**Hwa Chong Institution**
**H3 Pharmaceutical Chemistry 2008**
**Preliminary Examinations 2008 (Suggested Solutions)**

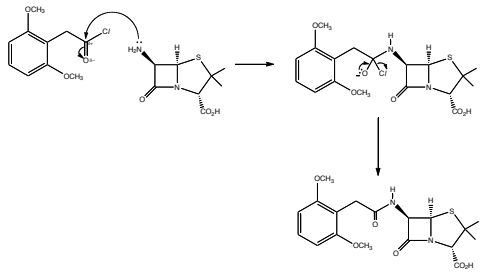
## Question 1

**(a)(i)** Penicillins inhibit irreversibly the enzyme transpeptidase involved in the final stage of bacterial cell wall formation

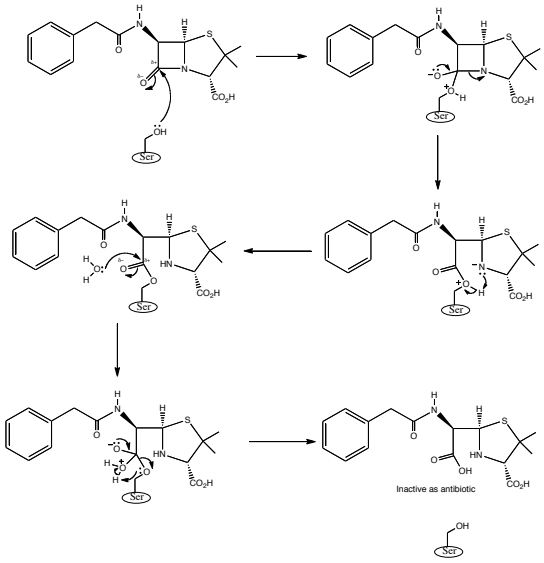
**(a)(ii)** R, R, S

**(a)(iii)** Chemical hydrolysis will not selectively hydrolyse the acyclic amide only, but will also lead to the hydrolysis of the strained β-lactam ring in penicillin-G

**(a)(iv)**



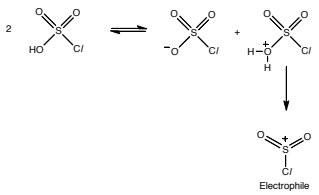
**(a)(v)**



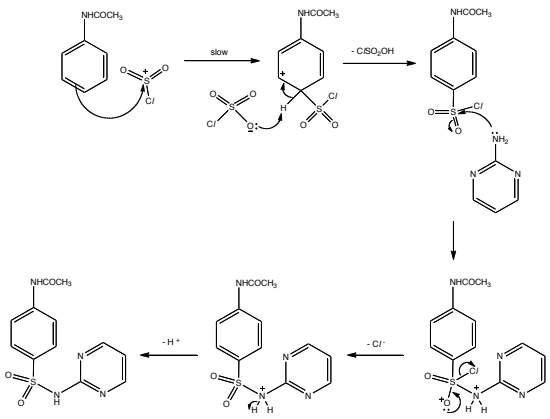

**(a)(vi)** By increasing the steric bulk of the side chain as in methicillin, the approach of a β-lactamase enzyme to the β-lactam ring is hindered in the semi-synthetic methicillin, giving it more resistance to enzymic hydrolysis

**(b)(i)** Sulphonamides behave as competitive inhibitors to the enzyme dihydropteroate synthetase, competing with the natural substrate 4-aminobenzoic acid and leads to the disruption of folic acid biosynthesis, which is vital for bacterial growth.

**(b)(ii)** Chlorosulphonic acid is a very strong acid and protonates itself to give the electrophile, explaining why OH is the leaving group and why chlorosulphonation rather than sulphonation is the result.




**(b)(iii)**




**(c)(i)** **<u>Any two:</u>**

The amino functional group ($-NH_2$) is essential for activity

The amino and the sulphonyl group have to be para to each other, i.e. a para-disubstituted ring is essential.

The anilo ($Ph-NH_2$) amino group may be disubstituted, but optimum activity is observed with the unsubstituted form.

Replacement of the central benzene ring (aromatic) or additional functional groups on the benzene ring diminishes activity.

N-monosubstitution on $SO_2NH_2$ increases potency, especially with heteroaromatic groups.

N-disubstitution on $SO_2NH_2$ leads to inactive compounds.

**(c)(ii)** Prodrug – it is metabolised to sulphanilamide in the body, accounting for its in vivo activity

**Question 2**

**(a)** Stimulants

**(b)**

| Caffeine | Nicotine |
|---|---|
| Competitive antagonist to adenosine receptors | Agonist to acetylcholine receptors |
| Works by increasing amount of adrenaline and noradrenaline | Works by increasing amount of adrenaline and other alkaloids |
| Inhibits an enzyme that breaks down cyclic-AMP | Production of alkaloids inhibit monoamine oxidase enzymes that destroy dopamine |

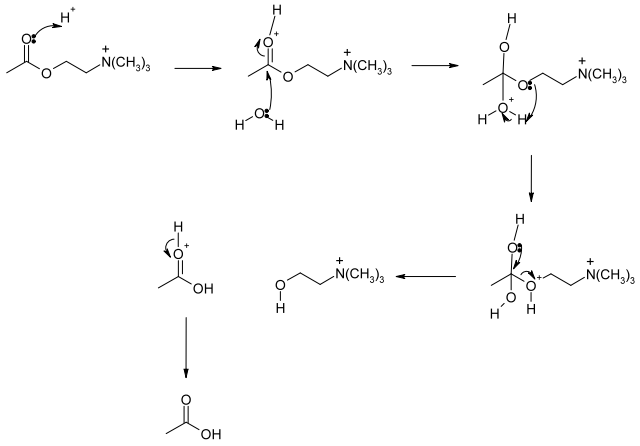
**(c)(i)**

- For caffeine, delocalized pi system <u>throughout the molecule</u>; for nicotine, delocalized pi system for <u>pyridine ring</u>
- Conjugation of pi bonds decreases the energy gap between $\pi$ and $\pi^*$ orbitals, shifting absorption to higher wavelength in UV absorption.

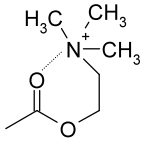
**(ii)**

- Caffeine
- Because of more delocalized pi system / extra conjugated ring

**(d)(i)**

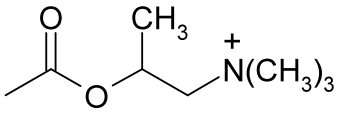


**(ii)**



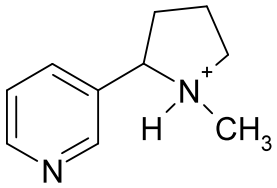
- positively charge N interacts with carbonyl oxygen
- making carbon more electron deficient. Thus the carbonyl carbon is more prone to nucleophilic attack.

**(iii)**



**(e)** <u>Basic</u> because the N attached to $-CH_3$ has an <u>available lone pair</u> which can accept $H^+$.

**(f)**



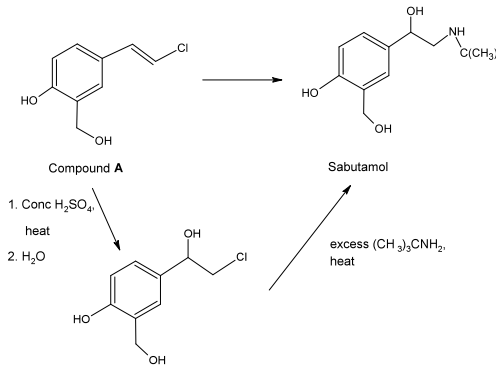

Nicotine is an agonist to acetylcholine and thus should have a positive charge like acetylcholine.

**(h)**

- causes increase in dopamine level
- receptors will decrease to reduce stimulation
- dosage needs to increase for same effect to be felt

**Question 3**

(a)




(b)

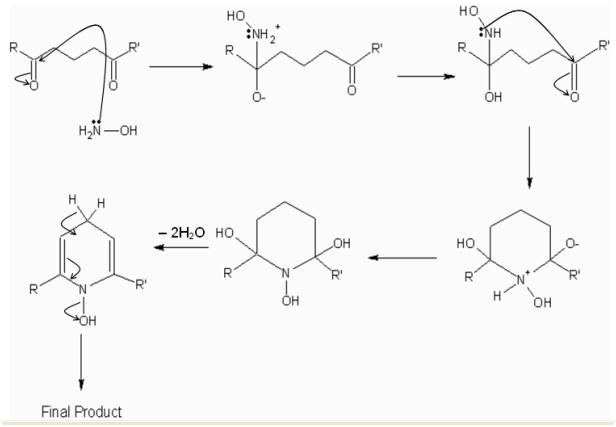
(i)

- The movement of a liquid mobile phase carrying solutes to be separated through a stationary phase
- The solute molecules partition themselves between the stationary phase and the mobile phase based on their polarities/ solubilities

(ii)

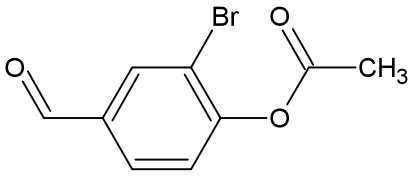
- Sabutamol is a polar molecule, the mobile phase should be polar and stationary phase non – polar
- Since it is a separation of optical isomers a chiral stationary phase should be used.

(c)



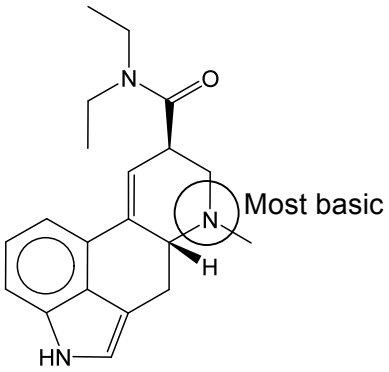

(d)

**B:**



**Question 4**

(a) (i)

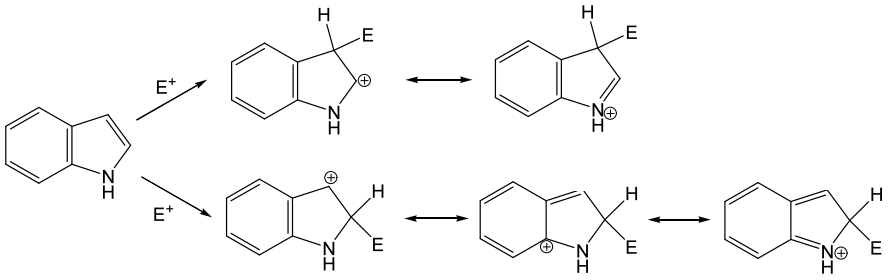



Lone pair on N of the amide group is delocalised over carbonyl group and lone pair on N of indole is part of delocalised $\pi$ electron cloud of aromatic system. Lone pair is localised on N of amine.

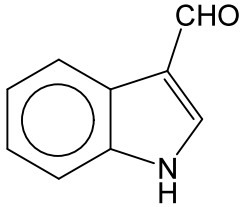
(a) (ii)

- -OH or $-NH_2$ functional group that can form hydrogen bond with amine functional group in LSD
- $-COO^-$ group that can form electrostatic interaction with $R_2NH_2^+$
- Polar functional group such as $-SCH_3$ that can form ion-dipole interaction with $R_2NH_2^+$
- Hydrophobic group such as $-C_6H_5$ that can form van der Waals interaction with hydrophobic groups in LSD

(a) (iii) I



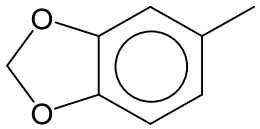

(a) (iii) II Peak at 1650 – 1700 $cm^{-1}$ $\Rightarrow$ presence of C=O functional group



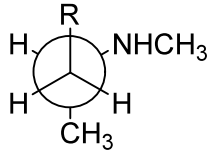

(b) (i) Retarding the re-uptake of neurotransmitters by the pre-synaptic nerve, by inhibiting the transporter proteins.

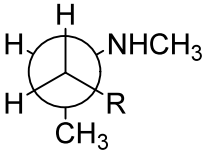
This results in a larger than normal concentration of neurotransmitter in the synapse, causing an over-simulation of the receptors on the post-synaptic nerve.

(b) (ii)

Let R = 

**Staggered: (all correct [1])**


I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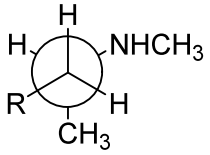
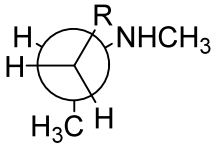

V

**Eclipsed: (all correct [1])**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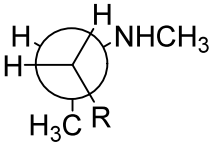
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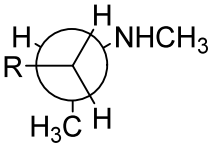
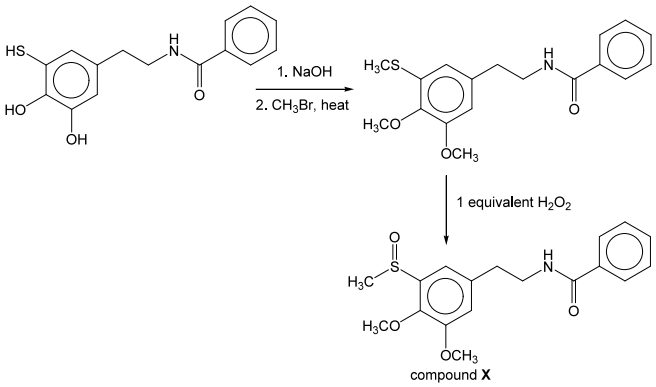
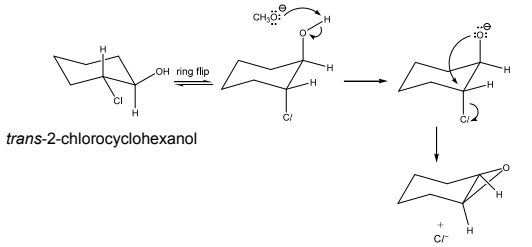

VI

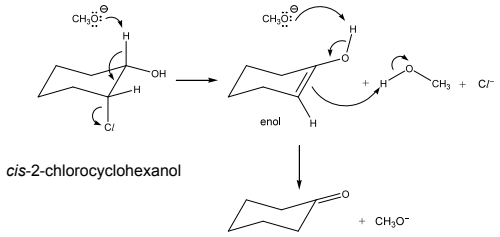
Correct energy profile and labelling required.

(b) (iii)



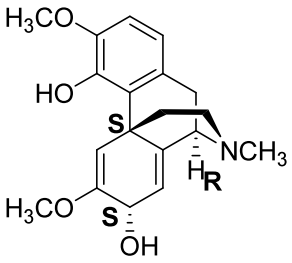

(c)



**Question 5**

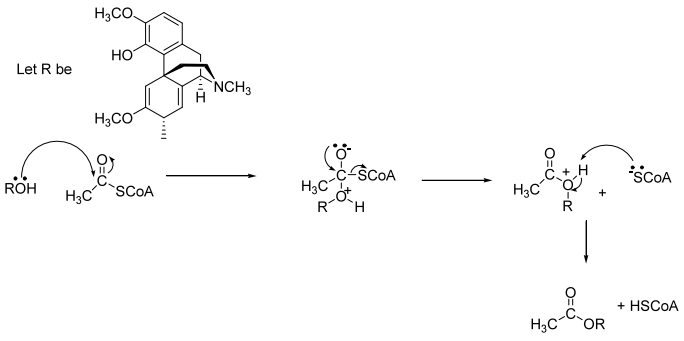
**a (i)**



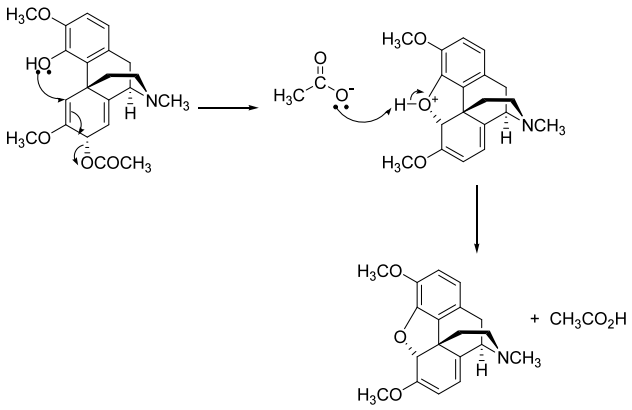
salutaridinol

**(ii)** It is chiral as ring inversion about N is prevented due to the large and bulky ring system.

**(b) (i)** Ester formation mechanism (acid/base)




**(ii)**




**(iii)** $CH_3COO^-$ is a better leaving group than $OH^-$.

**(c) (i)** Morphine is a substance that depresses the activity of the central nervous system resulting in pain relief.

**(ii)** Polar mobile phase such as ethanol/ water
Non-polar stationary phase such as carbowax

**(iii)** The larger alkyl group on the nitrogen atom binds/ fits better into the receptor site
It binds to the receptor site without activating the receptor

**(iv)**
- used to reverse morphine overdose.
- Test for morphine dependence in morphine users.

[any reasonable clinical use]

**(v)** The nitrogen oxide formed is more hydrophobic/charged and prevents it from passing through the hydrophobic blood brain barrier/ cell membrane.

**(d)** **(i)** If true: The nmr spectrum will show an additional labile proton at approximately 7 ppm due to phenolic −OH group.
If false: The nmr spectrum will show a singlet at approximately 2 ppm due to the $CH_3CO-$ group.

**(ii)** The protons in both functional groups are deshielded by the electronegative O atom
However, the proton in $-CO_2H$ is further deshielded by the diamagnetic anisotropic effect of –CO and thus have a much higher chemical shift.

**Question 6**

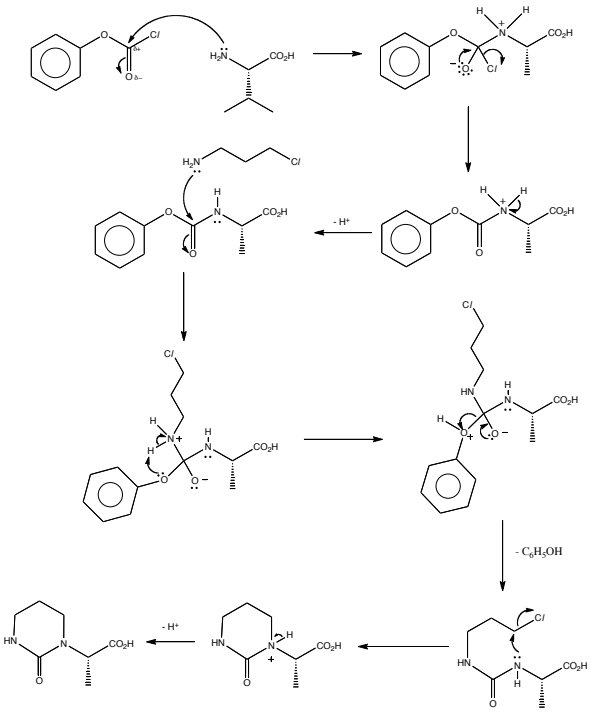
**(a)** Prevention of viral penetration into the host cell (or departure of new virus particles from the cell) by targeting the viral proteins in the capsid, either by blocking an ion channel in the virus membrane formed by a viral protein or inhibiting the viral enzyme neuramase. (Amantidine, Rimantadine and Zanamivir)

The inhibition of the synthesis of viral nucleic acids through the antiviral mimicking the nucleoside thymidine and getting incorporated into a growing DNA by the viral reverse transcriptase enzyme.

The inhibition of viral protein synthesis through the use of antivirals such as Tilorone, which is effective in inducing cells to produce their own interferon. Interferons are naturally occurring glycoprotein hormones that are produced by cells in response to a viral attack. Their viral action is due to the inhibition of the synthesis of viral proteins and/or viral mRNA that codes for these proteins.

**(b)** S, S, S, S

**(c){i)**




**(c)(ii)** Correct diagram and stereochemistry needed.

**(d)(i)** An extra ring of delocalised electrons in Y causes the gap between energy levels to decrease, hen shifting the absorption to longer wavelengths

**(d)(ii)** $7.39 \times 10^{-5}$ mol $dm^{-3}$

**(d)(iii)** 8790

**(d)(iv)** $SOCl_2$

**(e)** The presence of a specific antigen on the surface of a bacterium or virus particle triggers the *in vivo* synthesis of a protein, known as an antibody, in a particular B lymphocyte.

Each type of B lymphocytes makes only one sort of antibody.

Once a particular B lymphocyte recognises the particular antigen for its antibody, it starts to make many more antibody molecules to bond with the invaders and neutralise them.

Monoclonal antibodies are antibodies that have been “cloned” from one particular B lymphocyte.

The technique involves fusing B lymphocyte cells with bone marrow cancer (myeloma) cells to make hybridoma cells.

These cells divide indefinitely and produce masses of just the one antibody that the original B lymphocyte cell produced.

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