Loughborough University

Drugs: Mode of Action, Properties and Synthesis

22CMD402

Semester 2 22/23 Online Long-window Exam paper

This is an online long-window examination, meaning you have **23 hours** in which to complete and submit this paper. How you manage your time within the 23-hour window is up to you, but we expect you should only need to spend approximately **2 hours** working on it. If you have extra time or rest breaks as part of a Reasonable Adjustment, you will need to add this to the amount of time you are expected to spend on the paper.

It is your responsibility to submit your work by the deadline for this examination. You must make sure you leave yourself enough time to do so.

It is also your responsibility to check that you have submitted the correct file.

Exam Help

If you are experiencing difficulties in accessing or uploading files during the exam period, you should contact the Exam Helpline. For urgent queries please call **01509 222900**.
For other queries email examhelp@lboro.ac.uk

Answer **ALL** questions

You may handwrite and/or word process your answers, as you see fit. You may use a calculator and molecular model kits for this exam.

Where a question involves drawing molecular reaction schemes or mechanisms, you should include commentary explaining each step of the transformation. Diagrams *must* be hand drawn. When photographing your answers for upload, please check that all parts of your answer are clearly visible and legible in the recorded version.

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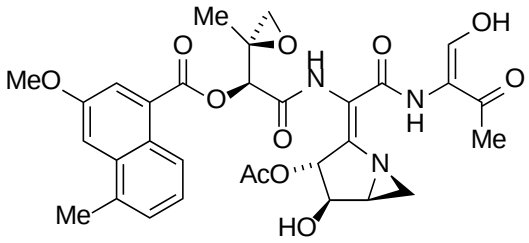
1. Answer **ALL** parts

a) Give one example of damage to deoxyribose nucleic acid (DNA) that can be caused by chemical carcinogens, and outline how this damage can cause cells to become cancerous. State the key properties of cancer cells which distinguish them from healthy functioning cells, and explain why cancers can be more difficult to treat than pathogenic diseases. [8 marks]

b) Azinomycin B, shown below, is a DNA binding molecule with antitumour properties, which unusually binds in the major groove.

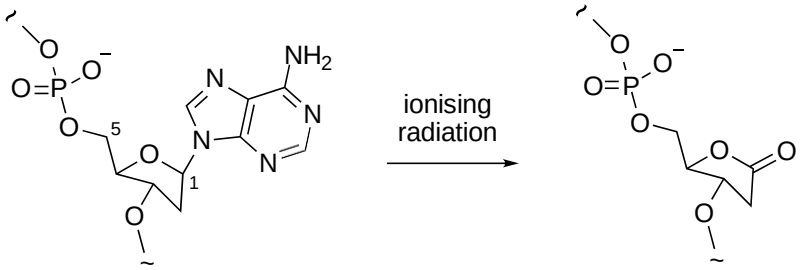


azinomycin B

(i) Explain briefly which the aid of a schematic diagram how groove binding molecules interact with double stranded DNA, and how they can act as anti-cancer agents. [4 marks]

(ii) Azinomycin B contains two functional groups which allow the molecule to bind *covalently* to DNA. Identify these groups and indicate a likely mechanism by which they react. State how this might enhance the activity of the compound. [5 marks]

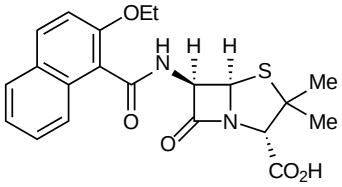
c) Ionising radiation is known to lead to strand cleavage in DNA at C-5 of the deoxyribose ring, but it can also lead to depurination at C-1, generating the sugar lactone shown below. Draw a plausible mechanism for this transformation, and explain how it could affect the functioning of the host cell.



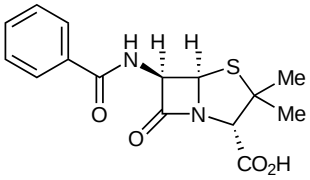
[8 marks]

2. Answer **ALL** parts

a) The 2nd generation β-lactam antibiotic Nafcillin is used to treat *staphylococci* gram-positive bacterial infections.



Nafcillin



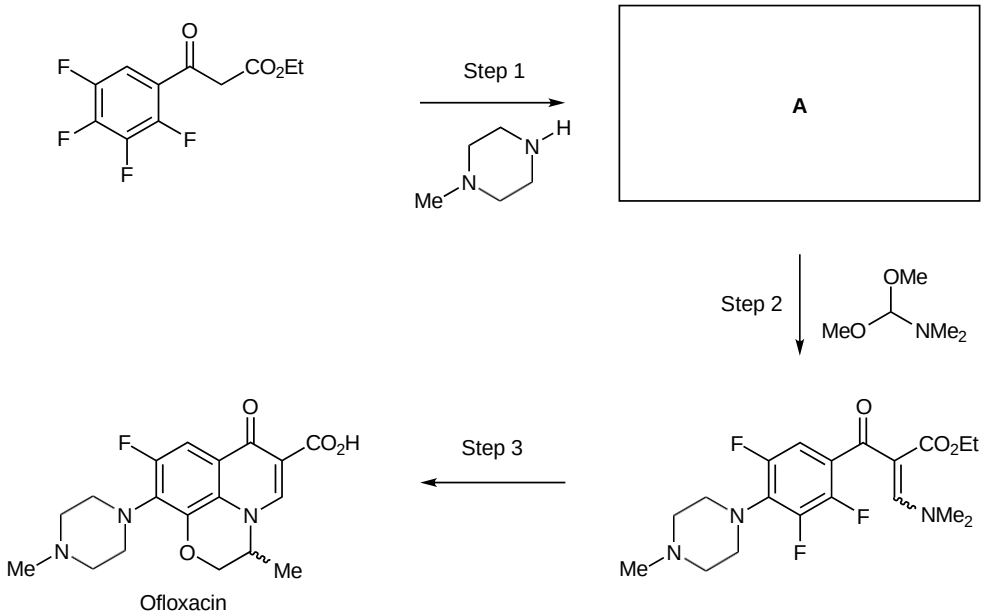
Penicillin G

(i) Explain how β-lactam antibiotics disrupt cell wall biosynthesis in gram- positive bacteria. [5 marks]

(ii) What structural feature of nafcillin is important in overcoming bacterial resistance? Provide mechanisms / diagrams to support your answer. [5 marks]

(iii) Provide a plausible chemical synthesis of nafcillin from penicillin G. Include relevant mechanisms. [5 marks]

b). Ofloxacin is a broad-spectrum fluoroquinolone antibiotic which is sold as a racemate.



Ofloxacin

(i) What is the mode of action of the fluoroquinolones, and comment on the structural elements essential for this activity. [2 marks]

continued...

(ii) Explain in detail with mechanisms, the chemistry in steps 1 and 2, and provide a structure of the unknown intermediate **A**. [4 marks]

(iii) Suggest reagents and conditions for step 3. More than one reaction is involved. Give a mechanism for each step. [4 marks]

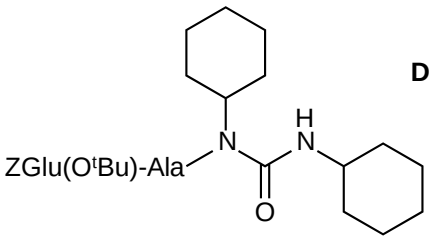
3. Answer **ALL** parts

An equimolar mixture of the protected dipeptide **A** and **B**, in an ethyl acetate solution, yields the protected tetrapeptide **C**, as the major product on addition of dicyclohexylcarbodiimde.

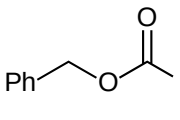
ZGlu(O^{t}Bu)-Ala-OH **A**

H-Ala-Ala-O^{t}Bu **B**

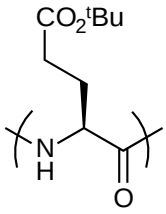
ZGlu(O^{t}Bu)-Ala-Ala-Ala-O^{t}Bu **C**



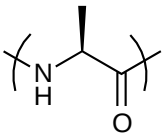
D



Z-



-Glu(^{t}Bu)-



-Ala-

a) Outline syntheses of **A** and **B** from constituent amino acids. [6 marks]

b) Explain, with a full mechanism, the chemistry of the coupling reaction indicated between **A** and **B** to give tetrapeptide **C**. [6 marks]

c) This coupling reaction gives two by-products: one is the epimer (one of the stereocenters has been inverted) and the other is **D**. Explain how these by-products are formed. [7 marks]

d) Outline an alternative approach to **C** which might be expected to give better results. [6 marks]

4. Answer **ALL** parts

a) Using HIV as an example, briefly outline the general features of the viral life cycle. [6 marks]

b) Nucleoside reverse transcriptase inhibitors such as azidothymidine (AZT) are commonly used in the treatment of HIV. Describe the process of reverse transcription and explain the mode of action of the drug AZT. You should include a diagram in you answer. [6 marks]

c) Mutations in the HIV reverse transcriptase can lead to a reduction in the binding and activity of drugs such as AZT. Explain how the combination therapy Eviplera^{TM} may help to overcome antiviral drug resistance. Use diagrams to illustrate the mechanism of action for this combination therapy. [13 marks]

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