

24.1 History of opium

The search for a safe, orally active, and non-addictive analgesic based on the opiate structure is one of the oldest fields in medicinal chemistry, yet one where true success has proved elusive. The term 'opiates' refers to narcotic analgesics, which are structurally related to morphine, whereas 'opioids' is the term used to cover all synthetic, semi-synthetic, naturally occurring and endogenous compounds that interact with opioid receptors in the central nervous system.

It is important to appreciate that the opioids are not the only compounds which are of use in the relief of pain: there are several other classes of analgesic, including **aspirin**. These compounds, however, operate by different mechanisms from those used by the opioids, and are effective against different types of pain.

The first of the opioids were extracted from opium—the sticky exudate obtained from the opium poppy (*Papaver somniferum*). Opium is perhaps the oldest herbal medicine known to humanity. The use of opium was recorded in China over 2000 years ago, and was known in Mesopotamia before that. Because of its properties, the Greeks dedicated the opium poppy to Thanatos (the god of death), Hypnos (the god of sleep), and Morpheus (the god of dreams). Later physicians prescribed opium for a whole range of afflictions including chronic headache, vertigo, epilepsy, asthma, colic, fevers, dropsies, leprosy, melancholy, and 'troubles to which women are subject'.

As a result of this, its fame spread, and by AD 632 knowledge of opium had reached Spain. The poppy was cultivated in Persia, India, Malaysia and China, and opium was used primarily as a sleeping draught (sedative), and as a treatment for diarrhoea.

Its use as an analgesic came much later, in the sixteenth century, when Paracelsus introduced preparations of opium known as **laudanum**. It soon became an extremely important medication, not least in the Royal Navy where it was invaluable in treating the many casualties resulting

from naval battles and campaigns as Britain expanded its empire. However, problems were also reported with its use. Doctors stated that stopping the drug after long-term use led to 'great and intolerable distresses, anxieties and depression of the spirit . . .'. These were the first reports of addiction and withdrawal symptoms.

Opium was first marketed in Britain by Thomas Dover—a one-time pirate who had taken up medicine.¹ Dover prepared a powder containing opium, liquorice, saltpetre and **ippecacuanha**. Ipecacuanha is an emetic, and had the advantage of making the consumers sick should they take too much of the concoction.

Another popular remedy dating from the eighteenth century was 'Godfrey's cordial', which contained opium, black treacle, and saffras. This was used as a teething aid, for rheumatic pains, and for diarrhoea. These preparations were freely available in grocery shops without prescription or restriction, despite the fact that many people became addicted to them.

It has to be appreciated that in those days opium was considered as legitimate as tobacco or tea, and that this view continued right up to the twentieth century. Indeed, during the nineteenth century, the opium trade led directly to a war between the UK and China.

During the nineteenth century, China was ruled by an elite class who considered all foreigners as nothing better than barbarians and wanted nothing to do with them. As a result, trade barriers were set up against all foreign imports, and China strove to be totally self-sufficient. Many nations felt aggrieved over this, including the British who were buying tea from China, and were not allowed to trade in return. Eventually, Britain thought it had the answer in opium.

Until the early seventeenth century, China had grown its own opium for use as an ingredient in cakes and as a

¹ Dover had another claim to fame. During his seafaring days, he rescued the marooned Alexander Selkirk from an uninhabited island. This was the inspiration for Defoe's *Robinson Crusoe*.

medicine, but strangely enough it was the introduction of tobacco which changed all that. Tobacco was introduced to Europe from the Americas in the fifteenth century, and European sailors soon introduced the habit into the Far East. In China, smoking became so widespread that the Emperor Tsung Chen banned it in 1644. Deprived of tobacco, the population started smoking opium instead! By the end of the century, about a quarter of the population was using the drug and the local crops were insufficient to keep up with demand. As India was a major producer of opium, the British East India company saw this as an opportunity to import the drug into China, and by the 1830s the company was supplying £1 million worth of opium per year. Due to China's embargo, however, most of this had to be smuggled in via the port of Canton by British and American merchants.

Eventually, the Chinese authorities decided to act. They seized and burnt a shipload of opium, then closed the port of Canton to the British. The British traders were outraged and appealed to Lord Palmerston, the British Foreign Secretary at the time. Relations between the two countries steadily deteriorated and led to the Opium Wars of 1839–42. China was quickly defeated and was forced to lease Hong Kong to Britain as a trading port. They were also forced to accept the principles of free trade and to pay reparations of £21 million. It may seem odd now, but at the time, the British saw the Opium War as a just war aimed at defending the principles of free trade. Furthermore, China was seen as a tyrannical regime where justice was harsh and penalties were even harsher (e.g. death by a thousand cuts). The Opium War was first and foremost a trade war, and it was not long before other European nations and the USA picked their own fight with China, and imposed their own trade settlements and trading ports.

In the mid-nineteenth century, opium was smoked in much the same way as cigarettes are today, and opium dens were as much a part of London society as coffee shops. These dens were used by many of the romantic authors of the day including Thomas de Quincy, Edgar Allan Poe, and Samuel Taylor Coleridge. De Quincy even wrote a book recording his opium experiences (*Confessions of an English Opium Eater*), and Coleridge was consuming around 4 pints of laudanum a week when he wrote the 'The Rime of the Ancient Mariner'. A later poem called 'Dejection' may have been inspired by his experience of withdrawal symptoms.

Towards the end of the nineteenth century, doubts were beginning to grow about the long-term effects of opium and its addictive properties. There were many who leapt to its defence though, and economic arguments were as powerful a weapon then as they are today. It was not until Chinese immigrants introduced opium on a large scale to the USA, Australia and South America,

that governments really cracked down on the trade. In 1909, the International Opium Commission was set up, and by 1914, 34 nations had agreed to curb opium production and trade. By 1924, 62 countries had signed up and the League of Nations took over the role of control, requiring countries to limit the use of narcotic drugs to medicine alone. Unfortunately many farmers in India, Pakistan, Afghanistan, Turkey, Iran, and the Golden Triangle (Burma, Thailand, and Laos) depended on the opium trade for survival. As a result, the trade went underground and has continued to this day.

24.2 The active principle: morphine

24.2.1 Isolation of morphine

Opium contains a complex mixture of over 20 alkaloids. The principle alkaloid in the mixture, and the one responsible for analgesic activity, is **morphine** (Fig. 24.1), named after Morpheus. Although pure morphine was isolated in 1803, it was not until 1833 that chemists at Macfarlane and Co. (now Macfarlane-Smith) in Edinburgh were able to isolate and purify it on a commercial scale. Because morphine was poorly absorbed orally, it was little used in medicine until the hypodermic syringe was invented in 1853, allowing doctors to inject the drug directly into the blood supply.

Morphine was then found to be a particularly good analgesic and sedative, and far more effective than crude opium. But there was also a price to be paid. Morphine was used during the American Civil War (1861–65) and the Franco-Prussian war. However, there was poor understanding about safe dose levels, the effects of long-term use, and the increased risks of addiction, tolerance, and respiratory depression (Box 24.1). As a result, many casualties were either killed by overdoses or became addicted to the drug.

24.2.2 Structure and properties

Morphine was an extremely complex molecule by nineteenth-century standards, and identifying its structure posed a huge challenge to chemists. By 1881, the functional groups on morphine had been identified, but it took many more years to establish the full structure. In those days, the only way to find out the structure of a complicated molecule was to degrade the compound into simpler molecules that were already known and could be identified. For example, the degradation of morphine with strong base produced methylamine, which established that there was an N-CH₃ fragment in the

BOX 24.1 Clinical aspects of morphine

Morphine is still one of the most effective painkillers available to medicine. It is especially good for treating dull, constant pain, rather than sharp, periodic pain. It acts in the brain and appears to work by elevating the pain threshold, thus decreasing the brain's awareness of pain. Unfortunately, it has a large number of side effects, which include:

- depression of the respiratory centre
- constipation
- excitation
- euphoria
- nausea
- pupil constriction
- tolerance and dependence.

Some side effects are not particularly serious, and some can even be advantageous. Euphoria, for example, is a useful

side effect when treating pain in terminally ill patients. On the other hand, the euphoric effects of morphine can encourage people to take the drug for the wrong reasons. Other side effects, such as constipation, are uncomfortable but can give clues to different possible uses for opioids. For example, opioids are used in the treatment of diarrhoea.

The dangerous side effects of morphine are those of tolerance and dependence, allied with the effects morphine can have on breathing. In fact, the most common cause of death from a morphine overdose is suffocation. Tolerance and dependence in the one drug are particularly dangerous and lead to severe withdrawal symptoms when the drug is no longer taken. Withdrawal symptoms associated with morphine include anorexia, weight loss, pupil dilation, chills, excessive sweating, abdominal cramps, muscle spasms, hyperirritability, lacrimation, tremor, increased heart rate, and increased blood pressure. No wonder addicts find it hard to kick the habit!

molecule. From such evidence, chemists would propose a structure. This is like trying to work out the structure of a bombed cathedral from the rubble.

Once a structure had been proposed, chemists would then attempt to synthesize it. If the properties of the synthesized compound were the same as those of the natural compound, then the structure was proven. This was a long drawn-out process, made all the more difficult because chemists then had few of the synthetic reagents or procedures available today. As a result, it was not until 1925 that Sir Robert Robinson proposed the correct structure of morphine. A full synthesis was achieved in 1952, and the structure proposed by Robinson was finally proved by X-ray crystallography in 1968 (164 years after the original isolation). The molecule contains five rings labelled A–E, and has a pronounced T shape. It is basic because of the tertiary amino group, but it also contains a phenol, alcohol, aromatic ring, ether bridge, and double bond.

24.3 Structure–activity relationships

Following the discovery of morphine, it was natural for chemists to use the known reactions of the day to synthesize various analogues and to see whether these had analgesic activity or not. This allowed some conclusions to be made regarding the importance or otherwise of different functional groups. For example, **heterocodeine**, **6-ethylmorphine**, **6-acetylmorphine**, **6-oxomorphine** and **dihydromorphine** (Fig. 24.2) are examples of structures where the alkene or 6-hydroxy groups have been modified or removed. Analgesic activity is retained in these structures, indicating that neither of these groups is crucial to activity. On the other hand, analgesic activity drops dramatically for **codeine** and **3-ethylmorphine** (Fig. 24.2), indicating the importance of the phenolic group.

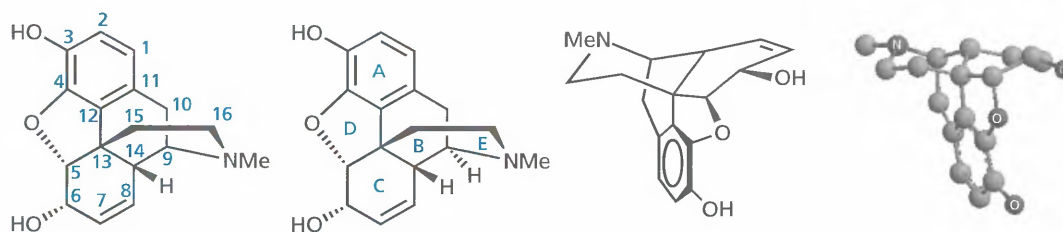


FIGURE 24.1 Structure of morphine.

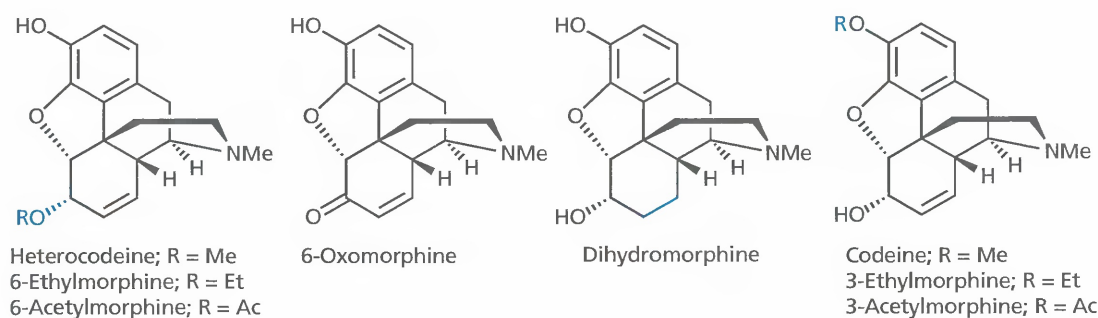


FIGURE 24.2 Analogues of morphine.

These and other results led to the conclusion that the important functional groups for analgesic activity are the phenol group, the aromatic ring and the tertiary amine, which is protonated and ionized when the drug interacts with its target binding site (Fig. 24.3).

At this stage, it is worth making some observations on the stereochemistry of morphine. Morphine is an asymmetric molecule containing several asymmetric centres, and exists naturally as a single stereoisomer. When morphine was first synthesized, it was made as a racemic mixture of the naturally occurring stereoisomer plus its mirror image (Fig. 24.4).

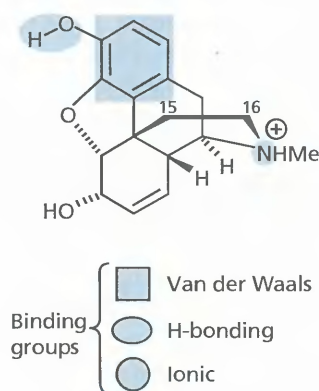


FIGURE 24.3 Important functional groups for analgesic activity in morphine.

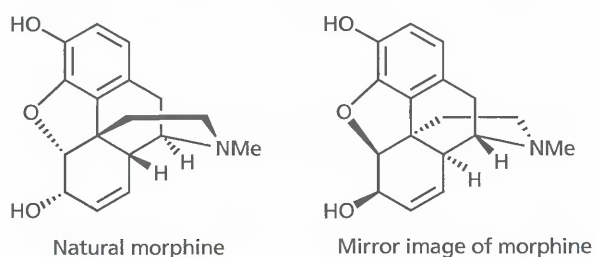


FIGURE 24.4 Morphine and its mirror image.

It was noticeable that the activity of synthetic morphine was half that of natural morphine, and when the stereoisomers were separated, it was found that the unnatural mirror image had no analgesic activity. This should come as no surprise since the macromolecules targeted by drugs are asymmetric, and are able to distinguish between the mirror images of asymmetric molecules.

Epimerization of a single asymmetric centre is not beneficial for activity either, since changing the stereochemistry at even one asymmetric centre can result in a drastic change of shape, which could affect how the molecule binds to a target binding site. For example, epimerization of the asymmetric centre at position 14 results in a stereoisomer that has only 10% the activity of morphine (Fig. 24.5).

To sum up, analgesic activity is not only related to the presence of important functional groups defined earlier, but to their relative position with respect to each other. Analgesic pharmacophores can be defined in different ways (section 13.2), either by defining a simple skeleton that links the important functional groups, or by pharmacophoric triangles where the corners correspond to functional groups or binding interactions (Fig. 24.6).

KEY POINTS

- Morphine is extracted from opium and is one of the oldest drugs used in medicine.
- Morphine is a powerful analgesic but has various side effects, the most serious being respiratory depression, tolerance, and dependence.
- The structure of morphine consists of five rings forming a T-shaped molecule.
- The important binding groups on morphine are the phenol, the aromatic ring and the ionized amine.

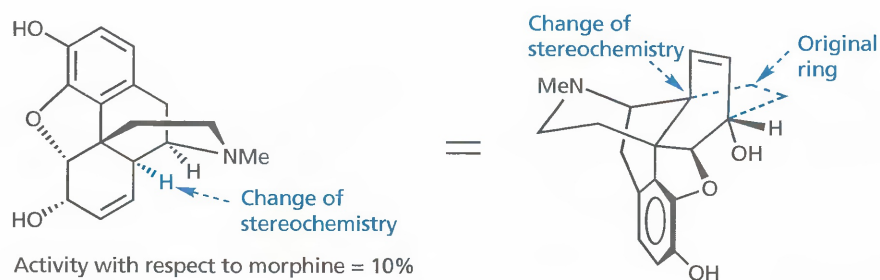


FIGURE 24.5 Epimerization of a single asymmetric centre.

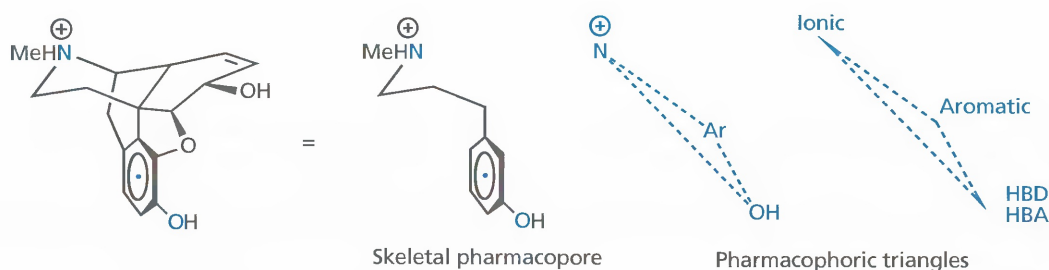


FIGURE 24.6 Analgesic pharmacophores for morphine and related opioids.

24.4 Molecular target for morphine: opioid receptors

Although morphine was isolated in the 19th century, it took many years to discover how it produced its analgesic effect. It is now known that morphine activates analgesic receptors in the central nervous system, which leads to a reduction in the transmission of pain signals to the brain. There are three main types of analgesic or opioid receptor which are activated by morphine, called the mu (μ), kappa (κ) and delta (δ) receptors. All of them are G-protein coupled receptors which activate G_i or G_o signal proteins (section 4.7 and chapter 5). Morphine acts as an agonist at all three types of receptor, and activation leads to a variety of cellular effects depending on the type of receptor involved. These include the opening of potassium ion channels, the closing of calcium ion channels or the inhibition of neurotransmitter release, all of which reduce the transmission of pain signals from one nerve cell to another. A newer form of terminology has now been introduced where the μ , κ and δ receptors are called the MOR, KOR and DOR receptors respectively. Nevertheless, we will continue to use the original nomenclature in this chapter since it is still more prevalent.

There are differences between the different opioid receptors in terms of their effects as well as their side effects. Activation of the μ receptor results in sedation and the strongest analgesic effect, but this receptor is also associated with the strongest and most dangerous side effects of respiratory depression, euphoria, and addiction.

Activation of the δ and κ receptors does not produce the same level of analgesia, but there are less side effects. For example, the δ receptor does not cause sedation, euphoria or physical dependence, while the κ receptor has no effect on breathing, is free of euphoric effects and has a low risk of physical dependence. The κ receptor is considered the safest of the three types of receptor, and is the preferred target for novel analgesics.

A fourth opioid receptor was later identified in the 1990s which shows a lot of structural similarity to the classical opioid receptors. It was therefore referred to as the 'opioid receptor-like' receptor (ORL1), but is now known as the NOR receptor. It was classed as an 'orphan receptor' since its endogenous ligand was not known, but an endogenous ligand has now been identified. There is some uncertainty whether activation of this receptor increases or decreases sensitivity to pain.

Morphine and most of its analogues bind strongly to the μ receptor, and less strongly to the κ or δ receptors. This explains why it has been so difficult to find a safe, powerful analgesic since the receptor with which they bind most strongly inherently produces the most serious side effects.

24.5 Morphine: pharmacodynamics and pharmacokinetics

Pharmacodynamics refers to the manner in which a drug binds to its target. Morphine is a T-shaped molecule, and the opioid receptors are thought to have a T-shaped

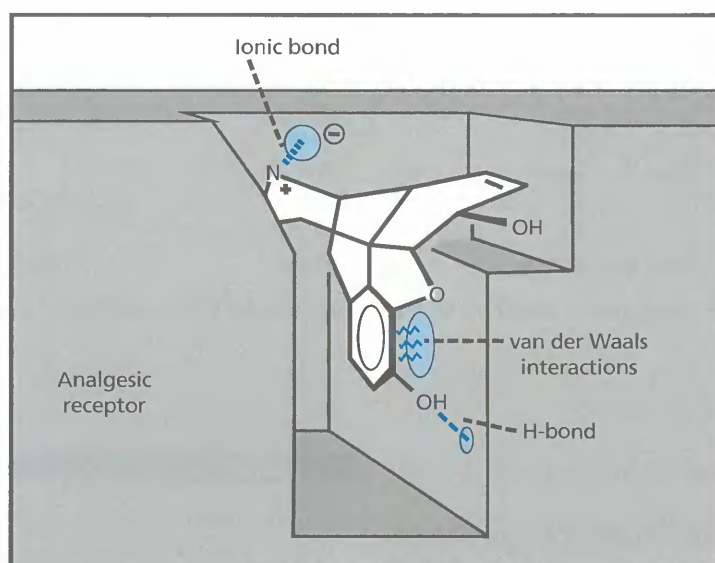


FIGURE 24.7 Binding interactions of morphine with the binding site of an opioid receptor.

binding site which matches that shape. The functional groups that are important to the activity of morphine act as binding groups in the following manner (Fig. 24.7):

- the amine nitrogen is protonated and charged, allowing it to form an ionic bond with a negatively charged region of the binding site
- the phenol is involved in a hydrogen bond with the binding site
- the aromatic ring is important for activity. The rigid structure of morphine means that the aromatic ring has a defined orientation with respect to the rest of the molecule allowing van der Waals interactions with a suitable hydrophobic location in the binding site. The nature of these interactions suggest that there has to be a close spatial relationship between the aromatic ring and the surface of the binding site.

Pharmacokinetics refers to the ability of a drug to reach its target and to survive in the body. Morphine is relatively polar and is poorly absorbed from the gut, and so it is normally given by intravenous injection. However, only a small percentage of the dose administered actually reaches the analgesic receptors in the central nervous system (CNS) due to the blood–brain barrier (section 11.3.5). This acts as a barrier to polar drugs and effectively prevents any ionized drug from crossing into the CNS. For example the *N*-methyl quaternary salt of morphine (Fig. 24.8) is inactive when it is administered by intravenous injection since it is blocked by the blood–brain barrier. If this same compound is injected directly

into the brain, however, it has a similar analgesic activity to morphine.

If morphine was fully charged, it would not be able to enter the brain either. However, the amine group is a weak base and so morphine can exist both as the free base and ionized forms. This means that morphine can cross the blood–brain barrier as the free base, then ionize in order to interact with the receptor. The pK_a values of useful analgesics should be 7.8–8.9 such that there is an approximately equal chance of the amine being ionized or unionized at physiological pH.

The extent to which different structures cross the blood–brain barrier plays an important role in analgesic activity. For example, normorphine (Fig. 24.8) has only 25% the activity of morphine. The secondary NH group is more polar than the original tertiary group, and so normorphine is less efficient at crossing the blood–brain barrier, leading to a drop in activity.

It is possible to get increased levels of morphine in the brain by using prodrugs (section 14.6) where some of the polar functional groups are masked. It is interesting to compare the activities of morphine, **6-acetylmorphine** (Fig. 24.2), and **diamorphine** (heroin) (Fig. 24.8). The most active (and the most dangerous) compound of the three is 6-acetylmorphine, which is four times more active than morphine. Heroin is also more active than morphine by a factor of two, but less active than 6-acetylmorphine. How do we explain this?

6-Acetylmorphine is less polar than morphine and will cross the blood–brain barrier into the CNS more quickly and in greater concentrations. The phenolic group is free

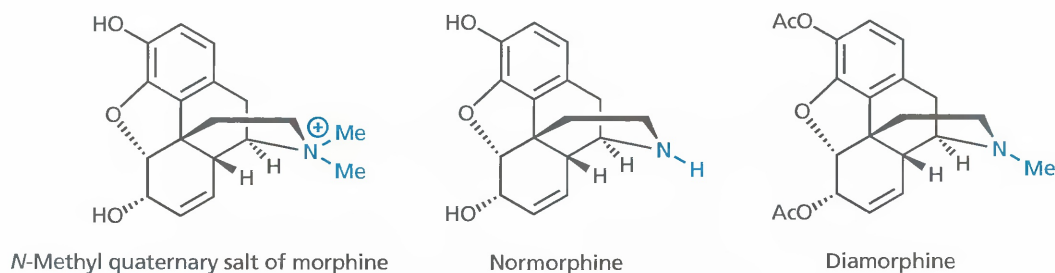


FIGURE 24.8 Analogues of morphine with differing abilities to cross the blood–brain barrier.

and therefore it will interact immediately with the analgesic receptors.

Heroin has two polar groups which are masked and is therefore the most efficient compound of the three in crossing the blood–brain barrier. Before it can bind to the opioid receptors, however, the 3-acetyl group has to be removed by esterases in the CNS. This means that it is more powerful than morphine because of the ease with which it crosses the blood–brain barrier, but less powerful than 6-acetylmorphine since the 3-acetyl group has to be hydrolysed.

Heroin and 6-acetylmorphine are both more potent analgesics than morphine. Unfortunately, they also have greater side effects as well as severe tolerance and dependence characteristics. Heroin is still used to treat terminally ill patients suffering chronic pain, but 6-acetylmorphine is so dangerous that its synthesis is banned in many countries.

The lifetime of morphine in the blood supply is quite short, with 90% of each dose being metabolized and excreted within 24 hours. The presence of the alcohol and phenol groups means that the molecule undergoes phase II conjugation reactions (section 11.4.5), and the resulting polar conjugates are quickly excreted.

Drug metabolism also plays an important role in the activity of different opioid structures. For example, codeine (Fig. 24.2) is the 3-methyl ether of morphine and has a binding affinity for the opioid receptor which is only 0.1% of morphine. It also has no analgesic activity when it is injected directly into the brain. This is not surprising since methylation of the phenol group would be expected to disrupt its ability to act as a binding group (section 13.1.1). What is surprising is the fact that codeine has an analgesic effect which is 20% that of morphine—much better than expected. Why is this? The answer lies in the fact that codeine is metabolized by *O*-demethylation in the liver to give morphine. Thus, codeine can be viewed as a prodrug for morphine. **Codeine** is present in opium and is used for treating moderate pain, coughs, and diarrhoea (see also section 11.4.6).

KEY POINTS

- The important binding interactions between morphine and opioid receptors are a hydrogen bonding interaction via a phenol group, an ionic interaction via a charged amine, and van der Waals interactions involving the aromatic ring.
- There are three different analgesic receptors (μ , κ and δ) with which morphine interacts. All require the presence of a pharmacophore involving the phenol, aromatic ring and ionized amine.
- Morphine binds most strongly to the μ receptor. This receptor is responsible for the serious side effects associated with morphine.
- The κ -receptor is responsible for analgesia and sedation, and lacks serious side effects.
- The δ -receptor is favoured by the enkephalins.
- The opioid receptors are G-protein linked receptors.
- The ability of opioids to cross the blood–brain barrier plays an important role in analgesic activity.
- Some analgesics such as codeine and diamorphine act as prodrugs for morphine.

24.6 Morphine analogues

Considering the problems associated with morphine, there is a need for novel analgesic agents which retain the analgesic activity of morphine, but which have fewer side effects and can be administered orally. The following sections illustrate how many of the classical drug design strategies described in chapter 13 were effective in obtaining novel analgesic structures.

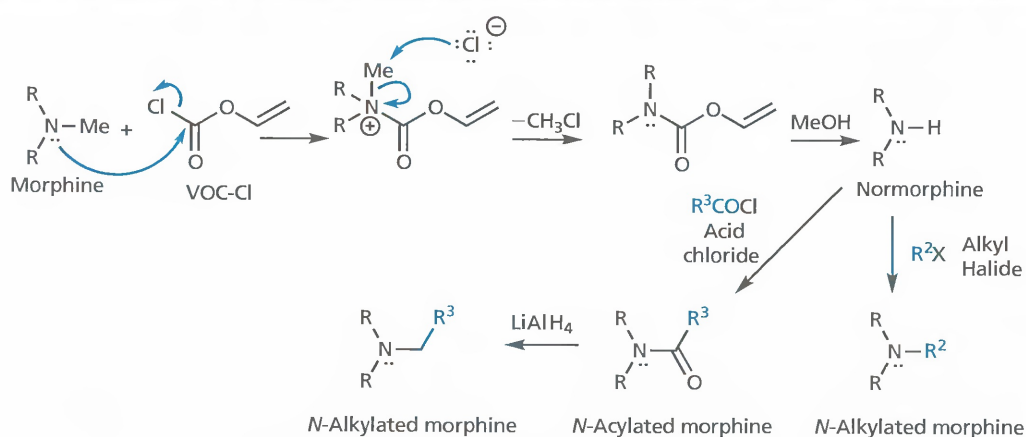
24.6.1 Variation of substituents

A series of alkyl substituents were placed on the phenolic group, but the resulting compounds were inactive or poorly active. We have already identified that the phenol group must be free for analgesic activity.

BOX 24.2 Synthesis of *N*-alkylated morphine analogues

The synthesis of *N*-alkylated morphine analogues is easily achieved by removing the *N*-methyl group from morphine to give **normorphine**, then alkylating the amino group with an alkyl halide. Removal of the *N*-methyl group was originally achieved by a von Braun degradation with cyanogen

bromide, but is now more conveniently carried out using a chloro-formate reagent such as vinyloxycarbonyl chloride. The final alkylation step can sometimes be profitably replaced by a two-step process involving an acylation to give an amide, followed by reduction.



The removal of the *N*-methyl group to give normorphine allowed a series of alkyl chains to be added to the basic centre (Box 24.2). These results are discussed in the next section.

24.6.2 Drug extension

The strategy of drug extension described in section 13.3.2 involves the addition of extra functional groups to a lead compound in order to probe for extra binding regions in a binding site. Many analogues of morphine containing extra functional groups have been prepared. These have rarely shown any improvement. There are two exceptions, however. The introduction of a hydroxyl group at position 14 (Fig. 24.9) increases activity and suggests that there might be an extra hydrogen bond interaction taking place with the binding site.

The other exception involves the variation of alkyl substituents on the nitrogen atom. As the alkyl group is increased in size from a methyl to a butyl group, the activity drops to zero (Fig. 24.10). With a larger group such as a pentyl or a hexyl group, activity recovers slightly. None of this is particularly exciting, but when a phenethyl group is attached, the activity increases 14-fold relative to morphine—a strong indication that a hydrophobic binding region has been located which interacts favourably with the new aromatic ring (Fig. 24.9).

To conclude, the size and nature of the group on nitrogen is important to the activity spectrum. Drug extension can lead to better binding by making use of additional binding interactions.

Before leaving this subject, it is worth describing important results which occurred when an allyl or a

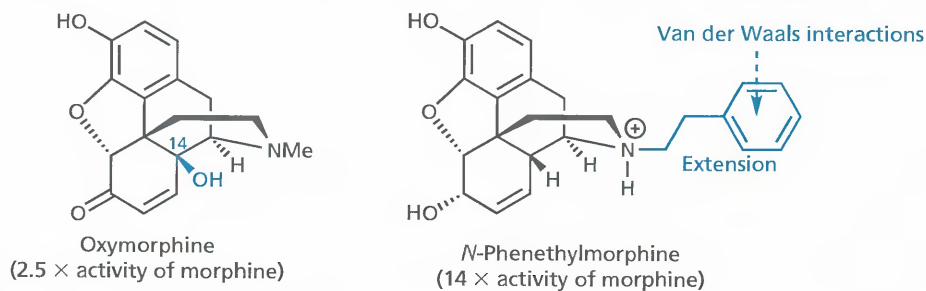


FIGURE 24.9 Extended analogues of morphine.

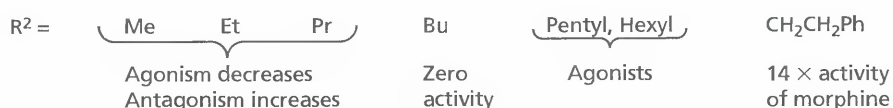


FIGURE 24.10 Change in activity with respect to alkyl group size.

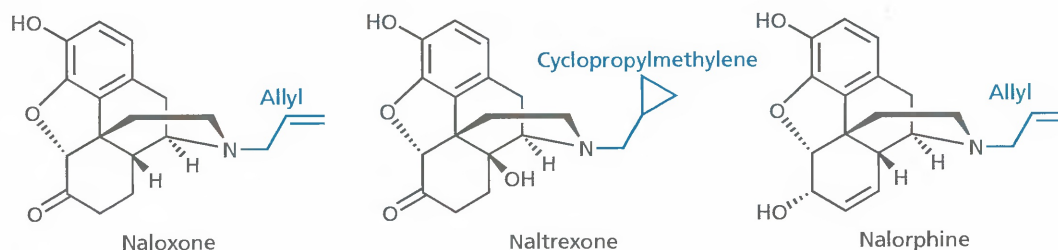


FIGURE 24.11 Antagonists to morphine.

cyclopropylmethylene group is attached to nitrogen (Fig. 24.11) (section 24.7). **Naloxone** and **naltrexone** have no analgesic activity at all, and **nalorphine** retains only weak analgesic activity. Not very exciting, you might think. What is important is that they act as antagonists to morphine, that is they bind to the analgesic receptors without ‘switching them on’. Once they have bound to the receptors, they block morphine from binding. As a result, morphine can no longer act as an analgesic. One might be hard pushed to see an advantage in this, and with good reason. If we are just considering analgesia, there is none. However, the fact that morphine is blocked from all its receptors means that none of its side effects are produced either, and it is the blocking of these effects that makes antagonists extremely useful. For example, accident victims have sometimes been given an overdose of morphine. If this is not treated quickly, then the casualty may die of suffocation. Administering nalorphine means that the antagonist can block morphine from binding to opioid receptors and lead to recovery.

Naltrexone is eight times more active than naloxone as an antagonist and is given to drug addicts who have been weaned off morphine or heroin. Naltrexone blocks the opioid receptors, blocking the effects that addicts seek if they restart their habit and making it less likely that they will do so.

There is another interesting observation related to these antagonists. For many years, chemists had been trying to find a morphine analogue without serious side effects. There had been so little success in this search that many believed that it would be impossible to separate the analgesic effects from the side effects. The fact that the antagonist naloxone blocks both the analgesic and side effects of morphine did nothing to change that view. However, the properties of nalorphine offered a glimmer of hope.

Nalorphine acts as an antagonist at the μ receptor, and as a weak agonist at the κ receptor. Therefore, the slight analgesia observed with nalorphine is due to partial activation of the κ receptor. Moreover, this activity appears to be free of the undesired side effects associated with morphine. This was the first sign that a non-addictive, safe analgesic might be possible if structures were made that were selective for the κ receptor. Unfortunately, nalorphine has hallucinogenic side effects, which are caused by the compound binding to a non-analgesic receptor in the brain called the sigma receptor (σ).

24.6.3 Simplification or drug dissection

We turn now to more drastic alterations of the morphine structure and ask whether the complete carbon skeleton is really necessary. If the molecule could be simplified, it would be easier to synthesize analogues (section 13.3.8). The structure of morphine has five rings (Fig. 24.12) and analogues were made to see which rings could be removed.

24.6.3.1 Removing ring E

Removing ring E leads to complete loss of activity. This emphasizes the importance of the basic nitrogen to analgesic activity.

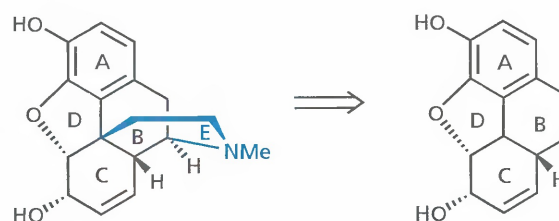


FIGURE 24.12 Removing ring E from morphine.

24.6.3.2 Removing ring D

Removing the oxygen bridge gives a series of compounds called the **morphinans** (Fig. 24.13), which have useful analgesic activity. This demonstrates that the oxygen bridge is not essential.

N-Methylmorphinan was the first such compound tested and is only 20% as active as morphine, but since the phenolic group is missing, this is not surprising. The more relevant **levorphanol** structure is five times more active than morphine and, although side effects are also increased, levorphanol has a massive advantage over morphine in that it can be taken orally and lasts much longer in the body. This is because levorphanol is not metabolized in the liver to the same extent as morphine. As might be expected, the mirror image of levorphanol (**dextrorphan**) has insignificant analgesic activity.

The same strategy of drug extension already described for the morphine structures was tried on the morphinans with similar results. For example, adding an allyl substituent on the nitrogen gives antagonists. Adding a phenethyl group to the nitrogen greatly increases potency. Adding a 14-hydroxyl group also increases activity.

To conclude:

- Morphinans are more potent and longer acting than their morphine counterparts, but they also have higher toxicity and comparable dependence characteristics.
- Modifications carried out on the morphinans have the same structure–activity relationship (SAR) results as they do with morphine. This implies that morphine and morphinans are binding to the same receptors in the same way.
- The morphinans are easier to synthesize since they are simpler molecules.

24.6.3.3 Removing rings C and D

Opening both rings C and D gives an interesting group of compounds called the **benzomorphans** (Fig. 24.14) which retain analgesic activity. One of the simplest of these structures is **metazocine**, which has the same analgesic activity as morphine. Notice that the two methyl groups in metazocine are *cis* with respect to each other, and represent the remnants of the C ring.

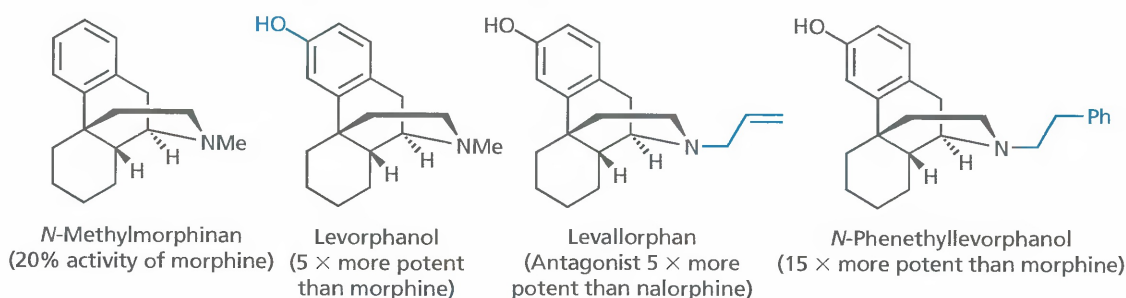


FIGURE 24.13 Examples of morphinans.

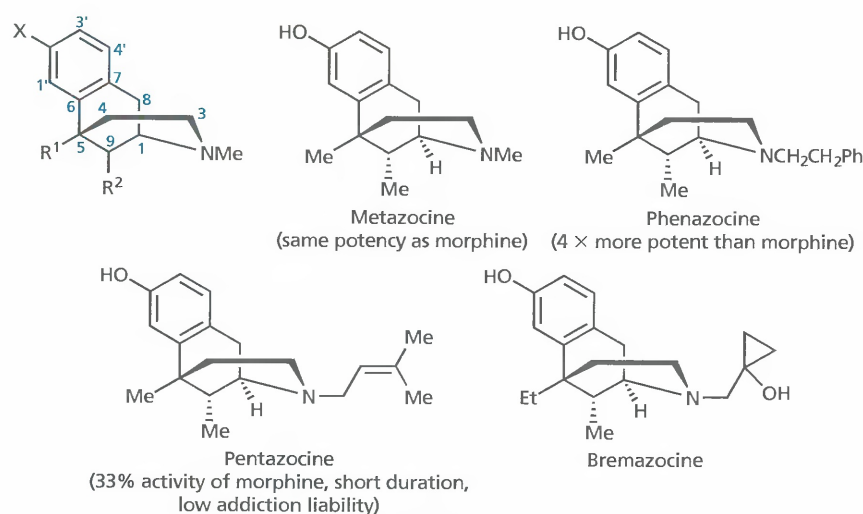


FIGURE 24.14 Benzomorphans.

The same chemical modifications carried out on the benzomorphans as described for the morphinans and morphine, produce the same biological effects, implying a similar interaction with the analgesic receptors. For example, replacing the *N*-methyl group of metazocine with a phenethyl group gives **phenazocine** which is four times more active than morphine, and is the first compound to have a useful level of analgesia without dependence properties.

Further developments led to **pentazocine** (Fig. 24.14), which has proved to be a useful long-term analgesic with a very low risk of addiction. Like nalorphine, pentazocine acts as an antagonist at the μ receptor, but unlike nalorphine it is a full agonist at the κ receptor rather than a partial agonist. Pentazocine also acts as a weak agonist at the δ receptor. Unfortunately, it acts as an agonist at the non-analgesic σ receptor, resulting in hallucinogenic side effects. A newer compound (**bremazocine**) has a longer duration, has 200 times the activity of morphine, appears to have no addictive properties, and does not depress breathing.

To conclude:

- Rings C and D are not essential to analgesic activity.
- Analgesia and addiction are not necessarily coexistent.
- 6,7-Benzomorphans are clinically useful compounds with reasonable analgesic activity, less addictive liability, and less tolerance.
- Benzomorphans are simpler to synthesize than morphine and morphinans.
- Benzomorphans bind to opioid receptors in the same manner as morphine and morphinans.

24.6.3.4 Removing rings B, C, and D

Removing rings B, C, and D gives a series of compounds known as 4-phenylpiperidines. The analgesic activity of these compounds was discovered by chance in the 1940s when chemists were studying analogues of cocaine for antispasmodic properties. Their structural relationship to morphine was only identified when they were found to be analgesics, and this is evident if the structure is drawn as shown in Fig. 24.15. Activity can be increased six-fold by introducing the phenolic group and altering the ester to a ketone to give **ketobemidone**.

Pethidine (meperidine) is a weaker analgesic than morphine, but shares the same undesirable side effects. On the plus side, it has a rapid onset and a shorter duration of action. As a result, it has been used as an analgesic in childbirth. The rapid onset and short duration of action mean that there is less chance of the drug depressing the baby's breathing once it is born.

The piperidines are more easily synthesized than any of the previous groups and a large number of analogues have been studied. There is some doubt as to whether they act in the same way as morphine at analgesic receptors, since some of the chemical adaptations we have already described do not lead to comparable biological results. For example, adding allyl or cyclopropyl groups does not give antagonists. The replacement of the methyl group of pethidine with a cinnamic acid residue increases the activity by 30-fold, whereas putting the same group on morphine eliminates activity (Fig. 24.16).

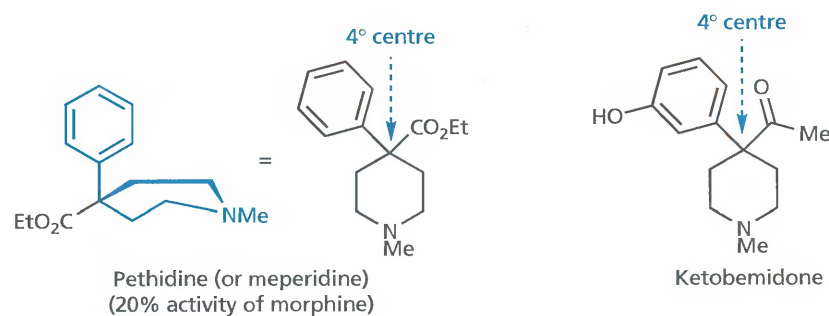


FIGURE 24.15 4-Phenylpiperidines.

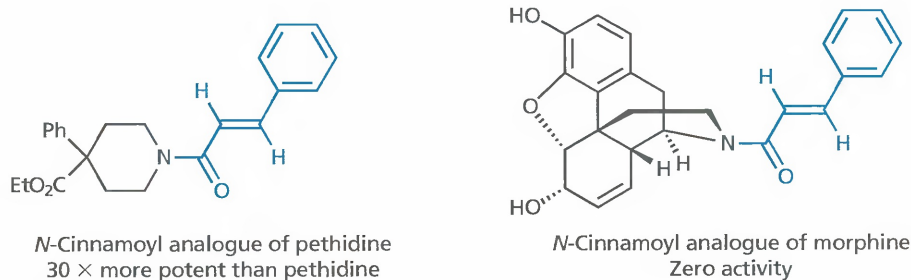


FIGURE 24.16 Effect of addition of a cinnamic acid residue on meperidine and morphine.

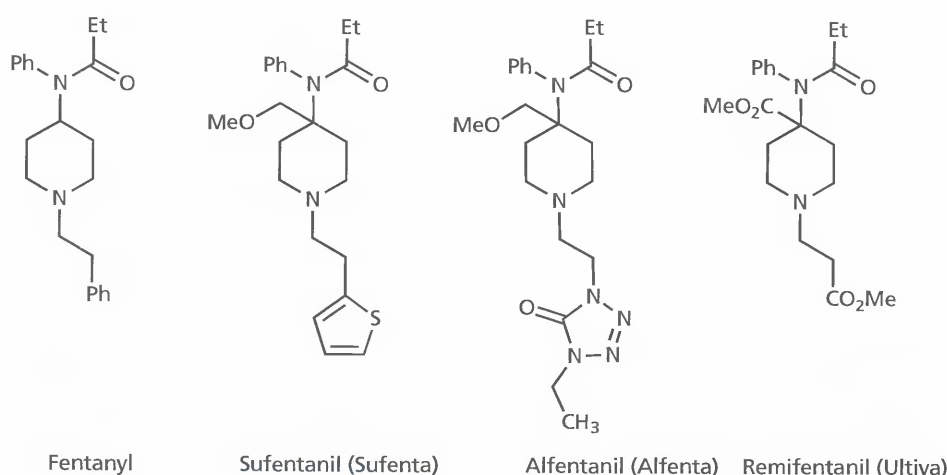


FIGURE 24.17 Fentanyl and fentanyl analogues.

These results might have something to do with the fact that the piperidines are more flexible molecules than the previous structures and are more likely to bind with receptors in different ways.

Fentanyl and its analogues (Fig. 24.17) represent some of the most successful piperidine derivatives, and are among the most potent agonists known for the μ receptor. These drugs lack a phenolic group and are very lipophilic. As a result, they can cross the blood–brain barrier more efficiently. Fentanyl itself is up to 100 times more active than morphine as a sedative and analgesic, and it is thought that the Russian authorities used it in an attempt to incapacitate a group of terrorists during the infamous cinema siege of recent years. Apparently, the drug was introduced as a gas through the ventilation system into the auditorium and it succeeded in rendering both terrorists and hostages unconscious. Unfortunately, the authorities waited too long to enter the building and many innocent people died as a result of suffocation. Like morphine, an overdose of fentanyl can stop breathing by depressing the respiratory centre in the brain.

Fentanyl and the shorter lasting **alfentanil** and **remifentanyl** are used during surgery for analgesia and to enhance anaesthesia. Remifentanyl was designed to have a very short duration of action by introducing ester groups which are rapidly metabolized by esterase enzymes. It can be administered as an intravenous drip, and since

it is rapidly broken down, it does not accumulate in the body. This reduces the risk of serious side effects such as depression of the respiratory centre.

To conclude:

- Rings C, D, and E are not essential for analgesic activity.
- Piperidines retain side effects such as addiction and depression of the respiratory centre since they are agonists at the μ receptor.
- Piperidine analgesics are faster acting and have a shorter duration of action than morphine.
- The quaternary centre present in piperidines is usually necessary (fentanyl is an exception).
- The aromatic ring and basic nitrogen are essential to activity, but the phenol group is not.
- Piperidine analgesics appear to bind with analgesic receptors in a different manner to previous groups.

24.6.3.5 Removing rings B, C, D, and E

The analgesic **methadone** (Fig. 24.18) was discovered in Germany during the Second World War and has proved to be a useful agent, comparable in activity to morphine. It is orally active and has less severe emetic and constipation effects. Side effects such as sedation,

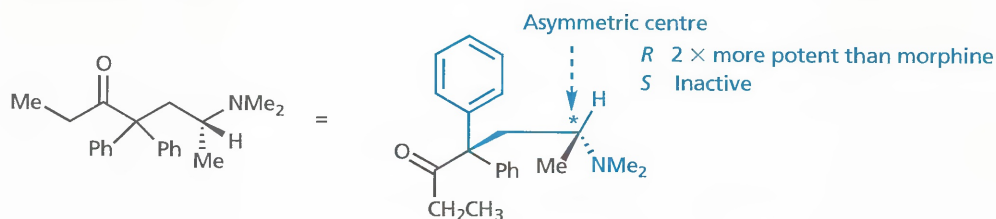


FIGURE 24.18 Methadone.

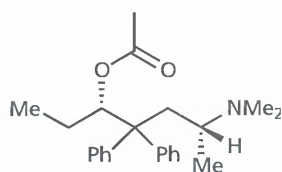


FIGURE 24.19
L- α -Acetylmethadol
(LAAM).

euphoria, and withdrawal symptoms are also less severe and therefore the compound has been given to drug addicts as a substitute for morphine or heroin in order to wean them off these drugs. This is not a complete cure, as it merely swaps an addiction to heroin or morphine for an addiction to methadone. This is considered less dangerous, however.

The molecule has a single asymmetric centre and when the molecule is drawn in the same manner as morphine, we would expect the *R*-enantiomer to be the more active enantiomer. This proves to be the case with the *R*-enantiomer being twice as powerful as morphine, whereas the *S*-enantiomer is inactive. This is quite a dramatic difference. Since the *R*- and *S*-enantiomers have identical physical properties and lipid solubility, they should both reach analgesic receptors to the same extent, and so the difference in activity is most probably due to receptor–ligand interactions.

Many analogues of methadone have been synthesized. Of these, L- α -acetylmethadol (LAAM) (Fig. 24.19), has been used as a longer acting alternative. A methadone-like structure has also been linked to the 4-phenylpiperidine

skeleton to produce a useful agent for the treatment of diarrhoea (Box 24.3).

24.6.4 Rigidification

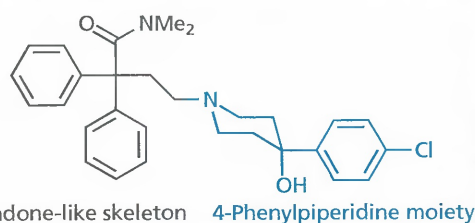
The strategy of rigidification is used to limit the number of conformations that a molecule can adopt. The aim is to retain the active conformation for the desired target and eliminate alternative conformations that might fit different targets (section 13.3.9). This should increase activity, improve selectivity and decrease side effects. The best examples of this tactic in the analgesic field are the **oripavines**, which often show remarkably high activity. A comparison of these structures with morphine shows that an extra ring sticks out from what used to be the crossbar of the T-shaped morphine skeleton (Fig. 24.20).

Some remarkably powerful oripavines have been obtained (Box 24.4). **Etorphine** (Fig. 24.21), for example, is 10 000 times more potent than morphine. This is a combination of the fact that it is a very hydrophobic molecule and can cross the blood–brain barrier 300 times more easily than morphine, as well having 20 times more affinity for the analgesic receptor binding site due to better binding interactions. At slightly higher doses than those required for analgesia, it can act as a ‘knock-out’ drug or sedative. It has a considerable margin of safety and is used to immobilize large animals such as elephants. Since the compound is so active, only very small doses are required and these can be dissolved in such small volumes (1 ml) that they can be placed in crossbow darts and fired into the hide of the animal.

BOX 24.3 Opioids as antidiarrhoeal agents

One of the main aims in drug design is to find agents that have minimal side effects, but occasionally it is possible to take advantage of a side effect. For example, one of the side effects of opioid analgesics is constipation. This is not very comfortable, but it is a useful property if you wish to counteract diarrhoea. The aim then is to design a drug such that the original side effect becomes the predominant feature. **Loperamide** is a

successful antidiarrhoeal agent which is marketed as **Imodium**. It can be viewed as a hybrid molecule involving a 4-phenylpiperidine and a methadone like structure. The compound is lipophilic, slowly absorbed, and prone to metabolism. It is also free from any euphoric effect, since it cannot cross the blood–brain barrier. All these features make it a safe medicine, free from the addictive properties of the opioid analgesics.



Methadone-like skeleton 4-Phenylpiperidine moiety

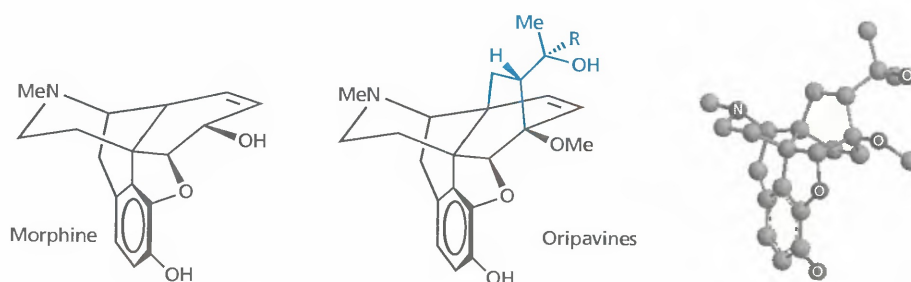


FIGURE 24.20 Comparison of morphine and oripavines.

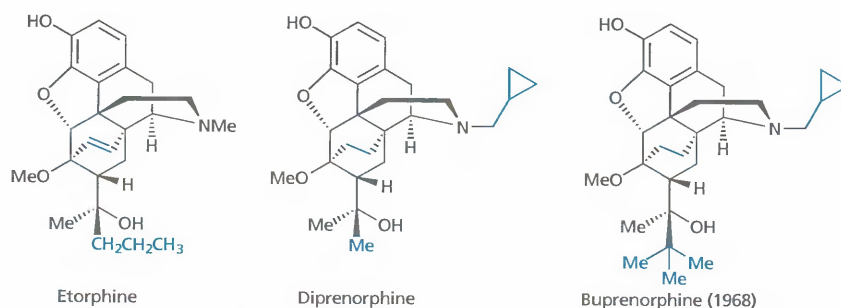


FIGURE 24.21 Etorphine and related structures.

BOX 24.4 Synthesis of the oripavines

The oripavines are synthesized from an alkaloid called **thebaine**, which is extracted from opium along with codeine and morphine. Although similar in structure to both these compounds, thebaine has no analgesic activity. There is a diene group present in ring C and when thebaine is treated with methyl vinyl ketone, a Diels–Alder reaction takes place to give an extra ring and increased rigidity to the structure.

Since a ketone group has been introduced, it is now possible to try the strategy of drug extension by adding various groups to the ketone via a Grignard reaction. It is noteworthy that this reaction is stereospecific. The Grignard reagent complexes to both the 6-methoxy group and the ketone, and is then delivered to the less-hindered face of the ketone in an asymmetric reaction.

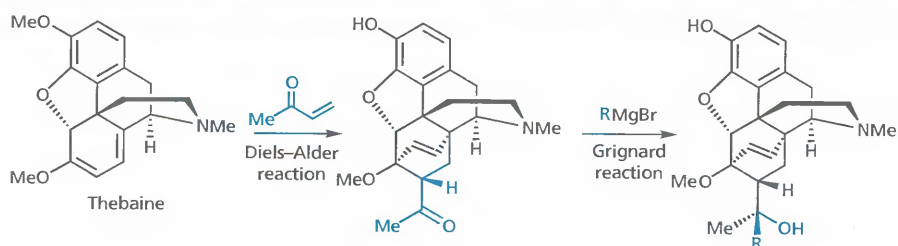


FIGURE 1 Formation of oripavines.

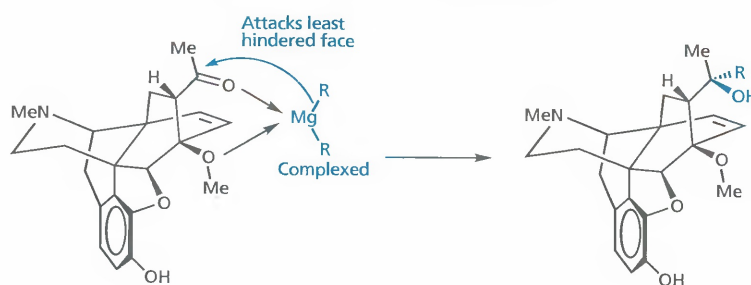


FIGURE 2 Grignard reaction leads to an asymmetric centre.

The addition of lipophilic groups (R in Fig. 24.20) is found to improve activity dramatically, indicating the presence of an extra hydrophobic binding region in the receptor binding site.² The group best able to interact with this region is a phenethyl substituent, and the product containing this group is even more active than etorphine. As one might imagine, these highly active compounds have to be handled very carefully in the laboratory.

Because of their rigid structures, these compounds are highly selective agents for the analgesic receptors. Unfortunately, the increased analgesic activity is also accompanied by unacceptable side effects due to strong interactions with the μ receptor. It was therefore decided to see whether nitrogen substituents, such as an allyl or cyclopropyl group, would give the oripavine equivalent of a pentazocine or a nalorphine—an agent acting as an antagonist at the μ receptor and an agonist at the κ receptor.

Adding a cyclopropyl group gives a very powerful antagonist called **diprenorphine** (Fig. 24.21), which is 100 times more potent than nalorphine and can be used to reverse the immobilizing effects of etorphine. Diprenorphine has no analgesic activity.

The related compound **buprenorphine** (Fig. 24.21) has similar clinical properties to drugs like nalorphine and pentazocine, in that it has analgesic activity with a very low risk of addiction. It is a particularly safe drug since it has very little effect on respiration, and what little effect it does have actually decreases at high doses. Therefore, the risks of suffocation from a drug overdose are much smaller than with morphine. Buprenorphine has been used in hospitals to treat patients suffering from cancer and also after surgery. Its drawbacks include side effects such as nausea and vomiting, as well as the fact that it cannot be taken orally. A further use for buprenorphine is as an alternative means to methadone for weaning addicts off heroin.

Buprenorphine has unusual receptor binding properties with respect to other opioids. It has a strong affinity for the μ receptor where it acts as a partial agonist, whereas it acts as an antagonist at the κ receptor. Normally, one would expect compounds that act as antagonists at the μ receptor and agonists at the κ receptor, to be the safer analgesics and so the clinical properties of buprenorphine are quite surprising. It is thought that the lack of serious side effects is related in some way to the rate at which buprenorphine interacts with the receptor. It is slow to bind, but once it has bound, it binds strongly and is slow to leave. Since the effects of binding are gradual, it means that there are no sudden changes in transmitter levels. Buprenorphine is the most lipophilic compound in the oripavine series of compounds and enters the brain very easily, and so the slow onset of binding has nothing to do with how easily it reaches the receptor. Since buprenorphine binds very

strongly, less of it is required to interact with a certain percentage of analgesic receptors than morphine. On the other hand, buprenorphine is only a partial agonist and is less efficient at switching the analgesic receptors on. This means that it is unable to reach the maximum level of analgesia which can be acquired by morphine. This means that buprenorphine can produce analgesia at lower doses than morphine. However, if the pain levels are high, buprenorphine cannot reach the analgesic levels required, and morphine has to be used. Nevertheless, buprenorphine provides another example of an opioid analogue where analgesia has been separated from dangerous side effects.

KEY POINTS

- The addition of a 14-hydroxyl group or an *N*-phenethyl group usually increases activity as a result of interactions with extra binding regions.
- *N*-Alkylated analogues of morphine are easily synthesized by demethylating morphine to normorphine, then alkylating with alkyl halides.
- The addition of suitable *N*-substituents results in compounds that act as antagonists or partial agonists. Such compounds can be used as antidotes to morphine overdose, as treatment for addiction or as safer analgesics.
- The morphinans and benzomorphans are analgesics that have a simpler structure than morphine and interact with analgesic receptors in a similar fashion.
- The 4-phenylpiperidines are a group of analgesic compounds that contain the analgesic pharmacophore present in morphine. They may bind to analgesic receptors slightly differently from analgesics of more complex structure.
- Methadone is a synthetic agent that contains part of the analgesic pharmacophore present in morphine. It is administered to drug addicts to wean them off heroin.
- Thebaine is an alkaloid derived from opium, which lacks analgesic activity. It is the starting material for a two-stage synthesis of oripavines.
- Oripavines are extremely potent compounds due to enhanced receptor interactions and an increased ability to cross the blood–brain barrier.
- The addition of *N*-cycloalkyl groups to the oripavines results in powerful antagonists or partial agonists, which can be used as antidotes for the treatment of addiction or as safer analgesics.

24.7 Agonists and antagonists

We return now to look at a particularly interesting problem regarding the agonist/antagonist properties of morphine analogues. Why should such a small change as replacing an *N*-methyl group with an allyl group result in such a dramatic

² It is believed that the phenylalanine aromatic ring on enkephalins (see later) interacts with this same binding region.

change in biological activity such that an agonist becomes an antagonist? Why should a molecule such as nalorphine act as an agonist at one analgesic receptor and an antagonist at another? How can different receptors distinguish between such subtle changes in a molecule?

We shall consider one theory proposed by Snyder and coworkers (Feinberg *et al.* 1976), which attempts to explain how these distinctions might take place, but it is important to realize that there are alternative theories. In this particular theory, it is suggested that there are two accessory hydrophobic binding regions present

in an analgesic receptor. It is then proposed that a structure will act as an agonist or as an antagonist depending on which of these extra binding regions is used. In other words, one of the hydrophobic binding regions is an agonist binding region, while the other is an antagonist binding region (Figs. 24.22–24.24). In the model, the agonist binding region is further away from the nitrogen and positioned axially with respect to it. The antagonist binding region is closer and positioned equatorially.

Let us now consider *N*-phenethylmorphine (Fig. 24.22). Like morphine, it binds using its phenol, aromatic, and

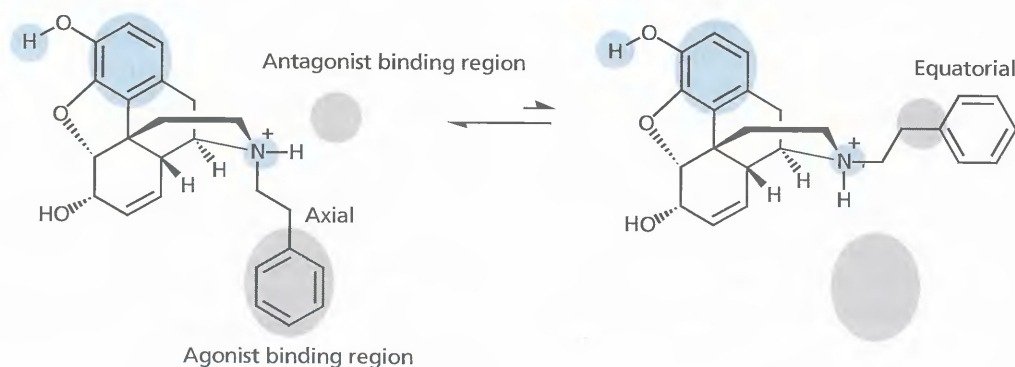


FIGURE 24.22 *N*-Phenethylmorphine binding interactions.

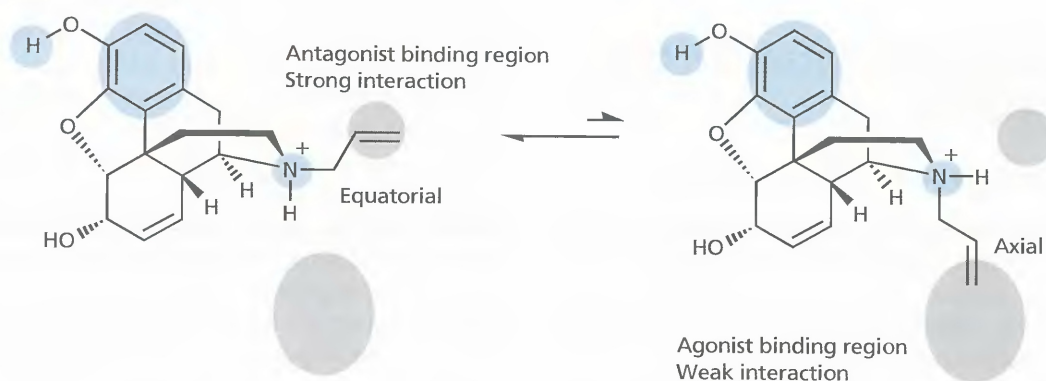


FIGURE 24.23 *N*-Allylmorphine binding interactions.

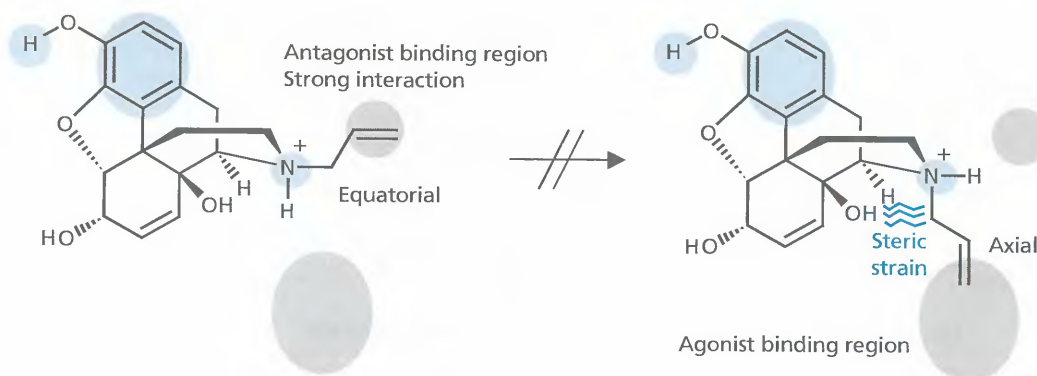


FIGURE 24.24 Influence of 14-OH on binding interactions.

amine functional groups. If the phenethyl group is in the axial position, the aromatic ring is in the correct position to interact with the accessory agonist binding region. If the phenethyl group is in the equatorial position, the aromatic ring is placed beyond the antagonist binding region and cannot bind to either of the accessory regions. The overall result is that the molecule binds with the phenethyl group axial, resulting in increased agonist activity.

Now consider what happens if the phenethyl group is replaced by an allyl group (Fig. 24.23). In the equatorial position, the allyl group binds strongly to the antagonist binding region, whereas in the axial position it barely reaches the agonist binding region, resulting in a weak interaction.

It is proposed that a molecule such as phenazocine with a phenethyl group acts as an agonist because it can only bind to the agonist binding region. A molecule such as nalorphine with an allyl group can bind to both agonist and antagonist regions and therefore acts as an agonist at one receptor and an antagonist at another. The ratio of these effects would depend on the relative equilibrium ratio of the axial and equatorial substituted isomers.

A compound which is a pure antagonist would be forced to have a suitable substituent in the equatorial position. It is believed that the presence of a 14-hydroxyl group sterically hinders the isomer with the axial substituent, and forces the substituent to remain equatorial (Fig. 24.24).

24.8 Endogenous opioid peptides and opioids

24.8.1 Endogenous opioid peptides

Morphine relieves pain by binding to analgesic receptors in the CNS. This implies that there are endogenous chemicals which interact with these receptors. The search for these natural analgesics took many years, but ultimately led to the discovery of the **enkephalins**. The term enkephalin is derived from the Greek, meaning 'in the head', and that is exactly where the enkephalins are produced. There

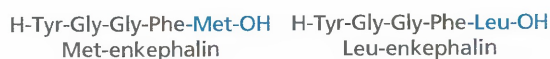


FIGURE 24.25 Enkephalins.



FIGURE 24.26 Production of the body's natural painkillers.

are two enkephalins called **Met-enkephalin** and **Leu-enkephalin** (Fig. 24.25). Both of the enkephalins are pentapeptides and have a preference for the δ -receptor (Box 24.5). It has been proposed that enkephalins are responsible for the analgesic effects of acupuncture.

At least 15 endogenous peptides have now been discovered (the enkephalins, **dynorphins** and the **endorphins**), varying in length from 5 to 33 amino acids. These compounds are thought to be neurotransmitters or neurohormones in the brain and operate as the body's natural painkillers, as well as having a number of other roles. They are mostly derived from three inactive precursor proteins—**proenkephalin**, **prodynorphin**, and **pro-opiomelanocortin** (Fig. 24.26).

All the above compounds are found to have either the Met- or the Leu-enkephalin skeleton at their *N*-terminus, which emphasizes the importance of this pentapeptide structure towards analgesic activity. It has also been shown that tyrosine is essential to activity, and much has been made of the fact that there is a tyrosine skeleton in the morphine skeleton (Fig. 24.27).

If the crucial part of these molecules is the *N*-terminal pentapeptide, why should there be so many different peptides carrying out the same task? One suggestion is that the remaining peptide chain of each molecule is responsible for targeting each peptide to particular types of analgesic receptor. It is known that enkephalins show preference for the δ -receptor, whereas dynorphins show selectivity for the κ -receptor, and β -endorphins show selectivity to both the μ and δ -receptors.

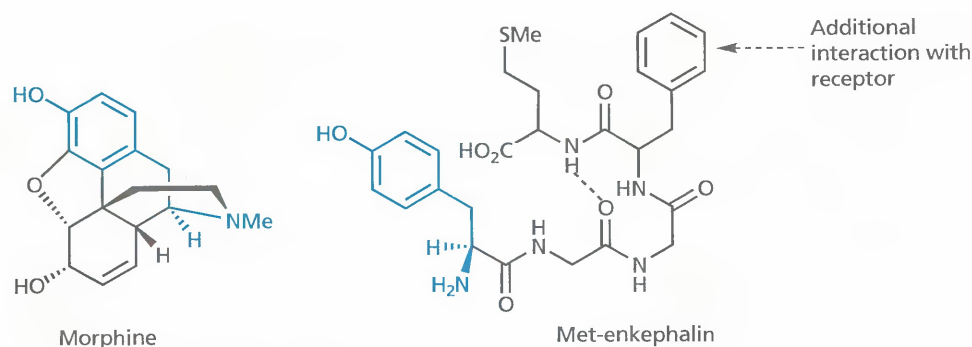


FIGURE 24.27 Comparison of morphine and met-enkephalin (dashed line is a H-bond).

BOX 24.5 Comparison of opioids and their effects on opioid receptors

Table 24.1 shows the relative activities of different opioids as agonists, partial agonists or antagonists at different opioid receptors. A plus sign indicates that the compound acts as an agonist, whereas a minus sign means that it acts as an antagonist. The number of plus signs or minus signs indicates the binding affinity. Plus signs in brackets indicate partial agonist activity.

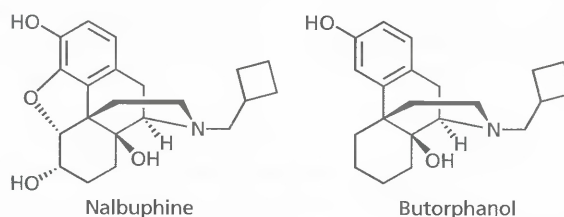
There is active research into finding orally active opioid structures that act as antagonists at the μ receptor, agonists

at the κ receptor, and have no activity at the σ receptor. The search for κ -selective agents has resulted in the clinically useful agents **nalbuphine** and **butorphanol**. Unfortunately, many of the κ -selective agents are limited in their utility since they are partial agonists, and as such provide analgesia to mild and moderate pain but not severe pain. They also show some activity at μ and σ receptors and produce side effects such as dysphoria and hallucinations. More specific κ agonists have not been fully studied (e.g. **niravoline**, **fedotozine**).

TABLE 24.1 Relative activities of opioids at opioid receptors

Receptor	Mor	Meth	Peth	Etor	Fent	Pent	Nal	Bup	Nalo	Nalt	Lenk	End	Dyn
μ	+++	+++	++	+++	+++	-	--	(+++)	---	---	+	+++	++
κ	+		+	+++		++	(++)	--	--	---		+++	+++
δ	+		+	+++	+	+			-	-	+++	+++	+

Mor (morphine); Meth (methadone); Peth (pethidine); Etor (etorphine); Fent (fentanyl); Pent (pentazocine); Nal (nalorphine); Bup (buprenorphine); Nalo (naloxone); Nalt (naltrexone); Lenk (Leu-enkephalin); End (β -endorphin); Dyn (dynorphin)

**FIGURE 1** Nalbuphine has the same activity as morphine, low addiction liability, no psychomimetic activity, but is orally inactive. Butorphanol is also orally inactive.

The most recent endogenous opioid ligand was discovered in 1995 by two groups and was named **nociceptin** or **orphanin-FQ**. It is a heptadecapeptide derived from the protein pronociceptin/orphanin FQ, and is a ligand for the ORL_1 -receptor. Curiously, the *N*-terminal amino acid is phenylalanine rather than tyrosine and it appears that this plays a crucial role in receptor selectivity. The endogenous opioids such as the enkephalins, endorphins and dynorphins have tyrosine at the *N*-terminus and have no affinity for the ORL_1 -receptor whereas nociceptin/orphanin-FQ has negligible affinity for the μ , κ and δ receptors.

The **endomorphins** (Fig. 24.28) have also been recently discovered. These are unlike previous opioid peptides. For

a start, they are tetrapeptides, whereas all other opioid peptides are pentapeptides or larger. Secondly, the second and third amino acids in their skeleton differ from glycine, another break from convention. Finally, they have a primary amide functional group at the C-terminus. They do, however, have the mandatory tyrosine and phenylalanine residues that are present in all other opioid peptides. These peptides have a strong affinity and selectivity for the μ -receptor. However, there is some doubt as to whether these are truly endogenous opioids, or whether they are merely break-down products from proteins, resulting from the extraction process used to isolate them.

24.8.2 Analogues of enkephalins

SAR studies on the enkephalins have shown the importance of the tyrosine phenol ring and the tyrosine amino group. Without either, activity is lost. If tyrosine is replaced

**FIGURE 24.28** Endomorphins.

by another amino acid, activity is also lost (the only exception being D-serine).

It has been found that the enkephalins are easily inactivated by peptidase enzymes *in vivo*, with the most labile bond being the peptide link between tyrosine and glycine. Efforts have been made to synthesize analogues which are resistant towards this hydrolysis. It is possible to replace either or both of the glycine units with unnatural D-amino acids such as D-alanine. Since D-amino acids do not occur naturally in the human body, peptidases do not recognize the structure and the peptide bond is not attacked. The alternative tactic of replacing L-tyrosine with D-tyrosine is not possible, as it completely alters the relative orientation of the tyrosine aromatic ring with respect to the rest of the molecule. As a result, the analogue is unable to bind to the analgesic receptor and is inactive.

N-Methylating the peptide link also blocks peptidase hydrolysis. Another tactic is to use unusual amino acids which are not recognized by peptidases or prevent the molecule from fitting the peptidase active site (Fig. 24.29). Unfortunately, the enkephalins also have some activity at the μ -receptor and so the search for selective agents continues.

The first non-peptide structure to show selectivity for the δ -receptor was **naltrindole** (Fig. 24.30) which acts as an antagonist. Several selective non-peptide agonists have since been developed such as **SB 213698** and **SNC-80** (Fig. 24.30).

H-L-Tyr-Gly-Gly-L-Phe-L-Met-OH	Met-enkephalin— δ agonist and some μ activity.
H-L-Tyr-D-AA-Gly-NMe-L-Phe-L-Met-OH	Resistant to peptidase. Orally active.
N,N-Diallyl-L-Tyr-aib-aib-L-Phe-L-Leu-OH	Antagonist to δ receptor (aib = α -aminobutyric acid).
Longer enkephalins/endorphins	Increase in κ activity. Slight increase in μ activity.

FIGURE 24.29 Tactics to stabilize the bond between the tyrosine and glycine residues.

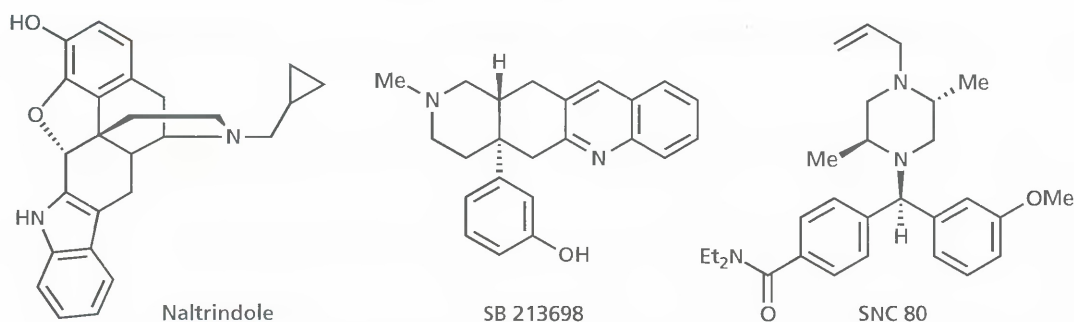


FIGURE 24.30 Non-peptide agonists and antagonists selective for the δ receptor.

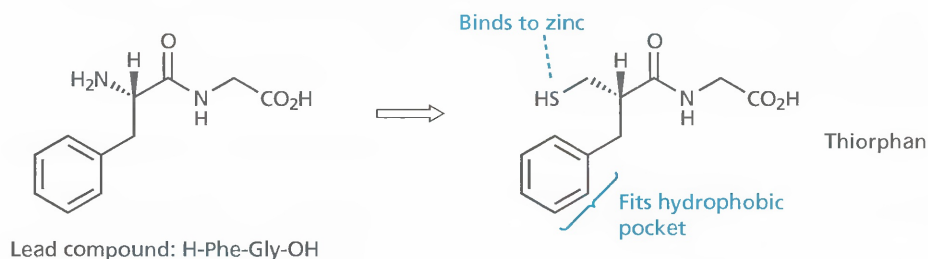


FIGURE 24.31 Development of thiorphan.

24.8.3 Inhibitors of peptidases

An alternative approach to pain relief is to enhance the activity of natural enkephalins by inhibiting the peptidase enzymes which metabolize them (enkephalinases). Studies have shown that the enzyme responsible for metabolism has a zinc ion present in the active site, as well as a hydrophobic pocket which normally accepts the phenylalanine residue present in enkephalins. A dipeptide (Phe-Gly) was chosen as the lead compound and a thiol group was incorporated to act as a binding group for the zinc ion. The result was a structure called **thiorphan** (Fig. 24.31), which was shown to have analgesic activity. It remains to be seen whether agents such as these will prove useful in the clinic.

24.8.4 Endogenous morphine

For many years, it was assumed that morphine itself could not possibly be an endogenous compound since the structure is an alkaloid produced by the poppy plant. Remarkably, morphine has now been identified as being present in tissues and body fluids, as has thebaine and codeine. It has also been demonstrated that human cells are capable of synthesizing morphine via a biosynthetic route similar to that used in the poppy plant. The levels of morphine are low and it is not yet clear what role it plays.

24.9 The future

There is still a need for orally active, analgesic drugs with reduced side-effects. The following approaches have been suggested for the future.

- **κ -Agonists** should have reduced side effects. However, a completely specific κ -agonist has not yet been found. Examples of selective agonists include **U-50,488**, which was used as the lead compound for the design of **spiradoline** and **enadoline** (Fig. 24.32). These compounds underwent clinical trials for the treatment of postoperative surgical pain, but were dropped since they were found to produce dysphoria as a CNS side effect.
- **Peripheral opioid receptors** have been identified in the ileum and are responsible for the antidiarrhoeal activity of opioids. Peripheral sensory nerves also possess opioid receptors (particularly κ receptors). Drugs might be designed to target these receptors and would not need to cross the blood–brain barrier. **Asimadoline** is one such drug and is quoted as having a use in treating the pain associated with osteoarthritis. It has also been shown to be effective against abdominal pain. **ADL 10-0101** has been shown in phase II clinical trials to reduce pain from a variety of internal organs.
- **Selectivity between μ receptor subtypes:** there are thought to be two subtypes of the μ receptor (μ_1 and μ_2), one of which may lack the serious side effects. An agent showing selectivity would prove if this theory is correct and be a useful analgesic.
- **Blocking postsynaptic receptors:** Opioids act on analgesic receptors on sensory nerves to modify the transmission of pain within a neuron or the release of a transmitter from a neuron. Another approach would be to block the postsynaptic receptors involved in the transmission of a pain signal from one neuron to

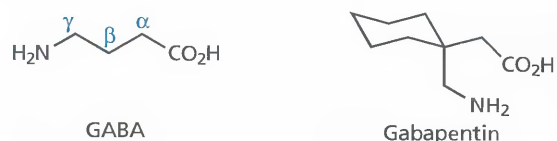


FIGURE 24.33 γ -Aminobutyric acid (GABA) and gabapentin.

another. This would involve finding selective antagonists for the various neurotransmitters involved. One promising lead is the neurotransmitter **γ -aminobutyric acid (GABA)** (Fig. 24.33), which appears to have a role in the regulation of enkephalergic neurons, and as such affects pain pathways. The clinically useful **gabapentin** (Fig. 24.38) was designed to mimic GABA, but the mechanism by which it relieves pain is not fully understood. Another chemical messenger involved in the role of pain mediation is an undecapeptide structure called substance P, which is an excitatory neurotransmitter.

- **Agonists for the cannabinoid receptor** may have a role to play in enhancing the effects of opioid analgesics, and may allow less opioid to be administered.

KEY POINTS

- It is proposed that there are two accessory hydrophobic binding regions in the receptor binding site. An agent will act as an agonist or antagonist depending on which of these regions it can access.
- Enkephalins, dynorphins, endomorphins and endorphins are peptides that act as the body's natural painkillers. The presence of an *N*-terminal tyrosine is crucial to activity.
- Analogues of enkephalins have been designed to be more stable to peptidases, by the inclusion of unnatural amino acids, D-amino acids or *N*-methylated peptide links.

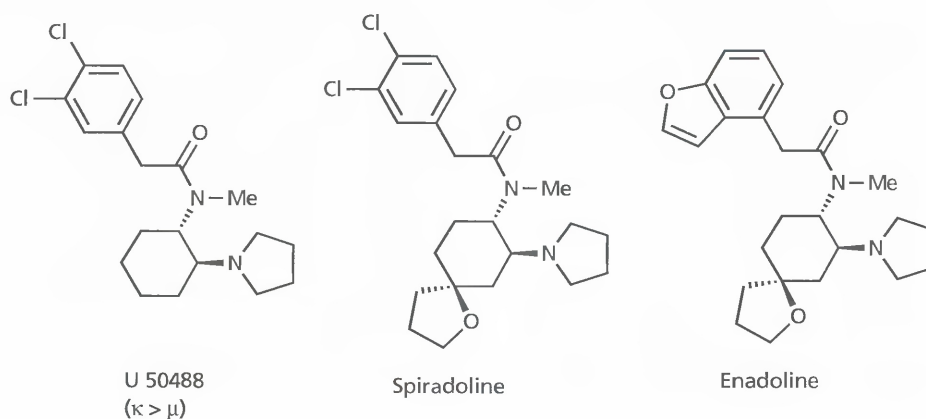
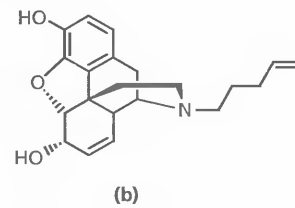
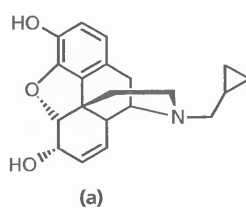


FIGURE 24.32 κ -Agonists.

QUESTIONS

- Morphine is an example of a plant alkaloid. Alkaloids tend to be secondary metabolites that are not crucial to a plant's growth and are produced when the plant is mature. If that is the case, what role do you think these compounds have in plants, if any?
- The synthesis in Box 24.2 shows that *N*-alkylated analogues can be synthesized by *N*-alkylation directly or by a two-stage process involving *N*-acylation. Why might a two-stage process be preferred to direct *N*-alkylation? What sort of products could not be synthesized by the two-stage process? Is this likely to be a problem?
- Show how you would synthesize nalorphine (Fig. 24.13).
- Pethidine has been used in childbirths as it is short acting and less hazardous than morphine in the newborn baby. Several drugs taken by the mother before giving birth can prove hazardous to the child after birth, but less so before birth. Why is this?
- Show how you would synthesize diprenorphine and buprenorphine.
- Why is buprenorphine considered the most lipophilic of the oripavine series of compounds?
- Identify the potential hydrogen bond donors and acceptors in morphine. Structure–activity relationships reveal that one functional group in morphine is important as a hydrogen bond donor or as a hydrogen bond acceptor. Which group is that?

- Propose the likely analgesic activity of 3-acetyl morphine relative to morphine, heroin and 6-acetylmorphine.
- Describe how you would synthesize the *N*-phenethyl analogue of morphine.
- The *N*-phenethyl analogue of morphine is known as a semi-synthetic product. What does this mean?
- Explain whether you think the following structures would act as agonists or antagonists.



- Thebaine has no analgesic activity. Suggest why this might be so.
- Morphine is the active principle of opium. What is meant by an active principle?
- Identify the asymmetric centres in morphine.
- How could heroin be synthesized from morphine, and what problems does this pose for drug regulation authorities?

FURTHER READING

- Abraham, D. J., (Ed.) (2003) Narcotic analgesics. *Burger's Medicinal Chemistry and Drug Discovery*, 6th edn. **6**, Chapter 7, John Wiley and Sons, New York.
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- Titles for general further reading are listed on p. 725.*