binding site. When this type of interaction occurs, there will be a greater fraction of amlodipine present in its unbound form. This leads to an increase in pharmacological activity resulting in hypotension (excessively low blood pressure).

Aripiprazole

1. Acidic and basic function groups are identified along with ranges and ionization state at pH = 5.6.



2. All other functional groups are identified along with their water or lipid nature.



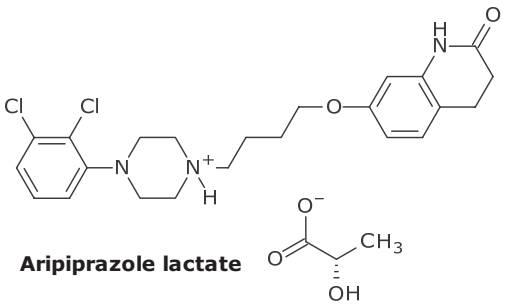
3. The tertiary amine, aromatic amine, amide, and ether oxygen atom provide adequate water solubility that allows aripiprazole to dissolve in the aqueous contents of the gastrointestinal (GI) tract. Once dissolved, aripiprazole must pass through the GI mucosal membrane to enter the blood stream. The dichloro phenyl ring, the alkyl chain, and the hydrocarbon portion of the bicyclic ring will provide adequate lipid solubility to allow for absorption. The tertiary amine will be primarily ionized within the GI tract, whereas the aromatic amine will be primarily unionized once it leaves the stomach. Remember that ionization is an equilibrium process with some fraction of unionized molecules present at all times. According to Le Chatelier's principle, as soon as one unionized molecule passes through the

GI membrane, the equilibrium will reset to provide additional unionized molecules. This same principle also allows ionizable functional groups to penetrate the blood brain barrier and enter the central nervous system (CNS). The same functional groups that allowed aripiprazole to pass through the GI mucosal membrane will also provide sufficient lipid solubility to allow it to cross the blood brain barrier and reach its target receptors within the CNS.

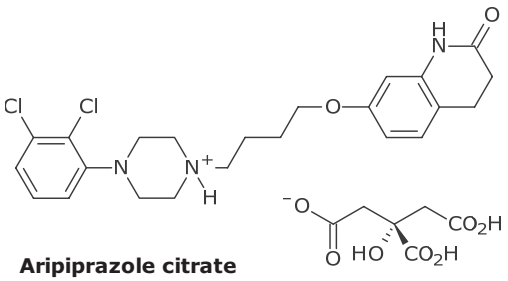
4. Aromatic amines are much less basic than primary, secondary, and tertiary aliphatic or alicyclic amines. The reason for this decreased basicity lies in the fact that an aromatic amine can donate its lone pair of electrons, through resonance, into the aromatic ring, thus making these electrons less available to bind with a proton. Within the structure of aripiprazole, the nitrogen atom of the aromatic amine is directly adjacent to *ortho* and *meta* chlorine atoms. Chlorine has a higher electronegativity than nitrogen and, through induction, each acts as an electron withdrawing group. This further decreases the availability of the lone pair of electrons on the nitrogen, resulting in a decrease in basicity. Thus, the pK_a for this particular aromatic amine would be expected to be at the lower end of this range (i.e., closer to 2).

5. The answer here is ***No***. Tolbutamide and losartan are acidic drug molecules, due to the presence of an acidic sulfonylurea and an ionizable tetrazole functional group, respectively. Aripiprazole is a basic drug molecule due to the presence of a tertiary amine and an aromatic amine. Acidic drug molecules primarily bind to albumin, whereas basic drug molecules primarily bind to α_1-glycoprotein. Plasma protein binding interactions (also known as plasma protein displacement interactions) occur due to the nonspecific nature of the plasma proteins that bind and transport drug molecules. These types of interactions are only therapeutically important when the drug molecules are highly plasma protein bound (i.e., over 90%). Although this is true of all three drugs, the difference in their acid/base nature significantly decreases the probability of a drug interaction due to plasma protein displacement.

6. Shown below are two examples of water-soluble organic salts using lactic acid and citric acid. There are a number of other water-soluble organic acids that could be used (e.g., fumaric acid, malic acid, maleic acid, tartaric acid).

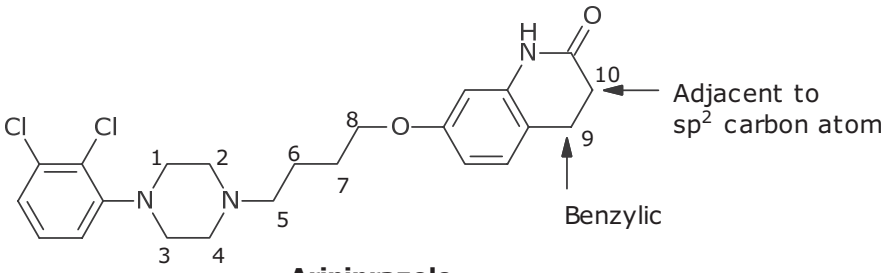


Aripiprazole lactate



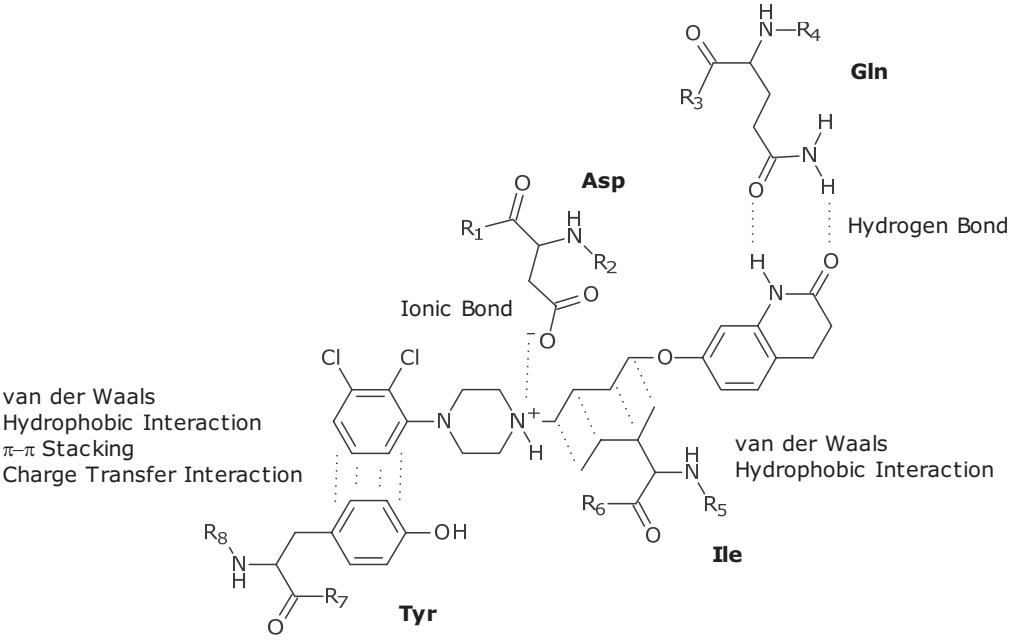
Aripiprazole citrate

7. There are only two methylene groups that would be expected to generate a chiral center via metabolism: the benzylic carbon atom and the carbon atom adjacent to the sp^2 carbonyl. Oxidation at either of these two positions will add a hydroxyl group and generate a chiral center. Oxidation of carbon atoms 1–5 will lead to oxidative *N*-dealkylation and the initial formation of an aldehyde. Similarly, oxidation of carbon atom 8 will lead to oxidative *O*-dealkylation and the initial formation of an aldehyde. Oxidation of methylene groups in the middle of an alkyl chain and adjacent to an sp^2 hybridized center generally does not occur.



Aripiprazole

8. One example is shown below. Other binding interactions are possible among these four functional groups and four amino acids. Isoleucine could form van der Waals and hydrophobic interactions with the halogenated aromatic ring, whereas tyrosine could form the same types of interactions with the alkyl chain. Aspartic acid could form an ion-dipole interaction (as the ion) with the amide, whereas glutamine could form an ion-dipole interaction (as the dipole) with the ionized tertiary amine. Please note that it is possible for tyrosine to form hydrogen bonds with the amide and an ion-dipole interaction (as the dipole) with the ionized tertiary amine. However, in the scenario given in this question, if tyrosine was used to form an interaction with either the amide or the ionized tertiary amine, neither aspartic acid or glutamine could be used to form van der Waals and hydrophobic interactions with the halogenated aromatic ring.

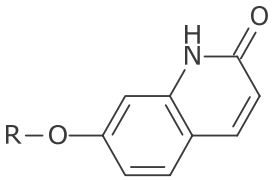


9. **Metabolite A:** Aromatic hydroxylation, Phase I

   Note: This is somewhat of an unexpected metabolite because the presence of halogen substituents on the aromatic ring generally deactivates these rings from oxidation. The difference in this particular drug molecule is the presence of an adjacent aromatic amine. This aromatic amine can donate electrons into the ring via resonance and either override or neutralize the electronic effects of the chloro groups, thus allowing for aromatic hydroxylation.

   Metabolite B: Benzylic oxidation, Phase I

   Note: Due to the ability to form a conjugated system, this secondary hydroxyl group readily undergoes dehydration to form the following metabolite.



Dehydration allows conjugation between the amide and the aromatic ring.

   Metabolite C: Oxidative *N*-dealkylation followed by oxidation of the resulting aldehyde to a carboxylic acid by aldehyde dehydrogenase, Phase I

Levonorgestrel

1. Answers provided below.

	Name of Functional Group	Character Hydrophobic, Hydrophilic, or Both	Function Contribute to Aqueous Solubility or Absorption
A	Ketone	Hydrophobic (R) Hydrophilic (C=O)	Absorption (R) Solubility (C=O)
B	Alkene	Hydrophobic	Absorption
C	Cycloalkane	Hydrophobic	Absorption
D	Alkyne	Hydrophobic	Absorption
E	Tertiary alcohol	Hydrophobic (R) Hydrophilic (OH)	Absorption (R) Solubility (OH)

R = carbon scaffolding.

2. Both the ketone and tertiary alcohol contain electronegative oxygen atoms, which inductively attract/withdraw electron density from the carbon atoms attached to them. This means that both the tertiary alcohol and ketone are electron withdrawing groups based on an inductive effect.

The tertiary alcohol is attached to aliphatic carbons and therefore cannot participate in any resonance effects. The ketone is part of an α, β unsaturated ketone and there is a limited amount of resonance contribution as an electron withdrawing group.

3. Levonorgestrel has several functional groups that are exclusively hydrophobic in character. This should promote absorption (lipid solubility) across the skin if the drug is formulated as a patch. Distribution into the plasma is facilitated by both the ketone and tertiary alcohol which are both hydrophilic in character and able to participate in H-bonding with water due to the electronegativity differences between the C and O atoms or O and H atoms (respectively). This hydrophilic character will contribute to aqueous solubility in the blood.

   Because levonorgestrel has functional groups that contribute to both the hydrophobic and hydrophilic character (as just described) of the drug, it is possible for it to be administered orally. Dissolution and solubility in the aqueous contents of the stomach, as well as distribution into the plasma are facilitated by those functional groups that contribute to the hydrophilic character of the drug. Absorption across the lipophilic GI membranes and then across target cell membranes is facilitated by those functional groups that contribute to the hydrophobic character of the drug.

4. In Chapter 3 we described a nonelectrolyte as a drug that does not dissociate into ions in solution (contains only neutral functional groups) and an electrolyte as a drug that does dissociate into ions in solution (contains one or more acidic or basic functional groups and/or a quaternary amine). Levonorgestrel is a nonelectrolyte. It does not contain any ionizable (acidic or basic) functional groups and is comprised only of neutral functional groups.

5. In Chapter 3 we discovered that human serum albumin (albumin) binds to a variety of endogenous substances and drugs. It is fairly nonspecific in its binding requirements, although prefers to interact with acidic molecules more so than basic molecules and prefers to interact with drugs that are hydrophobic in character more so than those that are hydrophilic in character. Levonorgestrel has no acidic or basic functional groups, but is comprised of functional groups that contribute a significant amount of hydrophobic character. Because of this hydrophobic character, levonorgestrel is suitable for binding to albumin.

6. In Chapter 5 we learned that log P represents a ratio of the solubility of the unionized drug in an organic solvent to the solubility of the same unionized drug in an aqueous environment. The structural evaluation of levonorgestrel reveals that this drug is unable to be ionized, so we are really looking at the ratio of the solubility of the drug in an organic solvent to the solubility of the same drug in an aqueous environment.

Part A:

If we want the log P value to decrease, we would need to increase the amount of drug that is soluble in an aqueous environment (larger denominator in the ratio). This means that our structural modification should add hydrophilic character to the drug molecule. In Chapter 5 we learned that a water-soluble prodrug could be created (e.g., create a sodium phosphate salt or a sodium succinate salt). The prodrug will be metabolically cleaved to reveal the parent drug. Another solution is to modify the drug structure by adding one or more hydrophilic functional groups (e.g., alcohol, amine). *A word of caution with this last recommendation*—functional group addition must not interfere with the critical binding interactions between a drug and its biological target.

Part B:

If we modify the molecule to increase the hydrophilic character of the molecule, then we will have also increased the water solubility of the molecule.

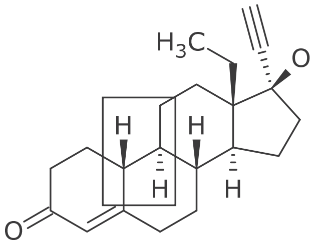
Part C:

Norgestimate has a log P = 4.11, which is larger than levonorgestrel. The numerator represents the solubility of the drug in an organic solvent. So, from a structural evaluation perspective, why is norgestimate more lipid soluble than levonorgestrel? As you can see, the tertiary alcohol has been converted into a lipid-soluble ester prodrug. This modification enhances the lipid solubility of the drug and contributes to the increase in log P value. In addition, the ketone has been converted into an oxime, which can be metabolically converted into the parent ketone. The oxime is actually more water soluble than the parent ketone, so this modification is not what is enhancing the lipid solubility and causing an increase in the log P value.

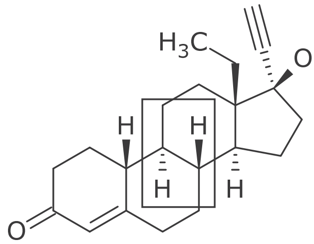
7. Both ethinyl estradiol and levonorgestrel contain a hydrophobic steroid scaffold (infrastructure) on which several substituents are positioned. The hydrophobic steroid skeleton resides in the hydrophobic cavity found as part of both the estrogen and progesterone receptors. Additional structural evaluation reveals that levonorgestrel contains a ketone (H-bond acceptor) and a tertiary alcohol (H-bond acceptor and donor) on opposite ends of the steroid skeleton. Ethinyl estradiol has a phenol (H-bond acceptor and donor) and a tertiary alcohol (H-bond acceptor and donor) on opposite ends of that steroid skeleton. Given that the estrogen receptor requires that receptor agonists interact with both the hydrophobic cavity, as well as via two critical H-bonding interactions, it is no surprise that levonorgestrel will have some agonist activity at the estrogen receptor.

8. **Part A:** As you learned in Chapter 7, the *trans* designation refers to substituents being located on opposite sides of a double bond or ring system in geometric isomers.

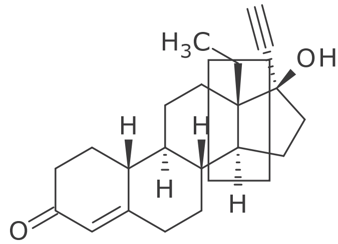
   Part B: In levonorgestrel there are several places where the *trans* designation is relevant. Each of the following shows a unique *trans* relationship within levonorgestrel.



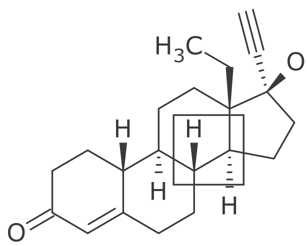
Levonorgestrel



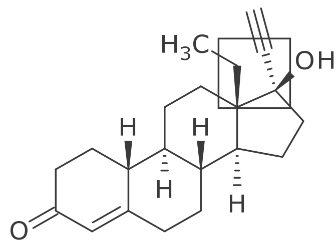
Levonorgestrel



Levonorgestrel

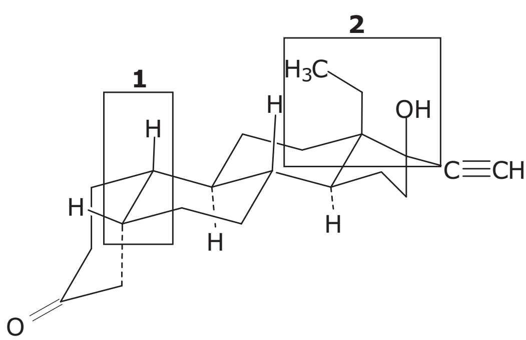


Levonorgestrel



Levonorgestrel
(*trans*: ethyl and ethynyl groups)

Parts C and D: When functional groups are *cis* to one another, they are found on the same side of a double bond or ring system. In the case of the levonorgestrel analog that has a mixture of *cis/trans* relationships, there are several *cis* relationships, two of which are boxed. Only one of these, box #1, has an effect on the overall shape of the steroid skeleton. As you can see from the picture below, the steroid is no longer flat as a result of the *cis* ring junction found in box #1. This would make interaction with the progesterone receptor's hydrophobic cavity less than optimal. Not only is the steroid skeleton a different shape, but the ketone is now located in a different place in space and is unlikely able to interact via H-bonding with the estrogen receptor. For both types of receptors, this *cis* configuration places a hydrophilic functional group (ketone) in the space that should be occupied only with hydrophobic functional groups. (*Note:* The structure activity relationships (SARs) for the progesterone receptor require the presence of the double bond in the A ring, so this analog does not bind to and activate the progesterone receptor.)



***cis/trans* Mixture**

9. **Part A:**

   As we learned in Chapter 8, a drug that is subject to first-pass metabolism is metabolized by the liver prior to reaching systemic circulation. This decreases the amount of drug that is bioavailable. Drugs that are lipid soluble are typically subject to first-pass metabolism.

   Part B:

   As we identified earlier in this evaluation, levonorgestrel contains a significant amount of hydrophobic character. You might have expected that it was sufficiently hydrophobic to undergo first-pass metabolism.

   Part C:

   Possible Phase I transformations: allylic oxidation; epoxidation/peroxidation; reduction

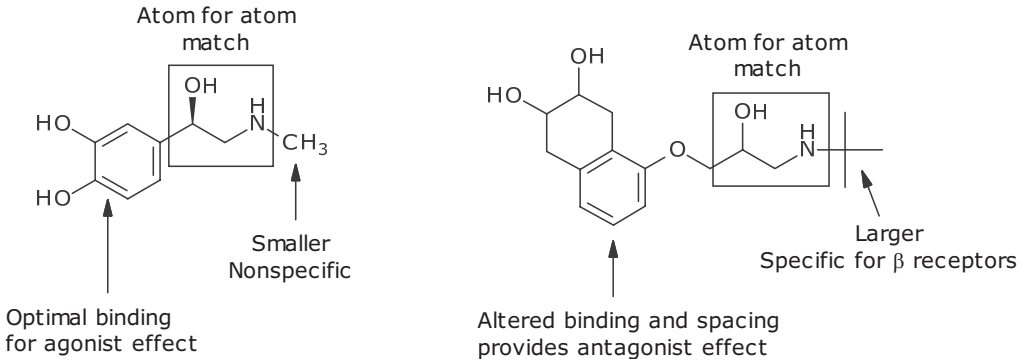
   Possible Phase II transformations: glucuronidation; sulfation (minor)

Nadolol and Other β-Adrenergic Antagonists

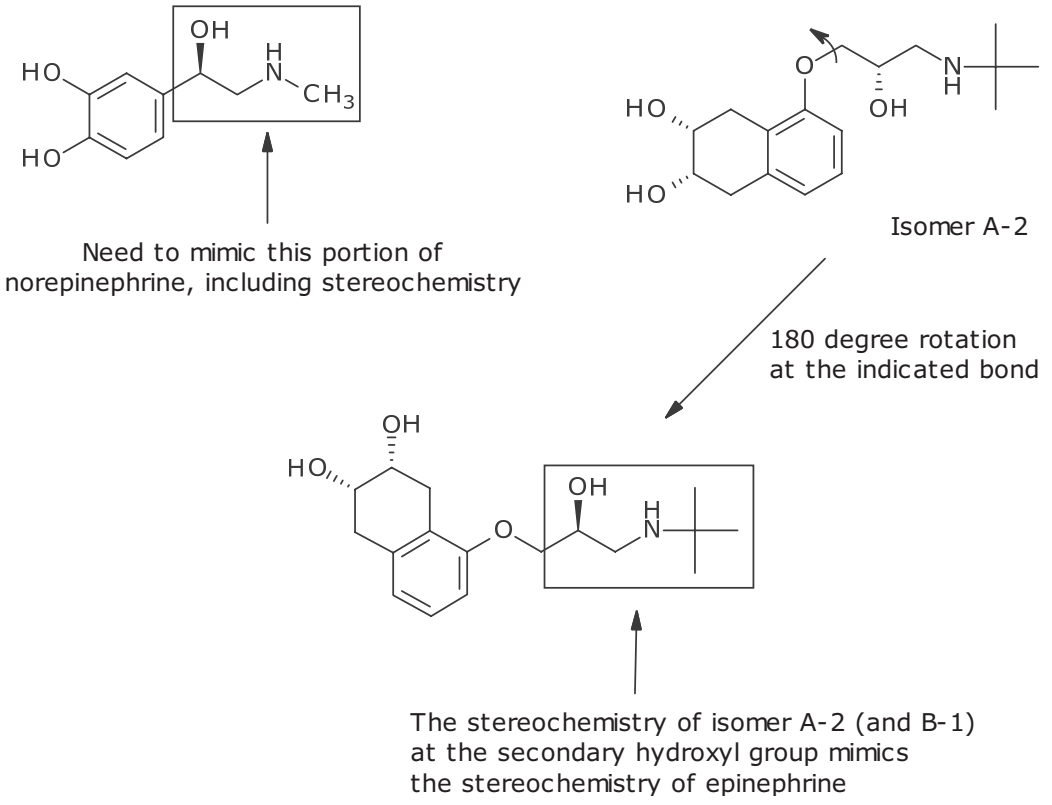
1. Functional group names and hydrophilic or hydrophobic character provided below.

Functional Group Name		Hydrophilic or Hydrophobic
A	Secondary hydroxyl (secondary alcohol)	**Hydrophilic** due to its ability to form hydrogen bonds with water as either a donor or an acceptor.
B	Ether oxygen	**Hydrophilic** due to its ability to form hydrogen bonds with water as an acceptor.
C	Alkyl group; alkyl chain; aliphatic chain	**Hydrophobic** due to its inability to ionize or form hydrogen bonds with water; hydrocarbon functional groups enhance lipid solubility.
D	Secondary amine	**Hydrophilic** due to its ability to ionize and form ion dipole-interactions with water and to participate in hydrogen bonds with water as either a donor or an acceptor in its unionized form.
E	Alkyl group; *t*-butyl group	**Hydrophobic** due to its inability to ionize or form hydrogen bonds with water; hydrocarbon functional groups enhance lipid solubility.
F	Aromatic ring; phenyl ring	**Hydrophobic** due to its inability to ionize or form hydrogen bonds with water; hydrocarbon functional groups enhance lipid solubility.

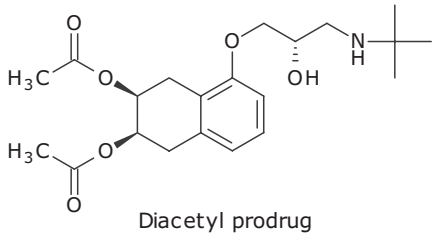
2. Epinephrine is a naturally occurring hormone that acts as an agonist on both α and β adrenergic receptors. The secondary amine, the secondary hydroxyl group, and the phenolic hydroxyl groups present within the structure of epinephrine provide key binding interactions with both the α and β adrenergic receptors. As discussed in Chapter 9, replacement of the *N*-methyl group of epinephrine with a larger alkyl group, such as the *t*-butyl group on nadolol provides selectivity for β adrenergic receptors due to a steric effect. The secondary amine, methylene, and secondary hydroxyl group of nadolol provides an atom-for-atom mimic of epinephrine. The major difference in these two structures lies in the spacing between the basic nitrogen atom and the aromatic ring systems, as well as the positioning/orientation of the phenolic or alicyclic hydroxyl groups. The orientation seen in epinephrine produces an agonist effect when it binds to the β adrenergic receptor, while the larger bicyclic ring system produces an antagonist effect.



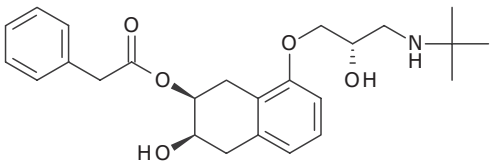
3. Epinephrine is a naturally occurring endogenous agonist at the β adrenergic receptors. The structure of epinephrine contains one chiral center with an *R* configuration that maximizes the binding interactions of the secondary hydroxyl group with the adrenergic receptors. In examining the four stereoisomers, the secondary hydroxyl groups in isomers A-2 and B-1 have the same stereochemistry as that seen in epinephrine and would be expected to exhibit better binding and pharmacological activity than those that had the opposite stereochemistry. This is illustrated below.



4. The use of salts and esters are two common chemical strategies used to enhance the oral absorption of a drug. Inorganic salts and water-soluble organic salts are commonly used to enhance the dissolution of a drug, while lipid-soluble esters are commonly used as prodrugs to enhance the lipid solubility of drugs. Based on its low log P value, it appears that nadolol has sufficient water solubility, but lacks sufficient lipid solubility to traverse the GI membranes. Thus, the use of lipid-soluble esters could be used to obtain a better water/lipid solubility balance. The alicyclic hydroxyl groups are a little less sterically hindered than the secondary hydroxyl group in the alkyl chain and could be esterified. Two examples of lipid-soluble esters of isomer B-1 are shown below.

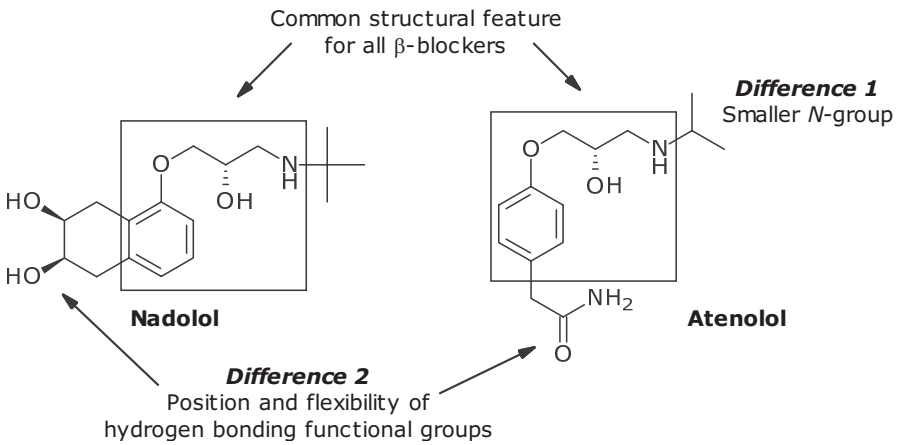


Diacetyl prodrug
of **nadolol**



Phenylacetyl prodrug
of **nadolol**

5. Both nadolol and atenolol share a key structural backbone that is found in all β-blockers. This backbone has been boxed in the structures below. The two structural differences are the *N*-alkyl groups and the substitutions on the respective aromatic rings. It can thus be concluded that one or both of these differences is responsible for the β_1 adrenergic receptor selectivity. Although this question assumes no prior knowledge of β-blocker SAR, you should be able to ***postulate potential binding differences***. The isopropyl group of atenolol may optimize interactions with the β_1 receptor, while the larger and slightly more bulky *t*-butyl found within the structure of nadolol does not. Similarly, the location and availability of functional groups capable of hydrogen bonding interactions may optimize binding interactions with the β_1 receptor. Both nadolol and atenolol have functional groups capable of acting as both hydrogen bond donors and/or acceptors; however, the amide present within the structure of atenolol is *para* to the ether oxygen atom, while the alicyclic hydroxyl groups within the structure of nadolol are oriented in a different direction. Additionally, the amide functional group is located on a flexible alkyl chain, while the alicyclic hydroxyl groups have a more ridged conformation. The combination of these structural differences and binding interactions may contribute to atenolol's selectively in blocking the β_1 adrenergic receptor.



6. Binding interactions and corresponding amino acids provided below.

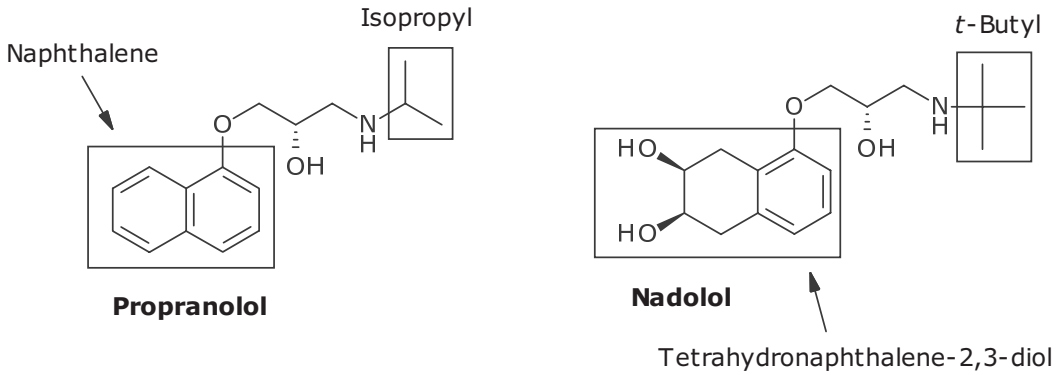
	Functional Group	Types of Binding Interactions	Amino Acids Capable of Forming Specific Binding Interactions*
A	Amide	Ion-Dipole (as the Dipole)	Asp, Glu (with carbon atom or hydrogen atoms); Arg, Lys, His** (with oxygen or nitrogen atoms) of the amide
		Dipole-Dipole	Ser, Thr, Tyr, Cys, Asn, Gln, His**
		Hydrogen Bond (Donor and/or Acceptor)	Ser, Thr, Tyr, Cys, Met, Asn, Gln, Trp, His**
B	Phenyl ring; aromatic ring; aromatic hydrocarbon	van der Waals; Hydrophobic	Tyr, Phe, Trp (better interaction***); Val, Leu, Ile, Met, Ala
		π-π Stacking	Tyr, Phe, Trp, His
		Cation-π Interaction	Arg, Lys, His (less likely*)
C	Secondary hydroxyl	Ion-Dipole (as the Dipole)	Asp, Glu (with hydrogen of hydroxyl); Arg, Lys, His** (with oxygen of hydroxyl)
		Dipole-Dipole	Ser, Thr, Tyr, Cys, Asn, Gln, His**
		Hydrogen Bond (Donor and/or Acceptor)	Ser, Thr, Tyr, Cys, Met, Asn, Gln, Trp, His*
D	Secondary amine	Ionic	Asp, Glu
		Ion-Dipole (as the Ion)	Ser, Thr, Tyr, Cys, Asn, Gln
E	Alkyl group; aliphatic hydrocarbon	van der Waals; Hydrophobic	Val, Leu, Ile, Ala (better interaction***); Tyr, Phe, Trp

*At a pH of 7.4, the side chains of Glu, Asp, Lys, and Arg will be primarily ionized; therefore, they can only participate in ionic bonds and ion-dipole interactions (as the ion).

**The side chain of histidine is primarily unionized at a pH = 7.4. The small fraction that is ionized could form an ion-dipole interaction with a partially negatively charged atom, while the unionized fraction can serve as a hydrogen bond donor or acceptor. Additionally, in its unionized form it can serve as the dipole in an ion-dipole interaction.

***Stronger van der Waals interactions occur when alkyl chains interact with alkyl chains; however, all of the listed amino acids could possibly interact with the indicated functional group.

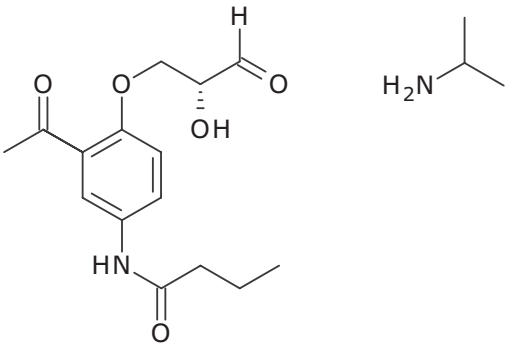
7. In comparing the structures of propranolol and nadolol, there are two sites of structural variation. The *t*-butyl group within the structure of nadolol is slightly larger and more lipid soluble than the isopropyl group within the structure of propranolol; however, the major difference lies in the ring systems. The structure of propranolol contains a lipid-soluble, bicyclic naphthalene ring, while the structure of nadolol contains a more water-soluble bicyclic ring. The two alicyclic hydroxyl groups within the structure of nadolol can form hydrogen bonds with water, an interaction not possible with propranolol. Thus, propranolol is expected to be more lipid soluble than nadolol. A comparison of their respective log P values verifies this expectation. The log P value for nadolol is 1.3 (given in Question 4), and the log P value for propranolol is 3.1. Since lipid-soluble drugs are more likely to undergo extensive first-pass metabolism than water-soluble analogs, it can be concluded that propranolol is extensively metabolized while nadolol is excreted unchanged. Additionally, because propranolol is more lipid soluble than nadolol, it can better penetrate the blood brain barrier and provide beneficial effects in the treatment of migraine headaches and anxiety.



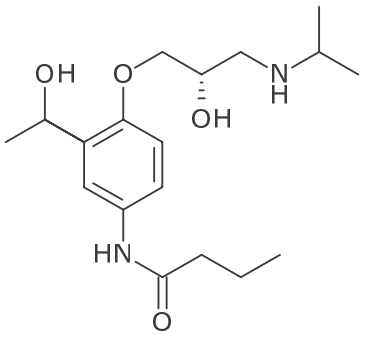
8. **Part A:** Hydrolysis of the amide followed by acetylation of the resulting aromatic amine.

Part B:

Pathway A: Oxidative deamination is a Phase I transformation. ***YES***. Although direct oxidative deamination is possible for secondary amines, oxidative *N*-dealkylation to a primary amine normally occurs prior to oxidative deamination.

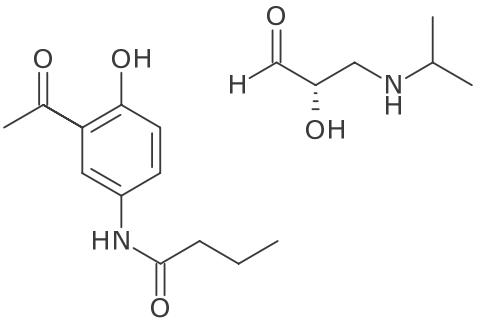


Pathway B: Reduction: Phase I, ***YES***

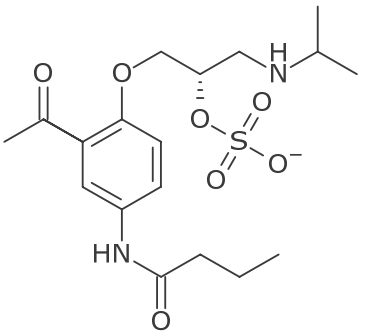


Pathway C: Benzylic oxidation is a Phase I transformation. ***NO***, it is not possible for acebutolol because the only benzylic carbon atom is a ketone and lacks a hydrogen atom.

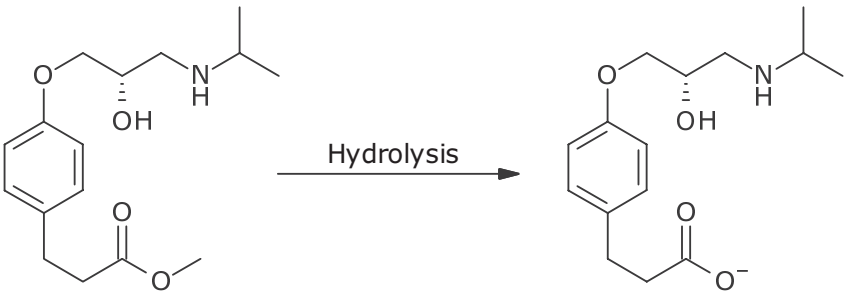
Pathway D: Oxidative *O*-dealkylation is a Phase I transformation. ***YES,*** it is possible; however, due to the location of the ether oxygen atom, it is sterically hindered and the probability of this metabolic transformation is low.



Pathway E: Sulfate conjugation: Phase II, ***YES***.



9. In comparing the structures of esmolol, acebutolol, and atenolol, it is found that the structure of esmolol contains an ester functional group, while the structures of acebutolol and atenolol contain amide functional groups. Esterase enzymes are readily available within the human body and can quickly hydrolyze ester functional groups. The hydrolysis of esmolol is shown below. The metabolite is inactive due to the fact that its binding interactions with the β_1 receptor have been significantly altered. An ionized carboxylic acid is unable to form the same binding interactions with the β_1 receptor as the original ester and is thus inactive.



Esmolol

Ofloxacin

1. Functional group names and other information provided below.

	Name of Functional Group	Hydrophobic and/or Hydrophilic	Contributes to Aqueous Solubility and/or Absorption
A	Tertiary amine + aniline/ aromatic amine (piperazine)	Hydrophobic (R) Hydrophilic (both N atoms)	Absorption (R) Solubility (both N atoms)
B	Halogen	Hydrophobic (R) Hydrophilic (F)	Absorption (R) Solubility (F)
C	Aniline	Hydrophobic (R) Hydrophilic (N)	Absorption (R) Solubility (N)
D	Ketone	Hydrophobic (R) Hydrophilic (C=O)	Absorption (R) Solubility (C=O)
E	Carboxylic acid	Hydrophobic (R) Hydrophilic (COOH)	Absorption (R) Solubility (COOH)
F	Alkene	Hydrophobic (R)	Absorption (R)
G	Ether	Hydrophobic (R) Hydrophilic (O)	Absorption (R) Solubility (O)

R = carbon scaffolding.

2. **Part A:** halogen; ether (inductive); ketone; carboxylic acid
   Part B: ketone (carbon atom)
   Part C: piperazine (tertiary amine + aniline/aromatic amine)
   Part D: ether (resonance), aniline (resonance)

3. Functional group names and other information provided below.

	Name of Functional Group	Acidic, Basic, or Neutral	pK_a Value/Range
A	Piperazine	Basic	pK_a 9–11 (methylated N atom) pK_a 2–5 (aniline/aromatic amine)
B	Halogen	Neutral	
C	Aniline	Basic	pK_a 2–5
D	Ketone	Neutral	
E	Carboxylic acid	Acidic	pK_a 2.5–5
F	Alkene	Neutral	
G	Ether	Neutral	

   Because ofloxaxin contains at least one acidic and one basic functional group, it is considered amphoteric.

4. Functional group ionization at different pH environments shown below.

Name of Functional Group	pH = 2 (stomach)	pH = 7.4 (plasma)	pH = 5 (urine)	pH = 8.5 (large intestine)
Piperazine (CH_3)	Ionized	Ionized	Ionized	Ionized
Piperazine* (Aniline/aromatic amine)	Ionized	Unionized	50%/50%	Unionized
Aniline	Ionized	Unionized	50%/50%	Unionized
Carboxylic acid	Unionized	Ionized	50%/50%	Ionized

*Note: Only one of the two nitrogen atoms in this piperazine ring will be ionized at a time. The more basic nitrogen atom, and the one that is more likely to be ionized, is the nitrogen atom with a methyl substituent.

Part A:

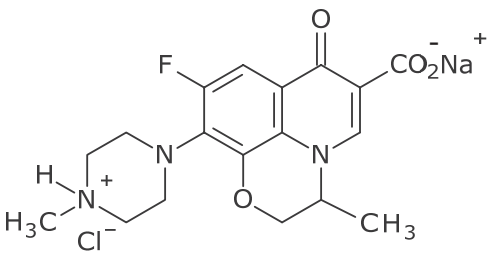
There are four possible atoms/functional groups that can be ionized in any given pH environment. In the urine (pH = 5), all four functional groups are either primarily ionized or are at least 50% ionized. This confers considerable hydrophilic character to the molecule [that already has a number of functional groups that are hydrophilic in character (halogen, ketone, ether) but are not ionizable], making it remarkably water soluble. As a result, elimination via the kidneys is expected, without the need for any Phase I or Phase II metabolism.

Part B:

Conducting a similar qualitative evaluation at pH = 6.5, we find that two of the four atoms/functional groups will be predominantly ionized at pH = 6.5. This will confer considerable water solubility to a molecule that already has a number of functional groups that are hydrophilic in character (halogen, ketone, ether) but are not ionizable. The considerable hydrophilic character makes the molecule suitable for delivery as an aqueous solution.

Piperazine (CH_3)	Primarily ionized
Piperazine (aniline/aromatic amine)	Primarily unionized
Aniline	Primarily unionized
Carboxylic acid	Primarily ionized

5. **Part A:** Ofloxacin can be formulated as both a hydrochloride and as a sodium salt. Both types of inorganic salts will enhance the water solubility of the drug.



Part B: Ofloxacin could be modified to form a lipid-soluble salt (e.g., benzathine or stearate salts). It could also be modified to form a lipid-soluble ester prodrug.

6. **Part A:**

   The top half of ofloxacin has a fluorine atom, a ketone, and a carboxylic acid. At physiological pH these functional groups will participate in H-bonding interactions (H-bond acceptor) via the fluorine and ketone functional groups and ion-dipole interactions (as the ion) with the carboxylic acid functional group (in its ionized form).

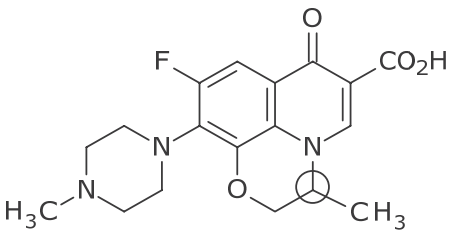
   Part B:

   The bottom half of ofloxacin includes a piperazine, an ether, an aniline and some hydrocarbon scaffolding. At physiological pH these functional groups will participate in H-bonding interactions (H-bond acceptor) via the ether group, ion-dipole interactions (as the ion) via the piperazine group (in its ionized form), and through hydrophobic interactions with the hydrocarbon scaffolding present.

   Part C:

   The fluoroquinolones self-associate into two pairs at the biological target. Each pair of drugs are stacked together via π-π stacking interactions. One drug pair then interacts with the other drug pair via the interactions mentioned in part B.

7. **Part A:** Chiral center has been circled.



Ofloxacin

   Part B: Enantiomers are possible at the chiral center. Diastereomers are not possible, as there is only one chiral carbon. Geometric isomers are not possible, as there are no double bonds or ring junctions that can adopt an alternate conformation. Conformational isomers are possible primarily via the piperazine ring, as it can adopt either a boat or chair conformation.

   Part C: Given that the chiral center is located on the bottom side of the molecule, it is likely that the interactions associated with drug pair associations will be affected by a change in stereochemistry at this center. Interactions with the DNA target will not be affected by a change in the stereochemistry at this center. Drug-drug pairing will also be unaffected by a change in the stereochemistry at this center.

8. **Part A:** Ofloxacin is highly hydrophilic in character and has several functional groups that are predominantly ionized in every physiological compartment. As a result, it is considered very water soluble. First-pass metabolism typically occurs on molecules that are highly hydrophobic in character and, therefore, it is unlikely that ofloxacin would undergo first-pass metabolism. Given that ofloxacin has 98% oral bioavailability, this confirms that first-pass metabolism does not occur.

Part B:

Phase I transformations: oxidative *N*-dealkylation; *N*-oxidation; oxidative *O*-dealkylation; aromatic hydroxylation (*ortho* and *para*)

Phase II transformations: glucuronidation; amino acid conjugation

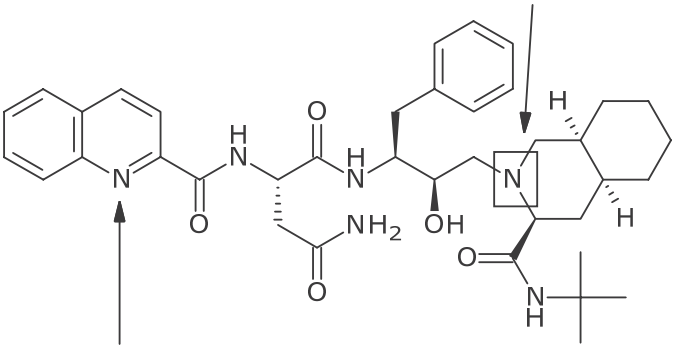
Part C:

Because ofloxacin is primarily excreted unchanged via a renal route and a small portion undergoes liver-based metabolic transformations, patients diagnosed with moderate-to-severe kidney and/or liver disease should not be given ofloxacin.

Saquinavir and Other HIV Protease Inhibitors

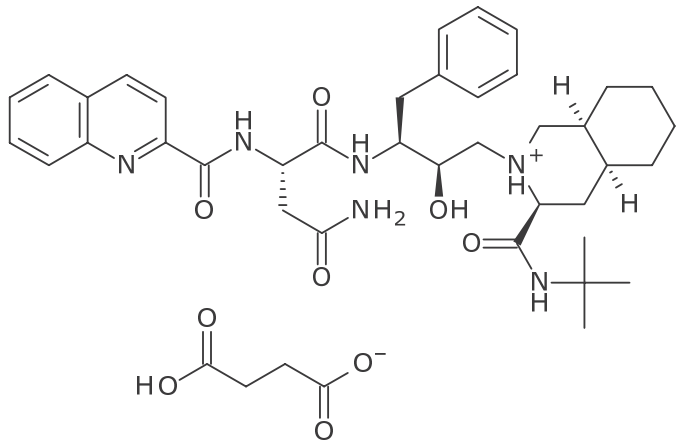
1. The most basic functional group has been identified along with pK_a range and other information.

Most Basic Functional Group
Tertiary Amine
Normal pK_a range: 9 to 11
Would be primarily ionized at a pH of 2.3

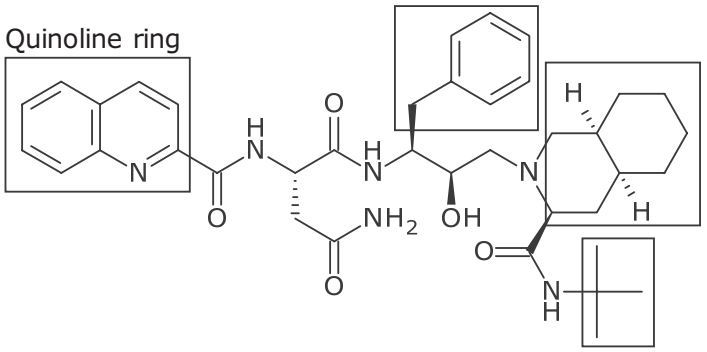


Only Other Ionizable Functional Group
Heterocyclic Amine (Basic functional group)
Normal pK_a range: 1 to 5
Primary form would depend on the specific pK_a
since a pH of 2.3 lies in the middle of this range

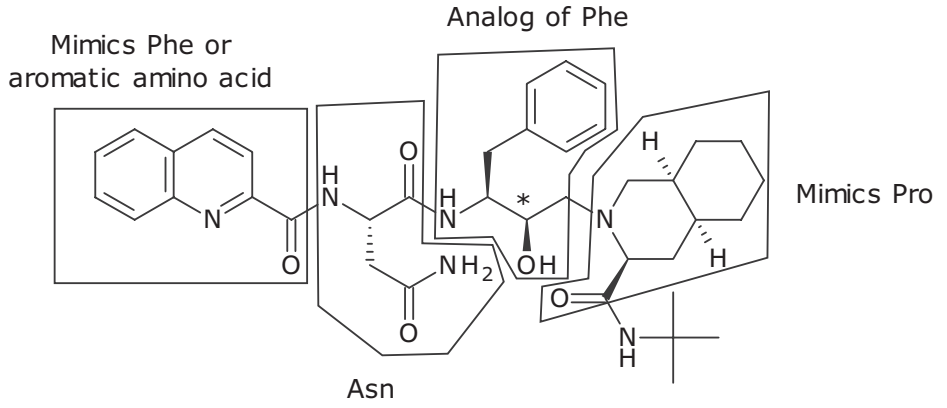
2. Water-soluble organic salts enhance the solvation, dissolution, and water solubility of drug molecules. Therapeutically, this can contribute to enhanced oral absorption as well as the preparation of concentration intravenous, ophthalmic, and otic solutions. Shown below is a succinate salt of saquinavir.



3. The ability of a drug molecule to be orally absorbed from the GI tract into the systemic circulation requires a balance between water- and lipid-soluble functional groups. The water-soluble functional groups allow the drug to dissolve in the GI tract, and the lipid-soluble functional groups allow the drug to pass through the GI membrane and enter the systemic circulation. The lipid-soluble functional groups within the structure of saquinavir have been boxed below. Please note that while the nitrogen atom of the quinoline ring can participate in hydrogen bonds, this aromatic ring system (as a whole) enhances lipid solubility.

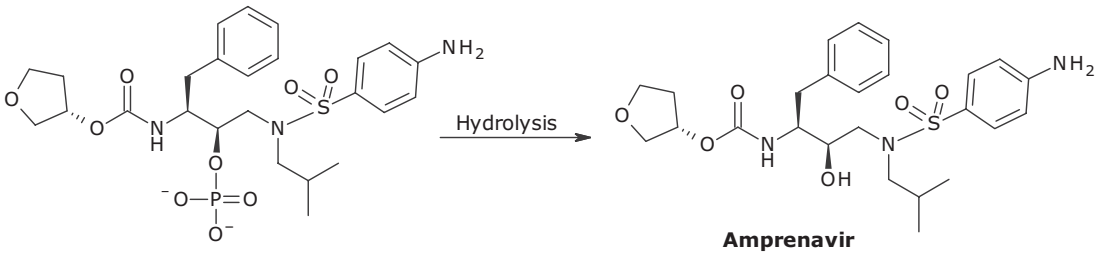


4. Saquinavir is able to inhibit HIV protease by acting as a stable mimic of the substrate of the above reaction. The structure of saquinavir is largely peptidic in nature as shown below. It contains three amide (i.e., peptide) bonds and functional groups that either match or mimic the side chains of amino acids normally found in the substrates for HIV protease. The labile peptide bond between the phenylalanine and the proline residues has been replaced with a stable hydroxyethyl group. The tetrahedral carbon atom (indicated with the asterisk) that is attached to the secondary hydroxyl group provides a stable mimic of the peptide bond hydrolysis intermediate. Due to these structural characteristics, saquinavir is considered to be a peptidomimetic and is able to bind to the active site of HIV. Since the labile bond has been replaced with a stable mimic, HIV protease is not able to cleave the bond and is thus inhibited by the binding of saquinavir.



5. As discussed in the previous question, saquinavir acts as a stable mimic of the substrates for HIV protease. In order to serve as a stable mimic of a protein, the stereochemistry of the amino acids (or amino acid analogs) must match that of the naturally occurring amino acids. Chiral centers 1, 2, and 4 match the normal stereochemistry found in naturally occurring *L*-amino acids; therefore, changing the stereochemistry of any of these chiral centers would likely result in a decreased ability to effectively mimic a protein substrate. The stereochemistry of chiral center 3 is also essential as it provides a stable mimic of peptide bond hydrolysis. Chiral centers 5 and 6 are part of the bicyclic ring that mimics proline. This bicyclic ring is larger than proline, and the *cis* orientation of the hydrogen atoms more than likely optimizes the binding of this larger ring to a hydrophobic pocket in the enzyme binding site. While the stereochemistry of chiral centers 5 and 6 may not be as ***essential*** as those at chiral centers 1-4, the optimal binding of this bicyclic ring would have been tested and established in the development of saquinavir.

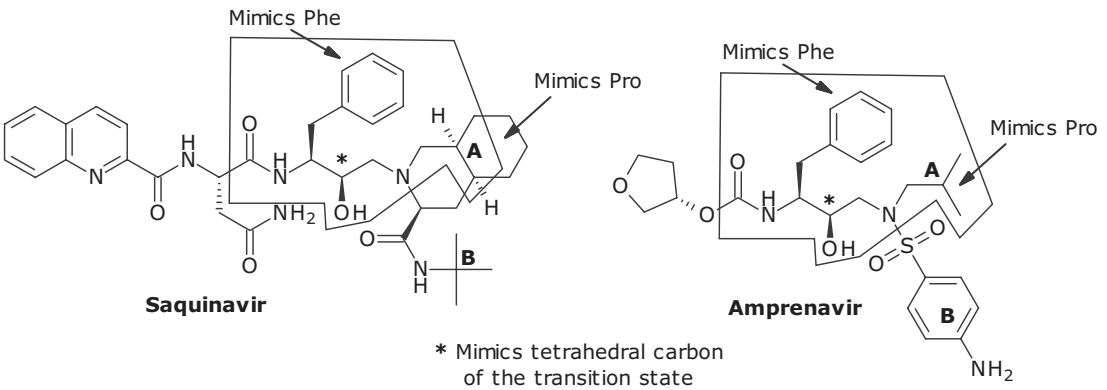
6. The information provided in the question provides multiple clues to the correct answers. Fosamprenavir is the prodrug, and amprenavir is the active metabolite. The only difference in these names is the "Fos" prefix. Examining the structure of fosamprenavir reveals the presence of a phosphate functional group. It can thus be concluded that the phosphate group of fosamprenavir is removed to produce the active drug amprenavir. The metabolic transformation that removes a phosphate group is a hydrolysis reaction.



Fosamprenavir **Amprenavir**

The phosphate functional group enhances the water solubility of amprenavir. Increasing the water solubility of a drug enhances its solvation and dissolution. This is required for oral absorption as well as the preparation of concentrated solutions. Given that fosamprenavir is administered orally, this prodrug is used to enhance the water solubility of amprenavir and to provide a better water-/lipid-solubility balance for oral absorption.

7. The first step in comparing the structural similarities of drug molecules is to ensure that all overlapping (or similar) functional groups are properly aligned. Because we have already examined the structure of saquinavir, we will use this as our prototype and leave it unaltered. In order to align the functional groups of amprenavir with those of saquinavir, all that needs to be done is to rotate about the sulfonamide nitrogen atom. This reveals an atom-for-atom match for a large portion of the structures of saquinavir and amprenavir (indicated by the polygons in the structures below). Both drugs have a mimic of Phe, a tetrahedral carbon atom that mimics the transition state of HIV protease, and a mimic of Pro. Additionally, the distance between carbon A in the bicyclic ring of saquinavir and the central *t*-butyl carbon B is exactly the same as that seen between carbon A of amprenavir's isobutyl chain and the center of its aromatic ring (B). This indicates that these two hydrophobic functional groups are located in similar positions and can provide similar binding interactions (i.e., van der Waals interactions) with hydrophobic binding pockets present within the structure of HIV protease. As a final note here, amprenavir was initially drawn in a manner in which all of the functional groups ***did not*** overlap with those of saquinavir. This was done intentionally. Drug structures that you will encounter may look or be drawn differently, depending on the source. A key skill to master is the ability to look at drug structures, identify the similarities, and if necessary, redraw the structures so that you can easily compare them.



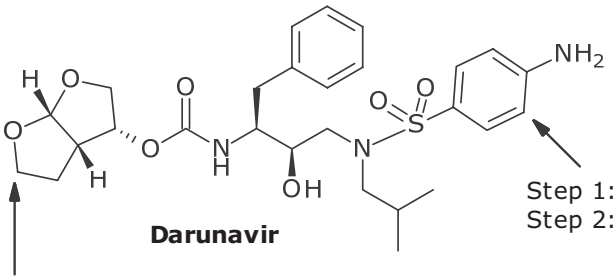
8. **Metabolic Path A:** *N*-Oxidation; this metabolic transformation is primarily catalyzed by FMO enzymes; however, it can be catalyzed by CYP3A4.

   Metabolic Path B: Hydrolysis; this metabolic transformation is catalyzed by hydrolase enzymes, not CYP3A4 isozymes.

   Metabolic Path C: Omega-1 oxidation (or oxidation of aliphatic carbon atoms); this metabolic transformation could be catalyzed by the CYP3A4 isozyme.

   Metabolic Path D: Oxidative *N*-dealkylation; this metabolic transformation could be catalyzed by the CYP3A4 isozyme.

9. There are two sites of metabolism. It does not matter which site is metabolized first; however, in both cases, step 1 must occur prior to step 2.



Darunavir

Step 1: Aromatic hydroxylation, ***phase I***
Step 2: Glucuronide conjugation, ***phase II***

Step 1: Oxidative *O*-dealkylation, ***phase I***
Step 2: Reduction of resulting aldehyde, ***phase I***

Sorafenib

1. Functional group names and other information provided below.

	Name of Functional Group	**Character** Hydrophilic and/or Hydrophobic	**Character** Acidic, Basic, or Neutral. Provide pK_a If Relevant.	**Function** Contributes to Aqueous Solubility and/or Absorption	**Function** Interaction(s) Possible with Biological Target at Physiological pH (7.4)
A	Halogenated aromatic hydrocarbon	Hydrophobic	Neutral	Absorption	Cl: Dipole-dipole Ion-dipole (as the dipole)
					Ar: van der Waals Hydrophobic π-π Stacking Cation-π interaction Charge transfer interaction

B	Halogenated aliphatic alkane	Hydrophilic (F)	Neutral	Solubility	H-bonding (A) Dipole–dipole Ion–dipole (as the dipole)
C	Urea	Hydrophilic (HNCONH) Hydrophobic (R)	Neutral	Solubility (HNCONH) Absorption (R)	H-bonding (A + D) Dipole–dipole Ion–dipole (as the dipole)
D	Ether	Hydrophilic (O) Hydrophobic (R)	Neutral	Solubility (O) Absorption (R)	H-bonding (A) Dipole–dipole Ion–dipole (as the dipole)
E	Pyridine (Azine)	Hydrophilic (N) Hydrophobic (R)	Basic (pK_a 1–5)	Solubility (N) Absorption (R)	Pyridine N atom: H-bonding (A) Dipole–dipole Ion–dipole (as the dipole)
					R: van der Waals Hydrophobic π-π Stacking Cation-π interactions Charge transfer interactions
F	Amide	Hydrophilic (CONH) Hydrophobic (R)	Neutral	Solubility (CONH) Absorption (R)	H-bonding (A+ D) Dipole–dipole Ion–dipole (as the dipole)

R = carbon scaffolding.

2. Functional group interactions provided below.

Functional Group	**Interacts with Cysteine[919] via a Hydrogen Bonding Interaction.** **Yes or No**	**Interacts with Aspartic Acid[1046] via a Hydrogen Bonding Interaction.** **Yes or No**	**Interacts with Phenylalanine[1047] via a Hydrophobic Interaction.** **Yes or No**
A	No	No	Yes
B	Yes	Yes	No
C	Yes	Yes	No
D	Yes	Yes	No
E	Yes	Yes	Yes
F	Yes	Yes	No

3. **Part A:** Possible types of binding interactions are listed below.

Leu[285]/Val[289]	**Asp[391]/Glu[286]**	**Thr[315]**	**Met[318]**	**Leu[298]/Val[299]/Phe[359]**
Hydrophobic	Ionic Ion–dipole (as the ion)	H-bonding Dipole–dipole Ion–dipole (as the dipole)	Hydrophobic Dipole–dipole H-bonding (A)	Hydrophobic van der Waals π-π Stacking Cation-π interactions

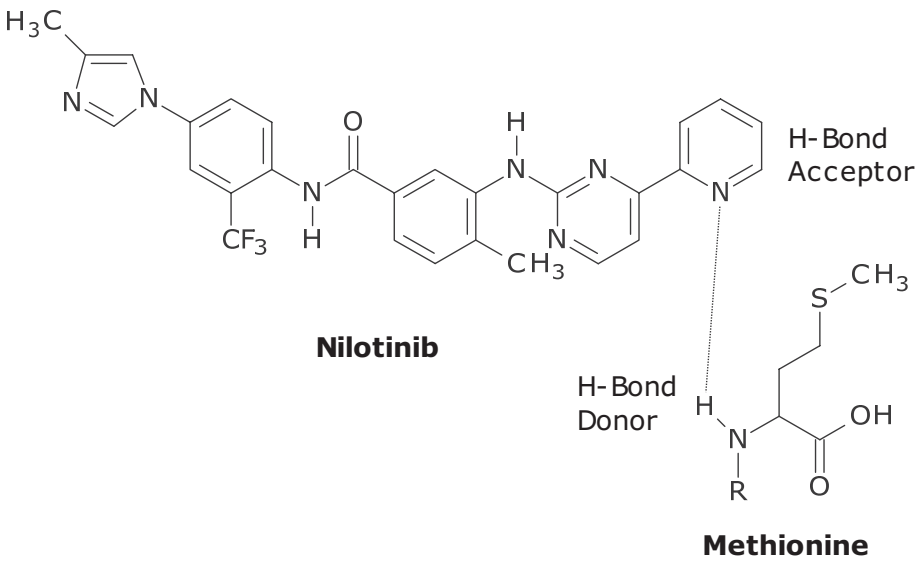
Part B: Possible types of binding interactions between amino acids and functional groups are provided below.

	Leu^{285}/Val^{289}	**Asp^{391}/Glu^{286}**	**Thr^{315}**	**Met^{318}**	**Leu^{298}/Val^{299}/Phe^{359}**
A	Hydrophobic	Ion–dipole (functional group as the dipole)	H-bonding (A) Dipole–dipole	Hydrophobic	Hydrophobic π-π Stacking
B	Hydrophobic van der Waals	None	H-bonding (A) Dipole–dipole	Hydrophobic	Hydrophobic van der Waals π-π Stacking Cation-π interactions
C	None	Ion–dipole (functional group as the dipole)	H-bonding (A+D) Dipole–dipole	H-bonding (Met is acceptor)	None
D*	None	Ion–dipole (functional group as the dipole)	H-bonding (A+D) Dipole–dipole	H-bonding (Met is acceptor)	None
E**	Hydrophobic	Ion–dipole (functional group as the dipole)	H-bonding (A) Dipole–dipole	None	Hydrophobic π-π Stacking Cation-π interactions

*Aniline-like nitrogen atom will not be ionized at physiological pH.

**Pyridine (azine) nitrogen atom will not be ionized at physiological pH.

Part C: Interaction between the pyridyl nitrogen atom and methionine is shown below.



4. The halogenated aromatic hydrocarbon, aromatic hydrocarbon, and the pyridine ring carbon atoms all contribute significantly to the hydrophobic character of sorafenib. It is important to note that the basic pyridine ring is unlikely to be ionized at physiological pH ($pK_a = 6 < pH = 7.4$). Although there appears to be significant hydrophilic character (halogenated aliphatic alkane, urea, ether, the nitrogen atom of the pyridine, amide) present in this molecule, sorafenib is practically insoluble in water. The lack of water solubility and clearly identifiable hydrophobic character allows for passive diffusion of the drug across the cellular lipid bilayer membrane.

5. Based on the information found in the structure evaluation grid for sorafenib, there are several functional groups that contribute to the overall hydrophobic character of the molecule (e.g., halogenated aromatic hydrocarbon, aromatic hydrocarbon, carbon atoms of pyridine/azine ring). Similar evaluation of nilotinib yields two aromatic rings, a pyrimidine ring (between functional groups D and E), a pyridine ring (functional group E), and even some hydrophobic character in the histidine ring (functional group A) that contribute to the overall hydrophobic character of the molecule. When you compare the sheer number of functional groups that contribute to the overall hydrophobic character for each drug, nilotinib wins!

6. The value of lipid-soluble organic salts is to decrease the water solubility and increase the lipid solubility of the parent drug (in this case sorafenib) (see Chapter 5). Typically lipid-soluble salts are used in the formation of lipid-soluble suspensions. In addition, they can improve the oral bioavailability of acid labile drug molecules and improve the palatability of liquid solutions. *p*-Toluenesulfonic acid (tosylic acid) is considered a strong organic acid and forms a strong counter-ion when dissociated from the drug molecule. Sorafenib is administered as a film-coated tablet for adults and as a liquid suspension for children.

   The value associated with the formation of inorganic salts is due to the improved aqueous solubility, solvation, and dissolution that results. In general, inorganic salts enhance the absorption of drugs that are administered orally because they improve both solvation and dissolution properties.

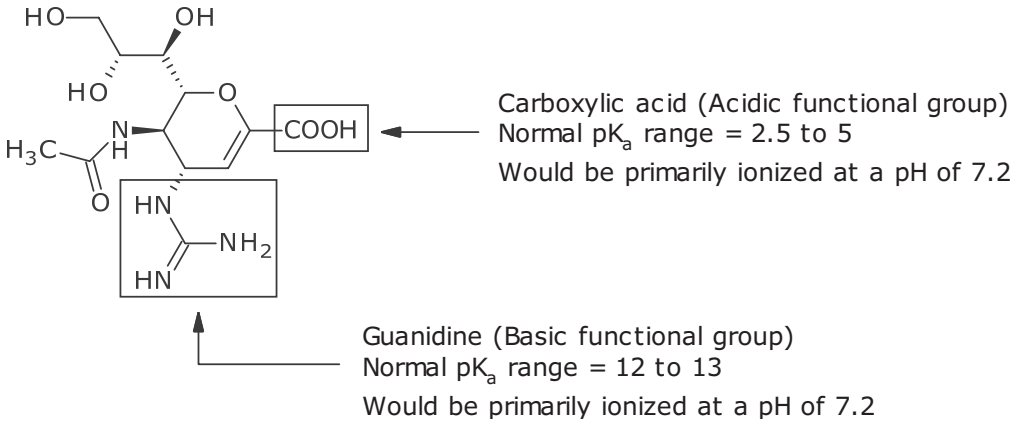
7. **Sorafenib:**
   Aromatic hydroxylation (*ortho*, *para*)
   N-oxidation
   Oxidative *N*-dealkylation (amide)

   Nilotinib:
   Aromatic hydroxylation (*ortho*, *para*)
   Benzylic oxidation
   N-oxidation

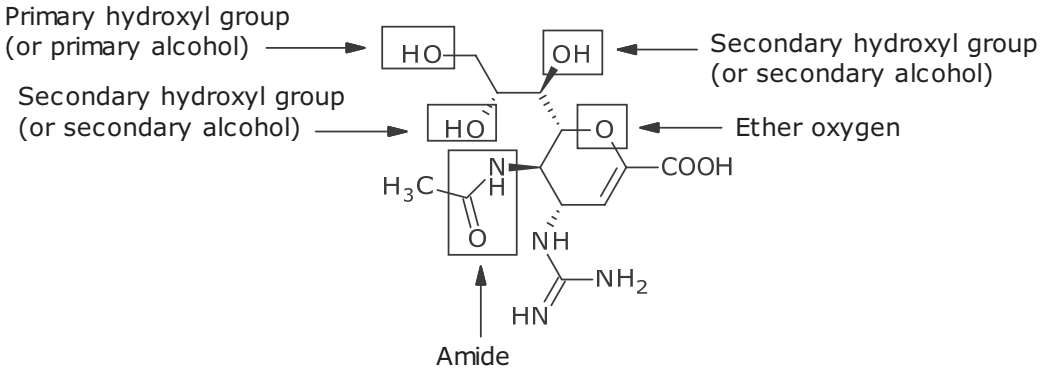
8. ***No***, when a drug molecule is bound to a serum protein, including serum albumin, it cannot undergo metabolic transformations, be eliminated from the body, or effectively interact with its biological target. Only the fraction of the drug "unbound" is eligible to exert its therapeutic effect and is subject to metabolic transformations. It should be noted that extensive protein binding can effectively increase the half-life of the drug.

Zanamivir and Oseltamivir

1. Acidic and basic function groups are identified along with ranges and ionization state at pH = 7.2.

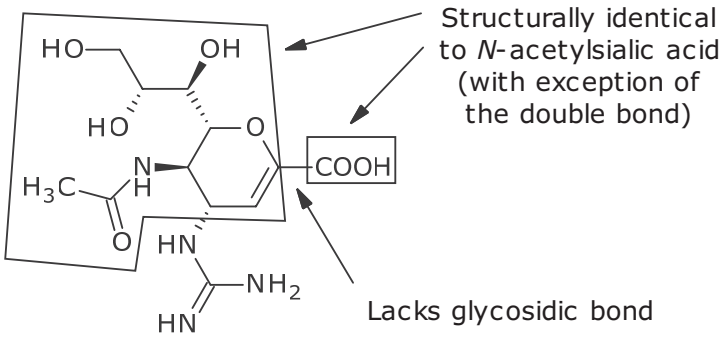


2. The amide and hydroxyl groups can act as hydrogen bond donors and acceptors and thus can form hydrogen bonds with water. The ether oxygen most likely contributes the least to water solubility; however, it can function as a hydrogen bond acceptor.



3. The structure of zanamivir contains multiple hydrophilic functional groups that will allow it to easily dissolve within the aqueous contents of the GI tract. The carboxylic acid and the guanidine functional groups will be extensively ionized at an intestinal pH = 5 which further increases the overall water solubility of the molecule. Although the structure of zanamivir contains a hydrocarbon chain and ring, the overall balance between water and lipid solubility hinders its ability to effectively cross the GI membrane. The oral absorption of zanamivir has been reported to be between 1% and 5%. Due to this, zanamivir must be administered via oral inhalation.

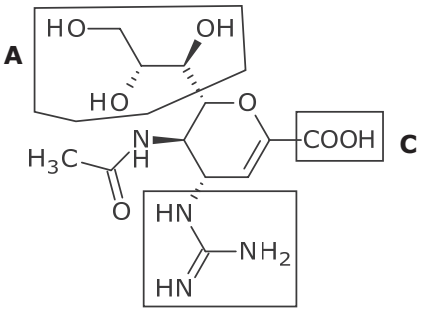
4. Zanamivir is a stable mimic of *N*-acetylsialic acid. As shown below, the structure of zanamivir retains many of the structural features of *N*-acetylsialic acid, but lacks a cleavable glycosidic bond.



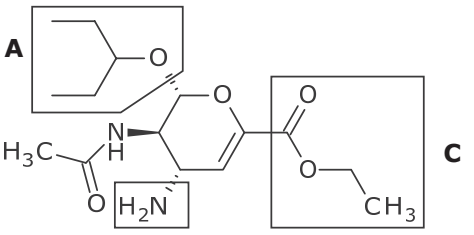
Zanamivir

The structural similarity allows zanamivir to interact with neuraminidase in the same manner as *N*-acetylsialic acid. Ionic or ion-dipole interactions with the carboxylic acid remain the same, as does the ability to form hydrogen bonds with the hydroxyl groups and the amide. Because zanamivir lacks a cleavable glycosidic bond, it can occupy the binding site without being metabolically transformed. The most significant difference between zanamivir and *N*-acetylsialic acid is the substitution of a secondary hydroxyl group with a guanidine group. Studies have shown that this basic functional group can form ionic interactions with neuraminidase. In summary, zanamivir structurally mimics the natural substrate for neuraminidase and is able to bind to the active site of the enzyme. This binding inhibits the ability of neuraminidase to cleave *N*-acetylsialic acid from viral glycoproteins, thus inhibiting the spread of a viral infection.

5. When comparing these two structures, there are three key structural differences. In all three instances, the functional group on oseltamivir is less water soluble (or more lipid soluble) than the analogous functional group on zanamivir.



Zanamivir **B**



B **Oseltamivir**

The glycerol side chain of zanamivir (**A**) is much more water soluble than the alkyl ether of oseltamivir (**A**). Although both drug molecules contain a basic functional group within their structure, the guanidine group in zanamivir (**B**) is more basic and will be more highly ionized than the primary amine (**B**) in oseltamivir. Finally, the ionizable carboxylic acid of zanamivir (**C**) has been esterified in oseltamivir (**C**). This ethyl ester is no longer acidic, cannot ionize, and therefore generates a more hydrophobic prodrug. Returning to Question #3, the key reason that zanamivir is not orally active is that it does not possess adequate lipid solubility to traverse the GI mucosal membrane. By incorporating these three structural changes, oseltamivir has a better water/lipid solubility balance that allows it to be administered orally in the treatment of influenza infections.

6. To solve this problem, we need to use the Henderson-Hasselbalch equation. Because the functional group, a primary amine, is basic, the ionized form (R-NH_3^+) is the Acid Form and the unionized form (R-NH_2) is the Base Form.

$$\mathrm{pH} = \mathrm{pK_a} + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$6.5 = 7.7 + \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$-1.2 = \log \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

$$0.063 = \frac{[\text{Base Form}]}{[\text{Acid Form}]} \text{ or } \frac{0.063}{1} = \frac{[\text{Base Form}]}{[\text{Acid Form}]}$$

This ratio indicates that for every one molecule that contains the functional group in the acid (or ionized) form, there is 0.063 molecule that contains the functional group in the base (or unionized) form. The following equations can then be used to correctly calculate the percentage of the molecules that are ionized and the percentage that are unionized.

$$0.063 \text{ molecule in Base Form} + 1.0 \text{ molecule in Acid Form} = 1.063 \text{ total molecules}$$

$$\text{Base Form} = \text{Unionized Form and Acid Form} = \text{Ionized form}$$

$$\text{Percent in Ionized Form} = \frac{1 \text{ Molecule in Ionized Form}}{1.063 \text{ Total Molecules}} \times 100\% = 94.1\%$$

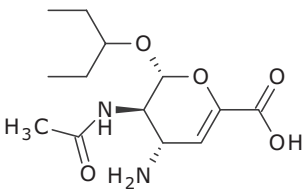
$$\text{Percent in Unionized Form} = \frac{0.063 \text{ Molecule in Unionized Form}}{1.063 \text{ Total Molecules}} \times 100\% = 5.9\%$$

Because the question asks for the percent that will be ionized, the correct answer is 94.1%.

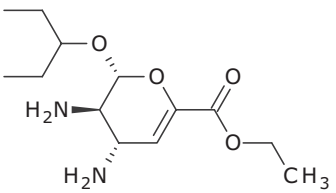
7. This stereoisomer has the opposite stereochemical configuration at all five chiral centers and has the exact same conformation as zanamivir; therefore, this is the ***enantiomer*** of zanamivir. None of the other stereochemical designations are correct.

   Given that zanamivir as well as oseltamivir exert their antiviral activity by mimicking *N*-acetylsialic acid, alteration of the stereochemistry decreases the resemblance to *N*-acetylsialic acid and would be predicted to cause a decrease in binding affinity to neuraminidase and a decreased antiviral effect.

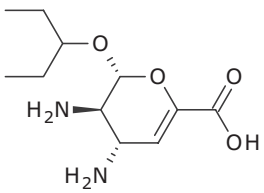
8. **Pathway A: Hydrolysis:** Phase I transformation. ***YES***, both the ester and amide functional groups can undergo hydrolysis. Ester hydrolysis produces the active metabolite of oseltamivir.



Ester hydrolysis

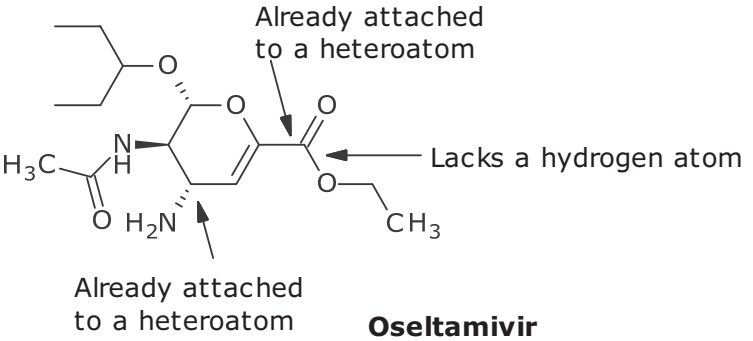


Amide hydrolysis



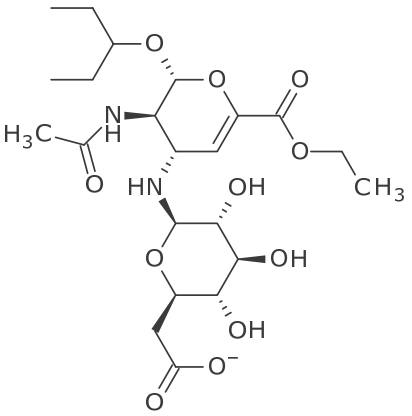
Ester and amide hydrolysis

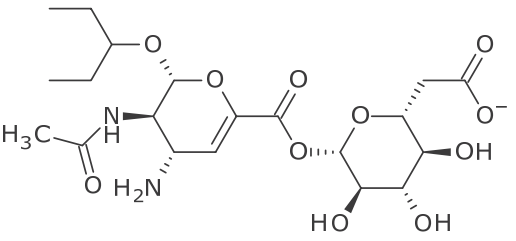
Pathway B: Allylic oxidation: Phase I transformation. ***NO***, it is not possible because both allylic carbon atoms are already attached to heteroatoms. Additionally, one allylic carbon atom lacks a hydrogen atom that is required for oxidation.



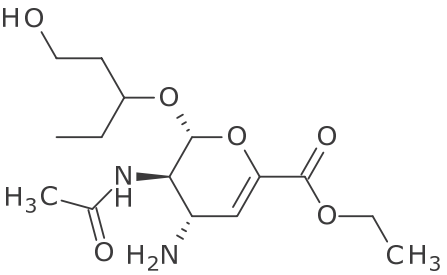
Oseltamivir

Pathway C: Glucuronide conjugation: Phase II transformation. ***YES***, it can occur directly with the secondary amine or with the carboxylic acid that results from Phase I ester hydrolysis.

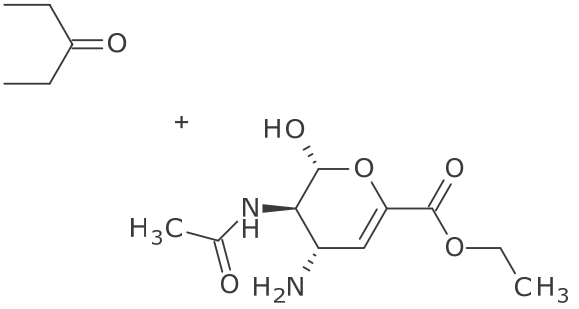




Pathway D: ω-Oxidation: Phase I, ***YES***



Pathway E: Oxidative *O*-dealkylation: Phase I, ***YES***



9. Zanamivir is very highly water soluble. Its chemical structure contains two ionizable functional groups as well as several others that can form hydrogen bonds with water. As such, zanamivir can be readily excreted without further metabolic transformation. Remember that the major purpose of drug metabolism is to enhance the removal of the drug from the body. If a drug molecule can be readily removed from the body, there is no need for metabolic transformations.