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 CODE: SAM821S	**COURSE NAME:** SYNTHETIC ASPECTS OF MEDICINAL CHEMISTRY
SESSION: JANUARY 2019	**PAPER:** THEORY
DURATION: 3 HOURS	**TOTAL MARKS:** 100

SUPPLEMENTARY / SECOND 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 10 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 underlined atoms is likely to be the strongest hydrogen bond acceptor?

A. Amide nitrogen (RNHCOR')
B. Aniline nitrogen ($ArNH_2$)
C. Amine nitrogen (RNH_2)
D. Carboxylate oxygen (RCO_2^-)

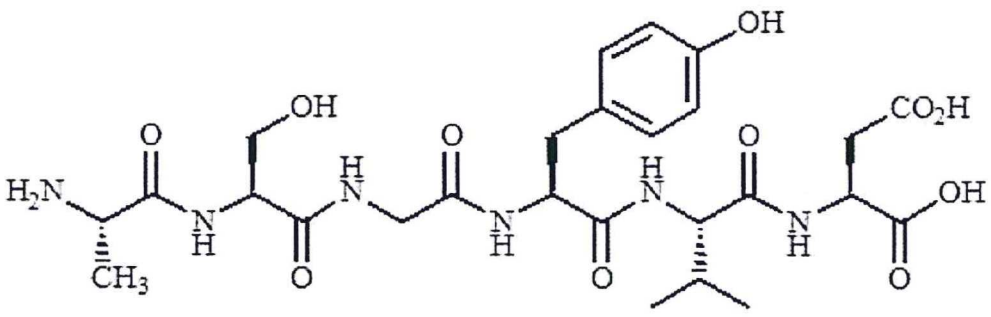
1.2 Which of the following functional groups is most likely to participate in a dipole-dipole interaction?

A. Aromatic ring
B. Ketone
C. Alcohol
D. Alkene

1.3 Which of the following statements is incorrect?

A. Desolvation is an energy expense process that involves the removal of water from polar functional groups prior to a drug binding to its binding site.
B. Water molecules surrounding a hydrophobic region of a drug form an ordered layer of molecules with low entropy.
C. Interaction between non-polar regions of a drug and the non-polar regions of a target require the removal of an ordered water coat and represents a gain in binding energy due to increase entropy.
D. An increase in entropy results in greater positive value for ΔG and greater chance of binding

1.4 Which of the following single letter codes represents the structure below?



A. DVYGSA
B. ASGYVD
C. EVFGSA
D. ASGFVE

1.5 Identify the strongest form of intermolecular bonding that could be formed involving the residue of the amino acid glutamic acid.

A. Ionic bond
B. Hydrogen bond
C. Van der Waals interactions
D. None of the above

1.6 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

1.7 Which of the following descriptions best describes an induced fit?

A. The process by which an active site alters shape such that it is ready to accept a substrate.
B. The process by which a substrate adopts the correct binding conformation before entering an active site
C. The process by which a substrate binds to the active site and alters the shape of the active site.
D. The process by which an active site alters the shape of the substrate such that it can adopt the necessary active conformation for binding.

1.8 Some enzymes require the presence of a non-protein substance if they are to catalyse a reaction. Which of the following terms is the best general term for such a substance?

A. Prosthetic group
B. Co-factor
C. Co-enzyme
D. Modulator

1.9 Consider the following amino acids: glutamate, phenylalanine, threonine, and serine. Which would use ionic bonding as an interaction in a given active site?

A. Serine
B. Glutamate
C. Phenylalanine
D. Tyrosine

1.10 Which of the following statements is not true about neurotransmitters?

A. Neurotransmitters are released by nerves.
B. Neurotransmitters are required to carry a 'message' from a nerve to a target cell.
C. Neurotransmitters only have small distances to cover to reach their target cells.
D. Neurotransmitters bind to receptors within target cells.

1.11 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.

1.12 The mechanism of gating involves the rotation of five kinked α-helices which traverse the cell membrane. Which of the following statements is untrue?

A. Each protein subunit making up the ion channel contributes one of the kinked α-helices.
B. It is the α-helix of the first transmembrane section that is involved.
C. Rotation of the helices opens up a central channel to allow the flow of ions.
D. The neurotransmitter binds to the *N*-terminal chain to produce a rapid response.

1.13 Which of the following enzymes catalyses a phosphorylation reaction?

A. Protein kinases
B. Phosphorylases
C. Esterases
D. Ligases

1.14 Which of the following descriptions best describes an allosteric 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.

1.15 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.

1.16 Which of the following descriptions best fits an antagonist?

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.

1.17 Which of the following terms best describes the study of which functional groups are important in binding a drug to its target binding site, and the identification of a pharmacophore?

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

1.18 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.

1.19 Which of the following properties is preferred for an orally administered drug?

A. Hydrophilic character.
B. Hydrophobic character.
C. A balance of hydrophilic and hydrophobic character.
D. None of the options given are correct.

1.20 Some orally active drugs do not obey the rule of five. For example, some polar drugs with a molecular weight between 200 and 500 are found to be orally active. Which of the following mechanisms is the most likely reason for this?

A. Transport by transport proteins.
B. Passage through pores between the cells of the gut wall.
C. Pinocytosis.
D. Ion channels.

1.21 Which of the following statements is true?

A. Drugs entering the blood supply are evenly distributed round the blood supply within one minute, resulting in an even distribution to different organs.
B. Drugs entering the blood supply are unevenly distributed round the blood supply within one minute, but are evenly distributed to different organs.
C. Drugs entering the blood supply are unevenly distributed round the blood supply within one minute resulting in an uneven distribution to different organs.
D. Drugs entering the blood supply are evenly distributed round the blood supply within one minute, and are unevenly distributed to different organs.

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 There are several sources and methods of discovering new compounds. Which of the following is most likely to lead to the discovery of a complex structure quite unlike any other previously discovered?

A. Combinatorial chemistry
B. Database mining
C. Screening plant extracts
D. Me too drugs

1.24 Natural products are often used as lead compounds in the design and synthesis of novel drugs. Which of the following general characteristics of a natural product is most likely to be a disadvantage in synthesising analogues?

A. Novelty of structure
B. Complexity of structure
C. Level of activity
D. Availability

1.25 Which of the intermolecular bonding interactions below are possible for an alkene?

A. Hydrogen bonding only
B. Van der Waals interactions only
C. Ionic bonding only
D. Both hydrogen bonding and ionic bonding

1.26 Which of the following major aims in drug design is not related to the pharmacodynamics of a drug?

A. The reduction of side effects
B. The maximisation of activity
C. The reduction of toxicity
D. The maximisation of oral bioavailability

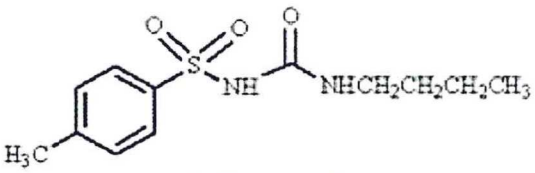
1.27 Which of the following statement is true about a drug with a highly flexible side chain?

A. A flexible molecule is more likely to be in its active conformation when it approaches its target binding site. This results in increased activity.
B. A flexible molecule is more likely to adopt conformations that will bind to different targets, resulting in side effects.
C. A flexible molecule may be able to bind to its target binding site in different binding modes, resulting in an increase in activity.
D. A flexible molecule is more likely to show target selectivity.

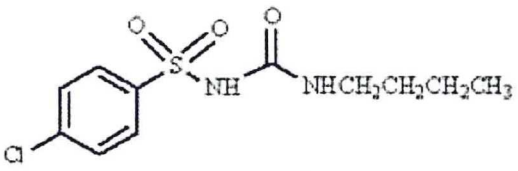
1.28 Which of the following strategies will increase the polarity and water solubility of a drug?

A. Removing polar functional groups
B. Adding extra alkyl groups
C. Replacing an aromatic ring with a nitrogen containing heterocyclic ring
D. Replacing an alkyl group with a larger alkyl group

1.29 Why does chlorpropamide have a longer antibiotic activity than tolbutamide?



Tolbutamide



Chlorpropamide

A. The chloro group of chlorpropamide has an electron-withdrawing effect on the aromatic ring and stabilises the molecule
B. The methyl group of tolbutamide is susceptible to drug metabolism whereas the chloro substituent of chlorpropamide is not.
C. The urea group of tolbutamide is more susceptible to hydrolysis than the urea group of chlorpropamide.
D. The sulphonamide group of tolbutamide is more susceptible to hydrolysis than the sulphonamide group of chlorpropamide.

1.30 What is meant by the therapeutic ratio or index?

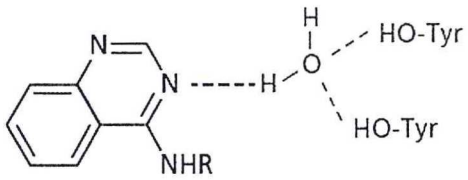
A. The ratio of ED50 to LD50
B. The ratio of LD50 to ED50
C. The ratio of LD1 to ED99
D. The ratio of ED99 to LD1

END OF SECTION A

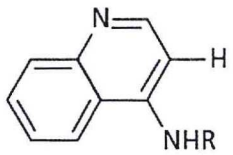
SECTION B: [40]

QUESTION 2 [10]

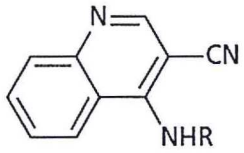
2.1 The quinazoline shown below is an inhibitor of the enzyme scytalone dehydratase. One of the binding interactions between the inhibitor and the active site is a hydrogen bond to a water molecule, which acts as a hydrogen-bonding bridge to two tyrosine residues. Explain why analogue I is 3 times less active, whereas analogue II is 20 times more active. (6)



Quinazoline



Analogue I



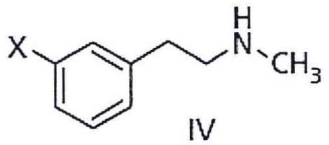
Analogue II

2.2 Benzene used to be a common solvent in organic chemistry, but is no longer used because it is a suspected carcinogen. Toluene is now used as a solvent in place of benzene. Toluene is oxidised by cytochrome P450 enzymes, but the metabolite is less toxic and is rapidly excreted. Suggest the metabolites for toluene. (4)

QUESTION 3 [10]

3.1 You are employed as a medicinal chemist and have been asked to initiate a research programme aimed at finding a drug which will prevent a novel tyrosine kinase receptor from functioning. There are no known lead compounds that have this property. What approaches will you consider or take to establish a lead compound? (5)

3.2 Explain the principles of rigidification and show how you would apply it to structure IV below in order to improve its pharmacological properties. Give two specific examples of rigidified structures. (5)

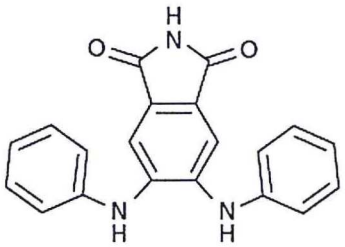


IV

QUESTION 4 [10]

4.1 A lead compound containing a methyl ester was hydrolysed to give a carboxylic acid. An in vivo bioassay suggested that the ester was active and the acid was inactive. However, an in vitro bioassay suggested that the ester was inactive and the acid was active. Explain these contradictory results. (6)

4.2 CGP 52411 is a useful inhibitor of a protein kinase enzyme. Studies on structure-activity relationships demonstrate that substituents on the aromatic ring such as chlorine, methyl or hydroxyl group are bad for activity. Drug metabolism studies show that para-hydroxylation occurs to produce inactive metabolites. How would you modify the structure to protect it from metabolism? (4)



CGP52411

QUESTION 5 [10]

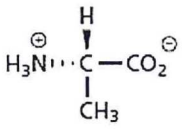
Differentiate between the following terms or approaches encountered in medicinal chemistry:

a. "Me too" drugs and SOSA (2)
b. Prodrug and Transition-state inhibitors (2)
c. Sensitization and Tolerance (2)
d. Phase I metabolism and Phase II metabolism (2)
e. Intrathecal injection and Intraperitoneal injection (2)

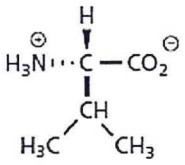
THE END

LIST OF AMINO ACIDS

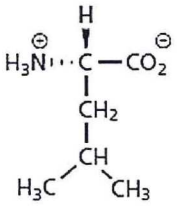
NON POLAR
(hydrophobic)



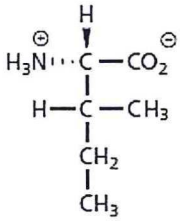
Alanine
(Ala or A)



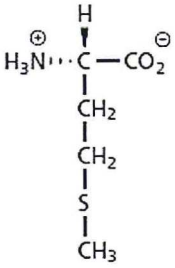
Valine
(Val or V)



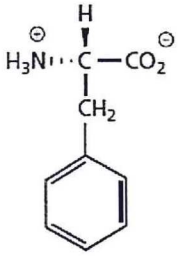
Leucine
(Leu or L)



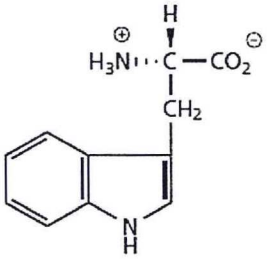
Isoleucine
(Ile or I)



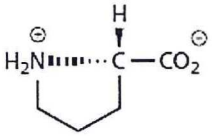
Methionine
(Met or M)



Phenylalanine
(Phe or F)

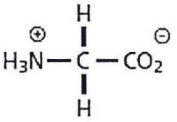


Tryptophan
(Trp or W)

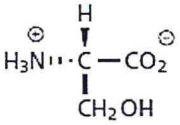


Proline
(Pro or P)

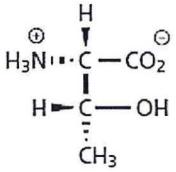
POLAR



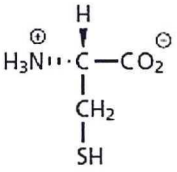
Glycine
(Gly or G)



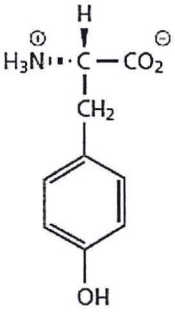
Serine
(Ser or S)



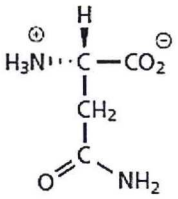
Threonine
(Thr or T)



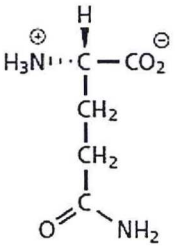
Cysteine
(Cys or C)



Tyrosine
(Tyr or Y)

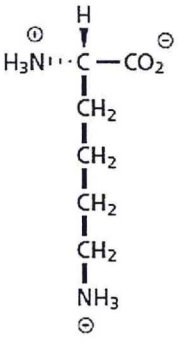


Asparagine
(Asn or N)

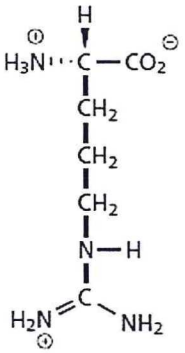


Glutamine
(Gln or Q)

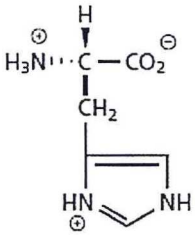
IONIZED



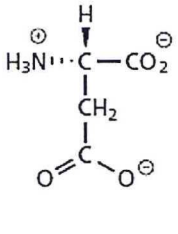
Lysine
(Lys or K)



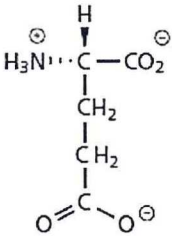
Arginine
(Arg or R)



Histidine
(His or H)



Aspartate
(Asp or D)



Glutamate
(Glu or E)