Problem Set 5

1.   Draw two plots (A and B together, then A and C together) that show how an enzyme-catalyzed reaction rate (velocity) varies with substrate concentration. For Case A, there is no inhibitor present. For Case B, there is a competitive inhibitor present. For Case C, there is a noncompetitive inhibitor present. Be sure to show the K_M and the V_{max} for each of the three cases on the two plots. Clearly describe the difference between competitive and noncompetitive inhibitors.

2.   For the three cases in the previous problem, draw two Lineweaver-Burk plots and clearly label each of these.

3.   For an enzyme catalyzed reaction, calculate the fraction of enzyme sites filled with substrate when the substrate concentration is 2/3 of the Michaelis constant (K_M).

4.   Examination of a receptor interaction study of three drugs undergoing clinical trials revealed affinity constants K_i's of 40 nM, 2 µM, and 900 pM for Drugs A, B, and C respectively. Drug A was found to have greatest efficacy, while Drug B was found to have the lowest efficacy.

        a.   Draw a dose-response plot that illustrates the curves for drugs A, B and C.

        b.   Clearly define what is specifically meant by a drug's efficacy and potency

        c.   Describe the relative potency and efficacy for drugs A, B, and C; clearly support your answer.

        d.   Compare the relative affinities of the three drugs for the receptor binding site and clearly support your answer.

5.   The side chain in cysteine has a pKa of 8.00. For a pH of 7.4, draw the complete Lewis structures of the two most concentrated forms of cysteine. Show which form is present at a greater concentration. Calculate the percentage of cysteine that is in the most concentrated form at this pH.

6.   Dopamine has a pK_a of 10.6; draw the Lewis structure of the most prevalent form of dopamine at physiological pH. Comment on the tendency of this form to cross the blood-brain barrier.

7.   Salmeterol is a β_2 adrenoreceptor agonist that is a bronchodilator with a slow onset and a long duration of action due to its log P value of 3.88.
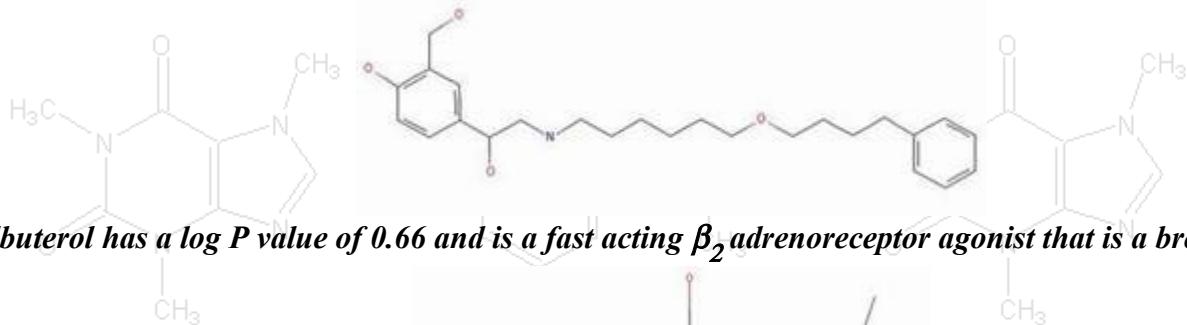
Albuterol has a log P value of 0.66 and is a fast acting β₂ adrenoreceptor agonist that is a bronchodilator.

a. Use thermodynamics and molecular structures to clearly explain the basis for the difference in P values for these two substances.

b. If 3 mmoles of albuterol were added to a mixture of 25 mL of water and 50 mL of 1-octanol, calculate the mmoles of albuterol that would partition to the 1-octanol phase.

c. Salmeterol has a β₂ adrenoreceptor affinity constant K_i of 53 nM and an efficacy of 65%; albuterol has β₂ adrenoreceptor affinity constant K_i of 2.5 μM and an efficacy of 85%. Formoterol has β₂ adrenoreceptor affinity constant K_i of 75 nM and an efficacy of 100%. Use the same graph to plot the dose-response curves for these three β₂ adrenoreceptor agonists.