

General and Local Anesthetics

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Local anesthetics

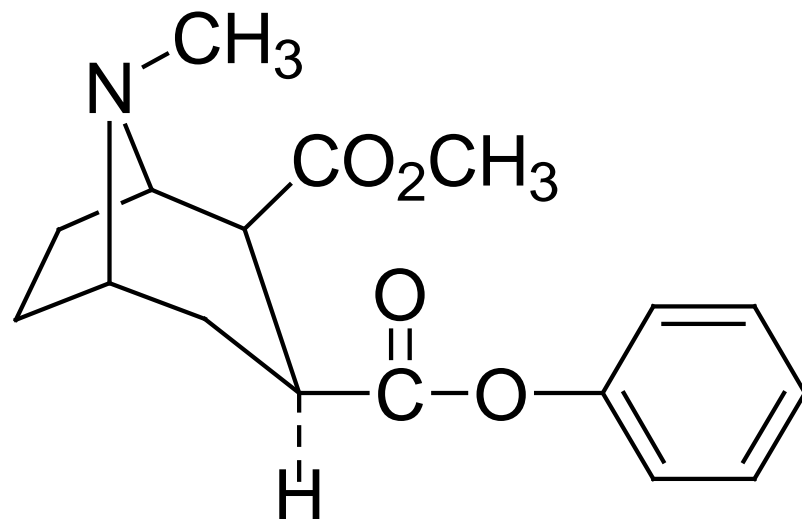
Local anesthetics

- Block the nerve that carries the pain sensation and automatic impulses in local areas of the body
- Prevent conduction and formation of an action potential by either full or partial blockage of **sodium ion channel**
- Used in dentistry, ophthalmology and minor surgical operations

Local ...

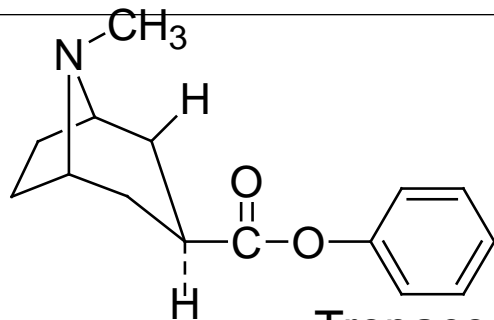
Ester and amide type

- Cocaine, an alkaloid from the leaves of *Erythroxylon coca*, was the first local anesthetic
 - The development of local anesthetics began after the discovery of local anesthetic properties of cocaine

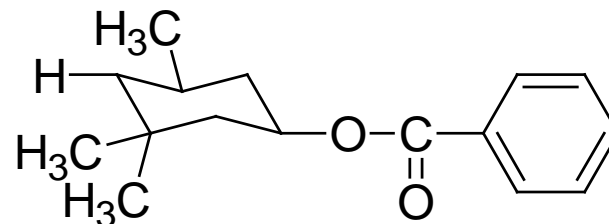


- Because of its **addictive** properties the search for non-habit forming local anesthetics began

Local ...

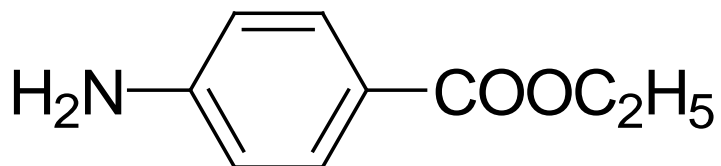


Tropacocaine



β-eucaine

- The **carbomethoxy** group is not required for local action as seen in **tropacocaine** which lack this group
- The synthesis and testing of **β-eucaine** showed a tropane ring is not a prerequisite for local anesthetic activity
- Based on the above findings many other simple analogs like procaine and benzocaine were synthesized



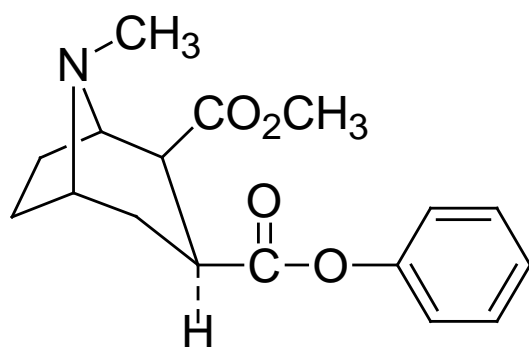
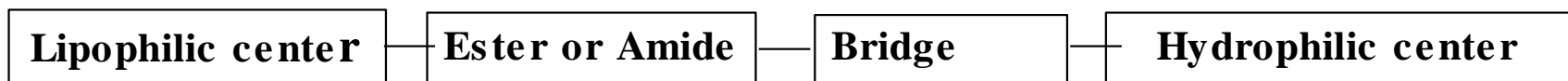
Benzocaine



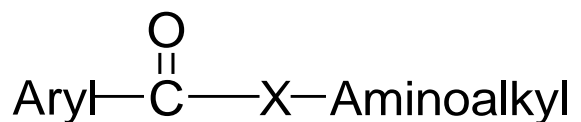
Procaine

Local ...

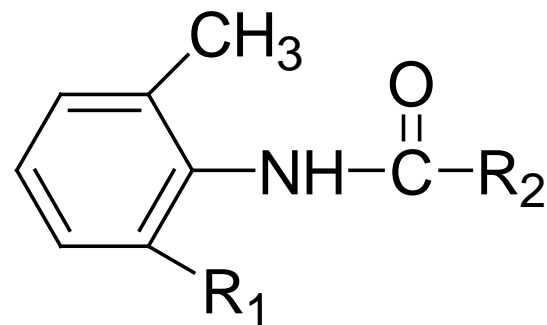
- General structural features



Cocaine



Benzoic acid derivatives



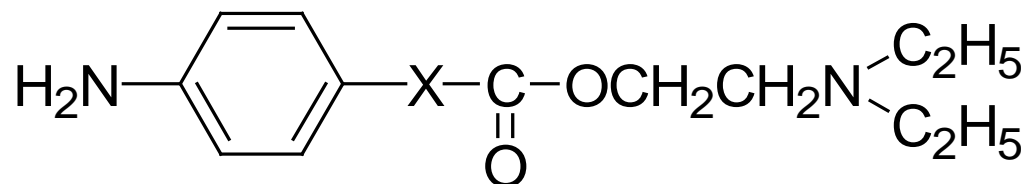
Anilides derivatives

Local ... SAR of local anesthetics

- The lipophilic center is usually either a **cyclic** or **heterocyclic** system
- The hydrophilic center is normally a secondary or tertiary amine, which may or may not be cyclic
 - **Tertiary amines** are more useful since they are less irritating to tissue
- The hydrophilic center may be attached to ester or amide by a short hydrocarbon chain
- The lipophilic center is responsible for lipid solubility as it affects cell penetration and their action

Local ...

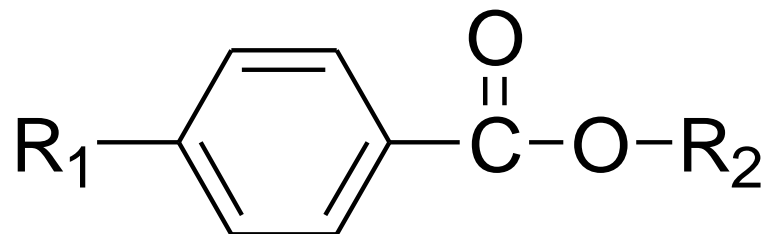
- The hydrophilic center provides water solubility and is believed to be involved in **binding to the receptor**
- For best action a balance between lipophilic and hydrophilic center is essential
- Ester type require a carbonyl group in **conjugation** with an aromatic ring or related system



- When $\text{X} = \text{CH}_2$, there is no activity; carbonyl is not conjugated
- When $\text{X} = -\underset{\text{H}}{\text{C}}=\text{CH}-$, there is activity as the aromatic ring is conjugated with carbonyl group

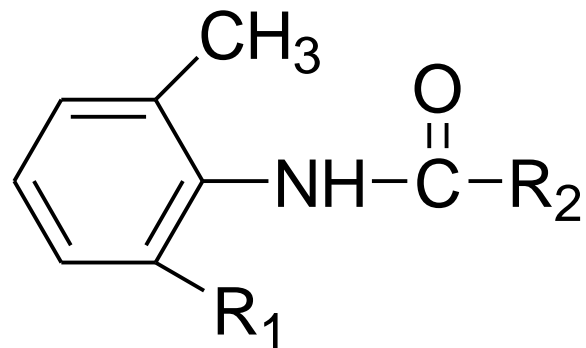
Local ...

- Benzoic acid derivatives



Generic name	R ₁	R ₂
Hexylcaine	H	$-\text{HC}(\text{CH}_3)_2\text{CH}_2\text{CHN}-\text{C}_6\text{H}_{11}$
Dyclonine	CH ₃ CH ₂ CH ₂ CH ₂ O-	$-\text{H}_2\text{CH}_2\text{C}-\text{N}-\text{C}_6\text{H}_{11}$
Piperocaine	H	$-\text{H}_2\text{CH}_2\text{CH}_2\text{C}-\text{N}(\text{CH}_3)-\text{C}_6\text{H}_{11}$

- In the lidocaine (the amino amide) series the ortho dimethyl groups are required for protection from amide hydrolysis ensuring desirable duration of action



Generic name	R ₁	R ₂
Etidocaine	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{CH}_2 \\ \\ \text{—NHCH}_2\text{OCH—N—} \begin{array}{l} \text{CH}_2\text{CH}_3 \\ \text{CH}_2\text{CH}_2\text{CH}_3 \end{array} \end{array}$
Mepivacaine	CH ₃	
Bupivacaine	CH ₃	
lidocaine	CH ₃	$\text{—NHCH}_2\text{OCH}_2\text{N} \begin{array}{l} \text{C}_2\text{H}_5 \\ \text{C}_2\text{H}_5 \end{array}$
prilocaine	CH ₃	$\begin{array}{c} \text{CH}_3 \\ \\ \text{—NHCOCHNHCH}_2\text{CH}_2\text{CH}_3 \end{array}$

General Anaesthetics

- General anaesthesia is a controlled reversible depression of the functional activity of the CNS
- The neurophysiologic state produced by general anesthetics is characterized by five primary effects:
 - Unconsciousness,
 - Amnesia,
 - Analgesia,
 - Inhibition of autonomic reflexes, and
 - Skeletal muscle relaxation.
- Early agents were ether, chloroform & nitrous oxide

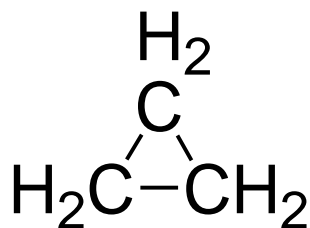
- Nowadays, multiple drug regimes are used including;
 - Pre-anaesthesia + skeletal muscle relaxants + drugs to control side effects + actual anaesthetic agent are used in combination
 - General anaesthetics are given either by **inhalation** or **i.v.**

General...

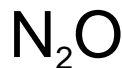
Inhalation anaesthetics (gases and liquids)

- Current inhalation drugs include halothane & several other F&Cl-containing molecules, and nitrous oxide.

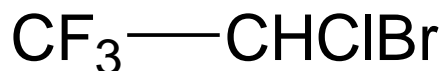
Gas inhalation anaesthetics



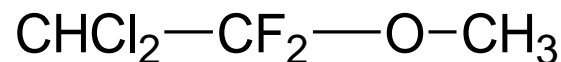
Cyclopropane



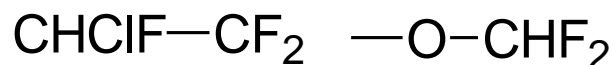
Nitrous oxide



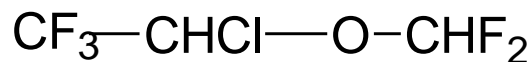
Halothane



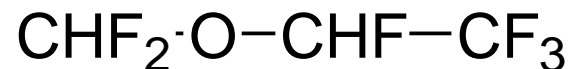
Methoxyflurane



Enflurane



Isoflurane



Desflurane

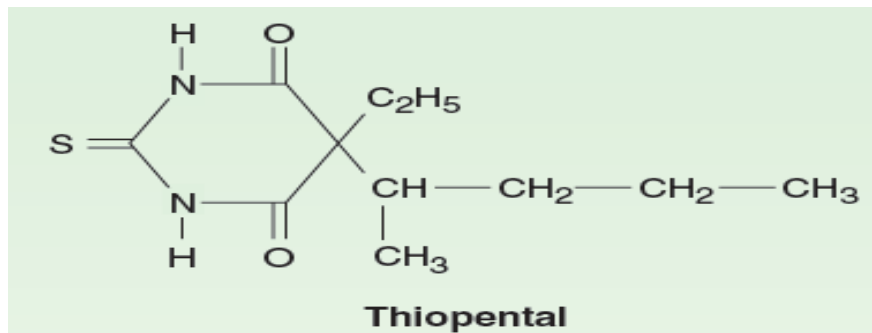
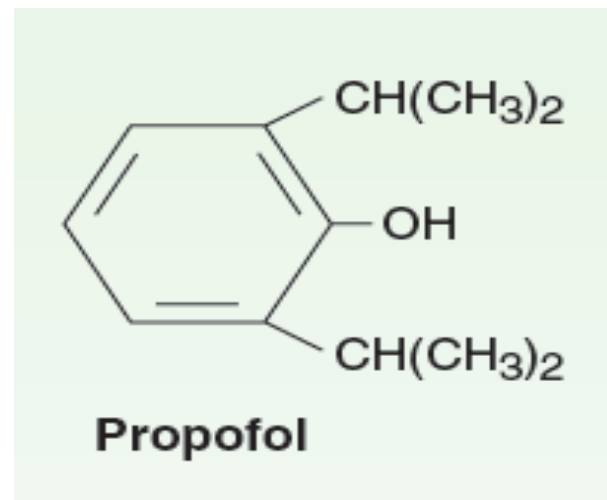
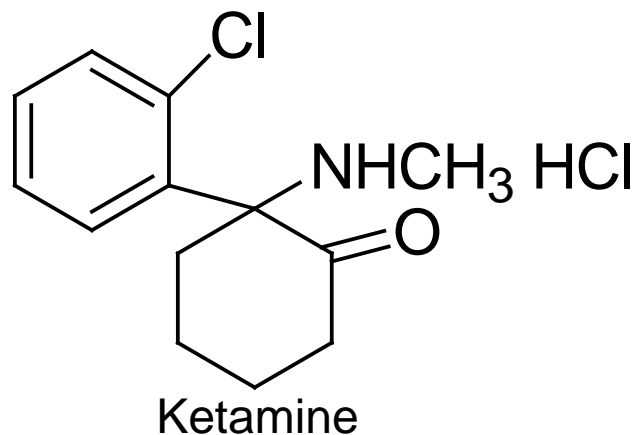
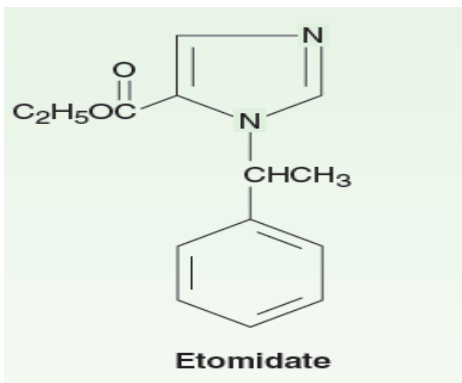
General ...

- **Intravenous anaesthetic**

- They produce **unconsciousness** but not sufficient depth to permit surgical procedures
- The intravenous anaesthetics is given prior to inhalation anaesthetics

- **Classification**

- Ultrashort acting barbiturates
- Benzodiazepines
- Ketamine hydrochloride
- Propofol
- Etomidate

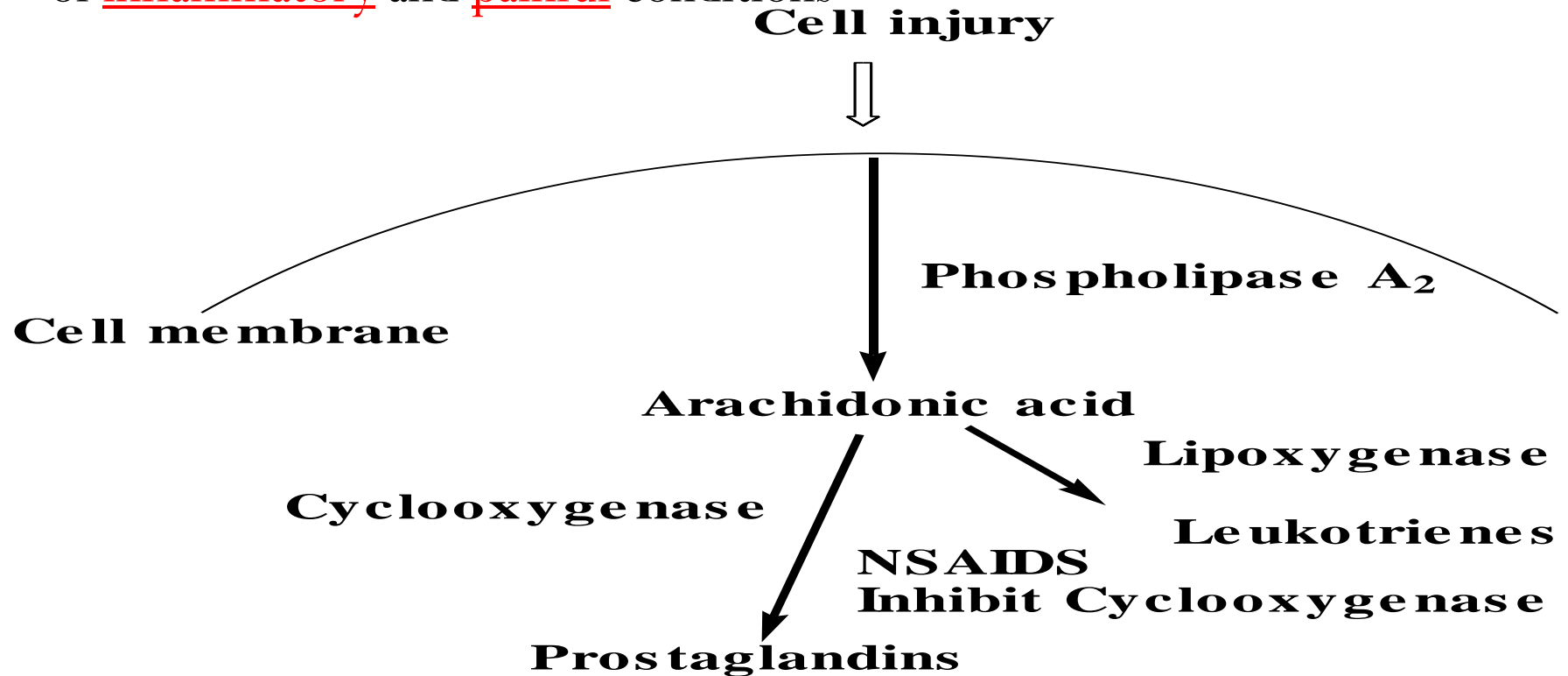


- The presumed mechanism of action of propofol is through potentiation of the chloride current mediated through the GABA_A receptor complex.
- Etomidate appears to have GABA-like effects and seems to act primarily through potentiation of GABA_A -mediated chloride currents,
- Ketamine's major effect is probably produced through inhibition of the **NMDA** receptor complex.

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NSAIDs...

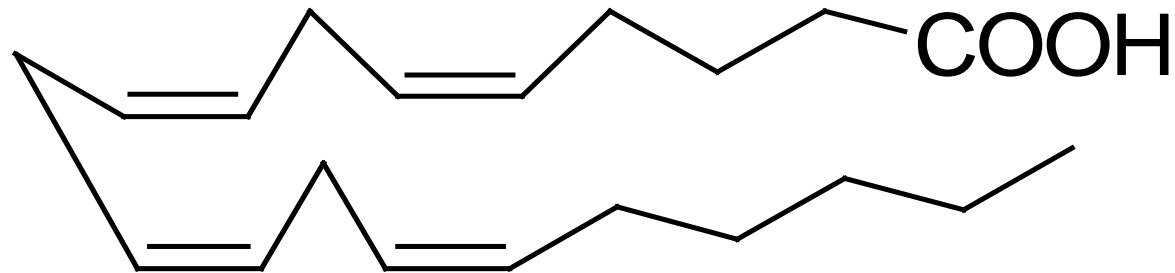
- These drugs are of different chemical structures and are used for treatment of inflammatory and painful conditions



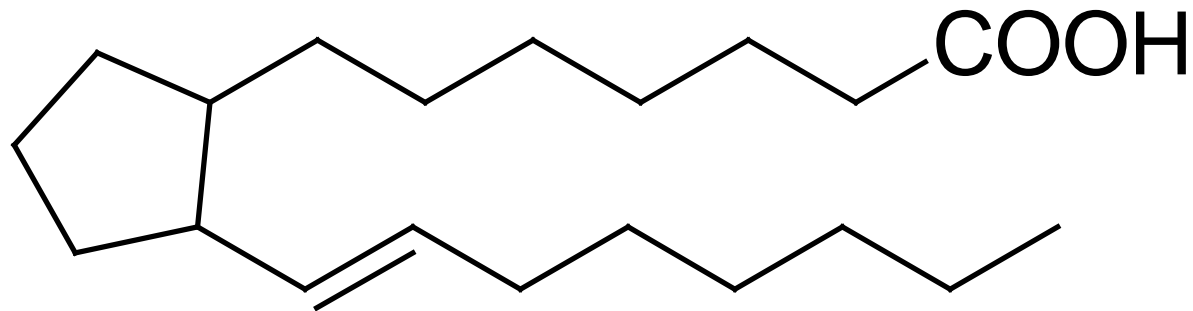
- The COX enzyme exists in at least two isoforms.
 - COX-1 is **constitutive** isoform that is responsible for the basal production of prostaglandins, prostacyclins, and thromboxanes.
 - COX-2 is inducible by cytokines and other inflammatory stimuli and is believed to predominate during chronic inflammation.

NSAIDs...

- Prostaglandins contribute to sign and symptoms of inflammatory processes including **pain** and **edema**



Arachidonic acid



Prostaglandins

Cell Membrane Phospholipid

Glucocorticoids \rightarrow (+) Annexins (Lipocortins) \rightarrow (-) Phospholipase A₂

Arachidonic acid $\xrightarrow{5'\text{-Lipoxygenase}}$ 5-HPETE

COX-1
COX-2

PGG₂

NSAIDs

5'-Lipoxygenase inhibitors

5-HPETE

PGF_{2α}

PGI₂

PGE₂

PGD₂

TXA₂

LTA₄

LTB₄

LTC₄

LTD₄

LTE₄

Chemotaxis
Phagocyte
activation

Leukotriene
antagonists

Bronchoconstriction
Uterine contraction
Aqueous humor
drainage

Vasodilation
Patent ductus
arteriosus
Inhibition of
platelet
aggregation
Pain sensitization
Gastric cyto-
protection

Vasodilation
Decreased gastric
acid secretion
Pain sensitization
Uterine contraction
Cervical ripening
Patent ductus
arteriosus
Bronchodilation
Fever

Bronchoconstriction
Vasodilation or
vasoconstriction

Bronchoconstriction
Platelet aggregation

Bronchoconstriction

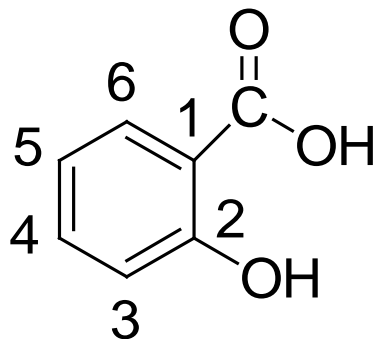
NSAIDs...

Non-steroidal ant-inflammatory drugs can be divided:

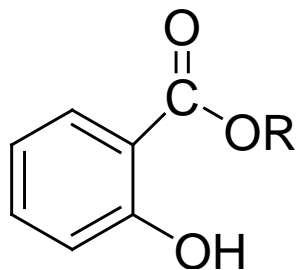
1. Salicylates
2. Para-aminophenol derivatives
3. pyrazolone and pyrazolidinediones derivatives
4. Arylacetic acids
5. Arylpropionic acids
6. Anthranilates
7. Arylsulfonamides
8. COX-2 Selective Inhibitors (diaryl pyrazole derivatives)

NSAIDs...

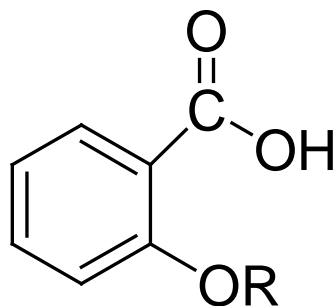
- Salicylates



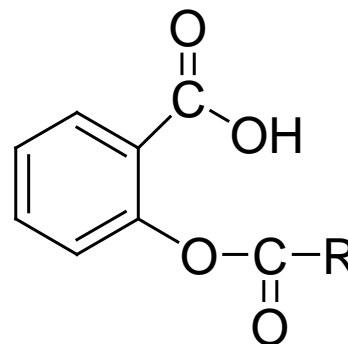
Are derivatives of salicylic acid and are two types (I and II)



Type I



Type IIa



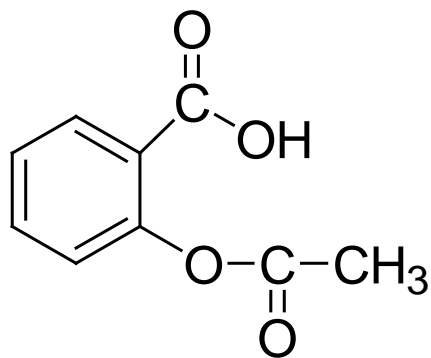
Type IIb

- Type I represents those that are formed by modifying the **carboxyl** group.
- Type II (a and b) represents those that are substitution on the **hydroxyl** group of salicylic acid
 - The derivatives were introduced to prevent gastric symptom and undesirable tests of some common salt of salicylate

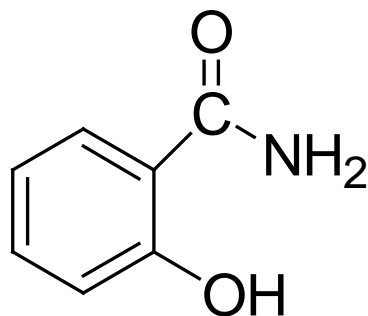
NSAIDs...

Structure activity relationship

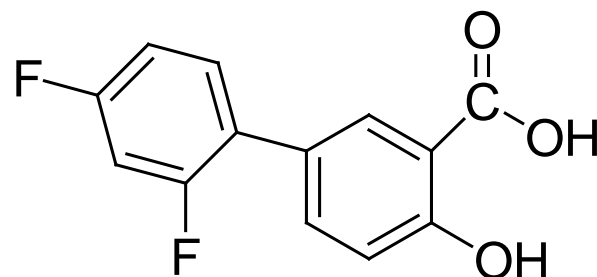
- The active moiety appears to be the **salicylate anion**
- Reduction of the **acidity of the carboxylic** group of the salicylate retain analgesic effect eliminating anti-inflammatory (Salicylamide)
- Shift of phenolic OH group to meta or Para to carboxyl abolish activity
- Halogen atom substitution on the aromatic ring enhances potency & toxicity
- Hydrophobic substituent at 5 position of salicylic acid improved activity



Aspirin



Salicylamide

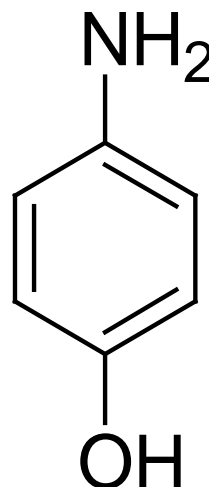


Diflunisal

NSAIDs...

2. Para- aminophenol derivatives

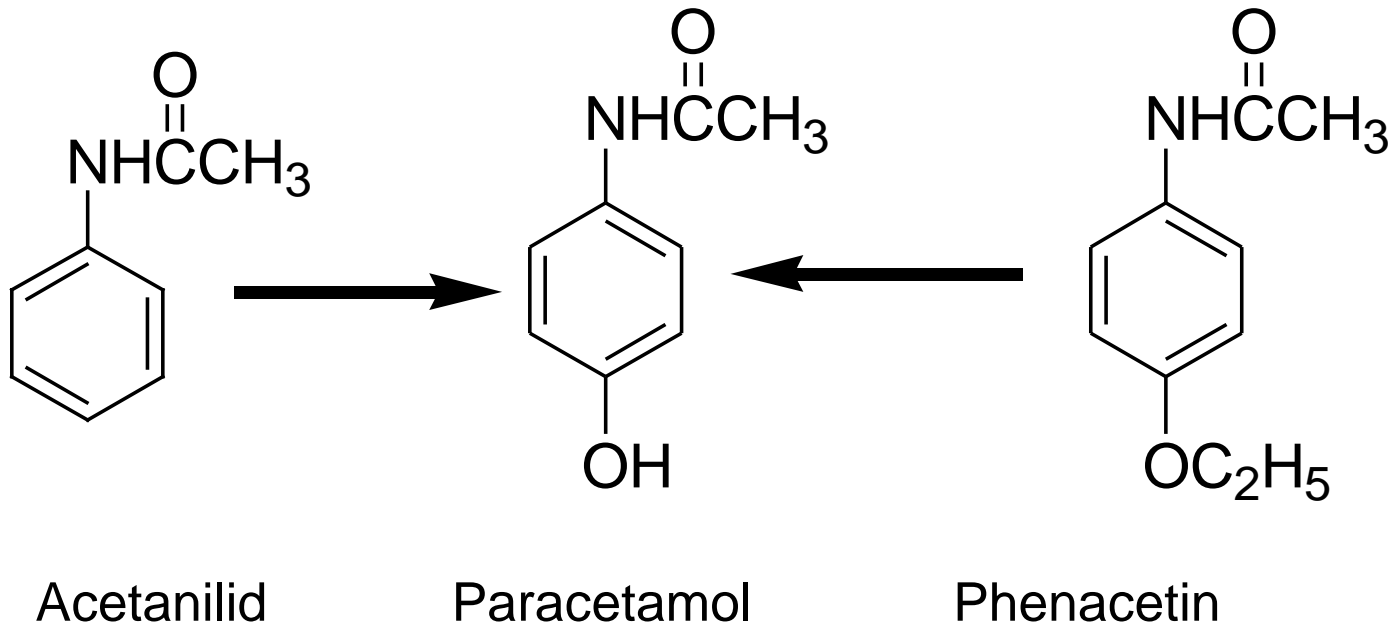
- Are para aminophenol derivatives



- They possess analgesic and antipyretic but not anti-inflammatory activity
 - Paracetamol is a prototype
- Based on the discovery that **aniline** and **acetanilide** have powerful antipyretic property

NSAIDs...

- Both are converted to paracetamol and are **more toxic**

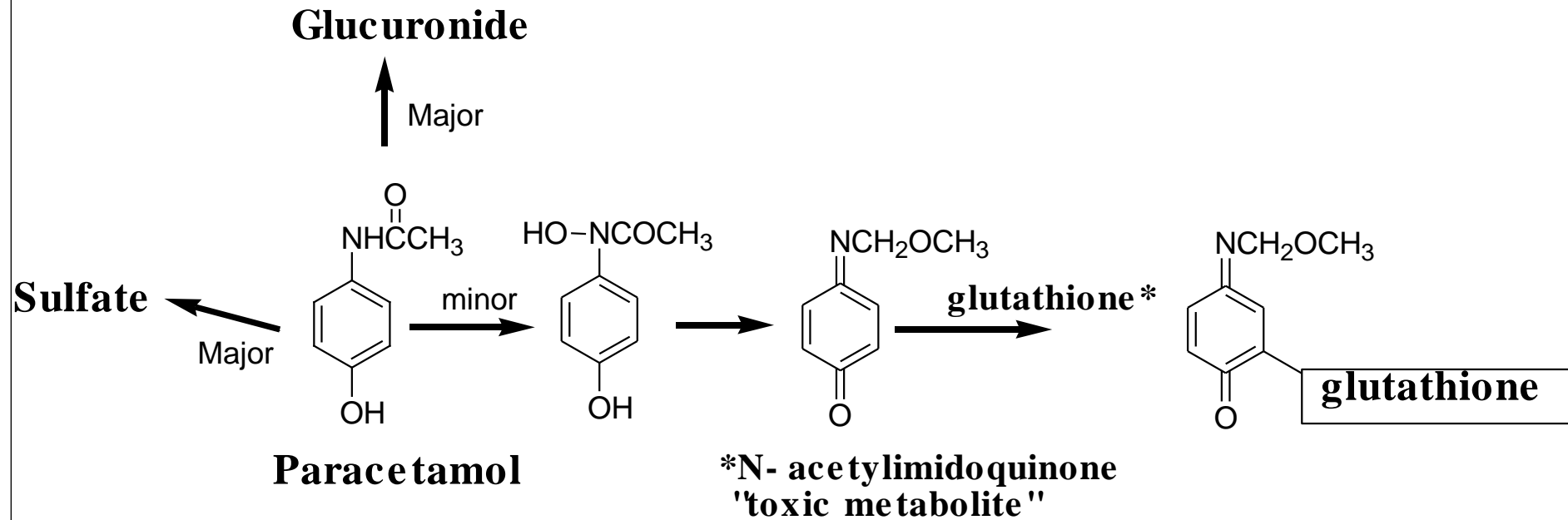


NSAIDs...

Structure activity relationship

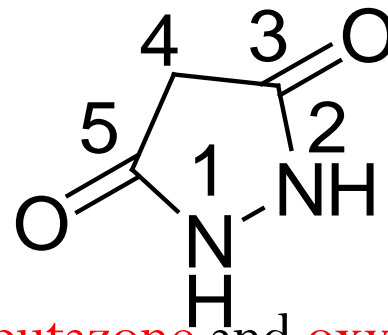
- Amino phenols are less toxic than corresponding aniline derivatives
- **Esterification** of phenolic group with methyl or propyl group produce more toxic derivative than ethyl
- Nitrogen substituents that **reduce its basicity** reduce activity unless it is metabolically removed
- Paracetamol overdose causes severe hepatotoxicity with necrosis and liver failure
 - Due to the formation of hepatotoxic metabolite

NSAIDs...

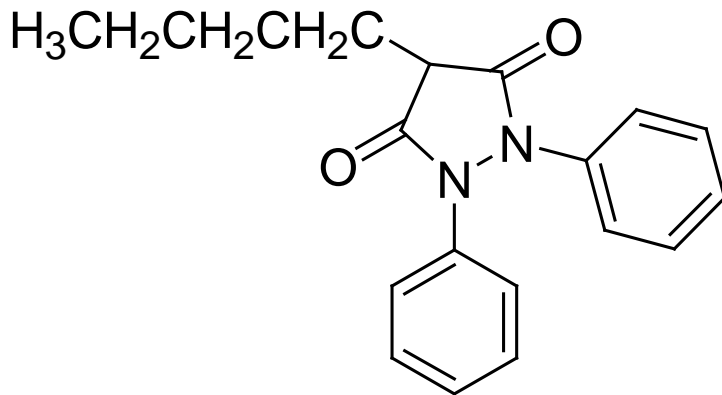


NSAIDs...

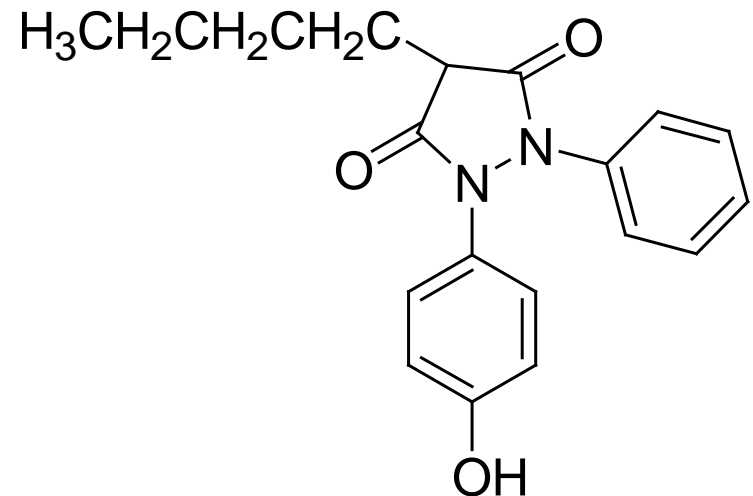
3. 3, 5-pyrazolidinediones



- The most important ones are **phenylbutazone** and **oxyphenylbutazone** (its metabolite)
- Both of them inhibit prostaglandin synthesis and stabilize lysosomal membranes
- Have **analgesic**, **antipyretic** and **anti-inflammatory** effects



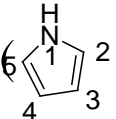

Phenylbutazone



Oxyphenylbutazone

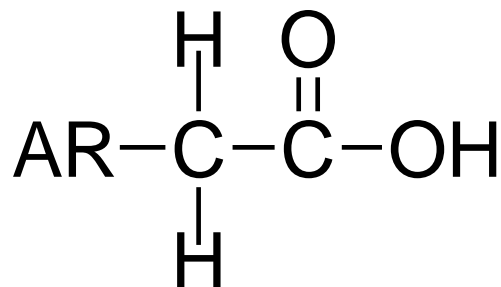
NSAIDs...

Structure activity relationship

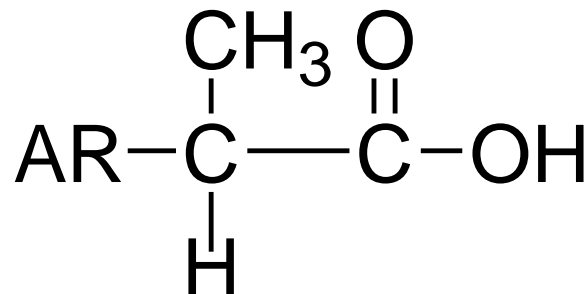
- Hydrogen atom at C4 is acidic & this is enhanced by the two-ketone groups
 - Decreasing / eliminating acidity abolishes activity
- If acidity increases too much **uricosuric activity** increases while anti-inflammatory decreases
- Single alkyl substituent at C4 enhances anti-inflammatory activity n-butyl is the most active
- The presence two phenyl groups in the ring nitrogen is not important for anti-inflammatory & analgesic activity
 - Pyrrole () and isoxazole () analogue of phenylbutazone retain activity

NSAIDs...

4. Arylalkanoic acids



Aryl or Hetero-aryl acetic acid analogs



Aryl or Hetero-aryl propionic acid analogs

- Arylalkanoic acid represents the largest numbers of NSAIDs
- Have analgesic, antipyretic and anti-inflammatory property

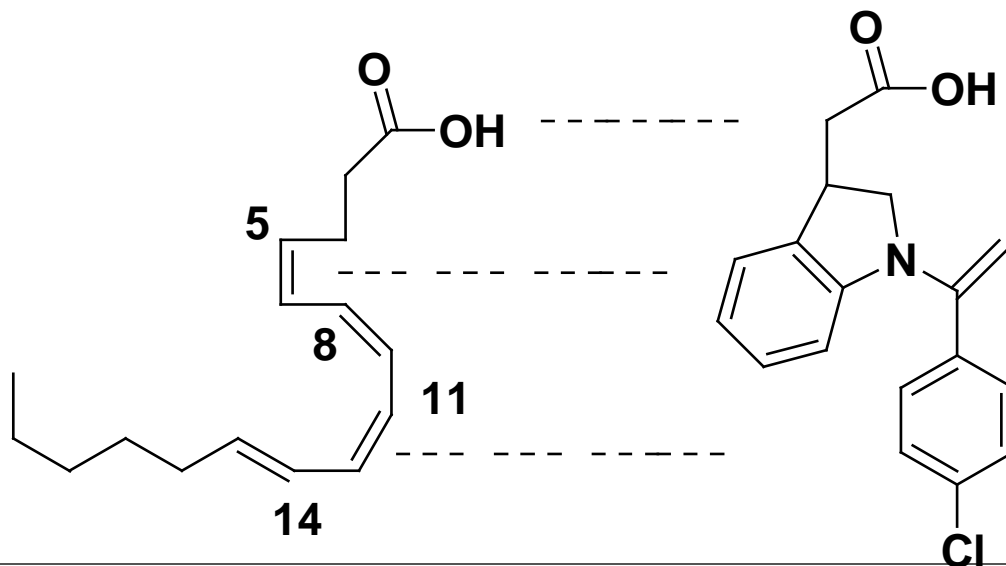
NSAIDs...

Structure activity relationship

- All agents have an **acidic** and **aromatic** center
- Derivatives of aryl or heteroaryl acetic/propionic acid correlates with carboxylic acid and double bond at position C5 and C8 of arachidonic acid
- The activity of **ester& amide derivatives** carboxylic acid is due to its metabolic hydrolysis
- The center of acidity is located **one** carbon atom from the aromatic ring
 - This distance is critical
 - Increase distance to two or three carbons generally diminishes activity

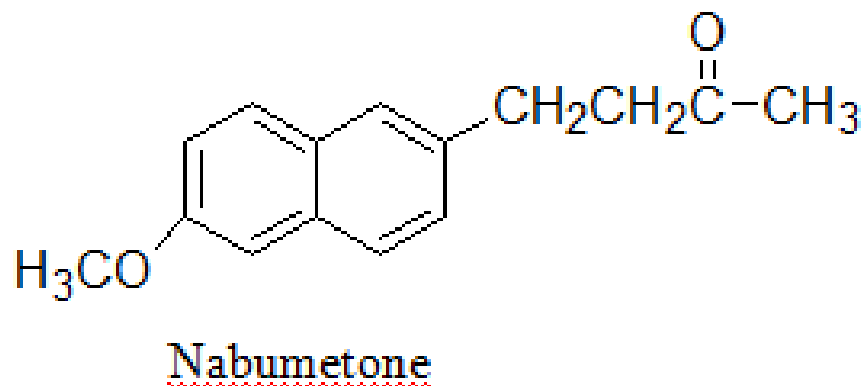
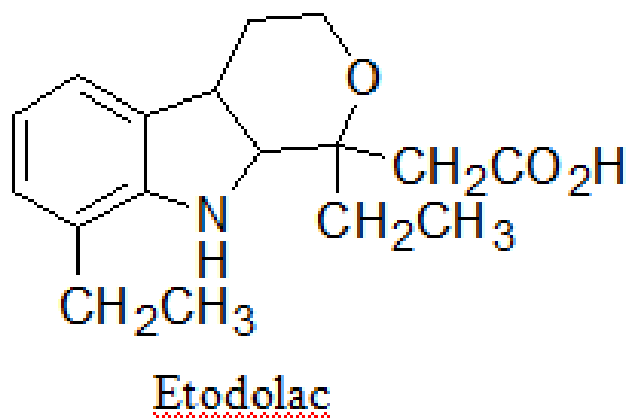
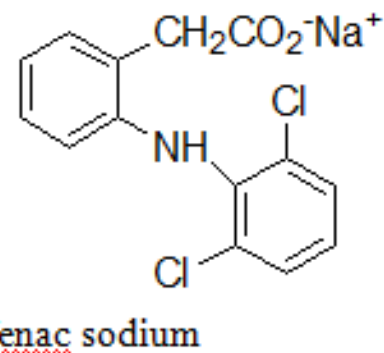
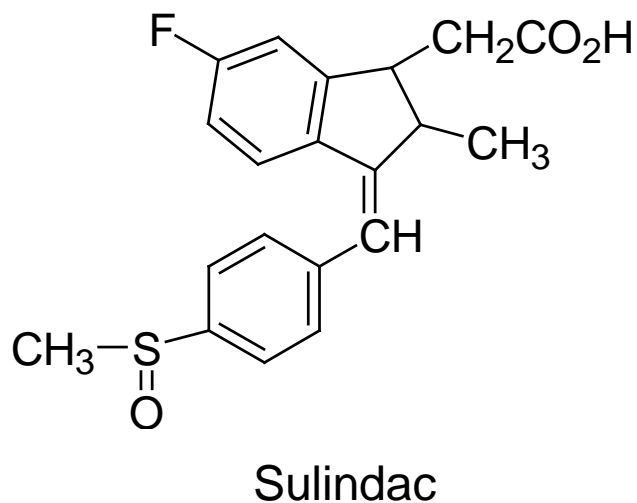
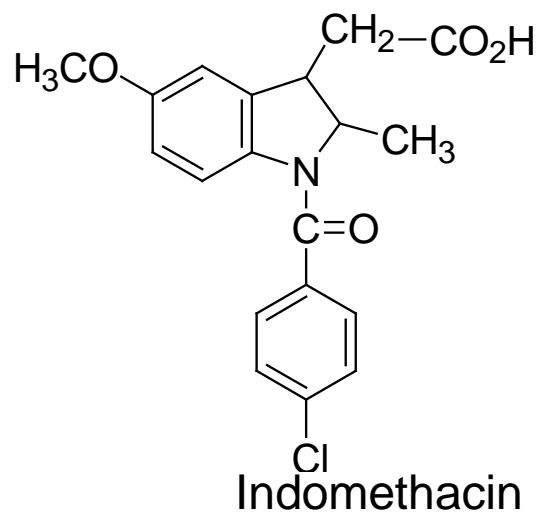
NSAIDs...

- **Methyl** substitution on the carbon atoms separating the acid and aromatic group **increases** anti-inflammatory activity
- Groups more than methyl decrease anti-inflammatory activity
- A second area of lipophilicity **non-coplanar** with aromatic ring enhances activity
 - This lipophilic area corresponds to the double bond of **C11** of arachidonic acid



NSAIDs...

- Aryl and heteroarylacetic acids



NSAIDs...

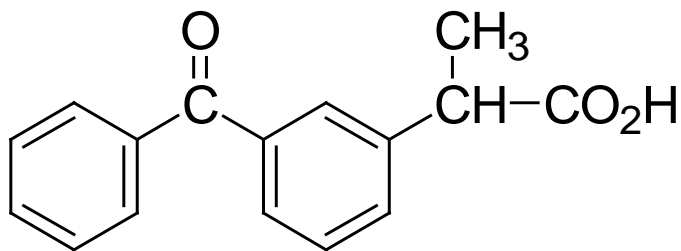
Structure activity relationship

- N-benzoyl derivatives substituted in the Para-position with fluoro, chloro, trifluoromethyl, or thiomethyl group are the most active
- The 5 -position of the indole ring is most flexible with regard to the nature of substituent, which enhances activity.
 - ❖ Substituents such as methoxy, fluoro, dimethylamino, methyl, allyloxy, and acetyl are more active than un-substituted indole ring
- The presence of an indole nitrogen is not essential for activity because the corresponding 1-benzylidenyl analogs (e.g., sulindac) are active
 - ❖ Sulindac is bioisoster of indomethacin

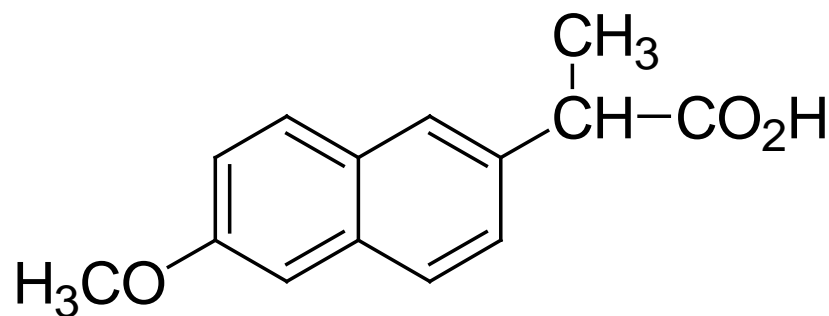
NSAIDs...

Aryl and heteroarylpropionic acid derivatives

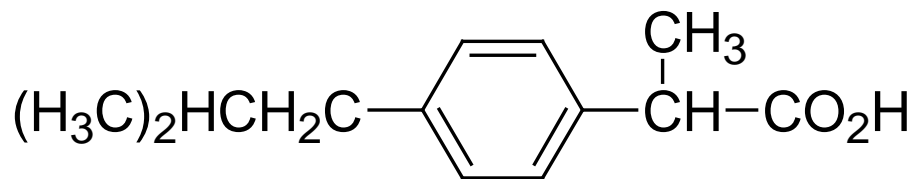
- The substitution of an α -methyl on the alkanolic acid portion of acetic acid enhances **anti-inflammatory** actions and reduces side effects



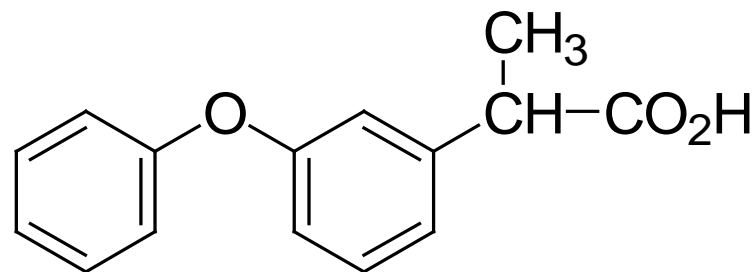
Ketoprofen



Naproxen



Ibuprofen



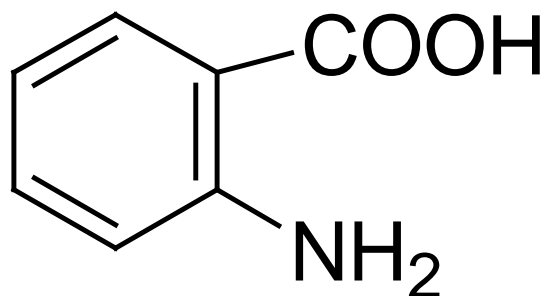
Fenopropfen calcium

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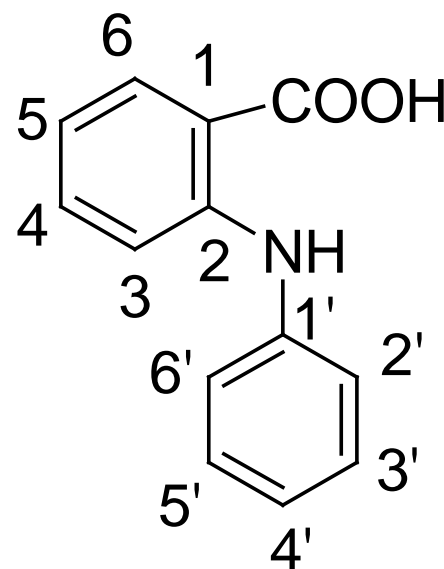
NSAIDs...

5. Arylanthranilic acids

- The anthranilic derivatives are nitrogen isosters of salicylic acid
- Are the results of the application of bioisosteric drug design

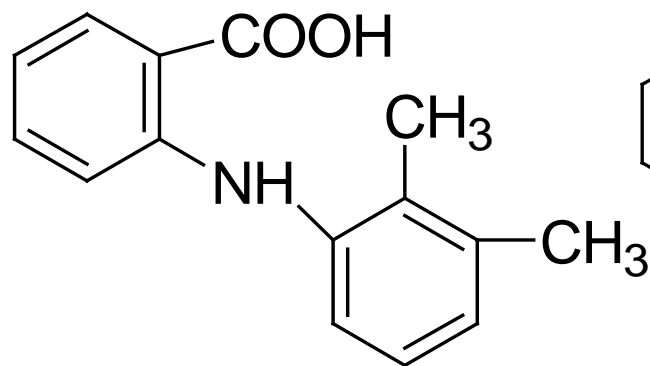


anthranilic acid

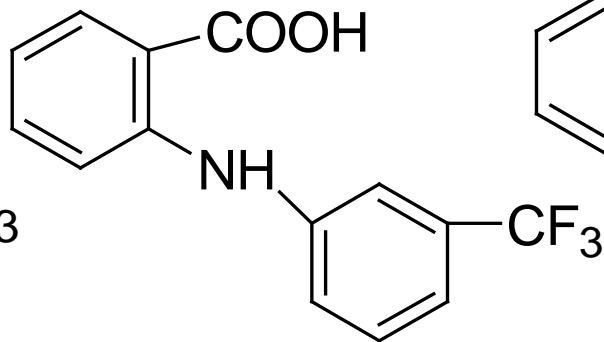


Structure of arylanthilic acids

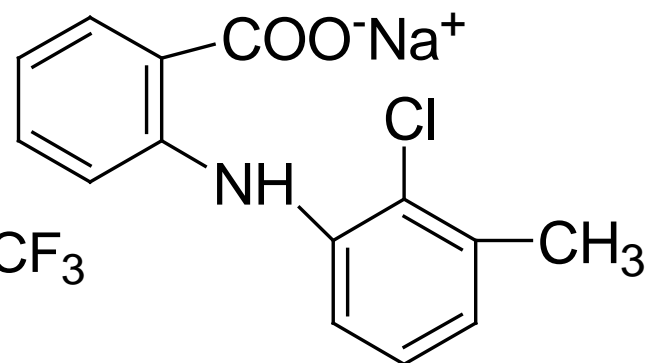
NSAIDs...



Mefenamic acid



Flufenamic acid



Meclofenamate sodium

- Substitution on the anthranilic acid ring generally **reduces** activity while substitution of the N-aryl ring can lead to **conflicting** results
- The most active ones have a small alkyl or halogen substituent at 2', 3' and/or 6' position of the N-aryl moiety
- Among disubstituted N-arylfenamates 2' and 3' derivatives are most active
- These Substituents serve to force the N-aryl ring **out of coplanarity** with anthranilic acid

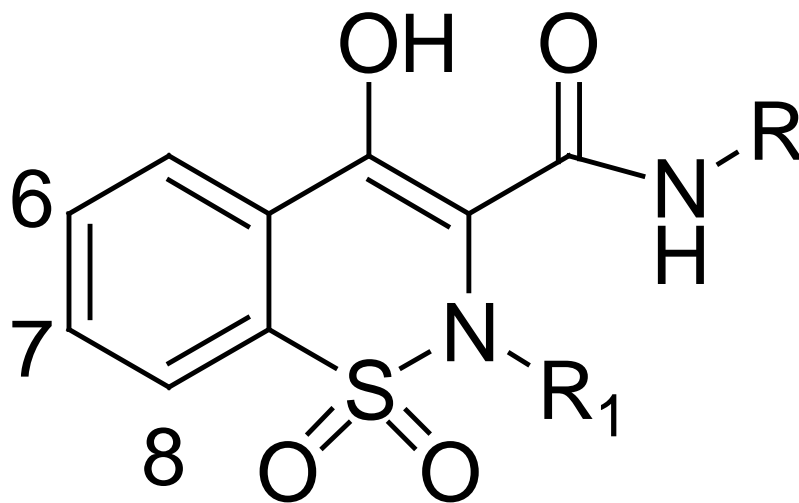
NSAIDs...

- NH moiety is essential for activity
- Replacement of NH with O, CH₂, S, SO₂, NCH₃ or NCOCH₃ significantly reduces activity
- ❑ The **position** rather than the **nature** of the acidic function is critical for activity
- Replacement of carboxylic acid function with **isosteric tetrazole** moiety has little effect on activity

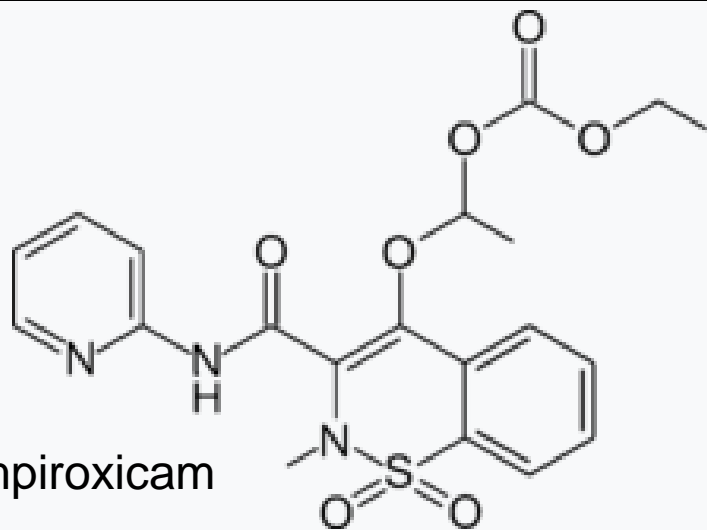
NSAIDs...

6. Arylsulfonamides (Oxicams)

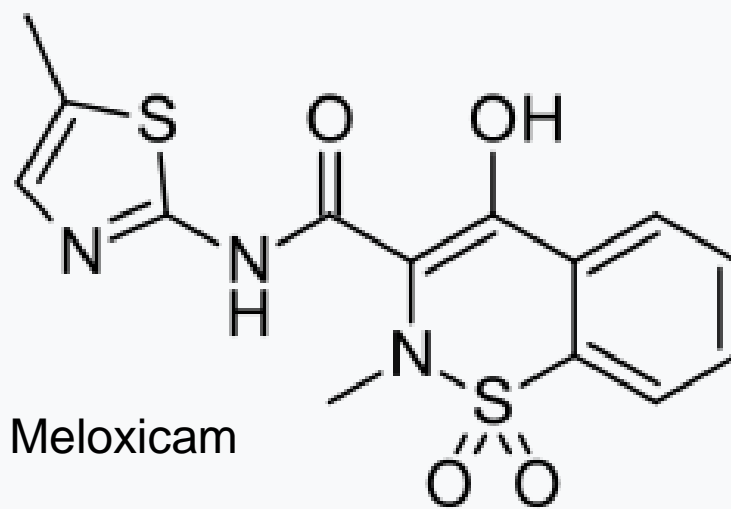
- The **oxicams** are a group of non-steroidal anti-inflammatory agents containing **2H-1, 2-benzothiazine-3-carboxamide 1,1-dioxide** moiety as common structure entity.



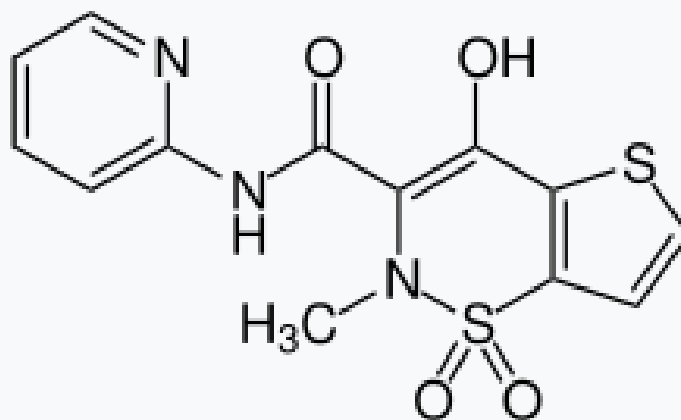
- Within the series of 4-hydroxyl-1, 2-benzothiazine carboxamides
 - Optimal activity is observed when R1 is **methyl** substituent
 - R (Carboxamides substituent) is generally an Aryl / heteroaryl substituent because alkyl substituent are less active
 - N-heterocyclic carboxamides are more acidic than the corresponding aryl carbamate
 - In the aryl series **meta**-substituted derivatives are generally more potent than **para**-isomers
 - In the aryl series maximum activity is observed with a meta-**Cl** substituent
 - **Eg, Ampiroxicam, Piroxicam, Tenoxicam, Droxicam, Lornoxicam**



Ampiroxicam



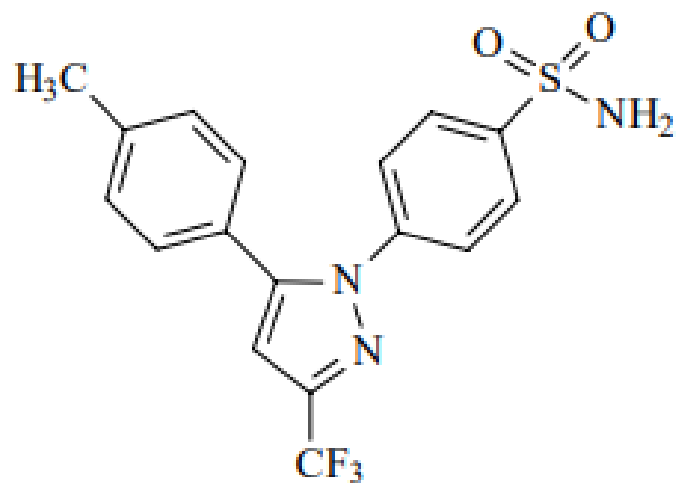
Meloxicam



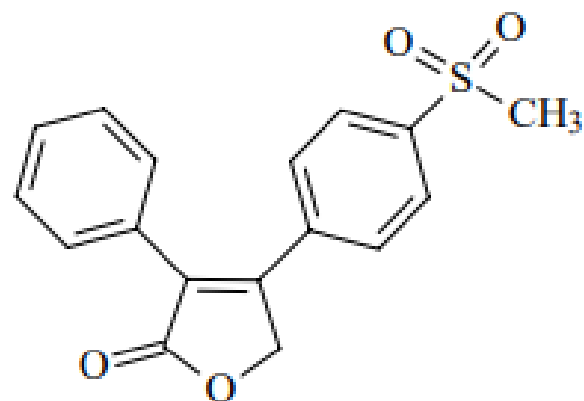
Tenoxicam

7. COX-2 Selective Inhibitors

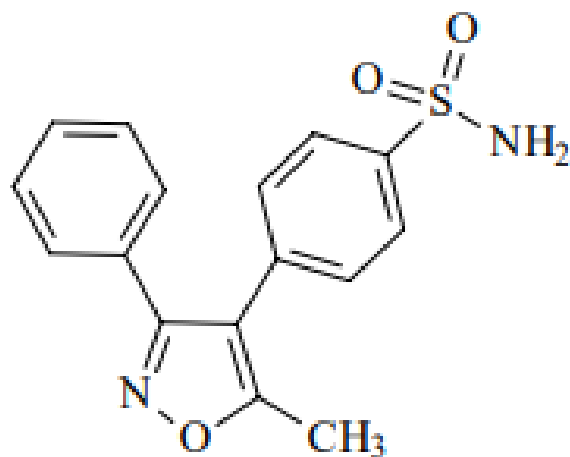
- All COX-2 inhibitors are diaryl-5-membered heterocycles.
- Celecoxib has a central **pyrazole** ring and two adjacent phenyl substituents,
- Rofecoxib has a central **furanone** ring and two adjacent phenyl substituents.
- Valdecoxib has a central **oxazole** ring
- The COX-2 inhibitors have **analgesic, antipyretic and inflammatory activity** comparable to other NSAIDs



Celecoxib (Celebrex™)



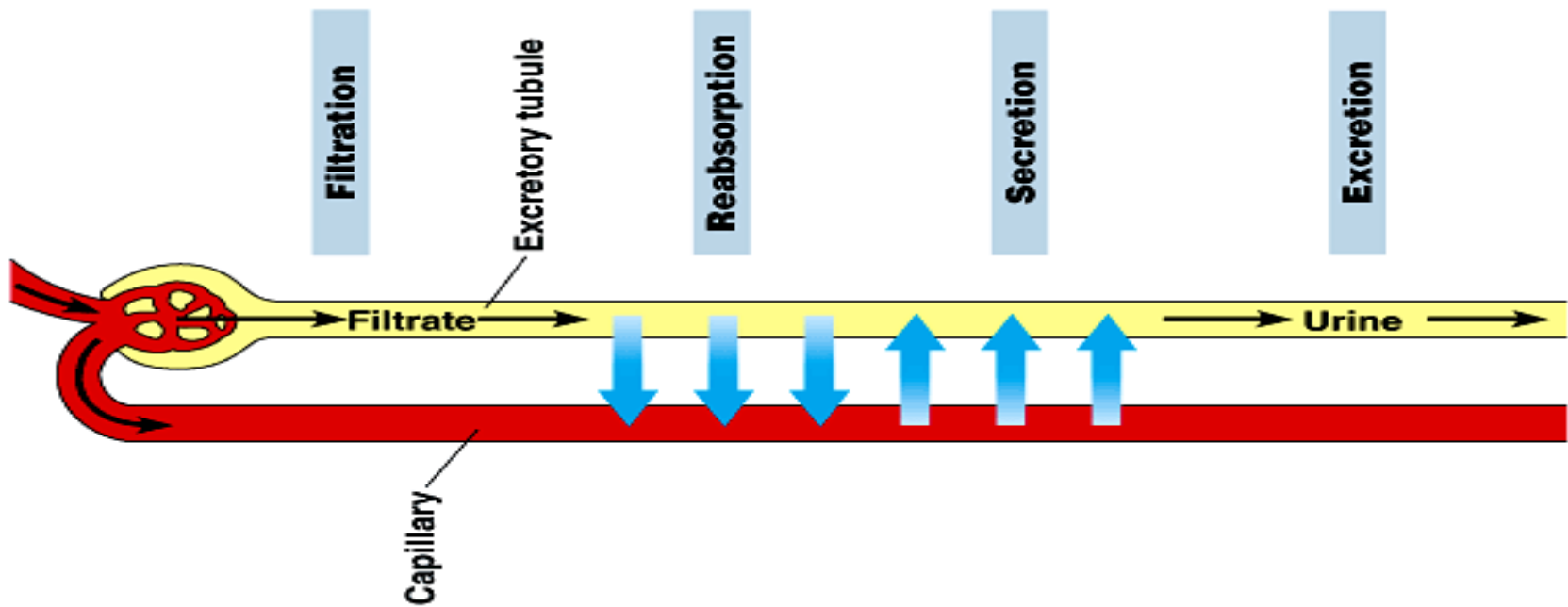
Rofecoxib (Vioxx™)



Valdecoxib (Bextra™)

- These compounds produce less GI ulceration and hemorrhage than NSAIDs due to their COX-2 selectivity.
- Also they do not inhibit platelet aggregation and have minimal renal and CV side effects.

DIURETICS



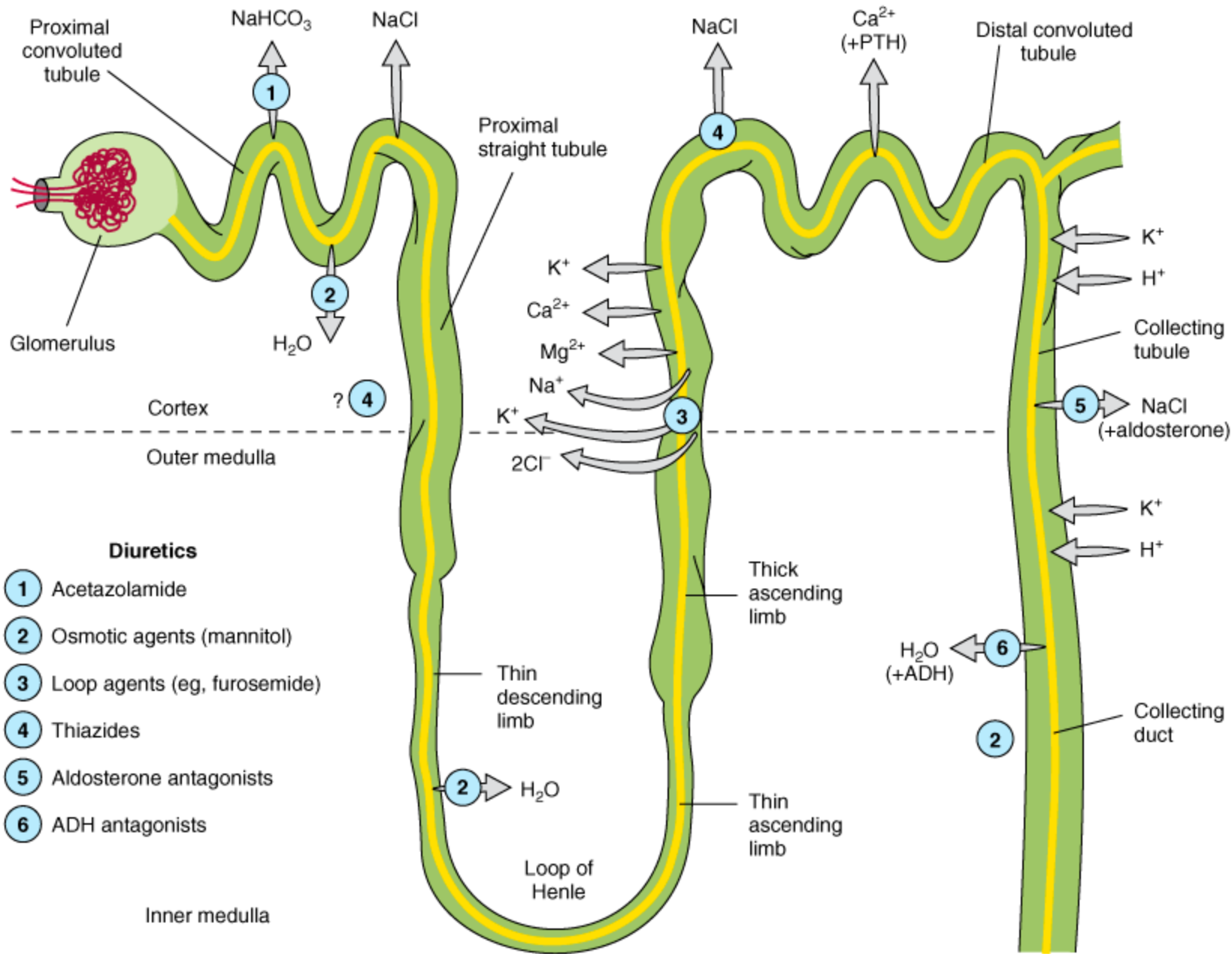
DIURETICS

- Diuretics are drugs that promote the output of urine excreted by kidney.
- Diuretics mainly promotes the excretion of the sodium ions(Na^+), chloride ions(Cl^-) or bicarbonate ions(HCO_3^-) and water from the body,
 - The net result being increase in urine flow.
- These drugs act by decreasing tubular reabsorption

DIURETICS...

- Diuretics Are Very Effective
 - For The Treatment Of Cardiac Edema (CHF)
 - Nephrotic Syndrome
 - Diabetes Insipidus
 - Hypertension
 - Nutritional Edema
 - Edema Of Pregnancy
 - Cirrhosis Of Liver
 - Lower the Intracellular And Cerebrospinal Fluid Pressure.

DIURETICS...



DIURETICS...

CLASSIFICATION

I. Carbonic anhydrase inhibitors (Site-I Diuretics)

Acetazolamide, Methazolamide, Dichlorphenamide,
Disulfamide, Ethoxzolamide.

II. Thiazide and Thiazide like Diuretics (Site-III Diuretics)

- Chlorthiazide, Benzthiazide, Hydrochlorothiazide,
Hydroflumethiazide, Bendroflumethiazide, Trichlormethiazide,
Methyclothiazide, Polythiazide, Cyclothiazide, Mefruside,
Clopamide, Xipamide, Indapamide, Quinethazone, Metolazone,
Clorexolone, Chlortalidone.

DIURETICS...

III. High ceiling or Loop Diuretics (Site-II Diuretics)

- Organo mercurials – Chlormerodine mercury, Meralluride, Mercaptomerin, Merethoxylline procaine, Mersalyl.
- 5-Sulfamoyl & 3-Amino Benzoic acid derivatives- Bumetanide, Furosemide,
- 4-Amino-3-pyridine sulphonyl ureas- Torsemide, Triflocin.
- Phenoxy acetic acids- Ethacrynic acid.

DIURETICS...

IV. Potassium sparing Diuretics (Site-IV Diuretics)

1. Aldosteron inhibitors – Spiranolactone, Metyrapone
2. 2,4,7-Triamino-6-aryl pteridines – Triamterene
3. Pyrazinoyl Guanidines – Amiloride. HCl.

V. Xanthine Derivatives -

- Caffeine, Theophylline, Theobromine.

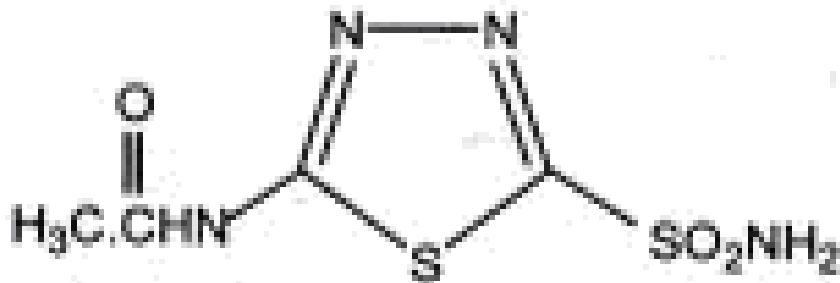
VI. Miscellaneous -

Mannitol, Potassium acetate, Sodium acid phosphate, Urea.

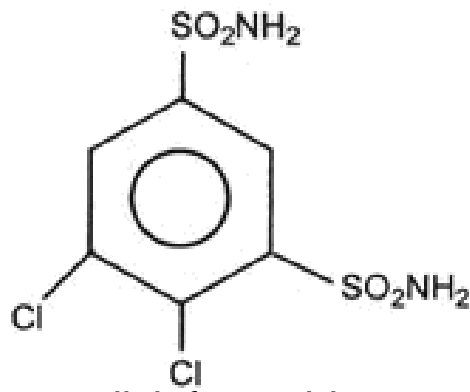
DIURETICS...

I. Carbonic anhydrase inhibitors (Site-I Diuretics)

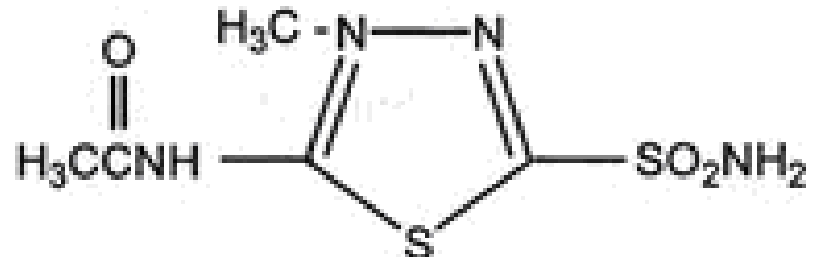
- Inhibit the enzyme carbonic anhydrase in proximal tubular epithelium.
- Decrease the exchange of Na^+ for H^+



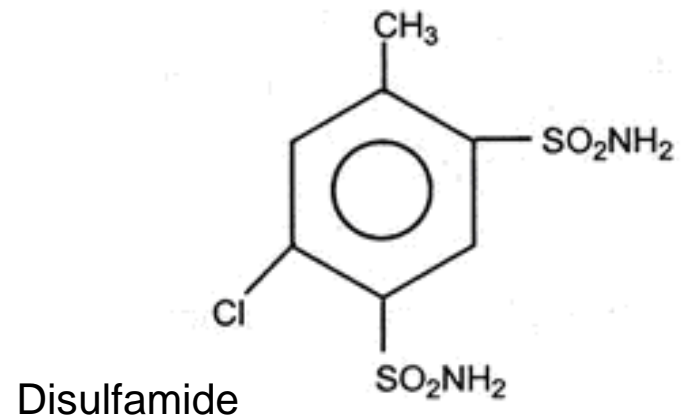
Acetazolamide



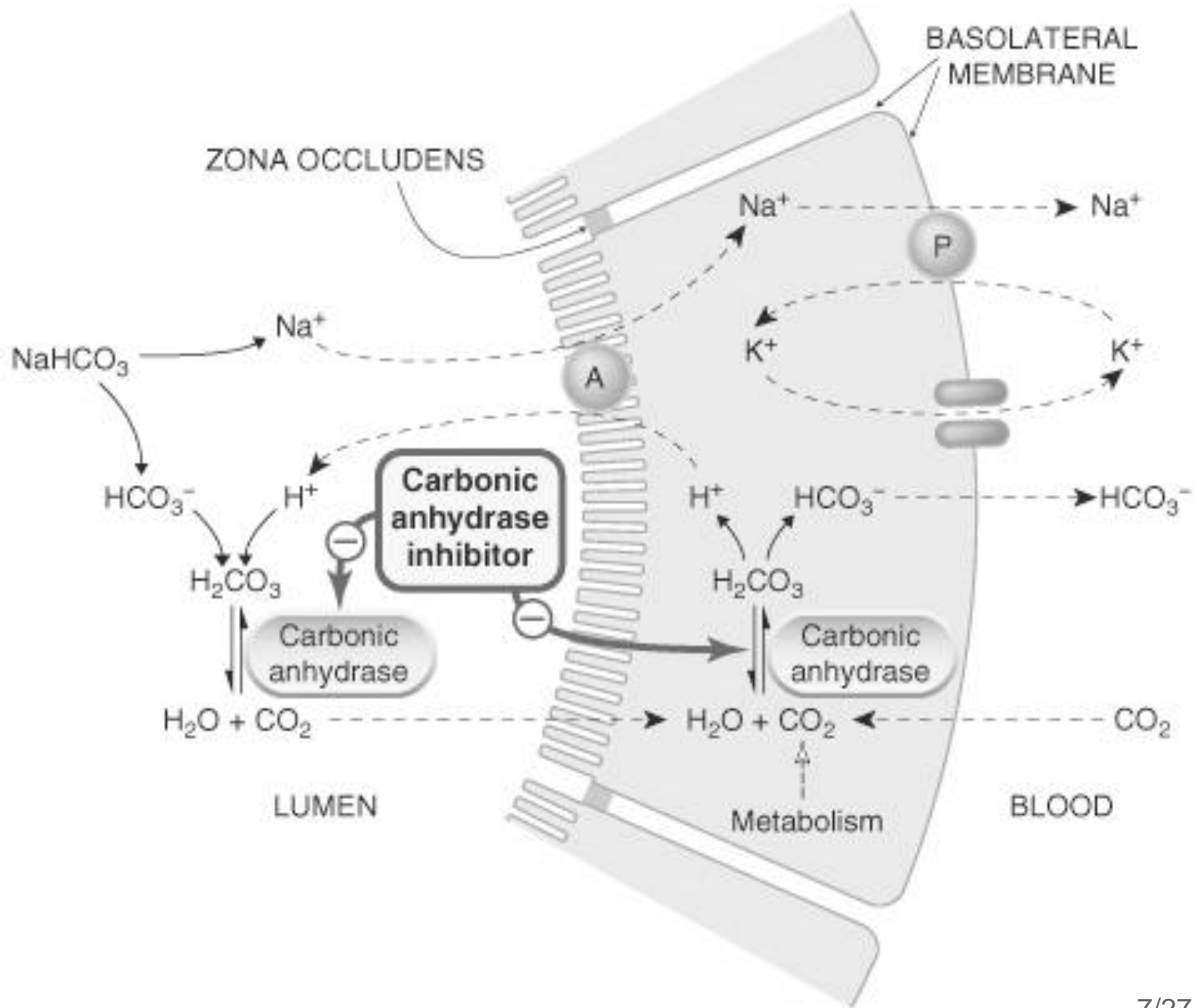
diclofenamide



Methazolamide



Disulfamide



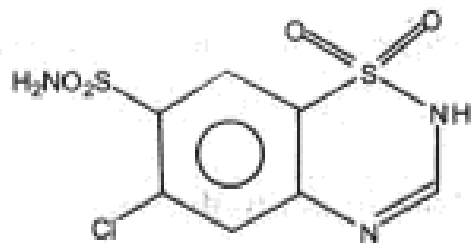
DIURETICS...

Structure Activity Relationship for CAI

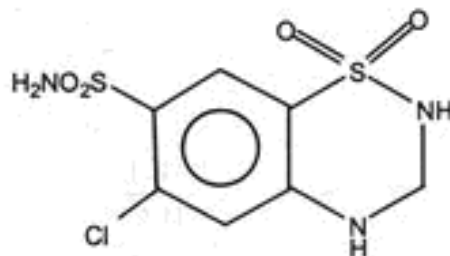
- The free **sulfamoyl** nitrogen is important for diuretic activity.
- Substitution of the methyl group on one of the ring nitrogen (Methazolamide) retains the activity.
- The heterocyclic sulphonamides have highest lipid/water partition coefficient and lowest pKa values
 - have greatest CA inhibitory and diuretic activity.
- The benzene meta sulphonamide derivatives have activity only when substituted with chlorine or methyl groups.

DIURETICS...

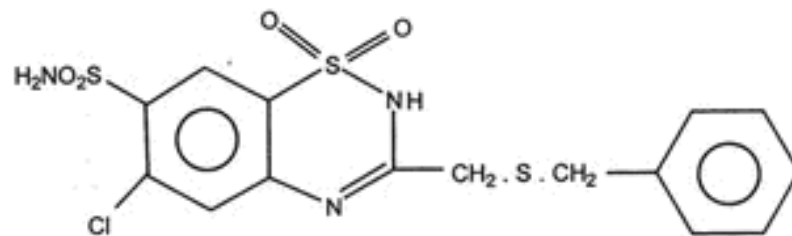
II. Thiazide and Thiazide like Diuretics (Site-III Diuretics)



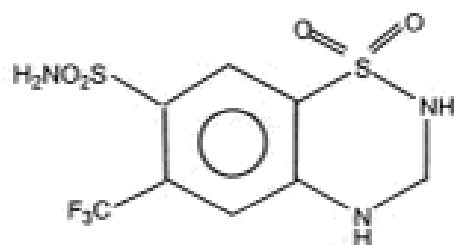
chlorthiazide



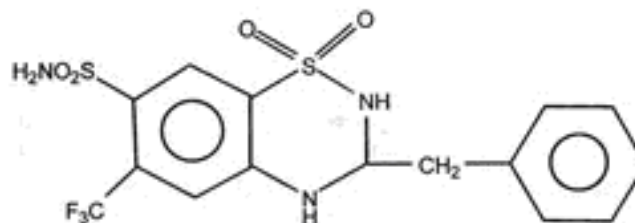
Hydrochlorthiazide



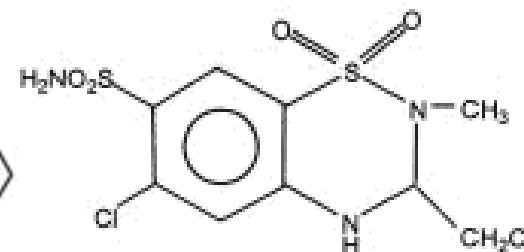
Benzthiazide



Hydroflumethiazide



Bendroflumethiazide



Methylchlorothiazide

DIURETICS...

Mechanism of action of Thiazides

- These drugs block the reabsorption of Na^+ , Cl^- exchange in the **distal convoluted tubule** by inhibiting the luminal membrane-bound $\text{Na}^+ / \text{Cl}^-$ co transport system.

Structure Activity Relationship for Thiazides

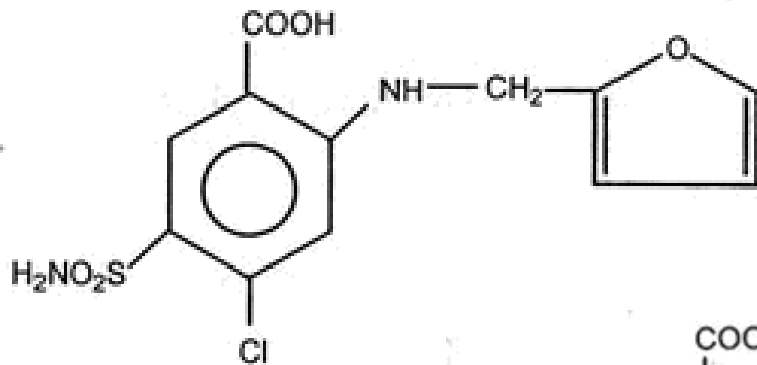
- Thiazides having **benzothiadiazine 1,1-dioxide** with weakly acidic character is important for good activity.
- Presence of electron withdrawing group at C-6 is necessary for good diuretic activity.
 - Substitution of chlorine at C-6 has good activity.

DIURETICS...

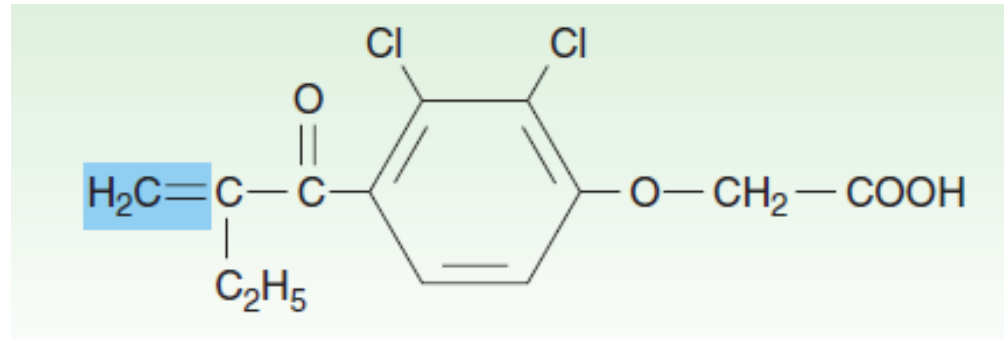
- Substitution of CF_3 group has more lipid soluble and larger diuretic action than Chloro compound.
- Presence of electron donating groups like methyl or methoxy at C-6 reduces the diuretic activity
- Removal or replacement of sulphonamide at C-7 reduces the diuretic activity.
- Saturation of double bond between 3&4 having 10 times more diuretic activity than unsaturated analogue.
- Introduction of lipophilic groups such as aralkyl, halo alkyl, thioether enhances the diuretic activity and increase the duration of action.
- Alkyl substitution at N_2 lowers the polarity and enhances the duration of action.

DIURETICS...

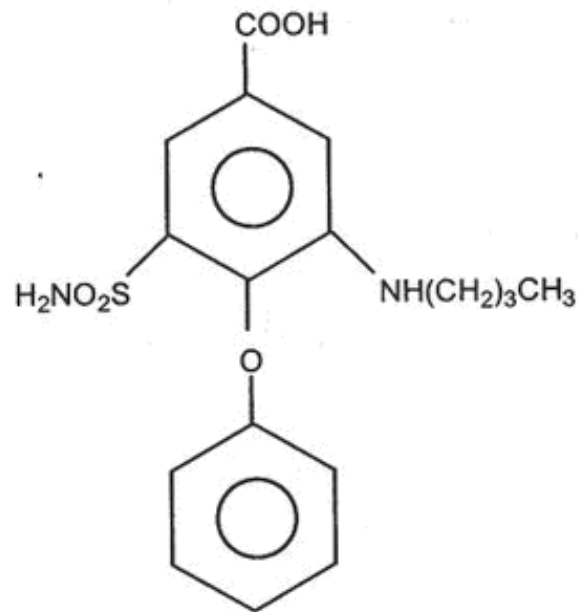
III. High ceiling or Loop Diuretics (Site-II Diuretics)



Furosemide



Ethacrynic acid

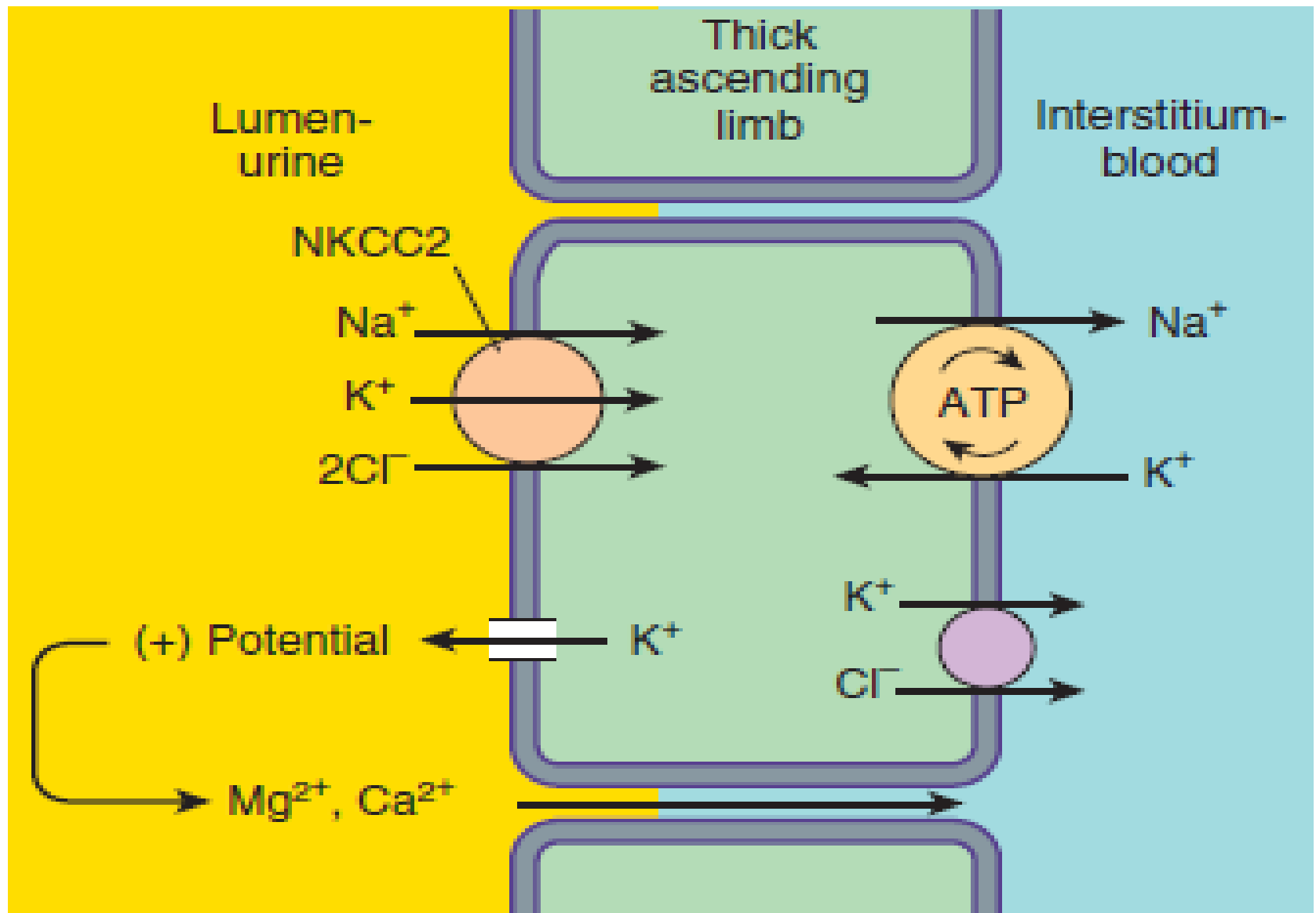


Bumetanide

DIURETICS...

Mechanism of action of Loop Diuretics

- The diuretics inhibit the $\text{Na}^+ / \text{K}^+ / \text{Cl}^-$ cotransport system located in the luminal membrane of cells in the limb of Henle's loop.
- The carboxylate moiety is responsible for their competing with Cl^- for the Cl^- binding site on $\text{Na}^+ / \text{K}^+ / \text{Cl}^-$ cotransport system.



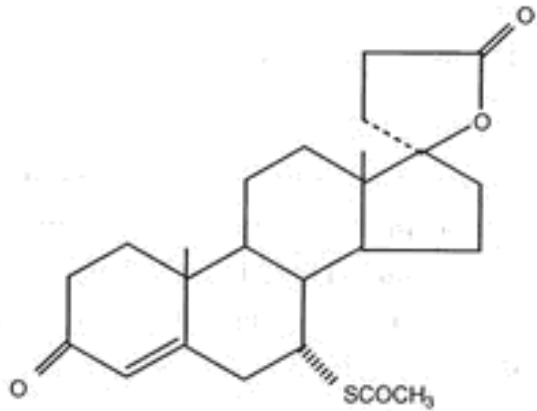
DIURETICS...

Structure Activity Relationship for Loop diuretics

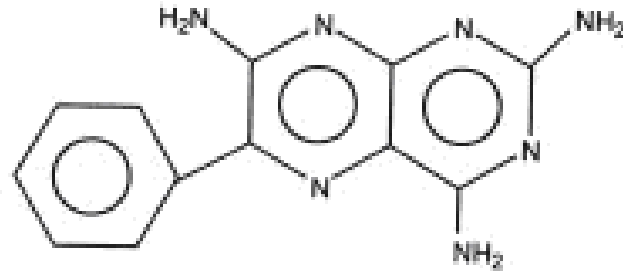
- 5-sulfomoyl and 2-aminobenzoic acid group is required for good diuretic activity.
- Substitution at 1st position must be acidic for good diuretic activity.
- The activating group at 4th ,can be Cl or CF₃ group, increases the activity.
- Phenoxy, alkoxy, anilino, benzyl or benzoyl groups substituted at 4th position **decreases** diuretic activity.
- **Furfuryl, benzyl and thienyl** methyl group at 2-position increases the activity.

DIURETICS...

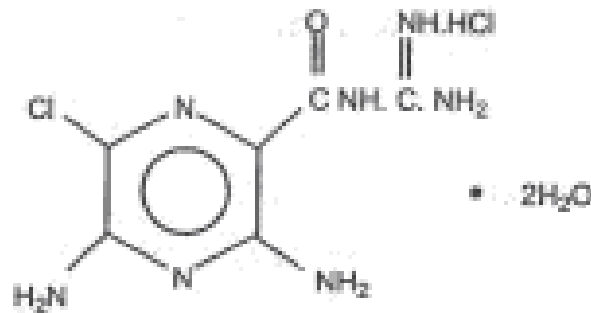
IV. Potassium sparing Diuretics (Site-IV Diuretics)



Spironolactone (aldactone)



Triamterene



Amiloride hydrochloride

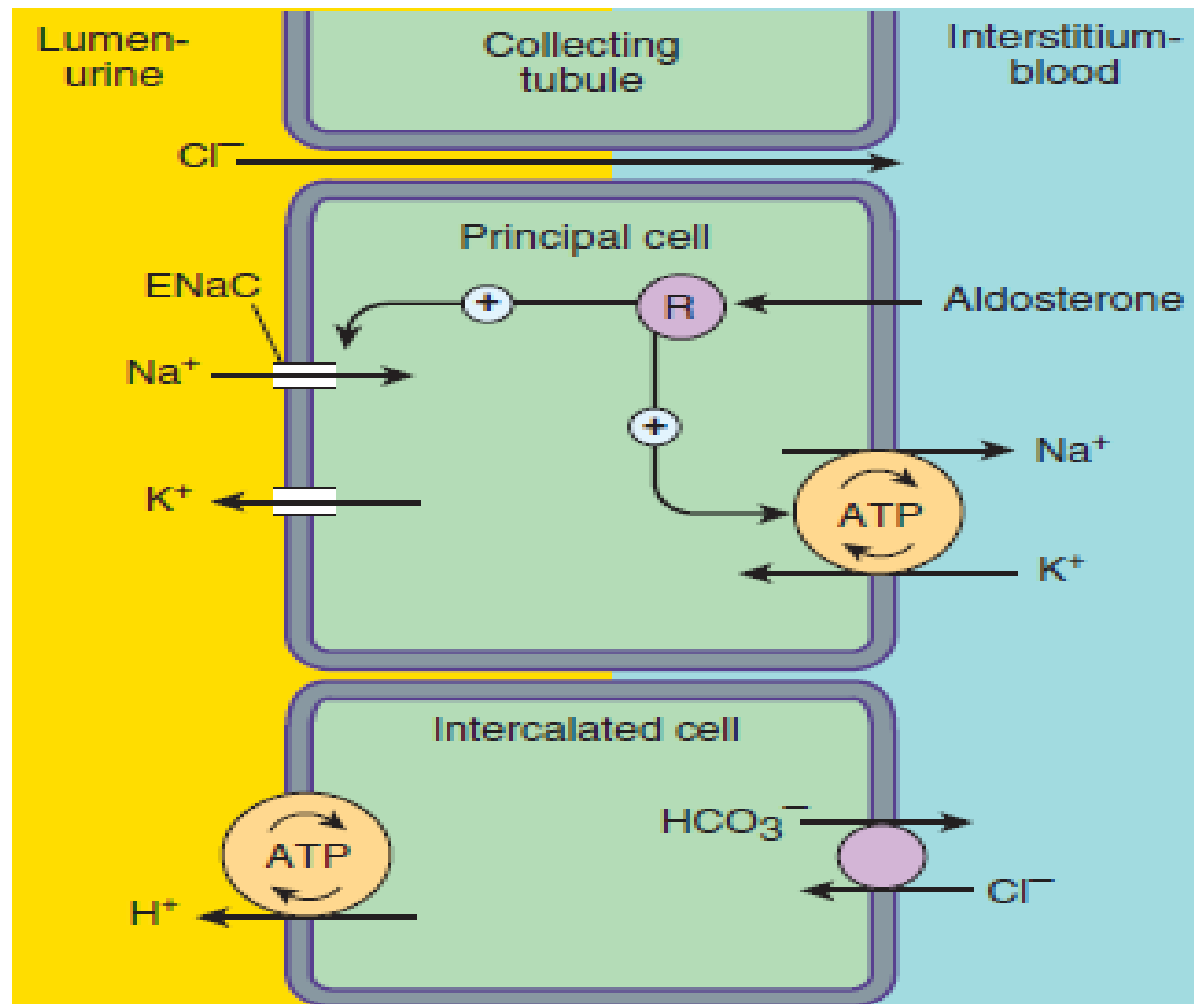


FIGURE Ion transport pathways across the luminal and basolateral membranes of collecting tubule and collecting duct cells. Inward diffusion of Na^+ via the epithelial sodium channel (ENaC) leaves a lumen-negative potential, which drives reabsorption of Cl^- and efflux of K^+ . (R, aldosterone receptor.)

DIURETICS...

Spiranolactone

- Inhibits the reabsorption of 2-3% of the filtered load sodium at site-IV by competitively inhibiting the action of aldosterones.
- Direct pharmacologic antagonism of mineralocorticoid receptors
- The aldosterone mineralocorticoid receptor (MR) complex binds on the DNA to specific **hormone response element**, which leads to gene specific **transcription**.

Triamterene& Amiloride

- Inhibition of **Na⁺** influx through ion channels in the luminal membrane at site-IV.