Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Part 1

Dr. Mai Ramadan

Non-Steroidal Anti-inflammatory Drugs (NSAIDs)

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Introduction:

NSAIDs mechanism of action: Noncompetitive inhibition of cyclooxygenase enzyme, inhibit synthesis of Prostaglandins[PGE2: Most associated with inflammation]

Cyclooxygenase [Prostaglandin endoperoxide synthase OR PGH synthase], the rate limiting enzyme responsible for biosynthesis of PGs.

Isoforms of the cyclooxygenase enzymes [COX-1, COX-2, COX-3].

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Introduction:

Cyclooxygenase-1 (COX-1):

A constitutive enzyme

Responsible for physiologic production of prostanoids:
Gastric cytoprotection, vascular homeostasis, platelet aggregation, and reproductive and kidney functions.

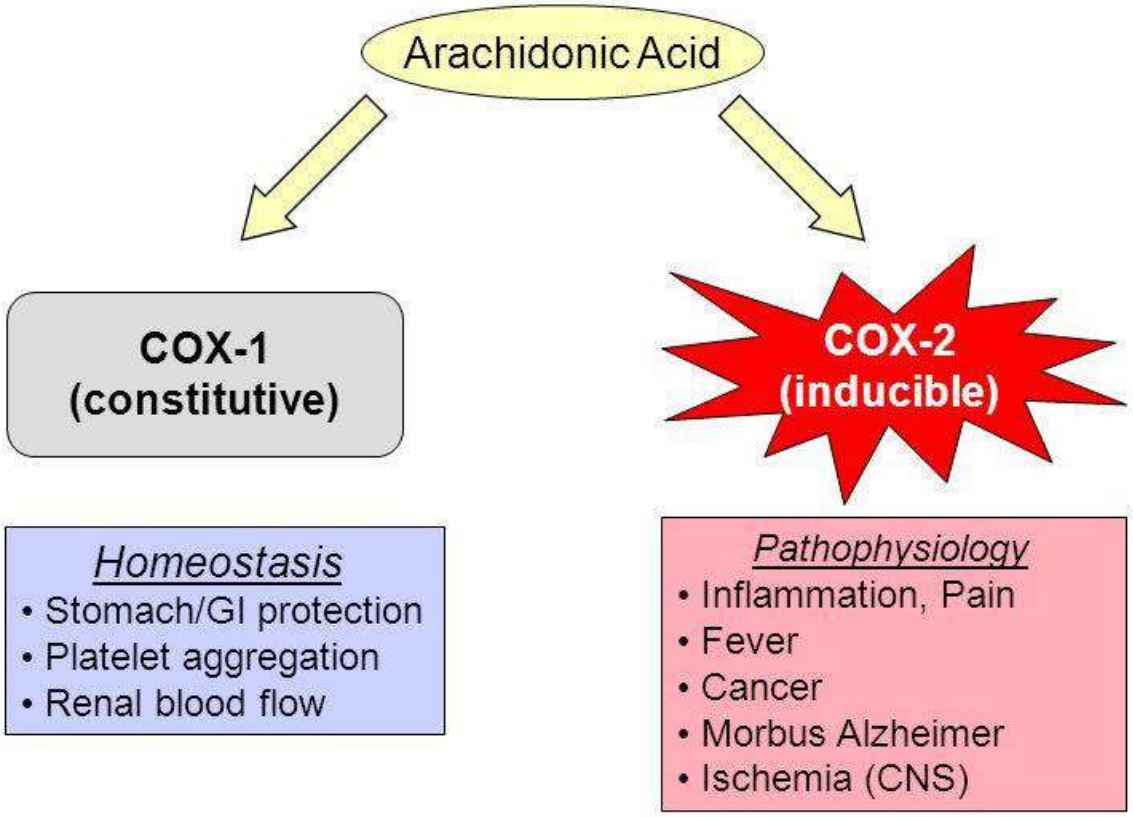
Cyclooxygenase-2 (COX-2)

Constitutive in tissues [brain, kidney, and bone]

Inducible during states of chronic inflammation

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

COXIII may represent a primary central mechanism by which acetaminophen is analgesic/antipyretic and little anti-inflammatory effect



Lipooxygenase pathway results in the production of leukotriene from arachidonic acid.

TABLE 31.2 Pharmacologic Properties of Prostaglandins, Thromboxane, and Prostacyclin

	PGE_2	$PGF_{2\alpha}$	PGI_2	TXA_2
Uterus	Oxytocic dilation	Oxytocic constriction		
Bronchi	Dilates	Constricts		Constricts
Platelets			Inhibits	Aggregation
Blood vessels	Dilation	Constriction	Dilation	Constriction

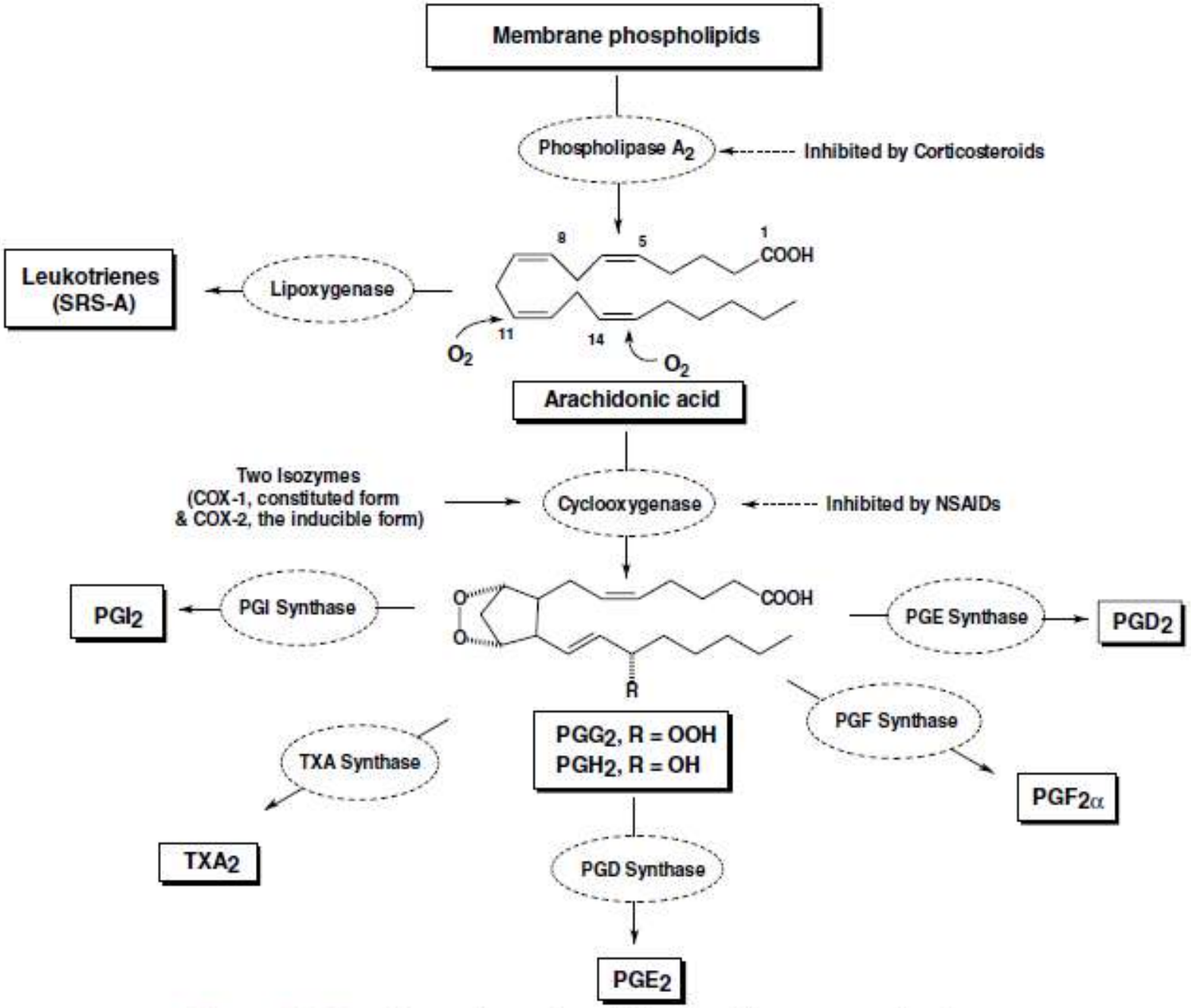
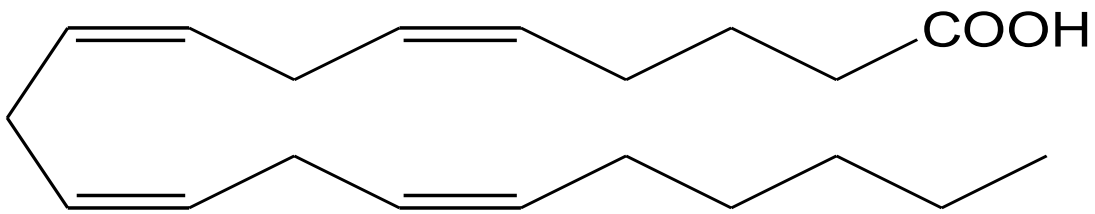
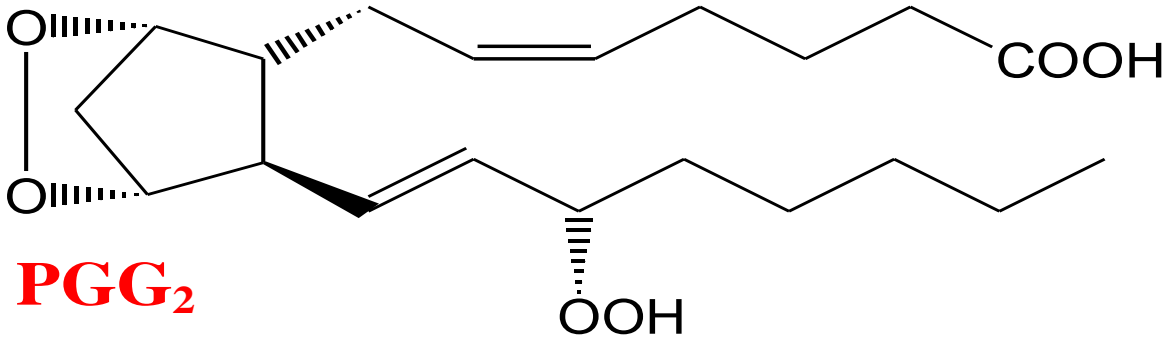


Figure 24.14 • Conversion of arachidonic acid to prostaglandins.



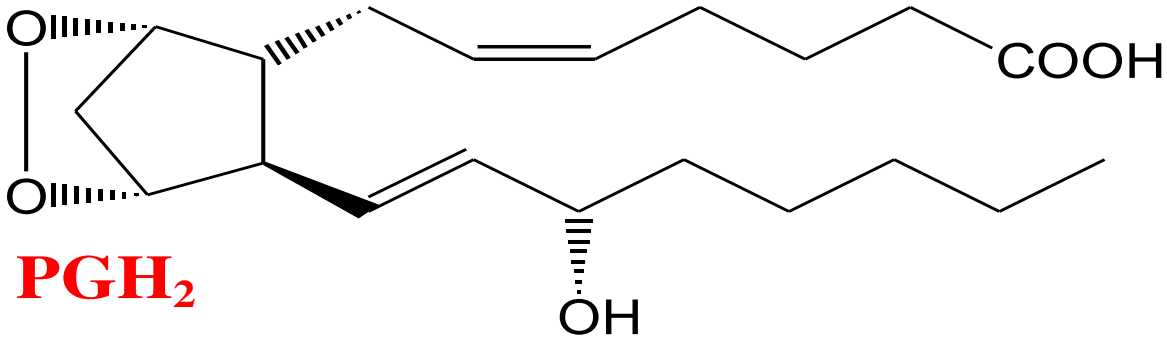
arachidonic acid

$2\ O_2$ ↓ Cyclooxygenase



PGG_2

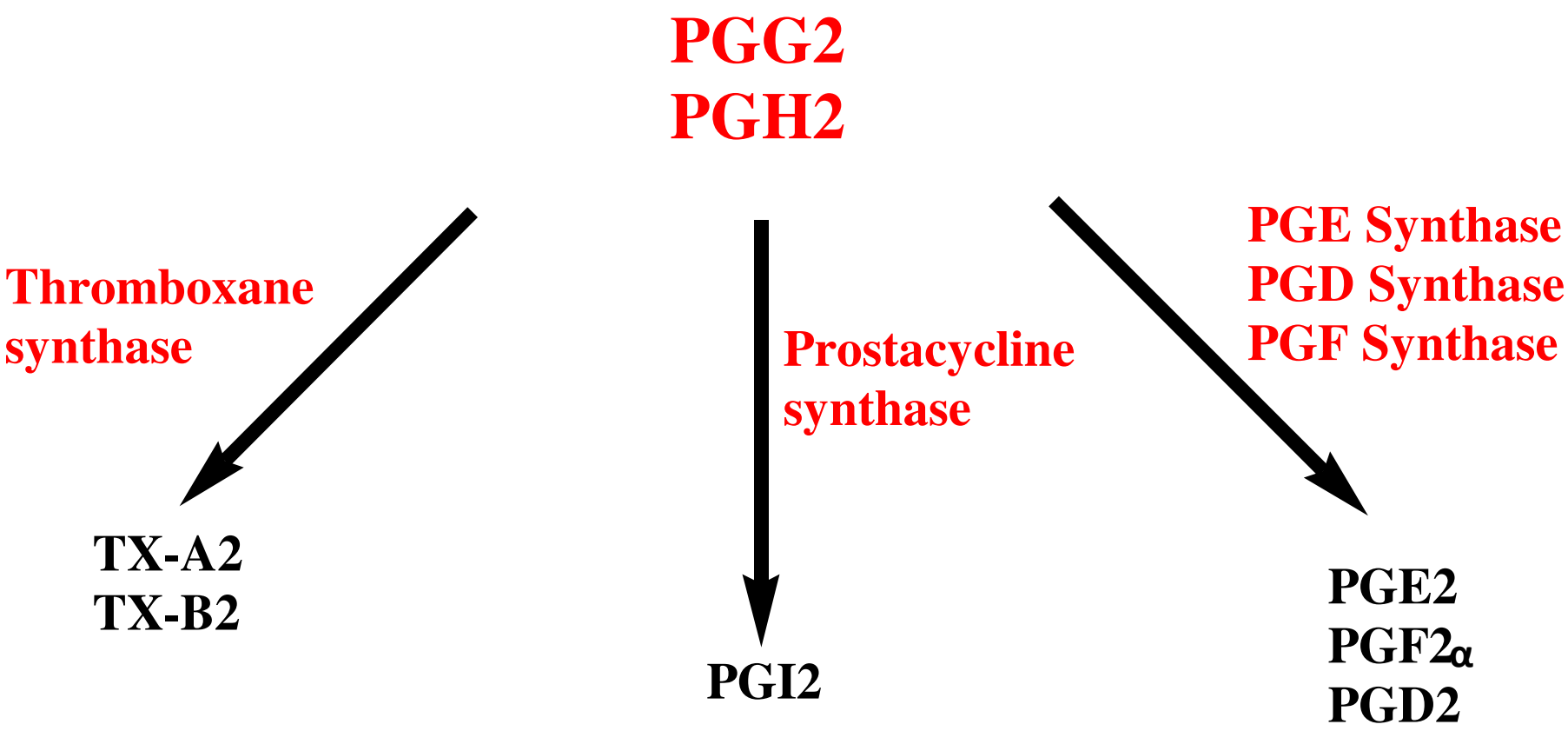
$2\ e^-$ ↓ Peroxidase



PGH_2

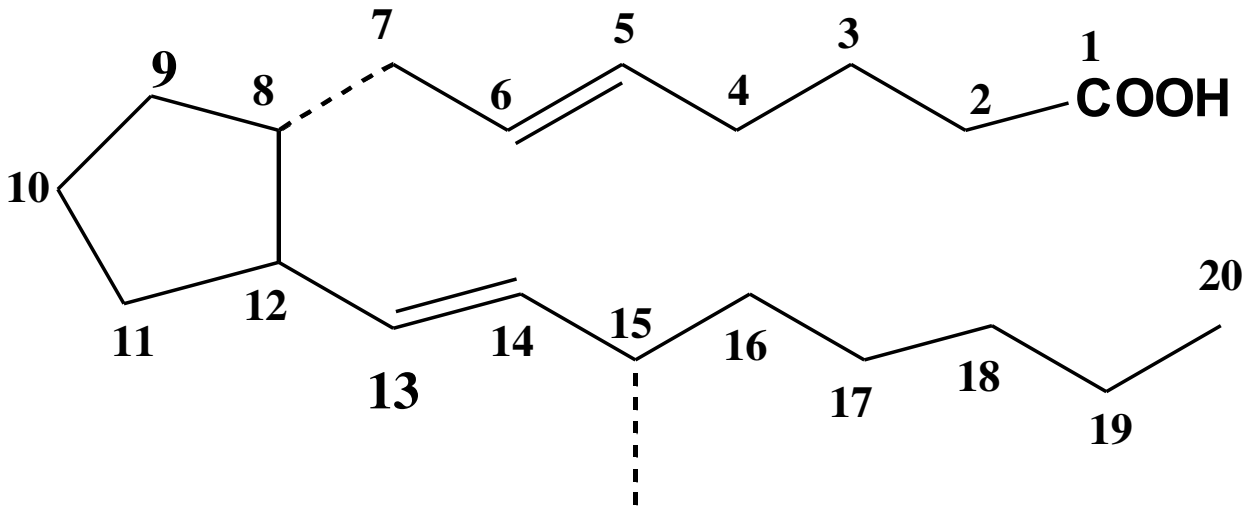
Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Introduction:



Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

Introduction:



General Structure of Prostaglandins

Non-Steroidal Anti-Inflammatory Drugs (NSAIDs)

COX:

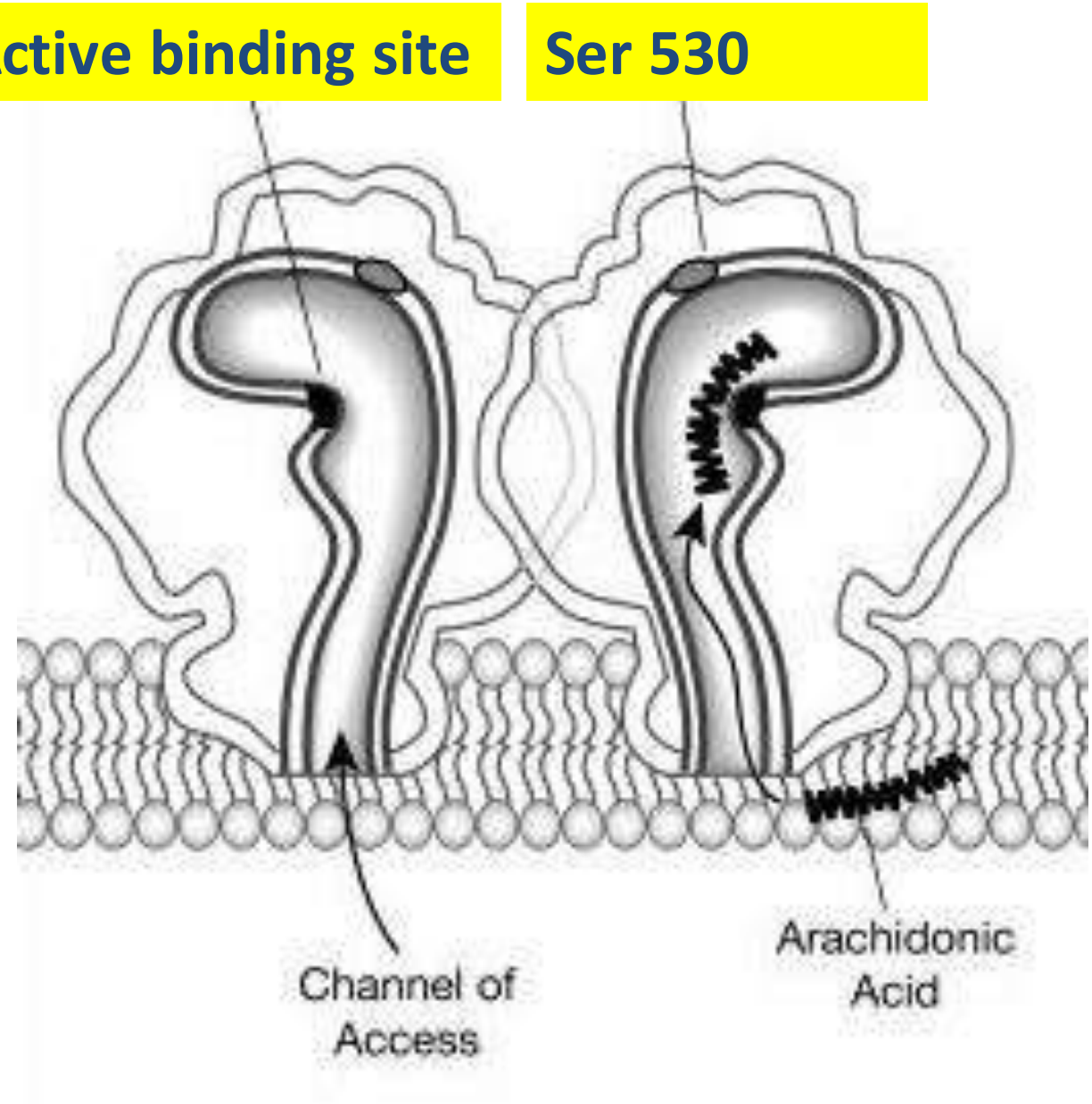
Structure isoform is almost identical 599 aa for COX-1 vs 604 aa for COX-2 with 60 % homology

COX enzymes are heme containing membrane proteins that exist as dimers

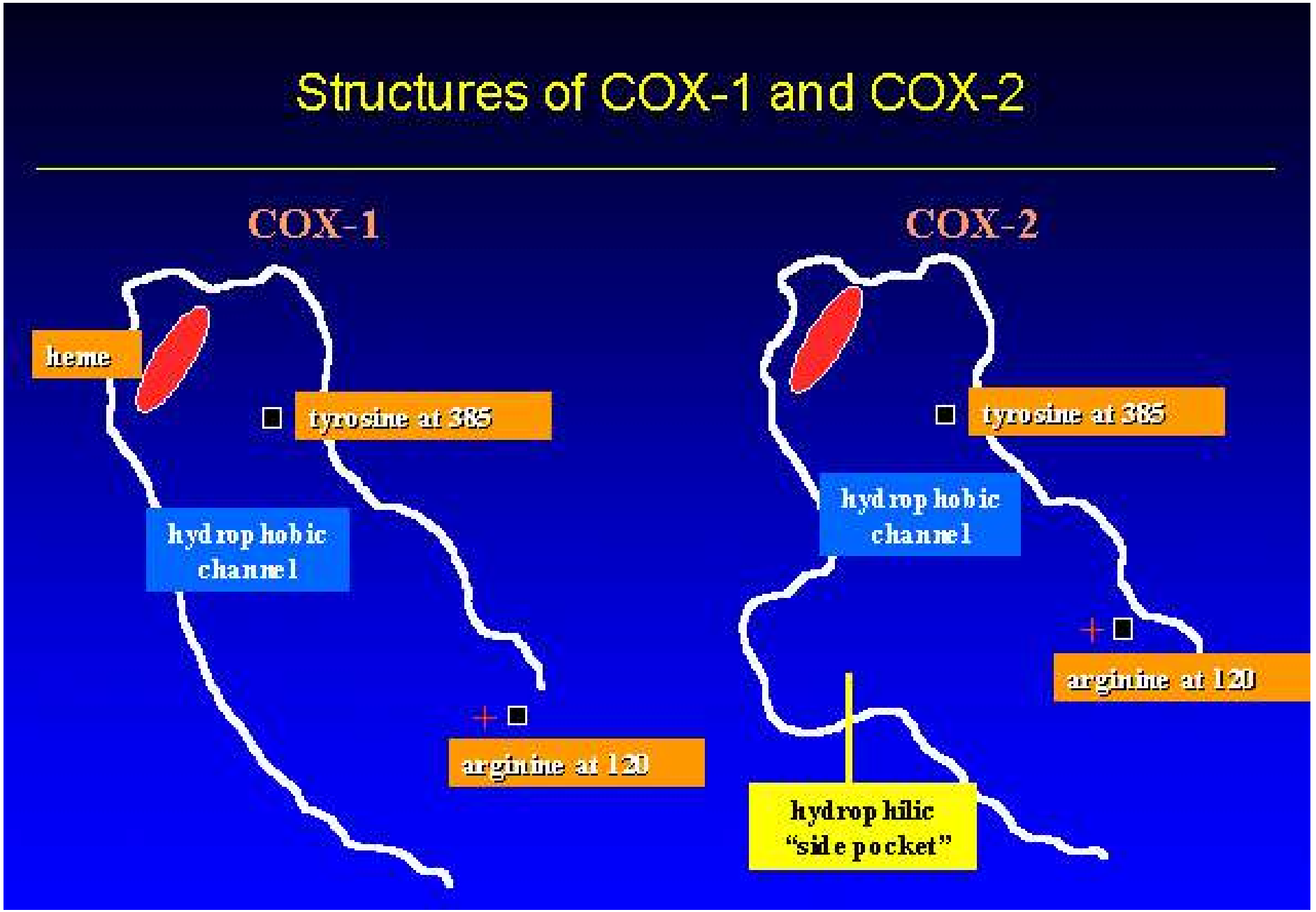
A little difference in binding site size and shape

Development of selective COX-2 inhibitors **by using additional hydrophilic side pocket**

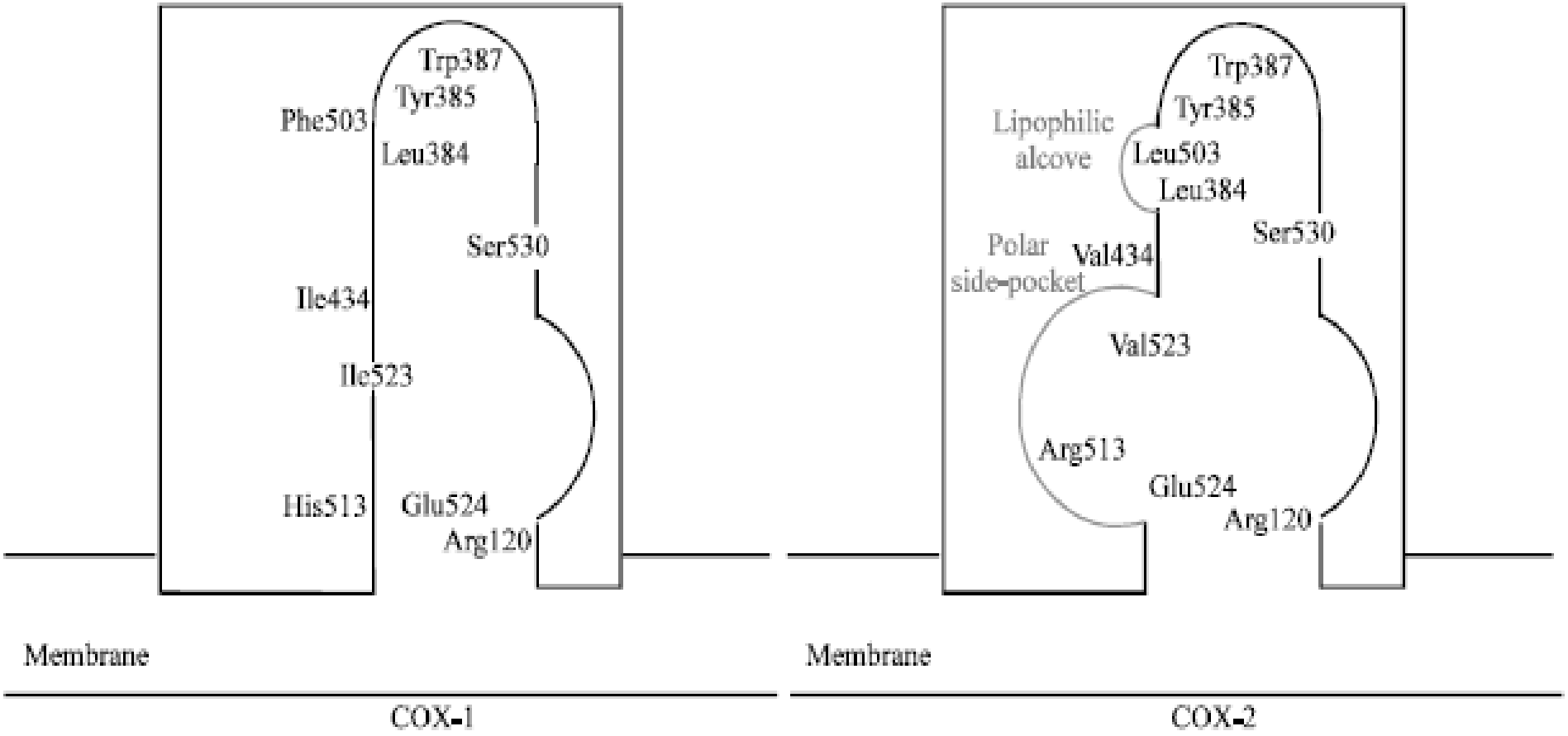
COX-I


Active binding site
Ser 530
Channel of Access
Arachidonic Acid

COX-Isoenzymes: Active binding site



COX-Isoenzymes: Active binding site



COX-Isoenzymes: Active binding site

The main difference between the two COX active sites:

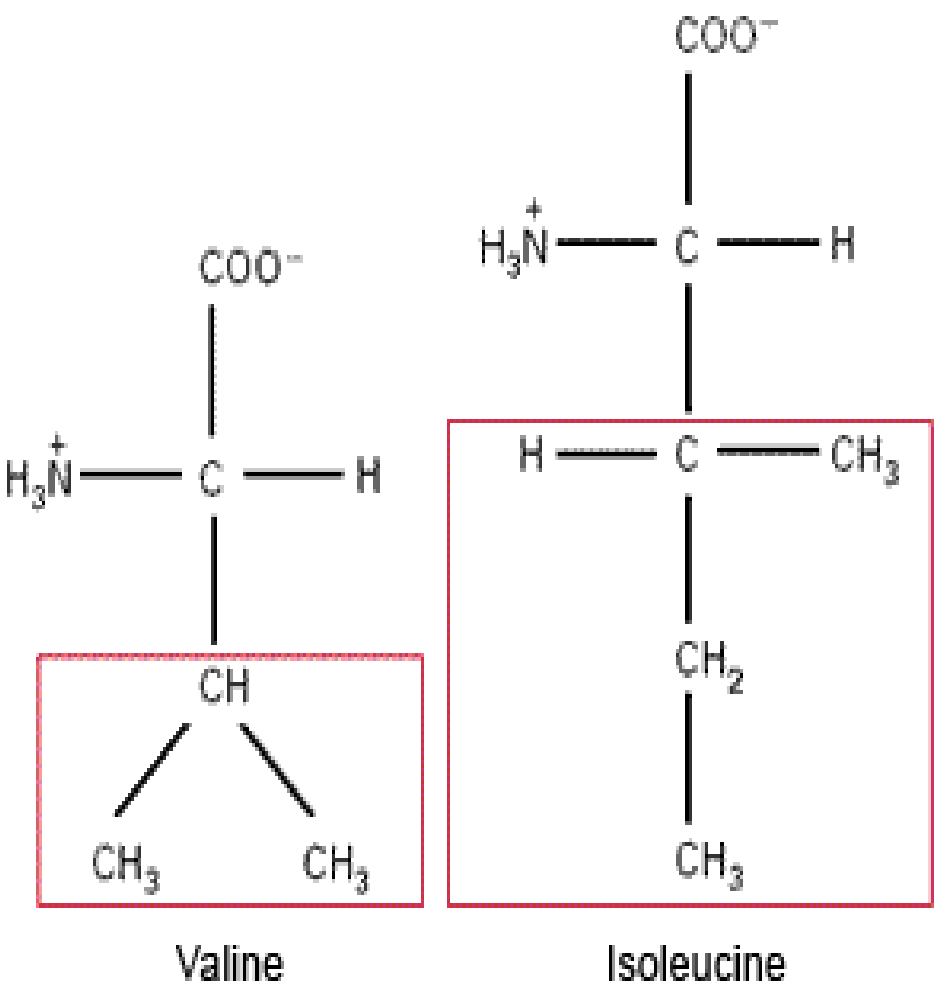
- Active site for COX- 2: 20% larger than the COX-1 binding site

- The isoleucine **(Ile)** at positions **434 and 523** in COX-1 is exchanged for valine **(Val)** in COX-2.

The smaller size of Val-523 in COX-2 allows inhibitor access to a side pocket off the main substrate channel, whereas the longer side chain of Ile in COX-1 sterically blocks inhibitor access

COX-Isoenzymes: Active binding site

The main difference between the two COX active sites:



COX-Isoenzymes: Active binding site

The main difference between the two COX active sites:

- In the apex of the COX-2 binding site, substitution of **Phe 503** in COX-1 by **Leu 503** generates a small hydrophobic alcove [Leu 384, Tyr 385 and Trp 387]

- COX-2 isozyme has an additional **hydrophilic side pocket** accessible for drug binding, extended from the main binding pocket

COX-Isoenzymes: Active binding site

❑ Substitutions **His-513** in COX-1 with a more basic Arg-513 in COX-2.
[**Determinant for the size and nature of hydrophilic side pocket]**

❑ This additional **Arg 513 in COX-2** is responsible for further ionic interaction with celecoxib

❑ COX-1 more specific [metabolize Arachidonic acid]
COX-2 accepts a wider range of fatty acid substrates [C18 and C20]

COX-Isoenzymes: Active binding site

In both Isoenzymes:

Arg 120:

Only positively charged amino acid residue in the COX active site, on one end of the active

Responsible for binding, via an ionic interaction, with the carboxylate anion of the substrate **(arachidonic acid)** and of NSAIDs

Tyr-385:

serve as the catalytic residue for activating O2 and addition to the 11-double bond of the substrate to form PGG2

Ser-530:

Irreversible inactivation by aspirin and NSAID action but not contributing to any substrate binding

Classes of NSAIDs: Analgesic, Antiinflammatory

Salicylate: Aspirin, Diflunisal, Salicylamide

Aryl and heteroarylacetic acid: Indomethacin, Diclofenac, Etodolac, Sulindac, Tolmetin, Nabumetone

Aryl and heteroarylpropioic acid: Ibuprofen, Ketoprofen, Fenoprofen, Naproxen, flurbiprofen, oxaprozin

N-Arylanthranilic acid [Fenamic acid]: Mefenamic acid, Meclofenamate

Oxicam: Piroxicam, meloxicam

Selective COX-2 Inhibitor: Celecoxib, Rofecoxib, lumiracoxib, valdecoxib

Non-Steroidal Anti-inflammatory Drugs NSAIDs

Part 2

Dr. Mai Ramadan

NSAIDs
Antipyretic/ Analgesic
p-Aminophenol derivative

Classes of NSAIDs: Analgesic, Antipyretic

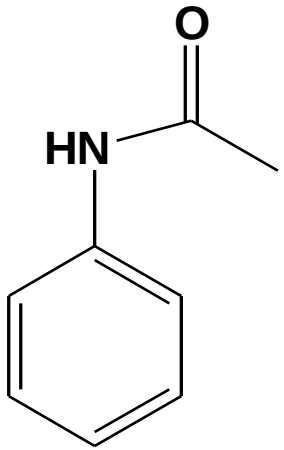
Anilide [p-Aminophenol derivatives]

Acetanilide was too toxic causes jaundice

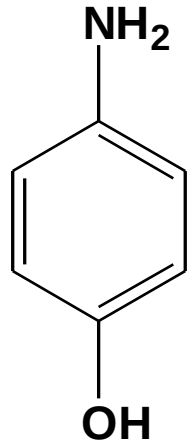
Phenacetin was withdrawn nephrotoxicity.

P-Aminophenol is too toxic to be used therapeutically

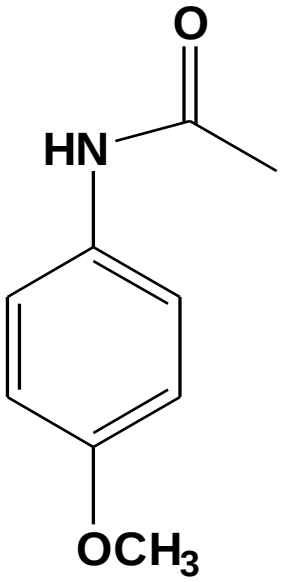
Acetaminophen is still used



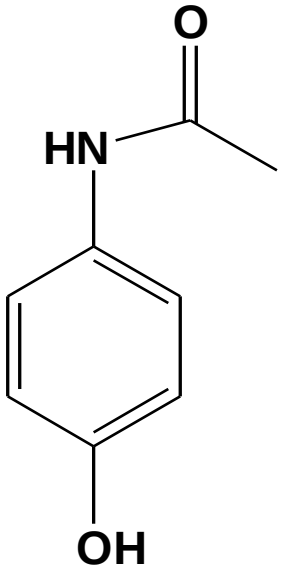
Acetanilide



p-Aminophenol



Phenacetin



Acetaminophen

Classes of NSAIDs: Analgesic, Antipyretic

Anilide [p-Aminophenol derivatives]

SAR:

Etherification of the phenolic functional groups with methyl or propyl groups produce derivatives with greater side effects than the ethyl derivative.

Substituents on the Nitrogen atom, which reduce the basicity, also reduce activity unless the substituent is metabolically labile e.g., acetyl.

Amides derived from **aromatic acid** e.g. Benzanilide are less active or even inactive

Anilide [p-Aminophenol derivatives]

Acetaminophen [Paracetamol]

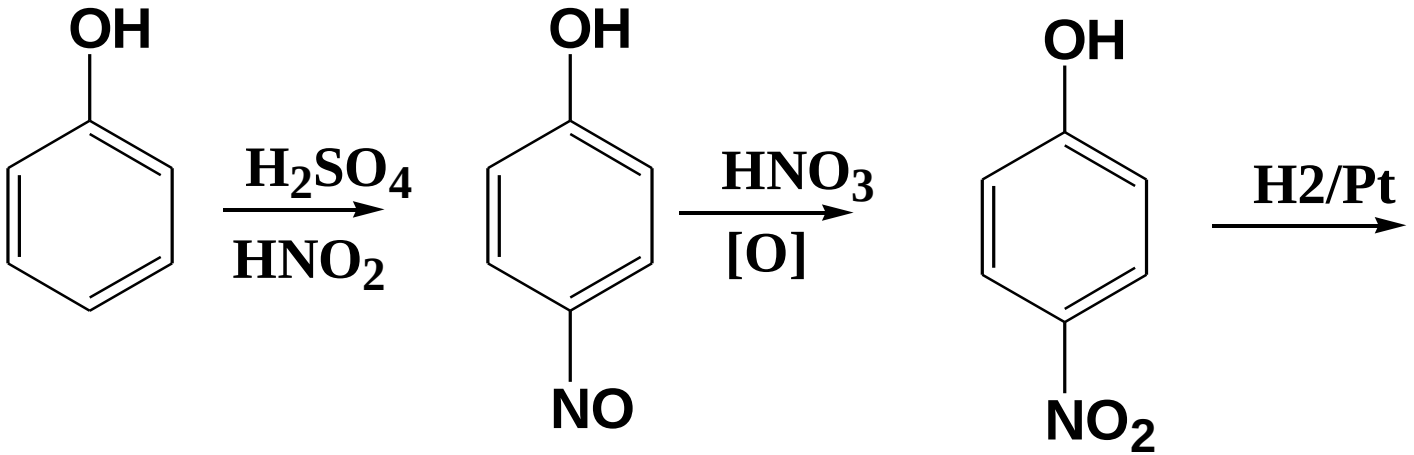
Weak inhibitor of COX1 and COX2 [NO anti-inflammatory effect, NO effect on platelet aggregation, and GIT]

Evidence of inhibition of COX3 in CNS

Analgesic antipyretic

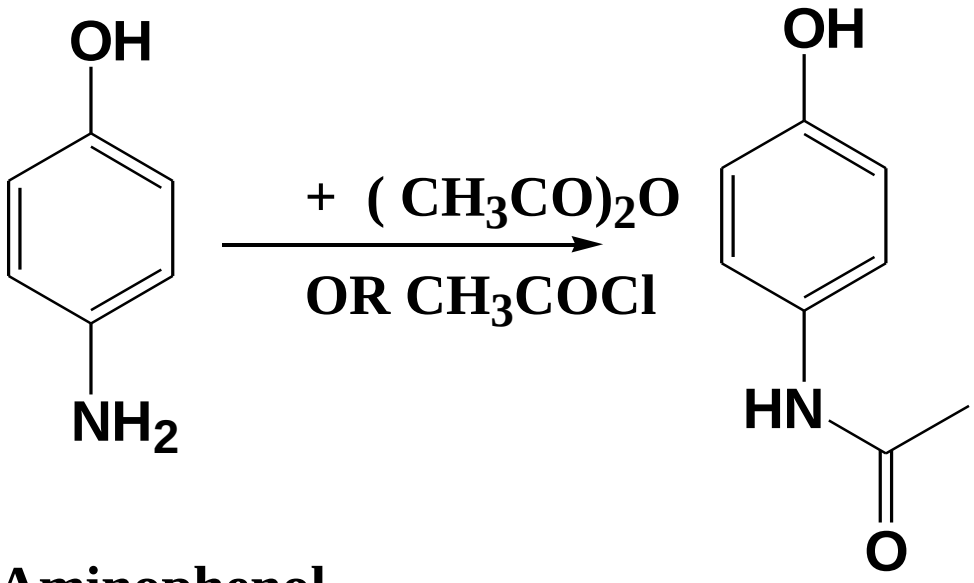
Anilide [p-Aminophenol derivatives]

Synthesis:



4-Nitrosophenol

4-Nitrophenol



p-Aminophenol

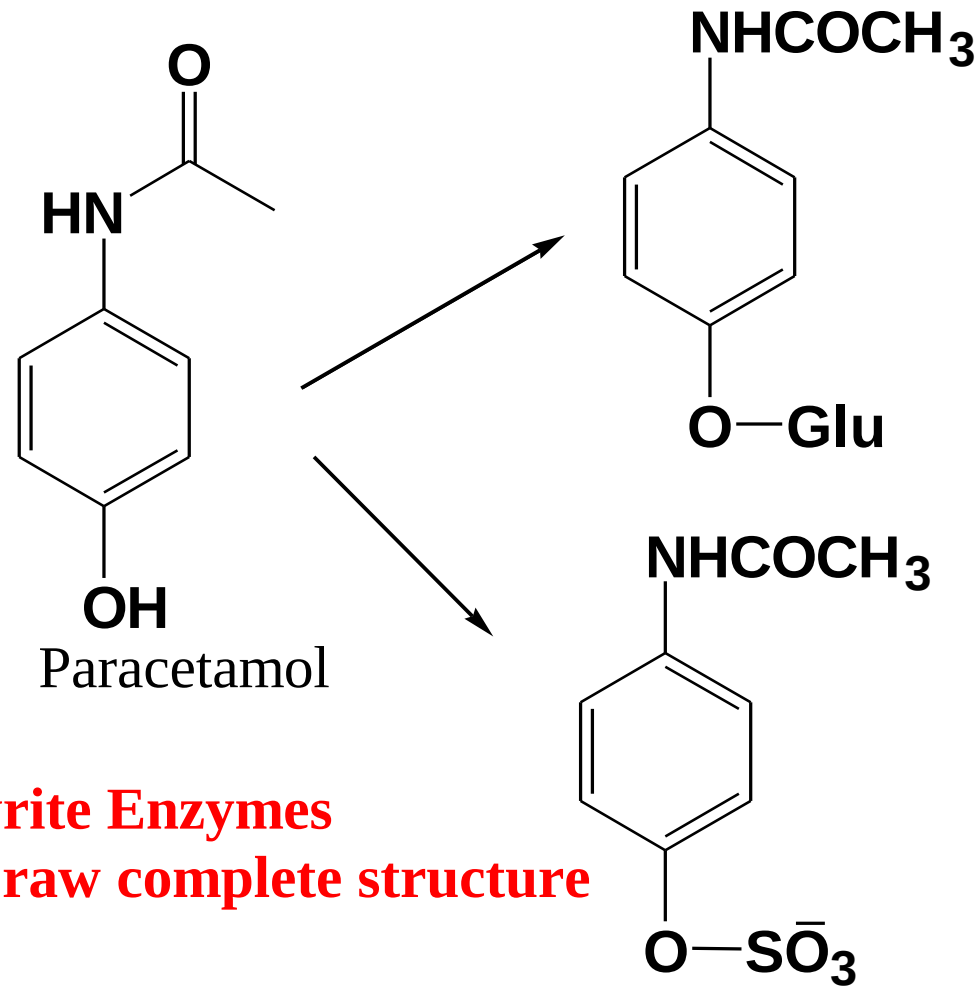
Acetaminophen

Anilide [p-Aminophenol derivatives]

Biotransformation and toxicity of paracetamol

Conjugation with Glucoronic acid and sulfate at phenolic OH

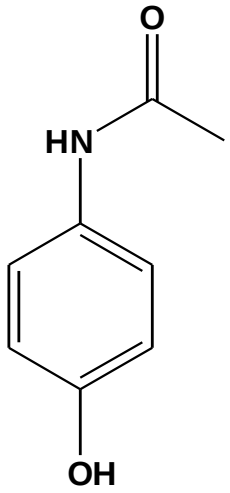
Produce O-Glucuronide and O-sulfate conjugate [**Major metabolite]**



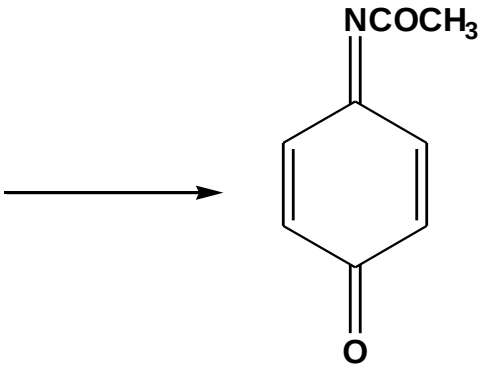
Paracetamol

write Enzymes
Draw complete structure

Biotransformation and toxicity of paracetamol



Paracetamol

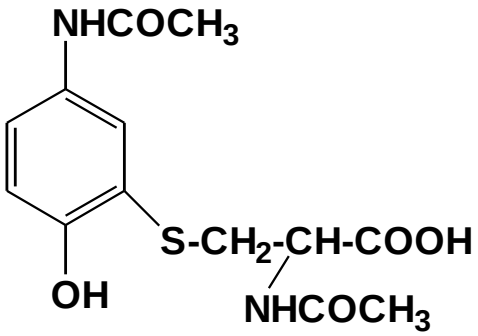


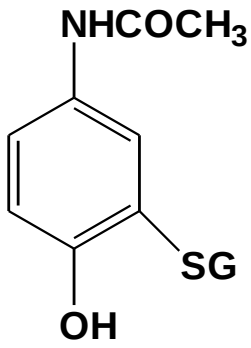
N-Acetyliminoquinone
Toxic metabolite

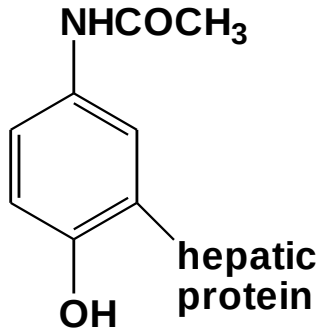
N-Acetylcysteine
is Antidote

Glutathione
GSH: Nucleophile

Hepatic proteins







Renal excretion
as mercapturic acid or
cysteine conjugate

liver necrosis

NSAIDs
Analgesic/ Anti-inflammatory
Salicylate derivative

Classes of NSAIDs: Analgesic, Anti-inflammatory

Salicylate: Aspirin, Diflunisal, Salicylamide

Aryl and heteroarylacetic acid: Indomethacin, Diclofenac, Etodolac, Sulindac, Tolmetin, Nabumetone

Aryl and heteroarylpropioic acid: Ibuprofen, Ketoprofen, Fenoprofen, Naproxen, flurbiprofen, oxaprozin

N-Arylanthranilic acid [Fenamic acid]: Mefenamic acid, Meclofenamate

Oxicam: Piroxicam, meloxicam

Selective COX-2 Inhibitor: Celecoxib, Rofecoxib, lumiracoxib, valdecoxib

Salicylate: Development

B.C. 5 Century, Chewing willow bark can relief pain

1838, Salicylic acid firstly isolated

1860, Kolbe firstly synthesized salicylic acid

1875, sodium salicylate clinically used as antipyretic analgesic

1886, phenol salicylate went on the market

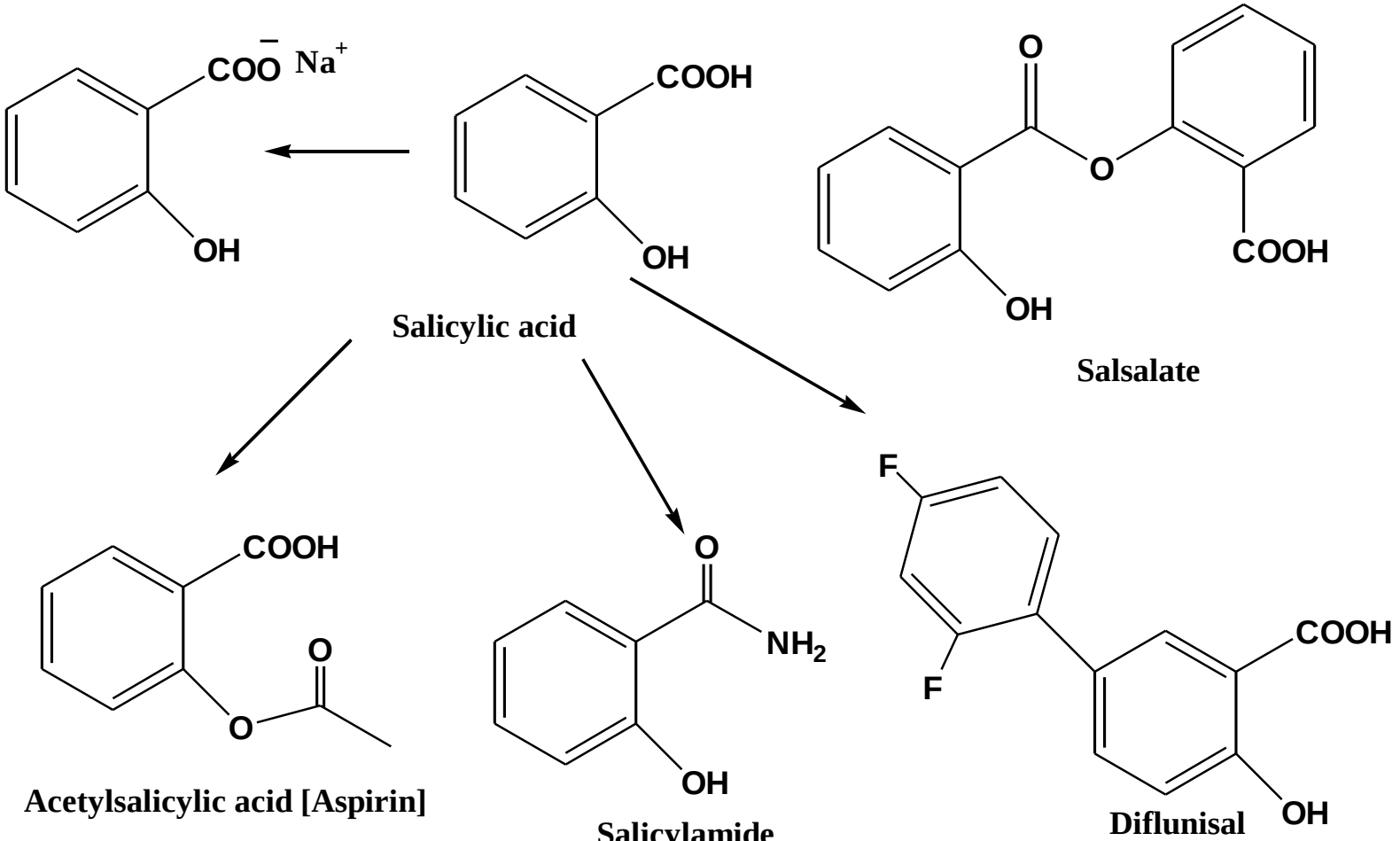
1899, aspirin introduced into medicine although it's first prepared in 1853

Salicylate: Development

The term “aspirin” was given to acetylsalicylic acid by Dreser, the director of pharmacology at Frederich Bayer and Company in Germany, as a contraction of the letter “**a**” from **acetyl** and “ **spirin,**” an older name given to **salicylic acid (spiric acid)** that was derived from a natural source in spirea plants.

Salicylate

Derivatives of salicylic acid: 2-Hydroxybenzoic acid



Analgesic
Antipyretic
Antiinflammatory

analgesic
No anti inflammatory

increased anti inflammatory

Salicylate

SAR of salicylic acid derivatives

Benzoic acid has mild anti inflammatory activity

2-hydroxybenzoic acid [Salicylic acid] is potent anti-inflammatory activity with mild analgesic and antipyretic activities

Placing OH in m- or p- position to carboxylic group abolishes this activity

Salicylate are mainly potent inhibitor of COX-1, responsible for GI-side effect

Reduce acidity of COOH [Salicylamide] maintain anlagesic but eliminate anti inflammatory activity

Substitution of halogen on aromatic ring increases potency and toxicity

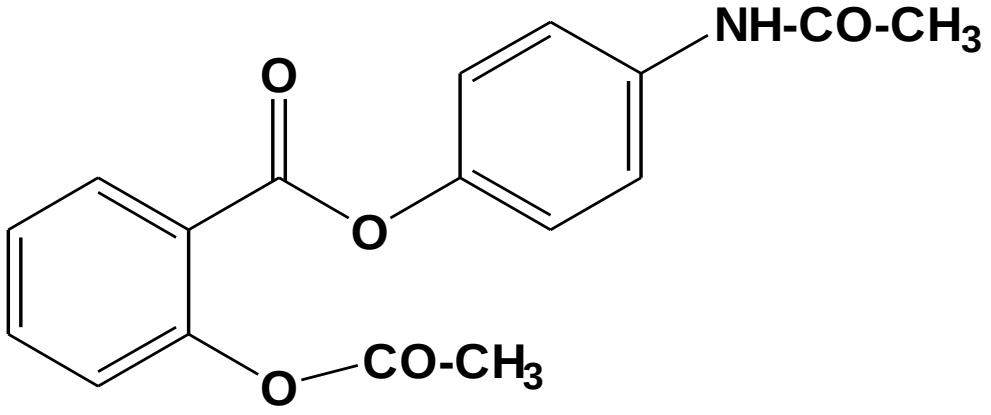
Salicylate

SAR of salicylic acid derivatives

Substitution on position 5 [diflurophenyl, lipophilic substituent]
Diflusinal increases anti inflammatory.

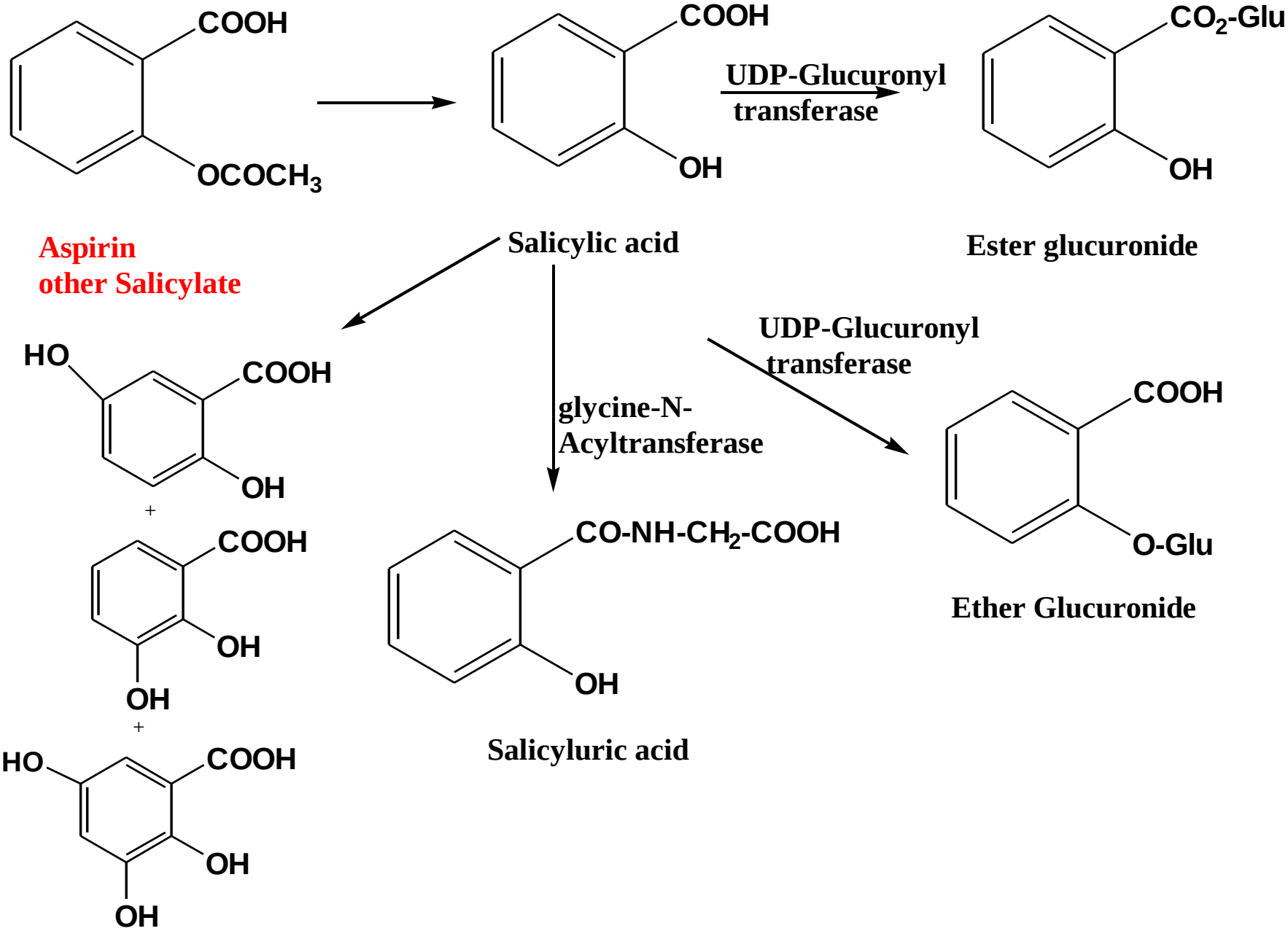
Methylation in position 3 remain analgesic activity, but metabolism is slower

Mutual prodrug of aspirin Benorylate: its action is more than paracetamol and aspirin

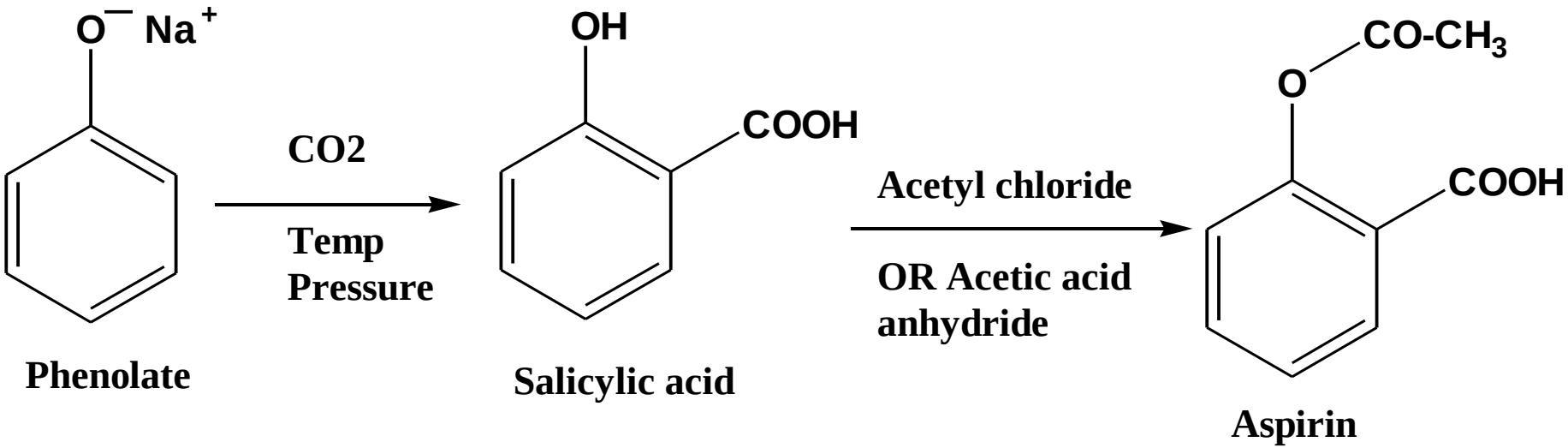


Benorylate

Salicylate Metabolism



Salicylate Synthesis



Phenolate

Salicylic acid

Aspirin

Salicylate

Salicylic acid:

Applied doses gastric irritation and ulceration.

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

Sodium salicylate:

Freely soluble in water
Rapid dissolution and faster absorption.
Only half as potent as an analgesic/antipyretic as Aspirin
Less GI irritation.
Stable, aqueous formulation is available

Salicylate

Magnesium salicylate:

Stable aqueous solution and show some success in overcoming the GI problems

Salsalate

Diester of salicylic acid, prodrug

Salsalate is insoluble in gastric pH but soluble in the small intestines, thus causing less gastric problems.

Further, it is useful in hypersensitivity to Aspirin.
Hypersensitivity to ASA is a result of acetylated plasma proteins.

Benorylate is Aspirin is esterified with Acetaminophen

Salicylate

Aspirin: Acetylsalicylic acid [ASA]

Searching for a less toxic better tolerated derivative of salicylic acid produced aspirin [pka 3.5].

It is slightly soluble in water, **absorbed as such partially from stomach**, but is hydrolyzed rapidly to salicylate and acetate by esterases

Pharmacological actions are attributed to both the aspirin and salicylic acid

Aspirin irreversibly inhibits the enzyme acetylating a serine residue

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

Salicylate

Salicylamide:

Carboxylic group is changed to non acidic amide [pka 8.6]
Stable in aqueous preparations and does not cause GI tract ulceration
Absorbed only in intestine.
Effective as Aspirin: analgesic/antipyretic but loss anti-inflammatory actions.

Diflunisal:

Diflunisal is absorbed only in intestine
Not soluble in gastric fluid.
Gastric bleeding and GI upset is not as common.
Longer duration of action than aspirin.
The potency is increased

ASPIRIN AND ITS COX-1 SELECTIVITY

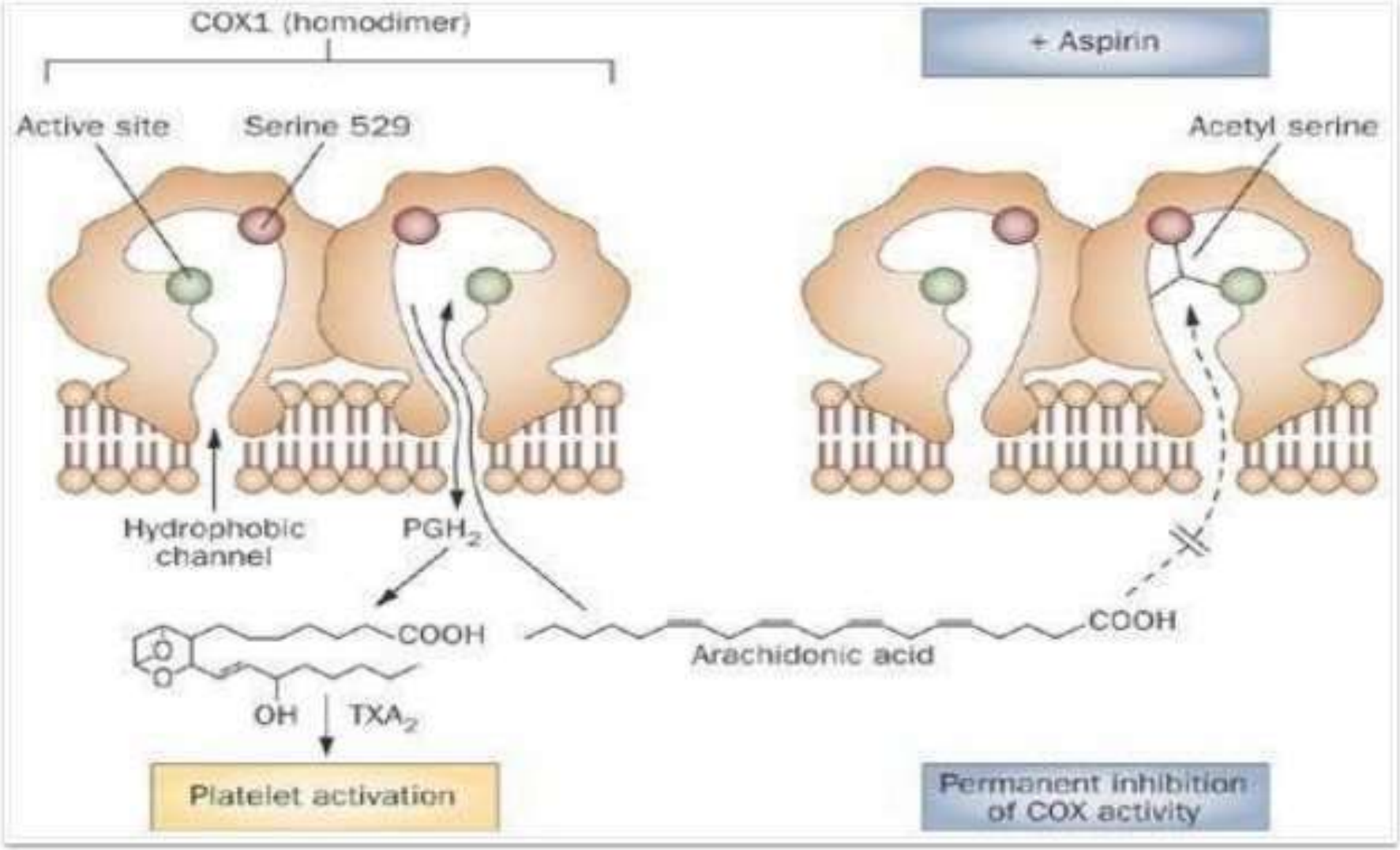
Aspirin **covalently binds** by acetylating the OH group of Ser-530 in COX-1 and COX-2.[**Irreversible inhibition**]

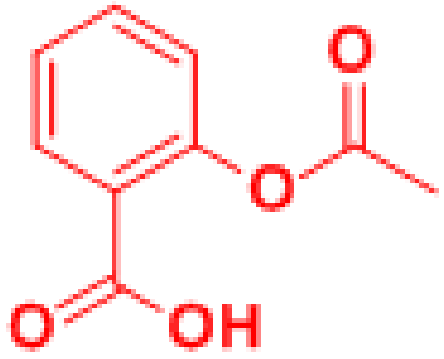
Ionic attraction between the carboxylate anion of aspirin and the cationic Arg-120 thereby positioning the acetyl group of aspirin for acetylating the COX isozymes.

Acetylation of COX-1 Ser residue totally blocks the accessibility of substrate AA from entering into the active site, whereas an acetylated COX-2 is still able to form a significant amount of PGG2.

Aspirin is a highly selective COX-1 Inhibitor [10-100 folds more potent against COX-1 more than COX-2] esp. in platelets.

Mechanism of action of Aspirin:-

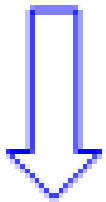


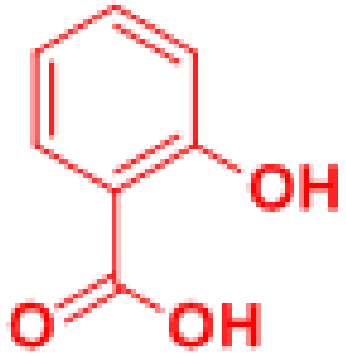


+ Enzyme-Ser-CH_2-OH

Aspirin

Active site of COX





+ Enzyme-Ser-CH_2-O-C(=O)-CH_3

Salicylic acid

Non-Steroidal Anti-inflammatory Drugs NSAIDs

Part 3

Dr. Mai Ramadan

COX 1 versus COX 2

Function (physiological and pathological roles) and activity

Active site aspects:
Substrate and shape
Differences and similarities in aa residues and their significance

Antipyretic/ Analgesic

Anilide (p-Aminophenol derivative)

Paracetamol (Structure, metabolism, toxicity, synthesis)

Antipyretic/ Anti-inflammatory

Salicylate

Sod salicylate, Diflusinal, salicylamide

Aspirin (Structure, metabolism, synthesis, mutual prodrugs, irreversible inhibition of COX1 in platelets)

Antipyretic/ Anti-inflammatory

Aryl- & heteroaryl acetic acid

Indomethacin (Structure)

Sulindac (Structure)

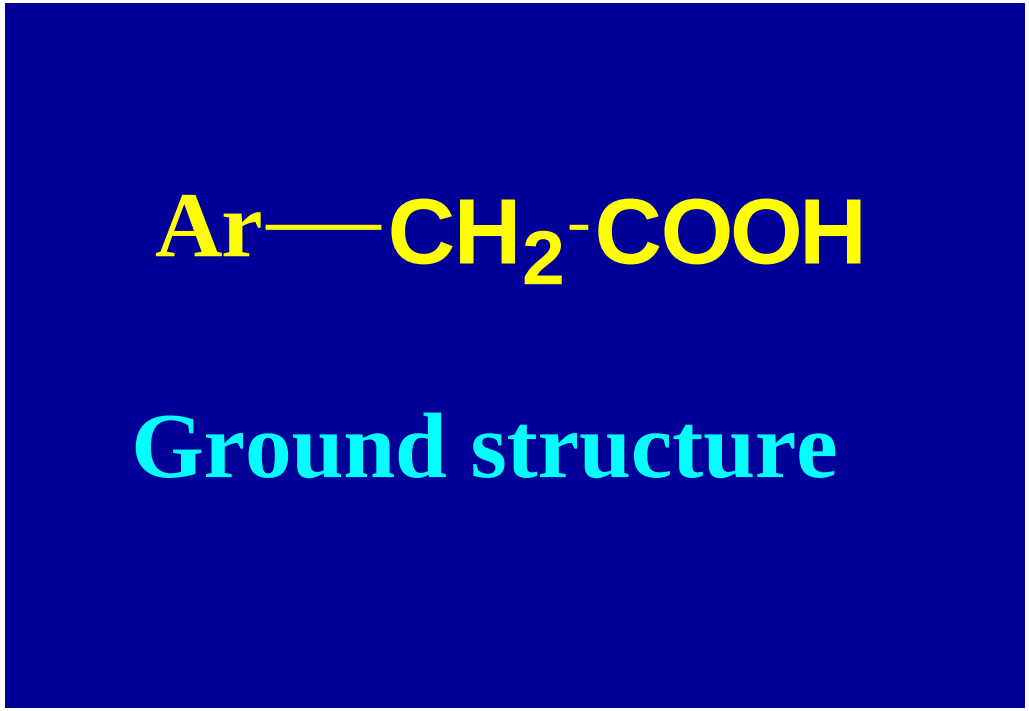
Tolmetin & zomepirac

Nabumetone

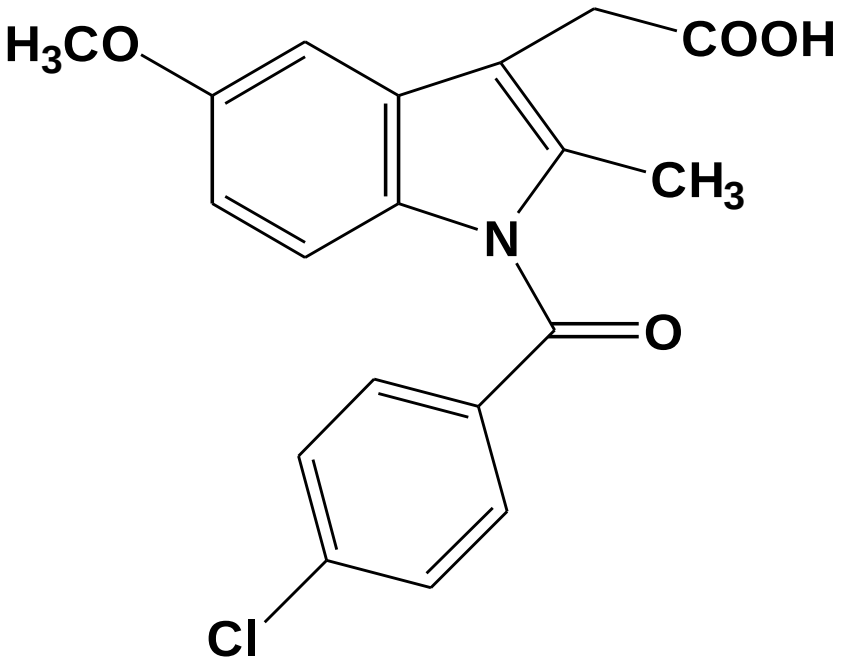
Diclofenac & lumiracoxib (Structure)

Etodolac

Aryl- & heteroaryl acetic acid

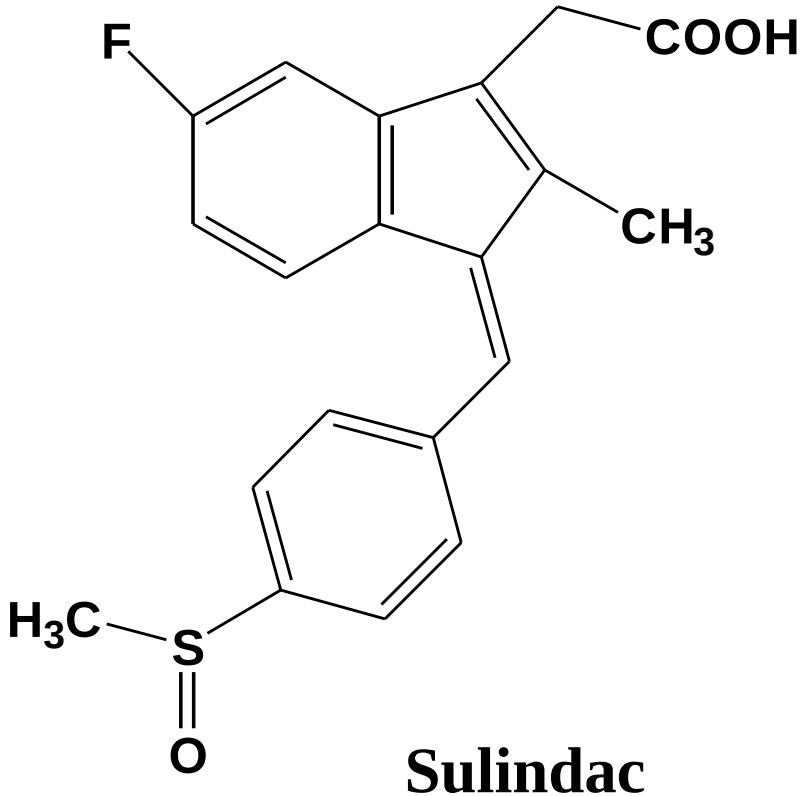


Aryl- Heteroarylacetic acid



Indomethacin

Indole ring



Sulindac

Indene
Isoster: anlgesic antiinflammatory
less CNS, GI irritation
longer duration
F: lipophilic
prodrug metabolite has long duration

Aryl- Heteroarylacetic acid

Indomethacin

A potent antipyretic more than acetaminophen and aspirin

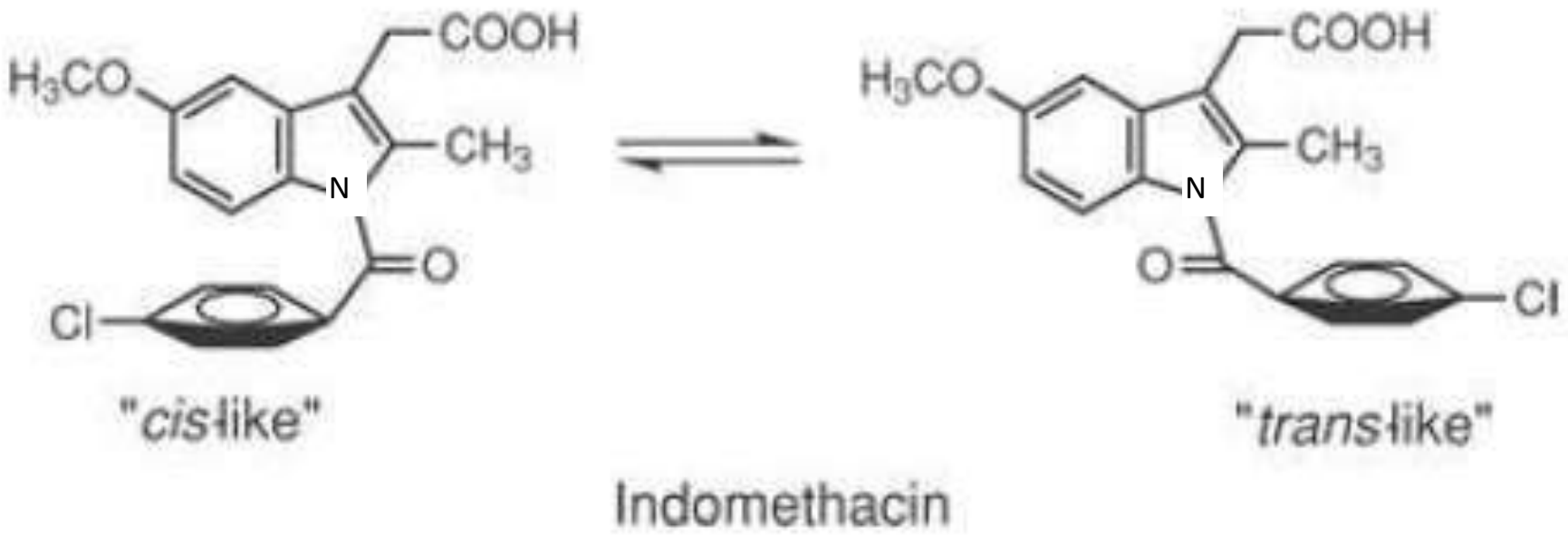
It is 10 folds more potent analgesic than aspirin

No aqueous solution [Instable like aspirin-----hydrolysis]

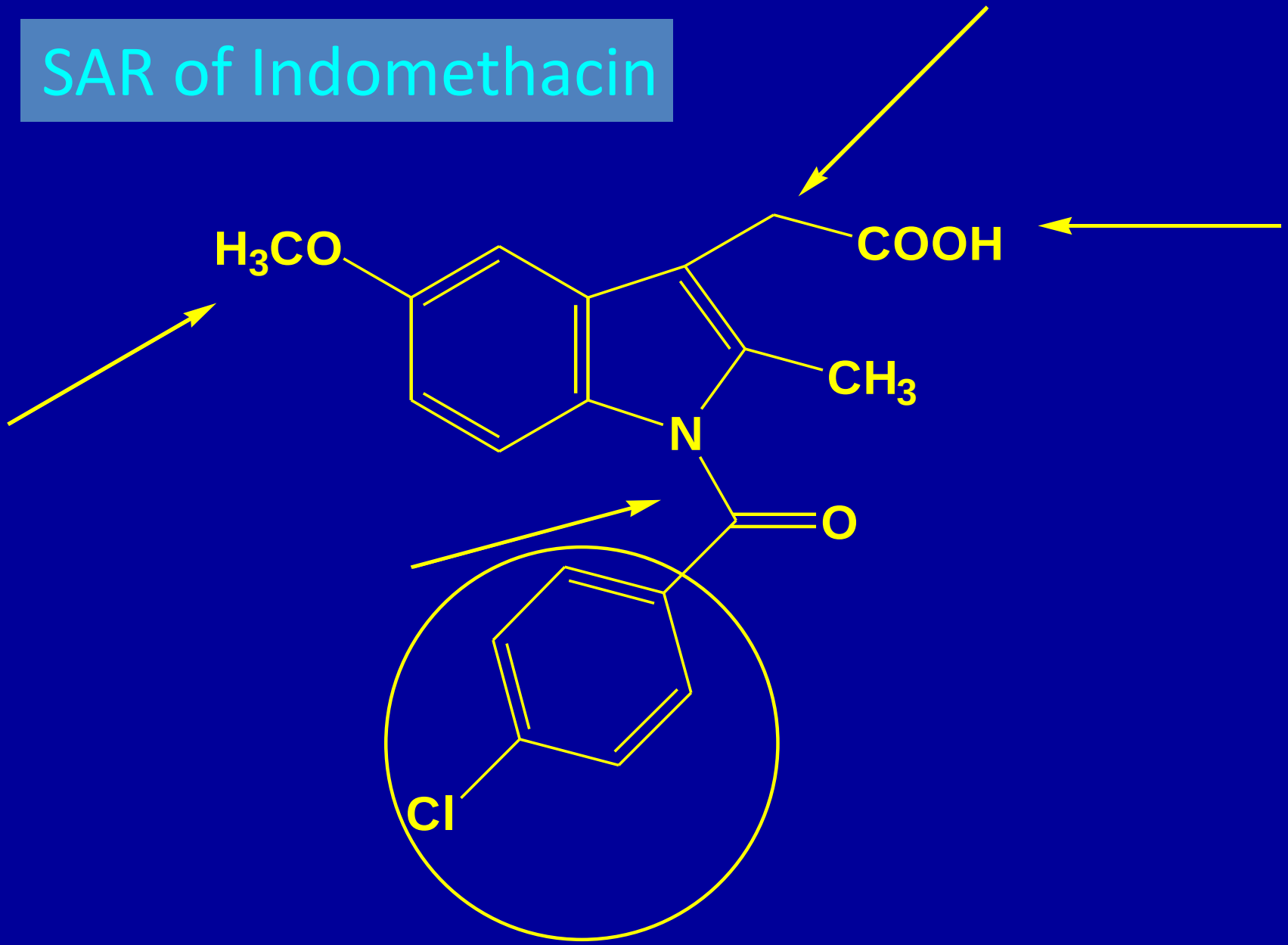
Side effect:
CNS side effect due to indole ring
GI irritation

Indole ring and phenyl are separated by one carbon (amide, partially double bond character, restricted rotation) and two sigma bonds.
Both rings **are not coplananar**

Aryl- Heteroarylacetic acid



SAR of Indomethacin



Aryl- Heteroarylacetic acid

SAR: Indomethain

❖ Molecule must have an ionizable acid group and an aromatic ring system. Amide analog are inactive

❖ Acylation of nitrogen in indole with p-chlorobenzoic acid is optimal

❖Acylation with aliphatic carboxylic acid and aralkylcarboxylic acid are less active

❖Substituents at position 5 of indole increases activity [methoxy fluoro, methyl, acetyl ,---]

❖Addition of methyl at α position to COOH produces active compound.

Aryl- Heteroarylacetic acid

SAR: Indomethacin

❖ Methyl at α position to COOH produced chiral center. **S(+) isomer** is only potent anti-inflammatory.

❖Indole nitrogen is not essential [Sulindac]

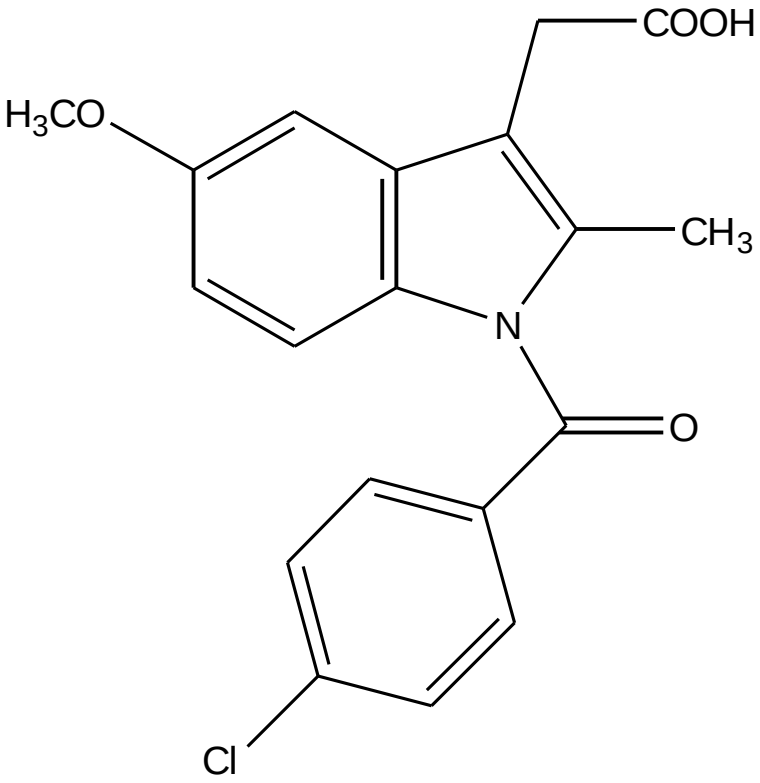
❖A second non coplanar aromatic ring increases potency.
P- chlorobenzoyl is not coplanar with indole due to 2-methyl and 7-hydrogen thus steric hindrance.

❖ Acetic acid side chain has different conformation

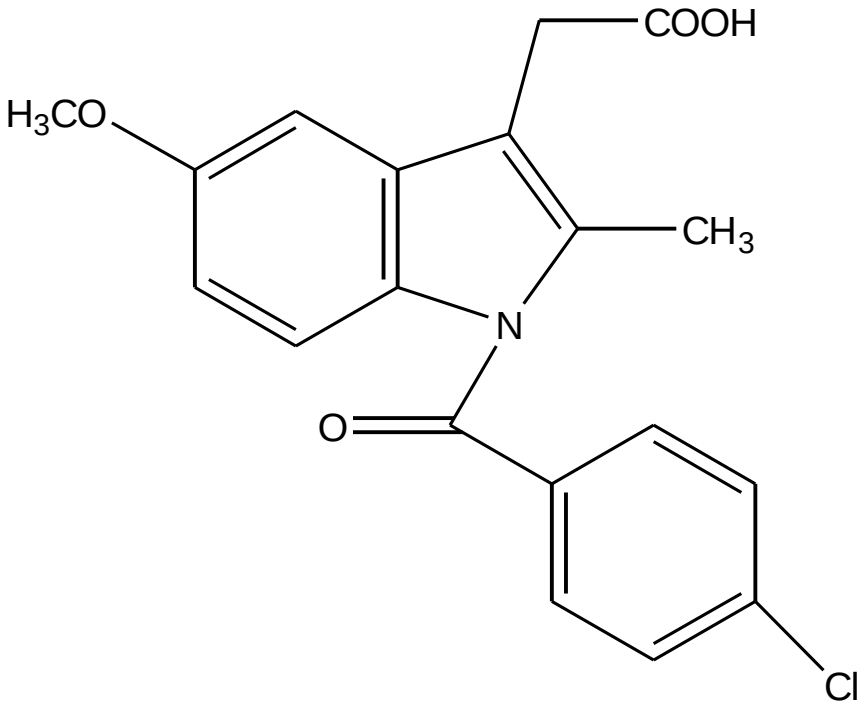
❖ A preferred conformation when p-chlorobenzoyl is directed away from acetic side chain (cis-like) conform

Aryl- Heteroarylacetic acid

Indomethacin

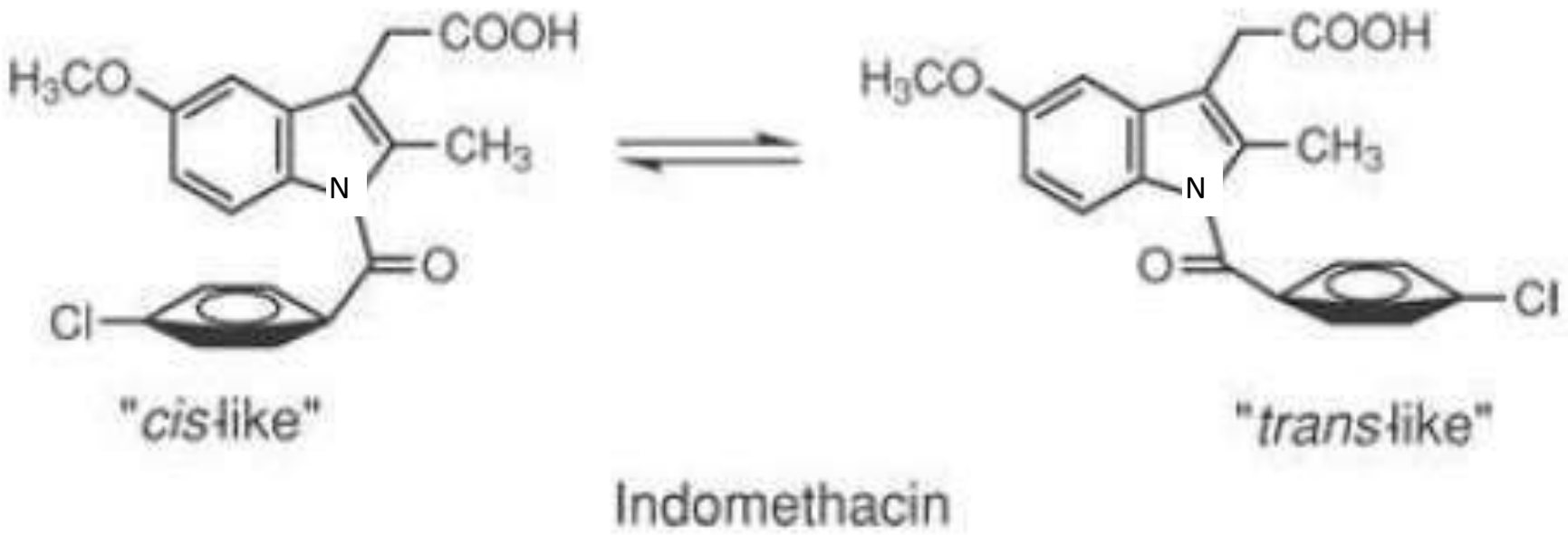


Z-like isomer

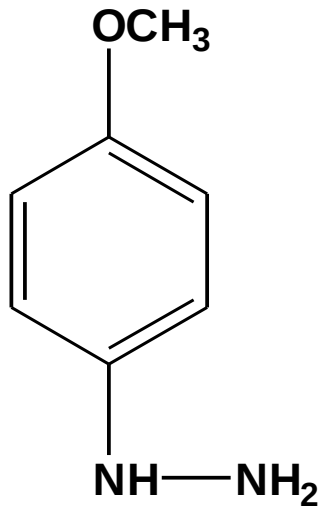


E-like isomer

Aryl- Heteroarylacetic acid

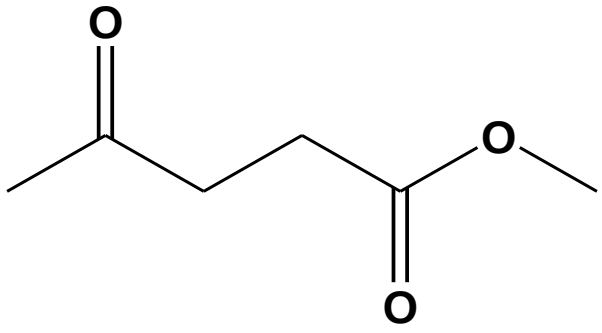


Synthesis: Indomethacin



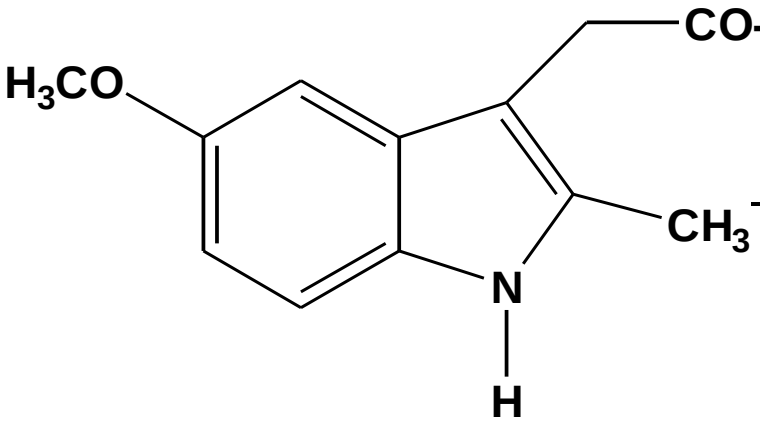
4-methoxyphenylhydrazine

+

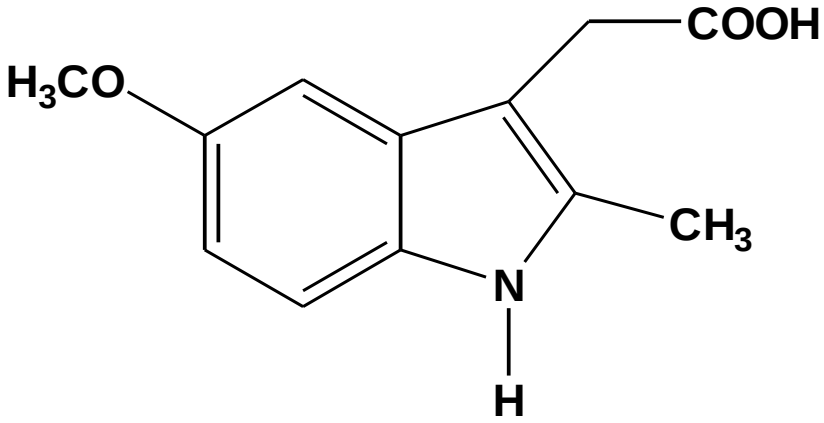


4-oxo-pentoic acid methylester

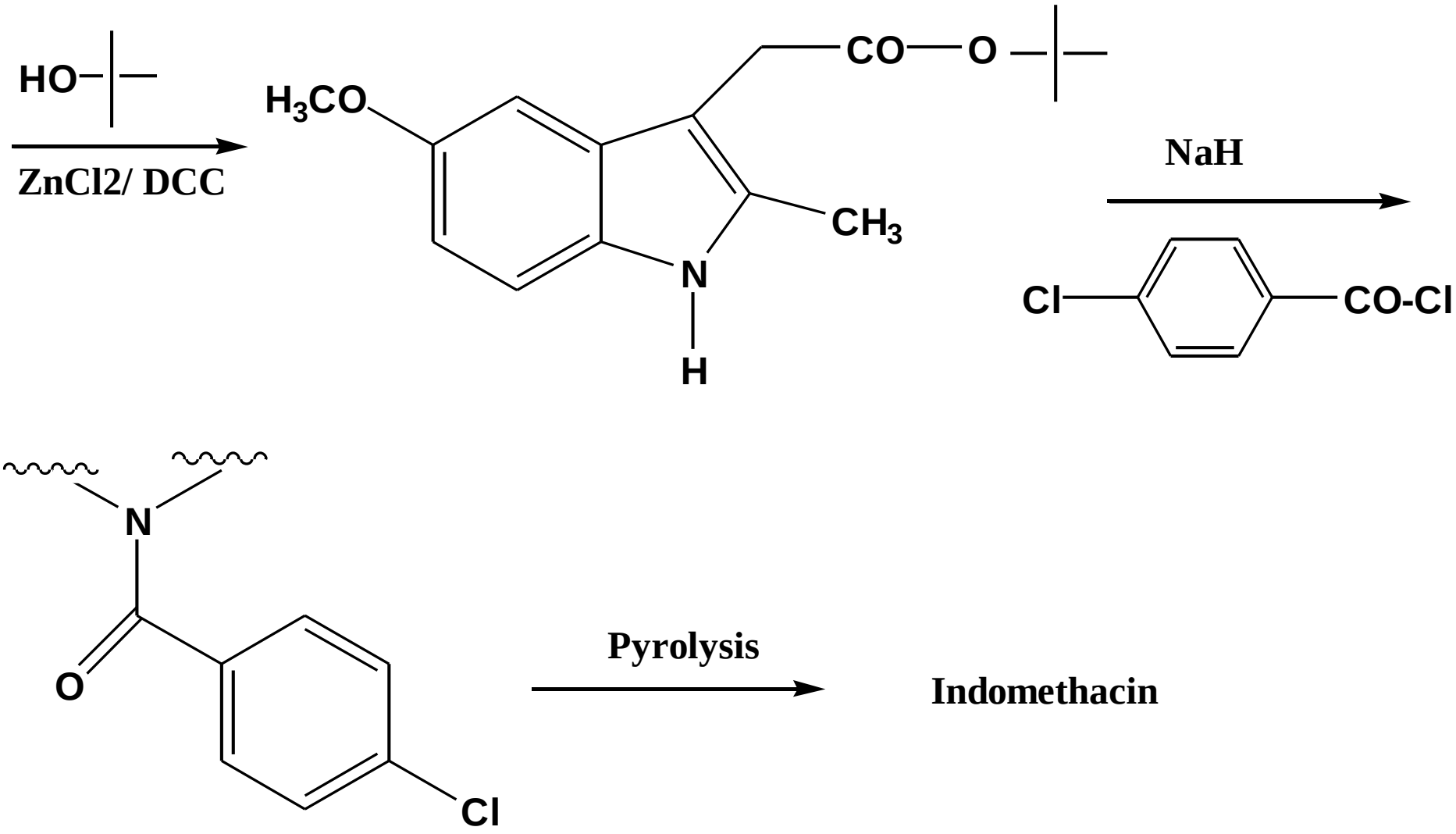
Cyclization →



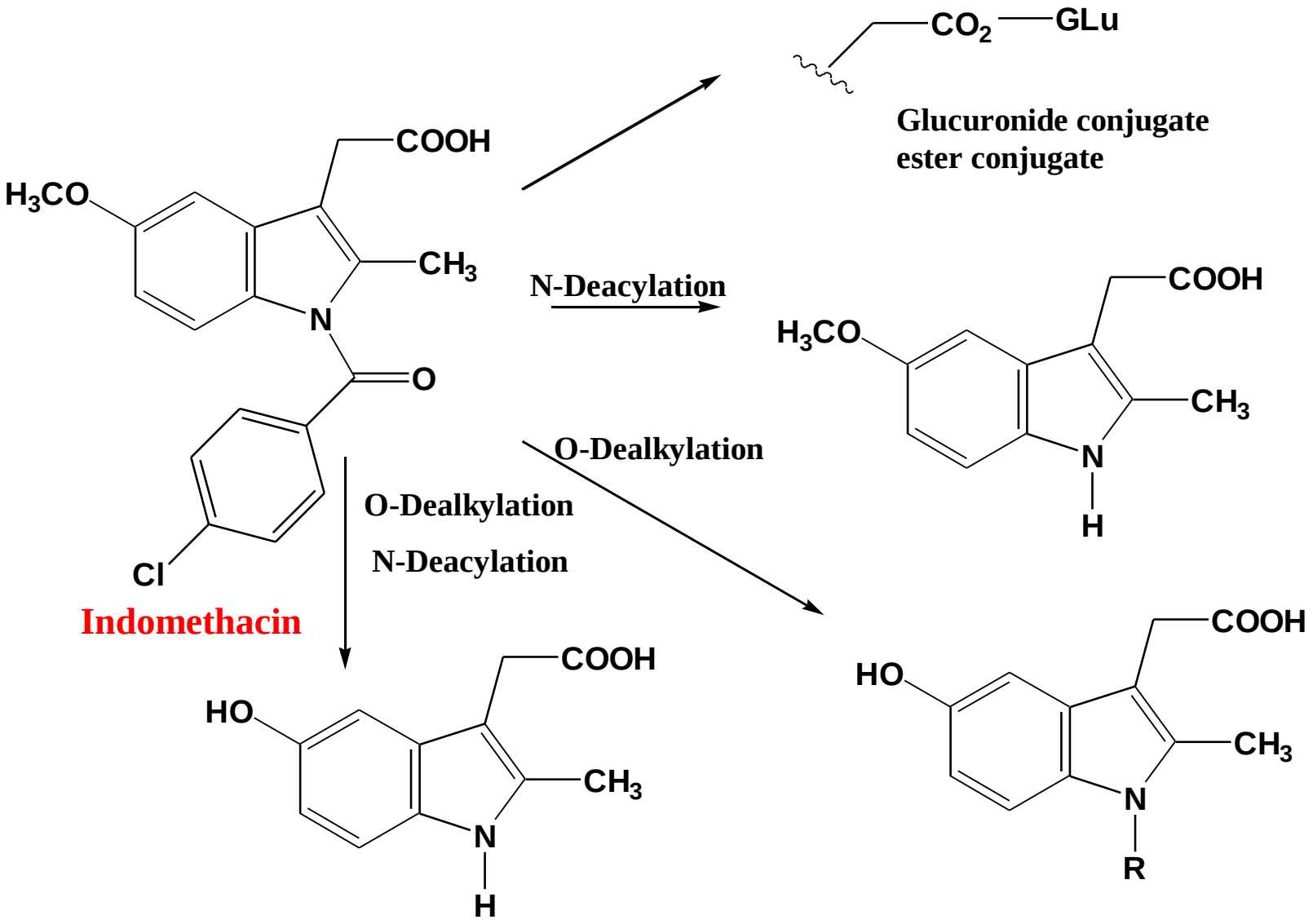
H^+ →



Synthesis: Indomethacin



Metabolism: Indomethacin



Aryl- Heteroarylacetic acid

Sulindac:

Isosteric replacement of indole with indene

Prodrug

Sulfoxide is reduced to **active metabolite sulfide**

F is lipophilic enhance analgesic effect

Z isomer is more potent anti-inflammatory than E-isomer

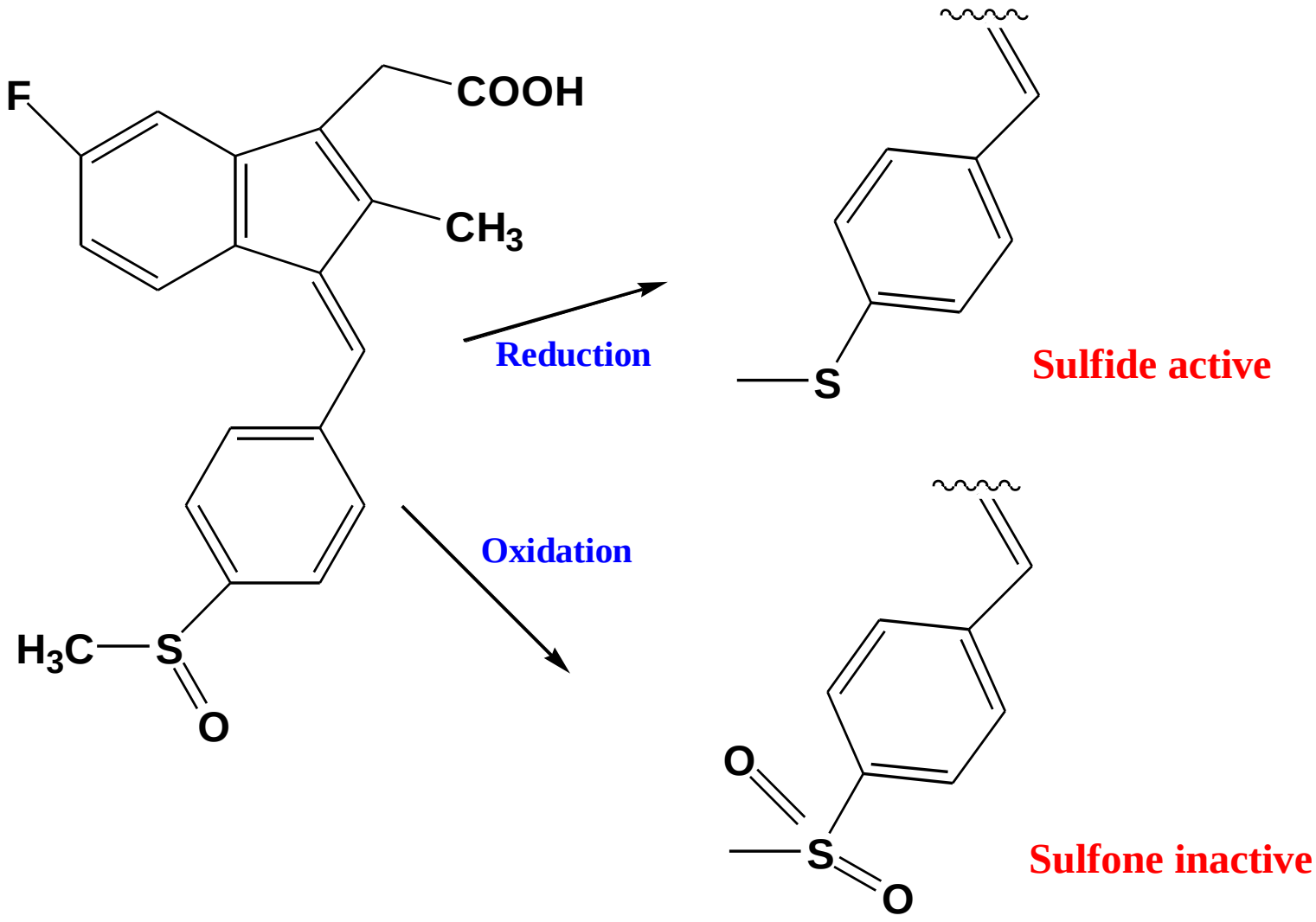
equipotent analgesic like indomethacin

Less anti-inflammatory than indomethacin

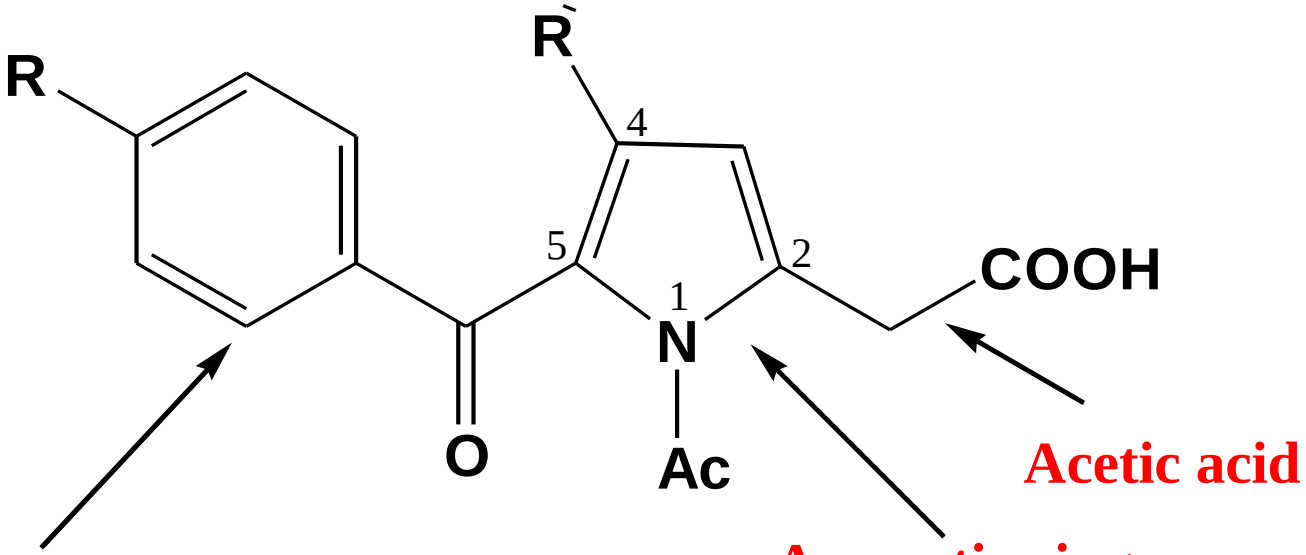
Less CNS and GI side effect

Aryl- Heteroarylacetic acid

Sulindac: Biotransformation



Aryl- Heteroarylacetic acid



R: CH3 R`: H Tolmetin

R: Cl R`: CH3 Zomepirac

Tolmetin

Flat carboxylic group

Aryl ring pyrrole instead of indole

Phenyl ring

Rings are non coplanar

Aryl- Heteroarylacetic acid

Tolmetin

Non selective COX inhibitor

Short duration of action [less than 5 h]

Zomepirac:

P-chlorobenzoyl Instead of 5-p-Toluoyl

CH3 at position 4

Zomepirac is more potent than tolmetin (4X)

longer duration of action (**Why**??)

Withdrawal from the market: Anaphylactic reactions

Aryl- Heteroarylacetic acid

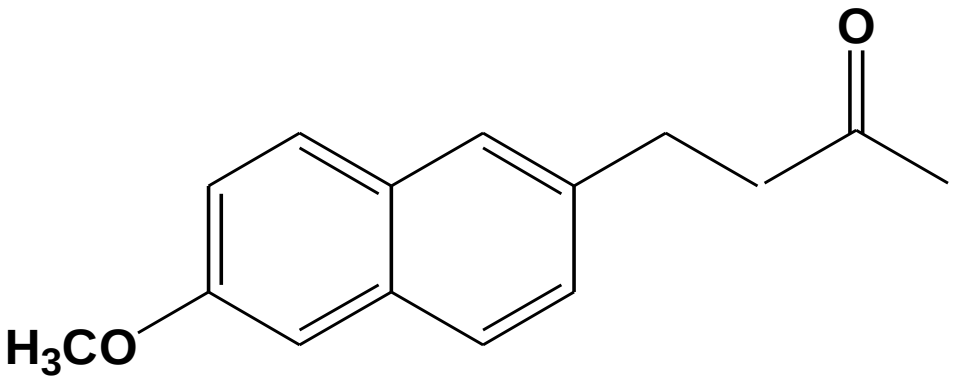
Nabumetone

Prodrug [Non-acidic ketone, alkanone]

Metabolized to give **6MNA active form** of the drug which has a long half-life (24hrs)

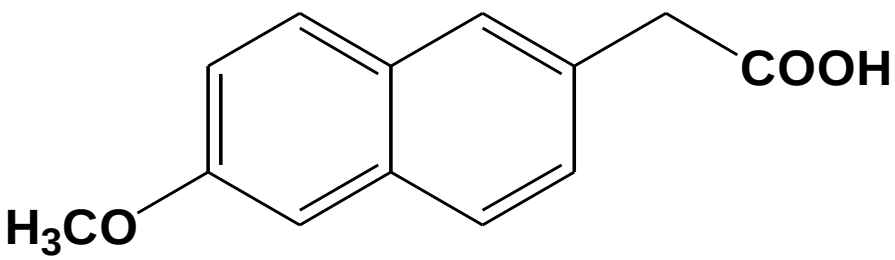
Preferential COX 2 inhibitor

Less GI side effect



Nabumetone (Prodrug)

Metabolism



6-Methoxynaphthalene-2-acetic acid (6MNA)
Active metabolite [Metabolite is related to naproxen]

Aryl- Heteroarylacetic acid

Diclofenac

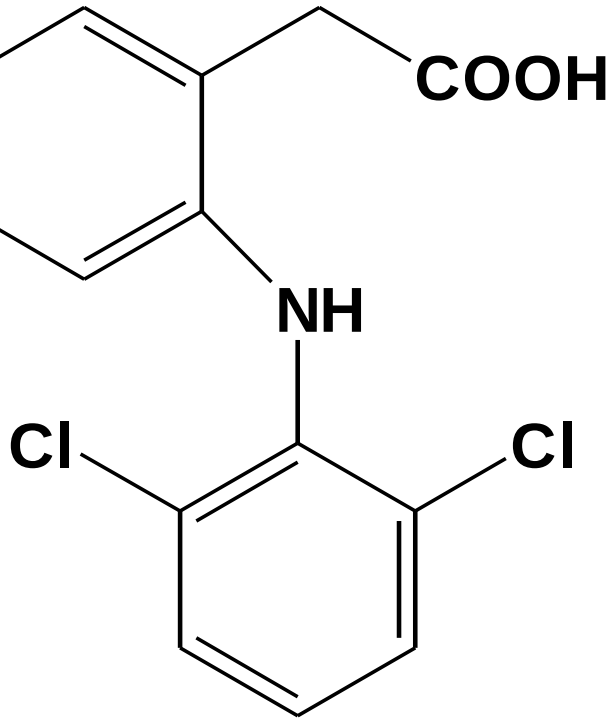
Arylacetic acid and anthranilic acid derivative (Na-, k- salts)

Analgesic, antipyretic, Anti-inflammatory [**look for MOA**]

Most widely used NSAIDs in the world

More potent than indomethacin and aspirin

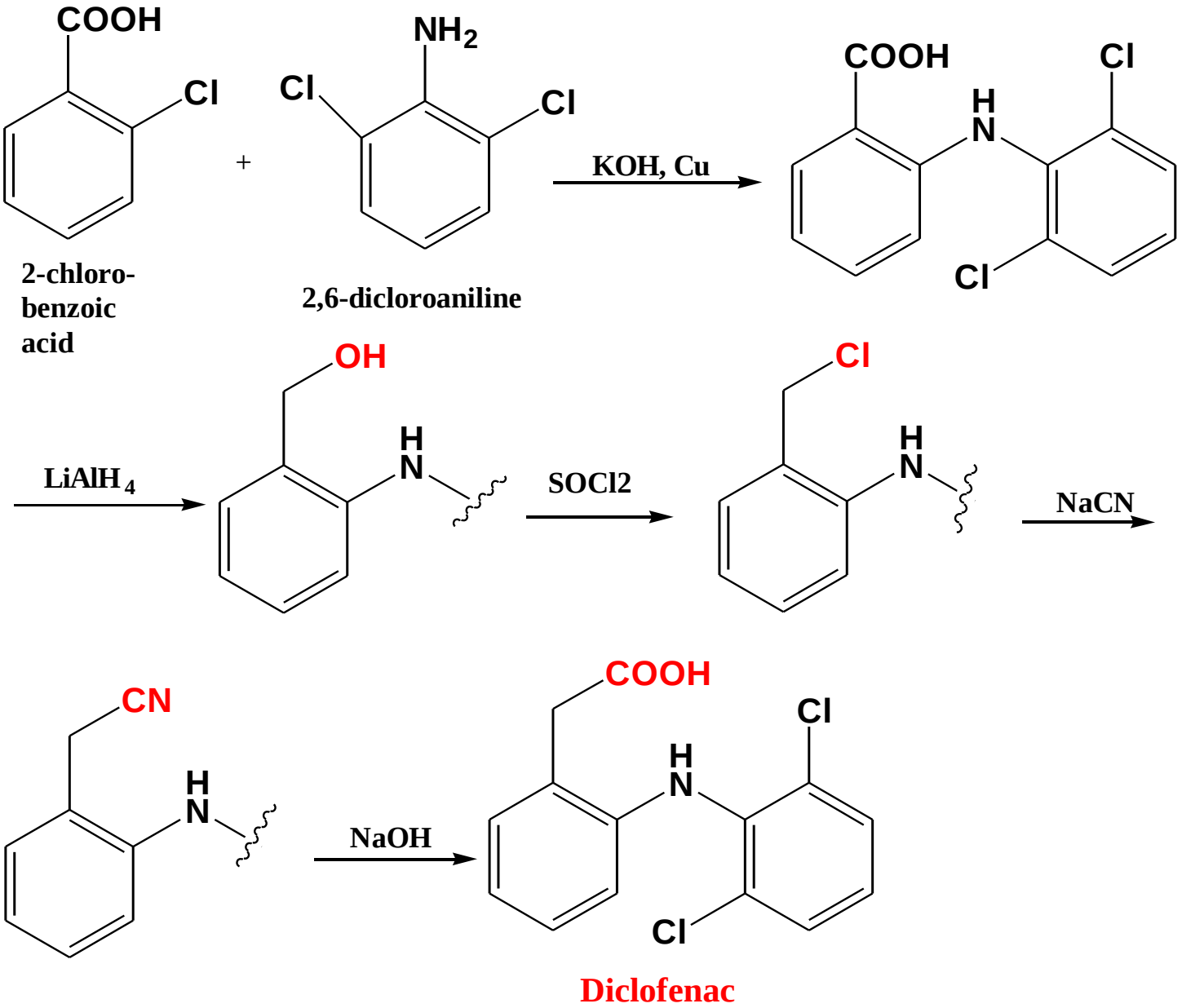
Two o-Chloro groups force the anilinophenyl ring out of plane of the phenyl acetic acid ring



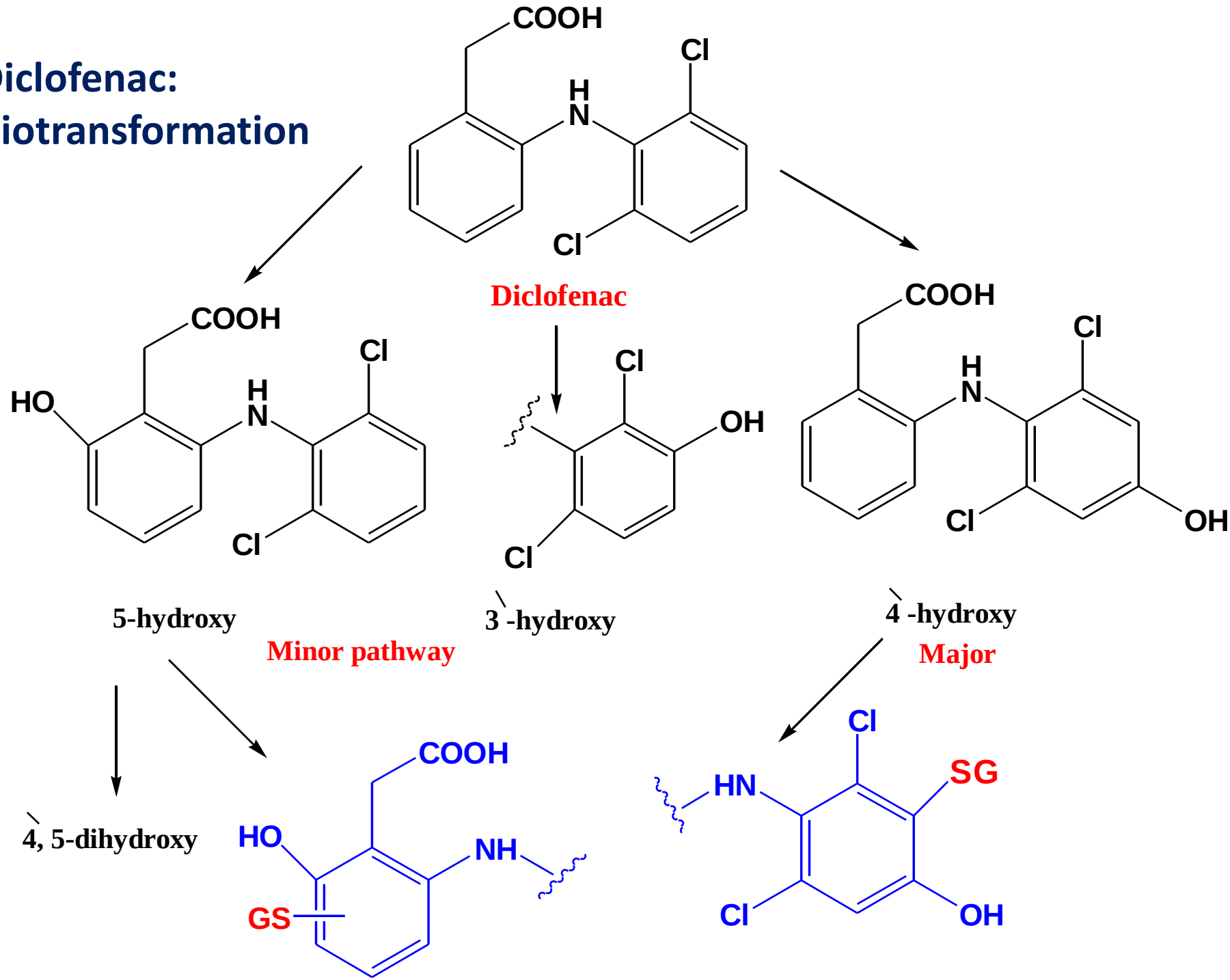
Diclofenac

Aryl- Heteroarylacetic acid

Diclofenac: Synthesis



Diclofenac: Biotransformation



Aryl- Heteroarylacetic acid

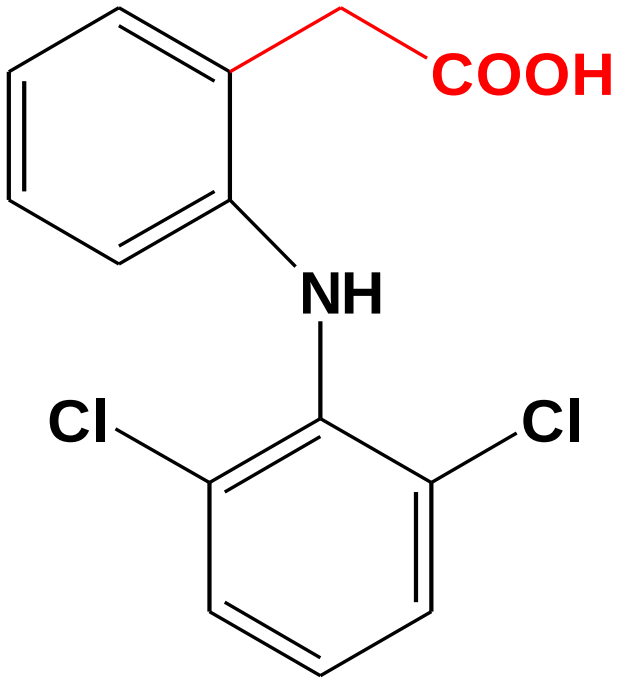
Diclofenac: Biotransformation

Aromatic hydroxylation
Major: 4`-hydroxymetabolite
Minor: 5-hydroxy and 3`-hydroxy, 5,3`-dihydroxy metabolite

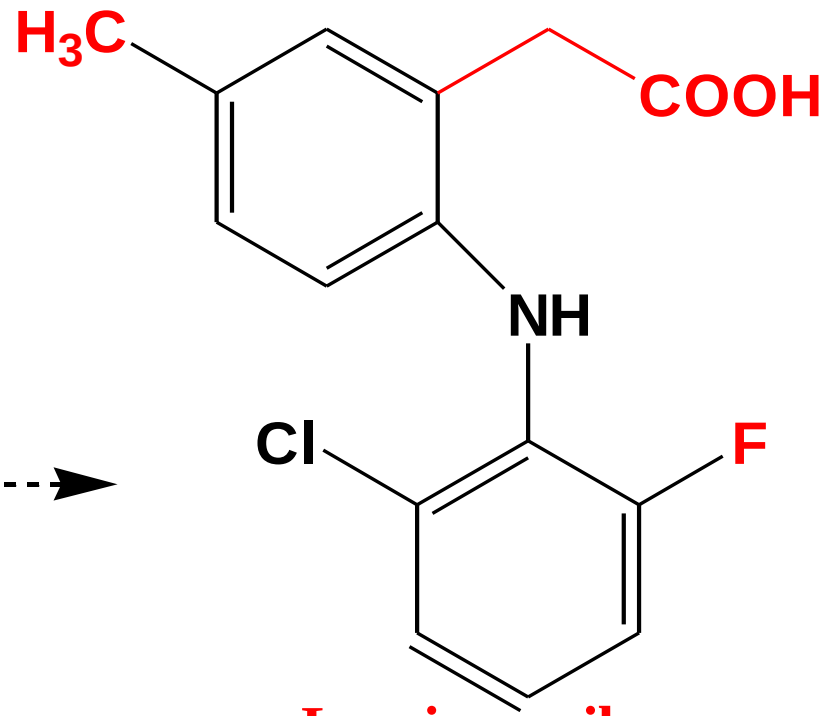
Hepatotoxicity more than other NSAIDs [**Benzoquinonimine**]

Deactivation of benzoquinoimine [An electrophile] by phase II conjugation with glutathione GSH
(**It was discussed in paracetamol)**

Aryl- Heteroarylacetic acid



Diclofenac



Lumiracoxib

Lumiracoxib: Potent selective COX-2 inhibitor

Marketed in 2004, withdrawn in 2007 [Serious adverse liver reactions]

Aryl- Heteroarylacetic acid

Etodolac:

Pyranocarboxylic acid

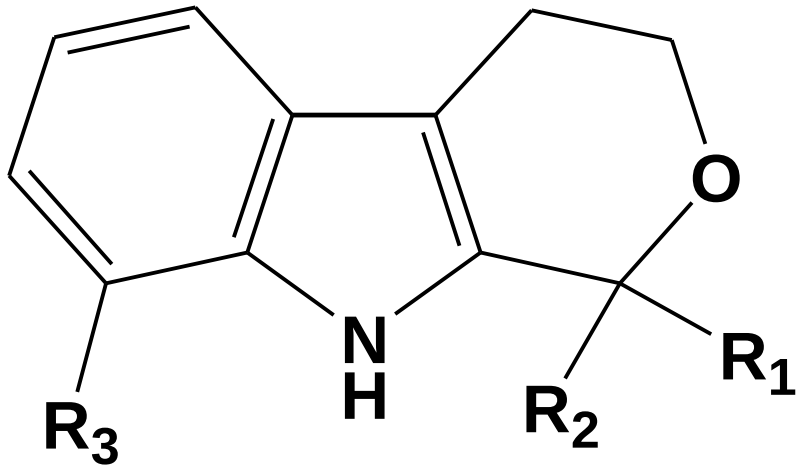
Two carbon separate COOH from indole ring but still belong to heteroaryl acetic acid derivative

Marketed as racemic mixture

Only S(+) enantiomer is active

Less GI side effect

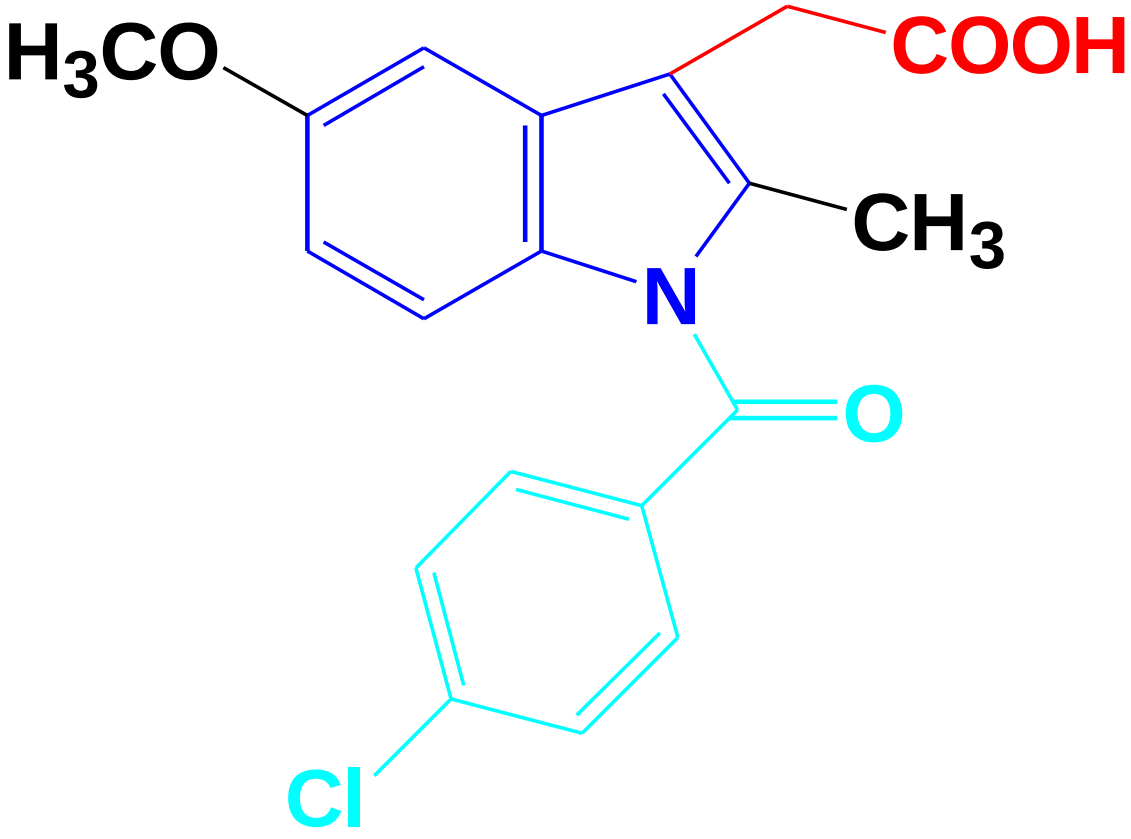
Antiinflammatory: 1/3 potency of indomethacin



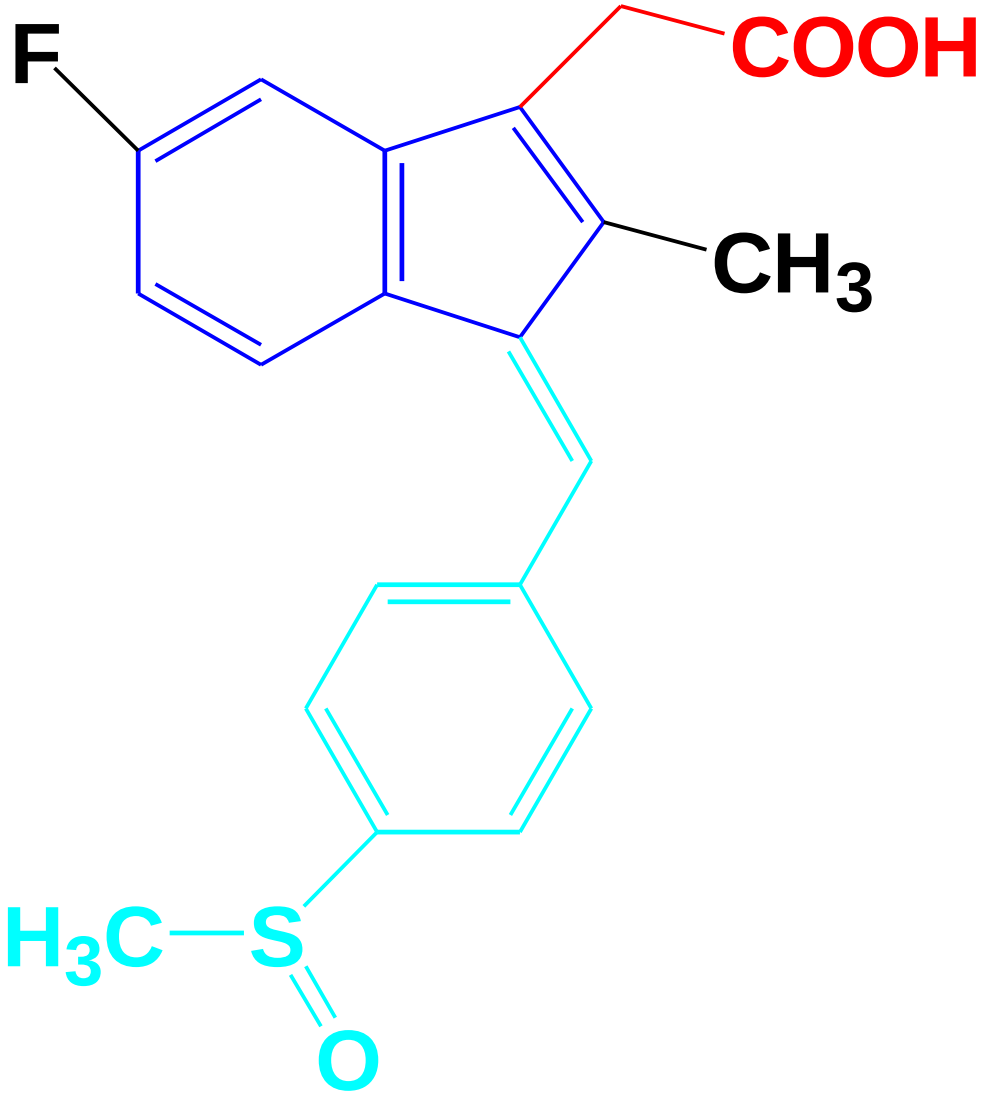
Etodolac

R1: -CH_2-COOH, R2: -C_2H_5, R3: -C_2H_5

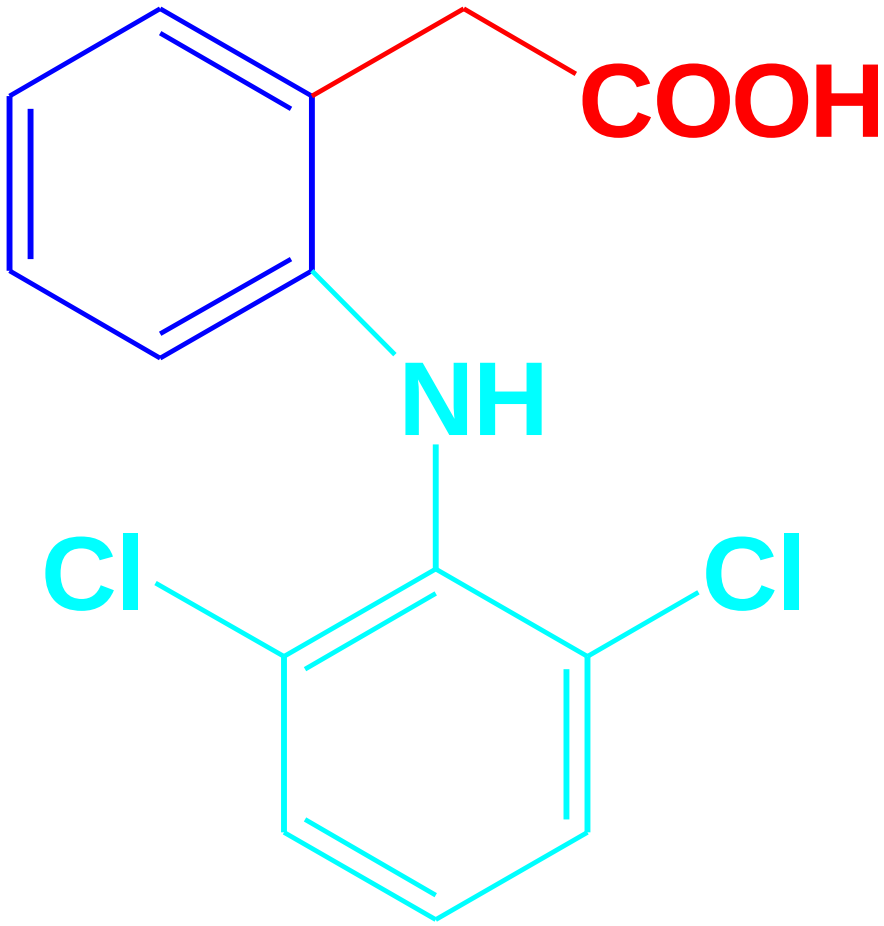
Selective COX 2 inhibitor later recognized



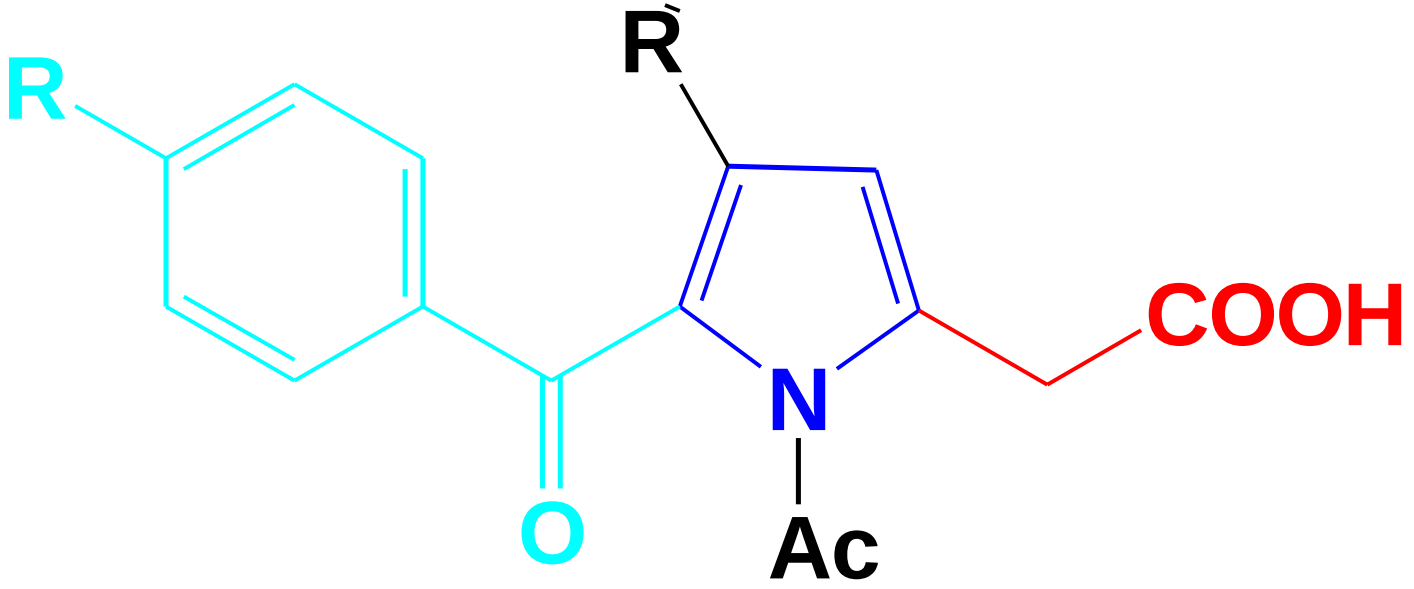
Indomethacin



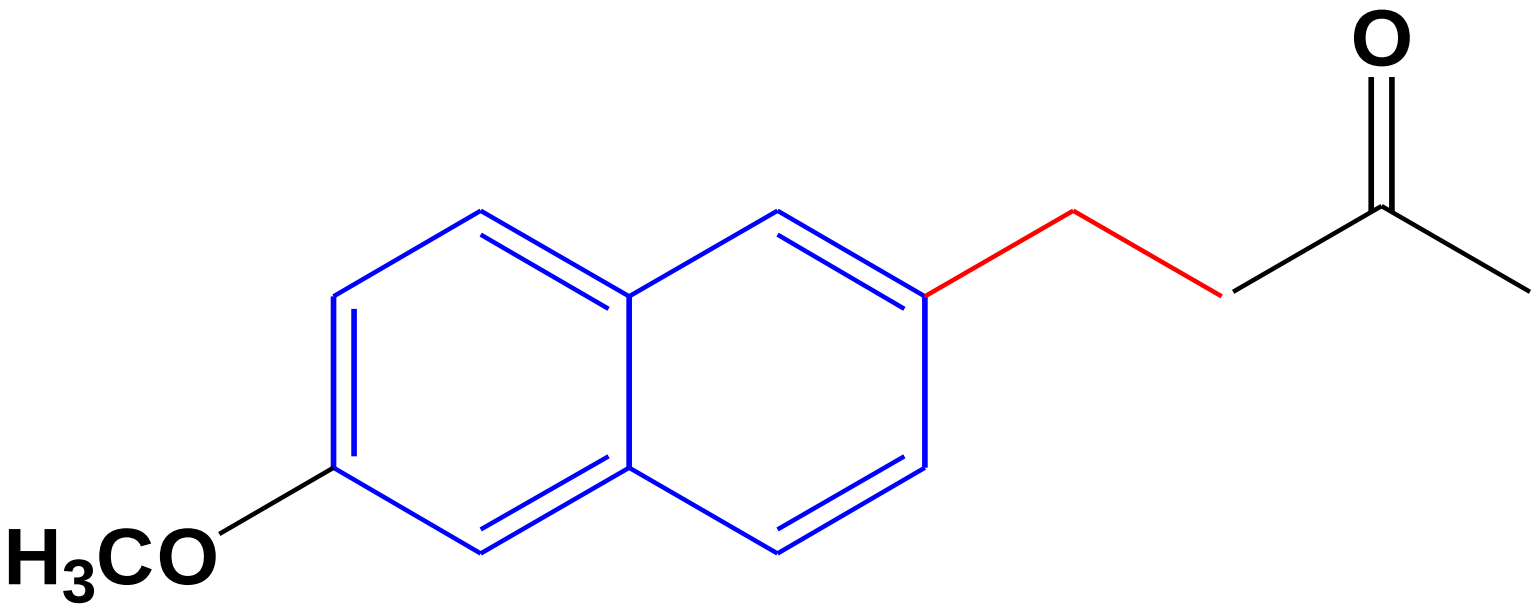
Sulindac (Prodrug)



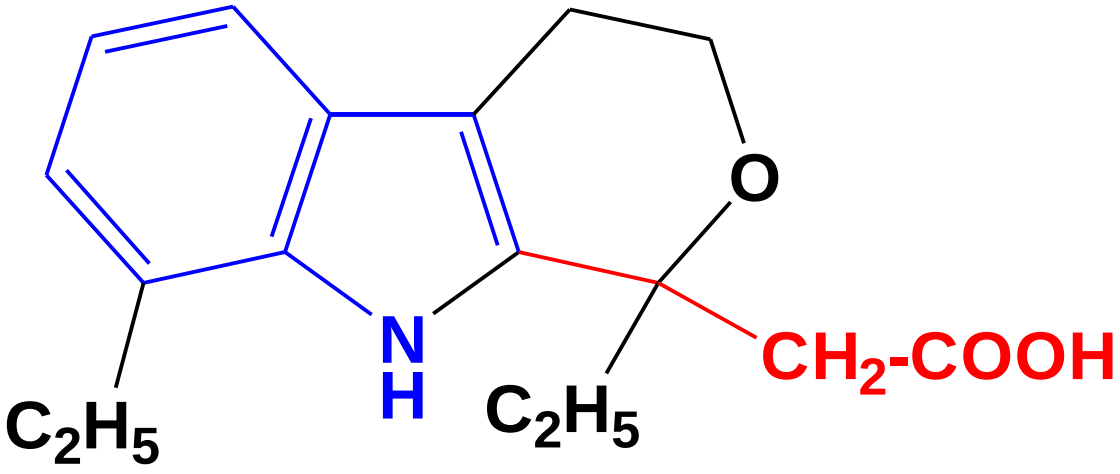
Diclofenac



Tolmetin & Zomiperac



Nabumetone (Prodrug)



Etodolac Pyranocarboxylic acid

Non-Steroidal Anti-inflammatory Drugs NSAIDs

Part 4

Dr. Mai Ramadan

COX 1 versus COX 2

Function (physiological and pathological roles) and activity

Active site aspects:
Substrate and shape
Differences and similarities in aa residues and their significance

Antipyretic/ Analgesic

Anilide (p-Aminophenol derivative)

Paracetamol (Structure, metabolism, toxicity, synthesis)

Antipyretic/ Anti-inflammatory

Salicylate

Sod salicylate, Diflusinal, salicylamide

Aspirin (Structure, metabolism, synthesis, mutual prodrugs, irreversible inhibition of COX1 in platelets)

Antipyretic/ Anti-inflammatory

Aryl- & heteroaryl acetic acid

Indomethacin

Sulindac

Tolmetin & zomepirac

Nabumetone

Diclofenac & lumiracoxib

Etodolac

Antipyretic/ Anti-inflammatory

Aryl- & heteroaryl propionic acid

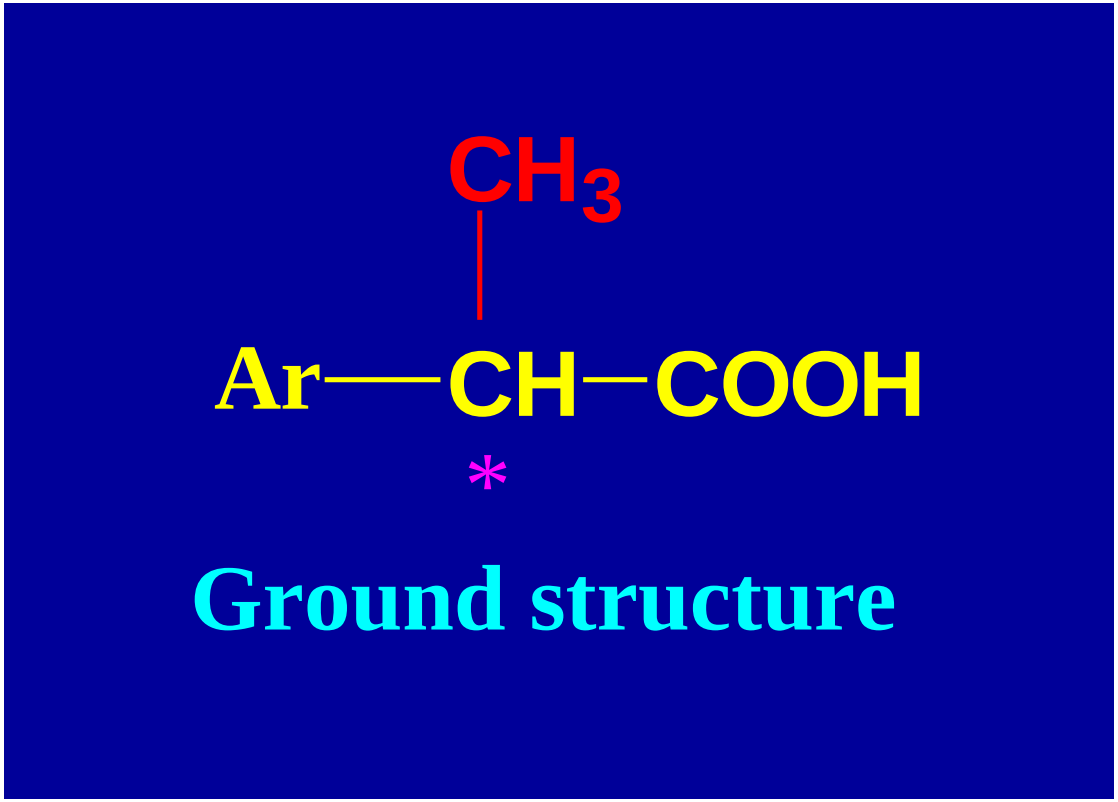
Profen (Ibuprofen)

Naproxen

Ketorolac

Oxaprozin

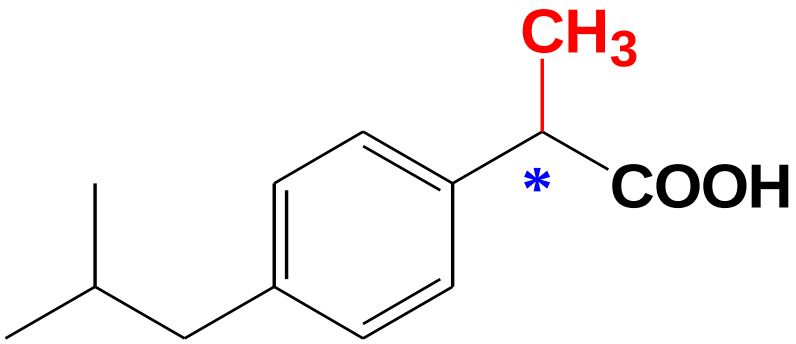
Aryl- & heteroaryl propionic acid



Ground structure

Aryl- Heteroarylpropionic acid

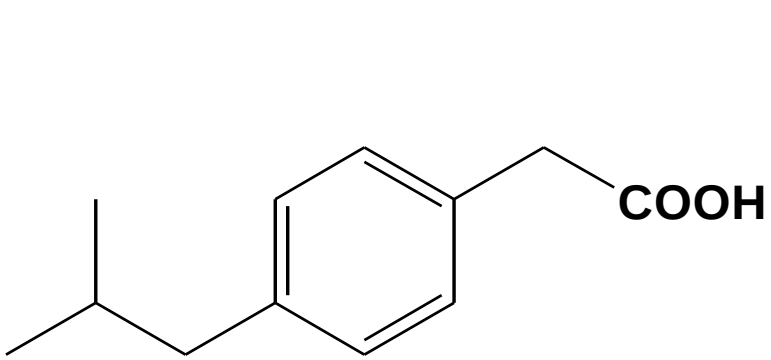
Profen:



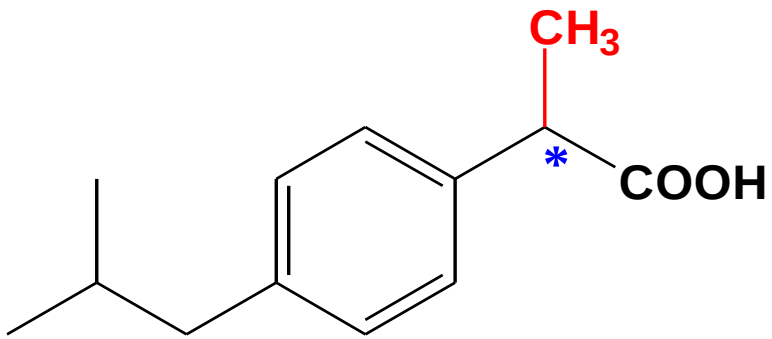
Ibuprofen

Aryl- Heteroarylpropionic acid

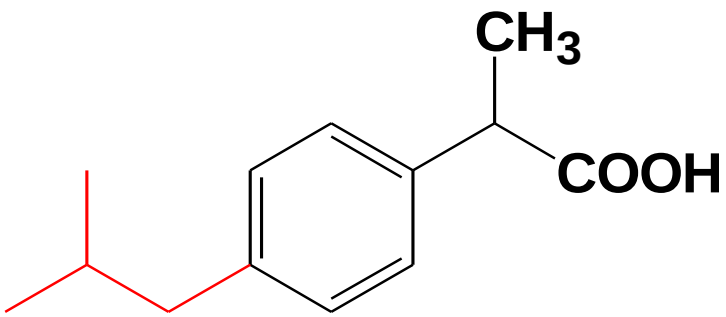
Profen:



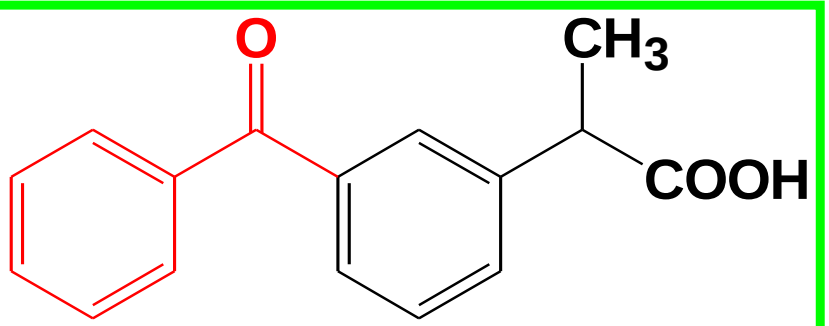
Ibufenac



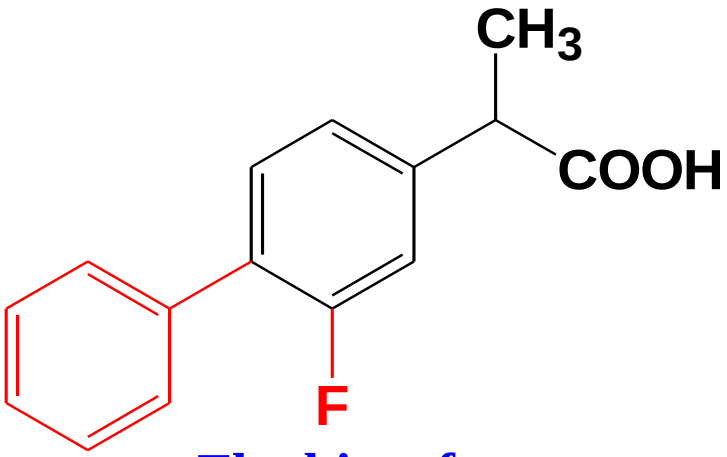
Ibuprofen



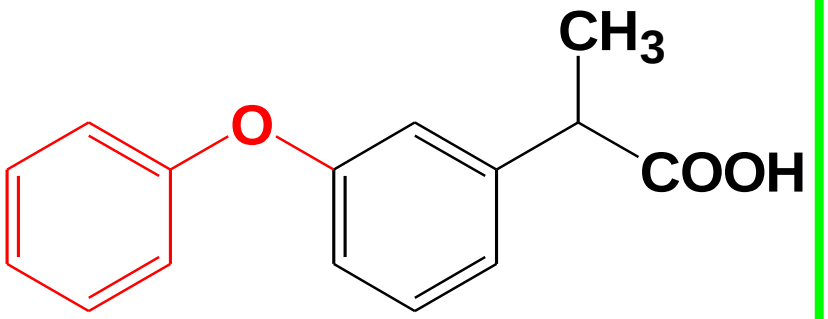
Ibuprofen



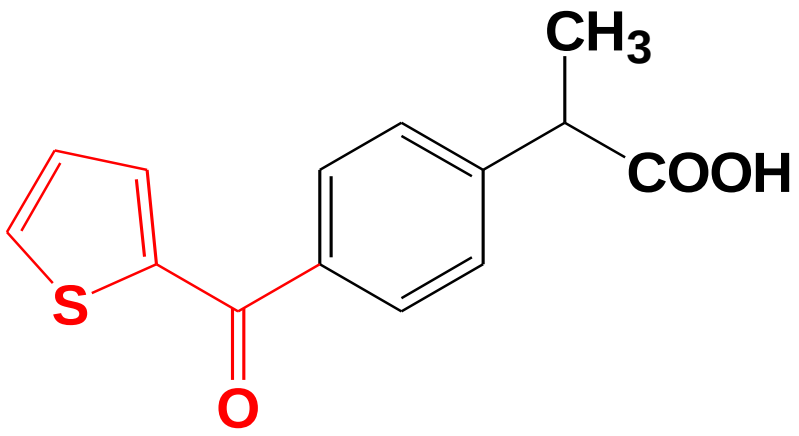
Ketoprofen



Flurbiprofen



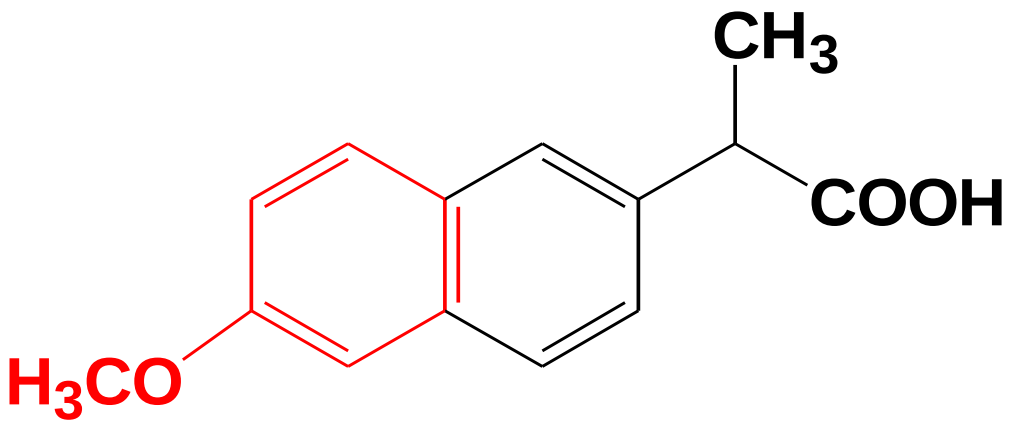
Fenoprofen



Suprofen

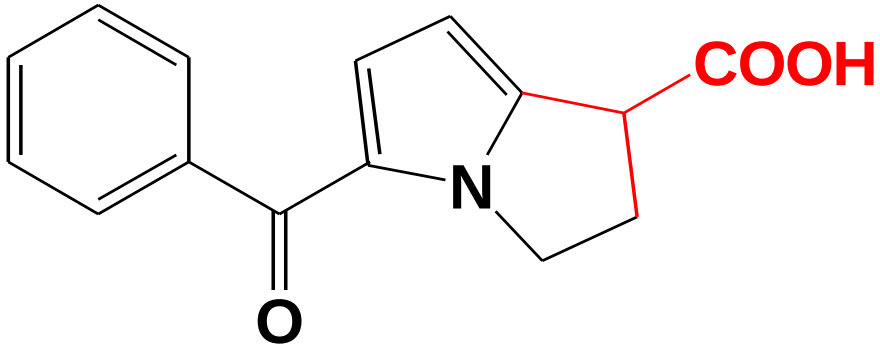
Aryl- Heteroaryl propionic acid

Aryl- Heteroarylpropionic acid

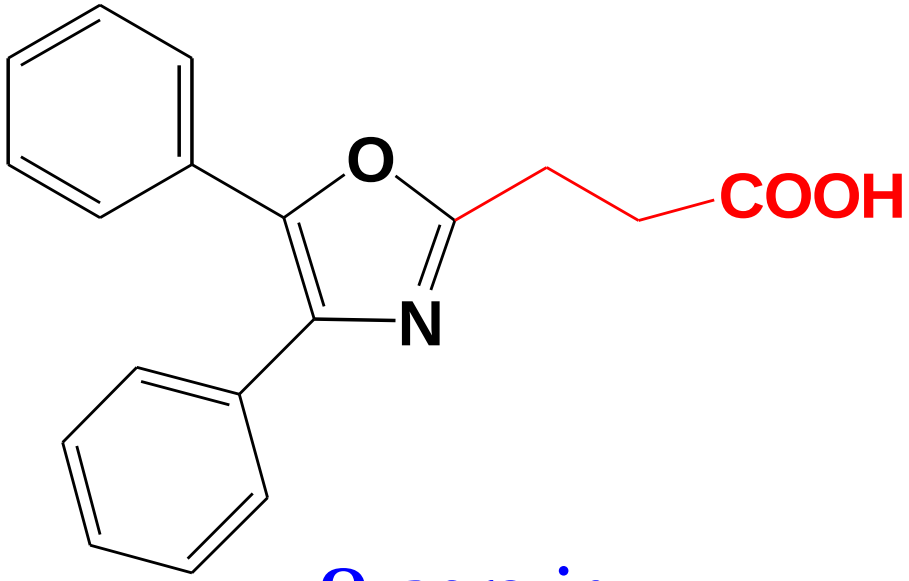


Naproxen

Aryl- Heteroarylpropionic acid



Ketorolac



Oxaprozin

Aryl- Heteroarylpropionic acid

Profen:

Ibuprofen , fenoprofen, Ketoprofen, Flurbiprofen,

Suprofen: withdrawal [due to transient renal failure] Reintroduced for occular application

Naproxen:

2-naphthylacetic acid derivative

Ketorolac

Oxaprozin

Aryl- Heteroarylpropionic acid

SAR of Profen:

The aryl propionic acids are characterized by the general structure Ar—CH(CH3)—COOH which conforms to the required general structure

Substitution of α-methyl group on alkanoic acid enhances anti-inflammatory activity and reduces side effects. Acetic acid analoge of ibuprofen is less potent and hepatotoxic (Ibufenac)

S (+)- enatiomer has greater activity

Isobutyl substituent has more activity with reduced toxicity.

Aryl- Heteroarylpropionic acid

Profen:

Replacement of carboxylic functional group with ester, amide or azole generally produces less active compound.

Placing the phenoxy group at ortho or para position of aryl propionic acid ⟶ less active compound e.g. fenoprofen.

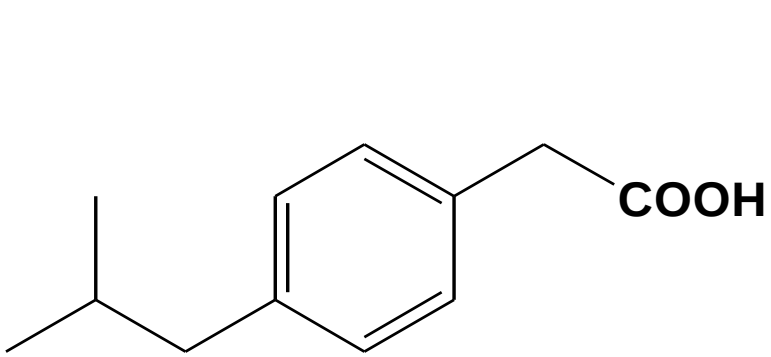
Replacement of oxygen with carbonyl in fenoprofen ⟶ yields ketoprofen which has more activity than ibuprofen.

Aryl substituent with -Cl, -F is best for activity (Flurbiprofen is more potent analgesic and anti-inflammatory than ibuprofen)

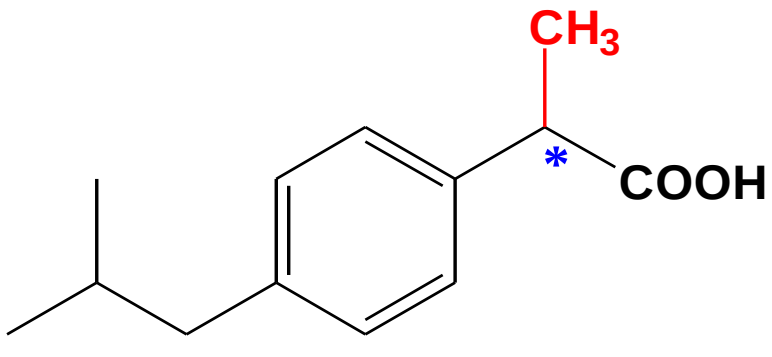
Substitued the aryl group with 2-naphthyl acetic acid leads to maximum activity (Naproxen)

Aryl- Heteroarylpropionic acid

SAR of Profen:



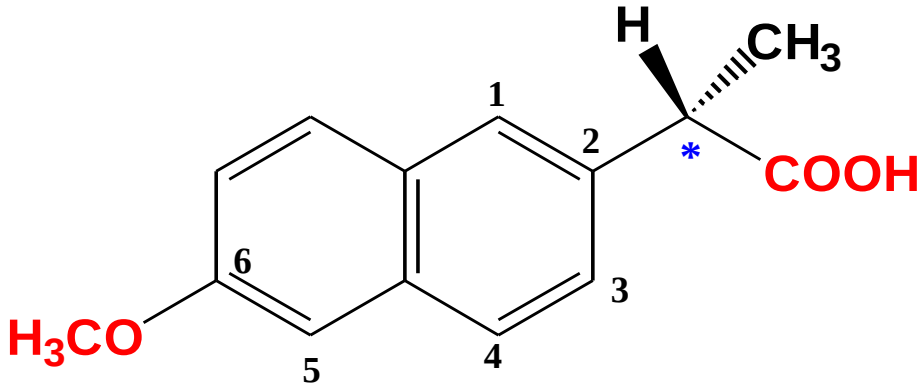
Ibufenac



Ibuprofen

Aryl- Heteroarylpropionic acid

SAR of 2-Naphthylacetic acid:
Naproxen is marketed as
Pure S- isomer



Replace –COOH group by a group [COOCH3, CHO, CH2OH], which is metabolized in vivo to -COOH retain activity

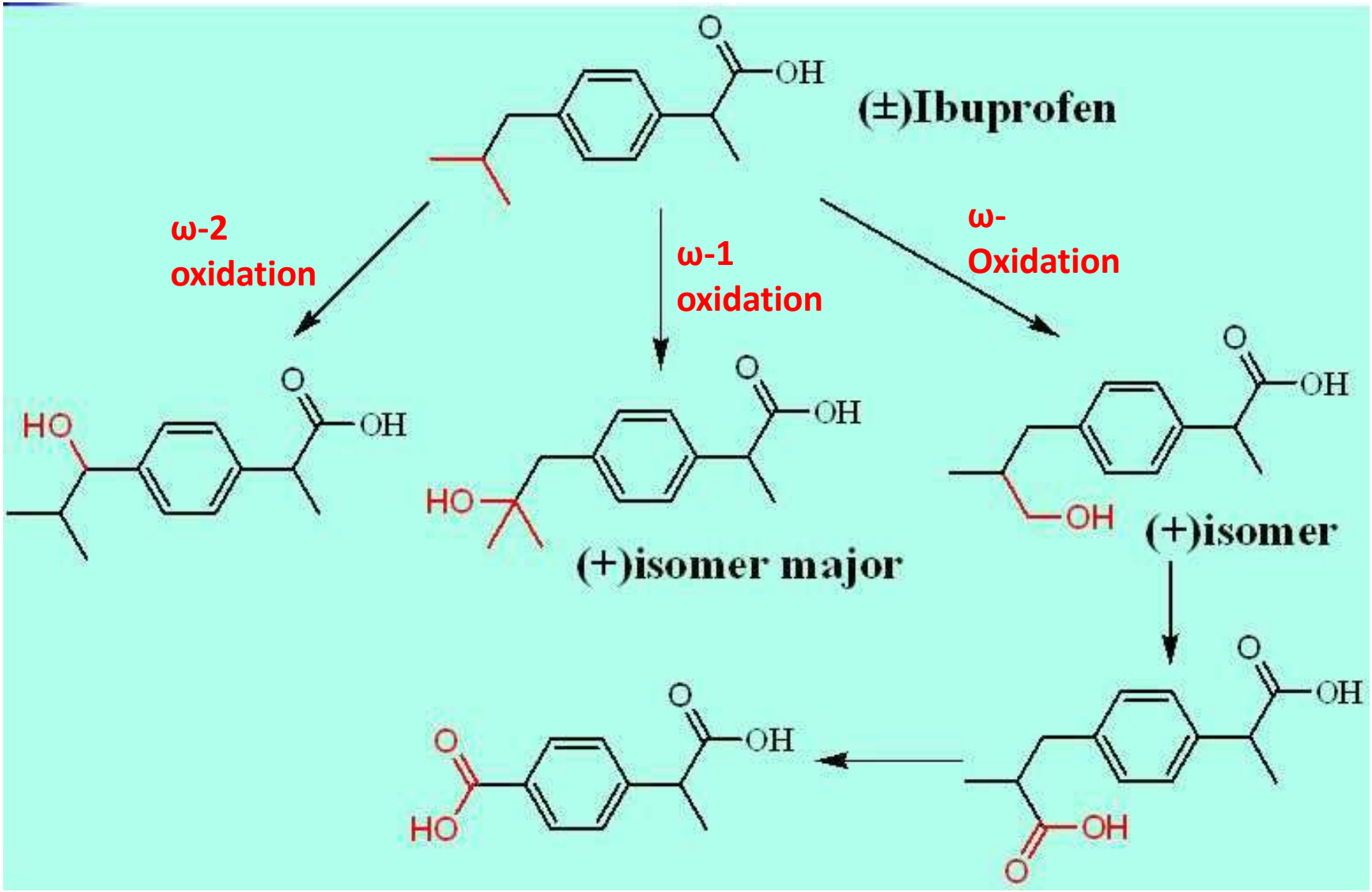
Remove –OCH3 decrease activity
Small lipophillic group at position 6 like -Cl, -SCH3, -OCHF2 yields active analogue. –OCH3 in naproxen is most potent.

Larger group on place of methoxy at position 6 yields less active compounds

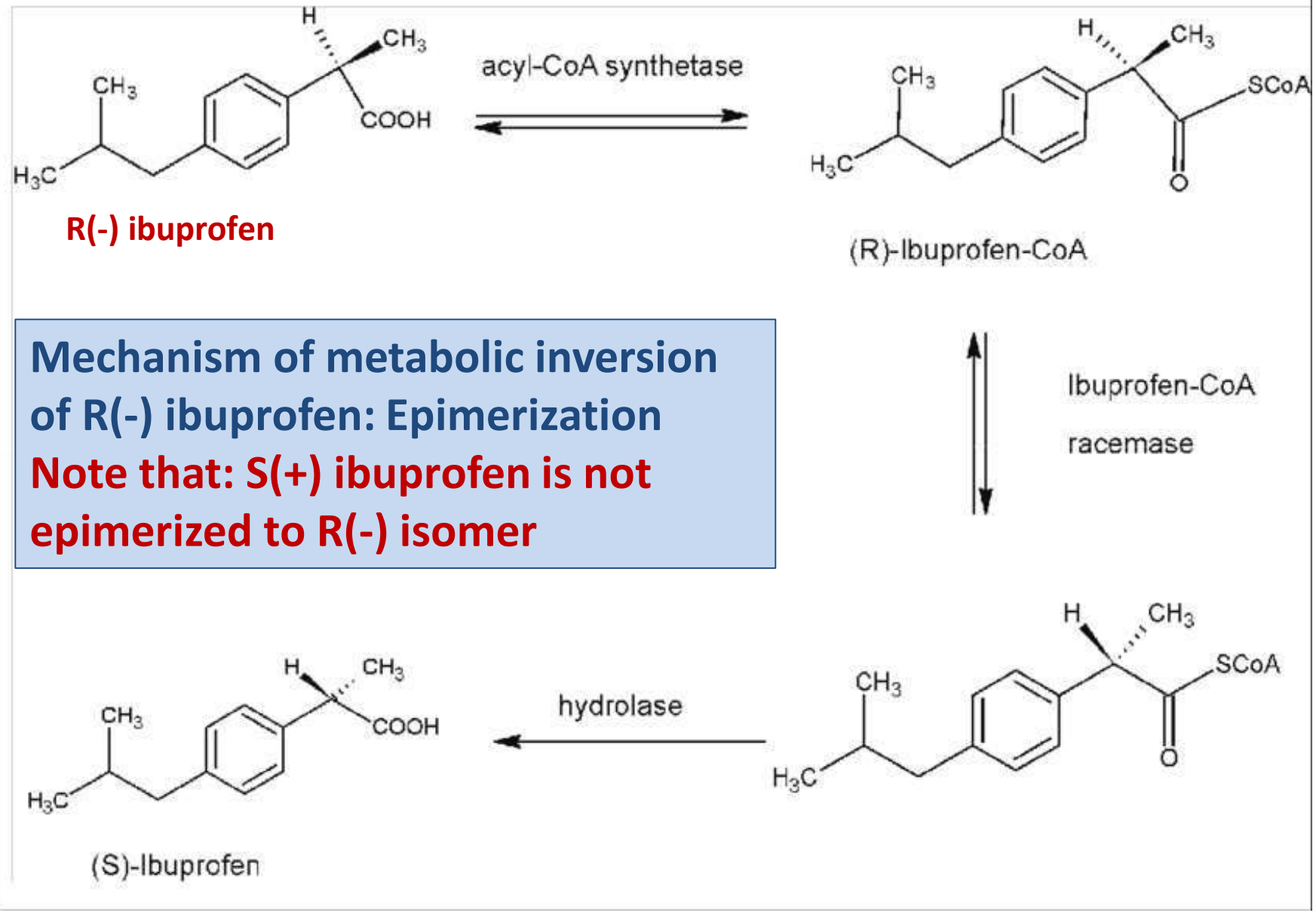
S(+)- is more potent isomer

Aryl- Heteroarylpropionic acid

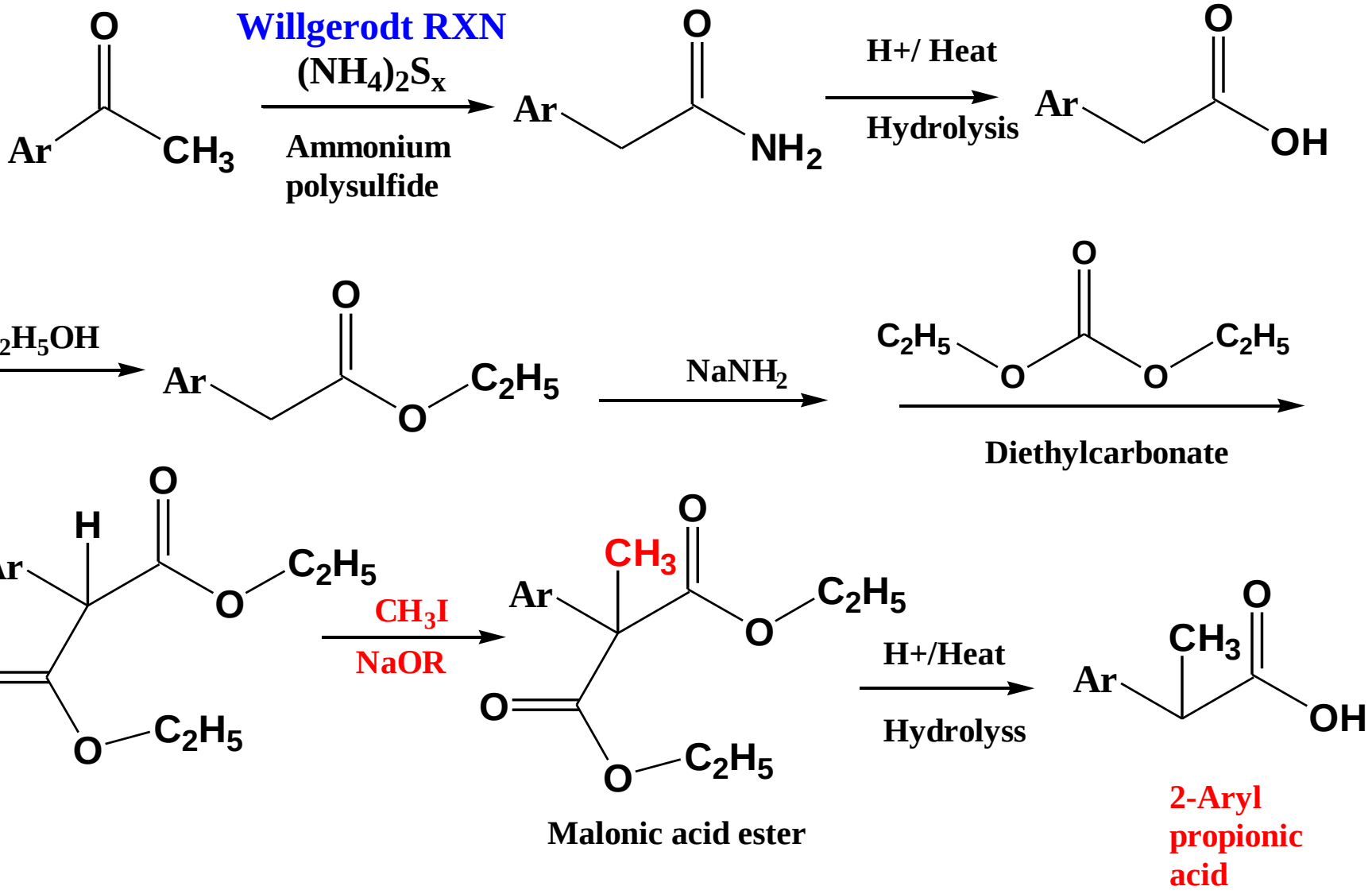
Metabolism of ibuprofen: All metabolite are inactive



Aryl- Heteroarylpropionic acid



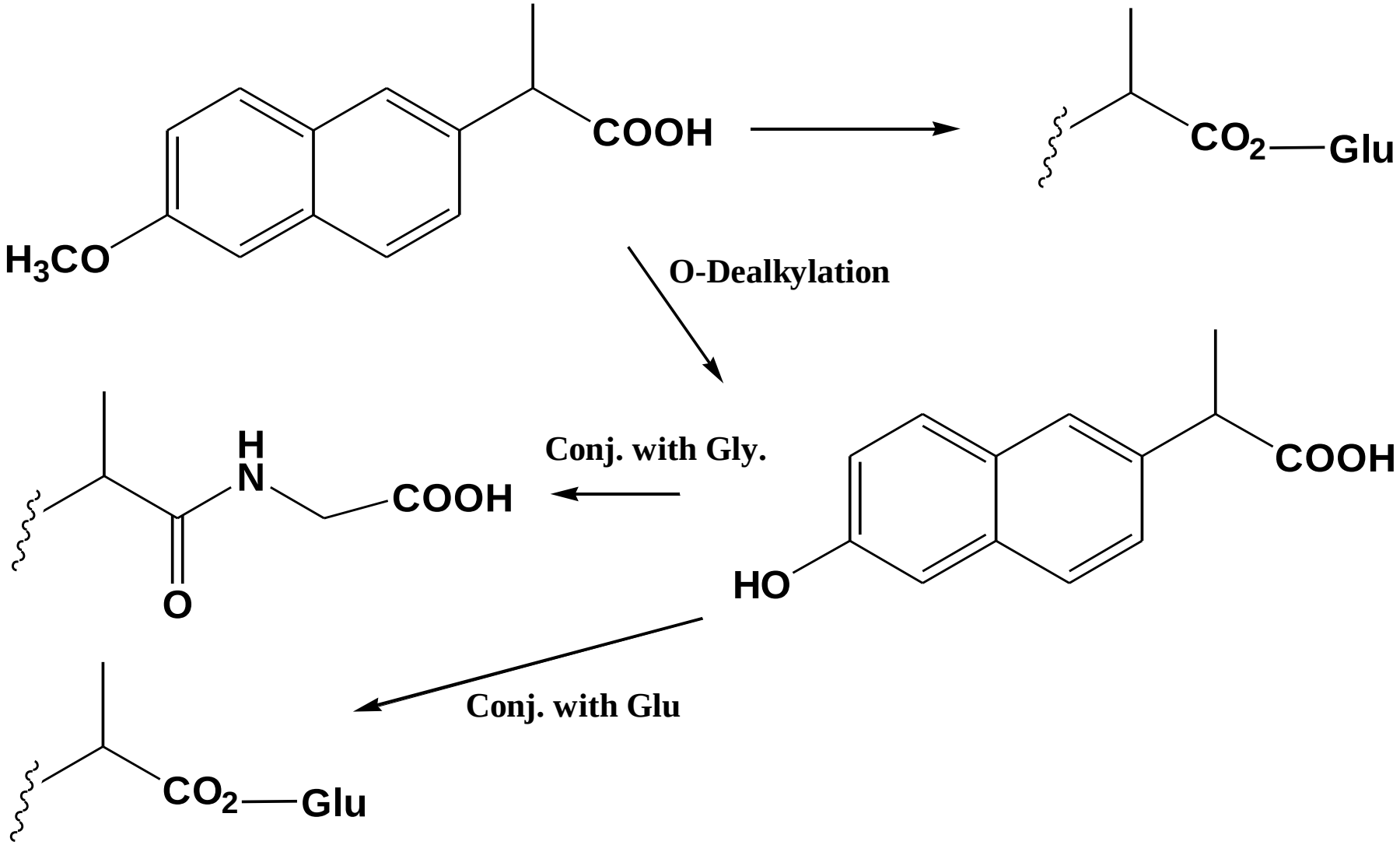
General synthesis of Aryl-propionic acid



Willgerodt RXN: Oxidation RXN of Aryl alkyl ketone to corrosponding amide and carboxylic acid

Aryl- Heteroarylpropionic acid

Naproxen biotransformation:

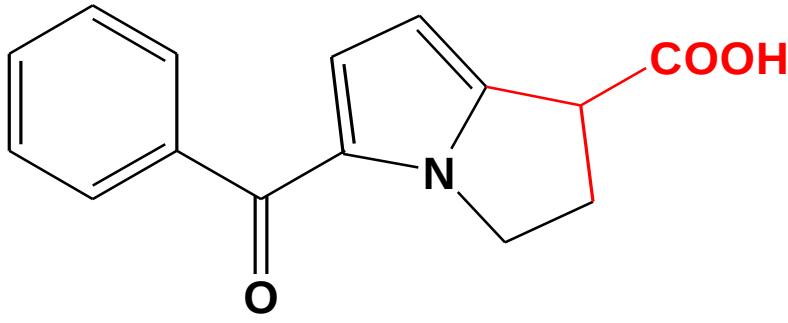


Aryl- Heteroarylpropionic acid

Ketorolac:

A cyclized, heteroaryl propionic acid derivative, with the α-methyl group being fused to the pyrrole ring.

Injection, newly orally
Analgesic [15-30 mg resemble activity
Of 12 mg morphine] effect after 10 min
Of injection



Ketorolac

available as the tromethanime salt.
The tromethamine moiety enhances water solubility.

Alternative for narcotic analgesics

Aryl- Heteroarylpropionic acid

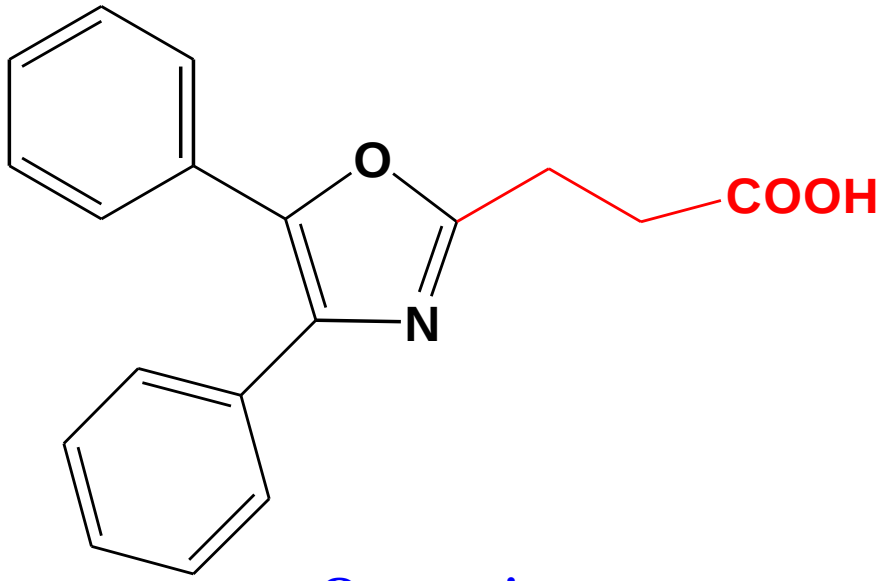
Oxaprozin:

Differ from α-methyl acetic acid

Long duration of action

Once daily dosing

Rash and mild photosensitivity



Oxaprozin

Non-Steroidal Anti-Inflammatory Drugs NSAIDs

Part 5

Dr. Mai Ramadan

Antipyretic/ Analgesic

Anilide (p-Aminophenol derivative)

Paracetamol

Antipyretic/ Anti-inflammatory

- Salicylate

Sod salicylate

Diflusinal

salicylamide

Aspirin

Mutual prodrug

Antipyretic/ Anti-inflammatory

❑ Aryl- & heteroaryl acetic acid

Indomethacin

Sulindac

Tolmetin & zomepirac

Nabumetone

Diclofenac & lumiracoxib

Etodolac

Antipyretic/ Anti-inflammatory

- ❑ Aryl- & heteroaryl propionic acid

Profen (Ibuprofen)

Naproxen

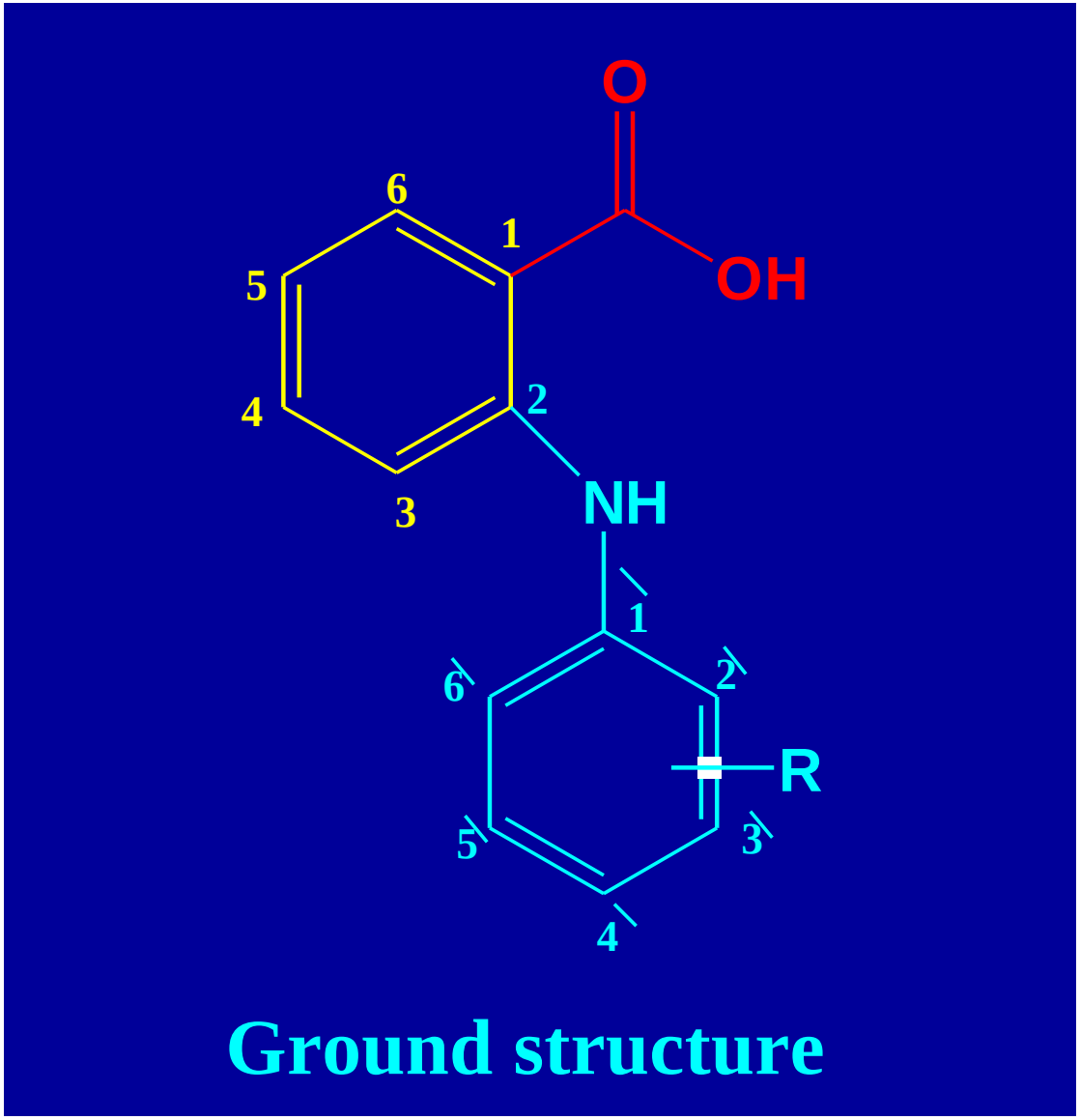
Ketorolac

Oxaprozin

Antipyretic/ Anti-inflammatory

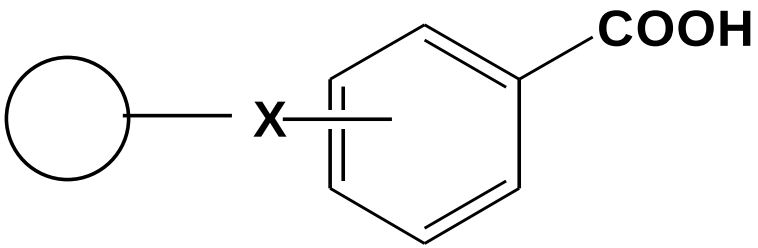
- N-Arylanthranilic acid [Fenamic acid]
- Oxicam [4-hydroxy-1,2-benzothiazine]

N- Arylranthranilic acid (Fenamic acid)

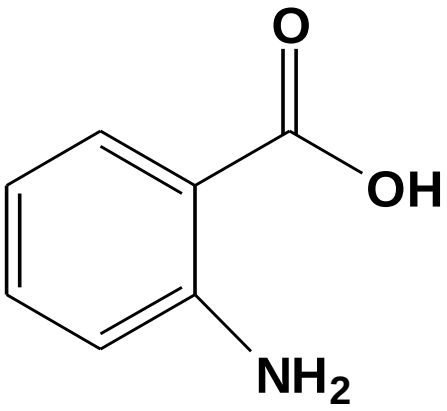


Ground structure

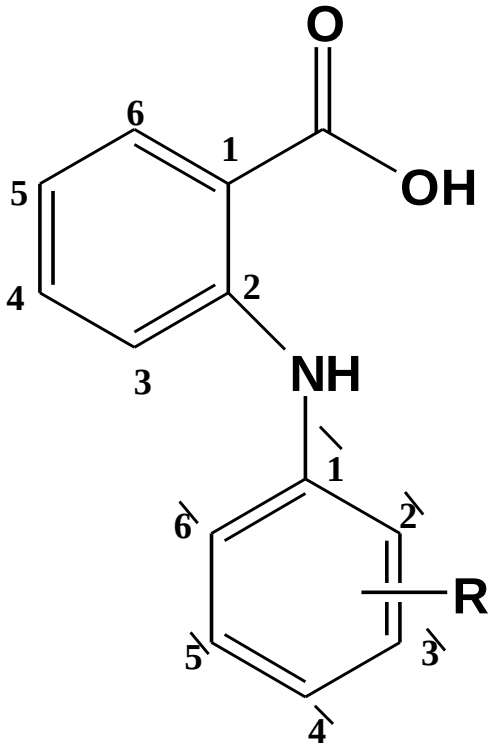
N-Arylanthranilic acid [Fenamic acid]



General structure of NSAIDs



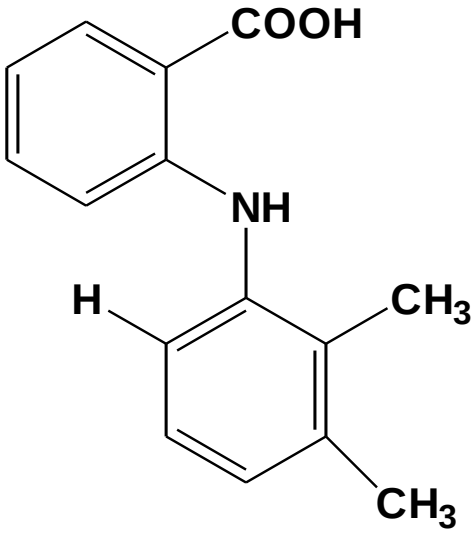
Anthranilic acid



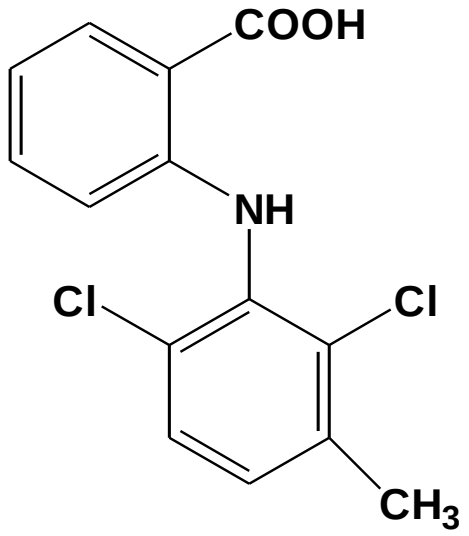
General structure of anthranilate

N-Arylanthranilic acid acid [Fenamic acid]

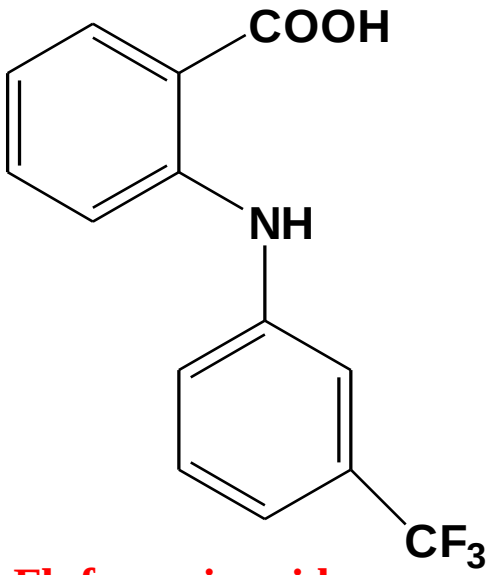
Anthranilic acid:
Classical bioisosteric replacement of salicylic acid (o-OH) by (o-NH2)



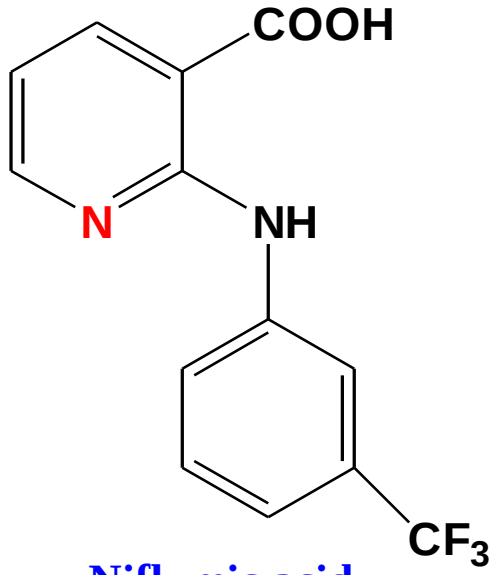
Mefenamic acid



Meclofenamic acid



Flufenamic acid



Niflumic acid

N-Arylanthranilic acid [Fenamic acid]

SAR of fenamic acid

Substitution on the anthranilic acid ring generally reduced the activity.

Substitution on the N-aryl ring can lead to conflicting results.

In the assay for the anti-inflammatory activity the order of activity was generally 3’>2’>4’ for mono substitution with CF3group (flufenamicacid).

The 2’Cl derivative being more potent than 3’Cl analogue.

In di-substituted derivatives, where the nature of two substituent is the same, 2’,3’ di-substitution appear to be the most effective (mefenamic acid).

N-Arylanthranilic acid [Fenamic acid]

Meclofenamic acid (two ortho-Cl) forcing this ring out of the plane of the anthranilic acid ring, over flufenamic acid (no ortho-substituents) and mefenamic acid (one ortho-CH3).

Meclofenamic acid possesses 25 times greater anti-inflammatory activity than mefenamic acid

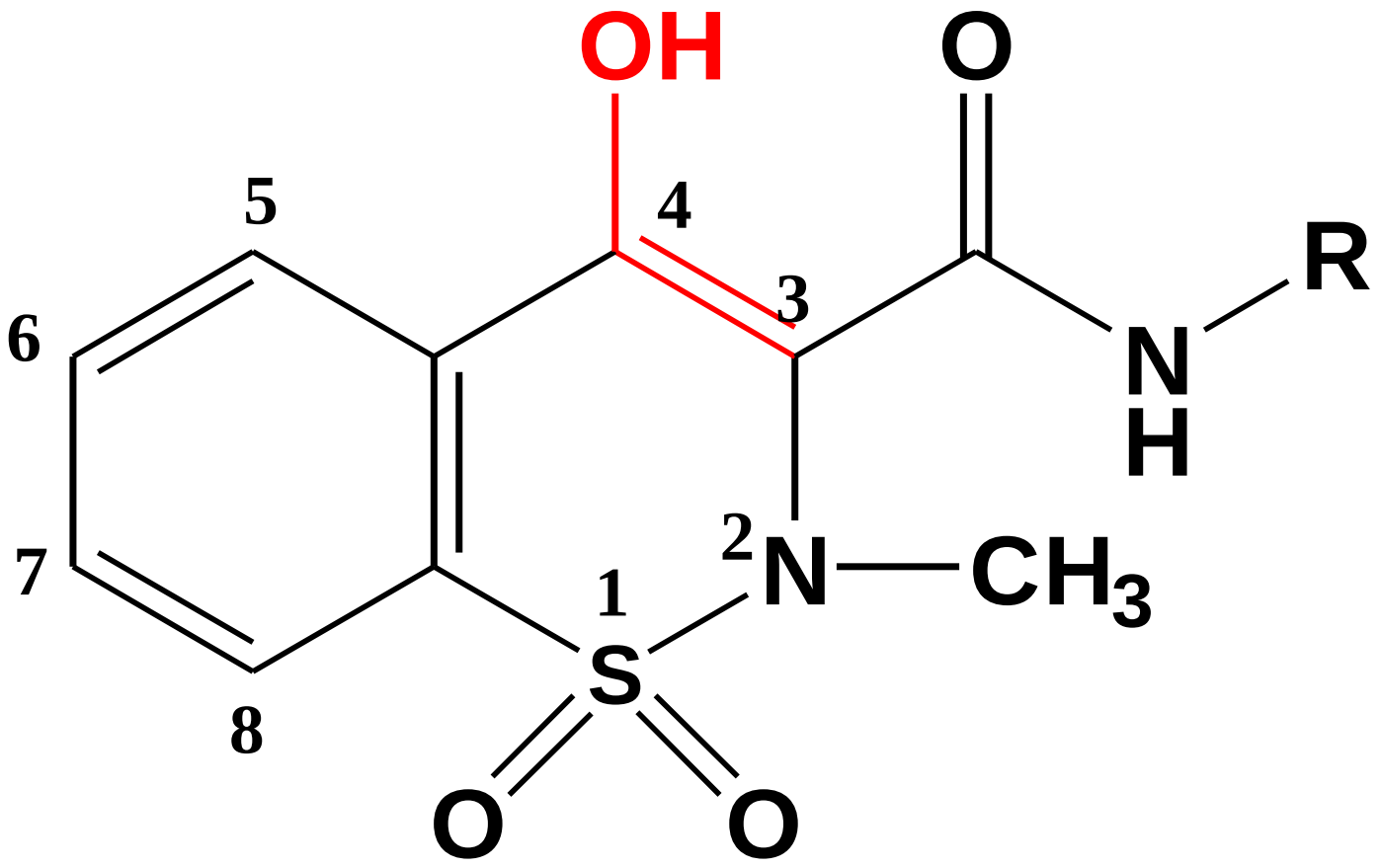
The NH moiety of anthranilic acid appears to be essential for activity since replacement of NH functional group with O, CH2, S, SO2, N-CH3 or N-COCH3 functionalities significantly reduce the activity.

Anthranilic acid derivatives are active. m- and p-Aminobenzoic acid analogs are not active.

Replacement of carboxylic acid functions with the isosteric **tretrazole** has little effect on the activity.

Oxicam

4-hydroxy-1,2-benzothiazine carboxamide



Oxicam

4-hydroxy-1,2-benzothiazine carboxamide

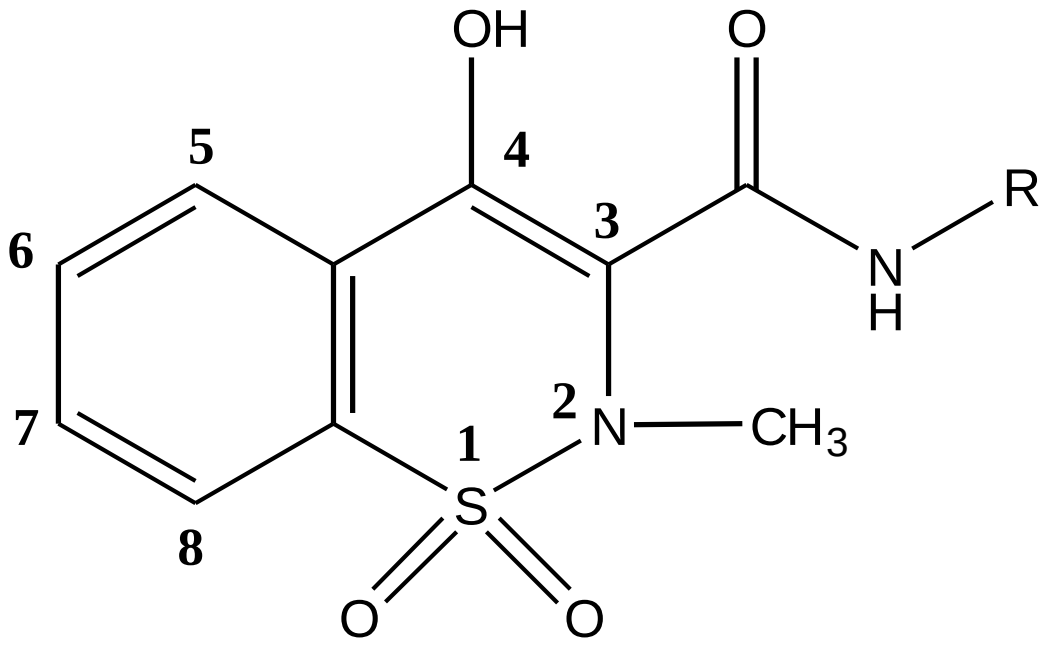
No free carboxylic group

Acidic group is **enol**

Analgesic
Anti-inflammatory

The advantage: long half life
Allow once daily dosing

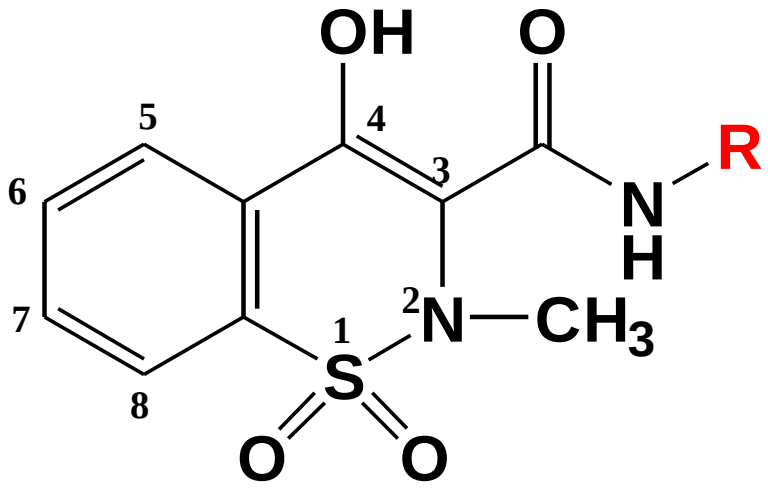
GI and CNS disturbances



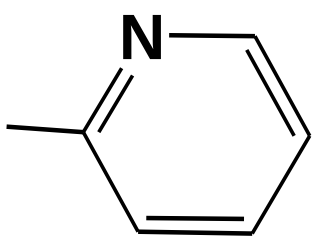
Oxicam

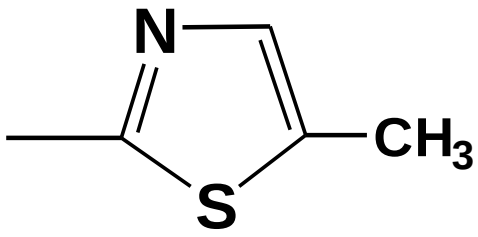
4-hydroxy-1,2-benzothiazine carboxamide

Meloxicam a selective COX 2 inhibitor



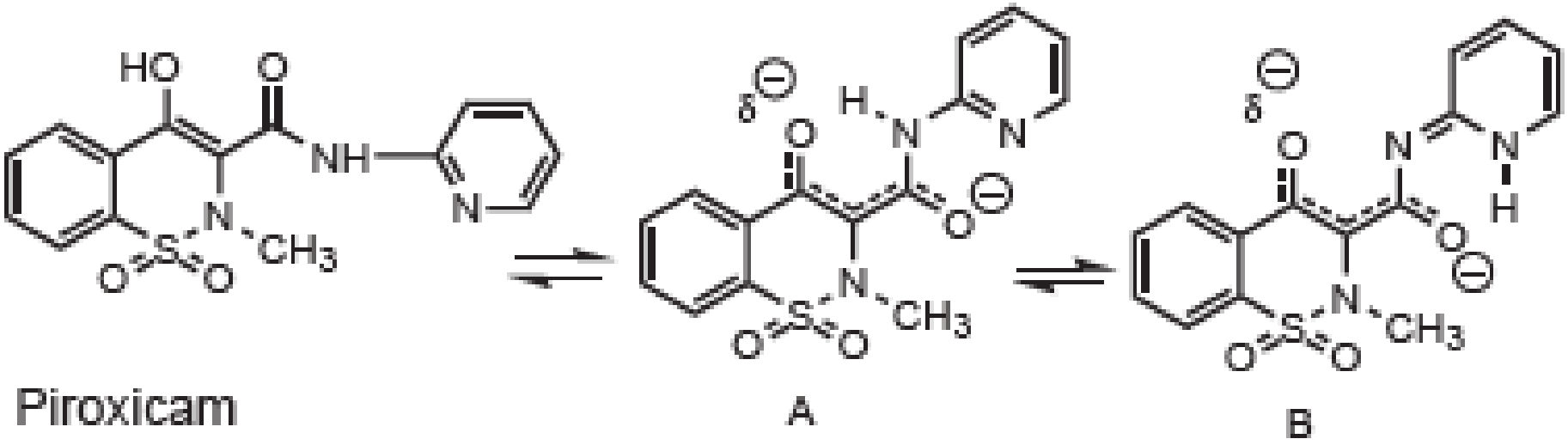
R





Compound
Piroxicam
Meloxicam

Oxicam: Stabilization of enolate anion



Piroxicam

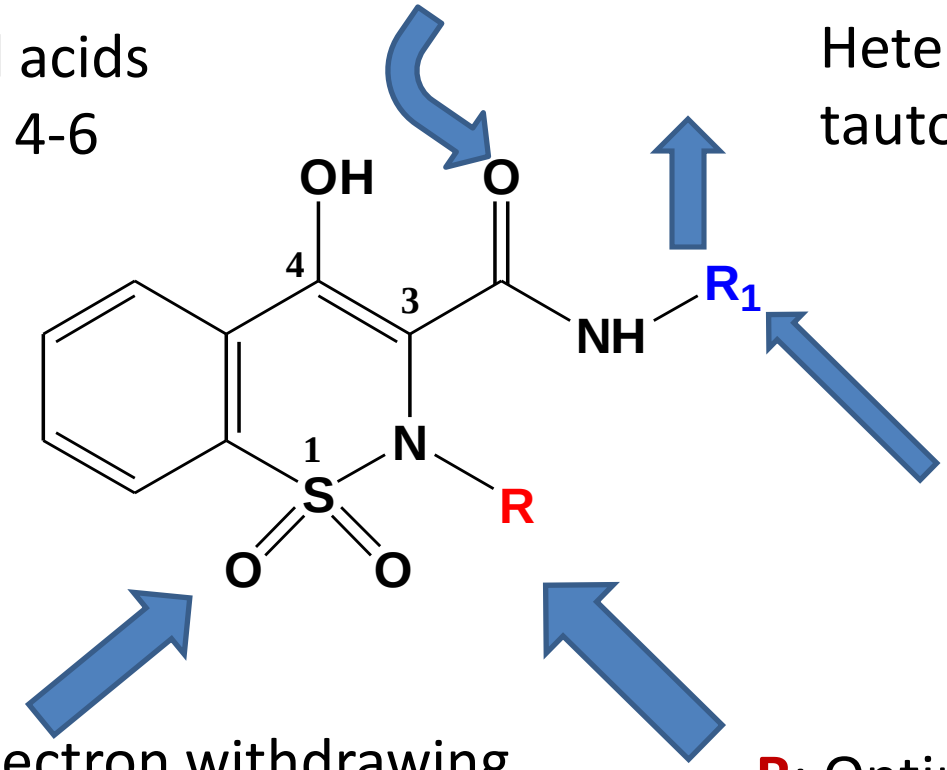
A

B

SAR of Oxicam

Carboxamide group (-CO-NH-) stabilize enolate anion

Enol acids
Pka: 4-6



R1: Heterocyclic enhances activity (7X) than aryl at carboxamide
Like 2-pyridyl, 2-thiazolyl, isoxazolyl Heterocycles lower pKa [See tautomerism]

Aryl substituent: meta position compound will be most potent than para or ortho e.g. -Cl group observe max. activity.

Electron withdrawing group at 1

R: Optimal activity -CH3

Next video

Selective COX II inhibitors

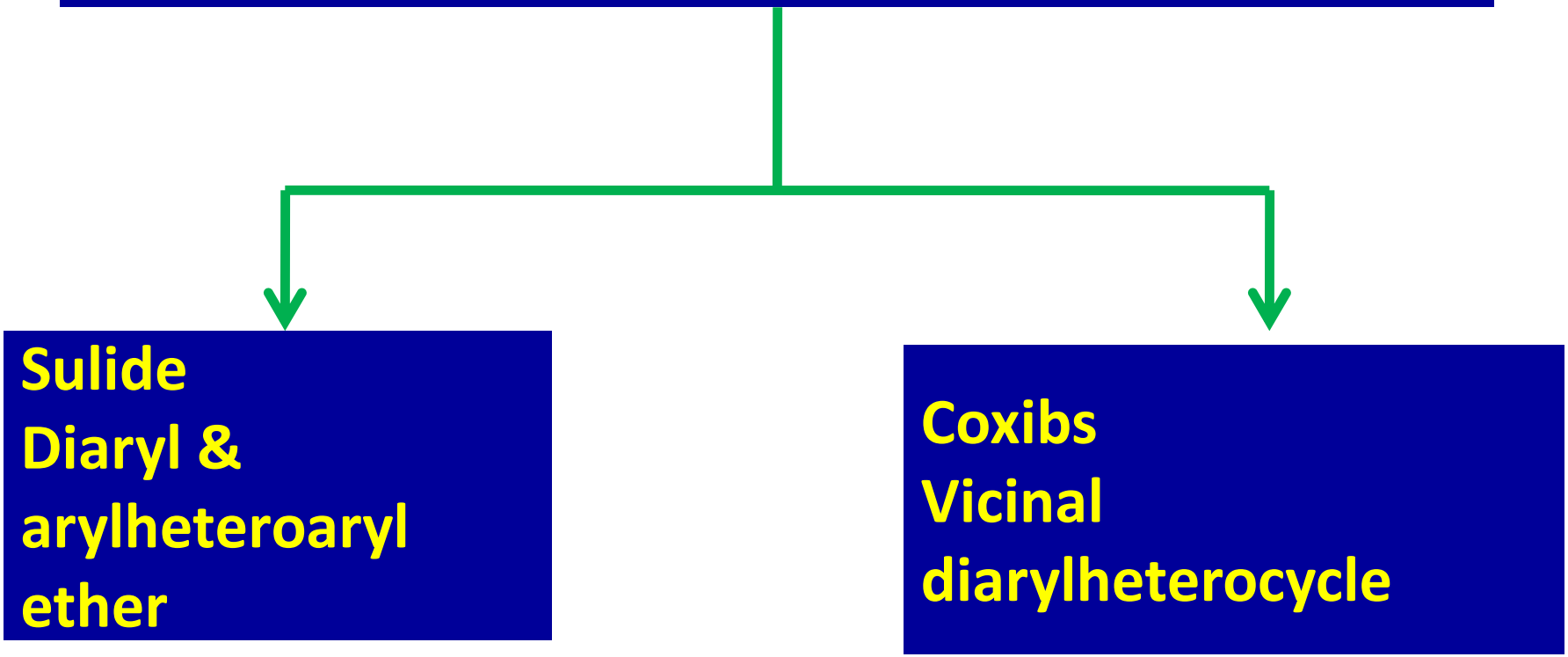
Review structure of COX active site

Non-Steroidal Anti-Inflammatory Drugs NSAIDs

Part 6

Dr. Mai Ramadan

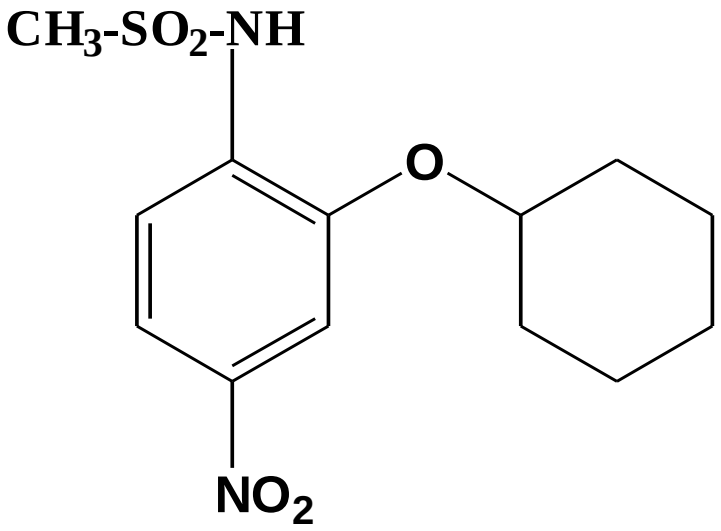
Selective COX II inhibitors



Selective COX-2 Inhibitor :

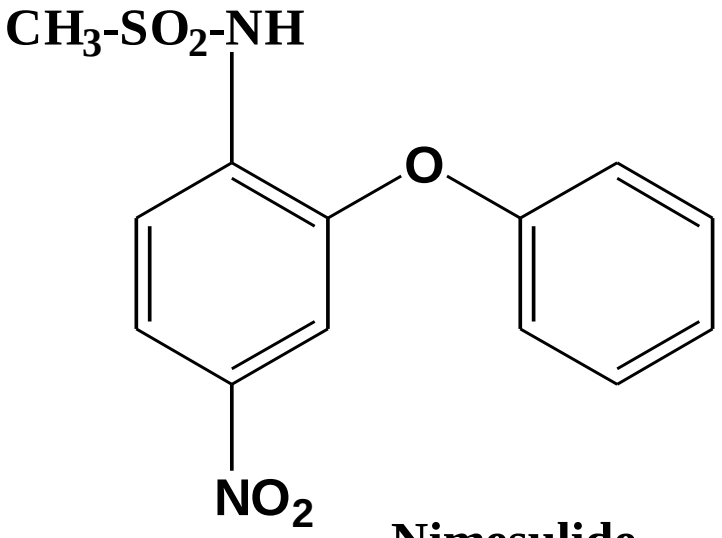
COX-2 inhibitors **do not contain carboxylic acid** groups. They have different chemical structures

Diaryl-and arylheteroaryl ether (sulfonanilide inhibitors): Known as sulides e.g. **Nimesulide, NS-398, flosulide**



NS-398

Lead compound



Nimesulide

Selective COX-2 Inhibitor:

Nimesulide

A relatively COX-2 selective

NSAID with pain medication and fever reducing properties.

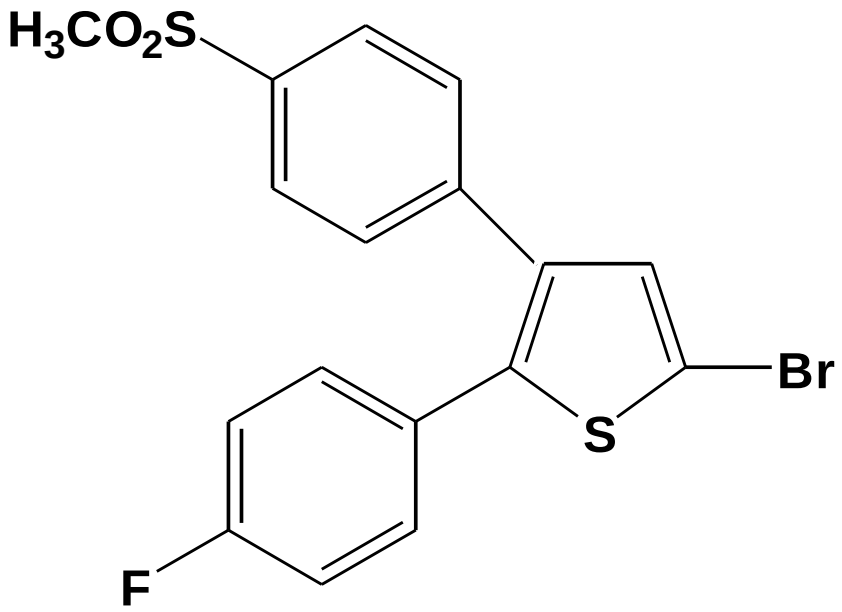
Its approved indications are the treatment of acute pain, the symptomatic treatment of osteoarthritis and primary dysmenorrhoea

Remember: NSAIDs known to have high COX-2 selectivity e.g. **Meloxicam, etodolac**

Selective COX-2 Inhibitor :

Vicinal diarylheterocycles: Coxibs

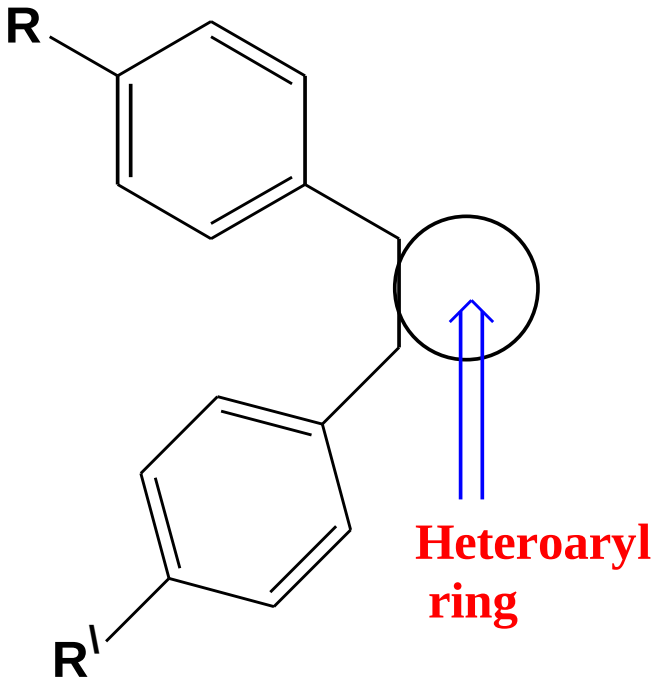
Celecoxib, rofecoxib, valdecoxib, pareocoxib



DuP 697
Lead compound

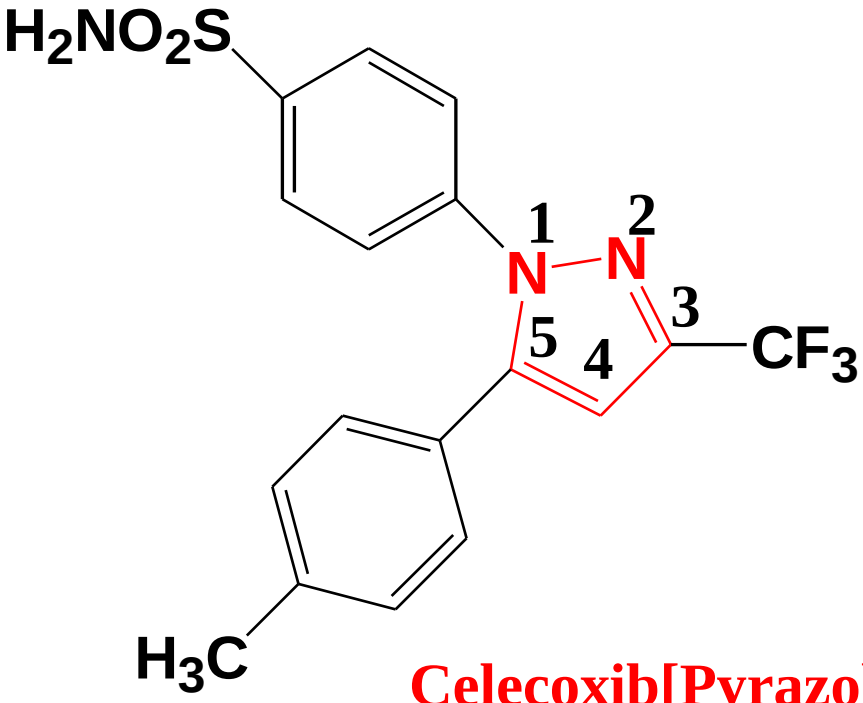
R: $-SO_2NH_2$, $-SO_2CH_3$

Sulfonamide, methylsulfone

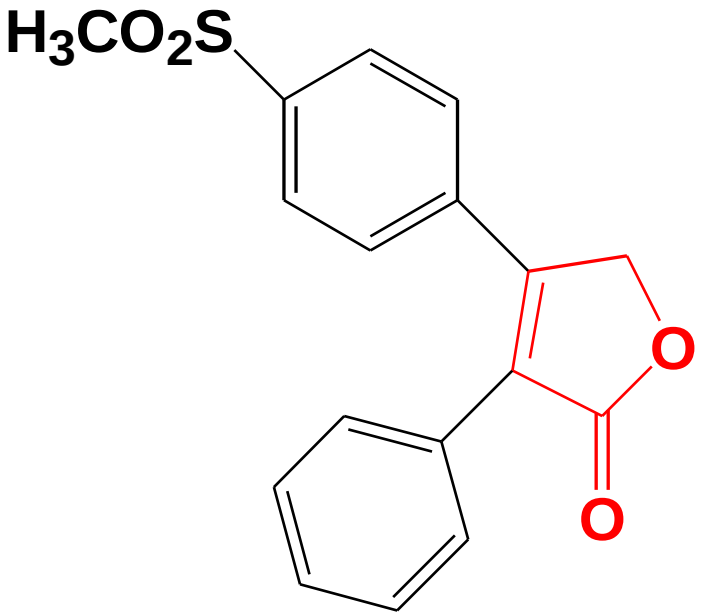


Ground structure

Selective COX-2 Inhibitor: Coxib



Celecoxib[Pyrazole]

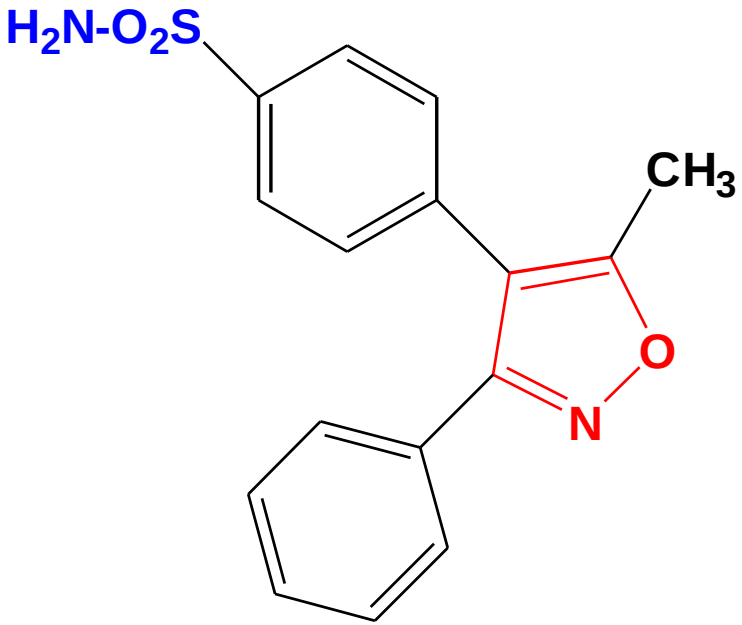


Rofecoxib [Furanone]

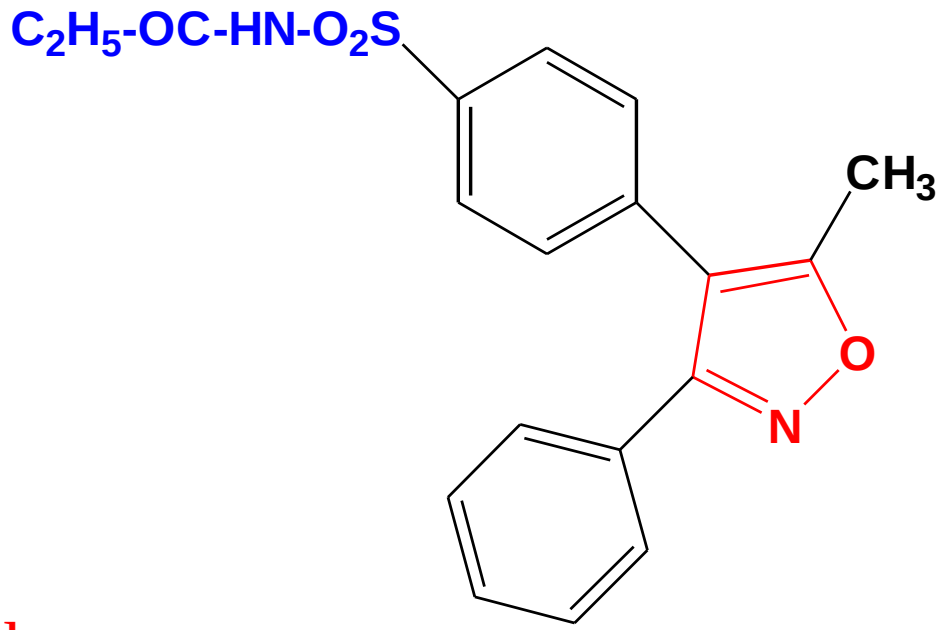
Selective COX-2 Inhibitor: Coxib

Parecoxib is a prodrug of valdecoxib

Precoxib sodium salt is a water-soluble and injectable



Valdecoxib [Oxazole]



Parecoxib

Selective COX-2 Inhibitor: Coxib

Long term clinical trial showed high risk of myocardial infraction.

Merck voluntarily withdrew rofecoxib from the U.S. market in 2004, followed by Pfizer's withdrawal of valdecoxib in 2005.

Celecoxib may cause an increased risk of serious cardiovascular thrombotic events, myocardial infarction, and stroke, which can be fatal. All NSAIDs may have a similar risk. This risk may increase with duration of use. .

Celecoxib **causes like other NSAIDs** an increased risk of serious GI adverse events, including bleeding, ulceration, and perforation of the stomach or intestines, which can be fatal.

Selective COX-2 Inhibitor : Coxib

SAR of celecoxib

Two aryl rings at **1,5** of pyazole heterocyclic ring are essential for activity.

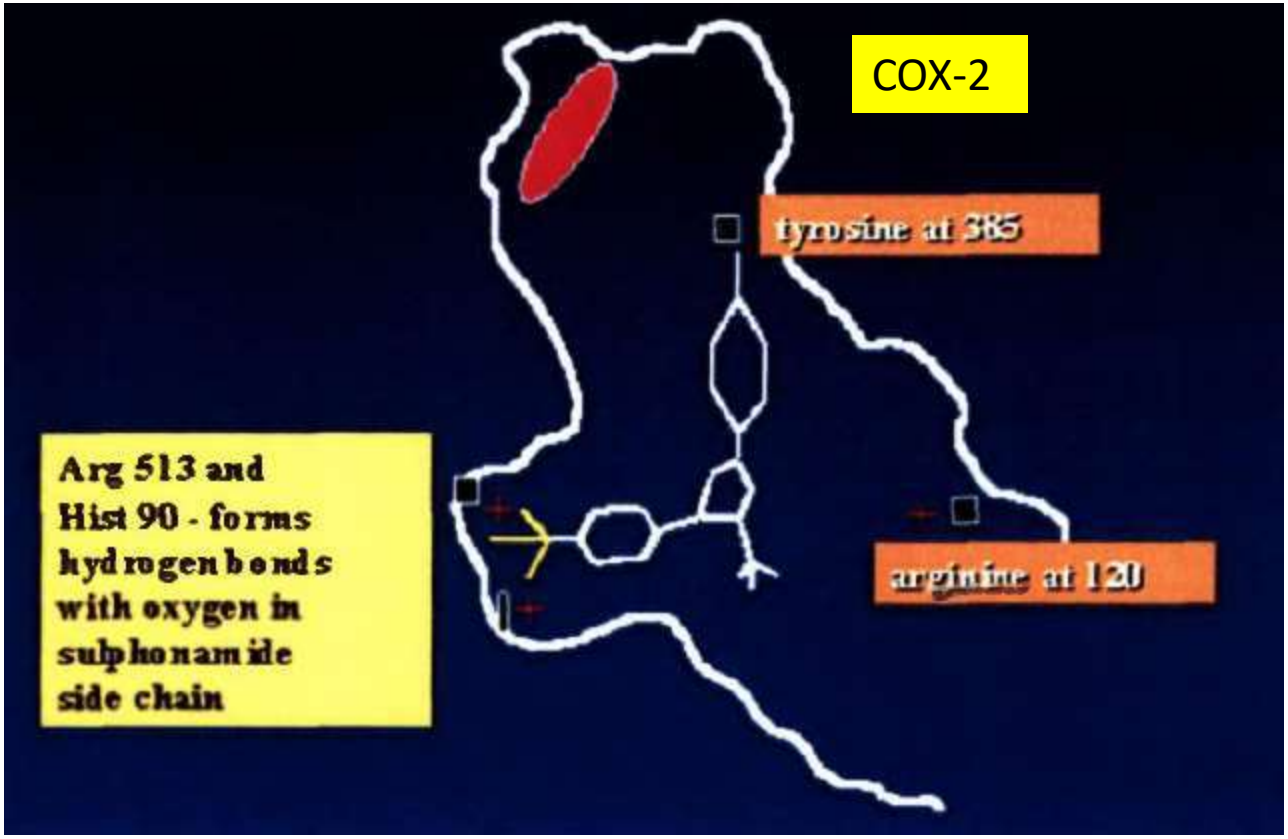
Substituent on **para**-position of one of the aryl rings play an important role in COX-2 selectivity

-SO_2NH_2 Or -SO_2CH_3 on p-phenyl ring is essential for activity and selectivity. Sulfide and sulfoxide are not selective COX-2

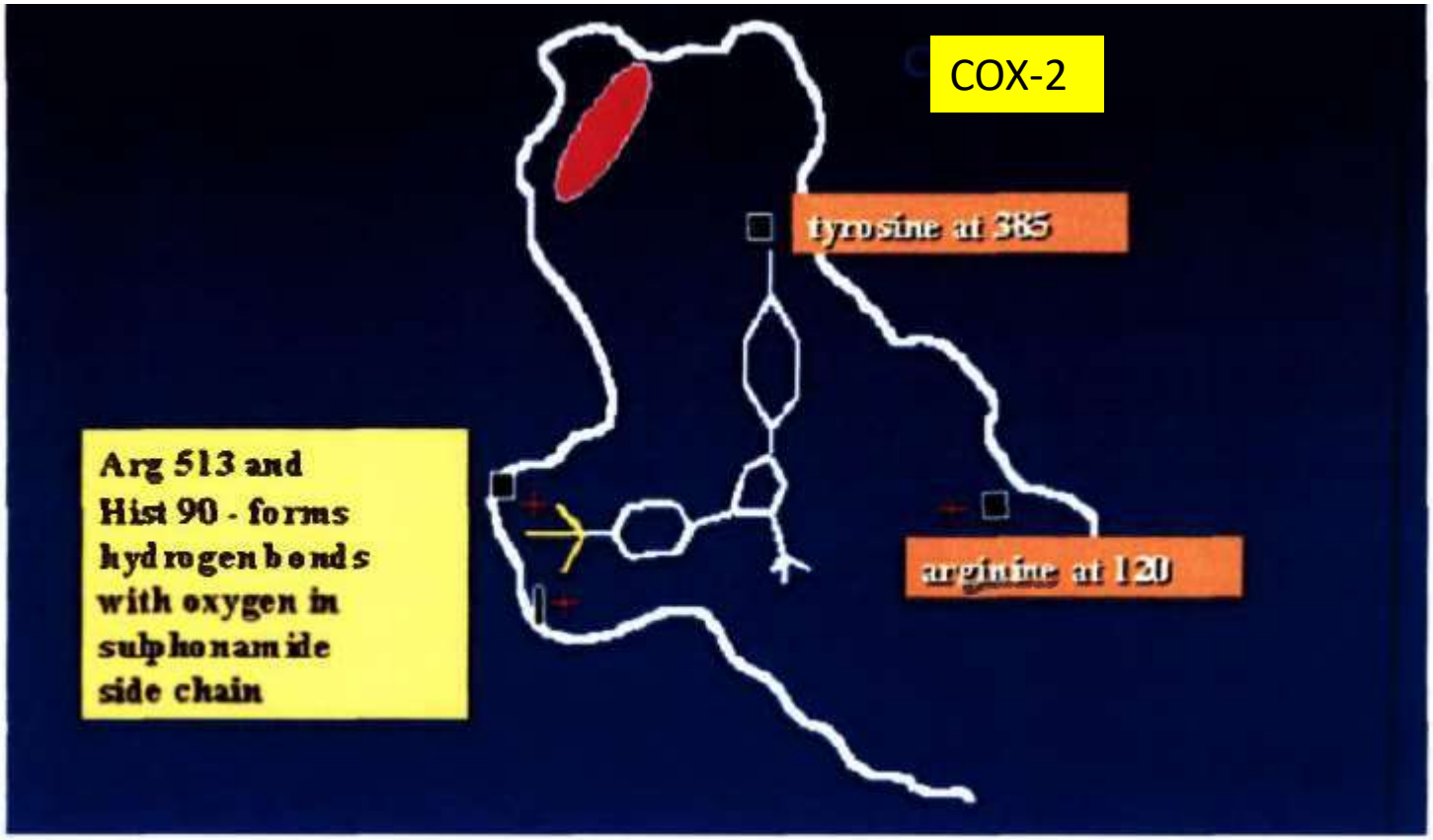
Replace -SO_2NH_2 by other group like -OCH3 a decrease of activity and selectivity.

At position **3** of pyrazole ring -CF_3 is optimal, -CHF_2 has high activity but -CH_2F or -CH_3 decreases activity and selectivity.

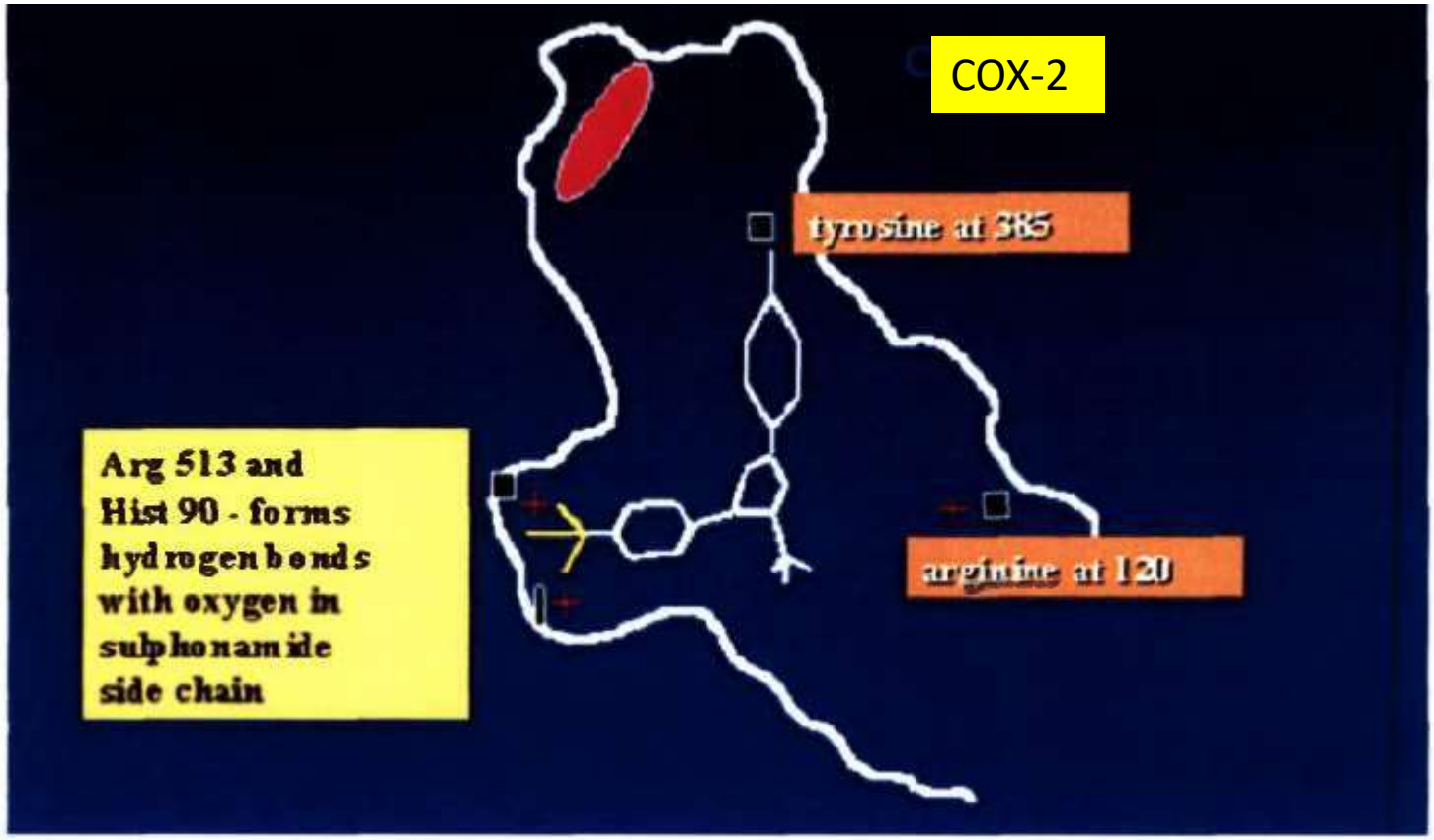
The COX-2 inhibitors lack COOH and binding with COX active site does not require ionic interaction with Arg120.



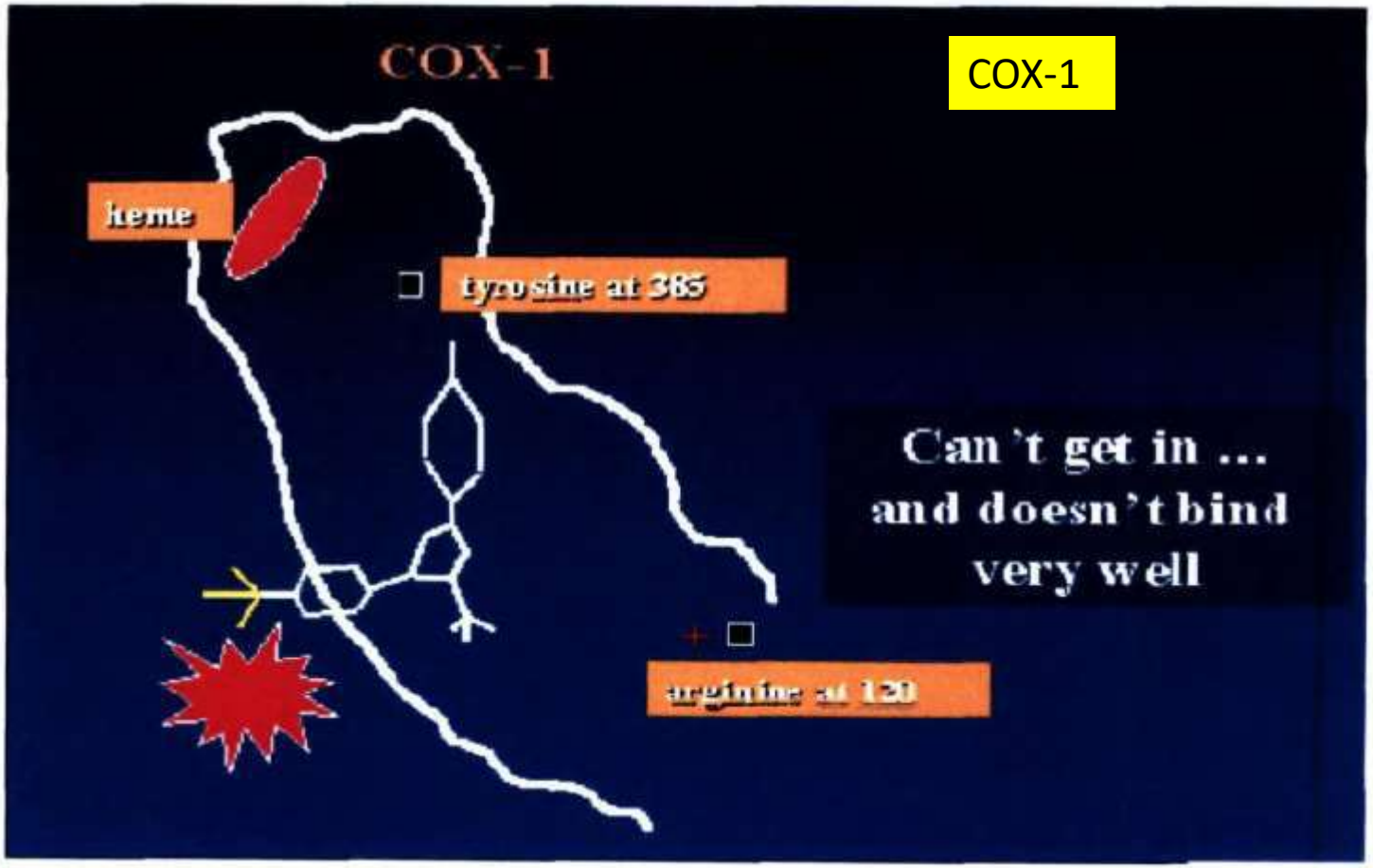
The hydrophilic side-pocket of COX-2, the oxygen of the sulfonamide (or sulfone) group interacts with **His 90, Arg 513, and Gln 192** and forms hydrogen bonds.



The substituted phenyl group at the top of the channel interacts with the side-chains of amino acid residues through hydrophobic and electrostatic interactions.



Tyr385 makes for some sterical restrictions of this side of the binding site so a small substituent of the phenyl group makes for better binding.



The bulky sulfonamide group in COX-2 inhibitors such as celecoxib and methylsulfone in rofecoxib prevent the molecule from entering the COX-1 channel

Selective COX-2 Inhibitor : Coxib

Metabolism of celecoxib occurs in the liver, involves hydroxylation of 4-methyl group to primary alcohol, which is subsequently oxidized to its corresponding carboxylic acid