LEC.5 4 STAG

Chemistry II Organic Pharmaceutical

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NSAIDs

NSAIDs:

Aspirin & Acetaminophen,two of the oldest pain medications that used for Rheumatic Arthritis(RA) & other degenerative inflammatory joint diseases.

Mechanism of action of NSAIDs include :
Inhibiting two isoforms of cyclooxygenase (COX-1,the constitutive isozyme & COX-2 ,the inducible isozyme),which is rate –limiting enzyme responsible for the biosynthesis of the proinflammatory PGs and thereby modulating pain transmission, attenuating inflammation and reducing fever.

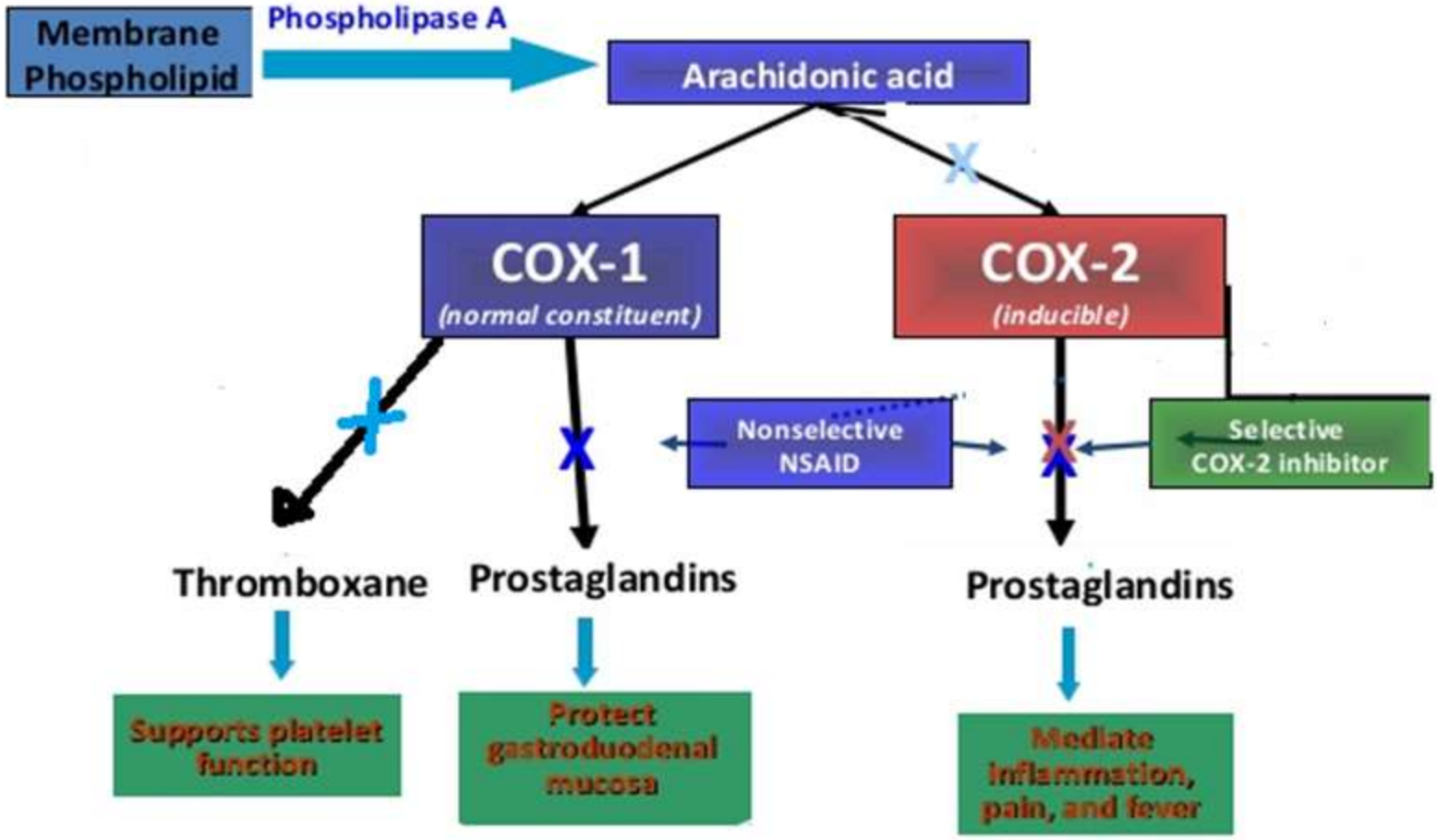
NSAIDs are also non narcotic analgesics having an antipyretic & sometime anti-inflamatory effects.

They act through inhibition of COX_{ase} ,thereby inhibit PGs & THX synthesis which play an important role in inflammation.

They have much lower analgesic in comparision with opioid (true analgesic)

& 2nd of princible features distingwishing these minor analgesic from the narcotic analgesics " low activity for a given dose & the fact that higher doses does not give any significant increase in effect.

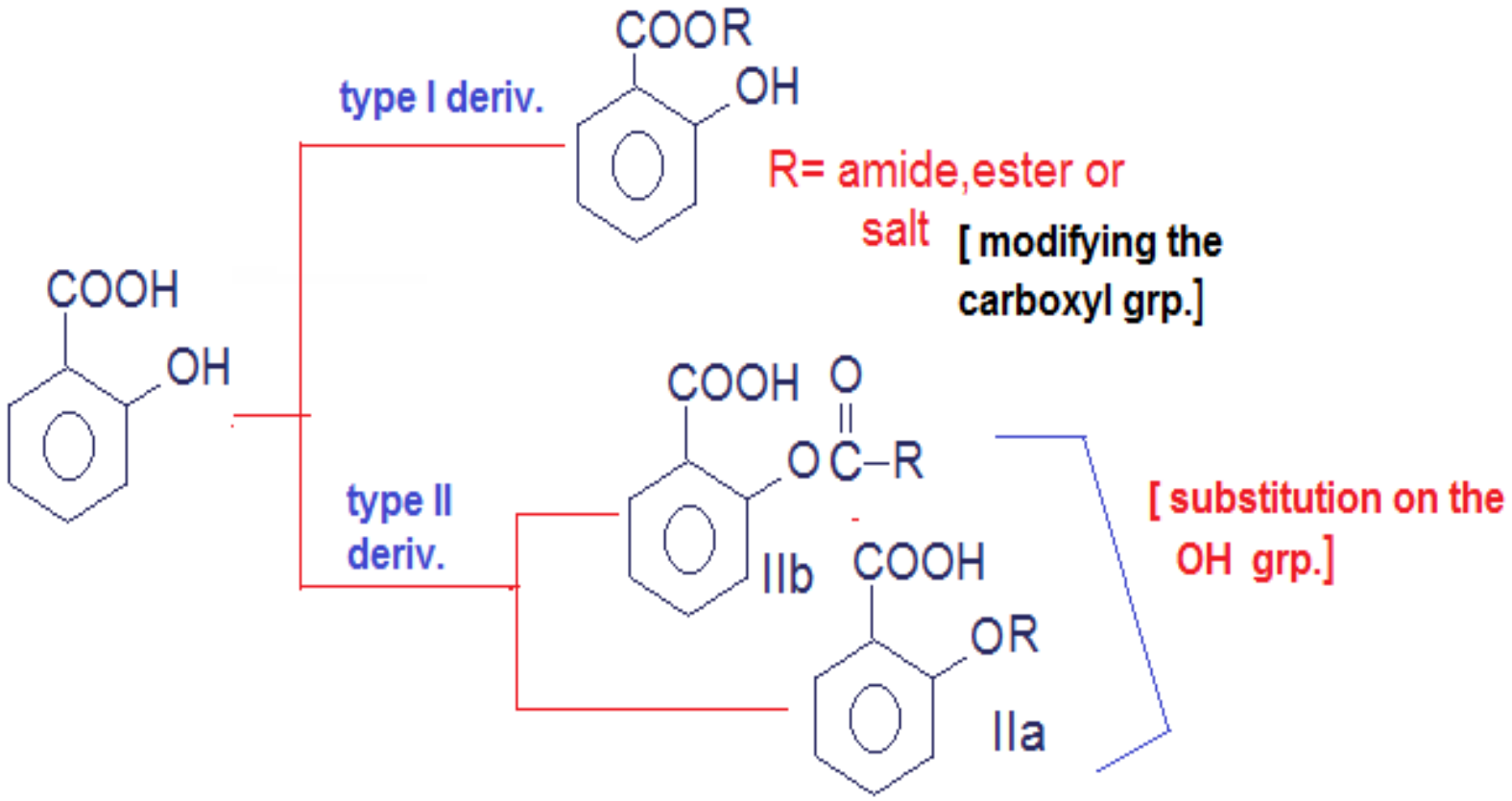
Proposed Mechanism: COX-1, COX-2



Chemical class of NSAIDs

1-Salicylate

two type



Salicylate exert their antipyretic effect infebrile patients by increasing heat elemination of the body through the mobilization of H_2O & consequent dilution of the blood.

This brings about prespiration,causing cutaneous dilation,but this does not occur in normal Temp. the antipyretic & analgesic actions occur in the hypothalamic area of brain.

Since it inhibit thromboxane synthesis,it exert an antithrombotic action.

Co-adminisration with p-aminobenzoic acid reduce or inhibition the metabolism & excretion of the salicylate in the urea ,so enhance their effect.

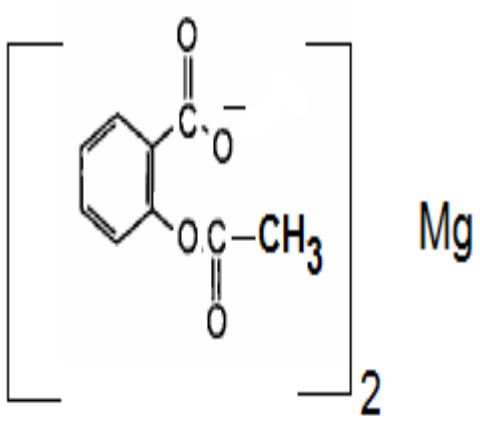
Compouds of type I:
type I derivative of SA to prevent the gastric irritation.
alkyl & aryl esters of SA used externally as counter irritant, where most of them are absorbed through the skin.
[there are not suitable to be used as analgesic (a little value as analgesic) & they cause extreme GI irritation.

E.g. choline salicylate, Na salicylate ,Na thiosalicylate ,Mg salicylate & other as Li,ammonium,strontium salts of SA.

Mg Salicylate :

it is claimed to produce less GI irritation.

It use when Na intake is restricted.



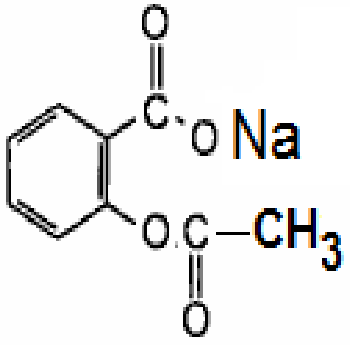
Na salicylate:

SA & $NaHCO_3$ = Na Salicylate

** even though not as potent as Asp.

for pain relief, also has less GI irritation

useful for patients who are hypersensitivity to Asp.

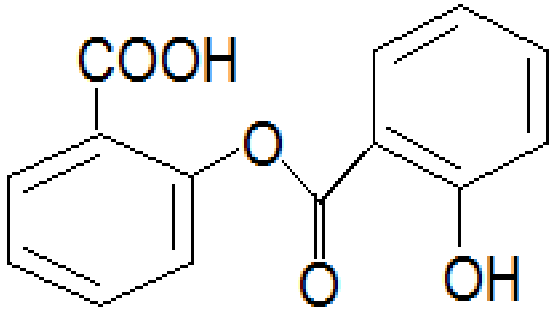


Salsalate:

is salicylsalicylic acid,is ester formed (.) 2 SA molecules ,it rapidly hydrolyzed to SA following its absorption.

It causes less gastric irritation than Asp.,

because it is relatively insoluble in the stomach & is not absorbed until it reaches the small intestine.

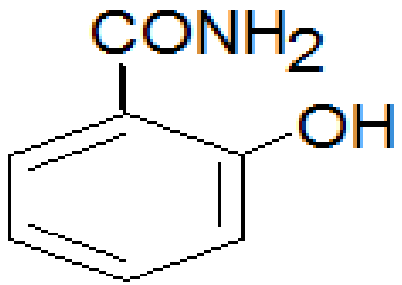


Salicylamide:

O-hydroxybenzamide ,is derivative of SA that is fairly stable to heat, light & moisture.

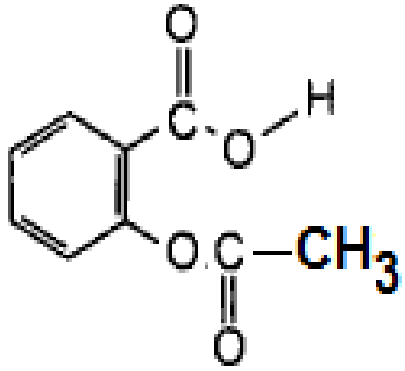
** it exerts a moderately quicker & deeper analgesic effect than Asp. b- of quicker CNS penetration.

** it has a lower analgesic & antipyretic effect than that of Asp.



Aspirin:

acetylsalicyclic Acid,kept under dry condition(slowly decomposed AA & SA)



Buffer w¯ Asp.

1-Na HCO_3 2-Al glycinate 3-Na citrate

4- $Al(OH)_3$ or 5-Mg trisilicate

this to counteract Asp. Acidic property

The more stable, non irritant Ca acetylsalicylate is formed & the glutamate portion(glutamic acid) maintains a pH of 3.5 to 5.
practically all salt of Asp.,expect those Al & Ca are unstable for pharmaceutical use.

These deriv. to have fewer undesirable S/E & induce analgesia faster than Asp.

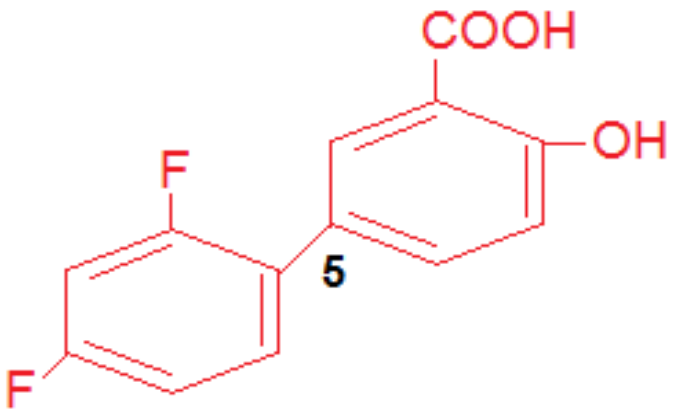
S/E: ulcer, stomach bleeding & tinnitus

Diflunisal:

is a longer acting & more potent drug than Asp. b̲ of its hydrophobic 2,4-difluorophenyl grp. attached to the 5-position of SA.

** with less GI complication than Asp.

** used for ttting mild to moderate postoperative pain as well as RA & OA.



Other salts salicylic Acid:

1- Na thiosalicylate is the sulfer or thio analog of Na salicylate

** it is more soluble & better absorbed ,thus allowing lower dosage .

* it is recommended for gout,rheumatic fever & muscular pains ,but it is available only for injection.

2-The conventional nonselective COX-Is:

Aryl & Heteroaryl acetic Acid:

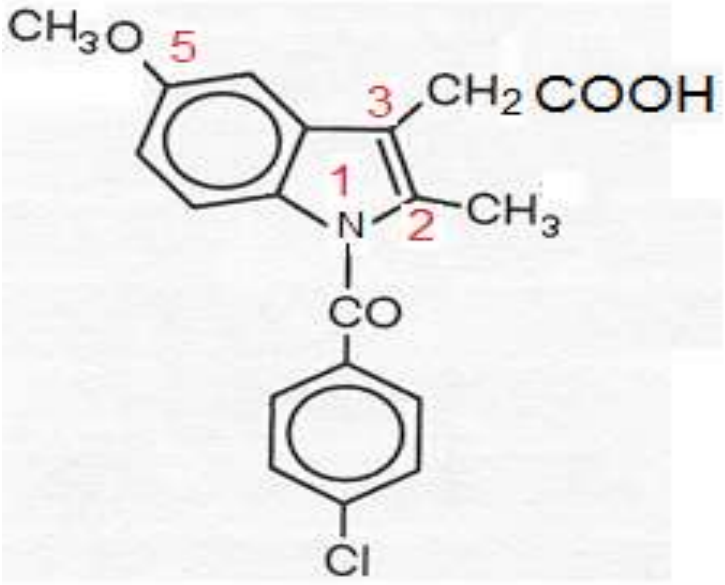
** this grp.,show high analgesic potency in addition to their potent anti-inflammatory activity, needed for treating inflammatory disease.

Indomethacin:

1-(p-chlorobenzoyl)-5-methoxy-2-methylindole-3-acetic acid.

* used as an analgesic to relieve inflammatory pain associated with RA,OA & ankylosing spondylitis & to a lesser extent in gout.

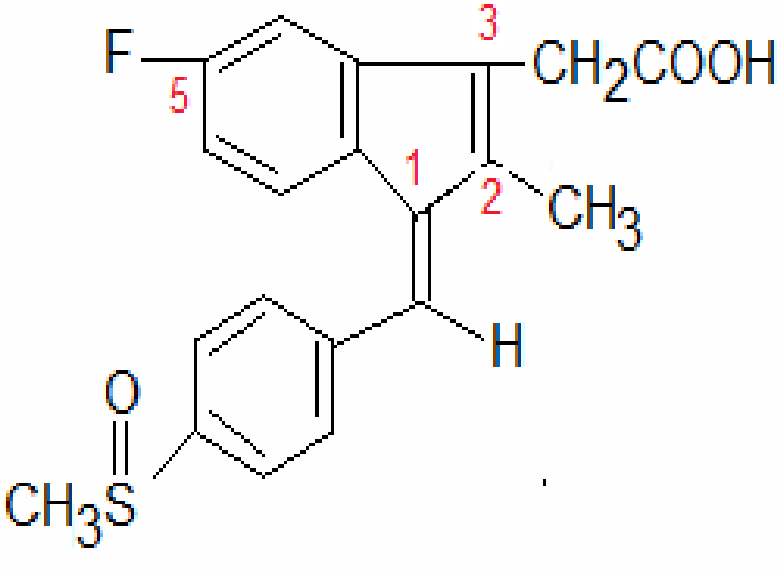
** it´s use is often limited because of frequent GI distress & headache.



Sulindac:

(z)-5-fluoro-2-methyl-1-([p-(methyl sulfinyl) phenyl]-1H-indene-3-acetic acid.

* is a prodrug that contain sulfoxide moiety because it undergoes in vivo reduction by the hepatic enzymes into active metabolite.

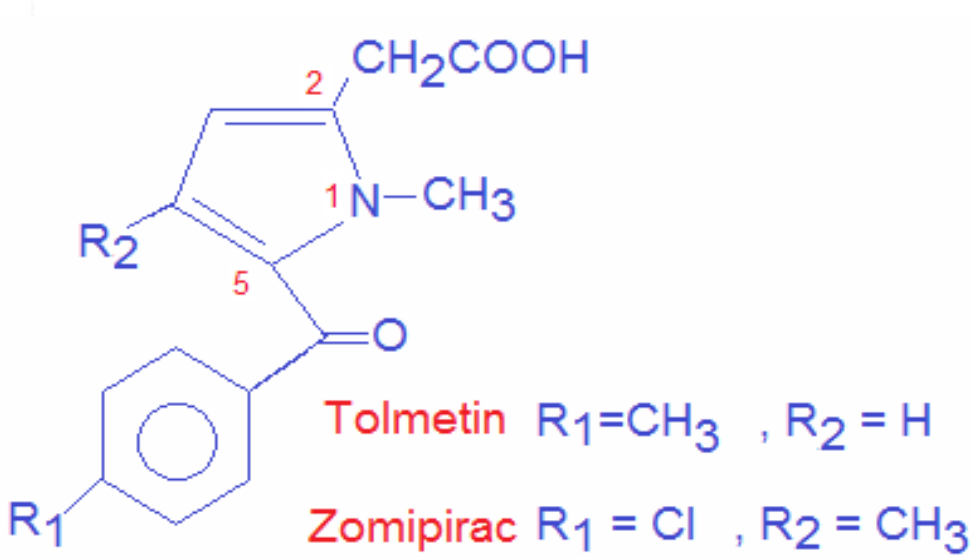


methylsulfide that exhibits potent & nonselective cox inhibition similar to indomethacin.

*** it recommended for RA,OA & ankylosing spondylitis.

Tolmetin:

tolmetin is an arylacetic acid deriv. with a pyrrole as the aryl grp.,this drug is well absorbed.



1-methyl-5-(p-touayl)pyrrole-2-acetic acid

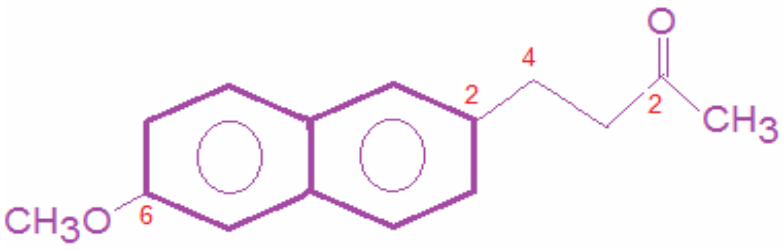
** it recommended for use in the mangement of a cute & chronic RA.

** tolmetin & especially its closely related drug,zomipirac can produce a rare but fatal anaphylactic rx. b/c of irreversible binding of their unstable acyl glucuronides.

Nabumetone:

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

is a non acidic NSAIDs prodrug, but ketone derivative, is classified as an aryl acetic acid, b/c it undergoes rapid hepatic metabolism to its active metabolite, 6-methoxy-2-naphthylacetic acid.



It used in short or long term mangment of RA & OA.

** Being nonacidic ,it does not produce significant 1ry insult to the GI mucosa lining & also has no effect on PG synthesis in gastric mucosa ,thus producing minimum secondry GI damage wn compared with other conventional NSAIDs.

Etodolac:

COX-2 selective NSAIDs drug, is possesses an indole ring as the aryl portion of this grp. Of NSAIDs.

** indicated for short- and long-term management of pain & OA.