Analgesics

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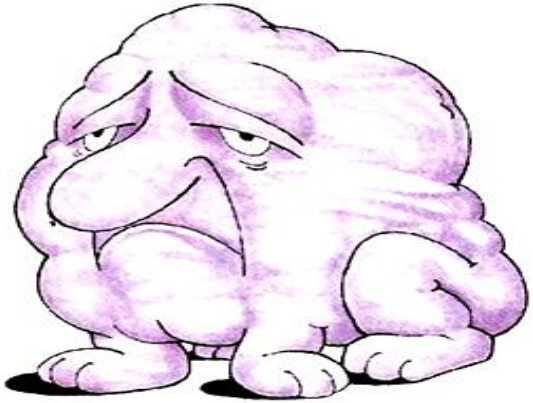
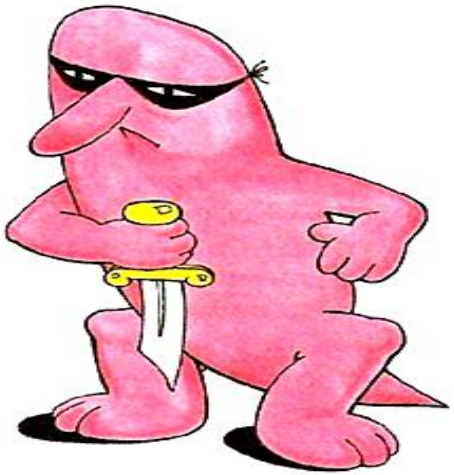
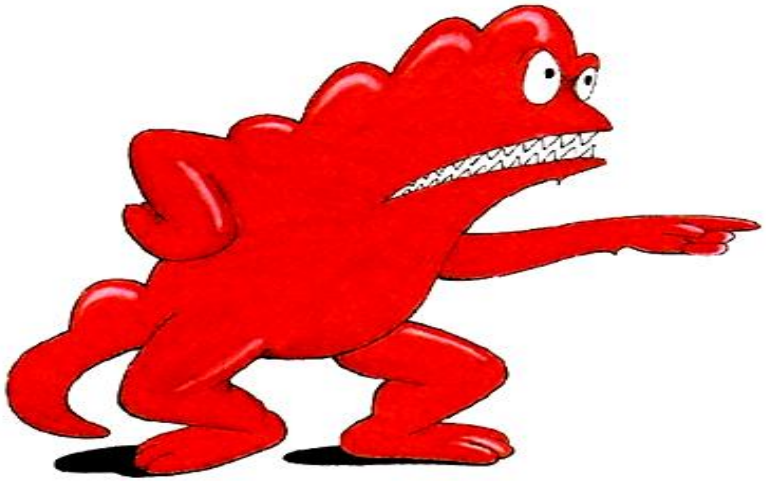
sharp pain



dull aching pain

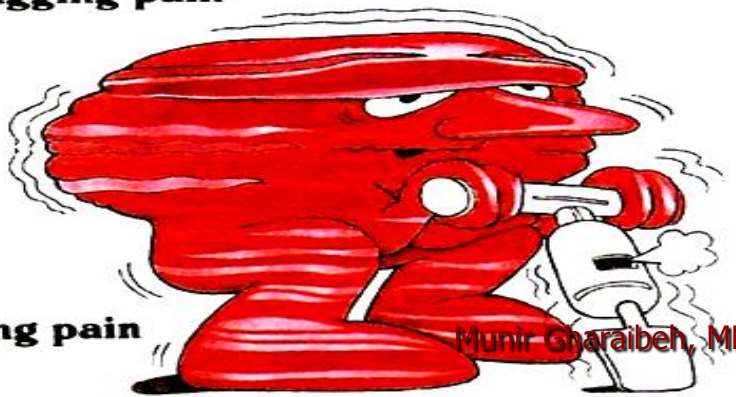


stabbing pain



nagging pain

burning pain



throbbing pain

boring pain

Comparison of Analgesics

Feature	Narcotic (Opioids)	Nonnarcotic (nonopioid)
Efficacy	Strong	Weak
Prototype	Morphine	Aspirin
Pain Relieved	Any Type	Musculoskeletal
Site of Action	Central	Peripheral and Central
Mechanism	Specific Receptors	PG Synthesis
Danger	Tolerance & Dependence	G.I irritation
Anti-inflammatory	No	Yes
Antipyretic	No	Yes
Antiplatelets	No	Yes

Non Narcotic Analgesics

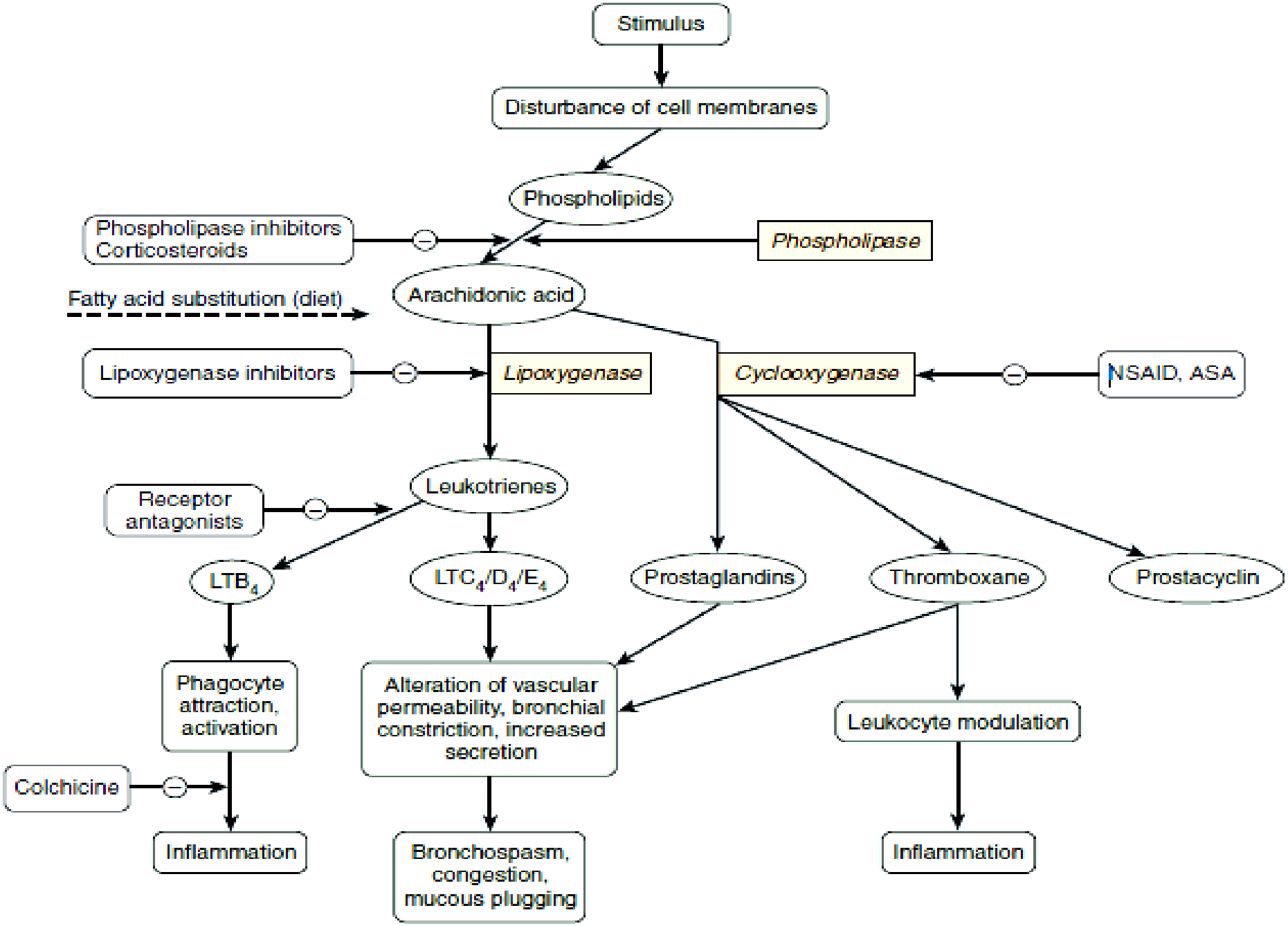
Non Steroidal Antiinflammatory Drugs or Agents (NSAID).

Non Opioid analgesics.

NSAID

Mechanism of Action:

- Inhibition of PG synthesis
  - Cyclooxygenase (COX) Enzyme:
    - COX-1 or Constitutional form of COX.
    - COX-2 or Induced form of COX.


Stimulus
Disturbance of cell membranes
Phospholipids
Phospholipase inhibitors
Corticosteroids
Phospholipase
Fatty acid substitution (diet)
Arachidonic acid
Lipoxygenase inhibitors
Lipoxygenase
Cyclooxygenase
NSAID, ASA
Receptor antagonists
Leukotrienes
LTB4
LTC4/D4/E4
Prostaglandins
Thromboxane
Prostacyclin
Phagocyte attraction, activation
Alteration of vascular permeability, bronchial constriction, increased secretion
Leukocyte modulation
Colchicine
Inflammation
Bronchospasm, congestion, mucous plugging
Inflammation

Pharmacological Actions of NSAID

- Antipyretic
- Analgesic.
- Anticoagulant.
- Antiinflammatory.

Pharmacological Actions of NSAID

- Fluid Retention
- Vasodilation
- Allergenic:
  - Bronchial Asthma
  - Anaphylaxis
- Renal Dysfunction:
  - Analgesic Nephropathy

Pharmacological Actions of NSAID

- **Gastric Irritation:**

  Direct Irritation: with acids.

  PG inhibition: all

  Variable response : according to:

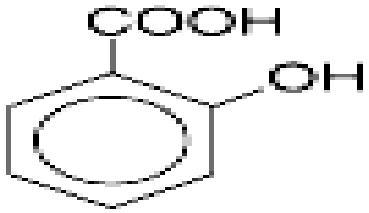
  Individual,
  Dose,
  Agent,
  Severity.

Pharmacological Actions of NSAID

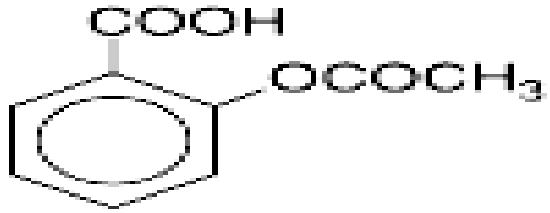
- **Hepatic Dysfunction:**
  - Especially with acetaminophen overdose.
- **Uric Acid Excretion:**
  - Inhibited with low dose
  - Enhanced with high dose.
- **Uterine relaxation.**

Salicylates

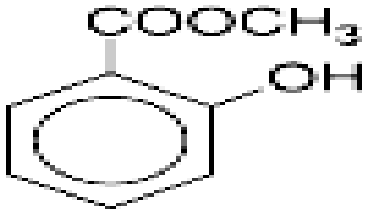
- Weak acids: pKa 3.5
- Protein Bound.
- Distribute to all tissues
- Elimination:
  - High doses: Zero Order
  - Low doses: First Order



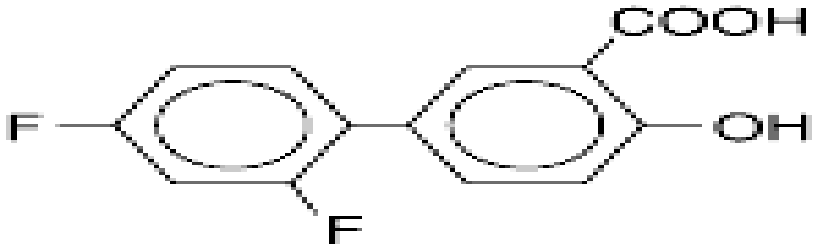
SALICYLIC ACID



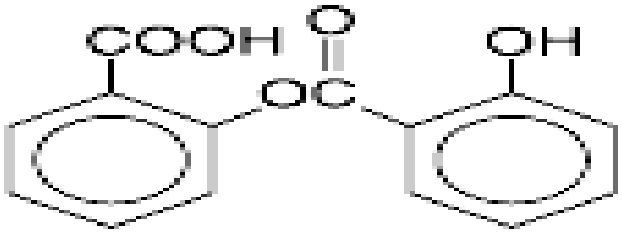
ASPIRIN



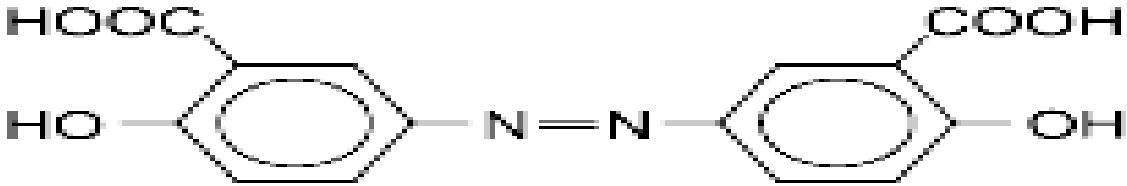
METHYL SALICYLATE



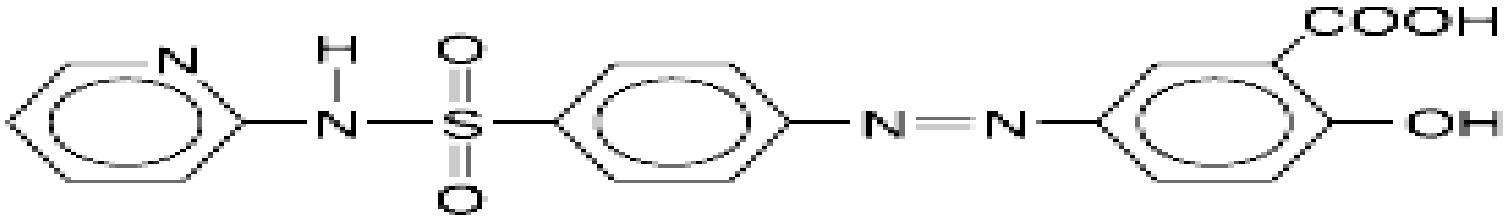
DIFLUNISAL



SALSALATE

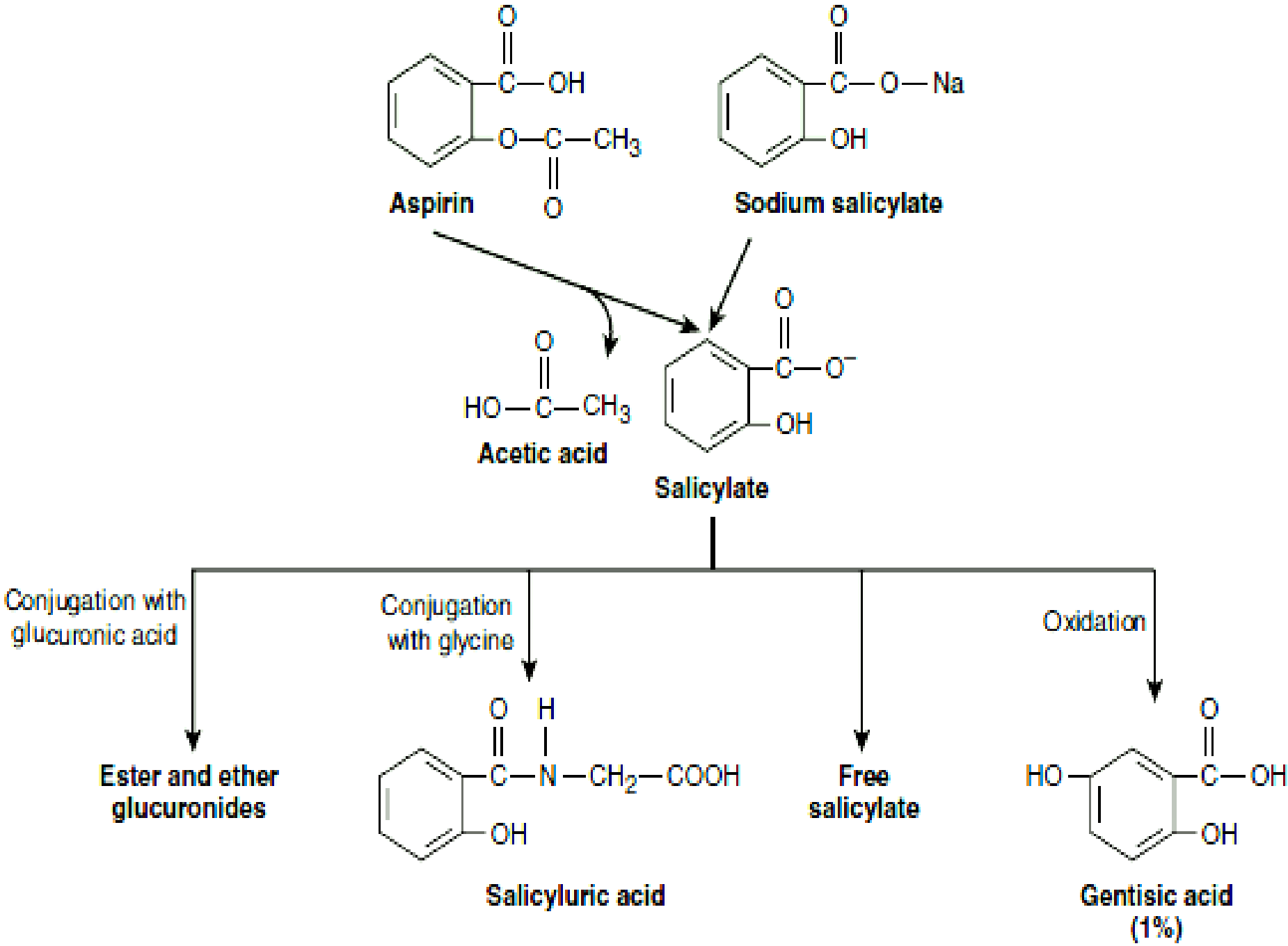


OLSALAZINE



SULFASALAZINE

Figure 26–1. Structural formulas of the salicylates.


Aspirin
Sodium salicylate
Acetic acid
Salicylate
Conjugation with glucuronic acid
Conjugation with glycine
Oxidation
Ester and ether glucuronides
Salicyluric acid
Free salicylate
Gentisic acid (1%)

ADRs & Overdose of Salicylates

- Hyperventilation
- Metabolic Acidosis
- Hypersensitivity: Salicylism

- Reye's Syndrome, in children.
- Bleeding
- Delayed Delivery
- Fetal Abnormalities
- Ulcerogenic

Acetaminophen = Paracetamol

- Less plasma protein bound than salicylates.
- Weak PG synthesis inhibitor
- CNS actions.
- Most widely used analgesic.
- Safest NSAID.

Acetaminophen = Paracetamol

- **Not:**
  - antiinflammatory
  - Platelets inhibitor
  - Ulcerogenic
  - Teratogenic

Acetaminophen = Paracetamol

- Toxicity
  - Severe hepatotoxicity with high doses

  - N- acetylcysteine is the antidote when given in the first 24hours.

Table 2 — Stages of acetaminophen-induced hepatotoxicity[9,10]

Stage	Postingestion Time	Signs and Symptoms	Laboratory Values	Comments
1	0.5–24 h	• Nausea • Anorexia • Emesis • Diaphoresis • Fatigue • Malaise • Pallor • Compromised hydration	• Subclinically elevated ALT (12 h postingestion) • Subclinically elevated AST (12 h postingestion)	May be asymptomatic; nonspecific symptoms may lead to further inadvertent acetaminophen administration
2	24–72 h	• Right upper quadrant abdominal pain and tenderness • Midline abdominal tenderness • Hepatomegaly • Oliguria • Tachycardia • Hypotension	• Elevated ALT • Elevated AST • Prolonged PT • Elevated bilirubin • Elevated BUN • Elevated creatinine	Stage 1 symptoms may improve or resolve
3	3–5 d	• Stage 1 symptoms • Jaundice • Hypoglycemia • Bleeding (coagulopathy) • Confusion • Lethargy • Coma	• Markedly elevated ALT • Markedly elevated AST • Elevated bilirubin • Elevated BUN • Elevated creatinine • Hyperammonemia • Uremia	Death from multiorgan failure occurs most often in stage 3
4	5–21 d	Eventual resolution	Eventual normalization	Complete hepatic recovery may take months

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; BUN, blood urea nitrogen; PT, prothrombin time

Rumack Nomogram

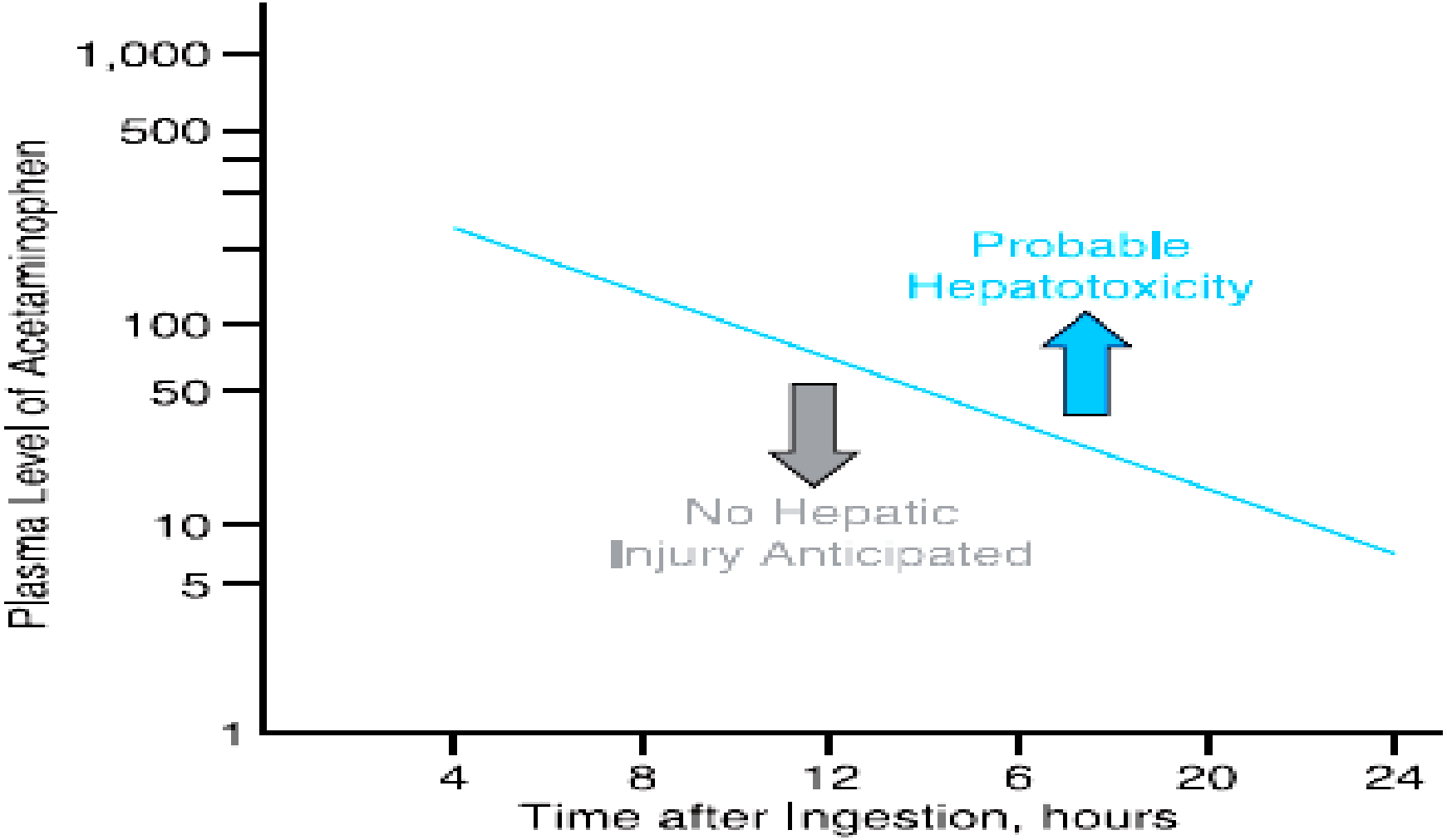
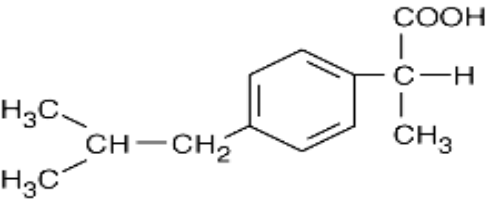


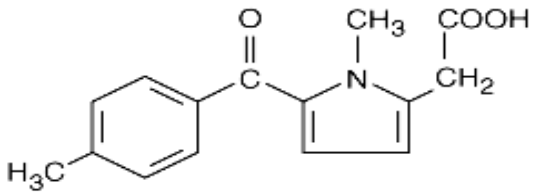
Figure 26–2. ***Relationship of plasma levels of acetaminophen and time after acute ingestion to hepatic injury.*** (Adapted with permission from Rumack *et al.*, 1981.)

Propionic acid derivative



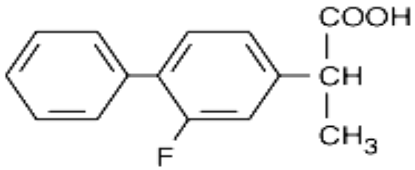
Ibuprofen

Pyrrolealkanoic acid derivative



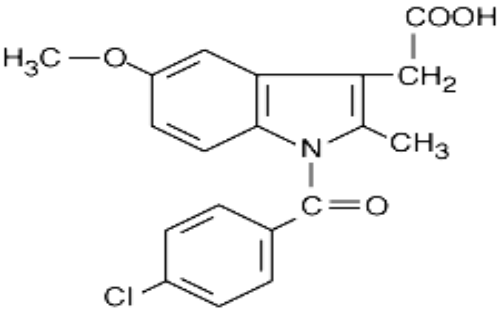
Tolmetin

Phenylalkanoic acid derivative



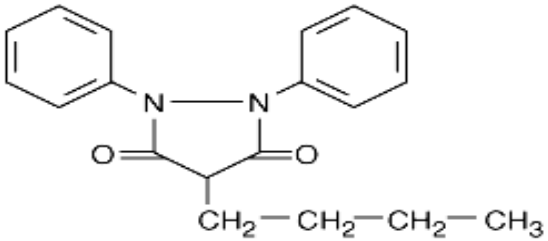
Flurbiprofen

Indole derivative



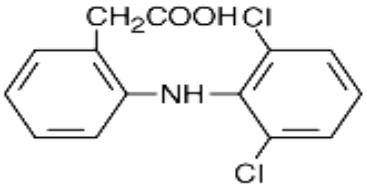
Indomethacin

Pyrazolone derivative



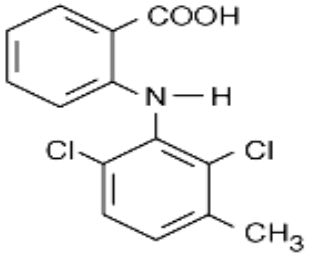
Phenylbutazone

Phenylacetic acid derivative



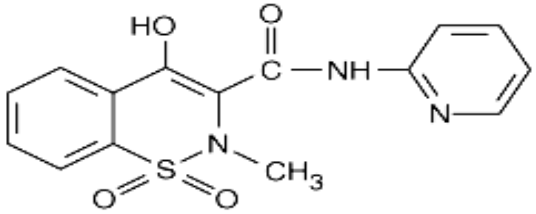
Diclofenac

Fenamate



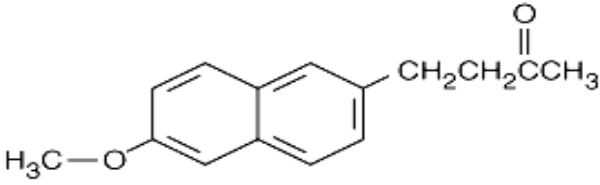
Meclofenamic acid

Oxicam



Piroxicam

Naphthylacetic acid prodrug



Nabumetone

Source: Katzung BG, Masters SB, Trevor AJ: *Basic & Clinical Pharmacology, 11th Edition*: http://www.accessmedicine.com

Phenyacetic Acid Derivatives

- **Diclofenac:**
  - Potent, widely used.
  - Available for oral, local(ophthalmic, topical gel), mouth wash, rectal and parenteral administration(for renal colic).

Propionic Acid Derivatives

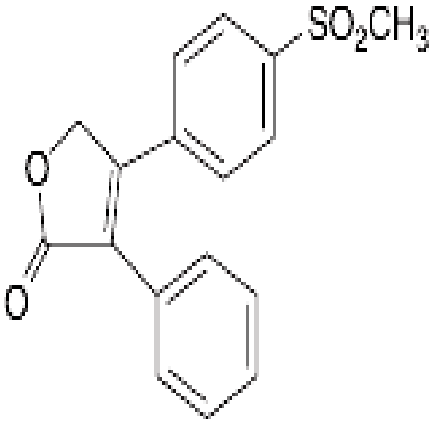
- Ibuprofen
- Ketoprofen
- Naproxin

Older Analgesics

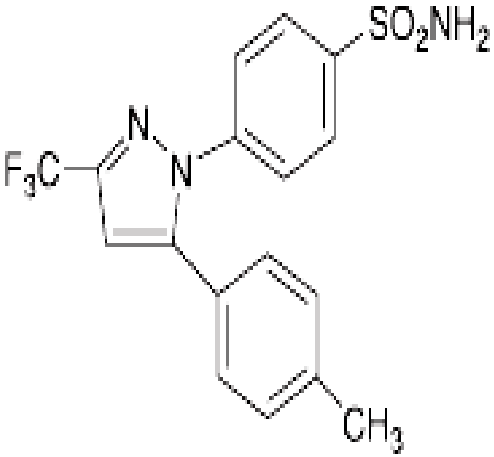
- Indomethacin
  - Pancytopenia
- Phenylbutazone
  - Aplastic Anemia
- Mefenamic Acid

Cyclooxygenase II Inhibitors

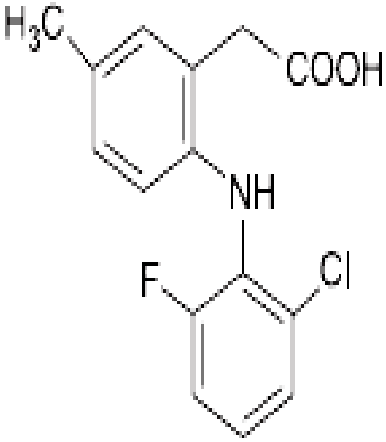
- Meloxicam
- Rofecoxib
- Celocoxib



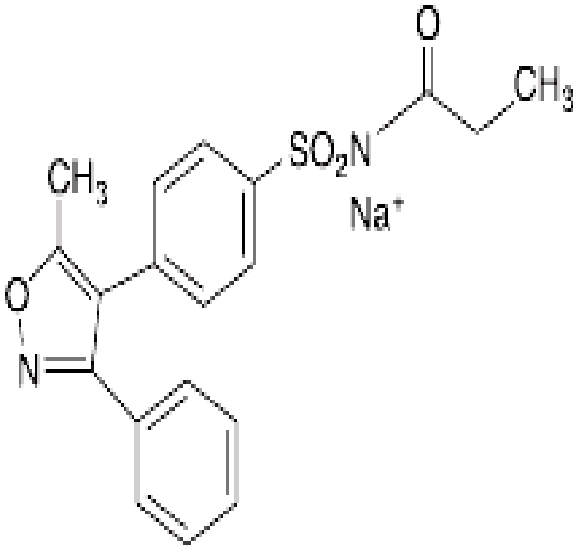
ROFECOXIB



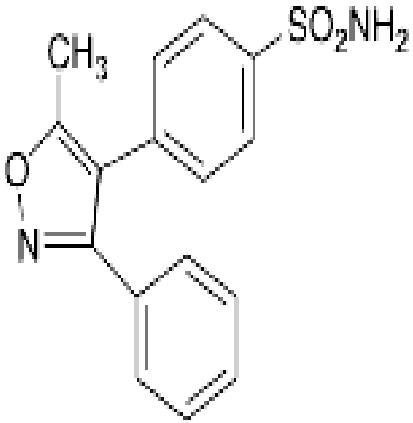
CELECOXIB



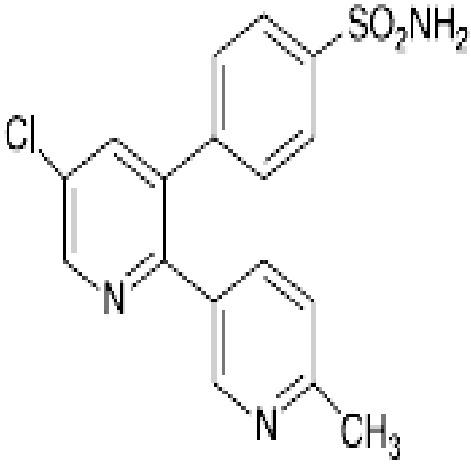
LUMARICOXIB



PARECOXIB



VALDECOXIB



ETORICOXIB

Figure 26–4. Chemical structures of the coxibs.

Cyclooxygenase II Inhibitors

- Do not affect platelet function.
- Less gastroirritant (half of non- selective drugs).
- May increase the incidence of edema and hypertension.
- Higher incidence of cardiovascular thrombotic events.
- Can cause renal toxicity like other NSAIDs

Disease -Modifying Antirheumatic Drugs "DMARDs"

- Rheumatoid arthritis is a chronic immunologic disease that causes significant systemic debilitating effects, shortens life, and reduces mobility and quality of life.
- DMARDs might arrest, or at least slow the progression of rheumatoid arthritis by modifying the disease itself.
- These drugs need weeks or months to work.
- **Nonbiologic:**
  - Mostly synthetic or semisynthetic.
- **Biologics:**
  - Usually monoclonal antibody

Disease -Modifying Antirheumatic Drugs "DMARDs"

- **Nonbiologic:**
  - Hydroxychloroquine.
  - Thalidomide.
  - Sulfasalazine.
  - Azathioprine.
  - Cyclosporin.
  - Methotrexate.
  - Sulfasalazine.
  - Gold Salts.

Disease -Modifying Antirheumatic Drugs "DMARDs"

- **Nonbiologic:**

- **Biologics:**
  - Abatacept
  - Adalimumab.
  - Infliximab.
  - Etarnecept.

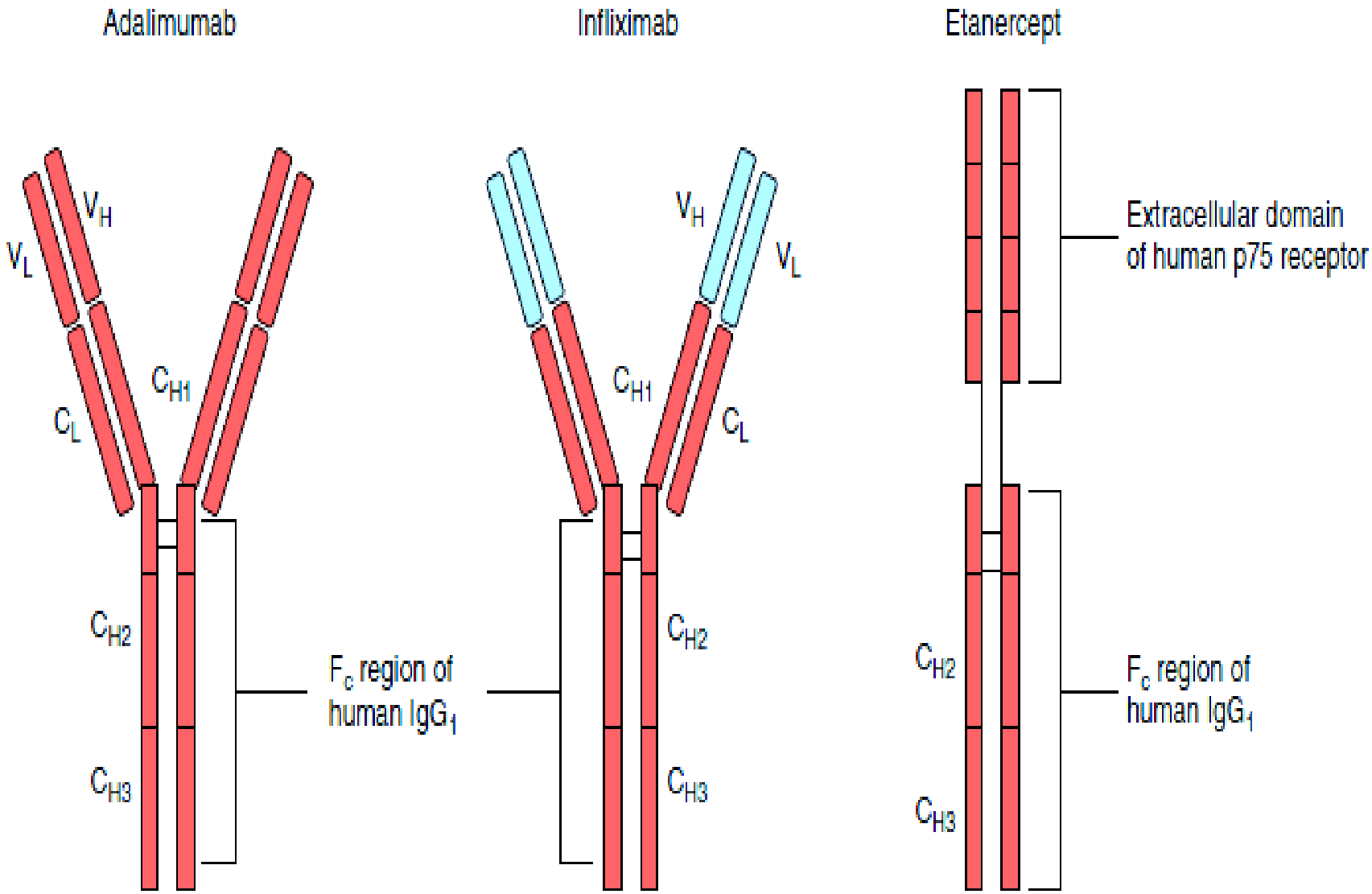


FIGURE 36–4 Structures of TNF-α antagonists used in rheumatoid arthritis. C_H, constant heavy chain; C_L, constant light chain; F_c, complex immunoglobulin region; V_H, variable heavy chain; V_L, variable light chain. Red regions, human derived; blue regions, mouse derived.

Gout

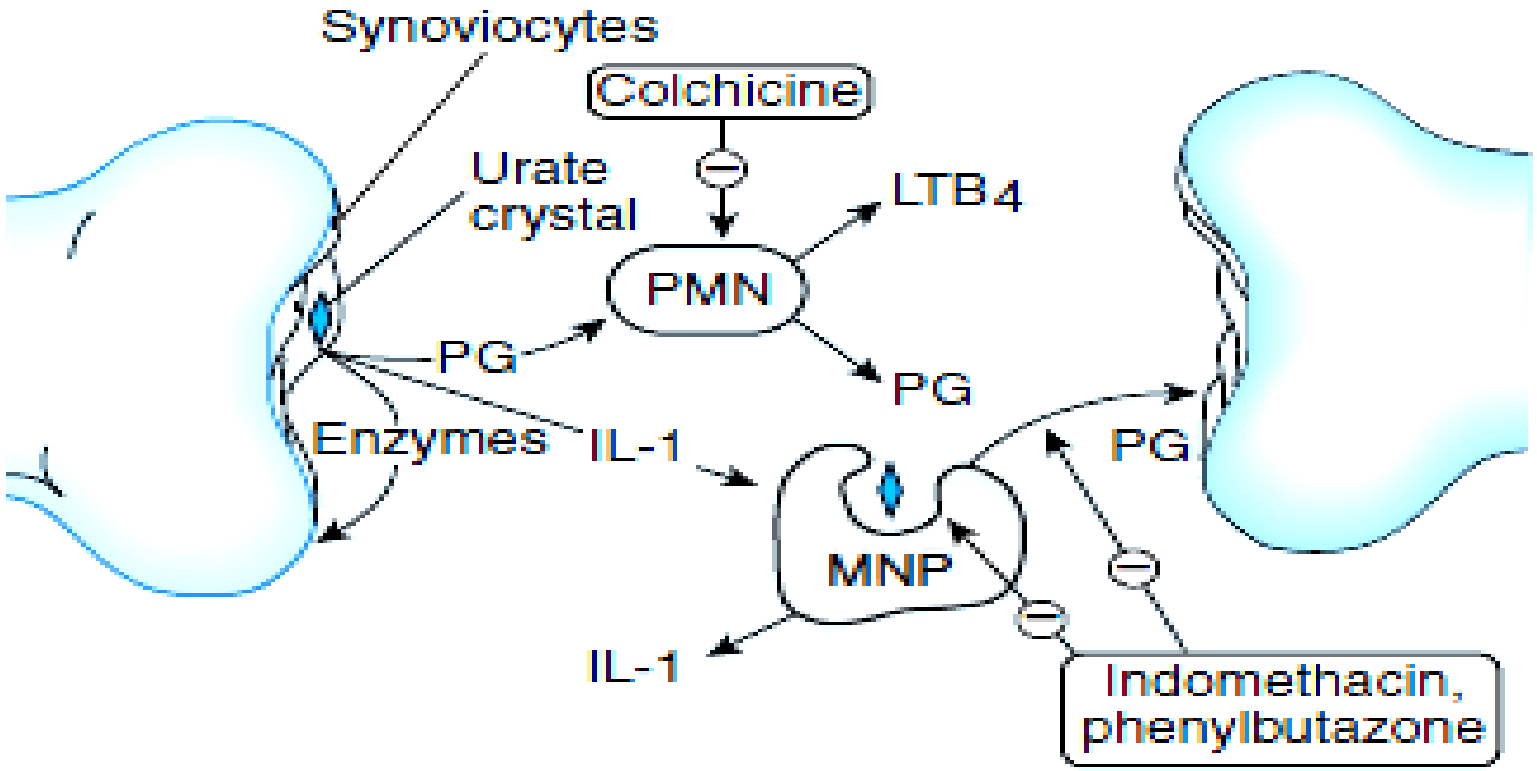
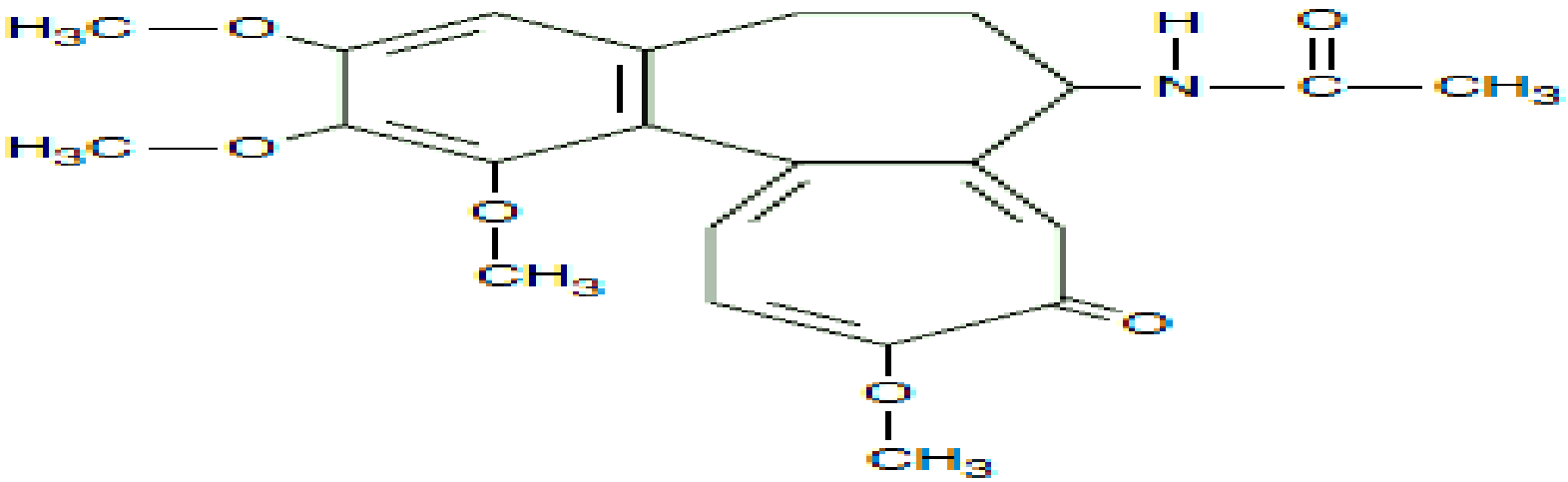
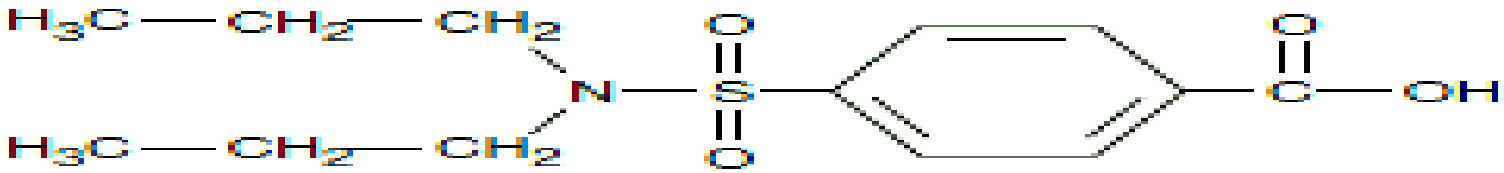


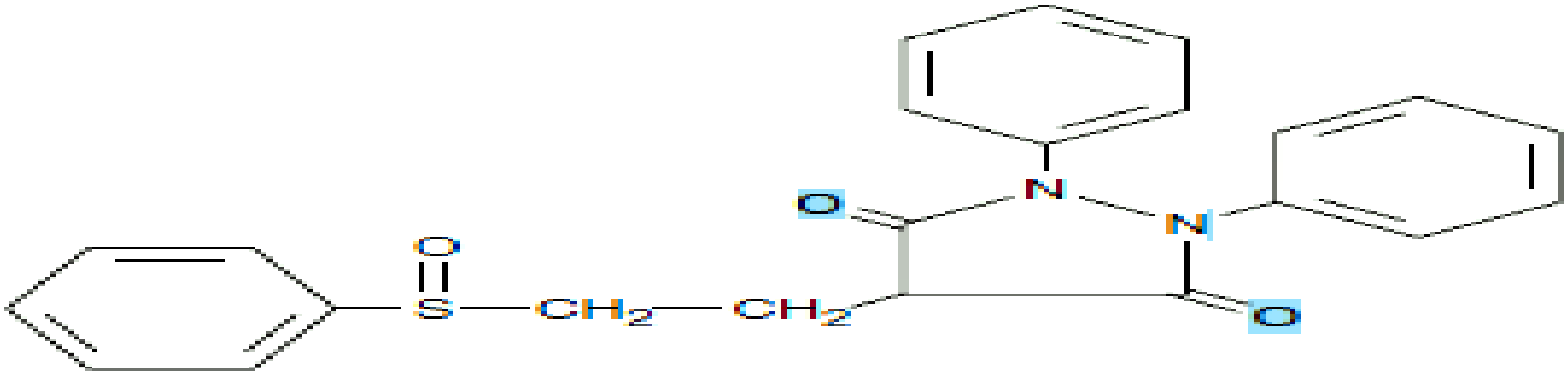
FIGURE 36–5 Pathophysiologic events in a gouty joint. Synoviocytes phagocytose urate crystals and then secrete inflammatory mediators, which attract and activate polymorphonuclear leukocytes (PMN) and mononuclear phagocytes (MNP) (macrophages). Drugs active in gout inhibit crystal phagocytosis and polymorphonuclear leukocyte and macrophage release of inflammatory mediators. PG, prostaglandin; IL-1, interleukin-1; LTB_4, leukotriene B_4.



Colchicine



Probenecid



Sulfinpyrazone

Colchicine

- Was the primary treatment for acute gout, but nowadays, NSAIDs are the first-line drugs.
- Also effective in Mediterranean fever.
- Rapidly absorbed, and rapidly effective(12-24hr.).
- Works on tubulin and prevents its polymerization, leading to inhibition of leukocyte migration, phagocytosis, and leukotriene B4 formation

Colchicine

- **Adverse Effects:**
  - Diarrhea, could be very severe and bloody.
  - N,V, abdominal pain.
  - Many other side effects (hepatic necrosis, renal failure, coagulation, seizures etc…).
  - Severe effects appeared with intravenous treatment.
  - NSAIDs are used instead of cholchicine to avoid these side effects.

NSAIDs

- **All NSAIDs can be used in acute cases.**
- **Indomethacin, an old NSAID is very effective.**
- **However, aspirin in low doses can cause uric acid retention.**

Uricosuric Agents

- Probenecid
- Sulfinpyrazone
  - Employed to decrease levels of urate in the body, or in patients with frequent attacks.
  - Act on the renal acid secretory mechanism to prevent reabsorption of uric acid.
  - Renal stone formation might be augmented, so urine volume should be increased with alkalinazation.

Allopurinol

- Xanthine oxidase inhibitor.
- Results in a fall in urate level.
- First line drugs for the treatment of chronic gout between the attacks.
- Started after NSAIDs.
- N, V, D, neuritis, bone marrow suppression, allergies, cataracts, …..etc.