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NANYANG JUNIOR COLLEGE
JC2 PRELIMINARY EXAMINATION
Higher 3

PHARMACEUTICAL CHEMISTRY 9812/01

Paper 1

29 September 2014

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, graphs or rough working.
Do not use staples, paper clips, highlighters, glue or correction fluid.

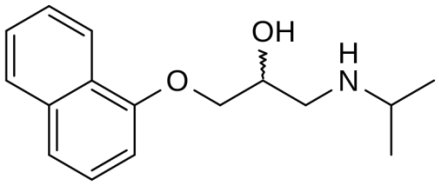
Answer any **five** questions.
At the end of the examination, fasten all your work securely together.

The number of marks is given in brackets [ ] at the end of each question or part question.
You may use a calculator.
You are reminded of the need for clear presentation in your answers.

[Turn over

1(a) Propranolol was the first successful beta blocker developed to treat hypertension. It was developed by the British scientist James W. Black in the 1960s. In 1988, he was awarded the Nobel Prize in Medicine for this discovery.

Propranolol acts as an antagonist to the β-adrenergic receptors in the smooth muscle tissues of the heart.



propranolol

(i) Describe what is meant by the terms *agonist* and *antagonist*. [2]

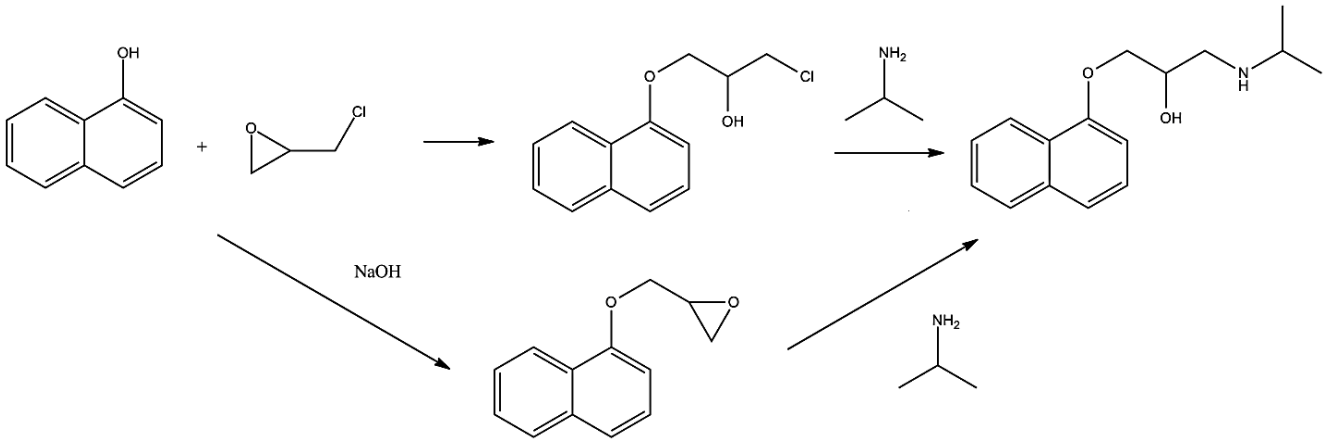
Propranol is sold as a racemate, a mixture of two isomers. The (R)-enantiomer is the beta-blocker for the heart and the (S)-enantiomer is a contraceptive.

(ii) Suggest why propranolol is sold as a racemate, even though only one of its enantiomers is useful for treating hypertension. [1]

(iii) Draw the two optical isomers of propranolol. [2]

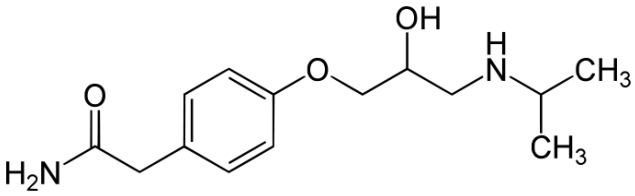
(iv) Suggest a method to separate the two isomers. [2]

Propranolol can be synthesised by the following two routes:



(v) Suggest a mechanism for **either** one of the routes. [4]

(b) Atenolol is another beta-blocker that was developed much later, in 1976, as a replacement for propranolol. Unlike propranolol, it does not pass through the blood-brain barrier easily thus avoiding various central nervous system side effects.

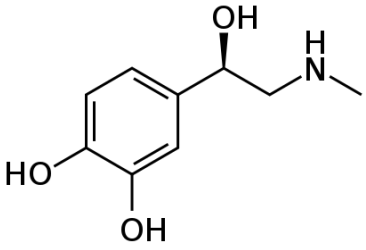


atenolol

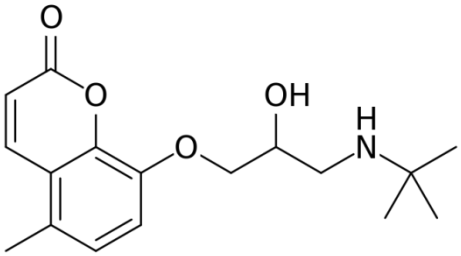
(i) Outline the processes that are likely to occur when propranolol crosses the blood-brain barrier at physiological pH 7.4. [3]

(ii) Suggest why atenolol crosses the blood-brain barrier less easily than propranolol. [1]

(c) Adrenaline (also known as epinephrine) is a hormone and a neurotransmitter. Bucumolol is a β-adrenergic blocking agent, like propranolol.

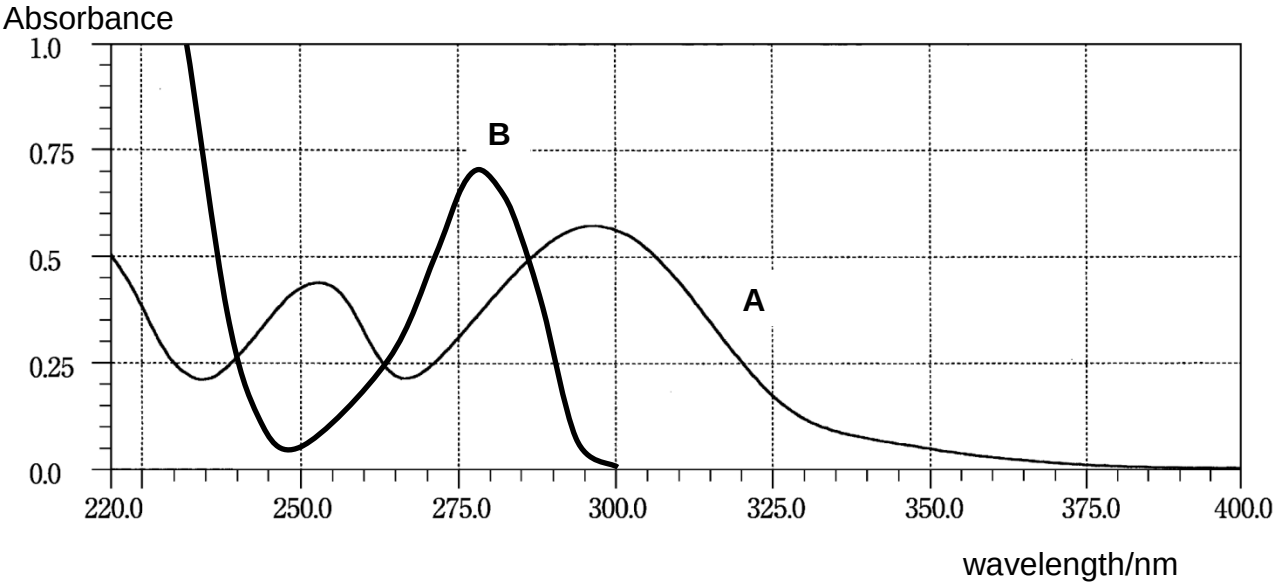


adrenaline



bucumolol

The graphs below show the UV absorption spectra **A** and **B** of two solutions, one containing adrenaline and the other containing bucumolol, each at an equal concentration of 2.5 x 10^{-4} mol dm^{-3}. The cells used had an optical path length (*l*) of 1.0 cm.



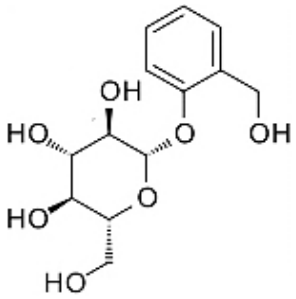
(i) Identify the two spectra, **A** and **B**, with appropriate reasons. [2]

(ii) A new sample containing a mixture of the two compounds was collected and analysed in a UV spectrophotometer at 280 nm and 300 nm. The absorbance at each wavelength was recorded below.

Wavelength/nm	Absorbance
280	0.88
300	0.42

Determine the concentrations of adrenaline and bucumolol in the new sample. [3]

2(a) Salicin is an analgesic which can be isolated from willow bark. It is closely related in chemical make-up to aspirin and its action is also very similar to aspirin.



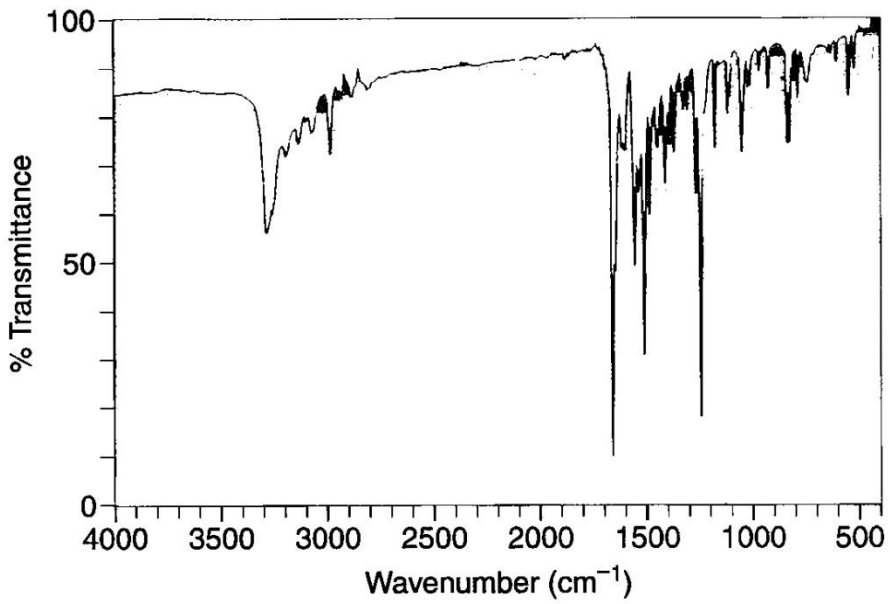
salicin

(i) Outline the different ways in which narcotic and non-narcotic analgesics relieve pain. [2]

(ii) State one advantage and one disadvantage of using salicin instead of paracetamol. [2]

(iii) Draw the Newman projection to illustrate the stable chair conformation of the six-membered ring in salicin. [1]

(b) Compound **D** is another analgesic compound containing C, H, N and O. Its IR, ^{1}H NMR and mass spectra are given below.



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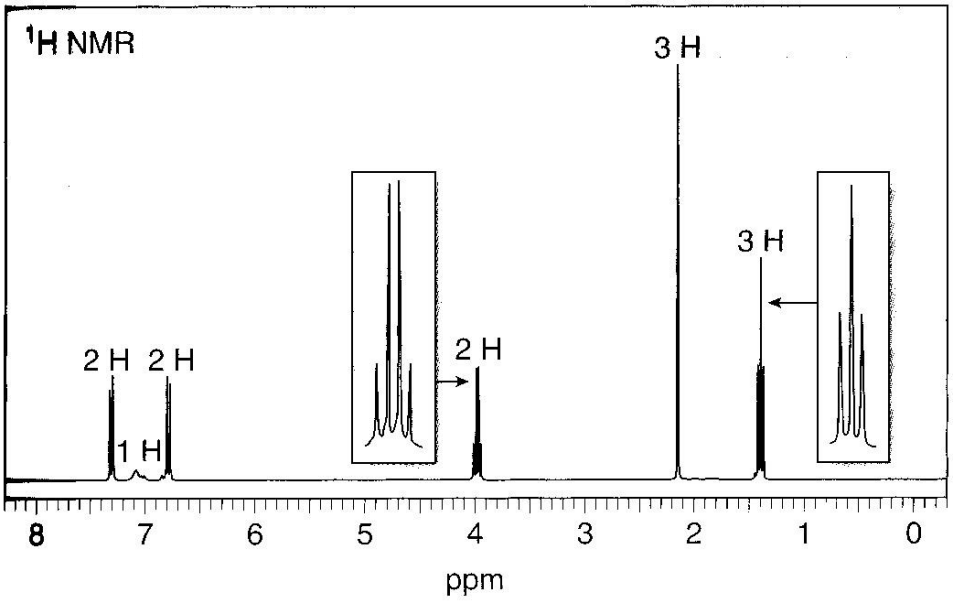
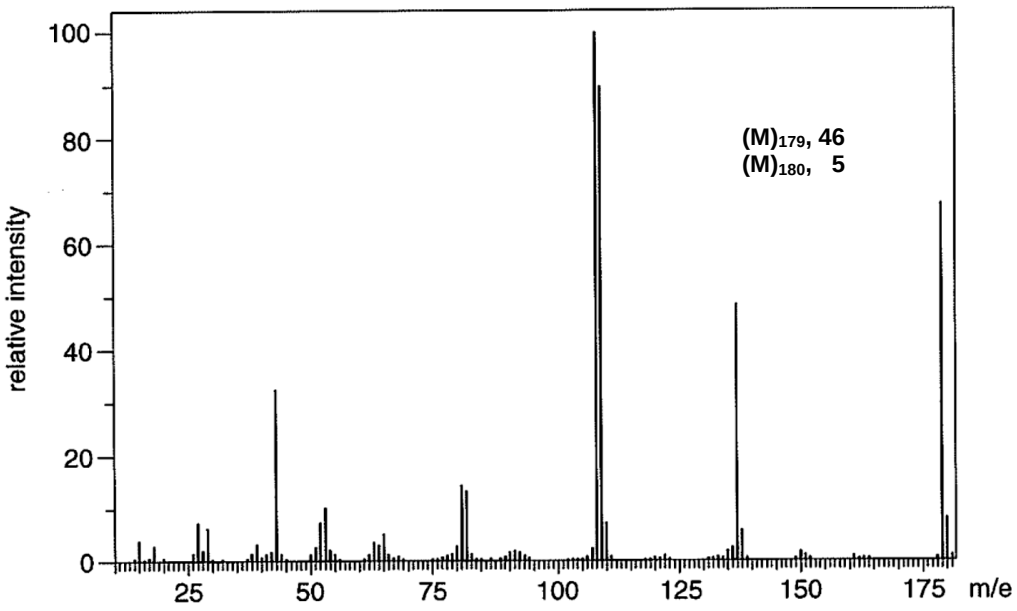
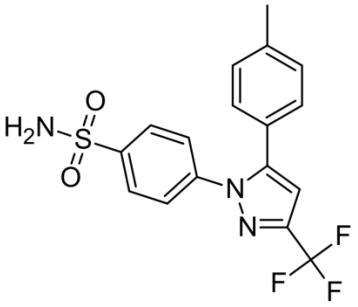


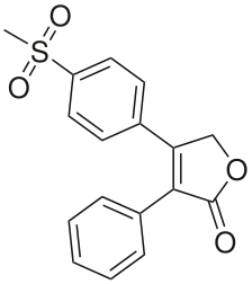


Deduce the molecular formula and the structural formula of compound **D**. Show your reasoning. [10]

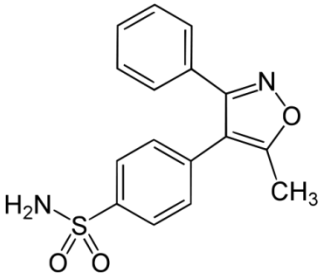
(c) Drugs such as celecoxib, rofecoxib and valdecoxib have been developed to be selective for the COX-2 isozyme, so that only the production of inflammatory prostaglandins is reduced. Such drugs would be better that aspirin as they do not cause any stomach bleeding by inhibiting COX-1.



celecoxib



rofecoxib



valdecoxib

A clinical trial was set up to evaluate how the analgesic activities of celecoxib, rofecoxib and valdecoxib compared to each other. Every 8 hours, hospital patients with chronic osteoarthritis pain were given, at random, capsules containing either celecoxib, rofecoxib, rofecoxib or an inert compound **X**. The patients were asked to assess the pain they felt two hours after each administration, on a 4-point scale (4 corresponding to severe pain; 3 for moderate pain; 2 for slight pain and 1 for no pain at all). Sometimes the patients were not given any medication at all, but were still asked to assess the pain they felt after 2 hours. The results for 100 patients over 1 week were as follows.

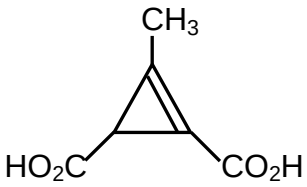
Substance	Average pain score
celecoxib	1.2
rofecoxib	2.4
valdecoxib	1.8
X	2.5
none	3.6

(i) What is the placebo effect? Explain how the above data illustrate this effect. [2]

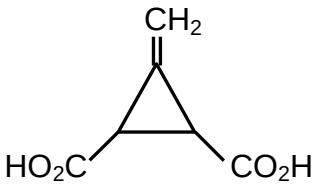
(ii) Use the above data to suggest which part of the three compounds shows greater effectiveness as an analgesic. [2]

(iii) Two of the drugs, rofecoxib and valdecoxib, were withdrawn in 2004 and 2005 respectively because long term use led to an increased risk in heart attacks in patients. Suggest a reason why even after extensive clinical trials, a drug can to be withdrawn from the market. [1]

3(a) Feist's acid, $C_6H_6O_4$, was discovered by Feist in 1893, from a deceptively simple reaction by the action of hot, concentrated hydroxide on 3-bromo-5- ethoxy-carbonyl-4,6-dimethyl-2-pyrone. Based on IR spectra, it was assigned structure **I** below.



Structure **I**



Structure **II**

Sixty years later, in 1950s, when the first NMR was invented, its structure was proved to be that of Structure **II**.

(i) IR and NMR spectroscopy are used to provide structural information about organic compounds. Outline the principles underlying these two forms of spectroscopy. [4]

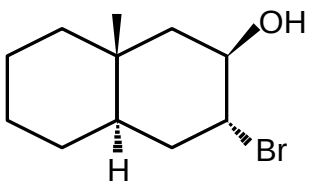
(ii) Based on Structure **I**, what are the absorptions that would be present in the IR spectrum? [2]

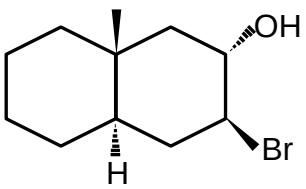
(iii) What evidence in the NMR spectrum would show that it is Structure **II** and not Structure **I**? [2]

(iv) What types of stereoisomerism are present in Structure **II**? Explain your answer. [2]

(v) Given that Feist's acid is optically active, draw the correct stereoisomer of Feist's acid. [1]

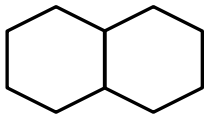
(b) Which of these two compounds would form an epoxide on treatment with a base? Explain with a mechanism of the reaction.



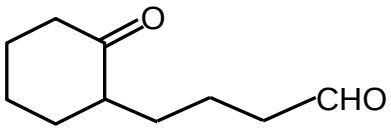


[3]

(c) An unknown compound **E** of molecular formula $C_{10}H_{18}O$ reacts with hot concentrated sulfuric acid to form two compounds, **F** and **G**, of molecular formula $C_{10}H_{16}$. **F** and **G** both react with hydrogen in the presence of platinum to form decalin. Mild oxidation of **F** forms **H**, and mild oxidation of **G** forms a diketone **J** of molecular formula $C_{10}H_{16}O_2$. Identify the structures of compounds **E**, **F**, **G** and **J**.



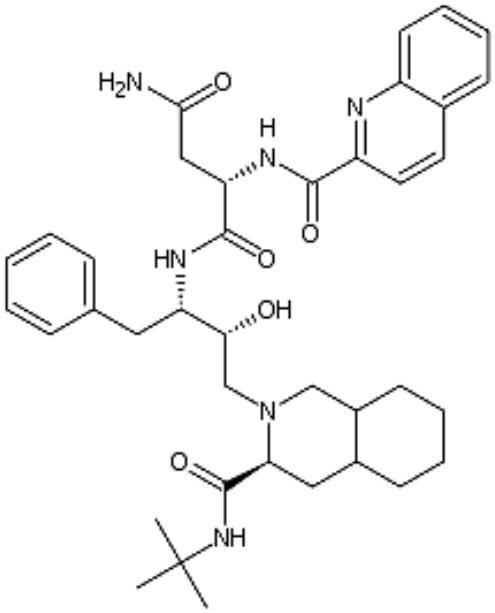
decalin



H

[6]

4(a) Saquinavir (trade name Invirase) belongs to a class of drugs called protease inhibitors, which are used to treat HIV (human immunodeficiency virus).



Saquinavir

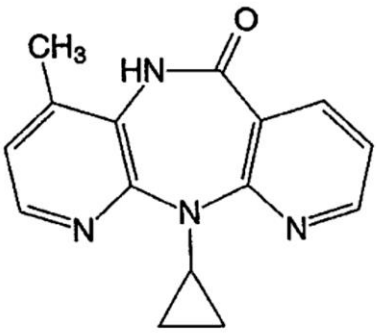
(i) What is understood by the terms competitive and non-competitive inhibitor? [2]

(ii) Locate all the chiral centres in saquinavir, and label each as R or S. [4]

(iii) Draw the enantiomer of saquinavir. [1]

(b) A natural product was isolated in the laboratory, and its observed rotation was –8° when measured in a 1 dm sample tube containing 2.5 g of compound in 10 cm^3 of water. What is the specific rotation of this compound? [2]

(c) Nevirapine (trade name *Viramune*) is another antiviral drug used to treat HIV-1 infection and AIDS. It is an allosteric inhibitor to the essential HIV-1 reverse transcriptase viral enzyme, which transcribes viral RNA into DNA.

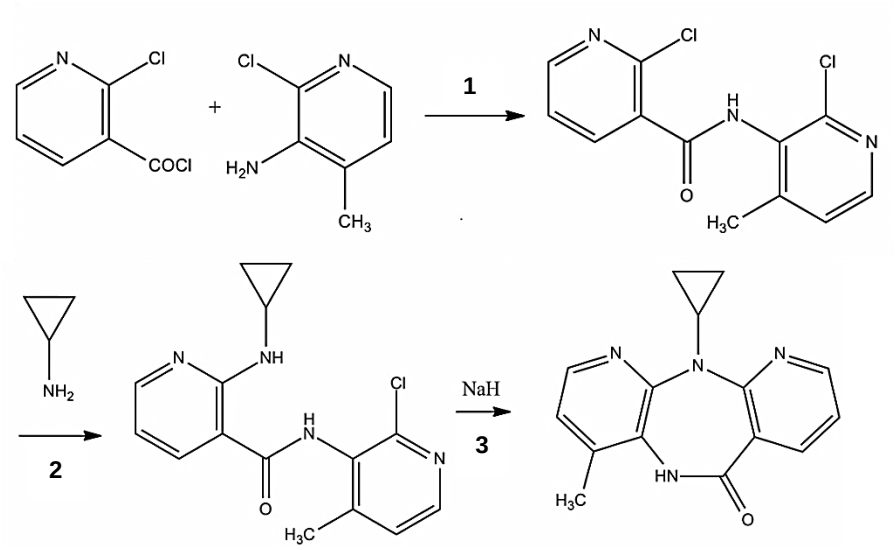


nevirapine

(i) Explain the term *allosteric inhibitor*. [1]

(ii) Outline the ways in which antivirals work, giving an example of each. [3]

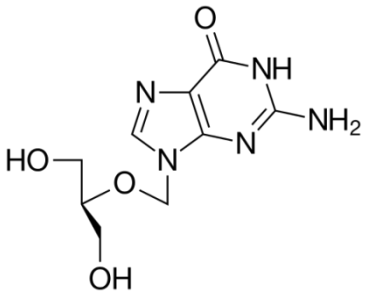
Nevirapine can be synthesised from two pyridine derivatives and cyclopropylamine as shown below.



(iii) What kind of reaction is step 2? [1]

(iv) Suggest the mechanism for step 2. [2]

(d) Ganciclovir is an antiviral medication used to treat or prevent cytomegalovirus infections.



ganciclovir

Ganciclovir was prescribed for a patient every 12 hours for a week starting at 0700h on the first day. The dose consists of a single 100 mg intravenous injection. The half-life of ganciclovir in the body is 4 hours.

(i) Other than intravenous injections, suggest two other ways drugs can be administered to the body. [2]

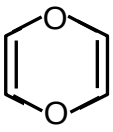
(ii) Calculate, to three significant figures, the equilibrium maximum and minimum amounts of ganciclovir in the body. These are reached after 3 doses. [2]

5(a) **(i)** Compare the relative aromaticity of furan, thiophene and pyrrole. [2]

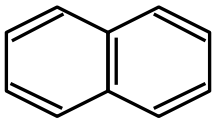
(ii) For each of the following species decide whether it is aromatic or not. Explain your decisions.

cyclobutadiene

tropylium cation



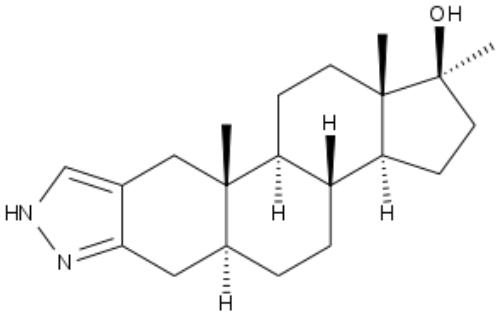
1,4-dioxin



naphthalene

[4]

(b) Stanozolol is an anabolic steroid that promotes muscle growth and is commonly used as a performance enhancing drug by athletes and body builders. It has been banned from use in sports competition under the auspices of the International Association of Athletics Federations (IAAF).



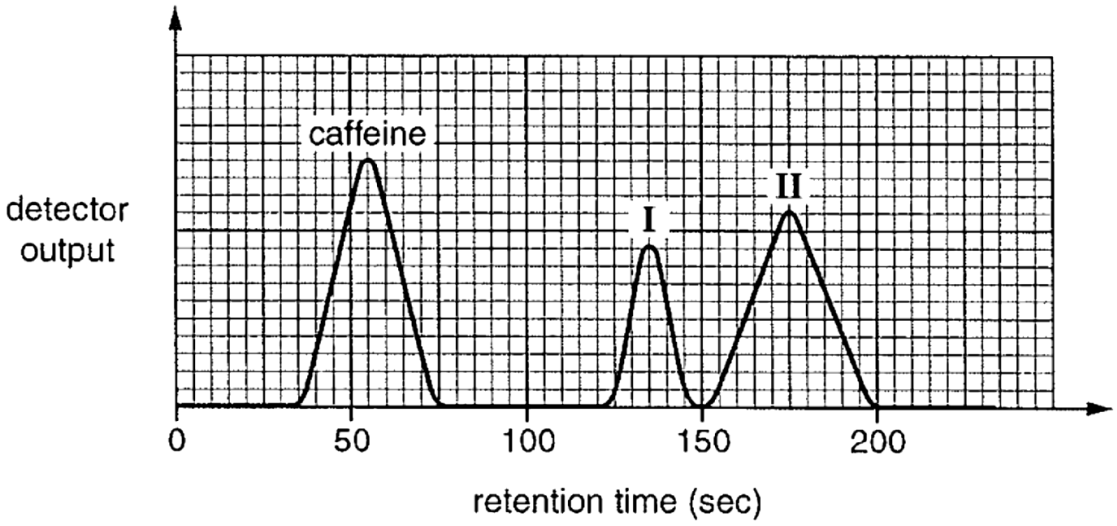
stanozolol

The drug has a high oral bioavailability which allows it to survive first-pass liver metabolism when ingested.

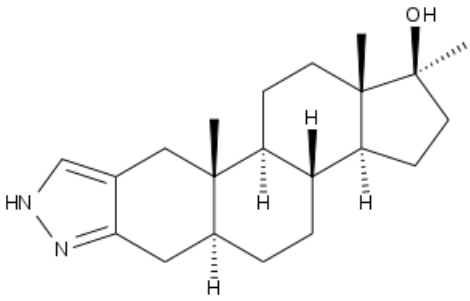
(i) Of the two nitrogen atoms in the pyrazole ring, which one is more basic? Explain your answer. [2]

(ii) What is meant by high oral bioavailability? [1]

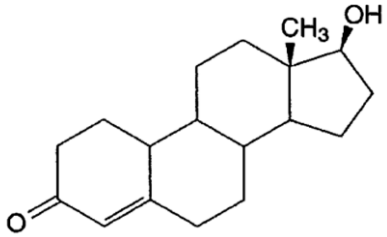
(c) At major athletic competitions, urine samples are taken randomly from athletes and analysed by HPLC for such anabolic steroids. An analysis was carried out of a sample derived from 1 cm^3 of an athlete's urine to which a known amount of caffeine had been added as an internal standard.



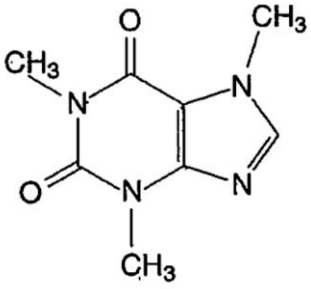
The two peaks **I** and **II** were identified as being due to the two anabolic steroids nandrolone and stanozolol (not necessarily in that order).



stanozolol



nandrolone



caffeine

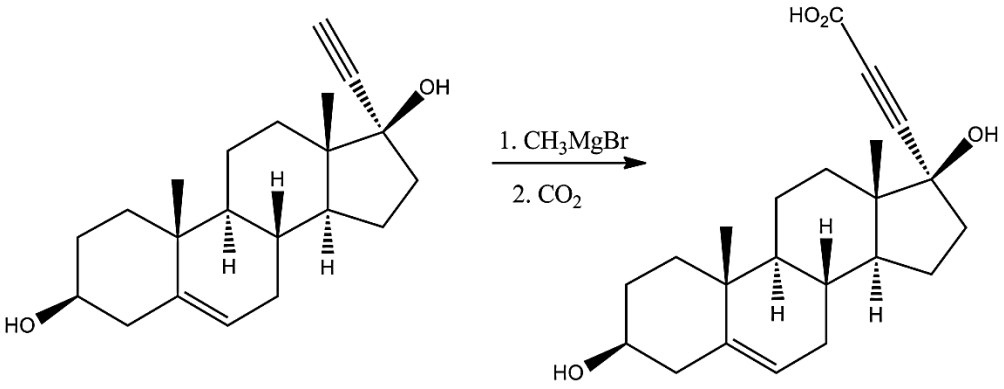
(i) By considering the polarities of the three molecules and the retention times of the three peaks, decide

- whether normal or reverse-phase HPLC was used to analyse the mixture
- which of the two anabolic steroids is responsible for each of the two peaks **I** and **II**.

Explain your reasoning. [2]

(ii) Given that the concentration of caffeine in the urine sample is 2.0×10^{-6} g dm^{-3}, calculate the concentrations of the two anabolic steroids. [3]

(d) Spironolactone is a drug primarily used to treat heart failure which contains a lactone ring. It acts predominantly as an antagonist of the mineralocorticoid and androgen receptors. One of the steps in its synthesis is as follows:



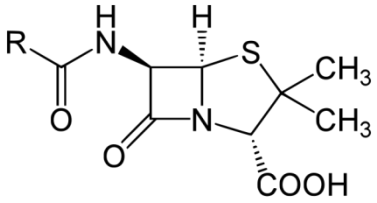
(i) Explain the use of the Grignard reagent, CH_3MgBr, followed by CO_2 in the above step. [2]

(ii) Suggest the mechanism for the intramolecular esterification of 4-hydroxybutanoic acid to form a lactone. [4]

6(a) **(i)** Describe the differences between the IR spectra of carbon disulfide and water. [2]

(ii) Predict the number of absorptions in the IR spectrum of carbon oxysulfide, O=C=S, and describe the vibrations that give rise to these absorptions. [2]

(b) Penicillin is the name given to a group of antibacterial drugs derived from *Penicillium* fungi. Discovered in 1928 by Alexander Fleming, they are the first drugs that were effective against many previously serious diseases and infections.



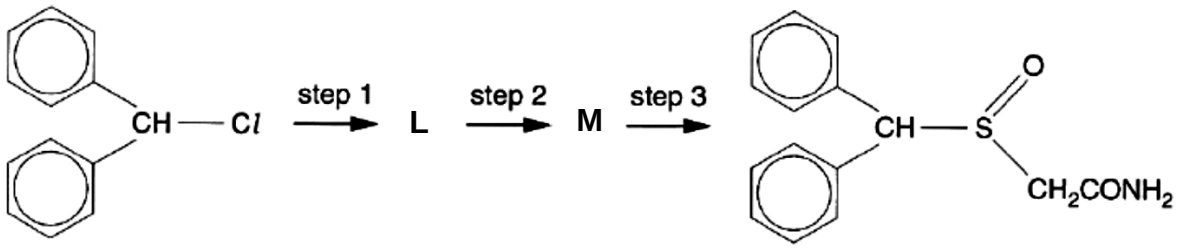
penicillin

(i) There are two amide links in penicillin. Which one is more easily hydrolyse? Explain your answer. [2]

(ii) Explain how penicillins work against bacteria. [2]

(iii) One of the problems with the use of penicillins is that bacteria can develop a resistance to them. Explain how the resistance of a population of bacteria can develop, and hence explain why it is always important for a patient to complete a course of antibiotic treatment, even if the symptoms of the infection have disappeared. [2]

(c) The drug modafinil is a central nervous system stimulant, which is sometimes prescribed to relieve excessive sleepiness and fatigue. It can be synthesised from diphenylchloromethane and bromoethanamide, $BrCH_2CONH_2$, by a 3-step route.



diphenylchloromethane modafinil

(i) Explain what is meant by the term stimulant. [1]

(ii) Suggest structures for the intermediates **L** and **M**, and suggest reagents and conditions for the three steps 1–3. [5]

(iii) Suggest a three-step route for the synthesis of diphenylchloromethane from methylbenzene and benzene. [4]