1. Of the three types of searches for drug discovery (random, rational and combinatorial), choose one that you believe is most effective and justify your answer in less than 10 sentences. (6 pts)

**Random Search:** is not very effective.

**Rational Search** is effective because it is expected to be most direct. If enough information has been collected about the system (either receptor, ligand or mechanism), then one can theoretically design a drug much rapidly because millions of compounds are not needed. Few compounds have to be screened, which should be more cost and time effective.

**Combinatorial search** is effective because it rapidly screens a large number of compounds and generates leads very rapidly. Thus the initial lead derivation is not very expensive in terms of time and perhaps cost.

2. Write an expression for $K_I$ in terms of the concentration of inhibitor $[I]$. (4 pts)

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

3. Define competitive inhibition of an enzyme. You may use a figure or diagram to support your answer. (4 pts). Name a drug that inhibits an enzyme competitively. (4 pts)

Competitive inhibition of an enzyme is defined as a process of occupying the same site of binding as the substrate by the inhibitor resulting in reduction of the enzymatic activity.

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

4. An example of a drug that inhibits an enzyme non-competitively is **hirudin**. (2 pts) The name of this enzyme is **thrombin**. (2 pts) The clinical use of this drug is as an **antiocoagulant**. (1 pts)

NOTE:  [please check an unusual name written here against literature report. If unsuccessful, deduct points and write clarify with Dr. Desai]
5. Several drugs continue to be used in the clinic today as discovered from nature. Name two drugs in use today that fall in this category, i.e., essentially unmodified from the natural structure, and identify their clinical usage. (4 pts)

<table>
<thead>
<tr>
<th>Drug</th>
<th>Used in the Clinic As</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heparin</td>
<td>anticoagulant</td>
</tr>
<tr>
<td>Digitoxin</td>
<td>cardiac failure</td>
</tr>
<tr>
<td>Quinine</td>
<td>anti-malarial</td>
</tr>
<tr>
<td>Quinidine</td>
<td>anti-arrhythmic</td>
</tr>
<tr>
<td>Reserpine</td>
<td>anti-hypertensive</td>
</tr>
<tr>
<td>Statins</td>
<td>anti-hyperlipidemic</td>
</tr>
<tr>
<td>Warfarin</td>
<td>anticoagulant</td>
</tr>
</tbody>
</table>

6. Natural products have been the main source of drugs for man today. List three advantages and three disadvantages these molecules carry in their use as clinically useful agents. (6 pts)

**Advantages**

- a) structural diversity
- b) apparently unlimited supply
- c) high potency
- d) high specificity

**Disadvantages**

- e) synthesis is difficult
- f) isolation may be difficult
- g) identification may not be easy