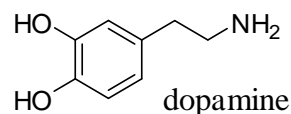
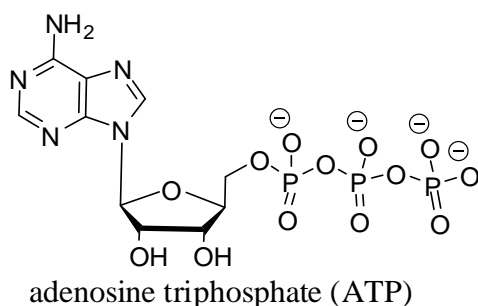


Read each question carefully before answering. Be certain you understand everything the question is requesting. Do the easy questions first. If questions appear confusing or exceedingly complex, then you may need to rethink the question. Keep in mind the intended examination topics.

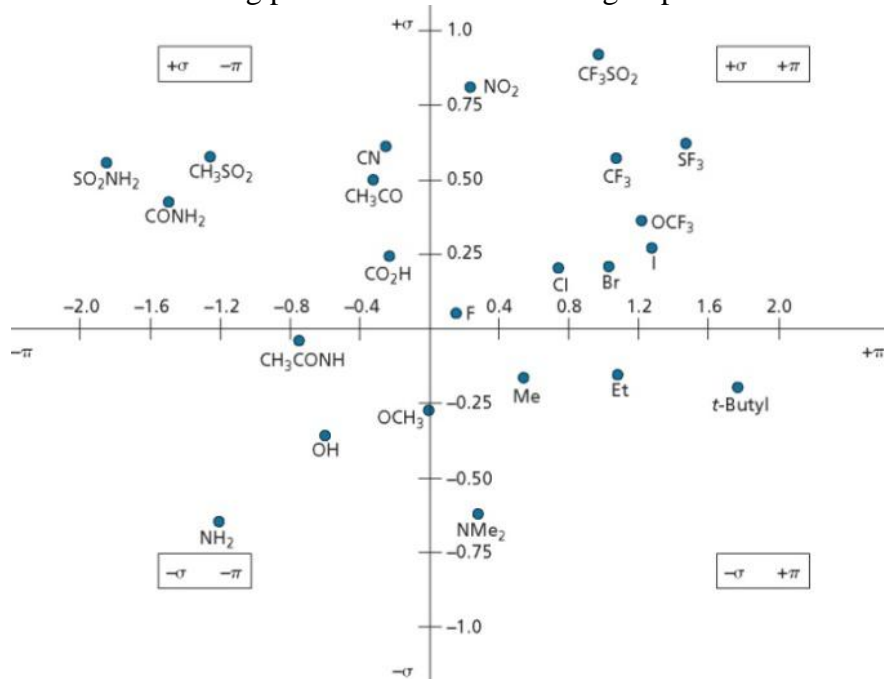
In medicinal chemistry, hand-drawn pictures convey specific information. Be sure the drawing you have made conveys the essential information required to answer the question. Make certain that three-dimensional pictures display the correct atom arrangements. Don't forget to include formal charges when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



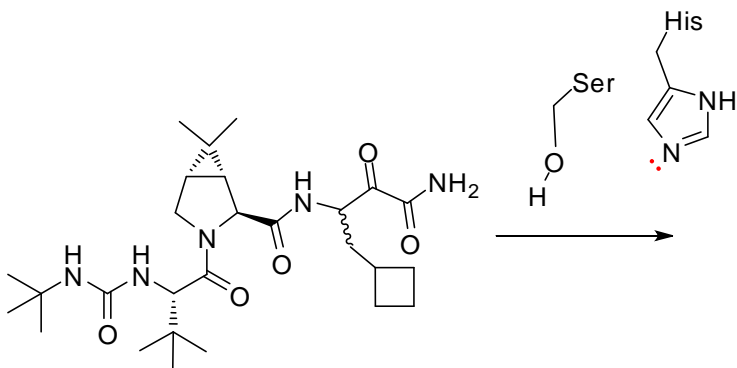
Craig plot of various functional groups:



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.

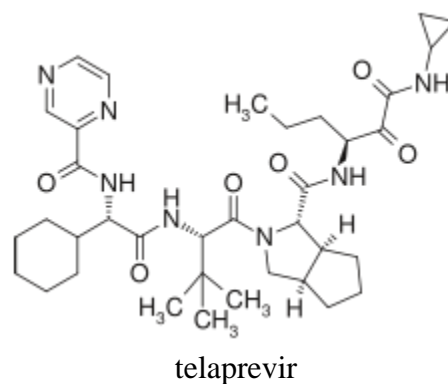
b) Using curved electron flow arrows, show the interaction that occurs with this serine protease and draw the result of this reaction.



c) There are two leucine isosteres in the boceprevir structure. Identify them.

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?

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?

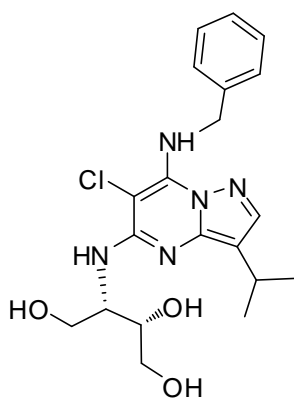


2. B-RAF kinase inhibitors

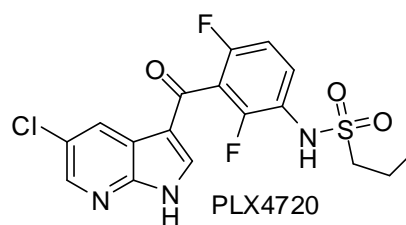
a) What reaction does B-RAF kinase catalyze? Show this reaction including the starting material(s), enzyme, co-enzyme(s) and product(s). Abbreviations are acceptable.

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

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

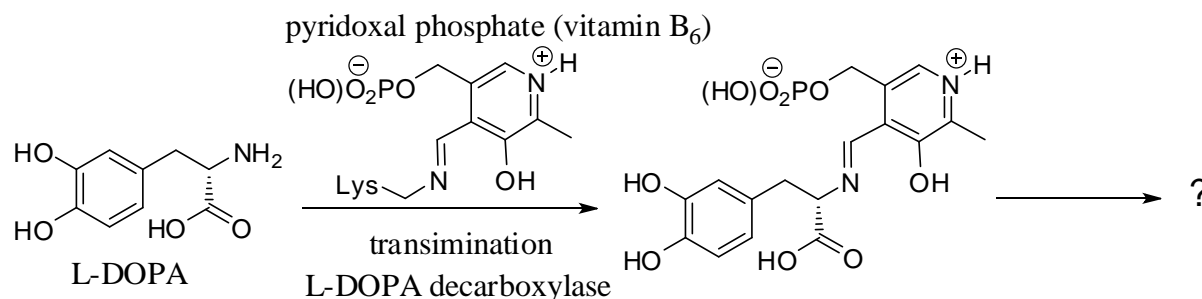


d) Genetic profiling of patients is becoming increasingly important in modern drug therapy. How does the development of the B-RAF kinase inhibitors, PLX4720 and PLX4032, for the treatment of melanomas illustrate the importance of having detailed genetic information about cancer patients?

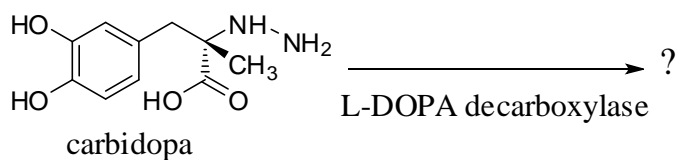
e) Many scientists and physicians see kinase inhibitors like PLX4032 as a revolutionary new way to treat cancer. In some ways, they are the proverbial 'magic bullet' that penicillin was to bacterial treatment. Why is this so?

3. Parkinson's disease treatment

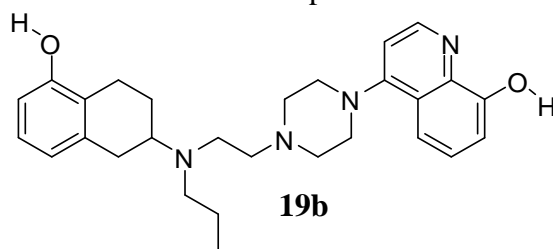
a) The primary treatment for Parkinson's disease for the past half century has been the use of L-DOPA. In vivo, L-DOPA undergoes the following reaction with L-DOPA decarboxylase and the co-enzyme, pyridoxal phosphate or vitamin B₆. Show the curved electron flow arrow mechanism of this reaction. You may 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.



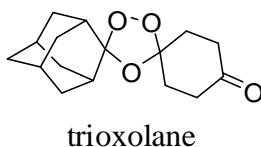
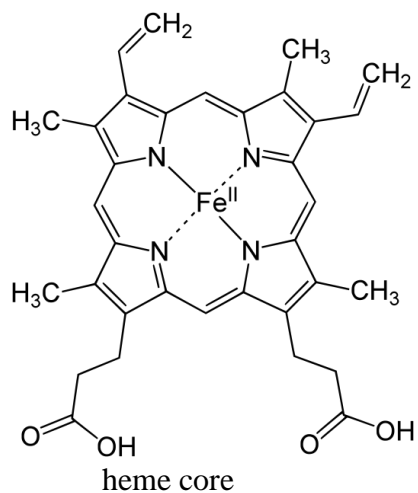
c) The structure of the most potent compound (**19b**) reported by Alope Dutta and co-workers is shown below. Dutta designed the molecule to be both a D2/D3 agonist and an iron chelator. Identify these two portions of the molecule as follows: (i) Show how iron might be chelated in the iron chelation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



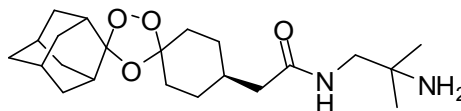
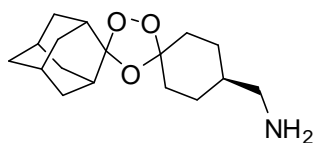
d) Compound **19b** has a slightly different approach to Parkinson's disease treatment than L-DOPA. Briefly explain what is happening in Parkinson's disease and describe the molecular basis of these different approaches to Parkinson's treatment.

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.



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.



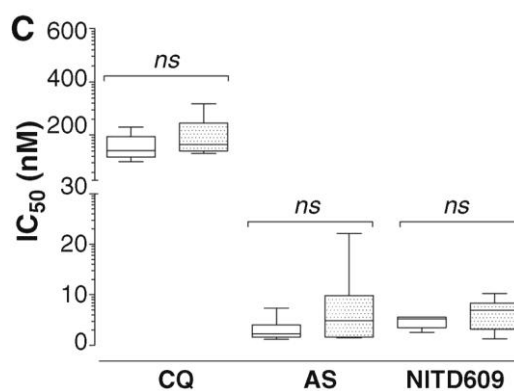
c) Figure 1C from Diagona et al. *Science* **2010**, 329, 1175-1180 is reproduced below. CQ is chloroquine, AS is artesunate and NITD609 was the new anti-malarial spiroindolone reported in the article. Answer the following questions about this figure.

(i) What does IC_{50} mean?

(ii) Which drug is the least potent?

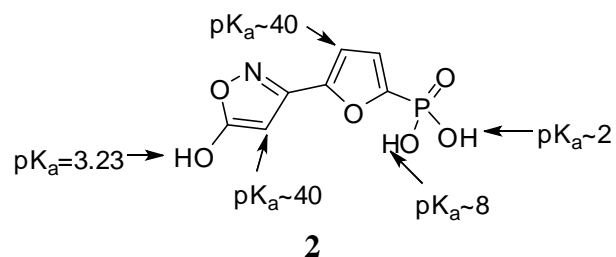
(iii) Which drug is the most potent?

(iv) What is the approximate potency of NITD609?



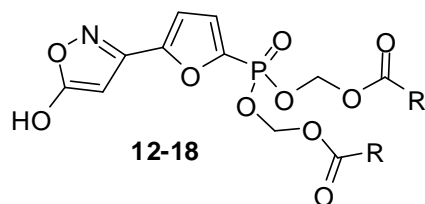
5. Type II diabetes treatment

a) Compound **2** was reported as a potent inhibitor of AMP-activated protein kinase (AMPK). How does compound **2** mimic adenosine monophosphate (AMP)?

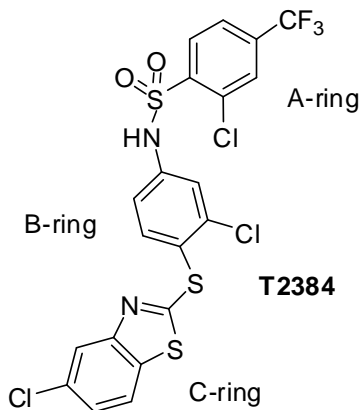


b) Compound **2** had a problem with bioavailability. Based on the pKa values shown and a physiological pH of ~7.4, what will be the most prevalent form of **2** in the blood stream and why is this a problem?

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**.



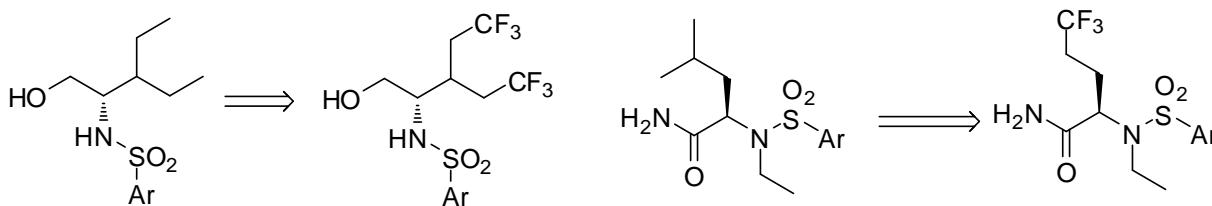
d) In their development of a peroxisome proliferator-activated receptor-gamma (PPAR γ) ligand, the researchers reported an X-ray crystal structure of T2384 bound to the PPAR γ active site. They showed one important anchor in holding T2384 in the active site was a π or aromatic stacking between the A 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?



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?

b) Modifications of lead structures from both articles are shown below. Describe why these modifications were made and how they affected drug action.

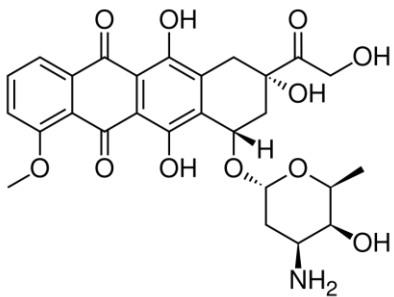


c) What is the goal of the gamma-secretase inhibitors in preventing Alzheimer's disease?

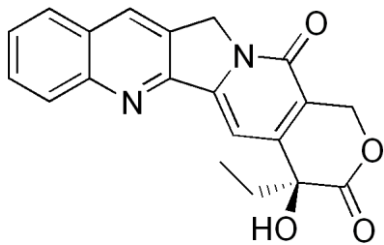
7. Drugs interacting with nucleic acids.

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.

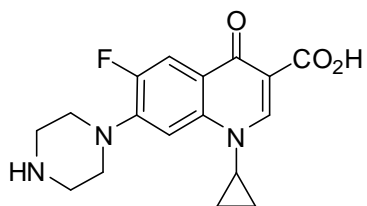
<i>drug</i>	<i>therapy</i>	<i>mode of action</i>
<p>chloroquine</p>		



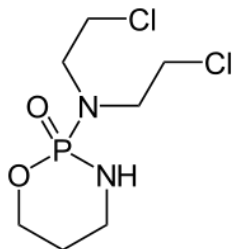
doxorubicin (adriamycin)



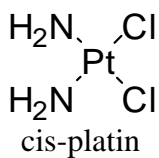
camptothecin



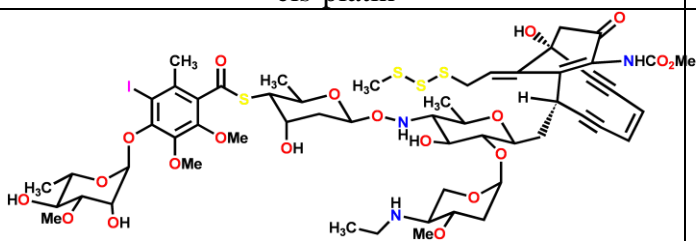
ciprofloxacin

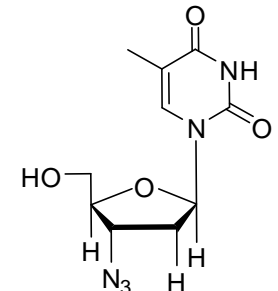
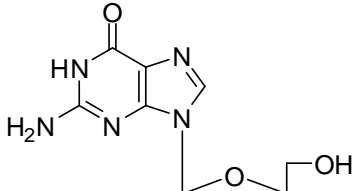


cyclophosphamide (cytoxan)



cis-platin

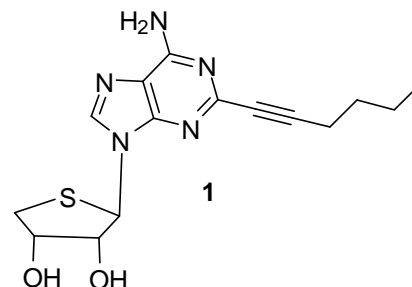


 <p>AZT (azidothymidine)</p>		
 <p>acyclovir</p>		
<p>5'-GCG TTT GCT CTT CTT CTT GCG-3', fomivirsen</p>		

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".

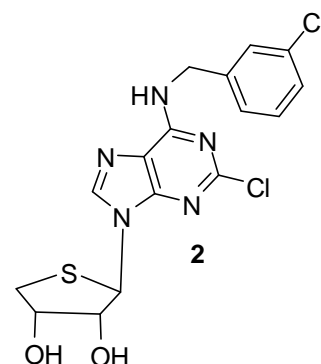
a) Draw the structure of the natural agonist of the adenosine receptor.



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

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

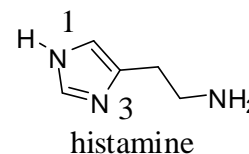
d) Structure **2** (below) is an antagonist of the same adenosine receptor. Based on structures **1** and **2**, suggest a general pharmacophore for an adenosine receptor agonist. Similarly, suggest a general pharmacophore for an antagonist. On the molecular level, describe how these two general structures 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.



9. Cimetidine

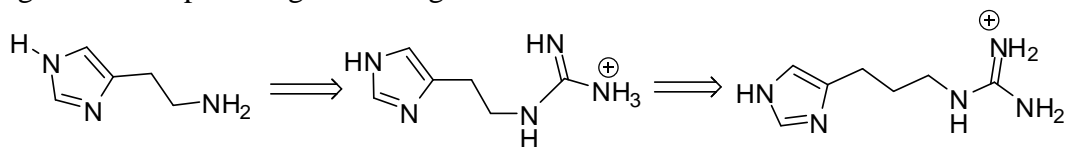
a) The structure of histamine is drawn below. In our discussion of histamine we talked about various tautomers (structural isomers) and physiologically relevant ionization states of the molecule that affected the action of histamine at the histamine receptor.

(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?



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.

