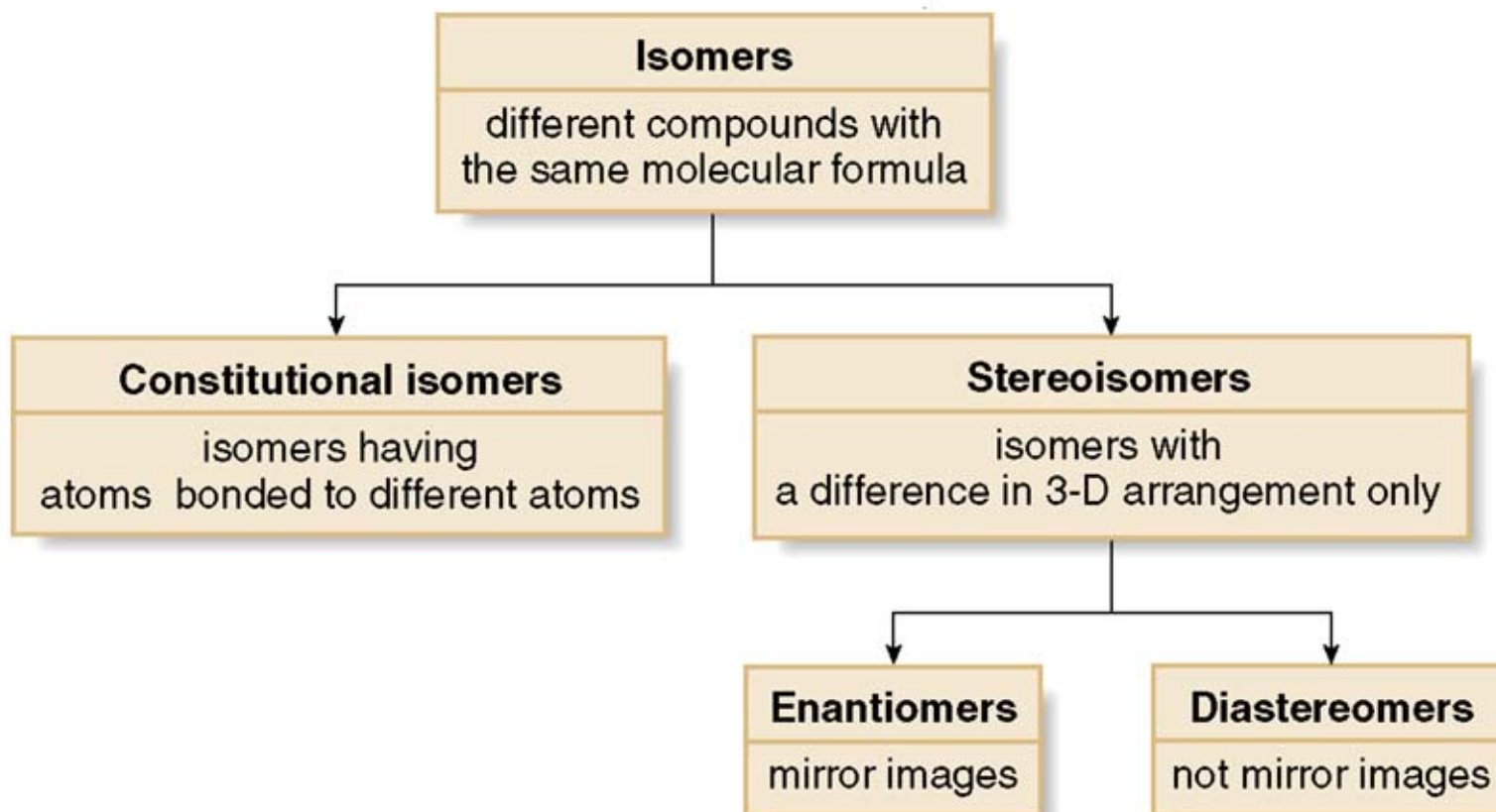


Drug chirality: Stereoselectivity in the action and disposition of anaesthetic agents

Isomerism

- **Isomers:** Drugs with the same chemical composition and molecular formula.

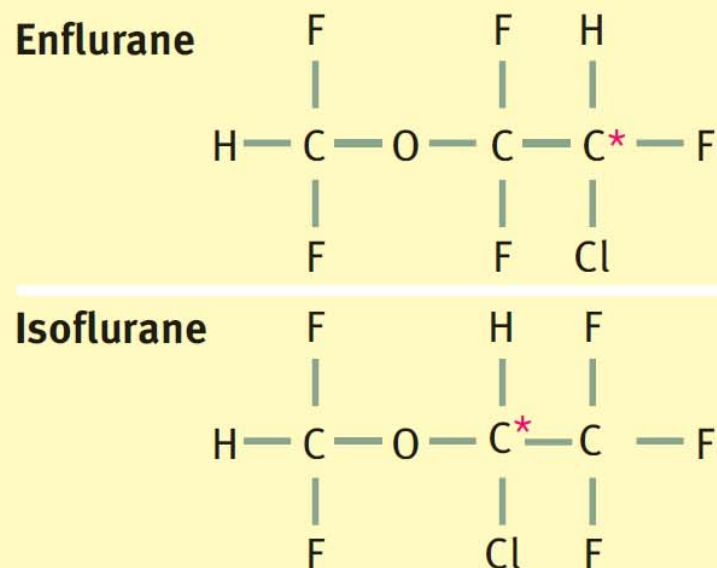



• **Constitutional / Structural isomerism:** Same molecular formula but different chemical structure as the arrangement of atoms is different.

Structural isomerism of enflurane and isoflurane

Enflurane and isoflurane have the same molecular formula ($F_5C_3H_2OCl$) but different chemical structures.

Both drugs also possess a chiral centre (*) and therefore exist in two enantiomeric forms



- 
- **Stereoisomerism:** Same molecular formula and chemical structure but a different configuration (i.e. different three dimensional spatial arrangement of their atoms)
 - **Two types:**
 1. Optical isomers
 2. Geometrical isomers



Optical isomerism

- **Enantiomers:**

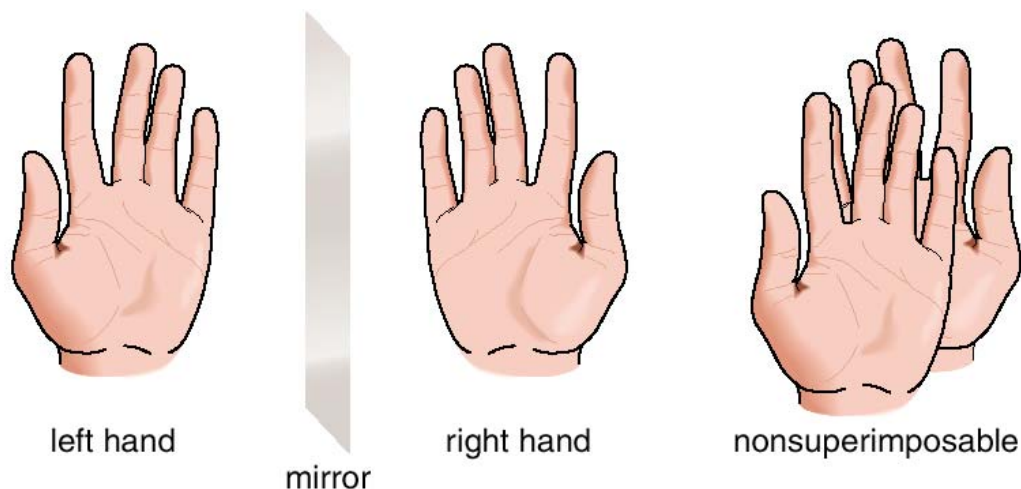
- ❖ A pair of stereoisomers that are non-superimposable mirror images of each other.
- ❖ **Cause of enantiomerism:** presence of a chiral centre.
- ❖ Physiochemical properties (solubility, melting and boiling points, ionization constant) are identical.
- ❖ Separation is difficult.

- **Diastereomers:**

- ❖ Stereoisomers that are not mirror images of each other and are not enantiomeric.
- ❖ Physiochemical properties are different.
- ❖ Separation is easy.

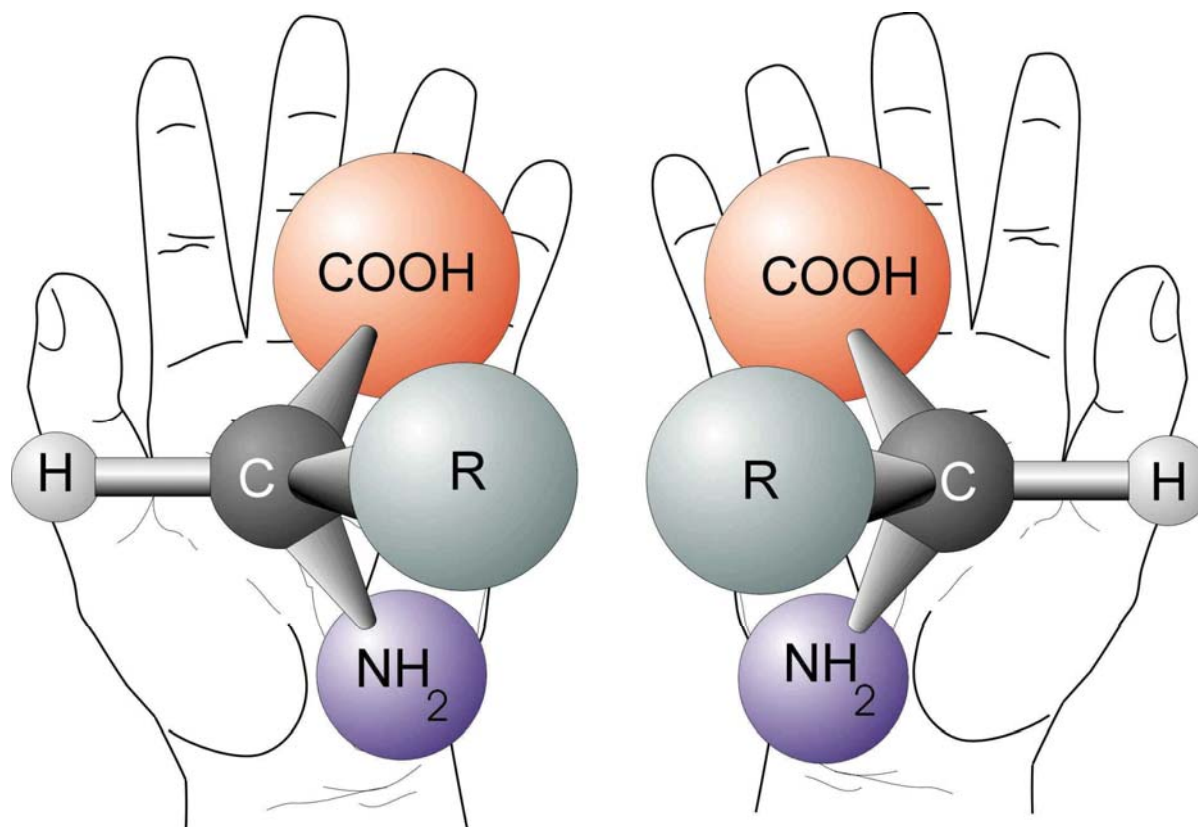
What is chirality?

- Chiral - derived from a Greek word *chiros*, meaning handedness.
- A molecule or object that is not superimposable on its mirror image is said to be chiral.

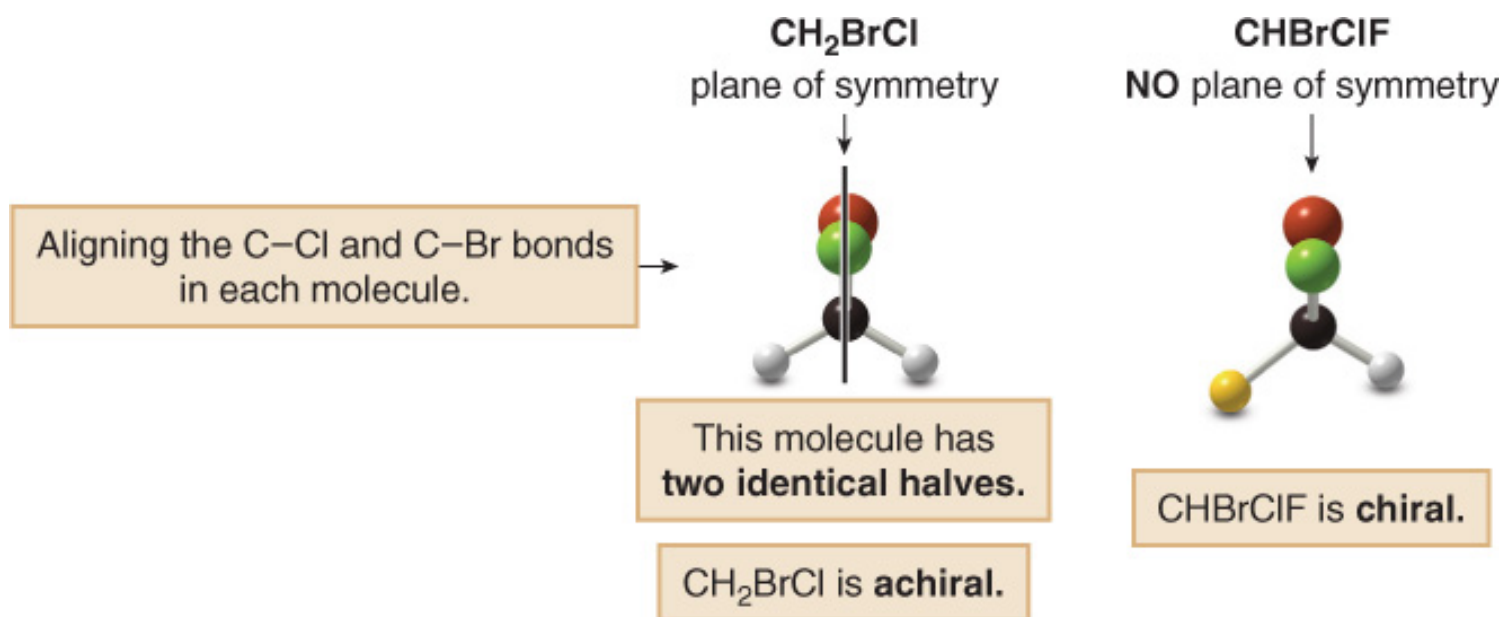


- A molecule (or object) that is *not* superimposable on its mirror image is said to be *chiral*.

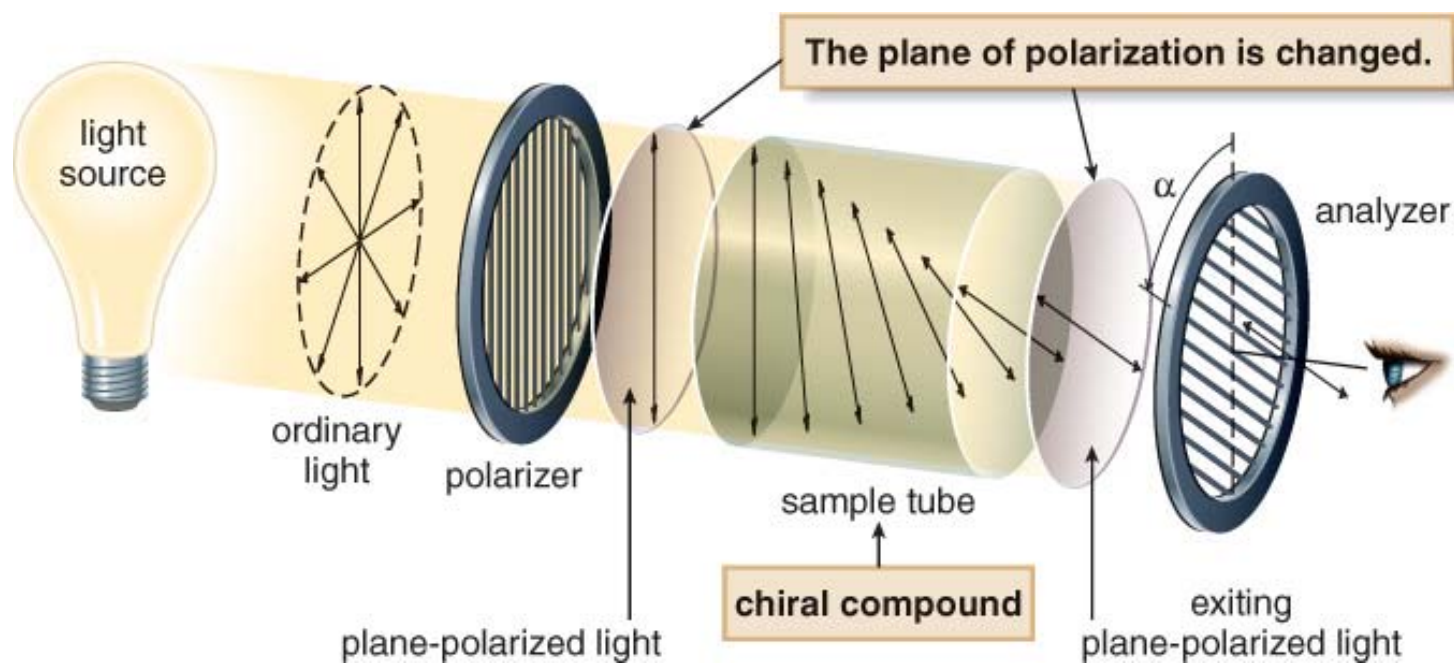
- **Chiral centre / asymmetric carbon / stereogenic centre** – A carbon atom attached to four different substituents.



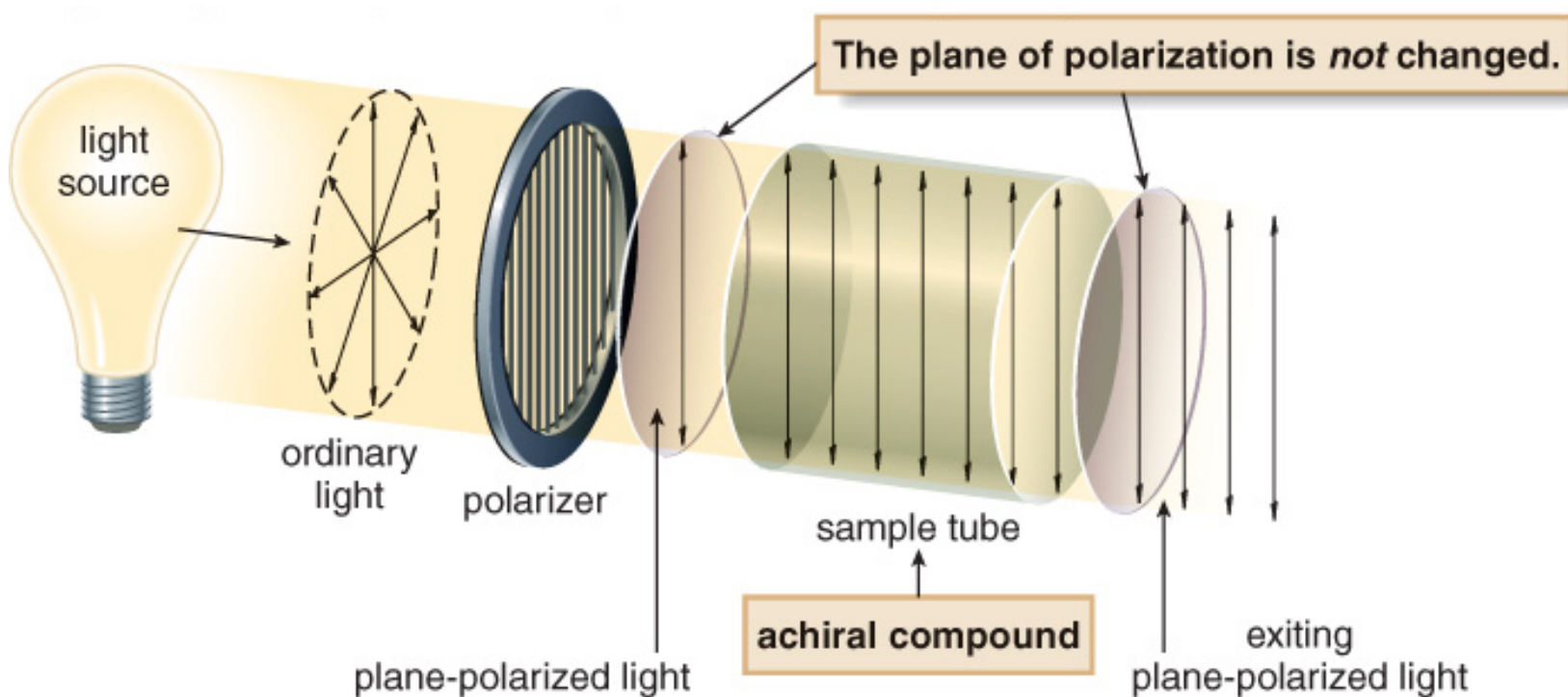
- Achiral molecules usually contain a **plane of symmetry** but chiral molecules do not.
- A **plane of symmetry** is a **mirror plane** that cuts the molecule in half, so that one half of the molecule is a reflection of the other half.

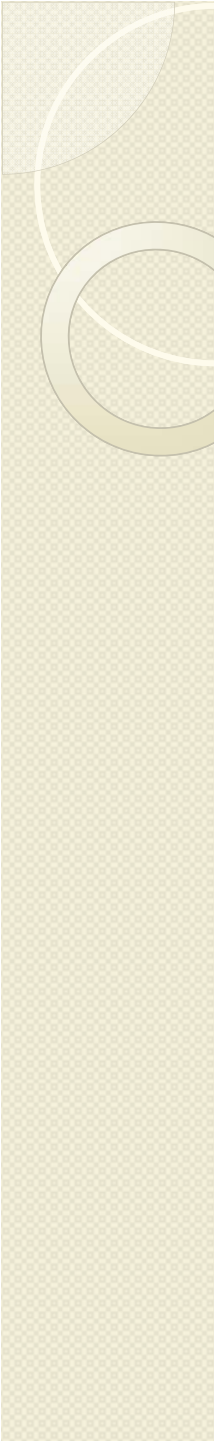


- With chiral compounds, the plane of the polarized light is rotated through an angle α . A compound that rotates polarized light is said to be **optically active**.



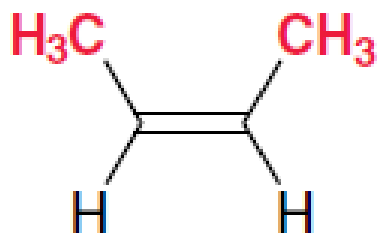
- With achiral compounds, the light that passes through the compound remains unchanged. A compound that does not change the plane of polarized light is said to be **optically inactive**.



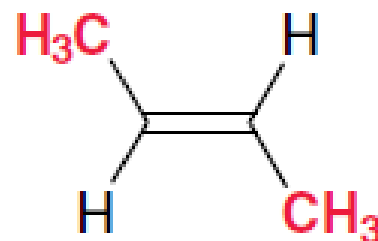
- 
- **Racemic mixture:** It is an equimolar mixture of the two right and left handed enantiomers and is thus optically inactive.
 - Most chiral drugs are administered as racemic mixtures.

Geometrical isomerism

- Stereoisomers that are without optically active centers.
- Result from restricted rotation as a result of a carbon-carbon double bond.



Cis-2-butene



Trans-2-butene

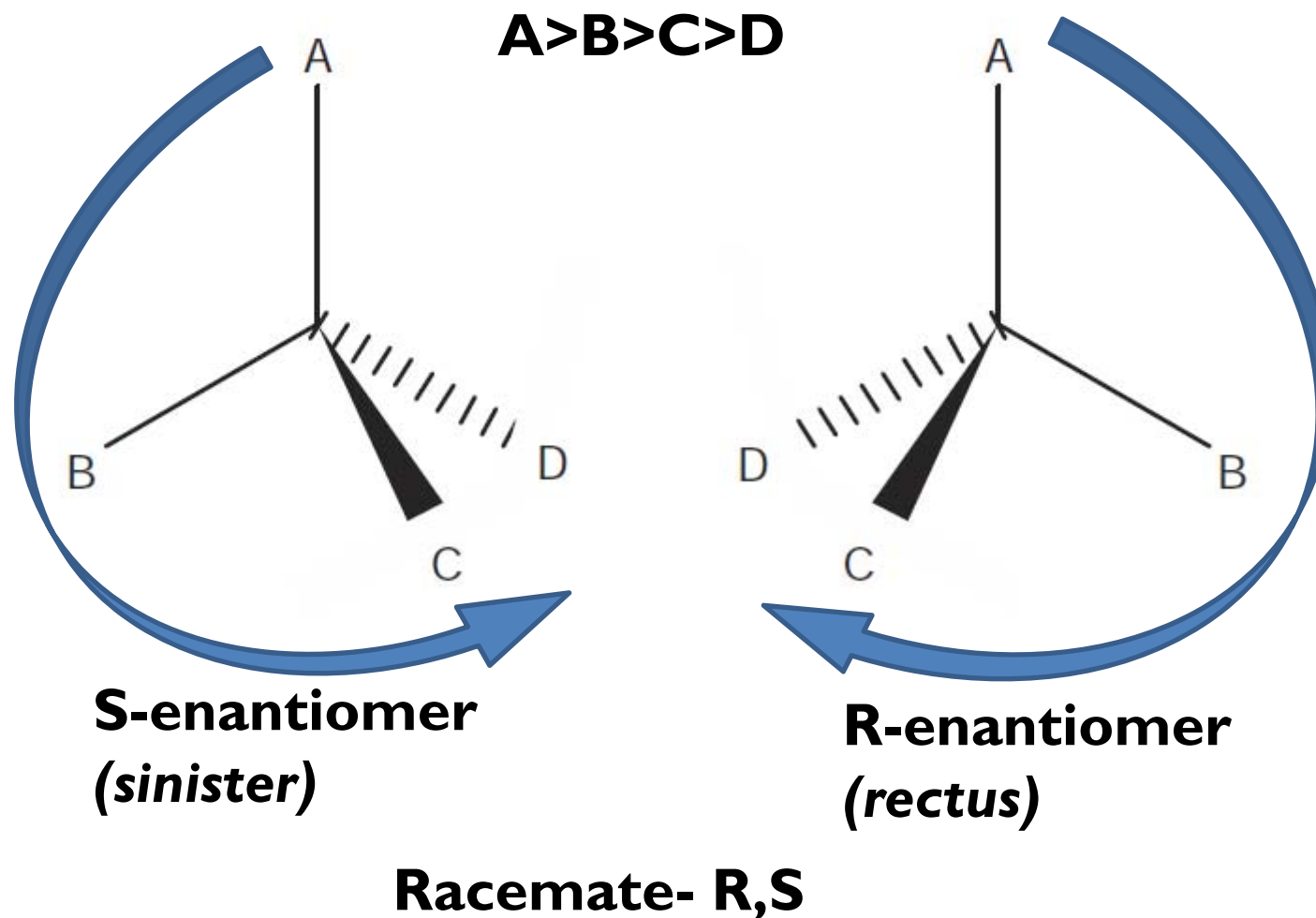
Naming convention

Based on optical activity

- Compounds that rotate the plane of polarized light to the right (clockwise) are called dextrorotary.
 - *d*
 - (+)IUPAC convention
- Compounds that rotate the plane of polarized light to the left (counterclockwise) are called levorotary.
 - *l*
 - (-)IUPAC convention
- Racemic mixture: *d,l* or *+,-*

Cahn-Ingold-Prelog Convention

This is the preferred *International Union of Pure and Applied Chemistry* (IUPAC)-endorsed method of naming and identifying stereoisomers

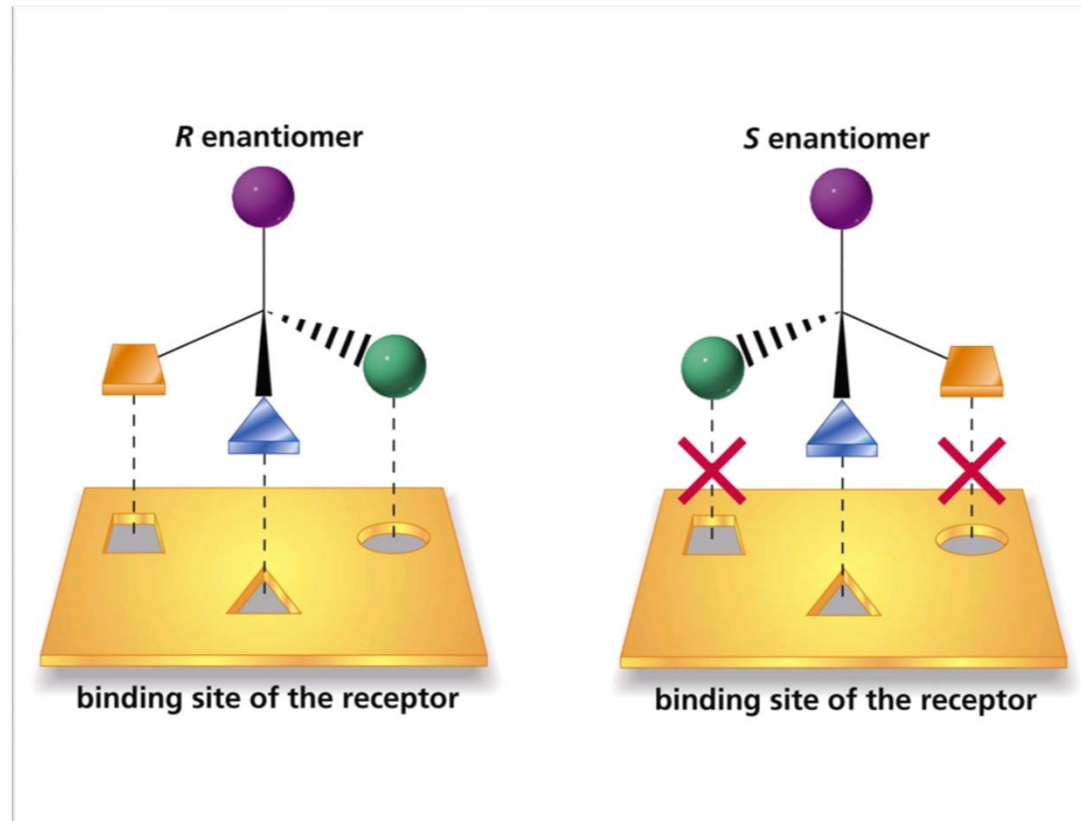




Stereoisomerism in biological system

- Biomolecules (sugars, amino acids, DNA, proteins, steroids) are chiral.
- Proteins are built from L-amino acids, which implies that enzymes – the catalysts of nature - are chiral.
- Also, receptors (drug, taste, biopharmaceuticals, agrochemicals) are chiral and the natural ligand to a receptor is often only one specific enantiomer.

Easson and Stedman model

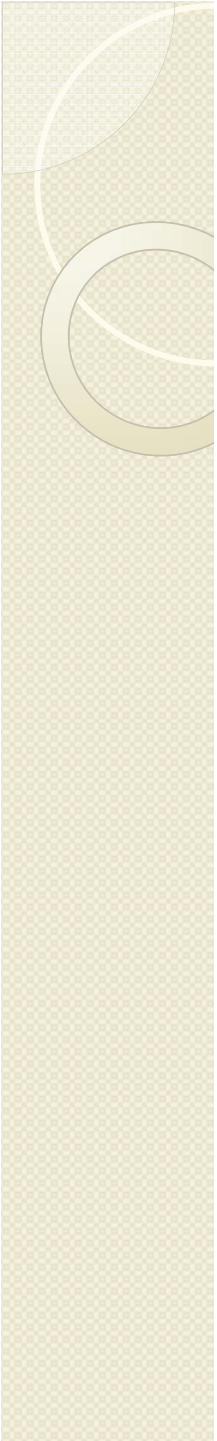


Interaction of a pair of enantiomer with a biological macromolecule.



Relevance of chirality to anaesthesia

- More than half of the synthetic agents used in anaesthesia are chiral.
- Most are administered as racemic mixtures, rather than as single pure enantiomers.
- Therapeutic activity resides mainly in one of the enantiomer.
- The other enantiomer may have undesirable properties.
- It is safer to avoid the use of therapeutically useless and potentially harmful enantiomer, known as the isomeric ballast, in the drug formulations.

- 
- The enantiomers differ in both pharmacodynamics and pharmacokinetics.
 - Chirality of the biological macromolecules results in stereospecific actions and different affinities of enantiomers.
 - Pharmacokinetics (absorption, tissue distribution, plasma protein binding, metabolism and elimination) of the enantiomers is also different.
 - Enantiomers differ in plasma protein or tissue protein binding and in various transport mechanisms.

Thalidomide-disastrous biological activity of the wrong enantiomer

- In 1960 in Europe, racemic thalidomide was given to pregnant females to cure morning sickness.
- This led to deformations in babies and neurotoxic effects.
- These were due to S-thalidomide.
- R-thalidomide contained the desired therapeutic activity.



Enantiomers differ

- Required activity resides in one enantiomer- antihypertensive (S)-alpha methyldopa.
- Enantiomers have different therapeutic indications-
 1. Dextropropoxyphene is analgesic, levopropoxyphene is anti-tussive.
 2. Levomethorphan is analgesic, dextromethorphan is anti-tussive.
- Required activity is predominantly with one enantiomer, adverse effects with other- Ketamine
- Beneficial effects reside in one enantiomer, the other enantiomer having antagonistic activity:
 - Levo-salbutamol (bronchodilator without pro-inflammatory properties)

Some chiral drugs used in anaesthetic practice

Single isomers

- Etomidate
- Levobupivacaine
- Ropivacaine
- Cisatracurium
- Vecuronium
- Pancuronium
- Rocuronium
- Hyoscine
- Morphine

Two isomers (racemic mixtures)

- Halothane
- Enflurane
- Isoflurane
- Desflurane
- Thiopental
- Ketamine
- Prilocaine
- Bupivacaine
- Epinephrine
- Norepinephrine
- Dobutamine
- Atropine
- Glycopyrronium

More than two isomers

- Atracurium
- Mivacurium

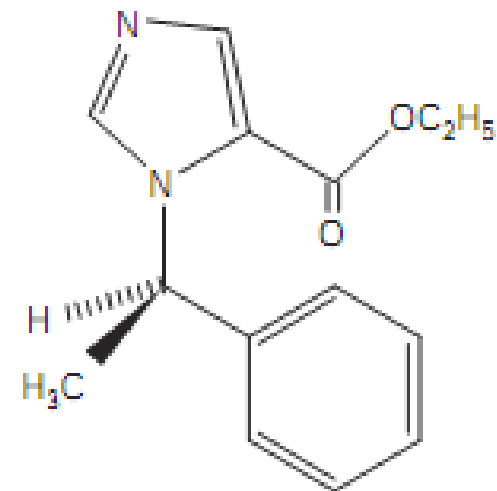


Intravenous anaesthetics

- Etomidate
- Ketamine
- Thiopentone

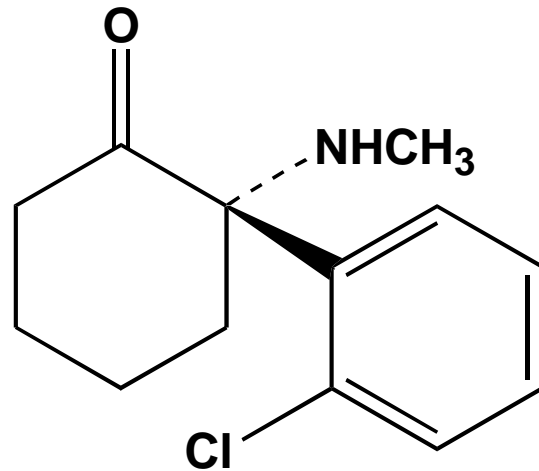
Etomidate

- Administered as a single isomer: R-isomer.
- Site of action: GABA_A receptor.
- R-isomer is 15 times more potent than the S-isomer.
- S-isomer lacks hypnotic activity.



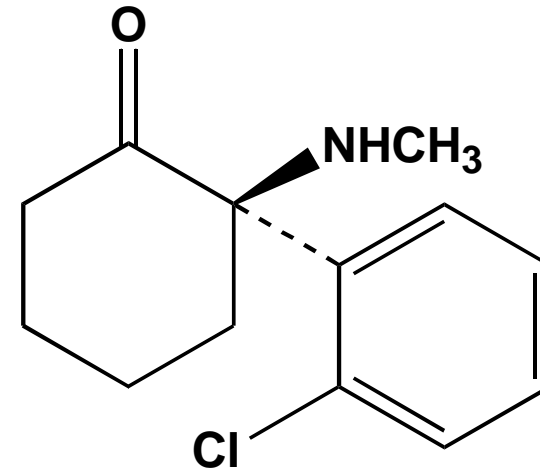
(R)-Etomidate

Ketamine



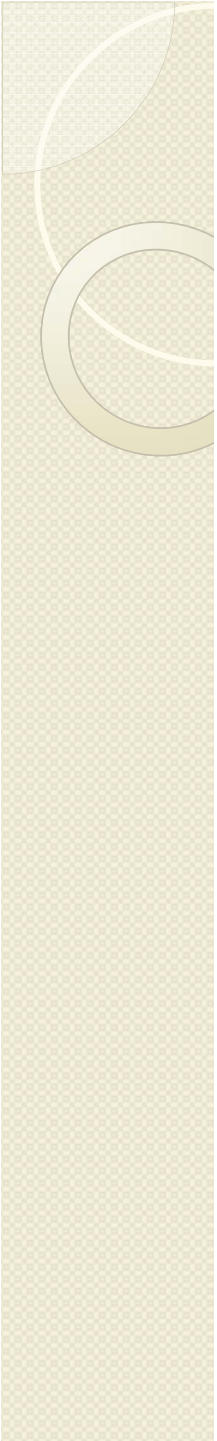
S-(+)-Ketamine

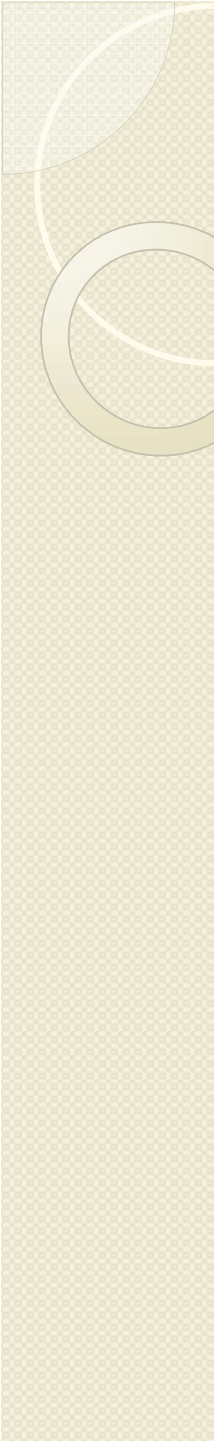
**2-4 times more potent than
R-(-)-ketamine in
anaesthesia**



R-(-)-Ketamine

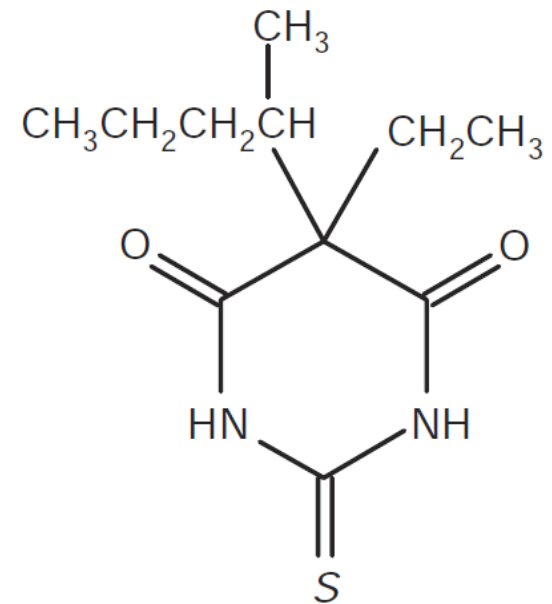
**Causes spontaneous motor
activity and post-emergent
distress**

- 
- Used as a racemate.
 - Action: Non-competitive inhibition of NMDA receptors. S-ketamine has 3-fold greater affinity for NMDA receptors than R-ketamine.
 - S-ketamine is 2-4 times more potent than R-ketamine as an anaesthetic and analgesic agent.
 - R-ketamine: Emergence reactions like hallucinations, vivid dreams and agitation.
 - Metabolism of S-ketamine by liver microsomes is 20% greater than R-ketamine and 10% greater than the racemate- faster clearance of the drug.

- 
- Ketamine has undergone chiral switch in Germany and is being marketed as S-enantiomer with following advantages:
 - ❖ Reduction in dose
 - ❖ More rapid recovery, less anterograde amnesia
 - ❖ Fewer psychomimetic emergence reactions

Thiopental

- MOA- potentiation of GABA at the GABA_A receptor.
- S-enantiomer is 2 times more potent than R-enantiomer in potentiation of GABA.



Thiopental

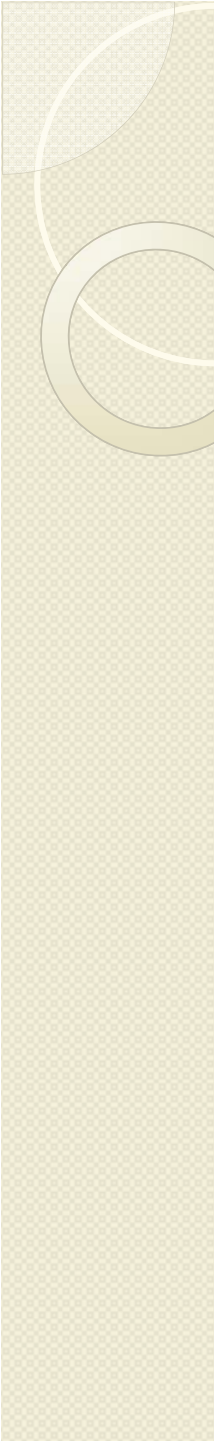
Table 1 Anaesthetic and lethal doses, corresponding arterial plasma concentrations and therapeutic index of thiopental enantiomers following intravenous infusion to rats

Stereoisomeric form	Dose (mg/kg)		Plasma concentration ($\mu\text{g/ml}$)		Therapeutic index	
	Anaesthesia	Lethality	Anaesthesia	Lethality	Dose	Concentration
<i>R</i>	55.8 \pm 2.4	176.2 \pm 11.2	66.3 \pm 4.5	89.8 \pm 5.2	3.16	1.37
<i>S</i>	35.6 \pm 1.9	74.2 \pm 5.2	55.0 \pm 1.9	64.1 \pm 2.8	2.10	1.17
<i>R,S</i>	39.3 \pm 2.1	97.5 \pm 3.9	56.7 \pm 2.0	77.8 \pm 2.8	2.52	1.32

Data expressed as mean \pm SEM, n = 7.⁸¹

Potency: $S > R,S > R$

Therapeutic index: $R > R,S > S$

- 
- R-thiopental can be used as a single enantiomer because of
 - ❖ greater distribution in the CNS
 - ❖ greater margin of safety
 - However studies have shown that there are just modest differences in the pharmacokinetic properties of the enantiomers like clearance and volume of distribution. This is unlikely to be of clinical significance.



Local anaesthetics

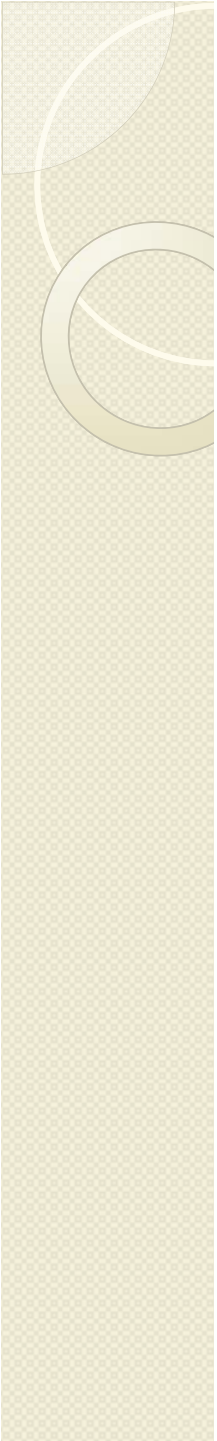
- Prilocaine
- Mepivacaine
- Bupivacaine

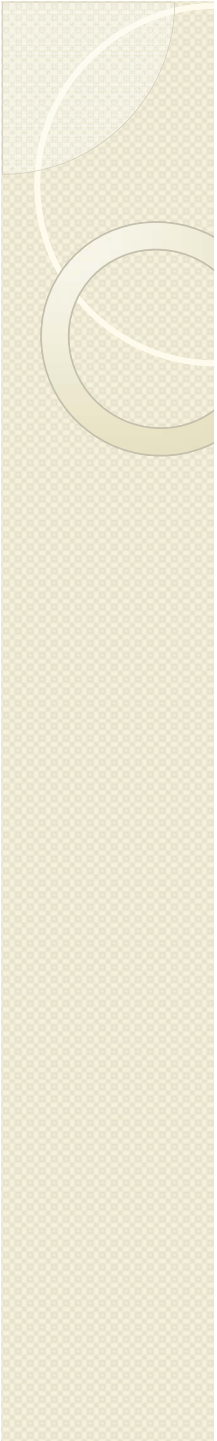
Bupivacaine

- Long acting local anaesthetic marketed as 50:50 racemic mixture.
- Reports of death due to
 - ❖ bupivacaine induced CNS toxicity and cardiotoxicity on accidental intravenous injection and
 - ❖ difficult resuscitation following cardiotoxicity.
- Safer alternatives:
 - ❖ Levobupivacaine
 - ❖ Ropivacaine

These are S-enantiomers of bupivacaine.

- Ropivacaine is the first 'pure' enantiomer containing >99% of the S-form.

- 
- S-enantiomers are less neurotoxic than bupivacaine.
 - Cardiotoxic potential:
Ropivacaine < levobupivacaine < racemic bupivacaine < R(+)-bupivacaine
 - Bupivacaine is more potent in blocking cardiac K⁺ channels than the S-enantiomers. Thus, levobupivacaine and ropivacaine have a lesser effect on mean stroke index, acceleration index and ejection fraction.

- 
- Potency depends on blockage of sodium channels and lipid solubility. Levobupivacaine and bupivacaine being more lipophilic are 50% more potent than ropivacaine .
 - Equipotency ratio of 1.5:1 of ropivacaine and other two drugs produces similar clinical profile and better motor preservation.
 - Ropivacaine thus produces similar sensory block and less motor blockade as compared to bupivacaine.
 - In obstetric population, ropivacaine produces a better patient satisfaction. However there is no difference in the rate of surgical delivery.

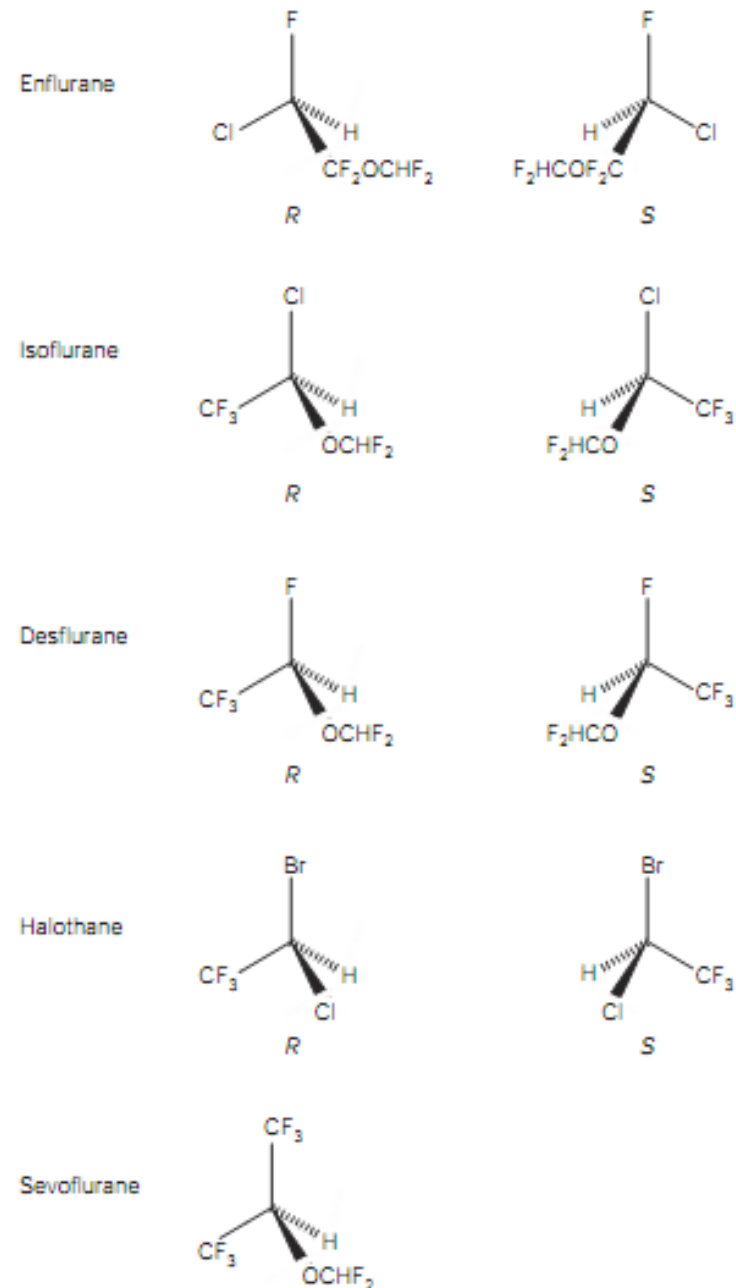


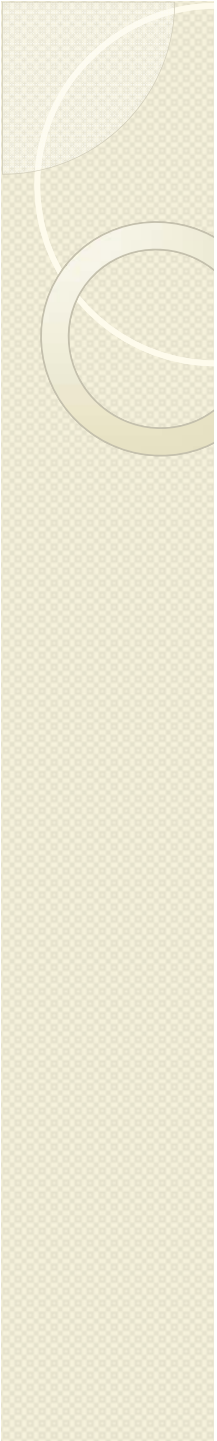
Inhalational agents

- Majority of the inhalational agents currently used are chiral except, sevoflurane.

Isoflurane

- Some studies have found S(+)-isoflurane to be 50% more potent than R(-)-isoflurane w.r.t. MAC while other studies have found no significant difference.
- Both enantiomers are equally soluble in the lipid bilayers.
- S-isoflurane induced about 50% longer sleep times than R-isoflurane.



- 
- Clinical advantages of using S-isoflurane as a single enantiomer are minimal.
 - By the study of enantiomers of volatile anaesthetics, the site of action of these agents have become clear. It is found to be protein ion channels rather than the membrane lipids.



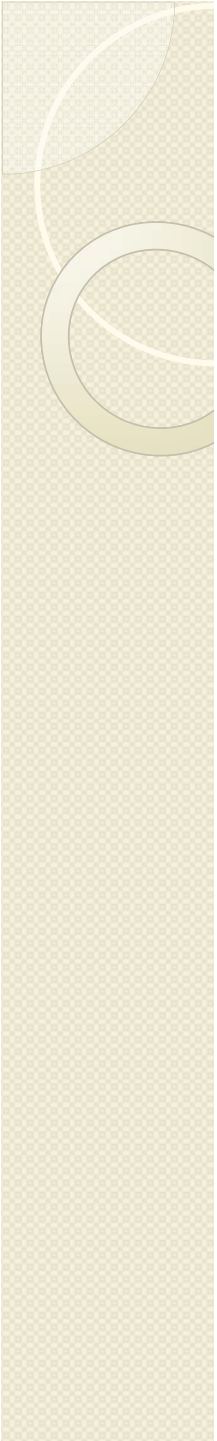
Neuromuscular blocking agents

- Pancuronium
- Vecuronium
- Rocuronium
- Atracurium
- Mivacurium



Atracurium

- Intermediate duration non-depolarizing neuromuscular blocker.
- Causes histamine release, transient hypotension, tachycardia, facial or truncal flushing.
- Continuous infusion in critical patients can lead to laudanosine accumulation, which is epileptogenic.
- Its structure contains 4 chiral centers and is a mixture of 10 optical and geometric isomers.

- 
- **Cisatracurium** is R-R' optical isomer representing 15% of the mixture.
 - It is more safe
 - Causes less histamine release
 - Not been reported to cause bronchospasm
 - Less amount of laudanosine is generated.

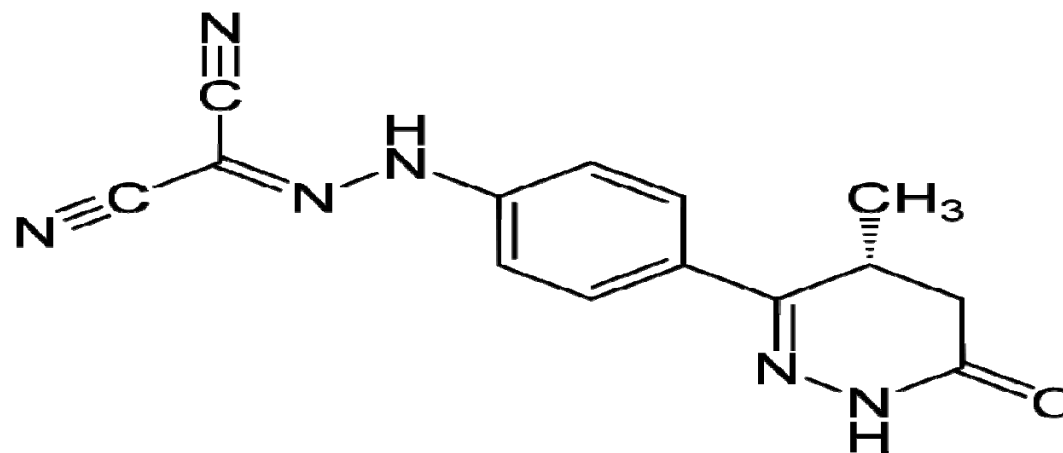


Other drugs

- Levosimendan
- Dexmedetomidine
- L-cysteine
- Tramadol
- NSAIDs
- Esomeprazole

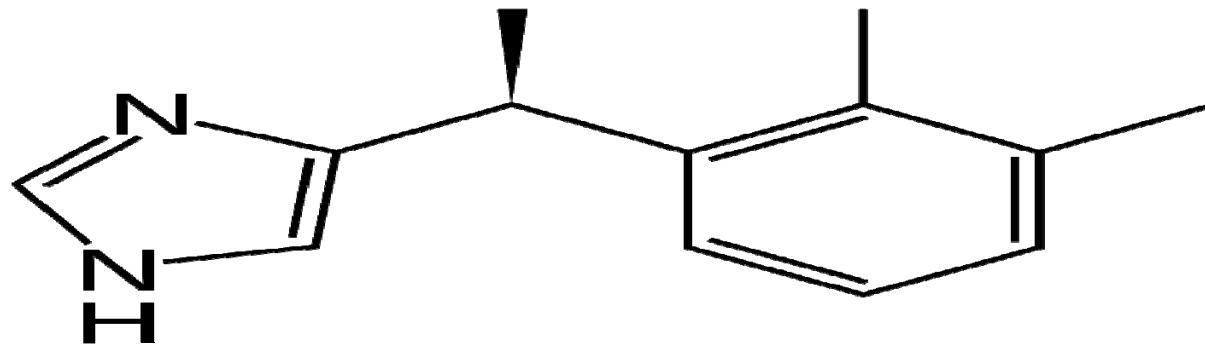
Levosimendan

- A calcium sensitizer.
- Positive inotropic effect by increasing calcium sensitivity of myocytes by binding to cardiac troponin C.
- Levosimendan 47 times more potent than dextrosimendan.
- Indication- management of acutely decompensated congestive heart failure.



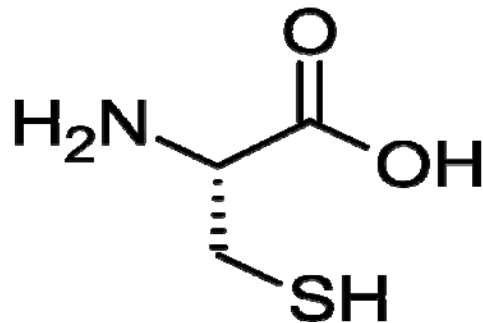
Dexmedetomidine

- Active enantiomer of medetomidine.
- Specific and selective agonism at alpha 2-adrenoreceptor.
- Responsible for the major sedative and antinociceptive effects.



L-cysteine

- Precursor of synthesis of coenzyme A.
- Sulphate donor in detoxification reaction.
- Neuroprotective- prevents entry of heavy metal ions across blood brain barrier.
- Neurotoxic at high doses
- Effects of Gantacurium, a chlorofumarate muscle relaxant, can be rapidly reversed by L-cysteine.
- Not been introduced in clinical practice.



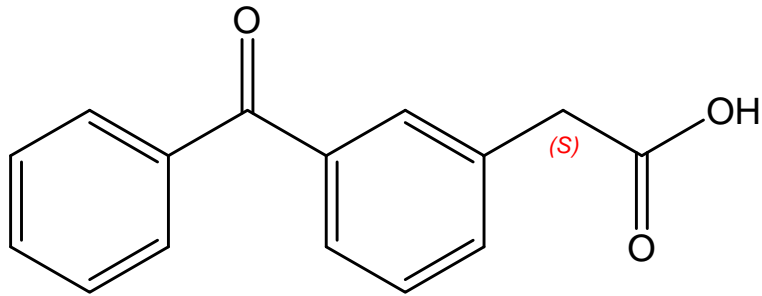
Tramadol

- Dual mode of action-
 1. Weak affinity for the mu-opioid receptors
 2. Increases the central levels of 5-HT and norepinephrine.
- Only (-)-tramadol blocked norepinephrine reuptake.
- (+)-tramadol is most potent inhibitor of serotonin reuptake.
- Nausea and vomiting was most frequent with (+)-enantiomer.
- After various studies it was concluded that the racemate was superior to both the enantiomers when efficacy and side-effects were considered together.

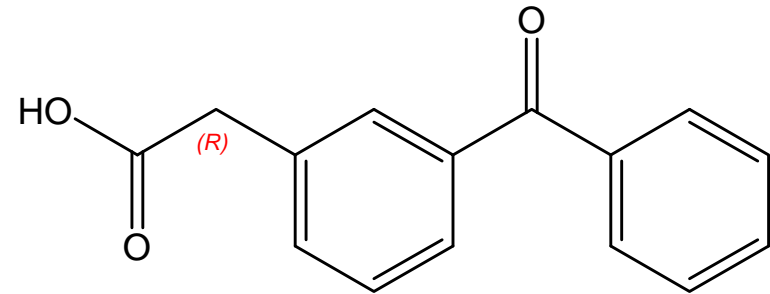


NSAIDs

- Inhibit the synthesis of prostaglandins.
- It has been found that major or exclusive in vitro inhibition of prostaglandins is due to S-enantiomer.
- Single enantiomer NSAIDs introduced:
 1. S-naproxen
 2. S-ibuprofen
 3. S-ketoprofen



S-ketoprofen
(Powerful analgesic, less side-effects)



R-ketoprofen
(Devoid of pharmacological activity,
increases risk of gastric ulceration)

- Advantages:
 1. Faster onset of action
 2. Enhanced potency
 3. Diminished side-effects
 4. Less drug interactions
 5. Less complex pharmacokinetic profiles



Esomeprazole

- S-enantiomer of omeprazole.
- Lower first-pass metabolism.
- Increased systemic availability.
- Maintains gastric $\text{pH} > 4$ in patients with gastro-oesophageal reflux disease for a longer duration as compared to R-enantiomer.

Chiral switch

- Development of a single enantiomer from a previously marketed racemate.

Table 4 Single enantiomers from marketed racemates: the Chiral Switch

Drug	Action/indication	Availability/comment
Dexfenfluramine	Anorectic	Withdrawn
Dilevalol	β -antagonist	Development stopped
Levofloxacin	Antimicrobial	Japan, UK, USA
Dexibuprofen	NSAID	Austria, Switzerland
Dexketoprofen	NSAID	Spain, UK
Levobupivacaine	Regional anaesthetic	UK
(S)-Ketamine	Anaesthetic	Germany
Esomeprazole	Proton-pump inhibitor	UK, USA
(R)-Salbutamol	β_2 -agonist	USA
(R)-Fluoxetine	Selective serotonin re-uptake inhibitor	Development stopped
Cisatracurium	Neuromuscular blocker	UK, USA
Levocetirizine	Antihistamine	UK
(R,R)-Methylphenidate	Attention-deficit hyperactivity disorder	USA
Escitalopram	Selective serotonin re-uptake inhibitor	USA, UK



Potential advantages of single enantiomer products

- Less complex, more selective pharmacodynamic profile
- Potential for an improved therapeutic index
- Less complex pharmacokinetic profile
- Reduced potential for complex drug interactions
- Less complex relationship between plasma concentration and effect



Economic considerations

- Until recently, the use of most synthetic chiral drugs was accepted uncritically as the expense involved in the separation of stereoisomers on an industrial scale was extremely high.
- During the past decade, progress in chemical technology has greatly simplified the separation and preparation of single enantiomers.
- In the future, it seems probable that all chiral anaesthetic drugs will be developed and administered as the single most active and safest enantiomer, rather than as chiral mixtures.

THANK YOU

