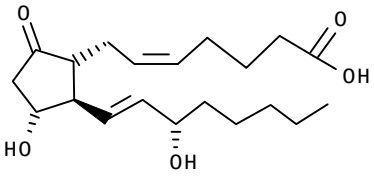
ANALGESIC - ANTIPYRETIC - ANTIINFLAMMATORY DRUGS (NSAIDS)

EFFECTS OF NSAIDS

A wide variety of molecules which are structurally fairly simple have powerful multiple effects, making them useful for alleviation of pain, reduction of fever, and suppression of inflammation; they are most commonly known as NSAIDs (non-steroidal anti-inflammatory drugs). Historically the most important is salicylic acid, a compound common in plants (notably willow bark) and used for centuries as a traditional medicine; it is still the cheapest and most readily available, primarily as the acetate ester known as aspirin. Among the side effects of NSAIDs are severe gastrointestinal disturbance and inhibition of the platelet aggregation necessary for blood clotting; the inhibition of clotting has a positive side - reduction in heart attack frequency for people on aspirin who are otherwise at risk. Amazingly enough, these diverse responses have all been shown to result from a single biochemical effect of NSAIDs: they inhibit the synthesis of a class of hormones called the prostaglandins, in particular PGE_2.



PGE_2

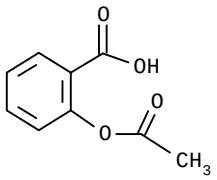
The process of inflammation requires PGE_2 to begin a series of reactions responsible for the observed swelling of the tissue (leukotrienes are involved); that sequence also releases molecules such as Factor P which sensitize the pain receptors. PGE_2 is necessary for the production of a fever, and produces one when injected into the hypothalamus. PGE_2 and other prostaglandins inhibit acid secretion by the stomach and promote secretion of protective mucus; NSAIDs damage the stomach by reducing this protection, rather than direct irritation (many are acidic). Clotting is mediated by thromboxanes, prostaglandins with the ring expanded by one oxygen.

It is interesting to speculate about the reason a plant might make a material such as salicylic acid. It was recently shown that salicylic acid actually provides disease resistance for plants. Other drugs made by plants serve to protect them from predators.

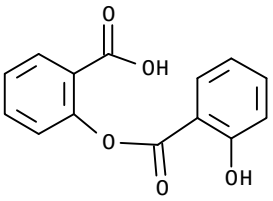
In the sample structures, the common drug name in given and a capitalized example of a tradename. Most are carboxylic acids and are frequently provided as salts to improve solubility and reduce direct irritation of the stomach, e.g. Naprosyn is available as the sodium salt, anaprox.

STRUCTURES OF NSAIDS

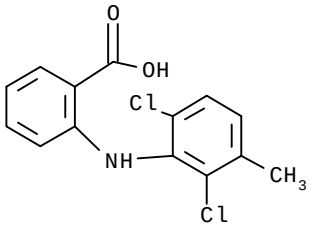
Benzoic acids: **salicylic** **anthranilic**



ASA, acetylsalicylic acid
Aspirin



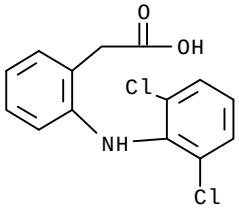
salicyl salicylic acid
salsalate, Disalcid



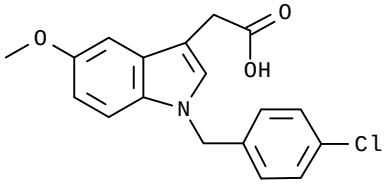
meclofenamate
Meclomen

Acetic Acids:

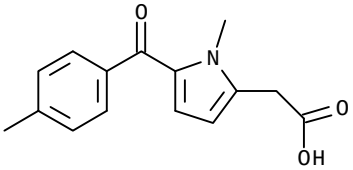
phenylacetic **indoleacetic** **pyrroleacetic**



diclofenac
Voltaren



indomethacin
Indocin

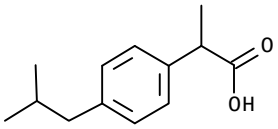


tolmetin
Tolectin

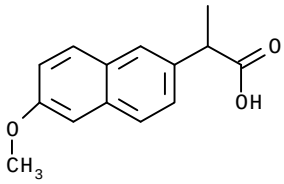
Propanoic (Propionic) Acids:

Each has a chiral center, and in each case the (S)-(+) enantiomer is the NSAID-active form. Chiral drugs are rapidly replacing racemates for several reasons: the other enantiomer may be inactive, or even toxic, or be useful for another ailment, and the production of chiral drugs is now technically and economically feasible.

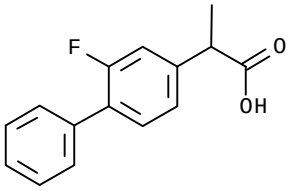
phenyl **naphthyl** **biphenyl** **benzophenone**



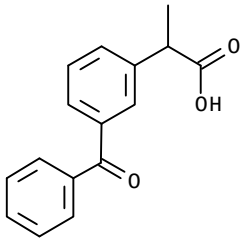
ibuprofen
Motrin



naproxen
Naprosyn, Anaprox



fluorbiprofen
Ansaid

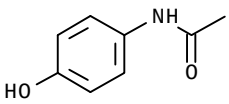


ketoprofen
Orudis KT

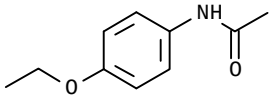
Enols and Phenols:

Note that p-aminophenol derivatives reduce fever and pain but have very weak anti-inflammatory activity and appear to act by a mechanism other than inhibition of PGE_2 synthesis, probably later in the process. They do not cause the stomach upset that NSAIDs cause, but acetaminophen (Tylenol) is more toxic than NSAIDs, causing liver damage and even death with modest overdoses, especially combined with alcohol.

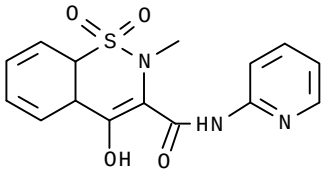
p-aminophenols **enols**



acetaminophen
Tylenol



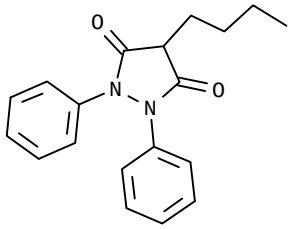
phenacetin



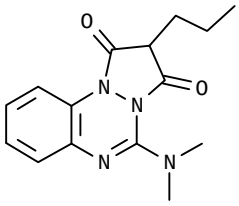
piroxicam
Feldene

Pyrazoles:

Each has a conjugated enol as tautomer, presumably less stable than the amide form shown.



phenylbutazone
Butazolidin



apazone

FURTHER READING

T. Gaffney *et al*, "Requirement of Salicylic Acid for the Induction of Systemic Acquired Resistance" *Science*, **1993**, *261*, 754 - 756.

P. A. Insel, "Analgesic-Antipyretics and Antiinflammatory Agents: Drugs Employed in the Treatment of Rheumatoid Arthritis and Gout", in A. G. Gilman, T. Rall, A. Nies and P. Taylor, eds, “Goodman and Gilman’s The Pharmacological Basis of Therapeutics”, Pergamon, NY, 1990, 638 - 681.

N.A. Nelson, R.C. Kelly, R.A. Johnson, "Prostaglandins and the arachidonic acid cascade", *Chem. Eng. News*, **1982** (Aug. 18), 30-44.

S. C. Stimson, "Chiral Drugs", *Chem. Eng. News*, **1993** (Sep. 27), 38-65; **1995** (Oct.9), 44-74.

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