NON-STEROIDAL ANTIINFLAMMATORY DRUGS (NSAIDS)

I. Introduction

The non-steroidal antiinflammatory drugs (NSAIDs) are widely used for the treatment of minor pain and for the management of edema and tissue damage resulting from inflammatory joint disease (arthritis). A number of these drugs possess antipyretic activity in addition to having analgesic and antiinflammatory actions, and thus have utility in the treatment of fever. Most of these drugs express their therapeutic actions by inhibition of prostaglandin biosynthesis as described in the sections that follow. Some of the primary indications for NSAID therapy include:

- Rheumatoid Arthritis (RA): No one NSAID has demonstrated a clear advantage for the treatment of RA. Individual patients have demonstrated variability in response to certain NSAIDs. Anti-inflammatory activity is shown by reduced joint swelling, reduced pain, reduced duration of morning stiffness and disease activity, increased mobility, and by enhanced functional capacity (demonstrated by an increase in grip strength, delay in time-to-onset of fatigue, and a decrease in time to walk 50 feet).
- Osteoarthritis (OA): Improvement is demonstrated by increased range of motion and a reduction in the following: Tenderness with pressure, pain in motion and at rest, night pain, stiffness and swelling, overall disease activity, and by increased range of motion. There are no data to suggest superiority of one NSAID over another as therapy for OA in terms of efficacy and toxicity. NSAIDs for OA are to be used intermittently if possible during painful episodes and prescribed at the minimum effective dose to reduce the potential of renal and GI toxicity. Indomethacin should not be used chronically because of its greater toxicity profile and its potential for accelerating progression of OA.

- Acute gouty arthritis, ankylosing spondylitis: Relief of pain; reduced fever, swelling, redness and tenderness; and increased range of motion have occurred with treatment of NSAIDs.

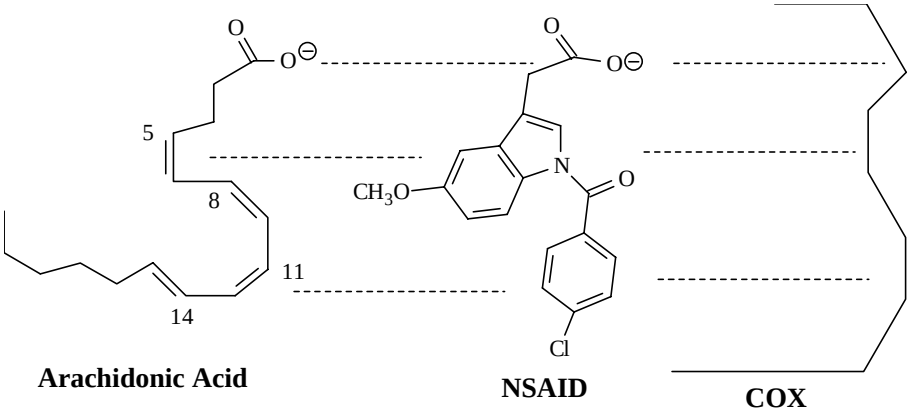
- Dysmenorrhea: Excess prostaglandins may produce uterine hyperactivity. These agents reduce elevated prostaglandin levels in menstrual fluid and reduce resting and active intrauterine pressure, as well as frequency of uterine contractions. Probable mechanism of action is to inhibit prostaglandin synthesis rather than provide analgesia.

II. NSAID Mechanism of Action

The major mechanism by which the NSAIDs elicit their therapeutic effects (antipyretic, analgesic, and anti-inflammatory activities) is inhibition of prostaglandin (PG) synthesis. Specifically NSAIDs competitively (for the most part) inhibit cyclooxygenases (COXs), the enzymes that catalyze the synthesis of cyclic endoperoxides from arachidonic acid to form prostaglandins (see Prostaglandin Chapter).

Two COX isoenzymes have been identified: COX-1 and COX-2. COX-1, expressed constitutively, is synthesized continuously and is present in all tissues and cell types, most notably in platelets, endothelial cells, the GI tract, renal microvasculature, glomerulus, and

collecting ducts. Thus COX-1 is important for the production of prostaglandins of homeostatic maintenance, such as platelet aggregation, the regulation of blood flow in the kidney and stomach, and the regulation of gastric acid secretion. Inhibition of COX-1 activity is considered a major contributor to NSAID GI toxicity. COX-2 is considered an inducible isoenzyme, although there is some constitutive expression in the kidney, brain, bone, female reproductive system, neoplasias, and GI tract. **The COX-2 isoenzyme plays an important role in pain and inflammatory processes.**



Inhibition of COX by NSAIDs

Generally, the NSAIDs inhibit both COX-1 and COX-2. Most NSAIDs are mainly COX-1 selective (eg, aspirin, ketoprofen, indomethacin, piroxicam, sulindac). Others are considered slightly selective for COX-1 (eg, ibuprofen, naproxen, diclofenac) and others may be considered slightly selective for COX-2 (eg, etodolac, nabumetone, and meloxicam). The mechanism of action of celecoxib and rofecoxib is primarily selective inhibition of COX-2; at therapeutic concentrations, the COX-1 isoenzyme is not inhibited thus GI toxicity may be decreased.

Other mechanisms that may contribute to NSAID anti-inflammatory activity include the reduction of superoxide radicals, induction of apoptosis, inhibition of adhesion molecule expression, decrease of nitric oxide synthase, decrease of proinflammatory cytokine levels (tumor necrosis factor-a, interleukin-1), modification of lymphocyte activity, and alteration of cellular membrane functions.

Central analgesic activity has been demonstrated in animal pain models by some NSAIDs such as diclofenac, ibuprofen, indomethacin, and ketoprofen. This may be because of the interference of prostaglandin (PGE1, F2 and F2a) mediated pain formation or with transmitters or modulators in the nociceptive system. Other proposals include the central action mediated by opioid peptides, inhibition of serotonin release, or inhibition of excitatory amino acids or N-methyl-D-aspartate receptors. NSAIDs are mainly effective against the type of pain in which PGs sensitize pain receptors (inflammation and tissues) including the pain of arthritis, bursitis, pain of muscular and vascula origin and dysmenorrhea. The effectiveness of these agents against headache may result from their ability to inhibit PG-mediated cerebral vascular vasodilation.

Antipyretic activity of NSAIDs results from inhibition of prostaglandin E2 (PGE2) synthesis in

circumventricular organs in and near the preoptic hypothalamic area. Infections, tissue damage, inflammation, graft rejection, malignancies, and other disease states enhance the formation of cytokines that increase PGE2 production. PGE2 triggers the hypothalamus to promote increases in heat generation and decreases in heat loss.

III. Other Actions of the NSAIDs

The NSAIDs also express a variety of other actions in addition to their antiinflammatory, analgesic and antipyretic activities as outlined below:

- GI Tract (N/V, ulceration and hemorrhage). In the gastric mucosa, prostaglandins play a cytoprotective role inhibiting the proton pump and thereby decreasing gastric acid synthesis, stimulating the production of glutathione that scavenges superoxides, promoting the generation of a protective barrier of mucous and bicarbonate, and promoting adequate blood flow to the gastric muscosal cells. Since NSAIDs block PG biosynthesis in the GI tract, they block these cytoprotective processes. The primary toxicity seen with the NSAIDs is GI irritation which may lead to the production of ulcers when used in large doses over a long period of time. This occurs quite frequently in patients with RA and it may become so severe that the drug must be discontinued. There have been a number of attempts to eliminate this side effect and some success has been achieved but since most of the compounds suppress the production of PGs involved in limiting the secretion of gastric acid and since this a consequence of their mechanism of action it has been difficult to completely eliminate this side effect. In additional to inhibition of PG biosynthesis, NSAID gastric irritation may also be due to a direct irritation of the gut by these acidic compounds.

- CNS: High NSAID doses cause CNS stimulation (confusion, dizziness, etc), tinnitus, etc. PGE2 may also cause fever via interactions within the hypothalamus

- Respiratory: Direct and indirect (increased CO_2 production) stimulation of respiratory centers, stimulation of O_2 consumption in muscle (increased CO_2); respiratory alkalosis. Also PGI2 and the PGEs cause bonchodilation while PGF2a, PGGs, PGH2, PGD2 and TxA2 are bronchoconstrictors (asthma)

- Acid-Base: Initial respiratory alkalosis. This is generally somewhat unique to the salicylates and is only seen with large doses.
- Cardiovascular: PGH2 and PGH2 cause transient vasoconstriction, but these intermediates are converted to PGI2 and other PGS (PGD2 PGF2a) which are vasconstrictors. At high doses NSAIDs cause vasodilation and depression of the vasomotor center.
- Uterus: PGF2a and PGE2 (in low concentrations) promoate uteral contraction while PGI2 and PGE2 in high concentrations promote uteral relaxation. NSAIDs decrease contractility and prolong gestation
- Blood clotting: PGS I2 (vascular endothelium), E2 and D2 inhibit platelet aggregation while TXA2 (platelets) promotes aggregation. NSAIDs may significantly increase clotting times and can be used for prophylaxis of thromboembolism and MI. However, patients with liver damage, vitamin K deficiency, hypoprothrombinemia or hemophilia should avoid aspirin

therapy.

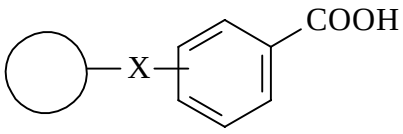
- Renal: The inhibition of PGE_2 and PGI_2 both of which produce vasodilation in the kidney results in a decrease blood flow to the kidneys due to constriction of afferent arterioles which is mediated by norepinephrine and Angiotensin II. NSAIDs may decrease sodium and fluid elimination resulting in edema
- Reye's syndrome: This is seen in children who take an NSAID such as aspirin while recovering from mild viral infection. Although it occurs rarely there is a 20-30% mortality seen with this type of side effect.

IV. General Structure and Properties of the NSAIDs

The NSAIDs can be sub-classified on the basis of chemical structure as follows:

- Salicylates
- Propionic Acids (Profens)
- Aryl and Heteroarylacetic Acids
- Anthranilates (Fenamates)
- Oxicams ("Enol Acids")
- Phenylpyrazolones
- Anilides

In general, NSAIDs structurally consist of an acidic moiety (carboxylic acid, enols) attached to a planar, aromatic functionality. Some analgesics also contain a polar linking group, which attaches the planar moiety to an additional lipophilic group. This can be represented as follows:



NSAID General Structure

As a result, the NSAIDs are characterized by the following chemical/ pharmacologic properties:

- All are relatively strong organic acids with pKas in the 3-5 range. Most, but not all, are carboxylic acids (see drug classes). Thus, salts forms can be generated upon treatment with base and all of these compounds are extensively ionized at physiologic pH. The acidic group is essential for COX inhibitory activity!

- The NSAIDs differ in their lipophilicities based on the lipophilic character of their aryl groups and additional lipophilic moieties and substituents.

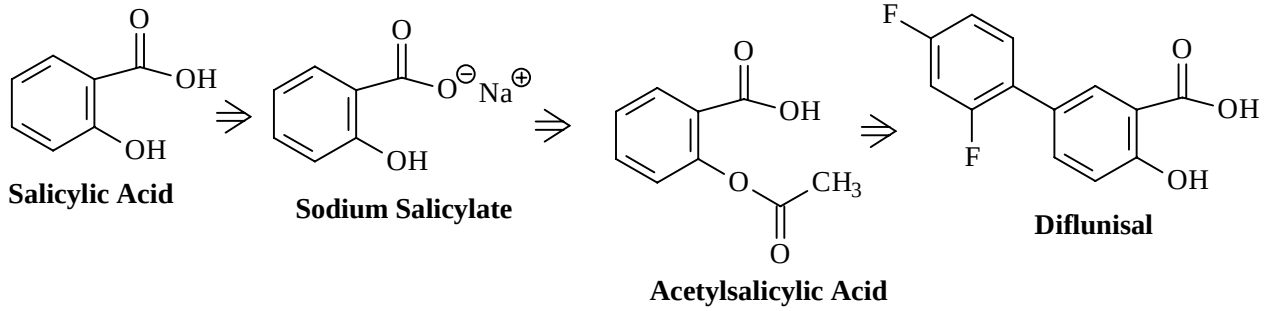
- The acidic group in these compounds serves a major binding group (ionic binding) with plasma proteins. Thus all NSAIDs are highly bound by plasma proteins (drug interactions!).

- The acidic group also serves as a major site of metabolism by conjugation. Thus a major

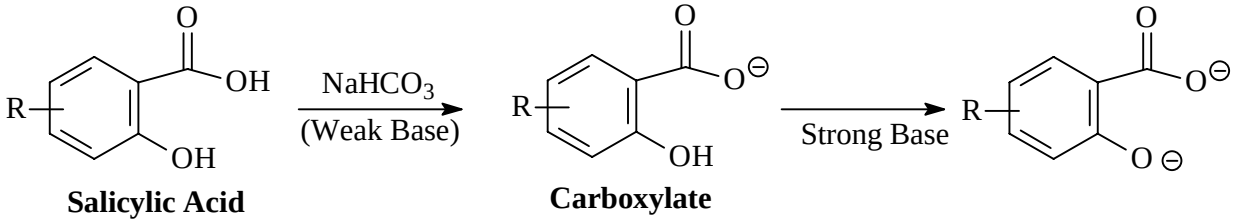
pathway of clearance for many NSAIDs is glucuronidation (and inactivation) followed by renal elimination.

V. Salicylates

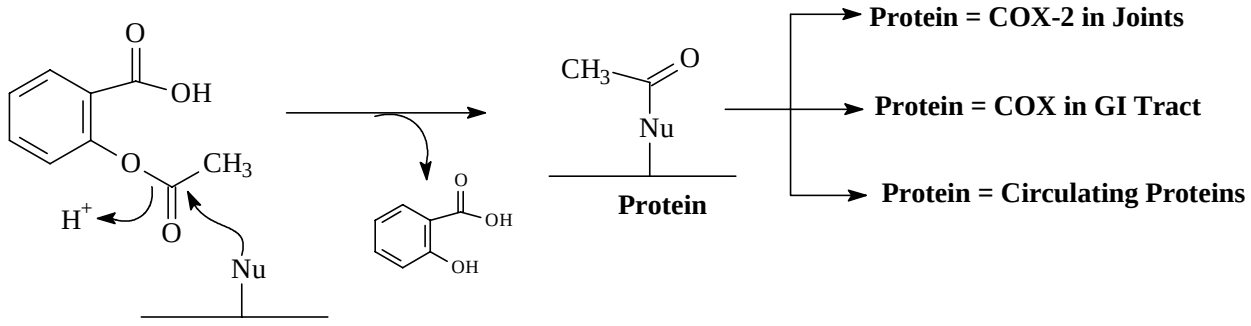
- Structure and Chemistry: The salicylates are derivatives of 2-hydroxybenzoic acid (salicylic acid). The salicylates were discovered in 1838 following the extraction of salicylic acid from willow bark. Salicylic acid was used medicinally as the sodium salt but replaced therapeutically in the late 1800s by the acetylated derivative, acetylsalicylic acid (ASA) or aspirin. Therapeutic utility is enhanced by esterification of the phenolic hydroxyl group as in aspirin, and by substitution of a hydrophobic/lipophilic group at C-5 as in diflunisal:



The salicylates are strong organic acids and readily form salts with alkaline materials. Note that the carboxyl group is substantially more acidic (and ionizes readily at physiologic pH) than the phenolic hydroxyl:



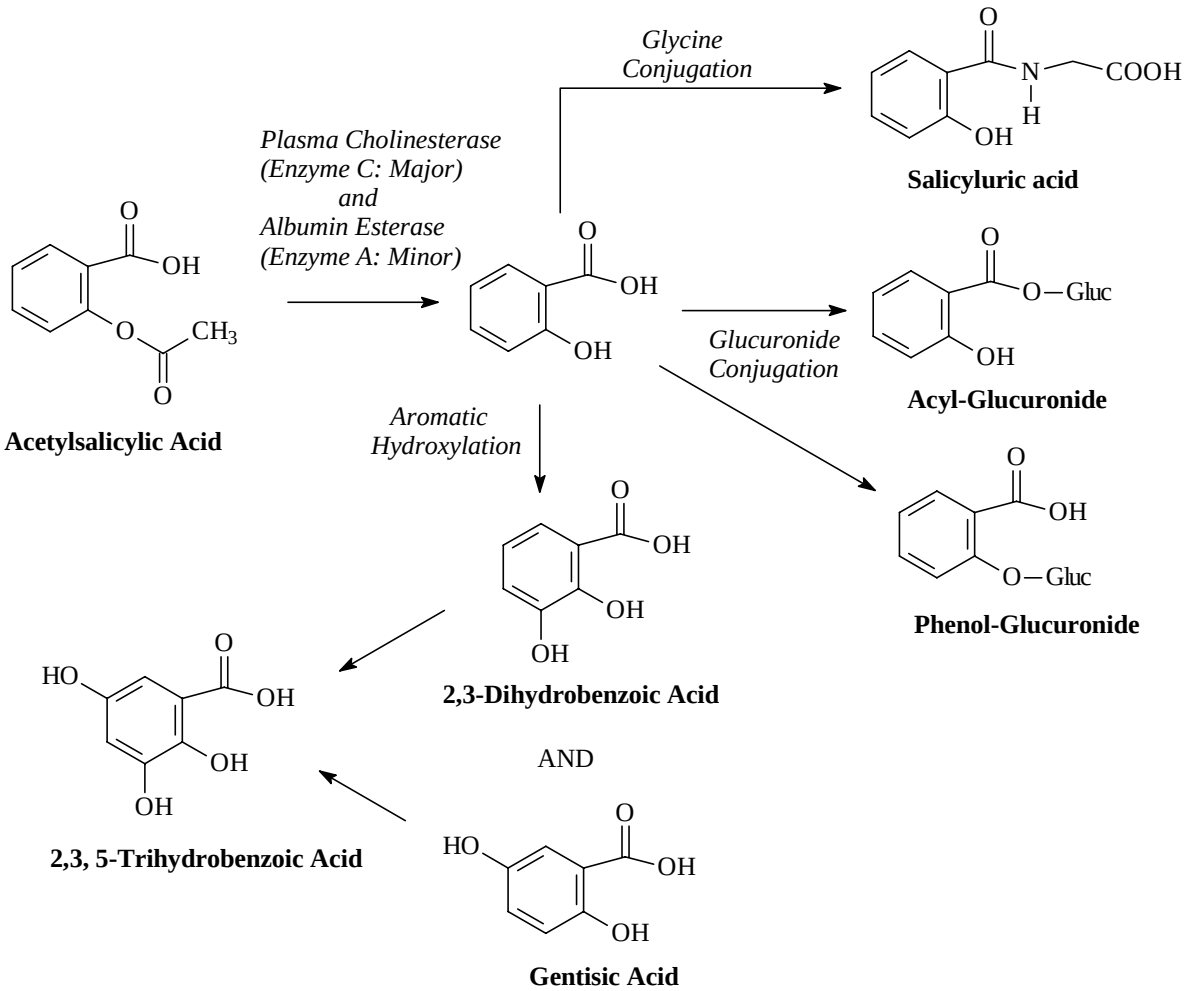
- Actions: The salicylates have potent antiinflammatory activity with mild analgesic and antipyretic activities. These compounds are mainly "COX-1 selective" – they are bound with higher affinity by COX-1. Toxicities include GI irritation, hypersensitivity reactions, inhibition of platelet aggregation, and ototoxicity (tinnitus). The therapeutic and certain of the toxic actions (i.e. gut) of aspirin can be related to its ability to inhibit COX in various tissues and participate in transacetylation reactions *in vitro*. For example, acetylation of COX results in irreversible inhibition of this enzyme and antiinflammatory effects in joints, and adverse effects in the GI tract. Also acetylation of circulating proteins may result in a hypersensitivity response.



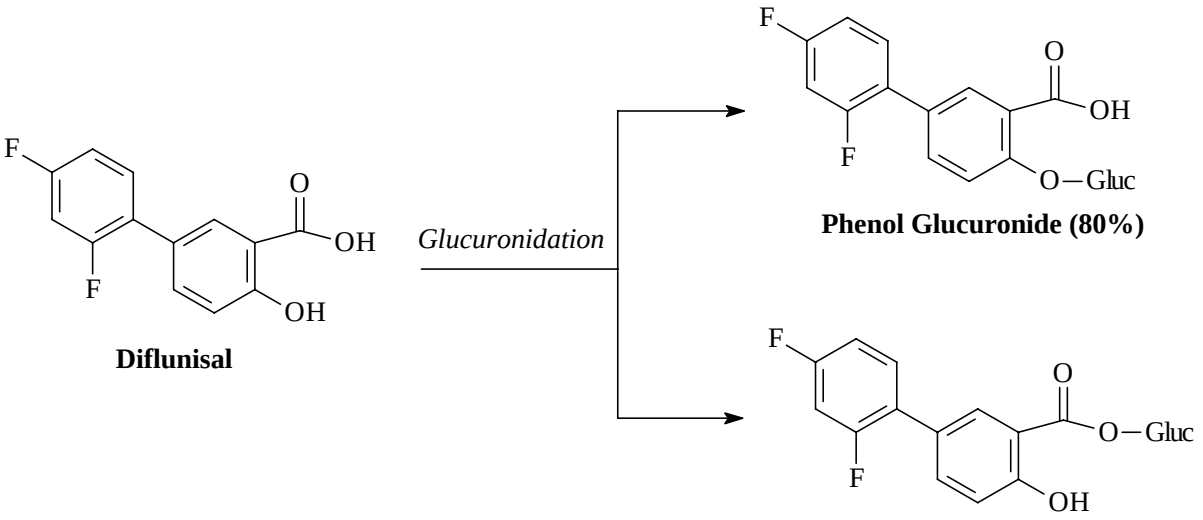
- Absorption and Distribution: When the salicylates are administered orally they are rapidly absorbed from primarily the small intestines and to a lesser extent the stomach. Generally, esters such as acetylsalicylic acid (ASA) appear to be absorbed more slowly, yet 70% of aspirin is absorbed within an hour and absorption is complete within 4 hours. It appears that a major determinant of absorption for this class of compounds is the physical characteristic of the tablet.

  ASA is absorbed primarily intact, and then is hydrolyzed by plasma and tissue (liver) esterases to salicylic acid. ASA and salicylic acid is extensively bound to plasma albumin – the ionized carboxyl and aromatic functionalites both contribute to plasma protein binding. This may result in drug-drug interactions with other anionic drugs that are administered concurrently and are also highly bound by plasma protein.

- Metabolism: Salicylic acid and drugs like ASA that are converted to salicylic acid undergo a variety of secondary metabolic transformations including: glycine conjugation to yield salicyluric acid, ring hydroxylation and carboxyl and phenol glucuronide conjugation. The salicylates and their metabolites are eliminated by renal mechanism.



- Diflunisal: The difluorophenyl analogue of salicylic acid differs from other members of the salicylate class and that it has primarily analgesic and antipyretic activity. It is used to treat the pain associated with RA, OA and muscle pain. It reported causes less GI tract ulceration than aspirin and has lower auditory side effects. This drug is cleared primarily by phenol and carboxyl O-glucuronidation similar to the salicylates



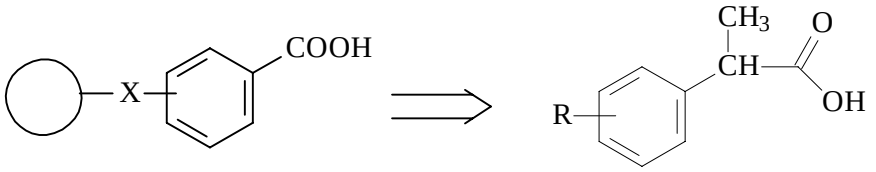
Diflunisal

Phenol Glucuronide (80%)

Ester Glucuronide (20%)

VI. Propionic Acid Derivatives ("Profens")

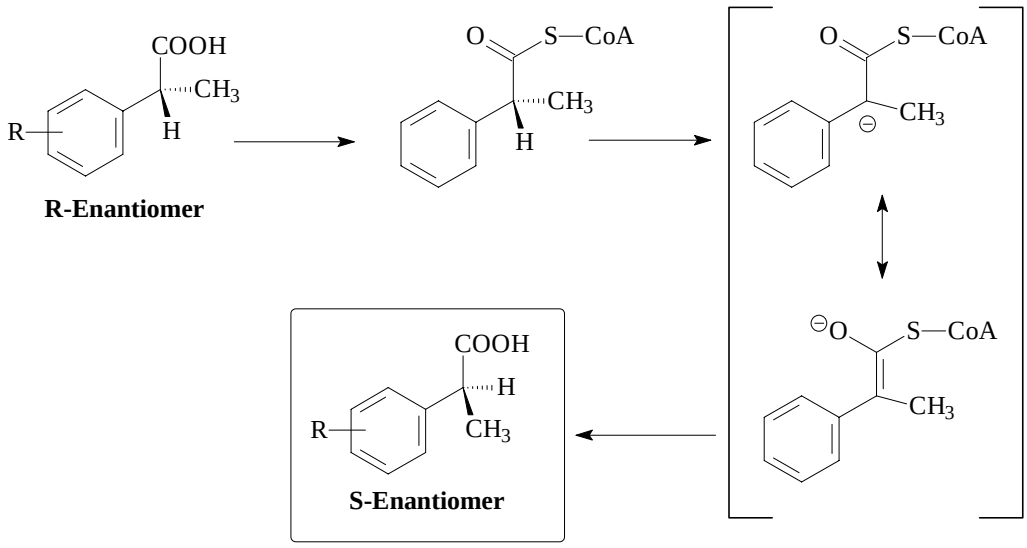
- Structure and Chemistry: Some of the most useful NSAIDs are structurally derived from arylacetic acids. These compounds are often referred to as the "profens" based on the suffix of the prototype member, ibuprofen. Like the salicylates these agents are all strong organic acids (pKa = 3-5)and thus form water soluble salts with alkaline reagents. The -arylpropionic acids are characterized by the general structure Ar-CH(CH_3)-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.



NSAID General Structure

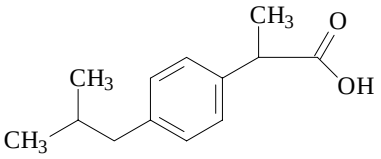
General Structure of Propionic Acid NSAIDs

The α-CH_3 substitutent present in the profens increases cyclooxygenase inhibitory activity and 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 (Naprosyn^{TM}), 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.

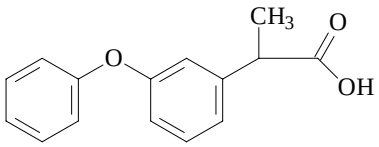


Isomerization of the Racemic Profens

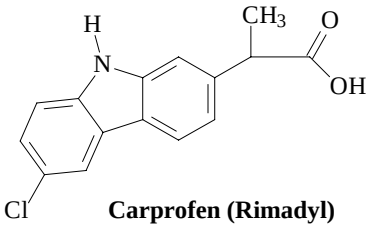
- Actions: The members of this series are shown below. These compounds are antiinflammatory agents with analgesic and antipyretic activity. Generally the profens are considered to be slightly "COX-1 selective"; naproxen appears to be more selective for COX-2 than other members of this series. The are used for RA, OA and as analgesics and antipyretics. They should not be used during pregnancy or nursing; they can enter fetal circulation and breast milk.). They produce less GI ulceration than the salicylates, but may cause some thrombocytopenia, headache, dizziness, fluid retention edema.



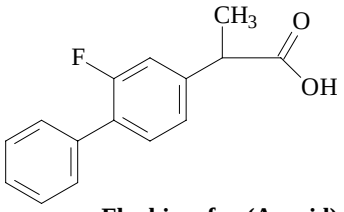
Ibuprofen (Motrin)



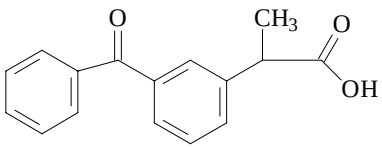
Fenoprofen



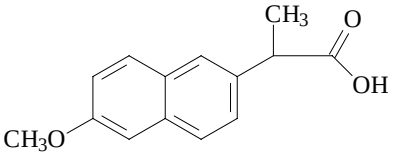
Carprofen (Rimadyl)



Flurbiprofen (Ansaid)



Ketoprofen (Orudis)

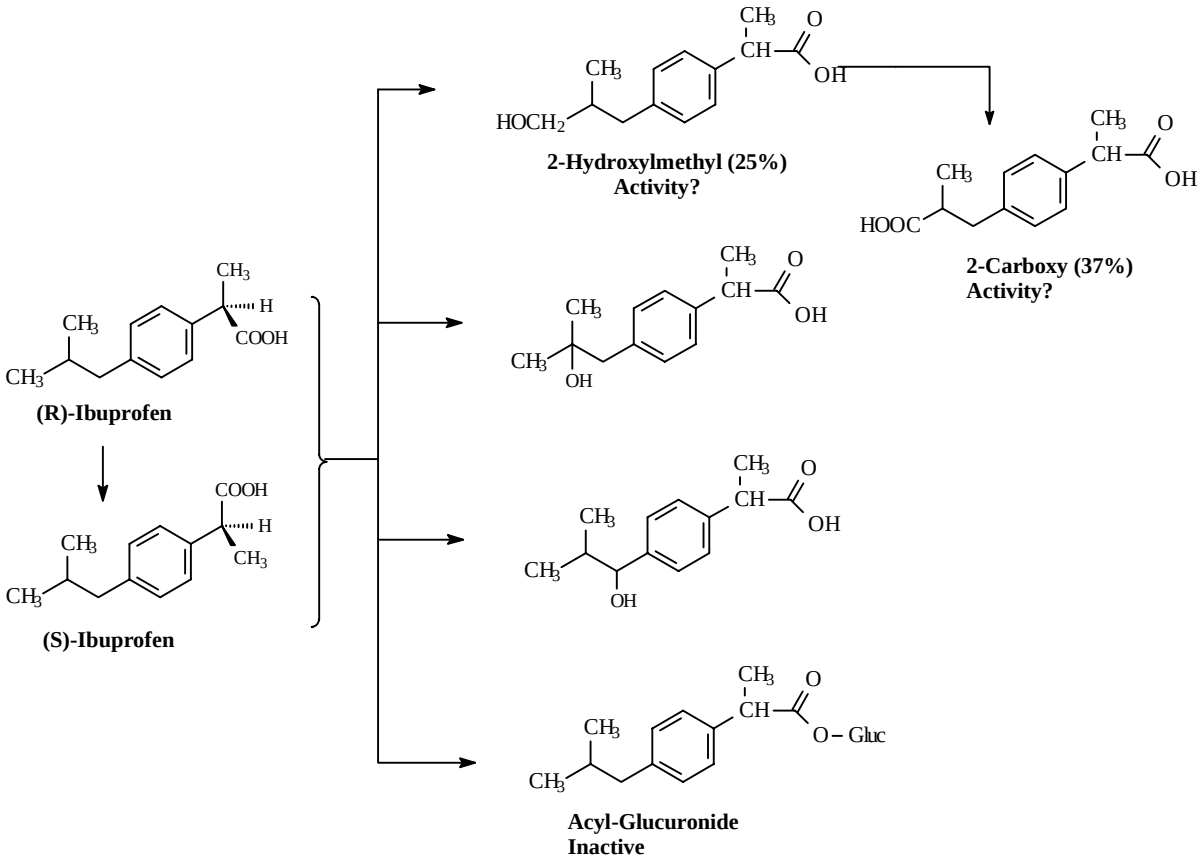


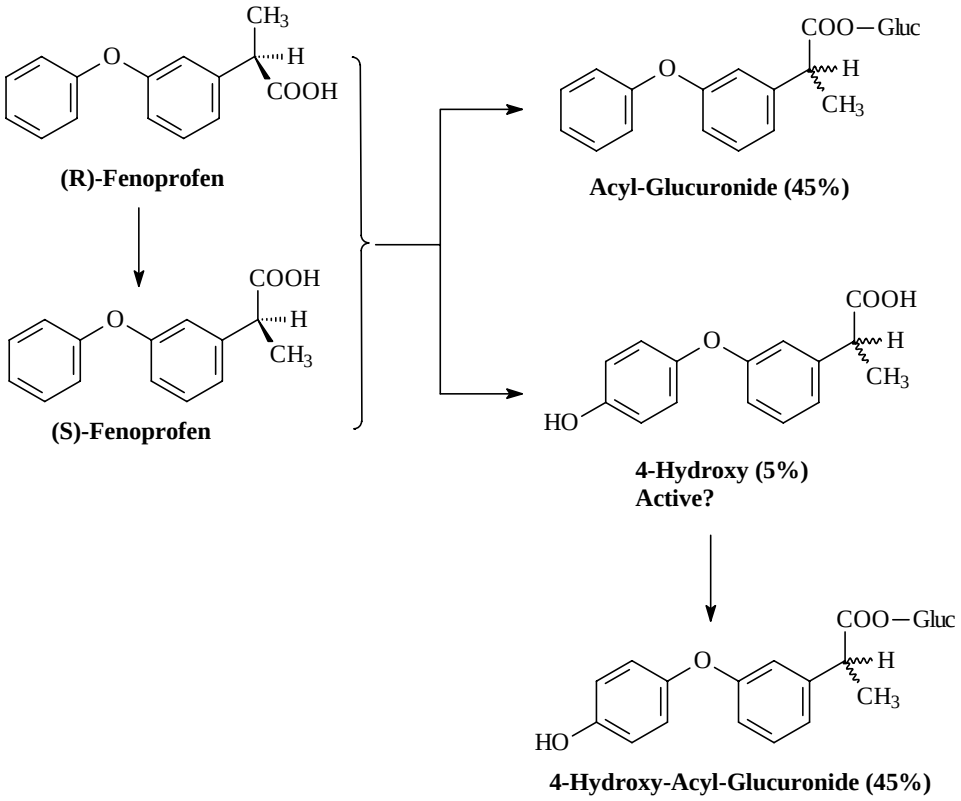
Naproxen (Aleve, Anaprox)

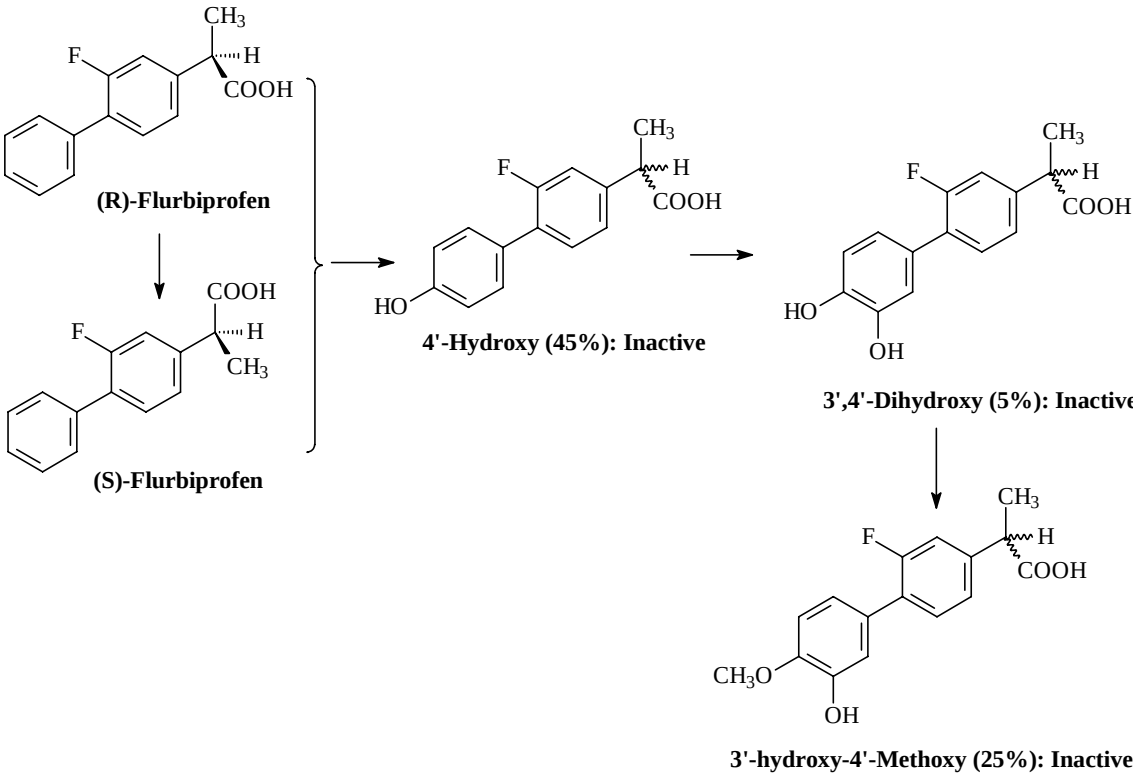
- Absorption and Distribution: These agents are well absorbed orally with high oral bioavailabilities and peak plasma times of 1-2 hours. Only ketoprofen ER and naproxen provide slower peak plasma levels. All of the profens >99% bound by plasma proteins.

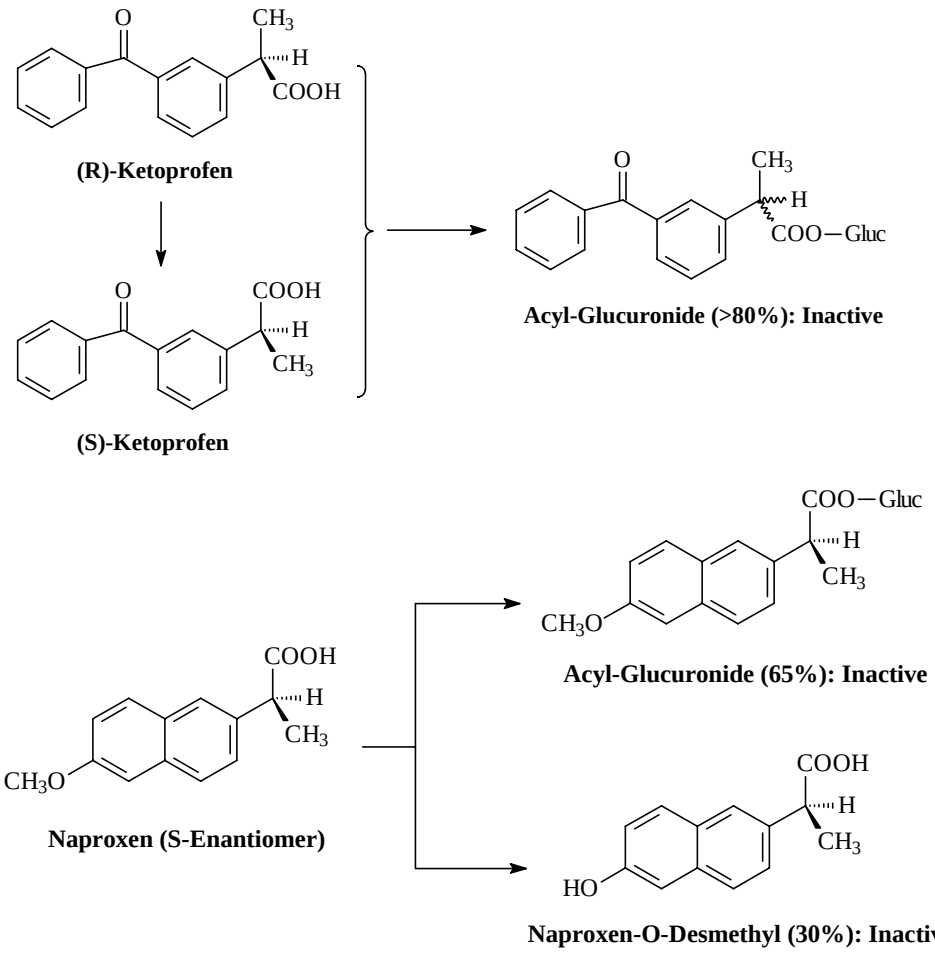
- Metabolism: All of these agents are carboxylic acids and thus are cleared, in part, as acyl-glucuronides (inactive). The other metabolic transformations different profens undergo are determined by the structure of the additional lipophilic functionality present in each compound and can be summarized as follows:

  Alkyl Substituted (Ibuprofen): ω, ω-1 and benzylic oxidation (loss of activity)
  Electron rich Aryl (Flurbiprofen, Fenoprofen): Ring oxidation (loss of activity)
  Electron deficient Aryl (Ketoprofen): No additional metabolism
  Methoxynaphthyl: Oxidative-O-dealkylation




CH3
H
O
COOH
(R)-Fenoprofen
COOH
H
O
CH3
(S)-Fenoprofen
COO—Gluc
H
O
CH3
Acyl-Glucuronide (45%)
COOH
H
O
CH3
HO
4-Hydroxy (5%)
Active?
COO—Gluc
H
O
CH3
HO
4-Hydroxy-Acyl-Glucuronide (45%)

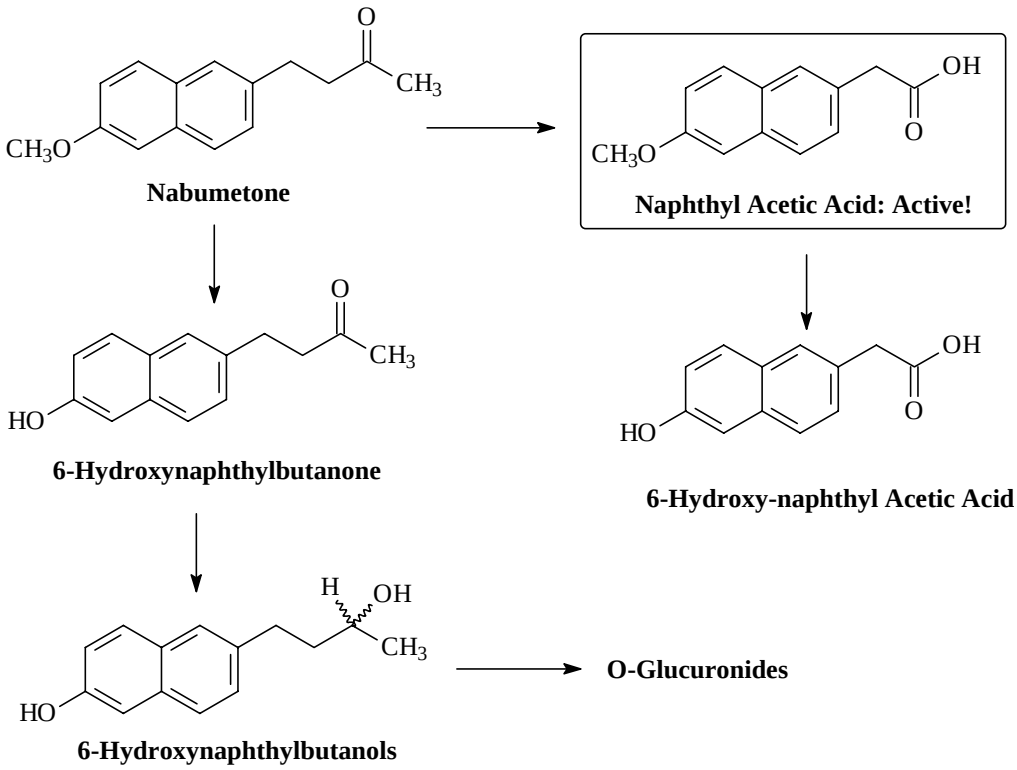

CH3
F
H
COOH
(R)-Flurbiprofen
COOH
F
H
CH3
(S)-Flurbiprofen
CH3
F
H
COOH
HO
4'-Hydroxy (45%): Inactive
CH3
F
H
COOH
HO
OH
3',4'-Dihydroxy (5%): Inactive
CH3
F
H
COOH
CH3O
OH
3'-hydroxy-4'-Methoxy (25%): Inactive



- Profen Half-life and Elimination: All of the profens are eliminated primarily in the urine as metabolites. Ibuprofen and flurbiprofen also have a significant non-renal component of elimination. All drugs in this class with the exception of lfurbiprofen and naproxen have half-lives of less than 4 hours.

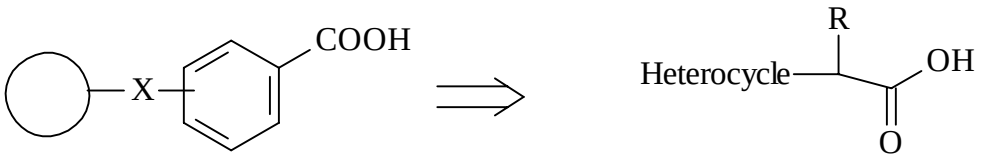
- Nabumetone (Relafen™): This agent is a prodrug which contains the non-acidic ketone (alkanone) functionality which is quickly metabolized to give the naphthylacetic acid derivative which is the active form of the drug and has a long half-life (24hrs) . This structure fits nicely into the analgesic pharmacophore identified previously and is closely related in structure to the propionic acids (profens). This compound was designed in an attempt to circumvent some of the gastrointestinal problems normally associated with the acidic functionality of these agents.

- Nabumetone exhibits antiinflammatory, analgesic and antipyretic properties and is used for RA and OA. It is somewhat selective for COX-2. Since no potent inhibitor of cyclooxygenase is present in the stomach, fewer GI problems are seen (GTD_{50}/ED_{50} =21 while for aspirin GTD_{50}/ED_{50}= 0.41). GTD_{50} is that dose which caused GI damage in 50% of the subjects. In spite of this, the most frequently reported side effect is still GI upset. This compound has a relatively long plasma half-life of 24 hours.



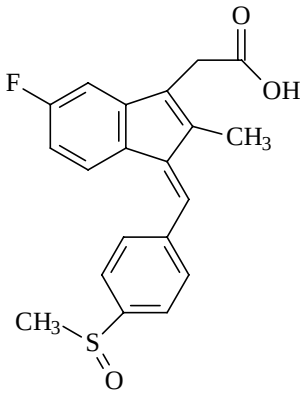
VII. Aryl and Heteroarylacetic Acids

- General Structure and Chemistry: These compounds are also derivatives of acetic acid, but in this case the substituent at the 2-position is a heterocycle or related carbon cycle. This does not significantly effect the acidic properties of these compounds. The heteroarylacetic acid NSAIDs marketed in this country can be further subclassified as the indene/indoles, the pyrroles and the oxazoles as shown below:

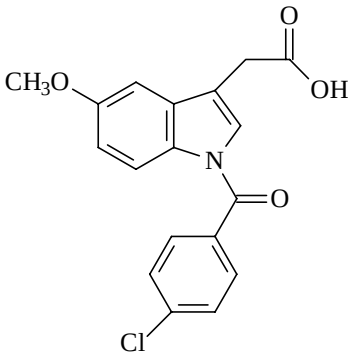


NSAID General Structure **General Structure for Heterocyclic Acetic Acids**

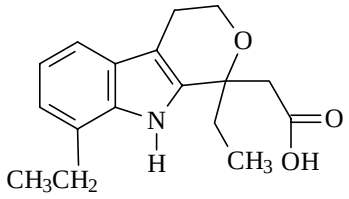
A. Indene and Indole Acetic Acids:



Sulindac (Clinoril)



Indomethacin (Indocin)



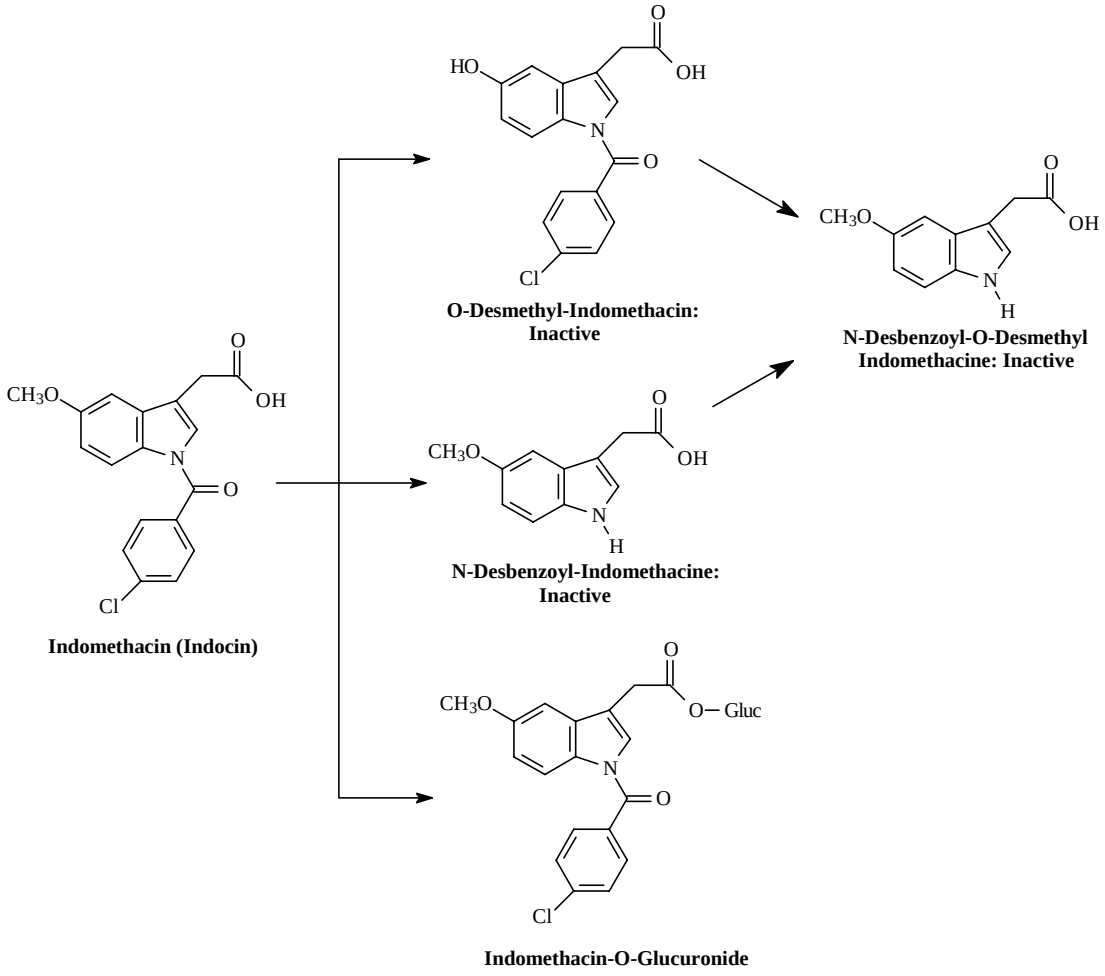
Etodolac (Lodine)

- Indomethacin Structure and Actions: contains a benzoylated indole nitrogen. The methyl group at the 2 position of the indole ring prevents free rotation about the C-N bond and keeps the two aromatic rings in the correct relationship for COX binding and therapeutic activity. Indomethacin is "COX-1" selective" and produces primarily antiinflammatory actions with some analgesic and antipyretic activity. It is used for RA, OA, ankylosing spondylitis, to suppress uterine contraction (preterm labor), and to promote closure of patent ductus artiosus in neonates (premature infants). GI ulceration and hemorrhage (these limit use). CNS toxicity ranging from headaches to delusions to psychoses and suicidal tendencies occur along with bone marrow depression: aplastic anemia and thrombocytopenia

- Indomethacin Kinetics: Well absorbed orally and should be taken with meals to reduce GI upset. Peak plasma levels are attained within 1-2 hours and half-life is 4.5 hours.

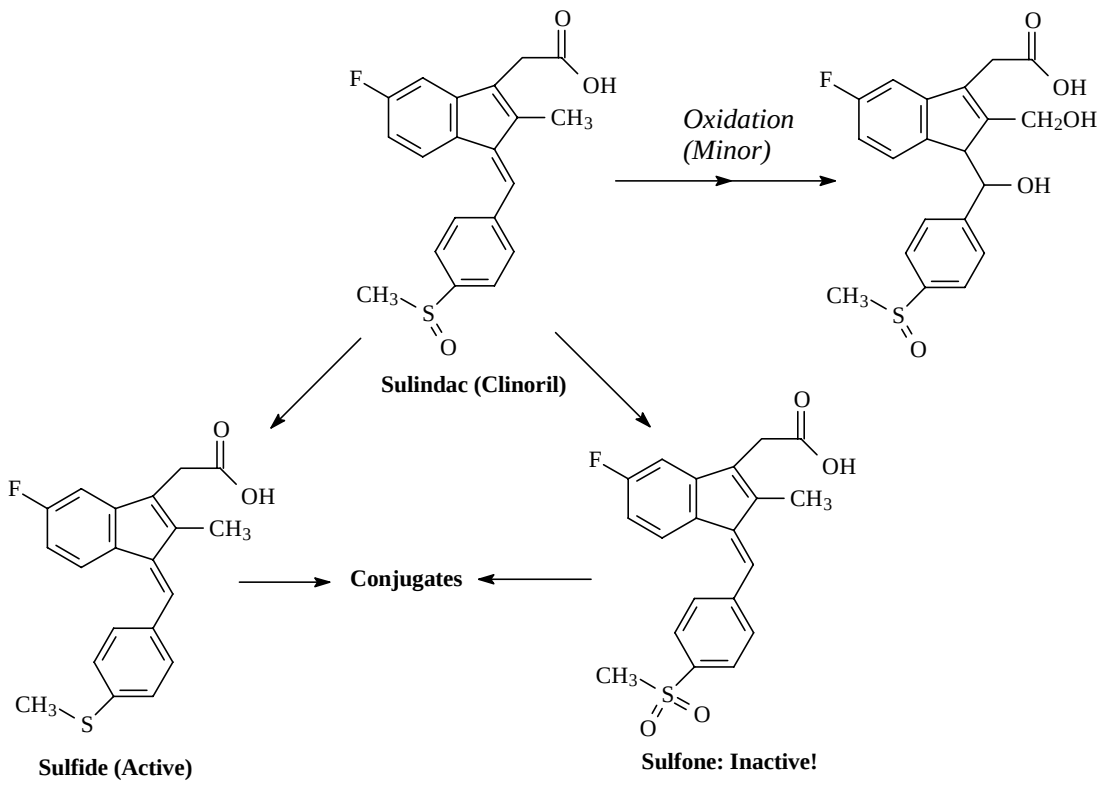
- Indomethacin Metabolism: The metabolism of indomethacin involves glucuronidation of the carboxyl group along with demethylation (increasing resemblance to 5-HT and CNS toxicity) and glucuronidation of the resulting phenol. In addition, the amide is more susceptible to hydrolysis than may normally be expected due to decreased resonance stabilization.

- Sulindac Structure: This relationship between aromatic rings observed for indomethacin is preserved by restricted rotation about the carbon-carbon double bond in sulindac. In this agent the indole N has been eliminated which reduces the drugs resemblance to 5-HT and therefore fewer CNS side effects are seen. This compound has pharmacologic actions similar to indomethacin (COX-1 selective and antiinflammatory primarily). However, sulindac is a prodrug function; it is reduced to a sulfide which is 50X more active. (see metabolism below). It is used for RA, OA, AS, acute gout and to inhibit uterine contractions. Overall sulindac produces less GI ulceration, probably as a result of its prodrug function. Some CNS toxicity, hepatic damage and prolongs clotting time.



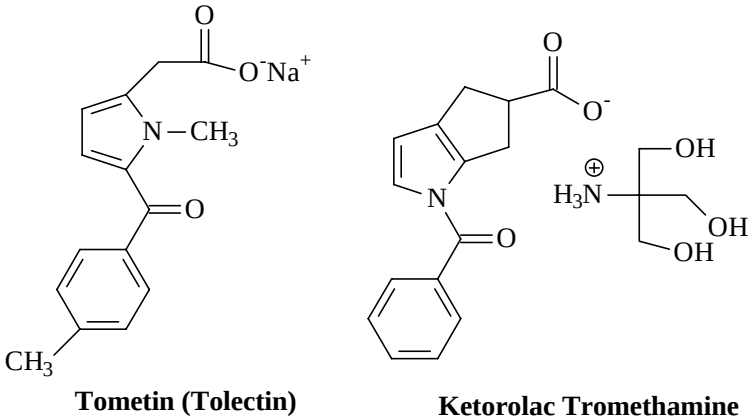
- Sulindac Kinetics: Rapidly and extensively absorbed when given orally and achieve Tp within 1 to 2 hours. The half-life for sulindac is 7-8 hours. The active sulfide has half-life of 18 hrs.

- Sulindac Metabolism: **Sulindac is a prodrug and therefore must be converted to an active form. This activation requires reduction to the sulfide which is then capable of inhibiting cyclooxygenase.** Alternatively, sulindac may be oxidized to the inactive sulfone. In the case of sulindac, glucuronidation of the carboxyl group may still occur but since the methoxy group has been replaced by a F substituent, ring demethylation does not occur.



- Etodolac (Lodine): Analogue of indomethacin and similar profile; antiinflammatory mainly with analgesic and antipyretic acitvity and uricosuric action. It is used for RA, OA and as a post-operative analgesic. It may cause GI ulceration and hemorrhage at high doses. This drug is well absorbed and has a half-life 7 hours.

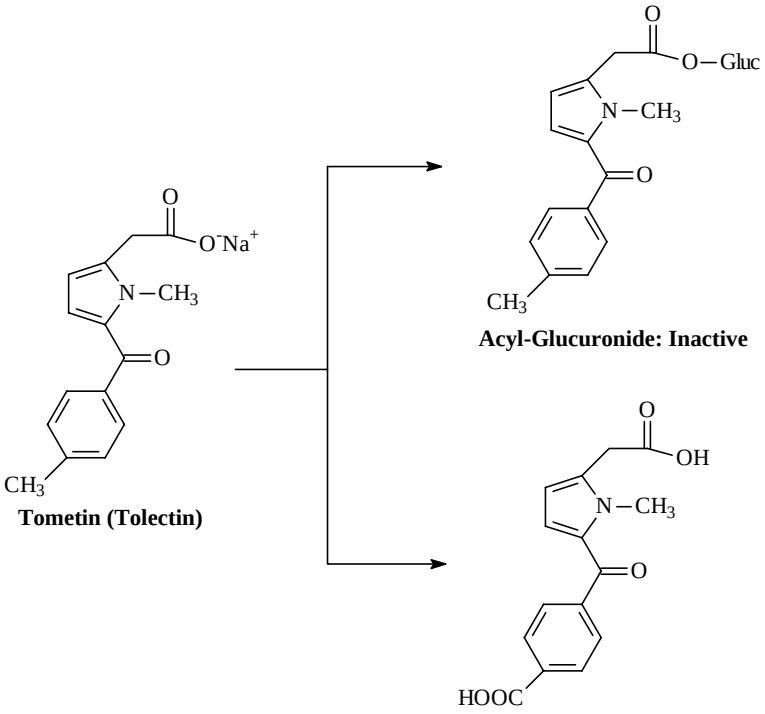
B. Arylacetic Acids: The Pyrrole Acetic Acids



Tometin (Tolectin) **Ketorolac Tromethamine**

- Tolmetin (Tolectin): Non-selective COX inhibitor with actions similar to other members in this class and it is used for RA, OA and AS. It is the shortest acting member of this class due in part to rapid Phase I oxidation of the para-methyl group to a benzylic alcohol initially and

eventually to the acid. These metabolites are subsequently glucuronidated and eliminated. As a result of this, tolmetin's half-life is typically less than 5 hours.

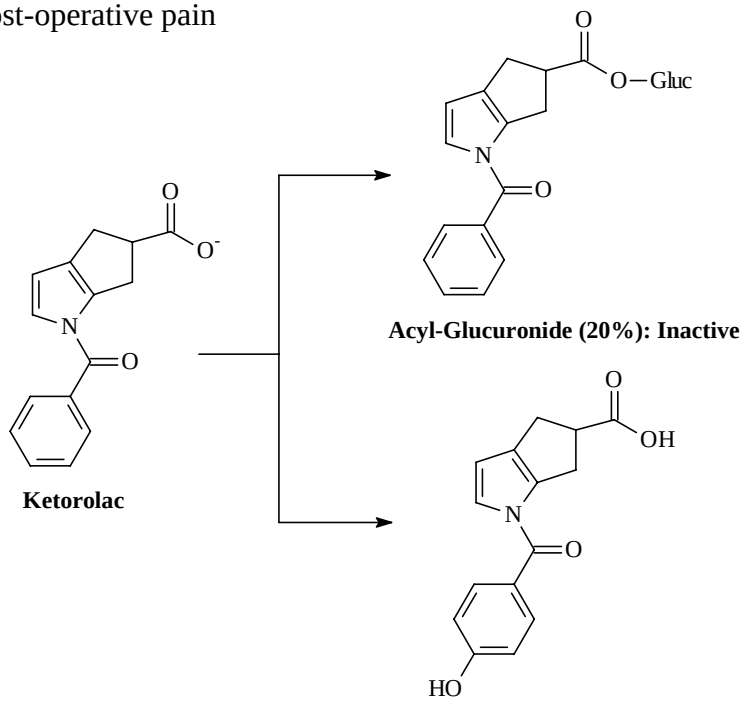


Tometin (Tolectin)

Acyl-Glucuronide: Inactive

4-Carboxy-Tometin: Inactive

- Ketorolac which lacks this benzylic methyl group is not susceptible to the type of oxidation observed for tolmetin and as a result its half-life is longer (4-6 hours). This drug is unique in that it is formulate for orally and IM administration. Good oral activity with primarily analgesic activity, but also has antiiflammatory activity and antipyretic actions. Use management of post-operative pain



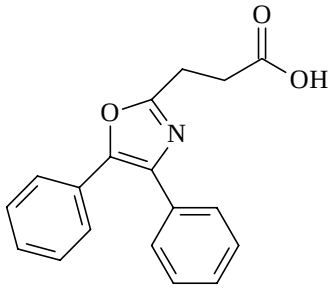
Ketorolac

Acyl-Glucuronide (20%): Inactive

4'-Hydroxy-Ketorolac (10%): Inactiv

C. Arylacetic Acids: Oxazole Acetic Acids

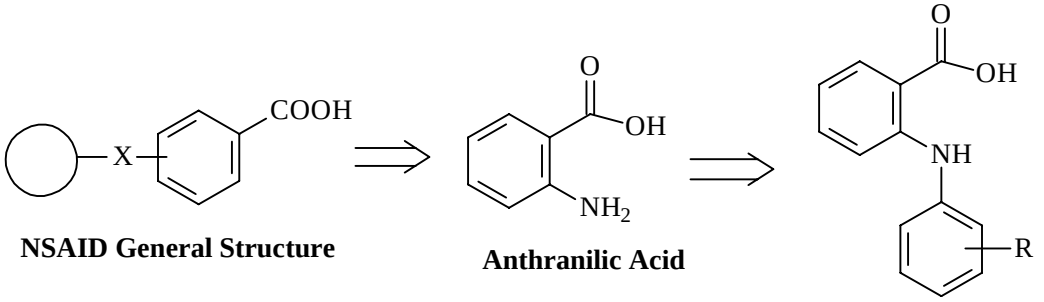
- A recent addition (1993) to this class of agents is oxaprozin (Daypro™) another non-seelective COX inhibitor. It differs slightly in that substitution of the propionic moiety is at the 3 position rather that at the 2 position as in other agents of this class. It is metabolized by glucuronidation and uncharacterized oxidation products.



Oxaprozin (Daypro)

VIII. Anthranilates

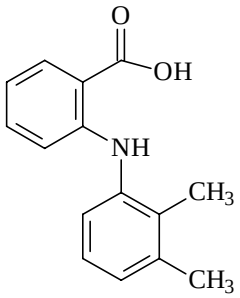
- Structure and Chemistry: These agents are considered to be N-aryl substituted derivatives of anthranilic acid which is itself a bioisostere of salicylic acid. These agents retain the acidic properties that are characteristic of this class of agents; however, note that while mefenamic acid and meclofenamic acid are derivatives of anthranilic acid, diclofenac is derived from 2-arylacetic acid. The most active fenamates have small alkyl or halogen substituents at the 2',3' and/or 6' position of the N-aryl moiety (meclofenamate is 25 times more potent than mefenamate- see below). Among the disubstituted N-aryl fenamates the 2',3'-derivatives are most active suggesting that the substituents at the 2',3'-positions serve to force the N-aryl ring out of coplanarity with the anthranilic acid. Hence this steric effect is proposed to be important in the effective interaction of the fenamates at their inhibitory site on cyclooxygenase.



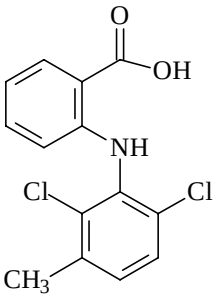
NSAID General Structure **Anthranilic Acid** **General Anthranilate Structure**

Actions: The anthranilates have primarily antiinflammatory with some analgesic and antipyretic activity and are non-COX selective. The anthranilates are used as mild analgesics and occasionally to treat inflammatory diseases. Diclofenac is used for RA, OA, AS and post-op pain, Meclofenanamte for RA (as a secondary agent), and Mefenamic acid as an analgesic for dysmennorhea. The utility of the class of agents is limited by a number of adverse reactions

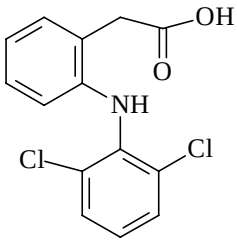
including nausea and vomiting, diarrhea, ulceration, headache, drowsiness and hematopoietic toxicity.



Mefenamic Acid (Ponstel)



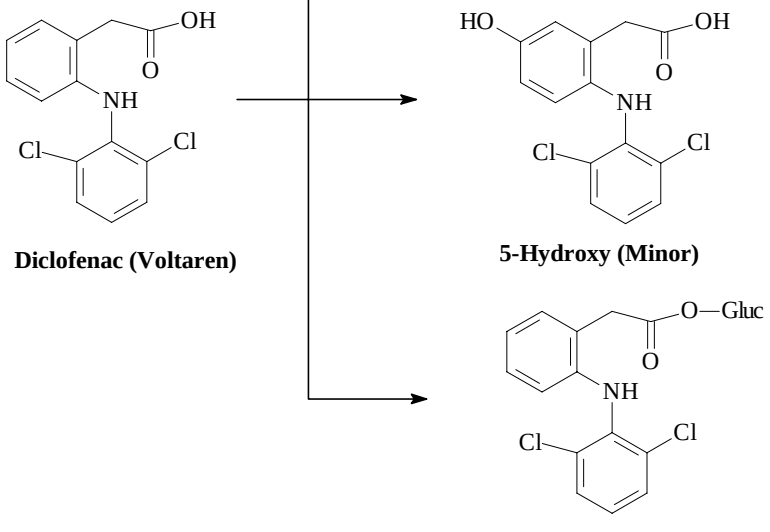
Meclofenamate (Meclomen)

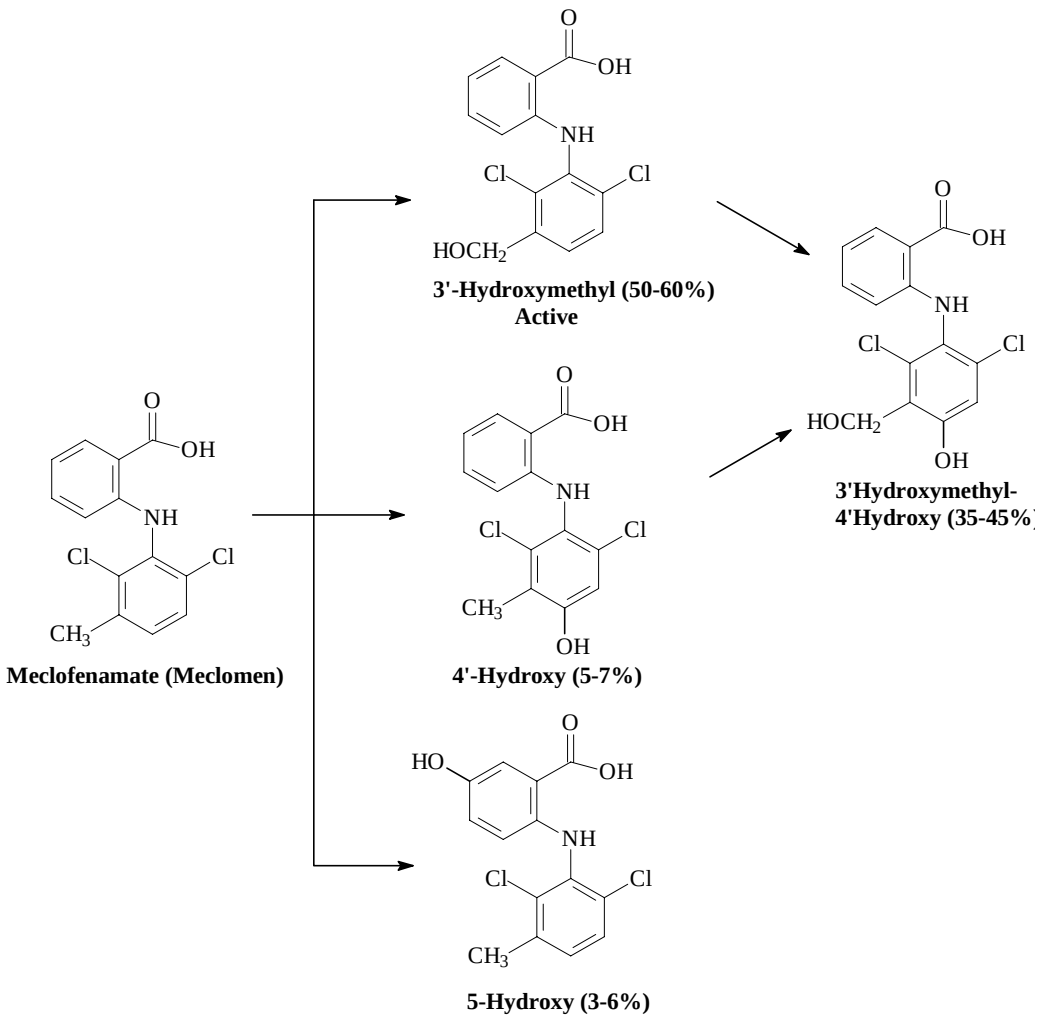


Diclofenac (Voltaren)

- Anthranilate Absorption and Distribution: The "true" anthranilates are well absorbed from the GI tract producing peak plasma levels within 2-4 hours; meclofenanmate is more lipophilic and absorbed more quickly. Diclofenac is less extensively absorbed but provide peak plasma levels within 2 hours. Diclofenac and meclofenamate are >99% bound by plasma proteins; the binding of mefenamic acid (less lipophilic) is lower.

- Anthranilate Metabolism: Both mefenamic acid and meclofenamic acid are metabolized by benzylic oxidation of the ortho methyl group and ring oxidation followed by eventual glucuronidation. Diclofenac is metabolized by acyl-O-glucuronidation and oxidation of the aromatic rings.



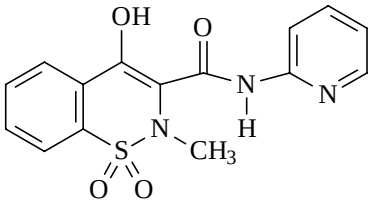


- Anthranilate Half-life and Elimination: All of the anthranilates are cleared efficiently by metabolism as shown above. **The anthranilates and their metabolites show more balanced excretion than other NSAIDs, with a greater fraction being eliminated in the feces.**

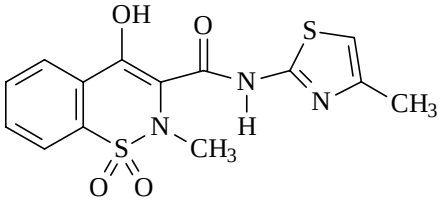
IX. Oxicams (Enolic Acids)

- Structure and Chemistry: Oxicams (Piroxicam and Meloxicam) are characterized by the 4-hydroxybenzothiazine heterocycle. The acidity of the oxicams is attributed to the 4-OH with the enolate anion being stabilized by intramolecular H-bonding to the amide N-H group. Also, the presence of the carboxamide substituent at the 3-position of the benzothiazine ring contributes toward acidity by stabilizing the negative charge formed during ionization (resonance stabilization). Although these compounds are acidic (pKa = 6.3), they are somewhat less acidic than carboxylic acids NSAIDs. Yet the oxicams are primarily ionized at physiologic pH and acidity is required for COX inhibitory activity.

- Actions: Higher COX-2 selectivity than many other NSAIDs, **particularly meloxicam**. These agents have utility in treatment of RA and OA.

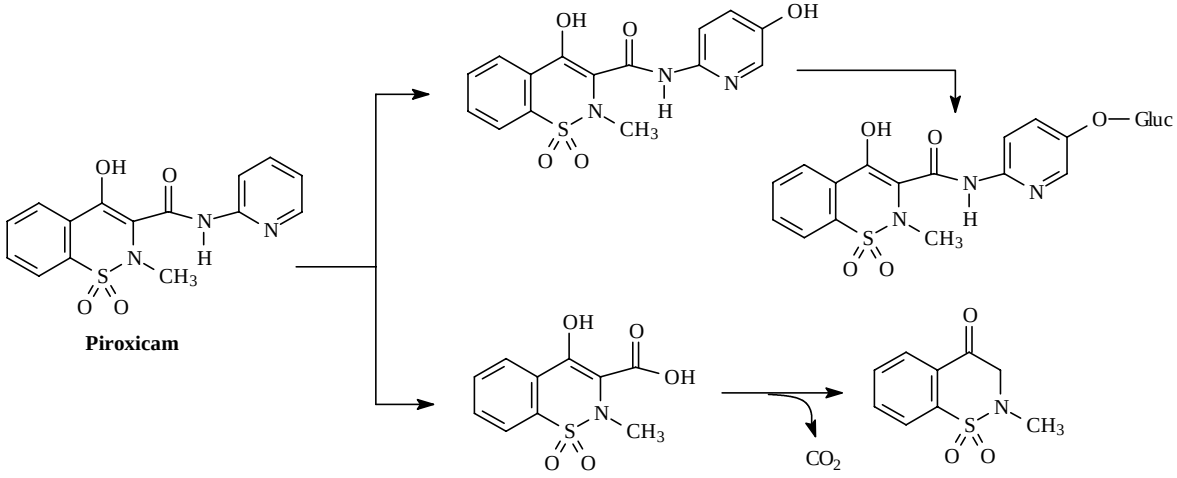


Piroxicam (Feldene)

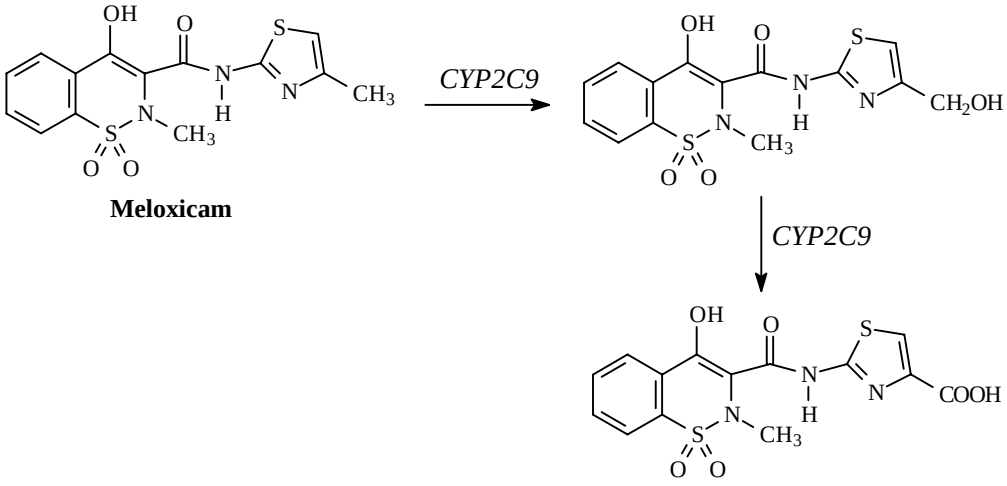


Meloxicam (Mobic)

- Oxicam Absorption and Distribution: The oxicams are well but slowly absorbed after oral administration (Tp = 3-5 hours). The long plasma half-life of these compounds (20-50 hours) allows for once a day dosing. The long half-life of this agent is due in part to the lack of a carboxylic acid functionality which can be readily glucuronidated and excreted.



Piroxicam



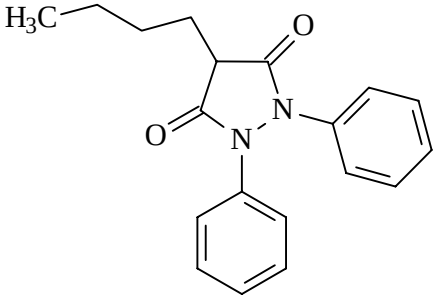
Meloxicam

5'-Carboxy-Meloxicam (60%)
Inactive

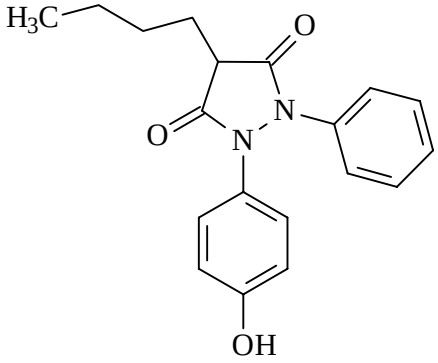
- Oxicam Metabolism: Due to the primary difference in their structures, piroxicam and meloxicam are metabolized by different routes as shown above. Piroxicam undergoes pyridine ring oxidation followed by glucuronidation; a small fraction also undergoes hydrolysis. Meloxicam undergoes slow hydrolysis of the "benzylic methyl" group of the thiazole side chain.

X. Phenylpyrazolones

- Structure and Chemistry: This class of agents is characterized by the 1-aryl-3,5-pyrazolidinedione structure. The presence of a proton which is situated to two electron withdrawing carbonyl groups renders these compounds acidic. The pKa for phenylbutazone is 4.5. Oxyphenbutazone is a hydroxylated metabolite of phenylbutazone.



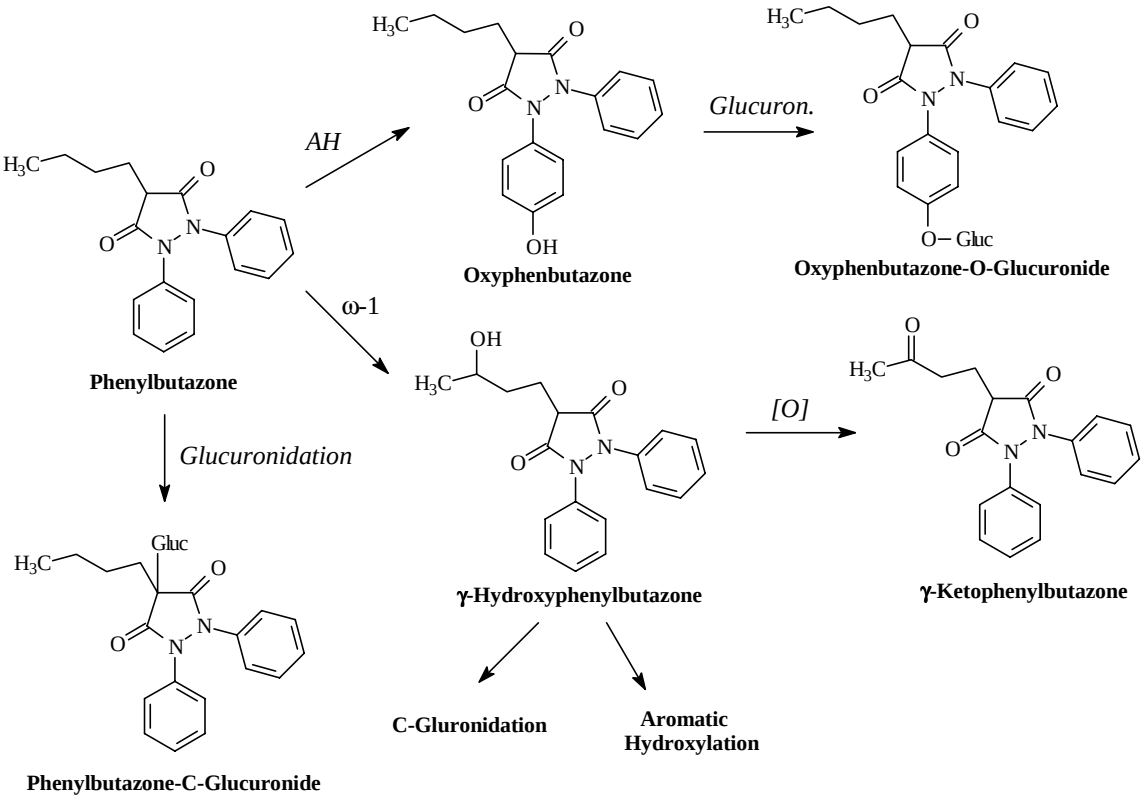
Phenylbutazone



Oxyphenbutazone

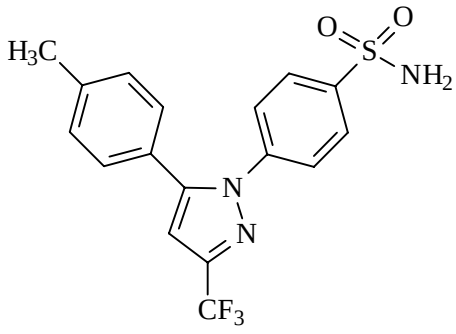
- Actions: Primarily and antiinflammatory, but has some analgesic and antipyretic. Also has mild uricosuric activity. Phenylbutazone and oxyphenbutazone are used primarily in the treatment of rheumatoid arthritis and osteoarthritis. The most common adverse reactions include GI irritation, Na+ and H_2O retention and blood dyscrasias. Therapy should be limited to 7-10 days due to bone marow depresion that may develop

- Kinetics: Coated tablets are well absorbed. These compouNnds are rapidly and completely absorbed following oral administration. As is common with many of the NSAIDs, these agents are extensively protein bound which results in a number of drug interactions with other acidic drugs such as anticoagulants, sulfonamides, hypoglycemics, other NSAIDs and glucocorticoids. Phenylbutazone is metabolized in the liver to para (oxyphenbutazone) and omega-1 metabolites. Half-life 50-65 hours

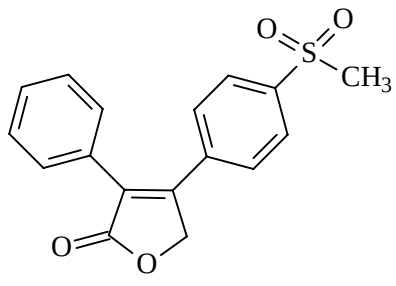


XI. COX-2 Selective Inhibitors

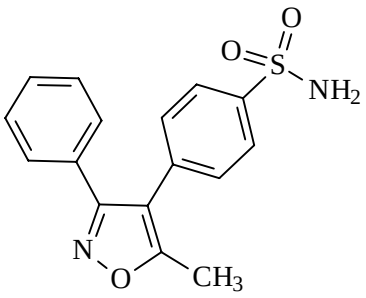
- Structure and Chemistry: All COX-2 inhibitors are diaryl-5-membered heterocycles. Celecoxib has a central pyrazole ring and two adjacent phenyl substituents, one containing a methyl group and the other a polar sulfonamide moiety; the sulfonamide binds to a distinct hydrophilic region that is present on COX-2 but not COX-1. Rofecoxib has a central furanone ring and two adjacent phenyl substituents, one containing a methyl sulfone group, unlike celecoxib. Valdecoxib has a central oxazole ring and one phenyl ring with a polar sulfonamide like celecoxib:



Celecoxib (Celebrex™)



Rofecoxib (Vioxx™)



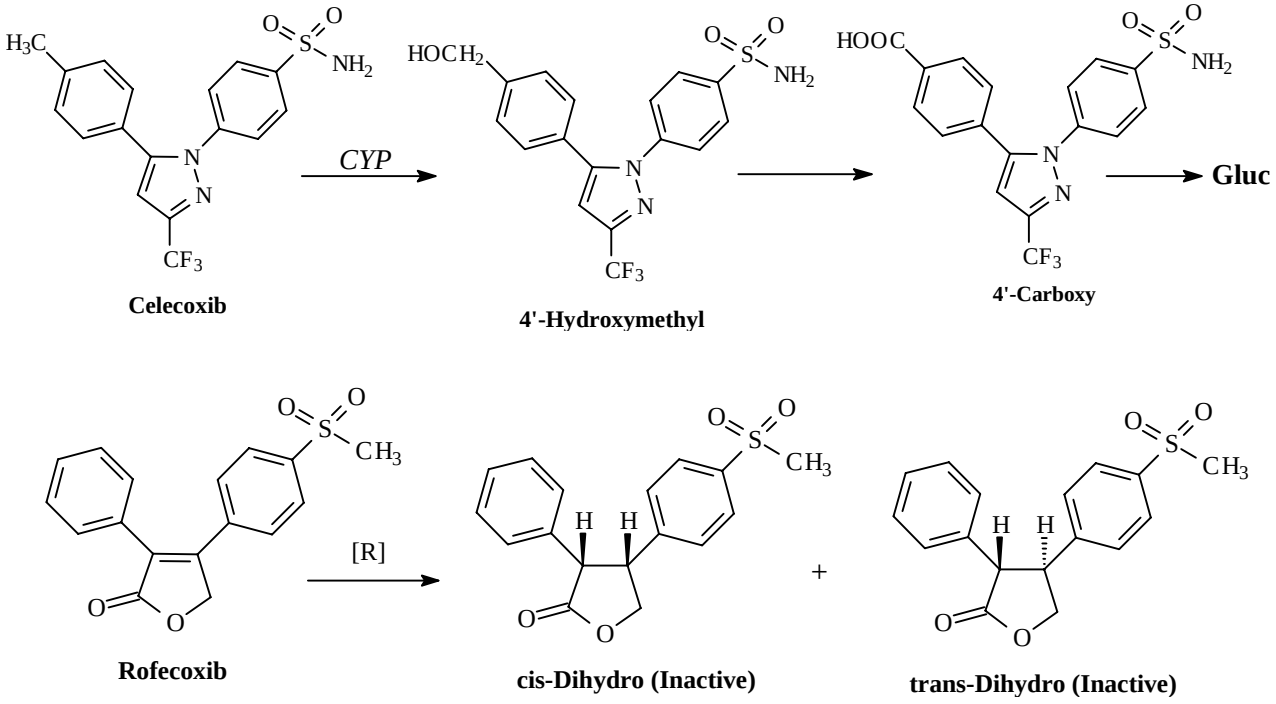
Valdecoxib (Bextra™)

- Actions: The COX-2 inhibitors have analgesic, antipyretic and inflammatory activity comparable to NSAIDs and are used therapeutically in OA (all), RA (celecoxib and Valdecoxib), acute pain (Celecoxin, Rofecoxib) andprimary dysmenorrhea (all). These compounds produce less GI ulceration and hemorrhage than NSAIDs due to their COX-2 selectivity. Also they do not inhibit platelet aggregation and have minimal renal and CV side effects. These drugs should not be used in 3rd trimester of pregnancy since they promote closure of ductus arteriosus.

- Absorption and Distribution: All three COX-2 inhibitors are well absorbed and provide peak plasma levels within 3 hours. Celecoxib and Valdecoxib are more acidic (sulfonamide versus sulfone) and are more highly bound by plasma proteins.

- Metabolism: Celecoxib contains only one functional group that is efficiently metabolized, the benzylic methyl. Complete oxidation and conjugation at this position results in drug inactivation and clearance. Rofecoxib does not contain a benzylic methyl, but its ring double bond may be reduced to yield two different stereoisomeric dihydro metabolites that are inactive. Valdecoxib is metabolized by oxidation, but metabolites have not been characterized (oxazole ring methyl and unsubstituted aromatic ring?).

- Half-life and Elimination: Both COX-2 inhibitors have a relatively long duration of action (>10 hours) due to relatively slow clearance; rofecoxicb is cleared more slowly and has the longer half-life. Both compounds display somewhat balanced excretion and celecoxib is eliminated primarily in the feces. Some of these drugs (valdecoxib) are also weak inhibitors of cytochromic enzymes.

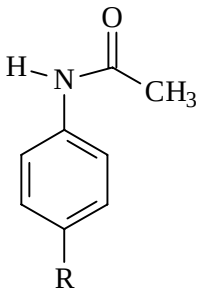


Celecoxib **4'-Hydroxymethyl** **4'-Carboxy**

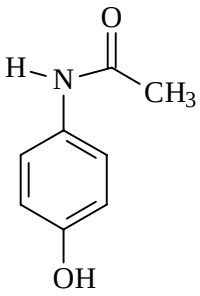
Rofecoxib **cis-Dihydro (Inactive)** **trans-Dihydro (Inactive)**

XII. Anilides

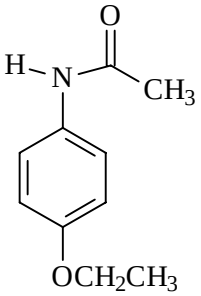
- Structure and Chemistry: The anilides are simple acetamides of aniline which may or may not contain a 4-hydroxy or 4-alkoxy group. Acetanilide is ring hydroxylated after administration to yield acetaminophen, the active analgesic/antipyretic while phenacetin (rarely used) undergoes oxidative-O-dealkylation to produce acetaminophen. Note that the anilides **do not possess** the carboxylic acid functionality and therefore they are classified as neutral drugs and possess little if any inhibitory activity against cyclooxygenase.



General Structure for Anilides



Acetaminophen

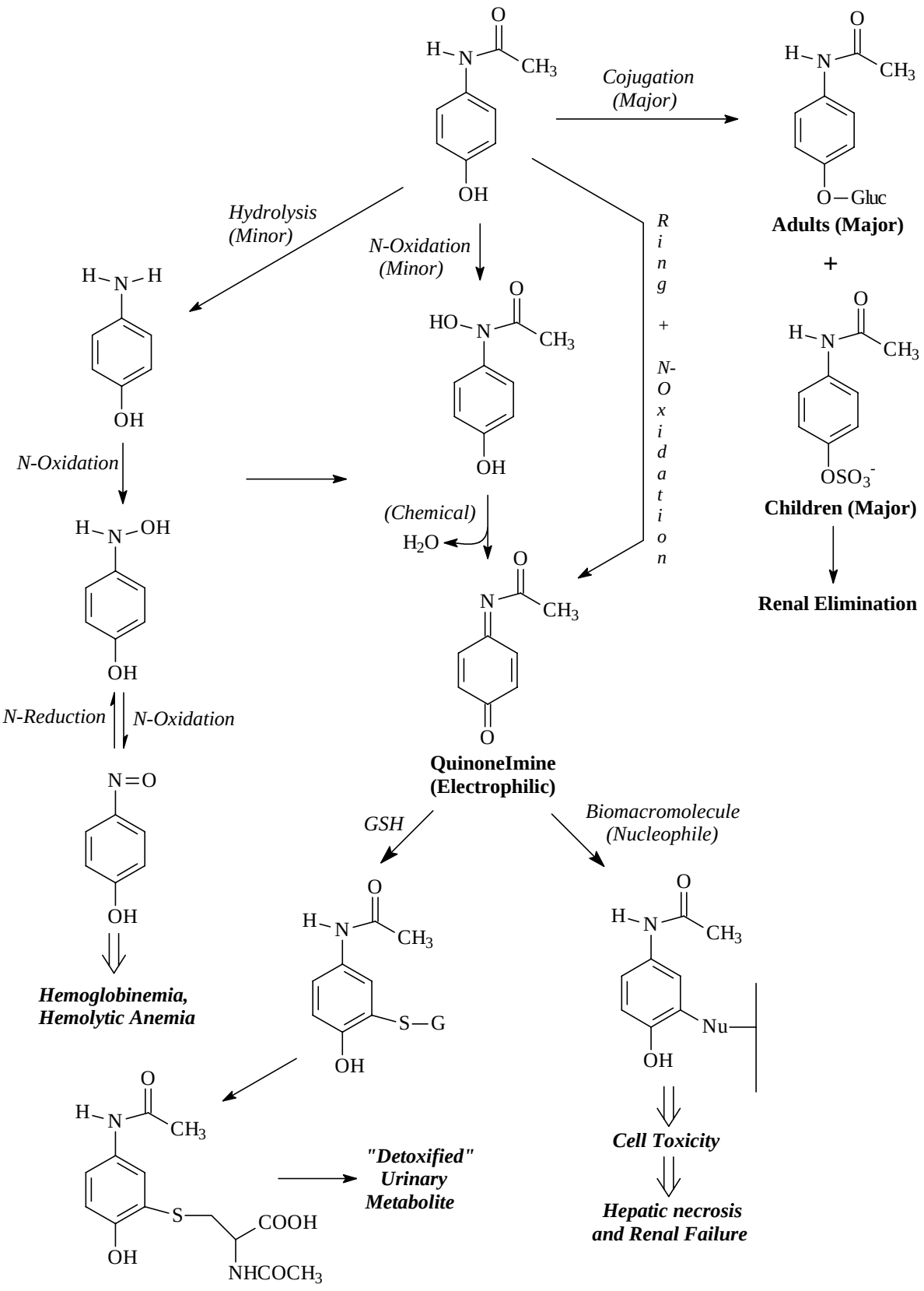


Phenacetin

- Actions: The anilides are somewhat different from other NSAIDs in their mechanism of action. They are believed to act as scavengers of hydroperoxide radicals. Hydroperoxide radicals are generated by invading leukocytes after injury has occurred. The hydroperoxide radicals have a stimulating effect on cylooxygenase. In areas of high leukocyte activity (significant injury and inflammation) the high concentration of hydroperoxides are able to overcome the anilides and prostaglandins are produced. Therefore the anilides have no antinflammatory action. They are only capable of suppressing cyclooxygenase activity in areas which are not inflamed. The lack of an acidic functionality and COX inhibitory activity in the anilides imparts several advantages to these agents including limited gastric irritation and ulceration, limited CV and respiratory effects and little effect on platelets (no increase in clotting).

- Adverse Reactions and Metabolism: The anilides being aromatic amines are capable of producing a number of problems including methemoglobinemia, anemia, hepatoxicity, and nephrotoxicity. These toxicities are related to metabolic transformations that these drugs undergo. Under normal conditions, acetaminophen is metabolized by glucuronidation (primarily in adults) or sulfation (in children) of the hydroxyl function. Minor pathways of anilide metabiolism include oxidation of the aromatic ring to the quinoneimine and hydrolysis and N-xidation as discussed below.

- Metabolic Intoxification: When anilide/acetaminophen concentrations are very high, as in an overdose, formation of a toxic quinoneimine becomes significant as shown below. This is normally detoxified by conjugation with glutathione; however, if glutathione is depleted, alkylation of tissue nucleophiles may occur. A molecular antidote for acetaminophen overdose is N-acetylcysteine (Mucomyst, Mucosol) which is capable of mimicking the action of glutathione and thereby detoxifying the quinoneimine. Ethanol potentiates acetaminophen toxicity by a variety of mechanisms.


Cojugation
(Major)
Adults (Major)
+
Children (Major)
Renal Elimination
Hydrolysis
(Minor)
N-Oxidation
(Minor)
Ring + N-Oxidation
N-Oxidation
(Chemical)
H2O
N-Reduction
N-Oxidation
QuinoneImine
(Electrophilic)
GSH
Biomacromolecule
(Nucleophile)
Hemoglobinemia,
Hemolytic Anemia
"Detoxified"
Urinary
Metabolite
Cell Toxicity
Hepatic necrosis
and Renal Failure

Pharmacokinetic Parameters/Maximum Dosage Recommendations of NSAIDs

NSAID	Bioavail (%)	Half-life (hours)	Volume of distribution	Clearance	Peak (hours)	Protein binding (%)	Renal elimin (%)	Fecal elimin (%)
Aryl and Heteroarylacetic Acids								
Indomethacin	98	4.5	0.29 L/kg	0.084 L/hr/kg	2	90	60	33
Sulindac	90	7.8	NS	» 2.71 L/hr	2-4	>93	50	25
Etodolac	≥80	7.3	0.362 L/kg	47 ml/hr/kg	»1.5	>99	72	16
Tolmetin	NS	2-7	NS	NS	0.5-1	NS	»100	-
Ketorolac	100	5-6	»0.2 L/kg	» 0.025 L/hr/kg	2-3	99	91	6
Oxaprozin	95	42-50	10-12.5 L	0.25-0.34 L/hr	3-5	>99	65	35
Propionic acids								
Fenoprofen	NS	3	NS	NS	2	99	90	-
Flurbiprofen	NS	5.7	0.1 to 0.2 L/kg	1.13 L/hr	»1.5	>99	>70	-
Ibuprofen	>80	1.8-2	0.15 L/kg	»3-3.5 L/hr	1-2	99	45-79	-
Ketoprofen	90	2.1	0.1 L/kg	6.9 L/hr	0.5-2	>99	80	-
Ketoprofen ER	90	5.4	0.1 L/kg	6.8 L/hr	6-7	>99	80	-
Naproxen	95	12-17	0.16 L/kg	0.13 ml/min/kg	2-4	>99	95	-
Naphthylalkanones								
Nambumetone	>80	22.5	0.1-0.2 L/kg	26.1 ml/min	9-12	>99	80	9
Fenamates								
Meclofenamate	»100	1.3	23 L	206 ml/min	0.5-2	>99	70	30
Mefenamic acid	NS	2	1.06 L/kg	21.23 L/hr	2-4	>90	52	20
Diclofenac	50-60	2	0.1-0.2 L/kg	350 ml/min	2	>99	65	-
Oxicams								
Piroxicam	NS	50	0.15 L/kg	0.002 L/kg/hr	3-5	98.5	NS	NS
Meloxicam	89	15-20	10 L	7 to 9 ml/min	4 to 5	99.4	50	50
COX-2 inhibitors								
Celecoxib	NS	11	400 L	27.7 L/hr	3	97	27	57
Rofecoxib	93	17	91 L	120-141 ml/min	2 to 3	87	72	14
Valdecoxib	83	8-11	86 L	≈ 6 L/hr	3	98	90	<5