Stereochemistry, Conformation and Configuration

Reference: P. Bruice, Organic Chemistry, 6th Edition, Chapters 2.1-2.15, 3.3-3.5, 5.1-5.8, 5.11-5.13, 5.17, 5.20-5.21.

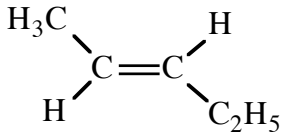
Stereochemistry - the arrangement of atoms in space.

Conformational isomers - those that rapidly interconvert at room temperature; they cannot be separated. They result from rotation about C-C single bonds (and from inversion of the electron pair on nitrogen).

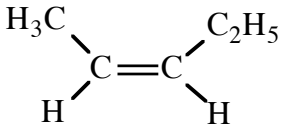
Configurational isomers - separable isomers that do not readily interconvert. Most would require "breaking" and "making" of bonds.

a. cis-trans (olefins)
b. chiral centers - absolute stereochemistry

Configurational isomers cis and trans olefins Note: no acetylenes

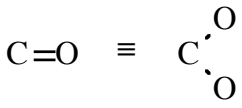


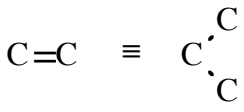
trans
E (entgegen)
(opposite)



cis
Z (zusammen)
(together)

Rules: 1. largest atomic number first $^{8}O > {}^{7}N > {}^{6}C$, I > Br > Cl > F
2. if same, go to second atom
3. most substituted



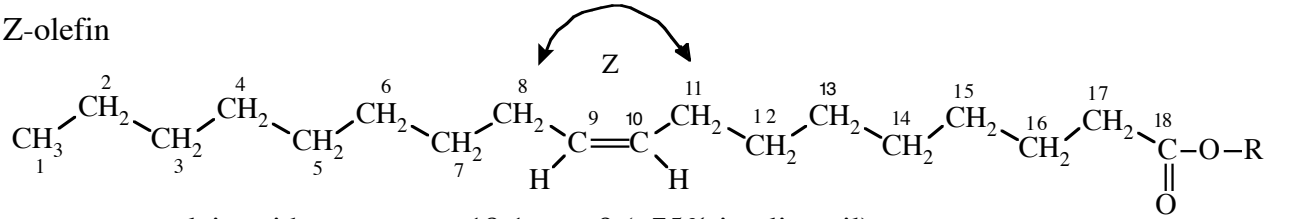


The stereochemistry of double bonds in dietary fats (fatty acid esters of glycerol) is important. "Trans"-fats are associated with increased risk of cardiovascular disease and are targeted for removal from the food supply. Partially hydrogenated cooking oils are the primary source of trans-fats.

Unsaturated fats are present in cooking oils, e.g. olive oil, corn oil, cottonseed oil, soybean oil, sunflower oil, canola oil, peanut oil, etc. Oils with more polyunsaturated acids (as glycerol esters in fats) are preferred, but more double bonds increase their ease of oxidation and temperature related decomposition. Saturated fats (animal sources) or partially hydrogenated cooking oils are more stable, but less preferred in the diet based principally on older, less robust data. Saturated fats are likely to be solids and are more stable to heat.

Peanut oil is mostly esters of 18:1, 18:2 and 16:0 acids. Corn oil and cottonseed oil contain more polyunsaturated fatty acid esters. Commercial fast food franchises and other restaurants and bakeries are moving to mixtures of vegetable oils for frying.

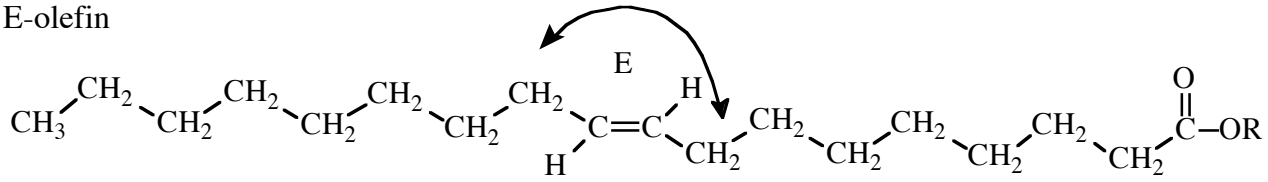
Z-olefin



oleic acid	18:1	ω-9 (~75% in olive oil)
palmitoleic acid	16:1	ω-7
linoleic acid	18:2	ω-9, ω-6
α-linoleic acid	18:3	ω-9, ω-6, ω-3
γ-linoleic acid	18:3	ω-12, ω-9. ω-6

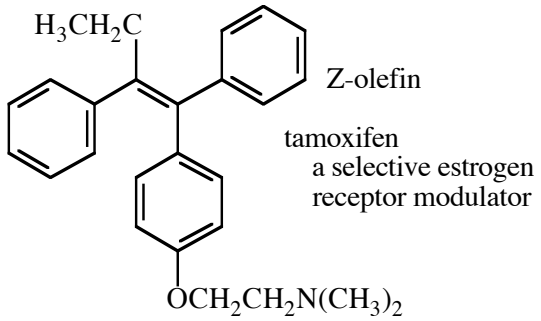
Glycerol esters - usually triesters - three fatty acids

E-olefin



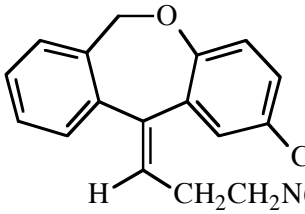
In the partial hydrogenation (H_2 Ni catalyst) polyunsaturated fatty acid esters are reduced but some double bonds are isomerized from Z to E (more stable).

Examples of drugs where one of the E- or Z-isomers is used are:



Z-olefin

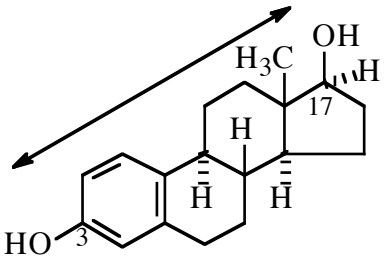
tamoxifen
a selective estrogen receptor modulator



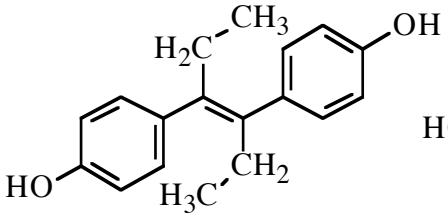
Z-olefin

olopatadine
a topical antihistamine

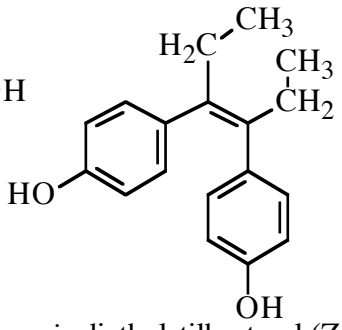
For estrogenic activity, structure activity relationship studies have led to the conclusion that the presence of two hydroxyl groups about 11-12 Å apart are sufficient. This specification can be met in estradiol or estrone by the phenolic hydroxyl group (C-3) and 17β-OH or ketone, and in DES by phenolic hydroxyl groups.



estradiol

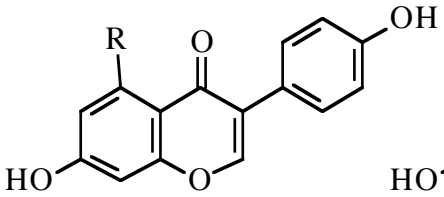


trans-diethylstilbesterol (DES) (E-)

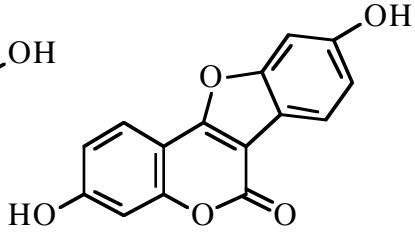


cis-diethylstilbesterol (Z-)

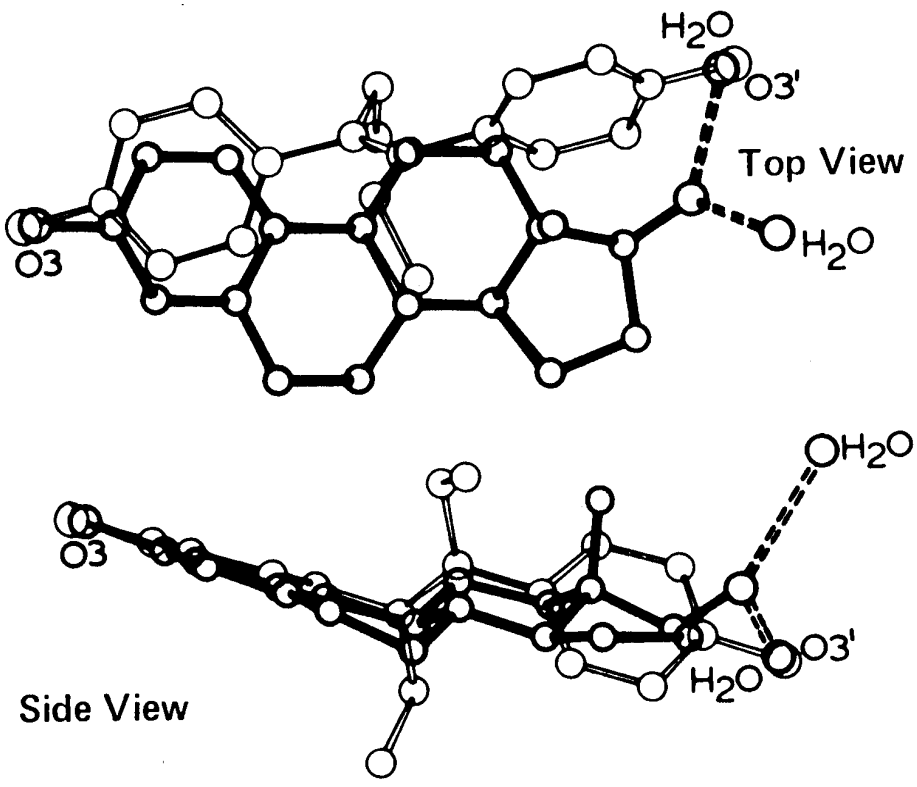
R = OH genistein
R = H daidzein



common in isoflavone phytoestrogens, e.g. soy products

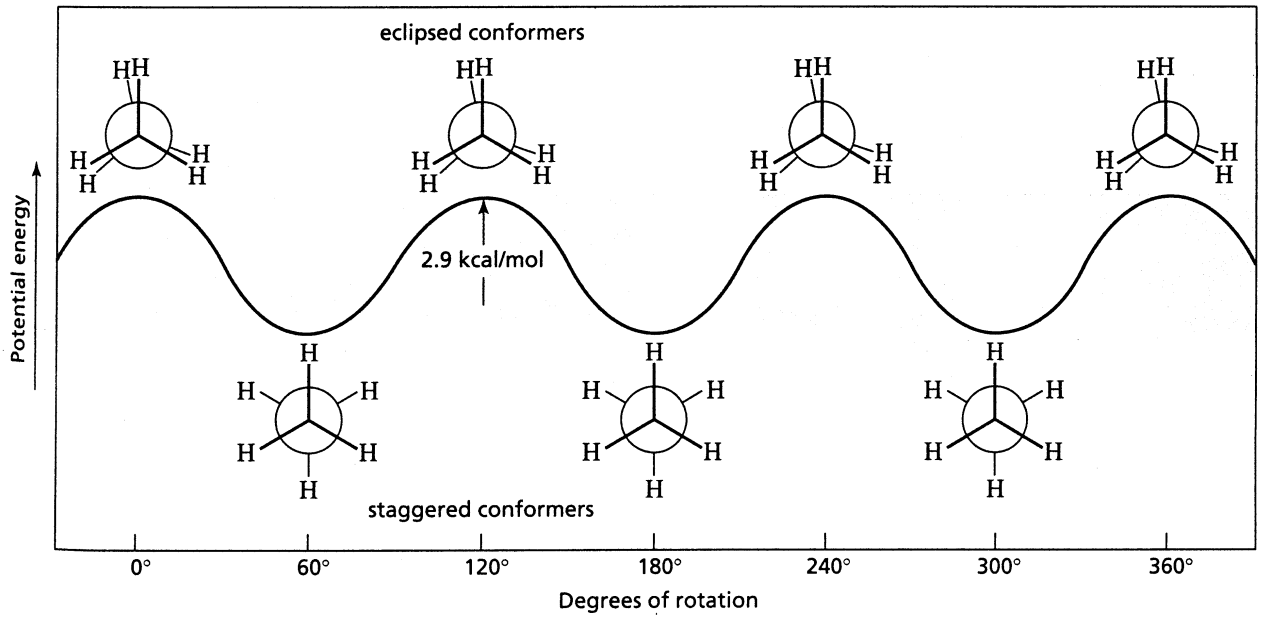


coumesterol



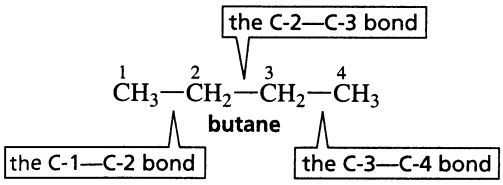
Estradiol $(H_2O)_2$ = dark lines
DES = light lines

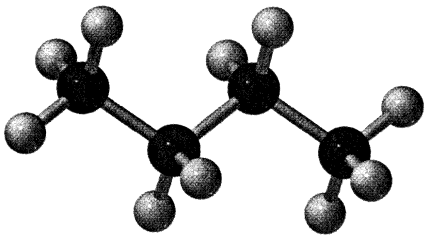
Ethane

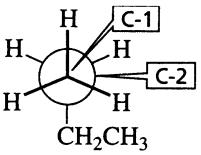


▲ **Figure 2.4**
Potential energy of ethane as a function of the angle of rotation about the carbon–carbon bond.

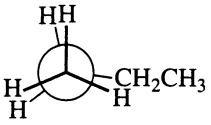
Butane



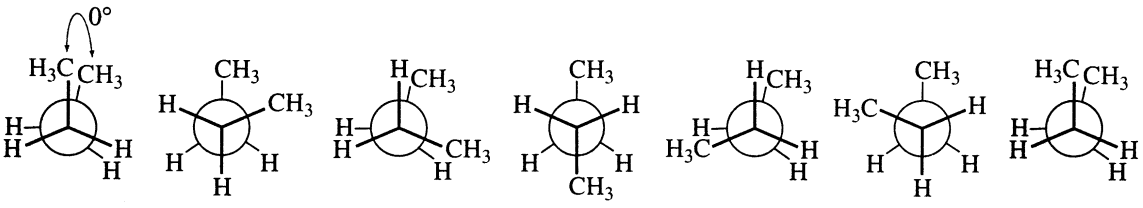


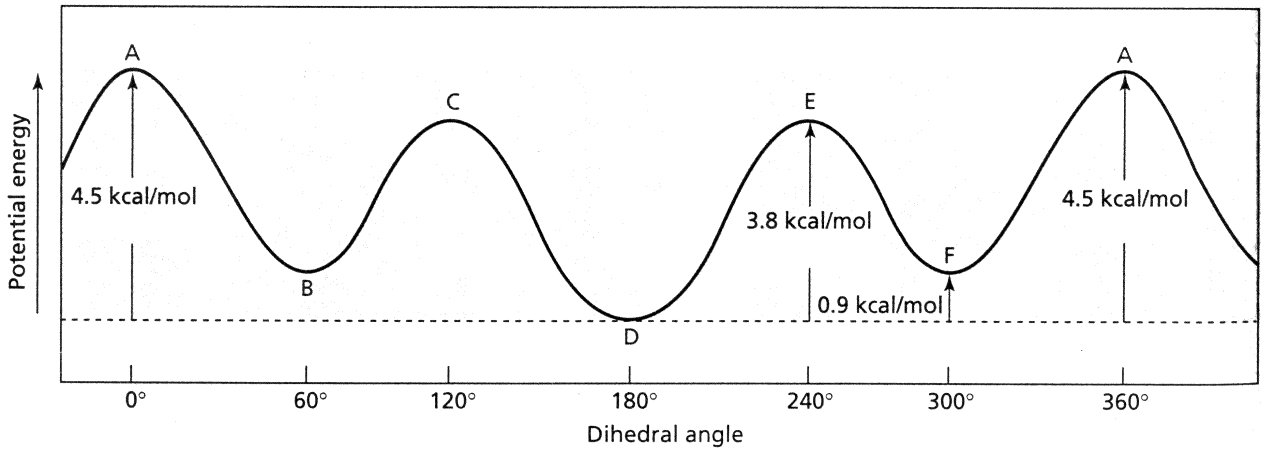


staggered conformation for rotation about the C-1—C-2 bond in butane



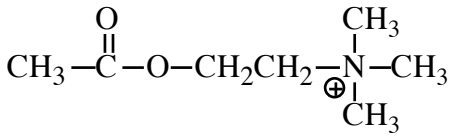
eclipsed conformation for rotation about the C-1—C-2 bond in butane



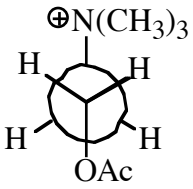


▲ Figure 2.5
Potential energy of butane as a function of the degree of rotation about the C-2—C-3 bond. Letters refer to the conformers (A–F) shown above.

Acetylcholine

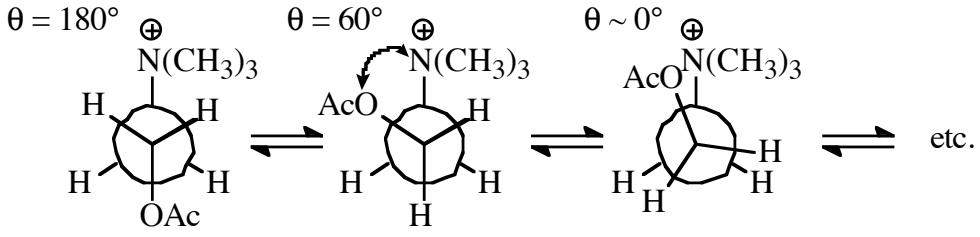


neurotransmitter

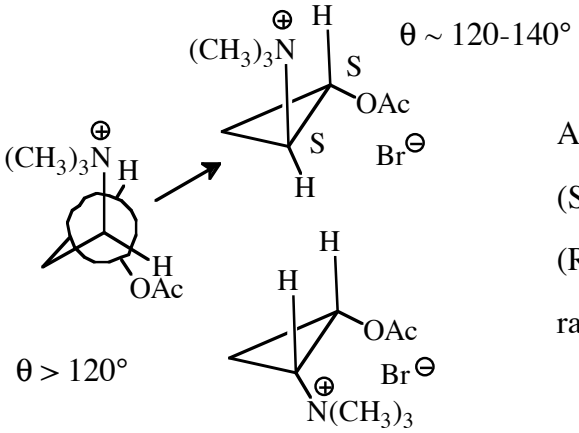


Conformational Considerations. For conformationally mobile agonists, it is probable that the molecule has to assume a particular specific conformation in the agonist-receptor complex in order for complexation to lead to drug action. Conformational changes in the receptor are also thought to occur. It has been postulated that acetylcholine in the drug-receptor complex could adopt different conformations at the muscarinic and nicotinic receptors. Research has been done to study conformationally rigid analogs of acetylcholine, rigid ring compounds which contain the acetylcholine functional groups in particular relative orientation in space, for example, trans or cis (or gauche like). A problem with this approach is that the rigid acetylcholine analogs cannot be formed without adding carbon skeleton to the ACh molecule and these structural changes modify the physical properties and add new stereochemical factors to the molecule. The simplest analogs prepared are the cyclopropane compounds.

Conformations of acetylcholine:



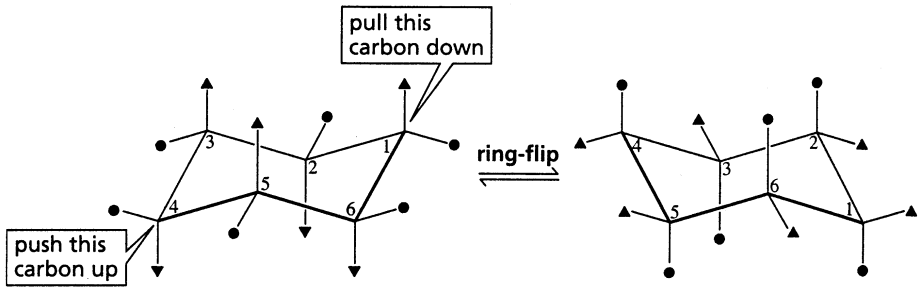
trans gauche approaching eclipsed

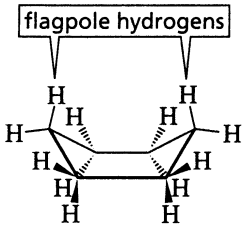


	Relative Potency	
	Guinea pig ileum	Dog blood pressure
ACh	100	100
(S,S)-(+)-trans	113	470
(R,R)-(-)-trans	0.22	2.3
racemic cis	0.10	

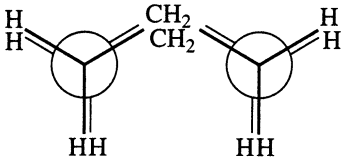
Cyclohexane

Figure 2.8 ▶
The bonds that are axial in one chair conformer are equatorial in the other chair conformer. The bonds that are equatorial in one chair conformer are axial in the other chair conformer.

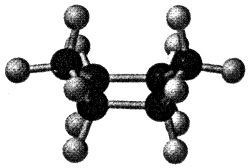




boat conformer of cyclohexane

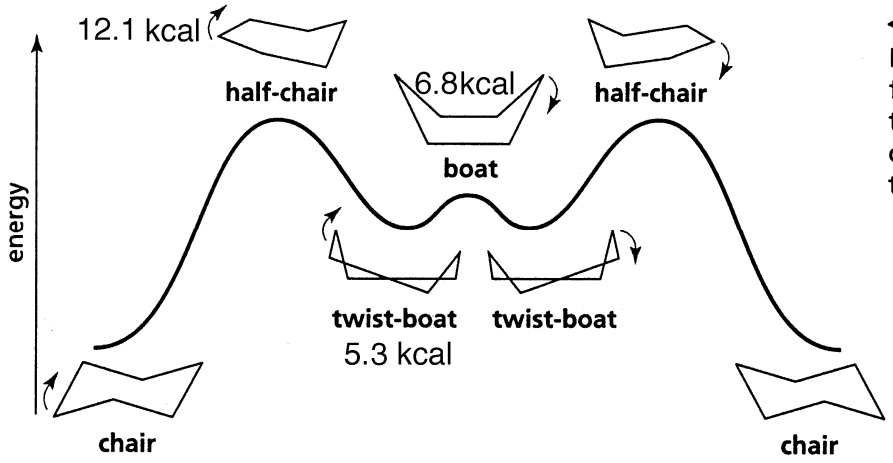


Newman projection of the boat conformer

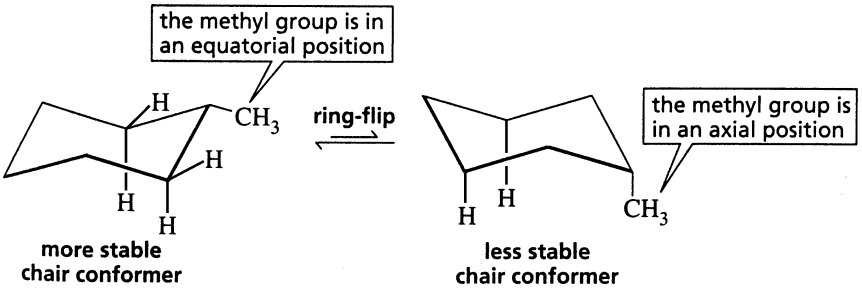


ball-and-stick model of the boat conformer of cyclohexane

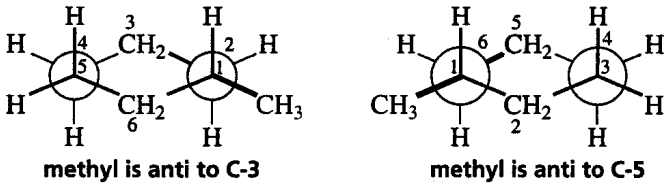
▲ Figure 2.9
The boat conformer of cyclohexane and the Newman projection of the boat conformer showing that some of the bonds are eclipsed.



◀ Figure 2.10
Diagram showing the conformers of cyclohexane (and their relative energies) as one chair conformer interconverts to the other chair conformer.

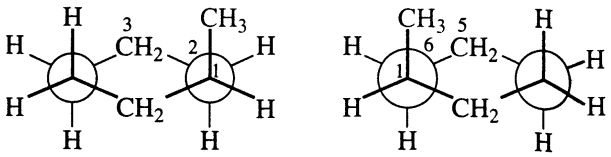


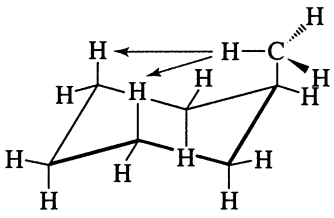
◀ Figure 2.11
A substituent is in the equatorial position in one chair conformer and in the axial position in the other chair conformer. The conformer with the substituent in the equatorial position is more stable.



◀ Figure 2.12
An equatorial substituent on the C-1 carbon is anti to the C-3 and C-5 carbons.

Figure 2.13 ▶
An axial substituent on the C-1 carbon is gauche to the C-3 and C-5 carbons.





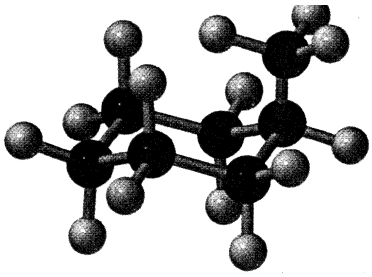
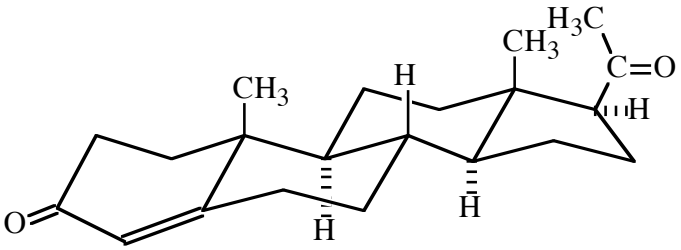


Table 2.10 Equilibrium Constants for Several Monosubstituted Cyclohexanes at 25°C

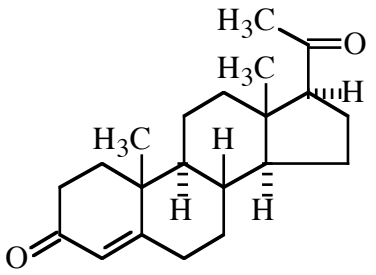
Substituent	K_{eq} Axial ⇌ Equatorial	Substituent	K_{eq} Axial ⇌ Equatorial	Bond	Length
H	1	F	1.5	C–F	1.39Å
CH_3	18	Cl	2.4	C–Cl	1.78Å
CH_3CH_2	23	Br	2.2	C–Br	1.93Å
$CH_3CH(CH_3)$	38	I	2.2	C–I	2.14Å
$CH_3C(CH_3)_2CH_3$	4000	HO	5.4	C–O	1.43Å

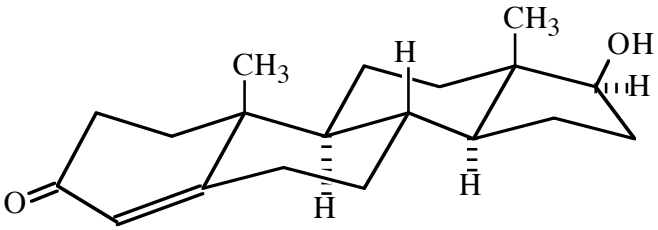
Steroids:

Scaffolds of functional groups held some distance apart.

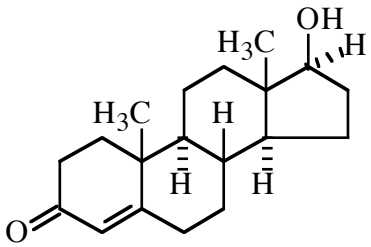


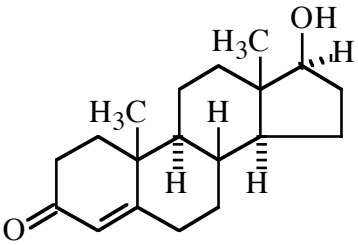
progesterone



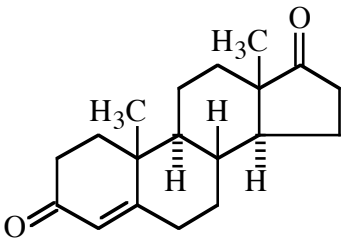


testosterone

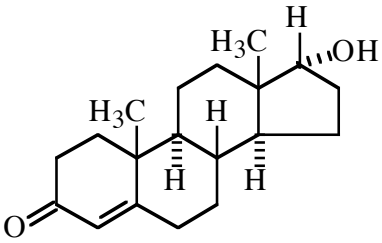




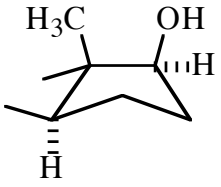
testosterone

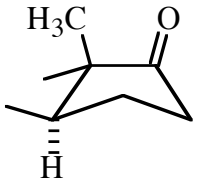


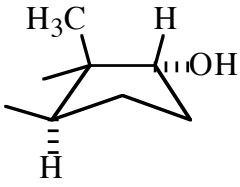
androstenedione



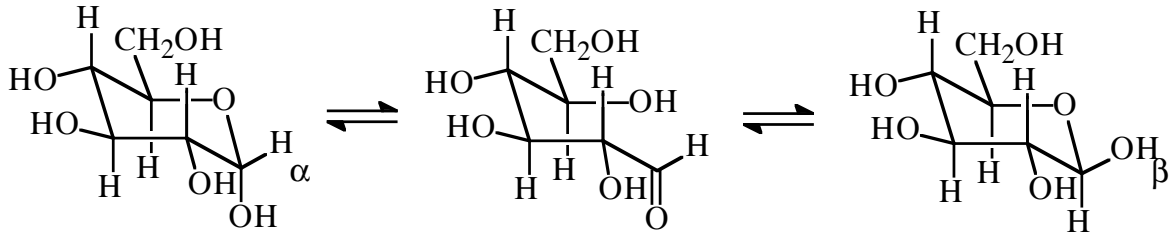
epitestosterone







Heteroatom-containing six-membered rings
Oxygen - hexoses

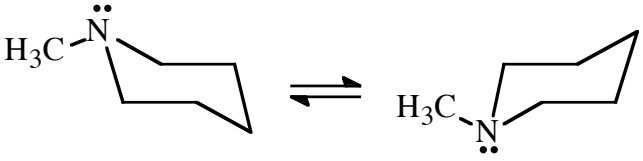


α-D-glucose (36%)
(all equatorial)
(except anomeric carbon)

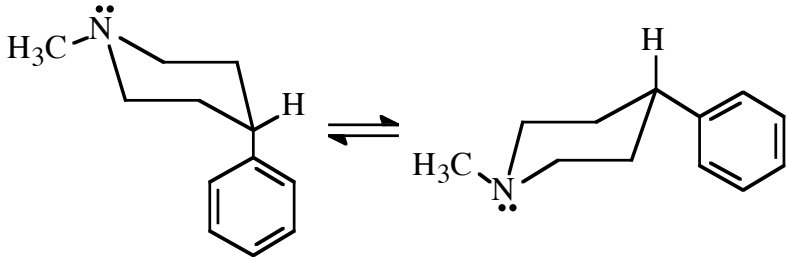
(0.02%)

β-D-glucose (64%)
(all equatorial)
(including anomeric carbon)

Nitrogen - piperidines



inversion

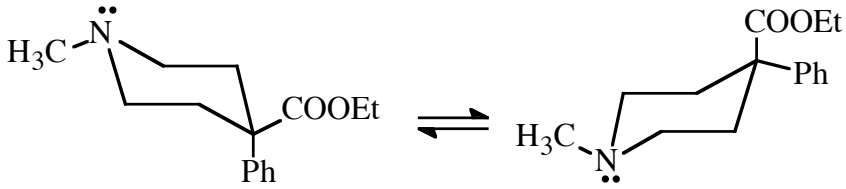


for Ph, $\Delta G \cong -2.7$ kcal/mol

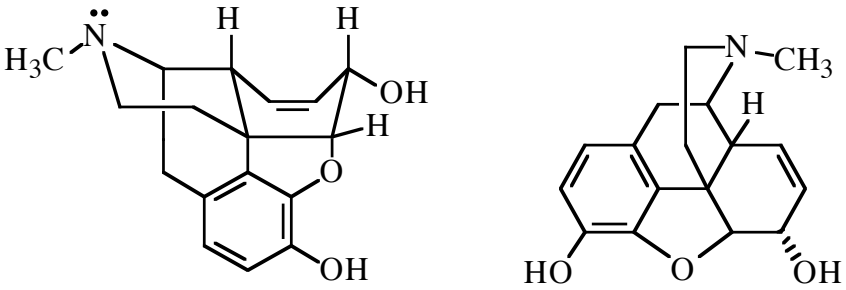
$\Delta G = -RT\ln K = -1.36 \log K$

$-2.7/-1.36 \cong 2 = \log K$

$10^2 = K$ (K ~ 99% equatorial)



analgesic
meperidine



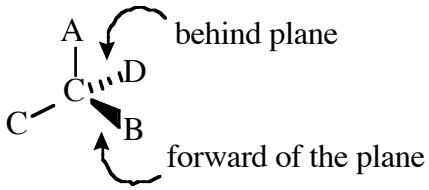
Morphine Ar ring is an axial substituent on the piperidine ring

Configurational isomers - separable isomers that do not readily interconvert

1. chiral centers - absolute stereochemistry

   sp^3 carbons (or nitrogens, or ...)

   chiral-handed (left or right)



2. enantiomers (enantio = opposite)

   non-identical (non-superimposable) mirror image

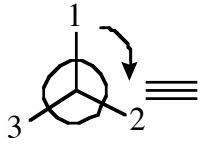
   R = recto (right-handed)
   S = sinestro (left-handed) Cahn-Ingold-Prelog

Priority Rules

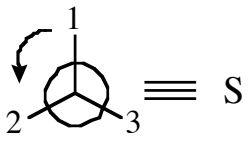
at the chiral center:

1. atomic number priority 1,2,3,4, largest atomic number first
2. if atoms same, go to next atom
3. C=C is  , C=O is 
4. isotopes - higher atomic mass

view with lowest priority group away

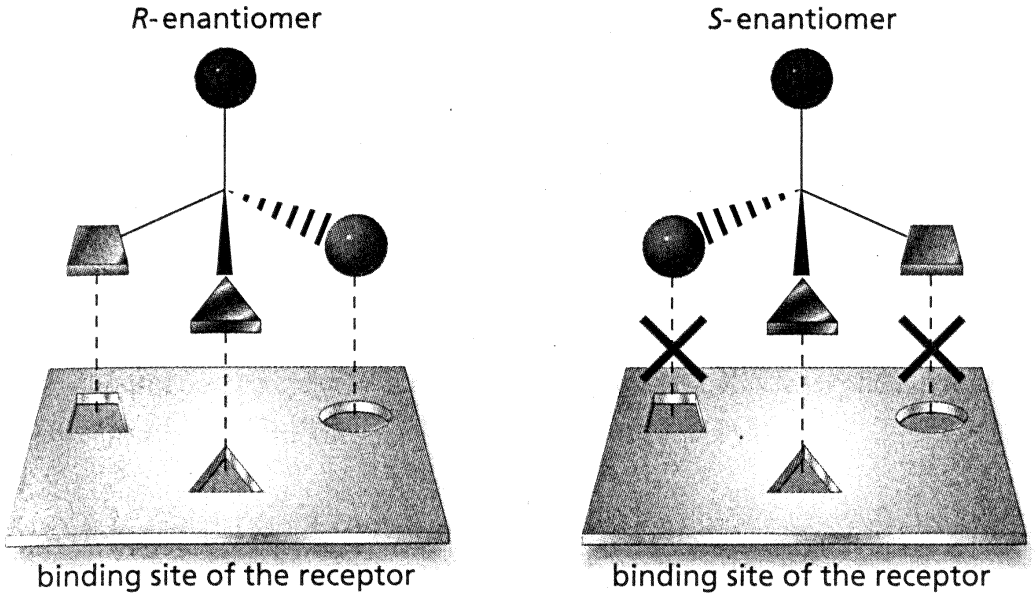


R

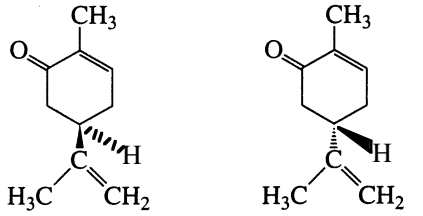


S

Receptors are proteins that bind particular molecules. Because a receptor is chiral, it will bind one enantiomer better than the other. In Figure 4.2, the receptor binds the *R*-enantiomer but it does not bind the *S*-enantiomer.



▲ **Figure 4.2**
Schematic diagram showing why only one enantiomer is bound by a receptor. One enantiomer fits into the binding site and one does not.



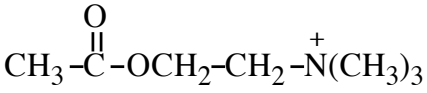
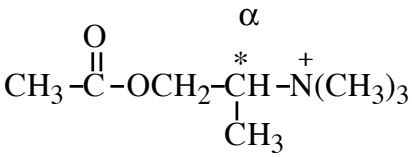
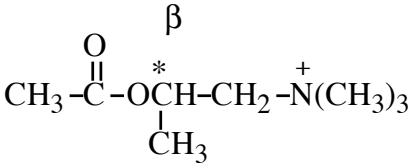
(*R*)-(–)-carvone
spearmint oil

$[\alpha]_D^{20\,°C} = -62.5°$

(*S*)-(+)-carvone
caraway seed oil

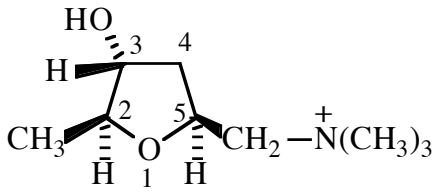
$[\alpha]_D^{20\,°C} = +62.5°$

Comparison in the α- and β-methylacetylcholine series:

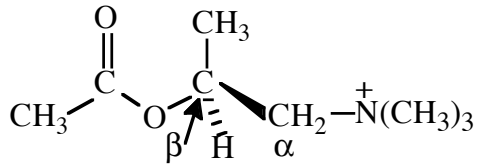
		Relative Potency (%) ACh = 100 [Conc. ACh/Conc. Drug] x 100		Muscarinic receptor related processes
 acetylcholine				
	α-CH_3	Racemic (-)-(S) (+)-(R)	2.0 0.43 3.6**	Substitution at the α–carbon reduces potency significantly, with only a small difference between enantiomers.
	β-CH_3	Racemic (+)-(S) (-)-(R)	63 100** 0.42	Substitution at the β–carbon provides a very potent S-enantiomer, and the very weak R-enantiomer, the difference being about 240-fold.

** more active enantiomer

Muscarine was obtained from the toxic mushroom Amanita. There are eight optical isomers of muscarine and the natural product (2S,3R,5S) is more than 100 times more potent in its cholinergic muscarinic activity (potency) than any of the other seven stereoisomers. Based on work with selective antagonists, there is now thought to be more than one muscarinic receptor, these are designated M_1, M_2, M_3.



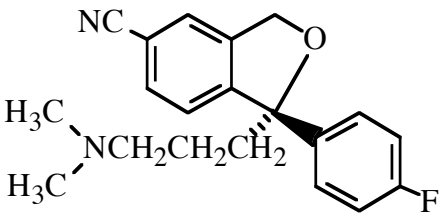
(+)-(2S,3R,5S)-Muscarine
About twice the potency of acetylcholine and about 700 times more potent than its enantiomer (-)-(2R,3S,5R)-muscarine.



(+)-(S)-β-Methylacetylcholine
[(+)-Methacholine]
Muscarinic effect about the same as for ACh and 240 times greater than for the (R) isomer. Sometimes used in diagnosis of bronchial airway hypersensitivity.

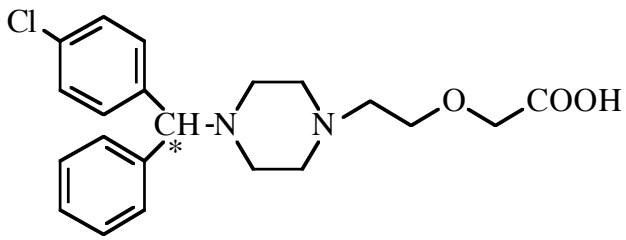
In 2009, the 10 most widely prescribed drugs (number of prescriptions) are all single enantiomers: atorvastatin, hydrocodone, L-thyroxine, amoxicillin, lisinopril, esomeprazole, escitalopram, montelukast, clopidogrel, and simvastatin. Six of the most widely prescribed drugs also appear in the top 20 in sales (> $2.7 billion), and four proteins, erythropoetin (used in chronic kidney failure), etanercept and infliximab (used in rheumatoid arthritis) and pegfilgrastim (used to decrease incidence of infections in cancer patients treated with myelosuppressive drugs).

Some Single Enantiomers of Drugs



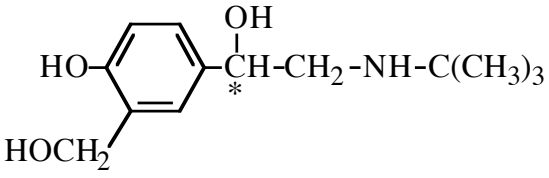
Escitalopram (S-citalopram)
S-enantiomer is more than 30x more potent than R-enantiomer in inhibition of serotonin reuptake. It is also an inhibitor of norepinephrine reuptake. These are different amine transporters.

The S-enantiomer [Lexapro] is an antidepressant. The racemic drug is Celexa. Interestingly, the therapeutic dose of the S-enantiomer is about 1/4 of the racemate-10 vs. 40 mg.

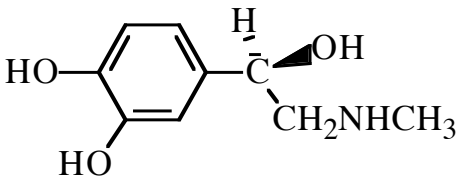


Cetirizine (antihistamine)

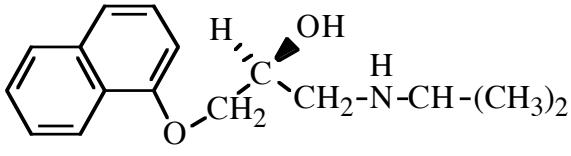
Levocetirizine [Xyzal]
(R-cetirizine)



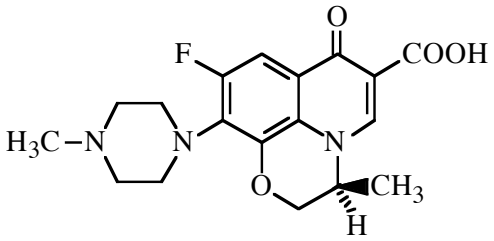
Albuterol - racemic
R-Albuterol [Xopenex]
used in treatment of asthma



R-Epinephrine

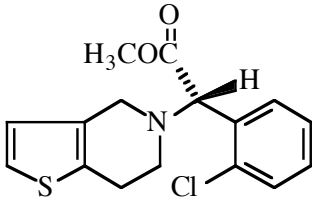


S-Propranolol



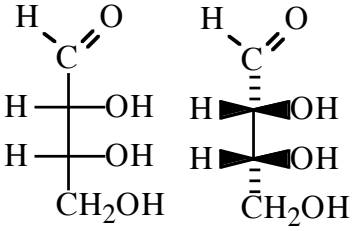
Levofloxacin [Levaquin]
(S-enantiomer)

Ofloxacin [Floxin]
(racemate)

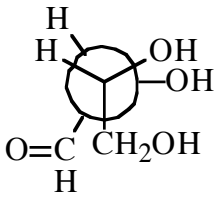


Clopidogrel [Plavix]
(S-enantiomer)

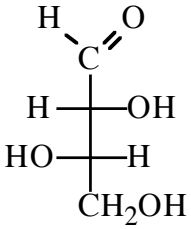
Two chiral centers - two diastereomers, each of which has an enantiomer, $2^2 = 4$ possible optical isomers. These are usually called erythro- and threo-, if the asymmetric centers are adjacent to each other and kind of "like" each other.



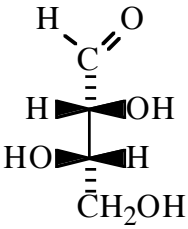
erythrose



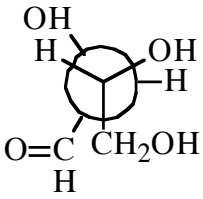
like groups
eclipse each other



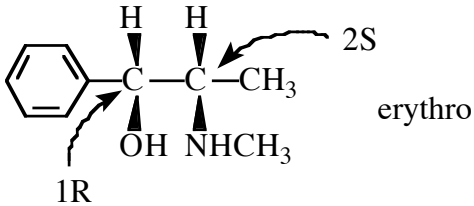
threose



all three like groups cannot
eclipse each other



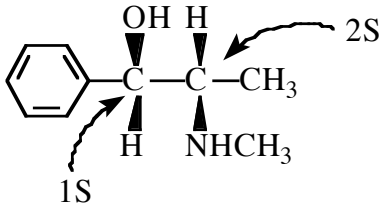
ephedrine



erythro

1R,2S-(-)-ephedrine

pseudoephedrine



threo

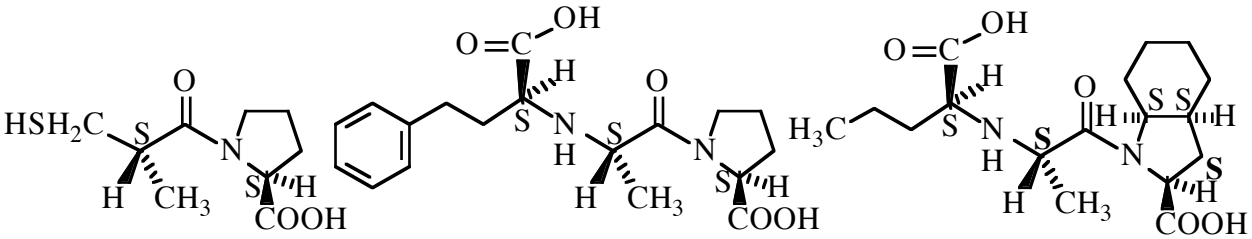
1S,2S-(+)-pseudoephedrine

Ephedrine is an effective oral adrenergic agonist. It is also available as a vasopressor to be used in shock. It has direct and indirect effects (releases norepinephrine). Ephedrine-containing natural products (ma huang) have been banned in the U.S. Pseudoephedrine is used principally as a decongestant; it is a less potent pressor agent. Restrictions apply to its purchase. Both are precursors for the clandestine synthesis of 2S-methamphetamine (reductive removal of the OH group). Ma huang products usually contain ephedrine and pseudoephedrine (4-5:1) and smaller amounts of N-methyl and N-desmethyl compounds.

Three chiral centers affords $2^3 = 8$ possible optical isomers, 4 sets of enantiomers - like muscarine.

Epimuscarine, allomuscarine and epiallomuscarine are the other three diastereomers.

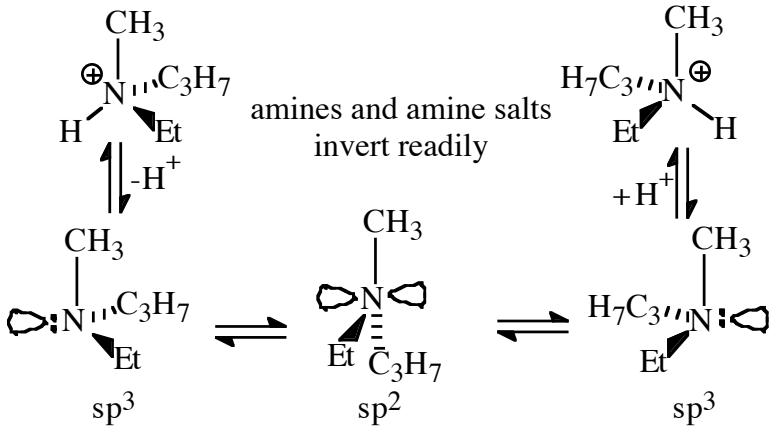
Several of the inhibitors of angiotensin converting enzyme (ACE inhibitors) used in hypertension have more than one chiral center.



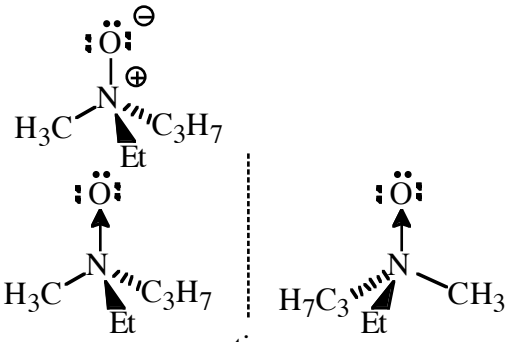
captopril enalaprilat perindoprilat

All thirty-two isomers of perindoprilat have been made and tested in vitro. Eight of them are much more potent than the others. All 8 of these have SS stereochemistry at the two chiral centers noted in bold face font.

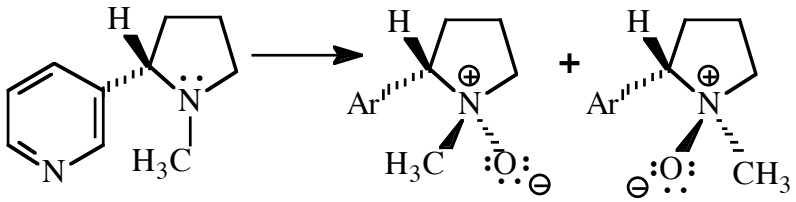
Chiral Nitrogen



Tertiary Amine N-Oxides

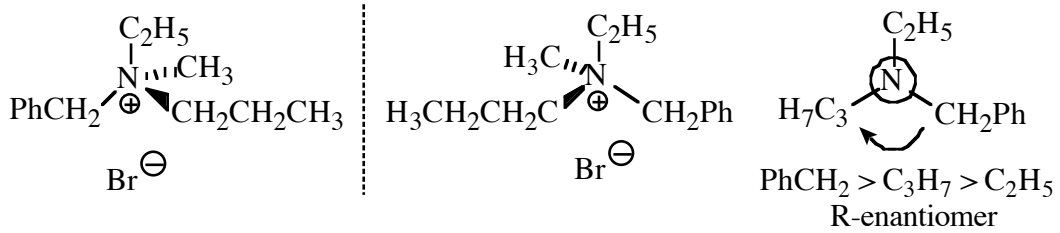


enantiomers



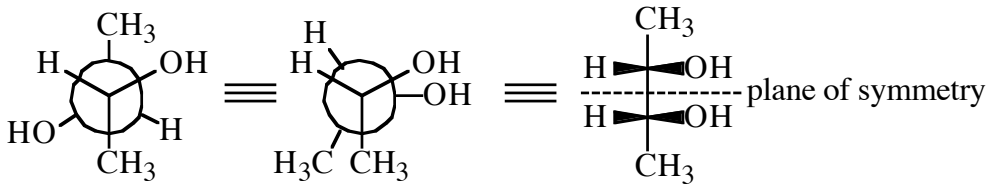
More 1S,2S-nicotine N-oxide is produced by humans than its 1R, 2S diastereomer.

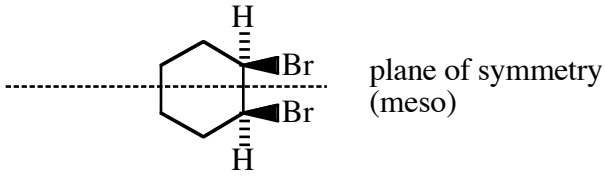
Quaternary Ammonium Ions

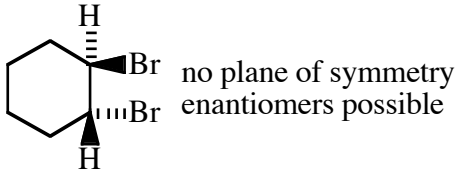


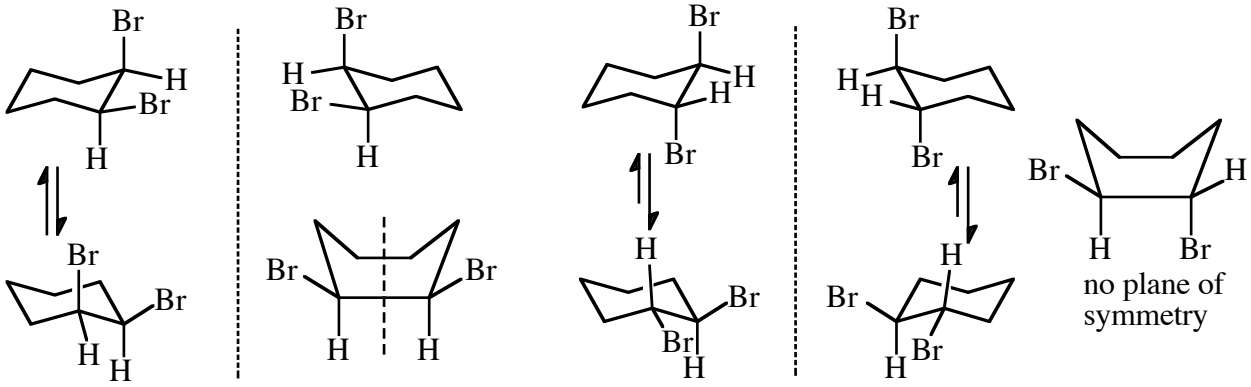
Meso forms are compounds with two or more chiral centers in which a plane of symmetry is present, thus no optical isomers and no rotation of polarized light.

Meso compounds



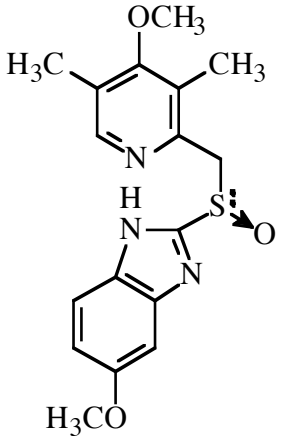






Chiral Sulfur Derivatives

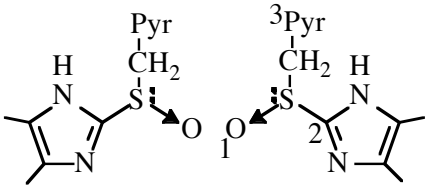
Omeprazole and Esomeprazole



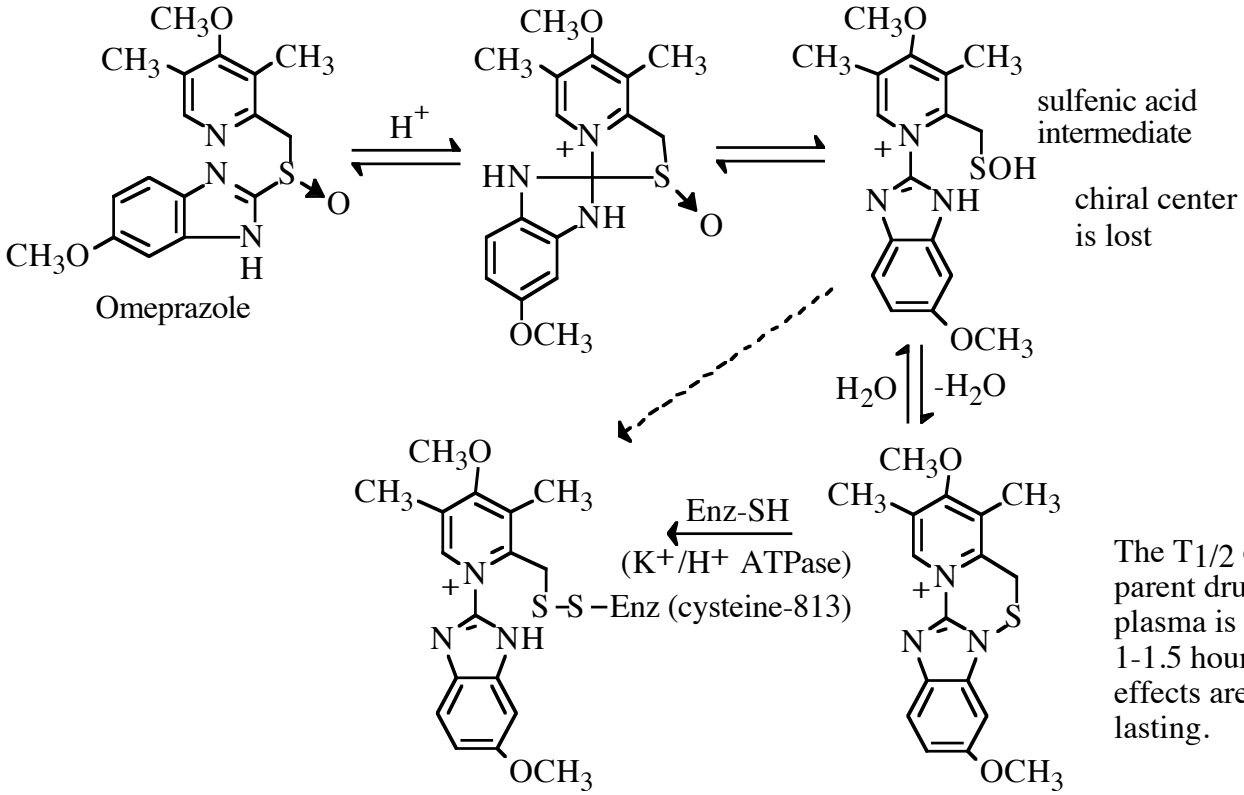
The racemic compound is Prilosec [omeprazole]. Generic products and an OTC product are available.

Nexium [esomeprazole] is heavily advertised. It is the S– enantiomer. Less hydroxylation by CYP2C19 and lower intrinsic clearance than R-enantiomer is reported.

These agents block gastric acid secretion in parietal cells in the final common pathway of gastric acid secretion, the hydrogen, potassium-ATPase proton pump. They block acid secretion regardless of stimulatory pathway (cholinergic, histaminergic or gastrinergic pathways).

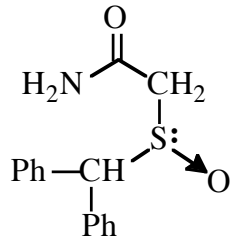


All of these agents form reactive products in the very acidic environment of the parietal cell. The intermediate probably reacts with a part of the K^+/H^+ATPase proton pump irreversibly blocking it. Note the chiral center is lost in the process. The effects are long lasting because these agents covalently bond to the proton pump, apparently irreversibly.



The $T_{1/2}$ of the parent drug in plasma is about 1-1.5 hours. The effects are longer lasting.

Modafinil [Provigil] and Armodafinil [Nuvigil]



R-modafinil

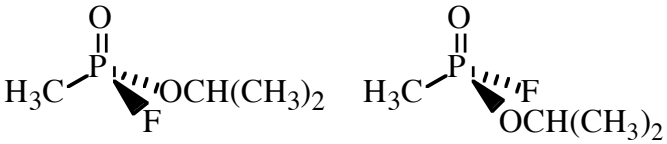
R-enantiomer has a half-life of ~10 hours, vs. 3 hours for the S-enantiomer.

Used in narcolepsy, obstructive sleep apnea/hypopnea syndrome, shift work sleep disorder, fatigue in multiple sclerosis.

Chiral Phosphorus Compounds

Sarin and soman are "nerve gases," really liquids. They are phosphonate esters that irreversibly inhibit acetylcholinesterase. Phosphoric acid esters, closely related, are used as insecticides in gardens and on lawns, etc.

The active site of this enzyme has a serine hydroxyl group that reacts with these compounds.

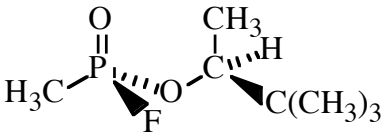


sarin

S_p (S at phosphorus) R_p (R at phosphorus)

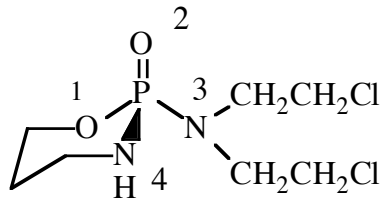
The S_p-enantiomer reacts with the enzyme acetylcholinesterase about 4000 times more rapidly than the R_p-enantiomer.

(F > OCH_2 > O CH_3 is lowest priority)



soman

One of the enantiomers of one of the diastereomers of soman. Biomolecular rate constant in the reaction with AChE of one enantiomer is about 10^4 times that of its enantiomer (red cell AChE).



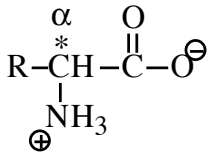
S-enantiomer

Cyclophosphamide – an alkylating agent used in treatment of cancer and autoimmune disease. The enantiomers are metabolized at different rates, the R-enantiomer being metabolized more rapidly.

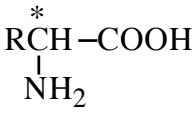
Amino Acids, Peptides, Proteins - Our Chiral World

α-Amino acids are building blocks for proteins, linear sequences of 100-500 amino acids (up to 4500 amino acids - lipoprotein B-100).

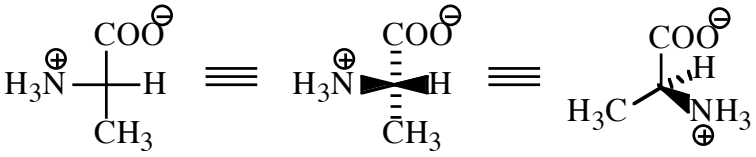
20 common amino acids



sometimes written as

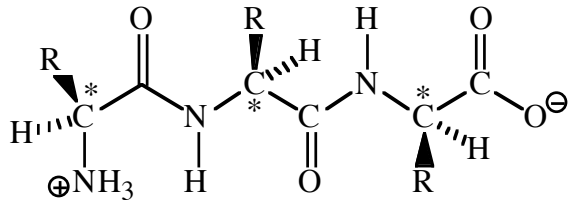


Stereochemistry



Fischer "L amino acids" S-alanine

All are "S" at C-α, except cysteine where sequence rules place CH_2SH > COOH. Threonine and isoleucine have an additional chiral center, and glycine has no chiral center.

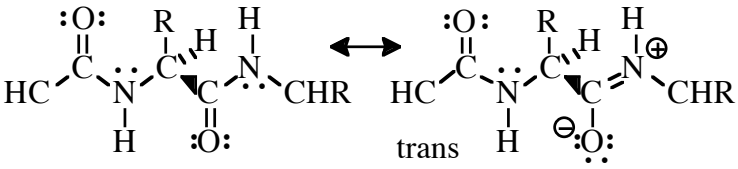


If R = Me Ala-Ala-Ala (AAA)

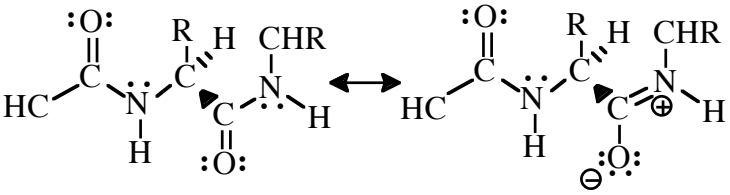
Amides, peptides - more than one amino acid, less than ~50-75. More than this number, they become proteins.

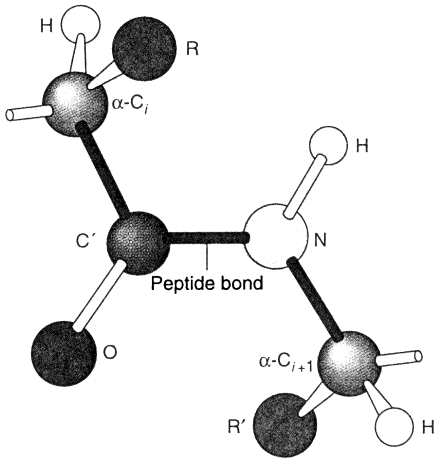
The C-N bonds in amides have considerable double bond character.

Trans conformations are more stable than cis ones usually and rotation is slow.

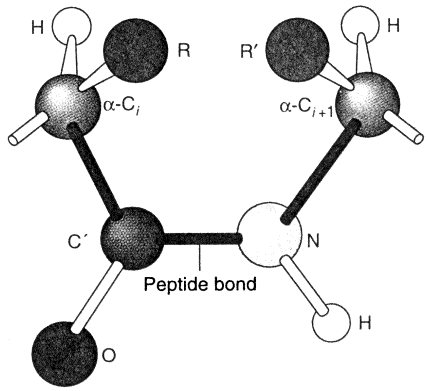


Here, biochemical "order" of groups is the α–carbon atom of one amino acid and the α–carbon of the adjacent amino acid are on opposite sides = trans.





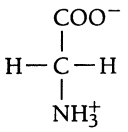
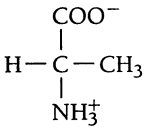
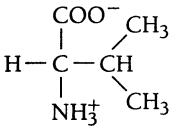
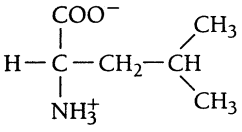
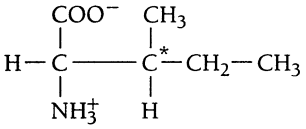
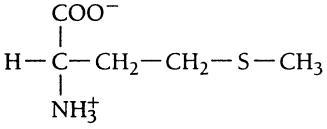
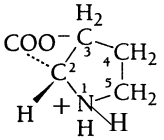
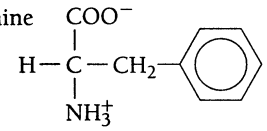
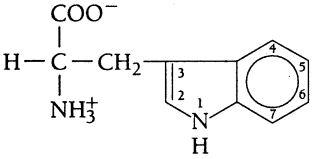
(a) trans configuration



(b) cis configuration

FIGURE 2.11
(*a*) *Trans*-peptide bond and (*b*) the rare *cis*-peptide bond.
The C′—N have a partial double-bond character.

Table 4-1. Key to Structure. **Covalent Structures and Abbreviations of the "Standard" Amino Acids of Proteins, and the p*K* Values of Their Ionizable Groups**

Name, Three-letter Symbol, and One-letter Symbol	*Structural Formula*[a]	pK_1 *α-COOH*[b]	pK_2 *α-NH_3^+*[b]	pK_R *Side Chain*[b]
Amino acids with nonpolar side chains				
Glycine Gly G		2.35	9.78	
Alanine Ala A		2.35	9.87	
Valine Val V		2.29	9.74	
Leucine Leu L		2.33	9.74	
Isoleucine Ile I		2.32	9.76	
Methionine Met M		2.13	9.28	
Proline Pro P		1.95	10.64	
Phenylalanine Phe F		2.20	9.31	
Tryptophan Trp W		2.46	9.41	

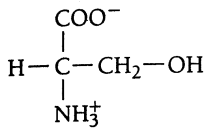
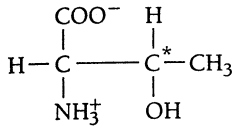
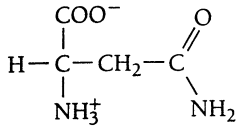
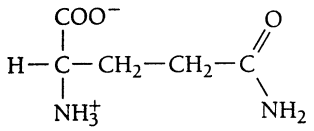
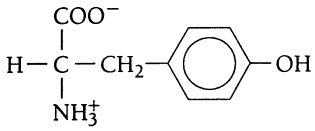
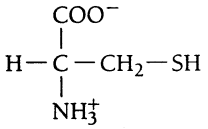
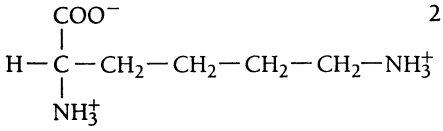
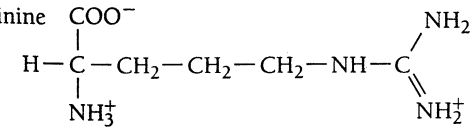
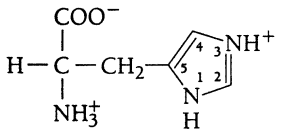
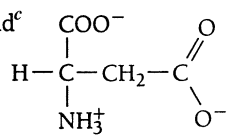
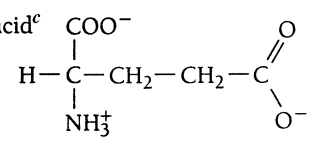
[a]The ionic forms shown are those predominating at pH 7.0 although residue mass is given for the neutral compound The C_α atoms, as well as those atoms marked with an asterisk, are chiral centers with configurations as indicated according to Fischer projection formulas. The standard organic numbering system is provided for heterocycles.

[b]Data from Dawson, R.M.C., Elliott, D.C., Elliott, W.H., and Jones, K.M., *Data for Biochemical Research* (3rd ed.), pp. 1-31, Oxford Science Publications (1986).

[c]The three- and one-letter symbols for asparagine *or* aspartic acid are Asx and B, whereas for glutamine *or* glutamic acid they are Glx and Z. The one-letter symbol for an undetermined or "nonstandard" amino acid is X.

[d]Both neutral and protonated forms of histidine are present at pH 7.0, since its pK_R is close to 7.0.

Table 4-1. (continued)

Name, Three-letter Symbol, and One-letter Symbol	Structural Formula[a]	pK_1 α-COOH[b]	pK_2 α-NH_3^+[b]	pK_R Side Chain[b]
Amino acids with uncharged polar side chains				
Serine Ser S		2.19	9.21	
Threonine Thr T		2.09	9.10	
Asparagine[c] Asn N		2.14	8.72	
Glutamine[c] Gln Q		2.17	9.13	
Tyrosine Tyr Y		2.20	9.21	10.46 (phenol)
Cysteine Cys C		1.92	10.70	8.37 (sulfhydryl)
Amino acids with charged polar side chains				
Lysine Lys K		2.16	9.06	10.54 (ε-NH_3^+)
Arginine Arg R		1.82	8.99	12.48 (guanidino)
Histidine[d] His H		1.80	9.33	6.04 (imidazole)
Aspartic acid[c] Asp D		1.99	9.90	3.90 (β-COOH)
Glutamic acid[c] Glu E		2.10	9.47	4.07 (γ-COOH)

Steric effects, charged side chains, conformations

Alkyl side chains are hydrophobic

Polar side chains (arginine, histidine, lysine) - amines

aspartate, glutamate - carboxylic acids

phenolic OH tyrosine

alcohol OH serine, threonine

sulfhydryl SH cysteine

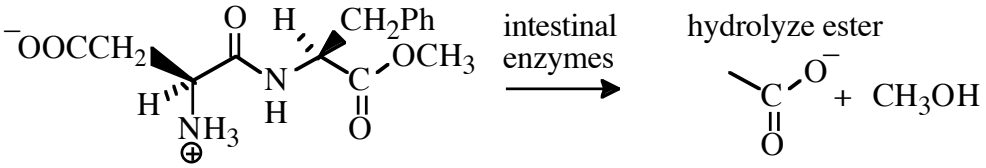
Possible isomers - L-amino acids in man (few exceptions)

A mixture of one gram of each diastereomer of one relatively small protein of 100 chiral amino acids (MW ~ 12,000) would have a mass of 2^{100} grams = $(2^{10})^{10}$ grams = $(1024)^{10}$ grams ~ 10^{30} grams or 10^{27} kg. This exceeds the mass of the earth, 6 x 10^{24} kg.

The number of possible combinations of 20 amino acids in a typical 350 amino acid protein is greater than the number of atoms in the universe [$20^{350} = 2^{350} \times 10^{350}$].

Stereochemical Aspects of Simple Peptides

Aspartame (S-Glu-S-Phe methyl ester) 200x as sweet as sugar



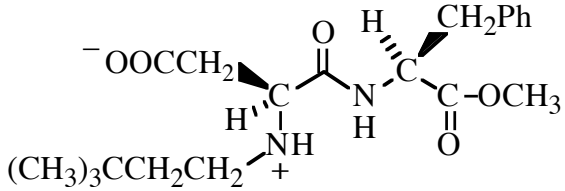
S-Glu S-Phe

enantiomer RR

diastereomers { RS, SR } bitter

Aspartame is stable at pH 4, 25°C for > 50 days, good enough for diet soda.

Neotame – newer – 8,000x as sweet as sugar

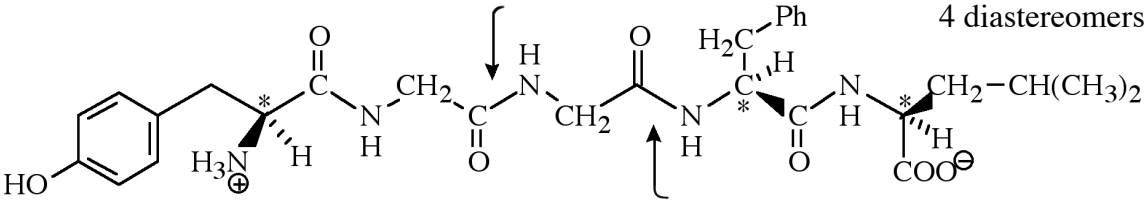


only SS enantiomer is sweet

Leucine enkephalin - naturally occurring peptide which may be a biochemical control of "pain" - analgesic.

(S)Tyr–Gly–Gly–(S)Phe–(S)Leu only Tyr, Phe, Leu are chiral

2^3 = 8 possible optical isomers
4 diastereomers

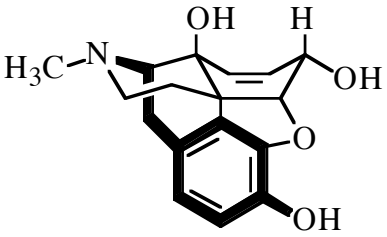


Easily hydrolyzed at glycyl residues (add R groups on α-carbons?), enkephalinases

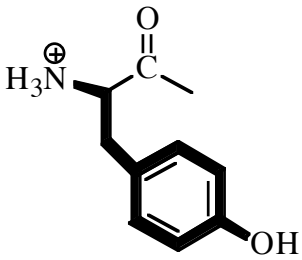
Its enantiomer (R)Tyr–Gly–Gly–(R)Phe–(R)Leu inactive in affinity assays at opiate receptors.

DADLE: LTyr–DAla–Gly–LPhe–DLeu more potent than Leu-Enk in affinity assays. This compound is (S)Tyr–(R)Ala–Gly–(S)Phe–(R)Leu, Ala and Leu having unnatural stereochemistry.

enant DADLE: DTyr–LAla–Gly–DPhe–LLeu is inactive.



morphine



tyrosine from Leu-Enk