

Analgetika – antipyretika

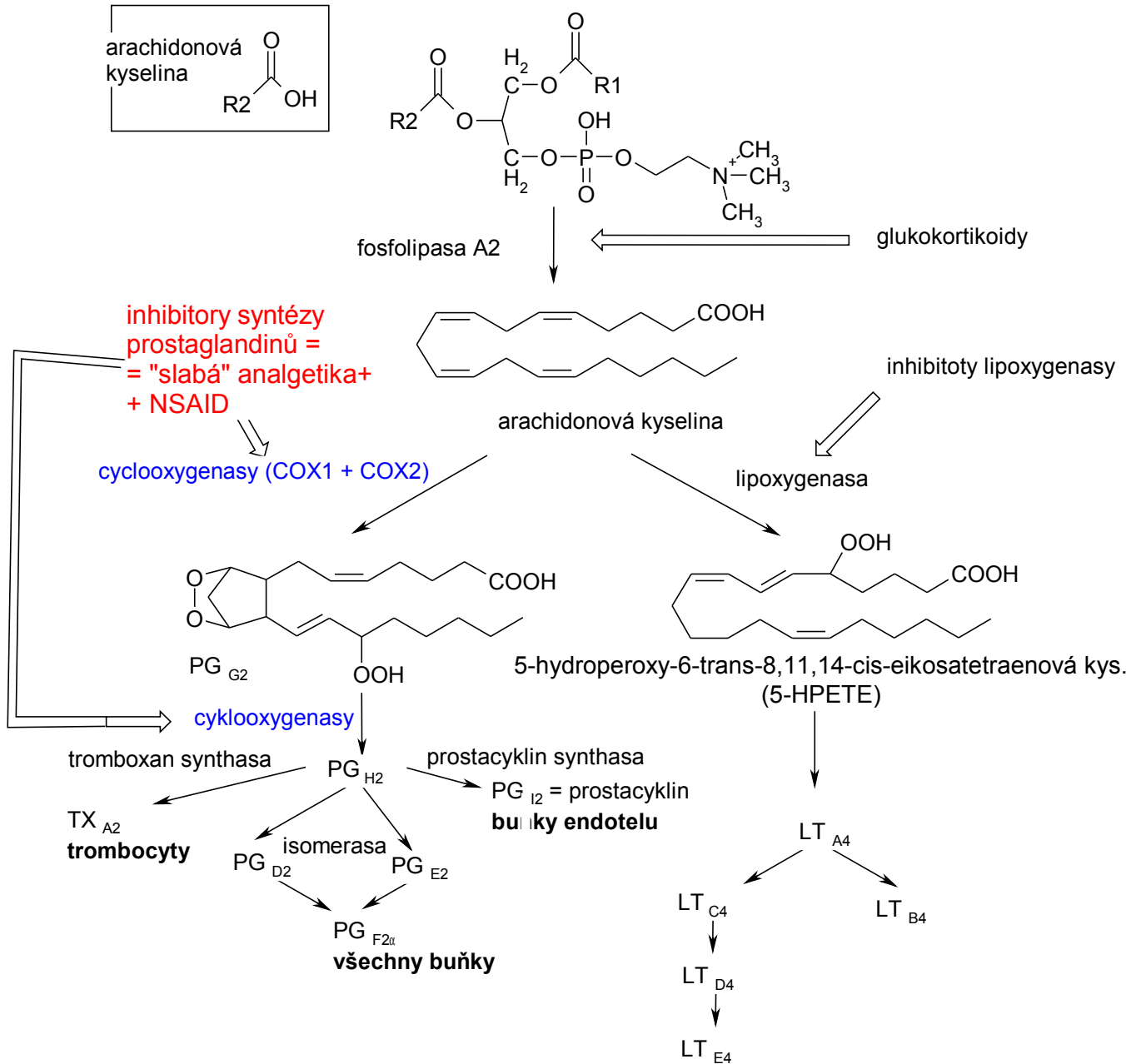
= „slabá“ analgetika

= neopioidní analgetika

Většina též

- nesteroidní antiflogisika
- antirevmatika

Metabolismus eikosanoidů



Účinky prostaglandinů

Prostaglandin E, F_{2α} : bolest, horečka, zánět, sekrece HCl↓, dilatace vlásečnic mukózní vrstvy žaludku, děložní stahy, ledviny: vylučování Na⁺ a H₂O ↑

Prostacyklin (prostaglandin I₂): vasodilatace, inhibice agregace trombocytů

Tromboxan: vasokonstrikce, aktivace agregace trombocytů

Leukotrieny: alergická reakce (např. asthma bronchiale)

Cyklooxygenasy (= prostaglandin G/H synthasy)

COX1

Konstitutivní: ve všech tkáních

Funkce:

- ochrana žaludeční sliznice (vasodilatace)
- diuréza
- agregace trombocytů (TXA)

COX2

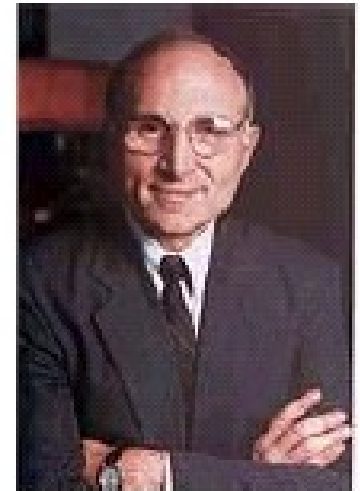
Konstitutivní: ledviny, mozek (kolokalizovaná s cykliny D₁ a E) objevitel izoenzymů COX

Indukovaná: makroágy, neutrofilny, fibroblasty, buňky endotelu

Funkce:

- vasodilatace (PG I₂)
- porod (děložní stahy)
- zánětlivé procesy

COX3 ?? (= COX1b; mozek ?)



Philipp Needleman

(1989)

Rozdělení inhibitorů COX (antipyretika, NSAID)

Neselektivní (COX1 + COX2)

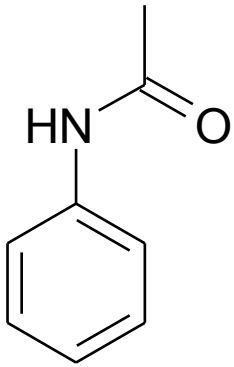
- Anilidy
- Salicyláty
- Fenamáty
- Aryl- a heteroaryalkanové kyseliny
 - Aryl- a heteroaryloctové kys.
 - Aryl- a heteroarylpropionové kys.
- Oxikamy
- 1,2-Dihydropyrazolidin-3-ony
- 2,5-Pyrazolididiony

Selektivní (COX1 < COX2)

Specifické (COX2)

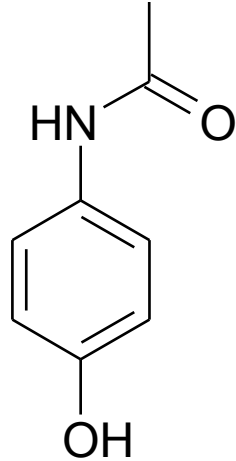
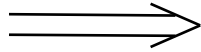
- Koxiby

Anilidy



acetanilid

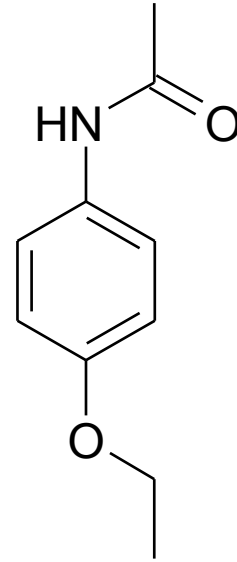
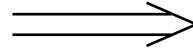
N-fenylacetamid



paracetamol

(acetaminophen)

4-(acetylamino)fenol



fenacetin

N-(4-ethoxyfenyl)acetamid

1886: Antifebrin® *para*-(acetylamino)fenol

p-(acetylamino)phenol

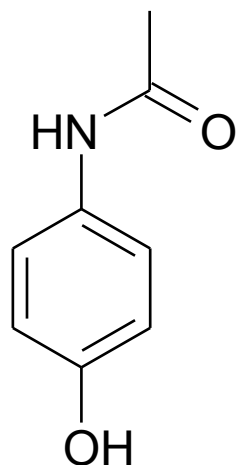
Paralen®, Panadol®....

nefrotoxicita

Dinyl® - analg. směs s kofeinem, aminofenazonem a barbiuráty

Paracetamol

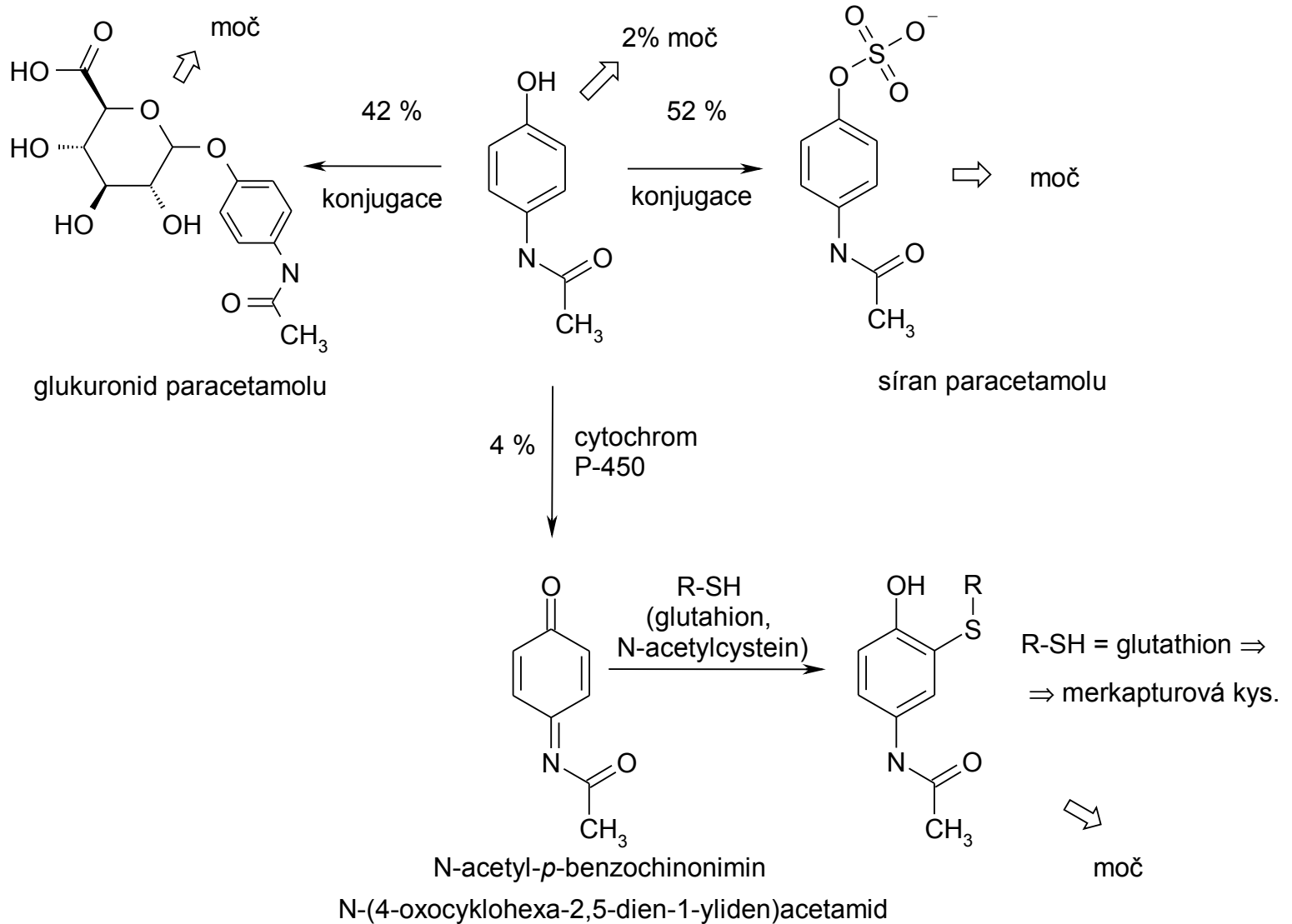
- inhibuje COX jen v CNS (COX3 ?), nikoliv na periférii ⇒
- účinek: analgetický, antipyretický (nikoliv antiflogistický, antirevmatický)



Použití ve směsích s(e)

- kodeinem, kofeinem ⇒ potenciace účinku (Korylan tbl.®, Panadol tbl.®, Efferalgan codein tbl. eff.®)
- expektorancii (guaifenesin, terpin)
- antitussiky (dextrometorfan)
- H₁-antihistaminiky (feniramin, chlorfenamin, dimenhydrinát, promethazin, doxylamin)
- \forall α -sympatomimetiky (fenylefrin, pseudoefedrin)
- spasmolytiky (pitofenon)
- myorelaxancii (chlorzoxan, karisoprodol)
- NSAID (acetylsalicylová kys., propyfenazon – Valetol®)

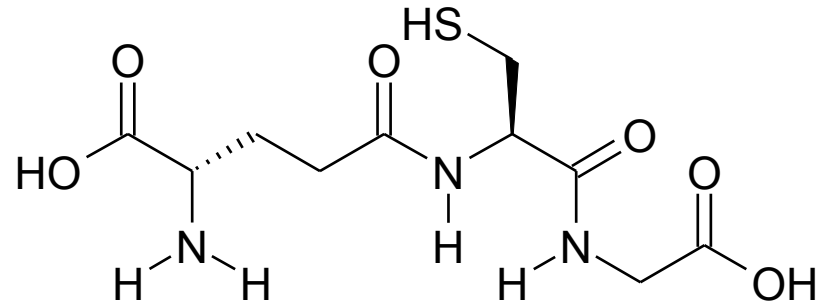
Metabolismus paracetamolu



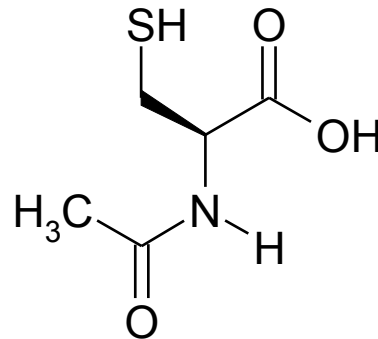
NAPQI
HEPATOTOXICKÝ

Thioly, detoxikující N-acetyl-*p*-benzochinonimin

γ -Glu-Cys-Gly



glutathion

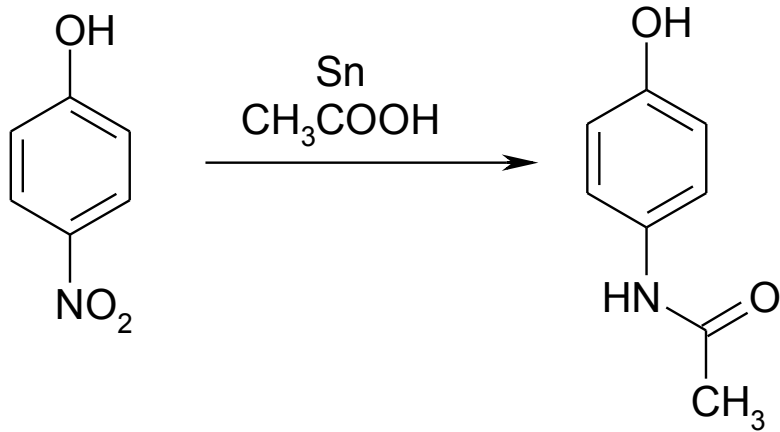


N-acetyl-L-cystein

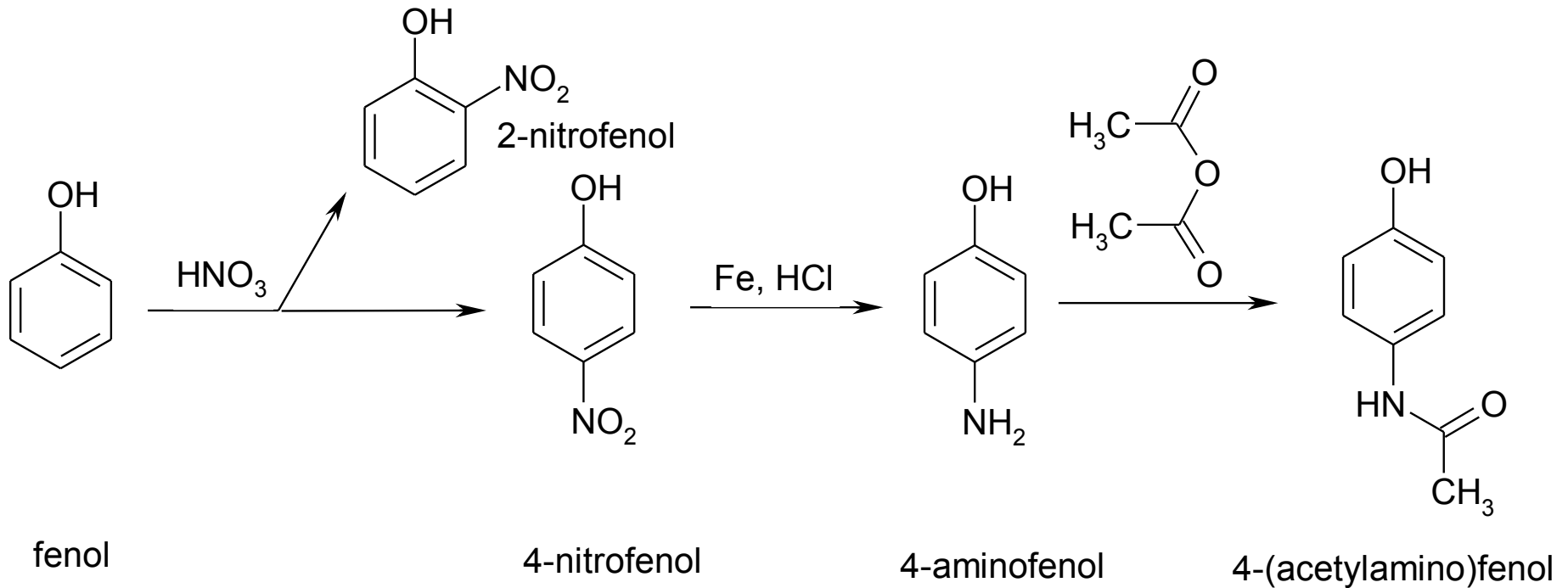
mukolytikum

ACC®, Mucobene®

Syntéza paracetamolu

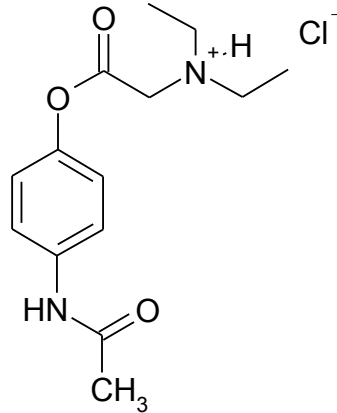


Morse, Chem. Ber. **11**, 232 (1878)



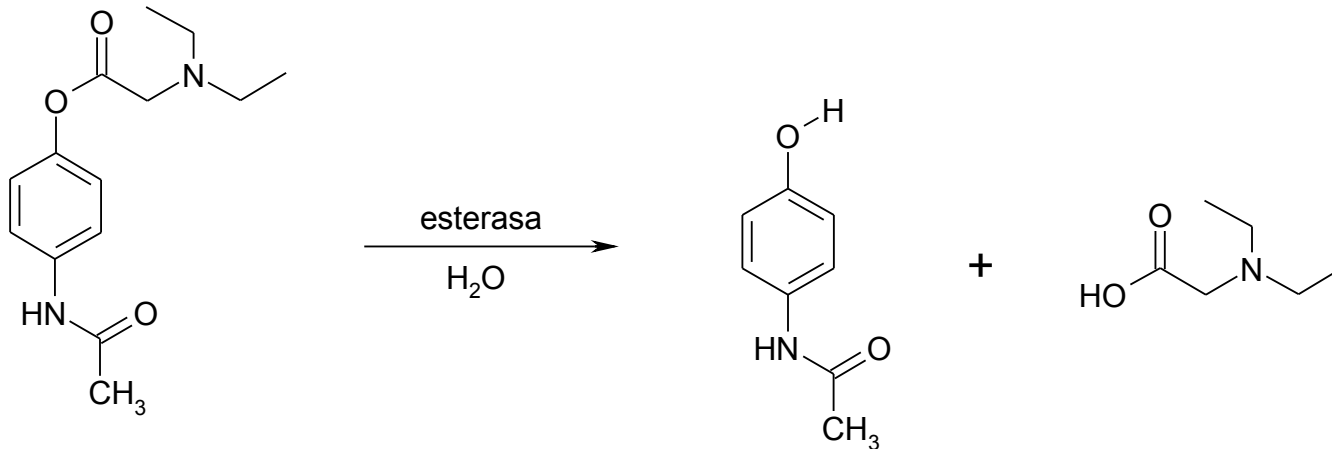
Propacetamol – proléčivo paracetamolu

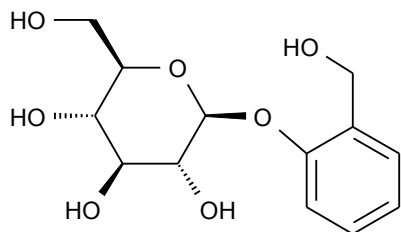
- pro intravenózní podání



4-(acetylamino)fenyl-N,N-diethyl glycinát hydrochlorid
2-[4-(acetylamino)fenoxy]-N,N-diethyl-2-oxoethanaminium chlorid
propacetamol hydrochlorid

Pro-Dafalgan® (*UPSA Laboratoires*)



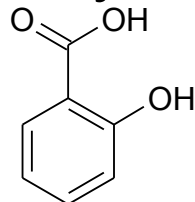


salicin
(2-hydroxymethylfenyl)-b-D-glukopyranosid

1827 Leroux: izolace z vrby

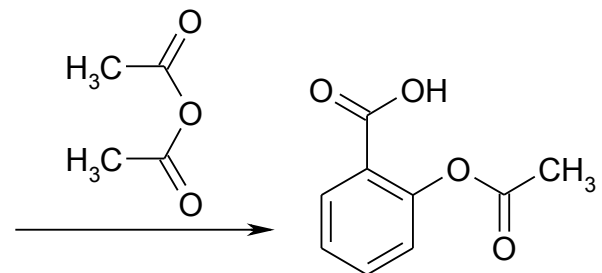
hydrolyza
oxidace

Salicyláty



salicylová kyselina
2-hydroxybenzoová kys.

1838 Piria: první syntéza
od r. 1878 použití jako antipyretikum
a antirevmatikum



acetylsalicylová kys.
2-acetoxybenzoová kys.

1897 Felix Hoffmann - syntéza
pro průmysl

1899 – Aspirin® (*Bayer*)



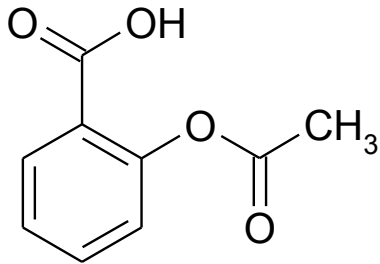
Felix Hoffmann



Sir John R. Vane



Účinky acetylsalicylové kyseliny



„Žádoucí“:

- antipyretikum
- analgetikum
- antiflogistikum
- antirevmatikum
- antitrombotikum (↓ agregaci trombocytů) – Anopyrin®



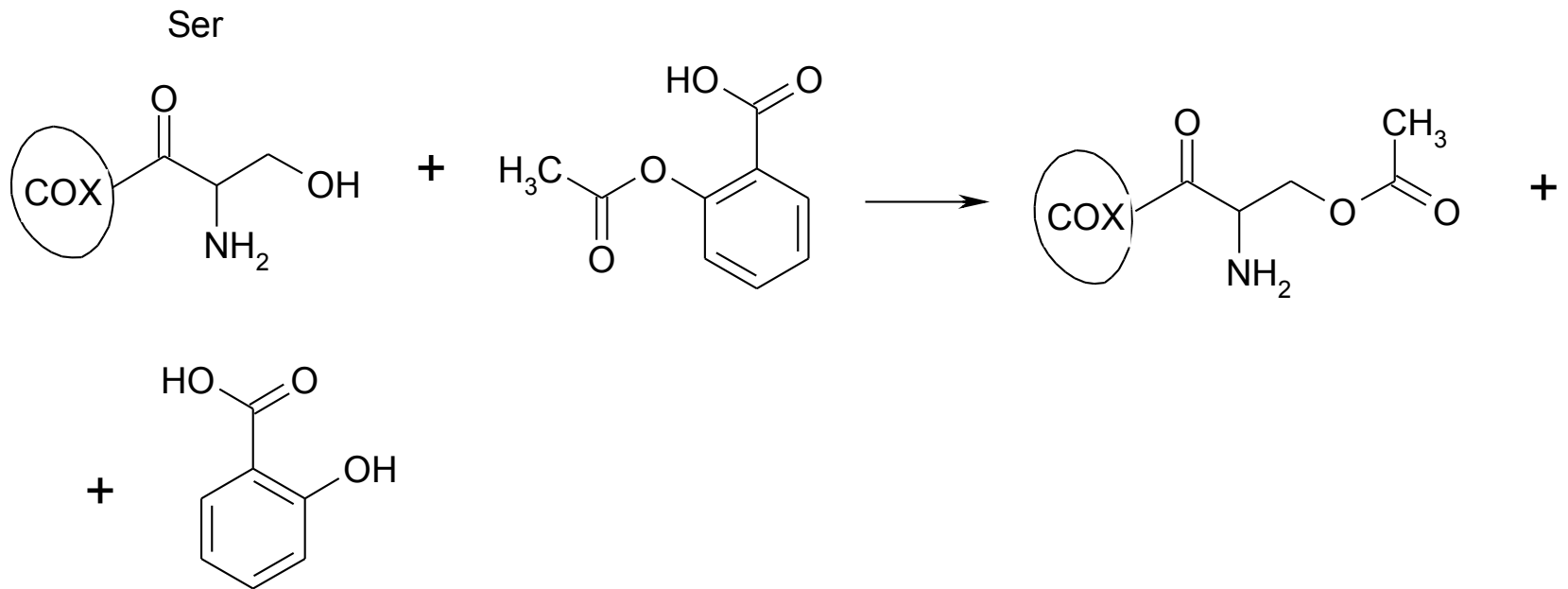
„Nežádoucí“:

- ulcerogenní působení
- Reyův syndrom u dětí po virové infekci (hepatopatie, encefalopatie) ⇒ **kontraindikace u dětí**
- krvácivost (např. z nosu - ↓ agregaci trombocytů)

Intoxikace = „salicylismus“ – postižení CNS (psychické poruchy, hučení v uších, závratě, hluchota), metabolická acidóza

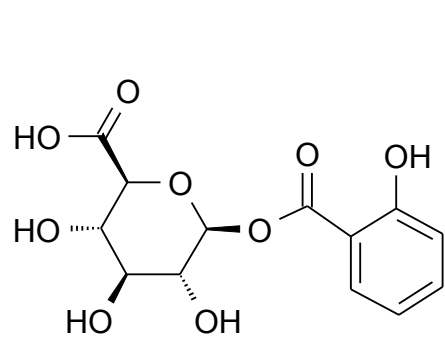
Mechanismus účinku acetylsalicylové kyseliny (ASA)

- ireverzibilní inhibice cyklooxygenas acetylací serinového zbytku

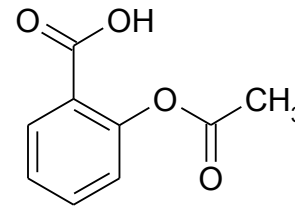


Metabolismus ASA

- probíhá v játrech
- všechny metabolity vylučovány močí

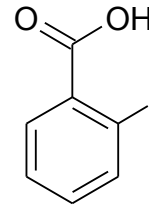


O¹-salicyloylglukuronová kys.
5 %



ASA

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



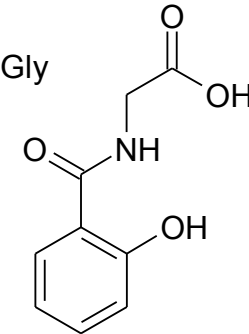
salicylová kys.
10 %

+ CH₃COOH

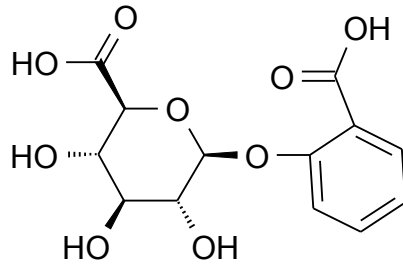
glukuronace

konjugace s Gly

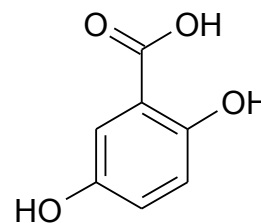
hydroxylace



salicylurová kys.
(N-salicyoylglycin)
75 %

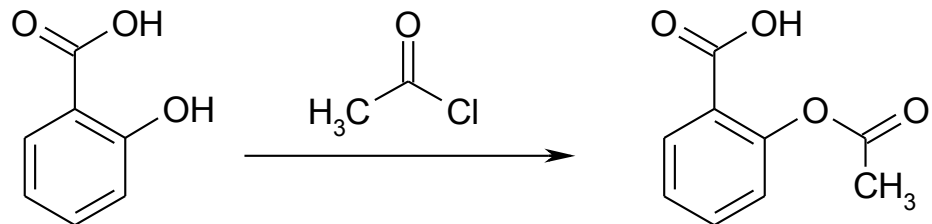


O¹-(2-karboxyfenyl)glukuronová kys.
10 %



gentisová kyselina
< 1 %

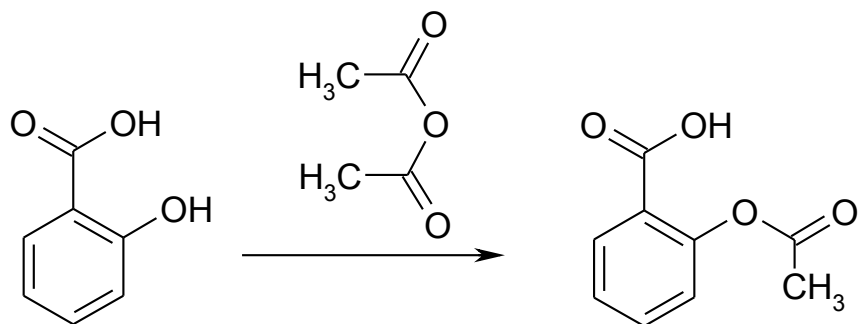
Syntézy ASA



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

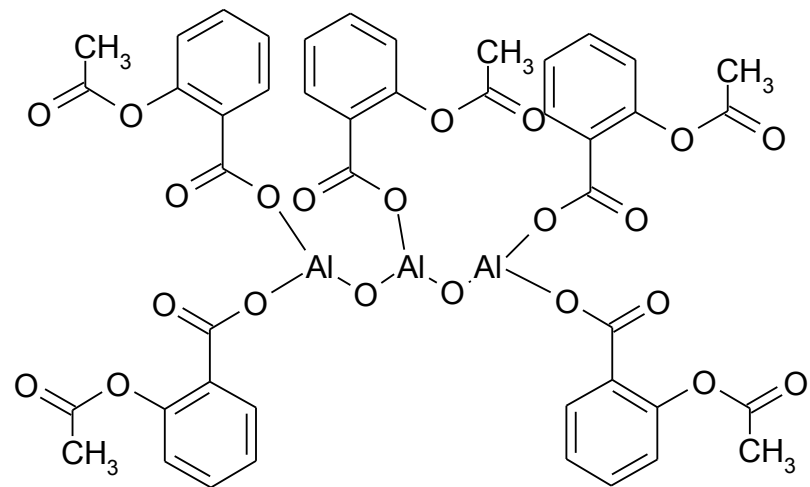
Gilm, Justus Liebigs Ann. Chem. **112**, 181 (1859)

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



Felix Hoffmann

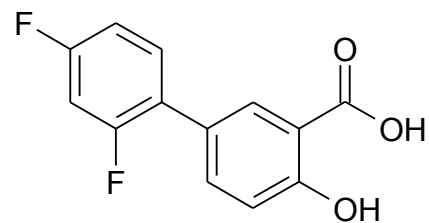
Další salicyláty



pentakis(acetylsalicyoyloxy)trialuminium dioxid

aloxiprin

Superpyrin®



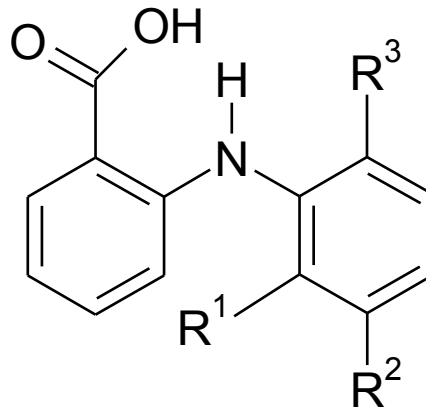
2',4'-difluoro-4-hydroxy-1,1'-bifeny-3-karboxylová kyselina

diflunisal

Unisal® tbl.

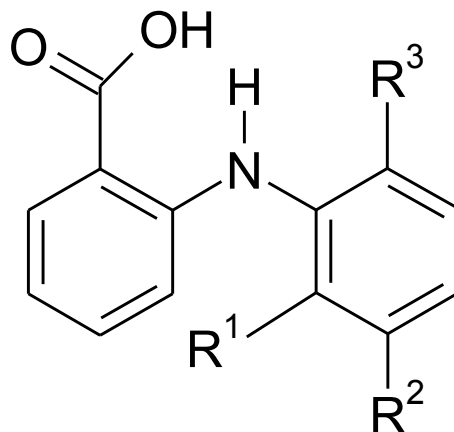
Deriváty anthranilové kyseliny – fenamáty

= substituční deriváty 2-fenylaminobenzoové kys.



- aromatické aminokyseliny
- substituce jen na anilinovém benzenovém kruhu
- inhibují COX1 i COX2 (selektivita?; COX3?)
- analgetika, antipyretika, antimigrenika, antiflogistika

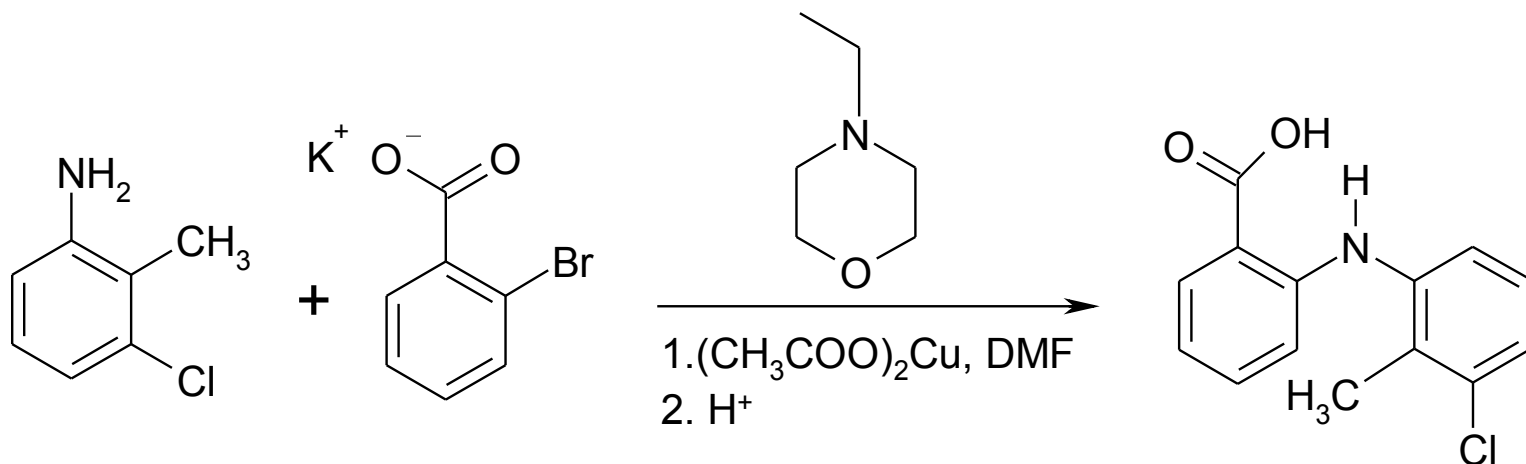
Fenamáty



R ¹	R ²	R ³	Chem. název	INN / přípravek
-CH ₃	-CH ₃	-H	2-(2,3-dimethylfenylamino)-benzoová kys.	mefenamová kys.
-Cl	-CH ₃	-Cl	2-(2,6-dichlor-3-methylfenylamino)benzoová kys.	meklofenamová kys.
-CH ₃	-Cl	-H	2-(3-chlor-2-methylfenylamino)benzoová kys.	tolfenamová kys. Migea rapid®
-H	-CF ₃	-H	2-(3-trifluormethylfenylamino)benzoová kys.	flufenamová kys.

Tolfenamová kyselina

Syntéza



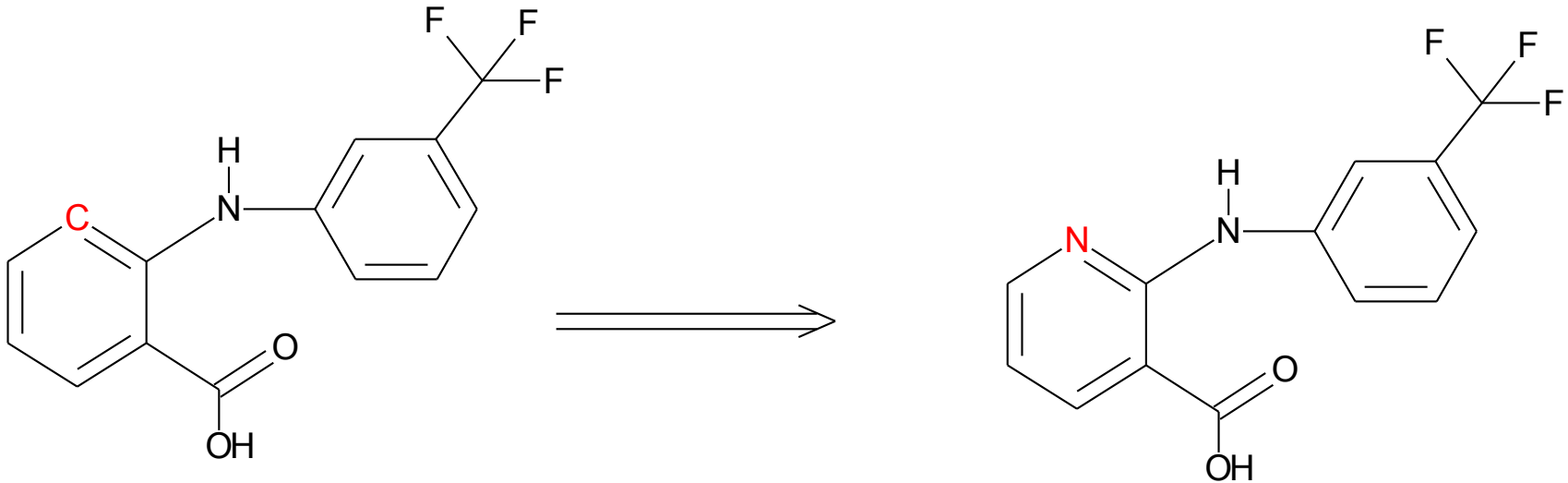
Kaltenbronn J.S. et al., *Arzneim.Forsch* **33**, 621-627 (1983)

Selektivita vůči COX

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

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

Niflumová kyselina a její estery



flufenamová kys.

2-[[3-(trifluormethyl)fenyl]amino]nikotinová kyselina

niflumová kys.

- izosterní záměna benzen \Rightarrow pyridin, resp. $-\text{CH}=\Rightarrow -\text{N}=\text{}$
- inhibují COX1 i COX2
- antiflogistika, antirevmatika; převážně topicky

Niflumová kyselina a její estery

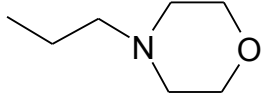
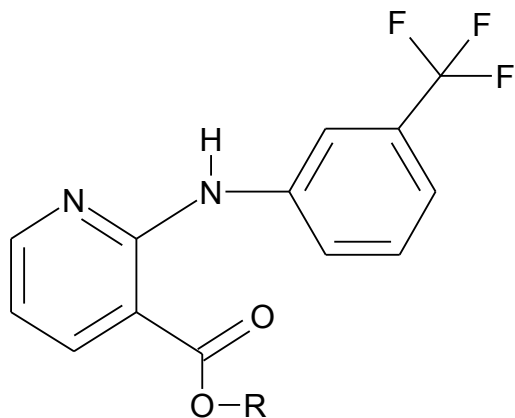
R

—H

2-[[[3-trifluormethyl]fenyl]amino]nikotinová kys.

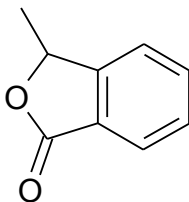
niflumová kys.

Niflugel[®], Nifluril[®]



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

morniflumát



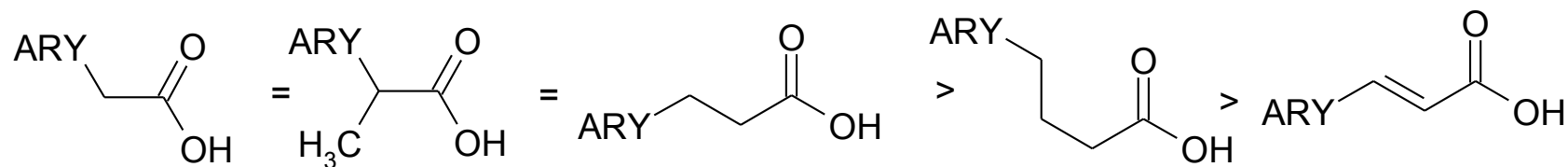
1-oxo-2-(3H)-benzofuran-3-ylester -||-

talniflumát

Aryl- a heteroarylalkanové kyseliny

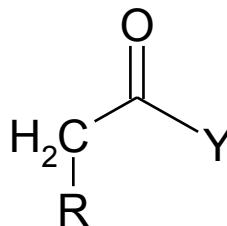
Vztah mezi strukturou a účinkem

- alifatická část je pro účinek specifitější než aromatická



ARY = aryl, heteroaryl

Deriváty aryl- a heteroaryloctových kyselin

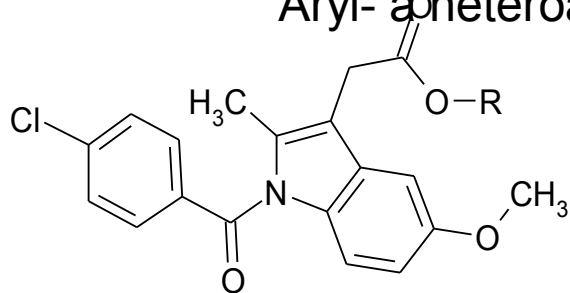


R = aryl nebo heteroaryl

Y = OH, NHOH, NHR, OCH₂COOH, popř. jiné

- antirevmatika, antiflogistika, analgetika, antipyretika
- inhibice COX1 i COX2
- NÚ jako u salicylátů

Aryl-~~ar~~aheteroaryloctové kyseliny (fenaky)



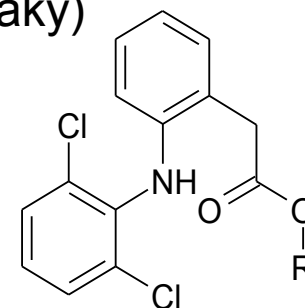
R = H

[1-(4-chlorbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]octová kyselina

indomethacin

používán od r. 1963

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



R = H

{2-[(2,6-dichlorfenyl)amino]fenyl}octová kyselina

diklofenak

používán od r. 1975

Voltaren[®], Veral[®], Myogit[®],
Dicloream[®]

R = OCH₂COOH

karboxymethylester

[1-(4-chlorbenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]octové kyseliny

acemetacin

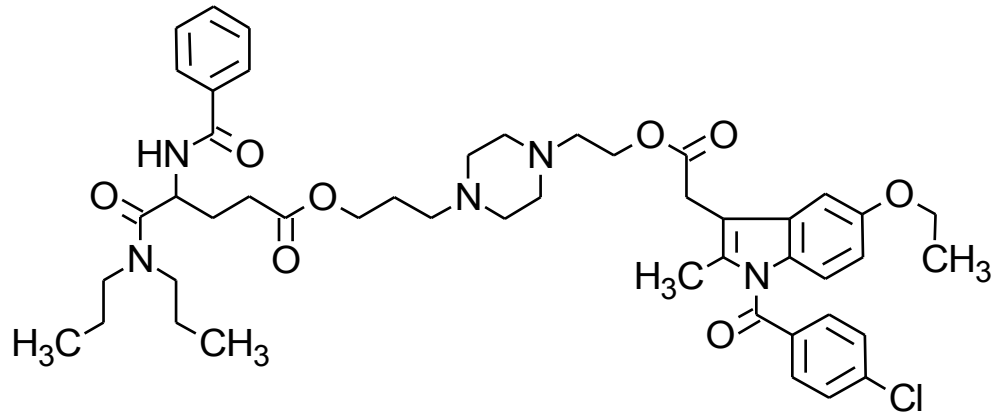
R = OCH₂COOH

karboxymethylester

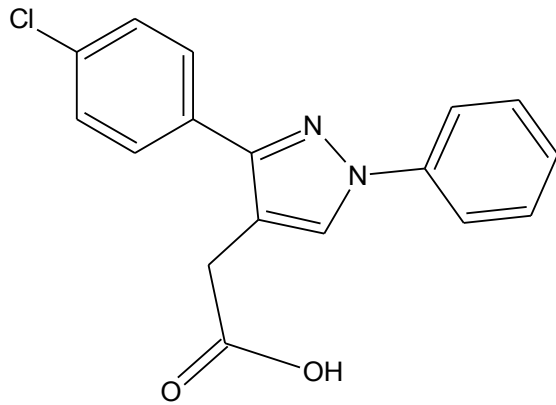
{2-[(2,6-dichlorfenyl)amino]fenyl}octové kyseliny

aceklofenak

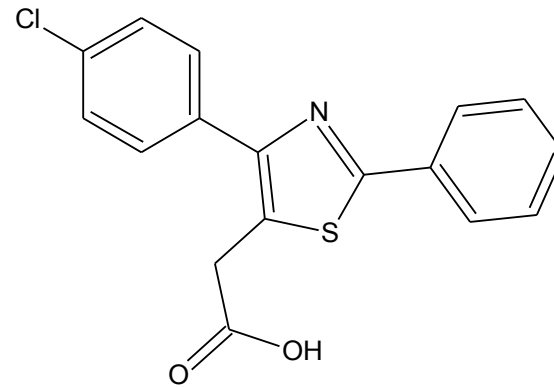
Heteroaryloctové kyseliny a jejich deriváty



proglumetacin

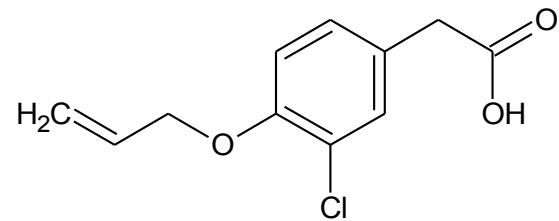


[3-(4-chlorofenyl)-1-fenyl-1H-pyrazol-4-yl]octová kyselina
lonazolac

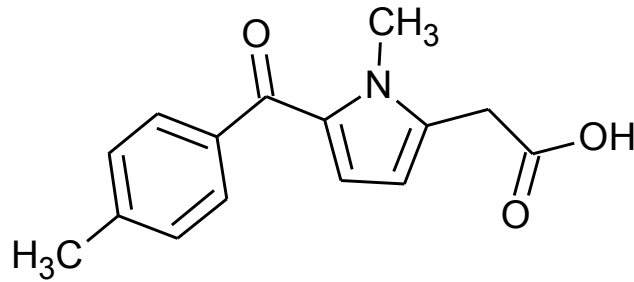


[4-(4-chlorofenyl)-2-fenyl-1,3-thiazol-5-yl]octová kyselina
fentiazac

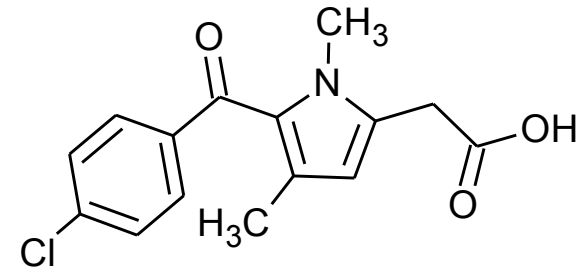
Aryl- a heteroaryloctové kyseliny



alklofenak



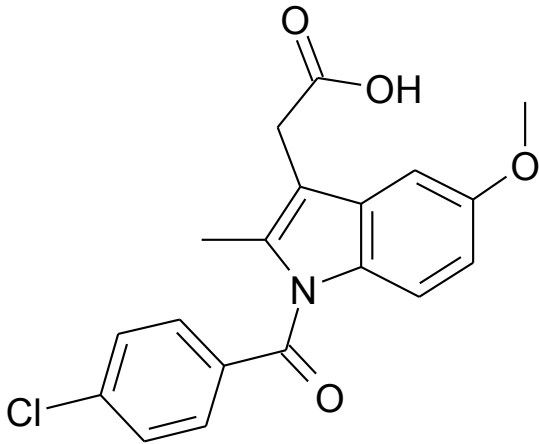
tolmetin



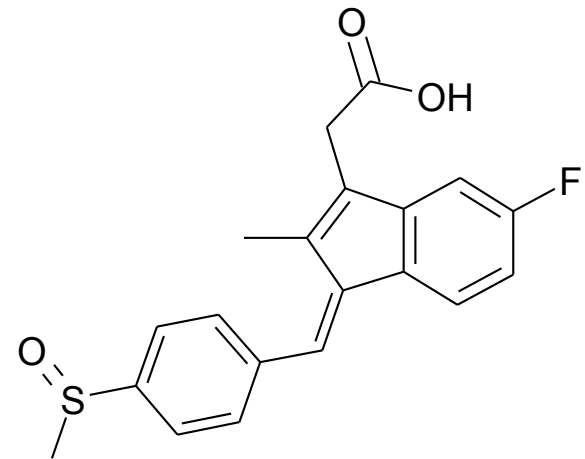
zomepirak

Aryl- a heteroaryloctové kyseliny

- příklad izosterie cyklů a funkčních skupin

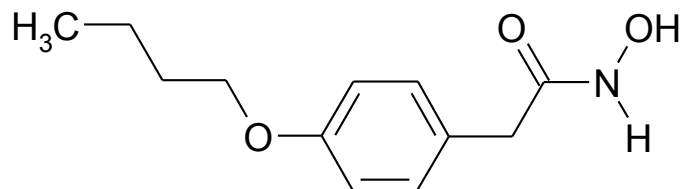


[1-(4-chlorbenzoyl)-5-methoxy-2-methyl-
1H-indol-3-yl]octová kyselina
indomethacin

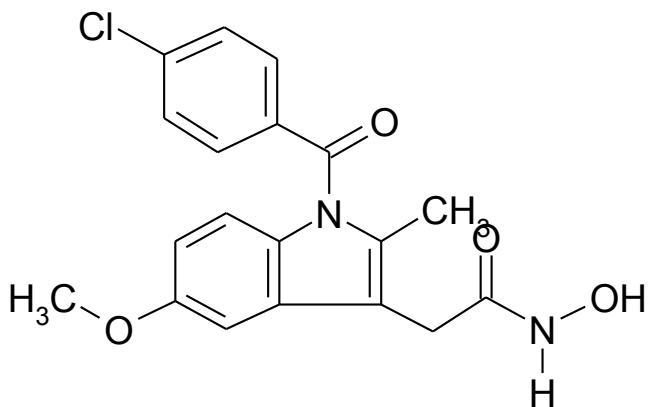


[6-Fluoro-3-(4-methansulfinyl-benzyliden)-2-methyl-
3H-inden-1-yl]-octová kyselina
sulindak

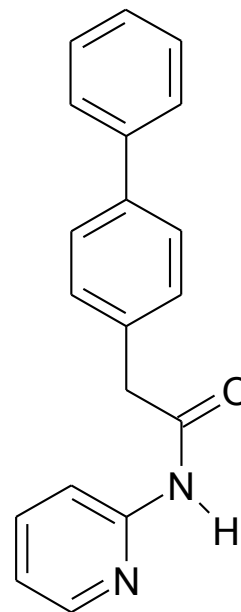
Dusíkaté funkční deriváty aryl- a heteroaryloctových kyselin



2-(4-butoxyfenyl)-N-hydroxyacetamid
2-(4-butoxyfenyl)aceto hydroxamová kys.
bufexamak

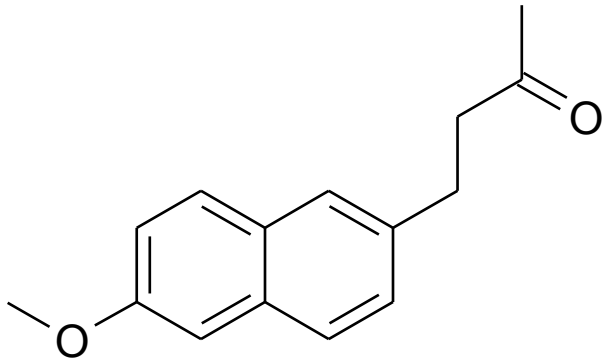


2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-
N-hydroxyacetamid
2-[1-(4-chlorobenzoyl)-5-methoxy-2-methyl-1H-indol-3-yl]-
aceto hydroxamová kyselina
oxametacin



1,1'-bifenyyl-4-yl-N-pyridin-2-yl-acetamid
difenpyramid

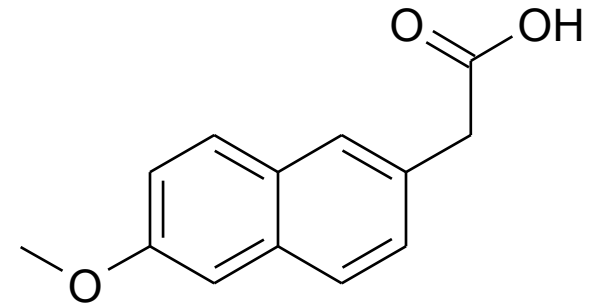
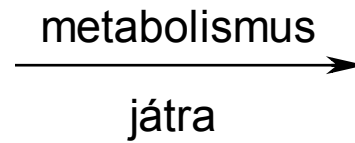
Nabumeton



4-(6-methoxy-2-naftyl)-butan-2-on

nabumeton

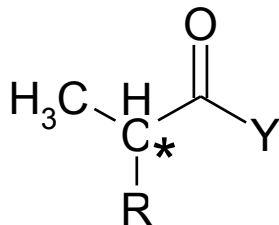
Relifex[®] tbl. obd.



(6-methoxy-2-naftyl)octová kyselina
(6MNA)

aktivní metabolit

Deriváty 2-aryl- a 2-heteroarylpropionových kyselin

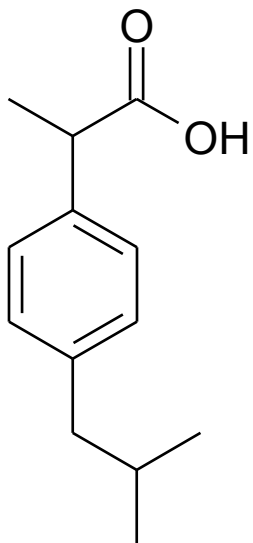


R = aryl nebo heteroaryl

Y = OH nebo NHOH

- chirální sloučeniny (S-enantiomer často mnohonásobně účinnější)
- analgetika, antirevmatika, antiflogistika, antipyretika
- inhibice COX1 i COX2; COX2 mírně převažuje
- NÚ jako u salicylátů; mírnější

Deriváty 2-arylpropionových kyselin



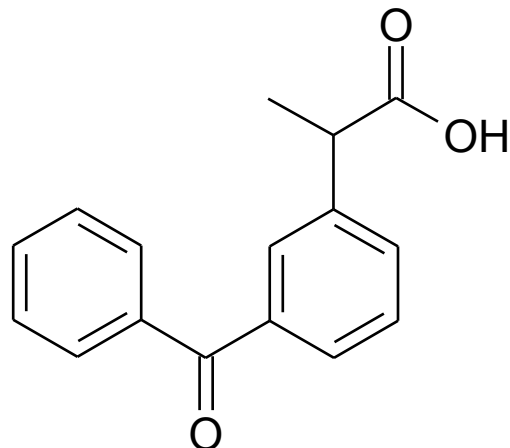
R = OH
(R,S)-2-(4-isobutylfenyl)-
propionová kys.

ibuprofen

Brufen[®], Ibalgin[®]

(S)- forma = dexibuprofen
Seractil[®]

R = NHOH **ibuproxam**

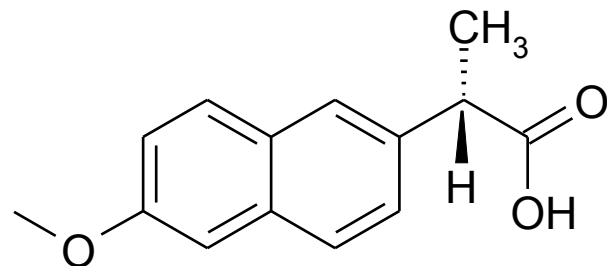


2-(3-benzoylfenyl)-
propionová kys.

ketoprofen

Fastum[®]Gel,
Kepabene[®]tbl

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

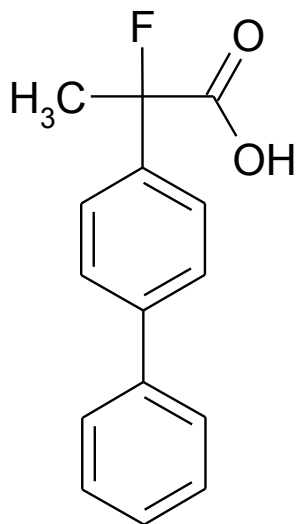


(+)-S-2-(6-methoxynaftalen-2-yl)-
propionová kys.

naproxen

Naprosyn[®],
Naprobene[®]

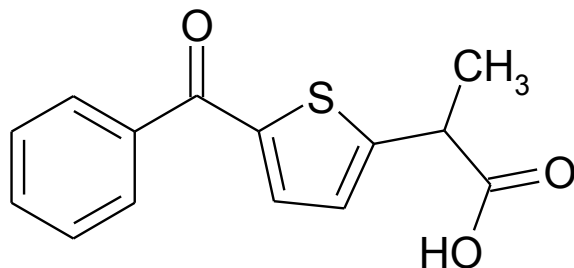
2-aryl- a 2-heteroarylpropionové kyseliny



2-bifenylyl-2-fluoropropionová kyselina

flurbiprofen

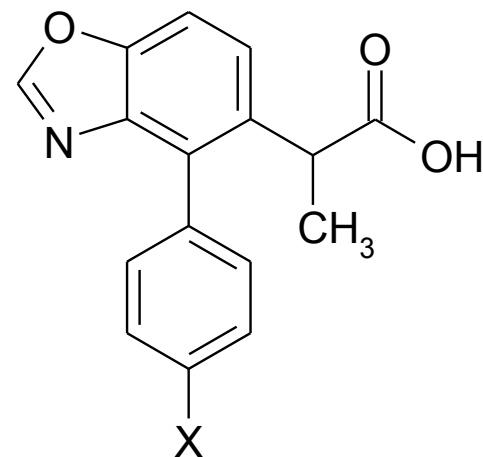
Ansaid[®], Flugalin[®]



2-(5-benzoylthiophen-2-yl)-propionová kys.

tiaprofenová kys.

Surgam[®], Thialgin[®]



X = Cl

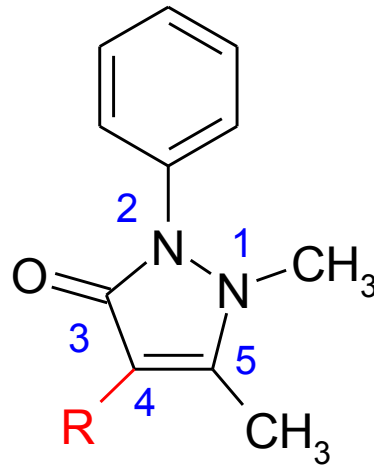
2-[4-(4-chlorfenyl)benzoxazol-5-yl]-propionová kys.

benoxaprofen

X = F

2-[4-(4-fluorfenyl)benzoxazol-5-yl]-propionová kys.

Deriváty 1,2-dihydropyrazol-3-onu



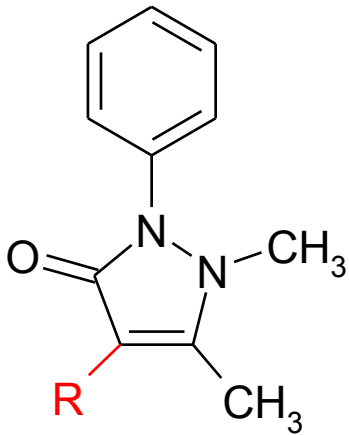
4-substituované-1,5-dimethyl-2-fenyl-1,2-dihydro-3H-pyrazol-3-ony

- inhibují COX1 i COX2
- analgetika, antipyretika
- použití dnes zpravidla ve směsích

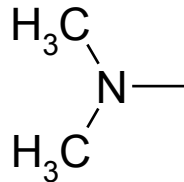
Deriváty 1,2-dihydropyrazol-3-onu

R = H

fenazon, syn. antipyrin
obsolentní



R =

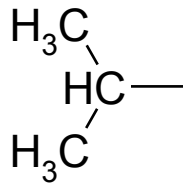


aminofenazon, syn. amidopyrin

Dinyl® (+ fenacetin, kofein, butobarbital,
allobarbital)

Eunalgit® inj. (+ allobarbital)

R =

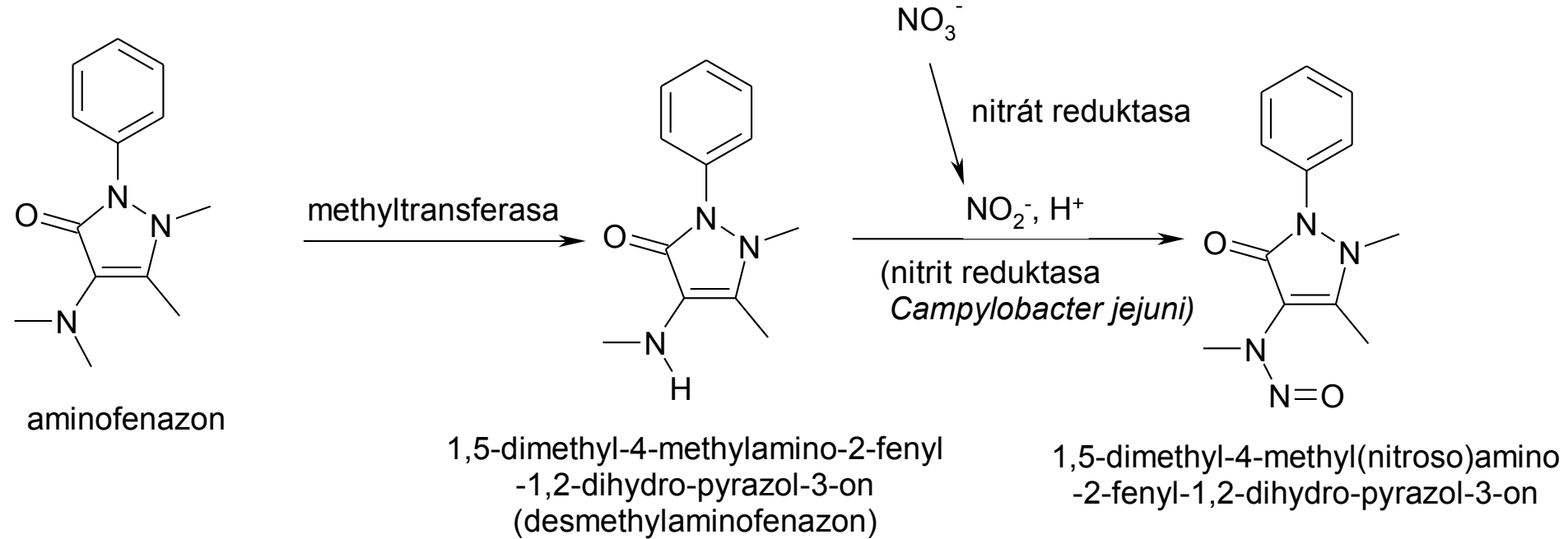


propyfenazon

Valetol®, Saridon® (+ paracetamol, kofein)

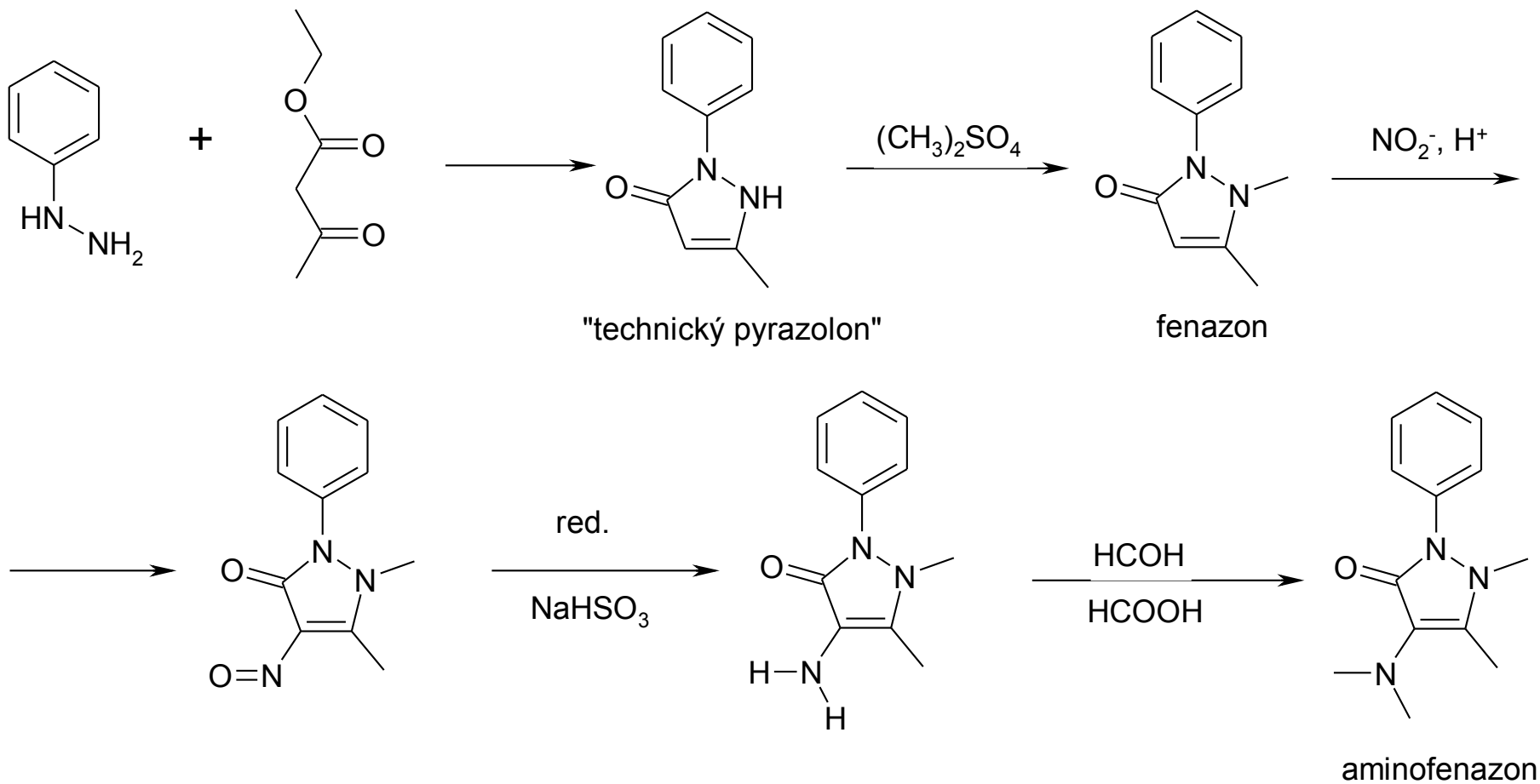
Spasmoveralgin neo® (+papaverin,
fenobarbital, efedrin, kodein, methylatropin)

Kancerogenita aminofenazonu

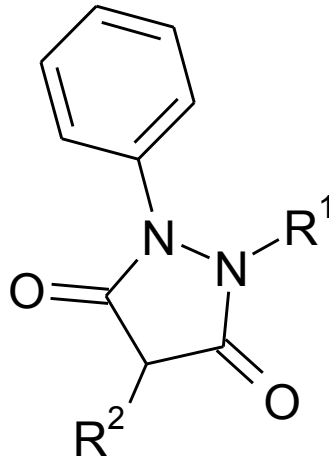


KANCEROGENNÍ

Syntéza aminofenazonu

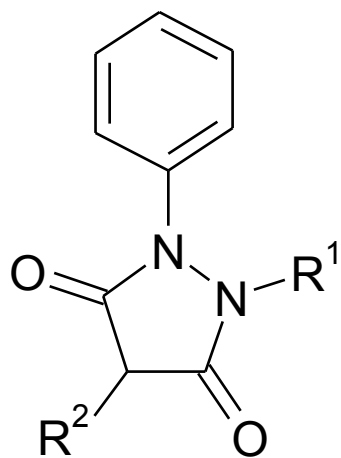


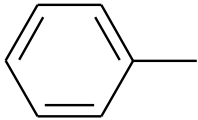
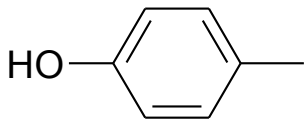
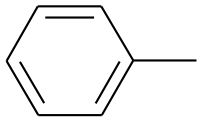
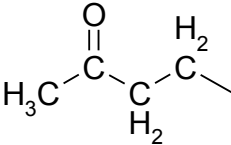
Deriváty pyrazolidin-3,5-dionu



- antiflogistika, analgetika, antipyretika
- inhibují COX1 i COX2
- v některých zemích vyhrazeny pro *M. Bechtěrev*
- v ČR jen externa a veterinaria
- NÚ: GIT intolerance, průjem, exacerbace vředové choroby a gastrointestinální krvácení, kožní eflorescence, cefalea. retence Na⁺ a H₂O, ↓ renálních funkcí, poruchy krvetvorby.

Deriváty pyrazolidin-3,5-dionu

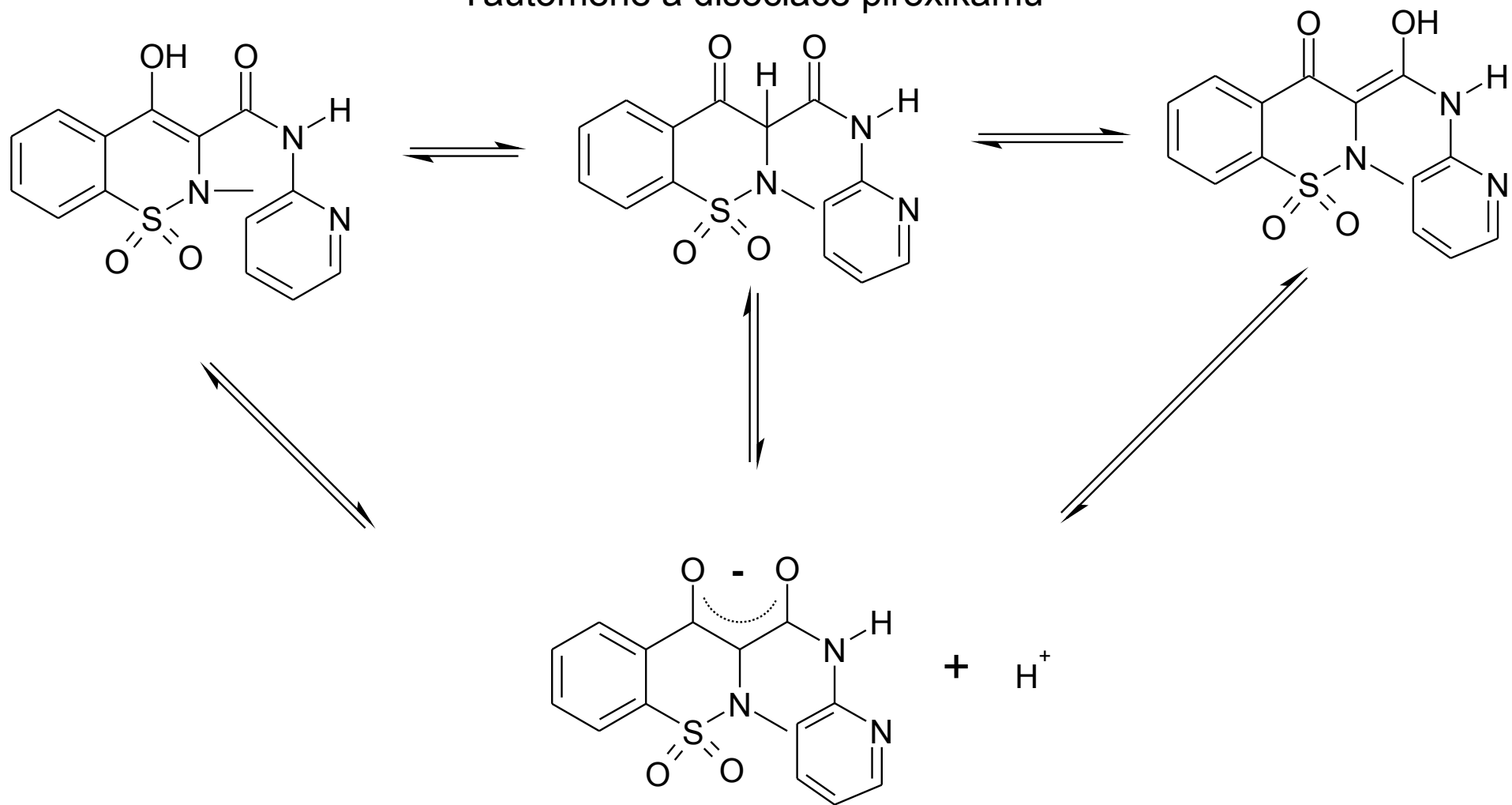


R ¹	R ²	Chemický název	INN / přípravky
	C ₄ H ₉ -	4-butyl-1,2-difenylnpyrazolidin-3,5-dion	fenylbutazon Butasan® a.u.v
	C ₄ H ₉ -	4-butyl-1-(4-hydroxyfenyl)-2-fenylnpyrazolidin-3,5-dion	oxyfenbutazon Tanderil® sup. <i>reg. v SR</i>
		1,2-difenyln-4-(4-oxobutyl)pyrazolidin-3,5-dion	kebuzon Ketazon® ung
H-	C ₄ H ₉ -	4-butyl-1-fenylnpyrazolidin-3,5-dion	mefebutazon

Heterocyklické enoly-“ketoenolické kyseliny“ -oxikamy

- obsahují „ketoenolický“ strukturní fragment

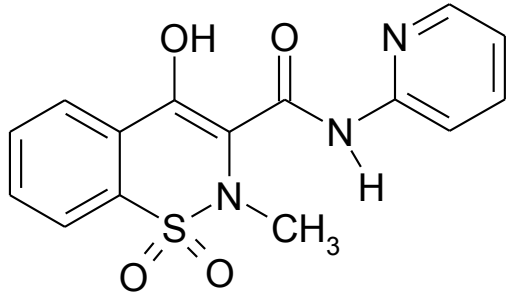
Tautomerie a disociace piroxikamu



Oxikamy

- kyselý charakter
- inhibují COX1 i COX2 (meloxikam asi 3x více COX2)
- účinky: antiflogistické, analgetické, antipyretické
- použití: artróza, revmatoidní artritida ...

Oxikamy

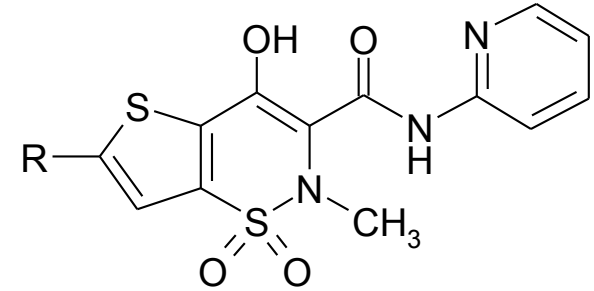


4-hydroxy-2-methyl-N-pyridin-2-yl-2H-1,2-benzothiazin-3-karboxamid-1,1-dioxid

piroxikam

Arthremin[®], Feldene[®],

Flamexin[®] - kombimace s
β-cyklodextrinem



R = H

4-hydroxy-2-methyl-N-pyridin-2-yl-2H-thieno[2,3-e][1,2]thiazin-3-carboxamid-1,1-dioxid

tenoxicam

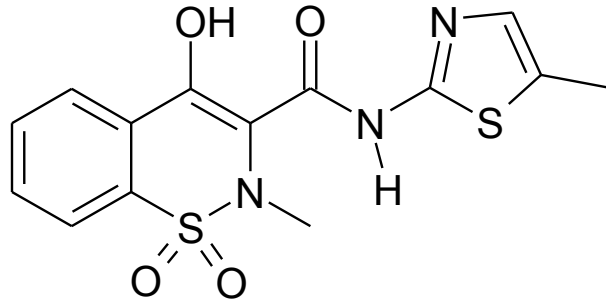
R = Cl

6-chloro-4-hydroxy-2-methyl-N-pyridin-2-yl-2H-thieno[2,3-e][1,2]thiazin-3-carboxamid-1,1-dioxid

lornoxikam

Xefo[®]

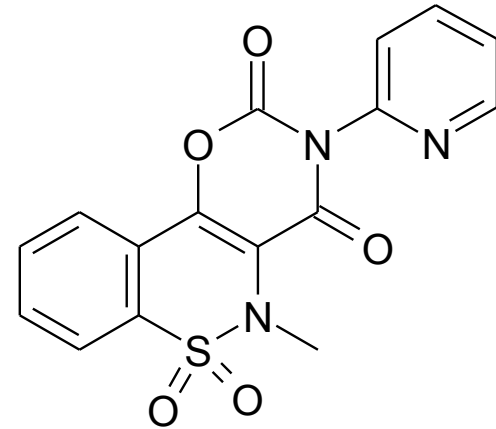
Oxikamy



4-hydroxy-2-methyl-N-(5-methyl-1,3-thiazol-2-yl)-2H-1,2-benzothiazin-3-karboxamid-1,1-dioxid

meloxicam

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

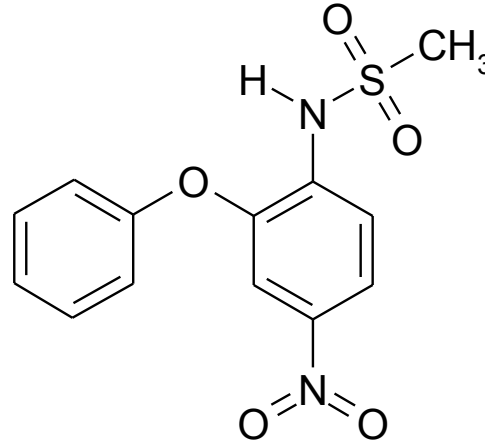


5-methyl-3-pyridin-2-yl-2H,5H-[1,3]oxazino[5,6-c][1,2]benzothiazin-2,4(3H)-dion-6,6-dioxid

droxicam

Selektivní inhibitory COX2

Nimesulid



N-(2-fenoxy-4-nitrofenyl)methansulfonamid
2'-fenoxy-4'-nitromethansulfonanilid
4'-**nitro-2'-phenoxy**methanesulfonanilide

nimesulid

Coxtral[®], Aulin[®], Mesulid[®]

Nimesulid

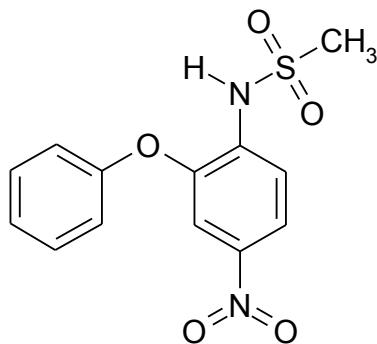
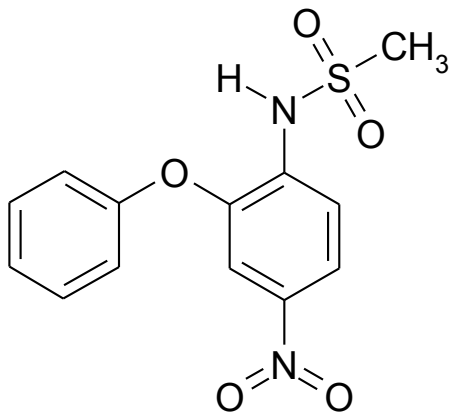
- inhibuje COX2 4x více než COX1 \Rightarrow \downarrow NÚ na GIT a trombocyty

- antirevmatikum, antiartrotikum, analgetikum

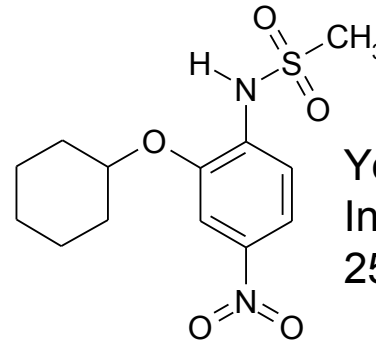
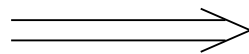
Aulin[®], Coxtral[®], Mesulid[®]

„Analogie radilálová“

- záměna benzen \Rightarrow cyklohexan



nimesulid



N-[2-(cyklohexyloxy)-4-nitrofenyl]methansulfonamid
NS-398

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

Selektivita
COX2:COX1

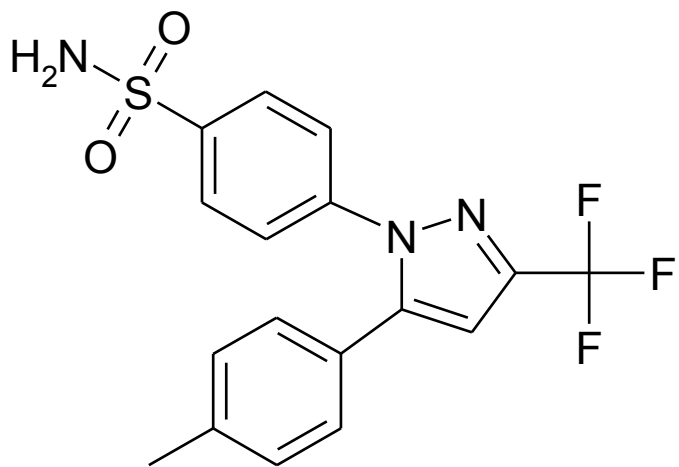
4 : 1

30 : 1

Specifické inhibitory COX2

Koxiby

- aromatické sulfonamidy nebo sulfony (výjimka: lumirakoxib)
- vysoká selektivita vůči COX2 \Rightarrow NÚ na GIT a trombocyty potlačeny
- použití: reumatoidní artritida, osteoartritida, primární dysmenorrhea
- též neurodegen. onemocnění (Alzheimer) – kolokalizace cykinů D_1 a E_1 s COX2 v neuronech CNS
- NÚ: \uparrow rizika náhlých kardiovaskulárních příhod (\Leftarrow \downarrow produkce prostacyklinu inhibujícího agregaci trombocytů, neovlivňují produkci TXA aktivujícího agregaci trombocytů), poškození kůže (hlavně valdekokoxib)



4-[5-(4-methylfenyl)-3-(trifluormethyl)-1H-pyrazol-1-yl]benzenesulfonamid

celecoxib

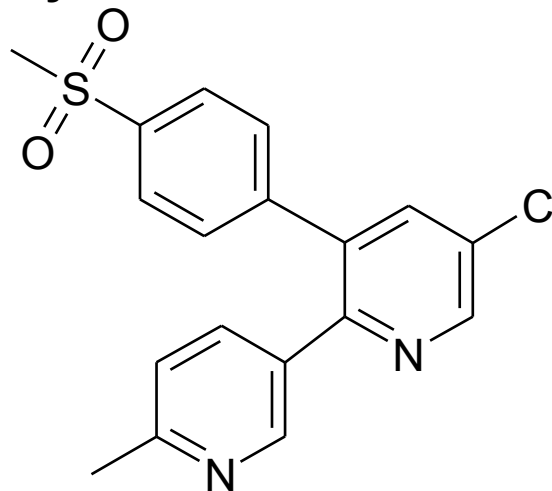
Celebrex[®]

Onsenal[®] – „orphan drug“ pouze pro familiální adematosní polypózu (FAP)

Selektivita
COX2 : COX1

30 : 1

Koxiby



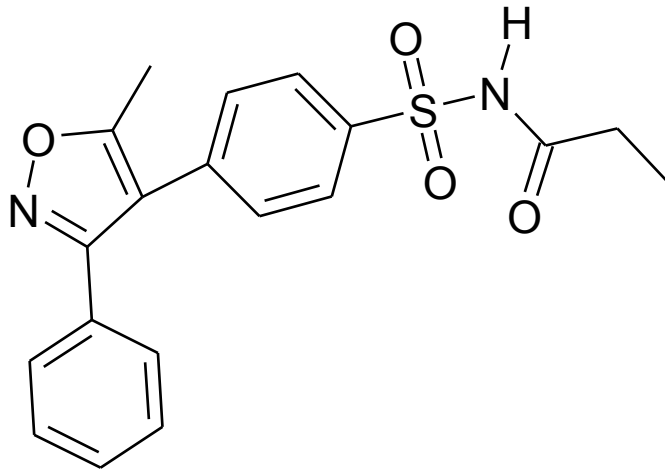
5-chloro-6'-methyl-3-[4-(methylsulfonyl)fenyl]-2,3'-bipyridin

etorikoxib

Arcoxia[®]

340 : 1

Koxiby



N-[[4-(5-methyl-3-fenylisoxazol-4-yl)
fenyl]sulfonyl]propanamid

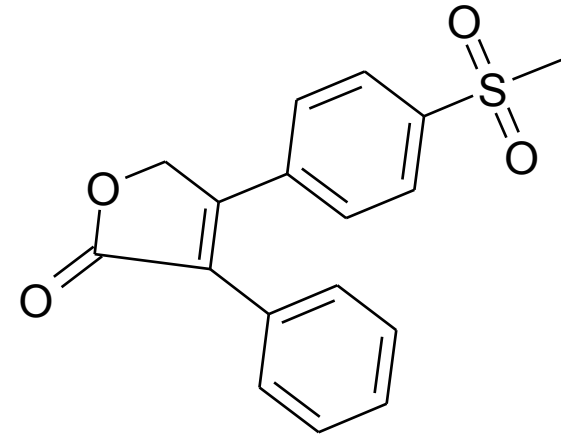
parecoxib

- alergické kožní rce, zejména u přecitlivělých na sulfonamidy

Dynastat[®] - jen pro postoperační bolesti

Selektivita

COX2 : COX1



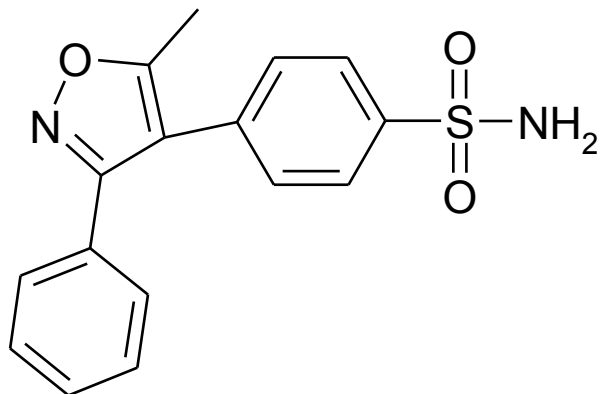
4-[4-(methylsulfonyl)fenyl]-
3-fenylfuran-2(5H)-on

rofecoxib

~~Ceeoxx[®], Vioxx[®]~~

staženy pro závažné
kardiovaskulární nežádoucí
účinky

270 : 1



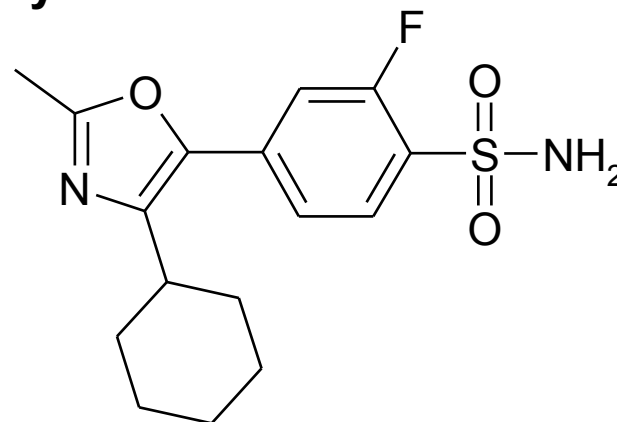
4-(5-methyl-3-fenylisoxazol-4-yl)benzensulfonamid

valdecoxib

Bextra®

stažen

Koxiby



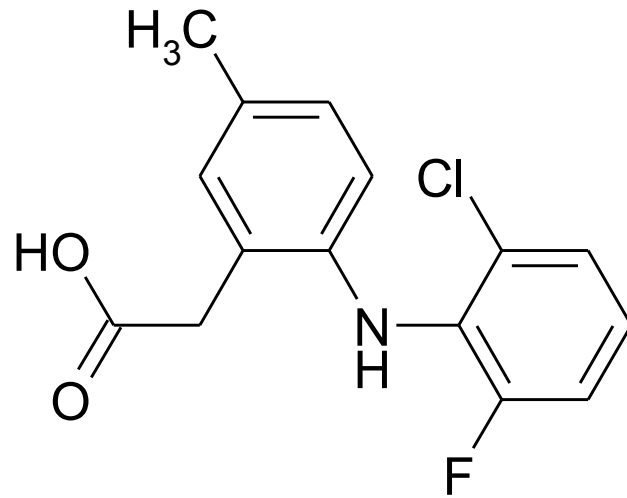
4-(4-cyclohexyl-2-methyl-1,3-oxazol-5-yl)-2-fluorobenzensulfonamid

tilmakoxib

Selektivita

COX2 : COX1 60 : 1

Koxiby



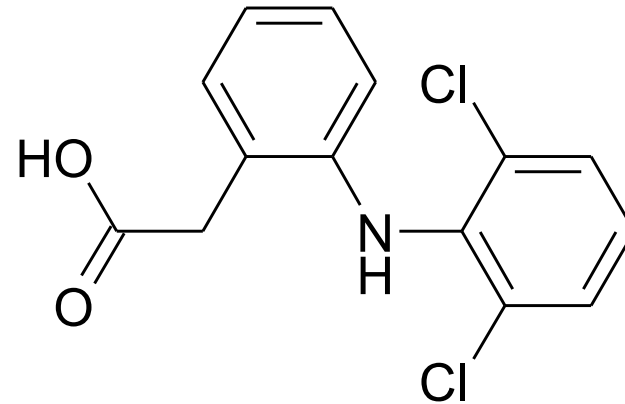
2-(2-fluor-6-chlorfenylamino)-5-methylfenyloctová kys

lumirakoxib

Prexige®

stažen

Pro srovnání:



diklofenak