# STEREOCHEMISTRY AND BIOLOGICAL ACTIVITY OF DRUGS

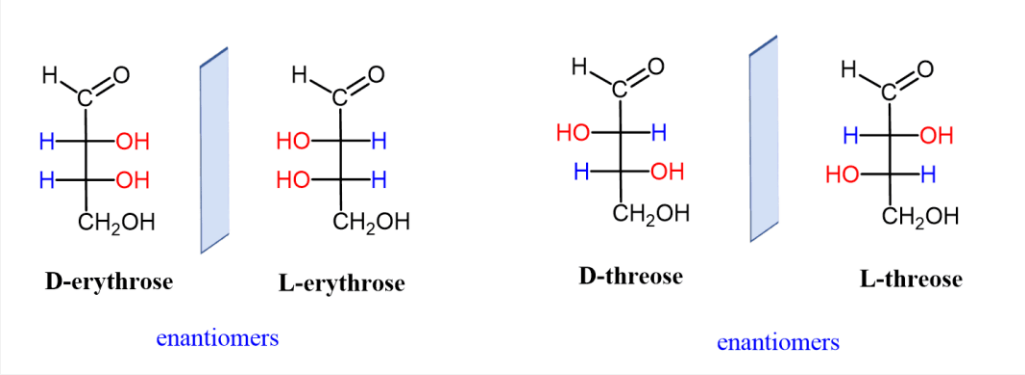
Prof Dr Sibel Süzen

# STEREOCHEMISTRY

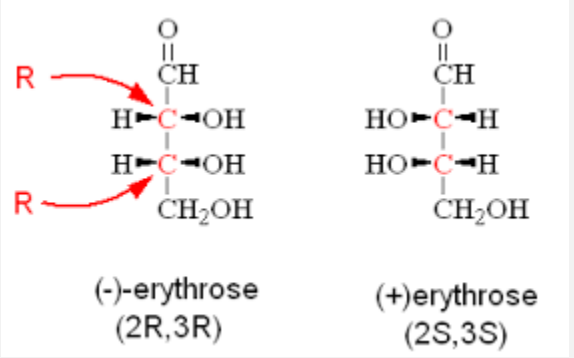
- **Stereochemistry,** a sub-discipline of chemistry, involves the study of the arrangement of atoms within molecules. it is also known as 3D chemistry
- This is an important topic in pharmaceutical chemistry because the shape of a drug molecule affects both its desired *biological activity* and its potential for exhibiting *undesired effects*.

- **Isomer**: Different compounds with the same molecular formula but different chemical structures are called *isomers*. There are different types of isomers.

- **Isomer types:**
  Since, different chemical structures have different properties such as melting point or boiling point, then they can be separated from each other (not always easy).
- It is important to be able to recognise isomers because they can have different chemical, physical properties and biological properties. This is why isomers are very important subject for drug molecules.



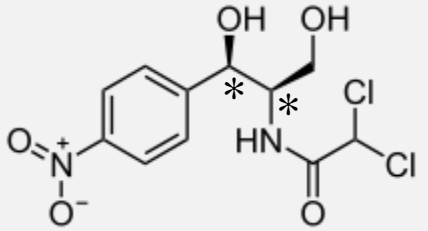

C4H7O4



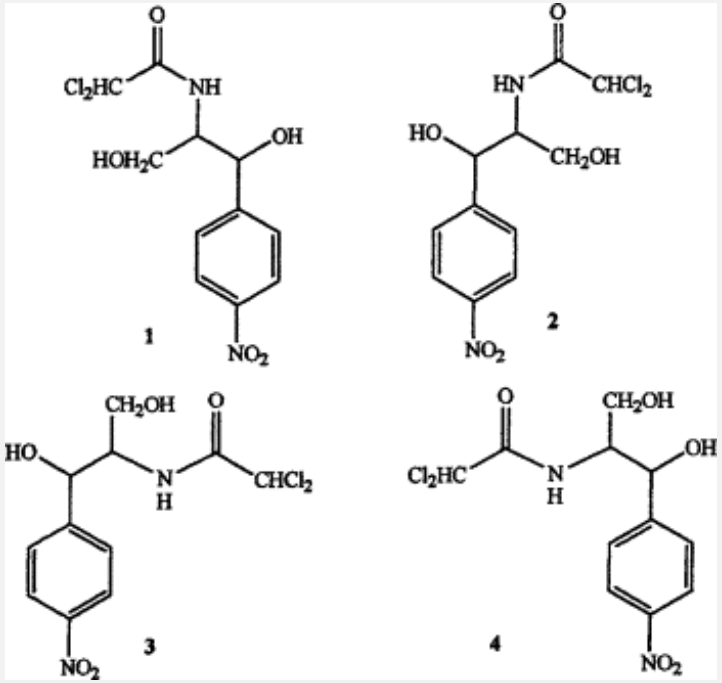
**Chloramphenicol** is an antibiotic useful for the treatment of a number of bacterial infections Common side effects include bone marrow suppression, nausea, and diarrhea. The bone marrow suppression may result in death. To reduce the risk of side effects treatment duration should be as short as possible.

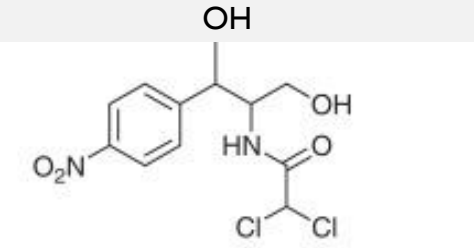
In young children a condition known as gray baby syndrome may occur which results in a swollen stomach and low blood pressure.

The antibiotic is a specific drug for the treatment of typhoid and paratyphoid fevers, dysentery, brucellosis, toxic dyspepsia, trachoma, and other diseases. Chloramphenicol is very effective against bacillary dysentery in children.



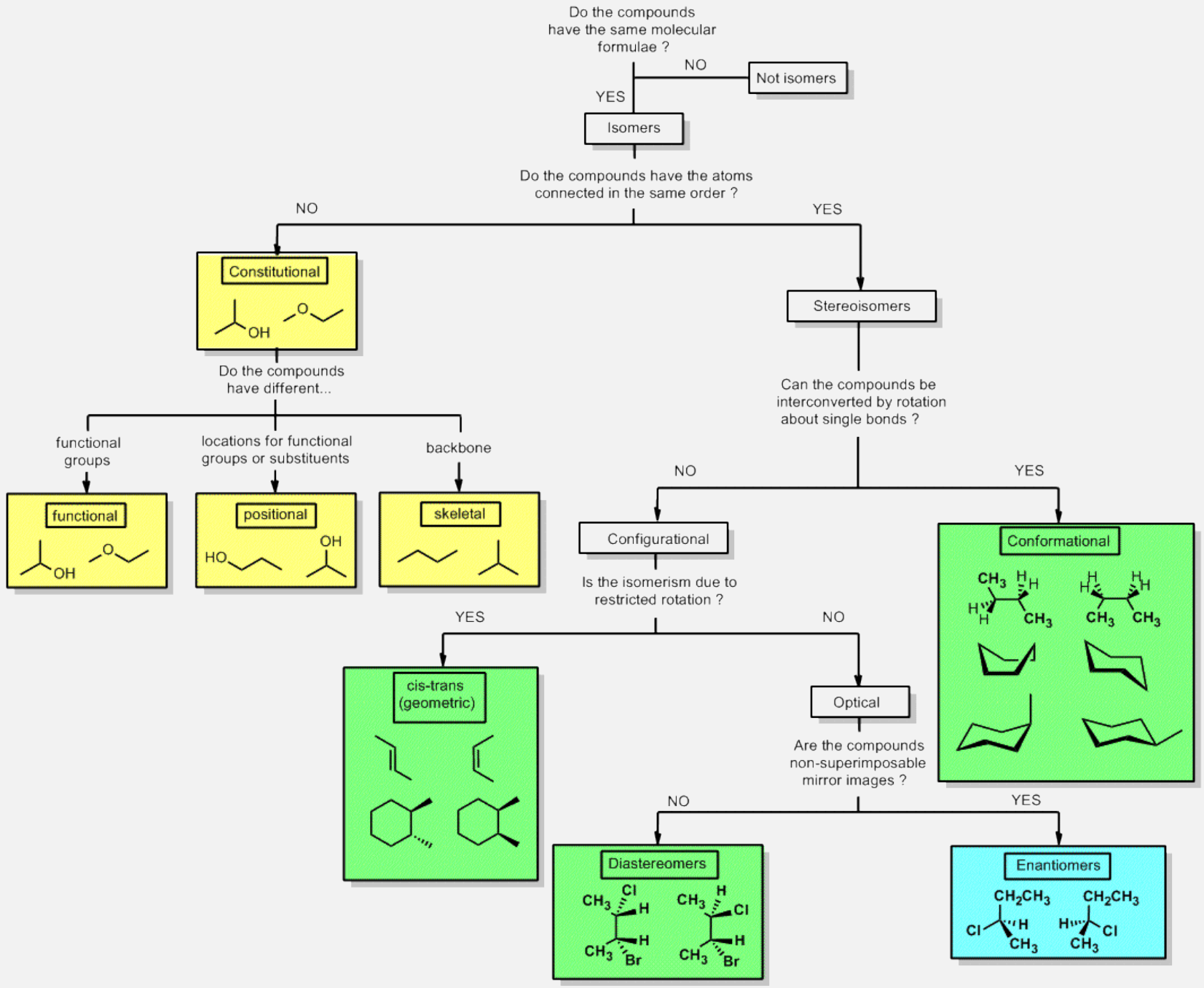
2,2-dichloro-N-((1R,2R)-1,3-dihydroxy-1-(4-nitrophenyl)propan-2-yl)acetamide
D-(-)Threo isomer



Chloramphenicol

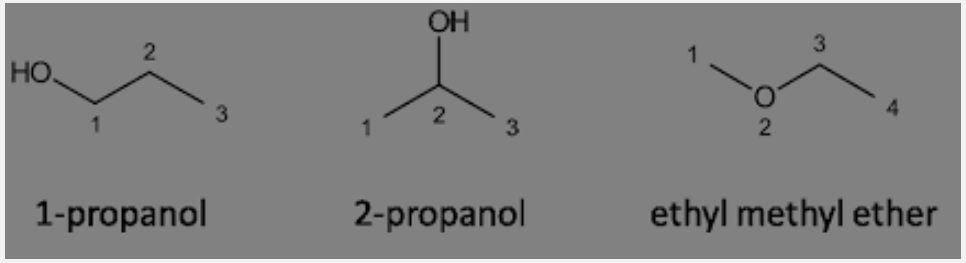
| *Configurations* | *Relative potency* |
|---|---|
| (1*R*,2*R*) | 100 |
| (1*S*,2*S*) | 0.4 |
| (1*S*,2*R*) | 0.4 |
| (1*R*,2*S*) | 2 |




https://www.chem.ucalgary.ca/courses/351/Carey5th/Ch07/ch7-1.html

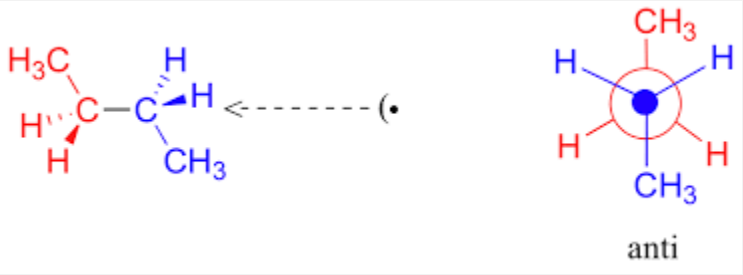
**Constitutional** isomers differ in the *order* in which the atoms are connected together. As a result they can contain different functional groups and / or bonding patterns (*e.g.* functional group location (positional) or hydrocarbon branching (skeletal)). The terms for each of these subclass variations (functional, positional and skeletal) are not particularly commonly used.

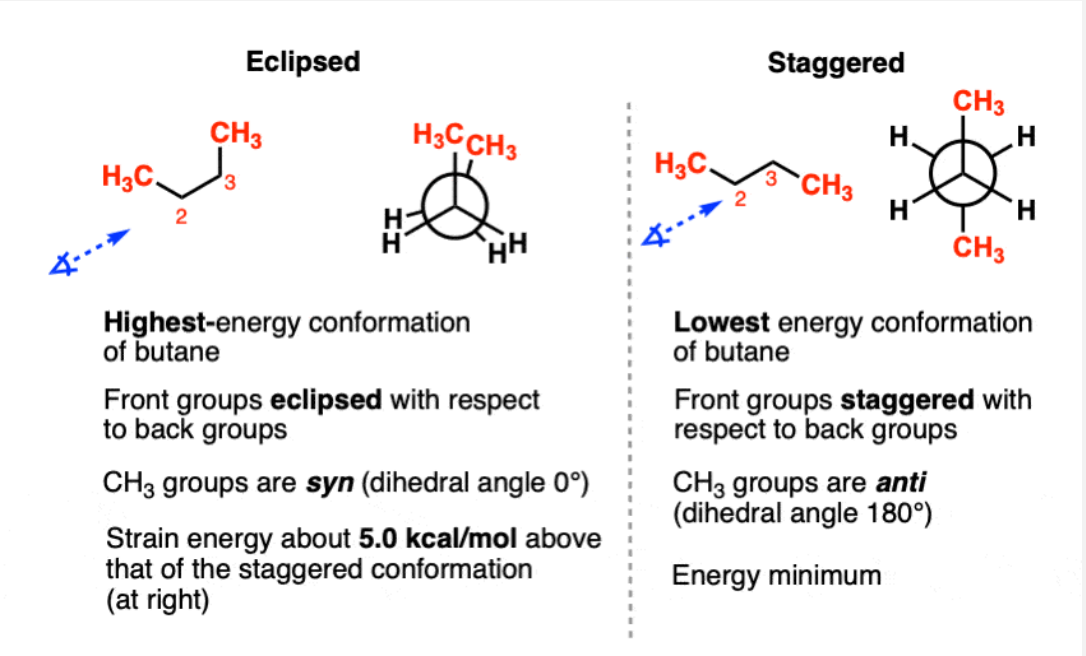
•*example:* 1-propanol, 2-propanol and ethyl methyl ether ($C_3H_8O$)



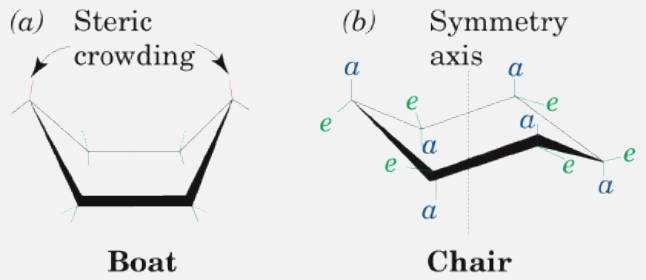

**Conformational isomers** (or conformers or rotational isomers or rotamers) are stereoisomers produced by rotation about s bonds, and are often rapidly interconverting at room temperature

example 1: butane : anti (left) and syn (center).



- *example 2*: cyclohexane : chair and boat conformations.These two forms can be interconverted by twisting the ring structure.




Conformations of the cyclohexane ring (*a*) in the boat conformation and (*b*) in the chair conformation

- **Configurational isomers** are stereoisomers that do not readily interconvert at room temperature and can (in principle at least) be separated. Interconversion of configurational isomers requires bond breaking and bond making.
- **Geometric isomers** (cis-trans isomers) Geometric isomers (or cis-trans isomers) are molecules with a double bond that form cis and trans isomers. • note that square planar molecules can also display geometric isomerism cis and trans refers to the orientation of functional groups within a molecule
- E-2-butene and Z-2-butene


cis-2-butene (Z)-2-butene

trans-2-butene (E)-2-butene

## Differences in Physical and Chemical Properties for Geometric Isomers

- undergo different chemical reactions.
- Stability (trans are usually more stable)
- Polarity
- Boiling/Melting point
- Solubility

## Geometric Isomers and Drugs

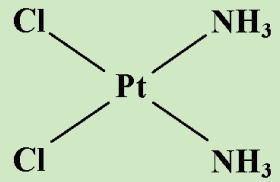
Because geometric isomers have different chemical and physical properties, they act differently as drugs in our bodies as well.

- Example : • **cis-platin** used for chemotherapy. it can enter cancer cells and interact with DNA

- Trans- platin - not active because

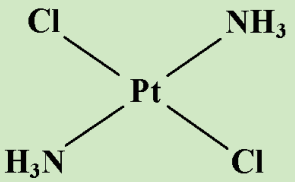
i) the kinetic instability promoting its deactivation and

ii) the formation of DNA adducts characterized by a regioselectivity and a stereochemistry different from those of cisplatin.




Cisplatin

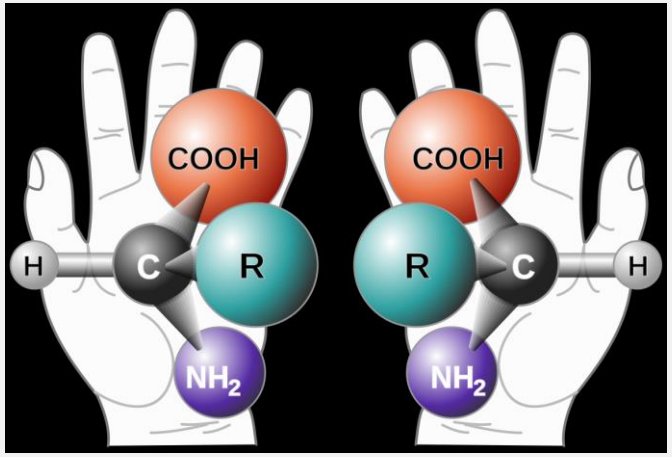
active



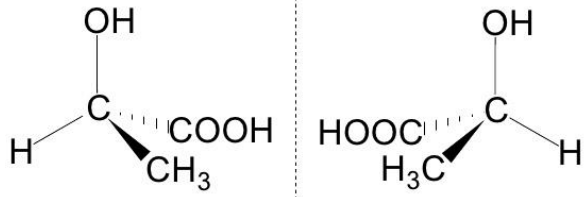

Transplatin

not active

- **Optical** isomers are configurational isomers that differ in the 3D relationship of the substituents about one or more atoms.
- Optical isomers • have a chiral center • non-super imposable mirror images



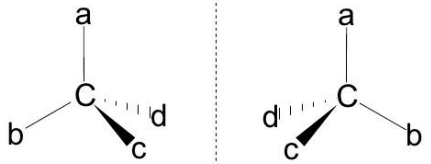

- For some molecules the mirror image is a different molecule (the mirror image is non-superimposable).

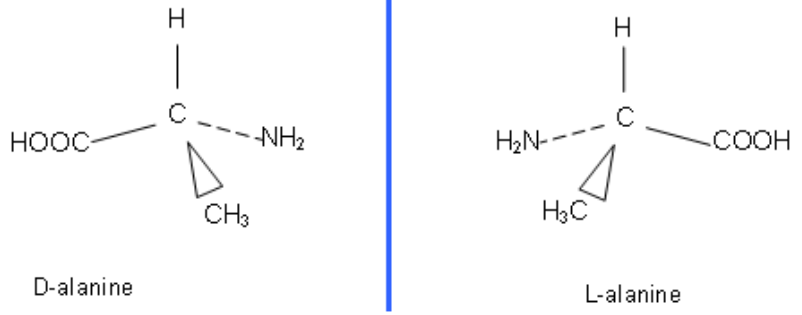



(-) lactic acid in sour milk

(+) lactic acid in muscles

- This usually happens when a molecule contains a C atom with four different groups attached (chiral / asymmetric C).
- Such molecules are said to be chiral or optically active.



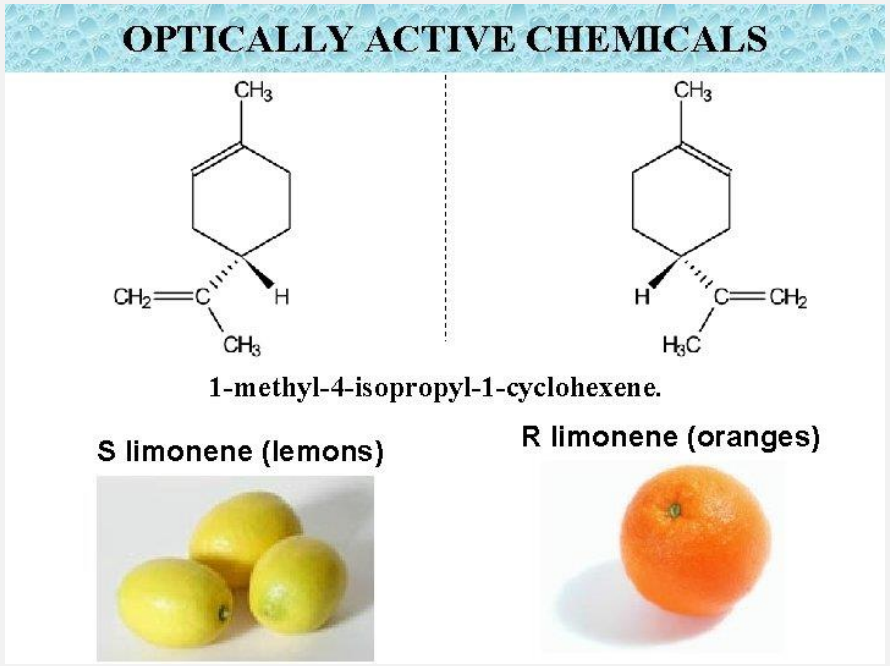




D-alanine

Imaginary Mirror

L-alanine

- **Optical Isomers Terminology**
- **Chiral**: if a molecule is chiral ( or displays chirality) this means the molecule has two optical isomers Chiral centre: the central carbon in an optical isomer with four bonds each attached to a different group.
- **Enantiomer**: another name for a molecule that is found in optical isomers. For example, ibuprofen has a two enantiomers, a left rotating enantiomer and a right rotating enantiomer.
- **Racemic mixture**: A mixture of 50% left rotating and 50% right rotating optical isomers.



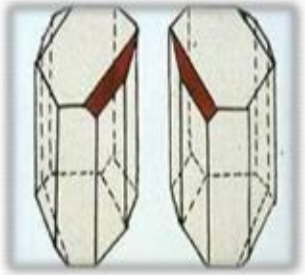

- Stereochemistry : A sub discipline of chemistry, concerned with three dimensional spatial arrangement of the atoms within a molecule.
- Stereoisomers : Compounds with the same molecular connectivity but differ in the spatial arrangement of their constituent atoms or groups.
- Enantiomers : Stereoisomers with non superimposable mirror images.
- Diastereomers : Stereoisomers which are not enantiomers.

3

# RECOGNITION OF CHIRALITY

- Chirality is the fundamental property of 3 –dimensional object.

- Chiral chemistry was identified by Lowis pasteur when in1948,for the first time seperated the 2-isomers of sodium potassium tartarate.

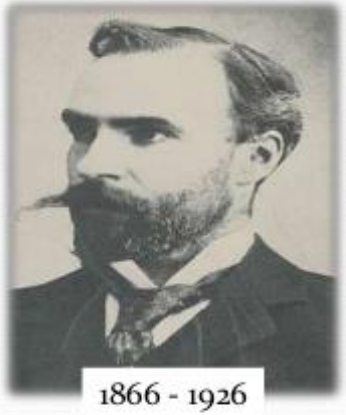


- He found that the two isomers were identical in physiochemical properties but different in their ability to rotate plane polarized light.

https://www.slideshare.net/santupolley/chiral-drugs

# ARTHUR R. CUSHNY & "CHIRAL" PHARMACOLOGY

- (-)-Hyoscyamine almost exactly twice as active as atropine [( )- hysocyamine] (1904).

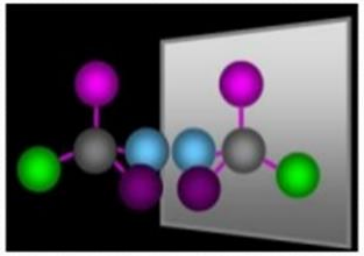


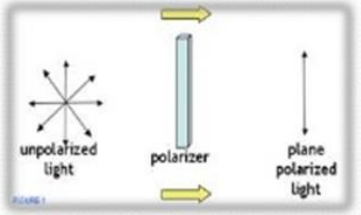
1866 - 1926

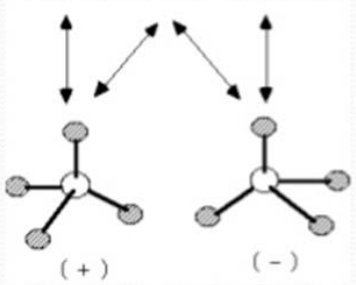
- (-)-Adrenaline twice the potency of ( )-adrenaline as a vasoconstrictor (1908). (-)-enantiomer 12-15 fold more potent than (+)-adrenaline on sympathetic vessels (1909).
- Biological Relations of Optically Isomeric Substances (1926).

# ENANTIOMERS

- Stereoisomers that are mirror images of each other.
- Molecule and mirror image cannot be superimposed into each other even after twisting and turning them.
- Identical physical and chemical properties



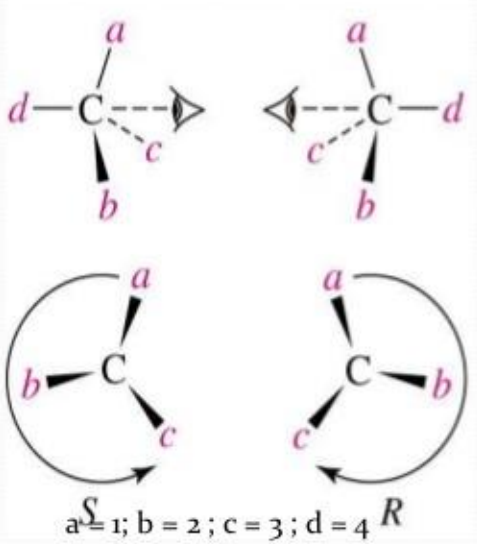



- Dextrorotatory ("+" / "d" form) - clockwise direction.
- Levorotatory ("-" / "l" form) - anti-clockwise direction.

# R/S SYSTEM

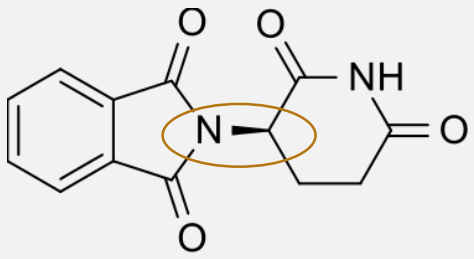
- Priority of an atom is determined by its atomic number
- Order of substituents going from highest to lowest priority.
- Clockwise – **R** (rectus).
- Anticlockwise – **S** (sinister).




- Unless established experimentally no idea whether (+) or (-) rotation is associated with R or S configuration.

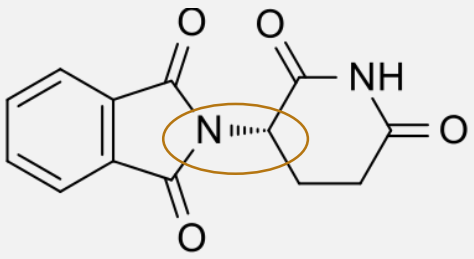
https://www.slideshare.net/santupolley/chiral-drugs

- **Optical Isomers and Drugs**
- • Optical Isomers interact differently in our bodies because our bodies themselves are chiral.
- • Thus important to make sure you have the right optical isomers in your drugs.
- • **Thalidomide tragedy-** one enantiomer stops morning sickness in pregnant women. The drug was sold as a racemic mixture to reduce costs. However, it was later discovered that the other enantiomer causes severe birth defects.
- Thalidomide was first marketed in 1957 in West Germany, where it was available over the counter. When first released, thalidomide was promoted for aniety, trouble sleeping, "tension", and morning sickness.
- While it was initially thought to be safe in pregnancy, concerns regarding birth defects arose in 1961 and the medication was removed from the market in Europe that year. The total number of embryos affected by use during pregnancy is estimated at 10,000, of which about 40% died around the time of birth.
- The mechanisms underpinning the teratogenic effects of thalidomide are unclear.




**(R)-thalidomide**

- R form sedative




**(S)-thalidomide**

**S form teratogenic**

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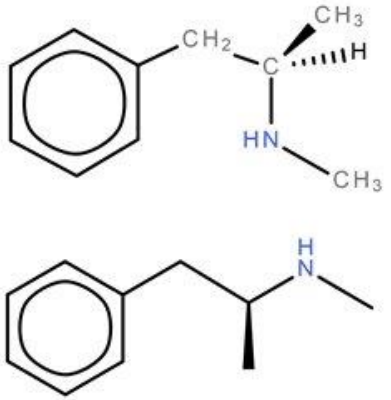
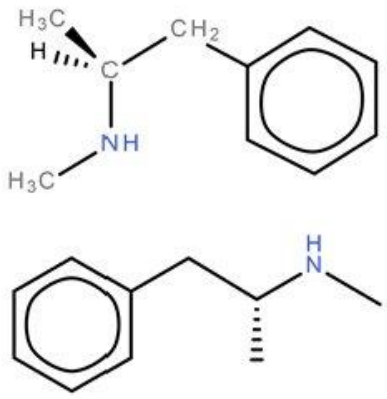
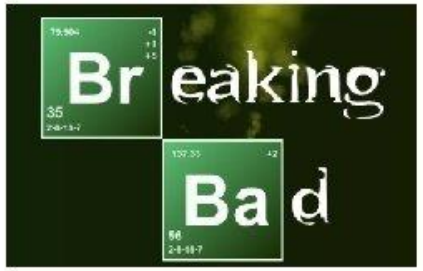
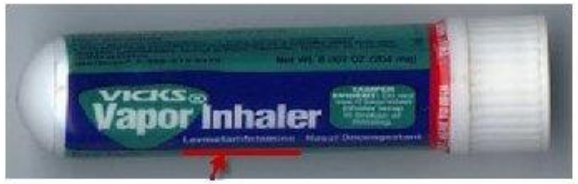


S methamphetamine
(illegal psychotic drug)



R methamphetamine
(nasal decongestant)

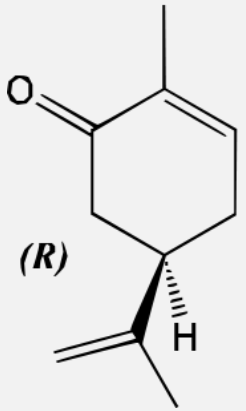


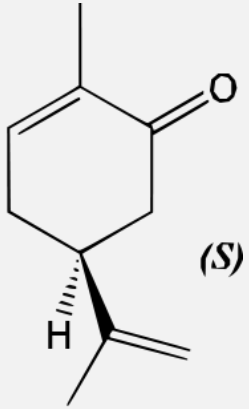




https://chem.libretexts.org/

Spearmint.

Caraway fruits.



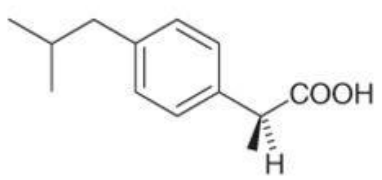

(R) smells like spearmint

(S) smells like caraway.

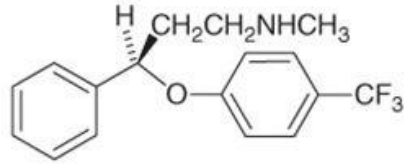
# Stereochemistry

## Chemical Properties of Enantiomers

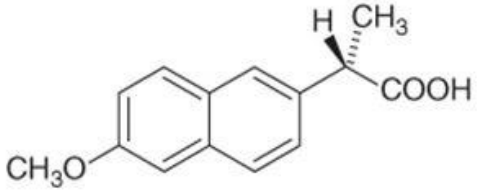
- **Two enantiomers have exactly the same chemical properties except for their reaction with chiral non-racemic reagents.**
- **Many drugs are chiral and often must react with a chiral receptor or chiral enzyme to be effective. One enantiomer of a drug may effectively treat a disease whereas its mirror image may be ineffective or toxic.**



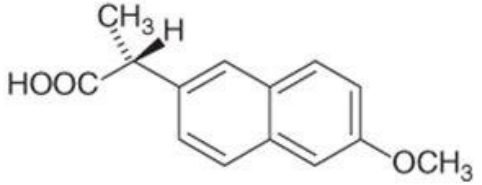

**(*S*)-ibuprofen**
anti-inflammatory agent




**(*R*)-fluoxetine**
antidepressant

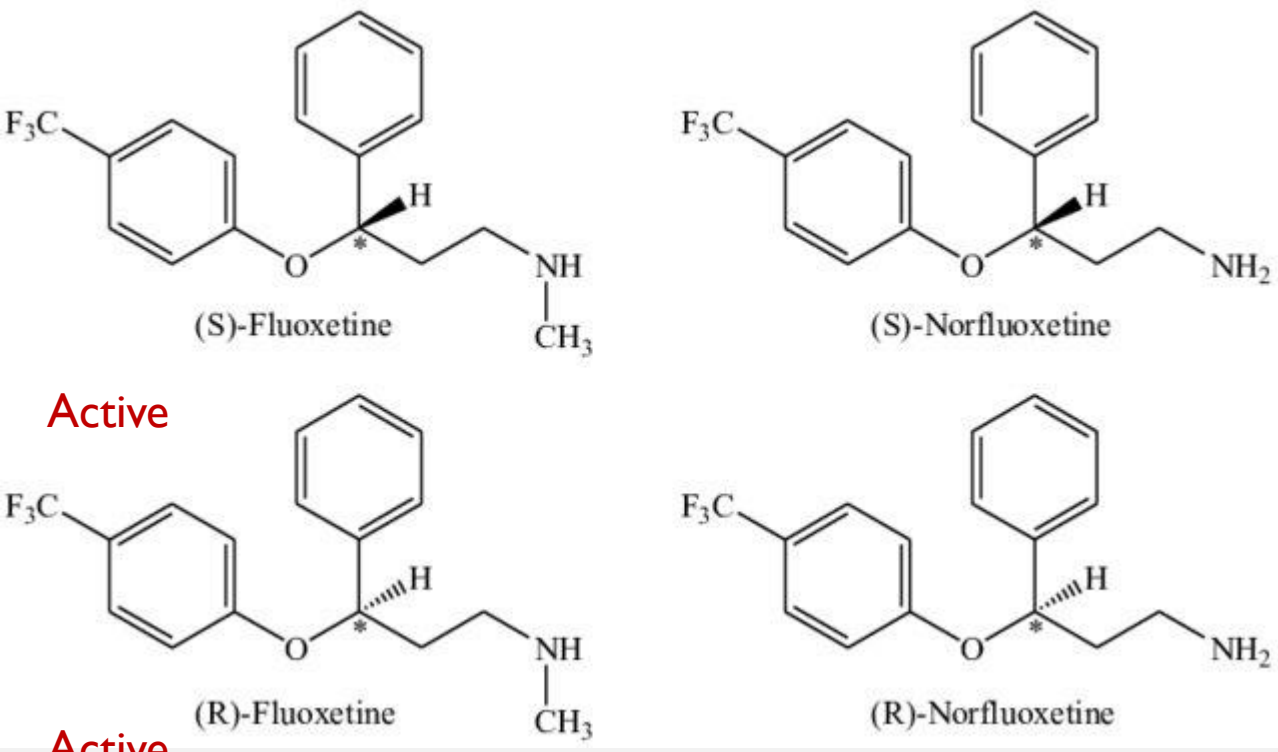



**(*S*)-naproxen**
anti-inflammatory agent




**(*R*)-naproxen**
liver toxin

# FLUOXETİNE




Used as rasemic mix.

Metabolites

- Fluoxetine (FLX) is the drug most frequently used for the treatment of depressive states during pregnancy and is available for clinical use as a racemic mixture of (+)-(S)-and (-)-(R)-FLX.
- FLX N-demethylation produces its active metabolite norfluoxetine (NorFLX).
- S-fluoxetine is an enantiomer of fluoxetine, a potent and selective inhibitor of the neuronal serotonin-uptake carrier and a clinically effective antidepressant.
- R-fluoxetine and S-fluoxetine enantiomers are nearly equipotent at blocking serotonin reuptake. In all biochemical and pharmacological studies, the eudismic ratio for the fluoxetine enantiomers is also near unity.
- A study examining the relative contributions of CYP enzymes to the metabolism of S-fluoxetine, and R-fluoxetine found dramatic differences. These data led to discovery programs between Lilly and Sepracor for the individual enantiomers. S-fluoxetine was studied in a phase 2 clinical trial for the prophylaxis of migraine, however, development was discontinued.

# NAPROXEN

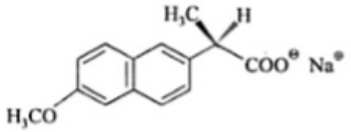
- Naproxen is a non-steroidal, antiinflammatory (NSAI) agent. It is a non-selective COX-1 and COX-2 inhibitör.
- Structurally, naproxen is a propionic acid-derived, non-steroidal, anti-inflammatory drug with a chiral center.
- The (+) form is the active isomer. It exhibits analgesic, antiinflammatory, and antipyretic properties in human clinical studies and animal models of inflammation.
- Naproxen • (S)-(+)-naproxen is used to treat arthritis pain, but (R)-(–)-naproxen causes liver poisoning with no analgesic effect.
- Mechanism of liver damage: The mechanism of hepatotoxicity from naproxen is not known, but it is metabolized by the cytochrome P450 system and idiosyncratic injury may be due to a toxic metabolite. Cross sensitivity to hepatic injury with fenoprofen suggests that the propionic acid may be responsible for the injury.
-

## CHEMICAL PROPERTIES

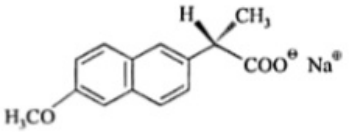
Enantiomers

(R) Isomers
- (R) Naproxen (inactive)

(S) Isomers
- (S) Naproxen (NSAID)




liver poisoning
no analgesic effect




active

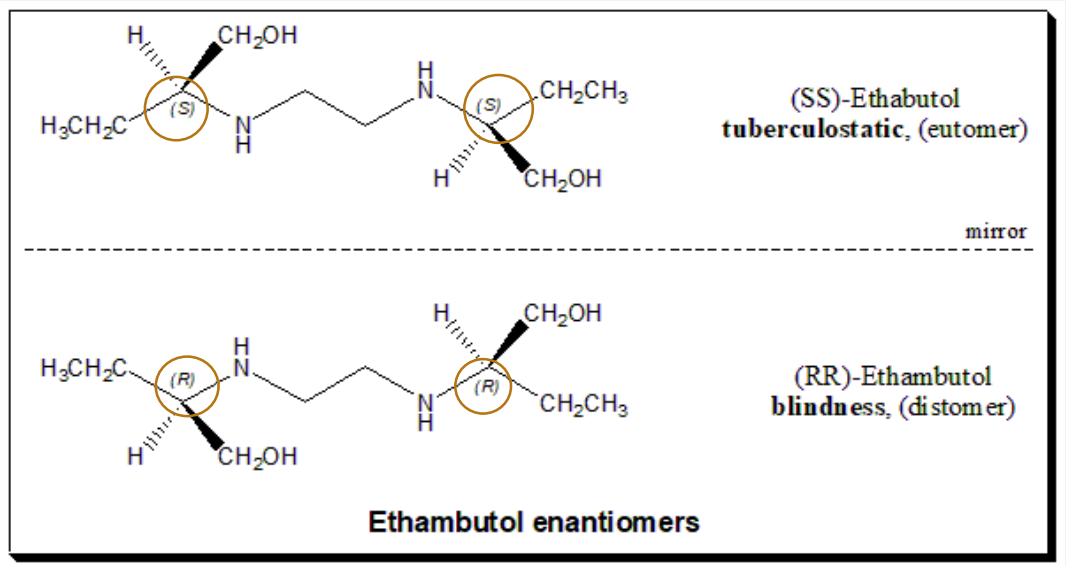
# ETHAMBUTOL

D-Ethambutol is an antituberculosis drug that can inhibit the transfer of mycolic acids into the cell wall of the tubercle bacillus.

It may also inhibit the synthesis of spermidine in mycobacteria.

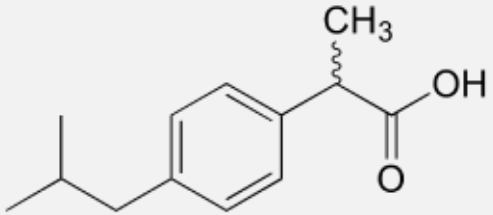
This decreases tubercle bacilli replication, thus preventing the spread of Mycobacterium tuberculosis in the human body. Nearly all strains of M. tuberculosis are sensitive to ethambutol.

The (R,R)-(–)-ethambutol causes blindness. Ethambutol-induced optic neuropathy (EON) is a well-known complication arising from the use of ethambutol, the severity of which is in a dose-dependent manner. It is not always safe to use racemic mixtures for drugs.

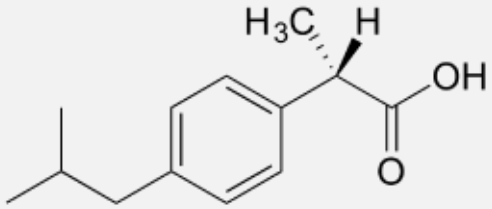


# IBUPROFEN

- The over-the-counter painkiller ibuprofen is currently sold as a racemic mixture, but only the *S* enantiomer is effective, due to the specific way it is able to bind to and inhibit the action of prostaglandin $H_2$ synthase, an enzyme in the body's inflammation response process. The *R* enantiomer of ibuprofen does not bind to prostaglandin $H_2$ synthase in the same way as the *S* enantiomer, and as a consequence does not exert the same inhibitory effect on the enzyme's action. Fortunately, (*R*)-ibuprofen apparently does not cause any harmful side effects, and is in fact isomerized gradually by an enzyme in the body to (*S*)-ibuprofen.
-




racemic ibuprofen



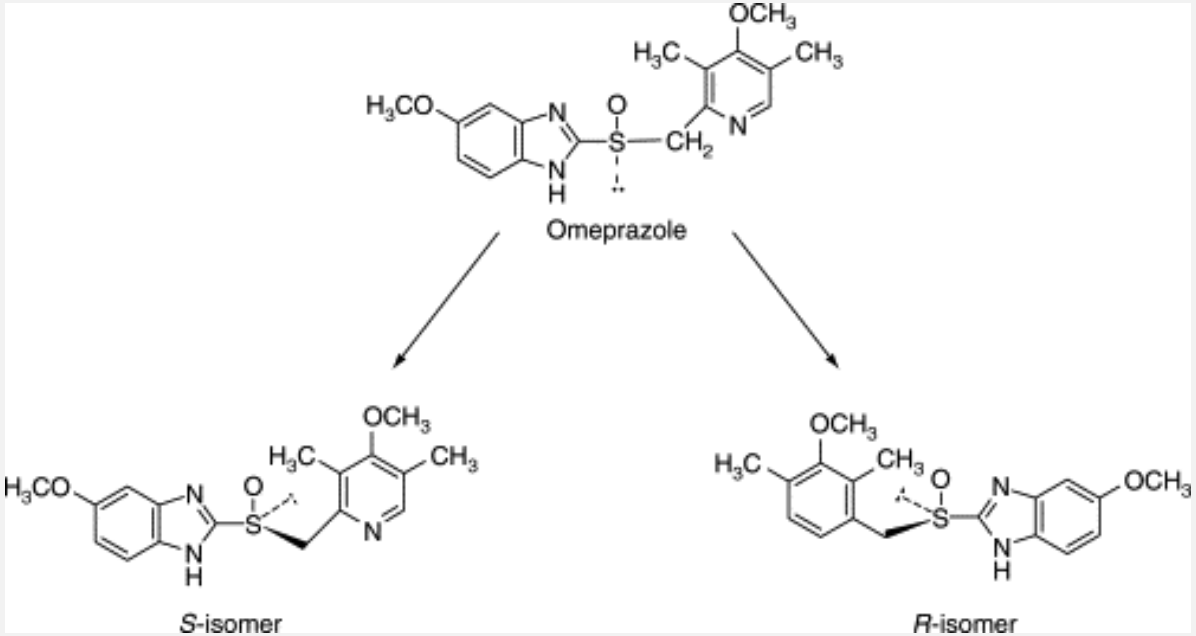

(*S*)-ibuprofen
(active enantiomer)

not cause any harmful side effects

Active

https://chem.libretexts.org/Bookshelves/Organic_Chemistry/Book%3A_Organic_Chemistry_with_a_Biological_Emphasis_v2.0_(Soderberg)/03%3A_Conformations_and_Stereochemistry/3.11%3A_Stereochemistry_in_biology_and_medicine

# OMEPRAZOLE

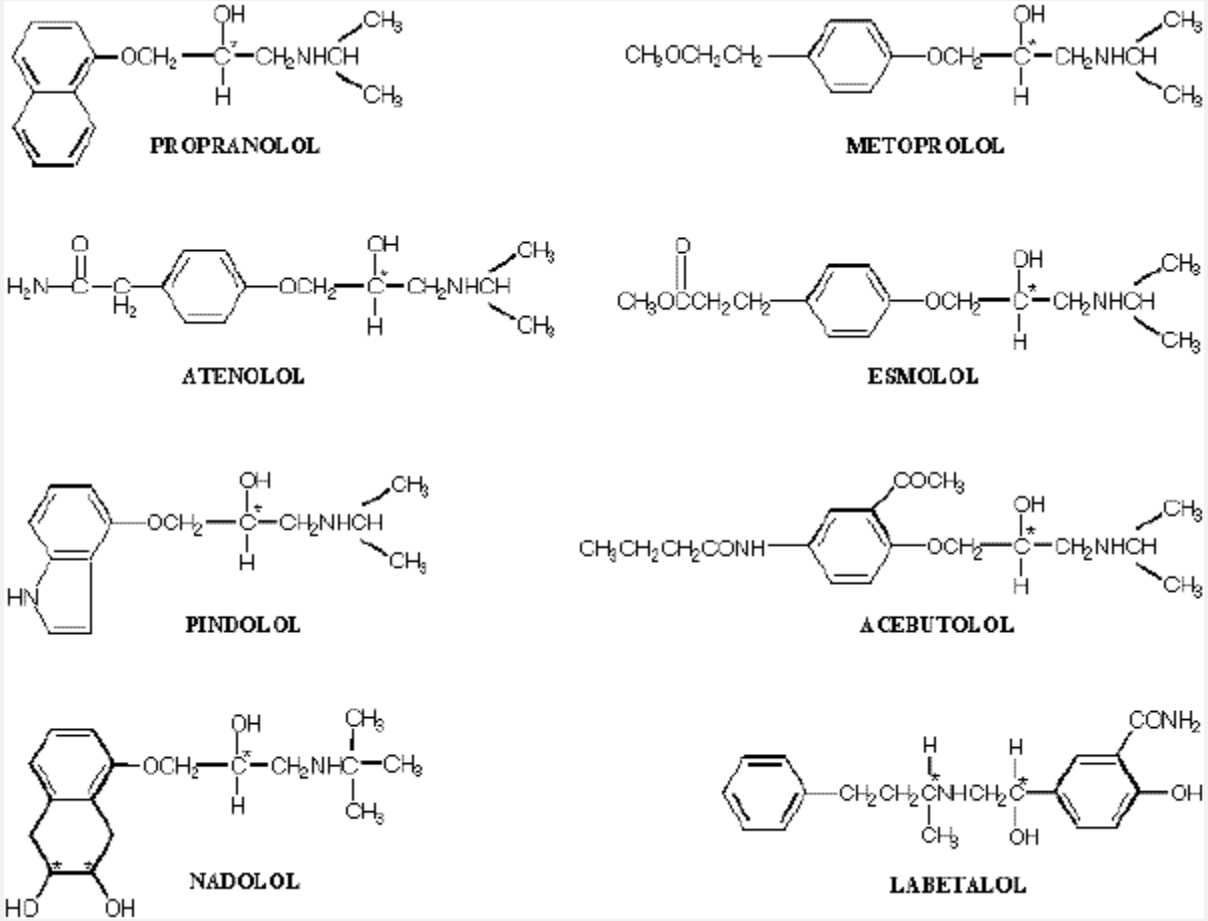



both enantiomers have the same activity

Omeprazole is a proton pump inhibitor (PPI) in gastric parietalcells and has been widely used in the treatment of peptic ulcer, reflux oesophagitis and Zollinger–Ellison syndrome. The molecular structure of omeprazole is composed of a substituted pyridine ring linked to a benzimidazole by a sulphoxide group

- Normally, this drug is a racemate with a chiral center in the sulphoxide group
- It was demonstrated that both enantiomers have the same in vitro capacity to decrease gastric acid formation, but stereoselective metabolism by cytochrome P450 2C19 (CYP2C19) results in different plasma concentrations.
- The S-(–)-enantiomer of omeprazole is less susceptible to small intestinal and hepatic metabolism than the (R)-isomer, and therefore, the chiral drug achieves between 70% and 90% higher steady-state serum concentration than the racemic omeprazole

# Beta-Blockers




The beta-blockers comprise a group of drugs that are mostly used to treat cardiovascular disorders such as hypertension, cardiac arrhythmia, or ischemic heart disease.

Each of these drugs possesses at least one chiral center, and an inherent high degree of enantioselectivity in binding to the beta-adrenergic receptor.

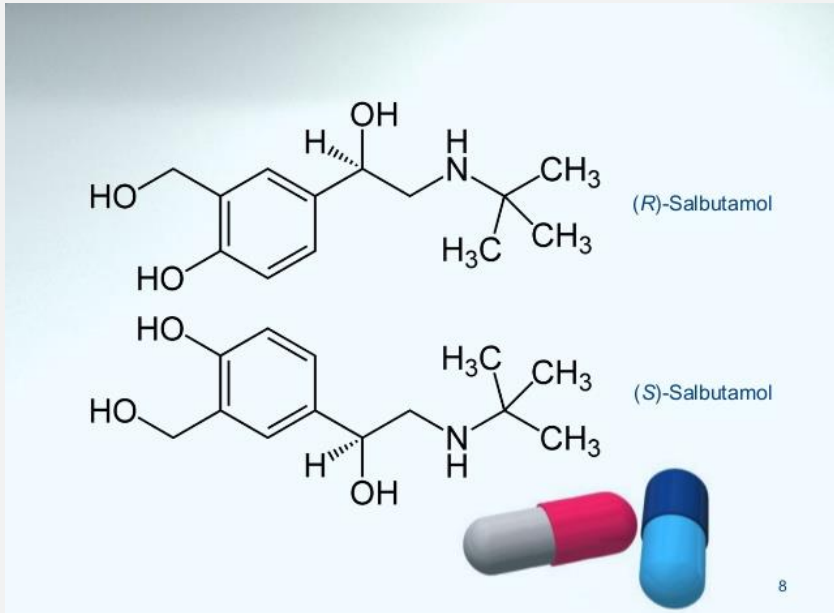
For beta-blockers with a single chiral center, the (-) enantiomer possesses much greater affinity for binding to the beta-adrenergic receptors than antipode.

**Except for timolol, which is marketed as S-enantiomer, each of the beta-blockers with one chiral center (e.g., propranolol, metoprolol, atenolol, esmolol, pindolol, and acebutolol) is marketed as a racemate consisting of two enantiomers.**

The nonselective beta-blockers, including propranolol, oxprenolol, pindolol, nadolol, timolol and labetalol, each antagonize both $beta_1$ - and $beta_2$ -adrenergic receptors. For the selective antagonists, including metoprolol, atenolol, esmolol, and acebutolol, each has much greater binding affinity for the $beta_1$ adrenergic receptor.

# SALBUTAMOL

- Salbutamol or albuterol is a short-acting β2- adrenergic receptor agonist used for the relief of bronchospasm in conditions such as asthma and chronic obstructive pulmonary disease.
- • Salbutamol was the first selective β2-receptor agonist to be marketed – in 1968.
- SAR: • The tertiary butyl group in salbutamol makes it more selective for β $-_2$ receptors.
- • The drug is sold as a racemic mixture mainly because the (S)-enantiomer blocks metabolism pathways while the (R)-enantiomer shows activity.
- Salbutamol has more effect on the respiratory tract, in the form of bronchial smooth muscle relaxation at recommended doses while producing fewer cardiovascular effects.
- • Also the R-enantiomer is sold in its pure form as Levalbuterol. • The presence of only the R-enantiomer produces fewer side-effects




https://www.slideshare.net/acchhabi/salbutamol-36407602

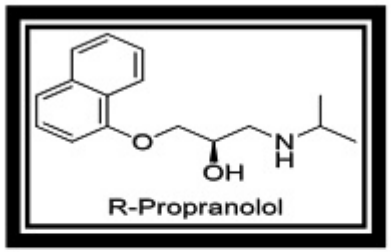
# PROPRANOLOL

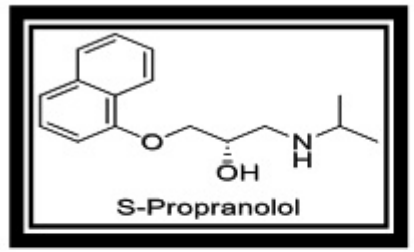
Propranolol is a widely prescribed, nonselective β-adrenergic receptor–blocking agent.

Propranolol is distributed as a racemic mixture ((R,S)-propranolol hydrochloride).

Although the (S)-enantiomer is the most active form in mammals (up to 100-fold difference), no information is available regarding the enantiospecific toxicity of propranolol to aquatic organisms.

**Ex//** the R-propranolol binding to albumin is greater than S-propranolol and the opposite is observed for $\alpha_1$ -acid glycoprotein.

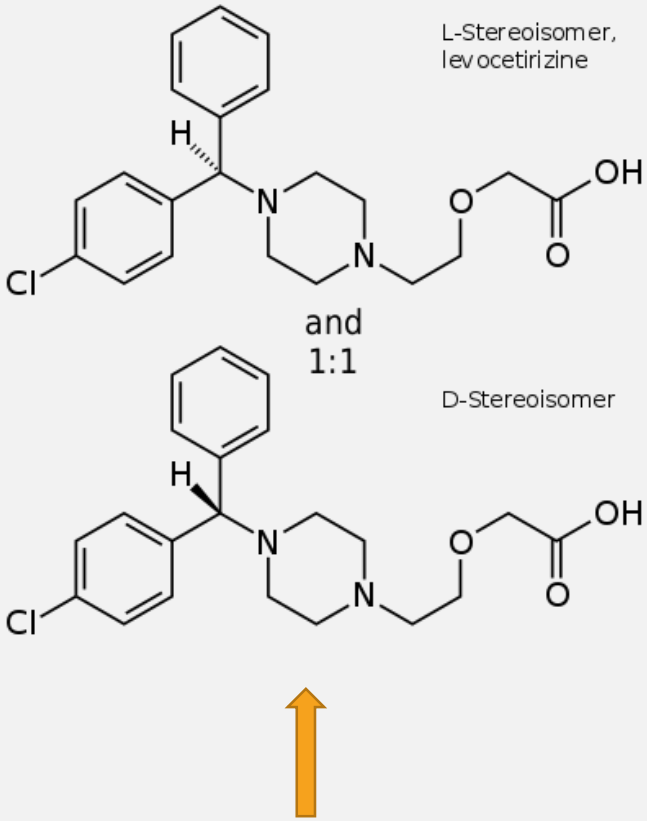



| | |
|---|---|
| * Highly albumin bound | *highly bound to AAG available as unbound |
| * Less potent | * 40-100 time more potent |
| * Highly metabolized | *Less metabolized |
| * Low plasma concentration | *High plasma concentration |

# CETİRİZİNE

- Cetirizine dihydrochloride is used as a Histamine H1 receptor antagonist, antihistaminic, piperazines.
- Inhibits activation of eosinophils and neutrophils.
- Non-sedating type histamine H1-receptor antagonist; major metabolite of hydroxyzine.
- Cetirizine acts as a highly selective antagonist of he histamine $H_1$ receptor.
- The $K_i$ values for the $H_1$ receptor are approximately 6 nM for cetirizine, 3 nM for levocetirizine indicating that the levorotatory enantiomer is the main active form.



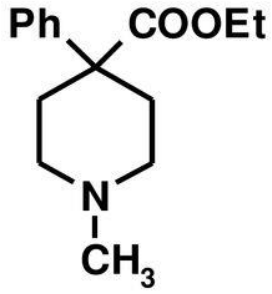

Used as enantiomer form.

# MEPIRIDIN

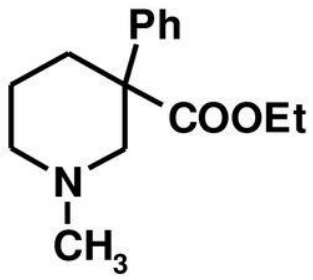
## Stereochemistry and Drug Action

- ✓ **Positional Isomers**

**Same molecular formula, same functional groups, but different positions of functional groups.**




**Mepiridine**
(Analgesic)



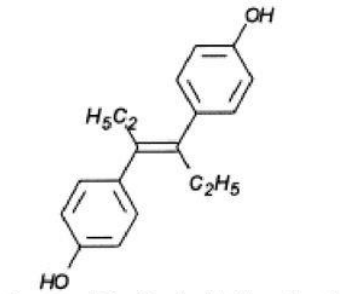

(not analgesic)

# Diethylstilbestrol

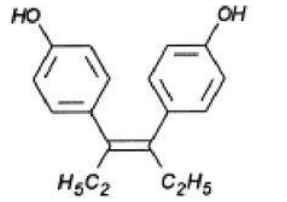
It is a synthetic and nonsteroidal estrogen. Compared to estradiol, DES has greatly improved bioavailability when taken by mouth, is more resistant to metabolism, and shows relatively increased effects in certain parts of the body like the liver and uterus.

13

- *Geometric isomers*, such as the *cis*- and the *trans*-isomers, hold structural features at different relative positions in space.
- These isomers also have significantly different physical and chemical properties.
- For example, diethylstilbestrol exists in two fixed stereoisomeric forms: *trans*-diethylstilbestrol is estrogenic, whereas the *cis*-isomer is only 7% as active.



*trans*-Diethylstilbestrol



*cis*-Diethylstilbestrol

most active form

- **Diastereomers** is the term that students are most likely to get incorrect. This is likely because of the ways in which they can be defined. Diastereomers can be defined as any stereoisomer that is not an enantiomer. This definition means that for configurational isomers with multiple chirality centres, the R- and S- designations can be used to make the isomer classification.
- However, in the broader sense of the definition, since geometric isomers and conformational isomers are types of stereisomer (they are below that branch in the tree diagram) then they are also technically a type of diastereomer but those terms (geometric or conformational) would be better because they are more precise.
- (S,R)- or (R,R)-2-bromo-3-chlorobutane