



INVESTICE DO ROZVOJE VZDĚLÁVÁNÍ

## Diuretics

= compounds used for  $\uparrow$  of urine excretion in order to  $\downarrow$  the excessive volume of extracellular liquid or for other therapeutical purposes

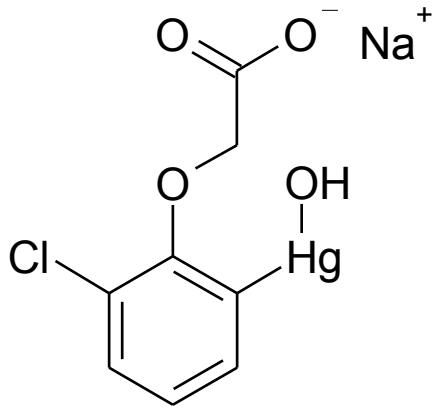
# History

## Mercury compounds

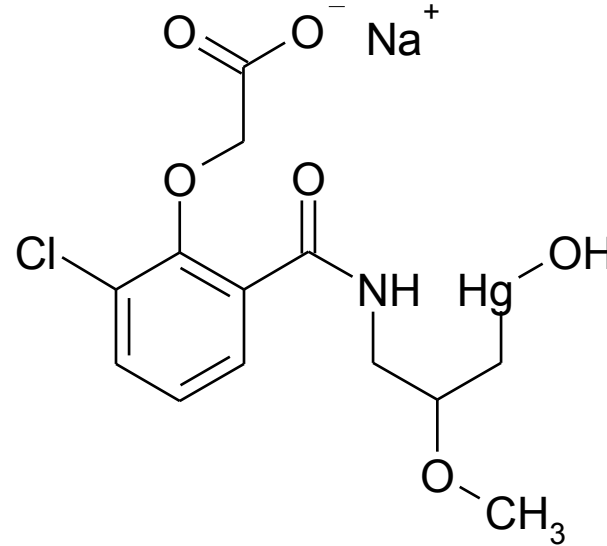
16<sup>th</sup> century – *Paracelsus* – red HgO (?)

19<sup>th</sup> century – Hg<sub>2</sub>Cl<sub>2</sub> „calomel“

beginning of the 20<sup>th</sup> 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 $-\text{SO}_2\text{NH}_2$ 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

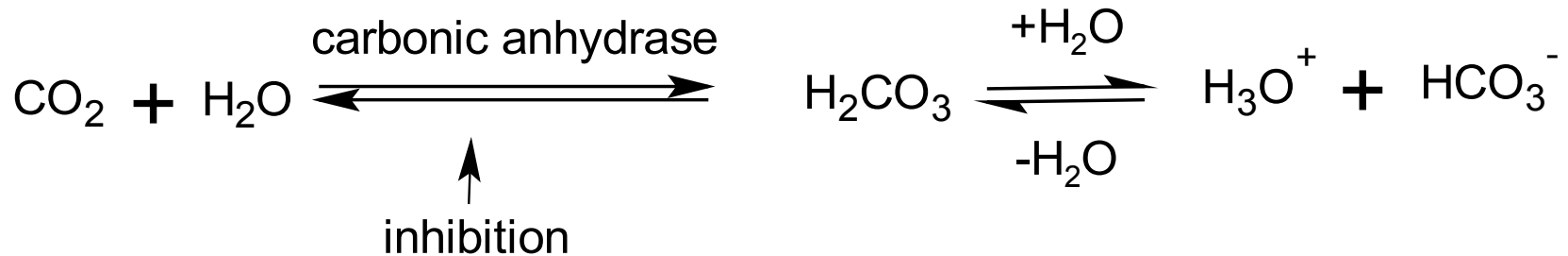
### (5. Purine alcaloida – xanthine derivatives)

# 1. Saluretics

- inhibit reabsorption (back resorption) of  $\text{Na}^+$  and  $\text{Cl}^-$  in more distal part of the nephron, ions bind water, which is then excreted
- they cause decrease of  $\text{K}^+$  in organism (exchange for  $\text{Na}^+$  and active secretion in distal tubule)

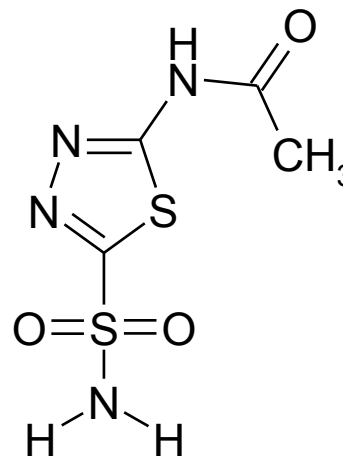
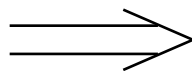
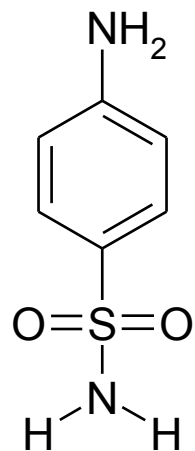
## 1.1. Sulfonamides

- diuretic activity of antibacterial sulfonamides observed as a side effect before 1940
- 1949 Schwartz: carbonic anhydrase inhibition



- the enzyme is inhibited  $\Rightarrow \downarrow \text{H}_2\text{CO}_3 \Rightarrow \downarrow \text{H}_3\text{O}^+$ , which normally exchanges for  $\text{Na}^+$ , in glomerular filtrate  $\Rightarrow \text{Na}^+$  remains in the renal tubule together with  $\text{HCO}_3^-$ , they bind osmotic equivalent of water  $\Rightarrow$  excretion of a large quantity of urine

### 1.1.1. Sulfonamides with acyclic $-\text{SO}_2\text{NH}_2$ group



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

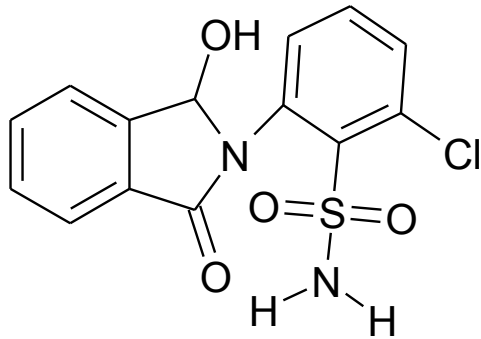
#### **sulfanilamide**

(lead compound of antibacterial sulfonamides)

#### **acetazolamide**

one of the first sulfonamide diuretics  
Diluran<sup>®</sup> - today treatment of glaucoma

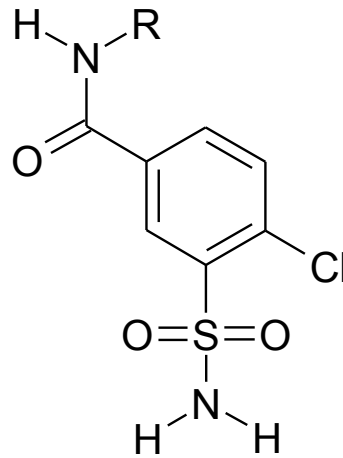
### 1.1.1. Sulfonamides with acyclic -SO<sub>2</sub>NH<sub>2</sub> group - continued



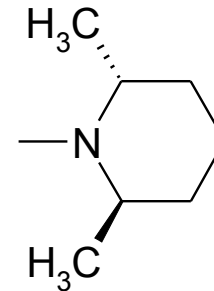
#### **chlorthalidone**

Urandil<sup>®</sup>

•hypertension,  
edema in heart  
insufficiency



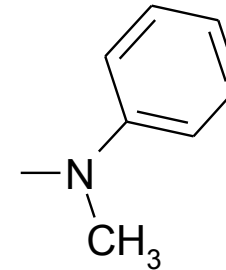
R =



#### **clopamide**

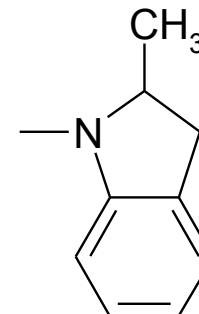
Crystepin<sup>®</sup>

(+ reserpin,  
dihydroergocristin)



#### **metipamide**

Hypotylin<sup>®</sup>



#### **indapamide**

•also antioxidant effect

Indap<sup>®</sup>

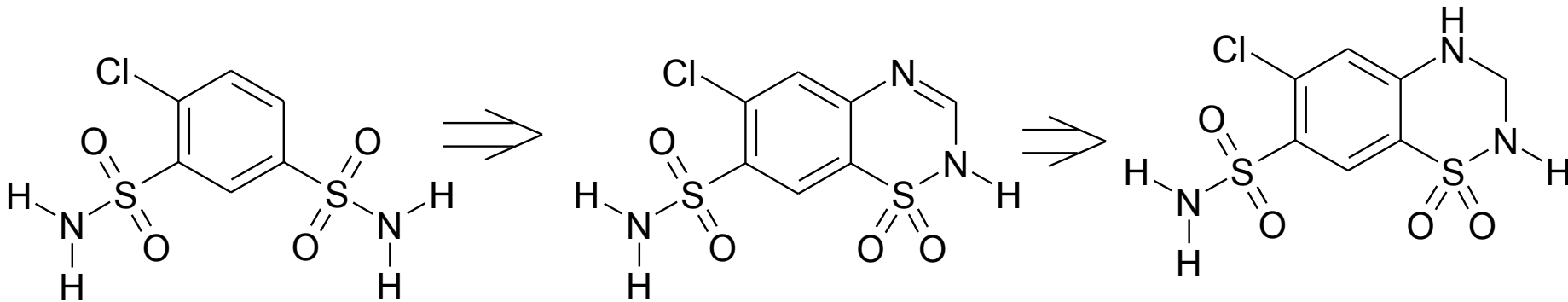
Noliprel<sup>®</sup>(+ perindopril)

Prenewel<sup>®</sup> ...

## 1.1.2 Thiazide diuretics

= sulfonamides with  $-\text{SO}_2\text{NH}-$  group in a cycle

Elicitation of their structure



### **clofenamide**

diuretic sulfonamide  
with acyclic  $-\text{SO}_2\text{NH}_2$   
groups; today  
obsolete

### **chlorothiazide**

1<sup>st</sup> „thiazide“  
diuretic; today  
obsolete

### **hydrochlorothiazide**

most frequently  
combined with  
amiloride (Moduretic<sup>®</sup>,  
Rhefluin<sup>®</sup>) or with  
quinapril (Accuzide<sup>®</sup>)  
for treatment of  
hypertension

Activity

1

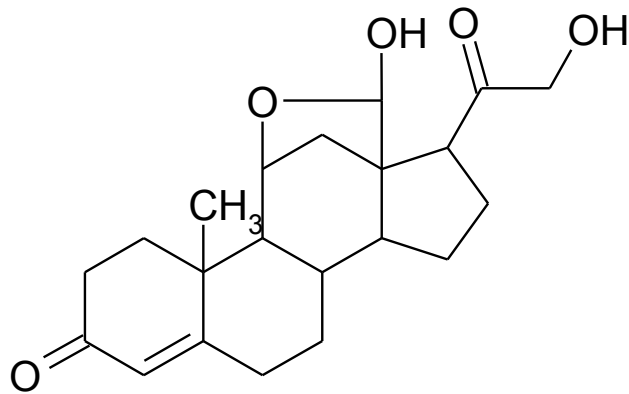
:

20

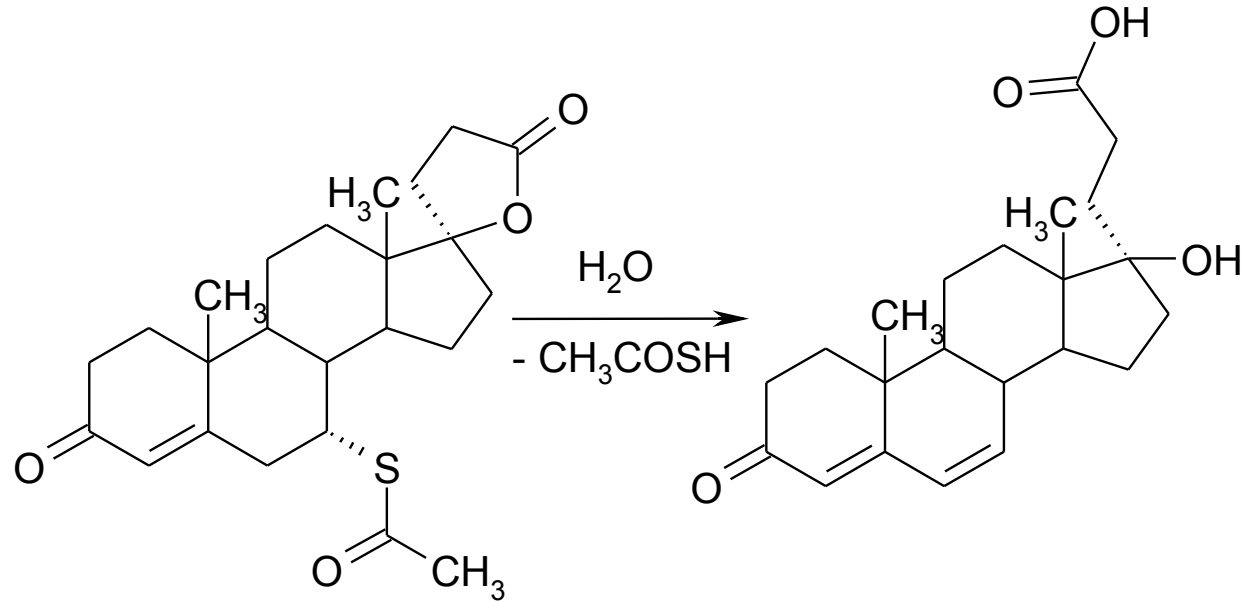
## 2. „Potassium conserving“ diuretics

- inhibit reabsorption of  $\text{Na}^+$  v distal tubule; retention of  $\text{K}^+$  occurs simultaneously

Aldosterone antagonists



aldosterone



### spironolactone

- prodrug of canrenoic acid
  - hyperaldosteronemia
- Verospiron® tbl.

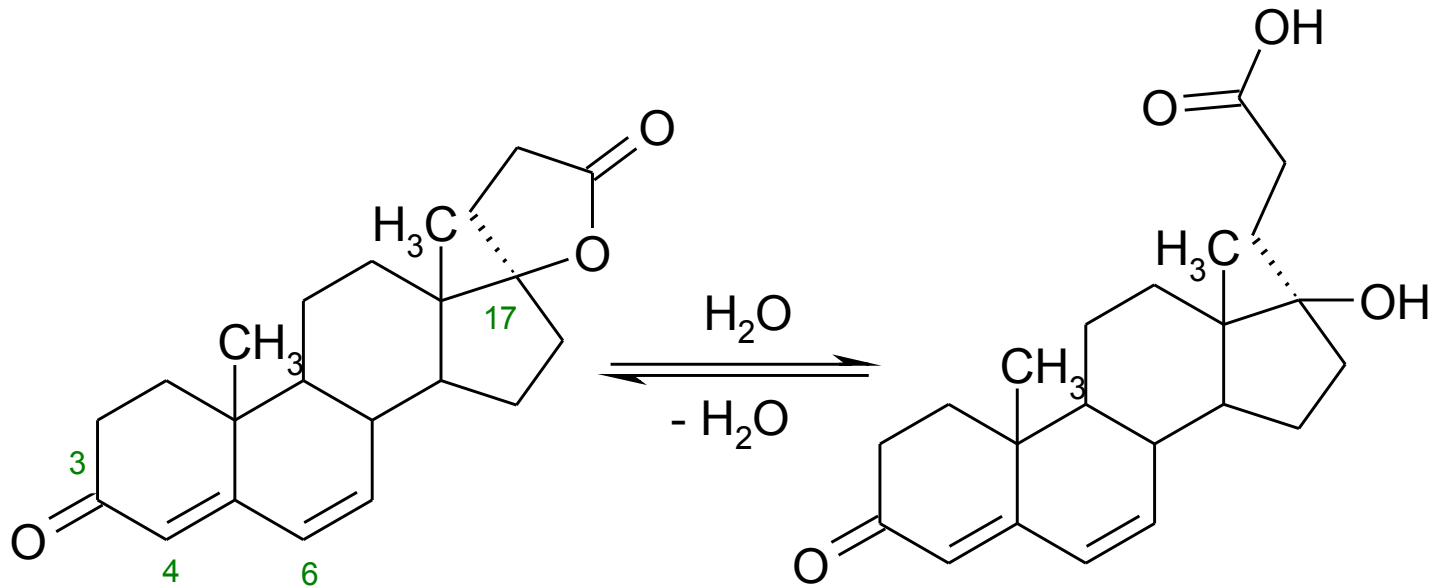
### canrenoic acid

- active compound
- Aldactone® inj. –  $\text{K}^+$  salt for parenteral application (*kalii canrenoas*)



# Canrenon and canrenoic acid

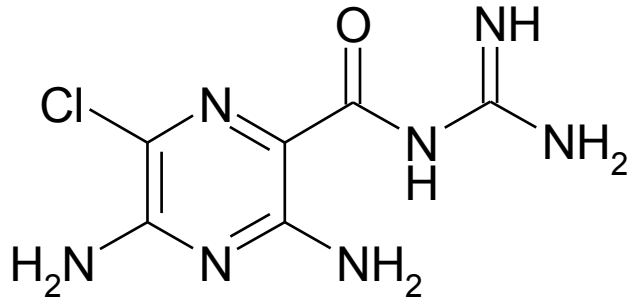
- both forms are in an equilibrium



canrenone  
(lactone)

canrenoic acid  
(a hydroxy acid)

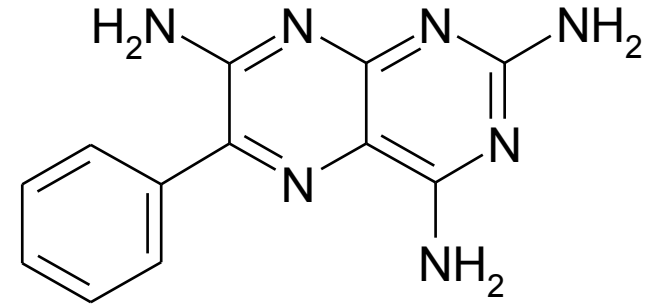
## 2. „Potassium conserving“ diuretics - continued



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

### **amiloride**

Amicloton<sup>®</sup>, Moduretic<sup>®</sup>, Loradur<sup>®</sup> (+  
hydrochlorothiazide) ...



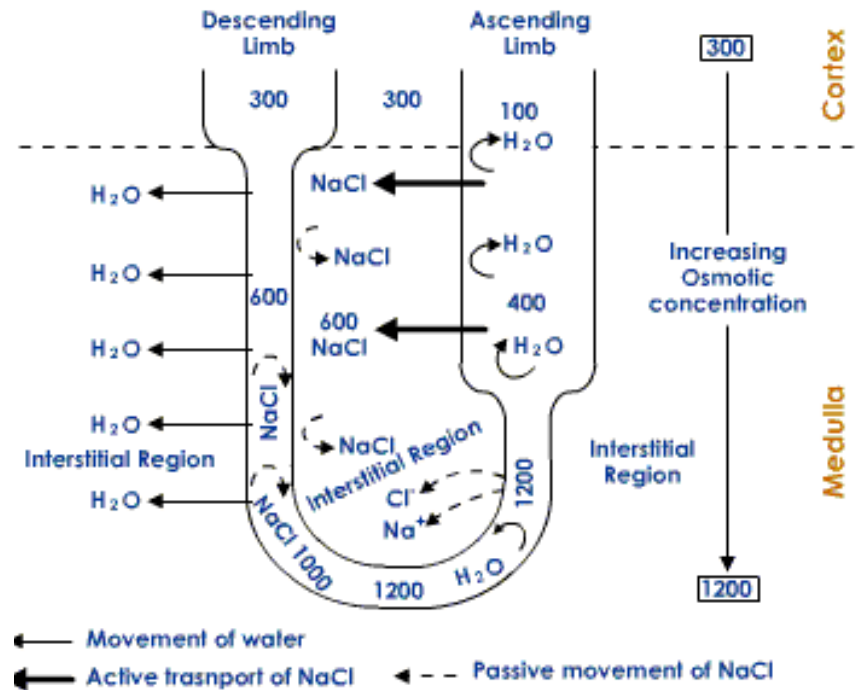
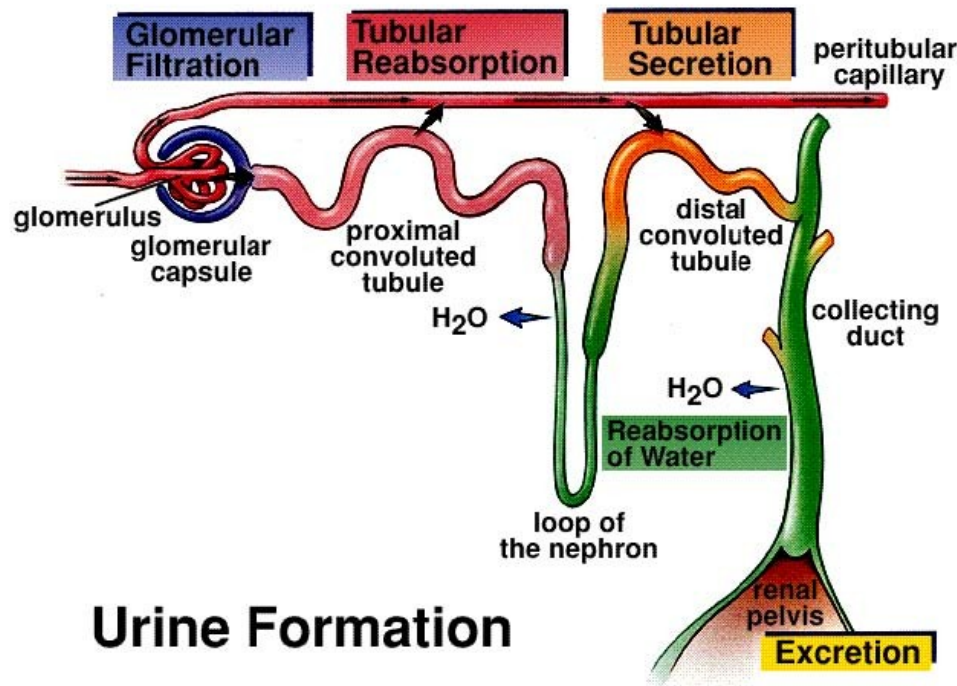
2,4,7-triamino-6-phenylpteridine

### **triamterene**

Dytac<sup>®</sup>-tbl.

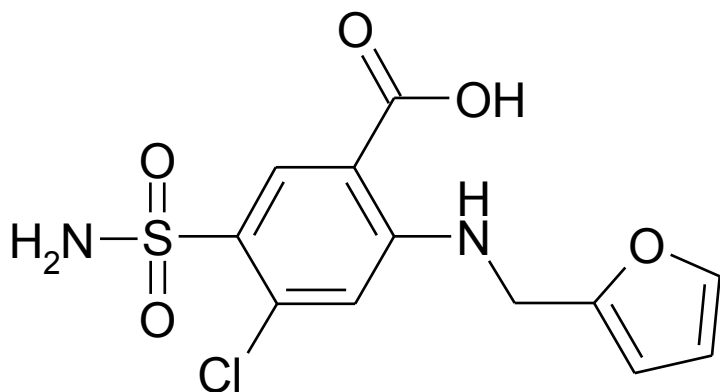
### 3. „Loop“ diuretics

- inhibit absorption of electrolytes ( $\text{Na}^+$ ,  $\text{K}^+$ ,  $\text{H}^+$  a  $\text{Cl}^-$ ) in the ascending limb of Henle loop  
( $\Rightarrow$  hyponatraemia, hypokalaemia, hypochloraemia and alkalosis possible)
- efficient also in  $\downarrow$  function of kidneys



### 3. „Loop“ diuretics

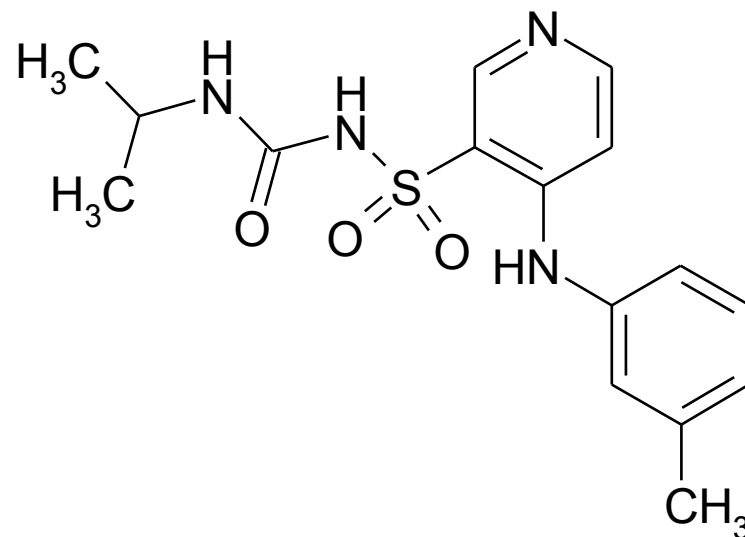
#### 3.1. Sulfonamides – amino(hetero)arenesulfonamide derivatives



#### **furosemide**

Furon<sup>®</sup> tbl.

•oedema, chron. renal insufficiency



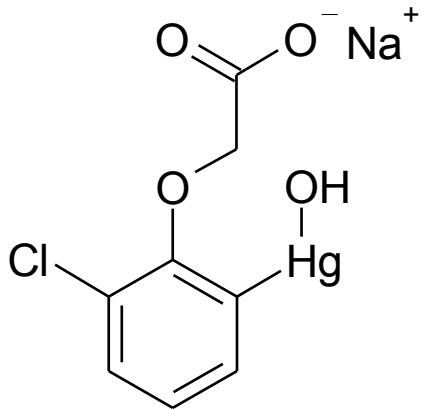
#### **torasemide**

syn. **torsemide** [USAN]

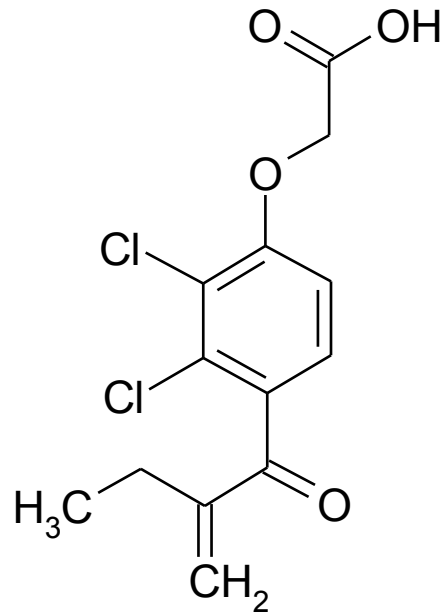
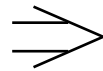
Trifas<sup>®</sup> tbl.

### 3.2. Phenoxyacetic acid derivatives

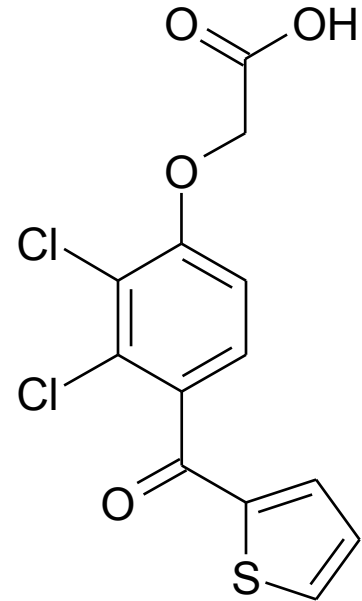
Derivation of the structure: directly from mercury diuretics



Novasurol



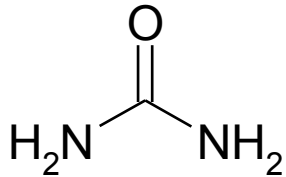
**ethacrynic acid**  
Uregyt<sup>®</sup> tbl.



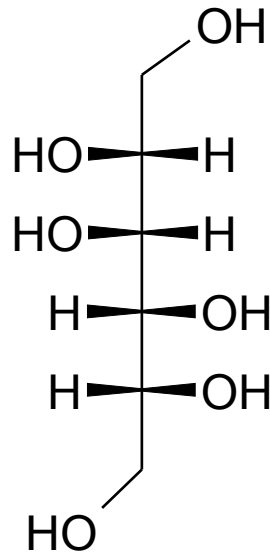
**tienilic acid**  
(syn. **ticrynafen** [USAN])

## 4. Osmotic diuretics

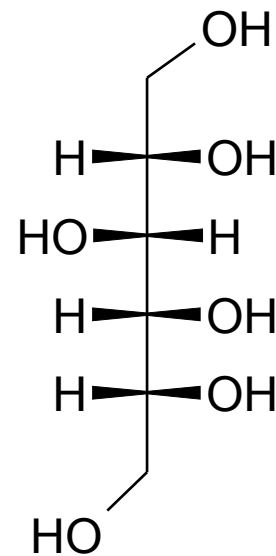
- osmotically active compounds,  $\uparrow$  osmotic pressure of the glomerular ultrafiltrate  $\Rightarrow$   $\downarrow$  its glomerular reabsorption
- administered only intravenously
- removal of intracranial hypertension in patients with brain oedema, treatment of acute renal failure, forced diuresis in intoxications



**urea**  
Urea VUAB<sup>®</sup> inf. sic.



**D-mannitol**  
Osmofundin 15% N<sup>®</sup> inf.



**D-sorbitol**  
syn. **D-glucitol**  
Infusio sorbitoli<sup>®</sup> inf. sol.