Answers to the Final Exam
CHM 535/435 Medicinal Chemistry
May 8, 2013

Print Name _____

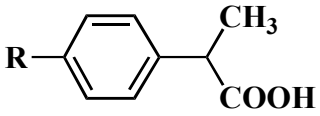
Sign Name _____

Post I.D. # _____

Please print your name of the last page too. This is the page (page 20 for this exam) where your grade will appear. Write answers only in spaces provided. Answers written on the back of pages will not be graded.

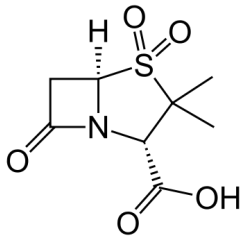
1. (60 pts) Multiple choice/fill in the blanks. Put your answer in the space provided.

A a) The following are the π values for various substituents R on the aromatic ring of the drug shown below. Which substituent will increase the lipid solubility of this drug the most?



A) CF_3 (1.07)
B) Br (0.94)
C) OCH_3 (-0.02)
D) CH_2OH (-1.03)
E) They will all make the drug equally lipophilic.

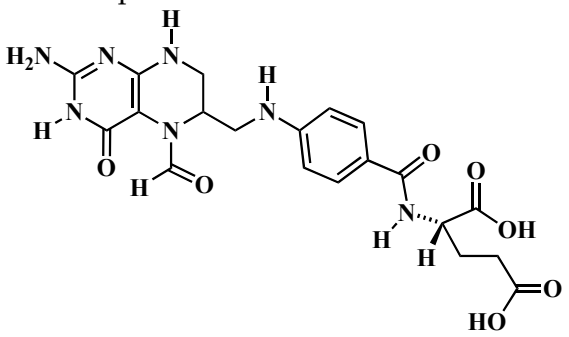
D b) The compound shown below:



I. Inhibits bacterial cell wall synthesis.
II. Inhibits β-lactamase.
III Is combined with a penicillin antibiotic to overcome resistance.

A) I only
B) III only
C) I and II only
D) II and III only
E) I, II, and III

C c) The compound shown below:

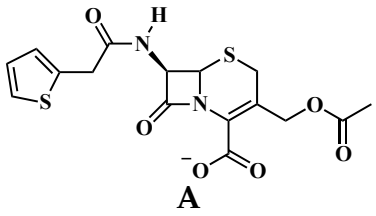


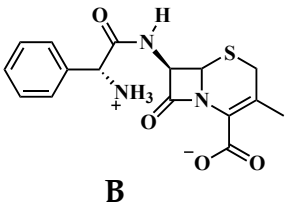
I. Is used for rescue therapy after high dose methotrexate.
II. Is used to enhance the activity of the cancer drug 5-fluorourcil.
III. Is an antifolate used in cancer chemotherapy.

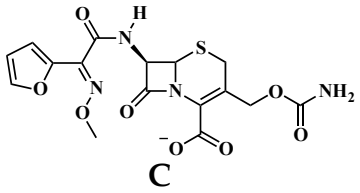
.

A) I only
B) III only
C) I and II only
D) II and III only
E) I, II, and III

E d) Which of the following cephalosporins possesses intrinsic β-lactamase activity?


A


B

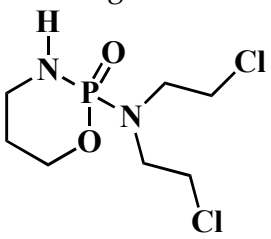

C

A) A
B) B
C) C
D) A and B
E) A and C

B e) In which part of the GI track will a carboxylic acid based drug be best absorbed?

A) Mouth (pH 6-7)
B) Stomach (pH 1-3)
C) Small Intestine (pH 7-7.5)
D) Colon (pH 8)
E) It is not absorbed when given orally.

D f) The drug shown below:



I. Is classified as a mitotic spindle poison.
II. Is classified as a prodrug.
III. Is classified as an alkylating agent.

A) I only

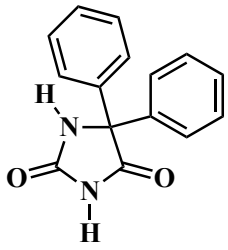
B) III only

C) I and II only

D) II and III only

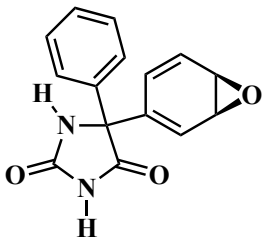
E) I, II, and III

A g) Which of the following phenytoin metabolites could be toxic?



Phenytoin

A)



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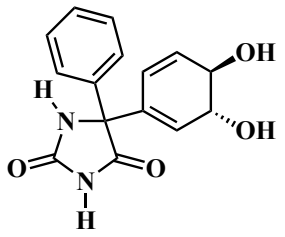
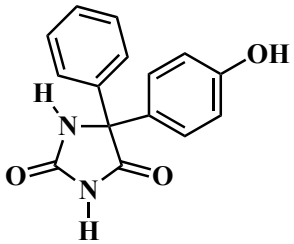
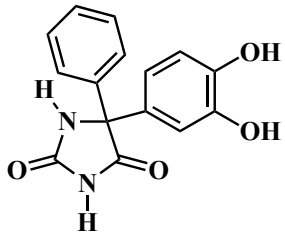


C)

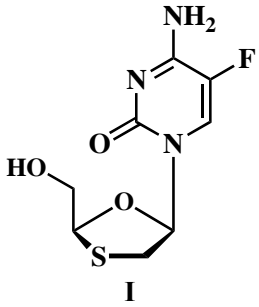


D)

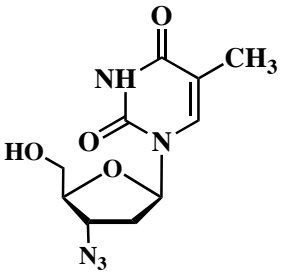


E) Both **B** and **D**

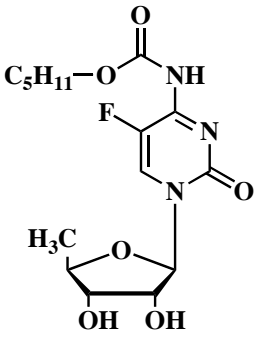
A h) The HAART regimen for the treatment of HIV requires two nucleoside reverse transcriptase inhibitors. Choose two nucleoside reverse transcriptase inhibitors from the following choices.



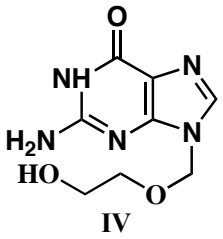
I



II



III



IV

A) I and II

B) II and III

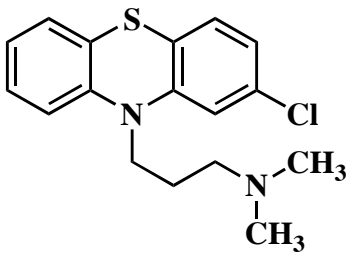
C) III and IV

D) I and III

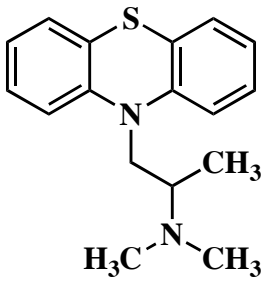
E) II and IV

B i) Which of the agents below is not a neuroleptic?

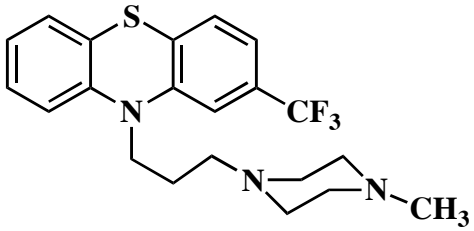
(A)



(B)



(C)



(D) None are Neuroleptics

(E) All are Neuroleptics.

B j) Mechanism of action for streptomycin:

A) Blocks reverse transcriptase

B) Blocks protein synthesis

C) Blocks RNA polymerase

D) Blocks the topoisomerase enzyme

E) None of the above

D k) Mechanism(s) of cellular resistance to polyfunctional alkylating drugs include:

A) Decreased DNA repair capability

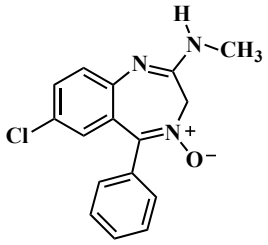
B) Reduced production of glutathione

C) Increased permeability to the drug

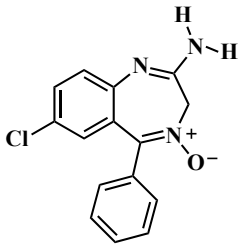
D) None of the above

E) All of the above

E l) Which of the following metabolites of the sedative hypnotic chlordiazepoxide is inactive?



Chlordiazepoxide

A)


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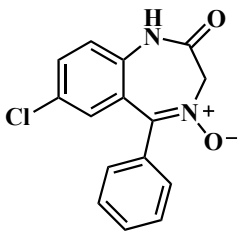
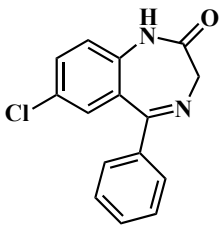
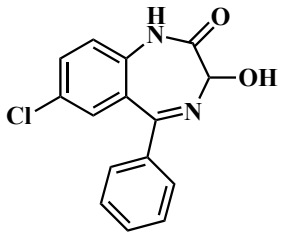


C)


D)


E) All metabolites shown are active.

D m) Erythromycin is:

A) Is a macrolide antibiotic.

B) Prevents A to P translocation on ribosomal RNA.

C) Interferes with bacterial cell wall formation.

D) A and B

E) B and C

E n) Lipid solubility and drugs:

A) More of the weak acid drug will be in the lipid-soluble form at alkaline pH.

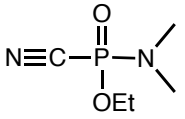
B) More of the weak acid drug will be in the lipid soluble form at acid pH.

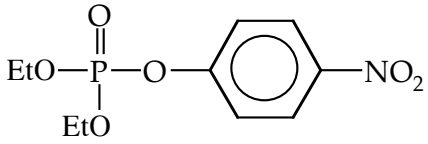
C) More of the weak base drug will be in the lipid soluble form at alkaline pH.

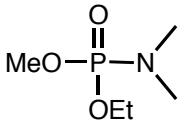
D) A & C

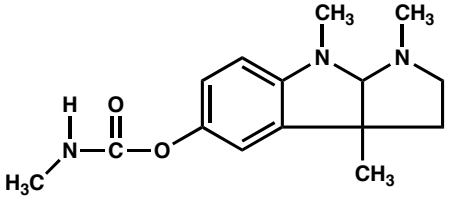
E) B & C

C o) All of the following are acetylcholinesterase inhibitors except:

A) 

B) 

C) 

D) 

E) None of these compounds are acetylcholinesterase inhibitors.

A p) A negative Hammett sigma value means that a functional group:

A) Donates electrons to a ring. **B)** Doesn't affect the ring.

C) Withdraws electrons from the ring **D)** Makes the ring more flexible

C q) Means by which physiological effects due to cAMP-dependent processes are terminated:

A) Reuptake

B) Gene regulation change

C) Cyclic-AMP Degradation

D) A & B

E) A, B & C

D r) Inhibitors of cyclic nucleotide phosphodiesterases (enzymes that degrade cyclic AMP and GMP)

A) Caffeine

B) Theophylline

C) Neither

D) Both

A s) Immediate biosynthetic precursor of epinephrine:

A) Norepinephrine

B) Isoproterenol

C) Metaraminol

D) Dopamine

E) L-DOPA

A t) Cytochrome-P_{450} INDEPENDENT oxidation

A) Monoamine oxidase

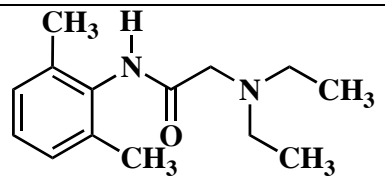
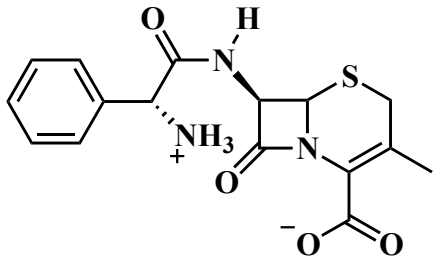
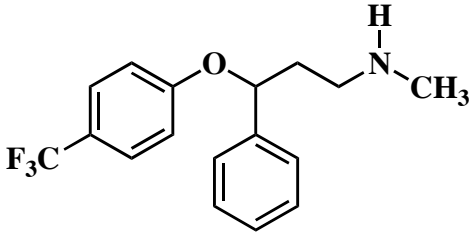
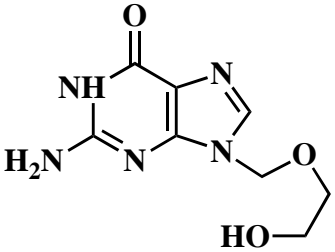
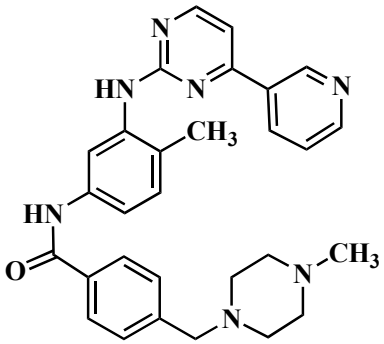
B) Epoxidation

C) N-oxidation

D) S-oxidation

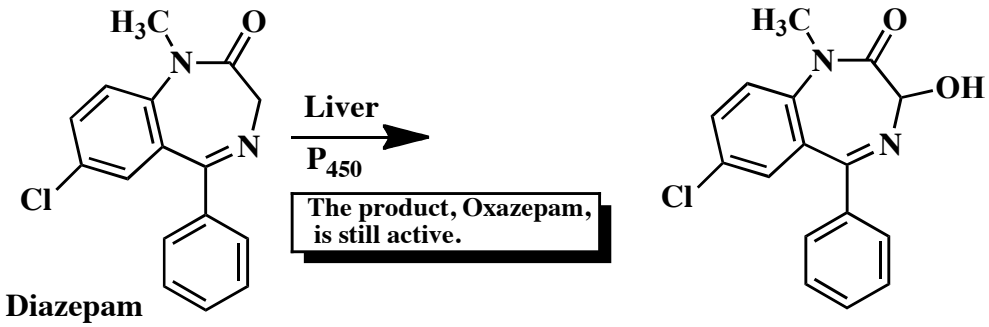
E) Deamination

2. (30 pts) Classify each of the following structures with respect to physiological activity and utility, if any, as a drug.

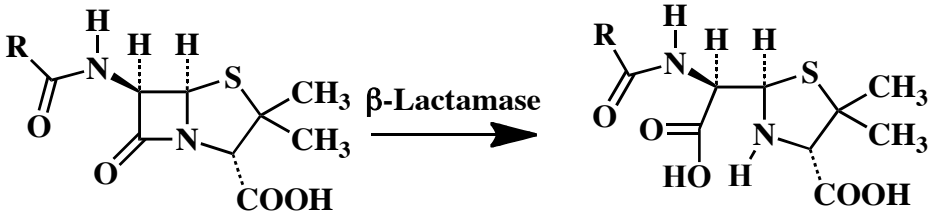
Structure	Physiological Action	Utility: What disease, if any, is the drug used to treat?
 Lidocaine	Interferes with sodium ion flux interaction with phospholipids	Local anesthetic
 Cefalexin (Keflex)	Cephalosporin – based inhibitor of bacterial peptidoglycan formation	Bacterial infections without β-lactamase resistance.
 Prozac	Prozac is a selective serotonin reuptake inhibitor. Acts at 5-HT_{2a} and 5-HT_{2c} receptors.	Used to treat depression
 Acyclovir	Acyclovir is phosphorylate by HSV kinases to afford the triphosphate. DNA polymerase incorporates acyclovir into viral DNA resulting in chain termination.	Used to treat herpes
 Gleevec (Imatinib)	Targets a tyrosine kinase, produced by an oncogenic mutation that is always activated.	Used to treat chronic myelogenous leukemia and other cancers.

3. (50 pts) Predict the products of the following reactions. If there is no reaction write "NR." Draw out complete phosphate structures for full credit.

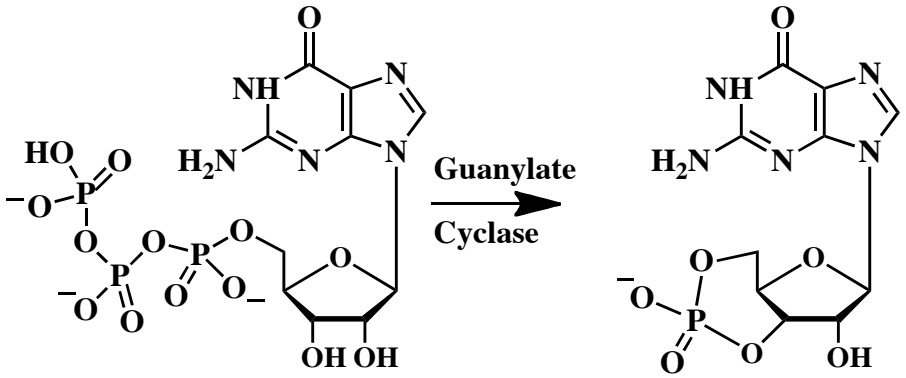
a)



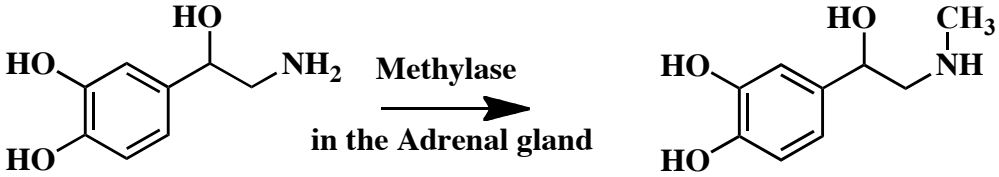
b)



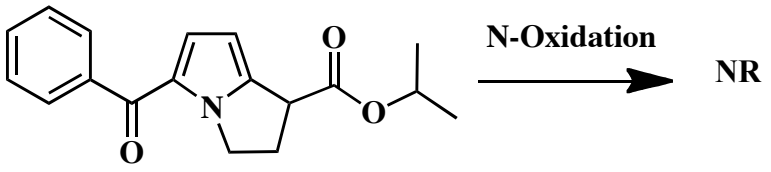
c)



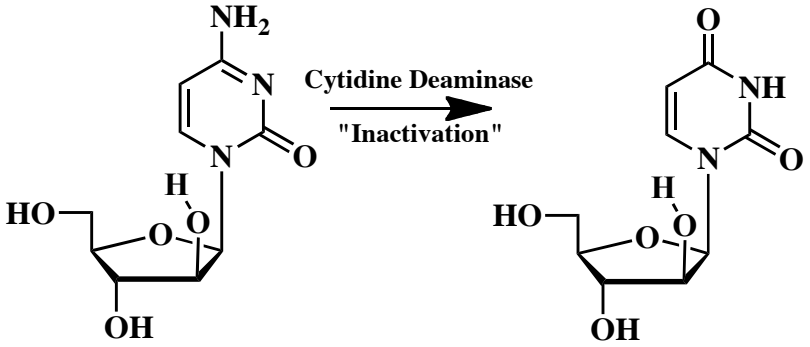
d)



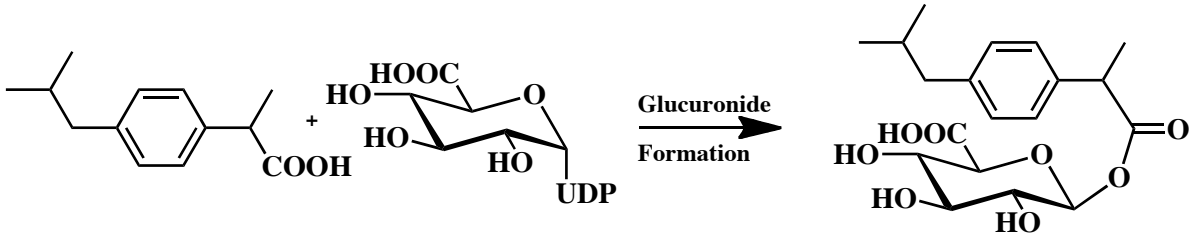
e)



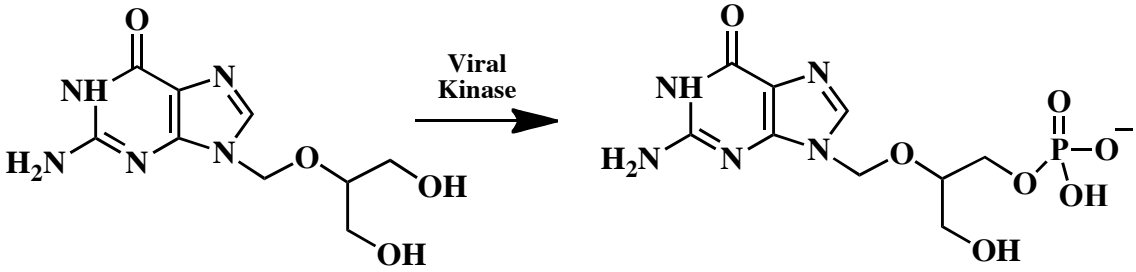
f)



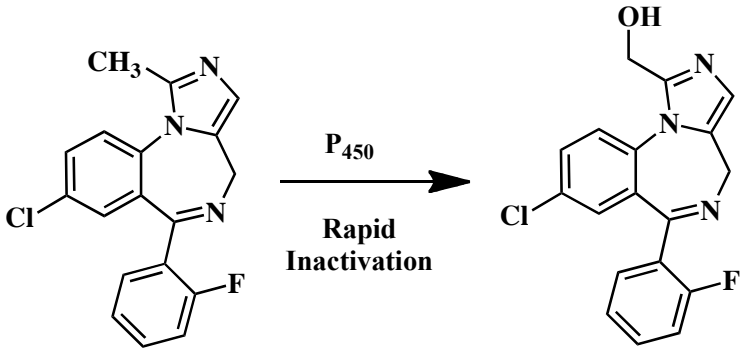
g)



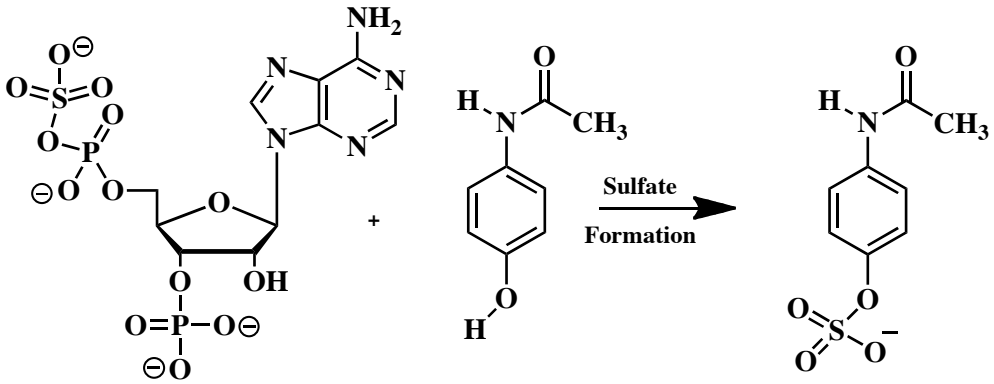
h)



i)

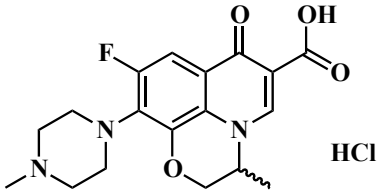


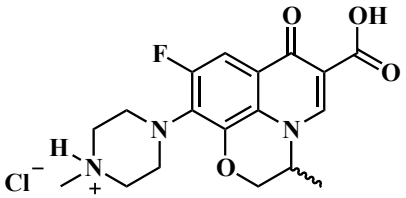
j) Only show the Acetaminophen metabolic product.



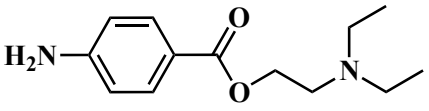
4. (45 pts) Repeat Problems from In Class Exams. The score on these questions will be used to decide borderline cases (within 25 pts/1000 pts from the next higher grade).

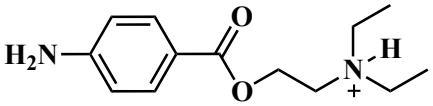
a) 10 pts Drugs are formulated as salts to increase solubility. Write the structure of the ionic form of each of the following drugs showing the cation and anion on the appropriate atoms.





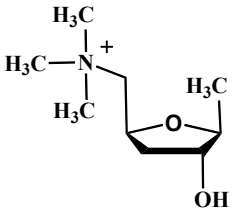
Ofloxacin HCl

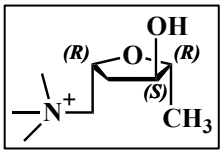




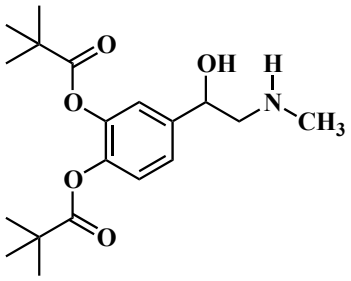
Procaine Hydrochloride

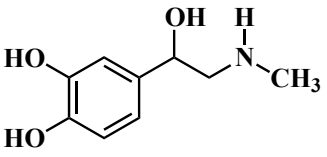
b) 5 pts Draw the (-) enantiomer of (+) muscarine shown below.



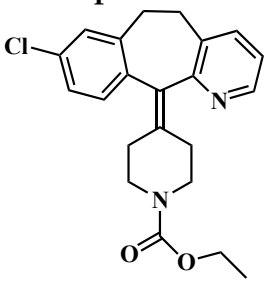


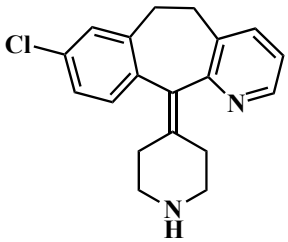
c) 10pts Prodrugs. Show the active metabolite structures formed from the following prodrugs. If the product is an inactive metabolite, show the structure and write "Inactive Metabolite."





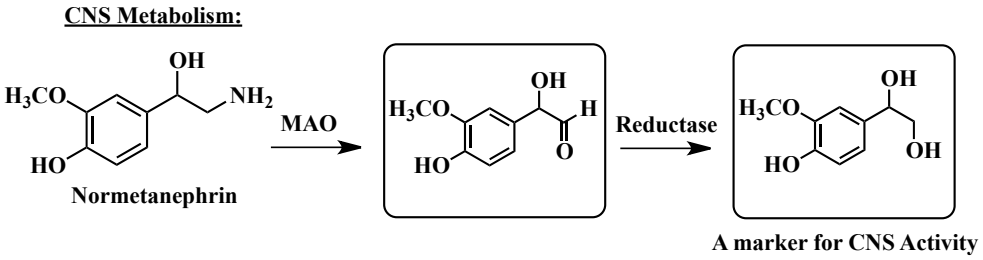
Dipivefrin



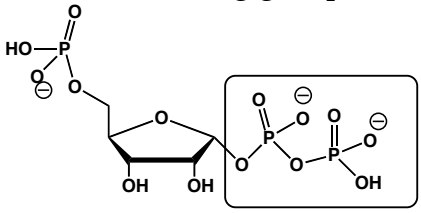


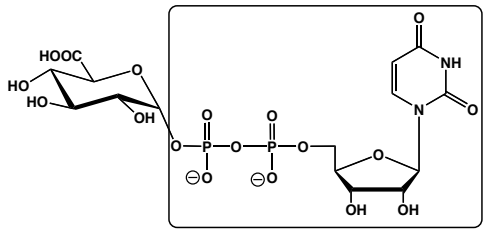
Claritin

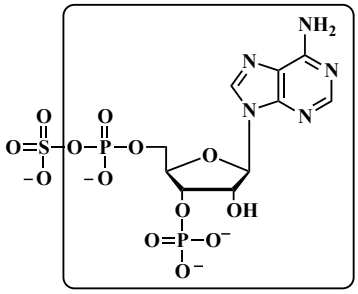
d) 5 pts Predict the product of the following reaction. If there is no reaction, write NR.



e) 10 pts Circle the leaving group in each of the following compounds.

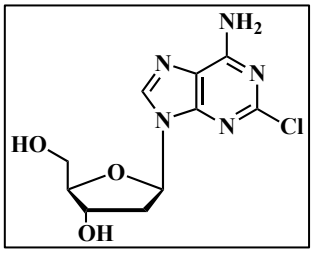






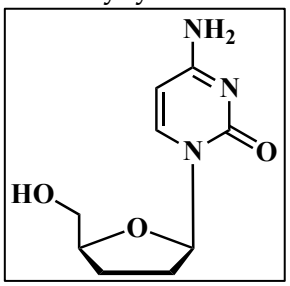
f) 5 pts Draw the requested structure with stereochemistry if needed.

Cladribine (2-chloro-2′-deoxyadenosine)

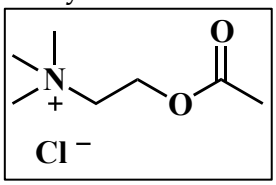


5. (50 pts) Nomenclature Provide names or structures of the following. Draw the requested structures with stereochemistry if needed. Please draw out phosphates.

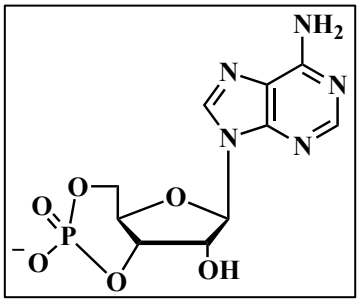
a) Dideoxycytidine



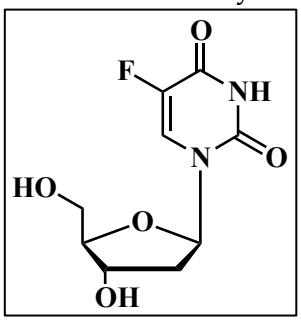
b) Acetylcholine Chloride



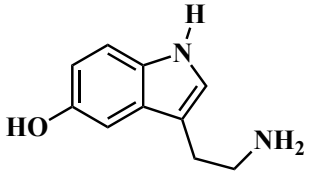
c) c-AMP



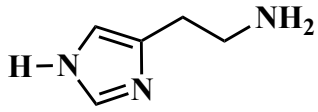
d) 5-Fluoro-2′-deoxyuridine



e) Serotonin

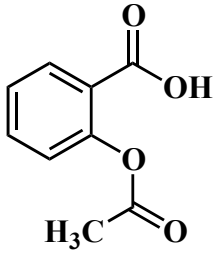


f) Common Name for



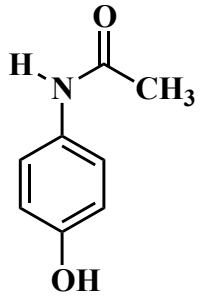
Histamine

g) Common Name for



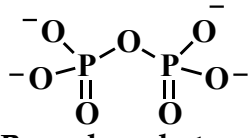
Aspirin

h) Common Name for



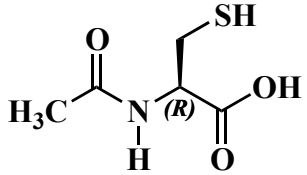
Acetaminophen (or Tylenol)

i) Common Name for



Pyrophosphate

j) Common Name for

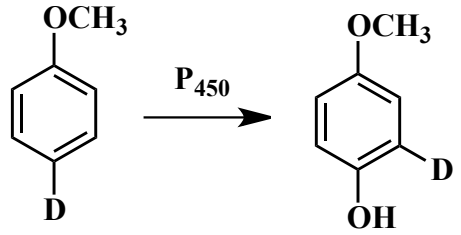


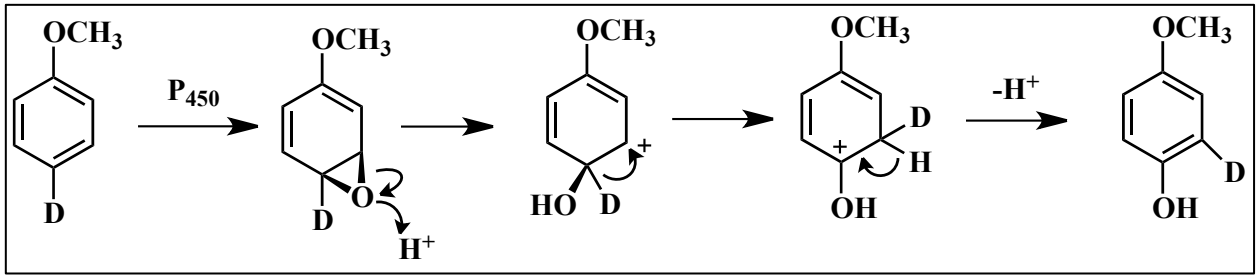
N-Acetylcysteine (Mucomyst or Acetadote)

6. (40 pts) Mechanism Problems

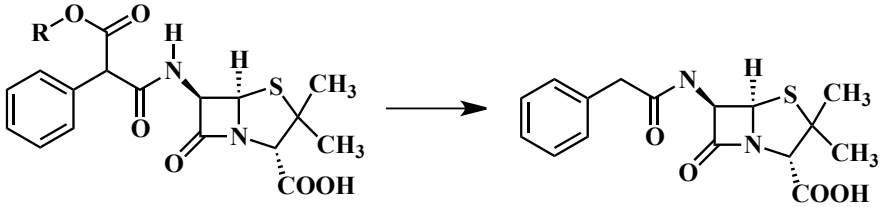
Provide a mechanism showing curved arrows and important intermediates for each of the following reactions.

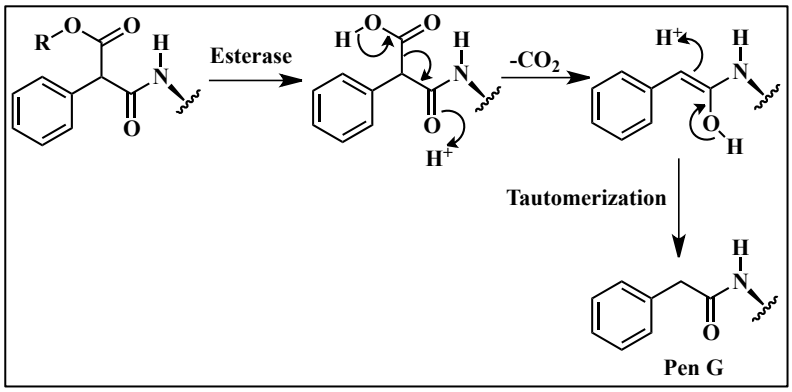
(a) The metabolism of 4-deuteriomethoxybenzene by P_{450} yields the product shown below. Provide a mechanism for the formation of this product.





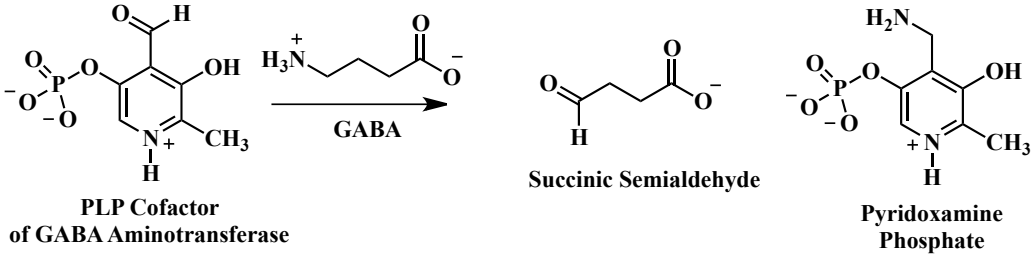
(b) Carbenicillin esters are metabolized to Pen G. Provide a mechanism.

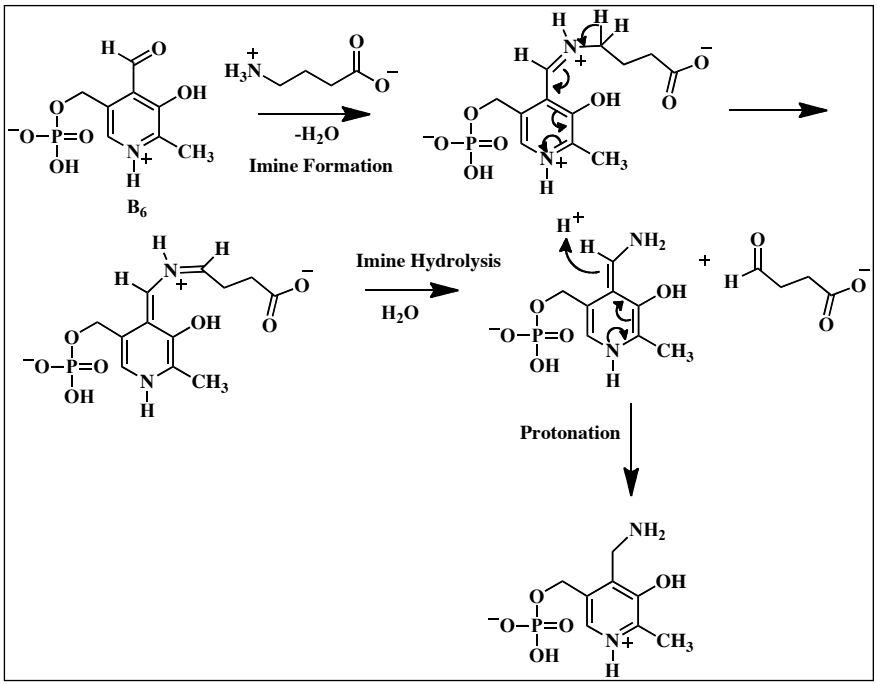




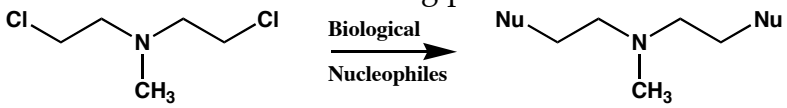
c) GABA Aminotransferase is a pyridoxal phosphate (PLP) -utilizing enzyme that catalyzes

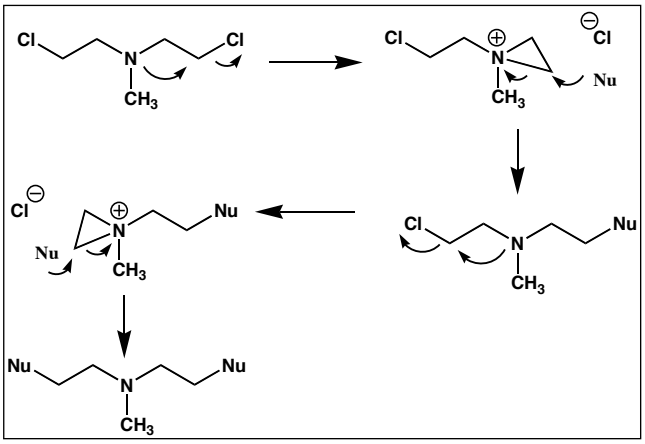
the formation of succinic semialdehyde and pyridoxamine phosphate from GABA. Show all intermediates in this process along with the curved arrows that afford the products shown. You do not have to show the mechanisms of imine formation and hydrolysis.





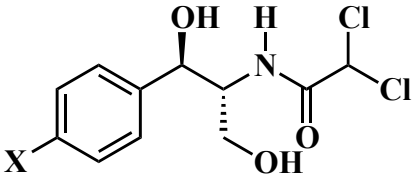
d) Nitrogen mustards are crosslinkers that are both chemical warfare agents and antitumor agents. Provide a mechanism for the crosslinking process.





7. (20 pts) QSAR. A series of substituted chloramphenicol derivatives were investigated to determine the influence of the aromatic substituent, X, on antibiotic activity (A). Analyze the following Hansch relationship:

$$\text{Log A} = 0.48\pi - 0.54\pi^2 + 2.14\,\sigma_m + 0.22$$



a) 5 pts. Why is σ_m used when the substituent X is in the *para* position?

The σ_m constant is used because the substituent influences antibiotic activity by an inductive substituent effect only, not because of the position of the substituent. A σ_p constant would be used if both inductive and withdrawing substituent effects contributed to biological activity.

b) 5 pts. Based on the Hansch Relationship, what type of substituent results in optimal activity? Check the appropriate box.

☒ Electron withdrawing

☐ Electron Releasing

(c) 5 pts. Determine the value for π that gives maximum activity. (Determining π will require some basic algebra)

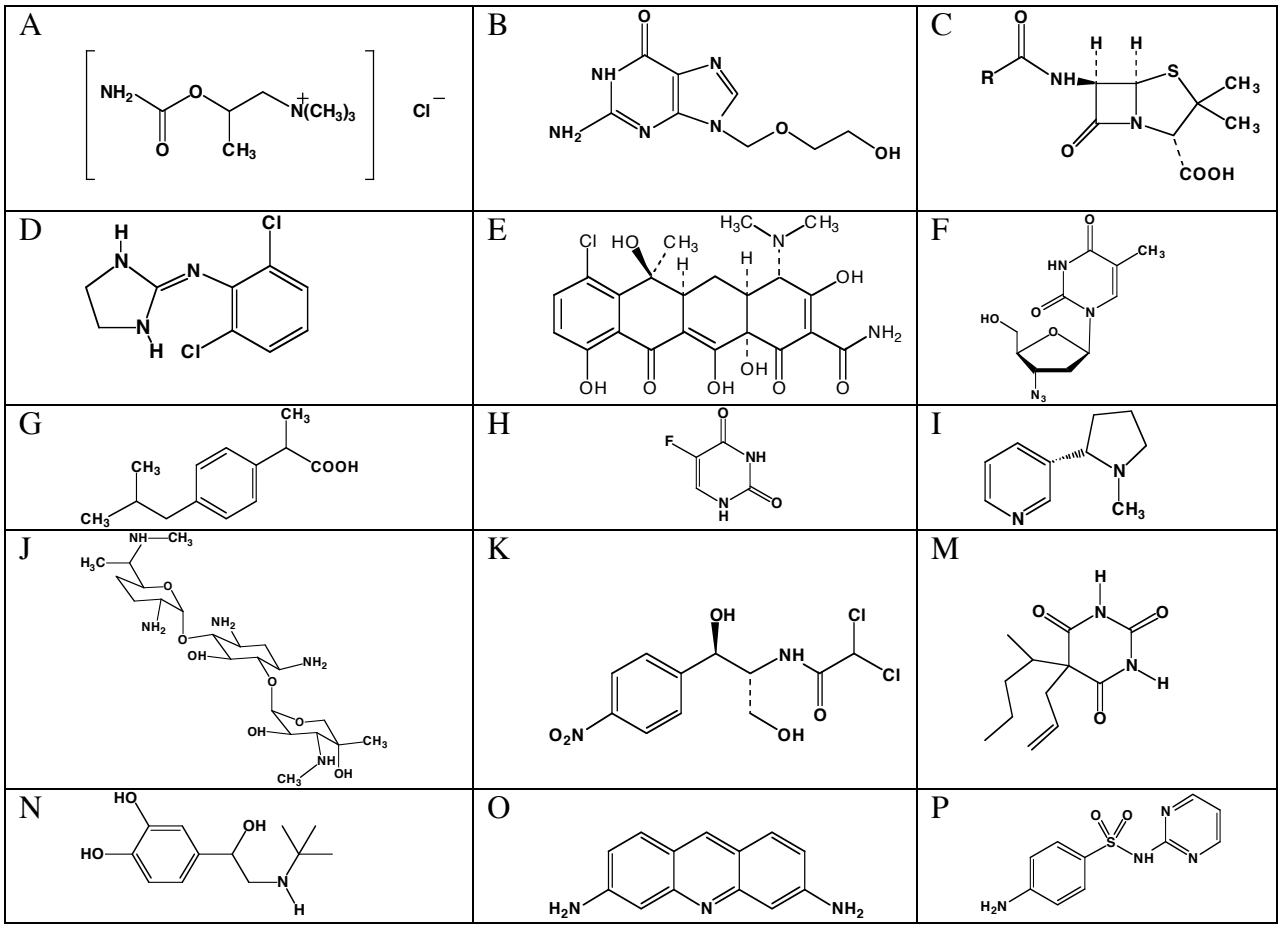
$$0 = \frac{d(LogA)}{d\pi} = 0.48 - 1.08\pi$$
$$0.48 = 1.08\pi$$
$$\pi = 0.44$$

(d) 5 pts. What is the meaning of the constant 0.22?

The constant is the value of Log A when X= H.

8. (40 pts) Match the structures A-M on the following page with the descriptions below:

I	An inhibitor of bacterial peptidylglycan crosslinking	C
II	Cyclooxygenase Inhibitor	G
III	Treats high blood pressure by stimulating α_2 receptors	D
IV	Inhibits bacterial ribosome function by blocking the A-site.	E
V	An inhibitor of viral reverse transcriptase	F
VI	Inhibits bacterial ribosome function by inhibiting pepidyl transferase	K
VII	An inhibitor of bacterial folate synthesis	P
VIII	A barbituate sedative hypnotic	M
IX	An antiviral causing DNA chain termination	B
X	A cholinergic agonist	A



9. (65 pts) Cancer Chemotherapy and HAART.

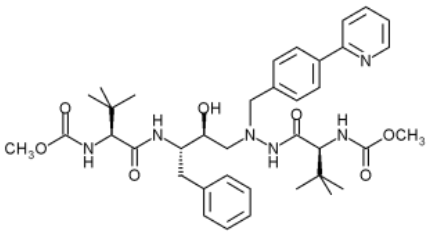
a) 15 pts FOLFIRI is a drug regimen used for treating metastatic colon cancer. State the role each of these drugs play in the treatment of colon cancer. The FOLFIRI drugs are:

Leucovorin, ***A 5-formyl derivative of tetrahydrofolic acid that increases the level of thymidylate synthase cofactor thereby enhancing the effect of 5-fluorouracil.***

Irinotecan, ***An analogue of camptothecin that inhibits Topoisomerase I.***

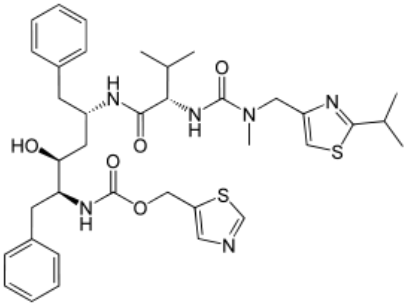
Fluorouracil, Converted to the ***thymidylate synthase inhibitor FdUMP. Thymidylate synthase inhibition results in "thymineless death" of the rapidly dividing cancer cells.***

b) 15 pts HAART (highly active anti retroviral therapy) involves treating HIV infections with a combination of drugs. The drugs used in a HAART regimen are provided below. State the role each of these drugs play in the treatment of HIV infections. Merely stating the drug's target is not a sufficient answer.



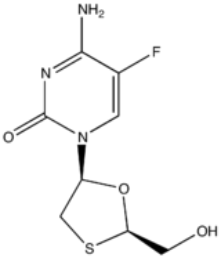
Atazanavir

Protease Inhibitor.
This compound competitively inhibits the proteolytic enzyme involved in maturation of virions.



Ritonavir

Protease Inhibitor.
This compound competitively inhibits the proteolytic enzyme involved in maturation of virions.

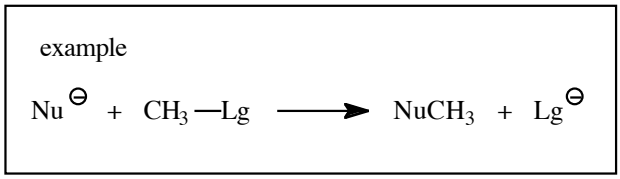


Emtricitabine

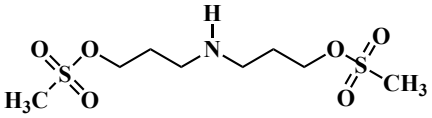
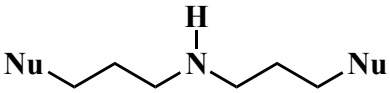
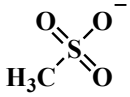
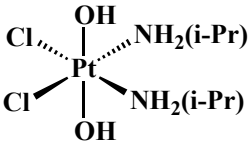
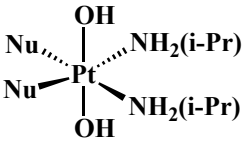
Nucleoside-Analog Reverse Transcriptase Inhibitors (NRTI).
These drugs inhibit viral RNA-dependent DNA polymerase (reverse transcriptase) and are incorporated into viral DNA resulting in chain termination.

c) 10 The following antitumor agents are either in clinical use or under investigation

pts at the National Cancer Institute. For each compound show the structure of the nucleophile substitution product using "Nu^-" as your generic nucleophile.



Note that some agents may react with a nucleophile more than once; show the product resulting from nucleophilic reaction at all possible sites. Also show the structure of the leaving group(s) resulting from these reactions.

Antitumor Agent	Nucleophile Substitution Product	Leaving Group(s)
		
		Cl^-

d) 25 pts Dacarbazine is one of the drugs used to treat Hodgkin's Lymphoma. The mechanism of action involves hepatic activation as a methylating agent. Provide the structures of the intermediates and final products.