

# Antihypertensives

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# Hypertension

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- 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 ventricle hypertrophy, retinopathy, angina pectoris, lung, liver, renal failure

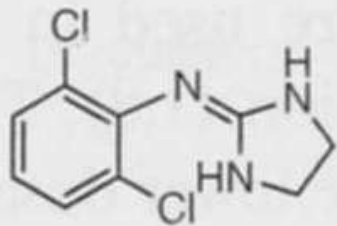


# Hypertension – drug therapy

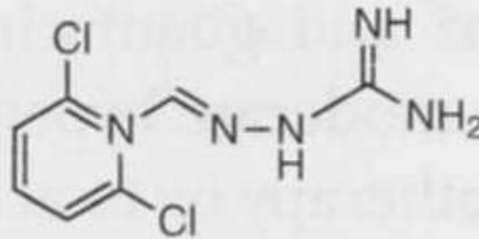
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- central and peripheral autonomic innervation
- blood vessel wall relaxation
- renin-angiotensin-aldosterone system
- diuretics
- other mechanism

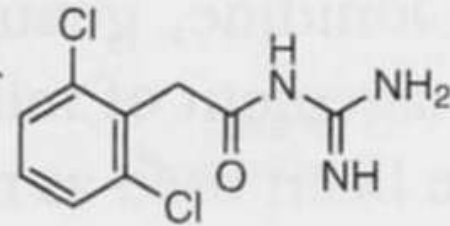
# $\alpha_2$ -adrenergic and imidazoline receptor agonists



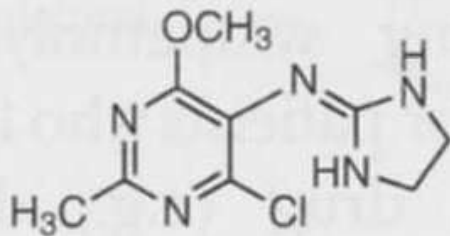
Clonidine



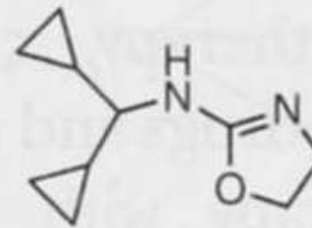
Guanabenz



Guanfacine



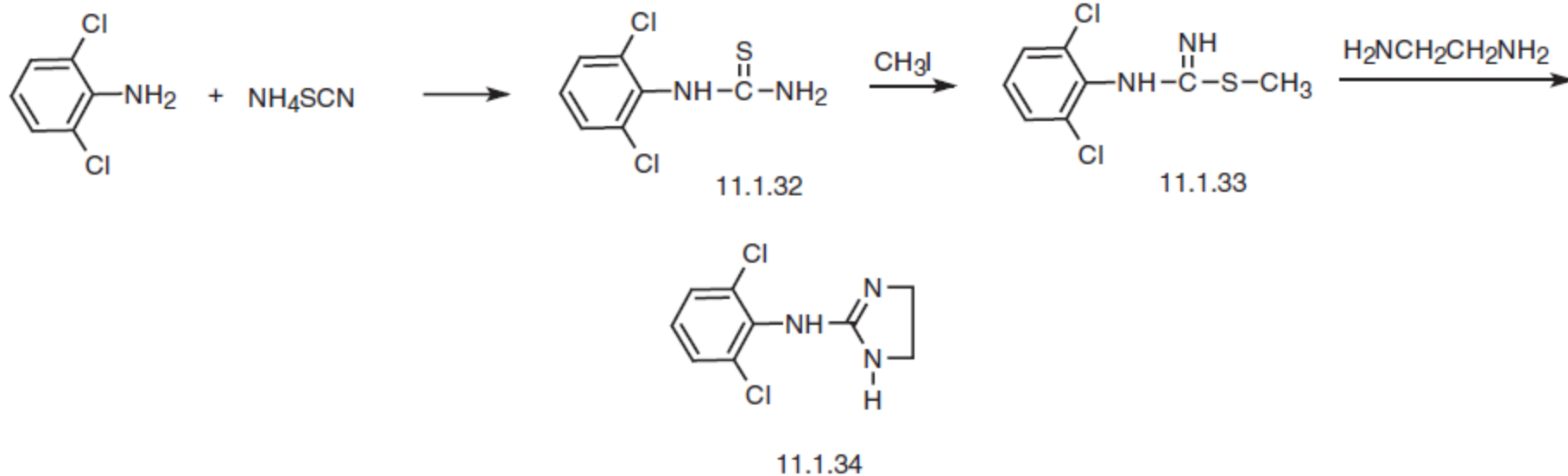
Moxonidine



Rilmenidine

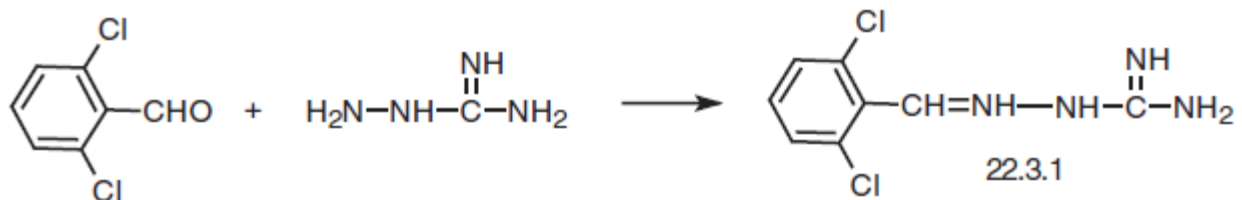
**Fig. 24.5.** Centrally acting sympatholytics.

# Clonidine synthesis



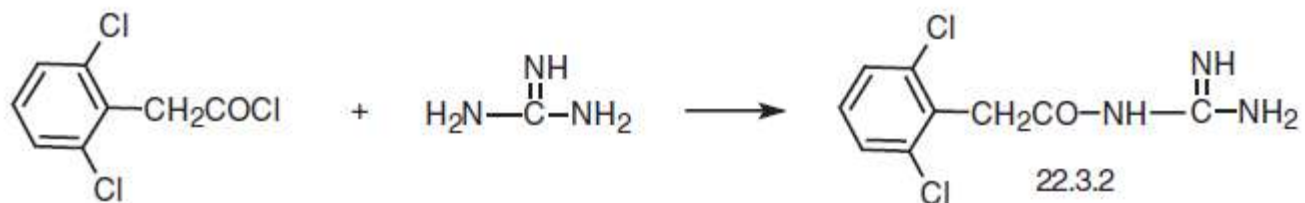
# Guanabenz synthesis

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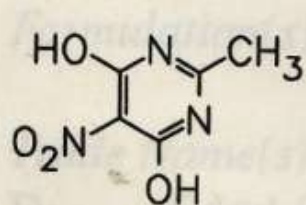


# Guanfacine synthesis

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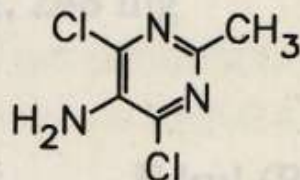
# Moxonidine synthesis



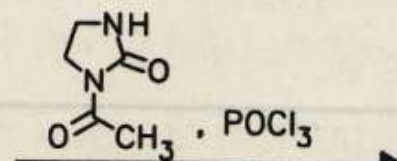
2-methyl-5-nitro-  
4,6-dihydroxy-  
pyrimidine

1. POCl<sub>3</sub>, HNO<sub>3</sub>

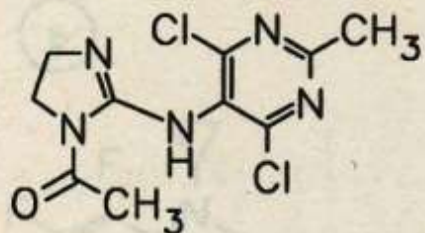
2. H<sub>2</sub>, Pd-C



5-amino-2-methyl-  
4,6-dichloro-  
pyrimidine



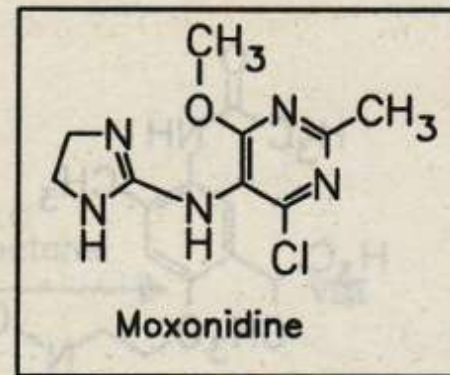
1-acetyl-2-imidazolidin-  
2-one



4,6-dichloro-2-methyl-  
5-(1-acetyl-2-imidazolin-  
2-ylamino)pyrimidine (I)

+ CH<sub>3</sub>-ONa

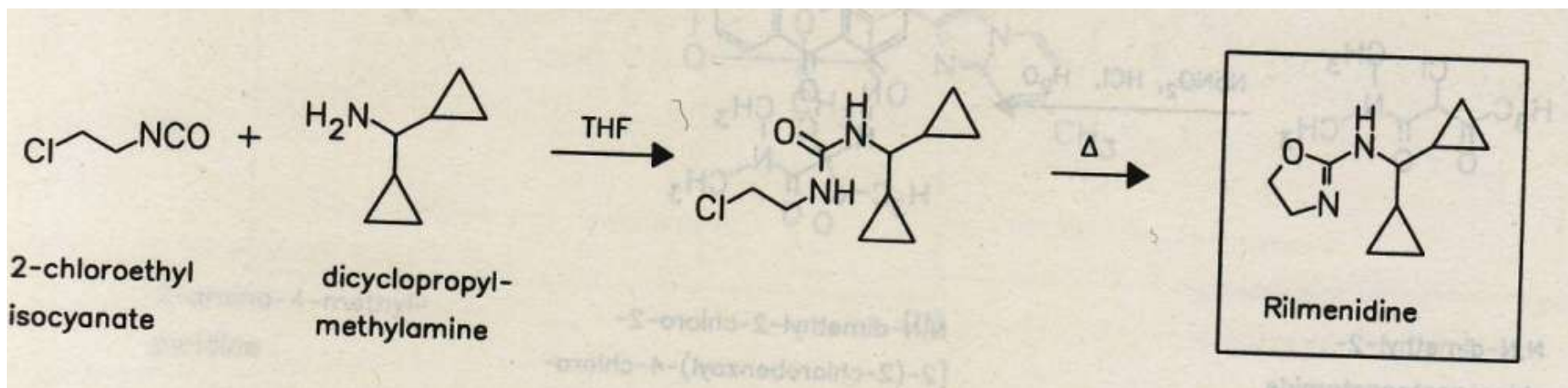
CH<sub>3</sub>OH



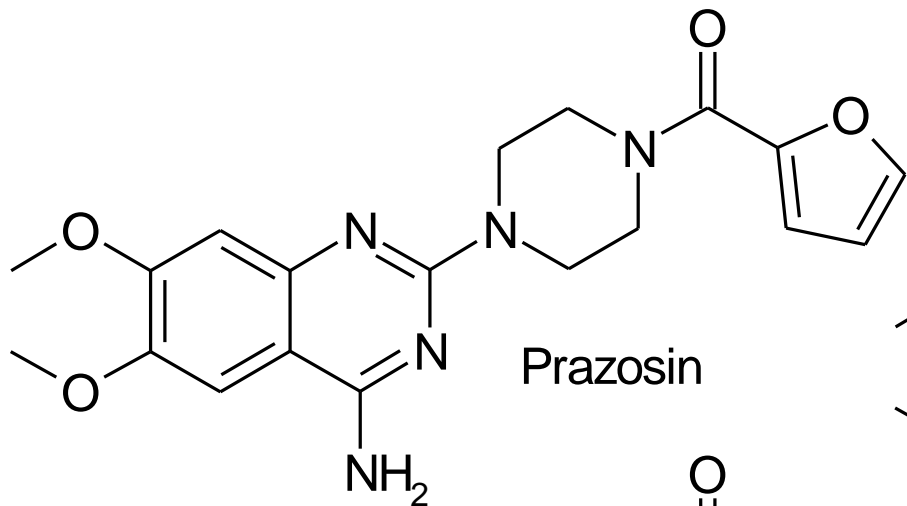
Moxonidine



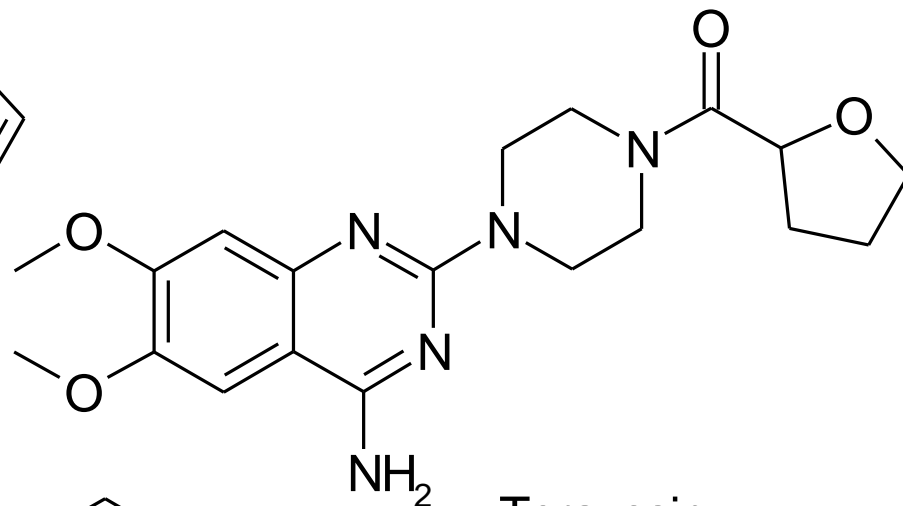
# Rilmenidine synthesis



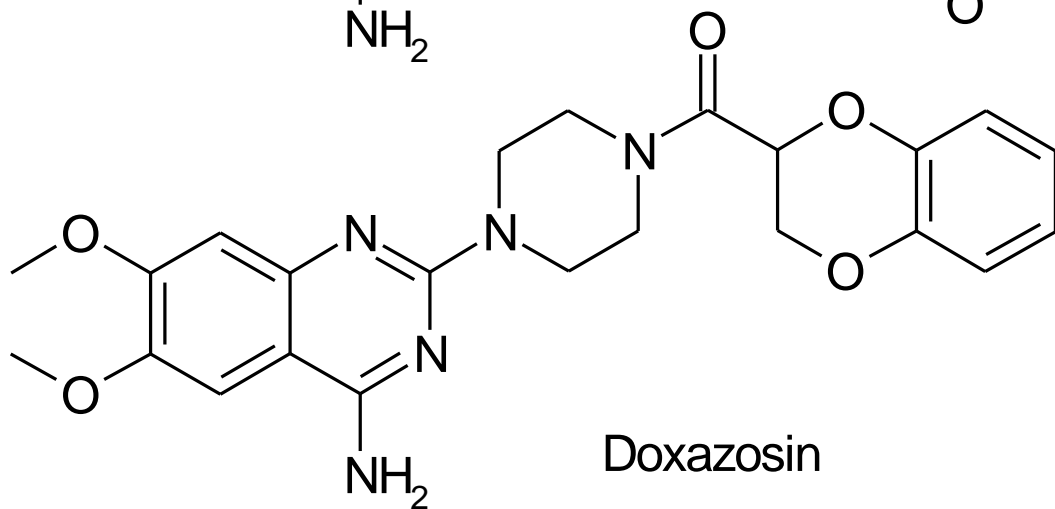
# $\alpha_1$ -adrenergic receptor antagonists



Prazosin

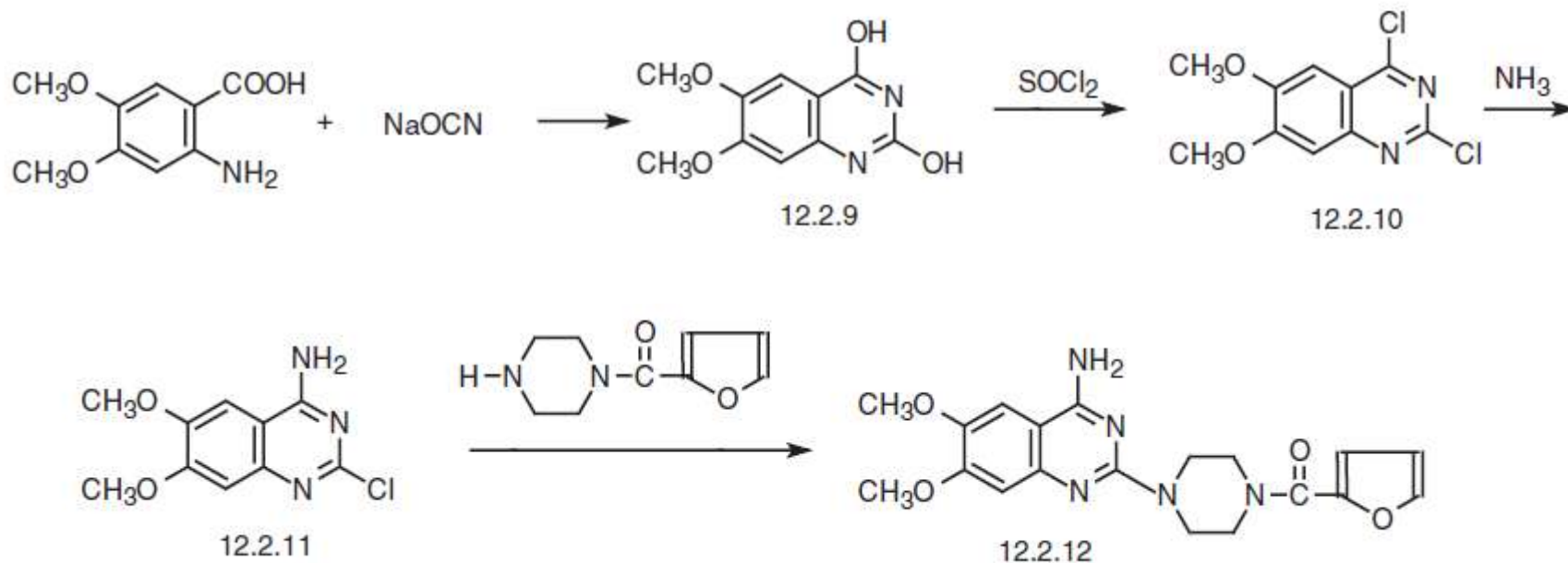


Terazosin

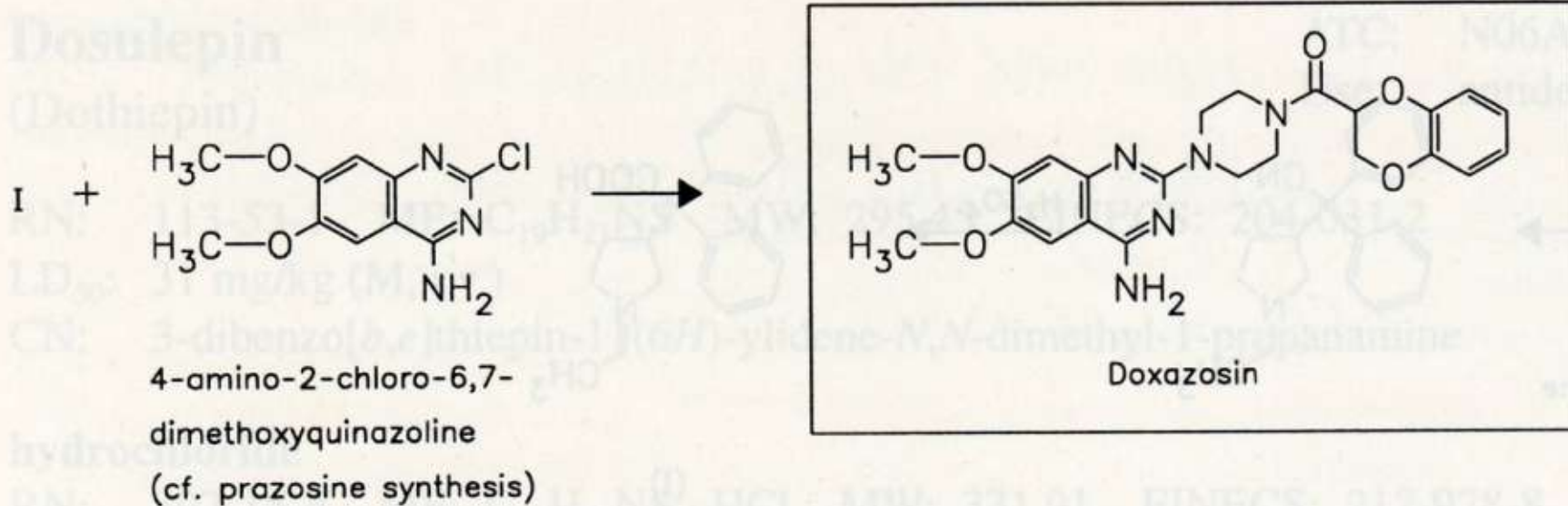
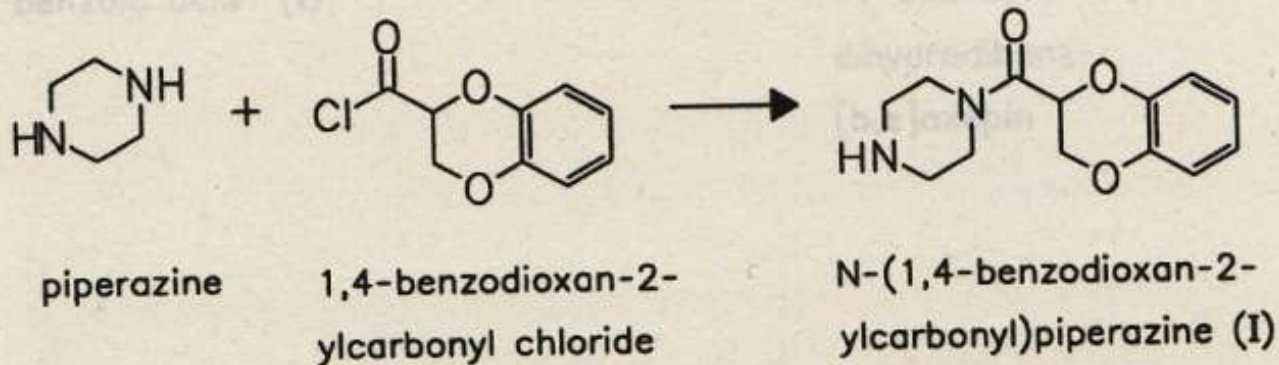


Doxazosin

# Prazosin synthesis



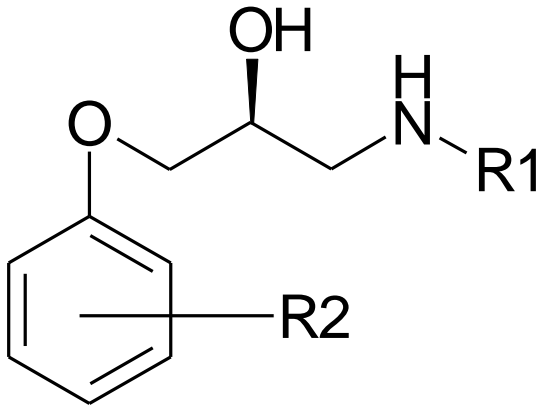
# Doxazosin synthesis



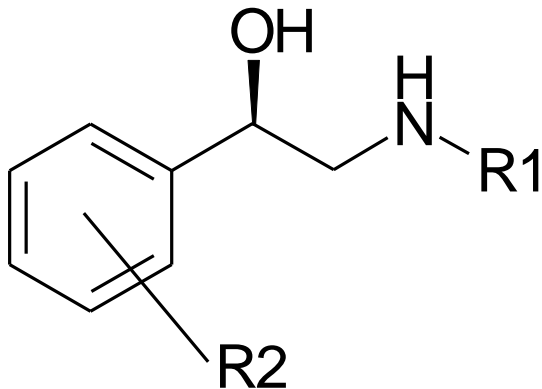
# $\beta$ -blockers

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□ general structure:



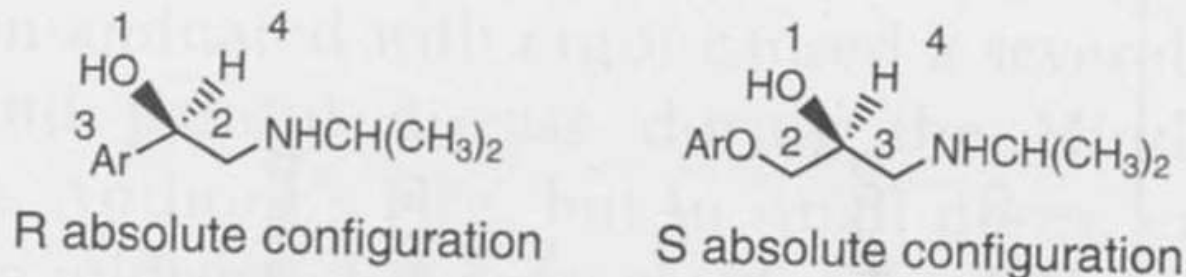
Aryloxypropanolamines



Arylethanolamines

# $\beta$ -blockers

- absolute configuration important



**Fig. 11.18.** Stereochemical nomenclature for aryloxypropanolamines 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.

# $\beta$ -blockers – non selective

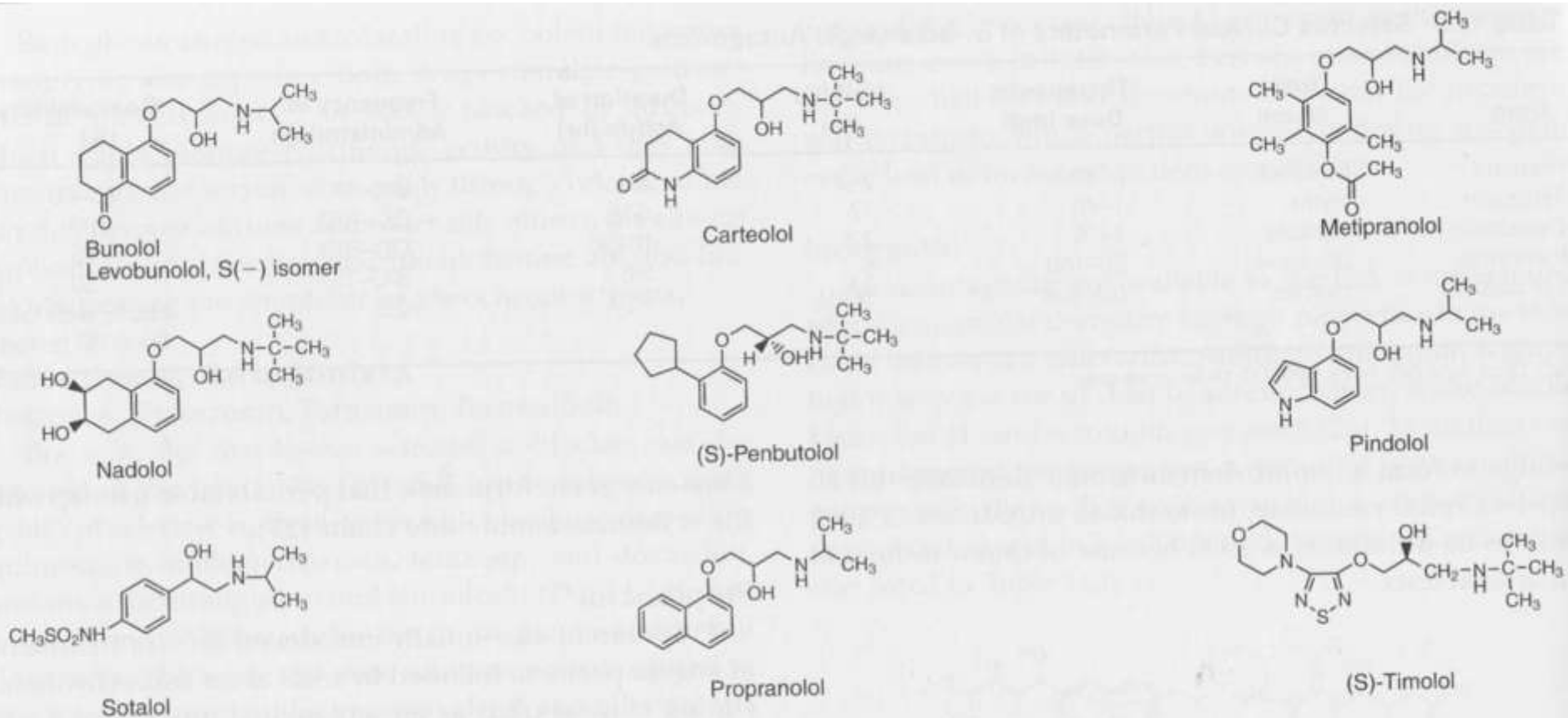
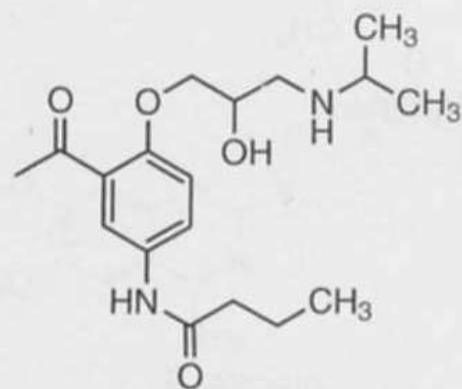
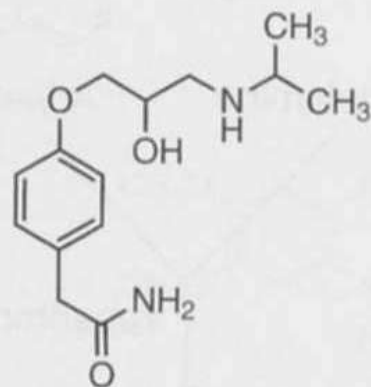


Fig. 11.15. Non-selective  $\beta$ -adrenergic antagonists.

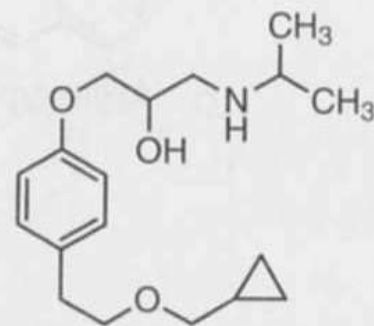
# $\beta$ -blockers - cardioselective



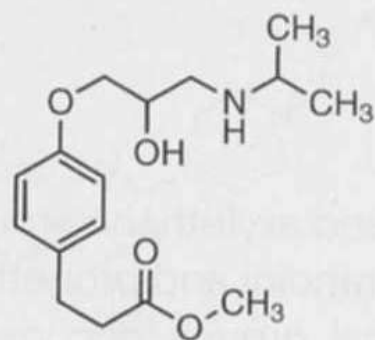
Acebutolol



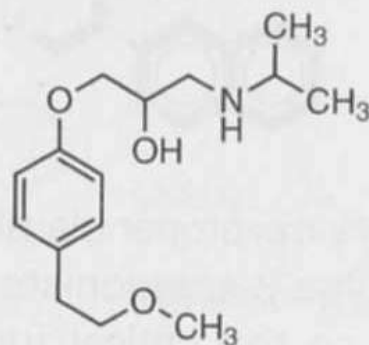
Atenolol



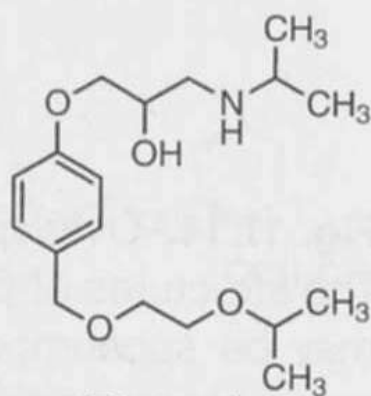
Betaxolol



Esmolol



Metoprolol



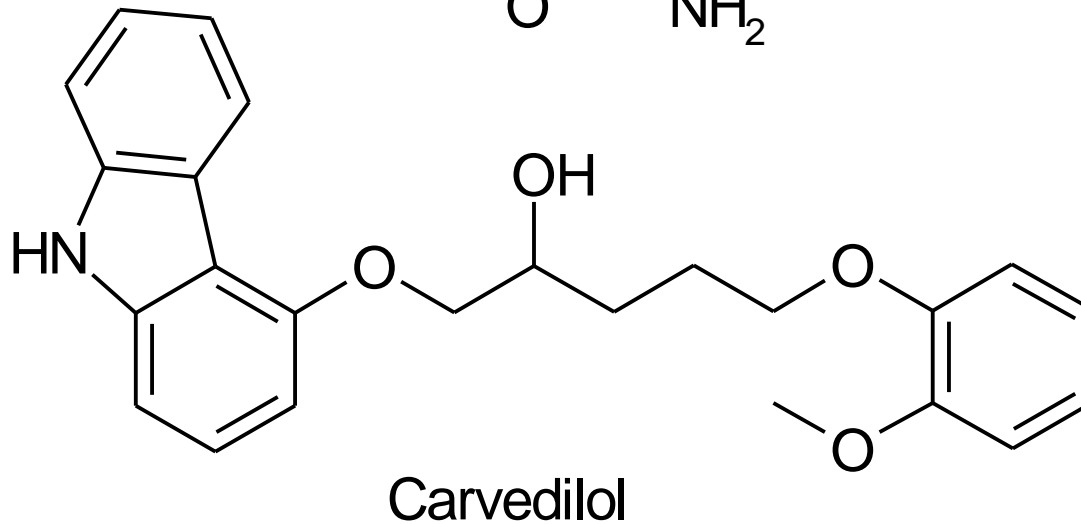
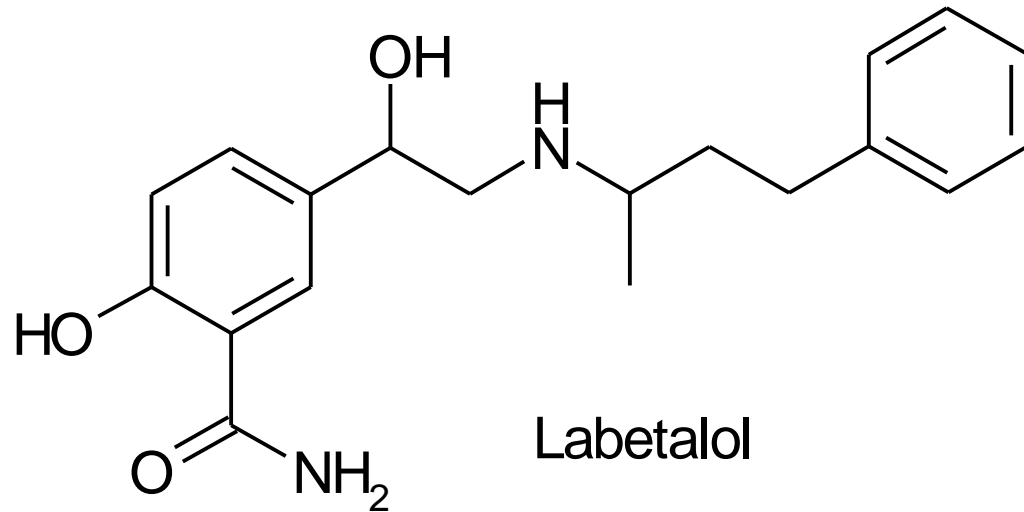
Bisoprolol

**Fig. 11.16.** Selective  $\beta_1$ -adrenergic antagonists.

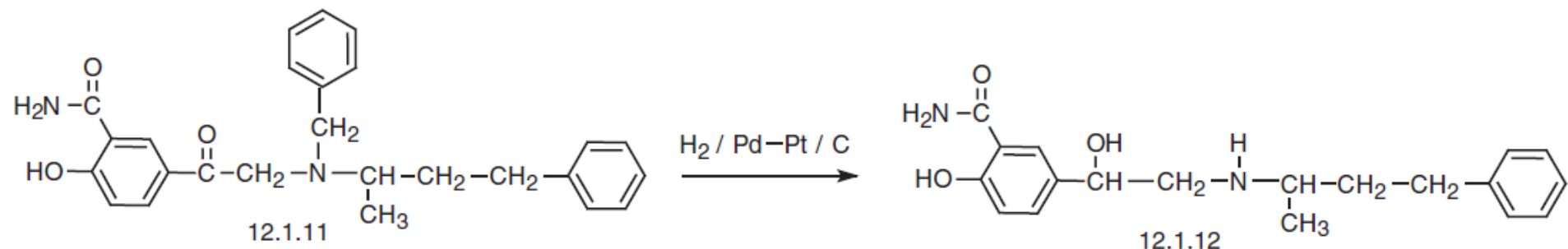
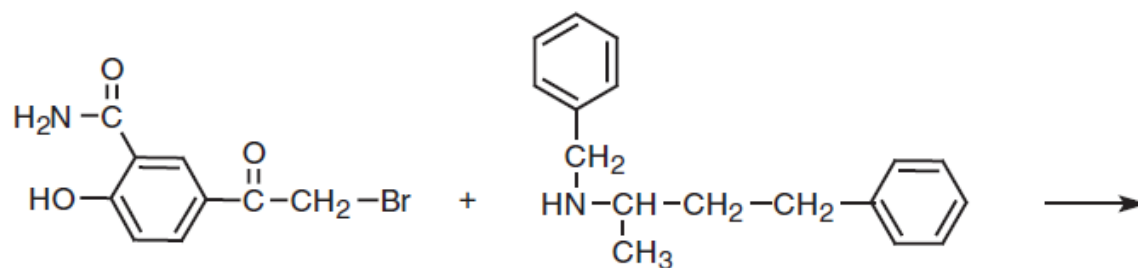


# Mixed $\beta$ + $\alpha$ antagonists

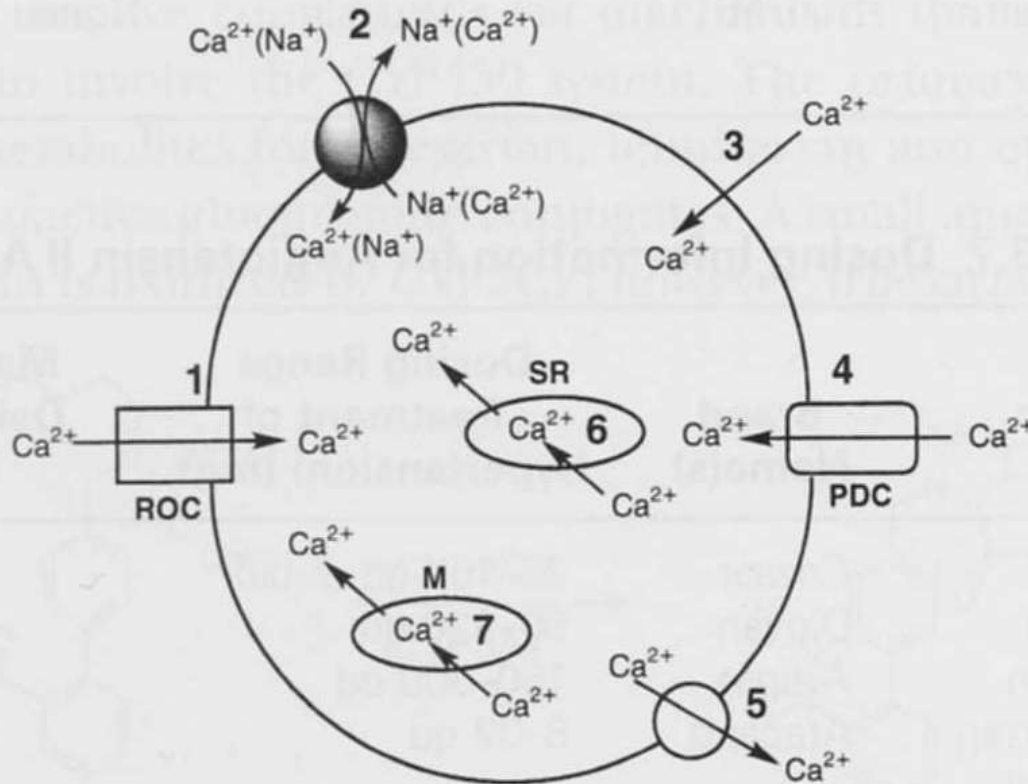
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# Labetalol synthesis



# Ca<sup>2+</sup> blockers

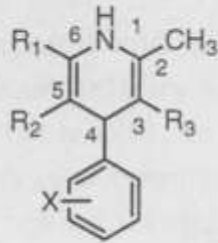


**Fig. 23.20.** Cellular mechanisms for the influx, efflux, and sequestering of Ca<sup>2+</sup>. Key: ROC = receptor-operated Ca<sup>2+</sup> channels; PDC = potential-dependent Ca<sup>2+</sup> channels; SR = sarcoplasmic reticulum; M = mitochondria.

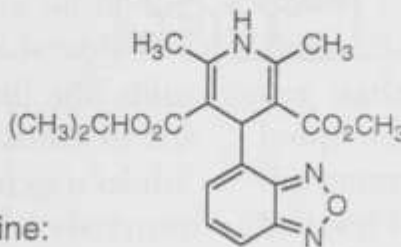
# Ca<sup>2+</sup>blockers

- Verapamil, diltiazem
- dihydropyridines

General structure:

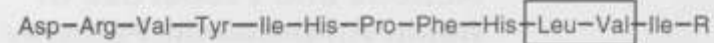


Isradipine:



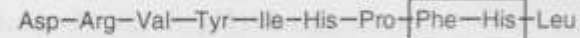
Compounds	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X
Amlodipine	CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	2-Cl
Felodipine	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	2,3-Cl <sub>2</sub>
Nicardipine	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> -NH-CH <sub>2</sub> ·C <sub>6</sub> H <sub>5</sub>	CO <sub>2</sub> CH <sub>3</sub>	3-NO <sub>2</sub>
Nifedipine	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	2-NO <sub>2</sub>
Nimodipine	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CH <sub>2</sub> OCH <sub>3</sub>	CO <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	3-NO <sub>2</sub>
Nisoldipine	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CH(CH <sub>3</sub> ) <sub>2</sub>	CO <sub>2</sub> CH <sub>3</sub>	2-NO <sub>2</sub>

# RAA system



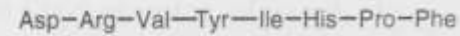
Angiotensinogen

↓  
*Renin*



Angiotensin I

↓  
*Angiotensin  
Converting  
Enzyme*



Angiotensin II

↓  
*Aminopeptidase*



Angiotensin III

↓  
*Endo- and Exopeptidase*

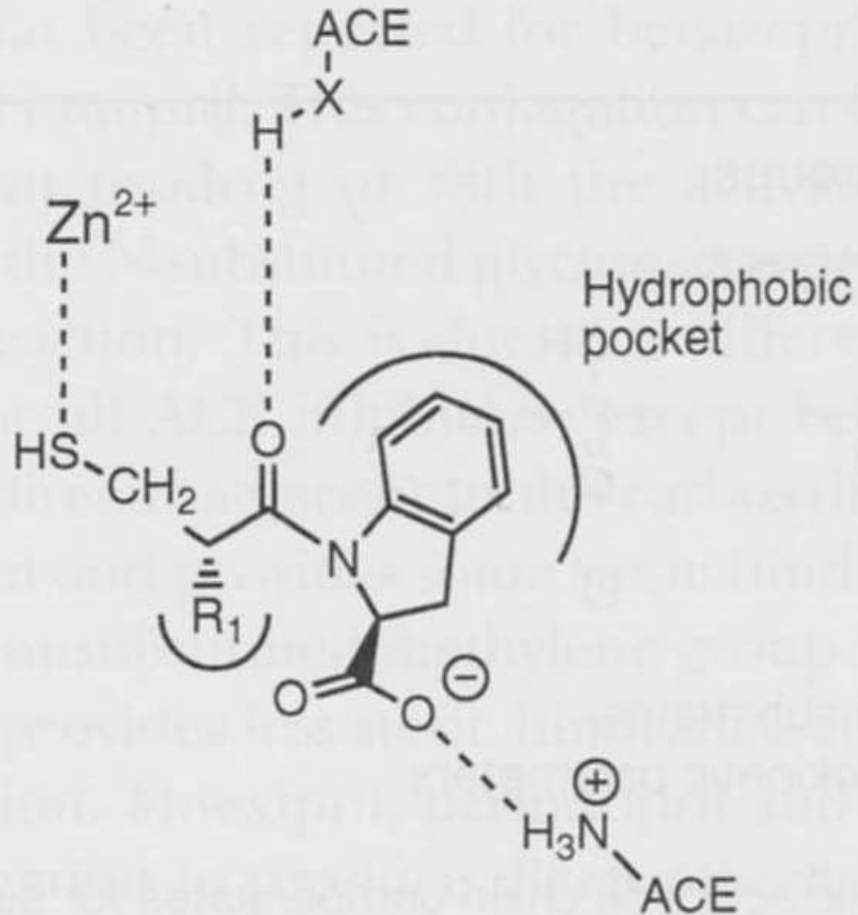
Inactive Peptides



Angiotensin 1-7

*Prolyl-endopeptidase*

# ACE inhibitors – mechanism of action

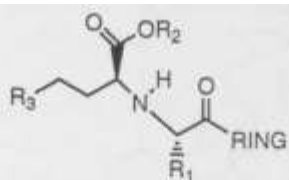


**Fig. 23.10.** A modified model of ACE inhibitor binding.

# ACE



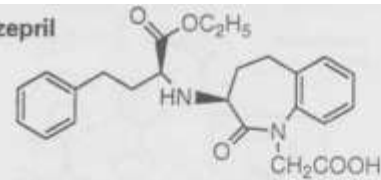
General Structure:



Compounds

Ring

Benazepril

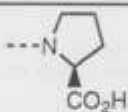


R<sub>1</sub>

R<sub>2</sub>

R<sub>3</sub>

Lisinopril

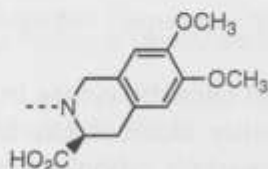


(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>

H



Moexipril

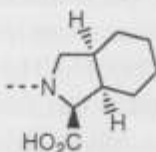


CH<sub>3</sub>

CH<sub>2</sub>CH<sub>3</sub>



Perindopril

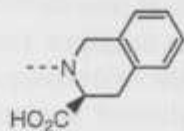


CH<sub>3</sub>

CH<sub>2</sub>CH<sub>3</sub>

CH<sub>3</sub>

Quinapril

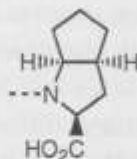


CH<sub>3</sub>

CH<sub>2</sub>CH<sub>3</sub>



Ramipril

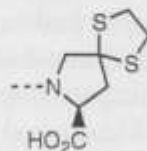


CH<sub>3</sub>

CH<sub>2</sub>CH<sub>3</sub>



Spirapril

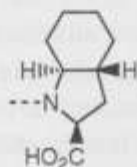


CH<sub>3</sub>

CH<sub>2</sub>CH<sub>3</sub>



Trandolapril



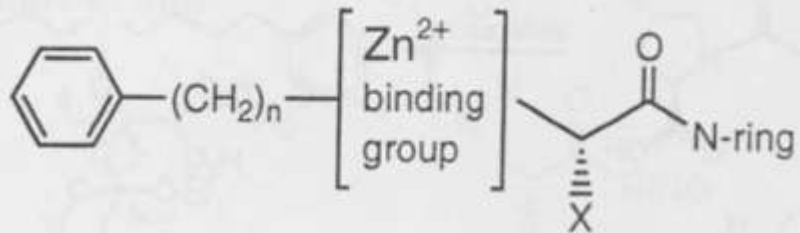
CH<sub>3</sub>

CH<sub>2</sub>CH<sub>3</sub>

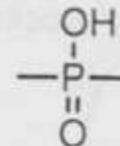
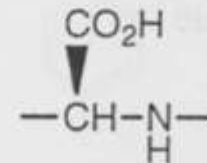


# ACE inhibitors

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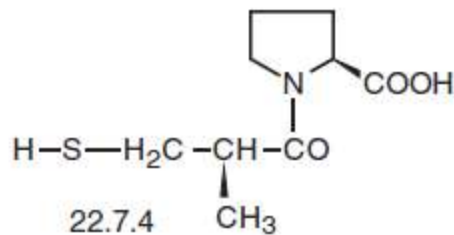
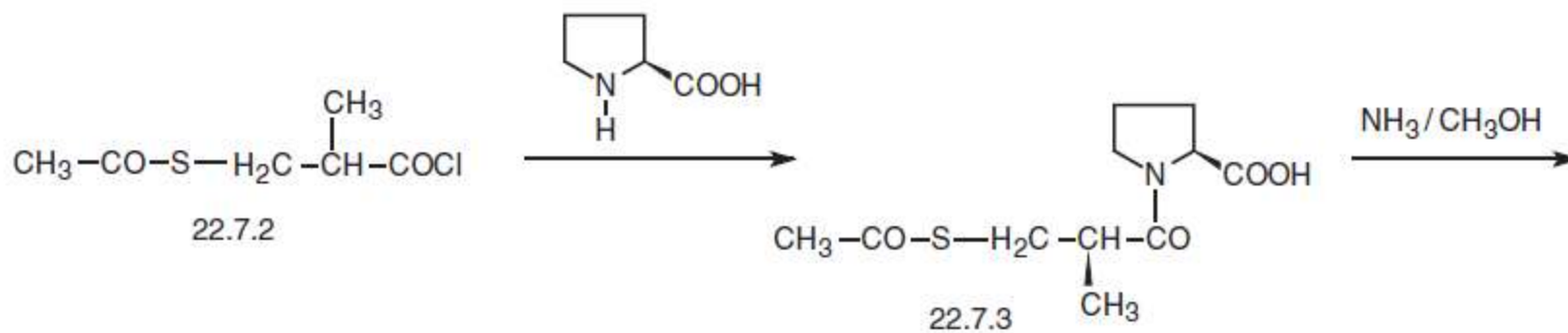
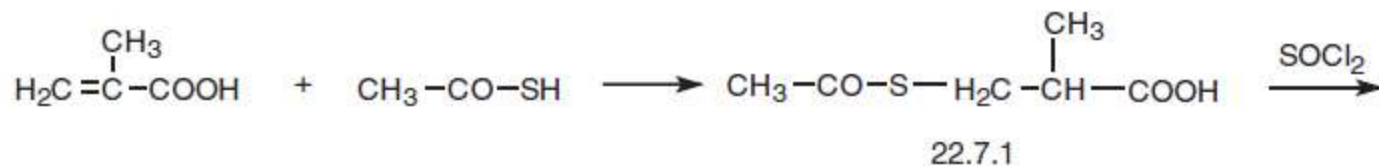


Zn<sup>2+</sup> binding groups

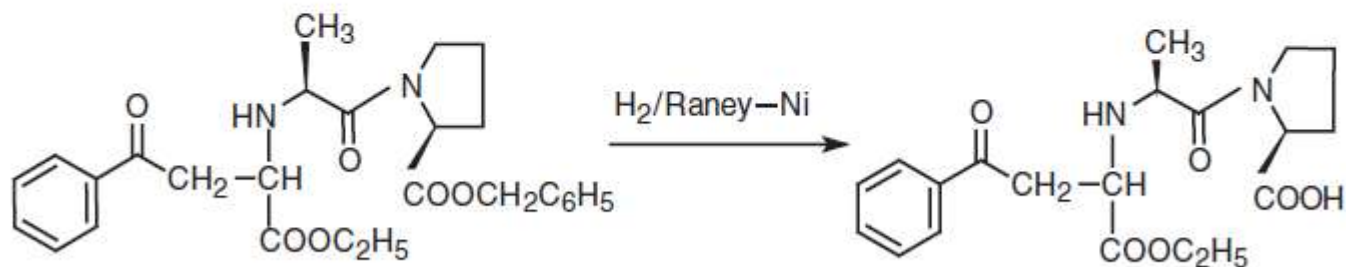
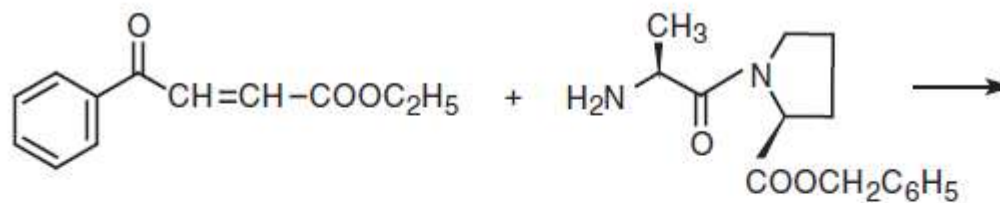




# Captopril synthesis



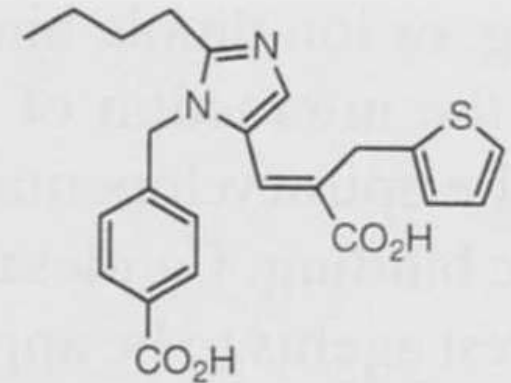
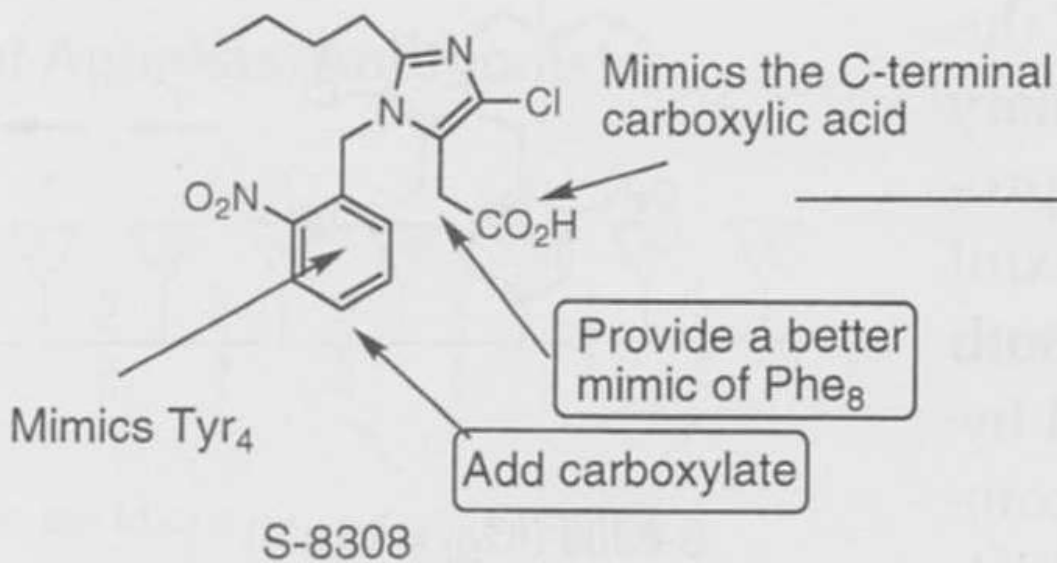
# Enalapril synthesis



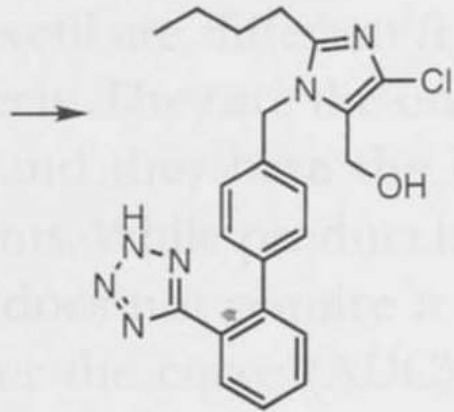
22.7.11

22.7.12

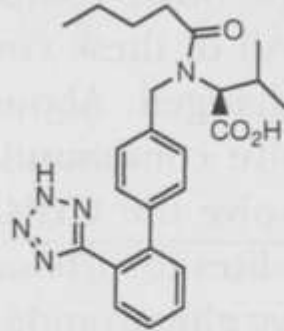
# Angiotensin II inhibitors



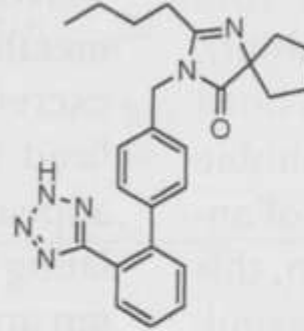
# Angiotensin II inhibitors



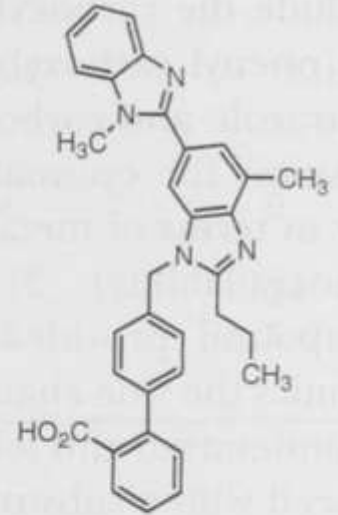
Losartan ( $IC_{50} = 0.019\mu M$ )



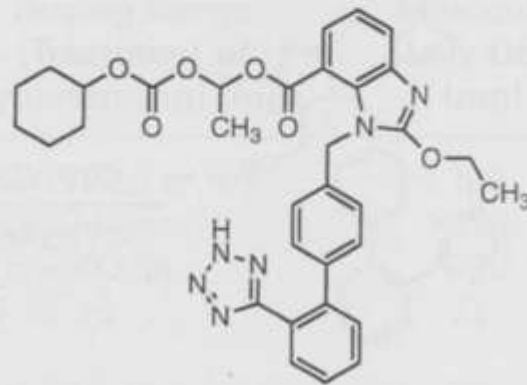
Valsartan



Irbesartan

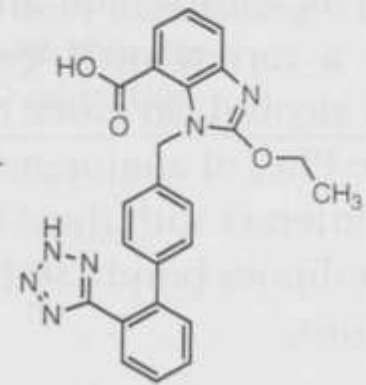


Telmisartan



Candesartan cilexetil

in vivo



Candesartan