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Drug Design – Macroconcepts: Models and Systems Interdisciplinary Links: Chemistry and Biology (Biochemistry and Enzymology)

Introduction:

In this activity, you will draw upon your knowledge of both chemical bonding and organic chemistry to design a drug that will inhibit an enzyme. **Figure 1** shows the active site of a hypothetical enzyme within the human body. Enzymes are proteins that function as catalysts within the human body, increasing the rate at which important biochemical reactions reach their equilibrium position. Enzyme activity needs to be carefully regulated, as excessive activity can lead to the development of disease. For example, excessive activity by the enzyme *serine protease* in joints leads to the breakdown of cartilage and connective tissue resulting in the development of *rheumatoid arthritis*.

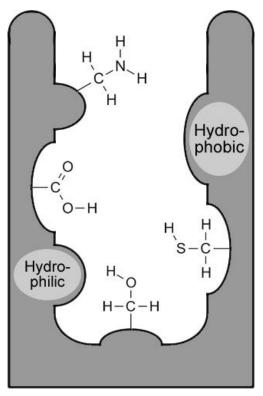


Figure 1: The active site of a hypothetical enzyme within the human body. Excessive activity by some enzymes within the human body can cause disease.

Enzymes that cause disease within the human body due to their excessive activity should be *inhibited*. There are a variety of different ways by which enzyme activity may be inhibited – one way is by designing and synthesising a drug that fits into the enzyme's active site. Once within the active site of the enzyme, a functional group on the drug should react with a functional group on the enzyme, thus bonding the drug to the enzyme and denying any other molecule access to the enzyme's active site.

Stage One – Thinking about functional groups:

Study the active site of the enzyme shown in Figure 1.

- a) Identify the functional groups that are present at the enzyme's active site and outline the unique chemical properties that each one has. How is the chemistry of these functional groups influenced by the pH of the environment in which the enzyme functions? Suggest which functional groups could be incorporated into the design of a drug with the objective of bonding the drug to at least one of the functional groups at the enzyme's active site.
- **b)** Describe the chemistry at the hydrophobic and hydrophilic regions of the enzyme's active site. How will the existence of the hydrophobic and hydrophilic regions influence the structure and function of a drug that is designed to fit into the enzyme's active site?

The electronegativity values of carbon, hydrogen, nitrogen, oxygen and sulphur have been provided forreference:C = 2.5H = 2.1N = 3.0O = 3.5S = 2.5

Stage Two – Thinking in three dimensions:

Draw on your knowledge of *valence shell electron pair repulsion theory* to deduce the desired threedimensional shape of a drug that will fit into the active site of the enzyme shown in **Figure 1**. Remember, in addition to controlling the chemical properties of a molecule, organic functional groups can also be used to influence the three-dimensional structure of a molecule.

Stage Three – Thinking like a Pharmaceutical Chemist:

- a) Consolidate your answers to Stage One and Stage Two by designing a drug that will inhibit the enzyme whose active site is shown in Figure 1. You should clearly show how you have designed the drug to fit into the enzyme's active site, including the way in which the drug bonds to at least one of the functional groups within the enzyme's active site. You should also include any relevant intermolecular forces of attraction that may contribute to stabilising and securing the drug within the enzyme's active site.
- **b)** Propose a systematic name for your drug.
- c) Propose a possible synthesis for your drug. Your synthesis should start with relatively simple reagents that contain no more than two or three carbon atoms each.

Stage Four – Thinking about macroconcepts:

- a) In this exercise, you have modelled the procedure for designing a drug to inhibit the activity of an enzyme within the human body. What are the strengths and the limitations of this model?
- **b)** Rationalise why each one of the following could be considered to be a system:
 - i) The active site of the enzyme.
 - ii) The drug that you have designed.
 - iii) The way in which the drug that you have designed interacts with the active site of the enzyme.

Stage Five – Thinking about thinking:

Which stage(s) of this exercise did you find challenging? How did your thinking and problem solving strategies change when faced with difficult questions? What influence has this exercise had on your critical and creative thinking skills?