NATIONAL UNIVERSITY OF LESOTHO

FACULTY OF HEALTH SCIENCES

DEPARTMENT OF PHARMACY

BACHELOR OF PHARMACY (HONOURS)

PHA 4301 – MEDICINAL CHEMISTRY

SUPPLEMENTARY EXAMINATION

AUGUST 2023 TIME: 3 HOURS TOTAL: 100 MARKS

INSTRUCTIONS:

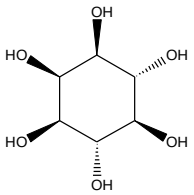
- **THIS PAPER CONSISTS OF 4 QUESTIONS**
- **ANSWER ALL QUESTIONS**
- **START EACH QUESTION ON A NEW PAGE**
- **MARKS ARE SHOWN IN PARENTHESIS AT THE END OF EACH QUESTION**

Question 1 **[25 marks]**

a. Define enantiomer [1]

b. *Myo*-Inositol, one of the isomers of 1,2,3,4,5,6-hexahydroxycyclohexane, acts as a growth factor in both animals and microorganisms.

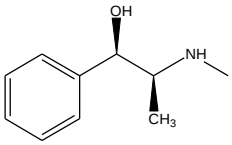
i. Draw the chair conformation of *myo*-inositol and its ring flipped alternative. [3]



myo-Inositol

ii. When all –OH groups in 1,2,3,4,5,6-hexahydroxycyclohexane have a *trans* relationship, the isomer is most stable. Draw the chair conformation of the most stable isomer of *myo*-inositol and its ring flipped alternative conformation. [3]

c. Ephedrine is an alpha and beta-adrenergic agonist which acts as both a direct and indirect sympathomimetic. However, it also causes the indirect release of norepinephrine from sympathetic neurons, inhibiting norepinephrine reuptake and displacing more norepinephrine from storage vesicles. Ephedrine is used for its vasoconstrictive, positive chronotropic, and positive inotropic effects. Below is the structure of ephedrine.



Ephedrine

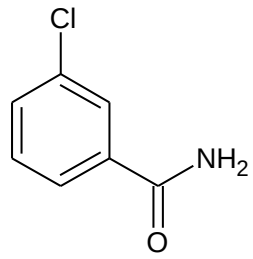
i. Draw all possible stereoisomers of ephedrine and indicate the configuration of their chiral carbons. [12]

ii. Show the relationship between all these stereoisomers [6]

Atomic number ranking: Br> Cl> S> P> O> N> C> ^{2}H> ^{1}H

Question 2 **[25 marks]**

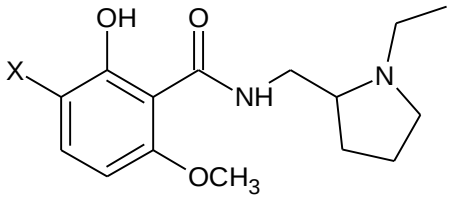
a. Calculate the logP value of 3-chlorobenzamide from the following data: benzene logP = 2.13, chlorobenzene logP = 2.84, and benzamide logP = 0.64. Substituent constants for Cl and $CONH_2$ are 0.71 and -1.49 respectively. [7]



3-chlorobenzamide

b. The influence of substituent X on Dopamine D_2 receptor antagonism in a series of potential anti-psychotic salicylamides has been studied. A Hansch analysis yielded the following equation:

$$\text{Log } (1/IC_{50}) = 1.28\pi - 0.518\pi^2 - 0.692\ \sigma_{meta} + 1.954$$



c. Define the following terms used in QSAR [8]

i. IC_{50}

ii. π

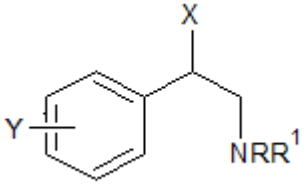
iii. σ

iv. LogP

d. Discuss how the hydrophobicity of drugs can be used to estimate their effective dose levels. [5]

e. A QSAR equation for the β-halo-arylamines (**V**) was derived as follows:

$$\text{Log } (1/C) = 1.22\pi - 1.59\pi + 7.89 \text{ (n = 22, } r^2 = 0.841 \text{ and s = 0.238)}$$



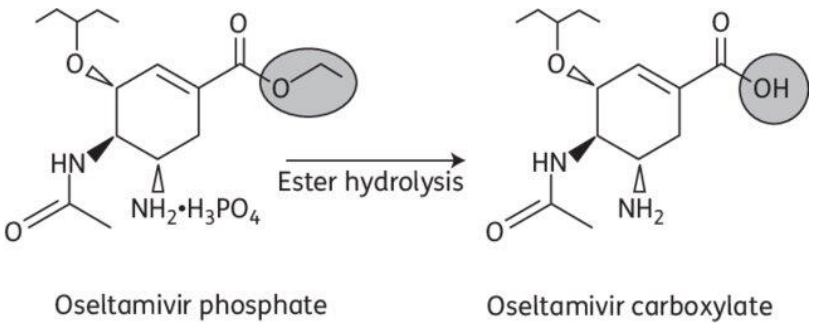
V

i. What is the significance of the terms r^2 and s? [5]

Question 3 **[25 marks]**

a. Discuss the advantages of using the Craig Plot in QSAR studies [10]

b. In many medications, a carboxyl functional group is essential for their pharmacological activity. However, its presence causes too high polarity for oral administration, and the fact that it is an ionisable group may prevent it from crossing a fatty cell membrane. This may be resolved by protecting the acid function as an ester (prodrug strategy). The less polar ester can cross fatty cell membranes and, once it is in the bloodstream, it is metabolised back to the free acid. Oseltamivir phosphate is one such drug and its activation pathway is shown below.



Oseltamivir phosphate Oseltamivir carboxylate

i. What challenges are faced by drugs that contain an ester functional group? [5]

ii. How can oseltamivir carboxylate interact with its binding site? [5]

iii. How would administering the carboxylate of oseltamivir affect its bioavailability? [5]

Question 4 **[25 marks]**

Discuss how the following drug optimization strategies may be used in drug design.

a. Variation of substituents (5)
b. Extension of the structure (5)
c. Ring fusions (5)
d. Simplification of the structure (5)
e. Rigidification of the structure (5)