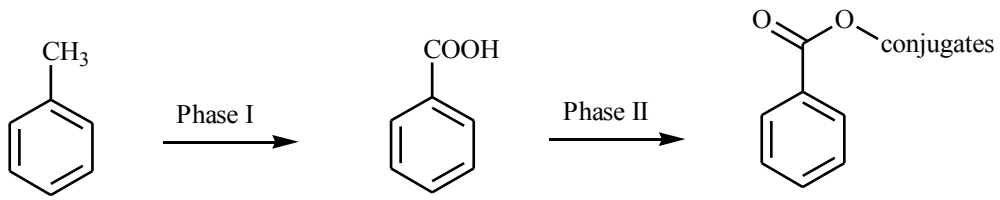
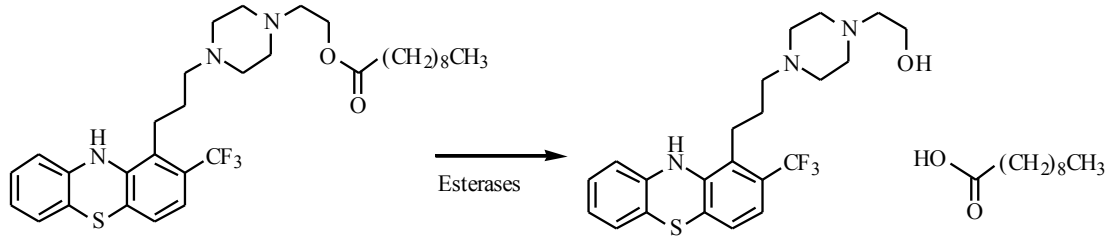
Answers to end-of-chapter questions

1) In contrast to benzene, toluene has an accessible methyl group which can be manipulated easily by metabolic enzymes. Exposed methyl groups are susceptible to oxidation, and so the most likely metabolite is benzoic acid which could undergo further phase II conjugation reactions and be quickly excreted.



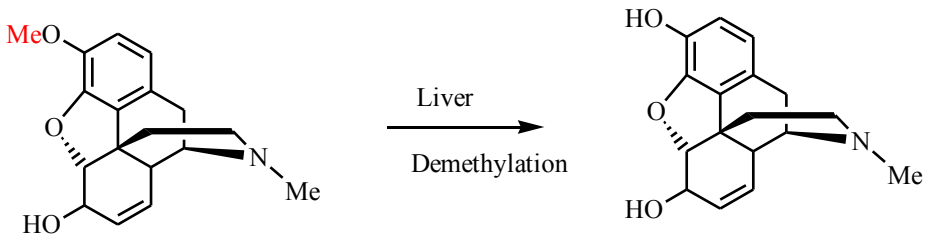
2) The fluphenazine prodrug contains an ester group which is susceptible to hydrolysis by esterases in the blood. If the drug is given by i.v. injection, the ester is quickly hydrolysed. If the ester is given by intramuscular injection, it takes longer for it to enter the blood supply and so its rate of hydrolysis is slower (see also section 14.6.2).



Fluphenazine prodrug

3) The quaternary salt of morphine contains a permanent positive charge. If the compound is administered *in vivo,* it has to cross the blood brain barrier in order to reach the analgesic receptors in the brain. However, the permanent positive charge prevents it from crossing. Thus, the observed inactivity *in vivo* is due to the inability of the compound to reach the receptors in the brain.
In vitro tests are carried out on isolated receptors or cells and so there is no blood brain barrier to cross (see also section 24.5).

4) When codeine is administered, a certain proportion of it undergoes a metabolic reaction in the liver which cleaves the methyl ether and generates morphine. This accounts for the analgesic activity observed (see also section 24.5).



Codeine Morphine

5) The Henderson Hasselbalch equation can be used to calculate this

$$pH = pKa + \log \frac{[RNH_2]}{[RNH_3^+]}$$

a) At pH5.74, the equation is as follows:

$$5.74 = 5.74 + \log \frac{[RNH_2]}{[RNH_3^+]}$$

$$\text{Therefore} \quad \log \frac{[RNH_2]}{[RNH_3^+]} = 0$$

$$\text{Therefore} \quad \frac{[RNH_2]}{[RNH_3^+]} = 1$$

$$\text{Therefore} \quad [RNH_2] = [RNH_3^+]$$

b) At pH 7.4, the equation is as follows:

$$7.4 = 5.74 + \log \frac{[RNH_2]}{[RNH_3^+]}$$

$$\text{Therefore} \quad \log \frac{[RNH_2]}{[RNH_3^+]} = 1.66$$

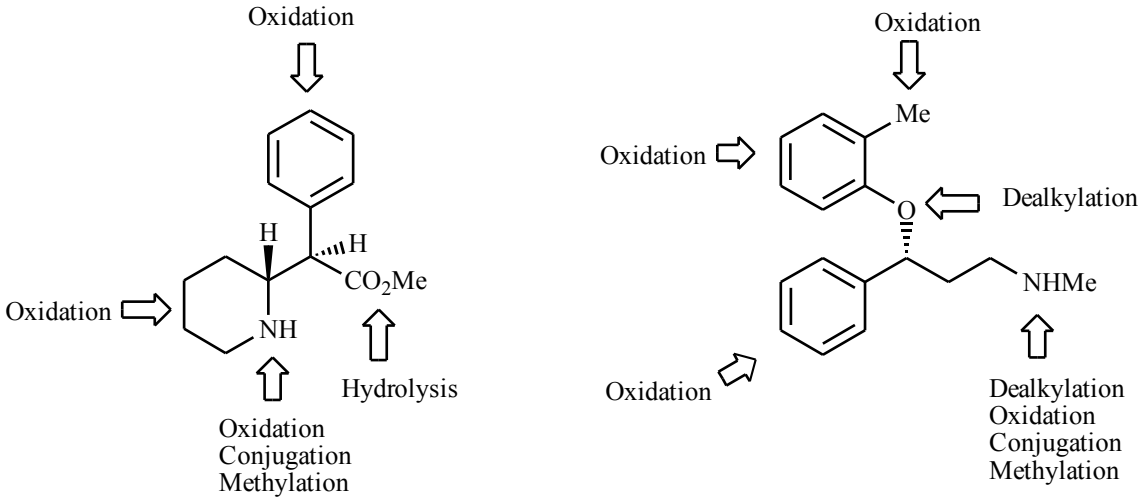
$$\text{Therefore} \quad \frac{[RNH_2]}{[RNH_3^+]} = 45.71$$

Therefore, the percentage levels of free base and ionized base at pH 7.4 are 98% and 2% respectively.

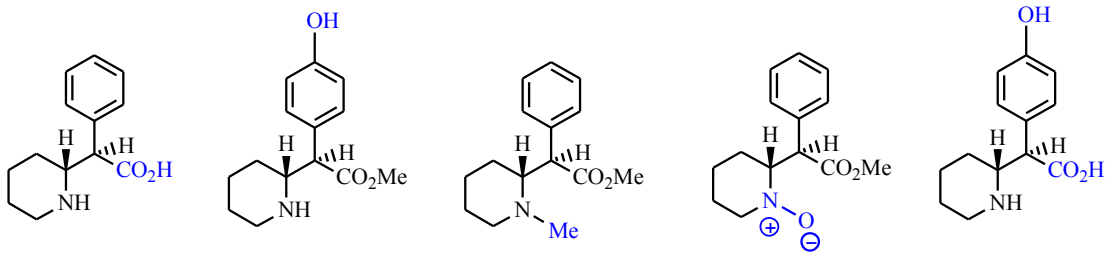
6) *In vitro* studies show that the drug has good activity against is target. The fact that the drug shows poor activity when it is administered orally can be put down to poor absorption from the digestive tract. Since the drug has a highly polar carboxylate group present, it will not pass through the hydrophobic cell membranes of the cells lining the gut wall.
If the drug is administered by intravenous injection, it is introduced directly into the blood supply and can now reach its target.
The ester of the drug acts as a prodrug. When administered orally, the prodrug can cross the cell membranes of the cells lining the gut wall because the ester masks the

polar carboxylate group. Once the prodrug is in the blood supply, esterases hydrolyse the ester to unmask the carboxylate group, and the drug can interact with its target. The prodrug itself is inactive when tested *in vitro* because the carboxylate group is masked. This indicates that the carboxylate group is an important binding group.

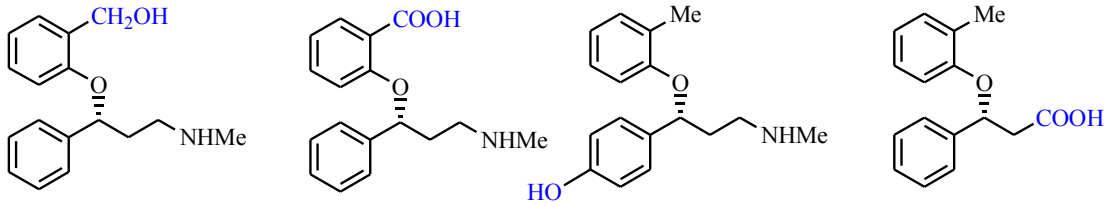
7) There are a variety of possible metabolites based on the groups present. The following are some possible metabolic reactions.



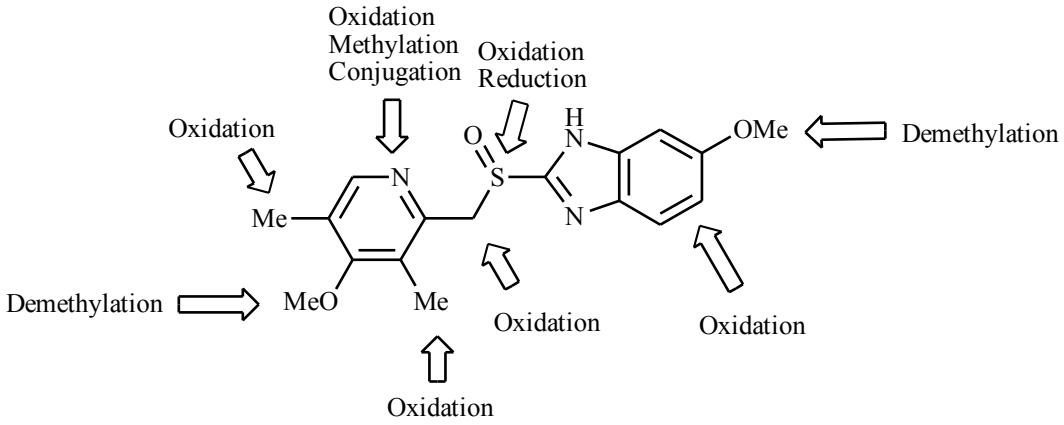
Various possible metabolites include the following for methylphenidate:



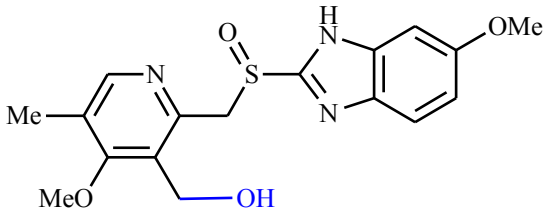
and for atomoxetine:

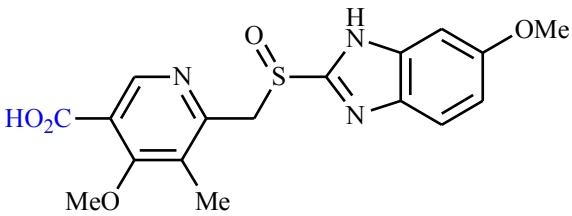


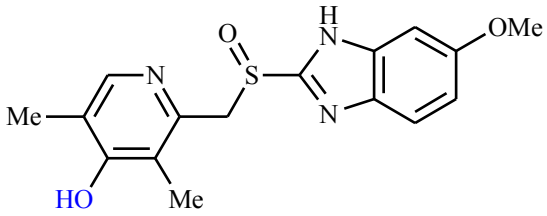
8) There are a variety of possible metabolites based on the groups present. The following are some possible metabolic reactions:

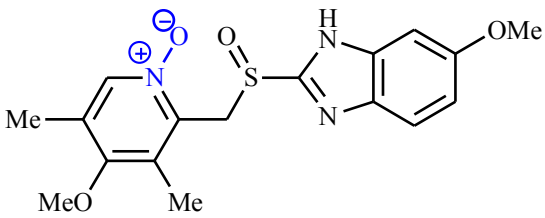


The following are just a few examples of the many possible metabolites. Note that more than one metabolic reaction may occur on the one molecule.

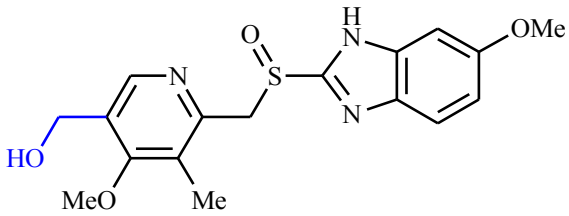


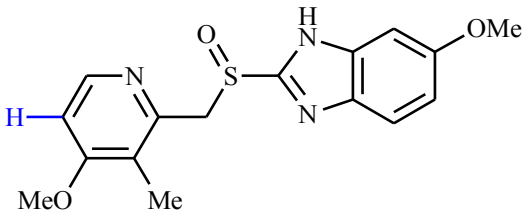






The following metabolites have actually been shown to be formed from the *S*-enantiomer of omeprazole.





9) After 4 hours, 50% of the drug remains. From then on, the remaining drug (shown in brackets) after each time period is as follows; 8 hours (25%), 12 hours (12.5%), 12 hours (6.25%), 16 hours (3.13%), 20 hours (1.56%) and 24 hours (0.78%).

10) Salicylic acid has a carboxylic acid group. This is unlikely to be ionized in the acidic conditions of the stomach and so effective absorption from the stomach is feasible. The pH present in the intestines is much less acidic and so an equilibrium between the ionized and non-ionized forms of salicyclic acid is likely. The ionized carboxylate form of salicylic acid will not easily cross the gut wall and so absorption is much less effective.
In contrast, quinine contains basic amine groups which are protonated in the acid conditions of the stomach. As a result, there is little chance of the drug being absorbed from the stomach. In the weakly acidic conditions of the intestines, it is possible that a certain percentage of quinine will be in its non-ionized free base form and will be more effectively absorbed.