

Medicinal Chemistry

CHEM 315/515

Mid-term Exam

Tuesday, October 26, 2010

Name: _____

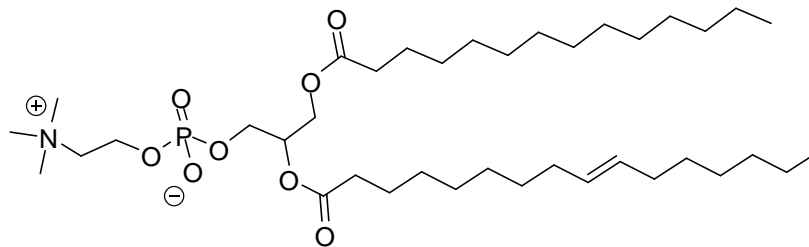
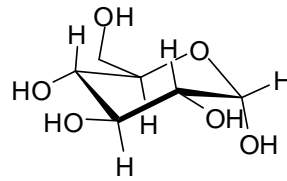
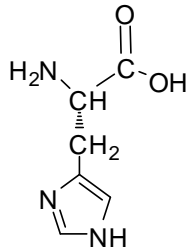
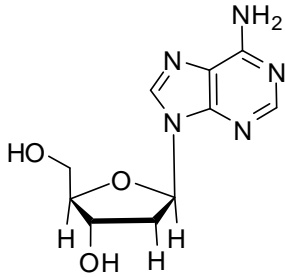
Read each question carefully before answering. Be certain you understand everything the question is requesting. Do the easy questions first. If questions appear confusing or exceedingly complex, then you may need to rethink the question. Keep in mind the intended examination topics.

In medicinal chemistry, hand-drawn pictures convey specific information. Be sure the drawing you have made conveys the essential information required to answer the question. Make certain that three-dimensional pictures display the correct atom arrangements. Don't forget to include formal charges when appropriate.

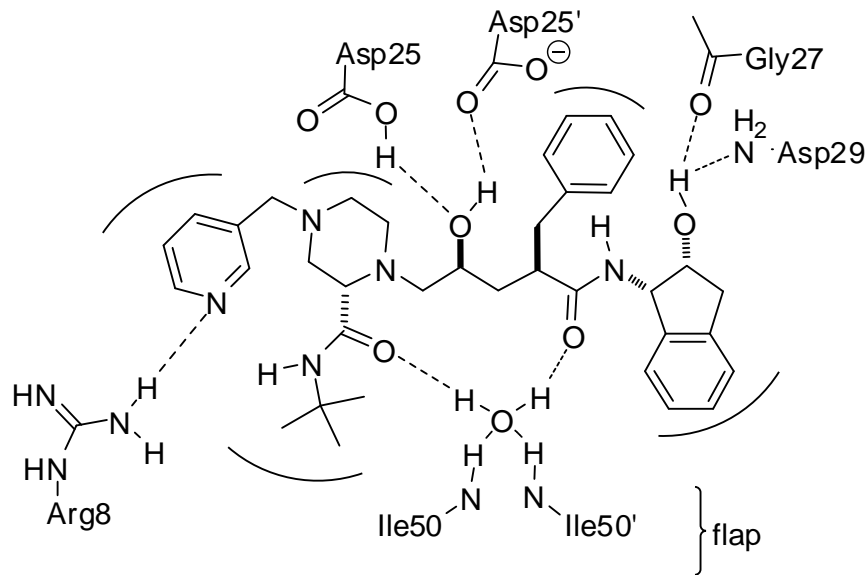
You may use scrap paper to work out problems before entering your final answer on the exam sheets. In addition, feel free to use the back side of the exam sheets for scrap. If necessary, you may enter exam answers on the back side of the exam sheets, however you must clearly indicate which problems are located on the back of the exam pages.

Undergraduate students answer 8 of 11 questions. Graduate students need to answer 10 of 11.

1. Identify the following biological structures as an α -amino acid, carbohydrate, nucleic acid, or phospholipid. In addition, select two and give a more precise structural name, e.g. guanine or aspartic acid. (10 pts.)



2. Shown below is the X-ray structure of Merck's drug indinavir (crivivan) fitting in the active site of a protease enzyme. The dashed lines represent interactions between the enzyme and the drug, and the curved arcs represent pockets in the enzyme. Answer the following questions based on your understanding of this drug, related protease drugs and their mode of action. (10 pts.)



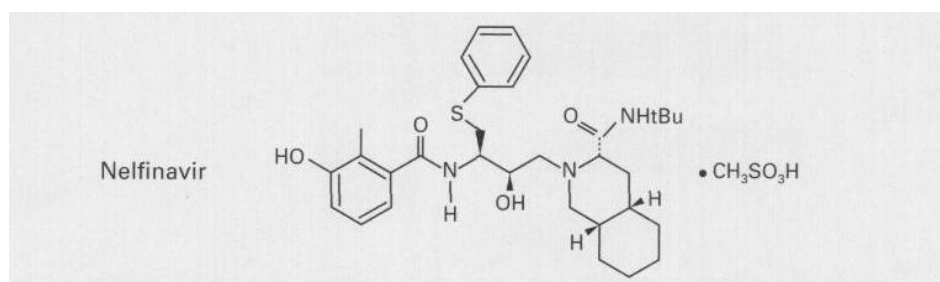
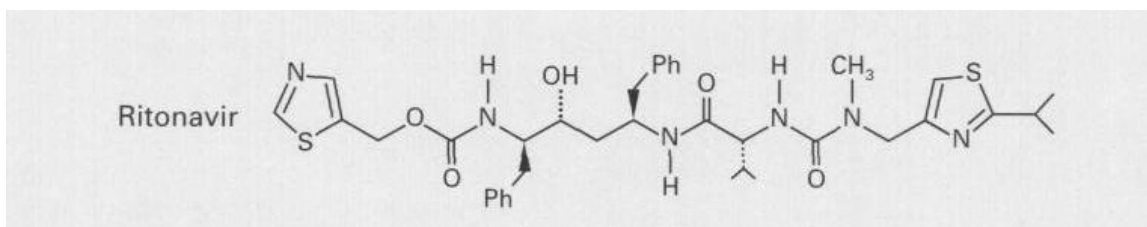
a) Identify all the hydrogen bonding interactions by writing 'H-B' next to them. Circle the H-bond acceptor in all the H-bonds.

b) What is the approximate binding energy of a hydrogen bond? A range is an acceptable answer.

c) Identify the hydrophobic interactions between indinavir and the enzyme by writing 'hydrophobic interaction' next to these contacts.

d) The pockets of the protease enzyme are occupied by several groups from indinavir. Identify these pockets by writing the proper designation, S_1 , S_1' , etc., next to the correct pocket.

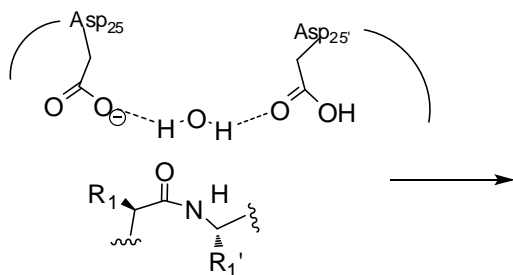
3. Indinavir represents a class of protease inhibitors that were designed to achieve their potency through a particular process. Other examples of protease inhibitors include ritonavir and nelfinavir. (10 pts.)



a) What is the mechanism by which these protease inhibitors block HIV protease? Be as specific as possible.

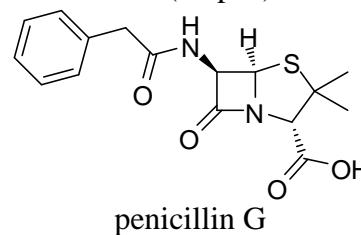
b) Explain why this mechanism can be so powerful in generating enzyme inhibitors.

4. Provide the curved electron flow arrows and intermediate structures for the mechanism of HIV protease. (10 pts.)



5. The structure of the antibiotic penicillin G is shown below. Answer the following questions based on our discussion of penicillin. Briefly describe how penicillin exerts its antibiotic action. (10 pts.)

a) How does penicillin act as an antibiotic, i.e. what bacterial process is undermined?



b) Show the basic steps in the reaction of penicillin with transpeptidase, a serine protease.

c) What type of enzyme inhibition is represented by this reaction of penicillin with transpeptidase?

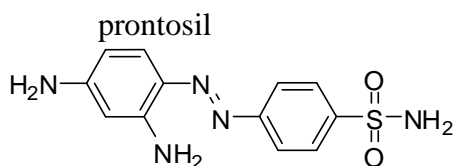
d) What is the key reactive functionality in penicillin and why is it so reactive?

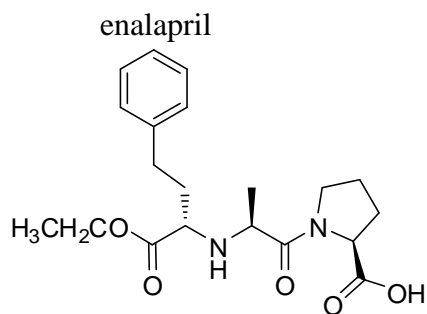
e) What does penicillin mimic that allows it to react with transpeptidase?

6. In the Billion-Dollar Molecule, Joshua Boger leaves Merck to revolutionize drug discovery. In particular, he wants to transform the way drugs are designed. What is this 'new' type of drug design or development process called? What happens in this process and why is this so different from previous drug design/development work in medicinal chemistry? (10 pts.)

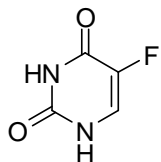
7. During the first half of the semester, we discussed prodrugs on several occasions. The three drugs shown below were all examples of prodrugs. (10 pts.)

a) For two of the three, identify the process that occurs to activate the drug and show the actual bioactive agent.



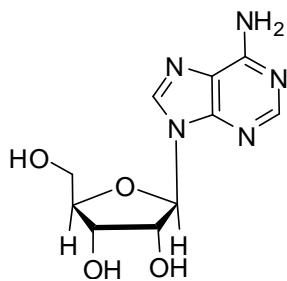


5-fluorouracil (note: this is a long process, an abbreviated description and the final structure is all that is necessary)

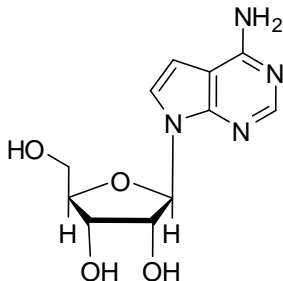


b) Two of the three drugs shown (or their bioactive derivative) are termed anti-metabolites. Choose one of these two drugs and describe what makes it an anti-metabolite and how this action creates a therapeutic effect.

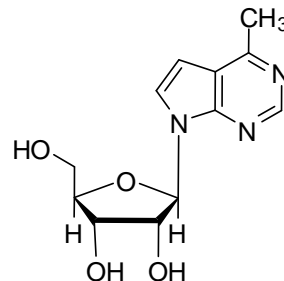
8. A recent article in the *Journal of Medicinal Chemistry* (ASAP, Oct. 22, 2010) reported a study of **B** and **C** (below) as potential anti-virals. You will recognize that both are a close structural analog of a well-known and important biological molecule, compound **A**. Analyze the different physicochemical properties of these molecules according to the criteria below. (10 pts.)



A



B



C

a) Rank the compounds shown by lipophilicity.

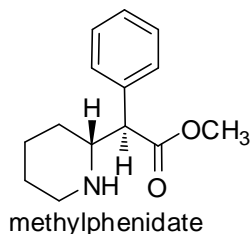
most lipophilic _____ > _____ > _____ least lipophilic

b) Rank the electronic nature of the bicyclic aromatic ring (consider rings as a whole, not individually).

most electron rich _____ > _____ > _____ least electron rich

c) The substitutions of atoms in **A** for different atoms in **B** and **C** represent an example of what kind of drug design replacement strategy?

9. a) Predict three possible metabolites of methylphenidate (Ritalin), the most commonly prescribed treatment for attention deficit hyperactivity disorder. At least one of the three must be a Phase I and at least one must be Phase II. You may show a Phase II step that occurs after one of your Phase I metabolic reactions. Each metabolic reaction should be titled with the type of reaction and the Phase (I or II). Reactions catalyzed by cytochrome P-450 should be noted with a 'CYP' designation. (10 pts.)



b) Take one of the metabolic products that you propose and propose an analogue of methylphenidate that would block this metabolic product.

10. Multiple choice. Circle the one best answer for each question. (10 pts.)

a) Which of the following statements best describes a competitive enzyme inhibitor?

- (i) A drug that binds to an active site and undergoes a reaction.
- (ii) A drug that binds to an active site and inhibits the enzyme, but which is displaced by increasing the concentration of substrate.
- (iii) A drug that binds to an active site and inhibits the enzyme, but which is not displaced by increasing the concentration of substrate.
- (iv) A drug that binds to a different binding site from the active site and affects the activity of the enzyme.

b) Which of the following descriptions best identifies an allosteric inhibitor?

- (i) A drug that binds to an active site and undergoes a reaction.
- (ii) A drug that binds to an active site and inhibits the enzyme, but which is displaced by increasing the concentration of substrate.
- (iii) A drug that binds to an active site and inhibits the enzyme, but which is not displaced by increasing the concentration of substrate.
- (iv) A drug that binds to a different binding site from the active site and affects the activity of the enzyme.

c) Which of the following is not a common source for discovery of a drug lead?

- (i) pharmaceutical company compound libraries
- (ii) pharmacophores found through enzyme co-factor screening
- (iii) natural product sources such as soil samples or mold growths
- (iv) bioactive metabolites identified through animal or clinical studies

d) Which is the most common correct goal in Phase 2 of clinical trials?

- (i) determine the safety of a new drug on healthy individuals
- (ii) test the bioavailability of the drug in healthy people
- (iii) prove the efficacy and reconfirm the safety of the drug in sick patients
- (iv) expand the study to a much larger set of sick patients to confirm efficacy and safety on a larger population of people

11. Choose one person in the Billion-Dollar Molecule and briefly describe one positive character trait and one negative character trait. (10 pts.)