

Short Answer.

1. List four different ways by which lead compounds have been discovered

- a. **traditional or folk medicine**
- b. **accidental exposure to poisons or toxins**
- c. **side effects of experimental pharmaceuticals**
- d. **systematic screening of compounds using a bioassay**

2. Define: Pharmacodynamics

Interaction of a drug with its biological target

3. Define: Pharmacokinetics

Absorption, distribution, metabolism and excretion of a drug.

4. List the "weak forces" that are involved in noncovalent association of small organic molecules with biological macromolecules.

Hydrogen bonding, ionic bonding, ion-dipole bonds, van der Waals interactions, hydrophobic bonding, charge transfer complexes...

5. Which weak force is probably provides the major contribution to the free energy (ΔG) of binding?

Hydrophobic bonding (See lecture notes and Homework problems 11d and 21)

6. Imagine that the binding pocket in particular protein is lined with leucine, valine and phenylalanine side chains. Do you expect the "effective dielectric constant" on the interior of this binding pocket to be... (circle the best answer)

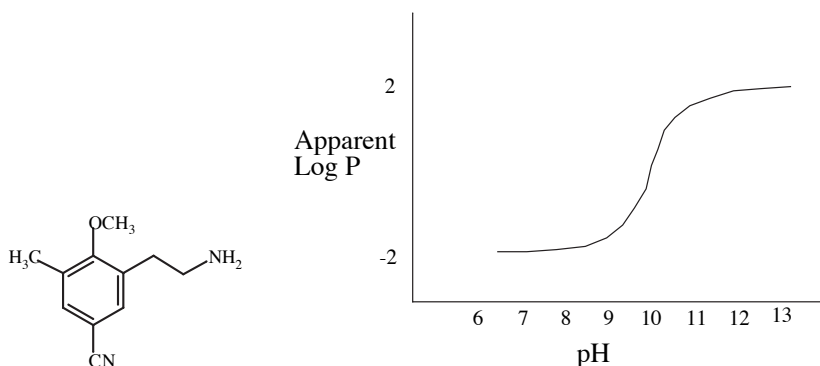
See homework problems 21 and 22 (and the answers to these problems)...

The dielectric constant of water (a polar solvent) is 78. The dielectric constants of organic solvents like hexane are lower (1.89). A binding pocket lined with "hexane-like" amino acid side chains presents a dielectric constant that is more like organic solvent... i.e. "LESS THAN 78"

greater than 78 less than 78 about 78 condensed expanded preorganized

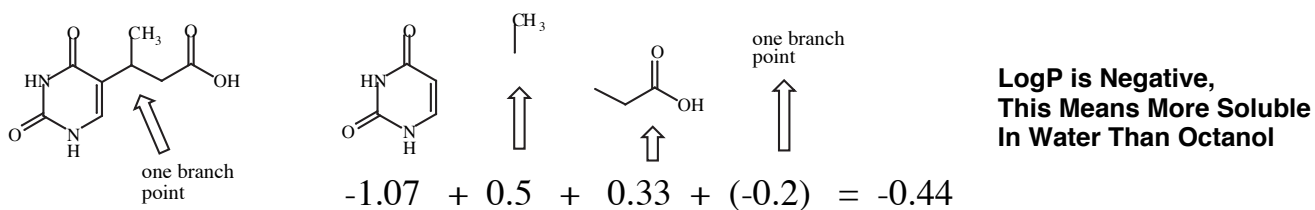
Short Answer (CONTINUED)

7. Very briefly explain why the measured Log P for the molecule shown changes as a function of pH. (Note: do *not* calculate a Log P for the molecule... simply explain the pH effect).

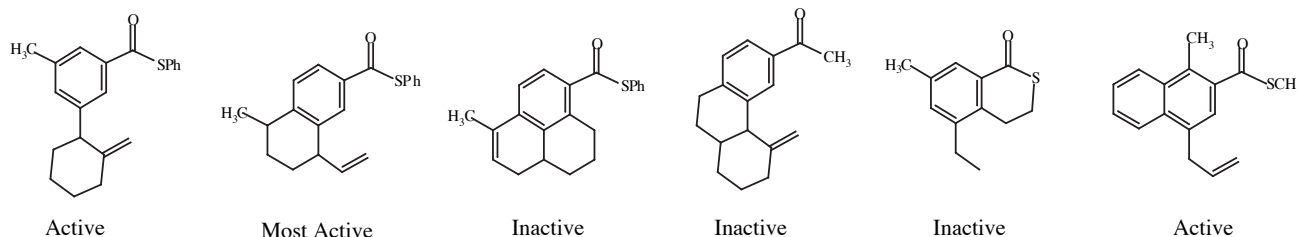


Looking at the provided table of amino acids (and the handout on the course website regarding acid-base calculations) we can see that the pK_a of RNH₃⁺ is about 10. At low pH the RNH₂ group is protonated, charged and water soluble. As pH increases the RNH₂ group is increasingly unprotonated, uncharged, and thus, more organic soluble (see Silverman book, problem 15, page 102).

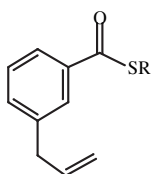
7. (a) Calculate log P for the molecule shown.



9. Given the structures and activities of the compounds shown below, draw the structure of the **pharmacophore** required for activity in this class of compounds.



Points deducted for missing functional groups or extra, unnecessary functional groups



R = CH₃ or Ph

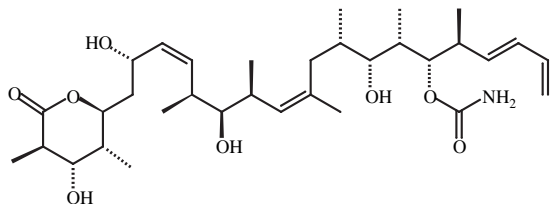
10. State Lipinski's "rule of fives".

A compound is likely to have poor drug properties if two or more of the following are true for the compound:

1. MW > 500
2. Log P > 5
3. Number of H-bond donors > 5
4. Number of H-bond acceptors > 10
5. Number of Freely Rotatable Bonds > 10

You need to know what a freely rotatable bond is... easiest to define what is NOT freely rotating bond: double bonds, triple bonds, and any bond that is part of a cyclic structure is NOT freely rotating. All other C-C or C-Heteroatom bonds are freely rotating. So you can check yourself... I count 17 freely rotating bonds in discodermolide. Note that rule number one and number five may be related (and even somewhat redundant). That is, the molecular weight rule may be related to the fact that, in general, larger compounds will have more freely rotating bonds. So, it is possible that the molecular weight itself is not all that important... rather it is the rigidity of drugs that is important. Specifically, drugs must be fairly rigid and preorganized to be good drugs.

11. The molecule shown below is called (+)-discodermolide and is in clinical development as an anticancer agent (see: *Chemical and Engineering News* 2004, March 1, pages 33-35). Does the rule of fives predict that discodermolide will be a useful drug? Briefly explain your answer. By the way, the log P of discodermolide is 3.3.



Predict that this will NOT be a good drug because it violates two of the rules. MW is > 500 and number of rotatable bonds is > 10.

Log P = 3.3. is OK

H-bond donors = 5 (four OH's and one NH₂) this is OK

H-bond acceptors = 9 (8 Oxygens and 1 N with electron lone pairs) this is OK

12. A combinatorial library of tetrapeptides containing Leu, Ser, Glu, and Ala was constructed using Merrifield's resin and Still's tag method for encoding.

(a) How many peptides are possible in this library? **$4^4 = 256$**

The active bead was isolated and photolyzed, and electron capture gas chromatography gave the following result: Tags 2, 5, 6, 7, 10 were detected

(b) Use your knowledge of Still's encoding method to determine the structure of the active peptide on the polymer bead (please indicate the carboxy and amino ends on your answer).

Assume: 001 = Leu 010 = Ser 011 = Glu 100 = Ala

See Silverman book, problem 10, page 101.

Peptides are "grown" from the C-terminus toward the N-terminus. So tags 1,2,3 encode the identity of the first amino acid... the one on the C-terminus, while tags 10, 11, 12 encode the identity of the fourth amino acid (at the N-terminus). Decoding shows us which amino acid is in each position:

C-term 010 011 100 100
C-term Ser Glu Ala Ala