Examination Candidate Number: __________

Desk Number: __________

BSc Degree Examinations 2018-9

Department:
BIOLOGY

Title of Exam:
Antibiotics

Time Allowed:
2 hours

Marking Scheme:
Total marks available for this paper: 100

The marks available for each question are indicated on the paper

Instructions:
Section A: Answer all questions in the spaces provided on the examination paper
Section B: Answer either question A or question B. Write your answer on the separate paper provided and attach it to the back of the question paper using the cable tie provided.

Materials Supplied:
CALCULATOR
Green Answer Booklet

For marker use only:                     Office use only:

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<th>Essay A</th>
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DO NOT WRITE ON THIS BOOKLET BEFORE THE EXAM BEGINS
DO NOT TURN OVER THIS PAGE UNTIL INSTRUCTED TO DO SO BY AN INVIGILATOR
SECTION A: Short Answer / Problem / Experimental Design questions

Answer all questions in the spaces provided

Mark total for this section: 50

1) Traditional screens for antibiotics have been very successful in identifying new compounds.

a) Explain the experimental stages in a ‘traditional’ forward screen to identify a new antibiotic from microbes in a soil sample. (4 marks)

b) Describe the two most common problems with this traditional pipeline. (2 marks)

2) Nicin is an antibiotic that has been used in the food industry for many years. What type of antibiotic is it and how does its biosynthetic route provide opportunities to engineer variants of this molecule? (3 marks)
3) The term ‘assembly line’ logic is used when describing the production of certain antibiotics. Describe two different types of ‘assembly line’ biosynthetic pathways and compare and contrast their common and distinguishing features. (6 marks)

4) Antibiotic resistance is now a major threat to public health.

a) Sub-inhibitory concentrations of antibiotics can lead to high levels of resistance in bacteria. Using trimethoprim as an example, describe a mechanism that allows a normally sensitive bacteria to develop resistance. What are the potential biological costs of resistance and how are these mitigated by the bacteria? (3 marks)
b) The cell wall is an important target for antibiotics. Name two antibiotics that target the cell wall and, for each, describe the mode of action and a specific mechanism that bacteria use to provide resistance. (6 marks)

5) Describe how the stringent response activates production of antibiotics in Streptomyces. (2 marks)

6) Rifampicin is often described as a “semi-synthetic” rifamycin.

a) What does “semi-synthetic” mean in this context? How might structural biology aid the production of a semi-synthetic drug with higher affinity for its target? (4 marks)
b) Rifamycins have selectivity in their activity for bacteria over humans. Describe what you understand by the term “selectivity” and describe how this selectivity occurs. Your answer should include information on the molecular target and function of rifamycins. (4 marks)

c) Resistance to rifamycins can occur through both “target modification” and “drug modification”. Provide one example of each mechanism for a rifamycin antibiotic. (4 marks)

The space above the line should be sufficient for your answer.
7) Compounds 1 and 2 have antibacterial activity \textit{in vitro} and are inhibitors of the proteins gyrase B and FtsZ, respectively.

\begin{itemize}
  \item \textbf{Gyrase B inhibitor 1} \\
      \textbf{IC}_{50} \text{ Gyrase B: } 5\ \text{nM} \\
      \text{S. aureus } \textbf{MIC}_{90}: 0.06\ \mu\text{g/ml} \\
      \text{LogP} = 2.3
  \end{itemize}

\begin{itemize}
  \item \textbf{FtsZ inhibitor 2} \\
      \textbf{MIC}_{50} \ 0.125\ \mu\text{g/ml} \\
      \text{LogP} = 5.4
  \end{itemize}

a) What is the inhibition mechanism for the following antibacterial targets:
   \begin{itemize}
     \item (i) Gyrase B \hspace{1cm} (2 marks)
     \item (ii) FtsZ \hspace{1cm} (2 marks)
   \end{itemize}

b) Explain the meaning of the measurements \textbf{IC}_{50}, \textbf{MIC}_{50} and \textbf{MIC}_{90} \hspace{1cm} (3 marks)
c) Giving your reasons, do you expect compounds 1 and 2 to be orally bioavailable? (5 marks)

The space above the line should be sufficient for your answer.
SECTION B: Essay question

Answer one question on the separate paper provided

Remember to write your candidate number at the top of the page and indicate whether you have answered question A or B

Mark total for this section: 50

EITHER

A) Describe how structural biology, and particularly cryo-electron microscopy, have transformed our understanding of how two different classes of ribosome protection proteins confer resistance to antibiotics.

OR

B) Antibiotic biosynthesis gene clusters are abundant in genome sequences but this hasn’t translated into an abundance of novel antibiotics. Using specific examples discuss the problems that hinder new antibiotic discovery and what methods are being used to overcome them.