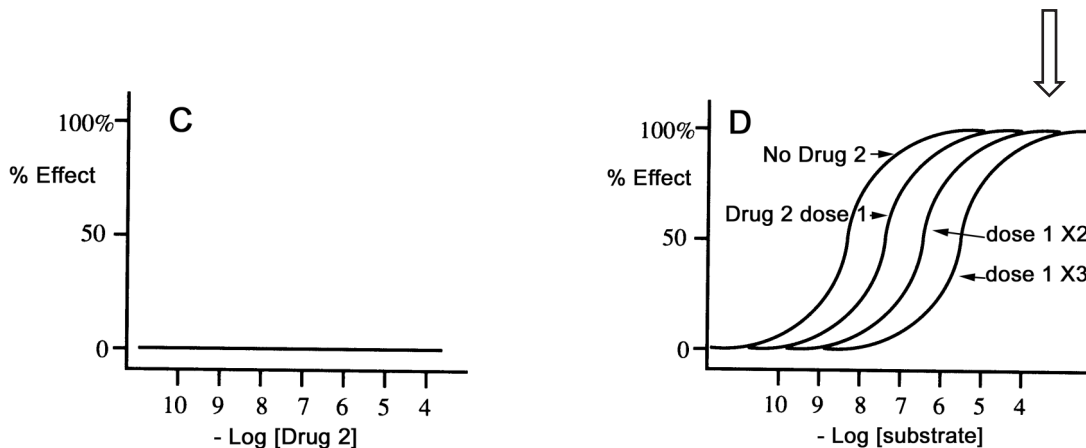


CHEM 317
Winter 2003, Exam #2

Avg 75. 100-82 = A; 81-60 = B; 40-59 = C

1. Please consider the graphs shown below that describe the interaction of a drug and the natural ligand (substrate) at a receptor.



(a) 8 pts. What is the term that medicinal chemists use to describe the receptor-binding properties of this drug?

Competitive Antagonist

(b) 8 pts. In the presence of the drug, does it require more or less of the substrate to achieve 100% response (effect) of this receptor?

MORE substrate is required to reach 100% response

(c) 8 pts. Explain the physical basis for your answer to part b. That is, HOW does drug alter the ability of the receptor to interact with its natural substrate?

The drug binds to the receptor, occupying the site where the autocooid (natural substrate) normally binds

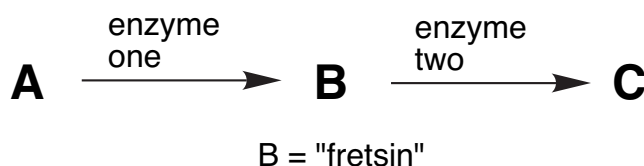
(d) 8 pts. What is the approximate value of K_D for the natural substrate? Give a number with units.

K_D is the concentration that gives 50% of the maximal response on the plot shown above. $-\text{Log}[S]=8.5$, $\text{Log}[S]=-8.5$, $[S] 3.2 \times 10^{-9}$ M (all of the plots we've looked at the units on the horizontal axis have been molar).

(f) 8 pts. Why, in all cases, do the curves in plot D plateau (level off) as we move to the right? (See arrow on plot D).

In each case, as the substrate concentration increases more and more of the receptor is in the "bound" form. At very high substrate concentrations ALL of the receptors are occupied by substrate. All receptor binding sites are saturated.

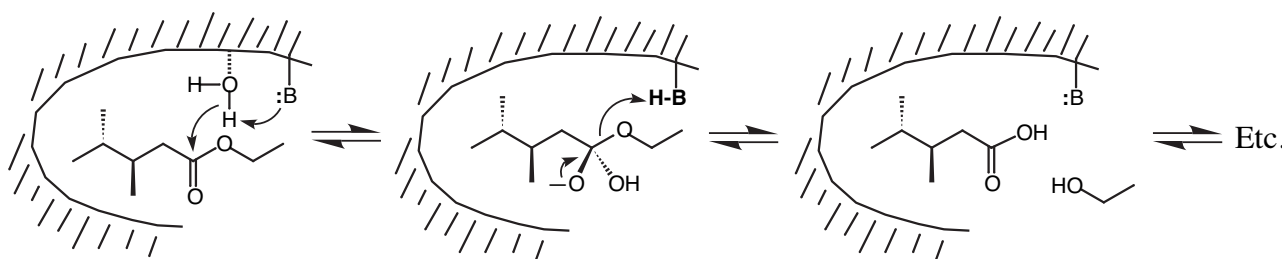
2. Consider the biosynthetic scheme shown below in which our body enzymatically converts a biologically inactive precursor **A** into an "active" form **B**. The active form, **B**, is then enzymatically degraded to an inactive metabolite **C**. Imagine that **B** is a molecule known as **fretsins**, which increases heart rate in mammals.



(a) 8 pts. Further imagine that screening of a combinatorial library of organic compounds has identified a molecule that inhibits **enzyme 2** in this biosynthetic pathway. What is the expected physiological effect resulting from administration of this enzyme inhibitor?

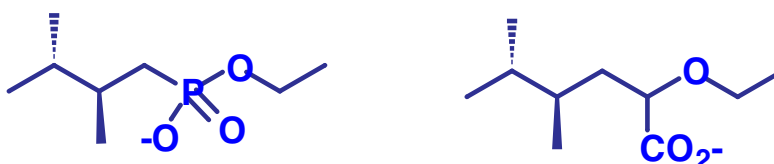
Inhibition of enzyme two blocks the degradation of B. Accordingly, concentrations of B (and possibly A) increase. As concentrations of B increase biological effects associated with this molecule will increase... in this case that means that heart rate increases.

3. Consider the enzymatic reaction shown below. The enzyme selectively hydrolyzes the stereoisomer shown (and not other stereoisomers).



(a) 9 pts. Design a transition state analog inhibitor for this enzyme.

The problem draws directly from our in-class discussion of transition state analogs. We discussed transition state analog inhibitors for angiotensin converting enzyme (ACE). ACE catalyzes the hydrolysis of amides. The mechanism involves a tetrahedral intermediate just like the mechanism for acetylcholinesterase. The goal is to design a STABLE molecule that resembles the structure of the transition state. In our discussion of ACE, we learned two stable chemical structures that mimic the tetrahedral intermediates seen in carbonyl reactions. They are shown below. In addition, we saw a common theme in almost all of the inhibitors that we looked at... they retain key structural elements seen in the normal substrate - but do not contain the bonds that are made or broken in the normal enzymatic reaction. The idea is this... we KNOW that the substituents seen in the natural substrate binds well to the active site of the enzyme... so let's use them to gain affinity for the active site.



(c) 9 pts. Design an affinity labeling agent for this enzyme.

As discussed in class, affinity-labeling agents contain two structural "domains" (1) the affinity domain will resemble the natural substrate - minus the bonds that are formed or broken in the normal enzymatic reaction and (2) the labeling domain is a moderately reactive functional group that forms a covalent bond with some nucleophilic amino acid residue at the active site of the enzyme. Here use the side chain from the normal substrate. And use one of the two possible labeling groups that I provided you in lecture.



4. 9 pts. List three general chemical strategies that enzymes use to catalyze reactions.

General acid-base catalysis, catalysis by proximity, covalent catalysis, electrostatic catalysis, ground state destabilization by strain and distortion or desolvation, selective transition state binding...

5. In lecture, and in the textbook, we had a chance to consider the development of the statin drugs (drugs like Lipitor). These drugs inhibit the enzyme known as HMG-CoA reductase.

Here are some facts:

K_M of natural substrate for HMG-CoA reductase is 1×10^{-5} M.

K_i of mevacor for HMG-CoA reductase is 6.4×10^{-10} M

(a) 8 pts. Which has a higher (better) noncovalent binding affinity for the enzyme, the natural substrate or mevacor? Give a *very brief* justification of your answer.

K_M and K_i are dissociation constants (K_D s), so lower numbers mean better binding.

Mevacor binds more tightly to the enzyme than the natural substrate.

(c) 8 pts. Imagine that inside a human patient taking mevacor the following conditions exist: Concentration of natural substrate = 1×10^{-8} M and the concentration of mevacor = 1×10^{-7} M Calculate the velocity of the enzyme under these conditions. Express your answer in terms of V_{max} .

Use this equation that I gave you...

$$v = \frac{V_{max} [S]}{K_M \left(1 + \frac{[I]}{K_i} \right) + [S]}$$

Plugging and chugging with the numbers that I gave you provides $v = 6 \times 10^{-6}(V_{max})$ That is, the enzyme is almost completely inhibited... nice.

6. 9 pts. How does aspirin work?

This question might seem vague at first... but at this point in your medicinal chemistry training you know that there are several distinct points that must be addressed to answer the question "how does this drug work?".

(a) What is the target? As we discussed in lecture, aspirin inhibits an enzyme called cyclooxygenase 2 (COX2)

(b) How does the drug action cause a biological effect? COX2 is responsible for the biosynthesis of molecules that cause inflammation. Blocking this enzyme blocks inflammation.

(b) How does the drug interact with the target? The drug is an affinity labeling agent. More specifically, aspirin transfers its acetyl group to a serine residue deep in the active site of the enzyme. As the article posted on the course website shows, this reaction is catalyzed by two tyrosine residues at the active site (I expect that you read the article, but I did not expect you to know this last part).

