Name_____

# MEDCHEM 562

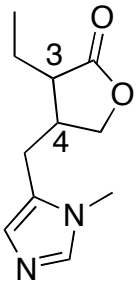
## First Midterm (KEY)

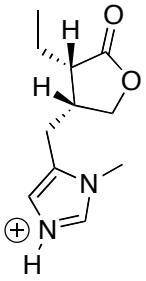
## October 15, 2012

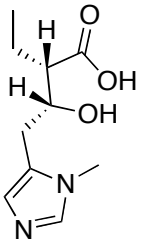
Instructions:

- 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. (25 points)** Pilocarpine is a muscarinic M3 agonist that has been used for over 100 years in the treatment of glaucoma. It is also given orally to reverse the effects of atropine or scopolamine poisoning and to treat mucositis following cancer chemotherapy. Answer the following questions.




a. (4) The active isomer has the 3S, 4R configuation. Using the structure above show the stereochemistry of the active isomer.

b. (4) In ophthalmic solutions, the carbon 3 C-H bond can undergo spontaneous slow epimerization to the inactive 3R, 4R isomer (called isopilocarpine). What type of isomers are the pilocarpine-isopilocarpine isomers and what would be their relative ratios when at equilibrium?

*Diastereoisomers: Ratio at equilbrium is 1:1*

c. (5) Pilocarpine has a pKa of 6.4 and a $\log D_{7.4}$ of 1. Indicate above the structure of the ionized species above. Which is the dominant species at pH 7.4? Estimate the logP of pilocarpine (integer value is fine). Show work and use a diagram if necessary.

*$H^+$ can be on either nitrogen; unionized:ionized ratio at pH 7.4 is 10:1*
*Ionized species is 10 percent of total in aqueous phase at this pH so logP is approximately equal to log $D_{7.4}$ or 1. The precise answer is log 11 or 1.04.*

d. (4)Where in the GI tract (upper, lower) would you expect absorption to take place following an oral dose? Why (<u>two sentences</u>)? *Absorption will be fastest in the region of the GI tract where the unionized:ionized ratio is highest. Distal small intestine is best answer, others accepted including lower GI.*

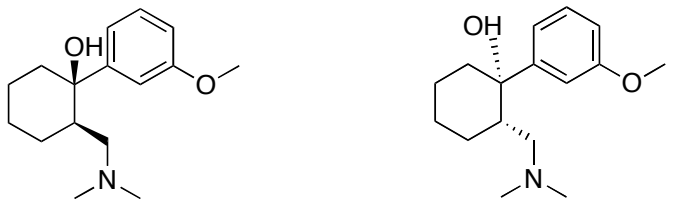
e. (4) Pilocarpine undergoes hydrolysis *in vivo*. Indicate the structure of the hydrolysis product next to the above structure. Would you expect pilocarpine itself or this metabolite to undergo renal excretion more rapidly? Provide two reasons for your answer based on lipophilicity and pKa comparisons of metabolite and drug (sentences).

*Structure shown above is hydrolysis of an ester (lactone). The carboxylate will be negatively charged at pH 7.4 so the metabolite is a modified amino acid and always charged. It is also more polar. Thus reabsorption of metabolite in the renal tubules will be slower than the parent compound which is partially unionized.*

f. (4) Binding of pilocarpine to the M3 receptor causes a rise in intracellular calcium. What is the natural ligand for the muscarinic M3 receptor? Briefly describe what happens when pilocarpine binds to the M3 receptor to cause the increase in calcium (2-3 sentences).

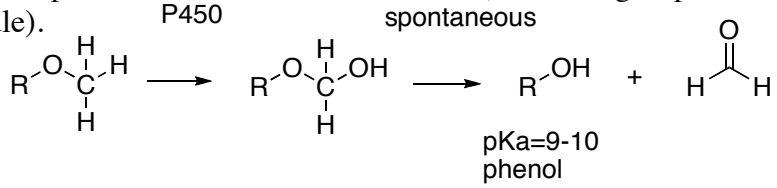
*The natural ligand is acetylcholine.*
*Pilocarpine is an agonist of the M3 receptor. It binds to the receptor and triggers a GPCR ($G_q$) that leads to an increase in inositol 3 phosphate (I3P) and release of calcium from the ER.*

2. **(25 points)** Tramadol is an analgesic used for the treatment of moderate to severe pain. The isomer shown below together with it's enantiomer are given as a 50/50 mixture. The tramadol isomers undergoes Phase 1 metabolism (N-dealkylation and O-dealkylation) and Phase II metabolism. The O-dealkylated metabolites (M1) are roughly 100 times as potent as the parent drug in binding to the μ-opioid receptor in vitro and it is suspected that the analgesic effect is partially due to the M1 metabolites. The AUC of tramadol and M1 are approximately the same while the half life of the parent is 1/3 that of the metabolite.




a. (5) Draw the complete structure of the enantiomer of the structure shown above.

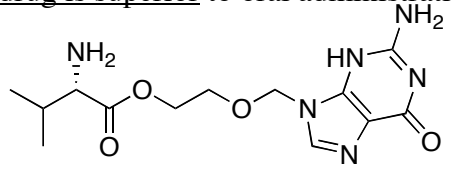
b. (5) Show the mechanism of O-dealkylation to M1 including the intermediate and indicate the pKa of the product at the site of metabolism (Use an R group for the unaffected part of the molecule).

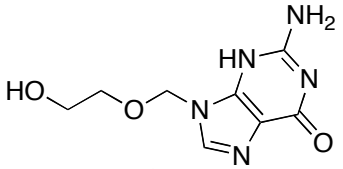



c. (5) What types of Phase 2 metabolites of M1 would you expect to find in urine? Two types, names only. Why would you find them in the urine?
*Glucuronide and sulphate conjugates of either hydroxyl groups. These conjugate functionalities are ionized and polar so would not expect reabsorption in the kidney tubules leading to high renal clearance. No reason to expect a glutathione/mercapturate.*

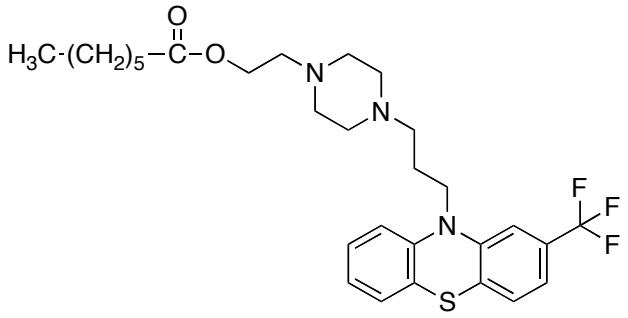
d. (5) Formation of M1 is catalyzed by CYP2D6 and there is some concern that CYP2D6 PM's would require different doses than EM's however this has not be shown. Briefly describe the CYP2D6 polymorphism by defining the EM and PM genotypes. What would you expect to observe in the AUCs of M1 in PM's vs EM's after administration of tramadol?
*EM-extensive metabolizers have two copies of the wild type gene.*
*PM-poor metabolizers have two copies of a mutant gene that doesn't produce active enzyme. Would expect that the AUC of M1 after administration of tramadol would be higher in the EMs than the PMs.*
e. (5) What would have to be true in order for tramadol to be considered a true prodrug? (2 sentences including a definition of a prodrug)
*A prodrug is a pharmacologically inactive compound that is transformed by a chemical or biochemical process into an active drug in vivo.*
*For tramadol to be a true prodrug it would have to have no intrinsic analgesic activity. Note but not required in answer: Since it binds to the μ-opioid receptor, albeit poorly, it is probably not a true prodrug.*

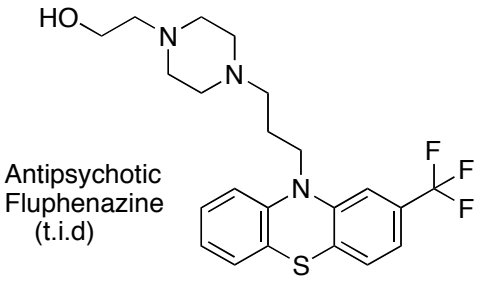
**3. (12 points)** The structures of two prodrugs (Valcyclovir and Fluphenazine heptanoate) are shown below. Indicate (arrow for site of cleavage and indicate active R group) the structure of the active drug. Briefly outline method of administration for each drug and tell me <u>why the prodrug is superior</u> to oral administration of the active drug in each case (sentences).






(6) *Valcylovir is given orally and is transported across the intestinal epithelium by an amino acid transporter (bioavailablity 50%). Oral Acyclovir is not transported so bioavailability is higher for the prodrug. Esterases cleave the ester bond to produce the alcohol acyclovir and the amino acid valine. Note that valcyclovir is not more lipophillic than acyclovir; the transporter is the key.*






*Fluphenazine heptanoate is a prodrug of the antipsychotic fluphenazine that is administered by depot injection. Plasma esterases hydrolyze the ester as it enters the systemic circulation and converts it to the active drug and heptanoic acid. Fluphenazine must be administered orally tid while the ester is injected every 2-3 weeks which increases compliance.*

**4. Cancer therapy (8 points)**

a. Besides chemotherapy, what are the other two major types of therapy used to treat cancer patients?

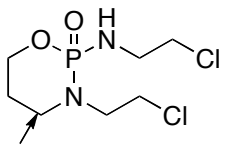
*1. Surgery*
*2. Radiation (or radiotherapy*

b. Various ancillary premedications are often given with chemotherapy drugs. What are the two major reasons for giving patients premedication?
*1. Nausea and vomiting (or anti-emetics or anti-emesis).*
*2. Hypersensitivity (or allergic reactions or infusion reactions)*

c. In bone marrow transplantation (BMT), or stem cell transplantation (SCT) a specific "toxicity" of certain cancer drugs is exploited prior to transplantation. What is this "toxicity"?

*Myelosuppression (or bone marrow suppression or bone marrow depression)*

**5. (10 points)** Ifosfamide (Ifex), an important anti-cancer drug, is shown below.



a. Name the class of chemotherapy agents to which ifosfamide belongs and the target.
*Alkylating agent (or nitrogen mustard)*
b. Ifosfamide must be bioactivated by P450 before it is active as an anticancer agent. Name the two forms of P450 involved in this bioactivation step. General question: Why is it advantageous to have two P450 enzymes catalyze this step?
*CYP3A4 and CYP2B6*
*Best if bioactivation is performed by more than one enzyme. Dependence on a single enzyme can make the activation step vulnerable to a drug-drug interaction or polymorphism.*

c. Name the reactive intermediate that is formed in this reaction and show, using an arrow, the carbon atom that is modified in the bioactivation reaction.
*Aziridine (or phophoramide also accepted)*
*The carbon that is modified in the bioactivation step is shown above.*

d. Ifosfamide can cause bladder toxicity and nephrotoxicity. Name the agent (different ones) that can be used to protect against each toxicity.

Bladder toxicity ____MesNa_____ Nephrotoxicity_N-acetyl cysteine (or NAC)

**6. (10 points)** A large class of anticancer drugs "mimics" endogenous molecules.

a) What is the common name for this class of anticancer drugs? Are they generally cell-cycle specific?
*Antimetabolites.*
*Yes, cell cycle specific.*

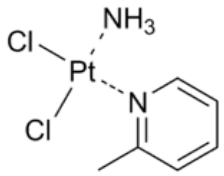
b) One drug in this class is cleared via catabolic metabolism by DPD (dihydropyrimidine dehydrogenase). DPD is expressed polymorphically in the population. What is the name of this drug and what is the target enzyme? This drug is also given in a prodrug form. What is the name of this prodrug and what is it's major advantage over the parent drug (sentence)?

*5-Fluorouracil (or 5-FU) and target is thymidine synthetase (or TS).*
*Prodrug form is Capecitabine (or Xeloda).*
*Major advantage of the prodrug over the parent drug is that 5-FU is preferentially formed in tumor tissues.*

c) Provide the name and target enzyme of another drug selected from this larger class of drugs.

*Methotrexate, which inhibits dihydrofolate reductase, DHFR (and TS indirectly).*
*Pemetrexed, which inhibits DHFR and GARFT (and TS indirectly).*

**7. (10 points)** Below is shown the structure of an anticancer agent that has recently been in clinical trials.




a. What class of drug does it belong to and what is the general mechanism of action of these agents (sentences). Are they cell cycle specific?

*Platinum agents (or platinum or cross-linkers)*
*No, not cell cycle specific.*

b. List 3 important toxicities that would be expected with this type of agent. Note: Do not list more than 3 and force me to guess which ones are important.

*Myelosuppression (or bone marrow suppression or bone marrow depression)*
*Nephrotoxicity (or kidney toxicity or renal toxicity)*
*Peripheral neuropathy (or neurotoxicity)*
*Bladder toxicity*

c. Why is proper hydration of the patient important for this class of agents (sentences)?

*Because the drug is extensively cleared by renal excretion, proper hydration will dilute the drug and help flush it out of the kidneys and bladder.*