Medicinal Chemistry

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Medicinal Chemistry

Medicinal chemistry is the branch of science that studies pharmaceuticals and their mode of action in the organism. **Pharmaceuticals** are substances, other than food, that are administered to alleviate the effects or treat the causes of disease. Medicinal chemistry draws from many fields of science: organic chemistry, physical chemistry, biochemistry, molecular biology, physiology and computer sciences, just to mention a few. Here we will discuss in some detail the area where medicinal chemistry and organic chemistry intersect.

By the end of our discussion you will look at organic chemicals from a different light. You will be able to examine any organic chemical and evaluate its potential as a pharmaceutical. You will not be able to tell whether the chemical would make an ***effective*** pharmaceutical or not, that comes only after long experimentation, but you will be in a position to judge if the compound has the ***potential*** to be one. To this effect you will learn some of the most important ideas and tools in the design of new drugs such as the therapeutic index, biophores, pharmacophores, solubility potentials, lipophilicity constants and quantitative structure-activity relationships.

I hope that this fresh and different look at organic chemistry will make you appreciate the full potential of this fascinating science.

1. A Little History

King Charles II of England died of kidney failure after having a severe seizure, or did he? E. A. Swinyard in his, "*History of the Antiepileptic Drugs*," describes what may have actually killed the king. Patient beware.

> *'In 1685, the king fell backward and had a violent convulsion. Treatment was begun immediately by a dozen physicians. He was bled to the extent of 1 pint from his right arm. Next, his shoulder was incised and cupped, depriving him of another 8 oz. of blood. After an emetic and 2 purgatives, he was given an enema containing antimony, bitters, rock salt, mallow leaves, violets, beet root, chamomile flowers, fennel seed. Linseed, cinnamon, cardamom seed, saffron and aloes. The enema was repeated in 2 hours and another purgative was given. The king's head was shaved and a burn blister was raised on his scalp. A sneezing powder of hellebore root and one of cowslip flowers were administered to strengthen the king's brain. Soothing drinks of barley water, licorice and sweet almond were given, as well as extracts of mint, thistle leaves, rue, and angelica. For external treatment, a plaster of Burgundy pitch and pigeon dung was liberally applied to the king's feet. After continued bleeding and purging, to which were added melon seed, manna, slippery elm, black cherry water, and dissolved pearls, the king's condition did not improve and, as an emergency measure, 40 drops of human skull extract were given to allay convulsions. Finally bezoar stone was forced down the king's throat and into his stomach. As the king's condition grew increasingly worse, the grand finale of Raleigh's antidote, pearl julep, and ammonia water were pushed into the dying king's mouth.'*

Further treatment was rendered more difficult by the king's death.

We think that our medicine has come a long way since Charles II's demise and it certainly has, but we should not fail to notice that the twelve doctors gathered around the king were probably the best in England, all at the top of their game and administering the best medicine that money and science could buy. Three hundred years from now, will our chemotherapies fare better than the king's remedies? We hope so.

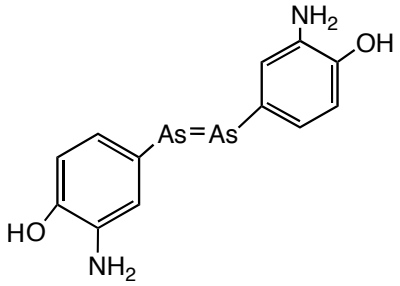
The major pitfall in the king's doctors approach was a lack of experimentation and scientific evidence. The best medicine that England could buy in 1685 hadn't caught up with the principles laid down by Avicenna almost seven hundred years earlier. Ibn Sina, or Avicenna as he is known in English, was a Persian physicist, mathematician, poet, astronomer, chemist and Islamic philosopher who is often regarded as the father of modern medicine. He introduced the concepts of infectious diseases, experimental medicine and clinical trials among many others. In his 1020 *Canon of Medicine* he laid out the rules and principles for testing the effectiveness of new drugs. A millennium later, they are still relevant and can be summarized as follows:

1) "The drug must be free from any extraneous accidental quality."
2) "It must be used on a simple, not a composite, disease."

3) "The drug must be tested with two contrary types of diseases, because sometimes a drug cures one disease by its essential qualities and another by its accidental ones."
4) "The quality of the drug must correspond to the strength of the disease."
5) "The time of action must be observed, so that essence and accident are not confused."
6) "The effect of the drug must be seen to occur constantly or in many cases, for if it did not happen, it was an accidental effect."
7) "The experimentation must be done with the human body, for testing a drug on a lion or a horse might not prove anything about its effect on man."

By the end of the nineteenth century western medicine hasn't progressed much from the days of Charles II. It was still a mixed bag of superstitions, half truths and folk remedies all kneaded together with a large dose of magical thinking under the false pretense of science. For instance, the recommended cure for syphilis was heating the patient in a sauna-like enclosure while breathing mercury fumes. The patient was guaranteed not to die from syphilis. Instead he would die of suffocation, anemia, kidney, heart or liver failure all caused by the mercury poisoning, a fact that many physicians apparently failed to notice. This was the state of affairs in medicinal chemistry only a hundred years ago.

…And along came Ehrlich. Paul Ehrlich was a Prussian doctor who developed the concept of the "magic bullet", a chemical that kills an infecting microorganism while the host remains unharmed. Despite its name, his approach was anything but magical. Ehrlich and coworkers systematically tried hundreds of different chemicals against the bacterium that caused syphilis until they found their "magic bullet" in an arsenic-containing aromatic compound, which was marketed in 1910 under the trade name of Salvarsan. Ehrlich's finding can be considered the beginning of modern medicinal chemistry. It paved the way for the discovery of sulfa drugs, penicillin and other antibiotics.



Salvarsan

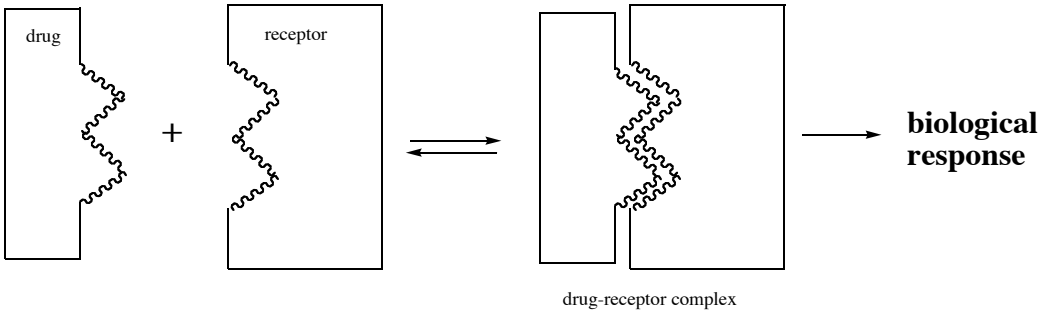
For more than 4500 years, the life span of humans remained almost unchanged at around 30-40 years. From 1750 until 1850 life expectancy was about 45 years. At the time of Ehrlich's experiments in the early 1900's it has risen to 46 years for males and 47 years for females. By the year 2000, life expectancy in the US was 72 years for males and 79 for females. What caused such a dramatic increase after millennia of rather constant numbers? The answer to this question can be found, if not completely at least in great part, in the development of organic chemistry and the birth of modern medicinal chemistry.

2. Basic Principles of Drug Design: Drug administration and distribution

A **drug** is a natural or synthetic substance, other than food, that when administered produces a noticeable response in the organism.

Drug molecules elicit their biological response by binding to specific sites called **receptors**. Receptors are structures made mainly of proteins and usually attached to the cell membranes. The interaction between the receptor and the drug molecule is very specific. Only certain molecules are able to bind to a specific receptor. Some of the properties of the drug molecule that control its binding include:

- functional groups present
- size and shape
- polarity
- ionization state
- capacity to form H-bonds



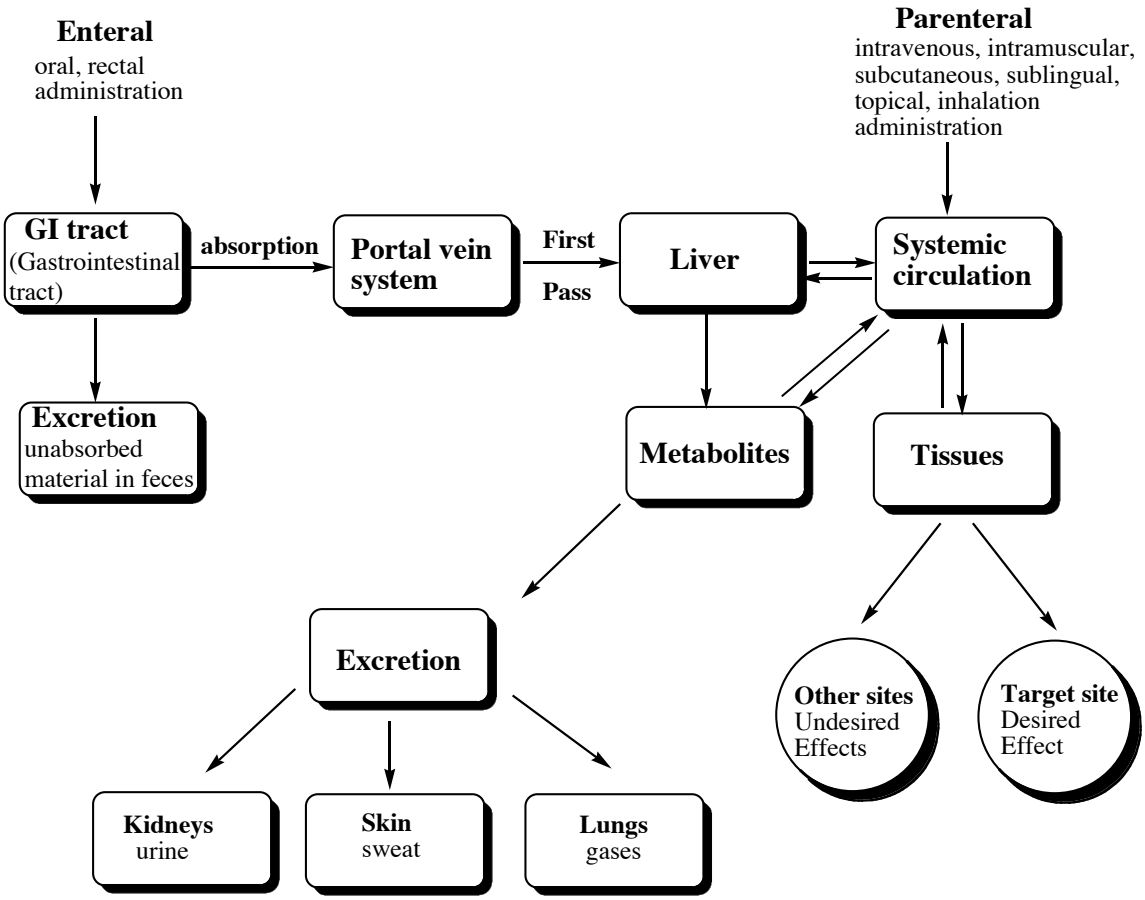
The binding between the drug molecule and the receptor is usually temporary. The **drug-receptor complex** is held together by intermolecular interactions such as ion-ion, dipole-ion and dipole-dipole interactions and H-bonds. Covalent bonds are not usually involved in the formation of these complexes (exceptions to this include the covalent bonds between penicillins and the bacterial enzyme transpeptidase and between antitumor alkylating agents and DNA).

From the moment a drug is administered until its excretion in urine, feces, lung gases or sweat the molecule undergoes different processes such as dissolution, ionization, absorption, binding to carrier proteins in the blood, crossing membranes, binding to the receptor and finally metabolism and degradation.

The most common ways of drug administration are **enteral** and **parenteral**. In **enteral administration** the drug enters the body orally or rectally and is absorbed through the stomach and intestine linings. After absorption in the **gastrointestinal tract** (GI tract), the drug molecule is carried by the portal vein system and delivered to the liver where it undergoes a "**first pass**" of metabolism. This first pass may result in the drug's degradation and loss of biological activity. From the liver the drug is transported to the rest of the body by the **systemic circulation**. The systemic circulation is the portion of the cardiovascular system that carries oxygenated blood from the heart to the tissues and

deoxygenated blood from the tissues back to the heart. In the tissues, the drug molecules or its metabolites reach the target sites where they elicit their desired (and often undesired) effects. The drug or its metabolites are finally excreted through the urine, sweat and gases produced in the lungs.

In **parenteral administration** the drug enters the body intravenously (injected into the veins), intramuscularly (injected into the muscles), subcutaneously (injected under the skin), sublingually (absorbed under the tongue), topically (applied on the skin) or by inhalation and is carried directly by the systemic circulation to the tissues and final targets. In parenteral administration the drug avoids the first pass through the liver before it reaches its final destination, and thus it has a better chance of reaching its target site intact.



From the moment the drug molecule is absorbed until it reaches the receptor and finally is metabolized and eliminated, it must cross several barriers in the form of cell and organelle membranes. For convenience, this long and complex journey has been divided into three distinct phases called **pharmaceutical**, **pharmacokinetic** and **pharmacodynamic**. The pharmaceutical phase is concerned with the question: *is the drug getting into the patient?* The pharmacokinetic phase deals with the question: *is the drug getting into the site of action, the receptor?* And finally, the question addressed in

the pharmacodynamic phase is: *is the drug producing the desired pharmacological and therapeutic effects?*

The **pharmaceutical phase** encompasses the processes from the moment of **administration** until the drug is absorbed into the bloodstream. The **dosage form** of the drug is the physical form in which it is administered. The medicine can be in solution, in a tablet form or even in the vapor phase. It always contains the **active ingredient** (the drug or drugs responsible for the pharmacological effect) plus inactive ingredients called **excipients**. Excipients are used as **solvents** for the drug (water, alcohol and oil being the most common), **fillers** to provide bulk (such as dextrose, lactose, microcrystalline cellulose), **binders** to keep the ingredients together in a tablet (for example, gelatin and starch), **antioxidants** to extend the shelf life of the medicine, etc. When the manufacturer produces the medicine, the inactive ingredients as well as possible contaminants present in the active ingredient, must be given serious consideration because they may affect the absorption, transport and eventually the biological response of the drug.

When the drug is administered orally it must survive the attack of amylases (enzymes that break down polysaccharides) in the saliva, then the attack of acids and proteases (enzymes that break down peptides and proteins) in the stomach and finally the attack of an array of proteins (peptidases, lipases, proteases, ribonucleases, etc.) at the alkaline pH of the intestine. In designing a new drug, the medicinal chemist must consider all these potential degradation processes and decide on the best route of administration for the drug in question. For example, insulin (a small protein used to medically treat diabetes) is administered by subcutaneous injection rather than orally to avoid its hydrolysis by the proteases in the GI tract.

The **pharmacokinetic phase** encompasses all the processes that the drug molecule undergoes from the moment of absorption until it reaches the receptor. They include its **absorption**, **distribution**, **metabolism**, and **elimination** (ADME). In all these processes the drug must traverse a variety of barriers in the form of cell membranes.

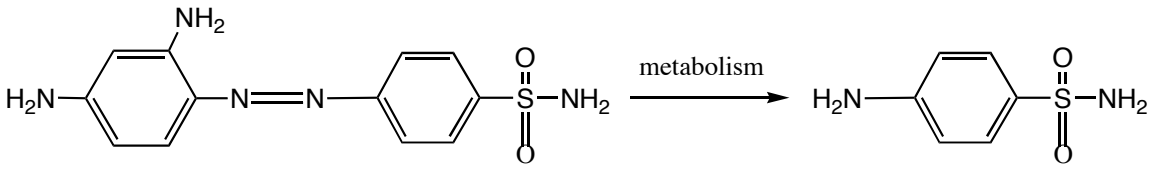
The **absorption** of the drug in the GI tract takes place mainly in the intestine. Little is absorbed in the stomach because of its smaller surface area. The intestine with its many folds provides a better conduit for absorption. To be absorbed, the drug molecule must cross the cell membrane which has a nonpolar core. Only uncharged molecules are able to cross this nonpolar barrier effectively. Thus, to be readily absorbed, the drug molecule must be uncharged at the point of absorption. Acidic compounds, such as carboxylic acids (pK_a 4-6) are largely dissociated at the intestinal pH (6-8.5) and, thus, are not easily absorbed through the intestine; they are more easily absorbed in the stomach where the pH is acidic (pH 1.4-2.1). Amines, on the other hand, are weakly basic (pK_a of the conjugate ammonium salt 5-9) and, thus, are uncharged at the intestinal pH where they can be easily absorbed.

One of the most important barriers a drug may need to cross is the **blood-brain barrier** (BBB) that protects the brain from chemicals in the blood. This barrier is made of tightly packed endothelial cells in the brain capillaries. Because of its tight packing, the BBB

restricts the movement of all molecules except for those which are small and soluble in lipids and, thus, can cross the barrier because of their high lipid solubility (for example oxygen, ethanol, steroid hormones). Very polar molecules and molecules with a molecular mass larger than 500 (except for those with specific transport system such as sugars and amino acids) cannot cross the BBB. Another barrier much like the BBB is the **maternal-placental barrier**. Chemicals that can cross the BBB can also cross the maternal-placental barrier. In designing new drugs, the medicinal chemist must consider whether the chemical should cross these barriers or not and modify its structure accordingly.

The main route of **distribution** is the circulatory system and to a much lesser extent the lymphatic system. In the bloodstream, hydrophobic drugs, which have very little tendency to dissolve in the aqueous serum, are transported by binding to carrier proteins such as human serum albumin.

Metabolism is the chemical transformation of the drug in the body. The products of such transformations are called **metabolites**. Metabolism begins in the mouth if the drug is taken orally and continues in the bloodstream by the reaction with blood enzymes. The liver is the most important place for metabolic processes such as reductions, oxidations and hydrolyses. If the drug is administered enterally (orally or rectally) it will undergo the first pass in the liver where it is likely to be metabolized. If the drug is rendered inactive by the liver metabolism, it should be administered parenterally so that the first pass is avoided. However, metabolism not always lowers the potency of drugs. Prontosil, the first sulfa drug to be commercialized (1930's), is effective only after it is metabolized in the body into sulfanilamide:



Prontosil
(inactive against bacteria)

Sulfanilamide
active against bacteria

Compounds such as Prontosil, that are inactive in their original form but are metabolized into active compounds in the organism are called **prodrugs**.

Elimination is the excretion of the drug and its metabolites. The main routes of excretion are the feces and the urine. Drug molecules which are very polar and, thus, very soluble in the aqueous serum (such as sulfonates and phosphonates) are easily and quickly excreted in the urinary tract. A rapid excretion lowers the **half-life** of the compound (the half-life is the time it takes for half the molecules administered to be excreted), making it necessary for the patient to take the drug more often.

In the **pharmacodynamic phase**, the drug interacts with the receptor and elicits its pharmacological effect. The interaction is very specific and relies on the complementarities of the drug molecule and the receptor. For example, if the drug molecule donates an H-bond, the receptor must have an O or N to accept it. The geometries of the drug and the receptor's binding site must also be complementary of one another. In designing effective drugs, the medicinal chemist should not only look into the drug's therapeutic effect caused by the binding to the desired receptor, but should also look into its toxicity caused by the binding of the drug or its metabolites to the undesired receptors.

In the following sections we will discuss some of the tools that the medicinal chemist has at his/her disposal to design effective drugs.

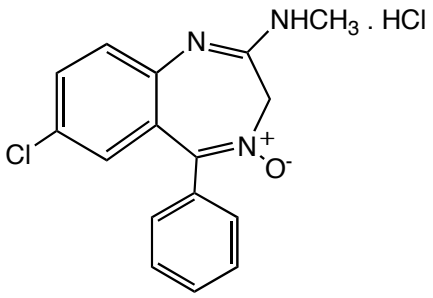
A summary of the pharmaceutical, pharmacokinetic and pharmacodynamic phases is outlined below.

Pharmaceutical phase	*from administration to absorption*
	Administration: **enteral** (oral, rectal); **parenteral** (intravenous, intramuscular, subcutaneous, sublingual, topical, inhalation) **Dosage form**: solution, tablet, vapor **Active ingredient:** pharmaceutical (drug) **Inactive ingredients** (**excipients**): solvents, fillers, binders, antioxidants
Pharmacokinetic phase	*from absorption to receptors*
	***A*bsorption**: GI tract; lungs; skin ***D*istribution**: circulatory system; lymphatic system ***M*etabolism**: in mouth, bloodstream, liver, other organs ***E*limination**: excretion in feces, urine, lung gases **Half-life**: time for half the molecules to go from administration to elimination
Pharmacodynamic phase	*interaction with receptors*
	Binding to receptors is driven by: - H-bonds - shape - polarity Binding elicits **pharmacological effect**

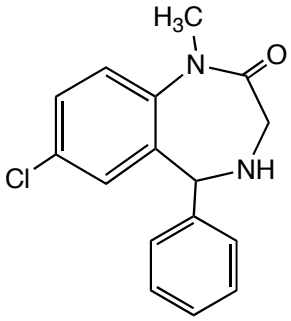
3. Rational Drug Design

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

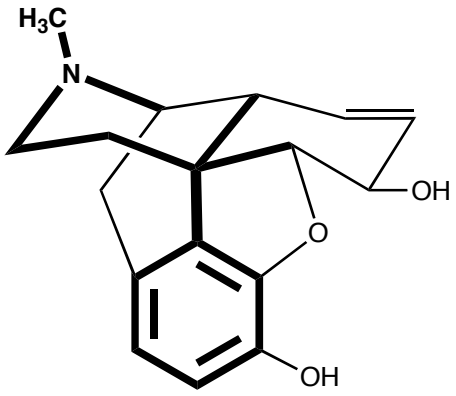
that kills 50% of the test animals and therapeutic ED_{50} is the effective dose that produces the maximum therapeutic effect in 50% of the test animals.

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

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**.

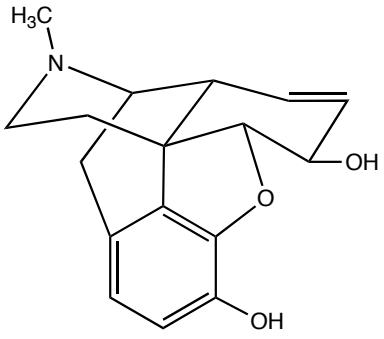
3.4 Identification of a pharmacophore

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.

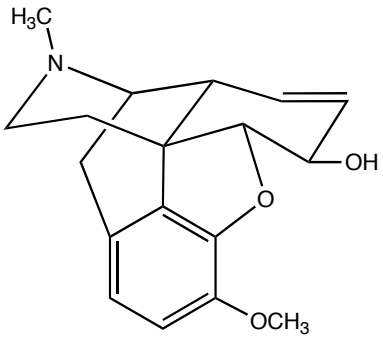
If the removal of a group of atoms leads to a decrease in potency, it can be concluded that those atoms were likely to be part of the pharmacophore. If the removal leads to an increase in potency, the conclusion would be that those atoms were not part of the pharmacophore but rather they constituted 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.

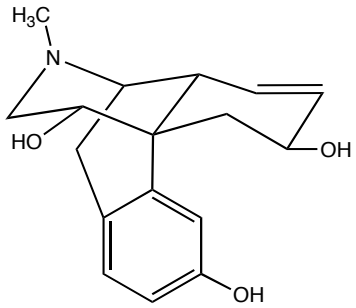


morphine



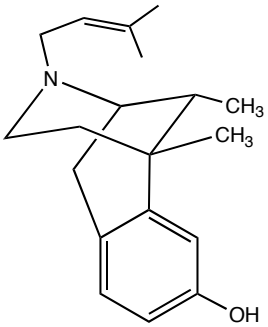
codeine

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

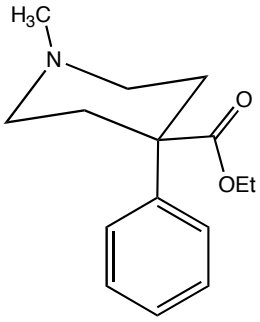


levorphanol

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.

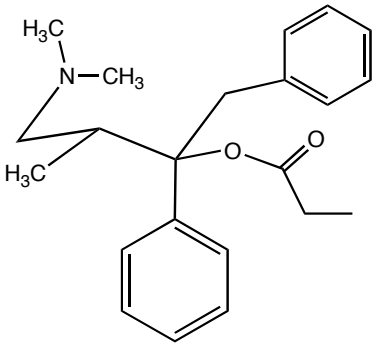


pentazocine

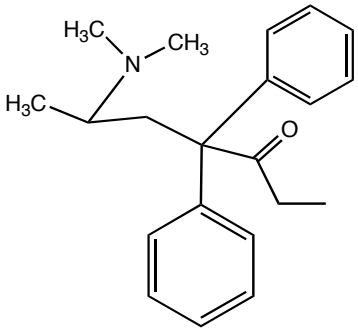


meperidine

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).

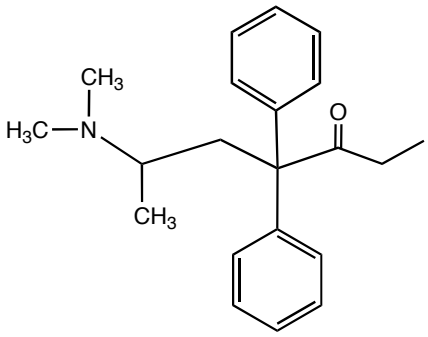


dextropropoxyphene



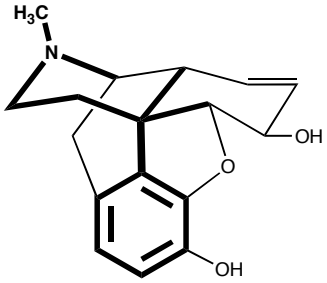
methadone

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.

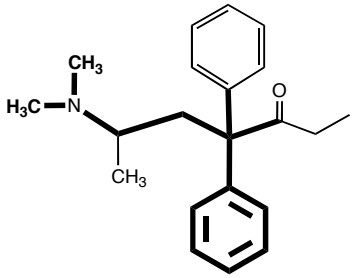


methadone

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

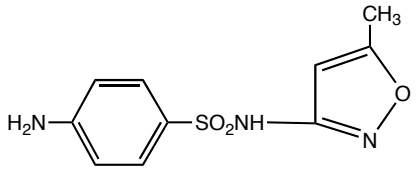


pharmacophore of methadone

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.

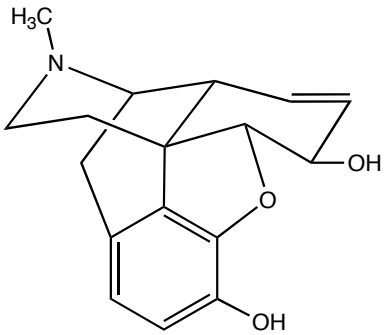
Solubility potential. Drugs administered orally must dissolve in the GI tract before they can reach the intended receptors. Since cells are made of about 65% water, water solubility is an essential property of most drugs. Drugs which are only sparingly soluble in water will be difficult to transport 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.



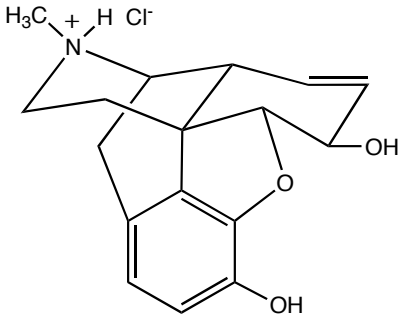
sulfamethoxazole

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

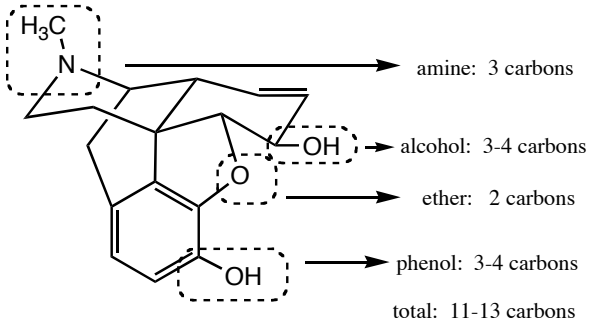
Whether an organic compound is soluble in water or not can be estimated using the concept of the **solubility potential** of the functional groups present in the molecule. The **solubility potentials** for different functional groups have been calculated empirically by T. Lemke. In a polyfunctional molecule, 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).

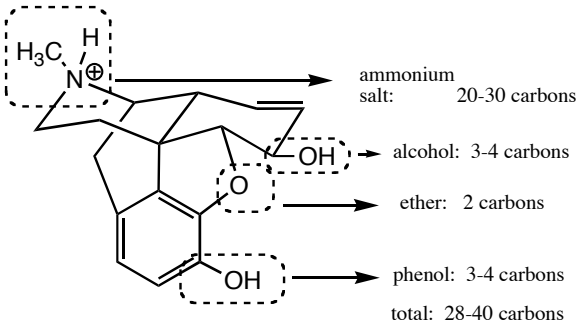
Consider for example the case of morphine. The molecule has 17 carbons. The functional groups present: amine, alcohol, ether and phenol have a combined solubility potential of only 11-13 carbons, thus morphine is expected to be insoluble in water (expected to have

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):

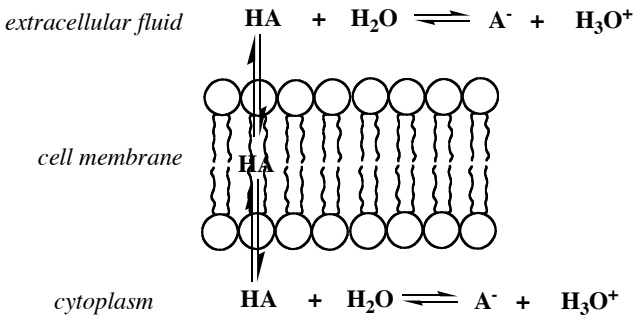
$$pH - pK_a = \log\frac{[A^-]}{[HA]} \qquad (2)$$

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.

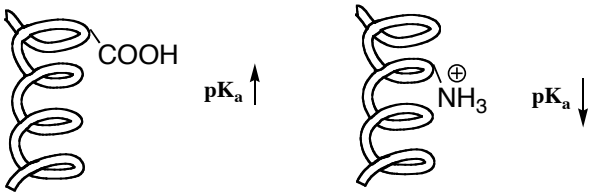


When the medicinal chemist is designing a new drug, he/she must consider the solubility of the molecule from the pharmaceutical perspective: is the drug soluble in water; is it dissolving in the GI tract? And also from the pharmacokinetic perspective: Is the drug crossing the membrane barriers and getting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