Organic Pharmaceutical Chemistry II

NONSTEROIDANTI-INFLAMMATORY DRUGS

AL NSAIDs including aspirin and acetaminophen, two of the oldest pain medications, for the treatment of rheumatic arthritis and other degenerative inflammatory joint diseases.

Although NSAIDs are very effective in relieving mild to moderate pains and inflammation, their use is also often associated with many undesirable side effects, including GI irritation and bleeding, platelet dysfunction, kidney damage, and bronchospasm.

With the exception of acetaminophen (Tylenol) and the newer "coxibs" drugs, the conventional NSAIDs (also commonly referred to as the *aspirin-like drugs*), share very similar therapeutic and side effect profiles.

The conventional NSAIDs exert their therapeutic action by inhibiting two isoforms of cyclooxygenase (COX-1, the constitutive isozyme and COX-2, the inducible isozyme), which is the rate-limiting enzyme responsible for the biosynthesis of the proinflammatory prostaglandins (PGs) such as the PGD2, PGE2, PGF2, and PGI2 and thereby modulating pain transmission, attenuating inflammation, and reducing fever. They also produce their undesirable side effects such as GI bleeding, ulcerations, or renal impairments by blocking the same cyclooxygenases responsible for synthesizing PGs that modulate platelet activity (TXA2 and PGI2), gastric acid secretion and cytoprotection (PGE2 and PGI2), and renal blood flow (PGE2).

In early 1990, Vane et al. hypothesized that the undesirable side effects of the conventional NSAIDs are a result of inhibition of the COX-1 isozyme, whereas the therapeutic effects are related mainly to their inhibitory action on the inducible COX-2 isozyme. This hypothesis has stimulated extensive drug development and hasty market introductions of many selective COX-2 inhibitors, or coxibs drugs. However, all of the marketed coxibs drugs except celecoxib (Celebrex), the first FDA-approved COX-2 drug in 1998, have been withdrawn from the market because of the potential risk of a cardiovascular event, including heart attack or stroke, especially in cardiac patients. Recent clinical trials have placed all NSAIDs under surveillance for their potential cardiovascular risk, thus the indiscriminate use of any NSAIDs including naproxen in cardiac patients should be avoided

Mechanism of Action and NSAID-Induced Side Effects

Cyclooxygenase (also known as prostaglandin endoperoxide synthase or PGH synthase) is the rate-limiting enzyme responsible for the biosynthesis of PGs. PGs are short-lived, lipidlike molecules that play a vital role in modulating many important physiological and pathophysiological functions including pain, inflammation, gastric acid secretion, wound healing, and renal function.

They are biosynthesized via a tissue-specific cyclooxygenase pathway (COX-1 or COX-2) either on an as-needed basis (mostly via the COX-1 isozyme) or via the induced and overexpressed COX-2 isozyme because of an injury, inflammation, or infection. Some of the salient features of the cyclooxygenase pathway involved in the biosynthesis of these PGs from arachidonic acid (AA) (5,8,11,14- eicosatetraenoic acid), a polyunsaturated fatty acid released from membrane phospholipids by the action of phospholipase A2, are depicted in Figure 24.14.

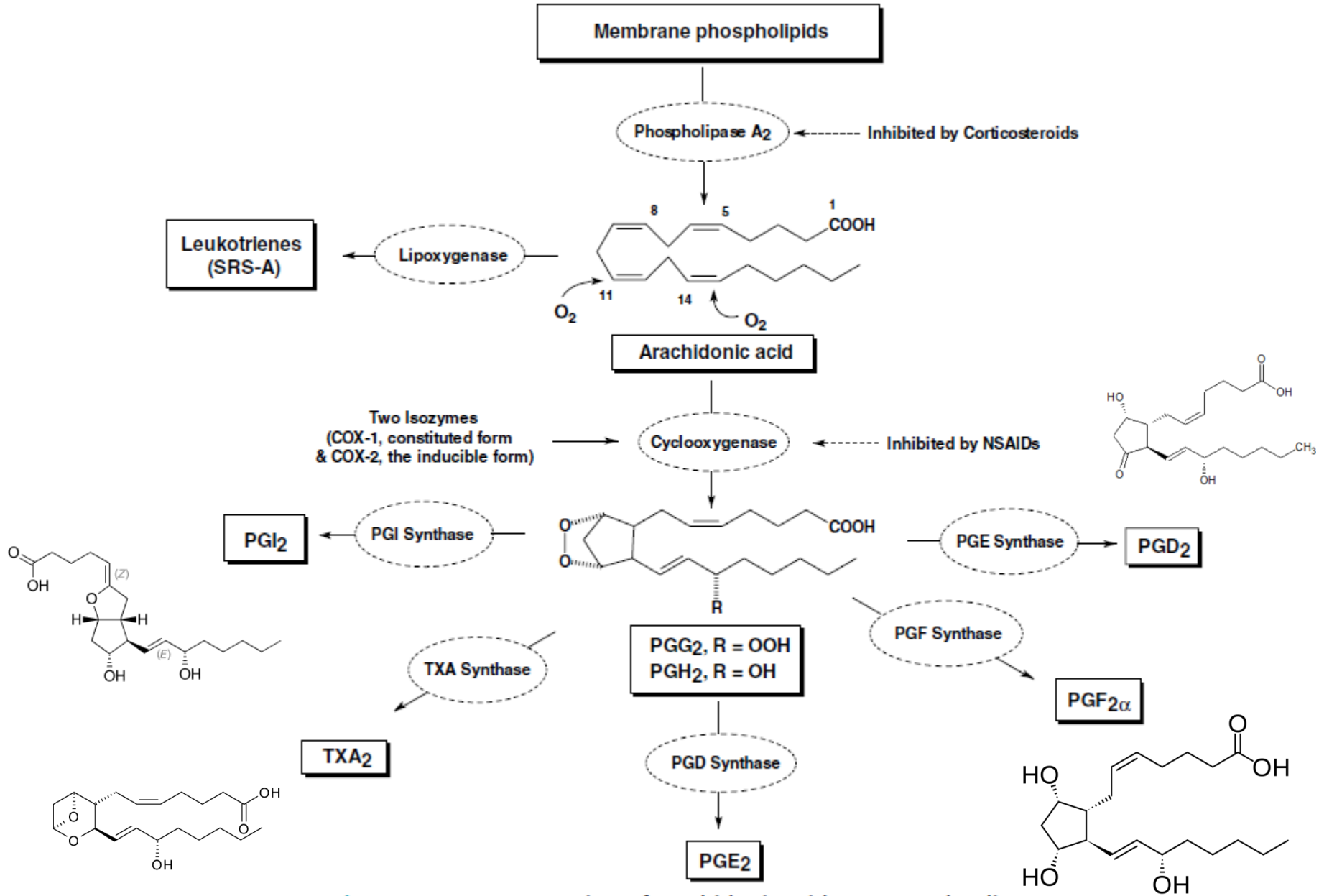


Figure 24.14 ● Conversion of arachidonic acid to prostaglandins.

As stated earlier, all classes of NSAIDs strongly inhibit prostaglandin synthesis in various tissues, especially at the site of the tissue damage or inflammation. This inhibition occurs at the stage of oxidative cyclization of AA, catalyzed by the rate-limiting enzyme, cyclooxygenase (or PGH synthase), to the hydroperoxy-endoperoxide (prostaglandin G2, PGG2) and its subsequent reduction to key intermediate, prostaglandin H2 (PGH2) needed for all prostaglandin biosynthesis. Blockade of PGH2 production, thus prevents its further conversion, by tissue-specific terminal prostaglandin synthases or isomerases, into different biologically active PGs

including PGE2, PGD2, PGF2, PGI2 (prostacyclin), and thromboxane A2 (TXA2) (Fig. 24.14). Among the PGs synthesized by the action of either COX-1 or COX-2 isozymes, PGI2 and PGE2 made at the site of injury (via COX-2 isozyme in the inflammatory cells such as monocytes and macrophages) and also in the brain, are known to play a dominant role in mediating inflammation and inducing hyperanalgesia. However, their synthesis in the GI tract (via COX-1 isozyme) and in the renal tubules (via COX-1 and COX-2 isozymes), is essential to provide cytoprotective action for restoring the integrity of the stomach lining and maintaining renal functions in an otherwise compromised kidney as a result of constant insult.

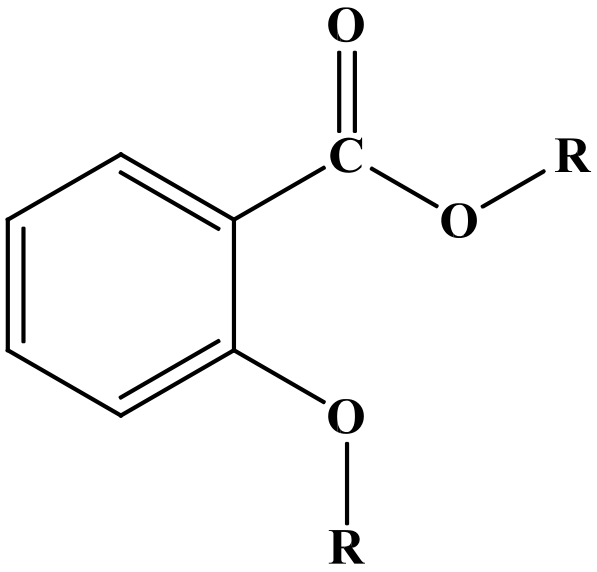
Thus, inhibition of PGE2 synthesis by the conventional NSAIDs in the parietal cells removes its ability to modulate histamine-mediated release of gastric acid from the parietal cells, whereas blockade of PGI2 and PGE2 synthesis in the epithelial cells in the stomach linings also prevents their action on the biosynthesis and release of bicarbonate and mucous gel desperately needed to repair damage resulting from erosion caused by gastric acid and other aggressive factors.

Thus, it should not be surprising to note that NSAID-induced gastric ulcers can only be prevented clinically with coadministration of misoprostol, a stable PGE analog, but not with either the histamine H2-antagonists, sucralfate, or any proton pump inhibitors such as omeprazole. Furthermore, maintenance of kidney function, especially in patients with congestive heart failure, liver cirrhosis, or renal insufficiency, is reliant on the action of PGI2 and PGE2 to restore normal renal blood flow. Thus, NSAID use (both COX-1 and COX-2 inhibitors) will increase the risk of renal ischemia and therefore is contraindicated in these patients.

Anti-inflammatory analgesics

These are non narcotic analgesics having an antipyretic and sometime anti-inflammatory effect. They act through inhibition of cyclooxygenase enzyme thereby inhibit prostaglandins PGs, thromboxine(TXA) synthesis which play an important role in inflammation. They have much lower analgesic activity in comparism with opoids (true- analgesics) and second of the principle feature distinguishing these minor analgesic from the narcotic analgesic are the low activity for a given dose and the fact that higher doses does not given any significant increase in effect.

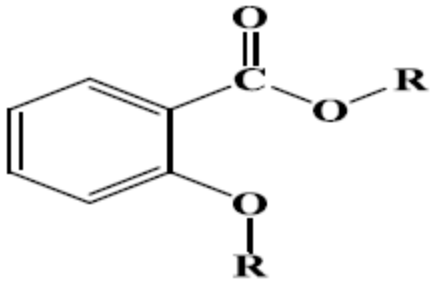
Salicylic acid derivatives



Mechanism of action of salicylate

Salicylates exert their antipyretic action in febrile patients by increasing heat elimination of the body via the mobilization of water and consequent dilution of the blood. This brings about perspiration, causing cutaneous dilatation, but this does not occur with normal temperatures. The antipyretic and analgesic actions are believed to occur in the hypothalamic area of the brain.

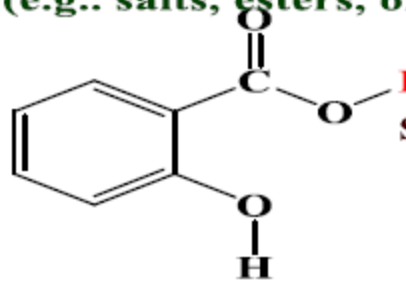
Since it inhibit the thromboxane (TXA) synthesis, it exert an antithrombotic action. Co administration with para aminobenzoic acid (PABA), reduce metabolism and excretion of salicylate so enhance their effect.



Salicylic acid derivatives

Type I

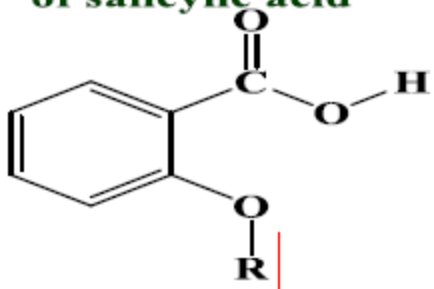
formed by modifying the carboxyl group (e.g.. salts, esters, or amides)



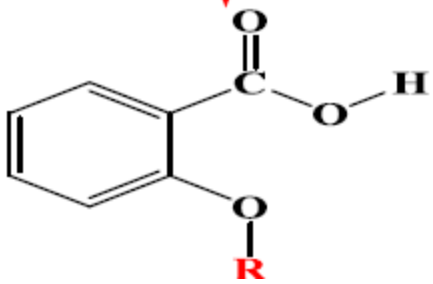
Salts, ester, amide

Type II

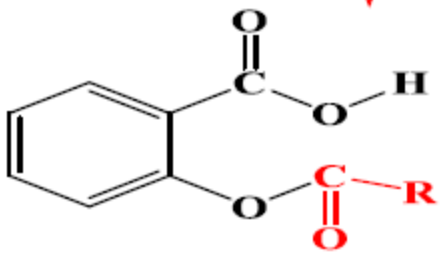
represents those that are derived by substitution on the hydroxyl group of salicylic acid



IIa



IIb



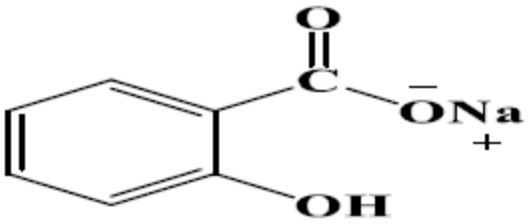
The derivatives of salicylic acid were introduced in an attempt to prevent the gastric
symptoms and the undesirable taste inherent in the common salts of salicylic acid. Most hydrolysis of type I take place in the intestine, and most of the type II compounds are absorbed unchanged into the bloodstream.

Compounds of type I

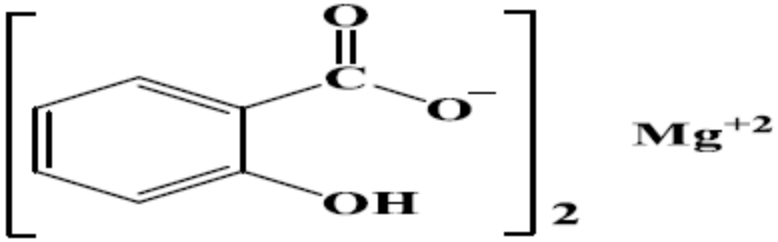
The alkyl and aryl esters of salicylic acid (type I) are used externally, primarily as counterirritants, where most of them are well absorbed through the skin.This type of compound have little value as an analgesic.

Example-:

A few inorganic salicylates ion used internally when the effect of the salicylate ion is Intended.

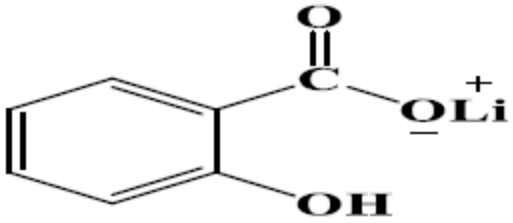


Sodium salicylate

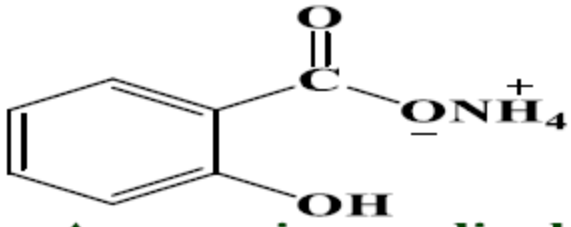


Magnesium salicylate

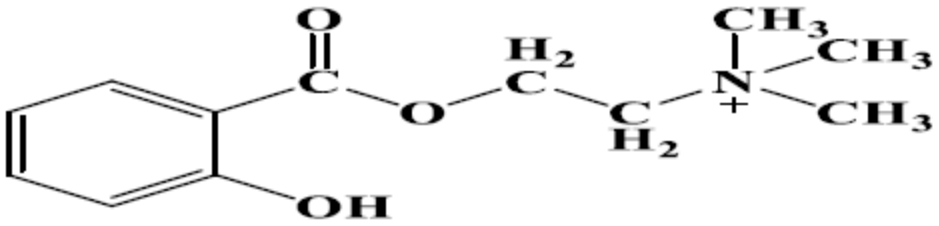
It is a sodium-tree salicylate preparation for use when sodium intake is restricted



lithium salicylate



Ammonium salicylate



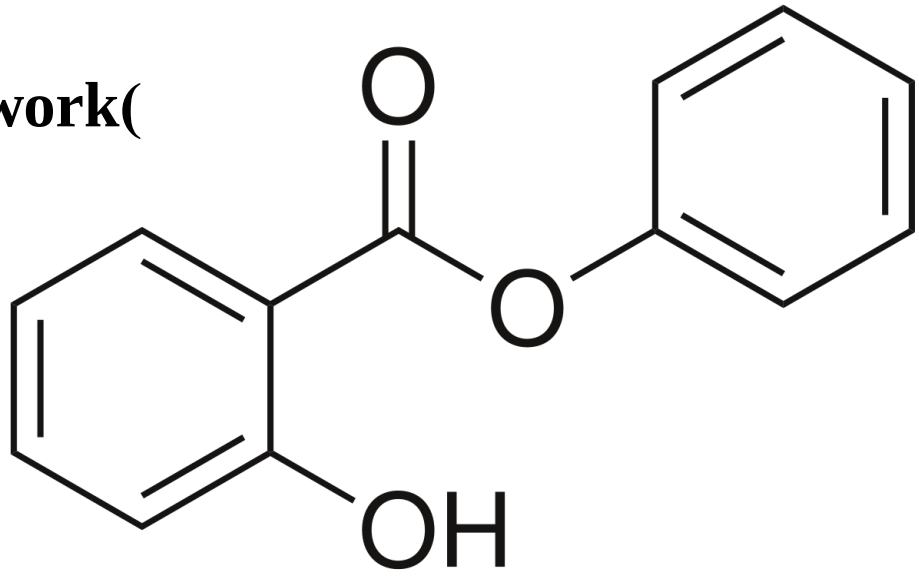
Choline salicylate

Salol princiole

Salol principle (Nencki :(1886

In salol, two toxic substances (phenol and salicylic acid) were combined into an ester that taken internally, will slowly hydrolyzes in the intestine to give the antiseptic action of its components. This type of ester is referred to as a full salol or true salol when both components of the ester are active compounds.

a. **Examples (structures homework(**



a. **Guaiacol benzoate.**
b. **β-naphthol benzoate.**
c. **salol.**

The salol principle can be applied to esters in which only the alcohol or the acid is the toxic, active or corrosive portion; this type is called a partial salol.

Examples

a. Partial salols that contain an active acid are ethyl salicylate and methyl salicylate.

b. Examples of partial salols that contain an active phenol are:- (structures homework)

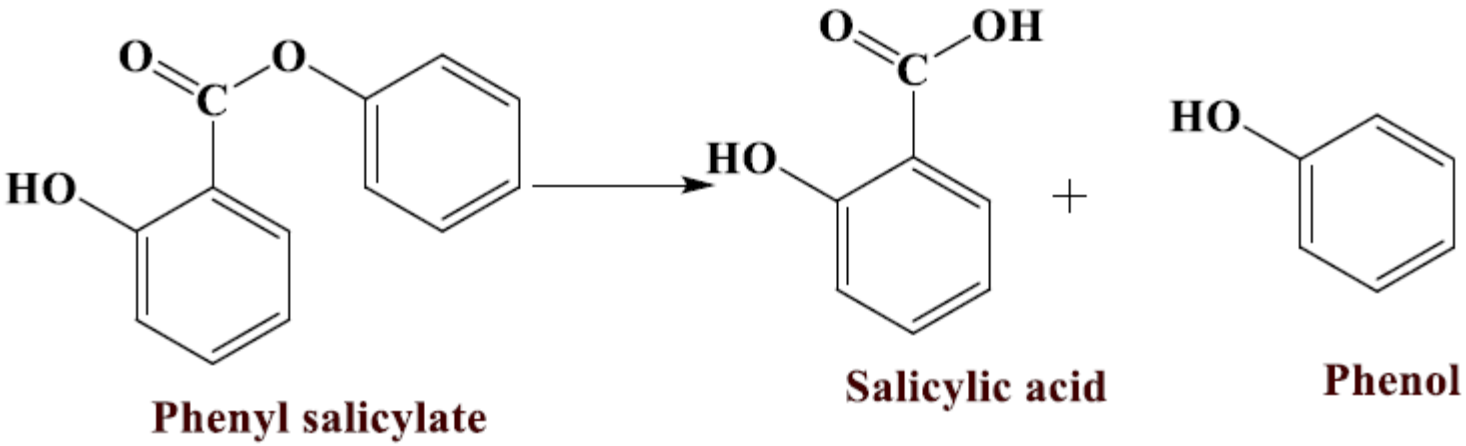
-1 creosote carbonate.

-2 thymol carbonate.

-3guaiacol carbonate.

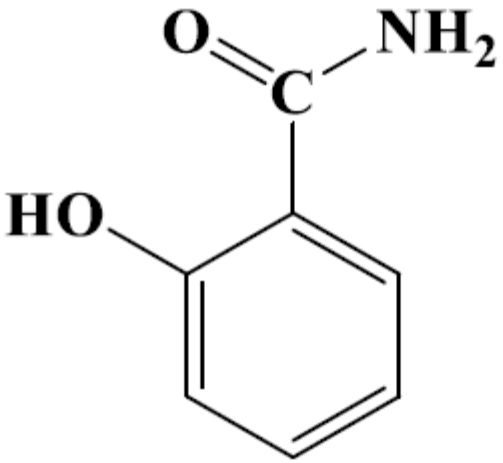
Salol have less therapeutic application

•Phenyl Salicylate



Salol is insoluble in gastric juice but is slowly hydrolyzed in the intestine into phenol and salicylic acid. So was used as an enteric coating for tablets and capsules, but not used now. It has also been used externally as a sun filter (10% ointment) for sunburn prevention (Rayderm).

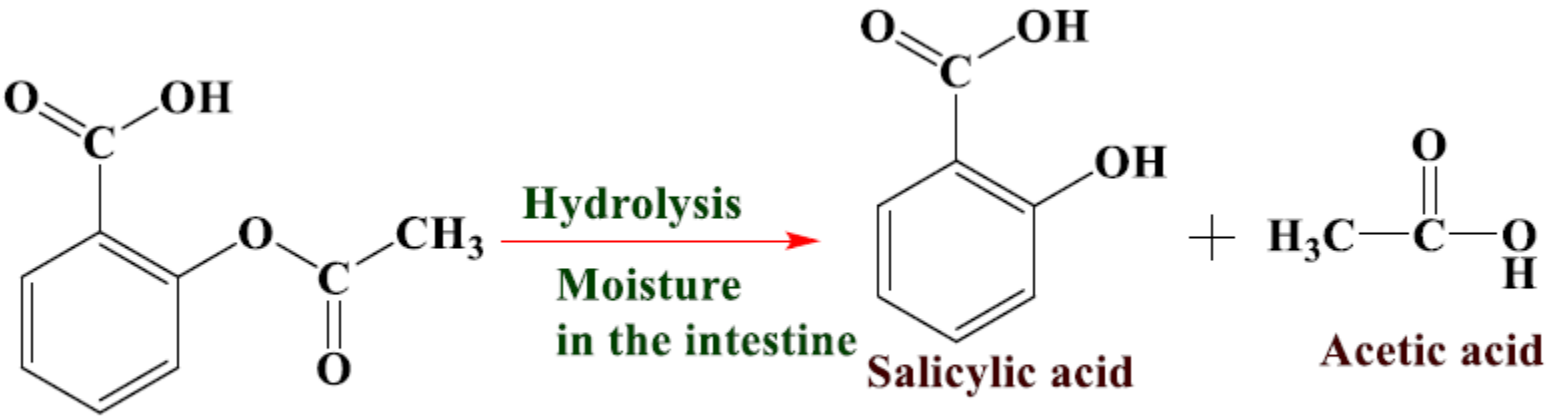
Salicylamide•



Salicylamide
o-hydroxybenzamide

It exerts moderately quicker and deeper analgesic effect than does aspirin, but has little unwanted side effect.

Aspirin, acetylsalicylic acid.



Aspirin
acetylsalicylic acid

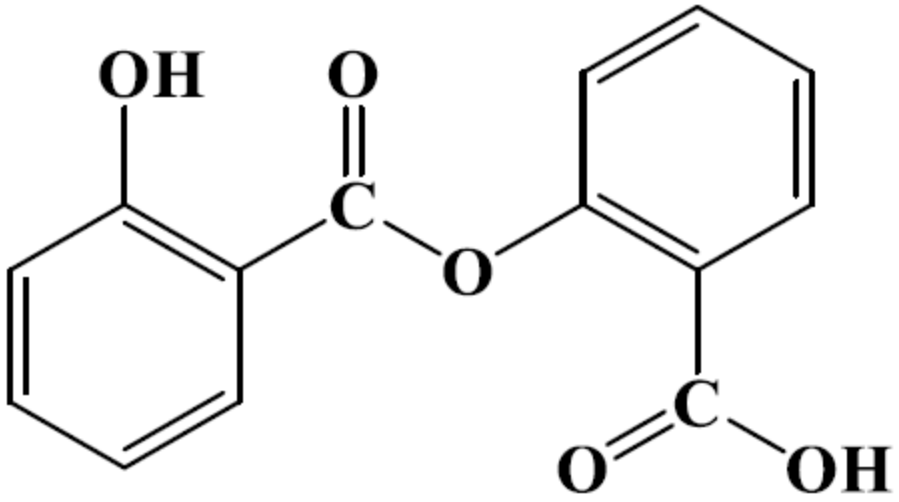
S/E of aspirin

- Cause gastric irritation due to-:
- Gastric mucosal irritation of aspirin to salicylic acid formation.
- The natural acidity of aspirin.
- The adhesion of undissolved aspirin to the mucosa.
- Asthma.
- Urticaria.

Uses of aspirin:- Antipyretic, analgesic and antirheumatic.

Salsalate (salicylsalicylic acid).

It is the ester formed between two salicylic acid molecules to which it is hydrolyzed following absorption.

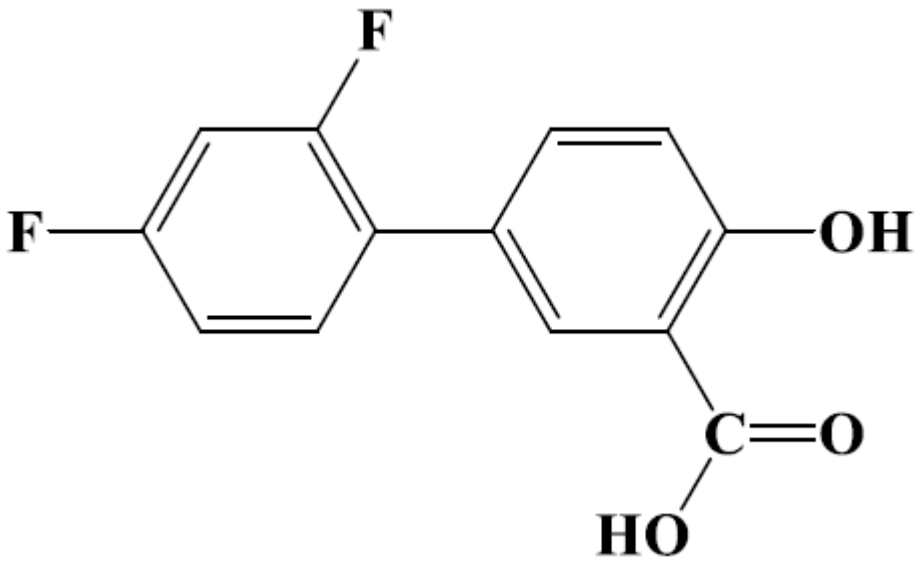


Salsalate
Salicylsalicylic acid

It causes less gastric upset than aspirin because is relatively insoluble in the stomach and is not absorbed until it reaches the small intestine.

Diflunisal

It is more potent, longer acting, and had less gastric irritation.

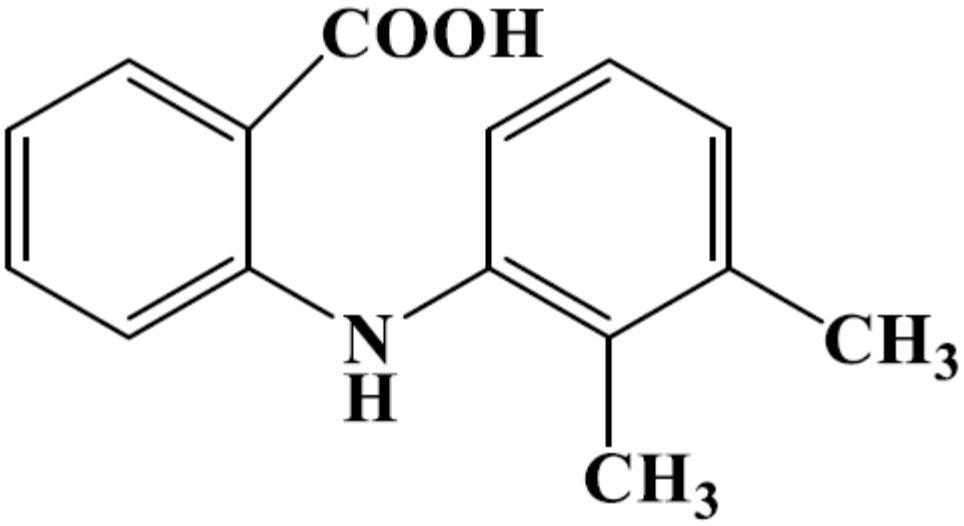


5-(2,4-difluorophenyl)salicylic acid

used for treatment RA and OA

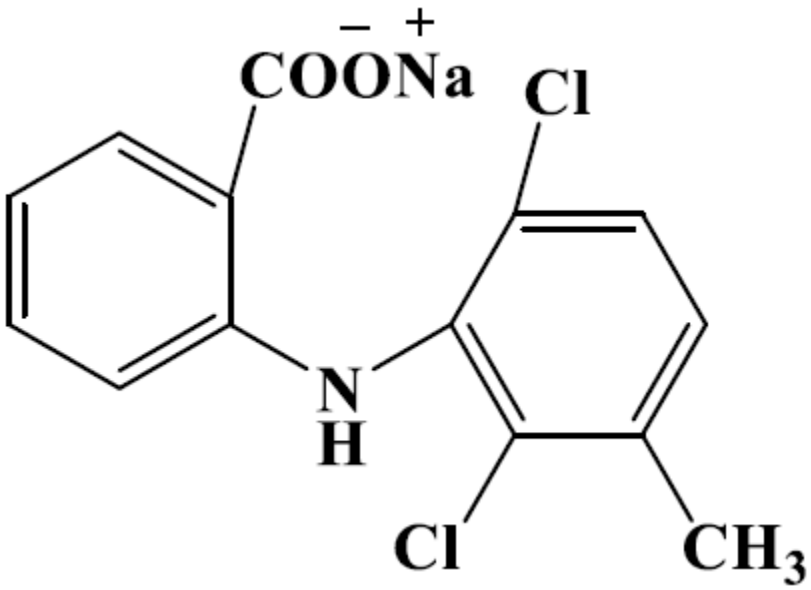
N-Arylanthranilic Acids

- **Mefenamic Acid**



N-(2,3-xylyl) anthranilic acid
used as antipyretic with low antiinflammatory

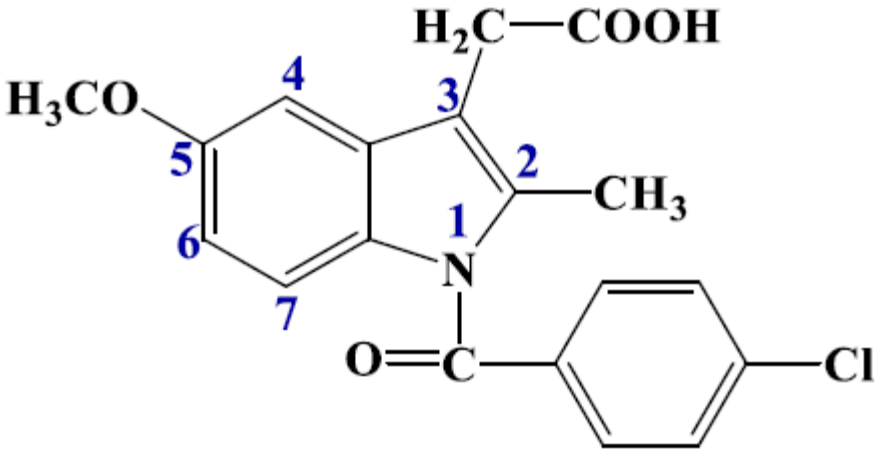
Meclofenamate Sodium•



N-(2,6-dichloro-m-tolyl) anthranilate
used in the treatment of acut and chronic RA

Arylacetic acid derivatives

•Indomethacin

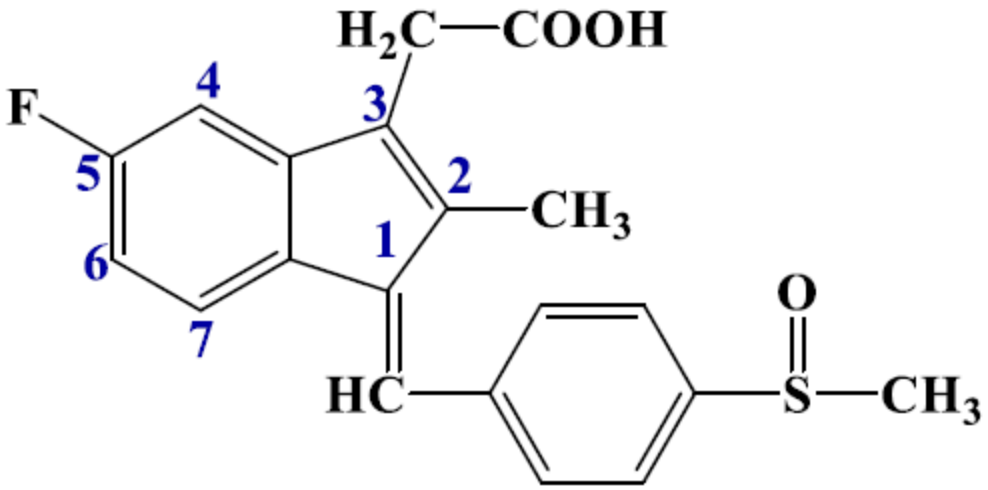


I -(*p*-chlorobenzoyl)-5-methoxy-2-methylindole-3-acctic acid

Uses:- **it has been widely used as an anti-inflammatory analgesic in RA, spondylitis, and osteoarthritis(OA), and to a lesser extent in gout.**

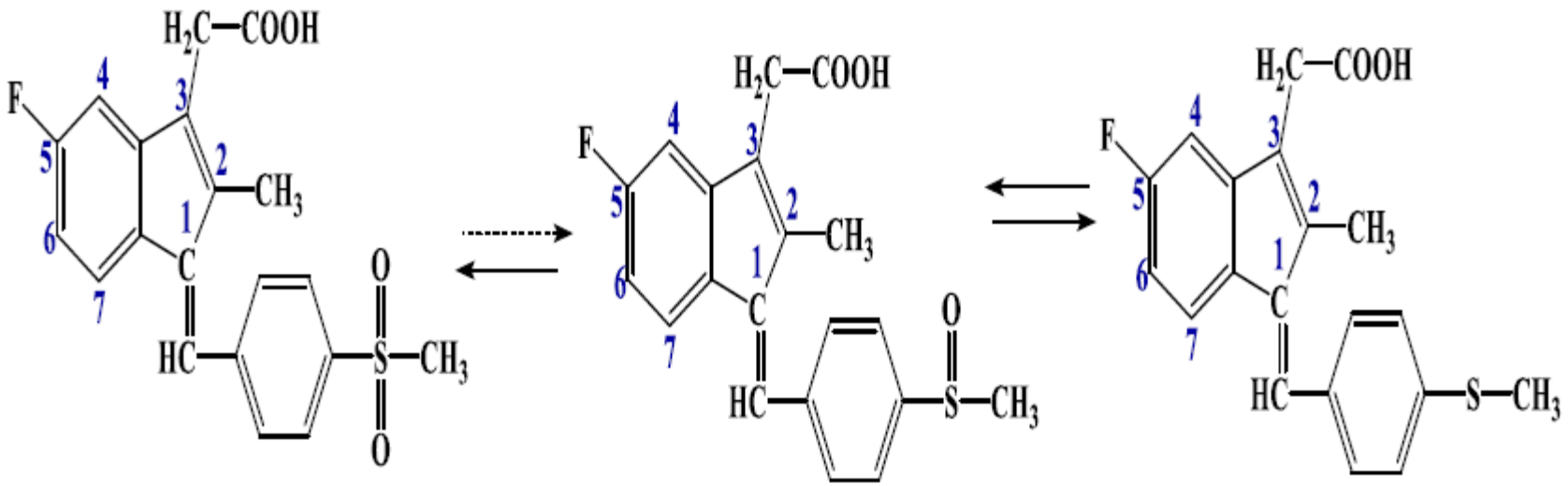
S/E:-The most frequent side effects are gastric distress and headache. It has also been associated with peptic ulceration, blood disorders, and possible deaths. The side effects appear to be dose related and sometimes can be minimized by reducing the dose.

Sulindac



(Z)-5-fluoro-2-methyl-1-[[*p*-(methylsulfinyl)phenyl]methylene]-1H-indene-3-acetic acid

Undergoes reversible metabolism as follow-:



inactive
sulfone

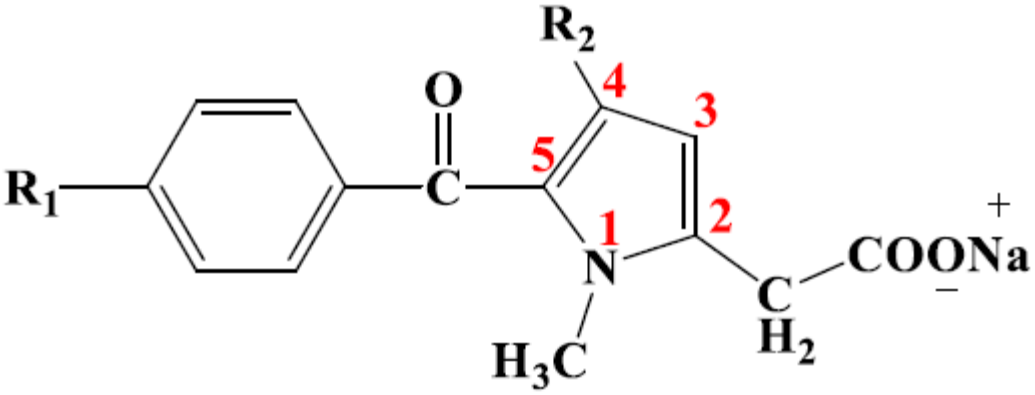
(inactive) sulfoxide
used as prodrug to reducing GI irritation

active (sulfide)
cause as gastric irritation
so used as sulfoxide prodrug

Sulindac have long half life due to extensive entrohepatic recirculation.

Uses:- Sulindac is recommended for RA, OA, and ankylosing spondylitis in a -150to 200-mg dose, twice daily.

Tolmetin Sodium•



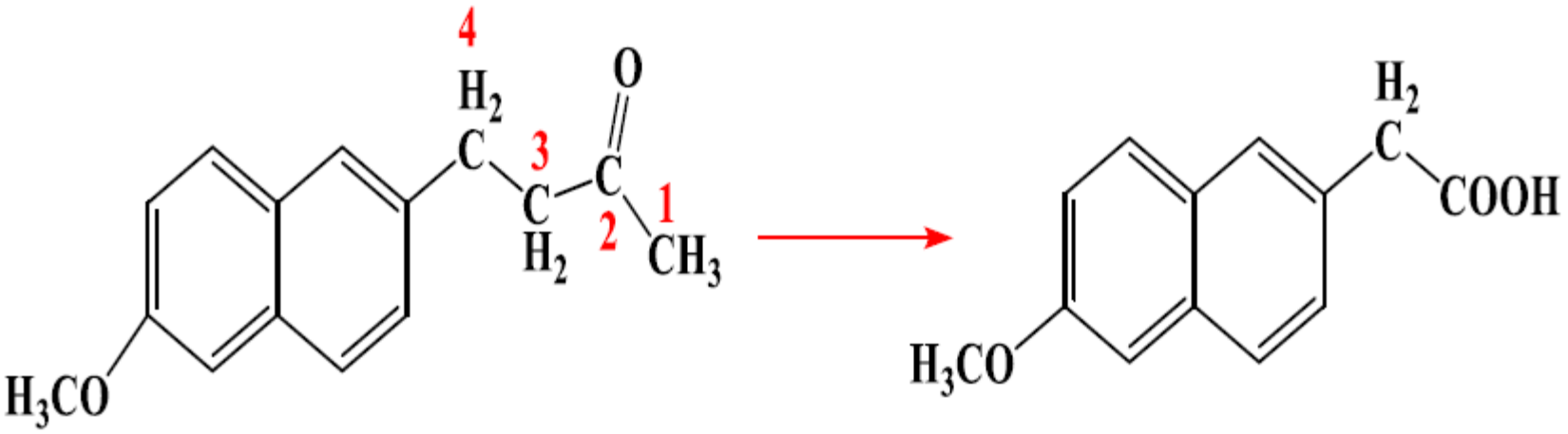
R1= CH_3, R_2=H= tolmetin

1-methyl-5(*p*-toluoyl)pyrrole-2-acetate dihydrate sodium

R1= Cl R_2=CH_3= zomepirac

Uses:- It is recommended use in the management of acute and chronic RA. It similar, but less frequent, adverse effects with aspirin.

Nabumetone•



4-(6-methoxy-2-naphthyl)-2-butanone

6-methoxy-2-naphthylacetic acid

It serves as a prodrug to its active metabolite. -6 methoxy-2-naphthylacetic acid. Like the other arylacetic acid drugs, it is used in short- or long-term management of RA and OA.