**Antiinflammatory, nonsteroid analgesics (NSAID)**

Drugs that relieve mild to moderate pain, lower body temperature in fever, reduce inflammatory effects. No narcotic effect.

Many of them influence the prostaglandin system, inhibit COX enzymes.

- Salicylic acid derivatives
- Aniline derivatives
- 3-Pyrazoline-5-one derivatives
- 3,5-Pyrazoline derivatives
- Anthranilic acid derivatives
- Aryl acetic and propionic acid derivatives
- Sulfonamide and other derivatives

**Salicylic acid derivatives**

- Medicines derived from willow trees (*Salix* sp.) and other salicylate-rich plants dates back to ancient Sumer.
- Leroux isolated salicin from willow bark (1827)
- Salicylic acid first synthesis Piria, 1838, prepared from wintergreen (*Gaultheria*) oil, Cahours, 1844, from spirea plants, etc.
- Acetylsalicylic acid: prepared by Gerhardt, 1853, pharm. activity Hoffmann, 1899 (→ Aspirin)

**Synthesis**

Kolbe-synthesis (industrial) for Phenyl-carbonate Na-salt

- Phenyl-carbonate Na-salt
- Kolbe-synthesis
- 125 °C
- 200 °C
- CO₂
- 4-Hydroxy-benzoic acid
- Para-ben
- Preservatives

**Derivatives of salicylic acid**

- Acetylsalicylic acid
- Methyl salicylate
- Salicylamide

**Salicylic acid**

- Acidum salicylicum
- Sodium salicylate
- Natrii salicylas

- Antipyretic and antirheumatic properties.
- Quite toxic for internal use (gastric irritation, sometimes allergy).
- Topical application in dermatology → ingredient in many skin-care products for the treatment of acne, psoriasis, calluses, corns, keratosis pilaris, and warts, shampoos used to treat dandruff ← causing the cells of the epidermis to slough off.
- Food preservative (to inhibit moulds). Not used in food industry anymore.
- Analytic: Blue-lilac complex formation with Fe(III) salts.
Salicylic acid derivatives

Methyl salicylate
Methylis salicylas

Applied locally in ointments to treat rheumatic pains.

Phenyl salicylate
Salol

Used in combinations as a mild urinary tract antiseptic and anagesic; sometimes in toothpastes.

Acetylsalicylic acid
Acidum acetylsalicylicum
Aspirin®, etc.

2-(acetyloxy)benzoic acid

Introduced into medicine in 1899.
Used as an antipyretic, analgesic and antirheumatic (~0.5 g/tablet)
Allergic reactions are possible
Number of proprietary combinations to counteract its acidic properties (pKa = 3.5), GI side effects: NaHCO₃, CaCO₃, Al-hydroxide, Mg-trisilicate, etc.
New use: inhibits thromocyte aggregation in small doses.

Metabolism

Acetylsalicylic acid

Gluconic acid, ~5-10%
Salicylic acid, ~70%
Salicyluric acid, ~75%
Gentisic acid, 1%

Aniline derivatives

Cahn & Hepp (1886): aniline and acetanilide with powerful antipyretic properties. Very toxic.
4-OH derivatives are considerably less toxic.
They return feverish conditions to normal, normal body temperature is not affected.
No anti-inflammatory properties.
Acting centrally: pain impulses are intercepted in the hypothalamus.

Phenacetin - Once very popular, now it is banned because of adverse effects. (renal toxicity, carcinogenic in animals)
Paracetamol

- Long known compound, used in medication since 1955.
- Analgesic and antipyretic action similar to those of aspirin, but not effective anti-inflammatory agent.
- Very commonly used for the relief of fever, headaches, etc.
- Often used in nonprescription combinations for cold and flu medications.
- Mechanism of action still unclear. a) Influences the COX family of enzymes without having anti-inflammatory effect; b) also modulates the endogenous cannabinoid system.
- Adverse effects: liver failure on long overdose. Rarely acute renal failure.

Synthesis

\[
\begin{align*}
\text{Nitrophenol} & \rightarrow \text{Amino-phenol} \\
\text{Paracetamol} & \rightarrow \text{Acetaminophen}
\end{align*}
\]

Paracetamol (INN)  
Paracetamolum  
Acetaminophen (USAN)  
Tylenol®, Panadol®, etc.  
4-Acetylamino-phenol

Biotransformation

Metamizole Na  
Metamizolum natricum (Novamidazophenum)  
Analgin®, Novalgin®, etc.

Pyrazolin-3-one derivatives

- Antipyrine discovered by Ludwig Knorr (1884), used since 1887.

Pyrazolin-3-one derivatives

- Phenazone  
  Phenazonum (Antipyrin)  
  2,3-Dimethyl-1-phenyl-1,2-dihydropyrazol-5-one

Pyrazolin-3-one derivatives

- Aminophenazone  
  Aminophenazonum (Pyramidon)  
  Used only externally (e.g. eardrops)

Pyrazolin-3-one derivatives

- Propyphenazone  
  Propyphenazonum (Sardion® (component))  
  Metamizole Na  
  Metamizolum natricum (Novamidazophenum)  
  Analgin®, Novalgin®, etc.
**Metamizole, novamidazophen**

- In use since 1922
- Very commonly used in many countries as a powerful painkiller and fever reducer.
- Side effect: small risk of causing severe agranulocytosis → banned or restricted in many countries, while freely available in others.

**Synthesis**

**Phenylbutazone**

- Slightly acidic compound because of enolization.
- Anti-inflammatory and analgesic, main uses: gouty arthritis, spondylitis, tendinitis, musculoskeletal sprain, overuse injuries, etc.
- Side effects similar to the other pyrazolones (rare, but serious suppression of white blood cell production and aplastic anemia.)

**Phenybutazone**

- Synthesis:
**Biotransformation:**

\[ \text{Phenyldiazene} \rightarrow \text{Oxaphenylphenacene active metabolite} \]

**Azapropazone**

**Azapropazonum**

**Rheumox®**

- Less toxic than the previous ones.
- Acute gout, inflammation of joints, spondylitis, etc.
- Not to be used: blood disorders, peptic ulcers, kidney problems.

**Structural relations:**

**Non-steroidal anti-inflammatory anthranilic acid derivatives**

**Mefenamic acid**

Acidum mefenamicum

Ponstel®, Ponstan®

2-(2,3-dimethylphenylamino)benzoic acid

- Used to relieve mild to moderate pain, including menstrual pain; arthritis, spondylitis, tendinitis, musculoskeletal pains.

**Niflumic acid**

Acidum niflumicum

- Very commonly used NSAID since 1965 to reduce fever, pain, stiffness, and swelling.
- Nonselective inhibitor of cyclooxygenase (COX) 1 and 2.
- Side effects: gastric distress and headache.

**Diclofenac sodium**

Diclofenac natrium

Cataflam®, Diclac®, Flector®, Voltaren®

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

- Widely used to reduce inflammation and as an analgesic reducing pain in musculoskeletal complaints, arthritis, ankylosing spondylitis or acute injury; pain management in case of kidney stones and gallstones.
- Often applied as gel for osteoarthritis etc.
- Mode of action is inhibition of prostaglandin synthesis by inhibition of COX.
- Most common side effects: gastrointestinal complaints.
Synthesis

Biotransformation

Hydroxylation and glucurinide formation

2-Arylpropionic acid derivatives

- Used for relief of symptoms of arthritis, primary dysmenorrhea, fever, headache, etc.
- (S)-(+)-ibuprofen (dexibuprofen) is the biologically active isomer. In vivo isomerase enzyme converts R to S → not necessary to use pure R isomer.

All of these are similar to ibuprofen
Naproxen (sodium)
Naproxenum (natricum)
Aleve®, Apranax®, Napmel®, Naprosyn®

- Commonly used to reduce pain resulting from osteoarthritis, rheumatoid arthritis, gout, ankylosing spondylitis, injury
- Adverse effects: disturbances in the GI tract.

Synthesis

Sulfonamides

Meloxicam
Meloxicamum
Movalis®, Melox®

Celecoxib
Celebrex®
4-(5-(4-methylphenyl)-3-trifluoromethyl)-1H-pyrazolo[1,5-a]pyrimidin-1-yl-sulfonamide

- Sulfonamide derivatives are similar to the previous ones (rheumatoid and osteoarthritis, primary dysmenorrhoea, postoperative pain), but with considerably longer plasma half-life.
Other anti-inflammatory, antirheumatic and gout drugs

Gout - hyperuricemia

- Gout (metabolic arthritis): overproduction and/or decreased clearance of uric acid → buildup of uric acid, deposition of crystals in the joints → inflammatory reaction.

- Allopurinol is also an inhibitor of the enzyme (rapid oxidation, very slow excretion).

- Oxypurinol is also an inhibitor of the enzyme (rapid oxidation, very slow excretion).

- Increases the renal excretion of uric acid

- Precursor for glycosaminoglycans → a major component of joint cartilage. Supplemental glucosamine may help to rebuild cartilage and treat arthritis.

Thiols and gold compounds

- Disodium aurothiomalate

- Auranofin

- D-penicillamine

- Gold salts can decrease the inflammation of the joint lining (probably by inhibiting lymphocyte proliferation, lysosomal enzyme release)