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QUALIFICATION: **BACHELOR OF SCIENCE HONOURS**	
QUALIFICATION CODE: **08BOSCH**	LEVEL: **8**
COURSE: **SYNTHETIC ASPECTS OF MEDICINAL CHEMISTRY**	COURSE CODE: **SAM821S**
DATE: **NOVEMBER 2024**	SESSION: **1**
DURATION: **3 HOURS**	MARKS: **100**

FIRST OPPORTUNITY: QUESTION PAPER

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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 underlined atoms is likely to be the strongest hydrogen bond acceptor?

A. Amide nitrogen (R<u>N</u>HCOR')

B. Aniline nitrogen (Ar<u>N</u>H_2)

C. Amine nitrogen (R<u>N</u>H_2)

D. Carboxylate oxygen (RC<u>O_2</u>$^-$)

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 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.

1.5 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

1.6 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

1.7 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.

1.8 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.

1.9 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.

1.10 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.

1.11 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.

1.12 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.

1.13 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.

1.14 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

1.15 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

1.16 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.

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

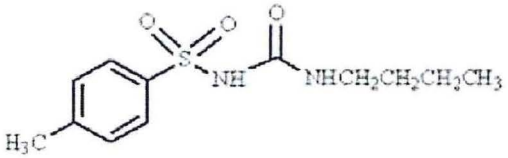
A. Removing polar functional groups

B. Adding extra alkyl groups

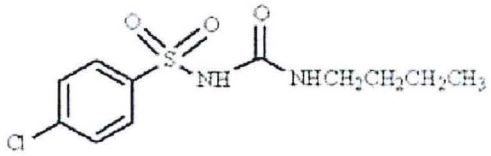
C. Replacing an aromatic ring with a nitrogen containing heterocyclic ring

D. Replacing an alkyl group with a larger alkyl group

1.18 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.

1.19 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

1.20 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

1.21 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

1.22 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

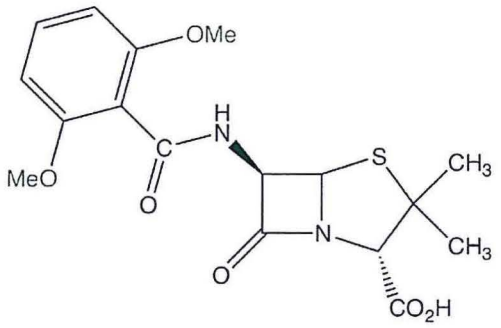
1.23 It is common practice to vary the length and size of alkyl groups when making analogues of a lead compound. Which of the following statements is true?

A. Replacing a straight chain alkyl group with a branched alkyl group may increase activity by filling up a hydrophobic pocket and increasing hydrogen bonding interactions
B. Increasing the chain length or size of an alkyl group may increase target selectivity if a hydrophobic binding region is more spacious in one binding site 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 hydrophilic region of the binding site

1.24 What strategy of drug design is frequently used on complex lead compounds derived from natural products?

A. Extension
B. Simplification
C. Rigidification
D. Conformational blocking

1.25 Methicillin was an important penicillin which was effective in the 1960's 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

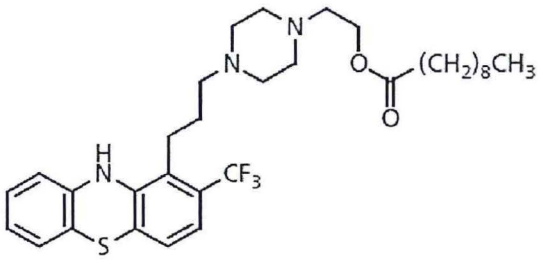
A. The methoxy groups act as steric shields to protect the aromatic ring from oxidation by metabolic enzymes in the body
B. The methoxy groups act as steric shields to protect the β-lactam ring from hydrolysis by enzymes produced by resistant bacteria
C. The methoxy groups act as conformational blockers 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: **[50 MARKS]**

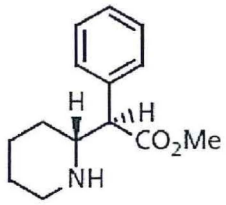
QUESTION 2 **[10]**

2.1 The prodrug of the antipsychotic drug fluphenazine shown below has a prolonged period of action when it is given by intramuscular injection, but not when it is given by intravenous injection. Suggest possible reasons for this observation, including drawing structures. (5)



Fluphenazine prodrug

2.2 Methylphenidate is used in the treatment of attention deficit hyperactivity disorder. Suggest 5 possible metabolites for these drug. (5)



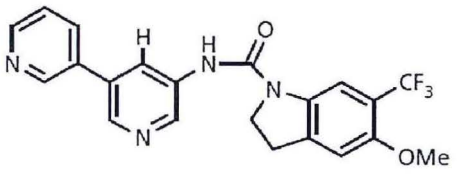
Methylphenidate

QUESTION 3 **[10]**

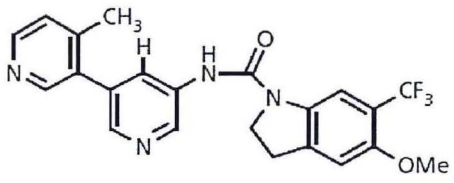
3.1 Structure VII is a serotonin antagonist. A methyl group has been introduced into analogue VIII, resulting in increased activity.

a. What role does the methyl group play and what is the term used for such a group? (2)

b. Explain why increased activity arises. (3)

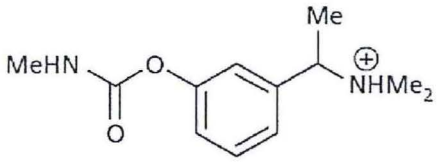


VII



VIII

3.2 Miotine has been used in the treatment of a muscle-wasting disease, but there are side effects because a certain amount of the drug enters the brain. Suggest how one might modify the structure of miotine to eliminate this side effect. (5)



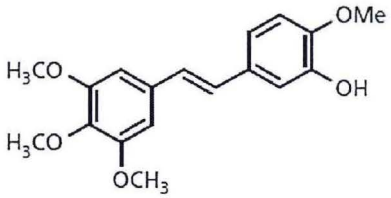
Miotine

QUESTION 4: **[10]**

4.1 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



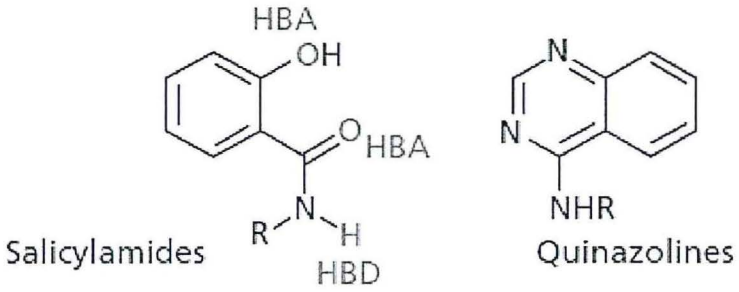
VI

a. What lead optimization strategy was used in designing analogues V and VI? (2)
b. Why is analogue V more active and analogue VI less active than combretastatin? (3)

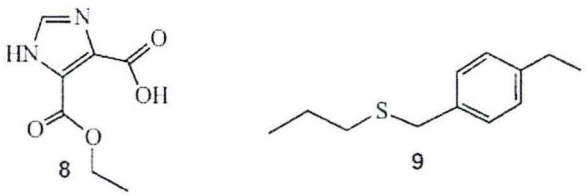
4.2 Steric, electronic, lipophilic and H-bonding effects are important parameters of molecules employed in computer-aided drug design. Why are each of these effects important in drug design? (5)

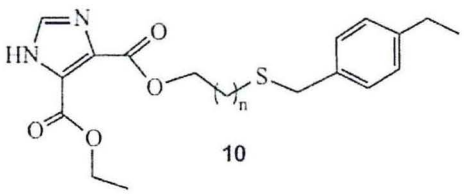
QUESTION 5: **[10]**

5.1 Salicylamides are inhibitors for an enzyme called scytalone dehydratase. SAR shows that there are three important hydrogen bonding interactions. Explain whether you think quinazolines could act as a bioisostere for salicylamides. (5)



5.2 Compounds **8** and **9** below were leads determined from an SAR by NMR study of a new receptor. Based on this analysis, **10** was synthesized, and *n* was varied, but all the compounds made had much lower potency than either **8** or **9.**



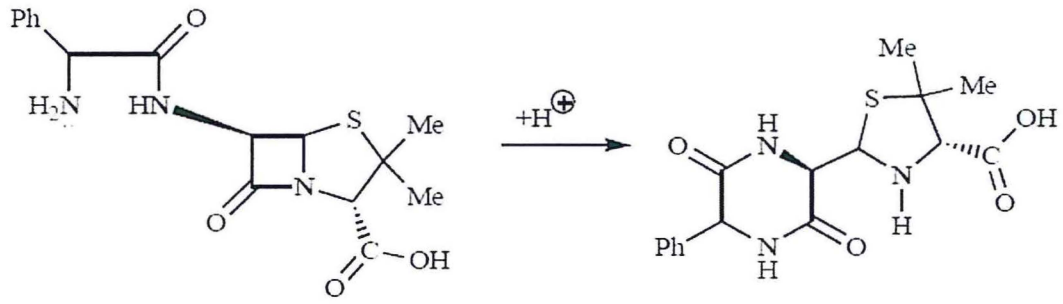


a. What conclusions can you draw from this result? (3)

b. Based on your answer in (a), draw a potential analogue of compound **10** which could potentially have a similar or higher potency as compound **8** or **9**. (2)

QUESTION 6: **[10]**

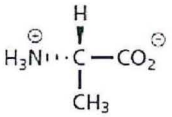
Draw a full detailed mechanism for the metabolic decomposition of ampicillin under acidic conditions, as depicted in the reaction scheme below. In order to receive full marks, show all the intermediates and the flow of electrons using the appropriate arrows.



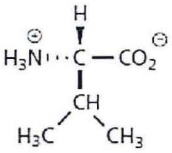
END OF QUESTION PAPER

LIST OF AMINO ACIDS

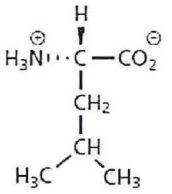
NON POLAR
(hydrophobic)



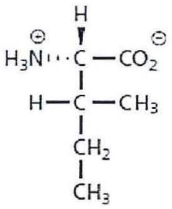
Alanine
(Ala or A)



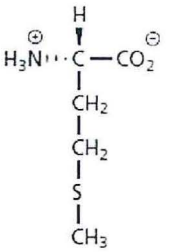
Valine
(Val or V)



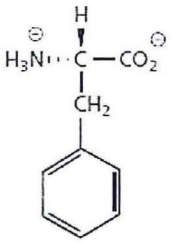
Leucine
(Leu or L)



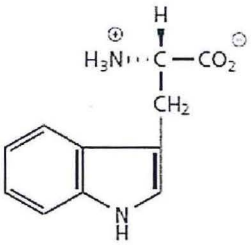
Isoleucine
(Ile or I)



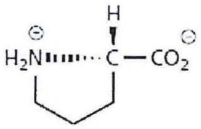
Methionine
(Met or M)



Phenylalanine
(Phe or F)

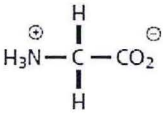


Tryptophan
(Trp or W)

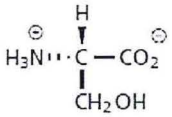


Proline
(Pro or P)

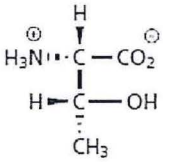
POLAR



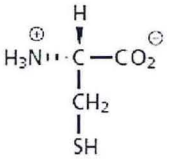
Glycine
(Gly or G)



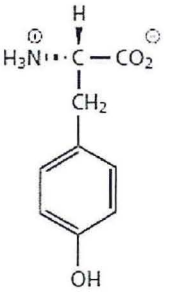
Serine
(Ser or S)



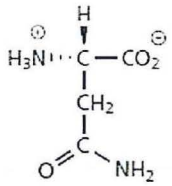
Threonine
(Thr or T)



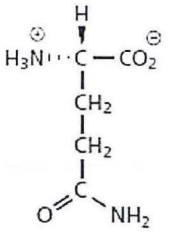
Cysteine
(Cys or C)



Tyrosine
(Tyr or Y)

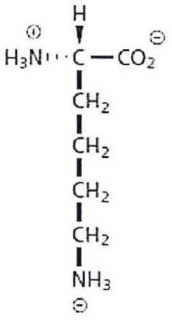


Asparagine
(Asn or N)

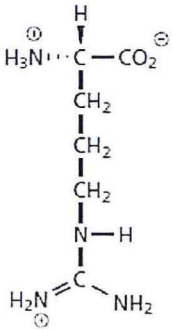


Glutamine
(Gln or Q)

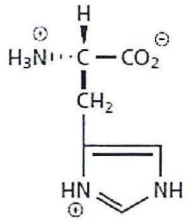
IONIZED



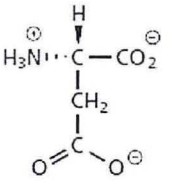
Lysine
(Lys or K)



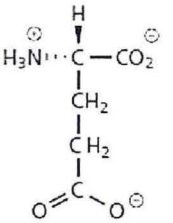
Arginine
(Arg or R)



Histidine
(His or H)



Aspartate
(Asp or D)



Glutamate
(Glu or E)