Diuretics

= compouns used for ↑ of urine excretion in order to ↓ the excessive volume of extraceallular liquid or for other therapeutical purposes

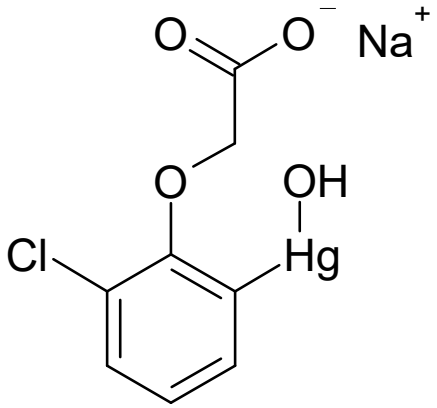
History

Mercury compounds

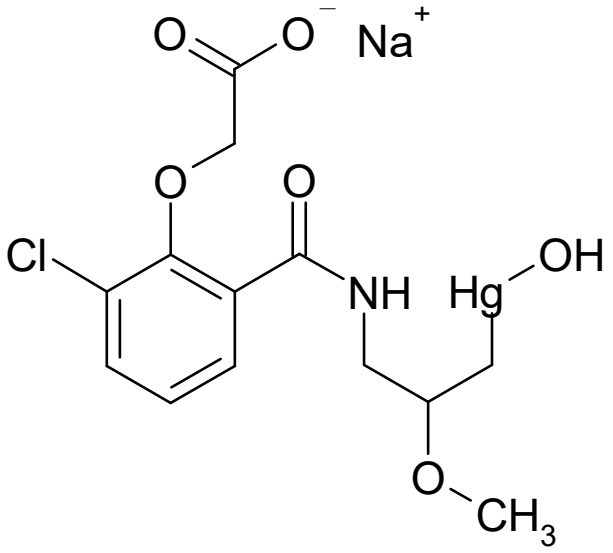
16th century – *Paracelsus* – red HgO (?)

19th century – Hg_2Cl_2 „calomel“

beginning of the 20th century – less toxic organic compounds with covalently bound Hg



Novasurol



mersalyl
Salyrgan®

Classification of actually used diuretics

1. Saluretics

1.1. Sulfonamides

1.1.1 Sulfonamides with acyclic -SO_2NH_2 group

1.1.2 Thiazide diuretics

2. „Potassium conserving“ diuretics

3. „Loop“ diuretics (= diuretics acting in the loop of Henle)

3.1. Sulfonamides – amino(hetero)arenesulfonamide derivatives

3.2. Phenoxyacetic acid derivatives

4. Osmotic diuretics

(5. Purine alcaloida – xanthine derivatives)

1. Saluretics

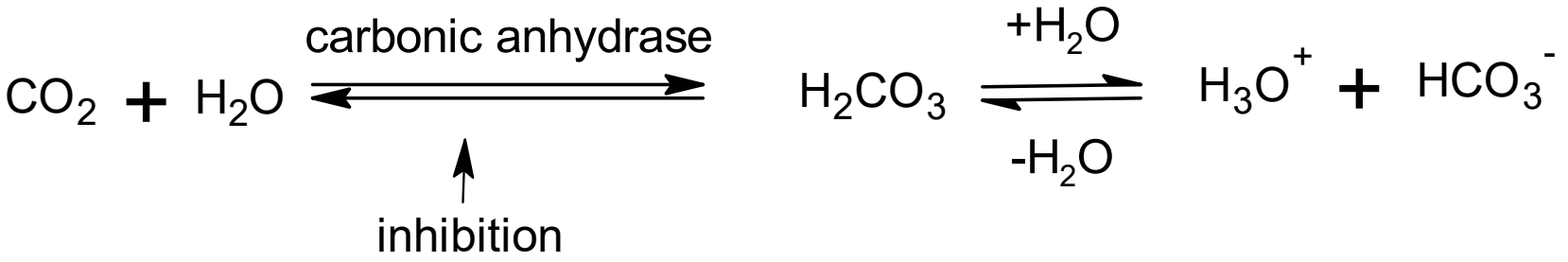
•inhibit reabsorption (back resorption) of Na^+ and Cl^- in more distal part of the nephrone, ions bind water, which is then excreted

•they cause decrease of K^+ in organism (exchange for Na^+ and active secretion in distal tubule)

1.1. Sulfonamides

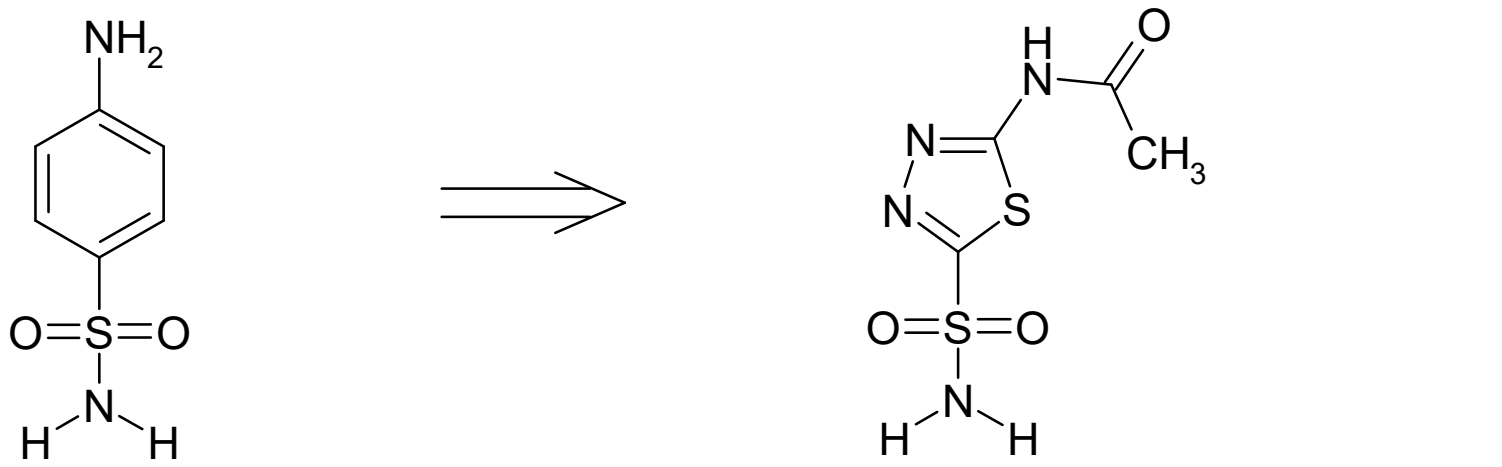
•diuretic activity of antibacterial sulfonamides observed as a side effect before 1940

•1949 Schwartz: carbonic anhydrase inhibtion



• the enzyme is inhibited $\Rightarrow \downarrow H_2CO_3 \Rightarrow \downarrow H_3O^+$, which normally exchanges for Na^+, in glomerular filtrate $\Rightarrow Na^+$ remains in the renal tubule together with HCO_3^-, they bind osmotic equivalent of water $\Rightarrow$ excretion of a large quantity of urine

1.1.1. Sulfonamides with acyclic -SO_2NH_2 group

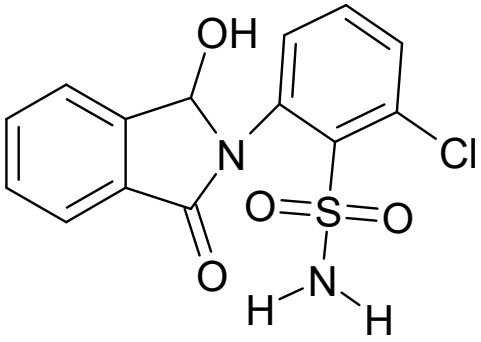


N-(5-sulfamoyl-[1,3,4]thiadiazol-2-yl)-acetamide

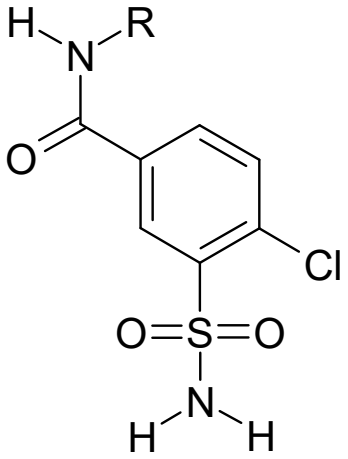
sulfanilamide
(lead compound of antibacterial sulfonamides)

acetazolamide
one of the firsr sulfonamide diuretics
Diluran® - today treatment of glaucom

1.1.1. Sulfonamides with acyclic -SO_2NH_2 group - continued



chlorthalidone
~~Urandil~~®
•hypertension, edema in heart insufficiency



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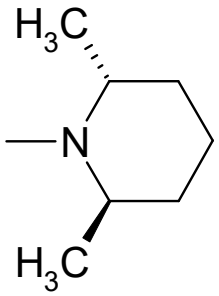
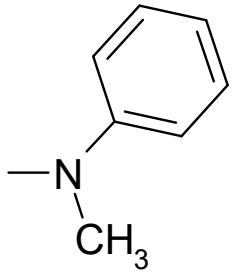
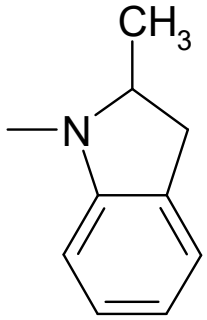


clopamide
~~Crystepin~~®
(+ reserpin, dihydroergocristin)



metipamide
Hypotylin®

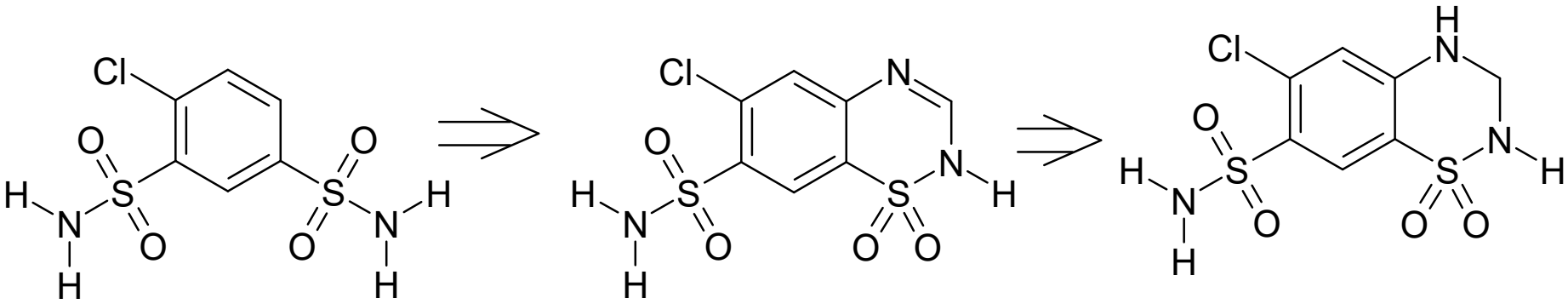


indapamide
•also antioxidant efffect
Indap®
Noliprel®(+ perindopril)
Prenewel ® ...

1.1.2 Thiazide diuretics

= sulfonamides with –SO_2NH- group in a cycle

Elicitation of their structure



clofenamide
diuretic sulfonamide with acyclic – SO_2NH_2 groups; today obsolete

chlorothiazide
1st „thiazide“ diuretic; today obsolete

hydrochlorothiazide
most frequently combined with amiloride (Moduretic®, Rhefluin®) or with quinapril (Accuzide ®) for treatment of hypertension

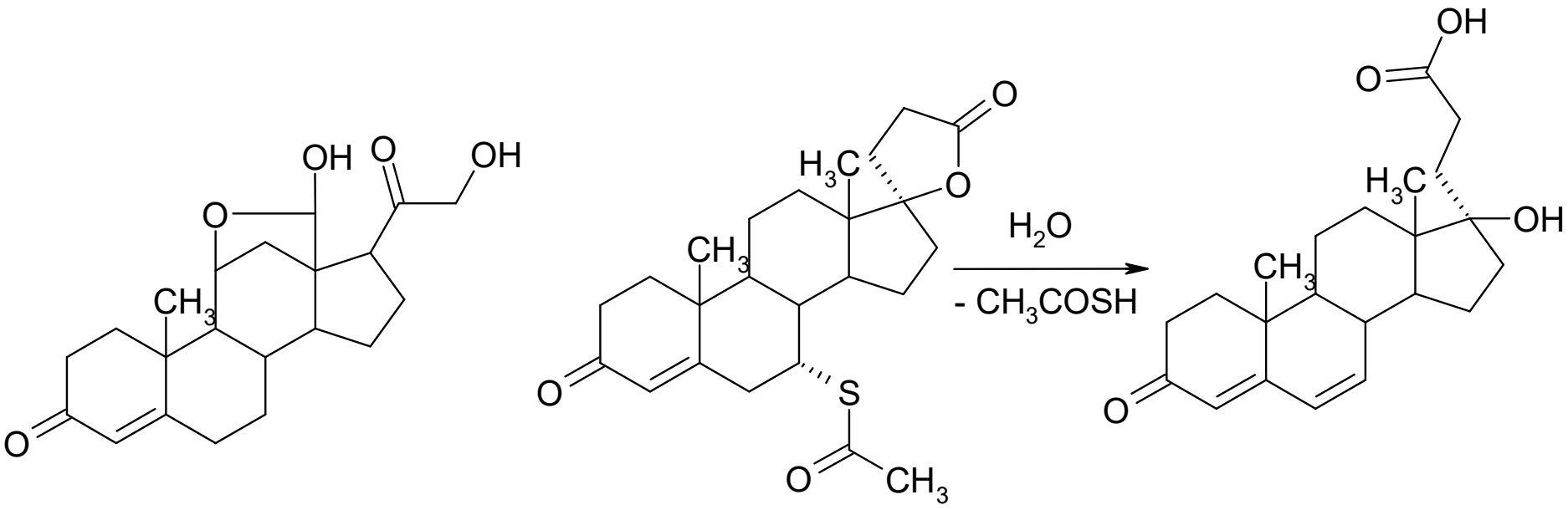
Activity

1 : 20

2. „Potassium conserving“ diuretics

•inhibit reabsorption of Na^+ v distal tubule; retention of K^+ occurs simultaneously

Aldosterone antagonists

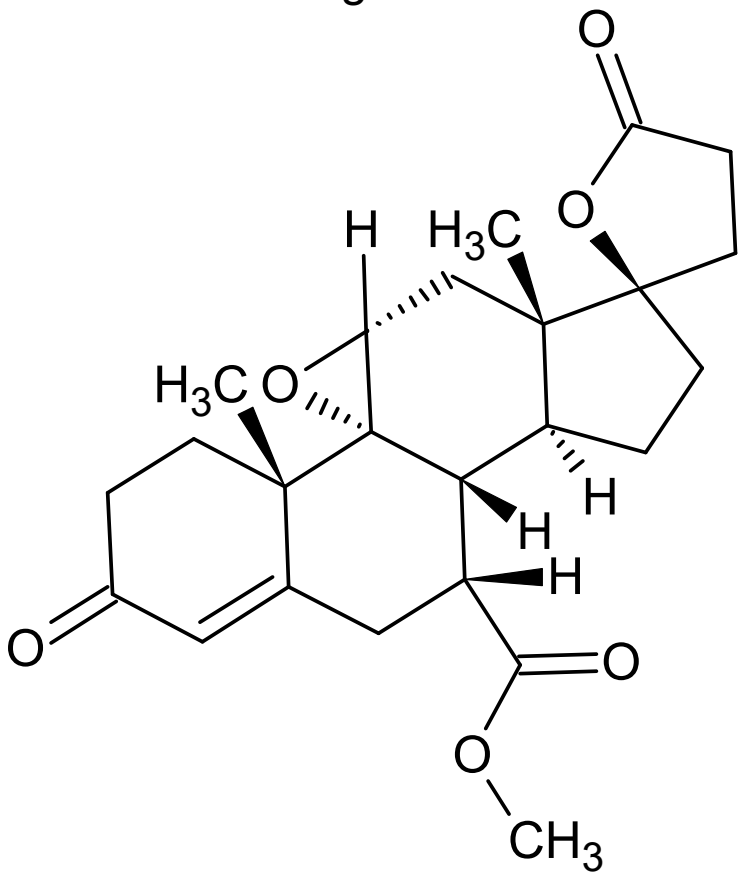


aldosterone

spironolactone
•prodrug of canrenoic acid
•hyperaldosteronemia
Verospiron® tbl.

canrenoic acid
•active compound
Aldactone® inj. – K^+ salt for parenteral application *(kalii canrenoas)*

Aldosterone antagonists continued



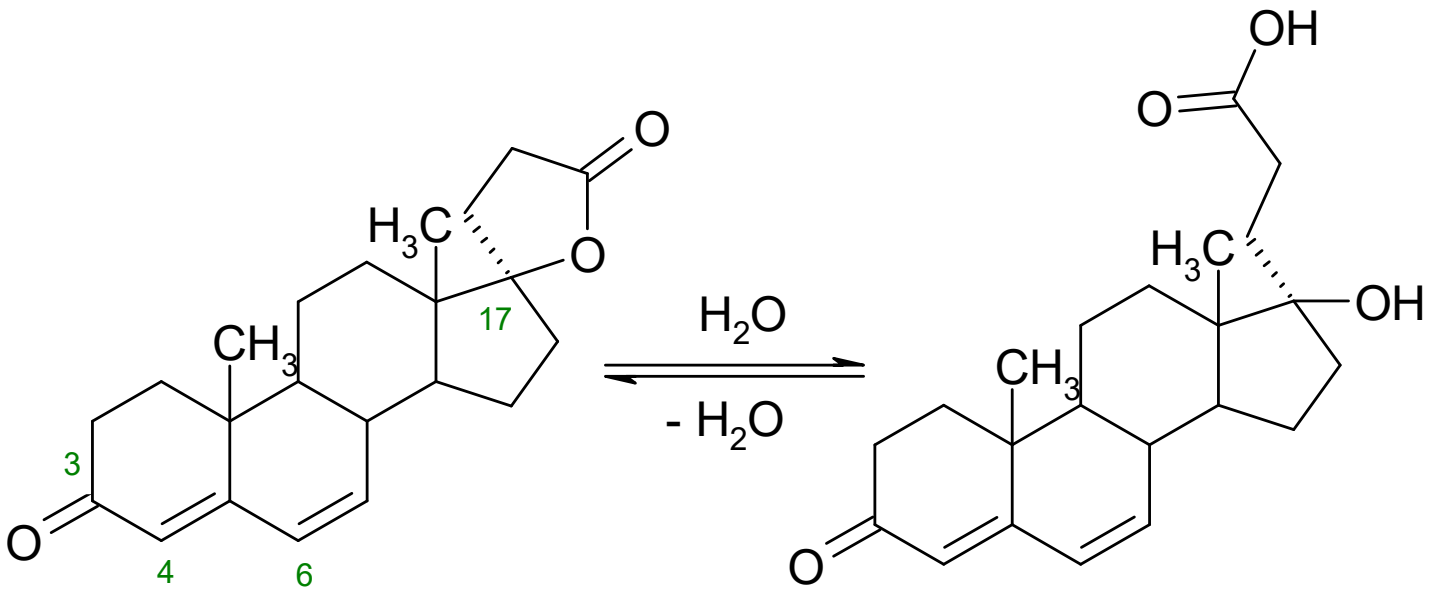
eplerenone

Inspra ® tbl., Aldoplewel ® tbl. …

- No oestrogenic activity

Canrenon and canrenoic acid

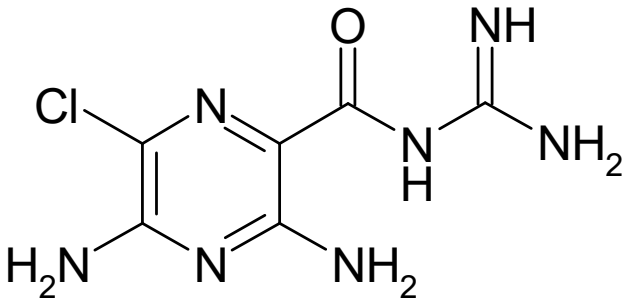
- both forms are in an equilibrium



canrenone
(lactone)

canrenoic acid
(a hydroxy acid)

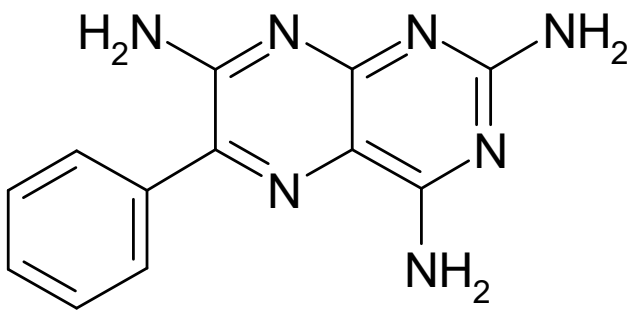
2. „Potassium conserving“ diuretics - continued



N-(3,5-diamino-6-chloropyrazine-2-carbonyl)-guanidine

amiloride

Amicloton®, Moduretic®, Loradur® (+ hydrochlorothiazide) …



2,4,7-triamino-6-phenylpteridine

triamterene

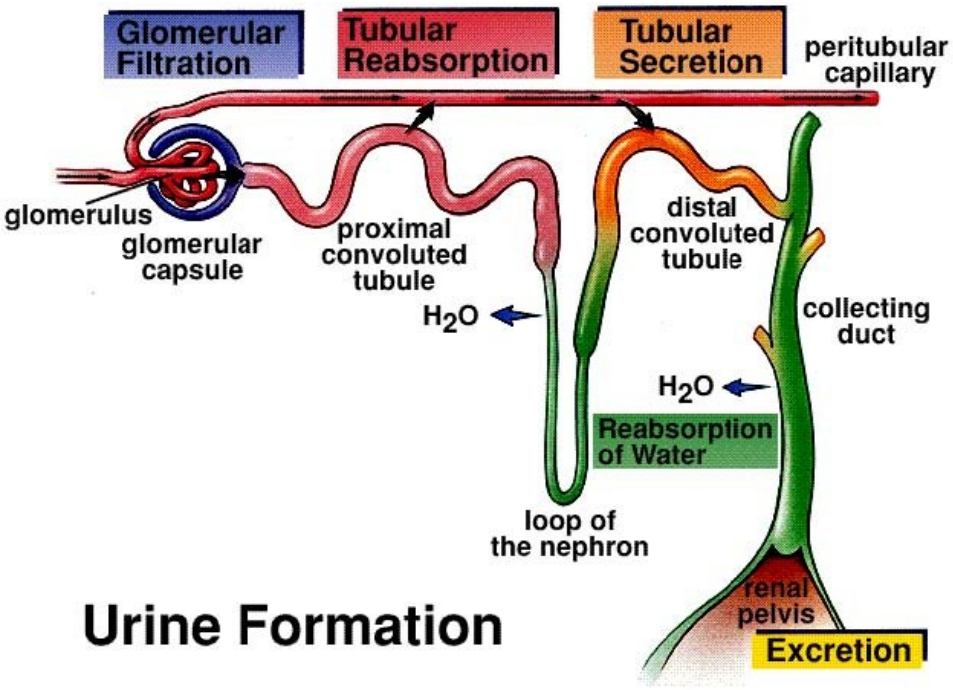
~~Dytac® tbl.~~

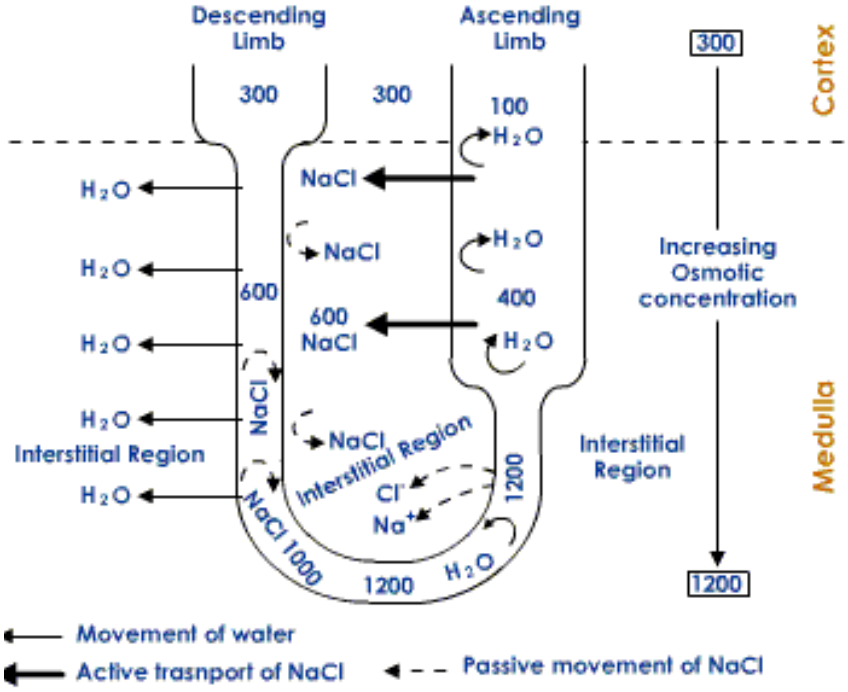
3. „Loop“ diuretics

•inhibit absorption of elektrolytes (Na^+, K^+, H^+ a Cl^-) in the ascending limb of Henle loop

($\Rightarrow$ hyponatraemia, hypokalaemia, hypochloraemia and alkalosis possible)

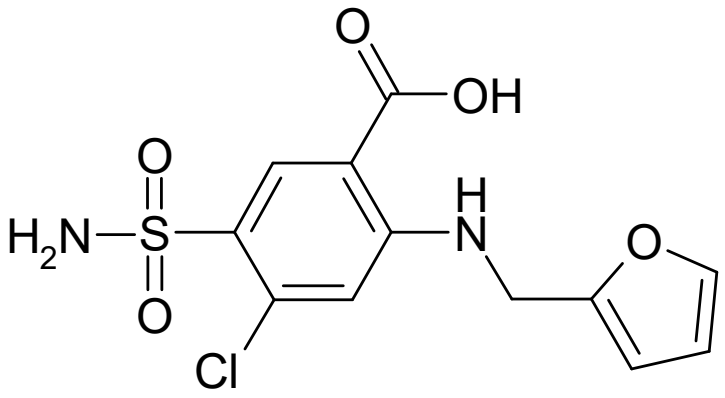
•efficient also in $\downarrow$ function of kidneys



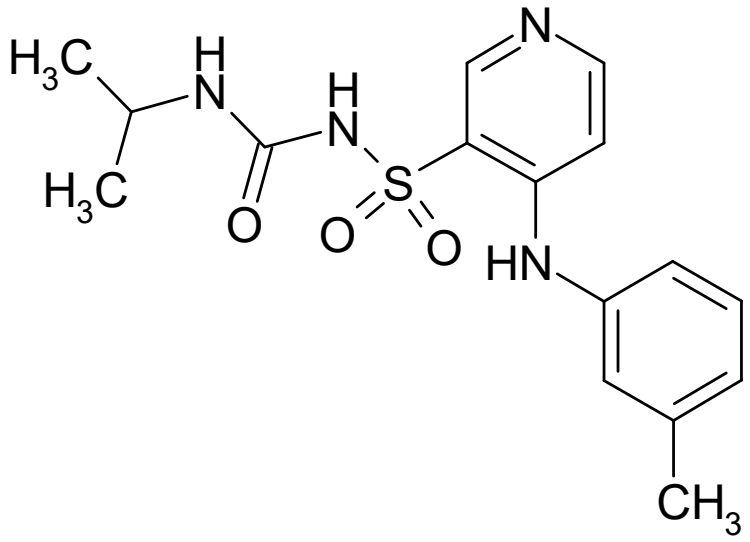


3. „Loop“ diuretics

3.1. Sulfonamides – amino(hetero)arenesulfonamide derivatives



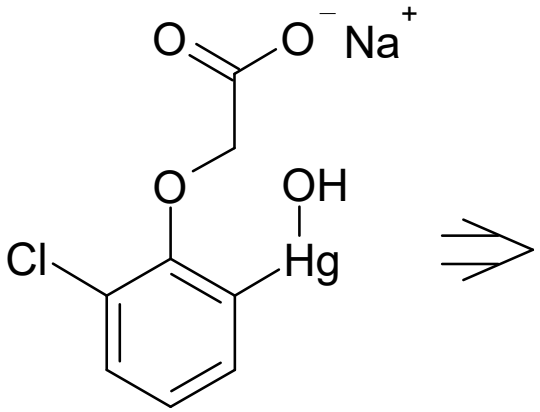
furosemide
Furon® tbl.
•oedema, chron. renal insufficiency

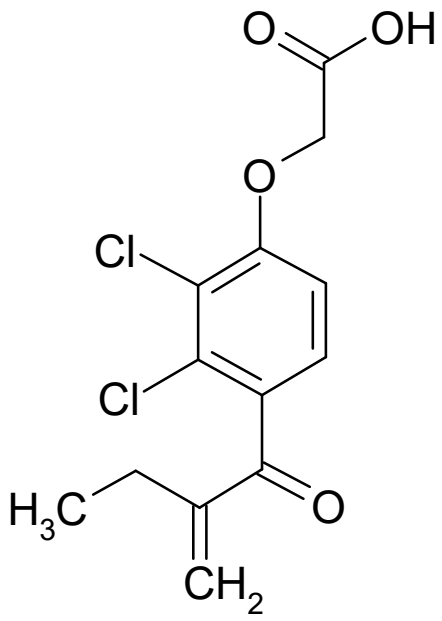


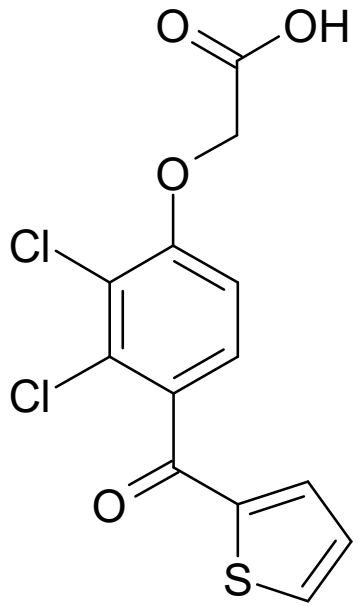
torasemide
syn. torsemide [USAN]
Trifas® tbl.

3.2. Phenoxyacetic acid derivatives

Derivation of the structure: directly from mercury diuretics







Novasurol

ethacrynic acid
Uregyt® tbl.

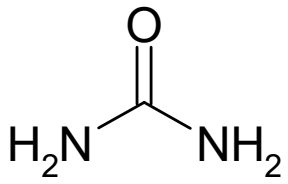
tienilic acid
(syn. **ticrynafen** [USAN])

4. Osmotic diuretics

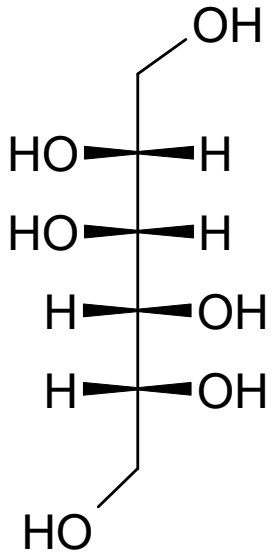
•osmotically active compounds, ↑ osmotic pressure of the glomerulal ultrafiltrate ⇒ ↓ its glomerular reabsorption

•administered only intravenously

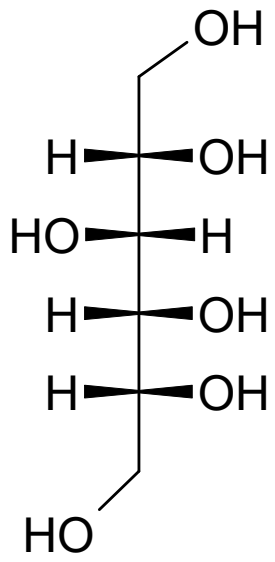
•removal of intracranial hypertension in patients with brain oedema, treatment of acute renal failure, forced diuresis in intoxications



urea
Urea VUAB® inf. sic.



D-mannitol
Osmofundin 15% N® inf.



D-sorbitol
syn. **D-glucitol**
Infusio sorbitoli® inf. sol.