WI-2-60-1-6

JOMO KENYATTA UNIVERSITY OF AGRICULTURE AND TECHNOLOGY

University Examinations 2025/2026

YEAR I SEMESTER I EXAMINATIONS FOR THE MASTER OF SCIENCE DEGREE IN MEDICINAL CHEMISTRY

UNIT CODE: TPS 3100

UNIT TITLE: QUANTITATIVE STRUCTURE ACTIVITY RELATIONSHIP

EXAMINATION DATE: AUGUST, 2026

Instructions:

Answer ANY FOUR questions

QUESTION ONE (25 MARKS)

a) Define the concept of drug design within the field of pharmaceutical science. **5 Marks**

b) Discuss the historical background of drug design. Highlight key milestones and how early practices contributed to the development of modern drug design techniques. **8 Marks**

c) Discuss the importance of drug design in modern medicine. Provide examples to support your evaluation. **7 marks**

d) Relate the historical evolution and current applications of drug design to explain how it has addressed contemporary medical challenges. **5 marks**

QUESTION TWO (25 MARKS)

You are developing a new drug aimed at targeting a specific receptor involved in inflammation. Using your understanding of drug-receptor interactions, pharmacodynamics and pharmacokinetics (ADME), and structure-activity relationships (SAR). (Support your answer with examples and relevant concepts)

a) Discuss the key pharmacological and pharmacokinetic factors that influence the efficacy and safety of a drug designed to target a specific receptor involved in inflammation. **9 marks**

b) Evaluate how specific chemical modifications to a drug's structure can enhance receptor binding and optimize pharmacokinetic properties (ADME). Provide at least two examples. **8 marks**

c) Propose a step-by-step strategy for designing a new drug candidate that achieves high efficacy with minimal adverse effects. **8 marks**

QUESTION THREE (25 MARKS)

a) Compare and contrast Ligand-based and Structure-based Drug Design approaches, including their principles, advantages, and limitations **6 marks**

b) Discuss how De novo drug design complements traditional CADD approaches in accelerating early-phase drug discovery **6 marks**

c) Evaluate the potential effectiveness of integrating Ligand-based, Structure-based, De novo, and CADD techniques in a unified workflow. Use relevant one example or case study to support your argument **7 marks**

d) Create a hypothetical outline for discovering a lead compound using a combination of the above strategies. Justify the tools, methods, and sequence you propose **6 marks**

QUESTION FOUR (25 MARKS)

a) Evaluate the reliability of molecular docking results when predicting ligand binding affinity in a novel protein target. What factors can affect the accuracy **6 marks**

b) Identify at least three potential reasons for this failure and suggest how each can be addressed. **6 marks**

c) i. Design a molecular dynamics (MD) simulation workflow to study the conformational flexibility of a protein-ligand complex. **4 marks**

ii. Explain how you would ensure the validity of your simulation results. **3 marks**

d) Discuss the use of structure-based virtual screening **6 marks**

compared to ligand-based virtual screening in early drug discovery.

QUESTION FIVE (25 MARKS)

a) i. Define Quantitative Structure-Activity Relationship (QSAR) and discuss its foundational principles. **3 marks**

ii. Summarize the key historical milestones in the evolution of QSAR, highlighting how these have shaped current methodologies. **4 marks**

b) i. Discuss the importance of QSAR in drug discovery, citing specific examples of its application **3 marks**

ii. Outline the main steps of a typical QSAR workflow, providing brief descriptions for each stage **4 marks**

c) i. Differentiate between 1D, 2D, and 3D molecular descriptors used in QSAR, explaining the specific molecular information captured by each and their respective limitations **5 marks**

ii. Evaluate the significance of key physicochemical descriptors such as logP and molecular weight in influencing biological activity predictions within QSAR models. Provide examples to support your evaluation. **3 marks**

d) Design a rationale for integrating multiple descriptor types in QSAR modeling to improve predictive accuracy. Discuss potential challenges in descriptor integration and how they might be addressed **3 marks**

QUESTION SIX (25 MARKS)

a) Define the following terms as used in QSAR: **4 marks**

i. Partition coefficient (log P)

ii. Hammett's substituent constant (σ)

iii. Taft's steric constant (Es)

iv. Hansch equation

b) Explain the difference between Hansch analysis and Free Wilson analysis in QSAR, highlighting: **2 marks**

i. How each uses structural information **1 marks**

ii. The type of parameters used **2 marks**

iii. The strength or limitation of each approach

c) Given the Hansch equation: **5 marks**

$$\log (1/C) = 0.6 \cdot \pi - 1.1 \cdot \sigma - 0.3 \cdot MR + 5.2$$

Calculate log(1/C) for a compound with: