

Enzymes: Mechanisms & Inhibition (Make-up: 5 pts total)

1. Transition state analogs are potent inhibitors of enzymes. Consider the following hypothetical enzymatic reactions and draw (using IsisDraw or a similar program) a structure of the reactant, the transition state, and the reaction product. Design a transition state analog that might inhibit each of these hypothetical enzymes and provide the structure of the inhibitor. You are encouraged to solve this problem without much help from the literature; if you use literature sources for your answer please provide full citation for your source.
 - a) Rearrangement of prephenate to chorismate
 - b) Interconversion of D-glucose-6-phosphate to D-fructose-6-phosphate
2. Acetylcholinesterase is a serine protease found in the synapse between nerve cells and muscle cells. Serine proteases use active site serine that in the first step acts as a nucleophile and covalently adds to electrophilic centers; in the second step the enzyme–intermediate adduct is hydrolyzed by a water molecule. One serine protease that you are probably well-familiar with is chymotrypsin.

The physiological role of acetylcholinesterase is to stop the action of the neurotransmitter acetylcholine by breaking it down into acetate and choline. The enzyme's activity is abolished by a number of compounds known as "nerve gases". The excess level of acetylcholine continuously stimulates acetylcholine receptors in muscle cells leading to intense spasms of heart muscle until death ensues.

You will likely need to use internet resources to answer this question, if so please provide references.

 - a) Using IsisDraw or any other chemical drawing program, create a reaction scheme that illustrates the mechanism of breakdown of acetylcholine by acetylcholinesterase.
 - b) Compound known as VX is one of the most lethal chemicals known. Its chemical formula was classified by U.S. government as secret until early 1970's. Using IsisDraw or any other chemical drawing program, propose chemical mechanism that explains the toxicity of the nerve agent VX toward acetylcholinesterase.
 - c) Outline your strategy to design a "drug" that protects people from nerve gases such as VX. Make sure to describe the molecular target and mode of action for your drug.