

# Antihypertensives

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# Hypertension

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- chronic 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



# Hypertensive crisis

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- acute blood pressure  $>180/120$  mmHg
- may damage vessels, cause heart attack or stroke

# Hypertension – drug therapy

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- Diuretics
- Aldosterone receptor antagonists
- Renin inhibitors
- Angiotensin II receptor antagonists
- ACE inhibitors
- Endothelin receptor antagonists
- Vasodilators
- Betablockers
- $\alpha_2$  – adrenergic receptor antagonists
- $\text{Ca}^{2+}$  channel blockers

# Hypertension – drug therapy

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Topics of other lectures:

- Diuretics
- Aldosterone receptor antagonists
- Betablockers
- $\alpha_2$  – adrenergic receptor antagonists

# Vasodilators

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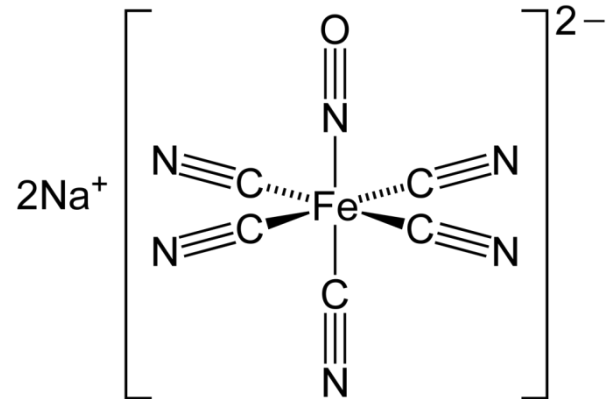


## Sodium Nitroprusside

releasing NO – rapid peripheral vasodilatation

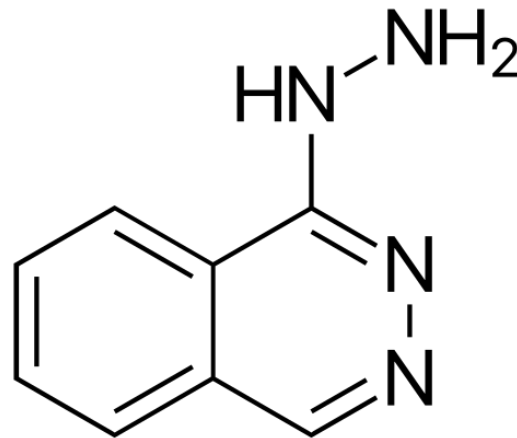
short acting

used in emergencies (malignant hypertension, aortic dissection)



# Vasodilators

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## **Hydralazine**

short term effect

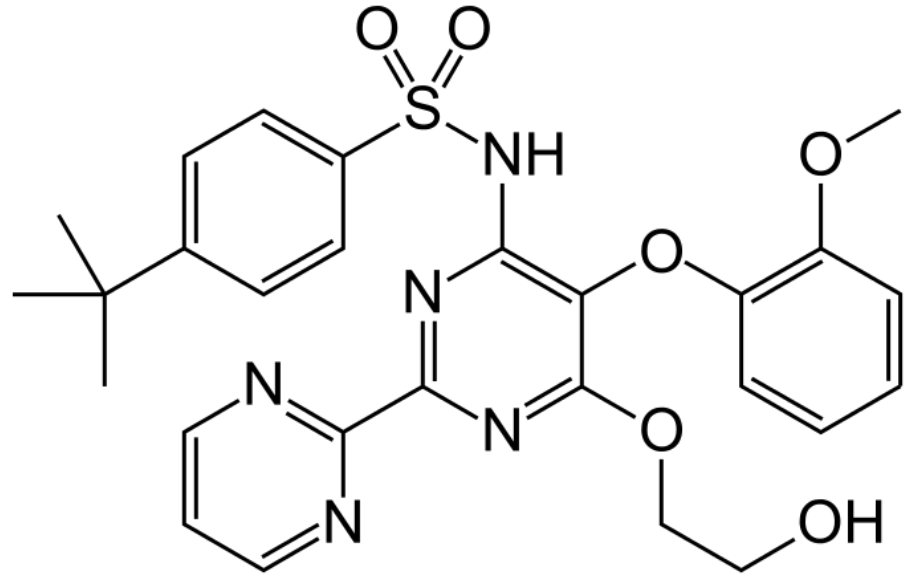
used for long time administration only in the combination with betablockers or diuretics

treatment of hypertension in pregnancy

# Endothelin inhibitors

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## Bosentan



competitive antagonist of endothelin-1

endothelin-1 causes constriction of the pulmonary vessels

therapy of pulmonary hypertension

risk of hepatotoxicity – liver functions has to be monitored



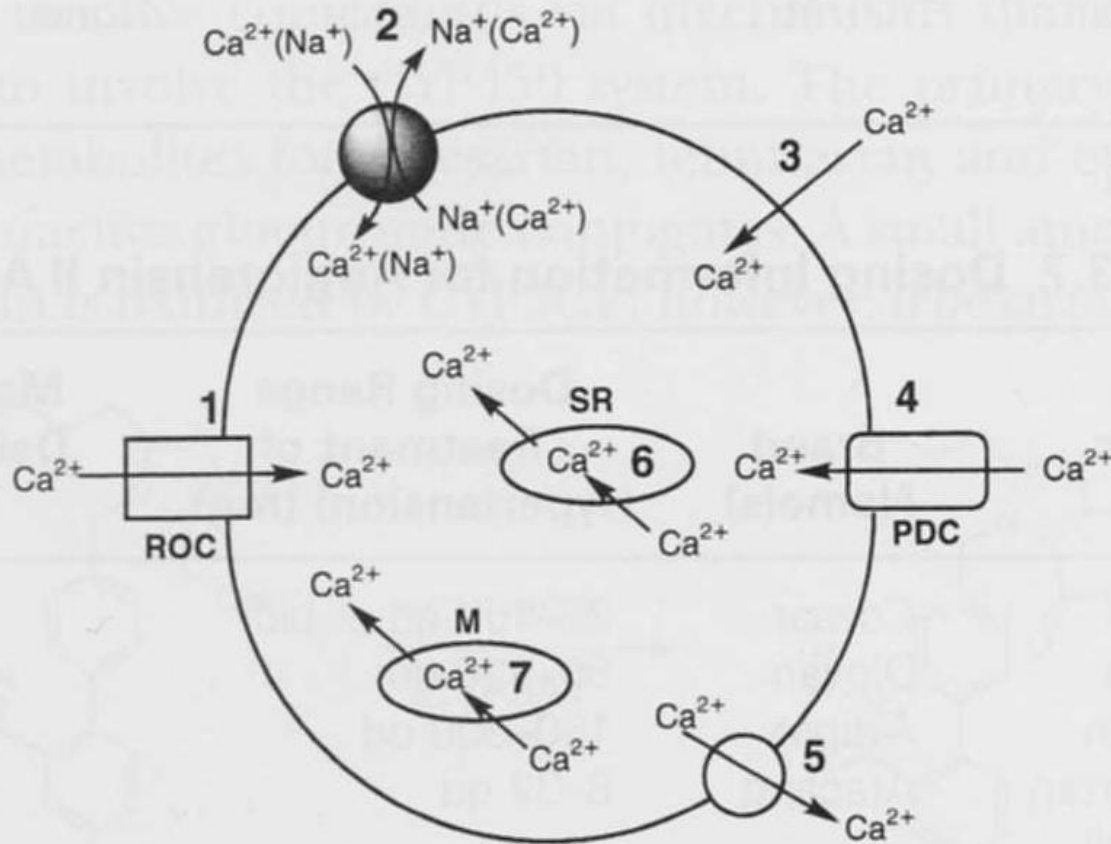


# Ca<sup>2+</sup>blockers

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- dihydropyridines
- non-dihydropyridines

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

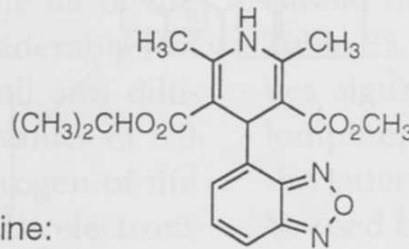
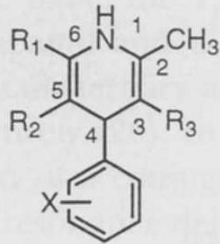


**Fig. 23.20.** Cellular mechanisms for the influx, efflux, and sequestering of Ca<sup>2+</sup>. Key: ROC = receptor-operated Ca<sup>2+</sup> channels; PDC = potential-dependent Ca<sup>2+</sup> channels; SR = sarcoplasmic reticulum; M = mitochondria.

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

## dihydropyridines

General structure:



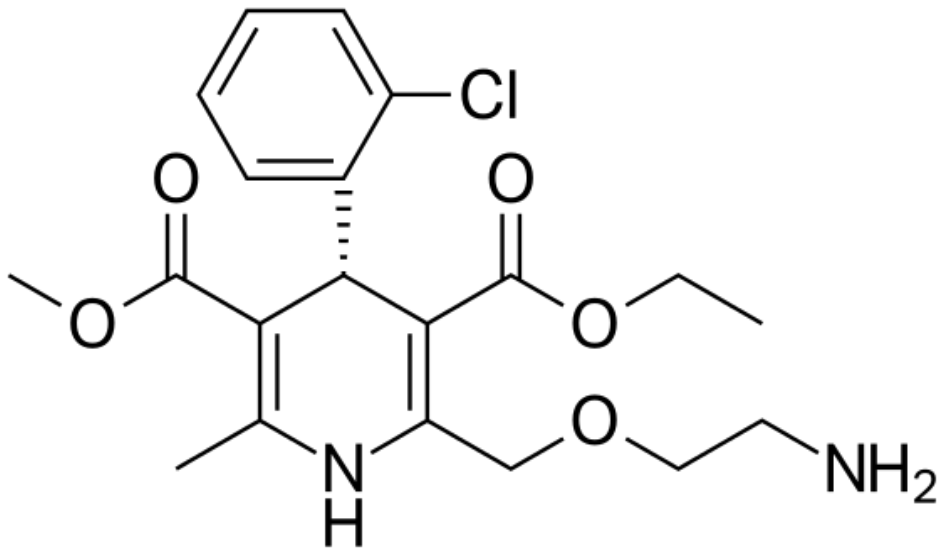
Compounds	R <sub>1</sub>	R <sub>2</sub>	R <sub>3</sub>	X
Amlodipine	CH <sub>2</sub> OCH <sub>2</sub> CH <sub>2</sub> NH <sub>2</sub>	CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CO <sub>2</sub> CH <sub>3</sub>	2-Cl
Felodipine	CH <sub>3</sub>	CO <sub>2</sub> CH <sub>2</sub> CH <sub>3</sub>	CO <sub>2</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>

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

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□ now marketed more than 20 derivatives

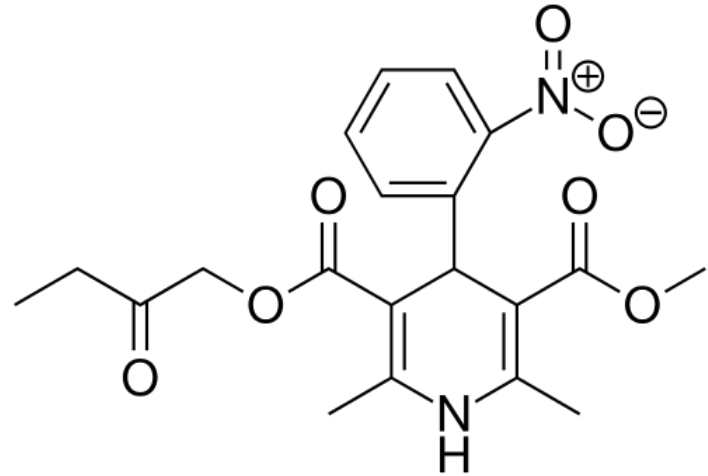
**levamlodipine:** pure enantiomer of amlodipine,  
lower occurrence of edema adverse effect



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

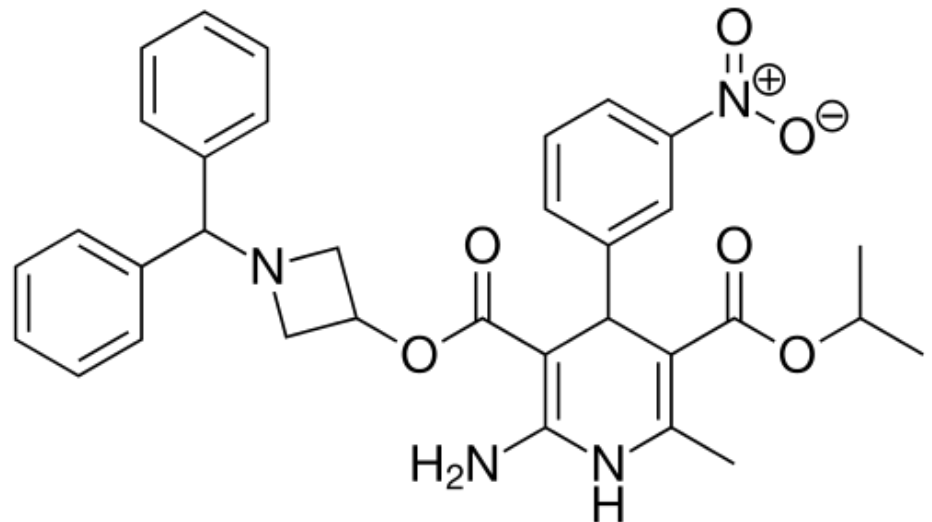
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## Aranidipine



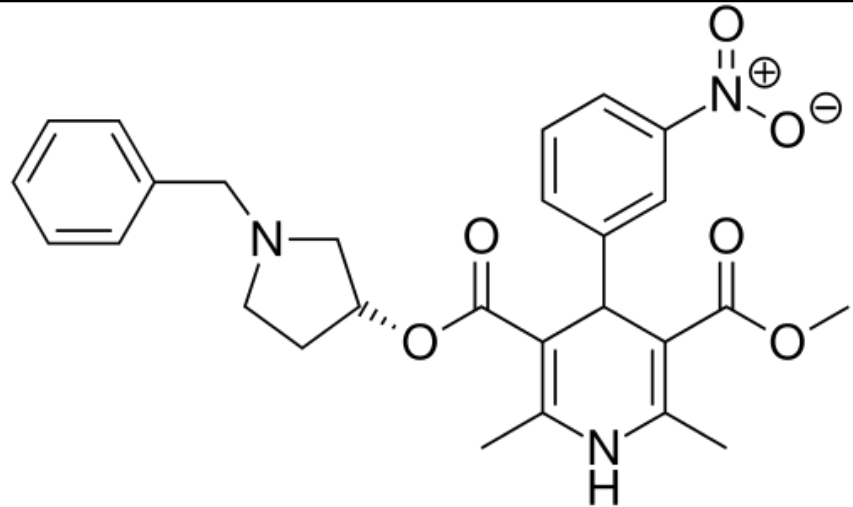
## Azelnidipine

both marketed in Japan

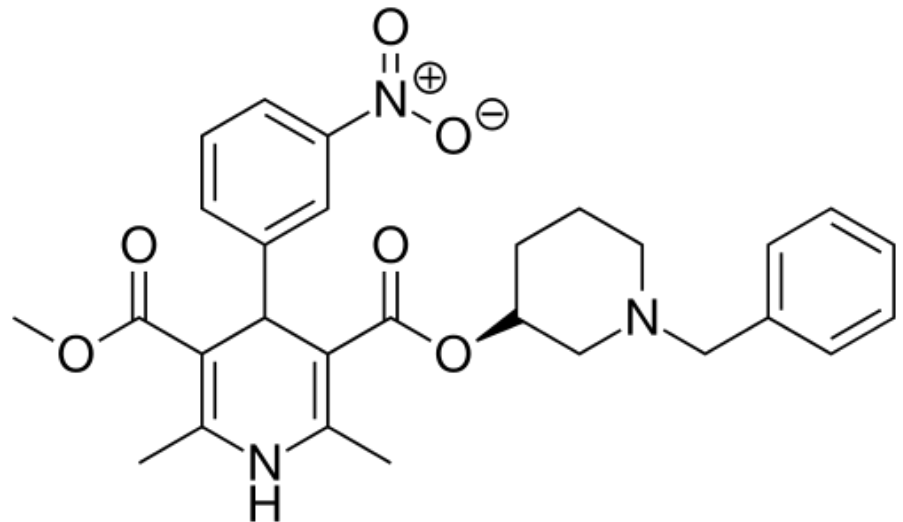


# Ca<sup>2+</sup>blockers

## Barnidipine



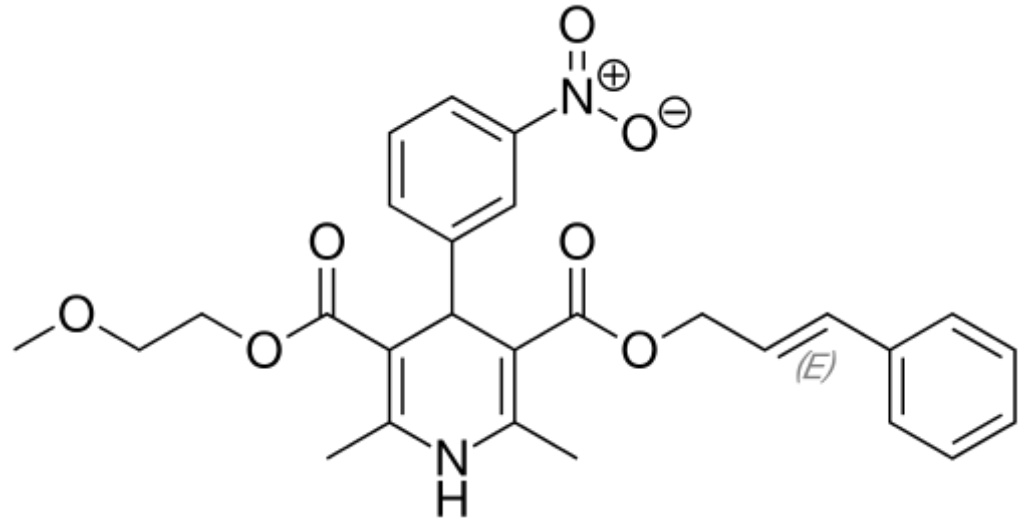
## Benidipine



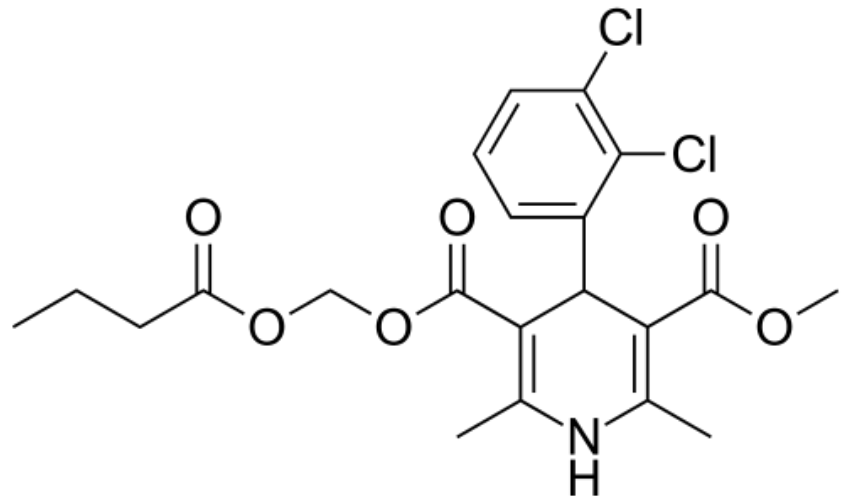
# Ca<sup>2+</sup>blockers

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## Cilnidipine



## Clevidipine

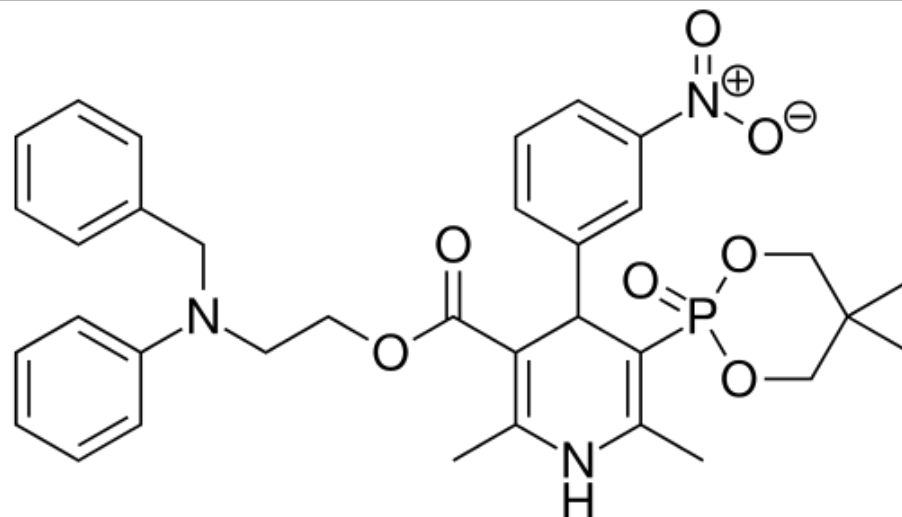


# Ca<sup>2+</sup>blockers

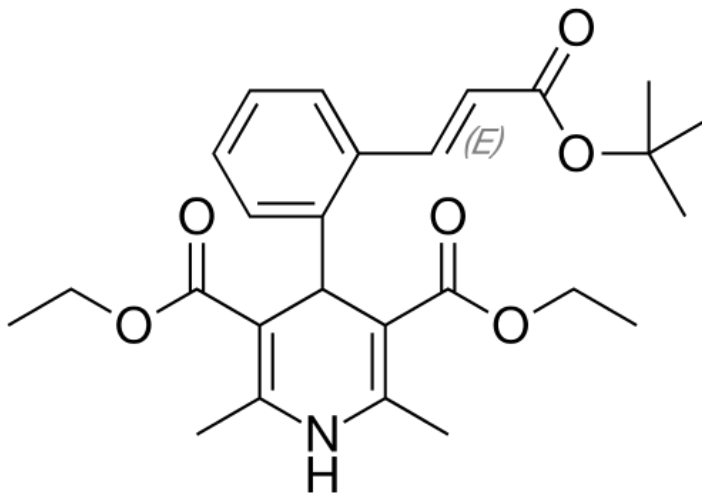
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## Efonidipine

marketed in Japan



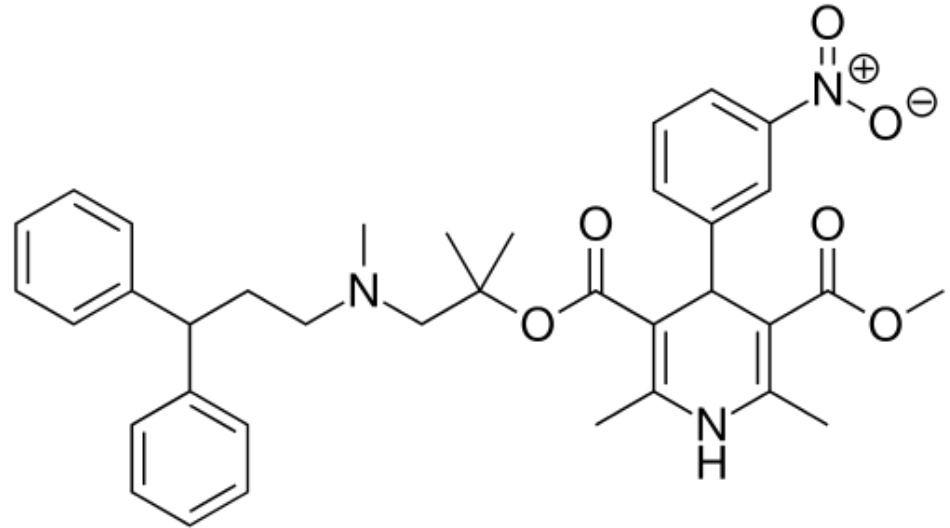
## Lacidipine



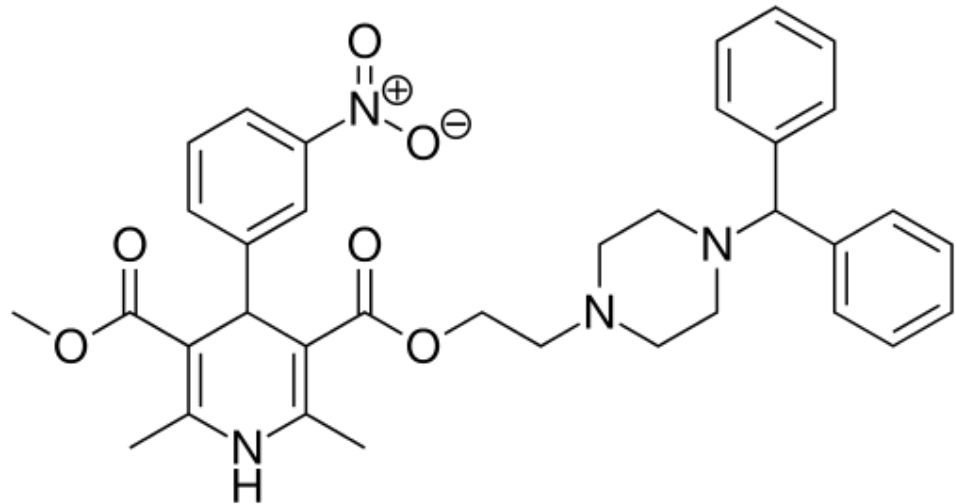


# Ca<sup>2+</sup>blockers

## Lercanidipine



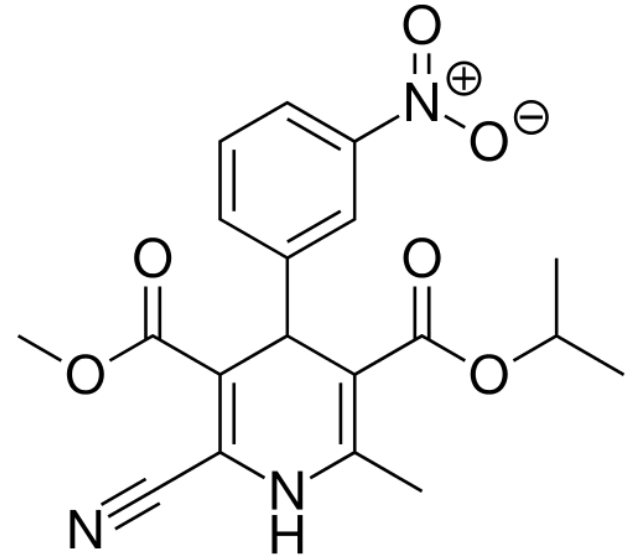
## Manidipine



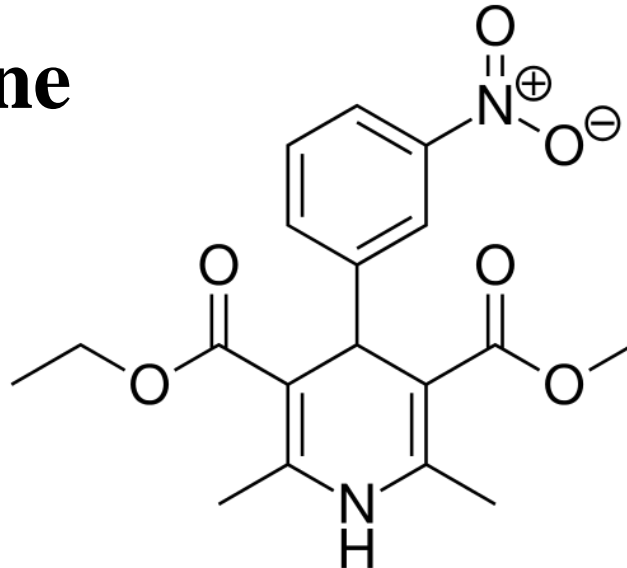
# Ca<sup>2+</sup>blockers

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## Nitvadipine



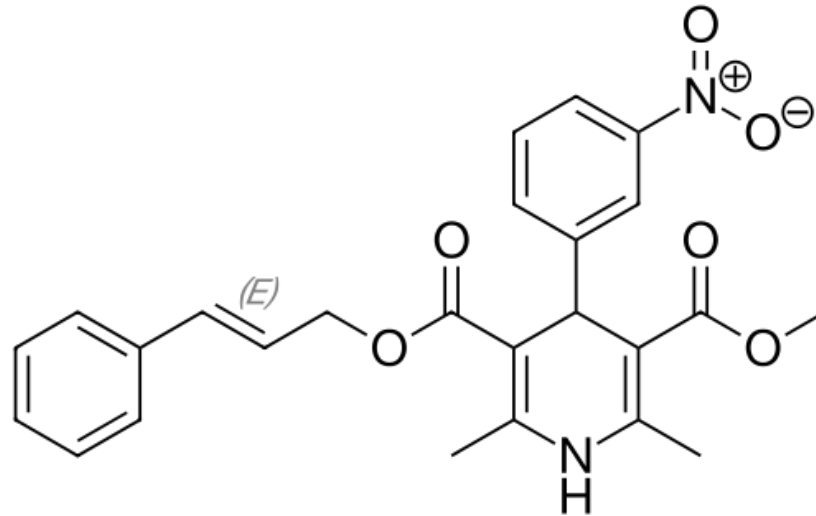
## Nitrendipine



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

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## Pranidipine





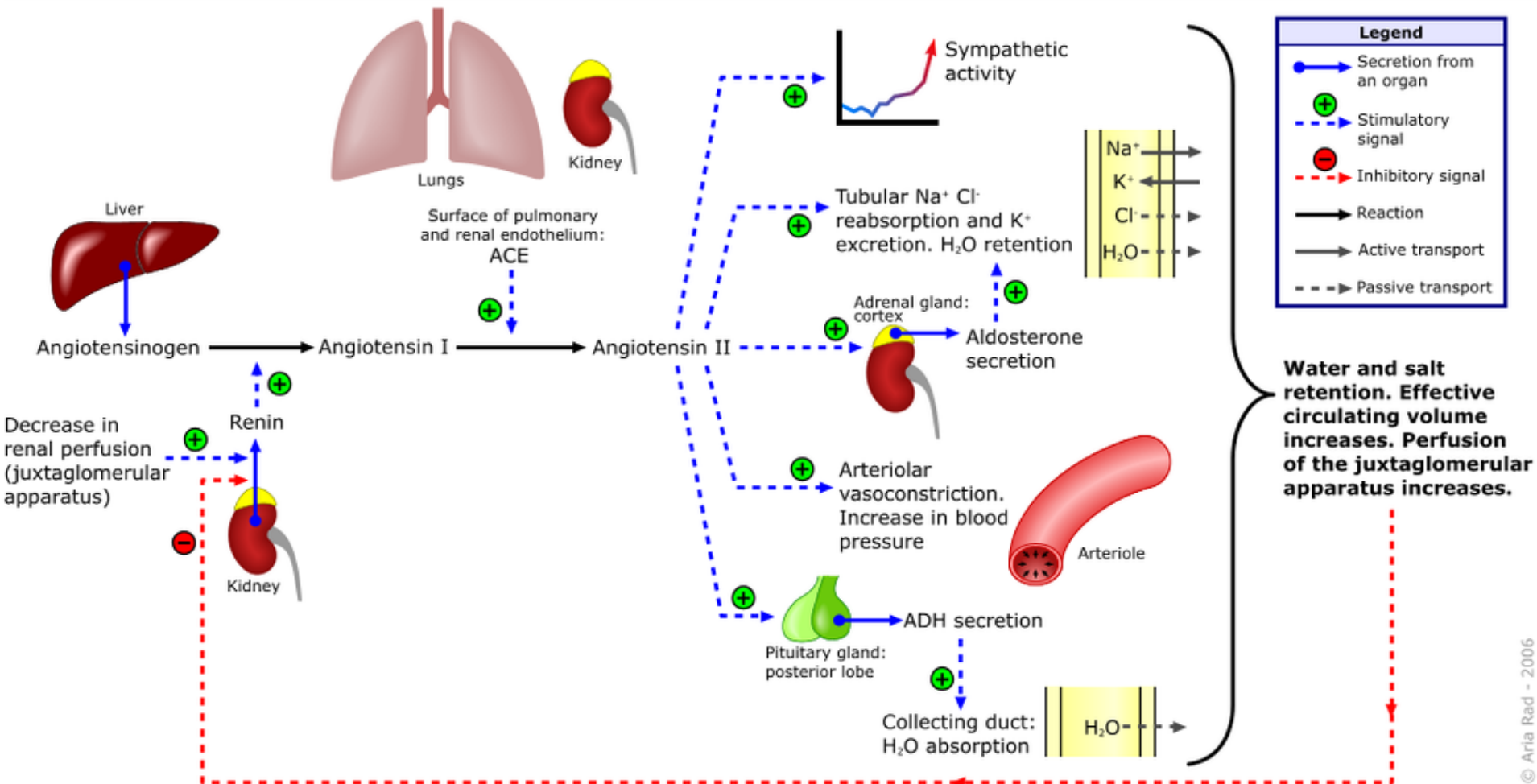
# Ca<sup>2+</sup>blockers

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- non-dihydropyridines:
- **verapamil**
- **diltiazem**

# RAA system

## Renin-angiotensin-aldosterone system



# RAA system biochemistry

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*

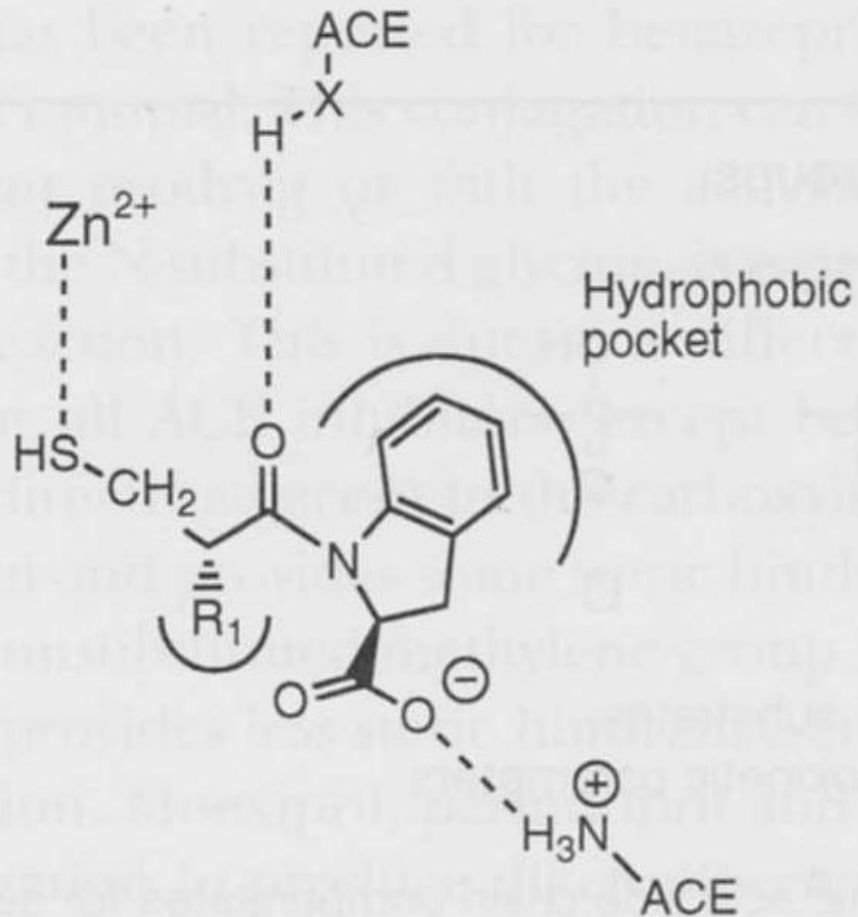
Inactive Peptides

Asp-Arg-Val-Tyr-Ile-His-Pro

Angiotensin 1-7

*Prolyl-endopeptidase*

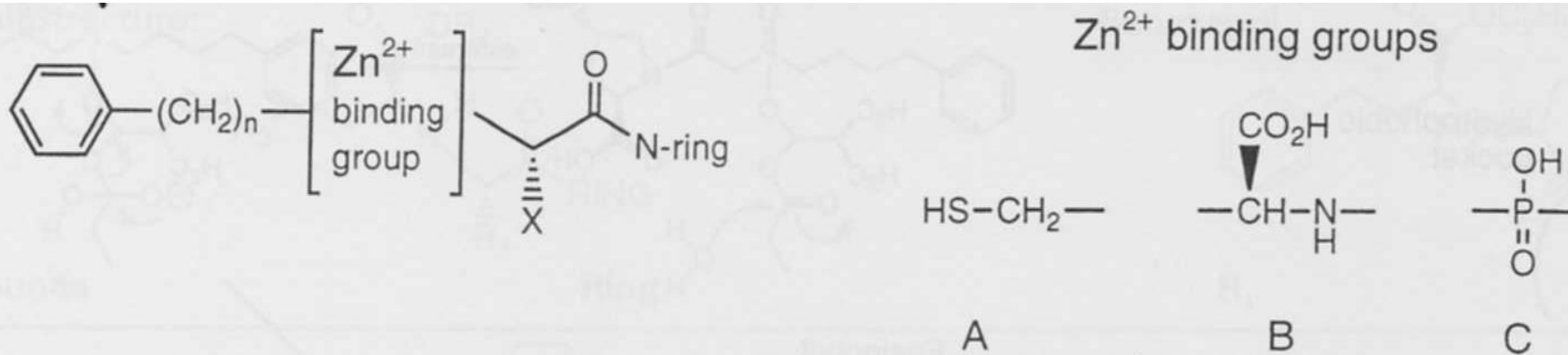
# ACE inhibitors – mechanism of action



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

# ACE inhibitors: general structure

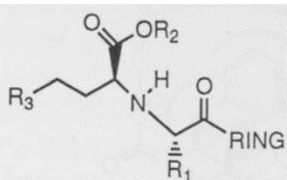
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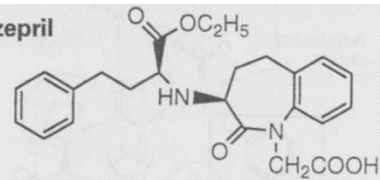


# ACE

General Structure:



Benazepril



Compounds

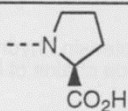
Ring

R<sub>1</sub>

R<sub>2</sub>

R<sub>3</sub>

Lisinopril

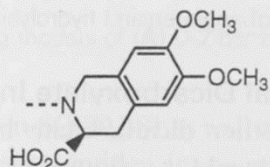


(CH<sub>2</sub>)<sub>4</sub>NH<sub>2</sub>

H



Moexipril

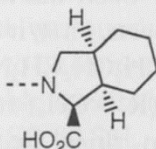


CH<sub>3</sub>

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



Perindopril

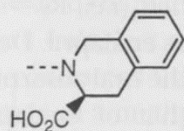


CH<sub>3</sub>

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

CH<sub>3</sub>

Quinapril

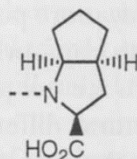


CH<sub>3</sub>

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



Ramipril

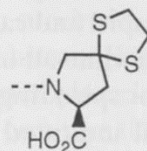


CH<sub>3</sub>

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



Spirapril

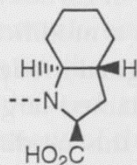


CH<sub>3</sub>

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



Trandolapril



CH<sub>3</sub>

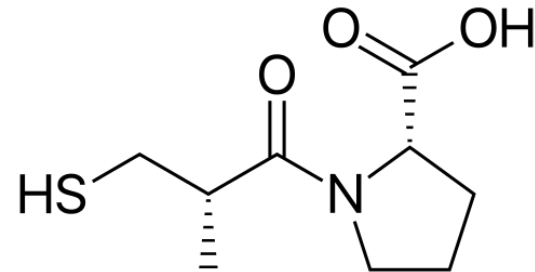
CH<sub>2</sub>CH<sub>3</sub>



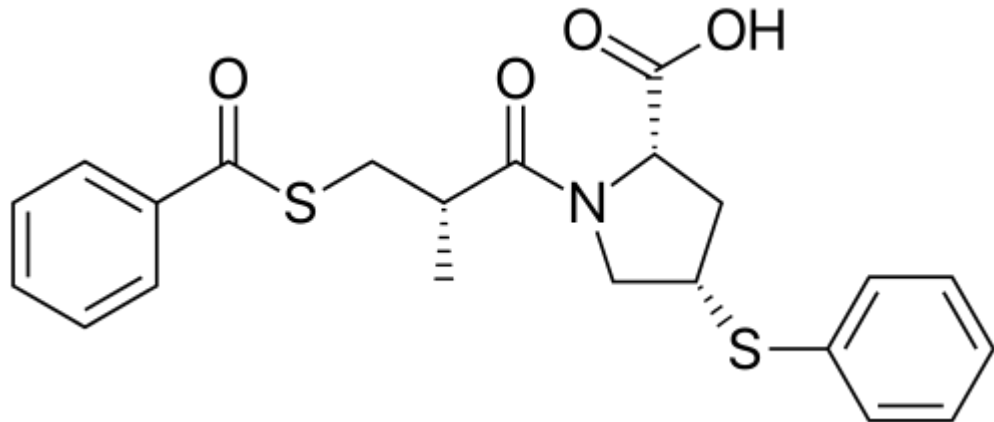
# ACE inhibitors

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**Captopril** – 2x a day

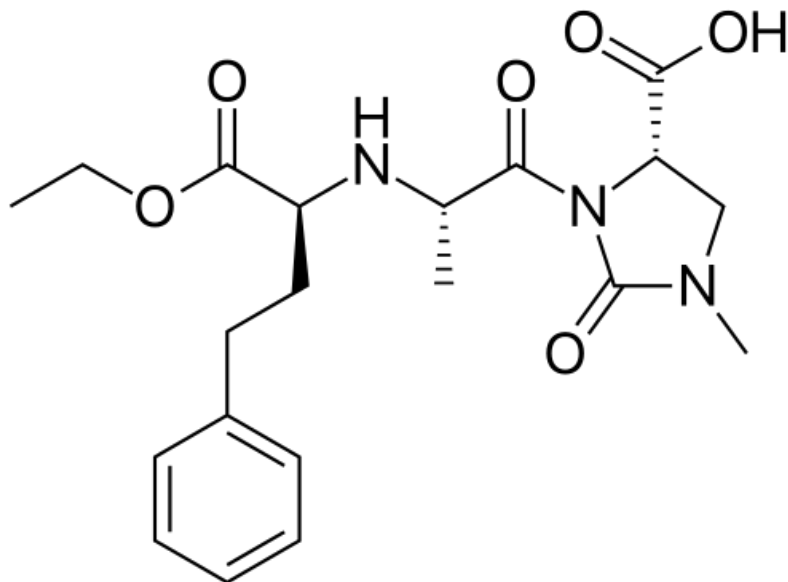


**Zofenopril**

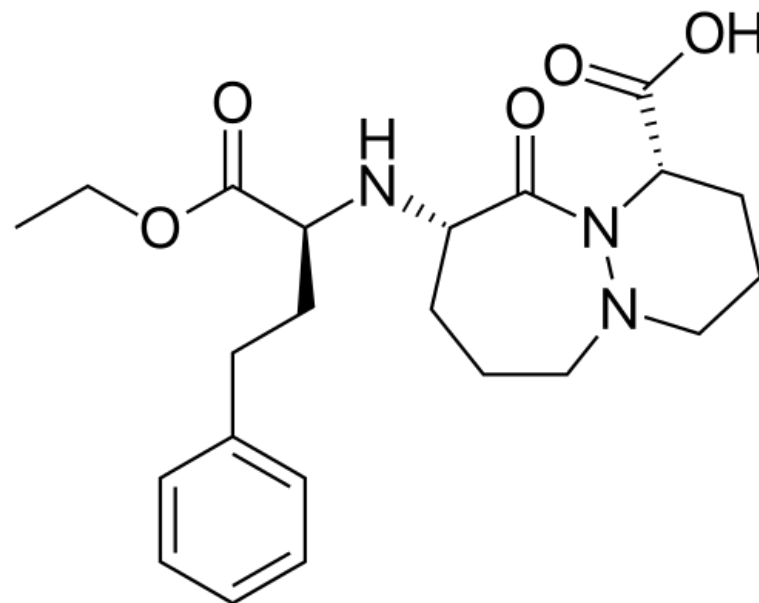


# ACE inhibitors

## Imidapril

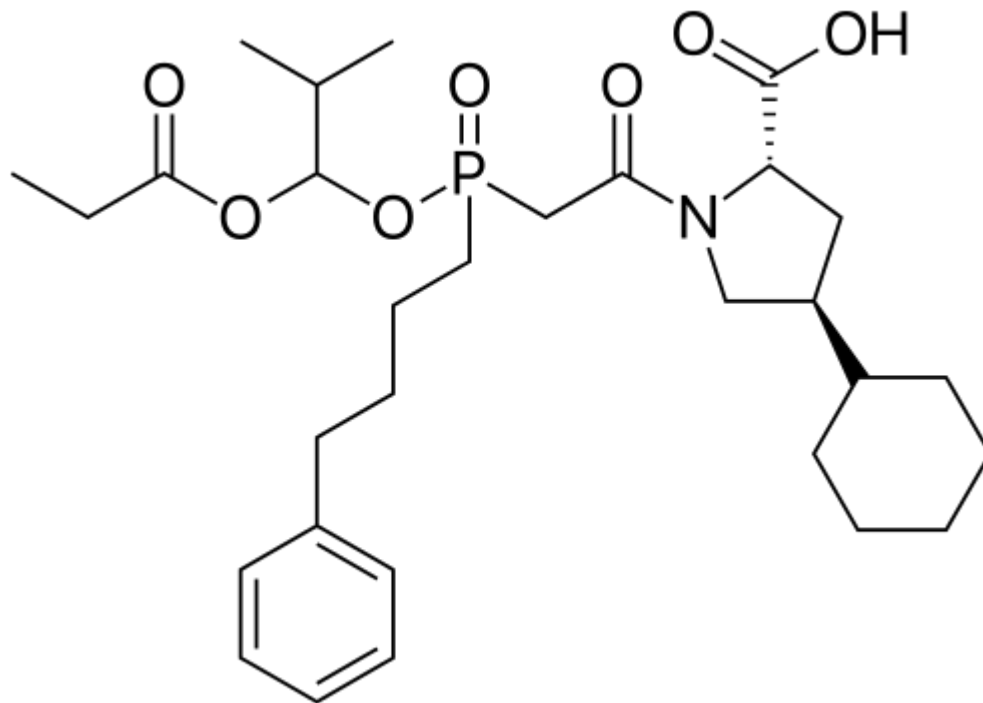


## Cilazapril

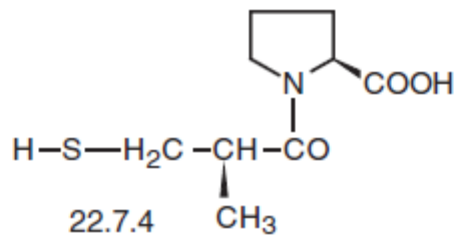
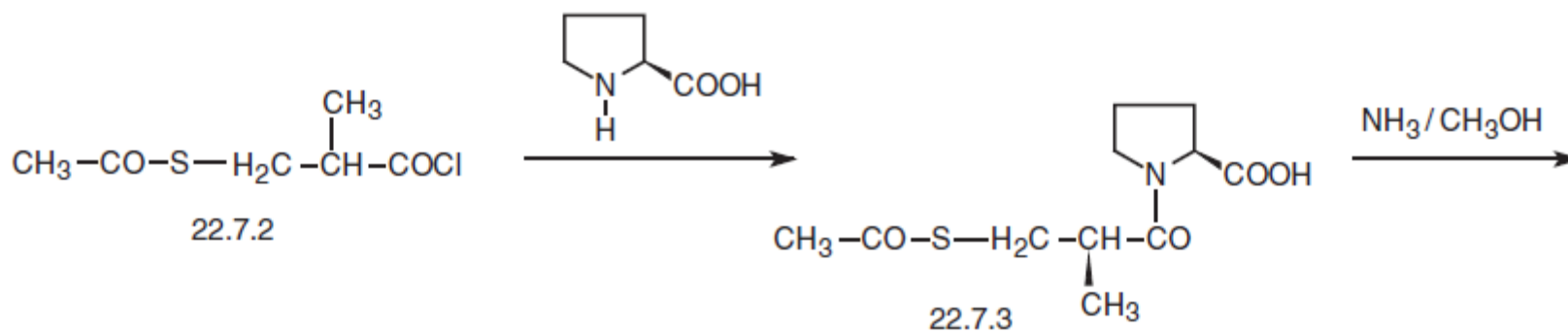
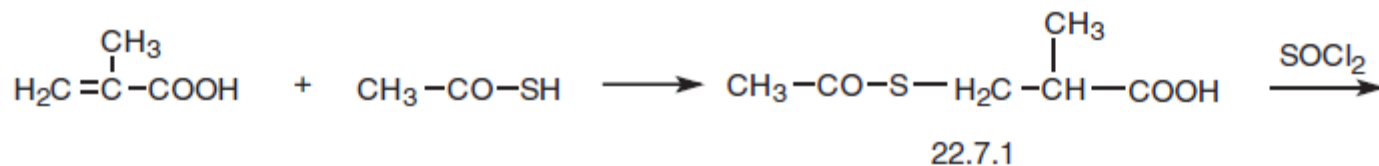


# ACE inhibitors

## Fosinopril

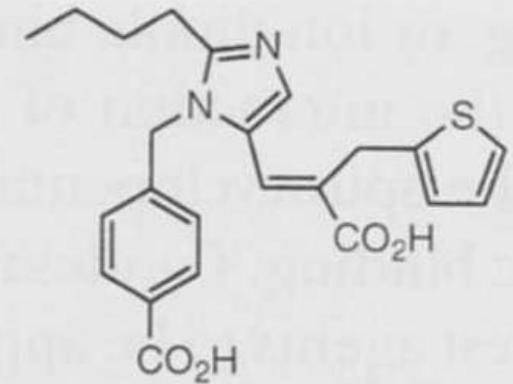
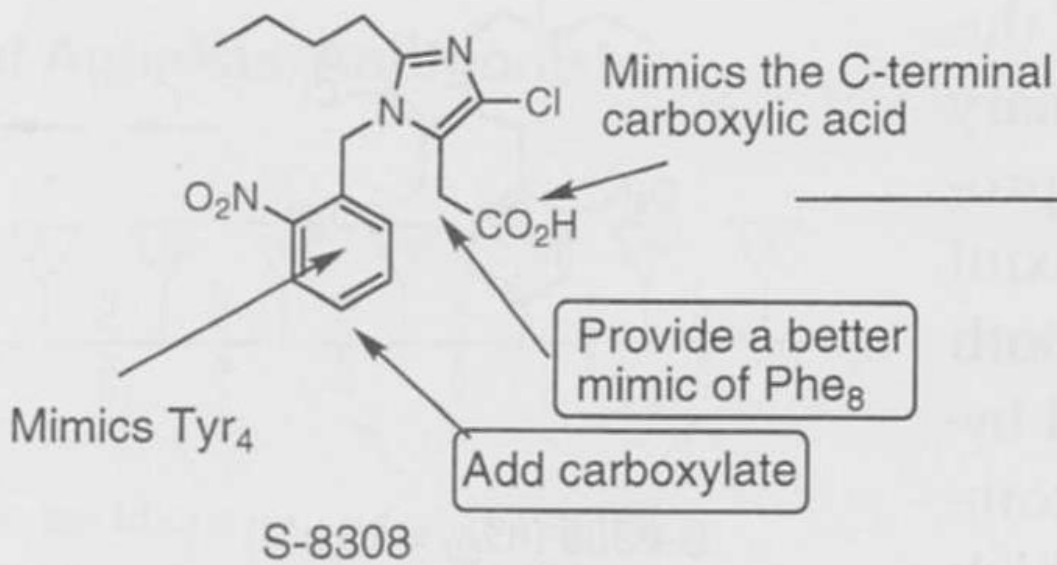


# Captopril synthesis



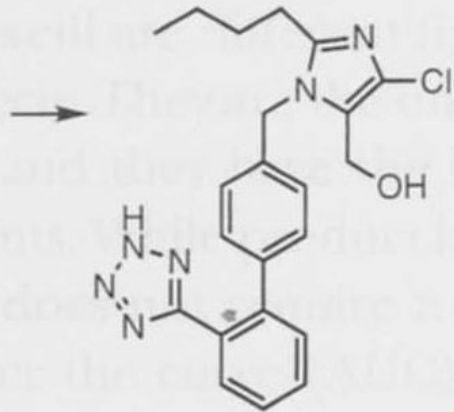


# Angiotensin II inhibitors

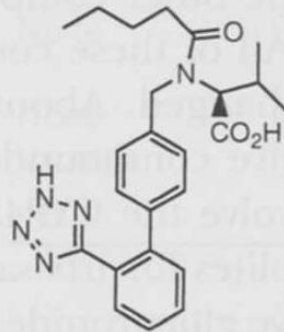


Eprosartan

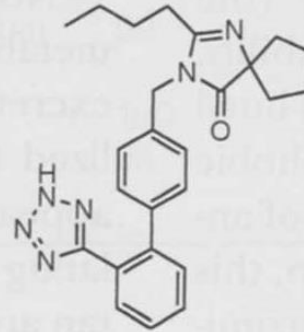
# Angiotensin II inhibitors



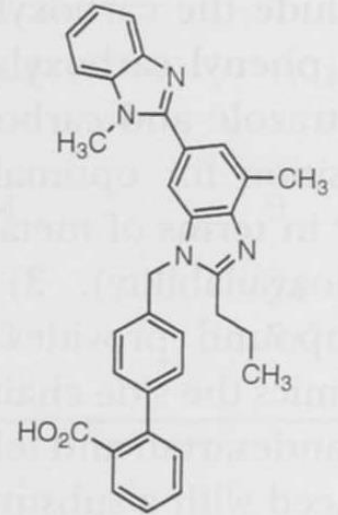
Losartan ( $IC_{50} = 0.019\mu M$ )



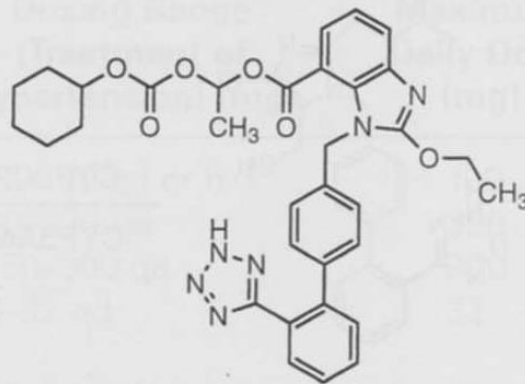
Valsartan



Irbesartan

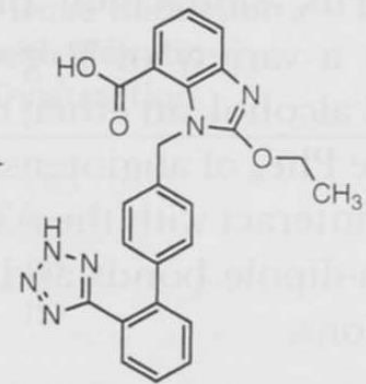


Telmisartan



Candesartan cilexetil

in vivo



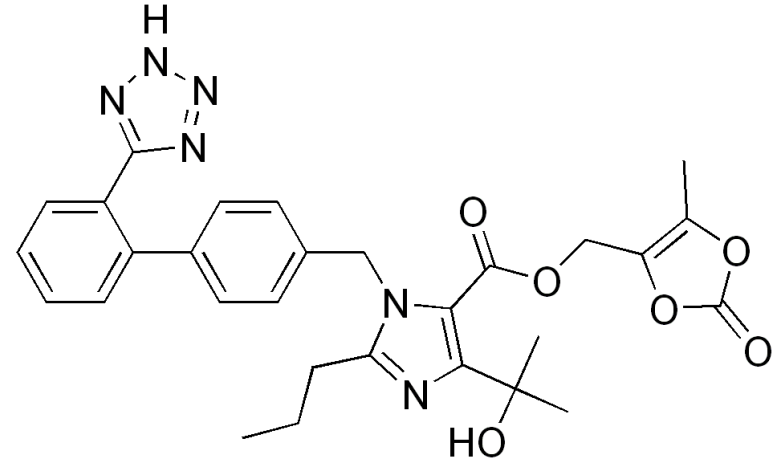
Candesartan



# Angiotensin II inhibitors

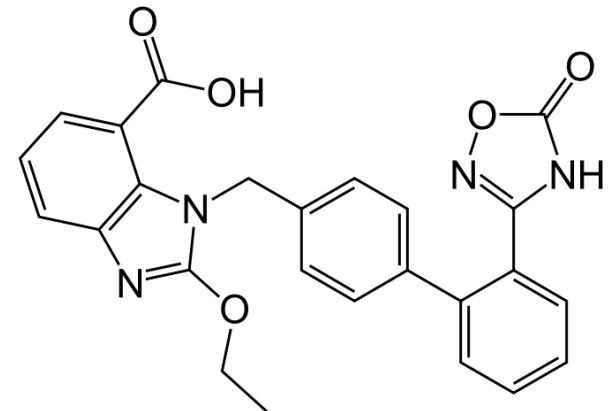
## □ Olmesartan medoxomil

since 2002



## □ Azilsartan

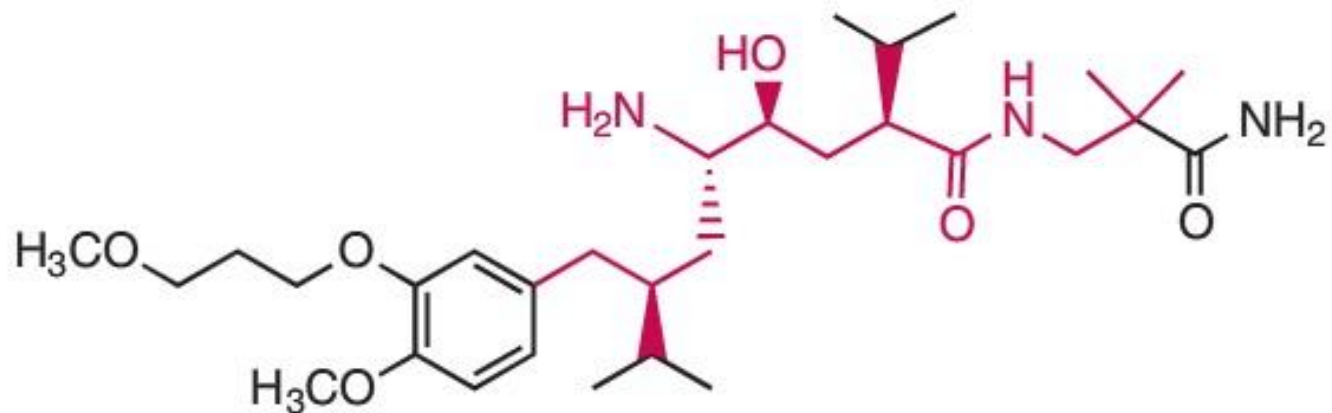
used as medoxomil 2011





# Renin inhibitor

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Aliskiren

used alone or in combination with Ca blockers or diuretics  
since 2006