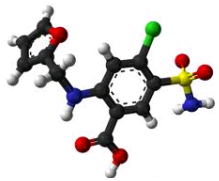
Diuretics and other masking agents

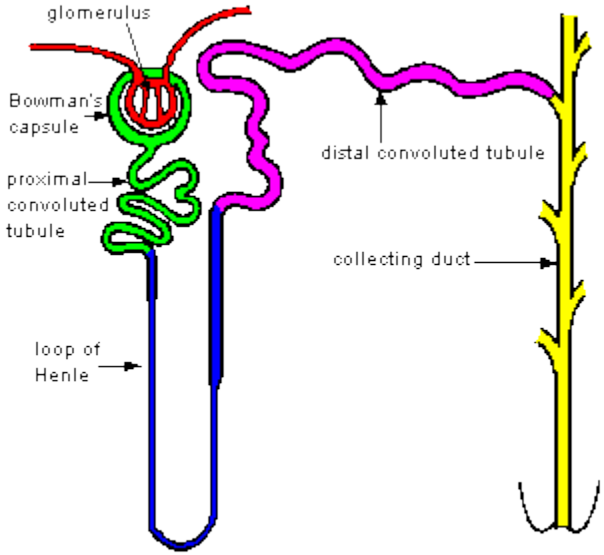


Diuretics:

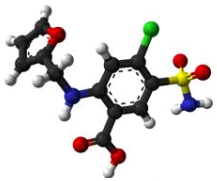
Increase in diuresis: excretion of electrolytes, hydrophilic and water-soluble compounds. Pharmacological effect in the case of edema / hypertension.

Kidney function:

- maintaining the homeostatic balance of electrolytes and water.
- excretion of water-soluble metabolites.
- Functional unit: *nephron*.



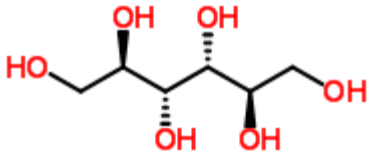
Diuretics (Masking agents)



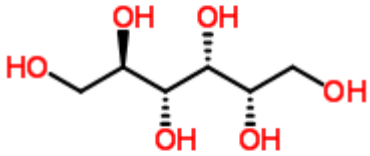
Osmotic diuretics: action on proximal convoluted tubule.

Polyalcohols/sugars:

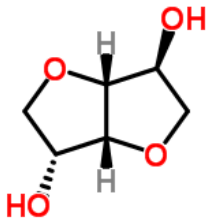
MANNITOL



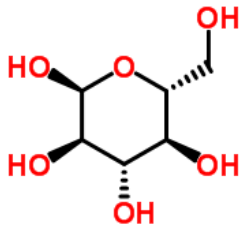
SORBITOL



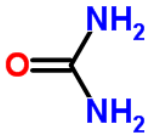
ISOSORBIDE



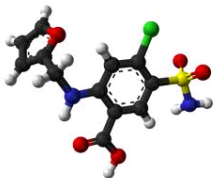
GLUCOSE



(UREA): pK_A 15.73, water solubility (25°C) 120 g / 100 g

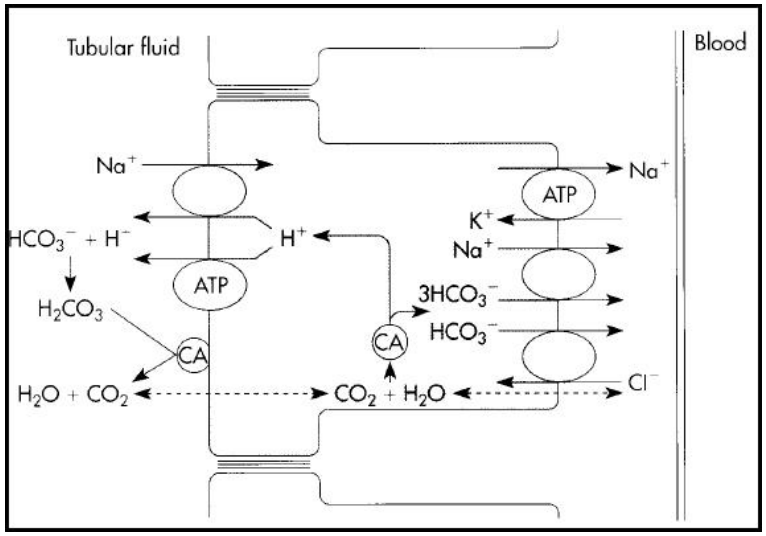


Diuretics



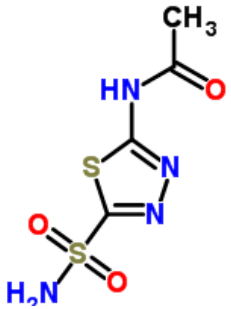
Carbonic anhydrase inhibitors: action on proximal / distal convoluted tubules. Urine alkalinization. Blood acidosis.

Catalyzed reaction: $H_2O + CO_2 \leftrightarrows H_2CO_3 \leftrightarrows H^+ + HCO_3^-$

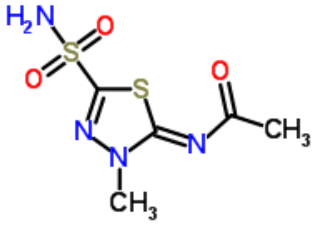


Sulphonamides : anti-glaucoma

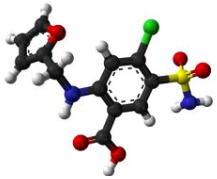
ACETAZOLAMIDE, pK_A 6.93



METAZOLAMIDE , pK_A 6.93

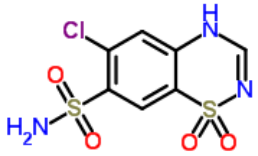


Diuretics



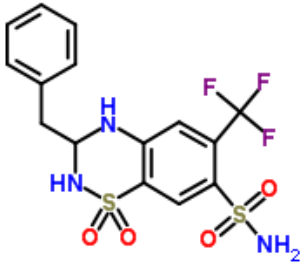
Thiazides: low effect as carbonic anhydrase inhibitors. The main mechanism of action involves the inhibition of Na^+/Cl^- co-transportation system in distal convoluted tubule (saluretics). Tox: hypokalemia.

Benzothiadiazines



CHLORTIAZIDE

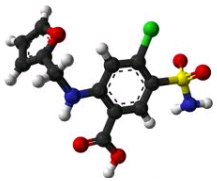
BENDROFLUMETHIAZIDE



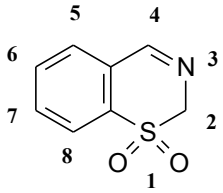
Name	**HYDROCHLOROTHIAZIDE**
Structure	
Systematic name	6-chloro-3,4-dihydro-2H-1,2,4-benzothiadiazine-7-sulfonamide 1,1-dioxide
Formula	$C_7H_8ClN_3O_4S_2$
MW	297.739
Monoisotopic mass	296.964474846
Mp	273-275°C
H bond acceptors	7
H bond donors	4
Acid p*Ka*	9.09 (primary sulphonamide); 9.83 (secondary sulphonamide); 11.31 (aniline)
Basic p*ka*	--
ACD Log D pH 5.5	-0.07
ACD Log D pH 7.4	-0.09
Solubility	water
LD50	3080 mg/Kg mouse p.o.
Therapeutic cat	diuretic
ATC C03AB03 hydrochlorothiazide and potassium C03EA01 hydrochlorothiazide and potassium-sparing agents C03AX01 hydrochlorothiazide, combinations	**C03AA03** C CARDIOVASCULAR SYSTEM C03 DIURETICS C03A LOW-CEILING DIURETICS, THIAZIDES C03AA Thiazides, plain
Receptors	nephron electroneutral Na+-Cl- co-transporter

Nomi commerciali (IT)	
ESIDREX	A, RR, compresse
ACCURETIC, ACEDIUR, ACEPLUS, ACEQUIDE, ACESISTEM, ALDACTAZIDE, AVEDAR, BENAZEPRIL IDR., BIFRIZIDE, BLOPRESID, CAPTOPRIL IDR., CIBADREX, CLORISIP, COAPROVEL, COMBISARTAN, CONDIUREN, CORIXIL, COTAREG, ELEKTRA, ENALAPRIL IDR., ENEFIN, ENSOR, ENULID, ESIDREX, FEMIPRES, FORZAAR, FOSICOMBI, FOSINOPRIL IDR., GENTIPRESS, HERZAPLUS, HIZAAR, IDROQUARK, INIBACE, INITISS, IVREX, KARVEZIDE, KRUPLUS, LISINOPRIL IDR., LOBIDIUR, LODOZ, LOSARTAN IDR., LOSAZID, LOZID, MICARDIPLUS, MODURETIC, NALAPRES, NEOLOTAN, NEOPREX, NOBIZIDE, NORAZIDE, OLMEGAN, OLPREZIDE, PLAUNAZIDE, PRECTIAZIDE, PRINZIDE, PRITORPLUS, QUINALAPRIL IDR., QUINAZIDE, RAMIPRIL IDR., RATACAND, SINERTEC, SPIRIDAZIDE, TENSADIUR, TENSOZIDE, TIARTAN, TRIATEC HCT, UNIPRIL DIUR, VASORETIC, ZANTIPRIDE, ZESTORETIC, ZINADIUR	associazione con antiipertensivi

Diuretics

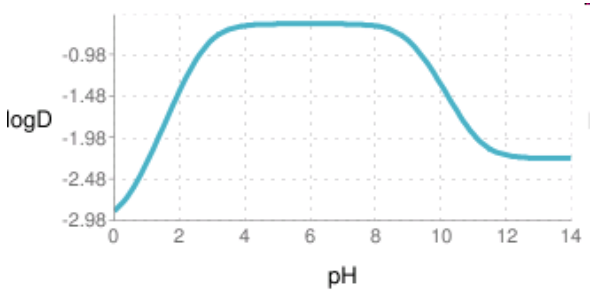


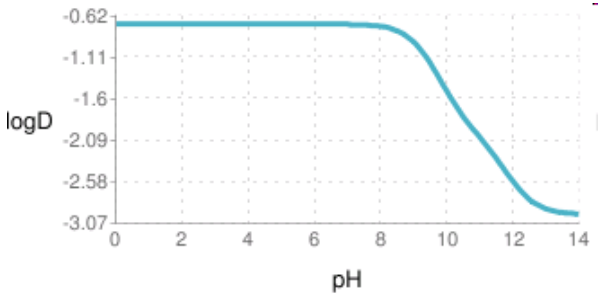
Thiazides:

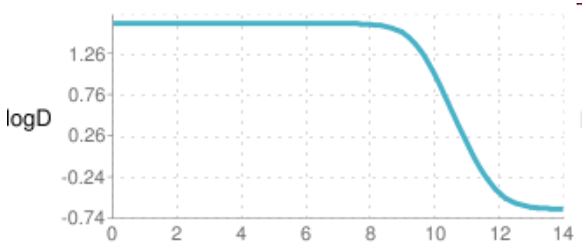


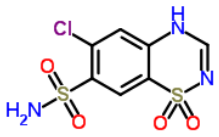
Benzothiadiazines SAR

EW in 6 is critical. Long duration of ation for high lipophilicity. The 7-sulphonamide group is indispensable. The introduction of a lipophilic group in 3 (or on the N 2) increases the activity.

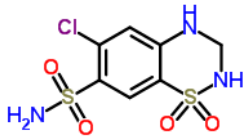




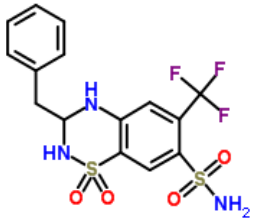




CHLORTIAZIDE

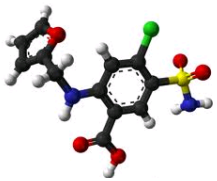


HYDROCHLORTIAZIDE



BENDROFLUMETHIAZIDE

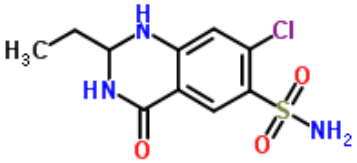
Diuretics



Quinazolinones, phtalimides, indolines: same mechanism of thiazides, long duration of action.

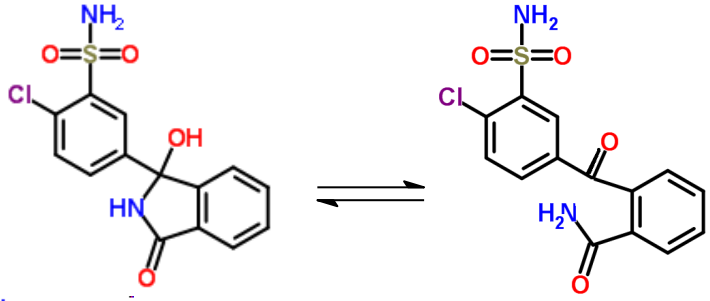
Quinazolinones

QUINETHAZONE



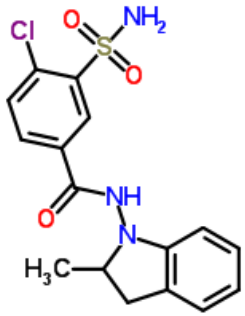
Phtalimides:

CHLORTHALIDONE

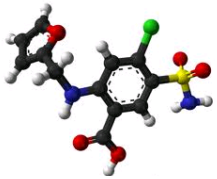


Indolines:

INDAPAMIDE



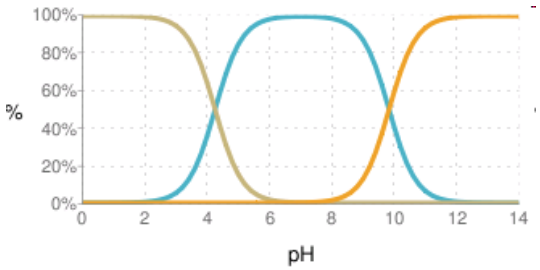
Diuretics



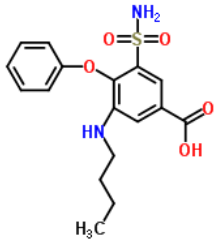
High-ceiling diuretics: Henle's loop Na^+/K^+ / $2Cl^-$ transportation. Short duration of action. Strong saluretic: -25% of plasmatic Na^+. Risk of hypokalemia.

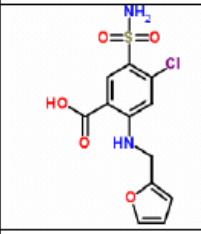
Anthranylic acid derivatives

Di-acidic compounds: **FUROSEMIDE**



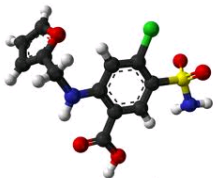
BUMETANIDE: 4 h action



Name	**FUROSEMIDE**
Structure	
Systematic name	4-chloro-2-[(furan-2-ylmethyl)amino]-5-sulfamoylbenzoic acid
Formula	$C_{12}H_{11}ClN_2O_5S$
MW	330.744
Monoisotopic mass	330.007719869
Mp	205°C
H bond acceptors	7
H bond donors	4
Acid p*Ka*	4.25 (carboxyl); 9.83 (sulphonamide)
Basic p*Ka*	--
ACD Log D pH 5.5	0.69
ACD Log D pH 7.4	-0.03
Solubility	water 0.006 mg/mL, methanol, basic soln.
LD50	2600 mg/Kg rat p.o.
Therapeutic cat	diuretic
ATC	**C03CA01** C CARDIOVASCULAR SYSTEM C03 DIURETICS C03C HIGH-CEILING DIURETICS C03CA Sulfonamides, plain
Receptors	Henle's loop $Na^+/K^+/Cl^-$ transportation

Nomi commerciali (IT)	
DIUREN, FUROSEMIDE, LASIX	A, RR, compresse, gocce, iniettabili

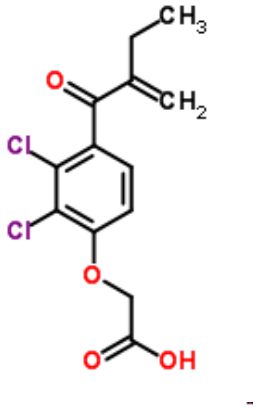
Diuretics



High-ceiling diuretics: Henle's loop $Na^+/K^+/2Cl^-$ transportation. Action on sulphidrylic enzymes for solute re-absorption.

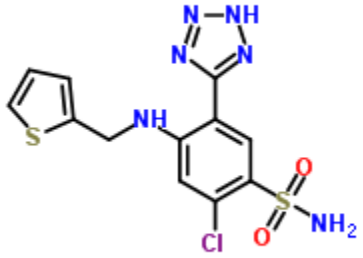
Phenoxyacetic acid derivatives

ETHACRYNIC ACID

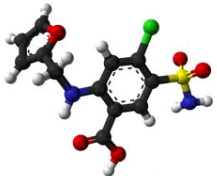


Tetrazoles: AZOSEMIDE

Tetrazole: carboxylic bioisostere



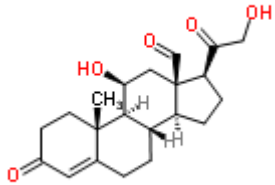
Diuretics



Potassium-sparing diuretics: Mineral-corticoid antagonists.

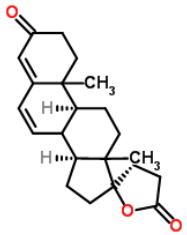
Anti-hormone diuretics

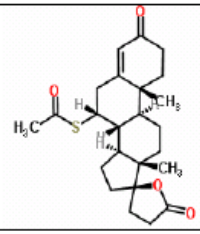
SPIRONOLACTONE: competitive ALDOSTERONE antagonist



It acts against Na^+/Cl^- reabsorption and favours K^+ retention.

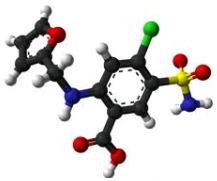
Metabolized to **CANRENONE**



Name	**SPIRONOLACTONE**
Structure	
Systematic name	[(7R,8R,9S,10R,13S,14S,17R)-10,13-dimethyl-3,5'-dioxo-1,2,3,4',5',6,7,8,9,10,11,12,13,14,15,16-hexadecahydro-3'H-spiro[cyclopenta[a]phenanthrene-17,2'-furan]-7-yl] ethanethioate
Formula	$C_{24}H_{32}O_4S$
MW	416.573
Monoisotopic mass	416.202130202
Mp	135°C
H bond acceptors	4
H bond donors	0
Acid p*Ka*	--
Basic p*ka*	--
ACD Log D pH 5.5	3.12
ACD Log D pH 7.4	3.12
Solubility	DMSO, ethanol
LD50	260 mg/Kg rat i.p.
Therapeutic cat	diuretic
ATC	**C03DA01** C CARDIOVASCULAR SYSTEM C03 DIURETICS C03D POTASSIUM-SPARING AGENTS C03DA Aldosterone antagonists
Receptors	Aldosterone

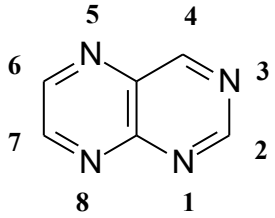
Nomi commerciali (IT)	
ALDACTONE, PRILACTONE, SPIROLANG, URACTONE e associazioni	A, RR, compresse, capsule

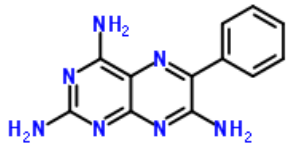
Diuretics

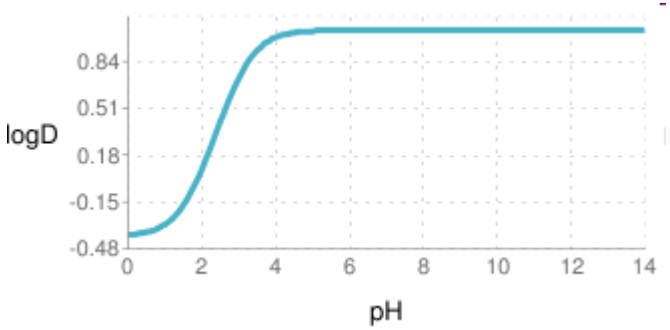


Potassium-sparing diuretics: Act inhibiting sodium reabsorption in the late distal convoluted tubules.

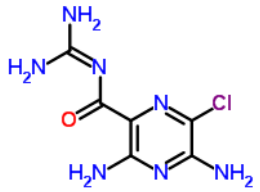
Pteridines





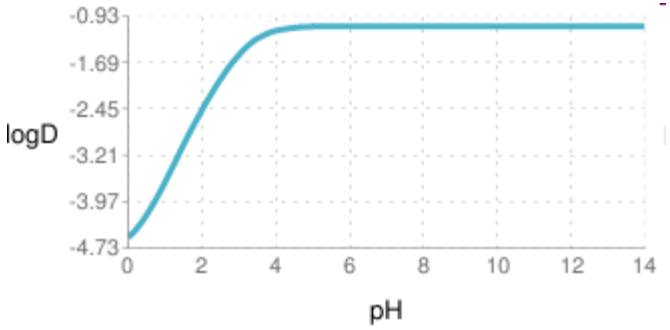


TRIAMTERENE: Basic compound ($pK_{A\ aromatic\ guanidine}$: 3.11) blocks the epithelial sodium channel on the lumen side of the kidney collecting tubule

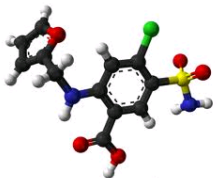


Aminopirazines.

AMILORIDE (pK_As: 1.44_{arom} 3.29_{guanid})



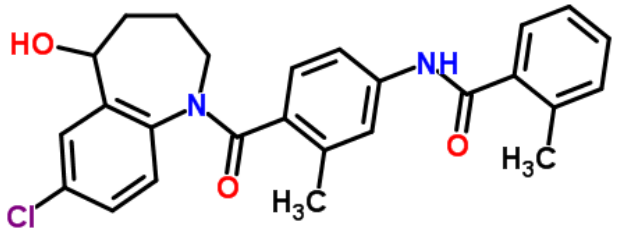
Diuretics



Vasopressin receptor antagonists: non-peptide inhibitor of antidiuretic hormone.

Benzazepines.

TOLVAPTAN: V2 receptor. used to treat hyponatremia occurring with heart failure



CONIVAPTAN: V1 and V2 receptors