NANYANG JUNIOR COLLEGE
JC2 PRELIMINARY EXAMINATION
Higher 3

# ANSWERS

## 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.

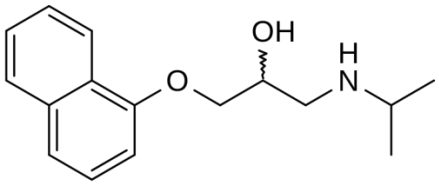
The number of marks is given in brackets [ ] at the end of each question or part question.
You may use a calculator.
You are reminded of the need for clear presentation in your answers.



**[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]

**Answers:**

**An agonist is a drug which mimics the natural ligand for a receptor.** ❶
**An antagonist is a drug which docks well to the binding site, but does not cause the required change of shape of the receptor.** ❶

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.

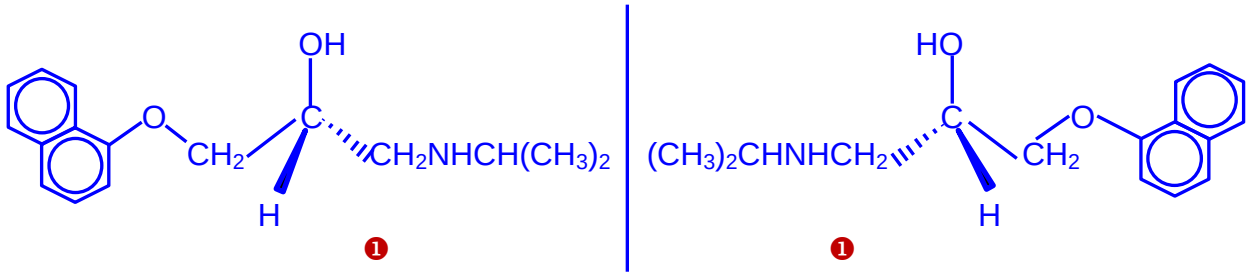
**(ii)** Suggest why propranolol is sold as a racemate, even though only one of its enantiomers is useful for treating hypertension. [1]

**Answers:**

**The other enantiomer is not hazardous for the body and it is cheaper to produce the racemate. Unless the person taking the drug is a woman who wants to get pregnant, the racemate should not cause any problems.** ❶

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

**Answers:**




❶ ❶

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

**Answers:**

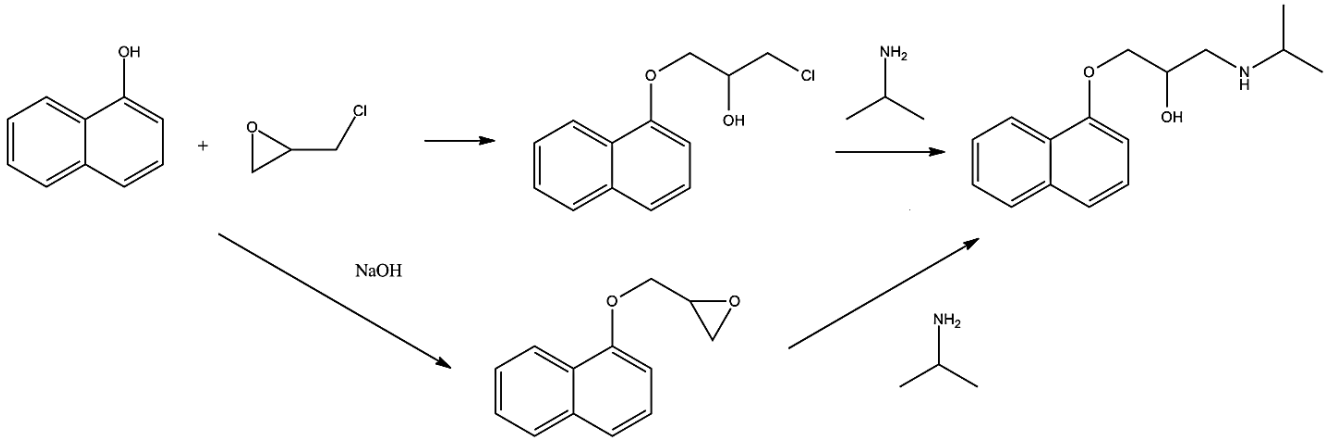
**Using chiral chromatography, where samples are separated or resolved by HPLC using a column packed with silica bonded to a chiral reagent such as cyclodextrin or hexahelicene to yield a chiral stationary phase.** ❶

**Enantiomers present in the sample interact differently with the chiral stationary phase and this forms the basis of the separation.** ❶

**or**

**The second method is to react the racemic mixture with an optically active compound to form two diastereomers with slightly different physical properties so that separation can be achieved.** ❶ ❶

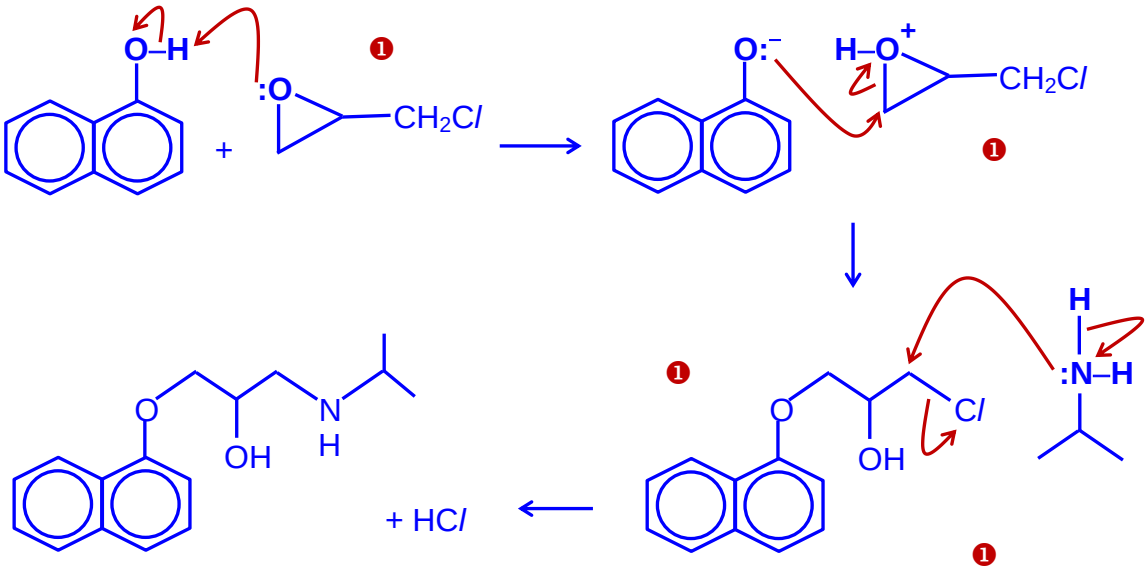
Propranolol can be synthesised by the following two routes:



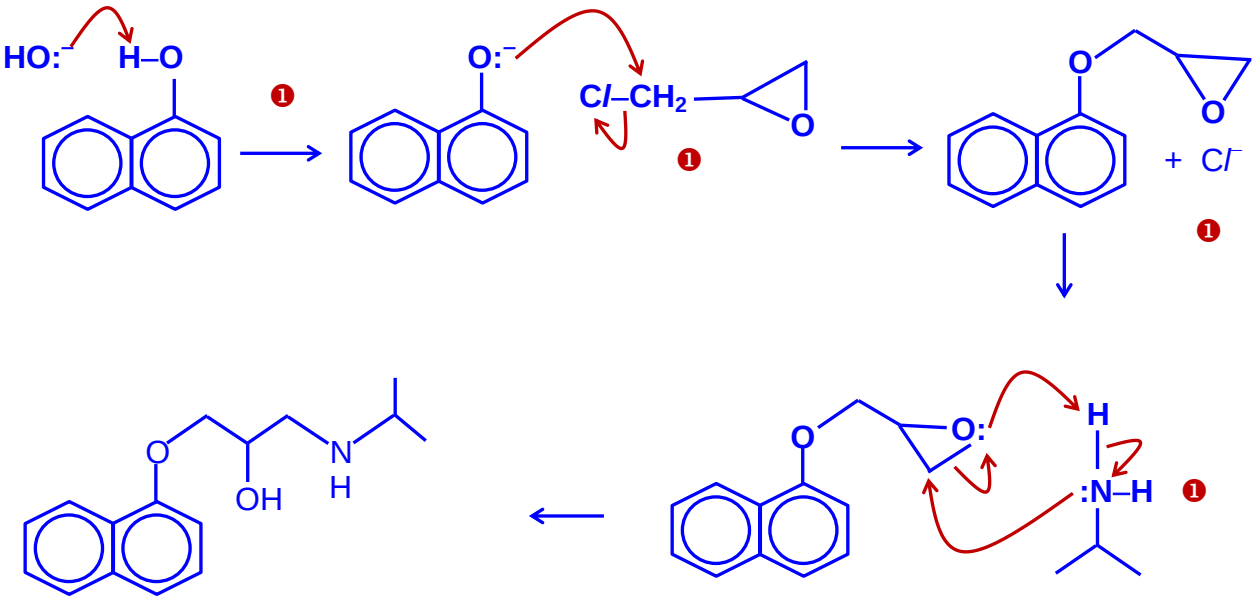

**(v)** Suggest a mechanism for **either** one of the routes. [4]

**Answers:**

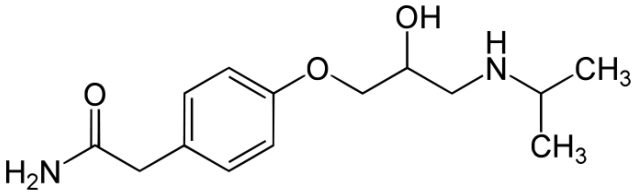
**Route 1**



**Route 2**



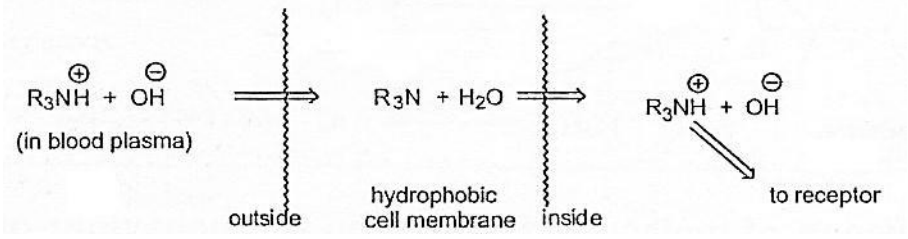

**(b)** Atenolol is another beta-blocker that was developed much later, in 1976, as a replacement for propranolol. Unlike propranolol, it does not pass through the blood-brain barrier easily thus avoiding various central nervous system side effects.




atenolol

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

**Answers:**




**The amine group in propranolol can exist in both the ionised and unionised forms at pH 7.4. Both forms are in rapid equilibrium with each other.** ❶

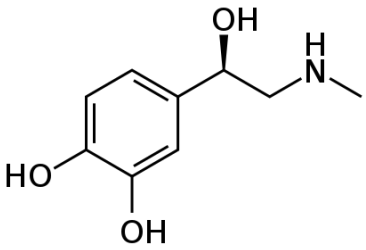
**This allows the amines to interact strongly with binding sites on receptors, when in their ionised form, but also to pass through plasma membranes, in their unionised form.** ❶

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

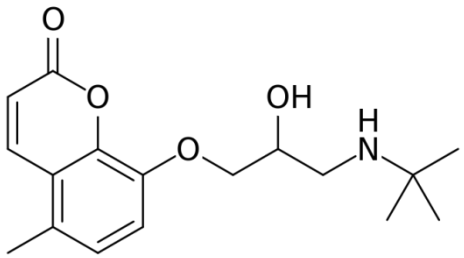
**Answers:**

**Atenolol has an extra amide group which is polar but not ionisable compared to propranolol and it is therefore more difficult for atenolol to pass through the hydrophobic cell membrane of the blood-brain barrier.** ❶

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

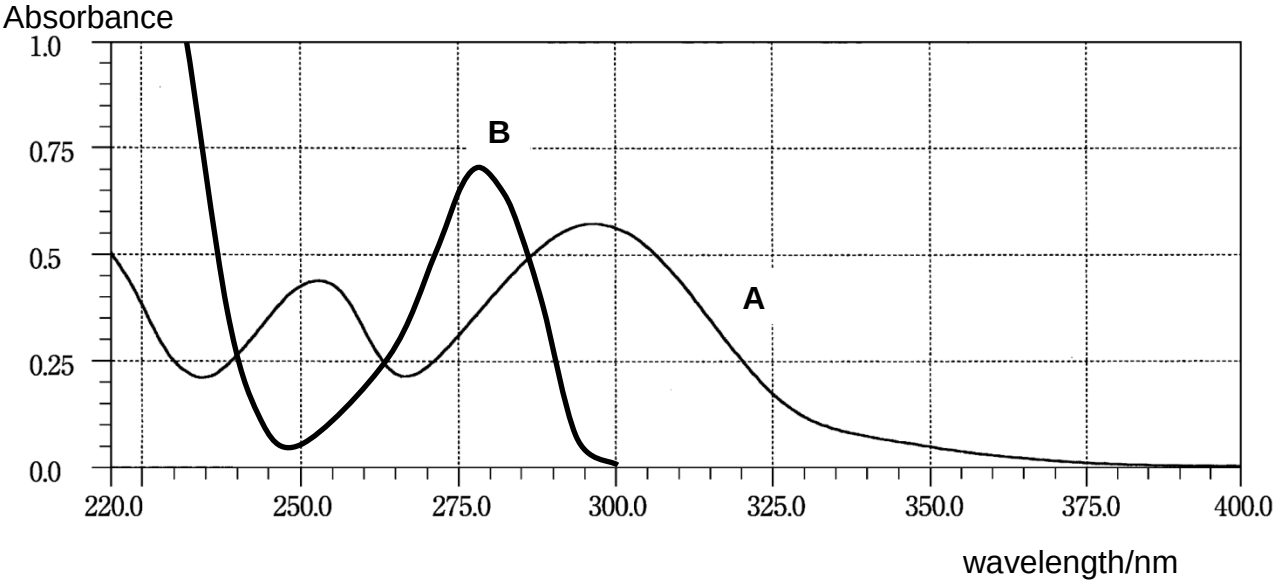



adrenaline




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.






**[Turn over**

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

**Answers:**

**Spectrum A belongs to bucumolol and spectrum B is that of adrenaline. There is higher degree of conjugation in bucumolol which causes the energy gap of $\pi \rightarrow \pi^*$ to decrease shifting the UV absorption to longer wavelength.** ❶

**(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]

**Answers:**

**Assumption: At 300 nm, there is no absorption due to adrenaline.**

**Therefore, [bucumolol] = $\frac{0.42 \times 2.5 \times 10^{-4}}{0.55} = 1.91 \times 10^{-4}$** ❶

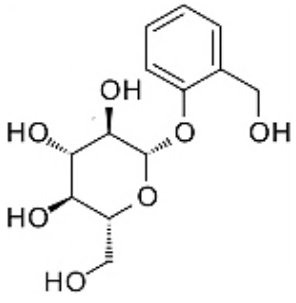
**Absorbance due to bucumolol at 280 nm = $\frac{0.375 \times 1.91 \times 10^{-4}}{2.5 \times 10^{-4}}$**

**= 0.286** ❶

**Absorbance due to adrenaline at 250 nm = 0.88 – 0.286 = 0.593**

**[adrenaline] = $\frac{0.593 \times 2.5 \times 10^{-4}}{0.7} = 2.12 \times 10^{-4}$ mol dm$^{-3}$** ❶

**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]

**Answers:**

**A narcotic analgesic is a substance that depresses the transmission of pain signals from one nerve cell to another in the central nervous system (CNS) by acting as agonist to the receptors.** ❶

**A non-narcotic analgesic work on the pain receptors themselves, preventing them from responding normally to pain stimuli by inhibiting the formation of prostanglandins.** ❶

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

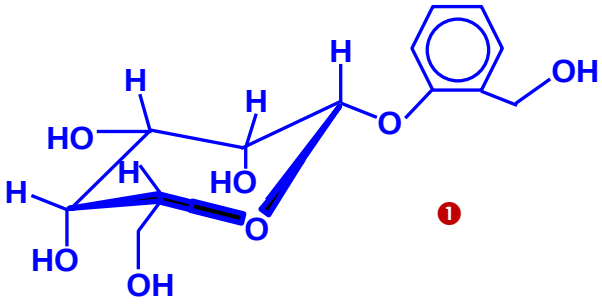
**Answers:**

**Advantage: It has anti-inflammatory effect.** ❶

**Disadvantage: It has anticoagulant property and can cause stomach bleeding and ulcers on prolong usage.** ❶

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

**Answers:**

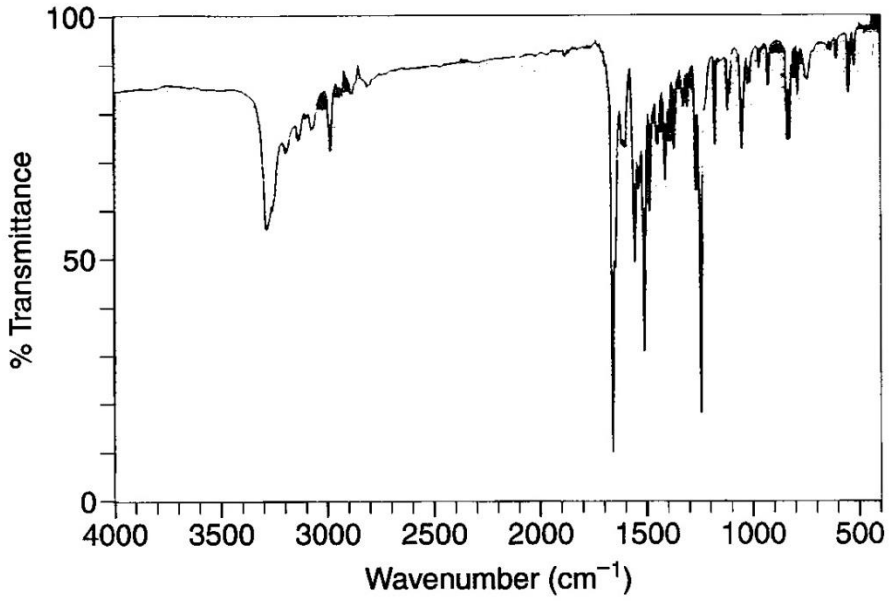


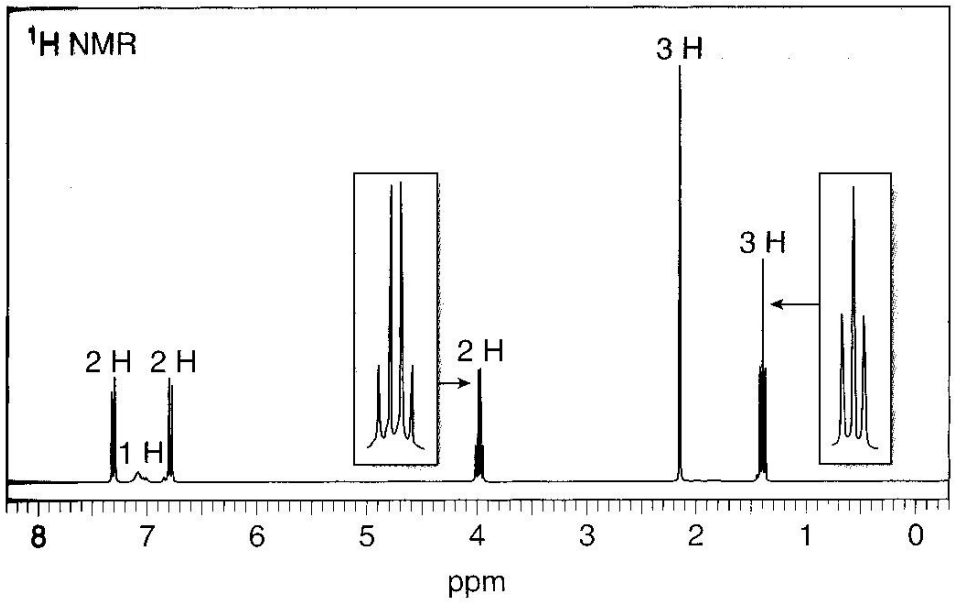

❶



**[Turn over**

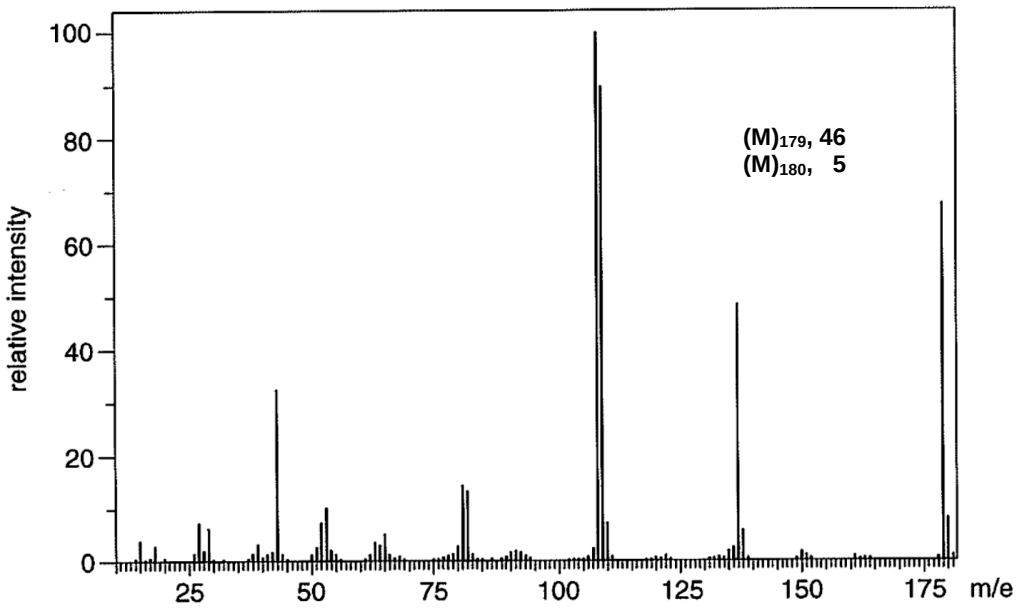
**(b)** Compound **D** is another analgesic compound containing C, H, N and O. Its IR, $^1$H NMR and mass spectra are given below.






**[Turn over**




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

**Answers:**

**Answers:**

**From the mass spectrum:**

**No. of C atoms = $\frac{100 \times 5}{1.1 \times 46}$ = 9.88 ~ 10** ❶

**Since $M_r$(179) is odd number, there is only one N atom.**

**From the NMR spectrum, there are 13 H atoms.**

**Therefore, no. of O atoms = $\frac{179 - (10 \times 12) - 14 - 13}{16}$ = 2.**

**Molecular formula of compound D is $C_{10}H_{13}NO_2$.** ❶

**From C:H ratio, likely presence of benzene ring.**

**From the IR spectrum:**

**Peak at 3300 $cm^{-1}$ ⇒ NH or OH vibrations**
**Peak at 1680 $cm^{-1}$ ⇒ C=O vibration**
**Peak at 1280 $cm^{-1}$ ⇒ C–O vibration** ❷

**From NMR spectrum:**

| δ | splitting | integration | deduction |
|---|---|---|---|
| 1.4 & 4.0 | triplet & quartet | 3H & 2H | A $CH_3CH_2$– (ethyl) group near a benzene ring or electronegative N or O atom ❶ |
| 2.2 | singlet | 3H | A $CH_3$– group near a benzene ring or electronegative N or O atom ❶ |

| | | | |
|---|---|---|---|
| **7.2** | **singlet** | **1H** | **An NH group of an amide** ❶ |
| **6.8 & 7.3** | **2 doublets** | **4H** | **4 protons in a disubstituted benzene ring.** ❶ |

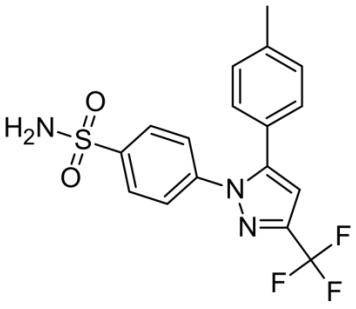
**From mass spectrum:**

| m/e | deduction |
|---|---|
| **179** | **Molecular ion peak or $C_{10}H_{13}NO_2^+$** |
| **137** | **179 – 137 = 42 ⇒ loss of ketene group ($CH_2$=C=O) ⇒ amide or ester group present.** ❶ |
| **108** | **137 – 108 = 29 ⇒ loss of an ethyl group.** ❶ |
| **43** | **Likely a $CH_3CO^+$ formed.** ❶ |

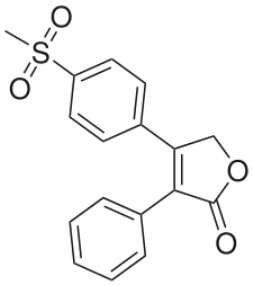
**Structure of compound D is** $CH_3CONH$–C$_6$H$_4$–$OCH_2CH_3$. ❶

**10 marks out of 12 marking points**

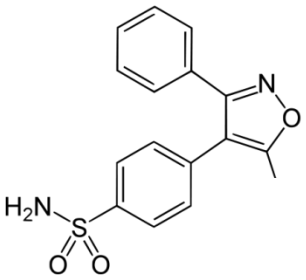
**(c)** Drugs such as celecoxib, rofecoxib and valdecoxib have been developed to be selective for the COX-2 isozyme, so that only the production of inflammatory prostaglandins is reduced. Such drugs would be better that aspirin as they do not cause any stomach bleeding by inhibiting COX-1.



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]

**Answers:**

**The placebo effect is defined as the measurable, observable, or felt improvement in health not attributable to treatment.** ❶

**The average pain score for the inert compound X was less than that for none illustrate the presence of the placebo effect.** ❶

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

**Answers:**

**Celecoxib has the lowest pain score showing that it is most effective. It contains three N atoms compared with valdecoxib which has one N atom and is the second most effective. Rofecoxib has no N atom and is the least effective of the three. Therefore, it shows that the presence of N atoms make the compound more effective as an analgesic.** ❷

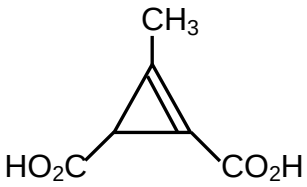
**(iii)** Two of the drugs, rofecoxib and valdecoxib, were withdrawn in 2004 and 2005 respectively because long term use led to an increased risk in heart attacks in patients. Suggest a reason why even after extensive clinical trials, a drug can to be withdrawn from the market. [1]

**Answers:**

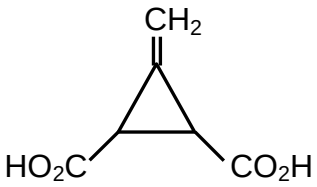
**Any one of the following reasons:** ❶

- **The clinical trials do not involve a very big sample and not all the side effects of the drug can be observed.**
- **The time for conducting the trials is short and some long-term effects are not seen.**
- **Different people react differently to the drugs and not all the side effects can be seen.**

**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]

**Answers:**

**IR spectroscopy:**

**Photons in the infrared region have insufficient energy to promote electrons, but they can bring about an increase in the vibrational energy of the covalent bonds in simple molecules. The various stretching and bending vibrations of a bond occur at certain quantised frequencies. When infrared light of that same frequency is incident on the molecule, energy is absorbed and the amplitude of that vibration is increased. Not all vibration modes are infrared active. Only those bonds which have a dipole moment are capable of absorbing infrared radiation.** ❷

**NMR spectroscopy:**

**In the presence of an applied magnetic field, the two equivalent spin states of a proton is split into two levels with a small energy difference within the radio frequency region.**
**When radio frequency of the right wavelength is passed through the substance, the nuclei aligned with the applied field can absorb this energy and change their spin orientation to that against the field. A signal can be detected and this phenomenon is called nuclear magnetic resonance.** ❷

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

**Answers:**

**Absorptions for C=C at 1610 to 1680 $cm^{-1}$, C–O at 1000 to 1300 $cm^{-1}$, C=O at 1680 to 1750 $cm^{-1}$ and O–H at 2500 to 3300 $cm^{-1}$ for 'hydrogen-bonded' acids.** ❷

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

**Answers:** ❶

**No singlet peak for 3 H atoms at δ 0.9 but a singlet peak at δ 4.5 to 6.0 for 2 H atoms for the $CH_2$ group outside the cyclopropane ring.** ❶

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

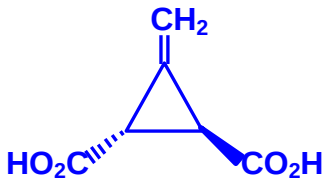
**Answers:** ❶

**Optical isomerism for the two chiral carbon atoms attached to the $CO_2H$ groups and cis/trans or geometric isomerism for the 2 $CO_2H$ groups in the ring.** ❶

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

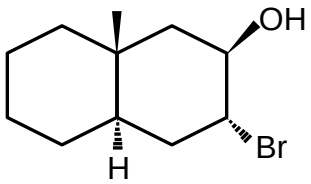
**Answers:**

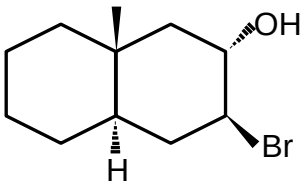
**The cis isomer has a plane of symmetry and is not optically active. Therefore the trans isomer is the optically active isomer.**




❶

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



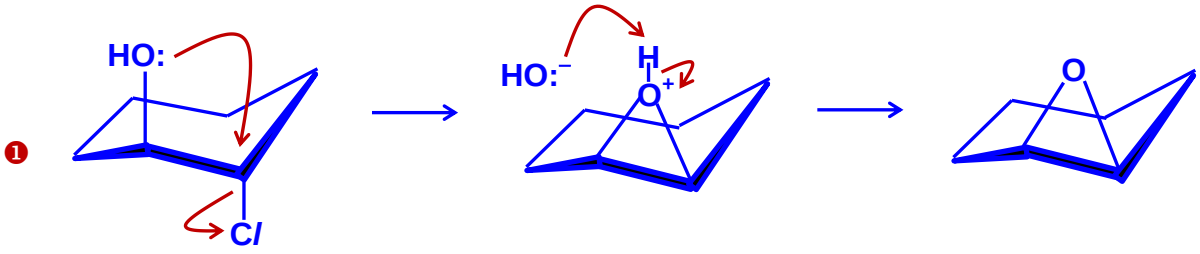




[3]

**Answers:**

**The 1st isomer is the trans isomer where both OH and Br are in axial positions and the 2nd isomer is the cis isomer where both OH and Br are in equatorial positions.**

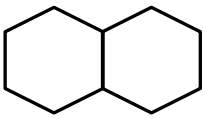
**The trans isomer can undergo $S_N2$ nucleophilic substitution to form the epoxide.**



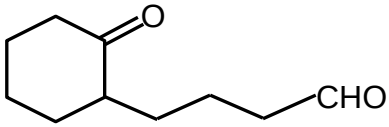

**trans isomer**

**The OH group can attack the C–Cl from the back (backside attack) and form a pentavalent activated complex which can break the C–Cl bond to form the epoxide.**

**(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

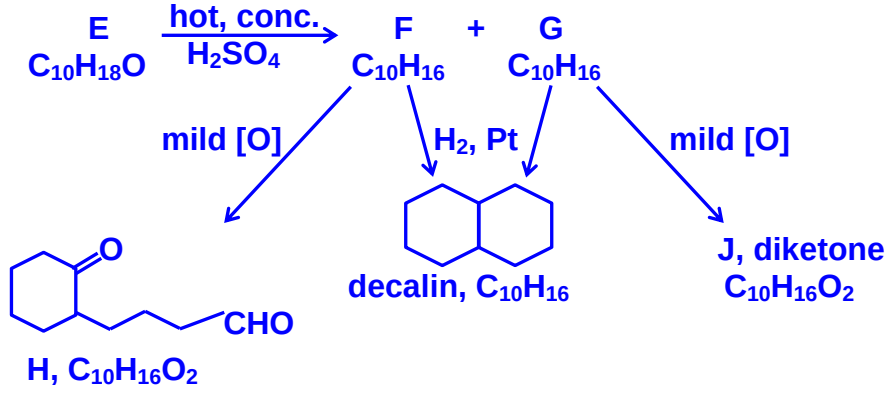



**H**

[6]

**Answers:**

**The flow-chart is as follows:**

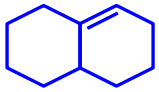




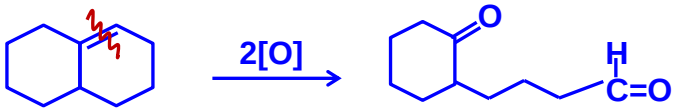

**[Turn over**

**From the flow-chart,**

- **decalin has 2 H atoms more than F and G ⇒ F and G has the decalin structure but with one C=C bond each** ❶
- **on mild oxidation, the C=C bond breaks and each C then gets an O atom ⇒ F must have this structure:**

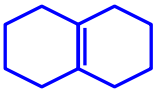
 ❶

**On oxidation,**

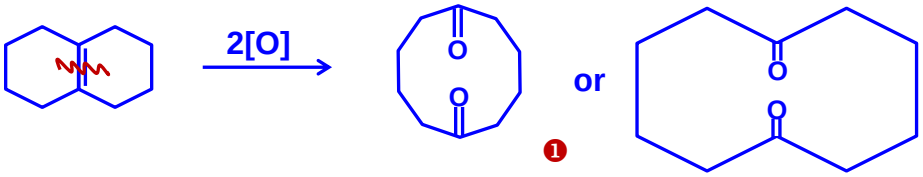



**compound H**

- **G gives a diketone on oxidation ⇒ the C=C double bond in G is in a highly substituted region, i.e. G is** ❶

 ❶

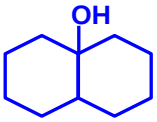
**which on oxidation:**




❶

**J, diketone**

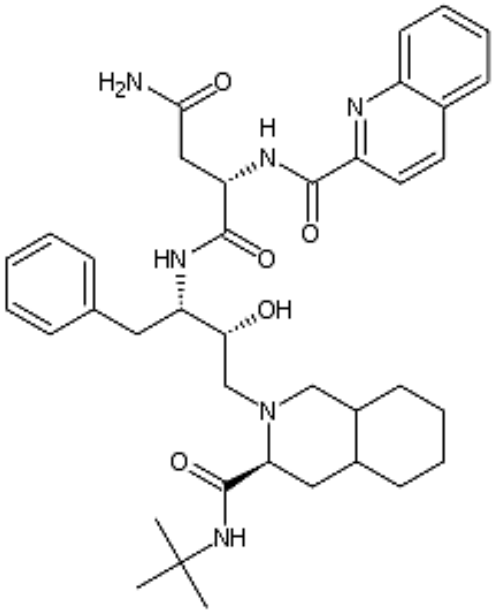
- **E must be an alcohol which on dehydration by conc. sulfuric acid gives two alkenes with elimination of H from either side of the OH group. E is** ❶




❶

6 marks out of 7 marking points

**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]

**Answers:**

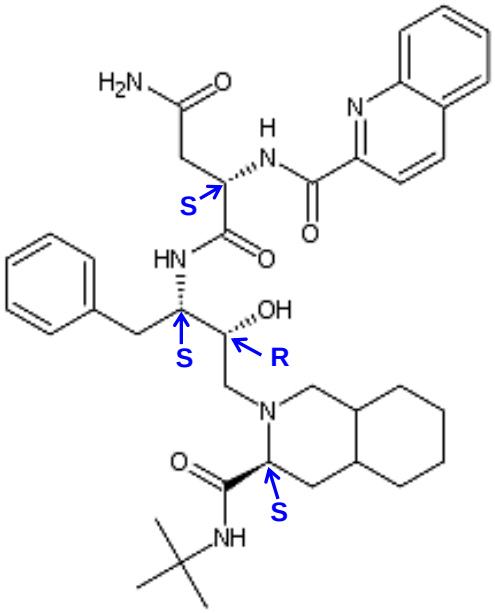
**A competitive inhibitor is structurally similar to the natural substrate and it binds to the active site by weak van der Waals' forces or hydrogen bonding. Because of the weak bonding it can be displaced by higher concentration of substrate and there is competition between the inhibitor and the substrate.** ❶

**A non-competitive inhibitor also fits into the active site, but, once it is there, it undergoes a chemical reaction to form a strong covalent bond with the enzyme, making the complex so stable that an increase in concentration of substrate cannot displace it and there is no competition.** ❶

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

**Answers:**

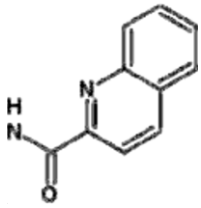
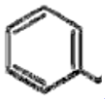
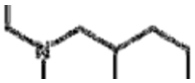
**Refer to diagram below.**



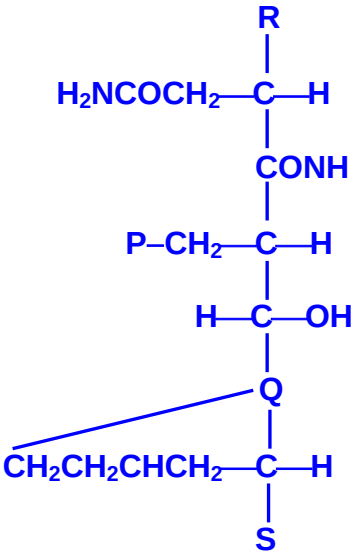
❶ mark each

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

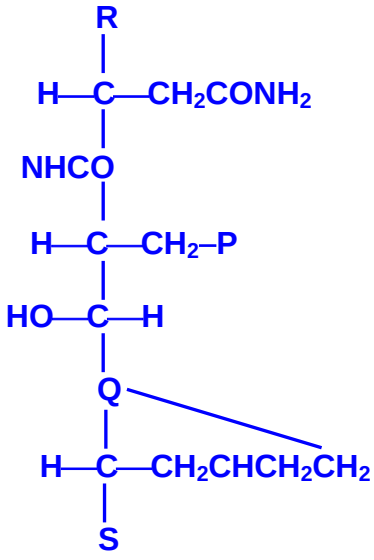
**Answers:**

**Let R be**  **,P be**  **, Q be**  **and S be**  **.**

**The enantiomer is**



**saquinavir**



**enantiomer**

❶

**(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]

**Answers:**

**Using** $[\alpha]_D^{25} = \alpha/cl$ ❶

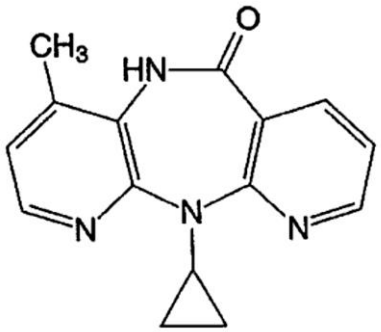
$$[\alpha]_D^{25} = \frac{-8 \times 10}{2.5} = -32°$$ ❶

**where** $\alpha$ **is the observed rotation in degrees (negative if the rotation is levorotatory and positive if it is dextrorotatory)**

**c is the concentration of the solution in g $cm^{-3}$ or density of the pure liquid in g $cm^{-3}$**

***l*** **is the length of the sample the light passes through, in dm.**

**(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]

**Answers:**

**An allosteric inhibitor binds itself to a different part of the enzyme than the active site. They gain their effect by altering the shape of the enzyme once they have become bound to it. This results in a change in the shape of the active site, hence not allowing the normal substrate to bind to it.** ❶

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

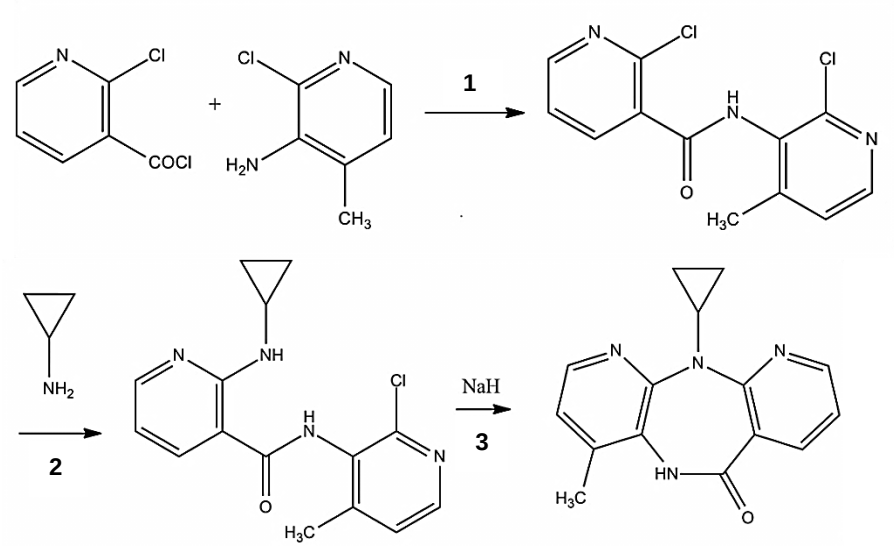
**Answers:**

**Any of the following:**

- **Prevention of viral penetration into the host cell (or departure of new virions from the cell) by targeting the viral proteins in the capsid. Examples are amantadine, rimantadine and zanamivir.** ❶

- **Inhibition of viral protein synthesis. Example is α-interferon.** ❶
- **Inhibition of viral nucleic acid synthesis. Examples are idoxuridine, azidothymidine (AZT), acyclovir and ganciclovir.** ❶

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



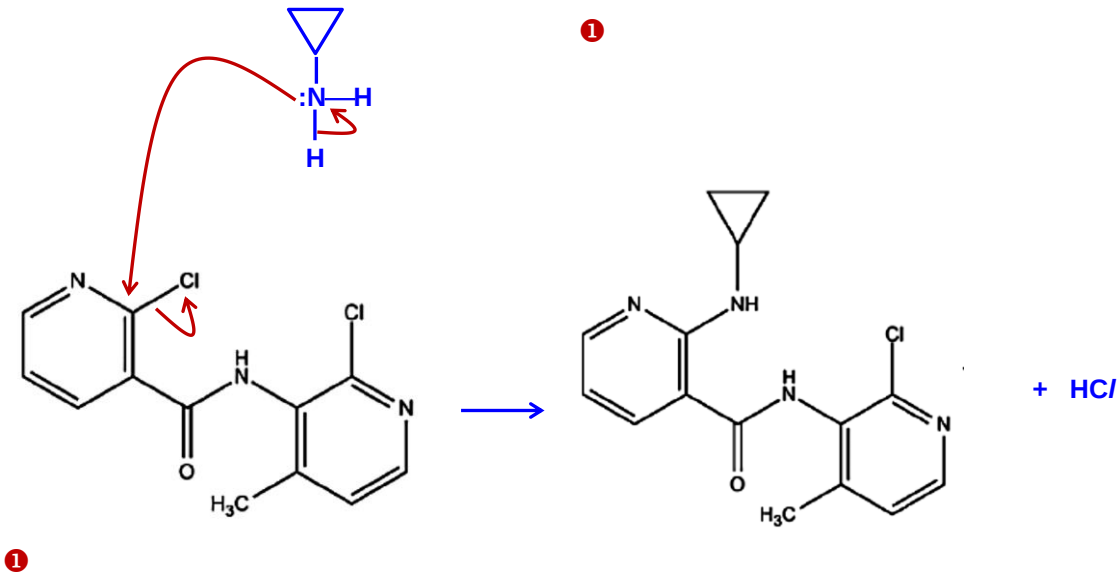

**(iii)** What kind of reaction is step 2? [1]

**Answers:**

**Nucleophilic substitution reaction.** ❶

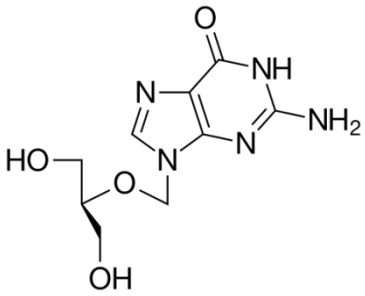
**(iv)** Suggest the mechanism for step 2. [2]

**Answers:**




❶ ❶

**(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 120 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]

**Answers:**

**Any two of the following:**

- **Oral ingestion**
- **Inhalation (nasal sprays, nicotine)** ❷
- **Transdermal (ointments, skin patches)**

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

**Answers:**

| **1st Day** | **2nd Day** | |
|---|---|---|
| **0700 h** | **0300 h** | |
| **120 mg** | **33.75 mg** | |
| **1100 h** | **0700 h** | **minimum amt = 16.9 mg** ❶ |
| **60 mg** | **16.875 + 120 mg** | **maximum amt = 136 mg** ❶ |
| **1500 h** | | |
| **30 mg** | | |
| **1900 h** | | |
| **15 + 120 mg** | | |
| **2300 h** | | |
| **67.5 mg** | | |

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

**Answers:**

**The order of aromaticity is furan < pyrrole < thiophene** ❶

**The extent of delocalisation (or aromaticity) varies inversely with the electronegativity of the heteroatom.**

**In terms of electronegativity: O, 3.5; N, 3.0; S, 2.5; C, 2.4.**

**Oxygen is the most electronegative heteroatom here and the most reluctant to 'donate' its lone pair of electrons to the ring, thus making furan the least aromatic. On the other hand, sulfur has an electronegativity similar to carbon and is able to effectively donate its electrons to the ring, making thiophene the most aromatic of the three.** ❶

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

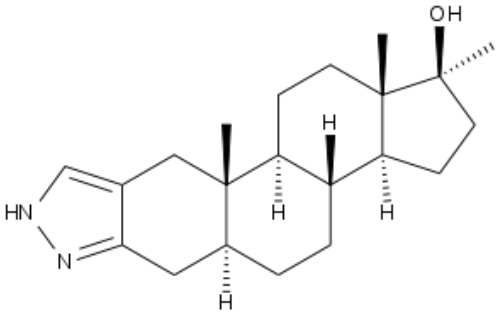

cyclobutadiene tropylium cation 1,4-dioxin naphthalene

[4]

**Answers:**

- **Cyclobutadiene is <u>not aromatic</u> as it does not have 4n+2 delocalised electrons. It only has 4 delocalised electrons not 6 as in benzene.** ❶
- **Tropylium ion is <u>aromatic</u> as it has a flat, cyclic structure with 4n+2 i.e. 6 delocalised electrons. The C atom with the positive charge is $sp^2$ hybridised (flat) with an empty $p_z$ orbital to be able to accept electrons from the other C atoms in the ring.** ❶
- **1,4-dioxin is <u>not aromatic</u> as it has 8 delocalised electrons (not 6). The 2 O atoms contribute 2 electrons each to the ring.** ❶
- **Naphthalene is <u>aromatic</u> as it has a flat cyclic structure with 10 (4n+2 where n=2) delocalized electrons.** ❶

**(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]

**Answers:**

**The N atom that is bonded to the H atom is similar to the N atom in pyrrole, which makes use of its lone pair of electrons to be delocalised into the ring. This makes it less available to attract a proton and thus less basic.** ❶

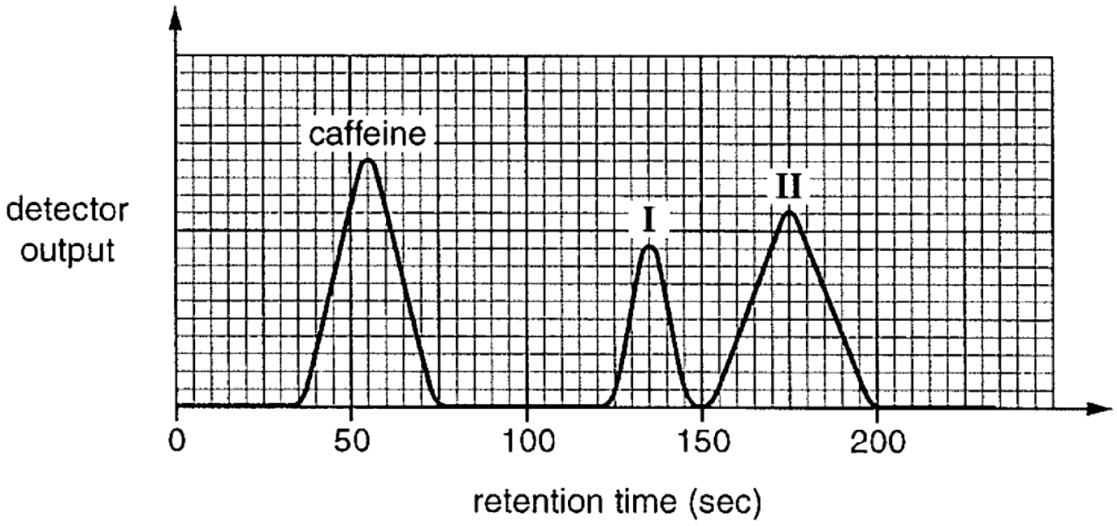
**The other N atom is similar to that of pyridine and it is not used for delocalisation and thus available to attract a proton and is more basic.** ❶

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

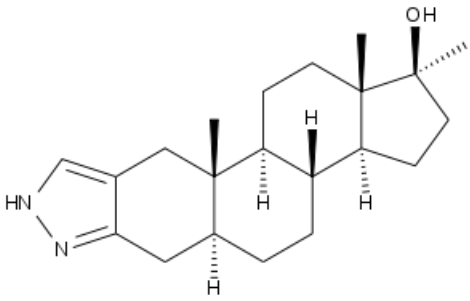
**Answers:**

**Bioavailability refers to the fraction of administered drug that reaches the blood supply in a set period of time. High oral bioavailability means that after taking the drug through oral ingestion, a high percentage can reach the blood stream quite quickly.** ❶

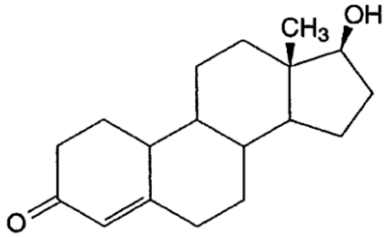
**(c)** At major athletic competitions, urine samples are taken randomly from athletes and analysed by HPLC for such anabolic steroids. An analysis was carried out of a sample derived from 1 $cm^3$ of an athlete's urine to which a known amount of caffeine had been added as an internal standard.



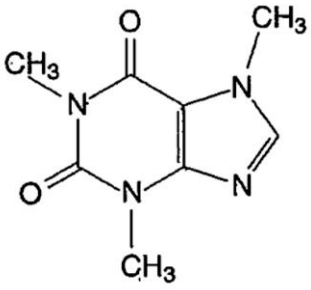

The two peaks **I** and **II** were identified as being due to the two anabolic steroids nandrolone and stanozolol (not necessarily in that order).




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]

**Answers:**

**The most polar compound is caffeine with 4 electronegative N atoms and 2 C=O bonds, followed by stanozolol which has two N atoms and 1 –OH group and finally nandrolone with one –OH group and one C=O group.**

**Caffeine is eluted first showing that the solvent is polar and the process is reverse-phase HPLC.** ❶

**Peak I is due to stanozolol and peak II due to nandrolone.** ❶

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

**Answers:**

**Ratio of caffeine: stanozolol: nandrolone is**

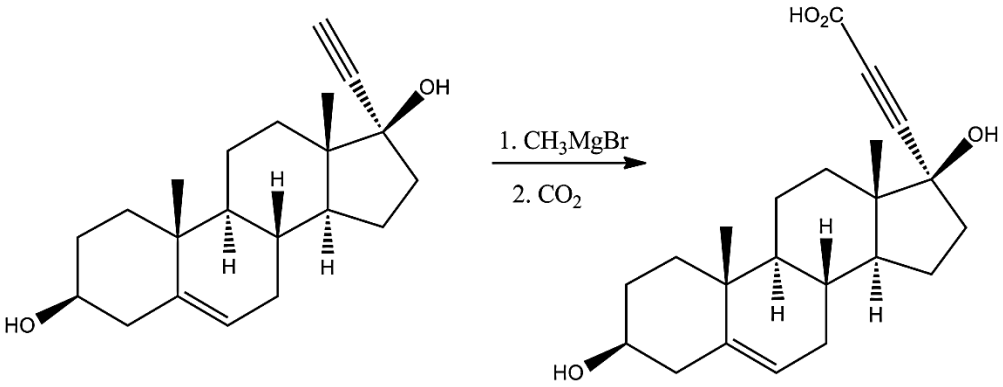
**$0.5 \times 40 \times 14 : 0.5 \times 25 \times 9 : 0.5 \times 50 \times 11 = 280 : 112.5 : 275$**

**(½ base x height) $= 2.49 : 1.00 : 2.44$** ❶

❶ **conc. of stanozolol = $1.00/2.49 \times 2.0 \times 10^{-6} = 8.03 \times 10^{-7}$ g $dm^{-3}$.**

❶ **conc. of nandrolone = $2.44/2.49 \times 2.0 \times 10^{-6} = 1.95 \times 10^{-6}$ g $dm^{-3}$.**

**(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]

**Answers:**

**Let the reactant in the above step be RCĐCH. The H atom at the terminal alkyne is acidic and can react with $CH_3MgBr$ to form RCĐCMgBr.** ❶

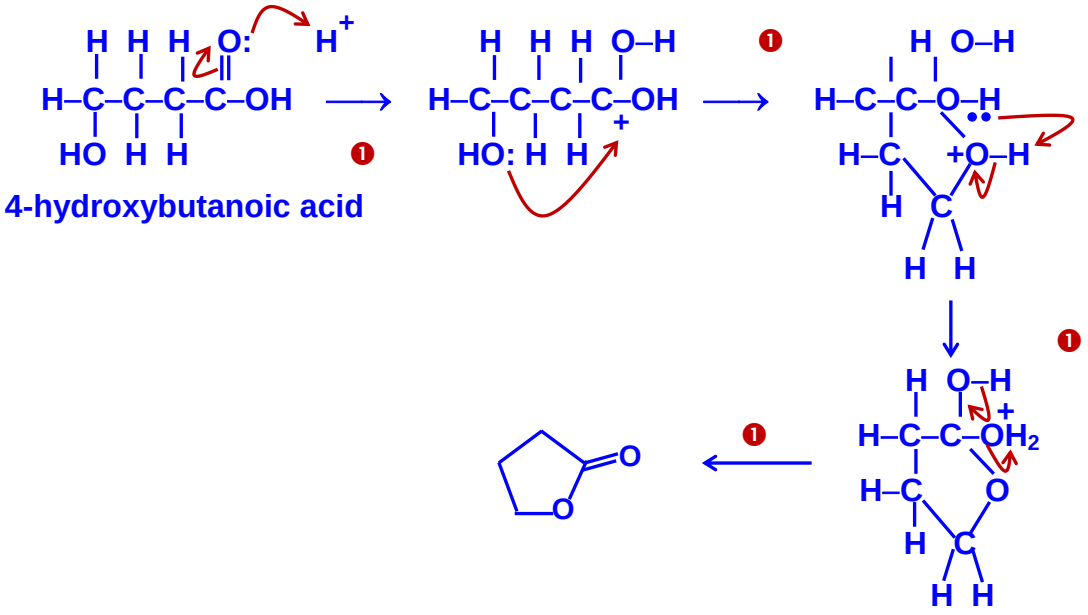
**$RC\text{Đ}CH + CH_3MgBr \longrightarrow RC\text{Đ}CMgBr + CH_4$**

**The RCĐCMgBr then behaves as a new Grignard reagent, reacting with $CO_2$ to form a carboxylic acid.** ❶

**$RC\text{Đ}CMgBr + CO_2 + H_2O \longrightarrow RC\text{Đ}C\text{–}CO_2H + MgBr(OH)$**

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

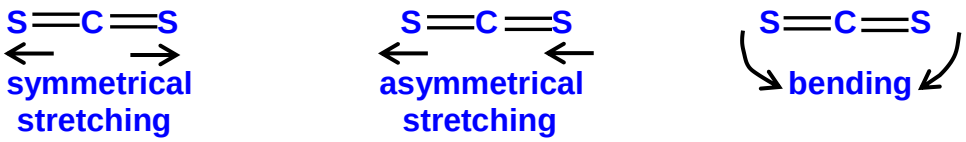
**Answers:**




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

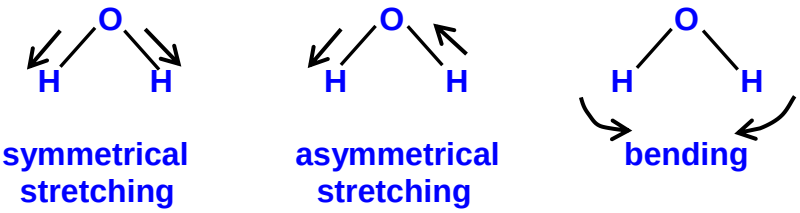
**Answers:**

**Carbon disulfide has a linear structure and the following modes of vibrations are possible:**




**Of the three modes, only the asymmetrical stretching and bending motions result in a change of dipole moment, and $CS_2$ has 2 absorption peak in its IR spectrum.** ❶

**For a non-linear molecules such as water, the vibrational modes are:**



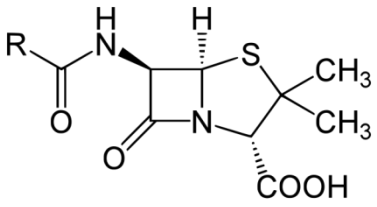

**All the three modes result in a change of dipole moment, and $H_2O$ has 3 absorption peaks in its IR spectrum.** ❶

**(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]

**Answers:**

❶ **Carbon oxysulfide has a similar shape to carbon disulfide but the dipoles on each side of the carbon atom are not the same because S and O have different electronegativities. Therefore even the symmetrical stretching would result in a change in dipole moment and O=C=S would have 3 absorption peaks in its IR spectrum.** ❶

**(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]

**Answers:** **Any 2 of the following:** ❷

**The amide that is cyclic or β-lactam ring is more easily hydrolysed. It is highly strained having a bond angle of 90° instead of 109° for the tetrahedral C atom.**

**Also the nitrogen atom has to be $sp^3$ hybridised to minimise the angle strain and there is lack of delocalisation of its lone pair of electrons over the amide group, unlike the other amide group.**

**The neighbouring acyl group can actively participate in a mechanism to open up the lactam ring.**

**Therefore β-lactam rings are easily hydrolysed to relieve the strains on the ring.**

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

**Answers:**

❶ **Penicillins inhibit the cross-linking of the peptidoglycan (murein) chains in the last stage of cell wall construction in bacteria. Because they are similar in structure to D-alanyl-D-alanine, the substrate for the transpeptidase enzyme, they can bind irreversibly to the active site and prevent the formation of the cell wall.** ❶

**(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]

**Answers:**

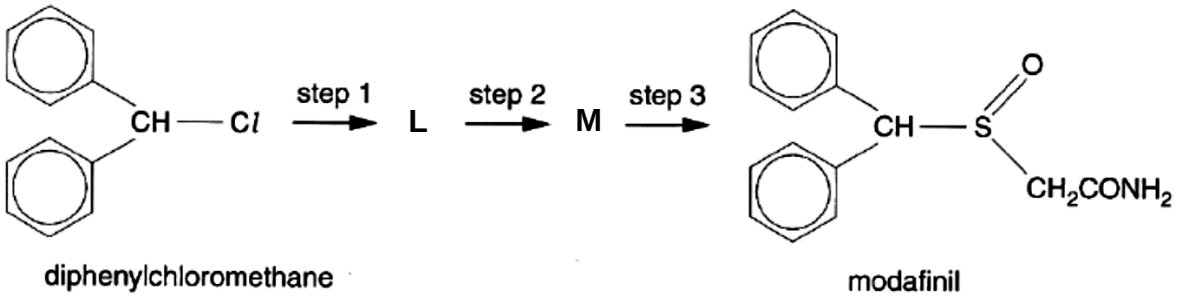
**Some bacteria can mutate and produce an enzyme, β-lactamase, that can hydrolyse the β-lactam ring of penicillin and render them ineffective. These bacteria may spread the infection to other patients and eventually the whole bacteria population will be penicillin resistant.**

**Another complication is that it is possible for one bacterium to confer resistance onto another (even of a different species) by the exchange of 'plasmids' (small lengths of DNA) which sometimes contain the gene for the production of the β-lactamase enzyme.** ❶

**It is important for a patient to complete a course of antibiotic treatment, even if the symptoms of the infection have disappeared because this will give the immune system time to destroy resistant bacteria while the penicillin copes with those that are not resistant.** ❶

**(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

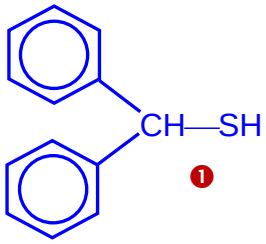
**(i)** Explain what is meant by the term stimulant. [1]

**Answers:**

**Stimulants are drugs that increase a person's state of mental alertness.** ❶

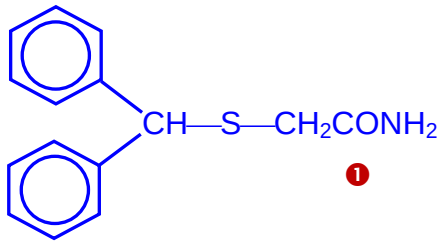
**(ii)** Suggest structures for the intermediates **L** and **M**, and suggest reagents and conditions for the three steps 1–3. [5]

**Answers:**




❶

**J**




❶

**K**

**Reagents and conditions:**

**Step 1: excess NaHS and heat in aqueous ethanol.** ❶

**Step 2: Na or NaOH and $BrCH_2CONH_2$, heat.** ❶

**Step 3: Equimolar amount of $H_2O_2$ or $NaIO_4$.** ❶

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

**Answers:**