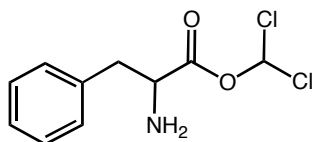
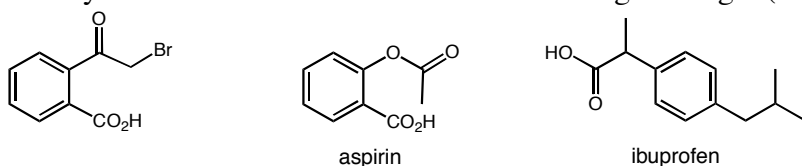


1. (10 pts) Suppose that a drug company has prepared the compound shown below as a mechanism-based inactivator of angiotensin converting enzyme (ACE). Propose a chemical mechanism to explain this enzyme inactivation process.



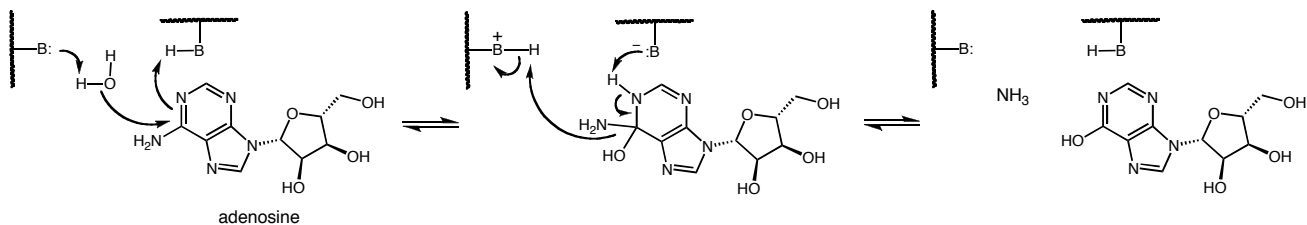
Answer: See class notes on mechanism-based inactivation and problem set 3. You will see two analogous (very closely related) strategies for mechanism-based inactivation of hydrolytic enzymes.

2. (10 pts) Imagine that the molecule shown below possesses anti-inflammatory activity similar to agents such as aspirin and ibuprofen. Suggest a reasonable molecular mechanism for this medicinal activity. Show a chemical reaction with a biological target (identify the biological target).



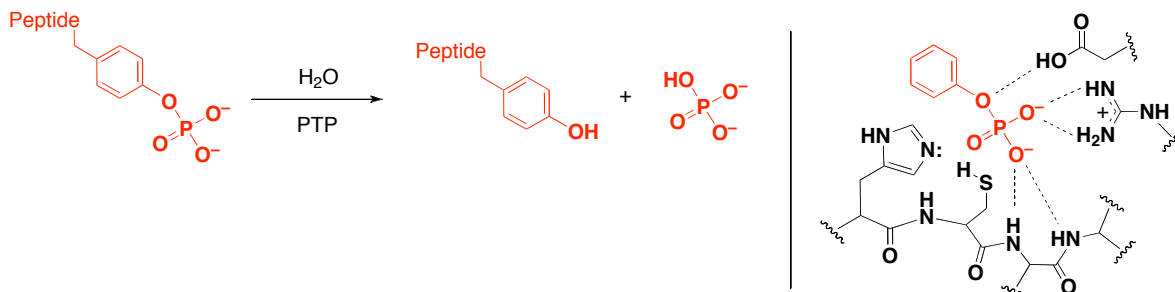
Answer: See class notes regarding affinity labeling. Also see paper posted on the course website for the recent details regarding “how aspirin works”.

3. (10 pts) The reaction mechanism for the enzyme adenosine deaminase is shown below. Propose a stable molecule that would serve as a transition state analog inhibitor or reaction intermediate analog inhibitor for this enzyme. Briefly explain the reasoning behind your design.



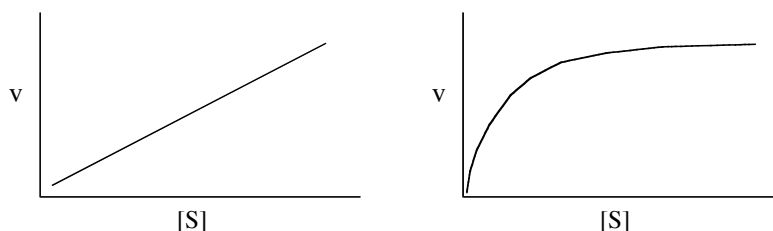
Answer: See class notes on transition state analog inhibitors. Also see posted exam answers from previous years.

7. (10 pts) Enzymes called protein tyrosine phosphatases (PTPs) carry out the net reaction shown below (left). Imagine that X-ray crystallography reveals the picture of a PTP enzyme bound to a substrate mimic shown below (right). (a) Propose a chemical mechanism for the enzymatic reaction and (b) point out all the different types of enzyme catalysis that are at work in your proposed mechanism. Hint: The reaction is very similar to that catalyzed by the cysteine-dependent proteases discussed in class.



Answer: See class notes regarding how enzymes catalyze chemical reactions. Also see class notes regarding mechanism-based inactivation of enzymes. Some fundamental aspects of phosphate hydrolysis are shown in problem set 3 (involving a different type of enzyme from the one discussed here – that is, the one on the homework is not a cysteine-dependent enzyme).

8. (10 pts) For many uncatalyzed chemical reactions, the velocity of the reaction increases in a linear manner as the concentration of a substrate increases (as shown below-left). Enzyme-catalyzed reaction rates increase in a non-linear manner as substrate concentration increases (right). What physical process accounts for (a) non-linear nature of the velocity-versus-[S] plot and (b) the plateau observed at high substrate concentration? Show a reaction scheme to help explain your answer.



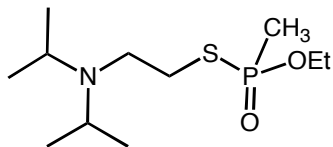
Answer: parts (a) and (b) both go all the way back to question 1 on problem set 2. Part of the foundation on which all of our thinking about reversible noncovalent binding of drugs to target rests.

Name _____

CHEM 4170 Exam 2

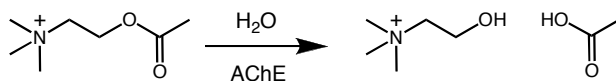
all answers must fit in space provided

9. (10 pts) The “nerve agent” VX is shown below. How does VX elicit its biological activity? Show the relevant noncovalent interactions and chemical reactions of VX with its biological target. What is the biological target?



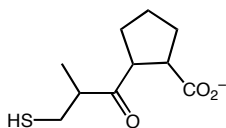
Answers: See class notes on affinity labeling agents. This general topic was also covered extensively on problem set 3.

10. (5 pts) Acetyl cholinesterase (AChE) catalyzes the destruction of the neurotransmitter acetylcholine via the reaction shown below. To counteract the negative health effects following exposure to VX, would it be wise to administer an acetylcholine receptor *agonist* or an acetylcholine receptor *antagonist*? Briefly justify your answer.



This one asks you to think about how different biological targets affect one another. Very important in medicinal chemistry. Inactivation of AChE will cause an “unnatural” rise in acetylcholine concentrations. These acetylcholine molecules will “over-stimulate” the acetylcholine receptors. To prevent this over-stimulation, one would need to administer an acetylcholine receptor antagonist like atropine. This is exactly what is done in practice. A correct answer must contain the reasoning behind your choice.

11. (5 pts) What is the primary role of the thiol (-SH) group in the ACE inhibitor captopril?



A ligand for the Zn(II) in the active site of ACE. Forms a reversible, coordinate covalent bond.