

**NATIONAL UNIVERSITY OF LESOTHO  
FACULTY OF HEALTH SCIENCES  
DEPARTMENT OF PHARMACY  
B. PHARM (HONOURS) EXAMINATION  
PHA 4301 – MEDICINAL CHEMISTRY**

**JANUARY 2024**

**TIME: 3 HOURS**

**TOTAL: 100 MARKS**

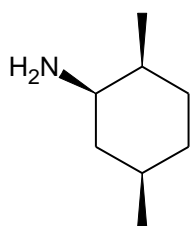
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**INSTRUCTIONS:**

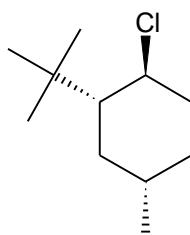
- **THIS PAPER CONSISTS OF 4 QUESTIONS**
- **ANSWER ALL QUESTIONS**
- **START EACH QUESTION ON A NEW PAGE**
- **MARKS ARE SHOWN IN PARENTHESIS AT THE END OF EACH QUESTION**

**Question 1****[25 marks]**

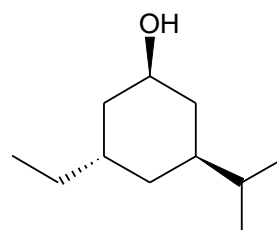
- a. Discuss the pharmaceutical significance of stereochemistry. [5]
- b. For each structure below, draw the most stable chair conformation (1) and its ring-flipped alternative (1), indicate whether the alkyl groups on the ring are Cis/Trans (1) and justify your answer. (1) [12]



i.

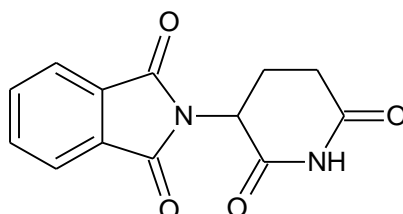


ii.



iii.

- c. Thalidomide was initially used as a sedative and an antiemetic until it was discovered that it was teratogenic, causing severe foetal deformities. This is because thalidomide is a racemic mixture of stereoisomers which are readily interchangeable between the sedative and the teratogen. Below is the structure of thalidomide.



- i. Identify the chiral carbon(s) of thalidomide with a star. [2]
- ii. Draw all stereoisomers of thalidomide. [2]
- iii. Indicate the configuration of the chirality centre(s) of each stereoisomer. [2]
- iv. Indicate the relationship(s) between all stereoisomers of thalidomide. [2]

**Atomic number ranking: Br > Cl > S > P > O > N > C > <sup>2</sup>H > <sup>1</sup>H**

**Question 2****[25 Marks]**

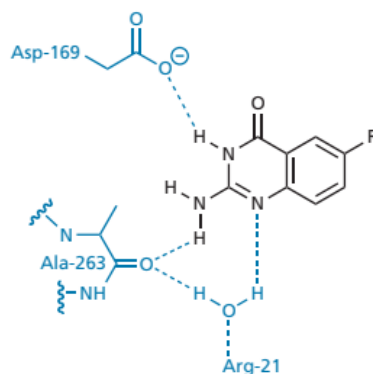
- a. Indicate how an increase in logP affects the following physicochemical properties of drugs
- i. Binding to enzymes/ receptors [1]
- ii. Aqueous solubility [1]

- iii. Absorption through biological membranes [1]
- iv. Binding to blood/tissue proteins [1]
- b. Discuss the importance of the solubility and partition coefficient of drug molecules. [4]
- c. Mention any two methods that can be used to improve the solubility of drugs [2]
- d. Discuss how the following physicochemical properties affect the biological activity of drugs.
  - i. Partition coefficient [5]
  - ii. Ionization [5]
  - iii. Hydrogen bonding [5]

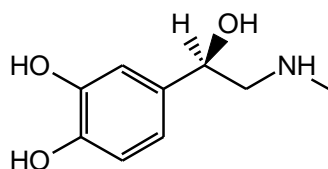
### **Question 3**

**[25 marks]**

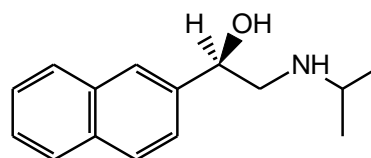
- a. Describe drug optimization (3) and discuss why it is important in drug discovery (3). [6]
- b. The following pteridine analogue is a thymidylate synthase inhibitor and a potential anticancer drug.



- i. From this structure, identify the binding interactions that hold the pteridine moiety in the active site. [3]
- ii. How would you optimize pteridine to create more derivatives in order to study their SAR? (2) Justify your answer (3) [5]
- iii. Which drug optimization strategy would you employ to improve the solubility of a hydrophobic drug? (2) Give reasons for your choice of optimization strategy (3) [5]
- c. Pronethalol is an analogue of adrenaline and it was the first beta-adrenoceptor antagonist used for the treatment of coronary heart disease and cardiac arrhythmias. Below are the structures of adrenalin and pronethalol. Indicate which drug optimization strategy was used to synthesise pronethalol (2) and mention two benefits of this strategy (4). [6]



Adrenaline

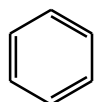
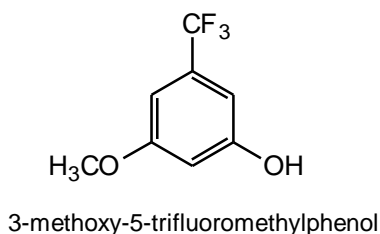


Pronethalol

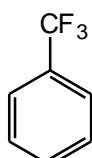
**Question 4**

**[25 marks]**

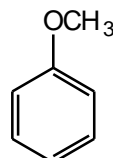
- a. Describe QSAR and mention its advantages in drug discovery and development [5]
- b. Calculate the logP value of 3-methoxy-5-trifluoromethylphenol from the following data: benzene logP = 2.13, trifluoromethylbenzene logP = 3.29, methoxybenzene logP = 2.11, and phenol logP = 1.46. Substituent constants for CF<sub>3</sub>, OCH<sub>3</sub> and OH are 1.16, -0.02 and -0.67 respectively. [7]



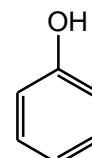
logP = 2.13



logP = 3.29



logP = 2.11



logP = 1.46

- c. Based on your answer in (b) above, comment on the possible biological activity of 3-methoxy-5-trifluoromethylphenol in comparison to phenol. [3]
- d. Discuss the importance of the Craig plot in QSAR [10]