Topic 9: Nonsteroidal anti-inflammatory drugs

Dr. Mohyeddin Assali
PhD. Medicinal chemistry-Nanomedicine
Department of pharmacy
Faculty of Medicine & Health sciences

❖ INTRODUCTION

➢ NSAIDs medications are the most widely prescribed drugs worldwide for the treatment of rheumatic arthritis and other degenerative inflammatory joint diseases.

➢Many of them possess antipyretic and analgesic properties

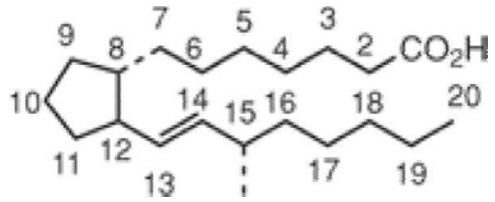
➢Some of these drugs possess analgesic/antipyretic properties but have no anti-inflammatory activity.

➢ They also associated with many undesirable side effects, including GI irritation and bleeding, platelet dysfunction, kidney damage, and bronchospasm.

NSAIDs mechanism of action

- Inhibition of two closely related cyclooxygenase enzymes COX-1 and COX-2.
  - These are the rate-limiting enzymes in the synthesis of:
    - The inflammatory prostaglandins PGE_2 and $PGF_{2\alpha}$
    - The cytoprotective prostaglandin PGE_1
    - The vasoactive prostanoids thromboxane A_2 (TXA_2) and prostacyclin (PGI_2).

Prostaglandines:

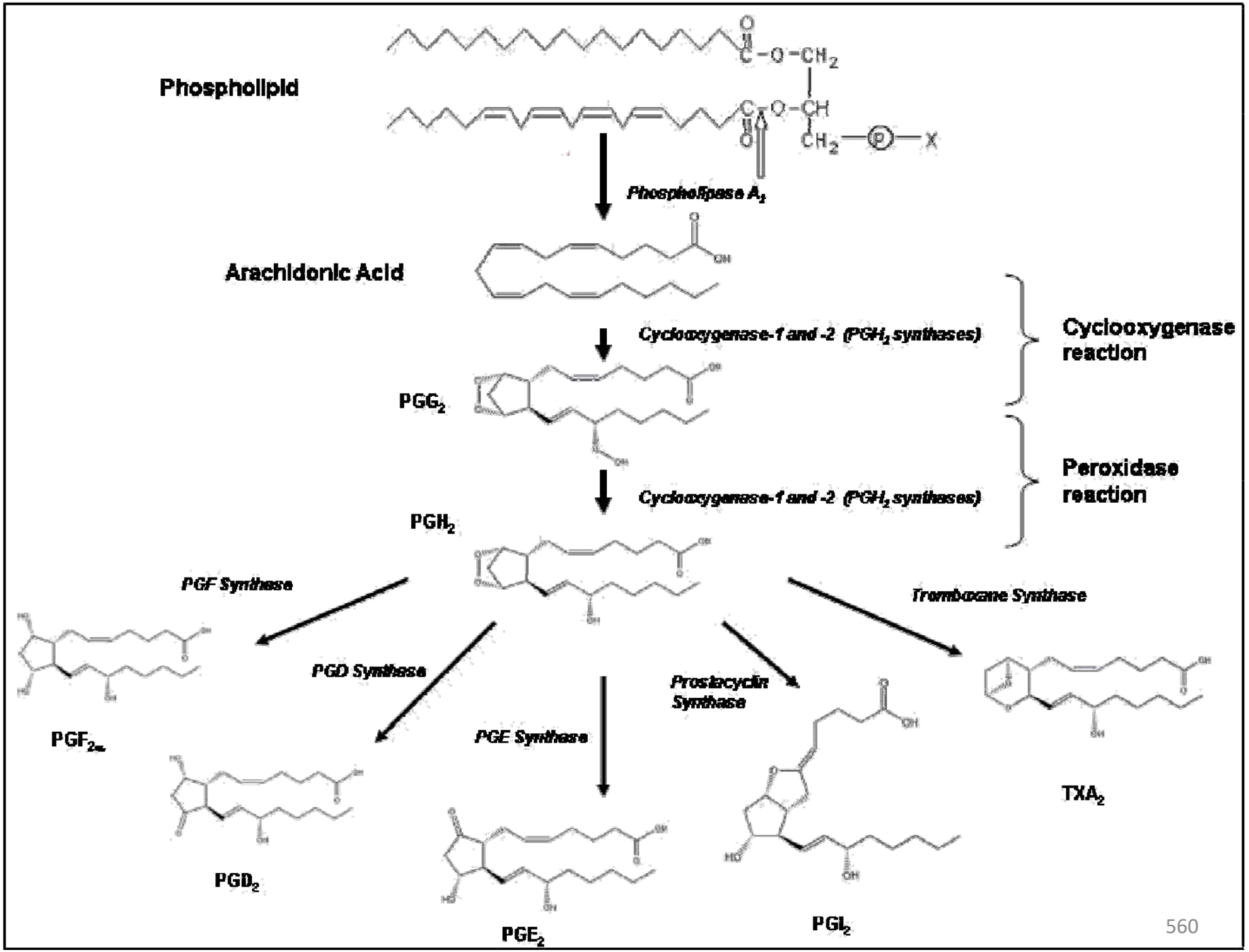


- The prostaglandins are classified by the capital letters A, B, C, D, E, F, G, H, and I (e.g., PGA, PGB, and so on)
  - Depending on the nature and stereochemistry of oxygen substituents at the 9- and 11-positions.
  - For example, members of the PGE series possess a keto function at C-9 and an α-hydroxyl group at C-11
  - Where as members of the PGF series possess α-hydroxyl groups at both of these positions.

• Prostaglandins “PG” are biosynthesized via a tissue-specific cyclooxygenase pathway (COX-1 or COX-2)

• The cyclooxygenase pathway involved in the biosynthesis of these PGs from arachidonic acid (AA), a polyunsaturated fatty acid released from membrane phospholipids by the action of phospholipase A2.

• 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.


Phospholipid
Phospholipase A2
Arachidonic Acid
Cyclooxygenase-1 and -2 (PGH2 synthases)
Cyclooxygenase reaction
PGG2
Cyclooxygenase-1 and -2 (PGH2 synthases)
Peroxidase reaction
PGH2
PGF Synthase
Tromboxane Synthase
PGD Synthase
Prostacyclin Synthase
PGE Synthase
PGF2α
PGD2
PGE2
PGI2
TXA2

Inhibition of prostaglandins by NSAIDs

- It is the cyclooxygenase step at which the NSAIDs inhibit prostaglandin biosynthesis
- cyclooxygenase inhibition would have a profound effect on the reduction of inflammation.
  - Because PGG2 and PGH2 themselves may possess the ability to mediate the pain, inflammatory responses and produce vasoconstriction,

- Most NSAIDs inhibit both COX-1 and COX-2, but with varying degrees of selectivity.
- Selective COX-2 inhibitors may eliminate side effects associated with NSAIDs
- The difference between COX-1 and COX-2 :
  - The difference is in physiological function
  - Little difference in structure.
  - Little COX-2 is present in resting cells
  - COX-2 produce prostaglandins at inflammatory sites.
  - COX-1 produce prostaglandins in normal cellular activity

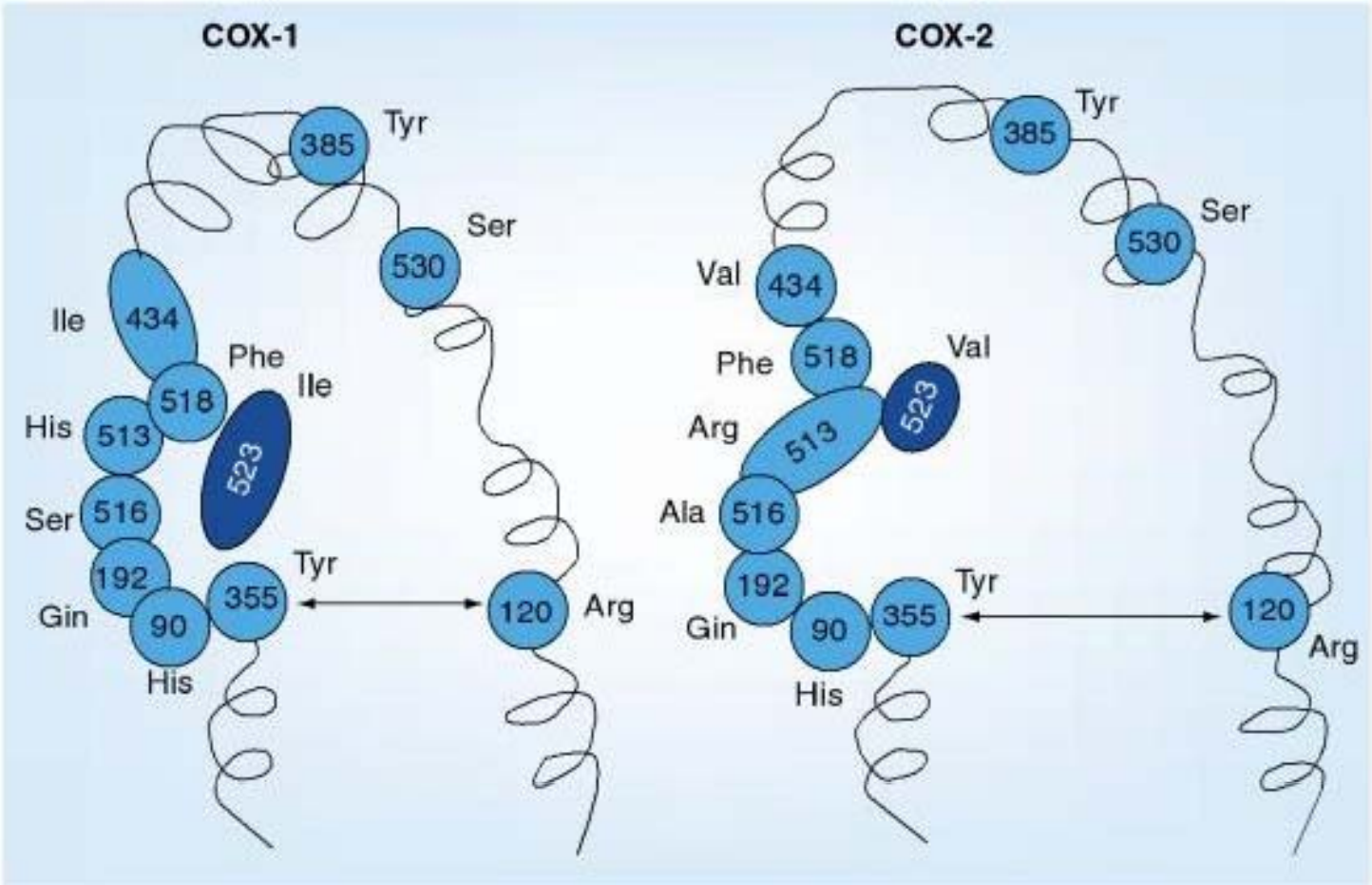
- Most drugs inhibit COX-1 in addition to COX-2
  - Most NSAIDs are mainly COX-1 selective (eg, aspirin, ketoprofen, indomethacin, piroxicam, sulindac).
  - Thus experiencing side effects:
    - Gastrointestinal (GI) distress as result of COX-1 inhibition in the stomach
    - Hemorrhage (inhibition of COX-1 on platelets)
    - Renal toxicity
- Slightly selective for COX-1 (eg, ibuprofen, naproxen, diclofenac)
- Slightly selective for COX-2 (eg, etodolac, nabumetone, and meloxicam).
- Primarily selective inhibition of COX-2 (celecoxib and rofecoxib)

- Treating inflammation by NSAIDs should ideally target COX-2
  - Since it is expressed during pathological conditions.
- COX-2 selective inhibitors:
  - Have lower risk of inducing GI distress and haemorrhage
    - (COX-1 mediated activities)
  - The risk of negative cardiovascular events
    - Due to inhibiting PGI_2 in the vessel wall (a COX-2 mediated action)
    - This increased cardiovascular risk led to removal of two COX-2 selective NSAIDs (rofecoxib and valdecoxib) from the market.

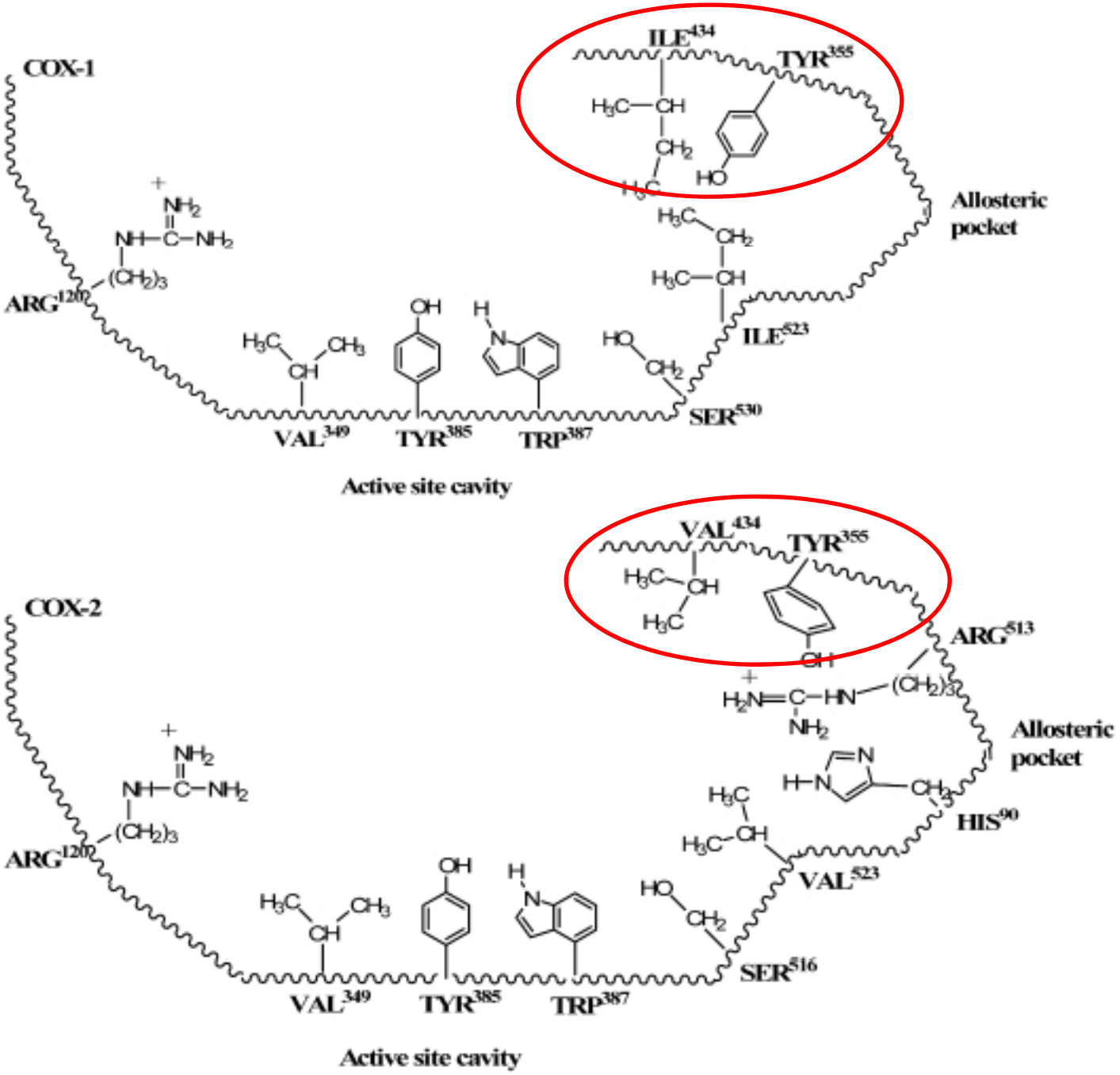
Structure of COX1 & COX2 enzyme:

- Both COX-1 and COX-2 are very similar in structure and almost identical in length.
- Despite their similarity, the active site for COX-2 is approximately 20% larger than the COX-1 binding site because of the replacement of Ile-523 in COX-1 with a smaller Val-523 in COX-2.
- So there are a total of 24 amino acid residues lining the largely hydrophobic side pocket with the only difference between Val and Ile.
- The isoleucine at positions 434 and 523 in COX-1 is exchanged for valine in COX-2.
  - The smaller size of Val-523 in COX-2 allows inhibitor access to a side pocket off the main substrate channel,
  - Whereas the longer side chain of isoleucine in COX-1 sterically blocks inhibitor access.
- The size and nature of the hydrophilic side pocket for binding in COX-2 is a result of substitutions Ile-434 and His-513 in COX-1 with a smaller Val-434 and a more basic Arg-513.
- All other residues that are essential to the catalytic activity of COX-1 are also present in COX-2.

➢ Arg-120 is the only positively charged a.a. residue in the COX active site, and is responsible for binding, via an ionic interaction, with the carboxylate anion of the substrate (AA) or the conventional NSAIDs.



- The orientation of tyrosine (TYR) 355 open up the COX-2 allosteric pocket for therapeutic manipulation.
- The bulkier ILE residues and the conformation of TYR355 in COX-1
  - Makes diarylheteroaromatic NSAIDs (eg celocoxib) can’t inhibit COX1 but specifically inhibits COX2


COX-1
ILE434
TYR355
Allosteric pocket
ARG120
ILE523
SER530
VAL349
TYR385
TRP387
Active site cavity
COX-2
VAL434
TYR355
ARG513
Allosteric pocket
HIS90
VAL523
ARG120
SER516
VAL349
TYR385
TRP387
Active site cavity

❖ CLASSES OF COX INHIBITORS

The COX inhibitors can be grouped into ***four classes*** based on their mechanism of action.

1. ***Irreversible inhibitors***. Aspirin is the only known member of this group
2. ***Reversible competitive inhibitors*** of both COX which is freely reversible
3. ***Slow time dependent inhibition*** of both COX—they bind and induce a conformational change in the enzyme thus binding very tightly and dissociated very slowly. It can take several seconds to minutes to reach equilibrium between the reversible and pseudo irreversible complex. *However, in vivo both mechanism 2 and 3 are essentially the same.*
4. ***Selective reversible competitive inhibitors COX–2***. These agents induce a slow conformational change in COX-2 but not in COX-1. The change increases the inhibitor affinity by >10 fold by binding very tightly and dissociating very slowly. Thus the isozyme selective induction of a conformation change in the enzyme leads to potent inhibition of COX-2 that is not seen for COX-1

❖ Binding of NSAID to COX enzymes

- The "classical" nonselective NSAIDs bind to both COX-1 and COX-2, interacting with the hydrophobic channel of the COX isoenzymes
- Aspirin, unlike other NSAIDs, irreversibly acetylates a serine residue in both COX-1 and COX-2 preventing arachidonic acid from reaching the catalytic site
- Other nonselective NSAIDs compete directly with arachidonic acid, inhibiting cyclooxygenase activity in a reversible manner
- Coxibs, the COX-2-selective inhibitors, preferentially bind to and inhibit COX-2. Coxibs are selective agents because they bind COX-1 poorly and in a rapidly reversible manner, whereas they bind COX-2 more tightly

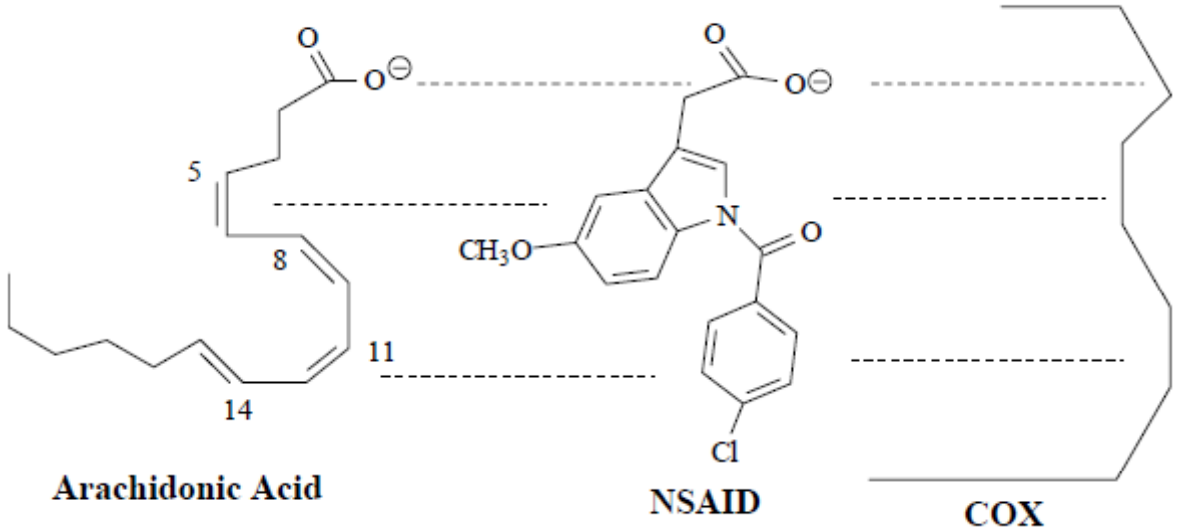
- Preferential inhibition of COX-2 is thought to be due to the additional space in the COX-2 hydrophobic channel, as well as to the presence of a side pocket in the channel. This side pocket can discriminate the coxibs from nonselective agents based on the different overall structures of these agents, in particular, by the presence in **coxibs** of **specific side chains**
- NSAIDs do not affect the peroxidase site

❖ THE COX BINDING SITE

1. A cationic center and two hydrophobic areas
2. The cationic site is attributed to a guanidinium group on Arginine
3. The first hydrophobic area is located adjacent to the cationic center
4. The second region lies under and out of the plane with the first hydrophobic area and is commonly referred to as a trough.

- Some agents can bind only the cationic center and the first hydrophobic area
- Others can bind all three, resulting in better binding
- The only way to bind both hydrophobic regions simultaneously is if the drug contains two aromatic ring systems that are perpendicular and not coplanar

- Binding to the trough can enhance potency. If the ring cannot fit into the trough then it bangs into the walls of the enzyme, sterically inhibiting binding
- If the two rings are separated by one or more sigma bonds, the two rings may assume a large number of possible conformations due to free rotation around a sigma bond, only a few compliment the receptor. Making rigid molecule with correct conformation gives potent drugs



Inhibition of COX by NSAIDs

❖ SAR Summary for COX Inhibitors

SAR1: Molecule must have an ionizable acid group and an aromatic ring system

SAR2: A second non coplanar aromatic ring increases potency by increasing bonding interactions

SAR3: Limiting the number of possible conformers increase potency

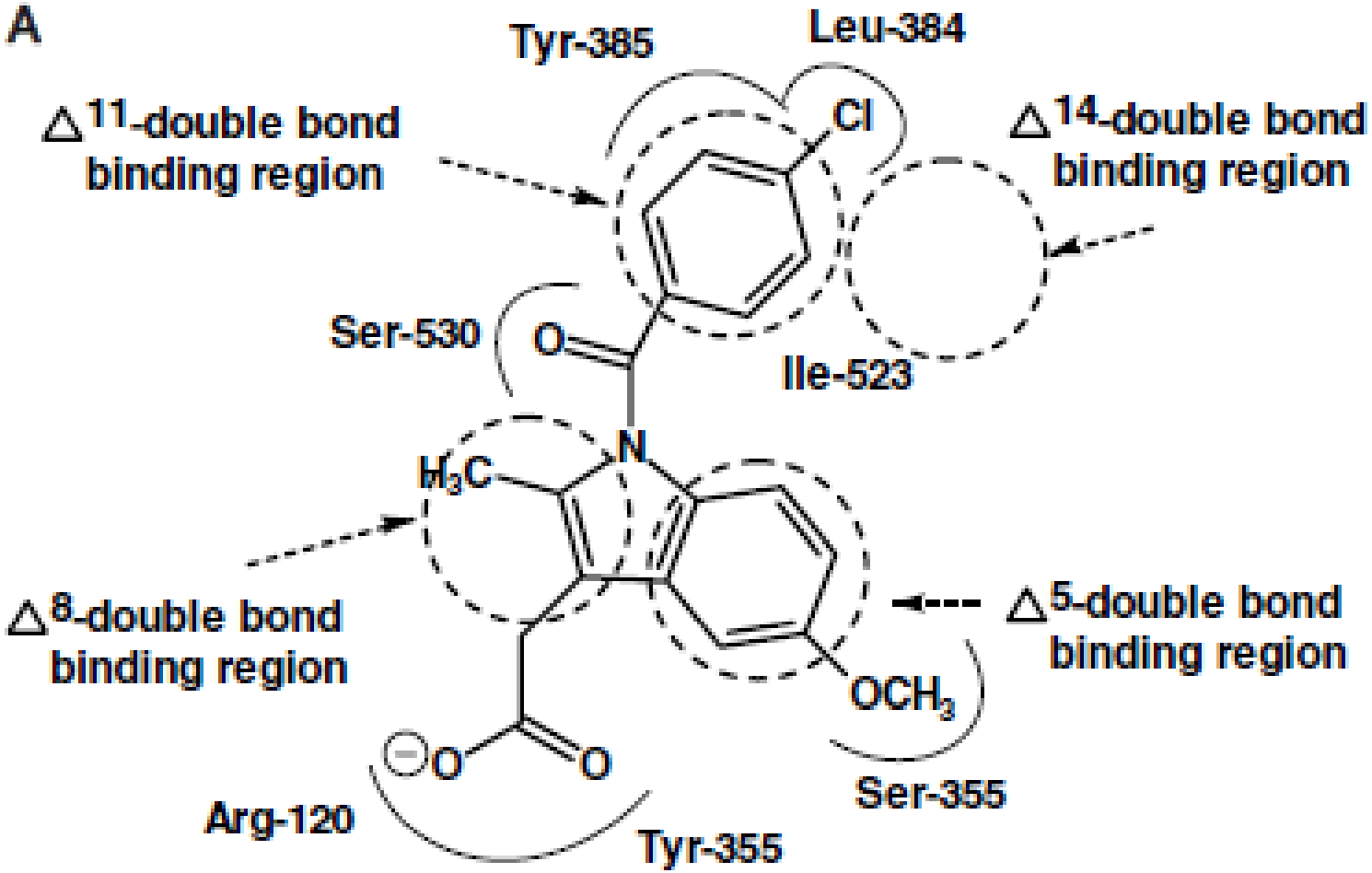
SAR4: A two atom separation between the anionic charge and the aromatic ring is the optimal

SAR5: Increasing the distance to 3 or 4 carbons generally decreases potency

SAR6: Introduction of a methyl at the first carbon increases potency and introduces a chiral center

SAR7: The S–isomers are the more potent isomers

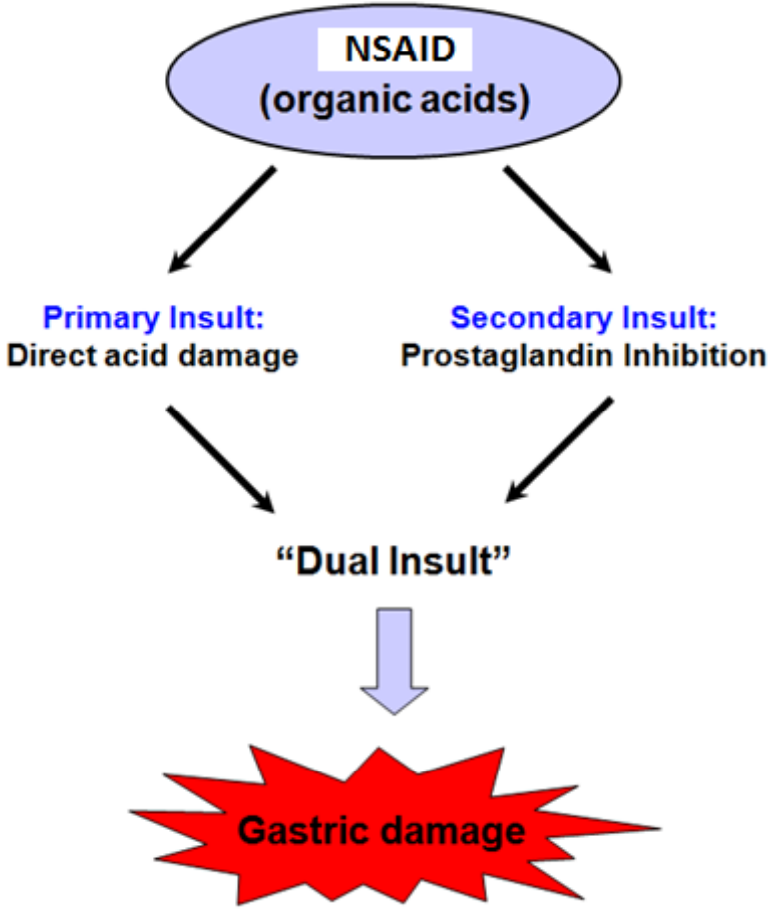
SAR8: Increasing the size of the alkyl decreases potency but incorporation of the alkyl into a heterocycle retains activity


A
Tyr-385
Leu-384
Δ11-double bond binding region
Cl
Δ14-double bond binding region
Ser-530
O
Ile-523
N
H3C
Δ8-double bond binding region
Δ5-double bond binding region
OCH3
O
O
Ser-355
Arg-120
Tyr-355

The dual insult

- NSAIDs can cause GI toxicity:
  - Dyspepsia, abdominal pain, heartburn, gastric erosion leading to wall perforation, peptic ulcer formation, bleeding, diarrhoea, renal disorders.
- Dual Insult:
  - *Primary Insult:* Because most NSAIDs are acidic substances that produce a direct acid damage
  - *The secondary insult:* Results from inhibition of prostaglandin biosynthesis in the GI tract (cytoprotective effect).

NSAID *"Dual Insult"*

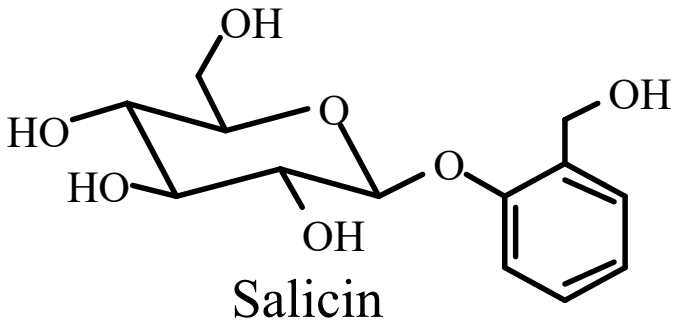


NSAID major chemical categories

- NSAID products can be categorized according to its chemical classes:
  1. Salicylates
  2. Fenamates (N-Arylanthranilic Acids)
  3. Aryl acetic acids
  4. Aryl propionic acids
  5. Oxicams
  6. Pyrazoles and Pyrazolidinediones
  7. Acetaminophen
  8. COX-2 selective diarylheteroaromatics.

1) THE SALICYLATES

- Salicylic acid is a natural product, present in the bark of willow and poplar trees
- The active ingredient, isolated by a French pharmacist in 1827, was Salicin, oxidized to Salicylic acid
- In 1875 a Swizz pharmacist, Lowig, distilled meadowsweet flowers and got salicylaldehyde

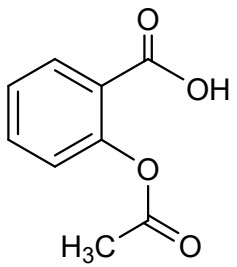


Salicin

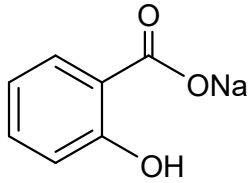
Salicylates

- Salicylate Salts
- Aspirin
- Salicylamide
- Diflunisal
- Salsalate
- Benorylates

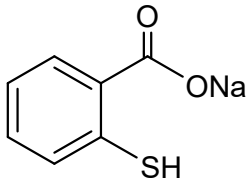
ASPIRIN



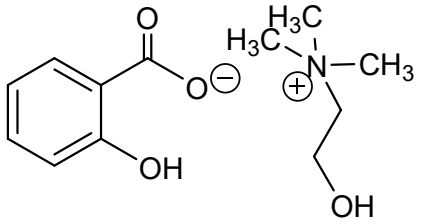
SODIUM SALICYLATE

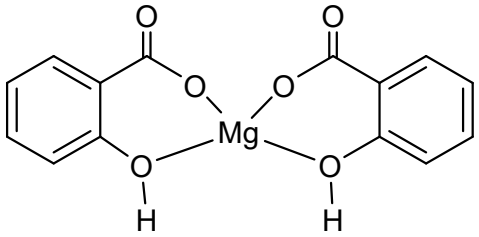


SODIUM THIOSALICYLATE

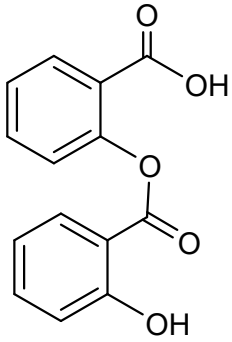


CHOLINE SALICYLATE

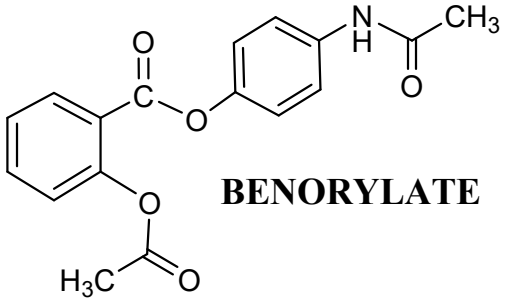




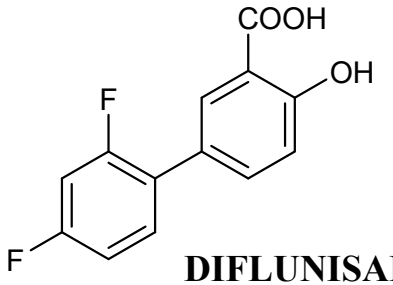
MAGNESIUM SALICYLATE



SALSALATE



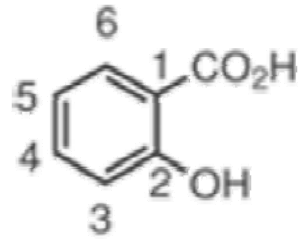
BENORYLATE



DIFLUNISAL

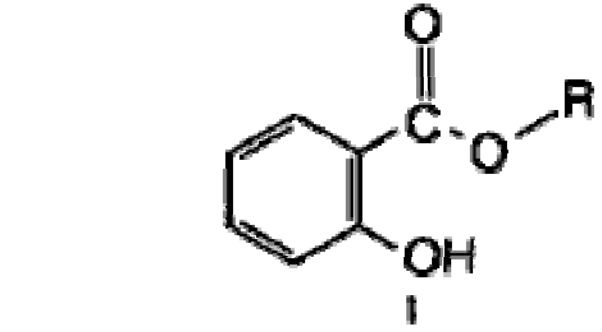
❖ Salicylate SARs

- The simplest active compound is the salicylic acid anion.
- The carboxylic group is necessary for activity and the hydroxyl group must be ortho to it.
  - Placing the phenolic hydroxyl group *meta* or *para* to the carboxyl group abolishes this activity.
- Intr~~oduction of electronegative groups and lipophilic groups increases anti-inflammatory activity and toxicity.~~
- The side effects of aspirin, particularly the GI effects is associated with the carboxylic acid function.
  - Reducing the acidity of this group (e.g., converting to an amide, salicylamide): Maintains the analgesic actions of salicylic acid derivatives, but eliminates the anti-inflammatory properties.

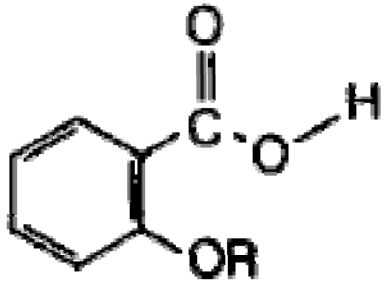


- Substitution on either the carboxyl or phenolic hydroxyl groups will affect potency and toxicity.
- Benzoic acid itself has only weak anti-inflammatory activity.
- Substitution of halogen atoms on the aromatic ring Increases the potency and toxicity.
- Substitution of aromatic rings at the 5-position of salicylic acid increases anti- inflammatory activity (e.g., diflunisal).

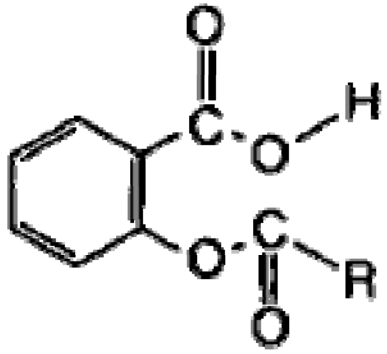
- The derivatives of salicylic acid are of two types I and II (a and b)
  - **Type I**: formed by modifying the carboxyl group (e.g. salts, esters, or amides).
  - **Type II** (a and b):derived by substitution on the hydroxyl group of salicylic acid.



I



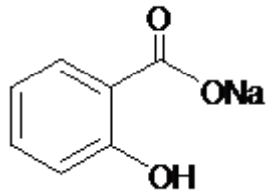
IIa



IIb

Salicylate Salts

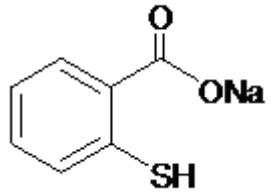
- These salts are used primarily to decrease GI disturbances
- Several salts of salicylic acid:
  a) Sodium salicylate
  b) Sodium thiosalicylate
  c) Magnesium salicylate
  d) Choline salicylate



a) Sodium Salicylate

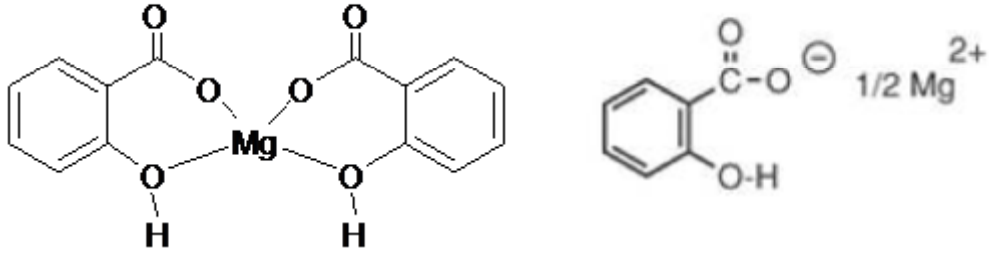
- Salicylic acid in the unionized form has a bad taste
- Thus the sodium salt is used more frequently

b)Sodium Thiosalicylate **(Rexolate ®)**



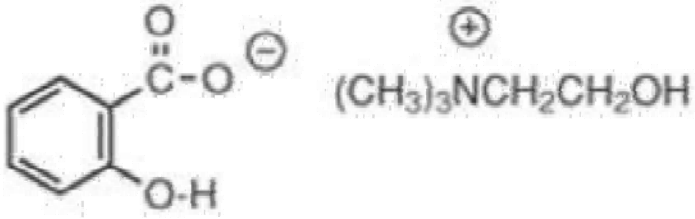
- Sodium thiosalicylate is the sulphur or thio analogue of sodium salicylate.
- It is more soluble and better absorbed
  - thus allowing lower dosages.
- It is recommended For:
  - Gout.
  - Rheumatic fever
- It is available only for injection.

C) Magnesium Salicylate



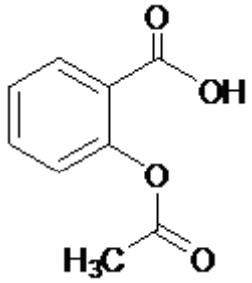
- Magnesium salicylate **(Mobidin®, Magan®)**
  - It is stable in aqueous solution
  - It showed some success in overcoming the GI problems.
  - Is a sodium-free salicylate preparation
    - Used when sodium intake is restricted.
  - The dosage and indications are the same as those for sodium salicylate.

d)Choline Salicylate **(Arthropan®)**



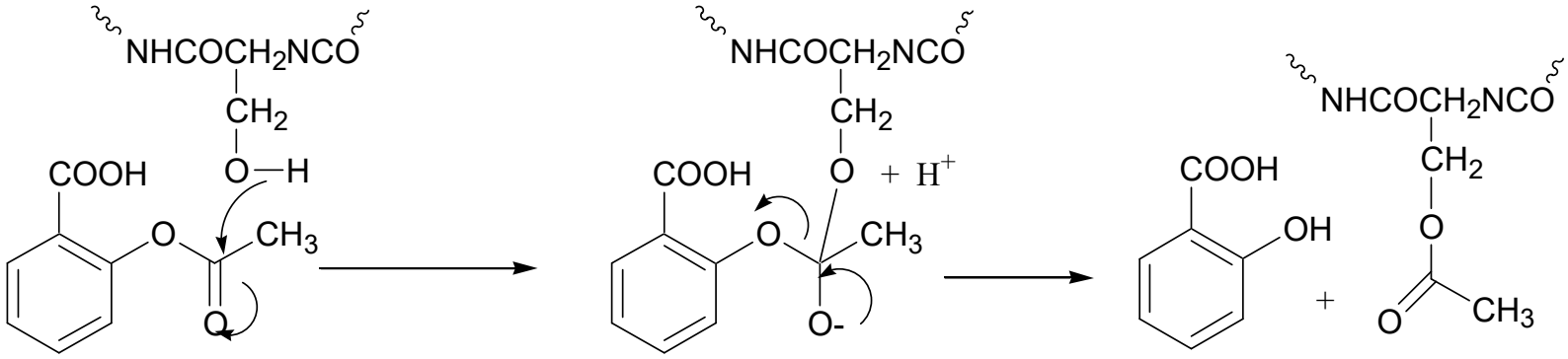
- Choline salicylate is absorbed faster than Aspirin
- Producing higher salicylate blood levels and an aqueous formulation is available.
- Choline salicylate is extremely soluble in water and is available as a flavoured liquid.
- It is claimed to be absorbed more rapidly than aspirin giving faster peak blood levels.
- It is also available in combination with magnesium salicylate **(Trilisate®, Tricosal®)**

Aspirin



- Acetylsalicylic acid was prepared in 1853 but was not used medicinally until 1899.
- Searching for a less toxic better tolerated derivative of salicylic acid produced aspirin.
- The knowledge that acetylation of the very toxic aniline produced the less toxic acetanilide, acetylation of salicylic acid with acetic anhydride produced Aspirin.
- It is slightly soluble in water, absorbed as such, but is hydrolyzed rapidly to salicylate and acetate by esterases
- Pharmacological actions are attributed to both the ASA and salicylic acid

- ASA irreversibly inhibits the enzyme acetylating a serine residue thus preventing access to the cyclooxygenase site
- So aspirin inhibit prostaglandin and block it irreversibly.
- Aspirin is the only NSAID that covalently binds to cyclooxygenase by acetylating Ser-530 of COX-1 and Ser-516 of COX-2
- Salicylic acid forms a reversible ionic bond with the cationic site on cyclooxygenase

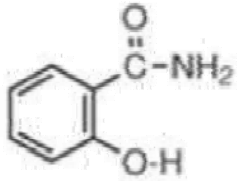


- Aspirin is 10 to 100 times more potent against COX-1 than against COX-2.
- In low doses (81 mg); aspirin will selectively inhibit platelet (COX1) this will decreases the risk of myocardial infarction and stroke.
- But COX-1 selectivity is lost when doses are increased
- The inhibition of COX-2 at higher doses can negate the cardiovascular protecting action by inhibiting the production of the anti-aggretatory prostanoid PGI2.
- Side effects Include: GI disturbances such as dyspepsia, gastro duodenal bleeding, gastric ulcerations, and gastritis
- Aspirin is not hydrolyzed on contact with acidic digestive fluids of the stomach
- Pharmacist counselling for patients using aspirin for cardiovascular health:

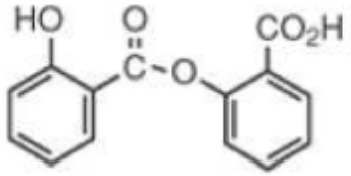
– Keep doses low

– Separate administration of aspirin and other NSAID which treat pain or inflammation by several hours (eg, ibuprofen, naproxen).

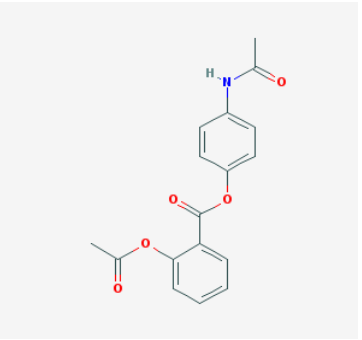
Salicylamide



- It is *o*-hydroxybenzamide.
- It is prepared from salicyl chloride and ammonia.
- It is has quicker and deeper analgesic effect than aspirin.
- Its metabolism differs from that of other compounds
  - It is not hydrolyzed to salicylic acid.
- It is useful for patients with a demonstrated sensitivity to salicylates.
- Salicylamide enters the CNS more rapidly than other salicylates
  - Thus it will cause sedation and drowsiness when administered in large doses.

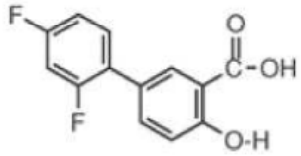


Salsalate & Benorylate



- Salsalate and Benorylate are prodrug esters.
- Salsalate is an ester of salicylic acid and benorylate is esterified with Acetaminophen.
- Salsalate is only half as potent as an analgesic/antipyretic as Aspirin but produces less GI irritation.
- The sodium salt is freely soluble in water
  - This helps in its dissolution and faster absorption.
- Salsalate is insoluble in gastric pH but soluble in the small intestines
  - Thus causing less gastric problems.

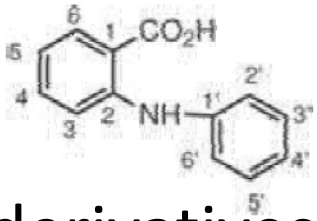
Diflunisal (Dolobid®)



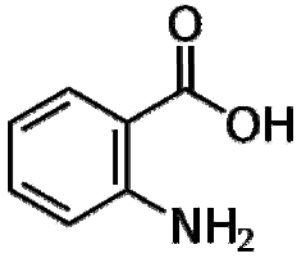
Diflunisal (Dolobid)

- Diflunisal is absorbed only in intestine
  - It is not soluble in gastric fluid.
  - Thus, gastric bleeding and GI upset is not as common.
- It is more potent than aspirin and lasts 3–4 times longer than aspirin. The increase in potency is due to:
  - the presence of a **second aromatic** ring which increase the binding to the receptor
  - **2,4-difluorophenyl** gp attached to the 5-position of the salicylic acid.
  - The proximity of the two phenyl rings, make the electron of the two radius to repel and thus keep the rings out of the same plane (**Non co -planarity**).

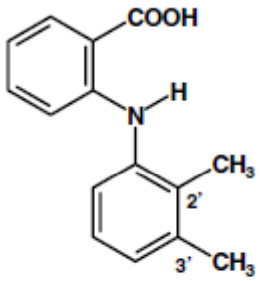
2) N-Arylanthranilic Acids (Fenamic Acids)



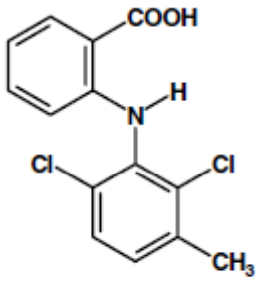
- The Fenemates are derivatives of Anthranilic acid, an isoster of salicylic acid.



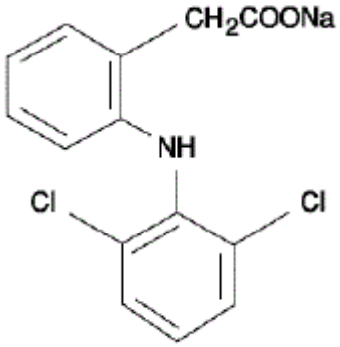
- It showed significant anti-inflammatory action
- They include:
  - Mefenamic acid **(Ponstel®)**,
  - Meclofenamic acid **(Meclomen ®)**
  - Diclofenac sodium
  - Flufenamic acid



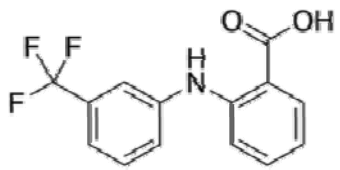
Mefenamic acid



Meclofenamic acid



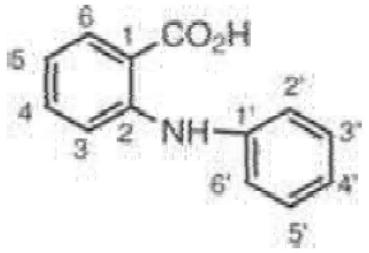
diclofenac sodium



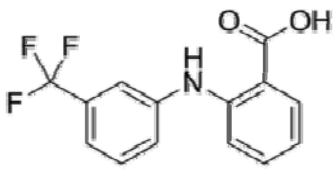
Flufenamic acid

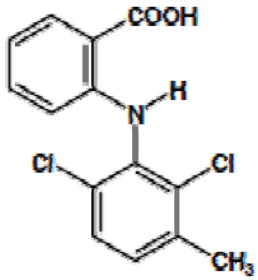
- The anthranilic acid class of NSAIDs is the result of the application of the bio-isosteric drug design concepts
  - They are nitrogen isosteres of salicylic acid.
- The fenamic acids are potent inhibitors of prostaglandin biosynthesis
- ~~This class offers no advantage over the salicylates~~
  - ~~There is little interest in developing an improving this class~~

SAR of fenamic acid derivatives:



- Substitution on the anthranilic acid ring generally reduces activity
- Whereas substitution of the N-aryl ring lead to conflicting results
  - The order of activity generally 3′ >2′ ≫ 4′
  - For monosubstitution, with the 3′-CF3 derivative (flufenamic acid) being particularly potent.
  - Other studies have shown that the 2′-Cl derivative (Meclofenamic acid) being more potent than the 3′-Cl analogue

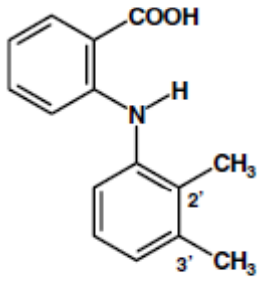




Meclofenamic acid

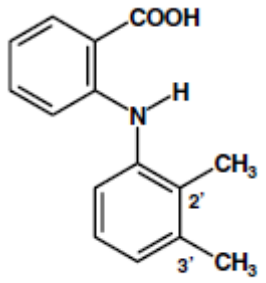
– The most potent analogs are those disubstituted at 2’ and 3’. This indicates that activity resides in compounds with the substituent on the second ring that keep it out of co-planarity by the ortho substituent

– (Mefenamic acid)



Mefenamic acid

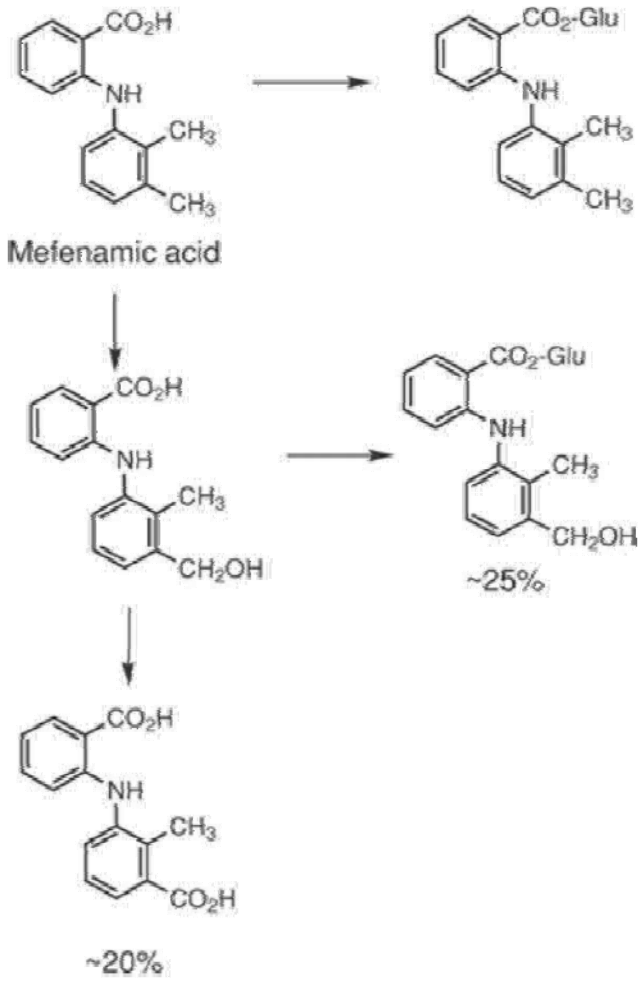
Mefenamic Acid:



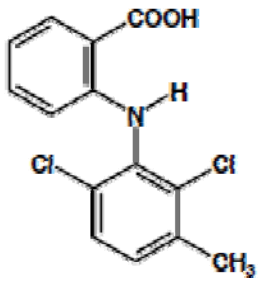
Mefenamic acid

- It is N-2,3-xylylanthranilic acid.
- Introduced in the United States
- Used as sodium salt
- Commonly used as an anti-rheumatic agent & analgesic.
- it has two methyl substituent at 2’ & 3’
  - This ensures non-coplanarity.

- Metabolism occurs through;
  - Selective oxidation of the 3’-methyl group
  - Glucuronidation of mefenamic acid & its metabolites.
  - These metabolites are essentially inactive.



Meclofenamate Sodium:



Meclofenamic acid

- The chlorine atoms of Meclofenamate
  - Assume the correct conformation and the drug is more potent.
- Meclofenamate is 25 times more potent
  - Thus normal dose for Meclofenamate is 25 mg while the dose for Mefenamic acid is 250 mg.

- The 25-fold anti-inflammatory activity enhancement of meclofenamic acid over mefenamic acid is due to
  - consistently non-coplanar orientation of aromatic rings
    - This is important for optimal binding COX active-site residues.
  - And enhanced lipophilicity provided by the two ortho-chlorine atoms.
- Meclofenamate sodium is rapidly and almost completely absorbed following oral administration

- Metabolism involves:
  - Oxidation of the methyl group,
  - Aromatic hydroxylation
  - ~~Monodehalogenation~~
  - Conjugation.
- The major metabolite is the product of 3′-methyl oxidation
  - It possesses anti -inflammatory activity

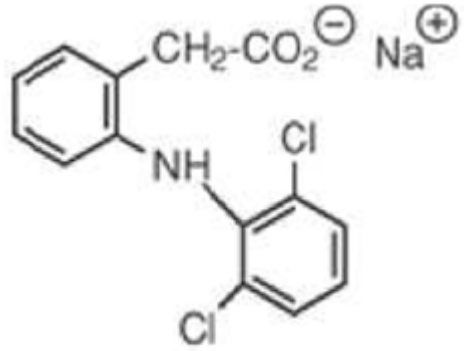
Meclofenamic acid 50-60% (active) 3-5% (inactive)

Diclofenac Sodium

- Diclofenac has a structural characteristics of both:
  - The arylalkanoic acid and the anthranilic acid
- Diclofenac is derived from 2- arylacetic acid.
- Diclofenac is the most widely used NSAID in the world
  - As an analgetic:
    - It is six times more potent than indomethacin
    - 40 times as potent as aspirin
  - As an antipyretic:
    - it is twice as potent as indomethacin
    - and more than 350 times as potent as aspirin.

- Diclofenac possesses three possible mechanisms of action:
  1. Inhibition of the arachidonic acid cyclooxygenase system
     - Decreased production of prostaglandins and thromboxanes;
  2. Inhibition of the lipoxygenase pathway
     - Decreased production of leukotrienes, particularly the pro-inflammatory LKB4
  3. Inhibition of arachidonic acid release and its reuptake
     - Reduction of arachidonic acid availability.

SAR of diclofenac

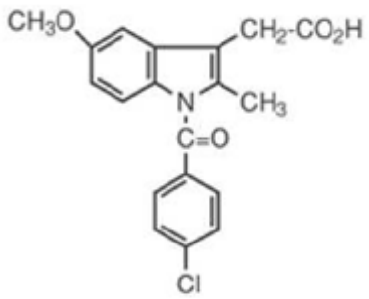


- The SARs in Diclofenac sodium are similar to those with the Fenemates.
- The two *o*-chloro groups is to force the anilino-phenyl ring out of the plane of the phenylacetic acid portion
  - This twisting effect being important in the binding
- The Sodium salt has a delayed release formulation
  - While the Potassium salt is used in a rapid release formulation (Cataflam®).

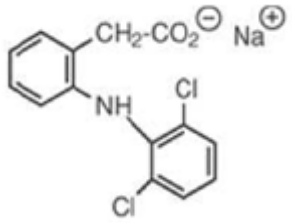
3)ARYLACETIC ACID DERIVATIVES

- Satisfy **SAR 1, SAR 2, SAR 4** as well as **SAR 3** thus are generally more potent than ASA
- The arylacetic acid has the most intensive attention for new clinical drugs.
- They show high analgesic potency in addition to their anti-inflammatory activity.
- This group include:

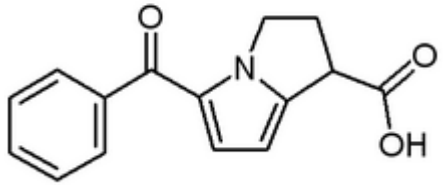
a) Indomethacin
b) Sulindac
c) Etodolac
d) Ketorolac
e) Nabumetone
f) We can consider the **Diclofenac Sodium** in this group Bcz it has arylacetic acid



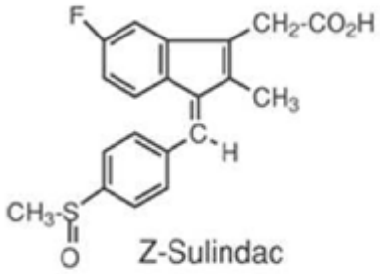
Indomethacin



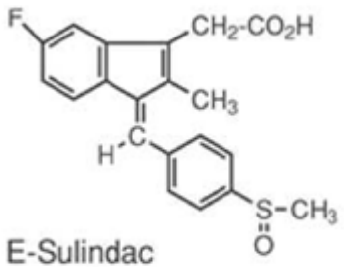
Diclofenac sodium



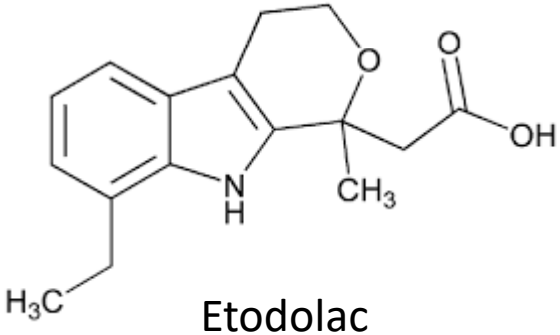
Ketorolac



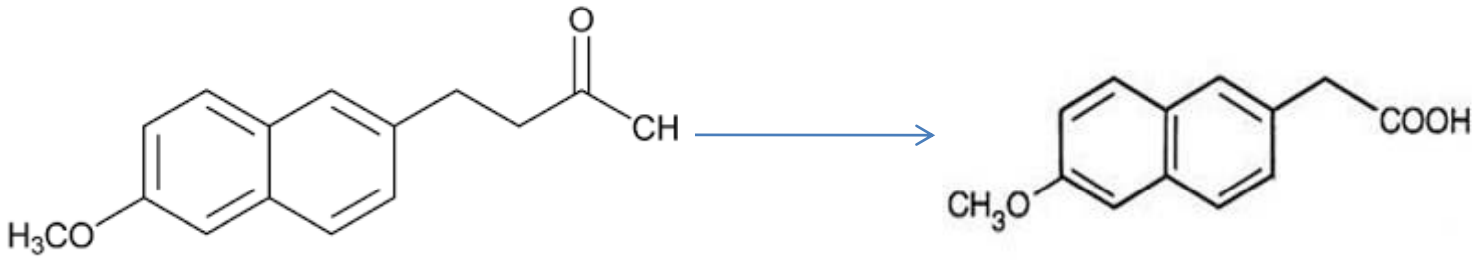
Z-Sulindac



E-Sulindac

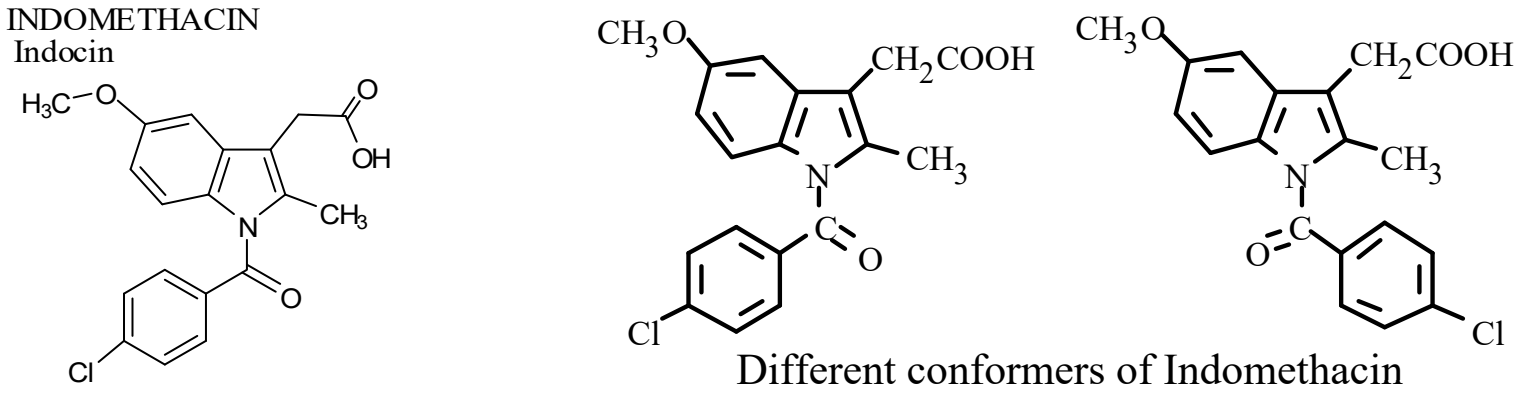


Etodolac



Nabumetone

a) Indomethacin (Indolin, indocaps)



Different conformers of Indomethacin

- **Indomethacin** was synthesized in 1961 at Merck as part of a study of indole derivatives as potential anti–inflammatory agents.
- 1*H*-Indole-3-acetic acid, 1-(4-chlorobenzoyl)-5-methoxy-2-methyl.
- Aqueous solutions of indomethacin are not stable:
  - Because of the ease of hydrolysis of the *p*-chlorobenzoyl group.

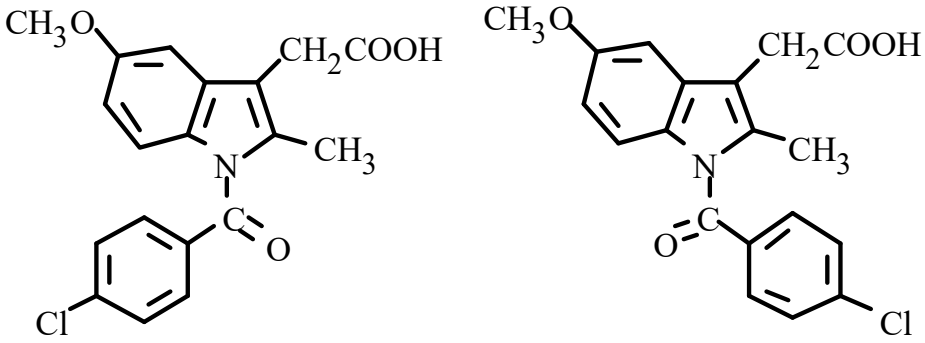
- Indomethacin is more potent antipyretic than aspirin.
- Indomethacin's time-dependent pseudoirreversible inhibition of COX-1
- Illustrates SAR 3

✓ The indole system and the phenyl ring are separated by one atom forming two sigma bonds.

✓ The double bond character of amide restrict rotation.

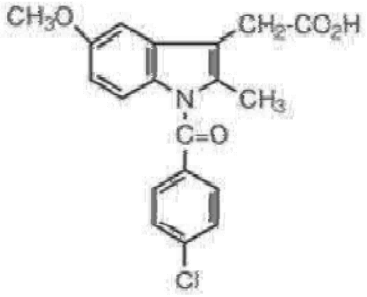
✓ 2-Methyl provides steric hindrance favoring the active conformer.

- Thus it gives two stable confirmation as shown below



Different conformers of Indomethacin

SAR of indomethacine

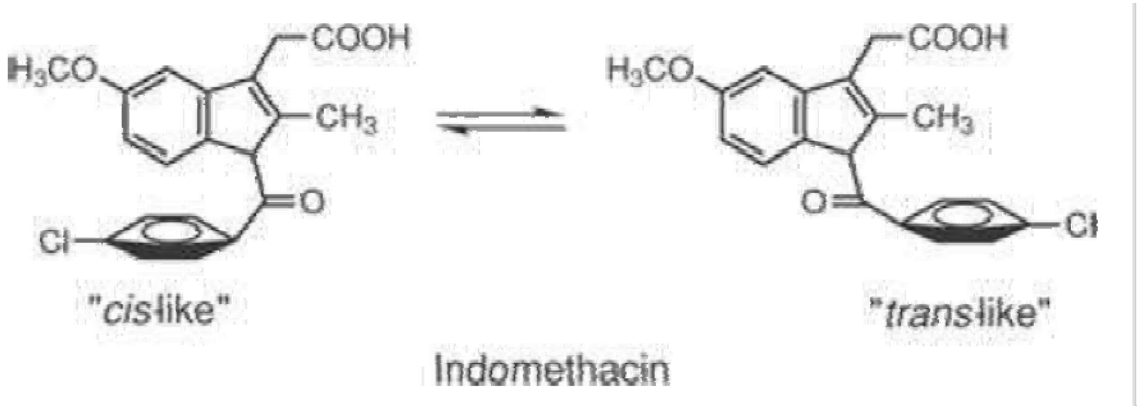


Indomethacin

- Carboxyl group:
  - Replacement of the carboxylic group with other acidic functionalities decreases activity.
  - Anti-inflammatory activity increases as the acidity of the carboxyl group increases and decreases as the acidity is decreased.
  - Amide analogues are inactive.
- Acylation of the indole nitrogen with:
  - Aliphatic carboxylic acids or Aralkylcarboxylic acids
    - Results in amide derivatives that are less active than those derived from benzoic acid.
  - N-Benzoyl derivatives substituted in the *para* position with fluoro, chloro, trifluoromethyl, or thiomethyl groups are the most active.

- The 5-position of the indole ring is most flexible with regard to the nature of substituents that enhance activity.
  - Substituents such as methoxy, fluoro, dimethylamino, methyl, allyloxy, and acetyl are more active than the unsubstituted indole ring.
- The presence of an indole ring nitrogen is not essential for activity,
  - 1-benzylidenyl indene analogues (e.g., sulindac) are active.
- Substitution of a methyl group at the α-position of the acetic acid side chain
  - With methyl group will give the corresponding propionic acid derivative they are equiactive analogues.
  - Substitution with an aryl substituents lower activity

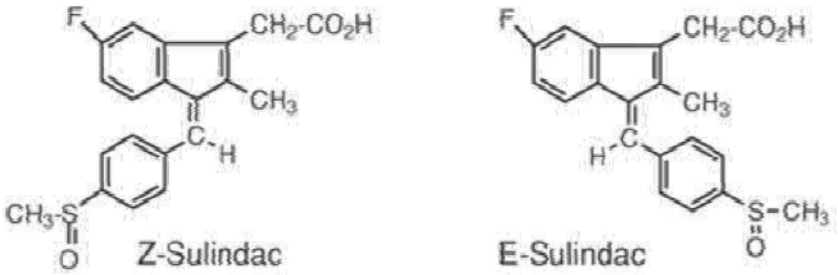
- The conformation of indomethacin
  - The acetic acid side chain is flexible and can assume a large number of different conformations
- The preferred and lower-energy conformation of the p-chlorobenzoyl group:
  - It is oriented away from the 2-methyl group
  - (it is cis to the methoxyphenyl ring of the indole nucleus)
  - It noncoplanar with the indole ring
    - because of steric hindrance produced by the 2-methyl group and the hydrogen atom at the 7-position.



Therapeutic uses of indomethacin

- Indomethacin is available for the treatment of:
  - acute gouty arthritis and osteoarthritis
- Because of its ability to inhibiting prostaglandin biosynthesis
  - It is used to prevent premature labour
  - ❖**Side effect :**Indomethacin has significant CNS side effects due to the indole nucleus.

b) Sulindac (Mobicol®)

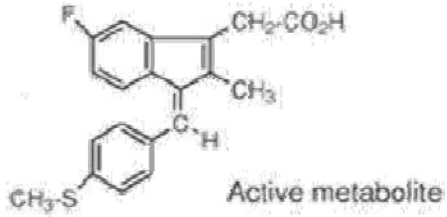


- It is a 1-benzylidenyl indene analogue
- Sulindac was a new developed:
  - Because Indomethacin has significant CNS side effects due to the indole nucleus.
  - Thus the heterocyclic nitrogen was removed
  - Thus giving the *indene* derivative
- A double bond introduced
  - Z isomer is the active form
    - It lacks the CNS side effects

SAR of Sulindac

- Aryl acetic acid is primary for the activity.
- A double bond introduced between aromatic rings restricted the rotation.
  - Z isomer is the active form
  - lacks the CNS side effects and causes less GI irritation but low water solubility
- Indene Ring (Indole without N) eliminate the CNS side effect.
- A methylsulfoxyl was introduced to increase solubility.
- Introduction of a fluoro to retaining potency.
- The phenyl is out of the plane (Non-coplanarity)

- Sulindac is a prodrug and is converted to an active metabolite
  - Its active form is the sulfide metabolite

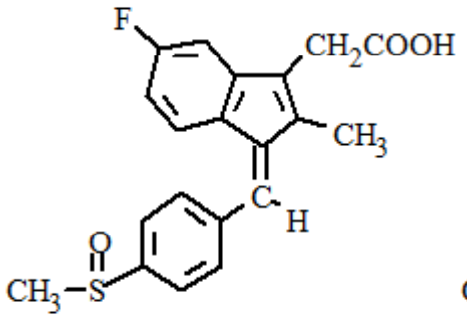


Active metabolite

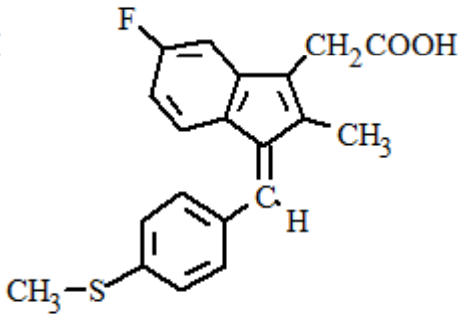
  - It has a longer half–life allowing for BID administration.
- Sulindac is approximately eight-fold as effectively as aspirin.
- In anti-inflammatory and antipyretic assays:
  - it is about half as potent as indomethacin
  - but is equipotent in analgetic assays.

Absorption and Metabolism of sulindac

- Sulindac is pro-drug
  - The sulfoxide is reduced to the active sulfide metabolite.
- The drug is absorbed as the inactive sulfoxide,
  - it causes fewer GI disturbances
    - (No prostaglandin biosynthesis inhibition in the stomach).



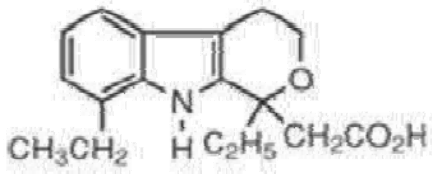
Sulindac



Sulfide of Sulindac

- In the circulatory system
  - It is reduced to the sulfide, which is an inhibitor of prostaglandin biosynthesis in the joints.
  - The thioether active metabolite has a plasma half-life approximately twice that of the parent compound (~16 hours versus 8 hours)

c) Etodolac (Etopan®)

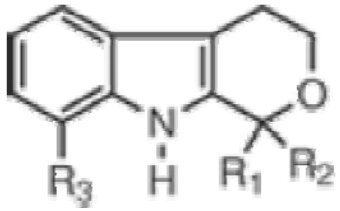


Etodolac

- Etodolac is pyrano-indoleacetic acid derivative
- It is not strictly an arylacetic acid derivative
  - (because there is a two-carbon atom separation between the carboxylic acid function and the hetero-aromatic ring)
  - It still possesses structural characteristics similar to those of the heteroarylacetic acids.
  - **It** can be considered a nonclassical bioisostere of the arylpropionic acids.
- It was introduced in the United States in 1991
  - Used in the management of osteoarthritis and as an analgetic.
  - It is 50x more potent than aspirin in inflammation, 33% as potent as indomethacin.
  - It shows a much better GI profile than aspirin or indomethacin and this can be a therapeutic advantage. It is a unique compound.

- Etodolac is marketed as a racemic mixture
  - Only the S-(+)-enantiomer possesses anti-inflammatory activity in animal models.
  - Etodolac also displays a high degree of enantio-selectivity in its inhibitory effects on the arachidonic acid cyclooxygenase system.
  - Its anti -inflammatory actions is 50 times more active than aspirin
- Etodolac has lower incidence of GI side effects
  - This represents a potential therapeutic advantage.
  - It produces less GI bleeding than indomethacin.
- Mechanism of action
  - Inhibition of the biosynthesis of prostaglandins at the cyclooxygenase
  - But no inhibition of the lipoxygenase system

SAR of Etodolac



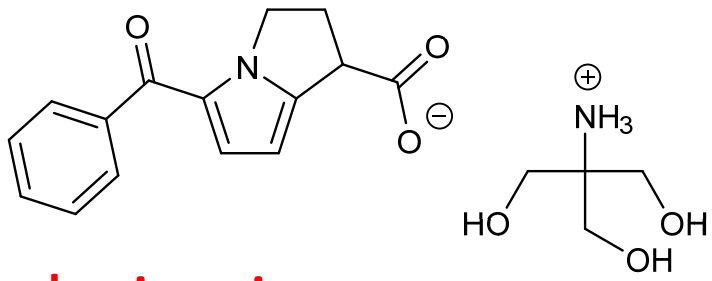
- Alkyl groups at R1 and an acetic acid function at R2 enhanced anti-inflammatory activity
- Lengthening the acid chain(R2):
  - Give inactive compounds.
- Increasing the chain length of the R1 substituent:
  - Increasing to ethyl or n-propyl gives derivatives that were 20 times more potent than methyl.
- Substituents at the 8-position (R3) were most beneficial
  - Among the most active were the 8-ethyl, 8-n-propyl , and 7-fluoro-8-methyl derivatives.
- Etodolac was found to possess the most favourable anti-inflammatory to gastric distress properties among these analogues.

Etodolac Metabolism

- Etodolac is metabolized to:
  - Three hydroxylated metabolites
  - To glucuronide conjugates,
  - But none of them possesses important pharmacological activity.
- Metabolism appears to be the same in the elderly as well as the general population,
  - So no dosage adjustment appears necessary.

KETOROLAC Tromethamine
Toradol, Acular

d) **Ketorolac**



- It is a heterocyclic acetic acid derivative
- Ketorolac was developed in 1989 by Syntex Corpused as an analgesic.
- It is related to Indomethacin because it has the pyrrole ring
- it is commercially available as the tromethamine salt. The tromethamine moiety enhances water solubility.
- The injectable formulation is incompatible with solutions of conjugate acids like meperidine hydrochloride (precipitation).

- It is about half as potent as Morphine when injected. After its success as a parenteral agent, an oral agent was marketed.
- Ketorolac acts by inhibiting the bodily synthesis of prostaglandins.
- Ketorolac in its oral (tablet or capsule) and intramuscular (injected) preparations
- It is given as a racemic mixture of both (S)-(−)-ketorolac, the active isomer, and (R)-(+)-ketorolac.
- Good oral activity with primarily analgesic activity, but also has antiiflammatory activity and antipyretic actions.
- Use management of post-operative pain

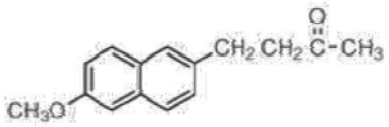
e) Nabumetone (Nambco®)

6MNA

- Nabumetone is non acidic pro-drugs
- Rapidly metabolized after absorption to form a major active metabolite, 6-methoxy naphthalene **acetic acid**.
- It is closely related in structure to the propionic acids
- The gastric side effects of nabumetone is minimum.
  - Nabumetone is non-acidic:
    - Thus does not produce a significant primary insult
  - It is not an effective inhibitor of prostaglandin cyclooxygenase in gastric mucosa
    - Thus it has a minimum secondary insult.

- Once it enters the circulatory system it is metabolized to 6-methoxynaphthalene-2-acetic acid (6MNA)
  - Which is an effective inhibitor of cyclooxygenase in joints.
- Nabumetone is a classic example of the prodrug approach in drug design.

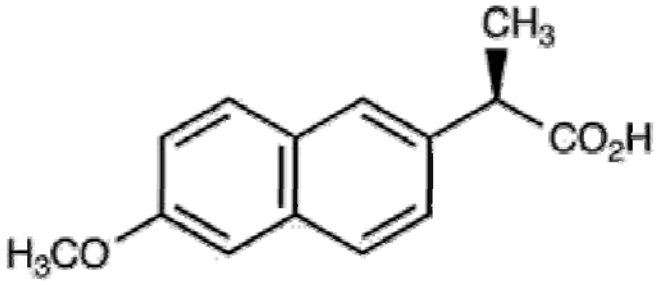
SAR of Nabumetone



- Introduction of methyl or ethyl groups on the butanone side chain:
  - reduce anti-inflammatory activity.
- Removal of the methoxy group at the 6-position reduced activity
- Replacement of the methoxy:
  - With a methyl or chloro group gave active compounds.
  - Replacement of the methoxy with hydroxyl , acetoxy, or N-methylcarbamoyl groups reduced activity
  - Positional the methoxy group at the 2- or 4-positions greatly reduce activity

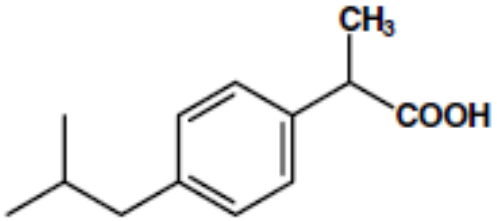
SAR

- The active metabolite, 6-MNA, is closely related structurally to naproxen
  - differing only by the lack of an α-methyl group.

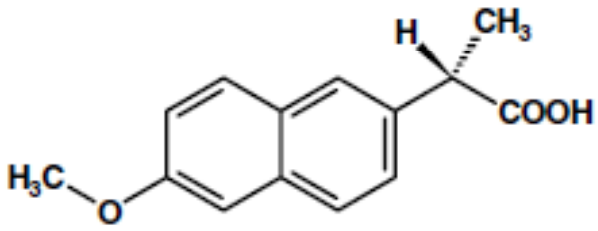


Naproxen

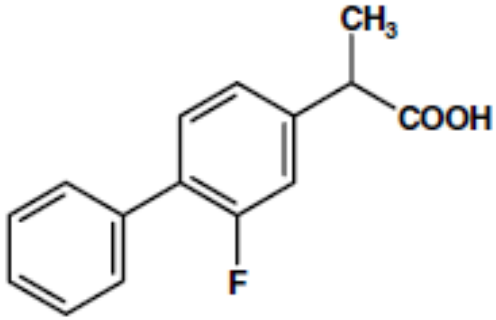
4) ARYLPROPIOANIC ACID DERIVATIVES (profens)



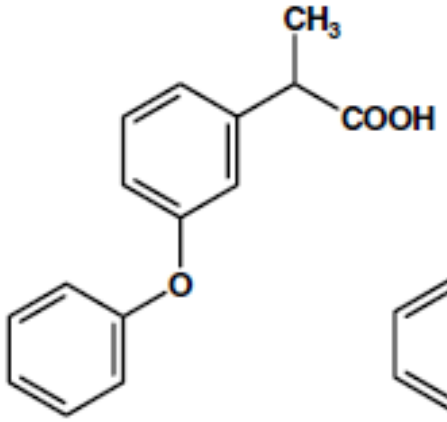
Ibuprofen



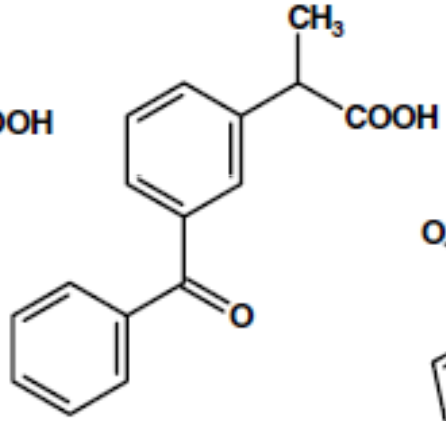
Naproxen



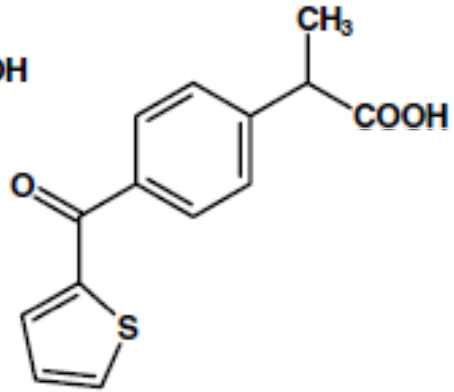
Flurbiprofen



Fenoprofen



Ketoprofen



Suprofen

- Some of the most useful NSAIDs
- Like the salicylates these agents are all strong organic acids
- Arylpropionic acids are characterized by the general structure **Ar-CH(CH3)-COOH** which conforms to the required general structure.
- All of these compounds are predominantly ionized at physiologic pH and more lipophilic than ASA or salicylic acid.
- These agents illustrate **SAR 1, 4, 6** and **7**

- The α-CH3 substitutent present in the profens:

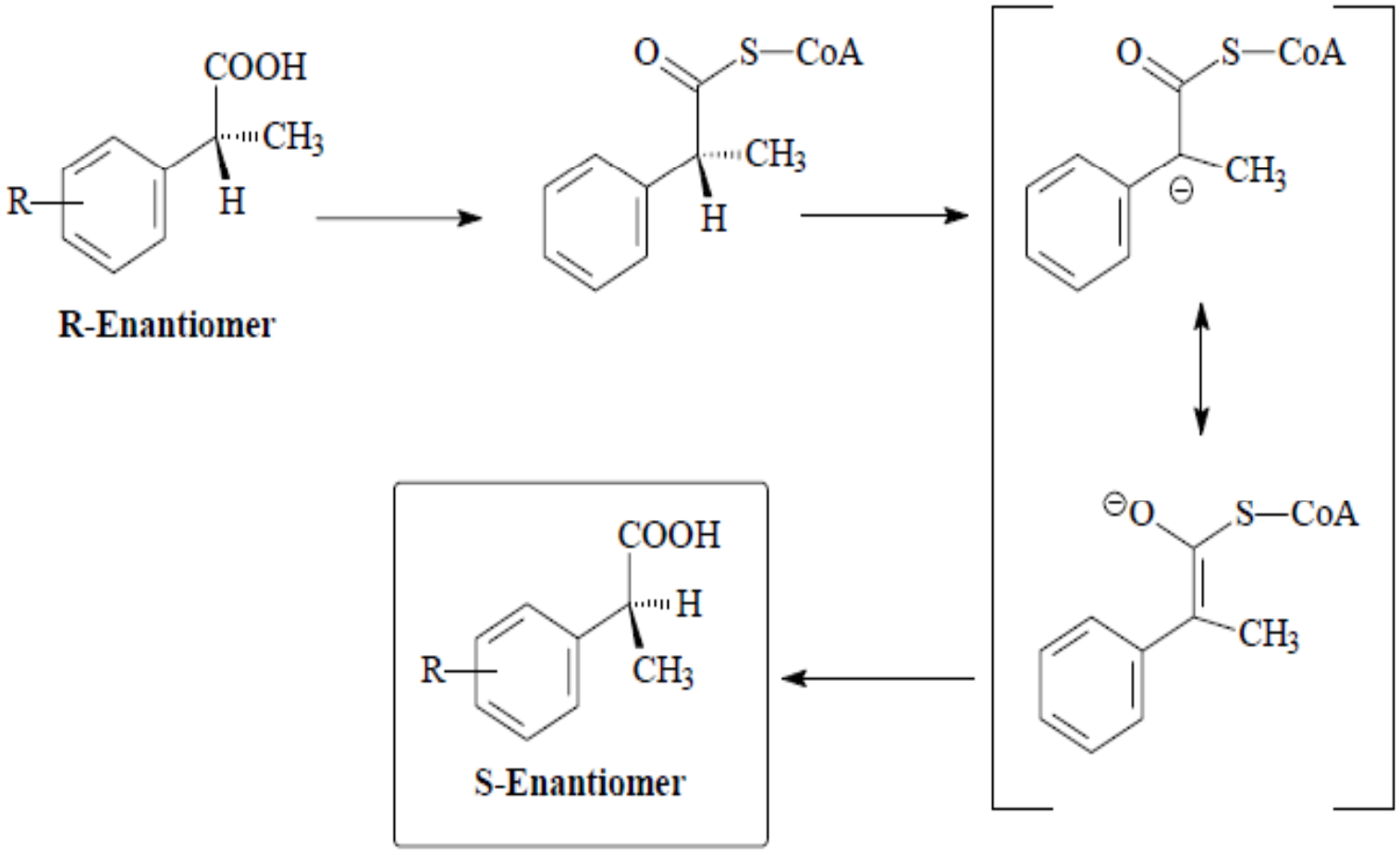
✓ increases cyclooxygenase inhibitory activity

✓ reduces toxicity of the profens.

- The α-carbon in these compounds is chiral and the S-(+)-

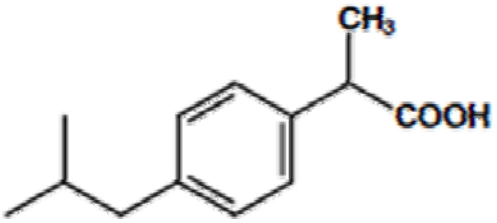
enantiomer of the profens is the more potent cyclooxygenase inhibitor.

- Most profen products, except naproxen (NaprosynTM), are marketed as the racemates.
- In addition to the metabolism described below, the profens undergo a metabolic inversion at the chiral carbon involving stereospecific transformation of the inactive R-enantiomers to the active S-enantiomers.
- This is believed to proceed through an activated (more acidic α-carbon) thioester intermediate.
- Normally only the S-(+) isomer is present in plasma.



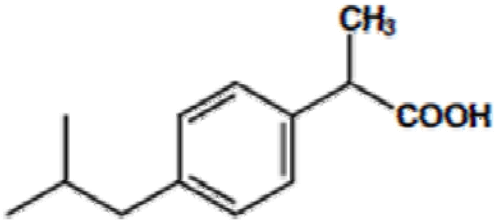
Isomerization of the Racemic Profens

Ibuprofen (Advil®, Trufen®)

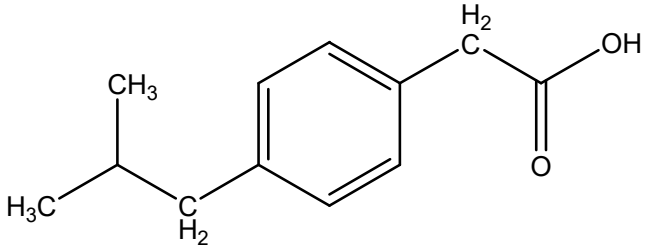


- Ibuprofen became the first prescription NSAIDs to become available as an OTC
- Ibuprofen:
  - Is more potent than aspirin
  - but less potent than indomethacin in anti-inflammatory assay
  - It produces moderate degrees of gastric irritation
  - Activity resides in the S isomer. ***in vivo*** some of the inactive R isomer is converted to the active S by isomerases, but not the S to R.
  - Another reference states that S–Ibuprofen is 160 times more active than R–Ibuprofen ***in vitro*** but they were equipotent ***in vivo.***

SAR of Iboprofen

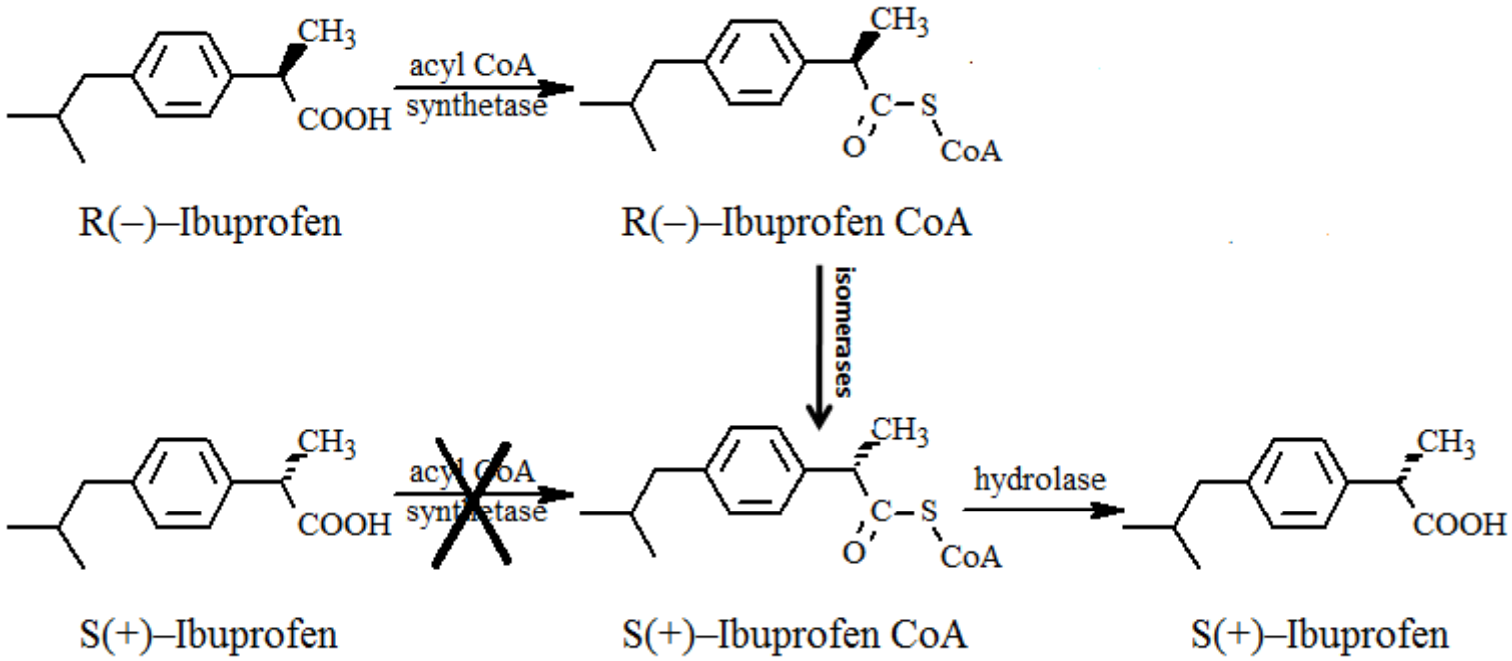


- Lacks second aromatic ring (**SAR 2**)
- The substitution of an α-methyl group on the alkanoic acid portion of acetic acid derivatives
  - Enhances anti-inflammatory actions and reduces many side effects
  - For example, the acetic acid analogue of ibuprofen, ibufenac (p- isobutylphenylacetic acid)
    - It is less potent and more hepatotoxic than ibuprofen.



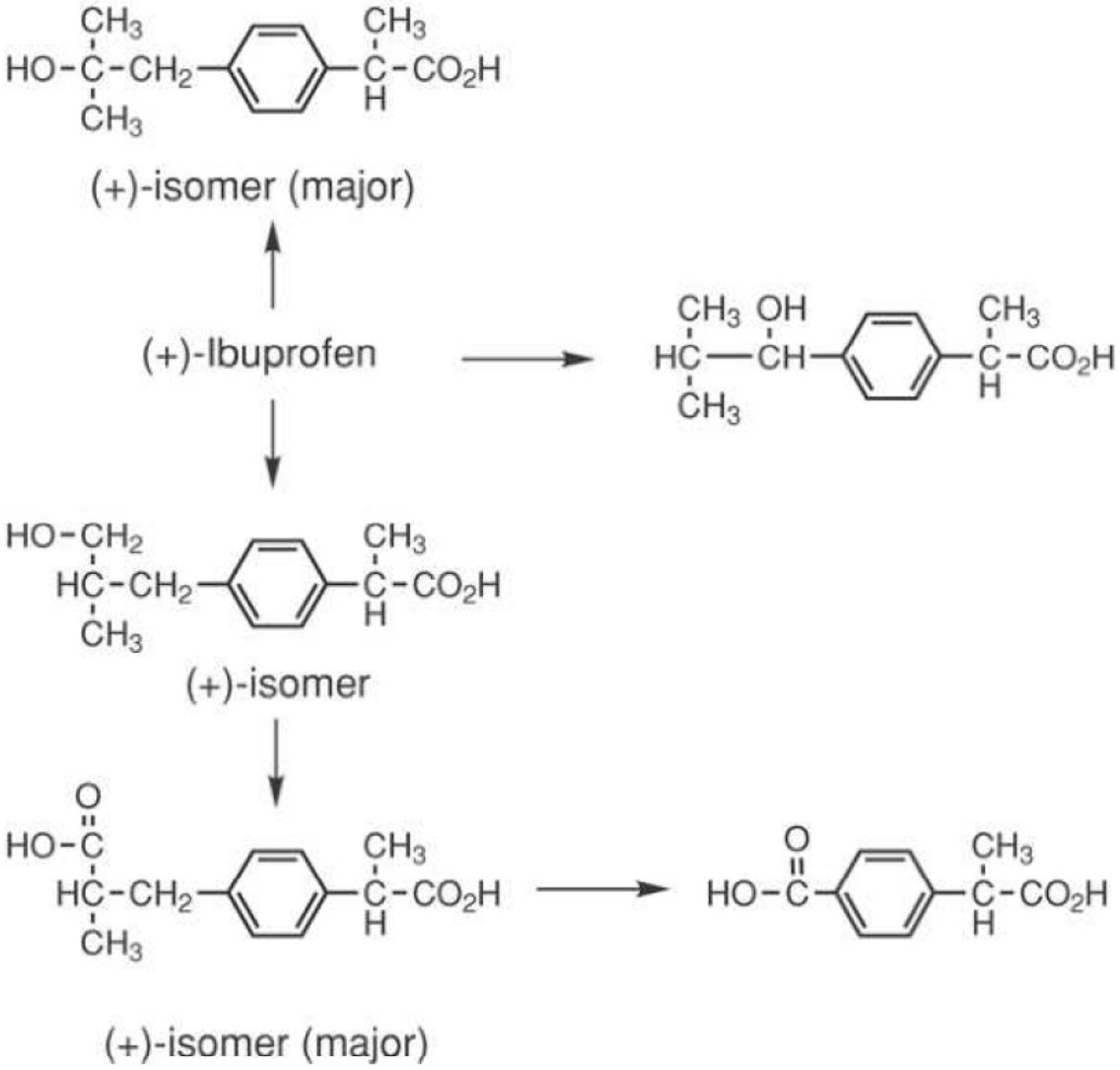
Ibufenac

- Ibuprofen is marketed as the racemic mixture
  - Although biological activity almost exclusively in the S-(+)-isomer
- When ibuprofen is administered as the individual enantiomers,
  - The major metabolite isolated is the S-(+)-enantiomer
  - Whatever the configuration of the starting enantiomer.
- The R-(–)-enantiomer is converted to the S-(+)-enantiomer in vivo
  - via an acetyl–coenzyme A intermediate
  - Thus the two enantiomers are bioequivalent in vivo.
  - The isomer is converted to the active S by isomerases, but not the S to R.
- This has also has been observed for other arylpropionic acids, such as:
  - ketoprofen, fenoprofen ~~and naproxen~~.


CH3
COOH
acyl CoA
synthetase
C
S
O
CoA
R(–)–Ibuprofen
R(–)–Ibuprofen CoA
isomerases
acyl CoA
synthetase
hydrolase
S(+)–Ibuprofen
S(+)–Ibuprofen CoA
S(+)–Ibuprofen

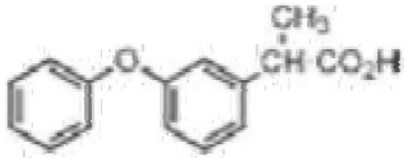
Absorption and Metabolism of ibuprofen

- Ibuprofen is rapidly absorbed by oral administration
  - Peak plasma levels attained within 2 hours
- Metabolism involve:
  - Primarily ω, and ω1- and ω2-oxidation of the p-isobutyl side chain
  - Followed by alcohol oxidation resulting from ω–oxidation to the corresponding carboxylic acid.
- All metabolites are inactive.


(+)-isomer (major)
(+)-Ibuprofen
(+)-isomer
(+)-isomer (major)

- Ibuprofen is indicated for:
  - Relief of the signs and symptoms of rheumatoid arthritis
  - Osteoarthritis
  - The relief of mild to moderate pain
  - The reduction of fever
  - The treatment of dysmenorrhea

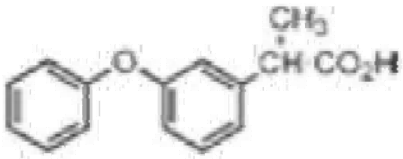
± Fenoprofen Calcium



Fenoprofen calcium

- The calcium and sodium salts of fenoprofen:
  - Both have similar bioavailability, distribution, and elimination characteristics.
  - It is the calcium salt that is marketed because it has the advantage of being less hygroscopic.
- Fenoprofen is less potent in anti -inflammatory assays than ibuprofen
- Stereochemistry:
  - In vitro prostaglandin assays indicate that the S-(+)-enantiomer is more potent than the R-(–)-isomer
  - Fenoprofen is marketed as a racemic mixture
  - No differences is observed in the in vivo anti-inflammatory or analgetic properties of the individual enantiomers.

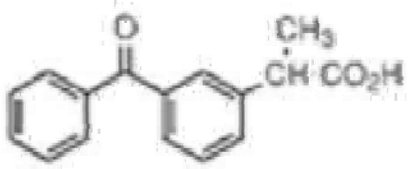
SAR of fenoprofen



Fenoprofen calcium

- Placing the phenoxy group in the *ortho*- or *para*-position of the arylpropionic acid ring
  - markedly decreases activity.
- Replacement of the oxygen bridge between the two aromatic rings with a carbonyl group
  - yields an analogue (ketoprofen) that also is marketed (Profenid®).

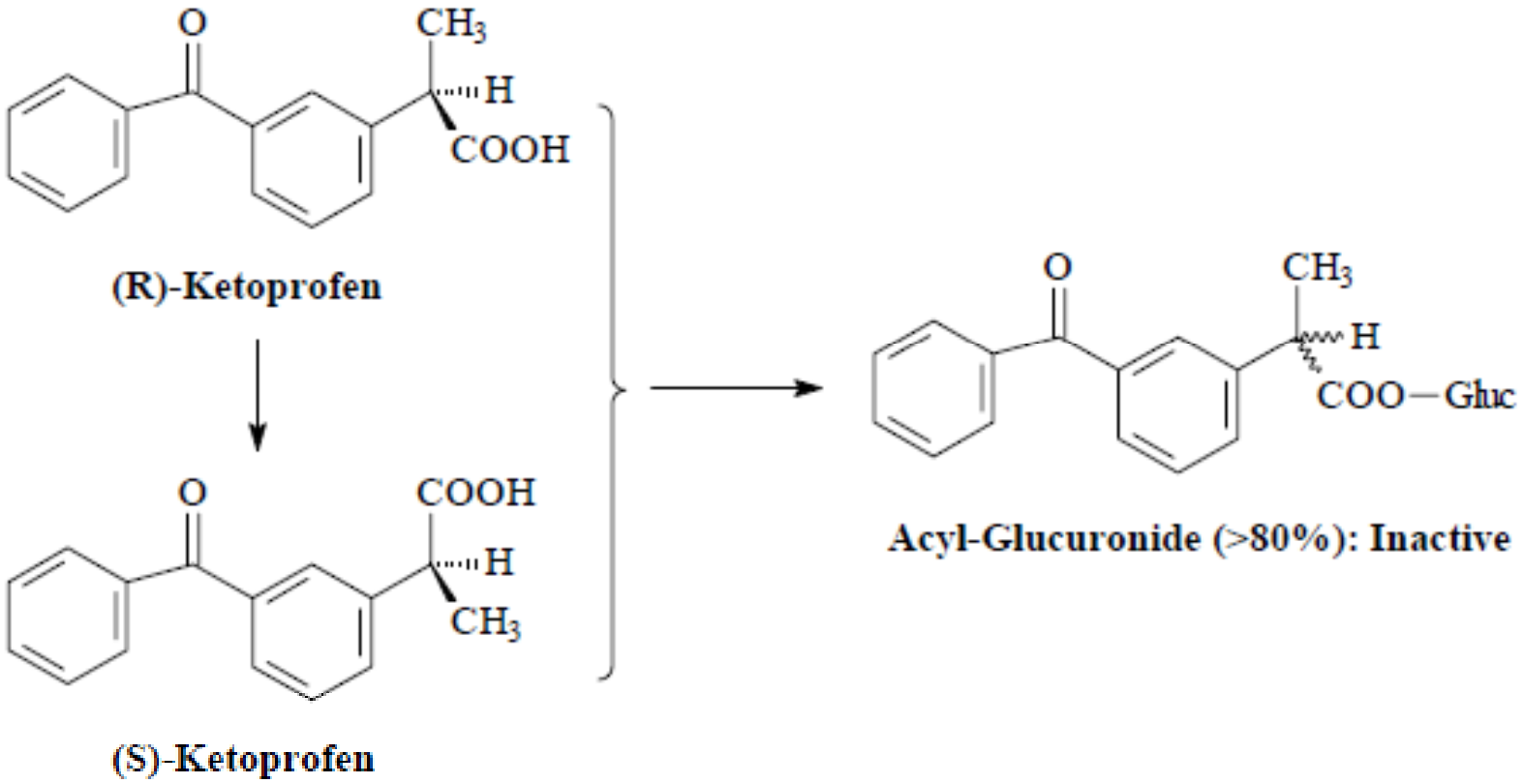
±-Ketoprofen (Profenid®)



Ketoprofen

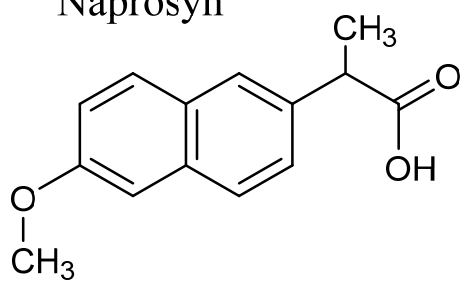
- Replacement of the oxygen bridge between the two aromatic rings of the fenprofen with a carbonyl group yields ketoprofen.
- Ketoprofen:
  - Inhibits leukotrienes and leukocyte migration into inflamed joints
  - It also inhibit the biosynthesis of prostaglandins
  - It stabilizes the lysosomal membrane during inflammation
    - Resulting in decreased tissue destruction.
  - Antibradykinin activity also has been observed.
    - Bradykinin is released during inflammation and can activate peripheral pain receptors.

- It is less potent than indomethacin as an anti-inflammatory but it produces the same gastric lesions.
- It is metabolized by:
  - Glucuronidation of the carboxylic acid
  - hydroxylation of the benzoyl ring
  - And reduction of the keto function.

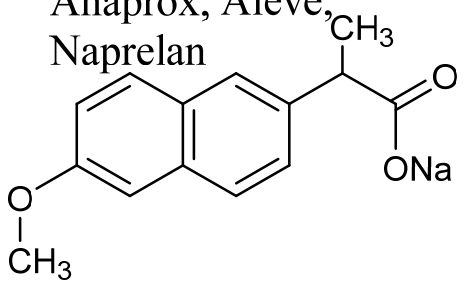

O
CH3
H
COOH
(R)-Ketoprofen
O
COOH
H
CH3
(S)-Ketoprofen
O
CH3
H
COO—Gluc
Acyl-Glucuronide (>80%): Inactive

Naproxen (Naprex®, Naxyn®)

NAPROXEN
Naprosyn



NAPROXEN Sodium
Anaprox, Aleve,
Naprelan



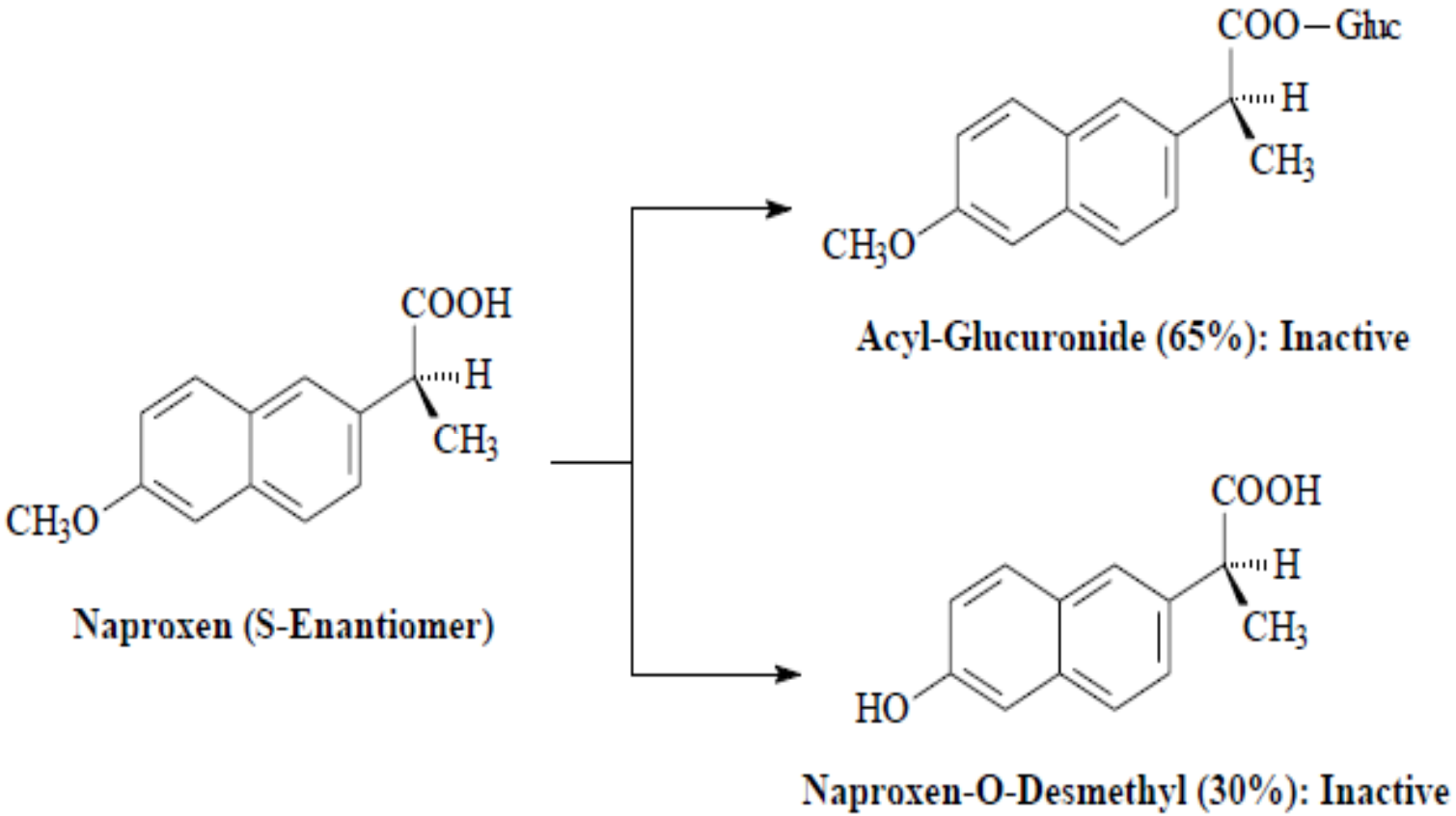
- Naproxen is synthesized from methoxynaphthalene.
- It is the only drug currently marketed in the optically pure form.
  - It is marketed as the *S (+)-enantiomer*
  - This is not due to resolution but is the result of the synthetic method used.
  - Interestingly the S isomer of Naproxen is (+) as most in this class are but the S isomer of the sodium salt is (–).

SAR of naproxen

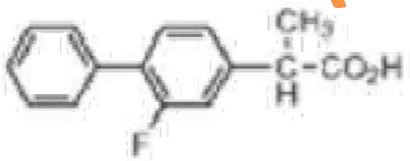
- Naproxen does not possess a second non coplanar ring
  - The naphthyl rings are fused, aromatic thus flat and planar.
- Its structure is related to the active metabolite, 6-MNA of nabumetone
  - 6-MNA lack the α-methyl group.
- The substitution of the 2-naphthylacetic acids at 6-position led to maximum anti-inflammatory activity.
  - Small lipophilic groups, such as Cl, CH_3S, and CHF_2O, were active analogues,
  - CH_3O being the most potent.
  - Larger groups were found to be less active.
- Derivatives of 2-naphthylpropionic acids are more potent than the
  - corresponding acetic acid analogues.
- Replacing the carboxyl group with:
  - functional groups capable of being metabolized to the carboxyl function (e.g., —CO_2CH_3, —CHO, or —CH_2OH) led to a retention of activity

Absorption and Metabolism

- Approximately 70% of an administered dose is eliminated as either:
  - Unchanged drug (60%)
  - Or as conjugates of unchanged drug (10%).
- The remainder is converted to the 6-*O*-desmethyl metabolite
  - The 6-O-desmethyl metabolite lacks anti-inflammatory activity.
  - The demethylated metabolite is further metabolite to the glucuronide conjugate.


COO—Gluc
H
CH3
CH3O
Acyl-Glucuronide (65%): Inactive
COOH
H
CH3
CH3O
Naproxen (S-Enantiomer)
COOH
H
CH3
HO
Naproxen-O-Desmethyl (30%): Inactive

±-Flurbiprofen (Ocufen®)

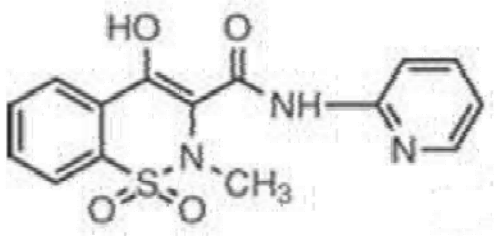


Flurbiprofen

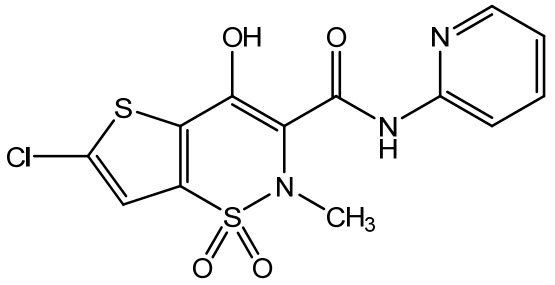
- Flurbiprofen was introduced in 1987 as sodium salt
- It is the first topical NSAID indicated for ophthalmic use in the United States (**Ocufen**).
- The indication for Ocufen is to inhibit intraoperative miosis induced by prostaglandins in cataract surgery.
- Flurbiprofen is an inhibitor of prostaglandin synthesis

- The 3–fluoro substituent helps ensure non–coplanarity.
- This compound had the most favorable therapeutic profile and was first introduced as a topical product for ophthalmic use (Ocufen).
- Later it was introduced for systemic use
- This drug is many times the potency of the other drugs.

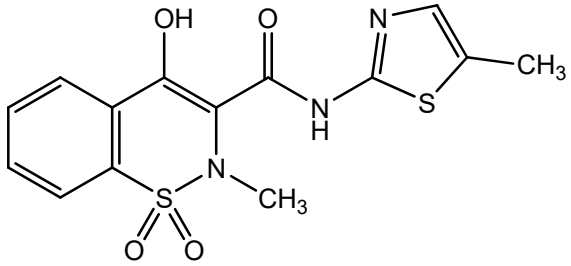
5) Oxicams (Enolic Acids)



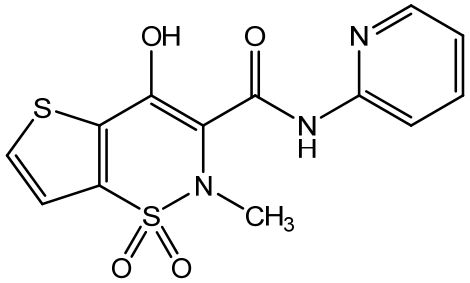
Piroxicam
(Pirox®)



Lornoxicam
(Xefo®)

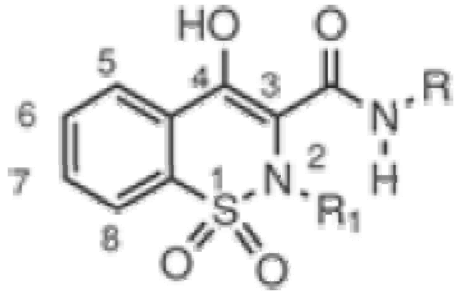


Meloxicam
(Movalis®)



Tenoxicam
Mobiflex®

Oxicams

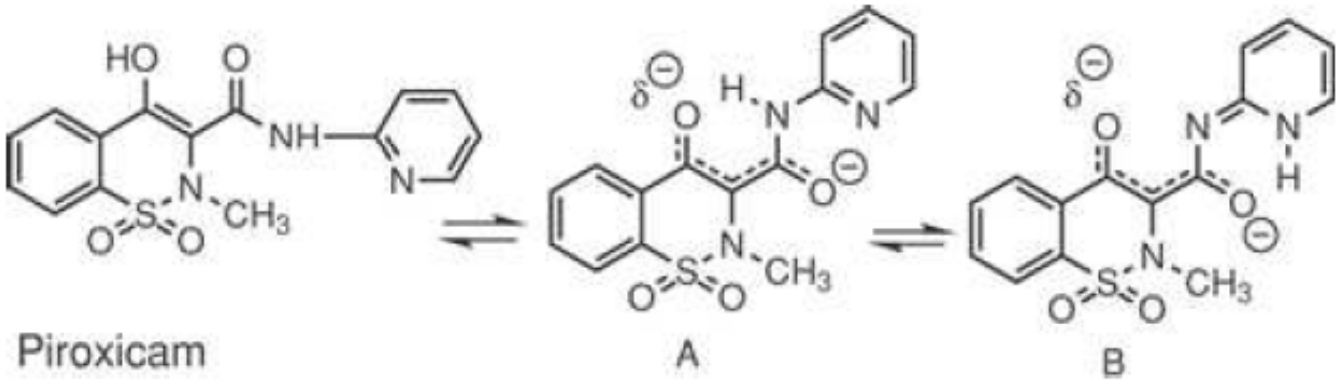


- These are structurally distinct substances
  - 4- hydroxybenzothiazine heterocycle.
- Innovated by the Pfizer group (**Feldene ®**)
  - They were developed in an effort to produce non carboxylic acid, potent, and well tolerated anti-inflammatory drugs.
- They are tautomeric and can exist as:
  - (keto-enol tautomerism) tautomer

SAR of oxicams

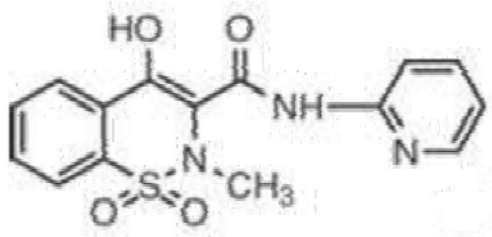
- Optimum activity was observed when R1 was a methyl substituent.
- The carboxamide substituent R
  - Generally is an aryl or heteroaryl substituent.
  - Because alkyl substituents are less active.

- N-heterocyclic carboxamides generally
  - They are more acidic than the corresponding N-aryl carboxamides
  - This enhanced acidity was attributed to stabilization of the enolate anion by the pyridine nitrogen atom
  - This is illustrated in tautomer A and additional stabilization by tautomer B:



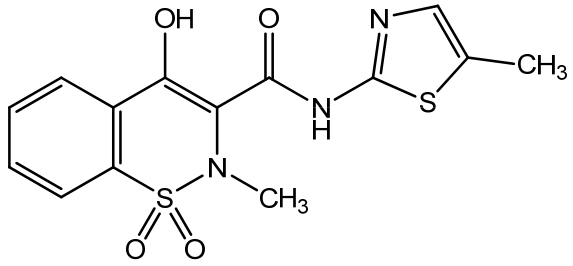
Piroxicam A B

Piroxicam (Pirox®, Feldene®).



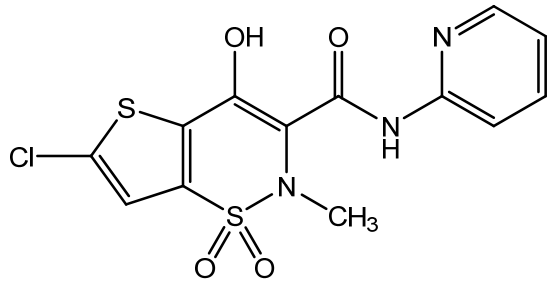
- The first member of this class,
- Piroxicam is an effective inhibitor of arachidonic acid cyclooxygenase
- Approximately 20% of individuals on piroxicam report adverse reactions and
  - The greatest incidence of side effects result from GI disturbances.

Meloxicam (Movalis®)



- Meloxicam is structurally related to Piroxicam.
- Although Meloxicam is frequently described in the literature as a selective COX-2 inhibitor
- It is considerably less selective for the COX-2 versus COX-1 isoenzyme when compared to Celecoxib or Rofecoxib.

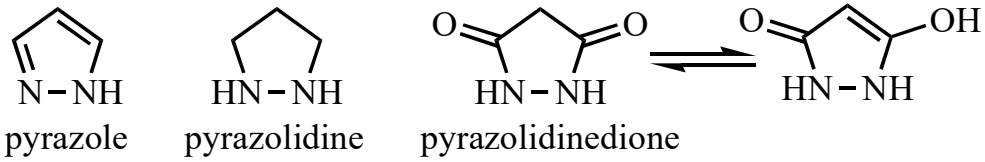
Lornoxicam (Xefo®)



- Is a new non steroidal anti-inflammatory drug (NSAID) of the oxicam class
- with analgesic, anti-inflammatory and antipyretic properties.
- Lornoxicam differs from other oxicam compounds in its potent inhibition of prostaglandin biosynthesis
- Present in dose of 8mg

6)Pyrazoles and Pyrazolidinediones

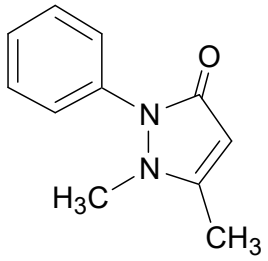
- Search for better drug produced the pyrazolidinediones
- They are acidic:
  - because the β-diketone tautomrizes into an acidic enol
- These drugs are able to ionize.
  - Thus they have an aromatic ring with an anionic charge.



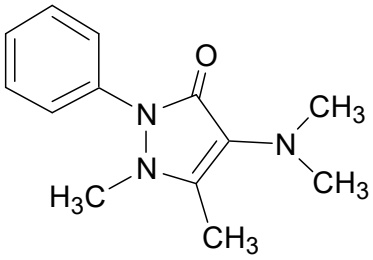
pyrazole pyrazolidine pyrazolidinedione

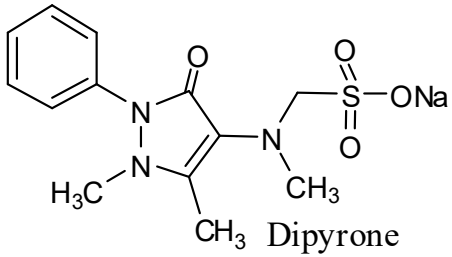
Pyrazoles

ANTIPYRINE
(Auralgan Otic)

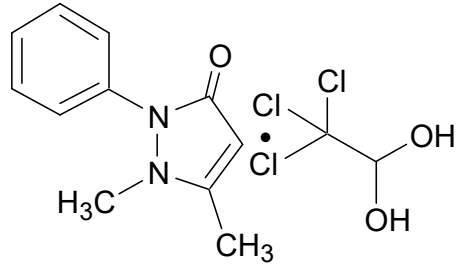


Aminopyrine





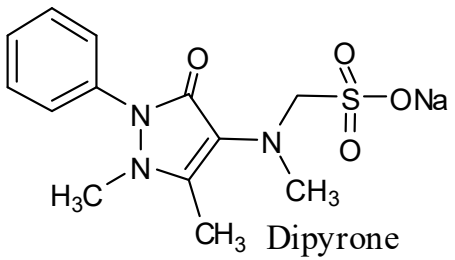
Dipyrone



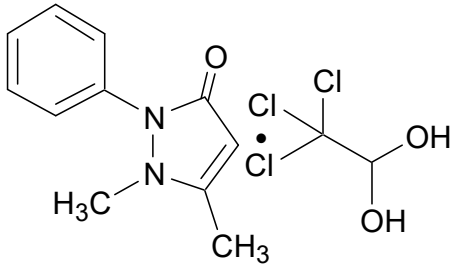
DICHLORALPHENAZONE
Antipyrine • Chloral Hydrate

Aminopyrine:

- Is Pyrazole analog
- Long acting
- It has a significant incidences of agranulocytosis
- Used only in otic drops



Dipyrone



DICHLORALPHENAZONE
Antipyrine • Chloral Hydrate

Dipyrone (Optalgin®):

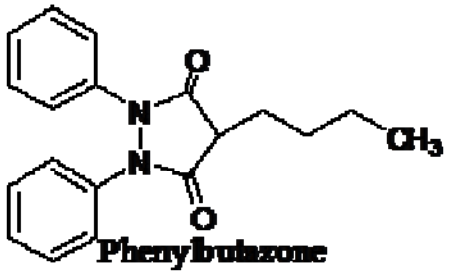
- Is a prodrug which decomposes in aqueous solutions to aminopyrine.
- It is banned in the US but available in other countries.

Dichloralphenazone:

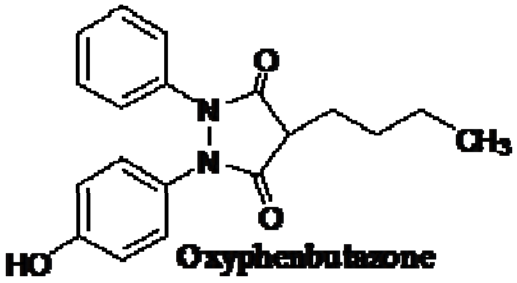
- It is a complex of Antipyrine and Chloral hydrate
- It is a common agent in many OTC analgesics.
- It is a mild sedative used in migraine /tension headache products.

Pyrazolidinediones

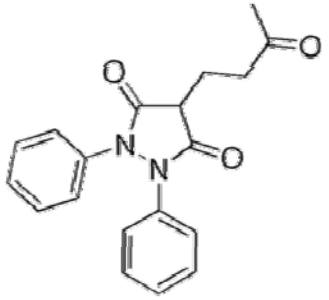
- **Phenylbutazone** It is equipotent to antipyrine
  - Serious **toxicities**, e.g., agranuylocytosis, peptic ulcers and bone marrow depression, limits its use in long term therapy.
- The hydroxyl metabolite give **Oxyphenbutazone**
  - Is better tolerated
  - With uricosuric activity but little anti–inflammatory activity
- The keto metabolite, **Kebuzone**, is marketed in Europe as a uricosuric agent.



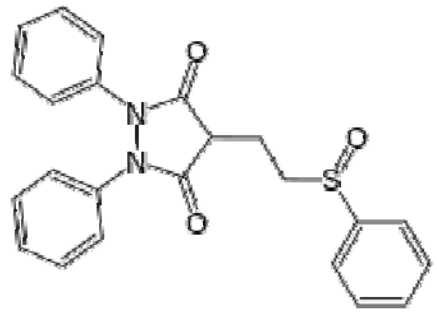
Phenylbutazone



Oxyphenbutazone



Kebuzone



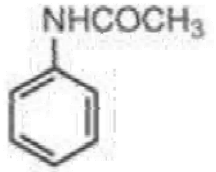
Sulfinpyrazone

Sulfinpyrazone

- is marketed in the US as a uricosuric.
- The two phenyl rings are not coplanar due to their close proximity, on adjacent nitrogens.
- The ortho hydrogens in each ring are effective at this close proximity.

7) *p*-Aminophenols

- This group is useful for pain and fever, but not inflammation.
- They have an aromatic ring, but do not have an acidic group ionizable at physiologic pH.
- The first drug **Acetanilide**:
  - Is out of market due of toxicity (both blood and liver disorders

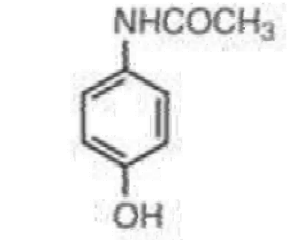


Acetanilide

- **Phenacetin** (1887) was used for decades:
  - But in the 1970s it was implicated in cases of liver and nephrotoxicity and was removed from the market

Phenacetin

Acetaminophen

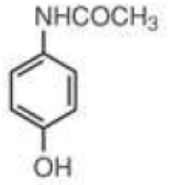


Acetaminophen

- A very old drug
  - Acetaminophen (paracetamol) introduced in 1893
  - It remained unpopular for more than 50 years
  - Until it was observed that it is a metabolite of both acetanilide and phenacetin
- It is a safe drug
  - Lower incidence of gastric bleeding compared to many of the other NSAIDs, probably
  - Better tolerance

- Acetaminophen is weakly acidic (pKa = 9.51)
- Synthesized by the acetylation of p-aminophenol
- Not recommended for long-term therapy because of potential hepatotoxicity issues.
- Acetaminophen, unlike aspirin, is stable in aqueous solution,
  - Making liquid formulations available
  - a particular advantage in pediatric cases.

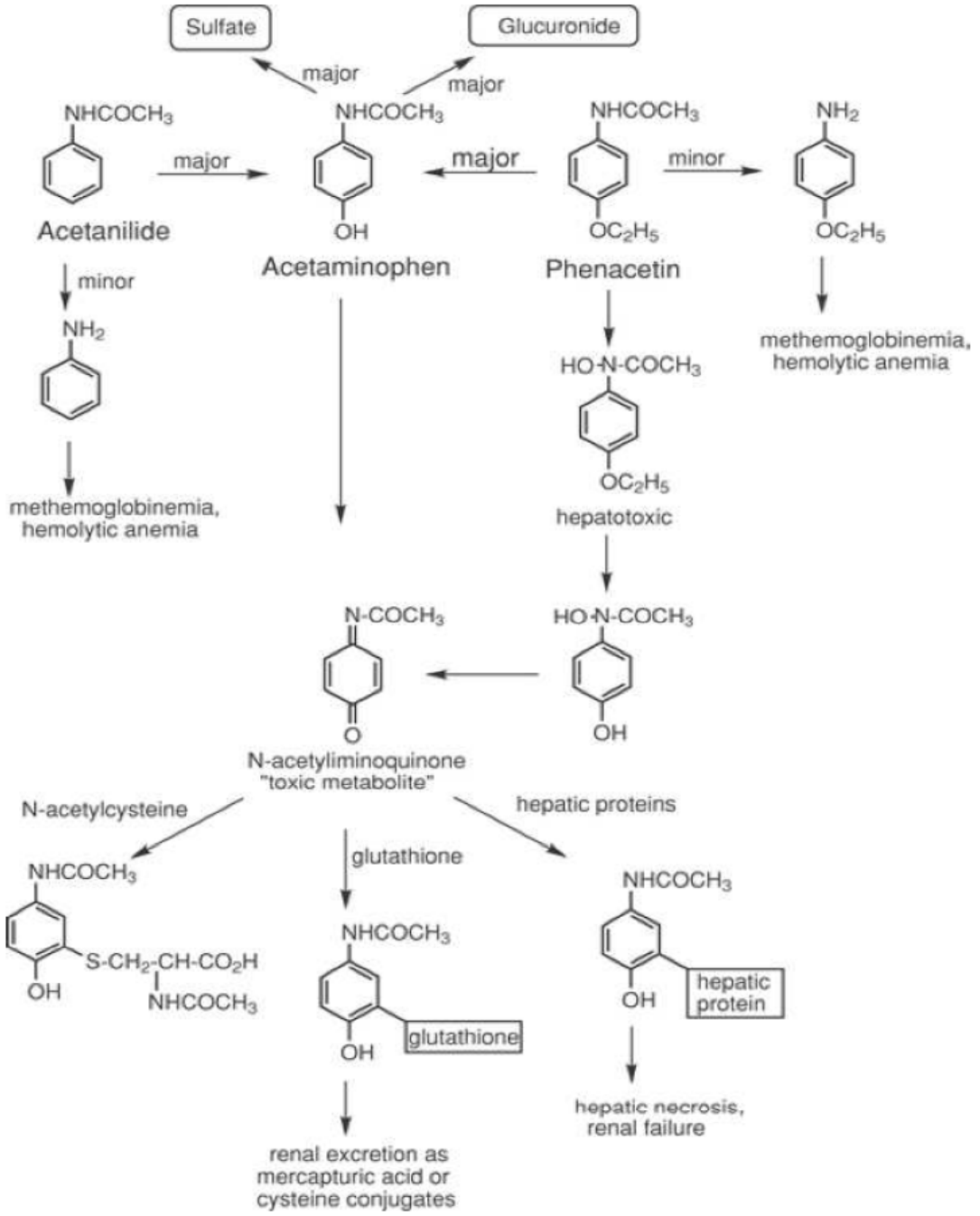
SAR of Aminophenol



- Aminophenols are less toxic than the corresponding aniline derivatives
  - although p-aminophenol itself is too toxic for therapeutic purposes.
- Etherification of the phenolic function with methyl or propyl groups
  - produces derivatives with greater side effects than with ethyl groups.
- Substituents on the nitrogen atom that reduce basicity reduce activity
  - unless that substituent is metabolically labile (e.g., acetyl).

Acetaminophen metabolism

- Acetanilide and pharncetine are metbloized in the body to aceaminophen
- acetaminophen and is metabolized by 3 pathways:
  - glucuronidation,
  - sulfation
  - glutathione conjugation.
- Glucuronidation and sulfation produce nontoxic metabolites for excretion.
- N-acetyl-p-benzoquinoneimine (NAPQI) is a toxic intermediate produced by cytochrome P450 metabolism.
- NAPQI is then conjugated by glutathione to form a nontoxic metabolite for excretion.


Sulfate
Glucuronide
major
major
major
major
minor
NHCOCH3
NHCOCH3
NHCOCH3
NH2
Acetanilide
Acetaminophen
Phenacetin
OH
OC2H5
OC2H5
minor
NH2
methemoglobinemia, hemolytic anemia
methemoglobinemia, hemolytic anemia
HO-N-COCH3
OC2H5
hepatotoxic
N-COCH3
HO-N-COCH3
O
OH
N-acetyliminoquinone "toxic metabolite"
N-acetylcysteine
hepatic proteins
glutathione
NHCOCH3
S-CH2-CH-CO2H
NHCOCH3
OH
NHCOCH3
glutathione
OH
NHCOCH3
hepatic protein
OH
hepatic necrosis, renal failure
renal excretion as mercapturic acid or cysteine conjugates

Background

Effect of COX2 inhibitor on platelets

- Prostacycline is release by capillary endothelium:
  - It causes vasodilatation and prevents platelet aggregation
- Thromboxane is released by platelets:
  - It causes vasoconstriction and platelet aggregation.
- COX1 & COX2:
  - Normally balance each other
  - The platelets use COX-1
  - And the capillaries use COX-2.
  - COX-2 selective inhibitors (Refecox) agents unbalance the system favoring thromboxane.
  - Thus it allows for an overproduction of Thromboxane A2 (platelet).
- However this is not the only factor in play since the other COX–2 selective agents have not shown the increase in MI

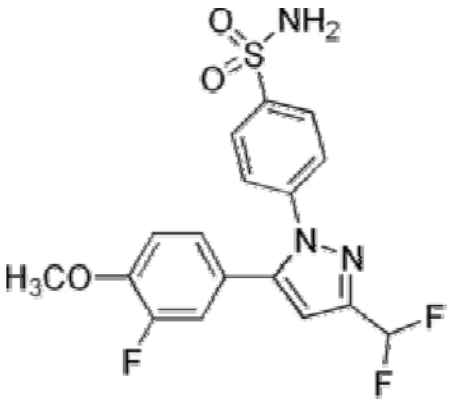
SAR of COX 2 selective inhibitors

- In contrary to the classic NSAIDs it lacks the carboxylic group
- Thus it affinity to COX-2 is without the formation of a salt bridge in the hydrophobic channel of the enzyme as in case of COX1.
- In general selective COX-2 inhibitors has a Tricyclics structural
  - (also known as ortho-diaryl)
- But there are also selective COX-2 that are Non-tricyclics
  - They lack the cyclic central core

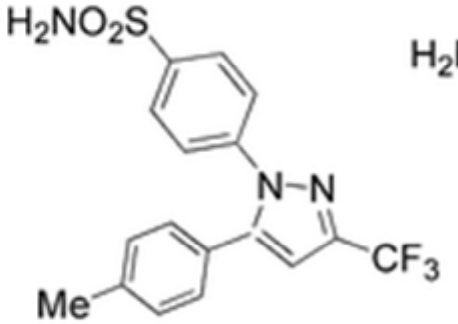
Tricyclic COX2 selective inhibiters

- All of the compounds in this class possess 1,2-diarylsubstitution on a central hetero or carbocyclic ring system
- Compounds belonging to this class can be sub-classified based on the size and type of the central heterocyclic or carbocyclic ring system

- A variety of 5-membered cores are COX-2 inhibitors:
  - pyrazole (celecoxib, Deracoxib),
  - furanone (rofecoxib),
  - isoxazole (valdecoxib)
- 6-membered cores:
  - The first structural types emerged in this category were pyridine series (etoricoxib)

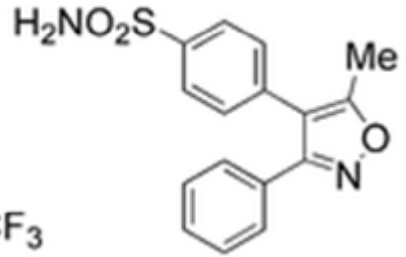


Deracoxib



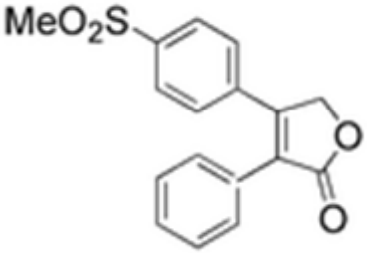
Celecoxib

Coxib®



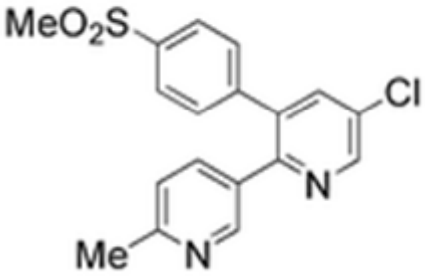
Valdecoxib

Bextra®



Rofecoxib

Vioxx®, Recox® Withdrawn !

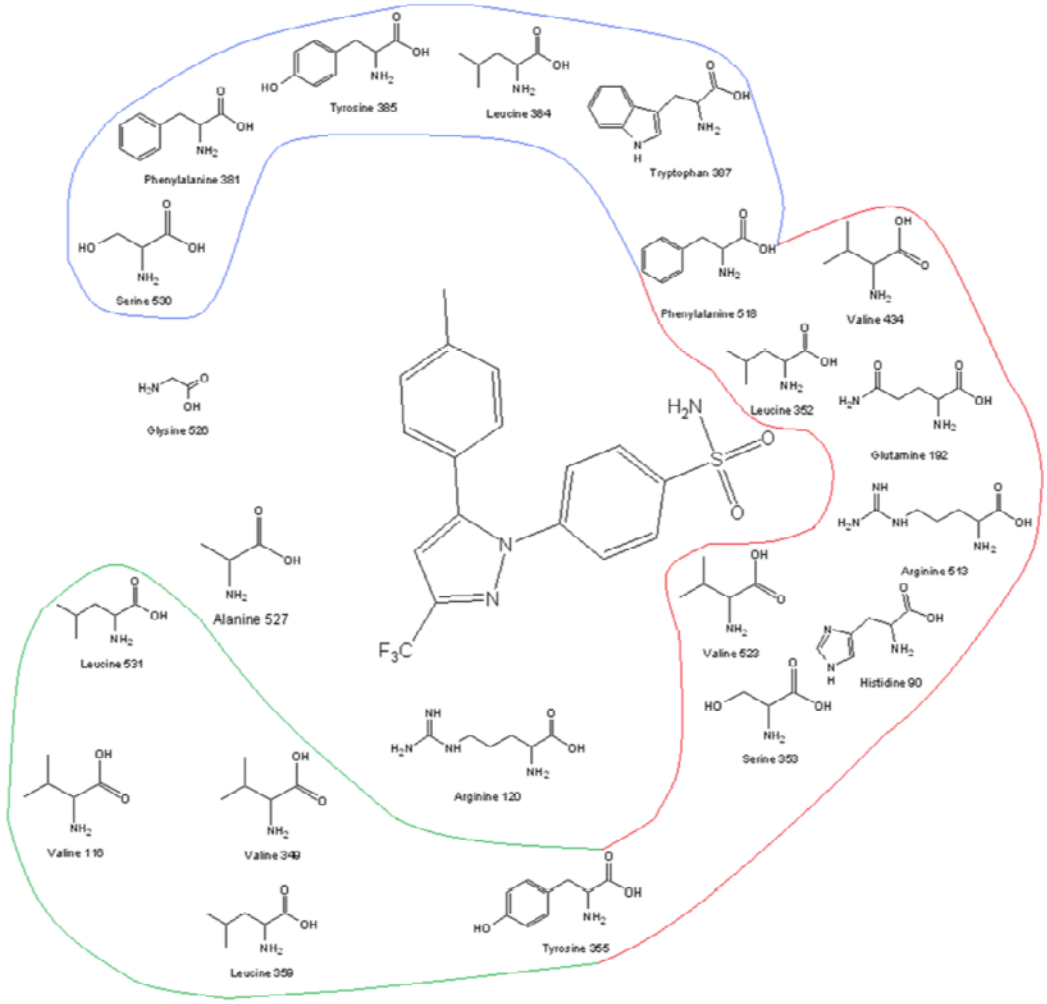


Etoricoxib

Arcoxia®

- **Celecoxib (Coxib®)**
  - was the first to be developed
- **Valecoxib (Bextra®)**
  - Also withdrawn from the market
- **Rofecoxib (Vioxx®, Recox®)**
  - With drawn form the market
- **Etoricoxb (Arcoxia®, Tericox®)**
- **Deracoxib:**
  - indicated for veterinary use

- The sulfonamide on one of the phenyl group
  - It is believed this phenyl group which is inserted into the extra space in COX–2 pocket
  - Thus there must be a warning to patients with a sulfonamide allergy
  - It can be a sulfamoyl
    - The non substituted form of sulfonamides
    - Compounds with this groups are weak acidic

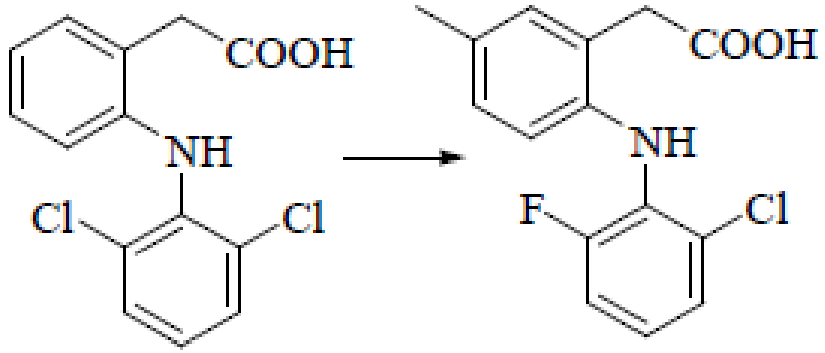

Tyrosine 385
Leucine 384
Phenylalanine 381
Tryptophan 387
Serine 530
Phenylalanine 518
Valine 434
Glycine 520
Leucine 352
Glutamine 192
Arginine 513
Alanine 527
Leucine 531
Valine 523
Histidine 90
Serine 353
Arginine 120
Valine 110
Valine 349
Leucine 359
Tyrosine 355

Modified NSAIDs

- Modifying well known NSAIDs into selective COX-2 inhibitors represents a new strategy.
- The methodology utilized in NSAID modification has no general scheme
- Indomethacin, diclofenac and many other NSAIDs have been successfully modified into the selective COX-2 inhibitors.

Diclofenac Modification:

- Novartis group described conversion of diclofenac into lumiracoxib **(Prexige ®)**
- It has 500 fold selectivity for COX-2 over COX-1

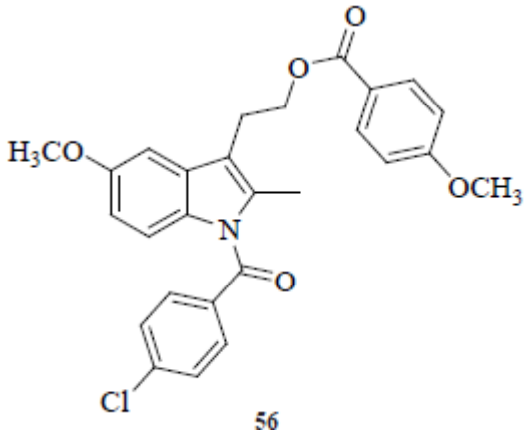


Diclofenac Lumiracoxib

Indomethacin modification:

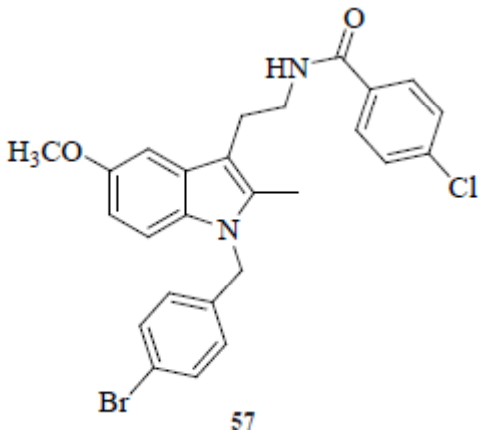
- The indomethacin modification into COX-2-specific inhibitors was done by functional group manipulations.
- The attempts were to shift the enzyme selectivity of indomethacin from COX-1 to COX-2 while keeping the potency at the same level and reducing the unwanted side-effects at the same time.
- In principle, the strategy consisted of introducing larger substituents to fit into the active site volume of COX-2.

- Conversion of non-selective NSAIDs to esters and amides is a strategy for generating COX-2 inhibitors but it has the limitation that indomethacin esters and possibly some amides may be hydrolyzed to indomethacin *in-vivo.*
- Thus indolyl esters and amides with essentially the ‘‘reverse’’ orientation have been reported that selectively inhibit COX-2.
- Such compounds eliminate or minimize the generation of indomethacin in-vivo.
- Compounds shown in the graph are the most potent and selective COX-2 inhibitors resulted from this strategy



56

COX-2 IC50 = 0.04 µM
COX-1 IC50 > 66 µM



57

COX-2 IC50 = 0.04 µM
COX-1 IC50 > 66 µM