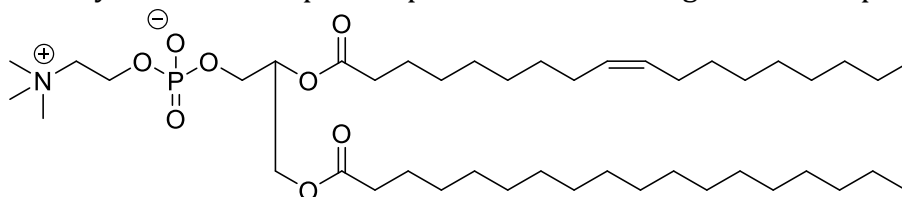


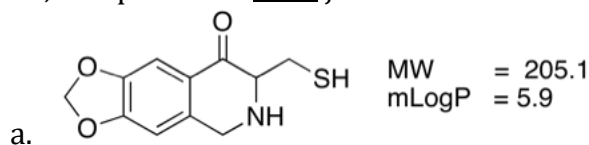
BPS 2110

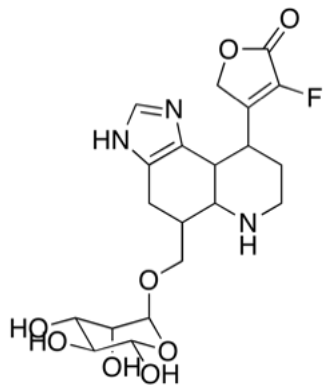
Assignment 3

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.
2. Why do solvent exposed binding sites on the surface of enzymes provide weaker binding for drugs than binding “pockets” do?
3. What is meant by the term “drug-like”? What is the major challenge in making a “drug-like” drug?
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.
 - b. Why are bases more common than acids?
 - c. Molecules that carry permanent charges are often a problem for drug delivery. Why do you think this is?
 - d. Why are weak acids or bases generally better drugs than strong acids or bases?
5. Identify the main component parts in the following membrane phospholipid.



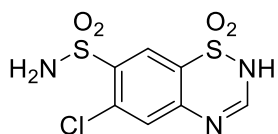
6. Predict whether the following compounds are likely to be orally bioavailable or not, and provide a brief justification for each.





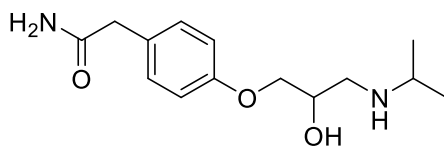
MW = 455.4
CLogP = 4.5

b.



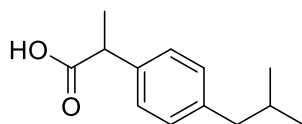
MW = 295.7
CLogP = -0.07

c.



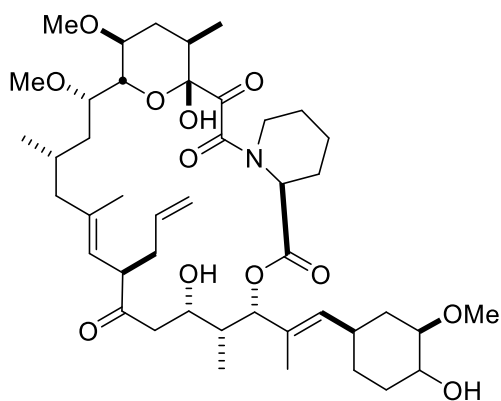
MW = 266.3
CLogP = 0.58

d.



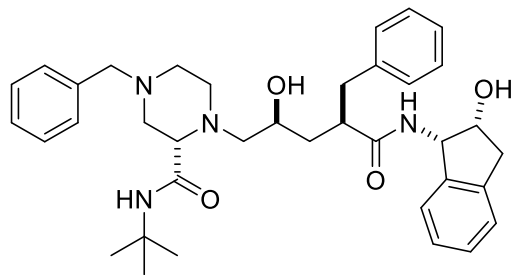
MW = 206.3
MLogP = 4.9

e.



MW = 804.02
MLogP = 4.5

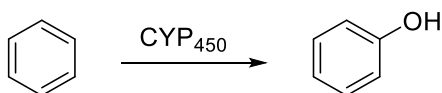
f.



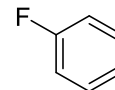
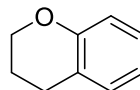
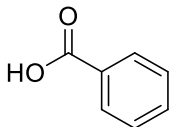
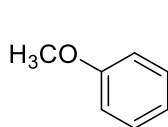
MW = 612.8
CLogP = 4.8

g.

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.
- Hydrogen bond donors
 - Hydrogen bond acceptors
 - Molecular weight
 - LogP
 - LogD
8. Provide a definition for each of the following:
- LogP
 - LogD
 - What are the main advantages and disadvantages of each method?
9. The following shows a general reaction describing the metabolism of an aromatic structure by CYP enzymes.



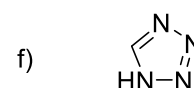
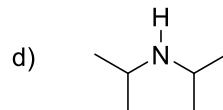
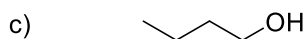
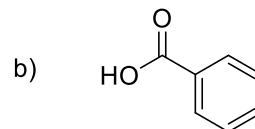
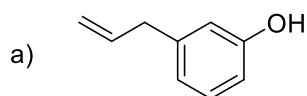
- Give the structure of the key intermediate in the metabolism of an aromatic substrate by CYP enzymes.
- Draw the mechanism for the conversion of this intermediate into the observed product.
- Which of the following substrates would be metabolized the most rapidly according to the above pathway?



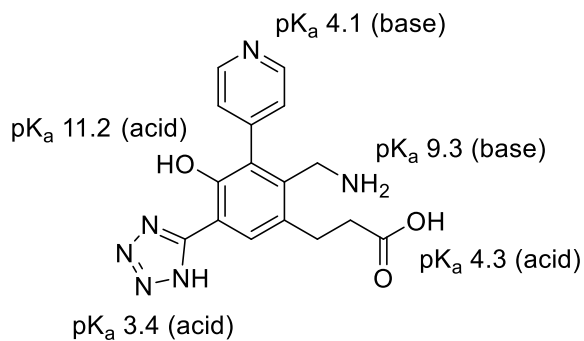
- Which of the above structures would be metabolized the slowest?

10. What is meant by the term pharmacophore?

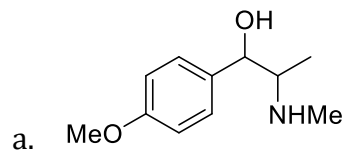
11. For each of the following molecules, write the pK_a expression(s) for the functional group present. Using the table provided, identify an appropriate pK_a , and using this value, indicate if the process is relevant or not for biological systems.

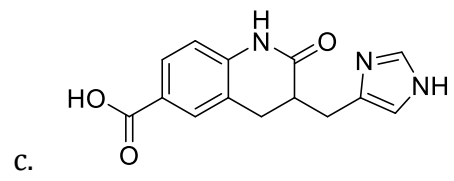
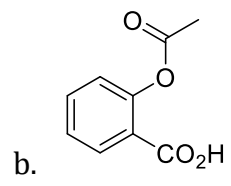


12. For the following molecule, identify the overall correct ionization state at pH 7.4, and predict whether the drug is likely to be water soluble or not at this pH. The pK_a 's listed are for the relevant behavior of each functional group in water as indicated.

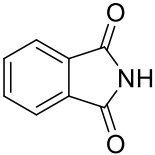
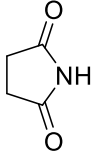

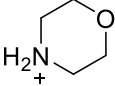
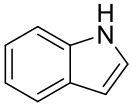
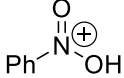

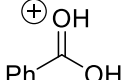

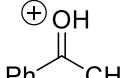
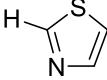
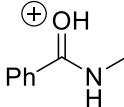

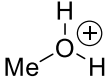
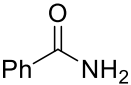
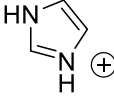
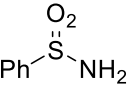
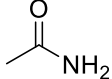
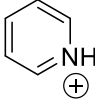


13. An analytical chemist must make a series of LogP measurements as part of the ADME effort at a major pharmaceutical company. For each of the molecules shown, predict the approximate pH at which each measurement should be made.





Selected pK_a Values

Protonated Nitrogen	Amines	Imides																				
NH ₄ ⁺ 9.2	HN ₃ 4.7	 8.30																				
EtNH ₃ ⁺ 10.6	NH ₃ 38																					
iPr ₂ NH ₂ ⁺ 10.75	iPr ₂ NH 36	 14.70																				
PhNH ₃ ⁺ 4.6	TMS ₂ NH 26																					
PhN(Me) ₂ H ⁺ 5.2	PhNH ₂ 31																					
Ph ₂ NH ₂ ⁺ 0.78	 44																					
H ₂ NNH ₃ ⁺ 8.12																						
Et ₃ NH ⁺ 11.1																						
 8.36																						
Heterocycles	Carboxylic acids	Protonated Species																				
 20.9	$X-C(=O)OH$ <table style="margin-left: 20px;"> <tr><td>X = CH₃</td><td>4.76</td></tr> <tr><td>CH₂NO₂</td><td>1.68</td></tr> <tr><td>CH₂F</td><td>2.66</td></tr> <tr><td>CH₂Cl</td><td>2.86</td></tr> <tr><td>CH₂Br</td><td>2.86</td></tr> <tr><td>CCl₃</td><td>0.65</td></tr> <tr><td>CF₃</td><td>-0.25</td></tr> <tr><td>H</td><td>3.77</td></tr> <tr><td>C₆H₅</td><td>4.2</td></tr> <tr><td>CH₃CHCH</td><td>3.0</td></tr> </table>	X = CH ₃	4.76	CH ₂ NO ₂	1.68	CH ₂ F	2.66	CH ₂ Cl	2.86	CH ₂ Br	2.86	CCl ₃	0.65	CF ₃	-0.25	H	3.77	C ₆ H ₅	4.2	CH ₃ CHCH	3.0	 -12.4
X = CH ₃		4.76																				
CH ₂ NO ₂		1.68																				
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CF ₃		-0.25																				
H		3.77																				
C ₆ H ₅		4.2																				
CH ₃ CHCH	3.0																					
 18.6		 -7.8																				
 4.9		 -6.2																				
 29.4		 -3.1																				
		 -2.05																				
		 -2.2																				
Amides	Protonated Heterocycles	Alcohols																				
 23.3	 6.0	<table style="margin-left: 20px;"> <tr><td>HOH</td><td>15.7</td></tr> <tr><td>MeOH</td><td>15.5</td></tr> <tr><td>iPrOH</td><td>16.5</td></tr> <tr><td>tBuOH</td><td>17.0</td></tr> <tr><td>C₆H₅OH</td><td>9.95</td></tr> <tr><td>pO₂NC₆H₄OH</td><td>7.1</td></tr> <tr><td>pOMeC₆H₄OH</td><td>10.2</td></tr> </table>	HOH	15.7	MeOH	15.5	iPrOH	16.5	tBuOH	17.0	C ₆ H ₅ OH	9.95	pO ₂ NC ₆ H ₄ OH	7.1	pOMeC ₆ H ₄ OH	10.2						
HOH	15.7																					
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