BPS 2110 Intro to Biopharm
Mid Term 1 Answers

1) Complete the following table describing clinical trials. (**6 Points**)

	Phase I	Phase II	Phase III
Goals	a) Safety b) Find max safe dose	a) Safety b) Efficacy c) Find effective dose	a) Safety b) Rare side effects c) Efficacy
Number of patients	~100	200-300	thousands
Type of patients	Healthy volunteers	patients	patients
Average time taken	< 1 year	~1 year	~1 year
Drug failure rate	30%	70%	70%

2) What are PAINS? Why are they a problem? List two types of chemical behavior that they generally have in common. (**4 Points**)
   - Pan Assay INterference compoundS (1)
   - Promiscuous bioactive compounds, they give positive results in virtually any biological test (1)

   Choose any 2 of following: (2)
   - Redox (oxidation or reduction)
   - Detergents
   - Strong acids or bases
   - Strong nucleophile or electrophile
   - Photoreactive
   - Chelator
   - Highly lipophilic

3) List three (3) different types of excipients and for each give one key function they provide in drug formulation. (**6 Points**)

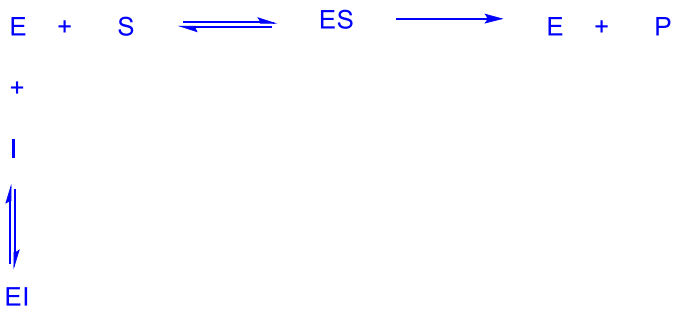
   Choose any 3 of following. Need name + function:

   Stabilizer – protect from chemical degredation (oxygen)
   Preservative – prevent mold or bacterial growth
   Fillers – ensure consistent dosing
   Disintegrants – speeds dissolution by breaking pill apart in presence of water
   Binders – hold pill ingredients together
   Lubricants – ease of manufacture, prevent sticking to machinery
   Flavors – mask taste (bitter or sweet)
   Colors – safety, helps identify pills

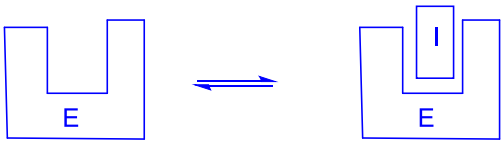
4) Name the four general types of secondary protein structure and describe how each is represented on a ribbon diagram. (**8 Points**)
   a) α-helix – appears as a coiled ribbon with arrow pointing toward C-terminus. In some structures may be a cylinder
   b) β-sheet (strand) – flat ribbon with arrow pointing toward C-terminus.
   c) Loop – thin tube, spaghetti like

d) Turn – tight shift in direction on a loop (180°)

5) Use a diagram to describe the way that a competitive enzyme inhibitor works. (**5 Points**)



inhibitor binds to same pocket as substrate does, preventing substrate binding

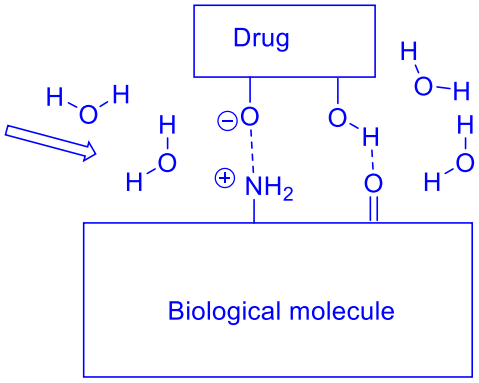


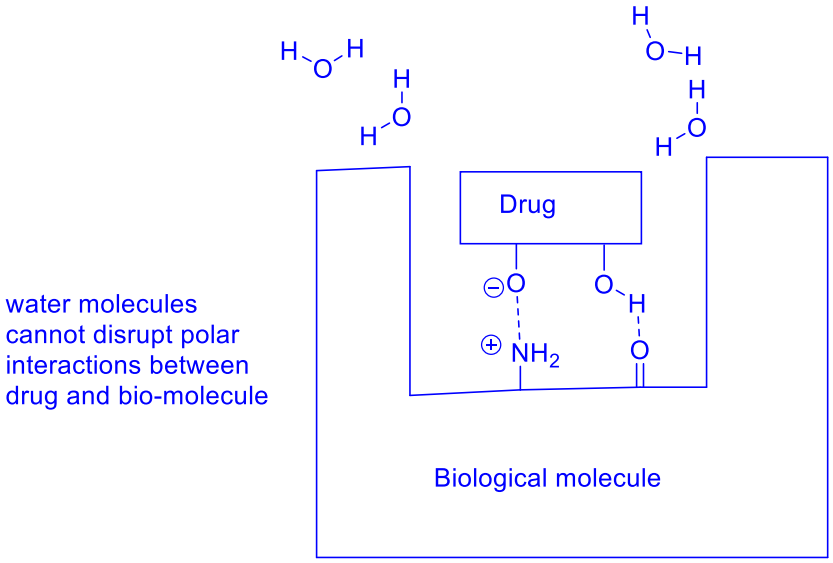
inhibitor occupies binding pocket, substrate cannot enter

6) Why do solvent exposed binding sites on the surface of enzymes provide weaker binding for drugs than binding pockets do (a diagram may be helpful in your answer)? (**4 Points**)

- Binding sites use non-covalent interactions (intermolecular forces) to bind to drugs
- Polar interactions such as hydrogen bonding, electrostatics or dipoles give strongest interactions
- On the surface of a protein, these interactions can be surrounded by water, the molecules of which interact with both the drug and protein
- This weakens the interactions between drug and protein

water molecules can easily disrupt polar interactions between drug and bio-molecule





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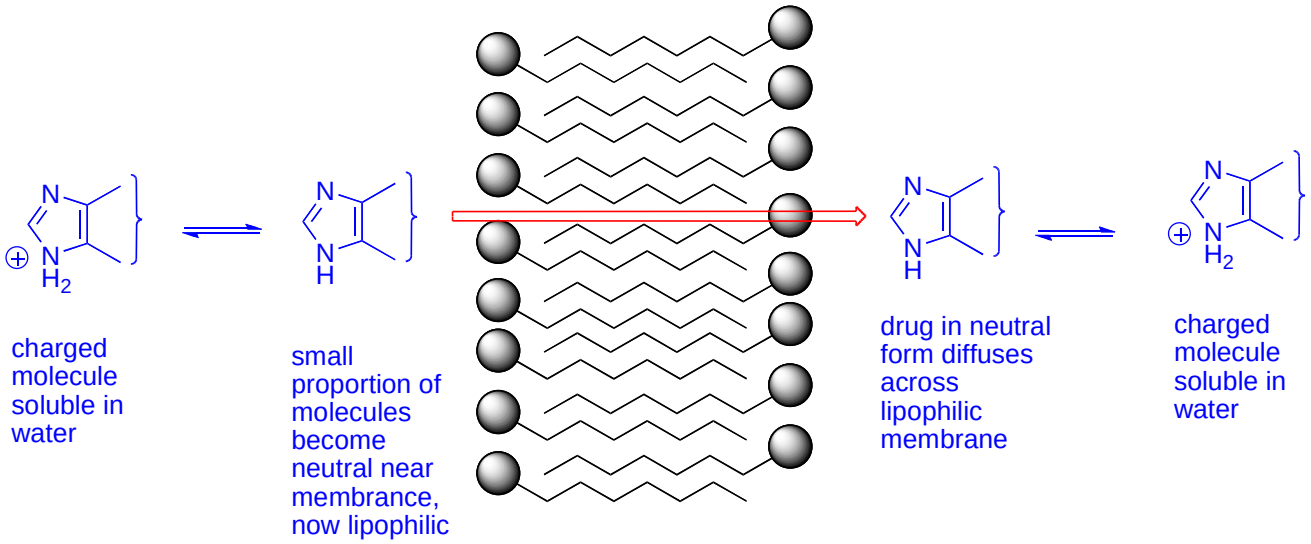
7) Most drugs approved for use in humans are acids or bases.
   a) Use a diagram to show why acids or bases generally make the best drugs (**5 Points**)

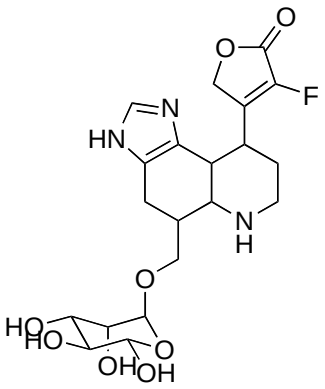
- acids and bases are usually charged at physiological pH
- this makes them soluble in water
- acid base equilibria makes them easy to convert to neutral forms to pass biological membranes



   b) Why are bases more common than acids? (**3 Points**)

- phosphate groups on outside of membranes are negative
- this creates region of negative charge very close to the surface of the membrane
- acids are usually negative at pH 7.4
- negatively charged molecules repelled at the surface of membranes, this makes it more difficult for them to pass through

8) Predict whether the following compounds are likely to be orally bioavailable or not, and provide a brief justification for each. (**6 Points**)
   a)

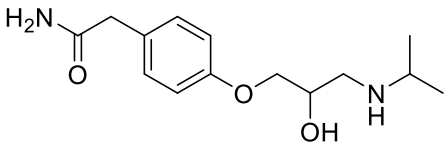


MW = 455.4
CLogP = 4.5

H bond donors = 6
H bond acceptors = 11

2 violations of Lipinsky's rules likely not bioavailable

b)

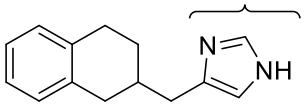


MW = 266.3
$LogD_{7.4}$ = 0.58

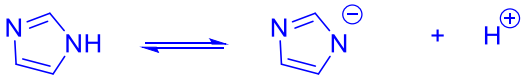
H-bond donors = 4
H-bond acceptors = 5

likely bioavailable, only violates one rule

9) The following molecule was once considered as a drug candidate by a large pharmaceutical company

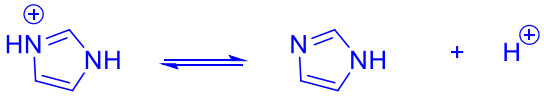


a) For the functional group indicated, write the pK_a expression for the group acting as an **acid** and identify an appropriate pK_a value using the table provided. (**3 Points**)



pKa = 18.6

b) For the functional group indicated, write the pK_a expression for the group acting as a **base** and identify an appropriate pK_a value using the table provided. (**3 Points**)

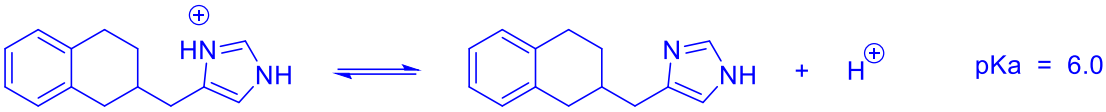


pKa = 6.0

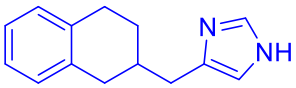
c) Use your pK_a data to predict whether the group will act as an acid or base when used as a drug. (**2 Points**)

- Group will act as a base
- The pKa of the group, acting as an acid is outside the range of allowed for water (-1.5 to 15.7).
- The pKa for the group acting as a base is inside this range, and is therefore relevant for this in water solution

d) Use your pKa data to predict whether the molecule is likely to be soluble at pH 7.4. (**2 Points**)



at pH 7.4, this molecule is in the non-protonated form



in this form it is neutral, and therefore not likely to be highly soluble in water