BPS 2110 Intro to Biopharm
Mid Term 1 Answers

1. Complete the following table describing the stages of drug development. (**7 points**)

	Average Time taken (years)	End Point Designation (Name + acronym)
Discovery	1 - 3	Drug Candidate
Development	1 - 2	Investigational New Drug (IND)
Clinical Trials	1 - 5	New Drug Application (NDA)
FDA Approval	0.5 – 1.5	

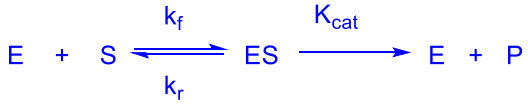
2. Name the four general types of secondary protein structure and describe how each is represented on a ribbon diagram. If applicable, how is the "direction" of each described? (**10 Points**)
   a) α-helix – appears as a coiled ribbon or cylinder. Flat end at N-terminus, arrow or point at C-terminus (pointing in direction of C-terminus).

   b) β-sheet (strand) – flat ribbon. Flat end at N-terminus, arrow or point at C-terminus (pointing in direction of C-terminus).

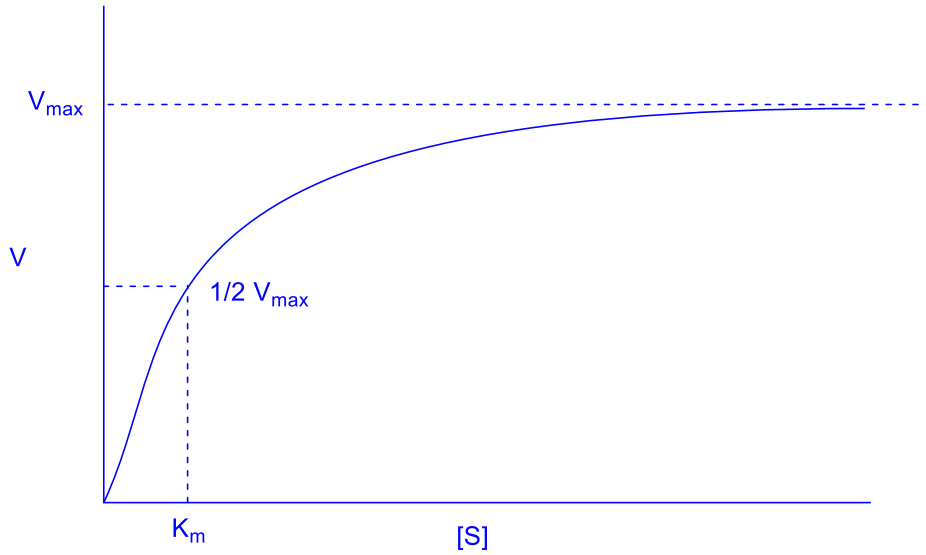
   c) Loop – thin tube, "spaghetti-like"

   d) Turn – sharp change in direction on a loop (approx 180°). May be a different color on some representations

3. The Michaelis-Menton equation is used to describe enzyme performance.
   a) What is the <u>chemical</u> equation used to describe enzyme function in terms of enzyme and substrate (be sure to include all parameters)? (**2 Points**)



   b) Draw a general kinetics plot (graph) that describes the rate of formation of product of an enzyme under Michaelis-Menton conditions (be sure to label the axes and key points on the graph). (**5 Points**)



c) What is the <u>mathematical</u> equation that describes the shape of the graph in part b? (**2 Points**)

$$V = \frac{dP}{dt} = \frac{V_{max}[S]}{Km + [S]}$$

d) Two key parameters are used when describing Michaelis-Menton kinetics. For each of the following parameters, describe what they are (definition), and how they can be used **(4 Points**)

i. K_{cat}

- turnover rate
- larger K_{cat} = faster (easier) reaction
- measure of efficiency of reaction of ES complex

ii. K_d

- Ratio k_r/k_f
- Measures tightness of binding between enzyme and substrate
- Small k_d = tight binding

e) How is the ratio Kcat/Km used? Provide two uses. (**2 Points**)

- index of enzyme efficiency (compare enzymes)
- specificity constant
- compare efficiency of different substrates
- high ratio = efficient enzyme

(any 2)

4. LogP and LogD are common measurements used in the pharmaceutical industry.

a) What do these parameters measure? (**1 Point**)

Lipophilicity

b) What is the equation used to measure LogP, and what conditions are required to use this equation? (**2 Points**)

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

Must measure at pH at which the drug is neutral

c) What are the two biggest disadvantages of using LogP? (**2 Points**)

- Each molecule requires different buffer (pH)
- Measurements may not be at physiological conditions (pH 7.4)

d) What is the key difference between LogP and LogD? (**1 Point**)

- LogD is measured at a defined pH (most common is 7.4)

e) What are the two methods used to measure LogP and LogD (brief description of each)? (**4 Points**)

Method A:

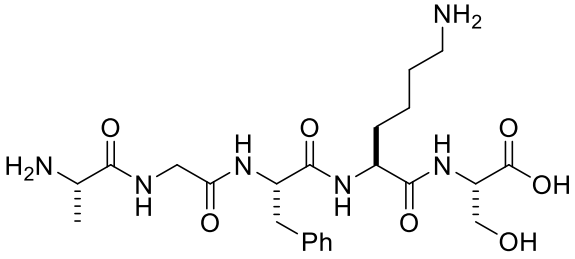
1. Make solution of drug in water (or octanol)
2. Add equal volume of octanol (or water)
3. Mix, then allow layers to separate
4. Measure concentration of drug in 1 or both layers

Method B:

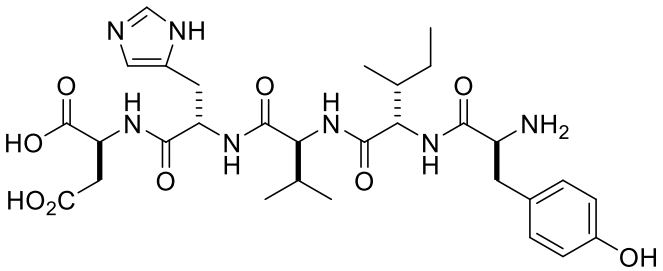
1- Run sample through special HPCLC column
2- Retention time used to calculate LogP or LogD

5. What is the amino acid sequence of the following peptides? (**4 Points**)

a)



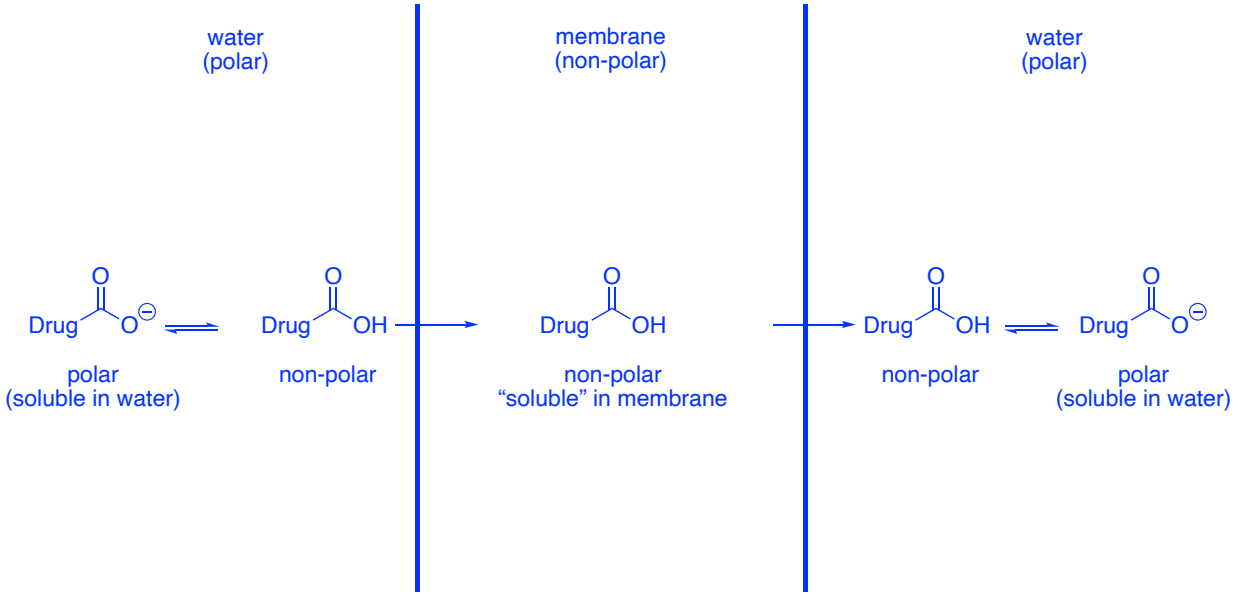
Alanine-Glycine-Phenylalanine-Lysine-Serine



Tyrosine-Isoleucine-Valine-Histidine-Aspartic Acid

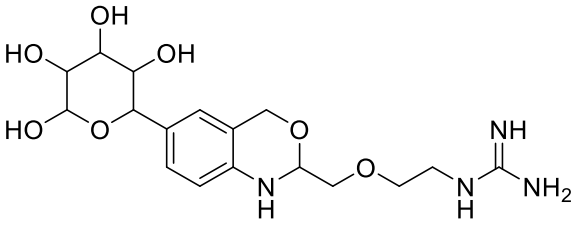
b) (list N-term to C-term)

6. Many drugs approved for use in humans are acids, which helps them enter cells. Use a diagram to show why acids generally can be transported into and out of cells. (**5 Points**)



7. Predict whether the following compounds are likely to be orally bioavailable or not, and provide a brief justification for each. (**5 Points**)

a)

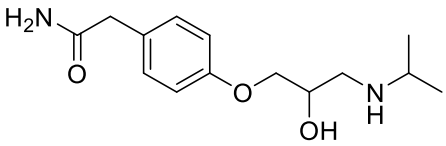


MW = 398.4
MlogP = 4.8 (>4.15)

H-bond donors = 9 (>5)
H-bond acceptors = 11 (>10)

likely not bioavailable, violates three rules

b)

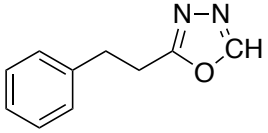


MW = 266.3
$LogD_{7.4}$ = 0.58 (<1)

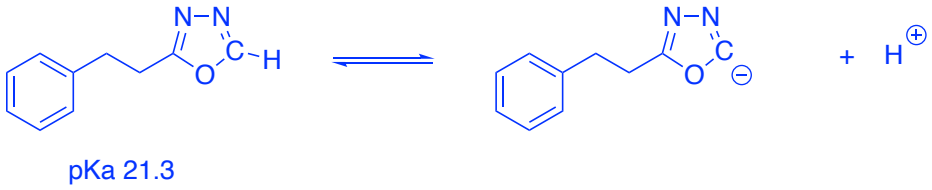
H-bond donors = 4
H-bond acceptors = 5

likely bioavailable, only violates one rule

8. The following molecule was once considered as a drug candidate by a large pharmaceutical company

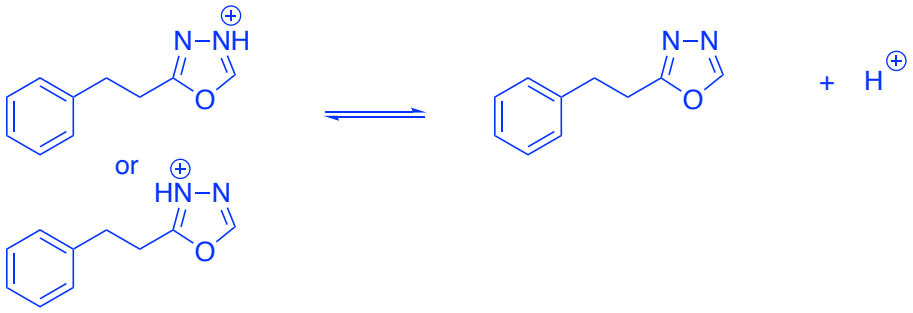


a) Write the pK_a expression for the drug acting as an **acid** and identify an appropriate pK_a value using the table provided. (**3 Points**)



pKa 21.3

b) Write the pK_a expression for the drug acting as a **base** and identify an appropriate pK_a value using the table provided. (**3 Points**)

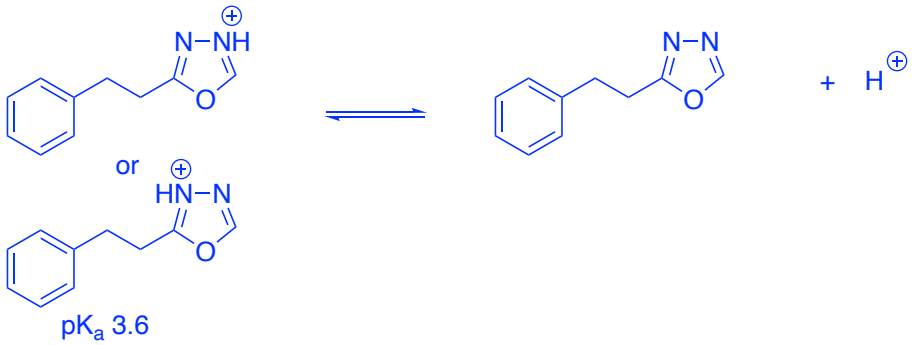


pK_a 3.6

c) Use your pK_a data to predict whether the drug will act as an acid or base when used as a drug, and briefly explain your answer. (**2 Points**)

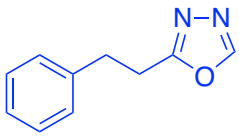
- Group will act as a base
- The pKa of the group, acting as an acid (part a) is outside the range of allowed for water (-1.5 to 15.7). this expression can be ignored (the drug can only be in the protonated form)
- The pKa for the group acting as a base (part b) is inside this range, and is therefore relevant for this molecule in water solution

d) Use your pKa data to predict whether the molecule is likely to be soluble at pH 7.4. (**2 Points**)



pK_a 3.6

pH is more than pKa. At pH 7.4 the molecule will be in the de-protonated state.



Drug is neutral and likely insoluble in water.