CHAPTER 18
MEDICINAL CHEMISTRY

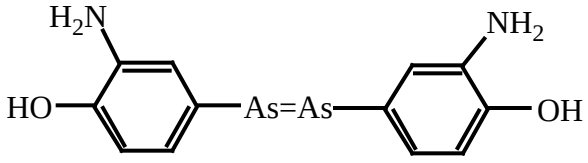
18.1 Introduction

The treatment of pain and disease is one of the most important goals of humankind. Since ancient times people have been using potions, natural products and even the dust of mummies for the treatment of health problems. The healing effects of remedies were often ascribed to spirits and mythical entities, but some of the herbal preparations did possess curative properties. In the 1800's scientists began to investigate potions to determine what chemicals were present that could cause the observed healing.

Thus, the early days of medicinal chemistry began with the study of naturally occurring materials that were effective in treating human disorders. The studies were tedious and required much sample purification and structure determination at a time when instrumental methods of analysis were unavailable. Also, screening methods for chemical efficacy against disease had to be developed so that humans were not used as trials.

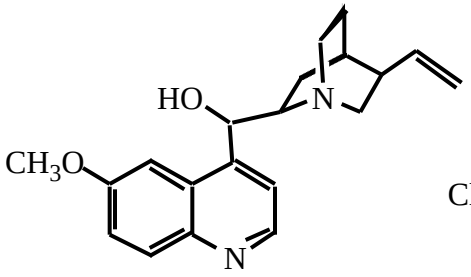
18.2. Antibiotics

Modern therapy by chemicals, chemotherapy, is attributed to Paul Ehrlich (Germany, Nobel Prize in 1908) who synthesized the first antibiotic, an arsenic compound patterned after an azo dye that he found to stain a microorganism selectively. The compound first called compound 606 was introduced commercially in 1910 as a treatment of syphilis under the name of Sylvarsan.

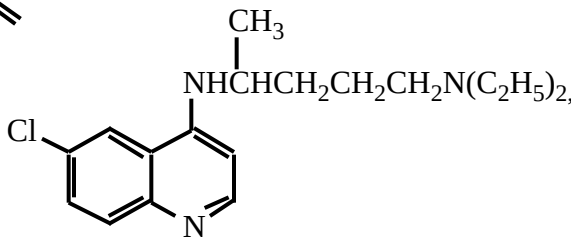


Arsphenamine
(sylvarsan)

Many compounds were investigated over the next 50 years as antibacterial agents. Some structures are very complex and necessitated the development of new synthetic organic reactions in order to prove their structures. An intense effort to develop medicinal agents against malaria was required because many soldiers were afflicted with the disease. Quinine, discovered active against malaria in 1990, was reasonably toxic, and other agents were required. Chloroquine (1946) was synthesized and found to be highly effective against malaria.

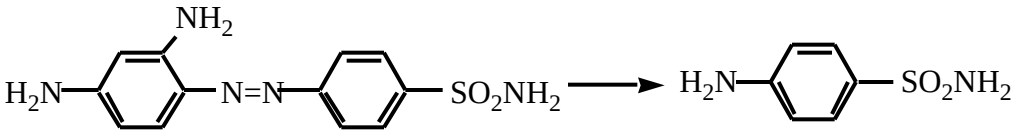


quinine
Isolated from cinchone bark.



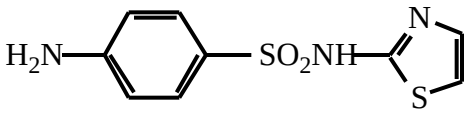
chloroquine

Careful studies of the antibacterial compound known as Prontisil (G. Domack, Nobel Prize, 1939), a dye that strongly stains proteins, showed that it was metabolized to sulfanilamide, a more effective antibiotic. Prontosil is therefore termed a **prodrug** as it is not the substance responsible for the biological effect but it does produce the effective drug.



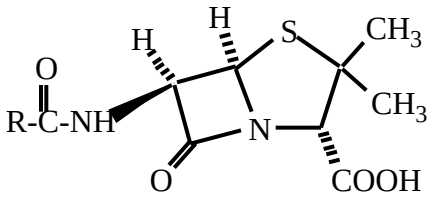
Prontisil sulfanilamide

These studies led to the investigation of compounds containing the sulfonamide function as potential antibiotics, and led to a number of very effective antibiotic agents. Many of these compounds are sulfanilamides that have an organic group in place of one of the hydrogens of the sulfonamide. Sulfathiazole proved to be a highly effective antibiotic.

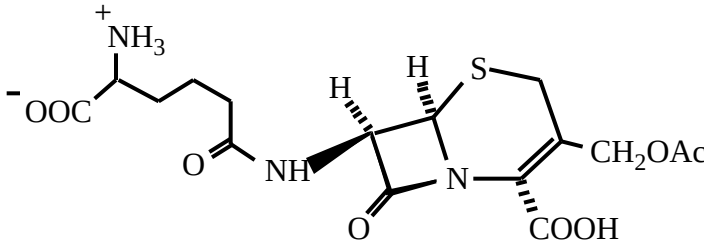


sulfathiazole

As the search for better antibiotics continued, a revolutionary drug was developed by H. W. Florey and E. Chain in 1938. Penicillin was produced by microorganisms of mold and was found to inhibit the growth of other microorganisms. Penicillin was so important in the treatment of bacterial infections that many research groups from all over the world combined their research efforts in the isolation, purification, testing and synthesis of penicillin drugs. The structurally related cephalosporin antibiotics were also discovered during this time.

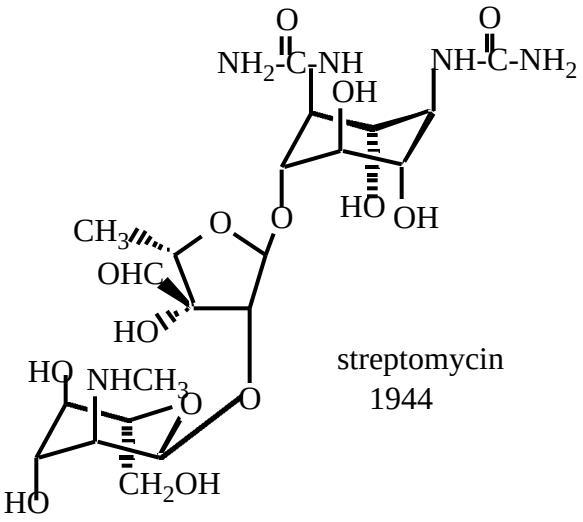


	R
Penicillin F	$CH_3CH_2CH{=}CHCH_2$
Penicillin G	$PhCH_2$
Penicillin V	$PhCH_2O$

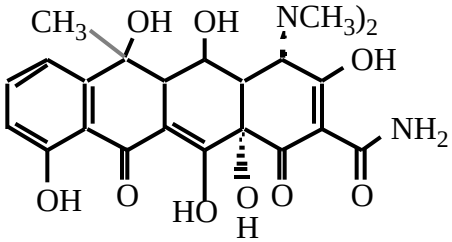


cephalosporin C 1956
broad spectrum antibiotic

The search for antibiotics continued to be successful with the isolation and structure determination of the complex antibiotics streptomycin and tetracycline.

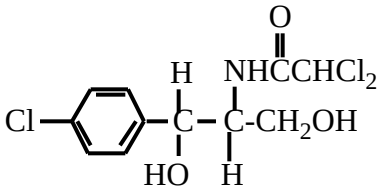


streptomycin
1944



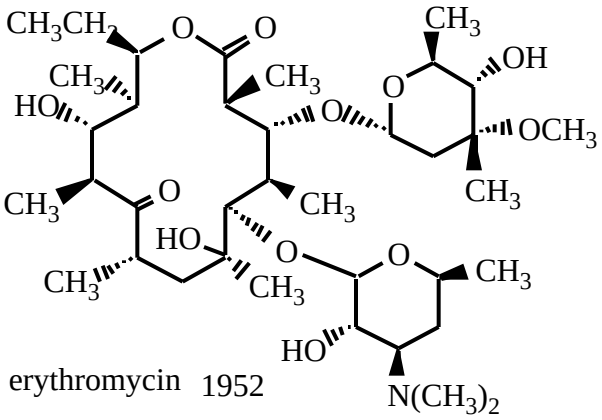
tetracycline 1953

Chloramphinacol, isolated in 1947, possesses a relatively simple structure. With its two chiral carbons, it has four stereoisomers. Studies at Parke, Davis and Co. showed that only the R, R stereoisomer is active against microorganisms. This finding began the study of stereoisomers as medicinal agents.

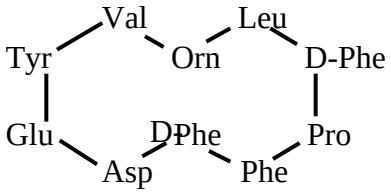


chloramphenicol 1947
treatment of typhoid fever

Antibiotic agents with large ring systems were also isolated. Erythromycin, a macrocyclic compound, is effective against penicillin resistant bacteria. Another large ring system that contains only amino acids is Tyrocidine A, a component of gramicidin antibacterial agents. Some cyclic peptides are used in the treatment of other diseases such as Hodgkin's disease.

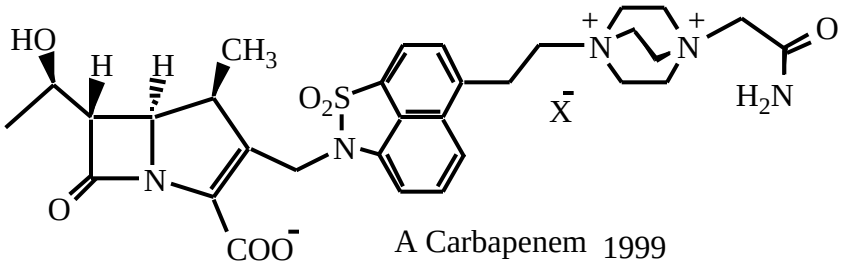


erythromycin 1952



Tyrocidine A 1939

The search for new antibiotics continues with an emphasis on discovery of drugs that are effective against drug-resistant bacteria. A βlactam class of antibiotics called carbapenems show promise with broad spectrum antibiotic properties. A new experimental carbapenem is shown below.



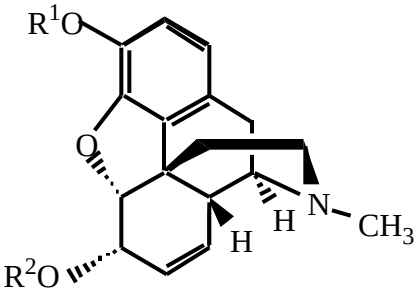
A Carbapenem 1999

18.3 Opiates

Opiates belong to a class of compounds known as alkaloids that are nitrogen containing substances found in several plant species. The naturally occurring nitrogen compounds found in dried opium seeds are called opiates and are well-known for their strong analgesic effects and for their highly addictive nature. Opium extracts have been used for many years to treat pain, but only in the early 1900's was the seed analyzed and found to contain over twenty alkaloids. Morphine accounts for about 10 % of the extract by weight. Scientists

studied morphine and similar compounds for many years until its structure was determined by synthesis in 1954. Two other pain-killing alkaloids with highly addictive properties are also found in opium, heroin and codeine.

Heroin is perhaps the most abused substance in today's society.



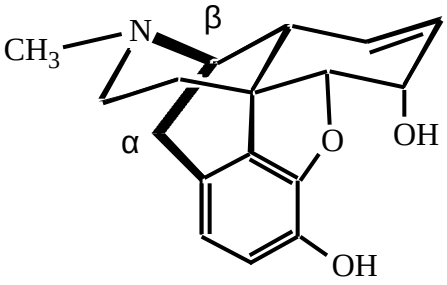
R^1, R^2= H Morphine

R^1, R^2= Ac Heroin

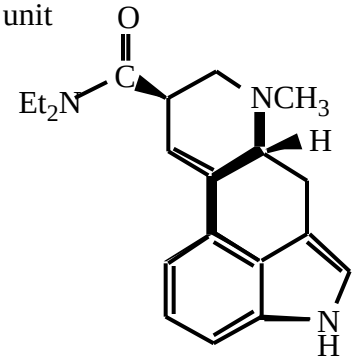
R^1 = H, R^2= CH_3 Codeine

Morphine, in medicinal chemistry, represents a very important lead compound for the derivation of new pain alleviating drugs. Morphine, and many other naturally occurring biological substances, contains the well-recognized β-phenethylamine structure outlined with heavy lines. This structural unit is also found in lysergic acid diethyl amide (LSD), another widely abused substance derived from an alkaloid.

β-phenethyl structural unit



Morphine

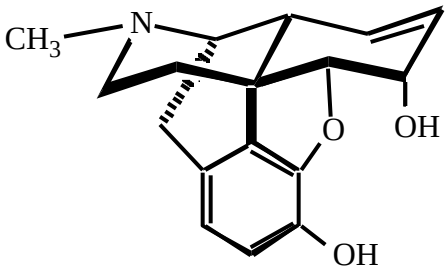


Lysergic Acid Diethyl Amide

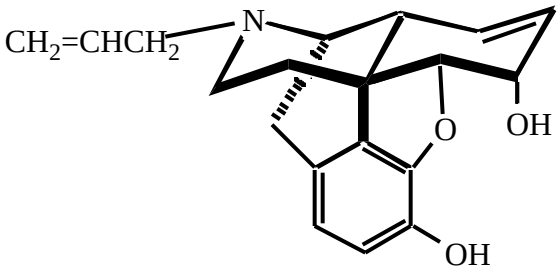
LSD

The many studies of morphine-like compounds have given some interesting facts about the structural requirements for the drug's activity. For

example, the N-methyl group, the secondary alcohol, and the alkene functions are unnecessary for drug activity. Replacement of the N-methyl with N-allyl produces nalorphine that acts against the activity of morphine and serves as a treatment for overdoses of morphine, but it has hallucinogenic side effects.

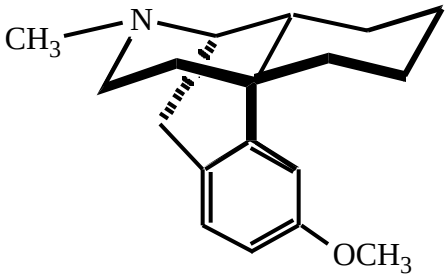


morphine



1941 nalorphine

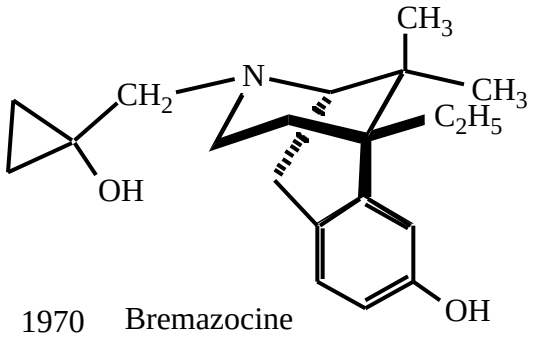
Modifications of the ring system are also possible and produce some interesting morphine-like drugs. Removal of the ether ring, along with the alcohol and alkene, produces after methylation, dextromethorphane a popular ingredient in cough syrup.



1956 dextromethorphane

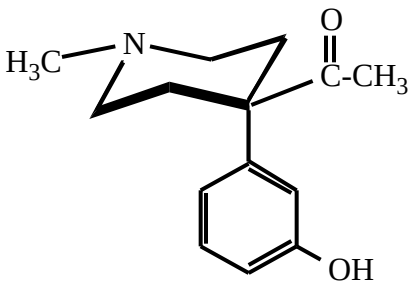
cough syrup

Removal of both the ether ring and the cyclohexenol ring, with addition of a cyclopropyl function on the nitrogen give bremazocine that is 200 times more active than morphine.



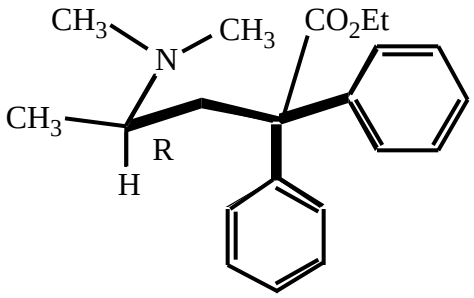
1970 Bremazocine

Further modification with removal of the ether ring, the cyclohexenol ring and the cyclopentane ring to leave a phenyl substituted piperidine ring produces the drug that is about six times as active as morphine.



1948 Ketobemidone

Finally removal of all the rings except phenyl produces the well-known methadone. Methadone is used in the treatment of morphine addiction because its side effects are less severe than that of morphine, but it is just as addictive.



1942 Methadone

Of course, thousands of compounds related to the morphine structure have been prepared and many without activity, and no compound has been found to halt the terrible addictive morphine properties. Used correctly, the morphine

family is an important class of analgesics, and their study represents an important contribution to the understanding of medicinal activity.

18.4 Methods of Drug Discovery

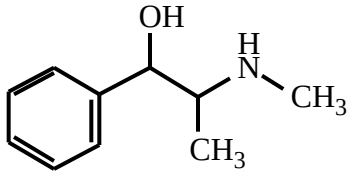
The discovery of new drugs is exemplified in the above sections on antibiotics and analgesics. The procedure is much more refined now than nearly a hundred years ago, but the steps in discovering new drugs or lead compounds to drugs are still similar.

18.4a Drug Screening

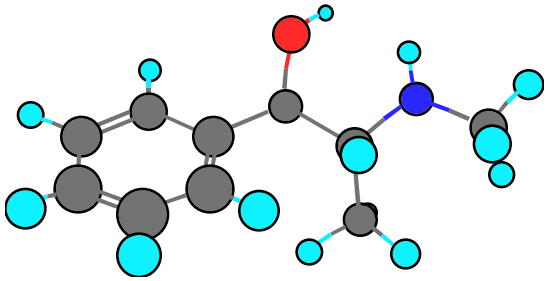
Perhaps the largest effort of the pharmaceutical industry is the search for new drugs. Many compounds from many sources, both natural and synthetic, are tested for effectiveness against many types of medical problems. Screening requires many involved tests in both test tubes and in live subjects. Analysts need to be very astute in their observations in order not to miss a new drug or to improperly evaluate an effective drug. Once a compound is found to be an effective medicinal agent, then it is the lead compound. New compounds are synthesized in the laboratory in order to find perhaps a better medicine or one with less toxicity. The process takes many years of intense work.

Some examples of compounds found in natural sources have been seen as the antibiotics or the analgesics. Scientists then follow up on the lead compounds and attempt to synthesize better compounds.

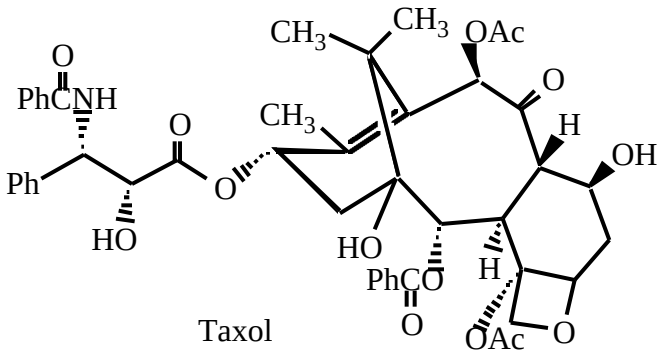
An older drug, ephedrine, was discovered in 1924 from the herbs of Chinese medicine as a treatment for breathing problems such as asthma. Medicinal chemists have modified the structure to provide a wide base of bronchodilator agents.



ephedrine

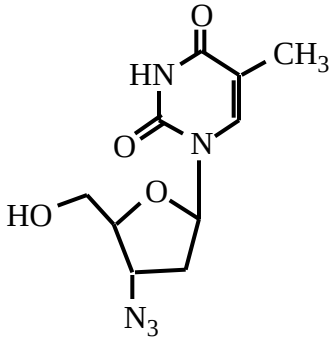


Taxol, is a very complicated substance found in the California yew tree bark. It is a very important new anti-cancer treatment, but it is in very short supply. Chemists are very active in the synthesis of taxol and related compounds in order to produce more effective and more available materials.



Taxol

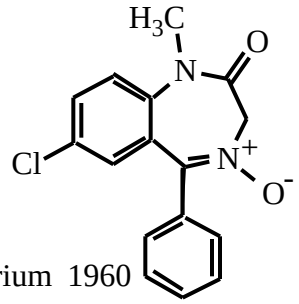
Other interesting drugs have been synthesized in the laboratory but their effectiveness as medicines was not discovered immediately. AZT, an important agent against HIV, was first prepared many years ago but was later screened as an anti-HIV agent because the AIDS virus was discovered after AZT was prepared.



3"-adido-3'-deoxythymidine

AZT

Librium, an important tranquilizer and somewhat abused drug, was tested two years after its first laboratory synthesis because it was not originally thought to be an important structure. As a lead compound Librium has led to several other important tranquilizers.



Librium 1960

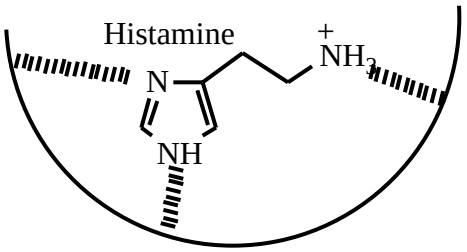
The examples shown above serve to illustrate the beginning of a process. Many other cases are known where drug discovery is based on unusual natural products, or materials based on herbal remedies, or from fortuitous accidents.

18.4b Drug Mechanism

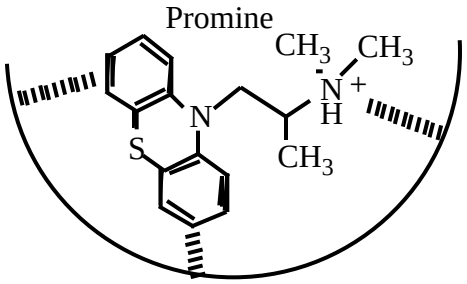
The mechanism of how a drug exerts its effect is a very significant finding in the determination of new and improved drugs. Early medicinal chemists had to rely on screening and drug modification for new drugs, but the inclusion of modern mechanistic theories into drug searches advances the field considerably. However, the fortuitous discovery of a drug without much knowledge of how or why it works still plays an important role in medicinal chemistry.

A major finding in drug mechanism is that many drugs react with a **receptor protein** that occurs in cell walls or in the cytoplasm of cells. The interaction between drug and receptor is similar to the enzyme-substrate interaction in which the drug must fit into a receptor cite by its molecular shape. The drug in its interaction with the receptor may cause an enhanced biological response (agonist), a decreased biological response (antagonist) or be delivered to a site in the cell where the drug effects beneficial changes. The body contains many receptor proteins that are present as receptor proteins for natural processes. The drug must compete with the natural chemicals for the protein in order to be effective.

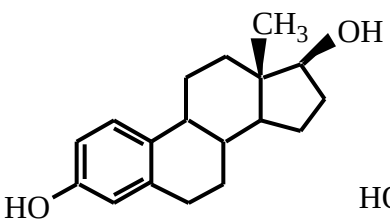
The study of histamine and its receptor permitted rational design of new drugs. In this case, histamine was found to bind with a receptor protein-called the histamine-2 receptor - as shown below. New drugs were deigned that would mimic histamine binding but would not permit histamine to bind. The effects of these types of drugs were to act as antihistamines.



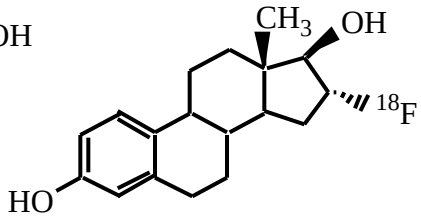
The interaction of the antihistamine promine with the histamine receptor is shown below.



A novel approach to the treatment of breast cancer is the use of agents that bind with the estrogen receptor protein. Mammary cancers are known to have a buildup of estrogen receptor protein and estradiol, the primary female hormone. An estradiol analog with a radioactive fluorine atom in the 16α position competes very strongly for the estrogen receptor protein. Thus the mammary cancer becomes labeled for diagnostic purposes and the radiation produced from the ^{18}F can destroy the nearby cancer cells. The radioactive fluorine compound is called a radiopharmaceutical.



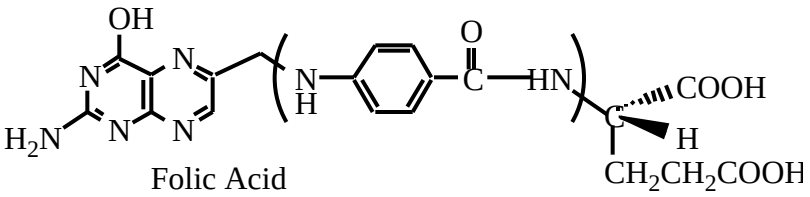
17β-estradiol



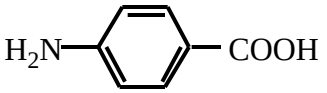
16α-[18]Fluoro-17β-estradiol

A very important type of drug is one that interacts with an enzyme. The enzyme is fooled into using the drug as a natural substrate, but the drug does not continue the function of the enzyme and its activity is inhibited. Such drugs are

called mechanism-based suicide inhibitors. The reaction mechanism is used to design the drug and the enzyme commits suicide when it accepts the drug. An example of this behavior is found with many antibiotic drugs that inhibit the growth of bacterial cells. Bacterial cells must synthesize folic acid whereas humans obtain folic acid from food. An enzyme named dihydropteroate synthetase is responsible for the synthesis of folic acid in a process that uses para-aminobenzoic acid. The enzyme also accepts sulfanilamide because of its similarity in structure to para-aminobenzoic acid, but the sulfanilamide binds tightly with the enzyme and prevents the enzyme from participating in further synthesis of folic acid. The cell dies without the folic acid.

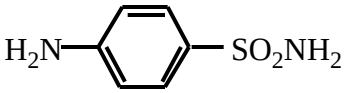


Folic Acid



p-aminobenzoic acid

substrate



sulfanilamide

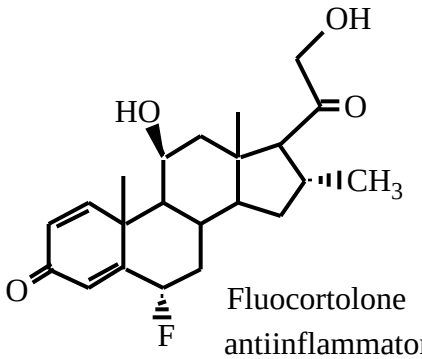
inhibitor

The mechanism of action of most drugs involves receptor binding and enzyme inhibition. The study of enzymes and the structure of active sites are thus major efforts in medicinal studies.

18.4c Drug Alteration

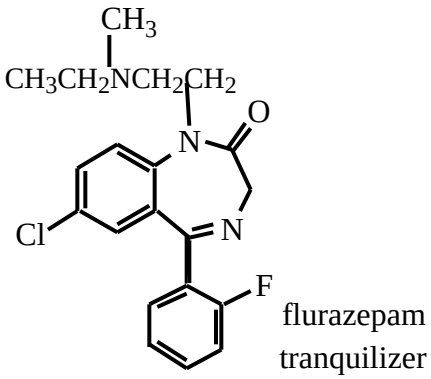
Once a lead compound with medicinal properties is discovered changes are done synthetically in the compound. Such changes were observed in the sulfa drugs above in which different substituents were placed on the nitrogen. Many changes in the structure of morphine-related compounds (opiates) were shown in which alkyl groups were changed and rings were removed systematically. The important finding is the lead compound, but very often the altered drug shows better properties or less toxicity. Another alteration of drugs is the incorporation of fluorine. Fluorine atoms allow the original structure to retain its molecular size because fluorine is a small atom. Also, the fluorine is very electronegative and thus introduces polarity into the molecule. The change can sometimes be very beneficial in drug discovery.

Steroid compounds are often used as anti-inflammatory agents and many with incorporation of fluorine atoms are effective at lower doses, as is the case with fluorocortolone shown below.



Fluocortolone
antiinflammatory

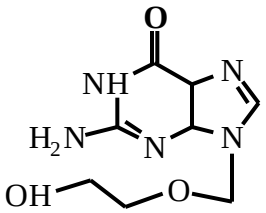
Synthetic incorporation of fluorine into other drug systems is also well-known and very effective. Fluorazepam is an often prescribed relative of valium.



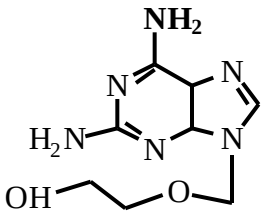
flurazepam
tranquilizer

Once a drug is discovered many experiments are conducted to determine the pharmokinetics of the drug. These studies show how the drug is delivered to the site of action, how the drug is distributed throughout the body and how the drug is metabolized. The results of the studies sometimes provide clues as to how the drug could be altered to improve its pharmokinetic properties and effectiveness.

Biodistribution studies of the drug acyclovir, used in the treatment of herpes simplex virus, show that it is only absorbed about 15% when taken orally. A better absorption is found when the carbonyl group is replaced by an amino group.

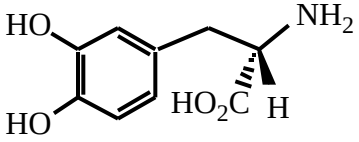


Acyclovir

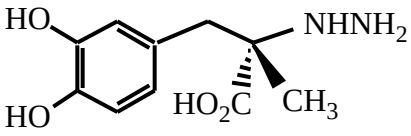


amino-acyclovir

L-Dopa is a well-know drug for the treatment of Parkinson's disease. It is actually a prodrug because it is decarboxylated to the amine that is the active drug. Only about 1 % of L-dopa actually enters the central nervous system because it is decarboxylated by enzymes in the liver. A solution to improving the uptake of L-dopa is to add another drug that inhibits the decarboxylation enzyme thus permitting more L-dopa to reach the active site. The administered dose of L-dopa can be reduced more than 50 % when used in conjunction with the enzyme inhibitor.



L-Dopa



enzyme inhibitor

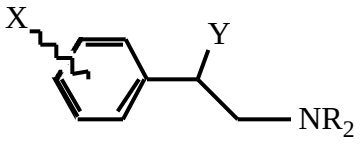
18.5 Computational Methods

18.5a Hansch Equation

A computational method to predict drug effectiveness based on physical properties instead of molecular structure was introduced by Hansch in 1960. In this method parameters on the hydrophobic (water dislike) character of the compound (P), the hydrophobic contributions of the substituents (p), electronic characteristics of the substituents (s, known as Hammett constants) and steric factors (E_S, known as Taft constants) are correlated with drug effectiveness. The general Hansch equation is shown below.

drug effectiveness $= k_1 \log P + k_2\ p + k_3\ s + k_4\ E_S + k_5$

The k values indicate the significance of each term. When applied to a number phenethylamine compounds related to ephedrine, the drug effectiveness was found to depend only on substituent (X and Y) hydrophobic and electronic properties.



drug effectiveness $= 1.2\,\pi - 1.6\,\sigma + 7.9$

The equation says that compounds with highly hydrophobic (positive p values) and electron donation (negative s values) will prove to have greater effectiveness.

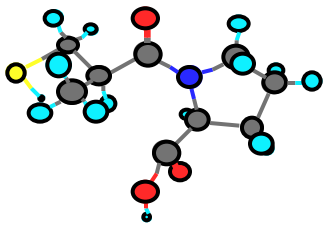
The Hansch equation for the above compounds is relatively simple, but for some drugs a very complicated relationship is observed. The Hansch study of drugs requires that many compounds be evaluated and correlated with the various parameters, not a simple task.

18.5b Molecular Modeling

Modern high-speed computers have the capability of carrying out many complicated calculations in a very short time. The structural parameters for a specific protein receptor (or enzyme) can be placed in a computer along with structural parameters for a drug molecule (real or hypothetical) and the computer will calculate and graph the fit of the drug with the protein active site. The molecules may be manipulated in three dimensions to enhance the view and show the best fit of the "docking" of the molecules. Such molecular modeling can be used to predict the structure and effectiveness of new medicinal agents.

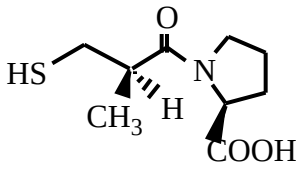
Below is a model of captopril, a blood pressure medication. This model is produced by drawing the structure with a ChemDraw program, and placing it into a Chem 3D program. The structure is presented in color and may be manipulated in 3D with the program. Examination of the structure when one has the shape of the enzyme active site can give information about the desired location of substituents.

Captopril

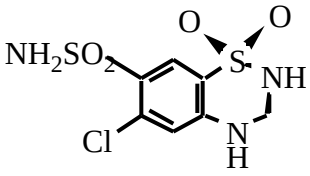


18.6 Successful Drugs

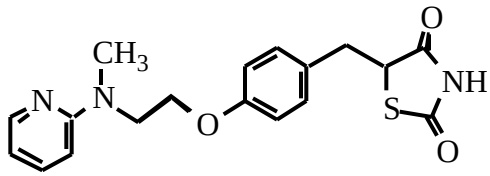
Medicines have been developed to treat almost every disease. The development of medicinal agents takes many years of intense work by many scientists skilled in different fields. A few of the commonly prescribed medications are shown below.



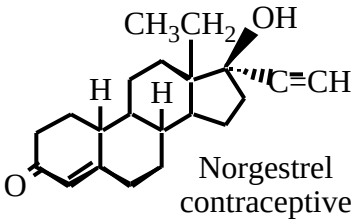
Captopril
anti-hypertensive



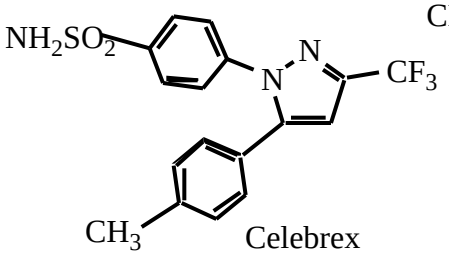
HCTZ (Hydrochlorothiazide)
diuretic



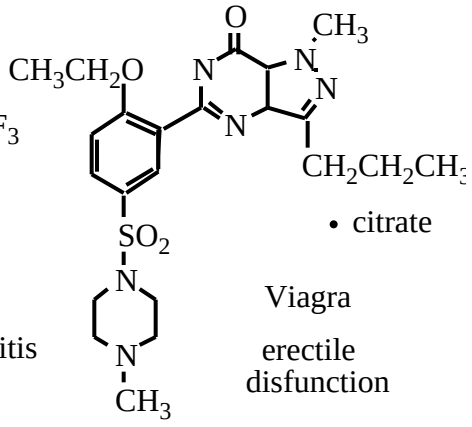
Avandia (Rosiglitasone)
anti-diabetic



Norgestrel
contraceptive



Celebrex
Rheumatoid arthritis
Osteoarthritis



Viagra
erectile
disfunction

18.7 Summary

Although various treatments for diseases have been used for centuries, the early history of chemotherapy, chemical treatment of disease, started with *Paul Ehrlich in the 1900' and his discovery of antibiotic compounds.* Many antibiotics with a wide variety of applications and structures are now known. Drugs known

as p*rodrugs* that release the true drug have become common through the studies of the mechanism of drug action.

The *opiate family* of drugs is used in the treatment of pain. Although, many are highly addictive, the systematic study of their mode of action has led to a modern approach for drug discovery. Now known drugs are modified according to structural features thought to be responsible for the drug activity. The well-known β-*phenethyl amine structural unit of opiates* is identified in many structures with known chemotherapeutic properties.

Drugs are often *discovered by extensive screening tests* of materials synthesized in the laboratory or obtained from natural sources. Studies are then conducted to gain information on the *mechanism of the drug action.* Drug *interactions with enzymes* as substrates or inhibitors then lead to the structural features required in designing new drugs. The drug structure is modified synthetically according to the drug mechanism in order to provide new drug molecules.

Computational methods are used to show the correlation of drug structure with physical and biochemical properties of the drug, and to determine the efficacy of the drug. The computations lead to drug modifications for changing the required properties. Computers are often used to *model drug chemistry.* Computer programs will allow the observation in *three-dimensions of a drug interaction with a protein, or permit the determination of the stereochemistry of the drug.*

18.8 Problem Set

18.1 Find in another book source or on the internet a short biography of Paul Ehrlich.

18.2 Many different chemical compounds are effective antibacterial agents. How can such a diverse range of structures accomplish this?

18.3 What are prodrugs?

18.4 What structural unit is found in penicillin and cephalosporin antibiotics?

18.5 In addition to the β-phenethyl amine unit found in the opiates, what other structural features affect the potency of opium drugs?

18.6 The accidental finding of drug activity is very important in drug therapy. How could nitroglycerine be found to be a heart stimulant.

18.7 What is a common structural feature of anti-viral drugs?

18.8 If possible search the internet for molecular modeling, obtain use of a chemistry modeling program such as Chem D. Draw structures of the drugs in section 18.6 and observe their 3D shapes. Try to model a protein and show its interaction with a drug.

18.9 What structural unit is found in many hormones, anti-inflammatory agents, and reproductive drugs.

18.10 Below is a model of morphine without hydrogen atoms. Try to use a ChemDraw and Chem 3D computer program to model some of the opiates such as LSD.