Final Yr. B.Pharmacy
Semester-VIII
Medicinal Chemistry-IV

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NSAIDs
Syllabus

steroidal anti-inflammatory agents, analgesics & antipyretics

(Ibuprofen, Diclofenac, Paracetamol, Piroxicam, Nabumetone)
Learning Objectives

• Elaborate the general aspects of the design, development and history of NSAID’s.
• Write the classification of salicylates derivatives.
• Explain the chemistry of salicylates derivatives.
• Explain the chemistry of propionic acid derivatives.
• Explain the chemistry of indole acetic acid derivatives.
• Explain the chemistry of alkanoic acid derivatives.
• Explain MOA, Toxicity and Therapeutic uses of NSAID’s.
• Outline the scheme of synthesis.
• **Inflammation:**

“It is part of the complex biological response of vascular tissues to harmful stimuli, such as pathogens, damaged cells, or irritants.”
Uricosuric - Promoting the excretion of uric acid in the urine.
• **Cause of inflammation**-

- Burns, Chemical irritants,
- Frostbite, Toxins,
- Infection by pathogens,
- Physical injury,
- Blunt or penetrating,
  (dull edge or point, *e.g* blunt pencil)
- Immune reactions due to hypersensitivity
- Ionizing radiation
- Foreign bodies

_Frostbite_ - injury or destruction of skin and underlying tissue.

_Toxin_ - is a poisonous substance produced within living cells or organisms.
**Nonsteroidal Anti-inflammatory Drugs:**

- Usually denoted by NSAIDs or NAIDs, but also referred to as nonsteroidal anti-inflammatory agents/analgesics (NSAIAs) or nonsteroidal Anti-inflammatory medicines (NSAIMs).
- These are the drugs with analgesic and antipyretic effect and which have in higher doses, anti-inflammatory effect.
- These are the **Medications** used widely in the therapy of mild-to-moderate pain and inflammation.
Characteristics of NSAIDS

- All of them are analgesic, antipyretic and anti-inflammatory, do not produce CNS depression or respiratory depression.
- Dose-dependent uricosuric action.
- Act by inhibiting prostaglandin synthesis, except nimesulide and nefopam.
- None of them are steroids.
CLASSIFICATION OF NSAIDs:

- **Nonselective COX-inhibitors:**
  - Salicylates: Aspirin
  - Propionic acid derivatives: Ibuprofen, Ketoprofen.
  - Acetic acid derivatives: Diclofenac, Aceclofenac
  - Fenamic acid derivatives: mefenamic acid
  - Pyrrolo-pyrrole derivatives: Ketorolac
  - Oxicam derivatives: Piroxicam, Meloxicam
  - Indole derivatives: Sulindac, Indomethacin
  - Pyrazolone derivatives: Phenylbutazone

- **Selective COX-2 inhibitors:**
  - Celecoxib, Rofecoxib

- **Preferential selective Cox-inhibitors:**
  - Nimesulide, Meloxicam, Nabumetone

- **Analgesic-antipyretic with poor anti-inflammatory effect:** paracetamol

Reference- https://www.google.com/search?q=classification+of+NSAIDs&safe
Salicylic acid derivatives

✓ Salicylic acid is also called as spiric acid obtained from salix alba, derivative of salicylic acid from oil of wintergreen i.e methyl salicylate.

✓ Salicylates are the compounds that have got central activity that is through hypotheleemic region of the brain.
Salol Principle:

It was discovered by Nenckl in 1986. In salol two toxic substances (Phenol and salicylic acid) were combined into an ester that taken internally. Slowly hydrolyzes in the intestine to give the antiseptic action of component.

Two types:

1. **True salol (Full salol)**: When both components of the ester are active compounds e.g., Phenyl salicylate and β napthol benzoate

2. **Partial Salol**: Salol principle can be applied to esters in which the alcohol or acid is toxic, active or corrosive portion of this type is called a partial salol. e.g. partial salol contain an active acid are ethyl salicylate and methyl salicylate.
1. Substitution of carboxylic acid group:

(i) The carboxyl group is essential for activity but COOH can be substituted by iso-steric group or some other acidic groups. But mainly we have derivatives which contain COOH group. So these compounds are also called as acidic analgesics.

(ii) Reducing acidity of this group, converting to amide, salicylamide maintains the analgesic activity of salicylic acid, but eliminates the anti-inflammatory properties.
2. Substitution of $-\text{OH}$ group:

(i) Different substitutions are carried out. One of the most important is acetylation and by this we have got acetyl salicylic acid that is aspirin.

![Chemical structure of aspirin](image)

(ii) OH must be present at ortho position, substitution of either carboxyl or phenolic hydroxyl group may affect potency and toxicity.

![Chemical structure illustrating the effect of OH substitution](image)
3. **Substitution at meta or para position:**

Placing the phenolic hydroxyl group at the meta or para position to the carboxyl group, abolishes the activity.

![Chemical structure](image)

Abolishes activity

4. **Substitution of halogen atom:**

   (i) Substitution of Halogen atom on aromatic rings at the 5th position of salicylic acids increases anti-inflammatory activity.

![Chemical structure](image)
8.4.2 Mode of Action NSAIDs

The most widely accepted mechanism of action consists of:

- When there is injury to tissue
  - Increase PG synthesis
    - Mediators of inflammation
    - Sensitize pain receptor at nerve endings

Salicylates mainly inhibits the PG synthesis by inhibiting cyclooxygenase enzyme:

- Cell membrane phospholipid injury
  - Phospholipase A₂
    - Arachidonic acid
      - Lipoxygenase
        - Leukotriens
      - Cyclooxygenase
        - Thromboxane synthetase TxA₂
          - TxB₂
          - Prostagladins
            - PGI₂
            - PGE
Toxicities & Side Effects

1) Reye’s syndrome
2) Seizure
3) Nausea, vomiting
4) Gastric ulceration/bleeding
5) Irregular heart beat
6) Yellowing of eyes.

Reye’s syndrome-
an uncommon, severe disorder occurring primarily in children after a viral illness, as influenza or chickenpox
Uses

1) Osteoarthritis
2) Rheumatoid arthritis
3) Acute gout
4) Headache and migraine
5) Renal colic
6) Mild to moderate pain
7) For myocardial infraction prophylaxis.
References

