Medicinal Chemistry - II

Nonsteroidal Anti-Inflammatory Drugs

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Nonsteroidal Anti-Inflammatory Drugs

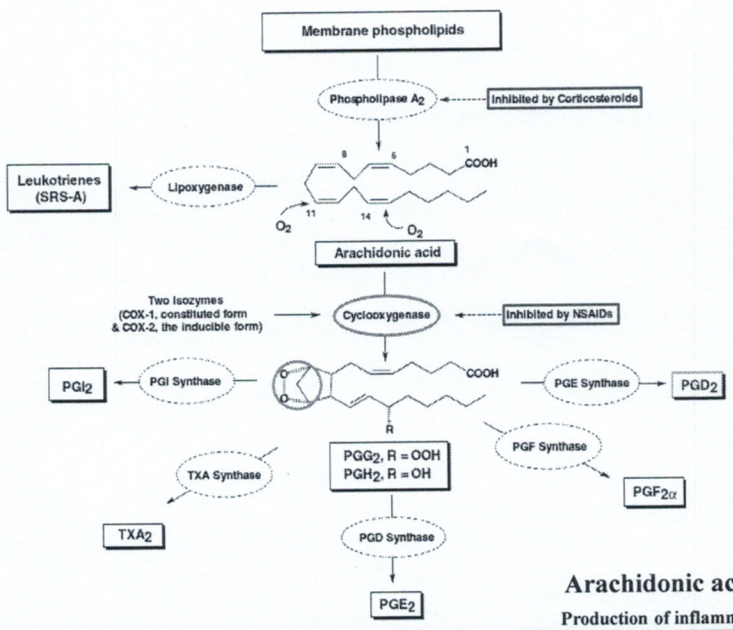
- NSAIDs
- Antipyretic, analgesic and anti-inflammatory
- Prototype is acetylsalicylic acid, aspirin
- Widely used drugs
- Prescription and nonprescription drugs
- Treatment of rheumatic arthritis and other degenerative inflammatory joint diseases
- NSAIDs effective in relieving mild to moderate pains and inflammation
- NSAIDs inhibit prostaglandin biosynthesis by cyclo-oxygenase (COX) enzyme inhibition
- COX inhibition have a profound effect on the reduction of inflammation
- Conventional NSAIDs therapeutic effect by inhibiting the two isoforms of cyclooxygenase: COX-1 and COX-2, but with varying degrees of selectivity
- Side effects including GI irritation and bleeding, platelet dysfunction, kidney damage and bronchospasm

Prostaglandins

- PGs
- Highly active endogenous mediators
- Exert diverse actions: depending on the prostaglandin and the tissue
- Play critical roles in tissue homeostasis: cytoprotective role in the kidney and gastric mucosa
- Implicated in the inflammatory response and in sensitizing pain receptors to the action of other mediators
- Produced at the site of inflammation, during acute and chronic inflammatory illness and mediate many of the symptoms of inflammation such as edema and pain
- Prostaglandins biosynthesis is enhanced by many physical, chemical and hormonal stimuli
- Prostaglandins are biosynthesized from Arachidonic acid
- Cyclooxygenase enzyme:

  Rate-limiting enzyme in PGs biosynthesis

Prostaglandins



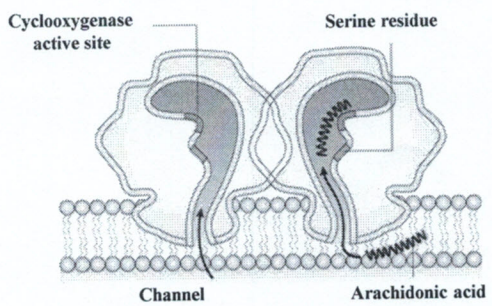
Arachidonic acid pathway

Production of inflammatory mediators

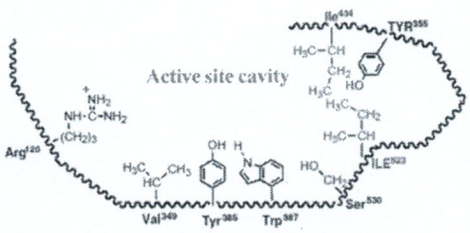
Cyclooxygenases

- Three isoforms: COX-1, COX-2 and COX-3
- COX-1 and COX-2:
- COX-1 is expressed in all tissues
- COX-1 is expressed in the stomach but not COX-2
- COX-2 is expressed notably in the brain and kidney
- Major difference in physiologic function rather than in structure
- NSAIDs benefit/risk profile is reflected by their COX selectivity
- Share high degree of sequence identity and very similar active site topography
- Active site is buried deep within the protein with a tunnel guiding arachidonic acid out of the membrane and into the enzyme for processing
- COX-1 and COX-2 are almost identical in length:
  - ✓ COX-2 lacks a sequence of 17 amino acids from the N-terminus but contains a sequence of 18 amino acids at the C-terminus
  - ✓ Similar binding site residues essential to activity, only different numbering
  - ✓ The isoleucine at positions 434 and 523 in COX-1 is exchanged for valine in COX-2
- Binding pocket of COX-2 is 20% to 25% larger than the COX-1 binding site

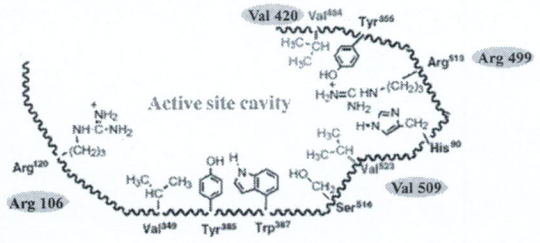
Cyclooxygenases



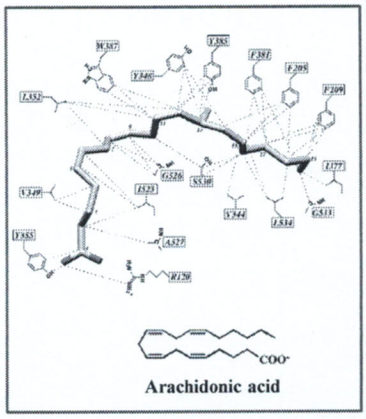
COX-1 and COX-2



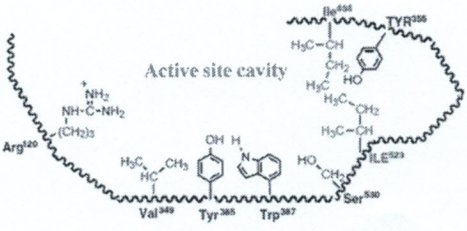
COX-1



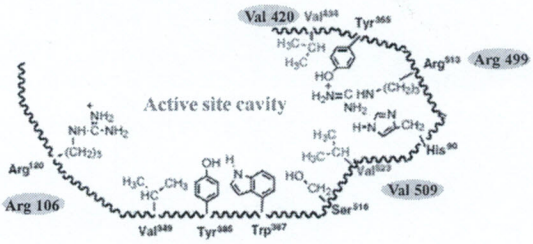
COX-2



COX-1 and COX-2

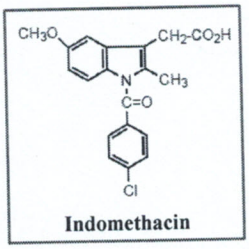


COX-1

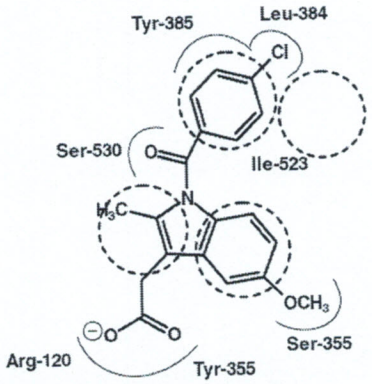


COX-2

NSAIDs Binding in Cyclooxygenases Binding Site

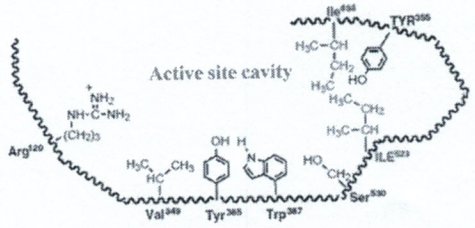


Indomethacin

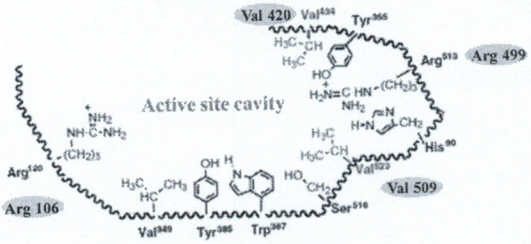


Hypothetical binding model of Indomethacin (conventional NSAID) to COX-1

COX-1 and COX-2

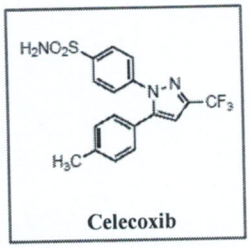


COX-1

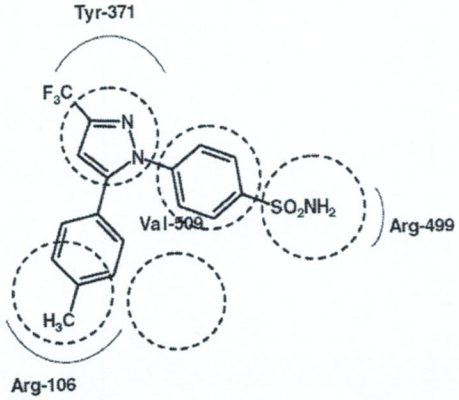


COX-2

NSAIDs Binding in Cyclooxygenases Binding Site



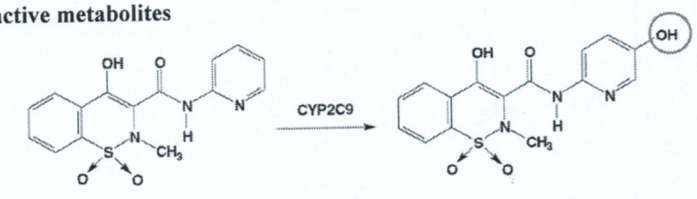
Celecoxib



Hypothetical binding model of Celecoxib (selective COX-2 inhibitor) to COX-2

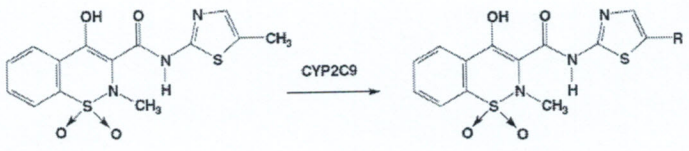
NSAIDs Binding in Cyclooxygenases Binding Site

- **Piroxicam and meloxicam nearly identical structural features**
- **Nine-fold difference in selectivity for meloxicam to COX-2 isozyme and an even larger difference in their relative risks for GI complications**
- **The drastic differences in their COX selectivity could be attributed to the involvement their active metabolites**



Piroxicam

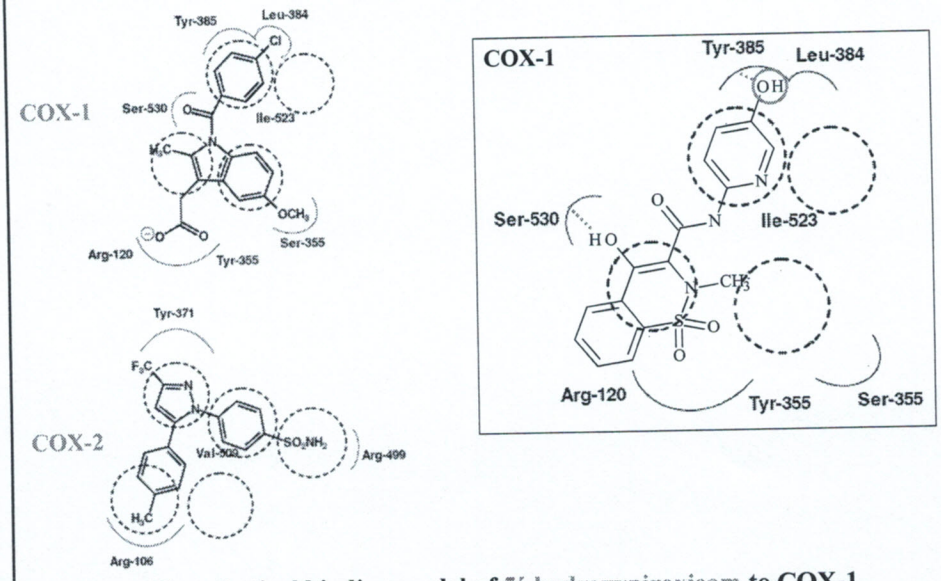
5'-Hydroxypiroxicam



Meloxicam

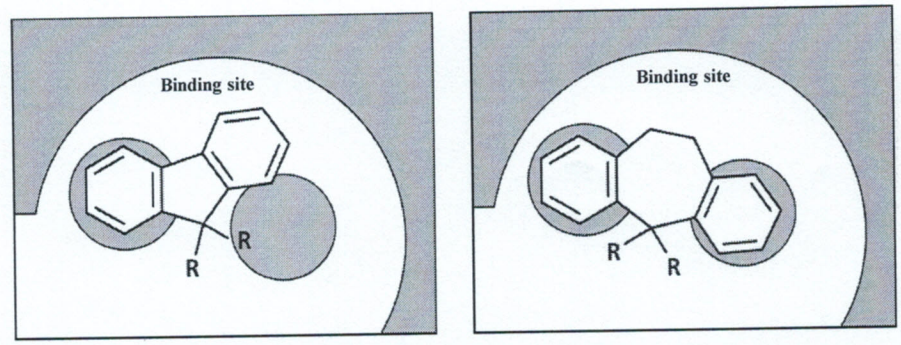
5'-Hydroxymethylmeloxicam, R = CH_2OH,
5'-Carboxymeloxicam, R = COOH

NSAIDs Binding in Cyclooxygenases Binding Site

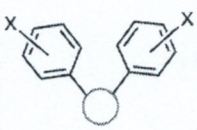


Hypothetical binding model of 5′-hydroxypiroxicam to COX-1

NSAIDs Binding in Cyclooxygenases Binding Site



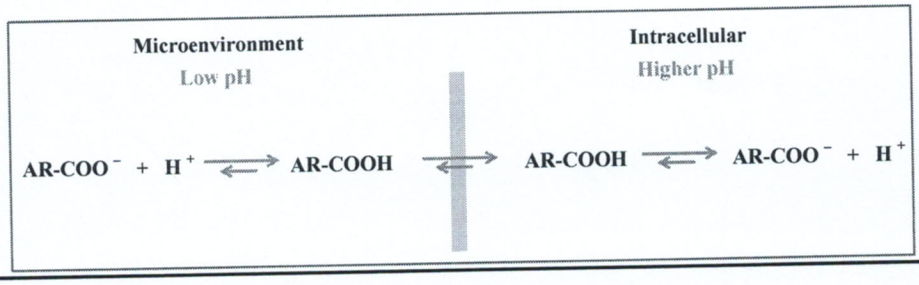
Hydrophobic binding regions



General structure for NSAIDs

NSAIDs GI Side Effects

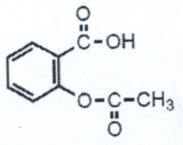
- Gastrointestinal (GI) bleeding:
  1. Inhibition of COX enzymes and biosynthesis of cytoprotective PGs
  2. Direct effects, local irritation to the GI mucosa:
     - ✓ NSAIDs are acidic substances, direct acid damage:
     - ✓ Decrease surface hydrophobicity of the mucus gel layer with subsequent loss of barrier properties
     - ✓ Increase in mucosal permeability
     - ✓ Back diffusion of acid
     - ✓ Ion trapping into the mucosal epithelium



Salicylates

➢ Aspirin

- Acetylsalicylic acid
- Antipyretic, analgesic and anti-inflamatory
- Inhibit prostaglandin biosynthesis by COX inhibition
- Gastric irritation and ulceration
- Only NSAID to form covalent bond: acetylating Ser530 (Ser516 in COX-2)
- 10 to 100 times more potent against COX-1 than against COX-2, highest selectivity toward the COX-1 among all conventional NSAIDs, especially platelets COX-1
- 50% of oral aspirin dose is rapidly deacetylated to form salicylic acid before reaching the general circulation
- Salicylic acid have comparable *in vivo* antipyretic and analgesic properties to aspirin but is a very weak inhibitor of cyclooxygenases
- Pharmacological actions are attributed to both the aspirin and salicylic acid

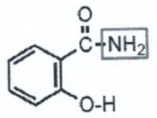


Aspirin

Salicylates

➢ Salicylamide

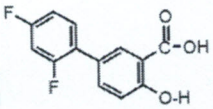
- Isostere of salicylic acid, OH replaced by NH2
- Non acidic amide which is stable in aqueous preparations
- Does not cause GI tract ulceration and is absorbed only in intestine
- Greater CNS penetration
- Similar analgesic and antipyretic effect to aspirin
- No anti-inflammaatory actions
- Possibly works through a different mechanism



Salicylamide

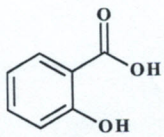
➢ Diflunisal

- Increased duration of action, 3 - 4 times longer than aspirin
- The increase in potency is attributed to an increase in binding to the receptor due to the second aromatic ring
- The proximity of the two phenyl rings, steric hindrance and thus keep the rings out of the same plane



Diflunisal

SAR of Salicylates

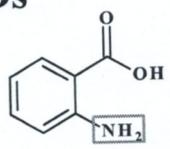


- Benzoic acid itself has only weak activity
- Simplest active compound is the salicylic acid
- Carboxylic group is necessary for activity and the hydroxyl group must be *ortho*, *meta* or *para* hydroxyl group to the carboxyl group abolishes activity
- Substitution on either the carboxyl or phenolic hydroxyl groups can affect potency and toxicity
- Introduction of electronegative groups and lipophilic groups increases anti-inflammatory activity and toxicity
- Side effects of aspirin is associated with the carboxylic acid
- Reducing the acidity of this group (e.g., salicylamide) maintains the analgesic actions of salicylic acid derivatives but eliminates the anti-inflammatory properties
- Substitution of halogen atoms (F, Cl, Br) on the aromatic ring enhances potency and toxicity
- Substitution of aromatic rings at the 5-position of salicylic acid increases anti-inflammatory activity (e.g., diflunisal)

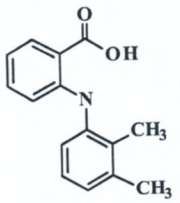
N-arylanthranilic Acid NSAIDs

- Fenemates: derivatives of anthranilic acid, salicylic acid isoster
- The most potent analogs are di-substituted at 2' and 3'
- *Ortho* substituents on the second ring keep the aromatic rings out of coplanarity
- The NH-moiety is essential for activity:

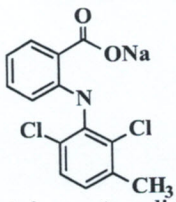
  replacement with O, CH2, S, SO2, N-CH3, or N-COCH3 significantly reduces activity
- The position, rather than the nature, of the acidic function is critical for activity:
  - ✓ *meta*- and *para*-aminobenzoic acid analogs are not active
  - ✓ replacement of the carboxylic acid with isosteric acid: little effect on activity
- Mefenamic acid: 2' methyl
- Meclofenamate sodium: 2' and 3'chlorine atoms: correct conformation, 25 times more potent
- Meclofenamate dose is 25 mg and Mefenamic acid dose is 250 mg
- No advantage over the salicylates with respect to analgesic or anti-inflammatory actions



Anthranilic acid



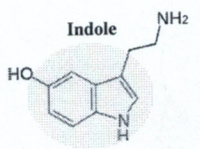
Mefenamic acid



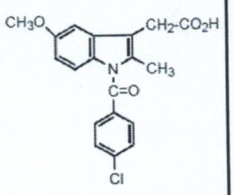
Meclofenamate sodium

Arylalkanoic Acid NSAIDs

- Largest group of NSAIDs
- General chemical structure
- Indomethacin synthesized in mid-1960s, investigate the anti-inflammatory activity of 350 indole acetic acid derivatives, related structurally to serotonin, potential mediator of inflammation
- More interest in the development of other aryl and heteroaryl acetic acid and propionic acid derivatives, arylalkanoic acids
- Introduction of ibuprofen in the 1970s followed by fenoprofe calcium, naproxen, and tolmetin
- Sulindac, indomethacin analog introduced in the late 1970s
- Ketoprofen, flurbiprofen, suprofen, and diclofenac sodium followed in the 1980s
- In the 1990s produced ketorolac, etodolac and nabumetone
- From 1997 to 2000 the development of selective COX-2 inhibitors, celecoxib, rofecoxib and valdecoxib

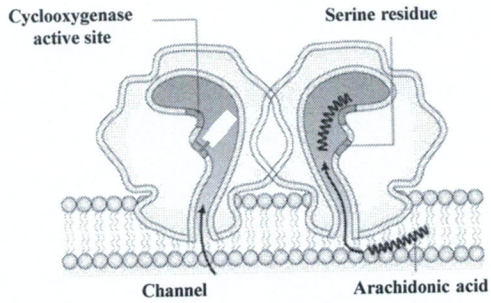


Serotonin

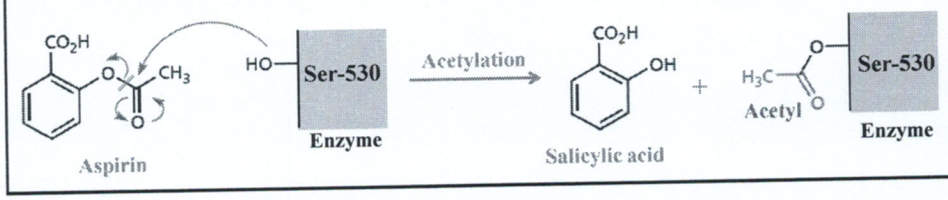


Indomethacin

Salicylates



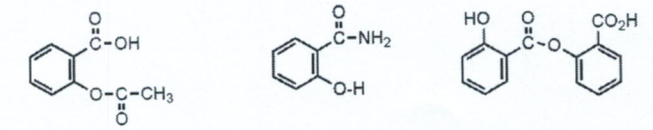
Ionic attraction between the carboxylate anion of aspirin and the arginine cation of Arg-120 (Arg-106 in COX-2) position the acetyl group of aspirin to acetylate Ser-530:

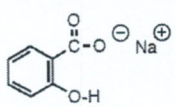


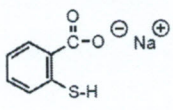
Salicylates

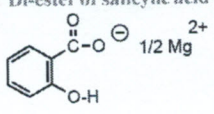
➢ **Salicylate Derivatives**

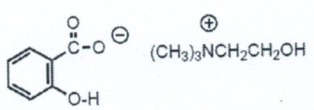
- **Salts of salicylic acid (sodium, magnesium, bismuth, choline or triethanolamine)**
- **Ester or amide derivatives (aspirin, salsalate and salicylamide)**

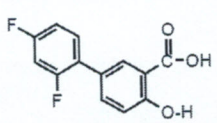






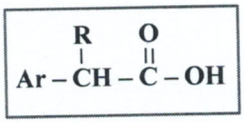






General SAR of Arylalkanoic Acid NSAIDs

General Structure:



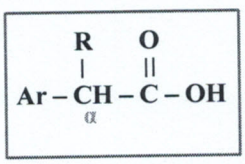
R: H, CH_3 or alkyl
Ar: Aryl or heteroaryl

1. All nonselective COX inhibitors possess an anionic centre:
   carboxylic acid, enolic, hydroxamic acid, sulfonamide, tetrazole ring:

R–COOH	Carboxylic acid	pKa 4-6
R–CONHOH	Hydroxamic acids	pKa (NH) 8-9
$R–SO_2NH_2$	Sulfonamide	pKa (NH) 9-10
	Enolic (phenol)	pKa (OH) 8-10
	Tetrazoles	pKa (NH) 4-6

2. The acidic centre is usually located one carbon atom to a aromatic or heteroaromatic ring, increasing this distance to two or three carbons diminishes activity
3. Derivatives of aryl or heteroaryl acetic or propionic acids are most common

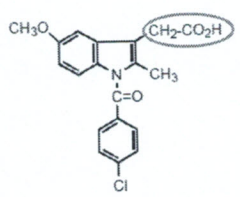
General SAR of Arylalkanoic Acid NSAIDs



R: H, CH_3 or alkyl
Ar: Aryl or heteroaryl

4. Substitution of a methyl group on the carbon atom separating the acid centre from the aromatic ring tends to increase anti-inflammatory activity:
   The α-methyl acetic acid, or 2-substituted propionic acid analogs: "profens", equiactive analogs
5. Larger groups decrease activity, but incorporation of this methyl group as part of an alicyclic ring system does not drastically affect activity
6. The methyl group creates a center of chirality: anti-inflammatory activity is associated with the *S*-(+)-enantiomer
7. A second area of lipophilicity that is noncoplanar with the aromatic or heteroaromatic ring usually enhances activity:
   This lipophilic function can consist of an additional aromatic ring or alkyl groups either attached to or fused with the aromatic centre

Arylalkanoic Acid NSAIDs



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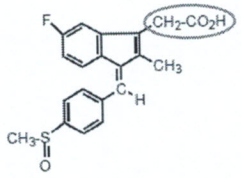
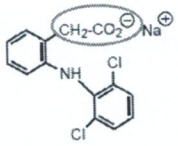
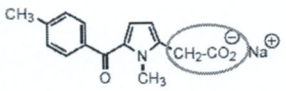


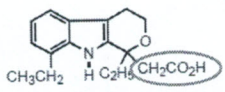
Sulindac



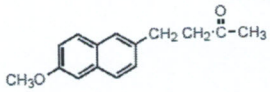
Diclofenac sodium



Tolmetin sodium



Etodolac



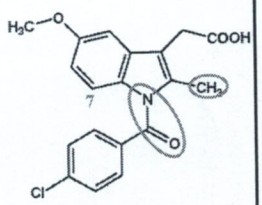
Nabumetone

Prodrug

Aryl- and heteroaryl-acetic acid derivatives

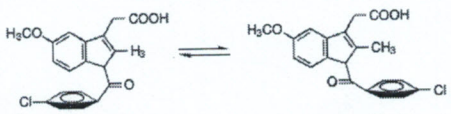
Arylacetic Acid NSAIDs

➢ **Indomethacin**



Indomethacin

- **The indole ring and the phenyl ring are separated by one atom**
- **The conformation of indomethacin have a crucial role in its anti-inflammatory actions**
- **The acetic acid side chain is flexible and can assume a large number of different conformations**
- **The preferred and lower-energy conformer have:**
  - ✓ ***p*-chlorophenyl ring is oriented away from the 2-methyl group (*cis* to the methoxyphenyl ring of the indole nucleus)**
  - ✓ ***p*-chlorophenyl ring is noncoplanar with the indole ring because of steric hindrance produced by the 2-methyl group and the hydrogen atom at the 7-position**



"*cis*-like" **"*trans*-like"**

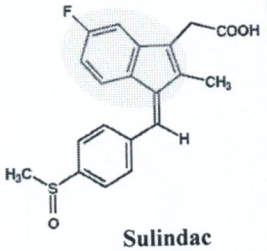
- **Indomethacin has significant CNS side effects due to the indole nucleus**

Arylacetic Acid NSAIDs

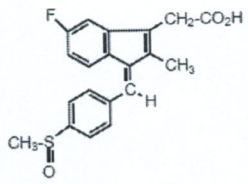
➢ **Sulindac**

- Isosteric replacement of the indole ring with the indene ring system
- *Z*-isomer is much more potent anti-inflammatory agent than the corresponding *S*-isomer and lacks the CNS side effects and causes less GI irritation
- Introduction of a fluoro and a methylsulfinyl increased activity
- Prodrug: active form is the sulfide metabolite which has a long half-life

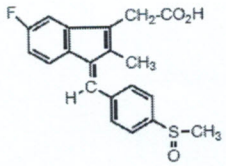
Indene



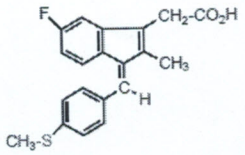
Sulindac



Z-Sulindac



E-Sulindac

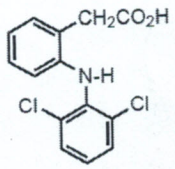


Active metabolite

Arylacetic Acid NSAIDs

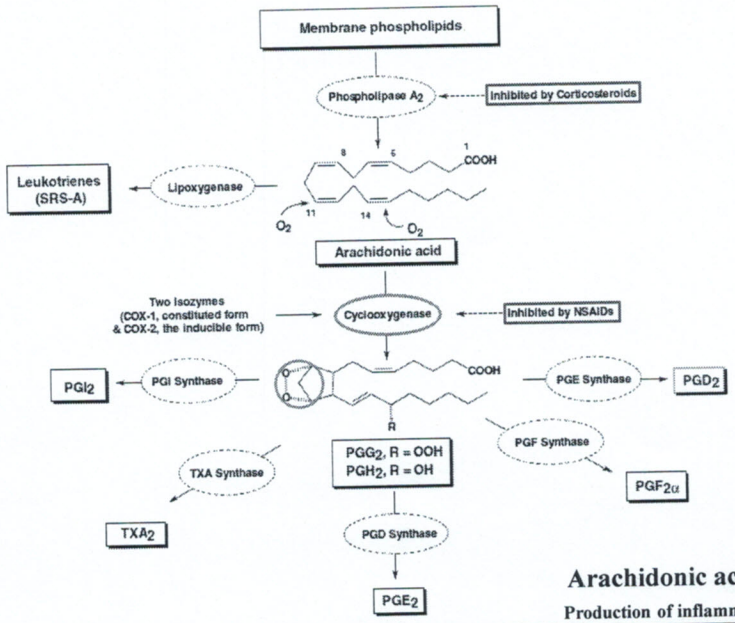
➢ **Diclofenac**

- Most popular NSAID in the world
- Structural characteristics of both arylalkanoic acid and the anthranilic acid
- Anti-inflammatory, analgesic and antipyretic properties
- Unique among the NSAIDs with three mechanisms of action:
  1. inhibition of COX enzyme resulting in a decreased production of prostaglandins and thromboxanes
  2. inhibition of the lipoxygenase pathway, resulting in decreased production of leukotrienes, particularly the proinflammatory LKB4
  3. inhibition of arachidonic acid release and stimulation of its reuptake, resulting in a reduction of arachidonic acid availability
- The two *o*-chloro groups is to force the anilino-phenyl ring out of plane of the phenylacetic acid portion, important for NSAIDs binding to the active site
- The sodium salt is a delayed release formulation while the potassium salt is used in rapid release formulations



Diclofenac

Prostaglandins

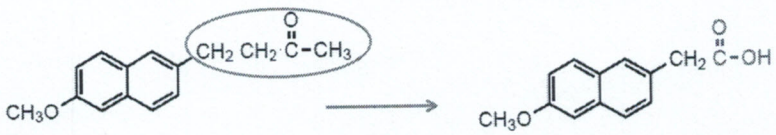


Arachidonic acid pathway

Production of inflammatory mediators

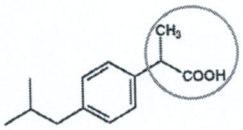
Arylacetic Acid NSAIDs

- **Nabumetone**
- **New class of nonacidic prodrugs**
- **Rapidly metabolized to form the major active metabolite: 6-methoxynaphthalene acetic acid (6MNA)**
- **Not acidic, minimal GI side effects**
- **6-methoxynaphthaleneacetic acid is structurally related to Naproxen**

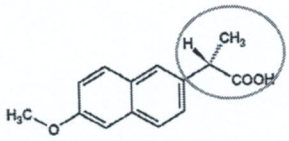


Nabumetone **6-methoxynaphthaleneacetic acid**

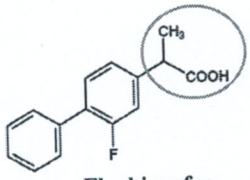
Arylpropioanic acid NSAIDs



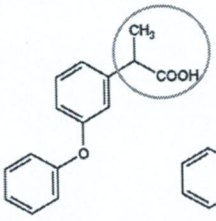
Ibuprofen



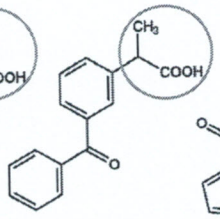
Naproxen



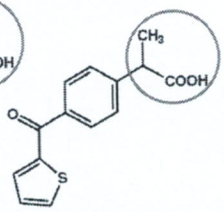
Flurbiprofen



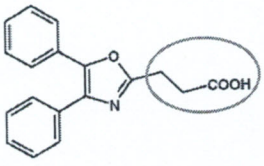
Fenoprofen



Ketoprofen



Suprofen



Oxaprozin

Propyl: not branched

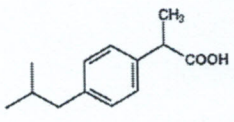
Aryl- and heteroarylpropionic acid derivatives

Arylpropioanic acid NSAIDs

- Most widely used, OTC
- α-methyl group in the carboxylic acid side chain results in a chiral carbon atom
- (+)-*S*-enantiomer is the active isomer, most drugs are marketed as racemates
- Rapid in vivo epimerization of the (−)-*R*-enantiomer to the active *S*-enantiomer isomerases, but not the *S* to *R*

➢ Ibuprofen

- Prototype
- Racemate
- Lacks second aromatic ring but possess a *sec*-butyl substituent: less potent
- GI distress

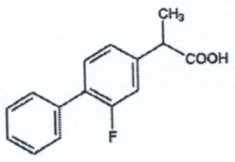


Ibuprofen

Arylpropioanic acid NSAIDs

➢ Flurbiprofen

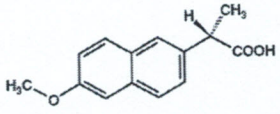
- Flurbiprofen resulted from a study of the SARs
- The 3–fluoro substituent helps ensure non–coplanarity
- Most favourable therapeutic profile
- Many times the potency of the other drugs



Flurbiprofen

➢ Naproxen

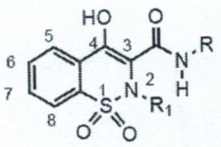
- Does not possess a second non coplanar ring
- Fused and aromatic naphthyl rings: flat and planar
- Only drug marketed in the optically pure form as a result of the synthetic method used
- It is marketed as the *S*-(+)-enantiomer, the sodium salt of the (−)-isomer is also on the market



Naproxen

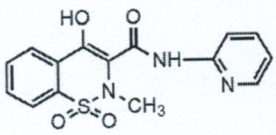
Arylpropioanic acid NSAIDs

- Enolic acid class of NSAIDs: Oxicams
- Series of 4-hydroxy-1,2-benzothiazine carboxamides
- Anti-inflammatory and analgesic properties
- Pfizer group efforts to produce noncarboxylic acid, potent and well-tolerated anti-inflammatory drugs led to the development of the oxicams
- First member of this class, piroxicam



➢ Piroxicam

- The enolic hydroxyl function as the acidic group and the pyridyl ring is the second aromatic ring
- GI side effects limit its use



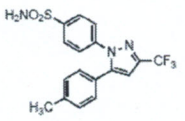
Piroxicam

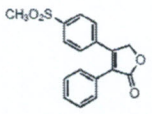
➢ Meloxicam

- Structurally related to Piroxicam
- Described as a selective COX-2 inhibitor, it is considerably less selective for the COX-2 versus COX-1 than Celecoxib

Selective COX-2 Inhibitors

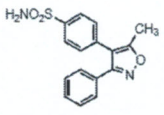
- Designed to fit the much larger NSAID binding site on COX-2 compared to the NSAID binding site on COX-1
- Larger, relatively rigid side-chain substituents, sulfamoyl or sulfonyl groups
- Many agents developed
- Safety risks and cardiovascular side effects

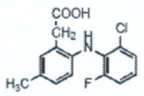

Celecoxib

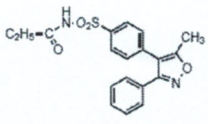

Rofecoxib

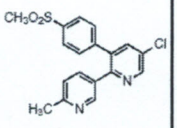
➢ **Celecoxib**

- First COX-2 selective inhibitor
- Prescription only
- Differs from other NSAIDS in that is only weakly acidic
- Sulfamyl group, warning in patients with a sulfonamide allergy


Valdecoxib


Lumiracoxib


Parecoxib

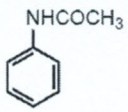

Etoricoxib

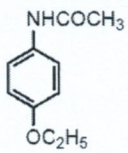
Antipyretic Analgesic Drugs

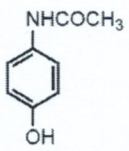
- Drugs possess analgesic and antipyretic actions but lack anti-inflammatory effects
- Acetaminophen and phenacetin
- Aromatic ring, no acidic ionizable group
- The first drug **Acetanilide** is out of market due of toxic blood and liver disorders
- **Phenacetin** implicated in cases of liver and nephrotoxicity and removed from the market

➢ **Acetaminophen**

- Metabolite of both phenacetin and acetanilide
- Safe drug: lower incidence of GI bleeding


Acetanilide


Phenacetin


Acetaminophen