المسكنات

Analgesic Agents

By Pr.Dr. M.A. Al–Khayat

Analgesics definition

Analgesic is a drug which can bring insensibility فقد الاحساس to pain without loss of consciousness الوعي.

-The history of analgesics was divided into 4 major eras:

1- The period of discovery and use of naturally occurring plant drugs اكتشاف الأدوية الطبيعية المتواجدة في النباتات

2. Isolation of pure plant principles عزل المكونات الفعالة بالحالة النقية (e.g.. alkaloids) from the natural sources and their identification with analgesic action

3- Development of organic chemistry and the first synthetic analgesics اصطناع المسكنات

4. Development of modem pharmacological techniques, making it possible to undertake a systematic منهجي testing of new analgesics تطوير طرائق فارماكولوجية منهجية لاختبار المسكنات الجديدة

Analgesic agents, pain

Pain

-Pain is divided into the following types: أنماط الألم

Physiological pain is the most common (e.g. touching hot object, getting a cut). فيزيولوجي

Inflammatory pain can be initiated in wide variety of ways (e.g. infection, tissue injury). التهابي

Neuropathic اعتلال عصبيis due to injury to the peripheral or central nervous system (CNS).

-There are different levels or categories of pain including:

Acute حاد , chronic مزمن , cancer pain, arthropathy اعتلال مفصلي(e.g. arthritis), visceral حشوي, neuropathic, diabetic pain, AIDS pain.

-These require different approaches to pain management.

Pain Drug Classes

Analgesics are divided into two groups :

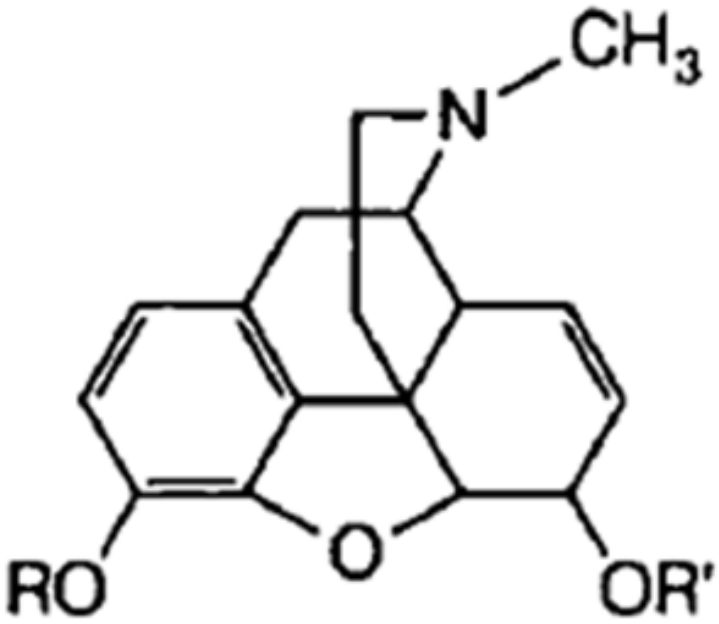
- **Morphines and related compounds** (“ true analgesics”)
- **Anti-Inflammatory analgesic** (NSAID’s)

Morphine and related compounds

Analgesic agents, Morphine and related compounds

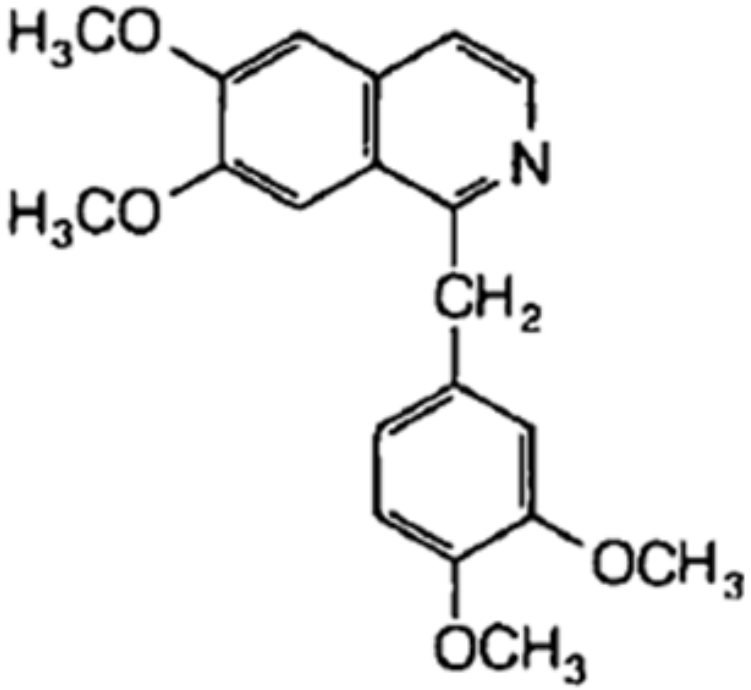
Opium alkaloids

-There are two structural types in the opium alkaloids: the phenanthrene type (morphine, codeine,) and isoquinoline type (Narcotine, papaverine).



Phenanthrene Type

Morphine: R, R' = H



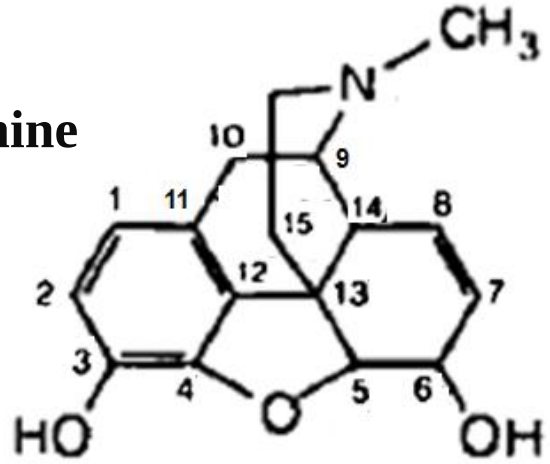
Benzylisoquinoline Type

Papaverine

Analgesic agents
Morphine and related compounds

Morphine and its salts

Morphine



-Morphine is obtained from the opium poppy.
- Morphine occurs in opium in amounts 5-20%.
- It was isolated in1803, and was determined at 1925
- Its synthesis was performed in1952.
-The free alkaloid occurs as levorotatory ميسر , odorless, white crystals, with bitter taste, insoluble in water.
-Morphine has five chirality centers مراكز يدوية : 5R, 6S, 9R, 13S, 14R

-Morphine possesses phenolic group and tertiary amino group:
-It can readily form water- soluble salts with most acids. E,g. sulfate and hydrochloride salts .

Analgesic agents
Morphine and related compounds

Morphine

-It is termed narcotic analgesic مسكن مخدر: analgesic that causes addiction إدمان .
-It is used for serious pain
- Side effects: addiction, respiratory depression خمود تنفسي , emetic properties إقياء , constipation امساك , nausea غثيان ….

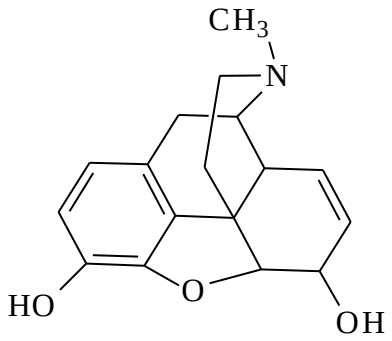
-The most used salts is the sulfate سلفات and to a lesser extent the hydrochloride.
-**Morphine sulfate** is white crystalline powder, soluble in water, slightly soluble in alcohol.
-Dosage:

- orally فمويا: 5-30 mg/ 4 h as needed
- Parenterally حقنا : IM , IV

Analgesic agents, Morphine and related compounds

Early morphine modifications

Synthetic derivatives of morphine



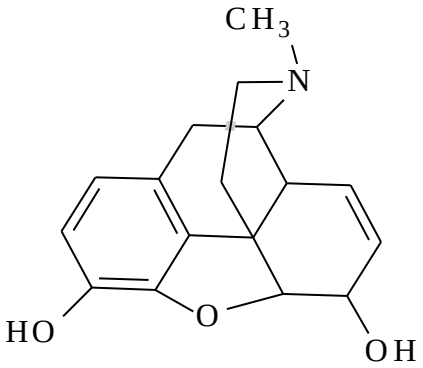
- Structural modifications on the peripheral groups give:

- **Codeine**
- **Dihydromorphine, Dihydrocodeine**
- **Diacetylmorphine** (Heroin)
- **Hydromorphone**, **Hydrocodone**
- **Oxycodone**

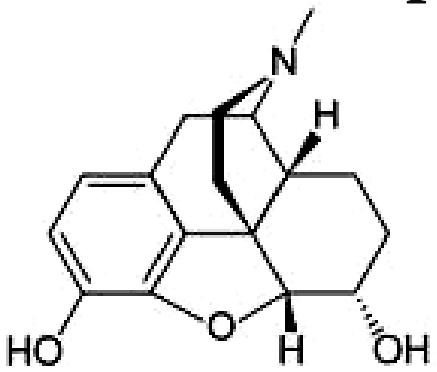
Analgesic agents, Morphine and related compounds

Early morphine modifications

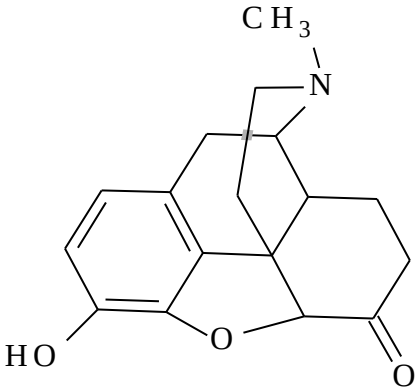
Synthetic derivatives of morphine



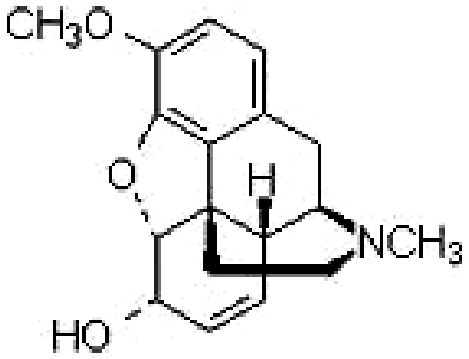
Morphine



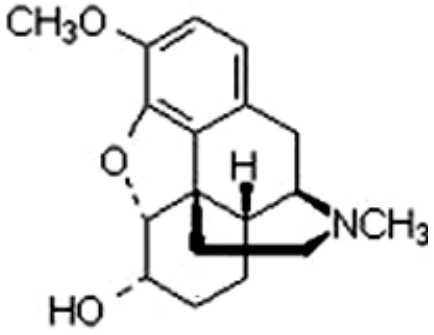
Dihydromorphine



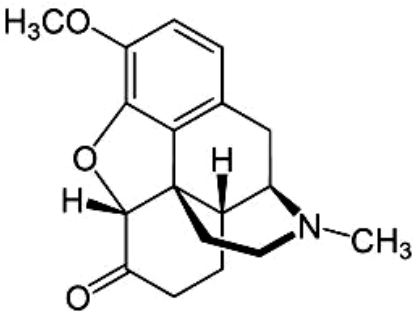
Dihydromorphinone
(Hydromorphone)



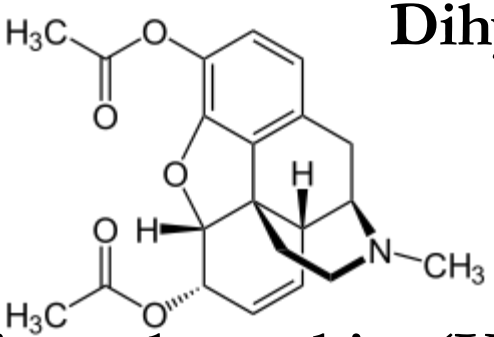
Codeine



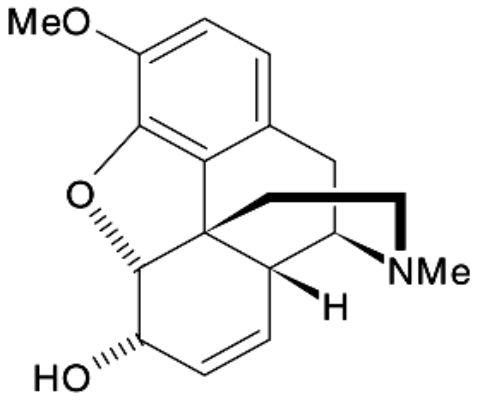
Dihydroodeine



Dihydrocodeinone
(Hydrocodone)



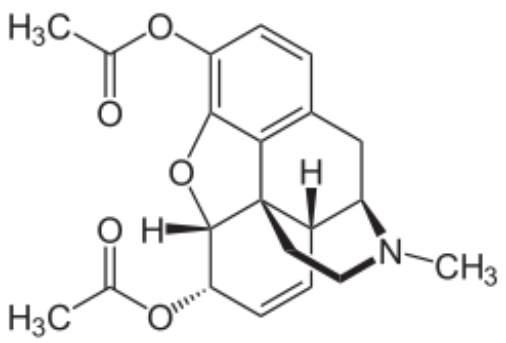
Diacetylmorphine(Heroine)



Codeine and its salts

Codeine is found is small amount in opium.

- It is a methylmorphine
- It occurs as levorotatory.
- White crystalline powder, light sensitive, slightly soluble in water
- **Codeine** possesses less analgesic potency than morphine (3-10 times, parenterally).
- It is used as antitussive in cough preparations.
- It is widely used morphine-like analgesics.
-It is considerably less addicting than morphine.
- Abuse معاقرة and misuse of the codeine containing products are frequent.
-It is used as salts such as **sulfate** (water soluble) and **phosphat**e (freely soluble in water).
- Dosage: the oral daily dose as antitussive: 15-20 mg/ 4-6 h..



Diacetylmorphine Hydrochloride

(Heroin hydrochloride)

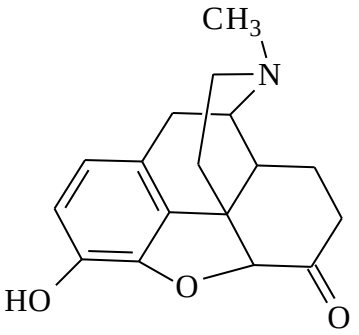
- It is 2 to 3 times more potent than morphine as an analgesic.
- Its sale and use are prohibited because of its intense addiction liability.
-It remains one of the most widely used narcotics for illicit غير مشروعة (محظورة) purposes.

Abuse liability is the potential that a drug has for addiction

Addiction liability/potential: the tendency to develop/produce an addiction

- A drug with high addiction liability : addiction develops quickly

Analgesic agents, Morphine and related compounds
Early morphine modifications



Hydromorphone and Hydromorphone chloride

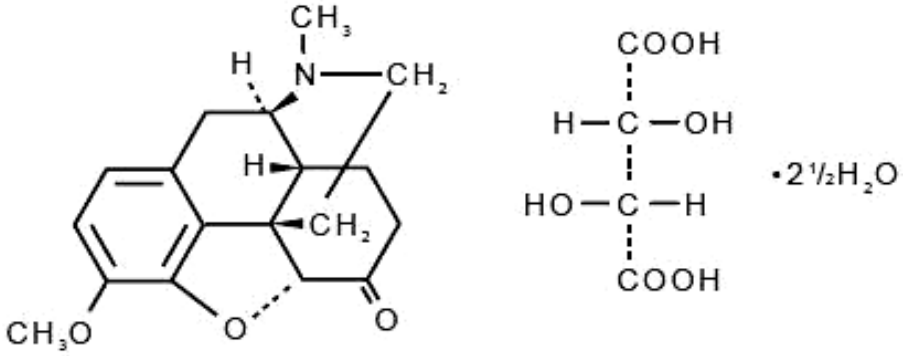
Hydromorphone

- It is a synthetic derivative of morphine.
- It is prepared by just heating the acidified morphine solution with a large amount of finely divided platinium metals that suffices to affect the simultaneous dehydrogenation/hydrogenation in good yields.
- Hydromorphone is similar in properties to morphine, it is slightly soluble in water, soluble in alcohol and chloroform.
- **Its analgesic activity is 5 times as potent as morphine.**
- **It is potent anti-tussive used in difficult control coughs**.
- **Hydromorphone HCl** is used in about one-fifth the dose of morphine for any of the indications of morphine.
-The dosage: orally 2-4 mg/ 4-6 hours.

Analgesic agents, Morphine and related compounds

Early morphine modifications

Hydrocodone bitartrate



Hydrocodone is prepared from codeine by catalytic reduction followed by oxidation of alcohol group.

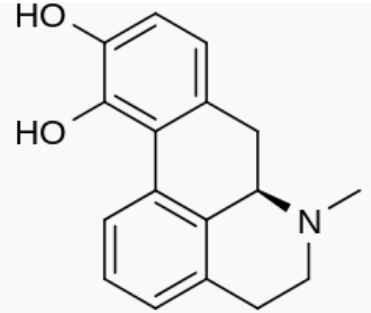
Hydrocodone bitartrate occurs as white crystalline powder, soluble in water.

-It is **more effective than codeine** as an antitussive.

- It is used primarily in many cough preparations.
- It is also marketed in combination with acetaminophen.
- Dosage: oral adult dose: 5-10mg/4 hours

Analgesic agents, Morphine and related compounds

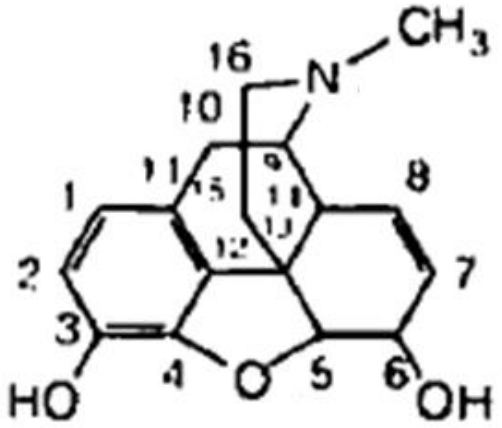
Apomorphine Hydrochloride



Apomorphine is prepared by heating the morphine under pressure with strong hydrochloric acid (35%), (a rearrangement reaction with loss of H_2O) .

- It is a non-selective dopamine agonist which activates both D_1- and D_2- receptors.
- Apomorphine HCl is a white, or grayish white crystals , sparingly soluble in water, light sensitive (turns green on exposure to air and light).
- It has **central stimulant emetic effect**.
-It is effective and safe emetics.
-It is also used for Parkinson disease for acute treatment of immobility episodes.
- It is ineffective orally.
-It is administered subcutaneously (prompt effect:10-15 minutes).

Analgesic agents, Morphine and related compounds



Structure Activity Relationship (SAR)

-The common structural features possessed by all known morphine- like analgesics are:

1. A tertiary nitrogen, with the group on the nitrogen being relatively small: basic center able to associate with an anionic site on the receptor surface.

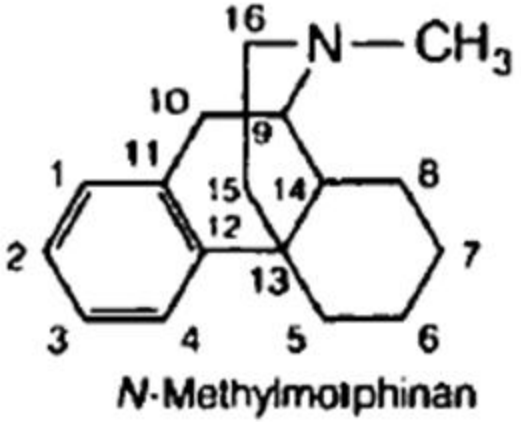
2. A central carbon atom (quaternary carbon), of which none of the valances is connected with hydrogen.

3. A phenyl group which is connected to the central carbon atom., allowing van der Waals bonding to a flat surface on the receptor site.

4. A two carbon chain separating the central carbon atom from the nitrogen for maximal activity.

Morphinan derivatives

Morphinan, N-methylmorphinan



N- methylmorphinan

- It is a synthetic compound (1946) , having no ether bridge, with high degree of analgesic activity (racemic mixture).

3- hydroxyl –N-methyl morphinan:**racemorphan**

- It is a racemic mixture :

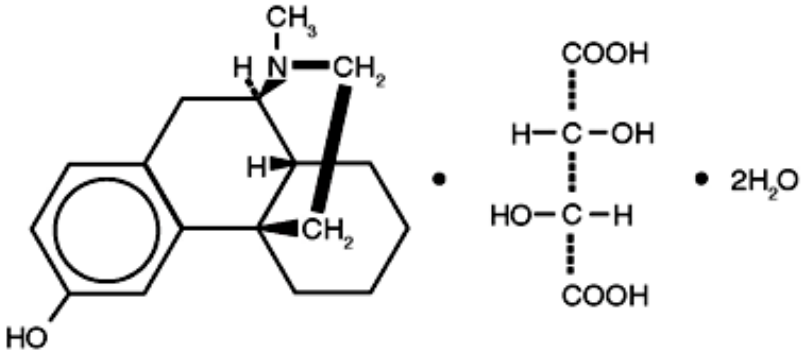
The levorotatory: **levorphanol** is the active analgesic -

The dextrorotatory 3-methyl ether (**dextromethorphan)**: a cough depressant.

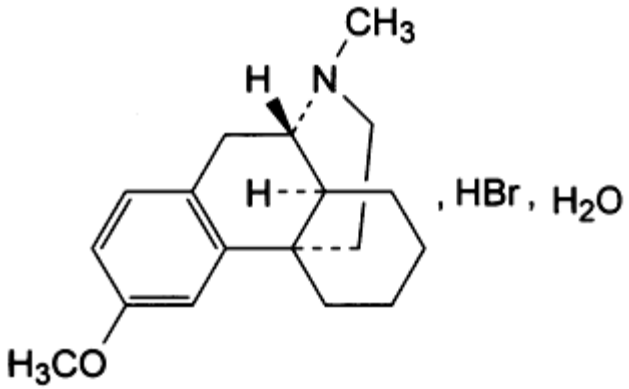
-The N- ethyl-3-hydroxymorphinan derivatives: No activity.

-The N-allylhydroxymorphinan :**levallorphan** is a potent morphine antagonist.

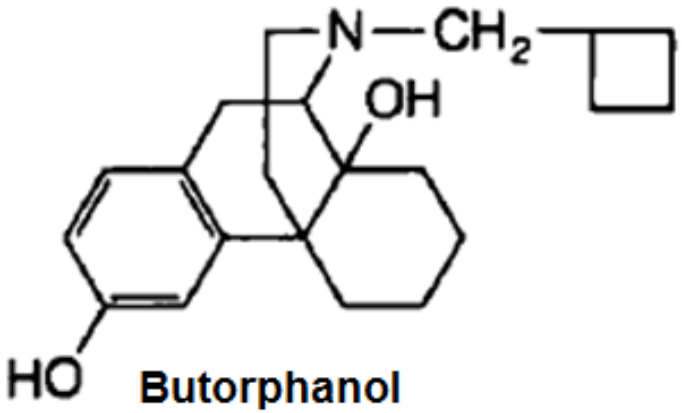
Morphinan derivatives



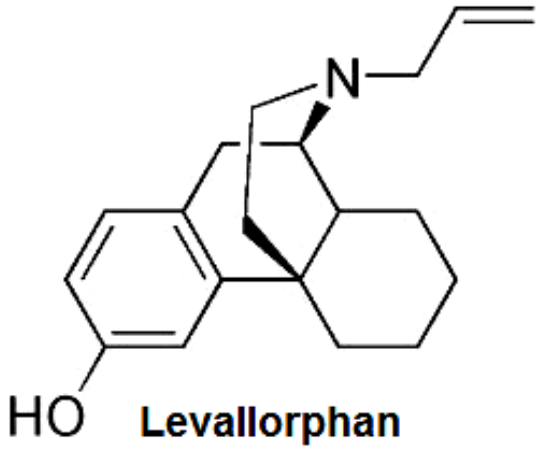
Levorphanol tartarte
Potent analgesic



Dextromrthorphan Hydrobromide
Non-narcotic antitussive



Butorphanol
Antagonist-type analgesic

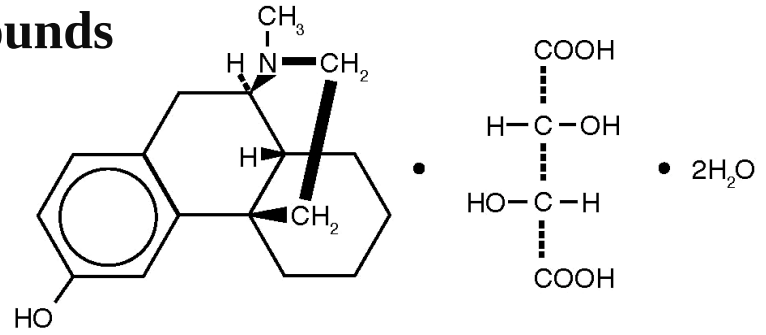


Levallorphan
Antagonist-type analgesic

Analgesic agents, Morphine and related compounds

Morphinan derivatives

Levorphanol tartrate



Levorphanol tartrate

Levorphanol tartrate,

(-) 3- hydroxy-N-methylmorphinan bitartrarte.

-The racemic mixture hydrobromide (racimorphan) salt is first introduced as **a potent analgesic.**

-Levorphanol is prepared by resolution of racimorphan.

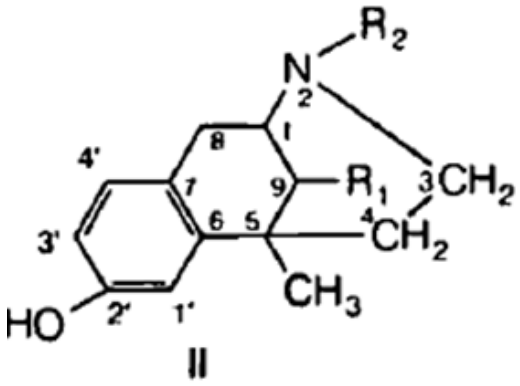
-Levorphanol tartrate is a colorless crystals sparingly soluble in water and insoluble in ether.

-It is **more potent analgesic (6-8 times) than morphine**

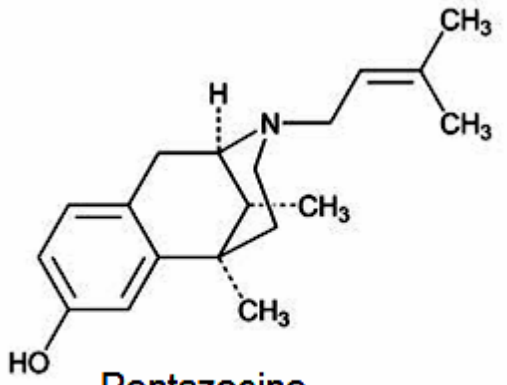
- The side gastrointestinal effect is significantly lower than that of morphine.

- Dosage oral tablets:2mg/8 hours, IM,IV: 1mg/ 8hours.

Benzomorphan derivatives



II



Pentazocine
Antagonist-Type Analgesic

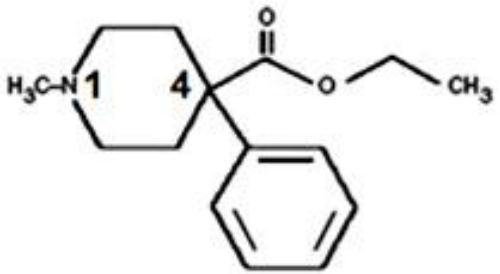
N-alkylbenzomorphan (structure II): Elimination of the ether bridge and the alicyclic ring from morphine structure gives N-methylbenzomorphan that retains the analgesic activity.

- A series of synthesized derivatives substituted on C_5,C_9,N are prepared:

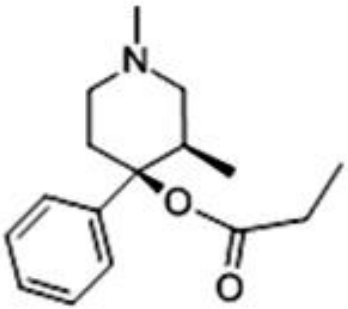
• **Pentazocine** (II. R_1 = -CH_3. R_2 = -$CH_2CH = C(CH_3)_2$: **<u>Antagonist-type analgesic</u>**: used to treat moderate and severe pain

Available: tablets 50mg (as HCl), injections (as lactate)

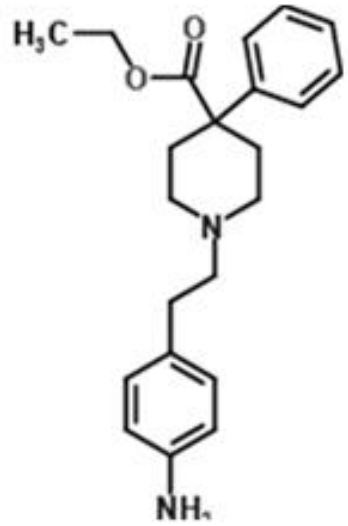
Compounds related to Meperidine



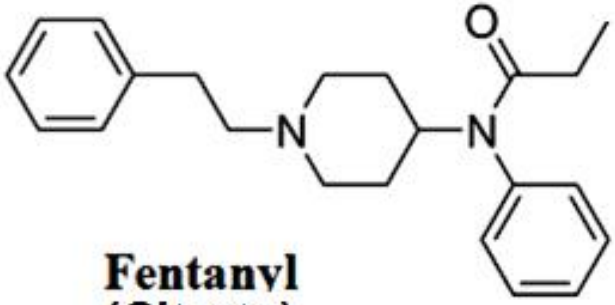
Meperidine (HCl)
(Pethidine)



alphaprodine (HCl)



Anileridine
(HCl)



Fentanyl
(Citrate)

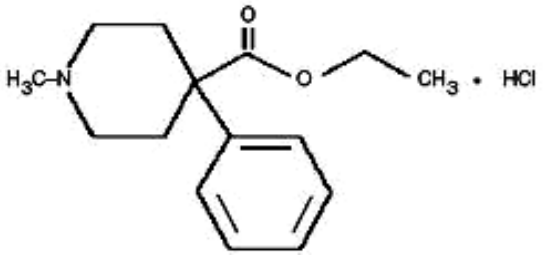
-In 1938, discovery that a simple piperidine derivative, now known as **meperidine**, possessed analgesic activity (also antispasmodic**).**

Compounds related to Meperidine

-Placement of the phenyl and ester groups at the 4 position of 1-methylpiperidine also gave optimum activity.
-Many structure modification are done concerning the three substituents on piperidine ring: compounds with more analgesic activity are obtained: e.g. **anileridine** and **fentanyl**.

Analgesic agents, Morphine and related compounds

Compounds related to Meperidine



Meperidine Hydrochloride, **Pethidine**, Ethyl 1-methyl-4-phenyl-4-piperidinecarboxylate hydrochloride.

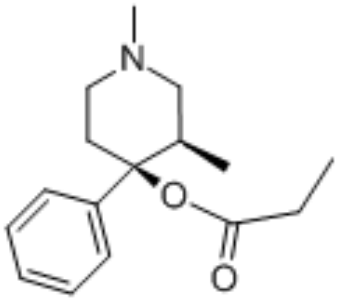
- Meperidine HCl is white odorless crystalline powder, very soluble in water.
- It exerts an **analgesic effect** that lies between those of morphine and codeine.
-It has **antispasmodic activity** (a papaverine-like depression of smooth muscles).
- It is used in spastic تشنجي pain (intestine, uterus, bladder and so on)

Its use in laborالمخاض : IM 50-100 mg every 4h as needed

- The oral dose: 50-150mg/ 3-4 hours as necessary.

Analgesic agents, Morphine and related compounds

Compounds related to Meperidine

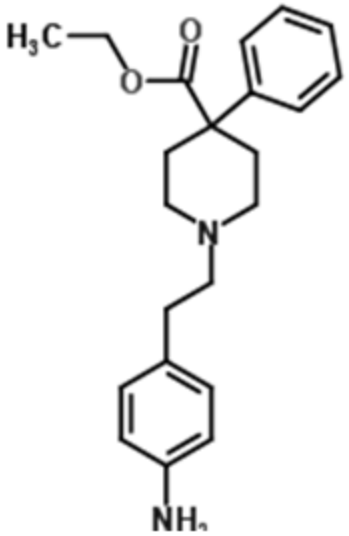


Alphaprodine hydrochloride. (±)- 1,3-dimethyl-4-phenyl-4-piperidinol propanoate hydrochloride.

It occurs as a white crystals that is freely soluble in water, alcohol.

-The compound is an effective analgesic, similar to Meperidine, and of special value in obstetric توليدي analgesia (quite safe: no respiratory depression in either mother or fetus).

Anileridine HCl



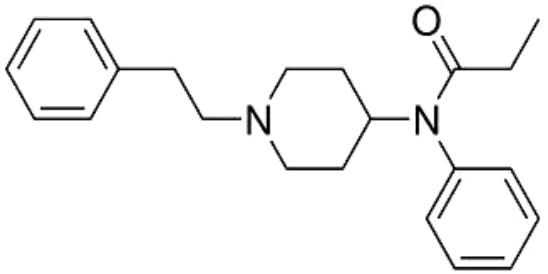
Anileridine HCl

- It is a white crystalline odorless powder, freely soluble in water.

-Anileridine is more active than meperidine and has the same usefulness and limitations.

Analgesic agents, Morphine and related compounds

Compounds related to Meperidine

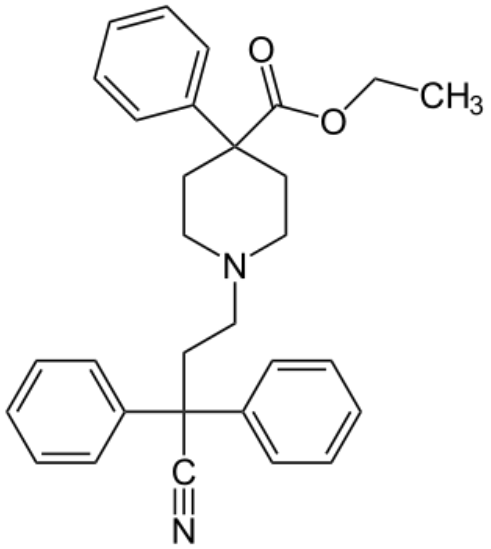


Fentanyl citrate , N-(1-Phenethyl-4-piperidyl) propionanilide citrate (1:1).

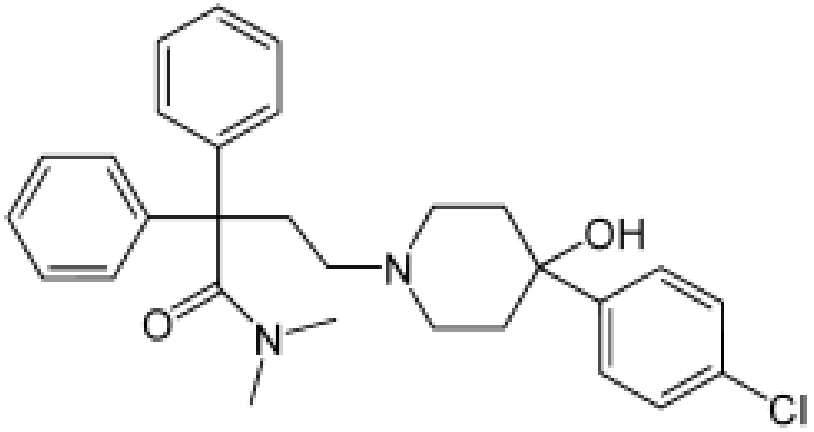
- It occurs as crystalline odorless powder, soluble in water and methanol.
- It is **novel anilide** derivative with analgesic activity **50 times** that of morphine in human, with **rapid onset and short duration of action**.
-Side effect particularly, respiratory depression and bradycardia.
-It is used primarily, as an **adjunct to anesthesia**, and as a neuroleptanalgesic مسكن تطميني in surgery (available in combination with droperidol).
-It is used for the **chronic pain** (available as a transdermal release system at total dose levels ranging from 20-100mg.
-It has dependence liability.

Compounds related to Meperidine

Diphenoxylate Hydrochloride and Loperamide



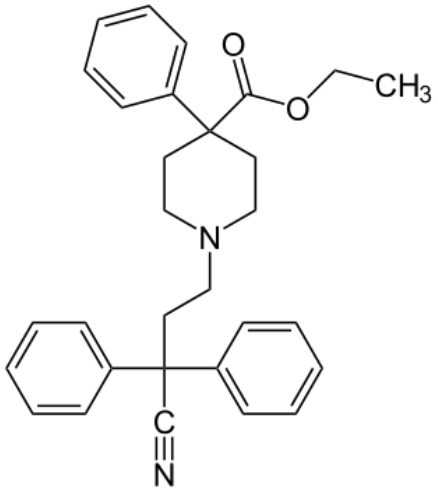
Diphenoxylate



Loperamide

Analgesic agents, Morphine and related compounds

Compounds related to Meperidine

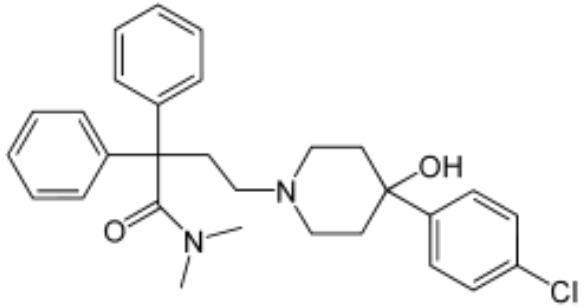


Diphenoxylate Hydrochloride (Lomotil)

- Diphenoxylate is a white odorless powder slightly soluble in water.
-It is able to inhibit excessive GI motility, with very little if any analgesics effect.
-It produces **no addiction** with ordinary dosage levels**.**
- It is used as antidiarrheal 5 mg /3-4 times per day.
-It is contraindicated (should not be use) in patients with impaired hepatic function or taking barbiturates. عليل
-Side effects are rare.

Analgesic agents, Morphine and related compounds

Compounds related to Meperidine



Loperamide

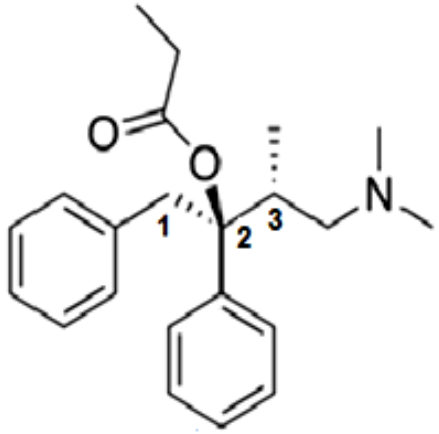
-It is closely related to diphenoxylate but is **more specific, more potent and longer acting**.

- Its trade name is: Imodium.

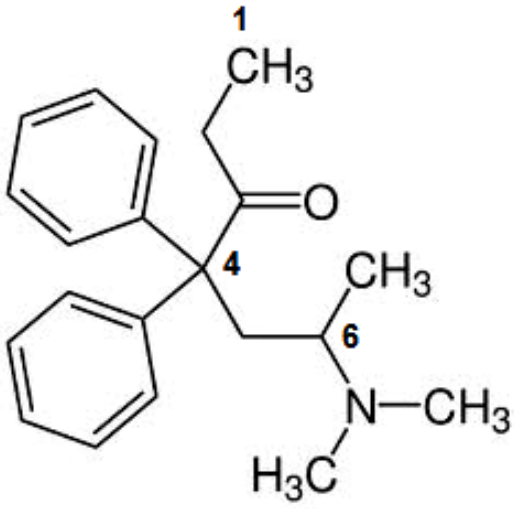
-It acts as an antidiarrheal by direct effect on the circular and longitudinal intestinal muscles.

-It is available as 2 mg capsules for treatment of acute and chronic diarrhea.

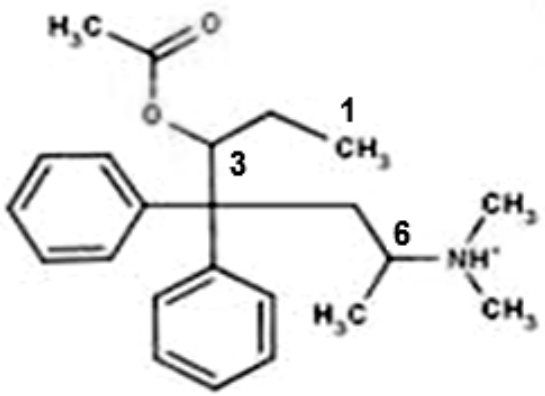
Compounds related to Methadone



Dextropropoxyphene
(2S,3R)
as Hydrochloride
or Napsylate



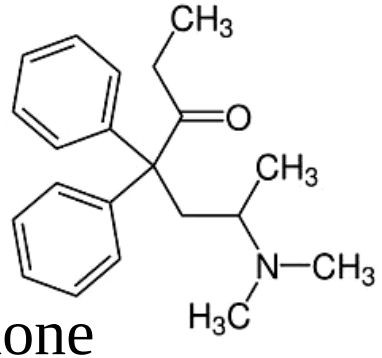
Methadone(as HCl)



3S,6S (-)-Levomethadyl
acetate HCl

Analgesic agents, Morphine and related compounds

Compounds related to Methadone



Methadone Hydrochloride

Methadone, 6-(Dimethylamino)-4,4-diphenyl-3-heptanone hydrochloride.

-The analgesic effect and other morphine-like properties are exhibited chiefly by the (-) form, called levanone.

- Methadone HCl is soluble in water, freely soluble in alcohol and chloroform, and insoluble in ether.

-Methadone is 3 to 10 times **more toxic** that of morphine, but its **analgesic effect is twice that of morphine** and 10 times that of meperidine.

-Methadone itself is used to alleviate many types of pain.

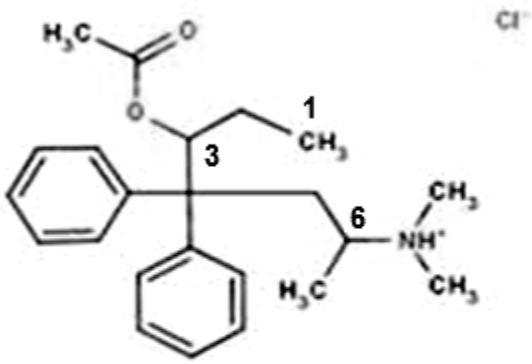
It is used quite extensively in **addict treatment** (morphine and Heroine addict).

-It has high addiction liability.

-Dosage, oral, IM,IV: 2.5-10mg/ 12hours

Analgesic agents, Morphine and related compounds
Compounds related to Methadone

Levomethadyl acetate HCl



3S,6S (-)-Levomethadyl acetate HCl

Levomethadyl acetate HCl , levo-α-acetylmethadol (LAAM).

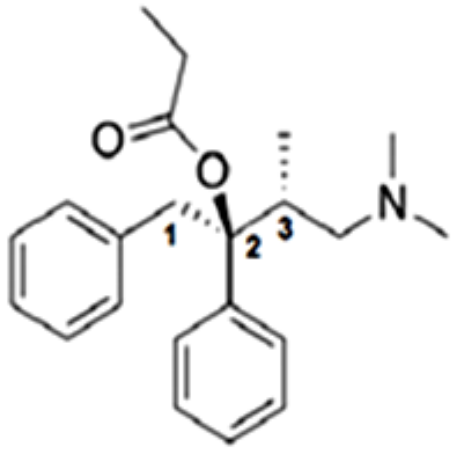
- Of the four possible methadol isomers, (3S,6S) isomer has the unique characteristic of long-lasting narcotic effects.

-It was actively investigated as an addict-maintenance drug to replace methadone (which should be administered daily).

Dosage: 80-100-mg dose 3 times a week suffices for routine maintenance.

- In 2001, LAAM was removed (**DISCONTINUED)** from the European market due to reports of life **threatening ventricular rhythm** disorders.

Analgesic agents, Morphine and related compounds
Compounds related to Methadone



Dextropoxyphene Hydrochloride

Dextropropoxyphene, (2S,3R)-(+)-4-(dimethylamino)-3-methyl- 1,2-diphenyl-2-butanol propanoate hydrochloride (1957).

-It occurs a bitter white crystalline powder soluble in water and alcohol.

-It is used to treat mild pain.

-In high doses, It is toxic and give **some euphoria (شمق (مرح الجنون**

-The **napsylate salt** (2-naphthalene sulfonate) : less prone to abuse

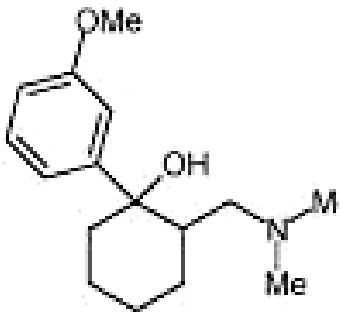
-Dosage:orally(tablets) 50-100mg/ 4hours as needed, or in combination with paracetamol (30- 50 mg propoxyphene, 300-600mg paracetamol)

Levopropoxyphene is **effective anti-tussive** (activity:one- half that of codeine)

Analgesic agents, Morphine and related compounds

Compounds related to Methadone

Tramadol Hydrochloride



Tramadol

Tramadol structure represents a fragment of codeine structure consisting of the phenyl and cyclohexane rings.

-Tramadol, marketed in 1977, is a **serotonin releaser**, **reuptake inhibitor of norepinephrine** and a **weak μ-opioid receptor agonist**.

-It has a **narcotic analgesic** activity, which is principally, attributed to the O-demethylated metabolite, which is 6 times more potent than the parent compound.

-It is used to treat moderate to moderately severe pain.

- It has lower morphine-like side effects.

- Its multiple use might cause **dependance**.

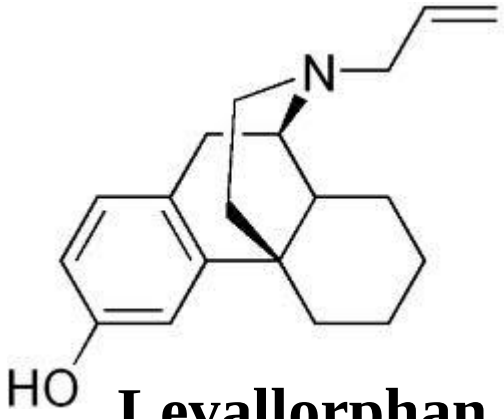
-Dosage: 50- 100 mg every 4-6 hours -

Available as tablets 50,100 mg

Analgesic agents, Morphine and related compounds

Narcotic antagonists

Antagonist-type analgesic

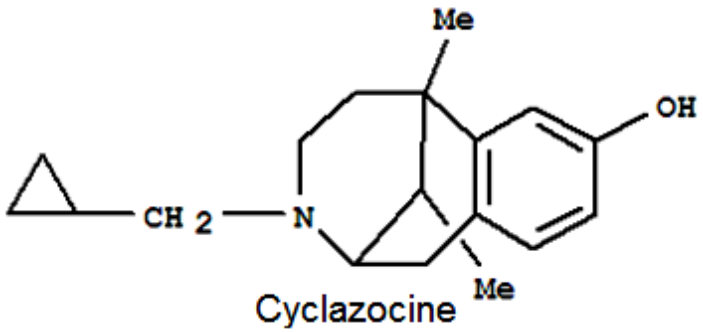


Levallorphan

Levallorphan tartrate: (-)-N-allyl-3-hydroxymorphinan bitartrate

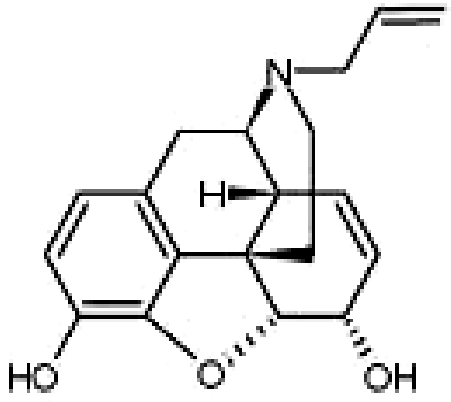
-It is used in combination with analgesic such as meperidine, levorphanol and others to prevent the respiratory depression side effects of these analgesics.

- **Cyclazocine** and **Nalorphine** : withdrawn because of undesirable psychotic side effects

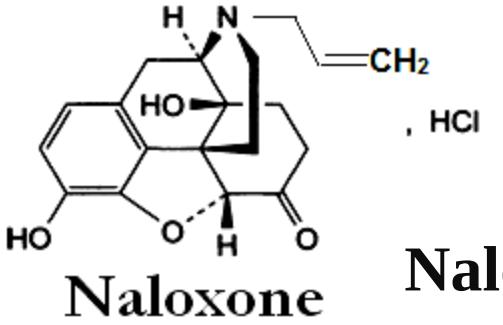


Cyclazocine

withdrawn



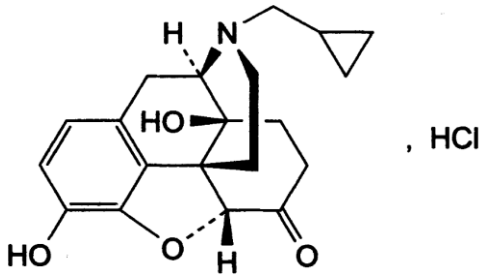
Nalorphine



Naloxone

Narcotic Antagonists

Naloxone HCl and Naltrexone HCl



Naltrexone

Naloxone HCl: N-allylnoroxymorphone

Naltrexone HCl: N-cyclopropylnoroxymorphone

Naloxone and naltrexone are pure antagonist with no morphine-like side effects.

Naloxone is used for treating narcotic overdosage for short duration of action (4h.).

Naltrexone : It is the preferred agent for treating opiate addicts.

– it is also used for alcoholisms.

- Preparations: oral doses 50 mg daily or 100 mg 3 times weekly; depot dosage forms.

Antitussive Agents

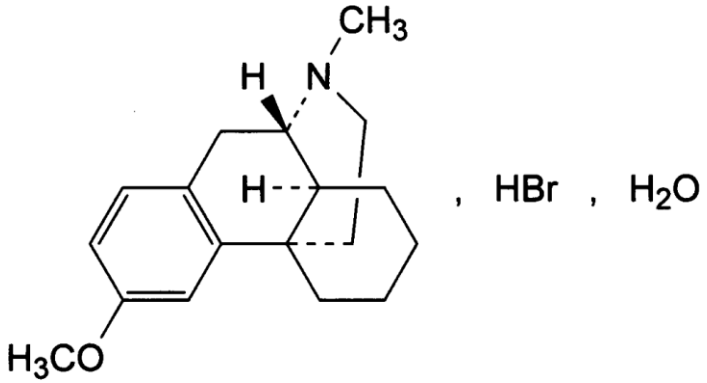
-Cough is a protective physiological reflex منعكس فيزيولوجي محصن that occurs in health as well as in disease. Many factors cause this reflex.
-Among the agents used in the control of cough are:

• Narcotic analgesics: **codeine, hydrocodone, hydromorphone**…). that act by depressing the cough center located in in the medulla.

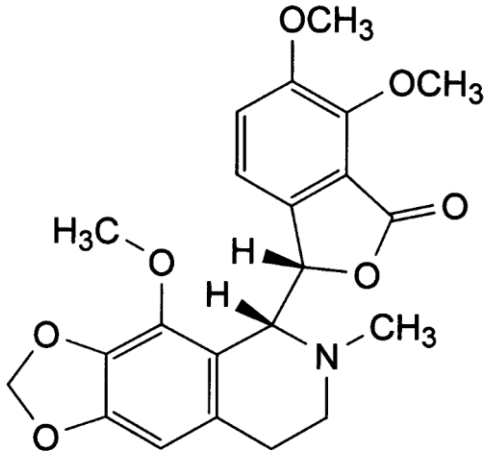
• In recent years, several compounds have been synthetized that possess antitussive activity without the addiction liability of the narcotic agents: **Dextromethorphan HBr**, **Benzonatate**, **levopropoxyphen napsylate** and **Carbetapentane citrate**

Analgesic agents, Morphine and related compounds

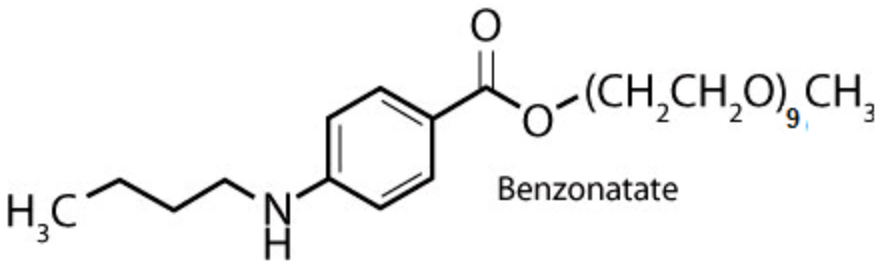
Antitussive Agents



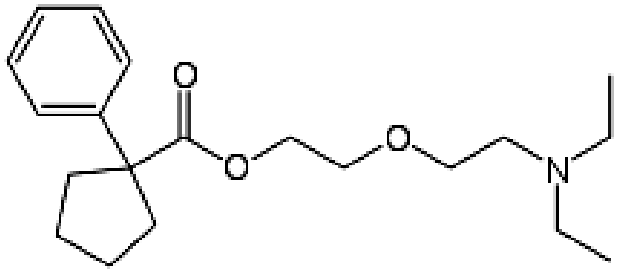
Dextromethorphan HBr



Noscapine (Narcotine)



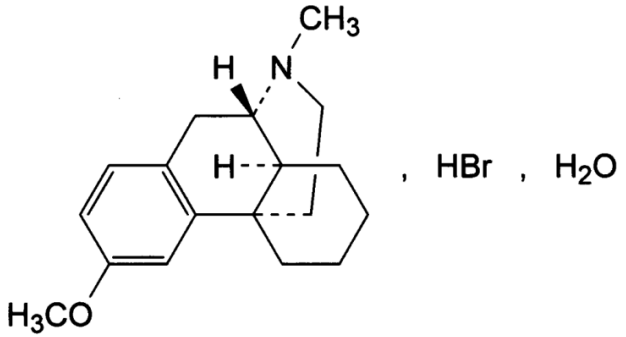
Benzonatate



Carbapentane

Analgesic agents, Morphine and related compounds

Morphinan derivatives



Dextromethorphan Hydrobromide

- It is the (+) 3- methyl ether of N-methylmorphinan

-Almost white, crystalline powder with a faint odor, sparingly soluble in water, freely soluble in alcohol. mp: about 125 °C.

-It possesses the anti-tussive properties of codeine without the analgesic, addictive, central depressant, and constipating features.

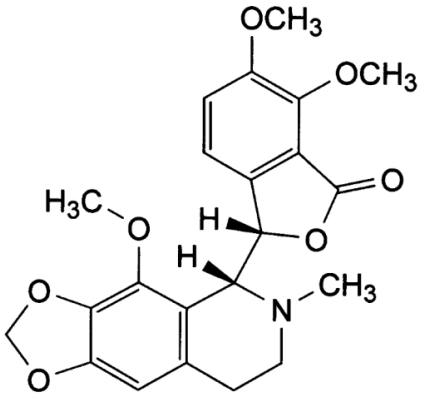
-It is more potent than codeine as **anti-tussive:10 mg dextromethorphan is as effective as 15 mg codeine.**

- It has largely replaced many older antitussive, including codeine, in prescription and nonprescription cough preparations.

-Dosage : usual adult dose :15-30mg qd (once daily) to qid (four times daily).

Analgesic agents, Morphine and related compounds

Antitussive agents



Noscapine or (-) **narcotine**

- It is a an opium alkaloid (0.75-9% of opium) of structure derived from isoquinoline nucleus.

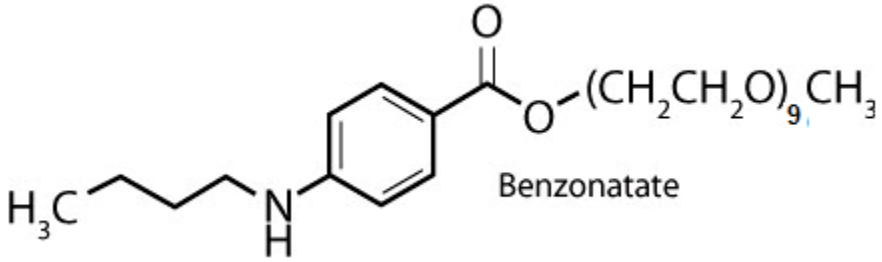
-It is a white, crystalline powder or colorless crystals, practically insoluble in water, soluble in acetone.

-It is not narcotic.

-It has anti-tussive properties.

Analgesic agents, Morphine and related compounds

Antitussive agents



Benzonatate

Benzonatate

- It is a pale yellow viscous liquid insoluble in water and soluble in most organic solvents.
- Introduced in 1956.
-It is chemically related to *p*-aminobenzoate local anesthetics except that the alcohol group of the ester is replaced by a methylated polyethylene glycol group.
-It has peripheral and central antitussive effect.
-It is not as effective as codeine but with fewer side effects and low toxicity.
-It is not an opioid, thus it is not prone to abuse.
-It is available in 100 mg capsules.
-Usual adult dose: 100mg tid (3 times daily).

Anti–Inflammatory analgesic

(Non–Steroidal Anti–inflammatoy Drugs: NSAID's)

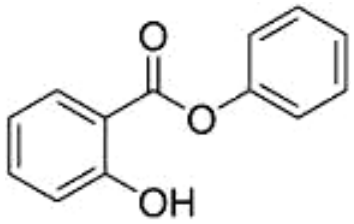
Anti-Inflammatory analgesic

Salicylic acid derivatives: sodium salicylate, Na thiosalicylate, Mg or choline salicylate, phenyl salicylate, salicylamide, aspirin, salsalate, diflunisal.
N-Arylanthranilic acid: mefenamic acid, Na meclofenamate.
Arylacetic acids derivatives : ibuprofen , naproxin, fenoprofen, ketoprofen, fluriprofen, indomethacine, sulindac, tolmetin, diclofenac , nabumetone, ketorolac, etodolac., oxaprozin,
Oxicams: piroxicam, meloxicam, tinoxicam.
Selective COX-2 inhibitors: Celecoxib, Rofecoxib,Valdecoxib, Etoricoxib, nimsulide.
Pyrazolone : antipyrine, aminopyrine, dipyrone.
Pyrazolidinedione: phenylbutazone, oxyphenbutazone.

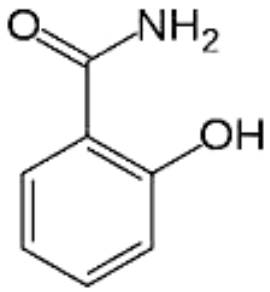
Paraaminophenol derivatives , the analgesic antipyretic acetaminophen.

Antiinflammatory Analgesics

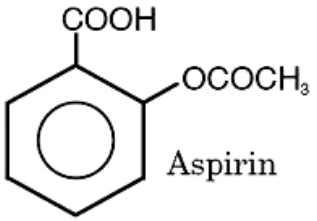
Salicylic acid derivatives



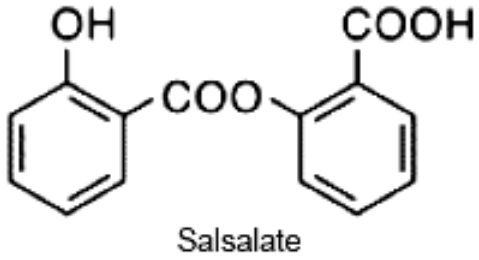
Phenyl salicylate (salol)



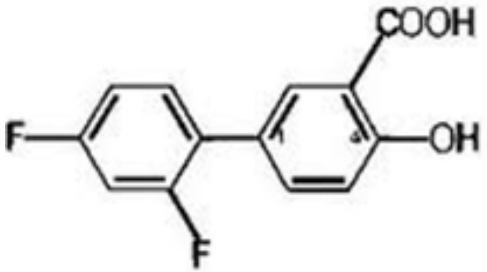
Salicylamide



Acetylsalicylic acid

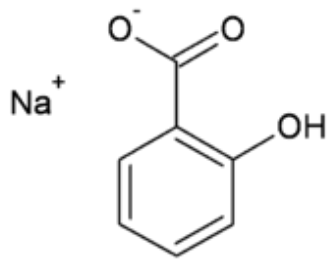


Salsalate

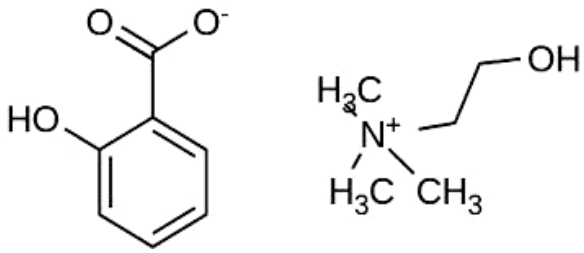


Diflunisal

Salicylic acid derivatives



Sodium salicylate



Choline salicylate

Salicylic acid: It causes severe gastric irritation, It is used externary .

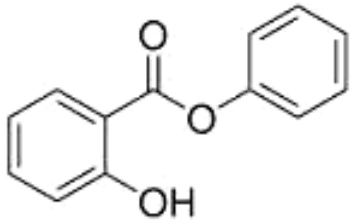
Na salicylate: white powder soluble in water with sweat saline taste, It is used as enteric coated tablets.

Na thiosalicylate: It is more soluble and better absorbed,

Mg Salicylate: Na-free salicylate.

Choline salicylate: extremely water soluble, and absorbed more rapidly than aspirin.

Salicylic acid derivatives



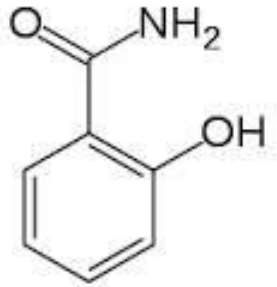
Phenyl salicylate (salol)

- It is a water- insoluble powder.

-It is hydrolyzed slowly in the intestine into phenol and salicylic acid.

-It is used as sun filter (10% ointment for sunburn prevention), as urinary antiseptic with methenamine (hexamethylenetetramine).

Salicylic acid derivatives



Salicylamide:2-hydroxybenzamide

- It is a white crystalline powder slightly soluble in water.

-It is used as analgesic and antipyretic.

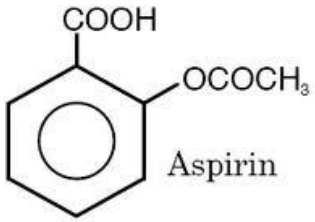
-Its activity is quicker but not greater than aspirin.

- Dosage forms: it is used in combination with paracetamol and diphenhydramine as suppositories and tablets.

Tablet:250mg salicylamide +150mg paracetamol + 10mg diphenhydramine HCl + 50mg cafeine citrate.

Antiinflammatory Analgesics

Salicylic acid derivatives



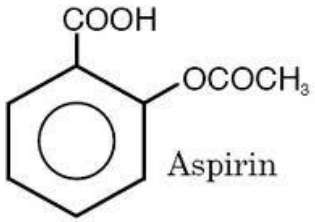
Acetylsalicylic acid

Aspirin: acetylsalicylic acid:

- It is a white crystalline powder slightly soluble in water, stable in dry air.
- It is hydrolyzed slowly in the presence of moisture into salicylic acid and acetic acid.
-It is hydrolyzed slightly in stomach and intestine, most absorbed unchanged.
-It is **unstable in aqueous solution** (no aqueous preparations.
-Aspirin has analgesic antipyretic and antiinflammatory activity.
-It is used in gout, rheumatoid arthritis.
- It is available as tablets, capsules, and suppositories.
-It has anesthetic action when applied locally in tonsillitis, pharyngitis, skin diseases.

Antiinflammatory Analgesics

Salicylic acid derivatives



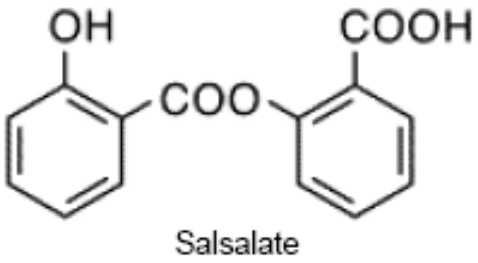
Acetylsalicylic acid

Aspirin

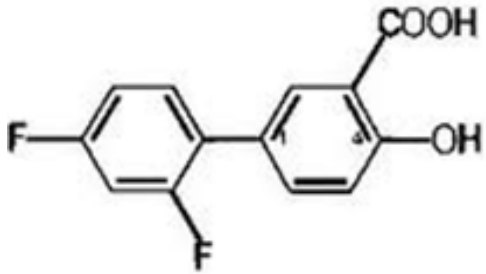
-Aspirin has antithrombotic مانع الخثار activity.
It is used in daily 81mg dose for individuals of cardiovascular diseases.
-It is non-selective NSAID's, it inhibits COX-1 and COX-2.
- Side effects :Gastric mucosal irritation.
Thus preparations of aspirin in combination with Aluminium hydroxide , Magnesium trisilicate are available.
- Dosage: as analgesic: oral tablets 0.5-1g three times/ day.

Antiinflammatory Analgesics

Salicylic acid derivatives



Salsalate



Diflunisal

Salsalate, salicylsalicylic acid:

-It is absorbed in the intestine, hydrolyzed after absorption,

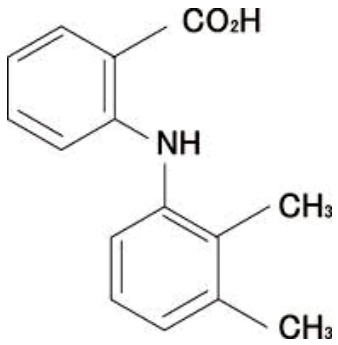
-It is as effective as aspirin but with fewer side effects: less gastric upset because it is relatively insoluble in stomach.

Diflunisal: 2',4'-difluoro-4-hydroxybiphenyl-3-carboxylic acid

–The introduction of hydrophobic groups (F, aromatic ring) makes it twice as effective and twice the duration of action compared to aspirin, and less side effects.

- Dosage forms: 250-500mg tablets.

N-Arylanthranilic acids



Mefenamic acid

N-Arylanthranylic acids are primarily NSAD's and secondarily some possess analgesic activity.

Mefenamic acid: 2-(2,3-dimethylphenyl)aminobenzoic acid

-It is an off- white crystalline powder insoluble in water.

-It possesses an antiinflammatory (antiphlogistic) analgesic activity; this is due to blocking COX enzymes.

-Its analgesic activity is more potent than aspirin (250mg mefenamic acid is superior to 600 mg aspirin).

Antiinflammatory Analgesics

N-Arylanthranilic acids

-Mefenamic acid has a lower gastric mucosal irritation than aspirin. Other side effects are diarrhea, headache, drowsiness….

-It has been proved for use in the management of primary dysmenorrhea عسر الطمث(PD).

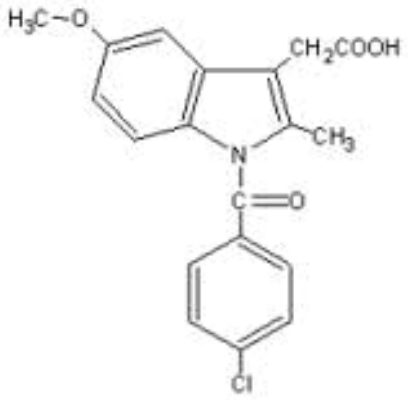
Dosage forms: 100,250,500mg/tablet, capsule, and50mg/5ml suspension.

Na meclofenamate:

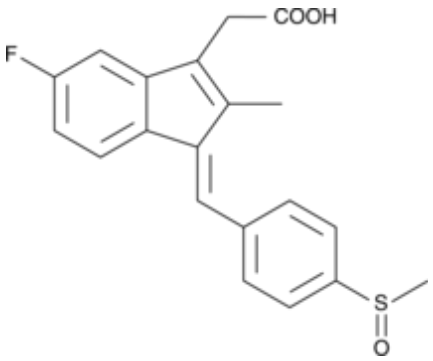
- It is available in 50-100mg capsules for use in the treatment of RA.

Antiinflammatory Analgesics

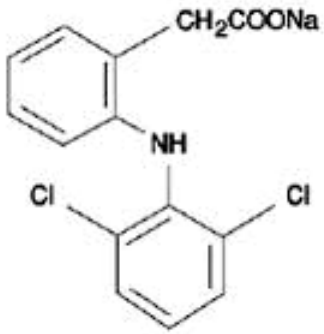
Arylacetic or propanoic acid derivatives



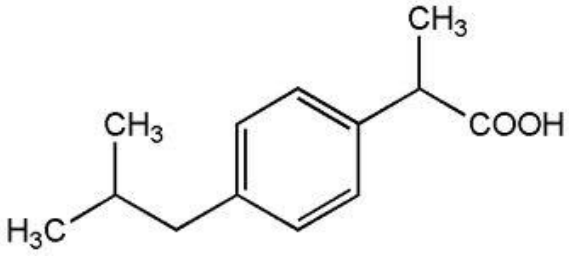
Indomethacin



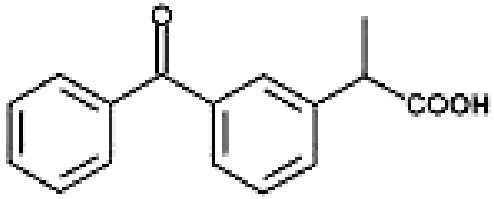
Sulindac



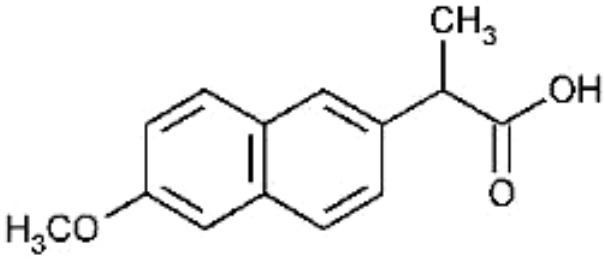
Diclofenac



Ibuprofen



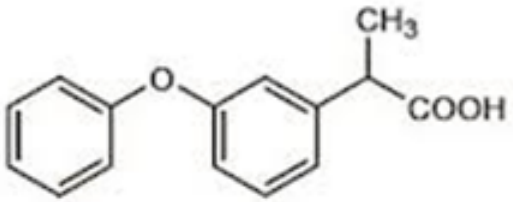
Ketoprofen



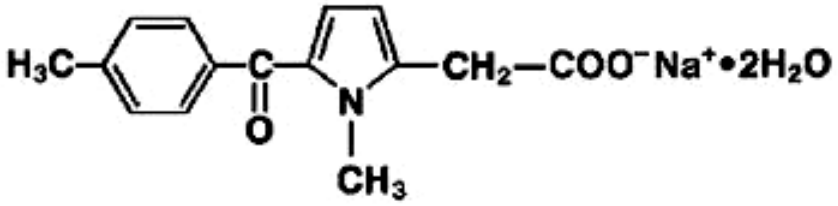
Naproxen

Antiinflammatory Analgesics

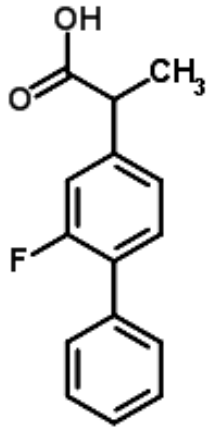
Arylacetic or propionic acid derivatives



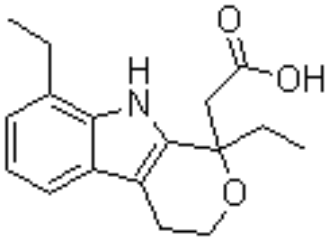
Fenoprofen



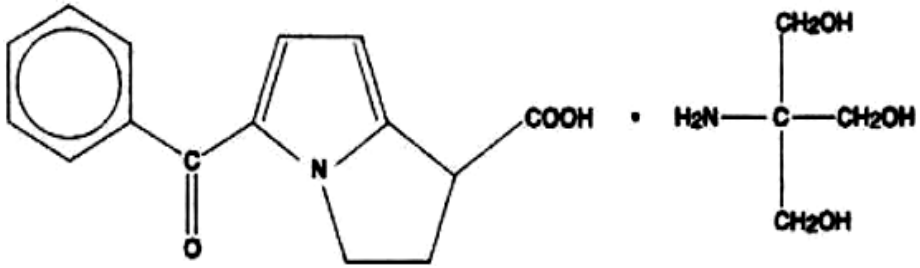
Tolmetin Na



Flurbiprofen

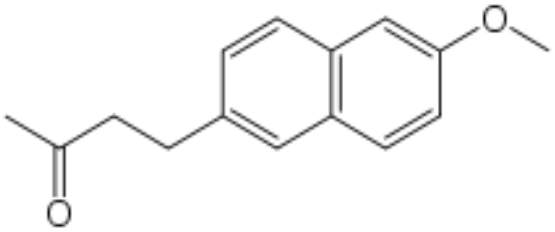


Etodolac

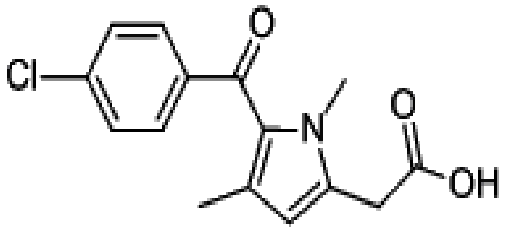


Ketorolac tromethamine

Arylacetic or propanoic acid derivatives

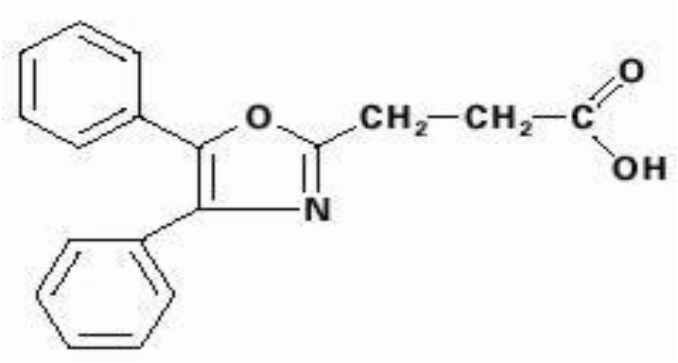


Nabumetone (prodrug)



Zolmepirac

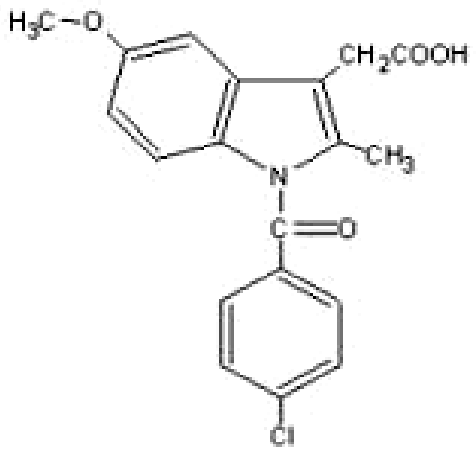
Metabolite: 6-methoxy-2-naphthylacetic acid



Oxaprozin

Antiinflammatory Analgesics

Arylacetic acid derivatives



Indomethacin: 2-{1-[(4-Chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid.

-It is pale yellow crystalline powder, insoluble in water.

- It shows high analgesic potency in addition to anti-inflammatory activity.

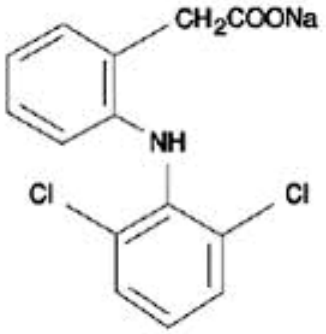
- It is used in rheumatoid arthritis التهاب المفاصل الروماتزمي , osteoarthritis and gout. **-**

Dosage forms**:** 25mg/cap. Dosage 25mg2-3times/day

- Side effects**:** Gastric distress, blood disorders, headache.

Antiinflammatory Analgesics

Arylacetic acid derivatives



Diclofenac Na or K: 2-(2-(2,6-dichlorophenylamino acid sodium or potassium salt.

- Indication: rheumatoid arthritis, osteoarthritis .

-The K salt is faster acting is indicated for the management of cute pain and primary dymenorrhea.

-Dosage forms and dosage:

25, 50,mg/ctd tablet , 75mg/3ml/amp, 75mg/liquid/vial, 100mg/supp.

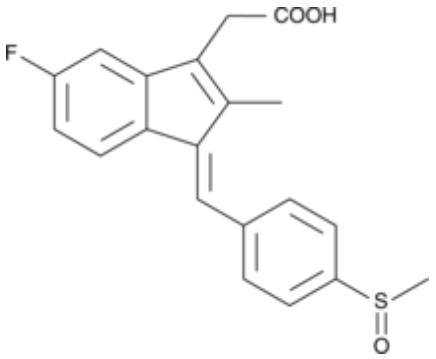
- Dosage: the oral daily dose 75-150mg/day in 2-3 divided doses, after meal.

-Side effects**:** **Gastric mucosal irritation ,** GI disturbance , diarrhea , vomiting, headache, dizziness, fatigue.

- Increased risks of heart attack نوبة قلبية and stroke, arterial thrombotic risk اختطار خثاري is similar to that of selective COX2 inhibitors, thus contraindicated with patients with vascular problems

Antiinflammatory Analgesics

Arylacetic acid derivatives



Sulindac: {(1*Z*)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)benzylidene]-1H-indene-3-yl}acetic acid

-It is a water- insoluble yellow crystals, soluble in alkaline solutions.

-It is a **prodrug;** it undergoes reversible metabolism: active sulfide, inactive sulfone derivative.

The half -life of the active sulfide is around 16 h.

It is excreted as inactive sulfone derivative.

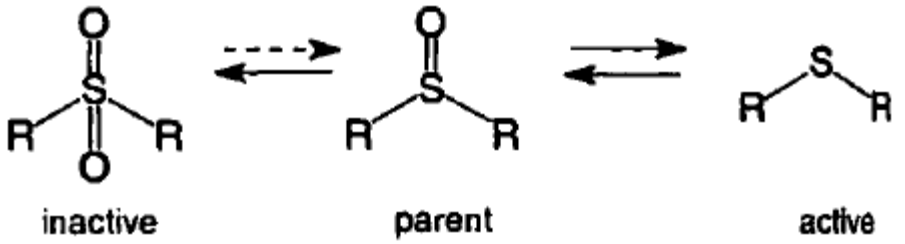
-Side effects**:** Gastric bleeding, nausea, diarrhea, dizziness,

-Indications**:** rheumatoid arthritis, osteoarthritis

-Dosage forms**:**

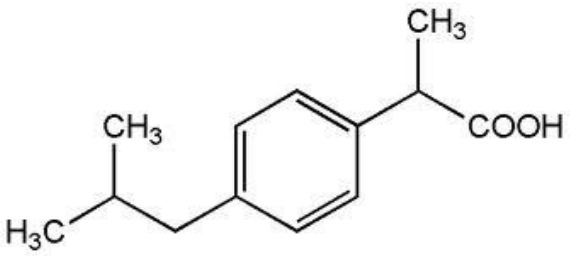
- 150-200 mg/tablet.

-Dosage 200mg twice daily



Antiinflammatory Analgesics

Arylpropionic acid derivatives



Ibuprofen:(*RS*)-2-(4-(2-methylpropyl)phenyl)propanoic acid

-It is comparable to aspirin in the treatment of rheumatoid arthritis with lower incidence of side effects.

-It is also used in the treatment of primary dysmenorrhea (PD)

-The **active isomer is the (S)-(+)-isomer.**

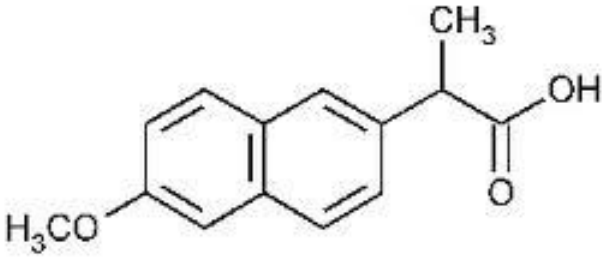
-Dosage forms**:** 200 , 400, 600mg/ctd tablet, 125mg/5ml/syrup cream, gel.

Dosage oral 1.2-1.8g/day in 3-4 divided doses

-Side effects**:** GI problems, edema, dizziness, rash.

Antiinflammatory Analgesics

Arylpropionic acid derivatives



Naproxen: (+)-(*S*)-2-(6-methoxynaphthalen-2-yl)propanoic acid.

- it is used in rheumatoid and gout arthritis.

-The analgesic activity of 300 mg naproxen is equivalent to 600 mg aspirin .

-it is not recommended for pregnant or lactating women or children under 16 years .

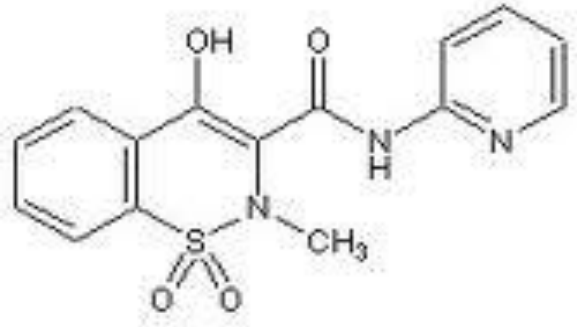
-Dosage forms: 125,250, 500mg /tablet, 125mg/5ml/suspension, 250, 500mg/supp.

Dosage: oral dose 500mg qd or in 2 divided doses

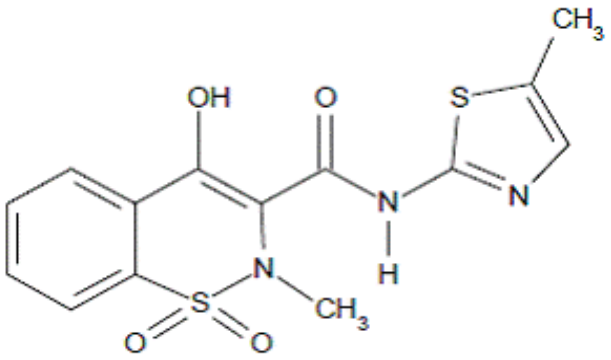
Antiinflammatory Analgesics

Oxicams

Piroxicam, Meloxicam, Tenoxicam



Piroxicam



Meloxicam

Piroxicam: 4-Hydroxy-2-methyl-N-(2-pyridinyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide.

- It is a **very long acting** drug with plasma half life: 50h.

-The daily dose:20-30mg giving results similar to 400mg of ibuprofen three times a day.

- It is available in 10, 20mg/cap, 20mg/supp.

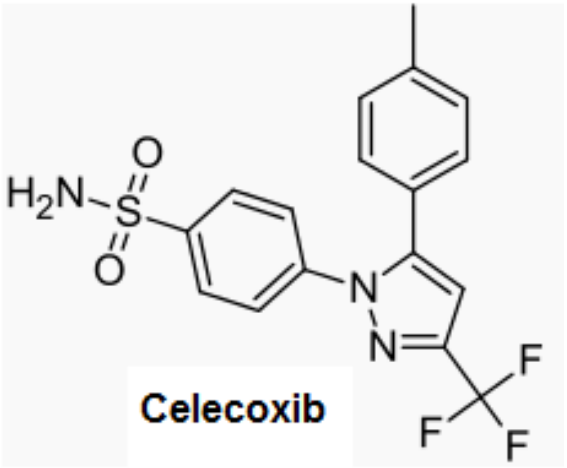
Meloxicam

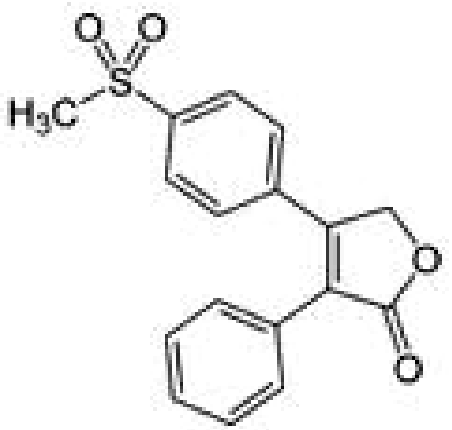
Tenoxicam

Antiinflammatory Analgesics

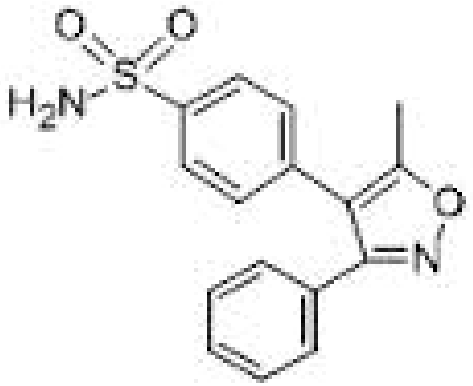
Celecoxib, Rofecoxib, Valdecoxib

Selective COX-2 inhibitors





Rofecoxib



Valdecoxib

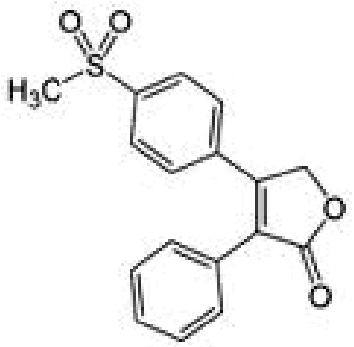
Celecoxib: 4-[5-(4-Methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide

-It is a selective COX-2 inhibitor, approved for use in RA and OA.

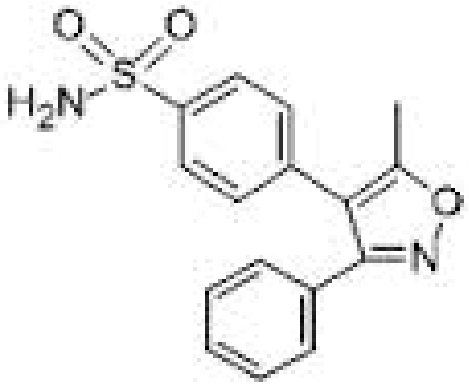
-It is Available in 100 and 200mg tablets.

Antiinflammatory Analgesics

SelectiveCOX-2 inhibitors



Rofecoxib



Valdecoxib

Rofecoxib:4-(4-methylsulfonylphenyl)-3-phenyl-5H-furan-2-one

-It is selective COX-2 inhibitor with greater potency and longer half life than celecoxib (17h versus11h) .

-It was withdrawn from the market in 2004 because of concerns about increased risk of heart attack اختطار نوبة قلبية (cardiovascular events) associated with long-term, high-dosage use.

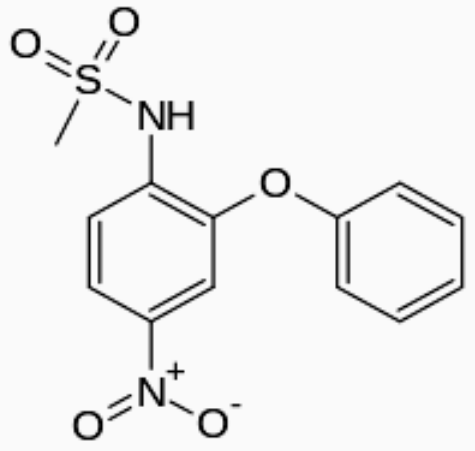
Valdecoxib:4-(5-methyl-3-phenylisoxazol-4-yl)benzenesulfonamide

- It is selective COX-2 inhibitor.

- It was removed from the market due to concerns about possible increased risk of heart attack (myocardiac : MI احتشاء العضلة القلبية).

Antiinflammatory Analgesics

SelectiveCOX-2 inhibitors



Nimsulide: *N*-(4-Nitro-2-phenoxyphenyl)methanesulfonamide,

- It is relatively COX-2 selective NSAID's.

-Nimesulide has been withdrawn from market in many countries, due to concerns about the risk of **hepatotoxicity.**

- Dosage forms

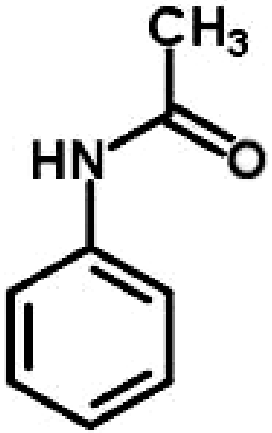
100mg/tablet

50mg/5ml/suspension.

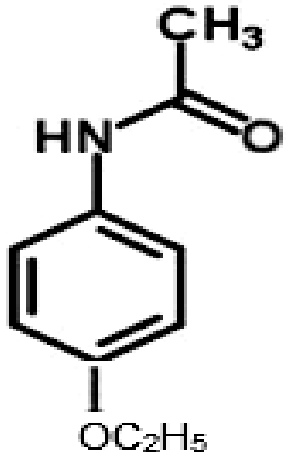
- The adult oral dose: 200mg, 2times/day.

Antipyretic , Analgesics

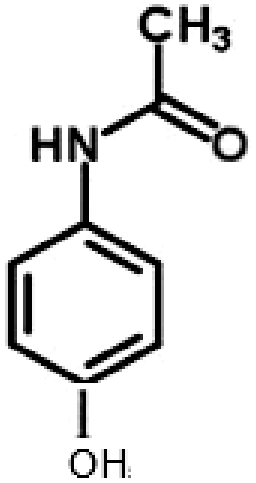
Aniline and p-Aminophenol derivatives



Acetanilid



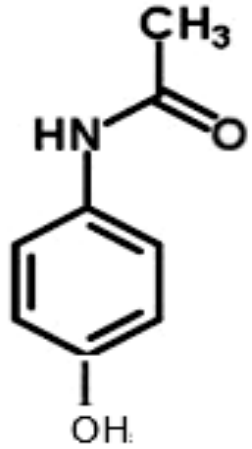
Phenacetin



Acetaminophen

Antipyretic Analgesics

Aniline and p-aminophenol derivatives



Acetaminophen, **paracetamol**,
N-(4-hydroxyphenyl)acetamide, N-acetylparaaminophenol, 4-hydroxyacetanilide.

- It may be prepared by reduction of p-nitrophenol in glacial acetic acid, followed by acetylation with acetic anhydride.

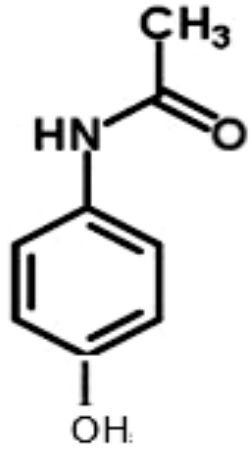
-It is a white odorless, slightly bitter crystalline powder, slightly soluble in water.

-It has **analgesic and antipyretic activities** (effects by central inhibition of COX enzyme, with very little peripheral effects).

- It shows little if any anti-inflammatory activities.

Antipyretic Analgesics

Aniline and p-aminophenol derivatives



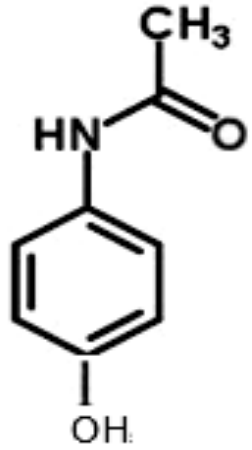
Acetaminophen

- Paracetamol is considered safer than acetanilid and phenacetin, in that the toxic effects occurs less frequently and are less severe.
Paracetamol produces **less methemoglobine** than acetanilid and phenacetin .
-The formation of methemoglobin is related to metabolites with free amino (anilino) group.
-Pharmacokinetics**:**
- its absorption from GI tract is rapid and complete.
It is metabolized primarily in the liver, into toxic and non-toxic products.

Antipyretic Analgesics

Aniline and p-aminophenol derivatives

Acetaminophen

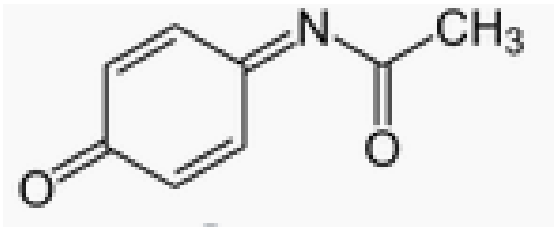


NAPQI (*N*-acetyl-*p*-benzoquinone imine) is toxic metabolite, which is irreversibly conjugated with glutathione.

-In recommended doses and for a limited course of treatment, the side effects of paracetamol are mild to non-existent.

-Dosage forms: tablets, drops, syrups.

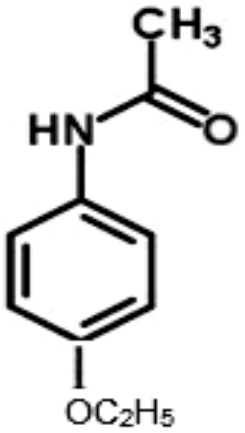
-Dosage: oral tablets 0.5-1g / 3times a day.



NAPQI

Antipyretic Analgesics

Aniline and p-aminophenol derivatives



Phenacetin, *N*-(4-ethoxyphenyl)acetamide,
4-ethoxyacetanilide.

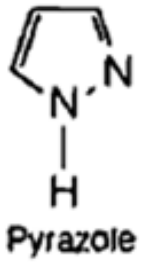
-It acts as analgesic and antipyretic agent, through its metabolite, acetaminophen.

- When it is used as a medicament, it produces more methemoglobin than acetaminophen.

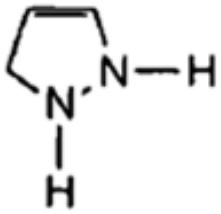
- It is no longer used. It is replaced by acetaminophen, which is considered safer.

Antiinflammatory Analgesics

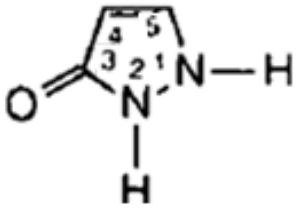
3-Pyrazolone derivatives



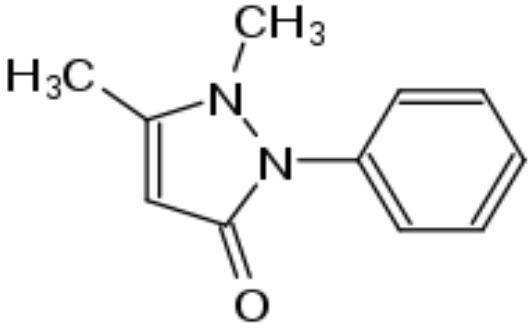
Pyrazole



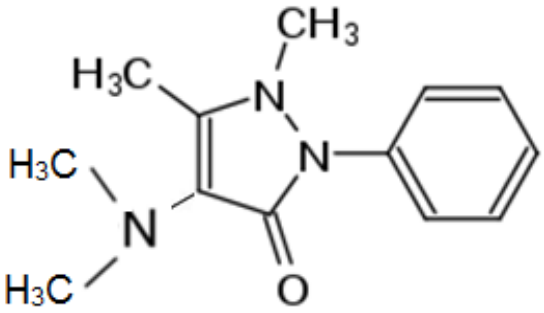
3-Pyrazoline



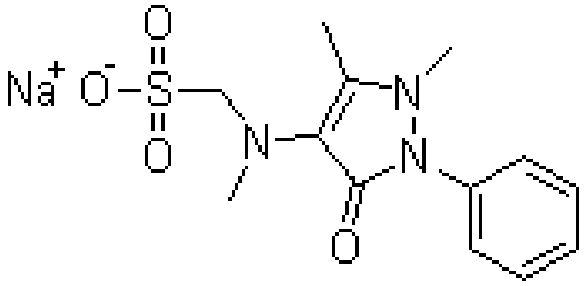
3-Pyrazolone



Antipyrine (Phenazone)



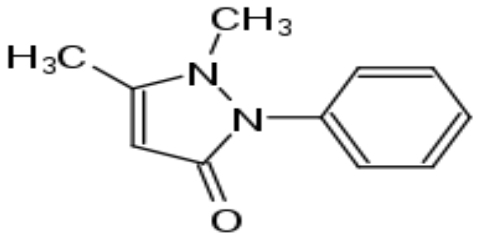
Aminopyrine



Dipyrone

Antiinflammatory Analgesics

Pyrazolone derivatives



Antipyrine, phenazone,, 1,2-Dihydro-1,5-dimethyl-2-phenyl-3*H*-pyrazol-3-one

-It is a colorless, odorless crystals, with slightly bitter taste, very soluble in water and alcohol.

-It is a weak base (nitrogen lone pair at position 1).

- Pharmacologic properties:

• **Analgesic, antipyretic** (action on thermal regulatory center) properties.

• **Anti-inflammatory** (greater than aspirin, indomethacin and phenylbutazone) properties.

• **Local Anesthetic** (paralytic action on the sensory and motor nerves)

• **Antiseptic effect**.

Antiinflammatory Analgesics

Pyrazolone derivatives

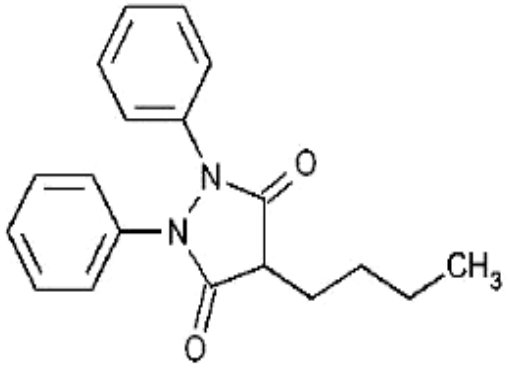
Antipyrine

-It is readily absorbed orally, excreted chiefly by kidney unchanged.
-Its use is limited to a combination with benzocaine as ear drops.

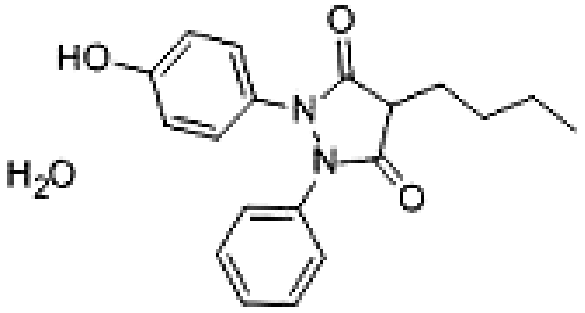
Antiinflammatory Analgesics

Pyrazolidinedione derivatives

Phenylbutazone and Oxyphenbutazone



Phenylbutazone



Oxyphenbutazone

Phenylbutazone and Oxyphenbutazone:
These drugs are no longer marketed.

The End