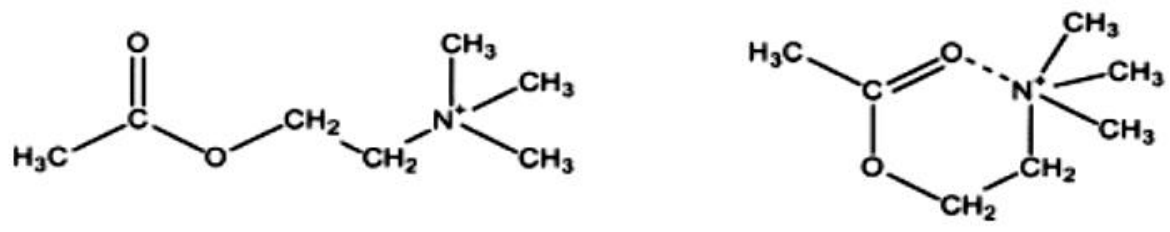
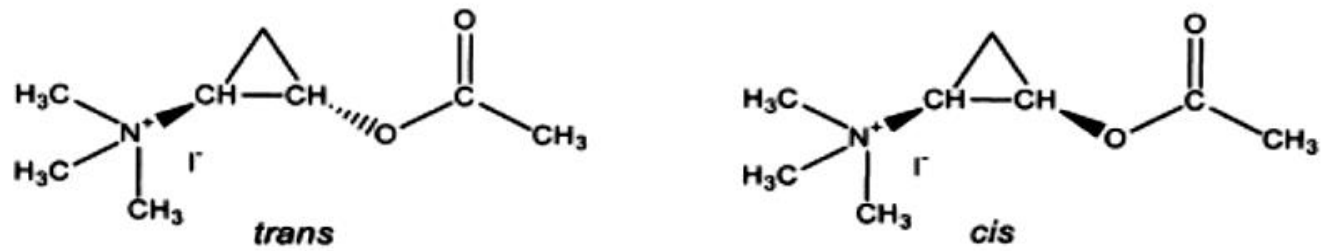
LEC.2
Conformational Flexibility and Multiple Modes of Action

Dr. Mohammed Abdulameer

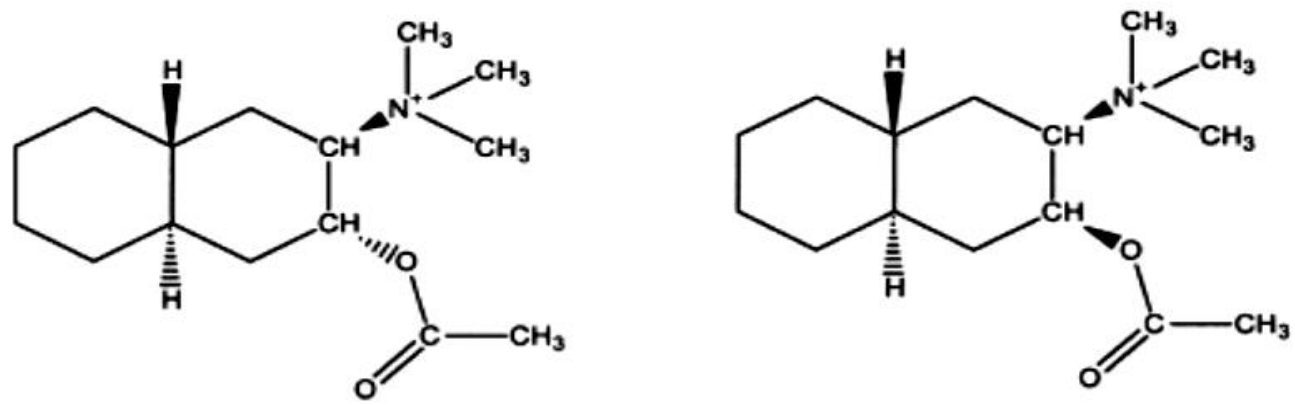
The conformational flexibility of most open-chain neurohormones such as acetylcholine, epinephrine, serotonin, histamine, and related physiologically active biomolecules **permits multiple biological effects to be produced by each molecule**, **by virtue of their ability to interact in a different and 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.



Acetylcholine



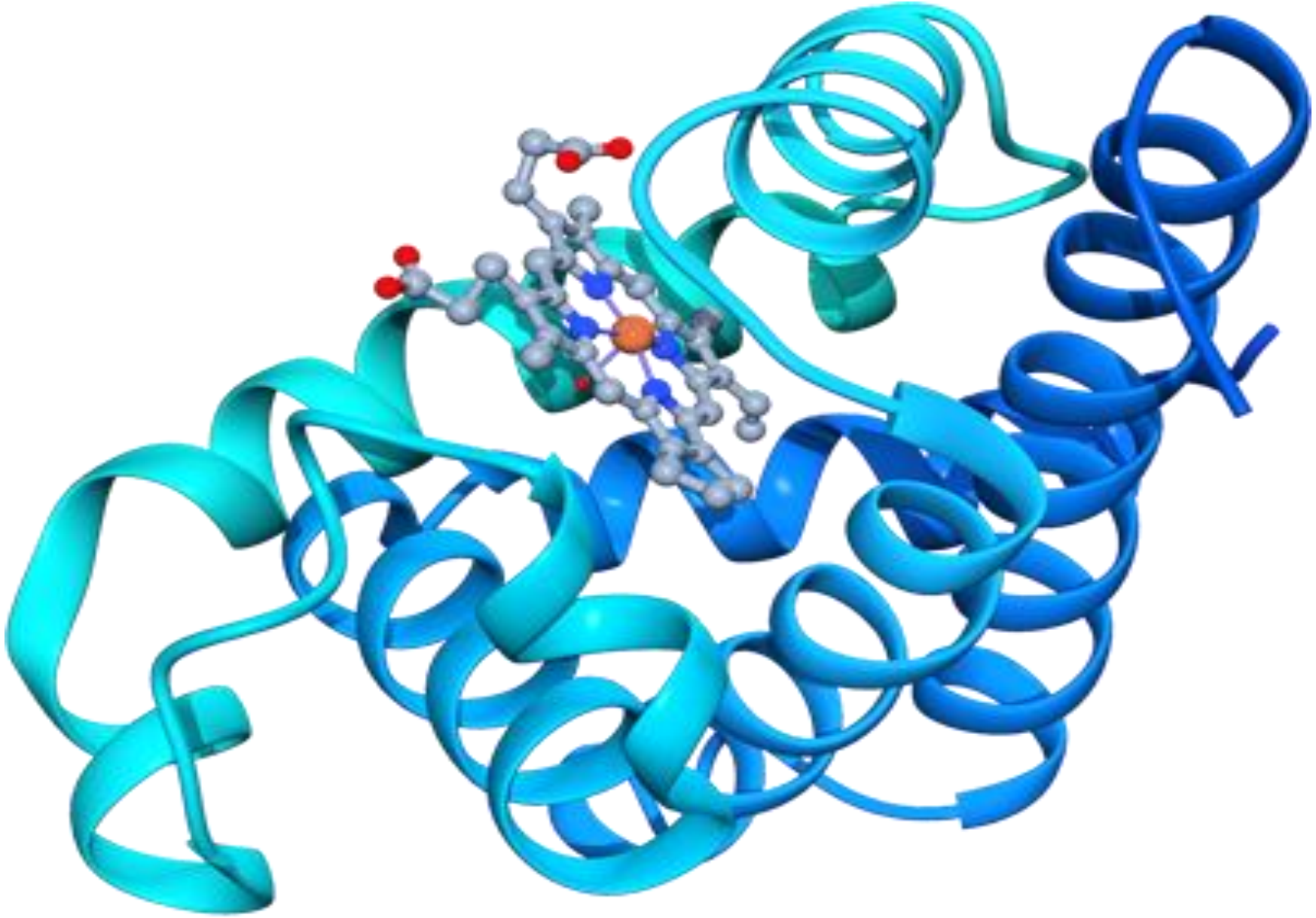
2-Acetoxycyclopropyl trimethylammonium Iodide



3-Trimethylammonium-2-acetoxydecalins

Figure 2.16 • Acetylcholine conformations (only one each of the two possible *trans*- and *cis*-isomers is represented).

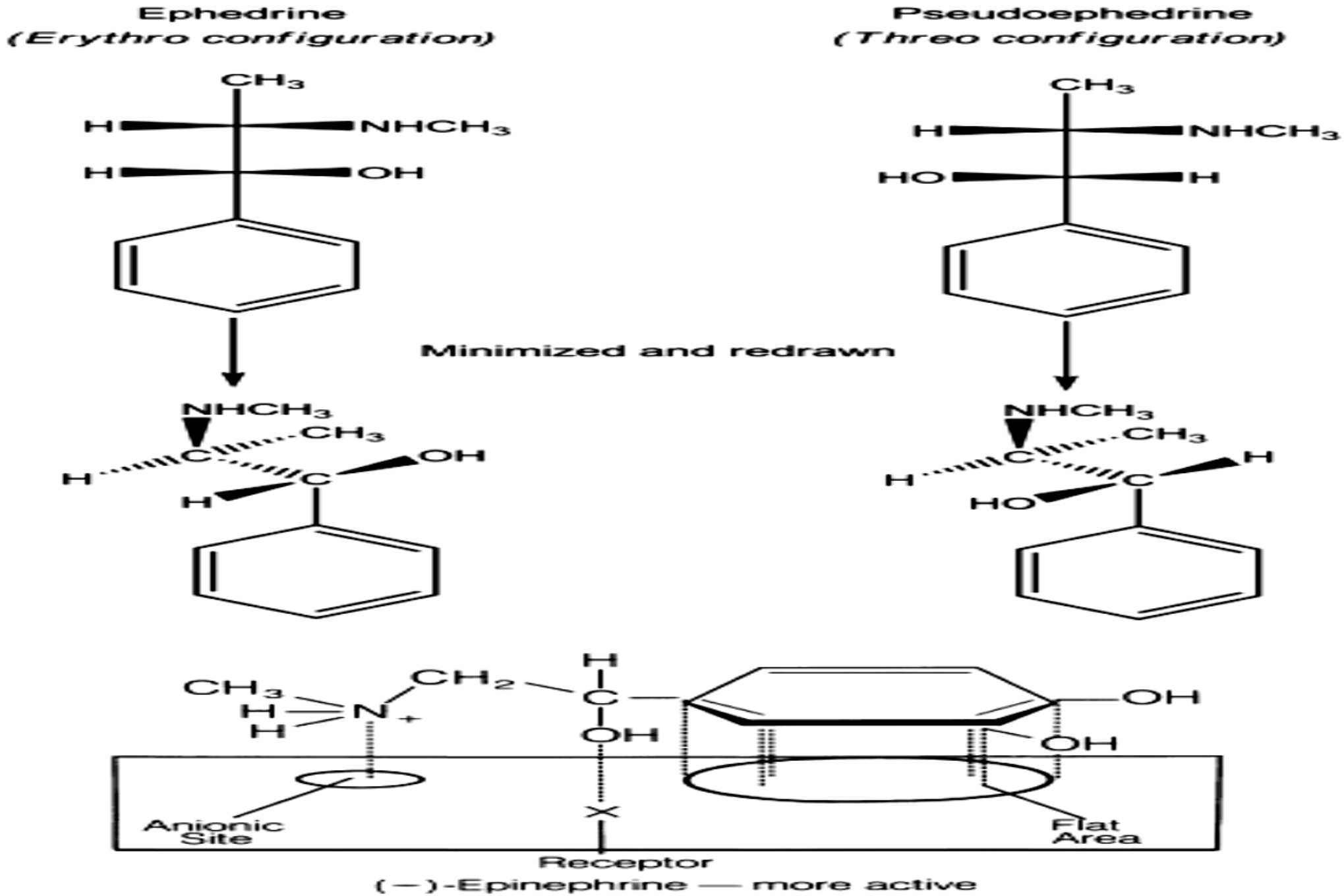
Optical isomerism and Biological Activity



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.

Well-known examples of this phenomenon include **(-)-hyoscyamine**, which exhibits 15 to 20 times more mydriatic activity than **(+)-hyoscyamine, and (-)-ephedrine**, which shows 3 times more pressor activity than **(+)-ephedrine**, 5 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 I5 times more vasoconstrictor activity than (+)-epinephrine.


Ephedrine
(Erythro configuration)
Pseudoephedrine
(Threo configuration)
Minimized and redrawn
Anionic Site
Receptor
Flat Area
(−)-Epinephrine — more active

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 centre on the receptor.**

The (+) isomer (the mirror image) will not align properly on the receptor.

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.

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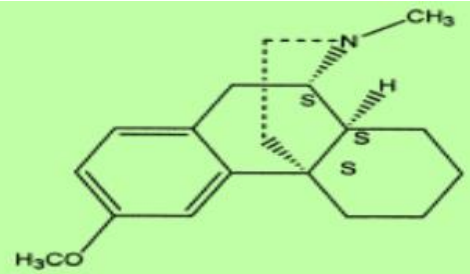
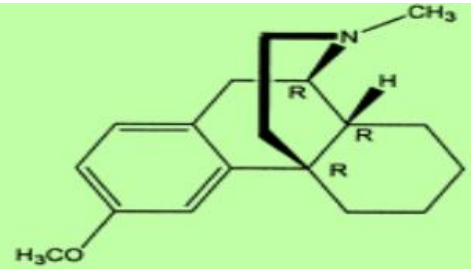
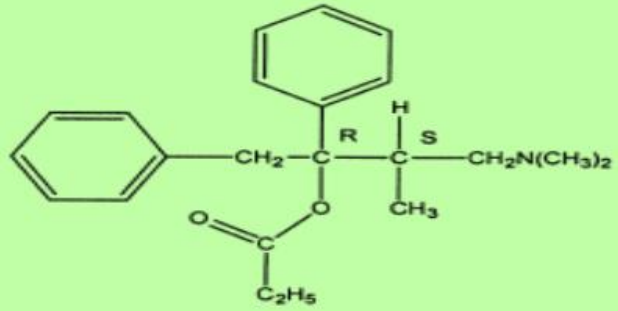
Escitalopram is the S-isomer of the antidepressant citalopram. There is some evidence that the R-isomer, which contains little of the desired selective serotonin reuptake inhibition, contributes more to the adverse reactions than does the S-isomer. Sometimes it may not be cost-effective to resolve the 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.



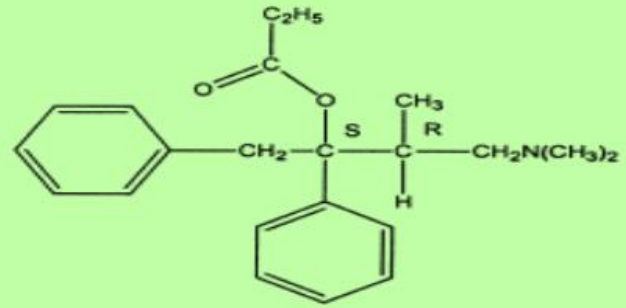
Dextromethorphan



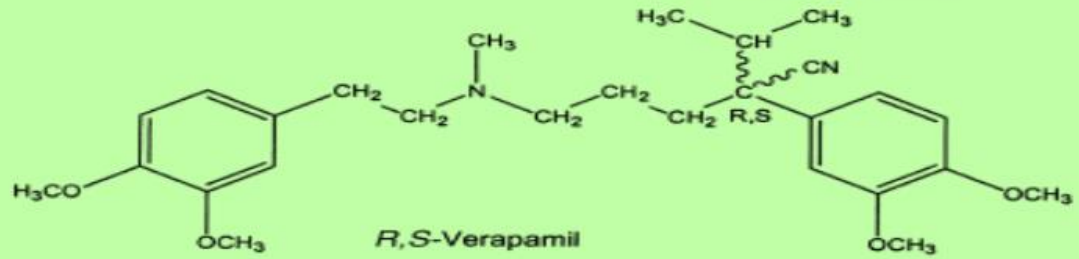
Levomethorphan



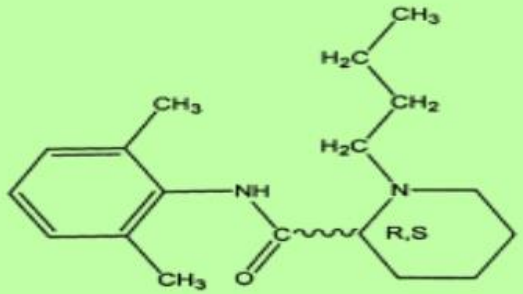
Levopropoxyphene



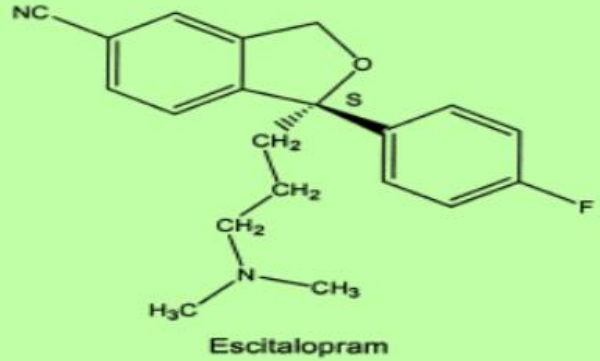
Dextropropoxyphene



R,S-Verapamil



R,S-Bupivacaine



Escitalopram

Figure 2.17 • Examples of drug stereoisomers.

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.

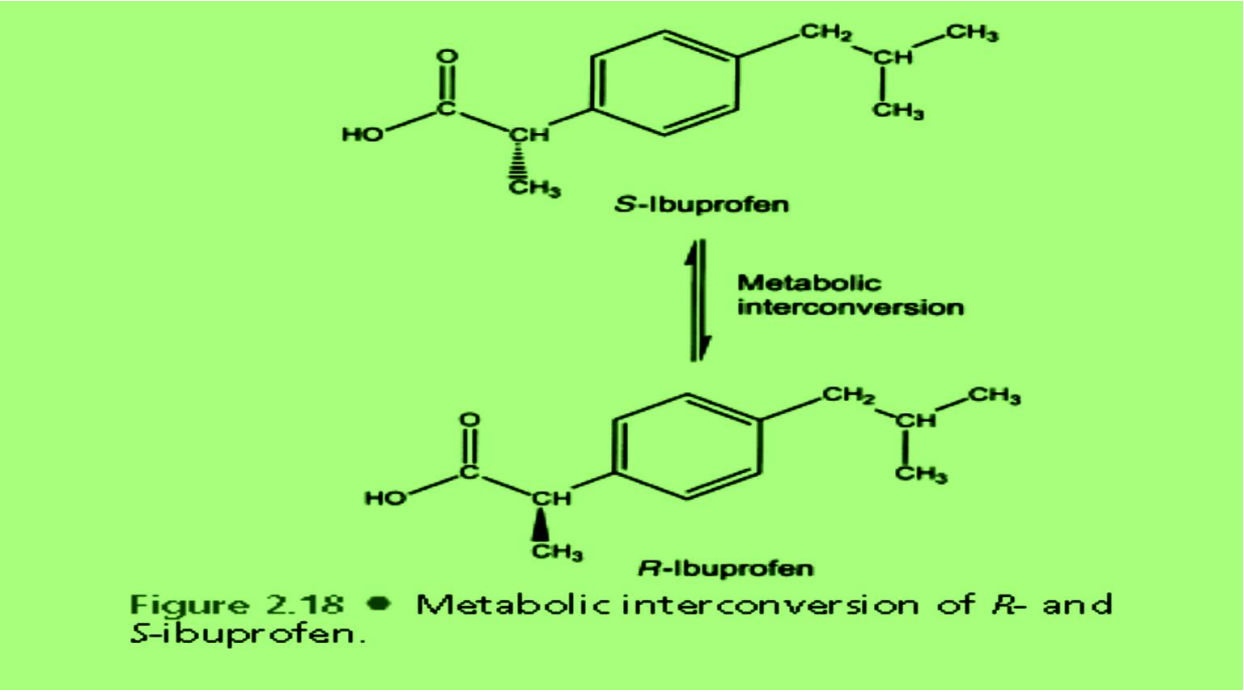


Figure 2.18 • Metabolic interconversion of *R*- and *S*-ibuprofen.

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**