Antagonisti angiotenzinskih receptorjev

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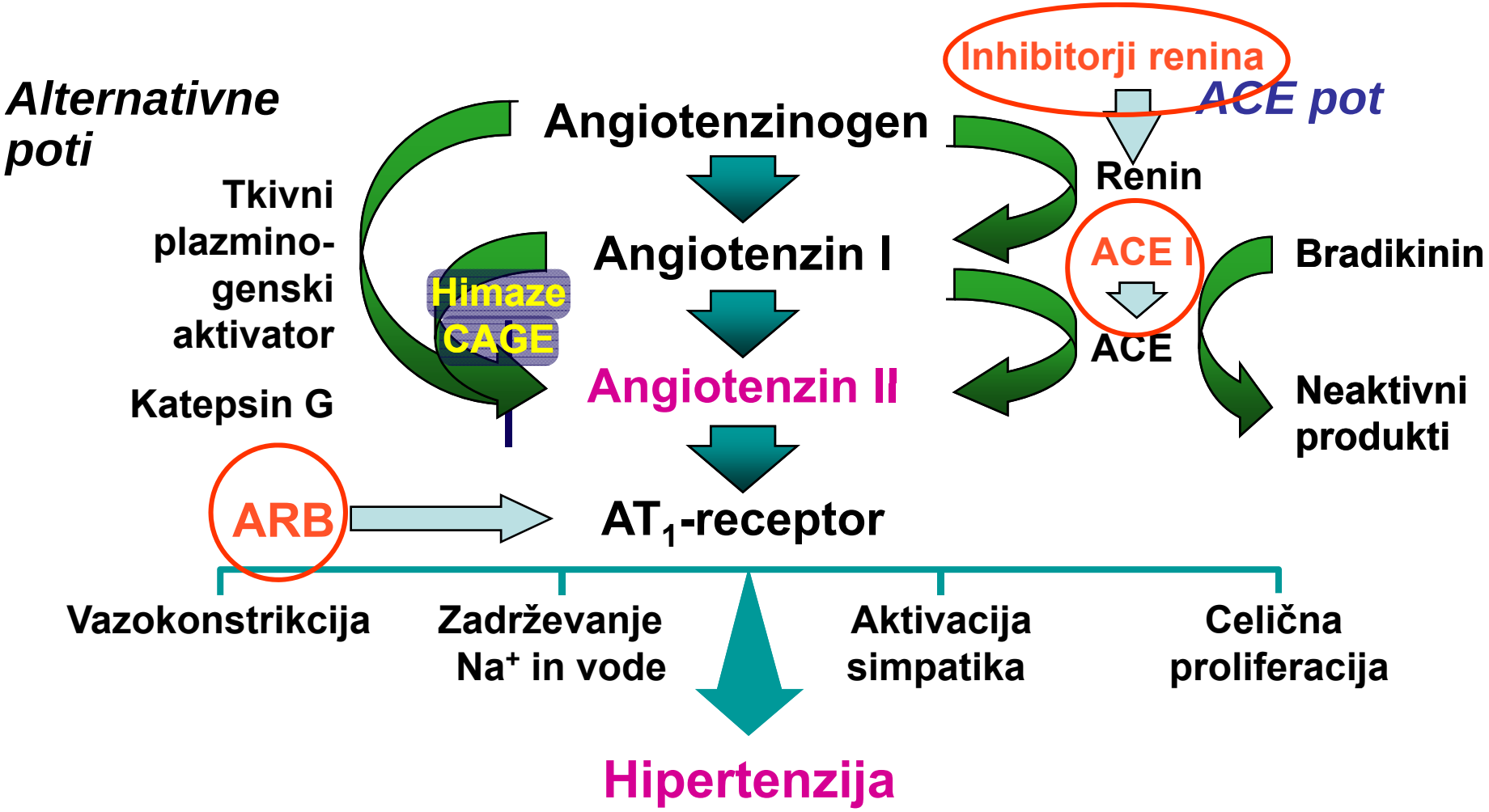
Inhibitorji ACE

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

Tarče v renin-angiotenzin sistemu



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

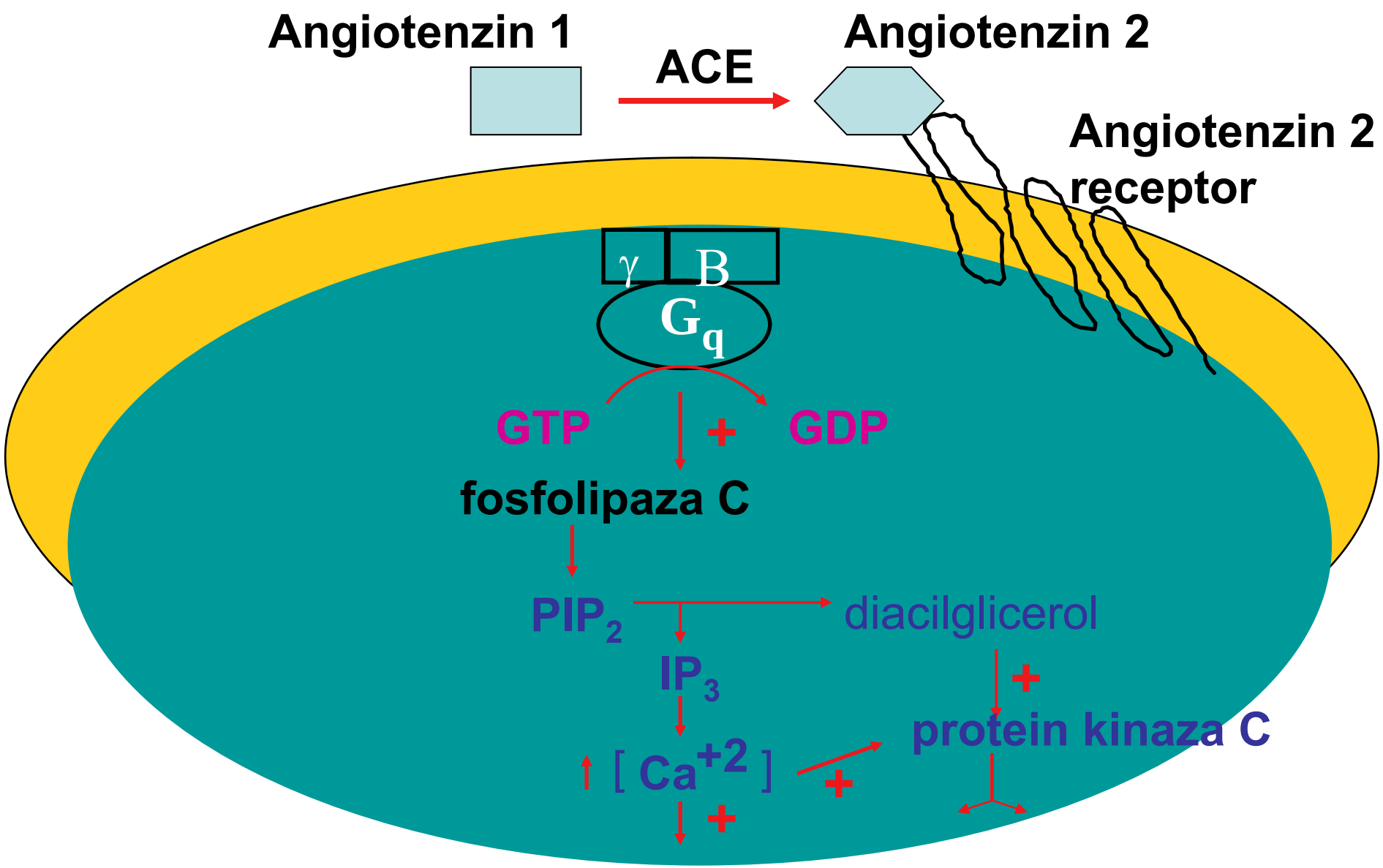
Razlike v učinkih preko AT_1 in AT_2 receptorjev

Vazokonstrikcija
Vaskularna proliferacija
Izločanje aldosterona
Proliferacija srčnih miocitov
Porast simpatičnega tonusa

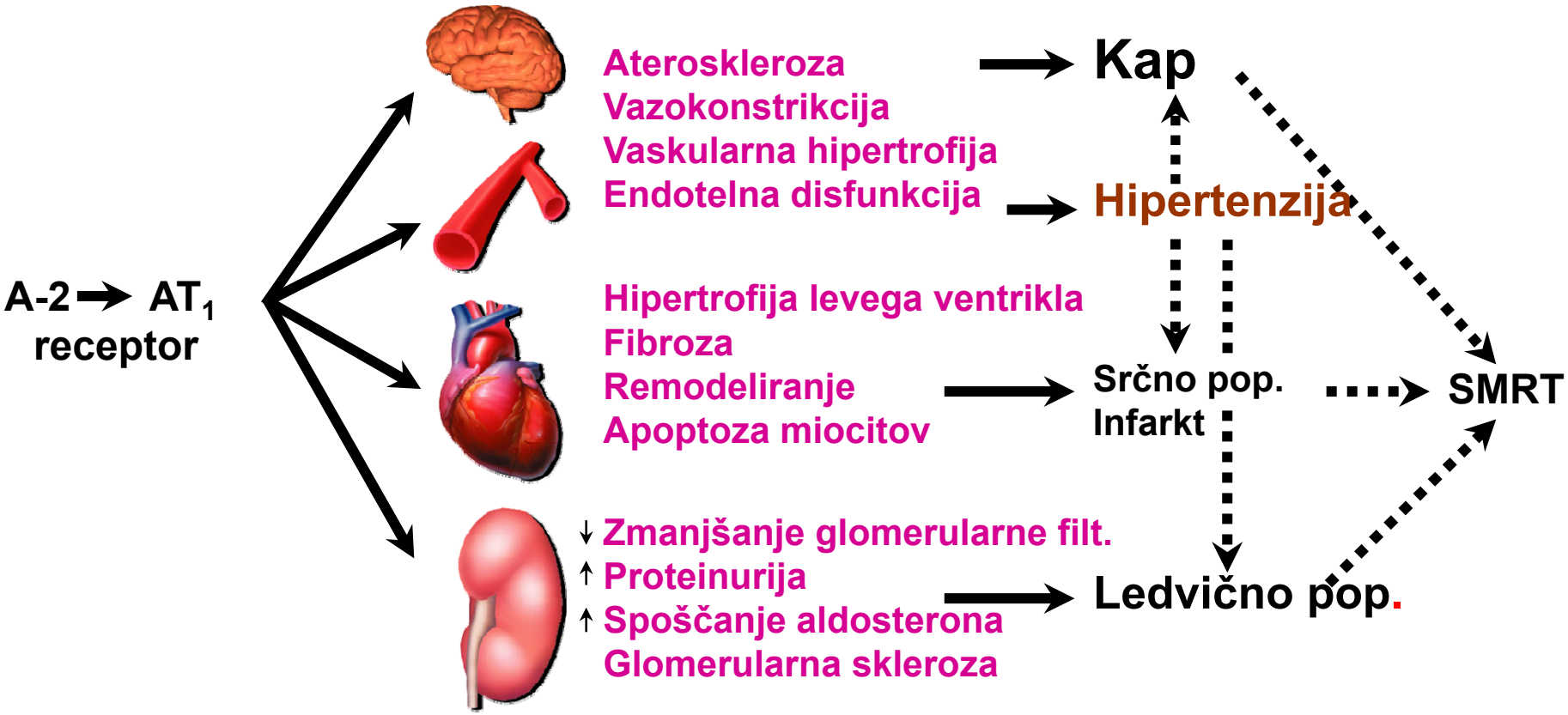
Vazodilatacija
Antiproliferacija
Apoptoza

AT_1 receptor

- Prvi opis 1970 (Lin in Goodfriend).
- družina s proteinom G sklopljenih receptorjev: 395 amino k.
- Angiotenzin-2 se veže na AT_1 receptor in povzroči konformacijsko spremembo, ki aktivira G proteinski kompleks


Angiotenzin 1
ACE
Angiotenzin 2
Angiotenzin 2 receptor
γ
B
Gq
GTP
+
GDP
fosfolipaza C
PIP2
diacilglicerol
IP3
+
protein kinaza C
[Ca+2]
+
+

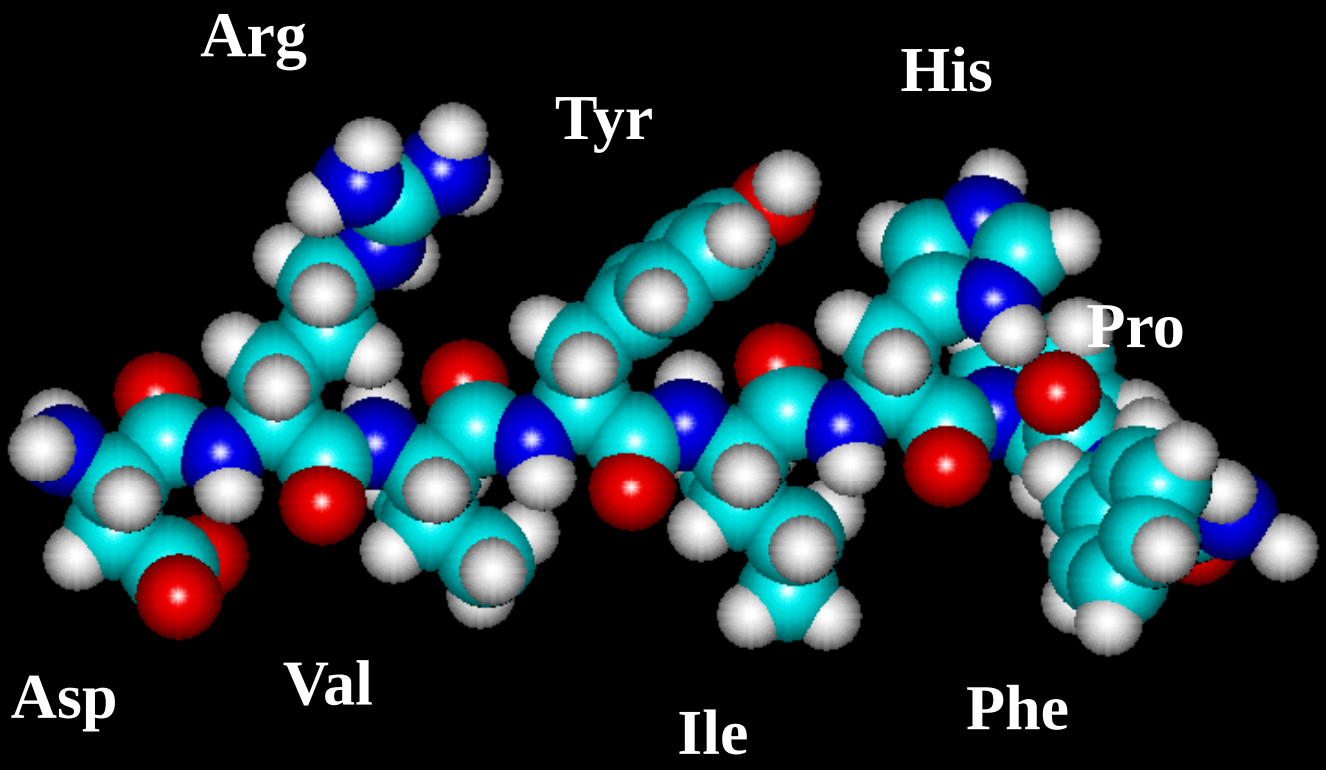
Angiotenzin 2 ima pomembno vlogo pri poškodbi organov



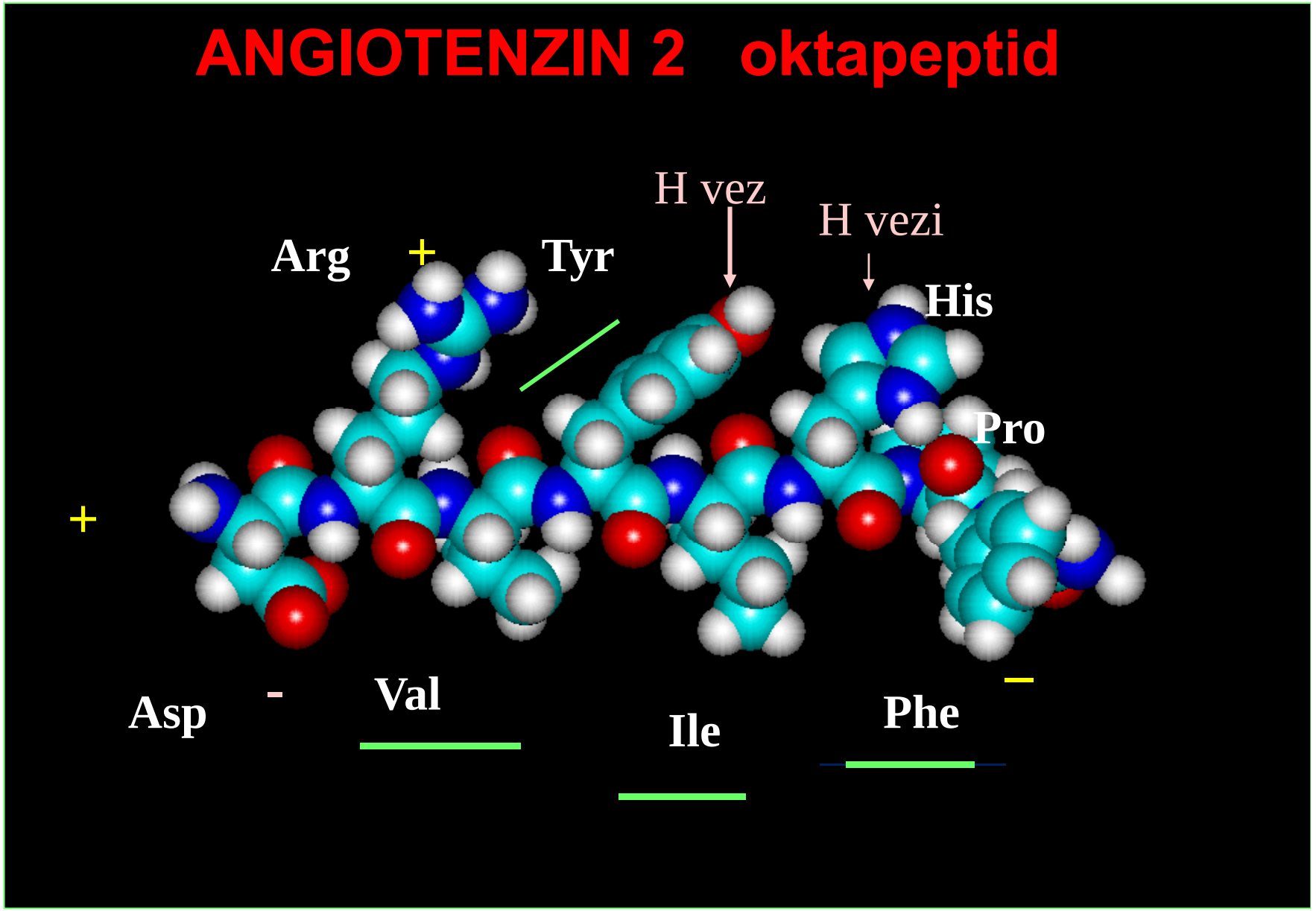
Načrtovanje sartanov

- Antagonisti AT_1
- Analogi nativnega liganda
- Selektivnost napram AT_1

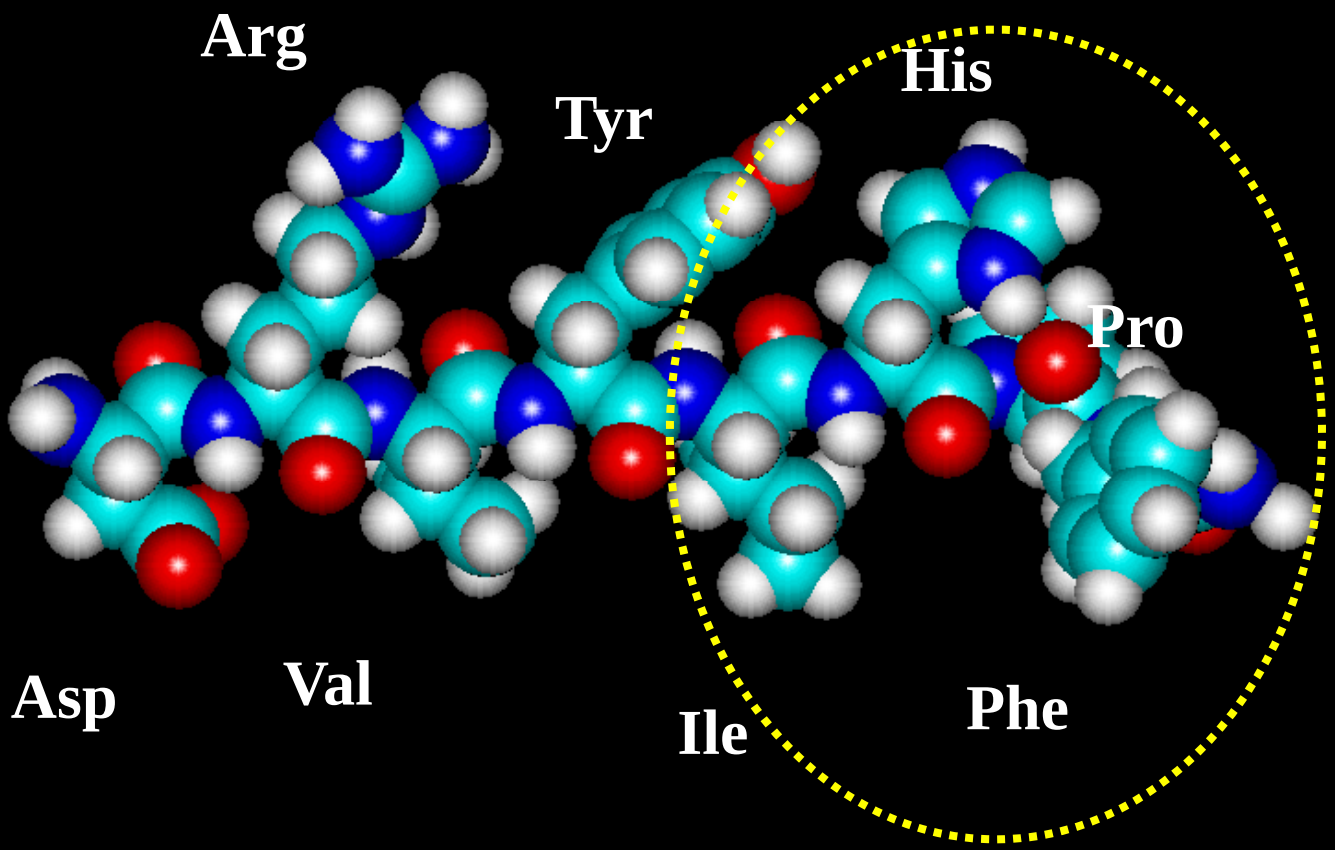
ANGIOTENZIN 2 oktapeptid



ANGIOTENZIN 2 oktapeptid



ANGIOTENZIN 2 oktapeptid



Načrtovanje sartanov

Angiotenzin II

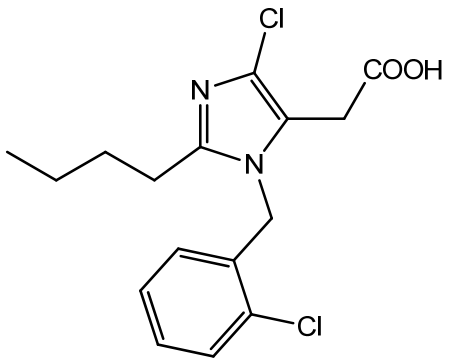
Asp-Arg-Val-Tyr-Ile-His-Pro-Phe

Saralazin

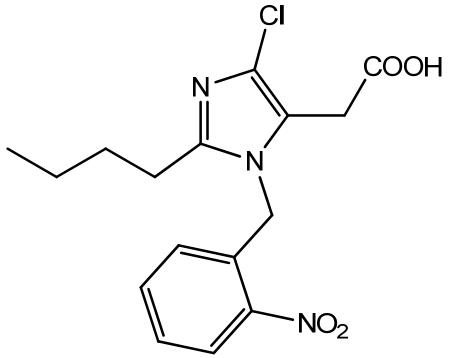
Sar-Arg-Val-Tyr-Ile-His-Pro-Sar

- Antagonist AT1
- Parcialni agonist
- Peptidna spojina

1-benzilimidazol-5-ocetne kisline



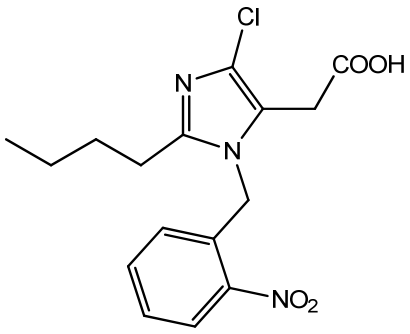
S-8307



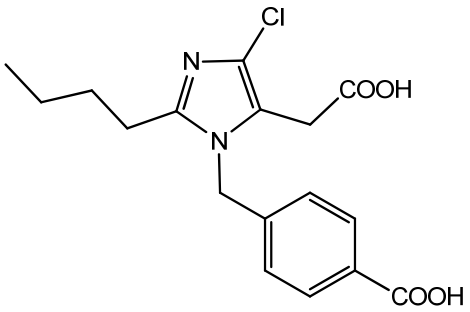
S-8308

- Antagonisti AT1
- Nizka jakost
- Selektivnost!

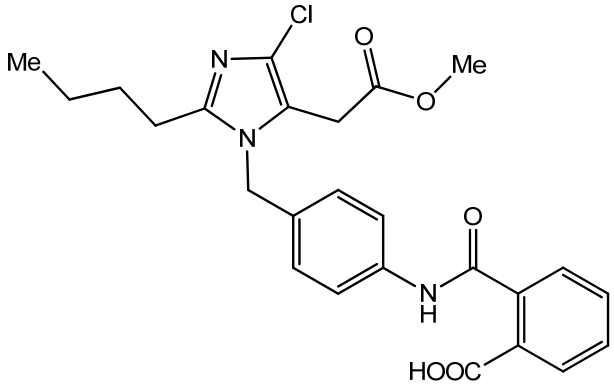
Načrtovanje sartanov



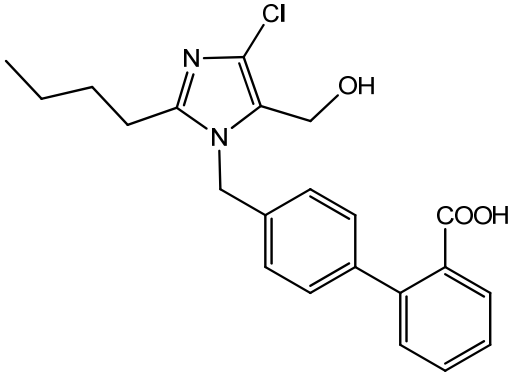
S-8308 (IC_{50}=15μM)



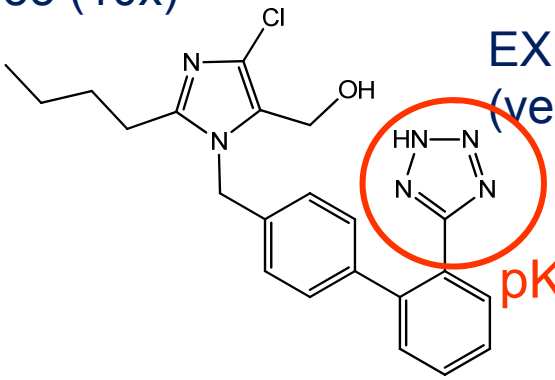
EXP-6155 (10x)



EXP-6803
(večja jakost, IV)



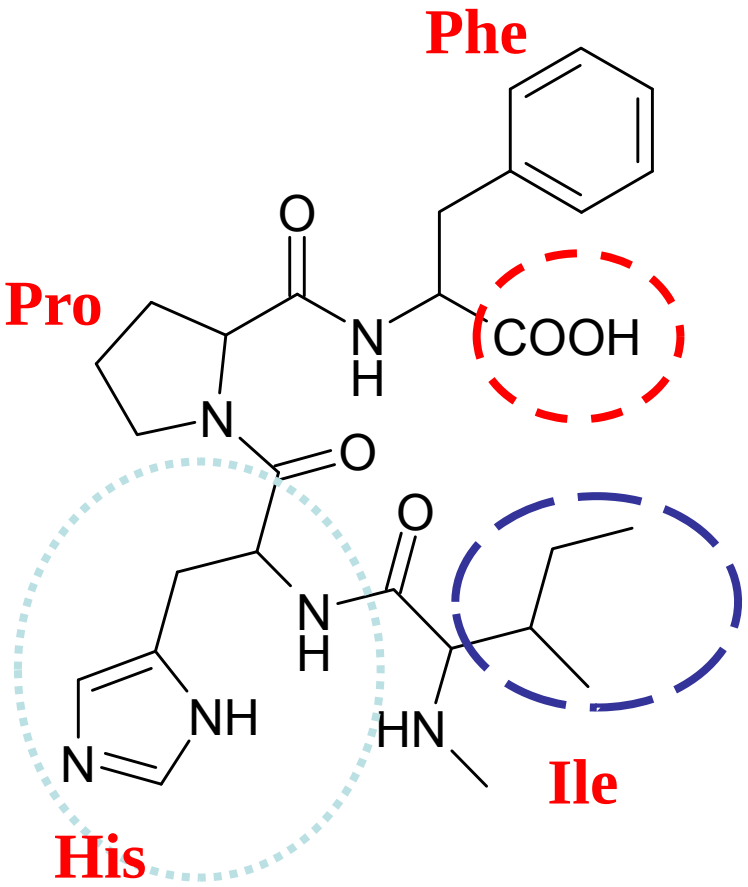
EXP-7711
(per os)



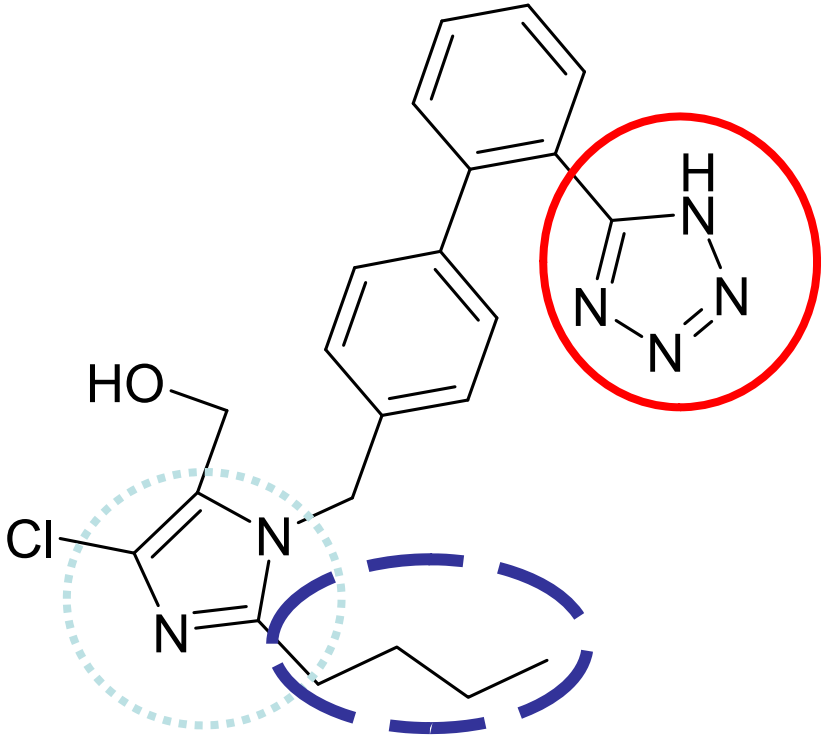
pKa(tetrazol)~6

LOSARTAN
(per os, IC_{50}=19nM)

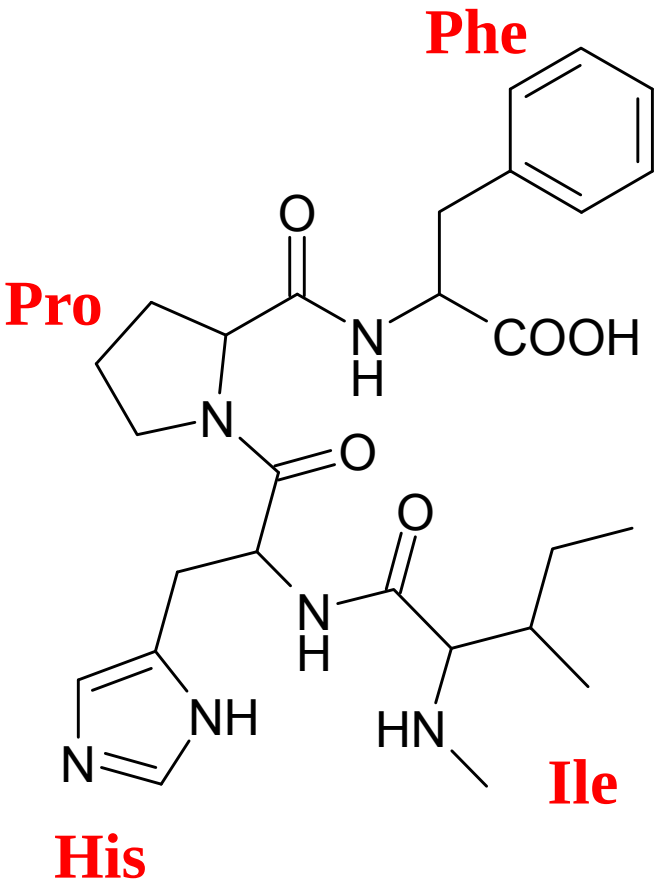
Zadnje štiri aminokisline Angiotenzina 2

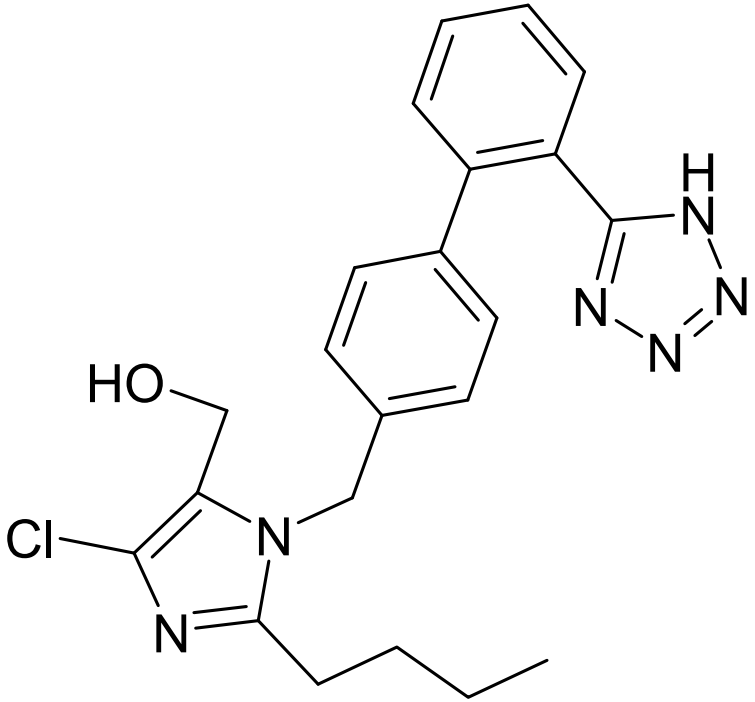


Molekula losartana

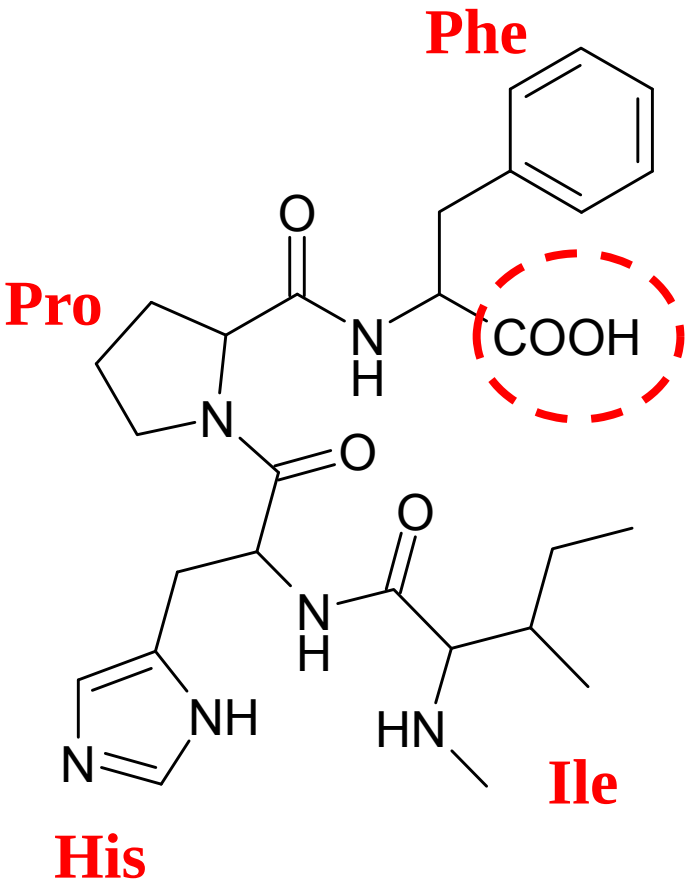


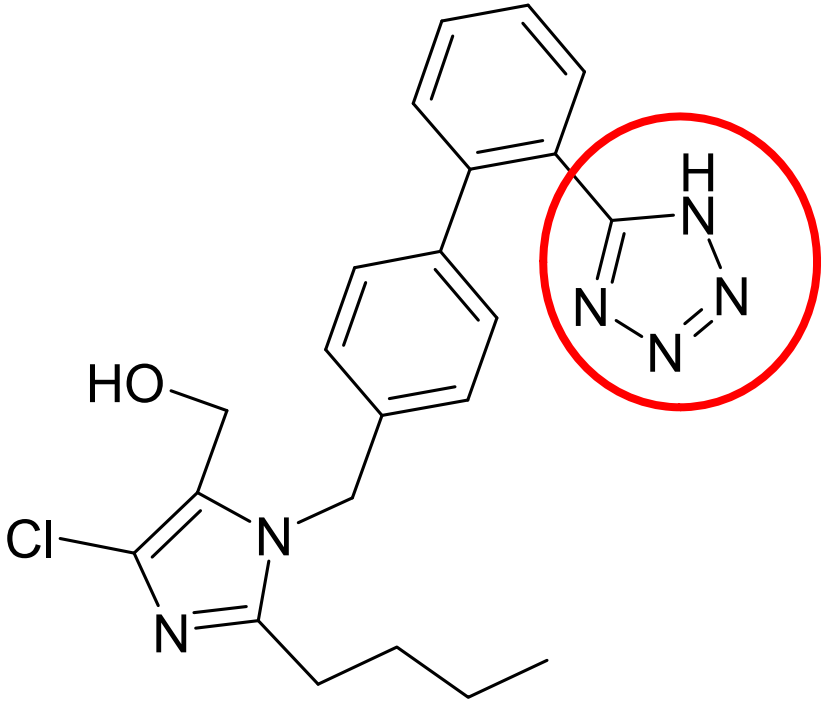
Angiotenzin 2 in losartan





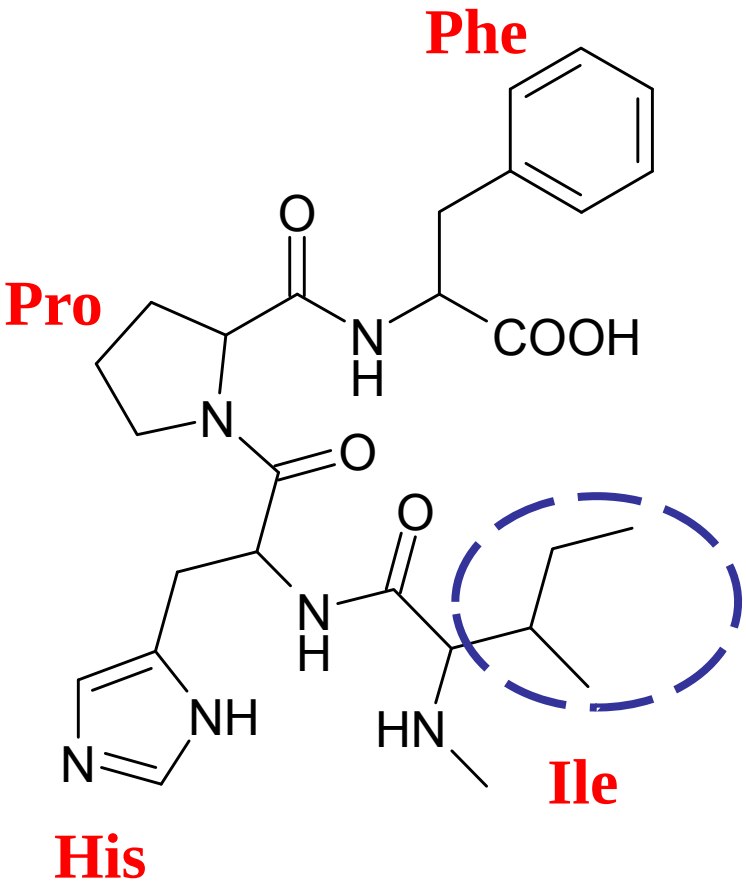
Angiotenzin 2 in losartan

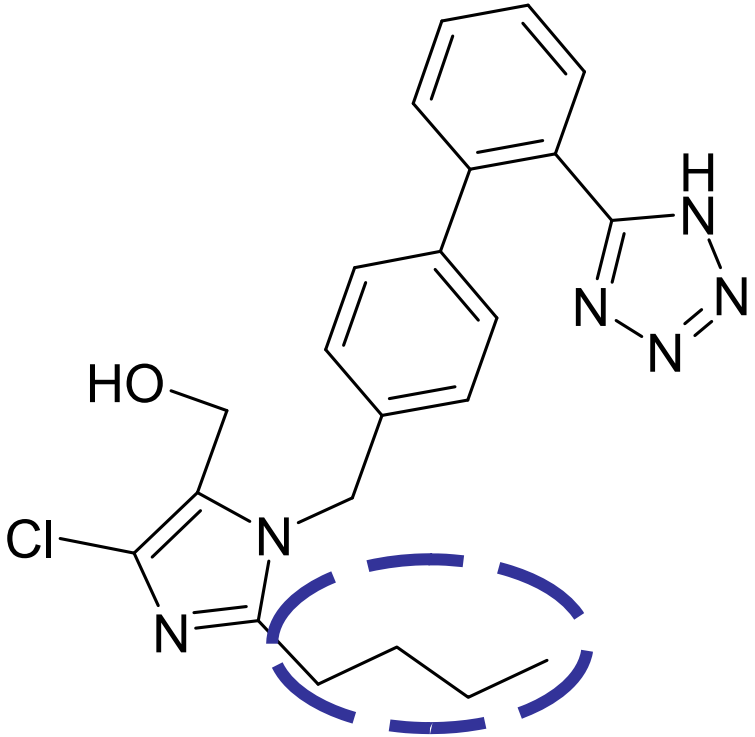




Podobnost v anionskem centru

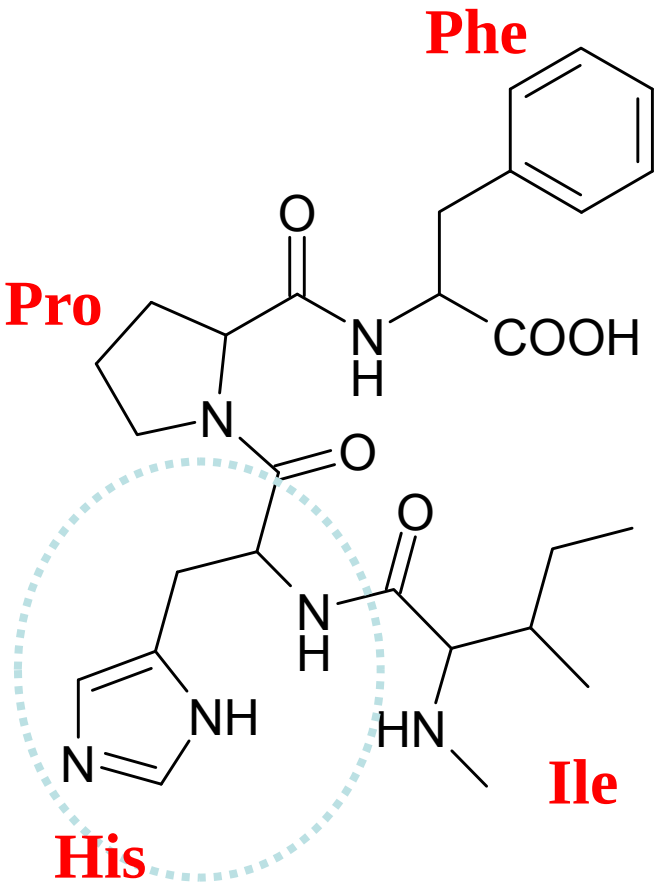
Angiotenzin 2 in losartan

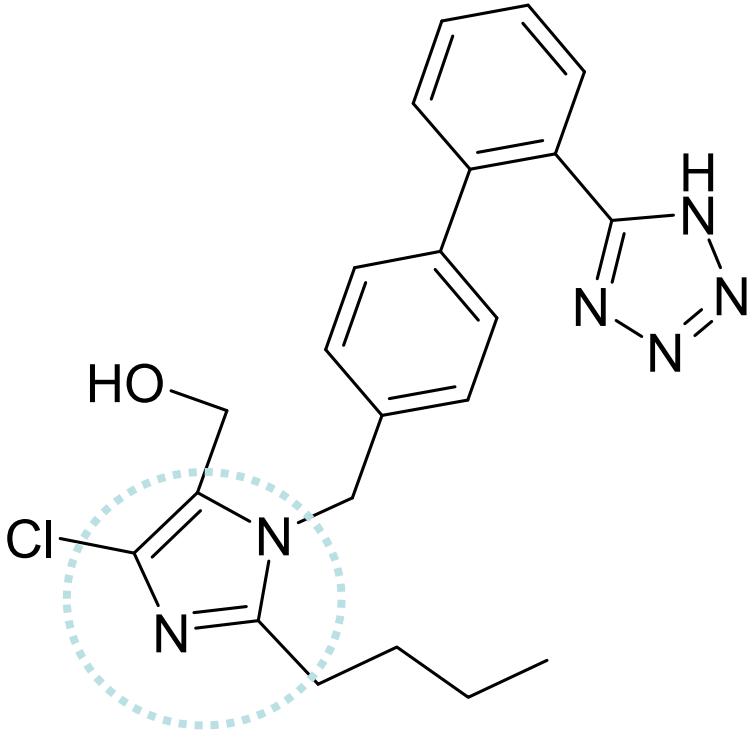




Podobnost v lipofilnosti

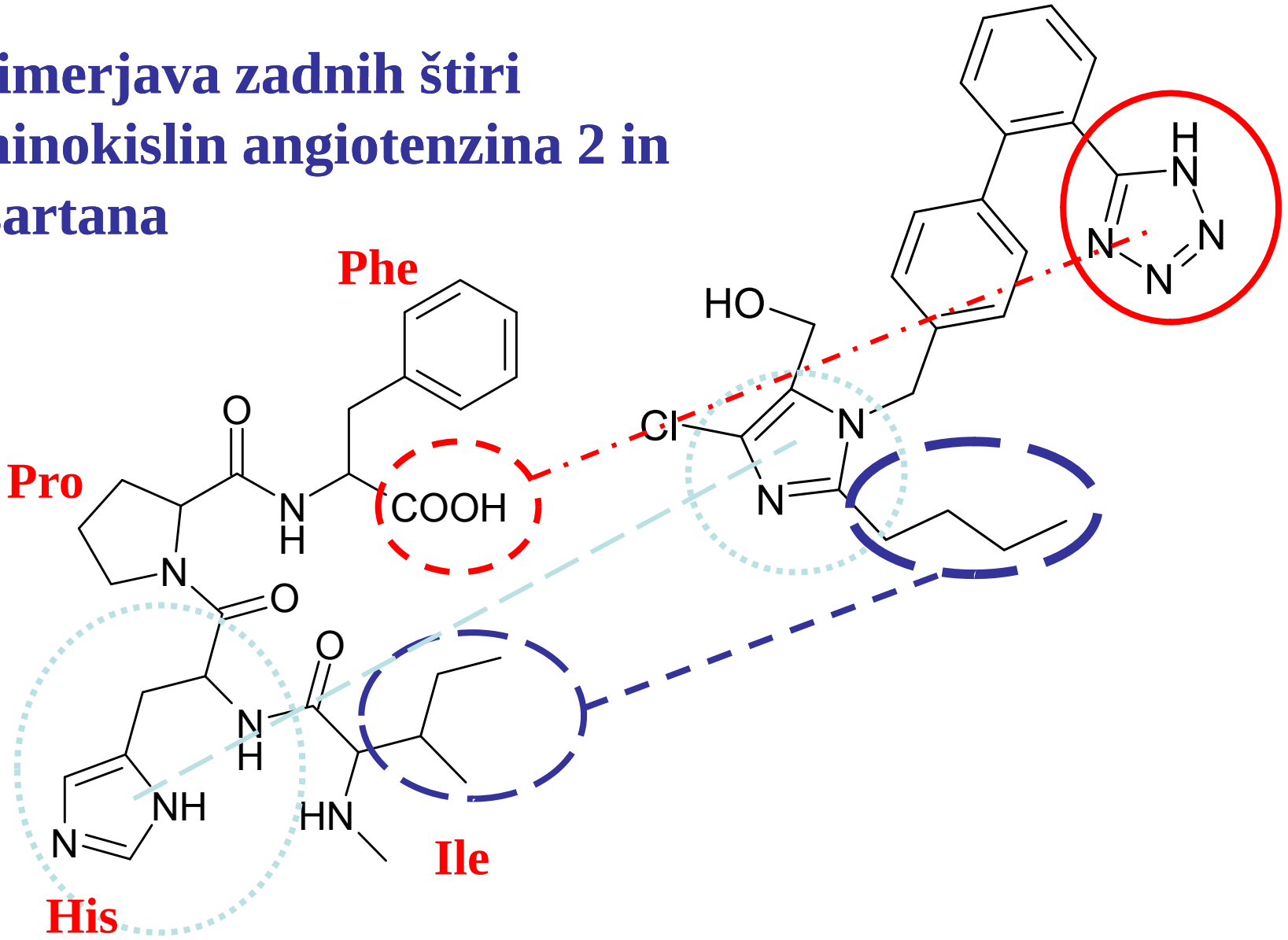
Angiotenzin 2 in losartan

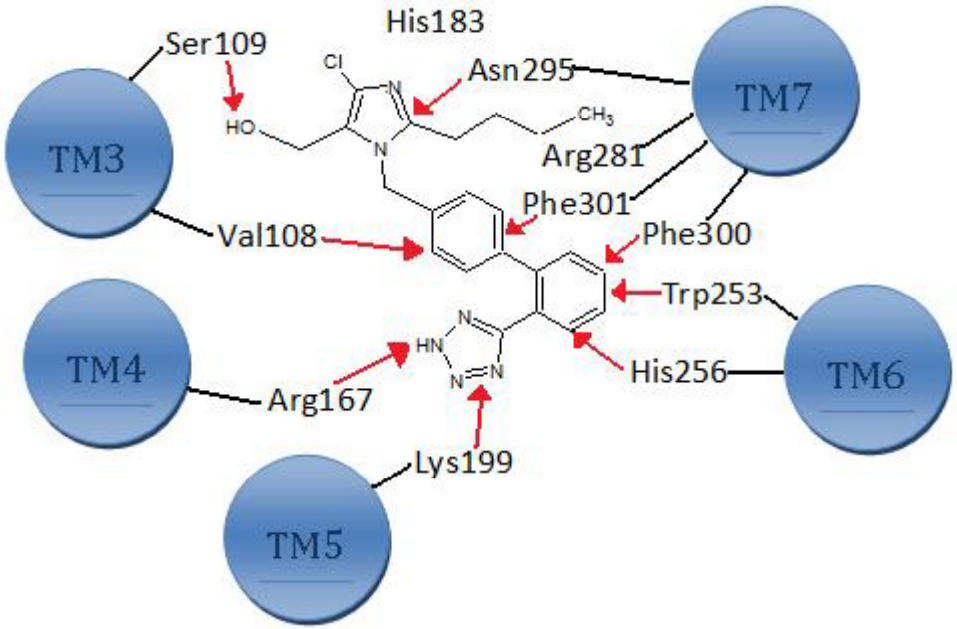




Prisotnost imidazola

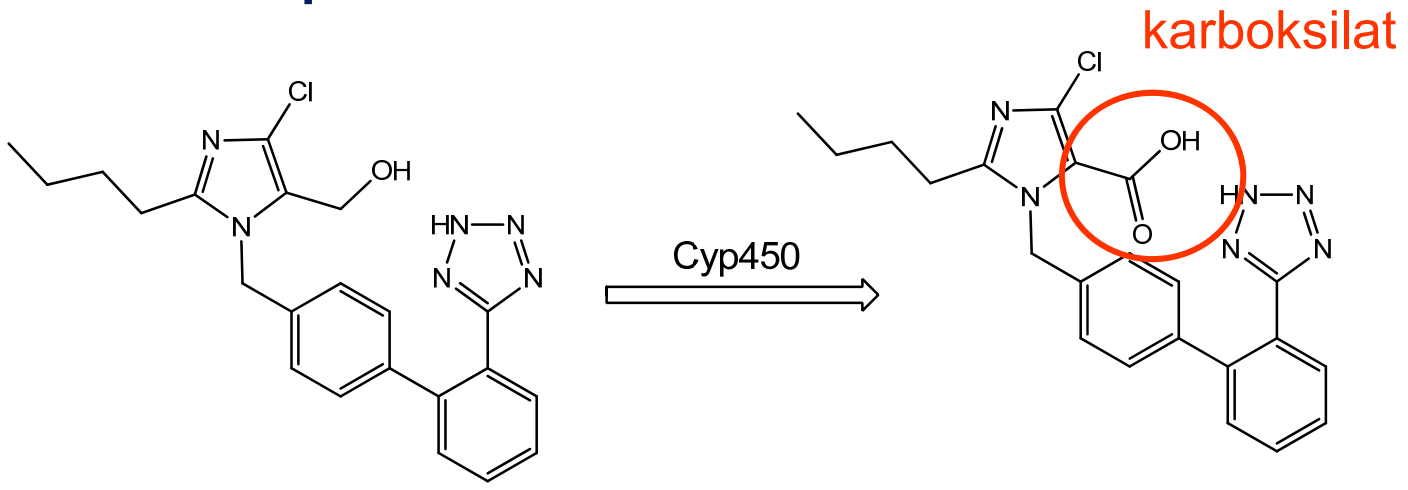
Primerjava zadnih štiri aminokislin angiotenzina 2 in losartana




His183
Ser109
Asn295
TM7
TM3
Arg281
Phe301
Phe300
Val108
Trp253
TM4
TM6
His256
Arg167
Lys199
TM5

Losartan

- Neke vrste predzdravilo



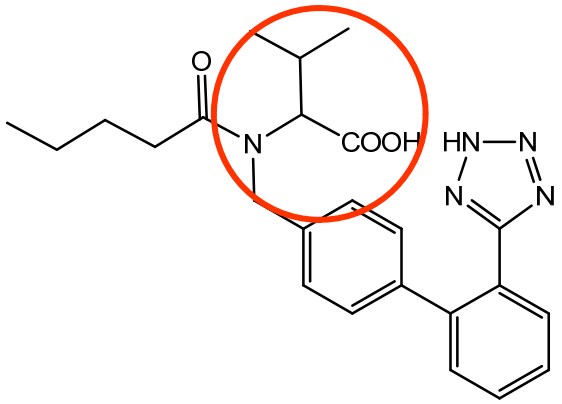
losartan

- Kratek $t_{1/2}$ ~2 uri!
- BU 33%

EXP-3174
10-40x močnejši
$t_{1/2}$ 6-9 ur

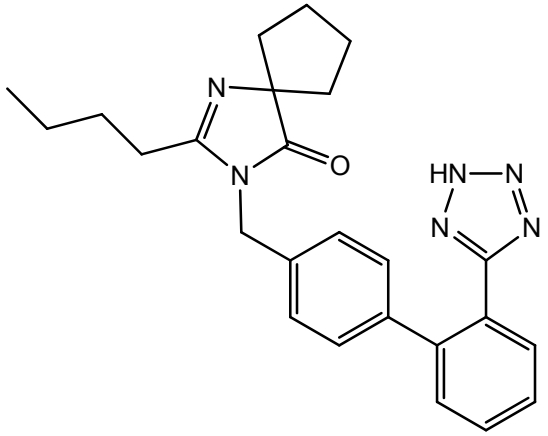
Valsartan

- Močnejši od losartana, IC_{50}= 8,9 nM
- Zelo selektiven napram AT1
- $t_{1/2}$ 6 ur
- BU~25%



Irbesartan

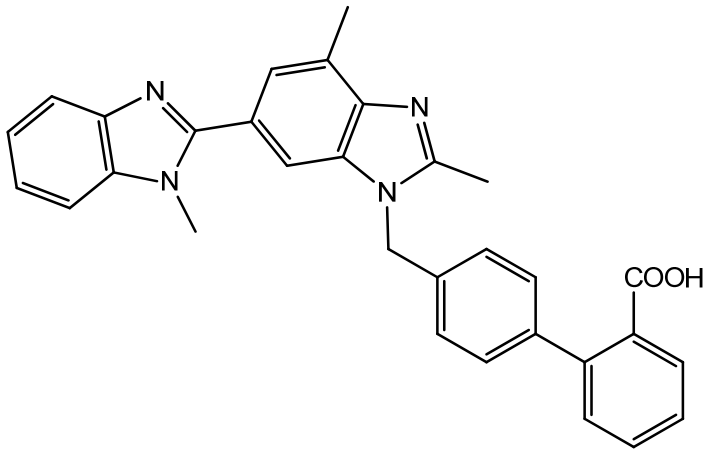
- Močnejši od losartana, IC_{50}= 1,3 nM
- Višja biološka razpoložljivost do 80%
- $t_{1/2}$ 11 ur
- Nima aktivnih metabolitov



irbesartan

Telmisartan

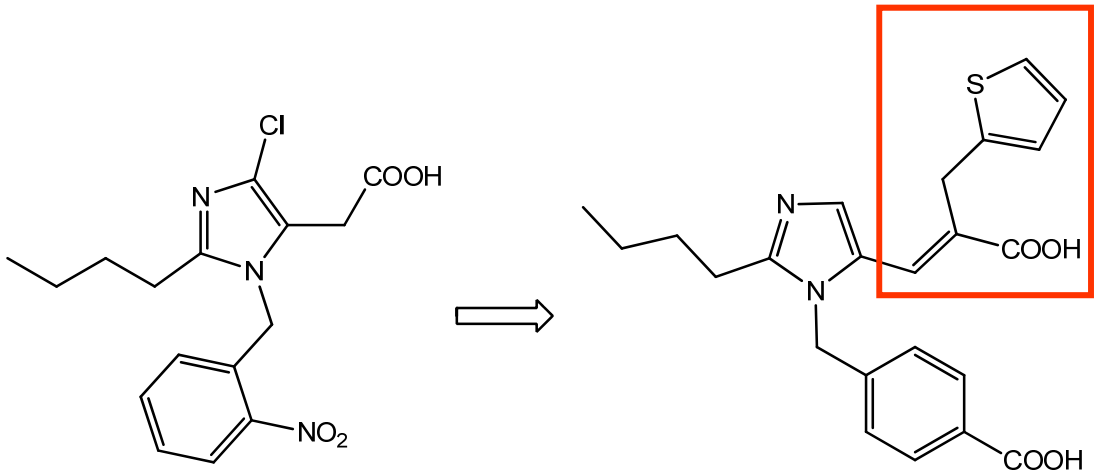
- Karboksilat!
- Večja lipofilnost
- BU do 42-58%
- Dolg $t_{1/2}$ = 24h
- Poleg AT1 deluje na PPARγ receptorje



telmisartan

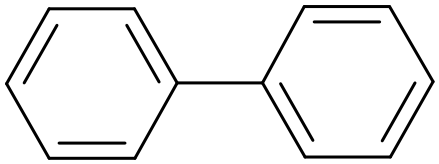
Eprosartan

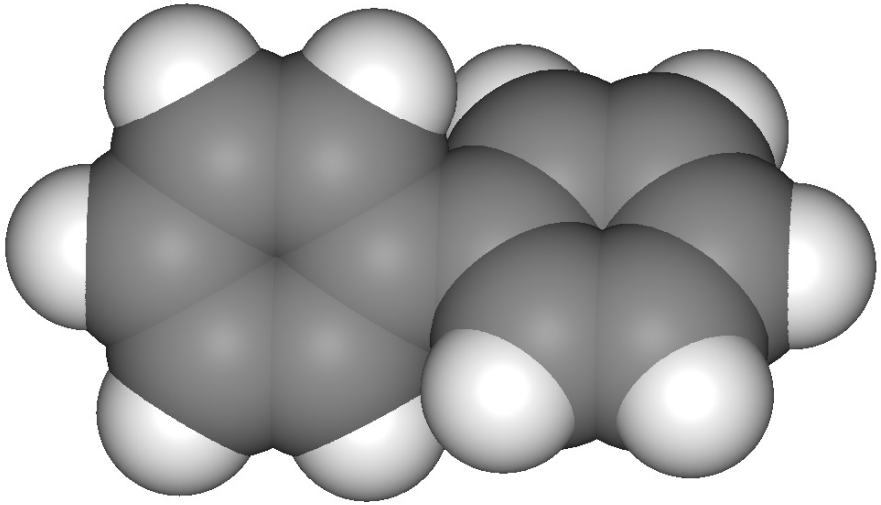
- Močan učinek, IC_{50}= 1,5 nM
- Ni bifenilnega fragmenta
- Struktura podaljšana proti C-terminalnemu delu

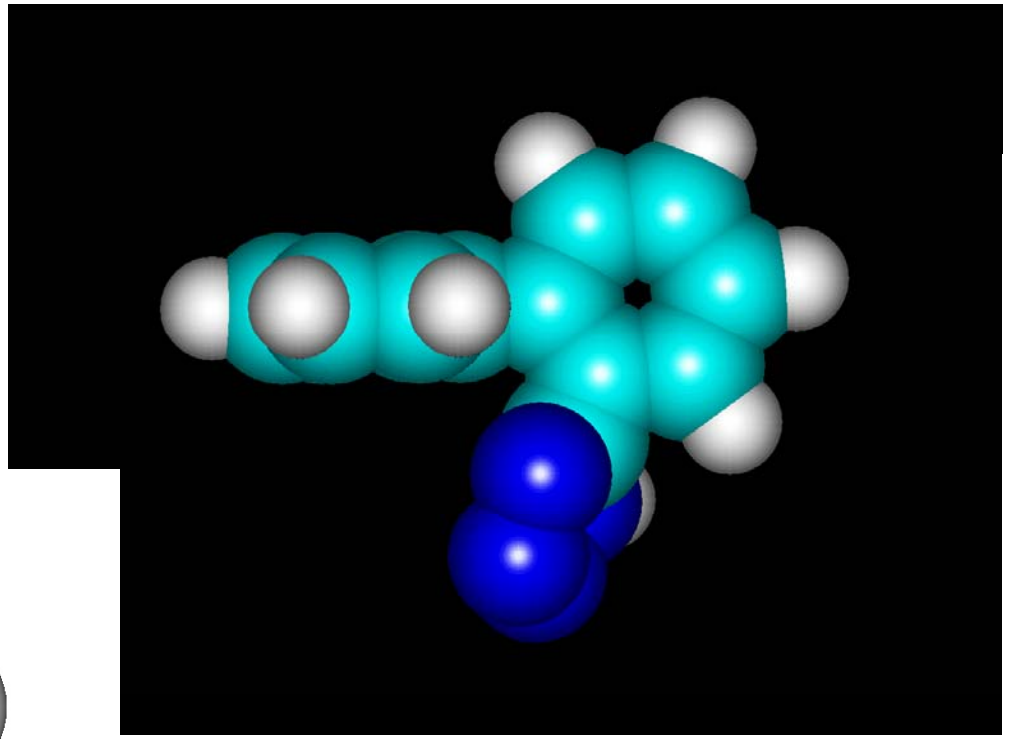


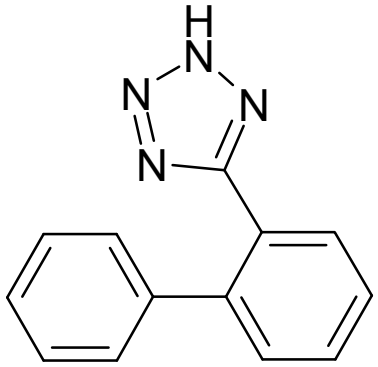
S-8308 eprosartan

Primerjava bifenila in ortotetrazolobifenila

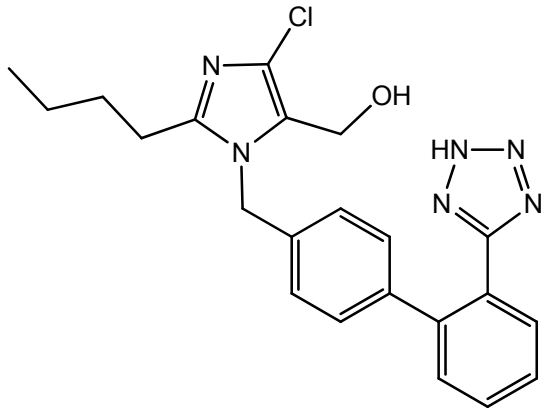




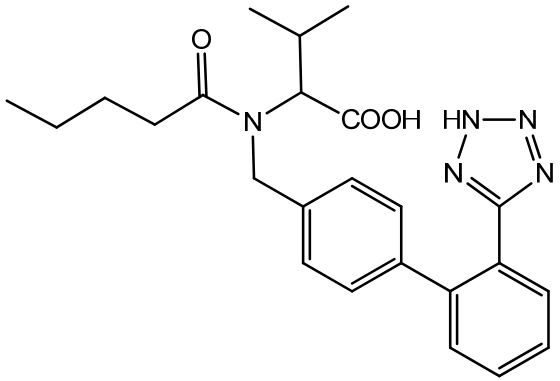


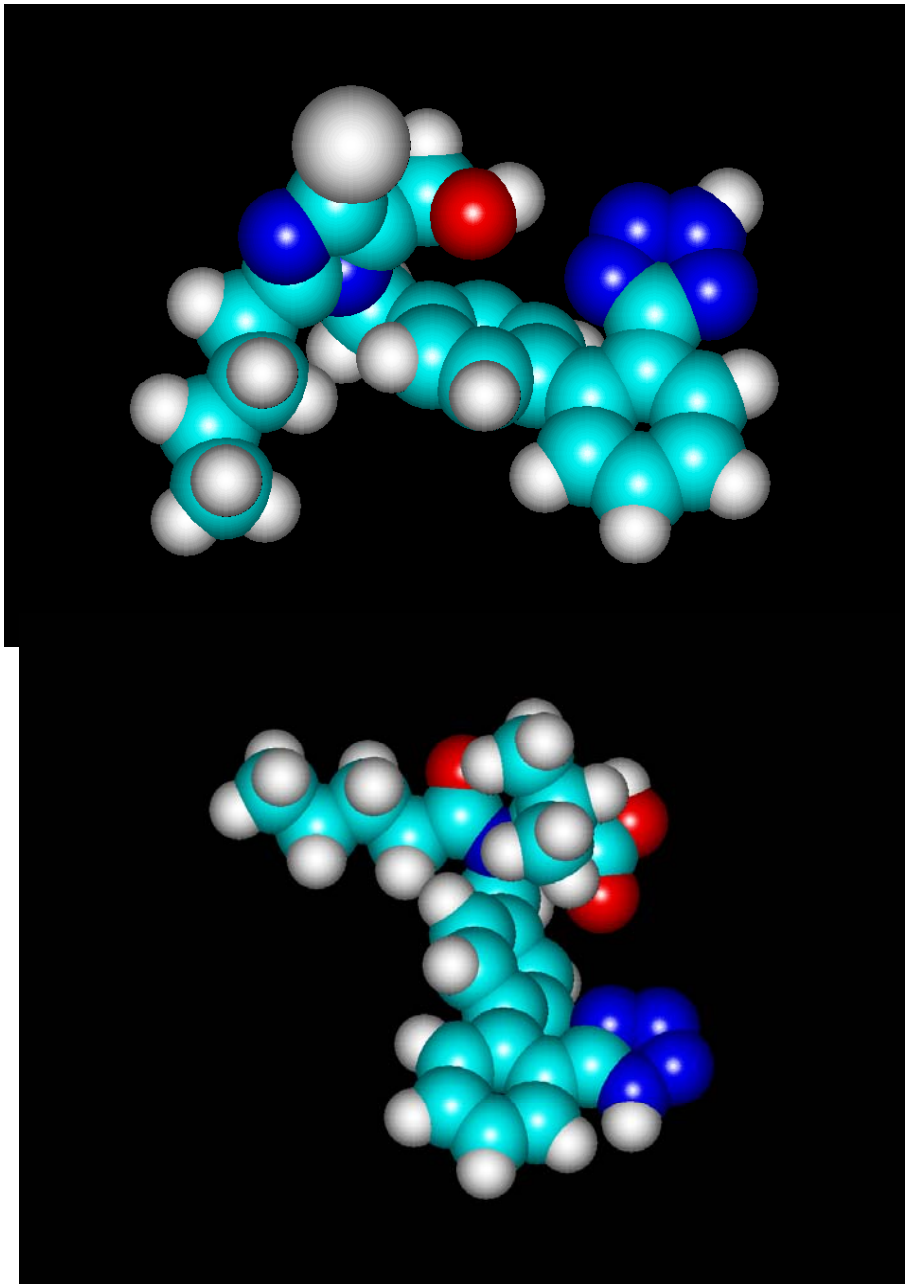


LOSARTAN

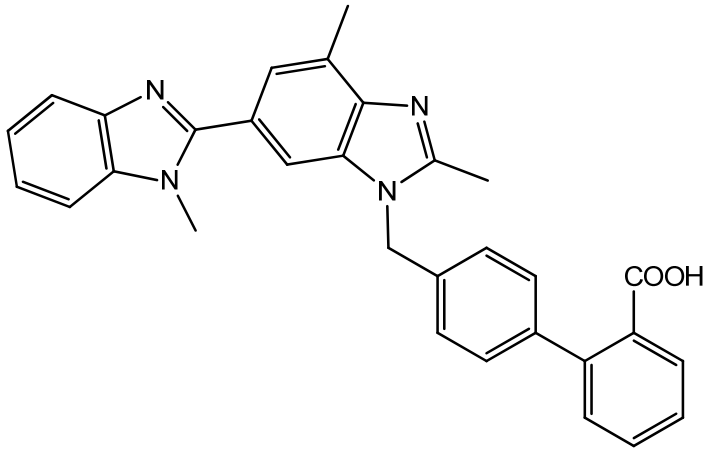


VALSARTAN

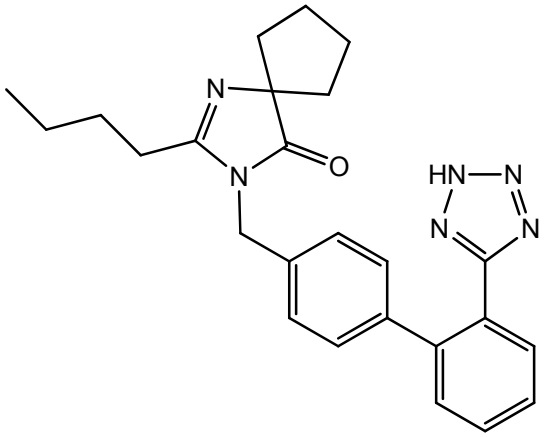


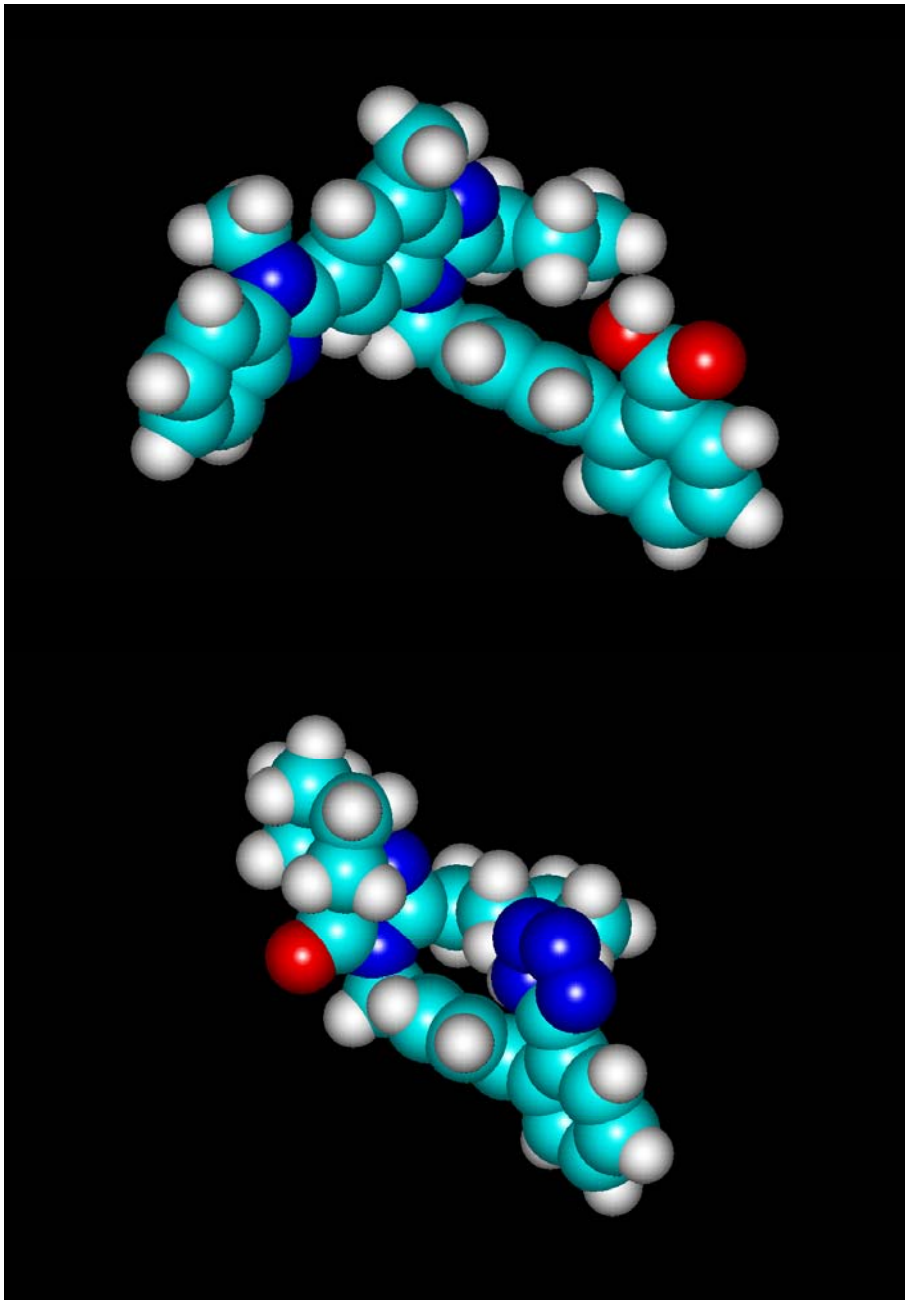


TELMISARTAN



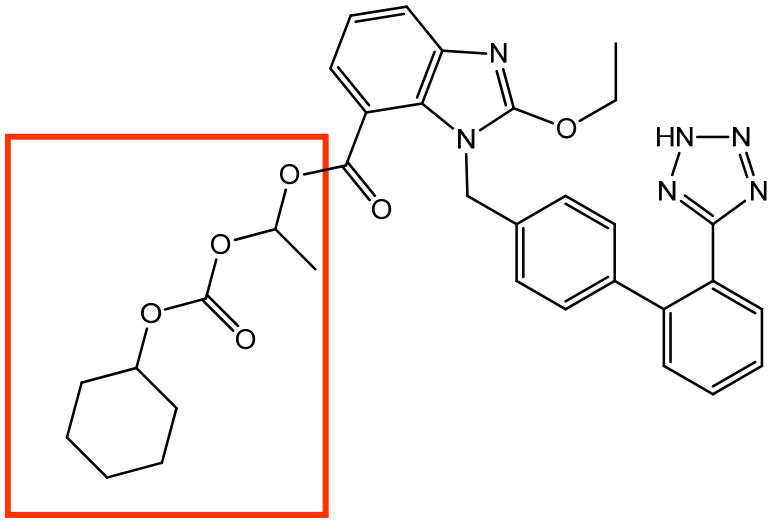
IRBESARTAN





Predzdravili

- Kandesartan cileksetil

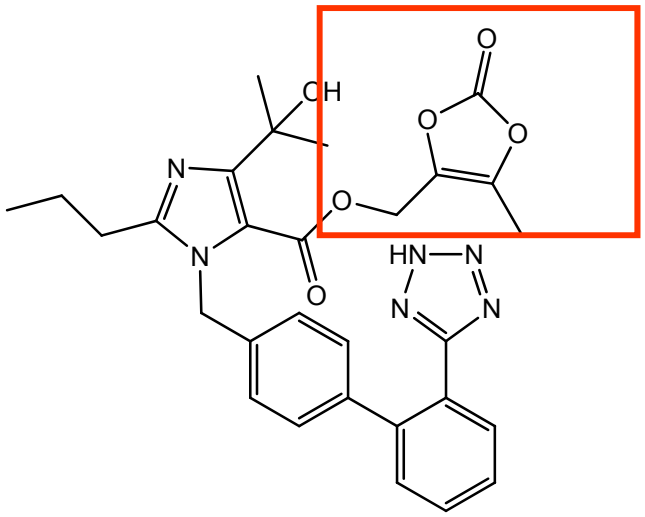


cileksetil

- Kandesartan – nizka BU
- Predzdravilo BU~15%

Predzdravili

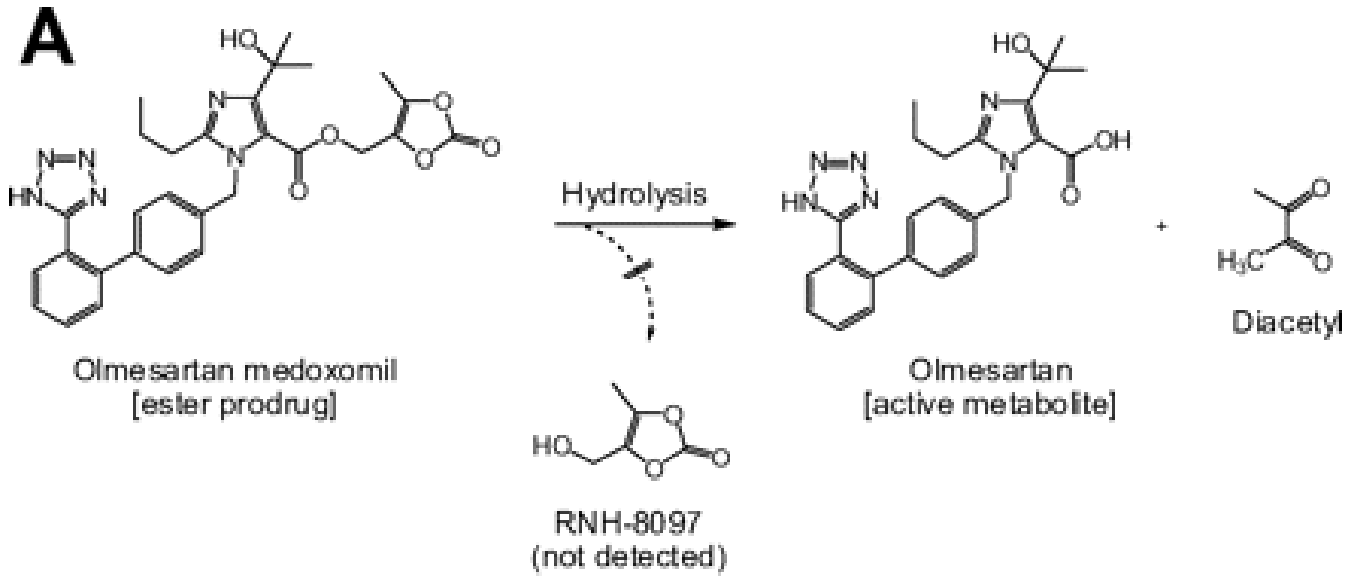
- Olmesartan medoksomil (medoksomililolmesartanat)



•Olmesartan – nizka BU
•Predzdravilo BU~26%

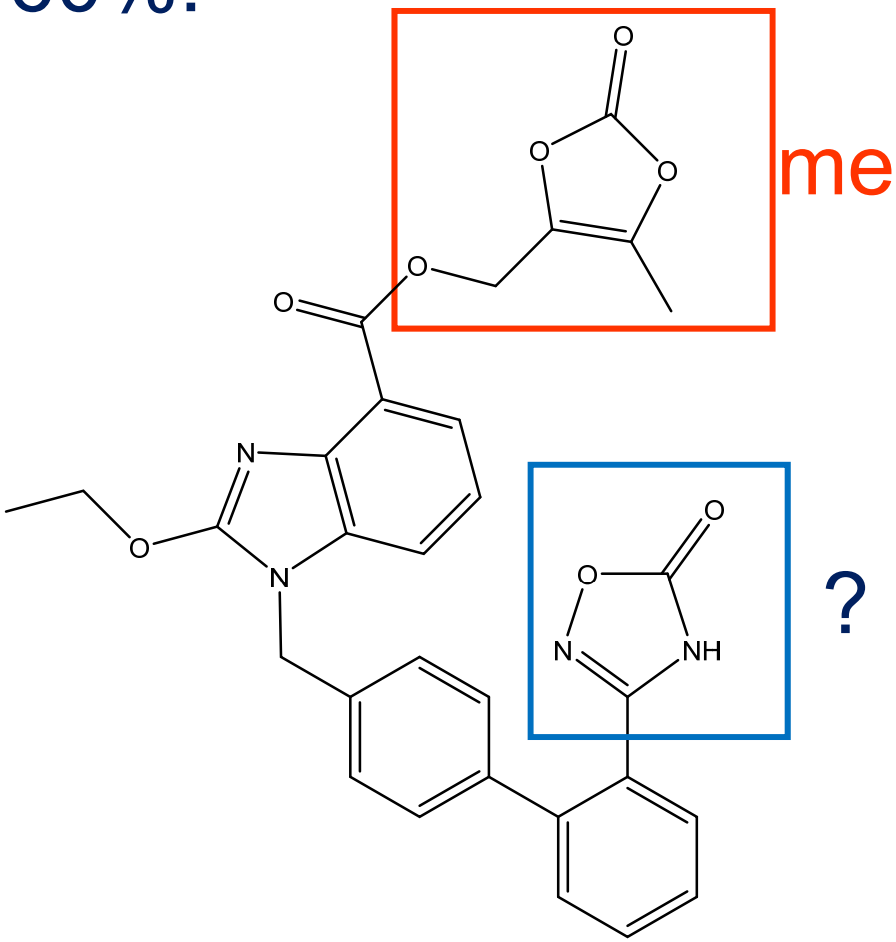
medoksomil

Bioaktivacija olmesartana medoksomila



Azilsartan medoksomil (Feb 2011)

- BU 60%!



medoksomil

SAR sartanov

- Kisla skupina pripeta na fenilni obroč: karboksilat, tetrazol
- Imidazol
- Mesto 2 imidazola – alkilna skupina (Bu, Pr)
- Mesto 4 imidazola – karboksilat, keton, hidroksimetil, benzilimidazol

Fiz-kem lastnosti sartanov

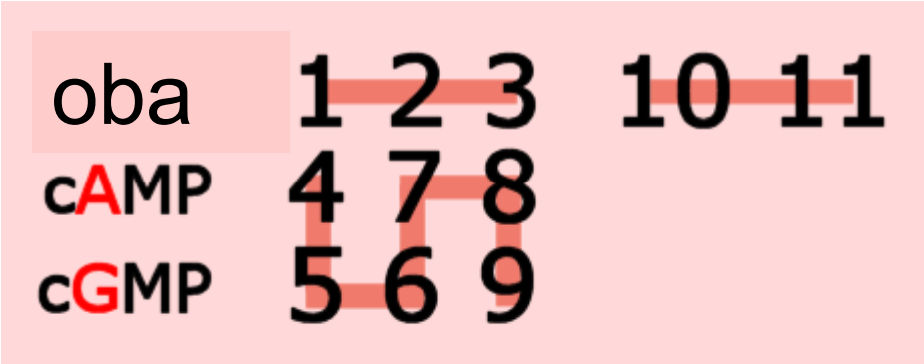
- Tetrazol: pKa ~ 6, vsaj 90% ioniziran pri fiziološkem pH
- karboksilat pri valsartanu, olmesartanu, kandesartanu
- Telmisartan in eprosartan imata pKa med 3–4; popolna ionizacija
- BU irbesartana (60–80%) in telmisartana (42–58%) visok, pri ostalih BU nizka (15–33%)

Metabolizem sartanov

- Oksidacija losartana!
- Ostali – izločanje večinoma v nespremenjeni obliki
- telmisartan in eprosartan se izločajo v obliki glukuronidov
- Tetrazol metabolno razmeroma stabilen

Fosfodiesteraze

- Cepijo fosfodiestersko vez cAMP ali cGMP
- PDE 1-11



Klinično pomembni

- PDE3 – cAMP
- PDE5 – cGMP

Neselektivni inhibitorji fosfodiesteraz

- Kofein
- Teofilin
- Teobromin

Inhibitorji fosfodiesteraze 3

- Učinki preko ↑ cAMP

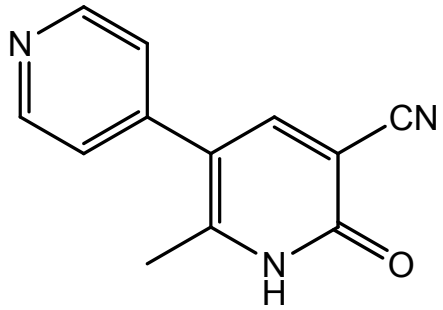
Močnejši učinek

srce	žile
kardiostimulatorni	inhibicija MLCK
povečana kontraktilnost (Inotropni učinek)	relaksacija
Povečan iztisni volumen	vazodilatacija
	znižanje pritiska

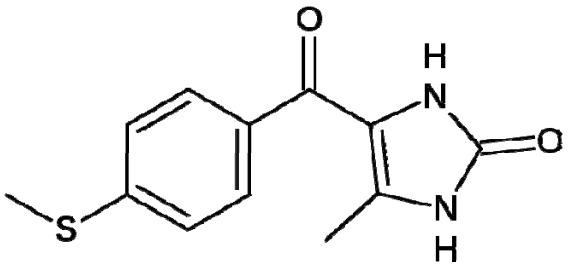
- Kontraindicirani pri dolgotrajni terapiji po poškodbi srca
- Indicirani pri akutnih težavah – dekompenzirano srce

Inhibitorji fosfodiesteraze 3

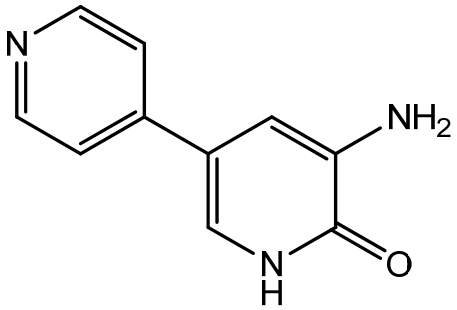
- milrinon

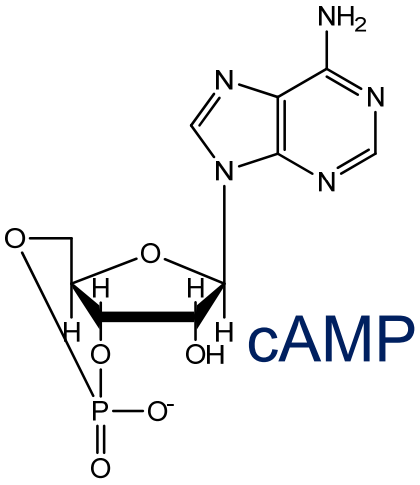


- enoksimon



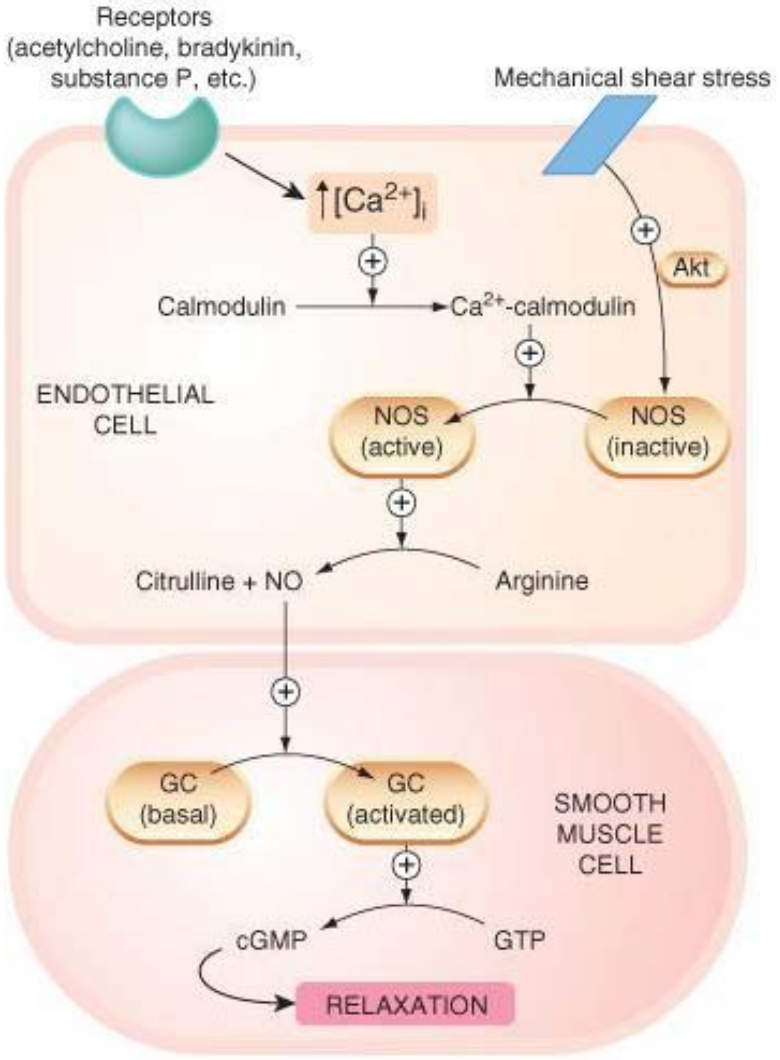
•amrinon





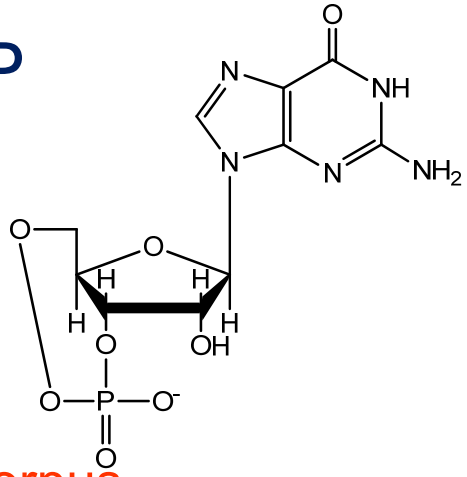
cAMP

Regulacija krvnega tlaka preko NO

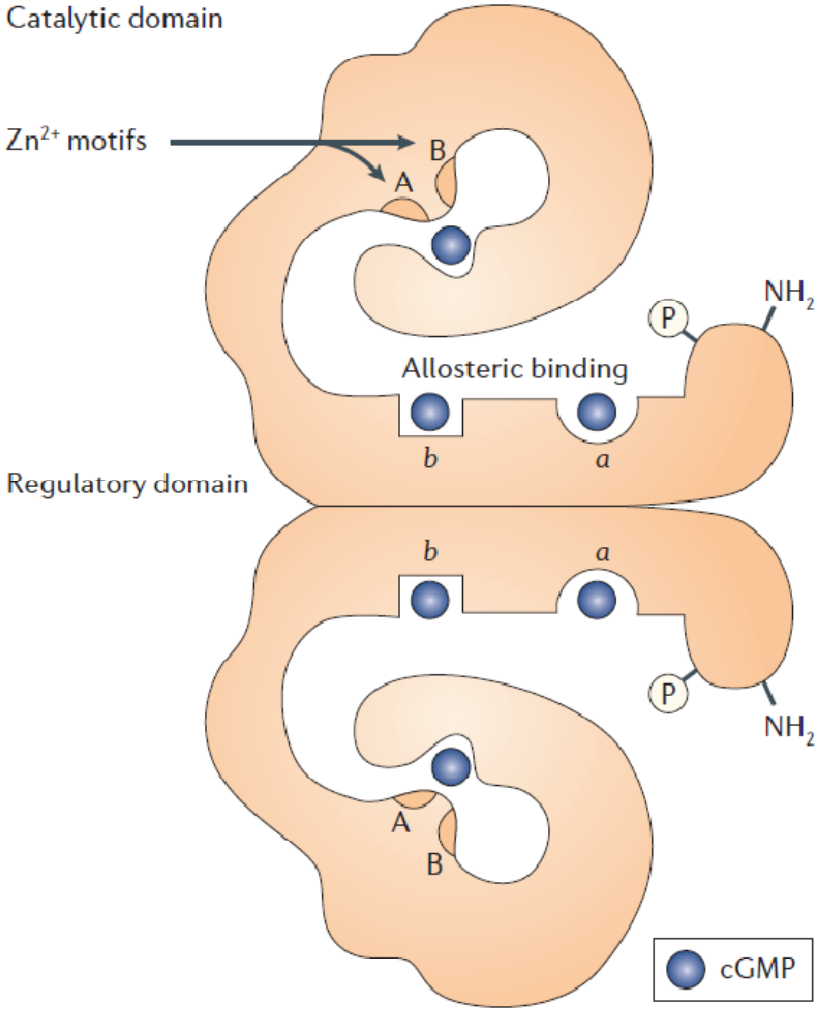


Fosfodiesteraza tipa 5

- Cepi cGMP

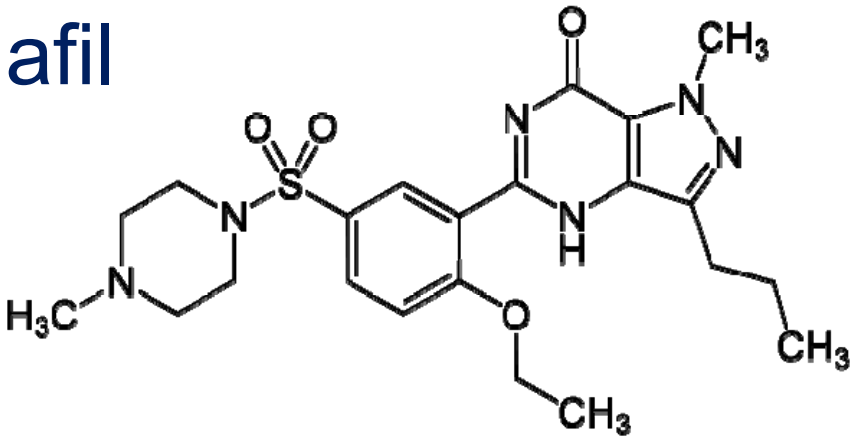


- Srce, pljuča, Corpus cavernosum, prostata, sečevod, retina, skeletne mišice

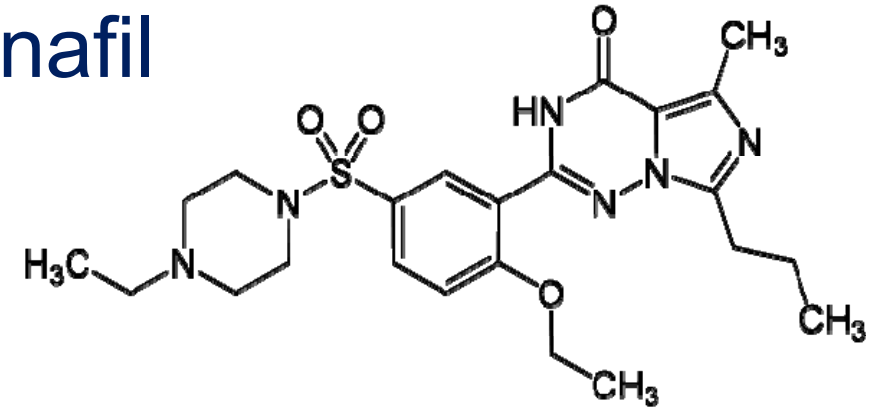


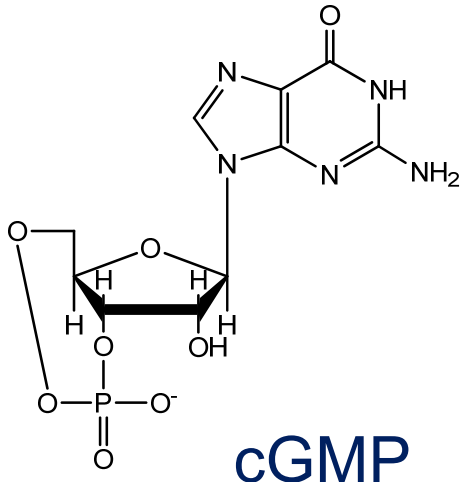
Inhibitorji fosfodiesteraze 5

- sildenafil



- vardenafil



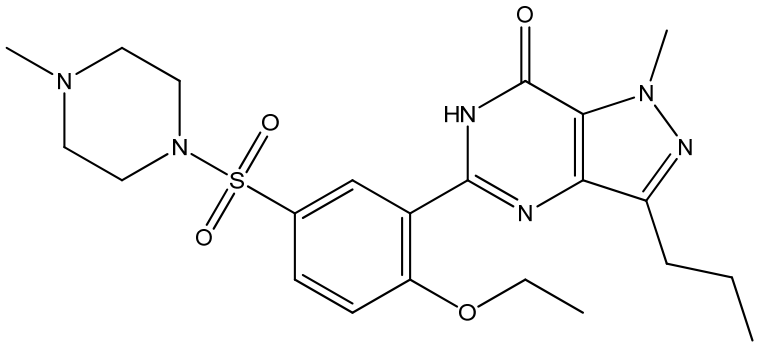


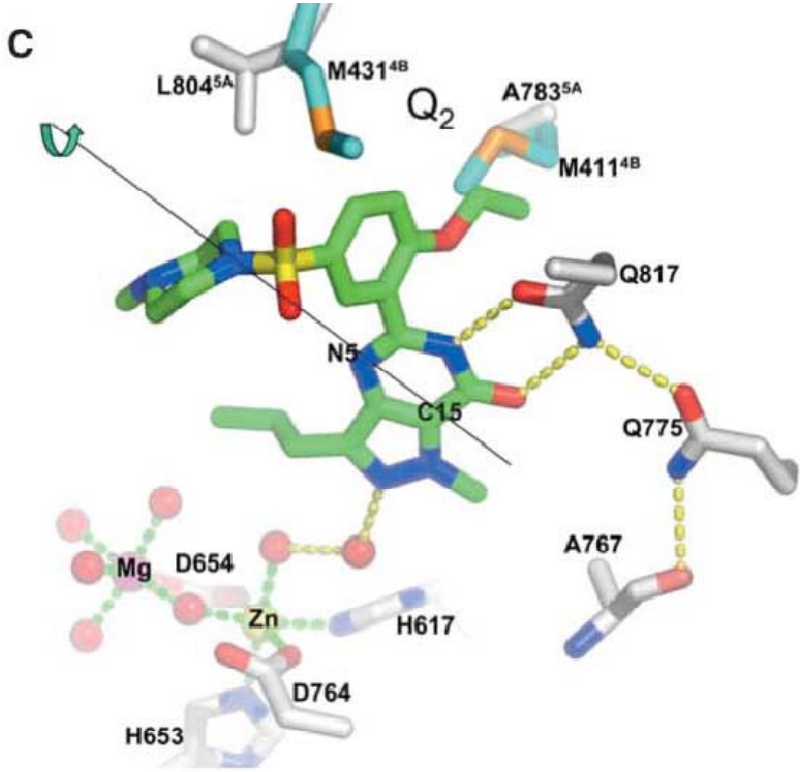
cGMP

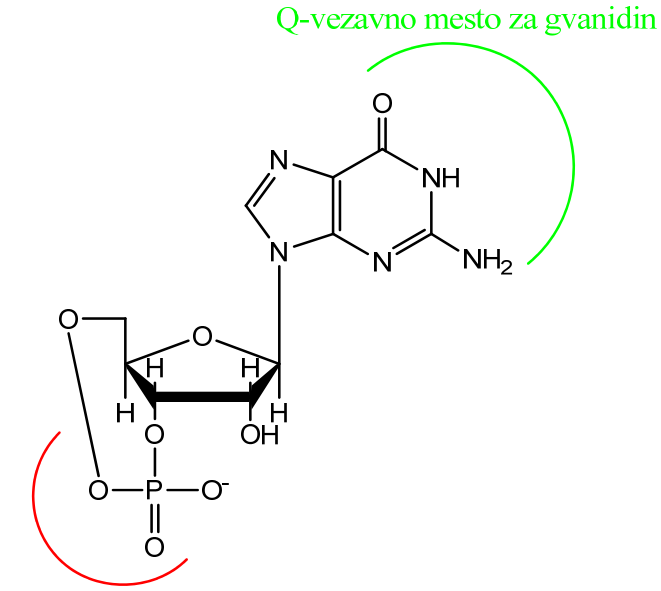
Ključna selektivnost!

Drug	Geometric mean IC_{50} values (μM) [fold selectivity versus PDE5 in parentheses]											
	PDE1	PDE2	PDE3	PDE4	PDE5	PDE6 (rod)	PDE6 (cone)	PDE7A	PDE8A	PDE9A	PDE10A	PDE11A
Sildenafil	0.281 [80]	>30 [>8,570]	16.2 [4,630]	7.68 [2,190]	0.00350	0.037 [11]	0.034 [10]	21.3 [6,090]	29.8 [8,510]	2.61 [750]	9.80 [2,800]	2.73 [780]
Tadalafil	>30 [>4,450]	>100 [>14,800]	>100 [>14,800]	>100 [>14,800]	0.00674	1.26 [187]	1.30 [193]	>100 [>14,800]	>100 [>14,800]	>100 [>14,800]	>100 [>14,800]	0.037 [5]
Vardenafil	0.070 [500]	6.20 [44,290]	>1.0 [>7,140]	6.10 [43,570]	0.00014	0.0035 [25]	0.0006 [4]	>30 [>214,000]	>30 [>214,000]	0.581 [4,150]	3.0 [21,200]	0.162 [1,160]

Sildenafil - cGMP



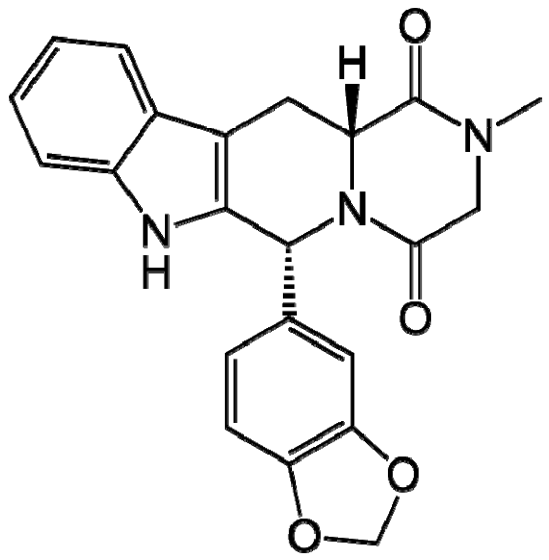




M - vezavno mesto; Zn^{2+}, Mg^{2+}

Inhibitorji fosfodiesteraze 5

- tadalafil



Literatura predavanj

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

- 28. poglavje
- 29. poglavje