Medicinal Chemistry

Medicinal chemistry is the discipline concerned with discovery and development of medicinal agents as well as with determining the influence of chemical structure on biological activity.

The process of establishing a new pharmaceutical is exceedingly complex and involves the talents of people from a variety of disciplines, including chemistry, biochemistry, molecular pharmacology, pharmaceutics, and medicine. Medicinal chemistry is concerned mainly with the organic, analytical, and biochemical aspects of this process, but its scientists must interact productively with those in other disciplines. Thus, it occupies a strategic position at the interface of chemistry and biology.

Drug discovery & Development – The Past:

Medicines, usually derived from plants and other natural sources, have been used by humans for thousands of years to alleviate pain, diarrhea, infection, and various other diseases. Before the twentieth century these medicines consisted mainly of herbs and potions, and it was not until the mid-nineteenth century that the first efforts were made to isolate and purify the chemical compounds, responsible for the medical properties, from these mixtures. The revolution in synthetic organic chemistry during the nineteenth century produced a concerted effort toward identification of the structures of the active constituents of these naturally derived medicines. The success of these efforts led to the birth of many of the pharmaceuticals we know today. Since then, many naturally occurring drugs have been obtained and their structures determined (e.g. morphine from opium, cocaine from coca leave, and quinine from the bark of the cinchona tree).

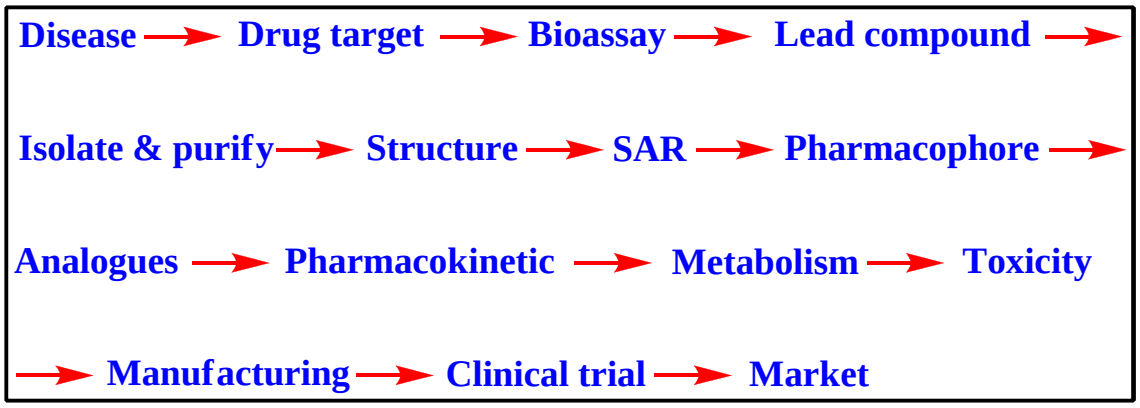
These natural products sparked off a major synthetic effort in which chemists made literally thousands of analogues in an attempt to improve on what nature had provided. Much of this work was carried out on a trial and error basis, but the results obtained revealed general principles behind drug design.

An overall pattern for drug discovery and drug development also evolved, but there was still a large element of trial and error involved in the process. The mechanism by

which a drug worked at the molecular level was rarely understood and drug research very much focused on what is known as the lead compound, the active principle isolated from the plant.

Drug discovery & Development – The Present:

In recent years, medicinal chemistry has undergone a revolutionary change. Rapid advances in the biological sciences have resulted in a much better understanding of how the body functions at the cellular and molecular levels. As a result, most research projects in the pharmaceutical industry now begin by identifying a suitable target in the body and designing a drug to interact with that target. An understanding of the structure and mechanism of the target is crucial to this approach and so research is now target-oriented. Generally, we can identify the following stages in drug discovery and drug development:



Choose a disease:

Choosing which disease to tackle is usually a matter for a pharmaceutical company's market strategists. How does a pharmaceutical company decide which disease to target when designing a new drug? Clearly, it would make sense to concentrate on diseases where there is a need for new and/or improved drugs. However, pharmaceutical companies have to consider economic factors as well as medical ones. A huge investment has to be made towards the research and development of a new drug. Therefore, companies must ensure that they get a good financial return for their investment. As a result, research projects tend to be biased towards first world diseases since this is the market best able to afford new drugs. A great deal of research is carried out on ailments

such as migraine, depression, ulcers, obesity, flu, cancer and cardiovascular disease. Less is carried out on the tropical diseases of the third world- diseases which can reduce life expectancies to thirties or forties. Only when such diseases start to make an impact on western society do the pharmaceutical companies sit up and take notice. For example, there has been a noticeable increase in antimalarial research because of an increase in tourism to more exotic countries and the spread of malaria into the southern states of the USA.

Choose a drug target:

Once a particular area of medical need has been determined, the next stage is to identify a suitable drug target (i.e. receptor, enzyme, or nucleic acid). An understanding of which enzymes or receptors are involved in a particular disease state is clearly important. This allows the medicinal research team to identify whether agonists or antagonists should be designed for a particular enzyme.

Identify a bioassay:

Choosing the right bioassay or test system is crucial to success of a drug research programme. The test should be simple, quick, and relevant since a large number of compounds usually need to be analyzed. Human testing is not possible at such an early stage and so the test has to be done *in vitro* (i.e. on isolated cells, tissues, enzymes, or receptors) or *in vivo* (on animals). In general, *in vitro* tests are preferred over *in vivo* tests.

Find a lead compound.

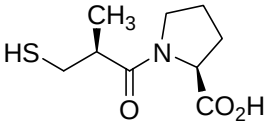
Once a target and a testing system have been chosen, the next stage is to find a lead compound, a compound which shows the desired pharmaceutical activity. The level of activity may not be very great and there may be undesirable side-effects, but the lead compound provides a start for the drug development process. There are many ways in which a lead compound might be discovered.

- Screening of natural materials (plant, bacteria, fungi, marine, and animals).
- Medical folklore.
- Screening of synthetic banks:

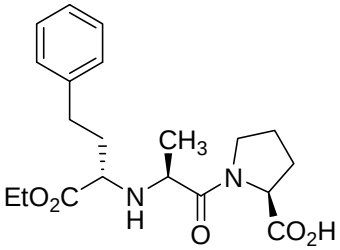
(Compounds which have been synthesized by the pharmaceutical companies and organic chemistry laboratories).

- Existing drugs:

1- Me too drugs: many companies use established drugs from their competitors as lead compounds to design a drug which gives them a foothold in the same market area. For example: the antihypertensive drug captopril was used as a lead compound by various companies to produce their own antihypertensive agents.

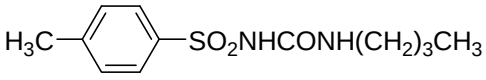


captopril
(Squibb)

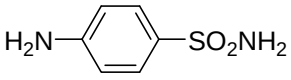


Enalapril
(Merck)

2- Enhancing a side-effect: A drug could act as a lead compound based on its side-effects. For example, most sulphonamides are used as antibacterial agents. However, some sulphonamides with antibacterial activity could not be used clinically because they had convulsive side-effects brought on by hypoglycemia. Clearly, this is an undesirable side-effect for an antibacterial agent, but the ability to lower blood glucose levels would be useful in the treatment of diabetes. Therefore, structural alterations were made to the sulphonamides concerned to eliminate the antibacterial activity and to enhance the hypoglycemic activity. This led to the antidiabetic agent tolbutamide.

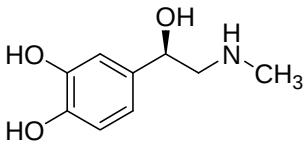


tolbutamide

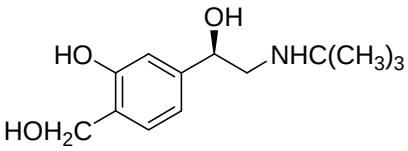


sulphanilamide

- Starting from the natural ligand for receptors: The natural ligand of a target receptor has sometimes been used as the lead compound. The natural neurotransmitters adrenaline and noradrenaline were the starting points for the development of adrenergic β–agonists such as salbutamol.

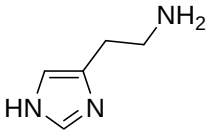


adrenaline

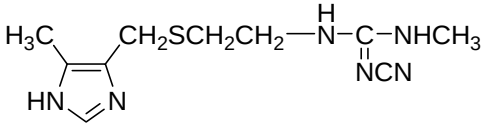


salbutamol

The natural ligand of a receptor can also be used as the lead compound in the design of an antagonist. For example, histamine was used as the original lead compound in the development of the H_2-histamine antagonist cimetidine.



histamine



cimetidine

- Combinatorial synthesis: The growing number of potentially new drug targets arising from genomic projects has meant that there is an urgent need to find new lead compounds to interact with them. Unfortunately, the traditional sources of lead compounds have not managed to keep pace and, in last decade or so, the pharmaceutical companies have invested greatly in a process called combinatorial synthesis to tackle this problem. Combinatorial synthesis is an automated solid phase procedure aimed at producing as many different structures as possible in as short time span as possible. The reactions are carried out on a very small scale and are often designed to produce mixtures of compounds, one of which may prove to be a useful lead compound.
- Computer-aided design: A detailed knowledge of a target binding site significantly aids in the design of novel lead compounds intended to bind with that target. In cases where enzymes or receptors can be crystallized, it is possible to determine the structure of the protein and its binding site by X-ray crystallography. Molecular modeling software programmes can then be used to study the binding site, and to design molecules which will fit and bind.

- Serendipity and the prepared mind: Frequently lead compounds are found as a result of serendipity (i.e. chance). However, it still needs someone with an inquisitive nature or prepared mind to recognize the significance of chance discoveries and to take advantage of these events. The discovery of penicillin is such example, but there are many more.

Isolate and purify the lead compound (if necessary):

Isolation and purification of the lead compound (or active principle) is necessary if it is present in a mixture of other compounds, whether the mixture be from a natural source or from a combinatorial synthesis. The ease with which the active principle can be isolated and purified depends very much on the structure, stability, and quantity of the compound.

Determine the structure of the lead compound:

In the past, determining the structure of a new compound was a major hurdle to overcome. A novel structure which may now take a week's work to determine would have provided 2-3 decades of work in the past. Today, structure determination is a relatively straightforward process and it is only when the natural product is obtained in minute quantities that a full synthesis is required to establish its structure. The most useful analytical techniques are X-ray crystallography, NMR, IR, and MSS.

Identify structure-activity relationships:

Once the structure of a biologically active compound is known, the medicinal chemist is ready to move on to study the structure-activity relationships (SAR) of the compound. The aim of such a study is to discover which parts of the molecule are important to biological activity and which are not. The chemist makes a selected number of compounds, which vary slightly from the original molecule, and studies what effect this has on the biological activity.

Identify the pharmacophore:

The pharmacophore summarizes the important functional groups which are required for activity and their relative positions in space with respect to each other.

Improve target interactions (Target-oriented drug design):

Once the important binding groups and pharmacophore have been identified, it is possible to synthesize analogues of the lead compound which contain the same pharmacophore. But why is this stage necessary? If a natural compound has useful biological activity, why bother making synthetic analogues? The answer is that very few drugs are ideal. Many have serious side-effects and there is an advantage in finding analogues which lack them. In general, the medicinal chemist is developing drugs with four objectives in mind:

1- To increase activity.
2- To reduce side-effects.
3- To provide easy and efficient administration to the patient.
4- Ease of synthesis.

Target-oriented drug design aims to modify the lead compound such that it interacts more effectively and selectively with its molecular target in the body. Stronger drug-target interactions should increase the activity of the drug while an increase in target selectivity will lower side-effects.

Improve pharmacokinetic properties (Pharmacokinetic drug design):

Some of the most active drugs discovered in vitro show no activity at all in vivo. This is because a clinically useful drug has to travel through the body to reach its target. There are many barriers and hurdles which can prevent a drug reaching its target. Pharmacokinetic drug design concentrates on designing drugs to overcome these barriers.

Study drug metabolism:

When drugs enter the body, they are attacked by a whole range of metabolic enzymes, mostly in the liver, whose role is to degrade or modify foreign structures such that they

can be excreted. As a result most drugs undergo some form of metabolic reaction, resulting in modified structures known as metabolites.

Drugs should be tested on animals and humans to see what metabolites are formed. This is safety issue, since it is important to ensure that no toxic metabolites are formed. Ideally, any metabolites which are formed should be inactive and quickly excreted.

Drug metabolism studies can sometimes be useful in drug design. On several occasions it has been found that a drug which is active in vivo is in active in vitro. This is often a sign that the structure is not really active at all, but is being converted to the active drug by metabolism (prodrug).

Test for toxicity:

Before the drug moves on to clinical trials it is tested for toxicity.

Design a manufacturing process:

The industrial synthesis of a drug should be efficient and economic. If a choice must be made between two drugs where one is slightly less active than the other but is easier to synthesize, then the less active structure may well be chosen for clinical trials and further development.

Carry out clinical trials:

Clinical trials involve testing the drug on volunteers and patients. Many promising drug candidates fail this final hurdle and, if this happens, further analogues may need to be prepared before a clinically acceptable drug is achieved. There are four phases of clinical trials:

1- Phase I studies: Carried on healthy volunteers to test whether the drug has the effect claimed. Tests are also carried out to test drug's potency, pharmacokinetics, and side-effects.
2- Phase II studies: The drug is tested on small group of patients to see if it has any effect and to find out what dose levels should be used.

3- Phase III studies: The drug is tested on a much larger sample of patients and compared with other available treatments. Alternatively, they may be compared with a placebo (i.e. a preparation which has no effect at all).
4- Phase IV studies: The drug is now placed on the market and can be prescribed. However, the drug is still monitored for its effectiveness and for any unexpected side-effects.

Conclusion

Many of these stages (of drug discovery & development) run concurrently and are dependent on each other. For example, drug metabolism studies, toxicity testing and the development of a large scale synthesis are usually carried out in parallel. Even so, the discovery and development of a new drug can take 10 years or more, involve the synthesis of over 10000 compounds and cost in the region of 360 million USD.

Physicochemical Principles of Drug Action

To design better medicinal agents, the medicinal chemist needs to understand not only the mechanism by which a drug exerts its effect but also the relative contributions that each functional group makes to the overall physicochemical properties of the drug molecule. The term "physicochemical properties" refers to the influence of the organic functional groups within a molecule on its acid-base properties, water solubility, lipid solubility, partition coefficient, stereochemistry, and so on. All these properties influence the absorption, distribution, metabolism, excretion, and toxicity of the molecule.

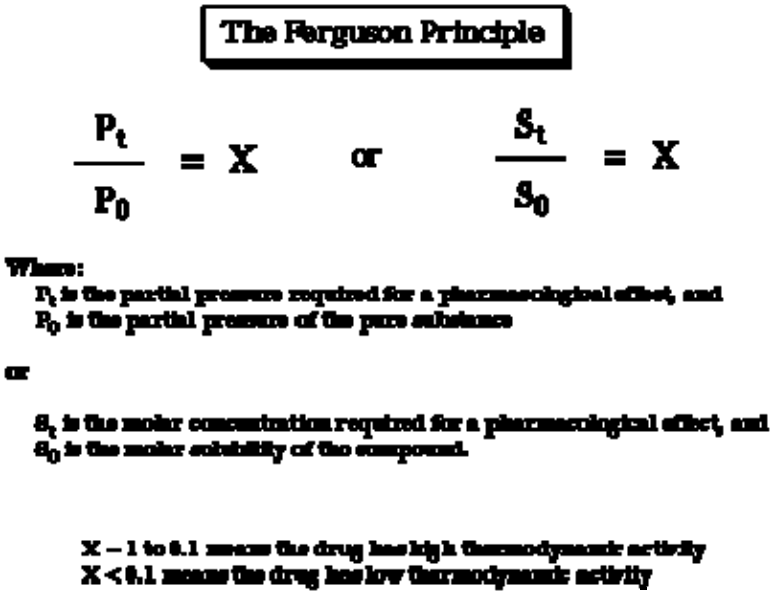
Partition coefficient:

A drug given orally or parenterally must traverse several semipermeable membranes before reaching its receptor. In order to elicit a pharmacological effect, drugs must be sufficiently soluble in water to be absorbed and distributed throughout the body. They must also have sufficient lipophilicity to be able to pass through biological membranes. Because drugs must encounter both aqueous and lipid environments in the body, they must have some measure of solubility in each phase. This propensity is measured by determining the partition coefficient (P), which is determined using the equation below:

$$P = \frac{[D]_{lipid}}{[D]_{water}}$$

The partition coefficient is simply the ratio of the solubility (concentration) of the drug in lipid and its solubility in biological fluid (concentration). Since partition coefficients are difficult to measure in living systems, they are usually determined *in vitro*, using *n*-octanol as the lipid phase and a phosphate buffer of pH 7.4 as the aqueous phase. The partition ratio of a given drug will determine its solubility in plasma, its ability to traverse cell membranes, and which tissues it will reach. On the one hand, extremely water-soluble drugs may be unable to cross lipid barriers and gain access to organs rich in lipids, such as the brain and other neuronal tissues. On the other hand, compounds that are very lipophilic will be trapped in the first site of loss like fat tissue, and will be unable to leave this site quickly to reach their target.

A number of theoretical representations of the relationship between physicochemical properties and drug action have been developed. One of the earliest of these is known as the **Overton-Meyer Hypothesis**. This theory was developed following the observation that neutral, lipid soluble substances have a depressant effect on neurons. The hypothesis states that, for these compounds, the higher the partition ratio P, the higher the pharmacological effect. This hypothesis was expanded upon by Ferguson, who extended the theory to include all drugs. The **Ferguson Principle** states that the concentration of a drug in plasma is directly proportional to its activity. This concentration can be measured, either as **molarity** or **partial pressure**. The Ferguson constant X is determined by measuring the molar concentration (or partial pressure) of a drug required for an effect, and dividing it by the molar solubility of the drug (or its partial pressure in the pure state). As seen below, if the value of X is between 0.1 and 1, the drug is said to have **high thermodynamic activity**. This means that the activity of the drug is based on its physicochemical properties only, such as in a gaseous anesthetic. Such drugs are known as **non-specific drugs**. When the value of X is less than 0.1, the drug is said to have **low thermodynamic activity**, meaning that the activity of the drug is based on its structure rather than physicochemical properties. Agents in this category are called **specific drugs**, and their activity at low concentrations infers that they have a specific receptor.



Depending upon the degree to which chemical structure affects biological action, drugs can be classified as:

- Structurally non-specific.
- Structurally specific.

Structurally non-specific drugs:

The biological characteristic of such drugs is solely linked with the physical properties of the molecule rather than the chemical features. They have no specific site of action and usually have lower potency. Similar biological activities may occur with a variety of structures. Examples of these drugs are gaseous anesthetics (diethyl ether, N_2O, $CHCl_3$), some sedative and hypnotics and many antiseptics and disinfectants.

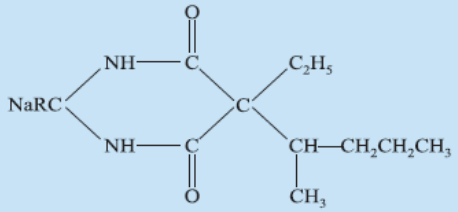
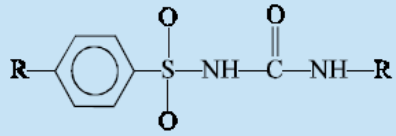
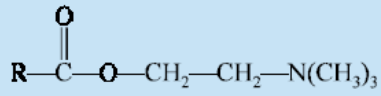
- The activity does not depend on chemical structure.
- The activity depends on physical properties.
- Minor modifications do not affect the activity.
- Effective only in high concentrations.

Structurally specific drugs:

A number of compounds that possess remarkable pharmacological actions are essentially the structurally specific drugs. Though the physical characteristics of the drug play an important role in the biological activity, yet the chemical properties do exert their influence on the activity. Structurally specific drugs act at specific sites, such as a receptor or an enzyme. Their activity and potency are very susceptible to small changes in chemical structure.

- Biological action is related to the chemical structure.
- Minor alterations in groups in parent structure bring about appreciable difference in activity.
- Effective in a relatively low concentration.
- Stereoisomers differ greatly in activity.

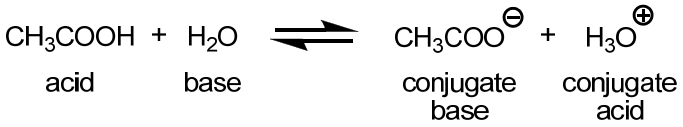
The apparent effect of structure on biological activity may be observed in the following examples where such a change is mainly due to minor group alterations.

Structure	Biological Activity	Pharmacological Classification
(*a*) 		
R = O, (pentobarbitone sodium)	Short-acting	Hypnotic
R = S, (thiopental sodium)	Ultra-shortacting	
(*b*) 		
$R = CH_3$, $R' = C_4H_9$ (tolbutamide)	Short-acting	Hypoglycemic
R = Cl, $R' = C_3H_7$ (chloropropamide)	Long-acting	
(*c*) 		
$R = CH_3$ (acetylcholine)	Short-acting	Cholinergic
$R = NH_2$ (carbamylcholine)	Long-acting	

For instance, alterations in groups in parent structure bring about appreciable difference in hypnotic, hypoglycemic and cholinergic activities. It is pertinent to mention here that such changes only affect the duration of action without any influence on the biological response.

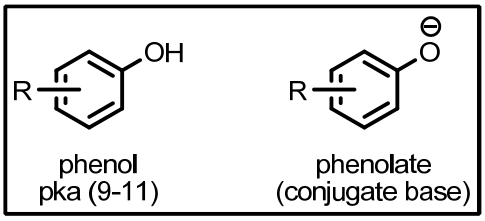
Acid-base properties

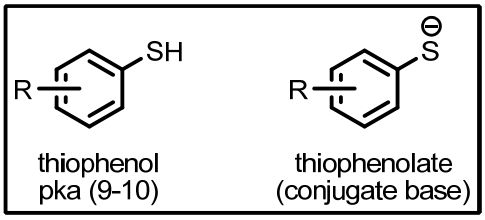
The acid-base properties of drug molecules directly affect absorption, excretion, and compatibility with other drugs in solution. According to the Bronsted-Lowery theory, an acid is any substance capable of yielding a proton (H^+), and a base is any substance capable of accepting a proton. When an acid gives up a proton to a base, it is converted to its conjugate base. Similarly, when a base accepts a proton, it is converted to its conjugate acid.

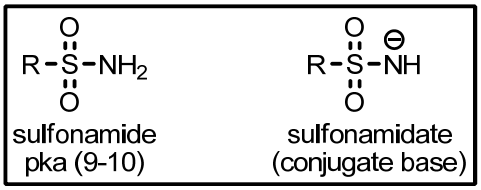


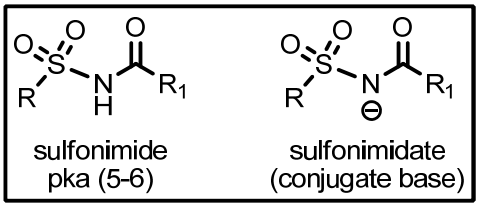
Being ionized, the conjugate base (acetate) is more water-soluble, and hence less lipid-soluble, than the original acid (acetic acid). Similarly, the conjugate acid (hydronium) is more water-soluble, and hence less lipid-soluble, than the original base (water).

Many different organic functional groups behave as acids, for examples:

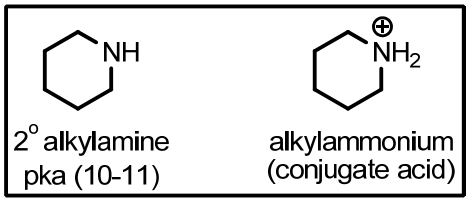


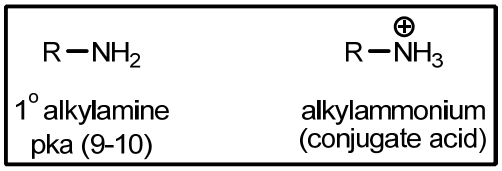


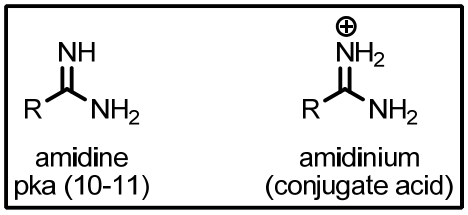


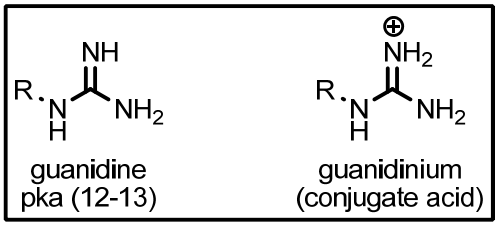


Most basic drugs usually are derived from primary, secondary, and tertiary amines or imino amines such as guanidines and amidines, for examples:

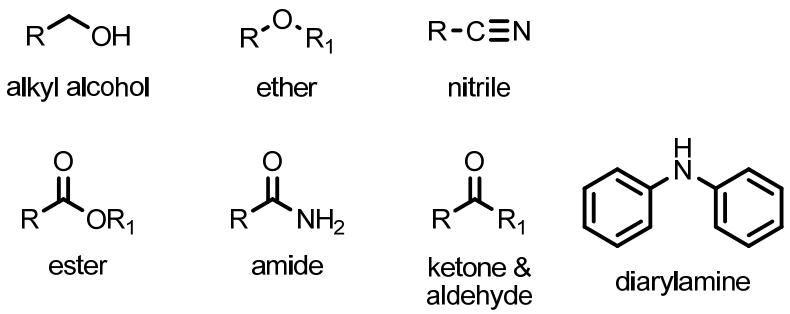




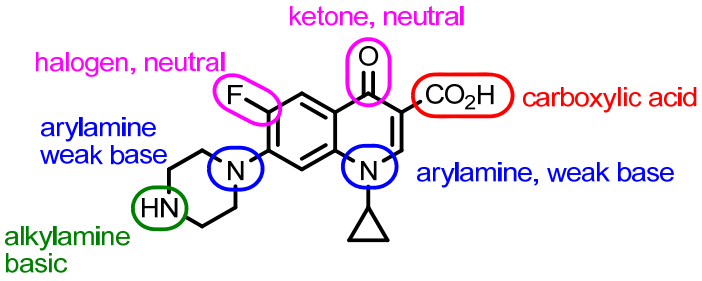




Organic functional groups that cannot give up or accept protons are considered to be neutral, for examples:

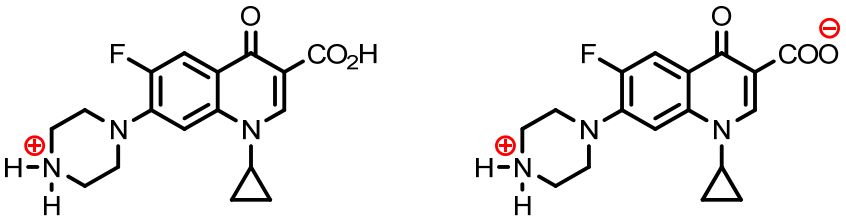


A molecule may contain multiple functional groups and, therefore, possess both acidic and basic properties. For example, ciprofloxacin, a fluoroquinolone antibiotic, contains a secondary alkylamine, two tertiary arylamines, and a carboxylic acid. The two arylamines are weakly basic and, therefore, do not contribute significantly to the acid-base properties of ciprofloxacin.



Depending on the pH of the solution (or tissue), this molecule will either accept a proton (secondary alkylamine), yield a proton (carboxylic acid), or both. Thus, it is amphoteric (both acidic and basic) in its properties. Accordingly, ciprofloxacin behaves differently at two different locations of the gastrointestinal tract. At the stomach (pH 1-3.5), only one of the functional groups is ionized while at colon (pH 5.6-7), both functional groups are ionized.

The concept of pKa not only indicates the relative acid-base strength of organic functional groups but also allows one to calculate, for a given pH, exactly how much of the molecule is in the ionized and un-ionized form, which therefore allows prediction of relative water solubility, absorption, and excretion for a given compound.



stomach (pH 1-3.5) colon (pH 5.6-7)

Thus, one needs to know which acid or base within a molecule containing multiple functional groups is the strongest and which acid or base is the weakest.

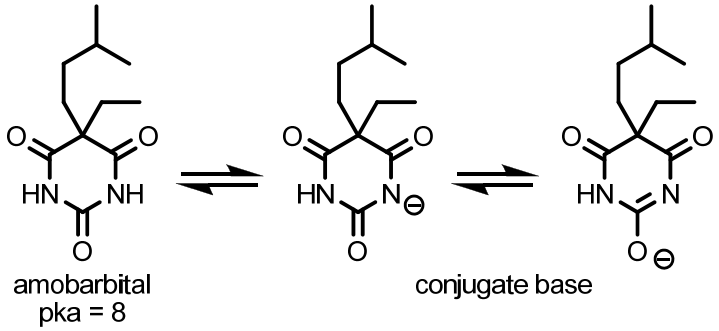
Predicting the degree of ionization of a molecule:

When a drug is a weak acid or weak base, its lipid solubility is greatly affected by the pH of the environment and by its degree of dissociation pka. This is through effect on percent of ionized (not lipid soluble) and unionized (lipid soluble).

To be able to quantitatively predict the degree of ionization of a molecule, however, one must know the pKa values of the acidic or basic functional groups that are present and the pH of the environment to which the compound will be exposed. This percentage ionization can be calculated from the Henderson-Hassalbach equation:

$$pKa = pH + \log \frac{[C_{ionized}]}{[C_{unionized}]}$$

Calculation of percentage of ionization of sedative hypnotic amobarbital (pka = 8, at pH = 7.4) indicates that 80% of the molecules are in the acid (un-ionized) form, leaving 20% in the conjugate base (ionized) form.



$$pKa = pH + \log \frac{[C_{ionized}]}{[C_{unionized}]}$$

$$8 = 7.4 + \log \frac{[C_{ionized}]}{[C_{unionized}]}$$

$$0.6 = \log \frac{[C_{ionized}]}{[C_{unionized}]}$$

$$10^{0.6} = \frac{[C_{ionized}]}{[C_{unionized}]} = \frac{3.98}{1}$$

$$\% \text{ un-ionized} = \frac{3.98 \times 100}{4.98} = 79.9\%$$

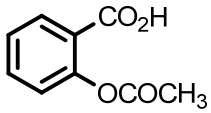
Drug transport represents a comprise between the increased solubility in plasma of the ionized form of a drug and the increased ability of the un-ionized form to penetrate the lipid bilayer of cell membrane. As a rule of thumb, drugs pass through membranes in an un-ionized form, but act as ions (if ionization is a possibility). A pka in the range of 6-8 (i.e. weak acids and weak bases) would seem to be most advantageous, because the un-ionized species would be of appreciable concentration and pass through lipid membranes and becoming ionized and active within the cell.

A high degree of ionization resulting from the drug being a strong acid or strong base can keep the drugs out of cells and decreased their penetration through cell wall membranes.

An orally administered drug will first encounter the acidic stomach (pH 1-6) depending on the presence of food. Drugs of pKas of 4 to 5 will tend to be un-ionized and hence be partially absorbed from the gastric mucosa (However, most acidic drugs are absorbed from the intestinal tract rather than the stomach because the microvilli of the intestinal

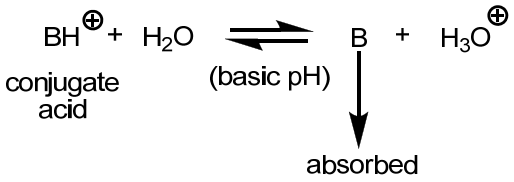
mucosa provide a huge surface area for absorption compared with that provided by the gastric mucosa of the stomach).

The useful drug Aspirin is a weak acid (pka 3.5). It is usually taken orally. Aspirin by applying the Henderson-Hassalbach equation will be found to be almost completely un-ionized and will be lipid soluble and absorbed appreciably in the stomach.



aspirin

In contrast, amines (pka 9-10) will be protonated (BH^+) and usually will not be absorbed until reaching the mildly alkaline intestinal tract (pH ~ 8) where the equilibrium system is obtained.



Stereochemistry and drug action:

Stereoisomers are compounds containing the same number and kinds of atoms, the same arrangement of bonds, but different three-dimensional structures; in other words, they only differ in three-dimensional arrangements of atoms in space. Stereoisomers are subdivided into two types, enantimoers and diastereoisomers.

Unlike enantiomers, diastereoisomers exhibit different physicochemical properties, including, but not limited to, melting point, boiling point, solubility, and chromatographic behavior.

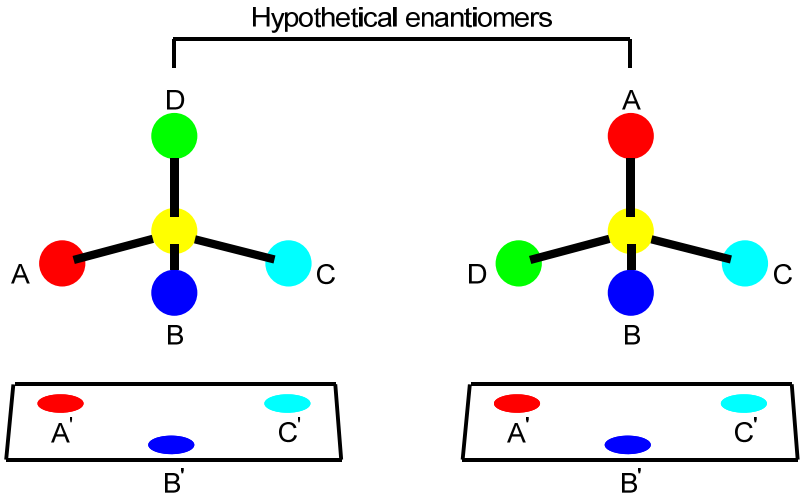
The physicochemical properties of a drug molecule are dependent not only on what functional groups are present in the molecule but also on the spatial arrangement of these groups. This becomes an especially important factor when a molecule is subjected to an asymmetric environment, such as the human body. Because proteins and other biological

macromolecules are asymmetric in nature, how a particular drug molecule interacts with these macromolecules is determined by the three-dimensional orientation of the organic functional groups that are present. If crucial functional groups are not occupying the proper spatial region surrounding the molecule, then productive bonding interactions with the biological macromolecule (or receptor) will not be possible, potentially negating the desired pharmacologic effect. If, however, these functional groups are in the proper three-dimensional orientation, the drug can produce a very strong interaction with its receptor. It therefore is very important for the medicinal chemist developing a new molecular entity for therapeutic use to understand not only what functional groups are responsible for the drug's activity but also what three-dimensional orientation of these groups is needed.

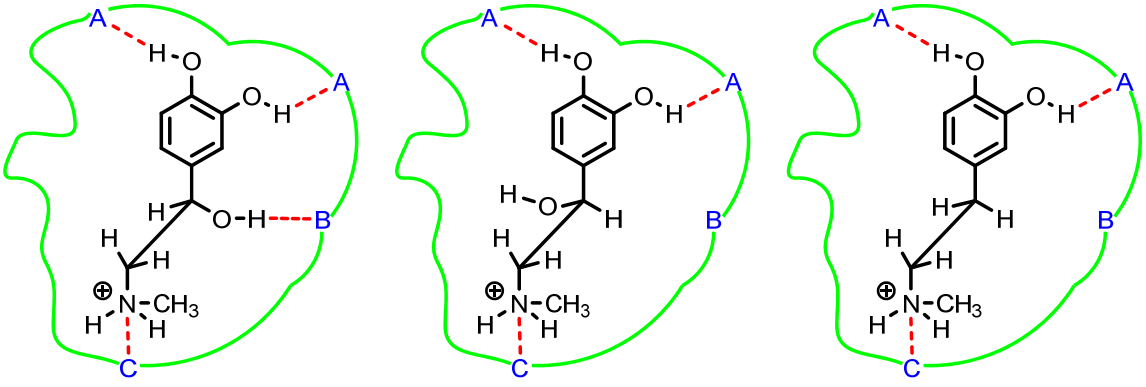
Enantiomers:

Enantiomers are compounds that are superimposable, mirror-image isomers. Such compounds can result from the presence of one chiral center in the molecule. They have identical physicochemical properties. In 1886, Piutti reported different physiologic actions for the enantiomer of asparagines, with (+)-asparagine having a sweet taste and (–)-asparagine a bland one. This was one of the earliest observations that enantiomers can exhibit different biological action. 1n 1993, Easson and Stedman reasoned that differences in biological activity between enantiomers resulted from selective reactivity of one enantiomer with its receptor. They postulated that such interactions require a minimum of three-point fit to the receptor. This is demonstrated in the following figure for two hypothetical enantiomers. The letters A, B, and C represent hypothetical functional groups that can interact with complementary sites on the hypothetical receptor surface, represented by A′, B′, and C′. Only one enantiomer is capable of attaining the correct orientation to enable all three functional groups to fit their respective sites on the receptor surface. The lack of achieving the same interactions by other enantiomer explains its reduced biological activity, because it is unable to properly fit into the receptor and, therefore, cannot trigger the appropriate change in the receptor conformation. The Easson-Stedman Hypothesis states that the more potent enantiomer

must be involved in a minimum of three intermolecular interactions with the receptor surface and that the less potent enantiomer only interacts with two sites.

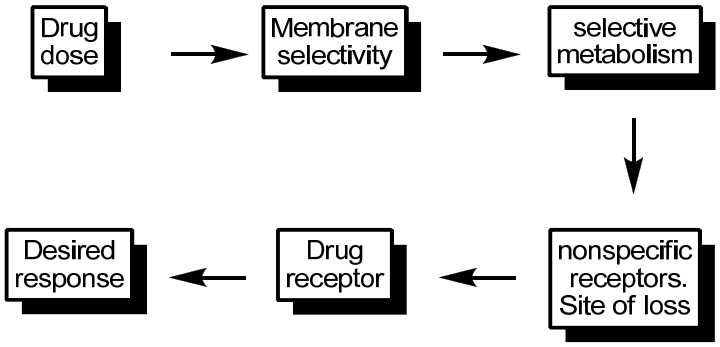


This can be illustrated by looking at looking at the differences in vasopressor activity of (R)-(–)-adrenaline, (S)-(+)-adrenaline, and the achiral *N*-methyldopamine. With (R)-(–)-adrenaline, the three points of interaction with the receptor site are the substituted aromatic ring, β-hydroxyl group, and the protonated secondary ammonium group. All three functional groups interact with their complementary binding sites on the receptor surface, producing the necessary interactions that stimulate the receptor. With (S)-(+)-adrenaline, only two interactions are possible (the protonated secondary ammonium and the substituted aromatic ring). The β-hydroxyl group occupies the wrong region of space and, therefore, cannot interact properly with the receptor. *N*-Methyldopamine can achieve the same interactions with the receptor as S)-(+)-adrenaline; therefore, it is not surprising that its vasopressor response is the same as that of S)-(+)-adrenaline and less than that of R)-(–)-adrenaline.



(R)-(-)-adrenaline (S)-(+)-adrenaline *N*-methyldopamine

Not all stereoselectivity seen with enantiomers can be attributed to differences in reactivity at the receptor site. Differences in biological activity also can result from differences in the ability of each enantiomer to reach the receptor site. Because the biological system encountered by the drug is asymmetric, each enantiome may experience selective penetration of membranes, metabolism, and absorption at sites of loss (e.g., adipose tissue) or excretion.

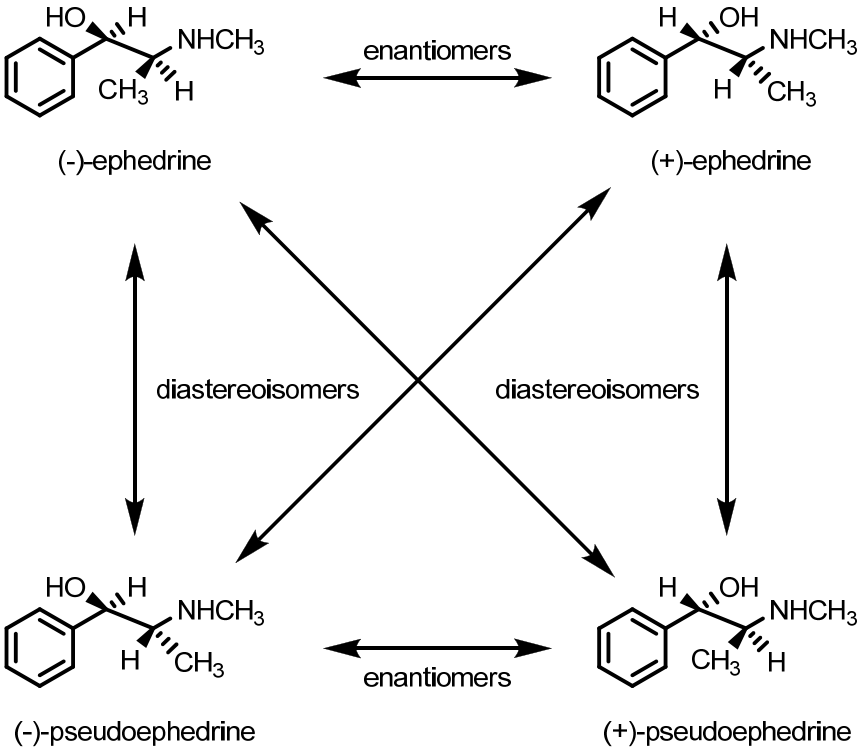


Diastereoisomers:

Diastereoisomers are compounds that are nonsuperimposable, nonmirror-image isomers. Such compounds can result from the presence of more than one chiral center in the molecule, double bonds, or ring systems. These isomers have different physicochemical properties; thus, differences in biological activity between such isomers often can be attributed to these properties.

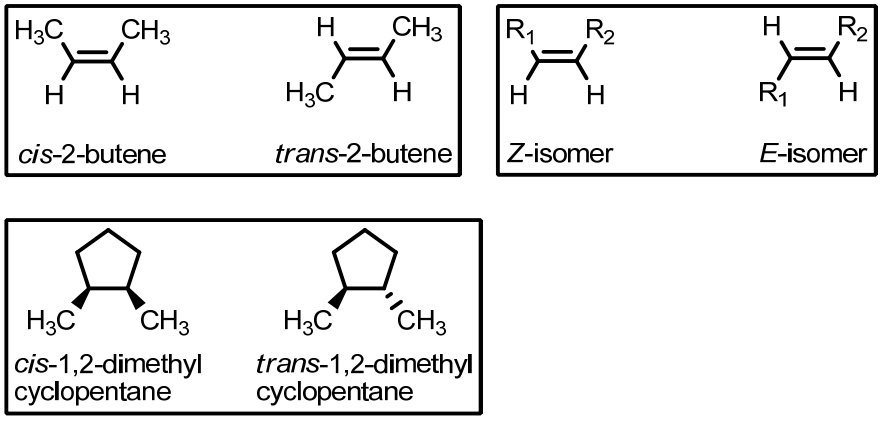
Compounds containing more than one chiral center probably are the most common type of diastereoisomer used as drugs. The classic example of compounds of this type is the

diastereoisomers ephedrine and pseudoephedrine. When a molecule contains two chiral centers, there can be as many as four possible stereoisomers consisting of two sets of enantiomeric pairs. For each enantiomeric pair, there is inversion of both chiral centers, whereas the difference between diastereoisomers is the inversion of only one chiral center.

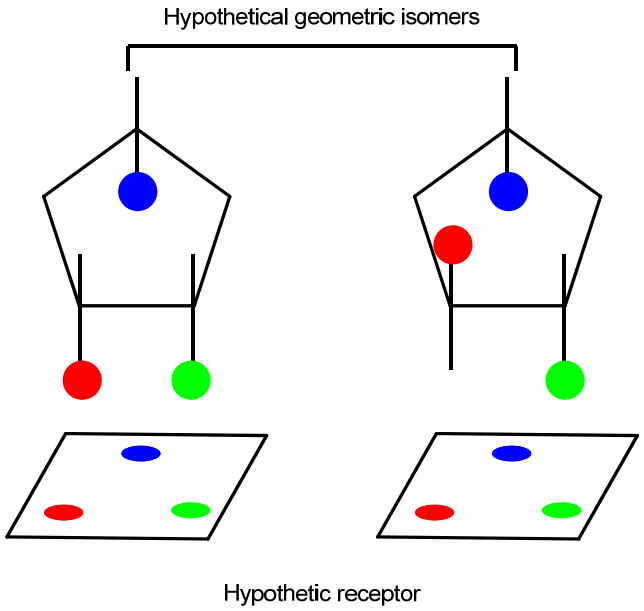


Geometric isomers:

These are isomers that owe their existence to restricted rotation as a result of a double bond or in rigid ring structure. They are nonsuperimposable, nonmirror-image isomers and hence are diastereoisomers having different physicochemical properties.

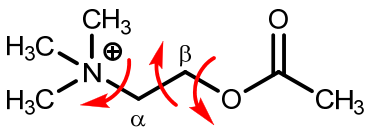


Geometric isomers have different reactivity at the receptor site.



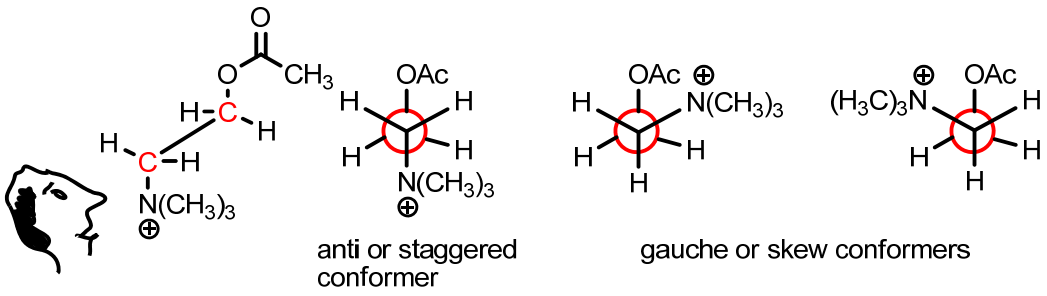
Conformational isomers:

Conformational isomerism takes place via rotation about one or more single bonds. Such bond rotation results in nonidentical spatial arrangement of atoms in a molecule. Change in spatial orientation of atoms because of bond rotation results in different conformations (or rotamers), whereas conversion of one enantiomer into another (or diastereoisomer) requires the breaking of bonds, which has a much higher energy requirement than rotation around a single bond. The neurotransmitter acetylcholine can be used to demonstrate the concept of conformational isomers.



acetylcholine

Each single bond within the acetylcholine molecule is capable of undergoing rotation, and at room temperature, such rotations readily occur. The energy barrier between the resulting conformers is sufficiently low at room temperature; therefore, acetylcholine exists in many interconvertible conformations. Close observation reveals that rotation around the central Cα–Cβ bond produces the greatest spatial rearrangement of atoms compared to rotation around any other bond within the molecule. When viewed along the Cα–Cβ bond, acetylcholine can be depicted in the saw-horse or Newman projections, as shown below:

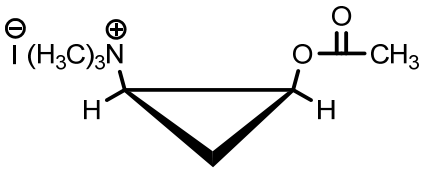


anti or staggered conformer

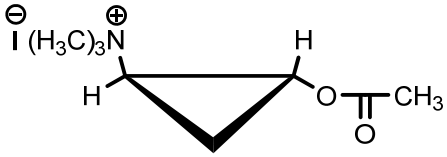
gauche or skew conformers

NMR studies, X-ray analysis, and molecular orbital calculations revealed that the preferred conformation between the ester oxygen and the quaternary nitrogen was the gauche conformation rather than the staggered one. The gauche conformation would be stabilized by intramolecular electrostatic interactions between the quaternary nitrogen and the carbonyl oxygen. However, the gauche conformation may not be the conformation preferred by the receptors. Indeed, the conformation of receptor-bound acetylcholine could be much different and might not be a thermodynamically preferred conformation. Studies have suggested that the gauche conformation is the form that binds to the nicotinic receptor. Whereas, the anti form binds to the muscarinic receptor. Conformationally rigid model of acetylcholine, namely cis- and trans-2-acetoxycyclopropyl-1-trimethylammonium iodide, have been synthesized and evaluated to test the validity of this assumption. Because this model is based on the cyclopropane

ring, the ester and quaternary ammonium functional groups cannot change their relative positions by bond rotation. The cis- and trans-isomers are rigidly constricted to the conformations shown below.

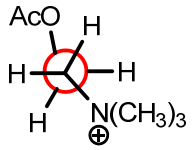


cis



trans

The (+)-trans-enantiomer was observed to be equally as or more potent, than acetylcholine at muscarinic receptors; it was much more potent than the (-)-trans-enantiomer. The racemic cis-compound had almost no activity in the same muscarinic receptor test system, and all compounds were very weak nicotinic agonists. The important conclusion drawn from this study was that acetycholine would most probably interact with muscarinic receptors in its less favored anticlinal conformation (the angle between the aster oxygen and the quaternary nitrogen is 137°).



anticlinal confomer

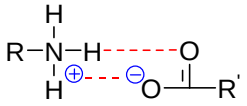
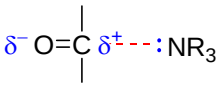
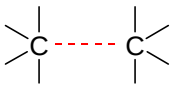
Drug receptor interaction:

The ability of a drug to produce an effect results from specific chemical interactions between the drug and specific sites (lipoprotein receptors, enzymes, biomembranes, nucleic acids or small molecules). When a drug interacts with a receptor, a number of chemical attractive forces are believed to be responsible for the initial interaction. Compounds that are attracted to a receptor macromolecule are said to have affinity for that receptor and may be classified as agonist and antagonist. Additionally, compounds with affinity also are referred to as ligands. Agonists are those compounds that have affinity for the receptor and are capable of producing biological response as a result of its

interaction with the receptor. The ability to produce a response is termed “efficiacy” or “intrinsic activity”. Drugs that are capable of interacting with the receptor but not of activating it to produce a response are classified as antagonists. This class of drugs is said to have affinity, but it lacks intrinsic activity.

The affinity of a compound for a receptor is dependent on its proper three-dimensional characteristics, such as its size, stereochemical orientation of its functional groups, and its physical and electrochemical properties (e.g. ionic and dipole interactions).

The binding of the drug to the receptor initially depends on the types of bonds that can be established between the drug and its receptor. The overall strengths of these bonds will vary and will determine the degree of affinity between the drug and the receptor. Interaction between the drug and the biologic receptor would be expected to take place by utilizing the same bonding forces involved as those when simple molecules interact.

Bond Type	Bond strength (kcal/mol)	Example
Covalent	40-140	H_3C-OH
Reinforced ionic	10	
Ionic	5	$R_4N^{\oplus}\cdots{}^{\ominus}I$
Hydrogen	1-7	—OH---- O═
Ion-dipole	1-7	$R_4N^{\oplus}\cdots:NR_3$
Dipole-dipole	1-7	
van der Waals'	0.5-1	
Hydrophobic	1	

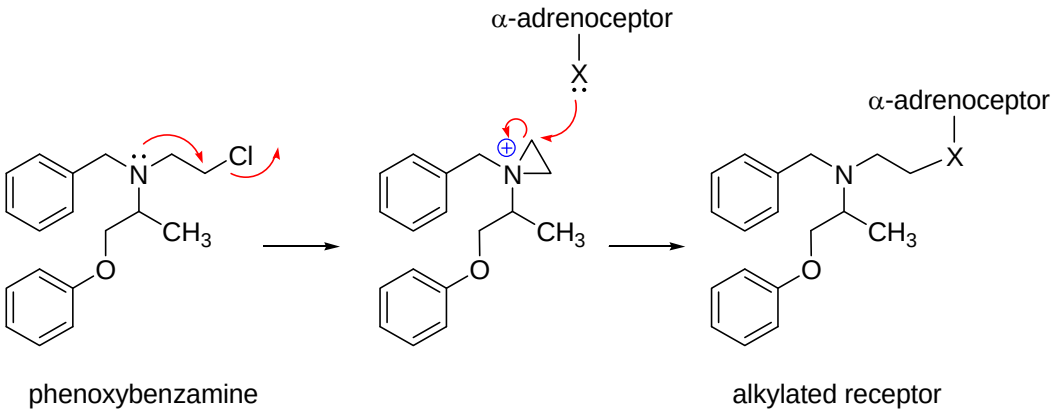
Most drugs do not possess functional groups of a type that would lead to ready formation of the strong and essentially irreversible covalent bonds between drug and biological

receptors. In most cases, it is desirable that the drug leave the receptor site when the concentration decreases in the extracellular fluids. Therefore, most useful drugs are held to their receptors by ionic or weaker bonds. When relatively long lasting or irreversible effects are desired (e.g. antibacterial, anticancer), drugs that form covalent bonds with the receptor are effective and useful.

Covalent bond:

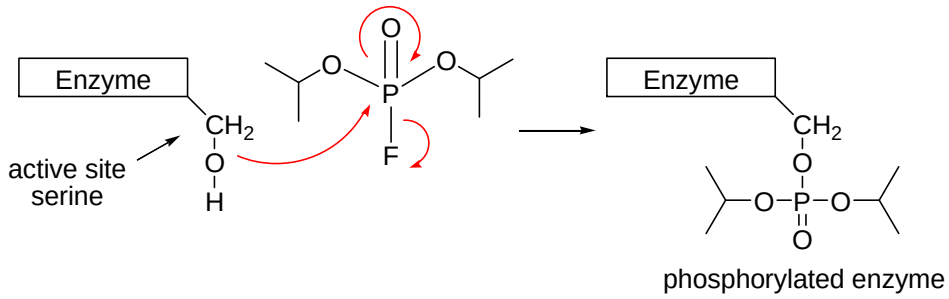
The strongest bonds involved in drug-receptor interactions is the covalent bond, in which two atoms, one from the ligand and one from the receptor, share a pair of electrons. Because of the significant strength of the covalent bond (50-150 kcal/mole), covalent bonding often produces a situation in which the ligand is irreversibly bound by the receptor and, thus, leads to the receptor's eventual destruction via endocytosis and chemical destruction. Full recovery of the cellular function, therefore, requires the synthesis of new receptors.

An example of an irreversible covalent bond formation between drug and receptor involves the long-lasting blockade of α-adrenoceptors by phenoxybenzamine. Once phenoxybenzamine is converted to a highly reactive carbonium ion intermediate, this haloalkylamine can covalently link, via alkylation with amino, sulfhydryl or carboxyl groups at the α-adrenoceptor. The receptor is thus rendered irreversibly nonfunctional and, eventually, destroyed. The synthesis of new receptors requires a number of days, thus accounting for extremely prolonged duration of the block associated with this agent.

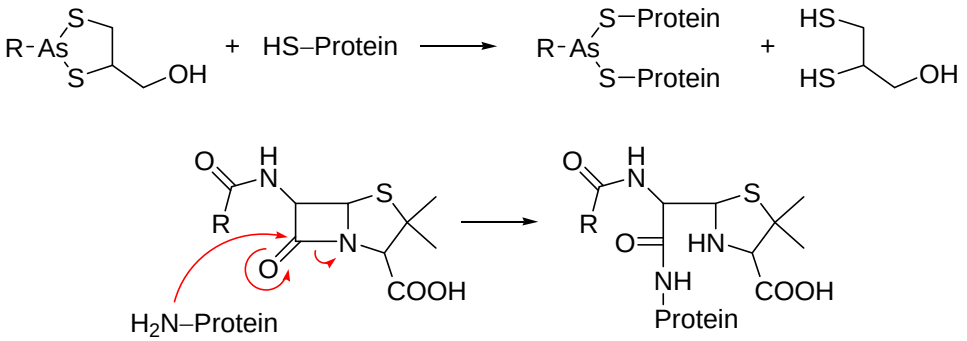


X is a nucleophile, such as S, N, or O.

Another important example of a class of compounds that produces its effect via a covalent bond to its receptor is the organophosphate acetylcholinesterase inhibitors. Examples of such agents include the insecticides parathion and malathion. These compounds are capable of alkylating the active sites of this enzyme that normally is responsible for metabolizing acetylcholine, the neurotransmitter found at the neuromuscular junction and within many sites of the autonomic and central nervous systems. Reaction of the enzyme with its normal substrate acetylcholine leads to a readily hydrolysable acetylated enzyme. Covalent bonding by the organophosphates, however, results in phosphorylation of a serine within the active site of the enzyme, which is extremely stable and essentially irreversible. Recovery of enzymatic function in the tissue requires the synthesis of new enzyme molecules.



Other examples of covalent bond formation between drug and biological receptor site include the reaction of arsenicals and Mercurials with cysteine sulfhydryl groups, the acylation of bacterial cell wall constituents by penicillin, and the phosphorylation of the serine hydroxyl moiety at the active site of cholinesterase by organic phosphates.



Considering the wide variety of functional groups found on a drug molecule and receptor, there will be a variety of secondary bonding forces. Ionization at physiologic pH would

normally occur with the carboxyl, sulfonamide, and aliphatic amino groups, as well as the quaternary ammonium group at any pH. These sources of potential ionic bonds are frequently found in active drugs. Differences in electronegativity between carbon and other atoms, such as oxygen and nitrogen, lead to an unsymmetric distribution of electrons (dipoles) that are also capable of forming weak bonds with regions of high or low electron density, such as ions or other dipoles. Carbonyl, ester, amide, ether, nitrile, and related groups that contain such dipolar functions are frequently found in equivalent locations in structurally specific drugs.

The relative importance of hydrogen bond in formation of drug-receptor complex is difficult to assess. Many drugs possess groups, such as carbonyl, hydroxyl, amino, and imino, with the structural capabilities of acting as acceptors or donors in the formation of hydrogen bonds. However, such groups would usually be solvated by water, as would the corresponding groups on a biologic receptor. Relatively little net change in free energy would be expected in exchanging a hydrogen bond with a water molecule for one between drug and receptor. However, in a drug-receptor combination, several forces could be involved, including the hydrogen bond, which would contribute to the stability of the interaction. Where multiple hydrogen bonds may be formed, the total effect may be sizeable, such as that demonstrated by stability of the protein α-helix, and by the stabilizing influence of hydrogen bonds between specific base pairs in the double helical structure of DNA.

Van der Waals' forces are attractive forces created by the polarizability of molecules and are exerted when any two uncharged atoms approach each other very closely. Their strength is inversely proportional to the seventh power of the distance. Although individually weak, the summation of their forces provides a significant bonding factor in higher molecular-weight compounds. For example, it is not possible to distill normal alkanes with >80 carbon atoms, because the energy of ~80kcal/mol required to separate the molecules is approximately equal to the energy required to break a carbon-carbon covalent bond. Flat structures, such as aromatic rings, permit close approach of atoms. With van der Waals' forces of ~0.5 to 1.0 kcal/mol for each atom, about six carbons (a benzene ring) would be necessary to match the strength of a hydrogen bond. The

aromatic ring is frequently found in active drugs, and a reasonable explanation for its requirement for many types of biologic activity may be derived from the contributions of this flat surface to van der Waals' binding to a correspondingly flat receptor area.

The hydrophobic bond is a concept used to explain attractive interactions between nonpolar regions of the receptor and the drug. Explanations such as the "isopropyl moiety of the drug fits into a hydrophobic cleft on the receptor composed of the hydrocarbon side chains of the amino acid valine, isoleucine, and leucine" are commonly used to explain why a nonpolar substituent at a particular position on the drug molecule is important for activity.