CONFIDENTIAL

1-58	56	
59	6	
60	10	
61	4	
62	6	
63	8	
64	5	
65	6	
66	2	
67	2	
Total	105	

SEAT NUMBER: ....

SURNAME: ....…...

(Block letters)

OTHER NAMES: ....

(Block Letters)

SID: ....………………………...........

FACULTY OF PHARMACY

BACHELOR OF PHARMACY DEGREE

Second Year

DRUG DISCOVERY AND DESIGN A (PHAR 2811)

June 2010   **Time Allowed: 2.5 Hours**

ANSWER **ALL** QUESTIONS

- **Questions 1 - 58** must be answered on the computer sheet provided.

- Use a soft pencil to mark the box corresponding to the most correct answer. Mark alphanumeric characters corresponding to your name and SID, and also write them on the computer sheet.

- Marks will **NOT** be deducted for incorrect answers in the multiple-choice questions.

- **Questions 59 to 67** are to be answered in the spaces provided on pages 27 – 35 of this examination paper**.**

- Non-programmable calculators may be used.

- **All copies of this examination paper are to be returned to the examiner with all pages intact.**

- **None of the examination paper may be removed from the examination room by candidates or supervisors, nor may any portion be copied.**

This examination paper consists of 36 pages, numbered 1-36 inclusive. There are 67 questions, numbered 1- 67 inclusive. Students are asked to check that their booklet is complete, and to indicate that they have done so by signing below.

I have checked this booklet and affirm that it is complete.

SIGNATURE: _____

Students finding an incomplete booklet should obtain a replacement from the examination supervisor immediately.

Read the questions carefully. Give only one answer.

1.   The central atom of all 20 standard amino acids is what is termed the α-carbon, which has four covalent bonds. Which of these would **NOT** be considered to be bonded to the α-carbon in a polypeptide:

    A. a carbon atom
    B. an amino group
    C. carboxyl group
   D. a side chain (R- group)
    E. an ethyl group

2.   Cysteine residues play an important role in the structure of many proteins by:

    A. changing the pI.
    B. providing covalent links between two parts of a protein molecule.
    C. terminating protein chains.
    D. forming disulfide bonds with another amino acid type.
    E. linking two protein chains using hydrophobic interactions.

3.   The isoelectric point, or pI, of an amino acid or a protein is

    A. the measure of how hydrophobic an amino acid or protein is.
    B. greater than 7.0 for acidic behaviour.
    C. the pH at which the amino acid or protein has no net charge.
    D. zero at pH 7.0.
    E. the pH at which the amino acid or protein is neither hydrophobic nor hydrophilic.

4.   The farnesyl group is one way in which a protein can be targetted to the plasma membrane. Part of the protein to which the farnesyl is covalently attached is shown in the figure. An aminoacid signature sequence to which the farnesyl is found to attach consists of the amino acid to which the farnesyl is covalently attached (shown) and then followed by two aliphatic amino acids.
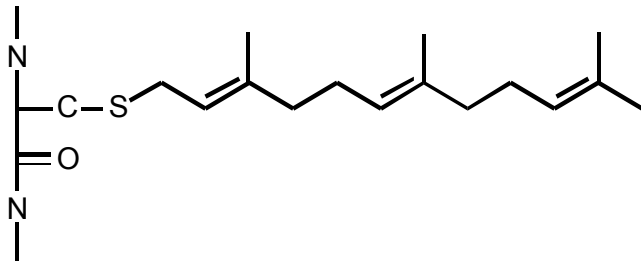
The amino acid sequence which has been described for farnesylation is

A.   Alanine (Ala) – Valine (Val) – Cysteine (Cys)

B.   Cysteine (Cys) – Cysteine (Cys) – Cysteine (Cys)

C.   Methionine (Met) – Alanine (Ala) – Alanine (Ala)

D.   Cysteine (Cys) – Alanine (Ala) – Alanine (Ala)

E.   Alanine (Ala) – Valine (Val) – Methionine (Met)

5.   Which of the following experimental techniques is useful for determining static 3D-protein structures?

A.   Circular Dichroism (CD) Spectroscopy

B.   Single crystal X-ray crystallography

C.   Nuclear Magnetic Resonance (NMR) Spectroscopy

D.   Powder X-ray crystallography

E.   Amino Acid Sequence analysis

6.   To determine the primary amino-acid sequence in a protein, a useful technique is:

    A.   Mass Spectrometry

    B.   Edman degradation

    C.   Molecular Modelling

    D.   Nuclear Magnetic Resonance (NMR) Spectroscopy

    E.   Circular Dichroism (CD) Spectroscopy

7.   The quaternary structure of a protein is:

    A.   A beta-pleated sheet

    B.   Two or more distinct protein units joined together

    C.   An alpha helix

    D.   A beta-turn

    E.   The amino acid sequence

8.   When a drug binds tightly to a target, which of the following is **INCORRECT**?

    A.   there is a high degree of structural complimentarity between drug and target

    B.   the electrostatics of drug and target should be mirror images to increase charge-charge   interactions

    C.   the drug isomeric form is important for steric interaction reasons

    D.   it is entropically unfavourable for the drug to bind, due to liberation of water molecules from the active site

    E.   the protein must remain flexible to allow the drug access to the active site

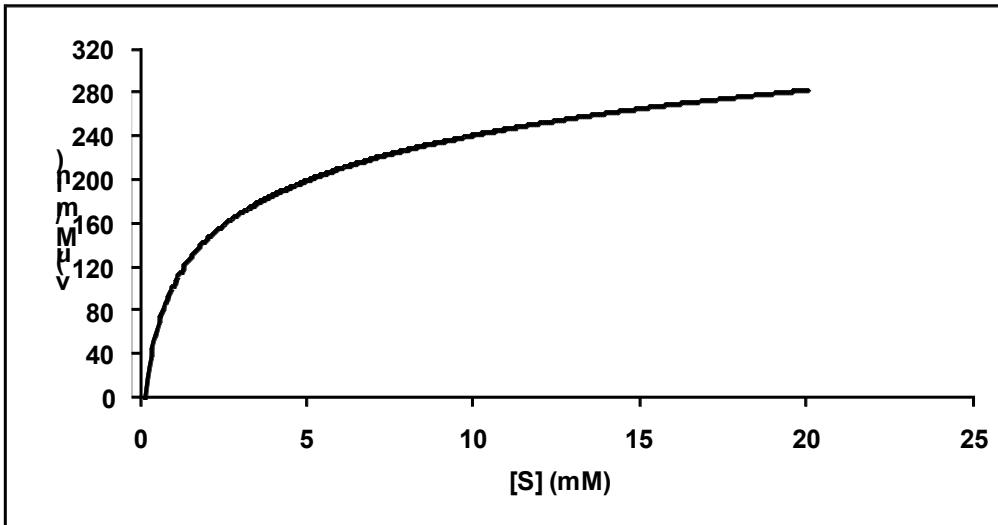9.   Identify the activation energy on the following energy diagram.
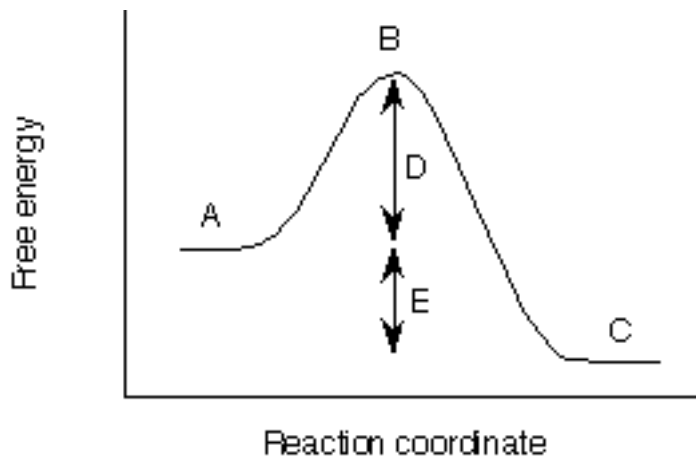
A.

B.

C.

D.

E.

10.   If a plot of v vs. [S] is sigmoidal, it most likely means that:

A.   the enzyme is allosteric

B.   there is a competitive inhibitor present

C.   there is a non-competitive inhibitor present

D.   there is a mechanism-based inhibitor present

E.   there is an irreversible inhibitor present

11.   As a check of the scanning procedure record an answer of A against question **11**.
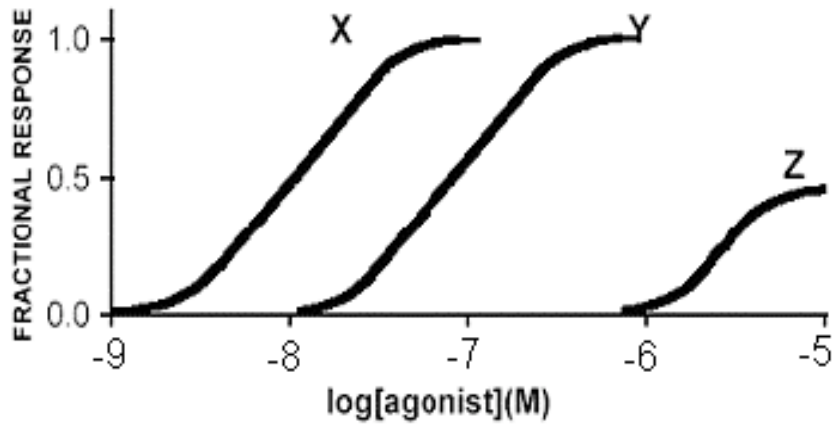
The following questions refer to the graph below:

12. Vmax estimated from the graph above is:

  A. 70 uM/min.

  B. 140 uM/min.

  C. 180 uM/min.

  D. 240 uM/min.

  E. 280 uM/min.

13. Km estimated from the graph above is:

  A. 0.2 mM.

  B. 1 mM.

  C. 2 mM.

  D. 10 mM.

  E. 20 mM.

The following diagram applies to Question 40 and shows the dose-response curves for agonists X, Y and Z.

40.   The EC_{50} value of agonist Y is:

A. 10^{-8}
B.   8.0
C.   -8.0
D. 10^{-7}
E.   7.0

41.   The existence of an irreversible antagonist used in a series of agonist concentration-occupancy curves of increasing concentration of antagonist would be identified by:

   A. curves identical except for the shifts along the concentration axis no matter what the antagonist concentration.

   B. lower responses at low antagonist concentrations and then curves identical except for the shifts along the concentration.

   C. curves identical except for the shifts along the concentration axis until the increased antagonist concentration produces a lower response.

   D. answers A and C are correct.

   E. answers B and C are correct.

42.   The *occupancy theory* of receptor theory of drug action:

   A. states that the effects observed upon drug binding to receptor is not directly proportional to the proportion of receptors occupied

   B. does not allow for a full response from a full agonist at low receptor occupancies.

   C. does not allow for spare receptors

   D. answers A and C are correct.

   E. answers B and C are correct.

43.   The *selectivity* of a drug for its receptor is the:

   A. production of drug effects by interaction with multiple receptors.

   B. production of a particular drug effect at a lower dose than that producing multiple effects

   C. ability of an agonist to produce its maximum response compared to a standard.

   D. ability of an agonist to produce the response of a standard agonist.

   E. negative log dose of a drug at which the receptor is half maximally occupied.

The Scatchard plot gives a straight line based on the equation, $B/F = B_{max}/K_D - B/K_D$. The diagram below is a Scatchard Plot and should be used for the following question (Question 44).
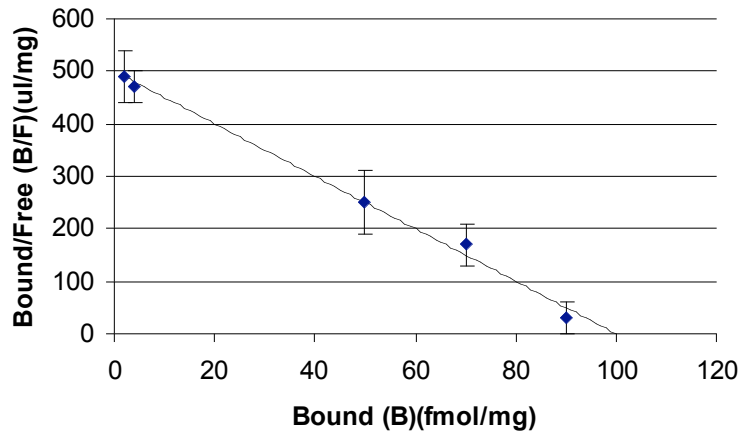
44.   The K_D of the binding is closest to (in nM):

      A.   0.2

      B.   5

      C.   10

      D.   100

      E.   200

45. Which of the following statements is INCORRECT? Enzyme-linked receptors

    A.   are transmembrane proteins with their ligand-binding domain on the outer surface of the plasma membrane

    B.   are characterised as having a cytosolic domain that either has an intrinsic enzyme activity or associates directly with an enzyme

    C.   include receptor-like tyrosine phosphatases, receptor serine/threonine kinases, but not receptor tyrosine kinases

    D.   includes the receptors for epidermal growth factor and vascular endothelial growth factor

    E.   both B and D

46.   G-protein linked receptors

    A.   indirectly activate or inactivate plasma-membrane bound enzymes via trimeric GTP-binding proteins

    B.   indirectly activate or inactivate plasma-membrane bound enzymes via trimeric ATP-binding proteins

    C.   are single polypeptide chains that threads back and forth across the membrane six times

    D.   are receptor tyrosine kinases

    E.   are nuclear receptors

47. G_s

    A.   inhibits adenylyl cyclase

    B.   activates adenylyl cyclase

    C.   causes the release of calcium ions

    D.   activates phosphodiesterases

    E.   inhibits phospholipase C-β

59.   (6 marks)

A)   Draw any two different natural occurring amino acids and label them with their name.
(3 marks)

B)   Describe the covalent bonding that gives rise to a polypeptide chain from amino acids.
A drawing may be appropriate to assist your description (2 marks)

C) What is the covalent bonding that also contributes to the overall stability of a folded polypeptide
chain? A drawing may also be appropriate here.(1 mark)

60.   (10 marks)

A) <u>Calculate</u> Vmax, Km, and Ki from the graph below. Show your working and units (to 4 d.p.).

Part marks will be awarded.

[I] = 5 uM
y = 12.136x + 1.4533

[I] = 2 uM
y = 7.7195x + 1.6189

[I] = 0 uM
y = 3.7919x + 2.1422
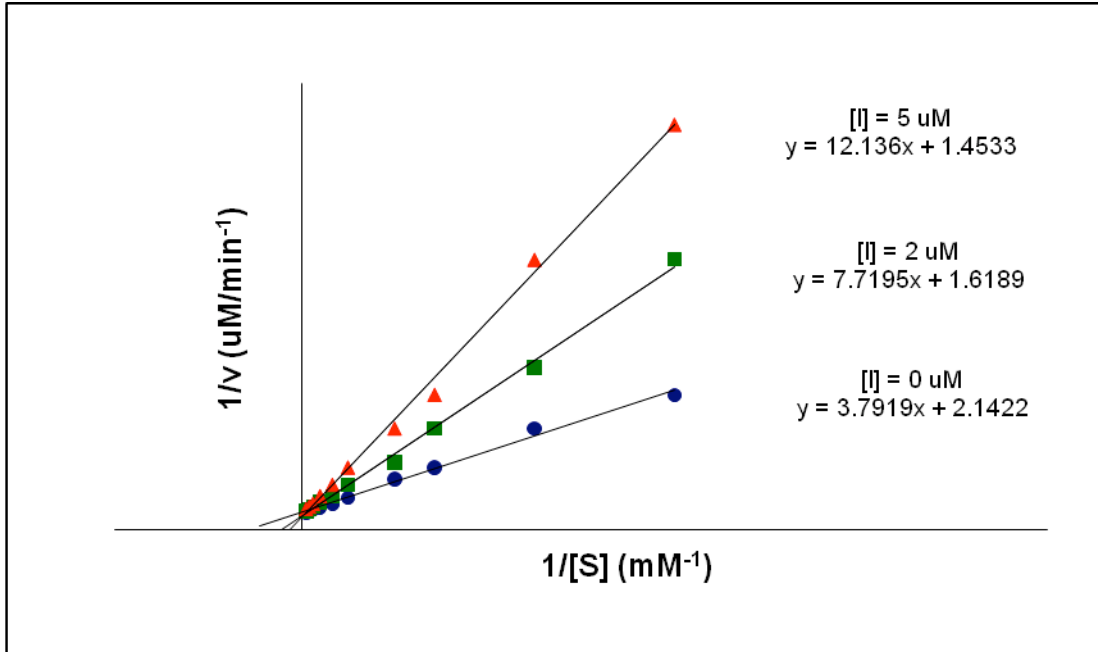
Note: $1/v = Km/Vmax(1+([I]/Ki))$. $1/S + 1/Vmax$

B) What is an allosteric site and how are they involved in feedback control?

65.   (6 marks)

Simple drug binding data for three compounds acting at a single receptor have been acquired (see table) and relate to Question 64 only.

Compound	X	Y	Z
Affinity	Low	High	High
Intrinsic Activity	High	High	None

Consider the series of compounds X, Y and Z. The compounds demonstrate a range of affinities and intrinsic activities as shown. Give possible explanations of these results giving some structural considerations. (6 marks)

66. (2 marks)

Describe how Ras acts a "molecular switch" .

67. (2 marks)

 Outline the molecular mechanism by which bronchospasm can be alleviated by phosphodiesterase inhibitors.

This is the last page

Rough work space

Rough work space