Answer *any* **five** questions.

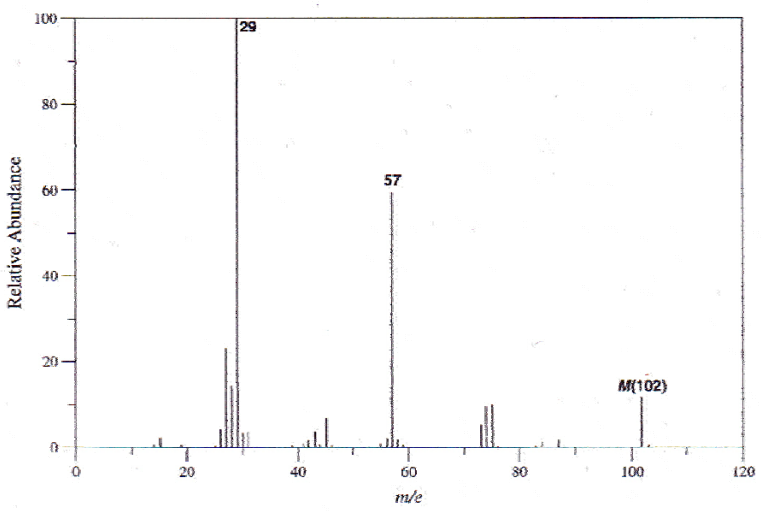
1 (a) ^{1}H NMR is a common analytical technique used to determine the molecular structures of various compounds.

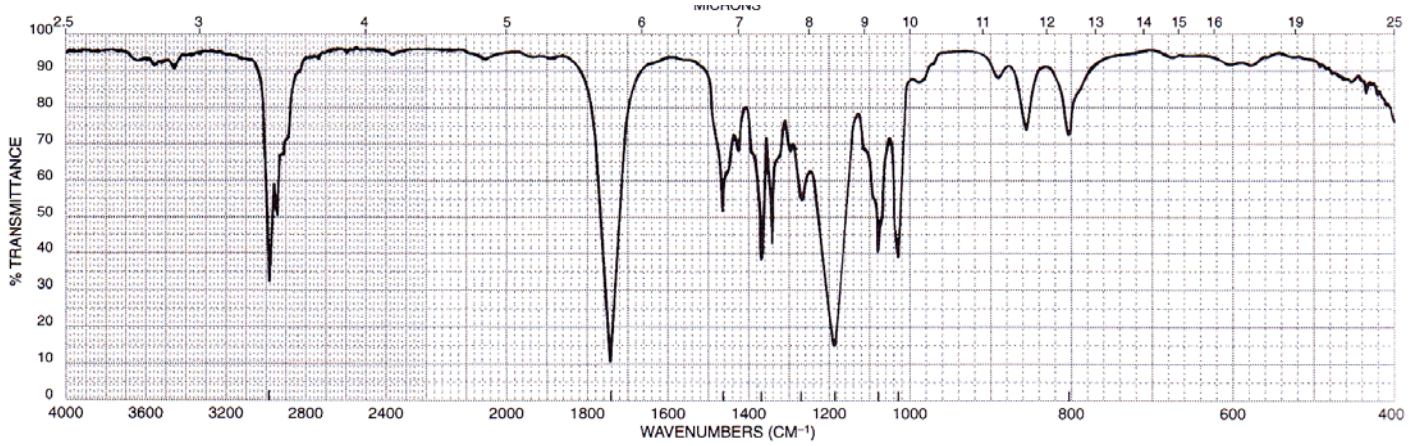
(i) Outline the basic working principles of NMR. [2]

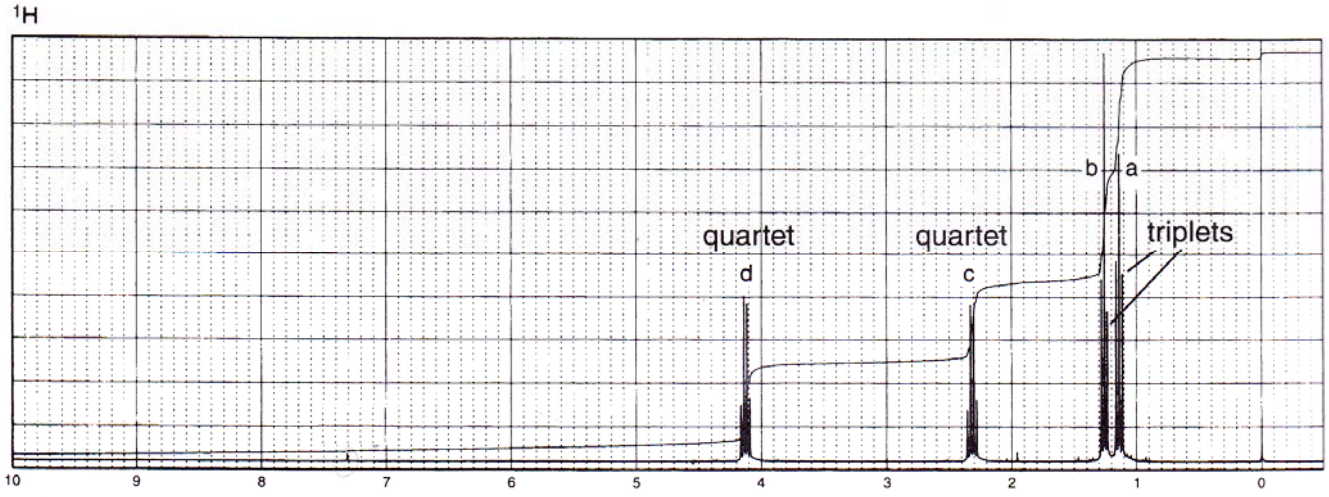
Nucleus of proton spins and **generates a magnetic moment[0.5]**. When a magnetic field is applied, the magnetic moment aligns with or against the applied magnetic field. To **switch from the lower energy spin state that aligns with the applied field to the higher energy state that aligns against the applied field[0.5]**, **radio–frequency radiation is absorbed[0.5]**. The **exact frequency of absorption depends on the chemical environment of the proton[0.5]**.

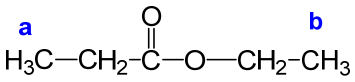
An unknown compound **A**, $C_5H_{10}O_2$, was synthesised in the laboratory. It is used to manufacture various propionates which are used as anti–bacterial agents. Its MS, IR and ^{1}H NMR spectra data given below.

(i) Deduce the structure of compound **A**, giving your reasoning. [8]







A:  [1]

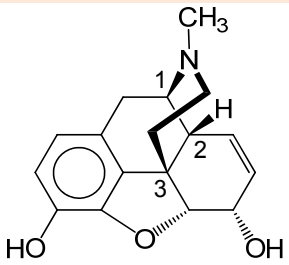
absorption	bond
1740	C=O
1200	C–O

- **Absence of peak at 3230 to 3500 cm^{-1}** suggests **absence of O–H stretch** ⇒ **No alcohol** [1]
- The **presence of a C–O** (strong and broad) **at 1200 cm^{-1}** and **C=O at 1740 cm^{-1}** confirm the identity of an **ester** functional group. [1]

chemical shift /ppm	splitting pattern	No. of adjacent protons	relative peak area	group responsible	
1.15	triplet	2	3	–CH_3 **(a)**	[1]
1.25	triplet	2	3	–CH_3 **(b)**	[1]
2.30	quartet	3	2	–CH_2CO– (adjacent to a –CO– and –CH_3)	[1]
4.15	quartet	3	2	–OCH_2– (adjacent to a –CO– and –CH_3)	[1]

m/e	species	
102	$(C_5H_{10}O_2)^+$	[1]
57	$(CH_3CH_2CO)^+$	
29	$(CH_3CH_2)^+$	

(b) Opium is the air–dried milky exudate, or latex, obtained by incising the unripe capsules of the opium poppy *Papaver somniferum*. It contains up to 12% morphine, an alkaloid, which is frequently processed chemically to produce heroin for the illegal drug trade. Morphine is also used as a narcotic analgesic and for the treatment of dry cough and diahorrea.



morphine

(i) Explain the term *narcotic analgesic*, using morphine as an example. [1]

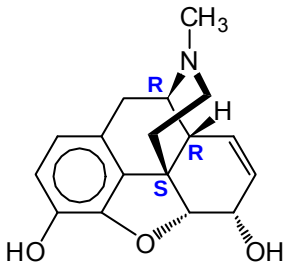
Narcotic analgesic, like morphine, is a substance that **depresses the activity of the central nervous system resulting in pain relief**.

(ii) Narcotic and non–narcotic analgesics act differently to prevent pain. Briefly outline the modes of action of non–narcotic analgesics. [1]

Non–narcotic analgesics work by **inhibiting the cox enzyme** and **reducing the biosynthesis of prostaglandins**.

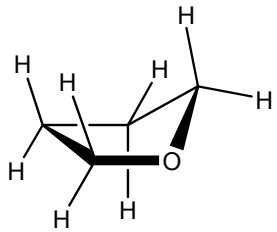
c

(iii) Assign the stereochemical configuration about the chiral carbon atoms 1, 2 and 3. [2]



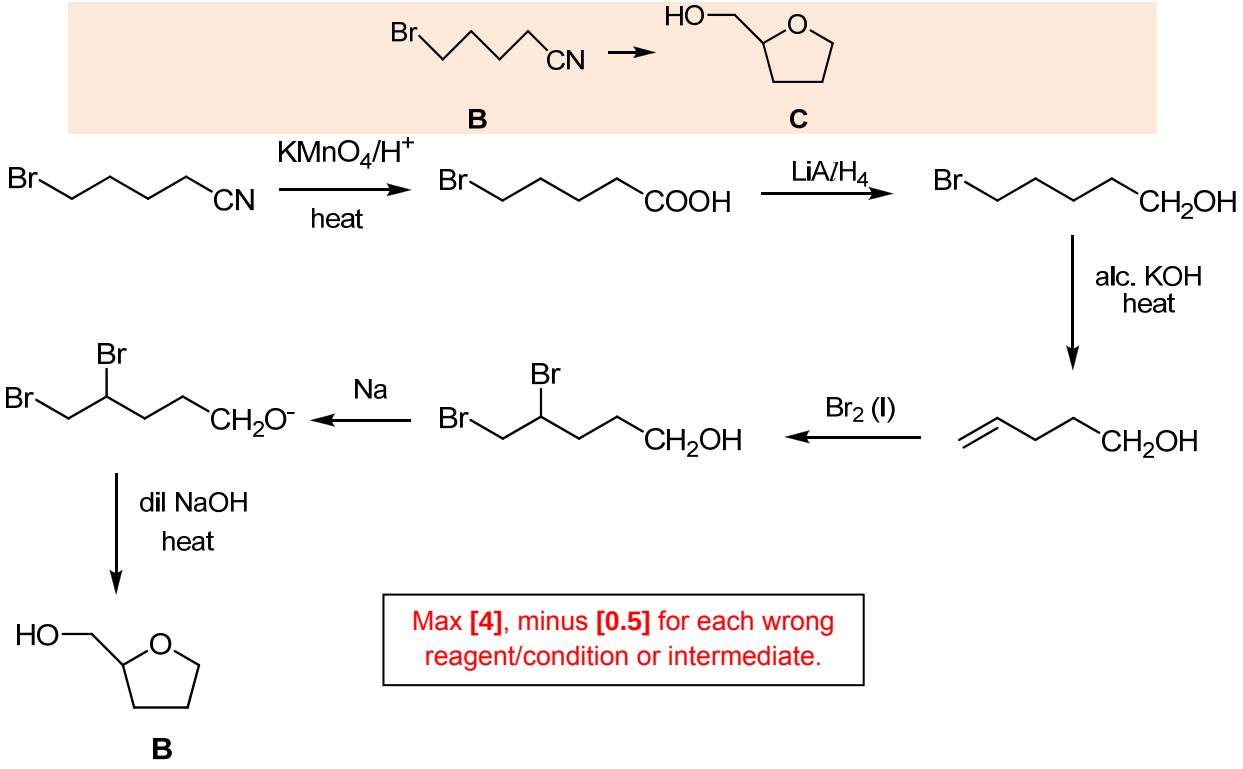
All correct **[2],** 1 correct **[0.5],** 2 correct **[1]**

(c) Many drugs, like morphine, contain the tetrahydrofuran ring in their structures. Shown below is the puckered conformation of tetrahydrofuran.



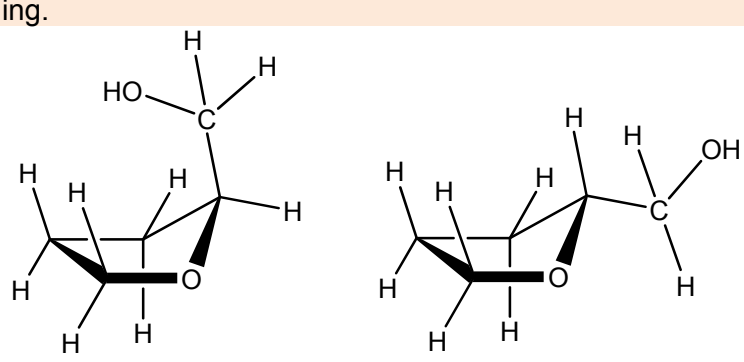
tetrahydrofuran

(i) Suggest a simple synthetic pathway for the formation of the cyclic ether, **C**, from compound **B**. State clearly all reagents and conditions required for the proposed steps of the synthesis. [4]



Max **[4]**, minus **[0.5]** for each wrong reagent/condition or intermediate.

(ii) Draw two different conformers of cyclic ether, **C**, showing the positioning of the substituent on the ring. State which of the two conformers is more stable, giving your reasoning. [2]



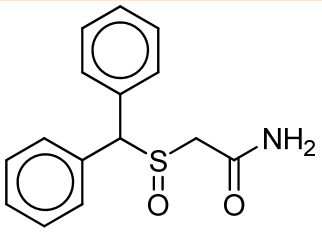
conformer **I** conformer **II**

Each [0.5]

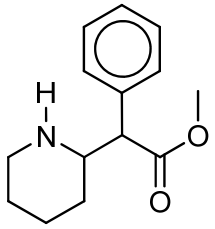
Conformer II is more stable[0.5] because the **bulky substituent at the axial position** in conformer **I** will **experience 1,3–diaxial interaction** [0.5] whereas in conformer **II**, the substituent at equatorial position experiences less repulsion.

[Total: 20]

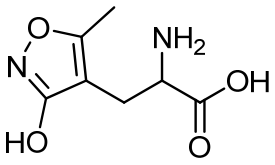
2(a) Stimulants are psychoactive drugs which induce temporary improvements in either mental or physical function or both. Modafinil, methylphenidate and ampakine are stimulant drugs approved by the U.S. Food and Drug Administration (FDA) for the treatment of various disorders. The structures of all three compounds are shown below.



modafinil



methylphenidate



ampakine

A mixture of these compounds can be analysed by reversed phase column HPLC. The compounds are detected as they emerge from the column using UV spectroscopy.

(i) Predict the order at which the compounds will be eluted and explain the difference in their retention times.

Order of elution: **Ampakine, methylphenidate followed by modafinil. [0.5]**

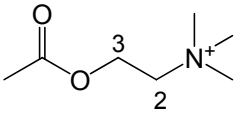
Ampakine molecule is **most polar[0.5]** as it has a **polar carboxylic acid group/ two hydroxyl groups/ more polar groups/ more O and N atoms[0.5]** than methylphenidate and modafinil molecules. Hence **more effective hydrogen bonding** can take place **between the sample and the polar solvent mobile phase[1]**. Hence ampakine is eluted earliest. **Modafinil** will be eluted last due to its relatively **larger non–polarity[0.5]** because of the presence of **two aromatic (or cyclic) ring [0.5]** in the molecule compared to methylphenidate.

(ii) Explain why the three compounds may be detected using UV, and state what happens in their molecules when UV radiation is absorbed.

All the three compounds are **chromophores** as they contain either isolated bond, and/or a conjugated system of double bonds**[0.5]**. Hence, **$\pi \rightarrow \pi^*$, $n \rightarrow \pi^*$ and $n \rightarrow \sigma^*$ transitions which corresponds to the UV/vis region are possible [0.5]**. When the photon is absorbed by a molecule, an **electron gains the photon's energy** and is **promoted to a higher electronic level**. **[0.5]**

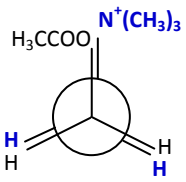
[5]

Some stimulants exert their effects by mimicking the action of the neurotransmitter acetylcholine.

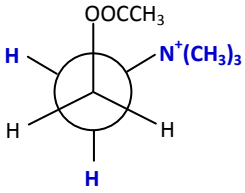


acetylcholine

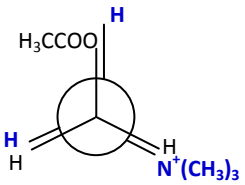
(iii) Draw and label the Newman projections (along the C2–C3 bond) to show the six conformations of acetylcholine. Sketch a potential energy profile diagram to illustrate the relative stability of these conformers. [4]



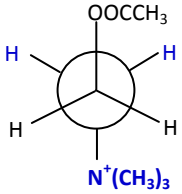
I (most unstable eclipsed)



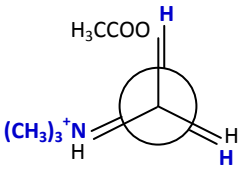
II (gauche)



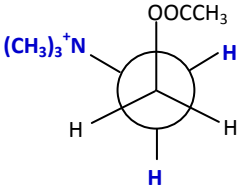
III (eclipsed)



IV (anti–staggered)



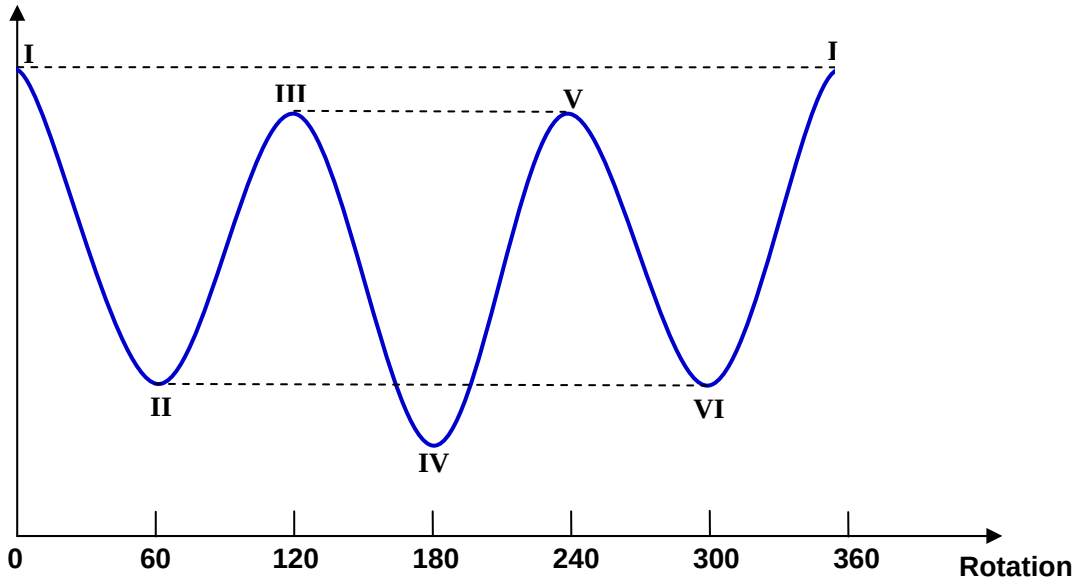
V (eclipsed)



VI (gauche)

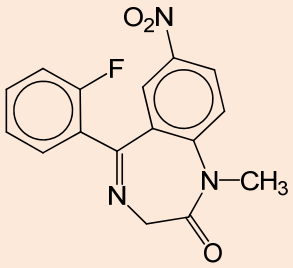
Correct projections and labellings max **[2]**, minus **[0.5]** for each wrong projection.

Potential energy

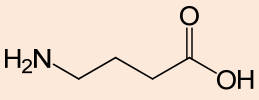


Correct diagram with labelling and axes, max **[2]**, minus **[0.5]** for each mistake.

(b) Rohypnol, a benzodiazepine derivative, is marketed as a highly potent hypnotic drug with sedative properties. It binds to the gamma–aminobutyric acid–A ($GABA_A$) receptors in the central nervous system and inhibits neurotransmission.



rohypnol



GABA

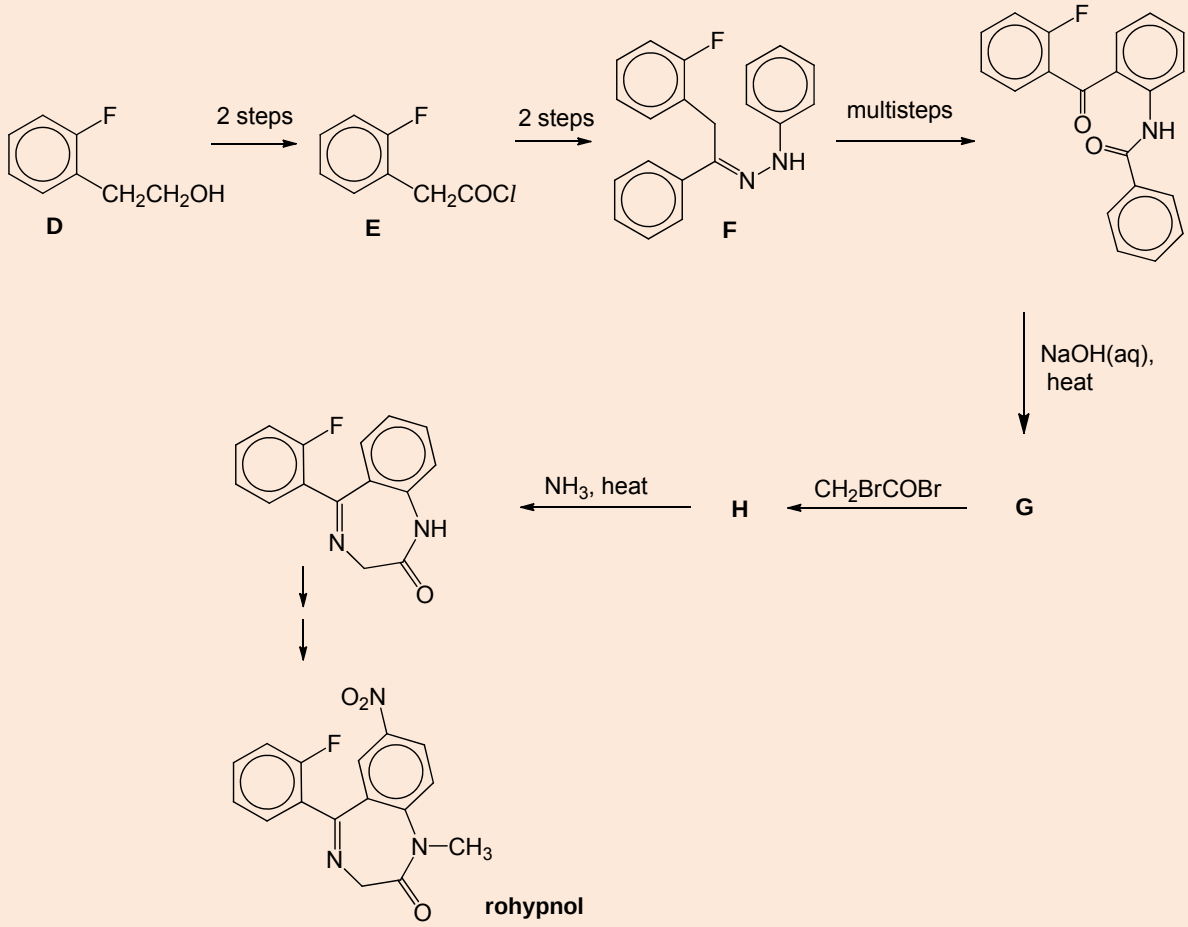
(i) Explain how agonists and antagonists differ in their interactions with receptors. [2]

Agonists **compete for the receptor site**, causing the necessary **change in shape** there. [1] Antagonists **block the site without causing the necessary change in shape**. [1]

(ii) Suggest with reason if rohypnol is more likely to be an agonist or antagonist. [1]

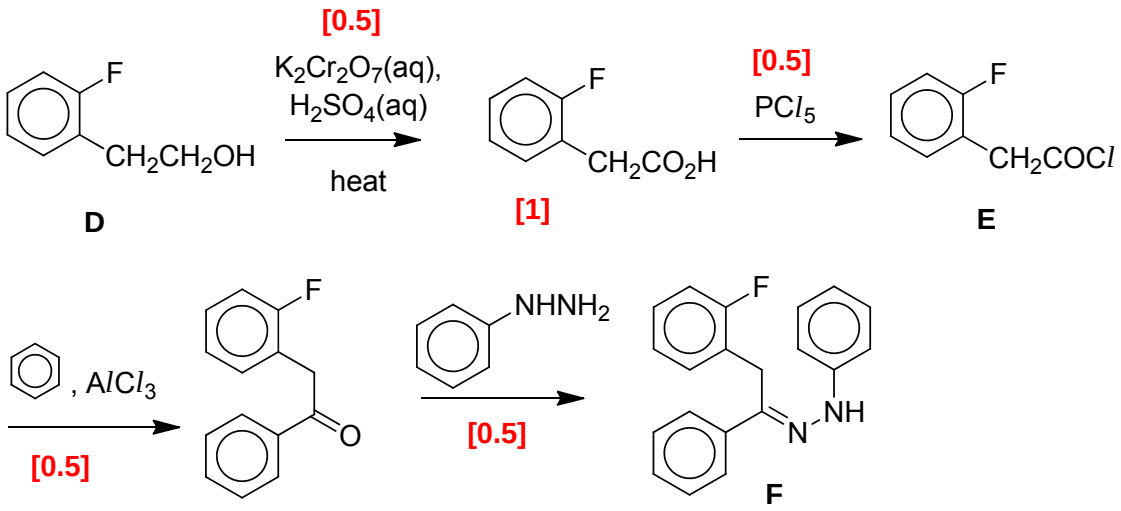
Antagonist. [0.5] Rohypnol has **different structural features compared to the natural ligand, GABA, [0.5]** and it contains larger hydrophobic groups to increase its binding strength.

The synthesis of Rohypnol from compound **D** is as outlined below.



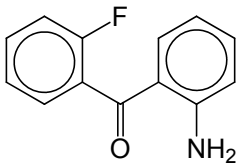
rohypnol

(iii) Suggest reagents and conditions for the conversion of **D** to **E** and subsequently to **F**. Include in your answers, the structures of all organic intermediates obtained during these multistep conversions. [4]

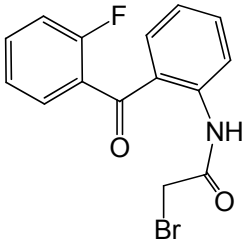


(iv) Give the structures of compounds **G** and **H**. [2]

G:



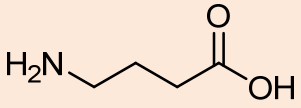
H:



Each **[1]**

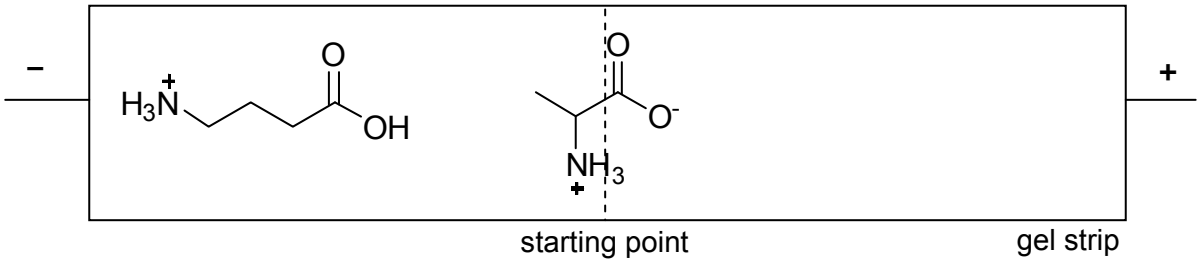
(c) Gel electrophoresis is often employed to separate and analyse mixtures of biological molecules like amino acids.

In this experiment, electrophoresis is used to separate GABA (pKa_1: 4.23, pKa_2: 10.43) and alanine, $H_2NCH(CH_3)COOH$ (pKa_1: 2.35, pI: 6.11, pKa_2: 9.87) in a solution pH 3.6.



gamma–aminobutyric acid (GABA)

The diagram below shows the gel strip obtained after electrophoresis. Indicate the positions of GABA and alanine by drawing their structures on the diagram printed behind the cover sheet. [2]



Correct structure and position **[1]** each

[Total: 20]

3 Alzheimer's disease (AD) is the most common form of dementia. It is hypothesized that AD is caused by the reduced synthesis of nerve cells in the forebrain, which are in turn mainly affected by two receptors M1 and M2. Receptor M1 provides linkages towards important nerve cell functions while receptor M2 causes a deficit in nerve cell transmission.

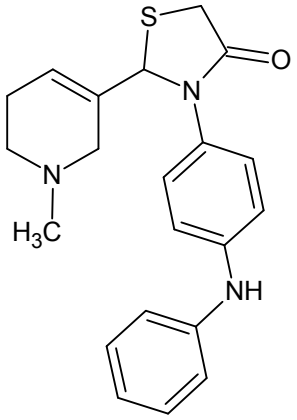
(a) (i) State **one** type of drug–receptor interaction. [1]

Hydrogen bonding or **ionic interactions** or **ion–dipole interactions** or **van der waals' interactions** **[1m for any answer]**

(ii) Using your knowledge on agonists and antagonists, suggest types of drugs that should be used to target each receptor M1 and M2, in the treatment of AD. [2]

An **agonist** should target **M1** **[1]** while an **antagonist** should target **M2**. **[1]**

(b) Compound **O** has been identified as a potential drug to treat AD.



O

State and explain **two** features of the molecule that allows it to be developed as an oral drug which can pass through the blood brain barrier. [2]

Compound **O** contains **three nitrogen atoms** which can exist as both **ionised and unionised forms**, which are in rapid equilibrium with each other. The ionised form can **bind strongly with receptors on binding sites** and the unionised form can **pass through membranes and the blood brain barrier**. **[1]**

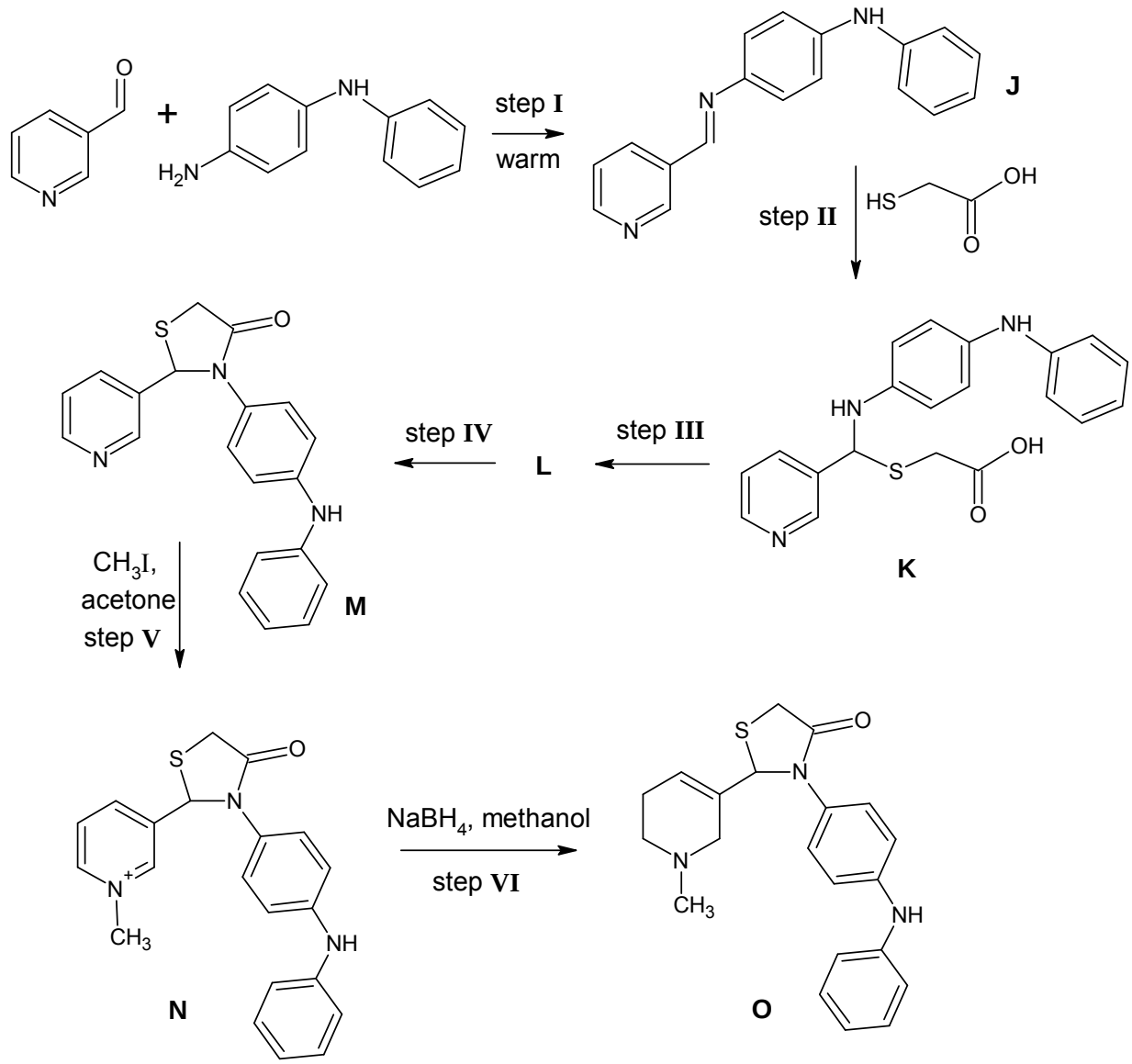
The **three nitrogen atoms** and the **carbonyl oxygen** can **form hydrogen bonds with water**. This allows the molecule to have a degree of **water solubility**. **[1]**

Compound **O does not contain any amide, ester or acyl chloride** functional groups and thus is not **easily hydrolysed under the strongly acidic environment** of the stomach. **[1]**

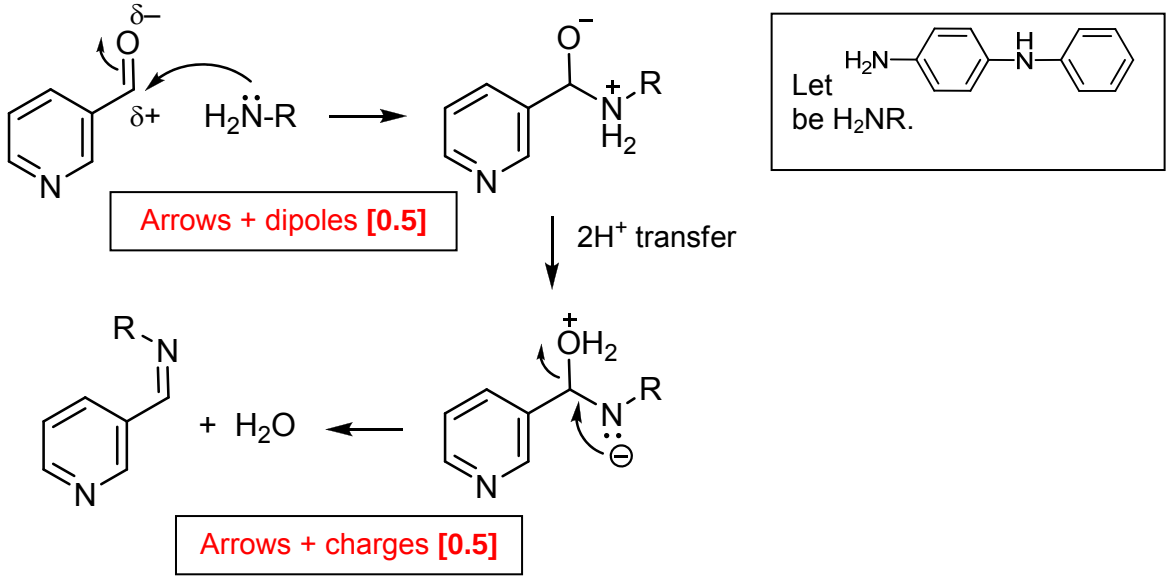
Compound **O** contains **hydrophobic benzene rings and alkyl groups** which **allow it to pass through membranes and the hydrophobic blood brain barrier**. **[1]**

[1m for any correct identification of structure and explanation]

(c) The following reaction scheme shows the synthesis of **O** in the laboratory.



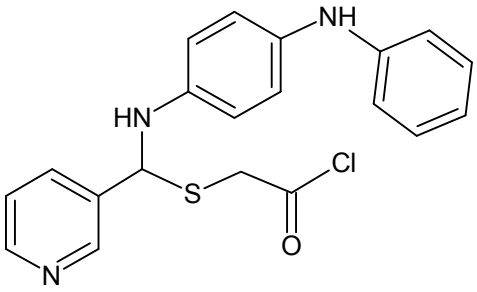
(i) Draw the mechanism for the formation of **J**, given that it was formed via addition–elimination. [2]



(ii) Suggest the structure of **L** and the reagent required for Step **III**. [2]

PCl_3 or **PCl_5** or **$SOCl_2$** **[1 for any correct reagent]**

L:



(d) (i) State and explain the type of reaction that the aromatic heterocycle in **M** is most likely to undergo. [2]

Nucleophilic substitution. **[1]** The nitrogen atom is electronegative, thus withdraws π electron density from the ring. In addition, it is also basic and is easily protonated by common electrophilic reagents, and the resulting cation is unlikely to undergo electrophilic substitution. Similarly, due to the **electronegativity of nitrogen** **[1]**, nucleophilic substitution is possible.

(ii) Explain why the aromatic heterocycle in **N** can be so easily reduced in step **VI**.

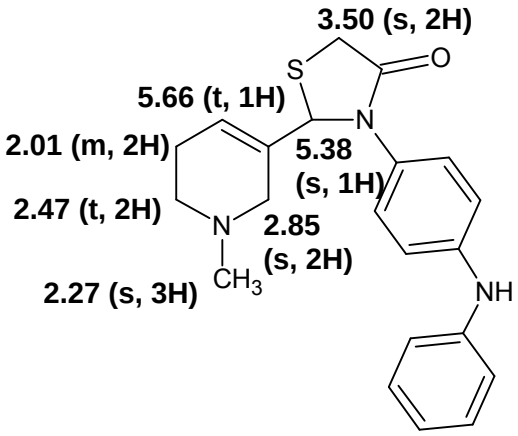
[3]

The mechanism of the reduction is **nucleophilic addition**. **[1]** The **positively charged nitrogen** **[0.5]** atom will have a **greater attraction towards the electrons of the C=N double bond** **[0.5]**, **increasing the size of the partial positive charge** **[0.5]** on the carbon adjacent to the nitrogen, making it **more susceptible to attack** **[0.5]** by nucleophiles.

(e) The ^{1}H NMR spectrum of compound **O** shows the following 8 signals.

δ/ppm	
2.01	(m, 2H)
2.27	(s, 3H)
2.47	(t, 2H)
2.85	(s, 2H)
3.50	(s, 2H)
5.38	(s, 1H)
5.66	(t, 1H)
6.5–7.3	(m, 9H)

(i) Assign **five** of the signals to particular protons in **O**. [5]



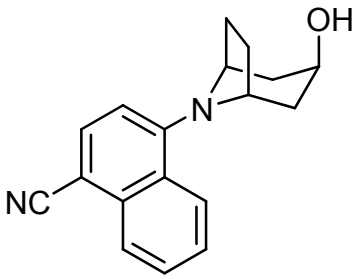
6.5–7.3 (m, 9H): protons on benzene ring

[1 for any proton correctly labelled]

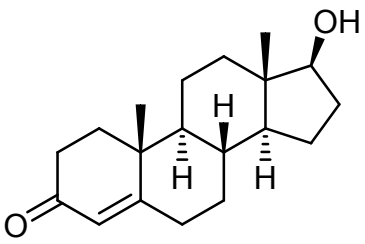
(ii) Given that a deuterated solvent was used in the ^{1}H NMR analysis, suggest the identity of the missing peak. [1]

The **labile proton of the amine** is missing. **[1]**

4 Many pharmaceutical companies are developing non–steroidal drugs to treeat various hormone related diseases and conditions. Some of these drugs bind competitively with the natural hormone molecules at the hormone receptors. For example, compound **G** was found to mimic the molecule testosterone in binding towards the androgen receptor.



P



testosterone

(a) State two similar structural features between compound **P** and testosterone. [2]

The first similarity is the polar **carbonyl group in testosterone** and polar **nitrile group in P**. **[1]**The second similarity is the presence of **hydroxyl group [1]** in similar position.

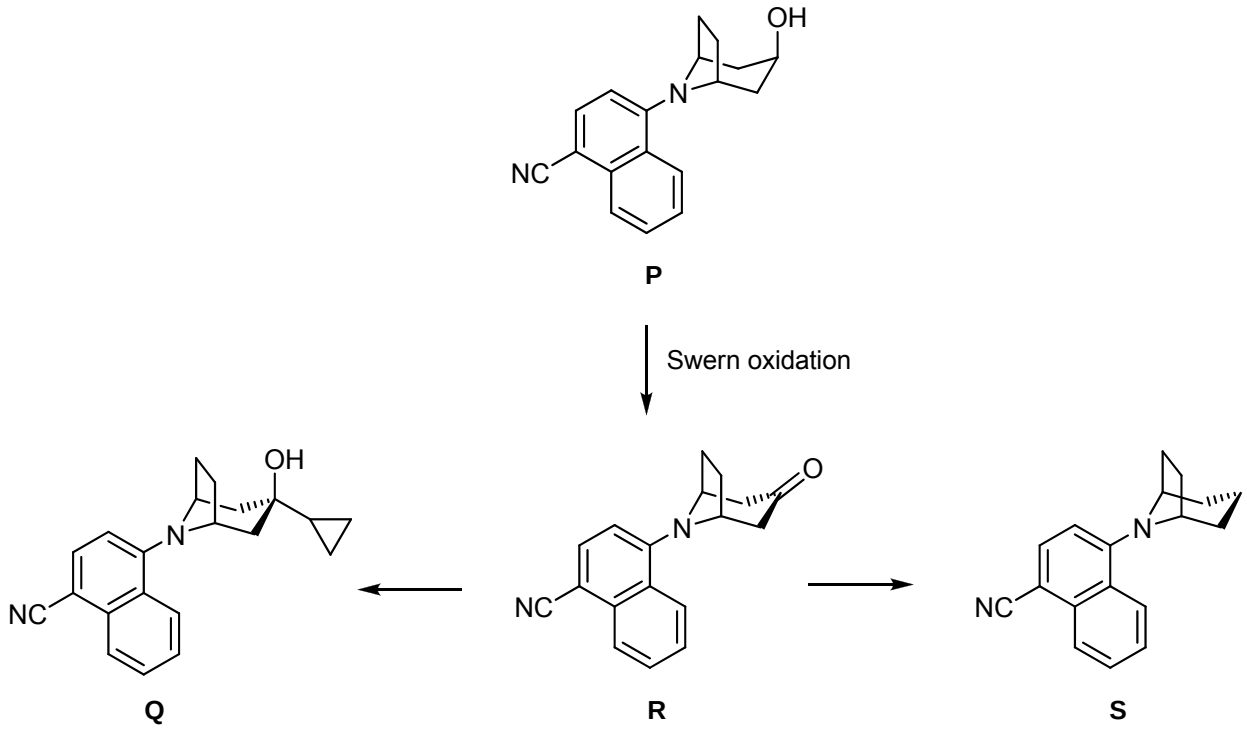
(b) State and explain if the six–membered ring in compound **p** would undergo a ring flip. [2]

No [1], the six–membered ring would not undergo a ring flip. The **hydroxyl group would collide with the napthyl group** connected to nitrogen. **OR** The **bulky groups would experience steric interactions[1].**

(c) State and explain if compound **P** contains an aromatic moiety. [2]

Yes. **[1]** There is a **ring of overlapping p orbitals** containing a total of **(4n+2)** electrons where **n = 2**. **[1]**

Analogues of compound **P** have been synthesised and tested using the bioassay procedure. The scheme below outlines main steps in the synthesis of compounds **Q**, **R** and **S** from compound **P**.



(d) (i) State the type of reaction occurred in the synthesis of **S** from **R**. [1]

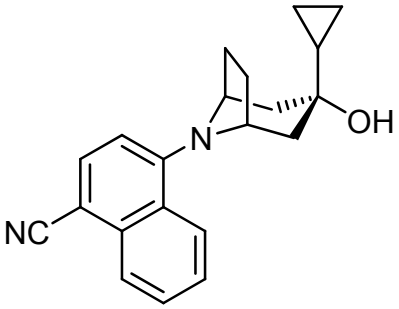
Reduction [1]

(ii) State the number of chiral carbons in compound **Q**. [1]

3 [1]

(e) Compound **Q** was synthesised from **R** using a Grignard reagent, cyclopropyl magnesium chloride. During the synthesis, a small amount another isomer was also produced in the ratio 9:1.

(i) Draw the structure of the isomer of compound **Q** formed. [1]



isomer of Q

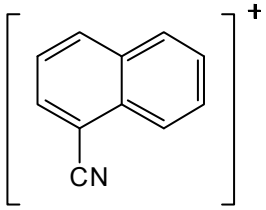
(ii) Suggest why **Q** is formed in preference when **R** was reacted. [2]

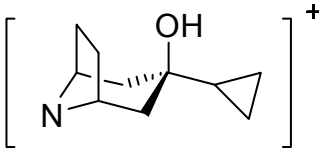
The nucleophile attacks the π bond of the C=O at an angle of 107°. The 2 **chiral centres present in R influence the emerging chiral centre** **[1]** of the nucleophilic addition. This effect is called **asymmetric induction** **[1]**. The nucleophile attacks from the bottom face as there are two alkyl groups near the top face hindering the attacking nucleophile.

(f) The mass spectrum of compound **Q** clearly shows a peak at 319, corresponding to the $[M+H]^+$ ion. Predict three other possible peaks in the mass spectrum of compound **Q**, and draw their respective fragments. [3]

[1 for any logical fragment. The list below is not exhaustive.]

41: 

152: 

166: 

275: $[M - CN - OH]^+$ **292:** $[M - CN]^+$ **301:** $[M - OH]^+$

(g) Predict **two** absorbances in the IR spectrum of compound **R**. [2]

C=O	1680 – 1750 cm^{-1}
C=C	1610 – 1680 cm^{-1}
C–H	2840 – 3095 cm^{-1}

[1 for any correct absorbance stated]

(h) The pure compound was separated from the crude mixture using reverse–phase HPLC.

(i) Outline the differences between reverse and normal phase HPLC. [3]

Normal phase HPLC is packed with **silica coated with very polar groups**, while reverse phase HPLC is packed with **silica coated with very non–polar groups**. **[1]**

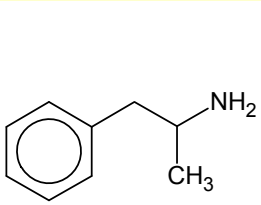
Normal phase HPLC uses **solvent of low polarity** while reverse phase HPLC uses **solvent of high polarity**. **[1]**

In normal phase HPLC, the **more non–polar compounds are eluted first** while in reverse phase HPLC, the **more polar compounds are eluted first**. **[1]**

(ii) Explain why reverse–phase HPLC was chosen over normal phase HPLC. [1]

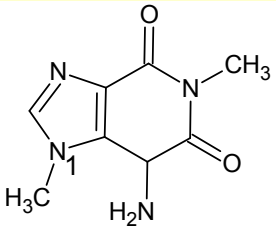
Compound **H contains polar functional groups** **[1]** such as alcohol, amine and nitrile.

5 Stimulants are drugs that are commonly used in the modern society. Amphetamine and caffeine are both stimulants but amphetamine is an illicit drug under the laws of Singapore whereas caffeine is commonly available. All compounds shown below show absorption peaks in their UV spectra.



amphetamine

$pK_b = 4.1$



caffeine

(a) (i) What is meant by the term *stimulant*? Describe briefly the pharmacological effect of amphetamine and caffeine. [4]

Stimulants are compounds that produce the physiological effects of "heightening" the CNS and to **increase the heart rate and blood pressure** [1]. Caffeine is similar to the adenine part of the adenosine molecule, and acts as **a competitive antagonist** [1] to adenosine receptors on the surfaces of cells in the CNS. Another effect of caffeine is to **inhibit an enzyme (cAMP–phosphodiesterase)** [1] that breaks down cyclic–AMP.
Amphetamine **open up the protein "carrier" molecule channels** [1] in the surface of the pre–synaptic nerve, allowing the stores of *noradrenaline* and *dopamine* to leak out of the nerve into the synapse

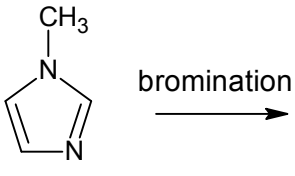
(ii) Identify the chromophore in amphetamine. [1]

The **benzene ring**. [1]

(iii) Predict, with a reason, the approximate pK_b of N_1 of caffeine. [2]

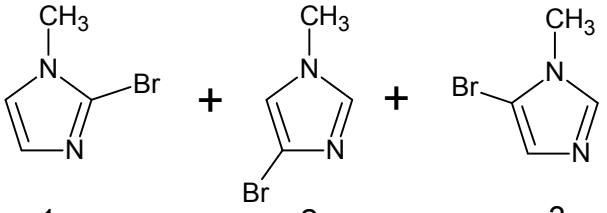
4.5–5.5 [1] The lone pair of electrons of N_1 of caffeine is **involve in the aromaticity of the imidazole ring** [1] and is less available for donation.

Caffeine contains the 1–methylimidazole ring as shown below. Under suitable conditions, 1–methylimidazole can undergo electrophilic substitution reaction to give three different products.



1-methylimidazole

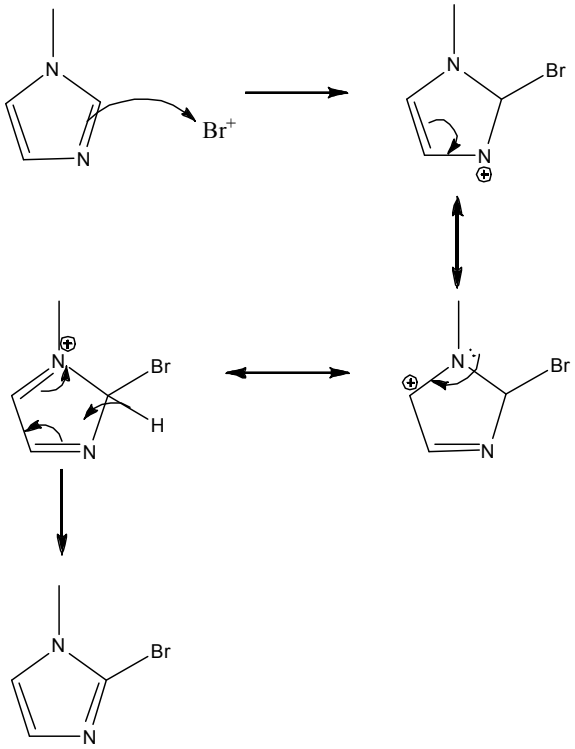
bromination



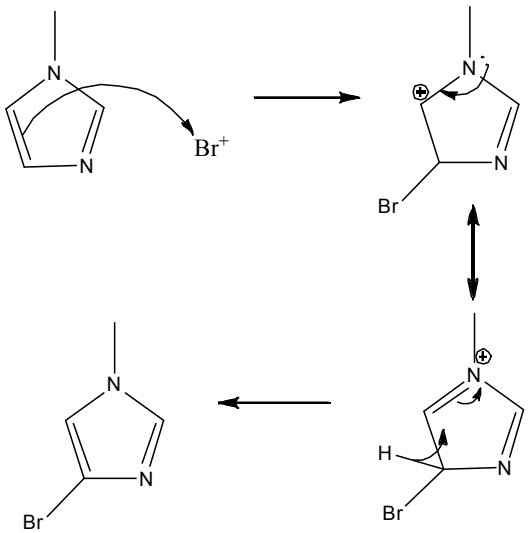
1 2 3

(b) (i) Draw the resonance structures of all the three intermediates and hence state the **major product** formed in this reaction. [4]

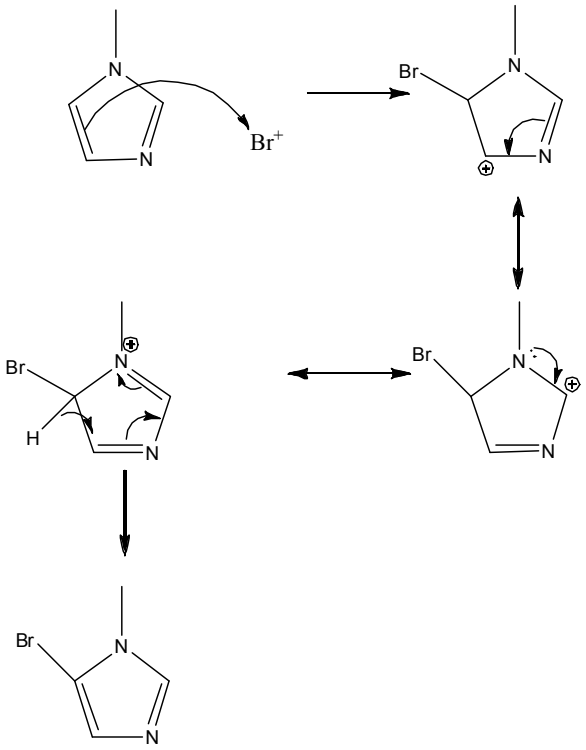
Formation of 1



Formation of 2



Formation of 3

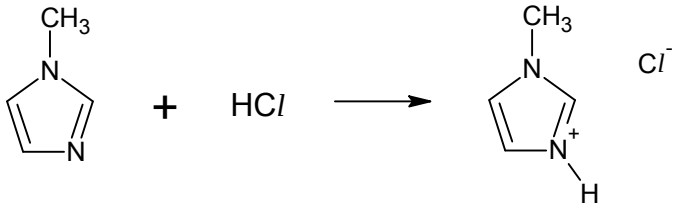


[1] for all resonance structures drawn.

The formation of product ***1*** is not as favourable because one of the mesomeric structures formed is unstable since the positive charge resides on the electronegative N as indicated.

The formation of product ***2*** is not as favourable since there are only two possible meomeric structures. **The major product is *3*** **[1]**.

(ii) Write a balanced equation when 1–methylimidazole is reacted with hydrochloric acid. [1]



[1]

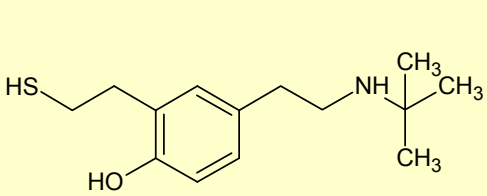
(iii) Compare the aromaticity between 1–methylimidazole and benzene. Suggest a reason for the difference.
[2]

1–methylimidazole is less aromatic **[1]** than benzene as the electronegative nitrogen exerts its **electron withdrawing effect and reduce the electron density** **[1]** of the imidazole ring.

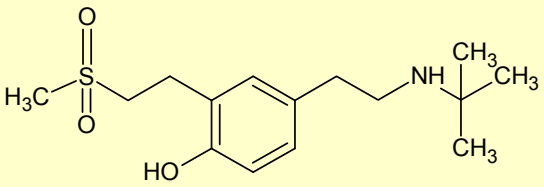
(iv) Predict the relative proton shift of benzene with respect to the proton shift of the protons of 1–methylimidazole. [1]

The proton shift of benzene is **more downfield** [1] as compared to the proton shift of 1–methylimidazole.

(c) **T** and **U** are sulfur–containing compounds that are derivatives of amphetamine.

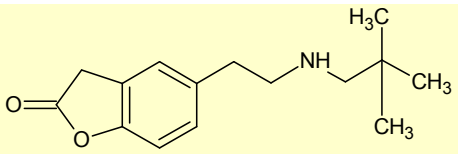


T

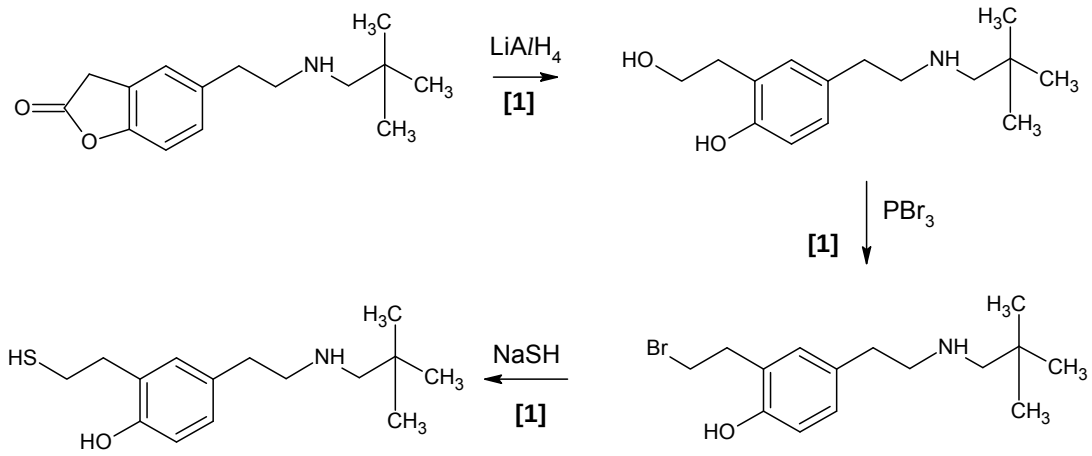


U

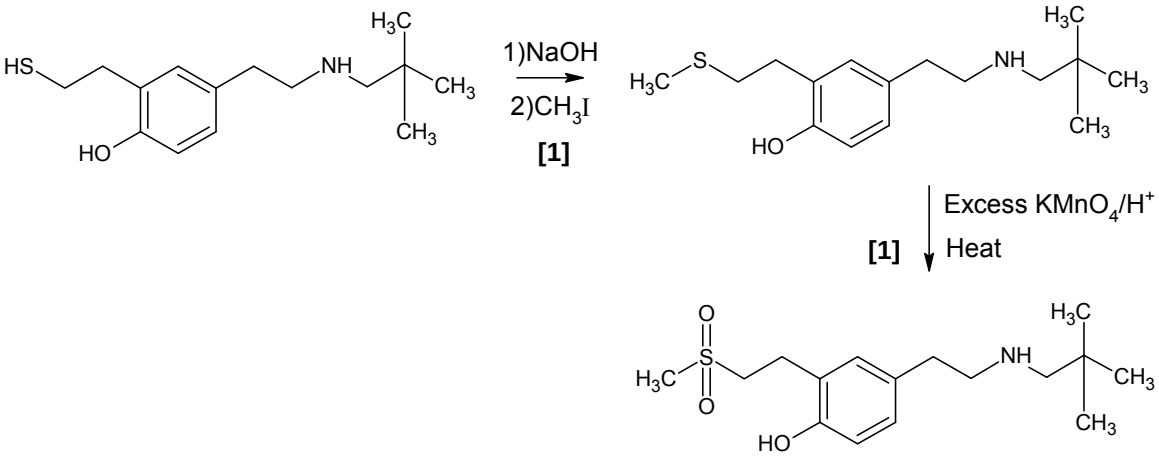
(i) Suggest how **T** may be prepared from the lactone.



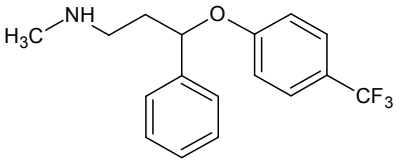
[3]



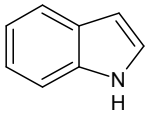
(ii) Suggest how **T** may be converted into **U**. [2]



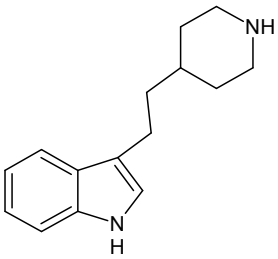
6 Indole is an aromatic heterocyclic organic compound with a bicyclic structure. Substituted indole represents as an interesting molecular architecture that exists in nature as well as synthetic drugs. Serotonin is a naturally occurring neurotransmitter that is responsible for the "feel good" effect. It is the research into this molecule that lead to the discovery of the first Selective Serotonin Reuptake Inhibitor (SSRI) – indalpine. Today fluoxetine which is a chiral drug is the most widely prescribed SSRI for treating depression and obsessive compulsive disorder. Unlike most sedating benzodiazepines, there has been no report of fluoxetine causing tolerance and dependency when used under medical supervision. Fluoxetine is a competitive inhibitor of serotonin uptake.



Fluoxetine



Indole



Indalpine

(a) (i) What is meant by the term *tolerance* and *dependency*? [4]

Tolerance is the process whereby **ever–higher concentrations of the antagonist are needed to achieve the same effect [1]**. This occurs as a result of the **response by the cell to produce more receptors [1].** Hence a higher dosage of the drug is required to produce the dampening effect.
Dependency is the term used to describe a patient whose **normal physiological functioning depends on the constant intake of the drug [1].** The cell has responded to the constant presence of the drug by producing more receptors. Hence, **any reduction in the intake of the drug will upset this balance [1]**.

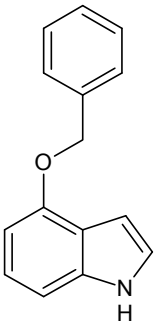
(ii) Briefly describe how a competitive inhibitor works. [2]

They **bind to the active site [1],** but because the bonding is an equilibrium process, they can be displaced by higher concentrations of the natural substrate. There is a **competition between the inhibitor and the substrate for active sites of the enzyme [1].**

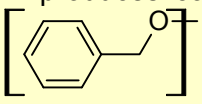
(iii) Suggest why the asymmetric synthesis of fluoxetine is important and how the enantiomers can be separated. [2]

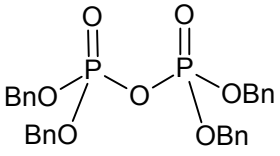
The enantiomers of fluoxetine may **elicit very different biological effect [1]** which may result in undesired outcomes in the patient.
Enantiomers may be separated by **enantioselective chromatography [1]** or forming different diastereomers and separating using fractional crystalisation**.**

A halloucinogen undergoing trials for the treatment of obsessive compulsive disorder is psilocybin $C_{12}H_{17}N_2O_4P$. Like indalpine, psilocybin is an indole based drug. The synthesis of psilocybin by David E Nicols *et al*. in 1999 is described below. The starting material is compound **V**, $C_{15}H_{13}NO$.



V

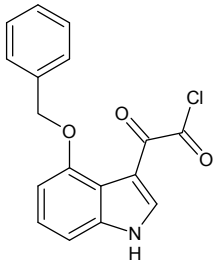
Compound **V** undergoes electrophilic substitution with $(COCl)_2$ at the 3 position of the indole ring to form compound **W**, $C_{17}H_{12}NClO_3$. On heating compound **W** with dimethylamine, compound **X**, $C_{19}H_{18}N_2O_3$ was obtained. When reacted with $LiAlH_4$ in dry ether, compound **X** produces compound **Y**, $C_{19}H_{22}N_2O$. Catalytic hydrogenolysis ofthe *O*–benzyl group  in **Y** produces a hydroxyl group in **Z**, $C_{12}H_{16}N_2O$. Upon reacting with *n*–BuLi, a nucleophile is produced which is further reacted with the phosphorylation agent TBPP. Further debenzylation produces psilocybin which is a phsophoester (ester form of phosphoric acid).



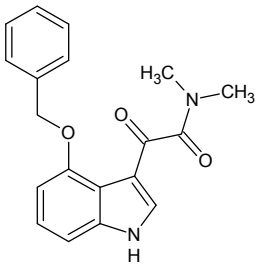
TBPP

Where OBn = *O*-benzyl group

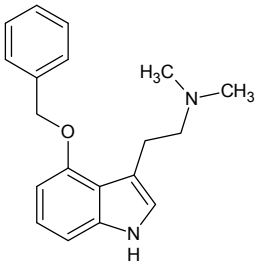
(b) (i) Suggest structures for **W**, **X**, **Y**, **Z** and psilocybin. [6]



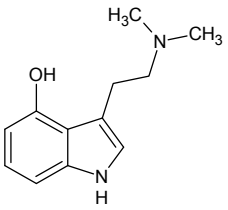
W



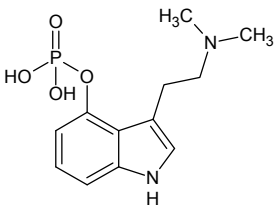
X



Y



Z



Psilocybin

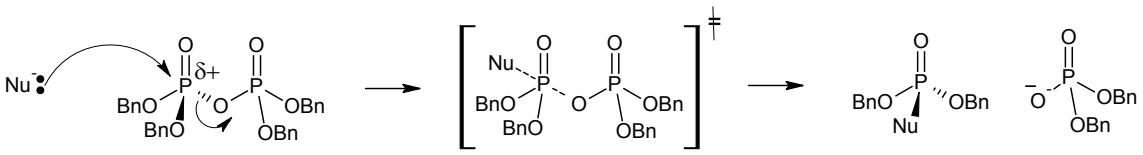
[1] for **W,X,Y,Z**

[2] for Psilocybin

(ii) What is the role of *n*–BuLi? [1]

It is acting as **a base [1].**

(iii) Suggest a mechanism for the S_N2 reaction between the nucleophile and TBPP showing clearly the stereochemistry at each stage. You may represent the nucleophile as Nu^-. [3]



[1] for partial charges and arrows, **[1]** for transition state, **[1]** for correct stereochemistry

(iv) The *O*–benzyl group serves as a protecting group which was removed at the later stage of the synthesis. Why is it not removed at the second step of the synthesis? [1]

The resulting **phenol may react with the acylating reagent at the first step [1].**

(v) Suggest, with a reason, the major difference between the UV spectra of indalpine and compound **V**. [1]

Compound **V** will show an **extra signal/peak [0.5]** on the UV spectra due to the additional ***O*–benzyl group which is UV active [0.5].**