NAMIBIA UNIVERSITY
OF SCIENCE AND TECHNOLOGY

FACULTY OF HEALTH AND APPLIED SCIENCES

DEPARTMENT OF NATURAL AND APPLIED SCIENCES

QUALIFICATION: BACHELOR OF SCIENCE HONOURS	
QUALIFICATION CODE: 08BOSH	**LEVEL:** 8
COURSE NAME: SYNTHETIC ASPECTS OF MEDICINAL CHEMISTRY	**COURSE CODE:** SAM821S
SESSION: NOVEMBER 2019	**PAPER:** THEORY
DURATION: 3 HOURS	**TOTAL MARKS:** 100

FIRST OPPORTUNITY EXAMINATION QUESTION PAPER	
EXAMINER(S)	DR. MARIUS MUTORWA
MODERATOR	DR. RENATE HANS

INSTRUCTIONS

1. Answer ALL questions.
2. Write clearly and neatly.
3. Number the answers clearly
4. All written work must be done in blue or black ink and sketches can be done in pencil
5. No books, notes and other additional aids are allowed

THIS QUESTION PAPER CONSISTS OF 11 PAGES
(Including this front page)

PERMISSIBLE MATERIALS

Non-programmable Calculators

ATTACHMENTS

List of Amino Acids

SECTION A [60]

QUESTION 1: Multiple Choice Questions [60]

- *There are 30 multiple choice questions in this section. Each question carries 2 marks.*
- *Answer ALL questions by selecting the best possible answer for each question, even if you think there is another possible answer that is not given.*

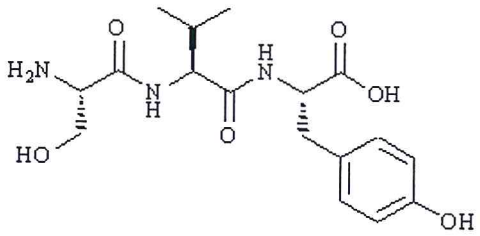
1.1 Which of the following statements is false regarding the phospholipid bilayer in cell membranes?

A. It is made up of two layers of phospholipid molecules with the tails interacting with each other
B. Water and ions are unable to cross the bilayer due to the hydrophobic tails of the phospholipid molecules
C. There are charged groups at the inner and outer surfaces of the cell membrane
D. The molecules in the bilayer are fluid and so the cell membrane is porous allowing the passage of ions and water across the cell membrane

1.2 Which of the following statements is true with respect to a binding site?

A. It is part of a macromolecule that acts as a drug target
B. It contains binding regions
C. It is normally a hollow or cleft on the surface of the drug target
D. all of the above

1.3 Identify the correct name for the following peptide.



A. L-seryl-L-valyl-L-tyrosine
B. L-seryl-L-valyl-L-phenylalanine
C. L-phenylalanyl-L-valyl-L-serine
D. L-tyrosyl-L-valyl-L-serine

1.4 Which of the following statements is untrue about protein tertiary structure?

A. Proteins fold up into a tertiary structure such that most amino acids with hydrophobic residues are exposed to the aqueous surroundings
B. Proteins fold up into a tertiary structure such that most amino acids with hydrophilic residues are exposed to the aqueous surroundings
C. Proteins fold up into a tertiary structure such that most amino acids with hydrophobic residues are in the centre and hidden from the aqueous surroundings
D. Interactions between amino acid residues are important in protein tertiary structure

1.5 Which of the following statements is not true regarding protein tertiary structure?

A. Van der Waals interactions between hydrophobic residues are the least important factors in tertiary structure
B. Covalent bonds can have an influence on tertiary structure
C. Hydrogen bonds, ionic bonds and van der Waals interactions all have a role to play in tertiary structure
D. Planar peptide bonds have an indirect influence on protein tertiary structure

1.6 Some enzymes have a binding site which is not recognised by the normal substrate, and affects the activity of the enzyme if it is occupied by a ligand. What term is used for such a binding site?

A. Active site
B. Allosteric binding site
C. Secondary binding site
D. Inhibitory binding site

1.7 Which of the following descriptions best describes a prosthetic group?

A. A non-protein substance that is required by an enzyme if it is to catalyse a reaction
B. A non-protein organic molecule that is required by some enzymes in order to catalyse a reaction on a substrate
C. A non-protein organic molecule that is bound covalently to the active site of an enzyme, and which is required if the enzyme is to catalyse a reaction on a substrate
D. A compound which is bound to the active site and undergoes a reaction

1.8 Which of the following amino acids acts as an acid-base catalyst in enzyme-catalysed reaction mechanisms?

A. Serine
B. Phenylalanine
C. Histidine
D. Tryptophan

1.9 Which of the following statements is **not** true regarding the binding site of a receptor?

A. The binding site is normally a hollow or cleft in the surface of a receptor
B. The binding site is normally hydrophilic in nature
C. Chemical messengers fit into binding sites and bind to functional groups within the binding site
D. The binding site contains amino acids which are important to the binding process

1.10 There is a fine balance required for the binding interactions of a neurotransmitter with its receptor. Which of the following statements best expands on this statement?

A. It is important that the binding interactions involve a mixture of van der Waals interactions, hydrogen bonds and ionic bonds since neurotransmitters have different functional groups
B. The binding interactions must be of the correct nature to match the functional groups of the neurotransmitter and the functional groups in the binding site
C. The binding interactions must be sufficiently strong that the neurotransmitter binds long enough to have an effect, but not too strong in case the neurotransmitter remains permanently bound
D. There must be the correct balance of hydrophilic and hydrophobic interactions to ensure that the chemical messenger can enter a hydrophobic binding site

1.11 Which of the following descriptions best describes a competitive enzyme inhibitor?

A. A drug that binds to an active site and undergoes a reaction
B. A drug that binds to an active site and inhibits the enzyme, but which is displaced by increasing the concentration of substrate
C. A drug that binds to an active site and inhibits the enzyme, but which is not displaced by increasing the concentration of substrate
D. A drug that binds to a different binding site from the active site and affects the activity of the enzyme.

1.12 What type of plots can be used to determine whether an enzyme inhibitor is competitive or non-competitive?

A. Michaelis-Menten plots
B. Schild plots
C. Displacement plots
D. Lineweaver-Burk plots

1.13 Which of the following agents act as irreversible inhibitors?

A. Sulphonamides
B. Penicillins
C. Statins
D. Protease inhibitors

1.14 Which of the following descriptions best fits an agonist?

A. A compound that has the same effect on a receptor as the endogenous chemical messenger
B. A compound that binds to a receptor, and activates it, but to a lesser extent than the endogenous chemical messenger
C. A compound that binds to a receptor fails to activate it and prevents the endogenous chemical messenger from binding
D. A compound that binds to a receptor fails to activate it and leads to a drop in inherent biological activity

1.15 Which of the following terms applies to the study of how a drug interacts with its target binding site at the molecular level?

A. Pharmacokinetics
B. Structure based drug design
C. Pharmacodynamics
D. Structure-activity relationships

1.16 Which of the following statements best describes the affinity of a drug?

A. The maximum biological effect resulting from a drug binding to its target
B. The measure of how strongly a drug binds to a receptor
C. The amount of drug required to produce a defined biological effect
D. The lifetime of the drug in the body

1.17 Which of the following symbols represents the concentration of a drug required to produce 50% of a maximum possible effect?

A. IC_{50}
B. K_i
C. K_d
D. EC_{50}

1.18 Which of the following is not a necessary requirement when designing an agonist?

A. The identical functional groups present in the endogenous chemical messenger
B. The presence of the correct binding groups
C. The correct size and shape of the molecule
D. The correct relative orientation of the binding groups

1.19 Which of the following situations is feasible as an explanation for tolerance and dependence?

A. An increased production of receptors to counteract the presence of an antagonist
B. An increased production of receptors to counteract the presence of an agonist
C. A decreased production of receptors to counteract the presence of an antagonist
D. A decreased synthesis of chemical messenger to counteract the presence of an antagonist

1.20 What is the pharmacokinetic advantage of drugs having amine functional groups?

A. They are strong bases and are fully ionised
B. They are very weak bases and are not ionised at all
C. They are weak bases and are in equilibrium between the ionised and free base forms
D. They are able to form hydrogen bonds

1.21 How can advantage be taken of the blood brain barrier in drug design?

A. Drugs can be made more hydrophobic such that they act in the brain and not peripherally
B. Drugs can be made more hydrophilic such that they act in the brain and not peripherally
C. Drugs can be made more hydrophobic such that they act peripherally and not in the brain
D. Drugs can be made more hydrophilic such that they act peripherally and not in the brain

1.22 Which of the following functional groups cannot be formed by a metabolic reaction catalysed by cytochrome P450 enzymes?

A. Ethers
B. Ketones
C. Alcohols
D. Carboxylic acids

1.23 Which of the following reflects the order in which various stages of the drug discovery and development take place?

A. Determining a target, establishing a bioassay, finding a lead compound, structure activity relationships
B. Establishing a bioassay, determining a target, finding a lead compound, structure activity relationships
C. Determining a target, establishing a bioassay, structure activity relationships, finding a lead compound
   Determining a target, finding a lead compound, structure activity relationships, establishing a bioassay

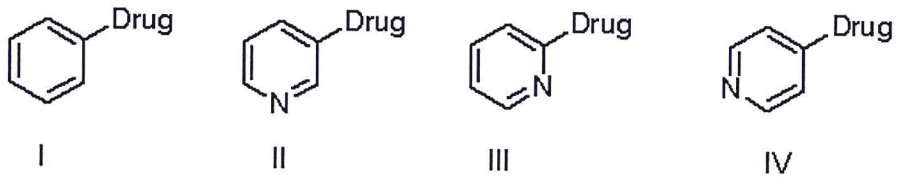
1.24 What term is used for the chemical which is chiefly responsible for the biological activity of a natural extract?

A. Active drug
B. Prime drug
C. Active principle
D. Prime principle

1.25 A secondary amide group in a lead compound was reduced to an amine functional group. *In vitro* tests showed that the lead compound was active and that the product was inactive. However, *in vivo* tests showed that both the amide and amine were inactive. Which of the following statements is not plausible?

A. The amide is an important binding group but the amine is not
B. Both the amide and the amine are important binding groups
C. The carboxyl group of the amide may be an important hydrogen bond acceptor group
D. In the *in vivo* bioassay, the amide is converted to the amine by metabolic or digestive enzymes

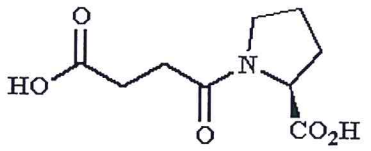
1.26 Structures (II-IV) are analogues of a lead compound containing an aromatic ring (structure I). Structures II and III had similar activity to the lead compound whereas structure IV showed a marked increase in activity. Which of the following explanations best fits the facts?



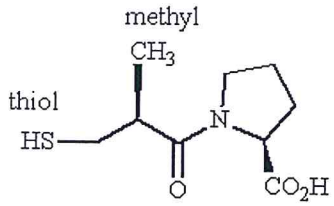
I II III IV

A. Introducing a nitrogen increases basicity and so increased basicity is good for activity
B. Introducing a nitrogen increases the polarity and water solubility of the analogues, and so increased polarity is good for activity
C. Introducing a nitrogen means that an additional hydrogen bonding interaction is possible with an extra binding region in the binding site
D. Introducing a nitrogen removes an aromatic hydrogen. The aromatic hydrogen removed may have been bad for activity for steric reasons

1.27 Succinyl proline was the lead compound for captopril which acts as an inhibitor of the angiotensin-converting enzyme. What is the relevance of the methyl group in captopril?



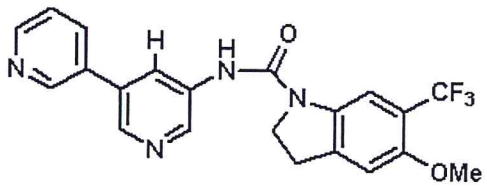
Succinyl proline



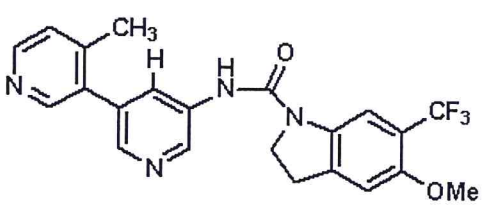
Captopril

A. It represents an extension strategy where the methyl group binds to an extra hydrophobic binding region
B. It acts as a conformational blocker and correctly orientates the important binding groups with respect to each other
C. It is an exposed group and is easily oxidised by metabolic enzymes to a carboxylic acid which binds by ionic interactions to a hydrophilic binding region
D. It introduces an asymmetric centre

1.28 Structure (III) is a serotonin antagonist. A methyl group has been introduced into analogue (IV) resulting in increased activity.



III



IV

A. The methyl group interacts with an extra hydrophilic binding region through van der Waals interactions
B. The methyl group increases the basicity of the ring nitrogen, making it a better hydrogen bond donor
C. The methyl group increases the basicity of the ring nitrogen, making it a better hydrogen bond donor
D. The methyl group prevents the pyridine rings from being coplanar and forces the molecule into the active conformation

1.29 Many drugs containing ester functional groups have a limited duration of action. There are several strategies which can be used to avoid this problem. Which of the following is not a suitable strategy?

A. Replacing the ester group with an amide
B. Adding a steric shield close to the ester
C. Adding an electron withdrawing group to the alkoxy moiety of the ester
D. Replacing the ester group with a urethane

1.30 Why should the addition of an alcohol or phenol group to a drug decrease the drug's duration of action?

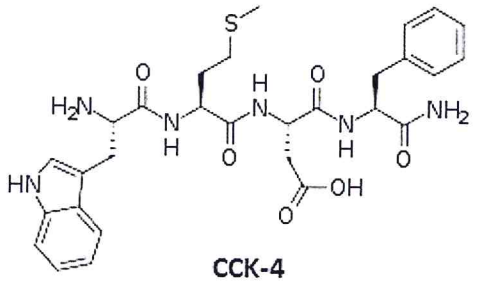
A. It acts as a 'polar handle' for conjugation reactions. The conjugates are excreted more quickly
B. It increases the polarity of the drug and reduces the amount of drug absorbed
C. It reacts with proteins in the body such that the drug is irreversibly linked to the proteins by a covalent bond
D. It acts as an electron withdrawing group and affects the binding strength of important binding groups

END OF SECTION A

SECTION B: [40]

QUESTION 2 [20]

2.1 Cholecystokinin (CCK) is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein. The presence of CCK causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively, and thus CCK functions in a number of processes such as digestion and hunger sensation. Cholecystokinin tetrapeptide (CCK-4) is a smaller peptide fragment (molecular weight = 596.7 and Log P = -2.1) derived from the larger peptide hormone cholecystokinin. Unlike CCK which has a variety of roles in the gastrointestinal system, CCK-4 acts primarily in the brain as an anxiogenic i.e. causes anxiety.



CCK-4

a) Discuss possible concerns you might have with using CCK-4 as a lead compound for an orally administered, active anti-anxiety drug? (8)

b) Discuss some alternative approaches you would consider to identifying an anti-anxiety lead compound. (8)

2.2 Discuss two advantages and two disadvantages of random screening as a technic in the drug discovery process. (4)

QUESTION 3 [10]

3.1 Candesartan cilexetil is an anti-hypertensive prodrug that antagonizes the AT1 angiotensin receptor. Within the structure of Candesartan cilexetil are four lead modification approaches which have been applied to synthesise the molecule.

a) Redraw the molecule and identify by circling and naming, the four lead modification approaches which have been used to synthesise the drug. (4)

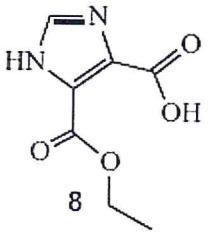
b) Working backward, draw a lead molecule from which Candesartan cilexetil may have been derived. (4)

3.2 What are the problems of using bioisosteric replacements as a strategy in lead optimization? (2)

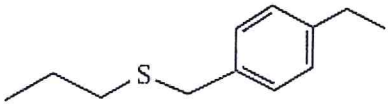
QUESTION 4

[10]

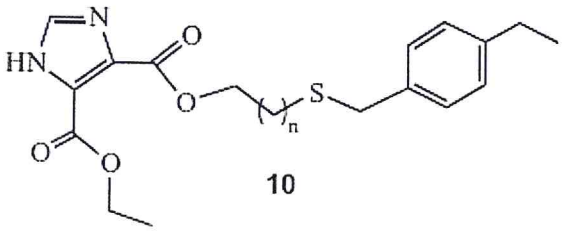
4.1 Compounds **8** and **9** below were leads determined from a Structure & Activity Relationship study conducted by NMR spectroscopy targeting a new receptor. Based on this analysis, compound **10** was synthesised and the number of methylene groups (n) was varied. However, all of the compounds synthesised with a varied n had much lower potency that either compound **8** or **9**.



8



9



10

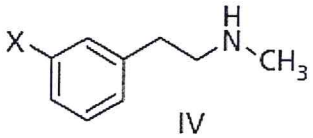
a) What conclusion can be made from the observed results described above? (3)

b) Based on you answer in (a) above, draw a possible structure that could potential exhibit a greater potency than either compound **8** or **9**. (2)

4.2

a) Explain the principles of rigidification. (3)

b) Show how you would apply a rigidification strategy to structure IV below in order to improve its pharmacological properties. Give two specific examples of rigidified structures. (2)

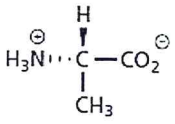


IV

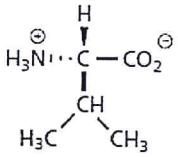
THE END

LIST OF AMINO ACIDS

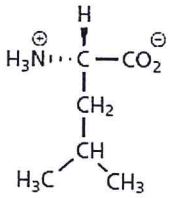
NON POLAR (hydrophobic)



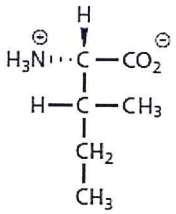
Alanine (Ala or A)



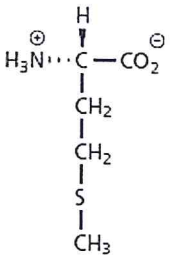
Valine (Val or V)



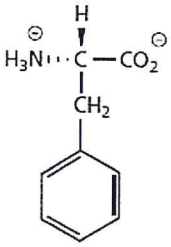
Leucine (Leu or L)



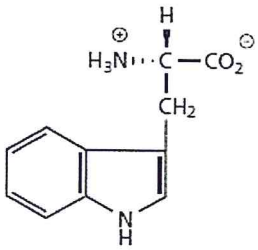
Isoleucine (Ile or I)



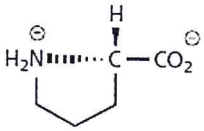
Methionine (Met or M)



Phenylalanine (Phe or F)

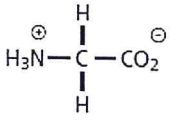


Tryptophan (Trp or W)

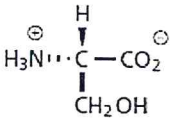


Proline (Pro or P)

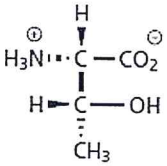
POLAR



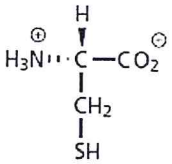
Glycine (Gly or G)



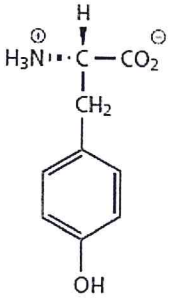
Serine (Ser or S)



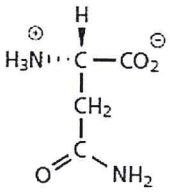
Threonine (Thr or T)



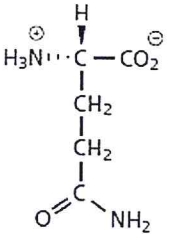
Cysteine (Cys or C)



Tyrosine (Tyr or Y)



Asparagine (Asn or N)



Glutamine (Gln or Q)

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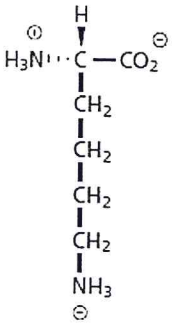
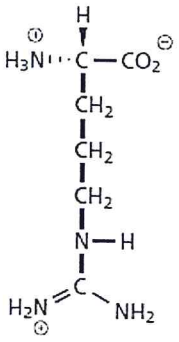
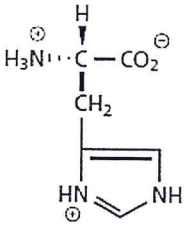


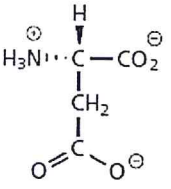
Lysine (Lys or K)



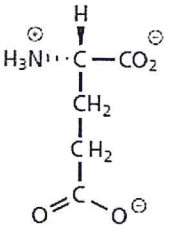
Arginine (Arg or R)



Histidine (His or H)



Aspartate (Asp or D)



Glutamate (Glu or E)