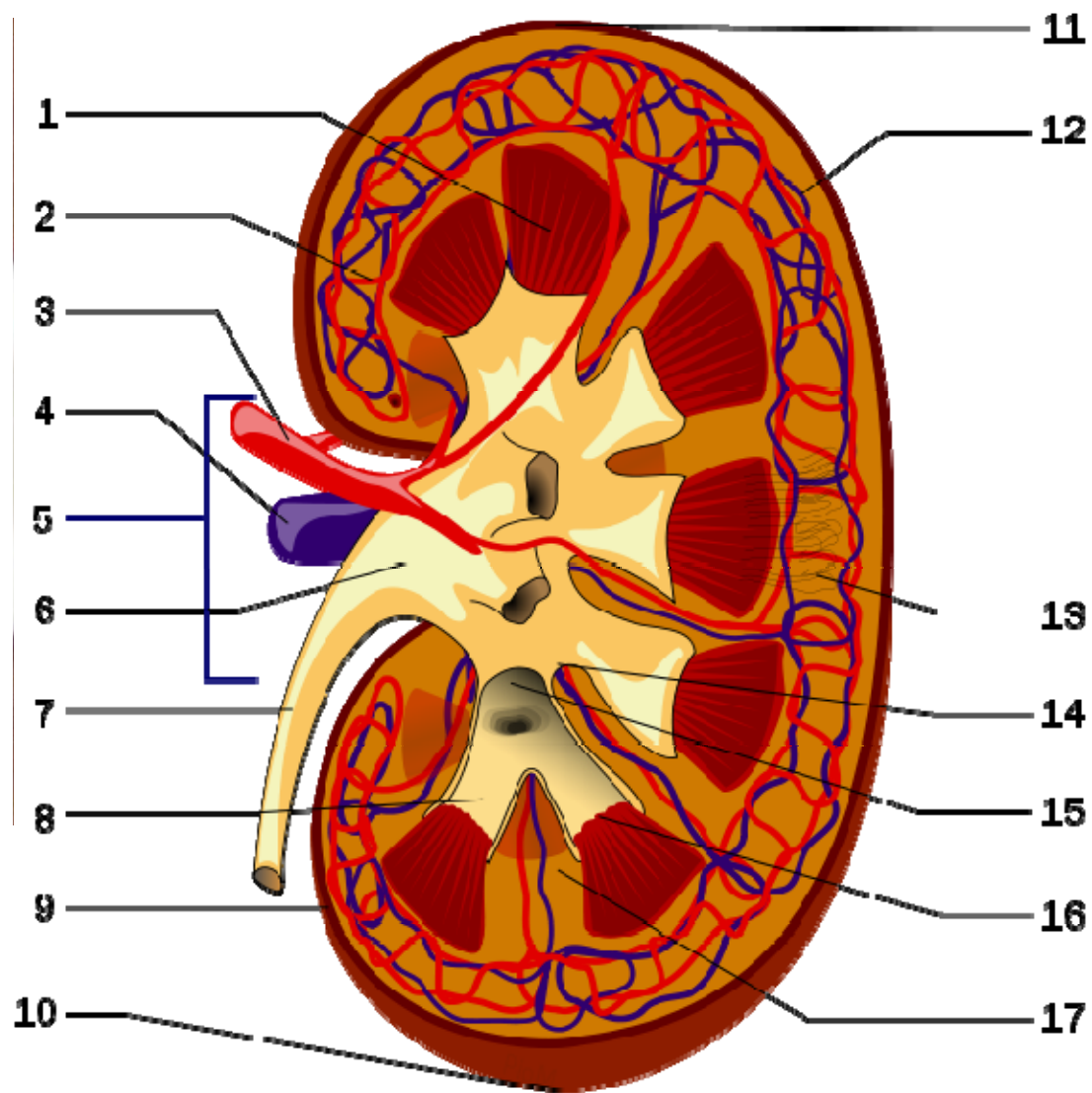


Diuretiki

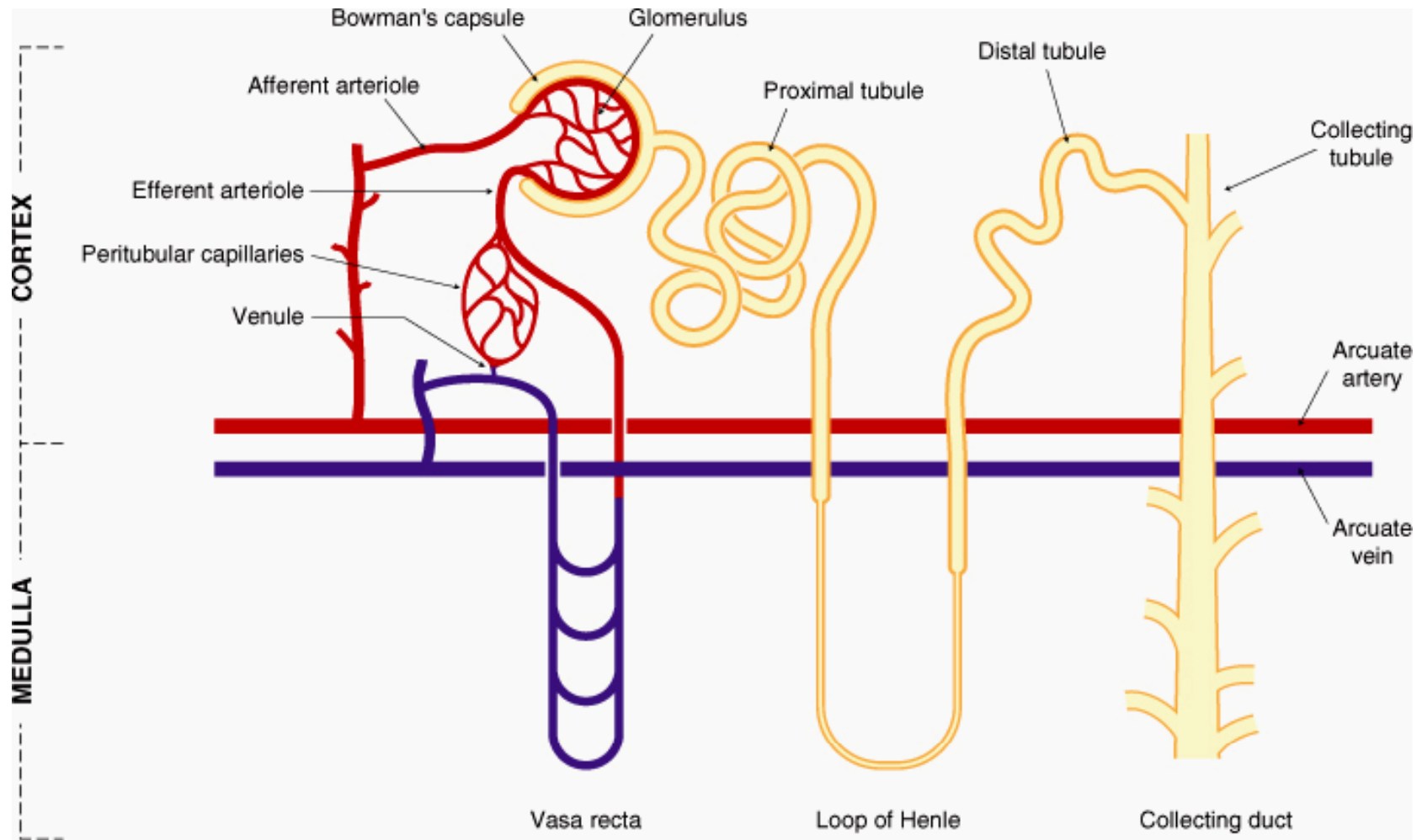
Izr. prof. dr. Marko Anderluh

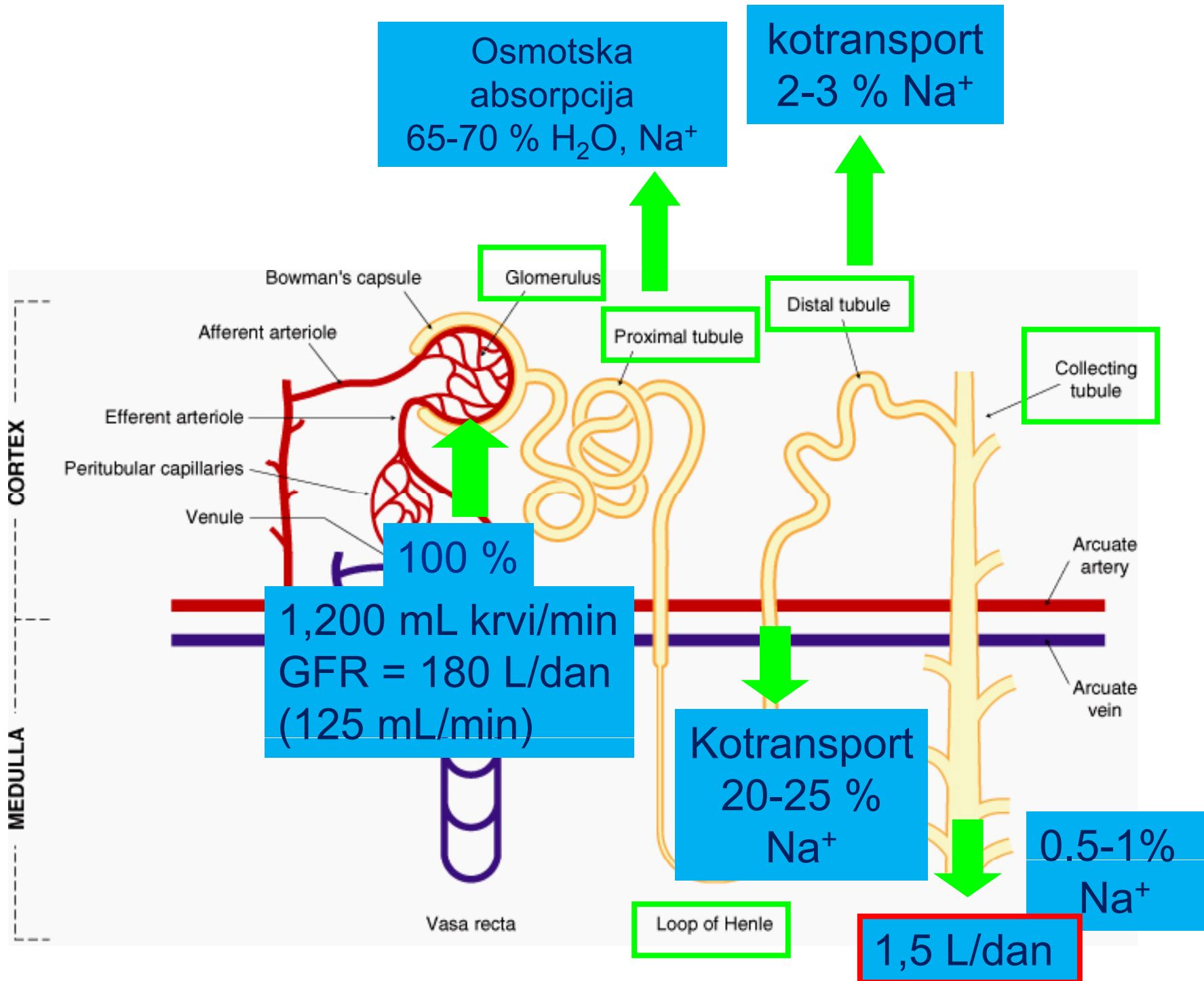
30. maj 2013

Ledvica



Nefron – osnovna funkcionalna enota





Mehanizmi diureze

- **VODA**: inhibicija izločanja antidiuretičnega hormona – vazopresina, lahko forsirana (npr. 2L tekočine naenkrat)
- Povišana konc. ionov

Mehanizmi antidiureze

- RAAS sistem
- Antidiuretični hormon iz nevrohipofize:
izločanje zavirata kofein in etanol

Bolezenska stanja

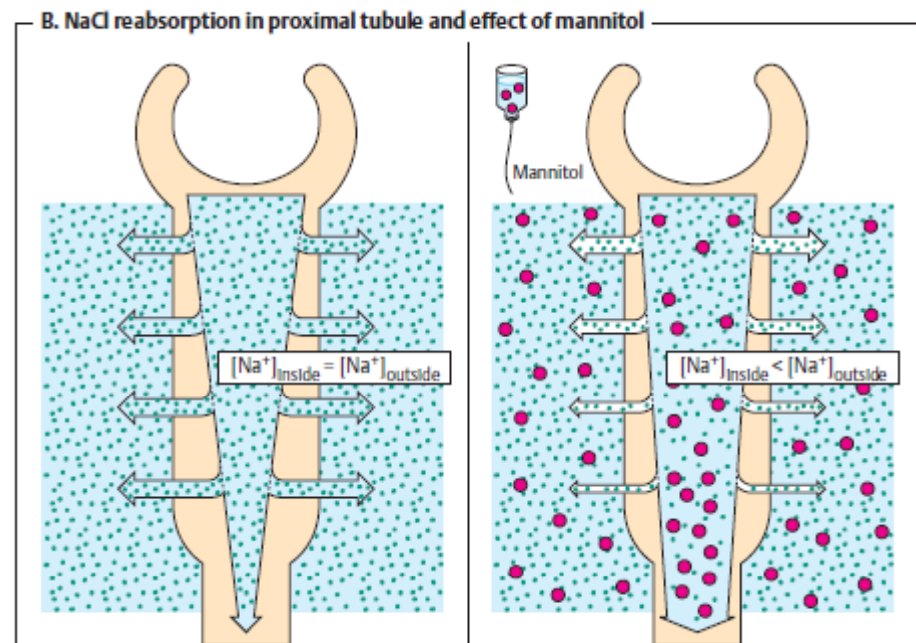
- Edemi; pljučni edem (disfunkcija levega srca), retenca elektrolitov in vode (disfunkcija ledvic)
- Hipertenzija; zmanjšanje periferne rezistence, zmanjšanje srčnega bremena
- Ostale bolezni: glavkom, povišan intrakranialni pritisk, diabetes insipidus, hiperkalcemija, primarni hiperaldosteronizem, osteoporoza

Vrste diuretikov

- Osmotski diuretiki (manitol)
 - Zaviralci karbonske anhidraze (acetazolamid)
 - Tiazidni diuretiki (klorotiazid)
 - Derivati kinazolin-4-onov (indapamid)
 - Diuretiki Henleyeve zanke (furosemid)
 - Diuretiki, ki varčujejo s kalijem
- Učinek narašča
-

Osmotski diuretiki

- Nizkomolekularne spojine – prosta filtracija skozi Bowmanovo kapsulo
- Ni absorpcije v tubulih, ohranjajo volumen filtrata, rezultat razredčen urin – osmotski princip

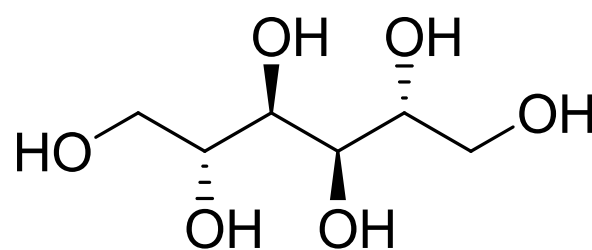


Ne v terapiji edema – povečajo volumen izvencelične tekočine

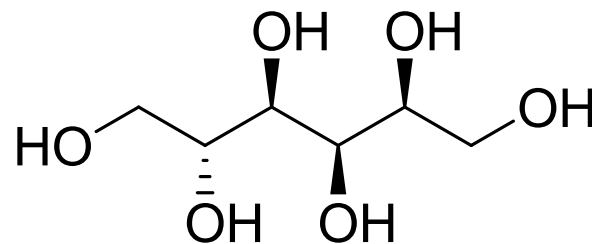
Osmotski diuretiki

Polioli

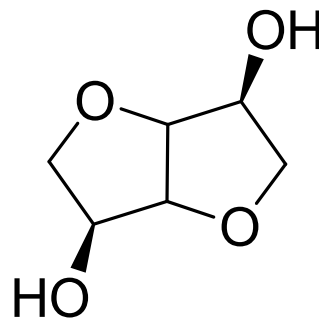
- Manitol



- Sorbitol



- Izosorbid



per os!

IV aplikacija
sicer laksativa!

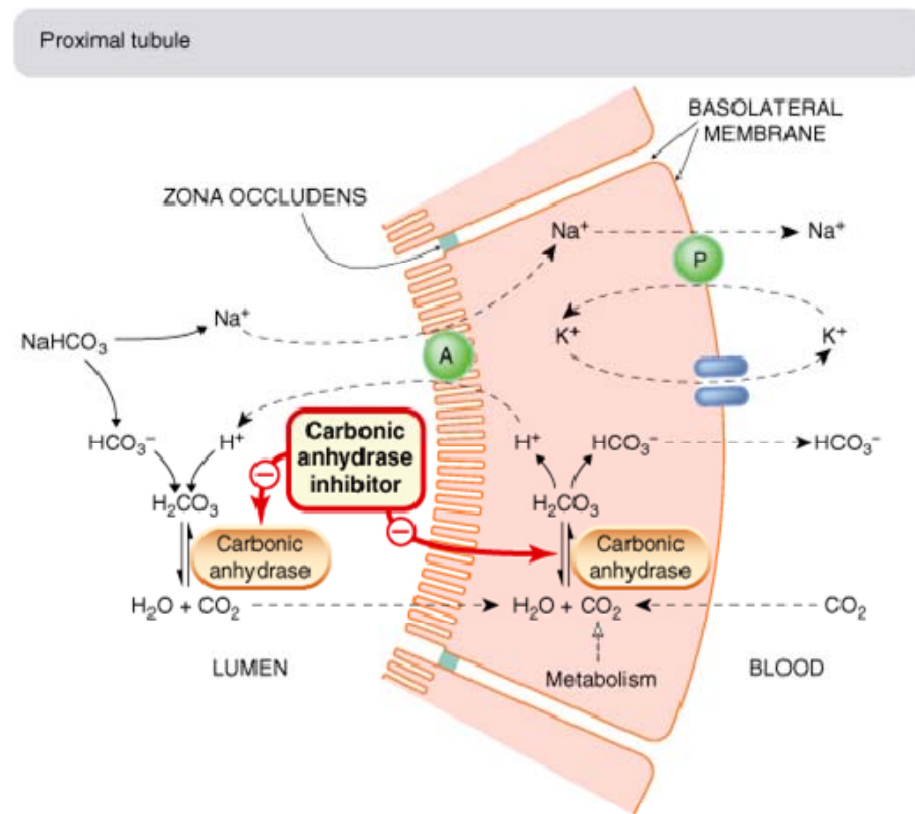
Osmotski diuretiki

Polioli

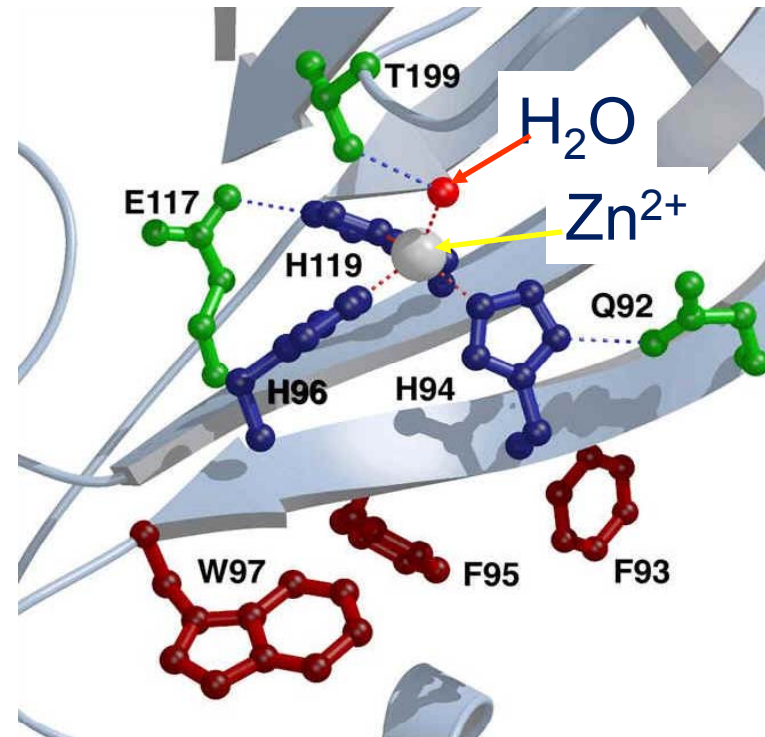
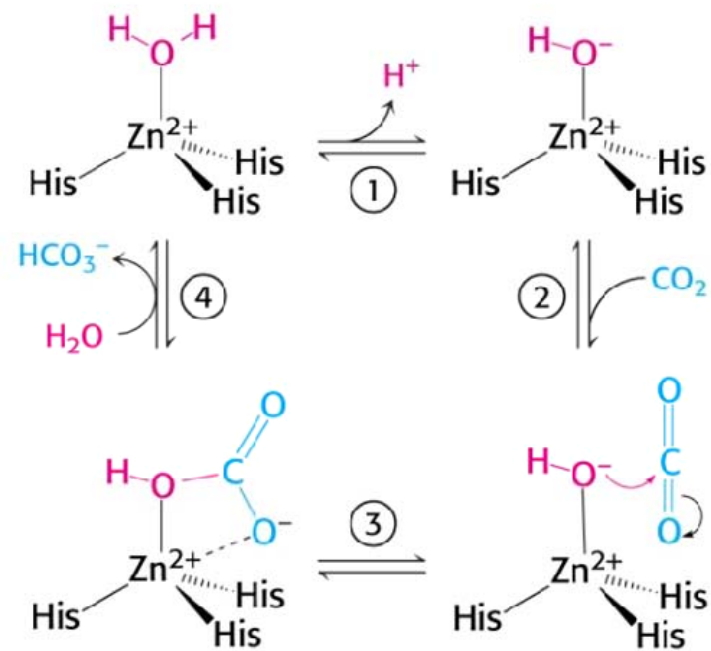
- Poznate še kakšne polirole?
- Še kakšna majhna molekula, ki se prosto filtrira in ne podleže resorpciji?

Zaviralci karbonske anhidraze (KA)

- KA – v proksimalnem tubulu: izmenjava Na^+ - H^+ ; Na^+ potuje v citosol, voda osmotsko zraven – ZAVIRANJE!
- Za diuretičen učinek - več kot 99% inhibicija KA, šibko učinkoviti
- Zaviralci KA: pH urina naraste, metabolna acidoza



Mehanizem delovanja KA

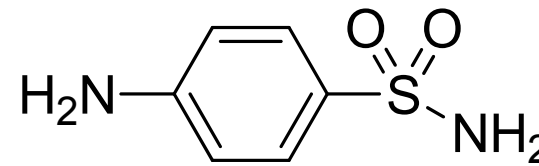


Zaviralci karbonske anhidraze (KA)

- Delovanje tudi v zbiralcu
- Uporaba: diuretiki, proti glavkomu, antiepileptiki

Zaviralci karbonske anhidraze (KA)

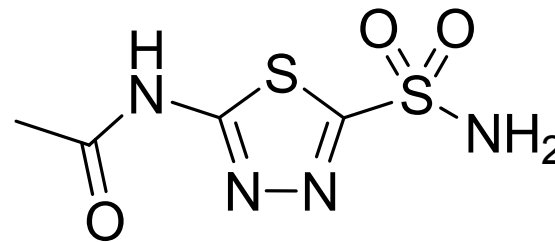
- Izhodišče – sulfonamidi; opazili naalkaljenje urina



Razmišljanje – bolj kisli derivati bi močnejše zavirali KA



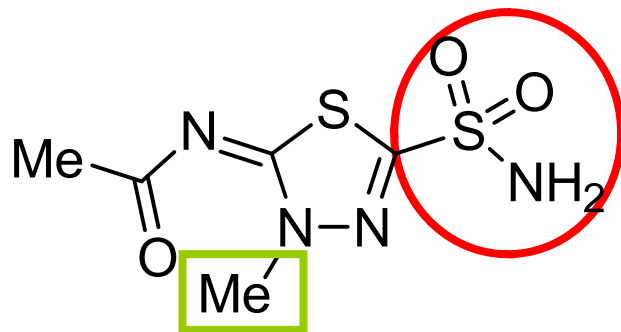
pKa = 7,2



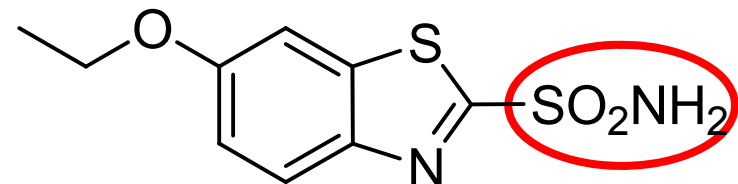
- Acetazolamid: substituiran aromatski amin, amin ni nujen

Zaviralci karbonske anhidraze (KA)

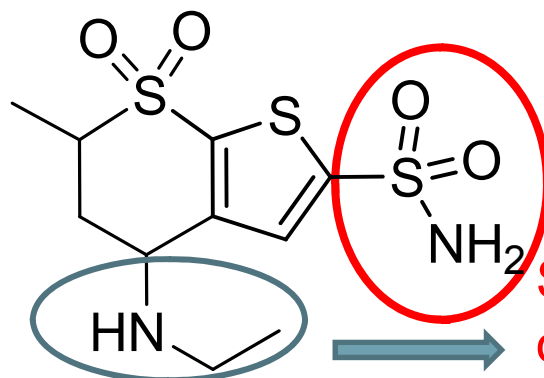
- Derivati acetazolamida



metazolamid

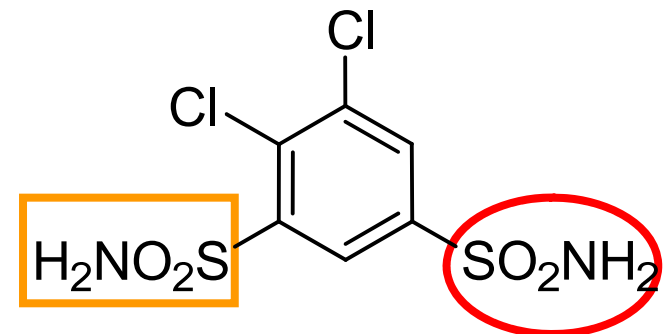


etoksazolamid



dorzolamid

Skupina, ki omogoča ionizacijo

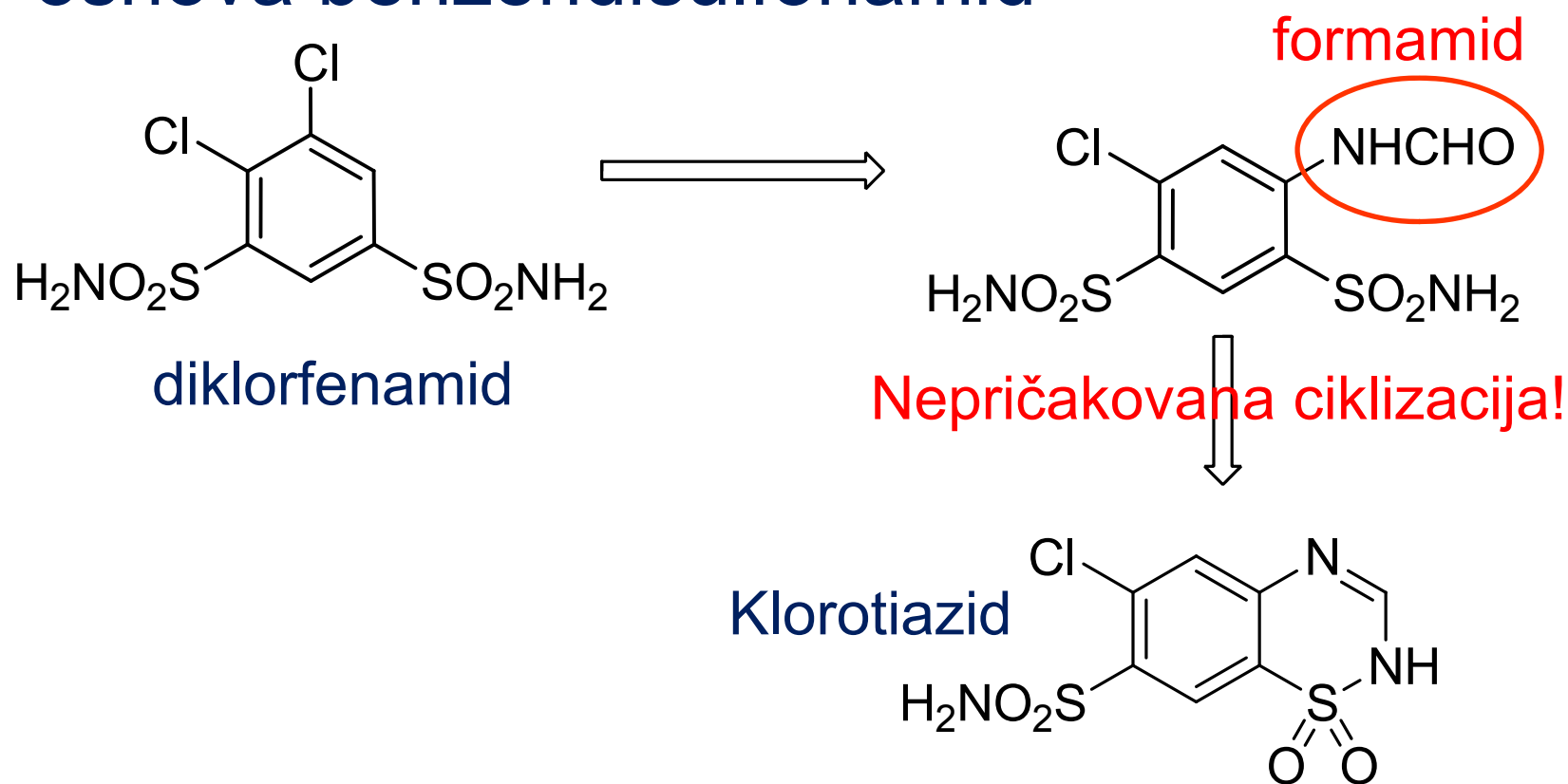


diklorfenamid

Topikalna aplikacija (kornea)

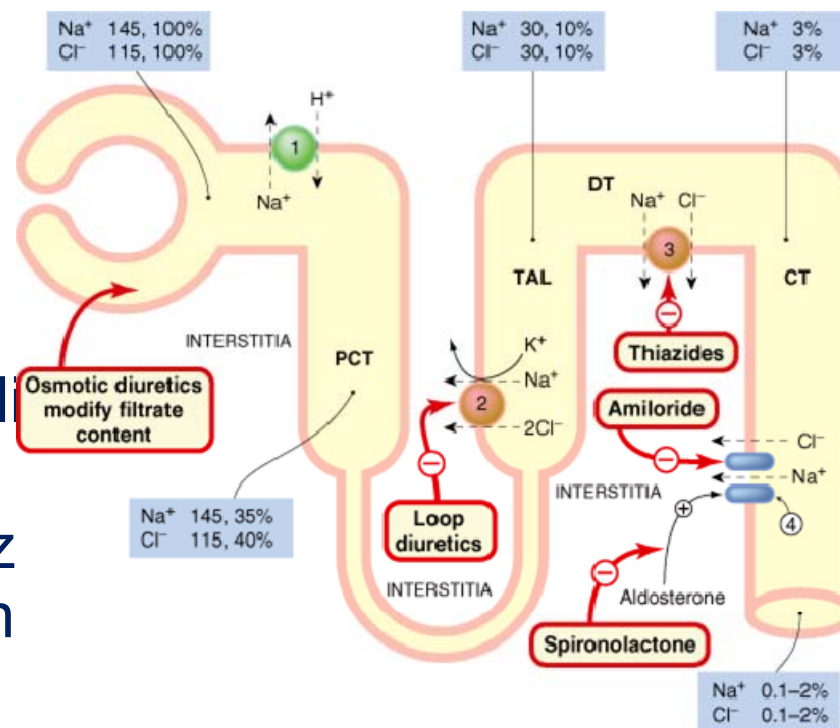
Tiazidni diuretiki

- Od diklorfenamida do klorotiazida – osnova benzendisulfonamid

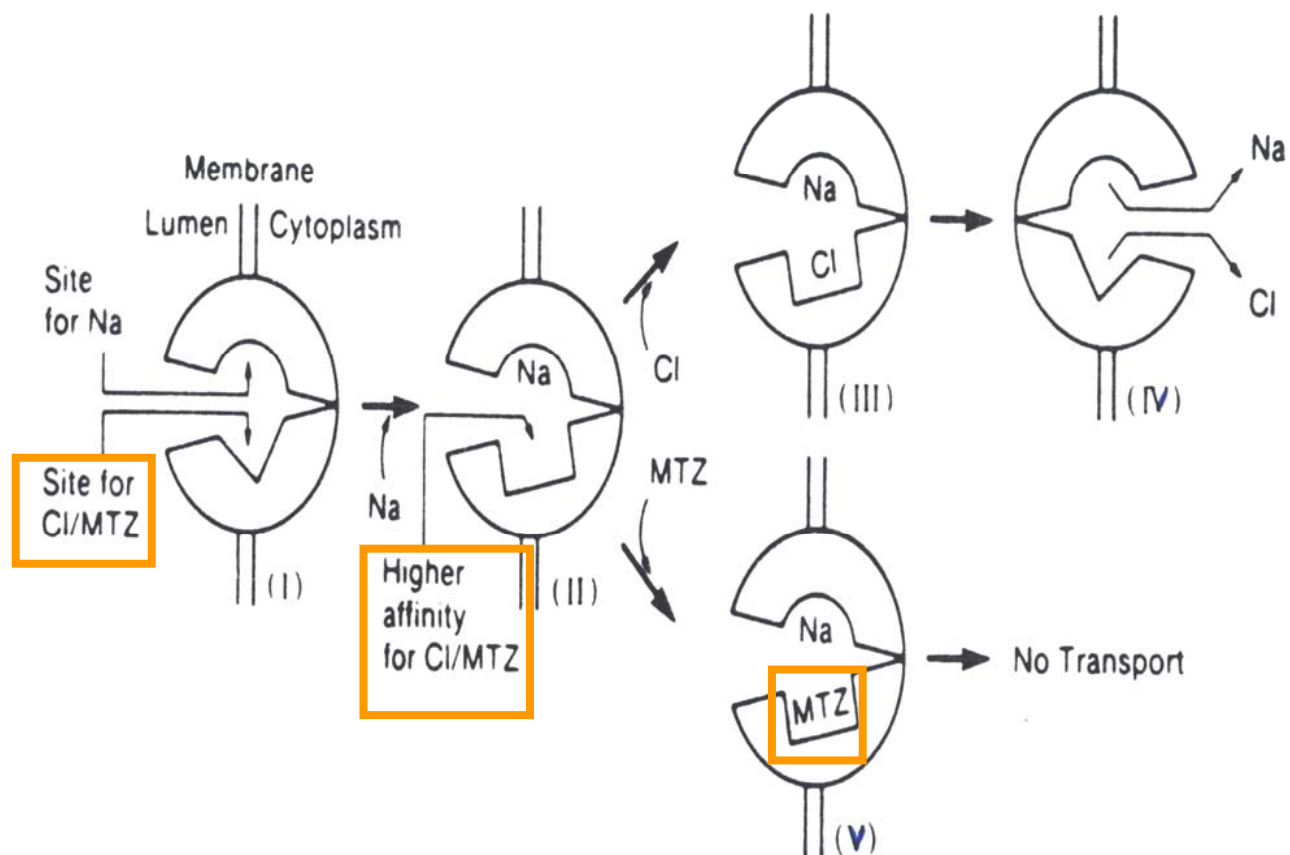


Tiazidni diuretiki

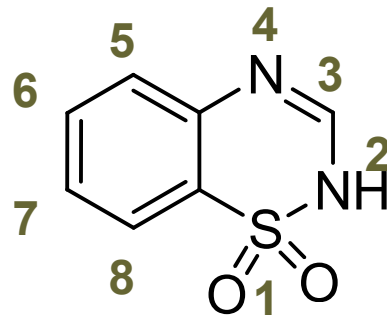
- Izločanje v proksimalnem tubulu
- Mehanizem delovanja – zaviranje Na^+/Cl^- simporterja distalnem tubulu
- Kompeticija s Cl^-
- Močno izločanje Na^+ , Cl^- , tudi K^+ - SALURETIKI
- Uporabljajo se v kombinaciji z diuretiki, ki varčujejo s kalijem
- Močno delujoči



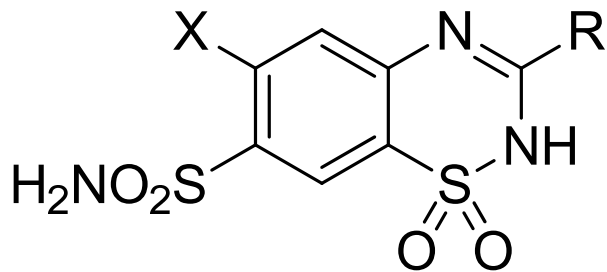
Tiazidni diuretiki



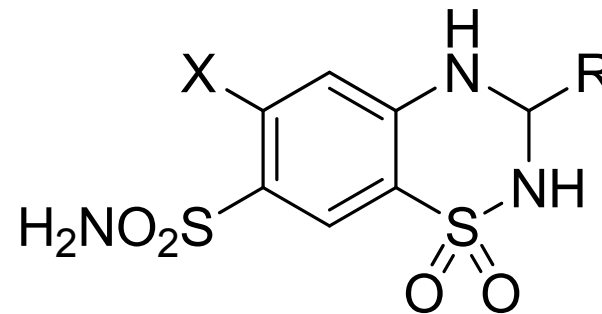
Tiazidni diuretiki



benzotiazidin



TIAZIDI



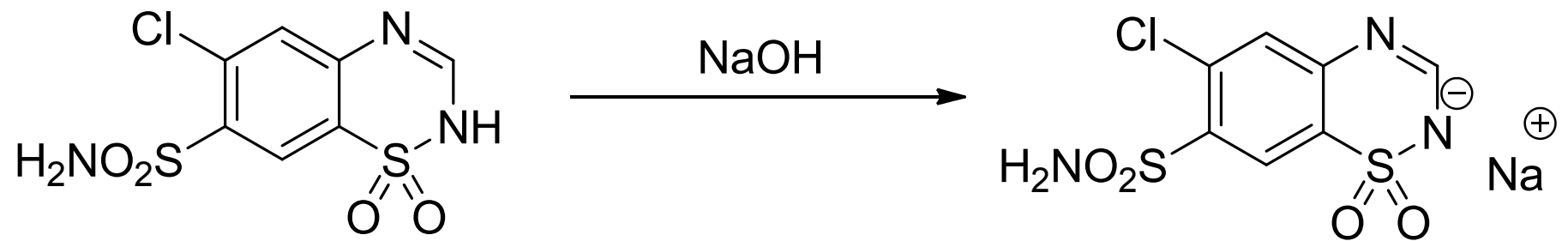
HIDROTIAZIDI

Klorotiazid

$pK_{a_1} = 6,7$ $pK_{a_2} = 9,5$

Tiazidni diuretiki

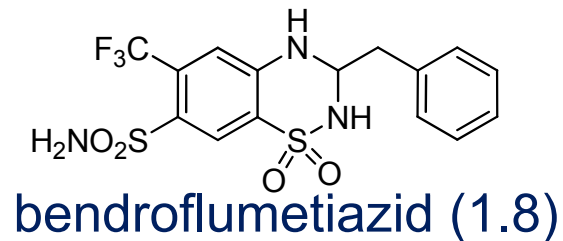
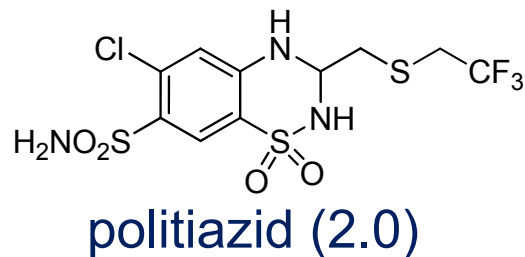
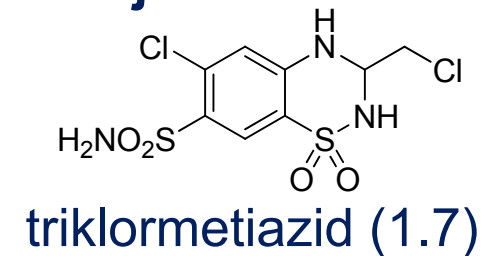
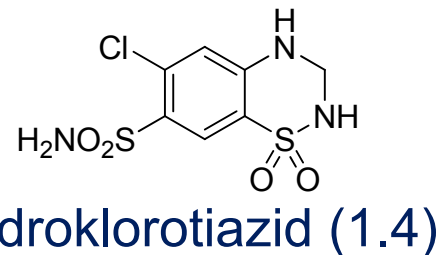
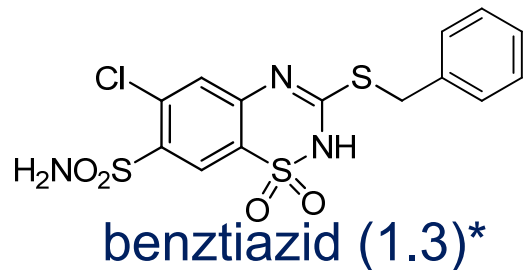
- Šibke kisline



Klorotiazid
 $\text{pK}_{\text{a}1} = 6,7$ $\text{pK}_{\text{a}2} = 9,5$

SAR tiazidnih diuretikov

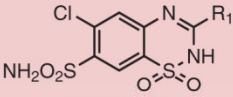
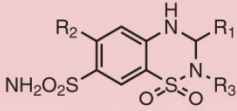
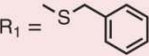
- Sulfonamid na mestu 7 – nujno
- Mesto 6: el. negativna skupina: Cl- < CF₃-, el. donorske skupine močno zmanjšajo učinek
- Redukcija = vezi na mestu 3,4 – 10x močnejši derivati (hidrotiazidi)
- Alkilne skupine na mestu 3 – daljši učinek, zaviranje KA



* Relativna jakost (0,8 = klorotiazid)

Tiazidni diuretiki

TABLE 22.3 Pharmacologic and Pharmacokinetic Properties for the Thiazide Diuretics

Generic Name	Trade Name	Structure	Relative Potency ^a	Carbonic Anhydrase Inhibition ^b	Bioavailability	Peak Plasma (hours)	Half-life (hours)	Duration of Effect (hours)	Elimination
		 <p>Structure I</p>							
		 <p>Structure II</p>							
Chlorothiazide	Diuril	Structure I: R ₁ = H	0.8	2 × 10 ⁻⁶	<25%	4	0.75–2	12–16	U
Benzthiazide	Exna	Structure I: 	1.3	~10 ⁻⁷	NA	4	3–3.9	12–16	NA
Hydrochlorothiazide	HydroDiuril Esidrix	Structure II: R ₁ = H, R ₂ = Cl, R ₃ = H	1.4	2 × 10 ⁻⁵	>80%	4–6	6–15	12–16	U
Trichlormethiazide	Diurese Metahydrin Naqua	Structure II: R ₁ = CHCl ₂ , R ₂ = Cl; R ₃ = H	1.7	6 × 10 ⁻⁵	Var	6	2–7	24	U
Methyclothiazide	Enduron Aquatensen	Structure II: R ₁ = CH ₂ Cl R ₂ = Cl; R ₃ = CH ₃	1.8		Var	6	NA	>24	U
Polythiazide	Renese	Structure II: R ₁ = -CH ₂ -S-CH ₂ -CF ₃ , R ₂ = Cl, R ₃ = CH ₃	2.0	5 × 10 ⁻⁷	Var	6	NA	24–48	U + 30% M
Hydroflumethiazide	Saluron Diucardin	Structure II: R ₁ = H, R ₂ = CF ₃ , R ₃ = H	1.3	2 × 10 ⁻⁴	Inc	3–4	17	18–24	U + M
Bendroflumethiazide	Naturetin	Structure II: R ₁ = benzyl, R ₂ = CF ₃ , R ₃ = H	1.8	3 × 10 ⁻⁴	>90%	4	8.5	6–12	U

^aThe numerical values refer to potency ratios (in humans) with the natriuretic response to that of a standard dose of meralluride, which is given a value of one;

^b50% inhibition of carbonic anhydrase in vitro.

NA, data not available; Var, variable absorption; Inc, incomplete absorption.

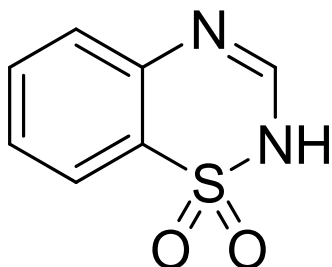
Data from AHFS Drug Information (2010), American Society of Health-System Pharmacists; Lexicomp Online (2011), Lexicomp, Inc.; Facts and Comparisons (2010), Wolters Kluwer Health.

U, urine unchanged; M, metabolized.

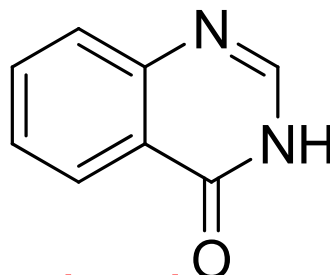
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Prehod na kinazolin-4-one

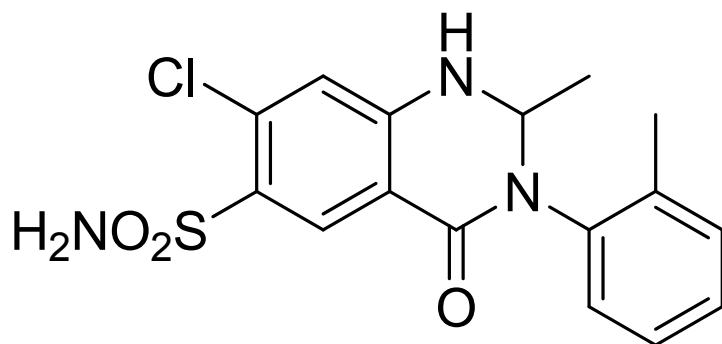
tiazidni skelet



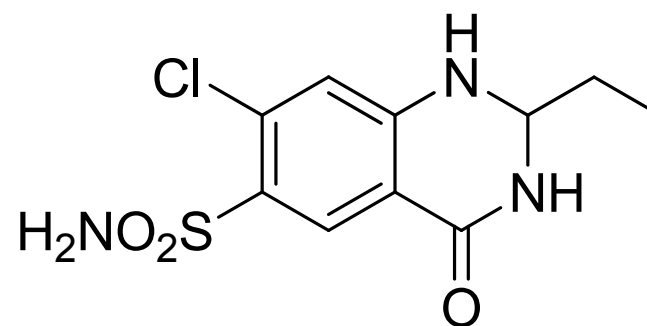
kinazolin-4-on



Enak mehanizem delovanja!

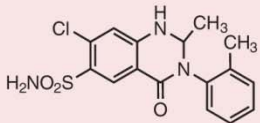
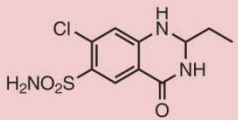
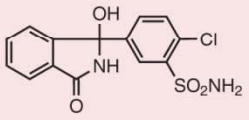
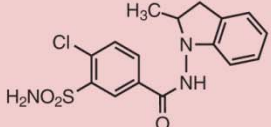


Metolazon (pKa = 9,7)



Kinetazon (pKa = 9,7)

Kinazolin-4-oni

TABLE 22.4 Pharmacokinetic Properties for the Thiazide-Like Diuretics							
Generic name	Trade name	Structure	Bioavailability	Peak Plasma	Half-life (hours)	Duration (hours)	Route of Elimination
Metolazone	Zaroxylon		<65%	8–12 h	14	12–24	Urine/feces (8:2), as parent drug (>70%)
Quinethazone	Hydromox		NA	6 h	6–15	18–24	Urine as parent drug
Chlorthalidone	Hygroton Thalitone [#]		Inc/var. >90%	4 h 2 h	35–50*	48–72	Urine, as parent drug (50–65%)
Indapamide	Lozol		>90%	2–3 h	14–18	8 wks	Urine/feces (6:2), as parent drug (<10%) and metabolites

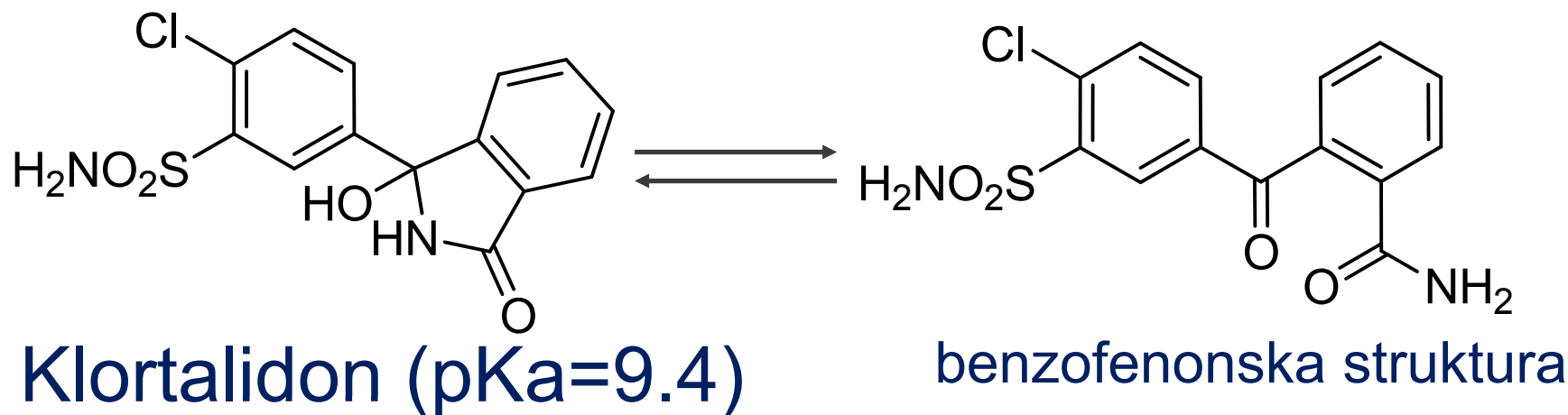
Data from AHFS Drug Information (2010). American Society of Health-System Pharmacists; Lexicomp Online (2011), Lexicomp, Inc.; Facts and Comparisons (2010), Wolters Kluwer Health.

*Strongly bound to red blood cells. #= not interchangeable with similar drug. NA = data not available. var. = variable absorption. inc.= incomplete absorption.

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Tiazidom podobni diuretiki

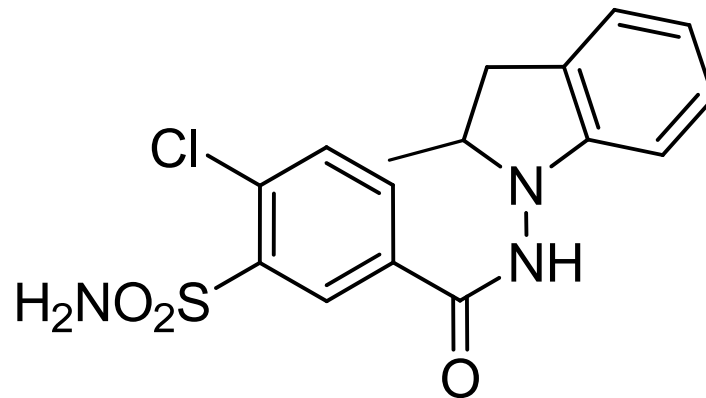
- Ftalimidin - klortalidon



$t_{1/2} = 35-50$ h (dolg čas delovanja 48-72 h)
Aplikacija 3x na teden!

Tiazidom podobni diuretiki

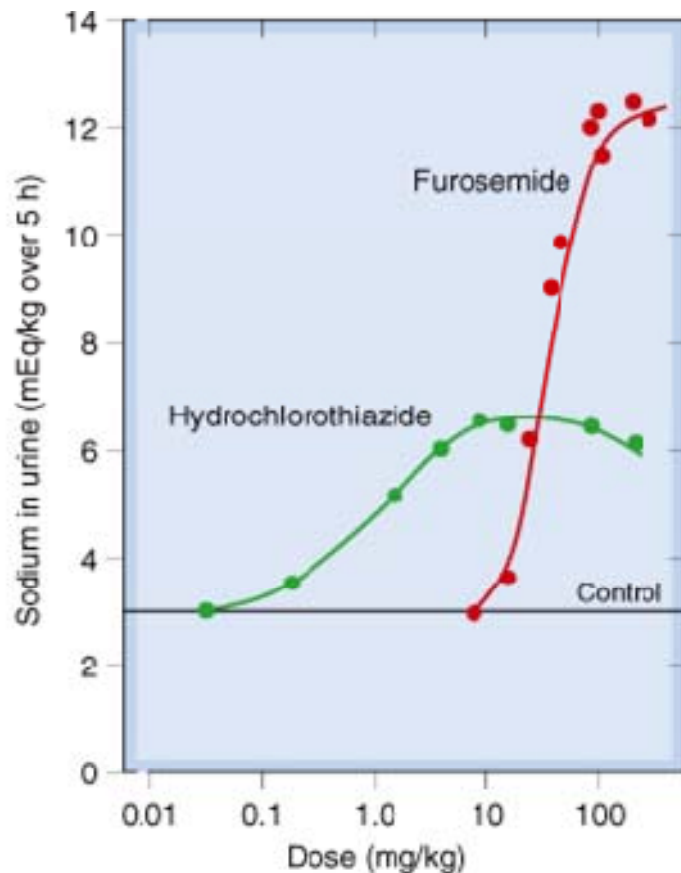
- Indolini - indapamid



Indapamid (pKa=8.8)

“odprt” derivat kinazolin-4-onov
Dolg čas delovanja – 24h

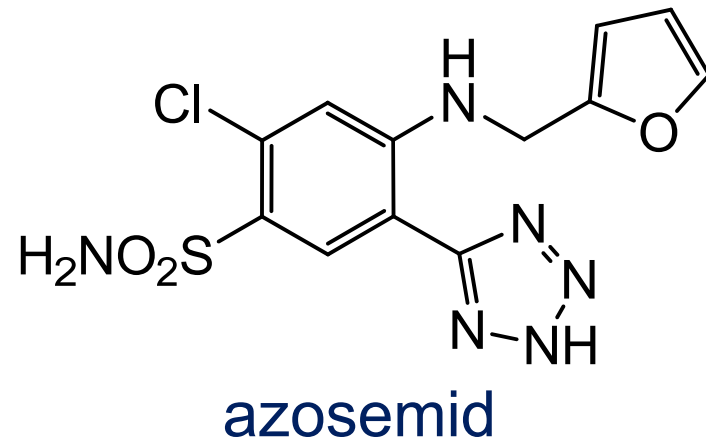
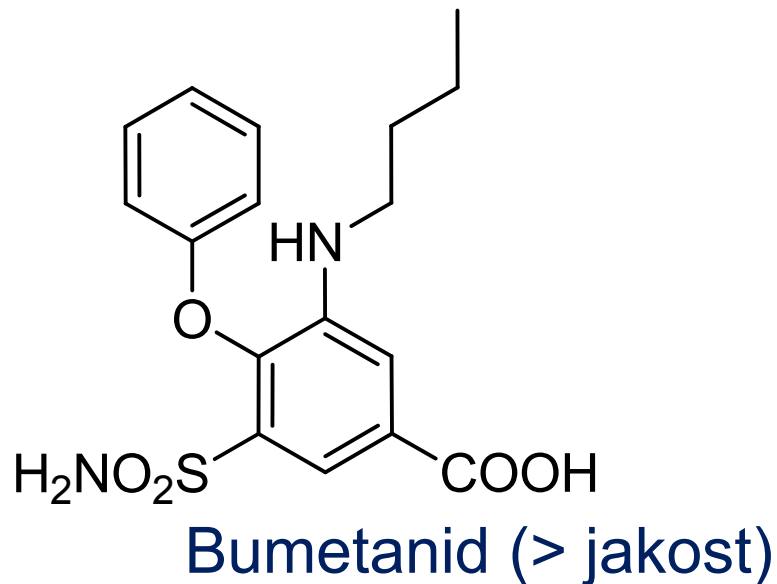
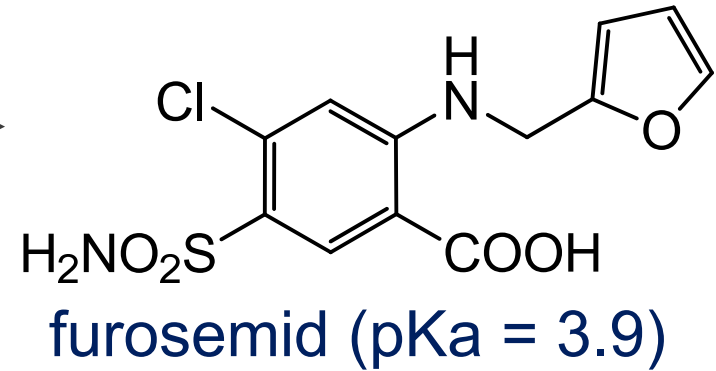
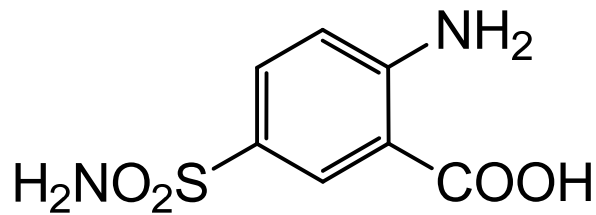
Učinnost / jakost diuretikov



**UČINKOVITOST (efficacy)
/ JAKOST (potency)
diuretikov?**

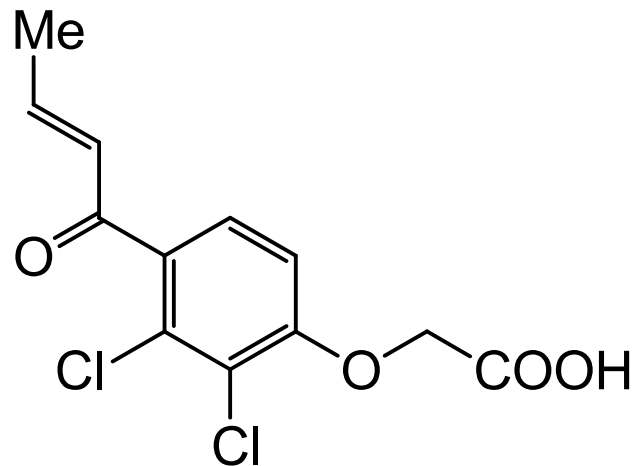
Diuretiki Henleyeve zanke

5-sulfamoilantranilna kislina



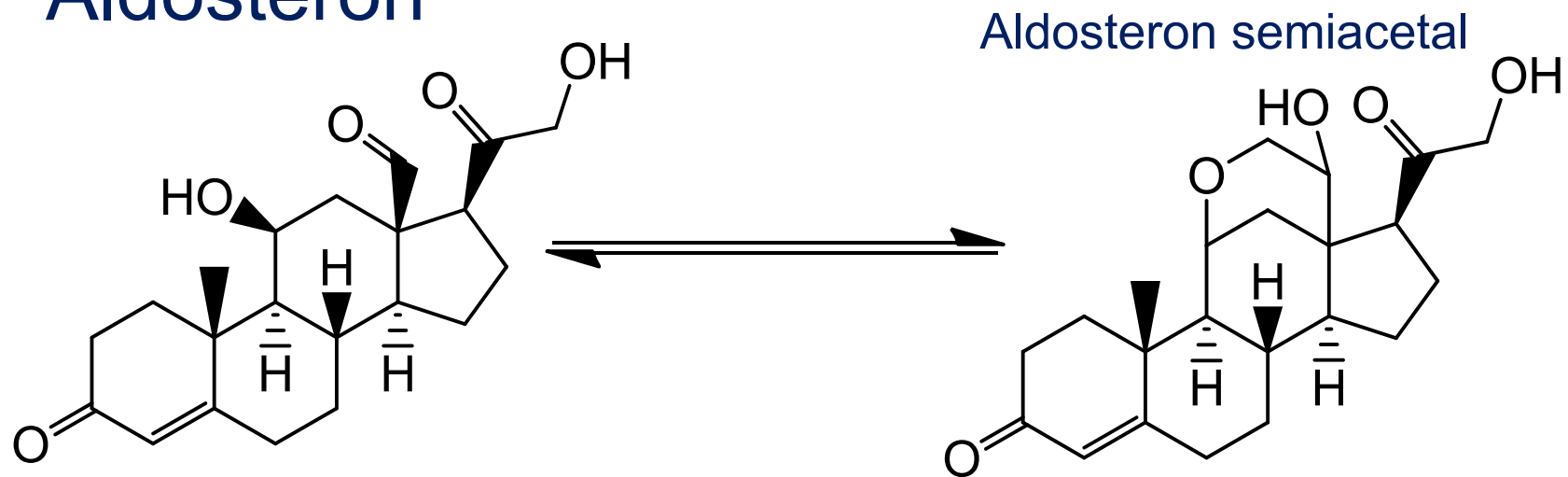
Diuretiki Henleyeve zanke

- Etakrinska kislina – ni sulfonamid, klinična uporaba pri alergiji na sulfonamide



Antagonisti mineralokortikosteroidnih receptorjev

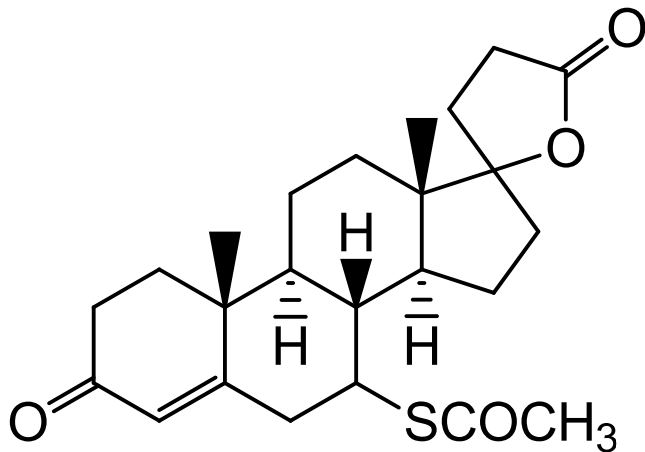
- Aldosteron



- Veže se na mineralokortikosteroidne receptorje (distalni tubul, zbiralce) – retencija vode, izločanje K^+ in H^+

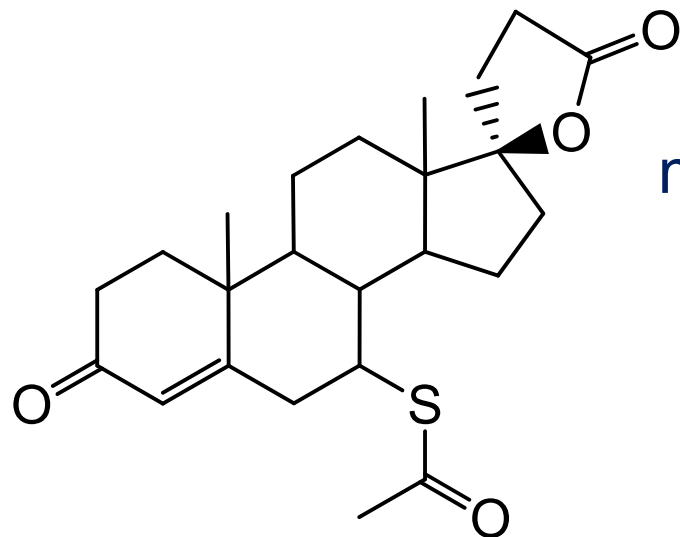
Antagonisti mineralokortikosteroidnih receptorjev

- **Spironolakton** – antagonist na mineralokortikoidnih receptorjih



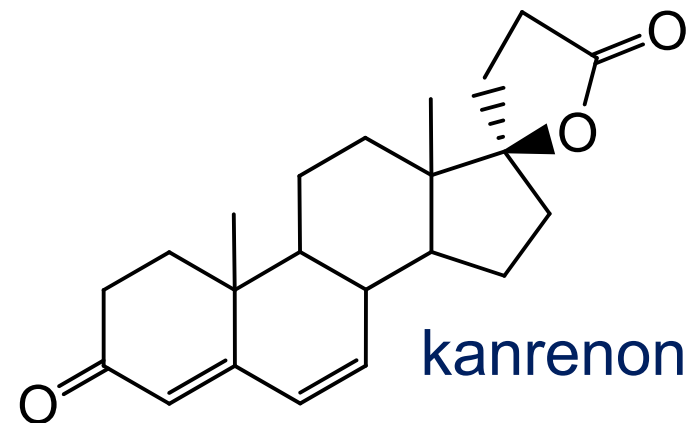
- **Posledica: ni reabsorpcije NaCl, ne izločata se K⁺, H⁺**

Antagonisti mineralokortikosteroidnih receptorjev

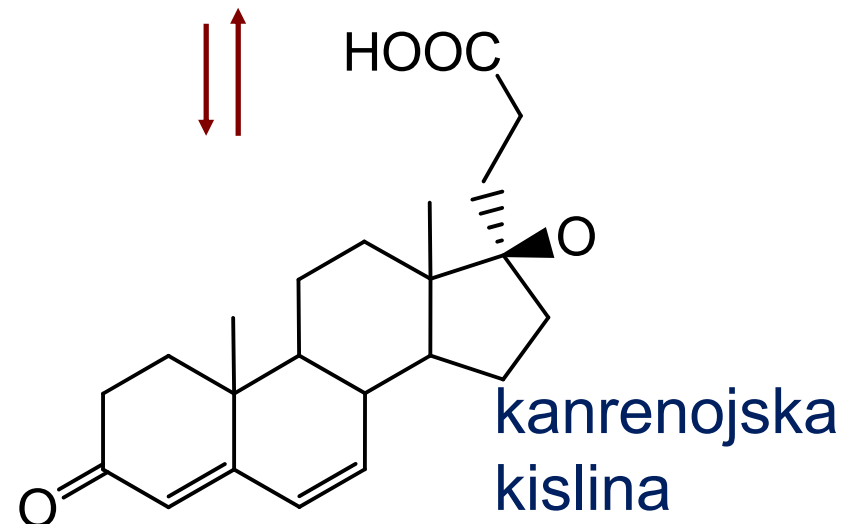


spironolakton (predzdravilo)

metabolična
aktivacija



kanrenon

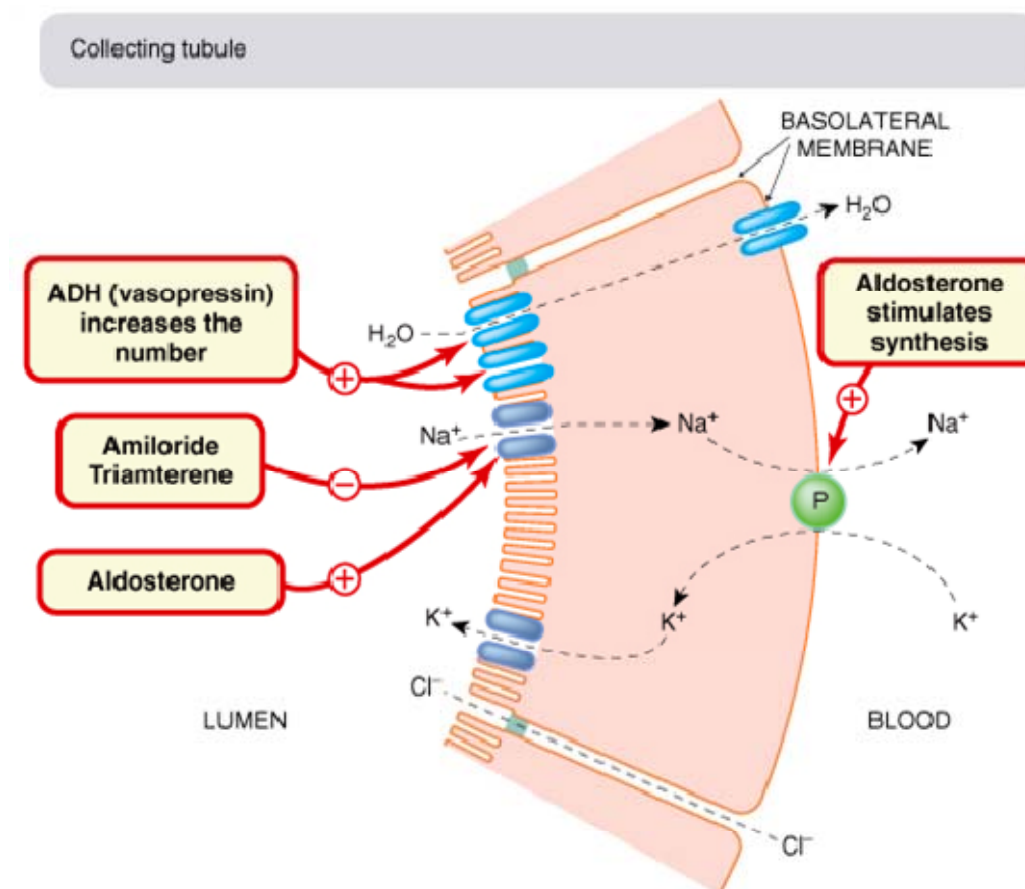


kanrenojska
kislina

Diuretiki, ki varčujejejo s kalijem

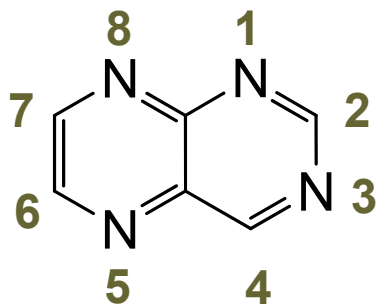
Mehanizem delovanja

- Zaviranje Na^+ kanalčkov v distalnem tubulu
- Stranski učinek: hiperkaliemija
- Uporaba v kombinaciji s tiazidi ali tiazidom podobnimi diuretiki

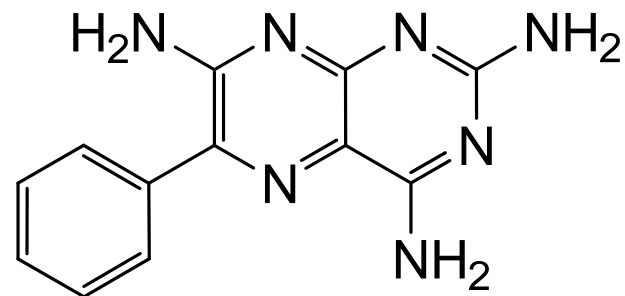


Diuretiki, ki varčujejo s kalijem

- Pteridinski derivat



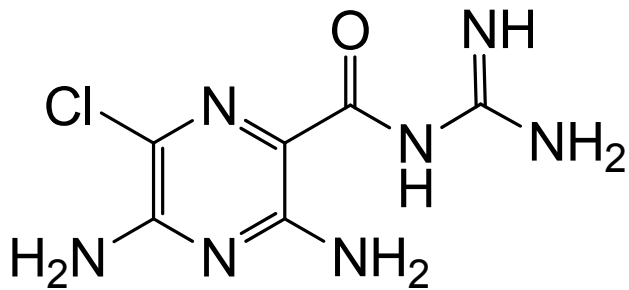
pteridin



triamteren

Diuretiki, ki varčujejo s kalijem

- amilorid



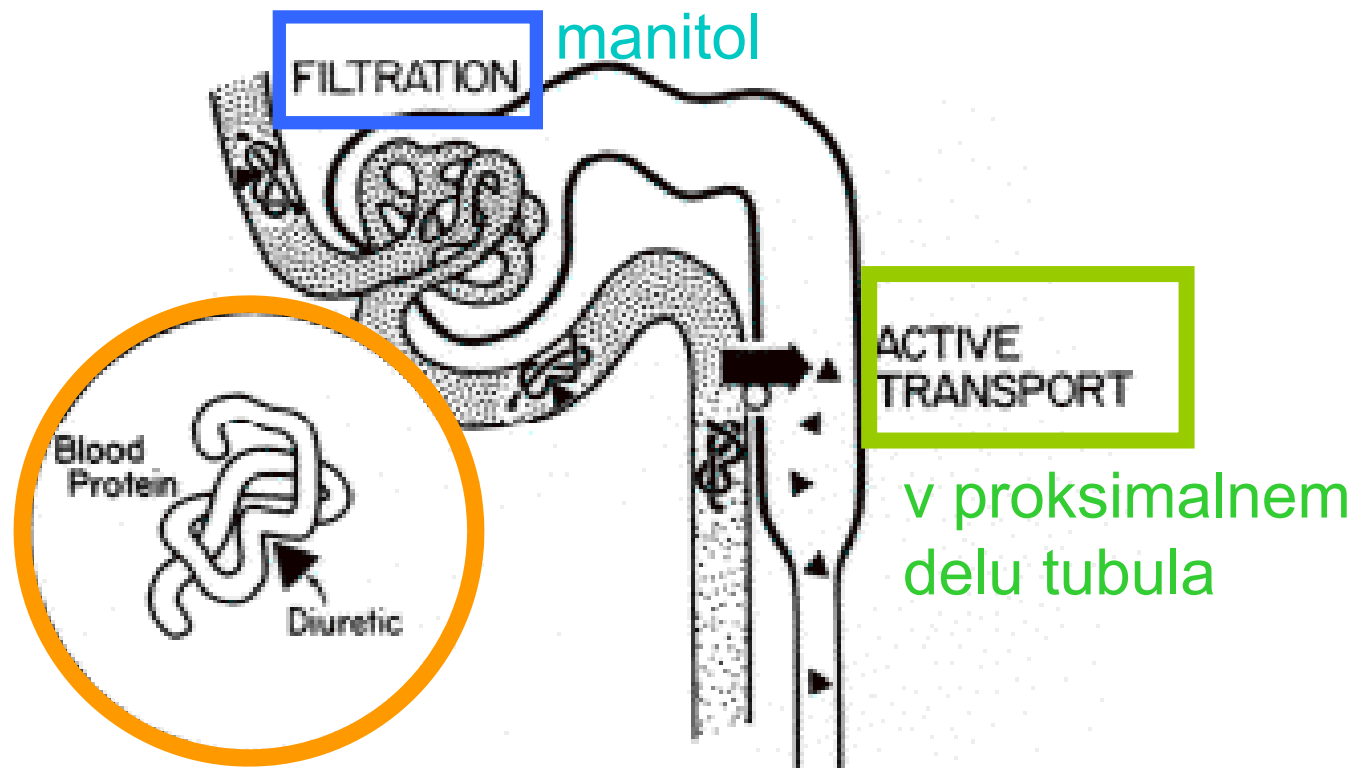
- Odprti analog pteridinov
- blokira luminalne Na⁺ kanalčke v distalnem delu tubula
- Blokira reabsorbcijo natrija, izločanje kalija
- Stranski učinek: hiperkaliemija

Primerjava diuretikov

Tabela 2. Hitrost tvorjenja urina (pretok), pH urina in koncentracije nekaterih elektrolitov v urinu pod vplivom diuretikov iz različnih skupin (2).

Diuretik	Pretok urina [ml/min]	pH	Na ⁺ [mmol/l]	K ⁺ [mmol/l]	HCO ₃ ⁻ [mmol/l]
Brez diuretika	1	6,0	50	15	1
Tiazidi	3	7,4	150	25	25
Furozemid	8	6,0	140	10	1
Triamteren	3	7,2	130	5	15
Amilorid	2	7,2	130	5	15

Kako pridejo diuretiki v tubule?



Zloraba diuretikov

- Diuretiki – maskirne učinkovine



NEPOSREDNO

s povečanjem hitrosti nastanka urina
in s tem povečanje volumna urina



POSREDNO

s spremembo pH urina,
s tem vplivamo na izločanje šibko
kislih in bazičnih učinkovin v doping.



ACETAZOLAMID

Zaradi povečanja pH urina se zmanjša
izločanje šibko bazičnih učinkovin kot
so: mefentermin, etilamfetamin, amfetamin...

Zloraba diuretikov

- Diuretiki – hitro zmanjšanje teže



FUROSEMID

odmerek: 1.5 mg/kg



2-4 % zmanjšanje
telesne teže, zaradi
povečanja volumna urina



Terapevtski odmerki furosemida, bumetanida in piretamida v 3-4 urah;
povečanje volumna urina od 800 do 1600 mL.

Literatura predavanj

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

- 27. poglavje

Foye's Principles of Medicinal Chemistry, 7.
izdaja:

- 22. poglavje