CATHOLIC JUNIOR COLLEGE
JC2 PRELIMINARY EXAMINATIONS
Higher 3

PHARMACEUTICAL CHEMISTRY

9812/01

Paper 1

Tuesday 29 August 2017
2 hours 30 minutes

Additional Materials: Answer Paper
Data Booklet

READ THESE INSTRUCTIONS FIRST

Write your name and class on all the work you hand in.
Write in dark blue or black pen on both sides of the paper.
You may use a soft pencil for any diagrams or graphs.
Do not use staples, paper clips, highlighters, glue or correction fluid.

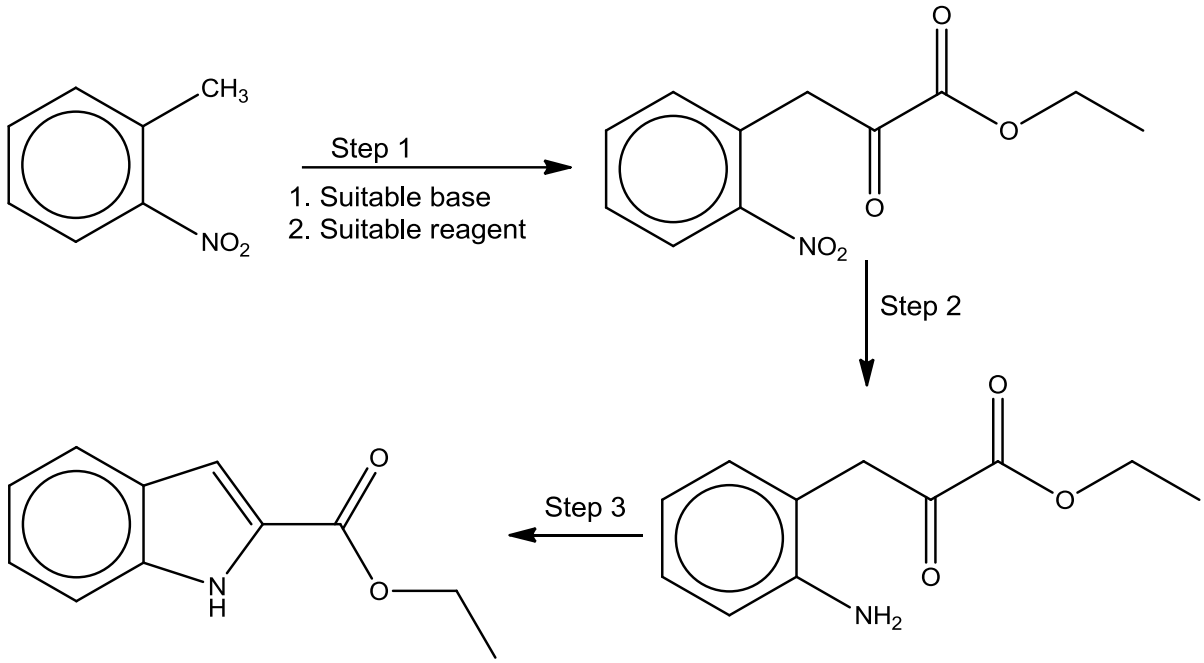
Answer any **five** questions.
At the end of the examination, fasten all your work securely together.

The number of marks is given in brackets [ ] at the end of each question or part question.
The use of an approved scientific calculator is expected, where appropriate.
You are reminded of the need for good English and clear presentation in your answers.

This document consists of **16** printed pages.

1 Indole derivatives are known for their medicinal properties in the pharmaceutical industry.

(a) The following diagram shows one route to synthesizing an indole derivative.



compound **A**

(i) A base is used in step 1 in order to deprotonate the methyl group attached to the benzene ring. Suggest the reagents and conditions required for step 1. [2]

(ii) Suggest the reagents and conditions required for step 2. [1]

(iii) Suggest a mechanism for step 3. [3]

(b) Outline in simple terms the principles of nuclear magnetic resonance. [4]

(c) Explain the use of the δ scale with TMS as the reference. [2]

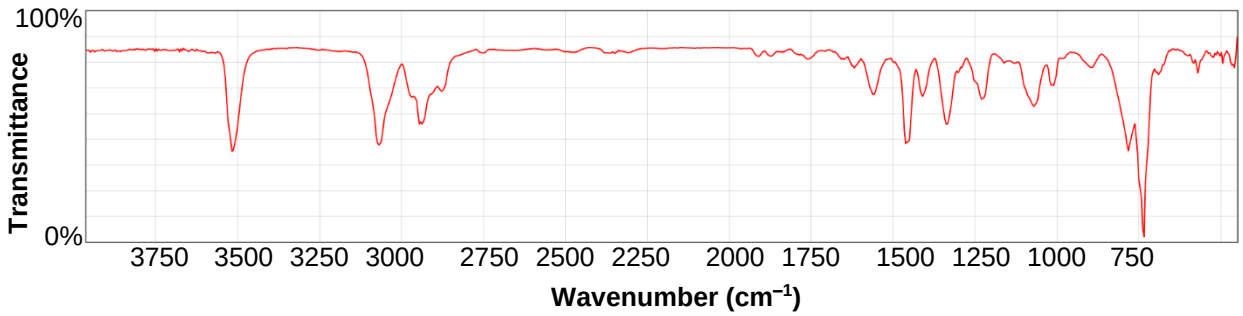
(d) Skatole, found in ice cream as a flavour enhancer, is structurally related to compound **A**. Skatole has the following NMR spectrum. The resonance at δ 6.99 disappears in the presence of D_2O.

δ 2.42 (d, 3H)
6.99 (s, 1H)
7.22 (m, 1H)
7.31-7.80 (m, 4H)

(s is singlet, d is doublet, m is multiplet)

The mass spectrum of skatole shows a molecular ion at m/e 131. The $(M+1)^+$ peak has an intensity 9.8% of that of the molecular ion.

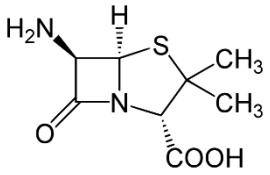
The infra-red spectrum of skatole is as shown below.



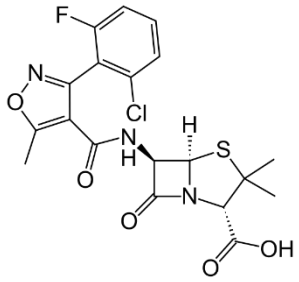
Use the above data to deduce the molecular formula and the chemical structure of skatole. [8]

[Total: 20]

2 Penicillins such as 6-aminopenicillanic acid and flucloxacillin are a group of antibiotics that disrupt the bacterial cell wall construction by forming permanent covalent links with a transpeptidase involved in their synthesis.



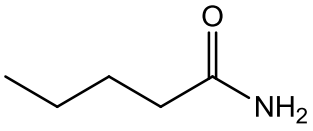
6-aminopenicillanic acid



flucloxacillin

(a) Suggest two other ways in which antibiotics work. [2]

(b) Suggest why β-lactam group in penicillins is more susceptible to hydrolysis than pentanamide.



pentanamide

[2]

(c) Bacteria sometimes develop a resistance against penicillin, causing the organ to be re-infected. Research has been done to develop new penicillin to counteract this problem.

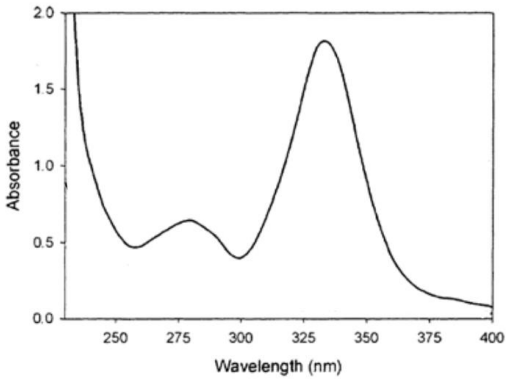
(i) Explain why the use of flucloxacillin can reduce the activity of penicillinases such as β-lactamase. [1]

(ii) Explain why the use of flucloxacillin allow it to be more easily absorbed through membranes of the intestinal villi. [2]

(d) A spectrophotometric method using UV-visible spectrophotometer was used to determine the amount of flucloxacillin and 6-aminopenicillanic acid in a pharmaceutical formulation of a drug.

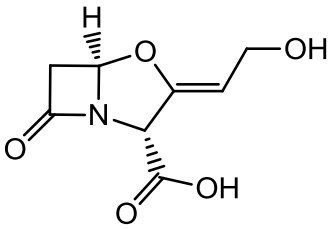
(i) Suggest why the flucloxacillin and 6-aminopenicillanic acid may be detected using UV and state what happens in these molecules when UV radiation is absorbed. [2]

(ii) Given the UV spectrum of 6-aminopenicillanic acid as shown below, suggest a suitable wavelength to measure concentration of 6-aminopenicillanic acid in the drug. [1]

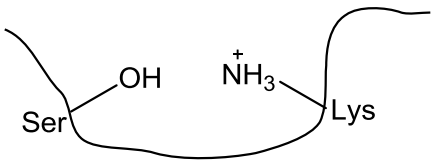


(iii) Using your answer in **(d)(ii)**, suggest a suitable wavelength to measure concentration of flucloxacillin in the drug sample and explain your answer.[2]

(e) Another approach to overcome the problem of bacteria resistance is to administer a strong β-lactamase inhibitor such as clavulanic acid together with penicillin. Clavulanic acid will inhibit transpeptidase similarly as penicillin.



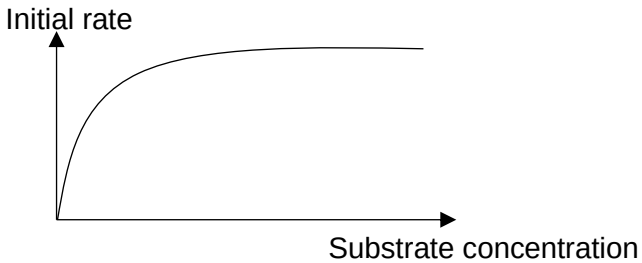
Clavulanic acid



transpeptidase active site

(i) With the aid of a labelled diagram, show how clavulanic acid can act as a transpeptidase inhibitor. [2]

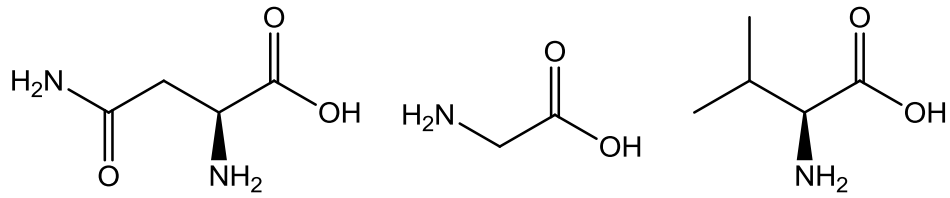
(ii) The graph below shows the initial rate of β-lactamase-catalysed reaction varies with substrate concentration. Re-draw the graph, and on the same axes show how the initial rate would vary with substrate concentration in the presence of clavulanic acid. Explain your answer. [3]



(f) Explain why failing to complete a prescribed course of penicillin antibiotics can increase the problem of bacterial resistance to penicillins. [3]

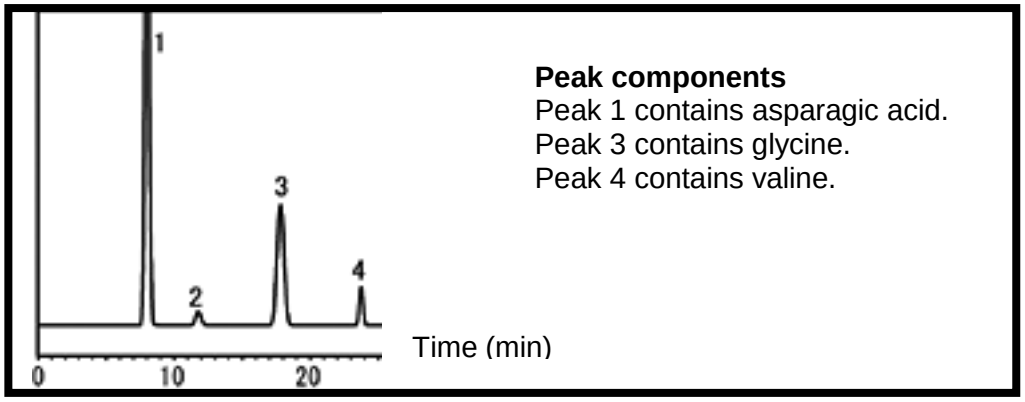
[Total: 20]

3 **(a)** Amino acids are essential for muscle building and storing nutrients. Athletes often take in drink supplement containing amino acids such as asparagic acid, glycine and valine to facilitate muscle repair.



asparagic acid glycine valine

The following shows a 1 cm^3 sample of a commercial amino acid drink supplement as analysed by HPLC. The peak components were identified as shown.



(i) By considering the polarities of the three molecules and the retention times of the three peaks, decide whether normal or reverse-phase HPLC was used to analyse the mixture. Explain your reasoning. [2]

(ii) Using standard solutions, peak areas of 1.00 cm^2 for glycine and valine in the chromatogram were found to correspond to concentrations of 50 mg dm^{-3} and 80 mg dm^{-3} respectively. Calculate the relative proportions by mass of each compound in the sample of amino acid beverage. [2]

(iii) Three amino acids, asparagic acid, glycine and valine from the amino acid beverage were isolated and subjected to electrophoresis.

(I) Briefly describe how the amino acids in the beverage can be separated by the process of electrophoresis. [3]

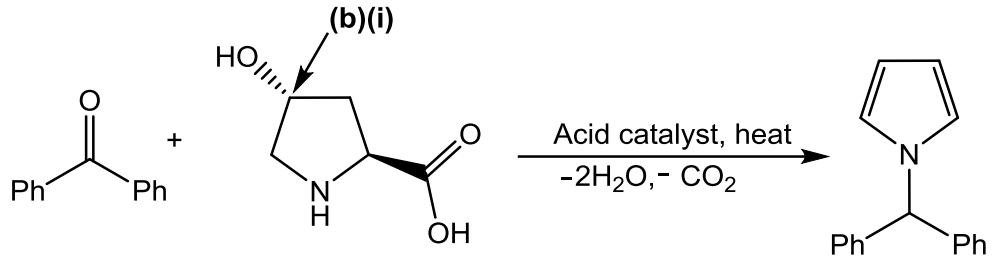
(II) How can the individual amino acids be detected after electrophoresis? [1]

(III) The isolectric point (pI) values of the three amino acids are given below.

compound name	abbreviation	isoelectric point
asparagic acid	Asp	2.77
glycine	Gly	5.97
valine	Val	5.96

Draw a diagram of the electrophoretogram and indicate the relative positions of the three amino acids when the electrophoresis buffer is set at pH = 5.00. [2]

(b) Pyrroles are building blocks in pharmaceutical chemistry. Thus, research has been ongoing to synthesize pyrroles in a single step from cheap and readily available materials. The diagram below shows the synthetic route of pyrroles from a modified amino acid, trans-4-hydroxyproline, in the presence of acid catalyst and heat.



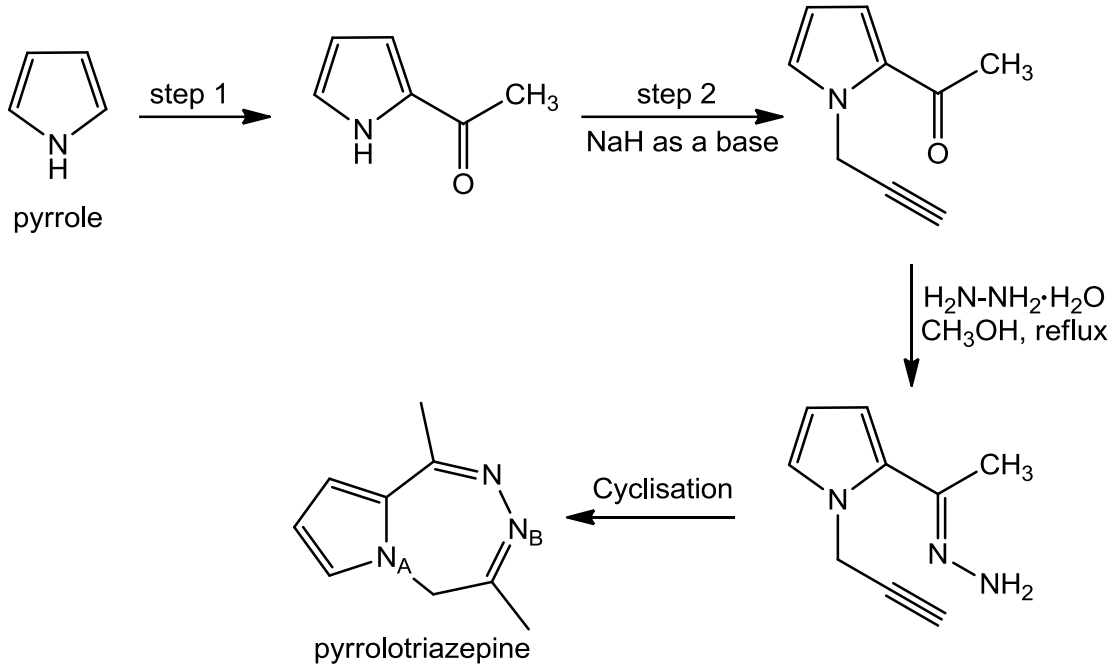
trans-4-hydroxyproline

(i) Determine the R/S configuration of the stereocentre labelled in the diagram above in trans-4-hydroxyproline. [1]

(ii) Suggest a possible mechanism for this reaction. [4]

(iii) A mixture of cis/trans isomers of 4-hydroxyproline was obtained. Suggest how the desired trans-4-hydroxyproline can be obtained. [1]

(c) Pyrroles can be used to synthesize pyrrolotriazepine derivatives which is being studied for its potential against diseases. The diagram below shows the synthetic route of a pyrrolotriazepine from pyrrole.



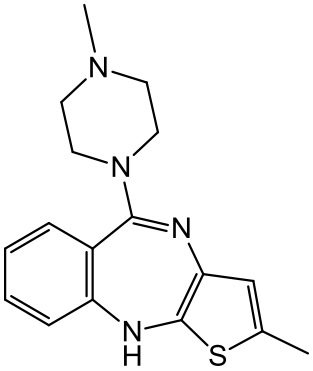
(i) State the reagents and conditions required for step 1. [1]

(ii) State the other reagent required for step 2. [1]

(iii) Suggest whether N_A or N_B in pyrrolotriazepine is less basic and explain why. [2]

[Total: 20]

4 **(a)** Olanzapine is an antipsychotic medication used to treat schizophrenia and bipolar disorder. It acts as an antagonist at the D_2 dopamine receptor.

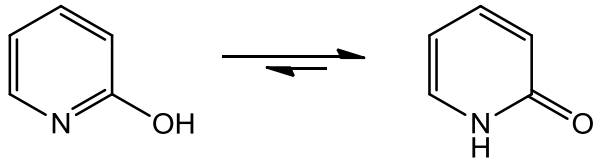


Olanzapine

(i) Determine the aromaticity of olanzapine, explaining your decision. [2]

(ii) Hence, suggest how the binding pocket of the receptor is shaped, and two possible binding interactions that can take place between olanzapine and the binding pocket. [2]

(b) **(i)** 2-hydroxypyridine can tautomerize (undergo isomeric conversion) to 2-pyridone as shown below.



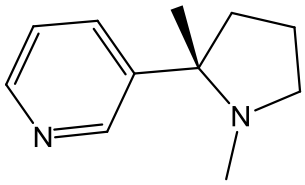
2-hydroxypyridine 2-pyridone

2-pyridone is a very weak base. Explain why this is so, and hence suggest why the position of the equilibrium shown above lies far to the right. [3]

(ii) Suggest why 3-hydroxypyridine does not tautomerize in a similar manner as 2-hydroxypyridine. [1]

(iii) 2-pyridone is rather readily deprotonated. By considering the structure of the anion derived from the deprotonation of 2-pyridone, explain why this is the case. [2]

(c) Nicotine is a potent stimulant which can be found in cigarette smoke. It also contains a pyridine ring.

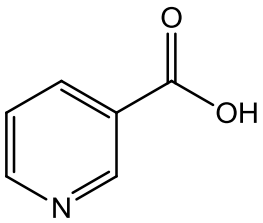


nicotine

(i) Outline four physiological effects of stimulants such as nicotine. [1]

(ii) Use the concept of drug-receptor interactions to explain long-term dependence on nicotine, which acts as an agonist. [3]

(d) Under suitable conditions, nicotine can be converted to nicotinic acid. Nicotinic acid is also known as niacin, and it is a component of vitamin B_3 complex.



nicotinic acid

Suggest the type of reaction undergone in this conversion, and suitable reagents and conditions to carry out this conversion. [1]

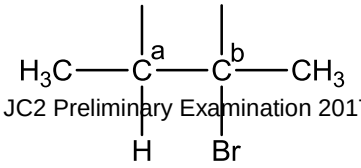
(e) Three compounds, each having the molecular formula C_3H_5NO, have the following features in their infra-red (IR) spectra:

Compound	Wavenumber / cm^{-1}	Features
K	> 3000	1 weak band
	~ 1700	1 strong band
L	> 3000	2 weak bands
	1600-1700	2 bands
M	> 3000	1 strong, sharp band
	~2200	1 band

By assigning each of the absorbances to the likely bond(s) involved, suggest a possible structure each for compounds **K**, **L** and **M**. [5]

[Total: 20]

5 **(a)** The most stable conformation for 3-bromobutan-2-ol is when the Br and OH groups are anti to e



(i) Using Newman projections, sight along the C_a-C_b bond and draw all possible stereoisomers of 3-bromobutan-2-ol, in their most stable conformation. Label the chiral carbons with the R, S configurations and indicate all stereoisomeric relationships. [3]

(ii) When the Br atom in 3-bromobutan-2-ol is replaced by C*l* to give 3-chlorobutan-2-ol, the m

(b) When an alcohol is reacted with HBr, a reaction occurs where HBr first protonates the oxygen atom, followed by attack at the alcohol carbon atom by Br^- and the loss of a water molecule.

$$ROH + HBr \rightarrow ROH_2^+ + Br^-$$

$$ROH_2^+ + Br^- \rightarrow RBr + H_2O$$

(i) State the type of reaction that has occurred. [1]

(ii) When the various stereoisomers of 3-bromobutan-2-ol in **(a)(i)** are reacted with HBr, the abovementioned reaction takes place, with the following observations:

In one of the enantiomeric pairs of 3-bromobutan-2-ol, each enantiomer gives the same two products – one which exhibits retention of configuration, and another which exhibits inversion of configuration. The two products are themselves enantiomers.

In the other enantiomeric pair of 3-bromobutan-2-ol, both enantiomers give the same product, and this product is optically inactive.

Suggest a possible mechanism for the reaction, and hence account for the above observations. You may make use of any suitable stereochemical representations in your answer. [4]

(c) **(i)** Explain the origin of infra red (IR) absorptions of simple molecules. [2]

(ii) For each of the molecules HF, CO_2 and OCS

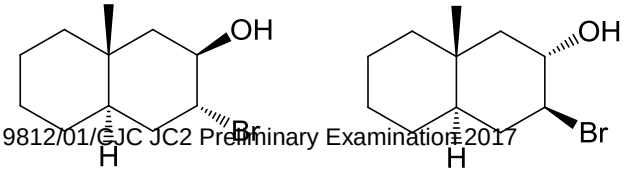
- predict the number of absorption bands in its IR spectrum,
- identify the molecular vibrations which give rise to these absorptions.

[4]

(iii) State and explain the difference between the IR spectra of ^{1}HF and ^{2}HF. [1]

(d) An epoxide is a cyclic ether with a three-membered ring.

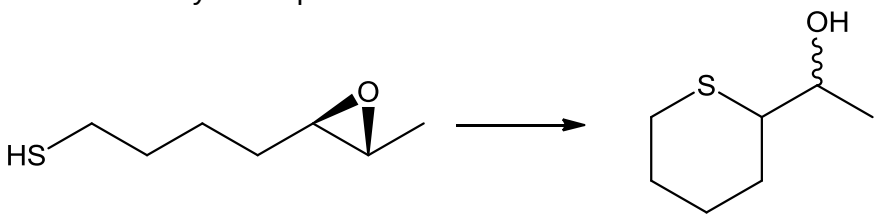
(i) State and explain which of the compounds below will give an epoxide upon reaction with a



Compound X **Compound Y**

[2]

(ii) Suggest a suitable reagent for the following reaction and deduce the stereochemistry of the product.



[2]

[Total: 20]

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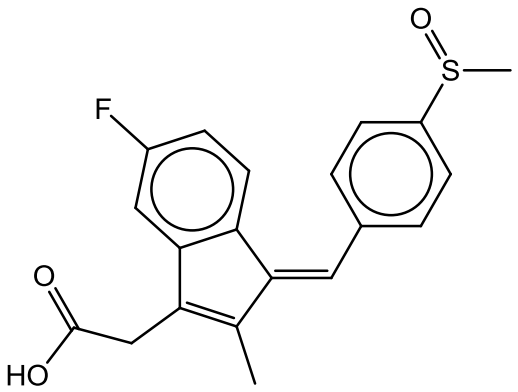
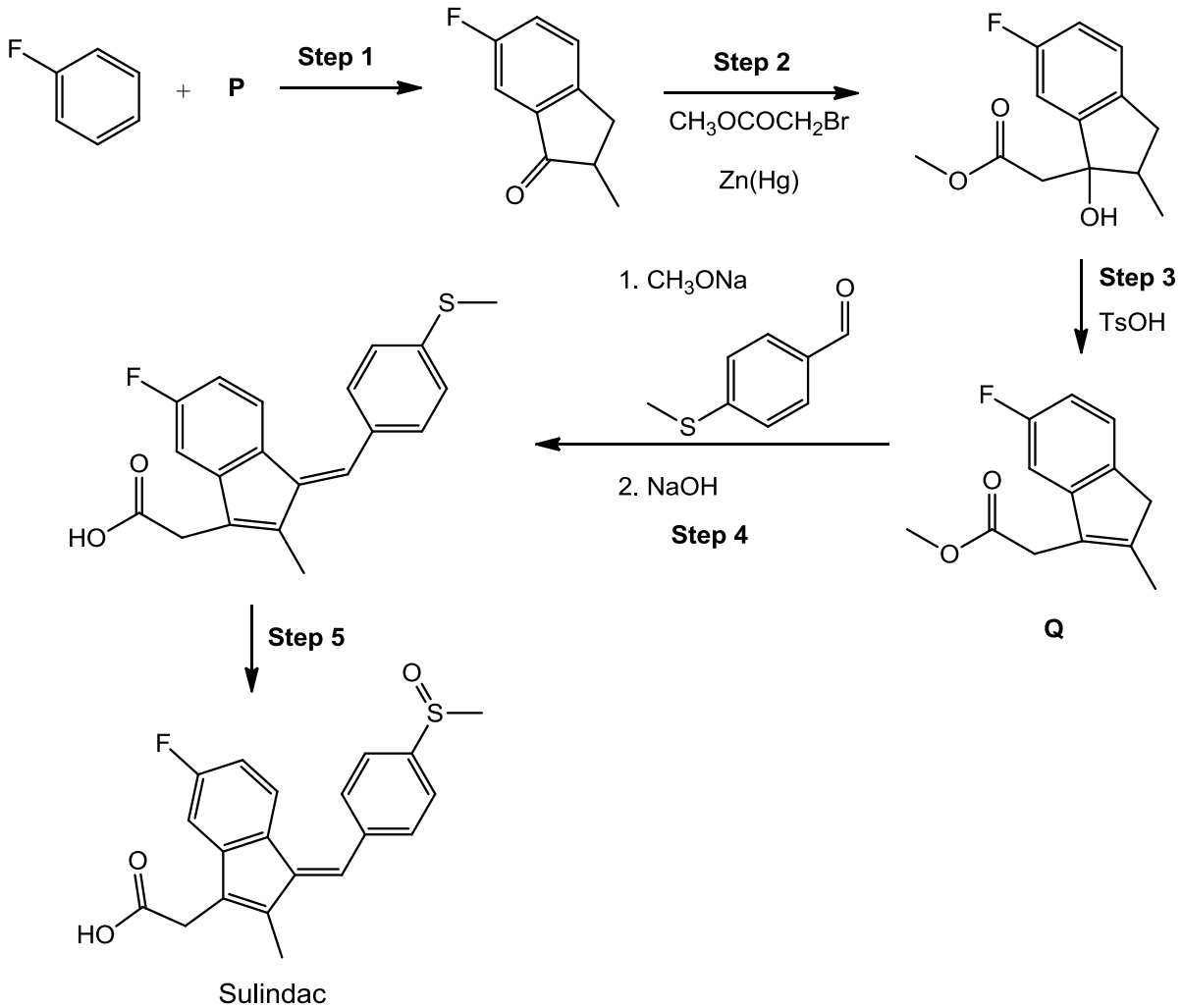
6 Sulindac is a non-steroidal anti-inflammatory drug (NSAID). It has an unusual property of reducing the growth of polyps and precancerous lesions in the colon, and may have other anti-cancer properties.



Sulindac

(a) Deduce the configuration of each C=C in sulindac. [2]

(b) Sulindac can be synthesized in the following manner:



(i) In Step 1, fluorobenzene reacts with compound **P** in the presence of a catalyst.

The mass spectrum of compound **P** contains peaks at m/e 228, 230 and 232 in a 1:2:1 ratio. The M^+ peak is at m/e 228. Additionally, there are two peaks of equal intensity at m/e 121 and 123.

Suggest structures corresponding to the peaks in the mass spectrum of compound **P**, and deduce the identity of the catalyst used. [4]

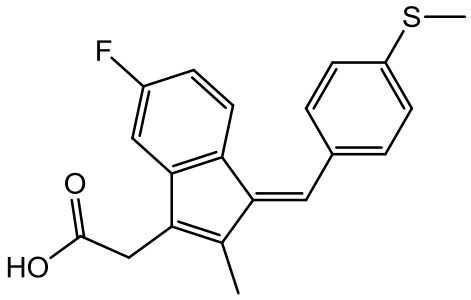
(ii) Name the types of reaction in Steps 2 and 3. [2]

(iii) In Step 4, the reaction starts off with the deprotonation of compound **Q** by sodium methoxide. Draw the structure of the conjugate base of compound **Q** and use it to explain why that particular proton was lost. [2]

(iv) Suggest the mechanism of the reaction in Step 4. You may start from the conjugate base of compound **Q** which you have drawn in **(b)(iii)**. [3]

(v) State the reagent used in Step 5. [1]

(c) Sulindac is metabolized in the body to give sulindac sulfide, which is the active drug. Suggest why sulindac is administered instead of its active metabolite sulindac sulfide.



Sulindac sulfide [2]

(d) The half-life of sulindac sulfide is 8 hours. During a course of treatment, a patient is given a dose of 100 mg of sulindac three times a day.

(i) Copy and complete the following table for as many lines as you need to determine the average steady state concentration of drug in the patient's body, in mg dm^{-3}.

Assume that the time taken for sulindac to be metabolized to sulindac sulfide is negligible, and that the blood volume of the patient is 5.0 dm^3.

time/h	amount of sulindac sulfide in body / mg	
	before dose	after dose
0	0	100
8		
16		
etc		

[3]

(ii) Sulindac was developed as a less toxic alternative to another NSAID, indomethacin.

The ratio between the toxic dose and the lowest effective dose is called the *therapeutic index*, TI.

$$TI = \frac{maximum\ dose\ before\ toxic\ symptoms\ occur}{minimum\ effective\ dose}$$

The maximum concentration of sulindac in the blood before toxic symptoms occur is 52 mg dm^{-3}.

Using the average steady state concentration calculated in part **(i)** as the minimum effective dose, calculate the therapeutic index of sulindac. [1]

[Total: 20]