

Analgesics - antipyretics

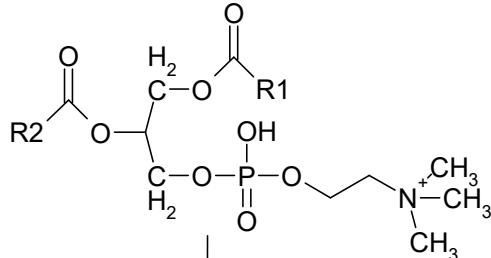
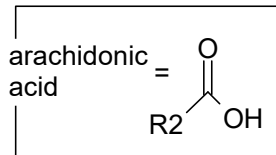
= „weak“ analgesics

= non-opioid analgesics

Most of them also

- non-steroidal anti-inflammatory drugs (NSAIDs)
- antirrhematics

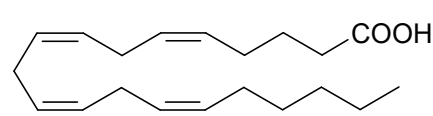
Metabolism of eicosanoids



phospholipase A2

glucocorticoids

inhibitors of prostaglandin synthesis = "weak" analgesics + NSAIDs

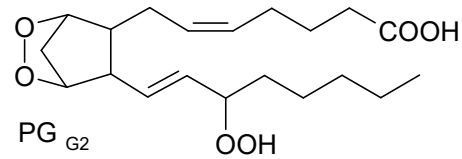


arachidonic acid

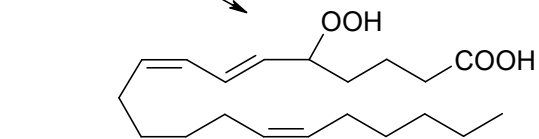
lipoxygenase inhibitors

cyclooxygenases (COX1 + COX2)

lipoxygenase



PG_{G2}



5-hydroperoxy-6-trans-8,11,14-cis-eicosatetraenoic acid (5-HPETE)

cyclooxygenases

tromboxan synthase

prostacyclin synthase

TX_{A2}

trombocytes

PG_{H2}

PG_{I2} = prostacyclin

endothelium cells

PG_{D2}

PG_{E2}

PG_{F2α}

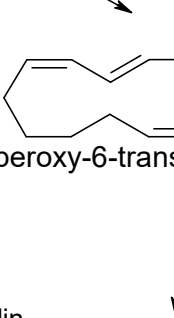
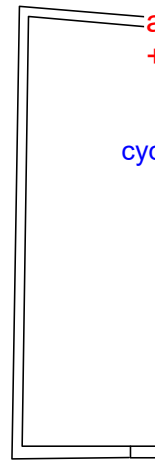
all the cells

LT_{C4}

LT_{B4}

LT_{D4}

LT_{E4}



Effects of prostaglandins

Prostaglandin E, $F_{2\alpha}$: mediators of ache, fever, inflammation; secretion of HCl↓, stomach mucosa capillaries dilation, contraction of uterus, kidneys: excretion of Na^+ and H_2O ↑

Prostacyclin (prostaglandin I_2): vasodilation, platelets aggregation inhibition

Tromboxan: vasokonstriction, platelets aggregation activation

Leukotriens: allergic reactions (e.g. asthma bronchiale)

Cyclooxygenases (= prostaglandin G/H synthases)

COX1

Constitutive: in all the tissues

Functions:

- protection of stomach mucosa (vasodilation)
- diuresis
- platelets aggregation (TXA)

COX2

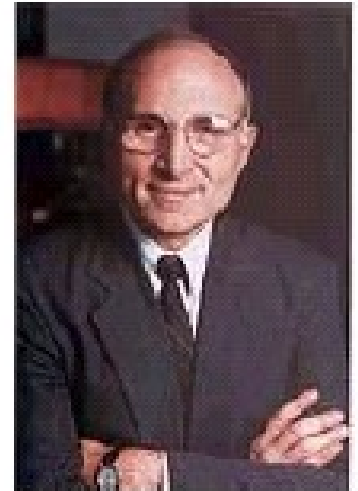
Constitutive: kidneys, brain (co-localized with cyclins D₁ and E)

Inducible: macrophages, neutrophils, fibroblasts, endothelium cells

Functions:

- vasodilatation (PG I₂)
- childbirth (uterus contractions)
- inflammation processes

COX3 ?? (= COX1b; brain ?)



Philipp Needleman
discoverer of COX
isoenzymes

(1989)

Classification of COX inhibitors (antipyretics, NSAIDs)

Non-selective (COX1 + COX2)

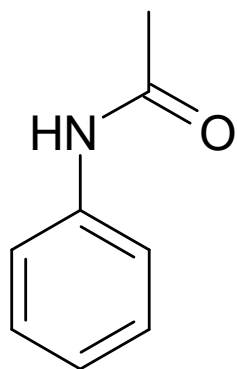
- Anilides
- Salicylates
- Phenamates
- Aryl- and heteroaryl alcanoic acids
 - Aryl- and heteroaryl acetic acids
 - Aryl- and heteroaryl propionic acids
- Oxicames
- 1,2-Dihydropyrazolidine-3-ones
- 2,5-Pyrazolidinediones

Selective (COX1 < COX2): nimesulide

Specific (COX2)

- Coxibes

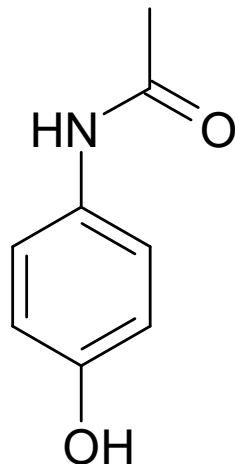
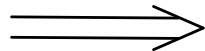
Anilides



acetanilide

N-phenylacetamide

1886: Antifebrin®



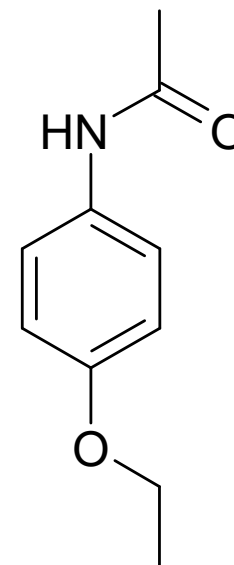
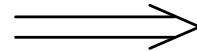
paracetamol
(**acetaminophen**)

4-(acetamino)phenol

para-(acetamino)phenol

p-(acetamino)phenol

Paralen®, Panadol®



phenacetin

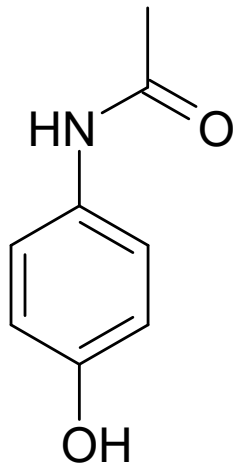
N-(4-ethoxyphenyl)acetamide

nephrotoxicity

Dinyl® - analg.
mixture with caffeine,
aminophenazone and
barbiturates

Paracetamol

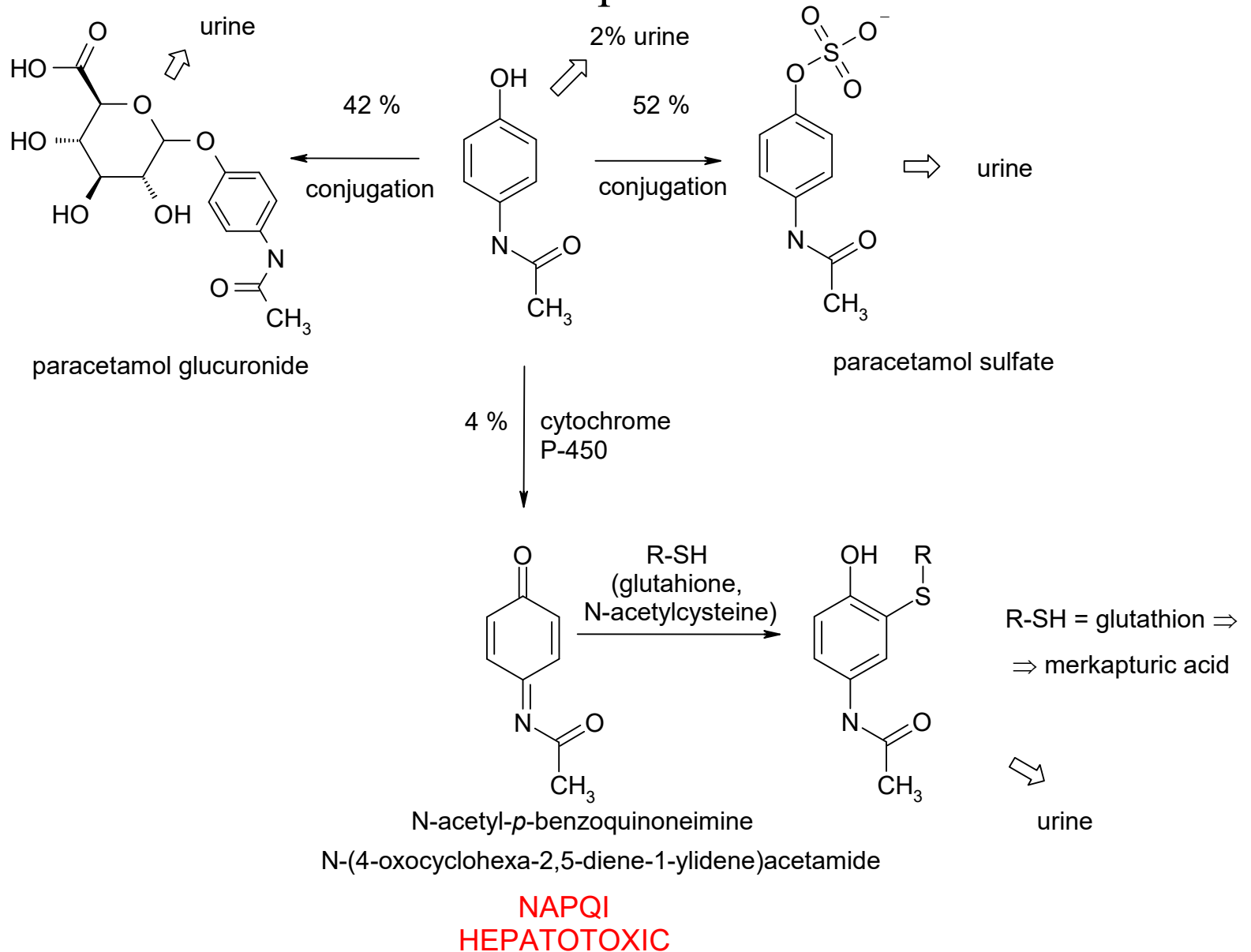
- inhibits COX only in CNS (COX3 ?) not in periphery ⇒
- effects: analgesic, antipyretic (not antiinflammatory, antirheumatic)



Usage in mixtures with

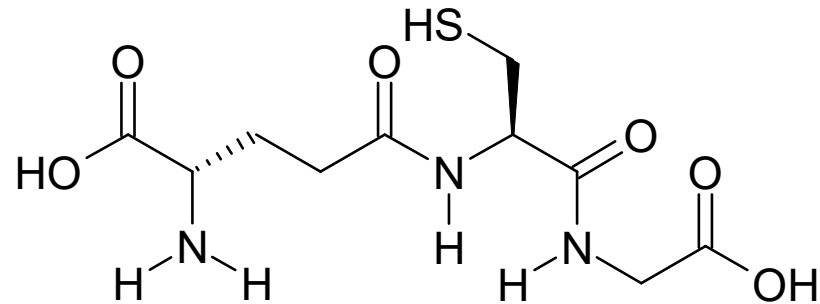
- codeine, caffeine ⇒ effect enhancement (Korylan tbl.®, Panadol tbl.®, Efferalgan codein tbl. eff.®)
- expectorants (guaifenesin, terpin)
- antitussives (dextromethorphan)
- H₁-antihistaminines (pheniramine, chlorphenamine, dimenhydrinate, promethazin, doxylamin) together with α -sympatomimetics (phenylefrine, pseudoephedrine)
- spasmolytics (pitophenon)
- myorelaxants (chlorzoxan, carisoprodol)
- NSAID (acetylsalicylic acid, propyphenazon – Valetol®)

Metabolism of paracetamol

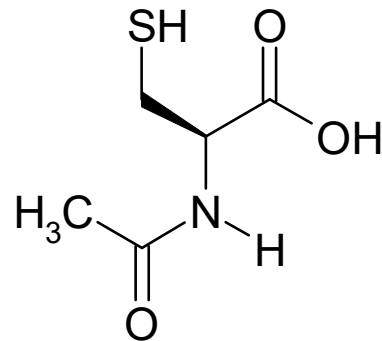


Thiols detoxicating N-acetyl-*p*-benzoquinoneimine

γ -Glu-Cys-Gly



glutathione

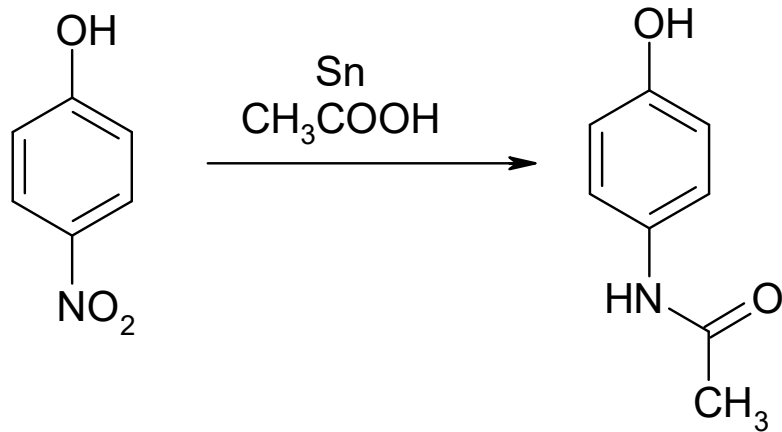


N-acetyl-L-cysteine

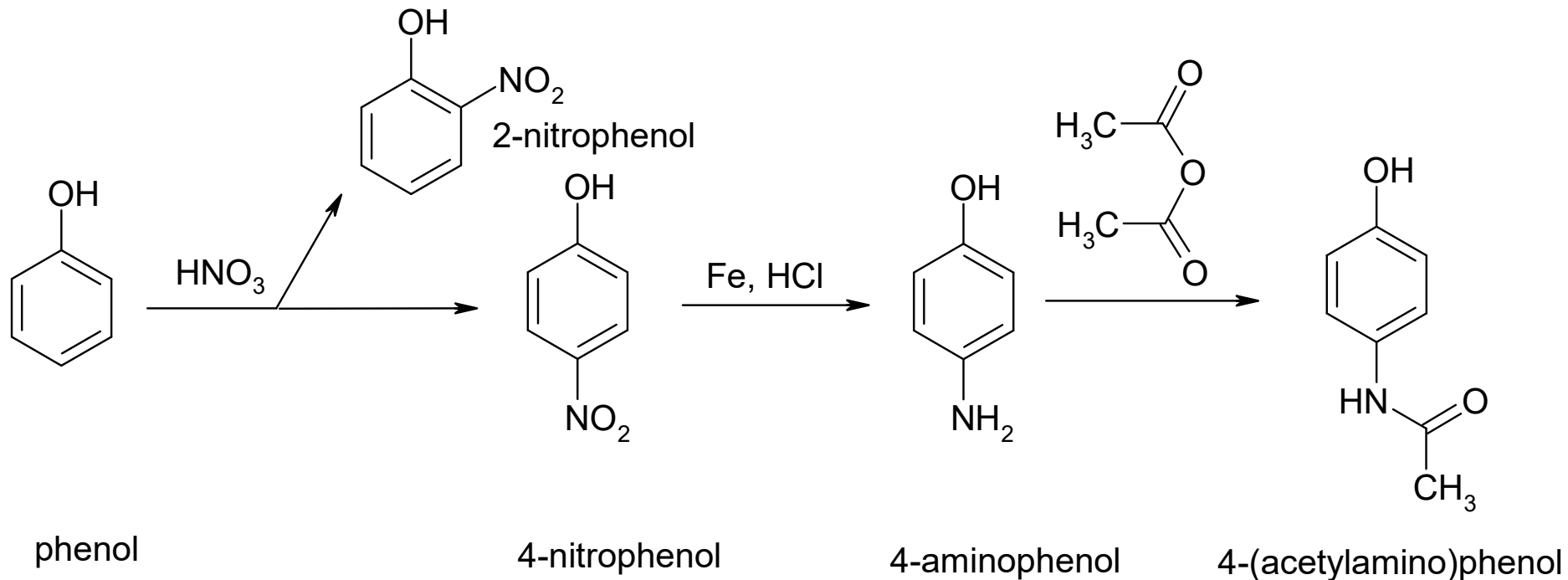
mucolytic

ACC®, Mucobene®

Synthesis of paracetamol

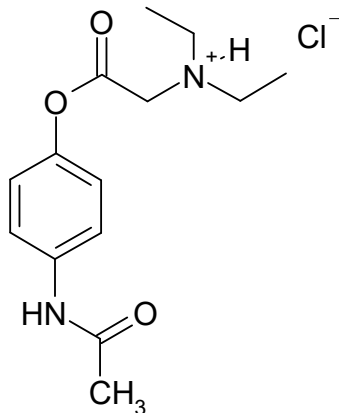


Morse, Chem. Ber. **11**, 232 (1878)



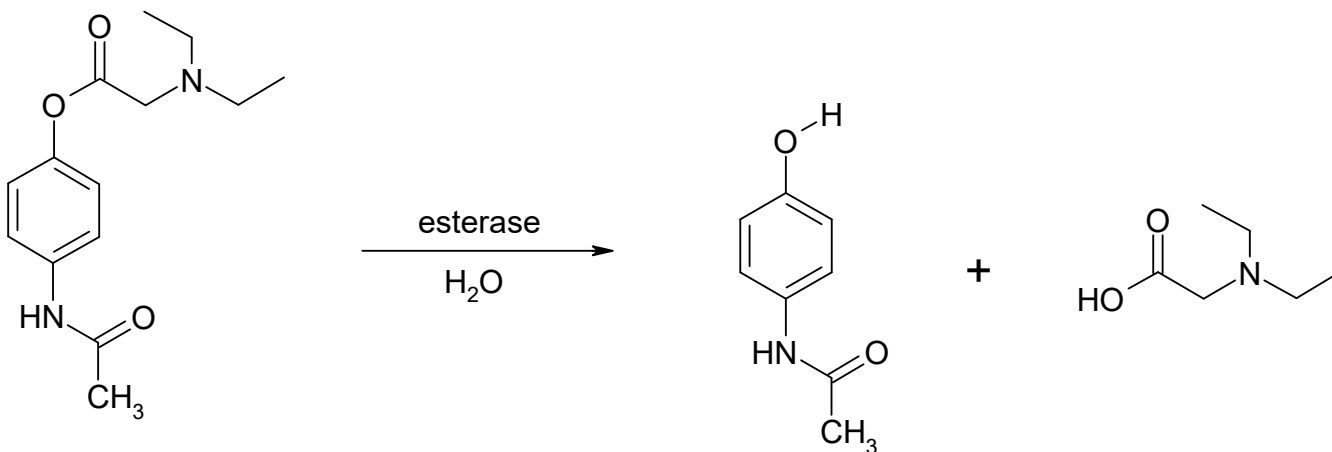
Propacetamol – paracetamol prodrug

- for intravenous application

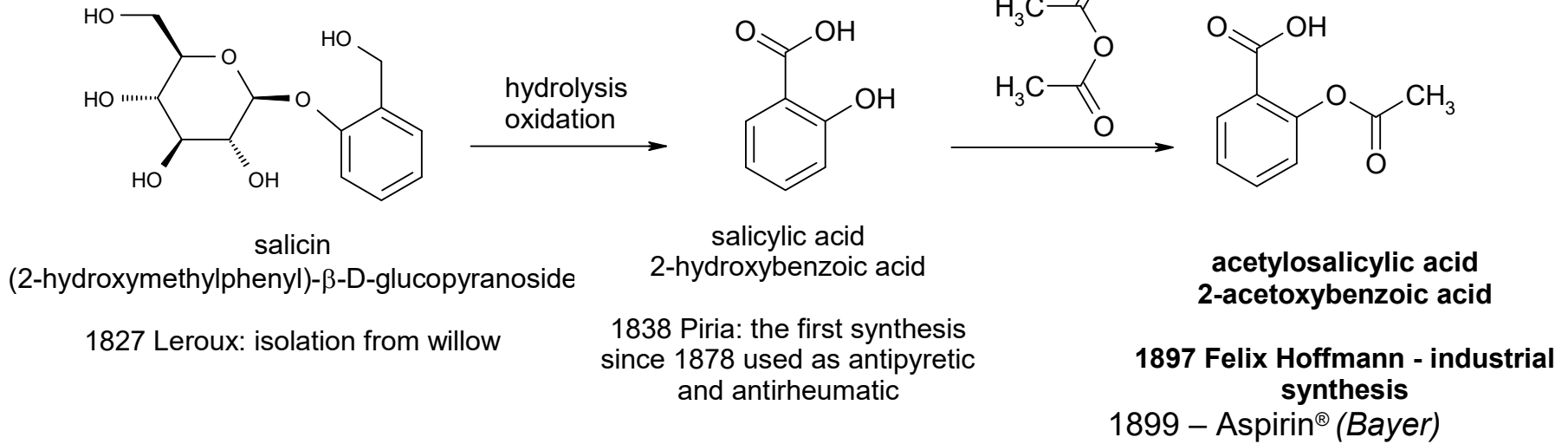


4-(acetamino)phenyl-N,N-diethylglycinate hydrochloride
2-[4-(acetamino)phenoxy]-N,N-diethyl-2-oxoethanaminium chloride
propacetamol hydrochloride

Pro-Dafalgan® (*UPSA Laboratoires*)



Salicylates



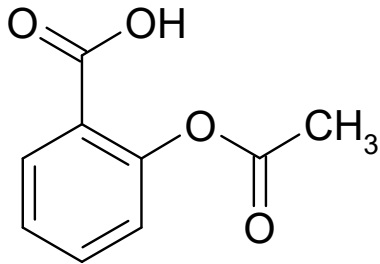
Felix Hoffmann



Sir John R. Vane



Effects of acetylosalicylic acid



„Wanted“:

- antipyretic
- analgesic
- anti-inflammatory
- antirheumatic
- antithrombotic (↓ platelets aggregation) – Anopyrin®



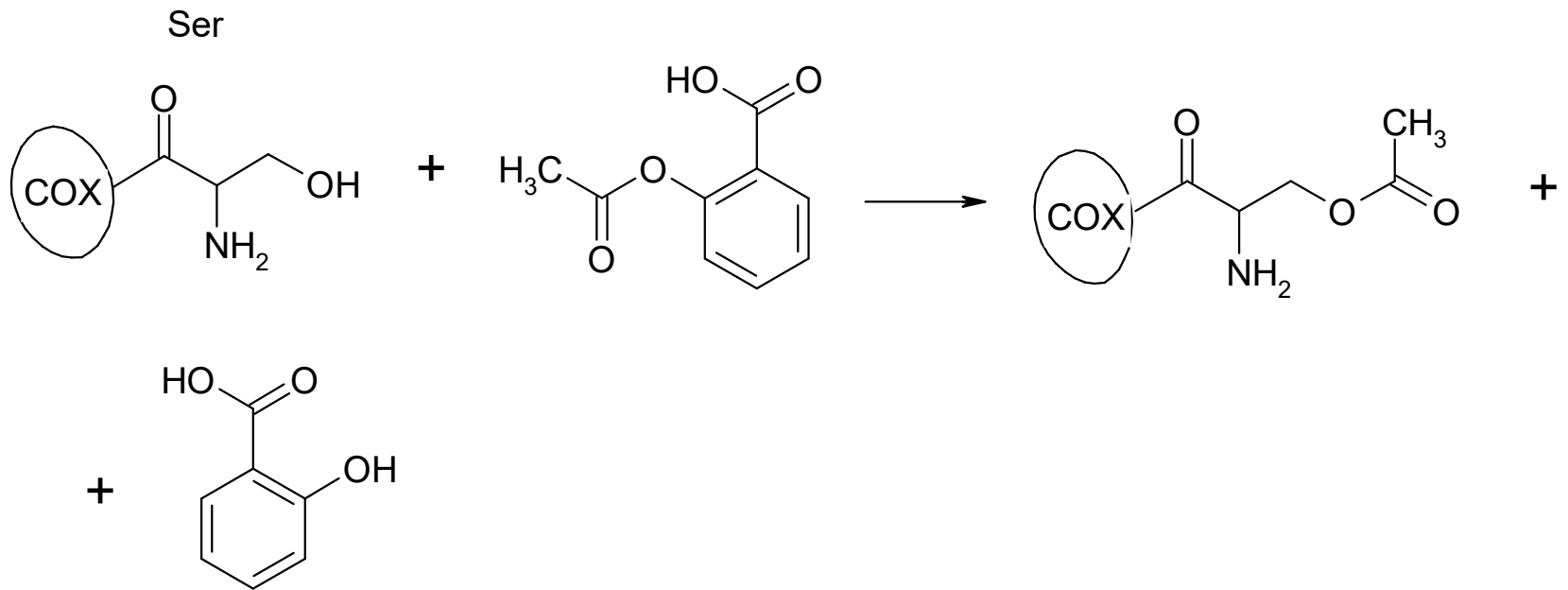
„Unwanted“:

- ulcerogenic
- Rey syndrom in children after viral infection (hepatopathy, encefalopathy) ⇒ kontra-indication **in children**
- bleeding (e.g. from nose - ↓ platelets aggregation)

Intoxication = „salicylism“ – infliction of CNS (psychical malfunctions, buzz in ears, dizziness, deafness), metabolic acidosis

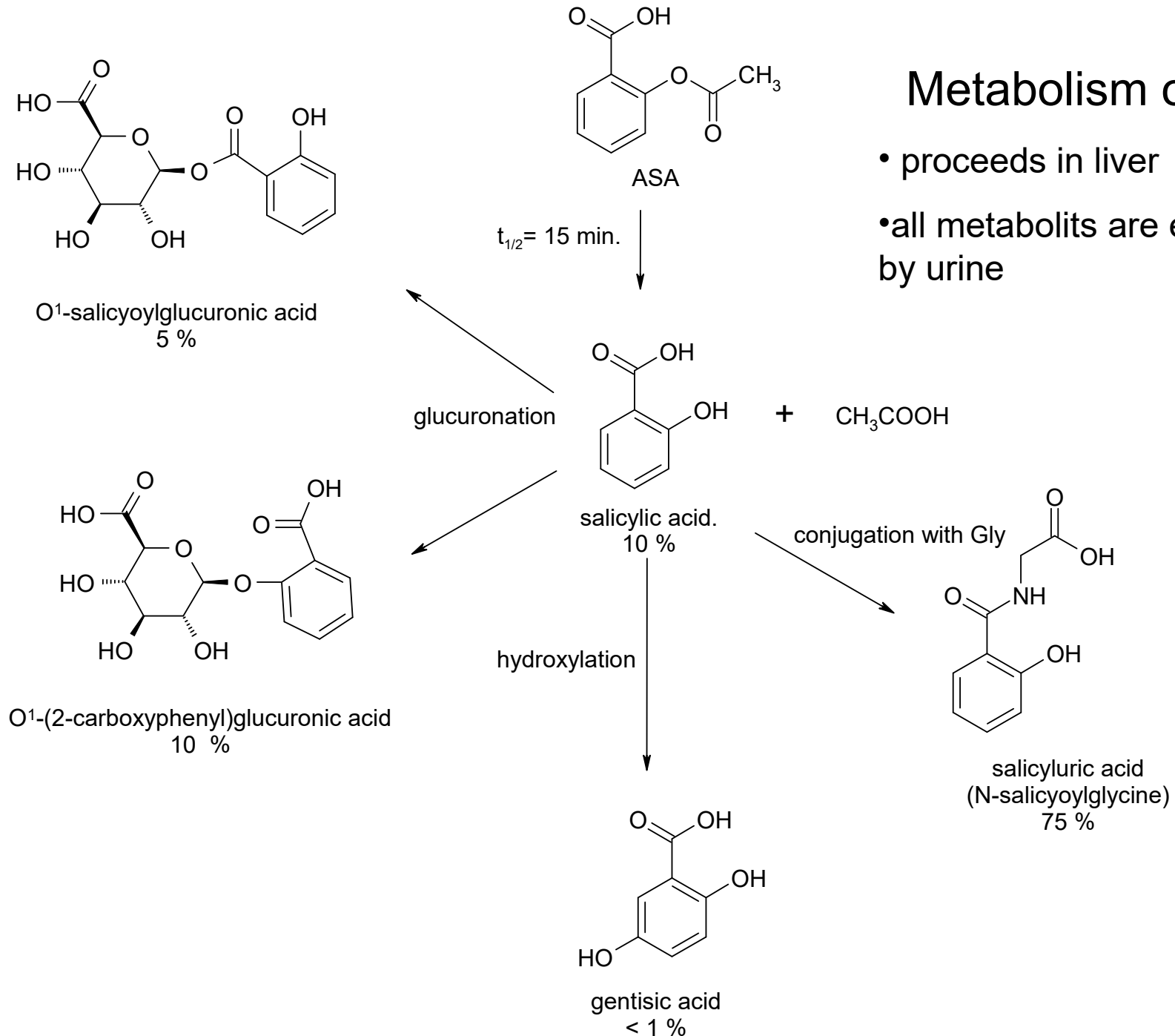
Mechanism of action of acetylosalicylic acid (ASA)

- irreversible inhibition of cyclooxygenases by acetylation of serine residue

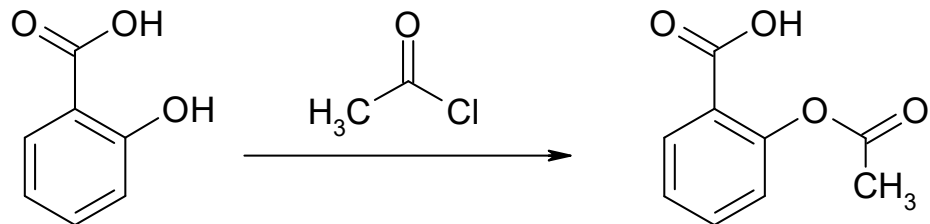


Metabolism of ASA

- proceeds in liver
- all metabolites are excreted by urine



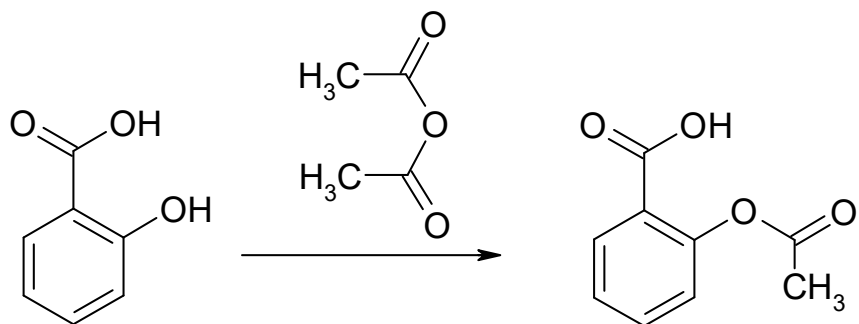
Syntheses of ASA



Gerhardt, Justus Liebigs Ann. Chem. **87**, 164 (1853)

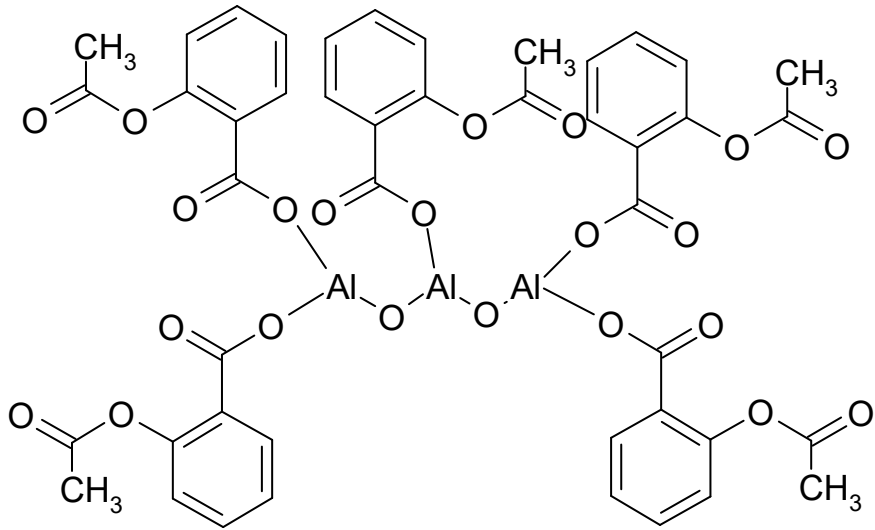
Gilm, Justus Liebigs Ann. Chem. **112**, 181 (1859)

Kraut, Justus Liebigs Ann. Chem. **150**, 10 (1869)



Felix Hoffmann

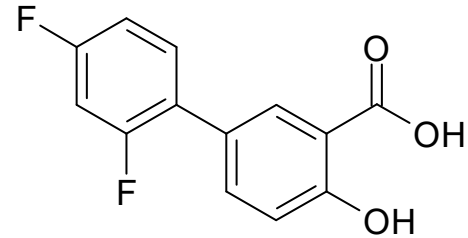
Other salicylates



pentakis(acetylosalicyoyloxy)trialuminium dioxide

aloxiprin

Superpyrin®



2',4'-difluoro-4-hydroxy-1,1'-biphenyl-3-carboxylic acid

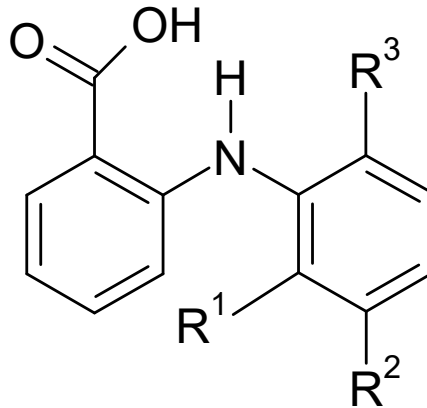
diflunisal

Unisal® tbl.

Anthranilic acid derivatives – phenamates

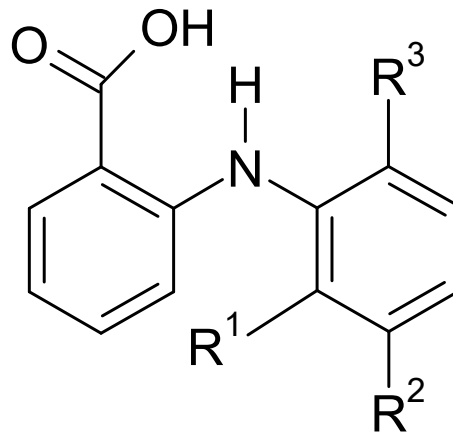
= substitution derivatives of 2-phenylaminobenzoic acid

- derived from salicylates by substitution of hydroxy group with (phenyl)amino moiety



- aromatic amino acids
- substituted on the aniline ring only
- inhibit both COX1 and COX2 (selectivity?; COX3?)
- analgesics, antipyretics, antimigranics, anti-inflammatory

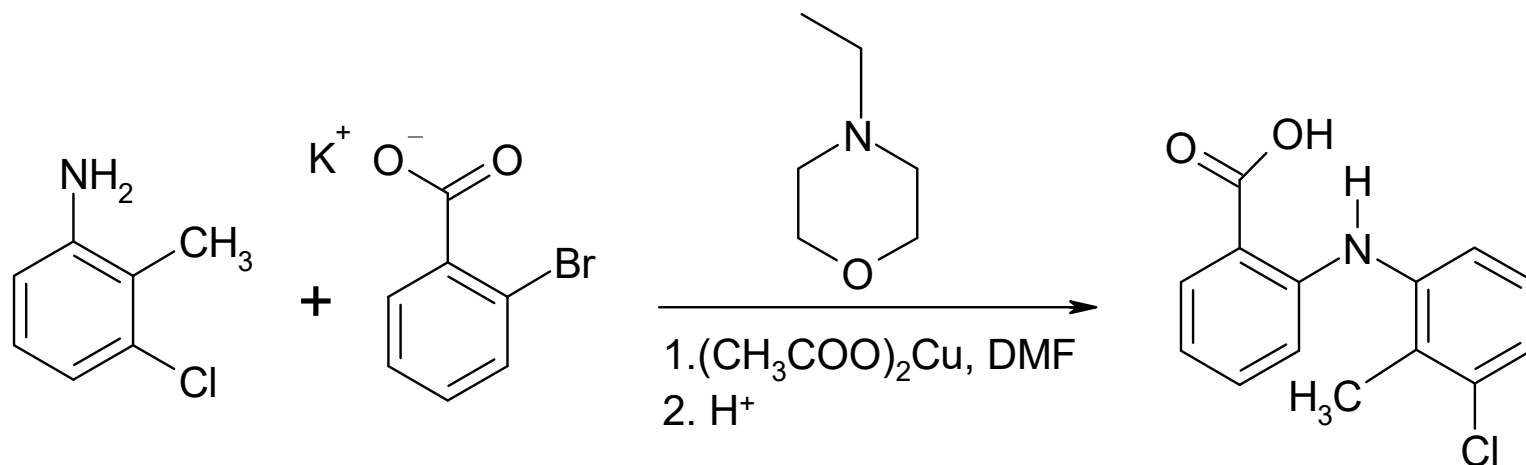
Phenamates



R ¹	R ²	R ³	Chemical name	INN / preparation
-CH ₃	-CH ₃	-H	2-(2,3-dimethylphenylamino)-benzoic acid	mephenamic acid
-Cl	-CH ₃	-Cl	2-(2,6-dichloro-3-methylphenylamino)benzoic acid	meclophenamic acid
-CH ₃	-Cl	-H	2-(3-chloro-2-methylphenylamino)benzoic acid	tolphenamic acid Migea rapid®
-H	-CF ₃	-H	2-(3-trifluoromethylphenylamino)benzoic acid	fluphenamic acid

Tolphenamic acid

Synthesis



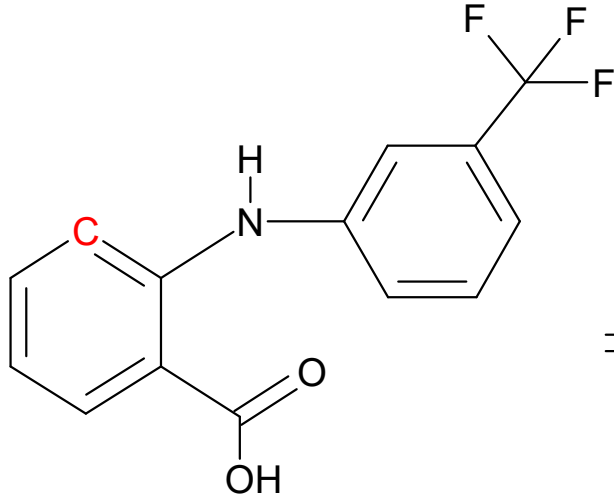
Kaltenbronn J.S. et al., *Arzneim. Forsch* **33**, 621-627 (1983)

Selectivity against COXs

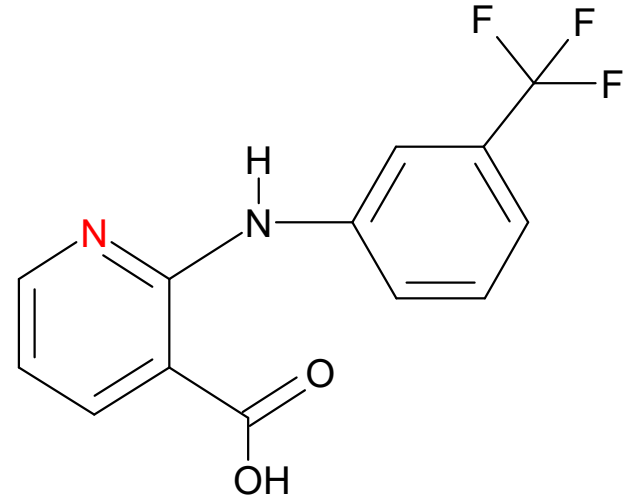
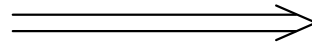
$$\frac{IC_{50}(\text{COX1})}{IC_{50}(\text{COX2})} = 10$$

Grossmann C. J. et al., *Inflammation Res.* **44**, 253-257 (1995)

Niflumic acid and its esters



fluphenamic acid



2-[[3-(trifluoromethyl)phenyl]amino]nicotinic acid

niflumic acid

- isosteric substitution benzene \Rightarrow pyridine, or $-\text{CH}=\Rightarrow -\text{N}=\text{N}=\text{C}$
- inhibit both COX1 and COX2
- anti-inflammatory, antirheumatics; usually topically administered

Niflumic acid and its esters

- esters are prodrugs which can better penetrate through the skin

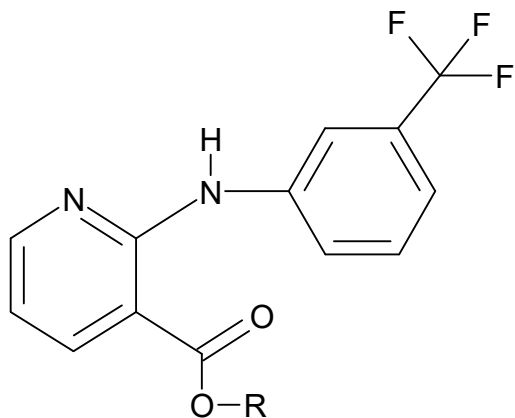
R

2-[[3-(trifluoromethyl)phenyl]amino]nicotinic acid

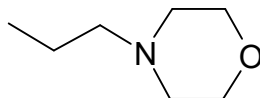
—H

niflumic acid

Niflugel[®], Nifluril[®]

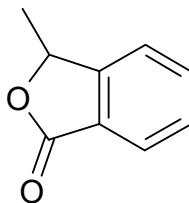


-||- 2-(morpholine-4-yl)ethylester



morniflumate

-||- 1-oxo-2-(3*H*)-benzofurane-3-ylester

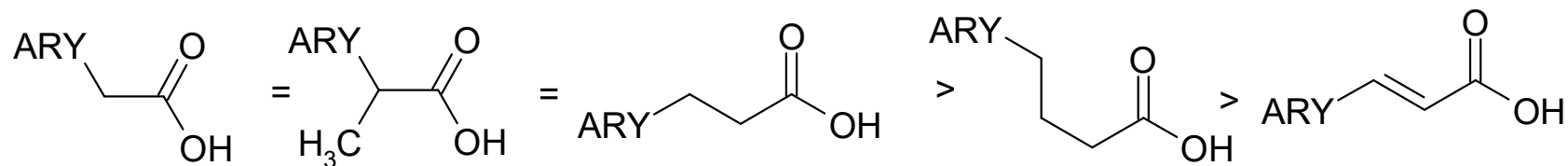


talniflumate

Aryl- and heteroarylalkanoic acids

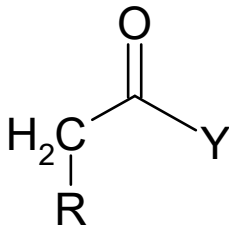
Structure-activity relationships (SAR)

- the aliphatic part of the molecule is more specific for the effect than the aromatic one



ARY = aryl, heteroaryl

Aryl- and heteroarylacetic acids and their functional derivatives

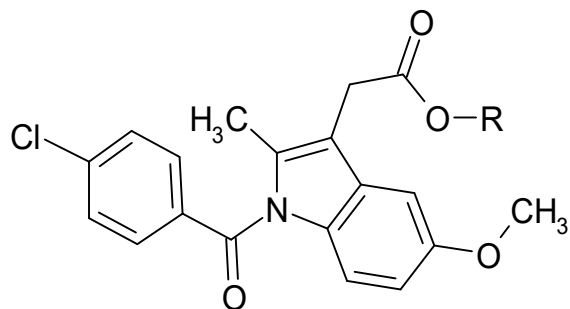


R = aryl or heteroaryl

Y = OH, NHOH, NHR, OCH₂COOH, or other

- antirheumatics, anti-inflammatory, analgesics, antipyretics
- inhibition of both COX1 and COX2
- adverse effects (AE) like in salicylates

Aryl- and heteroarylacetic acids and their functional derivatives (fenacs)



R = H

[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

indomethacin

- used since 1963
- now mainly topically

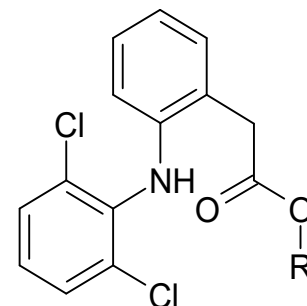
Indobene[®] cps, Bonidon[®] gel,
Elmetacin[®] spr

R = OCH₂COOH

[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]acetic acid

carboxymethylester

acemetacin



R = H

{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid

diclofenac

- used since 1975

Voltaren[®], Veral[®], Myogit[®],
Diclorem[®]

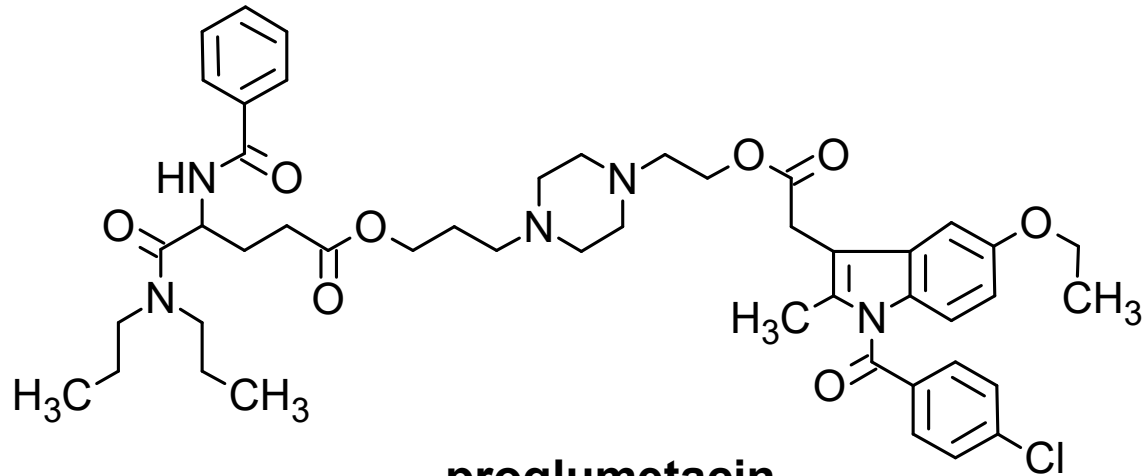
R = OCH₂COOH

{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid

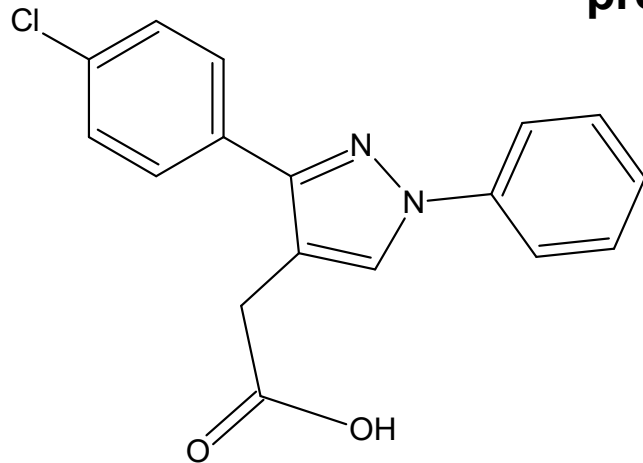
carboxymethylester

aceclofenac

Heteroarylacetic acids and their derivatives

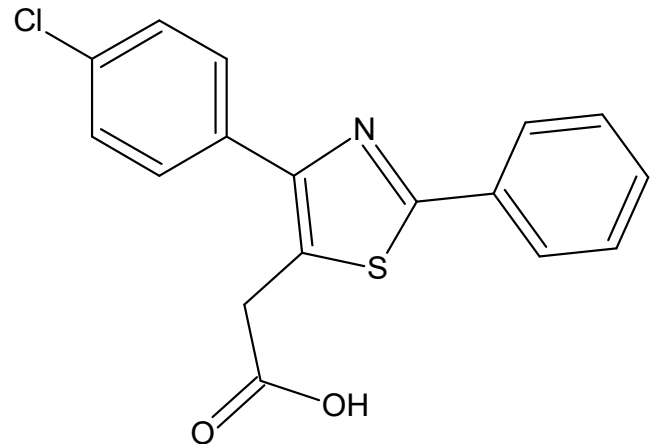


proglumetacin



[3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazole-4-yl]acetic acid

lonazolac

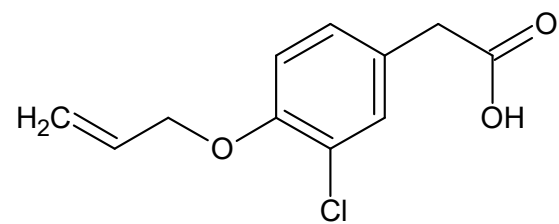


[4-(4-chlorophenyl)-2-phenyl-1,3-thiazole-5-yl]acetic acid

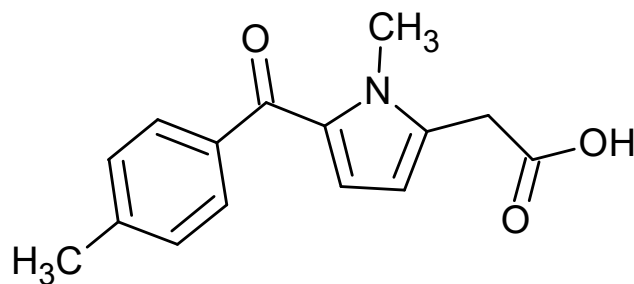
fentiazac

•isosteres

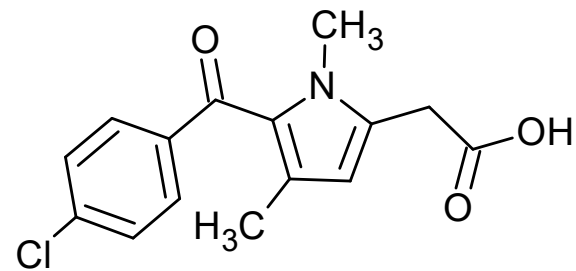
Aryl- a heteroarylacetic acids



alclofenac



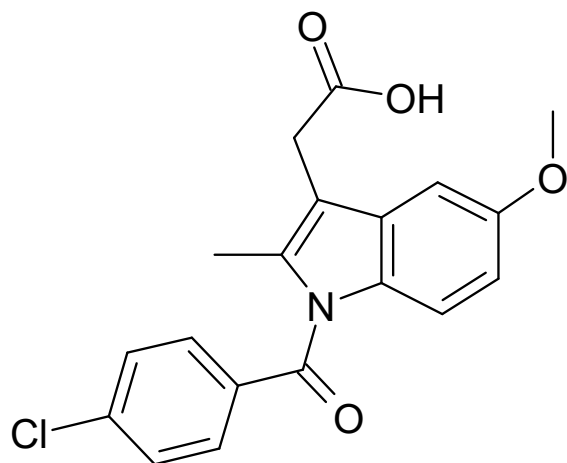
tolmetin



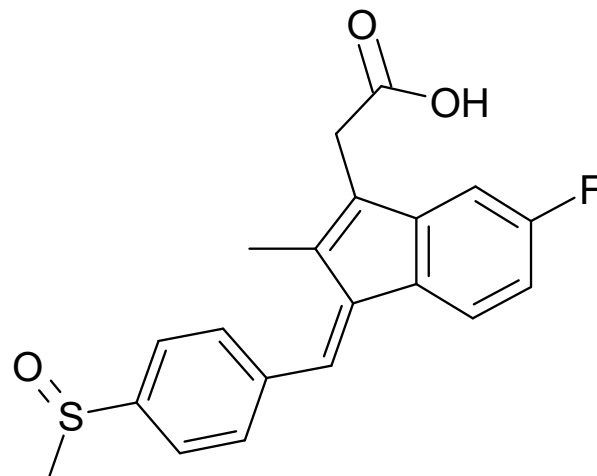
zomepirac

Aryl- a heteroarylacetic acids

- examples of isosterism of rings and functional groups

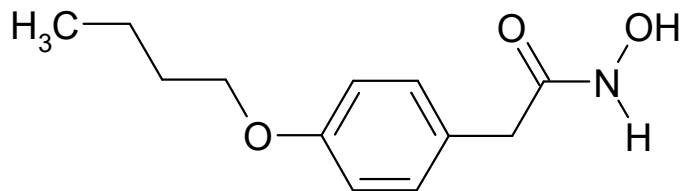


[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-
1H-indol-3-yl]acetic acid
indomethacin



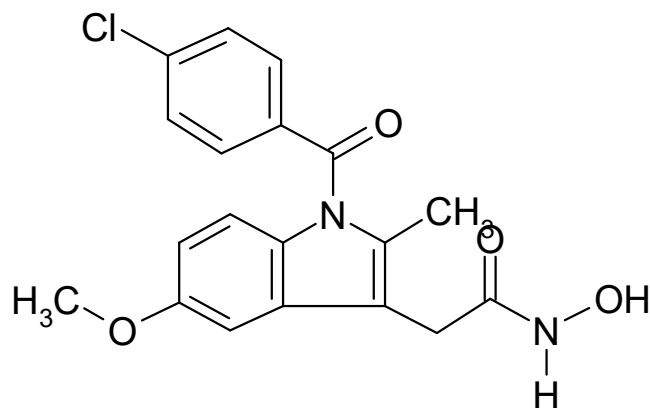
[6-fluoro-3-(4-methanesulfinylbenzylidene)-2-methyl-
3H-indene-1-yl]acetic acid
sulindac

Nitrogenous functional derivatives of aryl- and heteroarylacetic acids



2-(4-butoxyphenyl)-N-hydroxyacetamide
2-(4-butoxyphenyl)acetohydroxamic acid

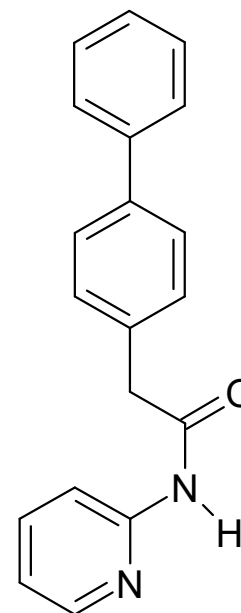
bufexamac



2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-yl]-
N-hydroxyacetamide

2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-yl]-
acetohydroxamic acid

oxametacin

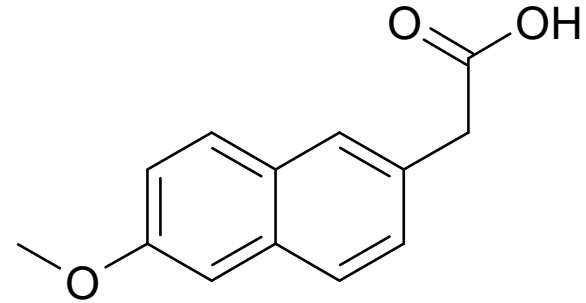
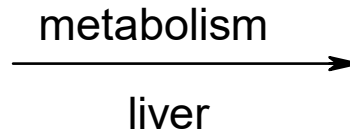
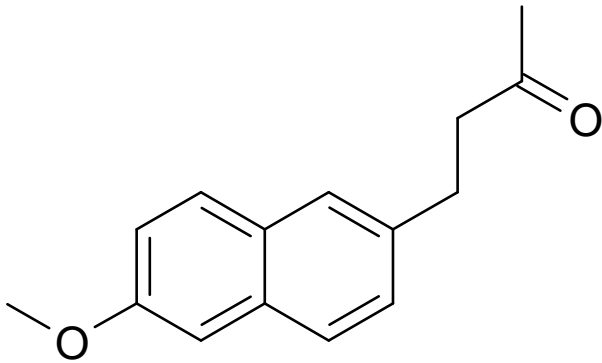


1,1'-biphenyl-4-yl-N-pyridine-2-yl-acetamide

difenpiramide

Nabumeton

- a prodrug



4-(6-methoxynaphthalene-2-yl)butan-2-one

2-(6-methoxynaphthalene-2-yl)acetic acid

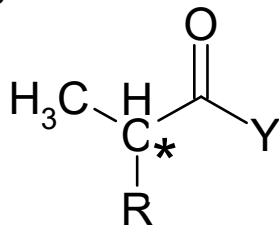
(6MNA)

nabumetone

active metabolit

Relifex[®] tbl. obd.

2-aryl- and 2-heteroarylpropionic acids and their functional derivatives

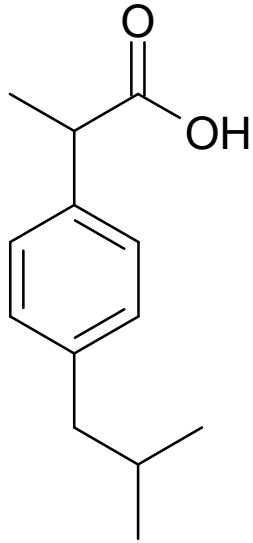


R = aryl or heteroaryl

Y = OH or NHOH

- chiral compounds (S-enantiomer often much more active)
- pain relief, antirheumatics, anti-inflammatory, antipyretics
- inhibition both COX1 and COX2; COX2 a little more
- AE like salicylates but weaker

2-arylpropionic acids



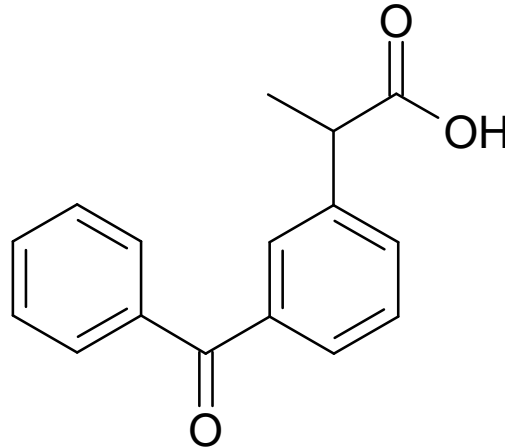
R = OH
(R,S)-2-(4-isobutylphenyl)-
propionic acid

ibuprofen

Brufen[®], Ibalgin[®]

(S)- form = dexibuprofen
Seractil[®]

R = NHOH **ibuproxam**

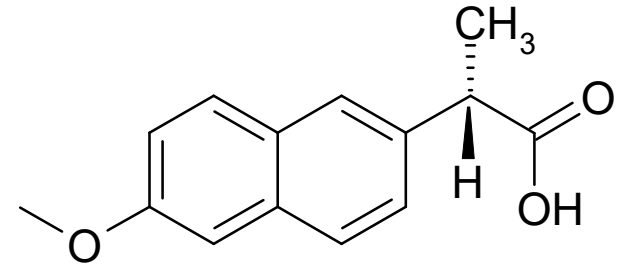


2-(3-benzoylphenyl)-
propionic acid

ketoprofen

Fastum[®]Gel,
Kepabene[®]tbl

(S)-form =
dexketoprofen
Sympal[®]
tbl.obd.

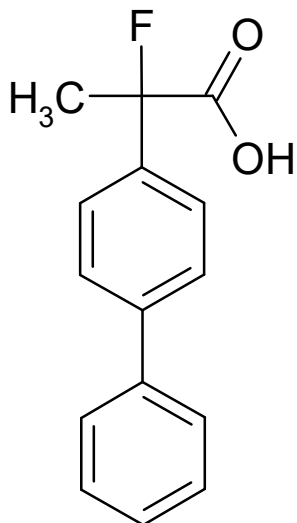


(+)-S-2-(6-methoxynaphthalene-2-yl)-
propionic acid

naproxen

Naprosyn[®],
Naprobene[®]

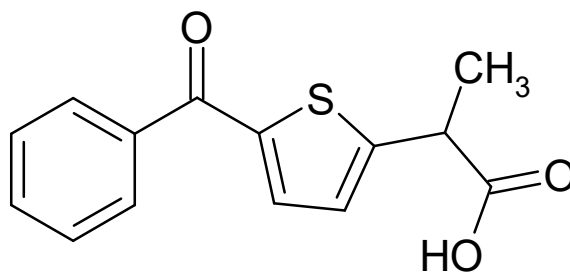
2-aryl- and 2-heteroarylpropionic acids



2-biphenyl-4-yl-2-fluoropropionic acid

flurbiprofen

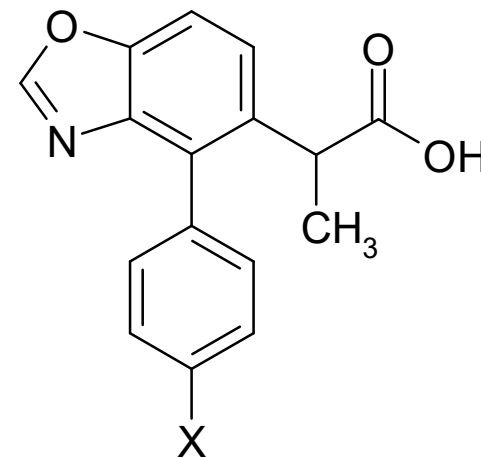
Ansaid[®], Flugalin[®]



2-(5-benzoylthiophene-2-yl)-propionic acid

tiaprofenic acid

Surgam[®], Thialgin[®]



X = Cl

2-[4-(4-chlorophenyl)benzoxazole-5-yl]-propionic acid

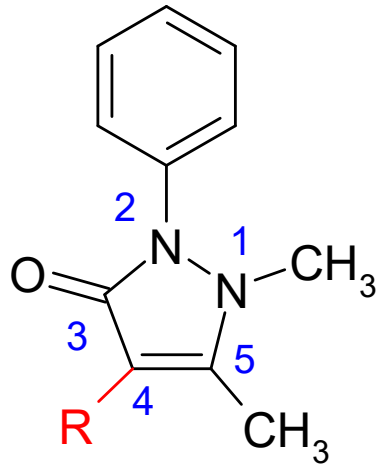
benoxaprofen

X = F

2-[4-(4-fluorophenyl)benzoxazole-5-yl]-propionic acid

flunoxaprofen

1,2-dihydropyrazole-3-on derivatives



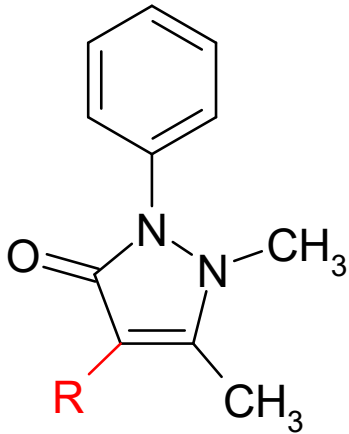
4-substituted-1,5-dimethyl-2-phenyl-1,2-dihydro-3*H*-pyrazole-3-ones

- inhibit both COX1 and COX2
- pain relief, antipyretics
- often used in mixtures

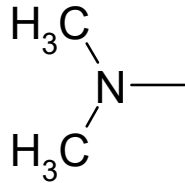
1,2-dihydropyrazole-3-on derivatives

R = H

phenazone, syn. antipyrine [JAN]
obsolete



R =



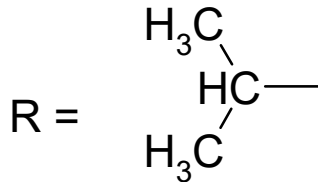
aminophenazone, syn. aminopyrine [JAN]

Dinyl® (+ phenacetin, caffeine, butobarbital, allobarbital)

Eunalgit® inj. (+ allobarbital)

obsolete

•isosterism ↓↓

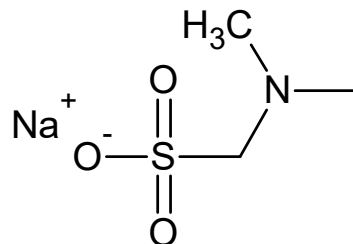


propyphenazone

Valetol®, Saridon® (+ paracetamol, caffeine)

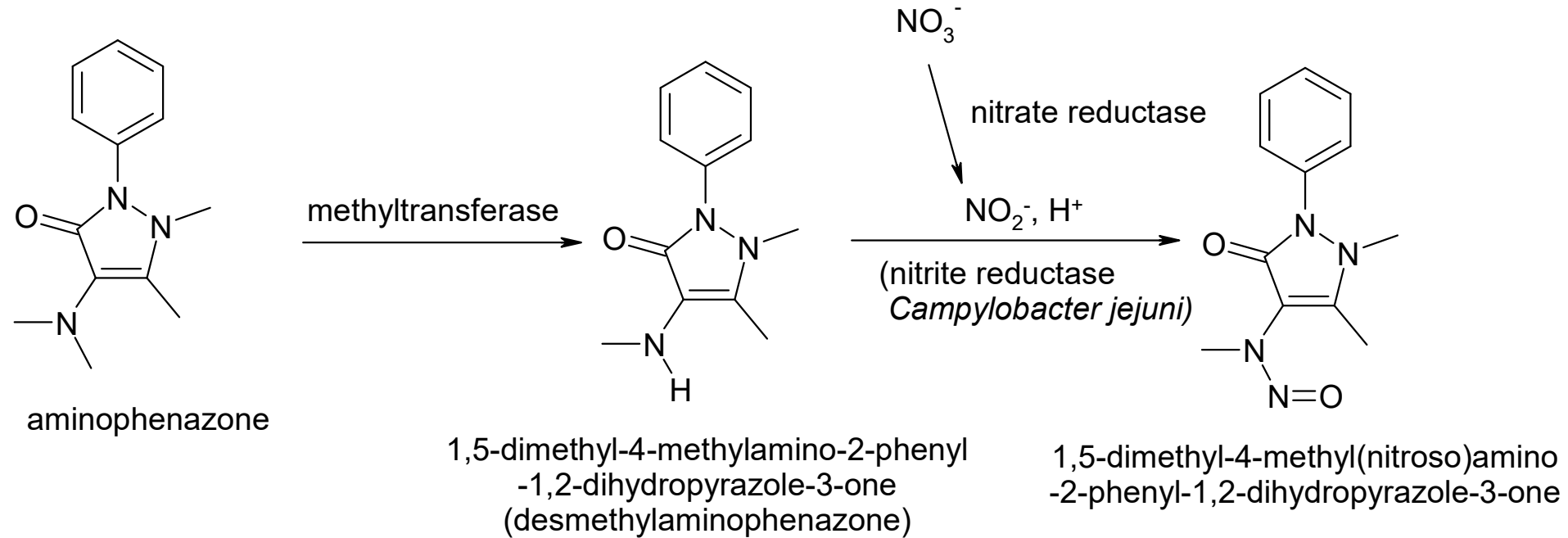
Spasmoveralgin neo® (+ papaverin, phenobarbital, ephedrin, codein, methylatropin)

R =



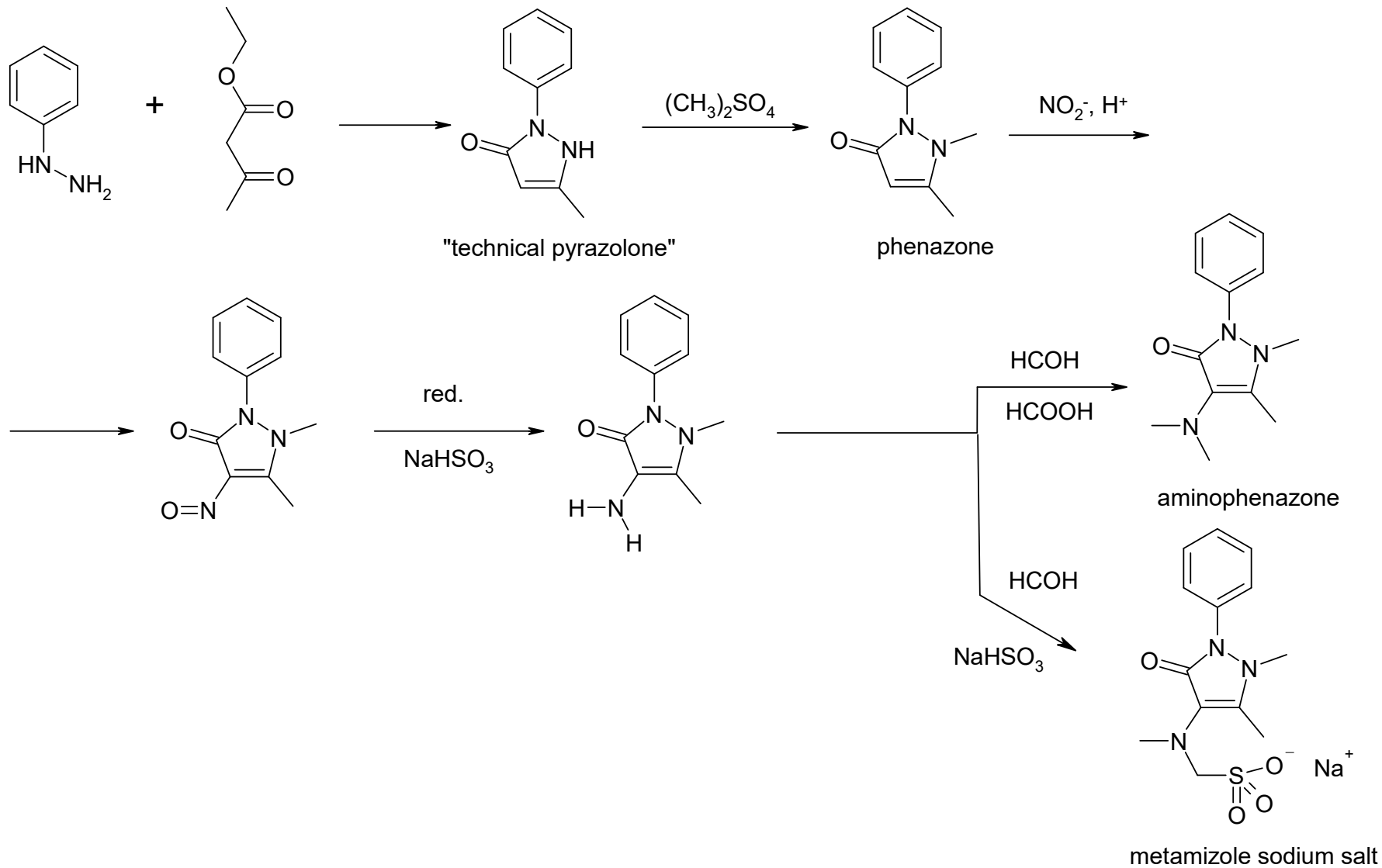
metamizol
Novalgin®

Aminophenazone cancerogenity

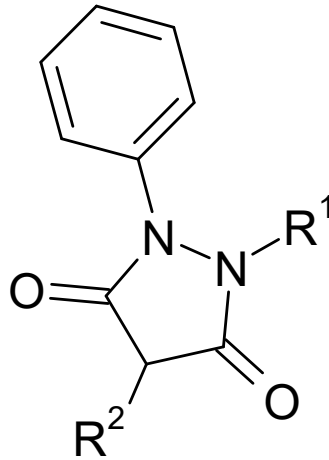


CANCEROGENIC

Synthesis of aminophenazone and metamizol

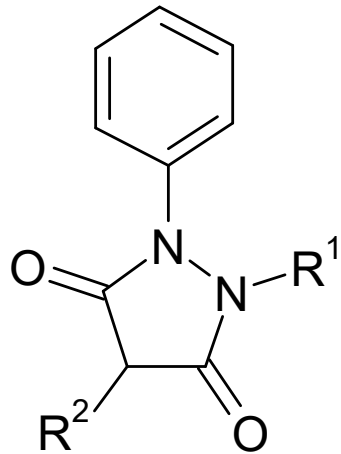


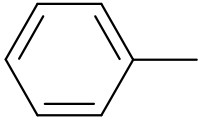
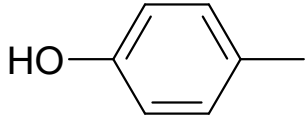
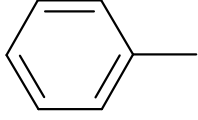
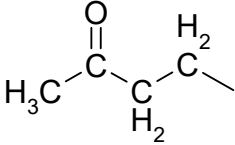
Pyrazolidine-3,5-dione derivatives



- anti-inflammatory, pain relief, antipyretics
- inhibit both COX1 and COX2
- reserved for *m. Bechterev* in some countries (CH ...)
- in CZ only external and veterinary preparations
- AE: GIT intolerance, diarrhoea, ulcer disease exacerbation and bleeding into GIT, skin rash, CNS disorders, Na⁺ and water retention, renal malfunctions, bone marrow disturbances

Pyrazolidine-3,5-dione derivatives

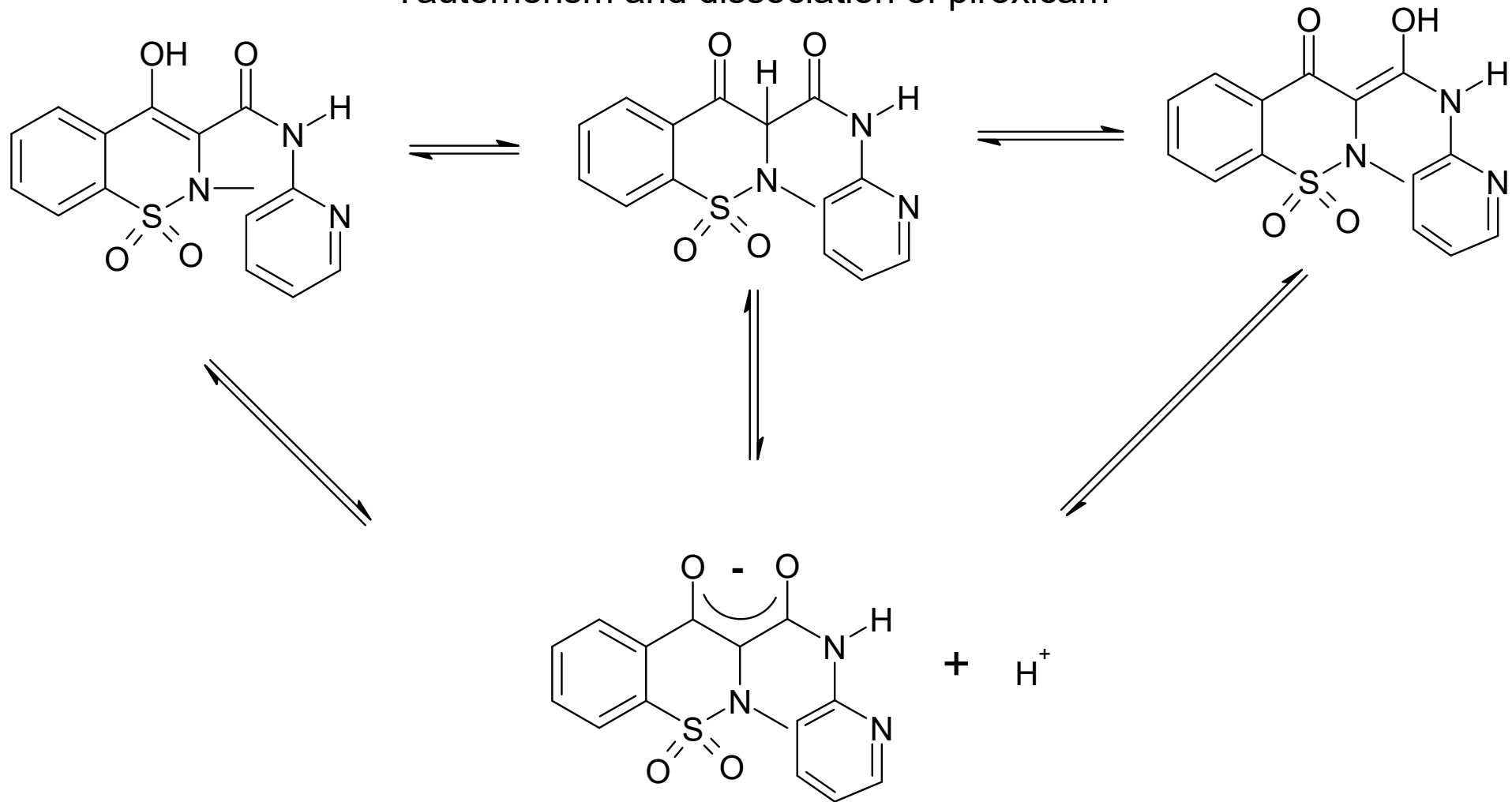


R ¹	R ²	Chemical name	INN / preparations
	C ₄ H ₉ -	4-butyl-1,2-diphenylpyrazolidine-3,5-dione	phenylbutazone Butasan® a.u.v
	C ₄ H ₉ -	4-butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione	oxyphenbutazone Tanderil® sup. <i>reg. in SR</i>
		1,2-diphenyl-4-(4-oxobutyl)pyrazolidine-3,5-dione	kebuzone Ketazon® ung
H-	C ₄ H ₉ -	4-butyl-1-phenylpyrazolidine-3,5-dione	mephebutazone

Heterocyclic enols-“keto-enolic acids“ - oxicams

- contain „keto-enolic“ structural fragment

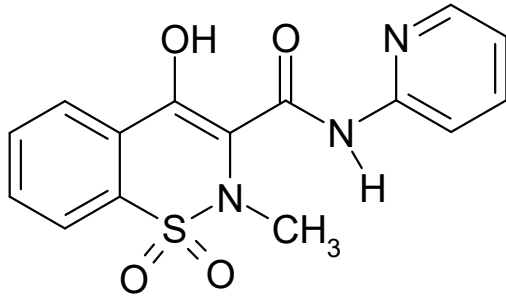
Tautomerism and dissociation of piroxicam



Oxicams

- acid character
- inhibit both COX1 and COX2 (meloxicam about 3x more COX2)
- effects: anti-inflammatory, pain relief, antipyretic
- using: arthrosis, rheumatoid arthritis ...

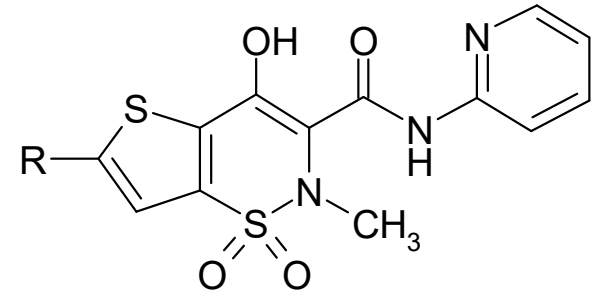
Oxicams



4-hydroxy-2-methyl-N-pyridine-2-yl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide

piroxicam

Arthremin[®], Feldene[®],
Flamexin[®] - complex with
β-cyclodextrine



R = H

4-hydroxy-2-methyl-N-pyridine-2-yl-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide-1,1-dioxide

tenoxicam

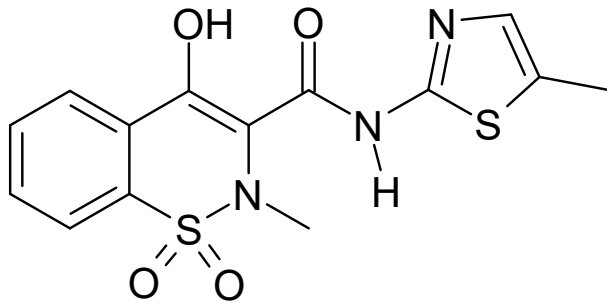
R = Cl

6-chloro-4-hydroxy-2-methyl-N-pyridine-2-yl-2*H*-thieno[2,3-*e*][1,2]thiazine-3-carboxamide-1,1-dioxide

lornoxicam

Xefo[®]

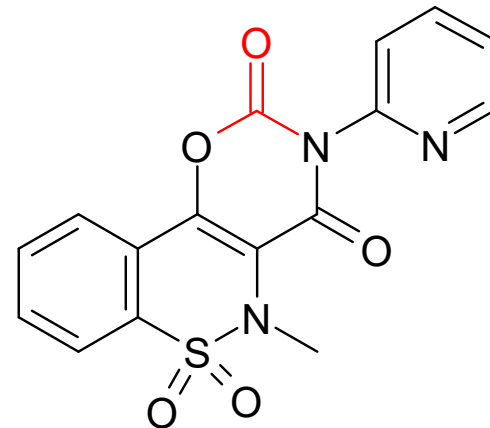
Oxicams



4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazole-2-yl)-2H-1,2-benzothiazine-3-carboxamide-1,1-dioxide

meloxicam

Movalis[®]tbl., Metacam[®] a.u.v.,
Melokssia[®]

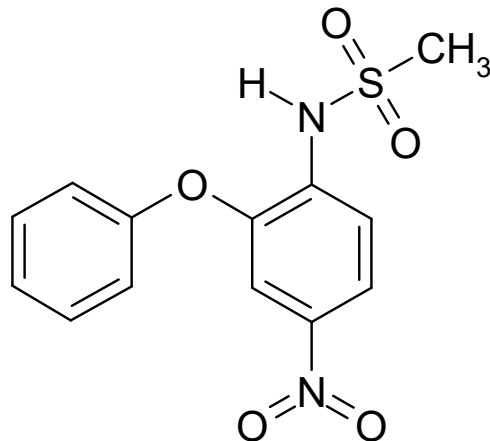


5-methyl-3-pyridin-2-yl-2H,5H-[1,3]oxazino[5,6-c][1,2]benzothiazine-2,4(3H)-dione-6,6-dioxide

droxicam

Selective COX2 inhibitors

Nimesulide

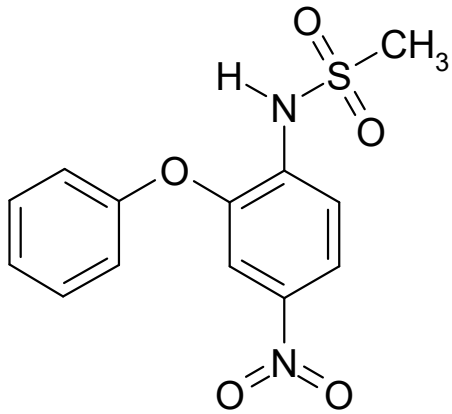


N-(2-phenoxy-4-nitrophenyl)methanesulfonamide
4'-nitro-2'-phenoxymethanesulfonanilide****

nimesulide

Coxtral[®], Aulin[®], Mesulid[®]

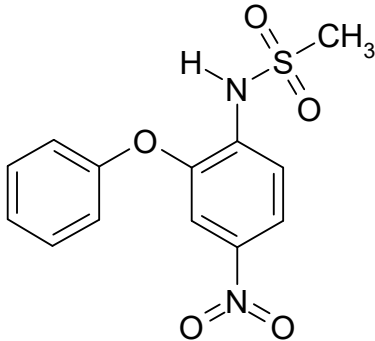
Nimesulide



- inhibits COX2 4x more than COX1 ⇒ ↓ AE in GIT and platelets
- antirheumatic, antiarthrotic, pain relief
- AE: hepatotoxicity; icreased in fever ⇒ not suitable as antipyretic

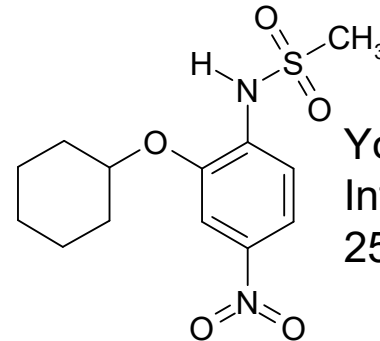
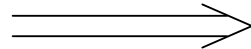
„Radical analogy“

- substitution benzene ⇒ cyclohexane



nimesulide

4 : 1



N-[2-(cyclohexyloxy)-4-nitrophenyl]methanesulfonamide
NS-398

30 : 1

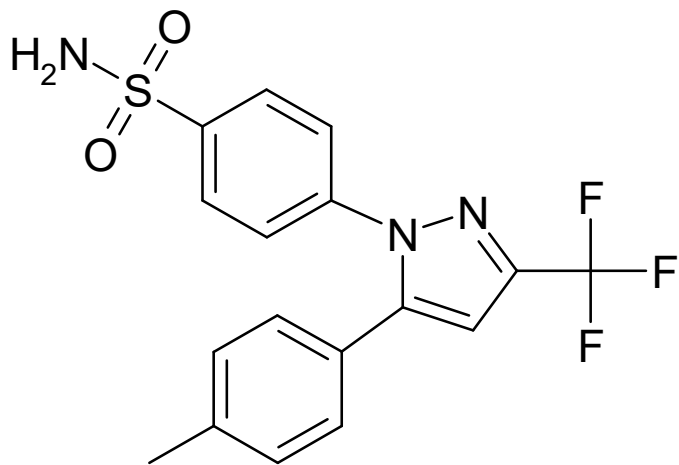
Young J.M. et. al.,
Inflammation Res. **45**, 246-
253 (1996)

Selectivity
COX2:COX1

Specific COX2 inhibitors

Coxibs

- aromatic sulfonamides or sulfones (exception: lumiracoxib)
- high selectivity to COX2 \Rightarrow AE to GIT and increased platelets aggregation eliminated
- usage: rheumatoid arthritis, osteoarthritis, primary dysmenorrhea
- also neurodegen. diseases (Alzheimer) – colocalization of cyclines D₁ and E₁ with COX2 in CNS neurones
- AE: \uparrow risk of sudden cardiovascular incidents (\Leftarrow \downarrow production of prostacycline which **inhibits** platelets aggregation but does not affect production of thromboxane which **activates** platelets aggregation), skin damage (mainly valdecoxib)



4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide

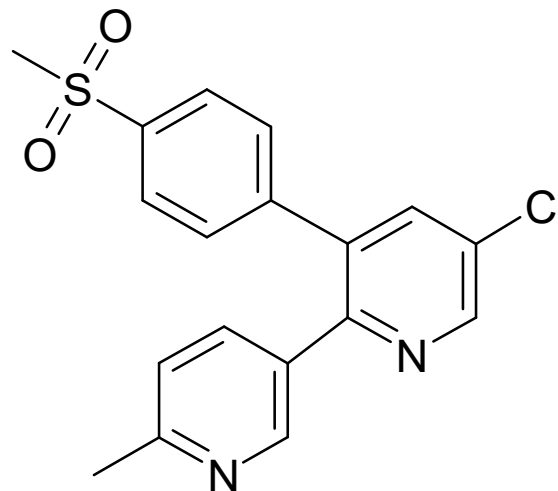
celecoxib

Celebrex[®]

Onsenal[®] – as an orphan drug for familial adenomatous polyposis (FAP) only

Selectivity
COX2 : COX1 30 : 1

Coxibs



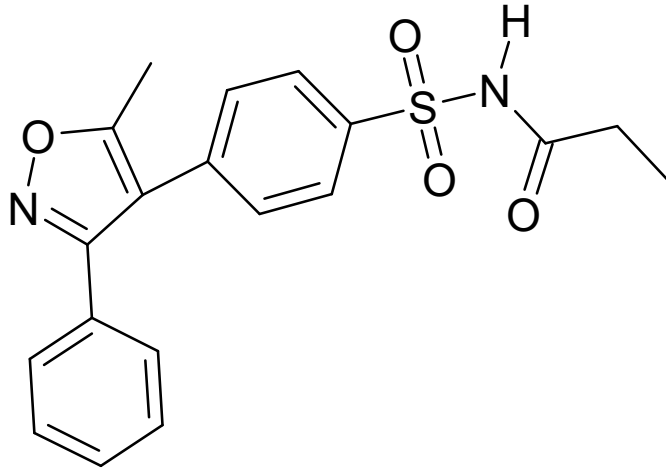
5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

etoricoxib

Arcoxia[®]

340 : 1

Coxibs



N-[[4-(5-methyl-3-phenylisoxazole-4-yl)phenyl]sulfonyl]propanamide

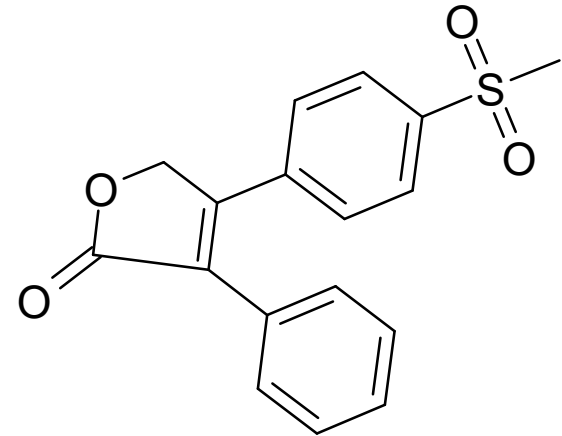
parecoxib

- allergic skin reactions mainly in persons hypersensitive to sulfonamides

Dynastat[®] - for postoperative pain only

Selectivity

COX2 : COX1



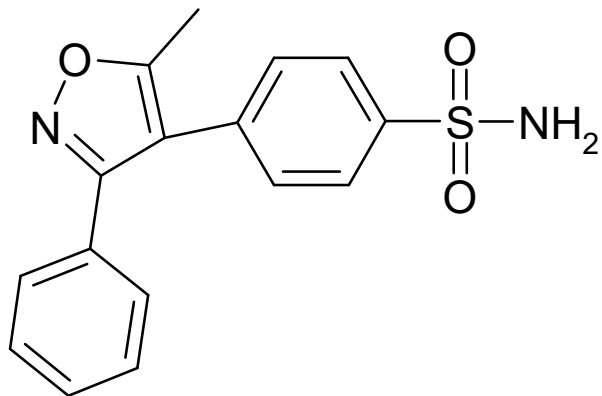
4-[4-(methylsulfonyl)phenyl]-3-phenylfuran-2(5H)-one

rofecoxib

~~Ceeox[®], Vioxx[®]~~

withdrawn due to dangerous cardiovascular effects

270 : 1

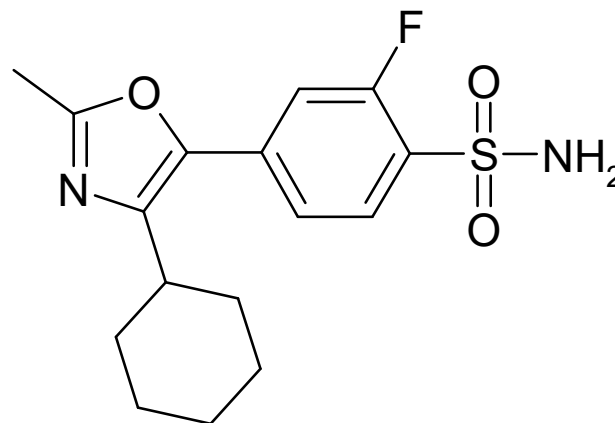


4-(5-methyl-3-phenylisoxazole-4-yl)benzenesulfonamide

valdecoxib

Bextra[®] withdrawn

Coxibs



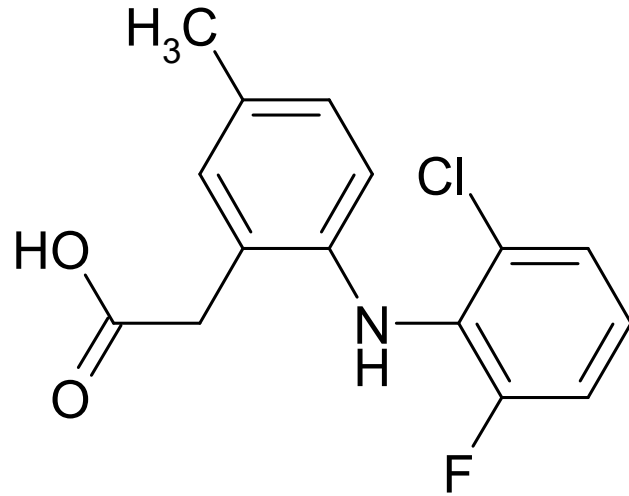
4-(4-cyclohexyl-2-methyl-1,3-oxazole-5-yl)-2-fluorobenzenesulfonamide

tilmacoxib

Selectivity

COX2 : COX1 60 : 1

Coxibs

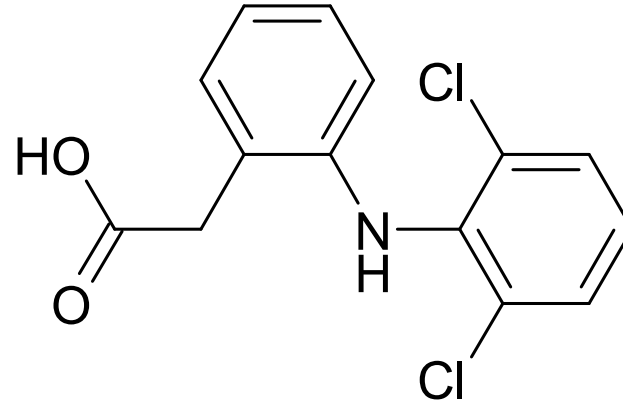


2-(2-fluoro-6-chlorophenylamino)-5-methylphenylacetic acid

lumiracoxib

Prexige®

For comparison:



diclofenac