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MEDICINAL CHEMISTRY – I

UNIT 5

TOPIC :

- **Narcotic and non-narcotic analgesics**

  Morphine and related drugs : SAR of Morphine analogues, Morphine sulphate, Codeine, Meperidine hydrochloride, Anilerdine hydrochloride, Diphenoxylate hydrochloride, Loperamide hydrochloride, Fentanyl citrate, *Methadone hydrochloride*, Propoxyphene hydrochloride, Pentazocine,
  Levorphanol tartarate.

  Narcotic antagonists : Nalorphine hydrochloride, Levallorphan tartarate,
  Naloxone hydrochloride.

  Anti-inflammatory agents : Sodium salicylate, Aspirin, Mefenamic acid, *Meclofenamate, Indomethacin, Sulindac, Tolmetin, Zomepriac, Diclofenac, Ketorolac, Ibuprofen*, Naproxen, Piroxicam, Phenacetin, Acetaminophen,
  Antipyrine, Phenylbutazone

Narcotic and Non-Narcotic Analgesics

- **Analgesics** = drugs that relieve pain without causing loss of consciousness.
- Two main types:
  1. **Narcotic (Opioid) Analgesics** – strong, CNS-acting painkillers.
  2. **Non-Narcotic (Non-Opioid) Analgesics** – mild/moderate pain relief, mostly peripheral action.

Narcotic Analgesics

- **Use:** Moderate to severe pain (post-surgery, cancer, trauma).
- **Effects:** Analgesia, sedation, drowsiness, euphoria.

Mechanism of Action (MOA):

- Bind to **opioid receptors** (μ, δ, κ) in brain and spinal cord.
- **Inhibit adenylate cyclase → ↓ cAMP**.
- **Close Ca^{2+} channels → ↓ neurotransmitter release**.
- **Open K^{+} channels → hyperpolarization**.
- **Result:** Pain signals blocked, analgesia, sedation, respiratory depression.

Examples:

- Morphine sulfate, Codeine, Meperidine HCl, Anileridine HCl, Diphenoxylate HCl, Loperamide HCl, Fentanyl citrate, Methadone HCl, Propoxyphene HCl, Pentazocine, Levorphanol tartrate.

Narcotic Antagonists:

- Naloxone HCl, Nalorphine HCl, Levorphanol tartrate → reverse opioid effects.

Non-Narcotic Analgesics

- **Use:** Mild to moderate pain, headache, muscle pain, inflammation.
- **Mechanism of Action:**
  - Inhibit **cyclooxygenase (COX) enzymes** → ↓ prostaglandin synthesis → ↓ pain, inflammation, swelling.

Examples:

- Paracetamol (Acetaminophen), Aspirin, Ibuprofen, Naproxen, Diclofenac, Ketorolac, Indomethacin, Piroxicam, Phenacetin, Mefenamic acid, Meclofenamate, Sulindac, Zomepirac, Phenylbutazone.

Morphine and Related Drugs

- Morphine: Naturally occurring alkaloid from *Papaver somniferum* (opium).
- Prototype narcotic analgesic: Used as a standard for comparing other opioid analgesics.

Mechanism of Action (MOA)

- Binds to μ-opioid receptors in the brain and spinal cord.
- Cellular effects:
  1. Inhibits adenylate cyclase → ↓ cAMP
  2. Closes Ca^{2+} channels → ↓ neurotransmitter release
  3. Opens K^{+} channels → hyperpolarization
- Result: Analgesia, sedation, pain signals blocked, respiratory depression.

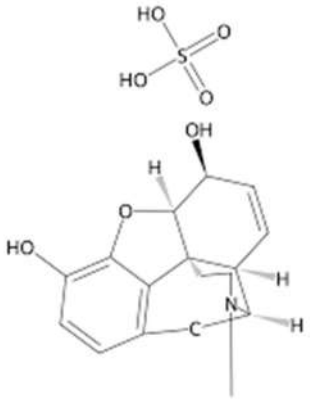
Example :

- Morphine sulphate,
- Codeine,
- Meperidine hydrochloride,
- Anilerdine hydrochloride,
- Diphenoxylate hydrochloride,
- Loperamide hydrochloride,
- Fentanyl citrate*,
- Methadone hydrochloride*,
- Propoxyphene hydrochloride,
- Pentazocine,
- Levorphanol tartarate.

Morphine Sulphate

Structure

- **Chemical class:** Opioid analgesic (phenanthrene derivative).
- **Chemical formula:** $C_{17}H_{19}NO_3 \cdot H_2SO_4$.
- **Physical properties:** White crystalline powder; soluble in water; usually available as tablets, injections, or oral solutions.



Mechanism of Action (MOA)

- **Opioid receptor agonist:**
  - Primarily binds to **μ (mu) opioid receptors** in the **brain, spinal cord, and gastrointestinal tract**.
- **Effects on cellular signaling:**
  - Inhibition of **adenylate cyclase → decreased cAMP**.
  - **Closure of voltage-gated Ca^{2+} channels** → reduces neurotransmitter release (substance P, glutamate).
  - **Opening of K^+ channels** → hyperpolarization of neurons → reduced excitability.
- **Net effect:**
  - Analgesia, sedation, euphoria, respiratory depression, and reduced GI motility.

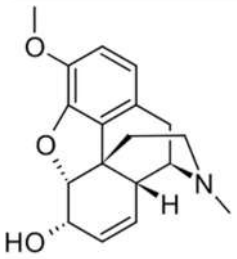
Therapeutic Uses

- **Severe acute pain:** Postoperative, trauma, myocardial infarction.
- **Chronic pain:** Cancer pain, palliative care.
- **Cough suppression:** In certain formulations (codeine preferred).
- **Diarrhea:** Occasionally in opioid preparations with limited CNS effect.

Codeine

Structure

- **Chemical class:** Opioid analgesic (methylated morphine derivative).
- **Chemical formula:** $C_{18}H_{21}NO_3$.
- **Physical properties:** White crystalline powder; soluble in water; usually available as tablets, syrups, or injections.
- **Structural difference from morphine:**
  - **Methylation of the hydroxyl group at position 3** → less potent than morphine but better oral bioavailability.



Mechanism of Action (MOA)

- **Opioid receptor agonist:**
  - Primarily binds to **μ (mu) opioid receptors** in the CNS and GI tract.
- **Cellular effects:**
  - Inhibition of adenylate cyclase → ↓ cAMP.
  - Closure of voltage-gated Ca^{2+} channels → reduced neurotransmitter release.
  - Opening of K^+ channels → hyperpolarization of neurons → decreased excitability.
- **Net effect:**
  - Analgesia (mild to moderate pain), antitussive effect (cough suppression), some sedation, and GI motility reduction.

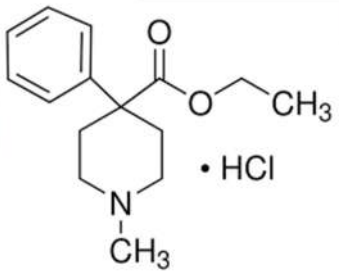
Therapeutic Uses

- **Pain management:** Mild to moderate pain (postoperative, musculoskeletal, or cancer-related).
- **Cough suppression:** Effective as antitussive.
- **Diarrhea management:** Occasionally used in limited doses due to opioid effect on gut motility.

Meperidine Hydrochloride (Pethidine HCl)

Structure

- **Chemical class:** Synthetic opioid analgesic (phenylpiperidine derivative).
- **Chemical formula:** $C_{15}H_{21}NO_2 \cdot HCl$.
- **Physical properties:** White crystalline powder; soluble in water; available as injection, tablets, or oral solution.
- **Structural features:**
  - Piperidine ring linked to a phenyl group.
  - Ester group at position 4 → contributes to pharmacokinetic properties.
  - Tertiary amine at position 1 → necessary for μ-opioid receptor activity.



Mechanism of Action (MOA)

- **Opioid receptor agonist:**
  - Binds primarily to **μ (mu) opioid receptors** in CNS.
- **Cellular effects:**
  - Inhibits adenylate cyclase → ↓ cAMP.
  - Closes voltage-gated Ca^{2+} channels → decreases neurotransmitter release.
  - Opens K^+ channels → hyperpolarizes neurons → reduced neuronal excitability.
- **Net effect:**
  - Analgesia (moderate to severe pain), sedation, respiratory depression, euphoria, and antitussive effect (mild).

Therapeutic Uses

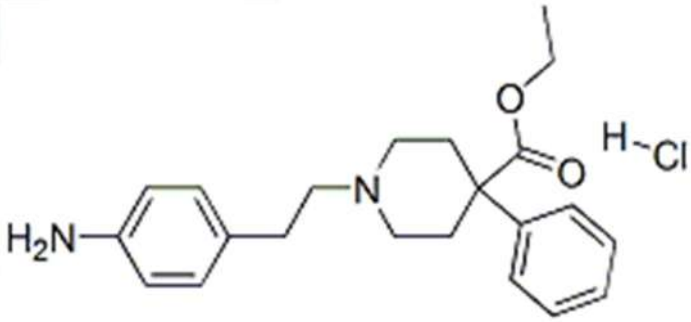
- **Pain management:** Moderate to severe acute pain (postoperative, labor pain).
- **Anesthesia:** As preoperative analgesic or adjunct to general anesthesia.

- **Shivering control:** Sometimes used to control postoperative shivering.

Anilerdine Hydrochloride

Structure

- **Chemical class:** Synthetic opioid analgesic.
- **Chemical formula:** $C_{18}H_{25}N{\cdot}HCl$.
- **Physical properties:** White to off-white crystalline powder; soluble in water and ethanol.
- **Structural features:**
  - Piperidine-based structure similar to meperidine derivatives.
  - Aromatic ring linked to a tertiary amine → essential for μ-opioid receptor binding.
  - Hydrochloride salt improves water solubility for parenteral administration.



Mechanism of Action (MOA)

- **Opioid receptor agonist:**
  - Binds primarily to **μ (mu) opioid receptors** in CNS.
- **Cellular effects:**
  - Inhibits adenylate cyclase → reduces cAMP.
  - Closes voltage-gated Ca^{2+} channels → decreases neurotransmitter release.
  - Opens K^+ channels → hyperpolarizes neurons → reduces neuronal excitability.
- **Net effect:**
  - Analgesia (moderate to severe pain), sedation, respiratory depression, and euphoria.

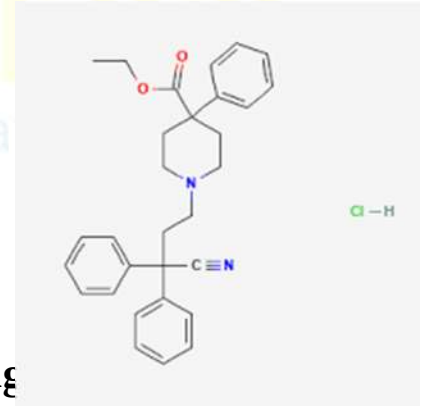
Therapeutic Uses

- **Pain management:** Moderate to severe pain where other opioids may not be suitable.
- **Pre-anesthetic medication:** Occasionally used as a premedication for sedation and analgesia before surgery.

Diphenoxylate Hydrochloride

Structure

- **Chemical class:** Synthetic opioid derivative (meperidine analogue).
- **Chemical formula:** $C_{22}H_{27}NO_2 \cdot HCl$
- **Physical properties:** White crystalline powder; soluble in water and ethanol.
- **Structural features:**
  - Piperidine ring with a tertiary amine → essential for opioid receptor binding.
  - Aromatic substitution → contributes to lipophilicity and activity.
  - Hydrochloride salt → increases water solubility for oral use.



Mechanism of Action (MOA)

- **Opioid receptor agonist (peripherally acting**
  - Acts mainly on **μ-opioid receptors in the gut**.
  - Reduces **GI motility** by decreasing longitudinal and circular smooth muscle contractions.
- **CNS effect:** Minimal central analgesic activity at therapeutic doses; crosses the BBB poorly.
- **Net effect:**
  - Decreases frequency and urgency of diarrhea.
  - Increases intestinal transit time → allows more water absorption from feces.

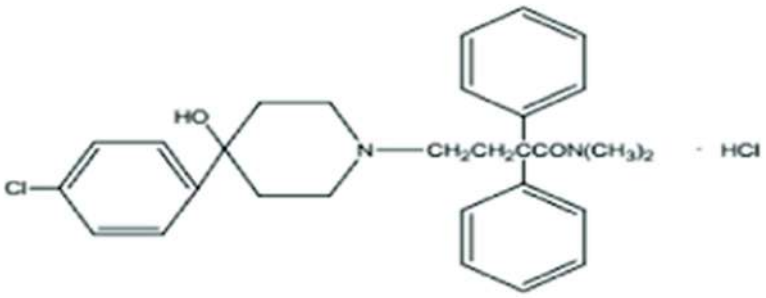
Therapeutic Uses

- **Primary use:** Symptomatic treatment of **diarrhea**, including acute nonspecific diarrhea.
- **Adjunct use:** Sometimes combined with **atropine** to discourage abuse (Lomotil formulation).

Loperamide Hydrochloride

Structure

- **Chemical class:** Synthetic piperidine derivative (opioid analogue).
- **Chemical formula:** $C_{29}H_{33}ClN_2O_2$
- **Physical properties:** White crystalline powder; practically insoluble in water but soluble in ethanol.
- **Structural features:**
  - Piperidine ring → essential for opioid receptor binding.
  - Two aromatic rings → enhance lipophilicity and receptor affinity.
  - Hydrochloride salt → improves stability and formulation.



Mechanism of Action (MOA)

- **Peripheral μ-opioid receptor agonist:**
  - Acts mainly on **μ-opioid receptors in the myenteric plexus of the gut**.
  - Reduces **peristaltic movements** and **prolongs intestinal transit time**.
- **Other effects:**
  - Increases **anal sphincter tone**, reducing fecal urgency.
  - Decreases **gastrointestinal secretion**.
- **CNS effect:** Minimal because it is actively pumped out of the CNS by **P-glycoprotein**, limiting abuse potential.

- **Net effect:** Controls diarrhea without significant analgesic or sedative CNS effects at therapeutic doses.

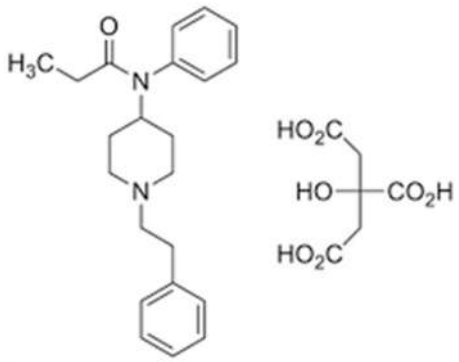
Therapeutic Uses

- **Primary use:** Symptomatic treatment of **acute and chronic diarrhea**.
- **Adjunct use:** Treatment of **traveler's diarrhea**, **irritable bowel syndrome (IBS)**, and **inflammatory bowel disease-related diarrhea**.

Fentanyl Citrate

Structure

- **Chemical class:** Synthetic opioid (phenylpiperidine derivative).
- **Chemical formula:** $C_{22}H_{28}N_2O \cdot C_6H_8O_7$ (as citrate salt)
- **Physical properties:** White crystalline powder, soluble in water and alcohol.
- **Structural features:**
  - **Phenylpiperidine nucleus:** Essential for μ-opioid receptor binding.
  - **N-phenylpropanamide group:** Enhances potency.
  - **Citrate salt:** Improves water solubility and stability for injection.



Mechanism of Action (MOA)

- **Strong μ-opioid receptor agonist**:
  - Binds to **opioid receptors in CNS**, mainly μ receptors.
  - **Inhibits adenylate cyclase → reduces cAMP**.
  - **Opens K^+ channels → hyperpolarization of neurons**.

- **Closes voltage-gated Ca^{2+} channels → reduces neurotransmitter release** (substance P, glutamate, acetylcholine).
- **Effects:** Analgesia, sedation, respiratory depression, euphoria.

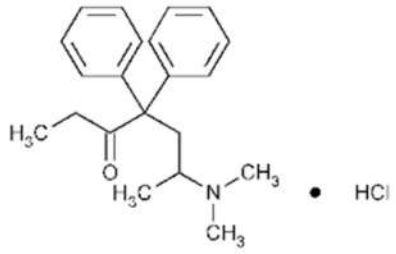
Therapeutic Uses

- **Analgesia:**
  - Severe acute pain (e.g., postoperative, trauma).
  - Chronic pain in opioid-tolerant patients (e.g., cancer pain).
- **Anesthesia adjunct:**
  - Used in balanced anesthesia protocols for surgical procedures.
- **Other:**
  - Transdermal patches for long-term chronic pain management.

Methadone Hydrochloride

Structure

- **Chemical class:** Synthetic opioid (diphenylpropylamine derivative).
- **Chemical formula:** $C_{21}H_{27}NO \cdot HCl$
- **Physical properties:** White crystalline powder, soluble in water (as HCl salt) and alcohol.
- **Structural features:**
  - **Diphenylpropylamine nucleus:** Confers strong μ-opioid receptor activity.
  - **Basic nitrogen atom:** Required for receptor binding.
  - **Hydrochloride salt:** Improves water solubility for oral or parenteral use.



Mechanism of Action (MOA)

- **Agonist at μ-opioid receptors:**
  - Binds in CNS to produce **analgesia, sedation, and euphoria**.
  - **Inhibits adenylate cyclase → reduces cAMP formation**.
  - **Opens K^+ channels → neuronal hyperpolarization**.

    - **Closes voltage-gated Ca^{2+} channels → reduces neurotransmitter release**.
- **NMDA receptor antagonism (weak):** May contribute to analgesic properties, particularly in neuropathic pain.
- **Effects:** Long-acting analgesia, suppression of opioid withdrawal symptoms.

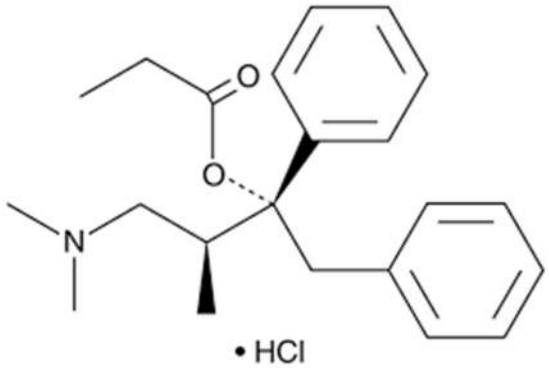
Therapeutic Uses

- **Analgesia:**
    - Moderate to severe chronic pain (e.g., cancer pain).
- **Opioid dependence treatment:**
    - Suppresses withdrawal symptoms in heroin or morphine addicts.
- **Anesthesia adjunct (occasionally):**
    - Used for preoperative analgesia or balanced anesthesia.

Propoxyphene Hydrochloride

Structure

- **Chemical class:** Synthetic opioid (phenylheptylamine derivative).
- **Chemical formula:** $C_{20}H_{27}NO{\cdot}HCl$
- **Physical properties:** White crystalline powder, soluble in water (as HCl salt).
- **Structural features:**
    - **Phenylpropylamine skeleton:** Confers weak μ-opioid receptor agonist activity.
    - **Basic nitrogen atom:** Necessary for receptor binding.
    - **Hydrochloride salt:** Improves water solubility and stability.



Mechanism of Action (MOA)

- **Weak agonist at μ-opioid receptors:**
  - Binds in CNS to provide **analgesia**, but less potent than morphine.
  - **Inhibits adenylate cyclase → reduces cAMP formation.**
  - **Opens K^+ channels → neuronal hyperpolarization.**
  - **Closes voltage-gated Ca^{2+} channels → reduces neurotransmitter release.**
- **Effects:** Mild to moderate pain relief with less euphoria and respiratory depression compared to strong opioids.

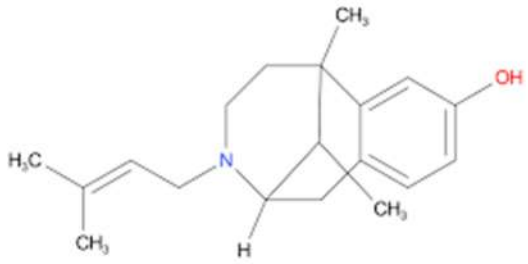
Therapeutic Uses

- **Analgesia:**
  - Mild to moderate pain relief (e.g., musculoskeletal pain, postoperative pain).
- **Adjunct to non-narcotic analgesics:**
  - Often combined with acetaminophen for enhanced effect.

Pentazocine

Structure

- **Chemical class:** Synthetic opioid (benzomorphan derivative).
- **Chemical formula:** $C_{16}H_{25}NO$
- **Physical properties:** White crystalline powder, slightly soluble in water.
- **Structural features:**
  - **Benzomorphan skeleton:** Provides mixed agonist-antagonist activity at opioid receptors.
  - **Tertiary amine:** Essential for receptor binding.



Mechanism of Action (MOA)

- **Mixed opioid receptor activity:**
  - **Partial agonist at κ-opioid receptors:** Produces analgesia and sedation.
  - **Weak antagonist or partial agonist at μ-opioid receptors:**
    - Reduces the risk of respiratory depression compared to full μ-agonists.
- **Cellular effects:**
  - **Opens K^+ channels → hyperpolarization of neurons.**
  - **Reduces Ca^{2+} influx → decreases neurotransmitter release.**
- **Result:** Pain relief with lower euphoria and lower dependence potential than strong μ-opioid agonists.

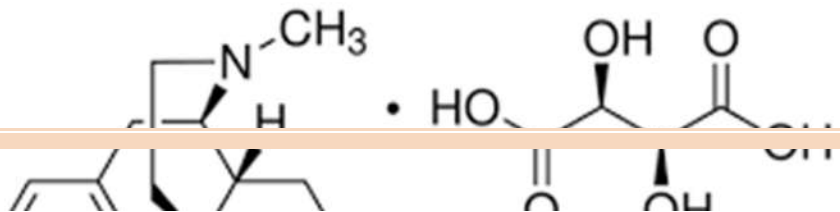
Therapeutic Uses

- **Moderate to severe pain relief:**
  - Musculoskeletal pain, postoperative pain.
- **Analgesic in patients at risk of opioid dependence:**
  - Less risk of abuse than morphine or codeine.

Levorphanol Tartarate

Structure

- **Chemical class:** Synthetic opioid (morphinan derivative).
- **Chemical formula:** $C_{21}H_{29}NO \cdot C_4H_6O_6$ (as tartarate salt)
- **Physical properties:** White crystalline powder, soluble in water.
- **Structural features:**
  - **Morphinan skeleton:** Related to morphine, retains opioid activity.
  - **Tertiary amine:** Important for binding to opioid receptors.
  - **Hydroxyl group at position 3:** Essential for analgesic activity.



Mechanism of Action (MOA)

- **Agonist at μ, δ, and κ opioid receptors:**
  - Strong **μ-receptor agonist** → potent analgesia.
  - Some κ and δ receptor activity contributes to analgesic and sedative effects.
- **Cellular effects:**
  - Opens K^+ channels → hyperpolarizes neurons.
  - Closes Ca^{2+} channels → decreases neurotransmitter release.
- **Result:** Potent analgesia, sedation, and reduced perception of pain.

Therapeutic Uses

- **Moderate to severe pain relief:**
  - Postoperative pain, cancer pain, chronic severe pain.
- **Alternative to morphine:**
  - Sometimes used when morphine is contraindicated or not tolerated.

Narcotic Antagonists

- Narcotic antagonists are drugs that block or reverse the effects of opioid (narcotic) drugs.
- Used in cases of opioid overdose or to counteract opioid-induced side effects.

Mechanism of Action (MOA)

- Bind to opioid receptors in the brain and spinal cord (μ, κ, δ).
- Block opioid drugs from binding, preventing their effects.

- Result: Reversal of opioid effects including:
  - Analgesia
  - Sedation / drowsiness
  - Respiratory depression

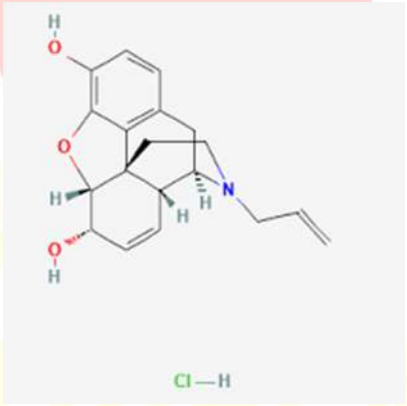
Examples of Narcotic Antagonists

- Nalorphine hydrochloride,
- Levallorphan tartarate,
- Naloxone hydrochloride

Nalorphine Hydrochloride

Structure

- Chemical class: Opioid partial agonist/antagonist (morphinan derivative).
- Chemical formula: $C_{19}H_{23}NO \cdot HCl$
- Physical properties: White crystalline powder, soluble in water.
- Structural features:
  - Morphinan skeleton (similar to morphine).
  - Tertiary amine at position 17.
  - Modifications confer mixed agonist–antagonist activity (blocks μ-receptors, activates κ-receptors).



Mechanism of Action (MOA)

- Opioid receptor interaction:
  - μ-receptor: Antagonist → reverses effects of pure opioids (e.g., morphine, fentanyl).
  - κ-receptor: Partial agonist → provides mild analgesia and sedation.
- Cellular effects:
  - Blocks μ-receptor-mediated K^+ and Ca^{2+} channel modulation → inhibits opioid-induced analgesia, sedation, and respiratory depression.
- Result:
  - Reverses opioid overdose effects.
  - Produces mild analgesia and sedation via κ-receptors.

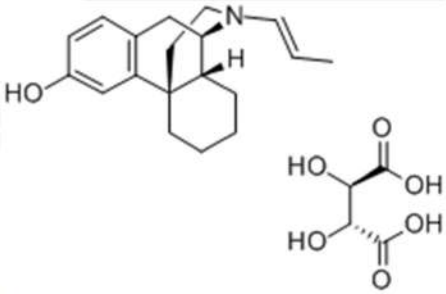
Therapeutic Uses

- Reversal of opioid overdose (especially respiratory depression).
- Opioid antagonism in anesthesia when partial reversal is desired.
- Research applications: Studying opioid receptor pharmacology.

Levallorphan Tartarate

Structure

- Chemical class: Opioid mixed agonist–antagonist (morphinan derivative).
- Chemical formula: $C_{20}H_{25}NO_4 \cdot C_4H_6O_6$ (as tartarate salt)
- Physical properties: White crystalline powder, soluble in water.
- Structural features:
  - Morphinan nucleus similar to morphine.
  - Tertiary amine at position 17.
  - Substitutions at the N-17 position confer μ-receptor antagonism and κ-receptor agonism.



Mechanism of Action (MOA)

- Opioid receptor interaction:
  - μ-opioid receptor: Antagonist → blocks effects of morphine and other μ-agonists.
  - κ-opioid receptor: Partial agonist → provides mild analgesic effect.
- Cellular effects:
  - Inhibits μ-receptor-mediated G-protein signaling → reverses opioid-induced analgesia, sedation, and respiratory depression.
  - Activates κ-receptor pathways → mild analgesia and sedation without strong respiratory depression.
- Result:
  - Reverses opioid overdose effects.
  - Produces mild analgesia and sedation.

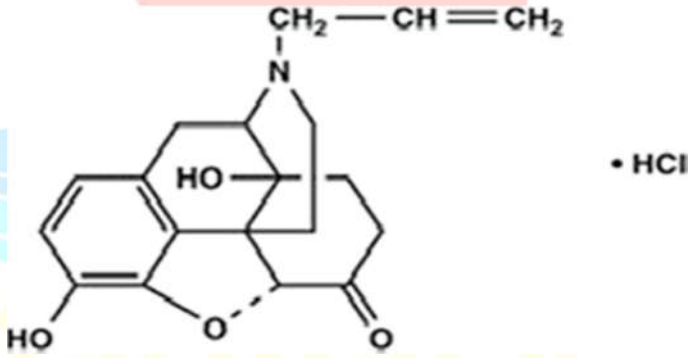
Therapeutic Uses

- Reversal of opioid overdose (especially morphine).
- Adjunct in anesthesia to counteract opioid effects.

Naloxone Hydrochloride

Structure

- Chemical class: Opioid pure antagonist (morphinan derivative).
- Chemical formula: $C_{19}H_{21}NO_4 \cdot HCl$
- Physical properties: White crystalline powder, soluble in water.
- Structural features:
  - Morphinan nucleus similar to morphine.
  - N-17 substituent (allyl group) → confers μ-opioid receptor antagonism.
  - Hydroxyl groups at positions 3 and 14 → important for receptor binding.



Mechanism of Action (MOA)

- Opioid receptor interaction:
  - μ, δ, and κ-opioid receptors: Competitive antagonist → blocks effects of agonists (morphine, fentanyl, heroin).
- Cellular effects:
  - Displaces agonists from receptors.
  - Reverses opioid-induced inhibition of adenylate cyclase → restores neurotransmitter release.
  - Reverses opioid-induced K^+ channel opening → depolarizes neurons.
- Result:
  - Rapid reversal of opioid-induced analgesia, sedation, respiratory depression, and euphoria.

Therapeutic Uses

- Emergency treatment of opioid overdose (respiratory depression).
- Reversal of opioid anesthesia post-surgery.

Anti-Inflammatory Agents (NSAIDs)

- Drugs that reduce pain, swelling, and fever without causing significant sedation.
- Widely used for minor pain, inflammatory joint diseases, and tissue injuries.
- Also called Non-Steroidal Anti-Inflammatory Drugs (NSAIDs).

Mechanism of Action (MOA)

- Inhibit cyclooxygenase (COX) enzymes (COX-1 and COX-2).
- COX enzymes catalyze the formation of prostaglandins, which mediate:
  - Inflammation
  - Pain
  - Fever
- Result: Reduced inflammation, analgesia, and antipyretic effects.

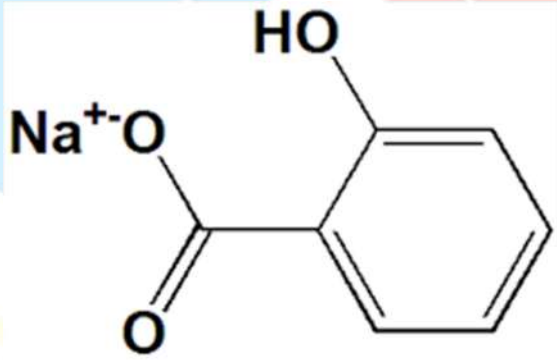
Examples of Anti-Inflammatory Agents

- Sodium salicylate, Aspirin,
- Mefenamic acid*, Meclofenamate,
- Indomethacin, Sulindac,
- Tolmetin, Zomepriac,
- Diclofenac, Ketorolac,
- Ibuprofen*, Naproxen,
- Piroxicam, Phenacetin,
- Acetaminophen, Antipyrine,
- Phenylbutazone

Sodium Salicylate

Structure

- **Chemical class:** Salicylate derivative (NSAID).
- **Chemical formula:** $C_7H_5NaO_3$
- **Physical properties:** White crystalline powder, soluble in water.
- **Structural features:**
  - Salicylic acid moiety (ortho-hydroxybenzoic acid).
  - Sodium salt → increases water solubility.



sodium salicylate

Mechanism of Action (MOA)

- Non-selective **COX (cyclooxygenase) inhibitor**.
- Blocks **COX-1 and COX-2 enzymes**, preventing conversion of arachidonic acid → prostaglandins.
- **Result:**
  - Reduces inflammation, pain, and fever.
  - Analgesic and anti-inflammatory effects without sedation.

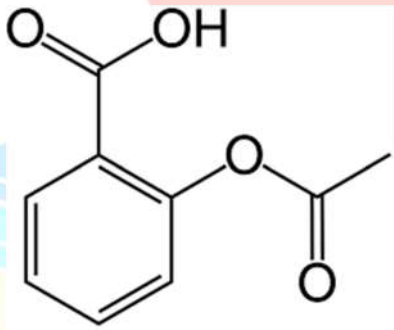
Therapeutic Uses

- Mild to moderate **pain** (headache, musculoskeletal pain).
- **Inflammatory conditions** (rheumatoid arthritis, osteoarthritis).
- **Fever** reduction.

Aspirin (Acetylsalicylic Acid)

Structure

- **Chemical class:** Salicylate derivative (NSAID).
- **Chemical formula:** $C_9H_8O_4$
- **Physical properties:** White crystalline powder; slightly soluble in water; soluble in ethanol.
- **Structural features:**
  - Acetyl group (-$COCH_3$) attached to phenolic hydroxyl of salicylic acid.
  - The acetylation distinguishes it from sodium salicylate.



Mechanism of Action (MOA)

- **Irreversible COX inhibitor** (COX-1 > COX-2): acetylates cyclooxygenase enzyme.
- Blocks conversion of **arachidonic acid → prostaglandins & thromboxanes**.
- **Effects:**
  - Analgesic → reduces mild to moderate pain.
  - Anti-inflammatory → reduces swelling and inflammation.
  - Antipyretic → reduces fever.
  - Antiplatelet → inhibits thromboxane A_2 synthesis → decreases platelet aggregation.

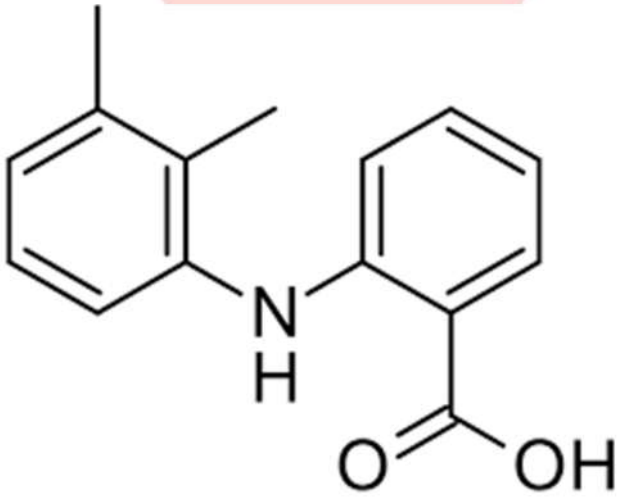
Therapeutic Uses

- **Analgesic:** headache, musculoskeletal pain, toothache.
- **Antipyretic:** fever reduction.
- **Anti-inflammatory:** rheumatoid arthritis, osteoarthritis.

Mefenamic Acid

Structure

- **Chemical class:** Anthranilic acid derivative (Fenamate group of NSAIDs).
- **Chemical formula:** $C_{15}H_{15}NO_2$
- **Physical properties:** White or pale yellow crystalline powder; practically insoluble in water; soluble in organic solvents like ethanol.
- **Structural features:**
  - Contains an **anthranilic acid core** (o-aminobenzoic acid) with a phenyl group substitution.
  - Carboxylic acid (-COOH) is responsible for its anti-inflammatory activity.



Mechanism of Action (MOA)

- Non-selective **COX inhibitor** (COX-1 and COX-2).
- Blocks conversion of **arachidonic acid → prostaglandins**, reducing pain, inflammation, and fever.
- Mainly acts peripherally to inhibit prostaglandin synthesis.
- Analgesic, anti-inflammatory, and antipyretic effects arise from **prostaglandin inhibition**.

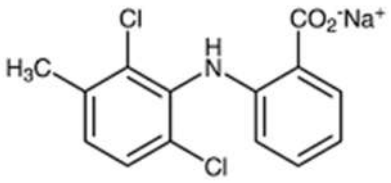
Therapeutic Uses

- **Pain:** mild to moderate pain, including dysmenorrhea (menstrual pain).
- **Inflammation:** rheumatoid arthritis, osteoarthritis.
- **Other uses:** post-operative pain, musculoskeletal pain.

Meclofenamate

Structure

- **Chemical class:** Anthranilic acid derivative (Fenamate group of NSAIDs).
- **Chemical formula:** $C_{14}H_{12}Cl_2N_2O_2$
- **Physical properties:** White to pale yellow crystalline powder; practically insoluble in water.
- **Structural features:**
  - Contains **two chlorine atoms** on the phenyl ring, which enhance potency.
  - Possesses an **o-aminobenzoic acid core** (anthranilic acid derivative).
  - Carboxylic acid (-COOH) group is essential for anti-inflammatory activity.



Mechanism of Action (MOA)

- Non-selective **COX-1 and COX-2 inhibitor**.
- Inhibits **prostaglandin synthesis** by blocking arachidonic acid conversion.
- Reduces **inflammation, pain, and fever** primarily by peripheral action.

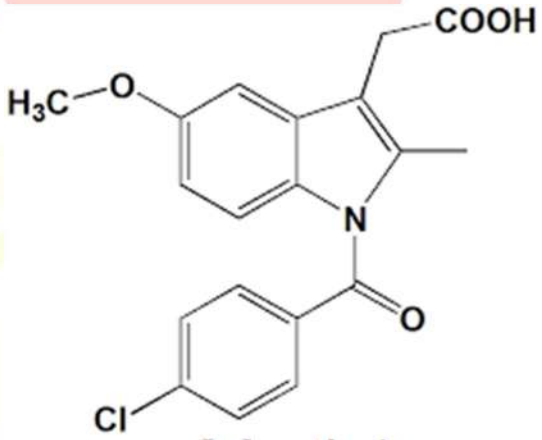
Therapeutic Uses

- **Pain management:** mild to moderate pain.
- **Inflammatory conditions:** rheumatoid arthritis, osteoarthritis, ankylosing spondylitis.

Indomethacin

Structure

- **Chemical class:** Indole acetic acid derivative (NSAID).
- **Chemical formula:** $C_{19}H_{16}ClNO_4$
- **Physical properties:** White to slightly yellow crystalline powder; sparingly soluble in water.
- **Structural features:**
  - Indole nucleus is essential for anti-inflammatory activity.
  - Contains a **chlorobenzoyl group** at the 1-position.
  - Carboxylic acid (-COOH) group contributes to COX inhibition and anti-inflammatory activity.



Indomethacin

Mechanism of Action (MOA)

- Non-selective **COX-1 and COX-2 inhibitor**.
- Inhibits **prostaglandin synthesis** → reduces inflammation, pain, and fever.
- Also inhibits **leukocyte migration** and **platelet aggregation** to some extent.

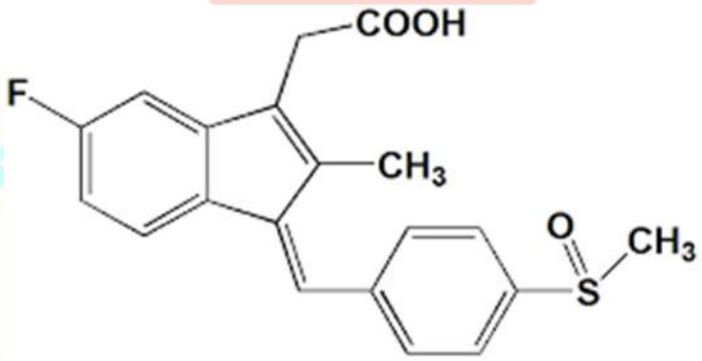
Therapeutic Uses

- **Inflammatory conditions:**
  - Rheumatoid arthritis, osteoarthritis, ankylosing spondylitis.
- **Acute gout attacks:** reduces pain and inflammation.
- **Pain management:** mild to moderate pain, especially in musculoskeletal disorders.
- **Patent ductus arteriosus (PDA) in neonates:** helps close PDA by inhibiting prostaglandin synthesis.

Sulindac

Structure

- **Chemical class:** Arylalkanoic acid derivative (NSAID).
- **Chemical formula:** $C_{20}H_{16}O_3S$
- **Physical properties:** White to off-white crystalline powder; sparingly soluble in water.
- **Structural features:**
  - Contains a **sulfinyl group (-S=O)** which is metabolically reduced to the active sulfide form.
  - Carboxylic acid (-COOH) group is crucial for COX inhibition.
  - Aromatic rings contribute to anti-inflammatory activity.



Sulindac

Mechanism of Action (MOA)

- Prodrug: **Converted to active sulfide metabolite** in the liver.
- **Non-selective COX inhibitor** → inhibits prostaglandin synthesis.
- Reduces **inflammation, pain, and fever**.
- May also **inhibit neutrophil migration**, contributing to anti-inflammatory effect.

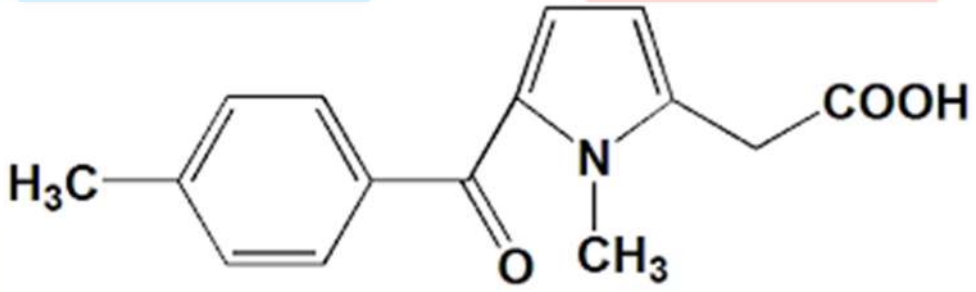
Therapeutic Uses

- **Rheumatoid arthritis**
- **Osteoarthritis**
- **Ankylosing spondylitis**
- **Acute gout attacks** (for pain and inflammation)

Tolmetin

Structure

- **Chemical class:** Arylacetic acid derivative (NSAID).
- **Chemical formula:** $C_{14}H_{14}O_3$
- **Physical properties:** White to off-white crystalline powder; slightly soluble in water, freely soluble in alcohol and chloroform.
- **Structural features:**
  - Contains a **carboxylic acid (-COOH) group** essential for COX inhibition.
  - Aromatic rings enhance anti-inflammatory and analgesic activity.
  - Methyl substituents improve lipophilicity and absorption.



Tolmetin

Mechanism of Action (MOA)

- **Non-selective COX inhibitor** → inhibits prostaglandin synthesis.
- Reduces **inflammation, pain, and fever**.
- Acts mainly by reducing prostaglandins responsible for pain and swelling in inflamed tissues.

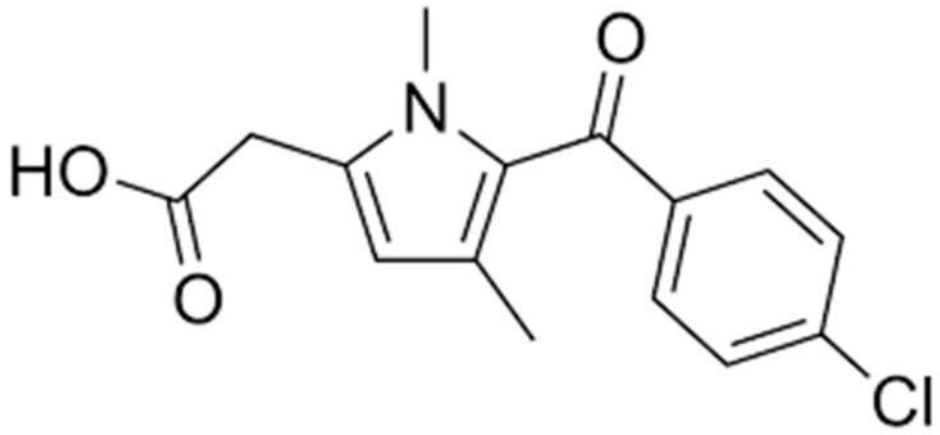
Therapeutic Uses

- **Rheumatoid arthritis**
- **Osteoarthritis**
- **Ankylosing spondylitis**
- **Acute musculoskeletal pain**
- Can be used for **mild to moderate pain relief** in other inflammatory conditions.

Zomepirac

Structure

- **Chemical class:** Pyrrole-acetic acid derivative (NSAID).
- **Chemical formula:** $C_{14}H_{13}NO_4$
- **Physical properties:** White to off-white crystalline powder; slightly soluble in water, soluble in organic solvents like ethanol.
- **Structural features:**
  - Contains **carboxylic acid (-COOH)** group essential for COX inhibition.
  - Aromatic and heteroaromatic rings contribute to **anti-inflammatory and analgesic activity**.
  - Nitrogen atom in pyrrole ring enhances receptor interaction and potency.



Mechanism of Action (MOA)

- **Non-selective COX inhibitor** → inhibits prostaglandin synthesis.
- Reduces **pain, inflammation, and fever**.
- Highly potent NSAID, providing **rapid analgesic effect** in acute pain conditions.

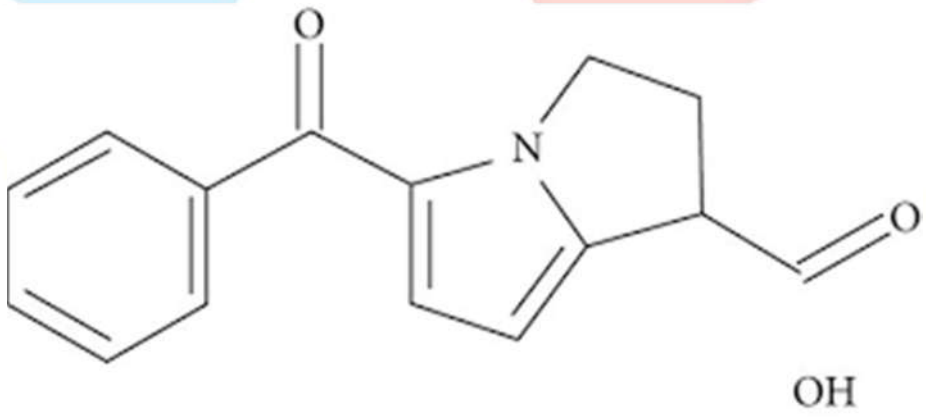
Therapeutic Uses

- **Acute musculoskeletal pain**
- **Postoperative pain management**
- **Rheumatoid arthritis**
- **Osteoarthritis** (less commonly, due to availability of safer alternatives)

Ketorolac

Structure

- **Chemical class:** Pyrrolizine carboxylic acid derivative (NSAID).
- **Chemical formula:** $C_{16}H_{13}NO_3$
- **Physical properties:** White to off-white crystalline powder; practically insoluble in water, soluble in organic solvents like ethanol.
- **Structural features:**
  - Contains **carboxylic acid (-COOH) group** essential for cyclooxygenase (COX) inhibition.
  - Aromatic and heteroaromatic rings contribute to **anti-inflammatory and analgesic activity**.
  - Pyrrolizine moiety increases **potency and bioavailability**.



Mechanism of Action (MOA)

- **Non-selective COX inhibitor** → inhibits **prostaglandin synthesis**.
- Reduces **pain, inflammation, and fever**.
- Provides **potent analgesic effect**, often used for **moderate to severe pain**, comparable to weak opioids.

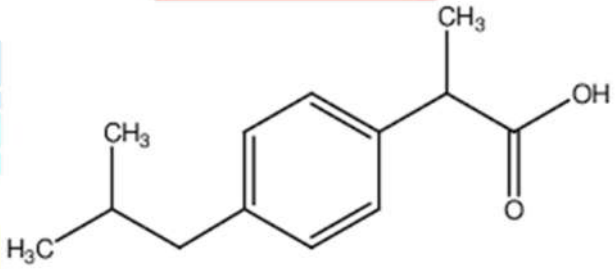
Therapeutic Uses

- **Acute musculoskeletal pain**
- **Postoperative pain management**
- **Dental pain**
- **Short-term management of moderate to severe pain**

Ibuprofen

Structure

- **Chemical class:** Propionic acid derivative (NSAID).
- **Chemical formula:** $C_{13}H_{18}O_2$
- **Physical properties:** White crystalline powder; practically insoluble in water; soluble in ethanol and methanol.
- **Structural features:**
  - Contains a **carboxylic acid (-COOH) group** → essential for COX inhibition.
  - **Aromatic ring** contributes to anti-inflammatory and analgesic activity.
  - **Isobutyl side chain** at α-position enhances **potency and selectivity**.



Ibuprofen

Mechanism of Action (MOA)

- **Non-selective cyclooxygenase (COX-1 and COX-2) inhibitor** → inhibits prostaglandin synthesis.
- Reduces:
  - **Pain (analgesic effect)**
  - **Inflammation (anti-inflammatory effect)**
  - **Fever (antipyretic effect)**
- Works primarily by **reducing prostaglandin-mediated sensitization of pain receptors**.

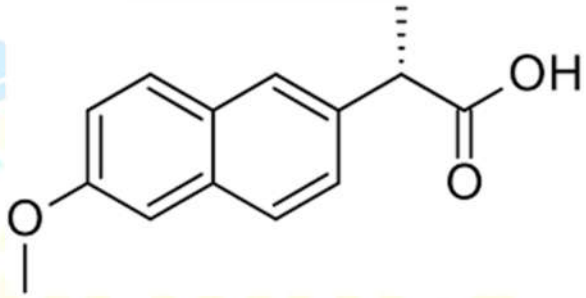
Therapeutic Uses

- Mild to moderate **pain**: headaches, toothache, muscle pain.
- **Inflammatory conditions:** rheumatoid arthritis, osteoarthritis, ankylosing spondylitis.
- **Fever reduction (antipyretic)**.

Naproxen

Structure

- **Chemical class:** Propionic acid derivative (NSAID)
- **Chemical formula:** $C_{14}H_{14}O_3$
- **Physical properties:** White or almost white crystalline powder; slightly soluble in water; soluble in alcohol and acetone.
- **Structural features:**
  - **Carboxylic acid (-COOH) group** → essential for COX inhibition.
  - **Naphthalene ring** → contributes to anti-inflammatory and analgesic activity.
  - **Chiral center (S-enantiomer is active)** → responsible for pharmacological activity.



Mechanism of Action (MOA)

- **Non-selective inhibitor of cyclooxygenase (COX-1 and COX-2)** → blocks prostaglandin synthesis.
- Reduces:
  - **Pain (analgesic effect)**
  - **Inflammation (anti-inflammatory effect)**
  - **Fever (antipyretic effect)**
- Acts by **reducing prostaglandin-mediated sensitization of pain receptors**.

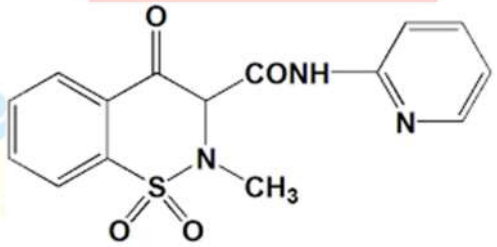
Therapeutic Uses

- **Pain relief:** headaches, dental pain, musculoskeletal pain, postoperative pain.
- **Inflammatory disorders:** rheumatoid arthritis, osteoarthritis, ankylosing spondylitis, juvenile arthritis.
- **Dysmenorrhea:** relief of menstrual pain.

Piroxicam

Structure

- **Chemical class:** Oxicam derivative (NSAID)
- **Chemical formula:** $C_{20}H_{18}N_2O_4S$
- **Physical properties:** Yellow crystalline powder; practically insoluble in water; soluble in alcohol and dimethylformamide.
- **Structural features:**
  - **Enolic hydroxyl group (-OH)** → essential for COX inhibition.
  - **Carboxamide moiety** → contributes to anti-inflammatory activity.
  - **Furan ring** → increases lipophilicity and tissue penetration.



Piroxicam

Mechanism of Action (MOA)

- **Non-selective inhibitor of cyclooxygenase (COX-1 and COX-2)** → inhibits prostaglandin synthesis.
- Reduces:
  - **Pain (analgesic effect)**
  - **Inflammation (anti-inflammatory effect)**
  - **Fever (antipyretic effect)**
- By decreasing prostaglandin-mediated sensitization of nociceptors, it alleviates pain and inflammation.

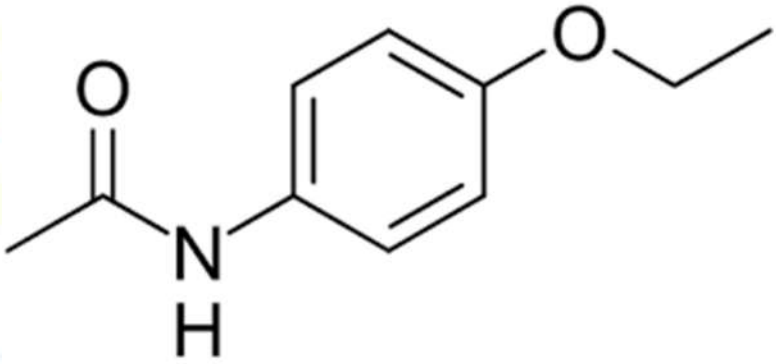
Therapeutic Uses

- **Rheumatic diseases:**
  - Rheumatoid arthritis
  - Osteoarthritis
  - Ankylosing spondylitis
- **Acute musculoskeletal pain**
- **Postoperative pain and inflammation**

Phenacetin

Structure

- **Chemical class:** Acetanilide derivative (non-opioid analgesic/antipyretic)
- **Chemical formula:** $C_{10}H_{13}NO_2$
- **Physical properties:** White crystalline powder; slightly soluble in water; soluble in alcohol.
- **Structural features:**
  - **Acetylated aniline group (-$NHCOCH_3$)** → responsible for analgesic activity.
  - **Ethoxy group (-OCH_2CH_3)** on aromatic ring → contributes to lipid solubility.



Mechanism of Action (MOA)

- **Analgesic and antipyretic effects:**
  - Metabolized in the liver to **paracetamol (acetaminophen)**, which inhibits prostaglandin synthesis in CNS.
  - Reduces **pain and fever** without significant anti-inflammatory action.
- **No significant peripheral COX inhibition** → less GI irritation compared to NSAIDs.

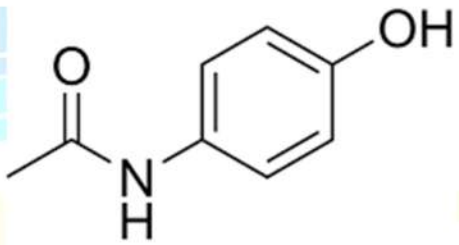
Therapeutic Uses

- **Mild to moderate pain relief**
  - Headache
  - Toothache
  - Musculoskeletal pain

Acetaminophen (Paracetamol)

Structure

- Chemical class: Para-aminophenol derivative (non-opioid analgesic/antipyretic)
- Chemical formula: $C_8H_9NO_2$
- Physical properties: White crystalline powder; freely soluble in hot water; slightly soluble in cold water; soluble in alcohol.
- Structural features:
  - Phenolic hydroxyl group (-OH) → responsible for analgesic and antipyretic activity.
  - Amide group (-$NHCOCH_3$) → contributes to CNS activity and reduced peripheral side effects compared to NSAIDs.



Mechanism of Action (MOA)

- Analgesic and antipyretic effects:
  - Inhibits central cyclooxygenase (COX) enzymes, reducing prostaglandin synthesis in CNS → decreases pain perception and fever.
  - Minimal inhibition of peripheral COX → less GI irritation and no significant anti-inflammatory effect.
- Antipyretic effect: Acts on hypothalamic heat-regulating center, promoting heat dissipation.

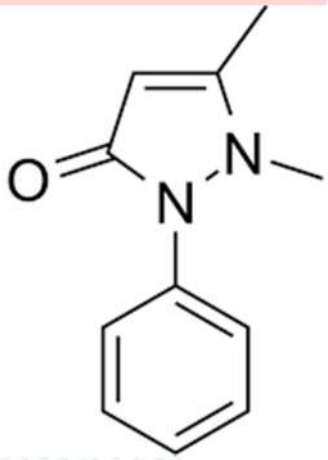
Therapeutic Uses

- Analgesic (pain relief):
  - Headache, toothache, musculoskeletal pain, postoperative pain.
- Antipyretic (fever reduction):
  - Fever due to infections or other causes.
- Safe alternative to NSAIDs in patients with peptic ulcer or bleeding risk.

Antipyrine (Phenazone)

Structure

- Chemical class: Pyrazolone derivative (non-opioid analgesic/antipyretic)
- Chemical formula: $C_{11}H_{12}N_2O$
- Physical properties: White crystalline powder; slightly soluble in water; soluble in alcohol and ether.
- Structural features:
  - Pyrazolone ring → central to its analgesic and antipyretic activity.
  - Substituted methyl and phenyl groups → modulate lipophilicity and potency.



Mechanism of Action (MOA)

- Analgesic and antipyretic effects:
  - Inhibits prostaglandin synthesis in CNS, decreasing pain perception and lowering fever.
  - Weak peripheral COX inhibition → minimal anti-inflammatory effect.
- Additional action: Mild central inhibition of pain and temperature-regulating centers in hypothalamus.

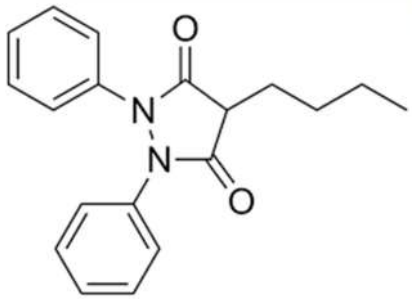
Therapeutic Uses

- Analgesic: Mild to moderate pain, including headache, toothache, musculoskeletal pain.
- Antipyretic: Fever reduction in infections or postoperative fever.
- Occasionally used as a topical ear analgesic in combination ear drops.

Phenylbutazone

Structure

- Chemical class: Pyrazolidinedione derivative
- Chemical formula: $C_{19}H_{20}N_2O_2$
- Physical properties: White or off-white crystalline powder; slightly soluble in water, soluble in alcohol and ether.
- Structural features:
  - Pyrazolidinedione ring → essential for anti-inflammatory and analgesic activity.
  - Phenyl groups at positions 1 and 2 → increase lipophilicity and activity.



Mechanism of Action (MOA)

- Primary action: Non-selective cyclooxygenase (COX) inhibitor, reducing prostaglandin synthesis.
- Effects:
  - Anti-inflammatory → reduces inflammation and edema.
  - Analgesic → decreases pain perception by lowering prostaglandin-mediated sensitization of nociceptors.
  - Antipyretic → lowers fever by acting on hypothalamic thermoregulatory centers.
- Additional: Can inhibit leukocyte migration, contributing to anti-inflammatory effect.

Therapeutic Uses

- Rheumatic diseases: Rheumatoid arthritis, ankylosing spondylitis, osteoarthritis (historically).
- Gout: Acute gouty arthritis attacks.
- Musculoskeletal pain: Severe pain due to soft tissue injuries (limited use now).