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: JANUARY 2023	**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 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 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

1.2 Which of the following descriptions best describes a cofactor?

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. 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

1.3 Which of the following amino acids commonly acts as a nucleophilic group in enzyme-catalysed reaction mechanisms?

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

1.4 When a membrane-bound receptor binds its chemical messenger, an induced fit takes place which leads to secondary effects, allowing a chemical message to be received within the cell. Which of the following mechanisms is not involved in this process?

A. The transport of the chemical messenger into the cell
B. The opening or closing of an ion channel
C. The activation of a signal protein
D. The activation of a membrane-bound enzyme

1.5 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

1.6 Which of the following reactions is catalysed by a tyrosine kinase?

A. The phosphorylation of an alcohol functional group
B. The esterification of an alcohol functional group
C. The phosphorylation of a phenol functional group
D. The esterification of a phenol functional group

1.7 Which of the following is inactive when glycogen is broken down in a liver cell?

A. Phosphorylase kinase
B. Glycogen synthase
C. The α-adrenoceptor
D. Phosphorylase *a*

1.8 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

1.9 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

1.10 Which of the following descriptions is most accurate regarding binding sites and binding regions?

A. A binding site is part of a binding region
B. A binding region is part of a binding site
C. A binding region is the same as a binding site
D. A binding region is part of a drug whereas a binding site is part of a macromolecular target

1.11 Which of the following statements is not true about G-protein coupled receptors?

A. They generally mediate the action of fast acting neurotransmitters
B. They mediate the action of some hormones
C. They activate signal proteins called G-proteins
D. Calcium ions can act as a ligand for some G-protein coupled receptors

1.12 Which of the following statements is true regarding the DNA binding region of intracellular receptors?

A. It contains nine cysteine residues
B. Four cysteine residues are involved in binding two zinc ions
C. It contains particular nucleotide sequences that can base pair to DNA
D. The DNA binding region is known as having 'thiol fingers'

1.13 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

1.14 Which of the following statements best describes the efficacy 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 binding site that is next to the binding site for an endogenous chemical messenger, and sterically blocks the messenger from binding?

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 is not a necessary requirement when designing an agonist?

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

1.17 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

1.18 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

1.19 Which of the following statements is the closest description of Phase I metabolism?

A. Reactions which add a polar molecule to a functional group that is already present on a drug or one of its metabolites
B. Reactions which occur in the blood supply
C. Reactions which add a polar functional group to a drug
D. Reactions which occur in the gut wall

1.20 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

1.21 Which of the following functional groups can be metabolised by cytochrome P450 enzymes?

A. Aromatic ring
B. Epoxide
C. Carboxylic acid
D. Ester

1.22 Which of the following properties of a drug is most likely to result in a minimum of side effects?

A. Good oral absorption
B. Fast metabolism
C. Target selectivity
D. Target affinity

1.23 Which of the following analytical techniques provides the greatest structural information on a lead compound?

A. Nuclear magnetic resonance spectroscopy
B. Ultra-violet spectroscopy
C. Infra-red spectroscopy
D. Elemental analysis

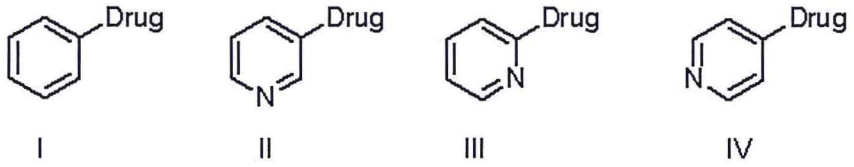
1.24 There are several sources and methods of discovering new compounds. Which of the following is an *in silico* method?

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

1.25 A lead compound contains a carboxylic acid functional group. This was esterified to give an analogue with an ester group. *In vitro* tests showed that the carboxylic acid was active whereas the ester was inactive. On the other hand, *in vivo* tests, where the test compounds were administered orally, showed that the ester was active, and the carboxylic acid was inactive. Which of the following explanations is not plausible?

A. The carboxylic acid is not absorbed in the *in vivo* studies
B. The ester is an important binding group but the carboxylic acid group is not
C. The ester is absorbed in the *in vivo* studies
D. The ester is metabolised to the carboxylic acid in the *in vivo* studies

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?



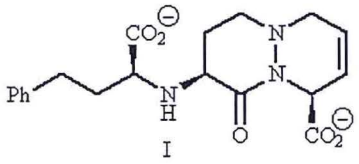
I II III IV

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

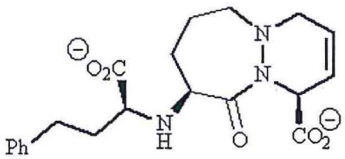
1.27 There are three general methods by which molecules can be simplified. Which of the following is not one of these methods?

A. Removal of excess rings
B. Removal of excess flexibility
C. Removal of excess functional groups
D. Removal of excess asymmetric centres

1.28 Cilazaprilat is an antihypertensive agent derived from the lead compound (I) by a ring expansion strategy. Why was this strategy successful in this situation?



I



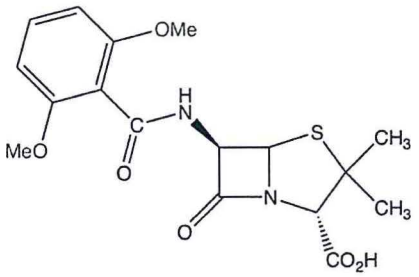
Cilazaprilat

A. It increased the hydrophobicity of the molecule
B. It locked the molecule into the active conformation
C. It increased the flexibility of the molecule
D. It placed important binding groups in the optimum position for binding to their respective binding regions

1.29 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, thus products are excreted quicker
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

1.30 Methicillin was an important penicillin which was effective against penicillin G resistant strains of *Staphylococcus aureus*. Although the drug is more effective than penicillin G against resistant strains, it is not as active against strains which are susceptible to penicillin G. The methoxy substituents of the aromatic ring play an important role in the drug's effectiveness against penicillin G resistant strains. Which of the following statements is the most likely explanation?



Methicillin

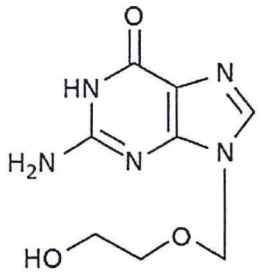
A. The methoxy groups act as steric shields to protect the aromatic ring from oxidation by metabolic enzymes in the body
B. The methoxy groups act as steric shields to protect the β-lactam ring from hydrolysis by enzymes produced by resistant bacteria
C. The methoxy groups act as conformational blockers to orientate the aromatic ring out of the plane of the side chain amide group, allowing better binding interactions with the target enzyme
D. The methoxy groups increase the electron density of the aromatic ring allowing better binding interactions with the target enzyme

END OF SECTION A

SECTION B: [40]

QUESTION 2 [10]

2.1 The oral bioavailability of the antiretroviral drug acyclovir is only 15 – 30%.



Aciclovir

a. Suggest possible reasons, including an annotated structure, why such a low oral bioavailability of acyclovir is observed. (2)

b. Briefly describe how you might modify the structure so as to increase the bioavailability of the drug and limit possible side effects. (6)

c. Differentiate between a rigidification strategy and an extension strategy which are used during optimizing drug-target interactions. (2)

QUESTION 3 [15]

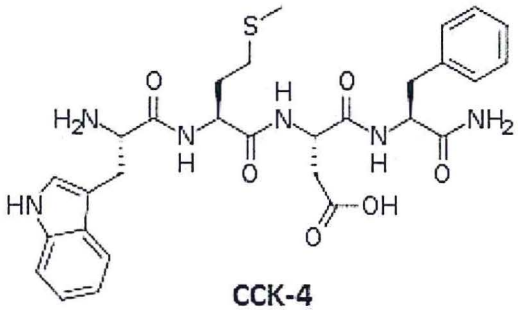
3.1 Candesartan cilexetil is an anti-hypersensitive prodrug that antagonizes the AT1 angiotensin receptor.

Candesartan cilexetil

a. Within the structure above are four lead modification approaches with which you should be familiar. Redraw the structure and point out where and which lead modifications were made. (4)

b. Working backward, draw a lead molecule from which the drug may have been derived. (3)

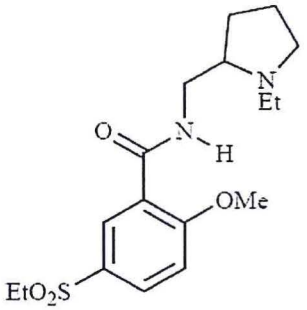
c. Cholecystokinin (CCK) is a peptide hormone of the gastrointestinal system responsible for stimulating the digestion of fat and protein. The presence of CCK causes the release of digestive enzymes and bile from the pancreas and gallbladder, respectively, and thus CCK functions in a number of processes 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. Discuss four possible concerns you might have with using CCK-4 as a lead compound for an orally administered, active anti-anxiety drug? (8)



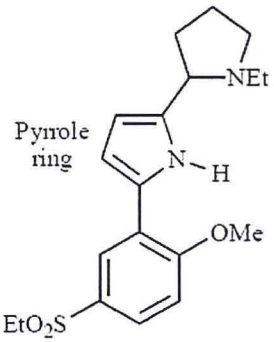
CCK-4

QUESTION 4 **[5]**

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)



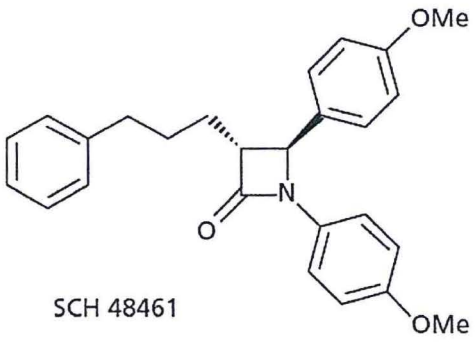
Sultopride



DU 122290

QUESTION 5 **[10]**

SCH 48461 has been found to lower cholesterol levels by inhibiting cholesterol absorption. Unfortunately, it is susceptible to metabolism. Identify the likely metabolic reactions which this molecule might undergo and what modifications could be made to reduce metabolic susceptibility.



SCH 48461

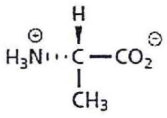
a. Identify the likely metabolic reactions which this molecule might undergo. (5)

b. Based on your answer in (a), what modifications could be made to reduce metabolic susceptibility? (5)

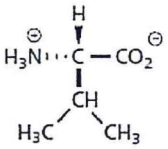
THE END

LIST OF AMINO ACIDS

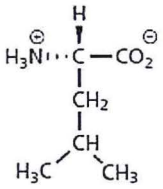
NON POLAR
(hydrophobic)



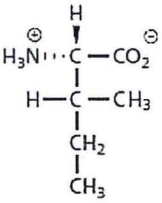
Alanine
(Ala or A)



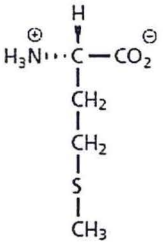
Valine
(Val or V)



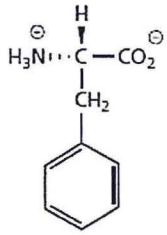
Leucine
(Leu or L)



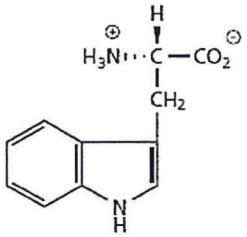
Isoleucine
(Ile or I)



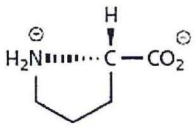
Methionine
(Met or M)



Phenylalanine
(Phe or F)

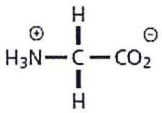


Tryptophan
(Trp or W)

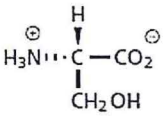


Proline
(Pro or P)

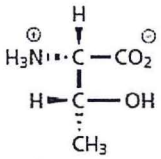
POLAR



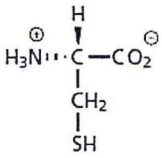
Glycine
(Gly or G)



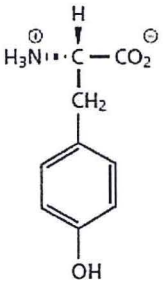
Serine
(Ser or S)



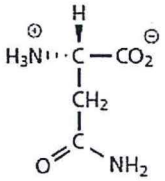
Threonine
(Thr or T)



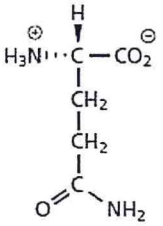
Cysteine
(Cys or C)



Tyrosine
(Tyr or Y)



Asparagine
(Asn or N)



Glutamine
(Gln or Q)

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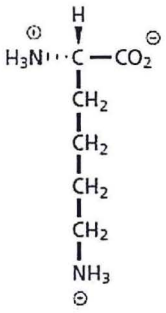
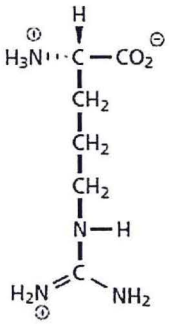
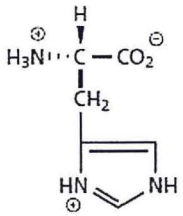


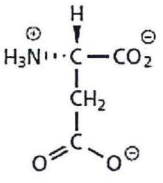
Lysine
(Lys or K)



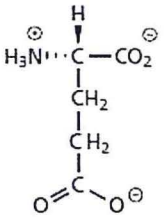
Arginine
(Arg or R)



Histidine
(His or H)



Aspartate
(Asp or D)



Glutamate
(Glu or E)