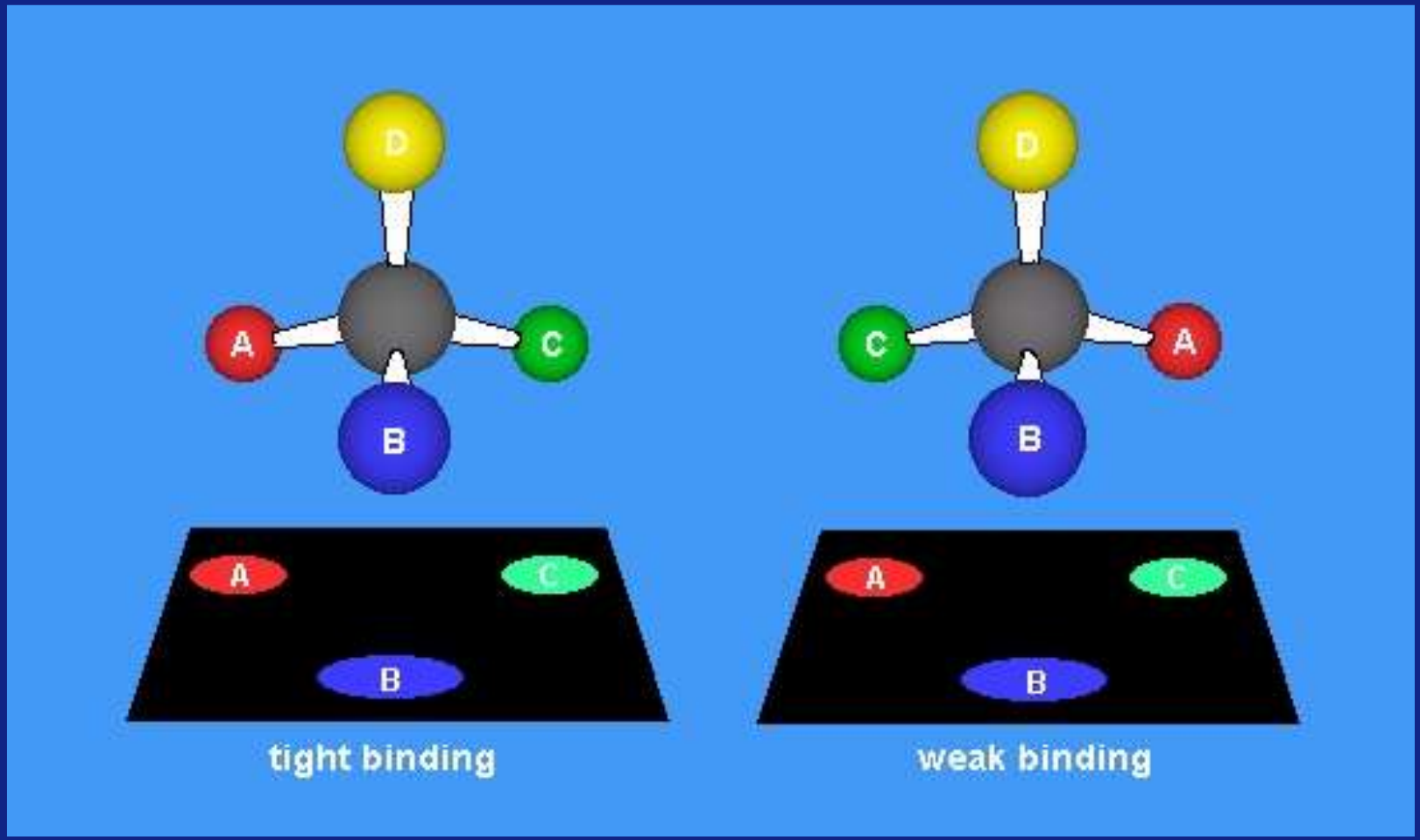
Stereochemical Aspects in Drug Receptor Interaction

- Drug molecules must generally interact with biomolecules in a very specific way to elicit a pharmacological response.

- Biomolecules are chiral, they often discriminate between isomers of a given drug molecule.

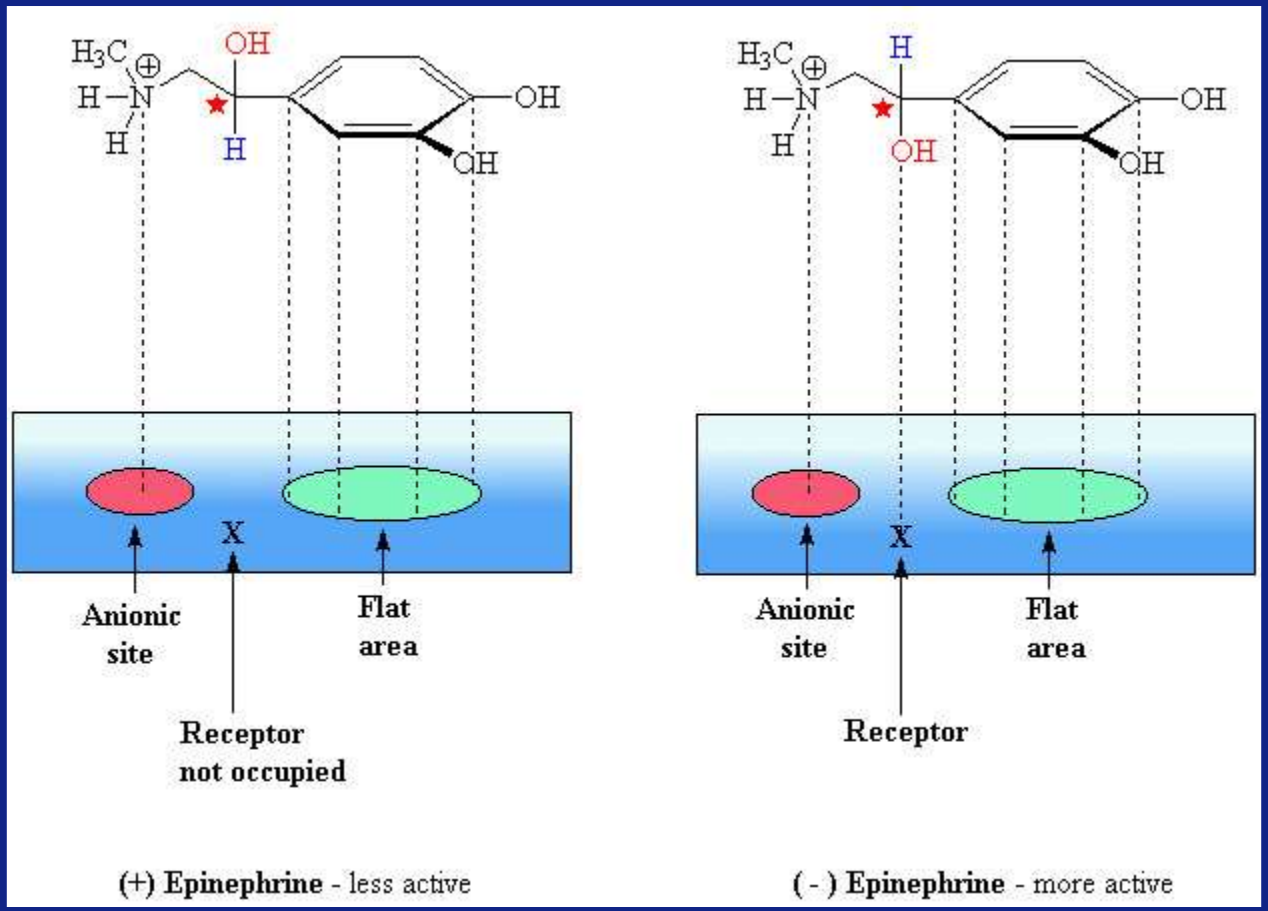
- The stereochemistry of a drug can impact its ability to bind to its target.

- The reason for chiral recognition by drug receptors is a three-point interaction of the agonist or substrate with the receptor or enzyme active site, respectively.



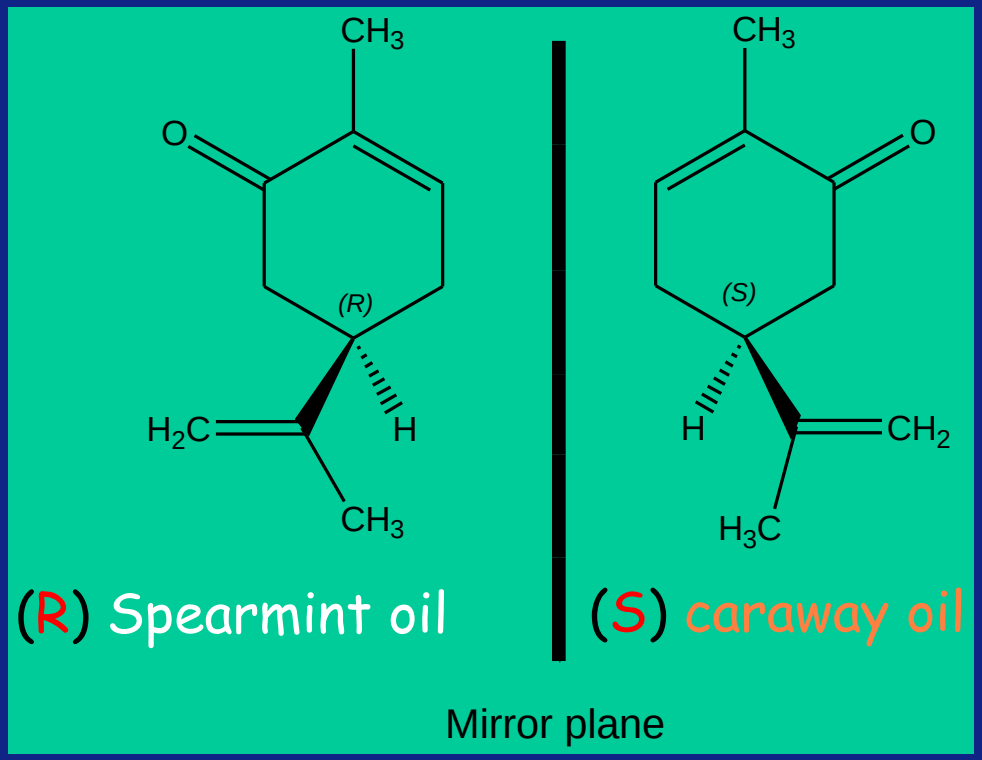
Examples:

- Only the (-) enantiomer of epinephrine has the OH group in the binding site, and therefore has a much more potent pressor activity.



- Enantiomers interact with living systems in very different ways and results for example in:

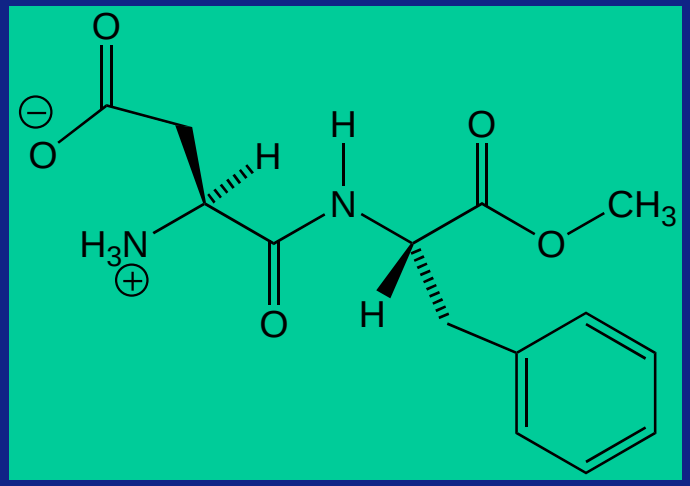
  - Different smell



Olfactory sensors are chiral

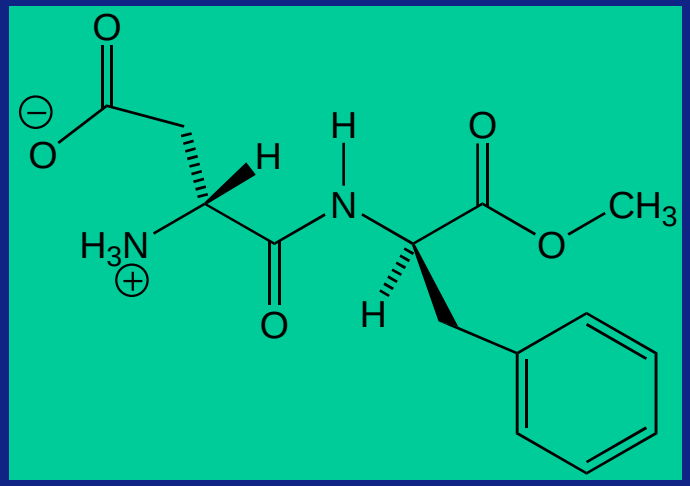
- Different taste

Aspartame



(S,S)

160 Times Sweeter than Sugar



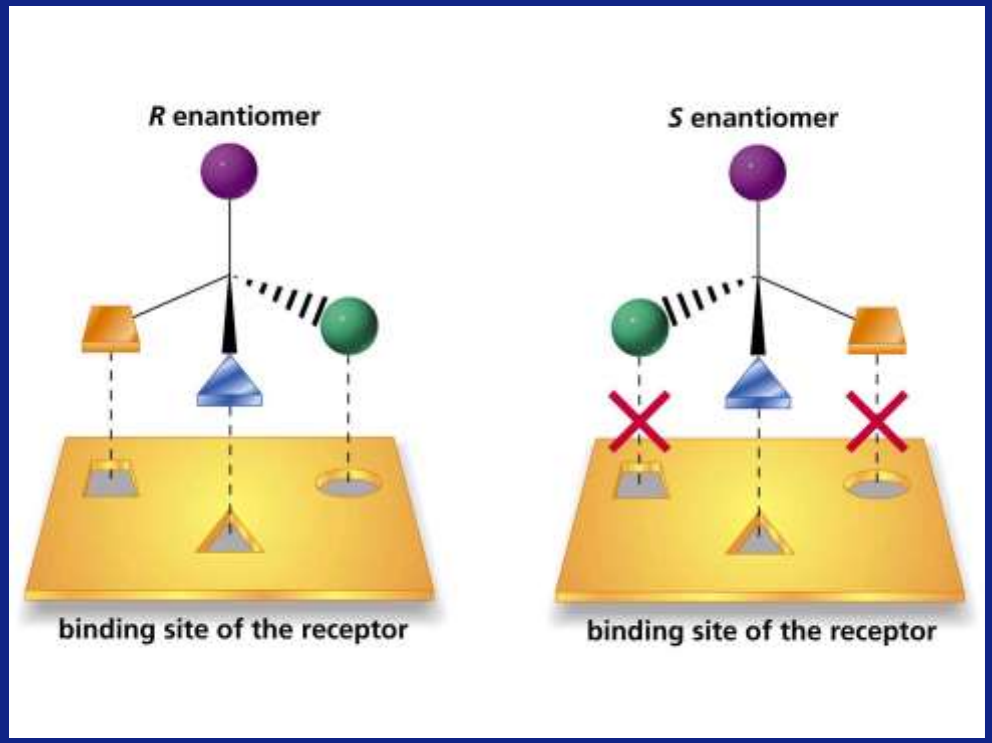
(R,R)

Bitter!!

Taste buds are chiral

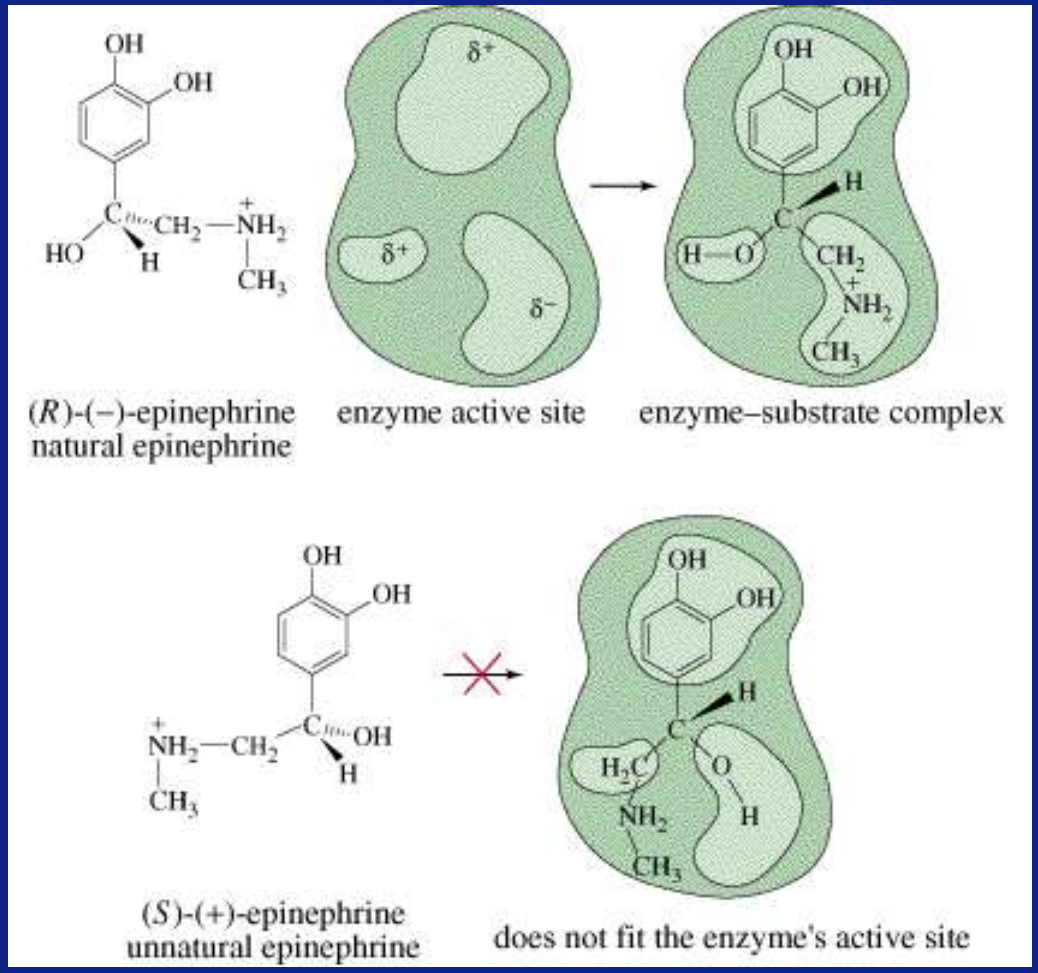
– Different drug effects

- Biomolecules, thus, can discriminate between enantiomers (isomers) of a given drug molecule.



- The net result is same or different pharmacologic/ pharmacokinetic/ toxicologic activities

Biological Discrimination



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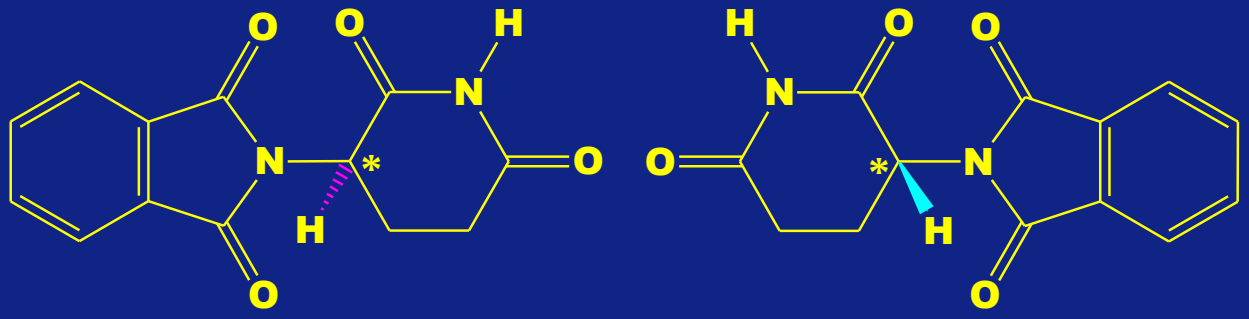
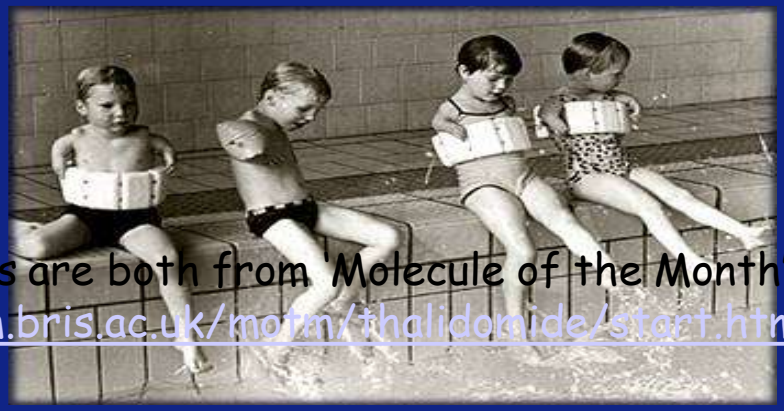
THALIDOMIDE: DISASTROUS BIOLOGICAL ACTIVITY OF THE "WRONG" ENANTIOMER



(R)-isomer

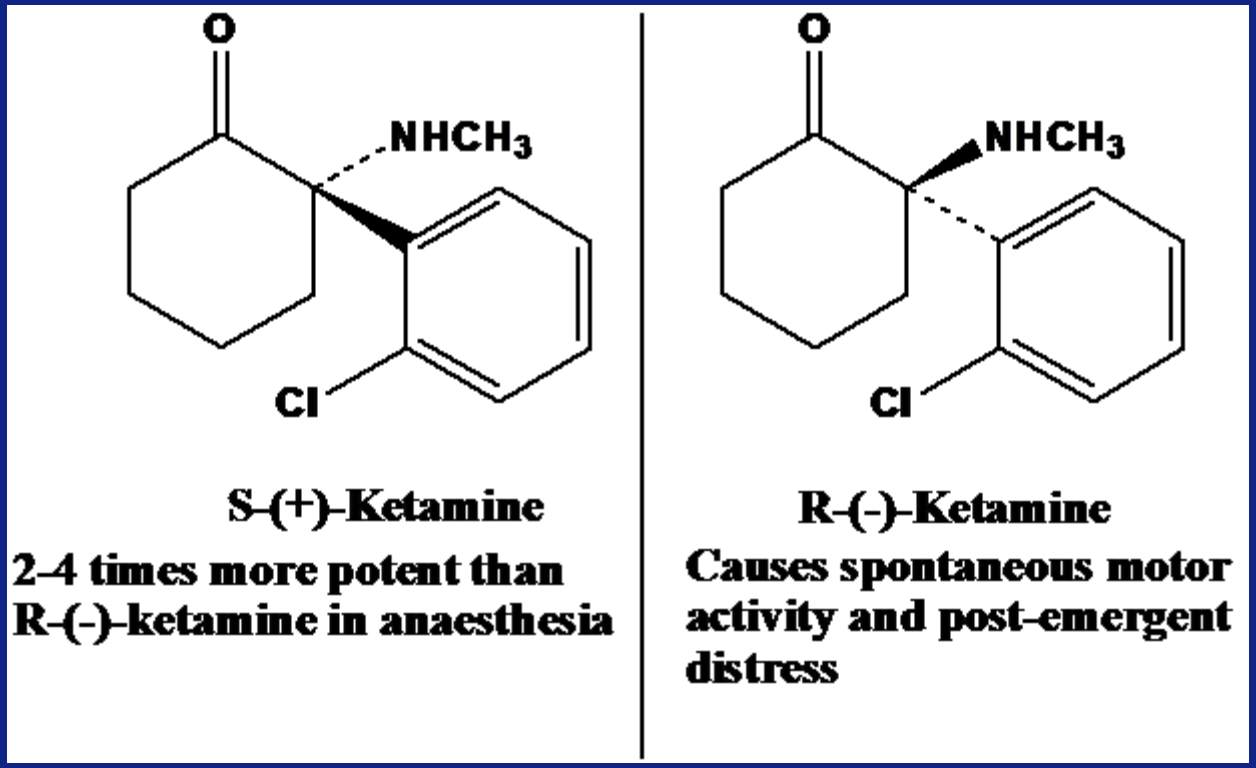
(S)-isomer

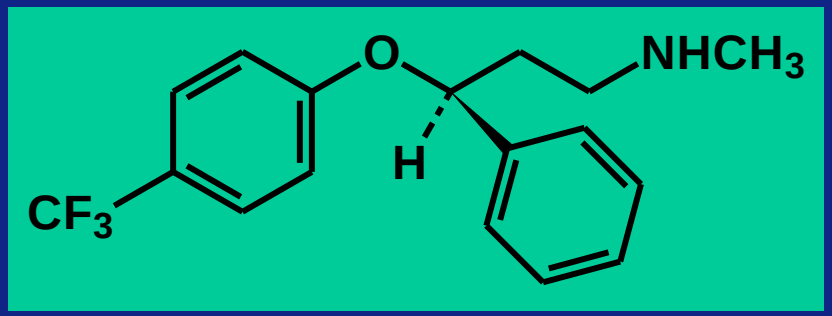
- In the 1960's thalidomide was given as racemic mixture (RS) to pregnant women to reduce the effects of morning sickness (Nausea and vomiting of pregnancy).
- This led to many disabilities in babies and early deaths in many cases.

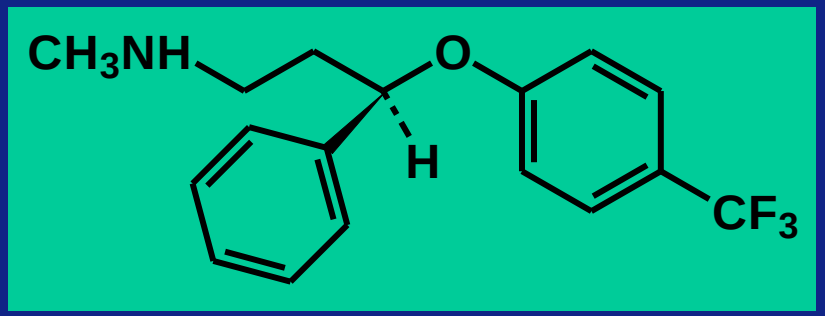


The photographs are both from 'Molecule of the Month' at Bristol University:
http://www.chm.bris.ac.uk/motm/thalidomide/start.html

- Later found that only the R-isomer can be used safely
- In 1998 thalidomide has been approved by FDA to reduce the immune system's inflammatory response in a host of illnesses, including arthritis, lupus, cancer, leprosy, and AIDs.



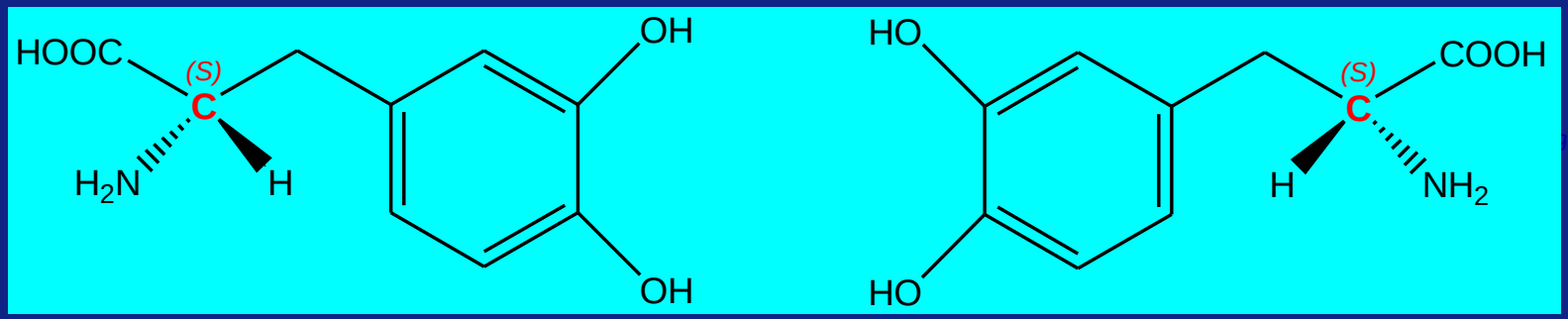




(S)-Fluoxetine

(R)-Fluoxetine

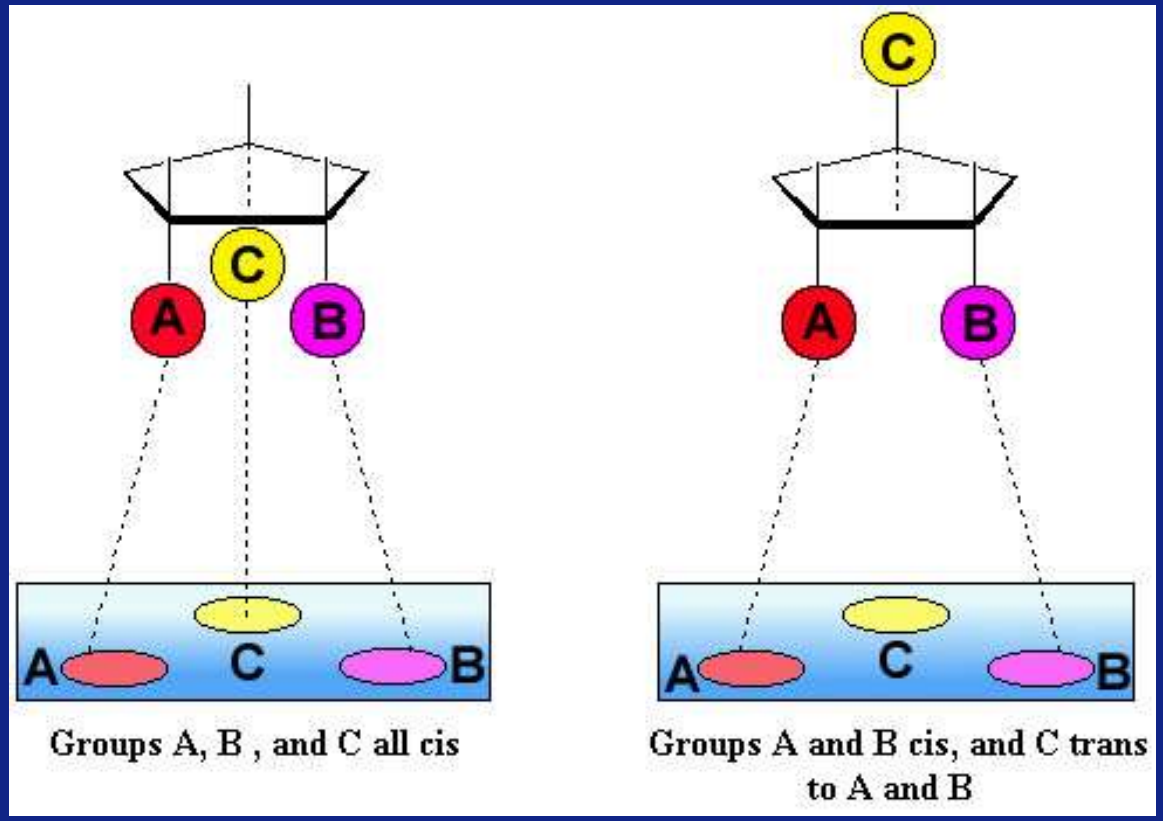
- The pure S enantiomer prevents migraines.
- A racemic mixture of fluoxetine (sold as the antidepressant Prozac) doesn't prevent migraines.

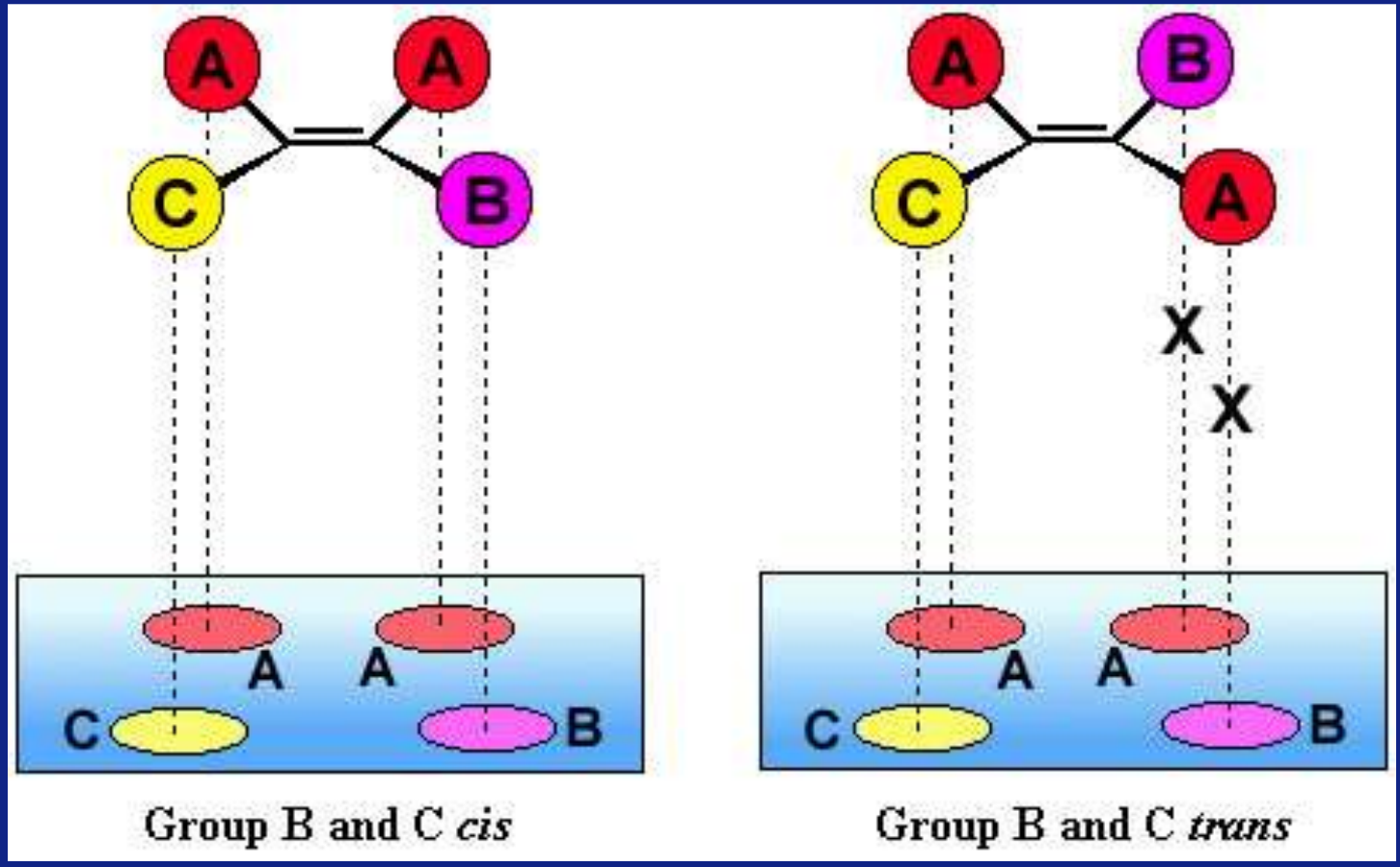


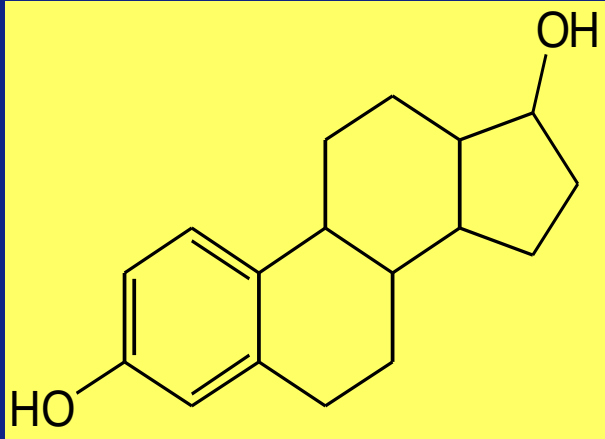
L-Dopa
Anti-Parkinson's disease drug

D-Dopa
Biologically inactive
has serious side effects

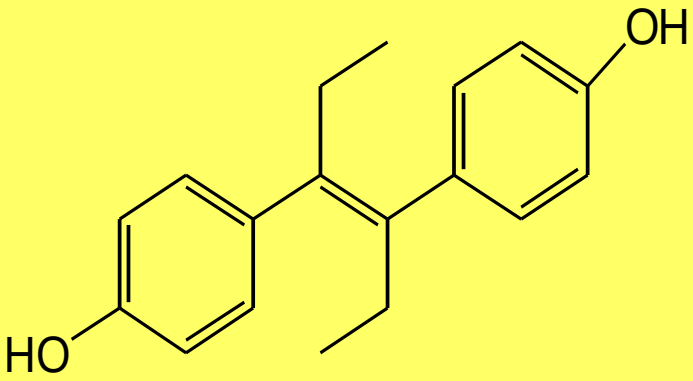
- Likewise, cis/trans isomers of cyclic compounds, or Z/E isomers of alkenes are also expected to have different binding potency and therefore also different biological activity.



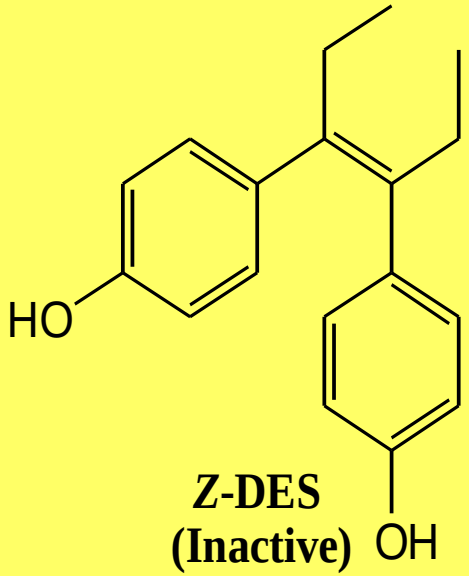

A
A
C
B
A
A
C
B
Group B and C *cis*
A
B
C
A
X
X
A
A
C
B
Group B and C *trans*



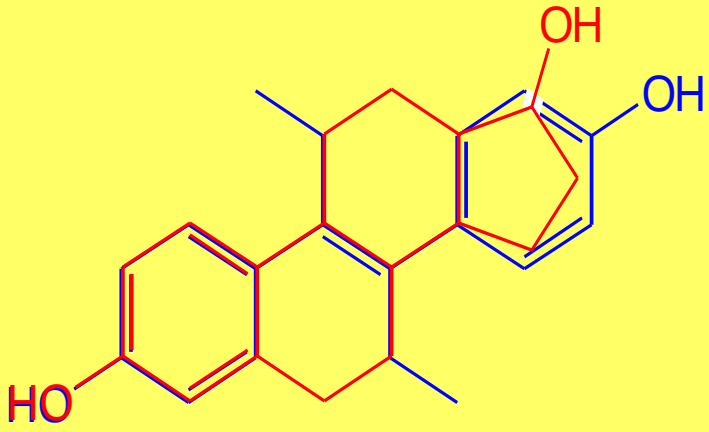
Estradiol



***E*-DES**
(Active)



***Z*-DES**
(Inactive)



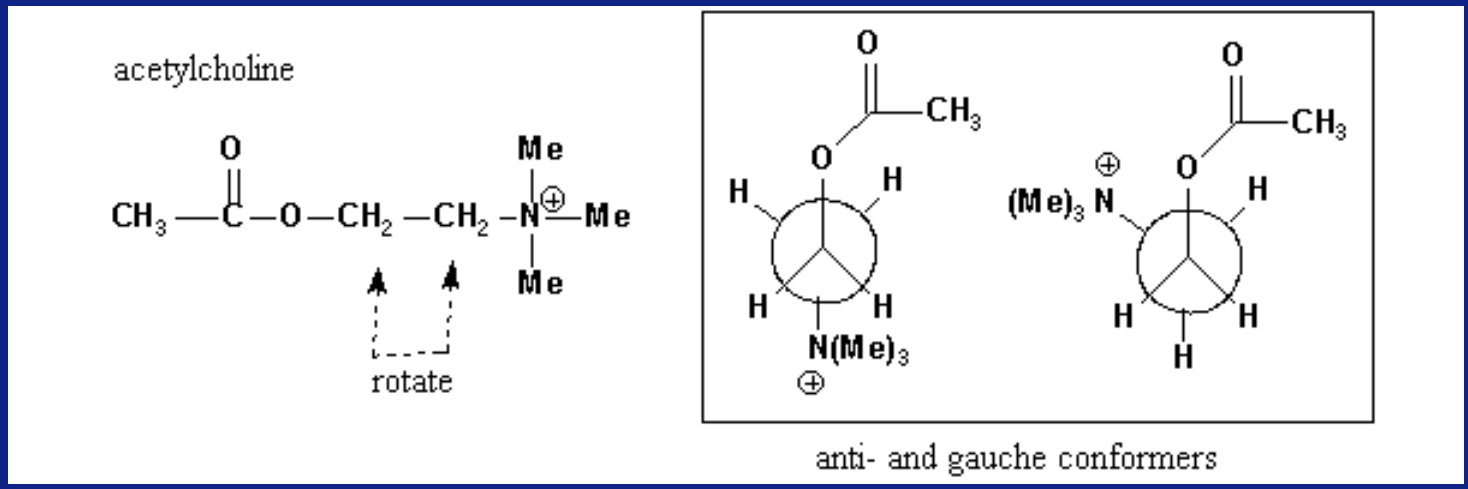
Estradiol & *E*-DES overlay

- According to this theory, the "right" isomer is called the **eutomer.**
- The "wrong" isomer is called the **distomer**.
- The ratio of the activities of the eutomer and the distomer is called the **eudismic ratio**, and converting the equation to log form affords the **eudismic index**, **EI**.

$$\frac{\text{activity of the eutomer}}{\text{activity of the distomer}} = \text{eudismic ratio}$$

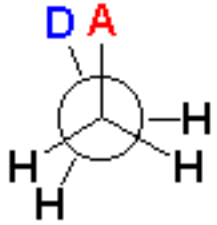
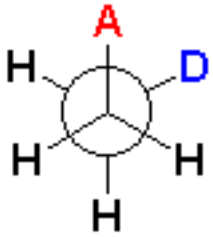
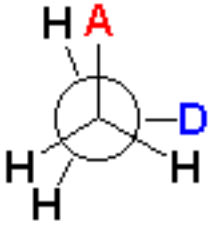
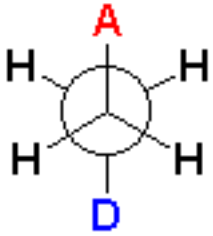
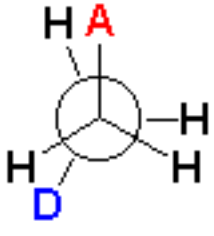
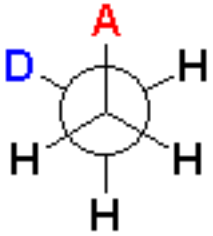
$$\log \text{affinity}_{EU} - \log \text{affinity}_{DIST} = EI \text{ (the eudismic index)}$$

- Acetylcholine may interact with the muscarinic receptor of postganglionic parasympathetic nerves and with Acetylcholine esterases in the fully extended confirmation and in a different more-folded structure with the nicotinic receptors at ganglia and at neuromuscular junctions.

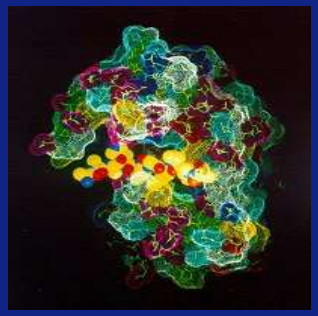


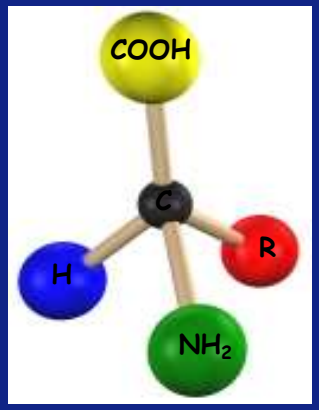
- Gauche conformer = muscarinic
- Anti conformer = nicotinic

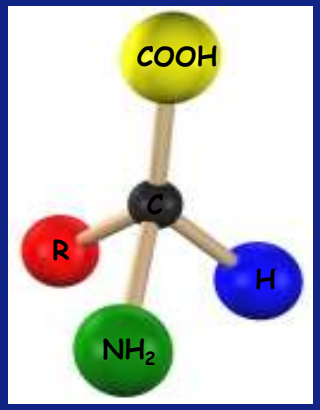
- **Conformation is a spatial arrangement of a molecule of a given constitution and configuration.**

Conf.						
angle	-30 +30	+30 +90	+90 +150	+150 +210	+150 +270	+270 +330
name	synperiplanar	+synclinal	+ anticlinal	+ antiperiplanar	-anticlinal	-synclinal
other name	eclipsed	+gauche		trans, anti		-gauche
abbreviation	sp	+sc	+ac	ap	-ac	-sc

Life is Chiral

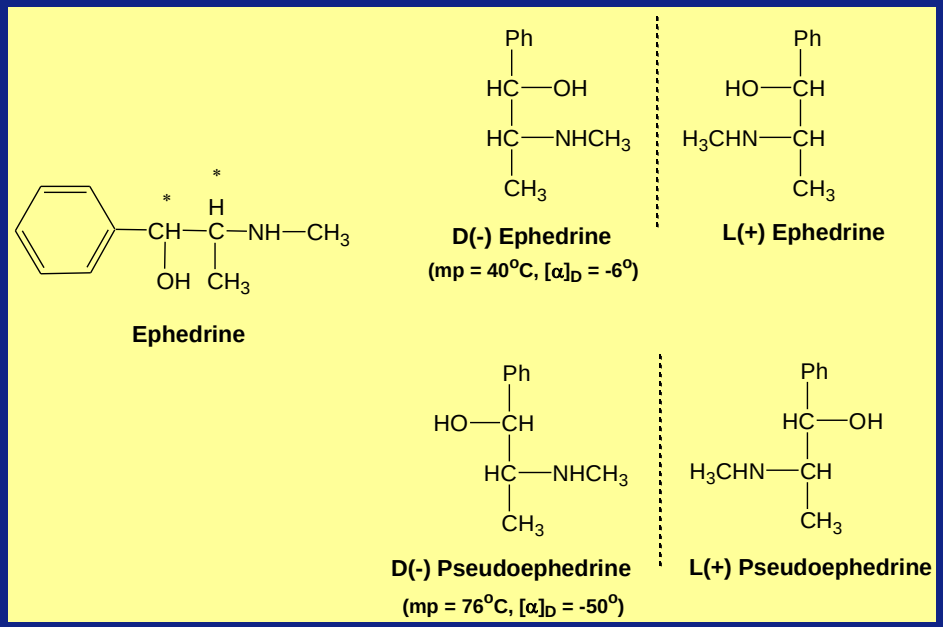




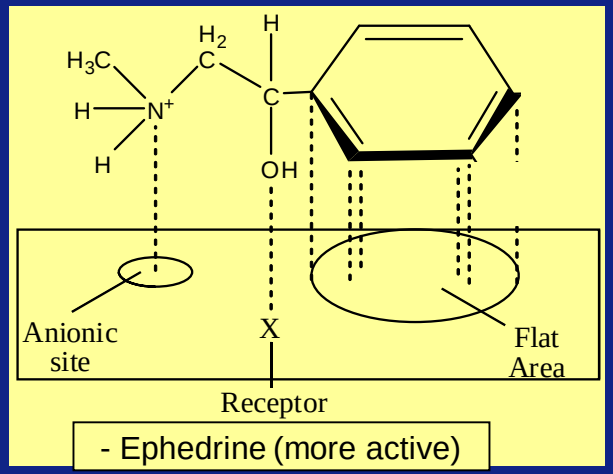


- Proteins are built from L-amino acids, which implies that enzymes - the catalysts of nature - are chiral
- Consequently, most biomolecules are chiral (sugars, DNA, proteins, amino acids, steroids)
- Also, receptors (drug, taste, biopharmaceuticals, agrochemicals) are chiral and the natural ligand to a receptor is often only one specific enantiomer
- This is why mirror image molecules can have radically different activities (effectivity, toxicity, taste) in the body.

Stereochemistry



- Enantiomers: Optical isomers which are mirror images
- Diastereoisomers: Optical isomers which are not mirror images
- Racemates: Mixture of equal parts of enantiomers



Pressor activities of ephedrines

Isomer	Relative Activity
D (-) Pseudoephedrine	1
DL Pseudoephedrine	4
L (+) Pseudoephedrine	7
L (+) Ephedrine	11
DL Ephedrine	26
D (-) Ephedrine	36