5

Drug metabolism

When drugs and medicines are administered to a patient, it is rare for the drug molecule to emerge from the patient unchanged. Most of the foreign compounds (or *xenobiotics*) taken into the body undergo a variety of chemical changes brought about by enzymes in the liver, intestine, kidney, lung and other tissues. These transformations (usually, but not exclusively, oxidation reactions) may give rise to compounds (or *metabolites*) that are toxic. These metabolites are capable of reacting with important macromolecules within the body (such as DNA and proteins) to cause toxicity. An insight into the mechanisms that give rise to the formation of drug metabolites is therefore important from a drug safety point of view.

The body's main strategy for dealing with these xenobiotics is to convert the molecule into a more hydrophilic or water-soluble derivative, which can then be excreted via the kidneys in the urine. Reactions of this type are known collectively as *drug metabolism*, although the body systems that carry out these biotransformations arose through evolution long before drugs were taken therapeutically. Our ancestors were exposed throughout their lives to environmental poisons and foreign chemicals in their diet and mechanisms evolved to detoxify these agents and protect the body.

Today, the situation is, if anything, even more complex. Consumption of 'recreational' drugs such as tobacco and alcohol expose the body to thousands of foreign compounds, many of them potentially toxic. Environmental poisons such as pesticide residues in food and carcinogens (cancer-causing agents) produced by high-temperature cooking of fats and proteins in meat add to the cocktail of non-essential exogenous compounds absorbed by modern humans that may be harmful to their health. The consumption of drugs and medicines for therapeutic purposes must be viewed against this backdrop and a student must become familiar with the reactions involved in drug metabolism and the effects these biotransformations have on pharmacological activity, duration of action and toxicity of drugs.

Metabolic pathways

Foreign compounds such as drugs taken into the body undergo enzymatic transformations, which usually result in a loss of pharmacological activity. This is known as *detoxification*. Occasionally, the action of these enzymes may convert an inactive compound (for example, a prodrug) into a pharmacologically active compound. In this case, the process is described as *bioactivation*. Prodrugs are pharmacologically inactive derivatives of the active molecule that are designed to break down within the body to release the active drug. The prodrug approach is often used in pharmacy to overcome problems such as poor absorption, instability or toxicity when the parent drug is given orally. Examples include anticancer agents such as cyclophosphamide or antibiotics such as pivmecillinam. The prodrug approach can also be used if the parent drug has an unpalatable taste or smell that needs to be disguised, as is the case in the disease nephropathic cystinosis, where the only drug treatment for the condition, cysteamine, tastes and smells so bad it affects patient compliance.

Biotransformations

There are two main types of biotransformation observed in the body, imaginatively called *Phase 1* and *Phase 2* reactions, although many drugs undergo both types of process. Phase 1 reactions are reactions in which a new functional group is introduced into the molecule, or an existing group is converted into another (usually more water-soluble) derivative. Phase 2 reactions, or conjugations, are where an existing functional group in the molecule is masked by the addition of a new group. The conjugate is formed between the drug and a hydrophilic compound such as glucuronic acid and the resulting conjugate (a glucuronide) will usually be much more water soluble than the parent drug. Most drugs are hydrophobic and so not inherently water soluble. Metabolism to a more water-soluble and less toxic derivative terminates drug action and allows the body to excrete the drug easily in the urine. If the administered drug is already hydrophilic, the molecule is often excreted unchanged.

The processes involved in drug metabolism involve simple chemical reactions such as oxidation (the most common), reduction and dealkylation and are influenced by a number of factors including:

- *Genetic factors*. Differences are observed between species (important since most medicines intended for human use are tested first in animals) and between individuals in a population. The science of *pharmacogenomics* has arisen to study the influence of genetic variation on drug action in patients and to study how the

extent of gene expression in an individual correlates with that person's response to drug therapy. The aim is to design 'personalised medicines' which are tailored to the unique genetic make-up of an individual.

- *Physiological factors*. These include age of the patient, gender, pregnancy and nutritional status. Very young patients whose livers have not developed fully and very old patients whose liver function has deteriorated metabolise drugs more slowly than the normal adult population. There are also differences in the rates of metabolism between men and women and between pregnant and non-pregnant women. The causes of these effects are unknown but are probably due to differences in body size and levels of circulating sex hormones.
- *Pharmacodynamic factors*. These were mentioned briefly in Chapters 2 and 3 and include dose, frequency and route of administration and extent of protein binding.
- *Environmental factors*. Examples of these are co-administration of other drugs, which can affect the rate and extent of drug metabolism. This can become literally a matter of life and death as a number of potentially fatal drug interactions involve liver enzyme induction and competition for drug-metabolism enzymes.

Cytochromes P450

The most important and most extensively studied drug metabolism system in the body is the superfamily of cytochrome P450 monooxygenases (CYP450). Many different forms of these enzymes exist (called *isoforms*), although they are all membrane-bound mixed-function oxidases located on the smooth endoplasmic reticulum of the liver. CYP450 acts as a very sophisticated electron transport system responsible for the oxidative metabolism of a large number of drugs and other xenobiotics, as well as endogenous compounds such as bile acids, prostaglandins and fat soluble vitamins.

There are approximately 60 different types of human CYP enzyme which are classified into families and sub-families depending on their nucleic acid and protein homology. Important drug-metabolising CYPs are CYP1A1 and 1A2, CYP1B1, CYP2D6 and CYP3A4. CYP2D6 is responsible for more than 70 different drug oxidations (including antidepressants such as paroxetine and fluoxetine, β-blockers and codeine) while the CYP3A4 enzyme is responsible for 40–45% of all CYP450 drug metabolism in humans. Substrates for CYP3A4 include drugs such as codeine, erythromycin and lidocaine as well as endogenous compounds such as testosterone and progesterone.

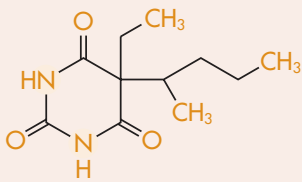
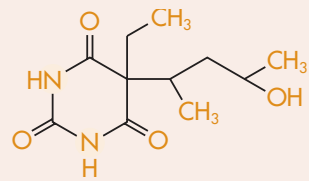
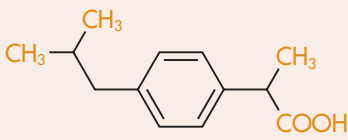
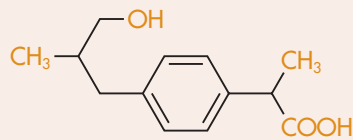
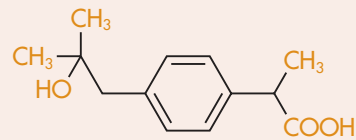
Cytochrome P450s accomplish all these metabolic transformations due to the presence of an ion of iron at the active site that can accept or donate electrons to allow oxidation reactions to take place. The iron in

CYP450 is bound within a haem co-factor and can exist in a number of oxidation states, of which Fe^{2+} (ferrous) and Fe^{3+} (ferric) are the most important.

A detailed description of the (fascinating) molecular mode(s) of action of this important enzyme system is beyond the scope of this book and the interested reader should consult textbooks of biochemistry, pharmacology, or medicinal chemistry for more information. What is important is that a student should understand the functional group interconversions brought about by CYP450 and appreciate the metabolic effects of these changes on the physicochemical properties of drugs.

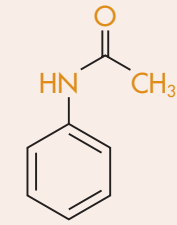
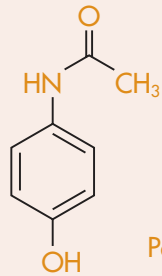
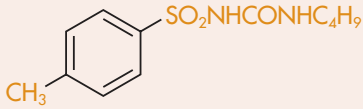
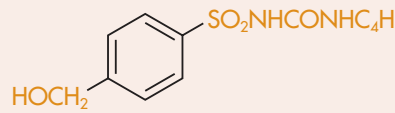
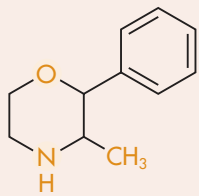
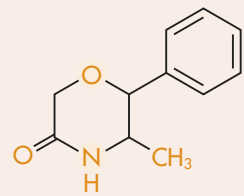
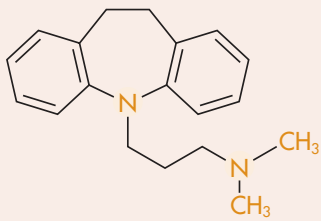
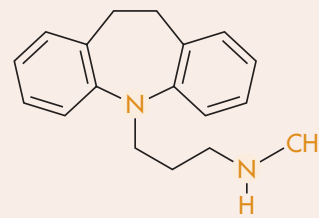
The oxidations brought about by CYP450 may be simple oxidation of a part of the drug molecule, e.g. a side-chain or aromatic ring, or may involve more complicated transformations in which a functional group is lost from the molecule in the course of the oxidation reaction. Examples of this type of transformation are *O*- and *N*-dealkylations (in which an alkyl group is lost) and deaminations (in which an amino group is lost). A list of the types of transformation catalysed by CYP450s is shown in Table 5.1. This list is not intended to be exhaustive; it merely indicates the range of chemical interconversions catalysed by this enzyme system.

Table 5.1 Oxidative biotransformations catalysed by CYP450

Substrate	Product(s)
1. Side-chain oxidation	
 Pentobarbital	
 Ibuprofen	 

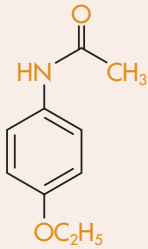
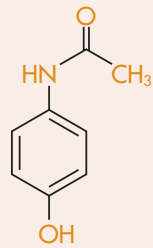
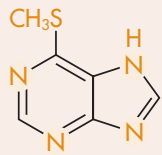
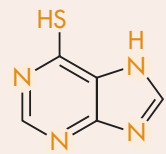
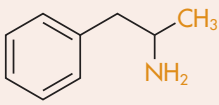
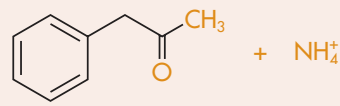
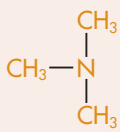
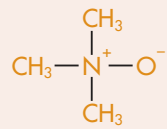
(*continued*)

Table 5.1 *Continued*

Substrate	Product(s)
2. Aromatic ring oxidation	
 Acetanilide	 Paracetamol
3. Methyl oxidation	
 Tolbutamide	
4. Heterocyclic ring oxidation	
 Phenmetrazine	
5. *N*-Dealkylation	
 Imipramine	 Desipramine

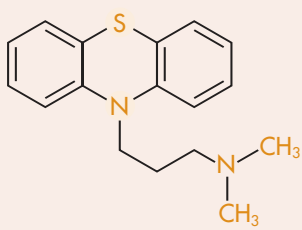
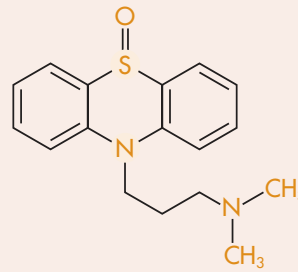
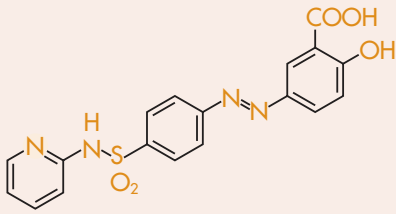
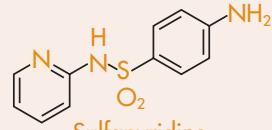
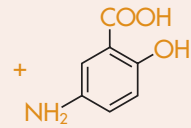
(continued)

Table 5.1 *Continued*

Substrate	Product(s)
6. *O*-Dealkylation	
 Phenacetin	 Paracetamol
7. *S*-Dealkylation	
 6-Methylmercaptopurine	 6-Mercaptopurine
8. Deamination	
 Amfetamine	
9. *N*-Oxidation	
 Trimethylamine	 Trimethylamine oxide

(*continued*)

Table 5.1 *Continued*

Substrate	Product(s)
10. Sulfoxidation	
 Chlorpromazine	 Chlorpromazine sulfoxide
11. Azoreduction	
 Sulfasalazine	 Sulfapyridine +  5-Aminosalicylic acid

Enzyme induction and inhibition

Many drugs and environmental compounds can enhance their own metabolism and that of other compounds. Prolonged administration of a xenobiotic can lead to an increased rate of metabolism of a wide variety of compounds. This process is known as *enzyme induction* and is dose-dependent. In effect, administration of a xenobiotic induces the synthesis of more enzyme by the organism to deal with the increased metabolic challenge caused by the xenobiotic. The increased levels of enzyme can metabolise not only the xenobiotic causing the induction but also other drugs metabolised by that enzyme system. The CYP450 enzyme system is responsible for a large number of biotransformations, so the possibility of drug interactions is very large.

Environmental chemicals such as polycyclic aromatic hydrocarbons (PAHs), present in cigarette smoke, xanthines and flavones in foods, halogenated hydrocarbons in insecticides and food additives can all alter the activity of CYP450 enzymes. Drugs that can cause CYP450 induction include antibiotics such as rifampicin and erythromycin, anticonvulsants such as phenobarbital and phenytoin, and recreational drugs such as ethanol. Co-administration of enzyme inducers along with other drugs (particularly drugs with a narrow therapeutic index, e.g. warfarin) can result in increased rates of metabolism of the drug and, consequently, a reduction in duration of action and therapeutic effect.

Not only can drug-metabolising enzymes be induced by xenobiotics, they can also be inhibited. In this case, administration of xenobiotic results in decreased rate of metabolism of the xenobiotic and any co-administered drug. Drugs interacting in this way with CYP450 include the histamine H_2-receptor antagonist cimetidine, the azole antifungals (ketoconazole, fluconazole, etc.) and the calcium channel blocker diltiazem. If drug metabolism is inhibited, the duration of action and plasma concentrations of co-administered drug will be increased, potentially leading to the appearance of side-effects and drug toxicity. CYP450 inhibitors can be split into three categories according to their mechanism of action.

- *Reversible inhibitors*, such as cimetidine, which interact with the complexed iron at the active site of the enzyme to inhibit oxidation of other drugs. The inhibition occurs before any oxidation of the inhibitor occurs and is reversible once the inhibitor is removed.
- *Metabolite intermediate complexation of CYP450*. In this case the drug is acted upon by the enzyme to form an oxidised derivative with a high affinity for the iron at the active site. Examples of this type of inhibition include alkylamine drugs that undergo oxidation to nitrosoalkane derivatives. Inhibition of this type renders the enzyme unavailable for further oxidation and synthesis of new enzyme is required to restore CYP450 activity.
- *Mechanism-based inactivation of CYP450* (or *suicide inhibition*) occurs when a non-toxic drug is metabolised by CYP450 to generate a metabolite that can bind irreversibly with the enzyme. The mechanism of inhibition usually involves free-radical alkylation or acylation of the active site and results in destruction of enzyme activity. Examples of drugs that act in this way include the antibiotic chloramphenicol and the anticancer agent cyclophosphamide.

Drug conjugation reactions (Phase 2)

Conjugation reactions are very important in the biotransformation of drugs and foreign chemicals within the body. Conjugation reactions involve

the attachment of very hydrophilic species such as glucuronic acid or glycine to xenobiotics and are usually considered to terminate pharmacological action. The drug conjugate is much less lipophilic and much more water soluble and is excreted easily by the kidneys. The situation is complicated, however, because drugs can be a substrate for more than one metabolising enzyme and there is no 'pecking order' or priority for enzyme action. This sequential conjugation can give rise to a bewildering array of metabolites and conjugates appearing in the urine or faeces when a drug is administered.

The major routes for drug conjugation are shown below.

Glucuronic acid conjugation

This is perhaps the most common route of Phase 2 drug metabolism because of the high levels of glucuronic acid in the liver and the relatively large number of functional groups that can act as a substrate for conjugate formation (alcohols, phenols, carboxylic acids, amines). The xenobiotic (or its Phase 1 metabolite) reacts with the activated form of glucuronic acid (uridine diphosphate glucuronic acid, or UDPGA) to give a derivative called a *glucuronide* as shown in Figure 5.1.

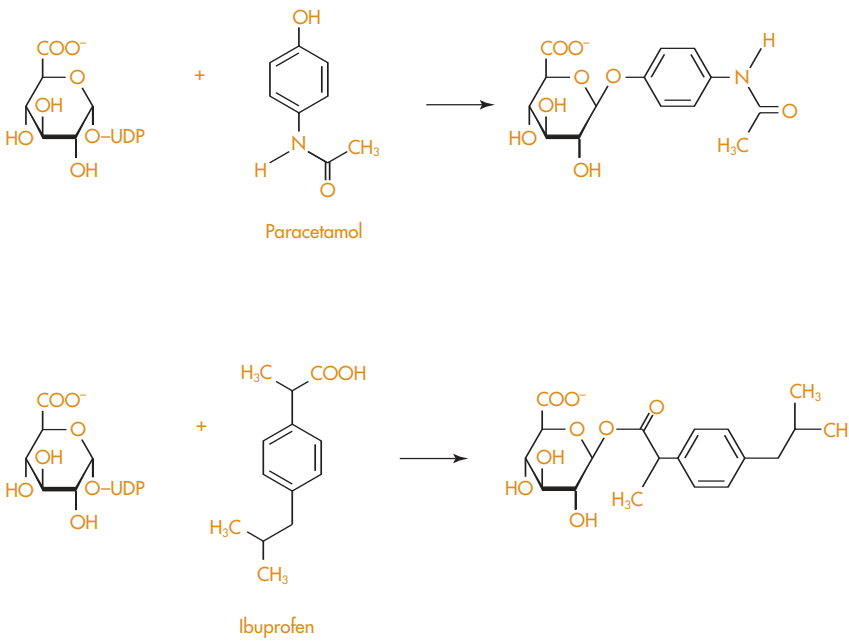
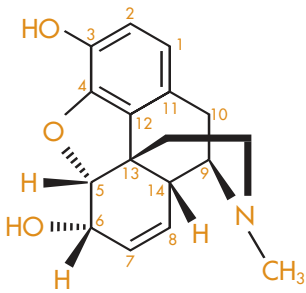
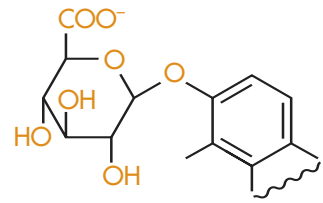


Figure 5.1 Formation of glucuronides.

The glucuronide derivatives formed in this way are much more water soluble than the parent drug. This is due to the large number of polar OH groups and a carboxylate group that will ionise at neutral pH. The glucuronide derivatives are less active pharmacologically and more easily excreted than the drug itself. Glucuronic acid conjugation is therefore, for most drugs, an example of a process that terminates drug action. An important exception to this is the analgesic morphine. This important drug forms a 3-*O*- and a 6-*O*-glucuronide, both of which are active at opiate receptors in the body (see Figure 5.2). The overall analgesic effect of morphine is a combination of the action of the drug and the effects of both active glucuronides and is, as a result, very complex.



Morphine



3-*O*-glucuronide

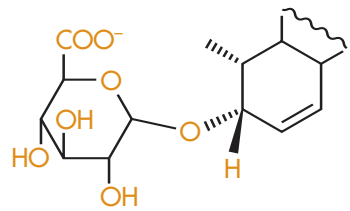


Figure 5.2 The structures of morphine and its 3-*O*- and 6-*O*-glucuronides.

Sulfate conjugation

Drugs and hormones that contain the phenolic functional group are metabolised by conjugation to a sulfate group (a process called sulfation). Examples of compounds metabolised in this way include the neurotransmitter noradrenaline (norepinephrine) as well as hormones such as

adrenaline (epinephrine), thyroxine and some steroids. In addition, the phenolic OH of tyrosine residues in proteins can act as a substrate for sulfation reactions, leading to a change in the physicochemical properties of the peptide or protein. The sulfur source is inorganic sulfate, which combines with ATP to form 3-phosphoadenosine 5-phosphosulfate (PAPS) and two phosphate groups. The enzyme sulfotransferase then attaches the sulfate group to the phenolic OH of the drug or hormone (Figure 5.3).

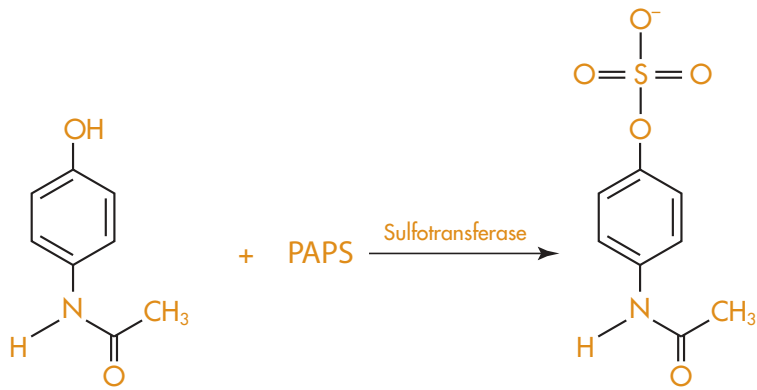


Figure 5.3 Sulfation of paracetamol.

If the dose of drug is high, the sulfate pathway can become saturated and other conjugation reactions (such as glucuronide formation) can take over. This is because the reservoir of inorganic sulfate in the body is finite and is easily overloaded.

The principal sites for sulfation reactions are the liver and kidneys, although an important site, especially after oral administration of drugs, is the small intestine. Sulfation in the gut can seriously affect the bioavailability of some drugs such as paracetamol (see Figure 5.3) and is the main reason why adrenaline (epinephrine) is not effective when given orally.

The sulfate conjugate of a drug is much more water soluble than the parent compound and is usually filtered by the kidneys and excreted in the urine. An important exception is steroid drugs, which are sulphated then excreted into the bile.

Amino acid conjugation

Conjugation with amino acids is an important route of Phase 2 metabolism for xenobiotics containing a carboxylic acid functional group. The amino acids involved include glycine, glutamine and taurine (an aminosulfonic

acid produced from cysteine). Conjugation occurs with formation of an amide bond between a carboxyl group of the drug and the NH_2 group of the amino acid after the xenobiotic has been activated by reaction with acetyl-coenzyme A. The major class of drug metabolised by this route is that of the non-steroidal anti-inflammatory drugs (NSAIDs) such as ibuprofen and ketoprofen. If the NSAID is chiral, conjugation with amino acid often results in inversion of the chiral centre. The reaction is illustrated in Figure 5.4 using benzoic acid as substrate. The product, hippuric acid, is present in human urine but was first isolated from the urine of horses and was named from the Greek word for horse, *hippos*. The amino acid conjugate of a drug is almost always more polar and more water-soluble than the parent molecule, due to ionisation of the carboxylic acid group at cell pH.

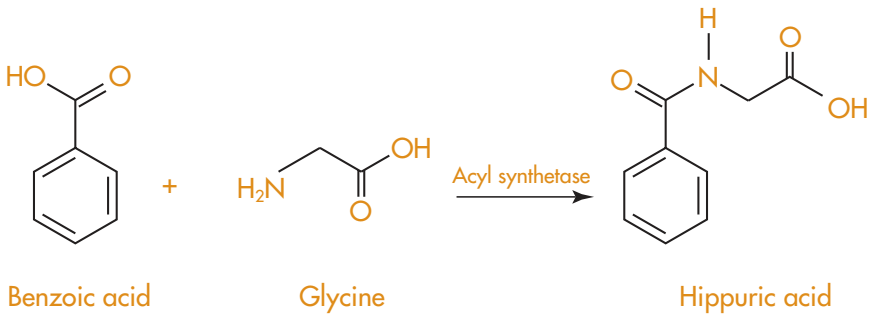


Figure 5.4 Glycine conjugation of benzoic acid.

Miscellaneous conjugation reactions

Several other types of conjugation reaction exist in the Phase 2 metabolism of drugs. Compounds possessing an amino group often undergo *N*-acetylation, primarily in the liver although other sites are known. The rate at which some patients carry out acetylation reactions is known to vary, with the population dividing into *fast acetylators* who can form *N*-acetyl derivatives quickly and so terminate drug action, and *slow acetylators* who cannot perform the transformation so rapidly and accumulate the drug. These two subgroups of the population display differences in the rates of metabolism of a number of drugs, including procainamide and isoniazid (shown in Figure 5.5). *N*-Acetylation of an amine is unusual in that the product formed is generally less water soluble than the parent amine, particularly if the solution is slightly acidic. This exception to the rule of 'metabolism to a more water-soluble derivative' can be rationalised as a termination of pharmacological action at the receptor. Acetylation of an amine removes a

key hydrogen-bonding site (the nitrogen lone pair of electrons) from the drug and hence destroys one of the specific three-dimensional interactions with the target macromolecule.

Figure 5.5 *N*-Acetylation of isoniazid.

Glutathione is another endogenous compound often found in drug conjugates. Glutathione is a tripeptide (γ-GluCysGly) found in high concentration in the liver. See Figure 5.6. The thiol group of glutathione is able to react with electrophilic drugs to protect other cell nucleophiles (such as DNA and proteins) from attack. This is often a detoxifying mechanism as in the case of *N*-acetylquinoneimine formed from paracetamol and epoxides formed as a result of CYP450 metabolism of double bonds (Figure 5.7).

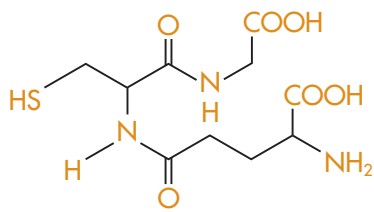


Figure 5.6 The structure of glutathione.

Paracetamol is the most popular 'over-the-counter' analgesic for adults and children on sale in the UK and is perfectly safe when taken at the recommended dosage (for an adult, currently not more that eight 500 mg tablets in any 24-hour period). When taken orally, paracetamol is quickly absorbed and transported in the bloodstream to the liver, where it is oxidised (by a CYP450 isoform) to *N*-acetyl-*p*-benzoquinoneimine as shown in Figure 5.7. This compound is reactive and will arylate essential cellular macromolecules (such as proteins), leading to toxicity that can cause liver failure and the need for transplantation. When paracetamol is taken at the approved dosage, there are sufficient levels of glutathione present in the body to reduce the toxic quinoneimine back to paracetamol.

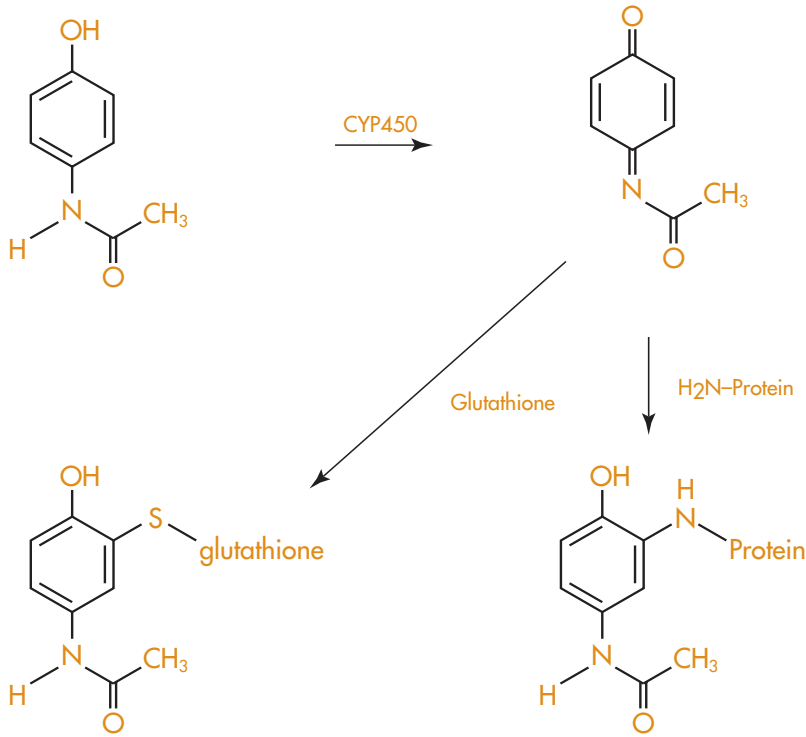


Figure 5.7 Role of glutathione in toxicity of paracetamol.

However, if paracetamol is taken in overdose, the levels of quinoneimine exceed the ability of glutathione to convert it back to paracetamol and toxicity to the liver results. In some cases, if treatment is not initiated in time, severe toxicity results, leading to death by acute liver failure. Treatment of paracetamol overdose is by administration of *N*-acetylcysteine (Figure 5.8). This compound (the acetyl derivative of the essential amino acid cysteine) functions as an alternative source of thiol (—SH) groups, which act in a similar manner to glutathione to detoxify the quinoneimine.

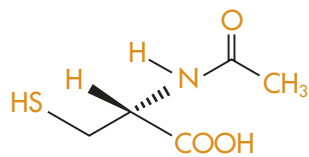


Figure 5.8 The structure of *N*-acetylcysteine.

A number of oxygen-, nitrogen- and sulfur- containing drugs can be metabolised by addition of a methyl group. *O*-Methylation and *N*-methylation are the most common reactions and are catalysed by methyltransferase enzymes such as catechol *O*-methyltransferase (COMT), one of the enzymes involved in terminating the action of adrenaline (epinephrine) and noradrenaline (norepinephrine). As in the case of acetylation reactions above, the *O*-methyl and *N*-methyl derivatives are more lipophilic and less water soluble than the parent drug. This metabolic transformation should also be viewed as a method of terminating pharmacological action rather than as a means of increasing water solubility prior to excretion by the kidneys. *N*-Methylation reactions are less common, although serotonin, histamine and tyramine are examples of endogenous hormones metabolised by methylation of the nitrogen.

Stereochemistry

Drug metabolism may be influenced by stereochemical factors if the molecule in question possesses one or more chiral centres. Examples of drugs that show stereochemical differences in rates of metabolism include α-methyldopa (where the (*S*) isomer is decarboxylated more rapidly than the (*R*) isomer) and the enantiomers of warfarin, which are reduced at different rates. The well-known endogenous compound mevalonic acid (3,5-dihydroxy-3-methylpentanoic acid) is chiral and exists as two enantiomers. When a racemic mixture of mevalonic acid is fed to animals, one optical isomer is absorbed and metabolised, while virtually all of the other isomer is excreted by the kidneys into the urine.

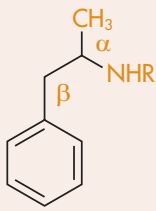
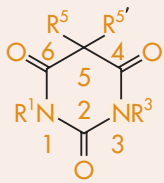
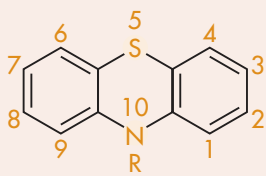
The fact that different rates of metabolism are observed when chiral drugs are used should not come as a surprise. Biotransformations are carried out in the body by enzymes, such as CYP450. These enzymes are themselves chiral since they are proteins and are composed of amino acids, which are, with the exception of glycine, all chiral. A chiral enzyme will, in general, interact differently with each enantiomer of a chiral drug. This effect is so widespread as to be considered normal.

Almost all drug–macromolecule interactions occurring in the body show chiral discrimination. This is true whether they are drug–enzyme or drug–receptor in nature. The situation is complicated further because some drugs show stereoselective absorption, distribution and excretion between enantiomers and it is difficult to determine which effects are due solely to metabolism and which are due to other biopharmaceutical factors.

Metabolic pathways for common drugs

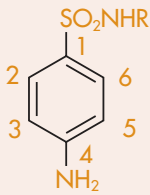
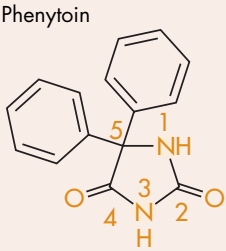
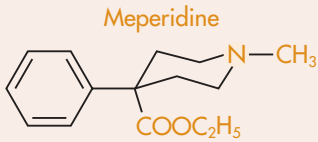
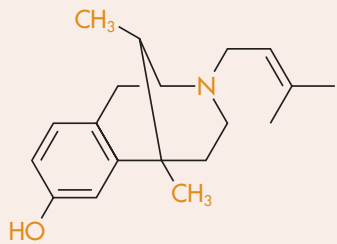
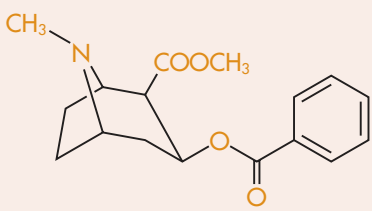
Drug metabolism is a complex subject. The range of small molecules used in medicine is huge and the number and extent of biotransformations carried out by the body are vast. It is impossible in this book to detail each metabolite of every drug used therapeutically, but Table 5.2 lists some common drugs and their metabolic pathways. This table should not be memorised (!) but rather used as a means of illustrating the range and diversity of compounds used as drugs and the many transformations carried out within the body.

Table 5.2 Common metabolic pathways

Drug	Pathway
Amfetamines 	Deamination (followed by oxidation and reduction of the ketone form *N*-oxidation *N*-dealkylation Hydroxylation of the aromatic ring Hydroxylation of the β-carbon atom Conjugation with glucuronic acid of the acid and alcohol products from ketone formed by deamination
Barbiturates 	Oxidation and complete removal of substituents at carbon-5 *N*-dealkylation at N^1 and N^3 Desulfuration at carbon-2 (thiobarbiturates) Scission of the barbiturate ring at the 1:6 bond to give substituted malonylureas
Phenothiazines 	*N*-dealkylation in the N^{10} side-chain *N*-oxidation in the N^{10} side-chain Oxidation of the heterocyclic S atom to sulfoxide or sulfone Hydroxylation of one or both aromatic rings Conjugation of phenolic metabolites with glucuronic acid or sulfate Scission of the N^{10} side-chain

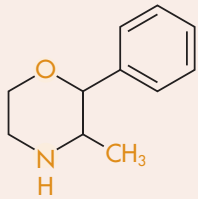
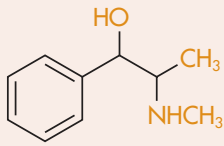
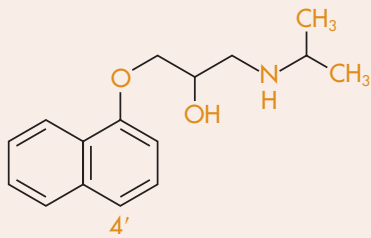
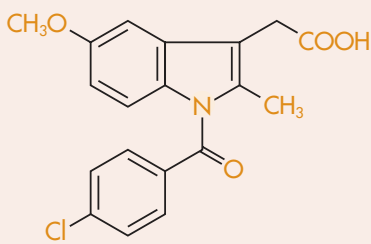
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Sulfonamides 	Acetylation at the N^4 amino group Conjugation with glucuronic acid or sulfate at the N^4 amino group Acetylation or conjugation with glucuronic acid at the N^1 amino group Hydroxylation and conjugation in the heterocyclic ring, R
Phenytoin 	Hydroxylation of one aromatic ring Conjugation of phenolic products with glucuronic acid or sulfate Hydrolytic scission of the hydantoin ring at the bond between carbons-3 and -4 to give 5,5-diphenylhydantoic acid
Pethidine 	Hydrolysis of ester to acid *N*-dealkylation Hydroxylation of aromatic ring *N*-oxidation Both *N*-dealkylation and hydrolysis Conjugation of phenolic products
Pentazocine 	Hydroxylation of terminal methyl groups of the alkenyl side-chain to give *cis* and *trans* (major) alcohols Oxidation of hydroxymethyl product of the alkenyl side-chain to carboxylic acids Reduction of alkenyl side-chain and oxidation of terminal methyl group
Cocaine 	Hydrolysis of methyl ester Hydrolysis of benzoate ester *N*-dealkylation Both hydrolysis and *N*-dealkylation

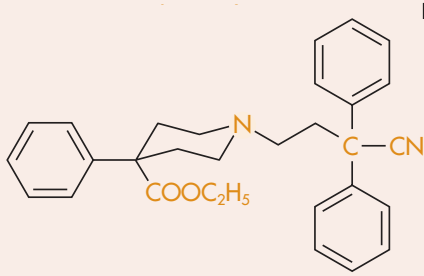
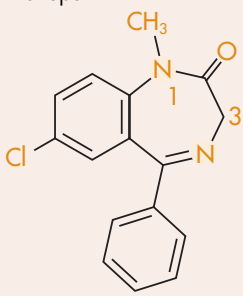
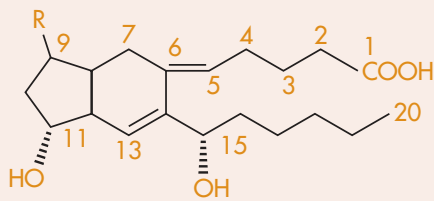
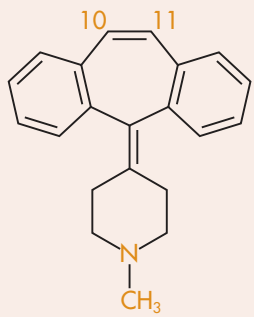
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Phenmetrazine 	Oxidation to lactam Aromatic hydroxylation *N*-oxidation Conjugation of phenolic products
Ephedrine 	*N*-dealkylation Oxidative deamination Oxidation of deaminated product to benzoic acid Reduction of deaminated product to 1,2-diol
Propranolol 	Aromatic hydroxylation at C-4′ *N*-dealkylation Oxidative deamination Oxidation of deaminated product to naphthoxylactic acid Conjugation with glucuronic acid *O*-dealkylation
Indometacin 	*O*-demethylation *N*-deacylation of *p*-chlorobenzoyl group Both *O*-dealkylation and *N*-deacylation Conjugation of phenolic products with glucuronic acid Other conjugation products

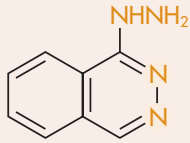
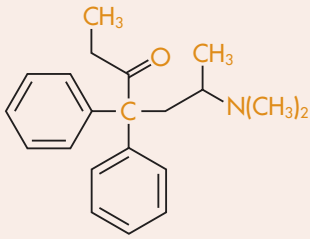
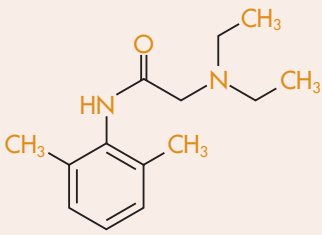
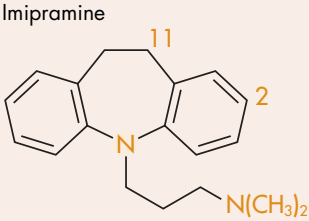
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Diphenoxylate 	Hydrolysis of ester to acid Hydroxylation of one aromatic ring attached to the *N*-alkyl side-chain
Diazepam 	*N*-dealkylation at N^1 Hydroxylation at carbon-3 Conjugation of phenolic products with glucuronic acid Both *N*-dealkylation of N^1 and hydroxylation at carbon-3
Prostaglandins 	Reduction of double bonds at carbons 5 and 6, and 13 and 14 Oxidation of 15-hydroxyl to ketone β-Oxidation of carbons 1, 2, 3 and 4 ω-Oxidation of carbon-20 to acid
Cyproheptadine 	*N*-dealkylation 10,11-Epoxide formation Both *N*-dealkylation and 10,11-epoxidation

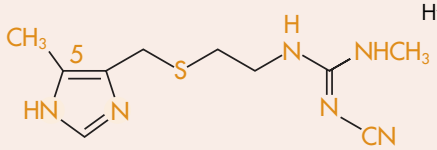
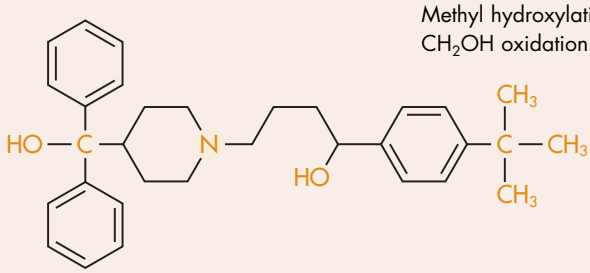
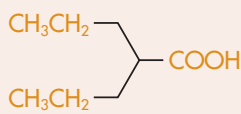
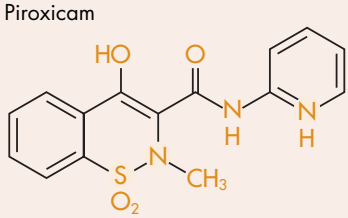
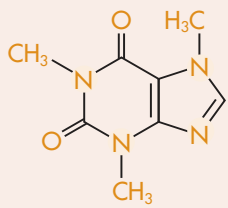
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Hydralazine 	*N*-acetylation with cyclisation to a methyl-*s*-triazolophthalazine *N*-formylation with cyclisation to an *s*-triazolophthalazine Aromatic hydroxylation of benzene ring Oxidative loss of hydrazinyl group to 1-hydroxy Hydroxylation of methyl of methyl-*s*-triazolophthalazine Conjugation with glucuronic acid
Methadone 	Reduction of ketone to hydroxyl Aromatic hydroxylation of one aromatic ring *N*-dealkylation of alcohol product *N*-dealkylation with cyclisation to pyrrolidine
Lidocaine (lignocaine) 	*N*-dealkylation Oxidative cyclisation to a 4-imidazolidone *N*-oxidation of amide N Aromatic hydroxylation *ortho* to methyl Hydrolysis of amide
Imipramine 	*N*-dealkylation Hydroxylation at C-11 Aromatic hydroxylation (C-2) *N*-oxidation Both *N*-dealkylation and hydroxylation

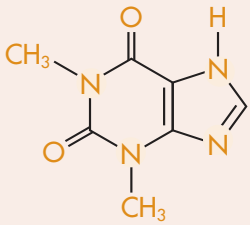
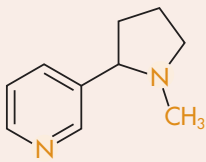
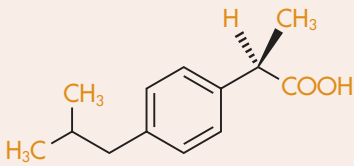
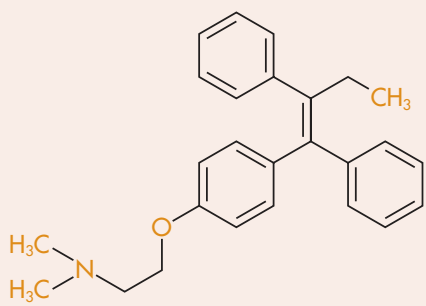
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Cimetidine 	*S*-oxidation Hydroxylation of 5-methyl
Terfenadine 	*N*-demethylation Methyl hydroxylation to CH_2OH CH_2OH oxidation to COOH
Valproic acid 	CoA thioester Dehydrogenation to (*E*)-2-ene Dehydrogenation to (*E*)-2,4-diene Dehydrogenation to 4-ene 3-Hydroxylation
Piroxicam 	Pyridine 3′-hydroxylation Hydrolysis of amide Decarboxylation
Caffeine 	N^3-demethylation N^1-demethylation N^7-demethylation to theophylline C-8 oxidation to uric acids Imidazole ring opened

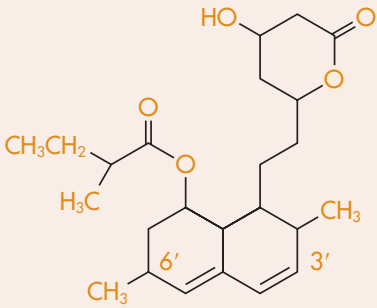
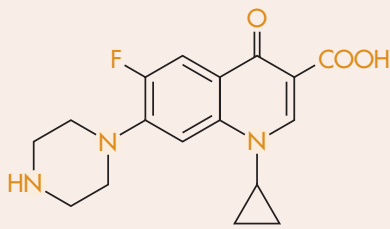
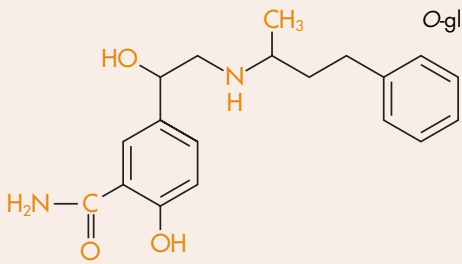
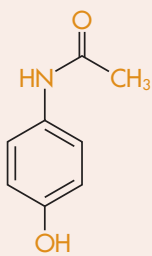
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Theophylline 	N^3-demethylation N^1-demethylation C-8 oxidation to uric acids 1-Methyl-xanthine to 1-methyl-uric acid with xanthine oxidase Imidazole ring opened
Nicotine 	Pyrrolidine 5′-hydroxylation to cotinine Pyrrolidine *N*-oxidation (FMO) *N*-demethylation (nornicotine and norcotinine) Pyridine *N*-methylation 3′-Hydroxylation of cotinine
Ibuprofen 	CoA thioester and epimerisation of (*R*)-(−) to (*S*)-(+)-enantiomer Methyl hydroxylation to CH_2OH CH_2OH to COOH Acylglucuronide
Tamoxifen 	*N*-demethylation 4′-Hydroxylation *N*-oxidation (FMO) 4-*O*-sulfate 4-*O*-glucuronide

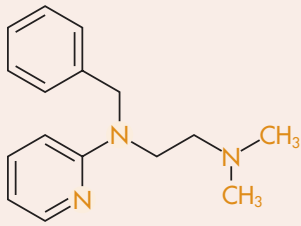
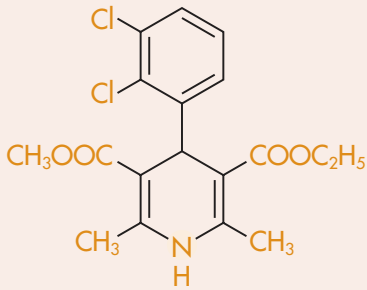
(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Lovastatin 	6′-Hydroxylation 3′-Side-chain hydroxylation 3′-Hydroxylation β-Oxidation of lactone *O*-glucuronides
Ciprofloxacin 	Piperazine 3′-hydroxylation *N*-sulfation
Labetalol 	*O*-sulfate (major) *O*-glucuronide
Paracetamol 	*O*-glucuronide *O*-sulfate Oxidation to *N*-acetyl-*p*-benzoquinoneimine Conjugation of *N*-acetyl-*p*-benzoquinoneimine with glutathione

(*continued*)

Table 5.2 *Continued*

Drug	Pathway
Tripelennamine 	*p*-Hydroxylation Benzylic C-hydroxylation *N*-depyridinylation *N*-debenzylation
Felodipine 	Aromatisation Ester hydrolysis Methyl hydroxylation

Tutorial example

Q Explain why the insecticide malathion (Figure 5.9) is toxic to insects but relatively non-toxic to humans.

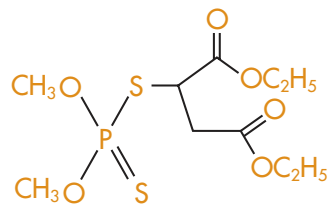


Figure 5.9 The structure of malathion.

A Malathion is an example of an organophosphorus insecticide, which works by inhibition of the enzyme acetylcholinesterase, responsible for the hydrolysis of the neurotransmitter acetylcholine. Inhibition of the enzyme allows the build-up of lethal concentrations of acetylcholine, convulsions and death. Malathion is a weak inhibitor of the enzyme and in humans is hydrolysed to the corresponding acid, which also has a low biological activity. In insects, malathion is oxidised to malaoxon which is 10 000 times more active than the parent compound. This causes an increase in levels of acetylcholine, which kills the insect (see Figure 5.10).

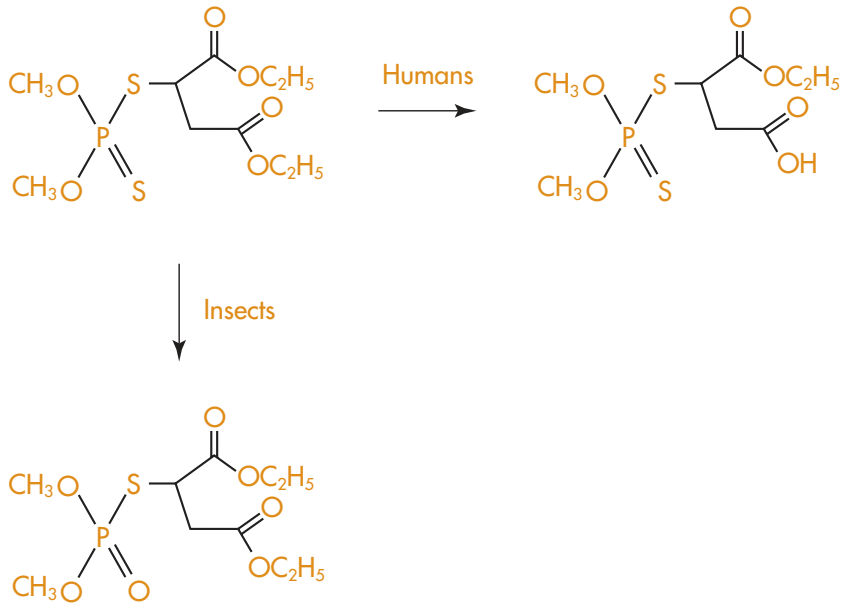
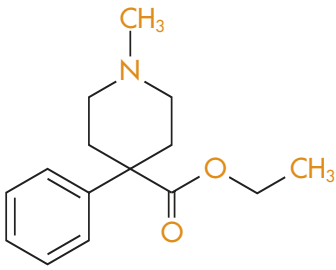


Figure 5.10 The metabolism of malathion.

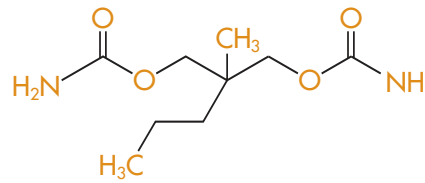
This example illustrates two important points. First, malathion is a selectively toxic compound in that it kills insects without harming humans. Second, different species may metabolise drugs in different ways and extreme care must be exercised when extrapolating results from one species to another, notably from animal toxicity data to humans.

Problems

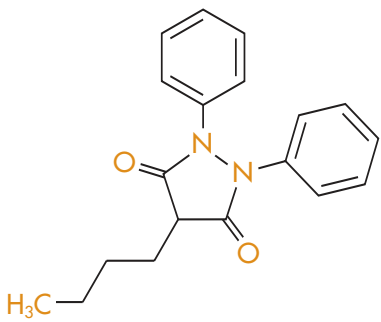
Q5.1 The primary metabolic step involves a different mechanism for each of the drugs listed in Figure 5.11. Select the appropriate transformation for each drug from the following list: *aliphatic hydroxylation*, *oxidative N-dealkylation*, *hydrolysis*, *aromatic hydroxylation*, *oxidative O-dealkylation*. Draw the structure of the primary metabolite in each case.



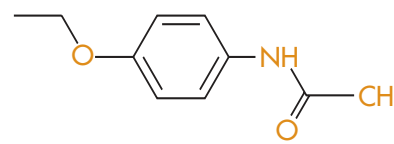
Pethidine



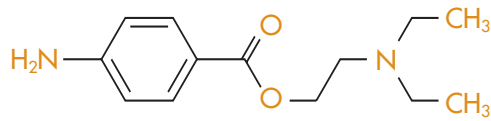
Meprobamate



Phenylbutazone



Phenacetin



Procaine

Figure 5.11 The structures of the drugs in Q5.1.

Q5.2 Reactions that metabolically modify drugs and other xenobiotics are sometimes classified as Phase 1 and Phase 2 reactions. Explain the difference(s) between these two processes and give an example of each type of metabolism.

(Answers to problems may be found on pp. 259–261.)