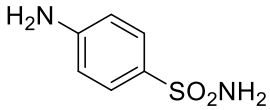
# BPS 2110
# Assignment 4 Answers

1. What is a classical isostere? Give an example.
   Atoms or groups that have the same valency or similar sizes.
   For example, an OH group could be replaced with any of the following isosteres: F, $NH_2$, $CH_3$ (same row of periodic table) or SH (same column of periodic table)

2. What is a non-classical isostere? Give an example.
   Atoms or groups that have similar chemical or biological properties. They usually differ in electronics or sterics, but behave in similar ways in biological systems.
   For example, a carboxylic acid could be replaced by acidic groups with similar pKa's.

3. Why was Salvarsan 606 not a commercial success?
   It was not very drug like. Because of insolubility and high toxicity, it was very inconvenient for the patient.

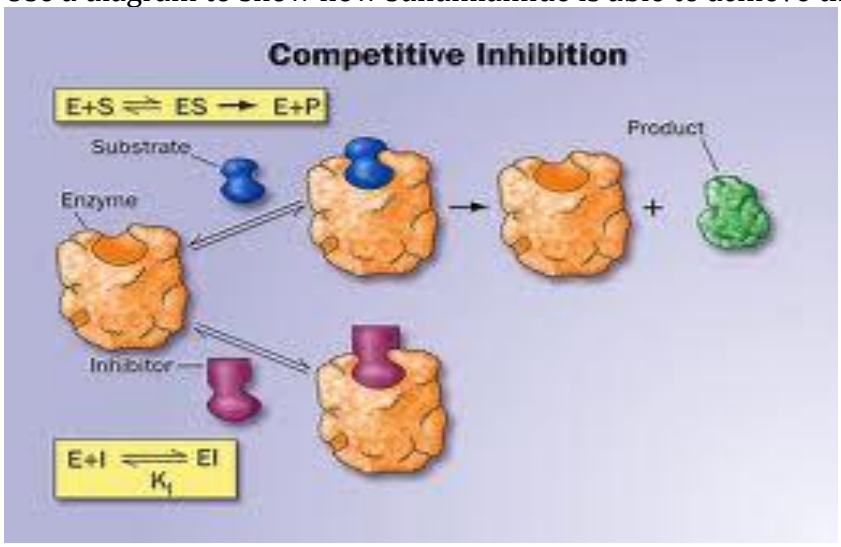
4. Sulfanilamide was the first commercially successful antibiotic.

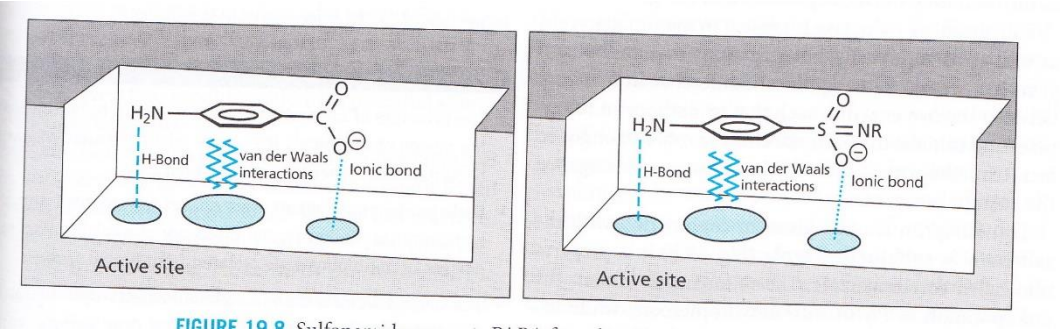



   a. How does sulfanilamide inhibit bacteria cell growth?
      Inhibits the bacterial enzyme dihydropteroate synthase, which is required to make coenzyme F. Without this coenzyme, bacteria are unable to grow.

   b. What mode of inhibition does it employ?
      Competitive inhibition

   c. Use a diagram to show how sulfanilamide is able to achieve this inhibition.






5. Penicillin kills bacteria by blocking cell wall synthesis.
    a. Why does the destruction of bacterial cell walls lead to bacterial death?
    Cell walls are needed to resist high osmotic pressure inside bacterial cells. Without an intact cell wall, the bacterial membrane bursts killing the bacteria.

    b. How does penicillin prevent cell wall synthesis?
    Inhibits transpeptidase, the enzyme that performs the cross linking to form the cell wall structure

    c. How does cross-linking increase the strength of polymer molecules?
    Prevents molecules from sliding or moving relative to one another. The structure becomes a giant molecule.

    d. What enzyme does penicillin inhibit?
    Transpeptidase

    e. What peptide structure does penicillin resemble?
    D-Ala-D-Ala

6. The enzyme that bacteria use for cell wall cross-linking is a serine protease.
    a. What is the role of the catalytic triad in a serine protease?
    OH of the serine is a nucleophile that reacts with the amide carbonyl. The Asp and His act together to form a base that deprotonates the OH of the serine.

    b. What three amino acids make up the catalytic triad?
    Aspartic acid, histidine, serine

    c. What is the role of the oxyanion hole in a serine protease?
    Stabilize the negatively charged oxygen that is part of the tetrahedral intermediate involved in amide bond hydrolysis

    d. Write out the general mechanism of a serine protease.

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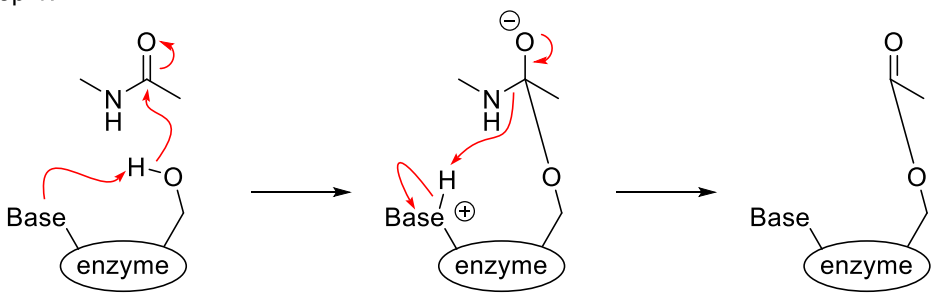
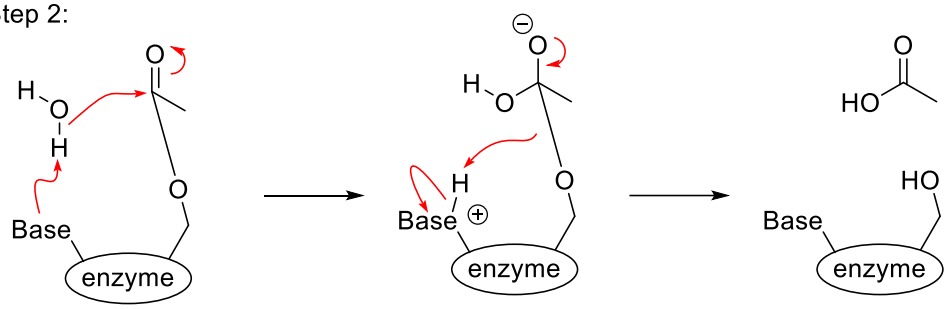
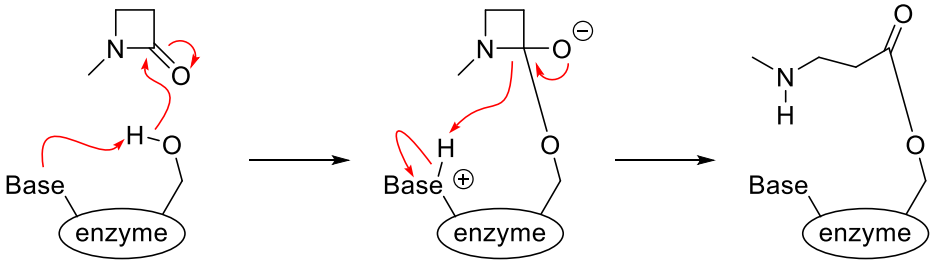



Step 2:

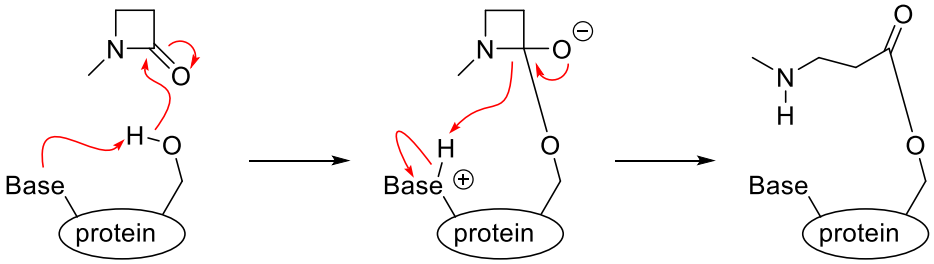



e. Give a mechanism to show how penicillin inhibits a serine protease.

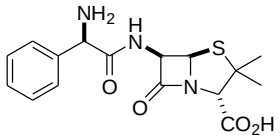



f. Why does the enzyme "stop" once it has reacted with penicillin?
Enzyme does not fold around the drug the same way that it folds around the cross-link precursor. After the first step, it is not in the proper conformation to perform the second step and gets "stuck" with the penicillin residue.

7. What is the source of the allergy side effect from penicillin?
Penicillin reacts chemically with a serine protease or protein with a nucleophilic side chain. This changes the human protein into something the immune system recognizes as foreign.

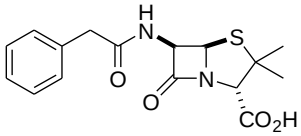


8. Would you expect the following compound to be a broad or narrow spectrum antibiotic? Why or why not?

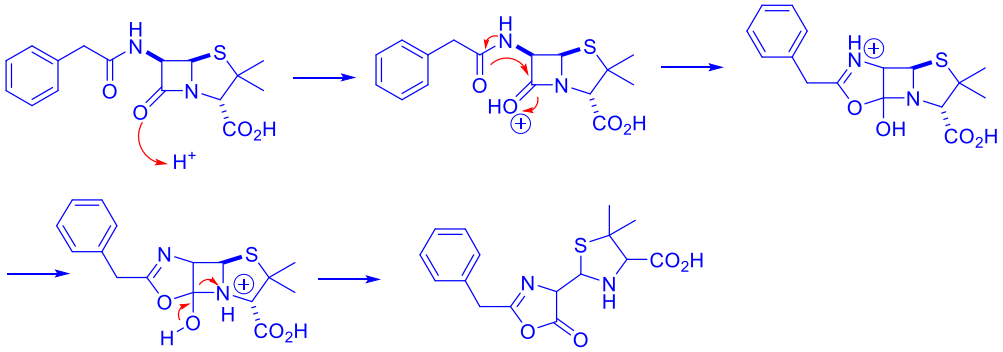


Compound is likely a broad spectrum antibiotic. $NH_2$ group on side chain is hydrophilic

9. The following compound shows poor oral bioavailability.

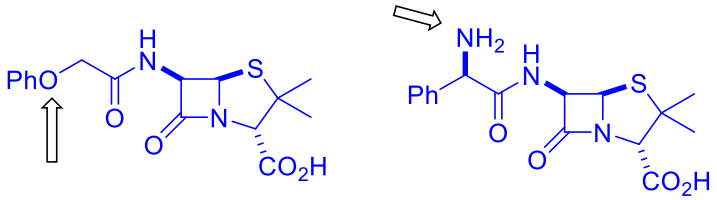


a. Give a mechanism to account for this.

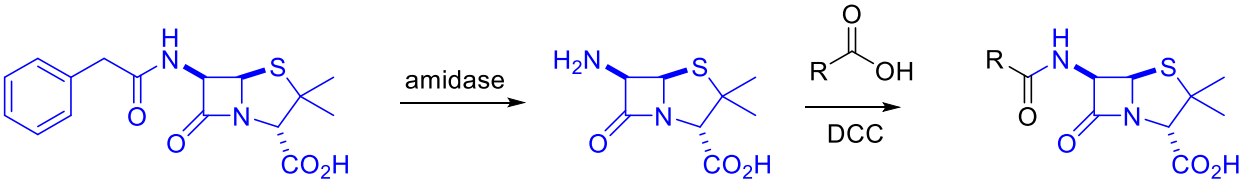


b. Suggest two ways of modifying the molecule to overcome this.
Add electron-withdrawing groups to left-hand side chain to reduce the nucleophilicity of the carbonyl oxygen

at pH 7.4 this group is protonated and positively charged. this makes it a very strong electron withdrawing group

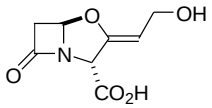


c. Outline the synthetic strategy that used to make artificial penicillin drugs.

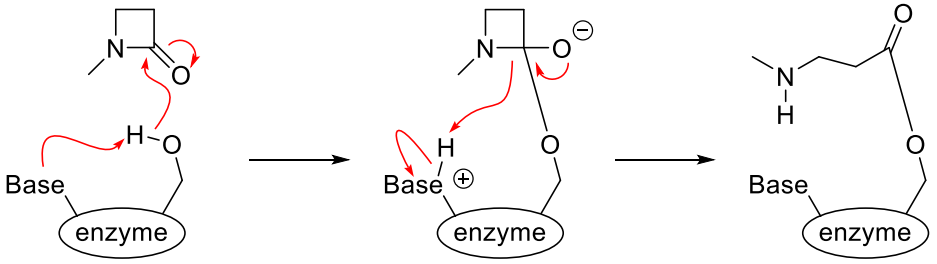


6-APA

10. The following compound is a highly proscribed β-lactam drug. Provide a rationale for its use in the clinic.




a. Give a mechanism to describe how it interacts with its target.




b. What is the structural basis for the enzyme selectivity of this drug? (why is it not an antibiotic)

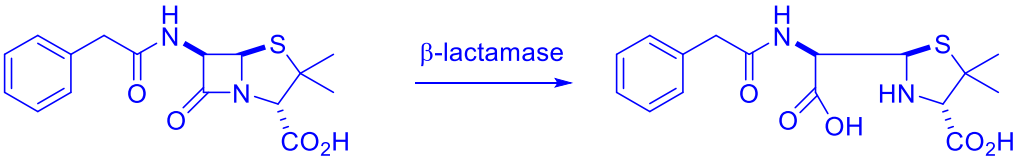
Transpeptidase normally has a very large substrate (cross-link precursor) and will only accept molecules that have a long side chain into the active site. There is no side chain on the β-lactam ring, and so this molecule will not fill enough of the transpeptidase pocket to give effective binding and inhibition.

11. Many modern bacteria have become resistant to penicillin.

a. What does drug resistance mean?

Bacteria are no longer affected by the drug.

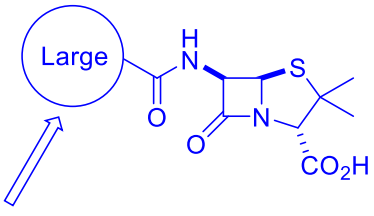
b. Show how bacteria use β-lactamase to become resistant to penicillin.




penicillin

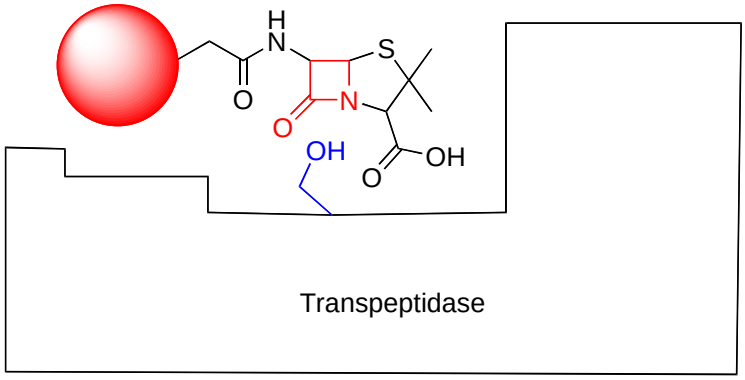
β-lactamase opens the β-lactam ring making the drug useless. in this form it cannot inhibit transpeptidase

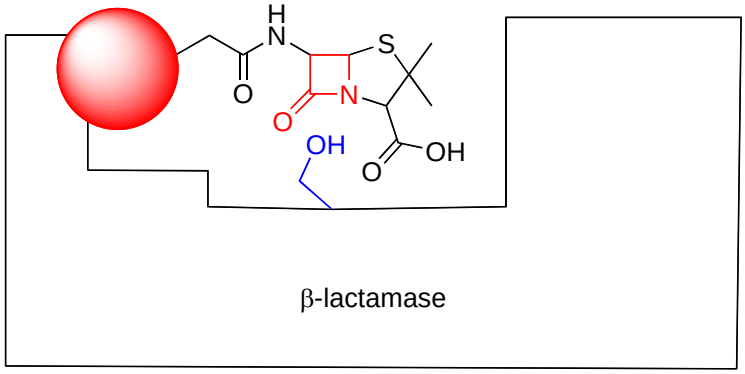
c. Show how penicillin can be modified to overcome this resistance.




modify the drug to place a large group at this position. this drug no longer fits into the active site of β-lactamase and therefore cannot be de-activated by it.
the drug still fits into transpeptidase and can inhibit transpeptidase

d. Provide a structural justification for your answer in part c.

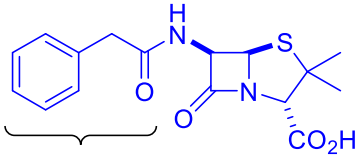



12. The first penicillin discovered had a narrow therapeutic window.
    a. What is meant by the term therapeutic window?
    The drug only affected a few bacteria types. In the case of penicillin, it was only effective against gram-positive bacteria.

    b. Why did the original penicillin drug show this behavior?
    Penicillin was unable to penetrate through the liopolysaccharide layer surrounding the cell walls of gram negative bacteria.

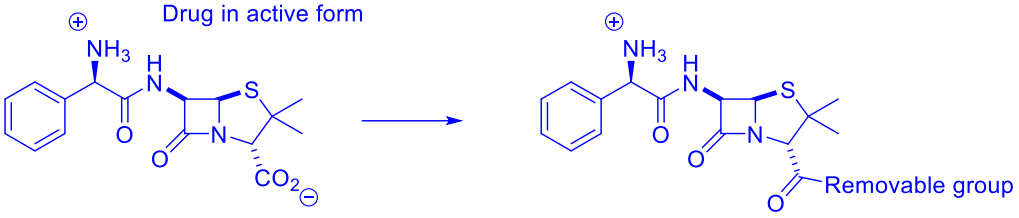
    c. What structural modifications can be made to penicillin to overcome this difficulty?
    Attach hydrophilic groups to the side chain of penicillin




add hydrophilic groups here

13. Describe how prodrugs can be used to improve penicillin bioavailability.
    Increase water solubility by ensuring the molecule is charged at pH 7.4. This is often done by attaching a removable group that blocks one of the charged sites on the drug.

a. What structural element in penicillin is used for this purpose?
Attachment is usually made on the carboxylic acid




at pH 7.4 the overall charge on this molecule is zero
this compound will not be very soluble in water

at pH 7.4 this molecule has a net charge of +1 and is soluble in water. Once in the blood, the removable group is removed, which regenerates the active form of the drug

b. Why are prodrugs necessary when making this structural change?
Both charges are necessary for this molecule to work. The $NH_3$+ is important for acid stability in the stomach, the $CO_2$- is necessary to fit into the active site of transpeptidase. Prodrugs provide a temporary way of blocking the $CO_2$-

14. What structural feature is common to penicillins and cephalosporins? Why is this chemical structure important?
β-lactam. This functional group is a strong electrophile, which is required to react with the active site OH nucleophile of transpeptidase

15. Describe the mode of inhibition of vancomycin.
Vancomycin binds tightly to D-Ala-D-Ala, which prevents transpeptidase from reacting with the tail end of the cell wall pre-cross-link chain