COMPUTER AIDED DRUG DESGIN CADD

A. Early Methods

Drug design is the process of finding new medicines for treating diseases. There are two main approaches to drug design:

1. The first one is based on modifying existing molecules, usually from natural sources, to make them more effective or less toxic. This approach has produced many important drugs, such as antibiotics, hormones, and painkillers.

2. The second one is based on understanding the cause of the disease and the structure of the target where the drug will bind. This approach uses computer tools to predict the biological activity and the best fit of potential drugs. This approach is called quantitative structure–activity relationships (QSAR).

   QSAR plays a crucial role in drug design and discovery by establishing mathematical relationships between the chemical structure of compounds (through certain structural parameters) and their biological activities. The main QSAR parameters include:

   1. **Molecular Weight:** Influences pharmacokinetic properties, such as absorption, distribution, metabolism, and excretion (ADME).
   2. **Partition Coefficient:** Partitioning between octanol and water. It reflects the compound's hydrophobicity and membrane permeability.
   3. **Number of Hydrogen Bond Donor/Acceptor:** Indicates the potential for forming hydrogen bonds. It influences the molecule's ability to form specific interactions with biomolecules (ex. Receptors).
   4. **Polar Surface Area:** The surface area of a molecule that is polar and capable of forming hydrogen bonds. It affects interactions with biological targets and influences the compound's permeability

   Some pharmacological concepts (biological activities parameters) that are useful for drug design are:

   - The **ED50**, which is the dose of the drug that produces the desired effect in half of the subjects. The lower the ED50, the more potent the drug is.
   - The **ED90**, which is the dose of the drug that produces the desired effect in 90% of the subjects.
   - The **LD50**, which is the dose of the drug that kills half of the subjects. The lower the LD50, the more toxic the drug is.

- The **MIC**, which is the lowest concentration of the drug that inhibits the growth of bacteria. The lower the MIC, the more effective the drug is against infections.

Partition Coefficient

The most common physicochemical descriptor is the molecule's partition coefficient in an octanol/water system. As emphasized previously, the drug will go through a series of partitioning steps: (a) leaving the aqueous extracellular fluids, (b) passing through lipid membranes, and (c) entering other aqueous environments before reaching the receptor.

In this sense, a drug is undergoing the same partitioning phenomenon that happens to any chemical in a separatory funnel containing water and a nonpolar solvent such as hexane, chloroform, or ether. The **partition coefficient (P)** is the ratio of the molar concentration of chemical in the nonaqueous phase (usually 1-octanol) versus that in the aqueous phase (Equation below).

$$P = \frac{[\text{chemical}]_{oct}}{[\text{chemical}]_{aq}}$$

To obtain a linear correlation between partition coefficient and concentrations, it is more common to use the logarithmic expression (Equation below).

$$\log P = \log\left(\frac{[\text{solute}]_{oct}}{[\text{solute}]_{aq}}\right)$$

A large percentage of drugs are amines whose pKa is such that at physiological pH 7.4, a significant percentage of the drug will be in its protonated, ionized form (BH^+). A similar statement can be made for the HA acids (carboxyl, sulfonamide, imide) in that at physiological pH, a significant percentage will be in their anionic forms(A^-). An assumption is made that the ionic form is water-soluble and will remain in the water phase of an octanol/water system. This reality has led to the use of **log D**, which is defined as the equilibrium ratio of both the ionized and un-ionized species of the molecule in an octanol/water system (Equation below). The percent ionization of ionized HA acids and BH protonated amines and acids can be estimated from previous equations and the log D become as follow:

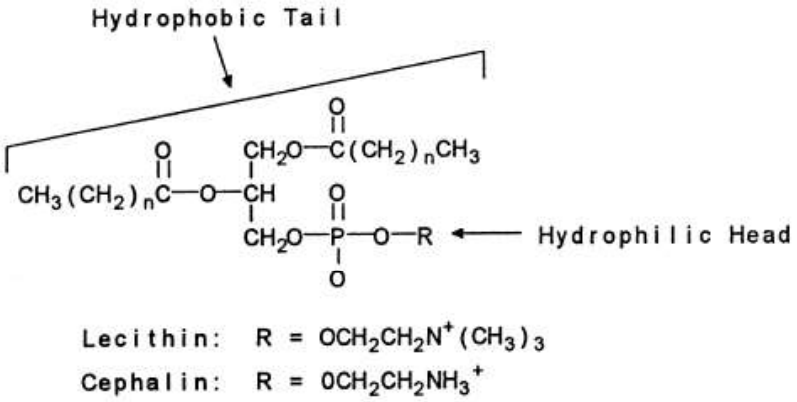
$$\log D = \log\left(\frac{[\text{solute}]_{oct}}{[\text{solute}]_{aq}^{ionized} + [\text{solute}]_{aq}^{nonionized}}\right)$$

$$\log D_{acids} = \log P + \log\left[\frac{1}{(1 + 10^{(pH - pK_a)})}\right]$$

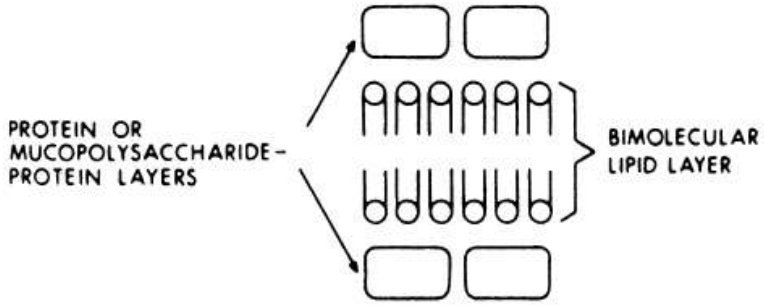
$$\log D_{bases} = \log P + \log\left[\frac{1}{(1 + 10^{(pK_a - pH)})}\right]$$

Because much of the time the drug's movement across membranes is a partitioning process, the partition coefficient has become the most common physicochemical property. The question that now must be asked is what immiscible nonpolar solvent system best mimics the water/lipid membrane barriers found in the body? It is now realized that the **n-octanol/water** system is an excellent estimator of drug partitioning in biological systems.

To appreciate why this is so, one must understand the chemical nature of the lipid membranes. These membranes are not exclusively anhydrous fatty or oily structures. As a first approximation, they can be considered bilayers composed of lipids consisting of a polar cap and large hydrophobic tail. **Phosphoglycerides** are major components of lipid bilayers (Fig. below). Other groups of bifunctional lipids include the **sphingomyelins**, **galactocerebrosides**, and **plasmalogens**. The hydrophobic portion is composed largely of unsaturated fatty acids, mostly with *cis* double bonds. In addition, there are considerable amounts of cholesterol esters, protein, and charged mucopolysaccharides in the lipid membranes. The final result is that these membranes are highly organized structures composed of channels for transport of important molecules such as metabolites, chemical regulators (hormones), amino acids, glucose, and fatty acids into the cell and removal of waste products and biochemically produced products out of the cell. The cellular membranes are dynamic, with the channels forming and disappearing depending on the cell's and body's needs (Fig. below).



General structure of a bifunctional phospholipid



Schematic representation of the cell membrane

For this cell membrane, the two outer layers, one facing the interior and the other facing the exterior of the cell, consist of the polar ends of the bifunctional lipids. These surfaces are exposed to an aqueous polar environment. The polar ends of the charged phospholipids and other bifunctional lipids are solvated by the water molecules. There are also considerable amounts of charged proteins and mucopolysaccharides present on the surface. In contrast, the interior of the membrane is populated by the hydrophobic aliphatic chains from the fatty acid esters.

A partial explanation can be presented as to why the n-octanol/water partitioning system seems to mimic the lipid membranes/water systems found in the body. Water-saturated octanol contains 2.3 M water because the small water molecules easily cluster around octanol's hydroxy moiety. The water in the n-octanol phase apparently approximates the polar properties of the lipid bilayer, whereas the lack of octanol in the water phase mimics the physiological aqueous compartments, which are relatively free of nonpolar components.

In contrast, partitioning systems such as hexane/water and chloroform/water contain so little water in the organic phase that they are poor models for the lipid bilayer/water

system found in the body. At the same time, remember that the n-octanol/water system is only an approximation of the actual environment found in the interface between the cellular membranes and the extracellular/intracellular fluids.

B. Newer Methods

Computational chemistry methods in drug design involve the application of computational techniques and softwares to model and analyze the chemical interactions between drugs and their biological targets. These methods are used to:

1. **Generating pharmacophores:** A pharmacophore is a theoretical framework that represents the essential structural and chemical features necessary for a molecule to interact with a specific biological target and exhibit a particular biological activity. These features include hydrogen bond donors/acceptors, hydrophobic regions, aromatic moieties, and the relative spatial arrangement.
2. **Virtual High Throughput Screening (vHTS):** is a computational approach used in drug discovery to rapidly assess large databases of chemical compounds in silico (using computer simulations), rather than through traditional experimental methods, to identify potential lead compounds with desired biological activity.
3. **Lead Compound Optimization:** A lead compound is an actual chemical entity identified during the early stages of drug discovery that exhibits promising biological activity against a specific target. The lead compound serves as a starting point for further optimization and development into a potential therapeutic agent. Lead compounds are selected based on their ability to interact with a target and their potential for further modification to enhance properties like potency, selectivity, and pharmacokinetics.
4. **In Silico ADME Modeling:** Predicts the Absorption, Distribution, Metabolism, and Excretion (ADME) properties of drugs using computational methods.

Forces Involved in Drug–Receptor Interactions

Keep in mind that it is desirable for most drug to have reversible effects. 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.

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. These compounds carry reactive groups capable of forming covalent bonds and may be irreversibly bound to the receptor by covalent bond formation with reactive groups adjacent to the active site. The diuretic drug ethacrynic acid is an α,β-unsaturated

ketone, thought to act by covalent bond formation with sulfhydryl groups of ion transport systems in the renal tubules. Other examples involve 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.

Therefore, relatively weak forces must be involved in the drug–receptor complex yet be strong enough that other binding sites will not competitively deplete the site of action. Compounds with high structural specificity may orient several weakly binding groups so that the summation of their interactions with specifically oriented complementary groups on the receptor provides total bond strength sufficient for a stable combination. Consequently, most drugs acting by virtue of their structural specificity will bind to the receptor site by:

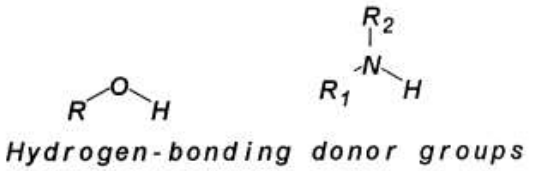
1. Hydrogen bonds,
2. Ionic bonds,
3. Ion–dipole and dipole–dipole interactions.
4. van der Waals and
5. hydrophobic forces.

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 physiological pH would

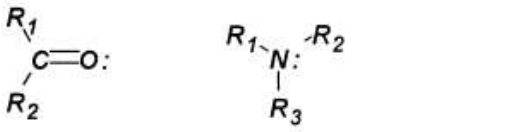
normally occur with the **carboxyl**, **sulfonamido**, and **aliphatic amino** groups, as well as the **quaternary ammonium** group at any pH. These sources of potential ionic bonds are frequently found in active drugs.

Differences in electronegativity between carbon and other atoms, such as oxygen and nitrogen, lead to an asymmetric 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 (dipole-dipole or ion-dipole). **Carbonyl**, **ester**, **amide**, **ether**, **nitrile**, and related groups that contain such dipolar functions, are frequently found in structurally specific drugs.

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, in a drug–receptor combination, several forces could be involved, including the hydrogen bond, which would contribute to the stability of the interaction.



Hydrogen-bonding donor groups



Hydrogen-bonding acceptor groups

Van der Waals forces are attractive forces created by the polarizability of molecules and exerted when any two uncharged atoms approach each other very closely. Although individually weak, the summation of their forces provides a significant bonding factor in higher molecular-weight compounds.

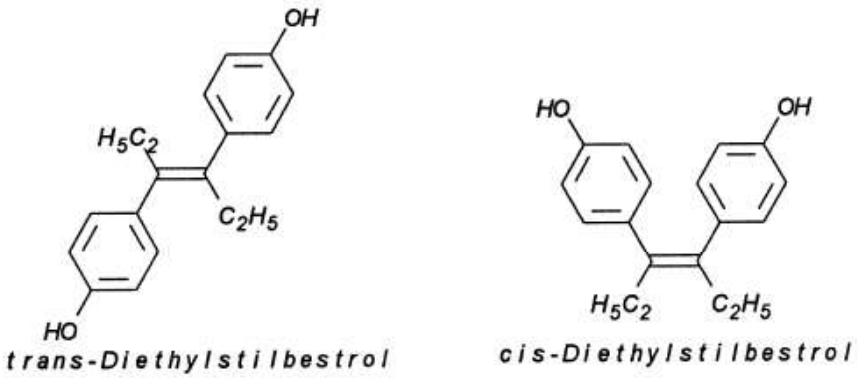
The hydrophobic bond is a concept used to explain attractive interactions between nonpolar regions of the receptor and the drug. Examples such as the isopropyl moiety of the drug fits into a hydrophobic cleft on the receptor composed of the hydrocarbon side chains of the amino acids valine, isoleucine,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

Steric Features of Drugs

To produce its effects, the drug must approach the receptor and fit closely to its surface. Steric factors determined by the stereochemistry of the receptor site surface and that of the

drug molecules are, therefore, of primary importance in determining the nature and the efficiency of the drug–receptor interaction.

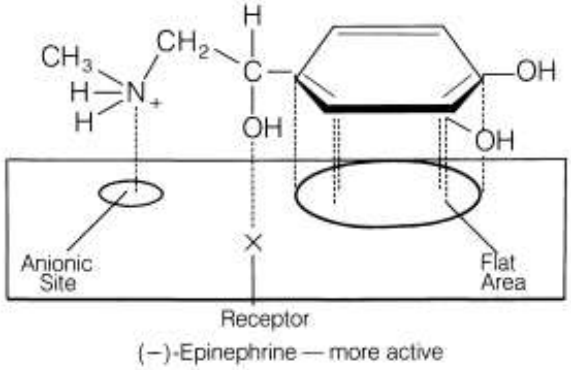
Some structural features contribute a high structural rigidity to the molecule. Example groups attached to aromatic ring will be restricted to the plane of this ring. Also the relative positions of atoms attached directly to multiple bonds are also fixed. For the double bond, *cis*- and *trans*-isomers result. For example, **diethylstilbestrol** exists in two fixed stereoisomeric forms: *trans*-diethylstilbestrol is estrogenic, whereas the *cis*-isomer is only 7% as active.



Geometric isomers (cis-trans isomerism or E-Z isomerism) of drugs not only differ in capabilities for interacting with a biological receptor, but also in their distribution, metabolism and excretion of the molecules because of the related changes in pKa values and rate of lipid solubility characteristics.

Like geometric isomers, conformational isomers (anti, eclipsed, and gauche) exist due to rotation the atoms or groups of atoms around a single bond. This rotation about bonds allows interconversion of conformational isomers. Differences in reactivity of functional groups or interaction with biological receptors may be caused by differences in steric requirements of the receptors. In certain semirigid ring systems, conformational isomers show significant differences in biological activities.

A postulated fit to epinephrine's receptor can explain why (-)-epinephrine exhibits 12 to 15 times more vasoconstrictor activity than (+)-epinephrine. This is the classical three-point attachment model. For epinephrine, the benzene ring, benzylic hydroxyl, and protonated amine must have the stereochemistry seen with the (-) isomer to match up with the hydrophobic or aromatic region, anionic site, and a hydrogen-bonding center on the receptor. The (+) isomer (the mirror image) will not align properly on the receptor.



(−)-Epinephrine — more active

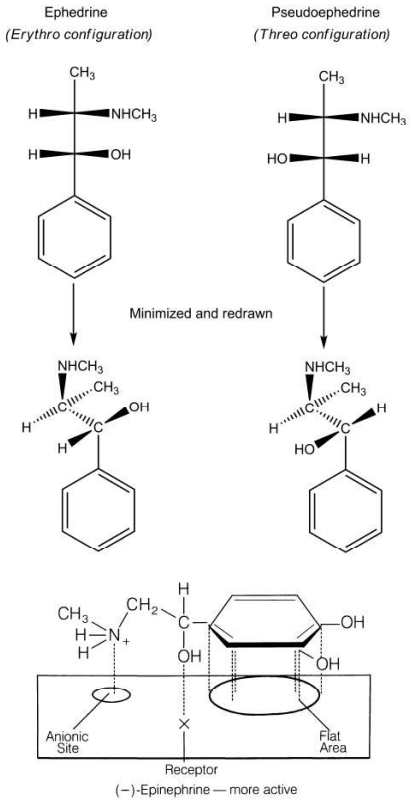
Conformational Flexibility and Multiple Modes of Action

It has been proposed that the conformational flexibility of most open-chain neurohormones, such as acetylcholine, epinephrine, serotonin, histamine, and related physiologically active biomolecules, permits multiple biological effects to be produced by each molecule, by virtue of their ability to interact in a different and unique conformation with different biological receptors. Thus, it has been suggested that acetylcholine may interact with the muscarinic receptor of postganglionic parasympathetic nerves and with acetylcholinesterase in the fully extended conformation and, in a different, more folded structure, with the nicotinic receptors at ganglia and at neuromuscular junctions.

Optical Isomerism and Biological Activity

The *optical activities* has been of particular importance in drug–receptor interactions. Most commercial drugs are asymmetric, meaning that they cannot be divided into symmetrical halves (i.e. optically active).

A large number of drugs are *diastereomeric*, meaning that they have two or more asymmetric centers. Diastereomers have different physical properties. Examples are the diastereomers **ephedrine** and **pseudoephedrine**. The former has a melting point of 79° and is soluble in water, whereas pseudoephedrine's melting point is 118°, and it is only sparingly soluble in water.

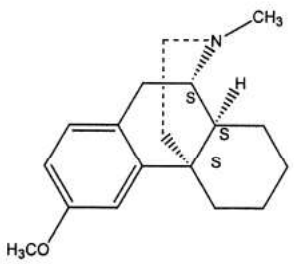


Optical isomers will also have different biological properties. Well known examples of this phenomenon include (-)-hyoscyamine, which exhibits 15 to 20 times more mydriatic activity than (+)-hyoscyamine, and (-)-ephedrine, which shows three times more pressor activity than (+)-ephedrine, five times more pressor activity than (+)-pseudoephedrine, and 36 times more pressor activity than (-)-pseudoephedrine.
All of ascorbic acid's antiscorbutic properties reside in the (-) isomer. A postulated fit to epinephrine's receptor can explain why (-)-epinephrine exhibits 12 to 15 times more vasoconstrictor activity than (+)-epinephrine.
Frequently, the generic name indicates a specific stereoisomer. Examples include levodopa, dextroamphetamine, dextromethorphan, levamisole, dexmethylphenidate, levobupivacaine, dexlansoprazole, and levothyroxine.
Sometimes, the difference in pharmacological activity between stereoisomers is dramatic. The dextrorotatory isomers in the morphine series are cough suppressants with less risk of substance abuse, whereas the levorotatory isomers contain the analgesic activity and significant risk of substance abuse. Dextropropoxyphene contains the analgesic activity, and the *levo*-isomer contains antitussive activity.
More recently drugs originally marketed as racemic mixtures are reintroduced using the active isomer. Examples include racemic citalopram and its S-enantiomer escitalopram; racemic omeprazole and its S-enantiomer esomeprazole.

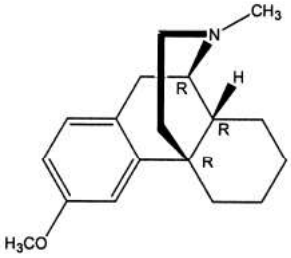
Some drugs were originally approved as racemic mixtures, and later a specific isomer was marketed with claims of having fewer adverse reactions in patients. An example of the latter is the local anesthetic **levobupivacaine**, which is the *S*-isomer of bupivacaine. Both the *R*- and *S*-isomers have good local anesthetic activity, but the *R*-isomer may cause depression of the myocardium leading to decreased cardiac output, heart block hypotension, bradycardia, and ventricular arrhythmias. In contrast, the *S*-isomer shows less cardiotoxic responses but still with good local anesthetic activity.

Escitalopram is the *S*-isomer of the antidepressant citalopram. There is some evidence that the *R*-isomer, which contains little of the desired selective serotonin reuptake inhibition, contributes more to the adverse reactions than does the *S*-isomer.

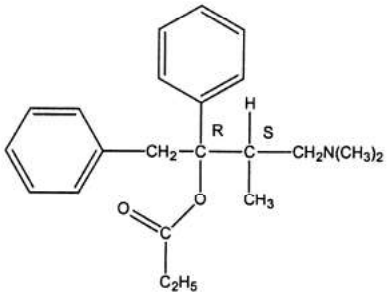
Sometimes it may not be cost-effective to resolve the drug into its stereoisomers. An example is the calcium channel antagonist **verapamil**, which illustrates why it is difficult to conclude that one isomer is superior to the other. *S*-verapamil is a more active pharmacological stereoisomer than *R*-verapamil, but the former is more rapidly metabolized by the first-pass effect.



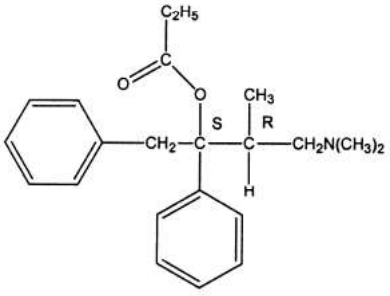
Dextromethorphan



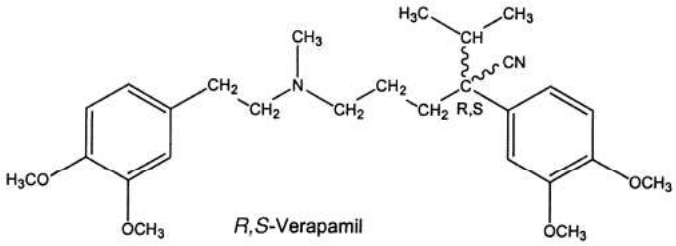
Levomethorphan



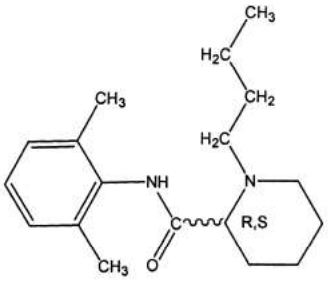
Levopropoxyphene



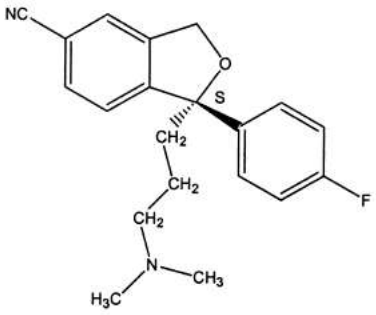
Dextropropoxyphene



R,S-Verapamil

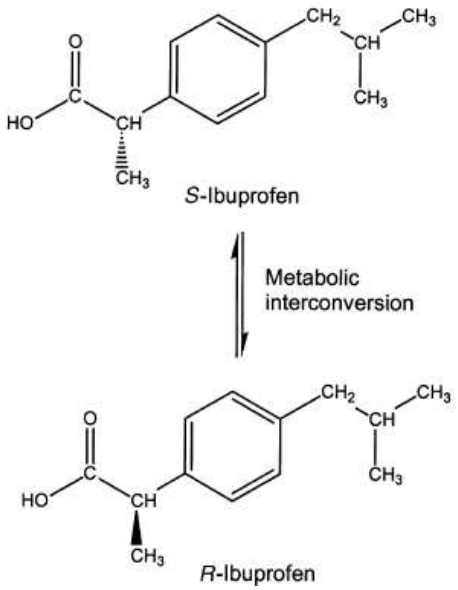


R,S-Bupivacaine



Escitalopram

Because of biotransformations after the drug is administered, it sometimes makes little difference whether a racemic mixture or one isomer is administered. The popular nonsteroidal anti-inflammatory drug (NSAID) **ibuprofen** is sold as the racemic mixture. The S-enantiomer contains the anti-inflammatory activity by inhibiting cyclooxygenase. The *R*-isomer does have centrally acting analgesic activity, but it is converted to the *S* form in vivo.



There are many reasons why stereoisomers show different biological responses, these includes:

1. Most receptors are asymmetric, that could accept one stereoisomer of drug rather than the other.
2. Active transport mechanisms involve asymmetric carrier molecules, which means that there will be preferential binding of one stereoisomer over others.
3. When differences in physical properties exist, the distribution of isomers between body fluids and tissues where the receptors are located will differ.
4. The enzymes responsible for drug metabolism are asymmetric, which means that biological half-lives will differ among possible stereoisomers of the same molecule. This is may be a very important variable because the metabolite may actually be the active molecule.

Chemical databases can contain hundreds of thousands of molecules that could be suitable ligands for a receptor. It is no matter how good the fit is to the receptor, the candidate molecule is of no use if the absorption is poor or if the drug is excreted too slowly from the body. Analysis of drugs has led to a set of "rules" called the *Lipinski Rule of Five* which states that a candidate molecule is more likely to have poor absorption or permeability if:

1. The molecular weight exceeds 500.
2. The calculated octanol/water partition coefficient exceeds 5.
3. There are more than 5 H-bond donors expressed as the sum of O–H and N–H groups.
4. There are more than 10 H-bond acceptors expressed as the sum of N and O atoms.