

# 1

## An introduction to drugs, their action and discovery

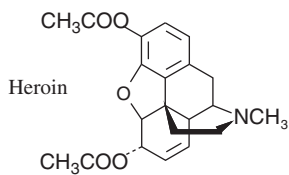
### 1.1 Introduction

The primary objective of medicinal chemistry is the design and discovery of new compounds that are suitable for use as drugs. This process involves a *team of workers* from a wide range of disciplines such as chemistry, biology, biochemistry, pharmacology, mathematics, medicine and computing, amongst others.

The discovery or design of a new drug not only requires a discovery or design process but also the synthesis of the drug, a method of administration, the development of tests and procedures to establish how it operates in the body and a safety assessment. Drug discovery may also require fundamental research into the biological and chemical nature of the diseased state. These and other aspects of drug design and discovery require input from specialists in many other fields and so medicinal chemists need to have an outline knowledge of the relevant aspects of these fields.

### 1.2 What are drugs and why do we need new ones?

Drugs are strictly defined as chemical substances that are used to prevent or cure diseases in humans, animals and plants. The *activity* of a drug is its pharmaceutical effect on the subject, for example, analgesic or  $\beta$ -blocker, whereas its *potency* is the quantitative nature of that effect. Unfortunately the term drug is also used by the media and the general public to describe the substances taken for their psychotic rather than medicinal effects. However, this does not mean that these substances cannot be used as drugs. Heroin, for example, is a very effective painkiller and is used as such in the form of diamorphine in terminal cancer cases.



Drugs act by interfering with biological processes, so no drug is completely safe. *All* drugs, including those non-prescription drugs such as aspirin and paracetamol (Fig. 1.1) that are commonly available over the counter, act as poisons if taken in excess. For example, overdoses of paracetamol can cause coma and death. Furthermore, in addition to their beneficial effects most drugs have non-beneficial biological effects. Aspirin, which is commonly used to alleviate headaches, can also cause gastric irritation and occult bleeding in some people. The non-beneficial effects of some drugs, such as cocaine and heroin, are so undesirable that the use of these drugs has to be strictly controlled by legislation. These unwanted effects are commonly referred to as *side effects*. However, side effects are not always non-beneficial; the term also includes biological effects that are beneficial to the patient. For example, the antihistamine promethazine is licenced for the treatment of hayfever but also induces drowsiness, which may aid sleep.



**Figure 1.1** Aspirin and paracetamol

Drug resistance or tolerance (*tachyphylaxis*) occurs when a drug is no longer effective in controlling a medical condition. It arises in people for a variety of reasons. For example, the effectiveness of barbiturates often decreases with repeated use because the body develops mixed function oxidases in the liver that metabolise the drug, which reduces its effectiveness. The development of an enzyme that metabolises the drug is a relatively common reason for drug resistance. Another general reason for drug resistance is the *downregulation* of receptors (see section 8.6.1). Downregulation occurs when repeated stimulation of a receptor results in the receptor being broken down. This results in the drug being less effective because there are fewer receptors available for it to act on. However, downregulating has been utilised therapeutically in a number of cases. The continuous use

of gonadotrophin releasing factor, for example, causes gonadotrophin receptors that control the menstrual cycle to be downregulated. This is why gonadotrophin-like drugs are used as contraceptives. Drug resistance may also be due to the appearance of a significantly high proportion of drug-resistant strains of microorganisms. These strains arise naturally and can rapidly multiply and become the currently predominant strain of that microorganism. Antimalarial drugs are proving less effective because of an increase in the proportion of drug-resistant strains of the malaria parasite.

New drugs are constantly required to combat drug resistance even though it can be minimised by the correct use of medicines by patients. They are also required for improving the treatment of existing diseases, the treatment of newly identified diseases and the production of safer drugs by the reduction or removal of adverse side effects.

### 1.3 Drug discovery and design: a historical outline

Since ancient times the peoples of the world have had a wide range of natural products that they use for medicinal purposes. These products, obtained from animal, vegetable and mineral sources, were sometimes very effective. However, many of the products were very toxic and it is interesting to note that the Greeks used the same word *pharmakon* for both poisons and medicinal products. Information about these ancient remedies was not readily available to users until the invention of the printing press in the fifteenth century. This led to the widespread publication and circulation of Herbals and Pharmacopoeias, which resulted in a rapid increase in the use, and misuse, of herbal and other remedies. Misuse of tartar emetic (antimony potassium tartrate) was the reason for its use being banned by the Paris parliament in 1566, probably the first recorded ban of its type. The usage of such remedies reached its height in the seventeenth century. However, improved communications between practitioners in the eighteenth and nineteenth centuries resulted in the progressive removal of preparations that were either ineffective or too toxic from Herbals and Pharmacopoeias. It also led to a more rational development of new drugs.

The early nineteenth century saw the extraction of pure substances from plant material. These substances were of consistent quality but only a few of the compounds isolated proved to be satisfactory as therapeutic agents. The majority were found to be too toxic although many, such as morphine and cocaine for example, were extensively prescribed by physicians.

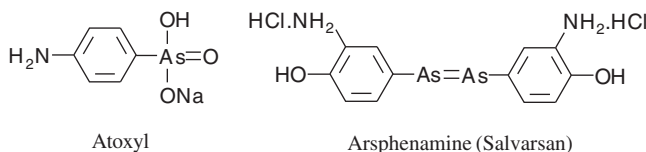
The search to find less toxic medicines than those based on natural sources resulted in the introduction of synthetic substances as drugs in the late nineteenth century and their widespread use in the twentieth century. This development was based on the structures of known pharmacologically active compounds, now referred to as *leads*. The approach adopted by most nineteenth century workers was to synthesise structures related to that of the lead and test these compounds for the required activity. These lead-related compounds are now referred to as *analogues*.

The first rational development of synthetic drugs was carried out by Paul Ehrlich and Sacachiro Hata who produced arsphenamine in 1910 by combining synthesis with reliable

biological screening and evaluation procedures. Ehrlich, at the beginning of the nineteenth century, had recognised that both the beneficial and toxic properties of a drug were important to its evaluation. He realised that the more effective drugs showed a greater selectivity for the target microorganism than its host. Consequently, to compare the effectiveness of different compounds, he expressed a drug's selectivity and hence its effectiveness in terms of its chemotherapeutic index, which he defined as:

$$\text{Chemotherapeutic index} = \frac{\text{Minimum curative dose}}{\text{Maximum tolerated dose}} \quad (1.1)$$

At the start of the nineteenth century Ehrlich was looking for a safer antiprotozoal agent with which to treat syphilis than the then currently used atoxyl. He and Hata tested and catalogued in terms of his therapeutic index over 600 structurally related arsenic compounds. This led to their discovery in 1909 that arsphenamine (Salvarsan) could cure mice infected with syphilis. This drug was found to be effective in humans but had to be used with extreme care as it was very toxic. However, it was used up to the mid- 1940s when it was replaced by penicillin.



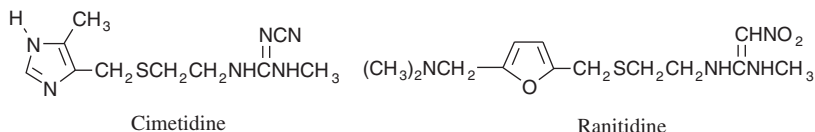
Ehrlich's method of approach is still one of the basic techniques used to design and evaluate new drugs in medicinal chemistry. However, his chemotherapeutic index has been updated to take into account the variability of individuals and is now defined as its reciprocal, the therapeutic index or ratio:

$$\text{Therapeutic index} = \frac{LD_{50}}{ED_{50}} \quad (1.2)$$

where  $LD_{50}$  is the lethal dose required to kill 50 per cent of the test animals and  $ED_{50}$  is the dose producing an effective therapeutic response in 50 per cent of the test animals. In theory, the larger a drug's therapeutic index, the greater is its margin of safety. However, because of the nature of the data used in their derivation, therapeutic index values can only be used as a limited guide to the relative usefulness of different compounds.

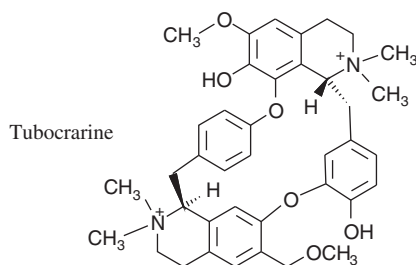
The term *structure–activity relationship* (SAR) is now used to describe Ehrlich's approach to drug discovery, which consisted of synthesising and testing a series of structurally related compounds (see Chapter 3). Although attempts to quantitatively relate chemical structure to biological action were first initiated in the nineteenth century, it was not until the 1960s that Hansch and Fujita devised a method that successfully incorporated quantitative measurements into structure–activity relationship determinations (see section 3.4.4). The technique is referred to as *QSAR* (*quantitative structure–activity relationship*).

QSAR methods have subsequently been expanded by a number of other workers. One of the most successful uses of QSAR has been in the development in the 1970s of the antiulcer agents cimetidine and ranitidine. Both SAR and QSAR are important parts of the foundations of medicinal chemistry.



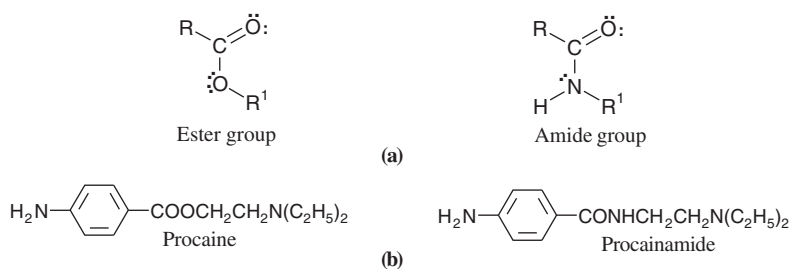
At the same time as Ehrlich was investigating the use of arsenical drugs to treat syphilis, John Langley formulated his theory of *receptive substances*. In 1905 Langley proposed that so-called receptive substances in the body could accept either a stimulating compound, which would cause a biological response, or a non-stimulating compound, which would prevent a biological response. These ideas have been developed by subsequent workers and the theory of *receptors* has become one of the fundamental concepts of medicinal chemistry. *Receptor sites* (see Chapter 8) usually take the form of pockets, grooves or other cavities in the surface of certain proteins and glycoproteins in the living organism. They should not be confused with active sites (see section 9.3), which are the regions of enzymes where metabolic chemical reactions occur. It is now accepted that the binding of a chemical agent, referred to as a *ligand* (see section 8.1), to a receptor sets in motion a series of biochemical events that result in a biological or physiological effect. Furthermore, a drug is most effective when its structure or a significant part of its structure, both as regards molecular shape and electron distribution (*stereoelectronic structure*), is complementary with the stereoelectronic structure of the receptor responsible for the desired biological action. Since most drugs are able to assume a number of different conformations, the conformation adopted when the drug binds to the receptor is known as its *active conformation*.

The section of the structure of a ligand that binds to a receptor is known as its *pharmacophore*. The sections of the structure of a ligand that comprise a pharmacophore may or may not be some distance apart in that structure. They do not have to be adjacent to one another. For example, the quaternary nitrogens that are believed to form the pharmacophore of the neuromuscular blocking agent tubocurarine are separated in the molecule by a distance of 115.3 nm.



The concept of receptors also gives a reason for side effects and a rational approach to ways of eliminating their worst effects. It is now believed that side effects can arise when the drug binds to either the receptor responsible for the desired biological response or to different receptors.

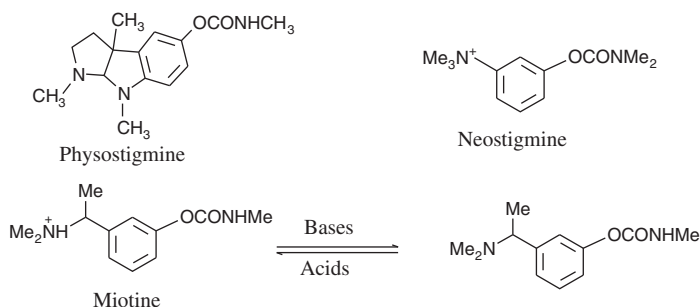
The mid- to late twentieth century has seen an explosion of our understanding of the chemistry of disease states, biological structures and processes. This increase in knowledge has given medicinal chemists a clearer picture of how drugs are distributed through the body, transported across membranes, their mode of operation and metabolism. This knowledge has enabled medicinal chemists to place groups that influence its absorption, stability in a bio-system, distribution, metabolism and excretion into the molecular structure of a drug. For example, the *in situ* stability of a drug and hence its potency could be increased by rationally modifying the molecular structure of the drug. Esters and N-substituted amides, for example, have structures with similar shapes and electron distributions (Fig. 1.2a) but N-substituted amides hydrolyse more slowly than esters. Consequently, the replacement of an ester group by an N-substituted amide group *may* increase the stability of the drug without changing the nature of its activity. This *could possibly* lead to an increase in either the potency or time of duration of activity of a drug by improving its chances of reaching its site of action. However, changing a group or introducing a group may change the nature of the activity of the compound. For example, the change of the ester group in procaine to an amide (procainamide) changes the activity from a local anaesthetic to an antiarrhythmic (Fig. 1.2b).



**Figure 1.2** (a) The similar shapes and outline electronic structures (stereoelectronic structures) of amide and ester groups. (b) Procaine and procainamide

Drugs normally have to cross non-polar lipid membrane barriers (see sections 7.2 and 7.3) in order to reach their site of action. As the polar nature of the drug increases it usually becomes more difficult for the compound to cross these barriers. In many cases drugs whose structures contain charged groups will not readily pass through membranes. Consequently, charged structures can be used to restrict the distribution of a drug. For example, quaternary ammonium salts, which are permanently charged, can be used as an alternative to an amine in a structure in order to restrict the passage of a drug across a membrane. The structure of the anticholinesterase neostigmine, developed from physostigmine, contains a quaternary

ammonium group that gives the molecule a permanent charge. This stops the molecule from crossing the blood–brain barrier, which prevents unwanted CNS activity. However, its analogue miotine can form the free base. As a result, it is able to cross lipid membranes and causes unwanted CNS side effects.



Serendipity has always played a large part in the discovery of drugs. For example, the development of penicillin by Florey and Chain was only possible because Alexander Fleming noted the inhibition of *staphylococcus* by *Penicillium notatum*. In spite of our increased knowledge base, it is still necessary to pick the correct starting point for an investigation if a successful outcome is to be achieved and luck still plays a part in selecting that point. This state of affairs will not change and undoubtedly luck will also lead to new discoveries in the future. However, modern techniques such as *computerised molecular modelling* (see Chapter 4) and *combinatorial chemistry* (see Chapter 5) introduced in the 1970s and 1990s, respectively, are likely to reduce the number of intuitive discoveries.

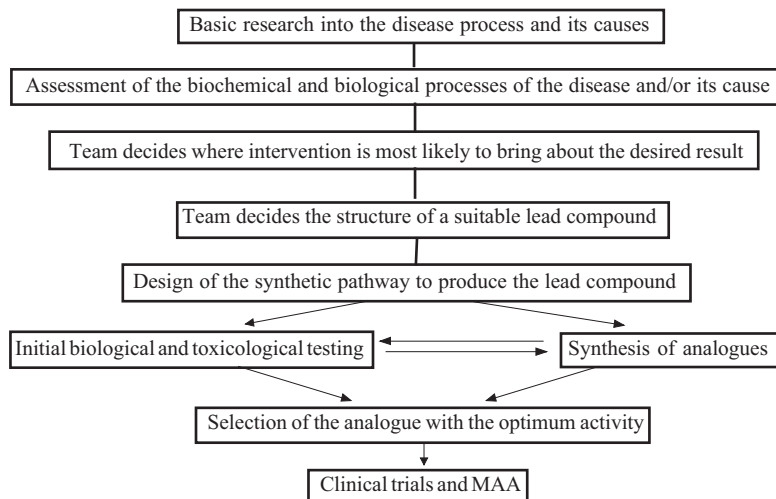
Two of the factors necessary for drug action are that the drug fits and binds to the target. *Molecular modelling* allows the researcher to predict the three-dimensional shapes of molecules and target. It enables workers to check whether the shape of a potential lead is complementary to the shape of its target. It also allows one to calculate the *binding energy* liberated when a molecule binds to its target (see section 4.6). Molecular modelling has reduced the need to synthesise every analogue of a lead compound. It is also often used retrospectively to confirm the information derived from other sources. Combinatorial chemistry originated in the field of peptide chemistry but has now been expanded to cover other areas. It is a group of related techniques for the simultaneous production of large numbers of compounds, known as *libraries*, for biological testing. Consequently, it is used for structure–activity studies and to discover new lead compounds. The procedures may be automated.

### 1.3.1 The general stages in modern-day drug discovery and design

At the beginning of the nineteenth century drug discovery and design was largely carried out by individuals and was a matter of luck rather than structured investigation. Over the last century, a large increase in our general scientific knowledge means that today drug discovery

requires considerable *teamwork*, the members of the team being specialists in various fields, such as medicine, biochemistry, chemistry, computerised molecular modelling, pharmaceuticals, pharmacology, microbiology, toxicology, physiology and pathology. The approach is now more structured but a successful outcome still depends on a certain degree of luck.

The modern approach to drug discovery/design depends on the objectives of the project. These objectives can range from changing the pharmacokinetics of an existing drug to discovering a completely new compound. Once the objectives of the project have been decided the team will select an appropriate starting point and decide how they wish to proceed. For example, if the objective is to modify the pharmacokinetics of an existing drug the starting point is usually that the drug and design team has to decide what structural modifications need to be investigated in order to achieve the desired modifications. Alternatively, if the objective is to find a new drug for a specific disease the starting point may be a knowledge of the biochemistry of the disease and/or the microorganism responsible for that disease (Fig. 1.3). This may require basic research into the biochemistry of the disease



**Figure 1.3** The general steps in the discovery of a new drug for a specific disease state

causing process before initiating the drug design investigation. The information obtained is used by the team to decide where intervention would be most likely to bring about the desired result. Once the point of intervention has been selected the team has to decide on the structure of a compound, referred to as a *lead compound*, that could possibly bring about the required change. A number of candidates are usually considered but the expense of producing drugs dictates that the team has to choose only one or two of these compounds to act as the lead compound. The final selection depends on the experience of the research team.

Lead compounds are obtained from a variety of sources that range from extracting compounds from natural sources (see Chapter 6), synthesis using combinatorial chemistry

(see Chapter 5), searching data bases and compound collections (see section 1.5.6) for suitable candidates and ethnopharmacological sources (see section 1.5.1). However, whatever the objective and starting point, all investigations start with the selection of a suitable bioassay(s) (see section 6.2), which will indicate whether the compound is likely to be active against the diseased state and also if possible the potency of active compounds. These assays are often referred to as *screening* programmes. They may also be carried out at different stages in drug discovery in order to track active compounds. Once an active lead has been found, it is synthesised and its activity determined. SAR studies (see Chapter 3) are then carried out by synthesising and testing compounds, referred to as *analogues*, that are structurally related to the lead in order to find the structure with the optimum activity. These studies may make use of QSAR (see section 3.4) and computational chemistry (see Chapter 4) to help discover the nature of this optimum structure for activity. This analogue would, if economically viable, be developed and ultimately, if it met the MAA regulations, placed in clinical use (see Chapter 16).

## 1.4 Leads and analogues: some desirable properties

### 1.4.1 Bioavailability

The activity of a drug is related to its *bioavailability*, which is defined as the fraction of the dose of a drug that is found in general circulation (see section 11.5). Consequently, for a compound to be suitable as a lead it must be bioavailable. In order to assess a compound's bioavailability it must be either available off the shelf or be synthesised. Synthesis of a compound could result in the synthesis of an inactive compound, which could be expensive both in time and money. In order to avoid unnecessary work and expense in synthesising inactive molecules, Lipinski *et al.* proposed a set of four rules that would predict whether a molecule was likely to be orally bioavailable. These rules may be summarised as having:

- a molecular mass less than 500;
- a calculated value of  $\log P$  less than 5;
- less than ten hydrogen bond acceptor groups (e.g. -O- and -N-, etc.);
- less than five hydrogen bond donor groups (e.g. NH and OH, etc.).

where  $P$  is the calculated partition coefficient for the octanol/water system (see section 2.12.1). Any compound that fails to comply with two or more of the rules is unlikely to be bioavailable, that is, it is unlikely to be active. Lipinski's rules are based on multiples of five and so are often referred to as the *rule of fives*. Other researchers have developed similar methods to assess the bioavailability of molecules prior to their synthesis. However, it should be realised that Lipinski's and other similar rules are only guidelines.

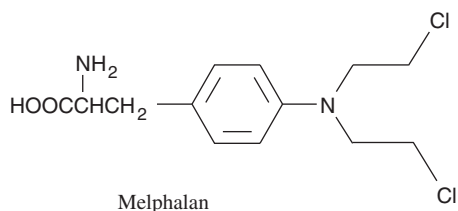
### 1.4.2 Solubility

Solubility is discussed in more detail in Chapter 2. However, a requirement for compounds that are potential drug candidates is that they are soluble to some extent in both lipids and water. Compounds that readily dissolve in lipid solvents are referred to as *lipophilic* or *hydrophobic* compounds. Their structures often contain large numbers of non-polar groups, such as benzene rings and ether and ester functional groups. Compounds that do not readily dissolve in lipids but readily dissolve in water are known as *hydrophilic* or *lipophobic* compounds. Their structures contain polar groups such as acid, amine and hydroxy functional groups. The balance between the polar and non-polar groups in a molecule defines its lipophilic character: compounds with a high degree of *lipophilic character* will have a good lipid solubility but a poor water solubility; conversely, compounds with a low degree of *lipophilic character* will tend to be poorly soluble in lipids but have a good solubility in water. It is desirable that leads and analogues have a balance between their water solubility and their lipophilicity. Most drugs are administered either as aqueous or solid preparations and so need to be water soluble in order to be transported through the body to its site of action. Consequently, poor water solubility can hinder or even prevent the development of a good lead or analogue. For example, one of the factors that hindered the development of the anticancer drug taxol was its poor water solubility. This made it difficult to obtain a formulation for administration by intravenous infusion, the normal route for anticancer drugs (see section 6.8). However, careful design of the form in which the drug is administered (the *dosage form*) can in many instances overcome this lack of water solubility (see sections 2.13 and 6.8). Drugs also require a degree of lipid solubility in order to pass through membranes (see section 7.3.3). However, if it has too high a degree of lipophilicity it may become trapped in a membrane and so become ineffective. The lipophilicity of a compound is often represented by the partition coefficient of that compound in a defined solvent system (see section 2.12.1).

### 1.4.3 Structure

The nature of the structures of leads and analogues will determine their ability to bind to receptors and other target sites. Binding is the formation, either temporary or permanent, of chemical bonds between the drug or analogue with the receptor (see sections 2.2 and 8.2). Their nature will influence the operation of a receptor. For example, the binding of most drugs or analogues takes the form of an equilibrium (see section 8.6.1) in which the drug or analogue forms weak, electrostatic bonds, such as hydrogen bonds and van der Waals' forces, with the receptor. Ultimately the drug or analogue is removed from the vicinity of the receptor by natural processes and this causes the biological processes due to the receptor's activity to stop. For example, it is thought that the local anaesthetic benzocaine (see section 7.4.3) acts in this manner. However, some drugs and analogues act by forming strong covalent bonds with the receptor and either prevent it operating or increase its

duration of operation. For example, melphalan, which is used to treat cancer, owes its action to the strong covalent bonds it forms with DNA (see section 10.13.4).



A major consideration in the selection of leads and analogues is their stereochemistry. It is now recognised that the biological activities of the individual enantiomers and their racemates may be very different (see section 2.3 and Table 1.1). Consequently, it is necessary to pharmacologically evaluate individual enantiomers as well as any racemates. However, it is often difficult to obtain specific enantiomers in a pure state (see section 15.3). Both of these considerations make the production of optically active compounds expensive and so medicinal chemists often prefer to synthesise lead compounds that are not optically active. However, this is not always possible and a number of strategies exist to produce compounds with specific stereochemical centres (see sections 6.5 and 15.3).

#### 1.4.4 Stability

Drug stability can be broadly divided into two main areas: stability after administration and shelf-life.

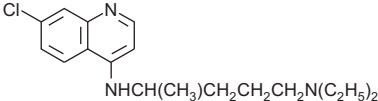
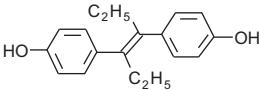
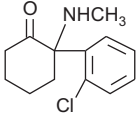
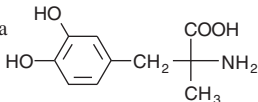
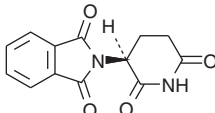
##### ***Stability after administration***

A drug will only be effective if, after administration, it is stable enough to reach its target site in sufficient concentration (see section 1.6) to bring about the desired effect. However, as soon as a drug is administered the body starts to remove it by metabolism (see section 1.7.1 and Chapter 12). Consequently, for a drug to be effective it must be stable long enough after administration for sufficient quantities of it to reach its target site. In other words, it must not be metabolised *too* quickly in the circulatory system. Three strategies are commonly used for improving a drug's *in situ* stability, namely:

- modifying its structure;
- administering the drug as a more stable prodrug (see section 12.9.4);
- using a suitable dosage form (see section 1.6).

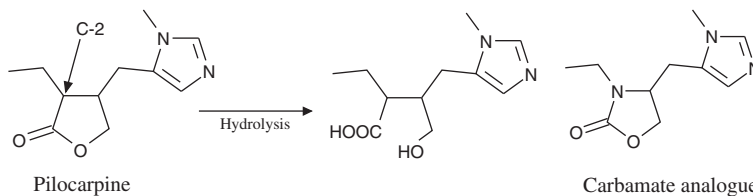
The main method of increasing drug stability in the biological system is to prepare a more stable analogue with the same pharmacological activity. For example, pilocarpine,

**Table 1.1** Variations in the biological activities of stereoisomers

| First stereoisomer | Second stereoisomer               | Example                                                                                                                                                                                                                                              |
|--------------------|-----------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| Active             | Activity of same type and potency | <p>The <i>R</i> and <i>S</i> isomers of the antimalarial chloroquine have equal potencies</p>                                                                      |
| Active             | Activity of same type             | <p>The <i>E</i> isomer of diethylstilbestrol, an oestrogen but weaker, is only 7% as active as the <i>Z</i> isomer</p>                                             |
| Active             | Activity of a different type      | <p><i>S</i>-Ketamine is an anaesthetic whereas <i>R</i>-Ketamine has little anaesthetic action but is a psychotic agent</p>                                        |
| Active             | No activity                       | <p><i>S</i>-<math>\alpha</math>-Methyldopa is a hypertensive drug but the <i>R</i> isomer is inactive</p>                                                        |
| Active             | Active but different side effects | <p>Thalidomide: the <i>S</i> isomer is a sedative and has teratogenic side effects; the <i>R</i> isomer is also a sedative but has no teratogenic activity</p>  |

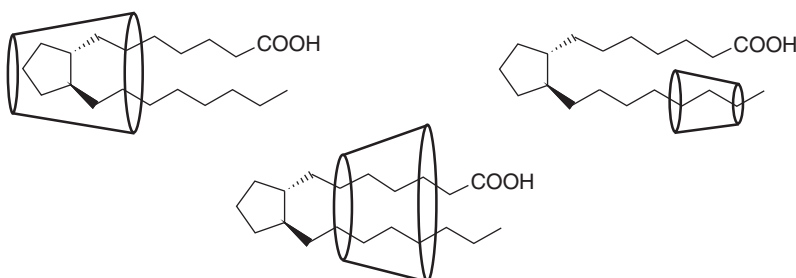
which is used to control glaucoma, rapidly loses its activity because the lactone ring readily opens under physiological conditions. Consequently, the lowering of intraocular pressure by pilocarpine lasts for about three hours, necessitating administration of 3–6 doses a day. However, the replacement of C-2 of pilocarpine by a nitrogen yields an isosteric carbamate

that has the same potency as pilocarpine but is more stable. Although this analogue was discovered in 1989 it has not been accepted for clinical use.



The *in situ* stability of a drug may also be improved by forming a complex with a suitable reagent. For example, complexing with hydroxypropyl- $\beta$ -cyclodextrin is used to improve both the stability and solubility of thalidomide, which is used to inhibit rejection of bone marrow transplants in the treatment of leukaemia. The half-life of a dilute solution of the drug is increased from 2.1 to 4.1 hours while its aqueous solubility increases from 50 to 1700  $\mu\text{g ml}^{-1}$ .

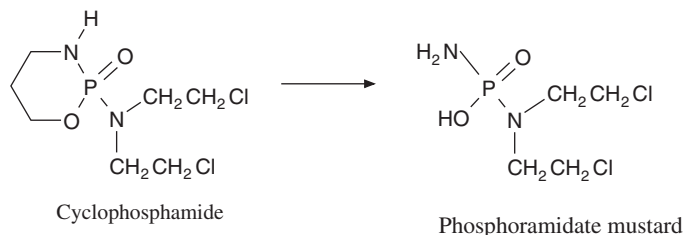
Cyclodextrins are bottomless flower-pot-shaped cylindrical oligosaccharides consisting of about 6–8 glucose units. The exterior of the ‘flower-pot’ is hydrophilic in character whilst the interior has a hydrophobic nature. Cyclodextrins are able to form inclusion complexes in which part of the guest molecule is held within the flower-pot structure (Fig. 1.4). The hydrophobic nature of the interior of the cyclodextrin structure probably means that hydrophobic interaction plays a large part in the formation and stability of the complex. Furthermore, it has been found that the stability of a drug *in situ* is often improved when the active site of a drug lies within the cylinder and decreased when it lies outside the cylinder. In addition, it has been noted that the formation of these complexes may improve the water solubility, bioavailability and pharmacological action and reduce the side effects of some drugs. However, a high concentration of cyclodextrins in the blood stream can cause nephrotoxicity.



**Figure 1.4** Schematic representations of the types of inclusion complexes formed by cyclodextrins and prostaglandins. The type of complex formed is dependent on the cavity size

Prodrug formation can also be used to improve drug stability. For example, cyclophosphamide, which is used to treat a number of carcinomas and lymphomas, is metabolised in

the liver to the corresponding phosphoramidate mustard, the active form of the drug.



The highly acidic gastric fluids can cause extensive hydrolysis of a drug in the gastrointestinal tract (GI tract). This will result in poor bioavailability. However, drug stability in the gastrointestinal tract can be improved by the use of enteric coatings, which dissolve only when the drug reaches the small intestine.

In many cases, but not all (see sections 2.2 and 8.2), once a drug has carried out its function it needs to be removed from the body. This occurs by metabolism and excretion and so a potential drug should not be too stable that it is not metabolised. Furthermore, the drug should not accumulate in the body but be excreted. These aspects of drug stability should be investigated in the preclinical and clinical investigations prior to the drug's release onto the market.

### ***Shelf-life***

Shelf-life is the time taken for a drug's pharmacological activity to decline to an unacceptable level. This level depends on the individual drug and so there is no universal specification. However, 10 per cent decomposition is often taken as an acceptable limit provided that the decomposition products are not toxic.

Shelf-life deterioration occurs through microbial degradation and adverse chemical interactions and reactions. Microbial deterioration can be avoided by preparing the dosage form in the appropriate manner and storage under sterile conditions. It can also be reduced by the use of antimicrobial excipients. Adverse chemical interactions between the components of a dosage form can also be avoided by the use of suitable excipients. Decomposition by chemical reaction is usually brought about by heat, light, atmospheric oxidation, hydrolysis by atmospheric moisture and racemisation. These may be minimised by correct storage with the use of refrigerators, light-proof containers, air-tight lids and the appropriate excipients.

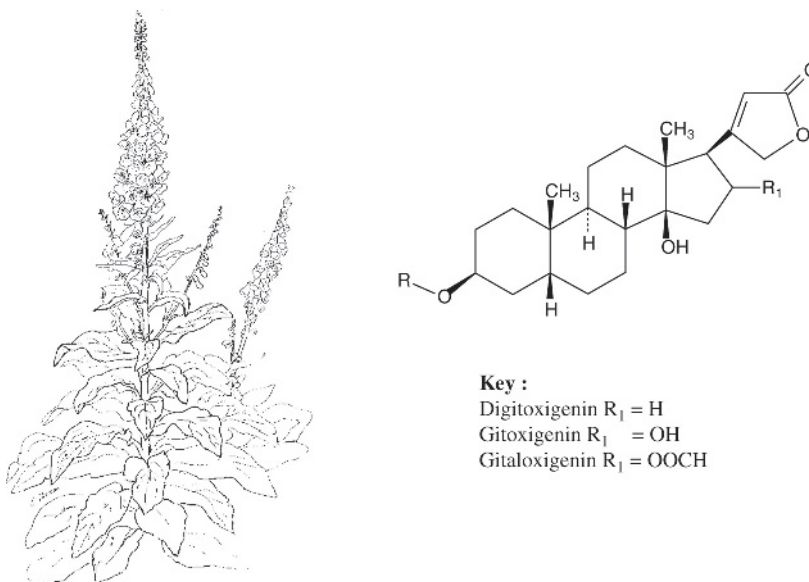
## **1.5 Sources of leads and drugs**

Originally drugs and leads were derived from natural sources. These natural sources are still important sources of lead compounds and new drugs, however the majority of lead compounds are now discovered in the laboratory using a variety of sources, such as local folk remedies (ethnopharmacology), investigations into the biochemistry of the pathology

of disease states and high-throughput screening of compound collections (see Chapter 5), databases and other literature sources of organic compounds.

### 1.5.1 Ethnopharmaceutical sources

The screening of local folk remedies (*ethnopharmacology*) has been a fruitful source of lead compounds and many important therapeutic agents. For example, the antimalarial quinine from cinchona bark, the cardiac stimulants from foxgloves (Fig. 1.5) and the antidepressant reserpine isolated from *Rauwolfia serpentina*.



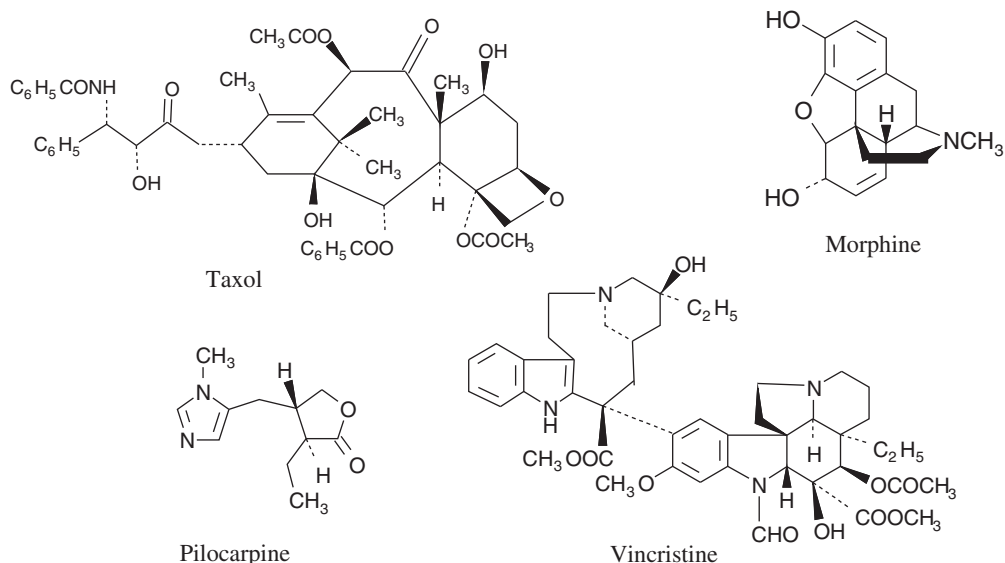
**Figure 1.5** *Digitalis purpurea*, the common foxglove. The leaves contain about 30 different cardioactive compounds. The major components of this mixture are glycosides, with aglycones of digitoxigenin, gitoxigenin and gitaloxigenin. Two series of compounds are known, those where R, the carbohydrate residue (glycone) of the glycoside, is either a tetrasaccharide or a trisaccharide chain. Many of the compounds isolated were formed by drying of the leaves prior to extraction. Digitoxin, a trisaccharide derivative of digitoxigenin, is the only compound to be used clinically to treat congestive heart failure and cardiac arrhythmias

### 1.5.2 Plant sources

In medicinal chemistry, 'plant' includes trees, bushes, grasses, etc., as well as what one normally associates with the term plant. All parts of a plant, from roots to seed heads and flowers, can act as the source of a lead. However, the collecting of plant samples must be carried out with due consideration of its environmental impact. In order to be able to repeat

the results of a collection and if necessary cultivate the plant to ensure supplies of the compounds produced by the plant, it is essential that a full botanical record of the plant is made if it does not already exist. This record should contain a description and pictures of the plant and any related species, where it was found (GPS coordinates) and its growing conditions. A detailed record of the collection of the samples taken must also be kept since the chemical constitution of a plant can vary with the seasons, the method used for its collection, its harvest site storage and method of preparation for onward transportation to the investigating laboratory. If the plant material is to be shipped to a distant destination it must be protected from decomposition by exposure to inappropriate environmental conditions, such as a damp atmosphere or contamination by insects, fungi and micro-organisms.. The drying of so-called *green samples* for storage and shipment can give rise to chemical constituent changes because of enzyme action occurring during the drying process. Consequently, extraction of the undried green sample is often preferred, especially as chemical changes due to enzyme action is minimised when the green sample is extracted with aqueous ethanol.

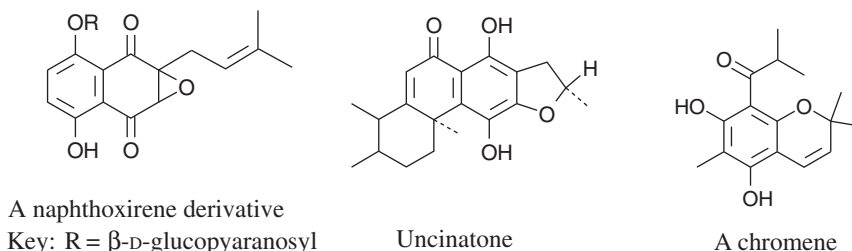
Plant samples are normally extracted and put through screening programmes (see Chapter 6). Once screening shows that a material contains an active compound the problem becomes one of extraction, purification and assessment of the pharmacological activity. However, the isolation of a pure compound of therapeutic value can cause ecological problems. The anticancer agent Taxol (Fig. 1.6), for example, was isolated from the bark of



**Figure 1.6** Examples of some of the drugs in clinical use obtained from plants. Taxol and vincristine are anticancer agents isolated from *Taxus breifolia* and *Vinca rosea* Linn, respectively. Pilocarpine is used to treat glaucoma and is obtained from *Pilocarpus jaborandi* Holmes *Rutaceae*. Morphine, which is used as an analgesic, is isolated from the opium poppy

the Pacific Yew tree (see section 6.8). Its isolation from this source requires the destruction of this slow-growing tree. Consequently, the production of large quantities of Taxol from the Pacific Yew could result in the wholesale destruction of the tree, a state of affairs that is ecologically unacceptable.

A different approach to identifying useful sources is that used by Hostettmann and Marston, who deduced that owing to the climate African plants must be resistant to constant fungal attack because they contain biologically active constituents. This line of reasoning led them to discover a variety of active compounds (Fig. 1.7).



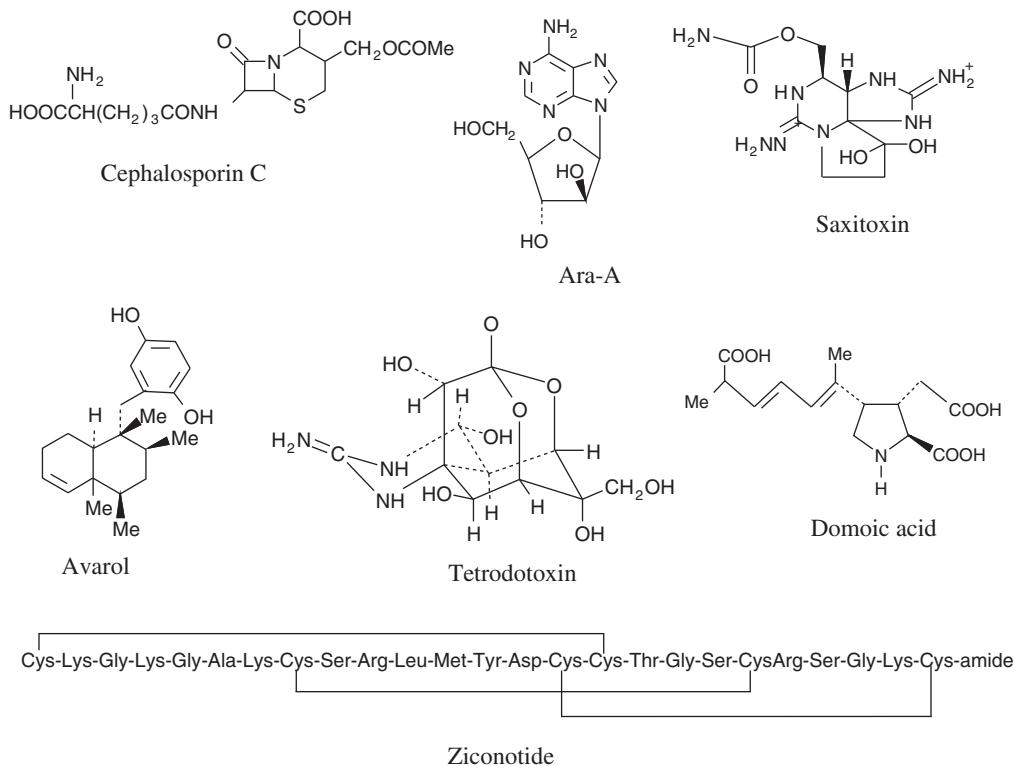
**Figure 1.7** Examples of the antifungal compounds discovered by Hostettmann and Marston

A number of the drugs in clinical use today have been obtained from plant extracts (see Fig. 1.6). Consequently, it is vitally important that plant, shrub and tree sources of the world are protected from further erosion as there is no doubt that they will yield further useful therapeutic agents in the future.

### 1.5.3 Marine sources

Prior to the mid-twentieth century little use was made of marine products in either folk or ordinary medicine. In the last 40 years these sources have yielded a multitude of active compounds and drugs (Fig. 1.8) with potential medical use. These compounds exhibit a range of biological activities and are an important source of new lead compounds and drugs. However, care must be taken so that exploitation of a drug does not endanger its marine sources, such as marine microorganisms, fungi, shellfish, sponges, plants and sea snakes. Marine microorganisms and fungi may be grown in fermentation tanks on a commercial scale. Microbial fermentation is a batch process, the required compound being extracted from the mature organisms by methods based on those outlined in Chapter 6. As well as drugs, microbial fermentation is also used to produce a wide range of chemicals for use in industry.

Marine sources also yield the most toxic compounds known to man. Some of these toxins, such as tetrodotoxin and saxitoxin (Fig. 1.8), are used as tools in neurochemical research work, investigating the molecular nature of action potentials and  $\text{Na}^+$  channels

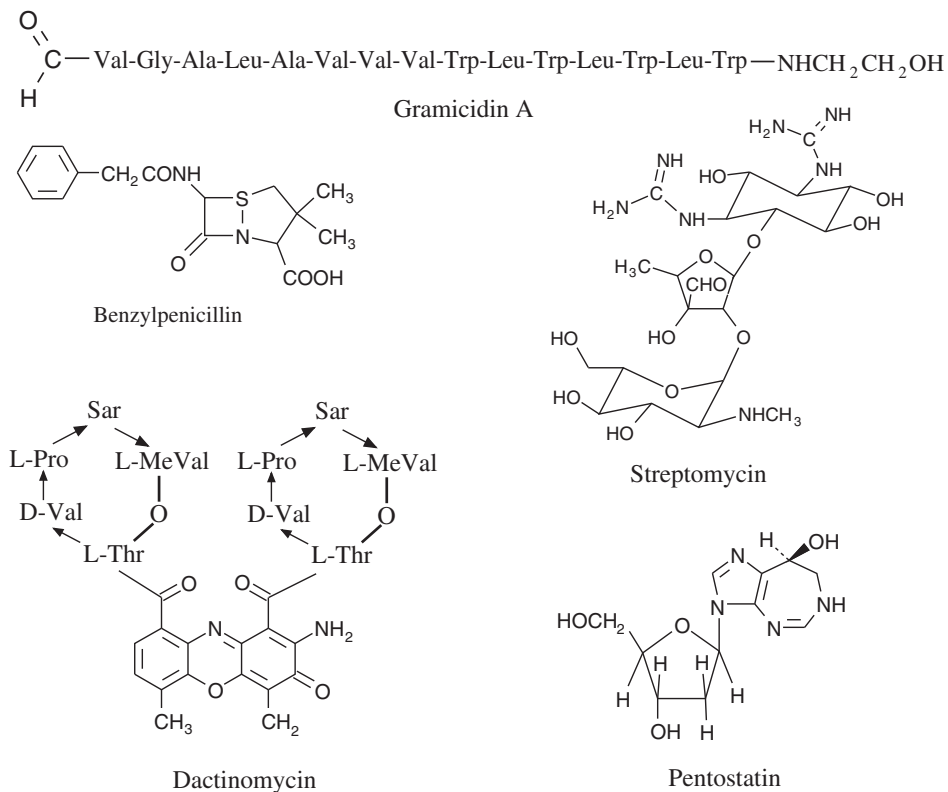


**Figure 1.8** Examples of active compounds isolated from marine sources (Me represents a methyl group). Avarol is reported to be an immunodeficiency virus inhibitor. It is extracted from the sponge *Disidea avara*. The antibiotic cephalosporin C was isolated from the fungus *Acremonium chrysogenum* (*Cephalosporin acremonium*). It was the lead for a wide range of active compounds, a number of which are used as drugs (see section 7.5.2). Domoic acid, which has anthelmintic properties, is obtained from *Chondria armata*. Tetrodotoxin and saxitoxin exhibit local anaesthetic activity but are highly toxic to humans. Tetrodotoxin is found in fish of the order *Tetraodontiformis* and saxitoxin is isolated from some marine dinoflagellates. Ara-A is an FDA - approved antiviral isolated from the sponge *Tethya crypta*. Ziconotide is the active ingredient of Prialt, which is used to treat chronic pain. It is an analogue of the  $\omega$ -conopeptide MVIIA, which occurs in the marine snail *Conus magus*.

(see sections 7.2.2 and 7.4.3). Although tetrodotoxin and saxitoxin are structurally different they are both believed to block the external opening of these channels.

#### 1.5.4 Microorganisms

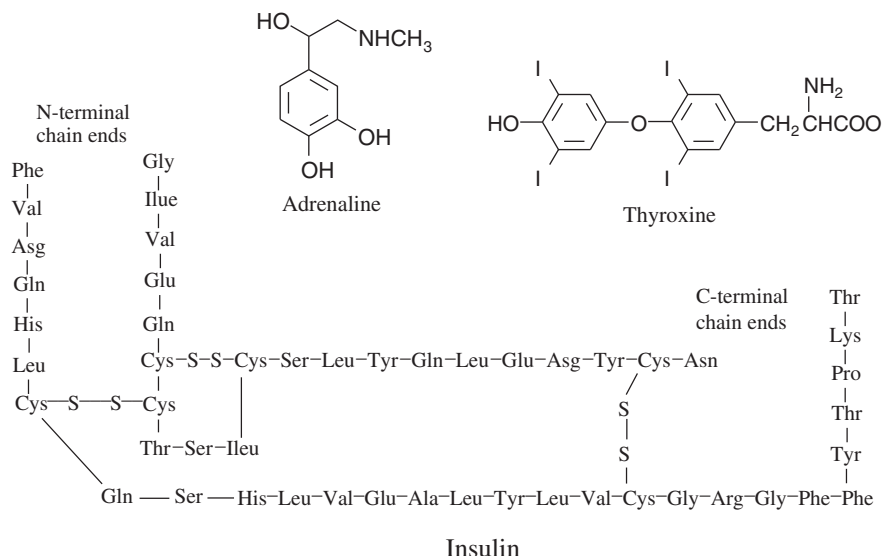
The inhibitory effect of microorganisms was observed as long ago as 1877 by Louis Pasteur, who showed that microbes could inhibit the growth of anthrax bacilli in urine. Later in 1920 Fleming demonstrated that *Penicillin notatum* inhibited *staphylococcus*



**Figure 1.9** Examples of drugs produced by microbial fermentation. Gramicidin A, benzylpenicillin (penicillin G) and streptomycin are antibiotics isolated from *Bacillus brevis*, *Penicillin notatum* and *Streptomyces griseus*, respectively. The anticancer agents dactinomycin and pentostatin are obtained from *Streptomyces parvulus* and *Streptomyces antibioticus*, respectively

cultures, which resulted in the isolation of penicillin (Fig. 1.9) by Chain and Florey in 1940. In 1941 Dubos isolated a pharmacologically active protein extract from *Bacillus brevis* that was shown to contain the antibiotic gramicidin. This was concurrent with Waksman who postulated that soil bacteria should produce antibiotics as the soil contains few pathogenic bacteria from animal excreta. His work on soil samples eventually led Schatz *et al.* to the discovery and isolation in 1944 of the antibiotic streptomycin from the actinomycete *Streptomyces griseus*. This discovery triggered the current worldwide search for drugs produced by microorganisms. To date several thousand active compounds have been discovered from this source, for example the antibiotic chloramphenicol (*Streptomyces venezuelae*), the immunosuppressant cyclosporin A (*Tolypocladium inflatum* Gams) and antifungal griseofulvin (*Penicillium griseofulvum*) (Fig. 1.9). An important advantage of using microorganisms as a source is that, unlike many of the marine and plant sources, they are easily collected, transported and grown in fermentation tanks for use in industry.

### 1.5.5 Animal sources



Animal-derived products have been used since ancient times. However, it was not until the late nineteenth century that thyroid and adrenal medullary extracts were used to treat patients. Investigation of adrenal medullary extracts resulted in the isolation of the pure hormone adrenaline (epinephrine) in 1901. However, it was not until 1914 that pure thyroxine was isolated. This was followed in 1921 by the isolation of insulin from pancreatic extracts by Banting and Best. This enabled insulin to be produced commercially from bovine and porcine sources. Some insulin is still produced from these sources. However, in the later part of the twentieth century insulin was produced from bacteria using recombinant genetic engineering (see section 10.15.2). Animal sources are still used for hormone research but are seldom used to commercially produce drugs.

### 1.5.6 Compound collections, data bases and synthesis

All large pharmaceutical companies maintain extensive collections of compounds known as *libraries*. Smaller libraries are held by certain universities. An important approach to lead discovery is to put the members of these libraries through an appropriate *high-throughput screening* (HTS) (see section 5.6). Screening of large numbers of compounds can be very expensive so pharmaceutical companies tend to test groups of compounds that are selected using criteria specified by the company. These criteria may consist of similar chemical structures, chemical and physical properties, classes of compound and the structure of the target.

Pharmaceutical companies also maintain databases of compounds and their properties where known. Leads are found by searching these data bases for compounds that meet the companies' criteria. These compounds, known as *hits*, are synthesised, if necessary, before being tested for biological activity by HTS.

The pharmaceutical industry makes extensive use of combinatorial chemistry (see Chapter 5) to synthesise compounds for testing in high-throughput screens. Molecular modelling techniques (see Chapter 4) may be used to support this selection by matching the structures of potential leads to either the structures of compounds with similar activities or the target domain. The latter requires a detailed knowledge of both the three-dimensional structures of the ligand and target site.

### 1.5.7 The pathology of the diseased state

An important approach to lead compound selection is to use the biochemistry of the pathology of the target disease. The team select a point in a critical pathway in the biochemistry where intervention may lead to the desired result. This enables the medicinal chemist to either suggest possible lead compounds or to carry out a comprehensive literature and database search to identify compounds found in the organism (*endogenous compounds*) and compounds that are not found in the organism (*exogenous compounds* or *xenobiotics*) that may be biologically active at the intervention site. Once the team have decided what compounds might be active, the compounds are synthesised so that their pharmaceutical action may be evaluated.

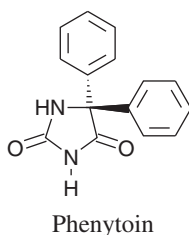
### 1.5.8 Market forces and 'me-too drugs'

The cost of introducing a new drug to the market is extremely high and continues to escalate. One has to be very sure that a new drug is going to be profitable before it is placed on the market. Consequently, the board of directors' decision to market a drug or not depends largely on information supplied by the accountancy department rather than ethical and medical considerations. One way of cutting costs is for companies to produce drugs with similar activities and molecular structures to those of their competitors. These drugs are known as the 'me-too drugs'. They serve a useful purpose in that they give the practitioner a choice of medication with similar modes of action. This choice is useful in a number of situations, for example when a patient suffers an adverse reaction to a prescribed drug or on the rare occasion that a drug is withdrawn from the market.

## 1.6 Methods and routes of administration: the pharmaceutical phase

The form in which a medicine is administered is known as its *dosage form*. Dosage forms can be subdivided according to their physical nature into liquid, semisolid and solid

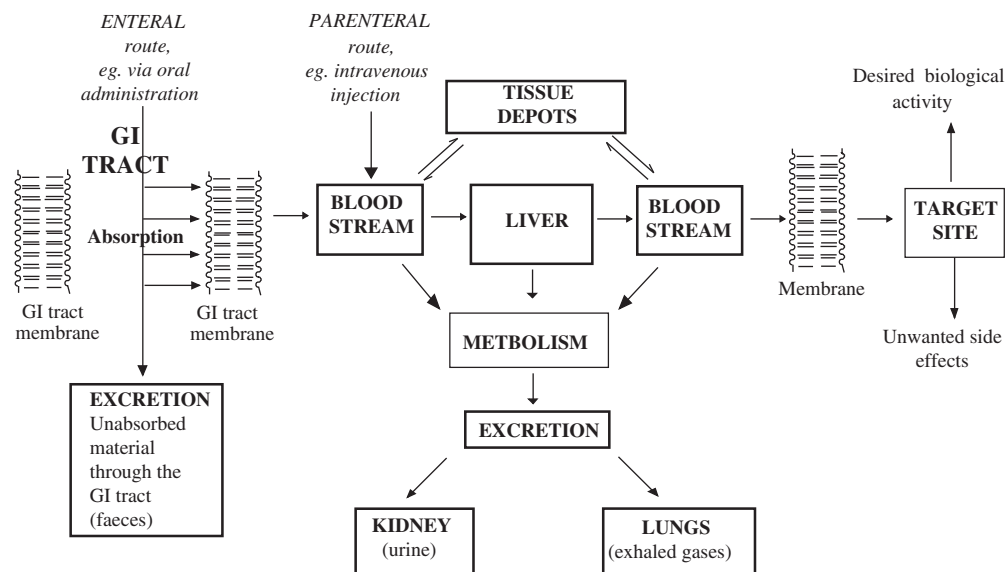
formulations. Liquid formulations include solutions, suspensions, and emulsions. Creams, ointments and gels are normally regarded as semisolid formulations, whilst tablets, capsules and moulded products such as suppositories and pessaries are classified as solid formulations. These dosage forms normally consist of the active constituent and other ingredients (*excipients*). Excipients can have a number of functions, such as fillers (bulk providing agent), lubricants, binders, preservatives and antioxidants. A change in the nature of the excipients can significantly affect the release of the active ingredient from the dosage form. For example, the anticonvulsant phenytoin was found to be rapidly absorbed when lactose is used as a filler. This resulted in patients receiving toxic doses. In contrast, when calcium sulphate was used as a filler, the rate of absorption was so slow that the patient did not receive a therapeutic dose.



Changes in the preparation of the active principle, such as the use of a different solvent for purification, can affect the bioavailability of a drug (see section 11.5) and consequently its effectiveness. This indicates the importance of having all-inclusive quality control procedures for drugs, especially when they reach the manufacturing stage.

The design of dosage forms lies in the field of the pharmaceutical technologist but it should also be considered by the medicinal chemist when developing a drug from a lead compound. It is no use having a wonder drug if it cannot be packaged in a form that makes it biologically available as well as acceptable to the patient. Furthermore, the use of an incorrect dosage form can render the medicine ineffective and potentially dangerous.

Drugs are usually administered topically or systemically. The routes are classified as being either *parenteral* or *enteral* (Fig. 1.10). Parenteral routes are those which avoid the gastrointestinal tract (GI tract), the most usual method being intramuscular injection (IM). However, other parental routes are intravenous injection (IV), subcutaneous injection (SC) and transdermal delivery systems. Nasal sprays and inhalers are also parenteral routes. The enteral route is where drugs are absorbed from the alimentary canal (given orally, PO), rectal and sublingual routes. The route selected for the administration of a drug will depend on the chemical stability of the drug, both when it is across a membrane (*absorption*) and in transit to the site of action (*distribution*). It will also be influenced by the age and physical and mental abilities of the patients using that drug. For example, age-related metabolic changes often result in elderly patients requiring lower dosages of the drug to achieve the desired clinical result. Schizophrenics and patients with conditions that require constant medication are particularly at risk of either overdosing or underdosing. In these cases a slow-release intramuscular injection, which need only be given once in every two to four

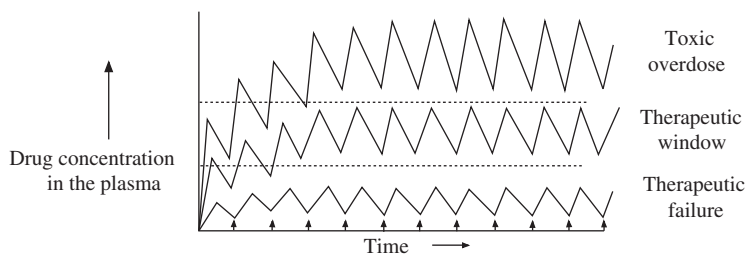


**Figure 1.10** The main routes of drug administration and distribution in the body. The distribution of a drug is also modified by metabolism, which can occur at any point in the system

weeks rather than a daily dose, may be the most effective use of the medicine. Consequently, at an appropriately early stage in its development, the design of a drug should also take into account the nature of its target groups. It is a waste of time and resources if it is found that a drug that is successful in the laboratory cannot be administered in a convenient manner to the patient.

Once the drug enters the blood stream it is distributed around the body and so a proportion of the drug is either lost by excretion, metabolism to other products or is bound to biological sites other than its target site. As a result, the dose administered is inevitably higher than that which would be needed if all the drug reached the appropriate site of biological action. The dose of a drug administered to a patient is the amount that is required to reach and maintain the concentration necessary to produce a favourable response at the site of biological action. Too high a dose usually causes unacceptable side effects, whilst too low a dose results in a failure of the therapy. The limits between which the drug is an effective therapeutic agent is known as its *therapeutic window* (Fig. 1.11). The amount of a drug the plasma can contain, coupled with *elimination* processes (see section 11.4) that irreversibly remove the drug from its site of action, results in the drug concentration reaching a so-called *plateau* value. Too high a dose will give a plateau above the therapeutic window and toxic side effects. Too low a dose will result in the plateau below the therapeutic window and ineffective treatment.

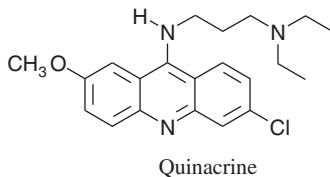
The dose of a drug and how it is administered is called the *drug regimen*. Drug regimens may vary from a single dose taken to relieve a headache, regular daily doses taken to counteract the effects of epilepsy and diabetes, to continuous intravenous infusions for



**Figure 1.11** A simulation of a therapeutic window for a drug, given in fixed doses at fixed time intervals (↑)

seriously ill patients. Regimens are designed to maintain the concentration of the drug within the therapeutic window at the site of action for the period of time that is required for therapeutic success.

The design of an effective dosage regimen requires not just a knowledge of a drug's biological effects but also its *pharmacokinetic* properties, that is, its rate of absorption, distribution, metabolism and elimination from the body. It is possible for a drug to be ineffective because of the use of an incorrect dosage regimen. When quinacrine was introduced as a substitute for quinine in the 1940s it was found to be ineffective at low dose levels or too toxic at the high dose levels needed to combat malaria. Quinacrine was only used successfully after its pharmacokinetic properties were studied. It was found to have a slow elimination rate and so in order to maintain a safe therapeutic dose it was necessary to use large initial doses but only small subsequent maintenance doses to keep the concentration within its therapeutic window. This dosage regimen reduced the toxicity to an acceptable level.



## 1.7 Introduction to drug action

The action of a drug is believed to be due to the interaction of that drug with enzymes, receptors and other molecules found in the body. When one or more drug molecules bind to the target endogenous and exogenous molecules, they cause a change in or inhibit the biological activity of these molecules. The effectiveness of a drug in bringing about these changes usually depends on the stability of the drug–target complex, whereas the medical success of the drug intervention usually depends on whether enough drug molecules bind to sufficient target molecules to have a marked effect on the course of the disease state.

The degree of drug activity is directly related to the concentration of the drug in the aqueous medium in contact with the target molecule. The factors effecting this

concentration in a biological system can be classified into the *pharmacokinetic phase* and the *pharmacodynamic phase* of drug action. The pharmacokinetic phase concerns the study of the parameters that control the journey of the drug from its point of administration to its point of action. The pharmacodynamic phase concerns the chemical nature of the relationship between the drug and its target, in other words, the effect of the drug on the body.

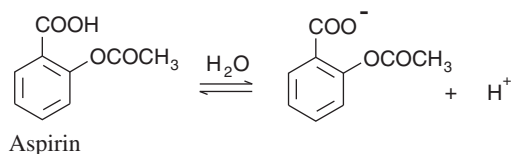
### 1.7.1 The pharmacokinetic phase (ADME)

The pharmacokinetic phase of drug action includes the *Absorption, Distribution, Metabolism* and *Excretion (ADME)* of the drug. Many of the factors that influence drug action apply to all aspects of the pharmacokinetic phase. Solubility (see Chapter 2), for example, is an important factor in the absorption, distribution and elimination of a drug. Furthermore, the rate of drug dissolution (see section 11.5.1) controls its activity when that drug is administered as a solid or suspension by enteral routes (see section 1.6)

#### **Absorption**

Absorption is usually defined as *the passage of the drug from its site of administration into the general circulatory system after enteral administration*. The use of the term does not apply to parenteral administration discussions. The most common enteral route is by oral administration. Drugs administered in this way take about 24 hours to pass through the gastrointestinal tract (GI tract). Individual transit times for the stomach and small intestine are about 20 minutes and 6 hours, respectively. Compounds may be absorbed throughout the length of the GI tract but some areas will suit a drug better than others.

The absorption of drugs through membranes and tissue barriers (see Chapter 7) can occur by a number of different mechanisms (see section 7.3). However, in general, neutral molecules are more readily absorbed through membranes than charged species. For example, ionisation of orally administered aspirin is suppressed in the stomach by acids produced by the parietal cells in the stomach lining. As a result, it is absorbed in this uncharged form through the stomach lining into the blood stream in significant quantities.



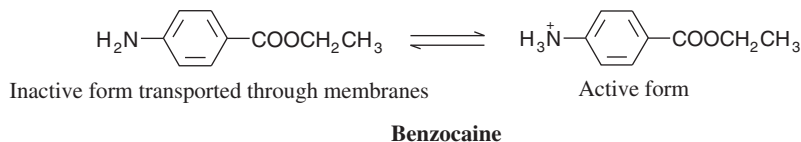
The main structural properties of a drug governing its good absorption from the GI tract are its aqueous solubility (see Chapter 2) and the balance between its polar (hydrophilic) and non-polar (hydrophobic) groups (see section 1.4.2). If the drug's water solubility is too low it will pass through the GI tract without a significant amount being absorbed. Drugs that are too polar will tend to be absorbed by paracellular diffusion, which is only readily

available in the small intestine and is usually slower than transcellular diffusion undergone by less polar and non-polar compounds (see section 11.5.2). Drugs that are absorbed by transcellular diffusion are usually absorbed along the whole length of the GI tract. If the drug is too non-polar (lipophilic) it will be absorbed into and remain within the lipid interior of the membranes of the cells forming the membrane. The Lipinski rule of fives (see section 1.4.1) is useful for assessing whether a compound is likely to be absorbed from the GI tract. However, this rule does have its limitations and the results of its use should only be used as a guide and not taken as being absolute.

The degree of absorption can also be related to the surface area of the region of tissue over which the absorption is occurring and the time the drug spends in contact with that region. For example, it can be shown by calculation using the Henderson–Hasselbalch equation (see section 2.11) that aspirin will be almost fully ionised in the small intestine. Consequently, aspirin should not be readily absorbed in this region of the GI tract. However, the very large surface area of the small intestine ( $300\text{ m}^2$ ) together with the time spent in this region ( $\sim 6$  hours) results in aspirin being absorbed in significant quantities in this region of the GI tract. Examples of *some* of the other factors that can effect the degree of absorption of a drug are:

- the pH of the medium from which absorption occurs (see section 2.11);
- the drug's partition coefficient (see section 3.7.2);
- the drug's dosage form (see section 1.6);
- the drug's particle size (see section 11.5.1); and
- for orally administered drugs, in either solid or emulsion form, their rate of dissolution (see section 11.5.1), amongst others.

It should be noted that the form of the drug that is absorbed is not necessarily the form that is responsible for its action. Benzocaine, for example, is absorbed as its neutral molecule but acts in its charged form.



### ***Distribution***

Distribution is the transport of the drug from its initial point of administration or absorption to its site of action. The main route is through the circulation of the blood although some distribution does occur via the lymphatic system. Once the drug is absorbed it is rapidly distributed throughout all the areas of the body reached by the blood. This means that the

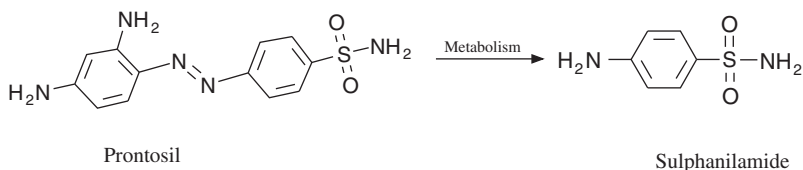
chemical and physical properties of blood will have a considerable effect on the concentration of the drug reaching its target site.

Drugs are transported in the blood stream as either a solution of drug molecules or bound to the serum proteins, usually albumins. The binding of drugs to the serum proteins is usually reversible.

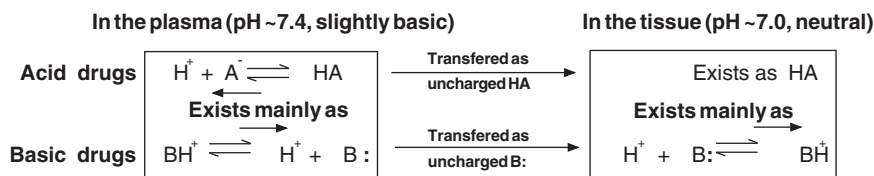


Drug molecules bound to serum proteins have no pharmacological effect until they are released from those proteins. Consequently, this equilibrium can be an important factor in controlling a drug's pharmacological activity (see section 11.4.1). However, it is possible for one drug to displace another from a protein if it forms a more stable complex, that is, has a stronger affinity for that protein. This aspect of protein binding can be of considerable importance when designing drug regimens involving more than one drug. For instance, the displacement of antidiabetic agents by aspirin can trigger hypoglycaemic shock and so aspirin should not be used by patients taking these drugs. Protein binding also allows drugs with poor water solubility to reach their target site. The drug-protein complex acts as a depot maintaining the drug in sufficient concentration at the target site to bring about a response. However, a low plasma protein concentration can also affect the distribution of a drug in some diseases such as rheumatoid arthritis as the 'reduced transport system' is unable to deliver a sufficient concentration of the drug to its target site. Protein binding can also increase the duration of action if the drug-protein complex is too large to be excreted through the kidney by glomerular filtration.

Major factors that influence distribution are the solubility and stability of drugs in the biological environment of the blood. Sparingly water-soluble compounds may be deposited in the blood vessels, leading to restriction in blood flow. This deposition may be influenced by the commonion effect (see section 2.4.1). Drug stability is of particular importance in that serum proteins can act as enzymes that catalyse the breakdown of the drug. Decompositions such as these can result in a higher dose of the drug being needed in order to achieve the desired pharmacological effect. This increased dose increases the risk of toxic side effects in the patient. However, the active form of some drugs is produced by the decomposition of the administered form of the drug. Drugs that function in this manner are known as *prodrugs* (see section 12.9). The first to be discovered, in 1935, was the bactericide prontosil. Prontosil itself is not active but is metabolised *in situ* to the antibacterial sulphanilamide. Its discovery paved the way to the development of a wide range of antibacterial sulphonamide (sulfa) drugs. These were the only effective antibiotics available until the general introduction of penicillin in the late 1940s.

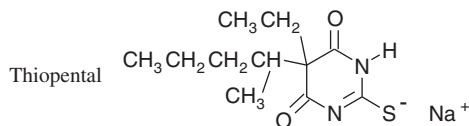


The distribution pattern of a drug through the tissues forming the blood vessels will depend largely on the nature of the tissue (see section 7.2.9) and on the drug's lipid solubility. For example, in general, the pH of the tissues ( $\sim$  pH 7.0) forming blood vessels is less basic than that of the plasma ( $\sim$  pH 7.4). Acidic drugs such as aspirin, which ionise in aqueous solution, exist largely in the form of their anions in the slightly basic plasma. Since uncharged molecules are transferred more readily than charged ions these acidic anions tend to remain in the plasma and not move out of the plasma into the tissues surrounding the blood vessel. Consequently, acids have a tendency to stay in the plasma rather than pass into the surrounding tissue. Conversely, a significant quantity of a basic drug tends to exist as neutral molecules in the plasma. As a result, bases are more likely to pass into the tissues surrounding the plasma. Furthermore, once the base has passed into the tissue the charged form of the base is likely to predominate and so the drug will tend to remain in the tissue. This means that the base is effectively removed from the plasma to favour the formation of the free base, which results in further absorption of the base into the tissue (Fig. 1.12). As a result, basic drugs, unlike acidic drugs, are likely to be more widely distributed in tissues.

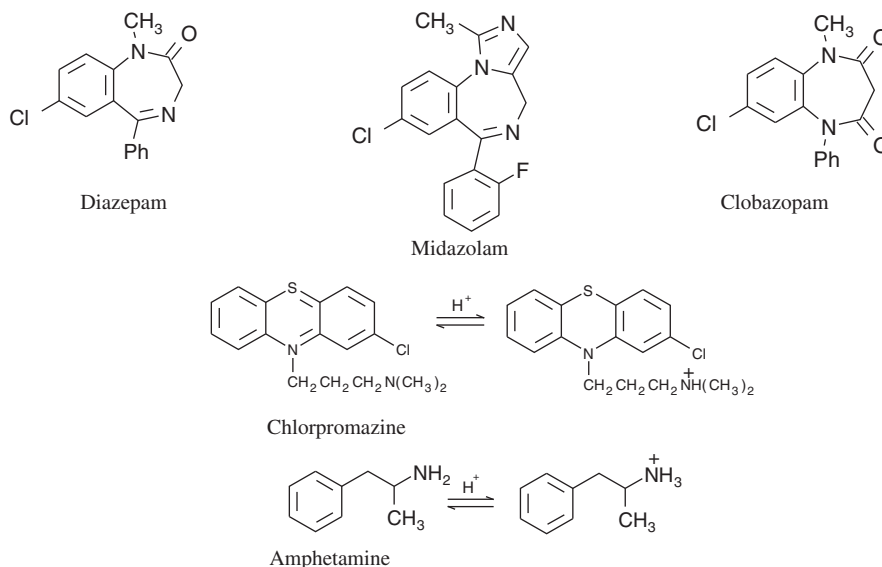


**Figure 1.12** The species involved in the transfer of acidic and basic drugs from the plasma to the surrounding tissues

A drug's lipophilicity (see sections 1.4.2 and 3.7.2) will also influence its distribution. Highly lipophilic drugs can readily enter and accumulate in the fatty deposits of humans. These fatty deposits, which form up to 15 per cent in the body weight of normal individuals and 50 per cent in obese persons, can act as pharmacologically inert depots for drugs, which could terminate their action. For example, the concentration of the ultra-short-acting anaesthetic thiopental rapidly falls after administration to an ineffective level because it accumulates in the fatty tissue deposits of the body. It is slowly released from these deposits in concentrations that are too low to cause a pharmacological response.



The distribution of drugs to the brain entails having to cross the *blood–brain barrier* (BBB) (see section 7.2.9). This barrier protects the brain from both exogenous and

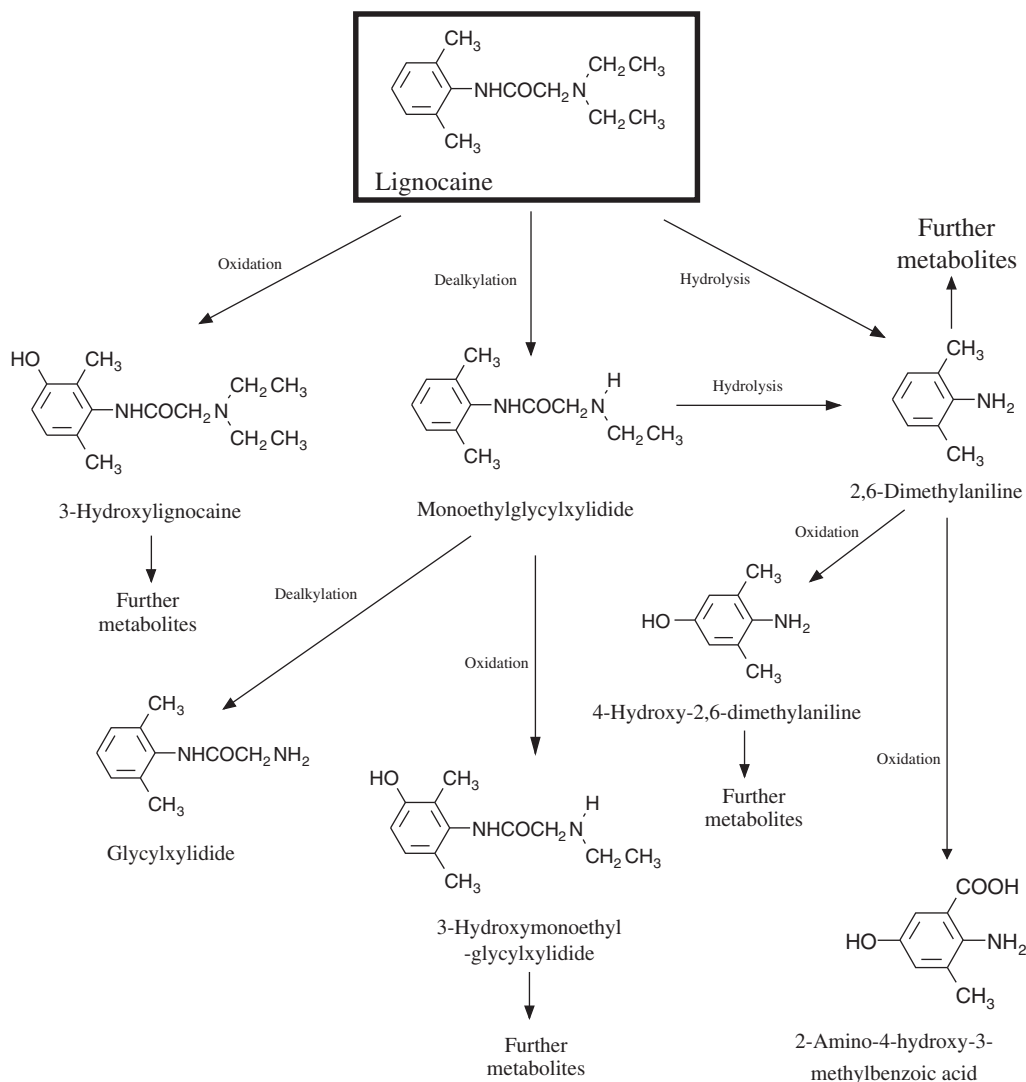


**Figure 1.13** The structures of some of the drugs that are able to cross the blood–brain barrier

endogenous compounds. The extent to which lipophilic drugs are able to cross this barrier varies: highly lipophilic drugs, such as diazepam, midazolam and clobazepam (Fig. 1.13), are rapidly absorbed while less lipophilic drugs are absorbed more slowly. Polar drugs are either unable to cross the BBB or only do so to a very limited extent. For example, calculations using the Henderson–Hasselbalch equation (see section 2.11) show that at blood pH, 99.6 per cent of amphetamine and 98.4 per cent of chlorpromazine exist in their charged forms (Fig. 1.13). However, these polar drugs are still sufficiently lipid soluble to cross the BBB. Some polar drugs may cross by an active transport mechanism (see section 7.3.5). Other polar endogenous compounds such as amino acids, sugars, nucleosides and small ions ( $Na^+$ ,  $Li^+$ ,  $Ca^{2+}$  and  $K^+$ ) are also able to cross the BBB.

### Metabolism

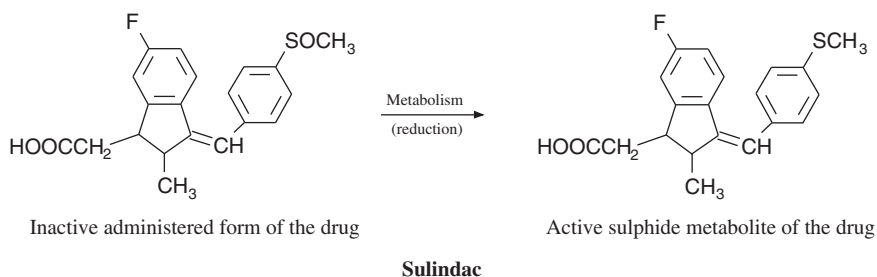
Drug metabolism (see Chapter 12) is the biotransformation of the drug into other compounds (*metabolites*) that are usually more water soluble than their parent drug and are usually excreted in the urine. It usually involves more than one route and results in the formation of a succession of metabolites (Fig. 1.14). These biotransformations occur mainly in the liver but they can also occur in blood and other organs such as the brain, lungs and kidneys. Drugs that are administered orally usually pass through the liver before reaching the general circulatory system. Consequently, some of the drug will be metabolised before it reaches the systemic circulation. This loss is generally referred to as either the *first-pass effect* or *first-pass metabolism* (see section 11.4.1). Further metabolic losses will also be encountered before the drug reaches its target site, which means it is



**Figure 1.14** An outline of the known metabolic pathways of the local anaesthetic lignocaine

important to administer a dose large enough for sufficient of the drug to reach its target site.

Drug metabolism may produce metabolites that are pharmacologically inert, have the same or different action to the parent drug or are toxic (see section 12.2). Exceptions are prodrugs (see sections 1.8.4 and 12.9) where metabolism is responsible for producing an active drug, for example the non-steroidal anti-inflammatory agent sulindac is metabolised to the active sulphide (Fig. 1.15). In addition, the metabolic products of a drug may be used as leads for the development of a new drug.



**Figure 1.15** An outline of the metabolic pathway for the formation of the active form of sulindac

## Excretion

Excretion is the process by which unwanted substances are removed from the body. The main excretion route for drugs and their metabolites is through the kidney in solution in the urine. However, a significant number of drugs and their metabolic products are also excreted via the bowel in the faeces. Other forms of drug excretion, such as exhalation, sweating and breast feeding, are not usually significant except in specific circumstances. Pregnant women and nursing mothers are recommended to avoid taking drugs because of the possibility of biological damage to the foetus and neonate. For example, the use of thalidomide by pregnant mothers in the 1960s resulted in the formation of drug-induced malformed foetuses (*teratogenesis*). It has been estimated that the use of thalidomide led to the birth of 10,000 severely malformed children.

In the kidneys drugs are excreted by either *glomerular filtration* or *tubular secretion*. However, some of the species lost by these processes are reabsorbed by a recycling process known as *tubular reabsorption*. In the kidney, the glomeruli act as a filter allowing the passage of water, small molecules and ions but preventing the passage of large molecules and cells. Consequently, glomerular filtration excretes small unbound drug molecules but not the larger drug-protein complexes. Tubular secretion on the other hand is an active transfer process (see section 7.3.5) and so both bound and unbound drug molecules can be excreted. However, both of these excretion systems have a limited capacity and not all the drug may be eliminated. In addition, renal disease can considerably increase or decrease the rate of drug excretion by the kidney.

Tubular reabsorption is a process normally employed in returning compounds such as water, amino acids, salts and glucose that are important to the well-being of the body from the urine to the circulatory system, but it will also return drug molecules. The mechanism of reabsorption is mainly passive diffusion (see section 7.3.3), but active transport (see section 7.3.5) is also involved, especially for glucose and lithium ions. The reabsorption of acidic and basic compounds is dependent on the pH of the urine. For example, making the urine alkaline in cases of poisoning by acidic drugs, such as aspirin, will cause these drugs to form ionic salts, which will result in a significantly lower tubular reabsorption since the passage of the charged form of a drug across a lipid membrane is more difficult than the passage of the uncharged form of that drug. Similarly, in cases of poisoning by basic drugs

such as amphetamines, acidification of the urine can, for a similar reason, reduce reabsorption.

Control of urinary pH is also required for drugs whose concentration reaches a level in the urine that results in crystallisation (crystalluria) in the urinary tract and kidney with subsequent tissue damage. For example, it is recommended that the urine is maintained at an alkaline pH and has a minimum flow of  $190 \text{ ml h}^{-1}$  when sulphonamides are administered.

Excretion also occurs via the intestines and bowel through *biliary clearance* from the liver. The liver is linked to the intestine by the bile duct and some compounds are excreted by this route. However, very large molecules are metabolised to smaller compounds before being excreted. However, a fraction of some of the excreted drugs are reabsorbed through the *enterohepatic cycle*. This reabsorption can be reduced by the use of suitable substances in the dosage form, for example the ion exchange resin cholestyramine is used to reduce cholesterol levels by preventing its reabsorption.

### ***Lead optimisation and ADME***

A drug must reach its site of action in sufficient quantity to be effective. One of the tasks of the medicinal chemist is to take an active compound and modify the structure to achieve the desired ADME properties. However, having satisfactory ADME properties is not the only requirement for a new drug. A drug candidate must also be:

- potentially effective in treating a patient;
- free of existing patents;
- produced in sufficient quantities;
- capable of being dispensed in a dosage form acceptable to the patient;
- must not be too toxic for use;
- must not exhibit teratogenicity or mutagenicity;
- and commercial development must be cost effective.

Failure to comply with these additional aspects of drug discovery and design will mean that work on the candidate is discontinued before the project proceeds past its preliminary stages.

### **1.7.2 The pharmacodynamic phase**

Pharmacodynamics is concerned with the result of the interaction of drug and body at its site of action, that is, what the drug does to the body. It is now known that a drug is most

effective when its shape and electron distribution, that is, its *stereoelectronic structure*, is complementary with the stereoelectronic structure of the target site.

The role of the medicinal chemist is to design and synthesise a drug structure that has the maximum beneficial effects with a minimum of toxic side effects. This design has to take into account the stereoelectronic characteristics of the target site and also such factors as the drug's stability *in situ*, its polarity and its relative solubilities in aqueous media and lipids. The stereochemistry of the drug is particularly important as stereoisomers often have different biological effects which range from inactive to highly toxic (see section 1.4.3 and Table 1.1).

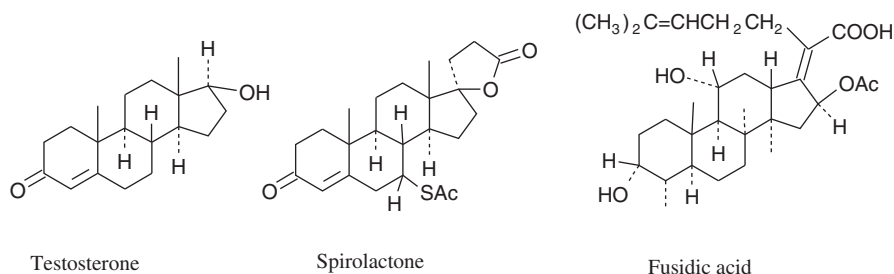
Drugs act at their target site by either inhibiting or stimulating a biological process with, hopefully, beneficial results to the patient. To bring about these changes the drug must bind to the target site, that is, its potency will depend on its ability to bind to that site. This binding is either reversible or permanent. In the former case, the bonding is due to weak electrostatic bonds such as hydrogen bond and van der Waals' forces. The binding takes the form of a dynamic equilibrium with the drug molecules repeatedly binding to and being released from their target site (see section 8.6). Consequently, in this instance, a drug's duration of action will depend on how long it remains at the target site. Permanent binding usually requires the formation of strong covalent bonds between the drug and its target. In this case, the duration of action will depend on the strength of the bond. However, in both cases, the drug structure must contain appropriate functional groups in positions that correspond to the appropriate structures in the target site.

## 1.8 Classification of drugs

Drugs are classified in different ways depending on where and how the drugs are being used. The methods of interest to medicinal chemists are chemical structure and pharmacological action, which includes the site of action and target system. However, it is emphasised that other classifications, such as the nature of the illness, are used both in medicinal chemistry and other fields depending on what use is to be made of the information. In all cases, it is important to bear in mind that most drugs have more than one effect on the body and so a drug may be listed in several different categories within a classification scheme.

### 1.8.1 Chemical structure

Drugs are grouped according to the structure of their carbon skeletons or chemical classifications, for example steroids, penicillins and peptides. Unfortunately in medicinal chemistry this classification has the disadvantage that members of the same group often exhibit different types of pharmaceutical activity. Steroids, for example, have widely differing activities: testosterone is a sex hormone, spironolactone is a diuretic and fusidic acid is an antibacterial agent (Fig. 1.16).



**Figure 1.16** Examples of the diversity of action of compounds belonging to the same class (Ac≡acetyl)

Classification by means of chemical structure is useful to medicinal chemists who are concerned with synthesis and structure–activity relationships.

### 1.8.2 Pharmacological action

This classification lists drugs according to the nature of their pharmacodynamic behaviour, for example diuretics, hypnotics, respiratory stimulants and vasodilators. This classification is particularly useful for doctors looking for an alternative drug treatment for a patient.

### 1.8.3 Physiological classification

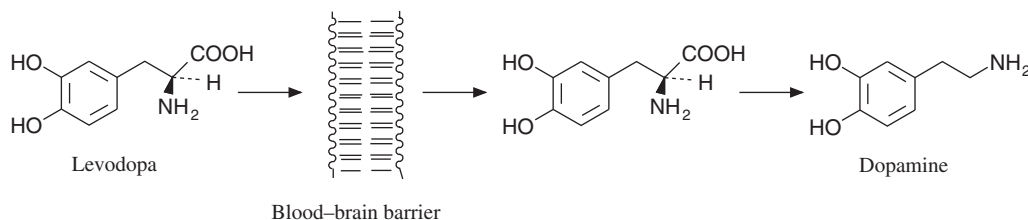
The World Health Organization (WHO) has developed a classification based on the body system on which the drug acts. This classification specifies seventeen sites of drug action. However, a more practical method but less detailed system often used by medicinal chemists is based on four classifications, namely:

1. *Agents acting on the central nervous system (CNS).* The central nervous system consists of the brain and spinal cord. Drugs acting on the CNS are the *psychotropic* drugs that effect mood and the *neurological* drugs required for physiological nervous disorders such as epilepsy and pain.
2. *Pharmacodynamic agents.* These are drugs that act on the body, interfering with the normal bodily functions. They include drugs such as vasodilators, respiratory stimulants and antiallergy agents.
3. *Chemotherapeutic agents.* Originally these were drugs such as antibiotics and fungicides that destroyed the microorganisms that were the cause of a disease in an unwitting host. However, the classification has also now become synonymous with the drugs used to control cancer.

4. *Miscellaneous agents.* This class contains drugs that do not fit into the other three categories, for example hormones and drugs acting on endocrine functions.

### 1.8.4 Prodrugs

Prodrugs are compounds that are pharmacologically inert but converted by enzyme or chemical action to the active form of the drug at or near their target site. For example, levodopa, used to treat Parkinson's syndrome, is the prodrug for the neurotransmitter dopamine. Dopamine is too polar to cross the blood–brain barrier but there is a transport system for amino acids such as levodopa. Once the prodrug enters the brain it is decarboxylated to the active drug dopamine (Fig. 1.17).

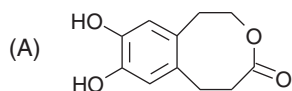


**Figure 1.17** A schematic representation of the formation of dopamine from levodopa

## 1.9 Questions

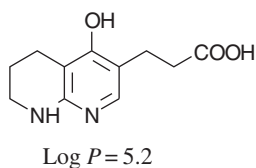
- Predict, giving a reason for the prediction, the *most likely* general effect of the stated structural change on either the *in situ* stability or the pharmacological action of the stated drug.
  - The introduction of *ortho* ethyl groups in dimethylaminoethyl 4-aminobenzoate.
  - The replacement of the amino group in the CNS stimulant amphetamine ( $\text{PhCH}_2\text{CH}(\text{NH}_2)\text{CH}_3$ ) by a trimethylammonium chloride group.
  - The replacement of the ester group in the local anaesthetic ethyl 4-aminobenzoate (benzocaine).
- State the general factors that need to be considered when designing a drug.
- Explain the meaning of the terms: (a) lead compound, (b) dosage form, (c) enteral administration of drugs, (d) drug regimen, (e) prodrug, (f) pharmacophore and (g) excipient.
- Define the meaning of the terms pharmacokinetic phase and pharmacodynamic phase in the context of drug action. List the main general factors that affect these phases.

- 5 The drug amphetamine ( $\text{PhCH}_2\text{CH}(\text{NH}_2)\text{CH}_3$ ) binds to the protein albumin in the blood stream. Predict how a reduction in pH would be expected to influence this binding? Albumin is negatively charged at pH 7.4 and electrically neutral at pH 5.0.
- 6 Discuss the general effects that stereoisomers could have on the activity of a drug. Draw the *R* and *S* isomers of the anaesthetic ketamine. Indicate which of the structures you have drawn is mainly responsible for its anaesthetic activity.
- 7 Suggest strategies for improving the stability of compound A in the gastrointestinal tract. What could be the general effect of these strategies on the pharmaceutical action of compound A?

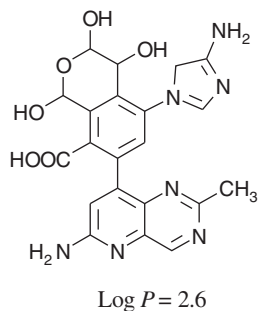


- 8 Explain the meaning of the term receptor.
- 9 What are the Lipinski rules? Use the Lipinski rules to determine which of the following compounds are *likely* to be orally bioavailable. Give a reason for your decision. (*Note*: the log *P* values are imaginary but should be taken as real for this question only!)

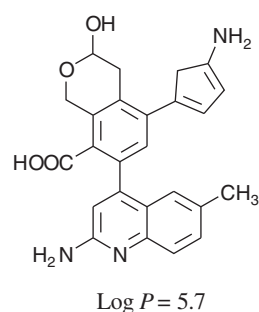
(a)



(b)



(c)



- 10 List the desirable requirements for a lead.