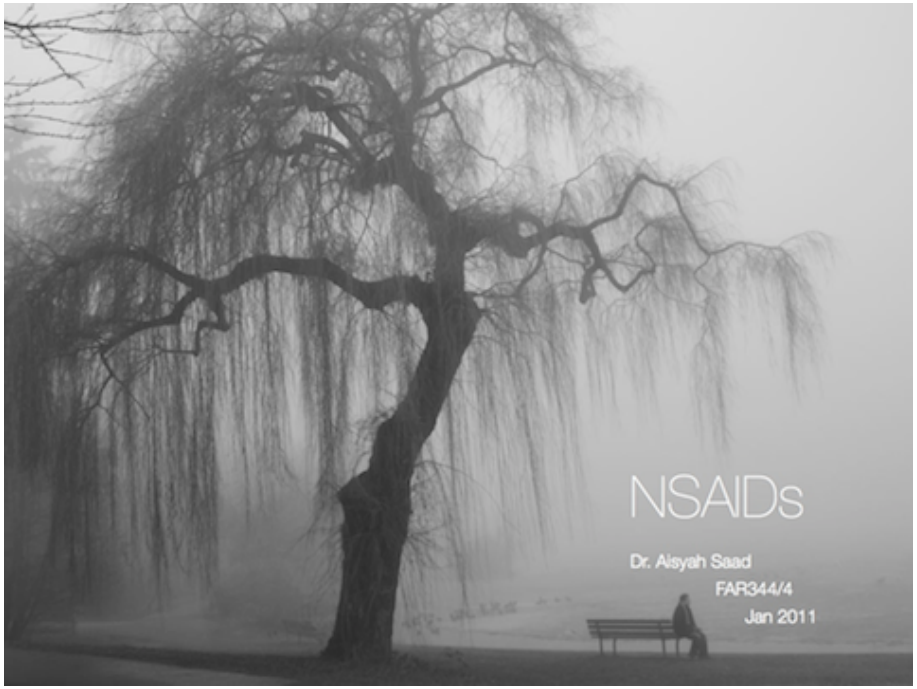
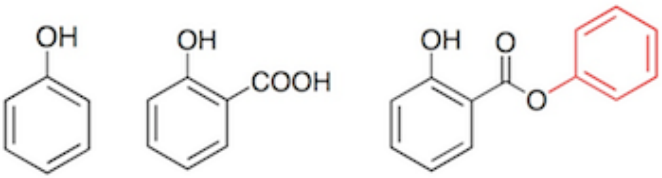


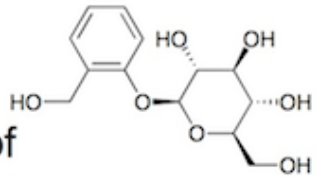


Phenol
1840's

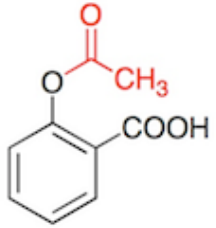
Salicylic acid
1870's

Phenyl salicylic acid
1883

The birth of Aspirin



Salicin

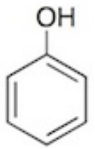


Acetylsalicylic acid
A~"Acetyl"; "spirin"~*Spirea ulmaria*

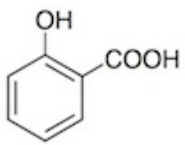
A product of steam-distillation of coal tar

Problem with phenol: Corrosive for external, let alone internal use...

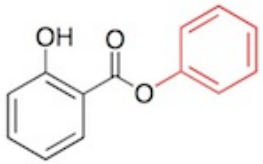
Problem with SA: Bitter thus, unpalatable



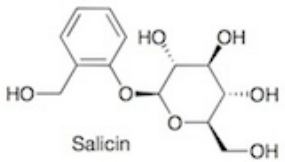
Phenol
1840's
As clear oil



Salicylic acid (SA)
1870's
Less corrosive than phenol

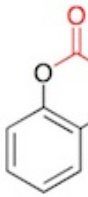


Phenyl salicylic acid
1883



Salicin

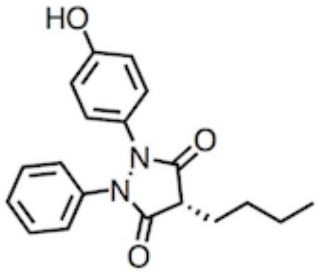
Problem PhSA: inconsistent therapeutic response



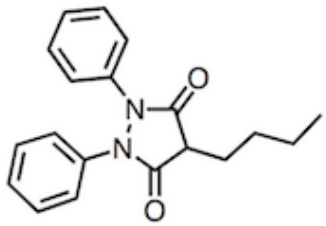
Acetylsalicylic acid
1900, Bayer

A ~"Acetyl";
"spirin"~ *Spirea ulmaria*

Updated on 19 March 2013, Dr Aisyah



Oxyphenbutazone



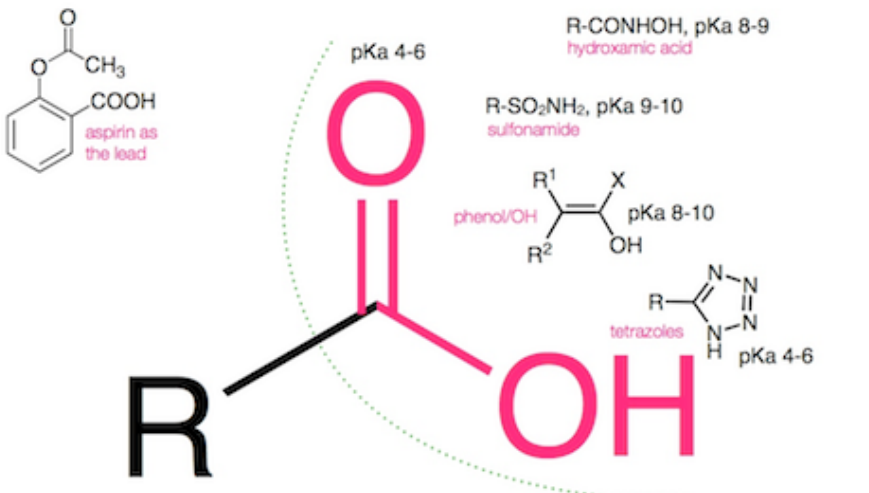
Phenylbutazone

Pyrazolone

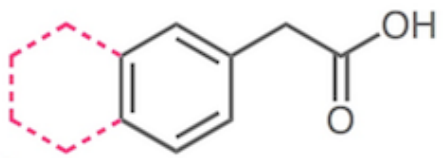
Accidental discovery

Discovered by John Burns who coined "NSAID"

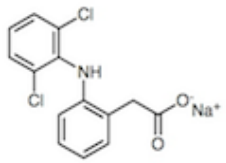
Indicated for arthritis



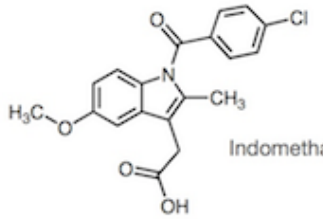
Essential for analgesic activity



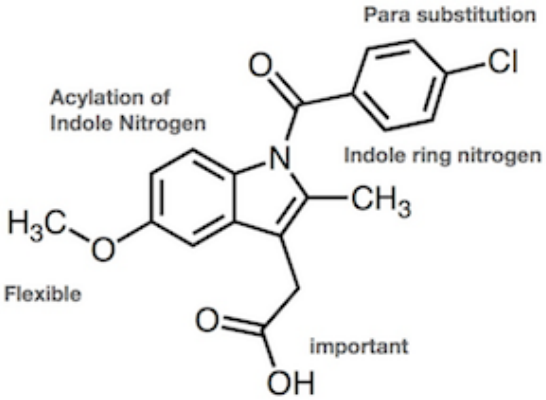
Arylacetic acids
or Heteroarylacetic acids



Diclofenac



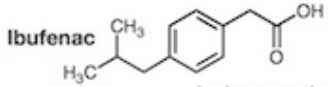
Indomethacin



Indomethacin

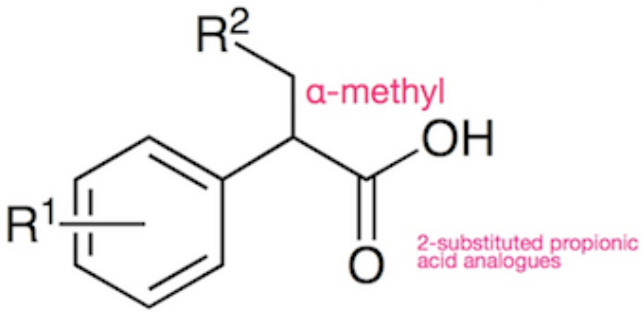
Arylproponic acids

Profens



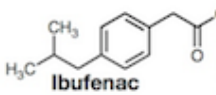
lacks α-methyl

less potent; more hepatotoxic than ibuprofen



2-substituted propionic acid analogues

Arylproponic acids



Ibufenac

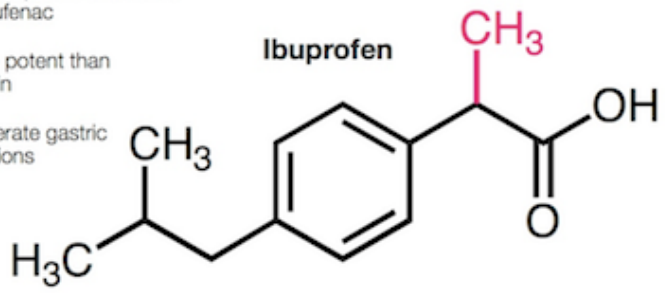
lacks α-methyl
less potent but more hepatotoxic than ibuprofen

an acceptable alternative to ibufenac

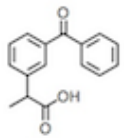
more potent than aspirin

moderate gastric irritations

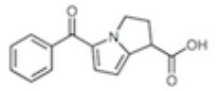
Ibuprofen



Safe, effective anti-inflammatory agent with analgesic and antipyretic properties



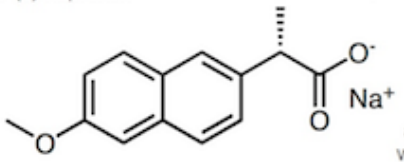
Ketoprofen



Ketorolac

More potent is *S*-(+)-naproxen

Naproxen

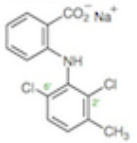


Retention of activity if swapped with -CO_2Me, -CHO or -CH_2OH

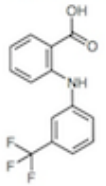
small lipophilic group
Cl-, CH_3S-, CHF_2O-
Larger groups result in less active analogues
Optimal: CH_3O-

Anthranilates
Fenamic acids

Meclofenamate Sodium

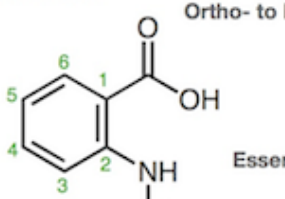


Flufenamic acid

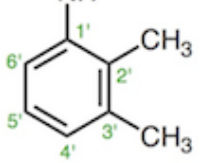


Mefenamic acid

Ortho- to N-aryl



Essential



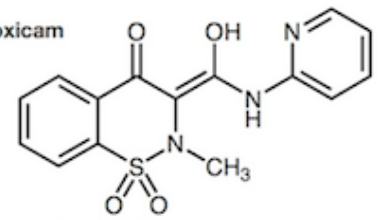
Monosubstituted 3'>2'>>4' activity

2',3'-Disubstitution of N-aryl ring renders it non-coplanar.

Oxicams

Aryl or heteroaryl substituent
Aliphatic groups diminishes anti-inflammatory activity

Piroxicam



Quite acidic compound
pKa 4-6

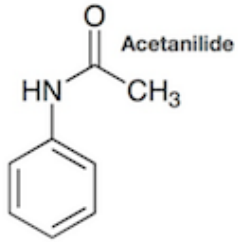
200x >> aspirin; similar potency to indomethacin

Potent but well-tolerated NSAIDs without the carboxylic acid moiety

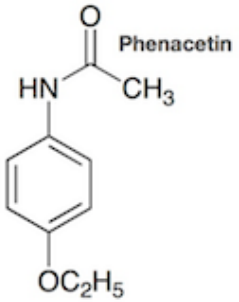
Para-Aminophenol

Unlike NSAIDs...

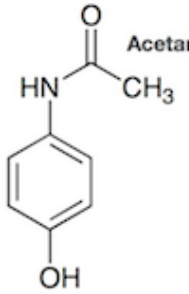
these have analgesic and antipyretic effects, but with little anti-inflammatory action.



withdrawn: methemoglobinemia & jaundice

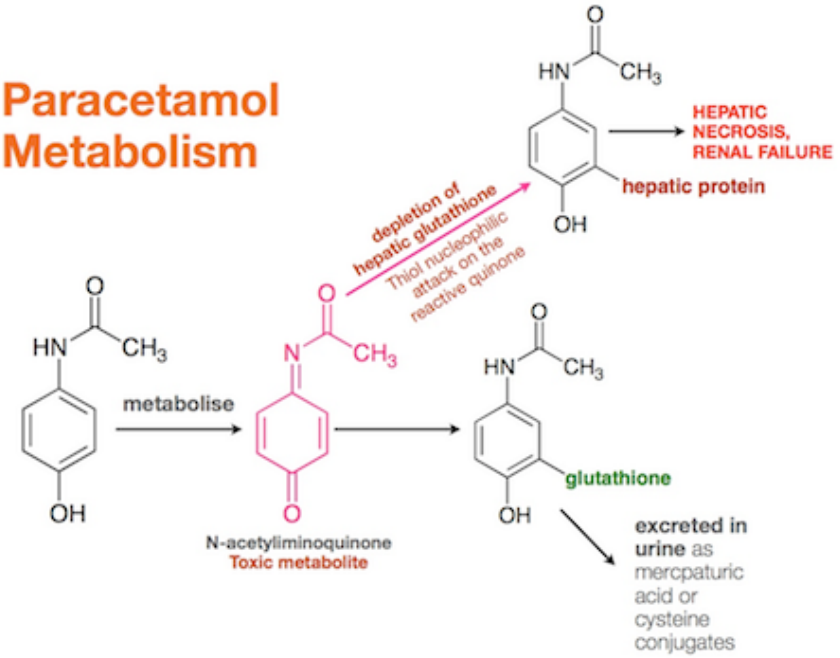


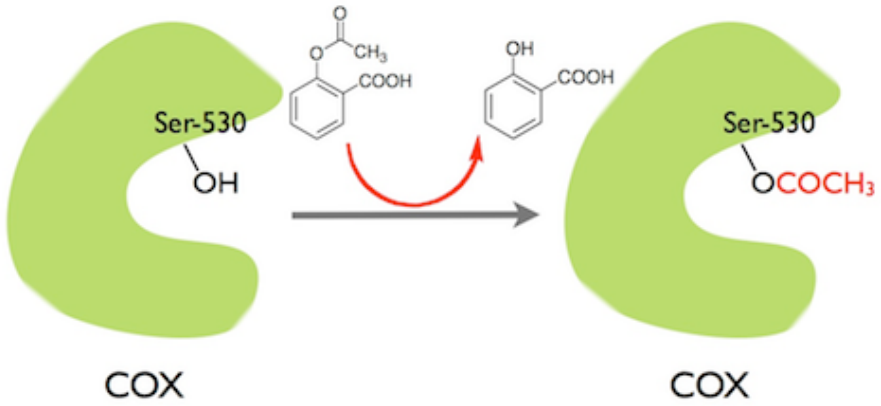
nephrotoxicity reports led to the end of its use in 1960s



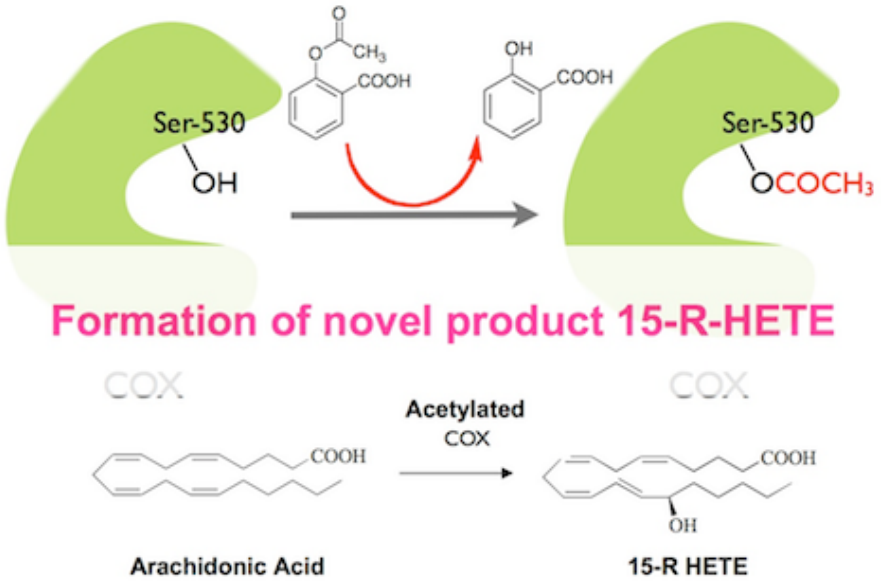
became popular in 1950s when metabolites are known i.e. acetanilide & phenacetin

Paracetamol Metabolism

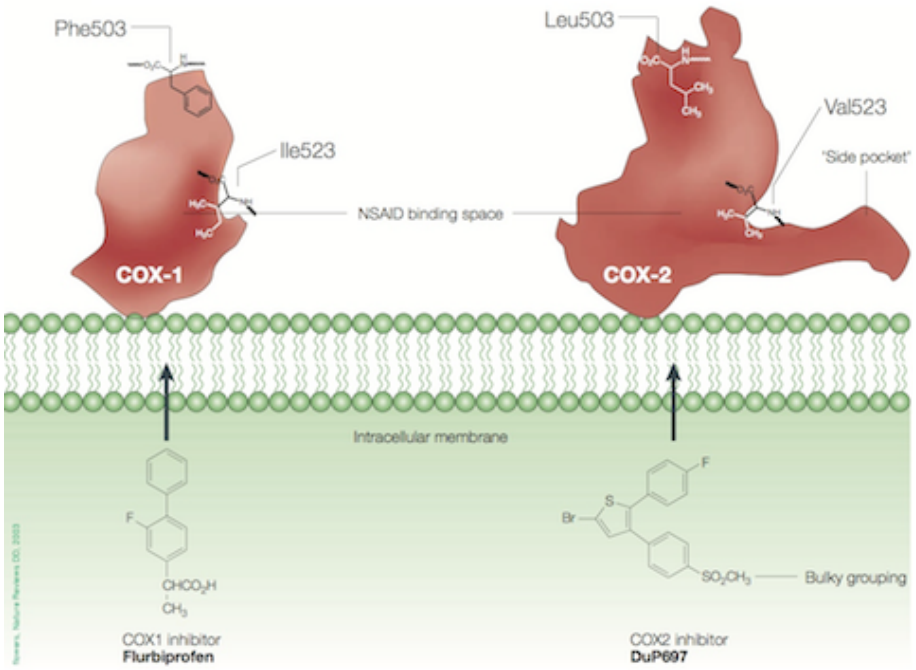


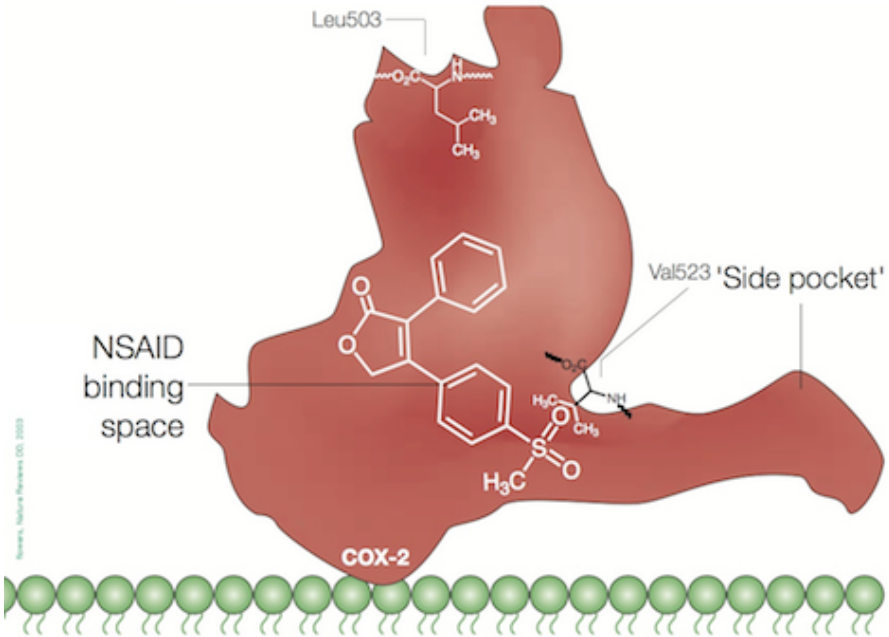


Acetylation of COX at Ser-530: Steric hindrance

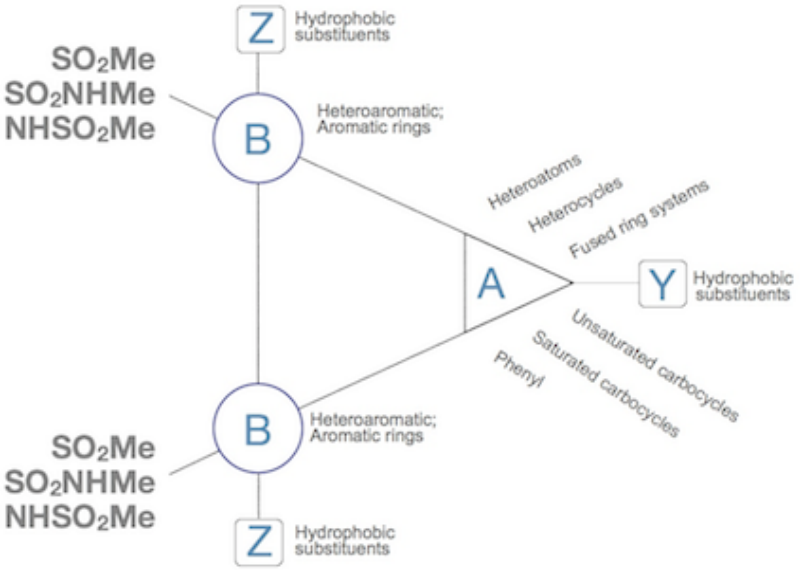


Selective COX-2 inhibitors

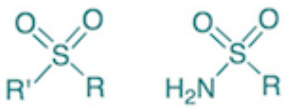


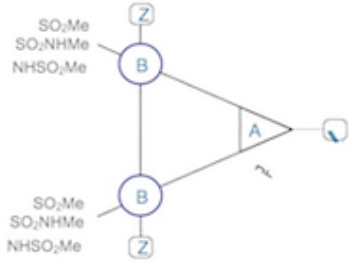


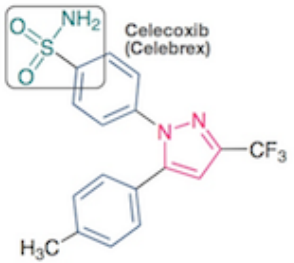
Pharmacophores of COX-2 inhibitors

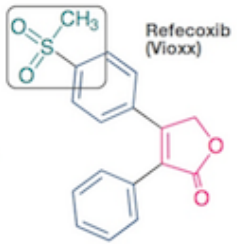


Oxidation states of Sulfur is important for selectivity towards COX-2









If VIOXX is taken for 18 months...

5X higher risk of MI than Naproxen