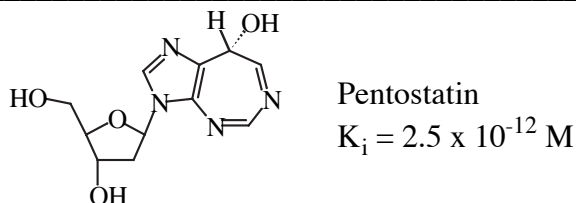
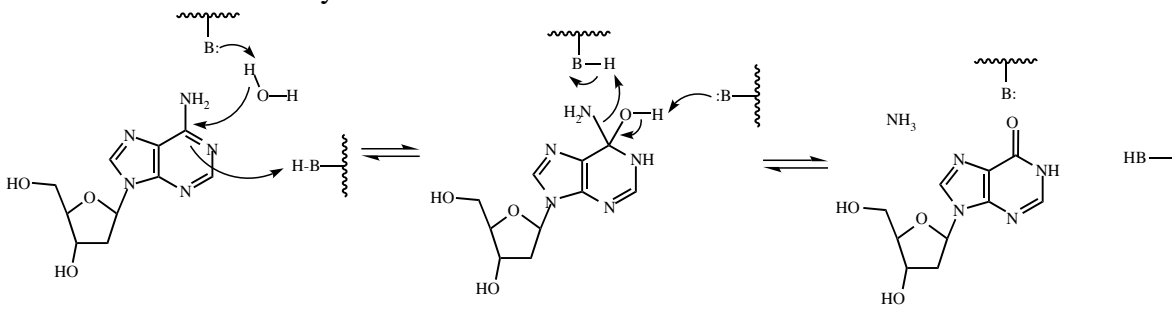


80-100 A; 66-79 B; 50-65 C; 36-49 D; 0-35 F

1. Adenosine deaminase catalyzes the reaction shown below.



(a) At low adenosine concentrations (when  $[S] \ll K_M$ ), what concentration of pentostatin will be required to cause 50% inhibition of adenosine deaminase? Briefly explain the basis of your answer.

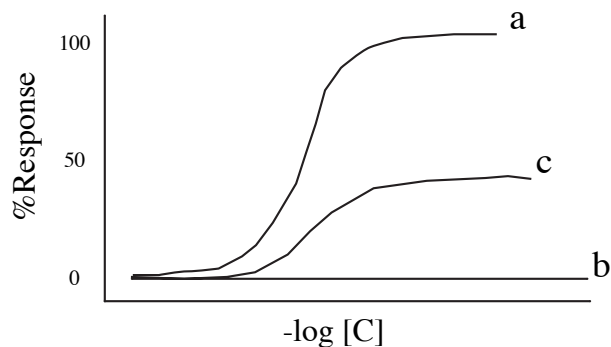
**6 pts. No calculations or equations needed. We learned that the  $K_i$  is the concentration required to yield a 50% decrease in enzyme activity (class notes, textbook and homework problem 19.**

(b) Provide an explanation for the activity of pentostatin.

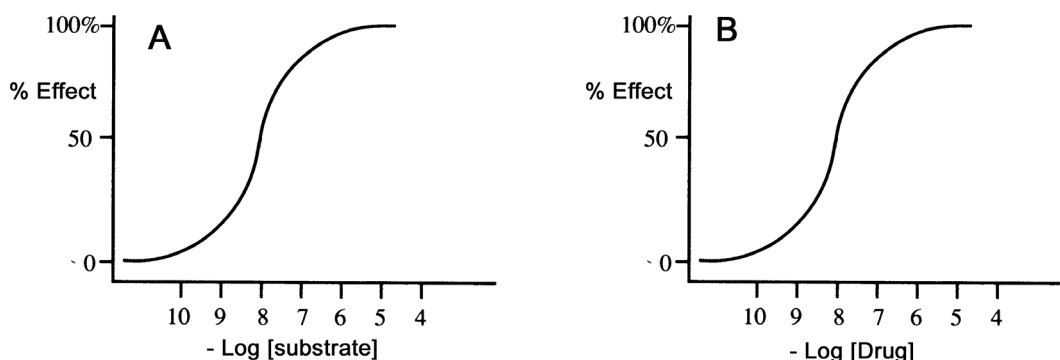
**6 pts. First note that pentostatin is a very potent enzyme inhibitor. Why? It is a transition state analog. A stable structure that resembles the transition state of the enzymatic reaction. According to Pauling's longstanding hypothesis, the transition state should be the most tightly bound species along the reaction coordinate.**

2. Draw and clearly label the dose-response curves for (a) a naturally-occurring neurotransmitter, (b) a competitive antagonist and, (c) a partial agonist.

12 pts (4 each curve)



3. Consider the plot shown below and answer the following questions:



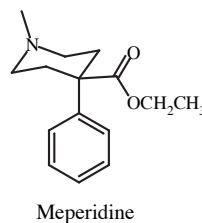
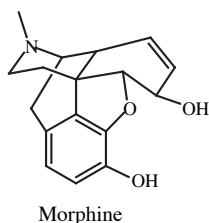
(a) What is the correct medicinal chemistry term to describe the drug?

**7 pts. Agonist**

(b) What is the  $K_D$  of the substrate?

**7 pts. The 50% response point tells you the  $K_D$ . Here, concentration equals  $-\log[8]$  or  $1 \times 10^{-8} \text{ M}$**

4. Morphine binds much more strongly to the opiate receptor than meperidine. Consider the structures of these two drugs and suggest a reason why morphine binds better than meperidine. Hint: morphine is can be viewed as a conformationally restricted analog of meperidine)

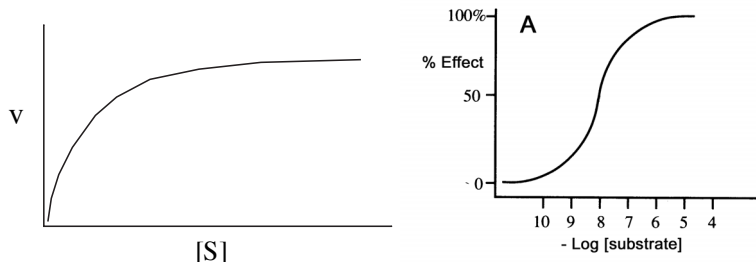


**10 pts. Conformationally restricted analogs contain a lot of rings to impart a rigid structure to the molecule. If such a rigid analog holds the proper functional groups into the proper positions for interaction with the receptor it is considered "preorganized" for binding. Thus, upon binding to the receptor does not pay an "entropic penalty" for the loss of conformational mobility (disorder) in the molecule.**

5. Explain how it is possible for very small quantities of receptor-targeted drugs to elicit a large physiological response?

**10 pts. Receptors bind selectively to their agonist. Importantly, binding of the agonist switches on (or off) a property of the receptor that serves to amplify the "signal" sent by the agonist. Properties like the flow of ions, transcription of a gene, or uptake of a neurotransmitter. Thus, small amounts of a drug provide a signal that is amplified. Conversely, antagonists block the signalling of autocoids that otherwise would be amplified.**

6. Consider the plot of the velocity of an enzyme-catalyzed reaction as a function of substrate concentration and the plot of receptor response versus substrate (autocoid) concentration. Why does each curve "flatten out" at high substrate concentration?

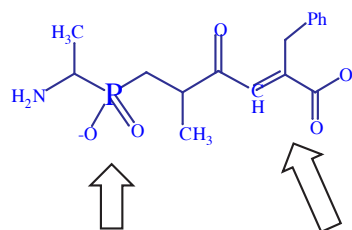
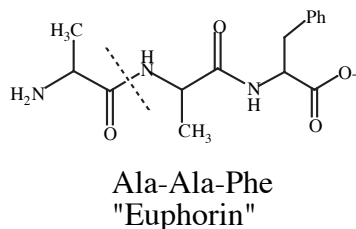


**10 pts.** In the case of the enzyme velocity on the left... as substrate conc increase the active site of the enzyme becomes saturated - all of the enzyme active sites are occupied by substrate... at this point the velocity (rate) of the enzyme-catalyzed reaction cannot get any higher.

In the case of the receptor binding curve on the right... as substrate (autocoid) concentration increases the binding site on the receptor becomes saturated - all of the receptor binding sites are occupied by autocoid... at this point the response of the receptor cannot get any higher.

The binding of small organic molecules by receptors and enzymes are fundamentally the same thing... equilibrium, noncovalent binding that can saturate at high substrate concentrations.

7. The normal substrate for a zinc protease known as "euphorase" is shown below. The amide bond that is cleaved by the enzyme is marked. Design a peptidomimetic transition-state inhibitor for this enzyme. **12 pts.**



Stable tetrahedral structure that mimics transition state of the enzymatic reaction. See: Monopril or enalaprilate from our discussion of ACE inhibitors.

Peptidomimetic. Contains most of the same functional groups found in peptides... except for the amide bonds which are easily degraded in vivo.

8. Imagine that Ala-Ala-Phe ("euphorin") is a endogenous (naturally occurring) neurotransmitter that is normally present in the human brain at low levels and induces feelings of extreme well being (euphoria). What pharmacological effect will your inhibitor have?

**10 pts.** Inhibits degradation of euphorin, euphorin concentrations increase, feelings of euphoria increase in the patient.

9. (a) If you wanted to design a euphorin receptor agonist, what would you use as a lead compound? **5 pts.** Use the natural substrate as a lead compound... it is the one compound that you are aware of that binds to the active site of the enzyme.

(b) What biological effect would such an agonist have? **5 pts.** A euphorin agonist would, like the autocoid, induce feelings of extreme well being in the patient.