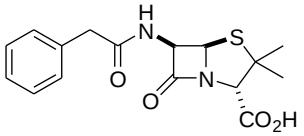
BPS 2110 Intro to Biopharm
Mid Term 2 Answers

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

	Risk characteristics	Type of lab protection (provide one or two)
Class 1	- No risk or low risk (limited risk)	Open bench
Class 2	- Moderate risk	- Limited lab access - Lab coat Laminar hood
Class 3	- High risk (death or serious illness)	- 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)	- 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.



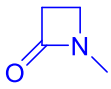
a) What enzyme does it inhibit? (**1 Point**)

transpeptidase

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

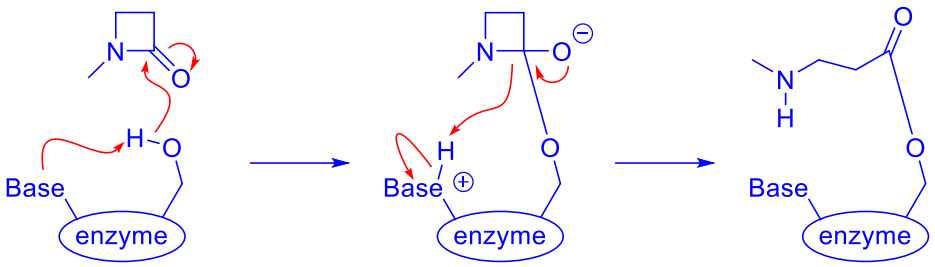
Bacteria cannot make cross-links in cell walls
Cell wall material is weakened
internal pressure (osmotic) causes the cells to rupture during cell division

c) What functional group structure in the molecule shown above is responsible for enzyme inhibition? (**1 Point**)



or β-lactam

d) Use a <u>mechanism</u> to show how this feature reacts with the enzyme to produce inhibition (**4 Points**)



e) This class of drug is very "clean" (very few side effects). Why does this drug show such a good side effect profile? (**3 Points**)

Human cells do not have cell walls
Transpeptidase does not exist in humans – drug has no human "target"

Normal substrate (D-amino acids instead of L-amino acids) for transpeptidase is very different from other protein structures, penicillin has a structure that does not easily "fit" human enzymes
Nothing like this substrate in humans- our enzymes are very different from transpeptidase

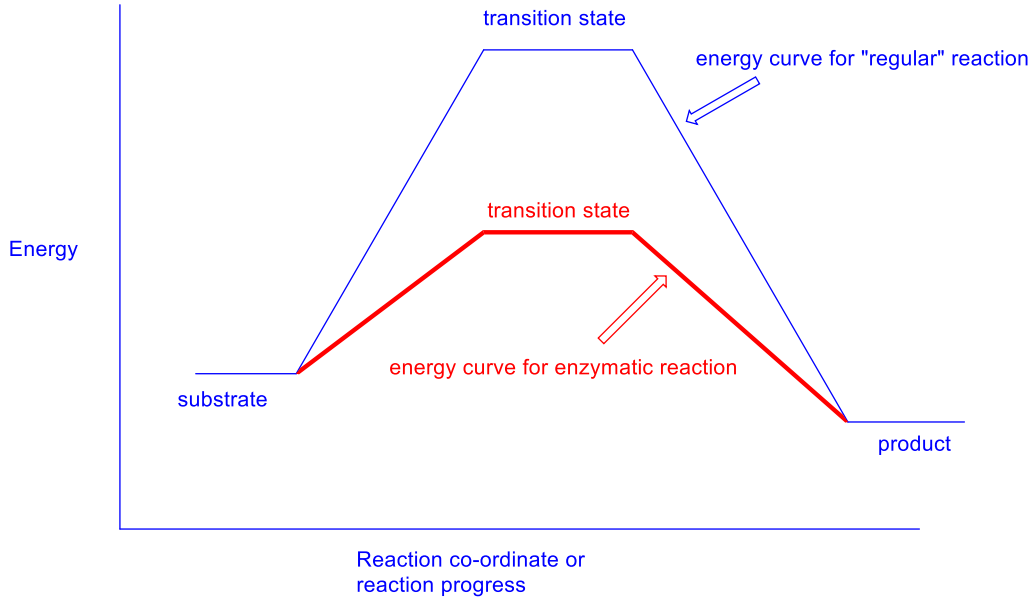
f) The major side effect associated with this class of drugs is allergy. Briefly explain how allergies to this drug arise (**4 Points**)

Humans do have serine proteases
May also have other proteins with nucleophilic side chains
Penicillin is a good electrophile, may react with one of these proteins
Creates a "new" protein which is now recognized as foreign by the body's immune system giving an allergic reaction

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 (**6 Points**)

Enzymes bind tightly to transition states and lower the energy of the transition state
This lowers the activation energy for the reaction



b) What **general inhibitor type** can be used to inhibit any enzyme? (**1 Point**)
Transition state mimic or analog

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) Describe how a chain terminator works when inhibiting an enzyme such as the one in part a. (**4 Points**)

- Requires a viral polymerase to work.
- 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.

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

- Chain terminator may be accepted by a host polymerase
- This will interfere with normal nucleic acid synthesis causing problems

d) Explain why 3TC and FTC are non-toxic chain terminating drugs. (**4 Points**)

- These drugs are pseudoenantiomers of the natural nucleosides
- Viral enzyme is "sloppy" and will accept the pseudoenantiomer in the active site resulting in chain termination

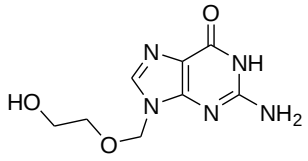
- Host polymerases are more discriminating, and will not accept the pseudoenantiomer as a substrate
- Normal host nucleic acid synthesis is not affected, toxicity is low

5) In 2009, the H1N1 virus caused serious concern.
   a) What does the designation H1N1 mean? (**2 points**)
   H = Hemagglutinin
   N = Neuraminidase

   b) Why is this system used to classify influenza viruses? (**2 Points**)
   Both proteins are found on the outside of the virus envelope
   Easy to detect using antibody tests

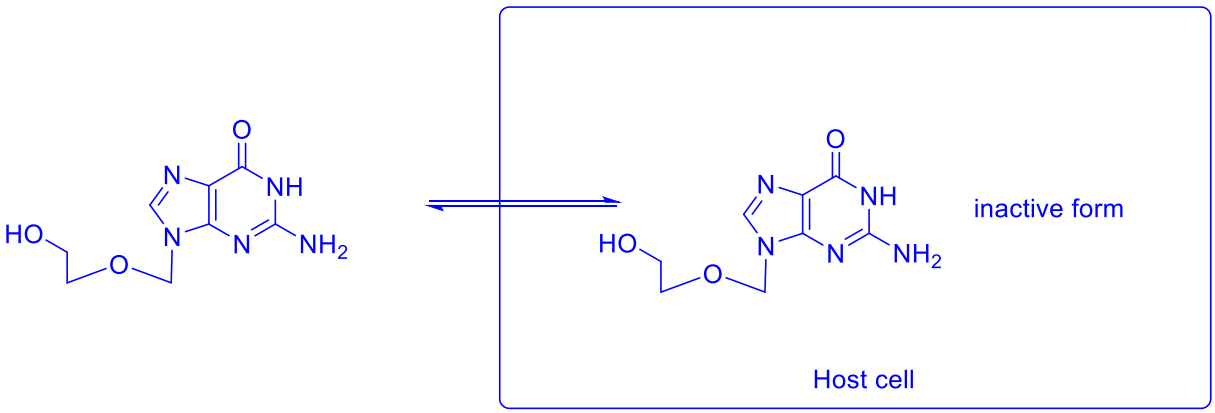
   c) Describe the general function of each of the components you identified in part a. (**4 Points**)
- Hemagglutinin sticks to human proteins that carry sialic acid on surface of human cells
- Binding between hemagglutinin and sialic acid allows the virus to enter cells
- Neuraminidase removes the sialic acid from human proteins on the outside of the virus envelope
- This prevents the virus particles from sticking to each other and becoming non-infectious

6) 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.