BPS 2110 Intro to Biopharm
Mid Term 1 Answers

1. Complete the following table describing the stages of drug development. (**7 points**)

	Average Time taken	End Point Designation (Name)
Discovery	1-3 years	Drug Candidate
Development	1-2 years	Investigational New Drug (IND)
Clinical Trials	1-5 years	New Drug Application (NDA)
FDA Approval	6 months to 1.5 years	

1) PAINS are a major problem during drug discovery.
   a) What does the acronym PAINS stand for? (**1 Point**)

Pan Assay INterference compoundS (1)

   b) Why are PAINS a problem? (**2 Points**)

Promiscuous bioactive compounds, they give positive results in virtually any biological test. This tends to clutter up search results and slow down drug discovery.

   c) List two types of chemical behavior that PAINS generally have in common. (**2 Points**)

Choose any 2 of following: (2)

- Redox (oxidation or reduction)
- Detergents
- Strong acids or bases
- Strong nucleophile or electrophile
- Photoreactive
- Chelator
- Highly lipophilic

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

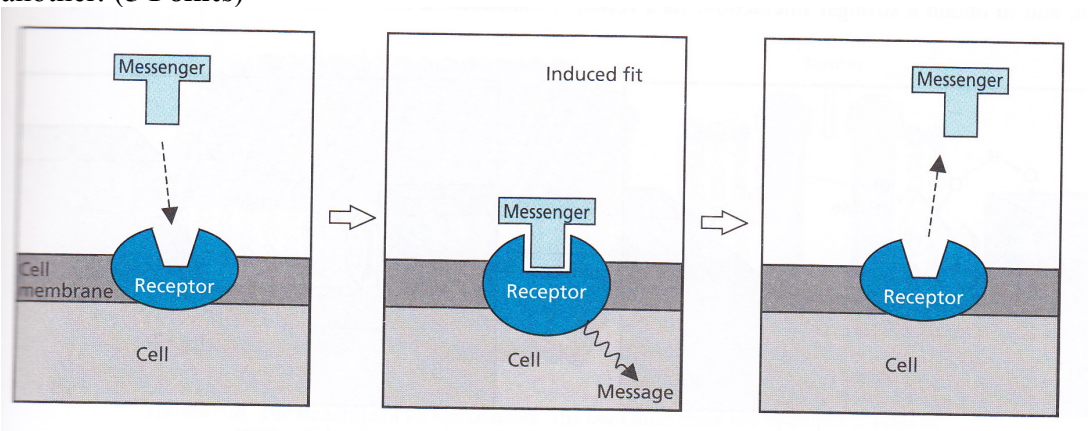
Choose any 3 of following. Need name + function:

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

3) 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.

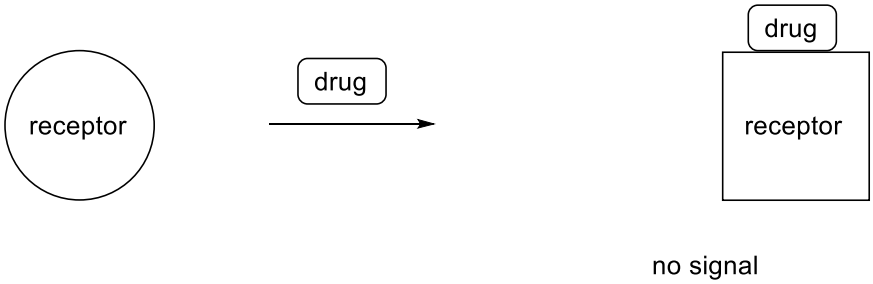
c) Loop – thin tube, spaghetti like
d) Turn – tight shift in direction on a loop (approx 180°)

4) Use a diagram to describe:
   a) The way that a receptor molecule transfers information from one side of a membrane to another. (**5 Points**)

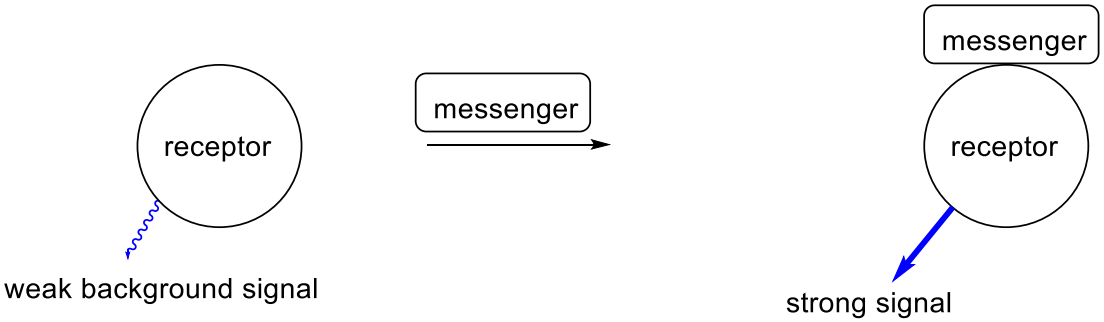


Shape change during induced fit triggers event inside the cell
- Binds/unbinds second messenger
- Activate/deactivate enzyme

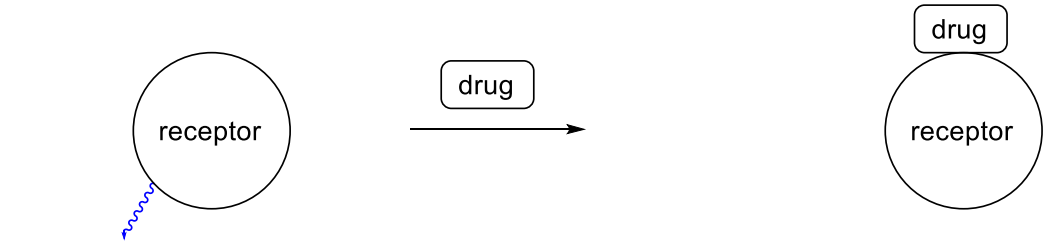
   b) The way that an antagonist works (**3 Points**)
Drug binds to receptor in such a way that an "abnormal" shape change is produced. This results in no signal transmitted. The drug prevents the messenger from binding, preventing signal from being produced.



   c) The way that an inverse agonist works (**5 Points**)
Inverse agonist occurs when the receptor molecule produces a weak background signal (signal produced in absence of a messenger)

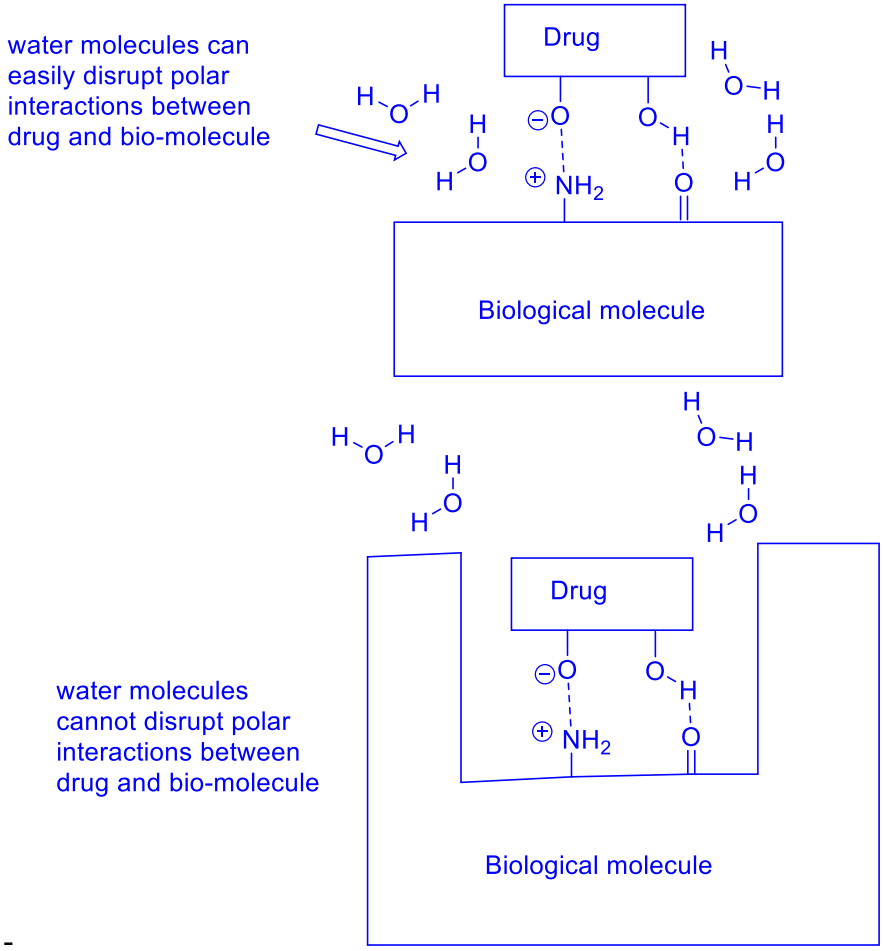


Inverse agonist behaves like an antagonist, binding to the receptor and changing shape to prevent signal production. This has the effect of shutting off the background signal, producing a reduction in signal relative to a "normal" antagonist.



5) 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



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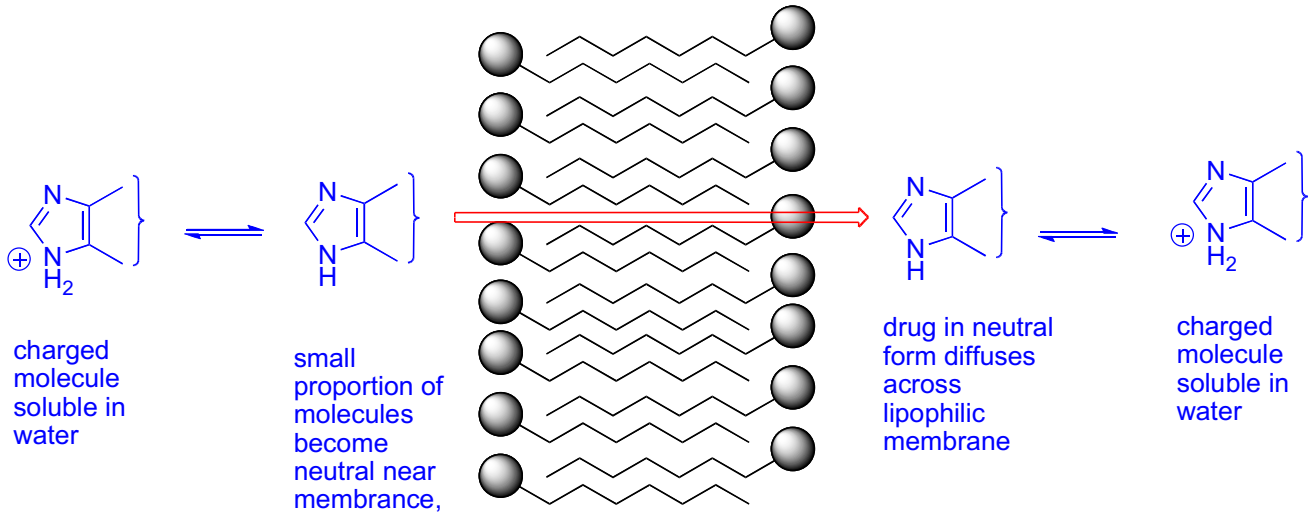
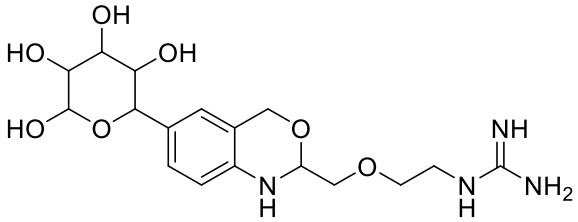
6) Most drugs approved for use in humans are acids or bases. Use a diagram to show why acids or bases generally are able to be transported widely in the body (**5 Points**)

- 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



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

a)

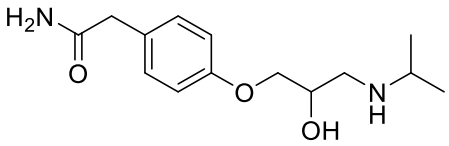


MW = 398.4
MlogP = 4.8

H-bond donors = 9
H-bond acceptors = 11

likely not bioavailable, violates three rules

b)

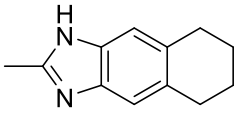


MW = 266.3
$LogD_{7.4}$ = 0.58

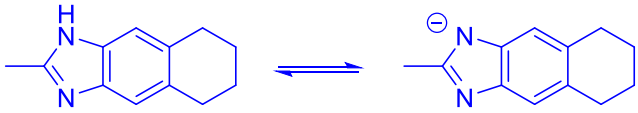
H-bond donors = 4
H-bond acceptors = 5

likely bioavailable, only violates one rule

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

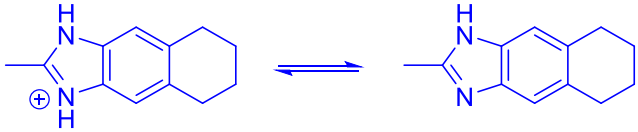


a) Write the pK_a expression for the drug acting as an **acid** and identify an appropriate pK_a value using the table provided. (**3 Points**)



pK_a 22

b) Write the pK_a expression for the drug acting as a **base** and identify an appropriate pK_a value using the table provided. (**3 Points**)



pK_a 3.2

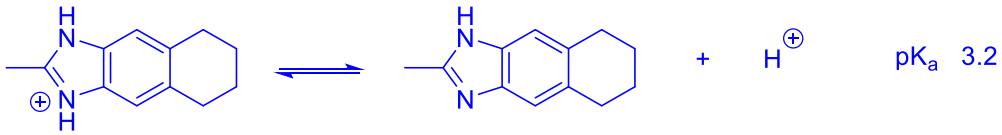
c) Use your pK_a data to predict whether the group will act as an acid or base when used as a drug. (**2 Points**)

Group will act as a base

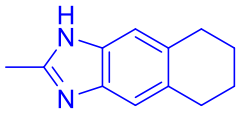
The pKa of the group, acting as an acid is outside the range of allowed for water (-1.5 to 15.7).

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**)



pH is greater than pKa. At pH 7.4 the molecule will be in the unprotonated state.



Drug is neutral and likely insoluble in water.