Non-Steroidal Anti-inflammatory Agents (NSAIDS)
lec3

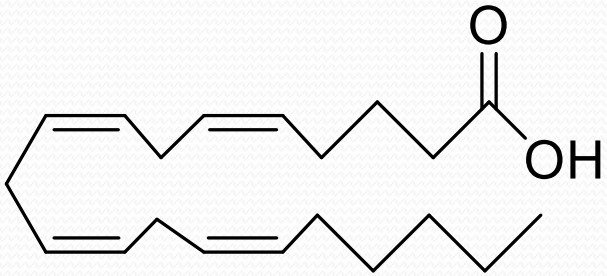
Lec.Dr.yahya saad yaseen

Introduction

- **Inflammation** is a normal protective response to tissue injury caused by *physical trauma, chemicals*, or *microbial agents*
- During the process certain mediators are released including prostaglandins and leukotrienes
- These may cause edema and pain and can also raise body temperature

Introduction

- These prostaglandins and leukotrienes are formed in the body from **arachidonic acid** and other **eicosanoids** (20-carbon essential fatty acids)

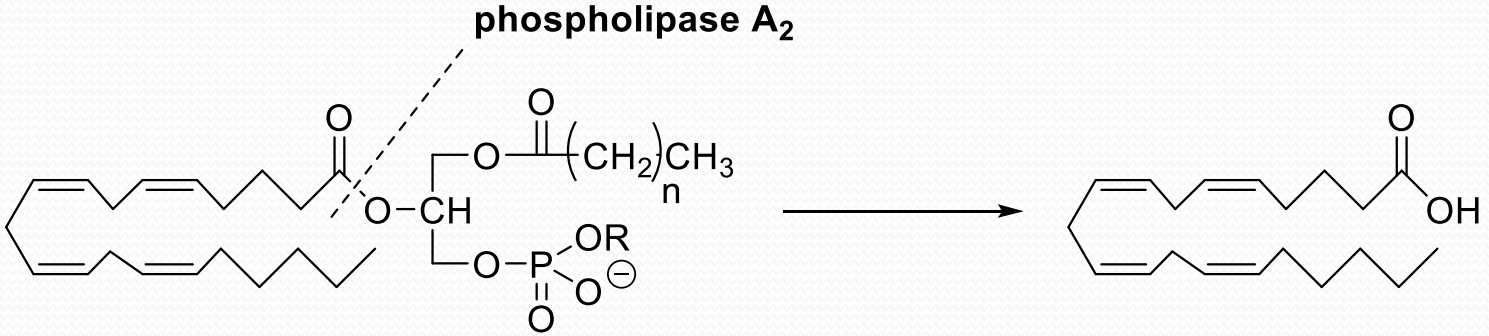


Arachidonic acid

- These species in turn are derived from dietary linoleic acid (9,12-octadecadienoic acid)

Introduction

- Arachidonic acid is stored in the body by forming an ester with various phospholipids found in cell membranes and thus the concentration of free arachidonic acid is very low
- When needed, arachidonic acid is released from the phospholipids by the action of *acyl hydrolases*, most notably, **phospholipase A_2**



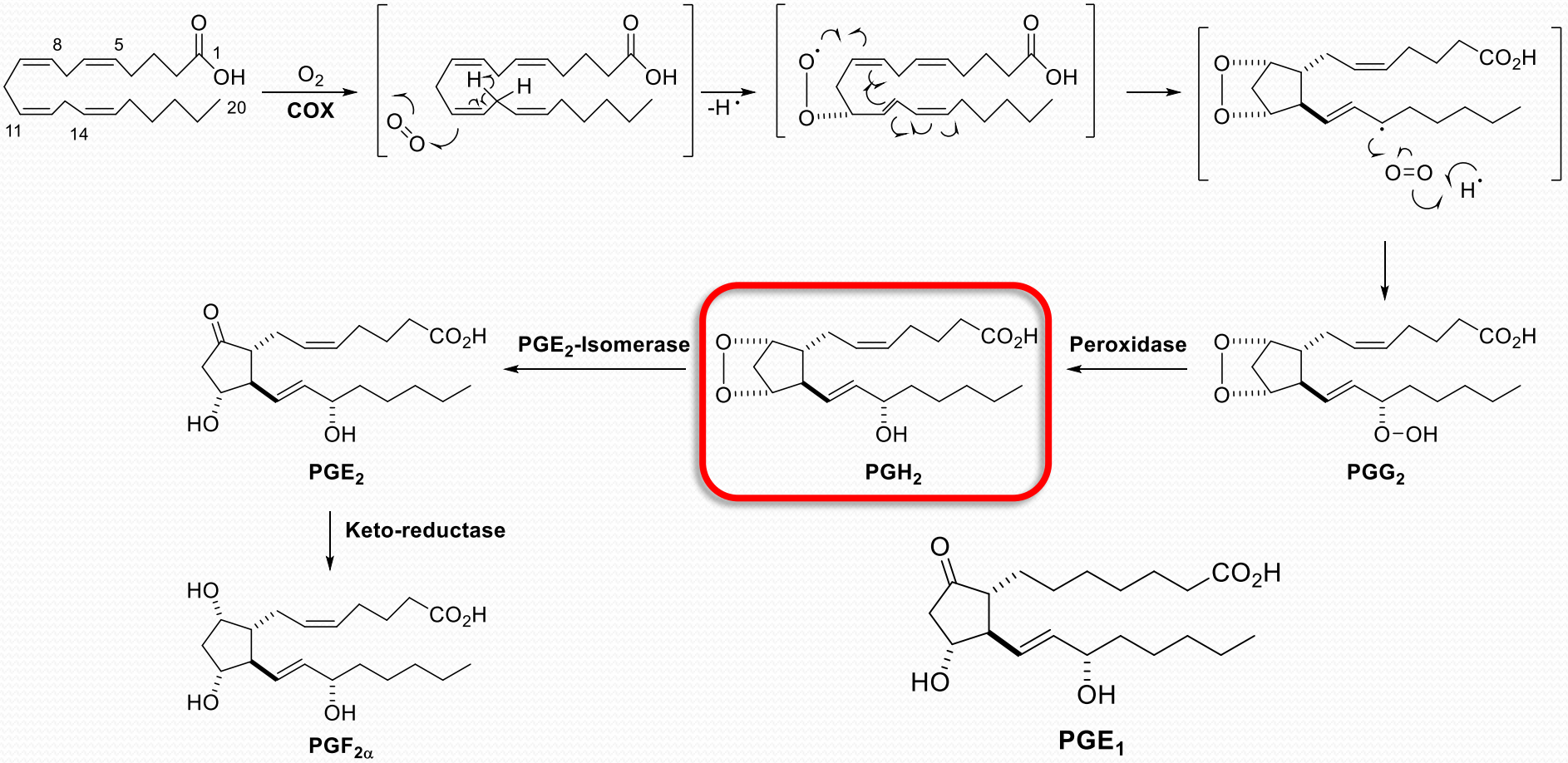
Phospholipid-esterified arachidonic acid

Arachidonic acid

Introduction

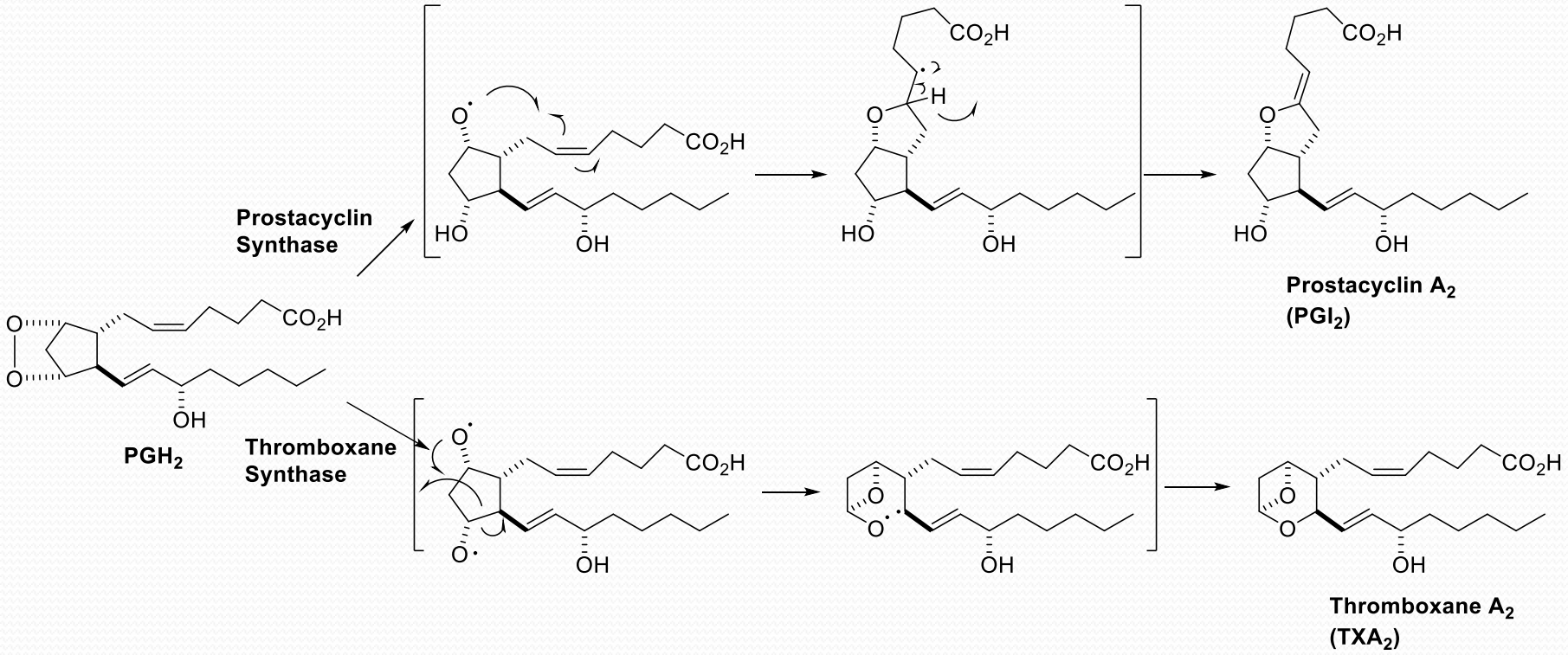
- Microbial products or physical trauma stimulates the release of, and activates Phospholipase A_2 to hydrolyze the esterified arachidonic acid
- The released arachidonic acid initiates a cascade of reactions catalyzed by **cyclooxygenase** (COX) or **5-lipoxygenase**
- These reactions lead ultimately to the production of prostaglandins and leukotrienes as well as several other products

Prostaglandin Biosynthesis

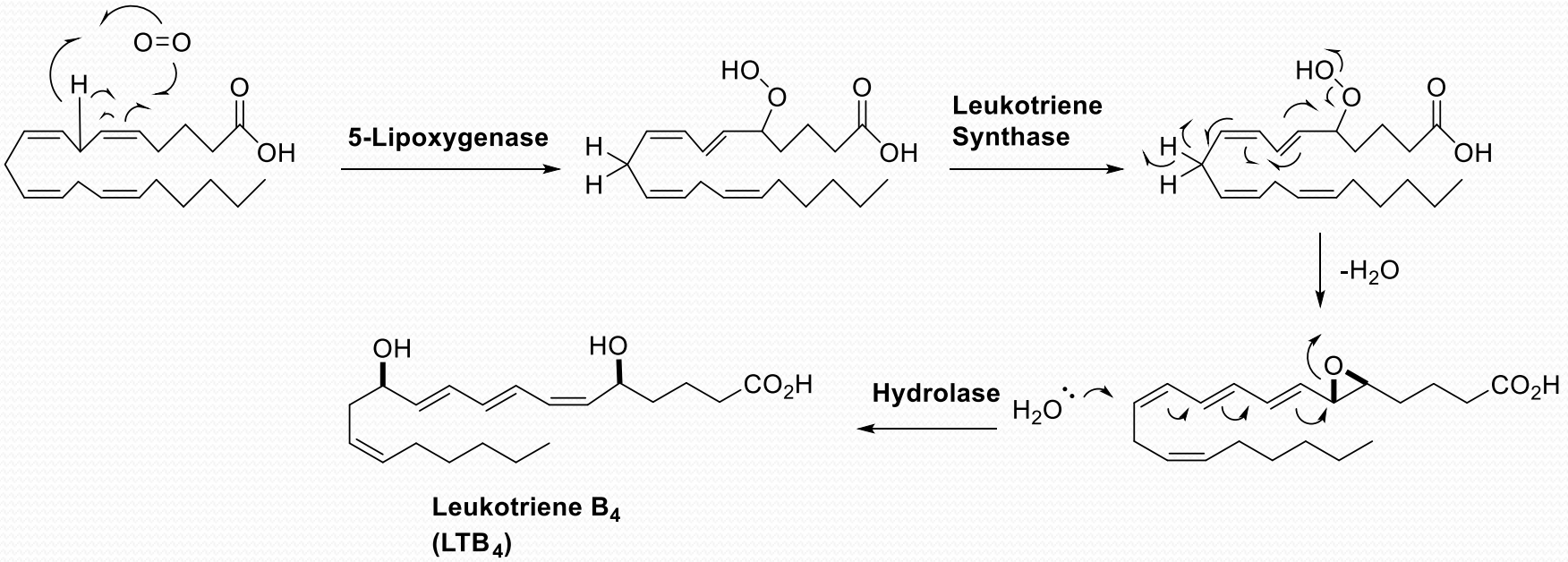


A similar sequence of reactions starting from 8,11,14-eicosa-trienoic acid produces **prostaglandin E1 (PGE_1)**

Prostaglandin Biosynthesis



Leukotriene Biosynthesis



Cyclooxygenase

- From the biosynthesis pathways it is seen that PGH_2 is a common intermediate for other prostaglandins, prostacyclins and thromboxanes
- The key step in formation of PGH_2 is the reaction of arachidonic acid with oxygen catalyzed by cyclooxygenase (COX)
- Therefore drugs that inhibit COX activity also decrease the production of these inflammation mediators
- This is the mechanism by which NSAIDS help to alleviate the symptoms of inflammation

Cyclooxygenase

- It should be noted that corticosteroids also have an anti-inflammatory effect
- Those drugs however work differently from the non-steroidal agents
- Corticosteroids inhibit the activation of phospholipase A_2 which prevents the release of free arachidonic acid
- Since COX only works on free arachidonic acid those steroids also inhibit the formation of PGH_2
- The focus here however will be on the non-steroidal anti-inflammatory agents

Cyclooxygenase

- Two cyclooxygenase enzymes have been identified in humans, COX-1 and COX-2
- A third, COX-3, is present in dogs but not in humans
- COX-1
  - Expressed in most tissues
  - Involved in cell-signaling and tissue homeostasis (the process by which cells are maintained in equilibrium e.g., temperature, blood pressure, and acid-base balance)
  - COX-1 also mediates the production of prostacyclin, which when released by the gastric mucosa is cytoprotective

Cyclooxygenase

- COX-2
  - Induced when inflammation is initiated in response to a stimuli
- Many of the unwanted side-effects associated with NSAIDs are due in large part to their inhibition of COX-1
- Since COX-2 expression is most closely associated with inflammation, inhibitors that are selective for COX-2 should, in concept, treat the inflammation while minimizing undesirable side-effects
- Unfortunately, several such agents induce serious cardiovascular effects which has led to their removal from the market

NSAID Indications

- The NSAIDs are a group of compounds which generally have three main actions:
  - Antipyretic Activity
  - Analgesic Activity
  - Anti-inflammatory Activity

Antipyretic Activity

- Body temperature is regulated in the hypothalamus which acts as a thermostat to ensure a balance between heat loss and heat production
- Under conditions that induce a fever interleukin-1 (IL-1) is released in the hypothalamus
- This activates phospholipase A_2 which liberates arachidonic acid from phospholipids and signals COX to form prostaglandin E_2

- In the hypothalamus PGE_2 induces an increase in cAMP
- This triggers an increase body temperature by increasing heat generation and decreasing heat loss
- Drugs that reduce fever generally need to cross the blood-brain barrier and enter the CNS

Antipyretic Activity

- NSAIDs help lower body temperature by inhibiting the synthesis of PGE_2 in the hypothalamus
- Once this has been accomplished the temperature-lowering mechanisms in the body take over
  - Dilation of peripheral blood vessels
  - Sweating

Analgesic Activity

- Several prostaglandins, including PGE_1 and PGE_2 sensitize nerve endings to pain mediators such as bradykinin and 5-hydroxytryptamine
- NSAIDs work by inhibiting the synthesis of these prostaglandins which then represses the sensation of pain

- NSAIDs are effective against pain associated with: arthritis, bursitis, pain of muscular or vascular origin, toothache, dysmenorrhea, cancer metastases in the bone, etc.
- NSAIDs are also effective against headaches by diminishing the vasodilation effect induced by prostaglandins in cerebral blood vessels

Antiinflammatory Activity

- NSAIDS reduce those components of inflammation and immune response in which prostaglandins play a role: vasodilation, edema and pain
- COX inhibitors *do not reverse tissue damage* resulting from chronic inflammatory conditions such as:
  - **Rheumatoid arthritis** (a systemic synovial inflammation)
  - **Osteoarthiritis** (a localized inflammation involving cartilage destruction, usually >50 yr old)
  - **Vasculitis** (inflammation of the small blood vessels)
  - **Nephritis** (inflammation of the kidney)
- Lipoxygenase inhibitors may prove more beneficial in this regard

GI Side-Effects

- Many NSAIDs cause gastro-intestinal upset and some may contribute to gastric ulcer formation
- This is based on two pharmacological factors:
  - Most NSAIDs are organic acids
    - In the low pH of the stomach, especially when empty, these organic acids are uncharged and readily cross into the mucosal cells, where they become ionized and are then present in the cells at high concentrations
    - For example at pH 1 a carboxylic acid (pK_a 4) would be only 0.1% ionized
    - Thus, these agents potentially can cause direct damage to those cells

GI Side-Effects

- Prostaglandins E_2 and I_2 (**prostacyclin**) are produced by gastric mucosa
- These prostaglandins inhibit the secretion of HCl and stimulate the secretion of mucus and bicarbonate that protect mucosal cells
- NSAIDs that inhibit the production of these prostaglandins therefore leave the mucosa cells more exposed to ulcerative effects

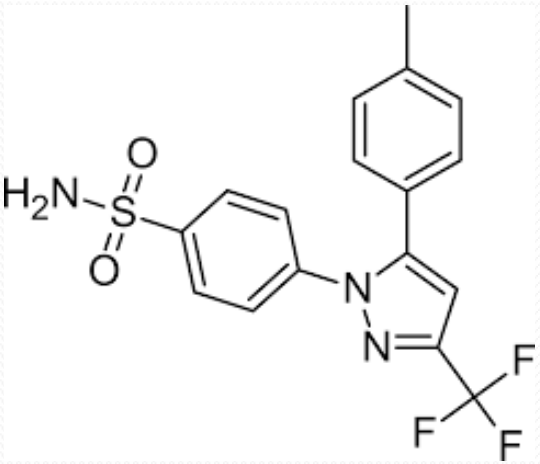
Selective COX-2 Inhibitors

- Individual NSAIDS show different potencies against COX-1 and COX-2 that correlates with variations in their side-effects
- Drugs with high potency against COX-2 and with high COX-2/COX-1 activity ratios have anti-inflammatory activity with fewer side effects in the stomach and kidneys
- Unfortunately, two selective COX-2 inhibitors, Rofecoxib (Vioxx) and Valdecoxib (Bextra), have been removed from the market due to cardiovascular effects

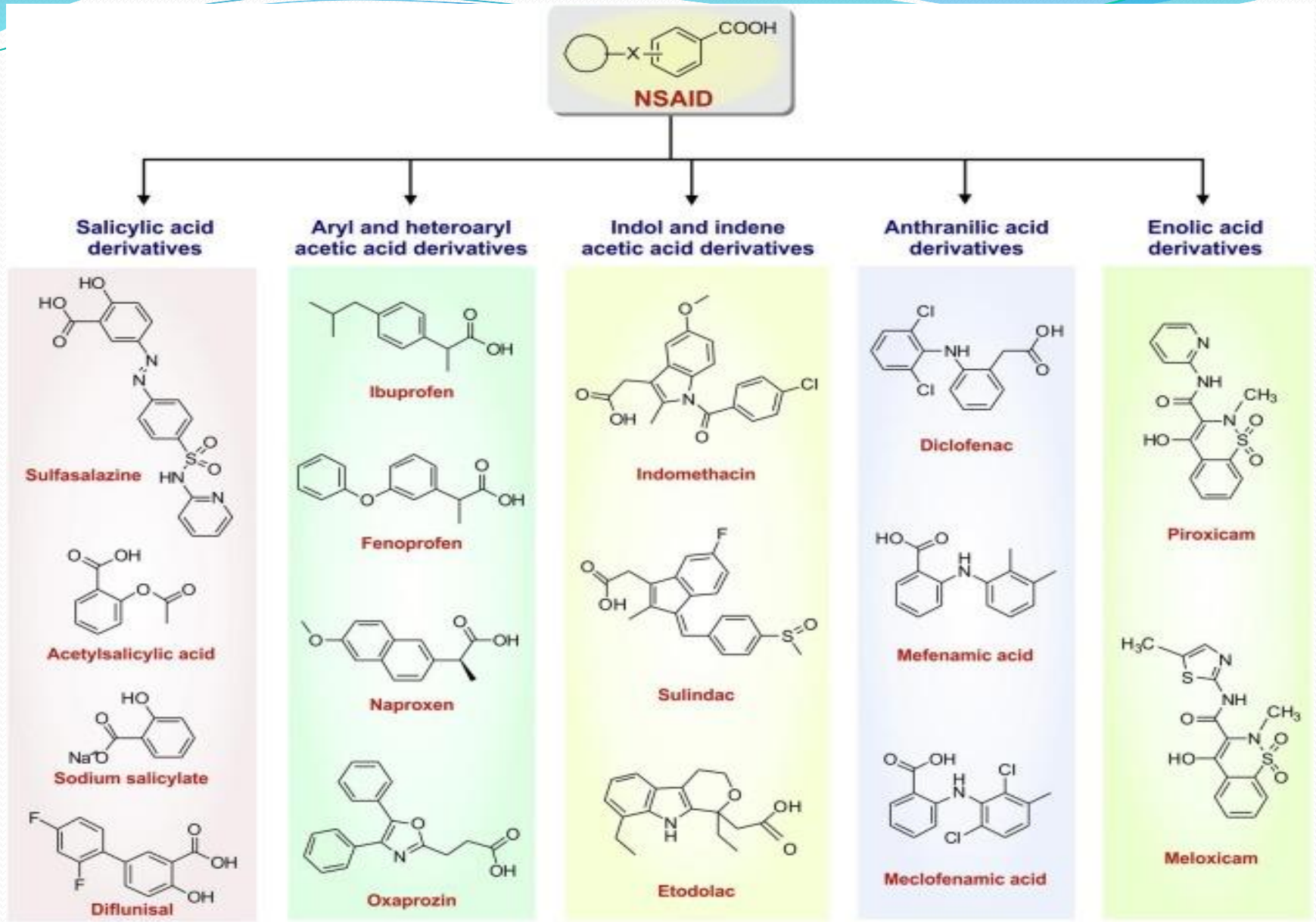
Selective COX-2 Inhibitors

Celecoxib, Celebrex®

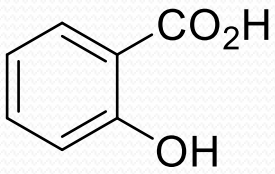
4-[5-(4-Methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]-benzenesulfonamide



- In 1998 Celebrex became the first selective COX-2 inhibitor in the US
- It is used for pain, fever and inflammation including arthritis
- Once or twice daily oral dosing
- The main phase I metabolite is the primary alcohol from oxidation of the methyl group
  - That can get further oxidized to a carboxylic acid, and both metabolites can form glucuronide conjugates
  - None of the metabolites are active


NSAID
Salicylic acid derivatives
Aryl and heteroaryl acetic acid derivatives
Indol and indene acetic acid derivatives
Anthranilic acid derivatives
Enolic acid derivatives
Sulfasalazine
Acetylsalicylic acid
Sodium salicylate
Diflunisal
Ibuprofen
Fenoprofen
Naproxen
Oxaprozin
Indomethacin
Sulindac
Etodolac
Diclofenac
Mefenamic acid
Meclofenamic acid
Piroxicam
Meloxicam

Salicylates



Salicylic Acid

- The salicylate class of NSAIDs are derivatives of salicylic acid
- In the U.S. alone 10-20 thousand tons are consumed annually
- These compounds have antipyretic, analgesic and anti-inflammatory activity
- As acids these compounds are highly protein bound
- Several side-effects are associated with some of the salicylates:
  - Bleeding
  - GI Upset
  - Reye's Syndrome

Salicylates

Bleeding

- From the biosynthesis slides it is seen COX is a key enzyme for the production of thromboxanes
- These compounds are involved in blood clotting
- Some salicylates may inhibit COX-1 in blood platelets which in turn inhibits production of thromboxanes which results in diminished ability of blood to clot
- This may lead to prolonged bleeding
- However, this problem has led to the use of aspirin as an antithrombotic agent for use in patients with prior heart attacks

Salicylates

GI Tract Upset

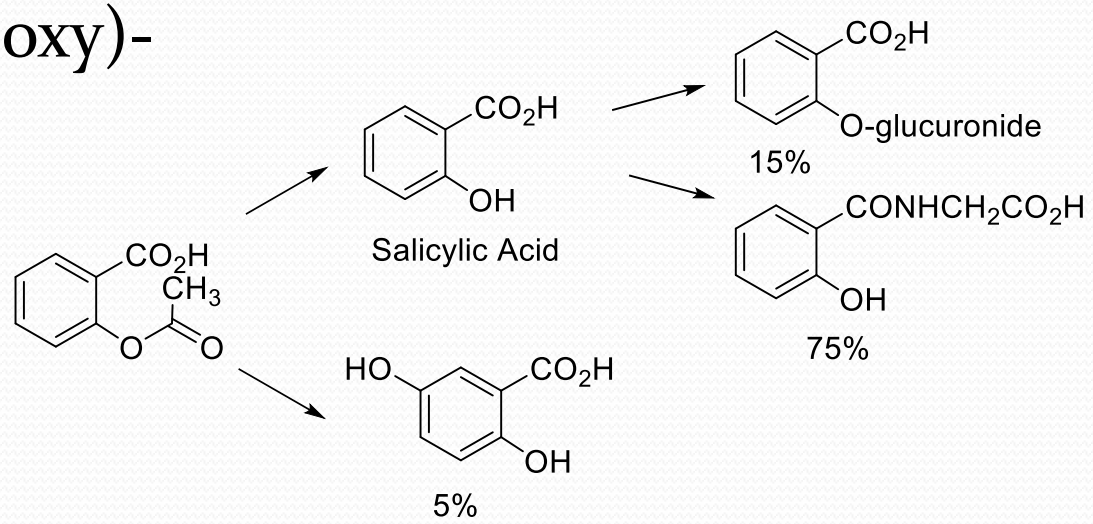
- This results from inhibiting COX-1 and thereby inhibiting formation of prostacyclin as described earlier

Reye's Syndrome

- This is usually only problematic in children under age 16 who have influenza, chicken pox or other flu-like symptoms
- Attempts to alleviate symptoms using salicylates may induce Reye's Syndrome which while rare can lead to vomiting, violent headache, unusual behavior and can even be fatal
- Acetaminophen is not associated with this condition and is recommended for use in children in such cases

Salicylates

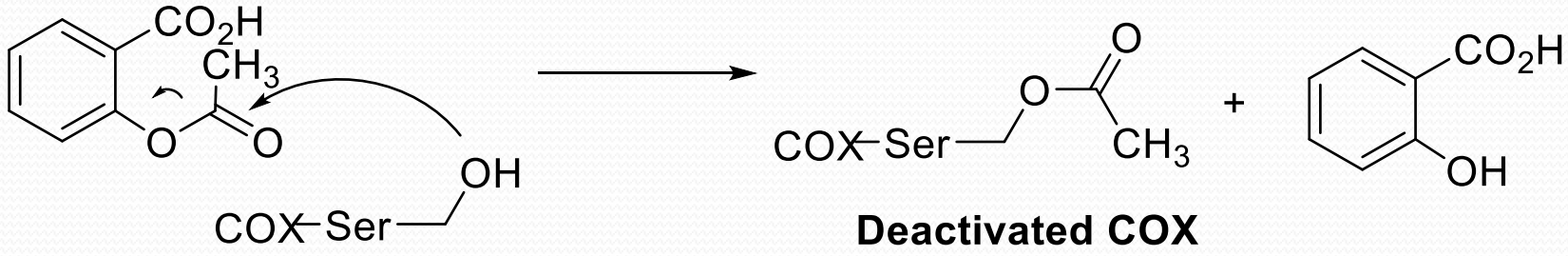
- **Acetylsalicylic acid, Aspirin®**
- Benzoic acid, 2-(acetyloxy)-



- Used for pain, inflammation and fever
- Metabolized mainly by ester hydrolysis with a small amount of aromatic hydroxylation
- The released salicyclic acid is conjugated as both a glucuronide and as a glycine conjugate

Acetylsalicylic acid

- Unlike most NSAIDS, is an <u>irreversible</u> inhibitor of COX
- The acetyl group gets transferred to a serine residue on COX which covalently alters the enzyme
- This then inhibits synthesis of thromboxane A_2 which is a platelet aggregating factor
- Platelets lack a nucleus and therefore cannot synthesize additional COX

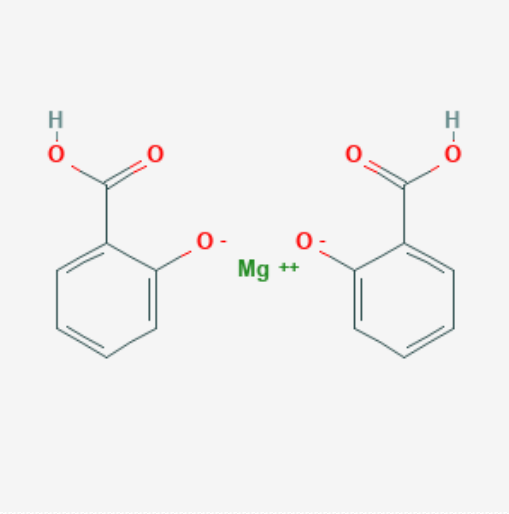


Acetylsalicylic acid

- For the lifetime of the platelet (7-10 days) thromboxane A_2 is blocked and bleeding may be prolonged for several days
- This has led to the use of aspirin to reduce the risk of death or nonfatal myocardial infarction in patients with previous infarction

Magnesium Salicylate, Doan's®

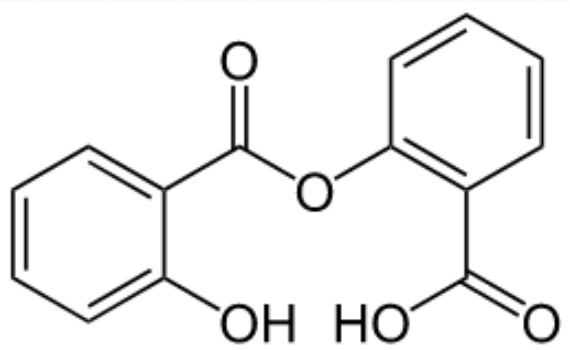
Magnesium Salicylate



- Used for arthritis, pain and backache
- Less irritating to the gastric mucosa than aspirin because magnesium has a buffering effect
- It does inhibit platelet aggregation, but not irreversibly like aspirin
- Possible magnesium toxicity in patients with renal insufficiency

Salsalate

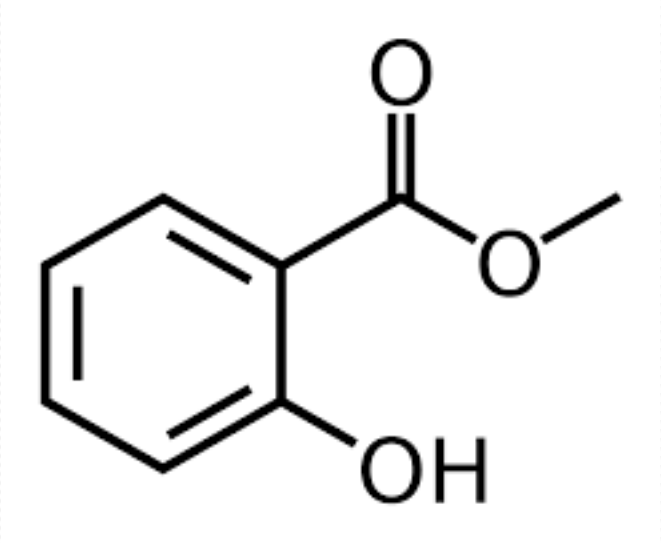
Benzoic acid, 2-hydroxy-, 2-carboxyphenyl ester



- Hydrolyzed into two molecules of salicylic acid
- Not absorbed until it reaches the small intestine
- As a nonacetylated salicylate it does not irreversibly alter platelet aggregation
- Causes less gastric upset than aspirin
- Salsalate is generally indicated only for arthritis and not for management of pain or fever

Methyl Salicylate

Salicylic Acid, methyl ester

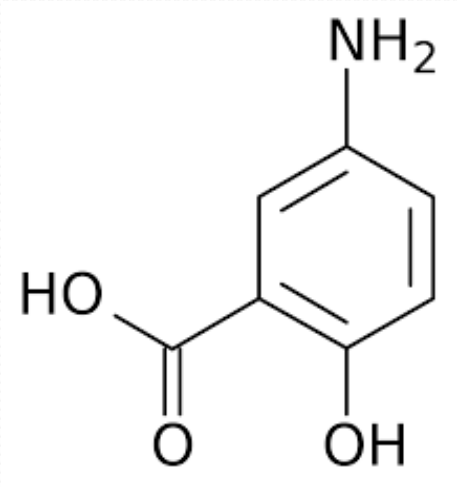


- Used topically for muscle aches

Salicylates Targeting the Colon

Mesalamine, Asacol®, Pentasa®, Rowasa®

5-Aminosalicylic acid

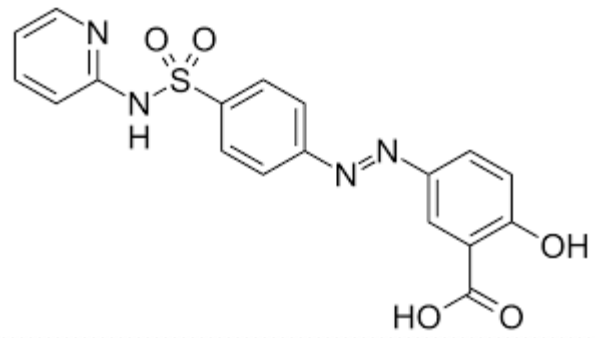


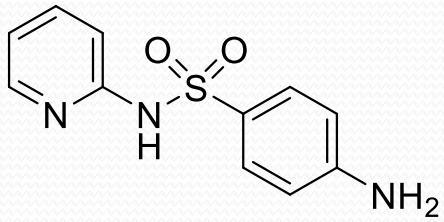
- Used for the treatment of ulcerative colitis
- Works topically in the colon by inhibiting COX
- Tablets are coated with an acrylic resin or ethyl cellulose that delays release of the drug until it reaches the ileum

Salicylates Targeting the Colon

Sulfasalazine, Azulfidine®

Benzoic acid, 2-hydroxy-5-[[4-[(2-pyridinylamino)sulfonyl]-phenyl]azo]-





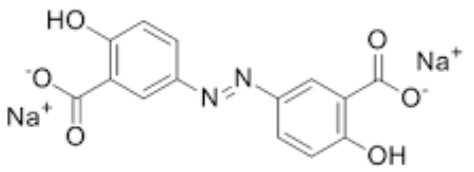
Sulfapyridine

- A prodrug used for ulcerative colitis and Crohn's Disease (a form of inflammatory bowel disease)
- Two-thirds of the oral dose reaches the colon unchanged where bacterial *nitroreductase* cleaves the azo-linkage forming sulfapyridine and **5-aminosalicylic acid** (the active drug)
- **Sulfapyridine** may cause nausea, vomiting and gastric distress

Salicylates Targeting the Colon

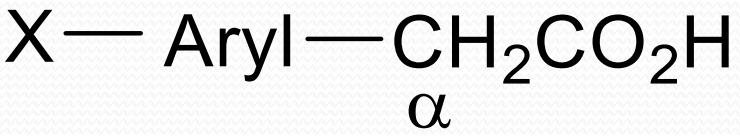
Olsalazine Sodium, Dipentum®

Disodium 5,5'-azodisalicylate



- Prodrug used for ulcerative colitis (especially for patients that cannot tolerate sulfasalazine due to allergic reactions to sulfonamides)
- 98-99% of the oral dose reaches the colon intact where it is metabolized by bacterial *nitroreductase* into two molecules of 5-aminosalicylic acid
- It works topically in the bowel mucosa to diminish colonic inflammation by inhibiting COX

ARYLACETIC ACIDS



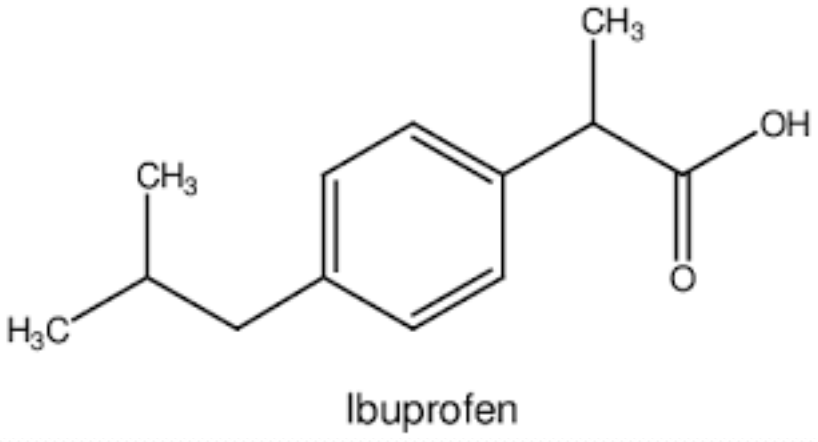
Structure-Activity

- An α-methyl group enhances activity
- With α-methyl analogs the (*S*)-enantiomer is the active form and is more potent as a prostaglandin synthesis inhibitor
- The (*R*)-enantiomer may be inverted *in vivo* into the active (*S*)-enantiomer in certain compounds and therefore many drugs in this class are administered as racemates
- A second area of lipophilicity (X) that is non-coplanar with the aromatic ring enhances activity and can be another aromatic ring or an alkyl group
- As acids all of the drugs in this class are highly protein bound

ARYLACETIC ACIDS

Ibuprofen, Motrin, Advil®

Benzeneacetic acid, α-methyl-4-(2-methylpropyl)-, (±)-



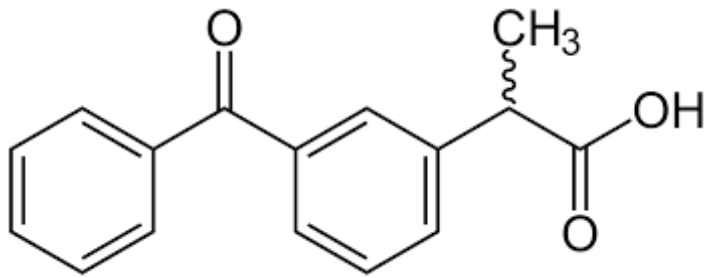
Ibuprofen

- Used for pain, arthritis and to reduce fever
- Has fewer side effects than aspirin
- Metabolites are products of ω- and ω-1 oxidation on the isobutyl group

ARYLACETIC ACIDS

Ketoprofen

Benzeneacetic acid, 3-benzoyl-α-methyl-

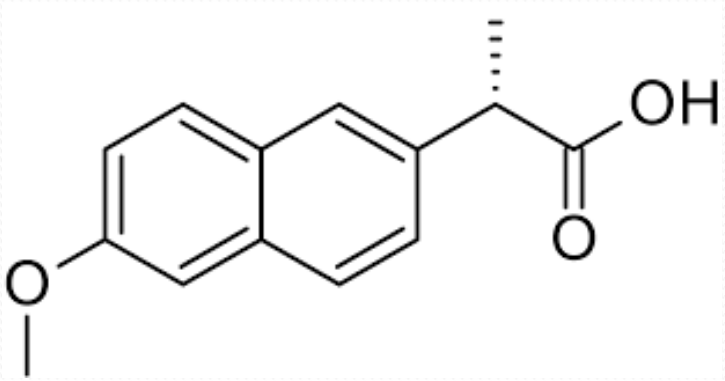


- Used for the long term management of arthritis, fever and pain
- This compound inhibits both cyclooxygenase and lipoxygenase
- It also has antibradykinin activity (which helps with pain management)
- Metabolized by reduction of ketone to alcohol and glucuronide conjugation of the acid

ARYLACETIC ACIDS

Naproxen, Naprosyn®, Anaprox®; Naproxen Sodium, Alleve®

2-Naphthaleneacetic acid, 6-methoxy-α-methyl-, (S)-

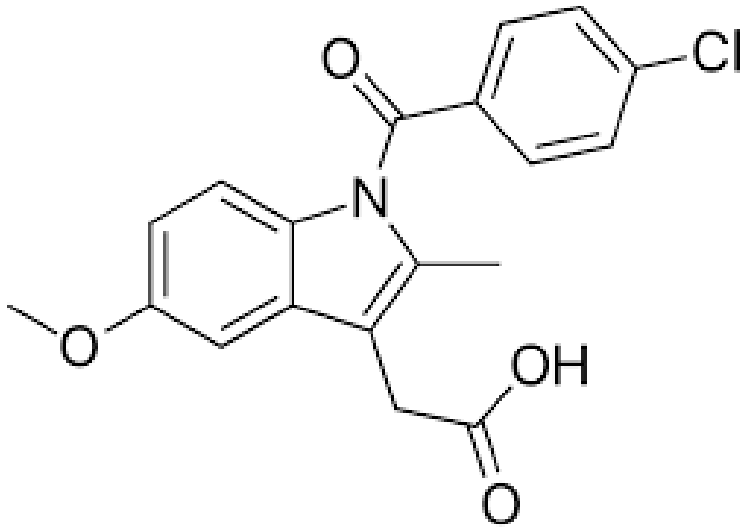


- Used for pain, fever, arthritis, ankylosing spondylitis (an inflammation of the sinovial joints of the backbone), tendinitis, bursitis, and acute gout
- Highly protein bound and displaces most other protein bound drugs meaning its use with other drugs must be done with caution
- It has a long half life (13 hr) and GI irritation is a side effect
- Metabolized by O-demethylation and then glucuronide formation

ARYLACETIC ACIDS

Indomethacin, Indocin®

1H-Indole-3-acetic acid,
1-(4-chlorobenzoyl)-5-methoxy
-2-methyl-

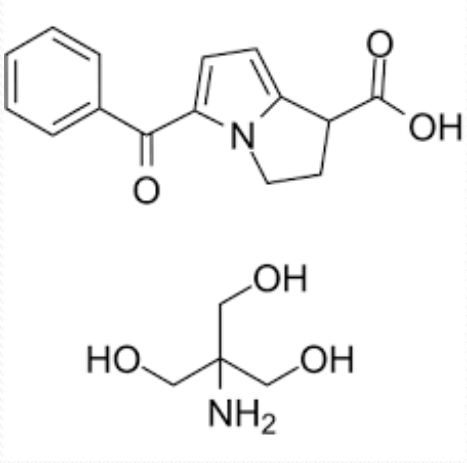


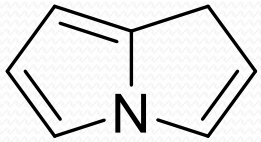
- Use for fever, pain, arthritis, ankylosing spondylitis, tendinitis, bursitis, acute gout and cluster headaches (unlabeled use)
- Very potent analgesic
- Side effects (dose related) include gastric distress and peptic ulcers
- Metabolites are derived from deacylation, O-dealkyation and glucuronide formation at the carboxylic acid group

ARYLACETIC ACIDS

Ketorolac Tromethamine, Acular (opthalmic)®

(±)-5-Benzoyl-2,3-dihydro-1H-pyrrolizine-1-carboxylic acid 2-amino-2-(hydroxymethyl)-1,3-propanediol salt (1:1)





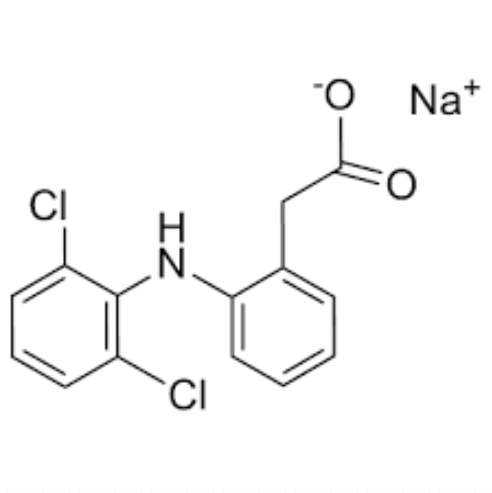
1H-Pyrrolizine

- Used short-term (5 days or less) for the management of moderately severe pain
- Given orally, by injection or intranasally
- This compound is a potent analgesic (equal to narcotic analgesics for controlling post-operative pain)

ARYLACETIC ACIDS

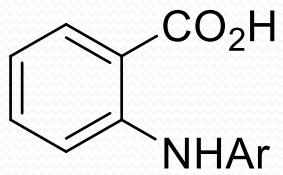
Diclofenac Sodium, Voltaren®

Benzeneacetic acid, 2-[(2,6-dichlorophenyl)amino]-, sodium salt



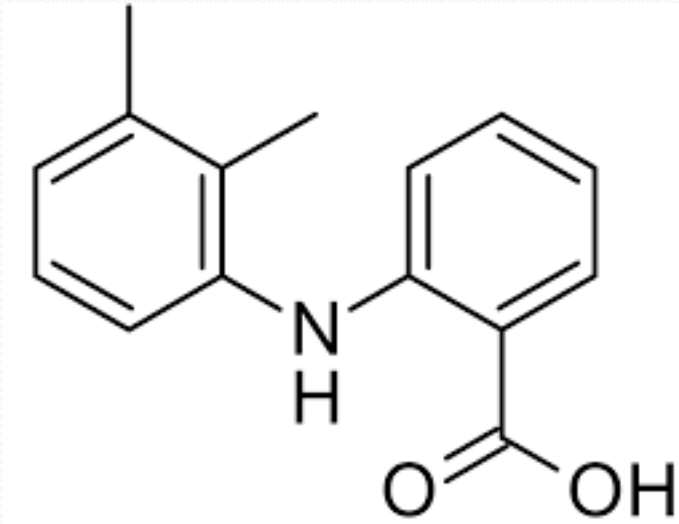
- Used for pain, migraine headaches, long-term treatment of arthritis and ankylosing spondylitis
- An opthalmic preparation is used for ocular inflammation and pain
- Metabolized by hydroxylation *p*-to the amino group in the non-chlorinated ring
- Inhibits COX, lipoxygenase and inhibits arachidonic acid release

N-Arylanthranilic Acids



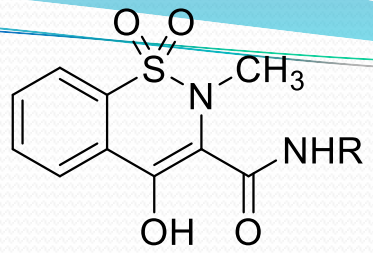
Mefenamic Acid, Ponstel®

Benzoic acid, 2-[(2,3-dimethylphenyl)amino]-



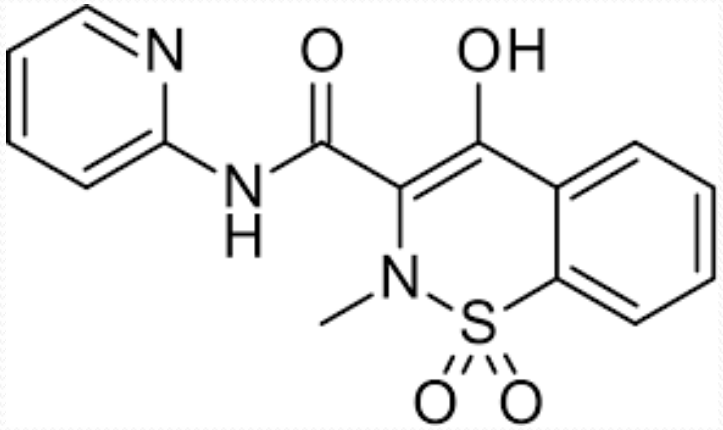
- Used for mainly for pain
- Only moderate anti-inflammatory activity
- Metabolized by oxidation of *m*-methyl group to a primary alcohol and then further to a carboxylic acid

Oxicams



Piroxicam, Feldene®

2H-1,2-Benzothiazine-3-carboxamide, 4-hydroxy-2-methyl-N-(2-pyridinyl)-, 1,1-dioxide

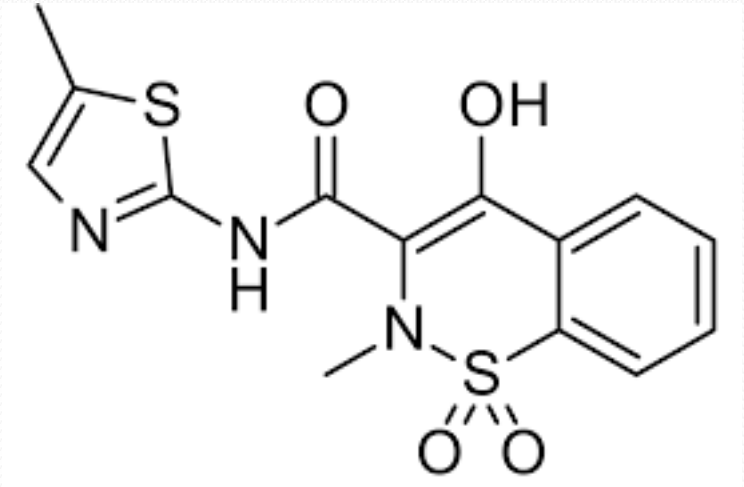


- Use for arthritis, both acute and long term
- Long lasting (38 hr $t_{1/2}$) allowing daily dosing
- Better tolerated than aspirin
- Metabolized by amide hydrolysis and hydroxylation in the pyridine ring (5-position)

Oxicams

Meloxicam, Mobic®

4-Hydroxy-2-methyl-N-(5-methyl-2-thiazolyl)-2H-1,2-benzothiazine-3-carboxamide 1,1-dioxide



- Used for arthritis
- Metabolized on the thiazole methyl group to a primary alcohol and then further to the carboxylic acid


Thank
you!