

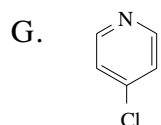
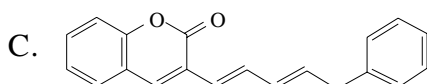
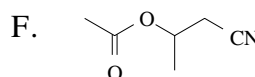
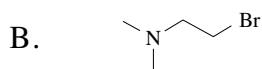
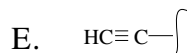
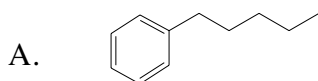
CHEM 4170

Homework #1

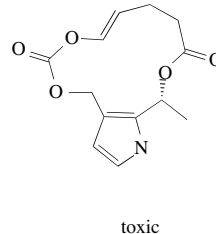
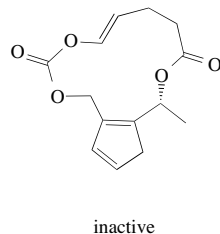
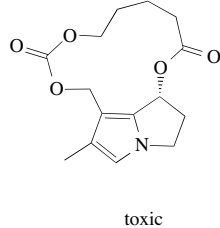
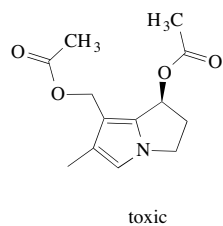
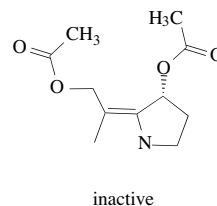
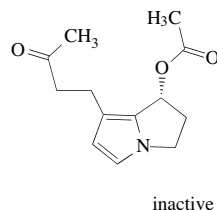
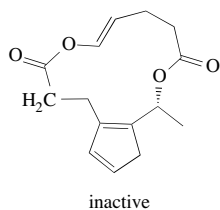
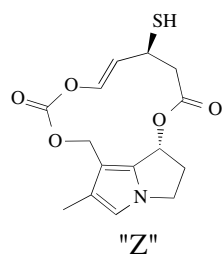
0. Work problems 1-18 at the end of Chapter Two and problem 1 at the end of Chapter Three in the textbook.

1. Why is the log P value of a drug important? (i.e. why is a balance of lipophilicity and hydrophilicity important?)

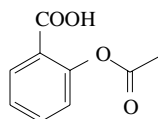
2. Use the log P table that I handed out in class to calculate either the log P for the given molecules or the π_x for the given substituents. There are many correct answers so you must show how you calculated your values. (Explain: why can there be different correct answers?)



3. This example, highlights the fact that the principles of medicinal chemistry carry over into the field of toxicology. Compound "Z" shown below is highly toxic. Given the series of compounds and their biological activities, draw the pharmacophore for the toxicity first observed in "Z". By definition, the pharmacophore is the *minimum structural* unit that retains the biological activity in question.



5. Draw three analogs of aspirin (3), each containing a single bioisosteric substitution.

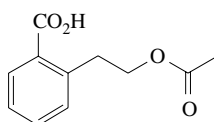


Aspirin (3)

6. Though the concept of bioisosteric modifications was introduced as a method of choosing *minor* modifications on lead compounds, sometimes major changes in biological activity result from a bioisosteric modification. Discuss the possible reasons why a bioisosteric change in a lead compound could cause *major* changes in biological activity. Use a specific isosteric pair as an example.

7. What is the difference between pharmacokinetics and pharmacodynamics? Is pharmacokinetics or pharmacodynamics more important in drug design?

8. A chain homologation approach for the structural modification of aspirin (3) provided the compound shown below. This compound is a less effective analgetic than aspirin. Suggest possible reasons why. Propose analogs of aspirin that fit the other general categories of lead modification (in addition to chain homologation) that we discussed.



9. Let's start this problem with a quick estimate for the volume of water in the human body:

Let's see... Assume an average human weighs 68 kilograms... 70% is water; therefore this human contains 48 kilograms of water. The specific gravity of water is 1 gm/mL, so remember that 1 kilogram of water (1000 gms) is one liter of water. Therefore, I guess that an average human contains about 50 liters of water. I have no idea if this is exactly correct... but we can use this value for our calculations and we'll learn something.

Now, let's use this figure in a calculation. If a drug's binding constant (K_B) for its medicinal target is $1 \times 10^6 \text{ M}^{-1}$ calculate the dose required to block 90% of the biological target's function (dose required to ensure that 90% of the biological macromolecule is bound by drug). For these calculations, assume that the concentration of the biological target is very low relative to drug.

Imagine that an improved analog has a K_B of $1 \times 10^9 \text{ M}^{-1}$. Now, calculate the dose required to block 90% of the biological target.

Hint: we discussed how to calculate fraction-of-target-bound in class. This is also covered on page two of the handout discussing the relationship of the free energy of binding and equilibrium constant.

10. For a compound that has a K_B of $1 \times 10^9 \text{ M}^{-1}$ for a particular biological macromolecule...

(a) Calculate the concentration of drug required to achieve 50% binding of the target.

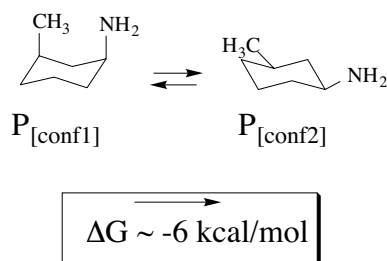
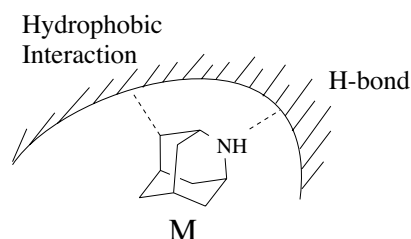
(b) I showed you in lecture how to use the K_B to calculate K_D for this compound. Calculate the K_D . Do you see an interesting, practical feature of the K_D ?

11. We discussed the importance of rigidity in drugs. Compound **M** binds very tightly to its biological target ($K_B = 1.3 \times 10^9 \text{ M}^{-1}$). Imagine that X-ray crystallographic studies have provided a structure showing that **M** interacts with its target as shown in the cartoon below.

(a) Do you think that the K_B of **P** for this biological target will be larger or smaller than that for **M**?

(b) Remember that the free energy of binding (ΔG) can be broken into two components: $\Delta G = \Delta H - T\Delta S$. As you recall, ΔH is known as *enthalpy* and consists largely of weak bonding interactions (sum bonds broken - sum bonds formed). As you also remember, ΔS is known as *entropy* and is a measure of disorder in the system (more disorder = favorable). Explain your answer to part (a) in terms of the enthalpy and entropy of the binding process for each compound.

(c) Given the information about the energy difference between the two conformers of **P** shown below, calculate the relative amounts of the two conformers present. (Hint: look at the equations on the handout that relates ΔG to K_{eq} - this is a different type of problem, but uses the same equations)



(d) After reading the paper on the contribution of hydrophobic interactions to the binding of drugs to their biological targets (posted on the course website), which interaction do you think would contribute more the free energy of binding for these compounds, the hydrophobic interaction or the hydrogen bond? If one of the interactions does not contribute significantly to the free energy of binding, please explain why.

(e) What is the chemical basis for hydrophobic binding interactions?

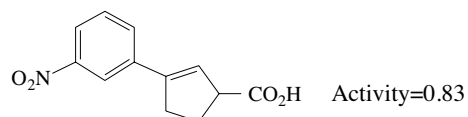
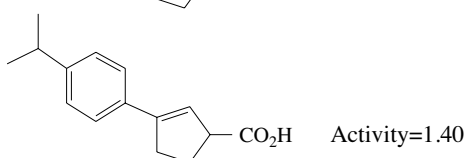
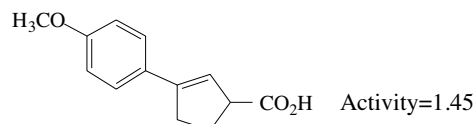
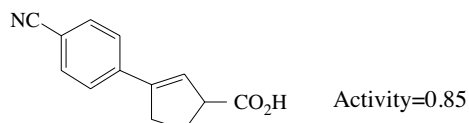
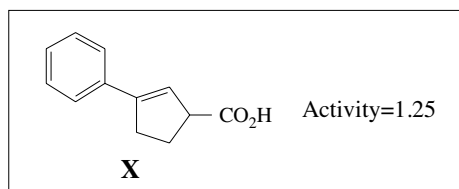
12. Drug **A** and **B** bind to the same biological target with the following binding constants:

A; $K_{eq} = 1 \times 10^5 \text{ M}^{-1}$
B; $K_{eq} = 2.5 \times 10^5 \text{ M}^{-1}$

Which compound binds more strongly to the target? Calculate the difference in the free energy of binding ($\Delta\Delta G$) between these two compounds.

Assuming that the target is present in the cell at low concentration, what fraction of the target biomolecule will be bound by **A** and **B** respectively?

13. Labratech pharmaceuticals has discovered a new lead compound (**X**) for the treatment of canine arthritis. They are now engaged in lead modification studies with the goal of developing this drug. They made four analogs and tested their activity in a bioassay. The results of these studies are shown below.

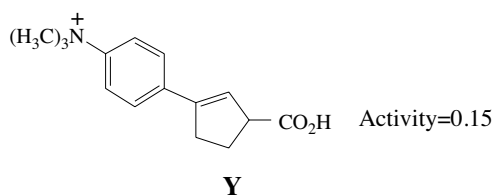


In the hope of limiting the number of analogs that need to be synthesized, Labratech is using QSAR methods to predict the structure of analogs that will be more active than any they have yet discovered.

(a) Construct a Hammett Plot for the series of compounds shown above. Is there a linear correlation (linear free energy relationship; i.e. does the system respond to substitution in a way that allows us to use Hammett sigma values to predict properties)? What is the value for ρ ? (When you look at the tables, use σ_p for para-substituents and σ_m for meta-substituents.)

(b) Using the tables of Hammett σ values posted on the course website, predict two analogs containing the pharmacophore **X** that might be *more active* than any yet prepared by the researchers at Labratech.

(c) Labratech researchers also tested compound **Y** and found its activity to be 0.15. Does this compound lie on the Hammett plot that you constructed in part (a)? If not, suggest possible reasons why.



14. Draw three amino acid side chains and indicate the possible types of "weak" bonding interactions that these functional groups can engage in with drug molecules.
15. What are the possible ways to discover lead compounds? What approach(es) is most widely used in modern drug discovery?
16. List three types of bioassay. Discuss the strengths and weaknesses of each.
17. In lecture, I discussed how the "rule of fives" has recently been developed as a guideline to describe "what a good drug should look like". Do your best to apply the "**rule of fives**" to penicillin (structure 2.2 on page 6 of your text) and valium (structure 2.7 on page 8). Either try to calculate the Log P using the table that I gave you. Or look at the list of "useful links" on my website and try one of the online "log P calculators".

What are the chemical and medicinal principles underlying the "rule of fives"?

18. Why did plants provide the first source of successful medicines?
19. What chemical techniques and strategies are used to prepare compounds for drug screening today? (Read the paper posted on the website regarding diversity oriented chemical synthesis.)
20. At pH 8, how much of the lysine side chain will exist in the protonated, cationic form? (See acid-base calculations handout posted on the course website).
21. The polarity of the environment can drastically alter the strength of weak binding forces. Take a look at the synthetic receptor shown in the "molecular recognition" paper that I posted on the website. Imagine that the two molecules shown in Equation (1) on the first page of the paper were dissolved in water (dielectric constant 78) rather than in chloroform (CHCl_3 , dielectric constant 4.8). The binding constants for these pairs of molecules in chloroform are shown in Table 1 on the first page of the paper. What do you think would happen to the strength of the hydrogen-bonding interactions? What would happen to the strength of the stacking interactions? What would happen to the overall K_a ?
- Note: dielectric constant (ϵ) is a commonly used measure of solvent polarity. The scale runs from water, which is very **polar** (78) to hexane which is very **nonpolar** (1.89). Another important factor to consider is that water is a hydrogen bonding solvent, whereas chloroform is not.
22. How do the ideas regarding solvent effects apply to the binding of drugs to binding pockets in biomolecules? (What is the "solvent environment" like inside most binding pockets of biological macromolecules?)