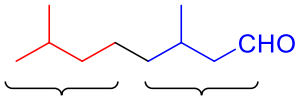
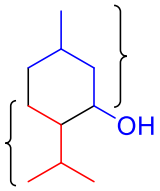
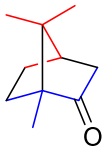
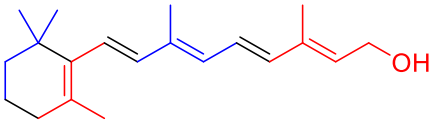
BPS 2110
Assignment 6 Answers

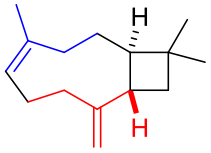
1. Identify the isoprene units in the following terpenes.

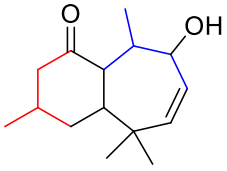
a. 

b. 

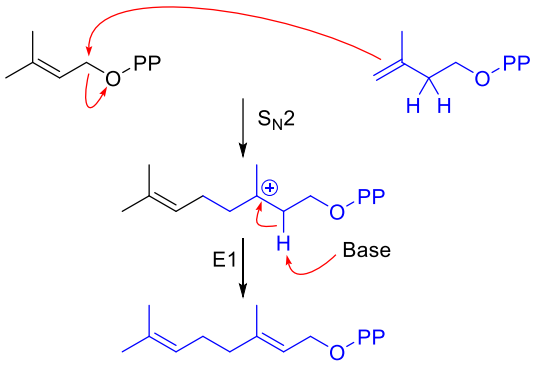
c. 

d. 

e. 

f. 

2. What is the reaction and mechanism of the process used to biosynthetically link isoprene units together?

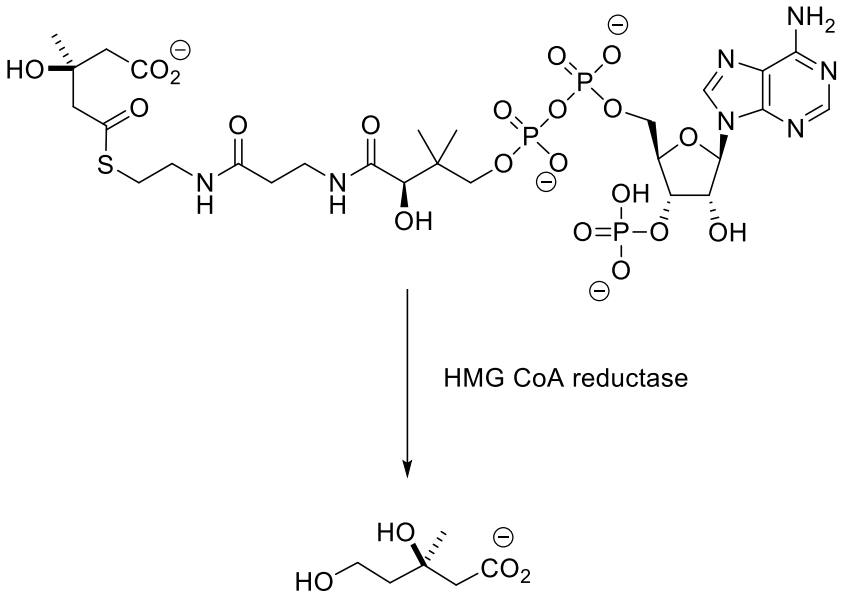


3. Cholesterol is an important molecule in living systems.
   a. What is the source of most of the cholesterol in humans?
   Biosynthesis in the liver. Production of cholesterol is associated with the intake of saturated fat.

b. Where is excess cholesterol stored in the body?
   Arterial walls
c. Why is this storage location a problem?
   Cholesterol storage eventually damages arterial walls. This damage can produce blood clots, which can block arteries. Partial blockages can be very dangerous if the clots dislodge they can produce a full blockage downstream (arteries get smaller the farther they are away from the heart)
d. What is a cholesterol deposit called?
   Plaque
e. Outline the key steps in the formation of a cholesterol-related blockage.
   - deposit of cholesterol in arterial wall
   - cholesterol is oxidized to cholestenone
   - macrophages enter the arterial walls and ingest the cholestenone becoming foam cells
   - foam cells secrete substances that damage the arterial walls
   - inflammation occurs somewhere else in the body releasing cytokines into the bloodstream. Cytokines in contact with the damaged arterial walls trigger tearing
   - tear in the arterial wall causes blood to clot

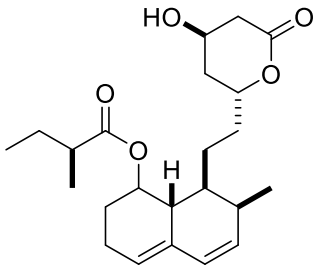
4. Triparanol, one of the first cholesterol-controlling medications, was withdrawn from the market shortly after its introduction.
   a. What side effect did it cause?
      cataracts
   b. How did it prevent the build-up of cholesterol?
      Inhibited the operation of the second-last enzyme in the biosynthesis of cholesterol
   c. Why was this prevention strategy a failure?
      Because the second-last enzyme was blocked, synthetic intermediates built up in the body. These compounds had low water solubility and built up deposits in the eye
   d. Why were the later statin drugs much safer?
      These drugs blocked the third enzyme in the biosynthesis. Synthetic intermediates did not build up as much, and those that did occur did not have properties that caused problems in the body.

5. Statin drugs are inhibitors of HMG CoA reductase, an enzyme that carries our the following reaction.



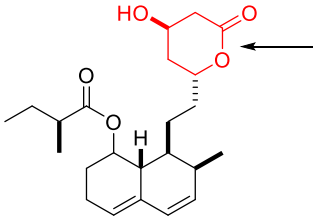
a. What are the roles of Coenzyme A (CoA) in this reaction (there are two)?
- Acts as a "recognition element" to transport HMG to the proper enzyme to transform it into mevalonic acid.
- Is a leaving group in the reduction reaction.

b. One of the first inhibitors of the enzyme is mevastatin. What kind of inhibitor is this?



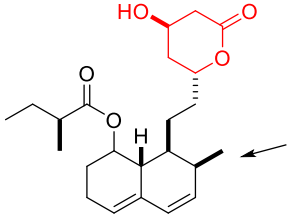
competitive inhibitor

c. What structural component of the inhibitor identifies its inhibition type and why?



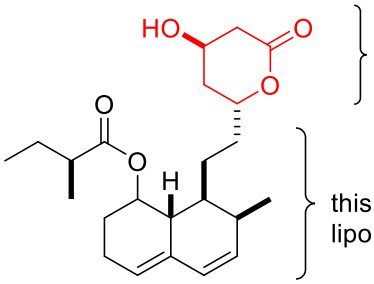
this part of the molecule resembles the HMG component of the normal substrate HMG-CoA
this fragment causes the molecule to bind to the same pocket that HMG-CoA does and act like a competitive inhibitor

d. Besides the key component, what purpose does the rest of the inhibitor molecule serve?



flat lipophilic structure resembles CoA and fills remainder of binding pocket

e. Using rational drug design, what components of the inhibitor can be changed, and what parts cannot?

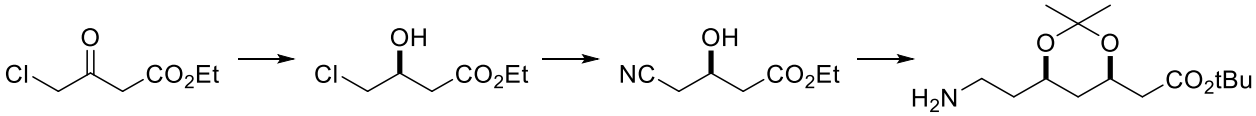


this part of the molecule cannot be changed a lot without affecting binding

this part of the molecule is variable. many flat, lipophilic ring structures will work

6. Several key clinical trials were important in the discovery of Lipitor.
   a. Why was the Four-S study performed?
      To convince doctors that prescribing cholesterol-lowering drugs was safe for patients
   b. What was the significance of the CURVES study?
      Showed that Lipitor was MORE effective at a lower dose (10 mg) than the dose that other drugs were administered at (20 mg)
   c. Explain the importance of arrival time on the market (1st, 2nd, 3rd etc) for gaining market share and profit.
      - first drug on the market makes the most money, established the therapy and is well know to doctors. Doctors develop the habit of prescribing this drug.
      - second drug on the market captures market share from the first drug and establishes new markets. Also has slightly lower development costs because first drug had to do extra work to establish the therapy. Generally has second-largest market share because many doctor's are already prescribing first drug and don't change habits.
      - third drug on the market captures market share from the first two. Also has slightly lower development costs. Generally has third-largest market share because many doctor's are already prescribing first two drugs and don't change habits.
      - subsequent drugs have difficulty being profitable, because doctors are reluctant to change prescribing habits unless there is a significant advantage for a subsequent drug over existing drugs.

7. One of the key reaction sequences in the synthesis of Lipitor is shown below.



   a. What kind of reagent is used to perform the **first** reaction in the sequence?
      Reaction is performed by a mixture of two enzymes
   b. Why is it necessary to use this kind of reagent?
      Most efficient was to perform chemical reactions is to use catalysts. Performing enantioselective reactions are normally very difficult. Enymes provide catalysis for enantioselective reactions.
   c. How is this reagent manufactured?

Genetically engineered bacteria used to produce recombinant enzymes.

8. What are the four basic models used to determine prices in the drug industry?
    - price based on cost to produce product plus profit. Calculate total costs to produce drug (R & D, manufacturing, sales etc)
    - price based on the cost of alternative treatment. Price drug slightly below the cost of other treatments such as surgery or existing expensive drug.
    - Price based on similar drugs. If other drugs in the therapy cost a certain amount, sell a product using a similar price
    - Price based on what the consumer is willing to pay. Works especially well when the patient is desperate (cancer)