NAMIBIA UNIVERSITY
OF SCIENCE AND TECHNOLOGY

FACULTY OF HEALTH, NATURAL RESOURCES 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 2022	**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 12 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 descriptions best describes a coenzyme?

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

1.2 What term is used for enzymes such as COX-1 and COX-2 which vary in structure and location but which catalyse the same reaction?

A. Isosteres
B. Isozymes
C. Isotopes
D. Isomers

1.3 Which of the following statements is true with respect to the Michaelis constant?

A. It is equal to the concentration of inhibitor at which the reaction rate is half of its maximum value
B. It is equal to the concentration of substrate at which the reaction rate is at its maximum value
C. It is equal to the concentration of inhibitor at which the reaction rate is zero.
D. It is equal to the concentration of substrate at which the reaction rate is half of its maximum value

1.4 Which of the following is not a neurotransmitter?

A. Glycine.
B. Cyclic GMP
C. g-Aminobutyric acid
D. Serotonin

1.5 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

1.6 Which of the following statements is true regarding intracellular receptors?

A. They consist of three protein subunits
B. They contain a ligand binding site near the *N*-terminal end
C. They contain a binding region for DNA near the middle of the protein
D. They are activated by hydrophobic molecules which are synthesised within the cell

1.7 Which of the following amino acids is phosphorylated by a protein kinase?

A. Cysteine
B. Tyrosine
C. Phenylalanine
D. Lysine

1.8 Which of the following statements is false?

A. Desolvation is an energy expensive process which 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 high entropy
C. Interaction between the 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 increased entropy
D. An increase in entropy results in a greater negative value of DG and a greater chance of binding

1.9 Which statement best describes the relevance of an allosteric binding site to medicinal chemistry?

A. It is more hydrophobic than normal binding sites and accepts hydrophobic drugs in preference to hydrophilic drugs
B. A larger variety of drug structures will bind to the allosteric site than to the active site
C. Drugs can be designed based on the structure of the endogenous chemicals which bind to allosteric sites and control enzyme activity
D. Drugs can be designed based on the transition state of the enzyme-catalysed reaction

1.10 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

1.11 Which of the following statements is true about a G-protein coupled receptor?

A. It contains five transmembrane hydrophobic sections
B. There are more extracellular loops than intracellular loops
C. The binding region for the G-protein involves two extracellular loops
D. The *N*-terminal chain is extracellular and the *C*-terminal chain is intracellular

1.12 The mechanism of gating involves the rotation of five kinked a-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 a-helices
B. It is the a-helix of the second 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 directly to the TM2 section to produce a rapid response

1.13 Which of the following descriptions best fits an inverse 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

1.14 Which of the following statements best describes the potency 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

1.15 What sort of agent binds to a receptor using a different binding site from that used by the endogenous chemical messenger, and distorts the binding site such that the endogenous messenger cannot bind?

A. An agonist
B. An allosteric antagonist
C. An antagonist acting by the 'umbrella' effect
D. An inverse agonist

1.16 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

1.17 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

1.18 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

1.19 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

1.20 Benzene is a suspect carcinogen since it is oxidised by cytochrome P450 enzymes to an electrophilic epoxide. As a result, benzene has been largely replaced by toluene as a solvent. Toluene is also oxidised by cytochrome P450 enzymes but the metabolite is less toxic and rapidly excreted. Suggest what the metabolite might be.

A. Benzoic acid
B. Benzyl alcohol
C. Benzaldehyde
D. *para*-Methylphenol

1.21 Which of the following is a phase II metabolic reaction?

A. Formation of a carboxylic acid from a primary methyl group
B. Formation of a sulfate from an alcohol
C. Formation of a carboxylic acid and alcohol from an ester
D. Formation of a ketone at a benzylic carbon

1.22 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

1.23 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

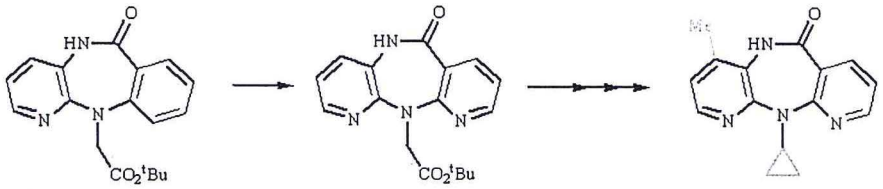
1.24 Natural products are often used as lead compounds in the design and synthesis of novel drugs. Which of the following general characteristics of a natural product is most likely to be a disadvantage?

A. Novelty of structure
B. Its availability
C. Level of activity
D. Side effects

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

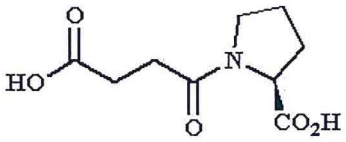
1.26 In the development of the antifungal agent, nevirapine, structure (II) was found to bind more strongly to the target enzyme than the lead compound (I). Which of the following statements is correct?



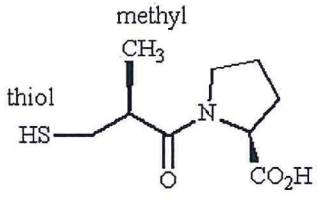
(I) Lead compound (II) Nevirapine

A. The strategy used was one of ring expansion
B. The extra nitrogen allows an extra binding interaction to take place through van der Waals interactions
C. The extra nitrogen in blue can act as a hydrogen bond donor
D. The strategy used could be described as extension since a further binding interaction has occurred

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

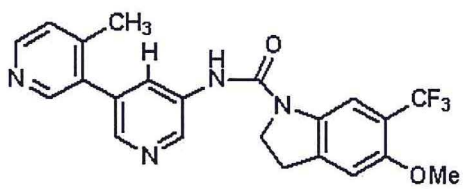


Captopril

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

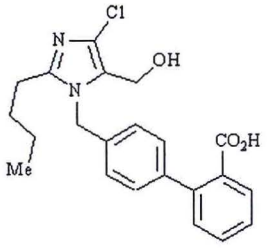


IV

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 Losartin was developed from structure (I) as an antihypertensive agent by replacing a carboxylic acid group with a tetrazole ring. Which of the following statements is incorrect?

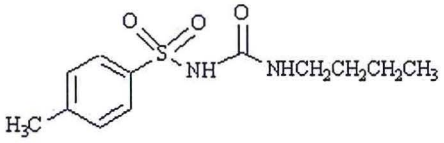


(I)

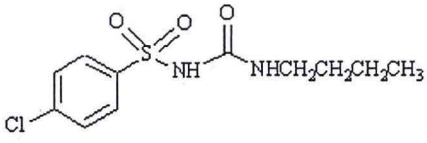
Losartan

A. The tetrazole ring represents a bio-isostere
B. The tetrazole ring mimics a carboxylic acid in being planar
C. The tetrazole ring is basic rather than acidic and so cannot mimic the acidic nature of a carboxylic acid
D. The tetrazole ring is less polar than a carboxylic acid

1.30 Chlorpropamide has a longer antibiotic activity than tolbutamide.

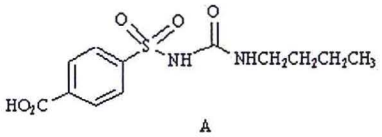


Tolbutamide

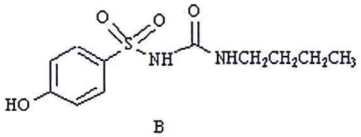


Chlorpropamide

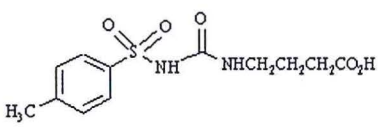
Which of the following structures is the most likely metabolite of tolbutamide?



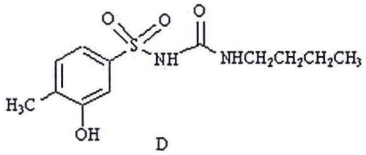
A



B



C



D

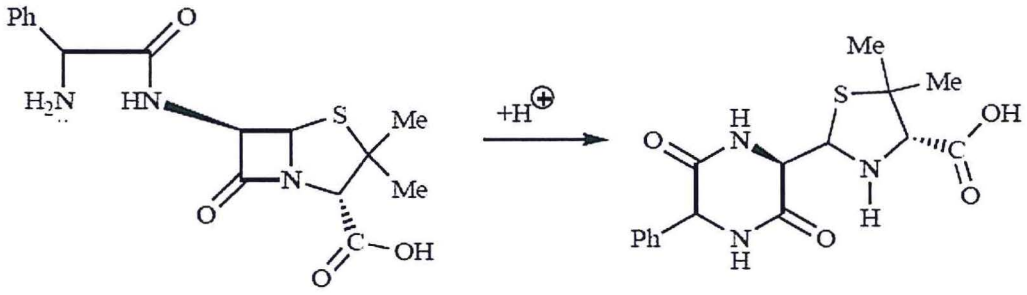
A. Structure A
B. Structure B
C. Structure C
D. Structure D

END OF SECTION A

SECTION B: [40]

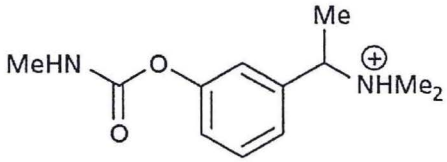
QUESTION 2 [13]

Draw a full detailed mechanism for the metabolic decomposition of ampicillin under acidic conditions, as depicted in the reaction scheme below. In order to receive full marks, show all the intermediates and the flow of electrons using the appropriate arrows.



QUESTION 3 [8]

3.1 Miotine has been used in the treatment of a wasting disease, but there are side effects because a certain amount of the drug enters the brain.

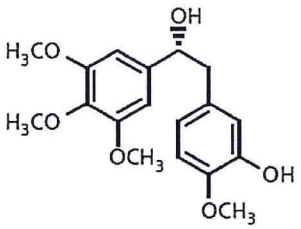


Miotine

a. Suggest possible reasons why miotine is able enter the brain and cause the observed side effects. (2)

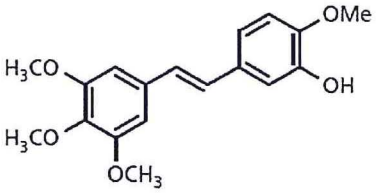
b. Briefly describe how you might modify the structure of miotine to eliminate the side effect observed. Draw the modified structure you suggested. (2)

3.2 Combretastatin is an anticancer agent discovered from an African plant. Analogue V is more active than combretastatin, whereas analogue VI is less active.



Combretastatin

V



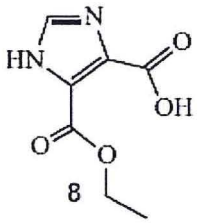
VI

a. What lead optimization strategy was used in designing analogues V and VI? (1)

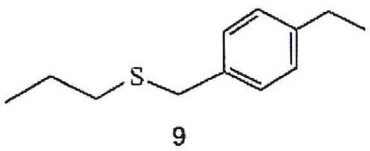
b. Why is analogue V more active and analogue VI less active than combretastatin? (3)

QUESTION 4 **[9]**

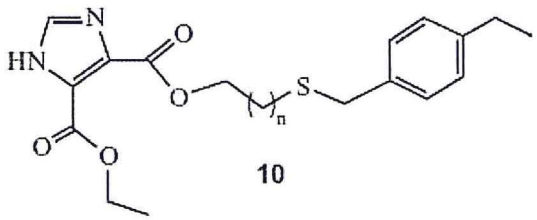
4.1 Compounds **8** and **9** below were leads determined from a Structure & Activity Relationship study conducted by NMR spectroscopy targeting a new receptor. Based on this analysis, compound **10** was synthesised and the number of methylene groups (n) was varied. However, all of the compounds synthesised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



8



9

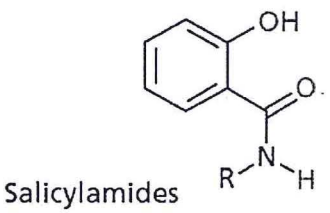


10

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 Salicylamides are inhibitors for an enzyme called scytalone dehydratose. SAR shows that there are three important hydrogen bonding interactions. Explain whether you think quinazolines could act as a bioisostere for salicylamides. (4)



Salicylamides

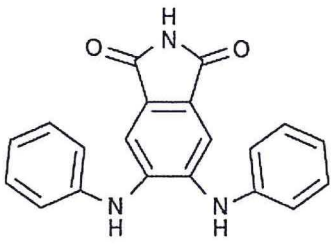
Quinazolines

QUESTION 5 **[10]**

5.1 methylphenidate is used in the treatment of attention deficit hyperactivity disorder. Suggest possible metabolites for this drug. (5)

Methylphenidate

5.2 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? (5)

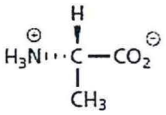


CGP52411

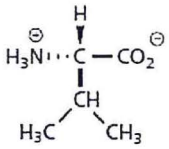
THE END

LIST OF AMINO ACIDS

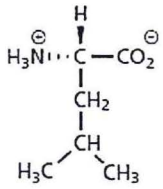
NON POLAR
(hydrophobic)



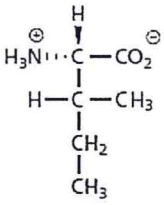
Alanine
(Ala or A)



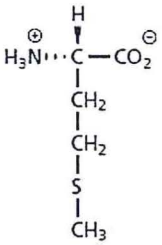
Valine
(Val or V)



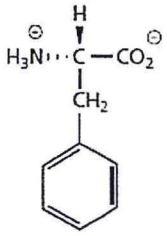
Leucine
(Leu or L)



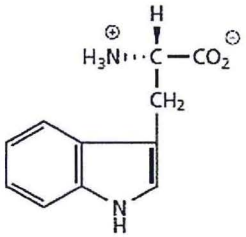
Isoleucine
(Ile or I)



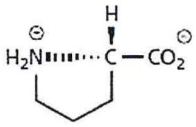
Methionine
(Met or M)



Phenylalanine
(Phe or F)

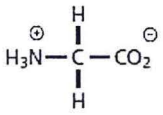


Tryptophan
(Trp or W)

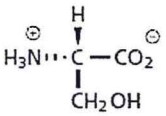


Proline
(Pro or P)

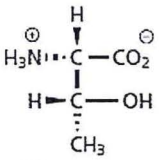
POLAR



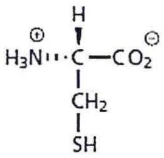
Glycine
(Gly or G)



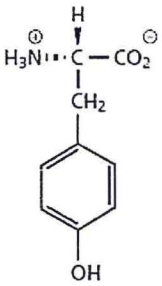
Serine
(Ser or S)



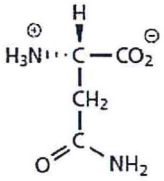
Threonine
(Thr or T)



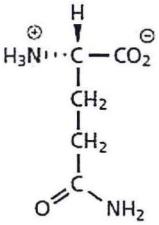
Cysteine
(Cys or C)



Tyrosine
(Tyr or Y)

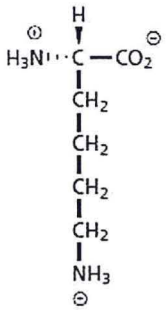


Asparagine
(Asn or N)

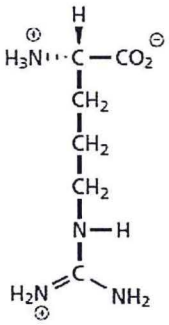


Glutamine
(Gln or Q)

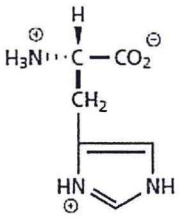
IONIZED



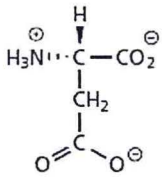
Lysine
(Lys or K)



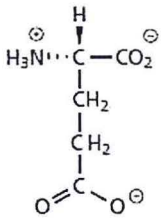
Arginine
(Arg or R)



Histidine
(His or H)



Aspartate
(Asp or D)



Glutamate
(Glu or E)