

Name: _____

Date: _____

**Topics in Organic Chemistry: Modern Medicinal Chemistry
(CHEM 515)
Final Examination**

Profs. Malachowski and White

Due: Dec. 14, 2005 at Noon
(earlier would be greatly appreciated !!)

Honor Code: You may take this examination while consulting your course lecture notes, handouts, and the information posted on the course Blackboard site. You are not to consult any other electronic or written material during the exam. You have **4** consecutive hours to complete the exam. You may word process your answers. You may use molecular models to assist you in answering the exam questions. You should not discuss the exam with anyone until all students have handed in their exam. There are a total of 15 questions on 16 pages.

General Questions: (you may want to leave these for last)
Question 1—15 points

Throughout the semester, we have seen that animals or their tissues are a very important part of the human drug development process. Discuss three specific, but different, uses of animals that have been described in class or in reading assignments. Give an example of animal research giving wrong or misleading results or a case when lack of animal research hampered drug development efforts. *(one page or less)*

Question 2—15 points

Based on your Ph. D. work, you decide that you have a great idea for a new pharmaceutical product that you would like to develop. Coincidentally, you win a \$20 million dollar lottery so you have enough money to start the Research and Development process.

What specific disease or condition will you work on? Explain why in three sentences or less.

If you could initially afford to hire only three Ph. D. scientists, what would their individual areas of expertise be and what would they do?

Describe a major hurdle that your pharmaceutical organization would need to overcome in its early days.

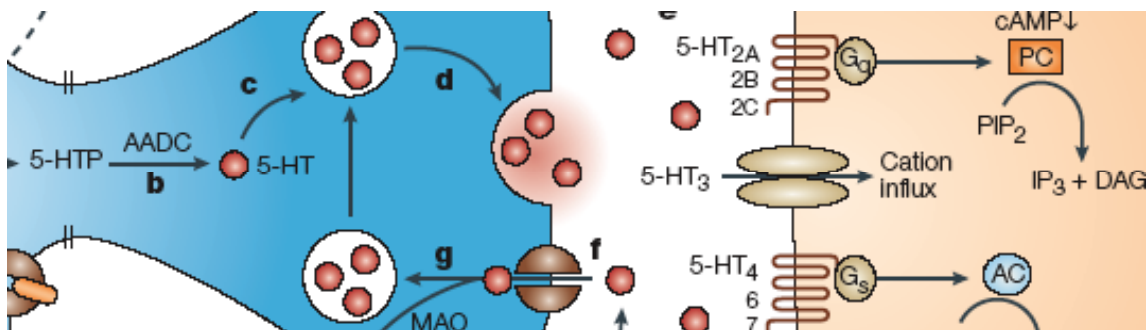
(Don't worry—Professors Malachowski and White are not planning to steal your idea and plan to stay at Bryn Mawr College for a long time)

Disease and Target Related Questions

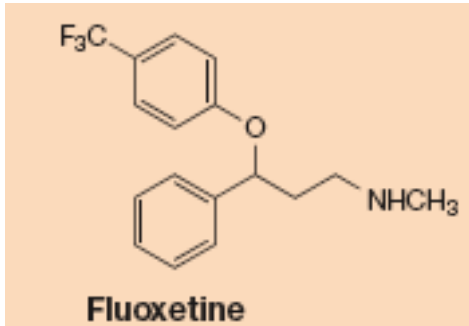
Question 3—10 points

Below is a diagram of a presynaptic nerve of the left, a synapse with serotonin, and the post-synaptic nerve on the right. Circle the site of Prozac action and explain the effect of Prozac in the serotonin synapse concentration. (*for color, please consult Blackboard*)

Describe an additional protein target in the figure below that could be stimulated or inhibited to produce the same effect on synapse serotonin concentrations.



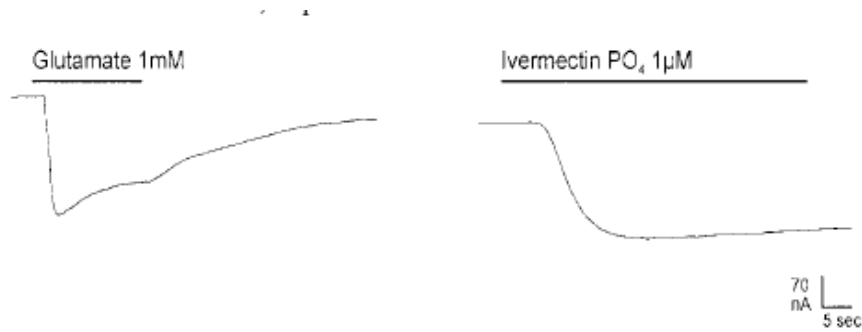
Annotate this figure to show clearly why this is a part of a salt. Add an example of the missing part.



Prozac has few side effects because of its selectivity for its target and biochemical experiments are ideal for measuring selectivity. Using charts or graphs, explain what is measured in a selectivity experiments and show the results obtained for hypothetical highly selective or non-selective drugs.

Question 4 –10 points

Ivermectin works by binding to and blocking a glutamate-gated nervous system channel.

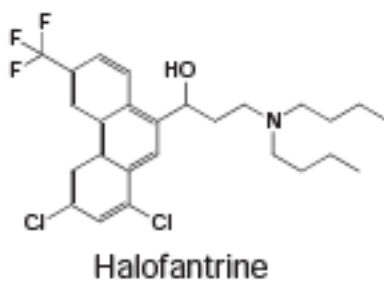
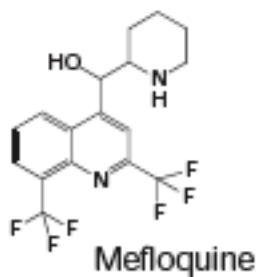
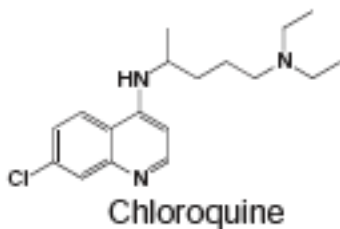
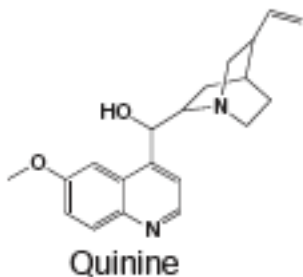


a) Using the data above, explain how ivermectin works.

b) Explain why neither humans nor horses are harmed by Ivermectin.

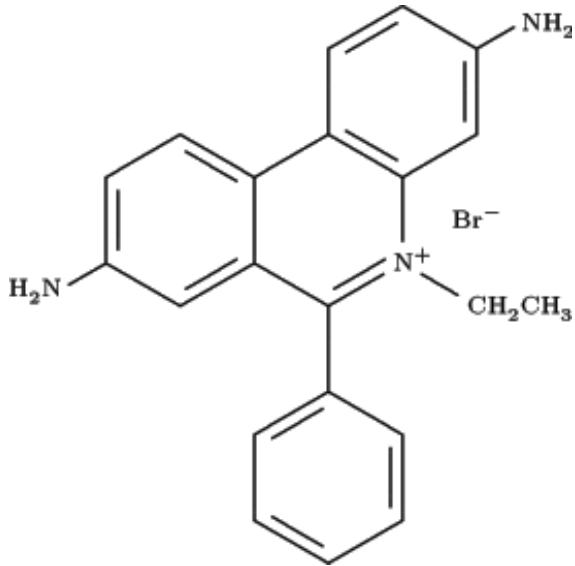
Question 6—10 points

Circle the important common features of the antimalarial drugs shown below and state how they are important for interaction with the drug target. Explain why resistance to quinine took decades to develop, but subsequently resistance to later drugs developed much more quickly.



Question 7—5 points

Below is the structure of ethidium bromide. Describe clearly two ways in which this molecule interacts with DNA and state what intermolecular forces are present.



Does this drug interact with DNA sequences selectively or indiscriminately?

Question 8—10 points

Schizophrenia has two major classes of symptoms. Examples of these two classes are

_____ and _____. Both _____

and _____ neurotransmitters are thought to be involved and drugs must

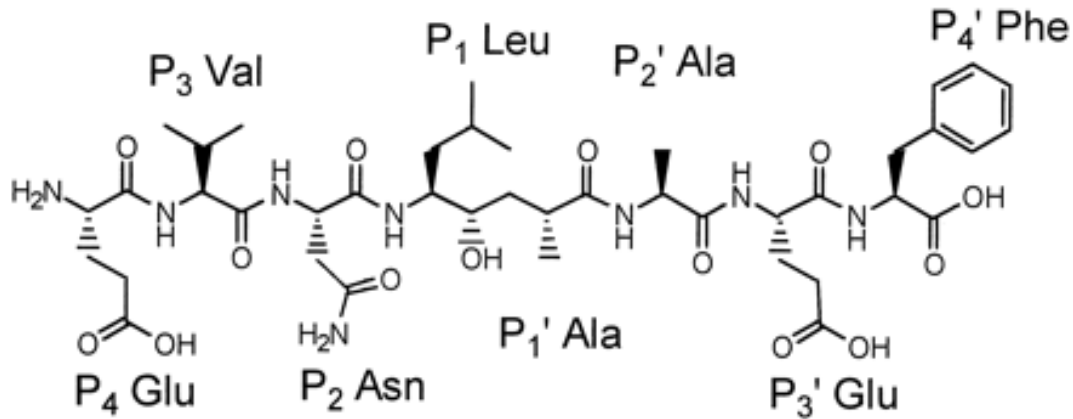
target the correct receptors to avoid side effects.

One of the earliest drugs resembled one of the neurotransmitters. Why is this not surprising?

This neurotransmitter was shown “modeled” into bovine rhodopsin. Why was this strategy used?

Question 9 10 points

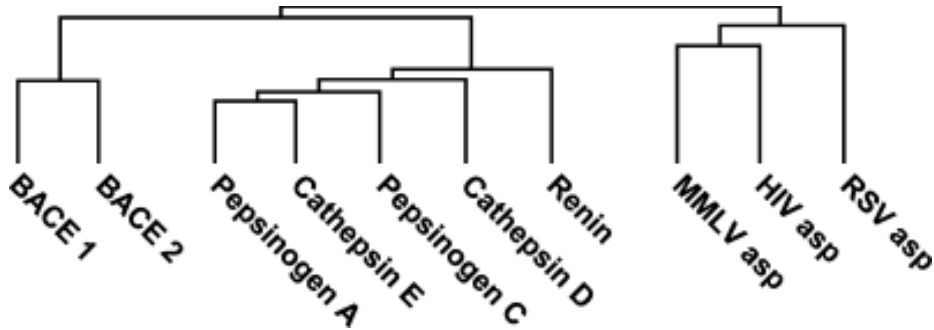
This peptide is a transition state inhibitor of the β -secretase. Circle the portion that mimics the transition state of the substrate.



β -secretase has several domains and one of these domains was crystallized. Draw a “cartoon” of the entire domain structure of the protein and indicate the appropriate location with respect to the cell’s membrane. Explain why the entire protein was not crystallized.

What evidence was presented to show that complete inhibition of β -secretase would not impair function?

According to this evolutionary tree, where line lengths are proportional to sequence differences, would a drug developed to work on Alzheimer's Disease work against the HIV virus?



Question 10-- 10 points

Three drugs commonly prescribed for the treatment of tuberculosis reportedly target cell wall biosynthesis. Name these three drugs, draw their structures and describe why cell wall biosynthesis is a common target for tuberculosis drugs.

Question 13-- 5 points

a) Draw the more active S isomer of warfarin.

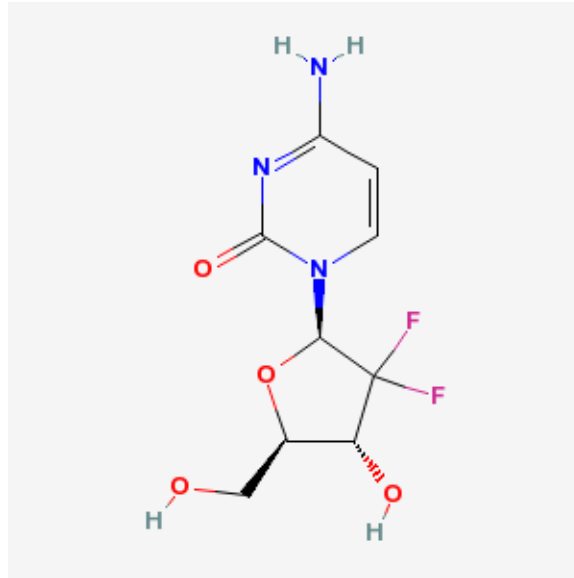
b) What type of interactions are involved in the binding of oligosaccharide 12 to thrombin and anti-thrombin? Draw an example of the groups on each of the molecules that are involved in this binding.

Question 14 10 points

Draw the structure of melatonin, the natural substrate for MT_1/MT_2 and ramelteon, the potent MT_1/MT_2 agonist. Identify three modifications to the ramelteon structure relative to melatonin and describe the effect these changes have on the receptor site binding or bioactivity of ramelteon.

Question 15 -15 points

Gemcitabine is an anti-cancer and anti-viral drug developed by Eli Lilly Pharmaceutical Company.



gemcitabine (GEM)

In November 2005, the American Association for Cancer Research (AACR) held a conference in Philadelphia and one of the meeting presentations involved gemcitabine. The abstract for that presentation is pasted below. Read this abstract and answer the questions that follow.

C273 Pharmacodynamics of Gemcitabine in Glioblastoma Multiforma. Godefridus J. Peters, Jennifer Sigmond, Sandra De Lange, Adrie C. Laan, Richard J. Honeywell, Tjeerd J. Postma, Clemens M. Dirven, Johannes C. Baaijen, Cornelius J. Van Groenigen, Giuseppe Giaccone. VU University Medical Center, Amsterdam, The Netherlands.

Glioblastoma Multiforma (GBM) has a poor prognosis and is poorly sensitive to cytotoxic drugs. Gemcitabine (GEM) is a very potent radiosensitizer. However, in order to apply GEM in combination with radiation in the treatment of GBM, the drug needs to be taken up by the brain into the tumor and metabolised to its active nucleotides. The aim of our study was to investigate whether GEM would pass the blood-tumor barrier and would be taken up at sufficiently high concentrations in the tumor to enable radiosensitization. In addition, we investigated whether critical enzymes in GEM metabolism would be expressed in GBM: deoxycytidine kinase (dCK), responsible for GEM activation, and deoxycytidine deaminase (CDA), converting GEM to difluorodeoxyuridine (dFdU), which is supposed to be an inactive metabolite. GEM was administered just before surgery or during anesthesia to 10 patients with recurrent GBM, at two doses of 500 and 1000 mg/m², each group consisting of 5 patients. Tumor samples were obtained between 2-4 hr after administration. GEM levels in plasma at the time of the biopsy varied from 0.9-9.2 μM, dFdU from 25-72 μM and that of the active metabolite, gemcitabine triphosphate, dFdCTP in white blood cells from 2-108 pmol/10⁶

Question 1 _____/15
Question 2 _____/15
Question 3 _____/10
Question 4 _____/10
Question 5 _____/10
Question 6 _____/10
Question 7 _____/5
Question 8 _____/10
Question 9 _____/10
Question 10 _____/10
Question 11 _____/5
Question 12 _____/10
Question 13 _____/5
Question 14 _____/10
Question 15 _____/15

Total _____/150