NAMIBIA UNIVERSITY
OF SCIENCE AND TECHNOLOGY

Faculty of Health, Natural Resources and Applied Sciences

School of Natural and Applied Sciences

Department of Biology, Chemistry and Physics

13 Jackson Kaujeua Street
Private Bag 13388
Windhoek
NAMIBIA

T: +264 61 207 2012
F: +264 61 207 9012
E: dbcp@nust.na
W: www.nust.na

QUALIFICATION: **BACHELOR OF SCIENCE HONOURS**	
QUALIFICATION CODE: **08BOSCH**	LEVEL: **8**
COURSE: **SYNTHETIC ASPECTS OF MEDICINAL CHEMISTRY**	COURSE CODE: **SAM821S**
DATE: **JANUARY 2025**	SESSION: **1**
DURATION: **3 HOURS**	MARKS: **100**

SECOND OPPORTUNITY / SUPPLEMENTARY: QUESTION PAPER

EXAMINER: **DR MARIUS MUTORWA**

MODERATOR: **DR RENATE HANS**

INSTRUCTIONS:

1. Answer ALL the 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.

PERMISSIBLE MATERIALS

Non-programmable calculators

ATTACHMENTS

1. List of Amino Acids

This paper consists of thirteen (13) pages including this front page.

SECTION A: **[50 MARKS]**

QUESTION 1: MULTIPLE CHOICE QUESTIONS

Evaluate the statements in each numbered section and select the most appropriate answer or phrase from the given possibilities. Fill in the appropriate letter next to the number of the correct statement/phrase on your ANSWER SHEET.

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 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

1.5 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

1.6 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

1.7 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

1.8 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

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

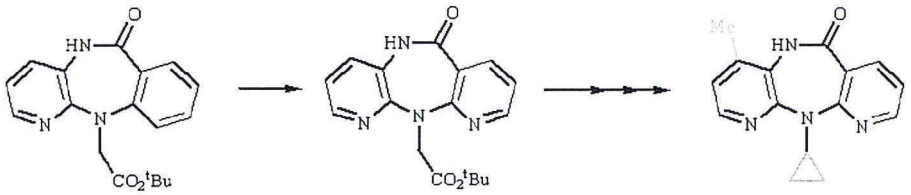
A. Determining a target, establishing a bioassay, finding a lead compound, structure activity relationships

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

D. Determining a target, finding a lead compound, structure activity relationships, establishing a bioassay

1.10 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

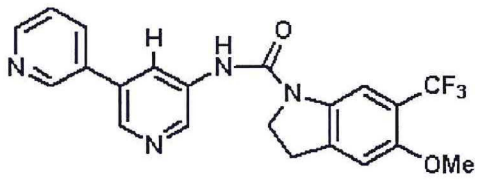
A. The strategy used was one of ring expansion

B. The extra nitrogen allows an extra binding interaction to take place through van der Waals interactions

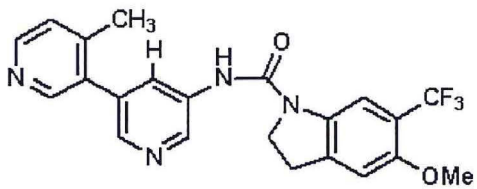
C. The extra nitrogen in blue can act as a hydrogen bond donor

D. The strategy used could be described as extension since a further binding interaction has occurred

1.11 Structure (III) is a serotonin antagonist. A methyl group has been introduced into analogue (IV) resulting in increased activity. What could be the reason for the observed increase in activity?



III



IV

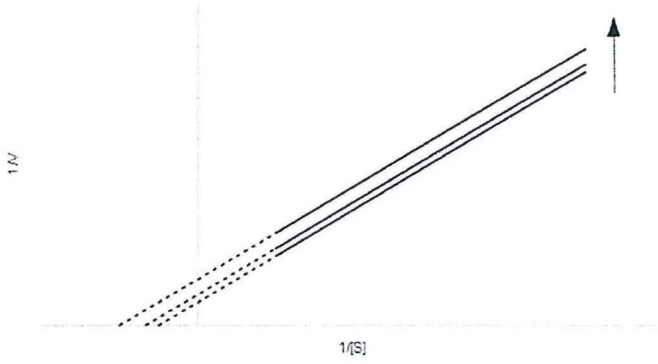
A. The methyl group interacts with an extra hydrophilic binding region through van der Waals interactions

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

1.12 Examine the Lineweaver-Burk Plot below, whereby the arrow indicates the trend of increasing inhibitor concentration. What type of inhibitor is being used in this series of plots?



A. Reversible competitive

B. Reversible uncompetitive

C. Reversible non-competitive

D. Irreversible

1.13 An enzyme has a K_m value of 750nM for its natural substrate. Three research groups investigate potential inhibitors for the same enzyme. The three groups report their data of the best inhibitor as IC_{50} values as shown in the table below. Based on the equation and values reported, which lab group developed the most potent inhibitor?

$$K_i = \frac{IC_{50}}{\left(1 + \frac{[S]}{K_m}\right)}$$

lab number	IC_{50} (nM)	tested [S] (nM)
1	40	3,000
2	25	2,000
3	10	200

A. Lab 1
B. Lab 2
C. Lab 3
D. Cannot be determined from the results provided

1.14 Which of the following agents act as irreversible inhibitors?

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

1.15 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.

1.16 An agonist contains an alcohol, amine and aromatic ring, all of which act as binding groups. Which of the following modifications is most likely to result in an antagonist?

A. Converting the alcohol to a methyl ether
B. Adding an extra aromatic ring to the structure
C. Synthesizing an analogue which lacks the aromatic ring
D. Converting the amine to an amide

1.17 It is common practice to vary the length and size of alkyl groups when making analogues of a lead compound. Which of the following statements is not true?

A. Replacing a straight chain alkyl group with a branched alkyl group may increase activity by filling up a hydrophobic pocket and increasing van der Waals interactions.

B. Increasing the chain length or size of an alkyl group may increase target selectivity if one target binding site is more spacious than another.

C. Increasing the chain length or size of an alkyl group increases activity and selectivity by stabilising the analogue.

D. Increasing the chain length of an alkyl group may increase activity by leading to better van der Waals interactions with a hydrophobic region of the binding site.

1.18 Which of the following is not an enzyme involved in catalysing Phase II metabolic reactions?

A. Adenosyl methionine.

B. Peptidase.

C. Glutathione transferase.

D. Sulfotransferase.

1.19 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.

1.20 Which of the following statements best describes a bio-isostere?

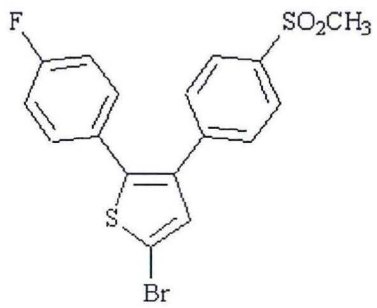
A. A group having the same valency as another group.

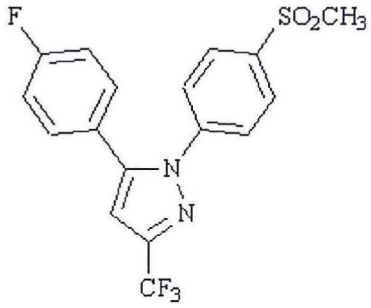
B. A group that is the same as a non-classical isostere.

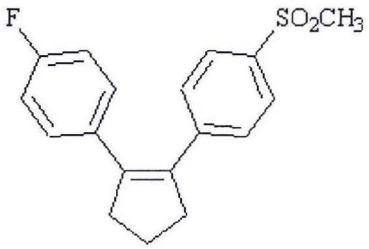
C. A group that can be used in place of another group whilst retaining the important biological activity of the drug.

D. A group having the same size as another group.

1.21 The following structures are various non-steroidal anti-inflammatory agents developed by a ring variation strategy. Which of the following terms has been used for drugs of this sort?







A. Family drugs.

B. Analogue drugs.

C. Me-too drugs.

D. Isosteric drugs.

1.22 Which of the following descriptions refers to the absorption process known as pinocytosis?

A. The process by which a drug is 'wrapped up' by a protein in the cell membrane such that it can be carried across the cell membrane.

B. The process by which small molecules can squeeze through the small pores that exist between different cells in the gut wall.

C. The process by which drugs of large molecular weight are enveloped by the cell membrane of a cell lining the gut wall, leading to the pinching off of a membane bound vesicle which carries the drug into the cell.

D. The process by which ion channels open to allow the crossing of ions across the cell membrane.

1.23 There are several sources and methods of discovering new compounds. Which of the following is an *in silico* method?

A. Combinatorial chemistry.

B. Database mining.

C. Screening plant extracts.

D. Me too drugs.

1.24 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.

1.25 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

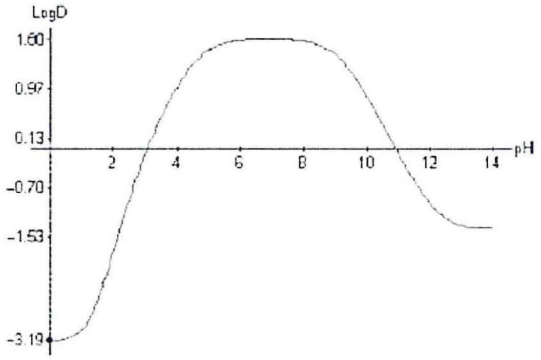
SECTION B: [50 MARKS]

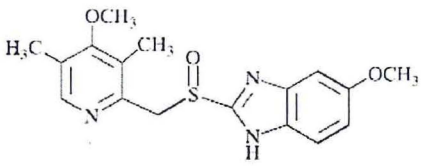
QUESTION 2 [10]

2.1 Candesartan cilexetil is an anti-hypersensitive prodrug that antagonizes the AT1 angiotensin receptor. Within the structure are four lead modification approaches with which you should be familiar. Working backwards, draw a lead molecule from which this drug may have been derived and point out where and which lead modifications occurred. (5)

Candesartan cilexetil

2.2 Explain the change in log D vs pH for omeprazole shown below. Refer to the structure when discussing the logD changes to pH. (5)



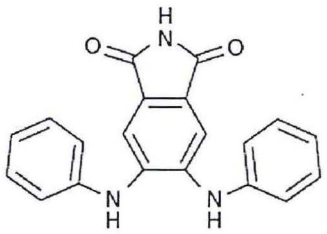


Omeprazole

QUESTION 3 [10]

3.1 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)

3.2 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)



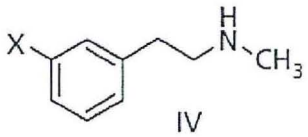
CGP52411

QUESTION 4: **[10]**

4.1 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)

4.2

a. Explain the principles of rigidification and show how you would apply it to structure IV below in order to improve its pharmacological properties. (3)

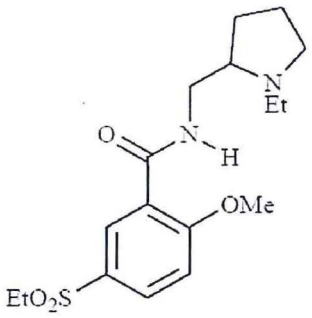


IV

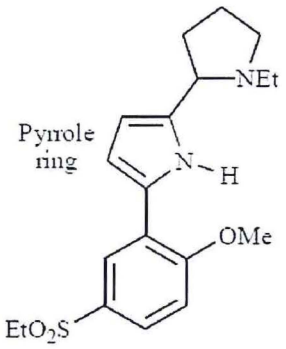
b. Give two specific examples of rigidified structures with respect to structure IV. (2)

QUESTION 5: **[10]**

5.1 Compound **DU 122290** was developed from **sultopride** (a dopamine antagonist). **DU 122290** shows increased activity towards the dopamine **receptor class D3-receptor**, rather than the dopamine **receptor class D2-receptor**. Additionally, **DU 122290** shows improved selectivity towards the D3-receptor over the D2-receptor. Suggest possible reasons for these observations. (5)

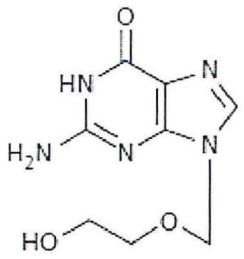


Sultopride



DU 122290

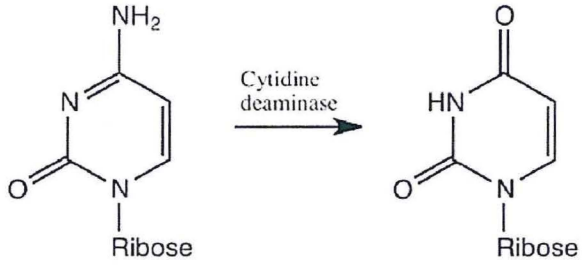
5.2 The oral bioavailability of the antiviral drug aciclovir is only 15–30%. Suggest why this may be the case and suggest two possible methods how one might increase the bioavailability of this drug. Explain which of the two methods you suggested is more plausible or preferred. (5)



Aciclovir

QUESTION 6: **[10]**

Cytidine deaminase is an enzyme that converts cytidine to uridine, as shown below.



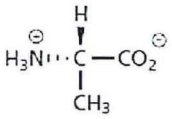
Cytidine **Uridine**

Draw a mechanism by which this reaction occurs, involving a highly conserved water molecule and a nucleophilic amino acid residue which are present in the active site. Hint: a histidine amino acid residue provides the proton (H^+) required in the mechanism. (10)

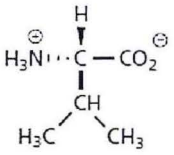
END OF QUESTION PAPER

LIST OF AMINO ACIDS

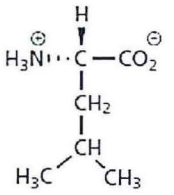
NON POLAR
(hydrophobic)



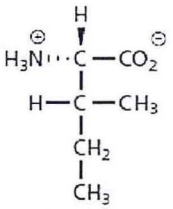
Alanine
(Ala or A)



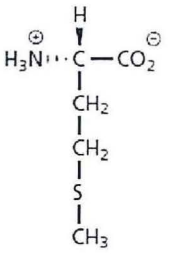
Valine
(Val or V)



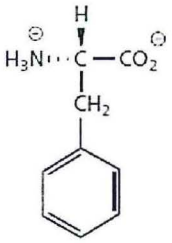
Leucine
(Leu or L)



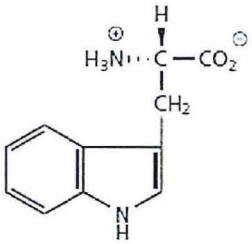
Isoleucine
(Ile or I)



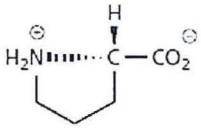
Methionine
(Met or M)



Phenylalanine
(Phe or F)

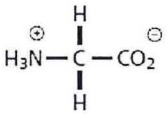


Tryptophan
(Trp or W)

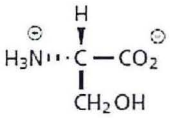


Proline
(Pro or P)

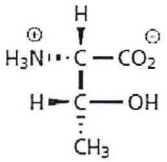
POLAR



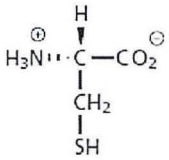
Glycine
(Gly or G)



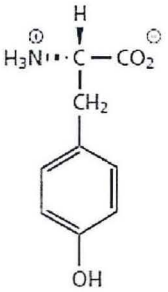
Serine
(Ser or S)



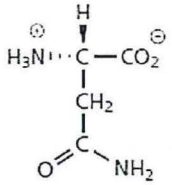
Threonine
(Thr or T)



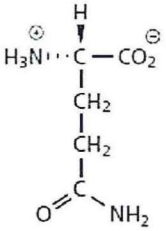
Cysteine
(Cys or C)



Tyrosine
(Tyr or Y)

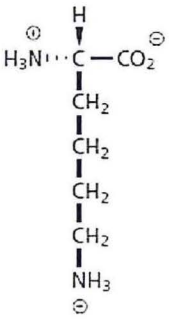


Asparagine
(Asn or N)

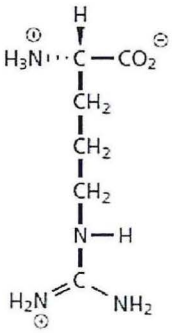


Glutamine
(Gln or Q)

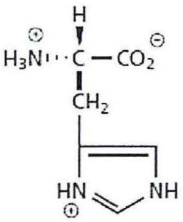
IONIZED



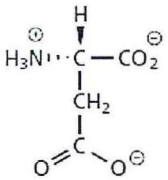
Lysine
(Lys or K)



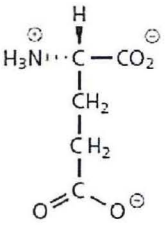
Arginine
(Arg or R)



Histidine
(His or H)



Aspartate
(Asp or D)



Glutamate
(Glu or E)