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Narcotic and non-narcotic analgesics

Presented By;-

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Specialization:- Pharmaceutical Chemistry

Narcotic and non-narcotic analgesics

1. Narcotic Analgesics (Opioid Analgesics)

Definition:
Drugs that relieve **severe pain** by acting on **opioid receptors (μ, κ, δ)** in the central nervous system. They also produce **sedation**, **euphoria**, and can cause **dependence**.

Examples:

- ✓ Morphine
- ✓ Codeine
- ✓ Fentanyl
- ✓ Pethidine (Meperidine)

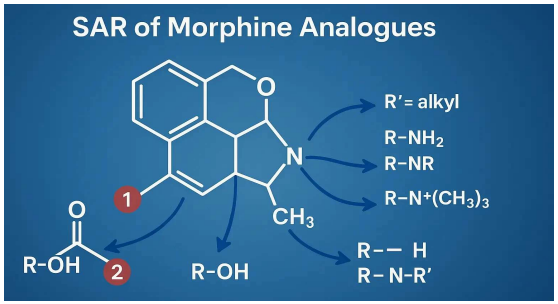
2. Non-narcotic Analgesics (Non-opioid Analgesics)

Definition:
Drugs that relieve **mild to moderate pain** without causing dependence or euphoria. These mainly act **peripherally** by inhibiting **prostaglandin synthesis**.

Examples:

- ✓ Paracetamol (Acetaminophen)
- ✓ NSAIDs: Aspirin, Ibuprofen, Diclofenac
- ✓ Selective COX-2 inhibitors: Celecoxib

SAR of Morphine analogues



1. Phenolic OH at C-3:

- ✓ **Essential** for activity via H-bonding with opioid receptors.
- ✓ **Methylation** (e.g., codeine) reduces potency but improves oral bioavailability.

2. Alcoholic OH at C-6:

- ✓ Modifications affect potency/duration.
- ✓ Oxidation to ketone (e.g., oxymorphone) boosts potency.
- ✓ Acetylation (e.g., heroin) increases lipid solubility and brain entry.

3. C-7/C-8 Double Bond:

- ✓ Reduction (e.g., dihydromorphine) usually increases potency.
- ✓ Removal adds flexibility, possibly reducing selectivity

4. Aromatic A-Ring:

- ✓ Needed for **π–π interactions** with receptors.
- ✓ Substitutions often reduce activity unless planarity/electron density are preserved.

5. Tertiary Amine at N-17:

- ✓ **Critical for activity** – binds receptor's negative site.
- ✓ **Small groups (methyl)** = agonist.
- ✓ **Bulkier groups (e.g., cyclopropylmethyl)** = antagonist or mixed activity.

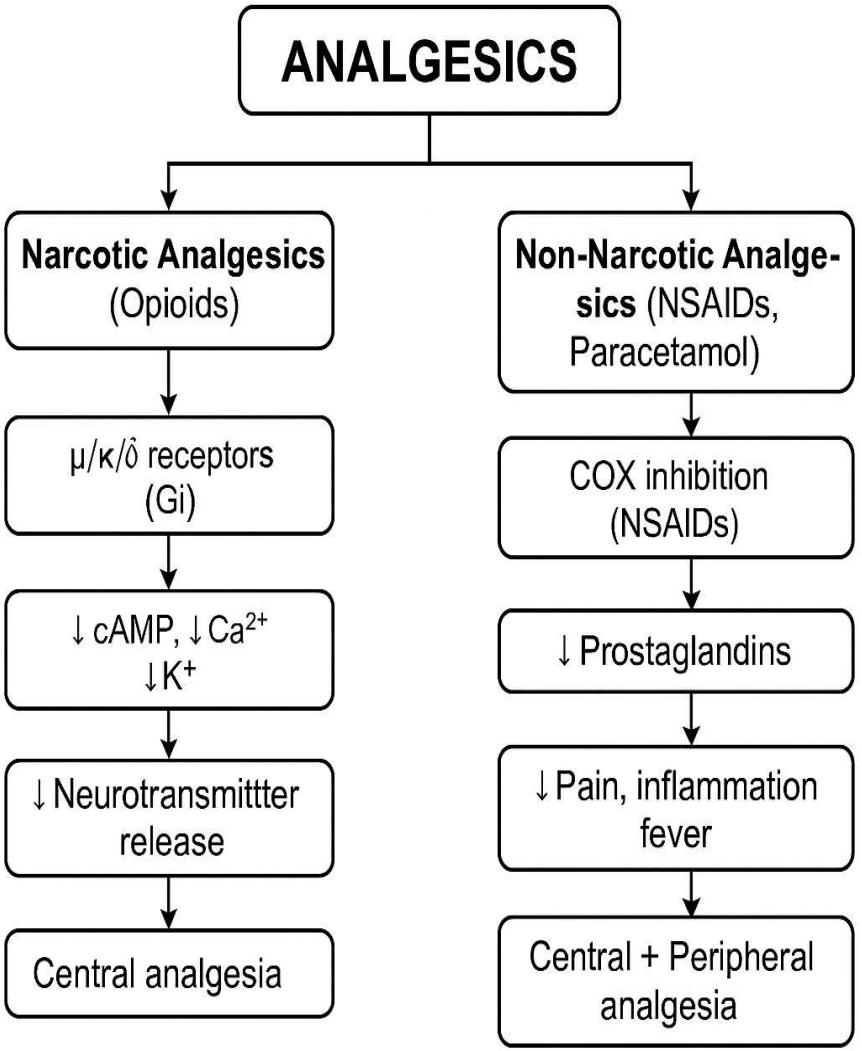
6. N-to-Aromatic Ring Distance:

- ✓ **2-carbon span is optimal**.
- ✓ Altering these spacing lowers activity.

7. Rigid Ring Conformation:

- ✓ Fused ring rigidity maintains receptor-binding orientation.
- ✓ Flexibility (in some analogues) may affect potency/selectivity.

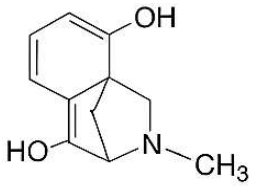
MOA of Narcotic and non-narcotic analgesics

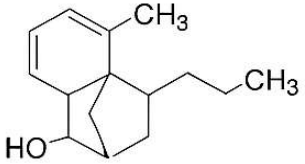


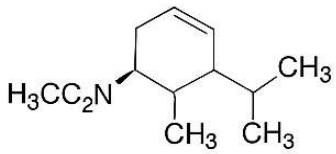
Classification of Narcotic and non-narcotic analgesics

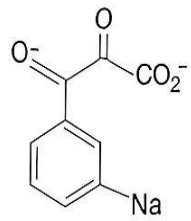
1. **Morphine and related drugs:-** Morphine sulphate, Codeine, Meperidine hydrochloride, Anilerdine hydrochloride, Diphenoxylate hydrochloride, Loperamide hydrochloride, Fentanyl citrate*, Methadone hydrochloride*, Propoxyphene hydrochloride, Pentazocine, Levorphanol tartarate.
2. **Narcotic antagonists:** Nalorphine hydrochloride, Levallorphan tartarate, Naloxone hydrochloride.
3. **Anti-inflammatory agents:** Sodium salicylate, Aspirin, Mefenamic acid*, Meclofenamate, Indomethacin, Sulindac, Tolmetin, Zomepriac, Diclofenac, Ketorolac, Ibuprofen*, Naproxen, Piroxicam, Phenacetin, Acetaminophen, Antipyrine, Phenylbutazone.

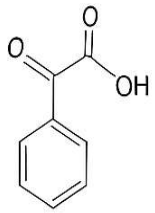
Chemical Structure

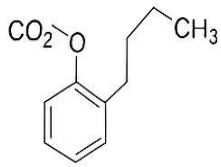

Morphine sulfate

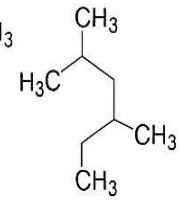

Codeine


Anileridine hydrochlorid

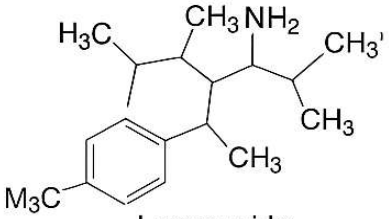

Sodium salicylate


Aspirin


Mefenamic acid*


Meclofenanate


Diphenoxylate hydrochloride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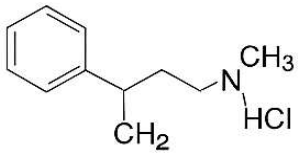
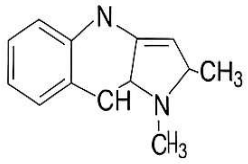
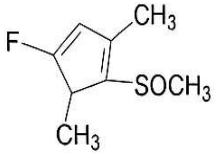
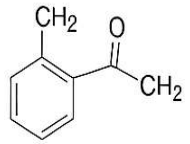
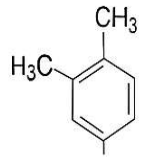

Fentanyl citrate


Indomethacin


Sulindac


Zomepriac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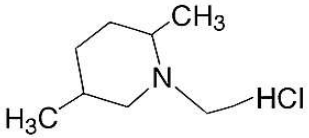
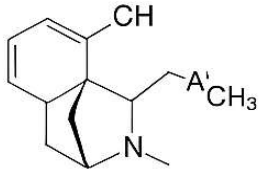
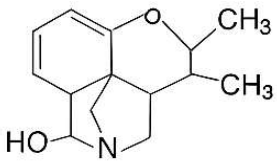
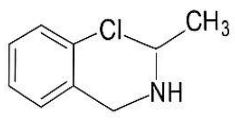
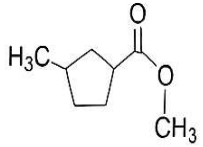
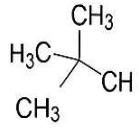

Propoxyphene hydrochloride

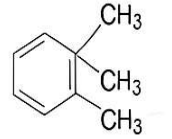

Levorphano tartrate

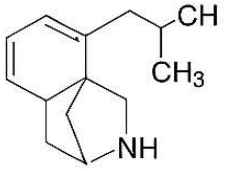

Nalorphine hydrochlorie

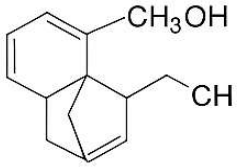

Diclofenac

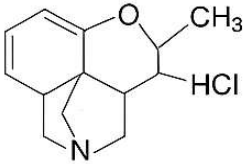

Ketorolac


Ibuprofen

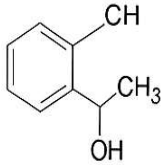

Naproxen

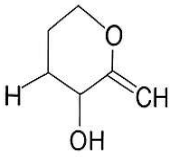

Propoxyphene hydrochloride

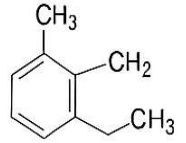

Levallorphan tartrate


Naloxone hydrochlorze


Phenacetin


Phenacetin

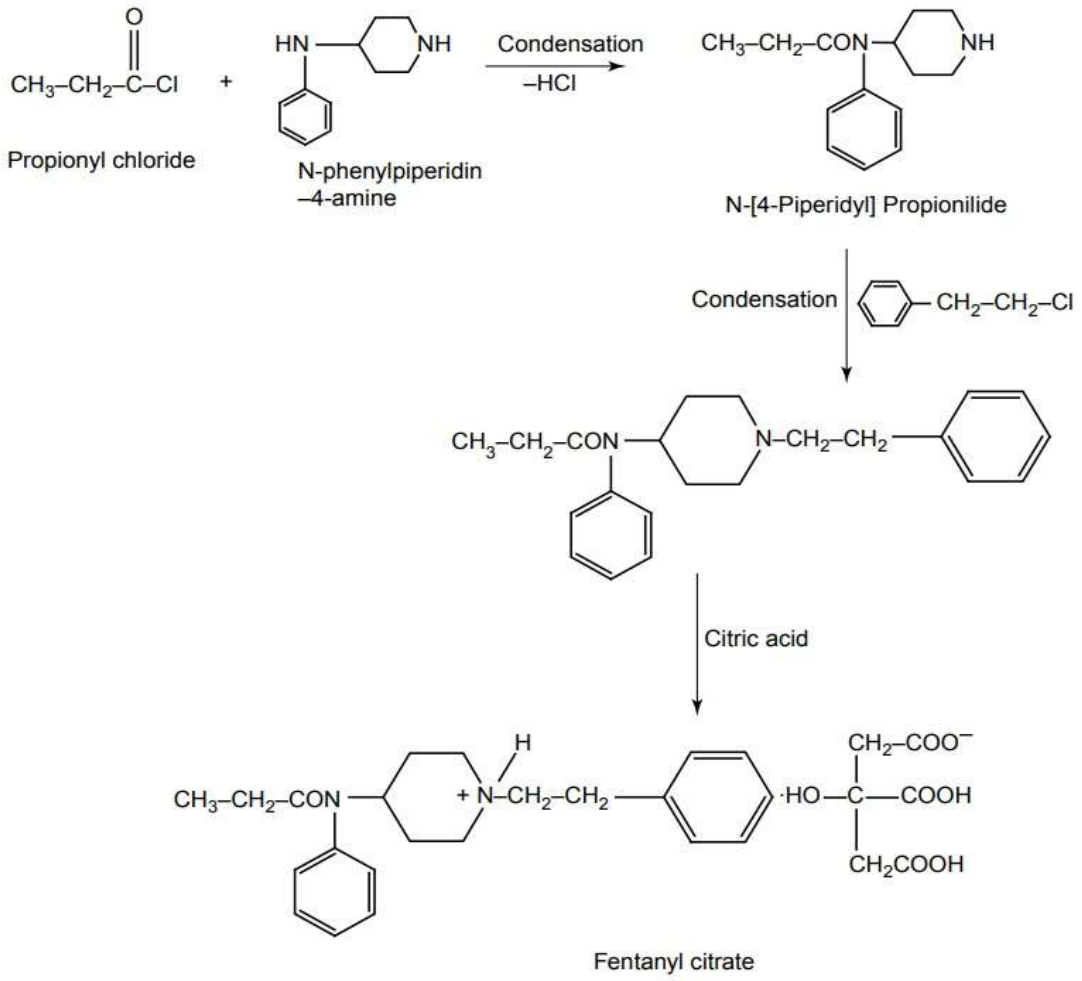

Acetaminophen


Antipyrine

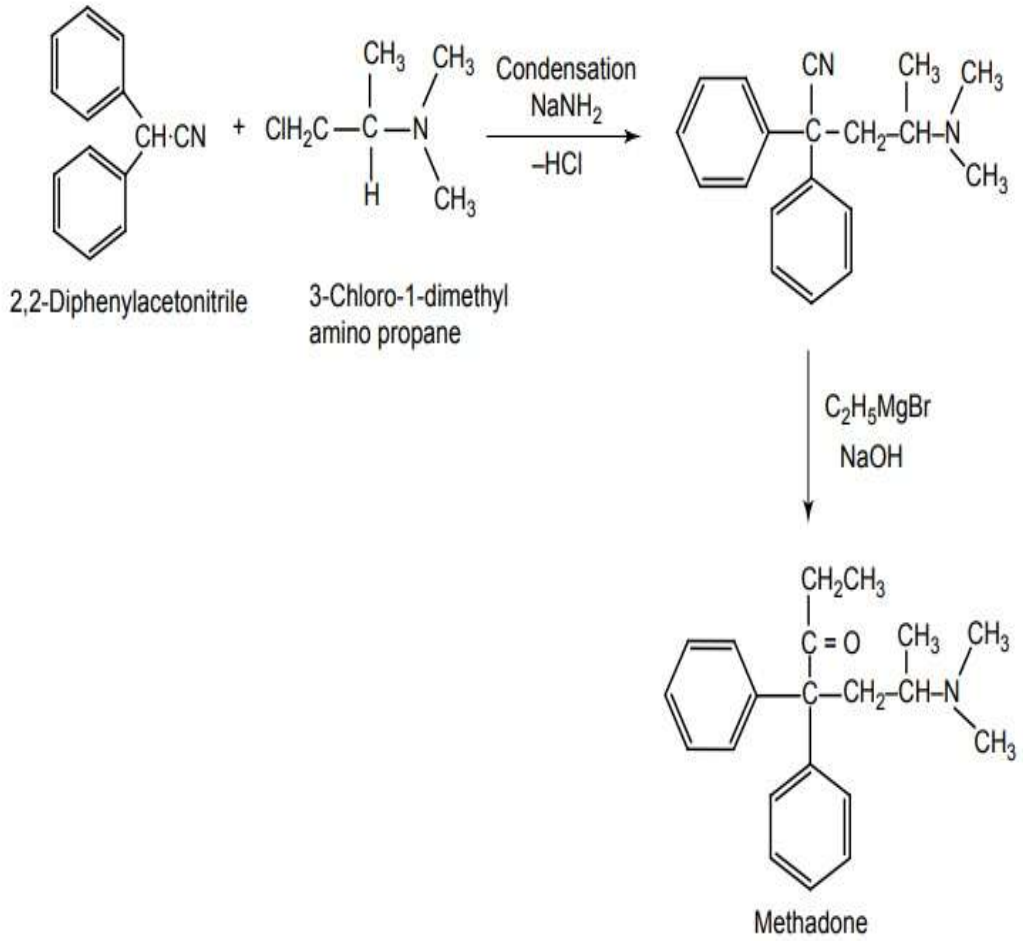
Morphine and related drugs

Drug	Introduction	Mechanism of Action (MOA)	Uses
Morphine sulphate	Prototype natural opioid analgesic; strong agonist.	Binds μ-opioid receptors → inhibits pain pathways, ↓ neurotransmitter release.	Severe pain, MI pain, postoperative pain, pulmonary edema.
Codeine	Natural methyl-morphine; weaker analgesic; good antitussive.	Weak μ-agonist; converted to morphine in body.	Mild–moderate pain, cough suppression.
Meperidine hydrochloride	Synthetic opioid; rapid onset; short duration.	μ-receptor agonist; inhibits pain signals; anticholinergic properties.	Moderate–severe pain, labor pain, postoperative pain.
Anileridine hydrochloride	Synthetic analogue of meperidine.	μ-receptor agonist → CNS analgesia.	Moderate–severe acute pain.
Diphenoxylate hydrochloride	Meperidine analogue used for diarrhea; low analgesia.	μ-receptor action ↓ GI motility; poor CNS penetration.	Diarrhea treatment (with atropine).
Loperamide hydrochloride	Peripherally acting opioid; does NOT cross BBB.	μ-receptor agonist in gut → slows peristalsis.	Diarrhea (OTC antidiarrheal).
Fentanyl citrate*	Very potent synthetic opioid (100× morphine); rapid onset.	Strong μ-receptor agonist → intense analgesia & anesthesia.	Anesthesia adjunct, severe pain, cancer pain, postoperative pain.
Methadone hydrochloride*	Long-acting synthetic opioid; oral efficacy high.	μ-agonist + NMDA antagonist; long duration.	Chronic pain, opioid dependence (withdrawal therapy).
Propoxyphene hydrochloride	Weak opioid analgesic (withdrawn in many countries).	Weak μ-receptor agonist; mild CNS depression.	Mild–moderate pain (historical use).
Pentazocine	Mixed agonist-antagonist opioid; κ-agonist.	κ-agonist, weak μ-antagonist → less respiratory depression.	Moderate pain, obstetric pain.
Levorphanol tartrate	Morphinan derivative; potent opioid.	Strong μ-, κ-, δ-agonist; inhibits NMDA receptors; inhibits reuptake of NE.	Severe chronic pain, neuropathic pain.

Synthesis of Fentanyl citrate



Synthesis of Methadone



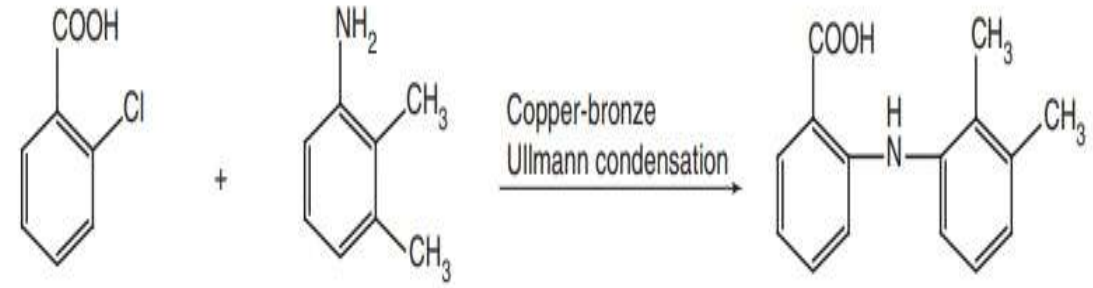
Narcotic antagonists

Drug	Introduction	Mechanism of Action (MOA)	Uses
Nalorphine hydrochloride	First opioid antagonist; mixed action (κ-agonist, weak μ-antagonist).	Blocks μ-opioid receptors → reverses respiratory depression; κ-agonist causes dysphoria.	Reversal of opioid-induced respiratory depression (rarely used today due to side effects).
Levallorphan tartrate	Potent opioid antagonist; similar to nalorphine but with fewer side effects.	Competitive μ-receptor antagonist; weak agonist at κ-receptors.	Antidote for opioid overdose; reversal of opioid anesthesia.
Naloxone hydrochloride	Pure opioid antagonist; short-acting; no agonist properties.	Strong competitive antagonist at μ, κ, and δ receptors; rapidly reverses all opioid effects.	Emergency treatment of opioid overdose, reversal of respiratory depression, diagnosis of opioid intoxication, antidote for newborns of opioid-treated mothers.

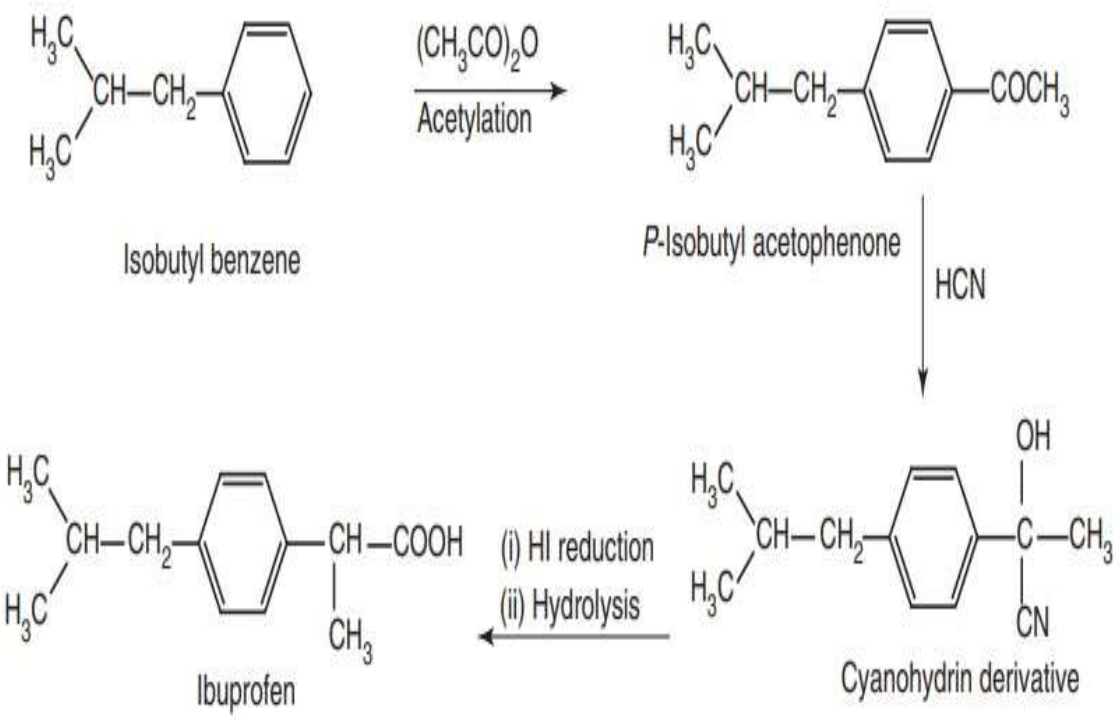
Anti-inflammatory agents

Drug	Introduction	Mechanism of Action (MOA)	Uses
Sodium salicylate	Oldest non-acetylated salicylate; mild analgesic.	Inhibits COX-1 & COX-2, ↓ prostaglandins.	Mild pain, fever, inflammatory conditions.
Aspirin (Acetylsalicylic acid)	Prototype NSAID; irreversible COX inhibitor.	Irreversibly acetylates COX-1/COX-2 → ↓ prostaglandins & thromboxane.	Pain, fever, inflammation, antiplatelet (MI, stroke prevention).
Mefenamic acid*	Fenamate class NSAID.	COX inhibition + inhibits prostaglandin receptors.	Dysmenorrhea, mild–moderate pain.
Meclofenamate	Fenamate NSAID; more potent than mefenamic acid.	Inhibits COX and antagonizes prostaglandins.	Acute pain, dysmenorrhea, arthritis.
Indomethacin	Potent nonselective NSAID; indole derivative.	Strong COX-1/2 inhibition; inhibits leukocyte migration.	Acute gout, RA, PDA closure in infants.
Sulindac	Indomethacin prodrug; less GI toxicity.	COX inhibition after hepatic activation.	RA, OA, acute gout, musculoskeletal pain.
Tolmetin	Pyrrole acetic NSAID.	Inhibits COX → ↓ prostaglandins.	Juvenile RA, OA, RA.
Zomepirac	Potent analgesic NSAID (withdrawn due to anaphylaxis).	COX inhibition; strong analgesia.	Historical use for severe pain.
Diclofenac	Phenylacetic acid NSAID; highly potent.	Preferential COX-2 inhibitor; ↓ prostaglandins.	RA, OA, ankylosing spondylitis, acute pain.
Ketorolac	Potent NSAID with opioid-level analgesia.	Strong COX inhibition; minimal anti-inflammatory effect.	Acute moderate-to-severe pain (post-operative).
Ibuprofen*	Propionic acid derivative; widely used OTC.	Reversible COX-1/2 inhibition.	Fever, pain, dysmenorrhea, arthritis.
Naproxen	Long-acting propionic acid NSAID.	Inhibits COX-1 & COX-2.	RA, OA, gout, dysmenorrhea.
Piroxicam	Oxicam derivative; long half-life (once-daily).	COX inhibition; inhibits neutrophil activation.	Chronic RA, OA.
Phenacetin	Older analgesic; metabolized to acetaminophen.	Weak COX inhibitor; central action.	Mild pain & fever (withdrawn in many countries).
Acetaminophen (Paracetamol)	Widely used antipyretic/analgesic; weak anti-inflammatory.	Inhibits central COX; no peripheral anti-inflammatory effect.	Fever, mild pain (safe in pregnancy & children).
Antipyrine	Old antipyrine derivative; analgesic & antipyretic.	Inhibits COX enzymes.	Mild pain, fever (mostly historical).
Phenylbutazone	Potent pyrazolone NSAID.	COX inhibition; uricosuric effect.	Acute gout, ankylosing spondylitis (limited due to toxicity).

Synthesis of Mefenamic acid



Synthesis of Ibuprofen



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