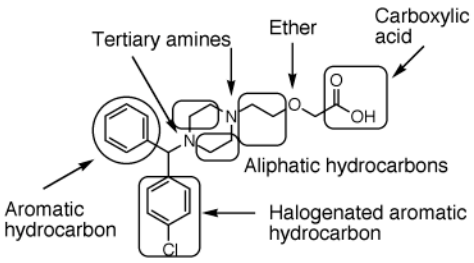
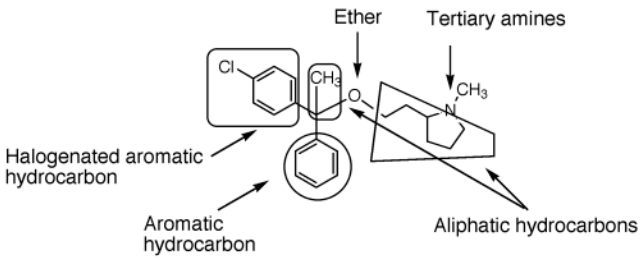
ANSWERS TO CASE STUDIES
Chapter 2: Drug Design and Relationship of Functional Groups to Pharmacologic Activity

Absorption/Acid-Base Case (p. 42)

Question #1:



Cetirizine (Zyrtec)



Clemastine (Tavist)

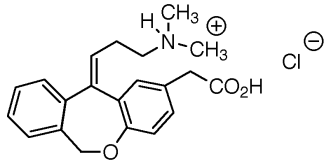
Drug	Functional groups present	Hydrophilic/ hydrophobic characteristics	Effect on absorption	Effect on ability to cross BBB
Cetirizine	Aromatic hydrocarbon	Hydrophobic	↑	↑
	Halogenated aromatic hydrocarbon	Hydrophobic	↑	↑
	Tertiary amine	Hydrophilic	↓	↓
	Ether	Hydrophilic	↓	↓
	Carboxylic acid	Hydrophilic	↑	↓
	Hydrocarbon	Hydrophobic	↑	↑
Clemastine	Aromatic hydrocarbon	Hydrophobic	↑	↑
	Halogenated aromatic hydrocarbon	Hydrophobic	↑	↑
	Tertiary amine	Hydrophilic	↓	↓
	Ether	Hydrophilic	↓	↓
	Hydrocarbon	Hydrophobic	↑	↑

Cetirizine is a second-generation H_1-antagonist and is purported to be nonsedating. Clemastine is a first-generation H_1-antagonist and is considered to be a sedating antihistamine. Based on the structure evaluation process, both cetirizine and clemastine contain several hydrophobic functional groups that would facilitate their crossing the blood-brain barrier. Both molecules contain an ionizable amine that will be predominantly ionized in the plasma. A key structural difference between these drug molecules is the presence of a carboxylic acid Cetirizine. This functional group is

hydrophilic and will be predominantly ionized in the plasma and therefore, may limit the extent of absorption across the blood-brain barrier. In order to limit the degree of drowsiness, it would be appropriate to recommend cetirizine (Zyrtec) for this patient.

Question #2:

Olopatadine hydrochloride is water soluble due to the solubilizing properties of the ion-dipole interaction between water and the ionized amine hydrochloride.



Olopatadine hydrochloride
(Patanol)

Questions #3:

Assumptions: pKa (tertiary amine) = 9.5
pKa (carboxylic acid) = 3.0

	pH=1 (stomach pH)	pH=10 (intestinal pH)
Tertiary amine (basic)	ionized	close to 50/50% ionized/unionized
Carboxylic acid (acidic)	unionized	ionized

Cetirizine: In both compartments there will be at least one ionized functional group. In the intestine roughly 50% of the time there will be two functional groups ionized, which will limit the extent of absorption from this site. Cetirizine is probably absorbed from both sites but is probably absorbed from the stomach to a greater extent.

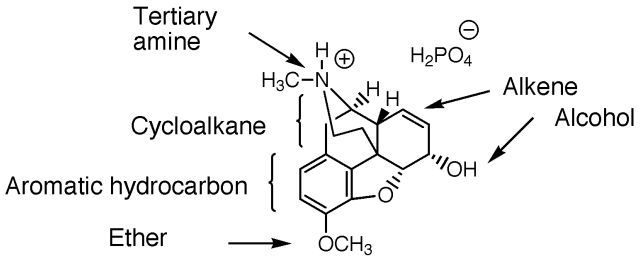
Clemastine: Absorbed best in the intestine where it is in its unionized form.

Question #4:

If the truck driver takes Cetirizine at the same time that he takes his TUMs, then the pH of the stomach will be elevated to 3.5 from pH=1. At this pH the carboxylic acid will become ionized and the extent of absorption from the stomach may be decreased to a limited extent. The truck driver may not receive the full antihistaminergic effect if he takes these two medications at the same time.

Acid Base Chemistry/Compatibility Case (p. 43)

Question #1:



Codine phosphate

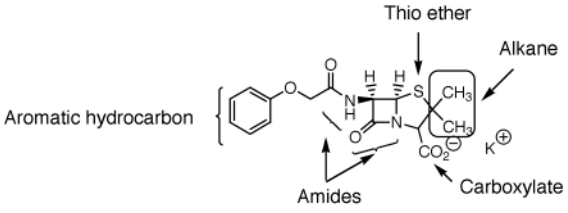
Acid/Base Evaluation of Codeine Phosphate:

Ethers – neutral
Alcohol – neutral
Aromatic Hydrocarbon – neutral
Cycloalkane – neutral
Alkene – neutral
Tertiary Amine (in salt form) – acidic (conjugate acid of a weak base)

Acid/Base Evaluation of Penicillin V Potassium:

Aromatic Hydrocarbon – neutral
Thioether – neutral
Amide – neutral
Ether – neutral
Alkane – neutral
Carboxylic acid (in salt form) – basic (conjugate base of a weak acid)

Question #2:



Penicillin V Postassium

Penicillin V Potassium contains several hydrophilic (polar) functional groups (amides, potassium salt of carboxylic acid) and only a moderate amount of hydrophobic character (aromatic hydrocarbon, thioether, alkane). Codeine phosphate, as originally drawn, contains a tertiary amine and an alcohol that are hydrophilic. It contains a couple of functional groups that have mixed hydrophobic/hydrophilic character (ethers) and a fair

amount of hydrophobic character (aromatic hydrocarbon, cycloalkane, alkene). For a drug to be water soluble it must be able to interact with water *via* hydrogen bonding or an ion/dipole interaction, which are characteristic of polar functional groups. Considering the structural features of both agents, Penicillin V Potassium will be more water soluble due to the presence of several polar functional groups, including an ionized functional group.

The ionized form of codeine is more water soluble than the free base form because it can participate in ion/dipole interactions with water (a strong interaction).

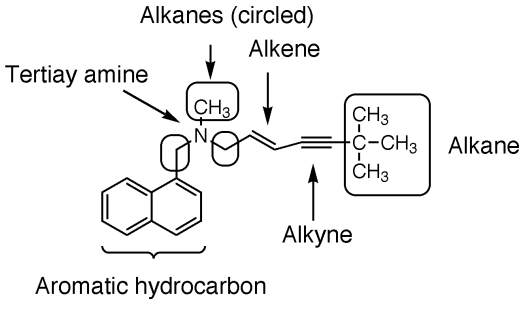
Question #3:

If these two salts are mixed into the same IV bag, then it is anticipated that the salts will dissociate. As individual agents, the free forms of the drugs (Penicillin V Potassium is an acid in its free form and Codeine Phosphate is a base in its free form) may not be as water soluble as their salt forms and it is possible that one or both of these agents could precipitate out of solution. When mixed together, it is certainly possible that these drugs (acid + base) could form a complex (ionic). This complex is not likely to be particularly water soluble and may form a precipitate in the IV bag.

Absorption/Binding Interactions Case (p. 45)

Question #1:

Those functional groups that are hydrophobic in character will facilitate the absorption of this medication into the skin.



Terbinafine (Lamisil)

Characteristics of functional groups present in Terbinafine:

Aromatic hydrocarbon - Hydrophobic, ↑ Penetration of skin.

Alkene - Hydrophobic, ↑ Penetration of skin.

Alkane - Hydrophobic, ↑ Penetration of skin.

Alkyne - Hydrophobic, ↑ Penetration of skin.

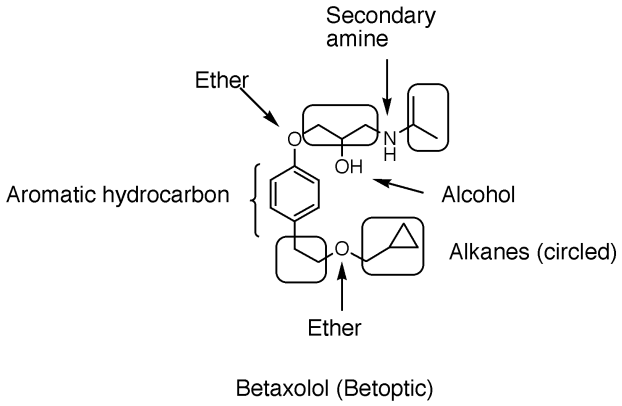
Tertiary amine - Hydrophilic, Hydrophobic, ↓ Penetration of skin.

Questions #2:

Selection of the amino acids is based on the types of interactions that are possible with the particular functional group. With the tertiary amine it is essential to consider the ionization of this functional group prior to pairing with an amino acid. For the ion/dipole interaction, it is important to determine whether the drug is participating as the ion or the dipole when coupling potential amino acids to this type of functional group.

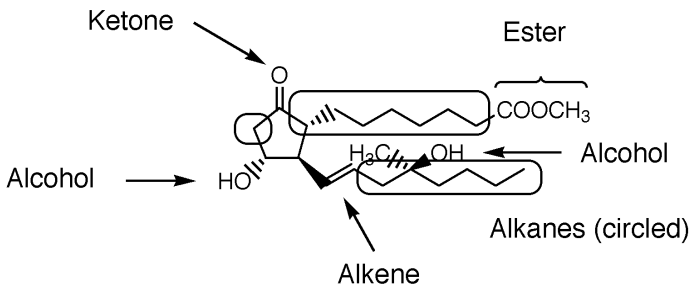
Functional groups in Terbinafine	Binding interactions possible with enzyme	Amino acids that could interact with group
Aromatic hydrocarbon	Hydrophobic staking interactions	Phenylalanine Tyrosine
Alkene	Hydrophobic	Isoleucine Leucine Valine Alanine Methionine
Alkane	Hydrophobic	Isoleucine Leucine Valine Alanine Methionine
Alkyne	Hydrophobic	Isoleucine Leucine Valine Alanine Methionine
Tertiary amine	H-bonding Dipole/dipole Ion/dipole Ionic	Serine Threonine Cysteine Tyrosine Glutamic acid etc.

Binding Interactions (p. 46)



Betaxolol (Betoptic)

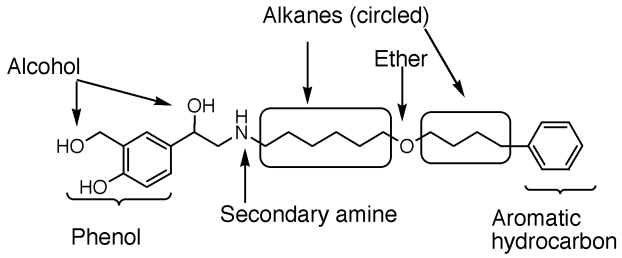
Functional groups in Betaxolol	Binding interactions possible with enzyme	Amino acids that could interact with group
Aromatic hydrocarbon	a. Hydrophobic b. Stacking interactions	a. Phenylalanine b. Tyrosine
Alkane	Hydrophobic	Leucine
Ether	a. H-bonding b. Dipole/dipole	a. Serine b. Threonine
Secondary amine	a. H-bonding b. Dipole/dipole c. Ion/dipole d. Ionic (amine salt)	a. Histidine b. Glutamine c. Cysteine d. Aspartic acid (ionized form)



Misoprostol (Cytotec)

Functional groups in Misoprostol	Binding interactions possible with enzyme	Amino acids that could interact with group
Alkane	Hydrophobic	Leucine

Ketone	a. H-bonding b. Dipole/dipole c. Ion/dipole	a. Cysteine b. Lysine c. Glutamic acid (ionized form)
Ester	a. H-bonding b. Dipole/dipole c. Ion/dipole	a. HiSerine b. Threonine c. Arginine (ionized form)
Alkene	Hydrophobic	Isoleucine

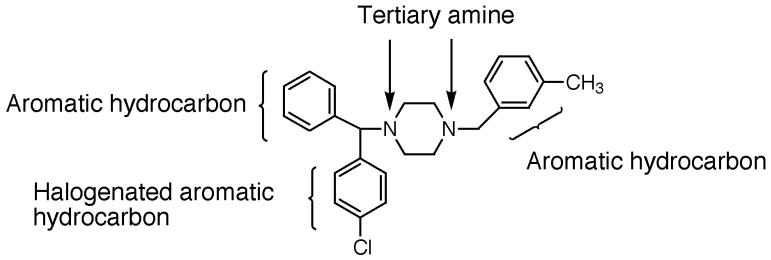


Salmeterol (Serevent)

Functional groups in Salmeterol	Binding interactions possible with enzyme	Amino acids that could interact with group
Aromatic hydrocarbon	a. Hydrophobic b. Stacking interactions	a. Phenylalanine b. Tyrosine
Alkane	Hydrophobic	Leucine
Ether	a. H-bonding b. Dipole/dipole	a. Serine b. Threonine
Secondary amine	a. H-bonding b. Dipole/dipole c. Ion/dipole d. Ionic (amine salt)	a. Histidine b. Glutamine c. Cysteine d. Aspartic acid (ionized form)
Phenol	a. H-bonding b. Dipole/dipole c. Ion/dipole	a. Tyrosine b. Threonine c. Cysteine

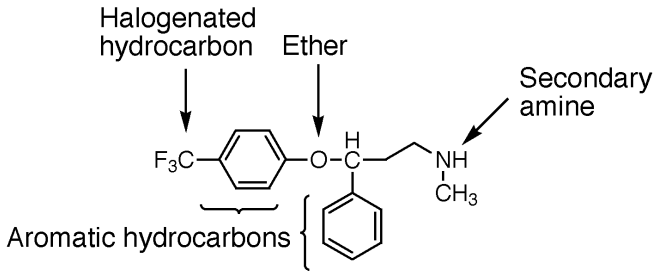
	d. Ionic (amine salt)	d. Lysine (ionized form)
Alcohol	a. H-bonding b. Dipole/dipole c. Ion/dipole	a. Glutamic acid b. Glutamine c. Arginine (ionized form)

Water/Lipid Solubility Case (p. 47)



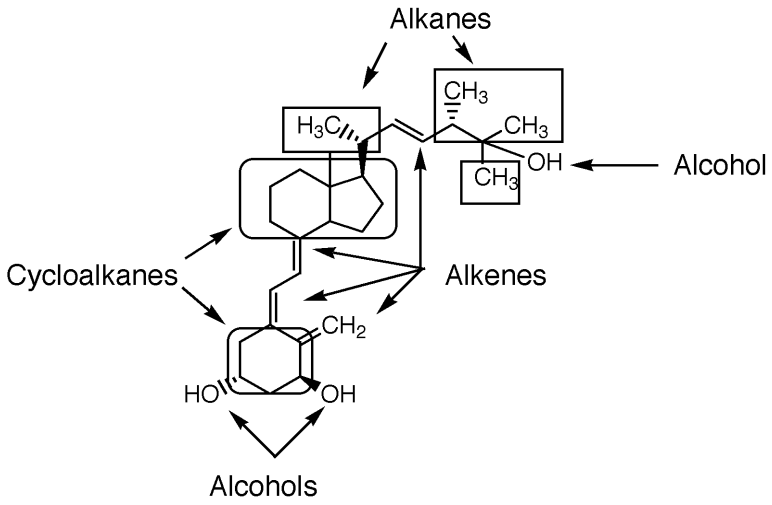
Meclizine
(Antivert)

Structural feature in Meclizine	Physical property
Aromatic hydrocarbon	Hydrophobic
Halogenated aromatic hydrocarbon	Hydrophobic
Tertiary amine	Hydrophilic



Fluoxetine
(Prozac)

Structural feature in Fluoxetine	Physical property
Aromatic hydrocarbon	Hydrophobic
Halogenated hydrocarbon	Hydrophobic
Secondary amine	Hydrophilic
Ether	Hydrophilic

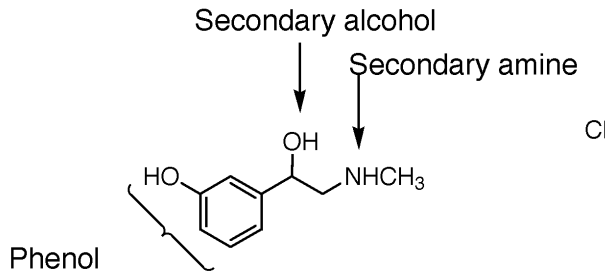


1,25-Dihdroxyergocalciferol
(Vitamin D)

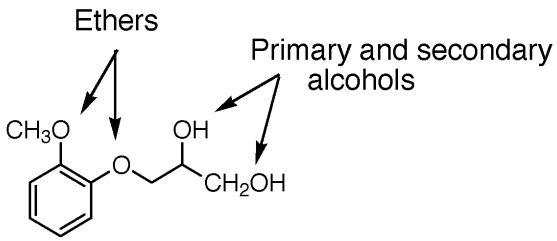
Structural feature in Vitamin D	Physical property
Cycloalkane	Hydrophobic
Alkane	Hydrophobic
Alkene	Hydrophobic
Alcohol	Hydrophilic

Binding Interactions/Solubility Case (p. 48)

Question #1:



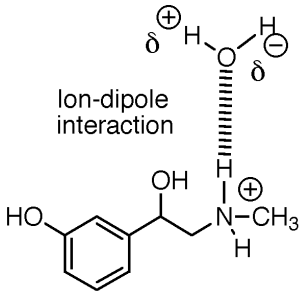
Phenylephrine



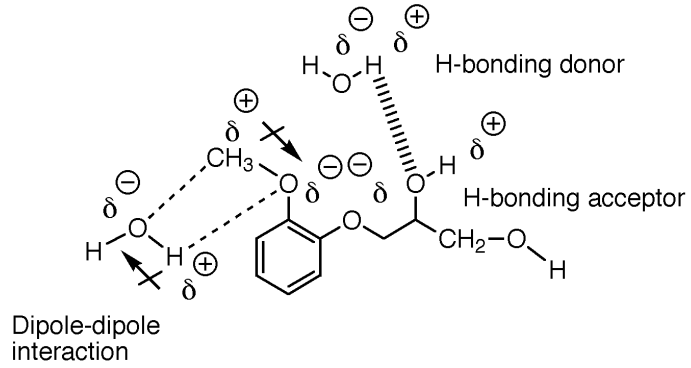
Guaifenesin

Functional groups in Phenylephrine contributing to water solubility	Interactions possible with water
Secondary alcohol	H-bonding, Dipole-dipole, Ion-dipole
Secondary amine	H-bonding, Dipole-dipole, Ion-dipole
Phenol	H-bonding, Dipole-dipole, Ion-dipole

Functional groups in Guaifenesin contributing to water solubility	Interactions possible with water
Primary and secondary alcohol	H-bonding, Dipole-dipole, Ion-dipole
Ether	H-bonding, Dipole-dipole, Ion-dipole

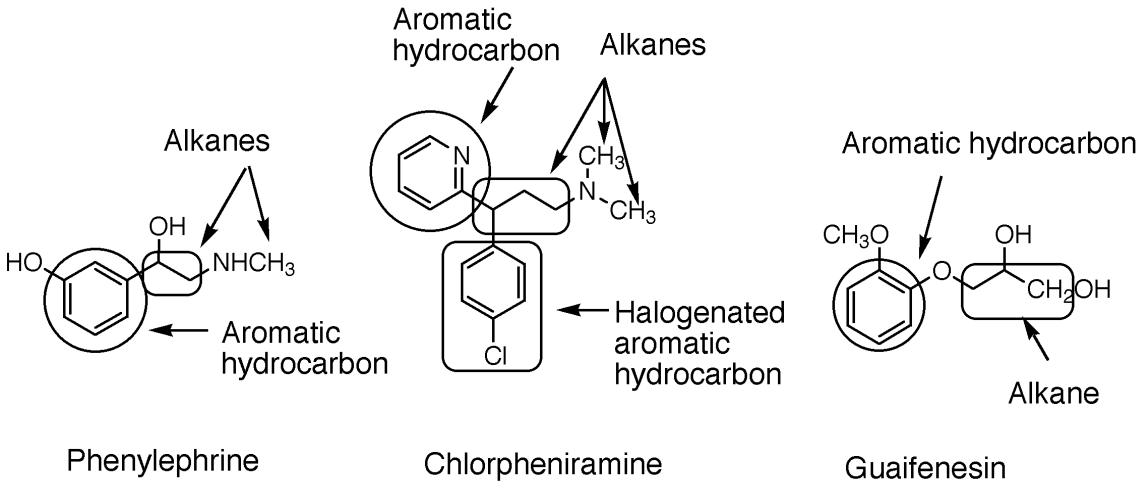


Phenylephrine



Guaifenesin

Question #2:



Functional groups in:	Characteristics of group:
Phenylephrine	
Alkane	Hydrophobic
Aromatic hydrocarbon	Hydrophobic
Chlorpheniramine	
Alkane	Hydrophobic
Aromatic hydrocarbon	Hydrophobic
Halogenated aromatic hydrocarbon	Hydrophobic
Guaifenesin	
Alkane	Hydrophobic
Aromatic hydrocarbon	Hydrophobic

The agent that has the most hydrophobic character is the one that is most likely to cross the lipophilic blood-brain barrier and have an effect on the child's alertness. Of these agents, chlorpheniramine has the most hydrophobic character (see list of structural features in question 1 and 2). The only hydrophilic group present in chlorpheniramine is the tertiary amine.

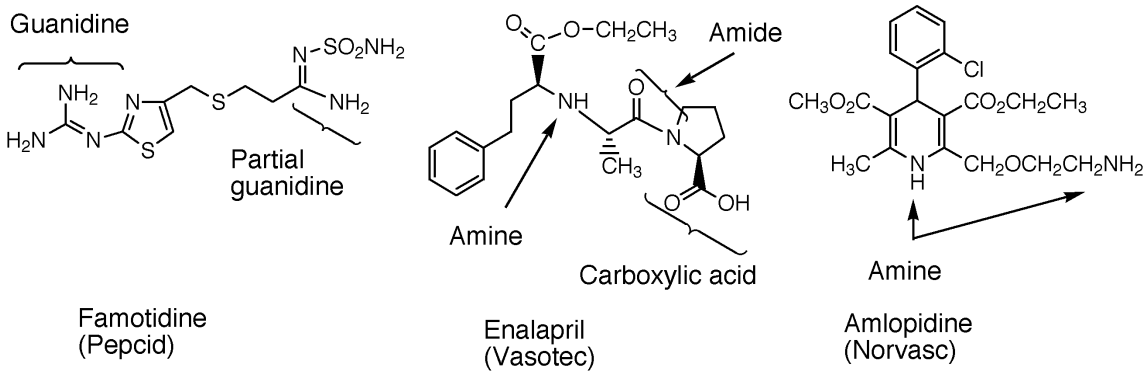
Question #3:

Functional groups in Chlorpheniramine	Binding Interaction possible with target of drug action
Aromatic hydrocarbon	Hydrophobic stacking
Halogenated aromatic hydrocarbon	Hydrophobic stacking
Alkane	Hydrophobic van der Waal
Tertiary amine	H-bonding

	Dipole-dipole Ion-dipole Ionic

Functional groups in Guaifenesin	Binding Interaction possible with target of drug action
Aromatic hydrocarbon	Hydrophobic stacking
Alkane	Hydrophobic van der Waal
Ether	H-bonding Dipole-dipole Ion-dipole
Primary and secondary alcohol	H-bonding Dipole-dipole Ion-dipole

Case Study p. 65.



Famotidine (Pepcid)

Enalapril (Vasotec)

Amlopidine (Norvasc)

	Amine/Guanidine	**Ketone**	**Carboxylic Acid**	**Amide**
Which drug(s) contain this functional group?	Famotidine Enalapril Amlodipine	None	Enalapril	Enalapril
Hydrophobic or Hydrophilic in character?	Hydrophilic	Hydrophilic	Hydrophilic	Hydrophilic
Acidic, basic, or neutral as drawn?	Basic	Neutral	Acidic	Neutral
Types of interactions possible with target for drug action	Ionic (if ionized) Ion/dipole Dipole/dipole H-bonding	H-bonding Dipole/dipole Ion/dipole	Ionic (if ionized) Ion/dipole Dipole/dipole H-bonding	Ion/dipole Dipole/dipole
Is this group a H-bond donor, H-bond acceptor, both or neither?	Both	H-bond acceptor only	H-bond donor and acceptor (as drawn)	Neither (as drawn)

Question #2:

Pepcid, in its hydrochloride salt form, is the conjugate acid of a weak base and is considered to have acidic character. At pH=1, Pepcid's guanidine group will be ionized in the stomach (pKa=10.5; the pH of the environment is less than the pKa of the basic drug, therefore the functional group will be ionized). At pH=3.5, the guanidine group will still be ionized (same rationale).

Question #3:

Enalapril: Amine: ionized at pH=1 and at pH=3.5
Carboxylic acid: unionized at pH=1, slightly more than 50% ionized at pH=3.5

Amlodipine: Amine: ionized at pH=1 and at pH=3.5

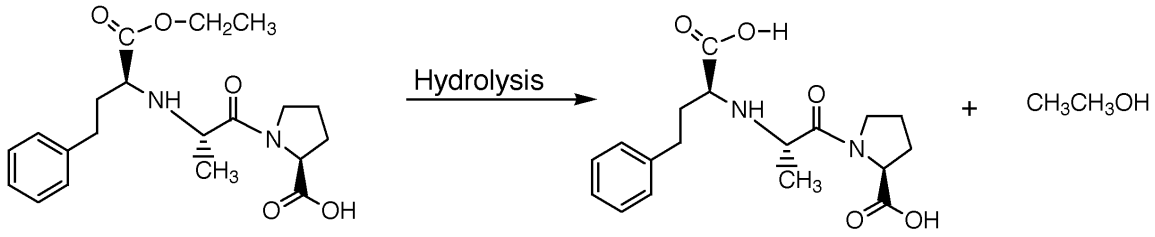
Both drugs will have at least one structural component in its ionized form at both pHs.

Question #4:

These agents will have ionic character at both pHs. This ionic character will increase the ability of the drug to be soluble in the aqueous contents of the stomach but will decrease its ability to be absorbed across the lipophilic lining of the stomach. In the presence of famotidine, the carboxylic acid in enalapril will be somewhat greater than 50% ionized, which may further hamper absorption from the stomach. To be on the safe side, the famotidine should be separated from at least the enalapril dose.

Question #5:

The products of hydrolysis of enalapril:



Acid/Base Chemistry, Solubility, and Absorption Case Study (p. 66)

Question #1:

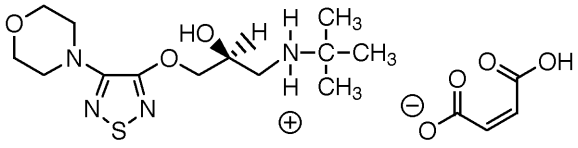
Acid/base character of Latanoprost as drawn: Neutral

Question #2:

Acid/base character of Timolol as drawn: Basic

Question #3:

Timolol is formulated as the salt of Maleic acid. The salt form of this drug is a conjugate acid of a weak base and has ACIDIC character.



Timolol maleate

Question #4:

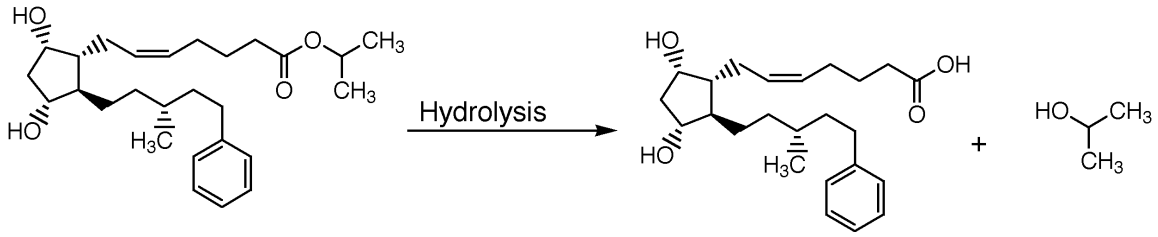
The functional groups that enhance solubility are those that can interact with water via H-bonding or dipole/dipole interactions. The secondary alcohol, the secondary amine, the heterocycle, and the morpholine heteroatoms can interact with water and improve the hydrophilic character of the molecule. Hydrophilic character is important for good water solubility.

Question #5:

There is considerably more hydrophobic character in Latanoprost than in Timolol. The aromatic hydrocarbon, cycloalkane, alkene, and hydrocarbon chains present in the Latanoprost all contribute to the hydrophobic character and therefore, aid in the absorption of the medication into the eye.

Question #6:

Latanoprost contains a labile ester functional group that can be readily hydrolyzed.



Latanoprost

Carboxylic acid

Alcohol