NON-NARCOTIC ANALGESICS

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ANALGESICS

- "A drug that selectively relieves pain by acting in CNS or on peripheral pain mechanism without significantly altering consciousness."
- Analgesic are divided into two categories:-

1. Opioid Analgesics

- Narcotic/Morphine like analgesic

2. Non opioid Analgesics

-NSAIDS/Non narcotic, aspirin like analgesics

INTRODUCTION

- Non-steroidal anti-inflammatory drugs

-non narcotic,nonopioid or aspirin like analgesics

- ACTIONS-
  - analgesic
  - antipyretic
  - anti-inflammatory

NSAIDS is a group of drugs which include

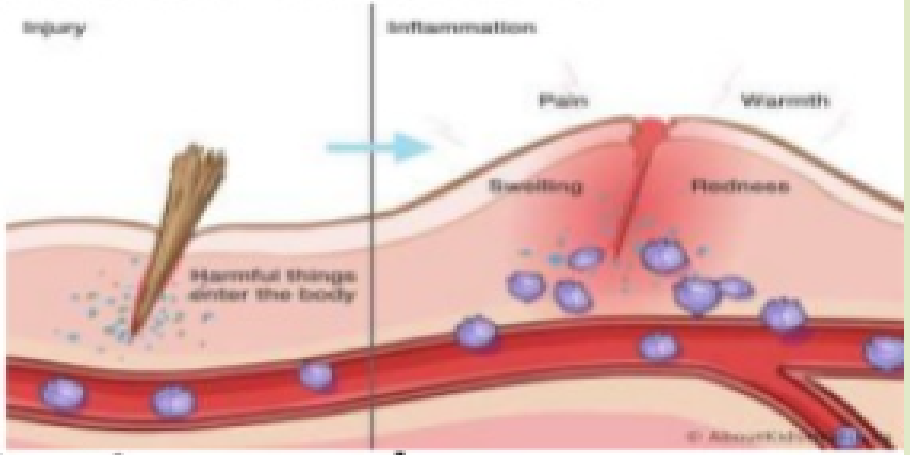
Antipyretics	• Drug curing fever.
Analgesics	• Drugs curing pain.
Anti-inflammatory	• Drugs curing inflammation.

Introduction of NSAIDs

- The drugs which comes under NSAIDs category have analgesic, antipyretic and anti-inflammatory action.
- These are the drugs without steroidal ring.
- NSAIDs don't depress CNS, don't produce physical dependence, have no abuse liability and are weaker analgesic instead morphine shows all characteristics.
- It's also known as Non-narcotic, non-opoids or aspirin like analgesic.
- Mainly NSAIDs act on peripheral pain mechanisms, but also in the CNS to raise pain threshold.

NSAIDs

- It produces anti-inflammatory action means it acts against the inflammation.



What's Inflammation

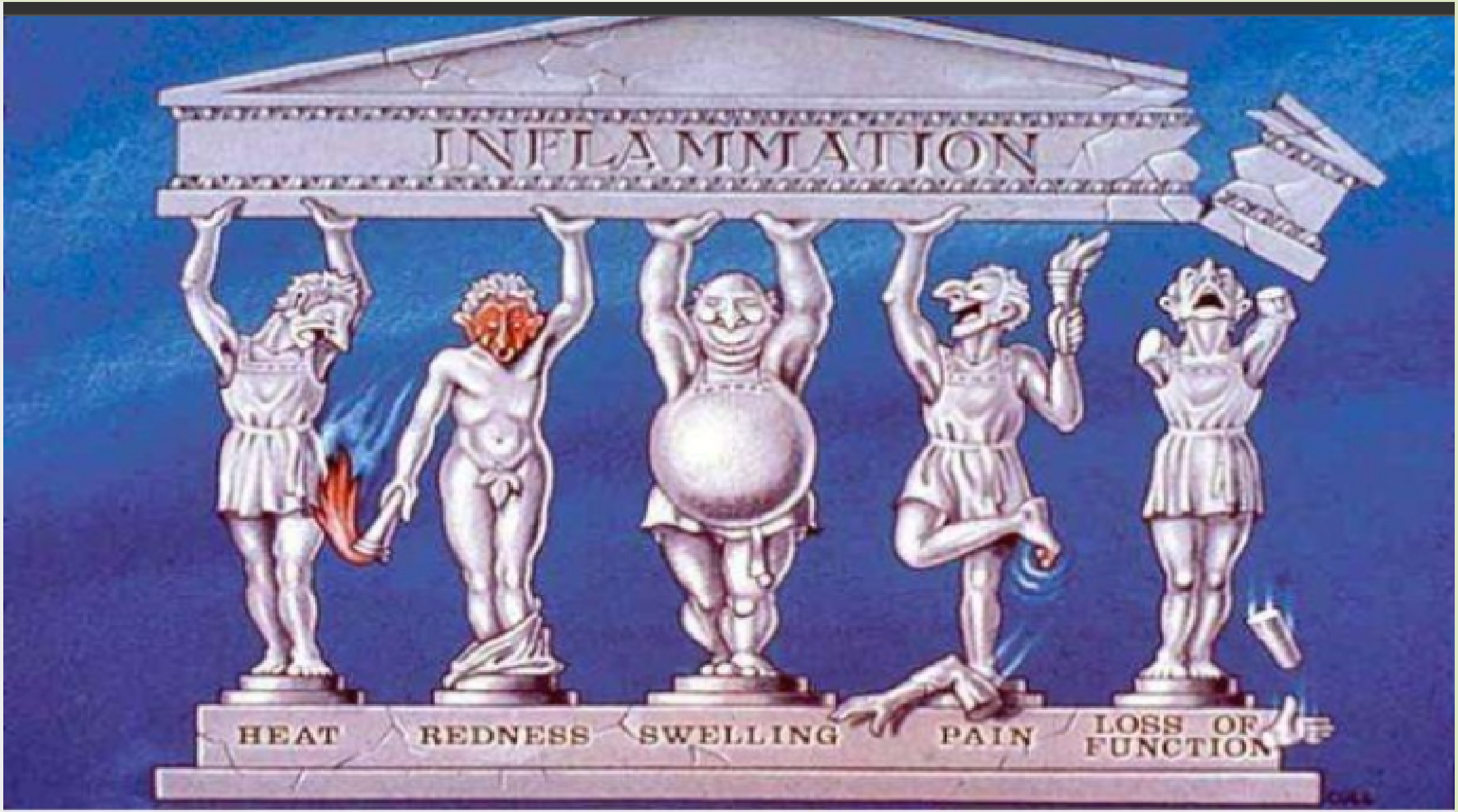
- Inflammation is derived from Latin word *inflammatio which means to set on fire.*
- It's a complex biological responses of body tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.
- this complex process involvesseveral immune cells, blood vessels and molecular mediators.

Importance of Inflammation

- Inflammation occurs in body to eliminate the initial causes of cell injury, clear out necrotic cells and tissue damage.

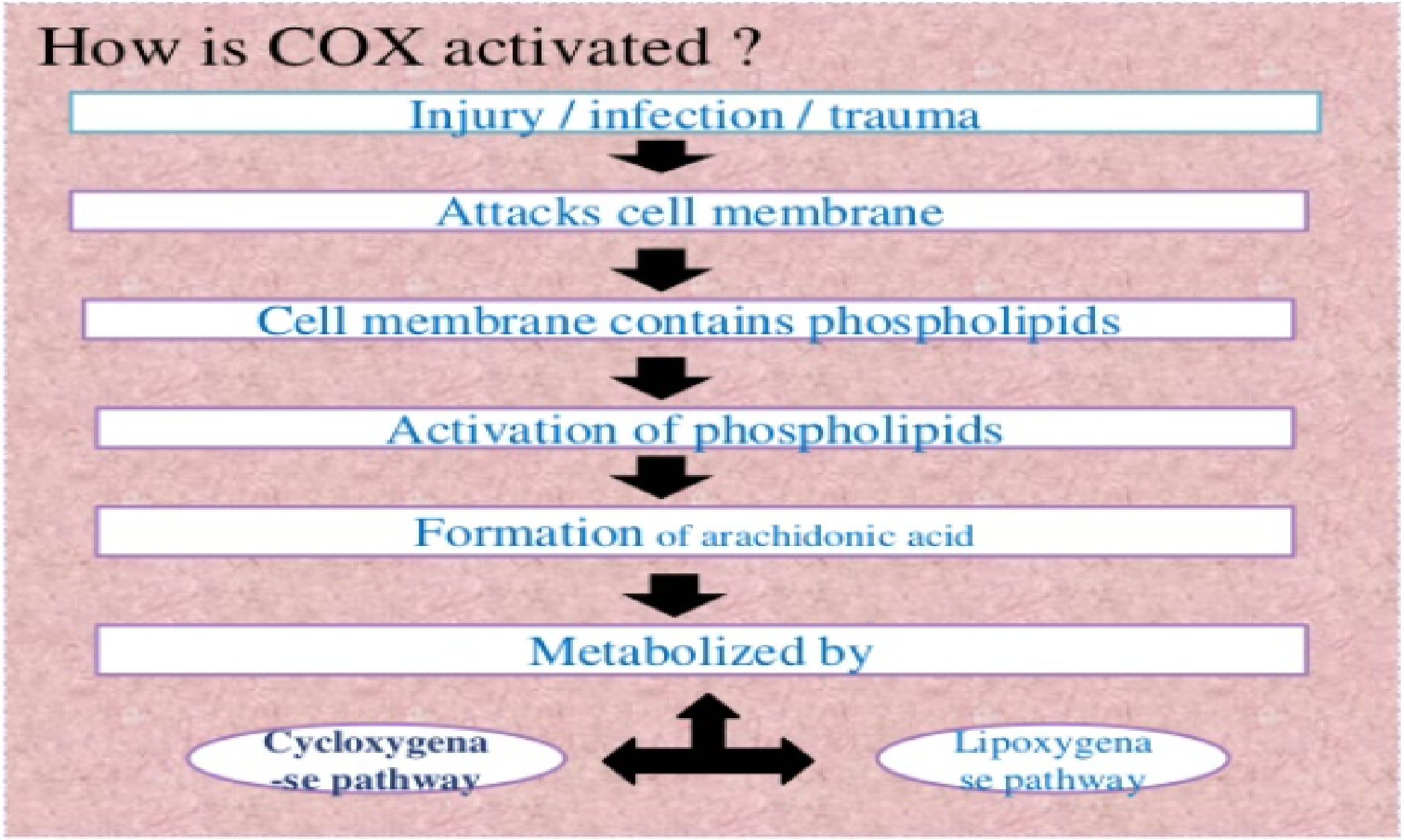
5 Signs of Inflammation

Latin Word	Meaning	Due to
Calor	Heat	Local vessel dilation
Dolor	Pain	Local release of enzymes & increased tissue pressure
Rubor	Redness	Local vessel dilation
Tumor	Swelling	Influx of plasma proteins & phagocytes cells into the tissue spaces
Functio laesa	Loss of functions	Lack of oxygen or nutrients, and insufficient blood flow to the area

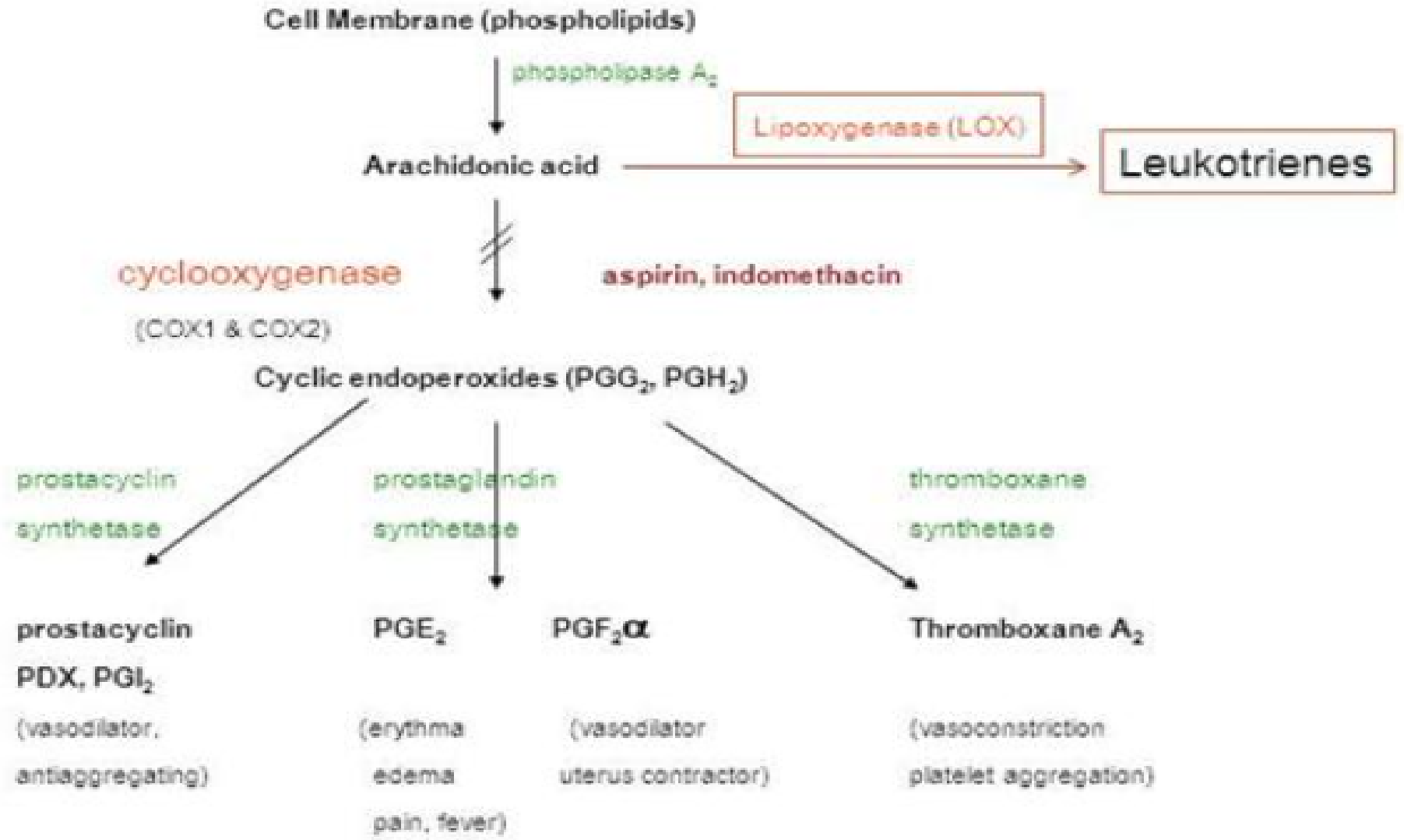


Calor *Rubor* Tumor *Dolor* *Functio laesa*

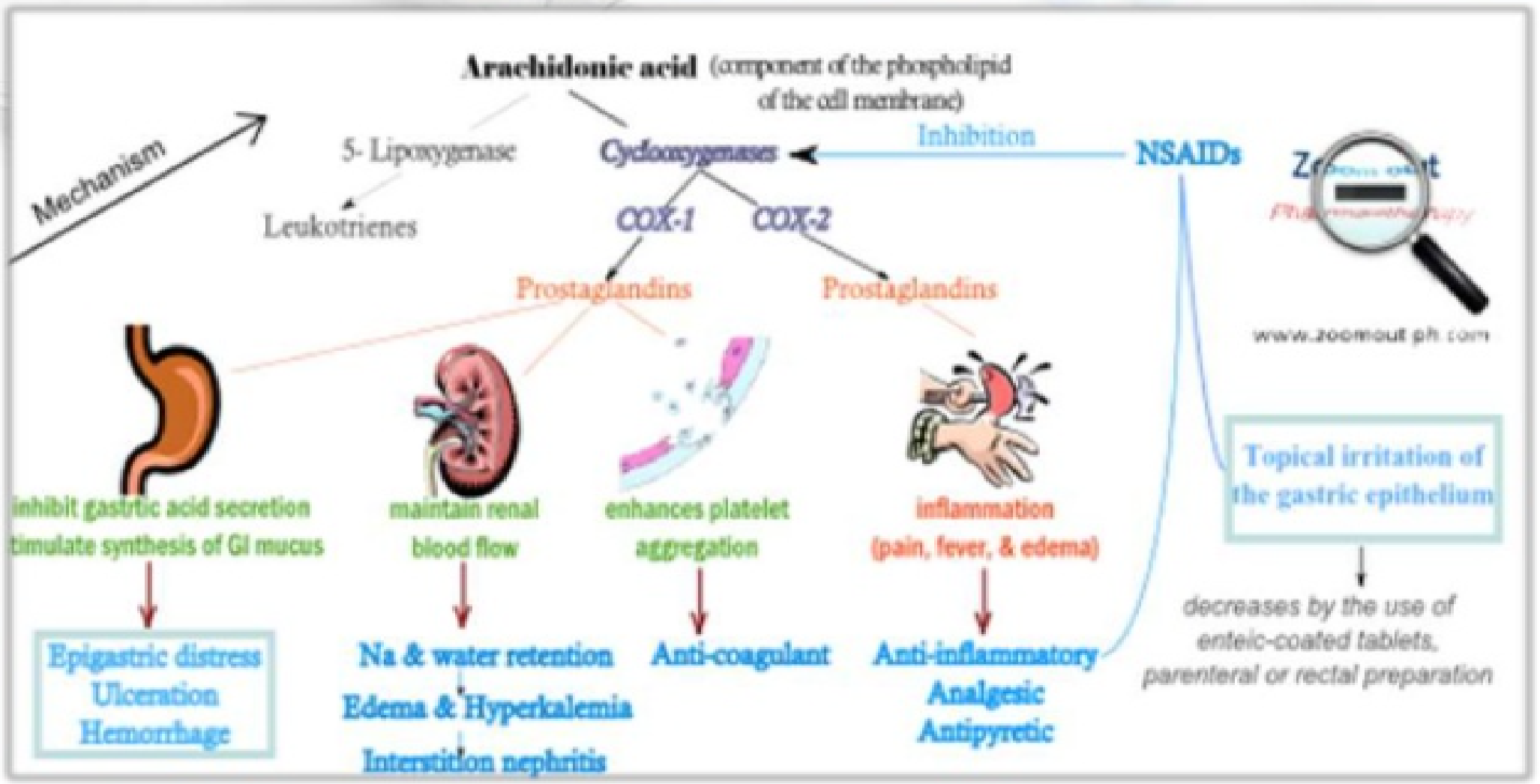
Mode of action: NSAIDs inhibit cycloxygenase (COX), the enzyme that catalyses the synthesis of cyclic endoperoxides, from the arachidonic acid to form PGs. The two COX isoenzymes are COX-1 and COX-2. The function of COX-1 is to produce PGs that are involved in normal cellular activity, (protection of gastric mucosa, maintenance of kidney function). While, COX-2 is responsible for the production of PGs at the inflammation sites. Most NSAIDs inhibit both COX-1 and COX-2 with varying degree of selectivity. Selective COX-2 inhibitor may eliminate the side effects associated with NSAIDs due to COX-1 inhibition, such as gastric and renal effect.

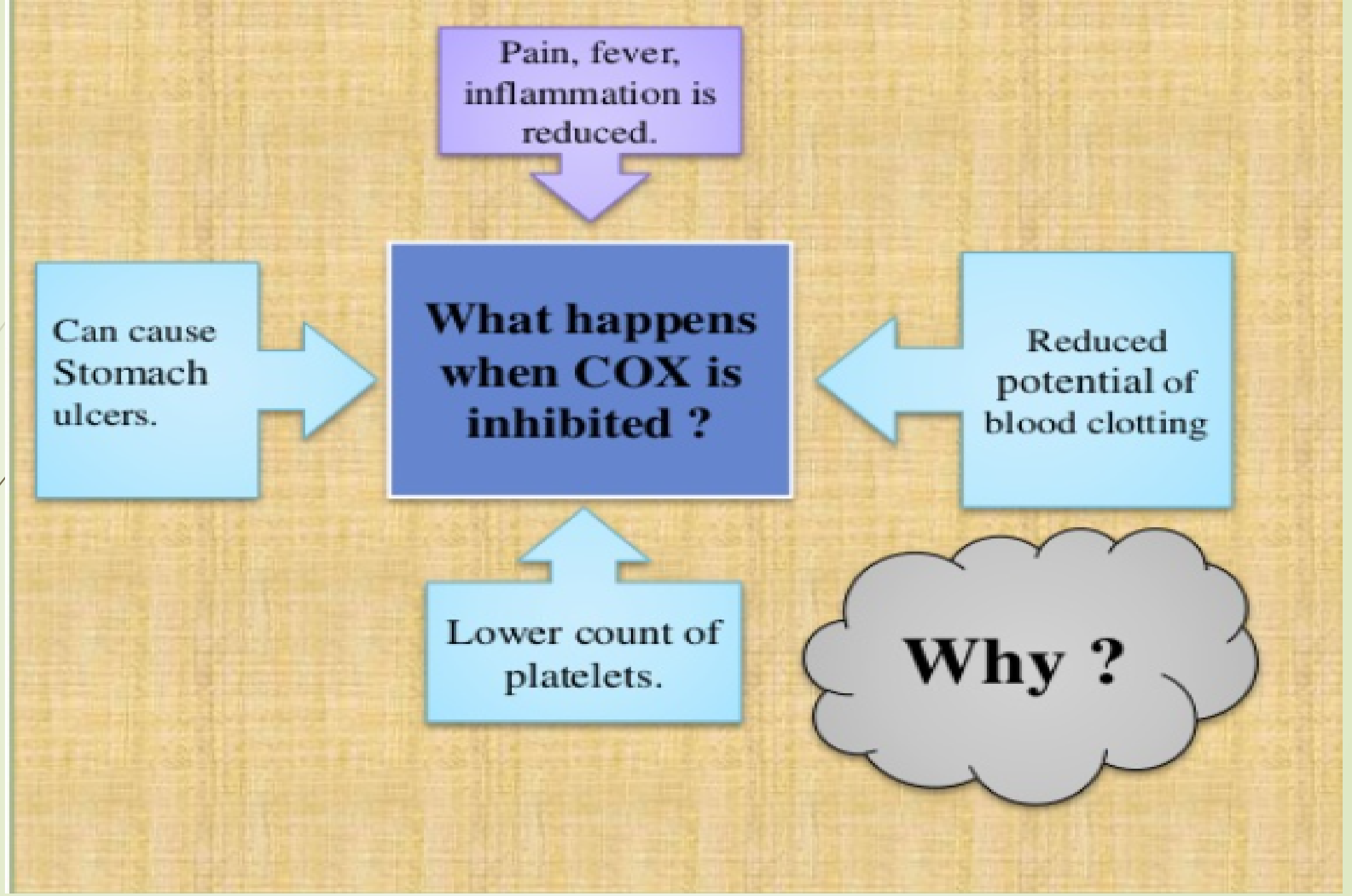

How is COX activated ?
Injury / infection / trauma
Attacks cell membrane
Cell membrane contains phospholipids
Activation of phospholipids
Formation of arachidonic acid
Metabolized by
Cycloxygena -se pathway
Lipoxygena se pathway

Prostaglandins (PGs) are derived from arachidonic acid



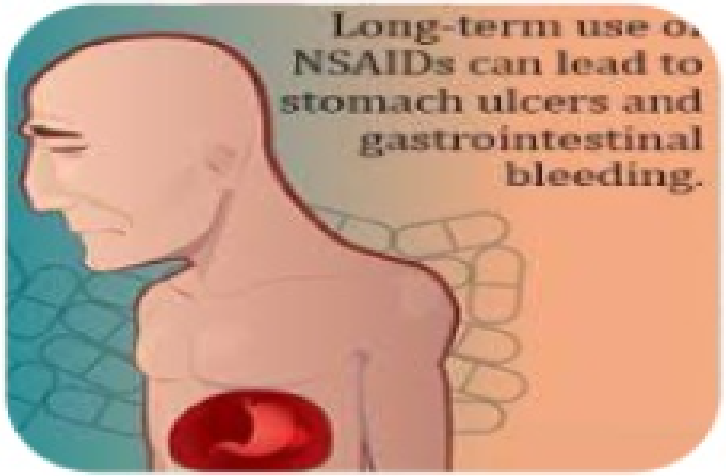
Mechanism of action of NSAIDs




Pain, fever, inflammation is reduced.
Can cause Stomach ulcers.
What happens when COX is inhibited ?
Reduced potential of blood clotting
Lower count of platelets.
Why ?

Side Effect

- NSAIDs are associated with a number of side effects. The most common side effect are Gastro Intestinal Tract (GIT) disturbance such as nausea, diarrhoea, constipation, vomiting, decreased appetite and peptic ulcer.
- NSAIDs may also cause fluid retention leading to oedema; the most serious side effects are kidney failure, Liver failure, Ulcer and prolonged bleeding after injury and surgery.



Non Selective COX Inhibitor

Trick :- **SOA**A**PP**-F

Salicylates	• Sodium Salicylate, Aspirin, Salol
Oxicam	• Tenoxicam,Piroxicam
Aryl Acetic Acid	• Sulindac, Indomethacin
Aryl Acetic Acid Derivatives	• Diclofenac,Acelofenac
Propionic Acid Derivatives	• Naproxen, Ibruprofen
Pyrazolone Derivatives	•Phenylbutazon, Oxyphenbutazon
Fenamate	•Mefanamic acid, Meclofenamic acid

Selective COX-II Inhibitor [COXIBs]

- Celecoxib, Valdecoxib, Etoricoxib, Parecoxib

Preferential COX-II Inhibitor

- Nimesulide,Meloxicam, Nabumetone

Analgeic and Anti-Pyretics

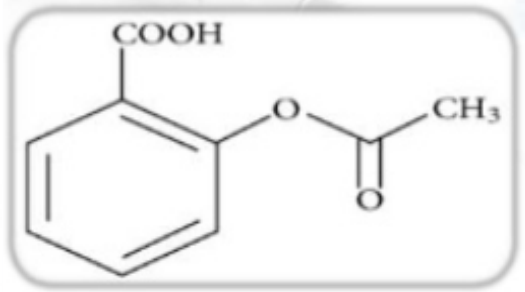
1. Para-aminophenol derivatives – Paracetamol
2. Pyrazolone derivatives – Metamizol, Propiphenazone
3. Benzoxazocine derivatives - Nefopam

Classification of NSAIDs. Anti-inflammatory agents:,

I. **Salicylic acid derivatives**: **Salicylates** not only possess antipyretic, analgesic, and anti-inflammatory properties, but also other actions that have been proven to be therapeutically beneficial because salicylates promote the excretion of uric acid and they are useful in the treatment of gouty arthritis. More attention has been given to the ability of salicylates (aspirin) to inhibit platelet aggregation, which may contribute to heart attack and strokes, and hence, aspirin reduces the risk of myocardial infarction. In addition, a recent study suggested that aspirin and other NSAIDs might be protective against colon cancer.

Examples. Sodium salicylate, Aspirin,

Salicylate (Asprin)



It's a Prototype OTC drug.

Aspirin is acetylsalicylic acid.

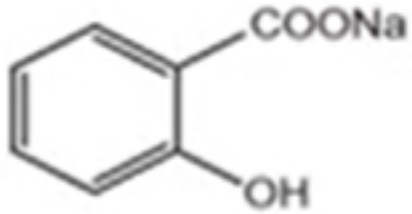
After administration in body it converts rapidly into the salicyclic acid which is responsible for most of the action.

Mainly it decreases the body temperature and pain threshold.

Regular use or high consumption of aspirin leads to death or other side effect.

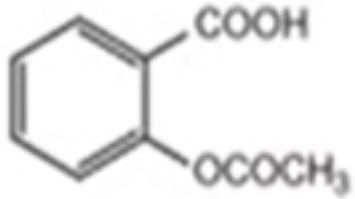
Natural Sources – Fruits, Vegetables, herbs, spices, nuts and tea.

i. Sodium salicylate. Properties and uses: Sodium salicylate is a white crystalline powder, soluble in water, sparingly soluble in alcohol. It is used for fever and for the relief of pain. It also possesses anti-inflammatory actions similar to aspirin and symptomatic therapy of gout.



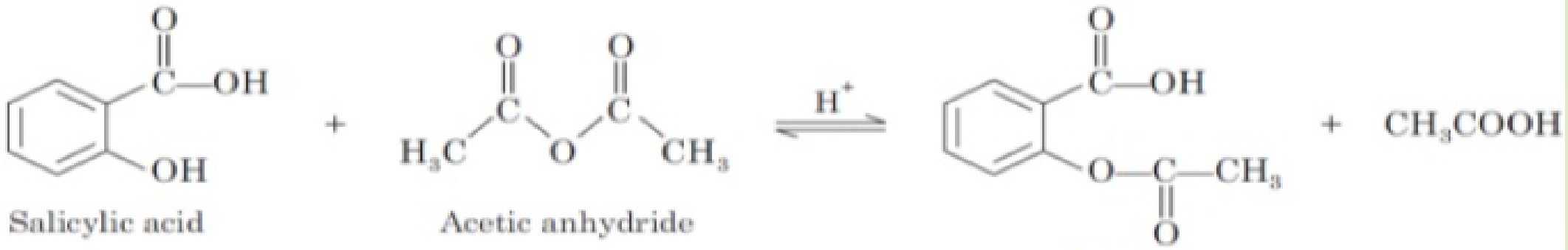
Sodium salicylate
Sodium 2-hydroxybenzoate

ii. Aspirin. Properties and uses: Aspirin is a white crystalline powder, slightly soluble in water and soluble in alcohol, indicated for the relief of minor aches and mild-to-moderate pain in the conditions such as arthritis and related arthritic condition. Also used in myocardial infarction prophylaxis.



Aspirin
2-Acetoxybenzoic acid (or) Acetyl salicylate

Synthesis of Asprin



Pharmacology of Aspirin

Pharmacodynamics :-

1. Analgesic, Antipyretic and Anti-inflammatory

- Aspirin → Produce analgesic effect by inhibiting the synthesis of PGs (Prostaglandins) and prevents sensitization of peripheral nerve ending.

- Aspirin → Also acts on temperature regulating centre and increase heat loss but doesn't affect the production of heat.
- Aspirin → Sometime it also increases the threshold level in body and decreases the sensation of pain.

2. Metabolic effect –

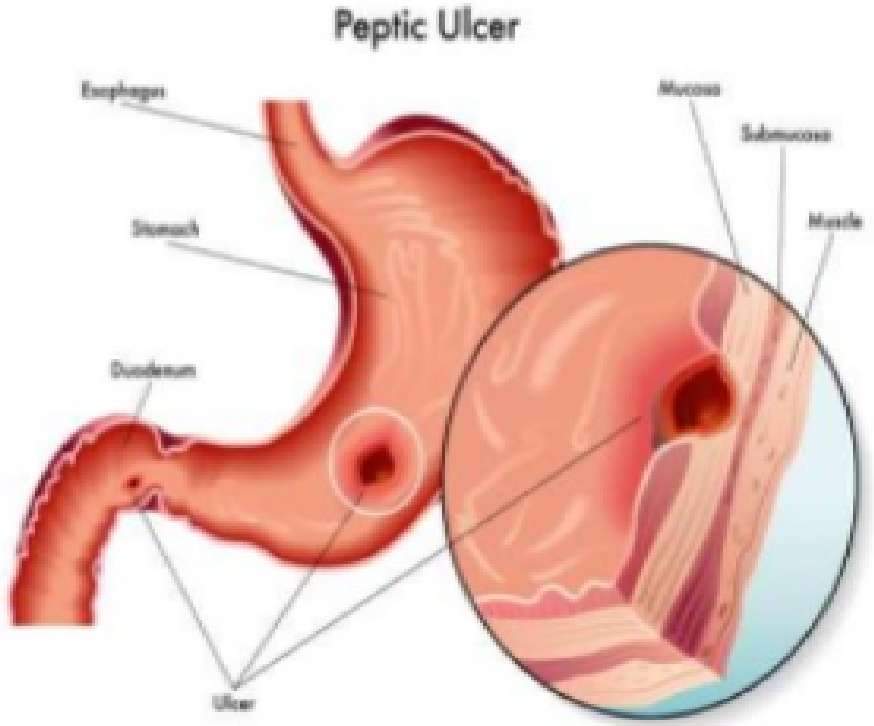
- Aspirin → Decreases utilization of glucose from peripheral tissue which produce hypoglycemia (condition produced mainly in diabetic patient).

5.Gastro-intestinal Tract (GIT) effect–

Aspirin/Salicyclic acid

Cause hyperacidity in stomach

And produces irritation in gastric mucosa , peptic ulcer, nausea and vomiting



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- **Uses –**
  - It is used to reduce fever and relieve mild to moderate pain from condition such as muscle aches.
  - If may also be used to reduce pain and swelling in condition of injury
  - It is used as an antipyretic, analgesic and anti-rheumatic.
  - It is also used in myocardial infarction.
- **Side effects –**
  - Nausea, Vomiting, Epigastric Distress
  - Increase occult blood loss in stools.
  - The most important adverse effect of aspirin is gastric mucosal damage and peptic ulceration.

SAR of Salicylates

a) Subst. on either the –COOH or –OH grp may affect the potency and toxicity.-

b) Reducing the acidity of –COOH grp retains the analgesic action but is devoid of-Anti-inflammatory property. E.g. Salicylamide-

c) Placing the –OH grp meta / para to –COOH grp totally **abolishes the analgesic activity**.-

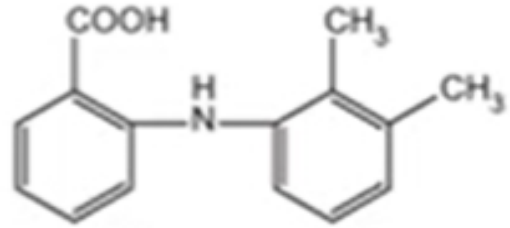
d) Subst. with halogens on the aromatic ring will **increases** the potency as well as toxicity.-

e) Subst. of aromatic ring at the 5^{th} posn of salicylic acid **increases** the anti-inflammatory activity. E.g. Diflunisal

III. Anthranilic acid derivatives (Fenamates):

Mefenemic acid,

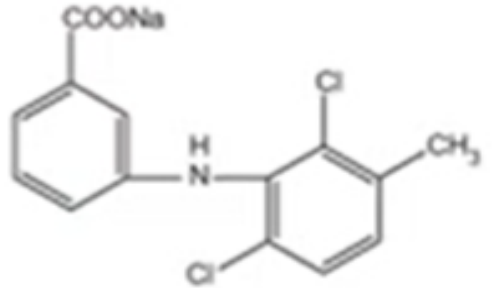
Used as an analgesic and anti-inflammatory agent.



Mefenamic acid
2-(2,3-Dimethylphenylamino)benzoic acid

Meclofenamate.

Used as an analgesic and anti-inflammatory agent.



Meclofenamate Sodium
Sodium 3-(2,6-dichloro-3-methylphenylamino)benzoate

Mefenamic acid **Synthesis**

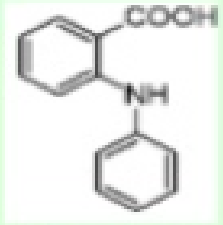
2-Chlorobenzoic acid + 2,3-Dimethylbenzenamine → Mefenamic acid

Anthranilic Acid Derivatives (Fenamate)

Pharmacodynamics

- It's used to treat pain and typically prescribed for oral administration.
- It exhibits anti-inflammatory, analgesic and antipyretic effects.
- The pharmacodynamic of Mefenamic Acid is quite similar to othre NSAIDs, isn't completely understood but may be related to prostaglandins (PGs) inhibition.

SAR of Anthranilic acid derivatives



- a) The position of the –COOH group is more **important** for the activity whereas the m & p-amino benzoic acid analogs are **not active**.

b) Replacement of –COOH group with the Isosteric tetrazole results in the **retention** of **anti-inflammatory** activity.

c) Subst. on the anthranilic acid ring generally **decreases** the activity.

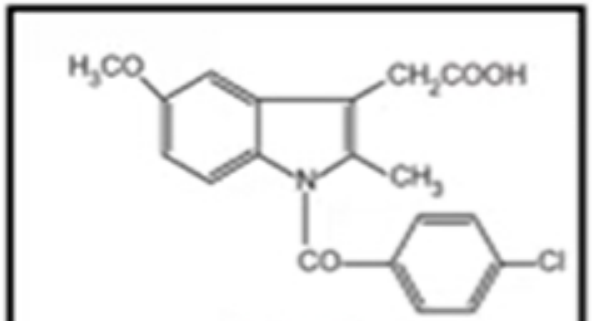
d) Subst. on the N-aryl ring can leads to **conflicting results**. (i.e.) In the UV erythema assay for anti-inflammatory, the order of activity was, 3'> 2'> 4' for monosubst. With CF_3 grp (Flufenamic acid) being particularly potent.

e) The **opposite** order of activity was observed in Rat Paw oedema assay, that is 2'-Cl > 3'-Cl analogs.

Continue….

- **Uses –**
  - Mephenamic acid is used in treatment of acute and chronic rheumatoid arthritis.
  - It has analgesic, anti-inflammatory and anti-pyretic action.
  - Mephenamic acid is indicated primary as analgesic in muscle, joint and tissue pain.
- **Adverse effect –**
  - Diarrhoea is the most important dose related side effect, Epigastric distresses complained but gut bleeding is not significant.
  - Skin rashes, dizziness and other CNS manifestation have occurred.
  - Haemolytic anaemia is a rare but serious complication.

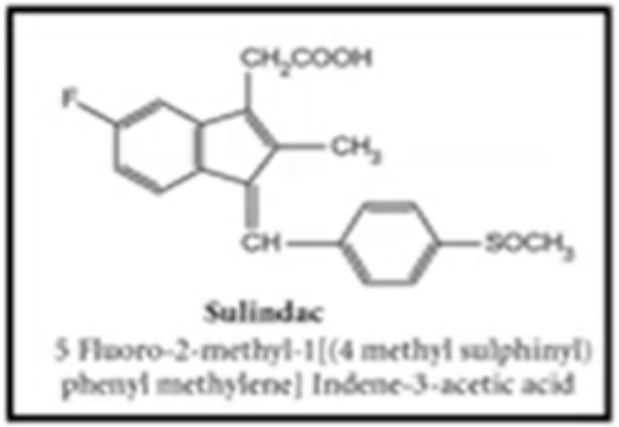
IV. Indole acetic acid: Indomethacin.



Indomethacin
1-(*p*-Chloro benzoyl)-5-methoxy-2 methyl indole-3-acetic acid.

Properties and uses: It is a white or yellow crystalline powder, insoluble in water and sparingly soluble in alcohol. Indomethacin is more effective than aspirin. The most frequent side effects are gastric distress and headache. It also has been associated with peptic ulceration, blood disorders, Used as anti-in?ammatory and analgesic in rheumatic arthritis, spondylitis, and to lesser extent in gout.

V. Indene acetic acid: Sulindac



Sulindac
5 Fluoro-2-methyl-1[(4 methyl sulphinyl) phenyl methylene] Indene-3-acetic acid

Properties and uses: Sulindac is a yellow crystalline powder, very slightly soluble in water. The (*Z*) isomer of sulindac showed much more potent anti-in? ammatory activity than the corresponding (E)-isomer. It has analgesic, antipyretic, and anti-in?ammatory properties. It is usually employed in the treatment of rheumatic and muscular skeletal disorders, acute gouty arthritis, and osteoarthritis.

SAR of Indole acetic acid derivatives

a) Replacement of the –COOH group at 3rd posn with other acidic functionalities **decreases** the activity. Amide analogs are inactive.

b) Subst. at R^1, useful for **increasing anti-inflammatory** activity are ranked as $C_6H_4CH_2 > CH_3 > H$

c) Acylation of the Indole Nitrogen with aryl / alkyl carboxylic acids results in the **decreasing** of activity.

d) The N-benzoyl derivatives subst. in the Para position with F, Cl, CF_3 & S-CH_3 groups are the most active.

e) At the 5th position, X-subst. activity are ranked as $OCH_3 > F > N(CH_3)_2 > CH_3 > COCH_3 > H$ than the unsubstituted analogs.

f) Presence of Indole ring nitrogen is **not essential** for activity because the corresponding 1-benzylidenylindene analogs (i.e. Sulindac) is also active.

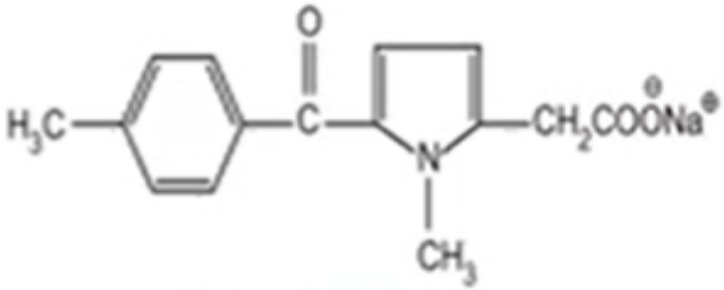
g) CH_3 group at 2nd position are more active than aryl subst. analogs.

h) Subst. of CH_3 group at the α-position of the acetic acid side chain leads to **equally active analogs**.

i) Anti-inflammatory activity is displayed only by the **dextrorotatory** enantiomer (25 times more active than phenylbutazone)

IX. Pyrrole acetic acid:

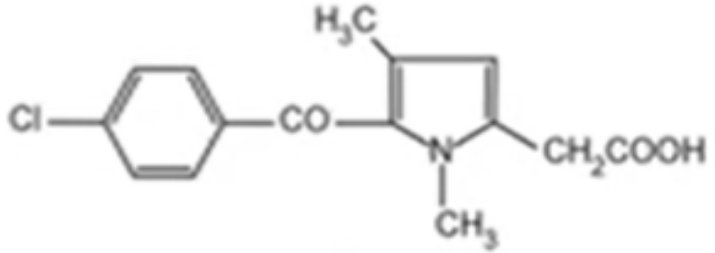
i. Tolmetin, Properties and uses: It is a light yellow, crystalline powder, soluble in water, slightly soluble in alcohol. It has antipyretic, analgesic, and anti-inflammatory actions. It is employed in the treatment of rheumatic and musculoskeletal disorders. The drug is, however, comparable to indomethacin and aspirin in the control and management of disease activity.



Tolmetin Sodium

Sodium 2-(1-methyl-5-(4-methylbenzoyl) -1*H*-pyrrol-2-yl)acetate

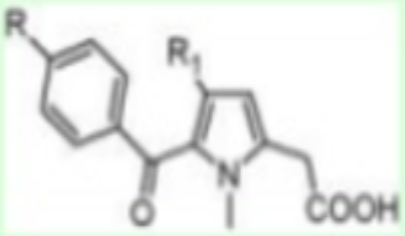
ii. Zormipirac. Properties and uses: A greater degree of analgesia for severe pain is claimed for Zomepirac. It is used as an analgesic and an ant-inflammatory drug. It is four times as potent as tolmetin.



Zomepirac

1, 4. Dimethyl-5-(*p*-chloro benzoyl) pyrrole-2-acetic acid

SAR of Pyrrole aceticacid derivatives



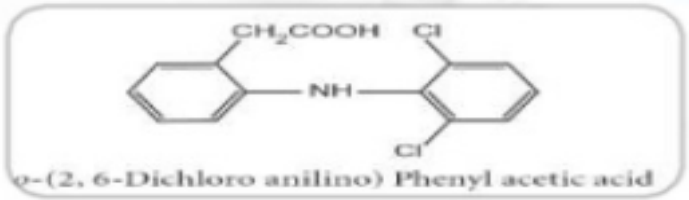
a) Replacement of p-Tolyl group with p-chloro benzoyl group produces **little effect** on activity.

b) Introduction of $-CH_3$ group in the 4^{th} position and p-chloro benzoyl analog (i.e. Zomepirac) was 4 times as **potent** as Tolmetin.

4. Aryl – acetic acid derivatives

Diclofenac

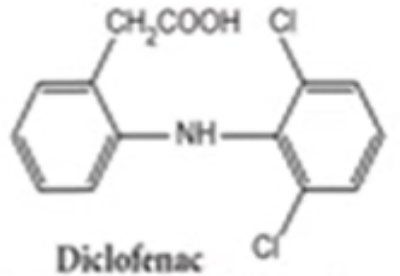
Structure –



o-(2, 6-Dichloro anilino) Phenyl acetic acid

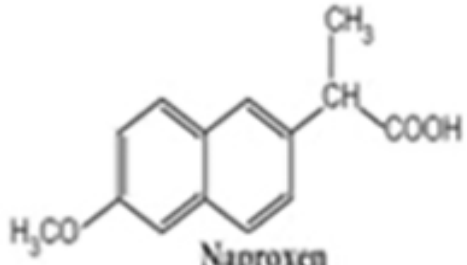
- **Uses –**
  - Diclofenac is used to treat pain, Inflammatory disorder and dysmenorrhea.
  - It is used in the treatment of rheumatoid arthritis and osteoarthritis
  - It is effective against menstrual pain and endometriosis.
  - Diclofenac is used commonly to treat mild to moderate postoperative or post-traumatic pain.
- **Side effect –**
  - Indigestion, gas, stomach pain, nausea and vomiting.
  - Diarrhoea, constipation, headache, dizziness, drowsiness, itching, increased sweating, increased blood pressure or swelling or pain in your arms or legs.

ii. Diclofenac. Properties and uses: Diclofenac sodium is a white or slightly yellowish crystalline slightly hygroscopic powder, sparingly soluble in water, soluble in methanol and alcohol, slightly soluble in acetone. Used in the treatment of rheumatic arthritis.



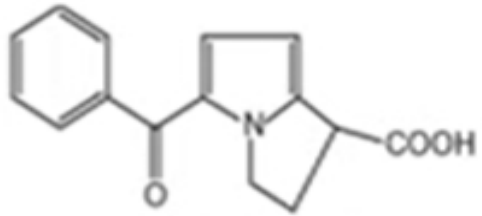
Diclofenac
o-(2, 6-Dichloro anilino) Phenyl acetic acid

iii. Naproxen, Properties and uses: Naproxen is a white crystalline powder, practically insoluble in water, soluble in ethanol and in methanol. It possesses analgesic, anti-inflammatory, and antipyretic actions, and it is used in the treatment of rheumatic arthritis, dysmenorrhea, and acute gout.



Naproxen
(±)2-(6-Methoxy-2-naphthyl) propionic acid

iv. Ketorolac, Properties and uses: Ketorolac is a white crystalline powder, soluble in water and in methanol, slightly soluble in ethanol, practically insoluble in methylene chloride. Ketorolac is a potent analgesic indicated for the treatment of moderately severe and acute pain.



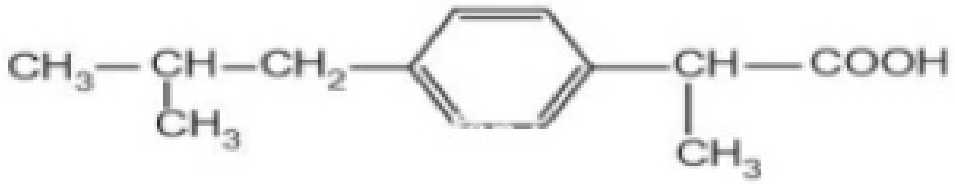
Ketorolac
5-Benzoyl-2 ,3-dihydro-1*H*-pyrrolizine
-1-carboxylic acid

2. Propionic acid derivatives

- Aryl propionic acid derivatives are effective and useful NSAIDS.
- They may offer significant advantage over aspirin and indomethacin since they are usually better tolerated.
- Ibuprofen was the first member of propionic acid derivatives.

Ibuprofen

- **Structure –**



2 (*p*-Iso butyl-phenyl) propionic acid

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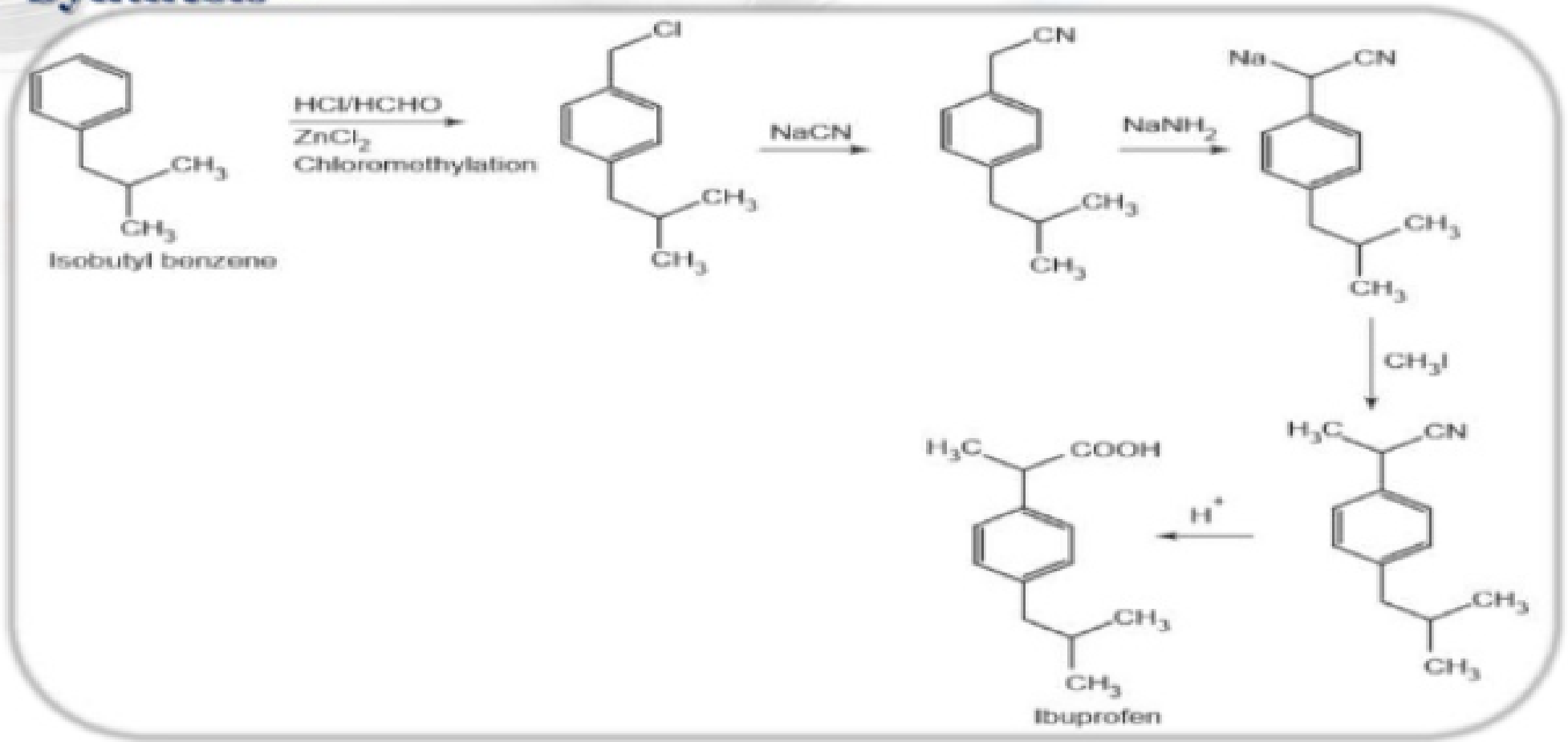
❖ **Synthesis –**



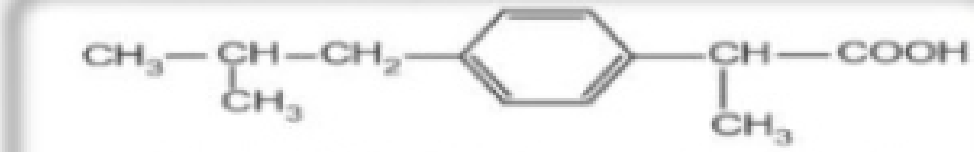
Pharmacodynamics / Mode of Action

- Ibuprofen acts by inhibiting the Cyclooxygenase (COX) enzyme, which converts the Arachidonic acid to prostaglandins (PGs).
- PGs are then converted into two PGs subunits by enzymatic process into PG G2 & PG H2 (which are act as mediators in pain, fever, inflammation, stimulates platelets aggregation and leads to the formation of blood clots.

Continue….

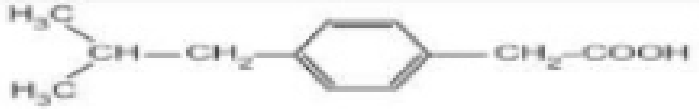
- **Uses –**
  - Ibuprofen is used as simple analgesic and anti-pyretic in the same way as low dose of aspirin.
  - It is particularly effective in dysmenorrhoea.
  - Ibuprofen and its congeners used in rheumatoid arthritis, osteoarthritis and musculoskeletal disorder.
- **Side effect –**
  - Gastric discomfort, nausea and vomiting though less than aspirin.
  - Gastric erosion and occult blood loss are rare.
  - CNS side effect include headache, dizziness, blurring of vision and depression.

SAR of Ibuprofen



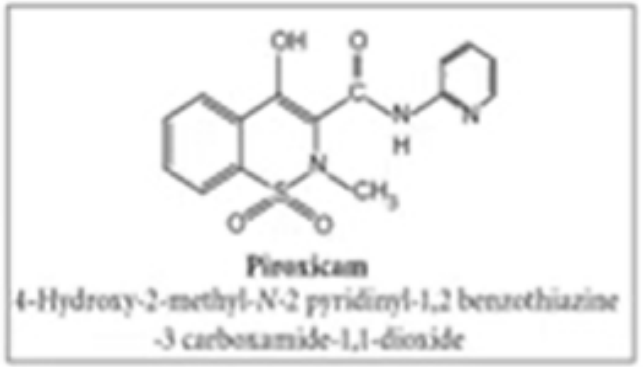
2 (*p*-Iso butyl-phenyl) propionic acid

- The substitution of an alpha methyl group on the alkanoic acid portion of acetic acid derivatives enhance anti-inflammatory action and reduce many side effects. For example – The acetic acid analogue of ibuprofen, ibufenac is less potent and more hepatotoxic than ibuprofen.
- The (+)- enantiomer of ibuprofen posses greater activity in vitro than (-) isomer.
- The S-isomer of ibuprofen is more active than R-isomer.



2-(*p*-Isobutyl-phenyl) acetic acid

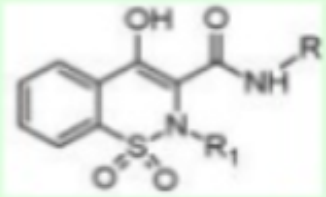
VII. Oxicams: Piroxicam,



Piroxicam
4-Hydroxy-2-methyl-*N*-2 pyridinyl-1,2 benzothiazine -3 carboxamide-1,1-dioxide

Properties and uses: Piroxicam is a white or slightly yellow crystalline powder, practically insoluble in water, soluble in methylene chloride, and slightly soluble in ethanol. It is employed for acute and long-term therapy for the relief of symptoms of osteoarthritis and rheumatoid arthritis. It also possesses uricosuric action and has been used in the treatment of acute gout.

SAR of Oxicams

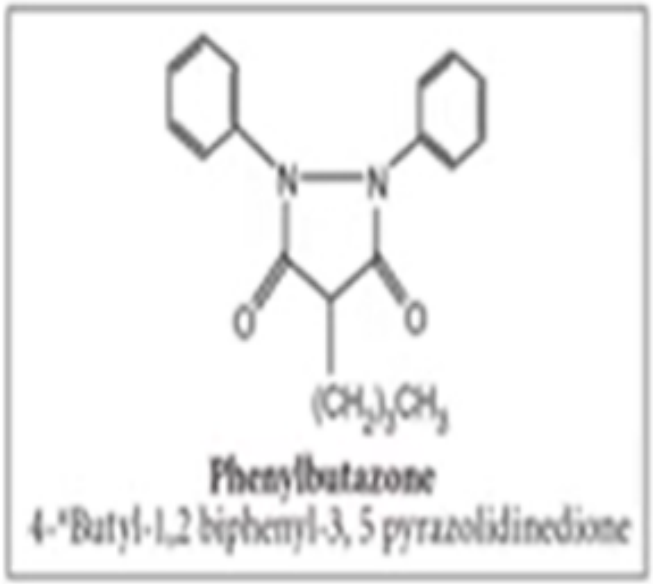


a) Most **active analogs** have subst. $-CH_3$ group on the N_2 and electron withdrawing subst. like Cl, CF_3 on the anilide phenyl group.

b) Introduction of heterocyclic ring in the amide chain significantly **increases** the anti-inflammatory activity. (e.g.) Sudoxicam (2-thiazolyl ring) is potent than Indomethacin.

c) Interchanging of benzene ring with Thiophene gives **biologically active** compounds. (e.g.) Tenoxicam.

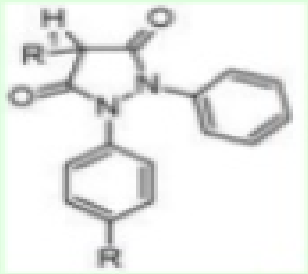
VIII. Pyrazolidine dione derivatives: Phenyl butazone.



Phenylbutazone
4-*Butyl-1,2 biphenyl-3, 5 pyrazolidinedione

Properties and uses: Phenylbutazone is a white crystalline powder, soluble in alcohol, and soluble in alkaline solutions. It is a pyrazole derivative that has antipyretic, analgesic, and anti-inflammatory actions, because of its toxicity it is not used as a general antipyretic or analgesic. It is a usual practice reserved for use in the treatment of osteoarthrosis, ankylosing spondylitis, artluritis, acute superficial thrombophlebitis, painful shoulder, and Reiter's disease, where less toxic drugs have failed.

SAR of 3,5-pyrazolidinediones



a) Pharmacological activity is related to the acidic H at 4th posn. Thus, presence of dicarbonyl grp at 3rd & 5th posn **increases** the acidity of H atom at the 4th posn.

b) Decreasing or eliminating the acidity by removing the acidic H at the 4th posn may completely **abolishes** anti-inflammatory activity. e.g. 4,4-dialkyl derivatives.

c) If acidity is increased too much, anti-inflammatory & Na retaining activity **decreases**, while other property such as the uricosuric effect **increases**.

d) A single alkyl grp at the 4th posn **increases** the anti-inflammatory activity. Although n-butyl group increases the activity more.

e) Presence of keto group in the γ-posn of the butyl side chain produces the **active compound** with better anti-inflammatory activity.

f) Presence of γ-OH-n-butyl derivative possesses **pronounced uricosuric** activity but gives **lesser anti-inflammatory** activity.

g) Subst. of 2-phenyl thio ethyl group at the 4th posn produces **anti-gout** activity e.g. Sulphin pyrazone.

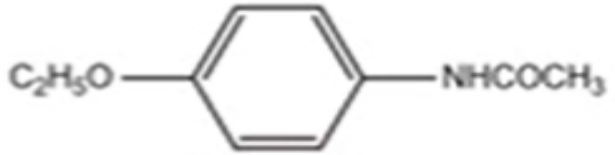
i) Presence of both phenyl group is **essential** for both **anti-inflammatory & analgesic** activity.

g) m-Subst. in one of the aryl rings gives **inactive** compounds, but p-Subst. with $-CH_3$, -Cl, NO_2 or OH in one of the phenyl rings **retains the activity**.

h) Replacement of one of the N_2 atom with an O_2 atom yields Isoxazole analogs which are as **active** as pyrazolidinediones.

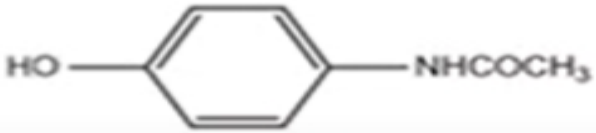
II. p-Amino phenol derivatives: These derivatives possess analgesic and antipyretic action, but lack anti-inflammatory effects.. Examples, Phenacetin. Acetaminophen, (Paracetamol),

i. Phenacetin. Properties and uses: It exists as a white glistering powder with a bitter taste, sparingly soluble in water and soluble in chloroform. It is an analgesic and an antipyretic with similar effectiveness as an aspirin. It has a greater potential for toxicity (hemolytic anaemia and methemoglobinaemia).



Phenacetin
p-Ethoxy acetanilide

ii. Acetaminophen, (Paracetamol), Properties and uses: Paracetamol exist as white crystalline powder, sparingly soluble in water, soluble in alcohol. Paracetamol produce antipyresis by acting on the hypothalamic heat-regulating centre and analgesia by elevating the pain threshold. Hepatic necrosis and death have been observed following over dosage; hepatic damage is likely in an adult who takes more than 10 g in a single dose or if a 2-year old child takes more than 3 g.



Paracetamol
Acetaminophen
Para-acetamino phenol

5. Para aminophenol derivatives

❖ Structure Activity Relationship

Acetaminophen

- Etherification of the phenolic function with methyl or propyl groups produces derivatives with greater side effects than ethyl derivatives.
- Substituents of the nitrogen atom, which reduce the basicity, also reduce activity unless the substituent is metabolically labile. Example—acetyl groups.
- Amides derived from aromatic acid. Example—N-phenyl benzamides that are less active or inactive.