PHARMACEUTICAL CHEMISTRY

(Analgesics)

Nonsteroidal anti-inflammatory drugs

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NON STEROIDAL ANTI- INFLAMMATORY DRUGS

NSAIDs including aspirin and acetaminophen, two of the oldest pain medications, are among the most widely prescribed drugs worldwide for the treatment of rheumatic arthritis and other degenerative inflammatory joint diseases.

Although NSAIDs are very effective in relieving mild to moderate pains and inflammation, their use is also often associated with many undesirable side effects, including GI irritation. NSAIDs (also commonly referred to as the aspirin-like drugs), share very similar conventional therapeutic and side effect profiles

The NSAIDs exert their therapeutic action by inhibiting two iso- forms of cyclooxygenase (COX-1, the constitutive isozymes and COX-2, the inducible isozymes), which is the rate-limiting enzyme responsible for the biosynthesis of the pro-inflammatory prostaglandins (PGs) bleeding, platelet dysfunction, kidney **d**amage, and broncho- spasm.

The conventional glandins (PGs) such as the PGD2, PGE2, PGF2, and PGI2 and thereby modulating pain transmission, attenuating inflammation, and reducing fever. They also produce their undesirable side effects such as GI bleeding, ulcerations, or renal impairments by blocking the same Cyclooxygenases responsible for synthesizing PGs that modulate platelet activity (TXA2 and PGI2), gastric acid secretion and cytoprotection (PGE2 and PGI2), and renal blood flow (PGE2).

. Mechanism of Action and NSAID-Induced Side Effects

All classes of NSAIDs strongly inhibit prostaglandin synthesis in various tissues, especially at the site of the tissue damage or inflammation. This inhibition occurs at the stage of oxidative cyclization of AA, catalyzed by the rate-limiting enzyme, cyclooxygenase (or PGH synthase), to the hydroperoxyendoperoxide (prostaglandin G2, PGG2) and its subsequent reduction to key intermediate, Prostaglandin H2 (PGH2) needed for all prostaglandin biosynthesis.

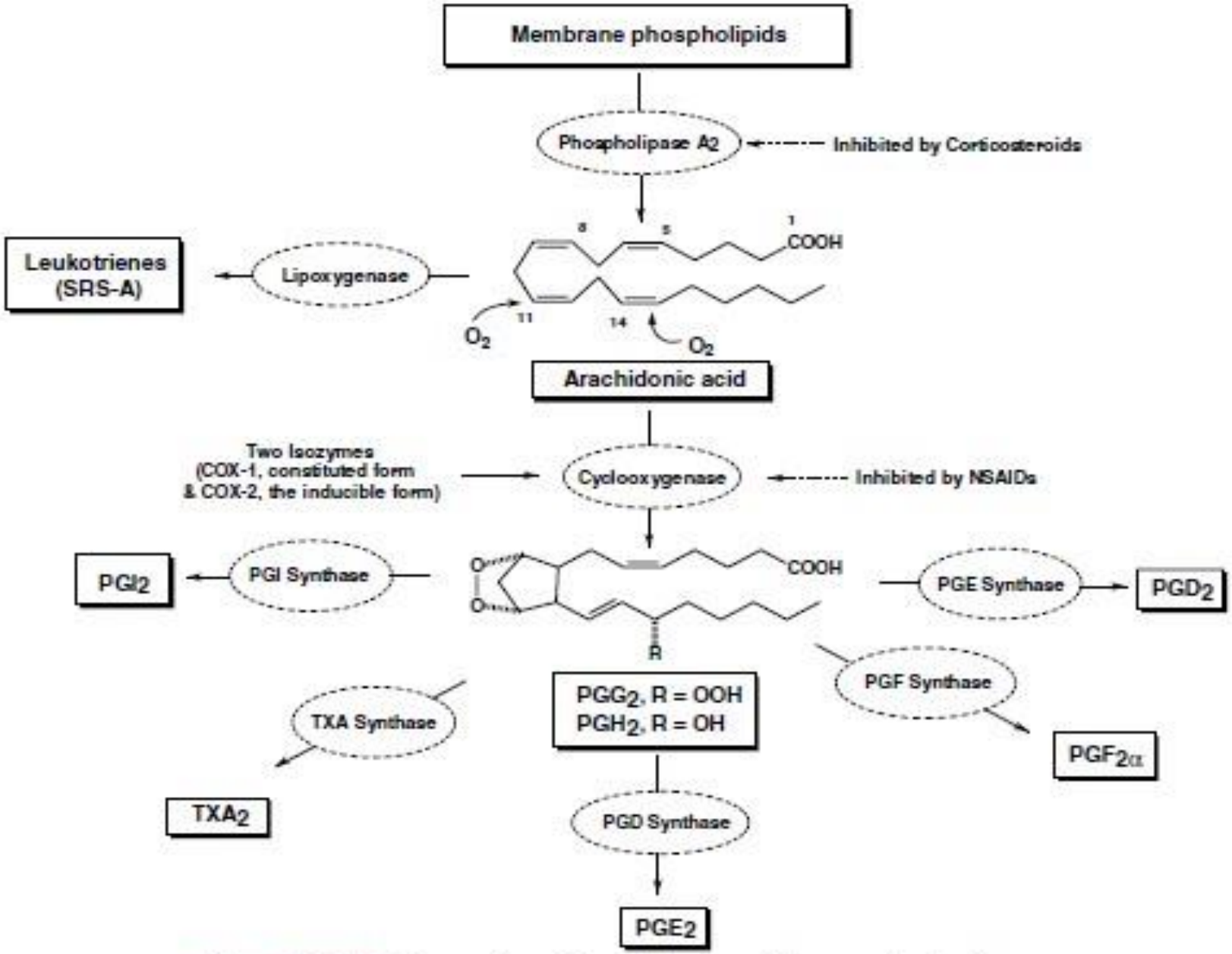


Figure 24.14 • Conversion of arachidonic acid to prostaglandins.

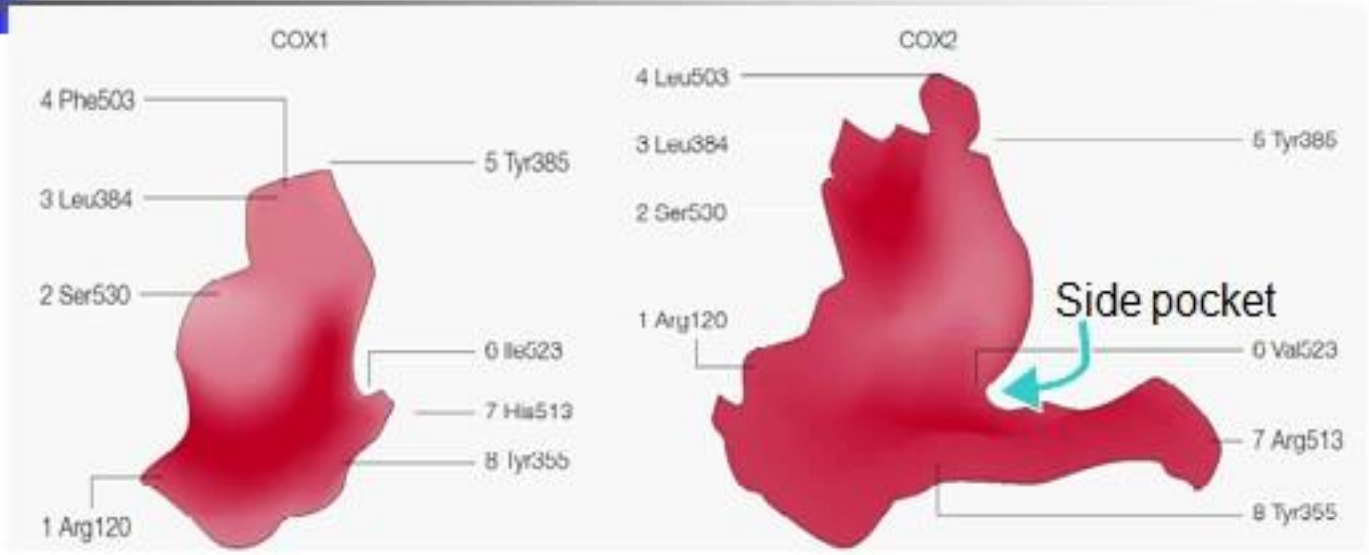
Structure–Activity Relationships of NSAIDs

Cyclooxygenases (COX-1 and COX-2) are heme-containing, membrane-bound proteins that share a high degree of sequence identity and also have very similar active site topography.

Most NSAIDs possess a free carboxylic acid (COOH) for an ionic interaction with the positively charged arginine residue at the active site of the Cyclooxygenases

Arg-120 in COX-1 or Arg-106 in COX-2 isozymes).

COX-1 & COX-2



- **In COX1** residues Arg120 &Tyr355 stabilize the anionic group present in most NSAIDs. NSAID aromatic rings are accommodated in the hydrophobic channel. Ser530 is the residue acetylated by aspirin. Note the presence of the relatively bulky Ile523
- **In COX2** residues Arg120, Tyr355 & Ser530 are present. However, residue 6 is Val523 which allows copening of a side pocket. This pocket accommodates the sulfonamide or isoster of COX2 inhibitors. They are stabilized by hydrogen bonding with Arg513.

from Nature Reviews Drug Discovery, **2**, 2003

COX-1 & COX-2 - II

- Overall structure and catalytic activity of both are similar
- Vivid distinctions in their regulation and expression
- COX-1 is constitutive and its expression is regulated by hormonal signals involved in maintaining physiologic homeostasis
- COX-1 is expressed in all tissues
- Importantly, COX-1 but not COX-2 is constitutively expressed in the stomach, where it is involved in mucosal defense and repair
- COX-2 expression and activity is largely responsive to adverse stimuli, such as inflammation and physiologic imbalances
- Control of COX-2 transcription and translation is thought to be the primary mechanism by which steroids such as hydrocortisone and dexamethasone modulate this enzyme. COX-2 has a binding site for steroids whereas COX-1 does not
- COX-2 is constitutively expressed notably in the brain and kidney

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

- With the exception of Aspirin, all the NSAIDS are reversible competitive inhibitors
- Aspirin is a nonreversible inhibitor, for it acetylates the active site which is the basis for its prophylactic use to prevent heart attacks
- Research suggests a role for PG in CNS transmission and raises the possibility that selective COX–2 inhibitors may modulate CNS function. This is relevant for those COX–2 inhibitors that lack an acidic group and thus can easily pass the BBB.
- COX–1 provides a cytoprotective role in the stomach and kidneys. It helps maintain the integrity of the mucosal epithelium and inhibition leads to gastric damage, hemorrhage, and ulceration
- The cytoprotective role in the stomach and kidney is largely due to the vasodilating properties of PGs which enhance mucosal blood flow
- Thus COX–1 produces prostaglandins that exert cytoprotective roles whereas COX–2 produces prostaglandins involved in inflammation, fever and pain; and COX–2 activation leads to inflammation
- Thus COX–2 inhibition produces therapeutic effects and COX–1 inhibition produces unwanted side effects. Unfortunately, most NSAIDS are more effective at inhibiting COX–1 than COX–2

NSAIDs & COX

- 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

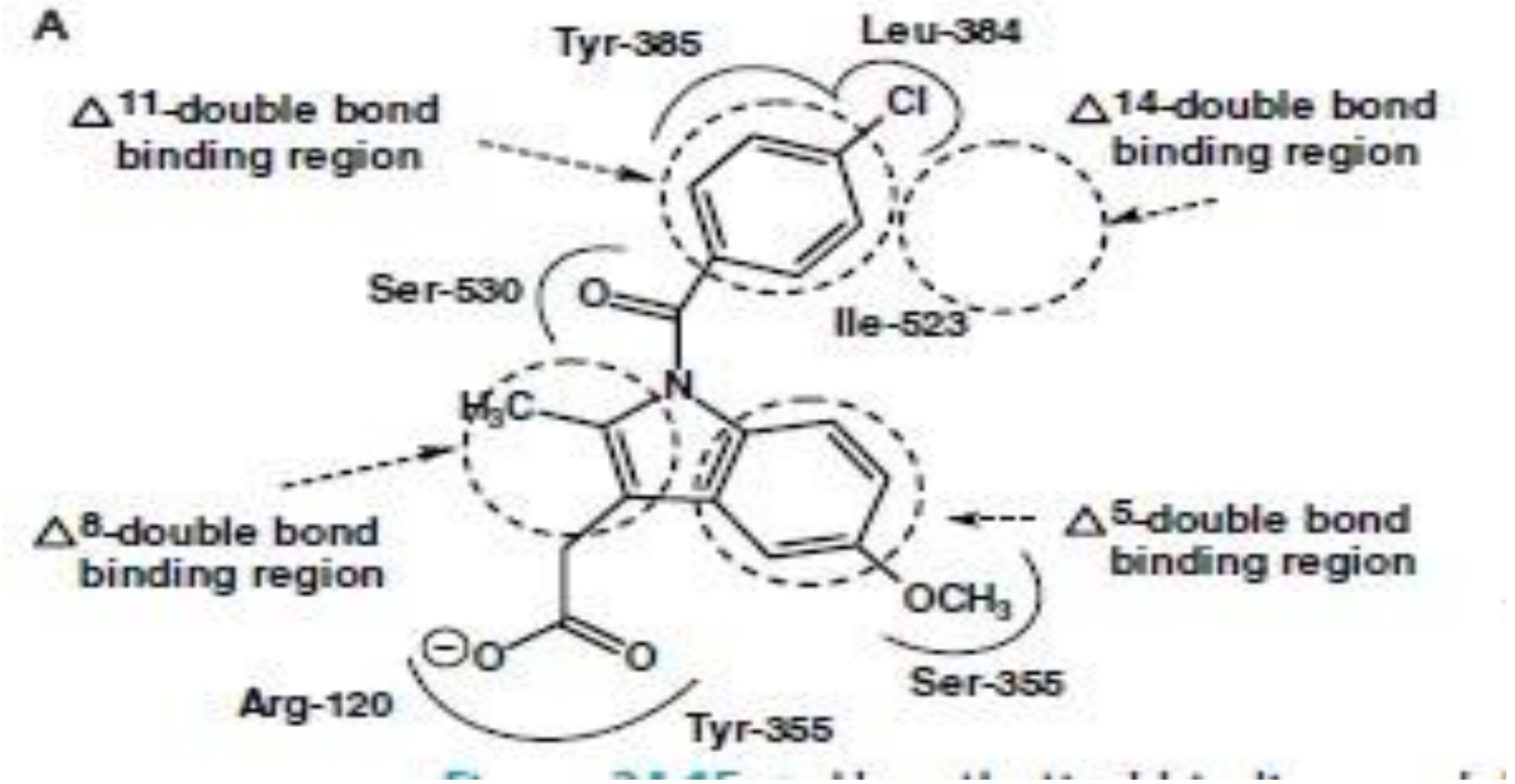
1. A cationic center and two hydrophobic areas
2. The cationic site is attributed to a guanidinium group on Arginine
3. The first hydrophobic area is located adjacent to the cationic center
4. The second region lies under and out of the plane with the first hydrophobic area and is commonly referred to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

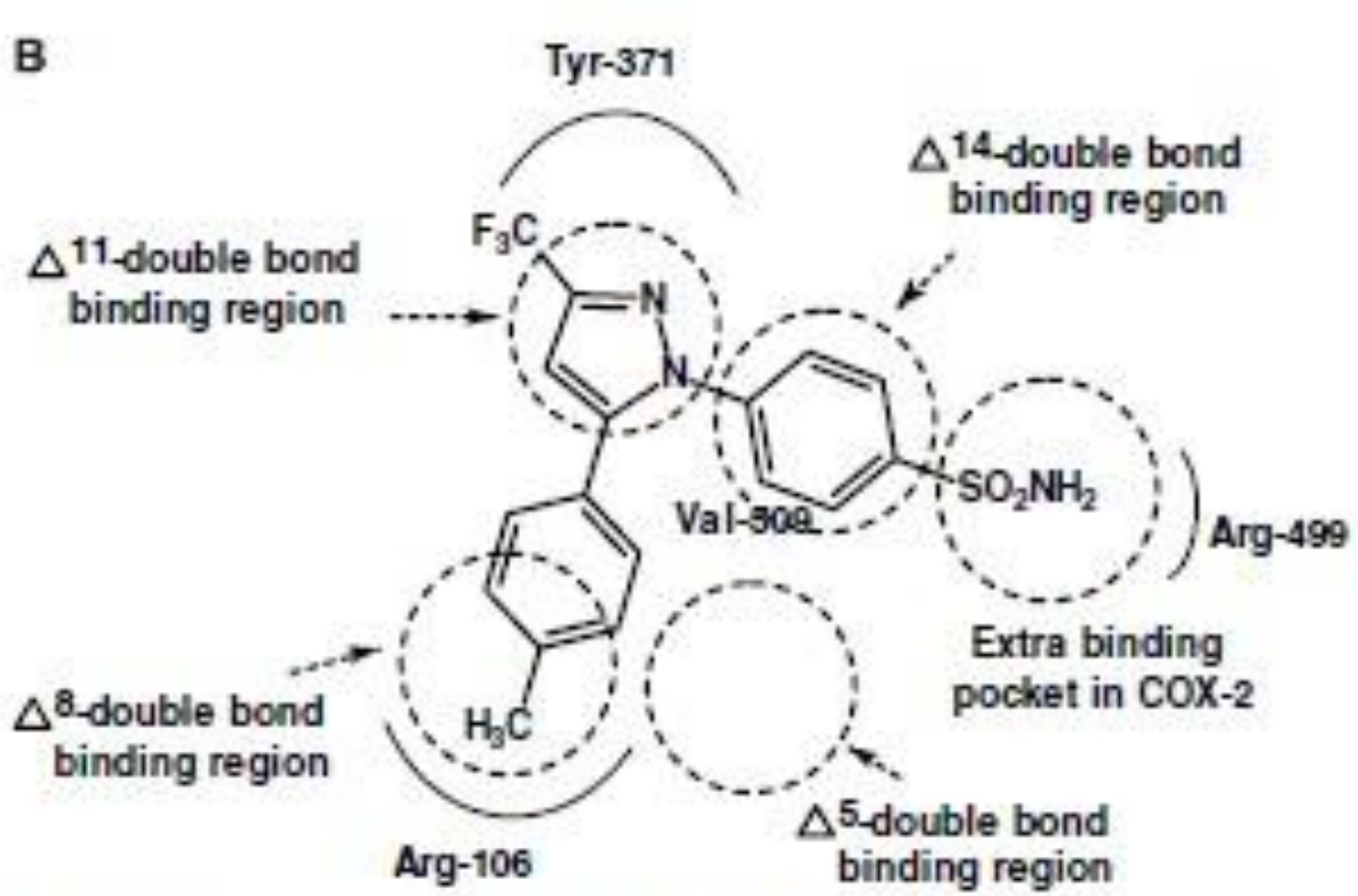
SAR Summary for COX Inhibitors

1. Molecule must have an ionizable acid group and an aromatic ring system
2. A second non coplanar aromatic ring increases potency by increasing bonding interactions
3. Limiting the number of possible conformers increase potency
4. A two atom separation between the anionic charge and the aromatic ring is the optimal
5. Increasing the distance to 3 or 4 carbons generally decreases potency
6. Introduction of a methyl at the first carbon increases potency and introduces a chiral center
7. The S–isomers are the more potent isomers
8. Increasing the size of the alkyl decreases potency but incorporation of the alkyl into a heterocycle retains activity

. Hypothetical binding models of indomethacin to COX-1

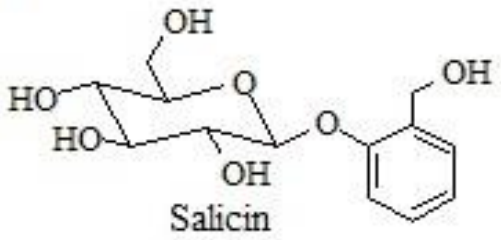


Hypothetical binding models of celecoxib to COX-2



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

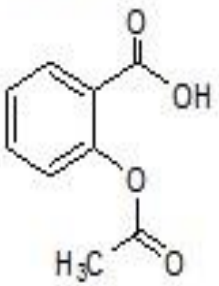


Salicin

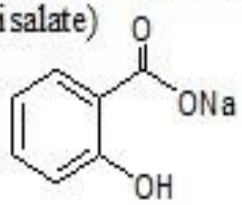
Salicylate SARs

- 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.
- Introduction of electronegative groups and lipophilic groups increases anti–inflammatory activity and toxicity.

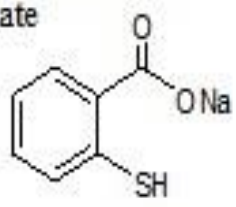
ASPIRIN



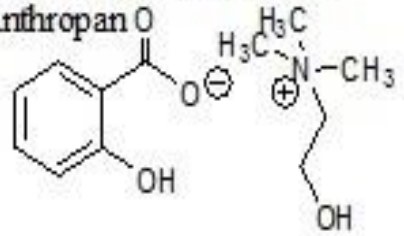
SODIUM SALICYLATE
(Bisalate)



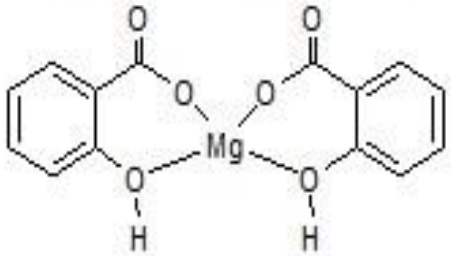
SODIUM THIOSALICYLATE
Rexolate



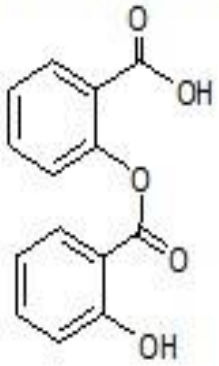
CHOLINE SALICYLATE
Anthropan



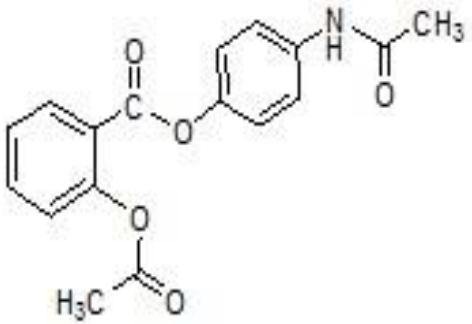
MAGNESIUM SALICYLATE
Magan, Mobidin, (Trisalate)



SALSALATE
Salflex, Disalcid



Benorylate



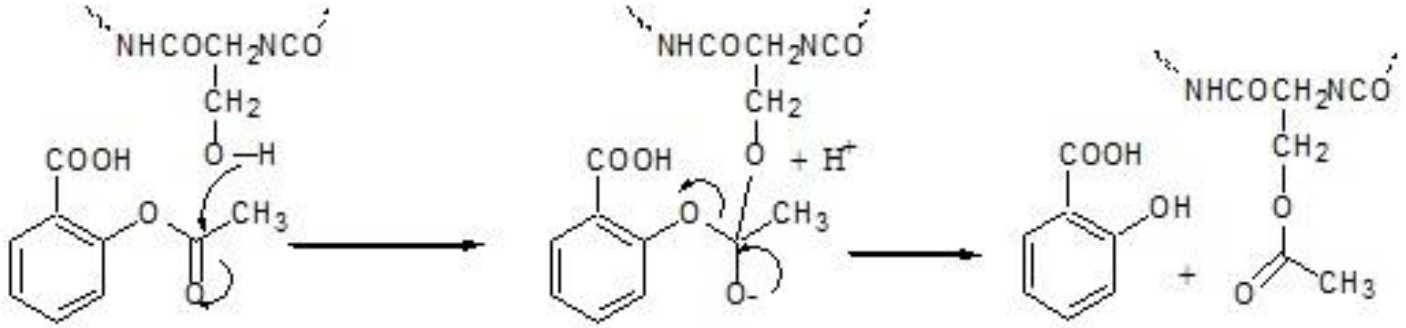
- **Salicylic acid and Sodium salicylate** were the original products used but required doses which had much gastric irritation and ulceration. Salicylic acid in the unionized form has a bad taste, thus the sodium salt is used more frequently

- **Salsalate** and **Benorylate** are prodrug esters. The sodium salt is freely soluble in water and helps in its dissolution and faster absorption. Salsalate is only half as potent as an analgesic/antipyretic as **Aspirin** but produces less GI irritation.
- Salsalate is a diester of salicylic acid and benorylate is esterified with Acetaminophen
- Salsalate is insoluble in gastric pH but soluble in the small intestines, thus causing less gastric problems.
- Further, it is useful in hypersensitivity to Aspirin. Hypersensitivity to ASA is a result of acetylated plasma proteins. Since it produces Salicylic acid it can be used in Aspirin sensitive patients
- **Sodium thiosalicylate** is used in rheumatic fever and acute gout and an injectable form is available
- Magnesium salicylate form stable aqueous solution and show some success in overcoming the GI problems
- **Choline salicylate** is absorbed faster than Aspirin producing higher salicylate blood levels and an aqueous formulation is available

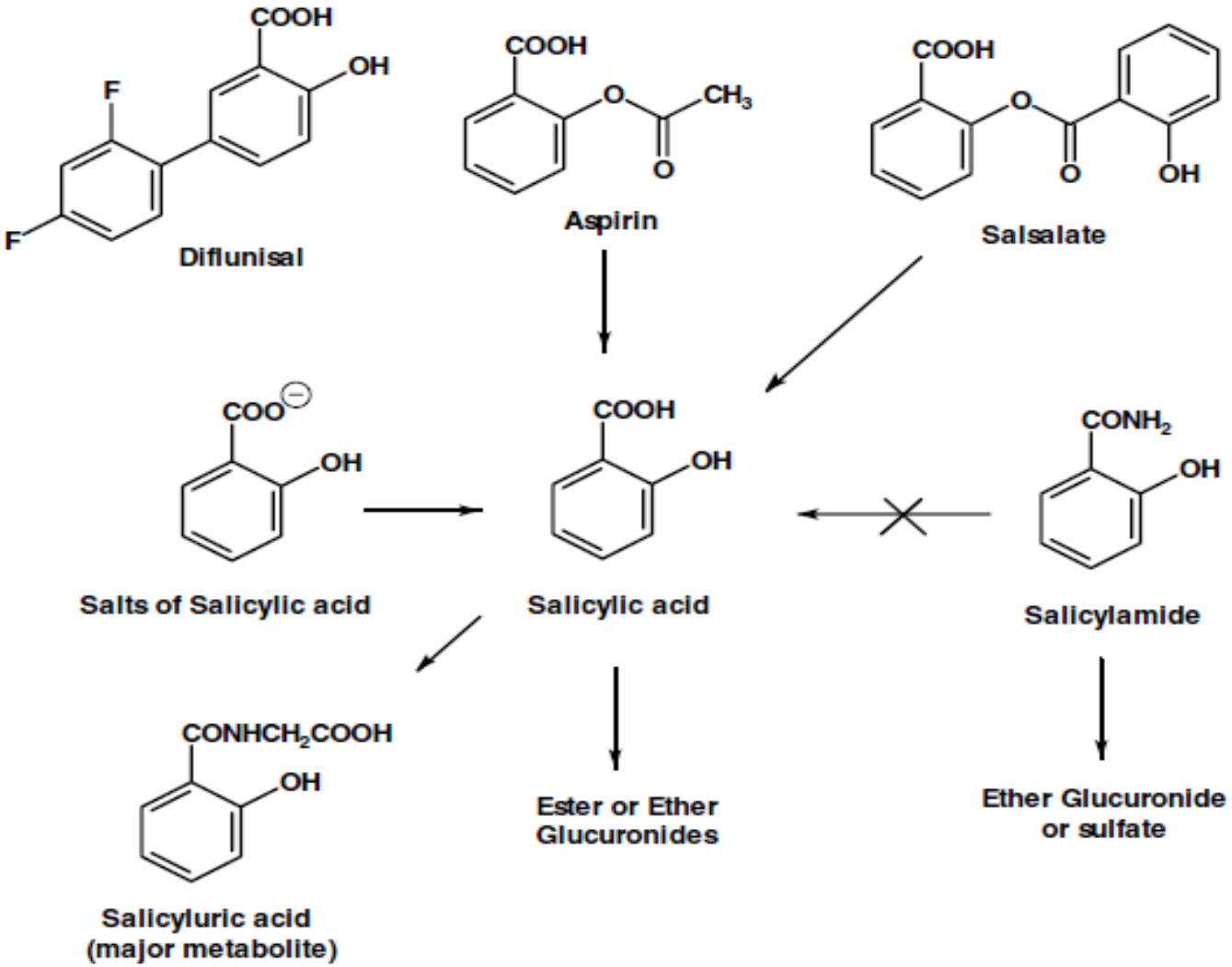
Aspirin

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 The name. ***Aspirin*** was coined by adding an ***a*** for acetyl to ***spirin*** from the name of the plant from which salicylic acid was first isolated

- 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
- Salicylic acid forms a reversible ionic bond with the cationic site on cyclooxygenase

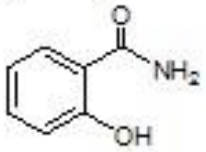


Salicylates and their metabolism.

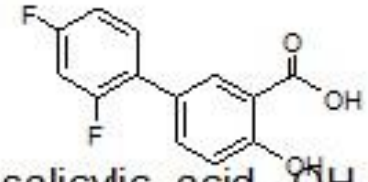


Salicylamide and Diflunisal

SALICYLAMIDE
(Bisalate)



DIFLUNISAL
Dolobid

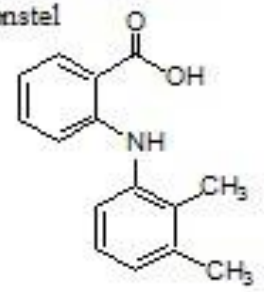


- **Salicylamide** is an isostere of salicylic acid, OH replaced by NH2 to produce a non acidic amide which is stable in aqueous preparations and does not cause GI tract ulceration and is absorbed only in intestine. It has greater CNS penetration. It is reported to be as effective as Aspirin as an analgesic/antipyretic and is effective in relieving arthritis pain but does not appear to have antiinflammaatory actions. It does not satisfy **SAR 1** possibly works through a different mechanism. It can be used by those allergic to Aspirin.
- **Diflunisal** has changed absorption profile and increased duration of action. Diflunisal is absorbed only in intestine; it is not soluble in gastric fluid. Thus, gastric bleeding and GI upset is not as common. It lasts 3–4 times longer than aspirin. The increase in potency is attributed to an increase in binding to the receptor since it has a second aromatic ring **SAR 2**. The proximity of the two phenyl rings allows for the ortho hydrogen van der Walls electron radii to repel and thus keep the rings out of the same plane.

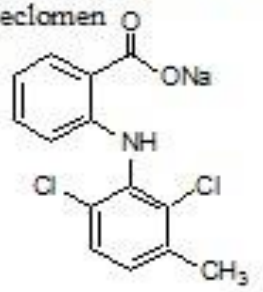
Fenemates

- The Fenemates are derivatives of Anthranilic acid, an isoster of salicylic 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 coplanarity by the ortho substituent
- **Mefenamic** acid has only one substituent, the 2' methyl, that ensures non coplanarity
- **Meclofenamate** sodium has two such groups, the chlorine atoms, and thus more molecules of Meclofenamate assume the correct conformation and the drug is more potent

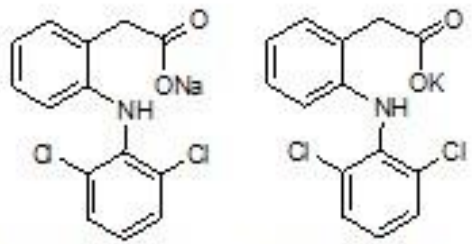
MEFENAMIC ACID
Ponstel



MECLOFENAMATE Sodium
Meclomen



- Meclofenamate is 25 times more potent thus normal dose for Meclofenamate is 25 mg while the dose for Mefenamic acid is 250 mg.
- Since this class offers no advantage over the salicylates with respect to analgesic or anti-inflammatory actions, there is little interest in developing this class



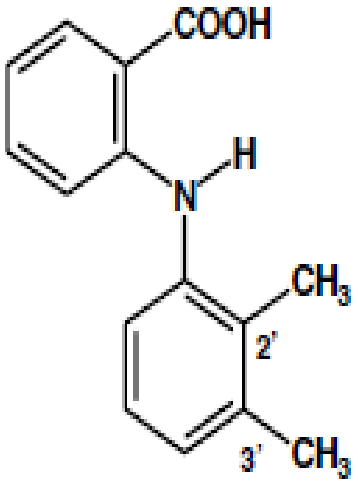
Diclofenac Na
Voltaren, (Arthrotec), Solaraze

Diclofenac K
Cataflam

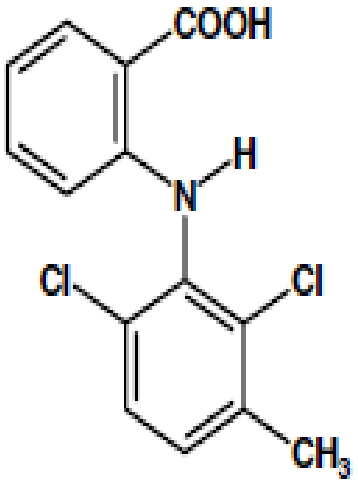
The SARs in Diclofenac sodium are similar to those discussed with the Fenemates. **Diclofenac** is probably the most popular NSAID in the world. Its mechanism of action may be a little different from the others. It is a COX inhibitor like the rest, but it also seems to inhibit *lipoxygenase* to some degree. This could account for its increased anti-inflammatory effectiveness and potency. The two Cl groups are necessary to force the two rings out of plane with each other. It has a profile of action similar to the others and favors anti-inflammation uses, rather than analgesic uses.

Diclofenac is also available in combination with Misoprostol as Arthrotec™. Why? The Sodium salt is a delayed release formulation while the Potassium salt is used in a rapid release formulation.

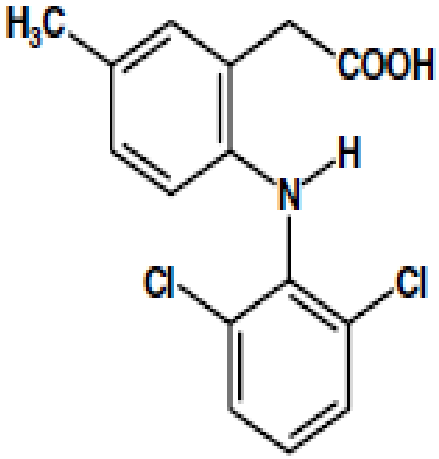
Diclofenac sodium is available in a gel form (Solaraze) for the treatment of actinic keratosis. The mechanism is unknown.



Mefenamic acid

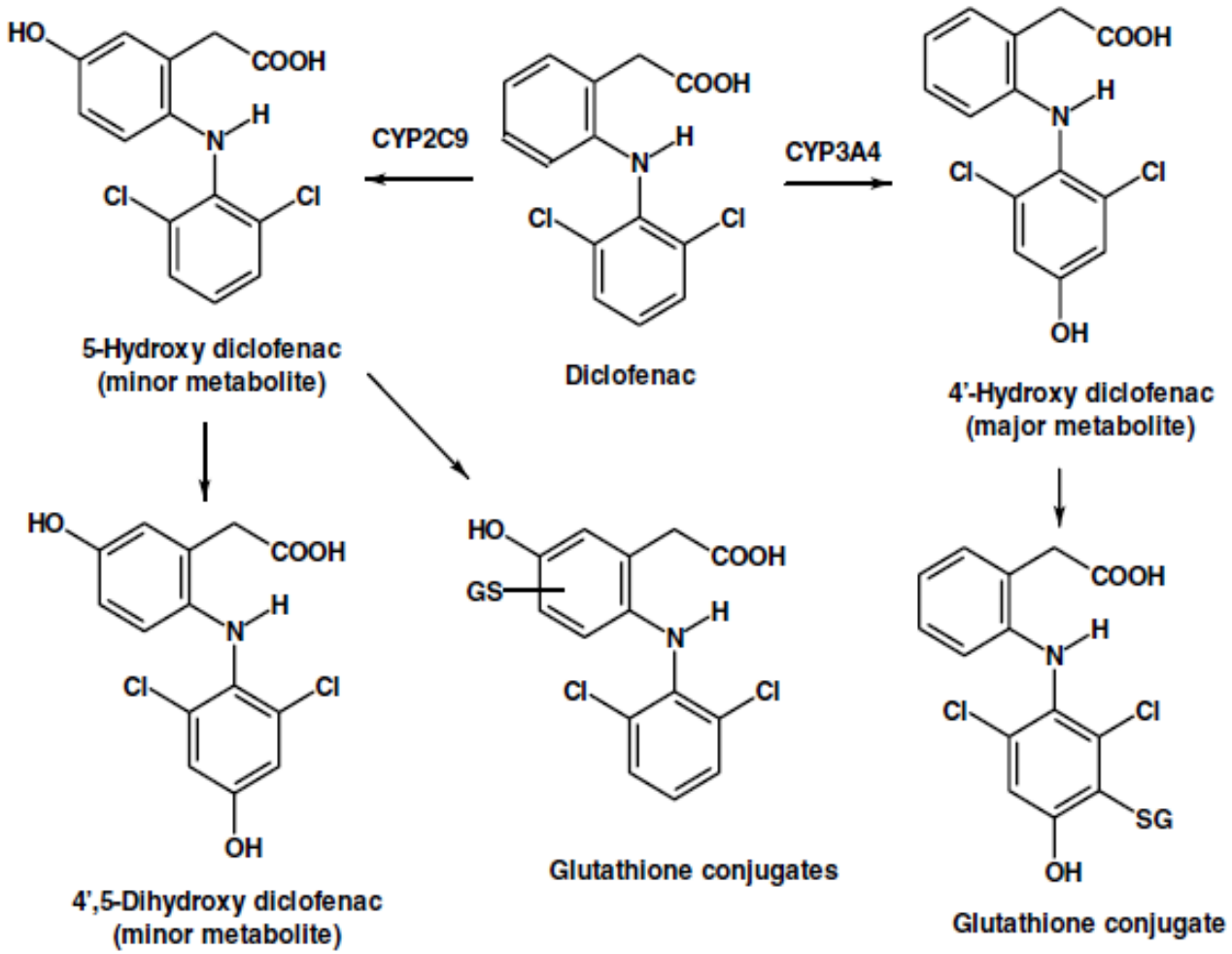


Meclofenamic acid

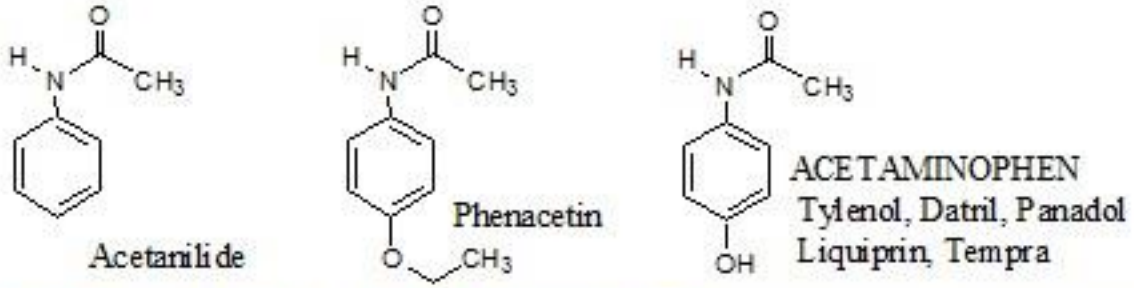


Lumiracoxib

METABOLISM OF DICLOFENAC



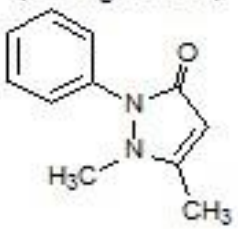
p-Aminophenols



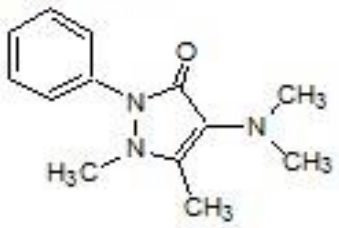
- Useful for pain and fever, but not inflammation. They have an aromatic ring, but do not have an acidic group ionizable at physiologic pH. Thus they do not comply with **SAR 1** possibly act by some other mechanism
- The first drug **Acetanilide** is out of market due of toxicity (both blood and liver disorders
- **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
- **Acetaminophen** is also a very old drug, a metabolite of both phenacetin and acetanilide, is a safe drug, producing much better tolerance and a lower incidence of gastric bleeding compared to many of the other NSAIDs, probably because of its apparently different mechanism of action
- You know the chemistry of toxicity for both phenacetin and acetaminophen

Pyrazoles and Pyrazolidinediones

ANTIPYRINE
(Auralgan Otic)



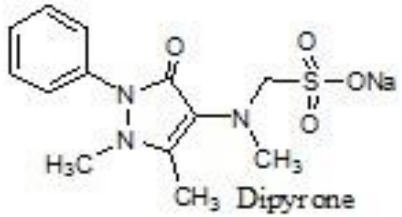
Aminopyrine



Antipyrine is the prototype and its antipyretic and analgesic activities were discovered by accident.

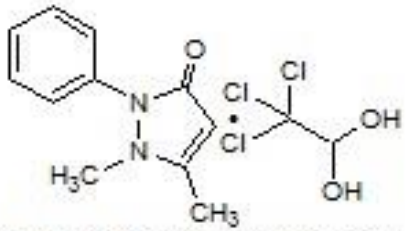
Aminopyrine is an analog, more potent and longer acting but both possess significant incidences of agranulocytosis leading to death and used only in otic drops

Dipyrone is a prodrug which spontaneously decomposes in aqueous solutions to aminopyrine. It is banned in the US but available in Mexico.



Dipyrone

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



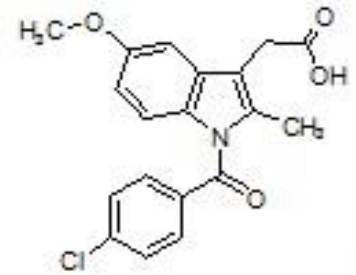
DICHLORALPHENAZONE
Antipyrine • Chloral Hydrate

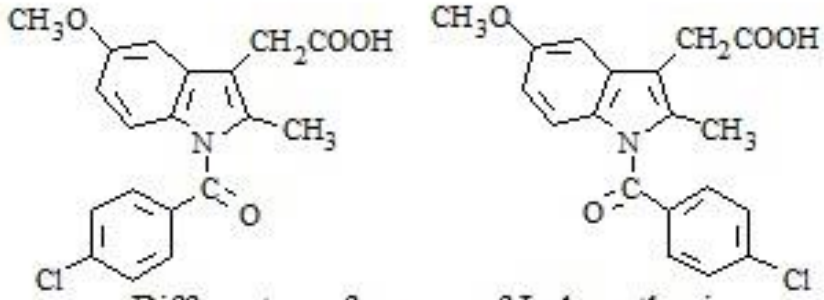
Although it appears that **SAR 1** does not apply, these drugs are able to tautomerize into enols, which in turn ionize. Thus they have an aromatic ring with an anionic charge two atoms away.

Arylacetic acid Derivatives

Satisfy **SAR 1, SAR 2, SAR 4** as well as **SAR 3** thus are generally more potent than ASA. **Indomethacin** was synthesized in 1961 at Merck as part of a study of indole derivatives as potential anti–inflammatory agents since **Serotonin**, which contains the indole nucleus, is a potential **mediator** of inflammation. The indole system and the phenyl ring are separated by one atom and thus two sigma bonds. Theoretically it could exist in millions of conformation, but it does not due to skillful molecular manipulations.

INDOMETHACIN
Indocin



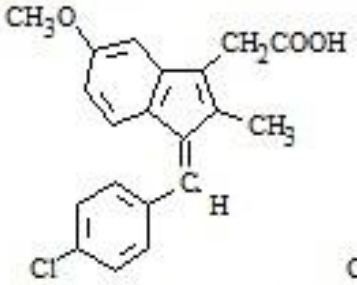


Different conformers of Indomethacin

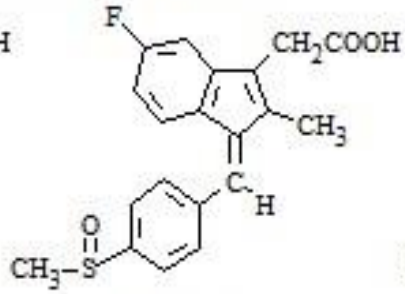
Illustrates **SAR 3**. **Partial double bond character** of amide restrict rotation. **2-Methyl** provides steric hindrance favoring the active conformer and the hydrogen atoms at 7 and 2' provide hindrance to ensure **non coplanarity**

Sulindac: Indomethacin has significant CNS side effects due to the indole nucleus. Thus the heterocyclic nitrogen was removed and a double bond introduced, giving the *indene* derivative. Z isomer is active, lacks the CNS side effects and causes less GI irritation but low water solubility. Introduction of a fluoro and a methylsulfinyl increased solubility while retaining potency. Sulindac is a prodrug. Its active form is the sulfide metabolite which has a long half–life allowing for BID administration. The phenyl is out of the plane

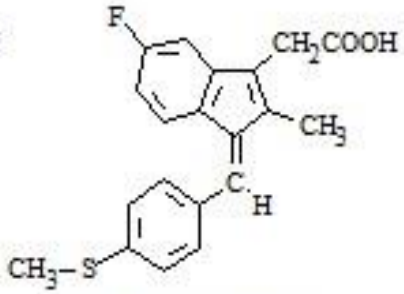
Sulindac
Clinoril



Indene analog of Indomethacin



Sulindac



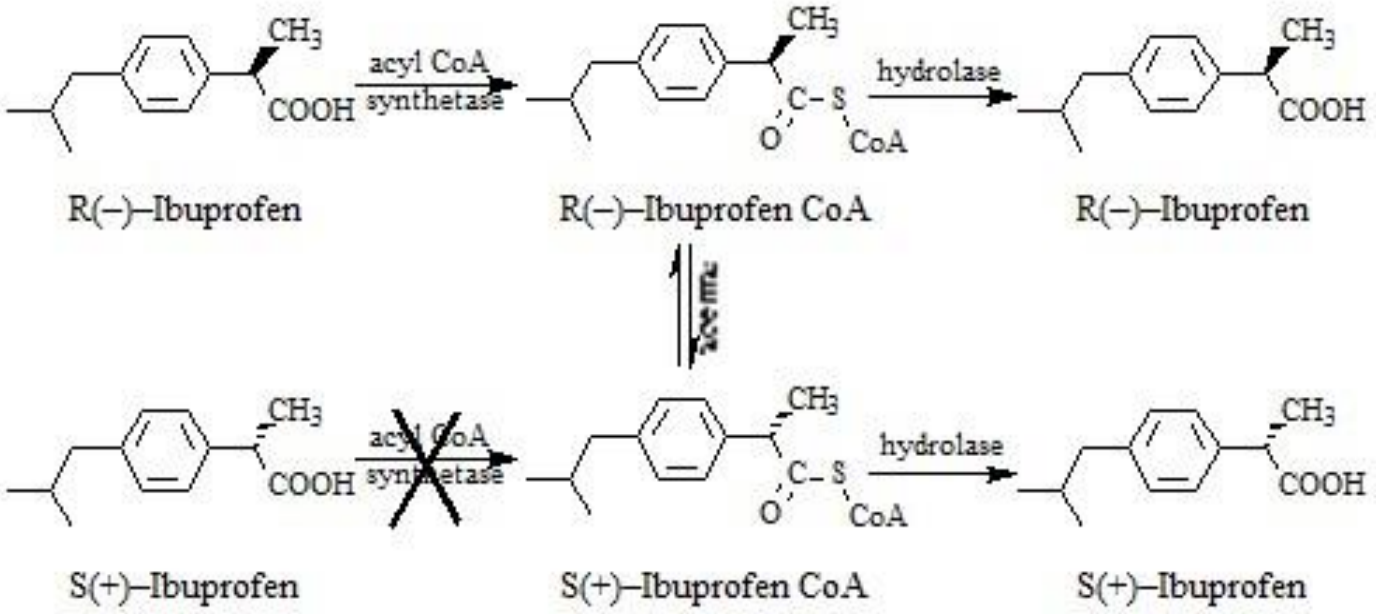
Sulfide of Sulindac

Clinically it has only about half the potency of Indomethacin in treating inflammation and reducing fever, but is equipotent in analgesic effect. Since the drug is absorbed as the inactive sulfoxide, it causes fewer GI disturbances (no prostaglandin biosynthesis inhibition in the stomach). The thioether metabolite (shown at the right) is longer-lived than the parent (ca. 16 hours).

Arylpropioanic acid Derivatives

These agents illustrate **SAR 4, 6** and **7**

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. One reference states that 60% of an Ibuprofen and 100% of a Fenoprofen dose undergo isomerization. Another reference states that S–Ibuprofen is 160 times more active than R–Ibuprofen ***in vitro*** but they were equipotent ***in vivo.***

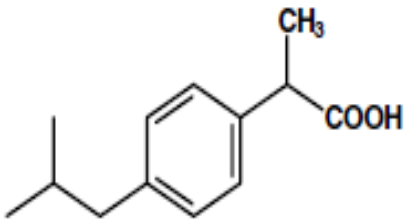


Ibuprofen is the prototype, marketed as the racemate. Lacks second aromatic ring (**SAR 2**) but possess a sec–butyl substituent that presumably renders the drug slightly less potent. Its profile is much like other NSAIDs in terms of GI distress.

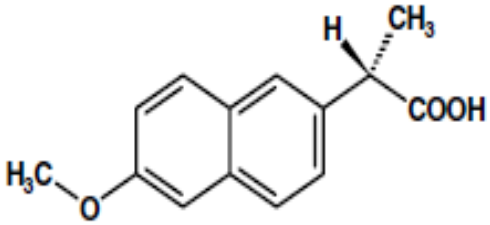
Flurbiprofen resulted from a study of the SARs. The 3–fluoro substituent helps ensure non–coplanarity. This compound had the most favorable therapeutic profile and was first introduced as a topical product for ophthalmic use (Ocufen). Later it was introduced for systemic use (Ansaid is reputed to stand for Another NSAID). This drug is many times the potency of the other drugs (100x phenylbutazone against inflammation), and is about half as potent as methylprednisolone (an anti-inflammatory steroid).

Ketoprofen (1986): The great potential advantage of this drug is that it inhibits the leukotriene pathway as well, although its structure does not predict that. It is clinically less potent than Indomethacin, but has about the same GI disturbance profile

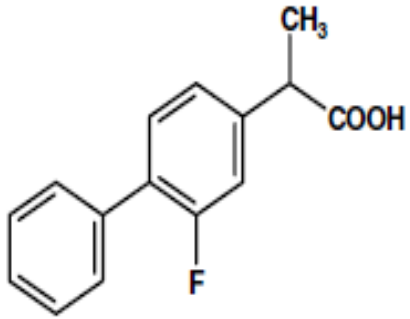
Aryl- and heteroarylpropionic acids.



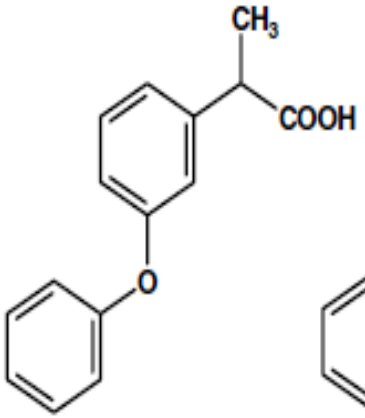
Ibuprofen



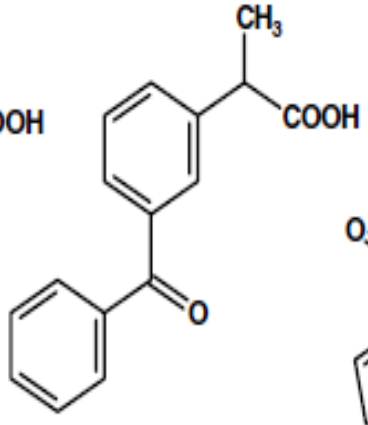
Naproxen



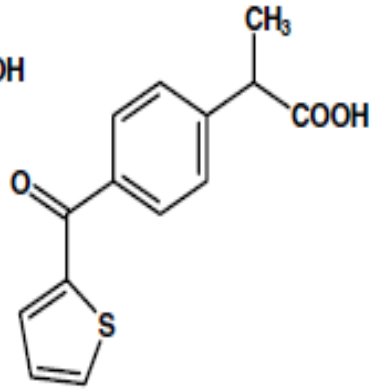
Flurbiprofen



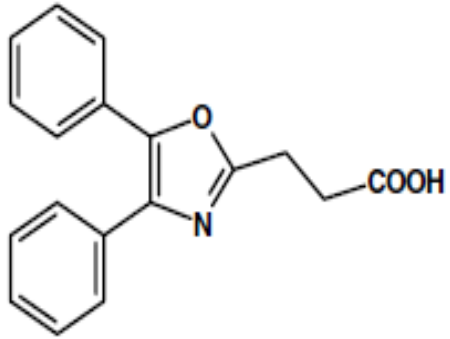
Fenoprofen



Ketoprofen

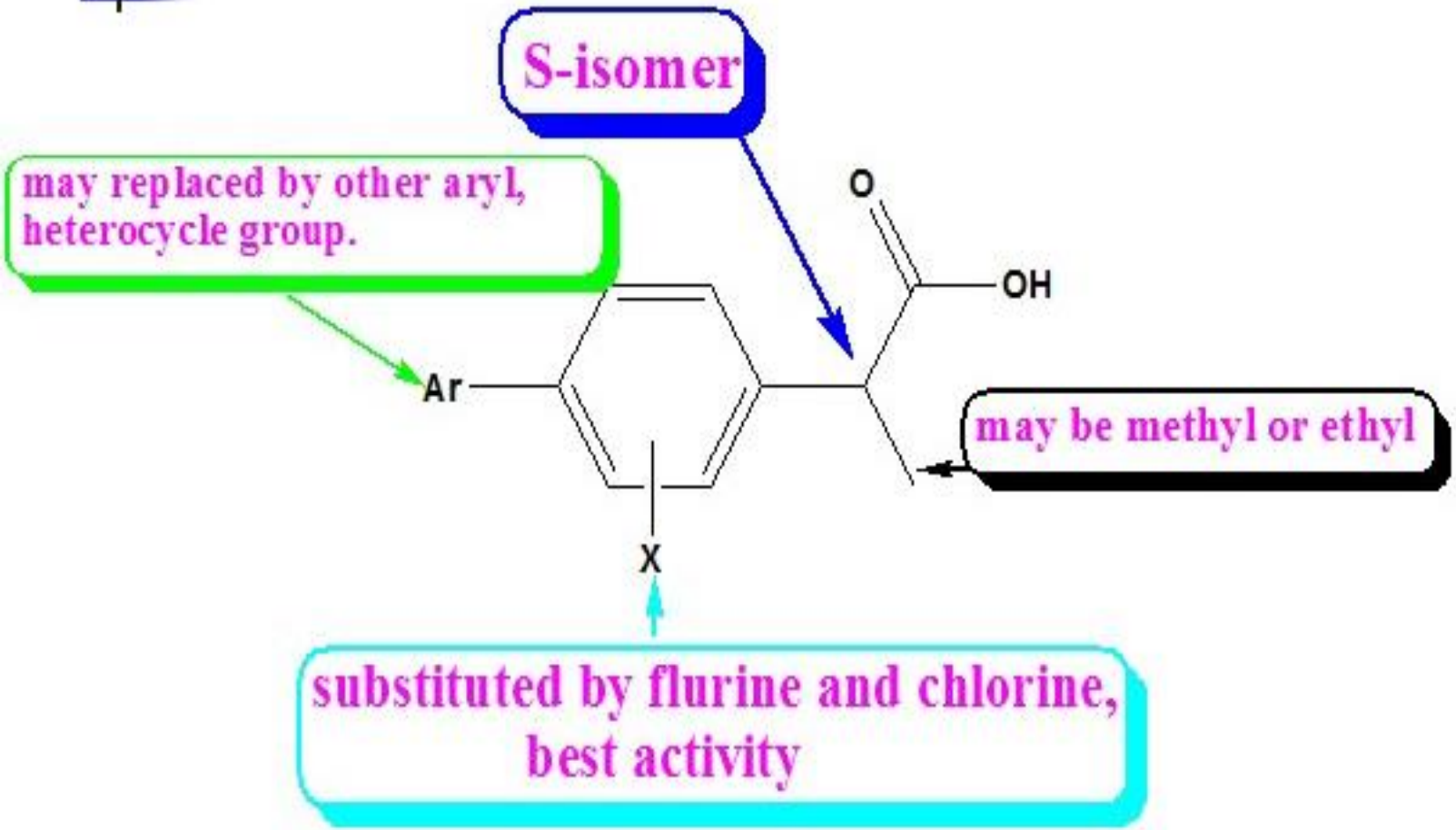


Suprofen



Oxaprozin

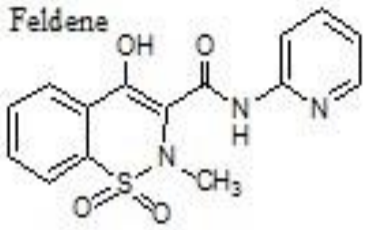
SAR of Ibuprofen



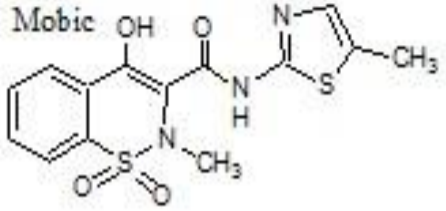
Oxicams

Pfizer developed this class to produce non–carboxylic acid NSAIDS

PIROXICAM
Feldene



MELOXICAM
Mobic

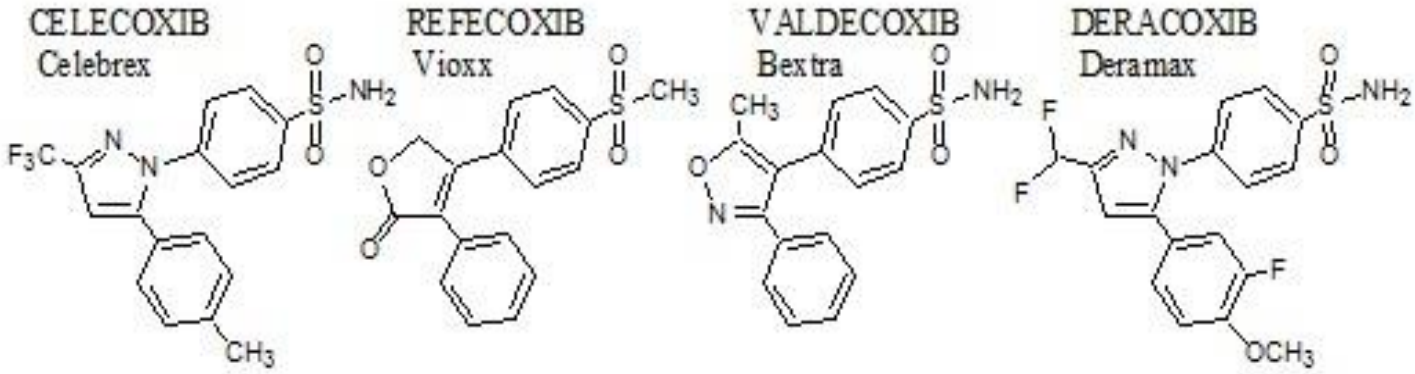


Piroxicam is the first member of this family marketed, however it possess the three structural requirements. The enolic hydroxyl is the acidic group and the pyridyl ring is the second aromatic ring. Although it has good potency, the GI side effects limit its usefulness. A typical half-life for Piroxicam is ca. 38 hours.

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.

- Oxicams, are first-generation NSAIDs that lack a free carboxylic acid side chain but with an acidic enolic 1,2-benzothiazine carboxamide ring.
- Several piroxicam prodrugs have been synthesized via derivatization of the enol alcohol group (amipiroxicam, droxicam, and pivoxicam) to reduce piroxicam-induced GI irritation.
- piroxicam and meloxicam have very different affinities for the COX isozymes, and therefore exhibit very different risks for GI complications.

COX - 2 Inhibitors



Celecoxib was the first. Structurally it differs from other NSAIDS in that is only weakly acidic. It does possess a sulfamyl group and has a warning about use in patients with a sulfonamide allergy

Valecoxib is also a sulfamyl and its package insert contains the same caution. It is this phenyl group which is inserted into the extra space in COX–2

Deracoxib is also acidic but is indicated for veterinary use

Rofecoxib is not acidic

Metabolic biotransformation of celecoxib.