NATIONAL UNIVERSITY OF LESOTHO

FACULTY OF HEALTH SCIENCES

DEPARTMENT OF PHARMACY

B. PHARM (HONOURS) EXAMINATION

PHA 5303 – DRUG DISCOVERY, DESIGN AND DEVELOPMENT

JANUARY 2024 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]**

1. Before the 20th century, medicines came from natural sources and they were found by trial and error from plants, roots, leaves, vines and fungi.
   a. Mention the plant source of nicotine (1) and the phytochemical class under which it falls (1). [2]
   b. Discuss how nicotine was discovered [2]
   c. Outline how nicotine was isolated from its source in the early discovery [5]
   d. Mention one condition for which nicotine is indicated [1]

2. There is an outbreak of a new epidemic in your region that affects the elderly above the age of 60. As a pharmaceutical company, you are tasked by your country to develop a drug that will treat this epidemic and halt its further spread.
   a. What considerations would you make in a search for a lead compound? [7]

3. Target identification and validation are crucial steps in the early stages of drug discovery.
   a. What characteristics must an ideal drug target possess? [4]
   b. Outline the purpose for target validation in drug discovery [4]

Question 2 **[25 marks]**

1. You are the pharmacist in charge at your pharmaceutical company and you and your team want to develop glycogen synthase kinase-3 (GSK-3) inhibitors that will treat type 2 diabetes mellitus. There is a divide in your team in that one group wants to use the normal drug discovery approach while the other group wants to use the computer-aided drug design (CADD) approach. After many deliberations, your team comes to a consensus that CADD is the way to go.
   a. In your own words, describe computer-aided drug design. [2]
   b. Justify your reasons for choosing CADD over the normal drug discovery [4]
   c. Knowing the structure of the binding side, which CADD strategy would you use to develop these inhibitors? (1) Support your answer (2). [3]
   d. Which alternative approach would you use if the structure of the target is unknown, but the structure of the ligand is known? (1) Support your answer (2). [3]
   e. Discuss the purpose of using homology modelling in drug design. [2]

2. After successfully carrying out the computational studies, the company decides to go to the wet lab to optimize the lead compound further to synthesize its analogues which

were screened *in vitro* against GSK-3. Acabet was among the screened compounds, and it inhibited glycogen synthase kinase 3 (GSK3) at nanomolar potency (i.e Acabet is a very potent GSK3 inhibitor). Your company then decides to patent the method of synthesis of Acabet.

a. Describe a patent [2]
b. Which 3 basic criteria must Acabet meet in order to be patented? [3]
c. What information must appear in a patent specification? [3]

3. Having obtained your permission to synthesise Acabet, a competitor company discovers an almost similar method of synthesis which is of a shorter duration, yields more product and is environmentally friendly, compared to your company's method. What agreement must be made between these 2 companies to synthesise Acabet using the competitor's method of synthesis? Explain [3]

Question 3 **[25 marks]**

1. KGM Pharmaceutical company embarked on a drug discovery and development project, in which they aimed to produce potent anticancer drugs by targeting protein kinases. They synthesised a series of 7-azaindole derivatives which were tested *in vitro* against a panel of recombinant protein kinases. Among the tested compounds, **KGM-07** was the most potent single inhibitor of cyclin-dependant kinase, with an IC_{50} of 14 nM. Preclinical studies were carried out for these compounds and **KGM-07** still demonstrated safe and superior activity over other tested compounds. The company then proceeded to clinical trials with **KGM-07.**

a. What are clinical trials designed for in drug development? [1]
b. What are the main phases of these clinical trials? With each one, elaborate on the objective of the particular phase and what activity is undertaken at each stage. [12]
c. During the drug development process, two applications must be filed. Mention these two applications (2), indicate when each application must be filed (2), and indicate the crucial information that must be covered by each application (2). [6]

2. Lack of adequate drug control systems or methods to investigate the safety of new chemical compounds in a country is a great risk because prefabricated drug products are broadly and freely distributed. Distribution of untested medication with no known safety

profiles is common in countries with no drug regulatory bodies, and it poses great danger to the general public.

a. Indicate the danger of not having a drug regulatory authority in a country. [1]
b. What are the functions of a country's drug regulatory authority in drug development? [5]

Question 4 **[25 marks]**

1. Targeted prodrugs for cancer therapy have achieved great diversity in terms of target selection, activation chemistry, as well as size and physicochemical nature of the prodrug. Discuss the following prodrug strategies (3) and give an advantage of each strategy (1) and an example of a prodrug in each strategy (1).
   a. Prodrugs with improved lipophilicity [5]
   b. Prodrugs with improved aqueous solubility [5]
   c. Prodrugs with lowered water solubility [5]

2. 5-Fluorouracil is an active form of a widely used prodrug in cancer treatment.
   a. Discuss in detail, the activation of 5-fluorouracil in cancer therapy. [8]
   b. Draw the chemical structure of 5-fluorouracil [2]