is that the mitochondria membrane is similar in nature to bacterial cell membranes, and so antibacterial agents may show selectivity for mitochondrial membranes over cell membranes.

14.5 Reducing toxicity

It is often found that a drug fails clinical trials because of toxic side effects. This may be due to toxic metabolites, in which case the drug should be made more resistant to metabolism as described earlier (section 14.2). It is also worth checking to see whether there are any functional groups present that are particularly prone to producing toxic metabolites. For example, it is known that functional groups, such as aromatic nitro groups, aromatic amines, bromoarenes, hydrazines, hydroxylamines, or polyhalogenated groups, are often metabolized to toxic products (see section 11.5 for typical metabolic reactions).

Side effects might also be reduced or eliminated by varying apparently harmless substituents. For example, the halogen substituents of the antifungal agent **UK 47265** were varied in order to find a compound that was less toxic to the liver. This led to the successful antifungal agent **fluconazole** (Fig. 14.17).

Varying the position of substituents can sometimes reduce or eliminate side effects. For example, the dopamine antagonist **SB 269652** inhibits cytochrome P450 enzymes as a side effect. Placing the cyano group at a different position prevented this inhibition (Fig. 14.18).

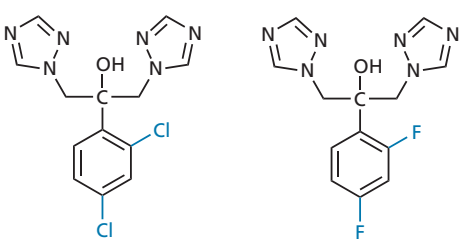


FIGURE 14.17 Varying aromatic substituents to reduce toxicity.

KEY POINTS

- Strategies designed to target drugs to particular cells or tissues are likely to lead to safer drugs with fewer side effects.
- Drugs can be linked to amino acids or nucleic acid bases to target them against fast-growing and rapidly-dividing cells.
- Drugs can be targeted to the gastrointestinal tract by making them ionized or highly polar such that they cannot cross the gut wall.
- The CNS side effects of peripherally acting drugs can be eliminated by making the drugs more polar so that they do not cross the blood–brain barrier.
- Drugs with toxic side effects can sometimes be made less toxic by varying the nature or position of substituents, or by preventing their metabolism to a toxic metabolite.

14.6 Prodrugs

Prodrugs are compounds which are inactive in themselves, but which are converted in the body to the active drug. They have been useful in tackling problems such as acid sensitivity, poor membrane permeability, drug toxicity, bad taste, and short duration of action. Usually, a metabolic enzyme is involved in converting the prodrug to the active drug, and so a good knowledge of drug metabolism and the enzymes involved allows the medicinal chemist to design a suitable prodrug which turns drug metabolism into an advantage rather than a problem. Prodrugs have been designed to be activated by a variety of metabolic enzymes. Ester prodrugs which are hydrolysed by esterase enzymes are particularly common, but prodrugs have also been designed which are activated by *N*-demethylation, decarboxylation, and the hydrolysis of amides and phosphates. Not all prodrugs are activated by metabolic enzymes, however. For example, photodynamic therapy involves the use of an external light source to activate prodrugs. When designing prodrugs, it is important to ensure that the prodrug is effectively converted to the active drug once it has been absorbed into the blood supply, but it is also important

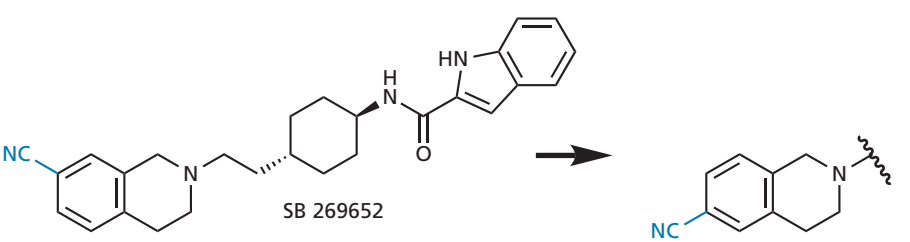


FIGURE 14.18 Varying substituent positions to reduce side effects.

to ensure that any groups that are cleaved from the molecule are non-toxic.

14.6.1 Prodrugs to improve membrane permeability

14.6.1.1 Esters as prodrugs

Prodrugs have proved very useful in temporarily masking an 'awkward' functional group which is important to target binding but which hinders the drug from crossing the cell membranes of the gut wall. For example, a carboxylic acid functional group may have an important role to play in binding a drug to its binding site via ionic or hydrogen bonding. However, the very fact that it is an ionizable group may prevent it from crossing a fatty cell membrane. The answer is to protect the acid function as an ester. The less polar ester can cross fatty cell membranes and, once it is in the bloodstream, it is hydrolysed back to the free acid by esterases in the blood. Examples of ester prodrugs used to aid membrane permeability include **enalapril**, which is the prodrug for the antihypertensive agent **enalaprilate** (Fig. 14.19, and Case study 2), and **pivampicillin**, which is a penicillin prodrug (Box 19.7).

Not all esters are hydrolysed equally efficiently and a range of esters may need to be tried to find the best one (Box 14.3). It is possible to make esters more susceptible to hydrolysis by introducing electron-withdrawing groups to the alcohol moiety (e.g. OCH_2CF_3, OCH_2CO_2R, $OCONR_2$, OAr). The inductive effect of these groups aids the hydrolytic mechanism by stabilizing the alkoxide leaving group (Fig. 14.20). Care has to be taken, however, not to make the ester too reactive in case it becomes chemically unstable and is hydrolysed by the acid conditions of the stomach or the more alkaline conditions of the intestine before it reaches the blood supply. To that end, it may be necessary to make the ester more stable. For example, cyclopropanecarboxylic acid esters have been studied as potential prodrugs because the cyclopropane ring has the ability to stabilize the carbonyl group of a neighbouring ester (Fig. 14.21). In this respect, it is acting as a bioisostere for a double bond (see also section 13.3.7). A conjugated double bond stabilizes a neighbouring carbonyl group due to interaction of the π-systems involved. It is proposed that the σ-bonds of a cyclopropane ring are orientated correctly to allow a hyperconjugative interaction that has a similar stabilizing effect on a neighbouring carbonyl group. The interaction proposed involves hyperconjugative donation to the anti-bonding π orbital of the carbonyl group.

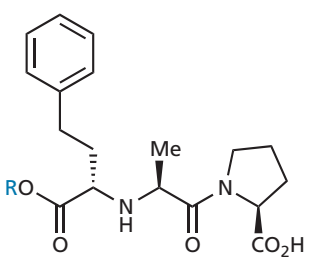


FIGURE 14.19 Enalapril (R = Et); Enalaprilate (R = H).

14.6.1.2 *N*-Methylated prodrugs

N-Demethylation is a common metabolic reaction in the liver, so polar amines can be *N*-methylated to reduce polarity and improve membrane permeability. Several hypnotics and anti-epileptics take advantage of this reaction, for example **hexobarbitone** (Fig. 14.22).

14.6.1.3 Trojan horse approach for transport proteins

Another way round the problem of membrane permeability is to design a prodrug which can take advantage of transport proteins (section 2.7.2) in the cell membrane, such as the ones responsible for carrying amino acids into a cell. A well-known example of such a prodrug is

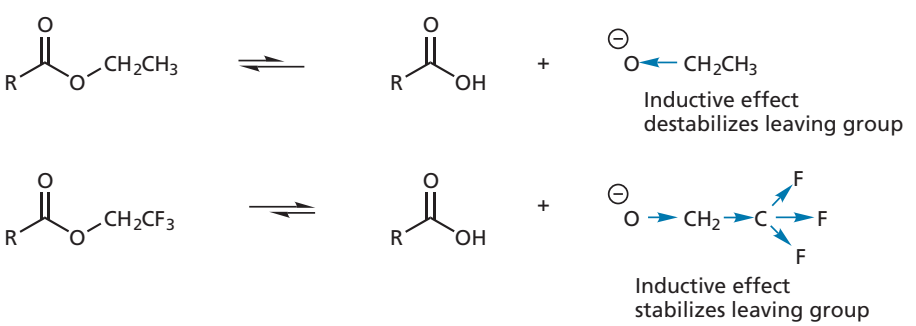


FIGURE 14.20 Inductive effects on the stability of leaving groups.

BOX 14.3 Varying esters in prodrugs

The protease inhibitor **candoxatrilat** has to be given intravenously because it is too polar to be absorbed from the gastrointestinal tract. Different esters were tried as prodrugs to get round this problem. It was found that an ethyl ester was absorbed but was inefficiently hydrolysed. A more activated ester was required and a 5-indanyl ester proved to be the best. The 5-indanol released on hydrolysis is non-toxic (Fig. 1).

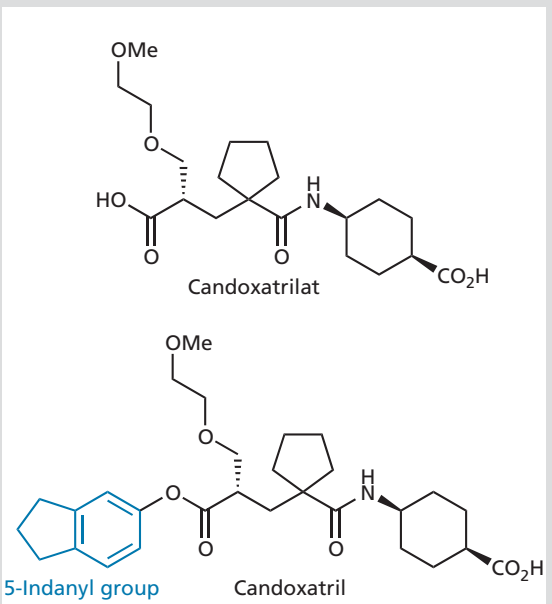


FIGURE 1 Protease inhibitors.

levodopa (Fig. 14.23). Levodopa is a prodrug for the neurotransmitter **dopamine** and has been used in the treatment of Parkinson's disease—a condition due primarily to a deficiency of that neurotransmitter in the brain. Dopamine itself cannot be used as it is too polar to cross the blood–brain barrier. Levodopa is even more polar and seems an unlikely prodrug, but it is also an amino acid, and so it is recognized by the transport proteins for amino acids which carry it across the cell membrane. Once in the brain, a decarboxylase enzyme removes the acid group and generates dopamine.

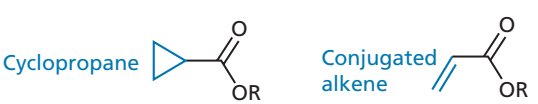


FIGURE 14.21 Cyclopropane carboxylic acid esters as prodrugs and bioisosteres for α,β-unsaturated esters.

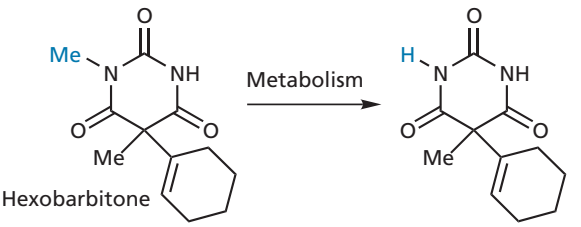


FIGURE 14.22 *N*-Demethylation of hexobarbitone.

14.6.2 Prodrugs to prolong drug activity

Sometimes prodrugs are designed to be converted slowly to the active drug, thus prolonging a drug's activity. For example, **6-mercaptopurine** (Fig. 14.24) suppresses the body's immune response and is, therefore, useful in protecting donor grafts. Unfortunately, the drug tends to be eliminated from the body too quickly. The prodrug **azathioprine** has the advantage that it is slowly converted to 6-mercaptopurine by being attacked by **glutathione** (section 11.5.5), allowing a more sustained activity. The rate of conversion can be altered, depending on the electron-withdrawing ability of the heterocyclic group. The greater the electron-withdrawing power, the faster the breakdown. The NO_2 group is therefore present to ensure an efficient conversion to 6-mercaptopurine, as it is strongly electron-withdrawing on the heterocyclic ring.

There is a belief that the well-known sedatives **Valium** (Fig. 14.25) and **Librium** might be prodrugs, and are active because they are metabolized by *N*-demethylation to **nordazepams**. Nordazepam itself has been used as a sedative, but loses activity quite quickly as a result of metabolism and excretion. **Valium**, if it is a prodrug for nordazepam, demonstrates again how a prodrug can be used to lead to a more sustained action.

Another approach to maintaining a sustained level of drug over long periods is to deliberately associate a very lipophilic group to the drug. This means that most of the drug is stored in fat tissue from where it is steadily and slowly released into the bloodstream. The antimalarial agent **cycloguanil pamoate** (Fig. 14.26) is one such agent. The active drug is bound ionically to an anion containing a large lipophilic group and is only released into the blood supply following slow dissociation of the ion complex.

Similarly, lipophilic esters of the antipsychotic drug **fluphenazine** are used to prolong its action (Fig. 14.27).

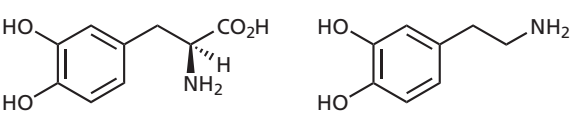


FIGURE 14.23 Levodopa and dopamine.

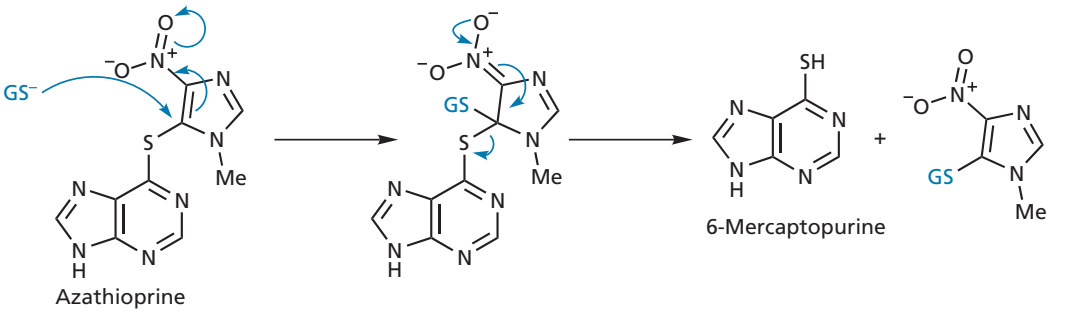


FIGURE 14.24 Azathioprine acts as a prodrug for 6-mercaptopurine (GS = glutathione).

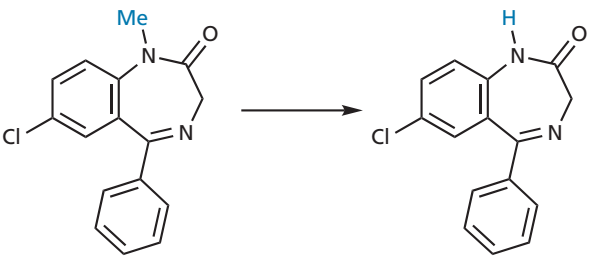


FIGURE 14.25 Valium (diazepam) as a possible prodrug for nordazepam.

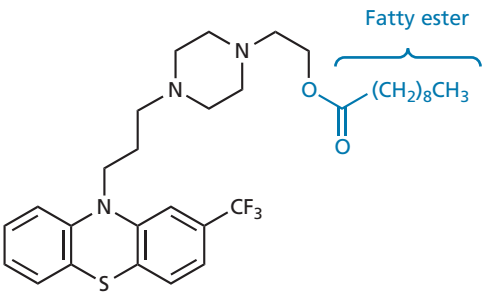


FIGURE 14.27 Fluphenazine decanoate.

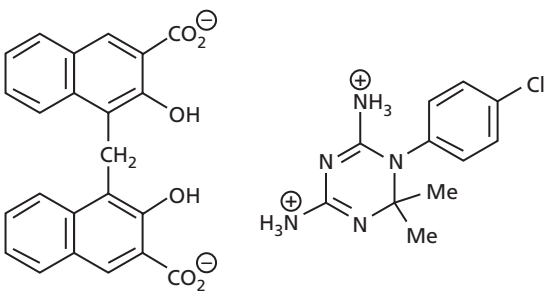


FIGURE 14.26 Cycloguanil pamoate.

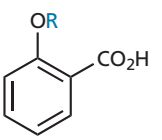


FIGURE 14.28 Aspirin (R = $COCH_3$) and salicylic acid (R = H).

The prodrug is given by intramuscular injection and slowly diffuses from fat tissue into the blood supply, where it is rapidly hydrolysed.

14.6.3 Prodrugs masking drug toxicity and side effects

Prodrugs can be used to mask the side effects and toxicity of drugs (Box 14.4). For example, **salicylic acid** is a good painkiller, but causes gastric bleeding because of the free phenolic group. This is overcome by masking the phenol as an ester (**aspirin**) (Fig. 14.28). The ester is later hydrolysed to free the active drug.

Prodrugs can be used to give a slow release of drugs that would be too toxic to give directly. **Propiolaldehyde** is useful in the aversion therapy of alcohol, but is not used itself because it is an irritant. The prodrug **pargyline** can be converted to propiolaldehyde by enzymes in the liver (Fig. 14.29).

Cyclophosphamide is a successful, non-toxic prodrug which can be safely taken orally. Once absorbed, it is metabolized in the liver to a toxic alkylating agent which is useful in the treatment of cancer (section 21.2.3.1).

Many important antiviral drugs such as **aciclovir** and **penciclovir** are non-toxic prodrugs which show selective toxicity towards virally infected cells. This is because they are activated by a viral enzyme which is only present in infected cells (sections 9.5 and 20.6.1). In a similar vein, the

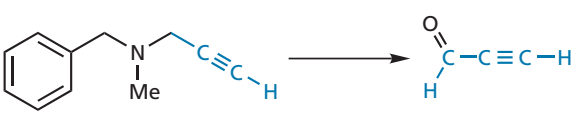
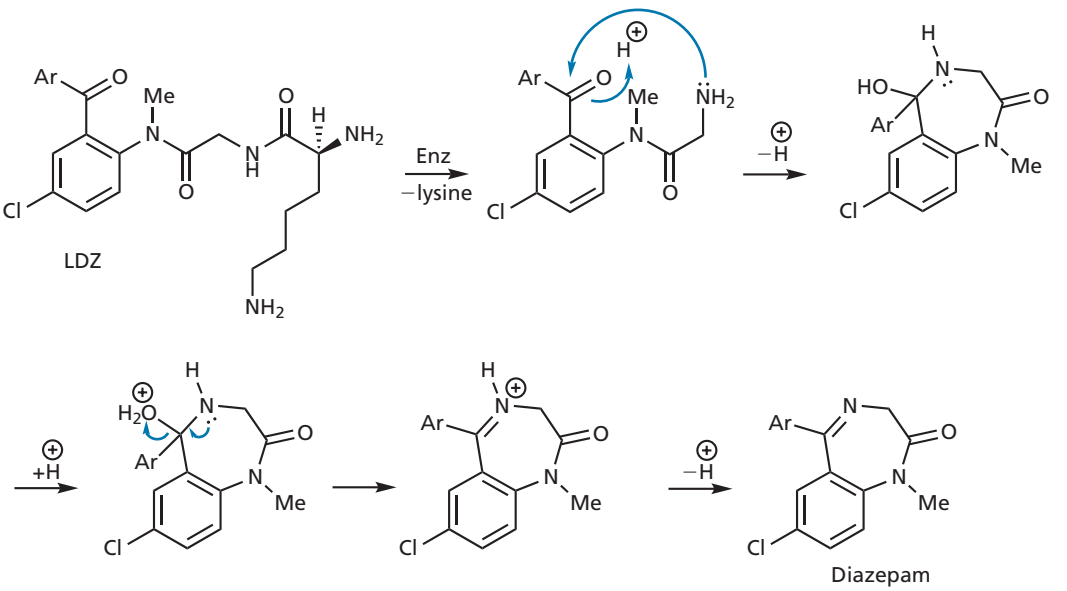


FIGURE 14.29 Pargyline as a prodrug for propiolaldehyde.

BOX 14.4 Prodrugs masking toxicity and side effects

LDZ is an example of a diazepam prodrug which avoids the drowsiness side effects associated with **diazepam**. These side effects are associated with the high initial plasma levels of diazepam following administration. The use of a prodrug avoids this problem. An aminopeptidase enzyme hydrolyses the prodrug to release a non-toxic lysine moiety, and the resulting amine spontaneously cyclizes to the diazepam (as shown).



LDZ as a diazepam prodrug.

anti-schistosomal agent **oxamniquine** is converted to an alkylating agent by an enzyme which is only present in the parasite (Case study 4).

14.6.4 Prodrugs to lower water solubility

Some drugs have a revolting taste! One way to avoid this problem is to reduce their water solubility to prevent them dissolving on the tongue. For example, the bitter taste of the antibiotic **chloramphenicol** can be avoided by using the palmitate ester (Fig. 14.30). This is more hydrophobic because of the masked alcohol and the long chain fatty group that is present. It does not dissolve easily on the tongue and is quickly hydrolysed once swallowed.

14.6.5 Prodrugs to improve water solubility

Prodrugs have been used to increase the water solubility of drugs (Box 14.5). This is particularly useful for drugs which are given intravenously, as it means that higher concentrations and smaller volumes can be used. For example, the succinate ester of **chloramphenicol** (Fig. 14.30) increases the latter's water solubility because of the extra carboxylic acid that is present. Once the ester is hydrolysed, chloramphenicol is released along with succinic acid, which is naturally present in the body.

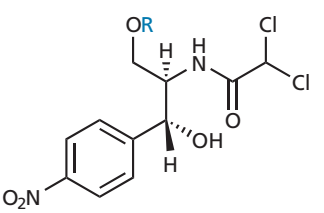
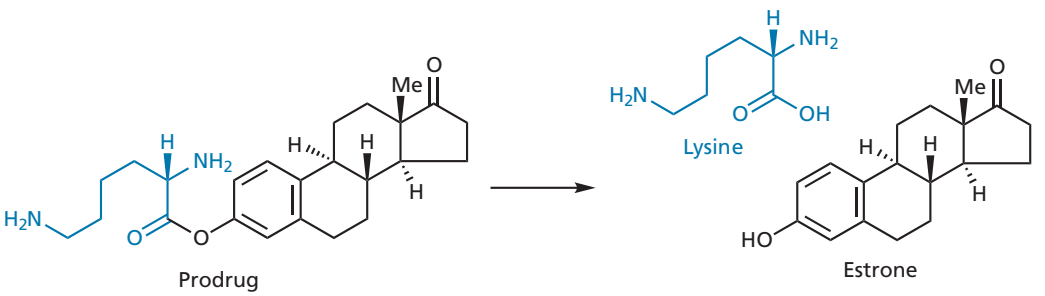


FIGURE 14.30 Chloramphenicol (R = H) and chloramphenicol prodrugs; chloramphenicol palmitate ($R = CO(CH_2)_{14}CH_3$); chloramphenicol succinate ($R = CO(CH_2)_2CO_2H$).

Prodrugs designed to increase water solubility have proved useful in preventing the pain associated with

BOX 14.5 Prodrugs to improve water solubility

Polar prodrugs have been used to improve the absorption of non-polar drugs from the gut. Drugs have to have some water solubility if they are to be absorbed, otherwise they dissolve in fatty globules and fail to interact effectively with the gut wall. The steroid **estrone** is one such drug. By using a lysine ester prodrug, water solubility and absorption is increased. Hydrolysis of the prodrug releases the active drug and the amino acid lysine as a non-toxic by-product.



The lysine ester of estrone to improve water solubility and absorption.

some injections, which is caused by the poor solubility of the drug at the site of injection. For example, the antibacterial agent **clindamycin** is painful when injected, but this is avoided by using a phosphate ester prodrug which has much better solubility because of the ionic phosphate group (Fig. 14.31).

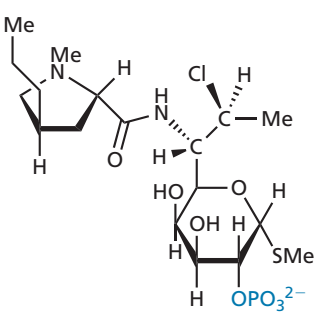


FIGURE 14.31 Clindamycin phosphate.

14.6.6 Prodrugs used in the targeting of drugs

Methenamine (Fig. 14.32) is a stable, inactive compound when the pH is more than 5. At a more acidic pH, however, the compound degrades spontaneously to generate **formaldehyde**, which has antibacterial properties. This is useful in the treatment of urinary tract infections. The normal pH of blood is slightly alkaline (7.4) and so methenamine passes round the body unchanged. However, once it is excreted into the infected urinary tract, it encounters

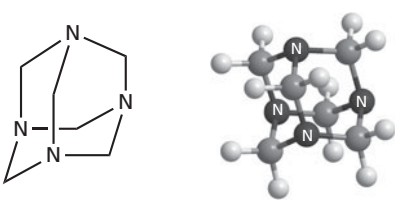


FIGURE 14.32 Methenamine.

urine which is acidic as a result of certain bacterial infections. Consequently, methenamine degrades to generate formaldehyde just where it is needed.

Prodrugs of sulphonamides have also been used to target intestinal infections (Box 19.2). Other examples of prodrugs used to target infections are the antischistosomal drug **oxamniquine** (Case study 4) and the antiviral drugs described in sections 9.5 and 20.6.1.

The targeting of prodrugs to tumour cells by antibody-related strategies was mentioned in section 14.4.1 and is described in more detail in section 21.9. Antibody–drug conjugates can also be viewed as prodrugs and are described in that section.

Finally, the **proton pump inhibitors** are prodrugs that are activated by the acid conditions of the stomach (section 25.3).

14.6.7 Prodrugs to increase chemical stability

The antibacterial agent **ampicillin** decomposes in concentrated aqueous solution as a result of intramolecular

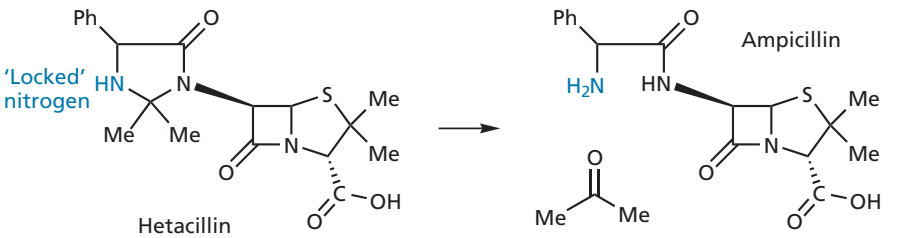


FIGURE 14.33 Hetacillin and ampicillin.

attack of the side chain amino group on the lactam ring (section 19.5.1.8). **Hetacillin** (Fig 14.33) is a prodrug which locks up the offending nitrogen in a ring and prevents this reaction. Once the prodrug has been administered, hetacillin slowly decomposes to release ampicillin and acetone. In the field of antiviral agents, cyclopropane carboxylic acid esters (section 14.6.1.1) are being studied as potential prodrugs of aciclovir in order to prolong chemical stability in solution.

14.6.8 Prodrugs activated by external influence (sleeping agents)

Conventional prodrugs are inactive compounds which are normally metabolized in the body to the active form. A variation of the prodrug approach is the concept of a 'sleeping agent'. This is an inactive compound which is only converted to the active drug by some form of external influence. The best example of this approach is the use of photosensitizing agents (such as **porphyrins** or **chlorins** in cancer treatment)—a strategy known as **photodynamic therapy**. Given intravenously, these agents accumulate within cells and have some selectivity for tumour cells. By themselves, the agents have little effect, but if the cancer cells are irradiated with light, the porphyrins are converted to an excited state and react with molecular oxygen to produce highly toxic singlet oxygen. This is covered in section 21.10.

KEY POINTS

- Prodrugs are inactive compounds which are converted to active drugs in the body, usually by drug metabolism.
- Esters are commonly used as prodrugs to make a drug less polar, allowing it to cross cell membranes more easily. The nature of the ester can be altered to vary the rate of hydrolysis.
- Introducing a metabolically susceptible *N*-methyl group can sometimes be advantageous in reducing polarity.
- Prodrugs with a similarity to important biosynthetic building blocks may be capable of crossing cell membranes with the aid of transport proteins.
- The activity of a drug can be prolonged by using a prodrug which is converted slowly to the active drug.
- The toxic nature of a drug can be reduced by using a prodrug which is slowly converted to the active compound, preferably at the site of action.
- Prodrugs which contain metabolically susceptible polar groups are useful in improving water solubility. They are particularly useful for drugs which have to be injected or for drugs which are too hydrophobic for effective absorption from the gut.
- Prodrugs which are susceptible to pH or chemical degradation can be effective in targeting drugs or increasing stability in solution prior to injection.
- Prodrugs which are activated by light are the basis for photodynamic therapy.

14.7 Drug alliances

Some drugs are found to affect the activity or pharmacokinetic properties of other drugs and this can be put to good use. The following are some examples.

14.7.1 'Sentry' drugs

In this approach, a second drug is administered with the principal drug in order to guard or assist it. Usually, the second drug inhibits an enzyme that metabolizes the principal drug. For example, **clavulanic acid** inhibits the enzyme **β-lactamase** and is therefore able to protect penicillins from that particular enzyme (sections 7.5 and 19.5.4.1).

The antiviral preparation **Kaletra**, used in the treatment of AIDS, is a combination of two drugs called **ritonavir** and **lopinavir**. Although the former has antiviral activity, it is principally present to protect lopinavir, which is metabolized by the metabolic cytochrome P450 enzyme (CYP3A4). Ritonavir is a strong inhibitor of this enzyme and so the metabolism of lopinavir is decreased, allowing lower doses to be used for therapeutic plasma levels (section 20.7.4.4).