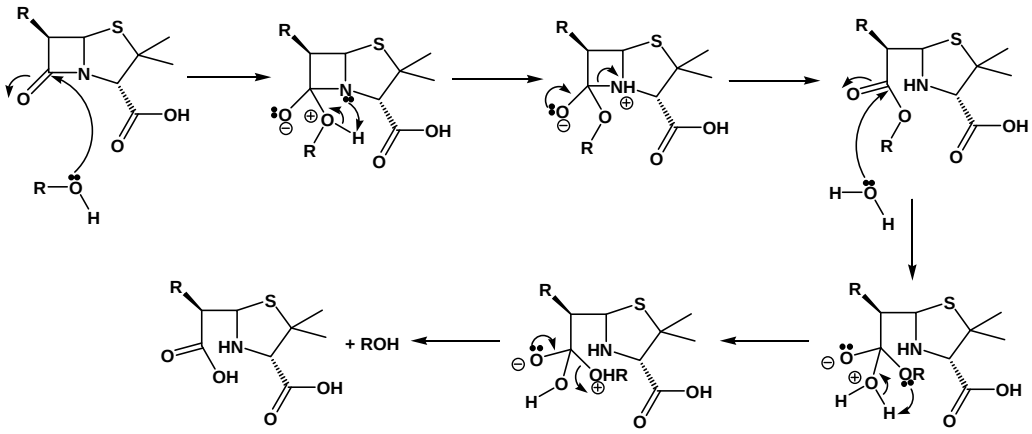
Answers for 2011 H3 Chemistry Prelims

1 (a) (i)

- Disruptions of the synthesis of folic acid
- Disruptions of protein synthesis
- Plasma membrane disruption
- Disruption of nucleic acid transcription

Any 2 of the above.

(ii)

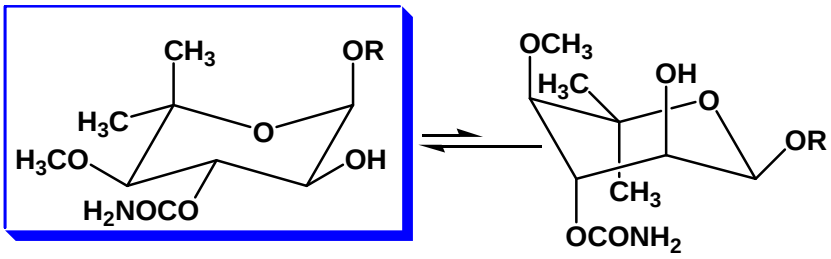


(iii) Penicilloic acid does not retain the rigid conformation as that of penicillin and thus will not be able to effectively interact with the D-Ala-D-Ala termini in glycopeptides transpeptidase.

Accept if students talk about the fact that the strained β-lactam ring is essential in the SAR.

(iv) It is an irreversible inhibitor as it covalently modifies the enzymes and this inhibition cannot be reversed.

(b)



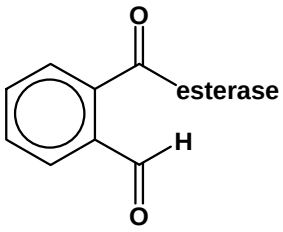
The more stable conformation is indicated in the box above.

It is more stable as it has minimal 1,3-diaxial interaction (two as compared to four). [Accept if student mention anomeric effect]

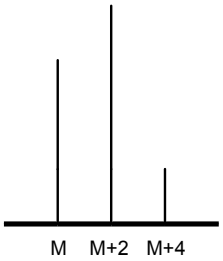
(c) (i) Pivampicillin is more lipophilic (non-polar) and thus can be better absorbed through the gut wall.

(ii) The ester group further away from the penicillin nucleus, is less sterically hindered as compared to the other ester group and thus more susceptible to attack by nucleophiles. Hence it undergoes hydrolysis more easily.

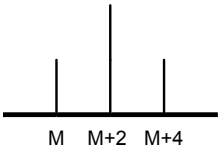
(iii)



(d) (i) Around the molecular ion peak, isoniazid-A and isoniazid-B will give the following pattern respectively:



isoniazid-A
3 : 4 : 1



isoniazid-B
1 : 2 : 1

(ii) (I) NaCN; nucleophilic substitution
(II) H_2NNH_2

2 (a) (i) Irreversible inhibition of the cyclo-oxygenase (COX) enzyme that it needed to turn arachidonic acid into prostaglandins.

As prostaglandins are hormones responsible for the transmission of pain information to the brain, inhibiting the enzyme will reduce the pain felt, hence the analgesic effect.

(ii) Since aspirin is less polar than benzoic acid, aspirin has greater affinity for the non-polar stationary phase and it eluted later. Thus peak 3 is due to aspirin.

(iii)

Peak area of component 1 = $\frac{1}{2} \times 0.3 \times 6.2 = 0.930$

Peak area of component 2 = $\frac{1}{2} \times 0.5 \times 2.5 = 0.625$

Peak area of component 3 = $\frac{1}{2} \times 1.0 \times 1.6 = 0.800$

Ratio of component 1 : 2 : 3 = 0.930 : 0.625 : 0.800

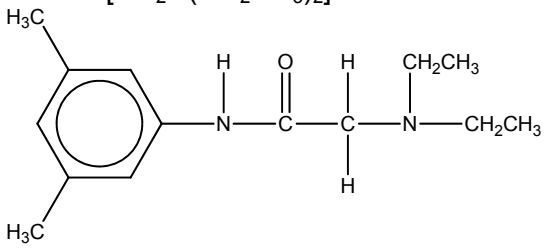
(b) Number of carbon = (100/1.1)(15.4/100) = 14

Molecular formula = $C_{14}H_{22}N_2O$

δ	Deduction
1.13 (t 6H)	2 CH_3 groups next to CH_2
2.29 (q 4H)	2 CH_2 groups next to CH_3
2.23 (s 6H)	2 CH_3 groups with no neighbouring proton
3.22 (s 2H)	CH_2 with no neighbouring proton; deshielded $\Rightarrow$ next to electronegative atom N
7.09 (m 3H)	3 protons of tri-substituted benzene
8.92 (s 1H)	Labile proton of –NH

Wavenumber / cm^{-1}	Deduction
3250	N–H stretch
1675	C=O stretch
2800 - 3000	sp^3 C–H stretch
1500	aromatic C=C stretch

Fragment ion at m/e 86: $[CH_2N(CH_2CH_3)_2]^+$

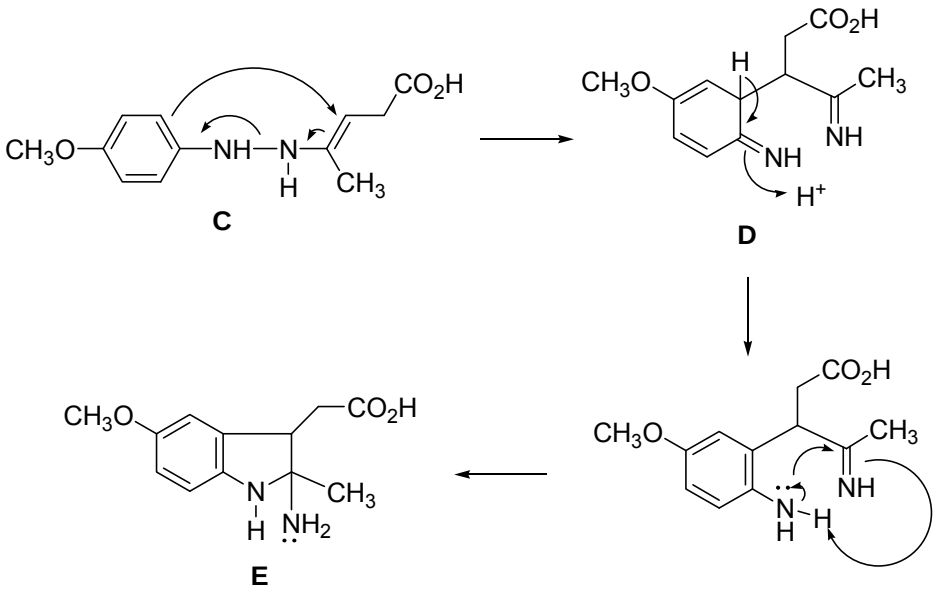


Structure:

(Can accept the methyl groups to be 2,6 substituted and/or interchange NH with CO in the amide group)

(c) **(i)** Step 1: NaOH (or Na), CH_3Br, heat
Step 2: $CH_3COCH_2CH_2CO_2H$

(ii)



C **D** **E**

3 (a) (i) Different modes of vibrations in a molecule give rise to different vibrational energy levels, such as stretching and bending.
For a vibrational mode to be active in the IR region, there must be a net change in the dipole moment of the molecule when the vibration takes place.

(ii) $BeCl_2$ has 2 absorption bands caused by asymmetric stretching and bending.
Cl_2O has 3 absorption bands caused by symmetric stretching, asymmetric stretching and bending.

(b) (i) serotonin: 2 characteristic peaks for N-H stretch (~3400 cm^{-1}) [also accept 3 peaks]
mCPP: 1 characteristic peak for N-H stretch (~3400 cm^{-1})

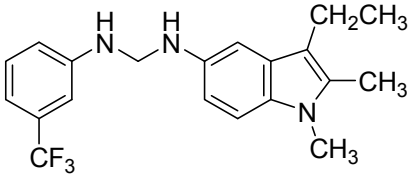
serotonin: Presence of peak for O-H stretch (~3300 cm^{-1})
mCPP: Absence of peak for O-H stretch

(ii) Benzene ring: dispersion forces
N atom beside the benzene ring: hydrogen bonding or ionic interactions
The other amine group: hydrogen bonding or ionic interactions

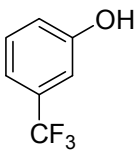
(c) (i) Compound **G** is able to bind to the receptor site via intermolecular forces similar to serotonin. Because it is able to fit better in receptor site, it is able to block the site without changing the shape of the receptor, hence there is no biological effect.

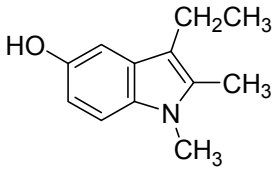
(ii) Compounds **G** and **H** give one and three reduction products respectively.

Product from **G**:

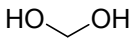


Two of the products from **H** are:





The last product from **H** can be any of these:



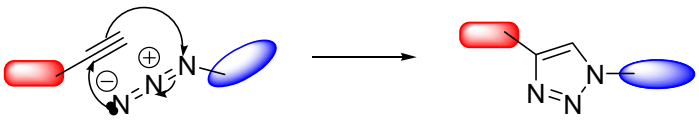
CH_3OH

(iii) The amide bonds are more resistant to hydrolysis than the ester bonds due to the partial delocalisation of the nitrogen lone pair over the carbonyl group. Hence compound **H** is more susceptible to hydrolysis.

(iv) Solubility: Any suggestion that will form more hydrogen bonding with water (e.g. adding OH and NH_2 groups, replacing benzene ring with pyridine).

Flexibility: Introduce a ring to the urea functional group to make the structure more rigid (e.g. reacting both NH groups with C*l*-CO-CH_2-CO-C*l* to form a ring)

(d) **(i)**



Deduct −0.5 for any mistake.
Driving force: Formation of a 6π electrons aromatic system.

(ii) Compound **J** is less conjugated than PTP1B inhibitor, therefore the gap between the energy level is greater. The maximum absorption will occur at a shorter wavelength for Compound **J**.

4 **(a)** **(i)** A stimulant is a drug that acts on the nerve synapses to "wake up" the central nervous system.

Accept any 2 of increased heart rate, blood pressure, respiratory rate, blood sugar levels, adrenaline levels etc.

(ii) Amphetamine binds to the protein carrier on the surface of the presynaptic nerve, allowing stores of neurotransmitter to leak out of the nerve to the synaptic cleft.

It inhibits the re-uptake of noradrenaline and dopamine into the presynaptic nerve.

(iii) As a prodrug, Vyvanse is in itself inactive, and time is required to hydrolyse the amide bond to get the active amphetamine, so because there is no euphoric rush, there is much less potential for abuse.

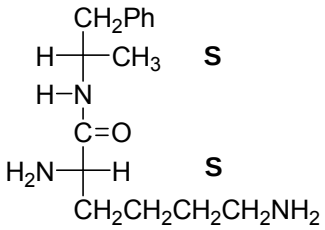
(iv) The body builds up a tolerance to the stimulant.

Assuming a drug acting as an antagonist at the receptor, depriving the receptor of its natural ligand may induce the cell to synthesise more receptors over time.

Hence a higher dose of the antagonist is required to suppress the binding of the natural ligand / for the same biological effect.

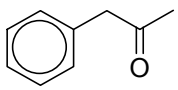
(to accept explanation based on agonist as well)

(v)

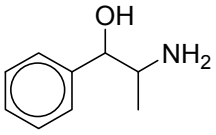


(vi)

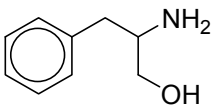
K:



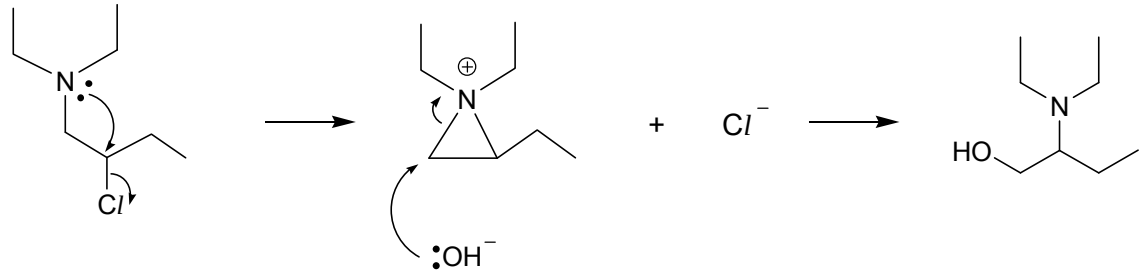
L:



or



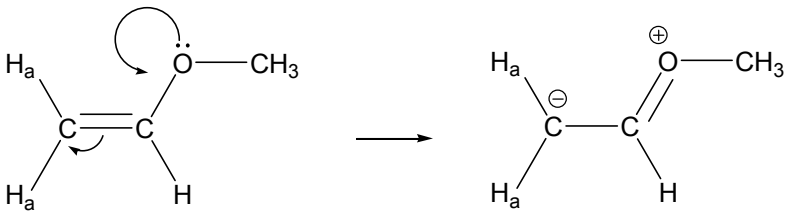
(b)



The intermediate is stable as there are electron-donating ethyl groups attached to the nitrogen / participation of the neighbouring amine group.
The OH^- nucleophile attacks the less sterically hindered carbon of the intermediate, hence the primary alcohol is formed.

(c) **(i)** Lithium is more electropositive than silicon.
Protons of CH_3Li more shielded than those in TMS.

(ii)



By mesomeric / resonance effect, the oxygen atom increases electron density at the terminal carbon, hence H_a is more shielded and δ is lower.

5 **(a)** **(i)** Movement of molecules through the gel support in an electric field is influenced by their charge.

Positively charged → cathode
Negatively charge → anode

Movement also influenced by size and shape. Smaller and more symmetrical molecules move further.

(ii) Any pH less than or equal to 1.70.

All amino groups and carboxylic groups will be protonated at that pH, peptides will have an overall positive charge.

(iii) Peptides without disulfide bridge are unaffected by oxidation with performic acid thus they do not experience mobility change. Spots developed will be on the diagonal.

Peptides with disulfide bridges will migrate off diagonal due to change in structure.

(iv) $R–CH_2SO_3H$

(b) **(i)**
- Nitrogen is more electronegative than carbon and it withdraws π electron density from the ring, thus decreasing the ease of electrophilic substitution.
- The non bonding electrons on the nitrogen atom are perpendicular to the π system, and they cannot stabilise the positively charged intermediate effectively.
- Electrophilic substitution of pyridine is further hindered by the tendency of the nitrogen atom to attack electrophiles and take on a positive charge. The positively charged pyridinium ion is even more resistant than pyridine to electrophilic substitution.

(ii) $-OCH_3$ and $-NH_2$ groups donate electrons into the pyridine ring by resonance and activate the ring to ensure greater ease of electrophilic substitution.

(iii)
- Formation of electrophile between H_2SO_4 and HNO_3
- Attack of electrophile on pyridine ring to form intermediate
- Drawing of mesomeric structures
- Formation of final compound

(c) **(i)** For a drug to cross the blood brain barrier, the drug must cross the lipophilic cell membrane.

Outside the cell, the drugs can be ionised where the amine groups are protonated. The ionised form can form ion-dipole interaction with water.

$R_3N + H^+ = R_3NH^+$
An equilibrium exists between the ionised form and the unionised form.

The ionised form will remain in the aqueous medium while the unionised form will be partitioned into the plasma membrane.

The unionised form forms dispersion forces with the hydrophobic plasma membrane as it contain large hydrophobic group such as benzene.

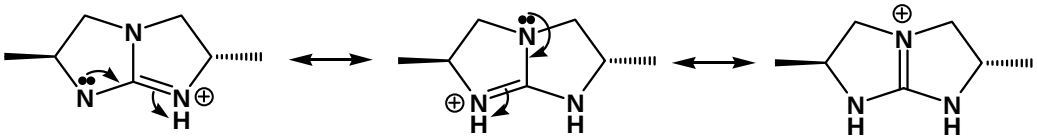
Once it has reached the inside of the cell which is aqueous in nature, the drug will be protonated and will interact with the negatively charged receptor via ionic interaction.

(ii) Heroin is more effective in crossing the blood brain barrier as the two polar –OH group are masked by the formation of an ester and an ether.

(iii) **(I)** Less effective
(II) Same effectiveness

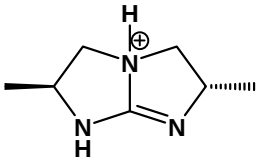
Important binding interaction of the phenolic OH is not present in 1, while the removal of the alkene in the ring system does not significantly alter the binding interactions.

6 **(a)**

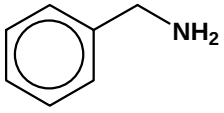


As illustrated in the above resonance structures, when nitrogen 1 is being protonated, the positive charge can be delocalised over the 3 nitrogen atoms.

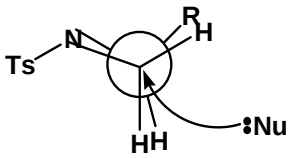
However if nitrogen 2 is protonated as shown below, delocalisation is not possible.



(b) **(i)**

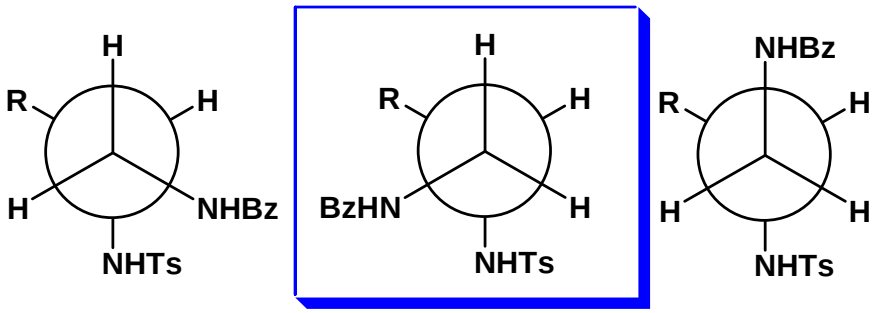


(ii)



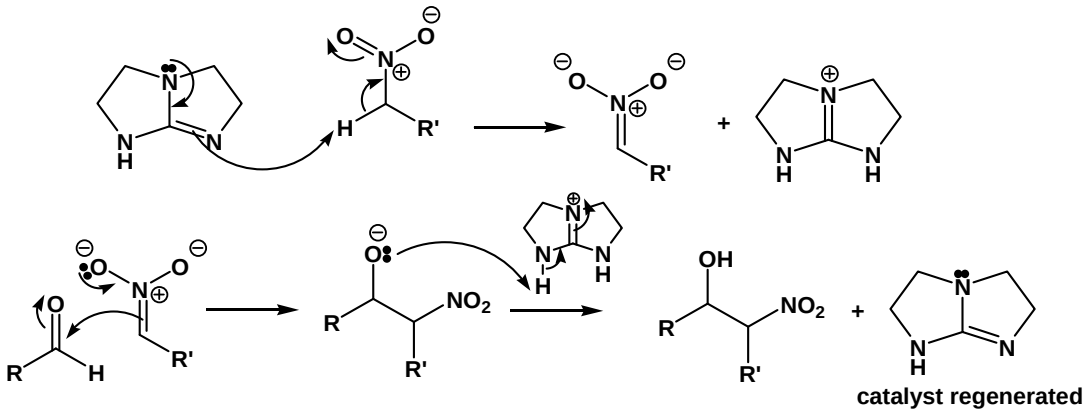
Correct Newman projection
Correctly labelled approach by nucleophile

(iii)

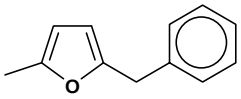


Most unstable conformation indicated (box)
It is because of the gauche interactions between the bulky groups.
The other two conformers drawn.

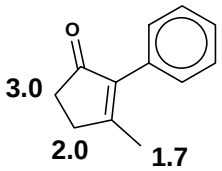
(c)



(d) **(i)**



(ii)



(e) Step 1: NaOH(aq)
Step 2: 1 equivalent of H_2O_2 or $NaIO_4$