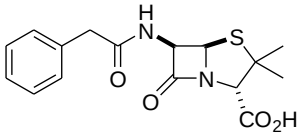
BPS 2110 Intro to Biopharm
Mid Term 2 Answers

1) Complete the following table describing pathogen classification. (**8 Points**)

	Risk characteristics	Type of lab protection (provide one or two as indicated)
Class 1	- No risk or low risk (limited risk)	a) Open bench
Class 2	- Moderate risk	2 of - Limited lab access - Lab coat - Laminar hood
Class 3	- High risk (death or serious illness)	2 of - Restricted access - Gowns, gloves - Respirators - Low pressure room - Airlocks - Liquids/gases filtered - All materials exiting autoclaved and incinerated
Class 4	- Extreme risk (Lethal highly infectious untreatable)	2 of - Restricted access - Low pressure room - Airlocks - Special training - "space suits" - Shower before entering/exiting - Liquids/gases filtered - All materials exiting autoclaved and incinerated

2) This structure is the basis of most modern antibiotics.



a) What enzyme does it inhibit? (**1 Point**)

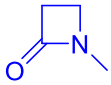
transpeptidase

b) How does inhibition of this enzyme cause bacterial death? (**4 Points**)

Bacteria cannot make cross-links in cell walls

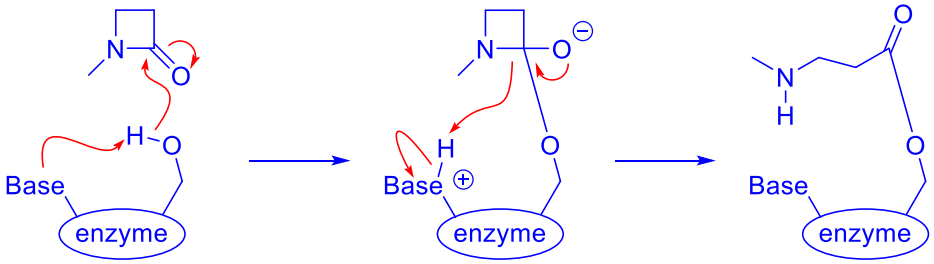
internal pressure (osmotic) causes the cells to rupture during cell division

c) What functional group structure in the molecule shown above is responsible for enzyme inhibition (name and structure)? (**2 Points**)

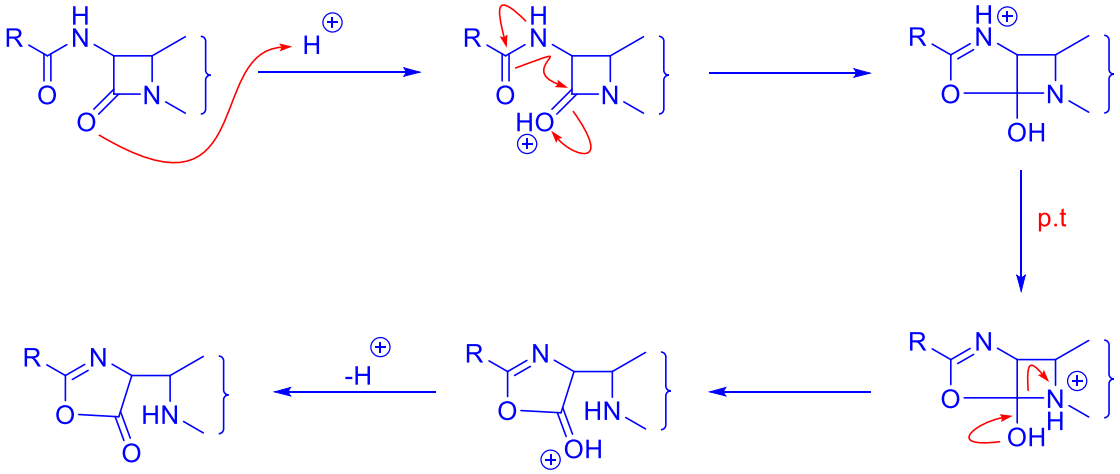


or β-lactam

d) Use a <u>mechanism</u> to show how this feature reacts with the enzyme to produce inhibition (**5 Points**)

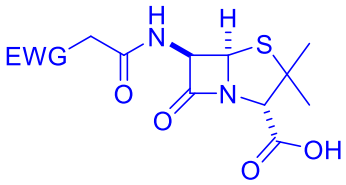


e) This class of drug is easily damaged by low pH conditions. Provide a mechanism to explain why this is. (**6 Points**)



f) Suggest one structural modification that could be made to the drug to make it more resistant to acid, and briefly explain how the change will work. (**2 Points**)

- Add EWG to left side of molecule
- Removes electrons from the nearby C=O making it a poor nucleophile

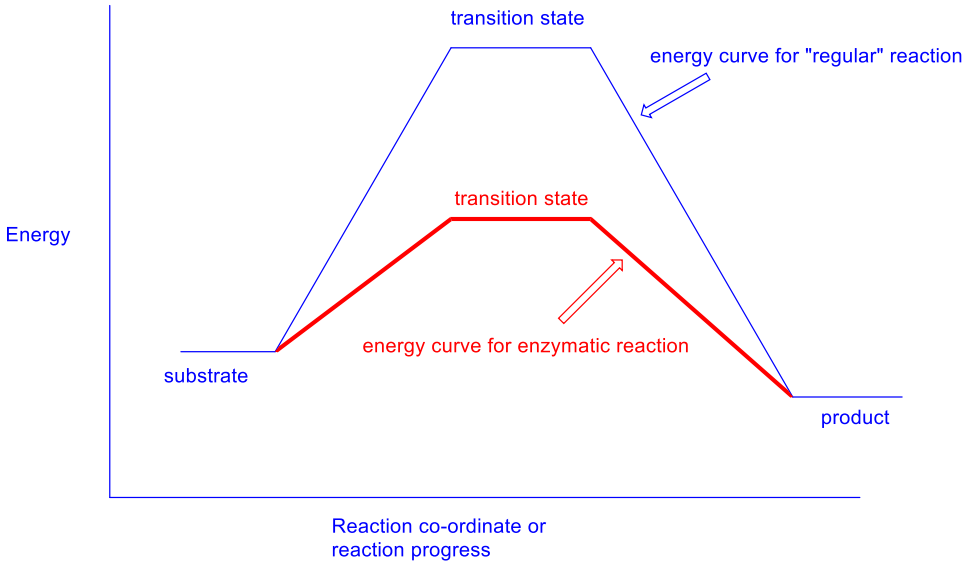


3) Enzymes are catalysts that carry out reactions in living things.

a) Use a reaction co-ordinate diagram to explain how enzymes are able to catalyze reactions (**4 Points**)

Enzymes bind tightly to transition states and lower the energy of the transition state

This lowers the activation energy for the reaction



b) Based on your answer to part (a), what **general inhibitor type** can be used, in principle, to inhibit <u>any</u> enzyme? (**1 Point**)
Transition state mimic (analog or inhibitor)

c) Why does this strategy work so well? (**3 Points**)

Enzymes bind very tightly to transition states
Enzymes therefore bind very tightly to molecules that resemble transition states
Can use the structure of the transition state to guide SAR

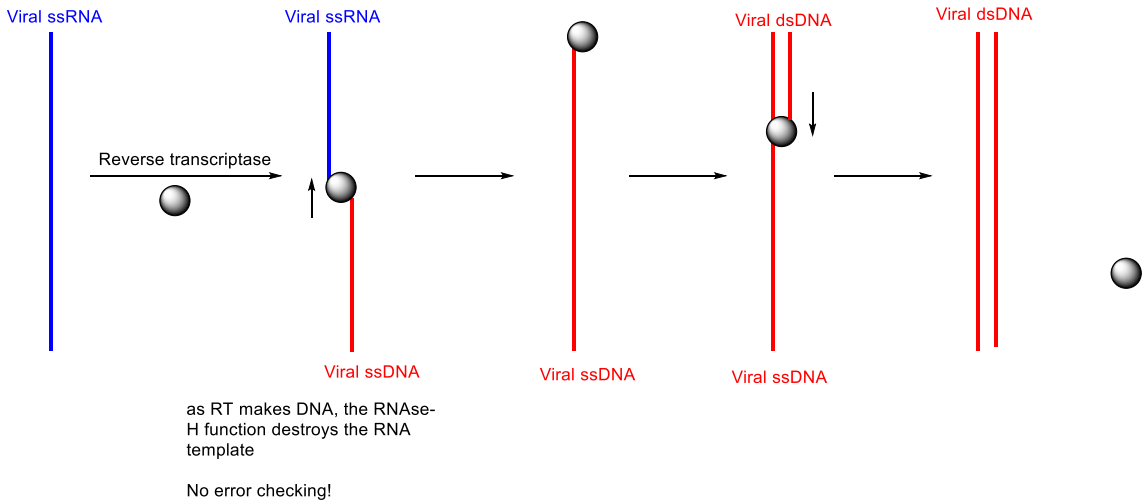
4) The HIV virus attacks the human immune system causing extensive damage.

a) What enzyme does the HIV virus use to convert RNA into DNA? (**1 Point**)
Reverse transcriptase

b) The enzyme in part (a) has a second catalytic "domain". What is the name of this enzyme? (**1 Point**)
RNAse H

c) The two functions of the enzyme are the major reason why HIV has such a high mutation rate. Explain how the two enzymatic functions produce such a high mutation rate for the virus. (**6 Points**)

- RT is sloppy, makes lost of mistakes
- RNAse H destroys RNA template, no error checking possible



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5) Many viruses carry polymerases, enzymes that replicate nucleic acids.

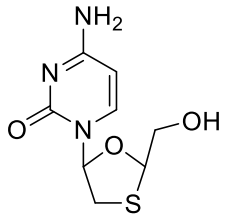
a) One popular class of antiviral drug involving polymerases are the chain terminators. Describe how a chain terminator works. (**4 Points**)

- During replication of nucleic acids, polymerases add one nucleotide at a time to the growing chain, using the 3'OH as a nucleophile to attach the next nucleotide in the sequence
- To make a chain terminator, replace the 3'OH in the nucleoside with a non-nucleophilic isostere.
- Viral polymerase accepts the drug as a substrate and incorporates it into viral nucleic acid.
- Nucleic acid chain now has a non-nucleophilic group at the 3' position and the enzyme cannot add another nucleotide.
- Enzyme stops, or makes a shortened nucleic acid.

b) Describe why chain-terminating drugs are often highly toxic. (**3 Points**)

Structures of nucleic acids same for host and virus
Chain terminator may be accepted by a host polymerase
This will interfere with normal nucleic acid synthesis causing problems

6) The antiviral drug 3-TC was the first drug for HIV to have a relatively "clean" side effect profile.



a) What structural element of this drug is responsible for the relative lack of side effects? (**2 Points**)

pseudoenantiomers of the natural nucleosides

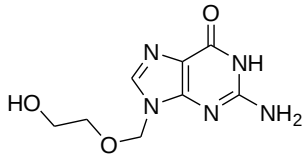
b) Why does this feature result in so few side effects? (**2 Points**)

Host polymerases are very discriminating
will not accept the pseudoenantiomer as a substrate
Normal host nucleic acid synthesis is not affected, toxicity is low

c) The company that invented the drug later lost the rights to sell it. Explain briefly how another person was able to gain ownership of the drug. (**3 Points**)

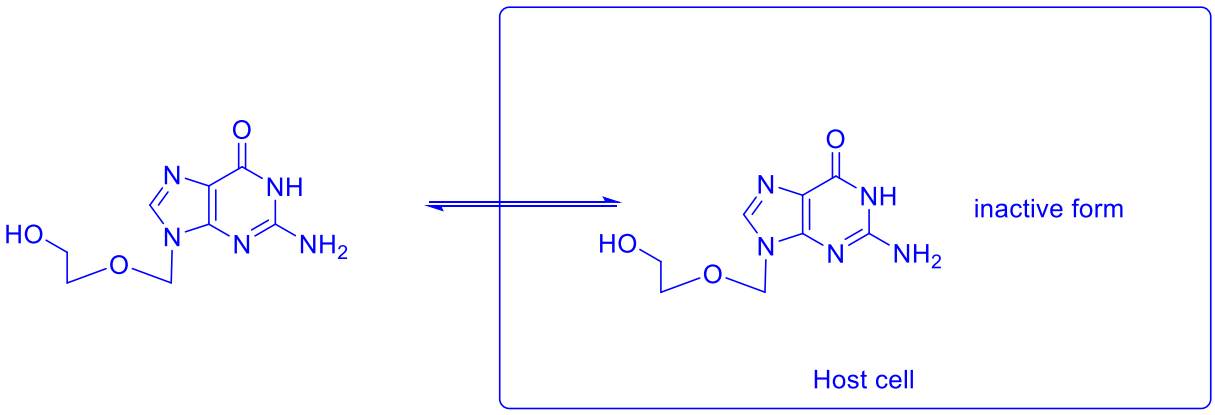
- Company did not describe how to make (separate) the two enantiomers
- Prof Liotta showed a method of doing this and "proved" he could make single enantiomer versions
- Wrote a patent covering the single enantiomer drug

7) The antiviral drug Acyclovir shows an unusual pattern of bioavailability that produces a very low incidence of side effects. Describe in detail how the drug is distributed in the body and in virally infected cells. It may be helpful to use a diagram for part of your answer. (**7 Points**)

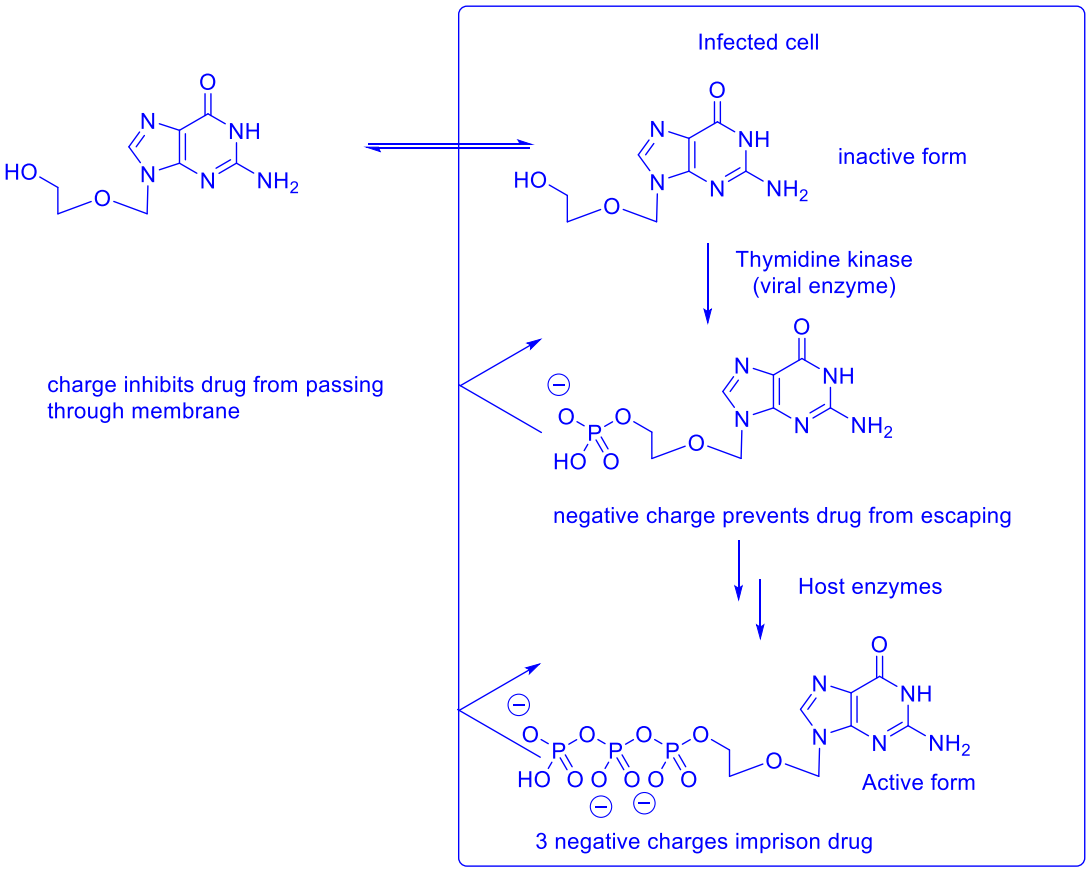


Acyclovir

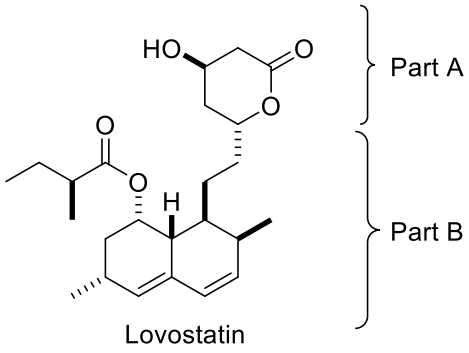
Drug is not phosphorylated by host enzymes. is able to freely diffuse in and out of host cells. becuase it is not phospharylated, the drug in in the inactive form, and cannot interact with polymerases.



Drug is phosphorylated by viral enzyme. once phosphorylated, host enzymes convert the mono-phosphate into a triphosphate. this carries multiple negative charges which prevent the triphosphate from passing through non-polar membranes and out of the cell. the drug accumulates in cells (LeChatelier's principle) as the triphosphate. this is also now the "active" form that can inhibit viral polymerase.



8) Lovastatin was the first of the statin drugs, which were effective in reducing blood cholesterol amounts.



Lovostatin

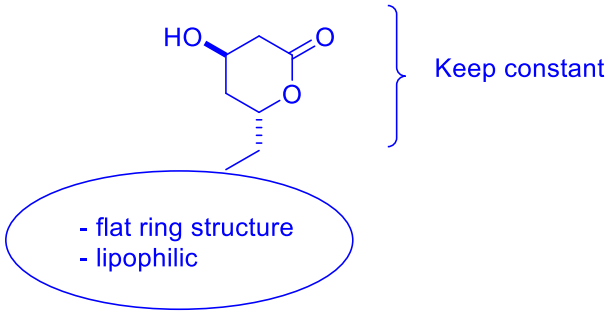
a) What enzyme does this drug inhibit? (**1 Point**)
HMG CoA reductase

b) Describe the general function of the identified parts of the drug. (**3 Points**)
Part A: transition state mimic

Part B: Lipophilic group, mimics CoA part of natural substrate

c) What kind of inhibition does this molecule produce? (**1 Point**)
competitive

d) Lovastatin was the inspiration for the design of Lipitor and other artificial statins. Draw a general design structure (strategy) of these artificial drugs. (**3 Points**)



e) What is this general method of <u>drug design</u> called? (**1 Point**)
Rational Drug Design
(drug is designed by using knowledge of substrate or mechanism)