BPS 2110
Assignment 3 Answers Updated

1. Describe the four major types of non-bonding interaction in terms of what the interaction consists of, relative strength, and any special considerations for drug design.
   - Electrostatics are the attraction between + and – charges. They are non-directional, and their strength depends on the distance between the charges. They give stronger interactions in non-polar environments
   - Hydrogen bonds are specialized dipole-dipole interactions involving slightly positive hydrogens attached to heteroatoms (N or O) forming a dipole interaction with unpaired electrons of nearby electron donors (N or O). Their strength depends on the distance between the electron pair donor and the hydrogen. These forces are directional, and get stronger as the X-H bond aligns with the orbital holding the unpaired electrons of the acceptor. They give stronger interactions in non-polar environments
   - Dipole-dipole interactions involving the attractions between partial positive and partial negative charges. These partial charges are usually the result of differences in electronegativity between atoms of different type bonded together. Slightly positive atoms are attracted to slightly negative ones. The strength of the interaction depends on the distance between the atoms. These forces are non-directional. They give stronger interactions in non-polar environments
   - Van der Waals interactions are small, temporary, induced dipole-dipole interactions between molecules. Random movement of electrons within molecules create areas of positive and negative charge. These small charges tend to attract or repulse electrons in nearby molecules, thus creating complimentary opposite charges that attract each other. These forces are non-directional. They give stronger interactions as the contact surface areas between molecules increases.

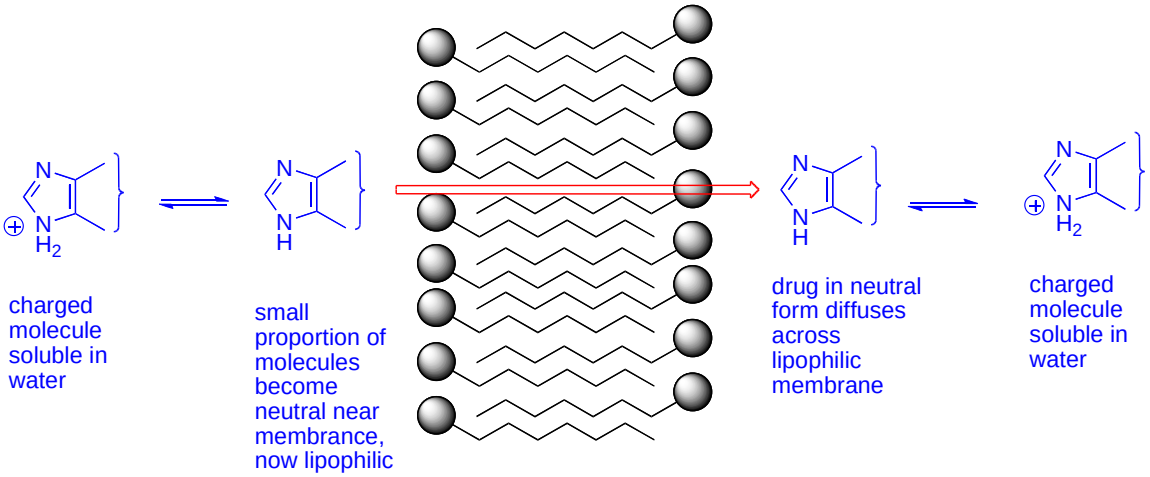
2. Why do solvent exposed binding sites on the surface of enzymes provide weaker binding for drugs than binding "pockets" do?
   Interactions on the surface of proteins can become surrounded by water molecules. These water molecules become attracted to the dipole interactions between the drug and the protein, which has the effect of diluting the attraction between the drug and protein. Inside binding pockets, the attractive forces between drug and protein are limited to each other. there are no extra water molecules around to participate, which strengthens the interaction between the drug and protein.

3. What is meant by the term "drug-like"? What is the major challenge in making a "drug-like" drug?
   Drug like refers to molecular properties which make a drug convenient for a patient to use. These properties create drugs which are "user friendly". The major challenge in doing this is that this process involves properties which

work in "opposite" directions (lipophilicity and hydrophilicity). Difficult to improve one property without making the other worse.

4. Most drugs approved for human use are acids or bases.
    a. Using a diagram, show how acid/base behavior can be a beneficial property for drugs.

- acids and bases are usually charged at physiological pH
- this makes them soluble in water
- acid base equilibria makes them easy to convert to neutral forms to pass biological membranes



    b. Why are bases more common than acids?

- phosphate groups on outside of membranes are negative
- this creates region of negative charge very close to the surface of the membrane
- acids are usually negative at pH 7.4
- negatively charged molecules repelled at the surface of membranes, this makes it more difficult for them to pass through

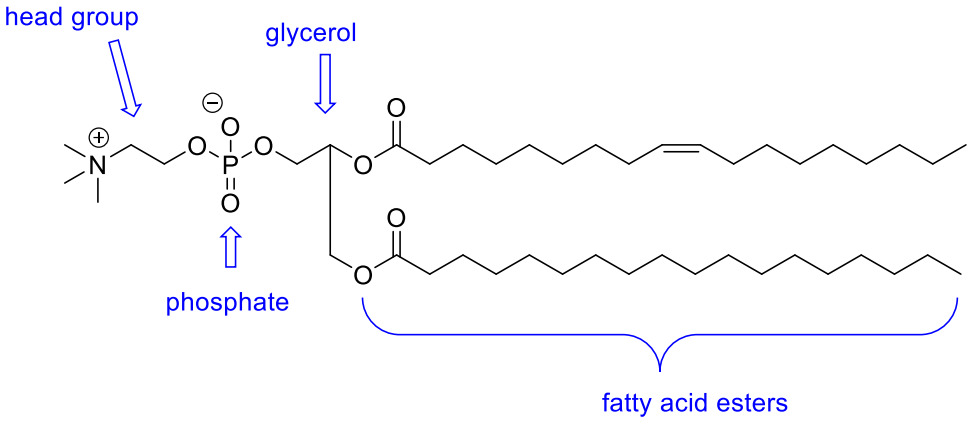
    c. Molecules that carry permanent charges are often a problem for drug delivery. Why do you think this is?

- permanent charges cannot pass membranes well, lipophilic environment of the membrane (50 angstroms wide) does not tolerate strongly charged molecules
- charged molecules more easily removed by the kidney

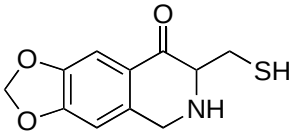
    d. Why are weak acids or bases generally better drugs than strong acids or bases?

- The pKa of weak acids and bases tend to have values near 7. This means that at pH 7, there will always be a small amount of the neutral form of the drug present. This increases the rate at which the drug can pass through membranes. Strong acids and bases tend to be charged almost all the time. The amounts of neutral form drug are so small that intake into membranes becomes very slow.

5. Identify the main component parts in the following membrane phospholipid.



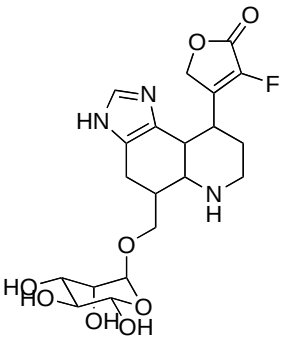
6. Predict whether the following compounds are likely to be orally bioavailable or not, and provide a brief justification for each.

a. 

MW = 205.1
mLogP = 5.9

H bond donors = 1
H bond acceptors = 4

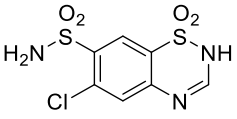
1 violation of Lipinsky's rules likely bioavailable

b. 

MW = 455.4
CLogP = 4.5

H bond donors = 6
H bond acceptors = 11

2 violations of Lipinsky's rules likely not bioavailable

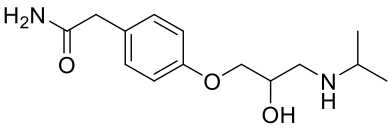
c. 

MW = 295.7

CLogP = -0.07

3 hydrogen bond donors
7 hydrogen bond acceptors

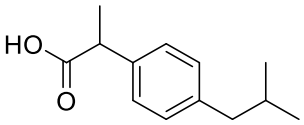
likely bioavailable

d. 

MW = 266.3
CLogP = 0.58

4 hydrogen bond donors
5 hydrogen bond acceptors

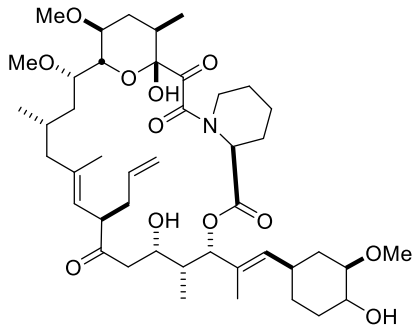
likely bioavailable

e. 

MW = 206.3
MLogP = 4.9

1 hydrogen bond donor
2 hydrogen bond acceptors

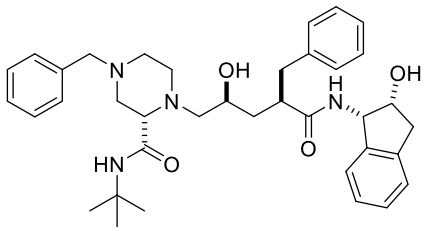
likely bioavailable (only violates 1 rule)

f. 

MW = 804.02
MLogP = 4.5

3 hydrogen bond donors
13 hydrogen bond acceptors

likely not bioavailable (violates 3 rules)

g. 

MW = 612.8
CLogP = 4.8

4 hydrogen bond donor
7 hydrogen bond acceptors

likely bioavailable (only violates 1 rule)

7. For each of the following aspects of the rules of five, describe the criteria applied and provide a brief explanation of why the rule helps to predict oral bioavailability.
   a. Hydrogen bond donors

Want fewer than 5 HBD's. HBD's help solubilize molecules, but if this number gets too large, the molecules become less lipophilic and cannot cross membranes

   b. Hydrogen bond acceptors

Want fewer than 10 HBA's. HBA's help solubilize molecules, but if this number gets too large, the molecules become less lipophilic and cannot cross membranes

   c. Molecular weight

Want MW less than 500. Large molecules tend to be less soluble in water (create too large a cavity) and less able to pass biological membranes (too big to slide between the fatty acid chains).

   d. LogP

Want CLogP less than 5, or MLogP less than 4.15. As log P gets larger, molecules become less water soluble.

   e. LogD

Want $LogD_{7.4}$ between 1 and 3. At values less than 1, the molecule is not lipophilic enough to cross biological membranes, at values more than 3, the molecule is not soluble enough in water to get to the biological membranes.

8. Provide a definition for each of the following:
   a. LogP

$$\text{LogP} = \text{Log}\left(\frac{[\text{Drug in octanol}]}{[\text{Drug in water}]}\right)$$

- Value is measured at a pH in which the molecule is neutral
-

b. LogD

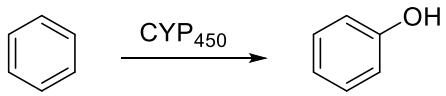
$$\text{LogD} = \text{Log}\left(\frac{[\text{Drug in octanol}]}{[\text{Drug in water}]}\right)$$

Value is measured at a defined pH (usually 7.4)

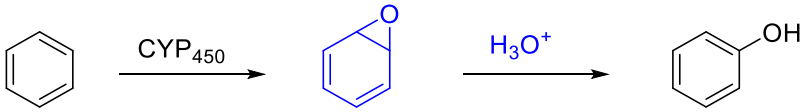
c. What are the main advantages and disadvantages of each method?

	Advantage	Disadvantage
LogP	-well established -works in rule of 5	-each molecule may require different buffer -measurement not at physiologic conditions
LogD	-well established -works in rule of 5 -easier to measure (consistent pH) -physiologically relevant	-less widely used (this is changing in the industry)

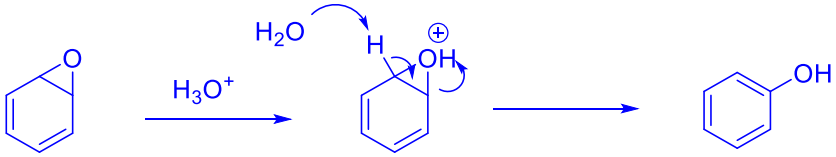
9. The following shows a general reaction describing the metabolism of an aromatic structure by CYP enzymes.



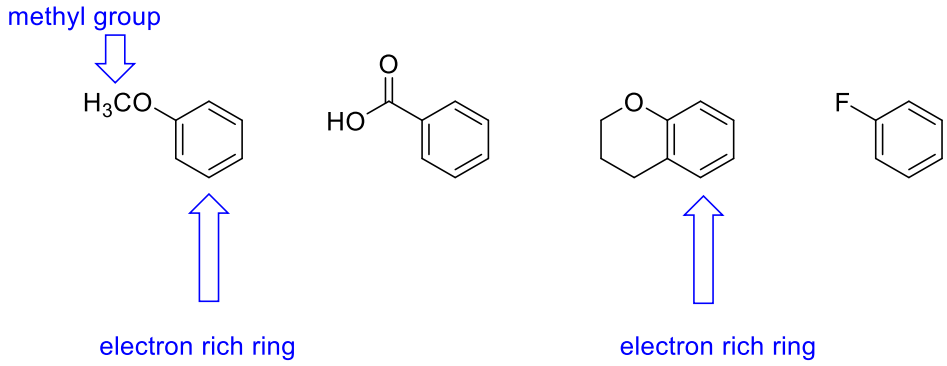
a. Give the structure of the key intermediate in the metabolism of an aromatic substrate by CYP enzymes.



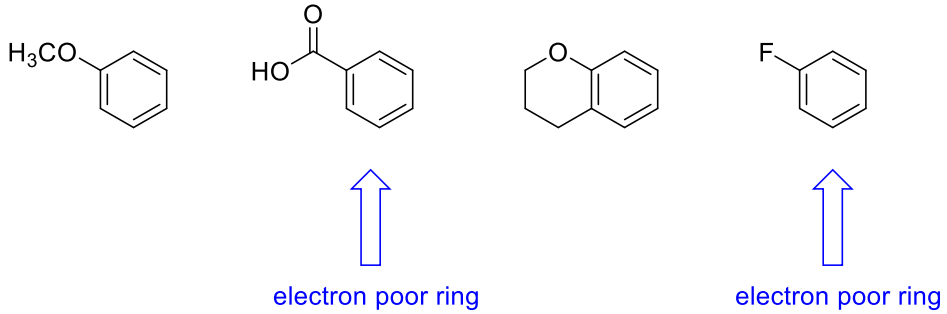
b. Draw the mechanism for the conversion of this intermediate into the observed product.



c. Which of the following substrates would be metabolized the most rapidly according to the above pathway?

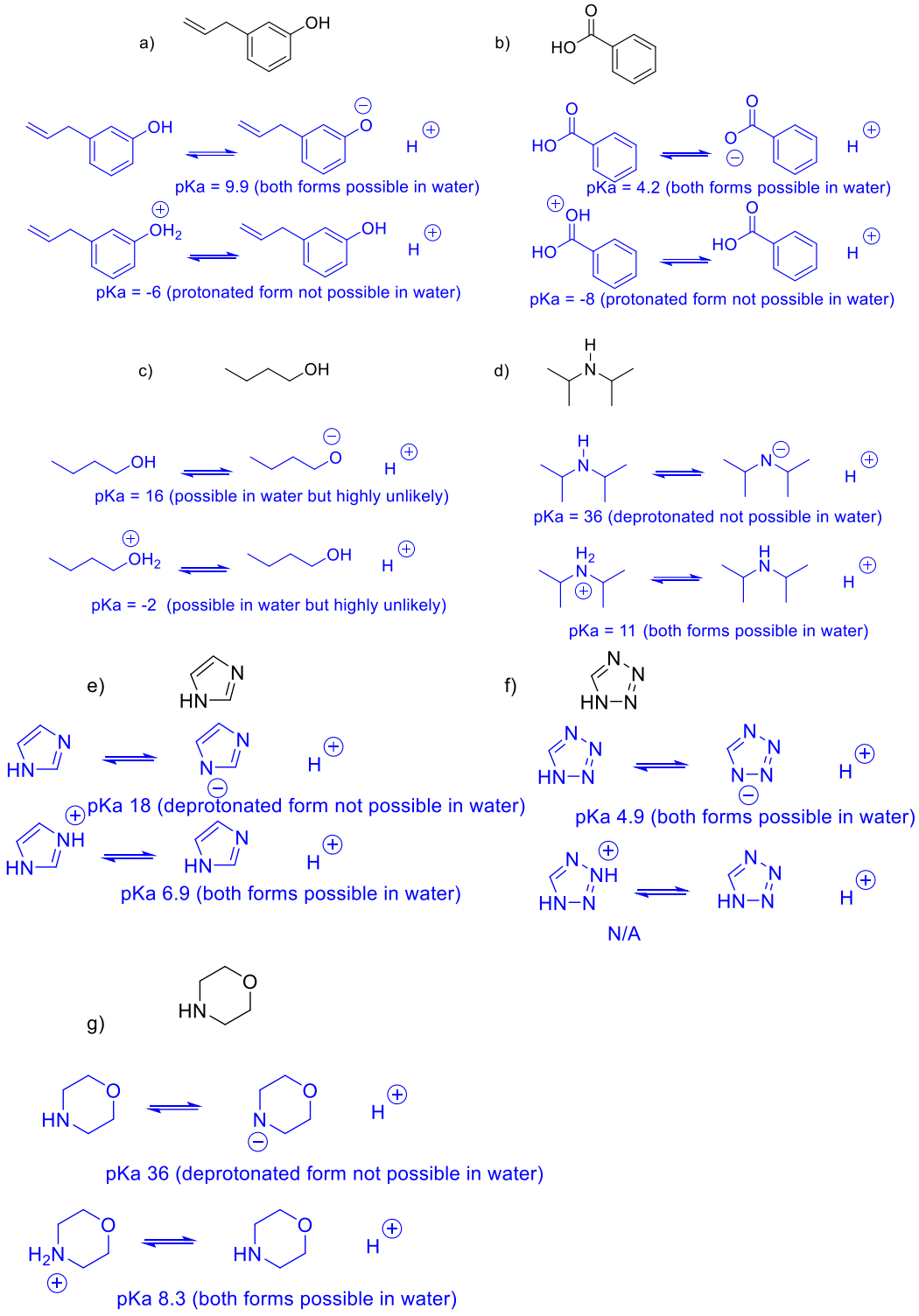


d. Which of the above structures would be metabolized the slowest?

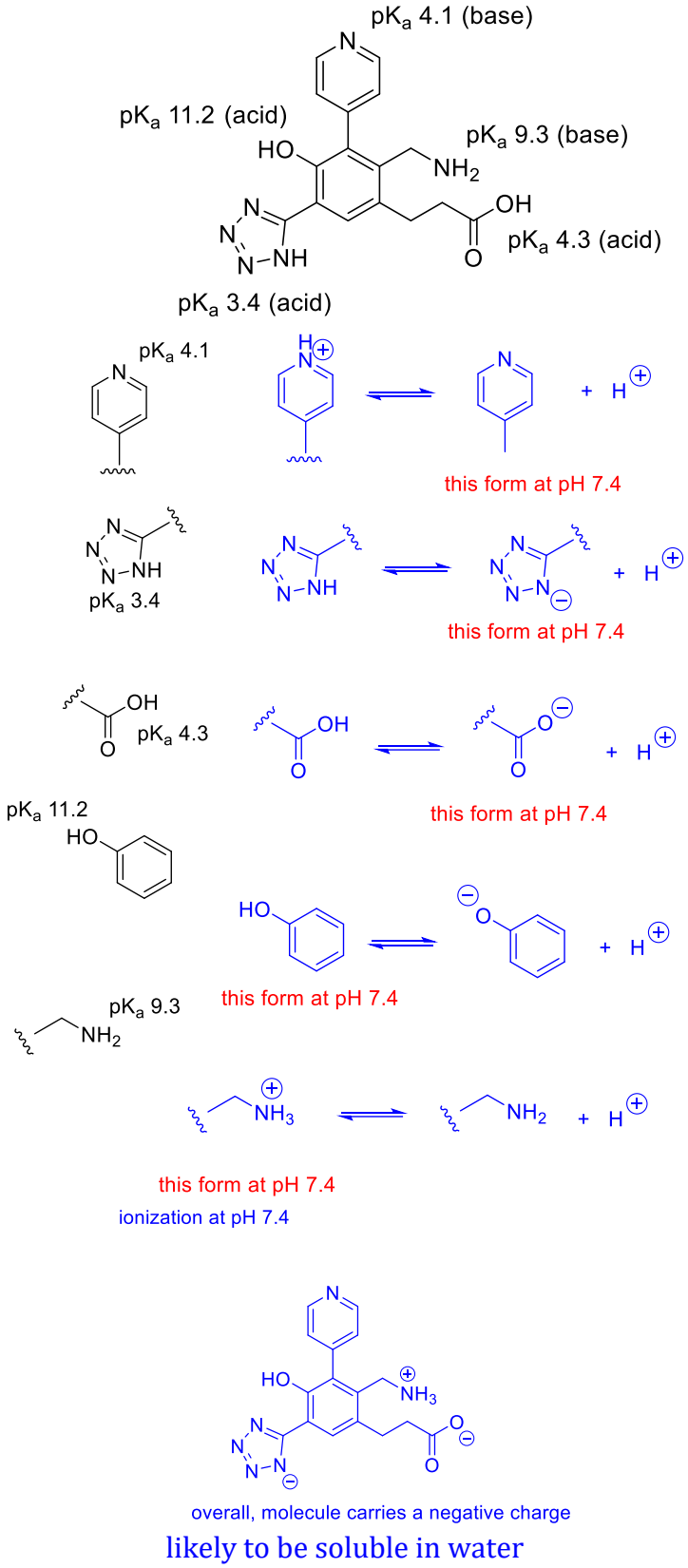


10. What is meant by the term pharmacophore?
    -identify groups or locations on a drug that are important for binding to biological targets
    -made a model of these interactions in three dimensions

11. For each of the following molecules, write the pK_a expression(s) for the functional group present. Using the table provided, identify an appropriate pK_a, and using this value, indicate if the process is relevant or not for biological systems.



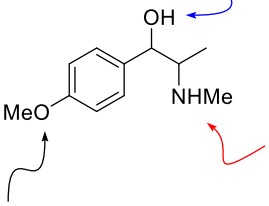
12. For the following molecule, identify the overall correct ionization state at pH 7.4, and predict whether the drug is likely to be water soluble or not at this pH. The pK_a's listed are for the relevant behavior of each functional group in water as indicated.



13. An analytical chemist must make a series of LogP measurements as part of the ADME effort at a major pharmaceutical company. For each of the

molecules shown, predict the approximate pH at which each measurement should be made.

a.



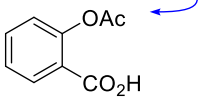
pKa for ROH_2^+ (ROH acts as base) is -2
pKa for ROH (ROH acts as acid) is approx 16
this group is neutral between pH -2 and 16 and will not be ionized in water

pKa for $R_2NH_2^+$ (RNHMe acts as base) is approx 10.7
pKa for R2NH is approx 36 (does not apply in water)
this group is neutral above pH 10.7
this group is positive below pH 10.7

no acidic hydrogens, this oxygen is a very weak base pKa < -2
this group is protonated at pH below -2
this group is neutral at pH above -2 and will not be ionized in water

this molecule will be neutral between pH 10.7 and 15.7 (highest pH in water)
measure LogP at pH above 10.7

b.



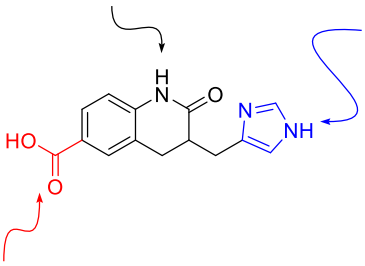
no acidic hydrogens, the carbonyl oxygen is a very weak base pKa < -7.8
this group is protonated at pH below -7.8
this group is neutral at pH above -7.8 and will not be ionized in water

pKa for $PhCO_2H$ (carboxylic acid) is 4.2
pKa for $PhCO_2H_2^+$ (oxonium) is -7.8 (can ignore in water)
this group is neutral below pH 4.2
this group is negative above pH 4.2

this molecule will be neutral at pH's below 4.2
measure LogP at pH below 4.2

c.

pKa for RCONHR (NH acts as acid) is approx 23
the carbonyl oxygen is a weak base pKa < -3.1
this group is negative above pH 23
this group is positive below pH -3.1
this group is neutral in water



pKa for imidazolonium (N acts as base) is 6.0
pKa for imidazole (NH acts as acid) is approx 18.6
this group is neutral between pH 6.0 and 18.6
this group is negative above pH 18.6 (not relevant in water)
this group is positive below pH 6.95

pKa for oxonium (C=O acts as base) is -7.8 (not relevant in water)
pKa for acid (acts as acid) is approx 4.2
this group is neutral at pH below 4.2
this group is negative above pH 4.2

this molecule will be neutral between pH 4.2 and 6.0
measure LogP between 4.2 and 6.0