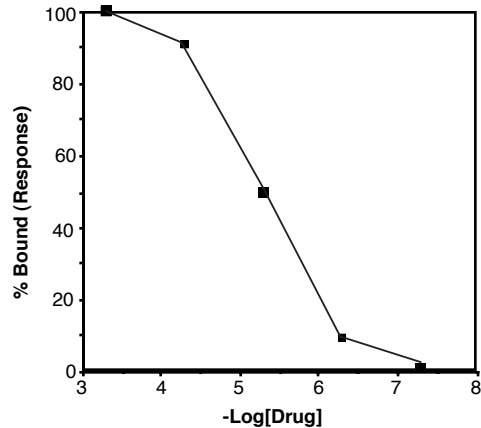
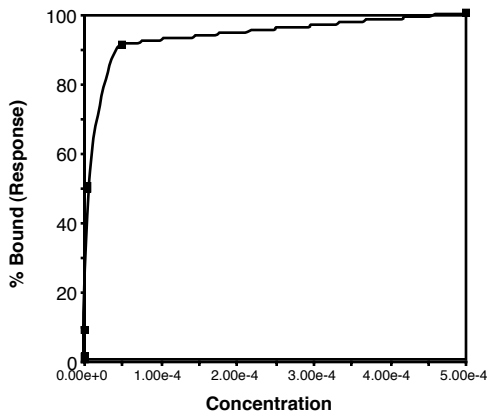


CHEM 4170 Homework 2 - ANSWERS

1. Receptor binding curves. Make a plot of %drug-bound versus $-\log[\text{drug}]$ for a drug whose K_D is 5×10^{-6} M. Make a plot of %drug-bound vs $[\text{drug}]$ for this same system. To do this calculate %drug-bound at drug concentrations of 5×10^{-8} M, 5×10^{-7} M, 5×10^{-6} M, 5×10^{-5} M, and 5×10^{-4} M. To calculate % drug bound, use the equation that we have used previously (shown below). Are there advantages that you see for the plot using $-\log[\text{drug}]$?

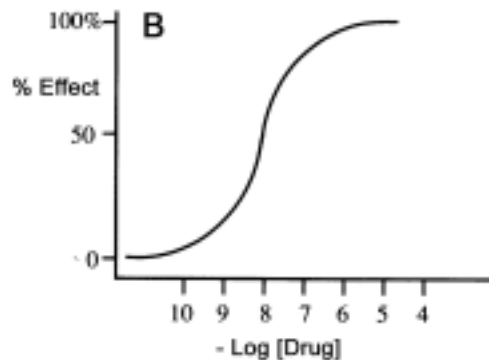
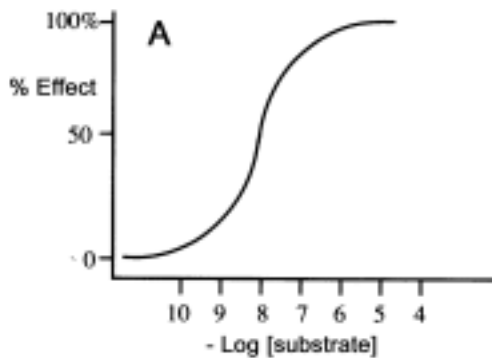
$$1/(K_{eq}D_{free} + 1) = T_{free}/T_{total}$$

Here are the plots:



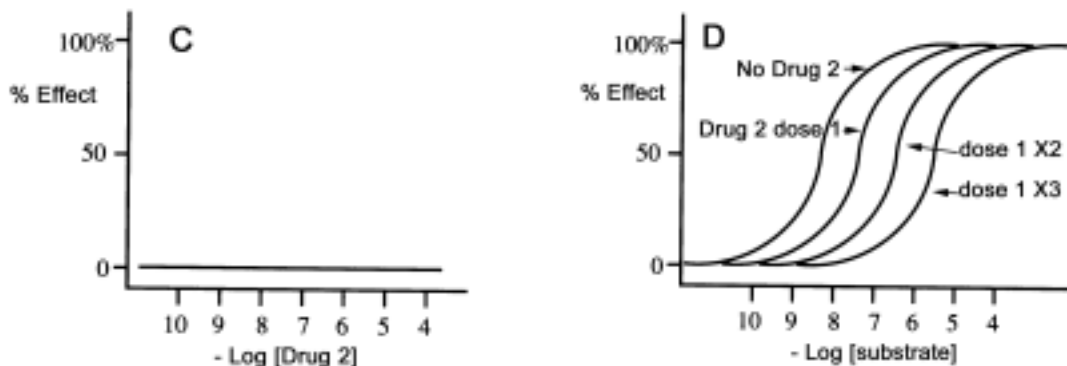
Advantages of the Log plot: Midpoint of the plot is K_D for drug. Easily identified by inspection. Data for several different drugs could be placed on one graph and it would be easy to tell which drug binds better.

2. In Panel A (below) a plot of the % effect (response) versus the log of the natural substrate concentration for this receptor is given. In Panel B we have a similar plot, except we see the response produced by drug binding at this receptor. What is the general term that is used for the natural ligand of a receptor? There is a generic name or term given to a compound which elicits a response such as this. What is it? How well does the drug bind to the receptor compared to the natural substrate? Be quantitative (what is the K_D for the drug and the natural substrate?)



- Natural ligand for receptor is call the "autocoid"
- "Agonist" gives same type of response as the autocoid.
- In this example it appears that drug and autocoid have identical K_D values.
- The K_D value looks like about 1×10^{-8} M (midpoint of the curve).

3. In Panel C we see the response of the same receptor when a second drug, Drug 2, is given by itself. In Panel D we see the results of a set of experiments with Drug 2 and the natural substrate for this receptor. In the first experiment drug 2 is absent and we see the dose response from the substrate. In the next experiment Drug 2 is given at one dose along with variable doses of the substrate so as to produce the dose response curve. Similar experiments are done to produce the other curves at 2 and 3 times the initial Drug 2 dose. A generic name or term is given to a compound such as Drug 2 which produces this type of effect. What is it?

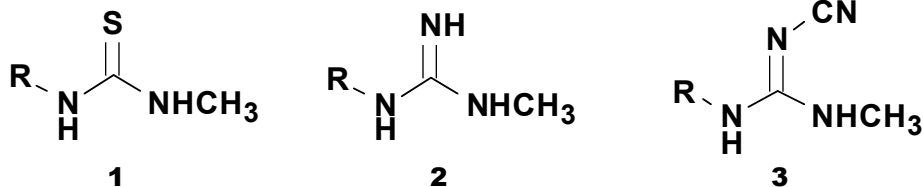


Drugs that give this type of response are called "competitive antagonists".

4. Explain the mechanism of action of Drug 2 and how it produces the phenomena exhibited in panel D above.

Normally, the autocoid binds to the receptor and activates the receptor. In this case the drug binds to the same site that the autocoid normally binds and blocks the ability of the autocoid to bind and activate the receptor.

5. In the development of the drug Cimetidine, which is used to decrease acid secretion into the stomach, and prevent the discomfort of heartburn, acid reflux and pre-ulcerative conditions, the molecules tested had an imidazole group at one end of the molecule, and, among others, one of the three groups shown below at the other end of the molecule.

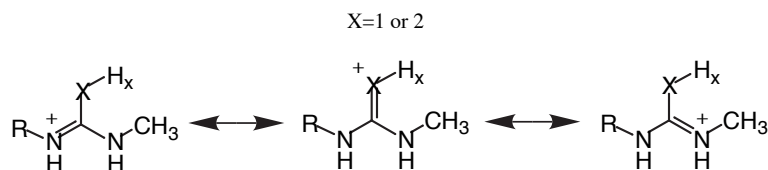


a. What was the rationale for including the imidazole ring?

The natural ligand, histidine, contains an imidazole ring. In this case the autocoid served as the lead compound in drug discovery.

b. Of the structures **1-3** shown above which is the most basic and why? In answering this question use words, resonance forms, etc. in your explanation. Which structure will be more easily protonated (at any given pH)?

The most basic is 2. In each case, you can draw the same resonance structure. So, what determines the basicity of the molecules is the electronegativity of X. The more electronegative X will be less basic. X=NH is the least electronegative, thus 2 is the most basic.



c. Which of the structures **1-3** was used in Cimetidine and what was the rationale for its inclusion?

Structure 2 was used in cimetidine. Hammett plots identified a QSAR suggesting that this functional group might be effective.

6. What are two key properties of receptors that allow small doses of an appropriate drug to elicit a significant biological response. (I discussed these key features in our first lecture on receptors).

Receptors SELECTIVELY bind an autocoid and AMPLIFY this signal. So, a single molecule of drug can block signal amplification (or activate a receptor resulting in an amplified signal). Thus, small amount of drug gives large effect... due to amplification.

7. Consider the following situation. The natural ligand for a receptor has a K_B of $1 \times 10^6 \text{ M}^{-1}$. A competitive antagonist for this receptor has a K_B of $1 \times 10^9 \text{ M}^{-1}$. Biological studies show that activation of the receptor occurs at natural ligand concentration of about $1 \times 10^{-6} \text{ M}$ ($1 \mu\text{M}$). Under these conditions, what concentration of drug will be required to place 90% of the receptor in the drug-bound form (i.e. 90% of the receptor is "blocked")? (We derived the necessary equations in class).

We derived the following relationship in lecture...

$$[\text{Rec} \cdot \text{Drug}] / [\text{Rec} \cdot \text{Autocoid}] = (K_{\text{Bdrug}} [\text{Drug}]) / (K_{\text{BAutocoid}} [\text{Autocoid}])$$

$$90/10 = (1 \times 10^9 \text{ M}^{-1} [\text{X}]) / (1 \times 10^6 \text{ M}^{-1} [1 \times 10^{-6} \text{ M}]) \quad \text{X} = 9 \times 10^{-9} \text{ M} \text{ (9 nM drug is required)}$$

8. Why did addition of a $-\text{CH}_3$ and a $-\text{OCH}_3$ group make the pyridine ring in omeprazole more basic? Why does this structural feature help omeprazole accumulate inside acidic compartments of the stomach-acid producing parietal cells? (Hint: draw the rxn in question... the protonation of the pyridine ring. Then use resonance structures to consider how substituents on the pyridine ring affect the stability of the compound on each side of the equation... that is, how substituents alter the equilibrium of the reaction).

The unprotonated pyridine is lipophilic and easily crosses membranes (into acidic compartments). Once inside an acid compartment the pyridine ring is protonated. This makes the molecule charged and very hydrophilic, thus unable to cross membranes and escape the acidic compartment.

Any electron-donating substituent will increase the basicity of the pyridine ring. Look at a table of Hammett substituent constants (sigma, σ) to find other electron donating substituents.

9. Suggest two other substituents that would have a similar effect on the basicity of the pyridine ring found in omeprazole.

Try -NH_2 and $\text{-CH}_2\text{CH}_3$

10. Imagine that you have been placed in charge of a drug-development team with the goal of developing a receptor antagonist. There are no known lead compounds. What would you use as the lead compound? (Note: this is a general question... you do not need to know anything about the structure of the natural ligand for the target receptor.). Could you use a similar strategy in the design of a reversible enzyme inhibitor?

Use the structure of the natural ligand, the autocoid, as a starting point ("lead") for drug discovery.