Antihypertensives

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Hypertension

- blood pressure >135/85 mmHg

- most common cardiovascular disease

- untreated = major risk of coronary artery disease, heart failure, stroke, renal failure

- long-time untreated hypertension: left ventricule hyperthropy, retinopathy, angina pectoris, lung, liver, renal failure
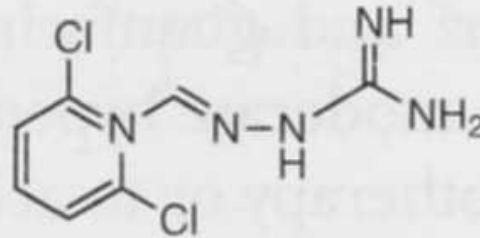
Hypertension – drug therapy

- central and peripheral autonomic inervation
- blood vessel wall relaxation
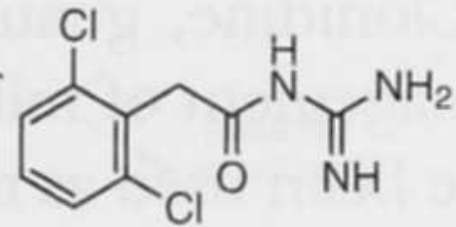- renine-angiotensine-aldosteron system
- diuretics
- other mechanism
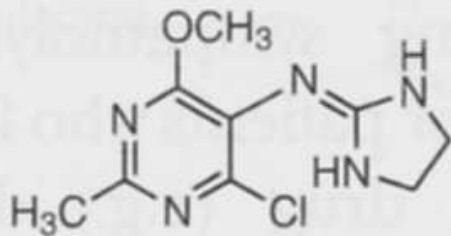
α₂-adrenergic and imidazoline receptor agonists
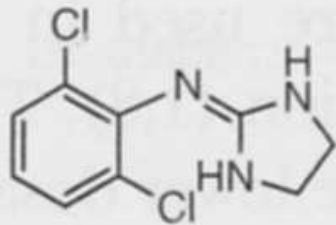
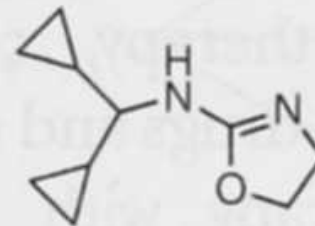**Fig. 24.5.** Centrally acting sympatholytics.

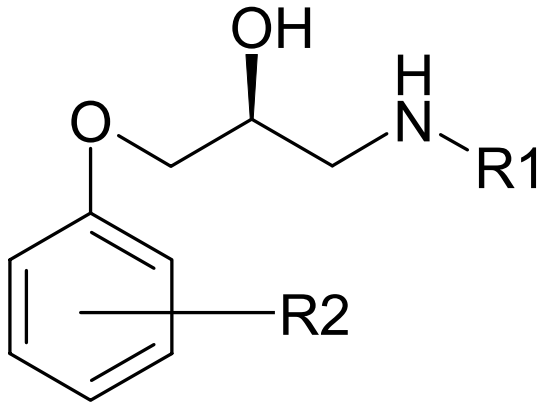# α₁-adrenergic receptor antagonists
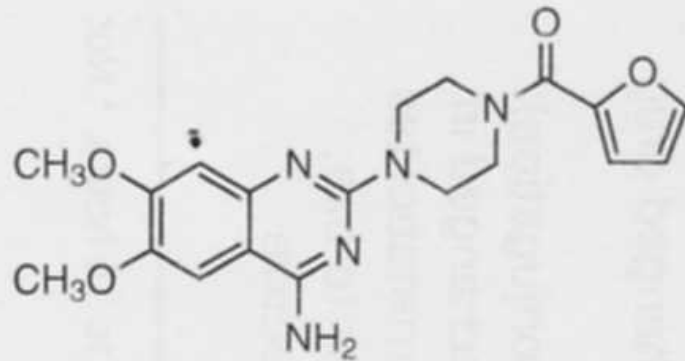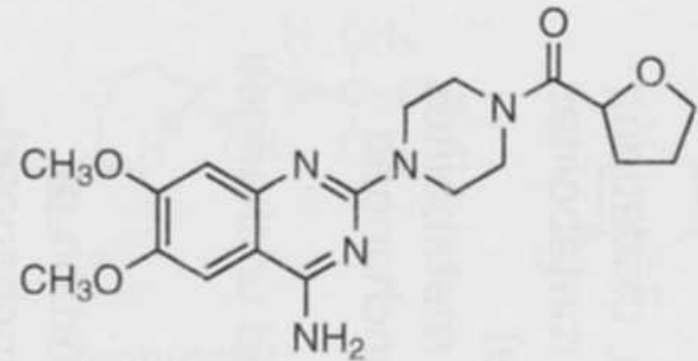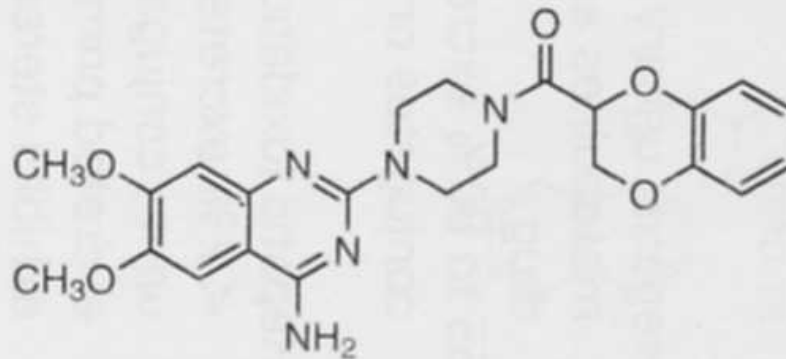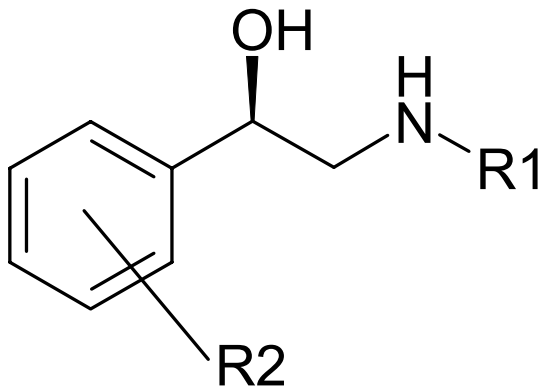

Fig. 24.3. α₁ selective adrenergic blockers.

β-blockers

- general structure:

Aryloxypropanolamines

Arylethanolamines

β-blockers

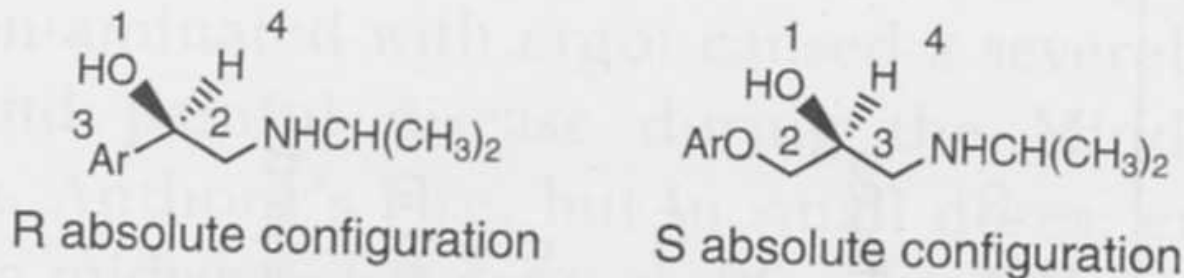□ absolute configuration important

Fig. 11.18. Stereochemical nomenclature for arylethanolamines versus aryloxypropanolamines. The relative positions in space of the four functional groups are the same in the two structures; however, one is designated (R) and the other (S). This is because the introduction of an oxygen atom into the side chain of the aryloxypropanolamine changes the priority of two of the groups used in the nomenclature assignment.
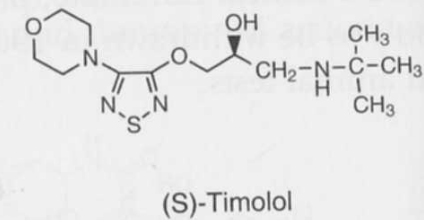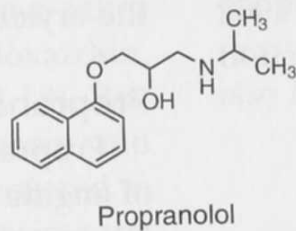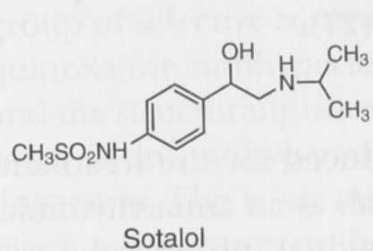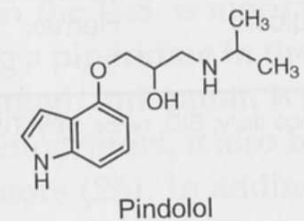
β-blockers – non selective
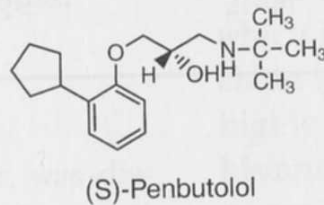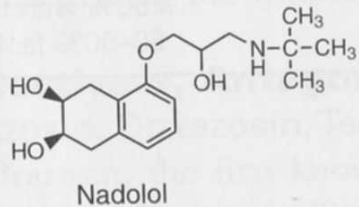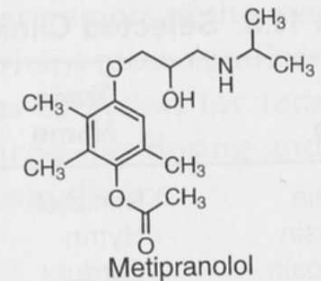
Fig. 11.15. Non-selective β-adrenergic antagonists.
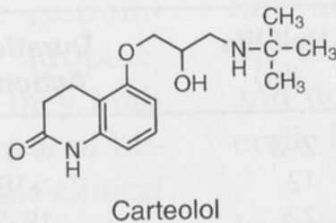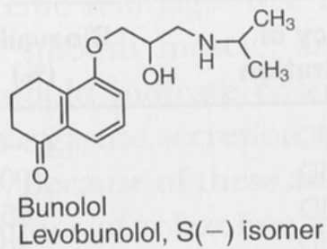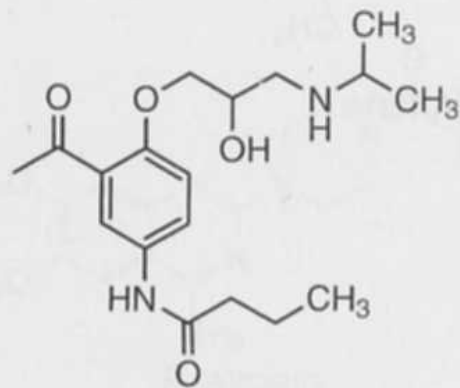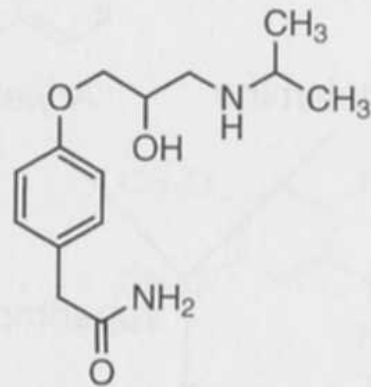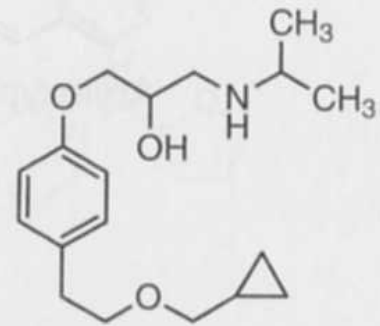
β-blockers - cardioselective
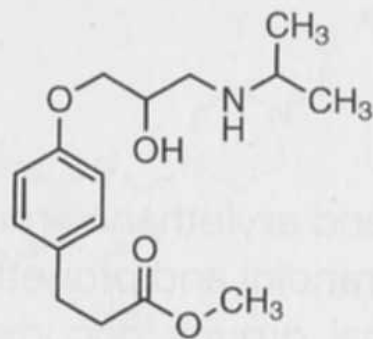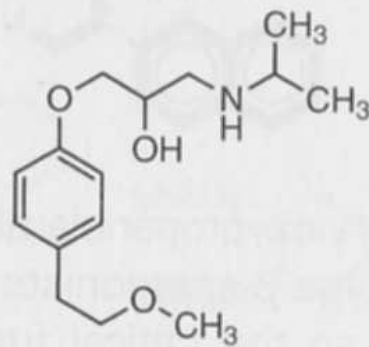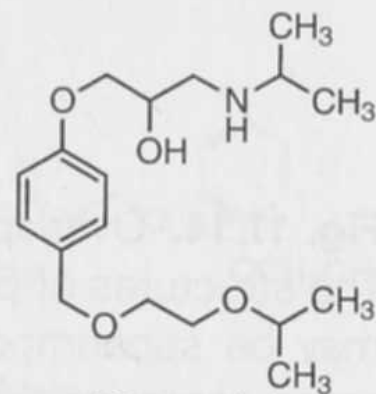
Fig. 11.16. Selective β$_1$-adrenergic antagonists.

Mixed β + α antagonists
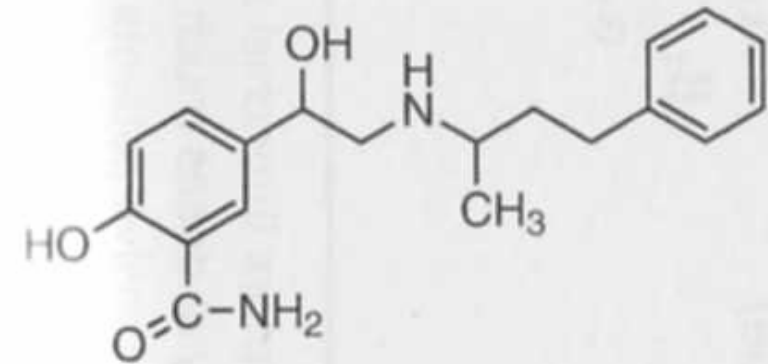
Labetalol
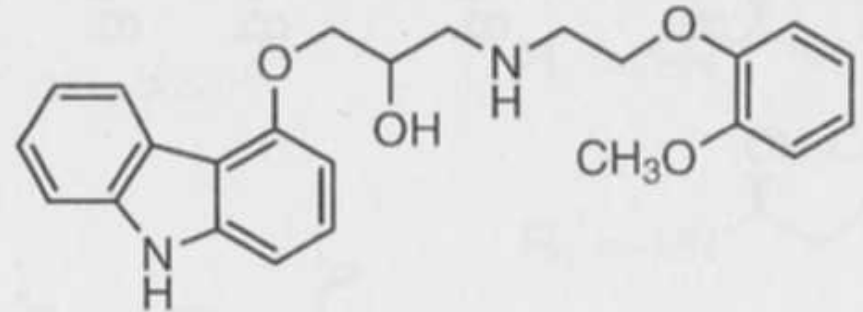
Carvedilol

Fig. 11.17. Mixed α/β-adrenergic antagonists.

Ca²⁺blockers

Fig. 23.20. Cellular mechanisms for the influx, efflux, and sequestering of Ca^{2+}. Key: ROC = receptor-operated Ca^{2+} channels; PDC = potential-dependent Ca^{2+} channels; SR = sarcoplasmic reticulum; M = mitochondria.
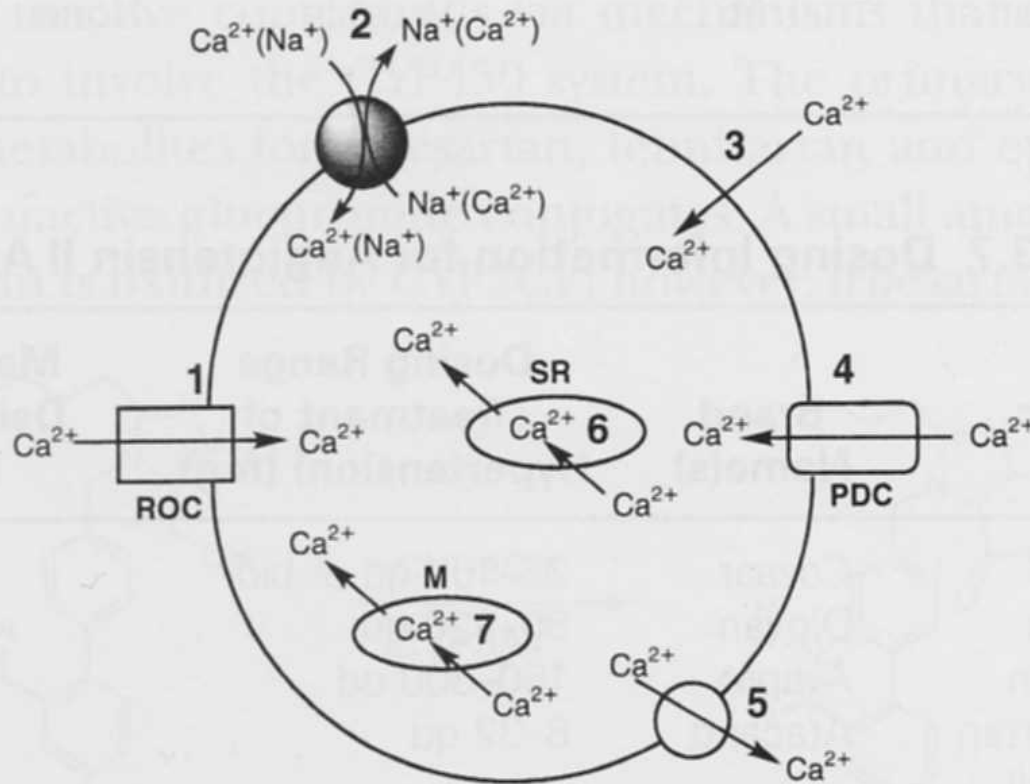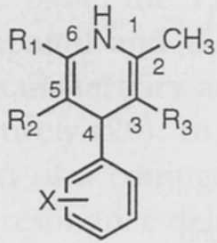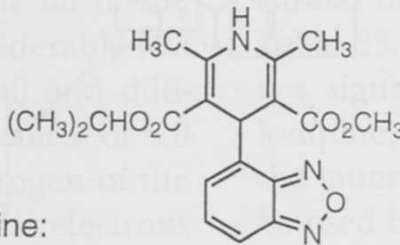
Ca²⁺blockers

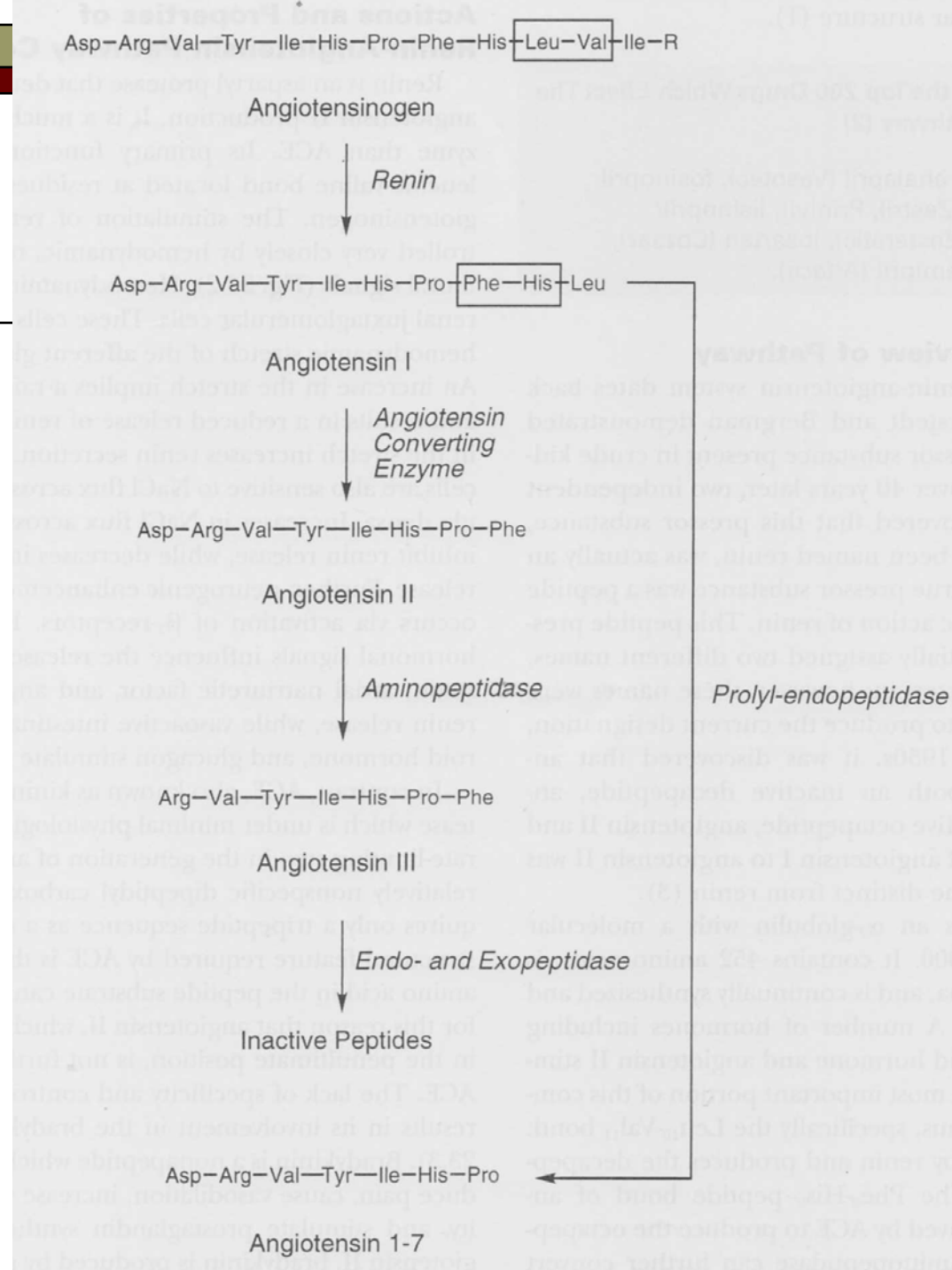- Verapamil, diltiazem
- dihydropyridines

General structure:

$$R_1 \underset{5}{\overset{6}{}} \underset{4}{\overset{H}{N}}{\overset{1}{}} CH_3$$

$$R_2 \quad R_3$$

$$X$$

Isradipine:

Compounds	R₁	R₂	R₃	X
Amlodipine	$CH_2OCH_2CH_2NH_2$	$CO_2CH_2CH_3$	CO_2CH_3	2-Cl
Felodipine	CH_3	$CO_2CH_2CH_3$	CO_2CH_3	2,3-Cl₂
Nicardipine	CH_3	$CO_2CH_2CH_2-NH-CH_2 \cdot C_6H_5$	CO_2CH_3	3-NO₂
	CH_3	$\overset{|}{CH_3}$		
Nifedipine	CH_3	CO_2CH_3	CO_2CH_3	2-NO₂
Nimodipine	CH_3	$CO_2CH_2CH_2OCH_3$	$CO_2CH(CH_3)_2$	3-NO₂
Nisoldipine	CH_3	$CO_2CH_2CH(CH_3)_2$	CO_2CH_3	2-NO₂

RAA system

□

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe—His—Leu—Val—Ile—R

Angiotensinogen

↓ *Renin*

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe—His—Leu

Angiotensin I

↓ *Angiotensin Converting Enzyme*

Asp—Arg—Val—Tyr—Ile—His—Pro—Phe

Angiotensin II

↓ *Aminopeptidase*

Arg—Val—Tyr—Ile—His—Pro—Phe

Angiotensin III

↓ *Endo- and Exopeptidase*

Inactive Peptides

Asp—Arg—Val—Tyr—Ile—His—Pro

Angiotensin 1-7

Prolyl-endopeptidase
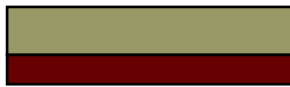
ACE inhibitors – mechanism of action
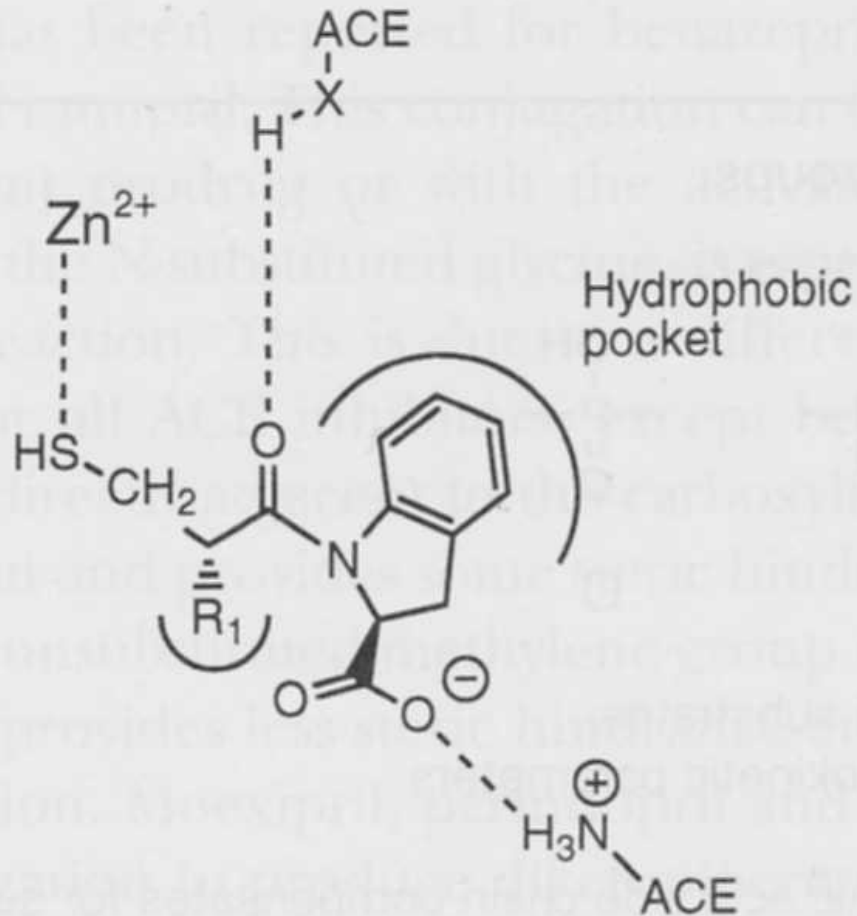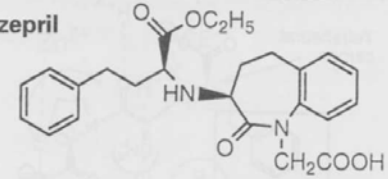

Fig. 23.10. A modified model of ACE inhibitor binding.

ACE

□

General Structure:
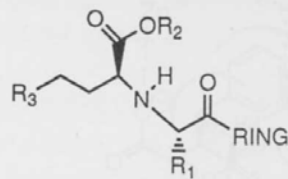
Benazepril

Compounds	Ring	R_1	R_2	R_3
Lisinopril		$(CH_2)_4NH_2$	H	
Moexipril		CH_3	CH_2CH_3	
Perindopril		CH_3	CH_2CH_3	CH_3
Quinapril		CH_3	CH_2CH_3	
Ramipril		CH_3	CH_2CH_3	
Spirapril		CH_3	CH_2CH_3	
Trandolapril		CH_3	CH_2CH_3	
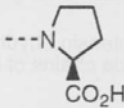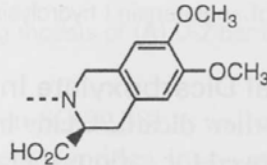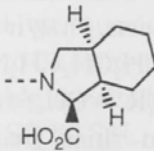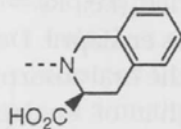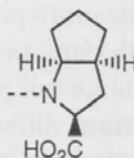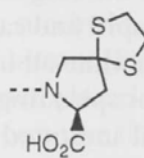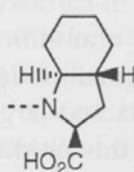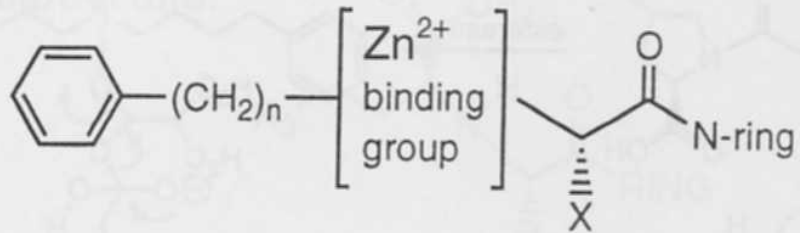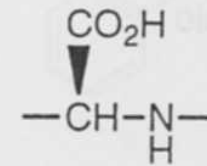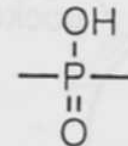
ACE ininhibitors

-

Angiotensin II inhibitors

□

Mimics the C-terminal carboxylic acid

Provide a better mimic of Phe$_8$
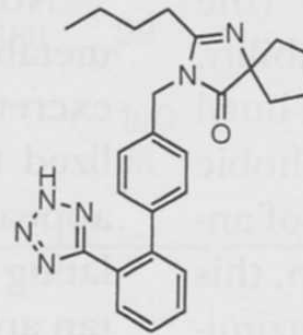
Add carboxylate

Mimics Tyr$_4$

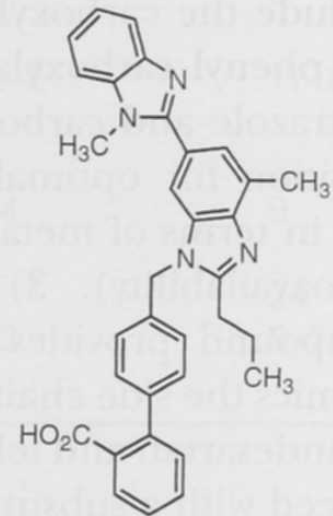S-8308

Eprosartan
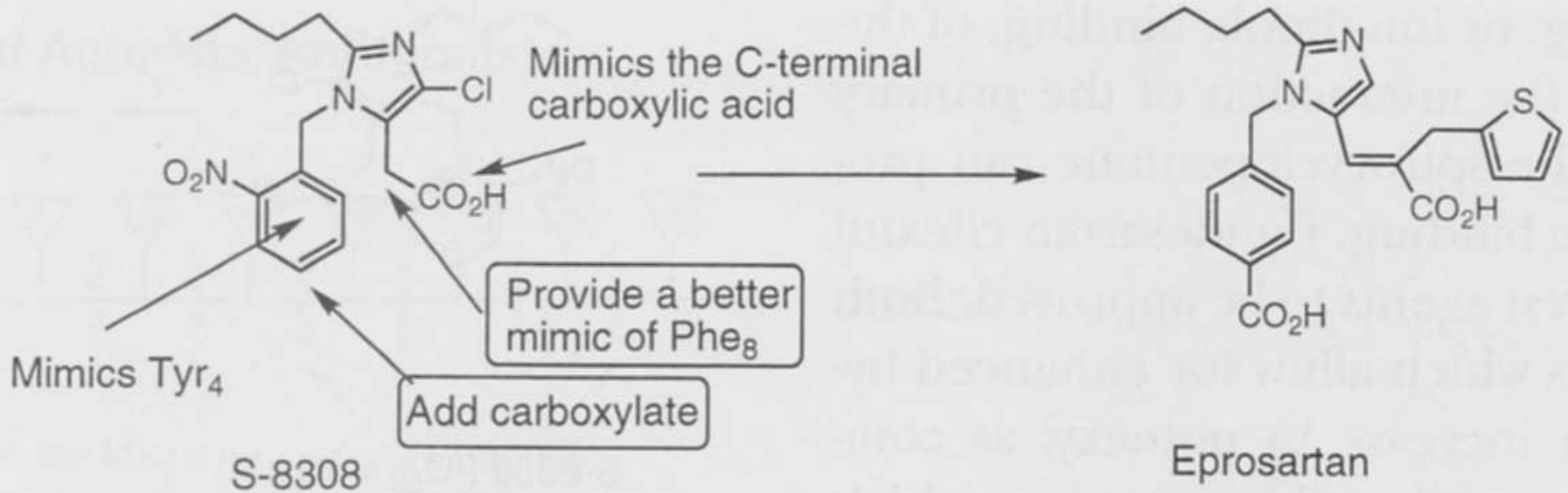
Angiotensin II inhibitors
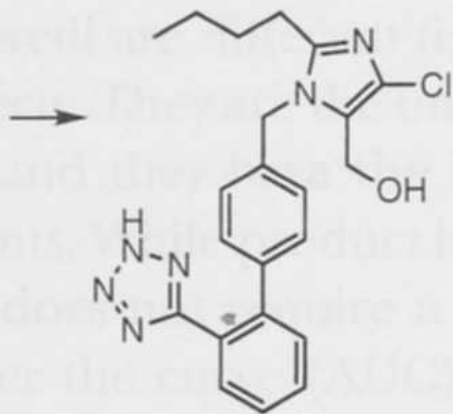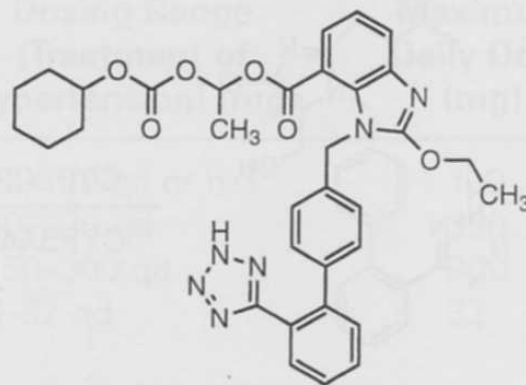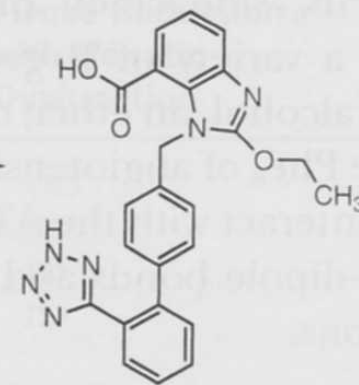

Losartan (IC$_{50}$ = 0.019μM)
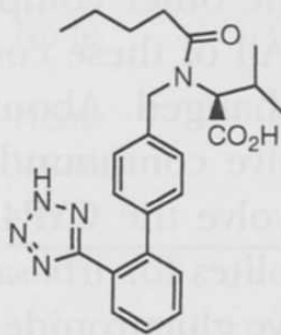
Valsartan

Irbesartan

Telmisartan

Candesartan cilexetil

in vivo

Candesartan