RAAS sistem
Zaviralci ACE
Zaviralci renina

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23. maj 2013

RAAS

- **R**enin
- **A**ngiotenzin
- **A**ldosteron
- **S**istem

Kompleksen sistem za varčevanje z vodo in elektroliti, vzdrževanje krvnega tlaka.

Regulacija krvnega tlaka

Več regulatornih sistemov

- Centralni – preko simpatika
- Hormonski – RAAS
- Lokalni – NO, Ca^{2+}

Zakaj regulacija krvnega tlaka?

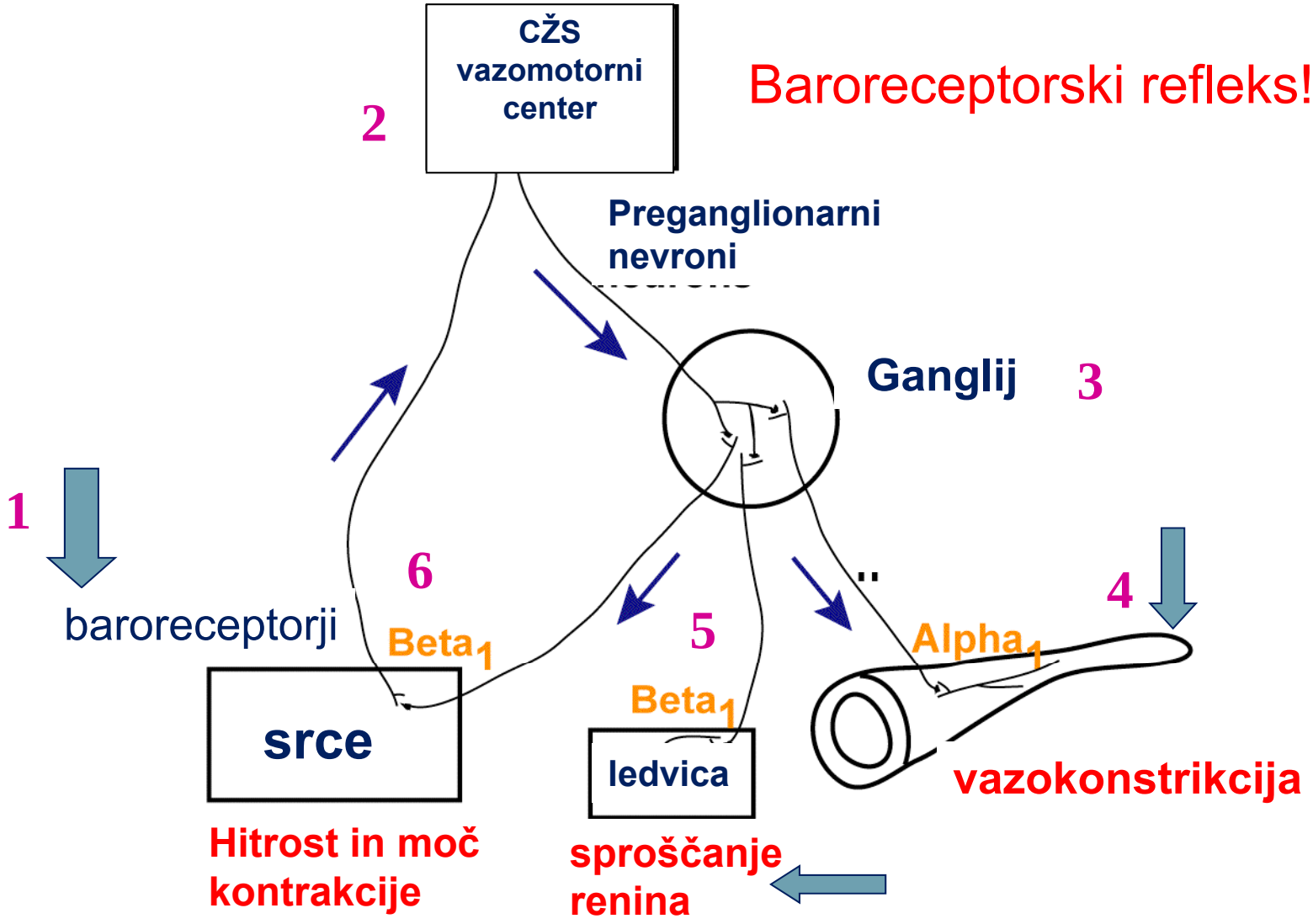
"Prazen žakelj ne stoji pokonci!"

- V zgodovini – zadostna preskrba tkiv s kisikom in hranivi
- Gonilna sila glomerularne filtracije
- Hipotenzija nevarna – izguba zavesti
- Hipertenzija? Kdaj je ugoden spazem žil?

Dejavniki, ki vplivajo na krvni tlak

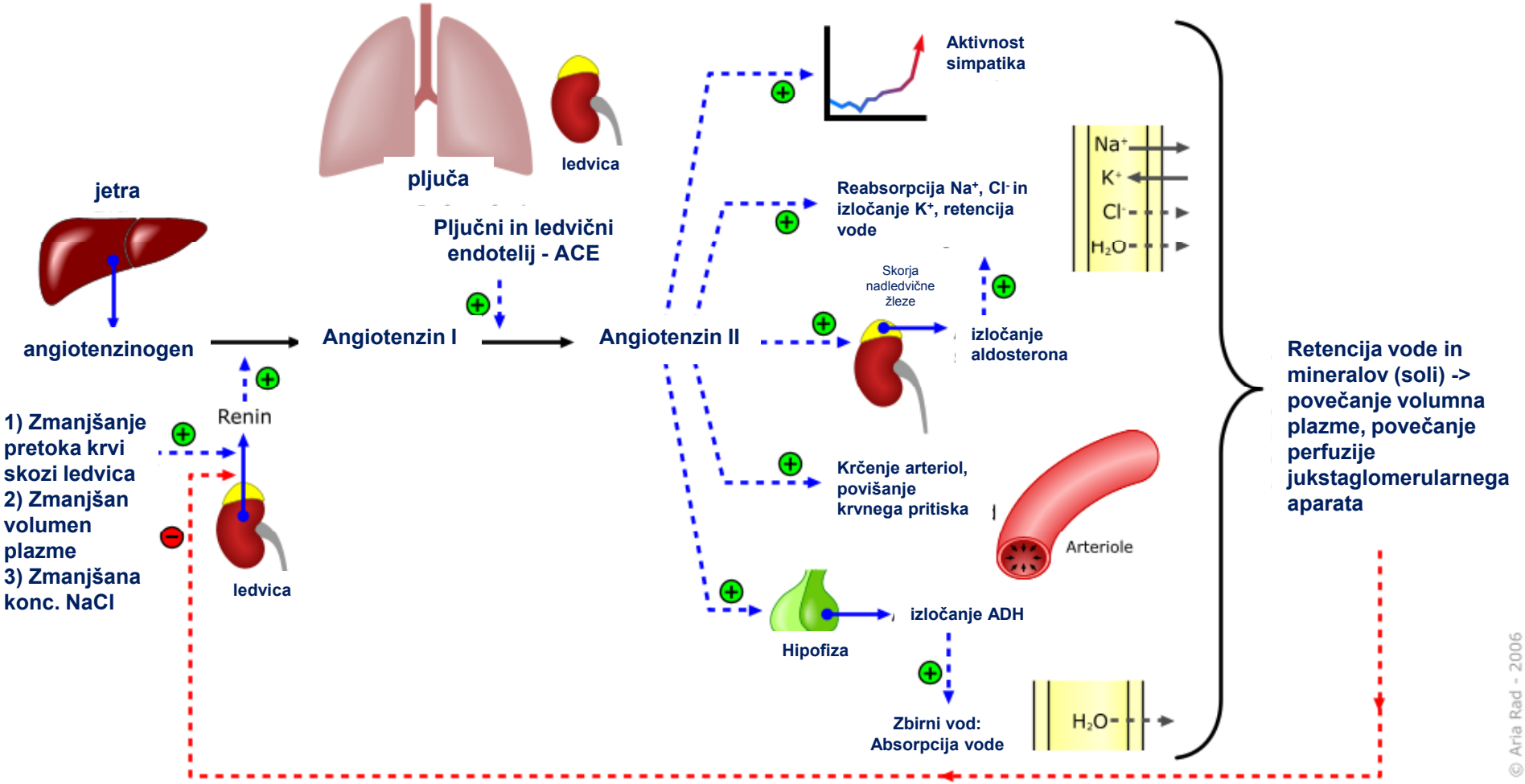
- Volumen krvi/plazme
- Periferni upor
- Viskoznost krvi
- Srčni iztis/minutni volumen srca

Simpatična regulacija krvnega tlaka



RAAS

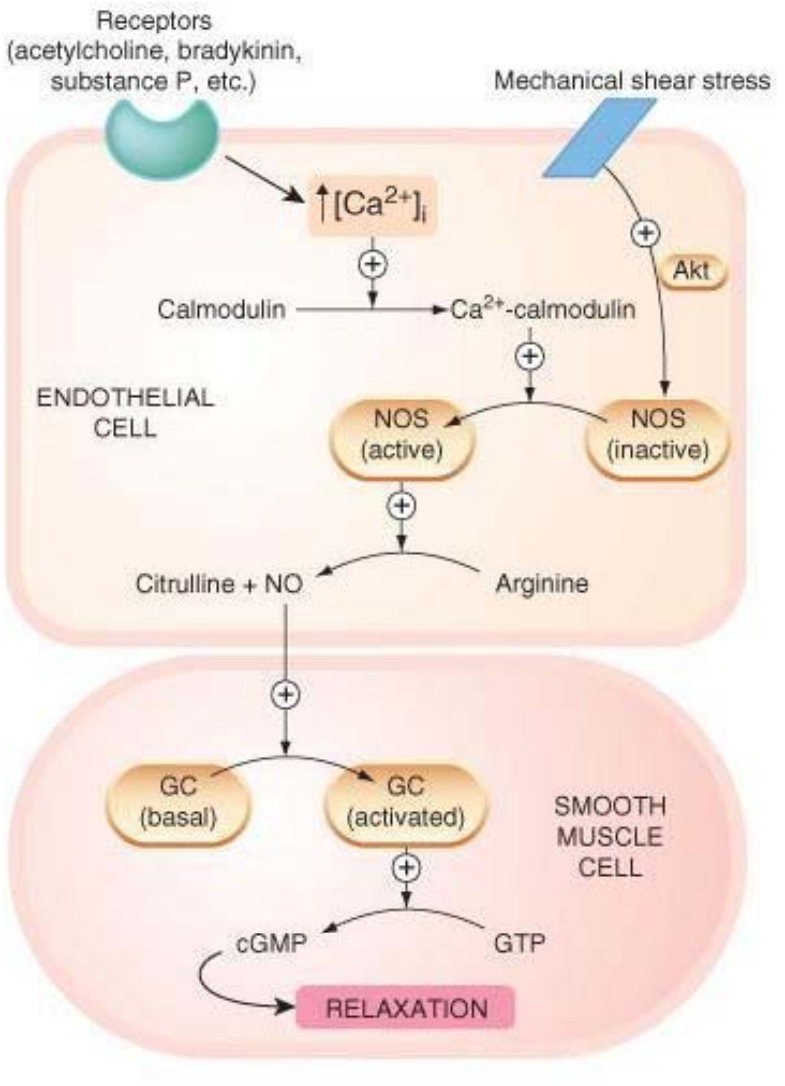
Dolgotrajna regulacija



Regulacija krvnega tlaka preko NO

- Celice ga ne skladiščijo, biosinteza “in-situ” z **NO-sintazo (NOS):**
- **eNOS** – endotelij (tudi miociti, renalne mesangialne celice, osteoklasti/blast, trombociti)
- **nNOS** – nevroni
- **iNOS** – inducibilna oblika (Kupfferjeve celice, makrofagi, fibroblasti, GMC, endotelij)

- Sproščanje NO je popolnoma odvisno od aktivnosti NOS: avtokrino, (para)endokrino.



Bolezen?

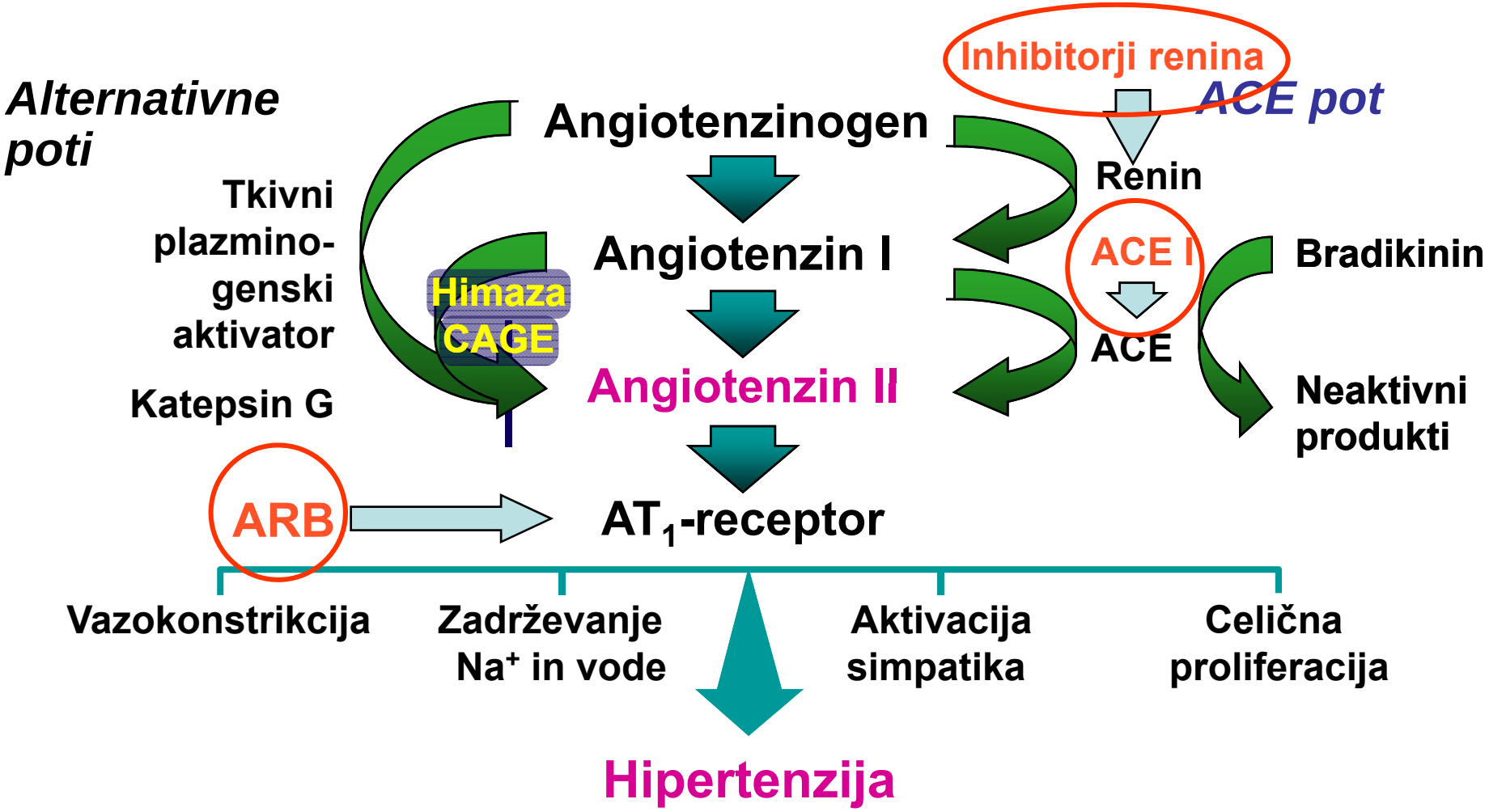
Terapija hipertenzije

- Vpliv preko α receptorjev (Klonidin)
- Vpliv preko β receptorjev (antagonisti)
- Vpliv preko ledvic na količino telesnih tekočin (diuretiki)
- Vpliv na tonus žilne muskulature (kalcijevi antagonisti, NO donorji)
- Vplivi preko RAAS: Inhibitorji ACE in AT antagonisti

RAAS - homeostaza krvnega tlaka

- Ledvica: preko delovanja angiotenzina II
- Ledvica: preko aldosterona in ADH zmanjšana resorpcija K^+, povečana resorpcija Na^+ in Cl^-
- Arteriole: krčenje gladkih mišic, porast tlaka
- Centralni učinek: +simpatikus, žeja, želja po soli, izločanje ADH in ACTH iz hipofize

Tarče v renin-angiotenzin sistemu

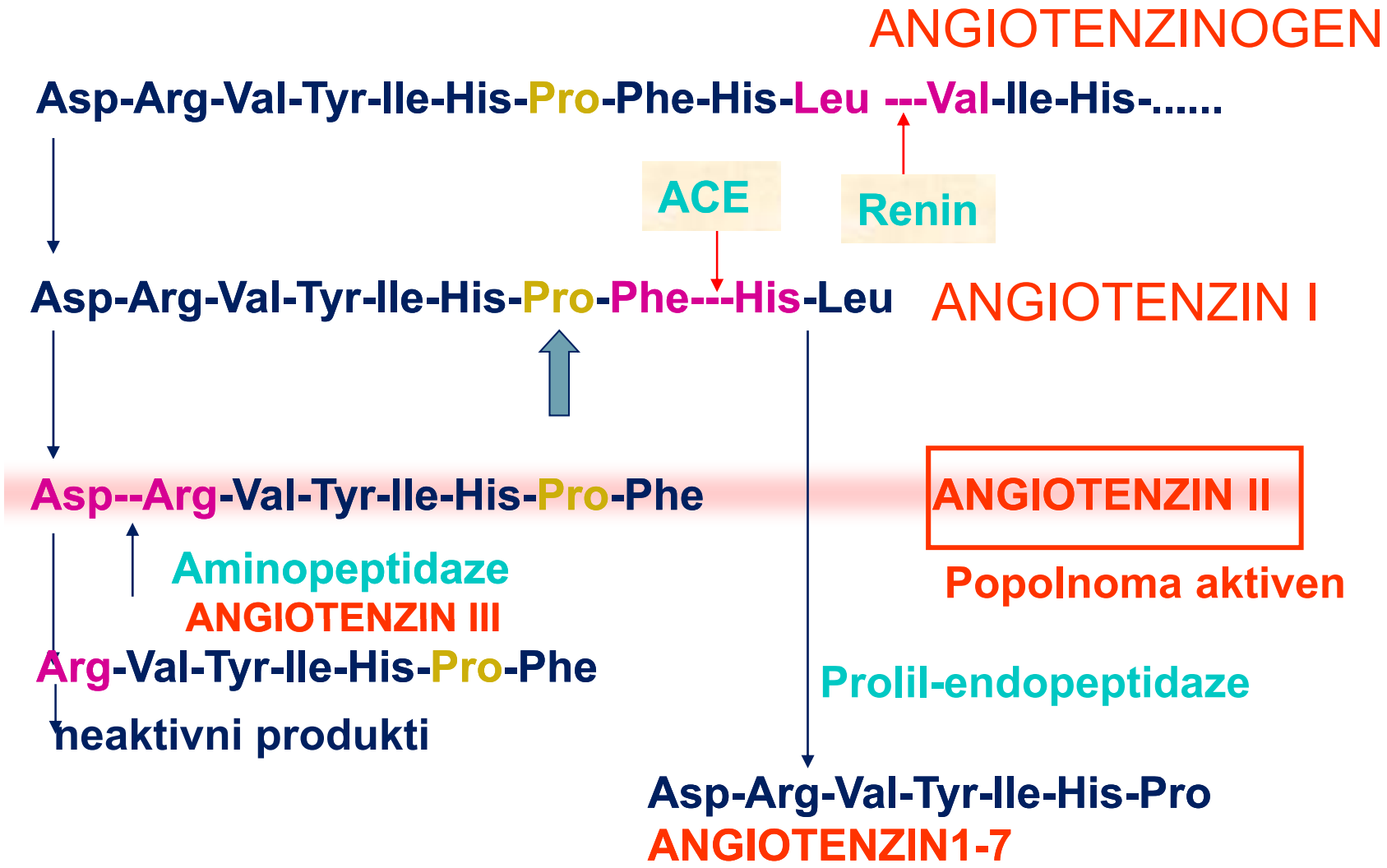


ARB = Angiotenzinski antagonisti;
CAGE = Himaza-"chymase angiotenzin generating enzyme".

Tarče v renin-angiotenzin sistemu

- http://pharmacologycorner.com/mechanism-of-action-video-animation-ace-inhibitors-angiotensin-ii-receptor-blockers-arbs-and-the-renin-angiotensin-aldosterone-system/

Sestavine RAAS



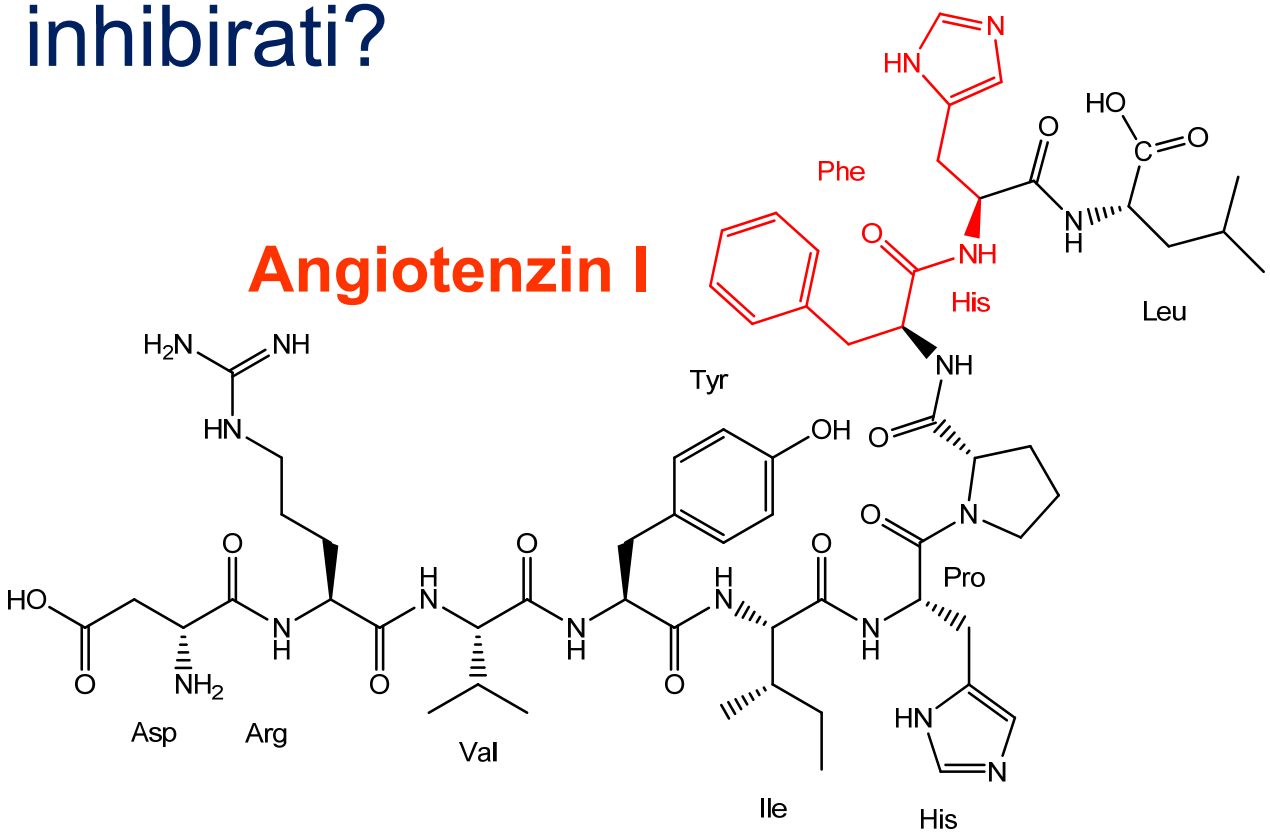
Angiotenzinska konvertaza (ACE)

- **metaloproteaza**, v aktivnem centru je Zn^{2+}
- **karboksidipeptidaza**,
- odceplja **dipeptidne** fragmente na C-koncu razen, če je (pred)zadnja aminokislina **prolin**,
- pretvarja **angiotenzin I** v **angiotenzin II** in **bradikinin** v neaktivne produkte.

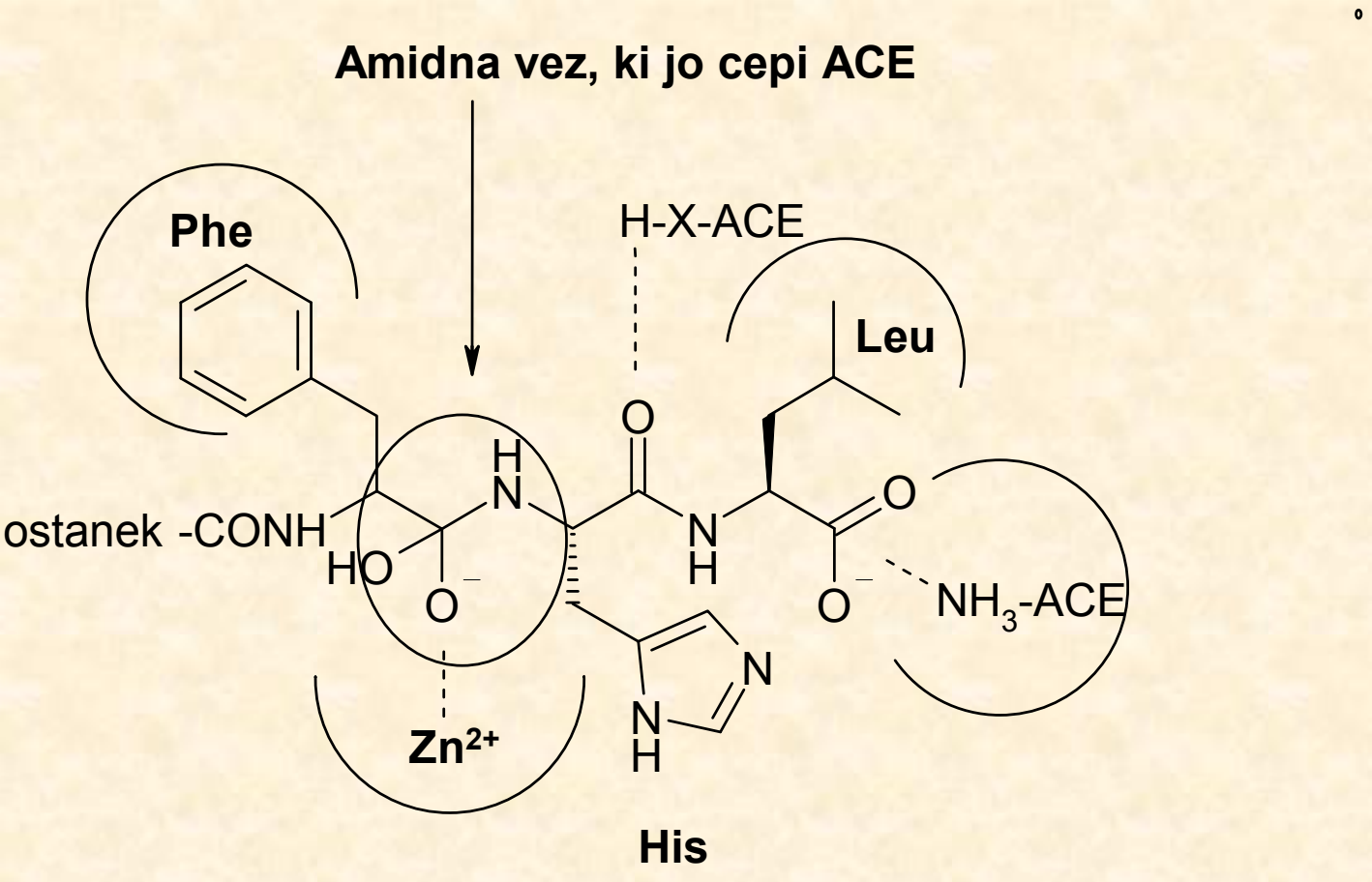
Karboksipeptidaze, aminopeptidaze, endo-, eksopeptidaze?

Inhibitorji ACE

- Kako inhibirati?



ACE: VEZAVA ANGIOTENZINA I V AKTIVNI CENTER



Inhibitorji ACE

Inhibitorji ACE – vodnica!

Nonapeptid **Teprotid**, inhibitor ACE

Nekateri peptidi iz strupa brazilskega gada in njihovi krajši fragmenti

Peptid	IC_{50}
Glu-Trp-Pro-Arg-Pro-Gln-Ile-Pro-Pro	**0,05 mg/L**
Glu-Lys-Trp-Ala-Pro	**0,05 mg/L**
Glu-Phe-Ala-Pro	**2,7 mg/L**
Phe-Ala-Pro	**1,7 mg/L**
Ala-Pro	**50 mg/L**

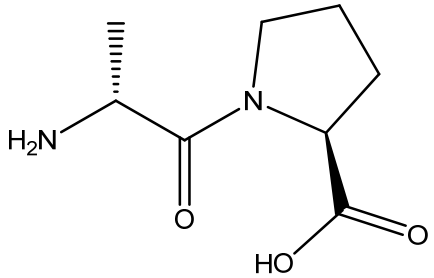
Inhibitorji ACE

Inhibitorji ACE – minimalno zaporedje

Teprotid (9 AK), IC_{50}= 100 nM

NH_2—Glu—Trp—Pro—Arg—Pro—Gln—Ile—Pro—Pro—COOH

Ala-Pro (2 AK), IC_{50}= 230 μM

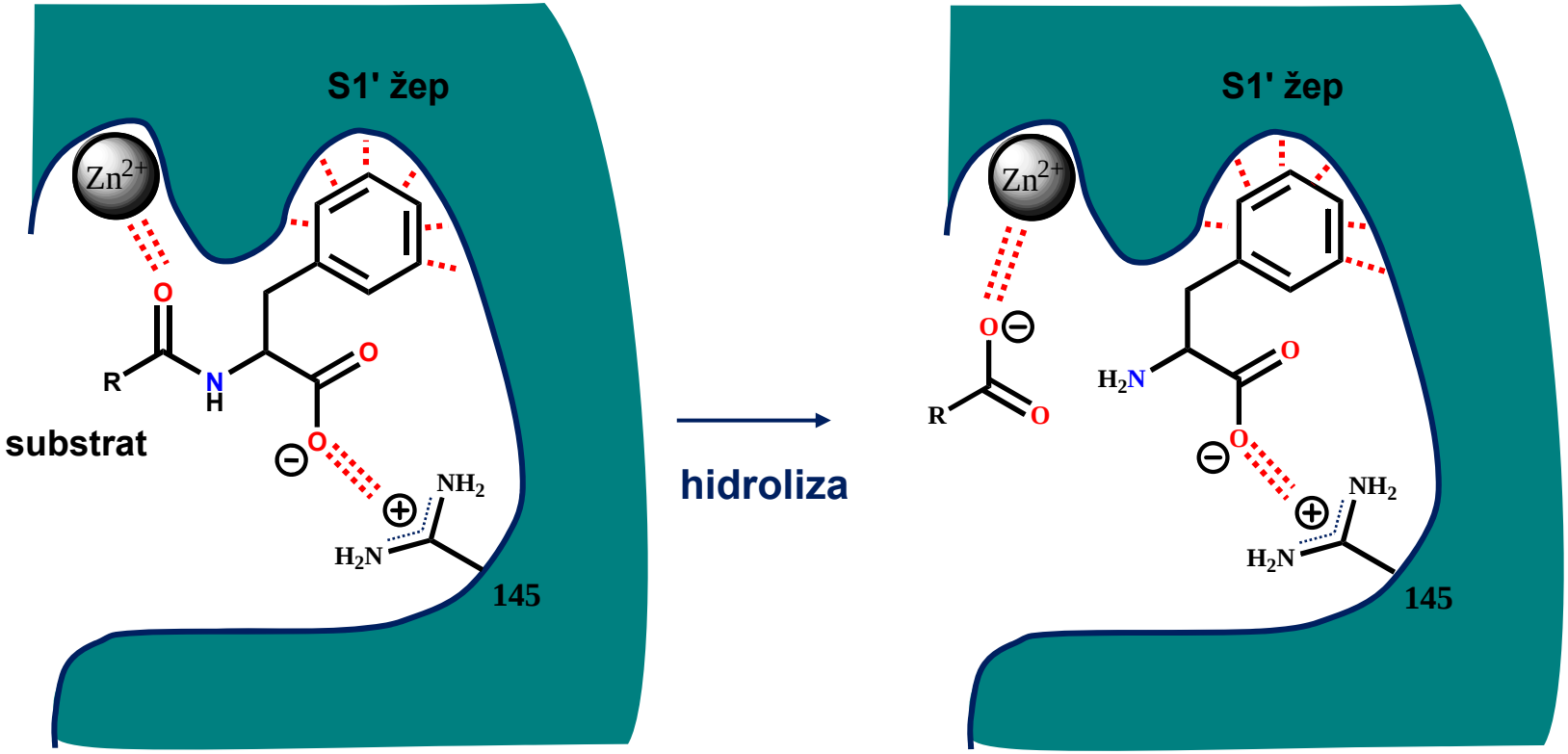


?

Inhibitorji ACE

Inhibitorji ACE – optimizacija vodnice

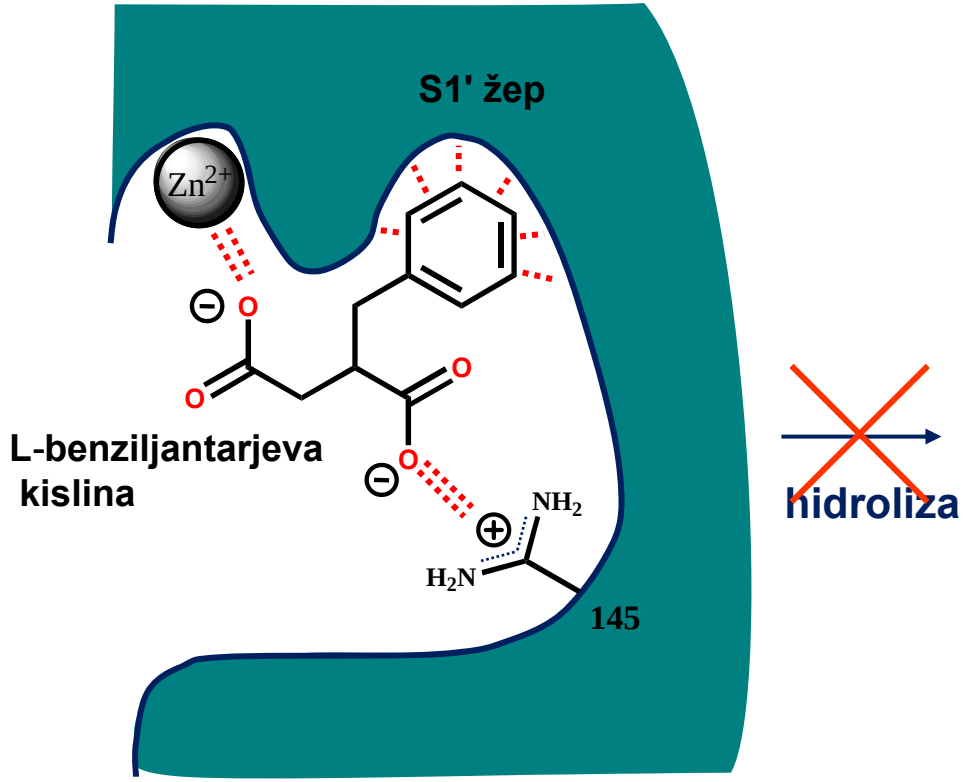
Karboksipeptidaza A



Inhibitorji ACE

Inhibitorji ACE – optimizacija vodnice

Karboksipeptidaza A

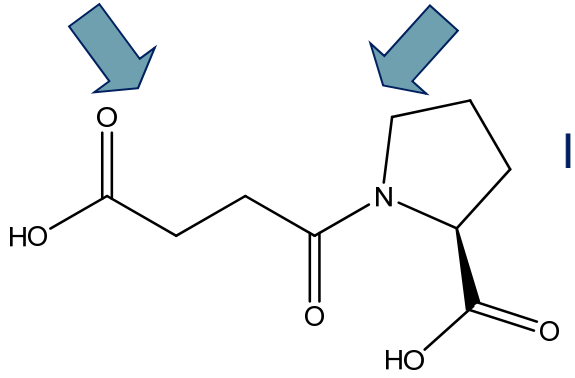


Inhibitorji ACE

Inhibitorji ACE – optimizacija vodnice

Ala-Pro (9 AK), IC_{50}= 230 μM

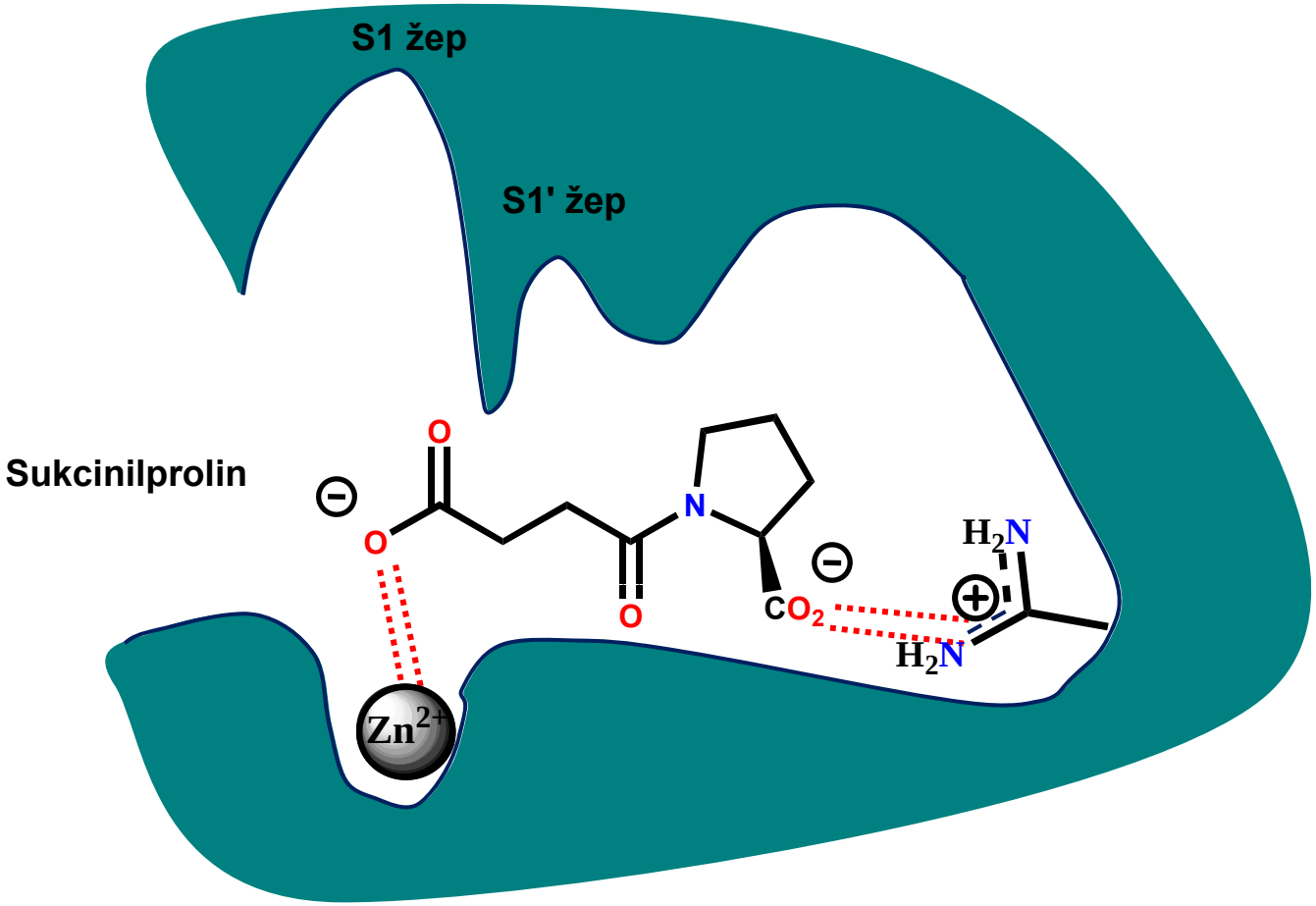
Sukcinilni fragment



IC_{50}= 330 μM

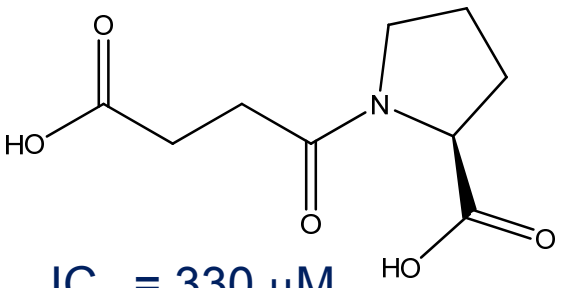
Inhibitorji ACE

Inhibitorji ACE – optimizacija vodnice

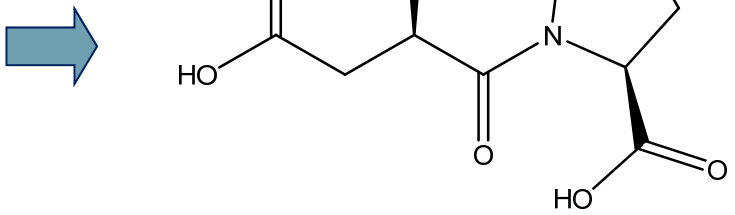


Inhibitorji ACE

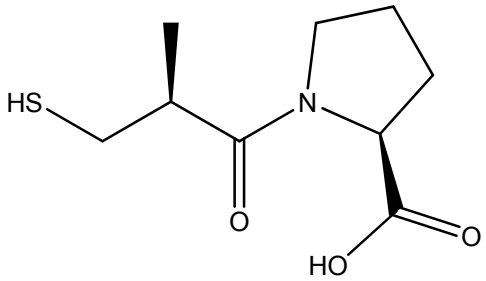
Inhibitorji ACE – optimizacija vodnice



IC_{50}= 330 μM

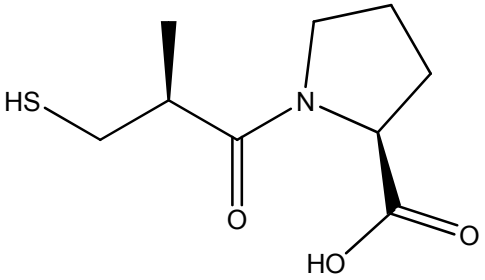


IC_{50}= 22 μM

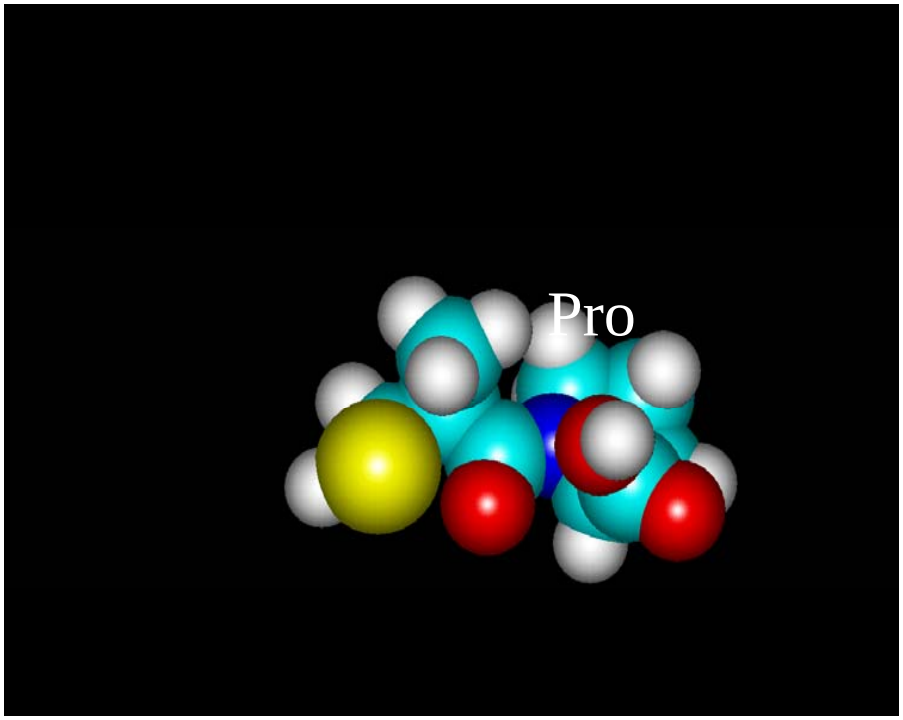


Kaptopril, IC_{50}= 23 nM

Kaptopril

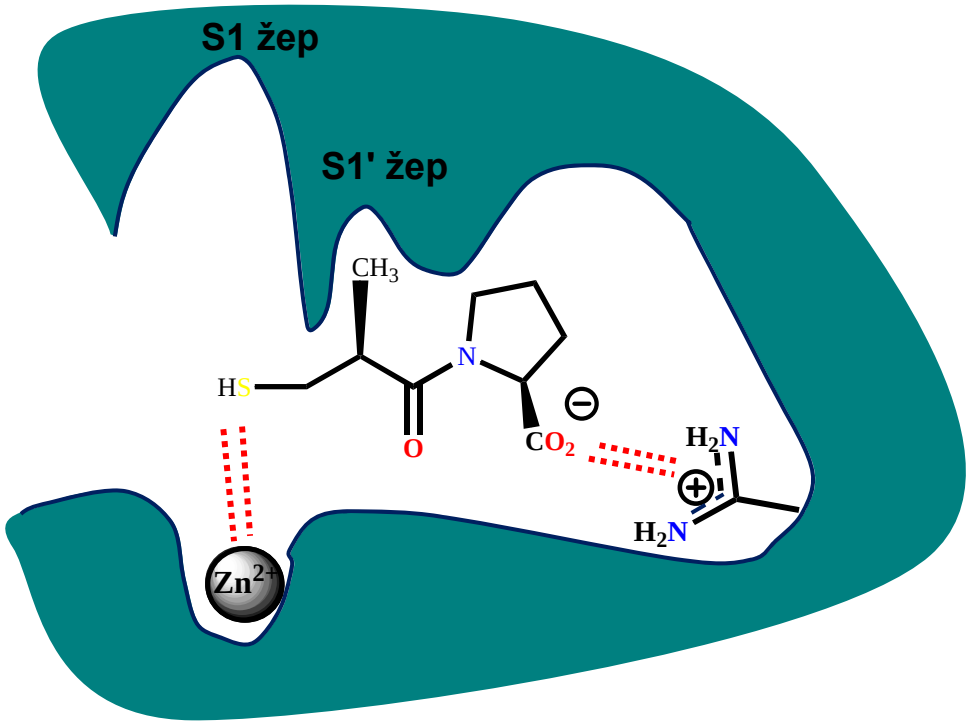


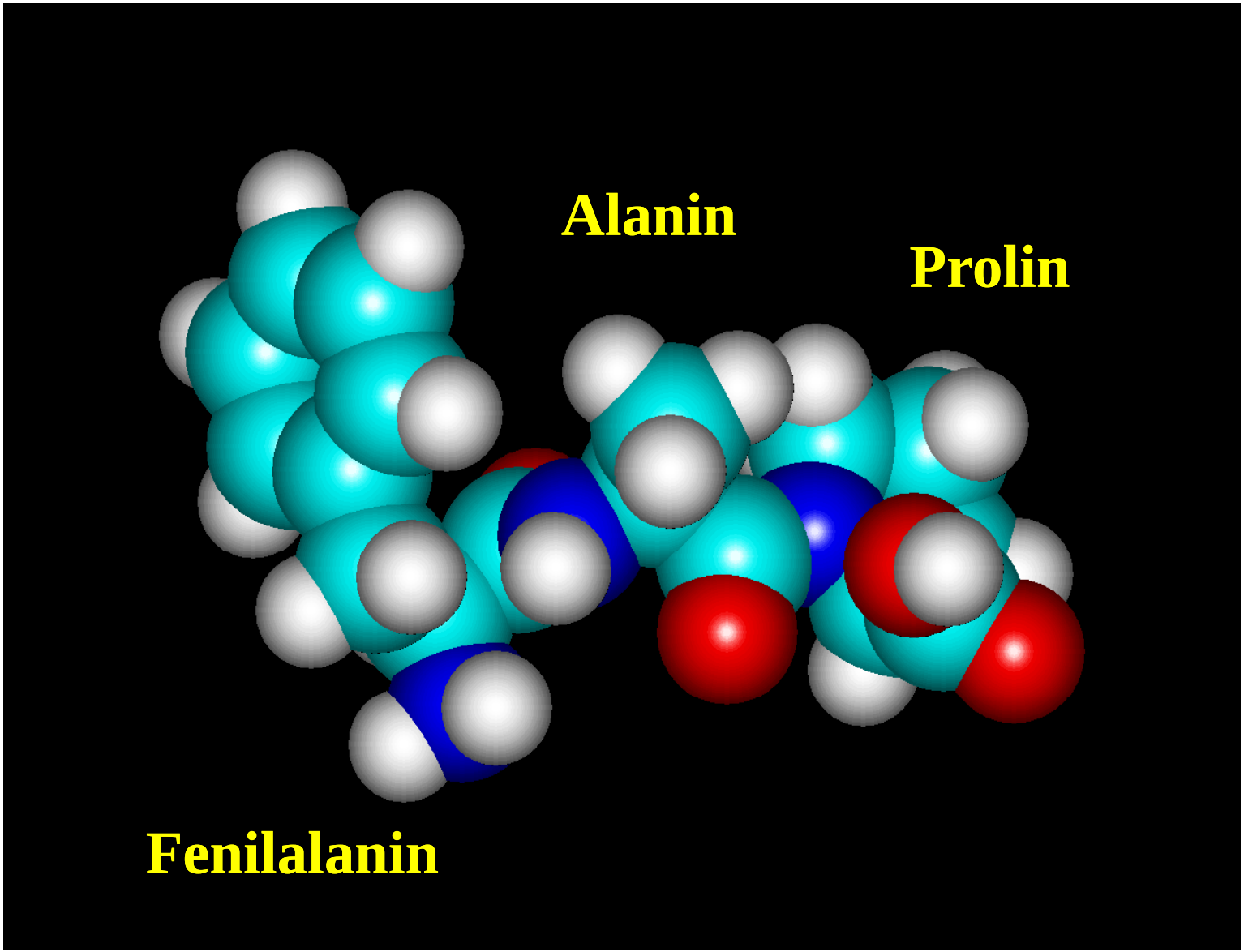
Kaptopril, IC_{50}= 23 nM



Inhibitorji ACE

Inhibitorji ACE – kaptopril

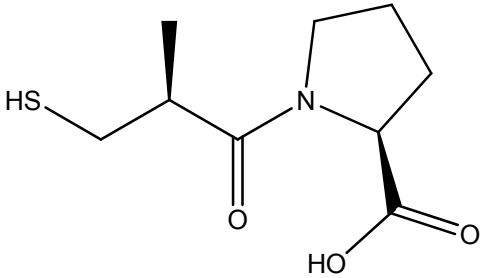



Alanin
Prolin
Fenilalanin

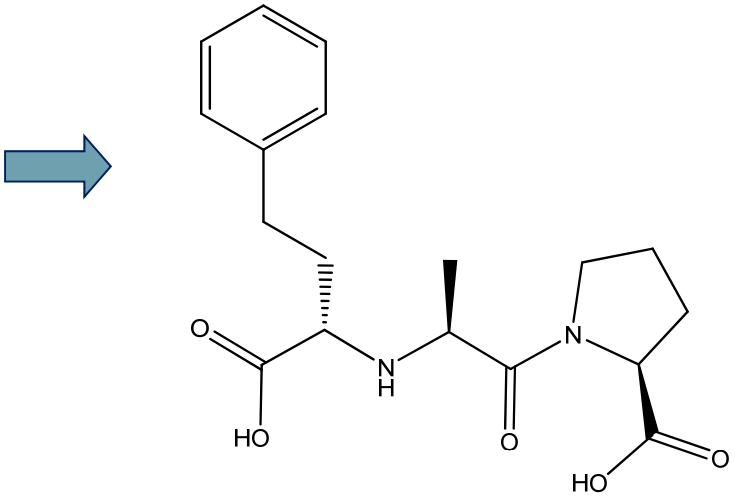
Inhibitorji ACE

Inhibitorji ACE – optimizacija kaptoprila

- Phe ostanek v nativnem substratu!



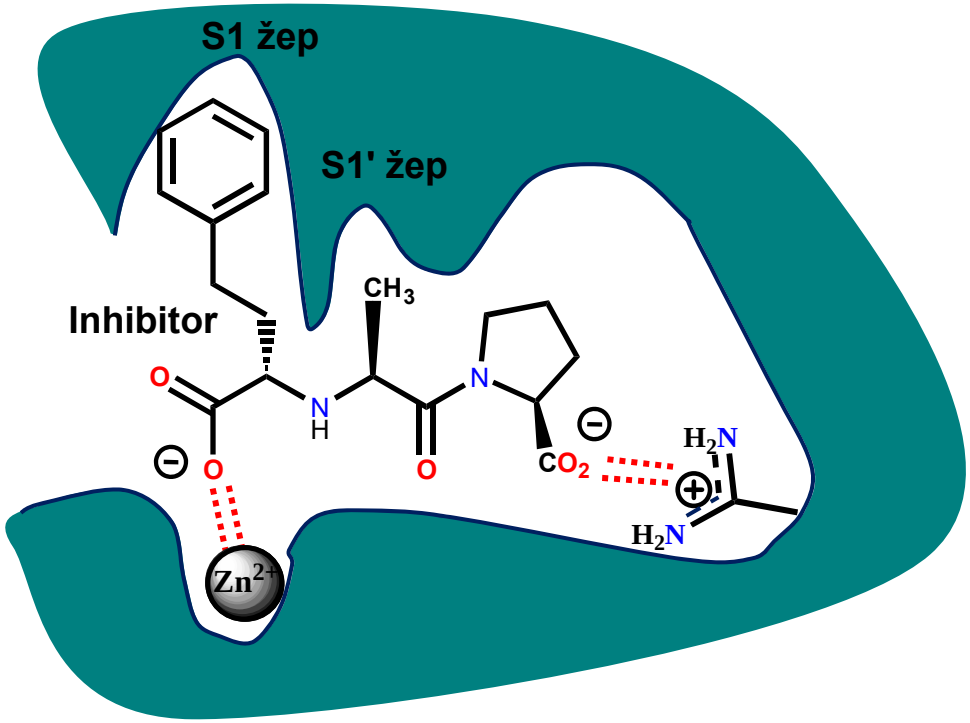
Kaptopril, IC_{50}= 23 nM



enalaprilat, IC_{50}= 1 nM

Inhibitorji ACE

Inhibitorji ACE – enalaprilat



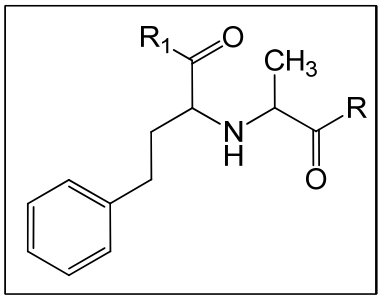
Inhibitorji ACE

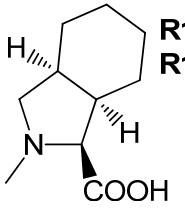
Problem!

- Nizka BU
- Tvorba estrov kot predzdravil
- Enalaprilat; BU~0%!
- Enalapril; BU~60%

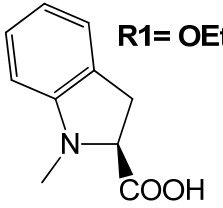
- Topnostni profil predzdravil?

ACE ZAVIRALCI, PODOBNI ENALAPRILATU ALI ENALAPRILU

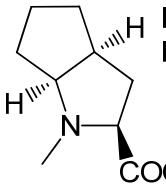




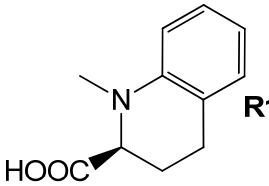
R1= OH, PERINDOPRILAT
R1= OEt, PERINDOPRIL



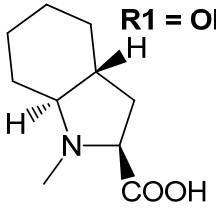
R1= OEt, INDOLAPRIL



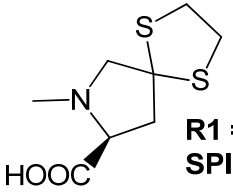
R1= OH, RAMIPRILAT
R1= OEt, RAMIPRIL



R1 = OEt KINAPRIL



R1 = OEt, TRANDOLAPRIL



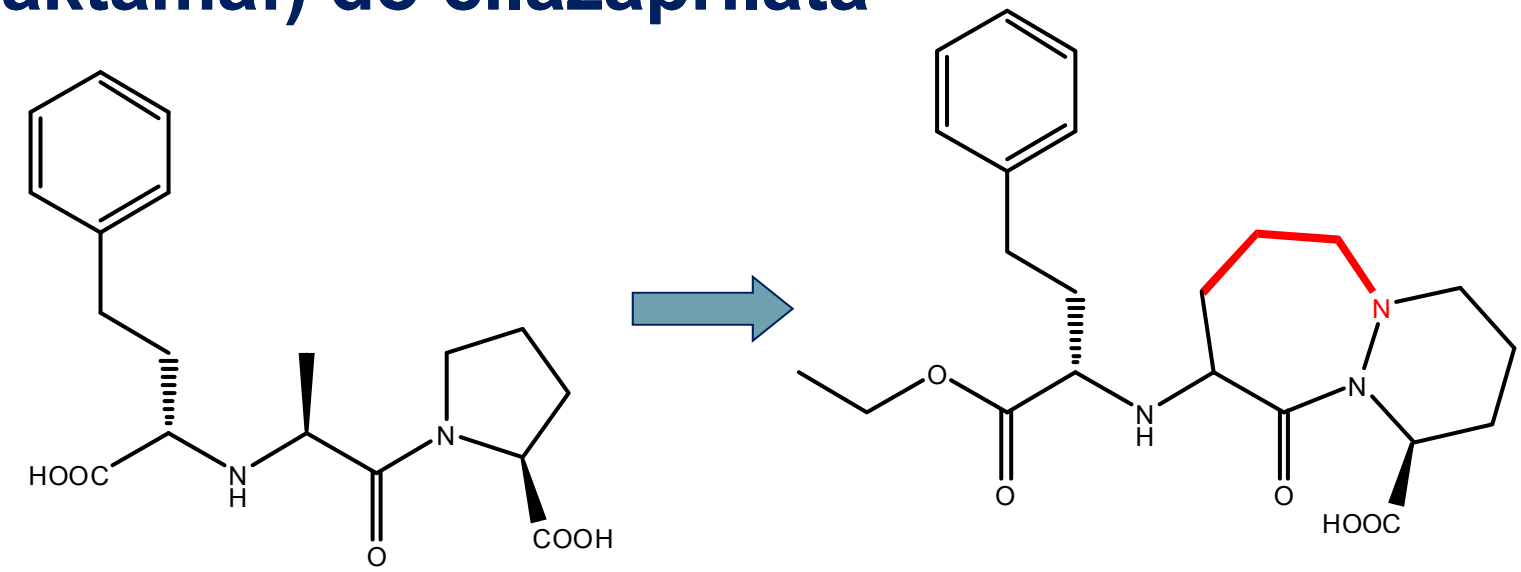
R1 = OEt, SPIRAPRIL

Nomenklatura?

- -il
- -ilat

Inhibitorji ACE

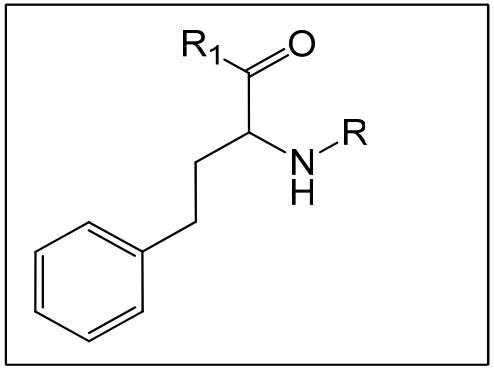
- **Inhibitorji ACE – rigidizacija (tvorba laktama!) do cilazaprilata**



enalaprilat

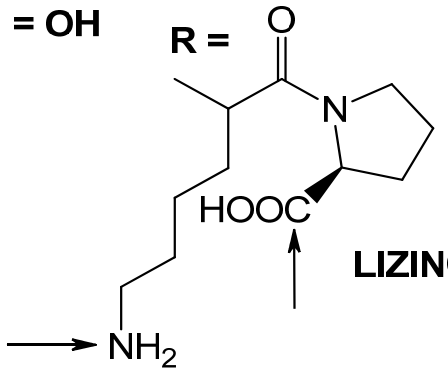
Cilazapril(at)
4,5 x močnejši!

ACE zaviralci manj podobni enalaprilatu



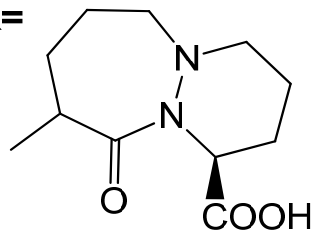
R1 = OH

R =



LIZINOPRIL

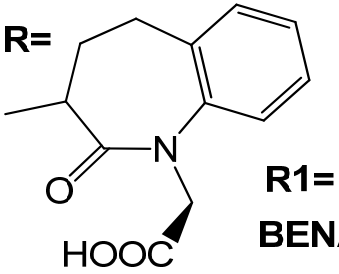
R=



R1 = OEt

CILAZAPRIL

R=



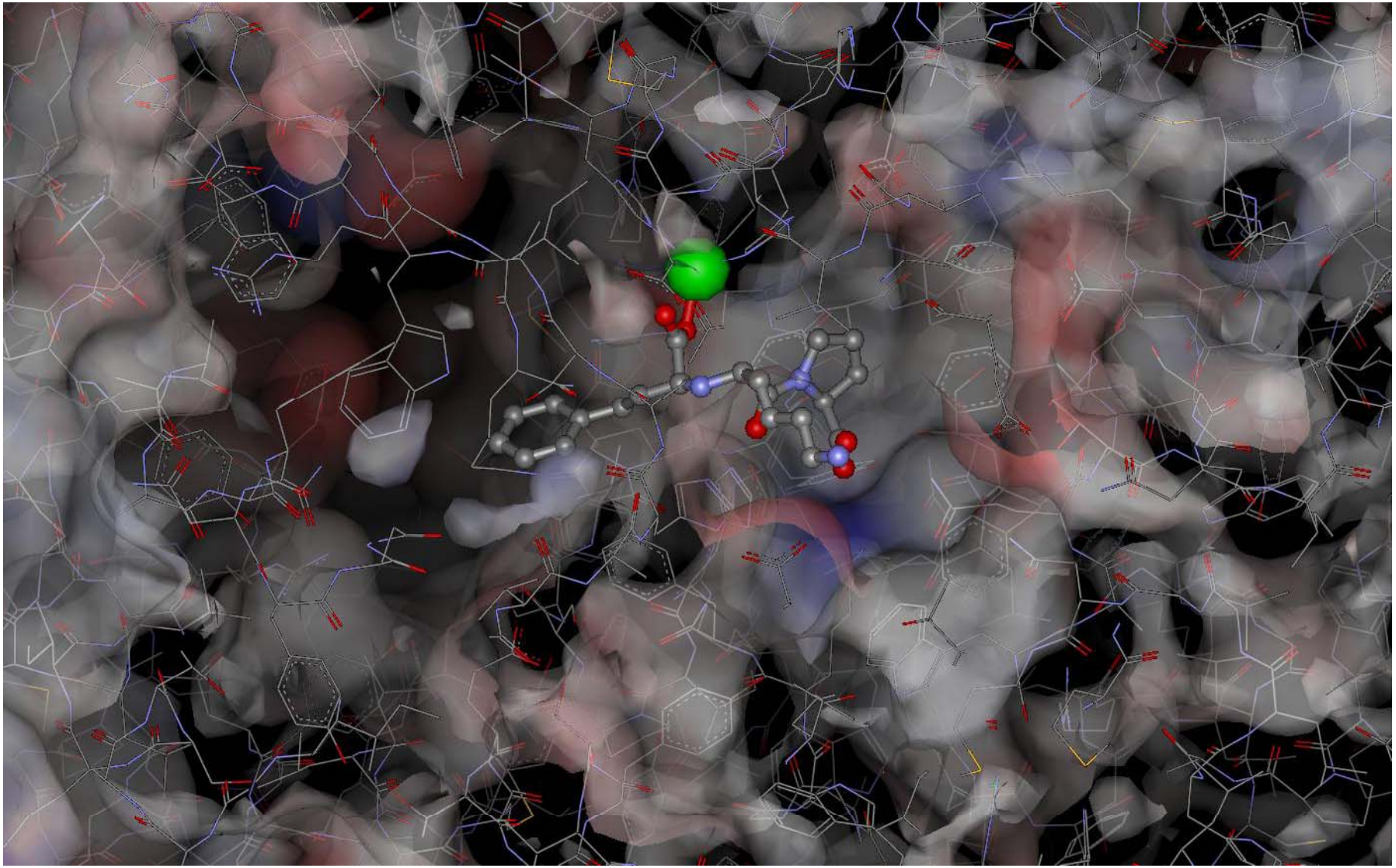
R1= OEt

BENAZEPRIL

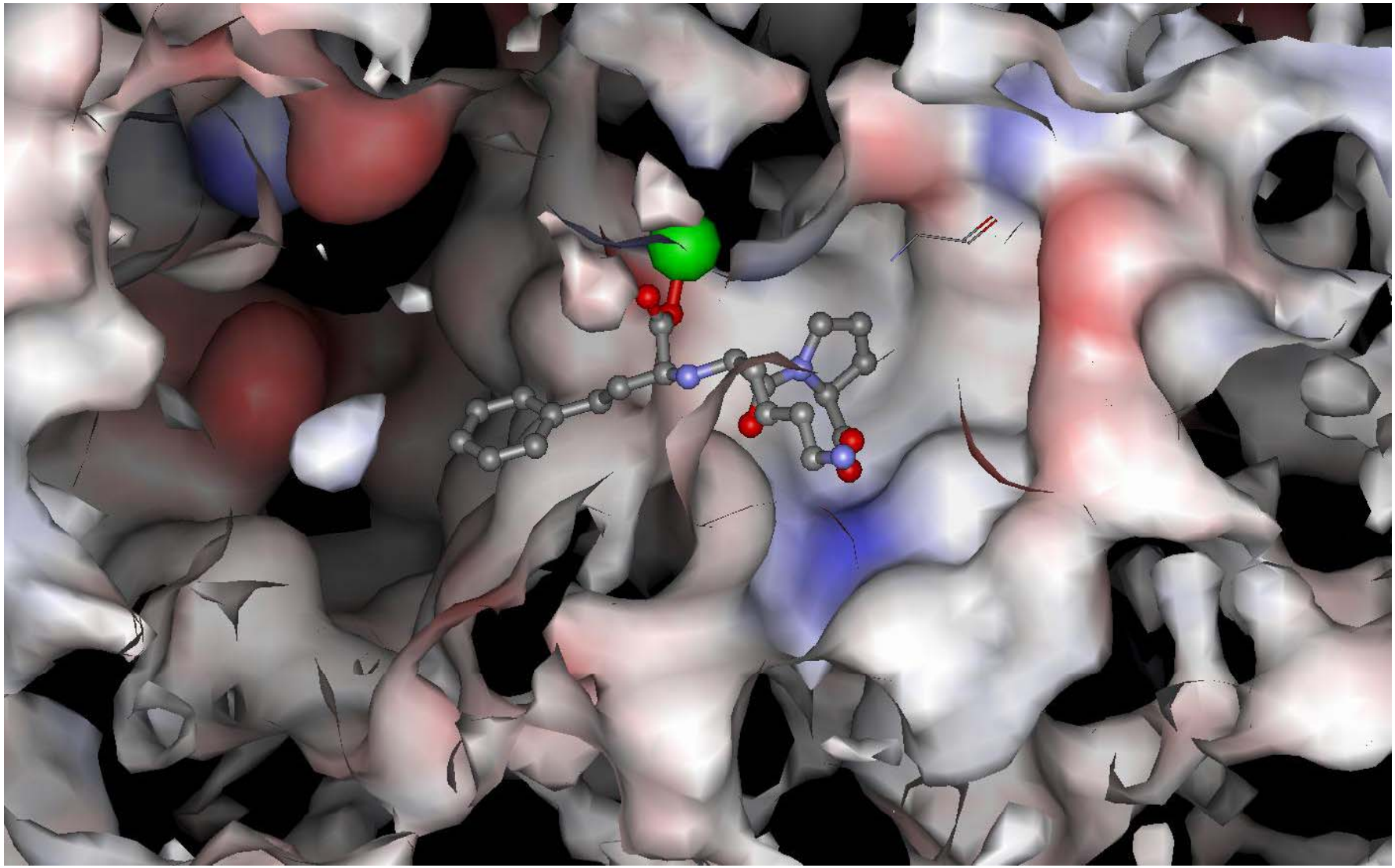
Lizinopril

- Dolg $t_{1/2}$
- Variabilna BU, 6-60% (~25%)
- Ni predzdravilo!
- Ion dvojček; intramolekularne ionske vezi – vpliv na vezavo?
- polarnost?

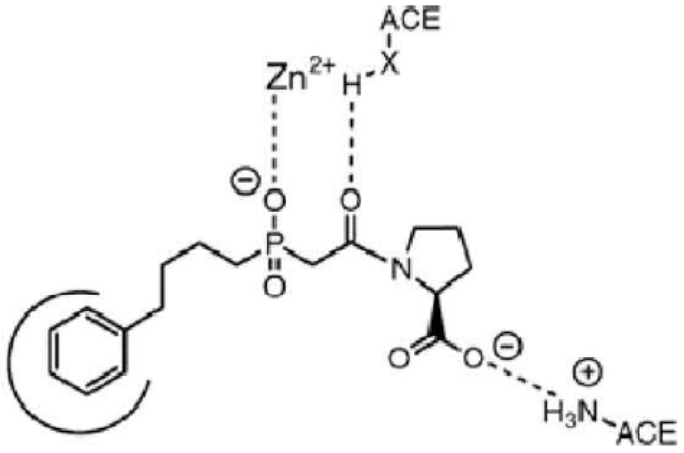
Lizinopril

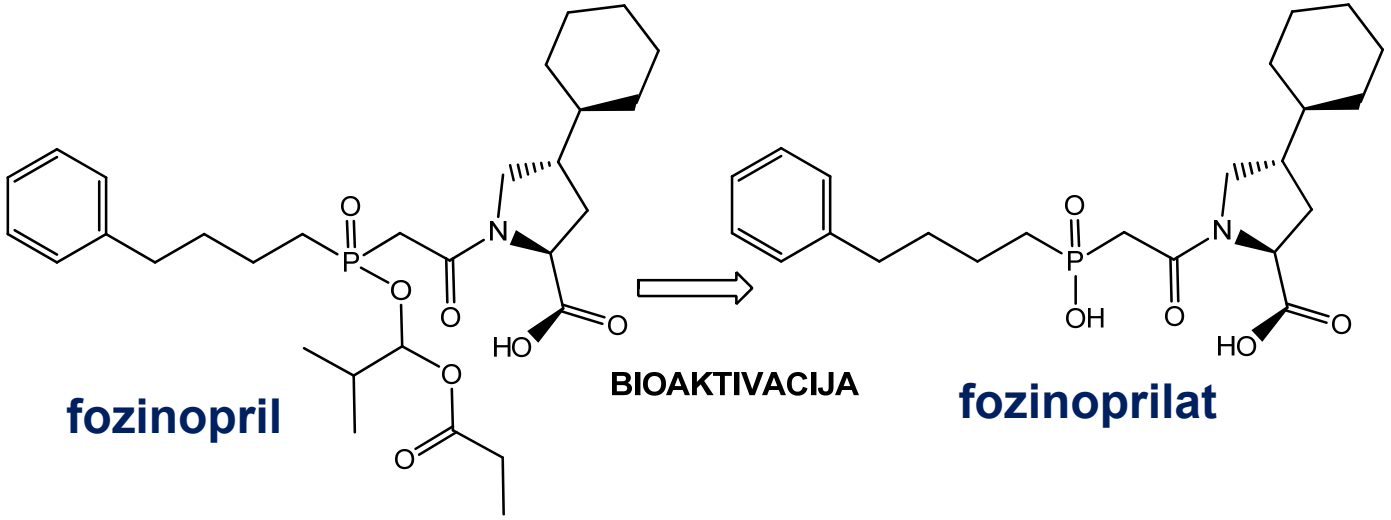


Lizinopril



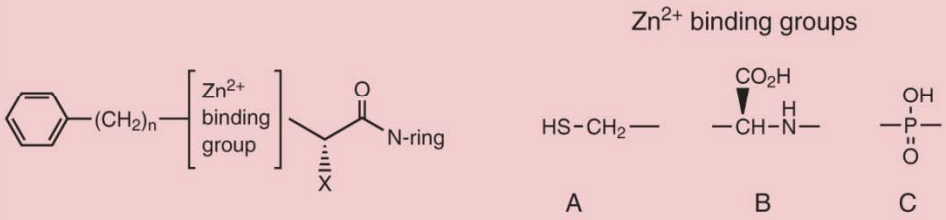
Fozinopril


ACE
X
Zn2+
H
O
O
P
O
N
O
O
H3N
ACE


O
P
O
N
O
HO
O
O
fozinopril
BIOAKTIVACIJA
OH
fozinoprilat

SAR inhibitorjev ACE

TABLE 23.2 Structure–Activity Relationship of ACE Inhibitors



a. The N-ring must contain a carboxylic acid to mimic the C-terminal carboxylate of ACE substrates.
b. Large hydrophobic heterocyclic rings (i.e., the N-ring) increase potency and alter pharmacokinetic parameters.
c. The zinc binding groups can be either sulfhydryl (A), a carboxylic acid (B), or a phosphinic acid (C).
d. The sulfhydryl group shows superior binding to zinc (the side chain mimicking the Phe in carboxylate and phosphinic acid compounds partially compensates for the lack of a sulfhydryl group).
e. Sulfhydryl-containing compounds produce high incidence of skin rash and taste disturbances.
f. Sulfhydryl-containing compounds can form dimers and disulfides, which may shorten duration of action.
g. Compounds that bind to zinc through either a carboxylate or phosphinate mimic the peptide hydrolysis transition state and enhance binding.
h. Esterification of the carboxylate or phosphinate produces an orally bioavailable prodrug.
i. X is usually methyl to mimic the side chain of alanine. Within the dicarboxylate series, when X equals n-butylamine (lysine side chain), this produces a compound that does not require prodrug for oral activity.
j. Optimum activity occurs when stereochemistry of inhibitor is consistent with L-amino acid stereochemistry present in normal substrates.

Fiz.-kem. lastnosti inhibitorjev ACE

- Amfoterni
- pKa kislin = 2,5-3,5
- pKa sek. amina močno variira: enalapril – pKa = 5,49, enalaprilat pKa = 8,02!
- Sovpliv ionizirajočih skupin
- Nepolarni substituenti vplivajo na +hidrofobnost – izboljšana BU

FK lastnosti inhibitorjev ACE

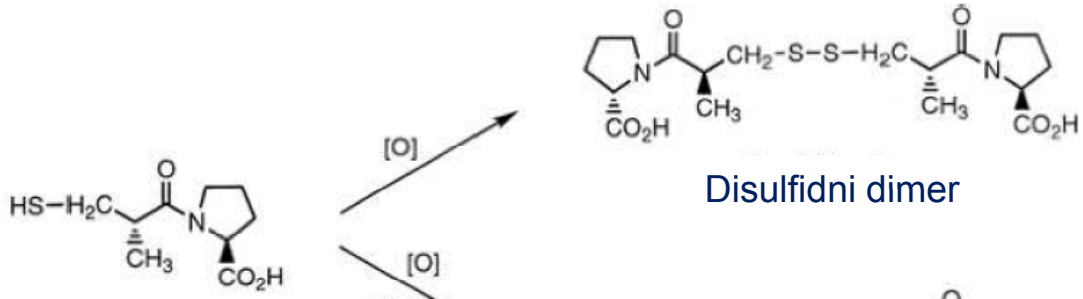
TABLE 23.3 Pharmacokinetic Parameters of ACE Inhibitors

Drug	Calculated LogP	Oral Bioavailability (%)	Effect of Food on Absorption	Active Metabolite	Protein Binding (%)	Onset of Action (hours)	Duration of Action (hours)	Major Route(s) of Elimination
Benazepril	5.50	37	Slows absorption	Benazeprilat	>95	1	24	Renal (primary) Biliary (secondary)
Captopril	0.27	60–75	Reduced	NA	25–30	0.25–0.50	6–12	Renal
Enalapril	2.43	60	None	Enalaprilat	50–60	1	24	Renal/fecal
Enalaprilat	1.54	NA	NA	NA	—	0.25	6	Renal
Fosinopril	6.09	36	Slows absorption	Fosinoprilat	95	1	24	Renal (50%) Hepatic (50%)
Lisinopril	1.19	25–30	None	NA	25	1	24	Renal
Moexipril	4.06	13	Reduced	Moexiprilat	50	1	24	Fecal (primary) Renal (secondary)
Perindopril	3.36	65–95	Reduced	Perindoprilat	60–80	1	24	Renal
Quinapril	4.32	60	Reduced	Quinaprilat	97	1	24	Renal
Ramipril	3.41	50–60	Slows absorption	Ramiprilat	73	1–2	24	Renal (60%) Fecal (40%)
Spirapril	3.16	50	—	Spiraprilat	—	1	24	Renal (50%) Hepatic (50%)
Trandolapril	3.97	70	Slows absorption	Trandolaprilat	80	0.5–1.0	24	Fecal (primary) Renal (secondary)

NA, not applicable; —, data not available.

Metabolizem

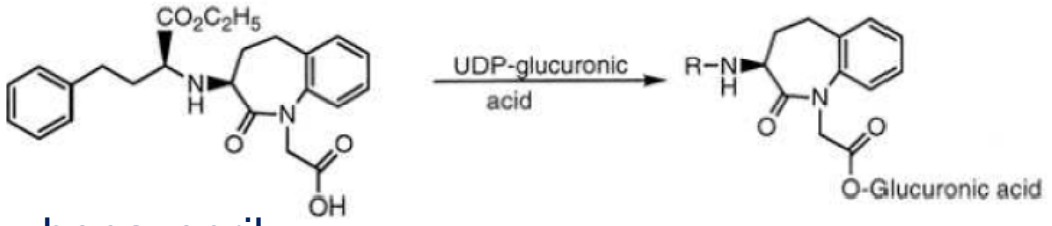
- Jetrne esteraze metabolizirajo predzdravila
- Lizinopril, enalapril – izločanje v nespremenjeni obliki
- Kaptopril – dimerizacija, konjugacija
- Benazepril – konjugacija
- Ramipril, perindopril - ciklizacija



kaptopril

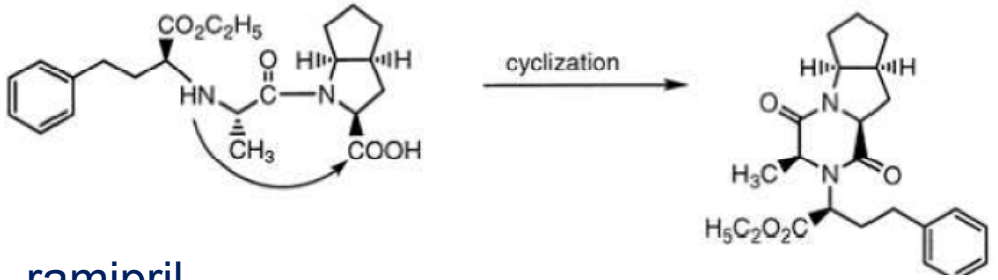
Disulfidni dimer

Disulfidni dimer s Cys



benazepril

Konjugat - glukuronid



ramipril

diketopiperazin

Inhibitorji ACE

- Bradikinin, substanca P – kašelj in stranski učinki inhibitorjev ACE
- Zakaj ravno kašelj – ACE v pljučih!
- Angioedemi (bradikinin, retencija tekočine)

Inhibitorji renina

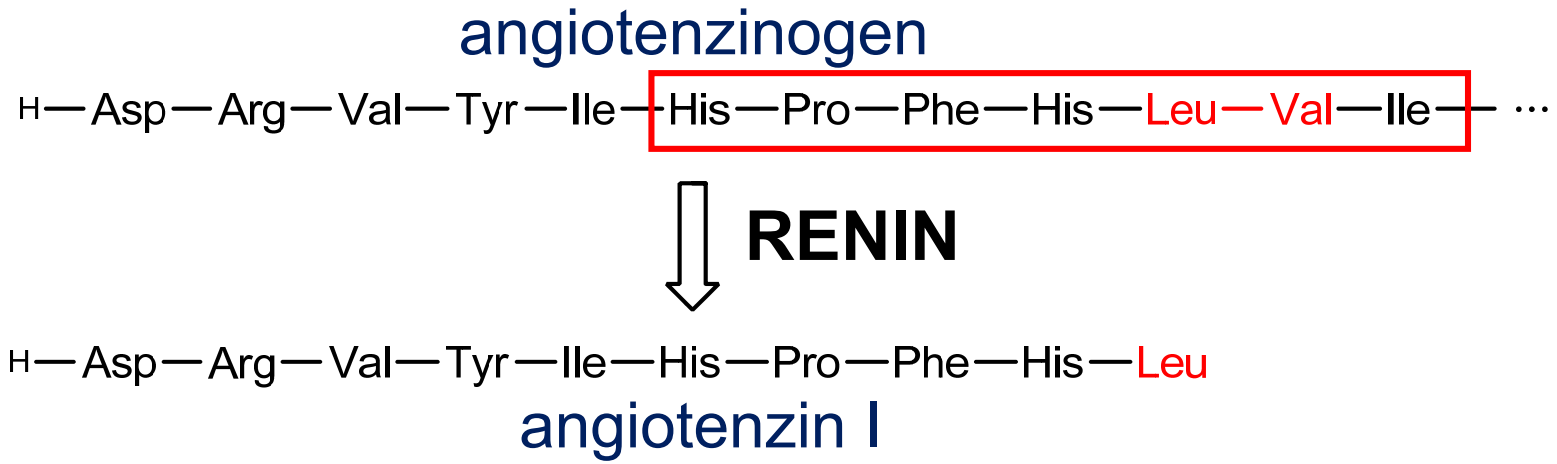
Renin

- ACE – več funkcij, posledica inhibicije so stranski učinki
- Renin - Aspartatna proteaza
- Izločanje zaradi hemodinamičnih, humoralnih ali nevrogenih signalov
- Zelo specifičen encim (bolj kot ACE)
- Prvi v kaskadi – inhibicija najbolj učinkovita!
- “rate-limiting step” v sintezi angiotenzina II
- Problem: oktapeptid His-Pro-Phe-His-Leu-Leu-Val-Tyr je namanjši substrat, podobno zaporedju angiotenzinogena His6-Pro7-Phe8-His9-Leu10-Val11-Ile12-His13

Inhibitorji renina

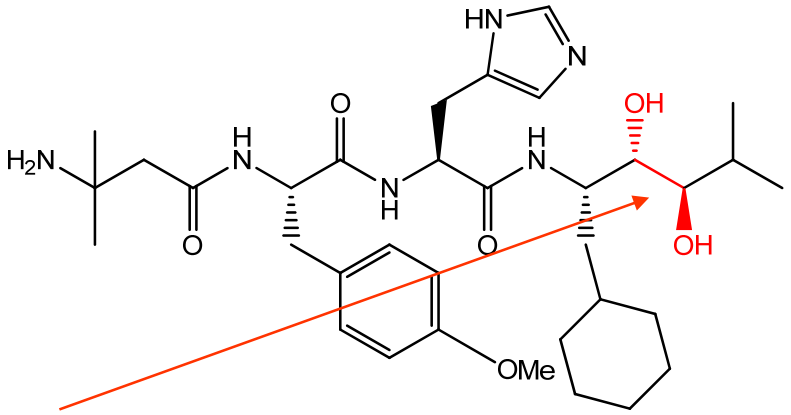
Renin

- Katalitična aktivnost: angiotenzinogen dolg 452 AK ostankov, cepitev na mestu med Leu10-Val11
- Angiotenzin I produkt (neaktiven)



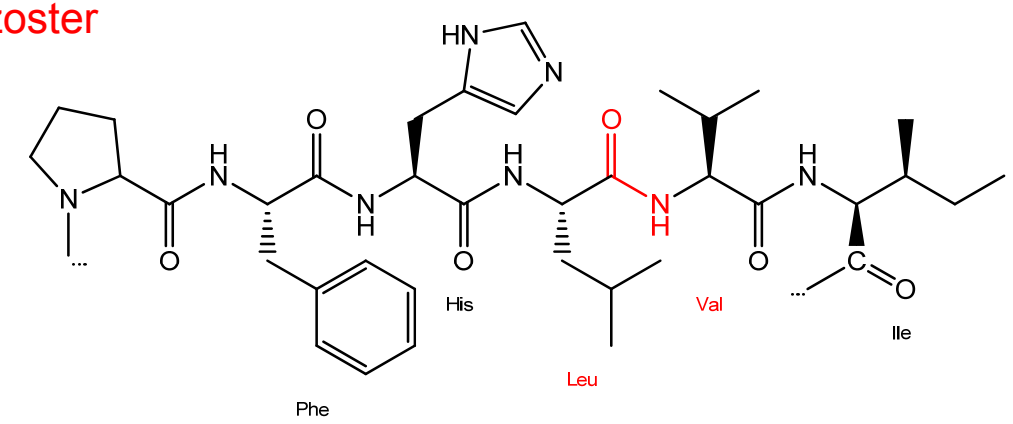
Inhibitorji renina

Enalkiren



Peptidomimetik!

-metabolno stabilni bioizoster peptidne vezi

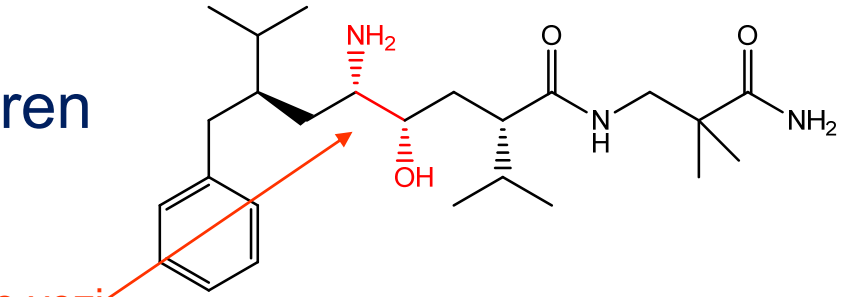


Inhibitorji renina

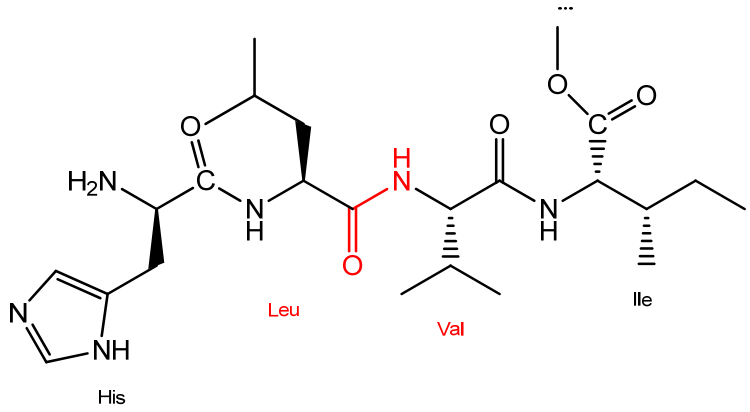
Aliskiren

- Peptidomimetik: posnetek AK angiotenzinogena na mestu cepitve

aliskiren



Bioizosterna zamenjava peptidne vezi
-t.i.”statin”
-metabolno stabilen analog
-mimetik prehodnega stanja



Inhibitorji renina

Slabosti

- Delno peptidna struktura
- Nizka BU: aliskiren 2,7%, remikiren <1,0%
- Slab klinični učinek – stimulacija sinteze renina

Prednosti

- Manj stranskih učinkov kot ACE
- Uporabni v kombinirani terapiji: IR + diuretiki, zaviralci Ca^{2+} kanalčkov

Povzetek

Literatura predavanj

Foye's Principles of Medicinal Chemistry, 6. izdaja:

- 28. poglavje
- 29. poglavje

G. L. Patrick: An introduction to medicinal chemistry, Oxford University press, 4. izdaja:

- Case study 2a