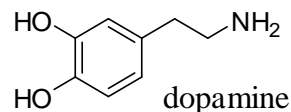
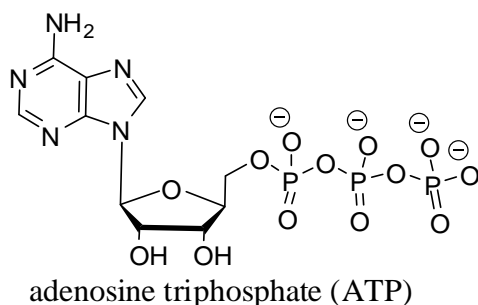


Read each question carefully before answering. Be certain you understand everything the question is requesting. Do the easy questions first. If questions appear confusing or exceedingly complex, then you may need to rethink the question. Keep in mind the intended examination topics.

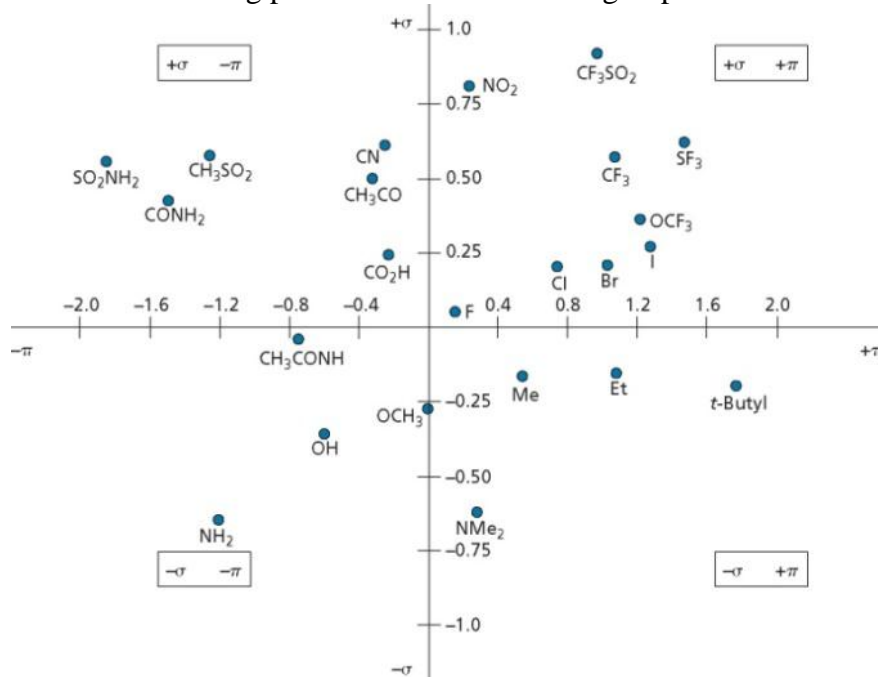
In medicinal chemistry, hand-drawn pictures convey specific information. Be sure the drawing you have made conveys the essential information required to answer the question. Make certain that three-dimensional pictures display the correct atom arrangements. Don't forget to include formal charges when 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 all parts of 7 of the 9 questions including question 7 (DNA drugs) and at least one part of the other 2 questions. Graduate students need to answer all parts of 8 of the 9 questions including question 7 (DNA drugs) and at least one part of the ninth question.



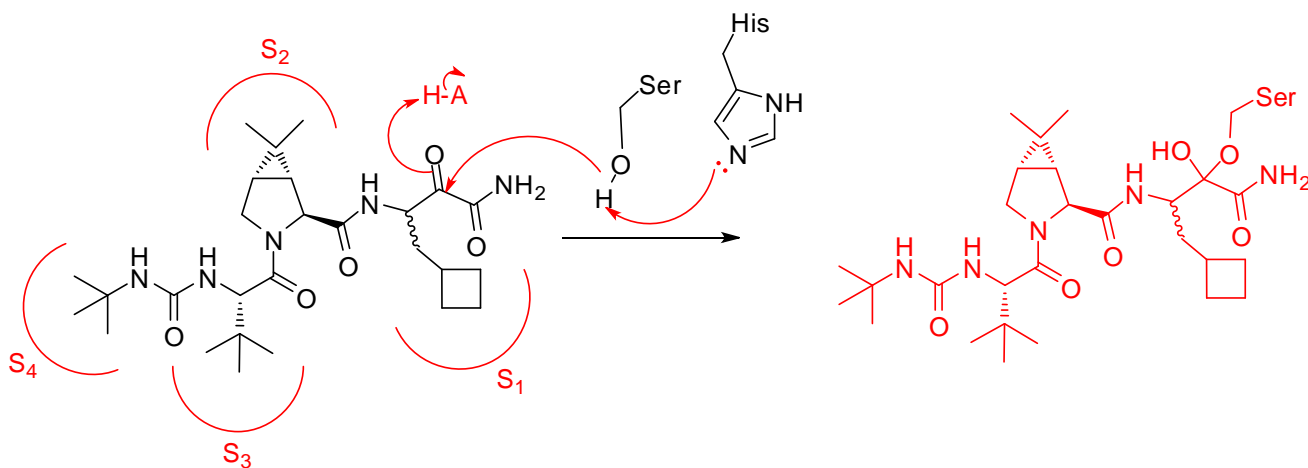
Craig plot of various functional groups:



1. Hepatitis C virus (HCV) protease inhibitors

a) The structure of the drug boceprevir is shown below. On the structure below, identify the enzyme pocket or subsite (S_1 , S_1' , etc.) interactions of boceprevir with HCV protease.

b) Using curved electron flow arrows, show the interaction that occurs with this serine protease and draw the result of this reaction.



Acc. Chem. Res. **2008**, *41*, 50-59.

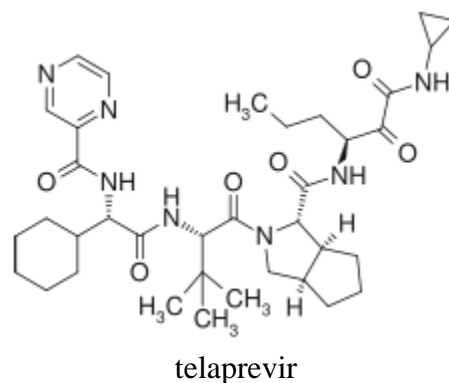
c) There are two leucine isosteres in the boceprevir structure. Identify them. **The S1 and S2 binding groups.**

d) Boehringer-Ingelheim produced another HCV protease inhibitor and reported it in the article entitled: "Discovery of a Potent and Selective Noncovalent Linear Inhibitor of the Hepatitis C Virus NS3 Protease". How did this approach fundamentally differ from that of the Schering-Plough medicinal chemists developing boceprevir? (*J. Med. Chem.* **2010**, *53*, 6466-6476)

The Boehringer drug did not form a covalent bond with the HCV protease, therefore it is a reversible inhibitor, while the Schering-Plough drug, boceprevir was an irreversible inhibitor because it did form a covalent bond with the serine protease enzyme.

e) Our heroes at Vertex developed another drug for HCV treatment that was called telaprevir. Based on the structure how do you believe this drug acts? (*Infectious Disorders - Drug Targets*, **2006**, *6* (1), 3-16.)

Telaprevir has the same electrophilic alpha-keto-amide structure found in boceprevir, so it likely behaves as an irreversible inhibitor as well. It probably reacts with the serine amino acid in the active site just like boceprevir.



2. B-RAF kinase inhibitors

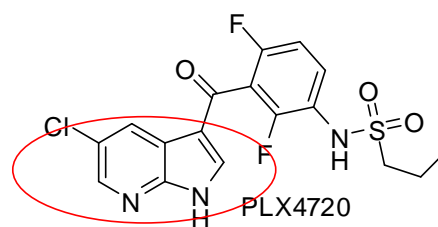
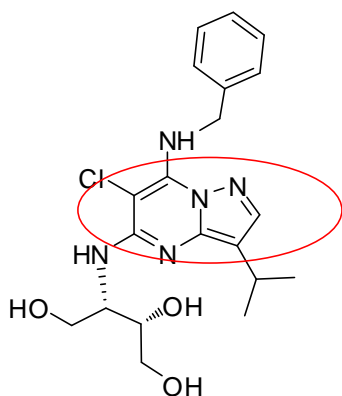
a) What reaction does B-RAF kinase catalyze? Show this reaction including the starting material(s), enzyme, co-enzyme(s) and product(s). Abbreviations are acceptable. (*Nature* **2010**, *467*, 596–599)



b) Why is this reaction a target for cancer treatment?

The phosphorylation of the amino acid side chain alcohols of serine, threonine, and tyrosine or the nitrogen of histidine initiates a cascade of cellular events that trigger cell growth. Uncontrolled cell growth is the hallmark of cancer.

c) The structure of a B-RAF inhibitor, PLX4720, and cyclin dependent kinase (CDK) inhibitor, compound **4k**, are shown below. They, like all kinase inhibitors developed to date, focus on binding in the adenosine triphosphate binding pocket of B-RAF kinase. Circle the specific portion of PLX4720 and compound **4k** that mimic adenosine's structure.



compound **4k** from *J. Med. Chem.* article on cyclin-dependent kinase (CDK) inhibitors (*J. Med. Chem.*, **2010**, *53* (24), pp 8508–8522)

d) Genetic profiling of patients is becoming increasingly important in modern drug therapy. How does the development of the B-RAF kinase inhibitors, PLX4720 and PLX4032, for the treatment of melanomas illustrate the importance of having detailed genetic information about cancer patients?

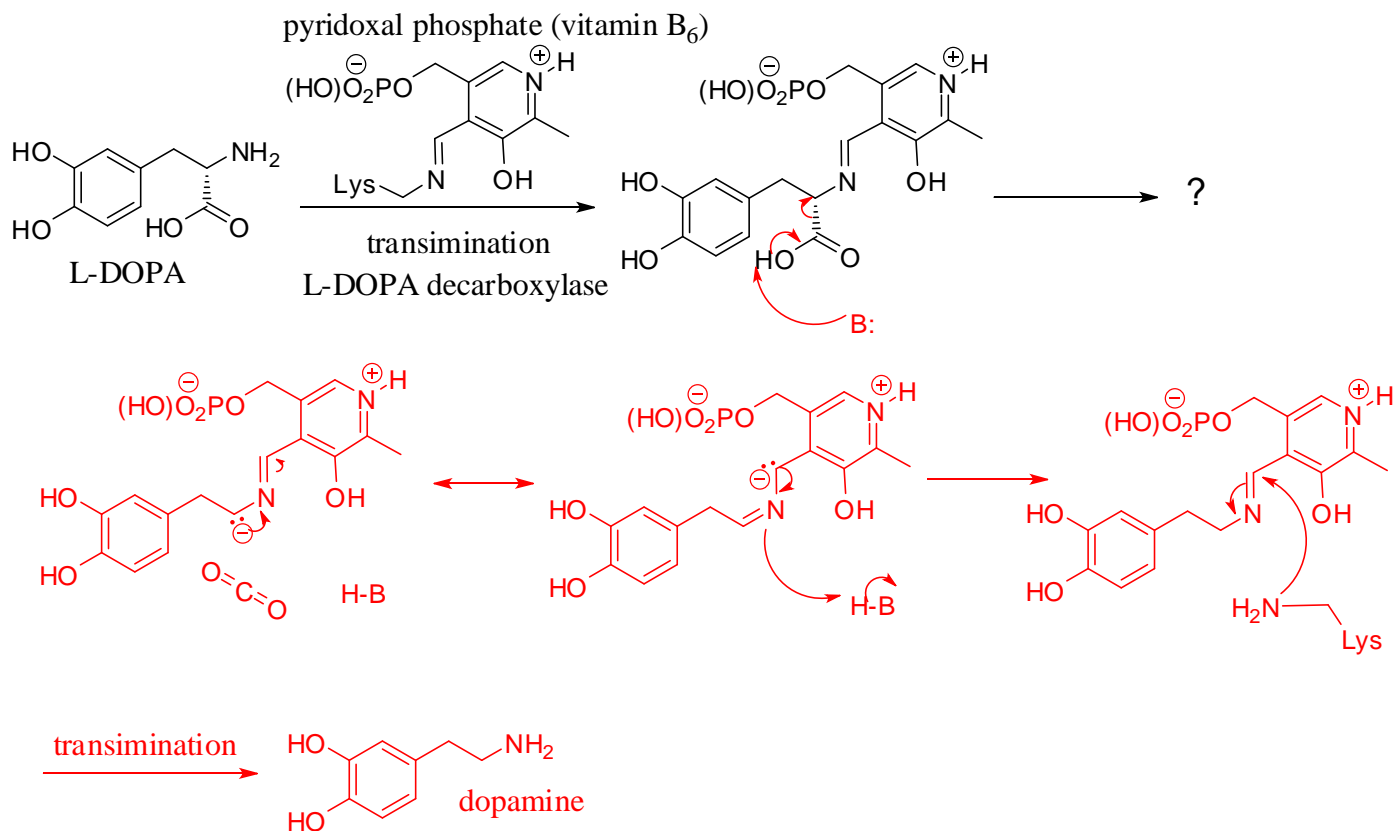
For PLX4720 and PLX4032 to be effective, the melanoma or cancer must have a particular mutation, V600E, in the B-RAF kinase enzyme. Most melanomas have this mutation in the kinase primary peptide sequence and it leads to the kinase enzyme being permanently switched on.

e) Many scientists and physicians see kinase inhibitors like PLX4032 as a revolutionary new way to treat cancer. In some ways, they are the proverbial 'magic bullet' that penicillin was to bacterial treatment. Why is this so?

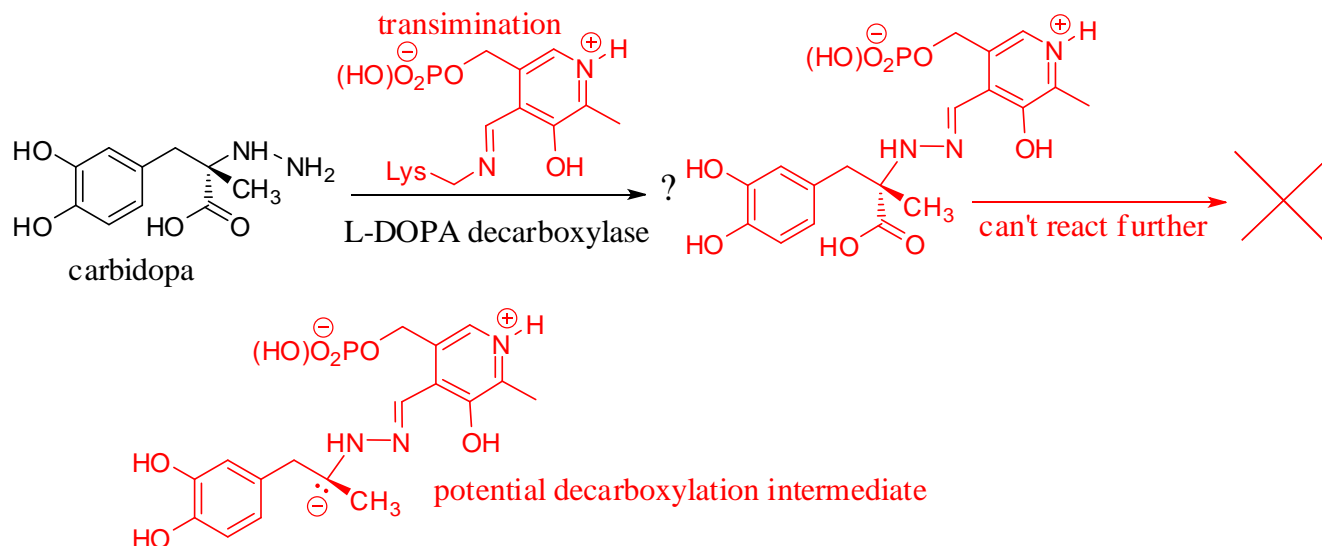
Because the kinase inhibitor PLX4032 selectively inhibits mutated B-RAF kinase, it does not have an effect on B-RAF kinase that is not mutated, i.e. B-RAF kinase in normal, healthy cells. This selective treatment of the infecting cells with no effect on the host cells is the meaning of 'magic bullet' treatment.

3. Parkinson's disease treatment

a) The primary treatment for Parkinson's disease for the past half century has been the use of L-DOPA. In vivo, L-DOPA undergoes the following reaction with L-DOPA decarboxylase and the co-enzyme, pyridoxal phosphate or vitamin B₆. Show the curved electron flow arrow mechanism of this reaction. You may abbreviate where necessary as long as the key atoms involved are shown. Note, I'm such a nice guy, I've given you the first step, the transimination, and you don't have to show any transimination reactions; just show the key reaction to convert L-DOPA to its product. You do need to show one resonance form of an intermediate in the mechanism.



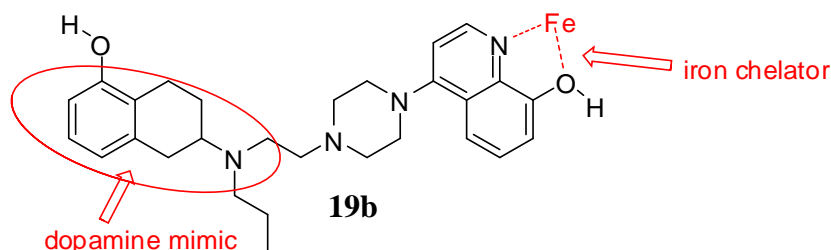
b) L-DOPA is often combined with carbidopa to prevent the L-DOPA decarboxylase reaction from happening in the peripheral nervous system before the L-DOPA gets into the central nervous system. Show how carbidopa might block the reaction with L-DOPA decarboxylase. Be sure to show the intermediate that forms and briefly explain why it can't react in the same way as L-DOPA.



The transimination reaction can occur, but the process stops there. The decarboxylation step would produce an unstable carbanion which does not have a resonance form allowing delocalization of the electrons into the electron deficient pyridine ring of pyridoxal phosphate.

c) The structure of the most potent compound (**19b**) reported by Alope Dutta and co-workers is shown below. Dutta designed the molecule to be both a D2/D3 agonist and an iron chelator. Identify these two portions of the molecule as follows: (i) Show how iron might be chelated in the iron chelation part of the molecule. (ii) Circle the portion of the molecule that is a structural mimic of dopamine and therefore will act as an agonist.

(*J. Med. Chem.*, **2010**, *53* (5), 2114–2125.)

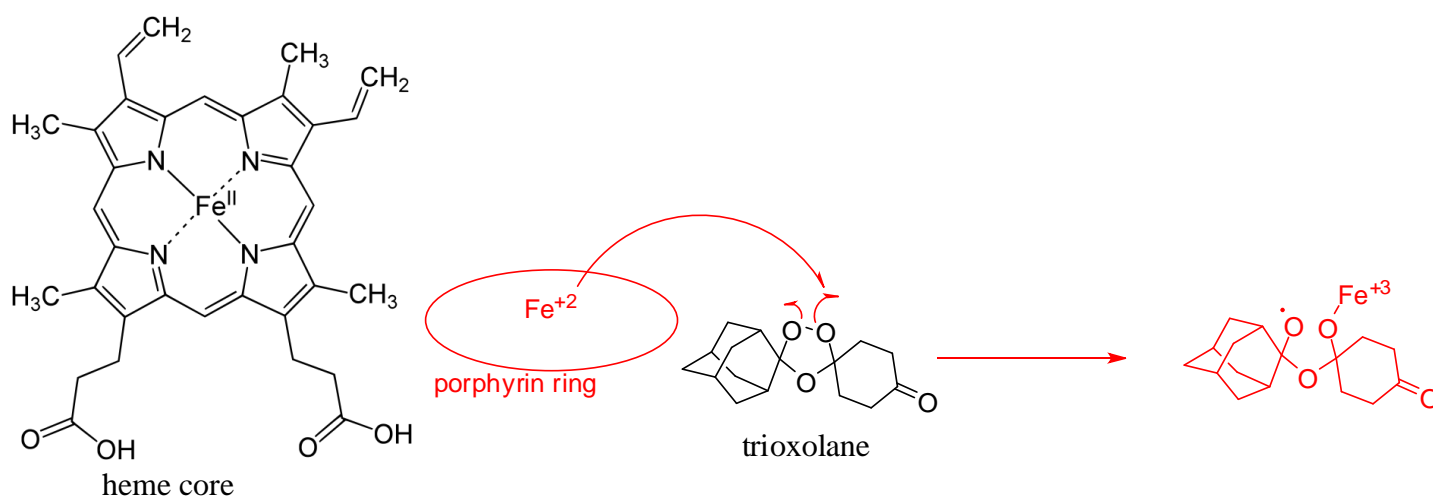


d) Compound **19b** has a slightly different approach to Parkinson's disease treatment than L-DOPA. Briefly explain what is happening in Parkinson's disease and describe the molecular basis of these different approaches to Parkinson's treatment.

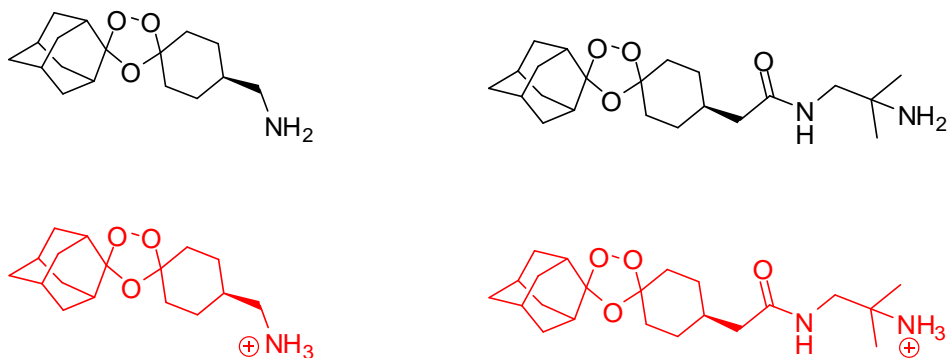
Parkinson's disease is the result of a degradation of the dopamine neurons in the brain. L-DOPA treatment aims to produce greater amounts of the neurotransmitter dopamine in the brain, thereby providing maximum neurotransmitter for the remaining dopamine neurons. Similar to L-DOPA, compound **19b** aims to produce more stimulation of the remaining dopamine neurons, but it does so by providing an artificial agonist, not the natural neurotransmitter. In addition, compound **19b** seeks to remove iron from the area around the nerve to prevent oxidative damage from hydroxyl radicals.

4. Anti-malarial treatment

a) Malaria digests host hemoglobin freeing the heme core (shown below) The trioxolane compound inhibits malaria by reacting with the heme structure. Show this reaction in the space below. Use curved electron flow arrows where appropriate. You may abbreviate as necessary. (*Nature* **2004**, *430*, 900-904.)



b) Although effective in reacting with heme, the trioxolane structure had poor bioavailability. The researchers created the following structures to address this problem. How do these structures address this problem? Draw the structure of these molecules at physiological pH.



Both of these structures add polar groups which have amines that will actually be protonated at physiological pH. These more polar molecules will be more aqueous soluble/hydrophilic and that will improve bioavailability.

c) Figure 1C from Diagona et al. *Science* **2010**, 329, 1175-1180 is reproduced below. CQ is chloroquine, AS is artesunate and NITD609 was the new anti-malarial spiroindolone reported in the article. Answer the following questions about this figure.

(i) What does IC_{50} mean?

The concentration of drug that yields 50% inhibition of whatever is being analyzed, in this case malarial growth.

(ii) Which drug is the least potent?

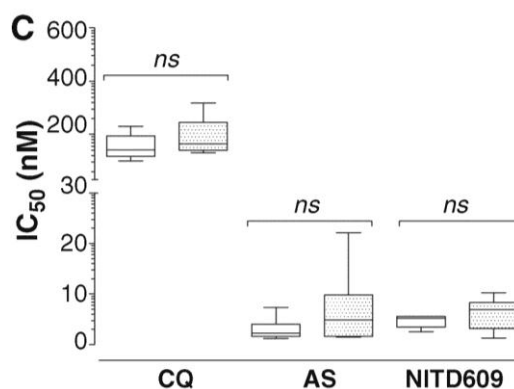
CQ or chloroquine

(iii) Which drug is the most potent?

Artesunate and NITD609 are approximately equipotent. Artesunate might be slightly more potent.

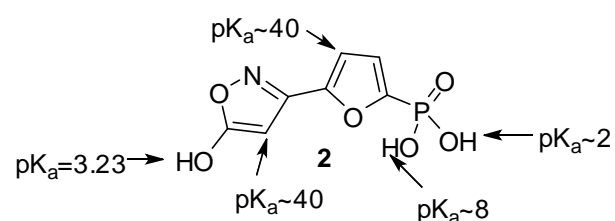
(iv) What is the approximate potency of NITD609?

Roughly 5 nM



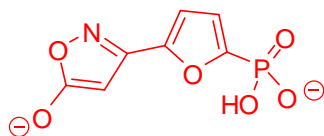
5. Type II diabetes treatment

a) Compound **2** was reported as a potent inhibitor of AMP-activated protein kinase (AMPK). How does compound **2** mimic adenosine monophosphate (AMP)? (*ACS Med. Chem. Lett.*, **2010**, 1 (9), pp 478–482)



Compound **2** has a phosphate group just like AMP and it has a flat aromatic portion just like the purine ring of adenosine.

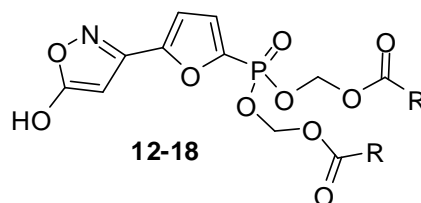
b) Compound **2** had a problem with bioavailability. Based on the pK_a values shown and a physiological pH of ~ 7.4 , what will be the most prevalent form of **2** in the blood stream and why is this a problem?



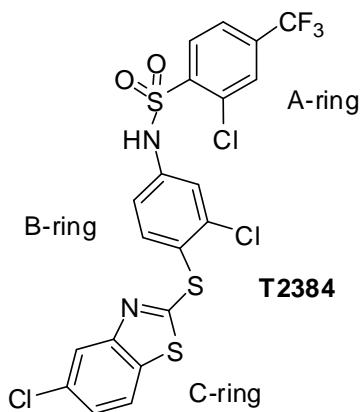
If a drug is too polar, then it cannot easily penetrate lipophilic cell membranes to get to a target within the cell.

c) The medicinal chemistry researchers modified **2** to make **12-18** as shown below. Describe what they did and why this worked to better deliver compound **2**.

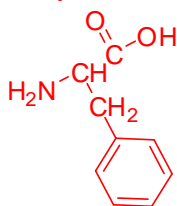
Compound **12-18** have changed the phosphonate acid to a phosphorus ester with a carboxylic ester on the end. The phosphorus ester groups will be more lipophilic and therefore be better able to cross lipophilic cell membranes. Once inside, the carboxylic ester groups are cleaved by esterases found in the cells. This creates the active agent **2**. This is an example of pro-drug design.



d) In their development of a peroxisome proliferator-activated receptor-gamma ($PPAR\gamma$) ligand, the researchers reported an X-ray crystal structure of T2384 bound to the $PPAR\gamma$ active site. They showed one important anchor in holding T2384 in the active site was a π or aromatic stacking between the A ring and Phe363. Draw the structure of phenylalanine and analyze the electronic nature of these two rings, i.e. are these rings electron rich or electron poor? It is often seen that an electron rich-electron poor π stacking interaction is much better than π stacking between two electron poor or two electron rich rings. Given this experimental fact does it make sense that ring A binds in this pocket rather than ring B or C?



Phenylalanine has the following structure:



Since the benzene ring is substituted by an electron releasing group alkyl group ($-CH_2$), this would be an electron rich ring. A-ring is substituted by a sulfonamide, a trifluoromethyl and a chloro group. These are all electron withdrawing groups (see Craig Plot on exam cover) making the A ring electron poor/deficient and capable of pi stacking well with phenylalanine's electron rich ring. B and C-ring both have electron releasing N and S groups which will make them more electron rich than A-ring and less likely to stack with the benzene ring of phenylalanine.

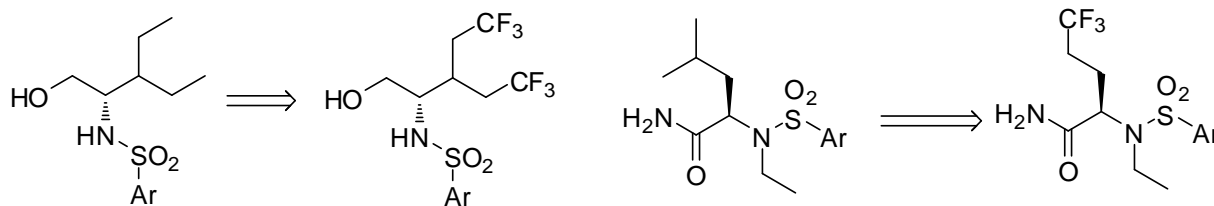
6. Alzheimer's disease treatment

a) What is pregnane X receptor and what does it do? Why is it a problem if drugs activate the pregnane X receptor? (*ACS Med. Chem. Lett.*, **2010**, 1 (3), pp 120–124)

The pregnane X receptor is a nuclear hormone receptor that triggers a cell response to a xenobiotic or foreign chemical. The receptor promotes transcription of cytochrome P450's which are the primary enzyme involved in

phase I metabolic reactions. Increased metabolic activity creates more challenges for getting a drug delivered to the site of action (pharmacokinetics). In addition, activation of pregnane X receptor can lead to greater metabolism of other drugs or xenobiotics.

b) Modifications of lead structures from both articles are shown below. Describe why these modifications were made and how they affected drug action. (*ACS Med. Chem. Lett.*, **2010**, *1* (3), pp 120–124 and *J. Med. Chem.*, **2008**, *51* (23), pp 7348–7351)



A common site of metabolism is terminal alkyl groups where cytochrome P450 enzymes will oxidize a terminal methyl group to a primary hydroxyl. Capping the terminal methyl with a CF₃ group prevents oxidation of the terminal position since the C-F bond is much more difficult to break than the C-H bond.

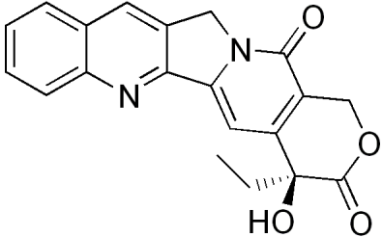
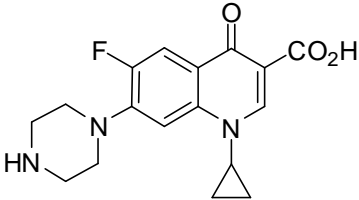
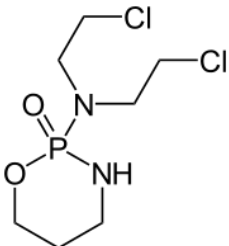
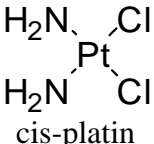
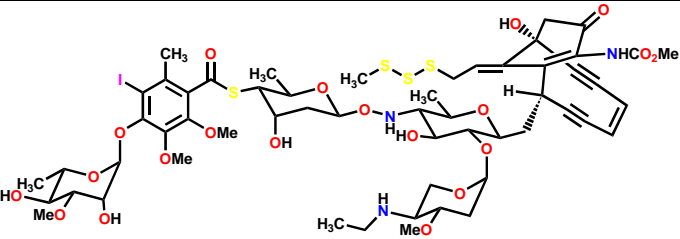
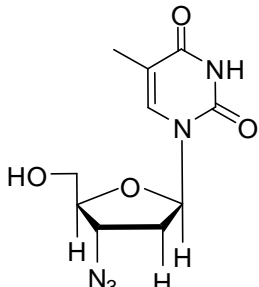
c) What is the goal of the gamma-secretase inhibitors in preventing Alzheimer's disease?

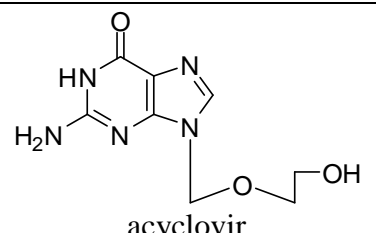
The gamma-secretase inhibitors are trying to block the cleavage of amyloid precursor protein to make amyloid-beta. Mis-shapen amyloid-beta creates plaques in the brain which are believed to contribute to Alzheimer's disease. More specifically, the gamma-secretase inhibitors are trying to reduce the formation of amyloid-beta with 40 and 42 amino acids.

7. Drugs interacting with nucleic acids.

Choose any six of the ten drugs in the table below and provide a succinct description of the mode of action and the disease therapy for which it is used.

<i>drug</i>	<i>therapy</i>	<i>mode of action</i>
<p>chloroquine</p>	anti-malarial drug	intercalating agent in DNA
<p>doxorubicin (adriamycin)</p>	anti-cancer drug	intercalating agent in DNA

 <p>camptothecin</p>	<p>anti-cancer drug</p>	<p>stabilizes topoisomerase-DNA complex</p>
 <p>ciprofloxacin</p>	<p>antibiotic</p>	<p>stabilizes topoisomerase-DNA complex</p>
 <p>cyclophosphamide (cytoxan)</p>	<p>anti-cancer drug</p>	<p>alkylating agent</p>
 <p>cis-platin</p>	<p>anti-cancer drug</p>	<p>alkylating agent</p>
	<p>anti-cancer drug</p>	<p>DNA chain cutter</p>
 <p>AZT (azidothymidine)</p>	<p>anti-viral</p>	<p>chain terminator</p>

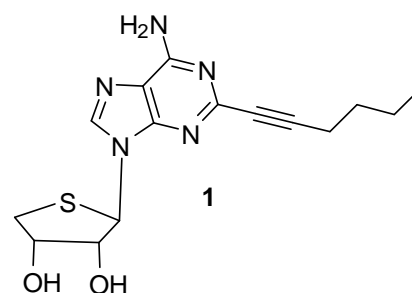
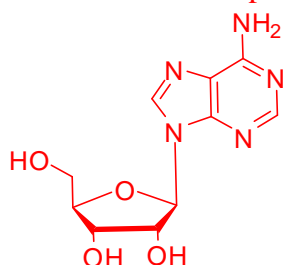
 <p style="text-align: center;">acyclovir</p>	anti-viral	chain terminator
<p>5'-GCG TTT GCT CTT CTT CTT GCG-3', fomivirsen</p>	anti-viral	anti-sense RNA

8. Drug-Receptor question.

Structure **1** (below) was recently featured in an article entitled "Discovery of A New Human A_{2A} Adenosine Receptor Agonist, Truncated 2-Hexynyl-4'-thioadenosine". (*ACS Med. Chem. Lett.*, **2010**, *1* (9), pp 516–520)

a) Draw the structure of the natural agonist of the adenosine receptor.

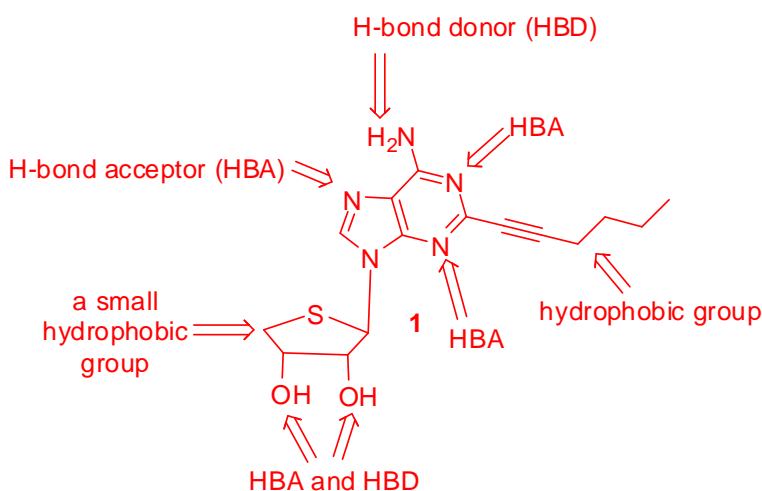
The natural agonist of the adenosine receptor would be adenosine:



b) Identify an isosteric replacement in structure **1** relative to the natural agonist of the adenosine receptor.

The sulfur atom in the five member ring would be a bivalent isostere of the ether oxygen in the ribose ring.

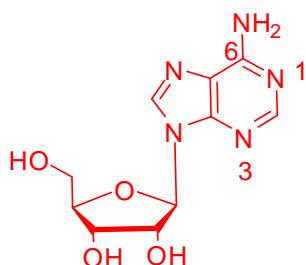
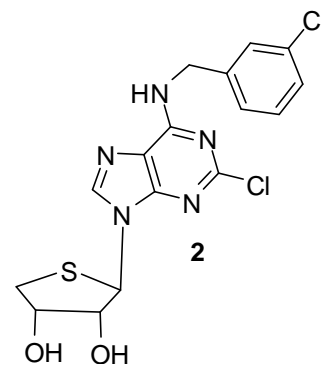
c) Identify the following potential intermolecular interactions on structure **1**: hydrogen bond acceptor, hydrogen bond donor, and a hydrophobic interaction.



d) Structure **2** (below) is an antagonist of the same adenosine receptor. Based on structures **1** and **2**, suggest a general pharmacophore for an adenosine receptor agonist. Similarly, suggest a general pharmacophore for an antagonist. On the molecular level, describe how these two general structures interact with the receptor target to afford the opposite responses. You do not need to describe the intimate details of the adenosine receptor, rather

simply describe a general mechanism that might explain the two different biological responses based on different intermolecular interactions.

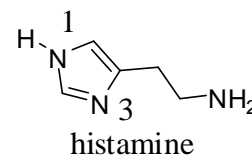
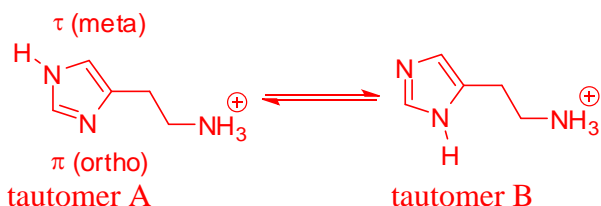
Adenosine agonists have large hydrophobic groups on the C-2 position of the adenosine core, while adenosine antagonists appear to prefer large hydrophobic groups on the C-6 amino group. Correspondingly, there must be two large hydrophobic pockets in the adenosine receptor site that are located in the areas of the C-2 and C-6 positions of the purine ring. The occupation of the hydrophobic pocket near the C-2 position does not preclude an induced fit of the receptor on the molecule and, in fact, its binding stimulates a biological response. Conversely, there must be a large hydrophobic pocket near the C-6 amino group that can accommodate a large greasy group, but upon binding in this region, there is no possibility for an induced fit and a biological response does not occur.



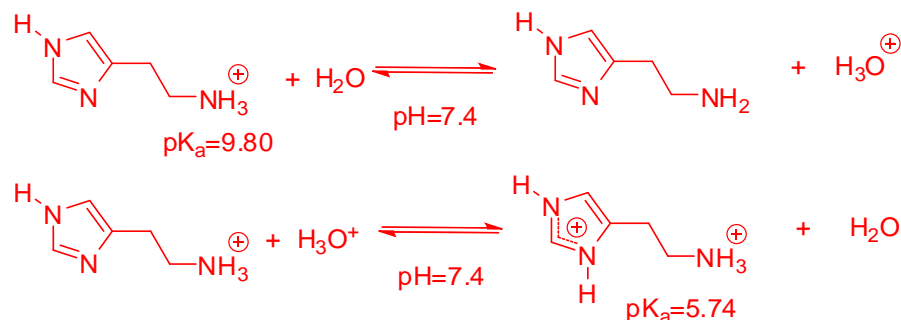
9. Cimetidine

a) The structure of histamine is drawn below. In our discussion of histamine we talked about various tautomers (structural isomers) and physiologically relevant ionization states of the molecule that affected the action of histamine at the histamine receptor.

(i) Draw the two tautomeric forms of histamine that we discussed.

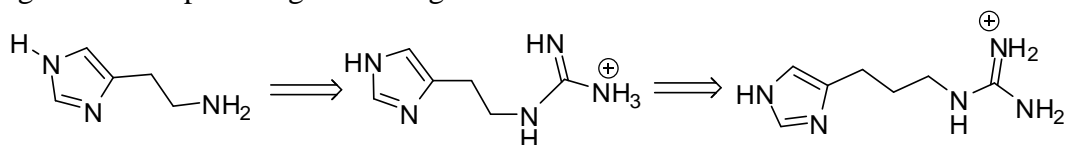


(ii) Draw the two different physiologically relevant ionization reactions of histamine. Draw them as acid-base equilibria.



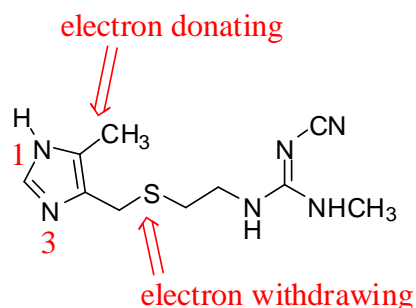
b) The progression of the drug development of cimetidine by James Black and co-workers is shown below. Explain the development of cimetidine as seen in these three structures. What drug development strategy were

they using and what was happening in the interactions at the H₂ histamine receptor to change the histamine agonist into a partial agonist/antagonist?



Cimetidine's drug development started with the natural neurotransmitter, histamine, shown on the left. Functional group replacement of the amine in histamine with a guanidiny group lead to the middle structure, which was the first structural modification that showed mild antagonist/partial agonist activity. Chain extension afforded a derivative on the right that had enhanced antagonist activity. Black and co-workers believed the guanidiny group and chain extension brought the nitrogen functional group out to a new binding region in the H₂ histamine receptor that was either an ionic interaction or an H-bonding site and that was not used by the natural substrate, histamine.

c) The structure of cimetidine is shown below. Identify the electron donating and electron withdrawing functionality that were added to favor the imidazole tautomer shown. Briefly explain how these two groups create their effect.



The C-5 methyl group is electron releasing and adds electron density to the N-1 nitrogen making it more basic. The S on the C-4 alkyl group has a mild polar/inductive effect that withdraws electron density from the proximal N-3 nitrogen making it less electron rich and less inclined to grab a proton. In combination, the two effects lead to more of the tautomer shown.