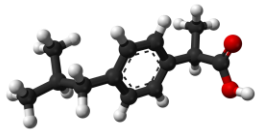
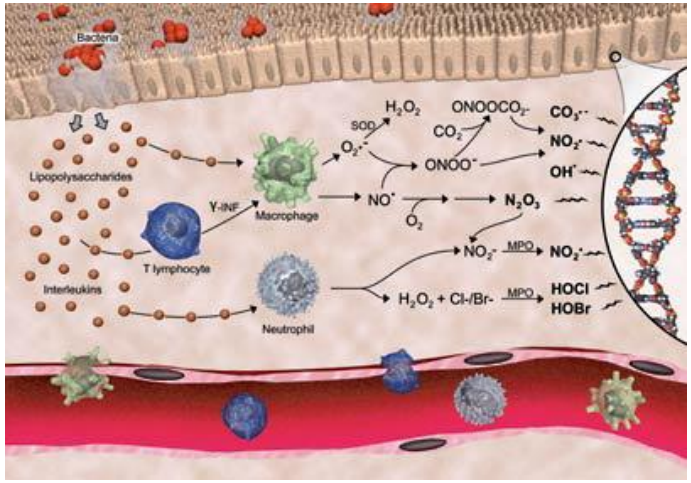
Anti-inflammatory drugs

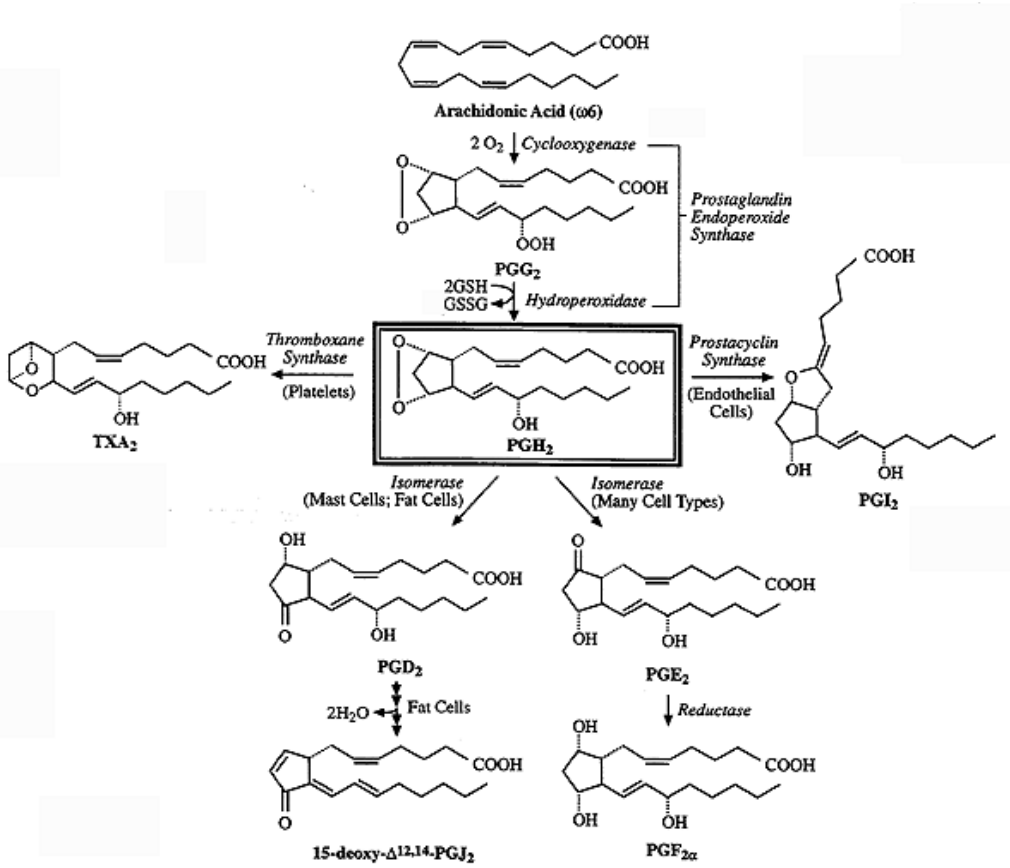


Inflammation:

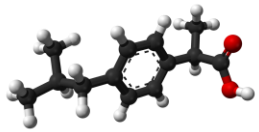
From pathogens, damaged cells, or irritants. Acute / chronic. Ex. Arthritis

Signs: ***rubor, tumor, calor, dolor, functio laesa***





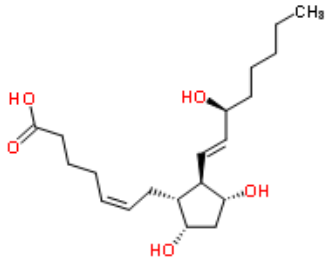
Anti-inflammatory drugs



Inflammation:

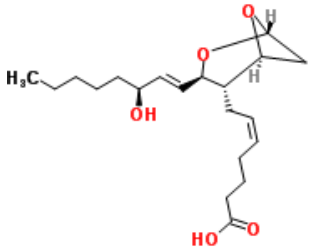
Prostaglandins

($PGF_{2\alpha}$)



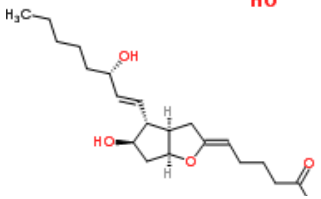
Tromboxanes

(TxA_2)

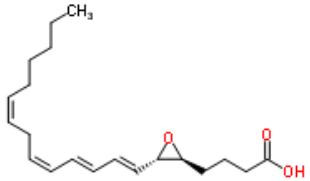


Prostacyclins

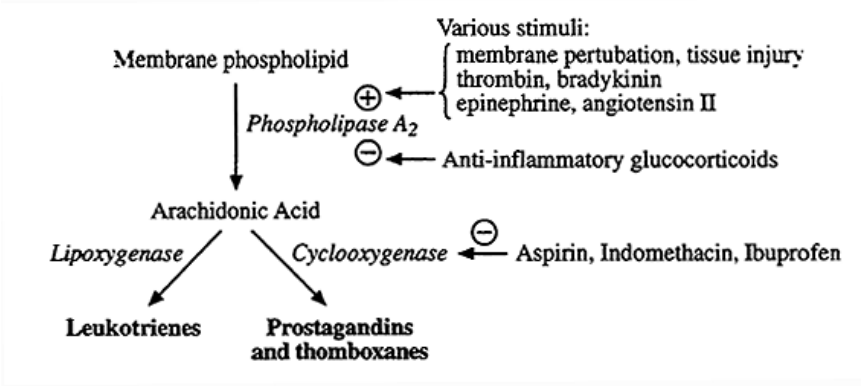
(PGI_2)



Leucotrienes (LTA_4)



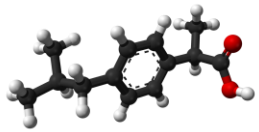
Arachidonic acid metabolism



COX-1: stomach/kidney

COX-2: inflammation sites

Anti-inflammatory drugs: NSAIDs

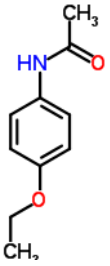


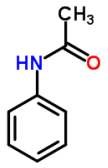
Analgesics-antipyretic:

PARACETAMOL

Analgesic and antipyretic; very low antiinflammatory effect.

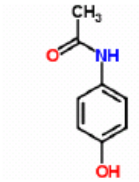
Its pro-drugs **ACETANILIDE** and **PHENACETIN**





are too toxic and no more used.

No anticoagulation/ulcerogenic activity.

Name	**PARACETAMOL**
Structure	
Systematic name	N-(4-hydroxyphenyl)acetamide
Formula	$C_8H_9NO_2$
MW	151.1626
Monoisotopic mass	151.063328537
Mp	169-172°C
H bond acceptors	3
H bond donors	2
Acid p*Ka*	9.46 (phenol)
Basic p*ka*	--
ACD Log D pH 5.5	0.475
ACD Log D pH 7.4	0.474
Solubility	methanol and ethanol but slightly in water
LD50	1944 mg/Kg rat p.o.
Therapeutic cat	analgesic-antipyretic
ATC	**N02BE01** N NERVOUS SYSTEM N02 ANALGESICS N02B OTHER ANALGESICS AND ANTIPYRETICS N02BE Anilides
Receptors	COX

Nomi commerciali (IT)	
ACETAMOL, ACTIDUE, ACTIGRIP, ADOLEF, BABYRINOLO, EFFERALGAN, GABBROCET, MINOFEN, NORMAFLU, PANADOL, PARACETAMOLO, PERFALGAN, PIROS, PRACETAM, SANIPIRINA, TACHIPIRINA, TERMOL	C, RR-OTC, supposte, compresse, polvere, sciroppo, gocce

Anti-inflammatory drugs: NSAIDs

Analgesics-antipyretics:

PARACETAMOL metabolism

Toxicity: GSH depletion and epatotoxicity (hepatic necrosis). Interaction with ethanol.

Children: O-sulphate

Adults: O-glucuronide

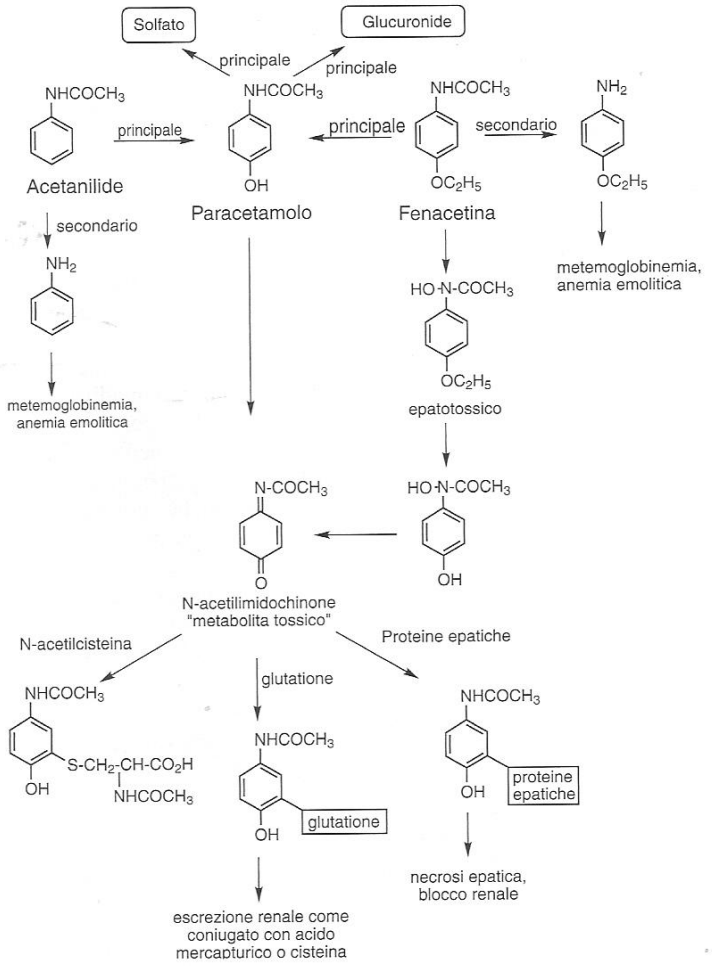
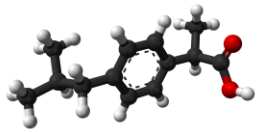


Fig. 36.8. Metabolismo del paracetamolo.

Anti-inflammatory drugs: NSAIDs



Antiinflammatory agents:

Salycilates: metabolism

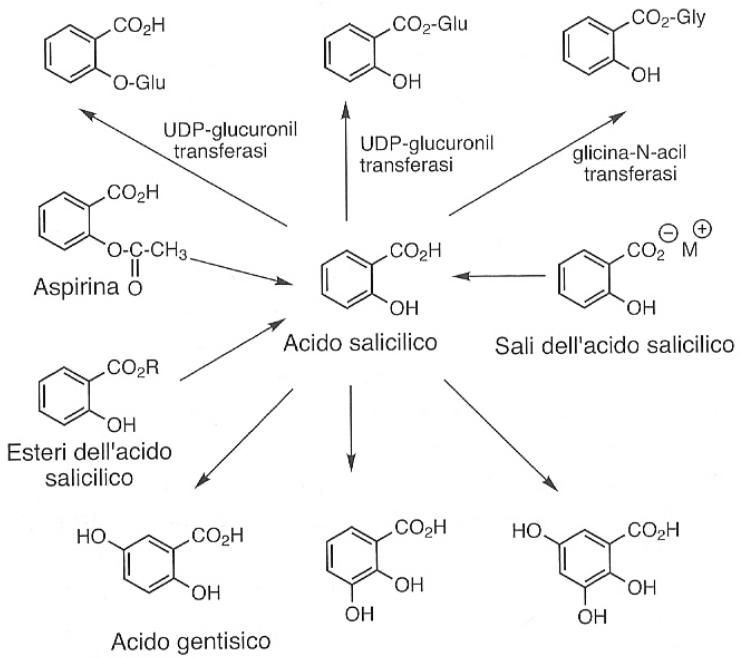
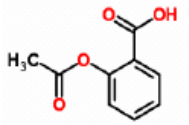
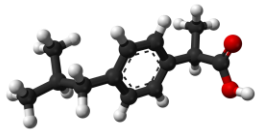


Fig. 36.9. Metabolismo dei derivati dell'acido salicilico (Glu, glucuronide; gly, coniugato con la glicina).

Name	**ASPIRIN**
Structure	
Systematic name	2-(acetyloxy)benzoic acid
Formula	$C_9H_8O_4$
MW	180.1574
Monoisotopic mass	180.042258744
Mp	134°C
H bond acceptors	4
H bond donors	1
Acid p*Ka*	3.41
Basic p*ka*	--
ACD Log D pH 5.5	-0.69
ACD Log D pH 7.4	-1.88
Solubility	ethanol, DMSO; 1g/100g water (37°C)
LD50	1010 mg/Kg rat p.o.
Therapeutic cat	antiinflammatory
ATC **A01AD05,** stomatological **B01AC06,** platelet aggregation inhibitor	**N02BA01** N NERVOUS SYSTEM N02 ANALGESICS N02B OTHER ANALGESICS AND ANTIPYRETICS N02BA Salicylic acid and derivatives
Receptors	COX-1, (COX-2)

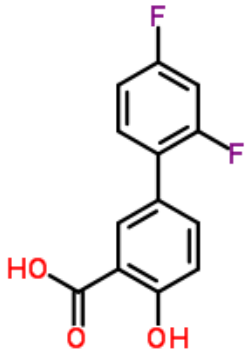
Nomi commerciali (IT)	
ACIDO ACETILSALICILICO, ASA50, ASCOPIR, ASPIRINA, ASPIRINETTA, ASPRO, CARDIOASPIRIN, GANADOL, NICCOPIR, SALICIL MIX, VIVIN	C, OTC-RR, compresse, polvere

Anti-inflammatory drugs: NSAIDs



Antiinflammatory agents:

Salycilates: DIFLUNISAL

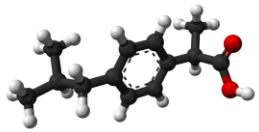


Arylalkanoic acids:

Ar-CHR-COOH

SAR: acidic moiety (carboxylic acids, enols, sulphonamides, tetrazoles, hydroxamic acids) related to arachidonic acid COOH. 2-3 C chain. Aromatic/heteroaromatic ring (related to 5, 8 ar. ac. double bonds). In some compounds there is a second, non coplanar, lipophilic area.

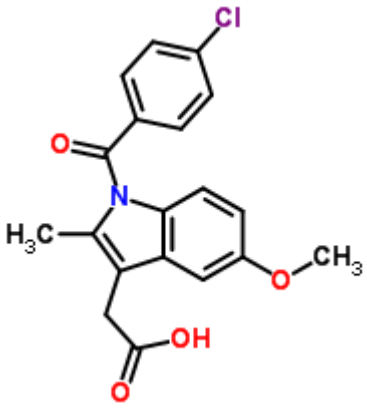
Anti-inflammatory drugs: NSAIDs



Antiinflammatory agents:

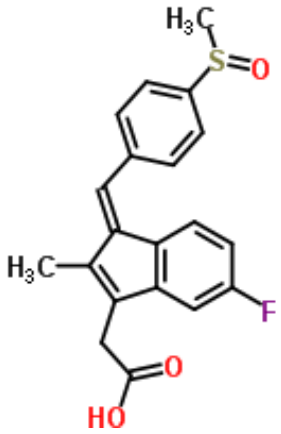
Arylacetic acids:

INDOMETHACIN



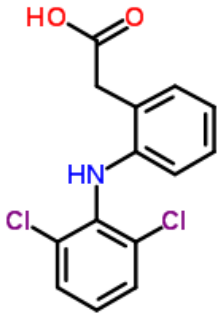
Analgesic: 10 × ASA

SULINDAC



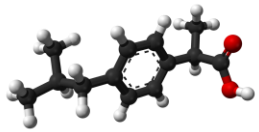
Analgesic: 10 × ASA

DICLOFENAC



Analgesic: 40 × ASA

Anti-inflammatory drugs: NSAIDs



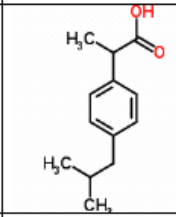
Antiinflammatory agents:

Arylpropionic acids:

IBUPROFEN

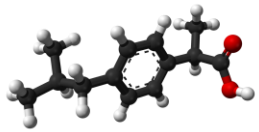
S-(+) active form. Lysine salt to increase solubility.

Metabolism: ω, ω-1, ω-2 oxidation of iBu lateral chain. Enantiomeric conversion to S(+).

Name	**IBUPROFEN**
Structure	
Systematic name	2-[4-(2-methylpropyl)phenyl]propanoic acid
Formula	$C_{13}H_{18}O_2$
MW	206.2808
Monoisotopic mass	206.13067982
Mp	76°C
H bond acceptors	2
H bond donors	1
Acid pK*a*	4.85
Basic pk*a*	--
ACD Log D pH 5.5	2.38
ACD Log D pH 7.4	0.58
Solubility	chloroform, octanol, in water <1 mg/mL
LD50	636 mg/Kg rat p.o.
Therapeutic cat	antiinflammatory
ATC **C01EB16*** CARDIAC THERAPY	**M01AE01** M MUSCULO-SKELETAL SYSTEM M01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS M01A ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS M01AE Propionic acid derivatives
Receptors	COX

Nomi commerciali (IT)	
ALGOFEN, ANTALFEBAL, ANTALGIL, BRUFEN, BUSCOFEN, CALMINE, CIBALGINA, FEBRALT, IBUPROFENE, KENDO, MABENECS, MOMENT, MOMENTACT, NUROFEN, PEDEA, SINIFEN, SPIDIFEN	C, OTC, compresse, sospensione, gocce, capsule molli, C, osp1, iniettabile *trattamento dotto arterioso neonatale

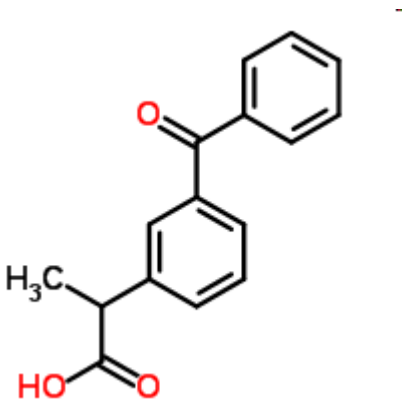
Anti-inflammatory drugs: NSAIDs



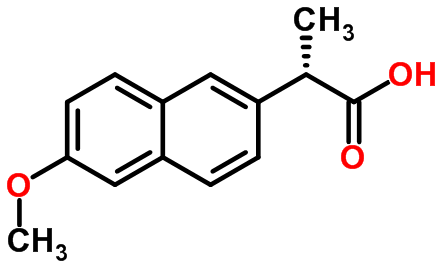
Antiinflammatory agents:

Arylpropionic acids:

KETOPROFEN

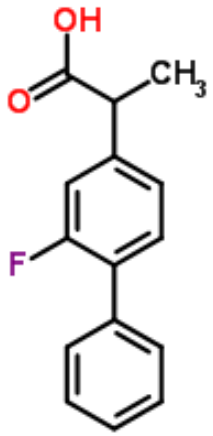


NAPROXEN



Analgesic: 7 × ASA

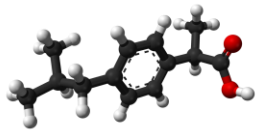
FLURBIPROFEN



Analgesic: 536 × ASA

Antipyretic 403 × ASA

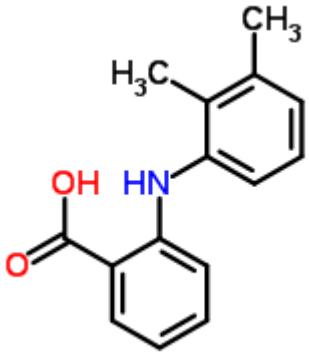
Anti-inflammatory drugs: NSAIDs



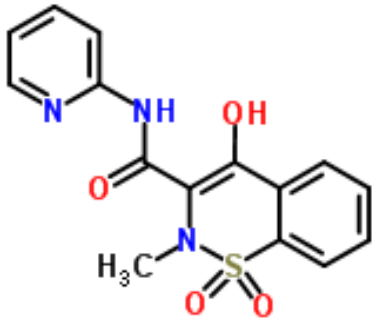
Antiinflammatory agents:

N-arylanthranilic acids, enolic acids, sulphonamides

MEFENAMIC ACID

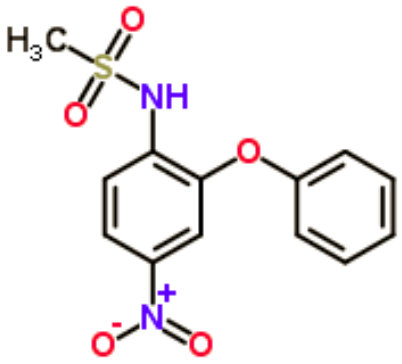


PIROXICAM



OH pK_A 4.76

NIMESULIDE

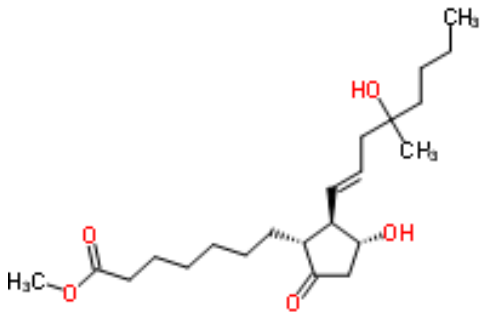


OH pK_A 6.86

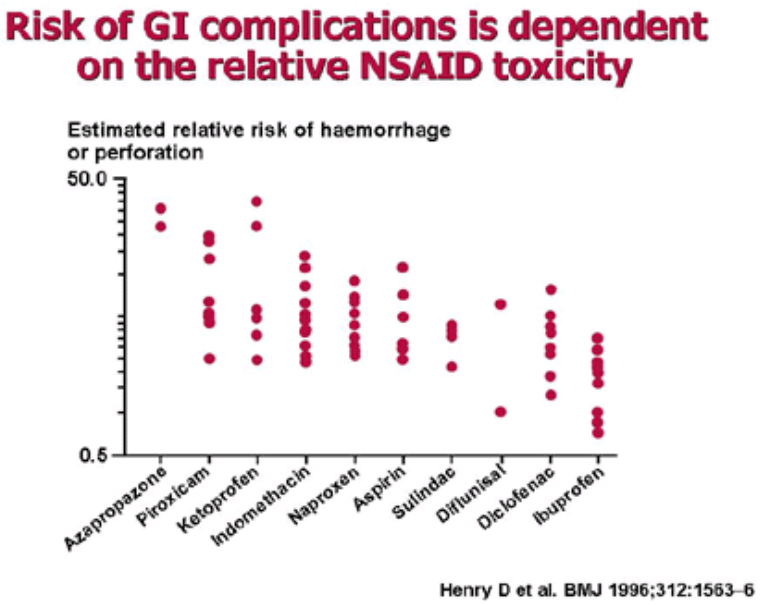
Anti-inflammatory drugs: NSAIDs

Antiinflammatory agents:

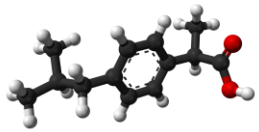
NSAIDs gastrophathy (PGE_1)



MISOPROSTOL



Anti-inflammatory drugs: NSAIDs



Antiinflammatory agents:

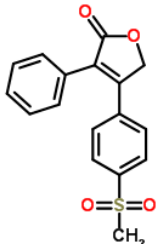
Selective COX-2 inhibitors

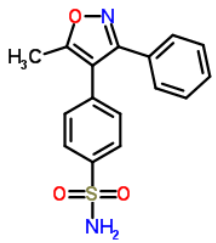
CELECOXIB

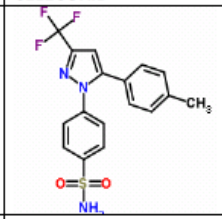
No g.im. Toxicity. Action on induced COX-2 (Alzheimer, colon carcinoma).

Cardiovascular toxic effects: inhibition of PGI_2 synthesis, atherogenesis, infarction.

ROXECOXIB, VALDECOXIB out of production

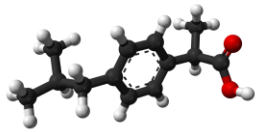




Name	**CELECOXIB**
Structure	
Systematic name	4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazol-1-yl]benzenesulfonamide
Formula	$C_{17}H_{14}F_3N_3O_2S$
MW	381.372
Monoisotopic mass	381.075882012
Mp	212-213°C
H bond acceptors	5
H bond donors	2
Acid pK*a*	10.70
Basic pk*a*	--
ACD Log D pH 5.5	3.9
ACD Log D pH 7.4	3.9
Solubility	*water 3.3 mg/L*
LD50	2000 mg/Kg rat p.o.
Therapeutic cat	anti-inflammatory
ATC **L01XX33** antineoplastic	**M01AH01** M MUSCULO-SKELETAL SYSTEM M01 ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS M01A ANTIINFLAMMATORY AND ANTIRHEUMATIC PRODUCTS, NON-STEROIDS M01AH Coxibs
Receptors	COX-2 (selective)

Nomi commerciali (IT)	
ARTILOG, CELEBREX	A, RR, capsule

Anti-inflammatory drugs: DMARDs



Antiinflammatory agents:

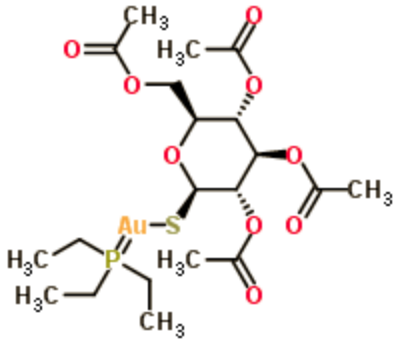
Synthetic disease-modifying antirheumatic drugs (DMARDs)

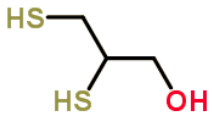
AURANOFIN

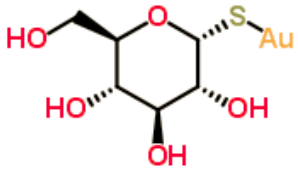
Immunology response suppression via macroglobulin formation inhibition. Inhibit lysosomial enzymes.

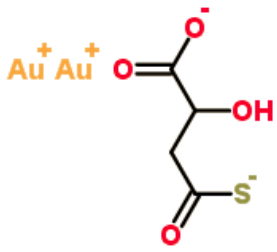
Skin, mouth, lung, kidney and blood toxic effects: Au elimination could be increased by use of ***dimercaprol***.

Other gold complexes**: AUROTHIOGLUCOSE, GOLD THIOMALATE**









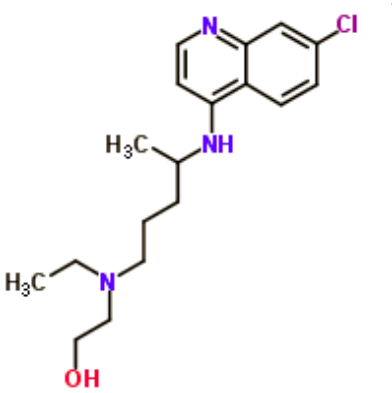
Anti-inflammatory drugs: DMARDs

Antiinflammatory agents:

Synthetic disease-modifying antirheumatic drugs (DMARDs)

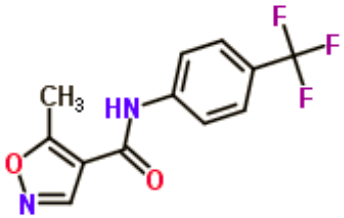
HYDROXYCLOROQUINE

Cornea/kidney toxic effects.

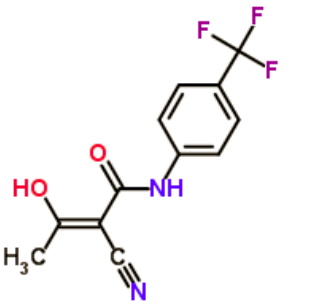


Immunosuppressive agents

LEFLUNOMIDE



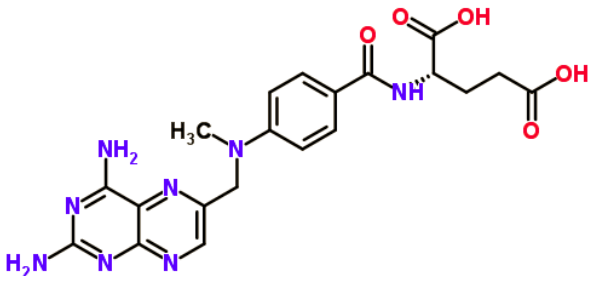
Antiinflammatory and immunosuppressive. Pro-drug of **TERIFLUNOMIDE** (α-cyanoenol). Both Inhibit proliferation of lymphocytes B via decreasing pyrimidinic nucleotides intracellular concentration.



Anti-inflammatory drugs: DMARDs

Antiinflammatory agents:

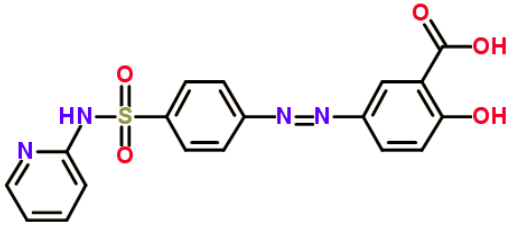
Synthetic disease-modifying antirheumatic drugs (DMARDs)



Immunosuppressive agents

METHOTREXATE DHFR inhibitor.

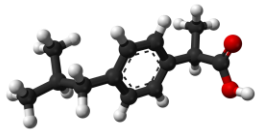
SULFASALAZINE Prodrug of 5-aminosalicylic acid.



Biological disease-modifying antirheumatic drugs (DMARDs)

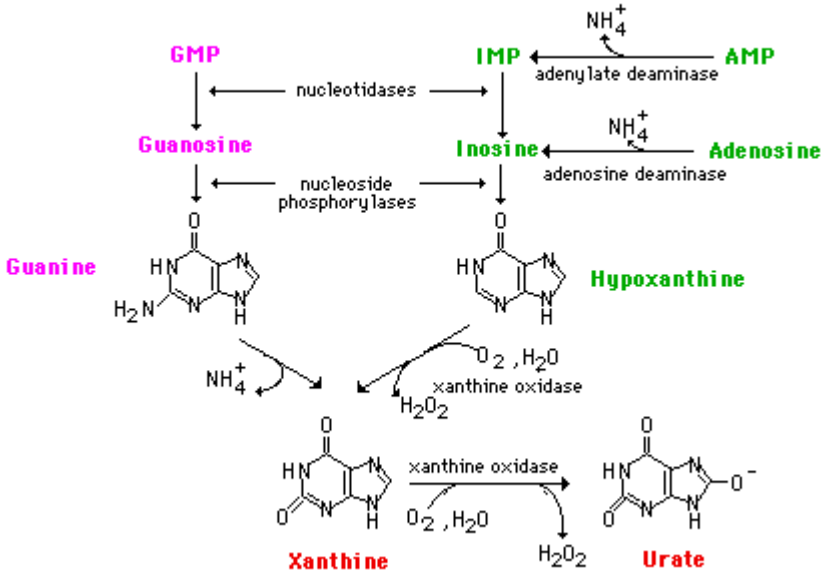
- Cytokines inhibitors: ***TNF (tumour necrosis factor) blockers.*** Antibodies
- Interleukyne-1 receptor antagonists
- Co-stimulation modulators

Anti-inflammatory drugs



Antiinflammatory agents:

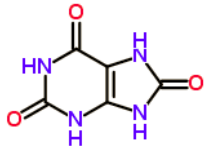
Anti-gout

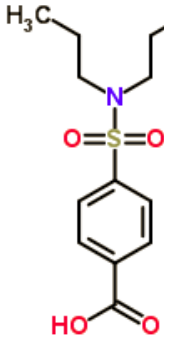


Uricosuric agents:

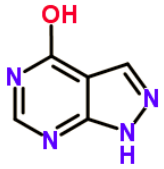
PROBENECID

increases ***uric acid*** excretion in the urine.





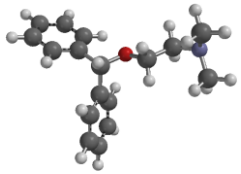
Uric acid synthesis inhibitors:



ALLOPURINOL

inhibitor of the enzyme xanthine oxidase. Antimetabolite.

Anti-histaminic drugs



Histamine:

Mast cells

Gastric mucous membrane

Neurons:

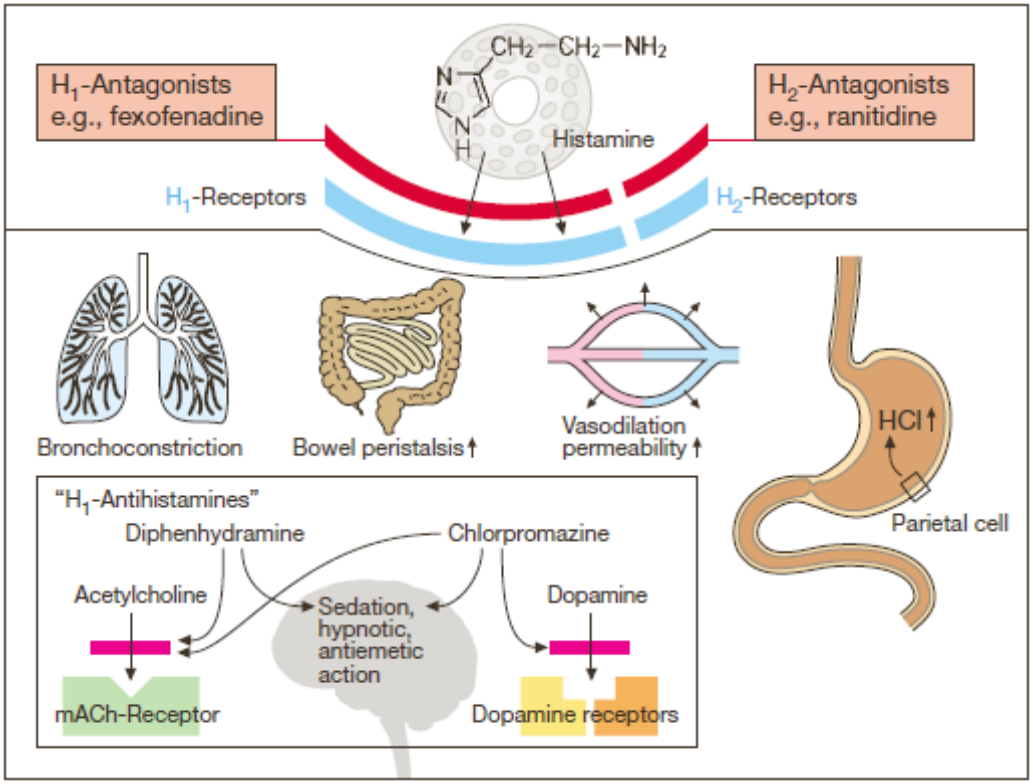
Autonomous nervous system

Central nervous system

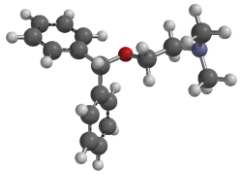
Main effects:

Allergic response

Gastric acid secretion



Anti-histaminic drugs

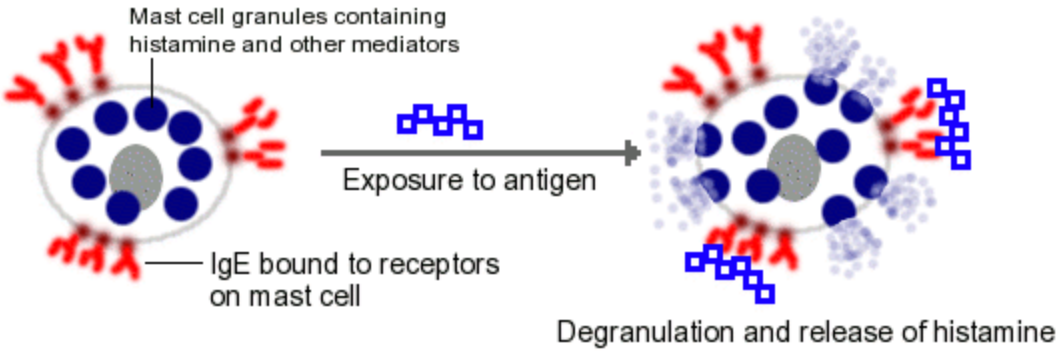


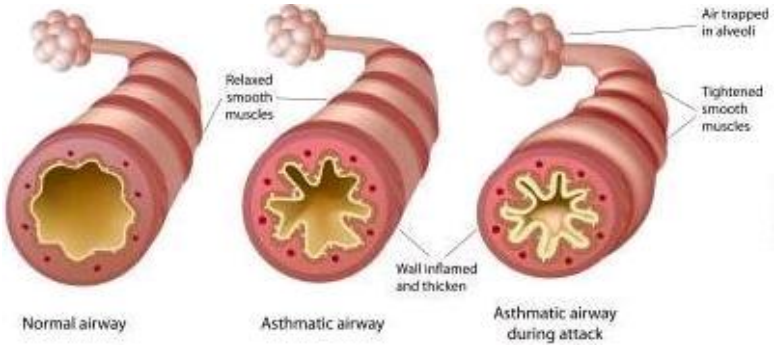
Histamine and inflammation/allergy:

Mast cells:

Released together with histamine:

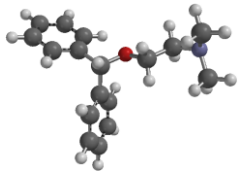
- leukotrienes
- prostaglandins
- platelet-activating factor (PAF)
- bradykinin
- proteases
- cytokines
- interleukins
- TNFα





bronchoconstriction

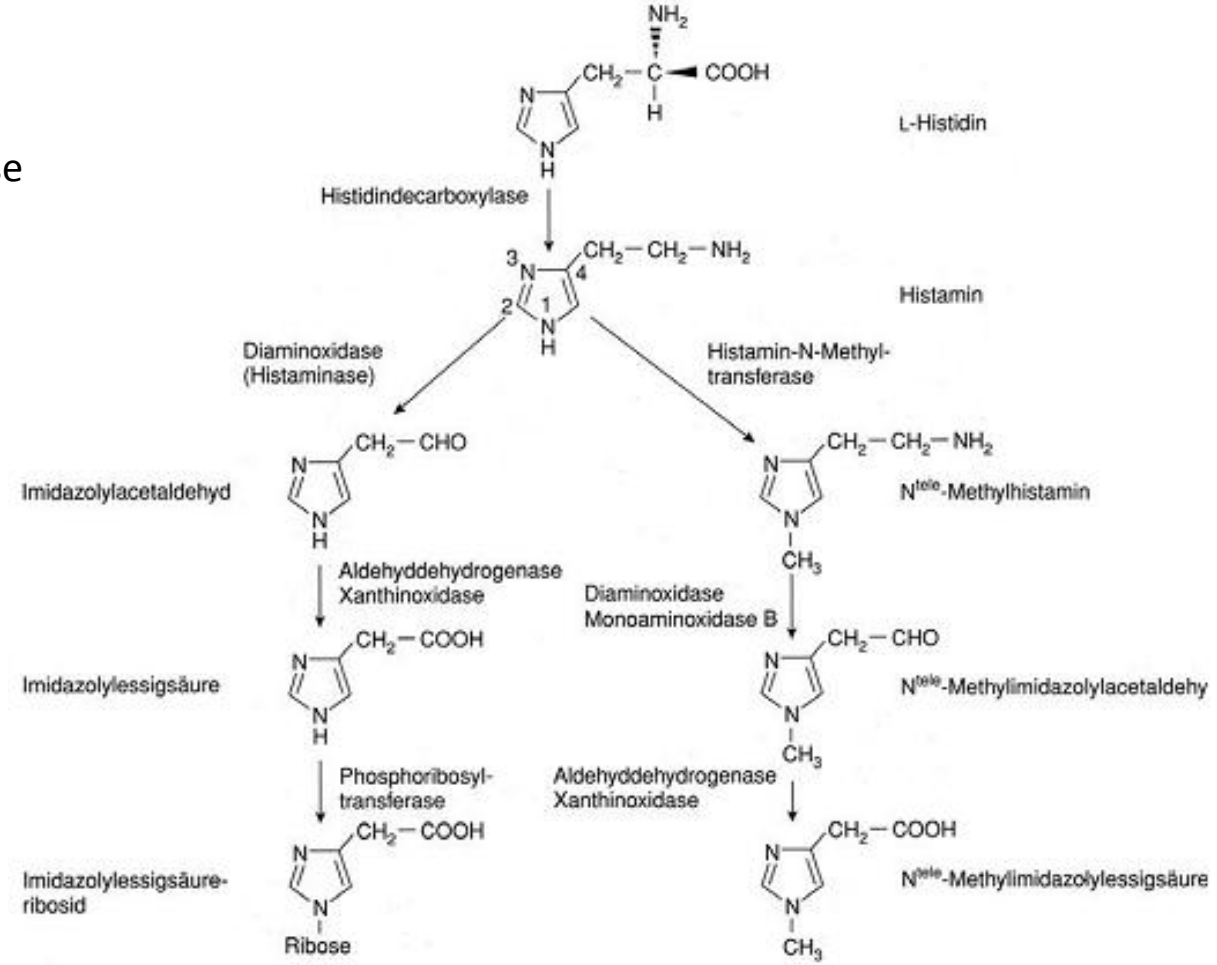
Anti-histaminic drugs



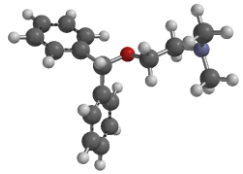
Histamine:

Biosynthesis:
L-histidine decarboxylase

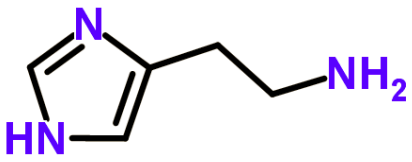
Metabolism:
N-methylation (HNMT)
Oxidation



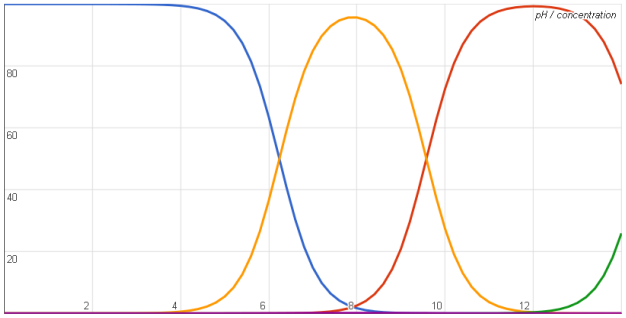
Anti-histaminic drugs



Histamine:

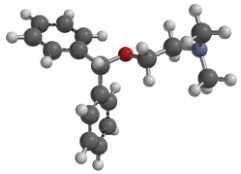


dication monocation neutral



Systematic name	2-(1H-imidazol-4-yl)ethanamine
Formula	$C_5H_8N_3$
MW	110.1371
Monoisotopic mass	110.071822271
Mp	89°C
H bond acceptors	3
H bond donors	3
Acid pK*a*	--
Basic pk*a*	9.48 (amine); 5.80 (imidazole)
ACD Log D pH 5.5	-4.41
ACD Log D pH 7.4	-3.65
Solubility	water
LD50	1550 mg/Kg rat i.p.
Therapeutic cat	histaminergic
ATC	**L03AX14** L ANTINEOPLASTIC AND IMMUNOMODULATING AGENTS L03 IMMUNOSTIMULANTS L03A IMMUNOSTIMULANTS L03AX Other immunostimulants
Receptors	H_1, H_2, H_3, H_4
Notes	Endogenous autacoid

Anti-histaminic drugs



Histamine receptors:

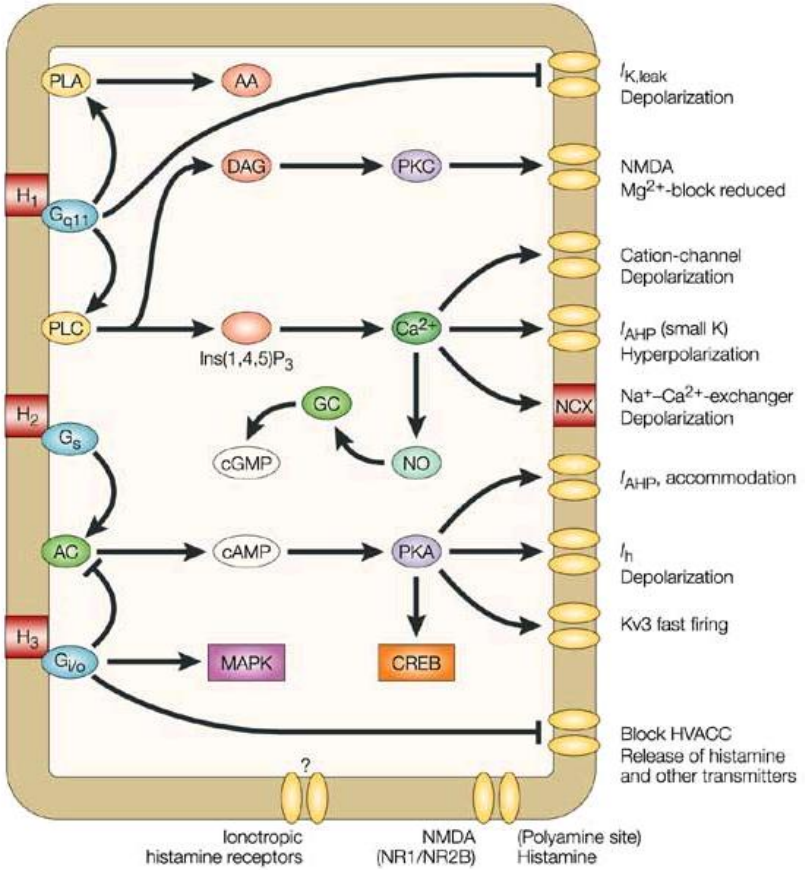
Transmembrane G-protein coupled receptors.

H_1: bronchi, intestine and uterus

H_2: stomach. 359 AA.

H_3: SNC (autoreceptors)

H_4: hemopoietic system / mast cells



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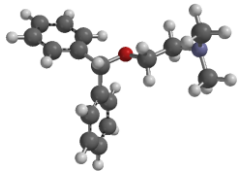
Anti-inflammatory, histamine-related



Leukotriene receptor antagonist (LTRA):

ZAFIRLUKAST is an oral LTRA for the maintenance treatment of asthma, often used in conjunction with an inhaled steroid and/or long-acting bronchodilator.

Reduces hyper-reactivity of bronchi to histamine, following allergens inhalation