DEPARTMENT OF MEDICINAL CHEMISTRY
SCHOOL OF PHARMACY

Advanced Medicinal Chemistry — MEDC 603
Dr. Umesh R. Desai — September 27, 2007

KEY

STUDENT NAME **HONOR PLEDGE**

***Instructions**: Answer all questions.*

1. Define a receptor (4 pts) and list at least two types of receptors (2 pts).

A macromolecule that recognizes 'drugs' through precise physicochemical and steric interactions.

G-protein coupled receptors,

Ion-channels

Enzyme-linked receptors

Nuclear receptors (intracellular receptors)

2. An equilibrium exists between inhibitor **I** and enzyme **E**. Write an expression of inhibition constant $\mathbf{K_I}$ in terms of the concentrations of the two (2 pts). If $\mathbf{K_I}$ of molecule X is 5 nM for an enzyme, while that of molecule Y is 5 μM, which molecule has higher affinity for the enzyme? (2 pts) What is the relative potency of the two molecules? (2 pts)

$$K_I = \frac{[E][I]}{[E:I]}$$

X has higher affinity for the enzyme than Y.

X is 1000-fold more potent than Y.

3. Name three drugs that are inhibitors of an enzyme. Name the corresponding enzymes too. (6 pts)

Drug	Enzyme that it inhibits
Statins	HMG CoA reductase
Azidothymidine, nevirapine	HIV Reverse Transcriptase
Argatroban, hirudin, bivalirudin	thrombin
Clavulinic acid	β-lactamase

TA: [please check an unusual name written here against literature report. If unsuccessful, deduct four points and write 'clarify with Dr. Desai']

4. For a receptor R binding to drug D, write an expression that quantifies the drug-induced response in the receptor to the concentration of the free drug present in the system. Define in clear words the terms involved in the expression. (4 pts)

$$drug\text{-}induced\ response = fraction\ of \cdot bound\ form\ (fb) = \frac{[D]}{K_D + [D]}$$

fb= fraction of drug bound = proportion of the receptor in complex with the drug;

[D] = concentration of drug present in free form

K_D = equilibrium dissociation constant of the drug – receptor interaction

5. The principle reason why natural products or derivatives of natural products constitute a major proportion of all known drugs even today is their **structural diversity** (2 pts)

   1. long duration of action
   2. ease of preparation
   3. structural diversity
   4. well-known age-old potency
   5. none of the above

6. A drug **D** inhibits an enzyme **E** in a competitive manner with an inhibition constant of $\mathbf{K_D}$. Enzyme **E** is important for hydrolysis of its natural substrate **S**, which is generates a physiologic response. What will happen to the efficacy of drug **D** if a person's genetic system synthesizes excessive quantities of substrate **S** (1 pt). Explain your answer few sentences using the Michaelis-Menten kinetic expression. (4 pts)

The efficacy of D will decrease as the concentration of S increases in the system. The Michaelis – Menten equation (below) shows that that initial rate of substrate S hydrolysis is proportional to the concentration of substrate S. As S increases, the contribution of the inhibition term $(I+[I]_O/K_I)$ decreases. Thus at high enough [S] the Vi can be made to reach the Vi value in the absence of I.

$$Vi = \frac{k_{CAT}\ [E]_O\ [S]}{K_M\ (1 + \frac{[I]_O}{K_I}) + [S]}$$

7. Lipinski's rule of five is an oft cited drug design tool. Write the four rules. (4 pts)

   6. MW < 500
   7. Fewer than five H-bond donating functions
   8. Fewer than 10 H-bond accepting functions
   9. Calculated logP (ClogP) between –1 and +5