Analgesics - antipyretics

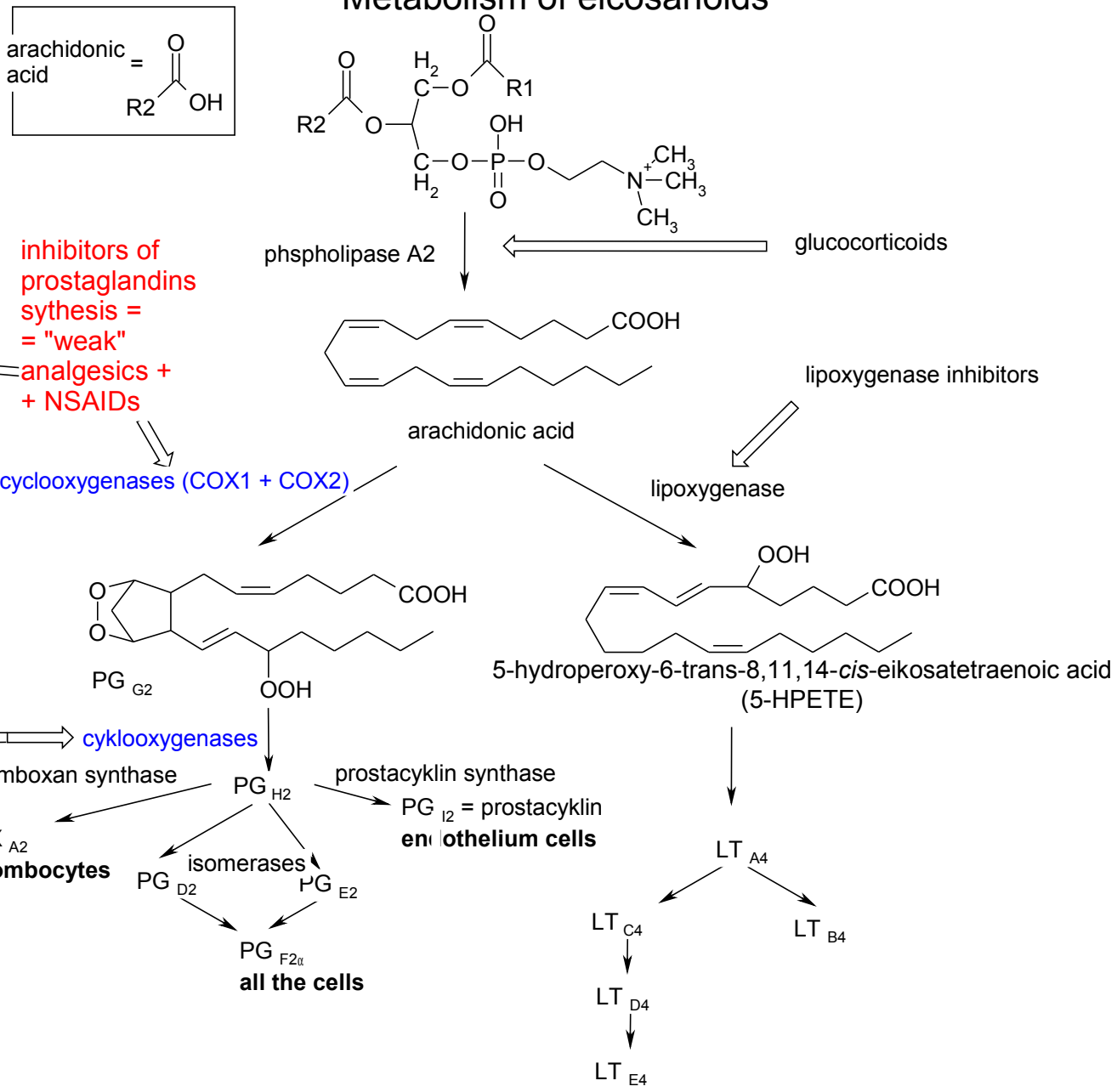
= „weak“ analgesics

= non-opioid analgesics

Most of them also

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

Metabolism of eicosanoids



Effects of prostaglandins

Prostaglandin E, $F_{2\alpha}$: ache, fewer, 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)

Philipp Needlemann

discoverer of COX isoenzymes

(1989)

COX2

Constitutive: kidneys, brain (co-localized with cyclins D_1 and E)

Inducible: macrophages, neutrophils, fibroblasts, endothelium cells

Functions:

- vasodilatation (PG I_2)
- childbirth (uterus contractions)
- inflammation processes

COX3 ?? (= COX1b; brain ?)

Classification of COX inhibitors

(antipyretics, NSAIDs)

Non-selective (COX1 + COX2)

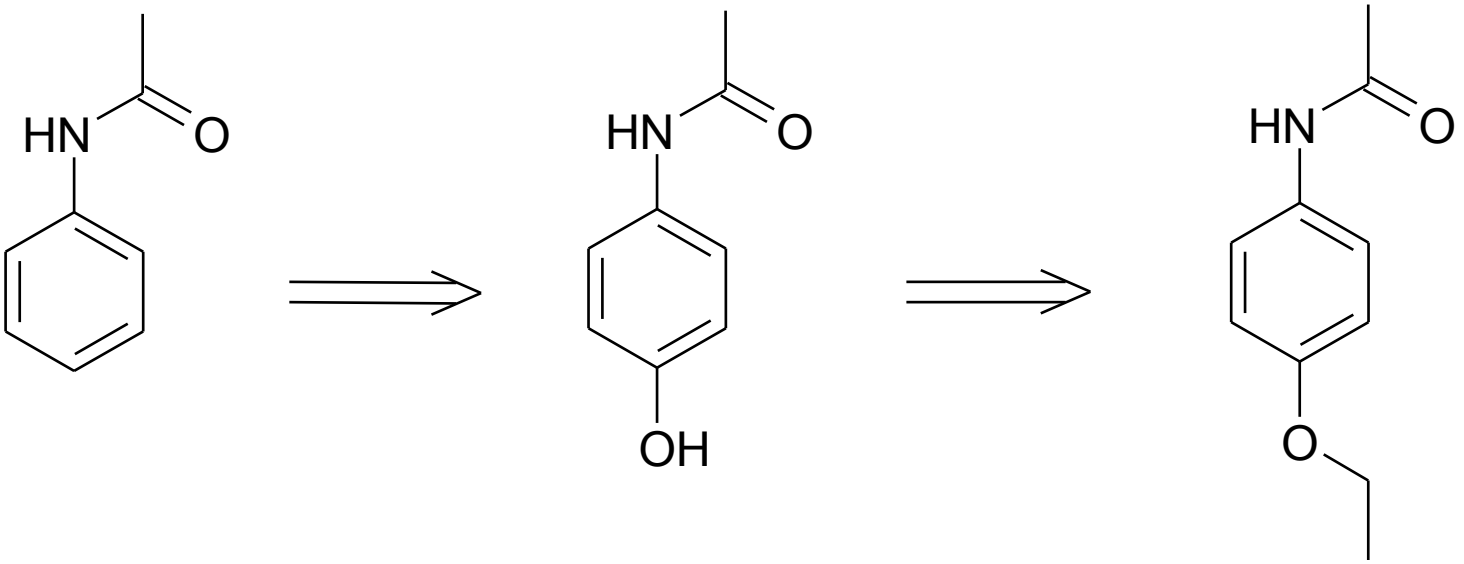
- Anilides
- Salicylates
- Phenamates
- Aryl- and heteroaryl alkanoic acids
  - Aryl- and heteroaryl acetic acids
  - Aryl- and heteroaryl propionic acids
- Oxicames
- 1,2-Dihydropyrazolidine-3-ones
- 2,5-Pyrazolidinediones

Selective (COX1<COX2): nimesulide

Specific (COX2)

- **Coxibes**

Anilides



acetanilide

N-phenylacetamide

1886: Antifebrin®

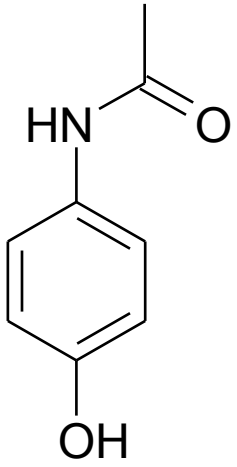
paracetamol
(**acetaminophen**)
4-(acetylamino)phenol

para-(**acet**yl**am**ino)phen**ol**
p-(**acet**yl**amino**)**phen**ol
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 antiinflamatory, antirheumatic)

Usage in mixtures with

•codeine, caffeine ⇒ effect enhancement (Korylan tbl.®, Panadol tbl.®, Efferalgan codein tbl. eff.®)

•expectorants (guajfenesin, terpin)

•antitussives (dextromethorphan)

•H_1-antihistaminines (pheniramine, chlorphenamine, dimenhydrinate, promethazin, doxylamin) together with

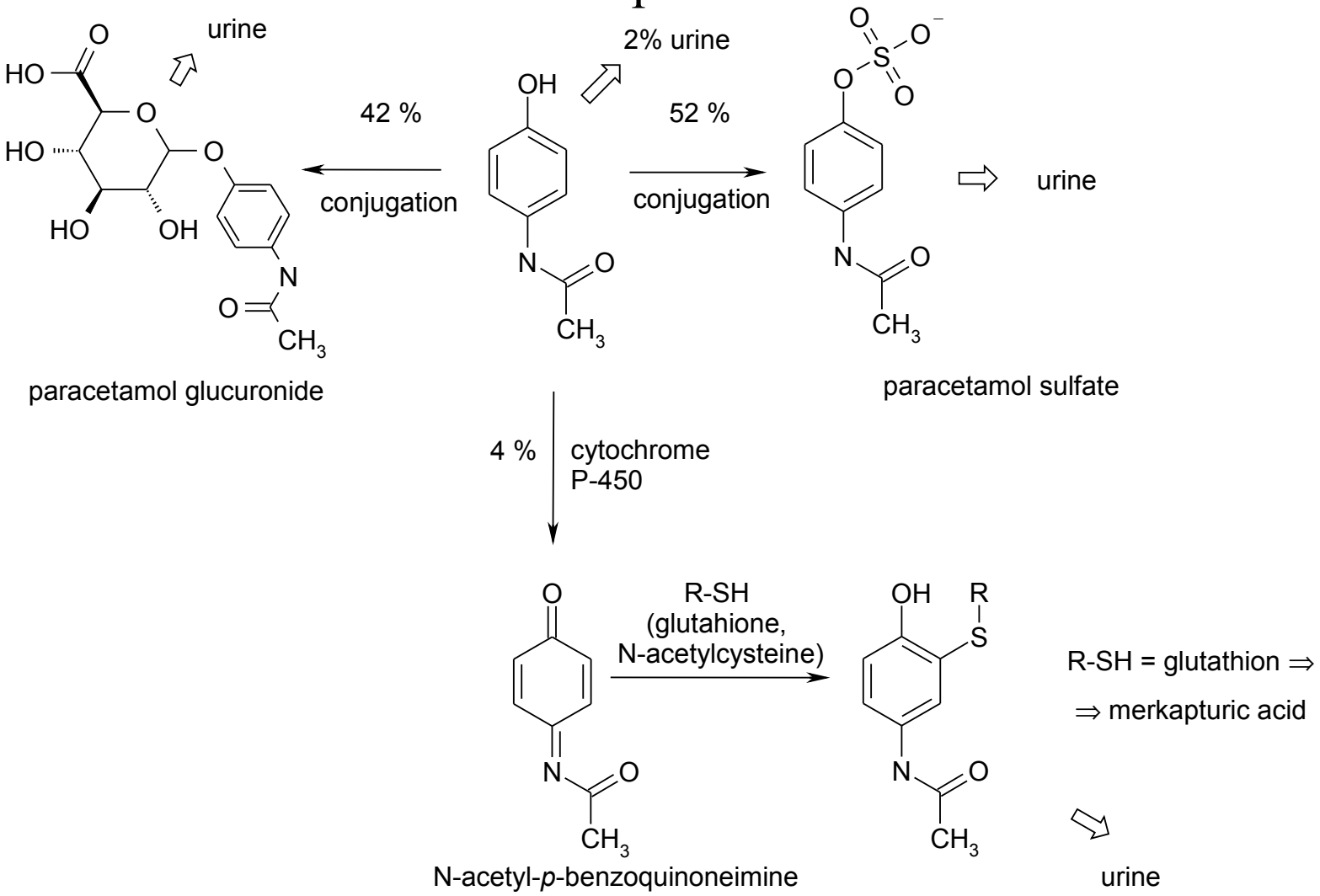
α-sympatomimetics (phenylefrine, pseudoephedrine)

•spasmolytics (pitophenon)

•myorelaxants (chlorzoxan, carisoprodol)

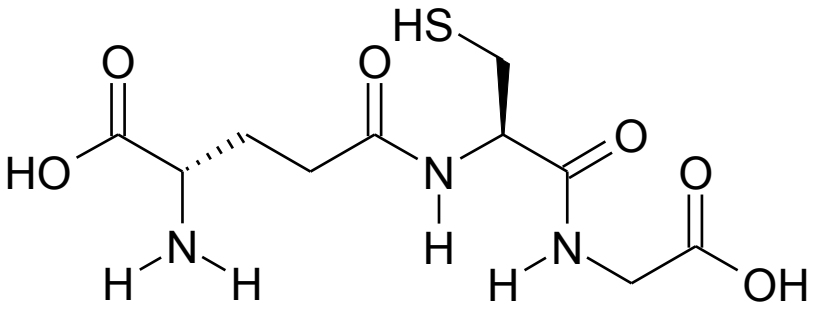
•NSAID (acetylsalicylic acid, propyphenazon – Valetol®)

Metabolism of paracetamol

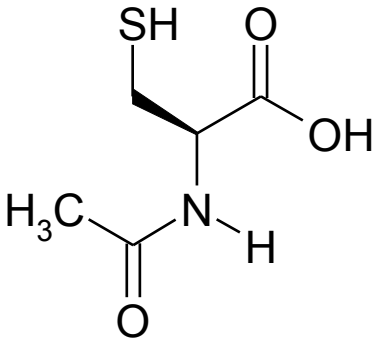


Thiols detoxicating N-acetyl-*p*-benzoquinoneimine

γ- Glu-Cys-Gly



glutathione

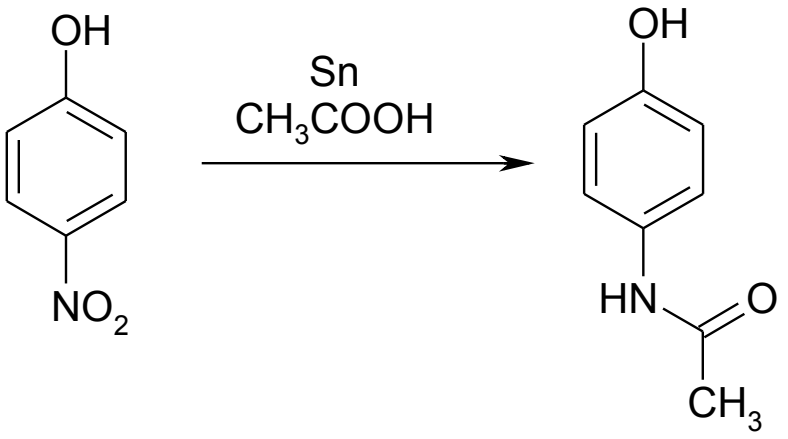


N-acetyl-L-cysteine

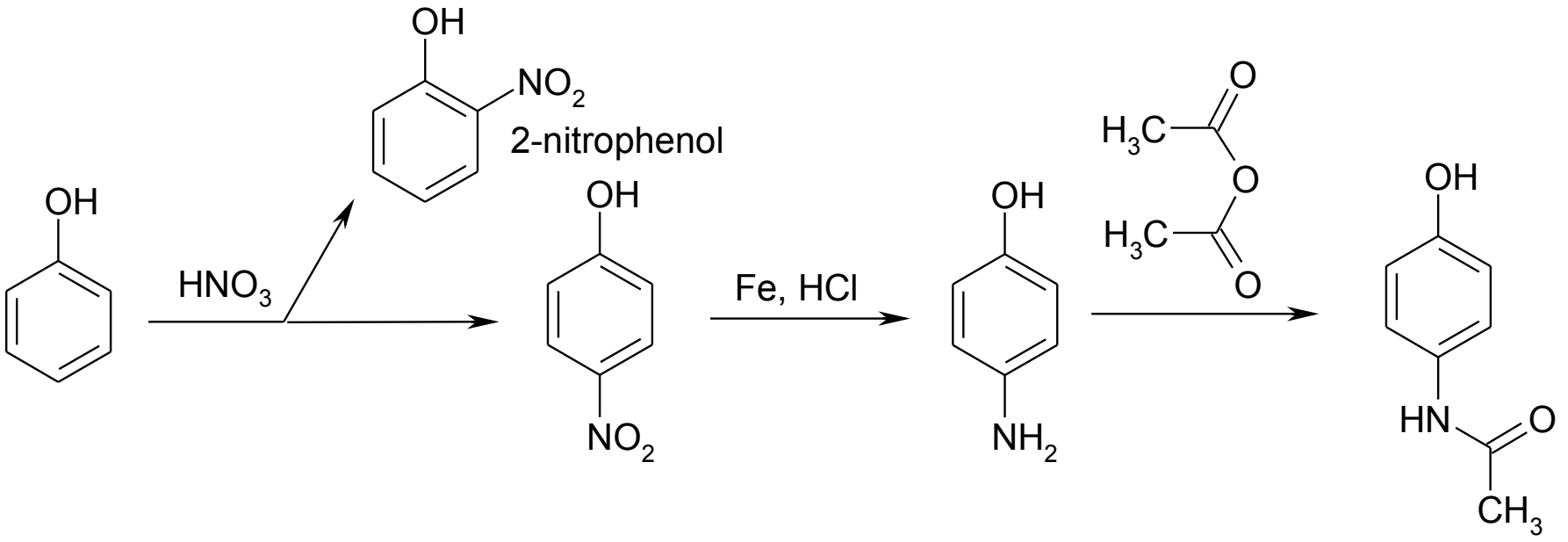
mucolytic

ACC®, Mucobene®

Synthesis of paracetamol



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



phenol

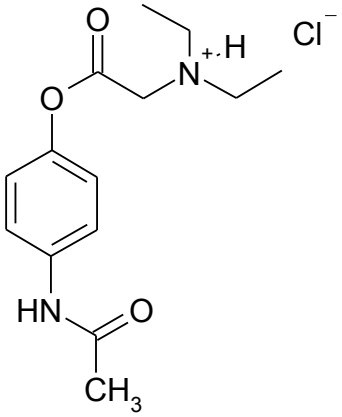
4-nitrophenol

4-aminophenol

4-(acetylamino)phenol

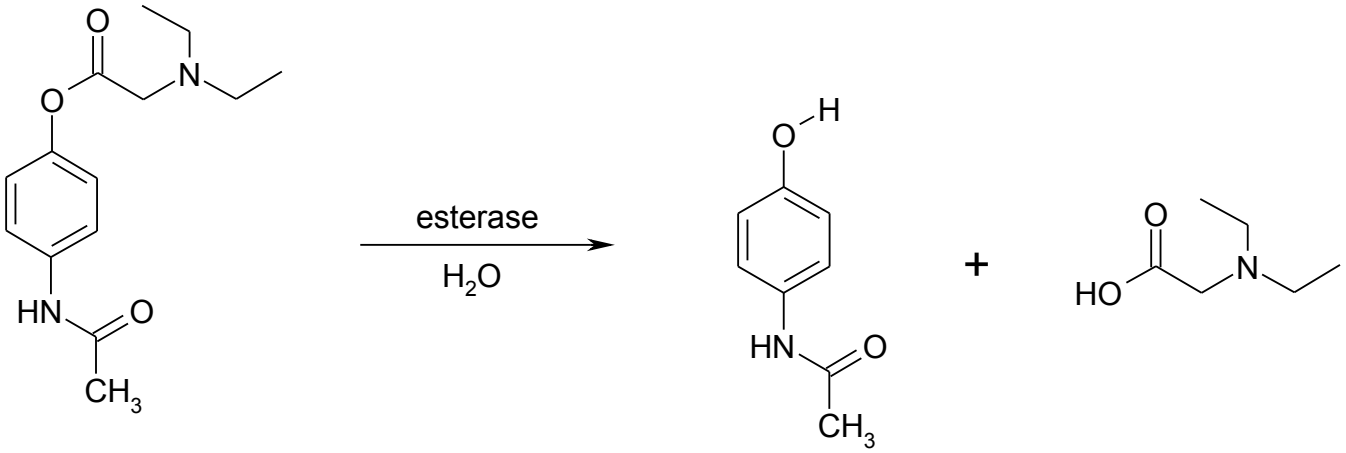
Propacetamol – paracetamol prodrug

- for intravenous application

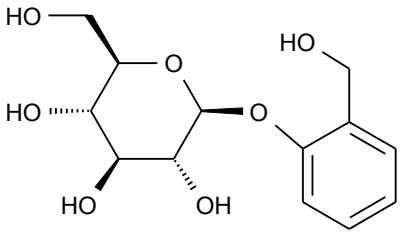


4-(acetylamino)phenyl-N,N-diethylglycinate hydrochloride
2-[4-(acetylamino)phenoxy]-N,N-diethyl-2-oxoethaneaminium chloride
propacetamol hydrochloride

Pro-Dafalgan® *(UPSA Laboratoires)*



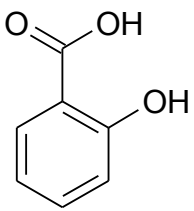
Salicylates



salicin
(2-hydroxymethylphenyl)-β -D-glucopyranoside

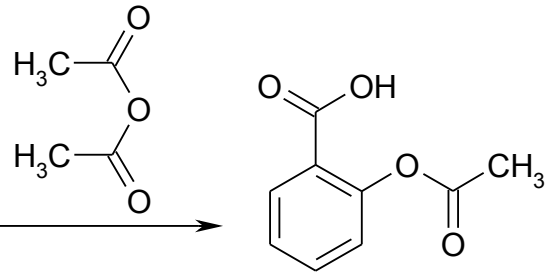
1827 Leroux: isolation from willow

hydrolysis
oxidation



salicylic acid
2-hydroxybenzoic acid

1838 Piria: the first synthesis
since 1878 used as antipyretic
and antirheumatic



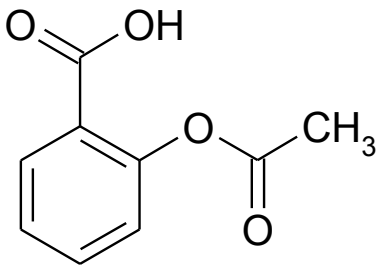
acetylosalicylic acid
2-acetoxybenzoic acid

1897 Felix Hoffmann - industrial synthesis
1899 – Aspirin® *(Bayer)*

Felix Hoffmann

Sir John R. Vane

Effects of acetylosalicylic acid



„Wanted“:

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

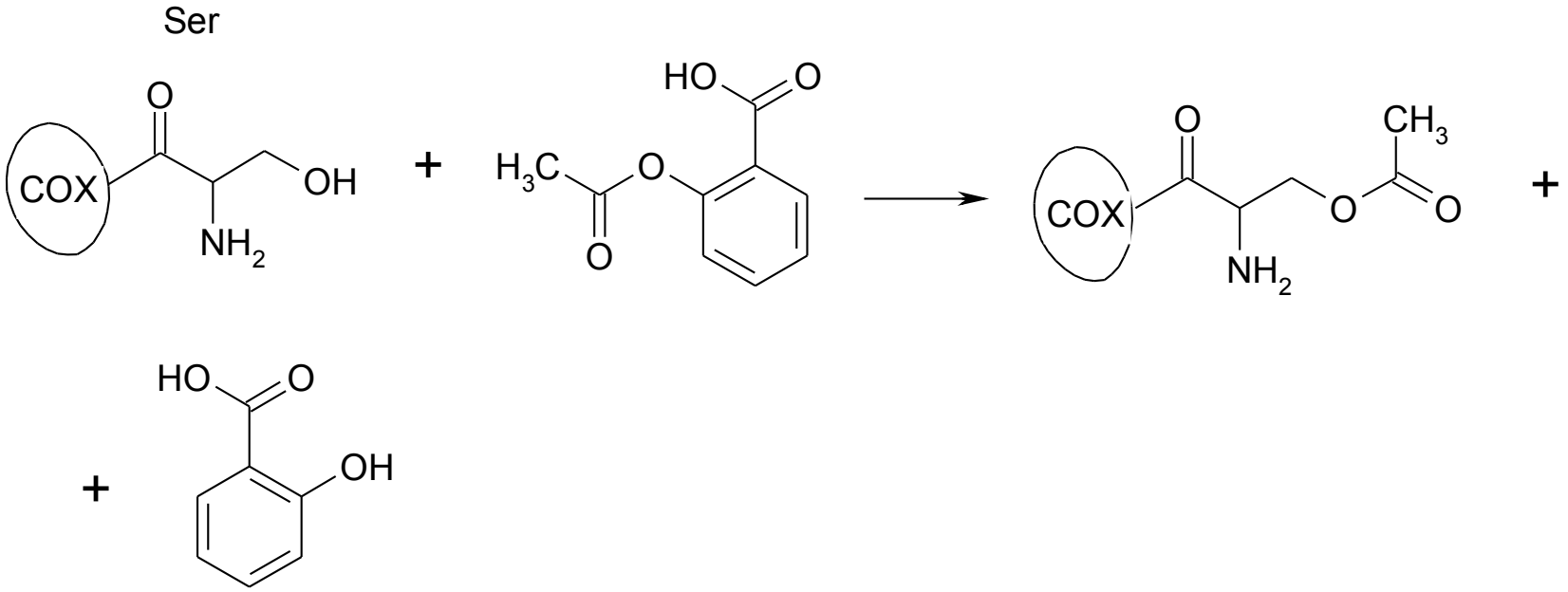
„Unwanted“:

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

Intoxication = „salicylism“ – infliction of CNS (psychical malfunctios, buzz in ears, dizzines, deafness), methabolic acidosis

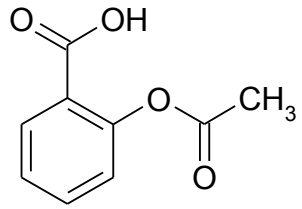
Mechanis of action of acetylosalicylic acid (ASA)

- irreversible inhibition od cyclooxygenases by acetylation of serine rest



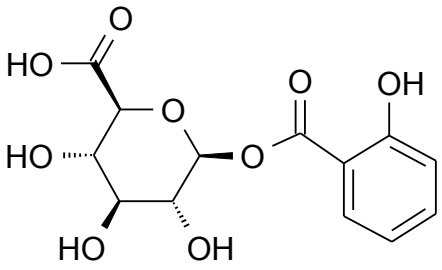
Metabolism of ASA

- proceeds in liver
- all metabolits are excreted by urine



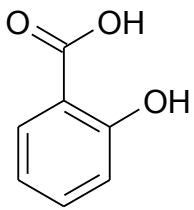
ASA

$t_{1/2}$= 15 min.



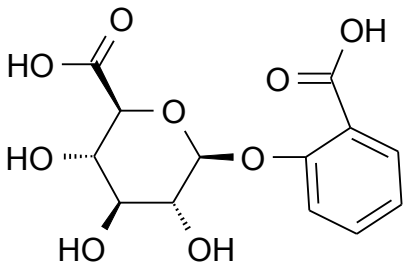
O^1-salicyoylglucuronic acid
5 %

glucuronation



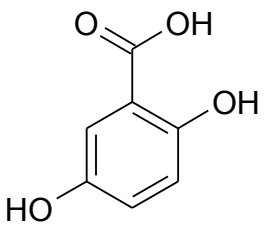
+ CH_3COOH

salicylic acid.
10 %



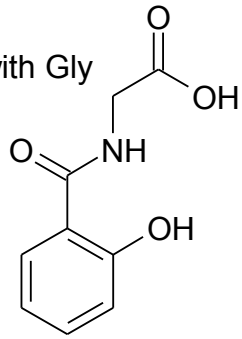
O^1-(2-carboxyphenyl)glucuronic acid
10 %

hydroxylation



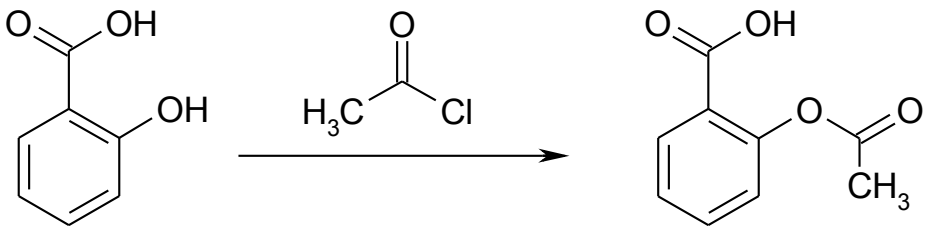
gentisic acid
< 1 %

conjugation with Gly

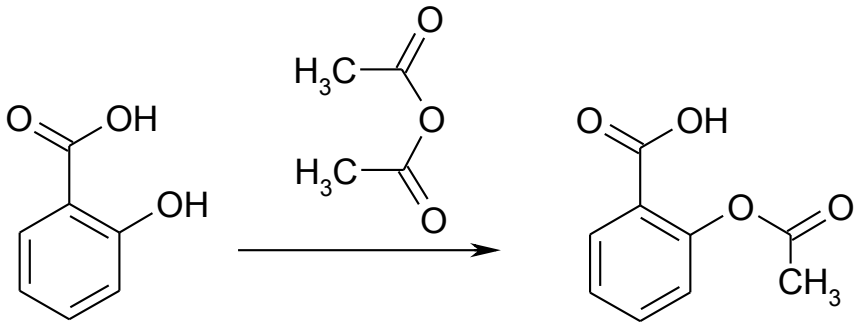


salicyluric acid
(N-salicyoylglycine)
75 %

Syntheses of ASA

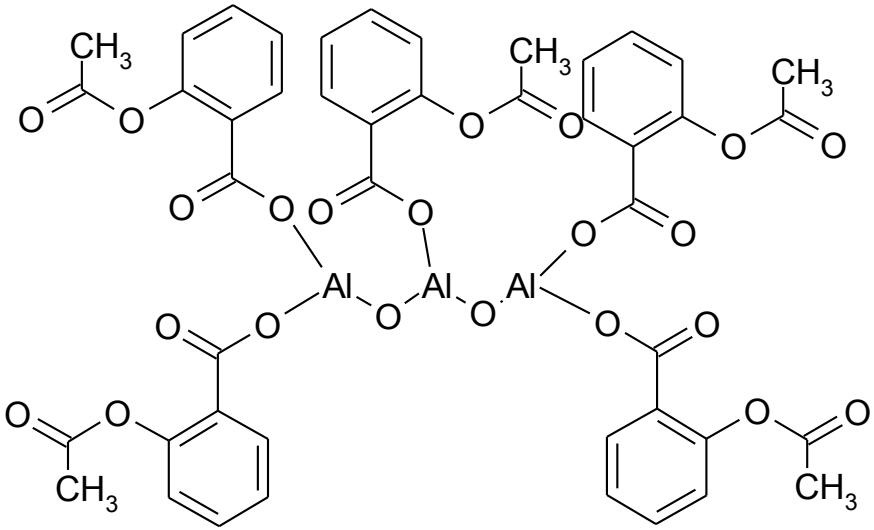


Gerhardt, Justus Liebigs Ann. Chem. **87**, 164 (1853)
Gilm, Justus Liebigs Ann. Chem. **112,** 181 (1859)
Kraut, Justus Liebigs Ann. Chem. **150**, 10 (1869)



Felix Hoffmann

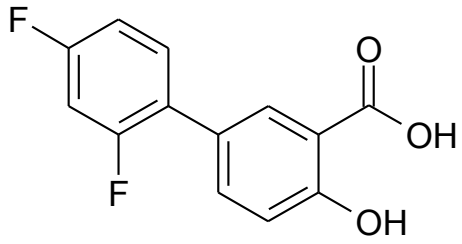
Other salicylates



pentakis(acetylosalicyoyloxy)trialuminium dioxide

aloxiprin

Superpyrin®



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

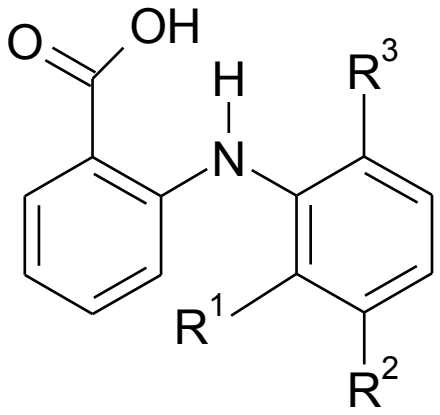
diflunisal

Unisal® tbl.

Anthranilic acid derivatives – phenamates

= substitution derivatives of 2-phenylaminobenzoic acid

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



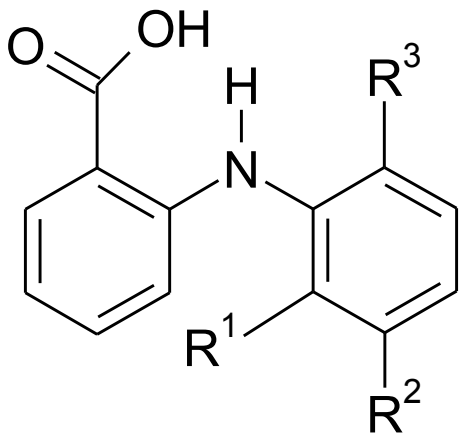
•aromatic amino acids

•substituted on the aniline ring only

•inhibit both COX1 and COX2 (selectivity?; COX3?)

•analgesics, antipyretics, antimigrenics, anti-inflammatory

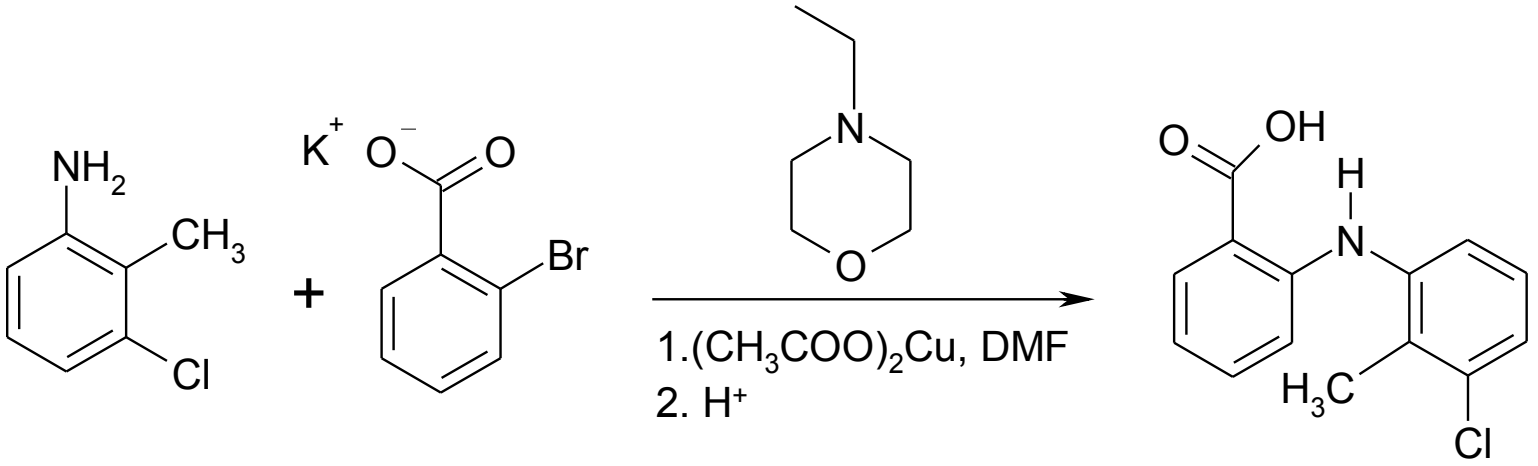
Phenamates



R^1	R^2	R^3	Chemica 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



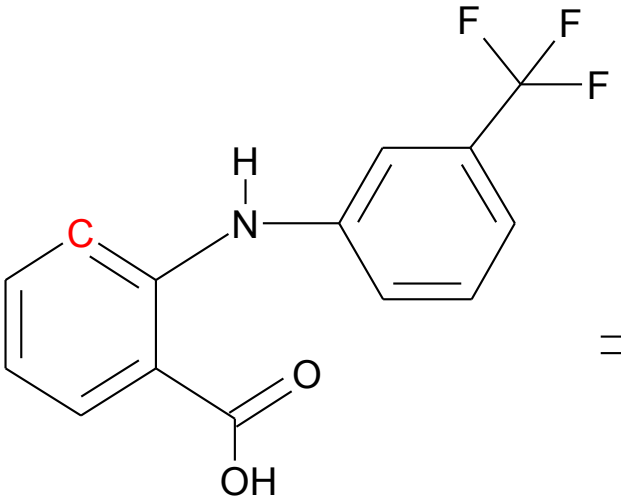
Kaltenbronn J.S. et al., Arzneim. Forsch **33**, 621-627 (1983)

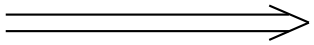
Selectivity against COXs

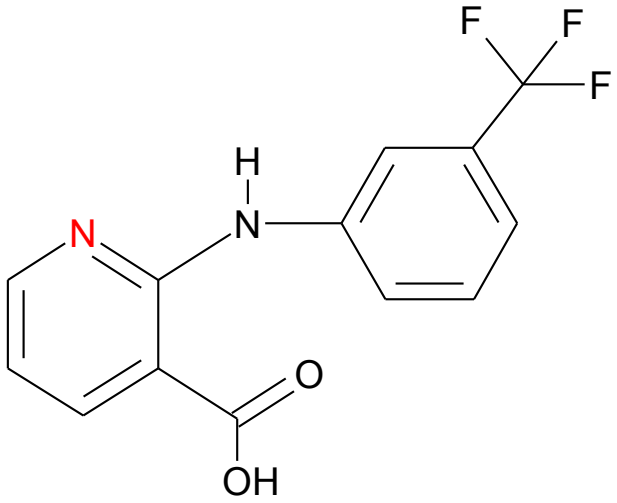
$$\frac{IC_{50}(COX1)}{IC_{50}(COX2)} = 10$$

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

Niflumic acid and its esters







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

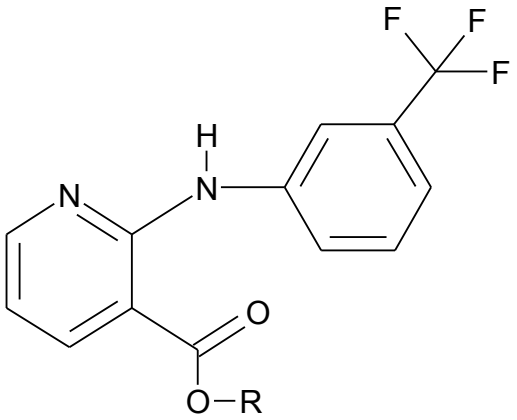
fluphenamic acid

niflumic acid

- isosteric substitution benzene ⇒ pyridine, or –CH= ⇒ -N=
- inhibit both COX1 and COX2
- anti-inflamatory, antirheumatics; usually topically administered

Niflumic acid and its esters

•esters are prodrugs which can better penetrate through the skin

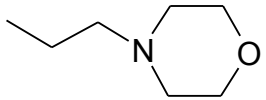


R

2-{[(3-trifluormethyl)phenyl]amino}nicotinic acid

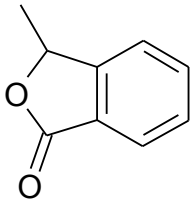
—H **niflumic acid**

Niflugel®, Nifluril®



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

morniflumate



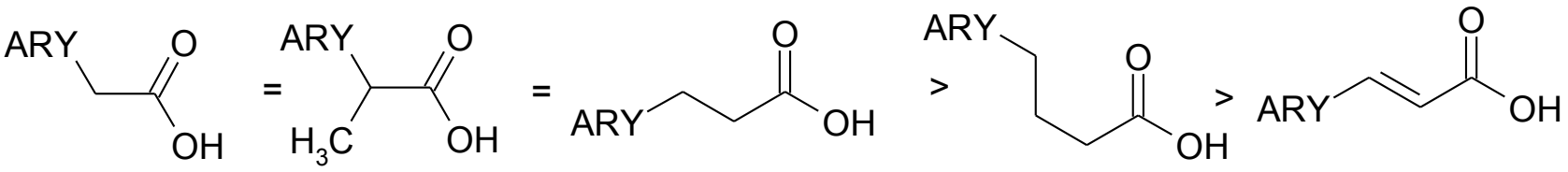
-||- 1-oxo-2-(3*H*)-benzofurane-3-ylester

talniflumate

Aryl- and heteroarylalkanoic acids

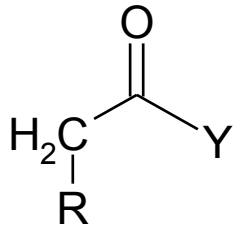
Structure-activity relationships (SAR)

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



ARY = aryl, heteroaryl

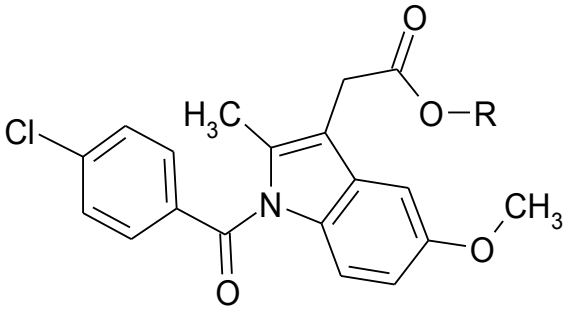
Aryl- and heteroarylacetic acids and their functional derivatives



R = aryl or heteroaryl
Y = OH, NHOH, NHR, OCH_2COOH, or other

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

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



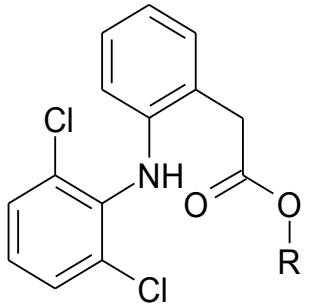
R = H

[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 = H

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

diclofenac

- used since 1975

Voltaren®, Veral®, Myogit®, Dicloreum®

R = OCH_2COOH

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

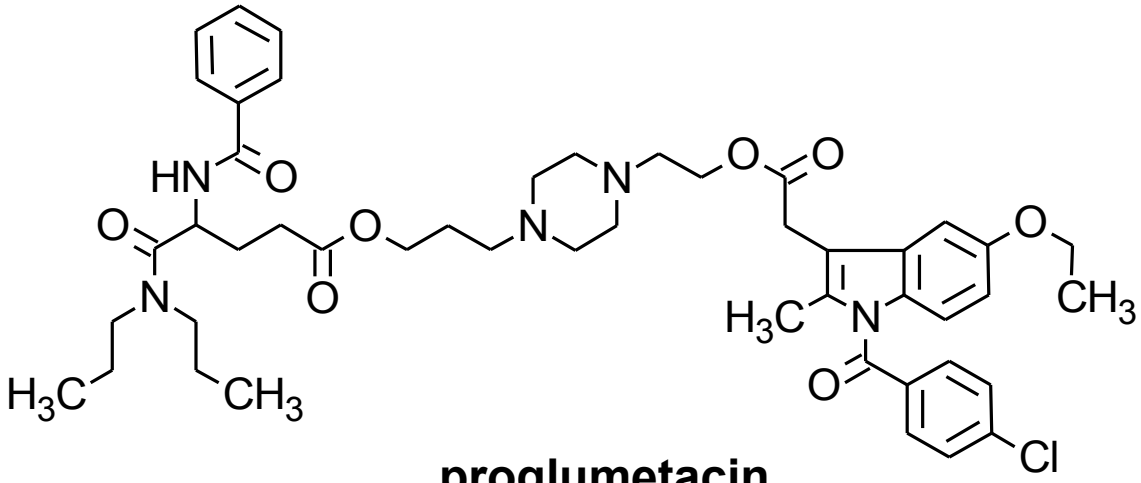
acemetacin

R= OCH_2COOH

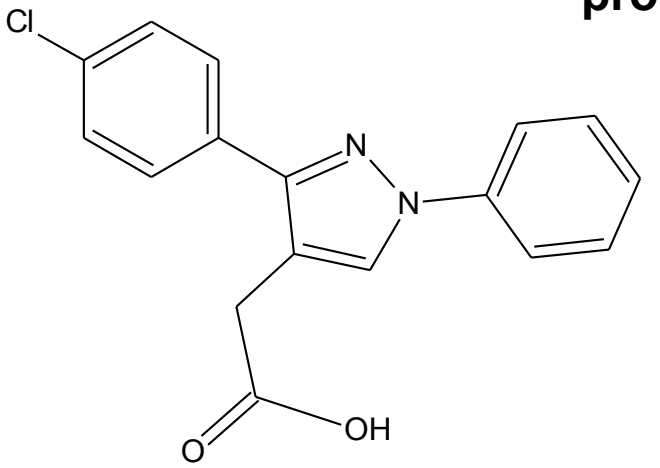
{2-[(2,6-dichlorophenyl)amino]phenyl}acetic acid carboxymethylester

aceclofenac

Heteroarylacetic acids and their derivatives

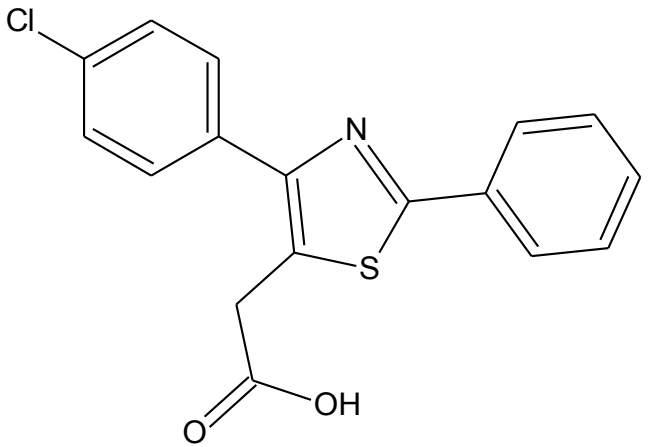


proglumetacin



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

lonazolac

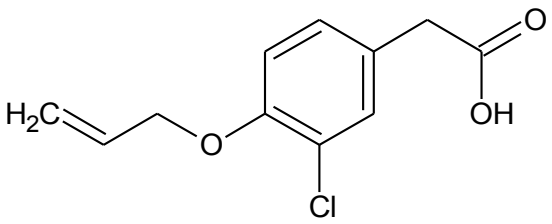


[4-(4-chlorophenyl)-2-phenyl-1,3-thiazole-5-yl]acetic acid

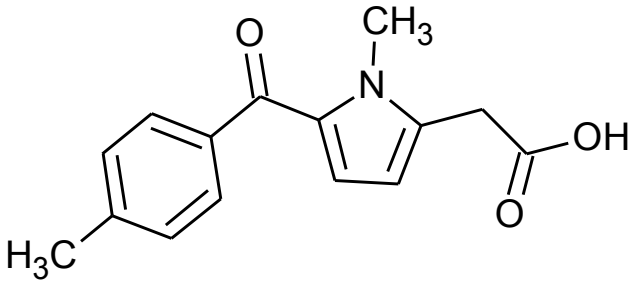
fentiazac

•isosteres

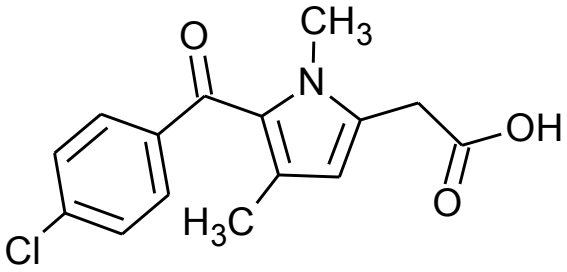
Aryl- a heteroarylacetic acids



alclofenac



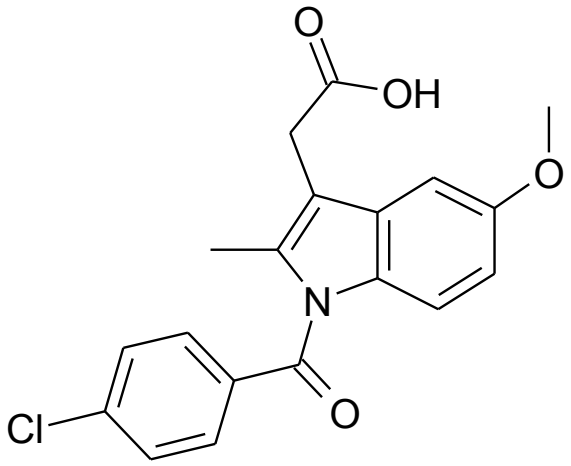
tolmetin



zomepirac

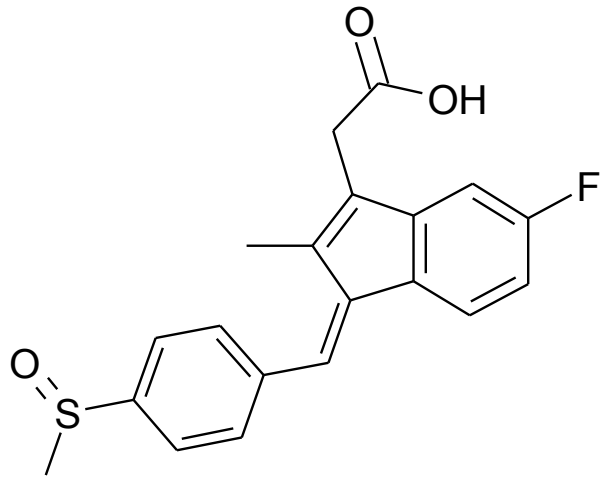
Aryl- a heteroarylacetic acids

- examples of isosterism of rings and functional groups



[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-ylacetic acid

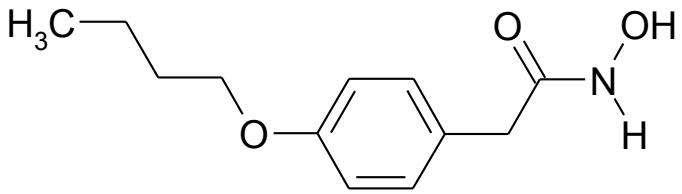
indomethacin



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

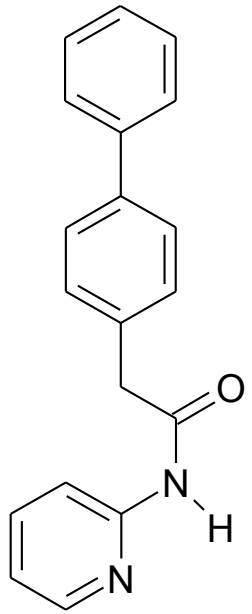
sulindac

Nitrogeneous functional derivatives of aryl- and heteroarylacetic acids



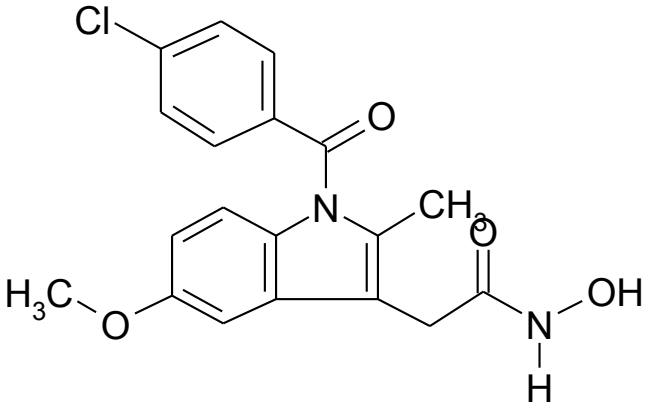
2-(4-butoxyphenyl)-N-hydroxyacetamide
2-(4-butoxyphenyl)acetohydroxamic acid

bufexamac



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

difenpiramide

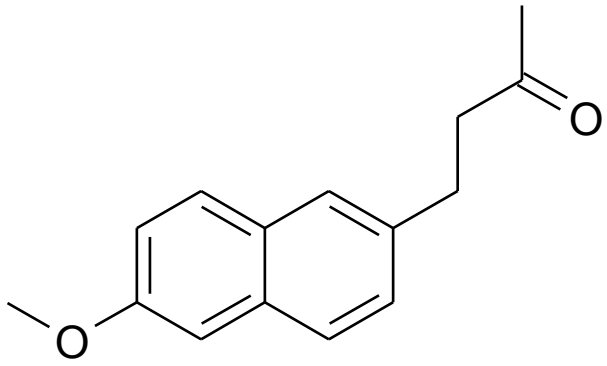


2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-yl]-
N-hydroxyacetamide
2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indole-3-yl]-
acetohydroxamic acid

oxametacin

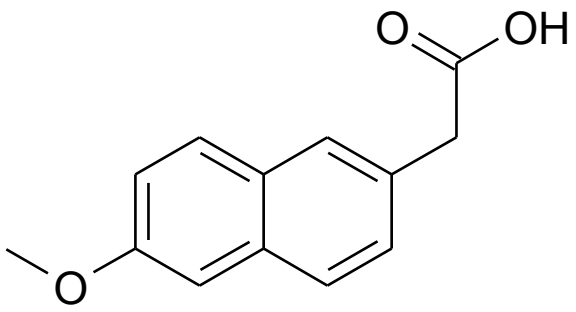
Nabumeton

•a prodrug



metabolism

liver



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

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

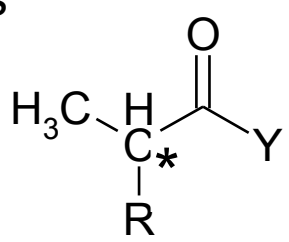
(6MNA)

active metabolit

nabumetone

Relifex® tbl. obd.

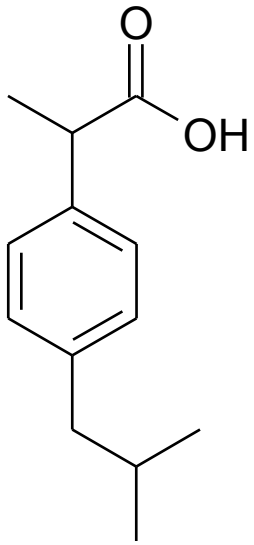
2-aryl- and 2-heteroarylpropionic acids and their functional derivatives



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



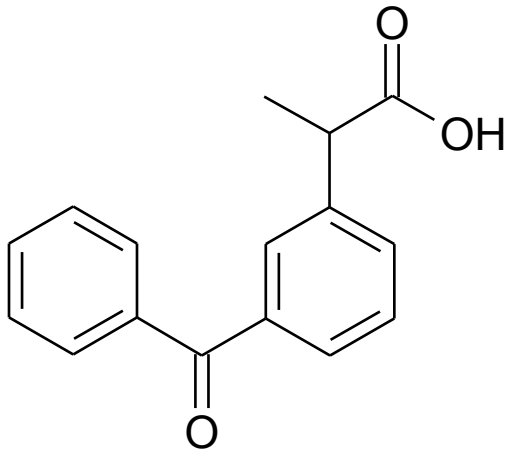
R = OH
(R,S)-2-(4-isobutylphenyl)-propionic acid

ibuprofen

Brufen®, Ibalgin®

(S)- form = dexibuprofen
Seractil®

R = NHOH **ibuproxam**

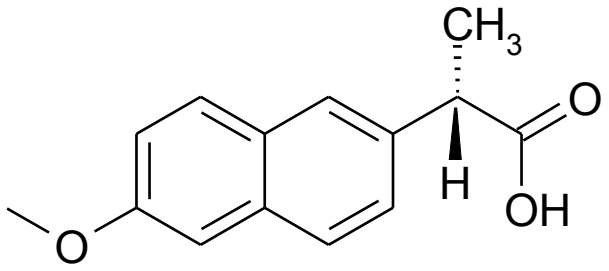


2-(3-benzoylphenyl)-propionic acid

ketoprofen

Fastum®Gel,
Kepabene®tbl

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

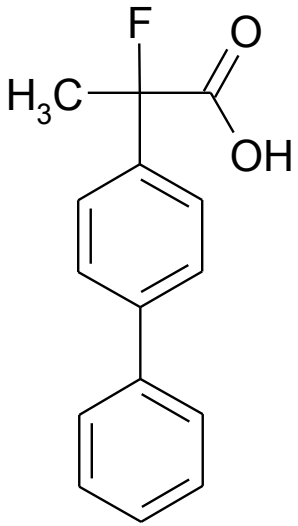


(+)-S-2-(6-methoxynaphtalene-2-yl--propionic acid

naproxen

Naprosyn®,
Naprobene®

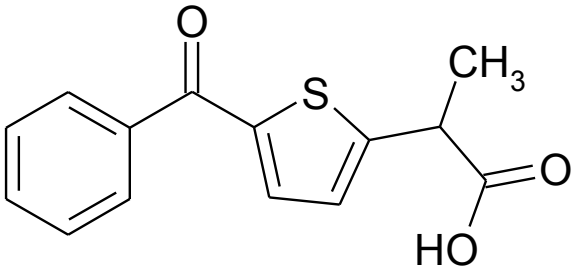
2-aryl- and 2-heteroarylpropionic acids



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

flurbiprofen

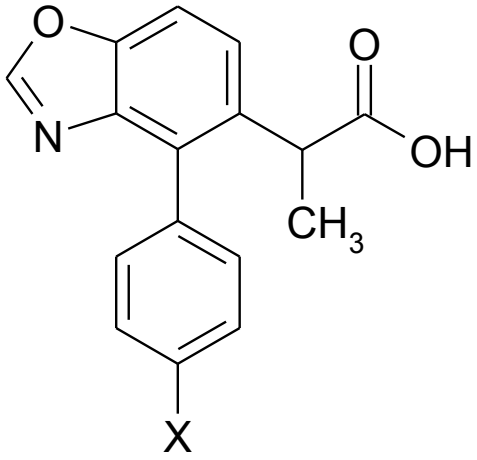
Ansaid®, Flugalin®



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

tiaprofenic acid

Surgam®, Thialgin®



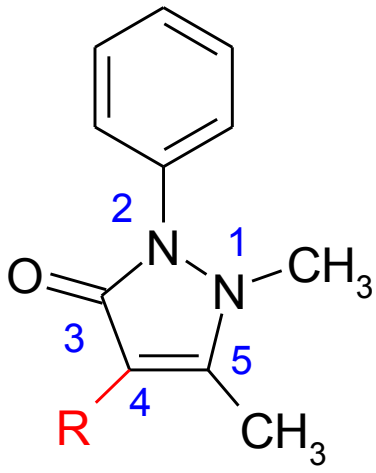
X = Cl
2-[4-(4-chlorophenyl)benzoxazole-5-yl]-propionic acid

benoxaprofen

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

flunoxaprofen

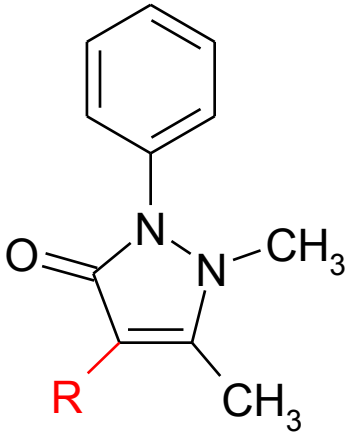
1,2-dihydropyrazole-3-on detivatives



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

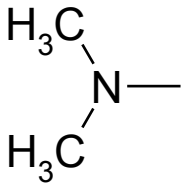
- inhibit both COX1 and COX2
- pain relief, antipyretics
- contemporarirly usually used in mixtures

1,2-dihydropyrazole-3-on derivatives



R = H

phenazone, syn. antipyrine [JAN]
obsolete

R = 

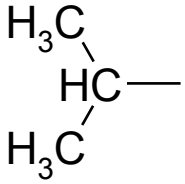
aminophenazone, syn. aminopyrine [JAN]

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

Eunalgit® inj. (+ allobarbital)

•isosterism ⇓

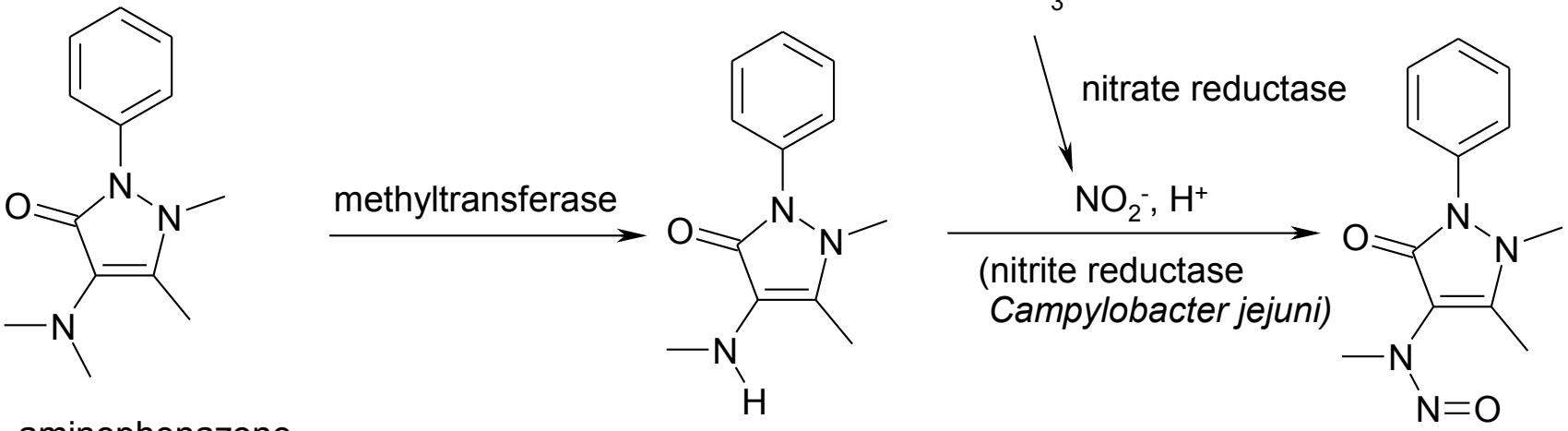
propyphenazone

R = 

Valetol®, Saridon® (+ paracetamol, caffeine)

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

Aminophenazone cancerogenity



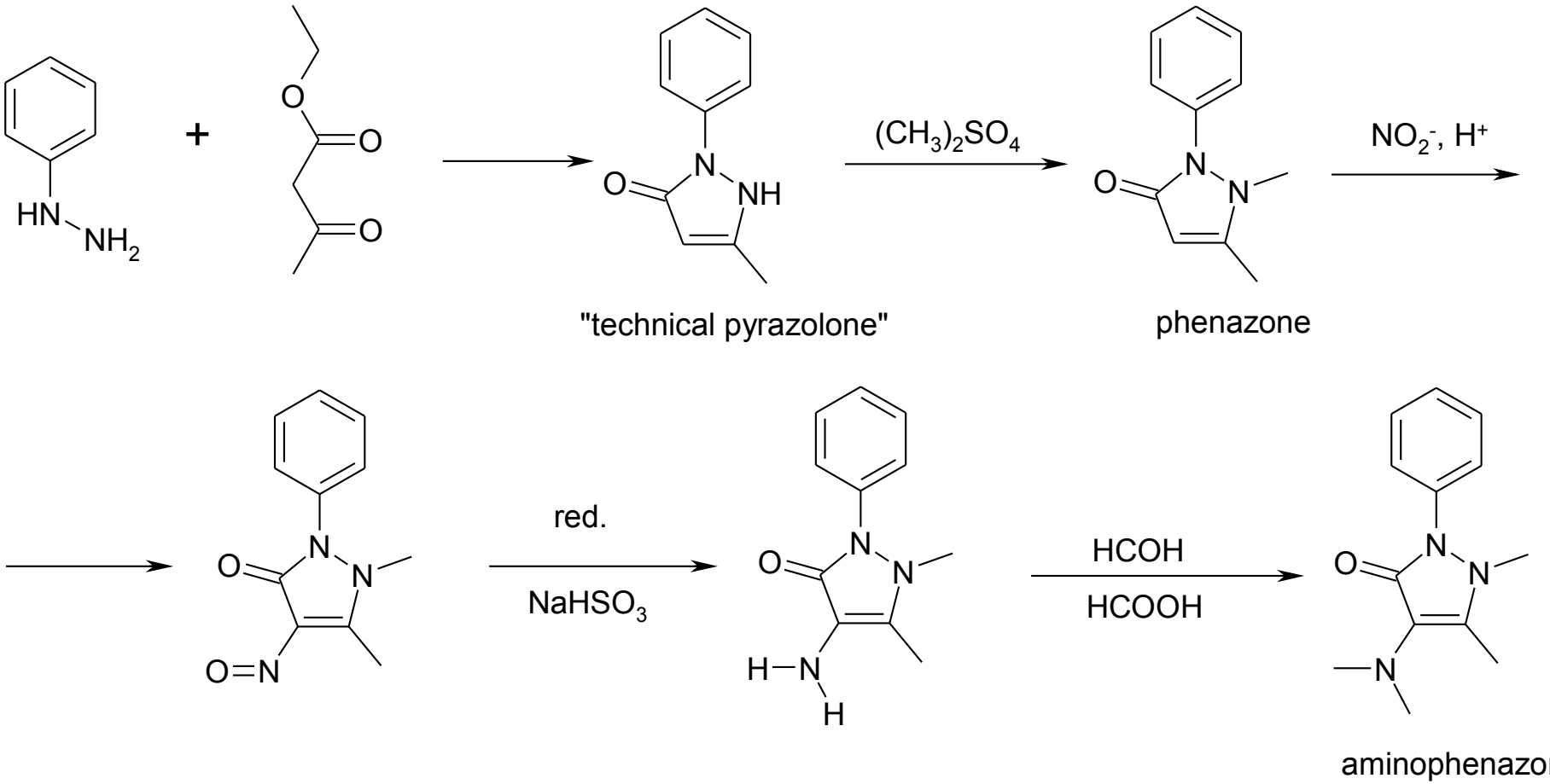
aminophenazone

1,5-dimethyl-4-methylamino-2-phenyl
-1,2-dihydropyrazole-3-one
(desmethylaminophenazone)

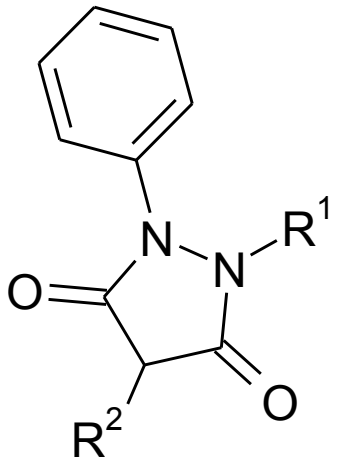
1,5-dimethyl-4-methyl(nitroso)amino
-2-phenyl-1,2-dihydropyrazole-3-one

CANCEROGENIC

Synthesis of aminophenazone

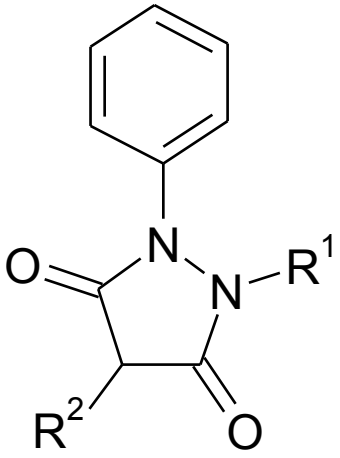


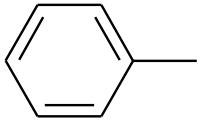
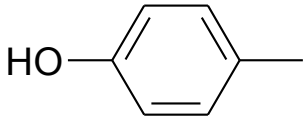
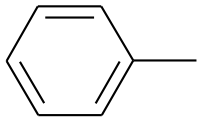
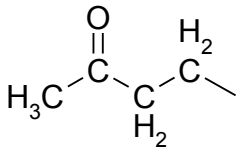
Pyrazolidine-3,5-dione derivatives



- 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

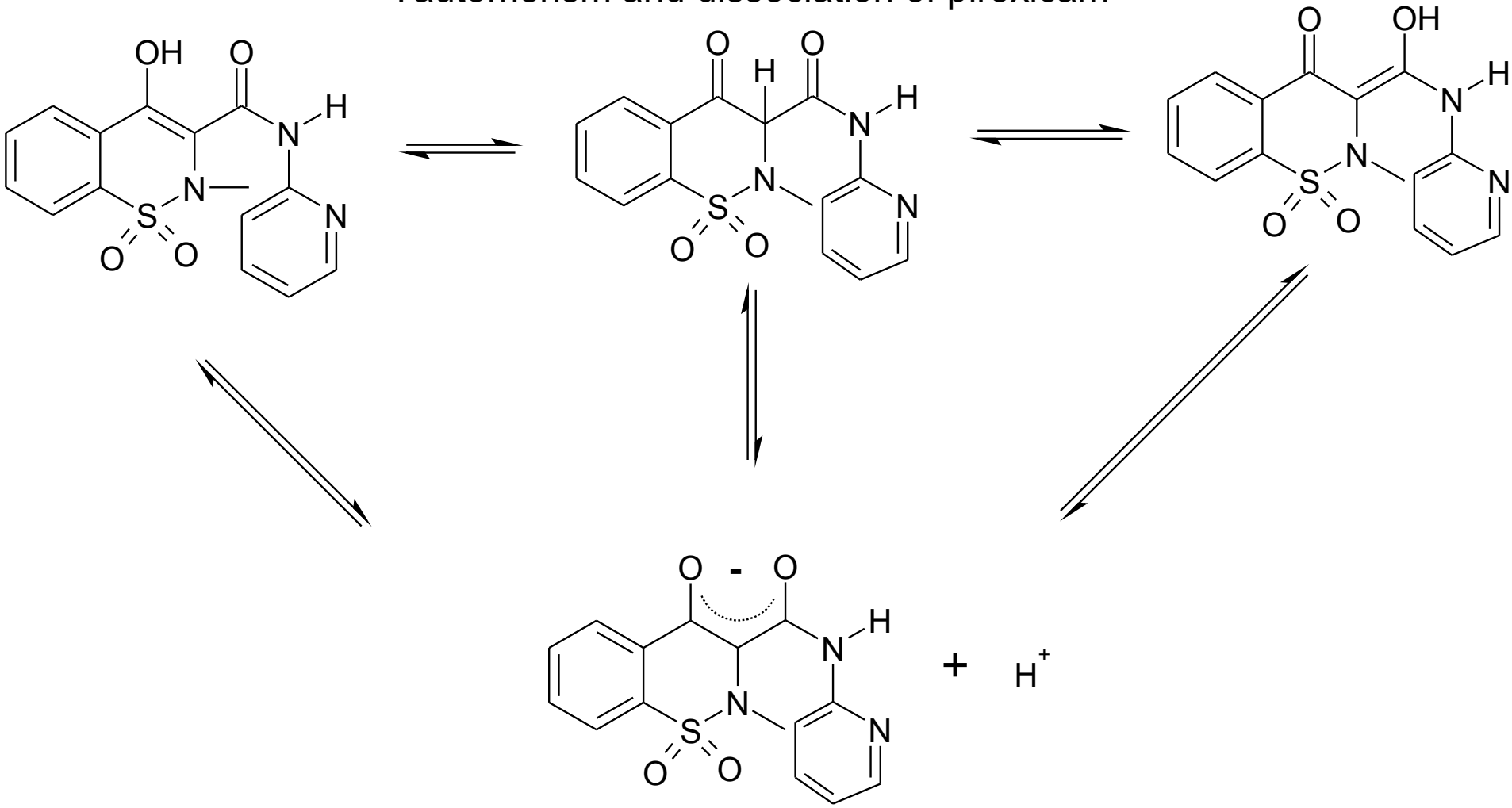


R^1	R^2	Chemical name	INN / preparations
	C_4H_9-	4-butyl-1,2-diphfenylpyrazolidine-3,5-dione	**phenylbutazone** Butasan® a.u.v
	C_4H_9-	4-butyl-1-(4-hydroxyphenyl)-2-phenylpyrazolidine-3,5-dione	**oxyphenbutazone** Tanderil® sup. *reg. in SR*
		1,2-diphenyl-4-(4-oxobutyl)pyrazolidine-3,5-dione	**kebuzone** Ketazon® ung
H-	C_4H_9-	4-butyl-1-phenylpyrazolidine-3,5-dione	**mephebutazone**

Heterocyclic enols-“keto-enolic acids“
-oxicams

•contain „keto-enolic“ structural fragment

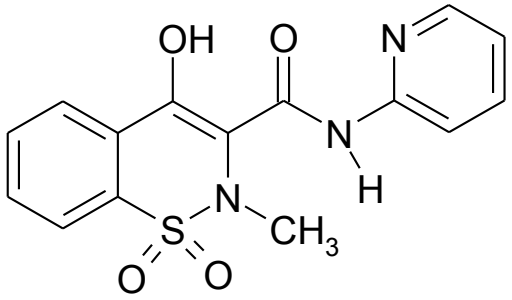
Tautomerism and dissociation of piroxicam



Oxicams

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

Oxicams

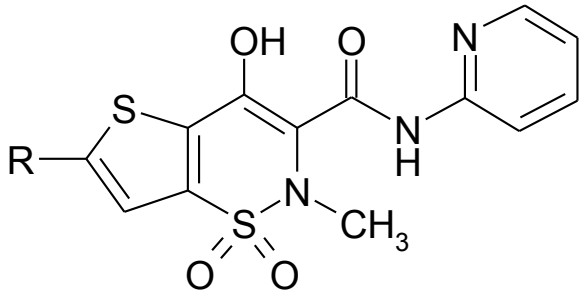


4-hydroxy-2-methyl-N-pyridine-2-yl-2*H*-1,2-benzothiazine-3-carboxamide-1,1-dioxide

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

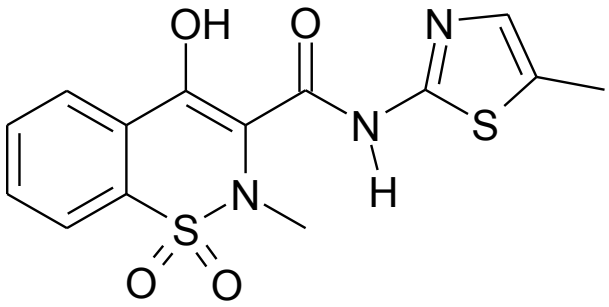
R = Cl

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®

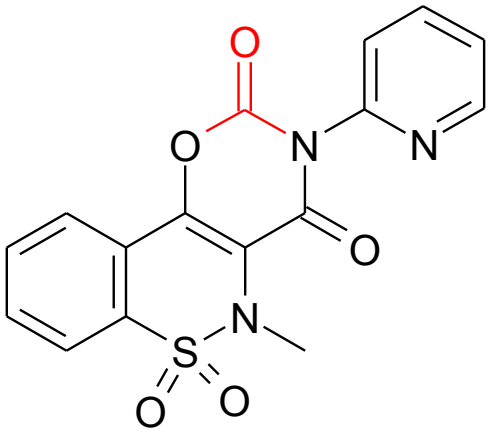
Oxicams



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

meloxicam

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

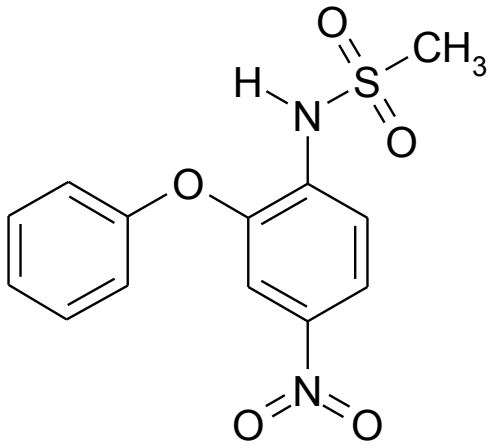


5-methyl-3-pyridin-2-yl-2*H*,5*H*-[1,3]oxazino[5,6-c][1,2]benzothiazine-2,4(3*H*)-dione-6,6-dioxide

droxicam

Selective COX2 inhibitors

Nimesulide



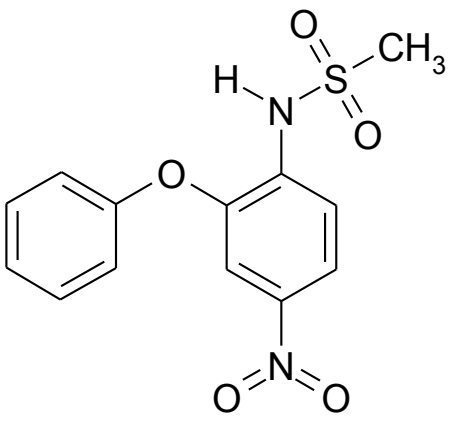
N-(2-phenoxy-4-nitrophenyl)methanesulfonamide

4´-**ni**tro-2´-phenoxy**me**thane**su**lfonani**lid**e

nimesulide

Coxtral®, Aulin®, Mesulid®

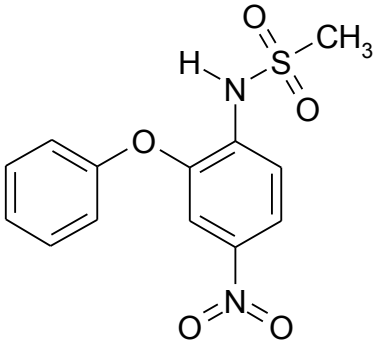
Nimesulide



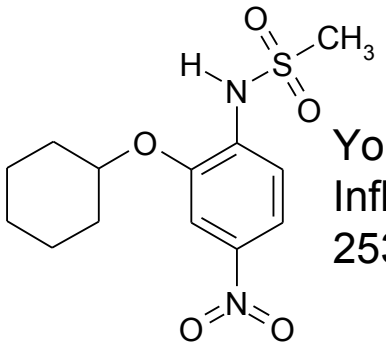
- inhibits COX2 4x more than COX1 ⇒ ↓ AE in GIT and platelets
- antirheumatic, antiarthrotic, pain relief
- AE: hepatotoxicity; icreased in fever ⇒ not suitable as antipyretic

„Radical analogy“

- substitution benzene ⇒ cyclohexane



nimesulide



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

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

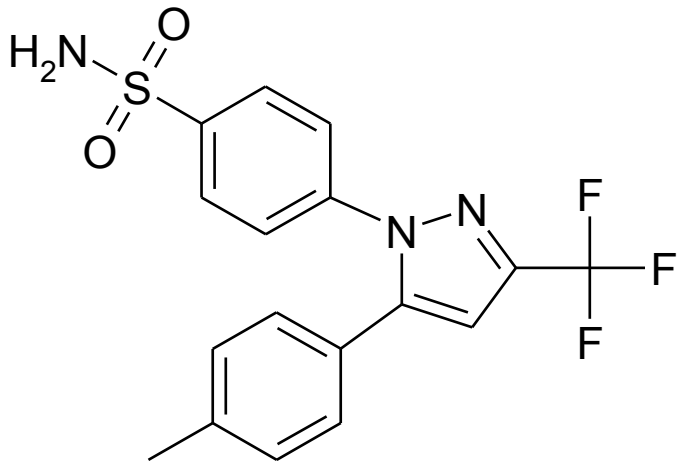
Selectivity COX2:COX1	4 : 1	30 : 1

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 D_1 and E_1 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)

Coxibs

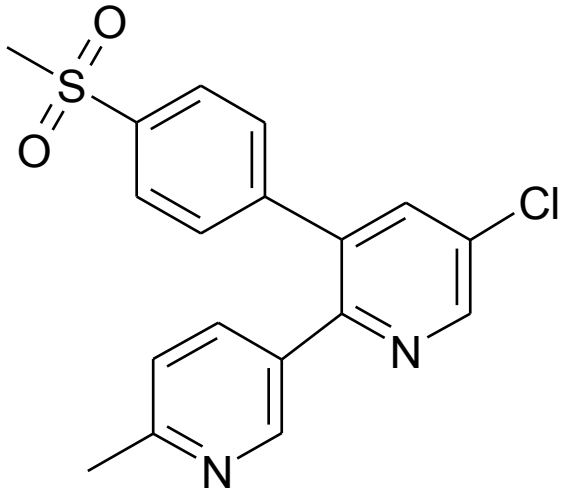


4-[5-(4-methylphenyl)-3-(trifluoromethyl)-1H-pyrazole-1-yl]benzenesulfonamide

celecoxib

~~Celebrex~~®

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



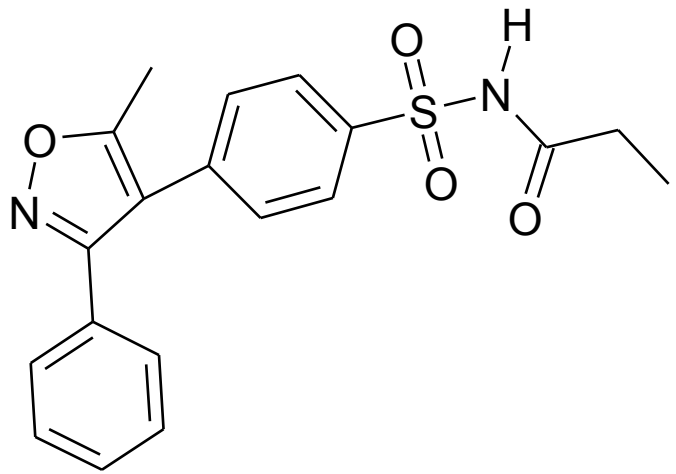
5-chloro-6'-methyl-3-[4-(methylsulfonyl)phenyl]-2,3'-bipyridine

etoricoxib

Arcoxia®

Selectivity COX2 : COX1	30 : 1	340 : 1

Coxibs

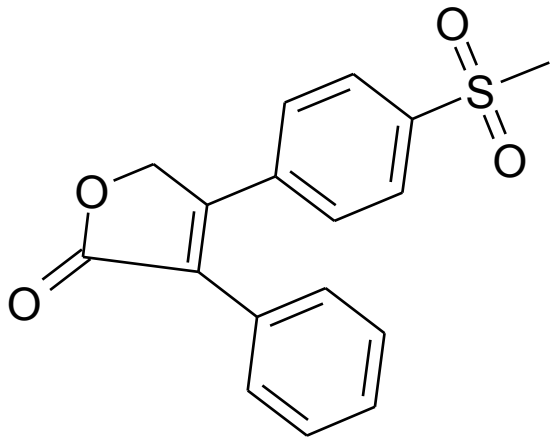


N-{[4-(5-methyl-3-phenylisoxazole-4-yl)phenyl] sulfonyl}propanamide

parecoxib

•alergic skin reactions mainly in persons hypersensitive to sulfonamides

Dynastat® - for postoperative pain only



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

rofecoxib

~~Ceeoxx®, Vioxx®~~

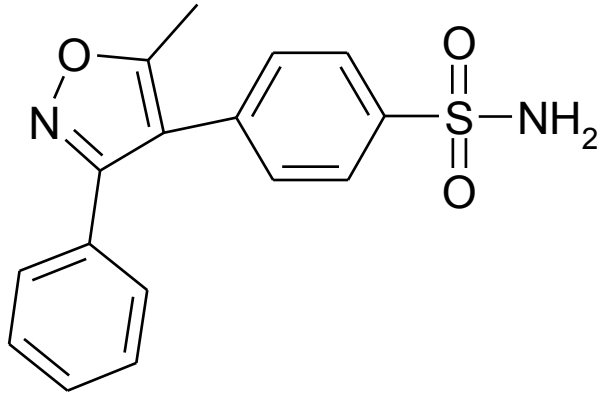
withdrawn due to dangerous cardiovascular effects

Selectivity

COX2 : COX1

270 : 1

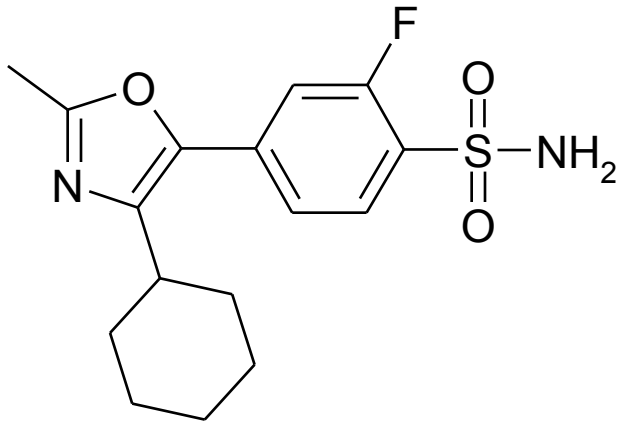
Coxibs



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

valdecoxib

~~Bextra®~~ withdrawn



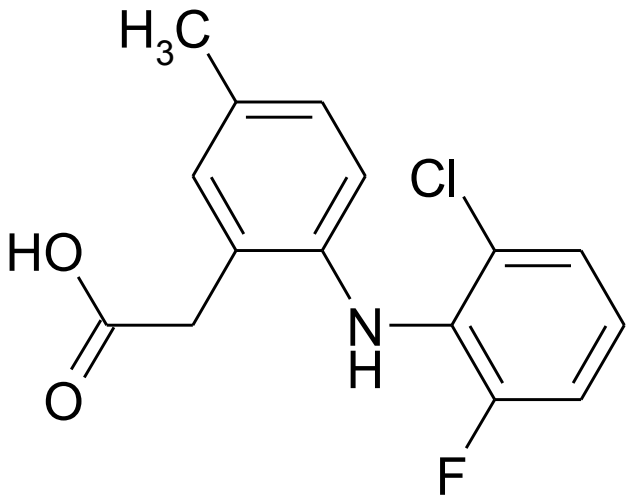
4-(4-cyclohexyl-2-methyl-1,3-oxazole-5-yl)-2-fluorobenzenesulfonamide

tilmacoxib

Selectivity

COX2 : COX1 60 : 1

Coxibs

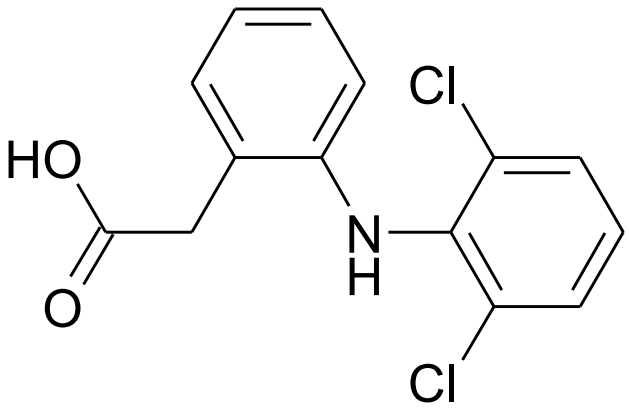


2-(2-fluoro-6-chlorfenylamino)-5-methylphenylacetic acid

lumiracoxib

~~Prexige ®~~

For comparison:



diclophenac