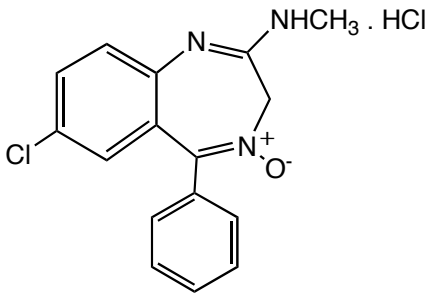
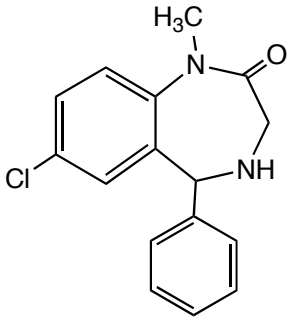
3. Rational Drug Design

3.1 Lead discovery

After a drug is discovered either serendipitously or by systematic methods it becomes a **lead compound** or, in other words, a compound that can be used as a starting point to design related molecules with better therapeutic properties and less toxicity. For example, chlordiazepoxide, a compound prescribed as a tranquilizer and marketed under the trade name Librium, was discovered serendipitously in 1954 at the Hoffmann-La Roche laboratories. The finding of this lead compound paved the way for the development of other compounds such as diazepam, the active component in Valium. Today, there are more than two dozen related compounds, collectively called **benzodiazepines**, used as hypnotics, anxiolytics and sedatives.



Chlordiazepoxide
(Librium)



Diazepam
(Valium)

Screening is the process by which the medicinal chemist finds out if a certain compound has biological activity. The most common type of screening in used today is **high-throughput-screens** (HTS) in which thousands of compounds can be tested in *in vitro* assays in a single day. These compounds are synthesized in parallel (basically all at once), and tested simultaneously until a **hit** (a compound or compounds with biological activity) is found. Structure elucidation of the hit molecule produces the **lead compound**. In planning structure modifications of the lead compound, the medicinal chemist must consider two factors: the **activity** of the compound and its **potency**. Activity is the particular biological effect of the compound, such as antibacterial activity, sedative activity, etc. Potency is its strength or the dose required to produce a desired effect. The lower the potency, the higher the dose.

3.2 Therapeutic index

When modifying a lead compound in search for better drugs, the medicinal chemist always aims at the maximum therapeutic effect with minimum toxicity. One way of quantifying these two opposing effects is through the **therapeutic index** (TI) also called the therapeutic ratio. There are different ways of measuring the TI but one of the most commonly used is the ratio of $\mathbf{LD_{50}}$ and the **therapeutic** $\mathbf{ED_{50}}$. LD_{50} is the lethal dose

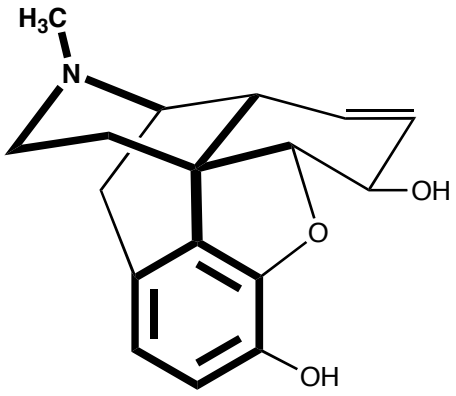
that kills 50% of the test animals and therapeutic ED_{50} is the effective dose that produces the maximum therapeutic effect in 50% of the test animals.

$$TI = \frac{LD_{50}}{therapeutic ED_{50}} \qquad (1)$$

Normally, the medicinal chemist wants the LD_{50} to be as large as possible (that means that a very large dose is needed to kill the test animals) and the therapeutic ED_{50} to be as small as possible (meaning that only a very small dose is required to produce maximum effect). The TI gives us an idea of the safety margin with which the drug operates. The larger the TI, the better. For lethal diseases such as cancer and AIDS, a TI of 1-5 could be admissible, especially if no other treatment is available, while for other less threatening diseases a TI of at least 10-100 may be expected.

3.3 Biophores

When a drug molecule interacts with a receptor, it uses only certain atoms or group of atoms for the binding. The rest of the molecule is rather passive and plays a minor role in the binding. The three-dimensional arrangement of atoms involved in the interaction with the receptor is called the **pharmacophore**. The rest of the molecule is called the **auxophore**. The pharmacophore of morphine is shown below by the highlighted bonds. It should be stressed that the pharmacophore is not a molecule but rather only certain atoms of a molecule.



morphine

The atoms or group of atoms in a drug molecule responsible for its toxicity are called the **toxicophore.** If the toxicophore and the pharmacophore overlap, toxicity and biological activity will go hand in hand and it will be difficult to design or modify a molecule to decrease its toxicity without altering its therapeutic effect.

The arrangement of atoms responsible for the metabolic degradation of the drug molecule is called the **metabophore**. Metabophore and pharmacophore often overlap because, usually, they both contain the most reactive functional group of the molecule.

Pharmacophore, auxophore, toxicophore and metabophore are collectively called **biophores**.

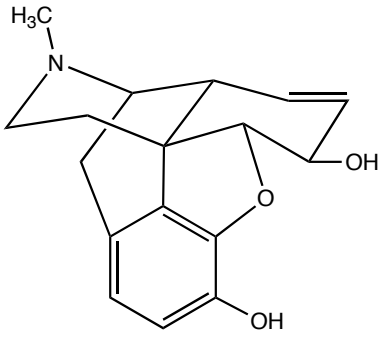
3.4 Identification of a pharmacophore

Identifying the pharmacophore, or the parts of a molecule responsible for its biological activity, is one of the many areas of research in medicinal chemistry. This effort relies not only on hard science, such as molecular modeling with the help of computer programs, but also on the intuition of the scientist. To find the pharmacophore the chemist removes certain atoms from the molecule by means of organic synthesis and studies the biological activity of the new compounds. In doing so, some general principles apply.

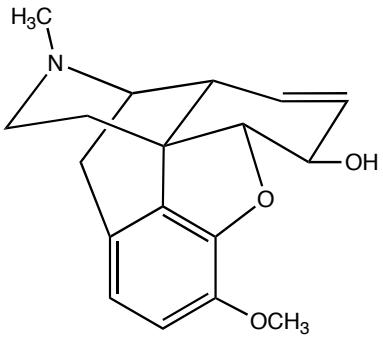
If the removal of a group of atoms leads to a decrease in potency, it can be concluded that those atoms were likely to be part of the pharmacophore. If the removal leads to an increase in potency, the conclusion would be that those atoms were not part of the pharmacophore but rather they constituted the auxophore but inhibited the binding of the pharmacophore. If no change in potency is observed, then it can be concluded that those atoms were forming part of the auxophore and did not interfere with binding. It should be noted that in carrying out these changes, not only the potency of the drug may be affected, but it is likely that a change in activity (which receptors are targeted) will be elicited as well.

The search for a pharmacophore is illustrated below with the family of **opioid alkaloids** of which morphine is the most important member. Opiod alkaloids are analgesics derived from opium. Like all alkaloids they are nitrogen containing compounds (and thus the name alkaloid, from alkaline, making reference to the basic properties of the nitrogen atom). Morphine was the first alkaloid to be isolated (1803).

Morphine and codeine are both analgesics but codeine, in which the phenolic OH group has been replaced by an ether OCH_3 group, is the less potent of the two.

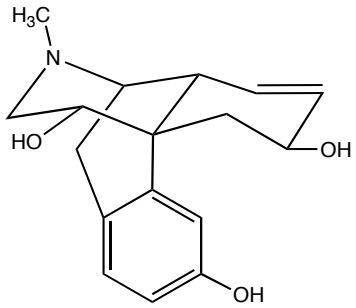


morphine



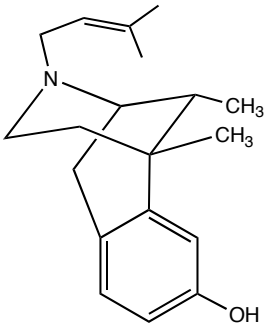
codeine

Removal of the oxygen of the dihydrofuran ring produces an analgesic that is 6-8 times as potent as morphine, levorphanol:

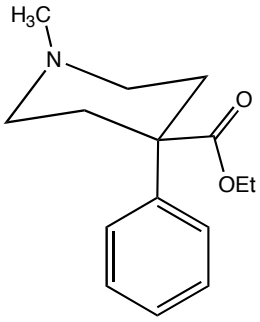


levorphanol

Cutting the fused cyclohexene ring and replacing it with two methyl groups produces an analgesic that seems to be more potent than morphine (at least in its pure enatiomeric form), pentazocine. Removing one of the methyl groups and the methylene bridge that connects the piperidine ring with the phenyl ring, and substituting the other methyl group by an ester group produces meperidine which is less potent than morphine but more than codeine.

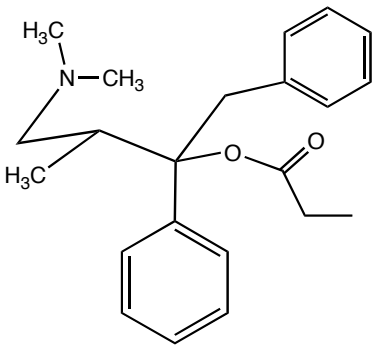


pentazocine

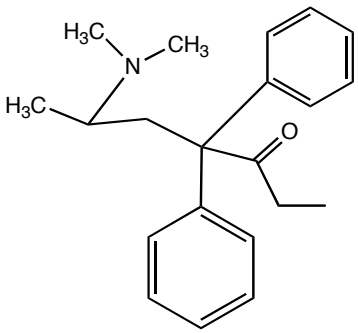


meperidine

Cutting a carbon-carbon bond in the piperidine ring still produces an analgesic, dextropropoxyphene, although less potent than morphine. Methadone, a compound used to treat heroin users, is almost as potent as morphine, although it has less severe withdrawal symptoms than morphine and heroin because it is metabolized more slowly. (Heroin is similar to morphine but has two acetates groups (CH_3COO) instead of OH groups).

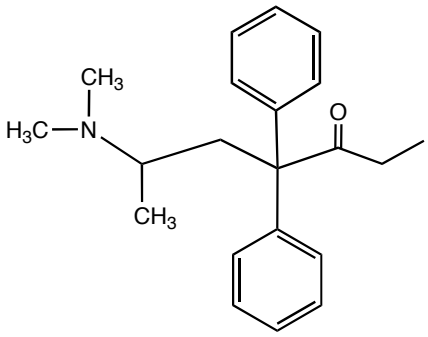


dextropropoxyphene



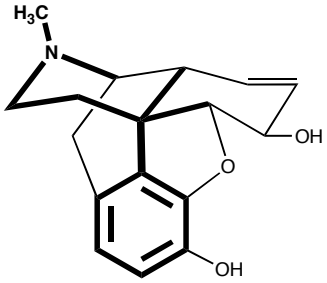
methadone

If we look at the structure of methadone, especially if we write it without any conformational undertones, it would be difficult to figure out that methadone and morphine share the same pharmacophore.

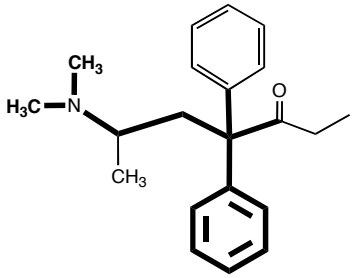


methadone

But they do. It is the flexibility of the methadone chain that allows this molecule to adopt the right conformation to bind to the opioid receptors.



pharmacophore of morphine

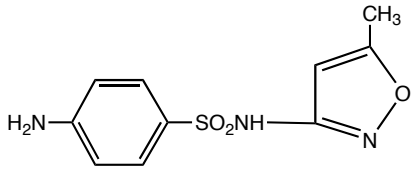


pharmacophore of methadone

3.5 Structural properties of drug molecules

The physicochemical properties of a compound, such as its solubility in water and in lipids, its partition coefficient and its pK_a affect the pharmaceutical, pharmacokinetic and pharmacodynamic phases of the chemical. Let's begin by analyzing how solubility and pK_a affect pharmaceuticals. In section 4 we will discuss the effects of the partition coefficient.

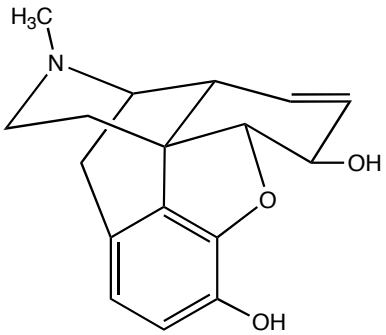
Solubility potential. Drugs administered orally must dissolve in the GI tract before they can reach the intended receptors. Since cells are made of about 65% water, water solubility is an essential property of most drugs. Drugs which are only sparingly soluble in water will be difficult to transport and may end up clogging blood vessels or depositing in tissues and causing undesirable side effects. For example, the antibacterial sulfonamides, such as sulfamethoxazole, have a tendency to crystallize in the kidney causing serious damage to this organ.



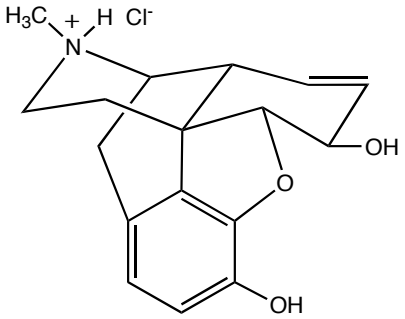
sulfamethoxazole

To increase the water solubility of a drug molecule, the medicinal chemist can add polar groups, preferentially those that can donate or accept H-bonds and thus interact favorably with water molecules, or ionizable groups, such as carboxylic acids and amines.

For alkaloids and other drugs that contain basic amino groups, it is common practice to increase their water solubility by forming the ammonium salts with strong inorganic acids such as HCl, H_2SO_4 or H_3PO_4. For example, morphine is sparingly soluble in water (0.02 g/100 mL), but its ionic hydrochloride is readily soluble (5.7 g/100 mL).



morphine
solubity in water: 0.02 g/100 mL



morphine hydrochloride
solubility in water: 5.7 g/100 mL

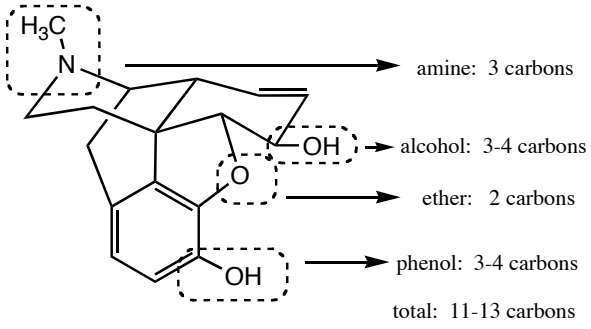
Whether an organic compound is soluble in water or not can be estimated using the concept of the **solubility potential** of the functional groups present in the molecule. The **solubility potentials** for different functional groups have been calculated empirically by T. Lemke. In a polyfunctional molecule, each functional group contributes to the overall solubility; the more functional groups present in a molecule, the larger the number of carbons that the molecule can have and still be soluble in water. For the present discussion we will consider that a compound is soluble if its solubility is at least 1 g/100 mL. Lemke estimated the solubility potential as the number of carbons that each functional group will help dissolve. If the sum of the solubility potentials of all the functional groups present in a molecule is larger then the total number of carbon atoms in the molecule, the compound will be soluble; if smaller, it will be insoluble. A table of solubility potentials is shown below (Table 1).

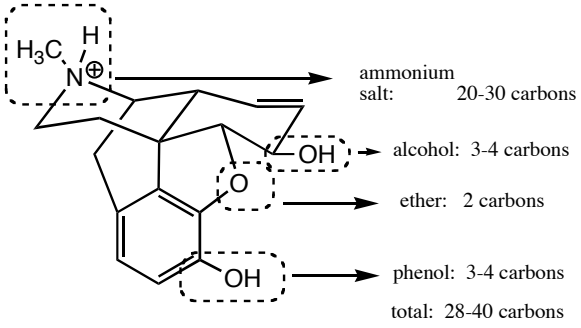
Consider for example the case of morphine. The molecule has 17 carbons. The functional groups present: amine, alcohol, ether and phenol have a combined solubility potential of only 11-13 carbons, thus morphine is expected to be insoluble in water (expected to have

a solubility lower than 1 g/100 mL). The experimental solubility value of 0.02 g/100 mL confirms that. By protonation of the amino group with HCl, the ammonium salt is formed and its presence increases the solubility potential by 20-30 carbons, bringing it to a total of 28-40 carbons which is larger than the total number of carbons in the molecule. Thus, morphine hydrochloride is expected to dissolve in water. The experimental solubility value of 5.7 g/100 mL confirms that.

Table 1. Solubility Potential

Functional Group	**Solubility Potential** (in a polyfunctional molecule)
Alcohol	3-4 carbons
Phenol	3-4 carbons
Amine	3 carbons
Carboxylic acid	3 carbons
Ester	3 carbons
Amide	2-3 carbons
Ether	2 carbons
Aldehyde	2 carbons
Ketone	2 carbons
Urea	2 carbons
Charged groups (N+: ammonium salts; O^-: carboxylates, phenolates, sulfates; N^-: sulfonamides)	20-30 carbons





Effects of pK_a. In this section we will discuss how the pK_a of a drug **affects** its **pharmaceutical**, **pharmacokinetic** and **pharmacodynamic phases**.

Ionization of organic compounds plays a crucial role in their solubility, therefore, a knowledge of the pK_a values of a drug molecule is of paramount importance to the medicinal chemist. Let's consider the dissociation of an acid HA:

$$HA + H_2O \underset{}{\overset{K_a}{\rightleftharpoons}} A^- + H_3O^+$$

As you remember from our discussion of acids and bases, the following relationship holds (Henderson-Hasselbalch equation):

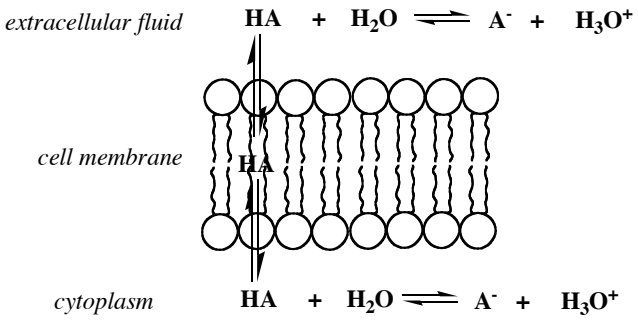
$$pH - pK_a = \log\frac{[A^-]}{[HA]} \qquad (2)$$

When the pH = pK_a, it follows that:

$$0 = \log\frac{[A^-]}{[HA]} \Rightarrow [A^-] = [HA]$$

which means that when the pH is equal to the pK_a, the concentration of the undissociated acid, [HA], equals the concentration of the anion, $[A^-]$, or in other words, half the molecules are in the dissociated or ionized form and half are undissociated (neutral in charge). (See section 9, *Acids and Bases*, Supplemental Material).

In crossing the cell membrane a pharmaceutical has to move from the aqueous environment of the extracellular fluid to the nonpolar interior of the cell membrane and from there to the aqueous cytoplasm. Therefore, its solubility in both aqueous and nonpolar solvents is of crucial importance. **Compared to undissociated molecules (HA**), **ions (A^-) are more soluble in water but less soluble in a nonpolar environment** such as that found in the cell membrane's interior. Only uncharged, undissociated molecules are able to cross the nonpolar environment of the cell membrane. This means that HA will be able to cross the membrane but A^- will not.

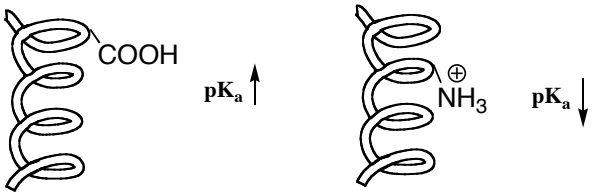


When the medicinal chemist is designing a new drug, he/she must consider the solubility of the molecule from the pharmaceutical perspective: is the drug soluble in water; is it dissolving in the GI tract? And also from the pharmacokinetic perspective: Is the drug crossing the membrane barriers and getting to the receptors? Is it soluble in lipids?

High solubility in water favors the pharmaceutical phase by ensuring easy delivery of the drug, but it may prevent an easy transport across the membranes making the

pharmacokinetic phase more difficult. Most of the drugs in use for medicinal purposes have pK_a values in the range of physiological pH (5-8). Thus, they exist as a mixture of dissociated and undissociated species in equilibrium. This ensures solubility in both water and lipids. The dissociated molecules, A^-, are responsible for the water solubility of the drug and, thus, guarantee an easy delivery, whereas the molecule in its neutral, undissociated form, HA, is able to cross the membranes. As the compound crosses the membrane and the concentration of HA diminishes in the extracellular fluid, A^- gets protonated to reestablish the equilibrium. This keeps happening until all (or most) of HA crosses the membrane. (We will come back to the effects of pK_a and solubility on the pharmacokinetic phase when we discuss partition coefficients, section 4).

The pK_a of the drug molecule also affects its pharmacodynamic phase. The drug molecule binds to receptors mainly through H-bonds and ion-ion interactions and thus, a knowledge of the **dissociation states of the drug and the receptor** is crucial. This is usually easier said than done since the microenvironment around the receptor's binding site will affect the pK_a values of the functional groups involved in the binding. Receptors are primarily made of a protein backbone from which polar functional groups, such as, -OH, $–COO^-$ and $–NH_3^+$ emerge. In the nonpolar environment of the protein backbone, the pK_a of carboxylic acids increases because they have less tendency to dissociate than in an aqueous environment, in which the pK_a is normally measured (this was discussed in section 7.6, *Acids and Bases*, Supplemental Material). Thus, the side chain of a glutamic acid residue that is expected to have a pK_a of 4.25 in aqueous solution, may have a pK_a of 8-9 in the binding site of a protein. Likewise, an ammonium group buried inside of a protein has a lower pK_a, (higher tendency to shed its proton) because the nonpolar environment favors the neutral amino form *vs*. the charged ammonium salt.



When an amino group is close to a carboxylic acid, as it is often the case in a receptor's binding site, the ionization of both groups is favored because the resulting ions are stabilized as a salt bridge. This means that the pK_a of the carboxylic acid decreases and the pK_a of the ammonium salt increases.