Structure modification

homology, analogy, isomeres, izosteres

Tomáš Goněc

Lead compounds

- biological effect

origin:

- local folk remedies
- natural products
- discovered by accident (often unexpected side effects)
- intrinsic signal molecules (neurotransmitters, peptide hormones)

Analogy-based drug research

aim to achieve better properties
- toxicity
- stability
- bio-availiability
- side effects
- biological half-time (elimination pathway)

Structure-activity relationships (SAR)

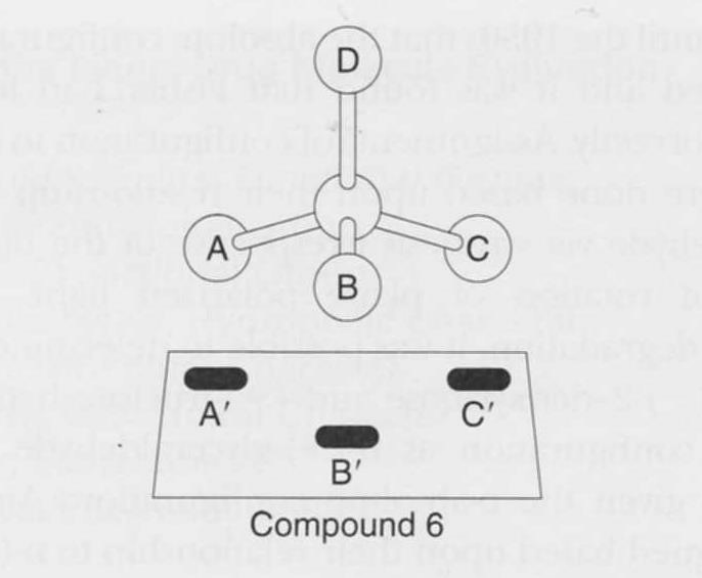
optimization of the structure
similar structures = similar properties

pharmacophore = parts of structure
necessary for biological effect

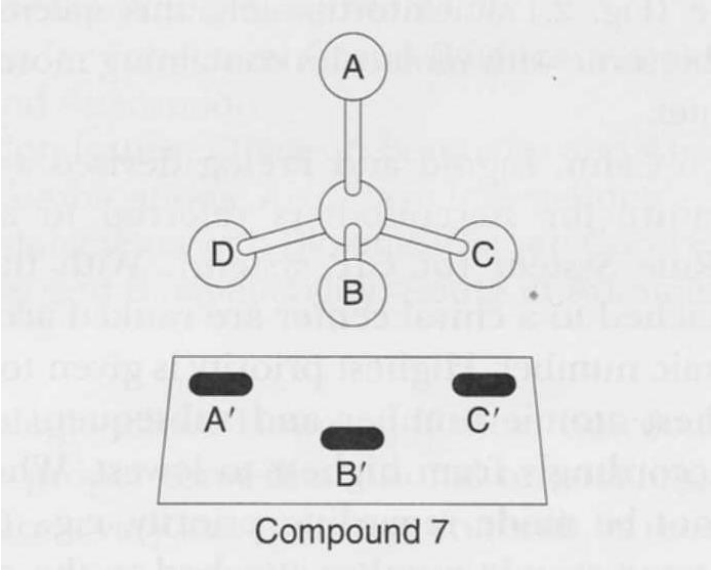
ISOMERES

■ proteins and macromolecules are assymetrical in nature

■ compound-target interaction is determined by its three-dimensional orientation



Compound 6



Compound 7

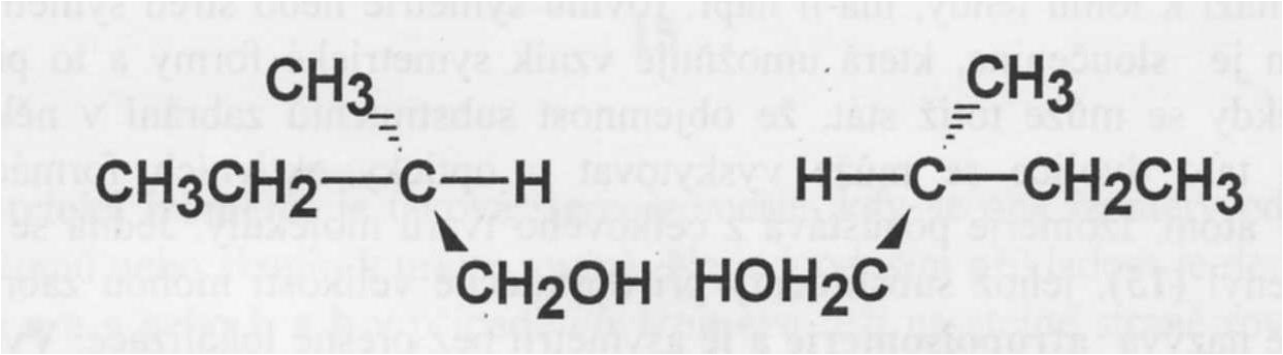
Enantiomeres

= isomeres with three-dimensional arrangement of atoms(groups) like mirror images

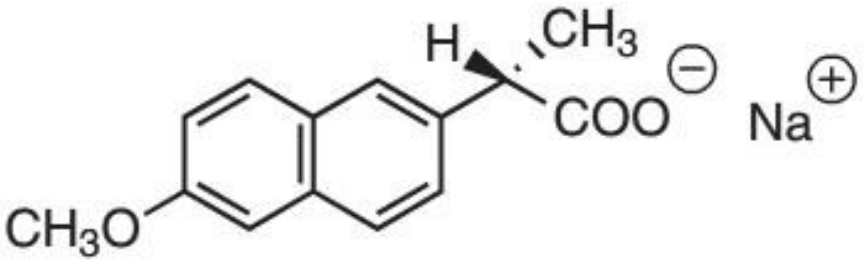
= chiral compounds, antipods, enantiomorphs

- identic physicochemical properties

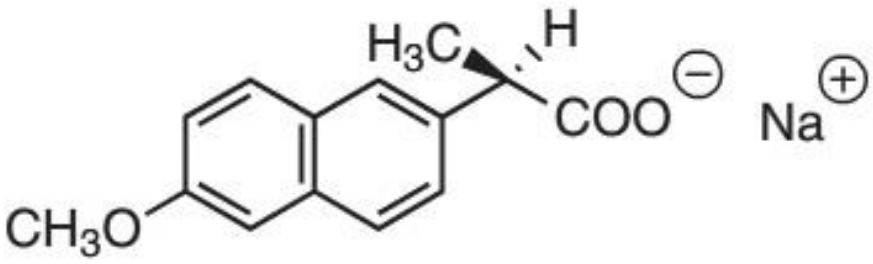
except of ability to rotate polarized light rays (optical activity)



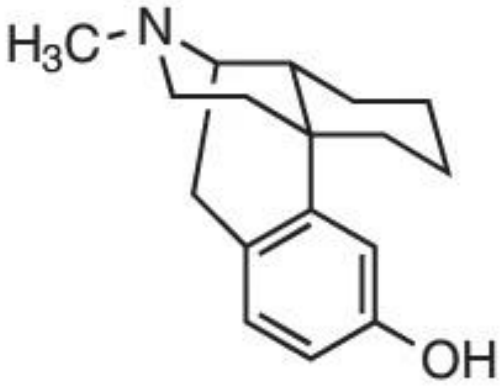
ENANTIOMERS



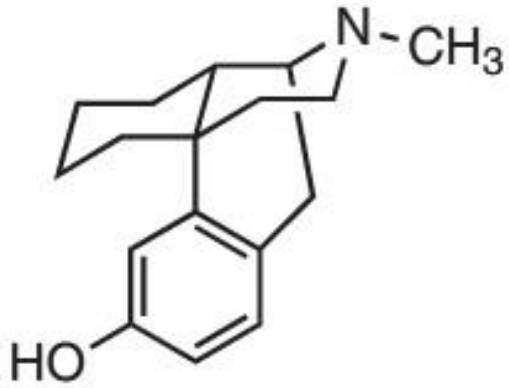
S-(+)-naproxen sodium



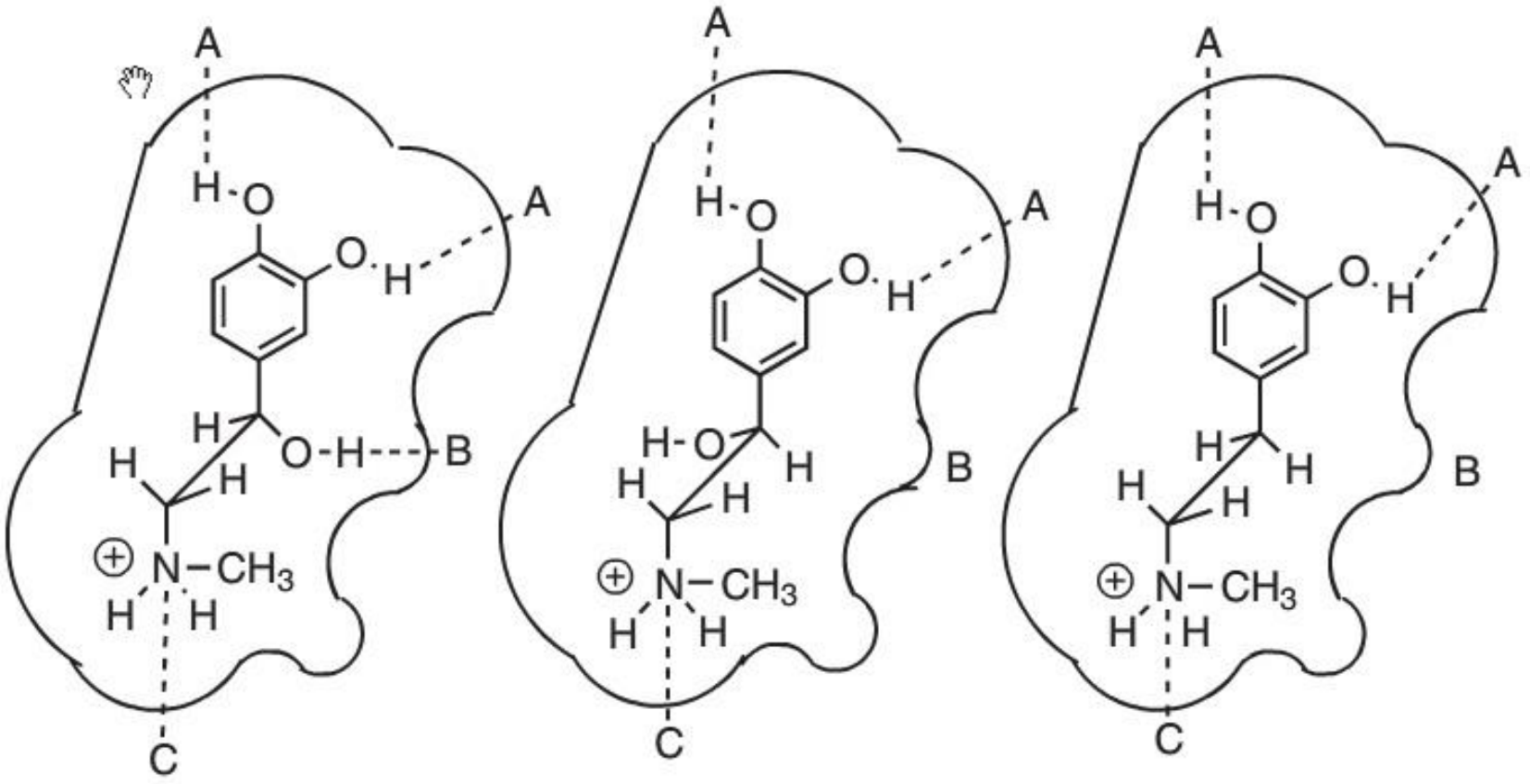
R-(-)-naproxen sodium



Levorphanol (anagesic)



Dextrorphan (antitussive)



R-(-)-Epinephrine *S*-(+)-Epinephrine *N*-Methyldopamine

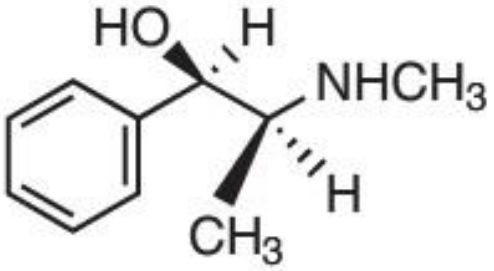
Diastereoisomers

= all stereoisomeric compounds that are not enantiomers

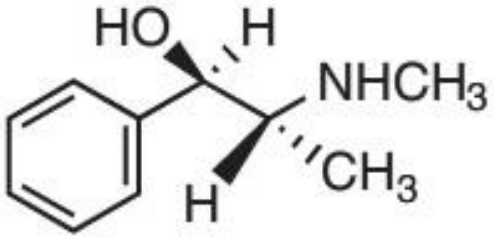
- structures containing substituted
  - double bonds
  - ring systems
  - more than one chiral centrum

- have different physicochemical properties

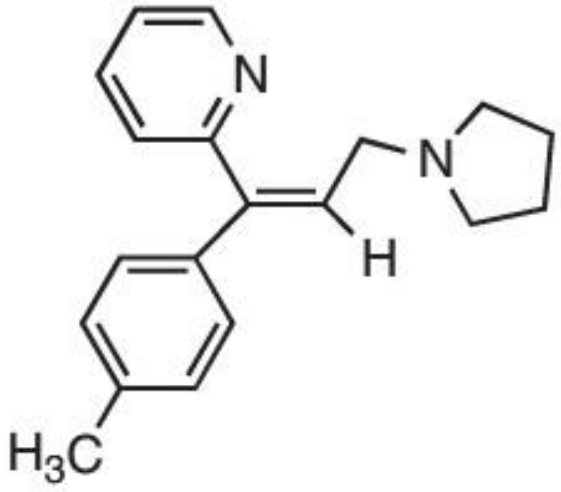
DIASTEREOISOMERS



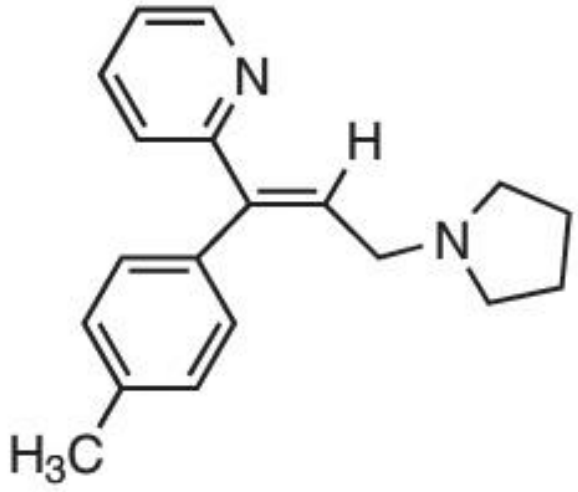
1*R*, 2*S*-(-)-Ephedrine



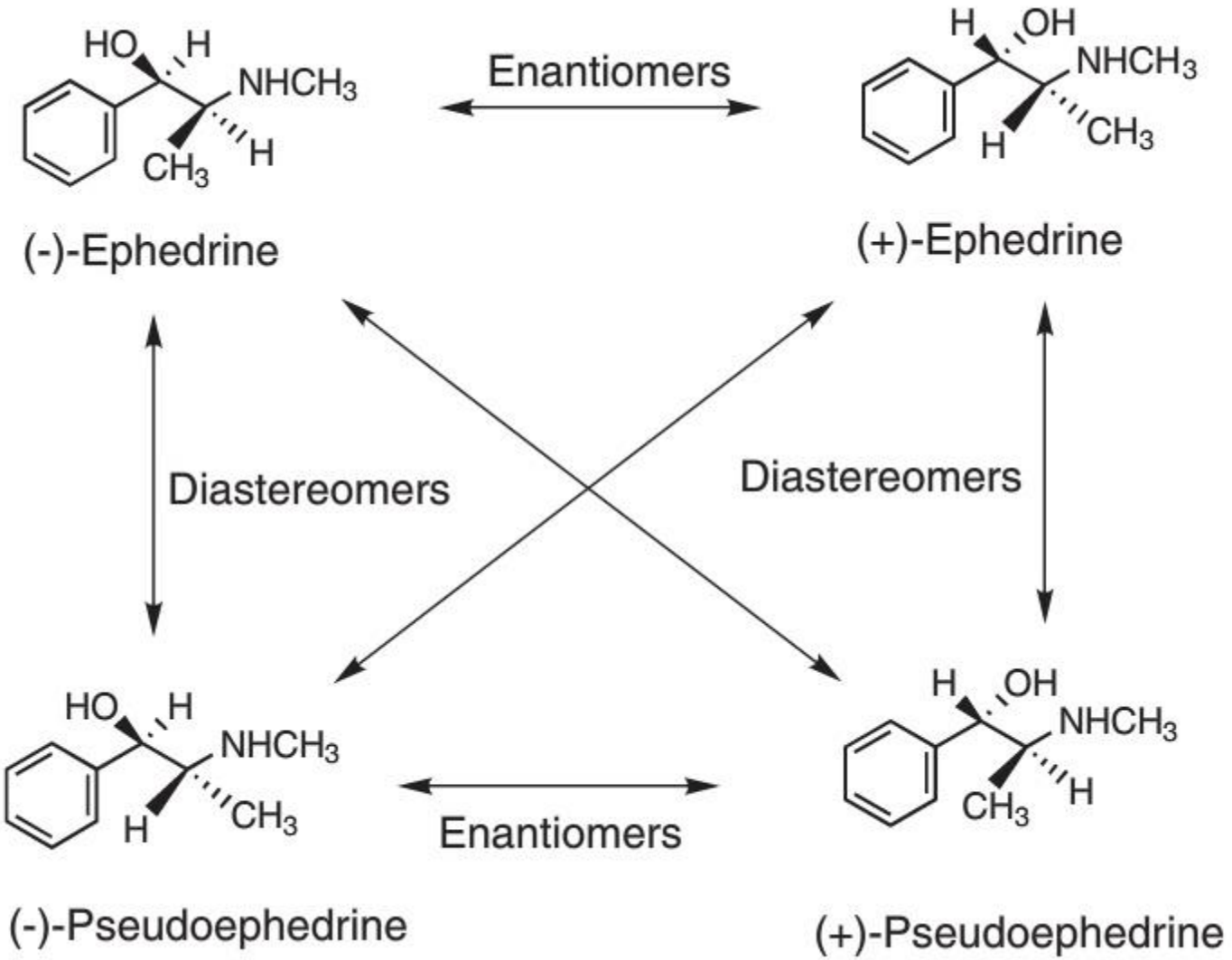
1*R*, 2*R*-(-)-Pseudoephedrine

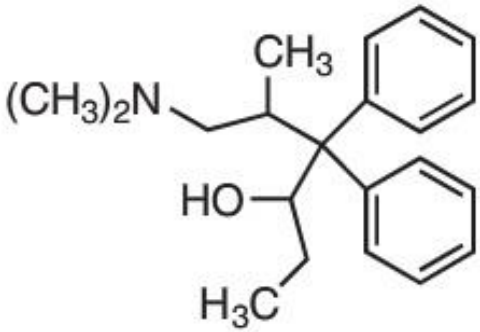


Z-triprolidine (inactive)

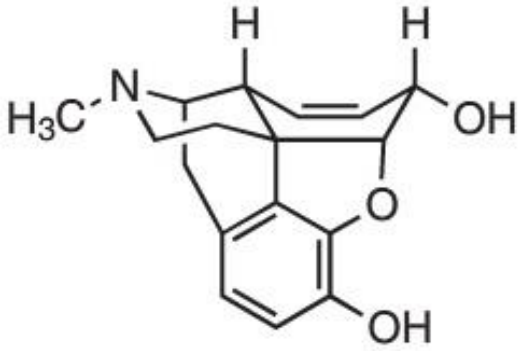


E-triprolidine (active)

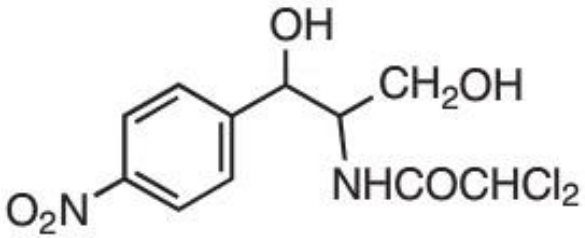

HO
H
NHCH3
CH3
H
Enantiomers
H
OH
NHCH3
H
CH3
(-)-Ephedrine
(+)-Ephedrine
Diastereomers
Diastereomers
HO
H
NHCH3
H
CH3
Enantiomers
H
OH
NHCH3
CH3
H
(-)-Pseudoephedrine
(+)-Pseudoephedrine



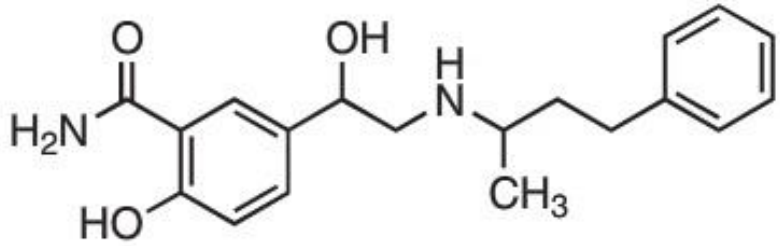
Isomethadol



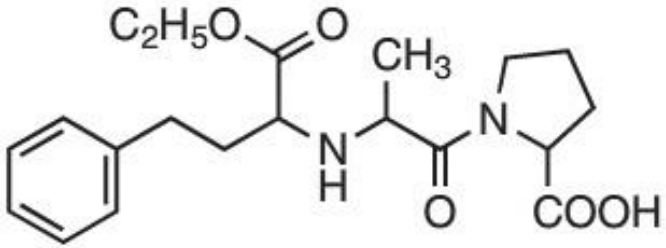
Morphine



Chloramphenicol



Labetalol



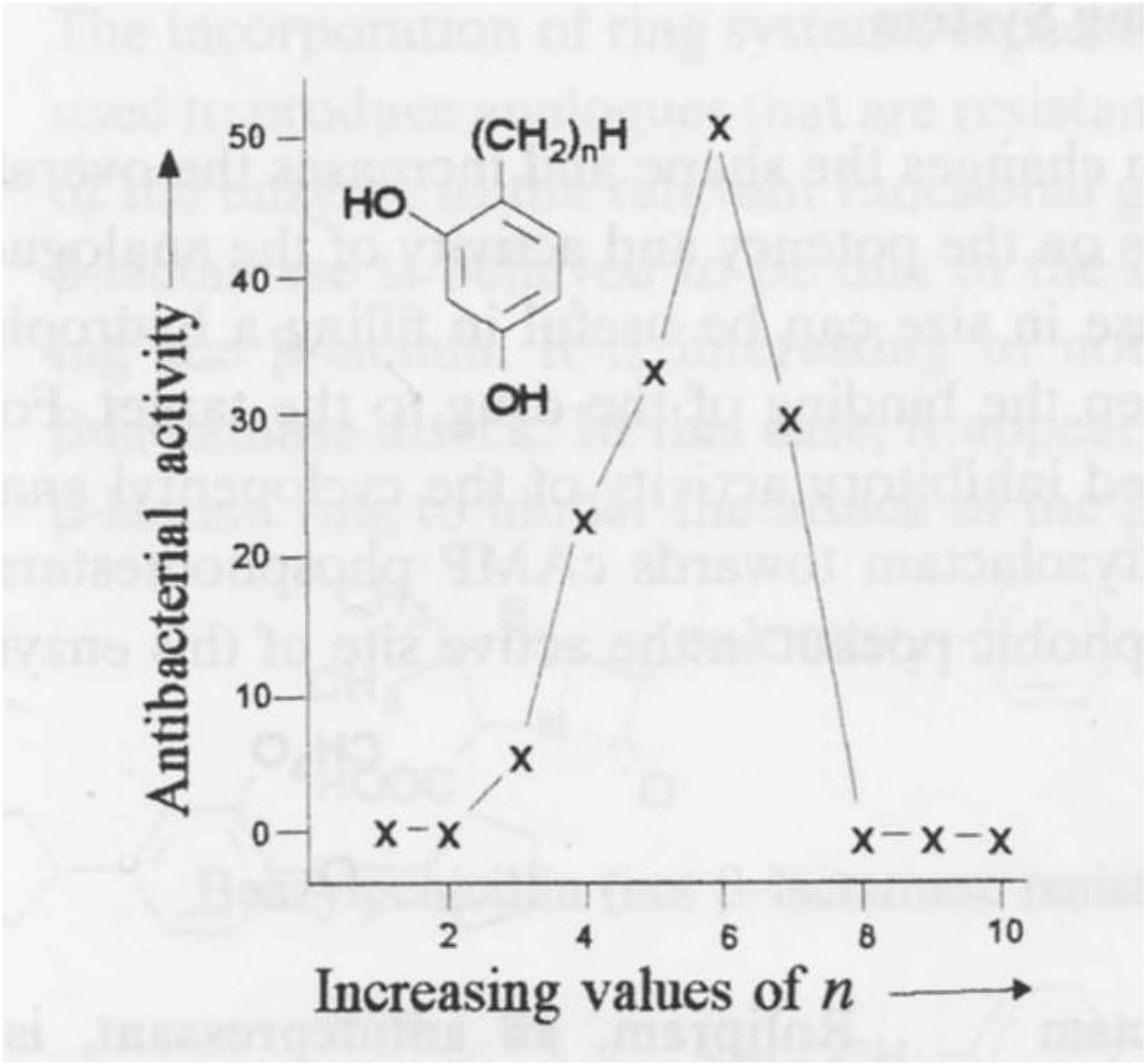
Enalapril

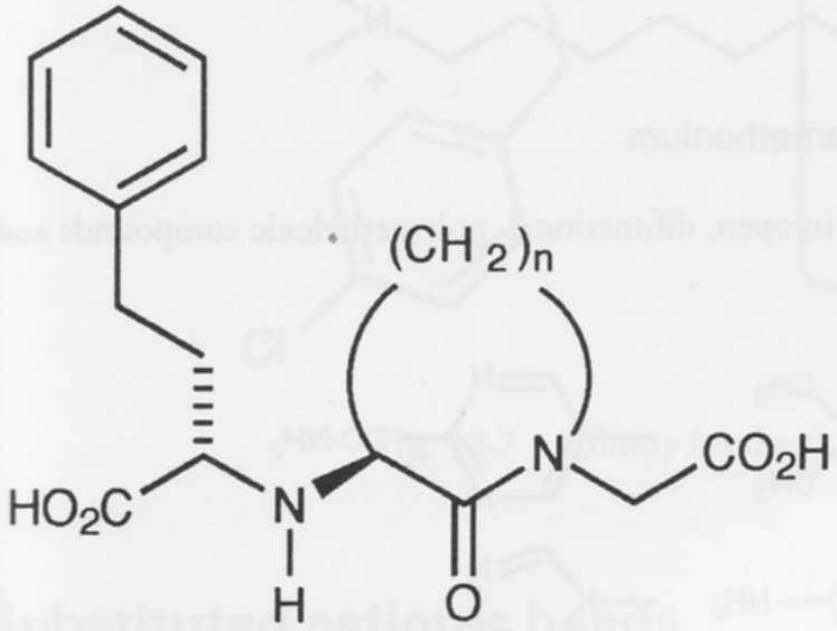
HOMOLOGY

increasing number of methylene groups
= increasing lipophilicity

low lipophilicity (hydrophilicity)
= poor membrane penetration

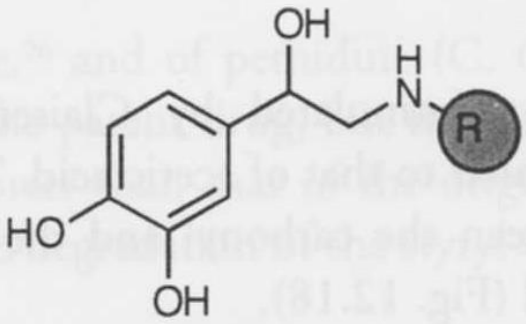
high lipophilicity
= poor biodistribution, accumulation in
adipose tissues


Antibacterial activity
50
40
30
20
10
0
(CH2)nH
HO
OH
X
X
X
X
X
X
X
X
X
X
X
X
2
4
6
8
10
Increasing values of n



Size	IC_{50} (nM)
n = 2	19,000
n = 3	1,700
n = 4	19
n = 5	4.8
n = 6	8.1

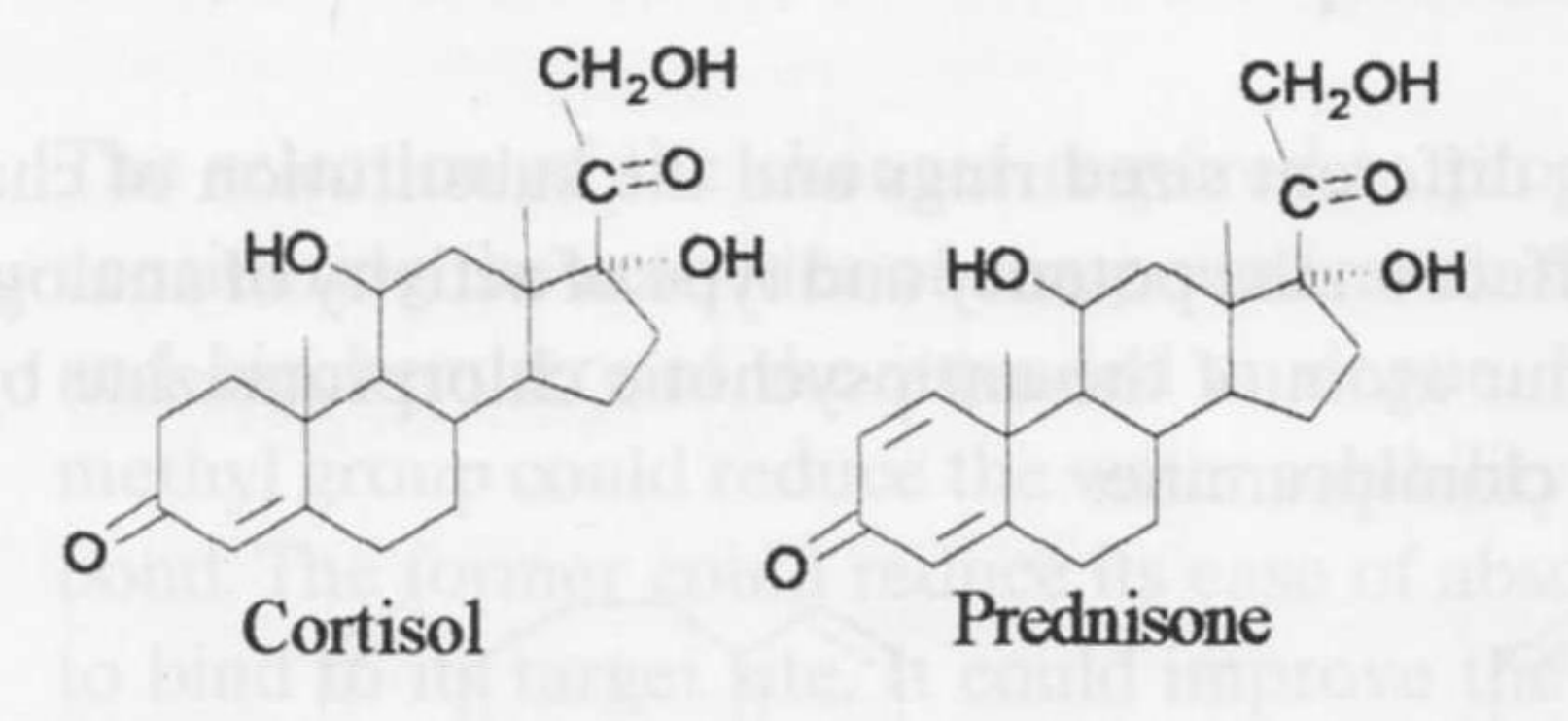
Fig. 12.2 Angiotensin-convertase inhibiting potency of enalaprilat analogues.[4]



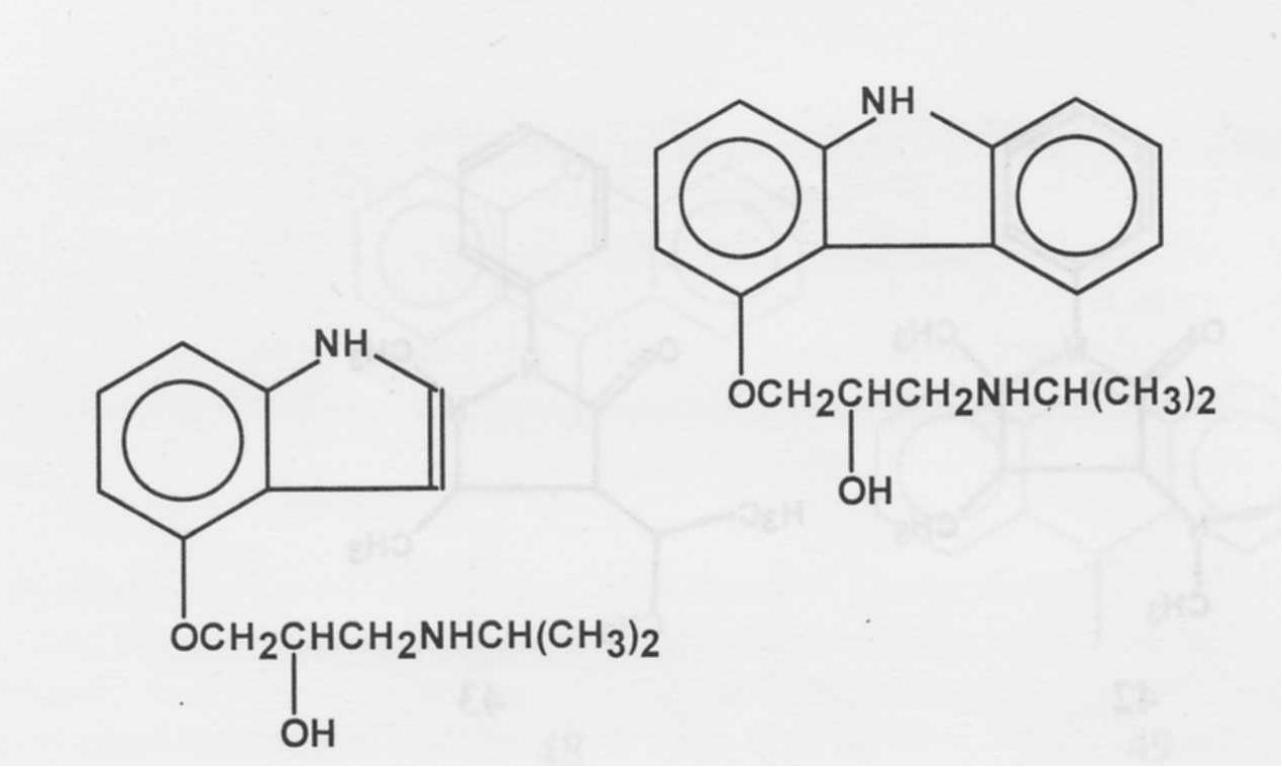
R	Blood pressure in the cat	
	Hypertensive	Hypotensive
Hydrogen	++	−
Methyl	++	−
Ethyl	+	+
Propyl	−	+
Isopropyl	−	++
Butyl	−	++
Isobutyl	−	++

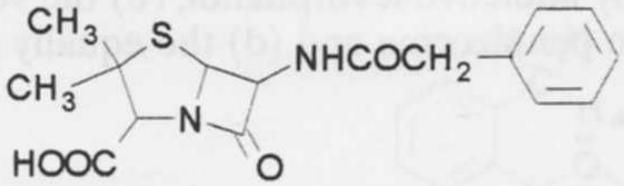
ANALOGY

removal of double bounds increase flexibility

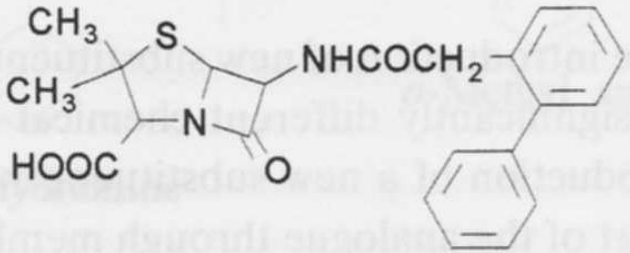


introduction or removal of ring systems changes overall size of the molecule

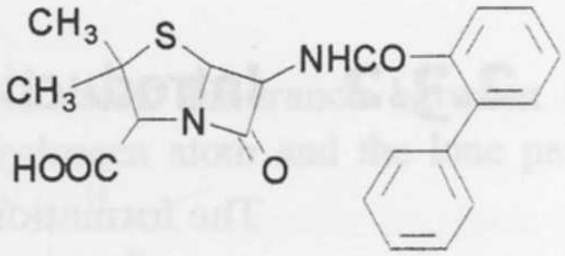




Benzylpenicillin (not β-lactamase resistant)

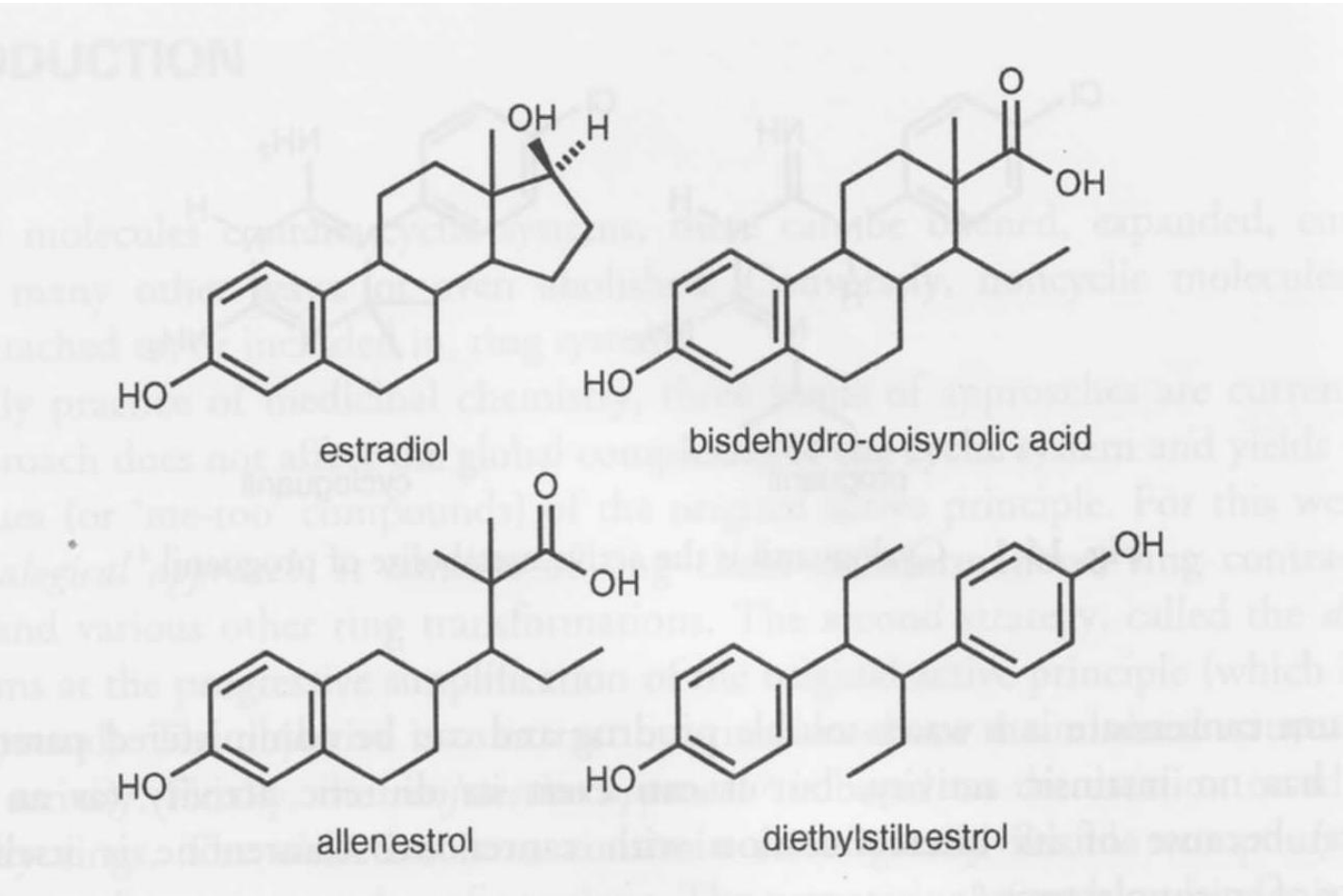


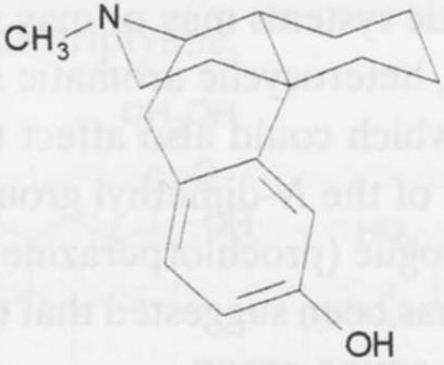
2-Phenylbenzylpenicillin (not β-lactamase resistant)



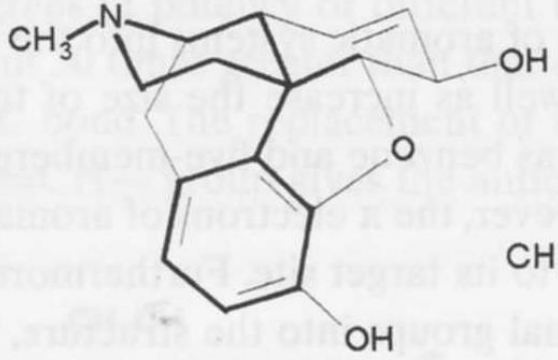
Diphenicillin (β-lactamase resistant)

some parts of natural compounds are not necessary for the effect and/or are responsible for side effects

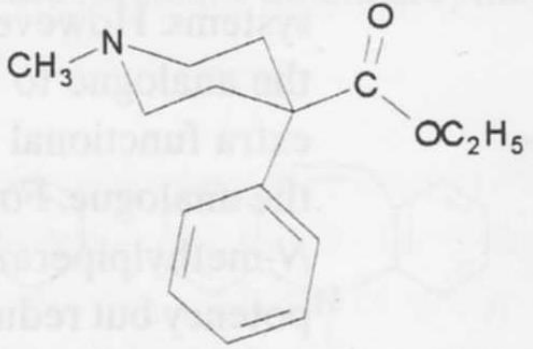




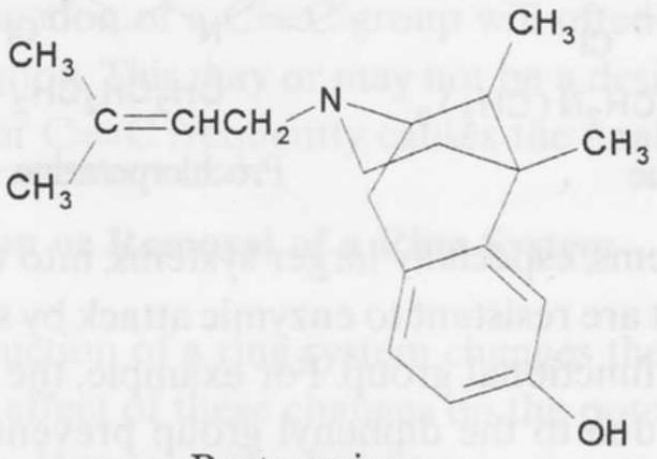
Levorphanol



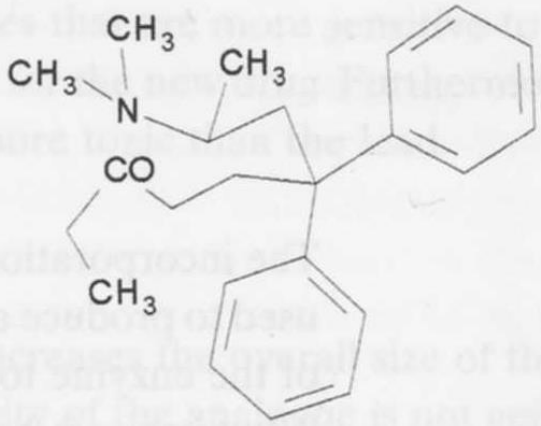
Morphine



Pethidine



Pentazocine



Methadone

ISOSTERES

isosteric groups exhibit similarities in chemical and physical properties

Classical isosteres

- atoms, ions and molecules with identical outer shells of electrons

$-CH_3$, $-NH_2$, $-OH$, $-F$, $-Cl$.

$-Cl$, $-SH$ $-PH_2$

$-Br$, isopropyl $-CH(CH_3)_2$

$-CH_2-$, $-NH-$, $-O-$, $-S-$

$-COCH_2R$, $-CONHR$, $-COOR$, $-COSR$

$-HC=$, $-N=$

In rings: $-CH=CH-$, $-S-$

$-O-$, $-S-$, $-CH_2-$, $-NH-$

$-CH=$, $-N-$

Monovalent bioisosteres

F, H

OH, NH

F, OH, NH or CH_3 for H

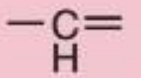
SH, OH

Cl, Br, CF_3

Divalent bioisosteres:

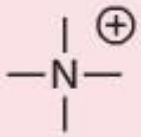
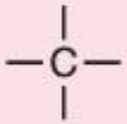
—C=S, —C=O, —C=NH, —C=C—

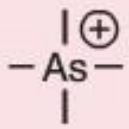
Trivalent atoms or groups:


, —N=

—P= , —As=

Tetrasubstituted atoms:

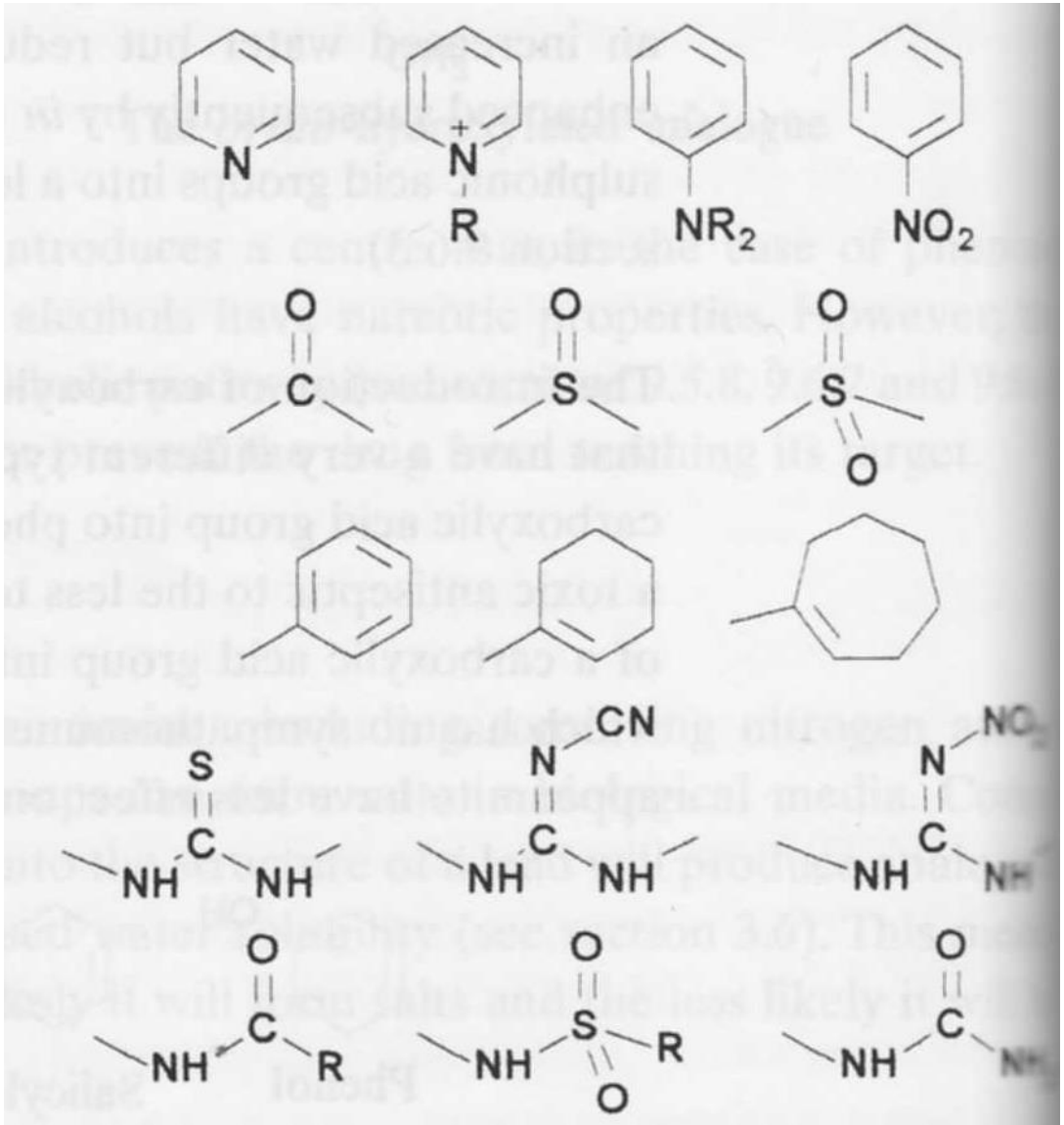



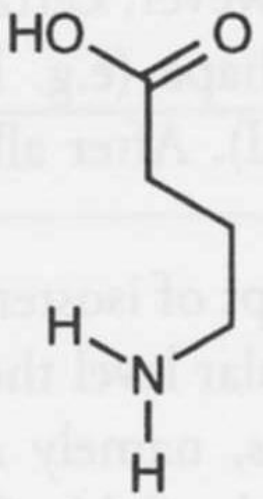


Ring equivalents:

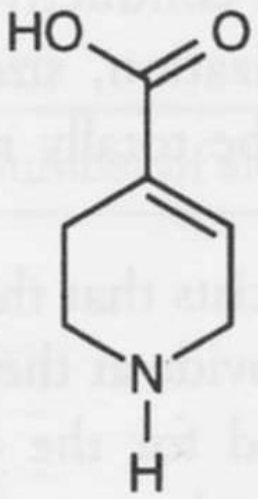
Bioisosteres

- groups with similar biological activity

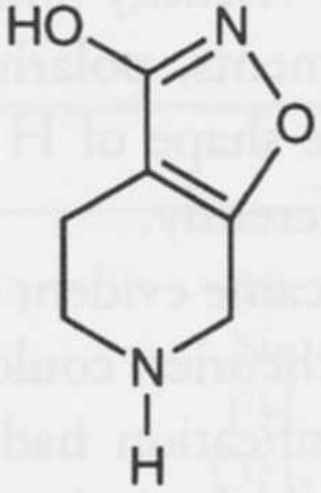




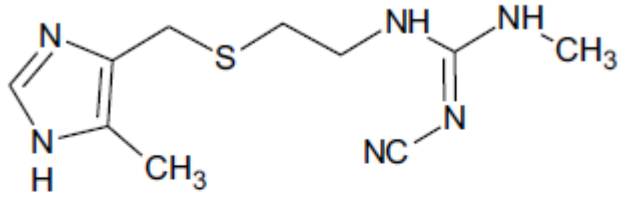
GABA



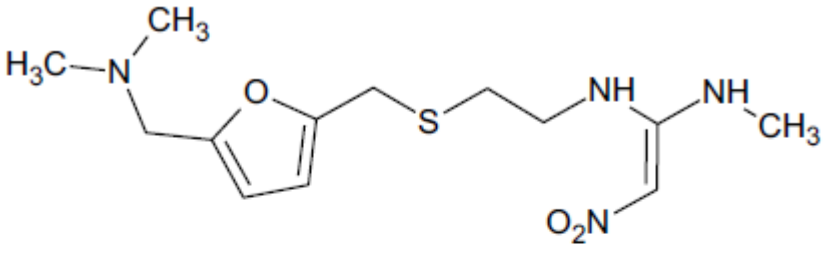
isoguvacine



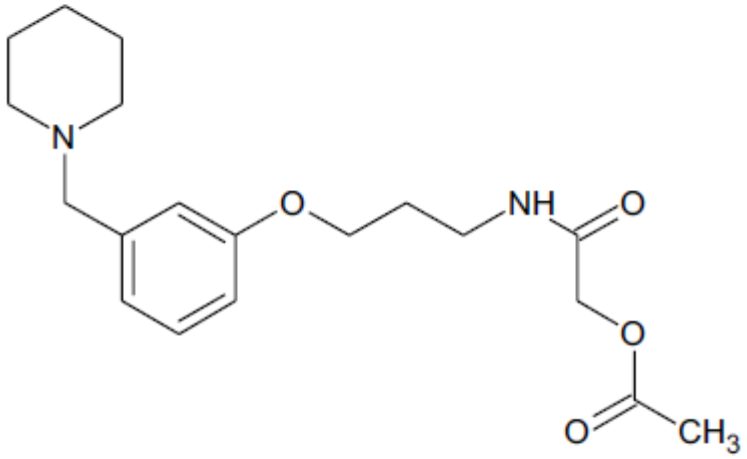
THIP



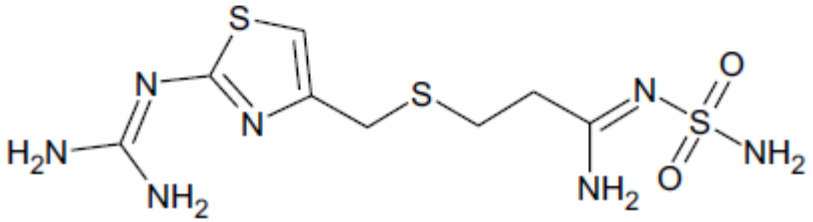
cimetidine



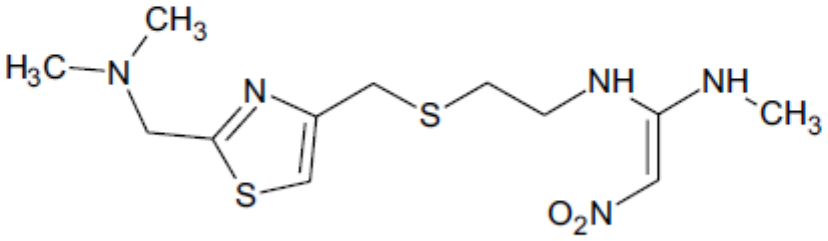
ranitidine



roxatidine



famotidine

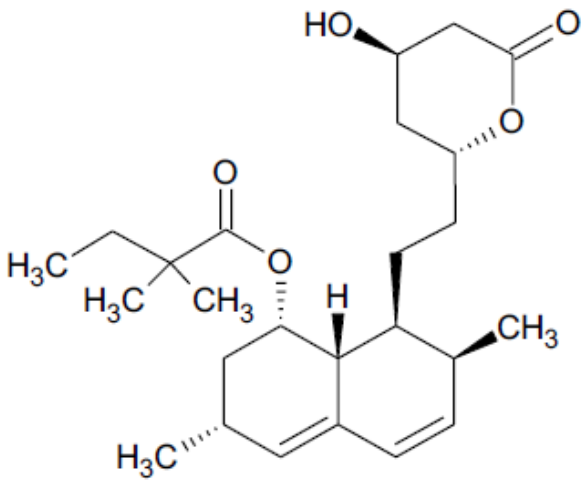


nizatidine

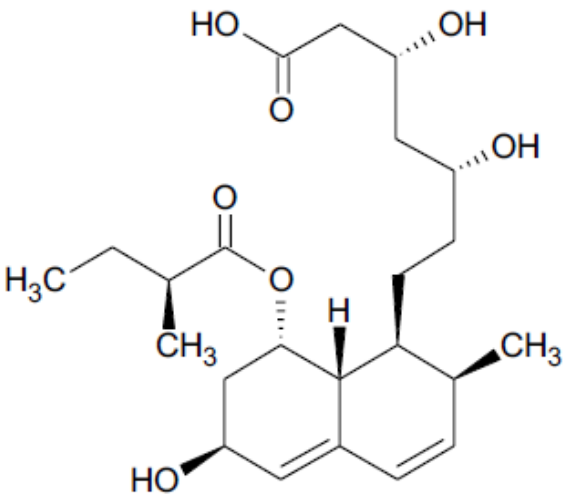
Table 1.1 Comparison of approximately equivalent daily doses of H_2-receptor antagonists.

Drug	Daily dose (mg)	Molecular weight (Da)
cimetidine	800	252
nizatidine	300	331
ranitidine	300	314
roxatidine	150	385[a)]
famotidine	40	337

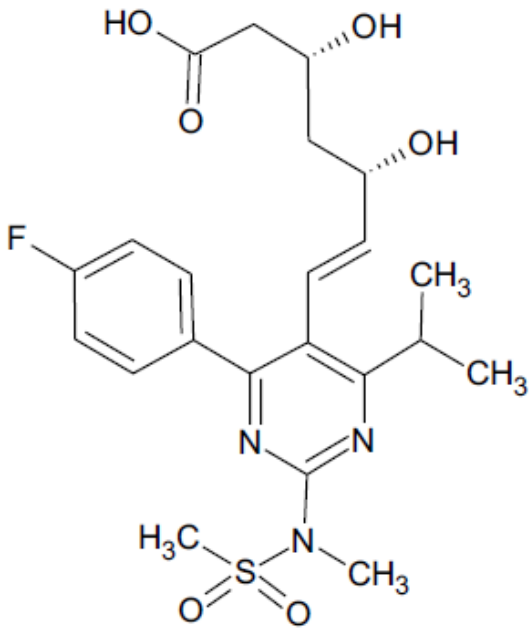
a) Administered as acetate hydrochloride.



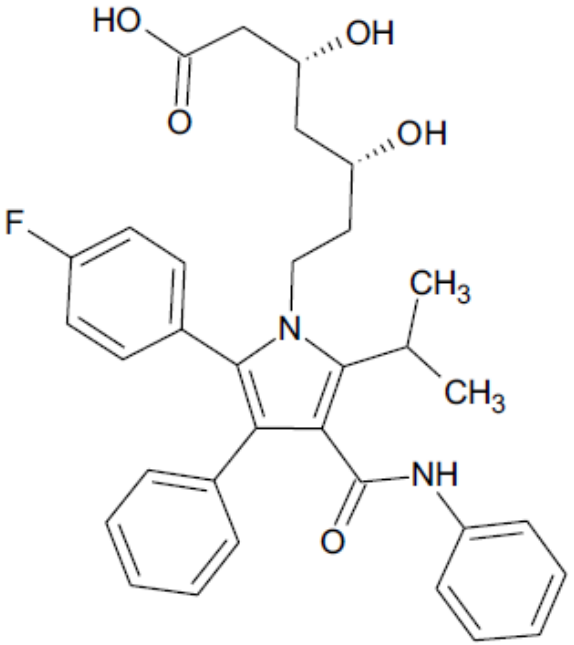
simvastatin



pravastatin



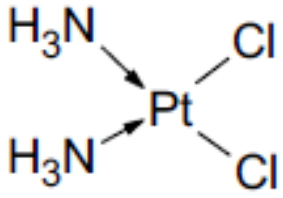
rosuvastatin



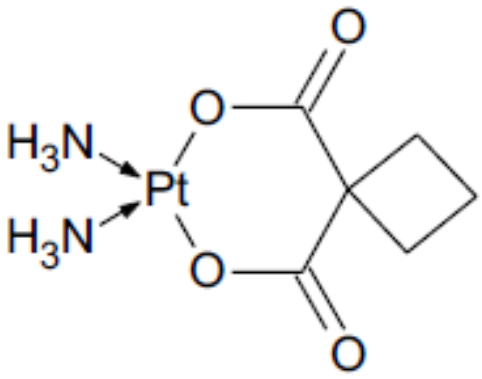
atorvastatin

Table 1.2 Inhibitory effects of various statins *in vitro*.

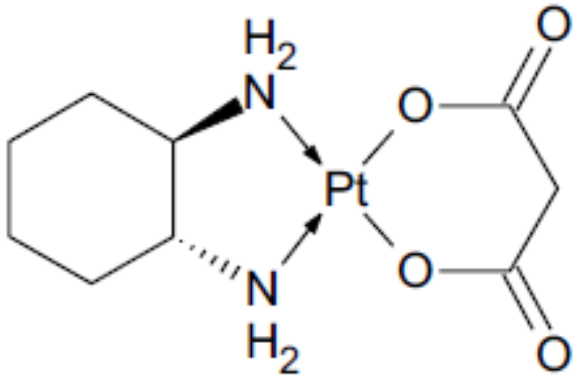
Drug	IC_{50} (nM)	Molecular weight (Da)
pravastatin	44.1	424
simvastatin	11.2	419
atorvastatin	8.2	559
rosuvastatin	5.4	482



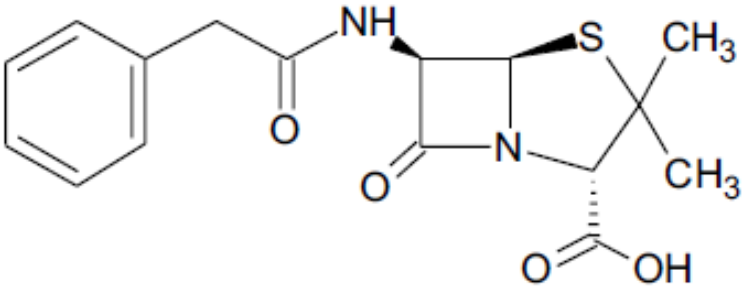
cisplatin



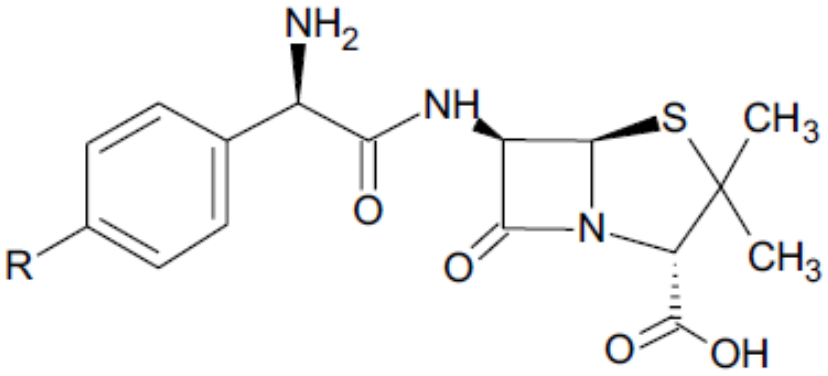
carboplatin



oxaliplatin



benzylpenicillin



ampicillin, R = H

amoxicillin, R = OH

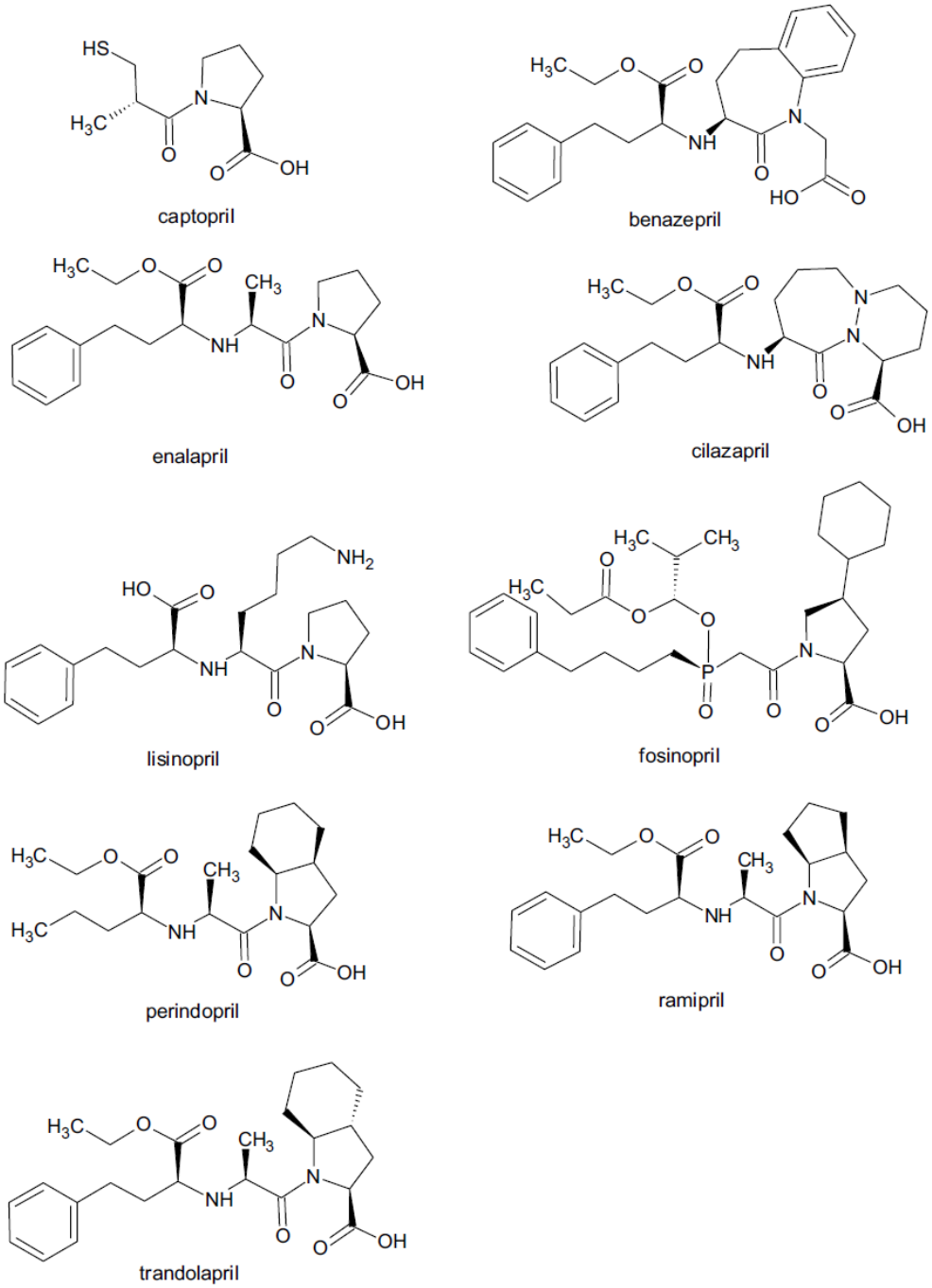


Figure 1.16 Structures of ACE inhibitors.

Table 1.4 Elimination half-life values of ACE inhibitors [31].

Drug	Elimination half-life (h)
captopril	2
benazepril	11
cilazapril	10
enalapril	11
fosinopril	12
lisinopril	12
perindopril	>24
ramipril	8–14
trandolapril	16–24