evropský sociální fond v ČR
EVROPSKÁ UNIE
MINISTERSTVO ŠKOLSTVÍ, MLÁDEŽE A TĚLOVÝCHOVY
OP Vzdělávání pro konkurenceschopnost
INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

Farmaceutická chemie I. 2. rok studia

Strukturní faktory ovlivňující účinek léčiv.

Doc. PharmDr. Oldřich Farsa, Ph.D.

Stereochemistry: Space arrangement of the atoms or three-dimensional structure of the molecule.

Stereochemistry plays a major role in the pharmacological properties because:

(1) Any change in stereospecificity of the drug will affect its pharmacological activity

(2) The isomeric pairs except the enantiomeric ones have different physical properties (partition coefficient, pK_a, etc.) and thus differ in pharmacological activity.

The following steric factors markedly influence pharmacological activity:

Geometric isomerism

Optical isomerism

Conformational versatility

Geometric isomerism (*cis-trans* or *E/Z*-isomerisms).

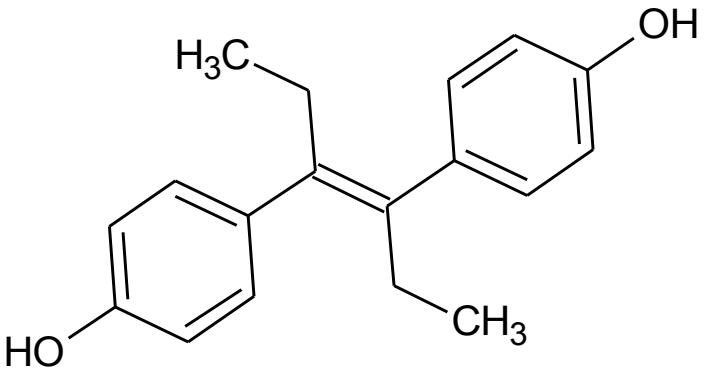
Occur as a result of restricted rotation about a chemical bond, owing to double bonds or rigid ring system in the molecule.

They are not mirror images and have different physicochemical properties and pharmacological activity. Because different distances separate the functional groups of these isomers.

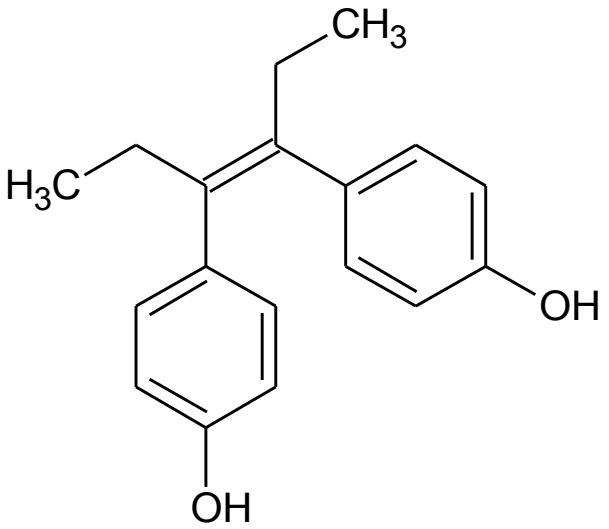
They generally do not fit to the same receptor equally well and if these functional groups are **pharmacophores** the isomers will differ in biologic activity.

- 2 pairs of the same substituents or situation on a ring or on a system of saturated fused rings $\Rightarrow$ *cis/trans*
- all the 4 substituents are different $\Rightarrow$ *E/Z* must be used; then is necessary to order the substituents in the sequence of decreasing atomic weights of the atoms bond directly to the multiple bond; if 2 heavier substituents are on the same side, then Z, if they are on different sides, then E; if the first atoms are the same, further ones have to be compared
  - Z assigned to German *zusamen* = together
  - E *entgegen* = opposite

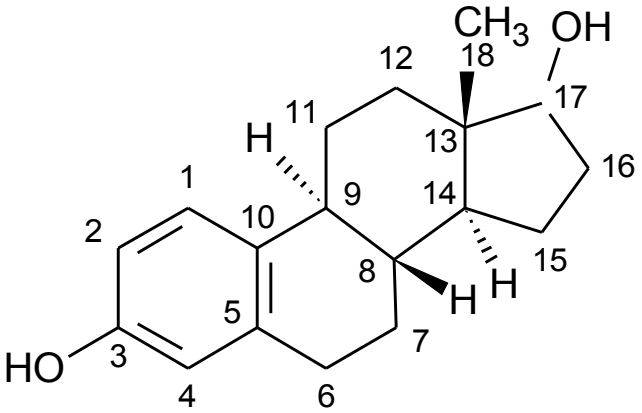
•*cis*-diethylstilbestrol has only 7 % of estrogenic activity of its *trans*-isomer



trans-diethylstilbestrol



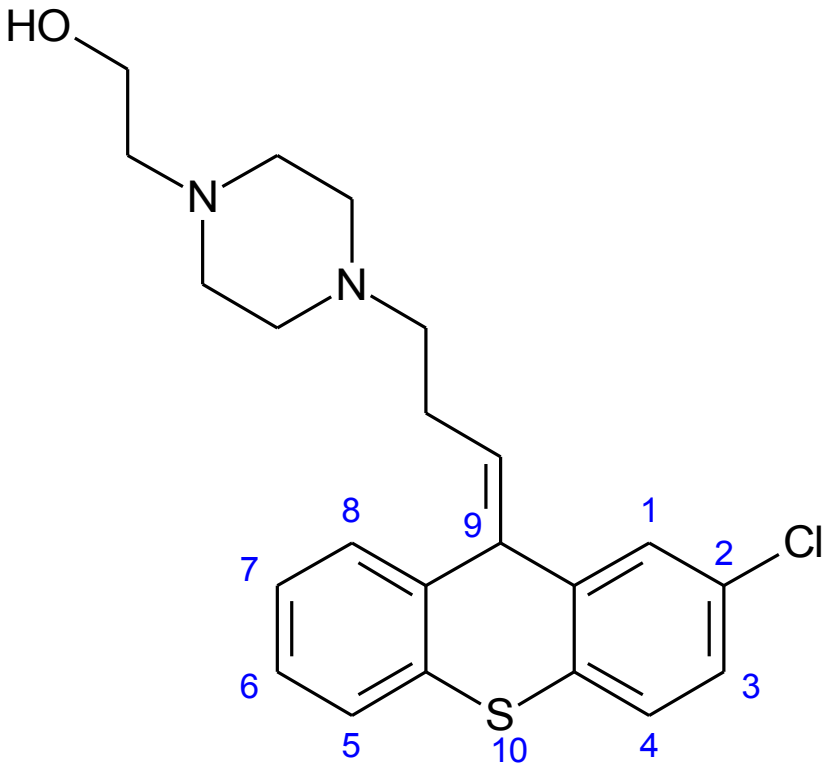
cis-diethylstilbestrol



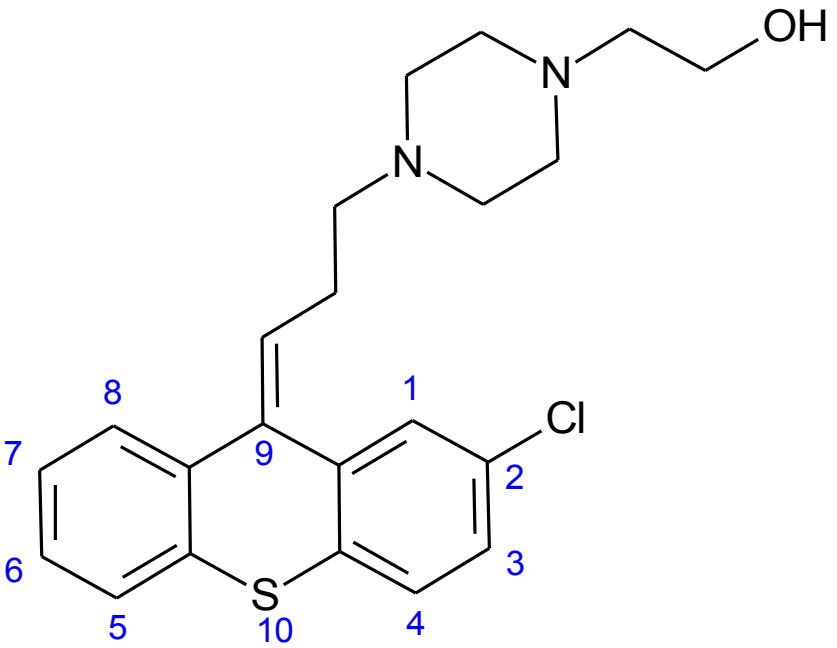
estradiol

•the distance between -OH groups of *trans*-diethylstilbestrol is approx. the same as in estradiol, it is differnt in *cis*-isomer

•tricyclic antipsychotics of thioxanthene series: *Z*-configuration is much more active



E-isomer: weakly active



•*Z*-isomer: **zuclopenthixol**

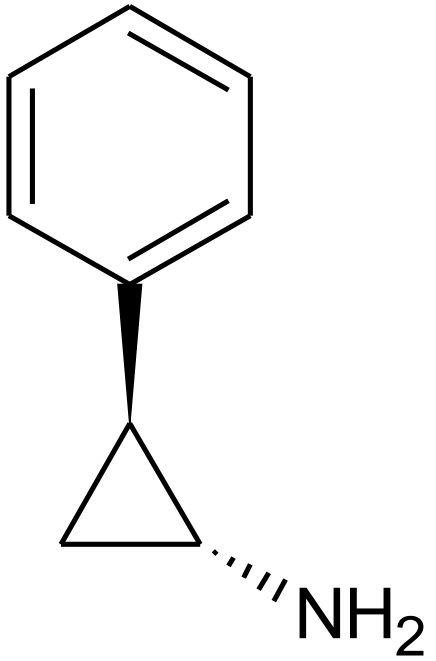
•highly active

Cisordinol ®

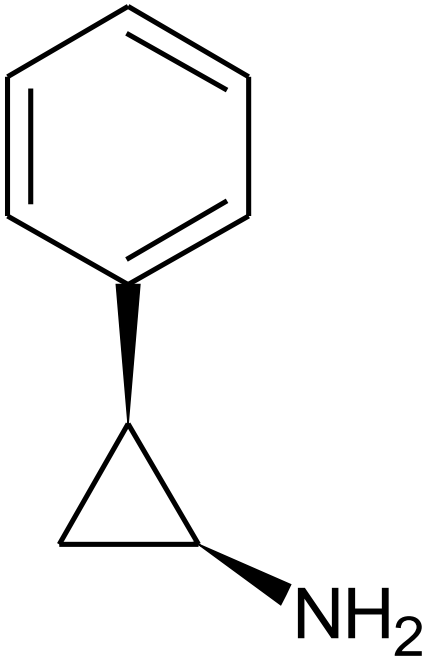
•mixture *E/Z:*

clopenthixol

•**situation on a ring:** MAO inhibitor tranylcypromine

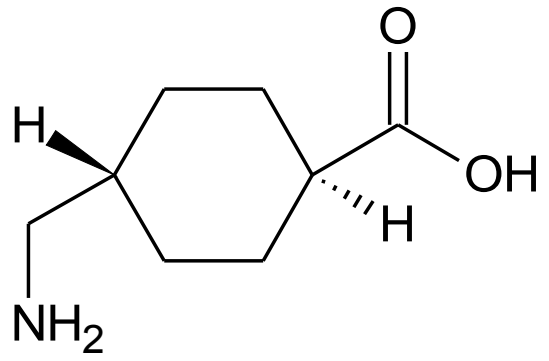


trans- 1-amino-2-phenylcyclopropane
tranylcypromine
•non-selective MAO inhibitor
•geometry similar to prefered dopamine conformation



cis- 1-amino-2-phenylcyclopropane
•nearly inactive

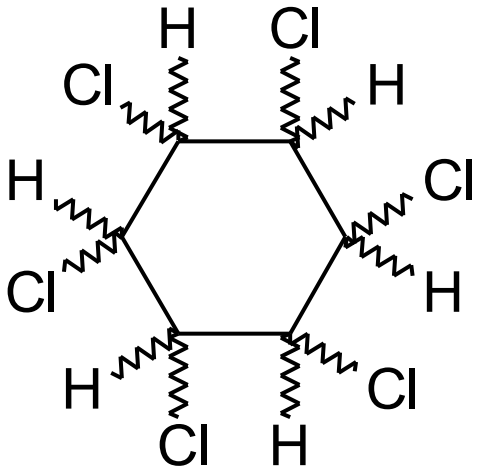
•**situation on a ring:** a fibinolysis inhibitor **tranexamic acid**

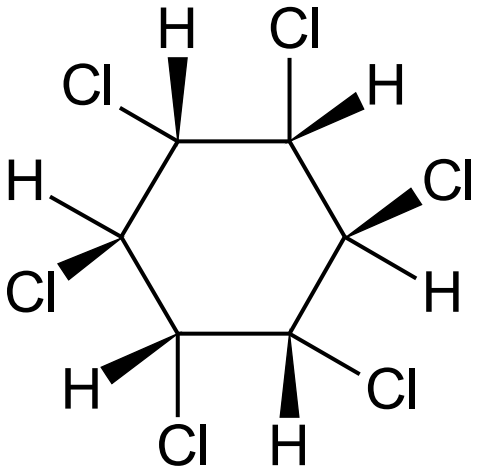


trans-4-(aminomethyl)cyclohexanecarboxylic acid

tranexamic acid
•inhibits transformation of plasminogene into plasmine
•used in conditions with increased fibrinolysis – bleeding conditions after adenectomy or tonsilectomy, hemorrhage due to the application of a fibrinolytic, primarirly generalized fibrinolytic conditions
Exacyl ® inj. sol.
•*cis*-isomer much less active

•**situation on a ring:** antiectoparazitic **lindane**

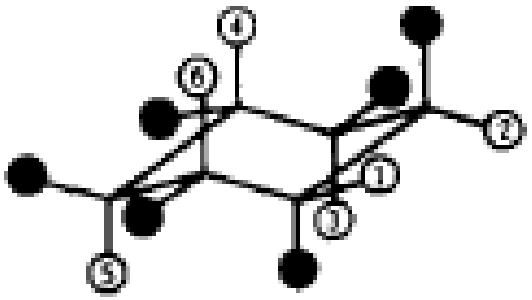




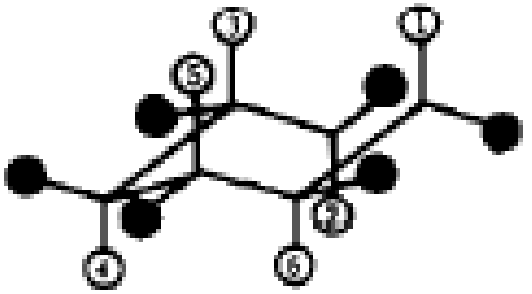
1,2,3,4,5,6-hexachlorocyclohexane
•5 stereoisomers assigned α - ε

(1α,2α,3β,4α,5α,6β)-hexachlorocyclohexane = γ-isomer
lindane
•the most active and the only one used in therapeutics
•pediculicide, scabicide (eg. treatment of lice and scabies)
~~Skabicid ®~~

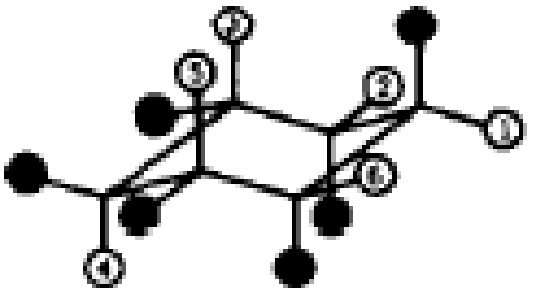
Conformation formulas of all the stereoisomers of 1,2,3,4,5,6-hexachlorocyclohexane



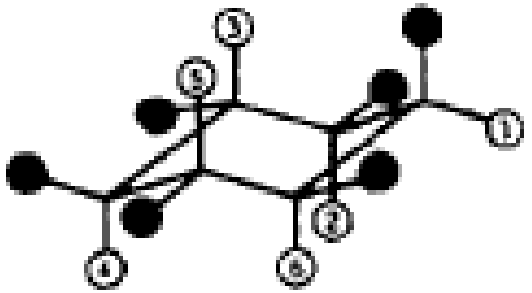
α



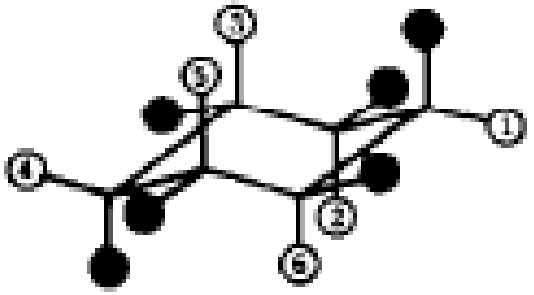
β



γ

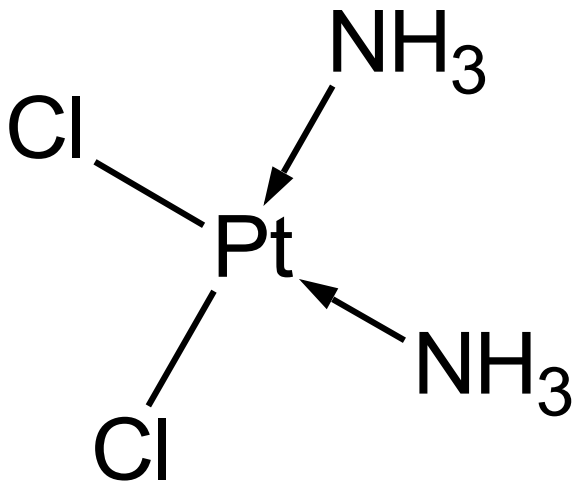


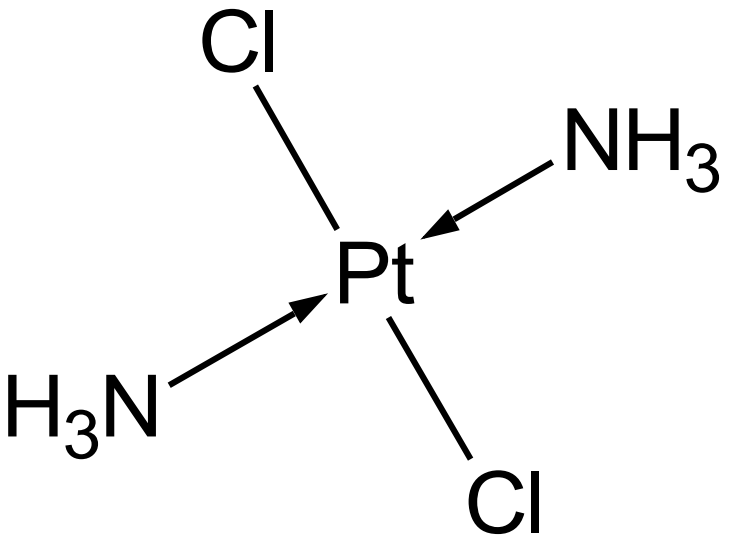
δ



ε

•**inorganic coordination compounds**: cisplatin and transplatin
•neutral square planar coordination complexes





cisplatin
cis-diamminedichloroplatinum(II)
•antineoplastic
•forms intra- and interstrand cross-links namely between N(7) of imidazole rings of adenins and guanins
•intrastrand cross-links are difficult to repair by cellular reparation mechanisms

trans-diamminedichloroplatinum(II)
•active *in vitro*, but not *in vivo*
•forms namely interstrand cross-links which are easy to repair

Optical isomerism and pharmacological activity

Chiral compounds are compounds that are able to rotate the plane of polarized light. It is due to some molecular asymmetry.

The (+) or dextrorotatory: isomer rotates light to the right (clockwise). The (-) or levorotatory: isomer rotates light to the left (counterclockwise). If isomers are mirror images which cannot be superimposed they are called enantiomers. Enantiomers have the same physical (melting or boiling point, density, viscosity, IR, NMR, UV-VIS, MS) and chemical properties. They have also the same absolute value of optical rotation but different signs (+) or (-). Optical isomers which are not mirror images are called diastereomers. Optical isomers very often differ in biological activity, because all their target structures (active sites of enzymes and receptors, nucleic acids etc.) transport systems (proteins) and enzymes taking part in their metabolism are chiral.

Useful terms in optical isomerism

- eutomer – more active (or less toxic) isomer
- distomer – less active (or more toxic) isomer
- racemate – mixture of equimolar amounts of enatiomers which does not show optical rotation

Main types of optical isomerism

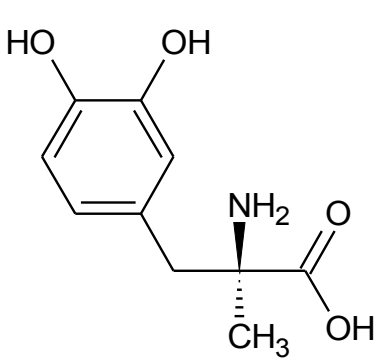
1. Central chirality

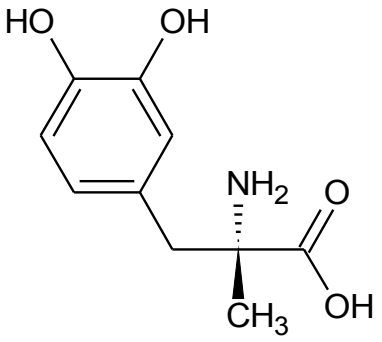
For total number of optical isomers $n = 2^m$ where m is number of chiral centres (except of chiral compounds with symmetry axis)

2. Atropoisomerism
3. Axial chirality
4. Helical chirality

1. Central chirality

- occurs in compounds which contain at least one central atom (C, S, P, N …) with four different substituents attached which is the chiral centre
- a free electron pair can in some cases also act as one of four substituents (S in H^+-pump inhibitors)
- the Cahn – Ingold – Prelog (CIP) convention is used for description of absolute configuration on every chiral centre (the *R, S* system)
  - the atoms attached to a chiral centre are ranked as per their atomic number according to the following laid-down norms:
    - Maximum (highest) priority is given to the atom with highest atomic number and subsequent atoms are ranked accordingly from highest to lowest
    - In a situation when a decision cannot be reached with respect to 'priority', i.e. 2 atoms having the same atomic number attached to the chiral centre, the process continues to the next atom until a decision could be arived
  - the molecule is then viewed from the side opposite to the lowest priority atom so that the bond between the central atom and the atom of the lowest priority can be considered to be an imaginary steering-wheel axis; and the sequence of priority form highest to lowest is determined
    - In case, the sequence is to the right, or clockwise, the chiral centre is designated as the *R* absolute configuration; when the priority sequence is to the left, or anticlockwise, the designation is *S*
- do not forget that CIP system is conventional and the thus the *R* configuration need not indicate that the compound is dextrorotatory just as the *S* isomer need not be levorotatory !





Drugs with one chiral carbon atom

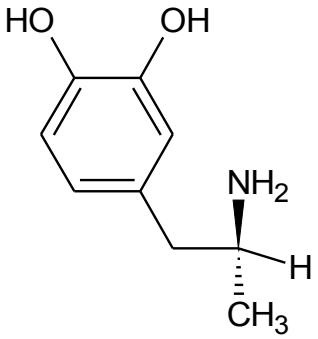
α-methyldopa – antihypertensive, α-adrenolytic

Dopegyt ® contains (-)-(*S*) sesquihydrate

2-amino-3-(3,4-dihydroxyphenyl)-2-methylpropanoic acid

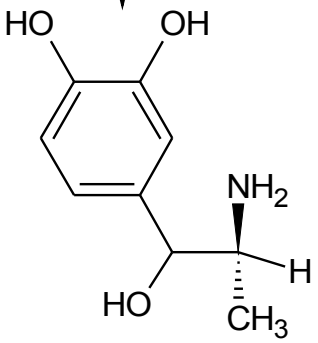
(-)-(*S*) (+)-(*R*) - inactive

decarboxylase



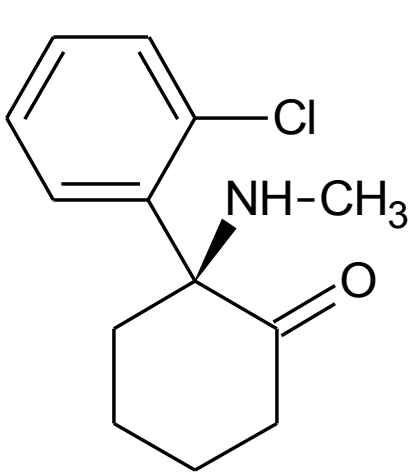
α-methyldopamine

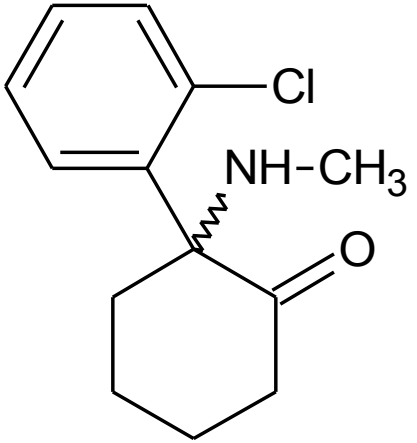
β -hydroxylase

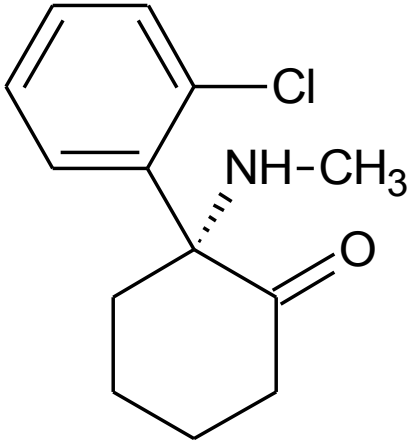


α-methylnoradrenaline – metabolite active as α_1 antagonist

Drugs with one chiral carbon atom
ketamine – intravenous general anaesthetic







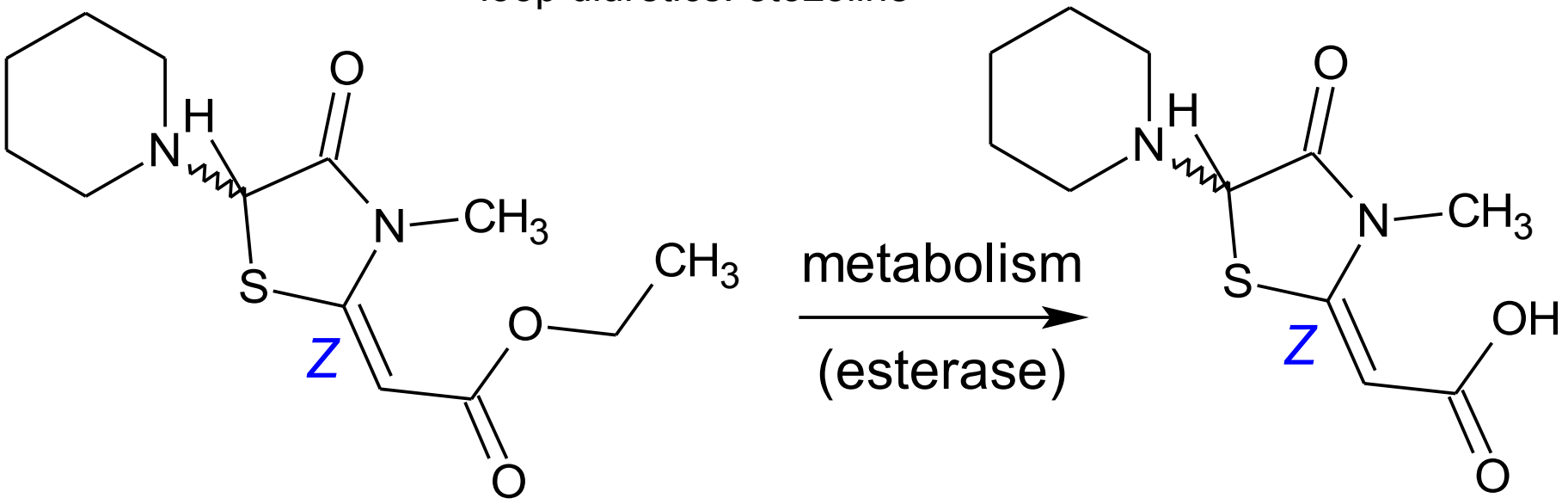
2-(2-chlorophenyl)-2-(methylamino)cyclohexanone

(*S*)-(+) base (*S*)-(-) hydrochloride syn. esketamine [INN]		(*R*,*S*)-(±) racemate		(*R*)-(-) base (*R*)-(+) hydrochloride
hypnotic, analgesic	**>**		**>**	
unwanted effects	**<**		**<**	

Unwanted effects: post operative restlessness, combativeness, loss of selfcontrol,agitation, disorientation

Calypsol ® inj. sol. and Narkamon ® 1% inf. sol. contain racemate

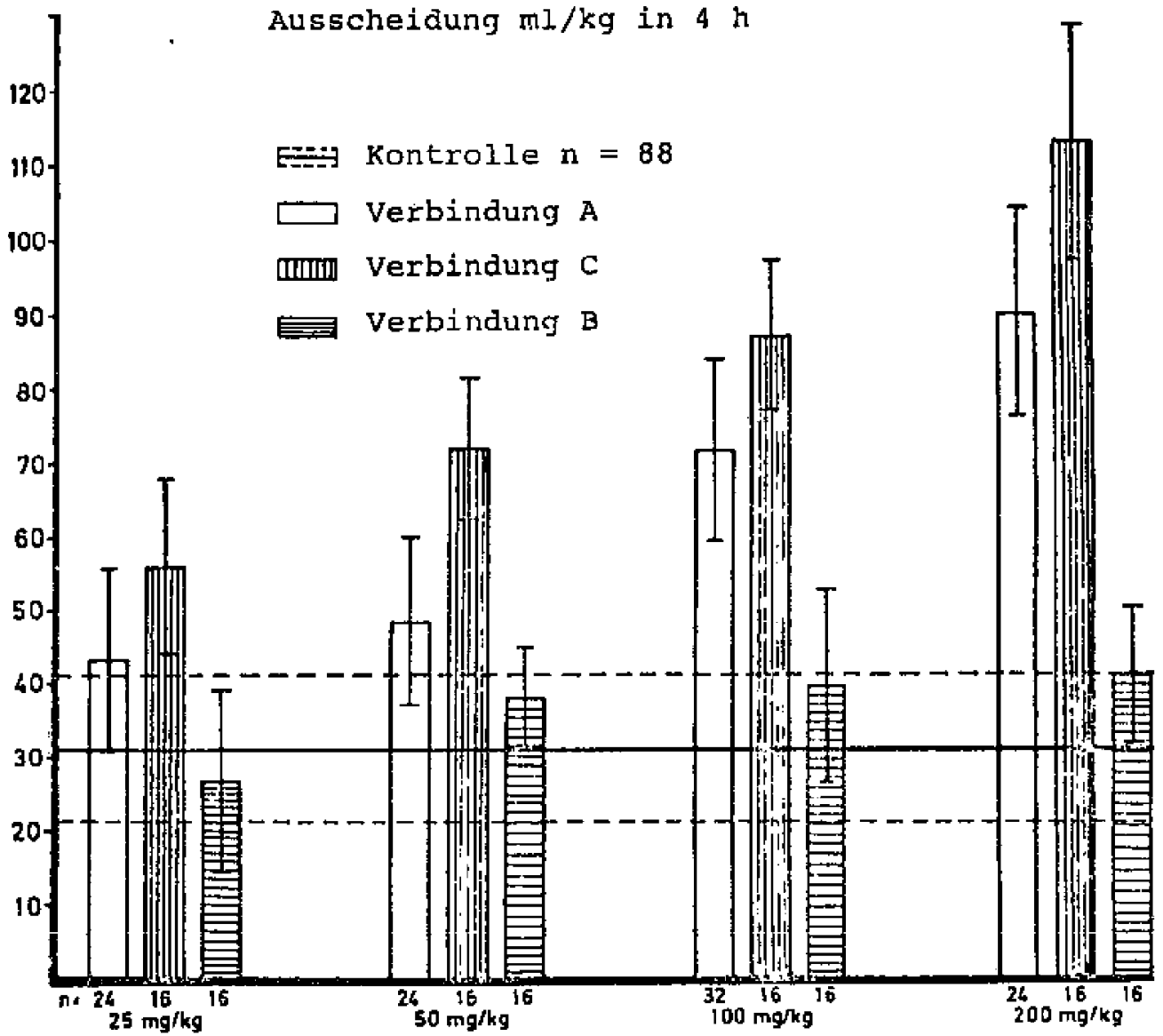
Drugs with one chiral carbon atom
•loop diuretics: etozoline



(±)-(*R,S*) **etozoline**
•used as diuretic and antihypertesive
•prodrug
(+)-(*S*) **dexetozoline**
•patented as an antihypertensive
DE 2911296 (1980)
•significantly more active diuretic than (±)-(*R,S*) and more than 2x active than (-)-(*R*)

(±)-(*R,S*) **ozolinone**
•experimental drug
(-) active as diuretic
(+) not diuretic; inhibits low doses of (-) and furosemide

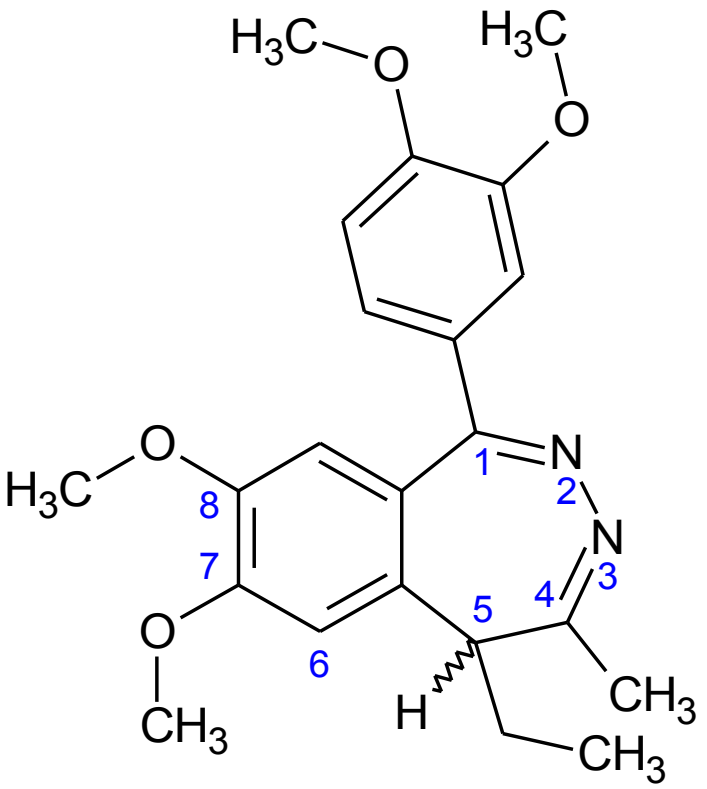
Diuretic effects of etozoline enantiomers in rats



Diurese an wachen Ratten bei intragastraler Verabreichung

A - (±)-(*R,S*) **etozoline**
B - (+)-(*S*) **dexetozoline**
C - (-)-(*R*)

Drugs with one chiral carbon atom
Anxiolytics: 2,3-benzodiazepins



(R,S)-(±): **tofisopam**

Grandaxin®

(R)-(+): **dextofisopam**

•anxiolytic, therapeutic of irritable colon and Crohn disease

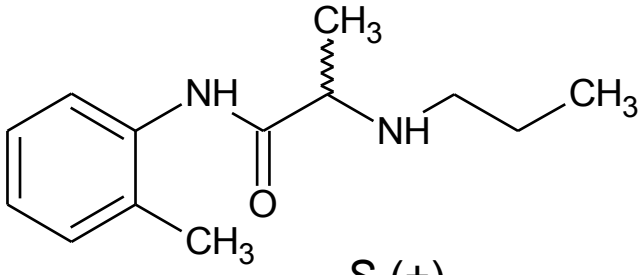
(S)-(-): **levotofisopam**

•anxiolytic

Drugs with one chiral carbon atom

Local anaesthetics of anilide series: **prilocaine**

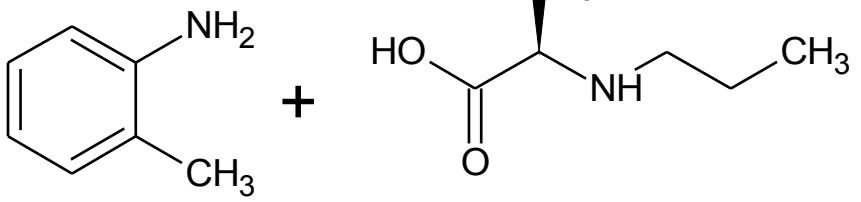
•anaesthetic activity of *R* and *S* enantiomers does not markedly differ



S-(+)

R-(-)

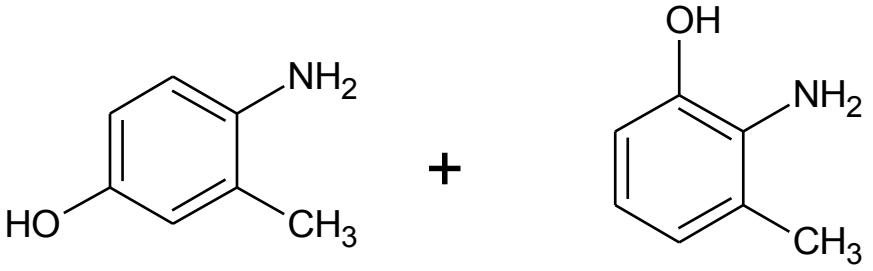
hydrolase



(2*R*)-2-(propylamino)propanoic acid

•administration of the pure *S*-(-) enantiomer can eliminate the toxicity

oxidation metabolism



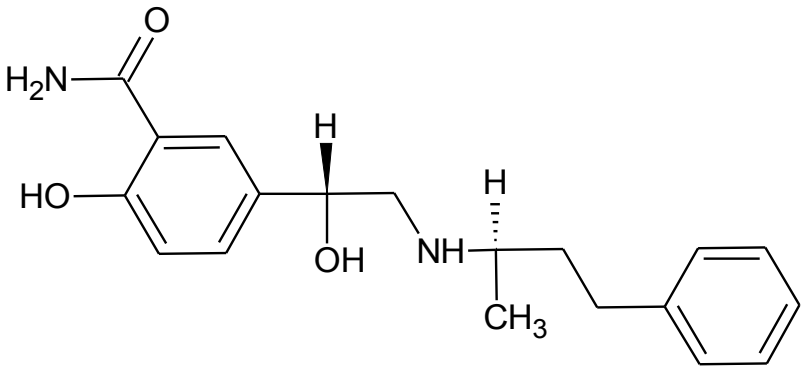
•toxic metabolites

•methemoglobinemia

Drugs with two chiral carbon atoms

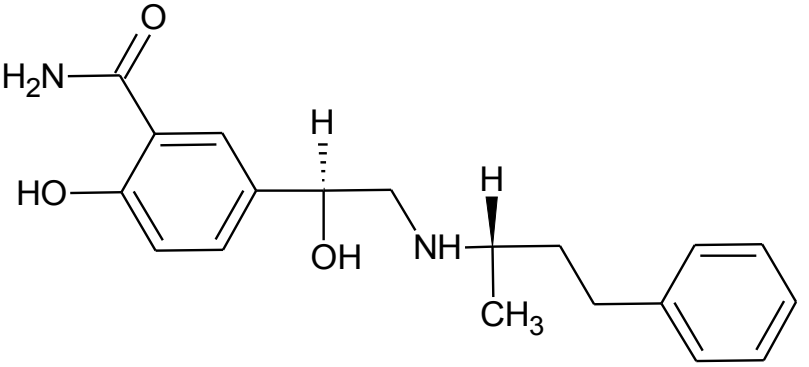
- adrenolytic for hypertension treatment: **labetalol**

2-hydroxy-5-[1-hydroxy-2-{(4-phenylbutan-2-yl)amino}ethyl]benzamide

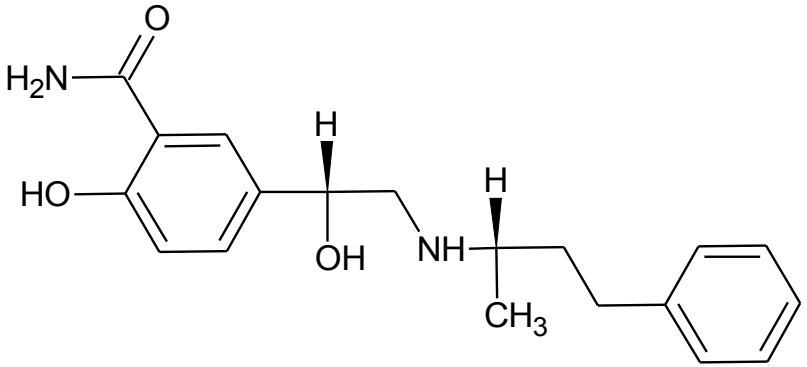


R,R α_1 0.15 β_1 2.27 β_2 2.18

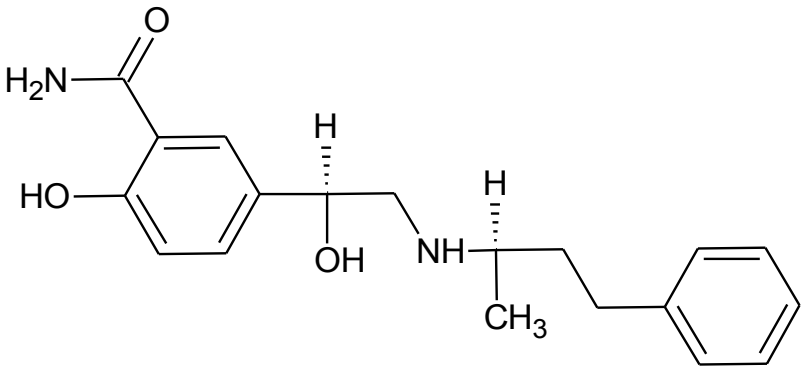
syn. **dilevalol**



S,S α_1 0.39 β_1 0.03 β_2 <0.02



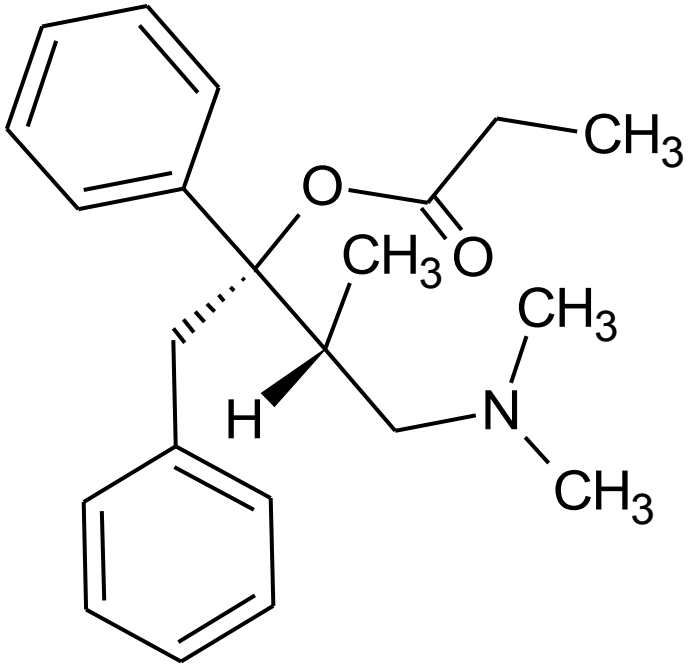
R,S α_1 0.23 β_1 0.15 β_2 0.09



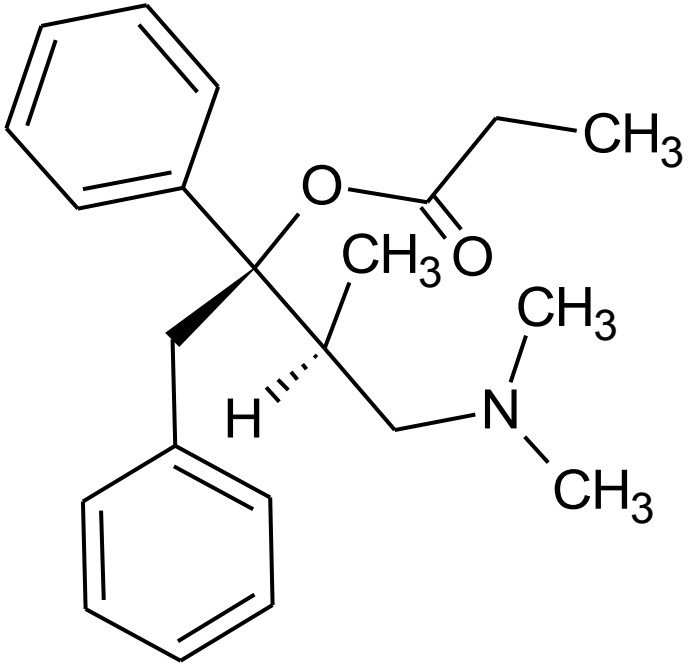
S,R α_1 1.74 β_1 0.04 β_2 0.02

- the equimolar mixture of all the four optical isomers has all the inhibiting activities defined as equal to one
- activities on α_1 and β_1 receptors are desirable while activity on β_2 unwanted (bronchoconstriction)

Drugs with two chiral carbon atoms
Synthetic opioids: phenylbutylamine derivatives



dextropropoxyphene
(+)-(2*S*, 3*R*)-analgesic; 1/10 of methadone activity
Darvon ® (USA)

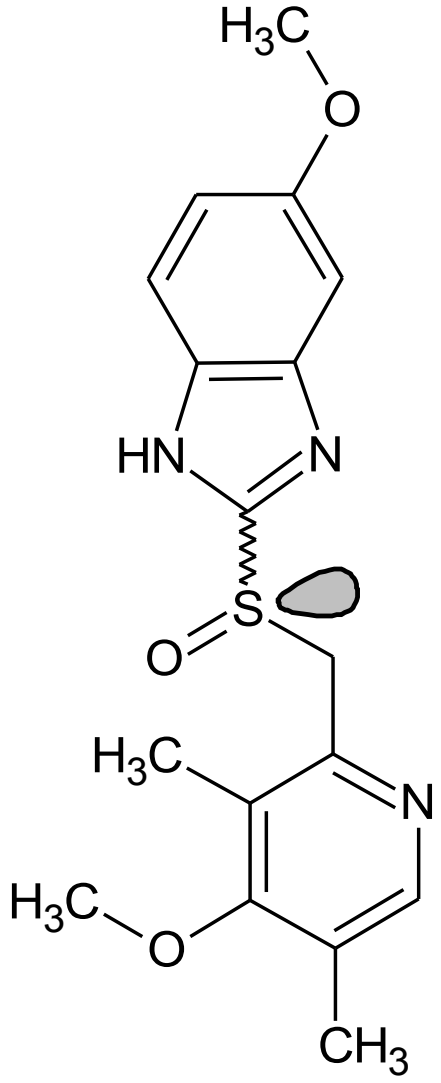


levopropoxyphene
(-)-(2*R*, 3*S*)-antitussive
•no analgesic activity
Novrad ® (USA)

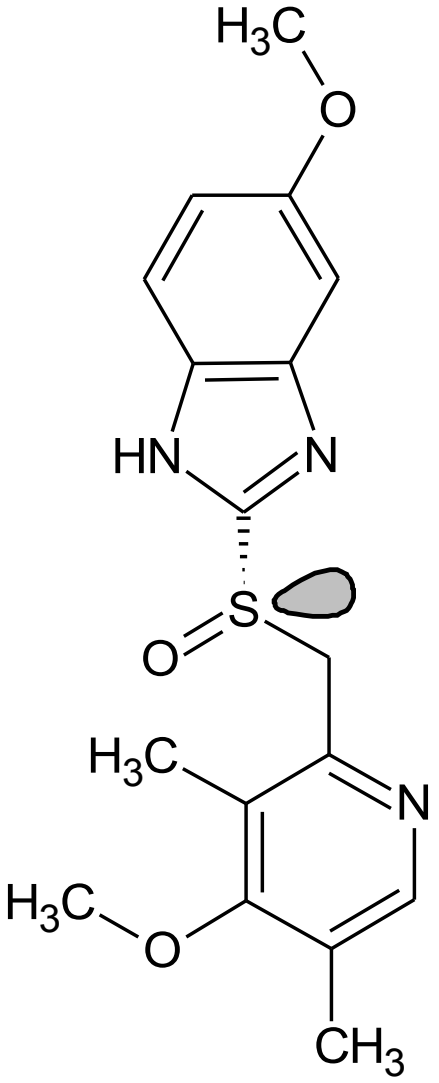
•(2*S*, 3*S*) and (2*R,* 3*R*) isomers have no important effects

Drugs with chiral sulphur atom

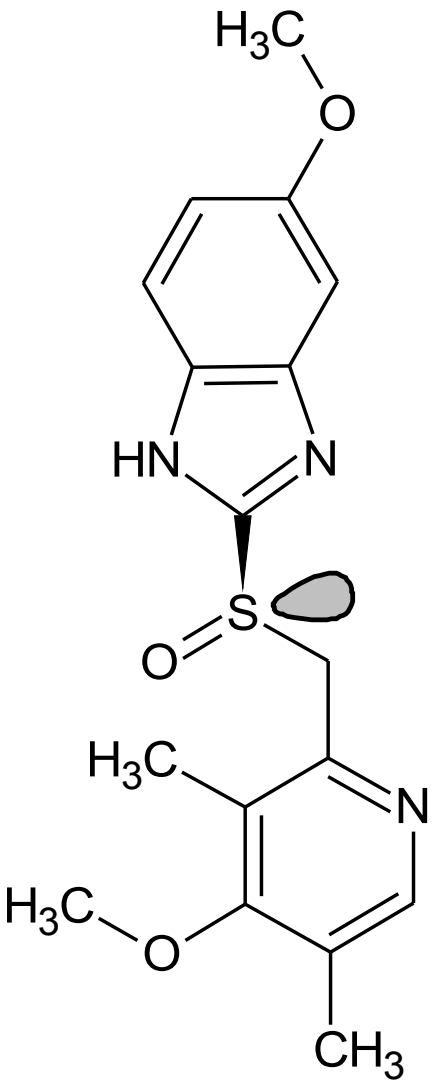
- H^+/K^+-ATPase (or proton pump) inhibitors: omeprazole
- a free electron pair on the sulphur atom is rigid and acts as the fourth substituent



(*R,S*)-(±)-**omeprazole**



(*S*)-(-)-omeprazole
esomeprazole

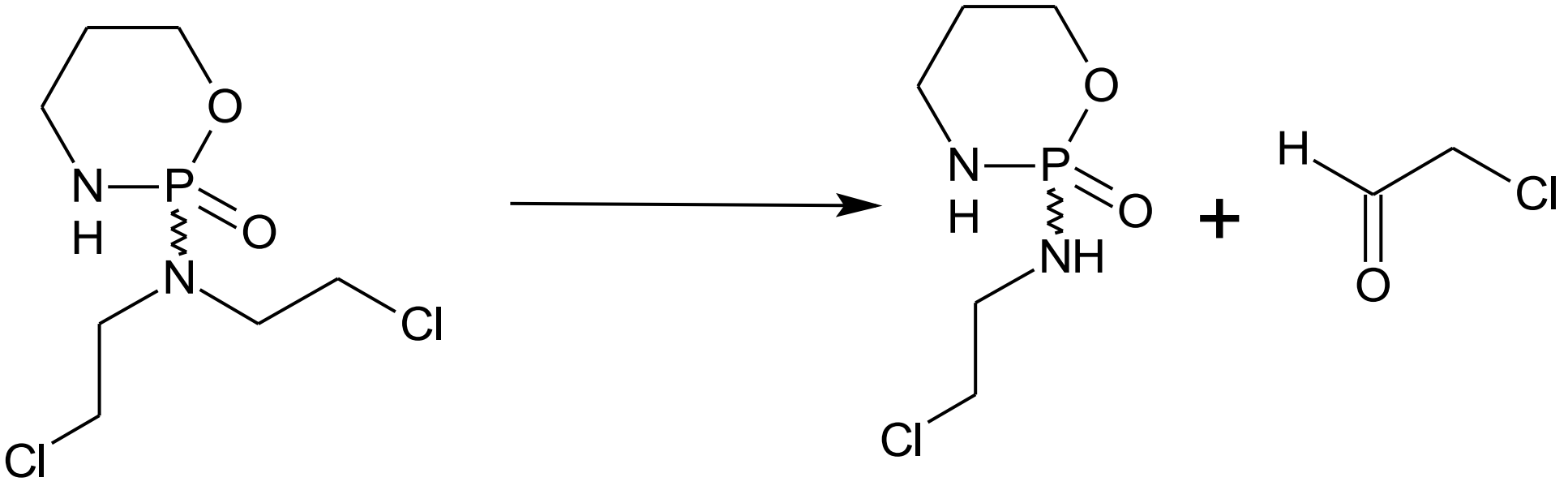


(*R*)-(+)-omeprazole

- both enantiomers have the same inhibition activity *in vitro*, but *R*-isomer is rapidly metabolized by CYP2C19 metabolizing enzyme ⇒ S-isomer reaches higher plasmatic levels and longer lasts in the body ⇒ **it is more effective in the treatment**

Preparations:	(*R,S*)-(±)-**omeprazole**	Asilar ® , Helicid ® , Lomac ® , …
	(S)-(-)-**esomeprazol**	Emanera ® , Emozul ® , Prazectol ® , ...

Drugs with chiral phosphorus atom
•antineoplastics – alkylating agents: **cyclophosphamide**



(*R,S*)-(±)-**cyclophosphamide**

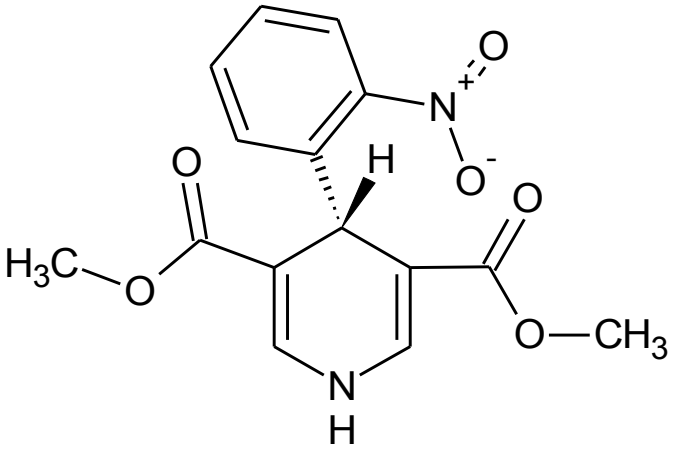
N-deschloroethylated metabolite
•inactive

•both enantiomers are equally active *in vitro*
•*R*- enantiomer is about twice more rapidly changed in N-deschloroethylated metabolite and 2-chloroacetaldehyde ⇒ it is **less active and more neurotoxic**

2. Atropoisomerism

•occurs namely in moleculs of biphenyl type substituted at least in one position corresponding to *o*-positin of every of both rings with bulky substituents
•free rotation around the single bond between both rings is here restricted so that two rotation isomers which are mirror images which cannot be superimposed can arise
•such isomers are then called atropoisomers

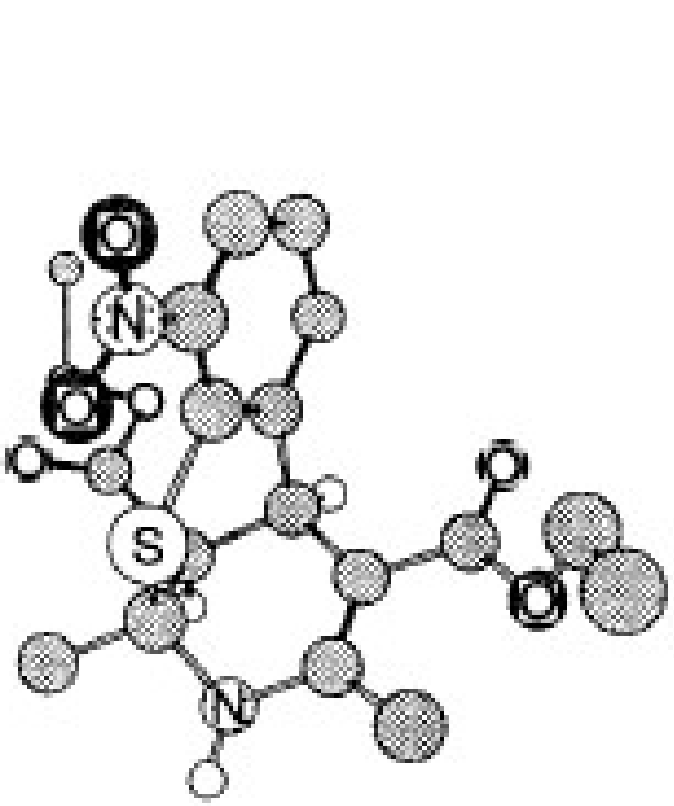
•antihypertensives – Ca^{2+} channel blockers of dihydropyridine series: **nifedipine**
•in 3,5-disubstituted-4-(2-nitrophenyl)-1,4-dihydropyridines meet atropoisomerism and chiral conformerism



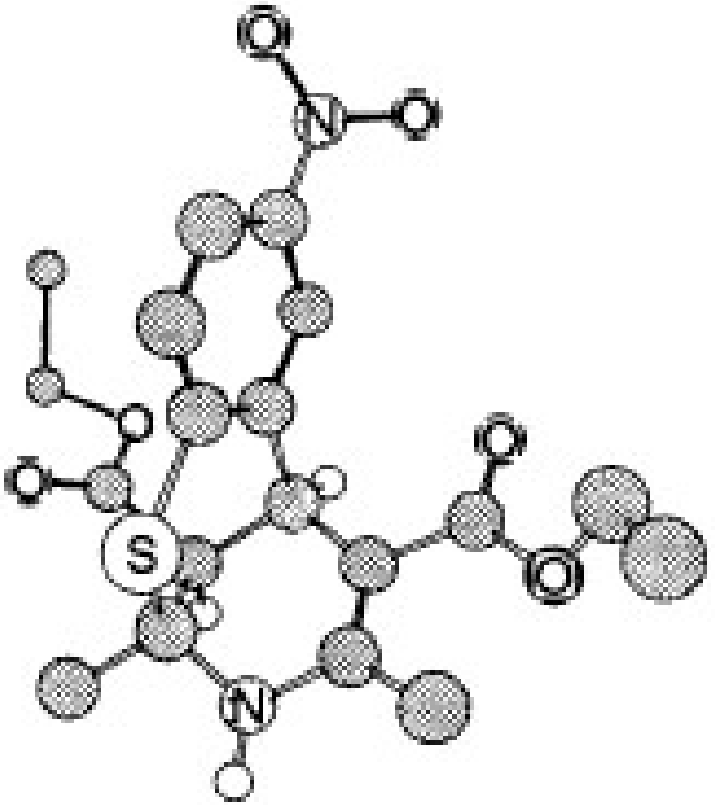
dimethyl 4-(2-nitrophenyl)-1,4-dihydropyridine-3,5-dicarboxylate

nifedipine
Cordipin ® , Nifecard ®

•nifedipine and other 1,4-dihydropyridine Ca^{2+} antagonists exist in 2 atropoisomers; the first one corresponds to antiperiplanar (ap) conformation and the second one to synperiplanar (sp) conformation
•sp isomer is 50times more active than ap



ap: inactive



sp: active

•the stereochemistry of 1,4-dihydropyridines has in its relationship to their chiral conformerism its special „sailing ship nomenclature“ which refers to parts of a ship

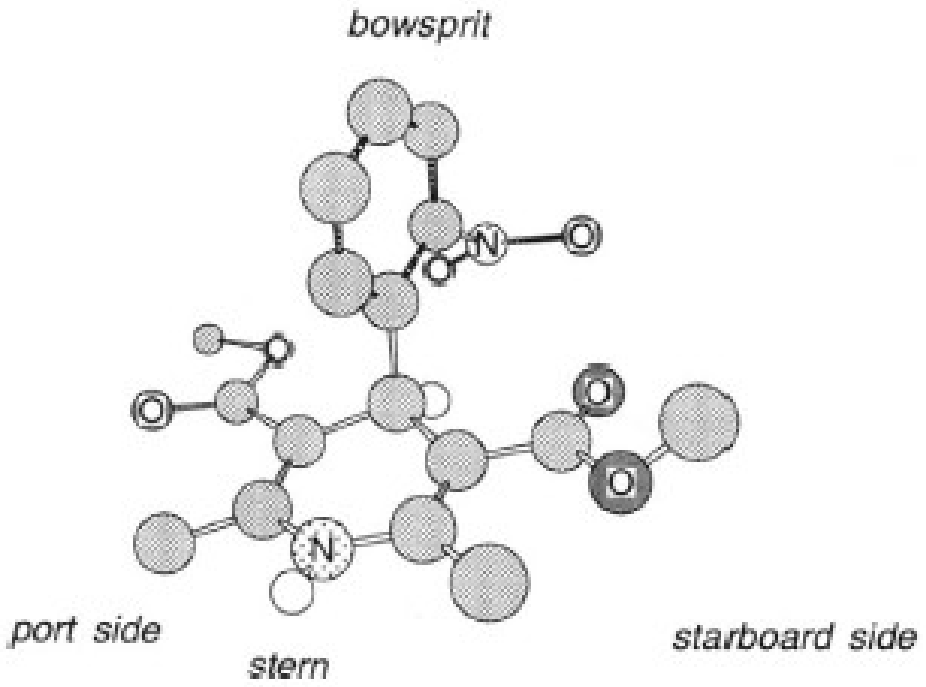


FIG. 7. The active conformation of nifedipine.