CHARLES DARWIN UNIVERSITY

Family Name	
Given Names	
Student Number	
Teaching Period	Semester 1, 2017

FINAL EXAMINATION	**DURATION**
PHA212 – Medicinal Chemistry	Reading Time: **10** minutes Writing Time: **180** minutes

INSTRUCTIONS TO CANDIDATES

Section A

Short Answer Questions

Total No of Marks for this section: 100

This section should be answered in the Answer Booklet provided.

Marks for each question are indicated. Suggested Time allocation for Section B: 180 mins

EXAM CONDITIONS

You may begin writing from the commencement of the examination session. The reading time indicated above is provided as a guide only.

This is a CLOSED BOOK examination

Any non-programmable calculator is permitted

No handwritten notes are permitted

No dictionaries are permitted

ADDITIONAL AUTHORISED MATERIALS	EXAMINATION MATERIALS TO BE SUPPLIED
No additional printed material is permitted	1 x 20 Page Book 1 x Scrap Paper

THIS EXAMINATION IS PRINTED DOUBLE-SIDED.

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Section A

Short Answer Questions

Total No of Marks for this section: 100

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Question 1. Drug development process and methods

(a) As chief scientific officer of a medium sized biopharma company specialising in oncology, you have been asked for you opinion on whether your company should buy the intellectual property relating to a new anti-bacterial chemotherapeutic from a university start-up. The project is targeting what is believed to be a novel mechanism for disrupting cell wall synthesis. The project has progressed to the stage of having several hits in a biophysical screening campaign.

What information would you expect the start-up to provide as part of the IP? Produce an annotated schematic that you could use as part of your briefing to the company board explaining the benefits and risks associated with taking on this project. Assume that the annotations need to be sufficient for the schematic to be understood without you being present to explain it.

This presentation should include a short discussion of cell wall growth inhibition

(Marks 10)

(b) Tropical diseases affect more than 1 billion people, mostly in developing regions of the world.

i. Give 2 examples of tropical diseases.

ii. Give four parameters for developing drugs targeting **neglected** tropical diseases and explain their importance

(Marks 10)

Question 2. Metabolomics and natural regulators

(a) Give examples of and explain the function of medicinal chemistry modifications to drug molecules that give rise to changes in their metabolic handling, compare and contrast this with the structural and chemical properties of natural regulators and explain the reasons why modifications to this class of lead compounds are required to make a marketable drug

(Marks 10)

(b) In one sentence define the following terms:

i. Metabolomics

ii. Lipidomics

iii. Metabolic footprinting

(Marks 3)

(c) Using a flowchart, outline the key steps in the metabolomics analysis (profiling) of tissue extracts taken from a study of 50 individuals. Include details on sample preparation and the suggested analytical platform to be used (note separation and detection method)

(Marks 7)

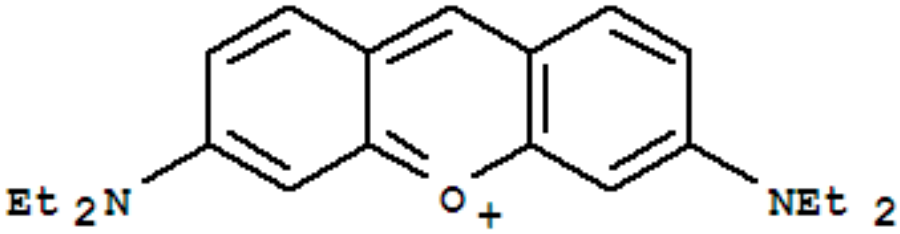
Question 3. Hit-to-lead chemistry

(a) Define:

i. Rational drug design
ii. Hanchz's rule
iii. CLog P
iv. The "rule of three" (2 marks)

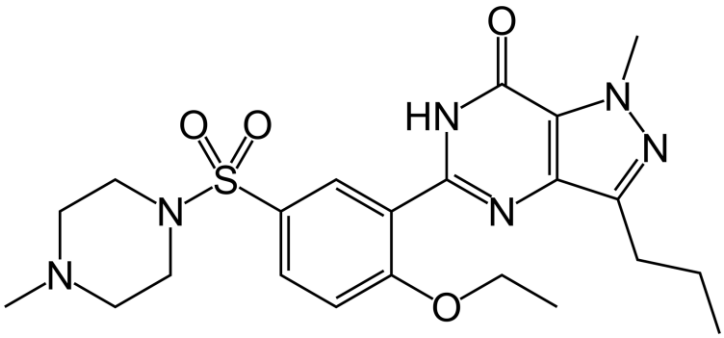
(Marks 5)

(b) Tricyclic moieties are common in drug molecule. However, the specific shape (conformation) of the molecule can be manipulated by changing the atoms in the central ring. What changes would need to be made to the atoms in the central ring of the following compound (a xanthylium salt) to effect the overall shape of the molecule.



(Marks 8)

(c) The compound below was discovered to be an effective enzyme inhibitor. What modifications would you make to this compound in order to discover the pharmacophore and which groups may be interfering with or improving target binding/engagement?



(Marks 7)

Question 4. Screening and structure based design

(a) Define:

i. High information content screen
ii. Agonist
iii. Biophysical screening
iv. Toxicophore

(Marks 4)

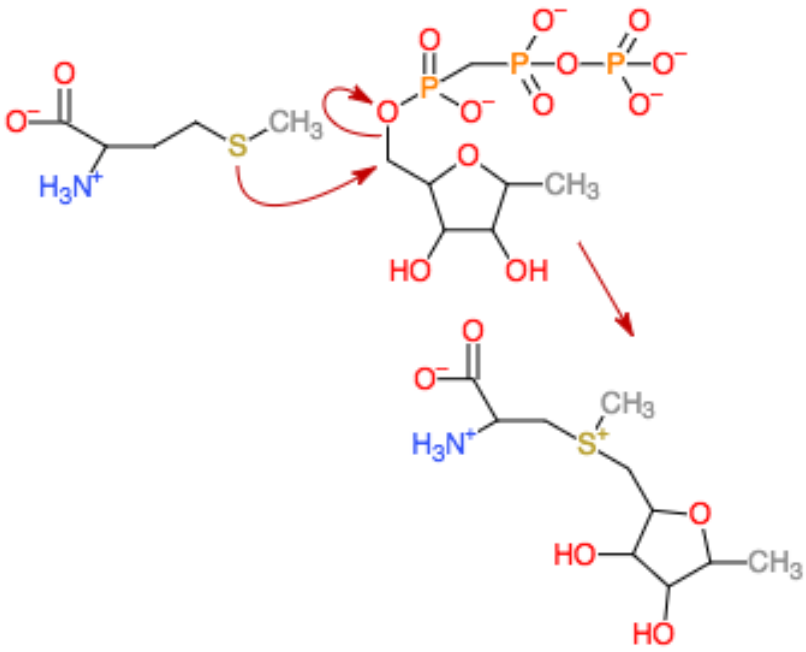
(b)

i. In the diagram below, what type of reaction is occurring?

Using the concept of bioisosteres:

ii. Design a reversible competitive inhibitor for the following reaction. Explain your reasoning

iii. Design a multi-substrate analogue inhibitor. Explain your reasoning



(Marks 7)

(c) Surface plasmon resonance, isothermal titration calorimetry and nuclear magnetic resonance are all common biophysical methods for screening compound libraries for binding to isolated target molecules.

In terms of structural information gathered, binding kinetics and thermodynamics, explain the relative advantages of these three techniques for screening a pharmaceutical compound library for binding to a soluble protein target.

(Marks 9)

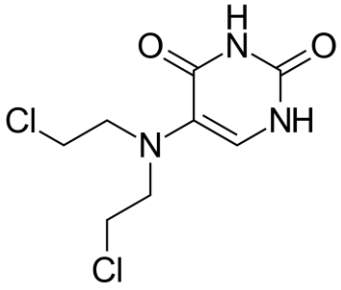
Question 5. Target interaction chemistry and oncology agents

(a) Describe how you would use the medicinal chemistry techniques of producing homologous series and/or the introduction of bio-isosteres into a chain to change the potency and selectivity of a drug designed to interact with an active site on a membrane transporter. Give examples of how this has been done

(Marks 8)

(b)

i. Draw, annotate and explain the organic chemical reaction mechanism for the interaction between the alkylating cytotoxic cancer chemotherapeutic cyclophosphamide (structure below) and DNA. Explain briefly why and how this agent preferentially kills cancer cells in the body



ii. Compare and contrast the DNA interaction of alkylating and intercalating agents

(Marks 8)

(c) Explain one aspect of medicinal chemistry that is not covered anywhere else in this exam paper

(Marks 4)