Apr 23: Presentations

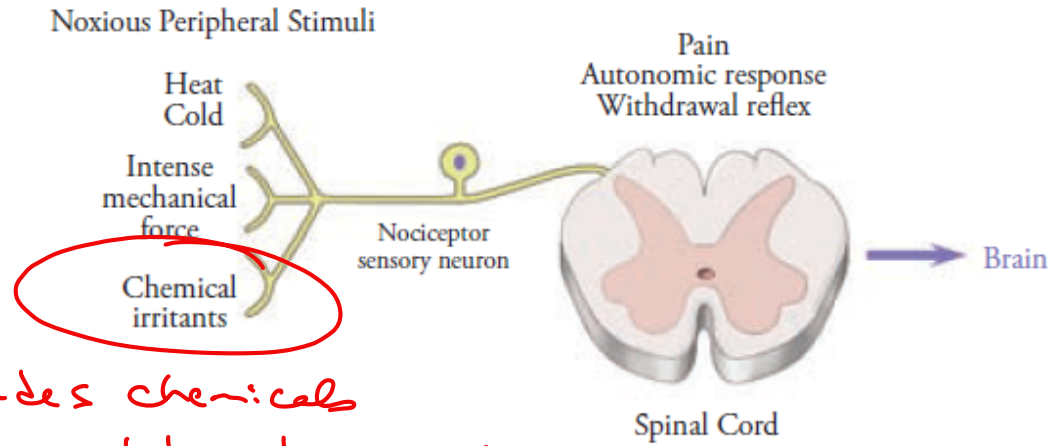
Apr 28:

Apr 30 last exam

NSAIDS

Non steroidal anti inflammatories

Pain Pathways



Includes chemicals released by damaged cells prostaglandins + leukotrienes

Epicritic pain

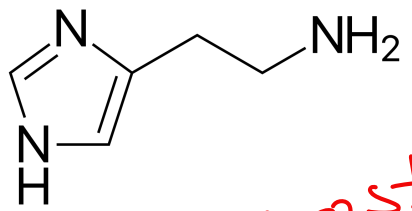
Proropathic pain

Neuropathic pain

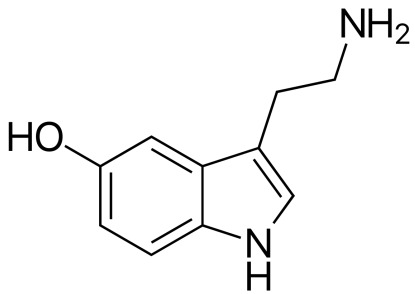
Inflammation

Initial injury releases of mediators like

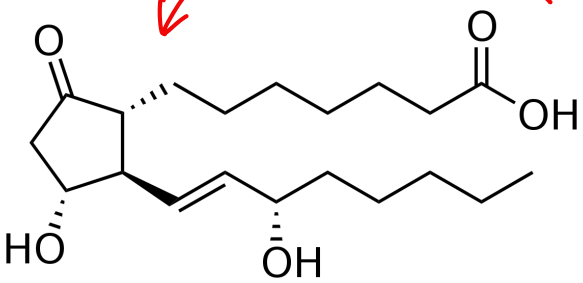
histamine
increased blood flow redness + swelling



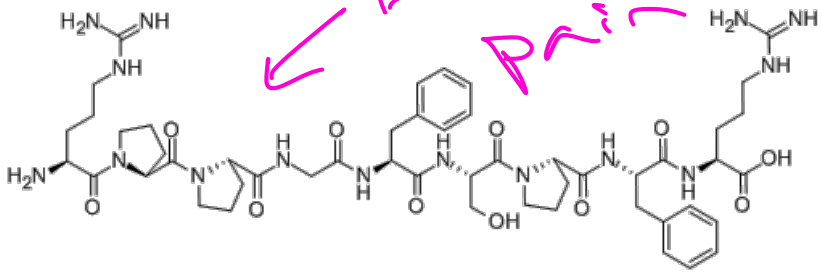
5-HT
vasoconstrictor
increases vascular permeability



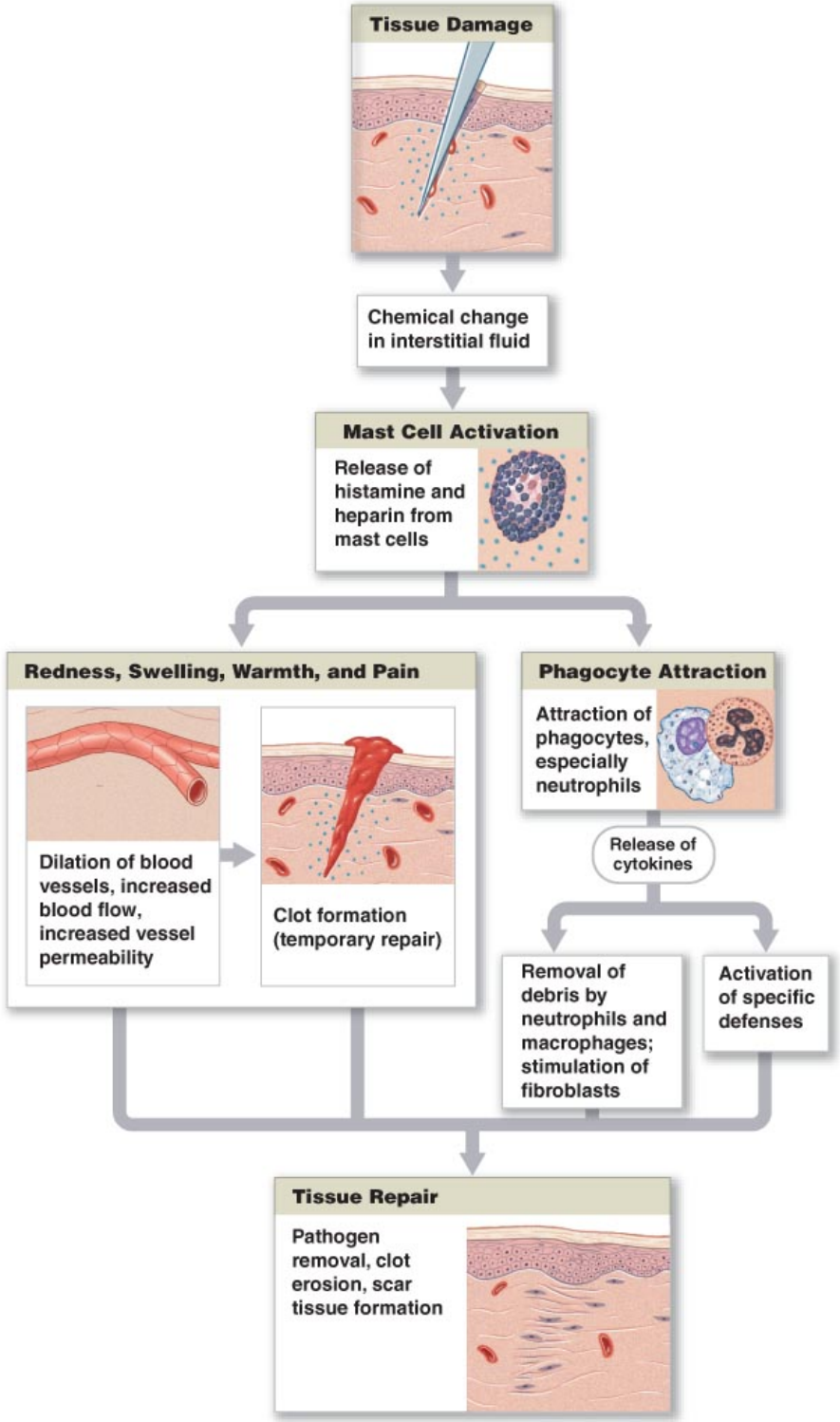
prostaglandins
pain
fever



Bradykinin
pain



The events in inflammation



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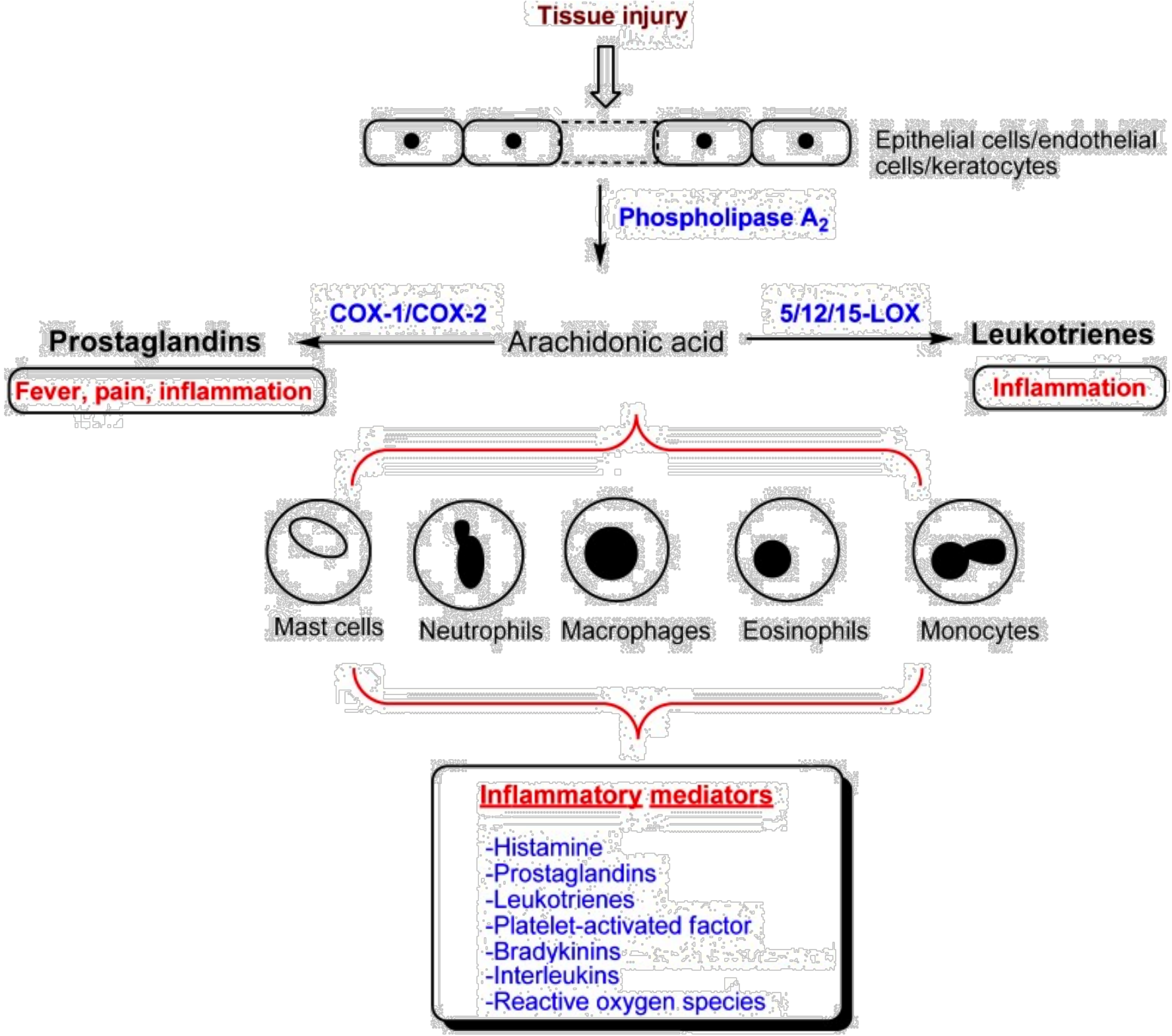
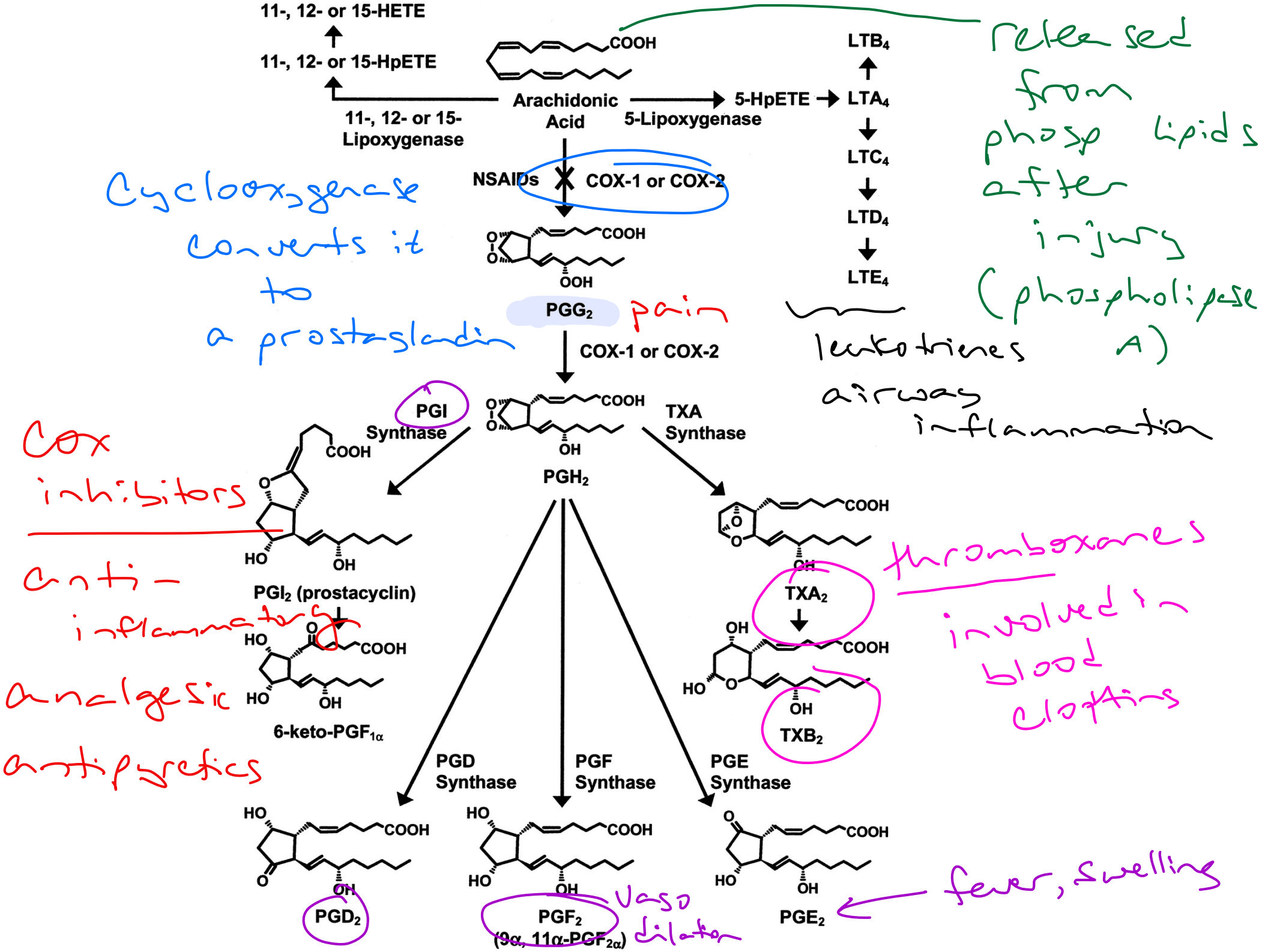
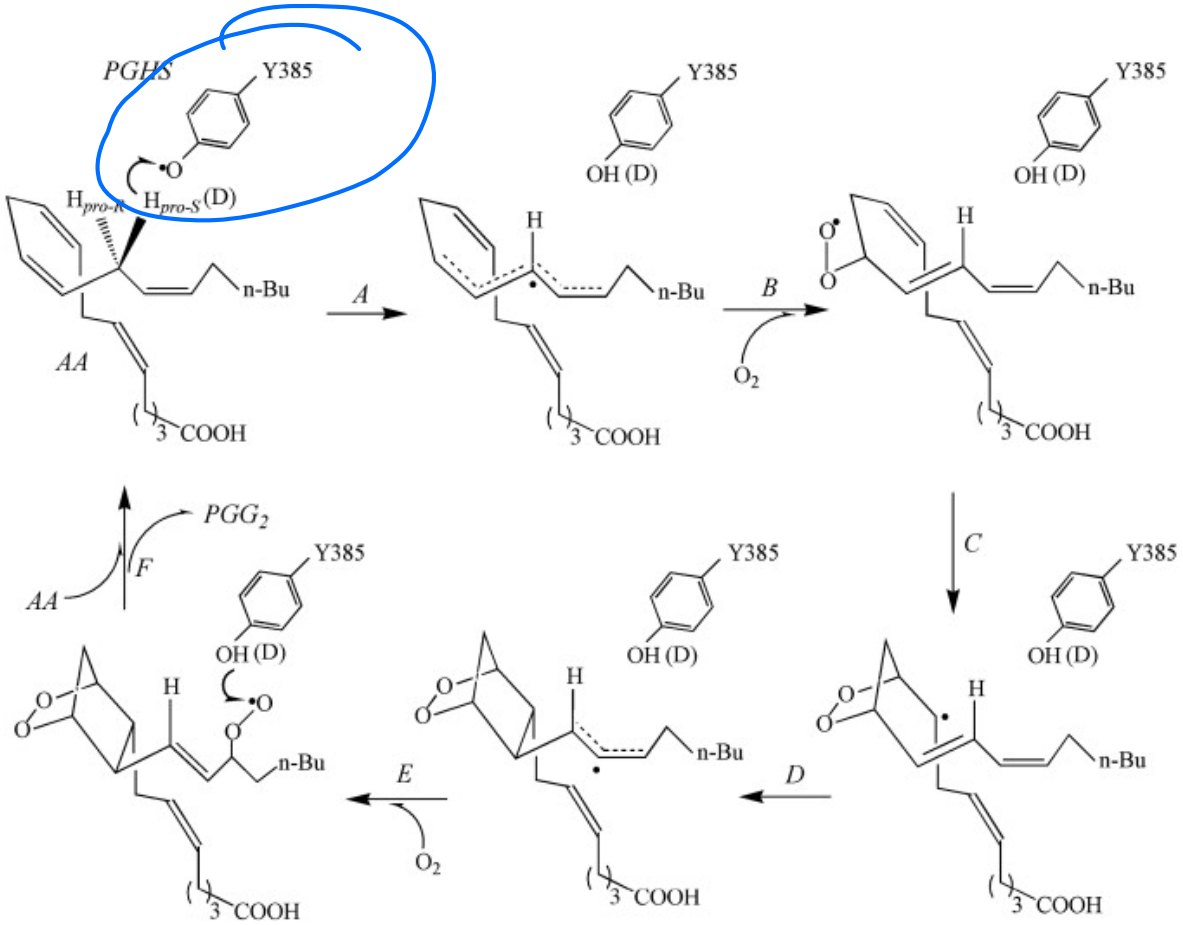
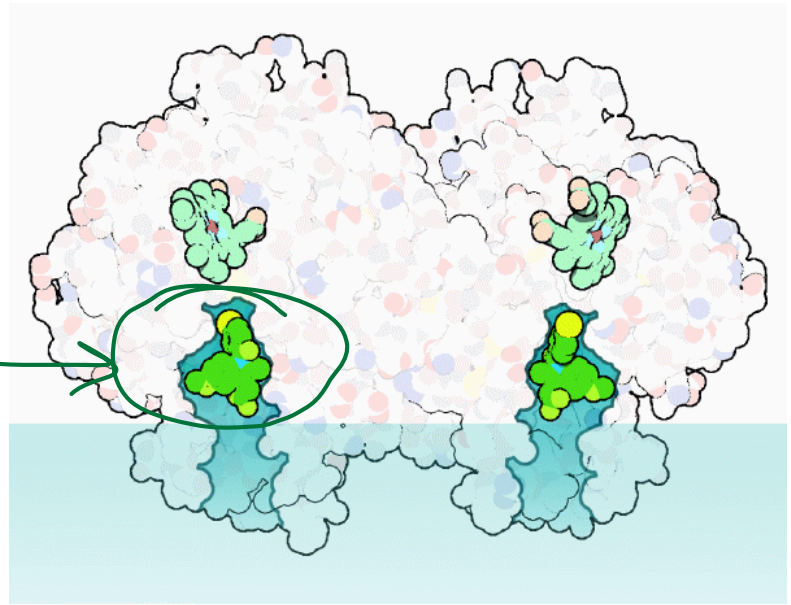

Tissue injury
Epithelial cells/endothelial cells/keratocytes
Phospholipase A2
COX-1/COX-2
5/12/15-LOX
Prostaglandins
Arachidonic acid
Leukotrienes
Fever, pain, inflammation
Inflammation
Mast cells
Neutrophils
Macrophages
Eosinophils
Monocytes
Inflammatory mediators
-Histamine
-Prostaglandins
-Leukotrienes
-Platelet-activated factor
-Bradykinins
-Interleukins
-Reactive oxygen species


11-, 12- or 15-HETE
11-, 12- or 15-HpETE
11-, 12- or 15-Lipoxygenase
Arachidonic Acid
5-HpETE
5-Lipoxygenase
LTB4
LTA4
LTC4
LTD4
LTE4
released from phosp lipids after injury (phospholipase A)
leukotrienes
airway inflammation
NSAIDs
COX-1 or COX-2
Cyclooxygenase converts it to a prostaglandin
PGG2
pain
COX-1 or COX-2
PGI Synthase
TXA Synthase
PGH2
COX inhibitors
anti-inflammatory
analgesic
antipyretics
PGI2 (prostacyclin)
6-keto-PGF1α
TXA2
TXB2
thromboxanes
involved in blood clotting
PGD Synthase
PGF Synthase
PGE Synthase
PGD2
PGF2 (9α, 11α-PGF2α)
PGE2
Vaso dilator
fever, swelling



Cyclooxygenase - free radical mechanism using a Tyr

NSAID (indomethacin) in COX binding site

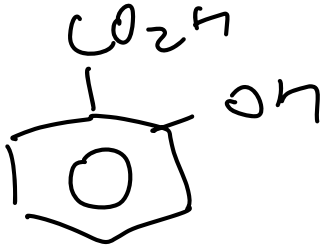


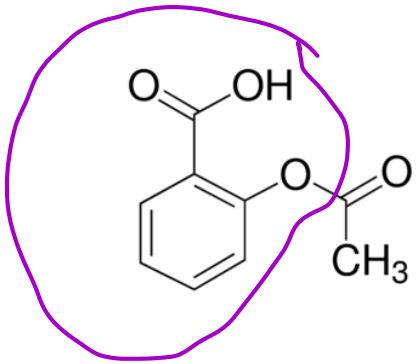
http://pdb101.rcsb.org/motm/17

Non Steroidal Anti Inflammatory Drug

NSAID Classification (6)

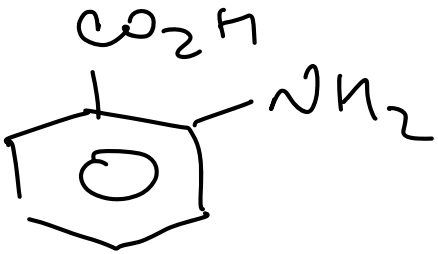
Salicylate Derivatives

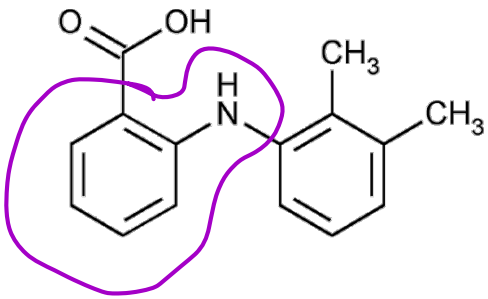




Aspirin

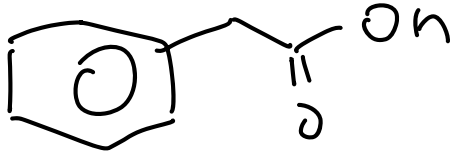
Arylanthranilic Acids

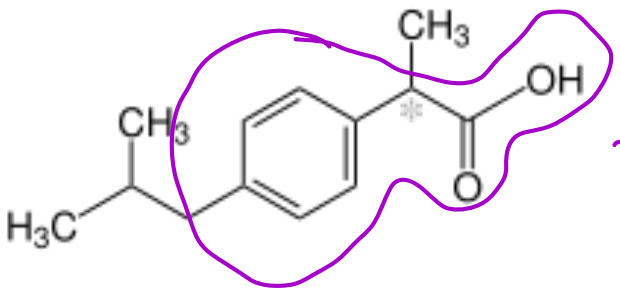




mefenamic acid

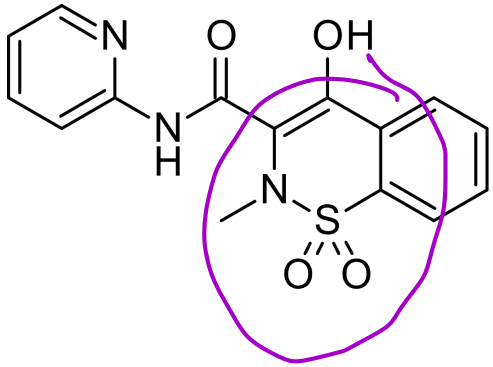
~~Arylpropionic Acids~~ (Phenylacetic acid derivatives)





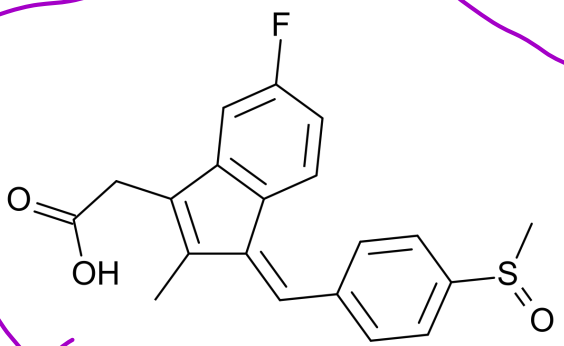
Ibuprofen

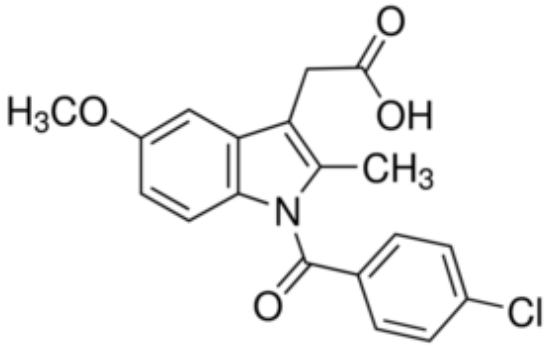
Oxicams



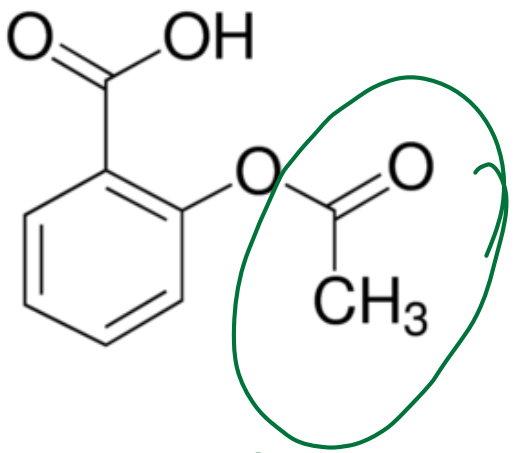
piroxicam

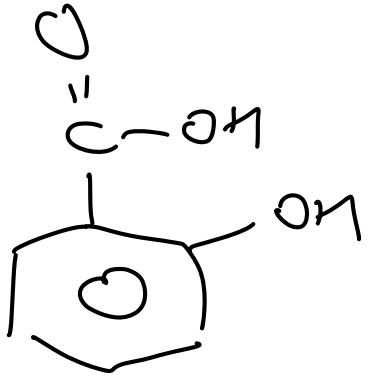
Indene and Indole Derivatives





Acetylsalicylic Acid





- salicylic acid
- found in willow bark

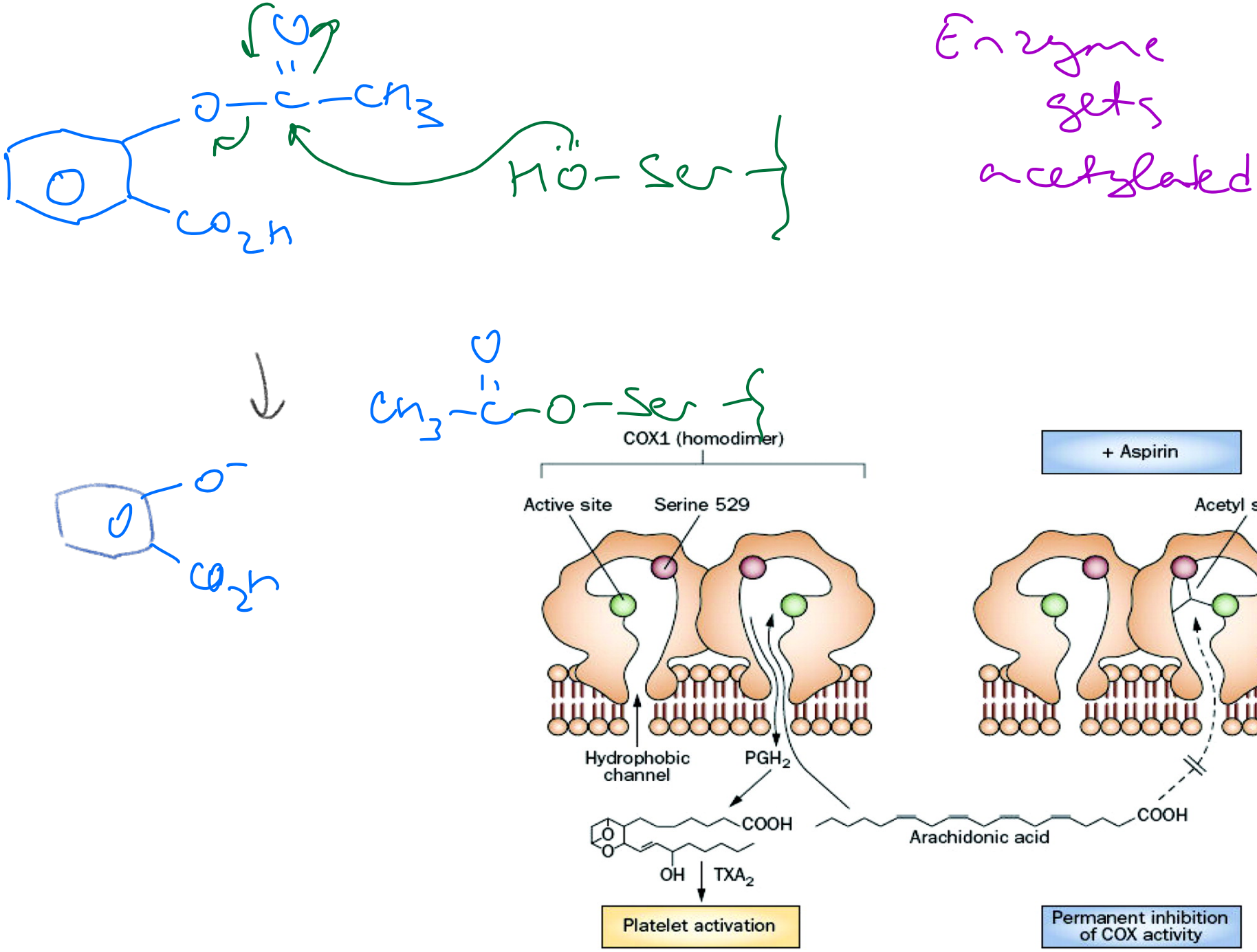
acidic

adding acetyl group makes less acidic decreases stomach irritation

a spirin

old name from spiric acid

acetyl


Enzyme gets acetylated
COX1 (homodimer)
+ Aspirin
Active site
Serine 529
Acetyl serine
Hydrophobic channel
PGH2
COOH
Arachidonic acid
COOH
OH
TXA2
Platelet activation
Permanent inhibition of COX activity

Reye's Syndrome — children + teenagers with fevers

- Swelling of liver + brain
- Liver failure

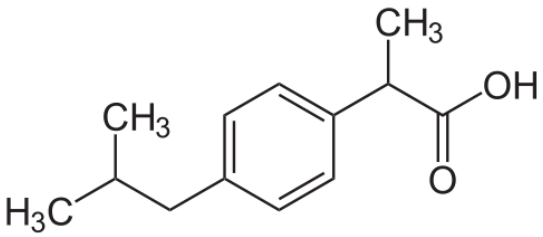
probably caused by mitochondrial damage

0.15 cases per 100,000 people / year

20-30% death rate

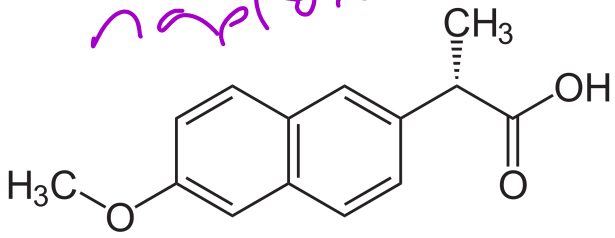
Phenylacetic Acid Derivatives

Ibuprofen (motrin, advil)



more potent than aspirin as anti-inflamm.

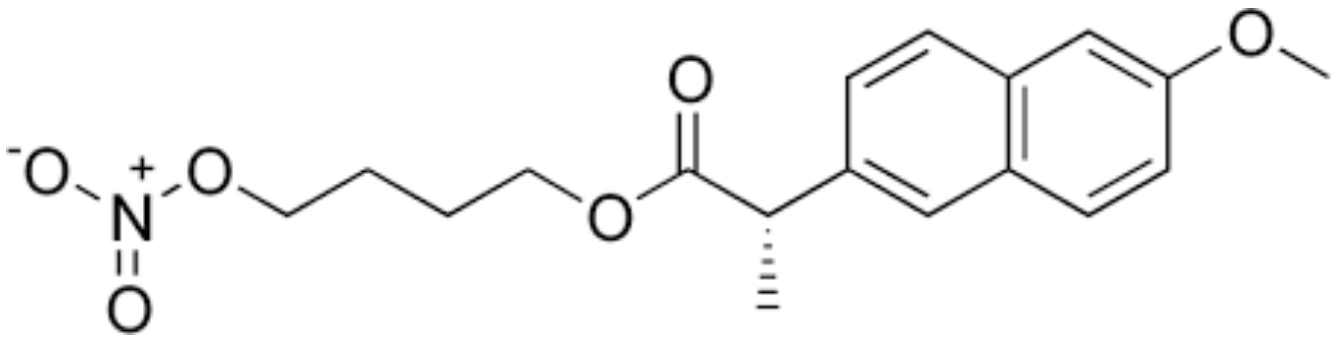
naproxen (naprosyn, aleve)



both highly bound to albumin in blood

⇑ 3-4x more potent than IBU as COX inhibitor

Both nonselective



Naproxcinod

A

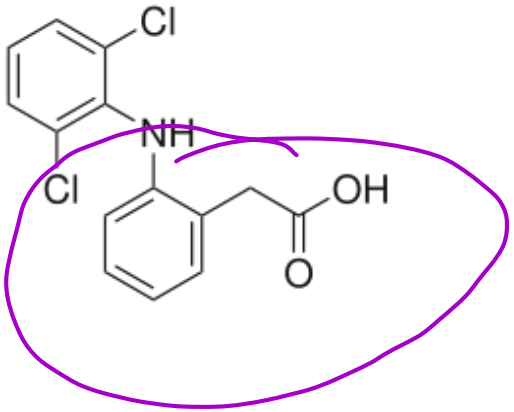
CINOD

COX inhibitor

nitric oxide donator

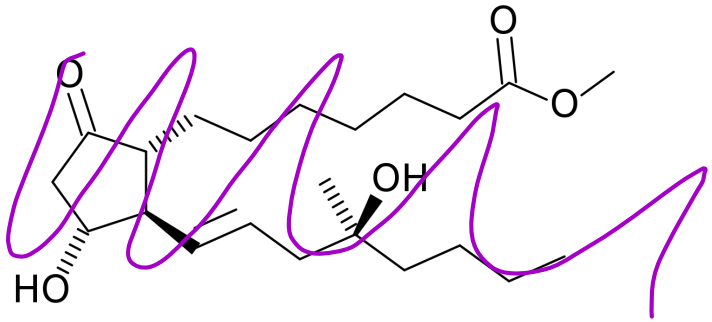
COX inhibitors can increase BP

NO acts as a vasodilator

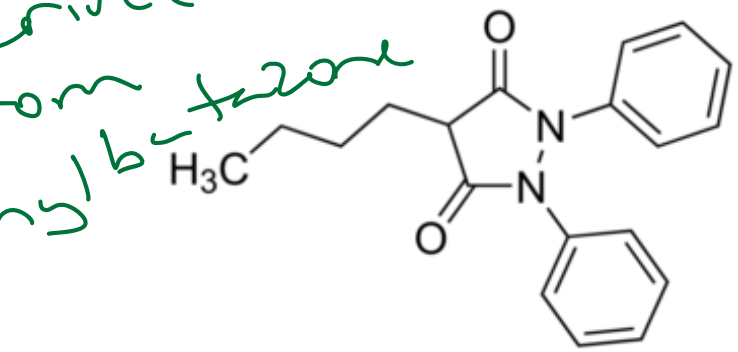


Diclofenac

Slightly selective for cox-2 over cox-1



Oxicams

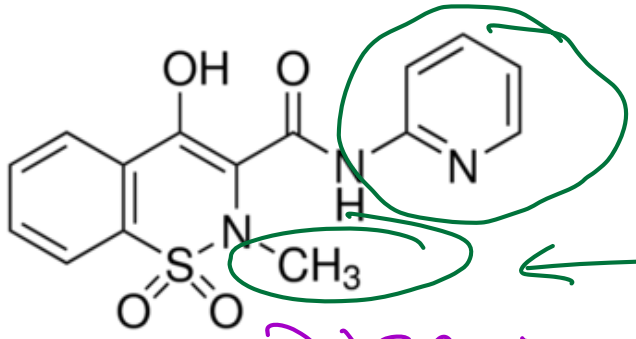


derived from phenylbutazone

still used by vets, not in people

designed as nonCA NSAIDs by pfizer

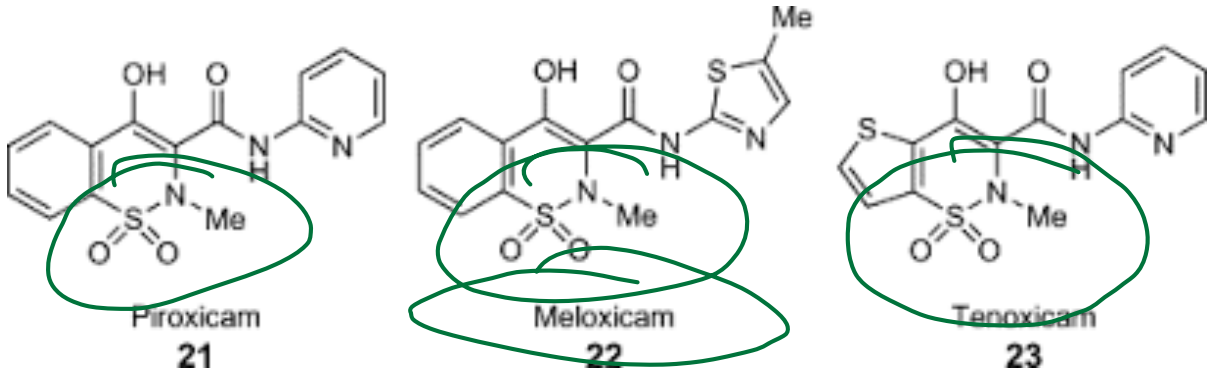
CA NSAIDs are quickly metabolized



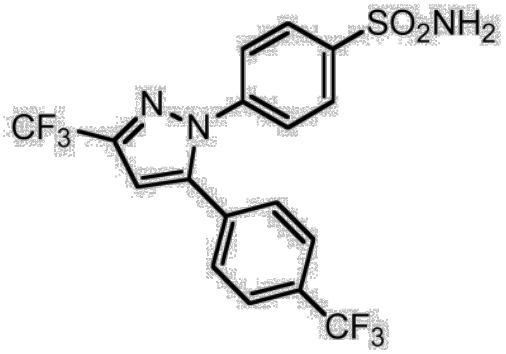
piroxicam

rigid + hydrophobic

methyl here good

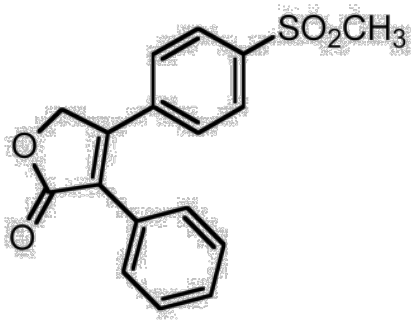


not very selective



Celecoxib

Celebrex

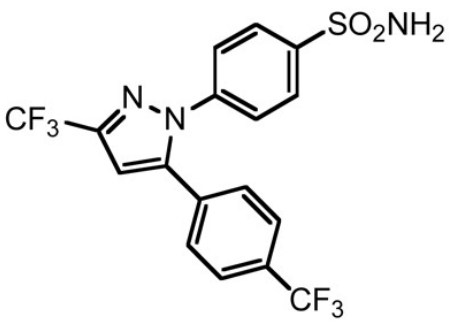


Rofecoxib

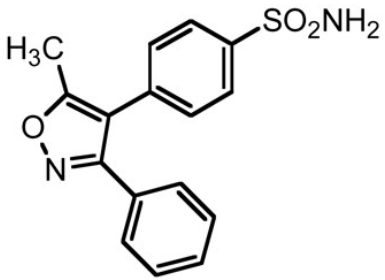
Vioxx

Cox-2 inhibitors

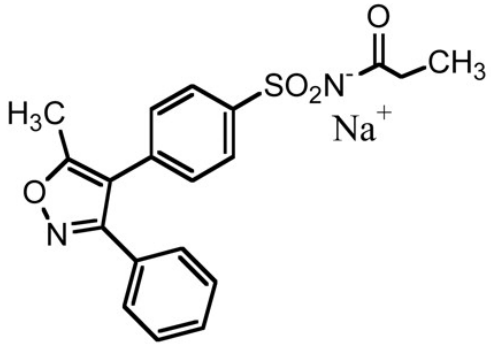
less likely to cause ulcers



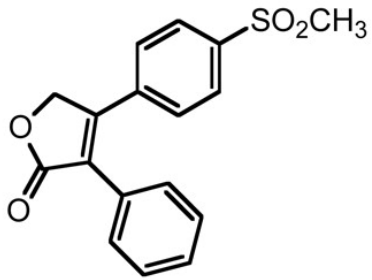
Celecoxib



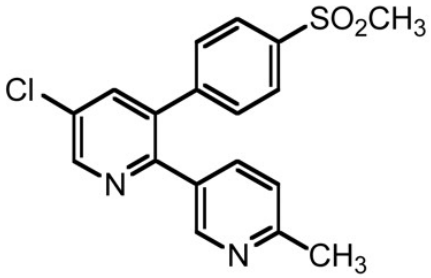
Valdecoxib



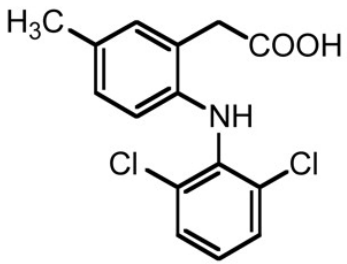
Parecoxib sodium



Rofecoxib



Etoricoxib



Lumiracoxib

Selective NSAID's

Cox -1

constitutive enzyme
always active
part of regular cell activity

inhibition → mucosal injury
renal damage

Cox-2

inducible
produces prostaglandins

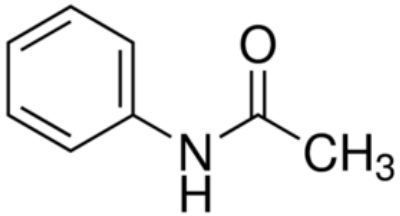
fever, pain mediating

larger binding site

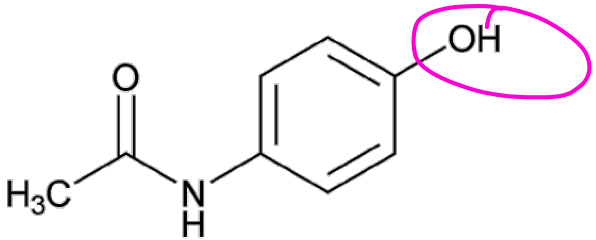
use drugs with larger side chains to get specificity for 2

Highly COX-2 Selective		**Moderately COX-2 Selective**	
Generic	Brand	Generic	Brand
Etoricoxib	Arcoxia	Celecoxib	Celebrex
Lumiracoxib	Prexige	Etodolac	Lodine
Parecoxib	Dynastat	Meloxicam	Mobicox
Rofecoxib	Vioxx		
Valdecoxib	Bextra		

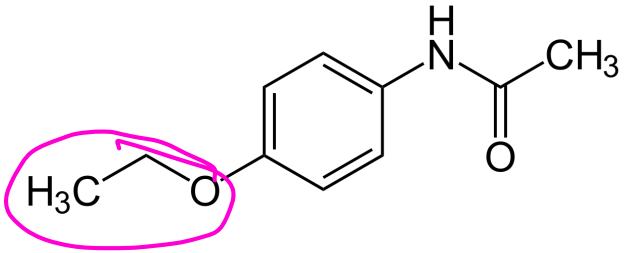
Acetominophen



Acetanilid



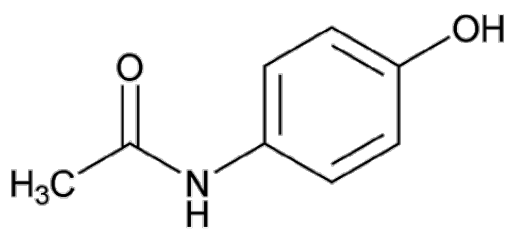
Acetominophen



Phenacetin

prodrug of acetominophen

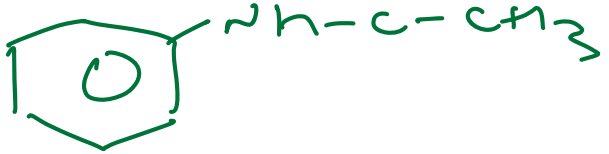
☆ nephrotoxic



Acetominophen (tylenol)

analgesic + antipyretic

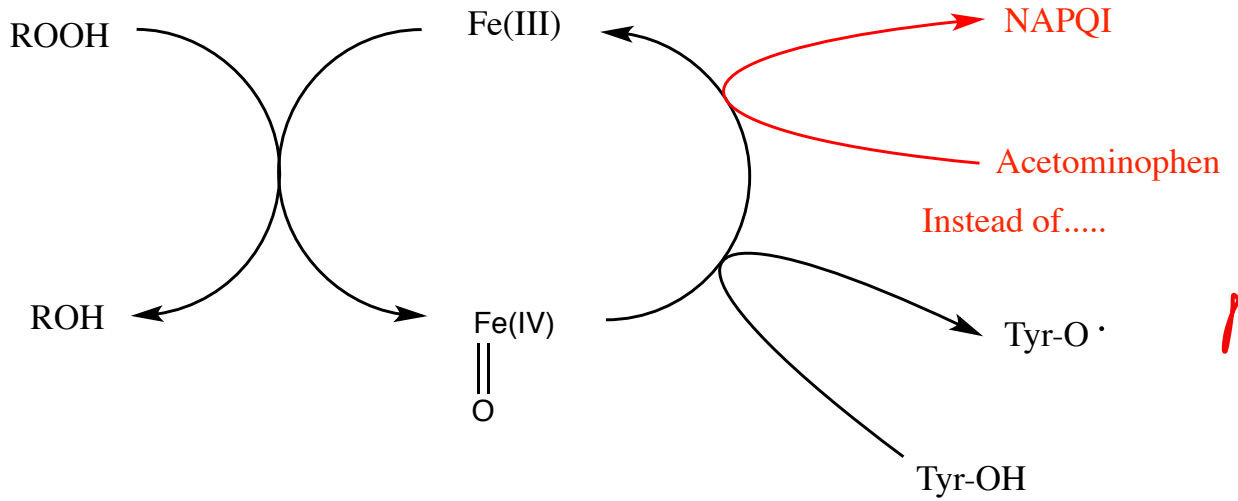
Discovered in 1880's Dr's trying to treat worms

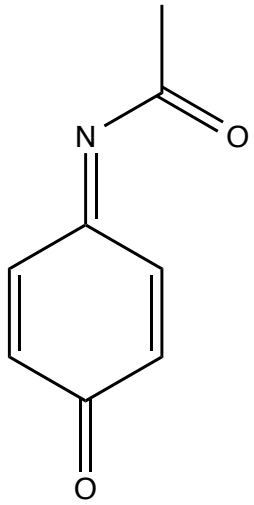
Acetanilide 

← accidentally gave people acetanilide instead of naphalene

- caused decrease in body temp

- Sold as Antifebrin



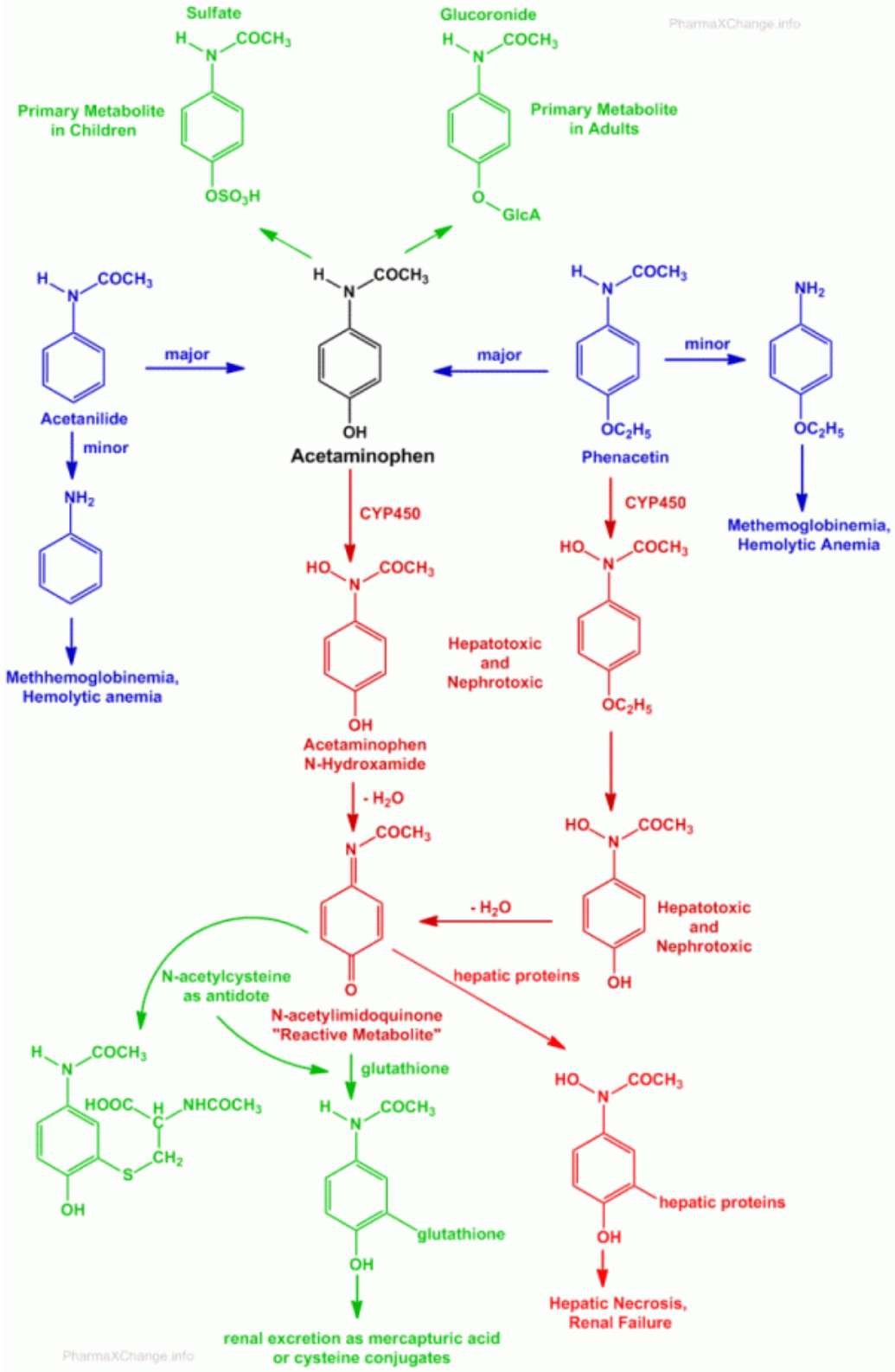


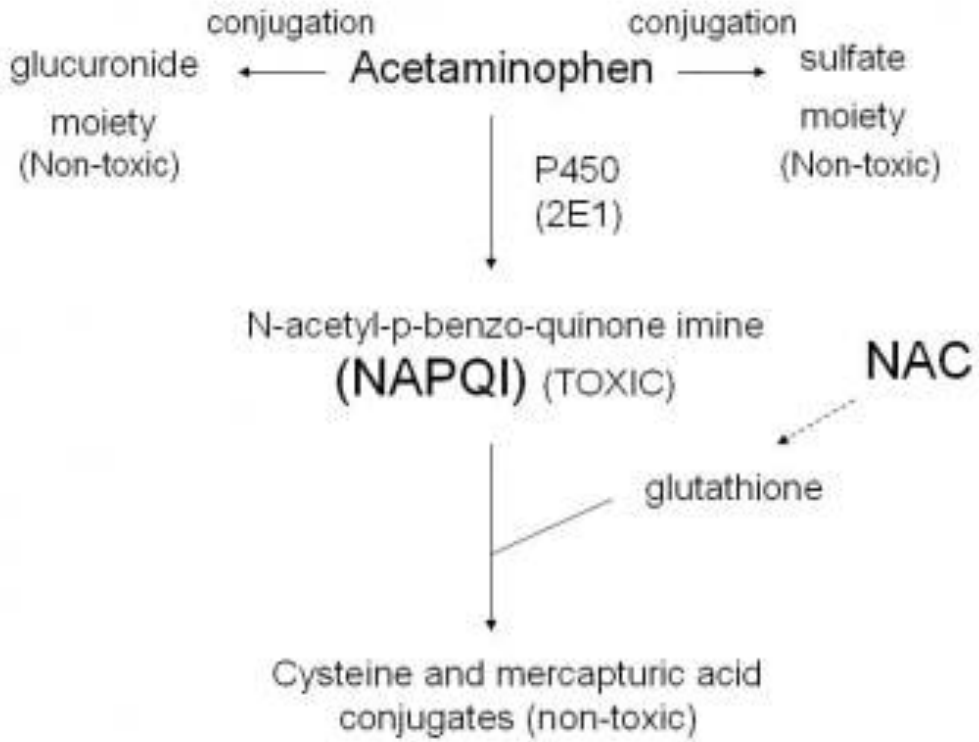
mode of action of tylenol might be to inhibit free radical formation

weak inhibitor for cox-1 + cox-2

may be a different cox (cox-3?)

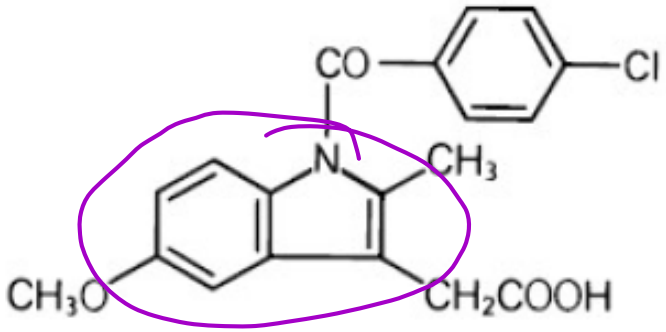
may be acting on cannabinoid receptors


Sulfate
Glucoronide
PharmaXChange.info
Primary Metabolite in Children
Primary Metabolite in Adults
major
major
minor
minor
Acetanilide
Acetaminophen
Phenacetin
CYP450
CYP450
Methemoglobinemia, Hemolytic Anemia
Methhemoglobinemia, Hemolytic anemia
Hepatotoxic and Nephrotoxic
Acetaminophen N-Hydroxamide
- H2O
- H2O
Hepatotoxic and Nephrotoxic
N-acetylcysteine as antidote
hepatic proteins
N-acetylimidoquinone "Reactive Metabolite"
glutathione
hepatic proteins
glutathione
Hepatic Necrosis, Renal Failure
renal excretion as mercapturic acid or cysteine conjugates
PharmaXChange.info


conjugation
conjugation
glucuronide
Acetaminophen
sulfate
moiety
(Non-toxic)
moiety
(Non-toxic)
P450
(2E1)
N-acetyl-p-benzo-quinone imine
(NAPQI) (TOXIC)
NAC
glutathione
Cysteine and mercapturic acid
conjugates (non-toxic)

Last group is indoles + indenes

Indomethacin



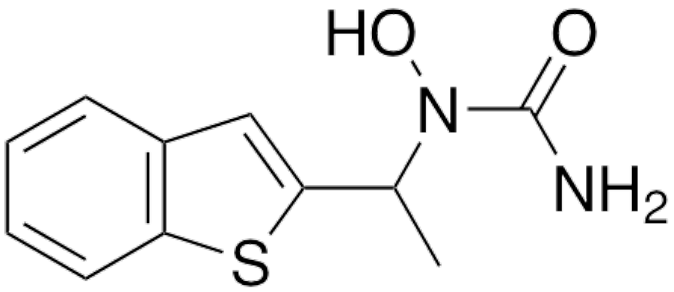
antipyretic

analgesic

off label to prevent premature labor

Cox inhibitors

5-lipooxygenase Inhibitors



Zileuton
Zyflo

↖ useful for asthma
prevent conversion of arachidonic acid to leukotrienes