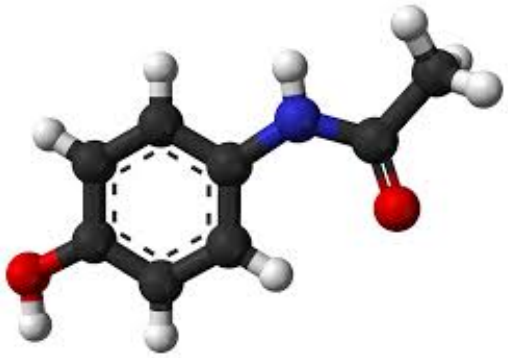


Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

NEPHAR 305
Pharmaceutical Chemistry I

Assist.Prof.Dr. Banu Keşanlı

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

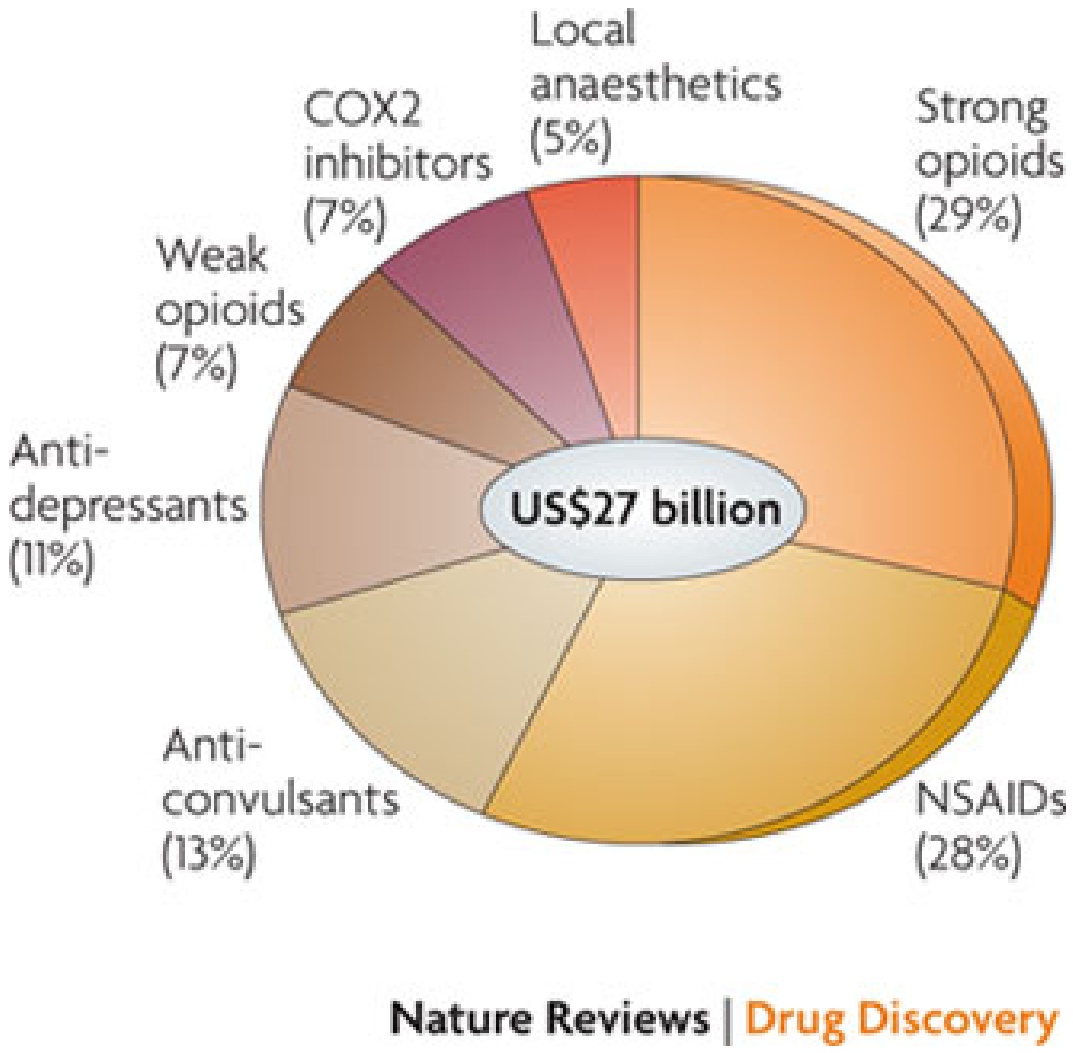
✓ **NSAIDs** are a class of drugs that relieve pain, reduce inflammation (redness and swelling) and bring down a high temperature (fever).

✓ NSAIDs are used to treat a wide range of conditions: Headaches, painful periods, toothache, sprains and strains infections, such as the common cold or the flu inflammation of the joints (arthritis) and other tissues

✓ NSAIDs work by blocking the production of prostaglandins, chemical messengers that often are responsible for the pain and swelling of inflammatory conditions.

Narcotic analgesics—the analgesics that have CNS effect.
Non-Narcotics—the analgesics that do not have CNS effect.

Market Share of Pain Medications in 2009



Total world pain market in 2013 is estimated to be above $25 billion

Mechanism of Actions for NSAIDs

✓ The prostaglandins are the mediation of inflammation. Inflammatory response is the body's natural response that occurs immediately following tissue damage.

✓ Most of the The NSAIDs are irreversible inhibitors of **cyclooxygenase** activity, thus they prevent the formation of prostaglandins and consequently reducing the signs and symptoms of inflammation.

✓ **Prostaglandins** are a family of chemicals that are produced by the cells of the body in response to illness or injury. They promote inflammation, pain, and fever; support the blood clotting function of platelets; and protect the lining of the stomach from the effects of acid.

✓ Prostaglandins are unsaturated carboxylic acids, consisting of a 20 carbon skeleton that also contains a five member ring. They are biochemically synthesized from the fatty acid, arachidonic acid.

What is the basic difference between traditional NSAIDs and COX-2 inhibitors?

✓ Prostaglandins are made by two different enzymes, cyclooxygenase-1 (COX-1) and cyclooxygenase-2(COX-2).

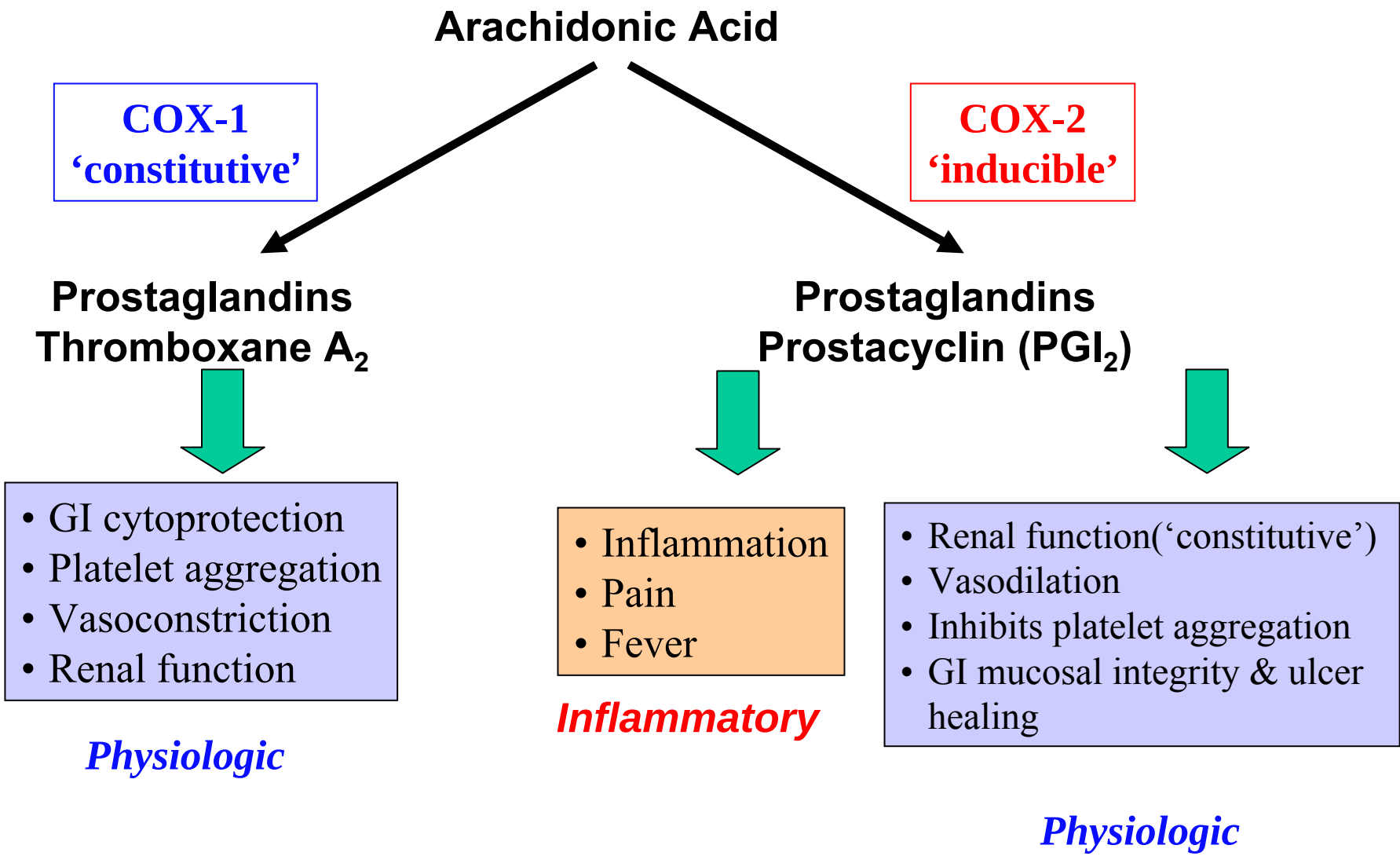
✓ The prostaglandins made by the two different enzymes have slightly different effects on the body.

✓ Selective COX-2 inhibitors are NSAIDs that selectively block the COX-2 enzyme and not the COX-1 enzyme. Blocking this enzyme prevents the production of prostaglandins by the COX-2 enzyme that often cause the pain and swelling of inflammation and other painful conditions. Because they selectively block the COX-2 enzyme and not the COX-1 enzyme, these drugs are uniquely different from traditional NSAIDs which usually block both COX-1 and COX-2 enzymes.

✓ With traditional antiinflammatory drugs such as aspirin, inflammation is reduced by blocking Cox-2, but the protective mucus lining of the stomach is also reduced because Cox-1 is blocked, which can cause stomach upset, ulceration, and bleeding from the stomach and intestines.

✓ Drugs that selectively block COX-2 do not present the risk of injuring the stomach that medications also blocking COX-1 can.

COX Isoform Functions



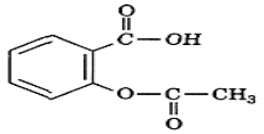
Review article: Hersh EV, et al., 2005
Curr. Med. Res. & Opin. 21:1217-26

Classification of NSAIDs

Chemical Classification and Representative Structures of Analgesic, Antipyretic, & Nonsteroidal Antiinflammatory Drugs

Salicylic acid derivatives

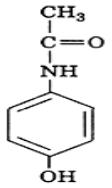
aspirin, sodium salicylate, iflunisal, choline-magnesium trisalicylate, salsalate, salicylsalicylic acid, sulfasalazine, olsalazine



Aspirin
(acetylsalicylic acid)

Para-aminophenol derivatives

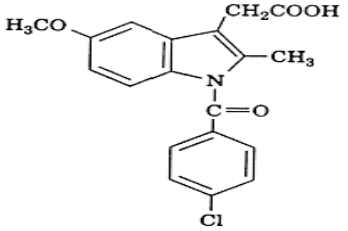
acetaminophen



Acetaminophen

Indole & indene acetic acids

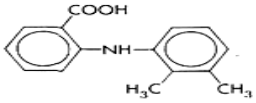
indomethacin, sulindac, etodolac



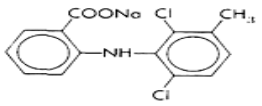
Indomethacin

Anthranilic acids (fenamates)

mefenamic acid, meclofenamic acid



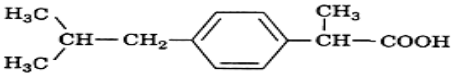
MEFENAMIC ACID



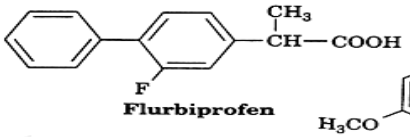
MECLOFENAMATE SODIUM

Arylpropionic acids

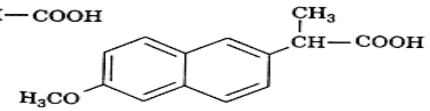
ibuprofen, naproxen, flurbiprofen, ketoprofen, fenoprofen, oxaprozin



Ibuprofen



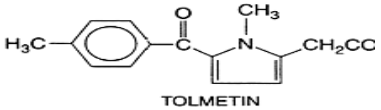
Flurbiprofen



Naproxen

Heteroaryl acetic acids

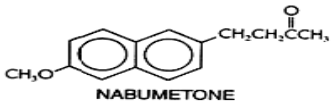
tolmetin, diclofenac, ketorolac



TOLMETIN

Alkanones

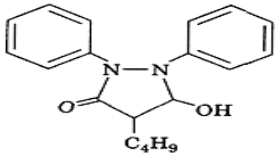
nabumetone



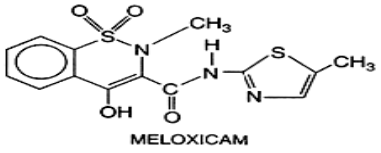
NABUMETONE

Enolic acids

oxicams (piroxicam, tenoxicam, meloxicam), pyrazolidinediones (phenylbutazone, oxyphenthatrazone)



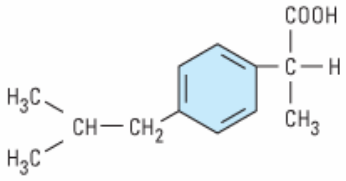
Phenylbutazone



MELOXICAM

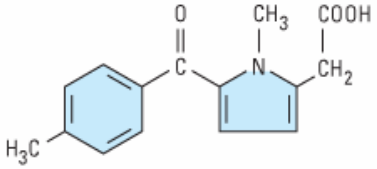
Classification of NSAIDs

PROPIONIC ACID DERIVATIVE



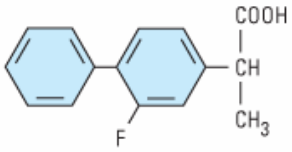
Ibuprofen

PYRROLEALKANOIC ACID DERIVATIVE



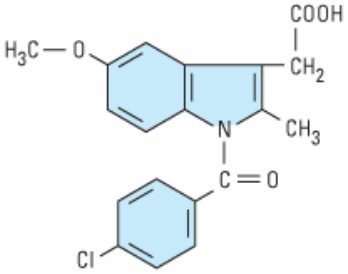
Tolmetin

PHENYLALKANOIC ACID DERIVATIVE



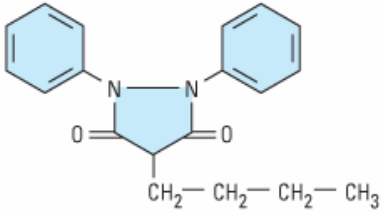
Flurbiprofen

INDOLE DERIVATIVE



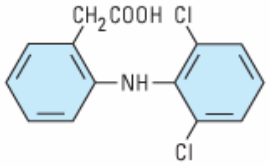
Indomethacin

PYRAZOLONE DERIVATIVE



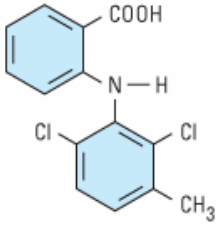
Phenylbutazone

PHENYLACETIC ACID DERIVATIVE



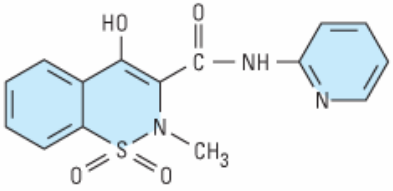
Diclofenac

FENAMATE



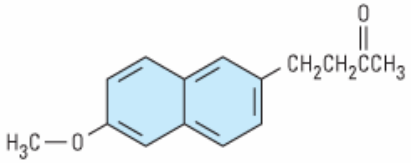
Meclofenamic acid

OXICAM



Piroxicam

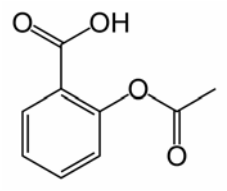
NAPHTHYLACETIC ACID PRODRUG



Nabumetone

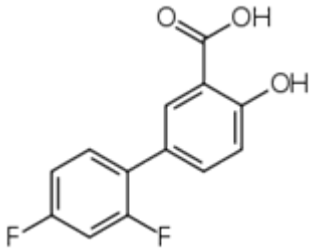
Examples of NSAIDs

Aspirin



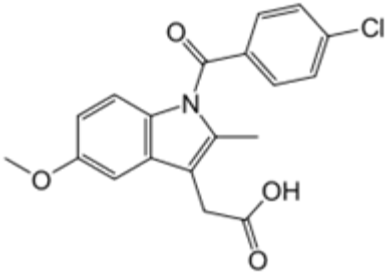
2-acetoxybenzoic acid

Diflunisal (Dolobid)



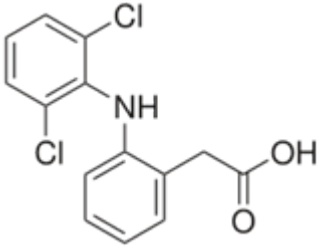
2',4'-difluoro-4-hydroxybiphenyl
-3-carboxylic acid

Indometacin (Indocin)



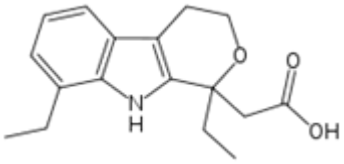
2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy
-2-methyl-1*H*-indol-3-yl}acetic acid

Diclofenac (Voltaren)



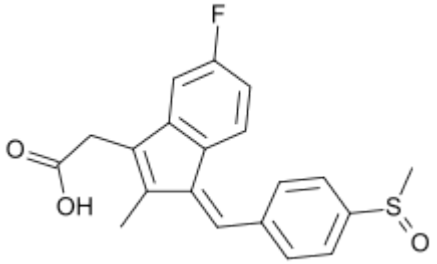
2-(2-(2,6-dichlorophenylamino)
phenyl)acetic acid

Etodolac (Lodine)



(*RS*)-2-(1,8-Diethyl-4,9-dihydro-3*H*-
pyrano[3,4-b]indol-1-yl)acetic acid

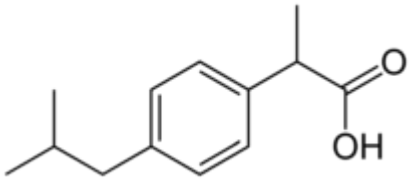
Sulindac (Clinoril)



{(1*Z*)-5-fluoro-2-methyl-1-[4-(methylsulfinyl)
benzylidene]-1H-indene-3-yl}acetic acid

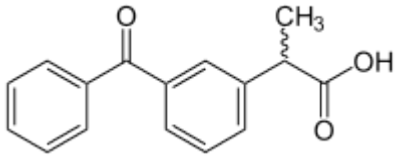
Examples of NSAIDs

Ibuprofen (Motrin)



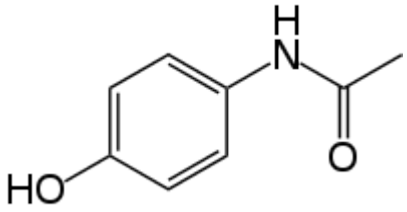
(*RS*)-2-(4-(2-methylpropyl)phenyl) propanoic acid

Ketoprofen (Orudis)



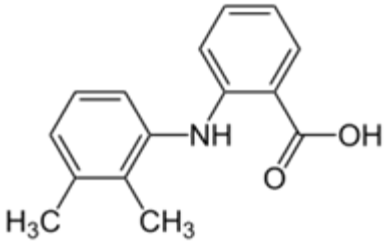
(*RS*)-2-(3-benzoylphenyl)propanoic acid

Paracetamol



N-(4-hydroxyphenyl)acetamide

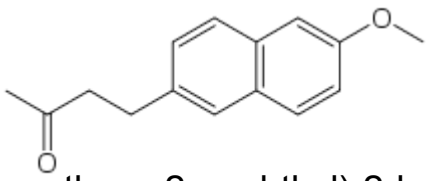
Mefenamic acid



2-(2,3-dimethylphenyl)aminobenzoic acid

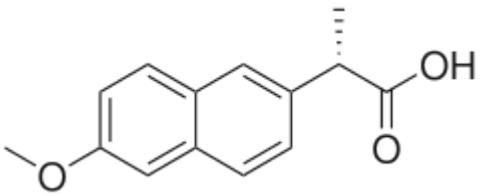
Examples of NSAIDs

Nabumetone (Relafen)



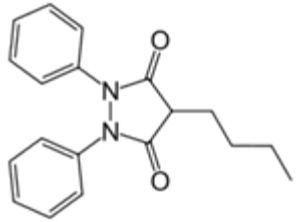
4-(6-methoxy-2-naphthyl)-2-butanone

Naproxen (Aleve, Naprosyn)



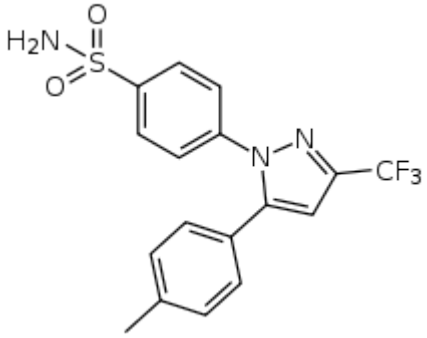
(+)-(*S*)-2-(6-methoxynaphthalen-2-yl) propanoic acid

Phenylbutazone



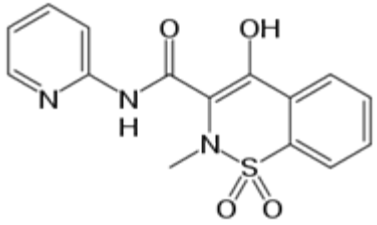
4-butyl-1,2-diphenyl-pyrazolidine -3,5-dione

Celecoxib (Celebrex)



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

Piroxicam (Feldene)

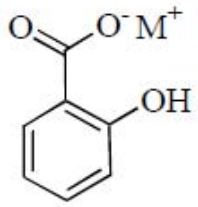


(8*E*)-8-[hydroxy-(pyridin-2-ylamino)methylidene]-9-methyl-10,10-dioxo-10λ6-thia-9-azabicyclo[4.4.0] deca-1,3,5-trien-7-one

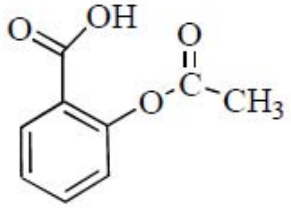
NSAIDs – Salicylate Derivatives

✓ Salicylates are derived from **Salicylic acid** which is a monohydroxybenzoic acid, and are nonsteroidal anti-inflammatory drugs.

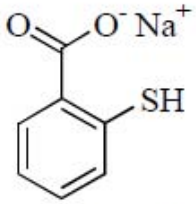
✓ They inhibit the synthesis of prostaglandin and other mediators in the process of inflammation and have anti-inflammatory, antipyretic and analgesic properties.



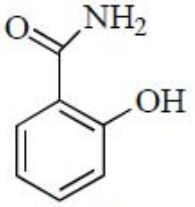
Salicylate



Acetylsalicylate

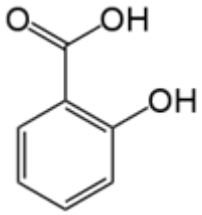


Sodium Thiosalicylate



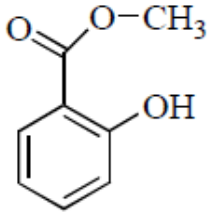
Salicylamide

M+ = Na^+, Sodium
M+ = 1/2 Mg^{2+} Magnesium

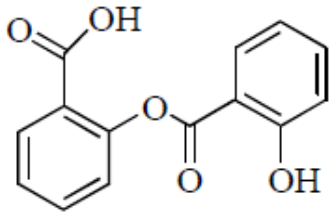


Salicylic acid (2-Hydroxybenzoic acid)

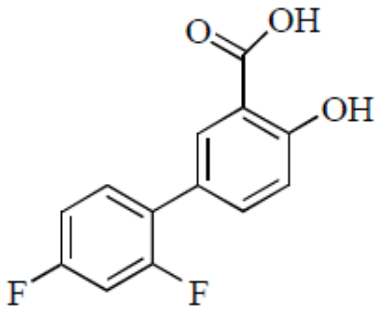
NSAIDs – Salicylate Derivatives



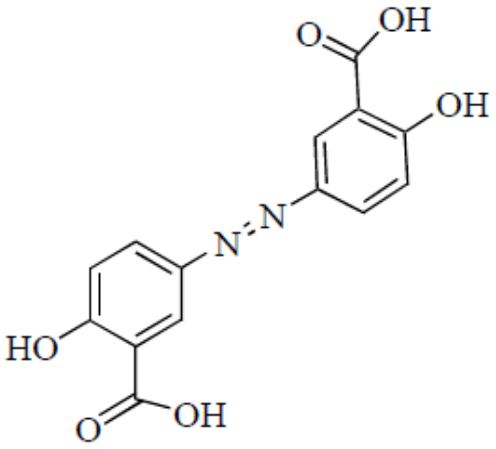
Methyl Salicylate



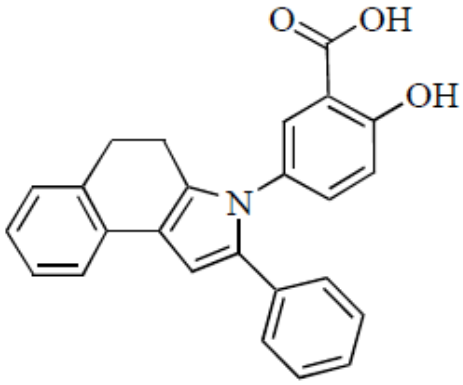
Salsalate



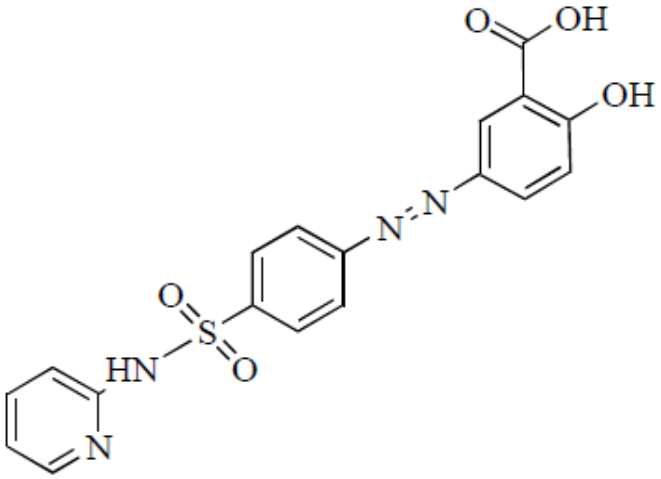
Diflunisal



Olsalazine



Fendosal

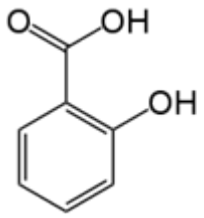


Sulfasalazine

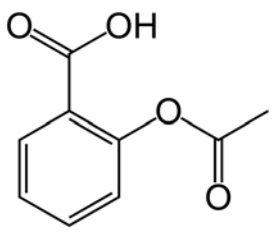
Structure Activity Relationship of Salicylates

- *Salicylates* generally act by virtue of their content of salicylic acid.
- The *carboxylate anion* is *required* for *anti-inflammatory action*.
- *Salicylamide* HAS ANALGESIC action but LACKS INFLAMMATORY action.
- Substitution on the carboxyl or hydroxyl groups change the potency or toxicity of salicylate compounds.

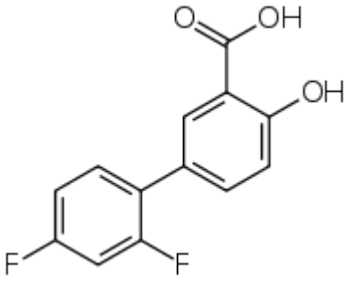
- Hydroxyl group should be ortho with respect to carboxylic group
- Halogen substitution enhances activity however make them toxic as well
- Substitution with hydrophobic aryl groups at the 5- position of the ring improves anti inflammatory activity



salicylic acid



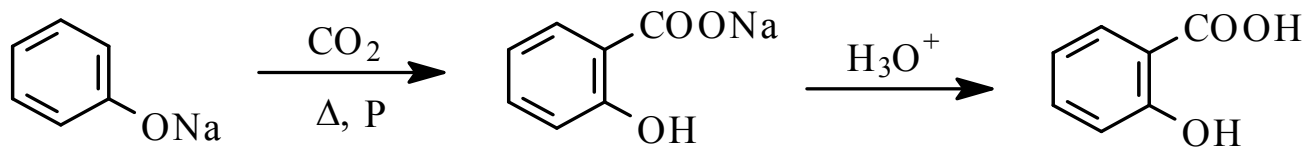
acetylsalicylic acid



diflunisal

Synthesis of Salicylic Acid

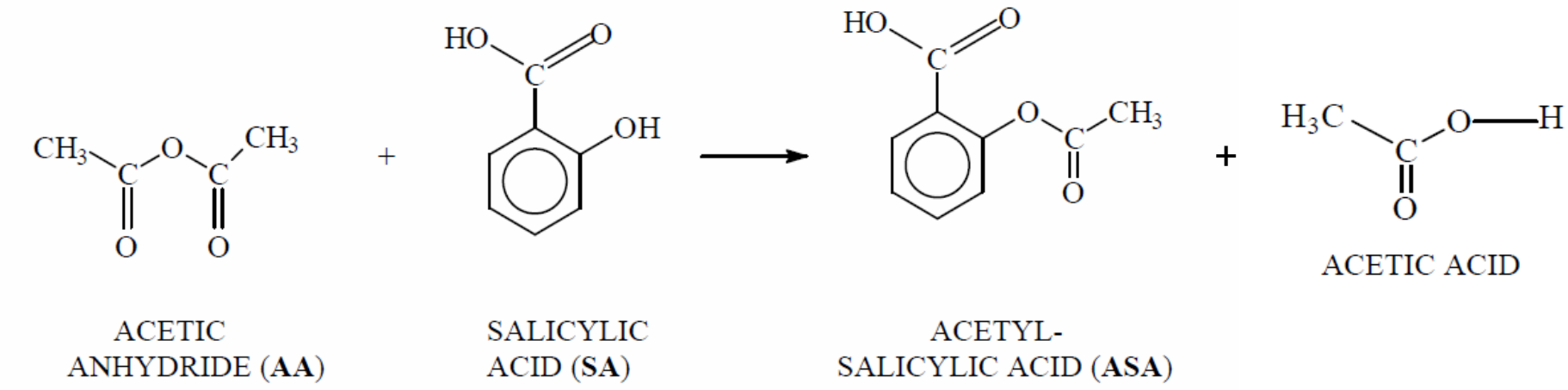
Kolbe-Schmitt Reaction



- yield about 90% at 150 – 160 °C and 5 bar (7atm) CO_2 pressure

Synthesis of Acetylsalicylic Acid (Aspirin)

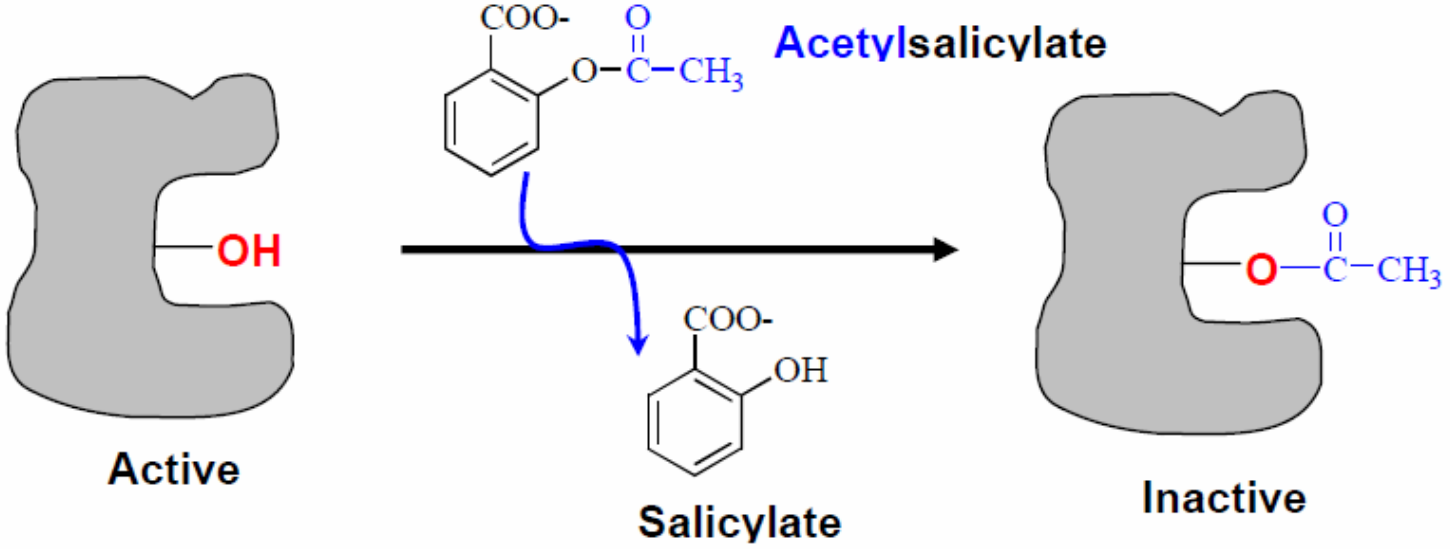
The synthesis of aspirin is classified as an esterification reaction



- Analgesic, antipyretic, anti-inflammatory, antiplatelet effect

The Mechanism-of-Action of Aspirin

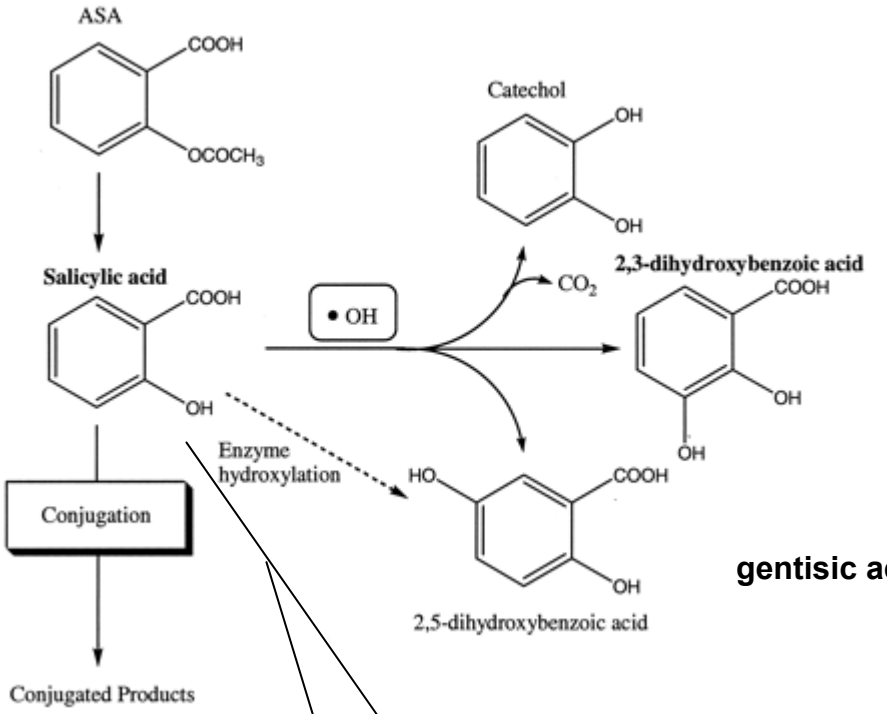
- Aspirin (acetylsalicylic acid) covalently and irreversibly modifies both Cox-1 and Cox-2 by acetylating Serine-530 in the active site.



- Acetylation of Cox-1 creates a steric block that prevents the binding of arachidonic acid at the cyclooxygenase active site.

- Acetylation of Cox-2 retains the cyclooxygenase activity although the reaction pproduces a novel product 15-R-HETE.

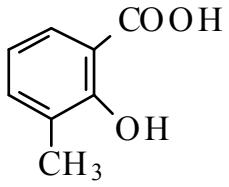
Metabolism of Acetylsalicylic Acid



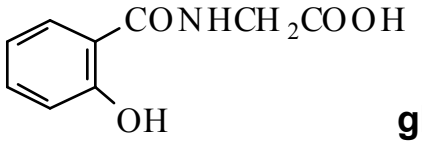
Glucuronic acid and glycine conjugation

gentisic acid

Glucuronic acid conjugation



Methylation at 3- position slows metabolism via hydrolysis of acetyl group

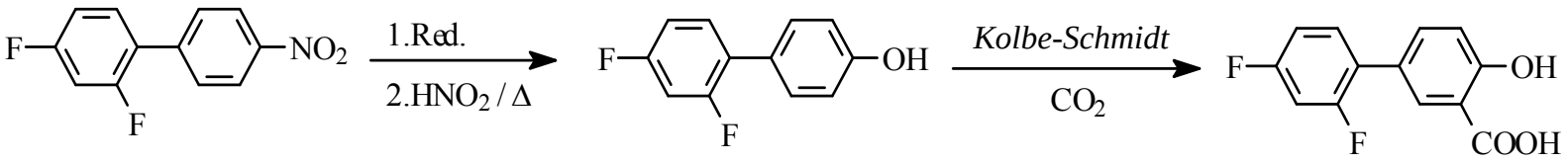


glycine conjugation

salicyluric acid (%50-80)

Synthesis of Diflunisal (Dolobid)

- Diflunisal can be made from 2,4-Difluoro-4-nitrobiphenyl;
first nitro group is reduced to phenol followed by *Kolbe-Schmidt* reaction

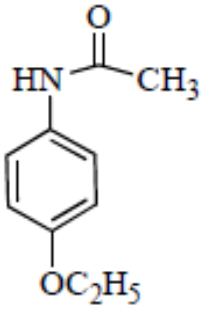


2',4'-difluoro-4-hydroxybiphenyl-3-carboxylic acid

- Metabolizes in kidneys through glucuronide conjugation

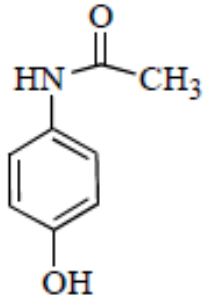
NSAIDs -The Para-amino Phenol Derivatives

Acetaminophen (Tylenol; paracetamol; N-acetyl-p-aminophenol) is the active metabolite of phenacetin (acetophenetidin), a so-called coal tar analgesic. In-vivo, phenacetin is converted to acetaminophen. Phenacetin is no longer available in the United States.



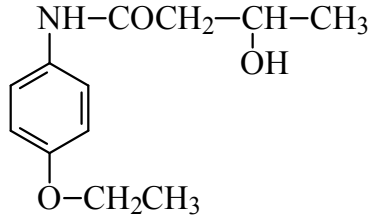
N-(4-Etoxyphenyl)acetamide

Phenacetin



N-(4-Hydroxyphenyl)acetamide

Acetaminophen



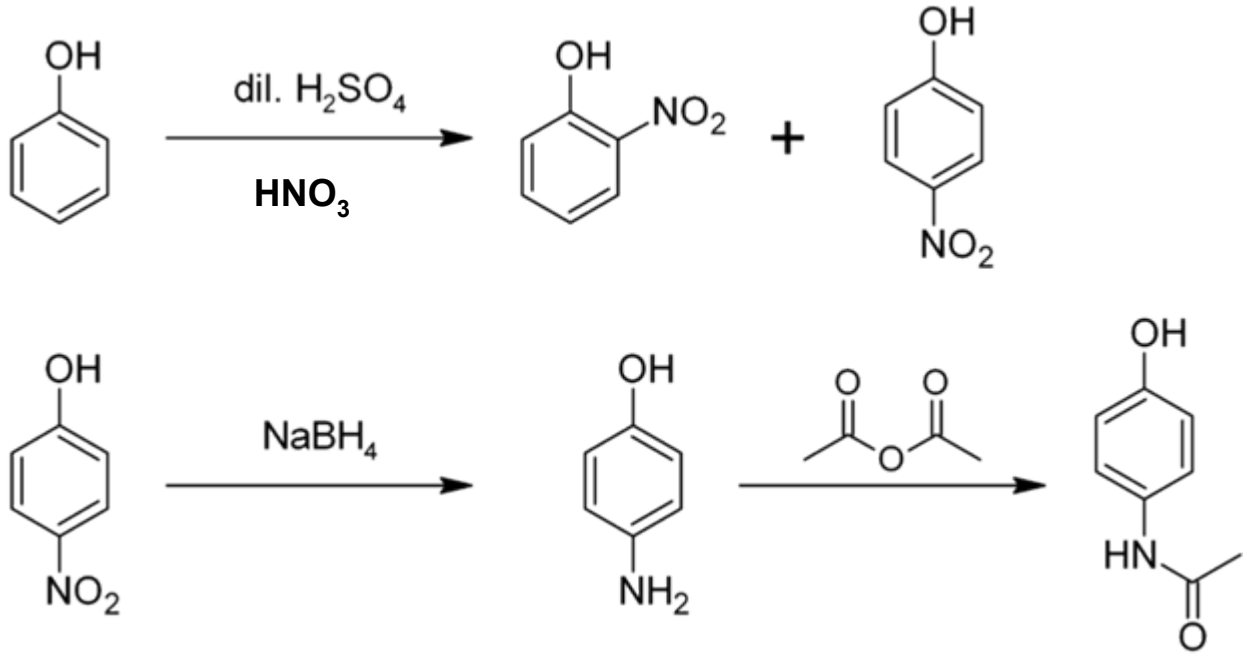
N-(4-Etoxyphenyl)-3-hydroxybutyramide

Bucetin

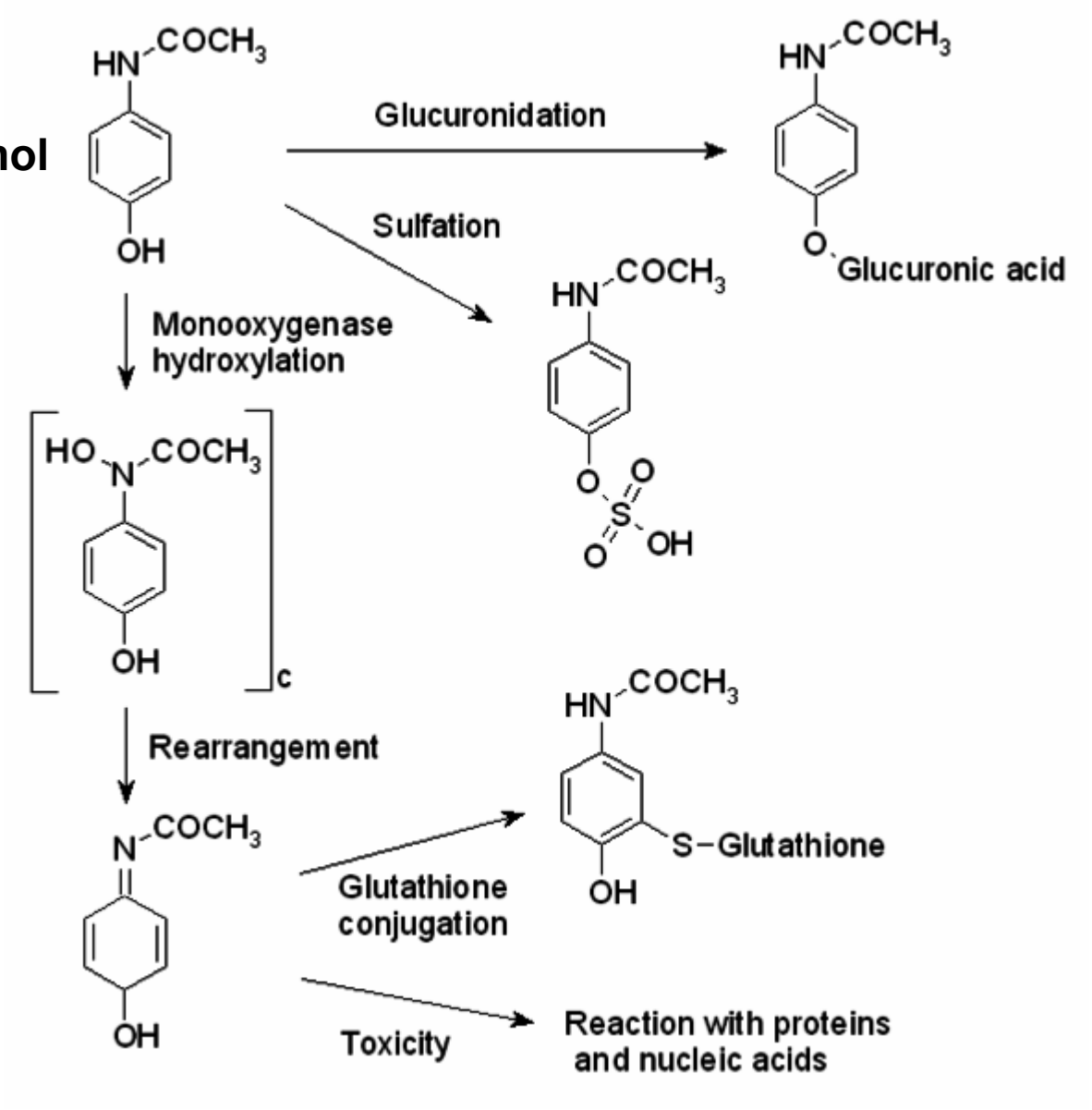
- Acetaminophen is effective as an analgesic and an antipyretic
- It has WEAK Anti-inflammatory action, possibly due to its weak inhibition of cyclooxygenase (as measured in the presence of high concentrations of peroxide found in inflammatory lesions) and hence its weak inhibition of prostaglandin synthesis.

Synthesis of Paracetamol

The nitro group on 4-nitrophenol was reduced with sodium borohydride. The resultant *4*-aminophenol is then acetylated with acetic anhydride.



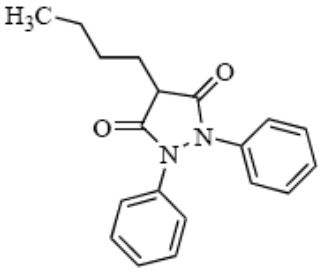
Metabolism of Paracetamol



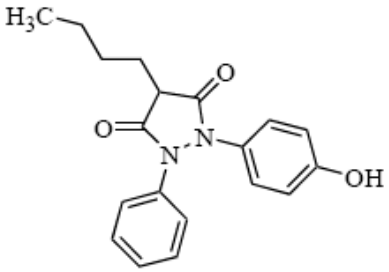
NSAIDs - Pyrazolone and Pyrazolidinedione Derivatives

- 1-phenyl-2,3-dimethyl-3-pyrazolin-5-one and 1,2-diphenylpyrazolidin-3,5-dione derivatives

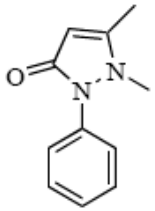
These drugs have been in clinical use for many years and include:



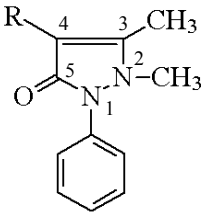
Phenylbutazone

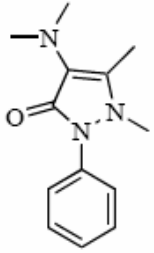


Oxyphenbutazone

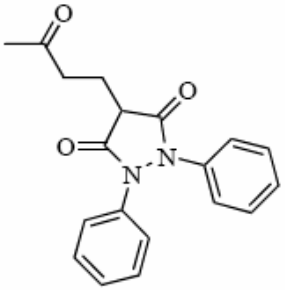


Antipyrine

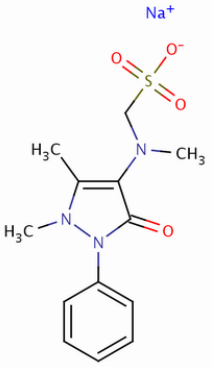




Aminopyrine



Kebuzone



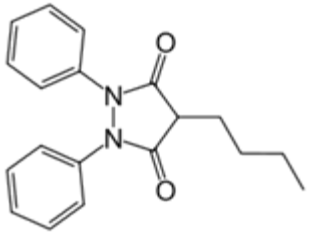
Dipyrone (metamizole)

Phenylbutazone was introduced in 1949 for the treatment of arthritis. Although not a first-line drug, it is the most important from the therapeutic, while the others are not used today.

Pyrazolidinedione Derivatives - Phenylbutazone

✓ Phenylbutazone is a nonsteroidal anti-inflammatory drug (NSAID) effective in treating fever, pain, and inflammation in the body.

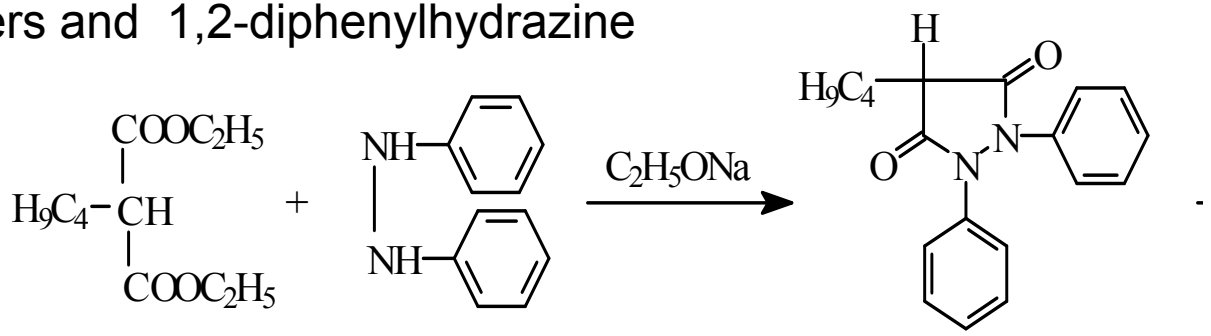
✓ Phenylbutazone has analgesic ve antipyretic effects with similar potency as aminophenazone and phenazon. It has enhanced antiinflammatory effects and is used to treat rheumatoid arthritis.



Phenylbutazone

4-butyl-1,2-diphenyl-pyrazolidine-3,5-dione

Synthesis: Phenylbutazone and its derivatives could be prepared from condensation of n-butylmalonic acid ester like substituted malonic acid esters and 1,2-diphenylhydrazine

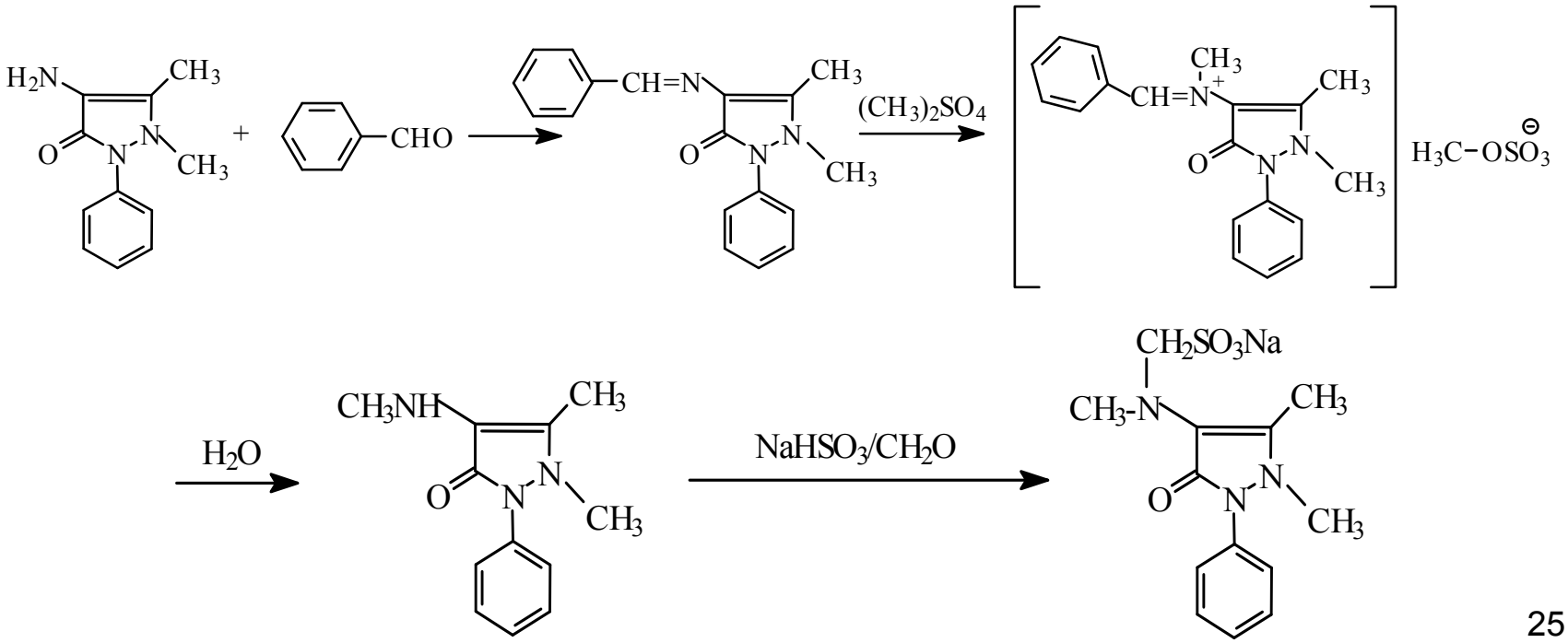


Phenylbutazone

Pyrazolone Derivative - Dipyrone (Novalgene, Metamizole sodium)

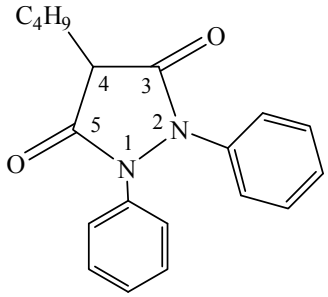
✓ A drug that has analgesic, anti-inflammatory, and antipyretic properties.
✓ Associated with acute condition involving a severe and dangerous leukopenia (lowered white blood cell count).

Synthesis: Aminoantipyrene reacts with benzaldehyde to give aldimine intermediate, which is methylated with dimethylsulfate followed by hydrolysis to give N-methylamino antipyrene. In the presence of formaldehyde and sodium bisulfate dipyrone is synthesized through *Eschweiler-Clarke* methylation reaction.

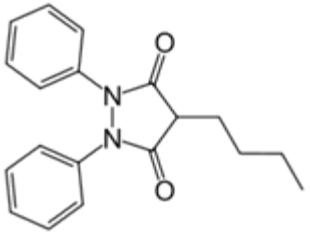


SAR for Pyrazolidinediones (and phenylbutazone)

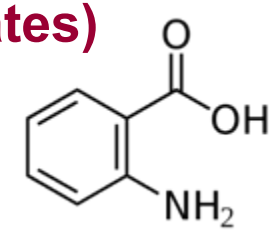
- The butyl group of carbon 4 may be replaced by propyl or allyl and show similar activity.
- The meta substitution of the aryl ring are inactive but para substitution such as CH_3, Cl, NO_2 or OH retains activity.
- Replacement of nitrogen in pyrazolidines with oxygen yield isoxazole analog which is as active as pyrazolidine derivatives.
- Decreasing pKa values of phenyl butazone analogs have shorter half lives decreasing anti inflammatory activity
- Substitution of Hydrogen at C-4 by methyl group or others destroys anti inflammatory activity since it is important to have a dicarbonyl group that could be enolized.
- If pyrazolidine ring is replaced with cyclopentane or cyclopenten the resulting compounds are inactive



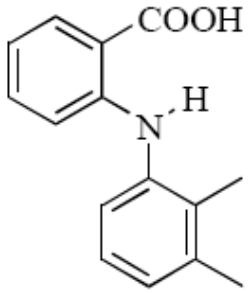
phenylbutazone



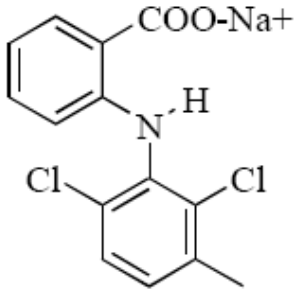
NSAIDs - N-Arylanthranilic acid derivatives (Fenamates)



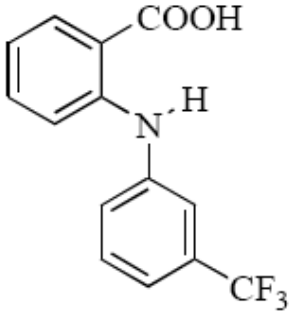
The fenamates are derivatives of N-phenylanthranilic acid. Therapeutically they have no clear advantages over other NSAID's and fequently they cause side effects such as diarrhea.



Mefenamic acid



Meclofenamate sodium

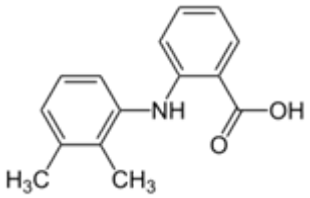


Flufenamic acid

- ✓ Fenamates are N containing analogues of salicylates

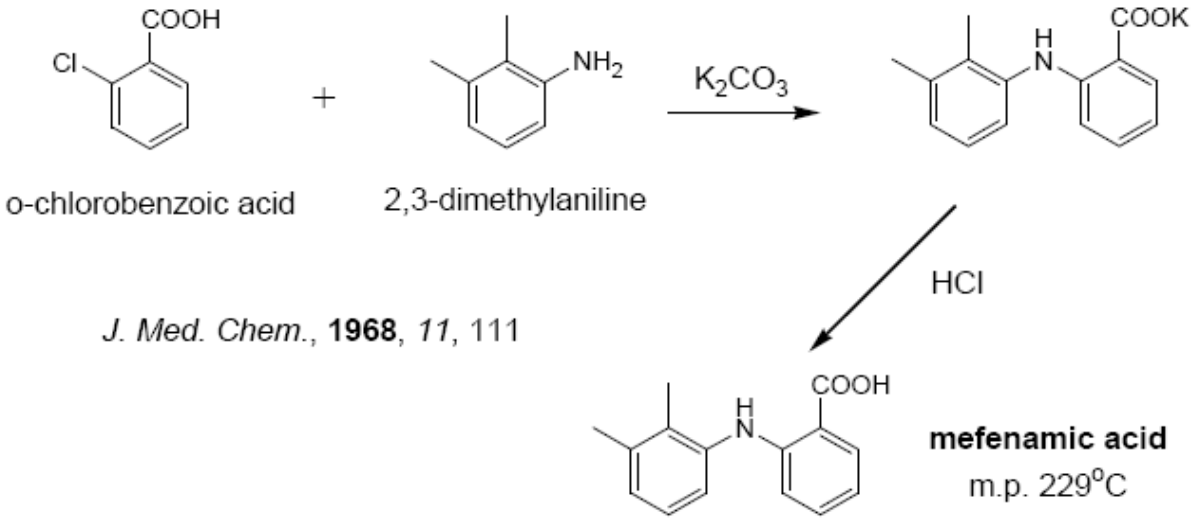
Fenamates- Mefenamic acid

✓ **Mefenamic acid** is an anti-inflammatory painkiller (NSAID).
✓ It is used to treat painful conditions such as arthritis, pain associated with heavy menstrual bleeding, and pain after surgical operations.
✓ Mefenamic acid is a competitive inhibitor of COX-1 and COX-2, which are responsible for the first step in prostaglandin biosynthesis



2-(2,3-dimethylphenyl)aminobenzoic acid

Synthesis: via reaction of 2-chlorobenzoic acid and 2,3-dimethylaniline



o-chlorobenzoic acid

2,3-dimethylaniline

J. Med. Chem., **1968**, *11*, 111

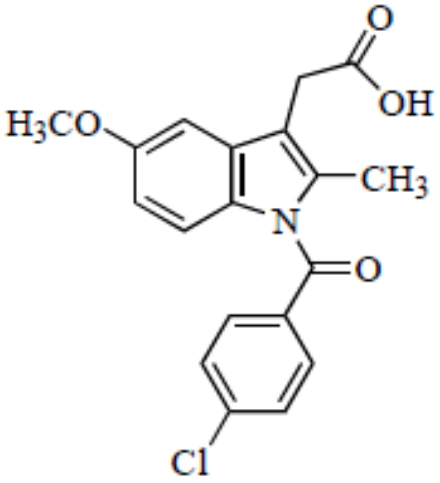
mefenamic acid
m.p. 229°C

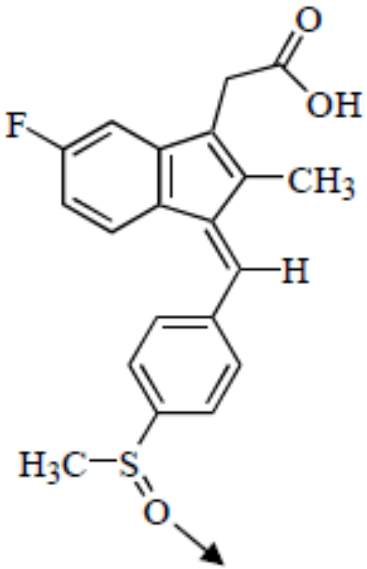
NSAIDs - Heteroaryl Acetic Acids and Propionic Acid Derivatives

- Important class of NSAID drugs, classified according to aryl and heteroaryl acetic acid derivative
- Typically used for treatment of rheumatoid arthritis

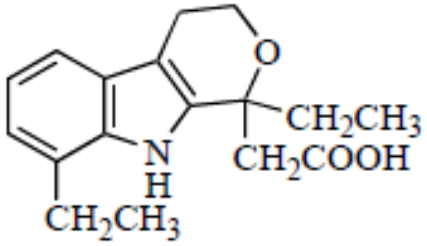
- ✓ **Indole and Indene Acetic Acids (Arylalkanoic acids)**
- ✓ **Propionic Acid Derivatives**
- ✓ **Heteroaryl Acetic Acids**
- ✓ **Enolic acids**
- ✓ **Alkanones: Nabumetone**

NSAIDs - Indole and Indene Acetic Acids (Arylalkanoic acids)





Becomes an -H



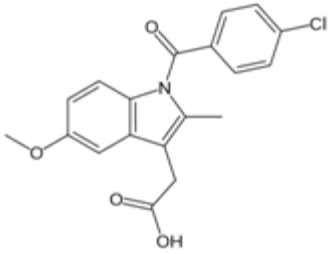
Indomethacin ***Sulindac*** ***Etodolac***

Indomethacin is a methylated indole derivative.

Sulindac (Clinoril) is a non-indole and contains a sulfoxide and is a PRODRUG since it is unlikely that this form has any pharmacological activity. Most of the activity resides in its sulfide metabolite which is more than 500 times more potent as an inhibitor of cyclooxygenase than sulindac.

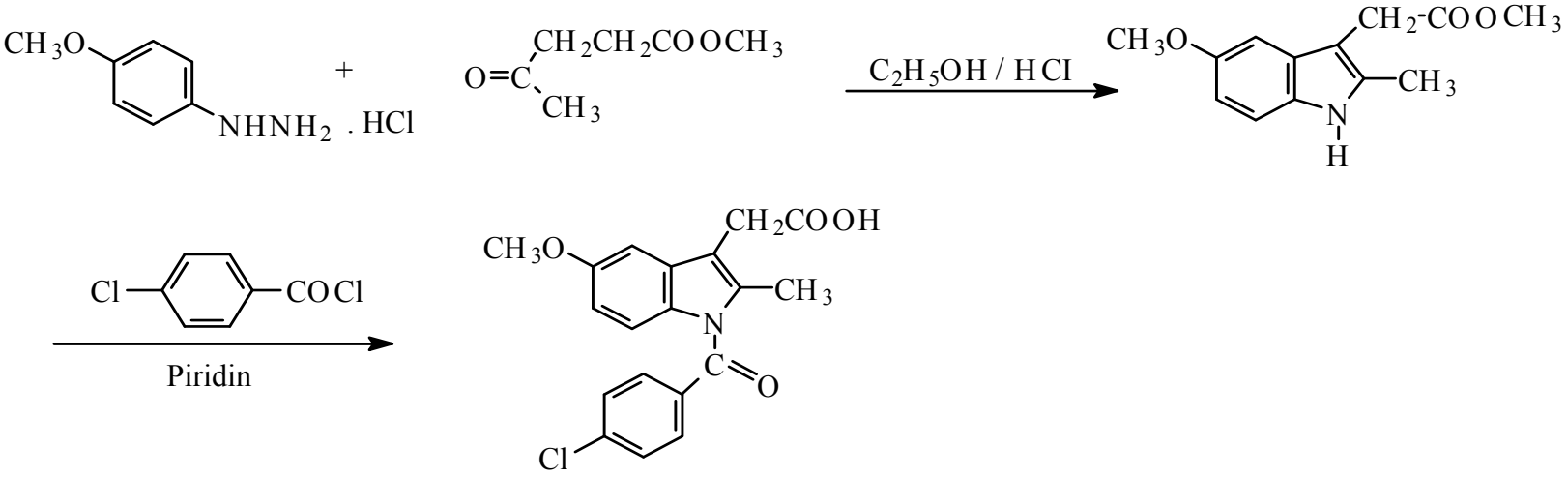
Indole and Indene Acetic Acids (Arylalkanoic acids) - Indometacin

Indometacin is one of the commonly used and the most effective NSAIDs to reduce fever, pain, stiffness, and swelling.

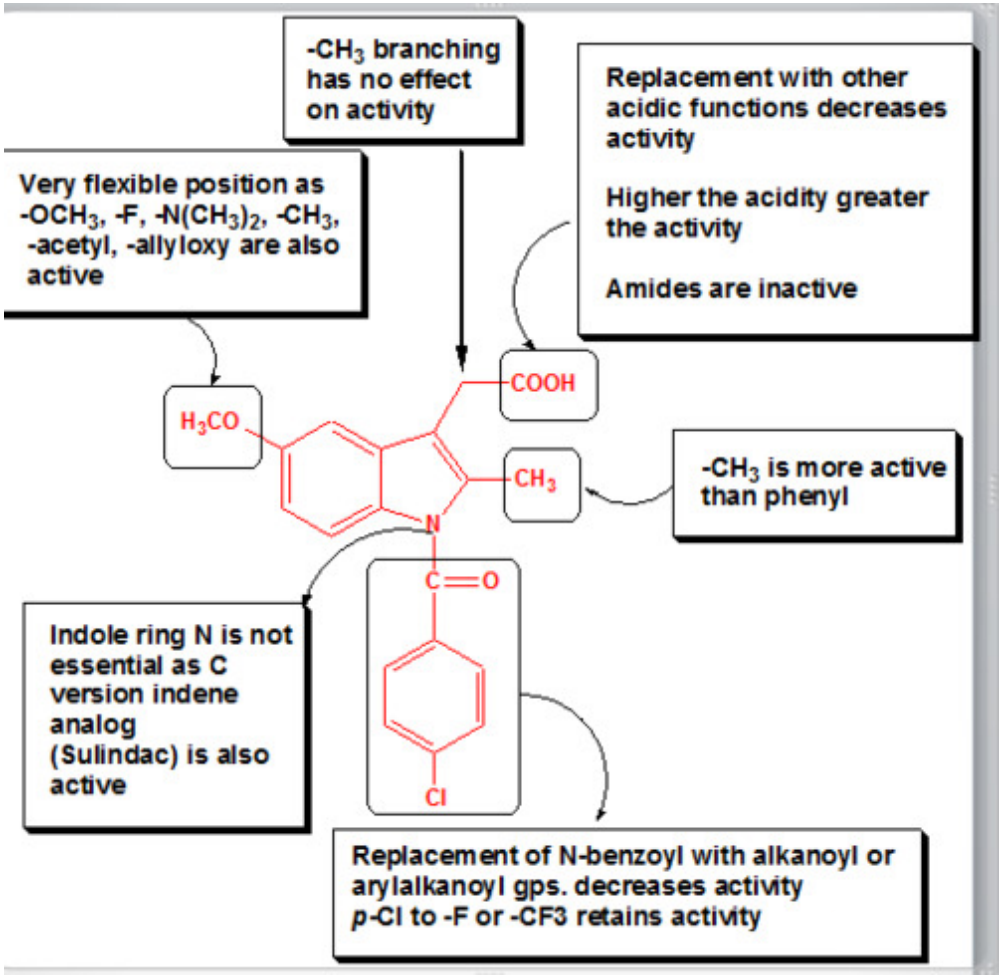


2-{1-[(4-chlorophenyl)carbonyl]-5-methoxy-2-methyl-1*H*-indol-3-yl}acetic acid

Synthesis: of methyl 4-oxopentanoate (methyl levulinate) and *p*-methoxy-phenylhydrazine hydrochloride raects giving methyl 5-methoxy-2-methyl indole-3-acetate, which undergoes acylation with *p*-chlorobenzoyl chloride giving indomethacin



Structure Activity Relationship of Indomethacin



Structure Activity Relationship for Indole Derivatives

✓ Carboxyl group is necessary for anti inflammatory activity. If carboxylate group is exchanged with hydroxyl type groups there is a decrease in activity. Antirheumatic activity increases with acidity.

✓ Changing aromatic acyl group at position 1 with alkyl, aliphatic acyl or alkyl group lowers activity.

✓ Substituting halogen, CF_3 or SCH_3 groups at para position of 1-benzoyl ring increases activity.

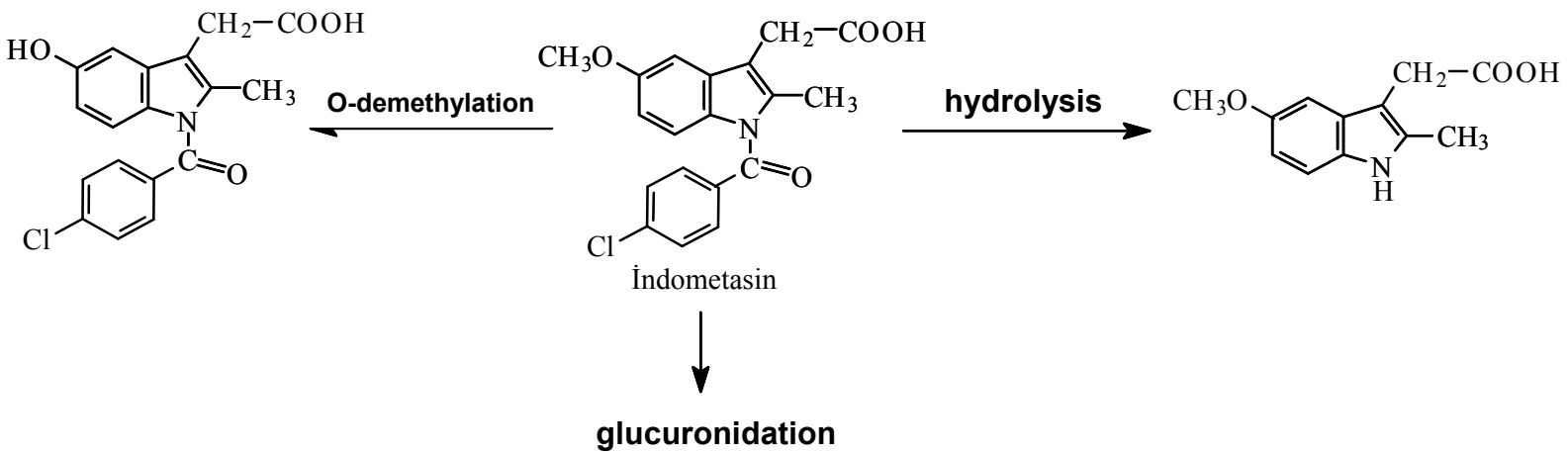
✓ Methyl group at position 2 forces the molecule to have a *cis* conformation therefore has pronounced effect on activity relative to aryl group.

✓ The bond at 3-acetic acid chain can freely rotate. Hydrogen or methyl substitution at α-position of the side chain gives similar activity whereas α,α-dimethyl or hydroxyl substitution lowers activity. S isomers are more effective.

✓ Substitution at position 5 of the indole ring is feasible and methoxy, dimethylamino, acetyl, methyl and fluoro substituents improve activity.

✓ Arylidene indenyl isostere shows similar activity as indole compounds. Cis isomer exhibits higher activity then trans compound.

Biotransformation of Indomethacin

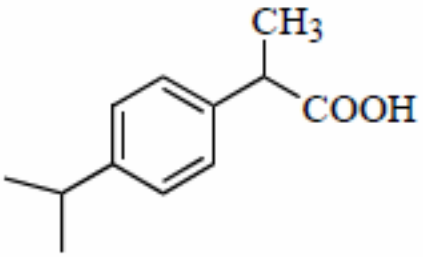


✓ Under *in vivo* condition inhibation of prostaglandin synthesis by indomethacin is more effective than phenylbutazone, however they show similar clinical profile for rheumatoid arthritis.

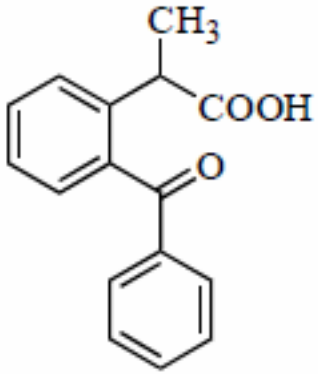
✓ Rate of absorption of Indomethacin is fast and complete. Its antipyretic activity is higher than acetaminophen and aspirin. Analgesic activity is effective for pain related to inflammation.

NSAIDs -Propionic Acid Derivatives

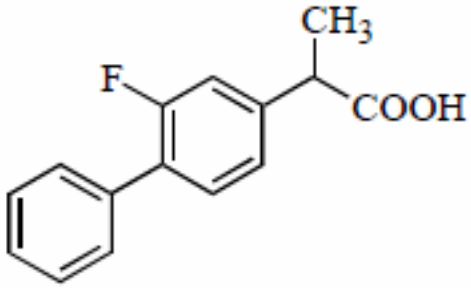
✓ Arylpropionic acid derivatives are effective and useful NSAID's. They may offer significant advantages over aspirin and indomethacin since they are usually better tolerated. However, they still share all of the detrimental features of all the NSAID's.



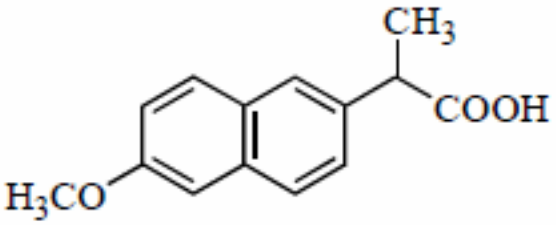
Ibuprofen



Ketoprofen



Flurbiprofen



Naproxen

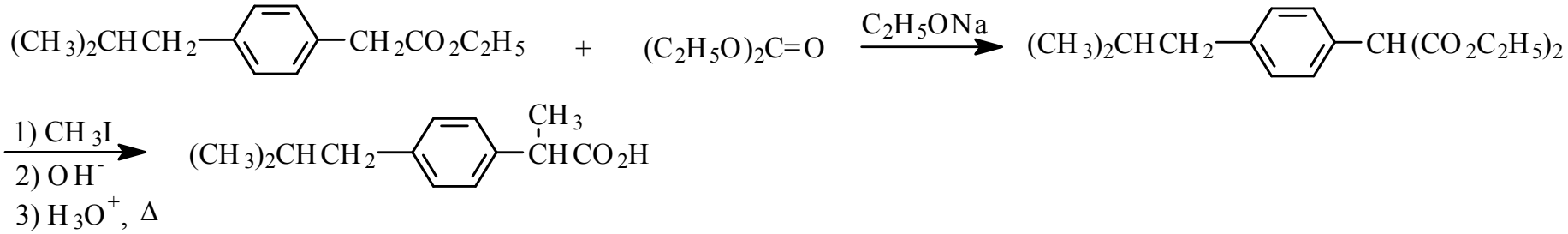
✓ **Ibuprofen** (Advil, Nuprin etc) was the first member of the propionic acid class of NSAID's to come into general use.

✓ The S-isomer is more active than the R-isomer

✓ **Naproxen** (Naprosyn, Aleve) is one of the most widely used NSAID's.

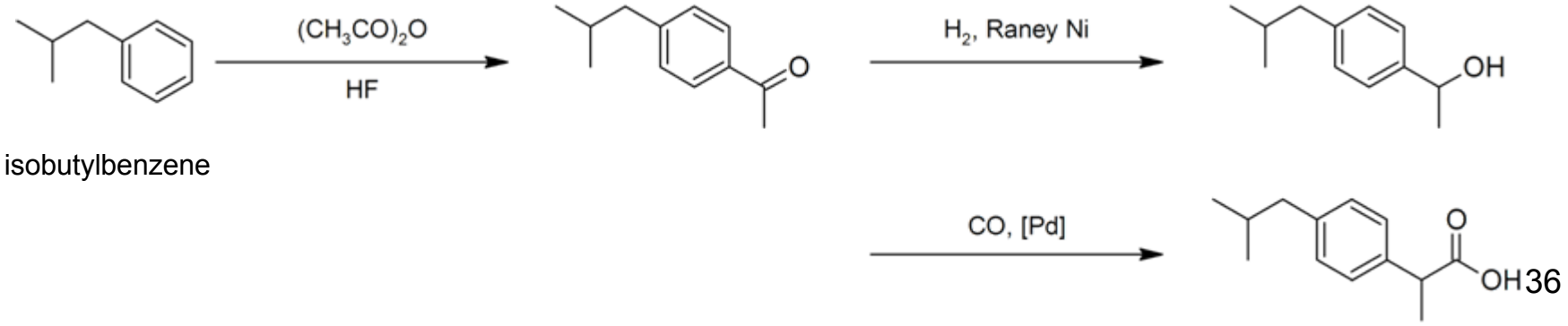
Synthesis of Ibuprofen

Ethyl 4-isobutylphenyl acetate, sodium ethoxide and diethylcarbonate condensation gives 4-isobutyl phenyl malonate. Methylation is done with methyl iodide and after decarboxylation ibuprofen is obtained.



Improved Synthesis of Ibuprofen

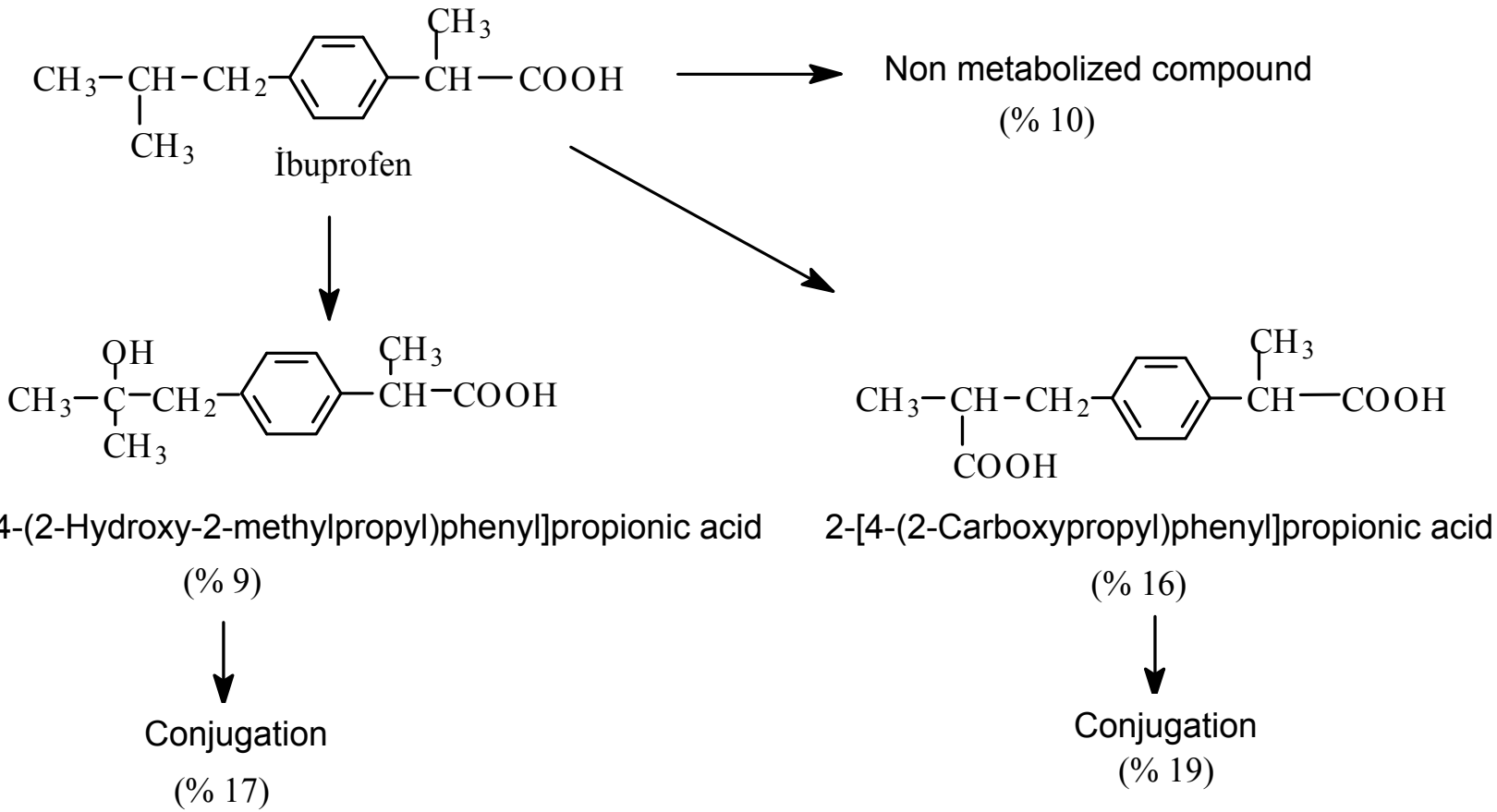
This improved synthesis won the Presidential Green Chemistry Challenge Greener Synthetic Pathways Award in 1997. After a similar acetylation, hydrogenation with Raney nickel gave the alcohol, which underwent palladium-catalyzed carbonylation.



isobutylbenzene

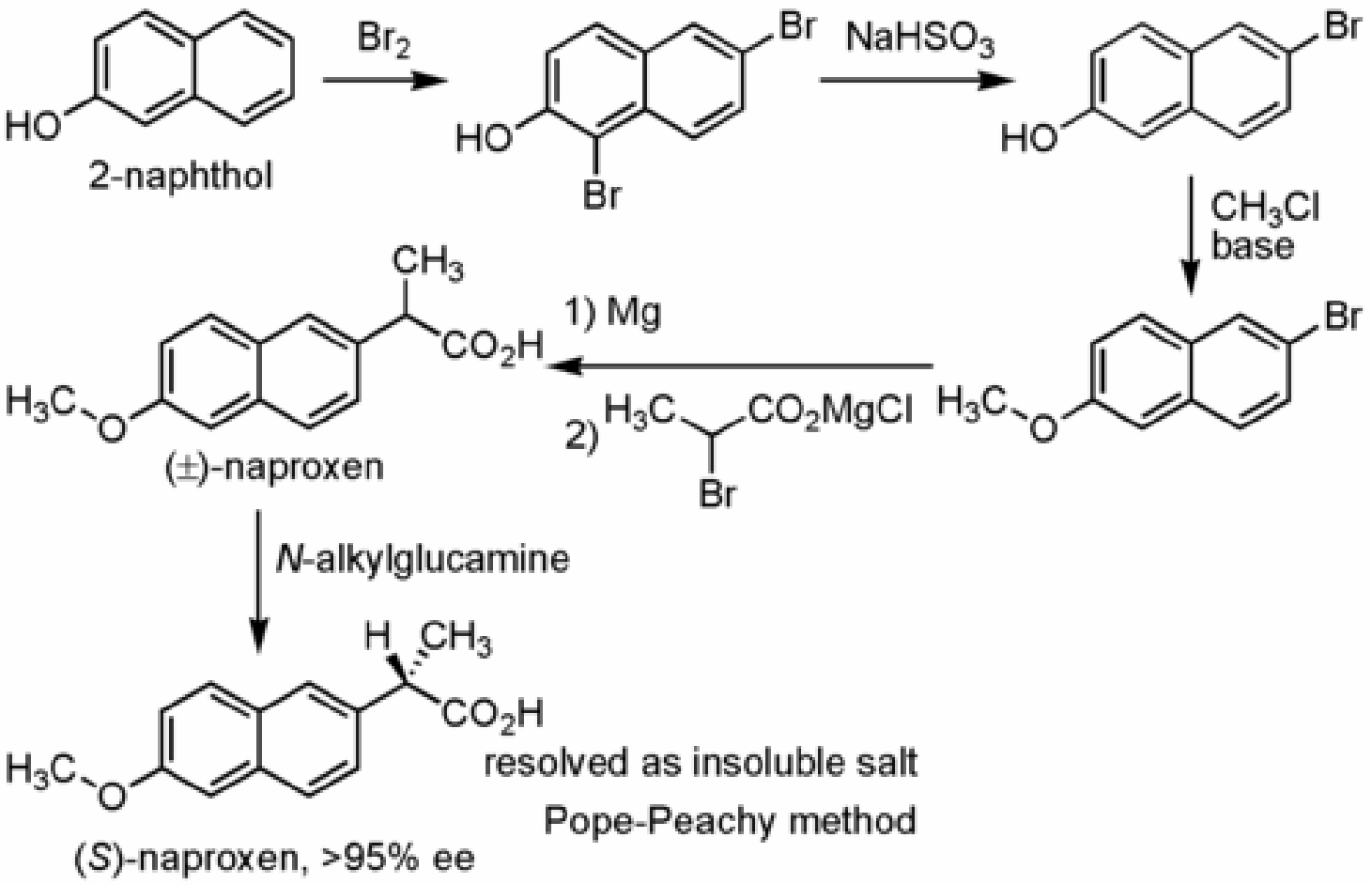
Biotransformation of Ibuprofen

✓ takes place mostly in liver and less than 10% of it is excreted in urine without being metabolized.



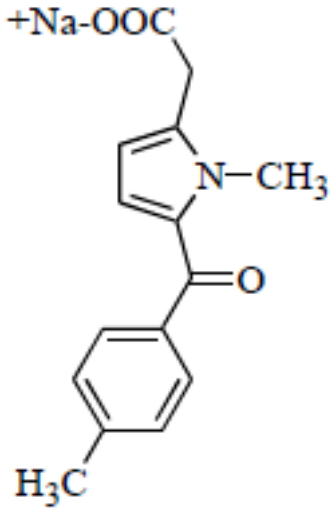
Synthesis of Naproxen

Naproxen has been industrially produced by Syntex as follows

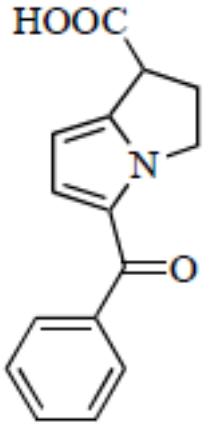


NSAIDs - Heteroaryl Acetic Acids

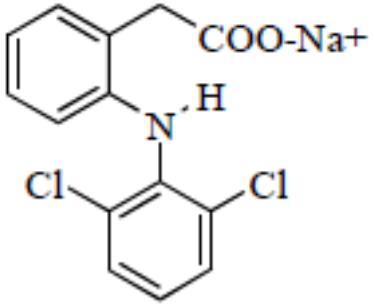
Tolmetin, ketorolac and zomepirac are structurally related heteroaryl acetic acid derivatives with different pharmacologic features. Diclofenac is a phenyl acetic acid derivitive.



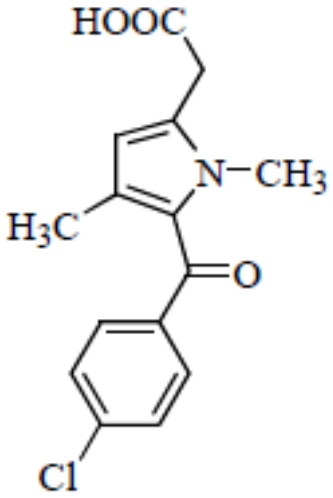
Tolmetin



Ketorolac



Diclofenac

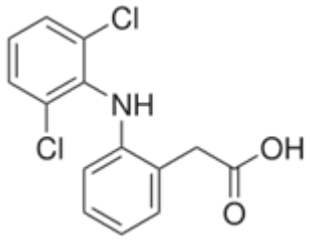


Zomepirac

✓ **Diclofenac** (Voltaren: sodium form) is one of the most potent NSAID's known clinically and in animal models for both inflammation and pain.

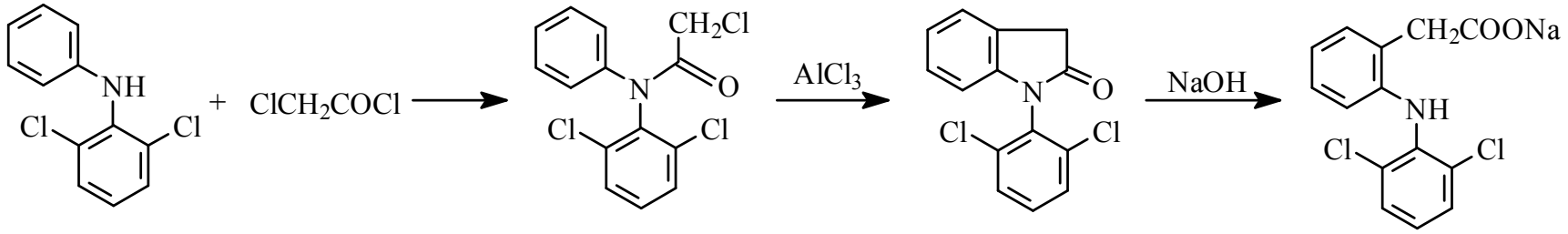
Heteroaryl Acetic Acids Derivatives - Diclofenac

✓ **Diclofenac** belongs to a class of drugs called (NSAIDs) that are used for the treatment of mild to moderate pain, fever, and inflammation



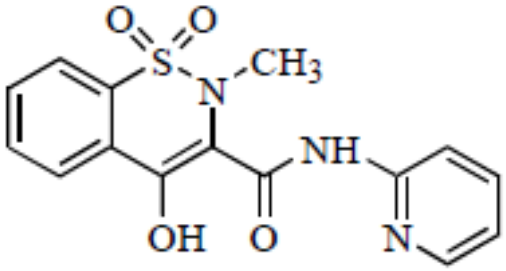
2-(2-(2,6-dichlorophenylamino)phenyl)acetic acid

Synthesis: N-phenyl-2,6-dichloroaniline and chloroacetyl chloride reaction forms chloroacetanilidine, which in the presence of aluminum chloride gives *Friedel Crafts* acylation reaction. Hydrolysis with sodium hydroxide affords diclofenac sodium.

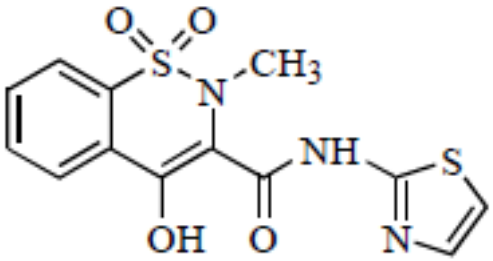


NSAIDs - Enolic Acids

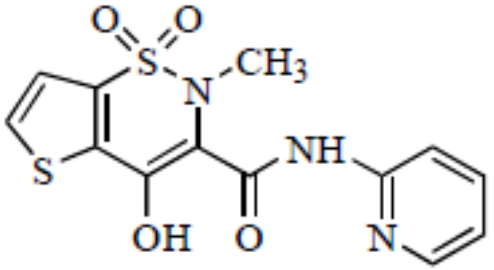
✓ The enolic acids include an oxicam family currently composed of piroxicam, meloxicam and tenoxicam (currently under study as well as others).



Piroxicam



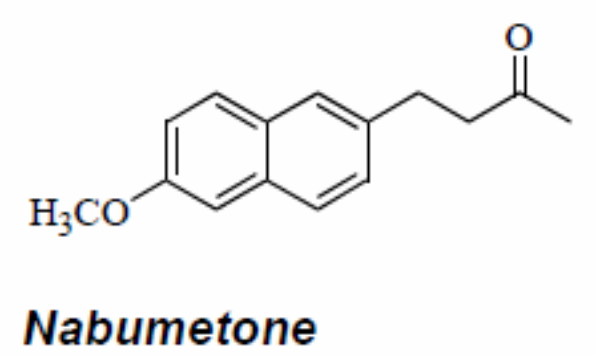
Meloxicam



Tenoxicam

Piroxicam appears to be the equivalent of aspirin, indomethacin, or naproxen for the long-term treatment of rheumatoid arthritis or osteoarthritis.

NSAIDs - Alkanones: Nabumetone



Nabumetone

4-(6-methoxy-2-naphthyl)-2-butanone

Nabumetone (Relafen) is an anti inflammatory agent recently approved for use in the United States.

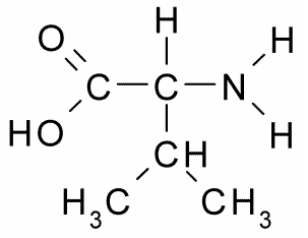
Structure and Binding of COX-1 and COX-2

✓ X-ray crystal structure analysis of COX-1 and COX-2 enzyme show differences in their structures (different amino acid sequence).

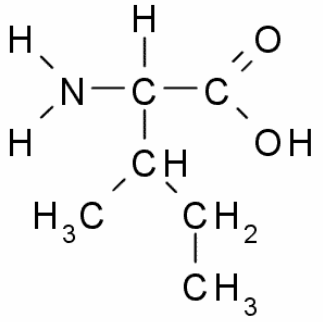
✓ COX-2 has smaller group valine in the active site whereas COX-1 has larger isoleucine. This results in an increased volume of side pocket in COX-2 enzyme which enables selective inhibition.

✓ This side pocket is limited (non existent) in COX-1. Larger pocket size in COX-2 Allows drugs with large substituents to enter to active site.

valine



isoleucine

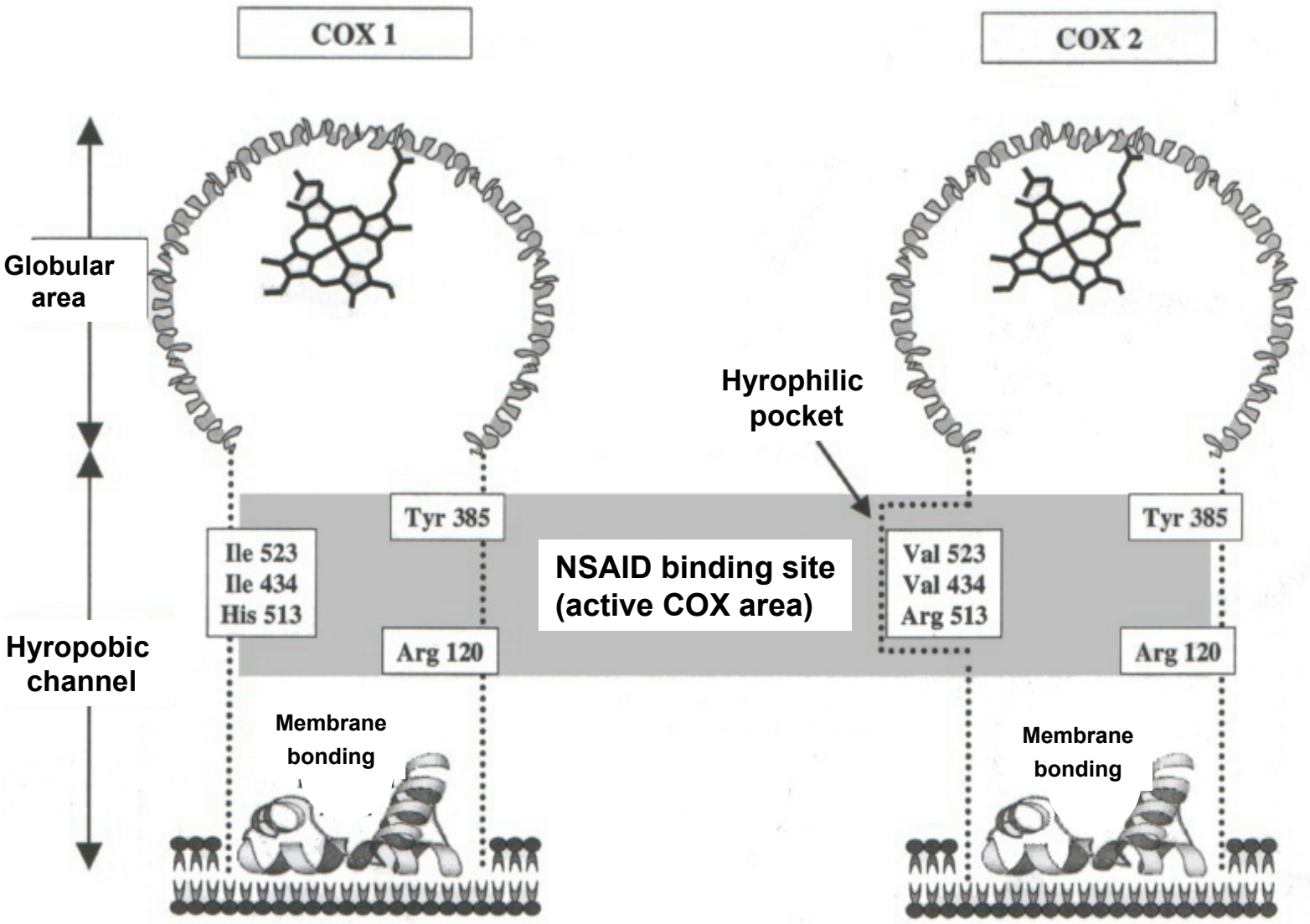


✓ The COX-2 inhibitors lack a carboxyl group and binding of these drugs within the COX active site does not require the charged interaction with Arg120.

✓ Instead, these larger methylsulfonylphenyl derivatives block the COX-2 channel in a time-dependent manner as the sulfonamide moiety slowly orientates within the hydrophobic side pocket

✓ Simple competitive inhibition of COX-1 by COX-2 inhibitors is thought to occur because of lack of access to the side pocket

Structures of COX-1 and COX-2 Enzymes



Selective COX-2 Inhibitors

✓ COX-2 inhibitors do not contain carboxylic acid groups. They have different chemical structures

✓ Diaryl- and arylhetero aryl ether (sulfonanilide inhibitors): **Nimesulide**, NS-398, flosulide, L-745337

✓ Vicinal diaryl heterocycles: **Celecoxib, rofecoxib**, valdecoxib, pareocoxib, DuP-697

✓ Modified NSAIDs known to have high COX-2 selectivity: **Meloxicam,** etodolac

✓ Antioxidant compounds

✓ 1,2-Diaryl ethylene derivatives (*cis*-stilbene)

Cox-2 Selective Drugs - Vicinal Diaryl Heterocycles

The most studied and important family of COX-2 inhibitors.

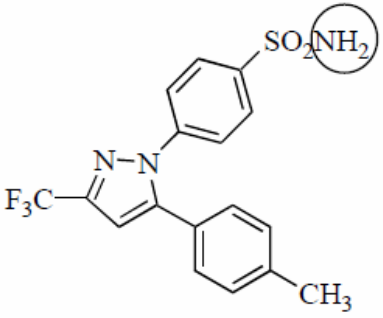
✓ Compounds are characterized by two vicinal aryl groups bonded to a heterocyclic ring.

✓ Heterocylic ring is responsible to insert the aromatic ring into COX-2 cavity and its coordination. Types of heterocyles include furan, pyrrole, thiazole, oxazole, imidazole, isoxazole, pyrimidine and thiophene.

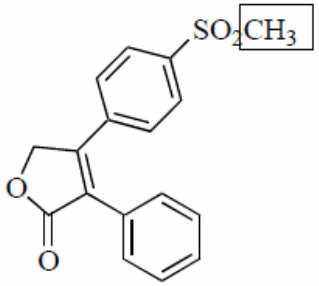
Tricyclic Compounds (...the Coxibs)

✓ The first two highly specific COX-2 inhibitors, Celecoxib (Celebrix®, Pfizer) and Rofecoxib (Vioxx® Merck, withdrawn) are now commercially available.

✓ **Coxibs** are selective COX-2 inhibitors. They exert antiinflammatory, analgesic, and antipyretic action with low ulcerogenic potential



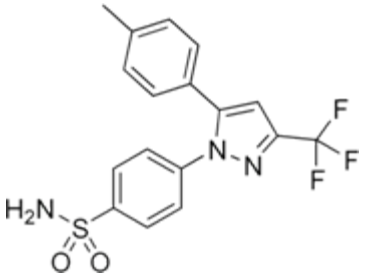
Celecoxib, Celebrex®



Refecoxib, Vioxx®

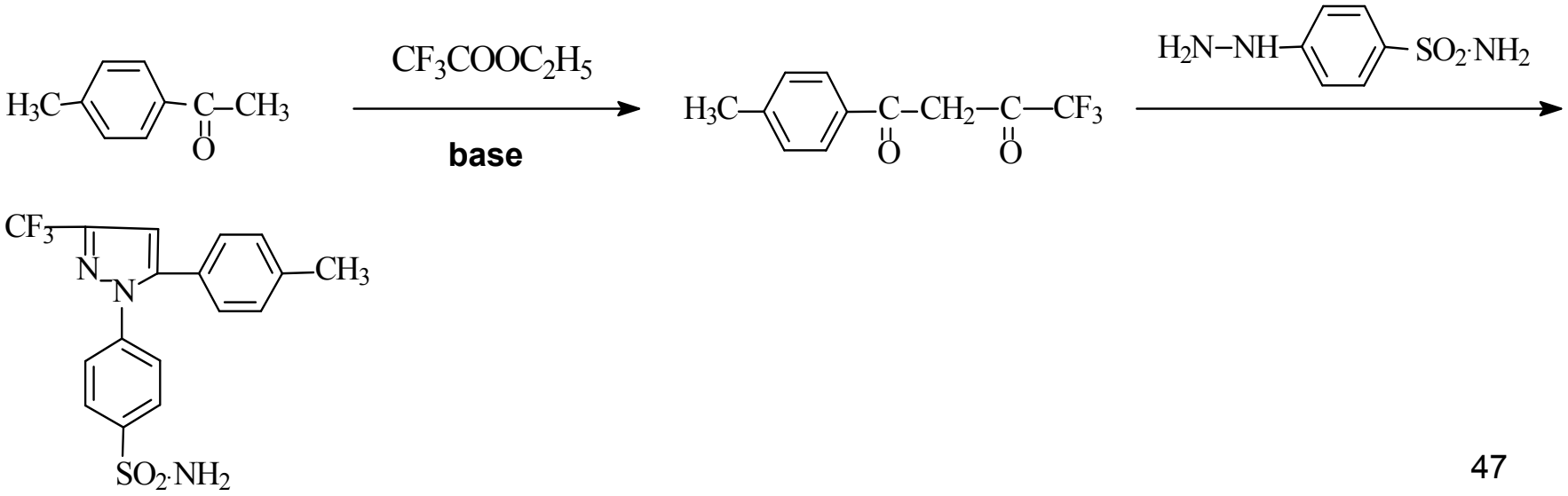
Selective COX-2 Inhibitors - Celecoxib

✓ Celecoxib is in a class of NSAIDs called COX-2 inhibitors
It is used to relieve pain, tenderness, swelling and stiffness caused by osteoarthritis and rheumatoid arthritis



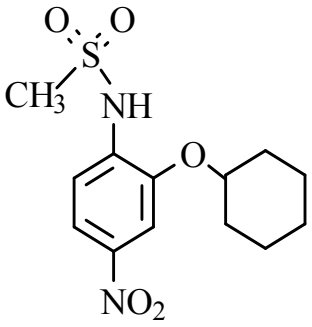
4-[5-(4-methylphenyl)-3-(trifluoromethyl)pyrazol-1-yl]benzenesulfonamide

Synthesis of Celecoxib: ethyl trifluoroacetate and 4-methylacetophenone react to give 4-methyltrifluoroacetyl benzophenone. Treatment with 4-hydrazinebenzensulfonamide results in closing of pyrazole ring to give celecoxib.

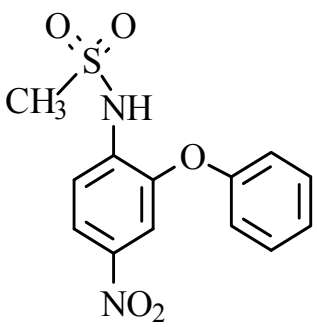


Preferential COX-2 inhibitors
Diaryl and arylheteroaryl ethers (sulfonanilide derivatives)

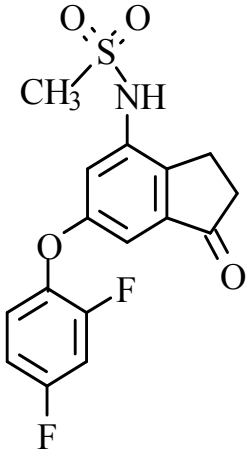
NS-398 was the first to be discovered. Has different chemical structure than non steroidal anti inflammatory drugs. Inhibits prostaglandin synthesis at inflammation site without gastrointestinal irritation.



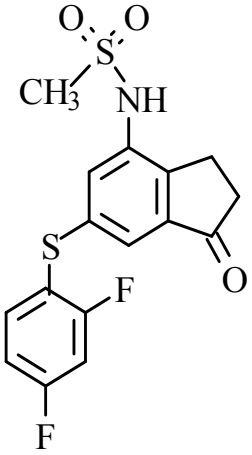
NS-398



Nimesulide



Flosulid



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