1 Drugs and drug targets: an overview

1.1 What is a drug?

In medicinal chemistry, the chemist attempts to design and synthesize a pharmaceutical agent that has a desired biological effect on the human body or some other living system. Such a compound could also be called a 'drug', but this is a word that many scientists dislike because society views the term with suspicion. With media headlines such as 'Drugs Menace', or 'Drug Addiction Sweeps City Streets', this is hardly surprising. However, it suggests that a distinction can be drawn between drugs that are used in medicine and drugs that are abused. Is this really true? Can we draw a neat line between 'good drugs' like penicillin and 'bad drugs' like heroin? If so, how do we define what is meant by a good or a bad drug in the first place? Where would we place a so-called social drug like cannabis in this divide? What about nicotine, or alcohol?

The answers we get would almost certainly depend on who we were to ask. As far as the law is concerned, the dividing line is defined in black and white. As far as the party-going teenager is concerned, the law is an ass. As far as we are concerned, the questions are irrelevant. Trying to divide drugs into two categories—safe or unsafe, good or bad—is futile and could even be dangerous.

First, let us consider the so-called 'good' drugs used in medicines. How 'good' are they? If a drug is to be truly 'good' it would have to satisfy the following criteria: it would have to do what it is meant to do, have no toxic or unwanted side effects, and be easy to take. How many drugs fit these criteria? The short answer is 'none'. There is no pharmaceutical compound on the market today that can completely satisfy all these conditions. Admittedly, some come quite close to the ideal. **Penicillin**, for example, has been one of the most effective antibacterial agents ever discovered and has also been one of the safest. Yet it too has drawbacks. It has never been able to kill all known bacteria, and as the years have gone by, more and more bacterial strains have become resistant.

Penicillin is a relatively safe drug, but there are some drugs that are distinctly dangerous. **Morphine** is one such example. It is an excellent analgesic, yet it suffers from serious side effects such as tolerance, respiratory depression, and addiction. It can even kill if taken in excess.

Barbiturates are also known to be dangerous. At Pearl Harbor, American casualties were given barbiturates as general anaesthetics before surgery. However, because of a poor understanding about how barbiturates are stored in the body, many patients received sudden and fatal overdoses. In fact, it is thought that more casualties died at the hands of the anaesthetists at Pearl Harbor than died of their wounds.

To conclude, the 'good' drugs are not as perfect as one might think.

What about the 'bad' drugs then? Is there anything good that can be said about them? Surely there is nothing we can say in defence of the highly addictive drug heroin?

Well, let us look at the facts about heroin. It is one of the best painkillers we know. In fact, it was named heroin at the end of the nineteenth century because it was thought to be the 'heroic' drug that would banish pain for good. Heroin went on the market in 1898, but 5 years later the true nature of its addictive properties became evident and the drug was speedily withdrawn from general distribution. However, heroin is still used in medicine today—under strict control, of course. The drug is called **diamorphine** and it is the drug of choice for treating patients dying of cancer. Not only does diamorphine reduce pain to acceptable levels, it also produces a euphoric effect that helps to counter the depression faced by patients close to death. Can we really condemn a drug that does that as being all 'bad'?

By now it should be evident that the division between good drugs and bad drugs is a woolly one and is not really relevant to our discussion of medicinal chemistry. All drugs have their good points and their bad points. Some

have more good points than bad and *vice versa*, but, like people, they all have their own individual characteristics. So how are we to define a drug in general?

One definition could be to classify drugs as 'compounds which interact with a biological system to produce a biological response'. This definition covers all the drugs we have discussed so far, but it goes further. There are chemicals which we take every day and which have a biological effect on us. What are these everyday drugs?

One is contained in all the cups of tea, coffee, and cocoa that we consume. All of these beverages contain the stimulant **caffeine**. Whenever you take a cup of coffee, you are a drug user. We could go further. Whenever you crave a cup of coffee, you are a drug addict. Even kids are not immune. They get their caffeine 'shot' from Coke or Pepsi. Whether you like it or not, caffeine is a drug. When you take it, you experience a change of mood or feeling.

So too, if you are a worshipper of the 'nicotine stick'. The biological effect is different. In this case you crave sedation or a calming influence, and it is the **nicotine** in the cigarette smoke which induces that effect.

There can be little doubt that **alcohol** is a drug and, as such, causes society more problems than all other drugs put together. One only has to study road accident statistics to appreciate that fact. If alcohol was discovered today, it would probably be restricted in exactly the same way as **cocaine.** Considered in a purely scientific way, alcohol is a most unsatisfactory drug. As many will testify, it is notoriously difficult to judge the correct dose required to gain the beneficial effect of 'happiness' without drifting into the higher dose levels that produce unwanted side effects such as staggering down the street. Alcohol is also unpredictable in its biological effects. Either happiness or depression may result, depending on the user's state of mind. On a more serious note, **addiction** and **tolerance** in certain individuals have ruined the lives of addicts and relatives alike.

Our definition of a drug can also be used to include compounds which at first sight we might not consider to be drugs.

Consider how the following examples fit our definition:

- morphine—interacts with the body to bring pain relief
- snake venom—interacts with the body to cause death!
- strychnine—interacts with the body to cause death!
- LSD—interacts with the body to produce hallucinations
- coffee—interacts with the body to wake you up
- penicillin—interacts with bacterial cells to kill them
- sugar—interacts with the tongue to produce a sense of taste.

All of these compounds fit our definition of drugs. It may seem strange to include poisons and snake venoms as drugs, but they too interact with a biological system and produce a biological response—a bit extreme perhaps, but a response all the same. The idea of poisons and venoms acting as drugs may not appear so strange if we consider penicillin. We have no problem in thinking of penicillin as a drug, but if we were to look closely at how penicillin works, then it is really a poison. It interacts with bacteria (the biological system) and kills them (the biological response). Fortunately for us, penicillin has no effect on human cells.

Even those drugs which do not act as poisons have the potential to become poisons—usually if they are taken in excess. We have already seen this with morphine. At low doses it is a painkiller. At high doses, it is a poison which kills by the suppression of breathing. Therefore, it is important that we treat all medicines as potential poisons and treat them with respect.

There is a term used in medicinal chemistry known as the **therapeutic index**, which indicates how safe a particular drug is. The therapeutic index is a measure of the drug's beneficial effects at a low dose, versus its harmful effects at a high dose. To be more precise, the therapeutic index compares the dose levels of the drug leading to toxic effects in 50% of cases studied to the dose levels leading to maximum therapeutic effects in 50% of cases studied. A high therapeutic index means that there is a large safety margin between beneficial and toxic doses. The values for cannabis and alcohol are 1000 and 10 respectively, which might imply that cannabis is safer and more predictable than alcohol. Indeed, it has been proposed that cannabis would be a useful medicine for the relief of chronic pain that is untreatable by normal analgesics (e.g. morphine). This may well be the case, but legalizing cannabis for medicinal use does not suddenly make it a safe drug. For example, the favourable therapeutic index of cannabis does not indicate its potential toxicity if it is taken over a long period (chronic use). For example, the various side effects of cannabis include dizziness, sedation, dry mouth, blurred vision, mental clouding, disconnected thought, muscle twitching and impaired memory. More seriously, it can lead to panic attacks, paranoid delusions, and hallucinations. Clearly, the safety of drugs is a complex matter and it is not helped by media sensationalism.

If useful drugs can be poisons at high doses or over long periods of use, does the opposite hold true? Can a poison be a medicine at low doses? In certain cases, this is found to be so.

Arsenic is well known as a poison, but arsenic-derived compounds are used as antiprotozoal agents. **Curare** is a deadly poison which was used by the native people of South America to tip their arrows such that a minor arrow wound would be fatal, yet compounds based on the **tubocurarine** structure (the active principle of curare)

are used in surgical operations to relax muscles. Under proper control and in the correct dosage, a lethal poison may well have an important medical role. Alternatively, lethal poisons can be the starting point for the development of useful drugs. For example, ACE inhibitors are important cardiovascular drugs that were developed, in part, from the structure of a snake venom.

Since our definition covers any chemical that interacts with any biological system, we could include all pesticides and herbicides as drugs. They interact with bacteria, fungi, and insects, kill them, and thus protect plants.

Sugar (or any sweet item for that matter) can be classed as a drug. It reacts with a biological system (the taste buds on the tongue) to produce a biological response (the sensation of sweetness). Even food can be a drug. Junk foods and fizzy drinks have been blamed for causing hyperactivity in children. It is believed that junk foods have high concentrations of certain amino acids which can be converted in the body to neurotransmitters. These are chemicals that pass messages between nerves. If an excess of these chemical messengers should accumulate, then too many messages are transmitted in the brain, leading to the disruptive behaviour observed in susceptible individuals. Allergies due to food additives and preservatives are also well recorded.

Some foods even contain toxic chemicals. Broccoli, cabbage, and cauliflower all contain high levels of a chemical that can cause reproductive abnormalities in rats. Peanuts and maize sometimes contain fungal toxins, and it is thought that fungal toxins in food were responsible for the biblical plagues. Basil contains over 50 compounds that are potentially carcinogenic, and other herbs contain some of the most potent carcinogens known. Carcinogenic compounds have also been identified in radishes, brown mustard, apricots, cherries, and plums. Such unpalatable facts might put you off your dinner, but take comfort—these chemicals are present in such small quantities that the risk is insignificant. There in lies a great truth, which was recognized as long ago as the fifteenth century when it was stated that 'Everything is a poison, nothing is a poison. It is the dose that makes the poison'.

Almost anything taken in excess will be toxic. You can make yourself seriously ill by taking 100 aspirin tablets or a bottle of whisky or 9 kg of spinach. The choice is yours!

To conclude, drugs can be viewed as actual or potential poisons. An important principle is that of **selective toxicity**. Many drugs are effective because they are toxic to 'problem cells', but not normal cells. For example, antibacterial, antifungal and antiprotozoal drugs are useful in medicine when they show a selective toxicity to microbial cells, rather than mammalian cells. Clinically effective anticancer agents show a selective toxicity for cancer cells over normal cells. Similarly, effective antiviral agents are toxic to viruses rather than normal cells.

Having discussed what drugs are, we shall now consider why, where, and how they act.

KEY POINTS

- Drugs are compounds that interact with a biological system to produce a biological response.
- No drug is totally safe. Drugs vary in the side effects they might have.
- The dose level of a compound determines whether it will act as a medicine or as a poison.
- The therapeutic index is a measure of a drug's beneficial effect at a low dose versus its harmful effects at higher dose. A high therapeutic index indicates a large safety margin between beneficial and toxic doses.
- The principle of selective toxicity means that useful drugs show toxicity against foreign or abnormal cells but not against normal host cells.

1.2 Drug targets

Why should chemicals, some of which have remarkably simple structures, have such an important effect on such a complicated and large structure as a human being? The answer lies in the way that the human body operates. If we could see inside our bodies to the molecular level, we would see a magnificent array of chemical reactions taking place, keeping the body healthy and functioning.

Drugs may be mere chemicals, but they are entering a world of chemical reactions with which they interact. Therefore, there should be nothing odd in the fact that they can have an effect. The surprising thing might be that they can have such *specific* effects. This is more a result of *where* they act in the body—the drug targets.

1.2.1 Cell structure

Since life is made up of cells, then quite clearly drugs must act on cells. The structure of a typical mammalian cell is shown in Fig. 1.1. All cells in the human body contain a boundary wall called the **cell membrane** which encloses the contents of the cell—the **cytoplasm**. The cell membrane seen under the electron microscope consists of two identifiable layers, each of which is made up of an ordered row of phosphoglyceride molecules such as **phosphatidylcholine (lecithin)** (Fig. 1.2). The outer layer of the membrane is made up of phosphatidylcholine whereas the inner layer is made up of phosphatidylethanolamine, phosphatidylserine, and phosphatidylinositol. Each phosphoglyceride molecule consists of a small polar head-group, and two long hydrophobic (water-hating) chains.

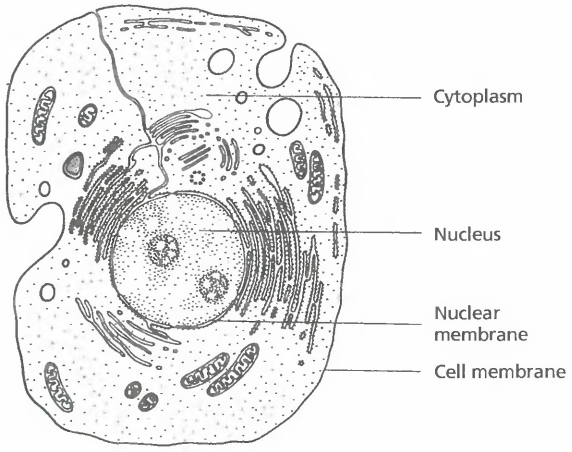


FIGURE 1.1 A typical mammalian cell. Taken from Mann, J. (1992) *Murder, magic, and medicine*. Oxford University Press, with permission.

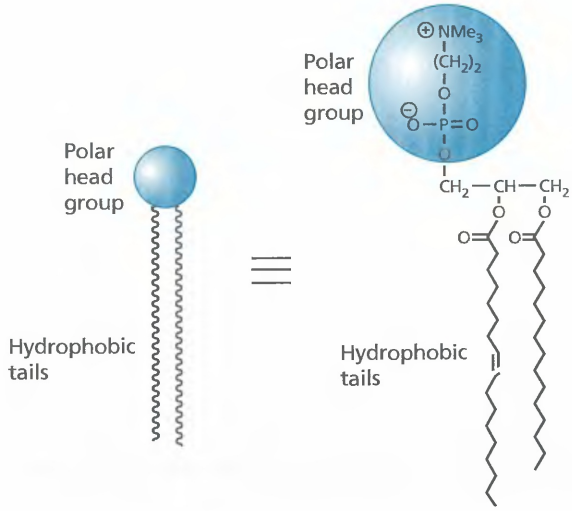


FIGURE 1.2 Phosphoglyceride structure.

In the cell membrane, the two layers of phospholipids are arranged such that the hydrophobic tails point towards each other and form a fatty, hydrophobic centre, while the ionic head-groups are placed at the inner and outer surfaces of the cell membrane (Fig. 1.3). This is a stable structure because the ionic, hydrophilic head-groups interact with the aqueous media inside and outside the cell, whereas the hydrophobic tails maximize hydrophobic interactions with each other and are kept away from the aqueous environments. The overall result of this structure is to construct a fatty barrier between the cell's interior and its surroundings.

The membrane is not just made up of phospholipids, however. There is a large variety of proteins situated in the cell membrane (Fig. 1.3). Some proteins lie attached

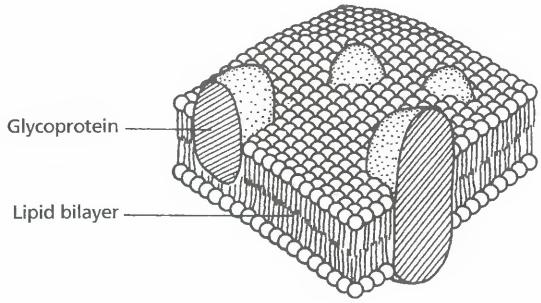


FIGURE 1.3 Cell membrane. Taken from Mann, J. (1992) *Murder, magic, and medicine*. Oxford University Press, with permission.

to the inner or the outer surface of the membrane. Others are embedded in the membrane with part of their structure exposed to one surface or both. The extent to which these proteins are embedded within the cell membrane structure depends on the types of amino acid present. Portions of protein that are embedded in the cell membrane have a large number of hydrophobic amino acids, whereas those portions that stick out from the surface have a large number of hydrophilic amino acids. Many surface proteins also have short chains of carbohydrates attached to them and are thus classed as **glycoproteins**. These carbohydrate segments are important to cell–cell recognition (section 10.7).

Within the cytoplasm there are several structures, one of which is the **nucleus**. This acts as the 'control centre' for the cell. The nucleus contains the genetic code—the DNA—which acts as the blueprint for the construction of all the cell's proteins. There are many other structures within a cell, such as the mitochondria, the Golgi apparatus, and the endoplasmic reticulum, but it is not the purpose of this book to look at the structure and function of these organelles. Suffice it to say that different drugs act on molecular targets at different locations in the cell.

1.2.2 Drug targets at the molecular level

We shall now move to the molecular level, because it is here that we can truly appreciate how drugs work. The main molecular targets for drugs are proteins (mainly enzymes, receptors and transport proteins), and nucleic acids (DNA and RNA). These are large molecules (**macromolecules**) having molecular weights measured in the order of several thousand atomic mass units. They are much bigger than the typical drug, which has a molecular weight in the order of a few hundred atomic mass units.

The interaction of a drug with a macromolecular target involves a process known as binding. There is usually a specific area of the macromolecule where this takes place, and this is known as the **binding site** (Fig. 1.4). Typically, this takes the form of a hollow or canyon on

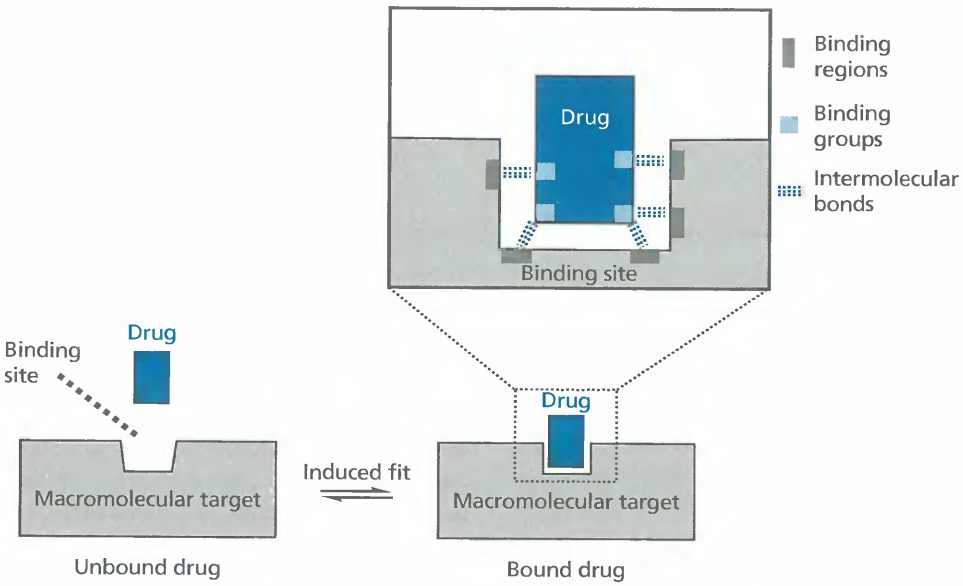


FIGURE 1.4 The equilibrium of a drug being bound and unbound to its target.

the surface of the macromolecule allowing the drug to sink into the body of the larger molecule. Some drugs react with the binding site and become permanently attached via a covalent bond that has a bond strength of 200–400 kJ mol^{-1}. However, most drugs interact through weaker forms of interaction known as **intermolecular bonds**. These include electrostatic or ionic bonds, hydrogen bonds, van der Waals interactions, dipole–dipole interactions and hydrophobic interactions. (It is also possible for these interactions to take place *within* a molecule, in which case they are called **intramolecular bonds**; see for example protein structure, sections 2.2 and 2.3). None of these bonds is as strong as the covalent bonds that make up the skeleton of a molecule, and so they can be formed, then broken again. This means that an equilibrium takes place between the drug being bound and unbound to its target. The binding forces are strong enough to hold the drug for a certain period of time to let it have an effect on the target, but weak enough to allow the drug to depart once it has done its job. The length of time the drug remains at its target will then depend on the number of intermolecular bonds involved in holding it there. Drugs having a large number of interactions are likely to remain bound longer than those that have only a few. The relative strength of the different intermolecular binding forces is also an important factor. Functional groups present in the drug can be important in forming intermolecular bonds with the target binding site. If they do so, they are called **binding groups**. However, the carbon skeleton of the drug also plays an important role in binding the drug to its target. As far as the target binding site is concerned, it too contains functional groups and carbon skeletons which can form intermolecular bonds with 'visiting' drugs. The specific regions where this takes place are known as **binding regions**. The study of how drugs interact with their targets through binding interactions is known as **pharmacodynamics**. Let us now consider the types of intermolecular bond that are possible.

1.3 Intermolecular bonding forces

There are several types of intermolecular bonding interactions, which differ in their bond strengths. The number and types of these interactions depend on the structure of the drug and the functional groups that are present (section 13.1). Thus, each drug may use one or more of the following interactions, but not necessarily all of them.

1.3.1 Electrostatic or ionic bonds

An ionic or electrostatic bond is the strongest of the intermolecular bonds (20–40 kJ mol^{-1}) and takes place between groups having opposite charges such as a carboxylate ion and an alkylammonium ion (Fig. 1.5). The strength of the interaction is inversely proportional to the distance between the two charged atoms, and it is also dependent on the nature of the environment, being stronger in hydrophobic environments than in polar environments. Usually, the binding sites of macromolecules are more hydrophobic in nature than the surface, and so this enhances the effect of an ionic interaction. The drop-off in ionic bonding strength with separation is less than in other intermolecular interactions, so if an ionic interaction is possible, it is likely to be the most important initial interaction as the drug enters the binding site.

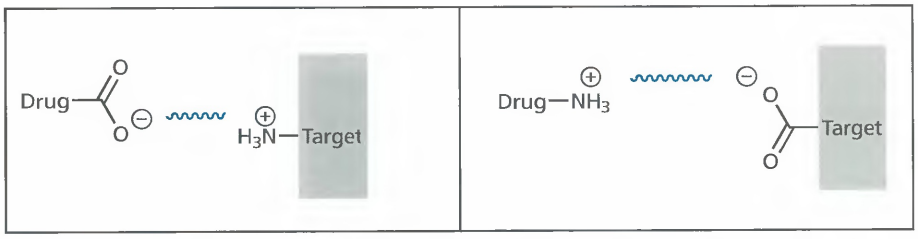


FIGURE 1.5 Electrostatic (ionic) interactions between a drug and the binding site.

1.3.2 Hydrogen bonds

A hydrogen bond can vary substantially in strength and normally takes place between an electron-rich heteroatom, and an electron-deficient hydrogen (Fig. 1.6). The electron-rich heteroatom has to have a lone pair of electrons and is usually oxygen or nitrogen.

The electron-deficient hydrogen is usually linked by a covalent bond to an electronegative atom such as oxygen or nitrogen. Since the electronegative atom (X) has a greater attraction for electrons, the electron distribution in the covalent bond (X–H) is weighted towards the more electronegative atom, and so the hydrogen gains its slight positive charge. The functional group containing this feature is known as a **hydrogen bond donor (HBD)** because it provides the hydrogen for the hydrogen bond. The functional group that provides the electron-rich atom to receive the hydrogen bond is known as the **hydrogen bond acceptor (HBA)**. Some functional groups can act both as hydrogen bond donors and hydrogen bond acceptors (e.g. OH, NH_2). When such a group is present in a binding site, it is possible that it might bind to one ligand as a hydrogen bond donor and to another as a hydrogen bond acceptor. This characteristic is given the term **hydrogen bond flip-flop**.

Hydrogen bonds have been viewed as a weak form of electrostatic interaction, because the heteroatom is slightly negative and the hydrogen is slightly positive. However, there is more to hydrogen bonding than an attraction between partial charges. Unlike other intermolecular interactions, an interaction of orbitals takes place between the two molecules (Fig. 1.7). The orbital containing the lone pair of electrons on heteroatom (Y) interacts with the atomic orbitals normally involved in the covalent bond between X and H. This results in a weak form of sigma (σ) bonding and has an important directional consequence that is not evident in electrostatic bonds. The optimum orientation is where the X–H bond points directly to the lone pair on Y such that the angle formed between X, H, and Y is 180°. This is observed in very strong hydrogen bonds. However, the angle can vary between 130 and 180° for moderately strong hydrogen bonds, and can be as low as 90° for weak hydrogen bonds. The lone pair orbital of Y also has a directional property, depending on its hybridization. For example, the nitrogen of a pyridine ring is sp^2 hybridized and so the lone pair points directly away from the ring and in the same plane (Fig. 1.8). The best location for a hydrogen bond donor would be the region of space indicated in the figure.

FIGURE 1.6 Hydrogen bonding shown by a dashed line between a drug and a binding site (X, Y = oxygen or nitrogen; HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

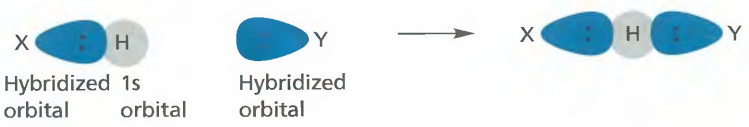


FIGURE 1.7 Orbital overlap in a hydrogen bond.

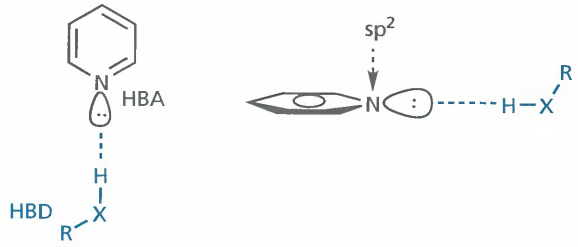


FIGURE 1.8 Directional influence of hybridization on hydrogen bonding.

The strength of a hydrogen bond can vary widely, but most hydrogen bonds in drug-target interactions are moderate in strength, varying from 16 to 60 kJ mol^{-1}—approximately 10 times less than a covalent bond. The bond distance reflects this, and hydrogen bonds are typically 1.5–2.2 Å compared with 1.0–1.5 Å for a covalent bond. The strength of a hydrogen bond depends on how strong the hydrogen bond acceptor and the hydrogen bond donor are. A good hydrogen bond acceptor has to be electronegative and have a lone pair of electrons. Nitrogen and oxygen are the most common atoms involved as hydrogen bond acceptors in biological systems. Nitrogen has one lone pair of electrons and can act as an acceptor for one hydrogen bond; oxygen has two lone pairs of electrons and can act as an acceptor for two hydrogen bonds (Fig. 1.9).

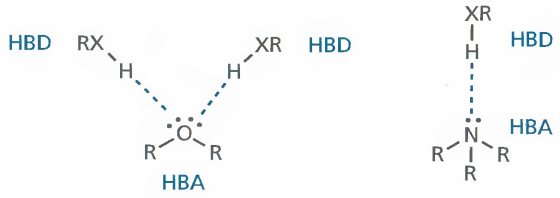


FIGURE 1.9 Oxygen and nitrogen acting as hydrogen bond acceptors (HBD = hydrogen bond donor, HBA = hydrogen bond acceptor).

Several drugs and macromolecular targets contain a sulfur atom, which is also electronegative. However, sulfur is a weak hydrogen bond acceptor because its lone pairs are in third-shell orbitals that are larger and more diffuse. This means that the orbitals concerned interact less efficiently with the small 1s orbitals of hydrogen atoms.

Fluorine, which is present in several drugs, is more electronegative than either oxygen or nitrogen. It also has three lone pairs of electrons, and this might suggest that it would make a good hydrogen bond acceptor. In fact, it is a weak hydrogen bond acceptor. It has been suggested that fluorine is so electronegative that it clings on tightly to its lone pairs of electrons, making them incapable of hydrogen bond interactions. This is in contrast to fluoride ions, which are very strong hydrogen bond acceptors.

Any feature that affects the electron density of the hydrogen bond acceptor is likely to affect its ability to act as a hydrogen bond acceptor, since the greater the electron density of the heteroatom the greater its strength as a hydrogen bond acceptor. For example, the oxygen of a negatively charged carboxylate ion is a stronger hydrogen bond acceptor than the oxygen of the uncharged carboxylic acid (Fig. 1.10). Phosphate ions can also act as good hydrogen bond acceptors. Most hydrogen bond acceptors present in drugs and binding sites are neutral functional groups such as ethers, alcohols, phenols, amides, amines, and ketones. These groups will form moderately strong hydrogen bonds.

It has been proposed that the pi (π) systems present in alkynes and aromatic rings are regions of high electron density and can act as hydrogen bond acceptors. However, the electron density in these systems is diffuse, and so the hydrogen bonding interaction is much weaker than those involving oxygen or nitrogen. As a result, aromatic rings and alkynes are only likely to be significant hydrogen bond acceptors if they interact with a strong hydrogen bond donor such as an alkylammonium ion (NHR_3^+).

More subtle effects can influence whether an atom is a good hydrogen bond acceptor or not. For example, the nitrogen atom of an aliphatic tertiary amine is a better

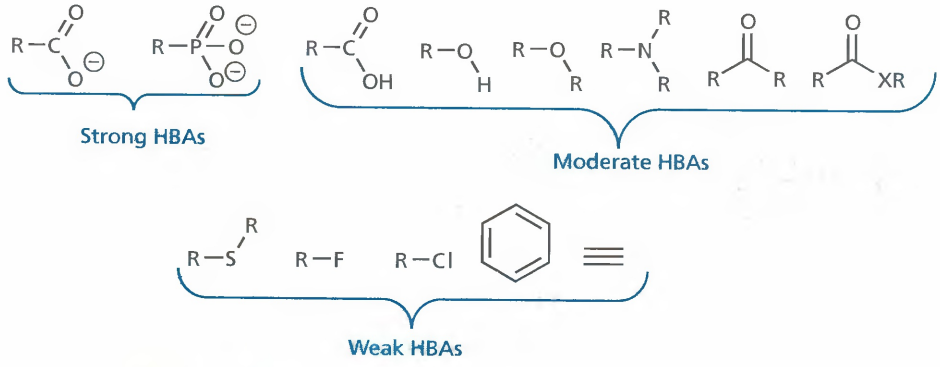


FIGURE 1.10 Relative strengths of hydrogen bond acceptors (HBAs).

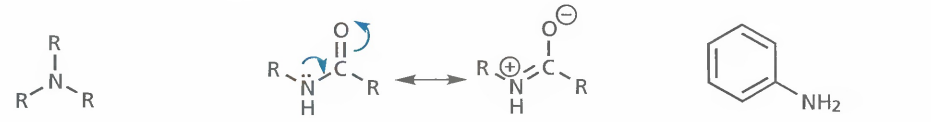


FIGURE 1.11 Comparison of different nitrogen-containing functional groups as hydrogen bond acceptors (HBAs).

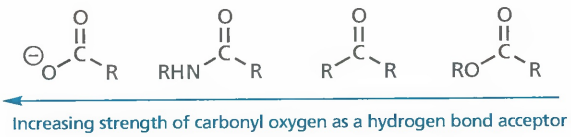


FIGURE 1.12 Comparison of carbonyl oxygens as hydrogen bond acceptors.

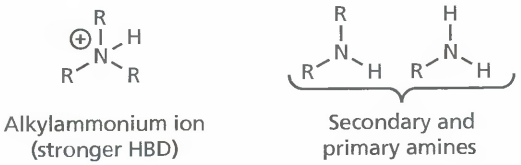


FIGURE 1.13 Comparison of hydrogen bond donors (HBDs).

hydrogen bond acceptor than the nitrogen of an amide or an aniline (Fig. 1.11). In the latter cases, the lone pair of the nitrogen can interact with neighbouring pi systems to form various resonance structures. As a result, it is less likely to take part in a hydrogen bond.

Similarly, the ability of a carbonyl group to act as a hydrogen bond acceptor varies depending on the functional group involved (Fig. 1.12).

Good hydrogen bond donors contain an electron-deficient proton linked to oxygen or nitrogen. The more electron-deficient the proton, the better it will act as a hydrogen bond donor. For example, a proton attached to a positively charged nitrogen atom acts as a stronger hydrogen bond donor than the proton of a primary or secondary amine (Fig. 1.13). Because the nitrogen is charged, it has a greater pull on the electrons surrounding it, making attached protons even more electron-deficient.

1.3.3 Van der Waals interactions

Van der Waals interactions are very weak interactions, typically 2–4 kJ mol^{-1} in strength, that involve interactions between hydrophobic regions of different molecules. These regions could be aliphatic substituents or the carbon skeleton of the molecules concerned. The electronic distribution in neutral, non-polar regions is never totally even or symmetrical, and there are always transient areas of high and low electron densities leading to temporary dipoles. The dipoles in one molecule can induce dipoles in a neighbouring molecule, leading to weak interactions between the two molecules (Fig. 1.14). Thus, an area of high electron density on one molecule can have an attraction for an area of low electron density on another molecule. The strength of these interactions falls off rapidly the further the two molecules are apart, decreasing to the seventh power of the separation. Therefore, the drug has to be close to the target binding site before the interactions become important. Van der Waals interactions are also referred to as **London forces**. Although the interactions are individually weak, there may be many such interactions between a drug and its target and so the overall contribution of van der Waals interactions can often be crucial to binding. Hydrophobic forces are also important when the non-polar regions of molecules interact (section 1.3.6).

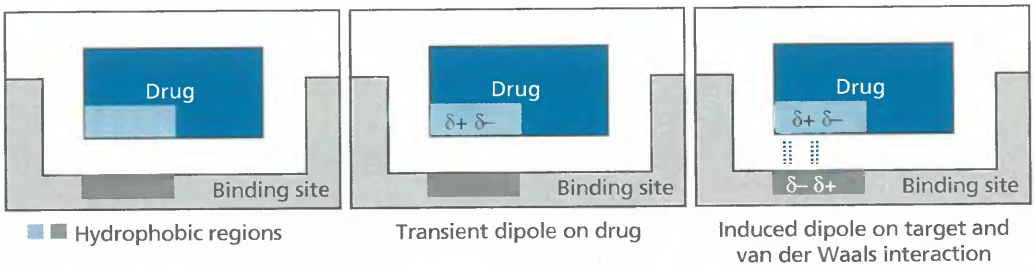


FIGURE 1.14 Van der Waals interactions between hydrophobic regions of a drug and a binding site.

1.3.4 Dipole–dipole and ion–dipole interactions

Many molecules have a permanent dipole moment resulting from the different electronegativities of the atoms and functional groups present. For example, a ketone has a dipole moment due to the different electronegativities of the carbon and oxygen making up the carbonyl bond. The binding site also contains functional groups, so it is inevitable that it too will have various local dipole moments. It is possible for the dipole moments of the drug and the binding site to interact as a drug approaches, aligning the drug such that the dipole moments are parallel and in opposite directions (Fig. 1.15). If this positions the drug such that other intermolecular interactions can take place between it and the target, the alignment is beneficial to both binding and activity. If not, then binding and activity may be weakened. An example of such an effect can be found in section 25.2.8.3. The strength of dipole–dipole interactions reduces with the cube of the distance between the two dipoles. This means that dipole–dipole interactions fall away more quickly with distance than electrostatic interactions, but less quickly than van der Waals interactions.

An ion-dipole interaction is where a charged or ionic group in one molecule interacts with a dipole in a second molecule (Fig. 1.16). This is stronger than a dipole–dipole interaction and falls off less rapidly with separation (decreasing relative to the square of the separation).

Interactions involving an induced dipole moment have been proposed. There is evidence that an aromatic ring can interact with an ionic group such as a quaternary ammonium ion. Such an interaction is feasible if the positive charge of the quaternary ammonium group distorts the π electron cloud of the aromatic ring to produce a dipole moment where the face of the aromatic ring is electron-rich and the edges are electron-deficient (Fig. 1.17). An example of this can be found in section 22.7.

1.3.5 Repulsive interactions

So far we have talked only about attractive forces, which increase in strength the closer the molecules approach each other. Repulsive interactions are also important. Otherwise, there would be nothing to stop molecules trying to merge with each other! If molecules come too close, their molecular orbitals start to overlap and this results in repulsion. Other forms of repulsion are related to the types of groups present in both molecules. For example, two charged groups of identical charge are repelled.

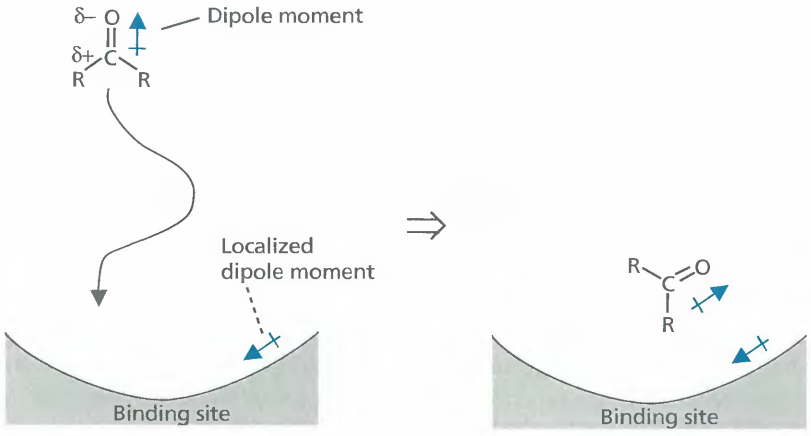


FIGURE 1.15 Dipole–dipole interactions between a drug and a binding site.

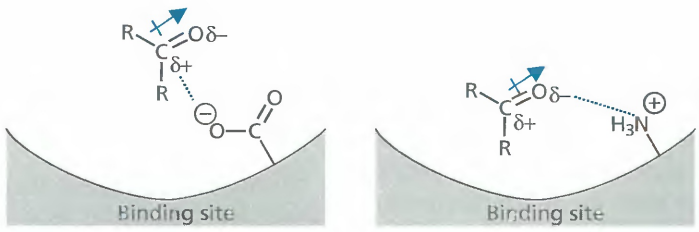


FIGURE 1.16 Ion–dipole interactions between a drug and a binding site.

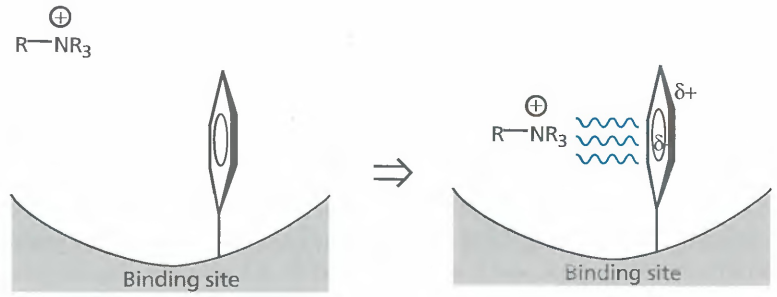


FIGURE 1.17 Induced dipole interaction between an alkylammonium ion and an aromatic ring.

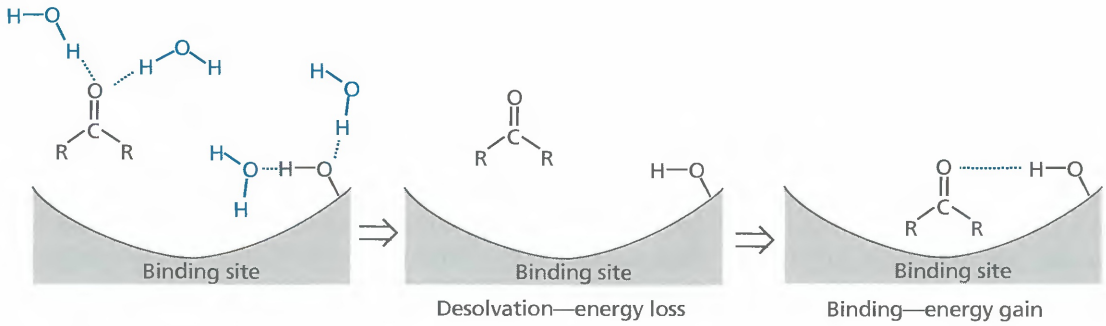


FIGURE 1.18 Desolvation of a drug and its target binding site prior to binding.

1.3.6 The role of water and hydrophobic interactions

A crucial feature that is often overlooked when considering the interaction of a drug with its target is the role of water. The macromolecular targets in the body exist in an aqueous environment and the drug has to travel through that environment in order to reach its target, so both the drug and the macromolecule are solvated with water molecules before they meet each other. The water molecules surrounding the drug and the target binding site have to be stripped away before the interactions described above can take place (Fig. 1.18). This requires energy, and if the energy required to desolvate both the drug and the binding site is greater than the energy gained by the binding interactions, then the drug may be ineffective. In certain cases, it has been beneficial to remove a polar binding group from a drug if that group binds less strongly to the target binding site than to water. This was carried out during the development of the antiviral drug ritonavir (section 20.7.4.4).

Sometimes polar groups are added to a drug to increase its water solubility. If this is the case, it is important that such groups are positioned in such a way that they protrude from the binding site when the drug binds; in other words they are solvent-accessible or solvent-exposed. In this way, the water that solvates this highly polar group does not have to be stripped away, and there is no energy penalty when the drug binds to its target (section 21.6.2.1 and case study 5).

It is not possible for water to solvate the non-polar or hydrophobic regions of a drug or its target binding site. Instead, the surrounding water molecules form stronger than usual interactions with each other, resulting in a more ordered layer of water next to the non-polar surface. This represents a negative entropy due to the increase in order. When the hydrophobic region of a drug interacts with a hydrophobic region of a binding site, these water molecules are freed and become less ordered (Fig. 1.19). This leads to an increase in entropy and a gain in binding energy.[1] The interactions involved are small at 0.1–0.2 kJ mol^{-1} for each square angstrom of hydrophobic surface, but overall they can be substantial. Sometimes, a hydrophobic region in the drug may not be sufficiently close to a hydrophobic region in the binding site, and water may be trapped between the two surfaces. The entropy increase is not so substantial in that case, and there is a benefit in designing a better drug that fits more snugly.

[1] The free energy gained by binding (ΔG) is related to the change in entropy (ΔS) by the equation $\Delta G = \Delta H - T\Delta S$. If entropy increases, ΔS is positive which makes ΔG more negative. The more negative ΔG is, the more likely binding will take place.

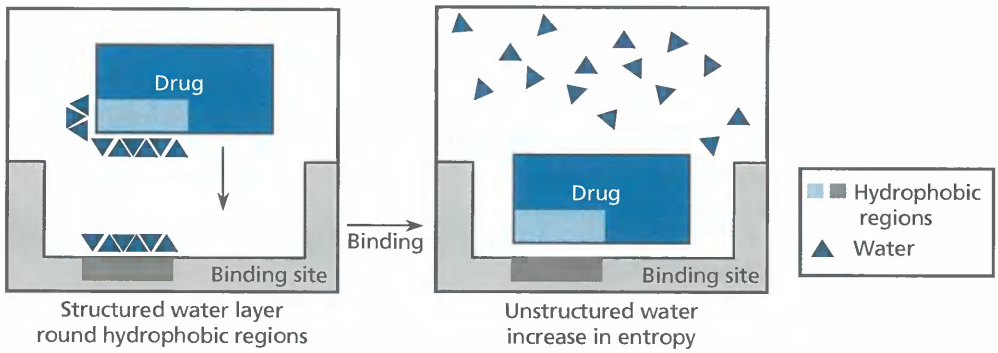


FIGURE 1.19 Hydrophobic interactions.

1.4 Pharmacokinetic issues and medicines

Pharmacodynamics is the study of how a drug binds to its target binding site. However, a drug capable of binding to a particular target is not necessarily going to be a useful clinical agent or medicine. For that to be the case, the drug not only has to bind to its target, it has to reach it in the first place. For an oral drug that involves a long journey with many hazards to be overcome. The drug has to survive stomach acids and digestive enzymes, and be absorbed from the gut into the blood supply. It has to survive the liver where enzymes try to destroy it (drug metabolism). It has to be distributed round the body and not get mopped up by fat tissue. It has to have a reasonable life time within the body, not too short and not too long. Finally, it should not be excreted too quickly. The study of how a drug is absorbed, distributed, metabolized and excreted (known as ADME in the pharmaceutical industry) is called pharmacokinetics. Pharmacokinetics can be viewed as 'what the body does to the drug' as opposed to pharmacodynamics—'what the drug does to the body'.

There are many ways in which medicinal chemists can design a drug to improve its pharmacokinetic properties, but the method by which the drug is formulated and administered is just as important. Medicines are not just composed of the active pharmaceutical agent. For example, a pill contains a whole range of chemicals which are present to give structure and stability to the pill, and also to aid the delivery and breakdown of the pill at the desired part of the gastrointestinal tract.

KEY POINTS

- Drugs act on molecular targets located in the cell membrane of cells or within the cells themselves.
- Drug targets are macromolecules that have a binding site into which the drug fits and binds.
- Most drugs bind to their targets by means of intermolecular bonds.
- Pharmacodynamics is the study of how drugs interact with their targets.
- Electrostatic or ionic interactions occur between groups of opposite charge.
- Hydrogen bonds occur between an electron-rich heteroatom and an electron-deficient hydrogen.
- The functional group providing the hydrogen for a hydrogen bond is called the hydrogen bond donor. The functional group that interacts with the hydrogen in a hydrogen bond is called the hydrogen bond acceptor.
- Van der Waals interactions take place between the non-polar regions of molecules and are caused by transient dipole–dipole interactions.
- Ion–dipole and dipole–dipole interactions are a weak form of electrostatic interaction.
- Hydrophobic interactions involve the displacement of ordered layers of water molecules that surround hydrophobic regions of molecules. The resulting increase in entropy contributes to the overall binding energy.
- Polar groups have to be desolvated before intermolecular interactions take place. This results in an energy penalty.
- The pharmacokinetics of a drug relate to its absorption, distribution, metabolism and excretion in the body.

1.5 Classification of drugs

There are four main ways in which drugs might be classified or grouped.

By pharmacological effect Drugs can be classified depending on the biological or pharmacological effect that they have; for example analgesics, antipsychotics, antihypertensives, anti-asthmatics and antibiotics. This is useful if one wishes to know the full scope of drugs available for

a certain ailment, but it means that the drugs included are numerous and highly varied in structure. This is because there is a large variety of targets at which drugs could act in order to produce the desired effect. It is therefore not possible to compare different painkillers and expect them to look alike or to have some common mechanism of action.

The chapters on antibacterial, antiviral, anticancer and anti-ulcer drugs (chapters 19–21, 25) illustrate the variety of drug structures and mechanisms of action that are possible when drugs are classified according to their pharmacological effect.

By chemical structure Many drugs which have a common skeleton are grouped together; for example penicillins, barbiturates, opiates, steroids, and catecholamines. In some cases, this is a useful classification since the biological activity and mechanism of action is the same for the structures involved; for example the antibiotic activity of penicillins. However, not all compounds with similar chemical structure have the same biological action. For example, steroids share a similar tetracyclic structure, but they have very different effects in the body. In this text, there are various groups of structurally related drugs which are discussed; for example penicillins, cephalosporins, sulfonamides and opioids (sections 19.4–19.5, and chapter 24). These are examples of compounds with a similar structure and similar mechanism of action. However, there are exceptions. Most sulfonamides are used as antibacterial agents, but there are a few which have totally different medical applications.

By target system Drugs can be classified according to whether they affect a certain target system in the body. An example of a target system is where a neurotransmitter is synthesized, released from its neuron, interacts with a protein target and is either metabolized or reabsorbed into the neuron. This classification is a bit more specific than classifying drugs by their overall pharmacological effect. However, there are still several different targets with which drugs could interact in order to interfere with the system, and so the drugs included in this category are likely to be quite varied in structure due to the different mechanisms of action that are involved. In chapters 22 and 23, we look at drugs that act on target systems—the cholinergic and the adrenergic system respectively.

By target molecule Some drugs are classified according to the molecular target with which they interact. For example, anticholinesterases (sections 22.15–22.17) are drugs which act by inhibiting the enzyme acetylcholinesterase. This is a more specific classification since we have now identified the precise target at which the drugs act. In this situation, we might expect some structural similarity between the agents involved and a common mechanism of action, although this is not an inviolable assumption.

However, it is easy to lose the wood for the trees and to lose sight of why it is useful to have drugs which switch off a particular enzyme or receptor. For example, it is not intuitively obvious why an anticholinesterase agent could be useful in treating senility or glaucoma.

1.6 Naming of drugs and medicines

The vast majority of chemicals that are synthesized in medicinal chemistry research never make it to the market place and it would be impractical to name them all. Instead, research groups label them with a code which usually consists of letters and numbers. The letters are specific to the research group undertaking the work and the number is specific for the compound. Thus, Ro31–8959, ABT-538, and MK-639 were compounds prepared by Roche, Abbott, and Merck pharmaceuticals respectively. If the compounds concerned show promise as therapeutic drugs they are taken into development and named. For example, the above compounds showed promise as anti-HIV drugs and were named **saquinavir, ritonavir,** and **indinavir**, respectively. Finally, if the drugs prove successful and are marketed as medicines, they are given a proprietary, brand or trade name which only the company can use. For example, the above compounds were marketed as **Fortovase®, Norvir®** and **Crixivan®** respectively (note that brand names always start with a capital letter and have the symbol® or™ to indicate that they are registered brand names). The proprietary names are also specific for the preparation or formulation of the drug. For example, Fortovase® (or Fortovase™) is a preparation containing 200 mg of saquinavir in a gel filled, beige coloured capsule. If the formulation is changed, then a different name is used. For example, Roche sell a different preparation of saquinavir called **Invirase®** which consists of a brown/green capsule containing 200 mg of saquinavir as the mesilate salt. When a drug's patent has expired, it is possible for any pharmaceutical company to produce and sell that drug as a generic medicine. However, they are not allowed to use the trade name used by the company that originally invented it. European law requires that generic medicines are given a **recommended International Non-proprietary Name** (rINN), which is usually identical to the name of the drug. In Britain, such drugs were given a **British Approved Name** (BAN), but these have now been modified to fall in line with rINNs.

Since the naming of drugs is progressive, early research papers in the literature may only use the original letter/number code since the name of the drug had not been allocated at the time of publication.

Throughout this text, the names of the active constituents are used rather than the trade names, although

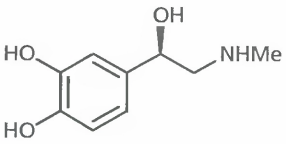
the trade name may be indicated if it is particularly well known. For example, it is indicated that **sildenafil** is **Viagra**® and that **paclitaxel** is **Taxol**®. If you wish to find out the trade name for a particular drug, these are listed in Appendix 6. If you wish to 'go the other way', the index contains trade names and directs you to the relevant compound name. Only those drugs covered in the text are included and if you cannot find the drug you are looking for, you should refer to other textbooks or formularies such as the British National Formulary (see General Further Reading).

KEY POINTS

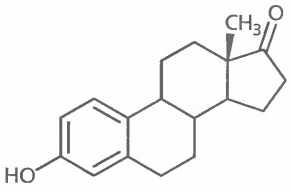
- Drugs can be classified by their pharmacological effect, their chemical structure, their effect on a target system or their effect on a target structure.
- Clinically useful drugs have a trade (or brand) name, as well as a recommended international non-proprietary name.
- Most structures produced during the development of a new drug are not considered for the clinic. They are identified by simple codes that are specific to each research group.

QUESTIONS

1. The hormone adrenaline interacts with proteins located on the surface of cells and does not cross the cell membrane. However, larger steroid molecules such as oestrone cross cell membranes and interact with proteins located in the cell nucleus. Why is a large steroid molecule able to cross the cell membrane when a smaller molecule such as adrenaline cannot?



Adrenaline



Oestrone

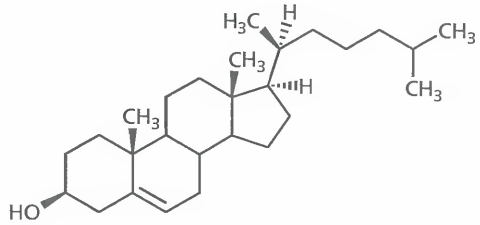
2. Valinomycin (Fig. 10.17) is an antibiotic that is able to transport ions across cell membranes and disrupt the ionic balance of the cell. Consider the structure of valinomycin and explain why it is able to carry out this task.

3. Archaea are microorganisms that can survive in extreme environments such as high temperature, low pH, or high salt concentration. It is observed that the cell membrane phospholipids in these organisms (see structure I below) are markedly different from those in eukaryotic cell membranes. What differences are present and what function might they serve?

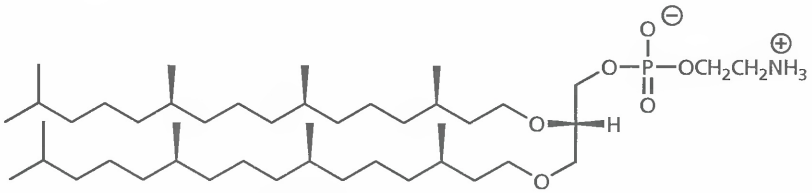
4. Teicoplanin (Fig. 19.59) is an antibiotic that inhibits the construction of bacterial cell walls. The cell wall is a barrier surrounding the cell membrane of bacterial cells and is not present in eukaryotic cells. Teicoplanin contains an alkyl chain highlighted in Fig. 19.59. If this chain is absent, activity drops. What role do you think this alkyl chain might serve?

5. The Ras protein is an important protein in signalling processes within the cell. It exists freely in the cell cytoplasm, but must become anchored to the inner surface of the cell membrane in order to carry out its function. What kind of modification to the protein might take place to allow this to happen?

6. Cholesterol is an important constituent of eukaryotic cell membranes and affects the fluidity of the membrane. Consider the structure of cholesterol (shown below) and suggest how it might be orientated in the membrane.



Cholesterol



Structure I

7. Most unsaturated alkyl chains in phospholipids are *cis* rather than *trans*. Consider the *cis*-unsaturated alkyl chain in the phospholipid shown in Fig. 1.2. Redraw this chain to give a better representation of its shape and compare it with the shape of its *trans*-isomer. What conclusions can you make regarding the packing of such chains in the cell membrane, and the effect on membrane fluidity?

8. The relative strength of carbonyl oxygens as hydrogen bond acceptors is shown in Fig. 1.12. Suggest why the order is as shown.

9. Consider the structures of adrenaline, oestrone, and cholesterol and suggest what kind of intermolecular interactions are possible for these molecules and where they occur.

10. Using the index and Appendix 6, identify the structures and trade names for the following drugs—amoxicillin, ranitidine, gefitinib, atracurium.

FURTHER READING

Hansch, C., Sammes, P. G., and Taylor, J. B. (eds) (1990) Classification of drugs. *Comprehensive Medicinal Chemistry*, Vol. 1, Chapter 3.1. Pergamon Press, ISBN 0-08-037057-8.

Howard, J. A. K., *et al.* (1996) How good is fluorine as a hydrogen bond acceptor? *Tetrahedron,* **52**, 12613–12622.

Jeffrey, G. A. (1991) *Hydrogen bonding in biological structures*. Springer-Verlag, London.

Mann, J. (1992) *Murder, magic, and medicine,* Chapter 1. Oxford University Press, Oxford.

Meyer, E. G., *et al.* (1995) Backward binding and other structural surprises. *Perspectives in Drug Discovery and Design,* **3**, 168–195.

Page, C., Curtis, M., Sutter, M., Walker, M., and Hoffman, B (2002) Drug names and drug classification systems. *Integrated Pharmacology,* 2nd edn, Chapter 2. Mosby, Elsevier, ISBN 0 7234 3221 X.

Titles for general further reading are listed on p. 725.

PART A

Drug targets

Medicinal chemistry is the study of how novel drugs can be designed and developed. This process is helped immeasurably by a detailed understanding of the structure and function of the molecular targets that are present in the body.

The major drug targets are normally large molecules (macromolecules) such as proteins and nucleic acids. Knowing the structures, properties and functions of these macromolecules is crucial if we are to design new drugs. There are a variety of reasons for this.

First, it is important to know what functions different macromolecules have in the body, and whether targeting them is likely to have a beneficial effect in treating a particular disease. There is no point designing a drug to inhibit a digestive enzyme if one is looking for a new analgesic.

Secondly, a knowledge of macromolecular structure is crucial if one is to design a drug that will bind effectively to the target. Knowing the target structure and its functional groups will allow the medicinal chemist to design a drug that contains complementary functional groups that will bind the drug to the target.

Thirdly, a drug must not only bind to the target, it must bind to the correct region of the target. Proteins and nucleic acids are extremely large molecules in comparison to a drug, and if the drug binds to the wrong part of the macromolecule, it may not have any effect. An appreciation of the target's structure and function will guide the medicinal chemist in this respect.

Finally, an understanding of how a macromolecule operates is crucial if one is going to design an effective drug that will interfere with that process. For example, understanding the mechanism of how enzymes catalyse reactions has been extremely important in the design of many important drugs; for example the protease inhibitors used in HIV therapy.

Proteins are the most important drug targets used in medicinal chemistry, and so it should be no surprise that the major focus in section A is devoted to them—chapters 2–5. However, there are some important drugs that interact with nucleic acids. The structure and function of these macromolecules are covered in chapter 6.

If you have a background in biochemistry, much of the material in this section may already be familiar to you, and you may wish to move directly to section B. Alternatively, you may find the material in section A a useful revision.