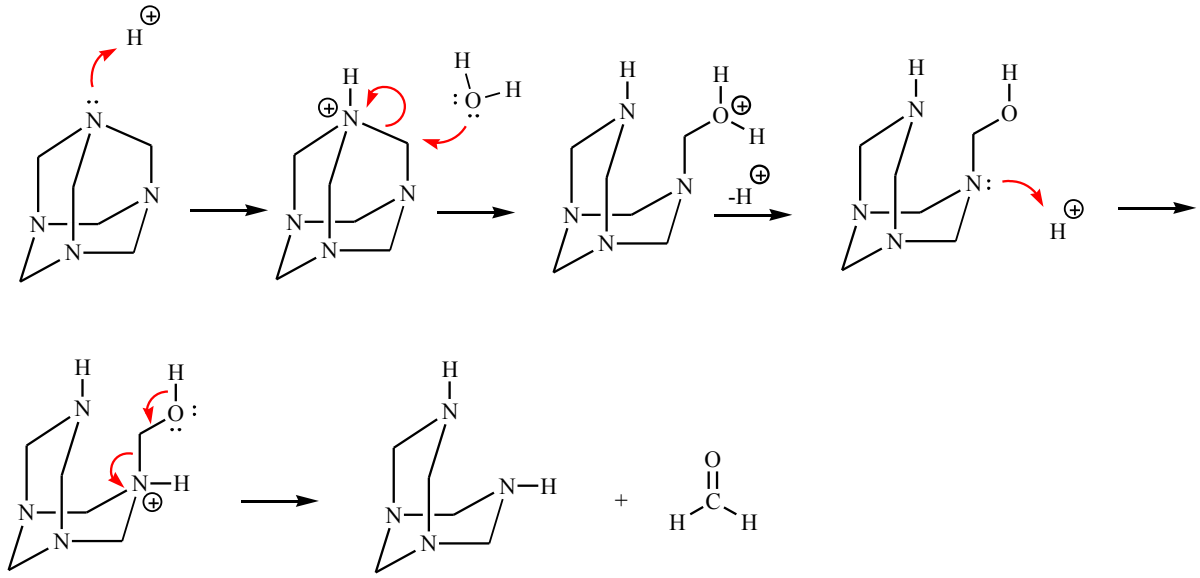
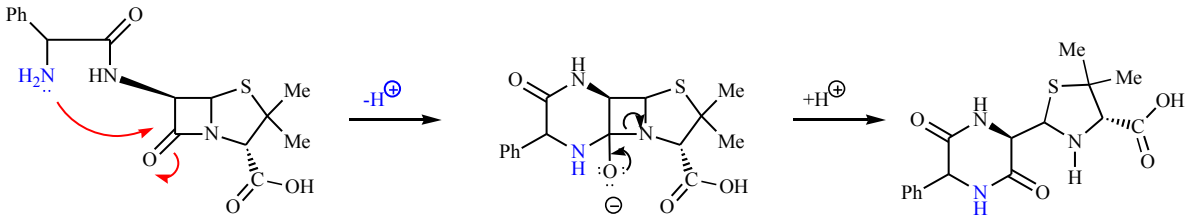
Answers to end-of-chapter questions

1) The mechanism below shows the release of one molecule of formaldehyde from methenamine. The mechanism can then be repeated to release a further five molecules of formaldehyde. Four molecules of ammonia will eventually be formed as well. Since acid is present, the ammonia molecules would be protonated and form an ammonium salt.



2)



3) The transport proteins that carry levodopa across the blood brain barrier are present in order to transport essential amino acids. Levodopa has a normal head group for an amino acid and is accepted as such. Carbidopa does not have the normal head group. It has a hydrazine group in place of am amino group. There is also a methyl group at the α-carbon instead of hydrogen. As a result, it is not accepted by the transport proteins.

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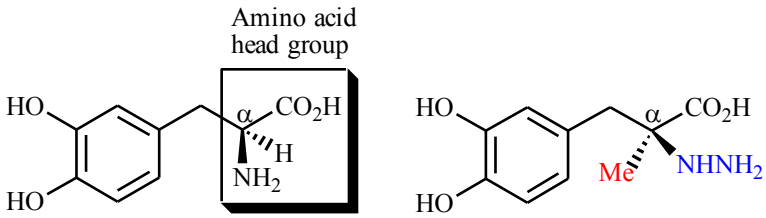
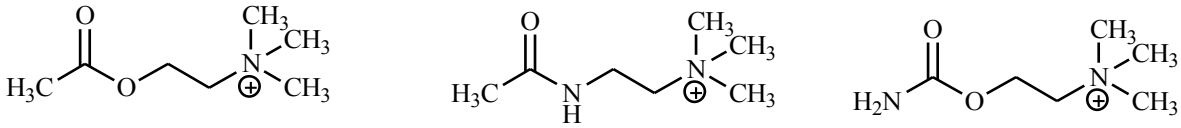


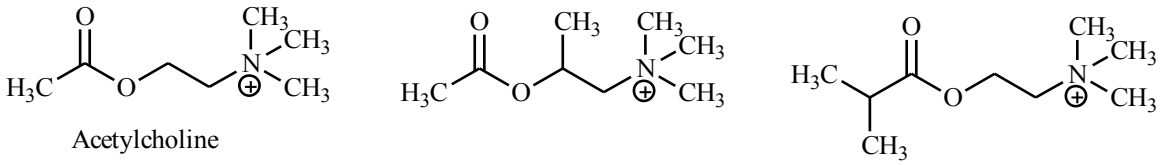
Levodopa Carbidopa

4) Electronic modifications could be carried out to stabilise the ester group. For example, the ester could be replaced with an amide or a urethane group.



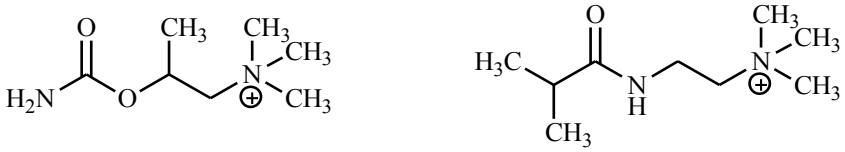
Acetylcholine

Steric shields could be added to hinder the access of nucleophiles or water to the carbonyl group.



Acetylcholine

A combination of both tactics could be used e.g.



Structures such as these should be more stable, but it is important to consider whether the changes made will affect the binding interactions of the compound. There is little point in designing a stable analogue of acetylcholine if it cannot fit the receptor binding site (see also section 22.7).

5) A metabolic reaction is required which would either neutralise the positive charges on the nitrogen or split the molecule such that both charges are no longer present on the same structure. One way of splitting the molecule in two would be to introduce an ester into the alkyl chain. It is well known that esters are easily hydrolysed by esterases. The following structures are examples of molecules which would be worth investigating (see also section 22.10.2.2).

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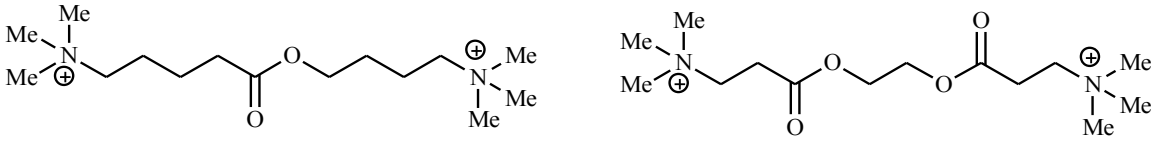
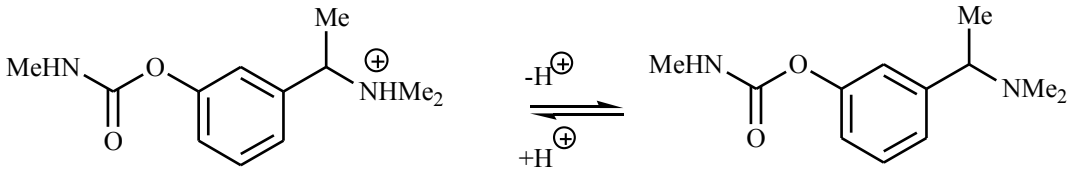


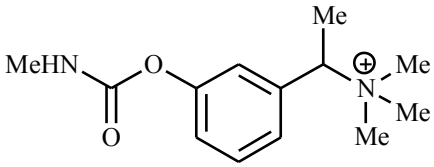
6) Miotine, as shown in the diagram, has a positive charge and should not be able to cross the blood brain barrier. However, it is possible for the molecule to lose a proton to form the free base and this structure can cross the blood brain barrier to produce the CNS effects observed.



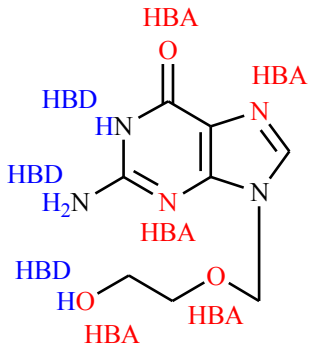
Miotine (ionised)

Miotine (free base)

In order to prevent this happening, the amine could be alkylated to form a quaternary structure. This cannot lose its positive charge and cannot cross the blood brain barrier (see also section 22.13.1.2).



7) Aciclovir contains several polar functional groups that can participate in hydrogen bonding. However, polar groups can hinder the passage of a drug across the fatty cell membranes of the cells lining the gut wall.



One way of solving this problem would be to mask a polar group such that the molecule is less polar and can cross cell membranes more easily. The group used to mask the polar group would have to be easily removed by a metabolic reaction in order to release the active drug once it has been absorbed. There are two accessible functional groups which could be masked - the primary amine or the alcohol. One could mask the amine as an amide or the alcohol as an ester. Masking the alcohol is

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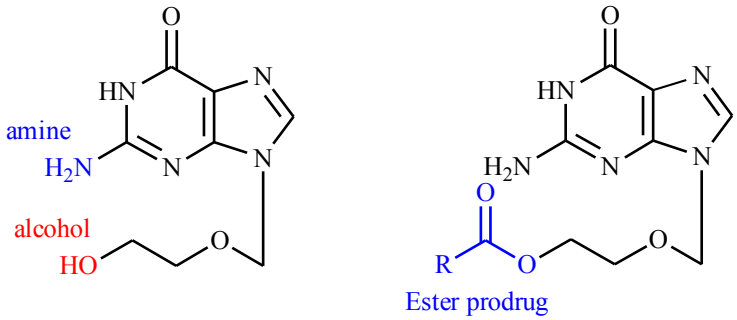
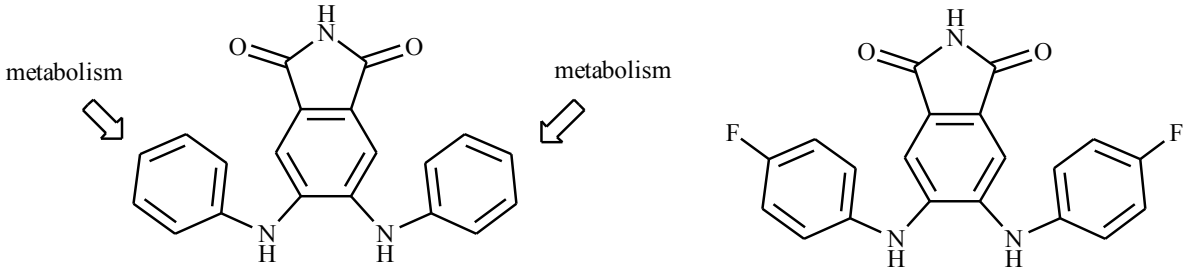
the better option since it is well known that esters are easily cleaved by esterases in the blood. Esters are also more susceptible to hydrolysis than amides. A variety of ester prodrugs could be tried out to find the best. It is also worth considering what will be released from the drug when the ester is hydrolysed. Preferably, this should be a naturally occurring chemical such as an amino acid (see also section 20.6.1).



8) The following diagram shows where metabolism occurs on this molecule. To prevent this from happening, metabolic blockers could be added to the *para* positions. Halogen atoms are often used for this purpose, but SAR results demonstrate that aromatic substituents are bad for activity. This may be a steric problem if the aromatic rings are fitting into small hydrophobic pockets in the binding site. Therefore, one should add fluoro substituents since fluorine is comparable in size with hydrogen.



9) The most likely explanation is that the two analogues lack a group that is easily metabolised, resulting in excessively long half lives. The methyl group of celecoxib is susceptible to oxidation which would result in a polar group such as a carboxylic acid. This could undergo a conjugation reaction resulting in a polar metabolite which would be rapidly excreted.

10) There are five main positions which are particularly susceptible to metabolism. More than one metabolic reaction may occur on the one molecule and it has been predicted that there are over 40 possible metabolites that could be formed based on these reactions alone.

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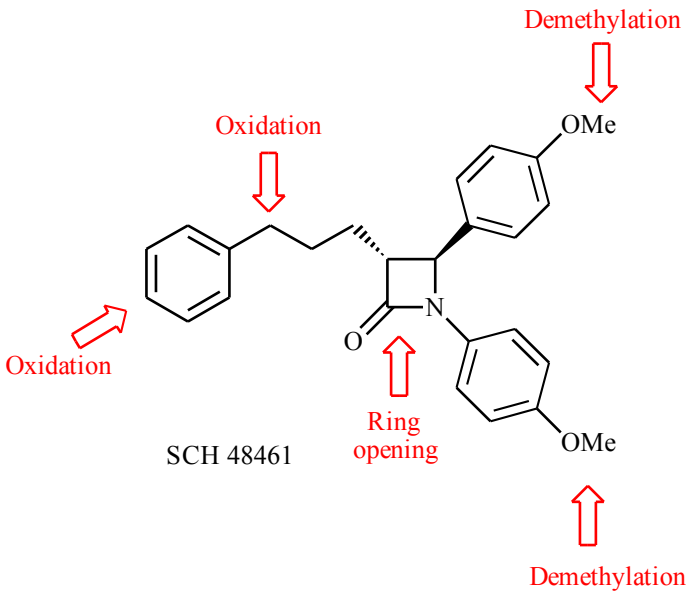

Oxidation of the aromatic ring at the *para* position could be blocked by introducing a fluoro-substituent. Demethylation could be prevented by changing the methyl group to a different alkyl group, or removing the methoxy group entirely. Benzylic oxidation could be blocked by introducing a substituent at that position to act as a steric shield. Another possibility might be to place *ortho* substituents on the aromatic ring to act as steric shields. The 4-membered lactam ring is susceptible to hydrolysis. Substituents on the aromatic ring linked to the lactam nitrogen might act as steric shields and help to make the ring less susceptible to hydrolysis.

It should be noted that metabolic reactions are not always detrimental to activity. Some may even improve activity. For example, benzylic oxidation and demethylation of one of the methoxy groups have been shown to be advantageous to activity. Such studies led to the design of the following structure which has improved activity. Note that two of the possible metabolic reactions have been blocked and that two groups introduced by metabolic reactions have been added because they are beneficial to activity.

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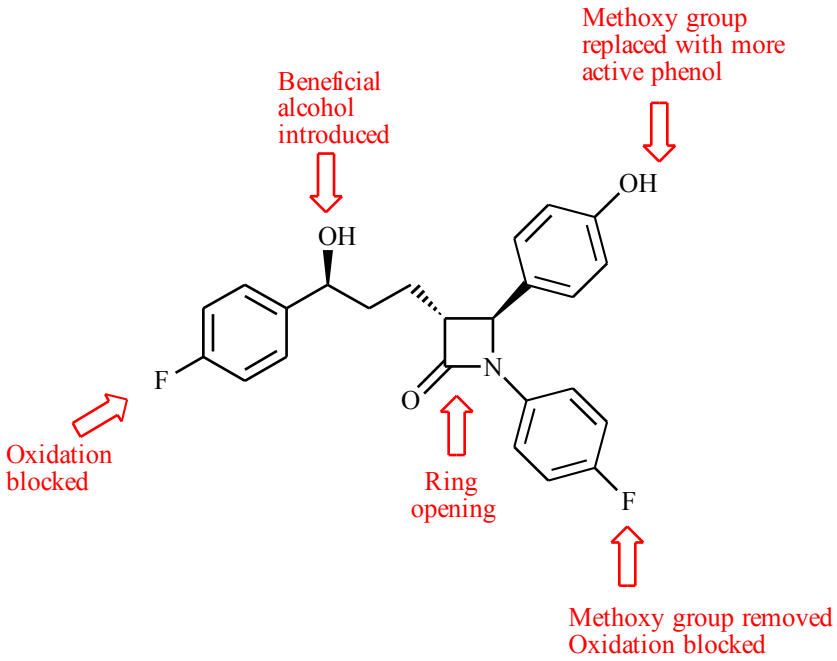

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