Name_____

MEDCHEM 562

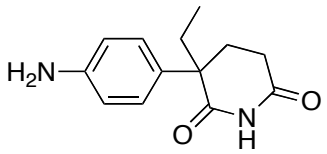
First Midterm

October 16, 2013

Instructions:

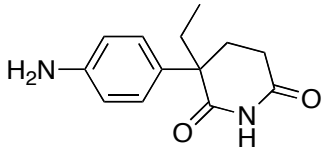
- Exam packet totals 5 pages.
- If you need additional space go to the back of that page and tell me you did so.
- Write legibly and in complete sentences when indicated.
- Read the questions carefully and answer the questions you know first.

1. (20 points) Aminoglutethimide is a non-steroidal inhibitor of aromatase that is used as a second line agent in the treatment of advanced breast cancer in post-menopausal women.

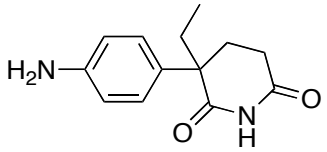


a. While the R isomer is 36 times more potent than the S isomer the drug is given as the racemate. Using the structure above show the stereochemistry of the R isomer. Circle the ionizable groups and indicate appropriate pKa ranges for each.

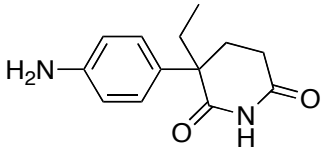
b. Below, indicate by addition or removal of proton(s) and charge(s) (+/-) the ionized state of this drug at pH 3, 7 and 11.



pH=3



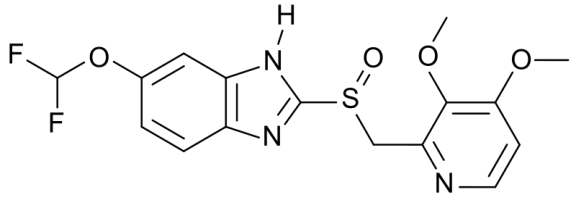
pH=7



pH=11

c. Based on your answer to part b, where along the GI tract would you expect absorption to be most favorable? Explain your answer using the basic principles learned in class.

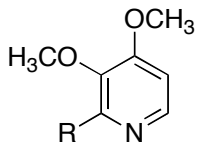
2**. (20 points)** Pantoprazole (Protonix) is a proton pump inhibitor with the same mechanism of action as omeprazole. It is administered as the racemate of two enantiomers. One of the two isomers is also marketed separately in India. There is no stereoselectivity for inhibition of the proton pump.



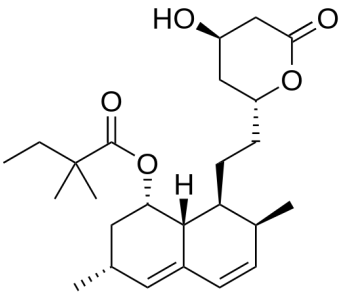
a. Circle the location of the stereocenter and show the partial structure of the S enantiomer.

b. After oral administration of the racemate the AUC's of the two isomers are the same in CYP2C19 extensive metabolizers (S/R ratio =1). However in PMs the AUC ratio is significantly different (S/R = 0.3)). Based on this information only which isomer would you expect to be marketed as the single isomer? Explain your reasoning in 2-3 sentences.

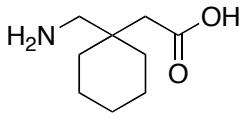
c. The major CYP2C19 pathway is O-dealkylation of the pyridine 4 methyl ether. Show the mechanism of this reaction, the relevant intermediate and products using the partial structure below.



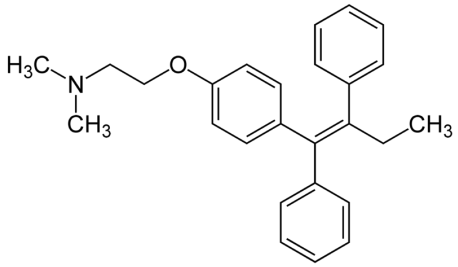
3. (6 points) The structure of the prodrug simvastatin is shown below. Indicate the structure of the active drug and discuss why absorption of the prodrug may be better than the active drug. Briefly describe the mechanism of action of simvastatin.



4. (6 points) Gabapentin is an antiseizure medication that is administered orally. Surprisingly the systemic bioavailability is adequate (60%) and penetration into the brain is reasonable Explain using basic principles why one <u>would not</u> expect this compound to have good bioavailability. What is the most likely reason for the good bioavailability?



5. (8 points) Tamoxifen is an anticancer prodrug with a pKa of 9 and a log P of 5. What is the log $D_{6.0}$ of tamoxifen? Closest integer value is fine. Show your work.



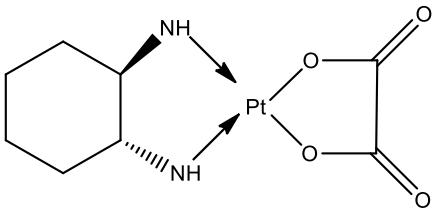
6. (12 points) Cancer therapy; general question
Oncogenes and tumor suppressor genes are both important to the mechanism of carcinogenesis.
a. Define an oncogene. Name an example.

b. Define a tumor suppressor gene. Name an example.

c. Define metastasis. Why is metastasis bad for a patient?

d. Discuss drug resistance in cancer chemotherapy and how it impacts drug therapy in treating cancer patients. (Three sentences can suffice.)

7. (12 points) Oxaliplatin is a relatively new anti-cancer drug and its structure is shown below.



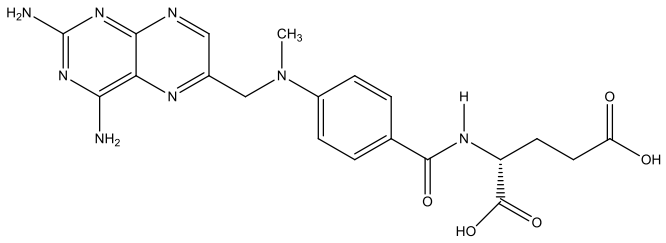
a. Name the important atom in the drug. What does this drug target in cells?

b. Name the main type of cancer that is treated with this agent.

c. This agent is used in a combination regimen. What is the name of this regimen?

d. Like many anti-cancer drugs the agent can cause myelosuppression, What is its major toxicity of oxaliplatin?

8. (16 points) Methotrexate is an important anti-cancer agent and its structure is shown below:



a. This drug mimics what endogenous molecule?

b. Circle on the structure above the two chemical modifications in methotrexate that make it different than the endogenous molecule it mimics.

c. What specific enzyme does methotrexate inhibit?

d. If an intentional high dose (or an overdose) of methotrexate is administered to a patient, what drug can be given to the patient to prevent severe toxicity or death?

e. Explain how methotrexate can be trapped inside cells.