Unit-5
Medicinal Chemistry-I

B.Pharma 4th Sem Notes

Unit: 5

- **Drugs acting on Central Nervous System**

General anesthetics:

- **Inhalation anesthetics:** Halothane*, Methoxyflurane, Enflurane, Sevoflurane, Isoflurane, Desflurane.
- **Ultra short acting barbitutrates:** Methohexital sodium*, Thiamylal sodium, Thiopental sodium.
- **Dissociative anesthetics:** Ketamine hydrochloride.*

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.

General anesthetics:

- General anesthetics are medications used to induce a controlled unconsciousness during surgery. This allows patients to be unaware of pain and remain completely still throughout the procedure.
- General anesthesia causes unconsciousness, blocks pain, and relaxes muscles. It's delivered through an IV or inhaled as a gas.
- The cardinal features of general anesthesia are:
  - Loss of all sensation, especially pain
  - Sleep (unconsciousness) and amnesia
  - Immobility and muscle relaxation
  - Abolition of somatic and autonomic reflexes.

Stage of General anaesthetics:

- General anaesthetics cause an irregularly descending depression of the CNS.
- The higher functions are lost first and progressively lower areas of the brain are involved but in the spinal cord lower segments are affected somewhat earlier than the higher segments.
- The description of these stages still serves to define the efforts of light and deep anesthesia.

Important features of different stages are –

1. **Stage I**
   - Analgesia state: Patient is conscious and rational, with decreased perception of pain.
2. **Stage-II**
   - Delirium stage: Patient is unconscious; body responds reflexively; irregular breathing pattern with breath holding.
3. **Stage-III**
   - Surgical anesthesia: Increasing degrees of muscle relaxation; unable to protect airway.
4. **Stage IV**
   - Medullary depression: There is depression of cardiovascular and respiratory centers.

Properties of an ideal anesthetic

A. For the patient

- It should be pleasant, non-irritating, should not cause nausea or vomiting. Induction and recovery should be fast with no after effects.

B. For the surgeon

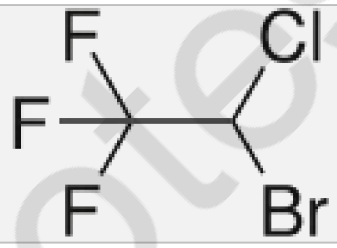
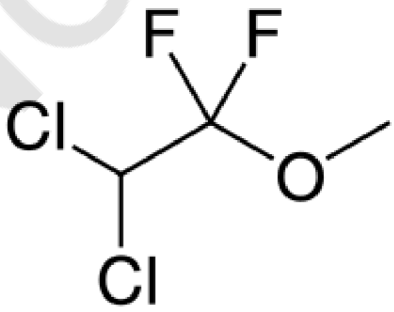
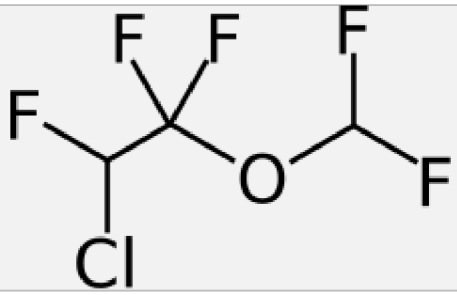
- It should provide adequate analgesia, immobility and muscle relaxation. It should be noninflammable and non-explosive so that cautery may be used.

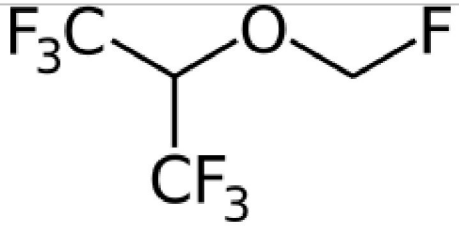
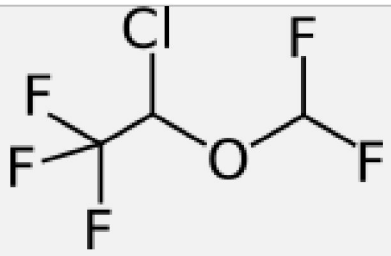
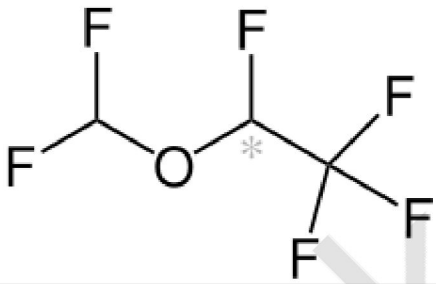
C. For the anesthetist

- Its administration should be easy, controllable and versatile.
- Margin of safety should be wide-no fall in BP. Heart, liver and other organs should not be affected.
- It should be potent so that low concentrations are needed and oxygenation of the patient does not suffer.
- Rapid adjustments in depth of anesthesia should be possible.
- It should be cheap, stable and easily stored. It should not react with rubber tubing or soda lime.

Classification of General anesthesia:

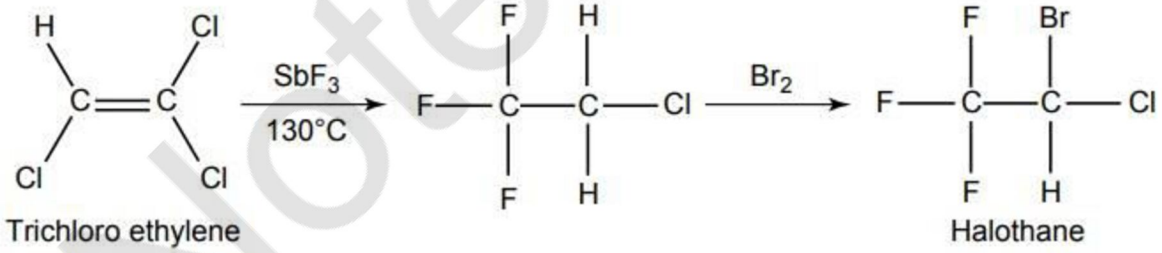
- **Inhalation anesthetics:** Halothane*, Methoxyflurane, Enflurane, Sevoflurane, Isoflurane, Desflurane.
- **Ultra short acting barbitutrates:** Methohexital sodium*, Thiamylal sodium, Thiopental sodium.
- **Dissociative anesthetics:** Ketamine hydrochloride.*

Drug	Structure	Mechanism of Action	Uses
Halothane		Acts on GABA receptors, enhancing inhibition. Also affects NMDA receptors.	General anesthesia in surgeries, especially in pediatric and obstetric patients.
Methoxyflurane		Acts as a volatile anesthetic by enhancing GABAergic inhibition.	Used for general anesthesia but limited due to nephrotoxicity. Now used primarily for analgesia in emergency settings.
Enflurane		Affects GABA receptors, similar to halothane, with lesser effects on myocardial contractility.	General anesthesia, particularly for outpatient surgeries.

Sevoflurane		Acts primarily by enhancing GABAergic inhibition, also has minimal effects on the myocardium.	Used for general anesthesia, especially in pediatric and outpatient surgeries.
Isoflurane		Potentiation of GABA receptors, leading to anesthesia, with minimal effects on myocardial contractility.	General anesthesia, commonly used in surgeries of various types.
Desflurane		Similar to isoflurane but with a more rapid onset and offset due to its lower solubility in blood.	General anesthesia, especially in fast-track surgeries requiring rapid recovery.

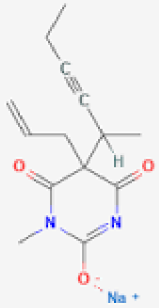
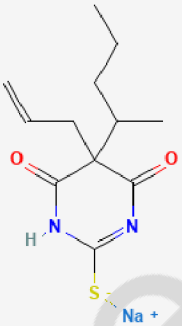
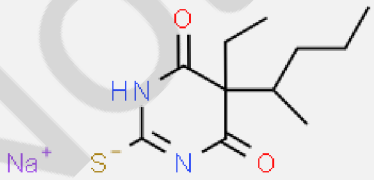
Synthesis of Halothane:

From: Trichloro ethylene

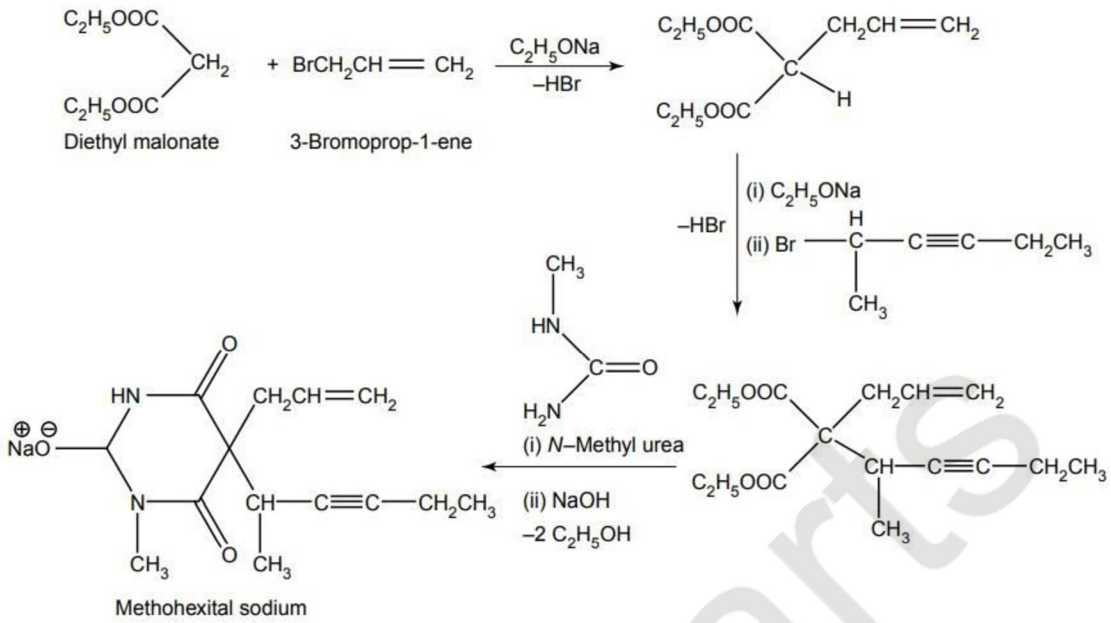


Ultra short acting barbitutrates:

- Barbiturates are a class of medications that were once widely used as general anesthetics.

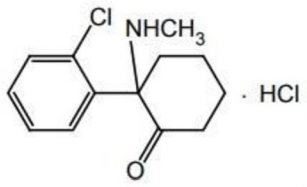
Drug	Structure	Mechanism of Action	Uses
Methohexital Sodium		Enhances GABAergic neurotransmission by binding to GABA-A receptors, leading to hyperpolarization and inhibition of neuronal firing.	Used for induction and maintenance of anesthesia, particularly in short surgical procedures or as a sedative for medical procedures.
Thiamylal Sodium		Acts similarly to methohexital by enhancing GABAergic neurotransmission.	Primarily used for induction and maintenance of anesthesia, particularly in short surgical procedures.
Thiopental Sodium		Enhances GABA-A receptor activity, leading to CNS depression and anesthesia. Additionally, it blocks NMDA receptors.	Used in anesthesia, particularly for rapid onset and short duration procedures, also used in critical care settings such as in the induction of coma for severe brain injuries or elevated intracranial pressure.

Synthesis of Methohexital sodium

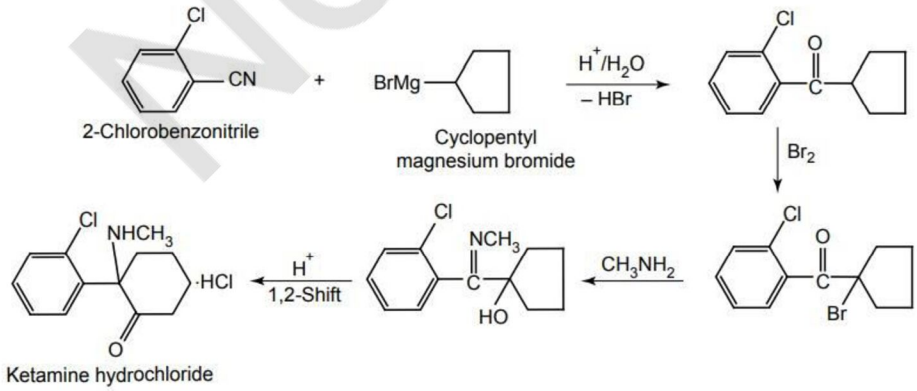


Dissociative anesthetics: Ketamine hydrochloride.*

Ketamine HCl



Synthesis



Uses:

- It is a rapidly acting nonbarbiturate general anaesthetic that produces anaesthesia and is characterized by profound analgesia.

Narcotic and non-narcotic analgesics

- Analgesics are a class of medications used to relieve pain. They work in different ways to achieve pain control. Here's a breakdown of the two main categories:

Narcotic Analgesics (Opioids):

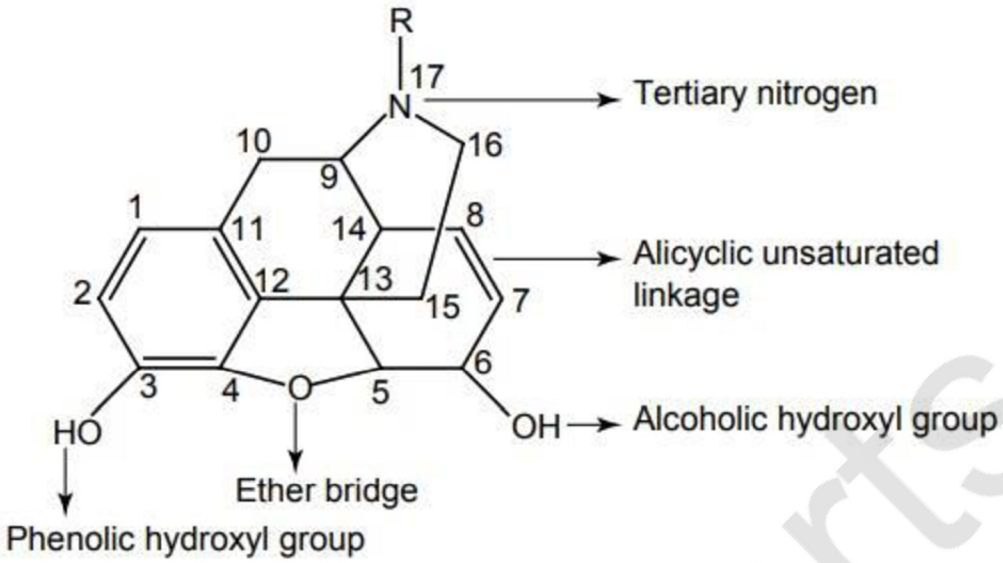
- **Mechanism of Action:** Bind to opioid receptors in the central nervous system (CNS), primarily mu-opioid receptors. This binding inhibits the transmission of pain signals, leading to pain relief.
- **Uses:** Primarily used for moderate to severe pain, such as post-surgical pain, cancer pain, and chronic pain.
- **Examples:** Morphine, codeine (weak opioid), oxycodone, hydrocodone, fentanyl, methadone, etc.
- **Side Effects:** Constipation, nausea, vomiting, drowsiness, respiratory depression (serious), addiction and dependence (potential for abuse).

Non-Narcotic Analgesics:

- **Mechanism of Action:** Work through various mechanisms depending on the specific medication. Some common examples include:
    - Inhibiting the production of prostaglandins, which are chemicals involved in inflammation and pain (e.g., aspirin, ibuprofen).
    - Increasing the pain threshold (e.g., acetaminophen).
- **Uses:** Generally used for mild to moderate pain, such as headaches, muscle aches, menstrual cramps, and fever.
- **Examples:** Aspirin, ibuprofen, naproxen, acetaminophen (paracetamol), etc.
- **Side Effects:** Generally milder than narcotics, but can include stomach upset, heartburn, and kidney problems (with high doses or prolonged use).

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

SAR of Morphine:



1. Modification on alicyclic ring

- The alcoholic hydroxyl group at C-6 when methylated, esterified, oxydized, removed, or replaced by halogen analgesic activity as well as toxicity of the compound increased.
- The reduction of C-6 keto group to C-6 β hydroxyl in oxymorphone gives Nalbupine, it shows antagonistic action of μ receptors.
- The saturation of the double bond at C-7 position gives more potent compound. Examples, Dihydro morphine and Dihydro codeine.
- The 14 β hydroxyl group generally enhances μ agonistic properties and decreases antitussive activity.

However, activity varies with the overall substitution on the structure.

- Bridging of C-6 and C-14 through ethylene linkage gives potent derivatives.
- Reaction of thebaine with dienophile (i.e diel's alder reaction) results in 6, 14 endo etheno tetrahydro thebaine derivatives, which are commonly called 'oripavines'. Some oripavines are extremely potent μ agonist, for example, Etorphine and Buprenorphine are the best known. These derivatives are about thousand times more potent than morphine as μ agonist.

2. Modification on phenyl ring

- An aromatic phenyl ring is essential for activity.
- Modification on phenolic hydroxyl group decreases the activity.
- Any other substitution on phenyl ring diminishes activity.

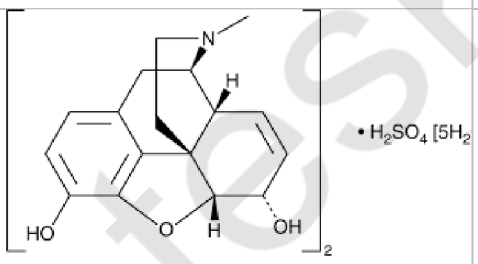
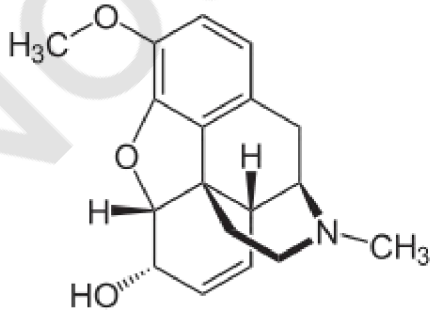
3. Modification of 3° nitrogen

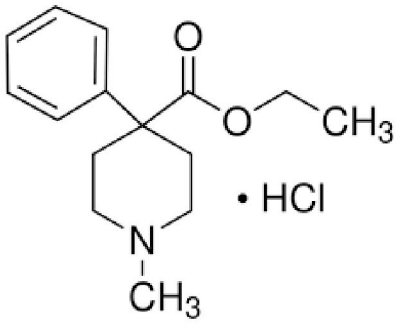
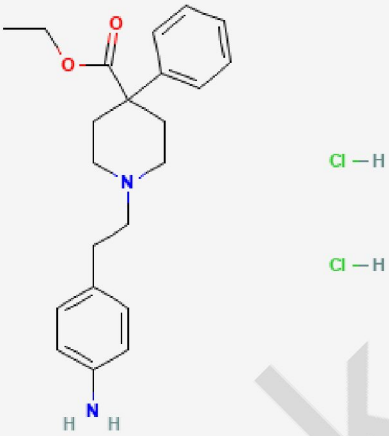
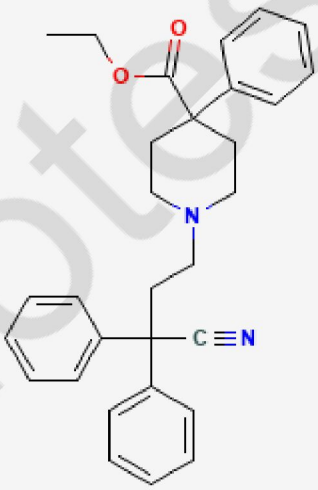
- A tertiary amine is usually necessary for good opioid activity.

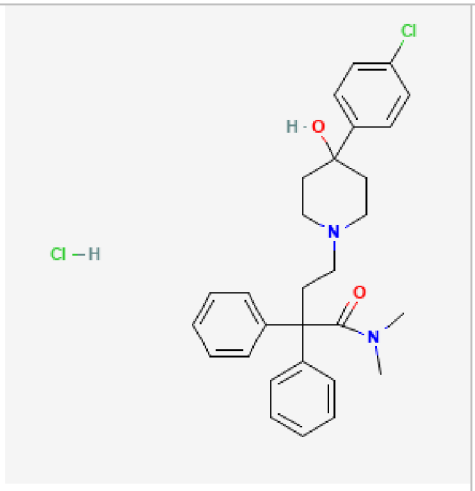
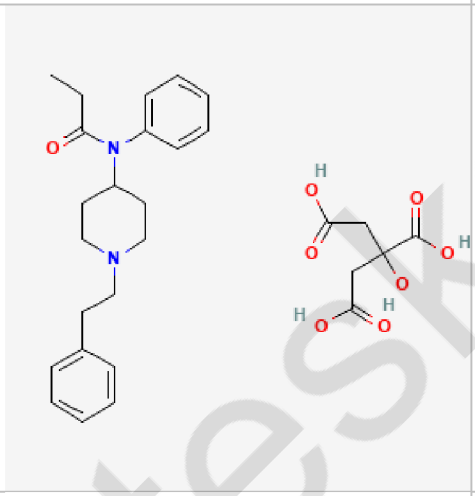
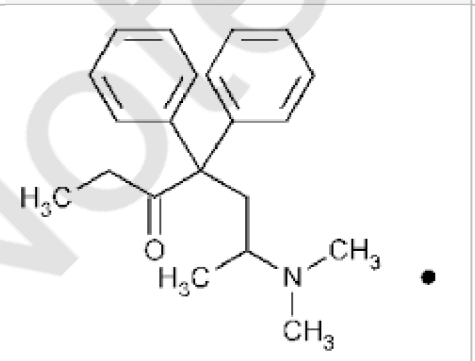
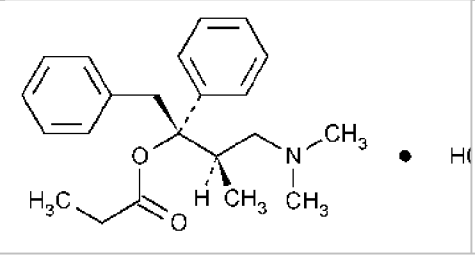
- The size of the N substitution can dictate the compounds potency and its agonists and its reverse antagonistic property.
- The *N*-methyl substitution is having good agonistic property, when increased the size of the substitution by 3–5 carbons results in antagonistic activity. Still larger substitutent on N returns agonistic property of opioids, for example, *N*-phenyl ethyl substitution is ten times more potent than *N*-methyl groups.
- *N*-allyl and *N*-cylo alkyl group leads to narcotic antagonistic property.

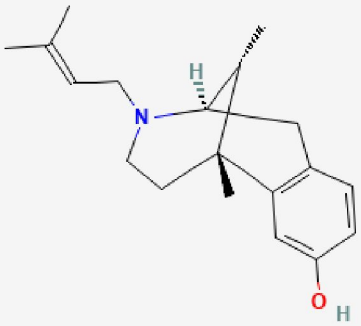
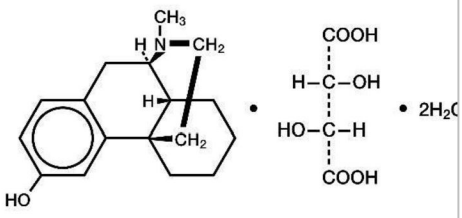
4. Epoxide Bridge

- Removal of 3,4 epoxide bridge in morphine structure result in the compound that is refered to as morphinans.
- The morphinans are prepared synthetically. As the synthetic procedure yielded compound is a racemic mixture, only levo isomer possesses opioid activity while the dextro isomer has useful antitussive activity, for example, Levorphanol and Butorphanol.
- Levorphanol is a more potent analgesic than morphine.

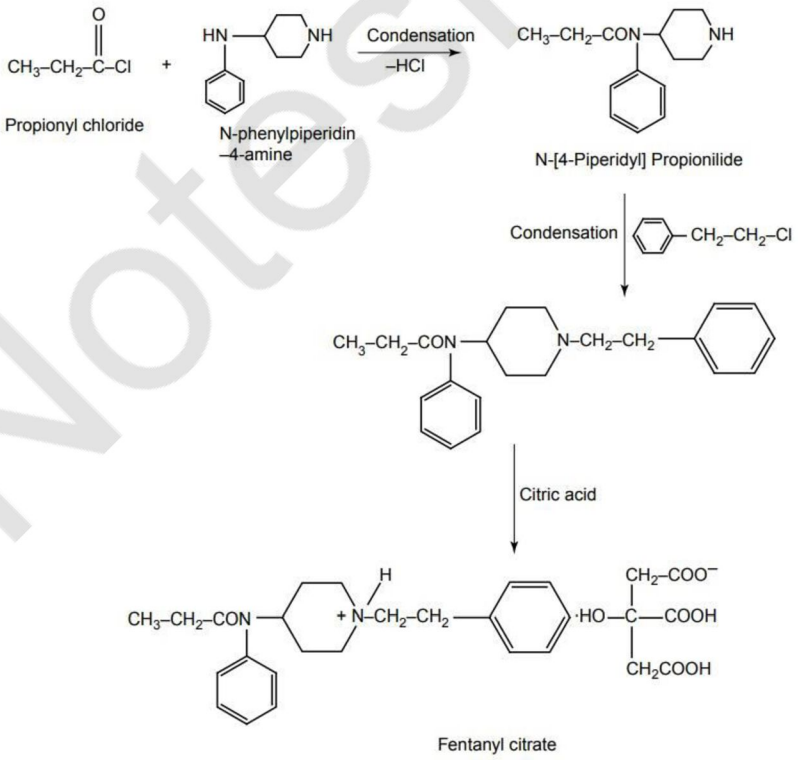
Drug	Structure	Mechanism of Action	Uses
Morphine Sulfate		Binds to mu-opioid receptors in the central nervous system, leading to inhibition of pain transmission and modulation of the perception of pain.	Severe acute and chronic pain management, particularly in post-operative and cancer pain.
Codeine		Acts on mu-opioid receptors, primarily metabolized into morphine. It also has antitussive properties.	Mild to moderate pain relief, cough suppression.

Meperidine Hydrochloride		Synthetic opioid agonist that acts on mu-opioid receptors, similar to morphine but with a shorter duration of action.	Acute pain management, preoperative medication, labor analgesia (though less preferred due to its side effects).
Anileridine Hydrochloride		Similar to meperidine, it is an opioid analgesic acting on mu-opioid receptors but with a shorter duration of action.	Used for moderate to severe pain management, especially in obstetrics and postoperative settings.
Diphenoxylate Hydrochloride		Opioid receptor agonist with antidiarrheal effects, used to slow intestinal motility.	Treatment of diarrhea, particularly in cases of severe diarrhea.

Loperamide Hydrochloride		Opioid receptor agonist with peripheral activity, used to decrease motility in the intestines and reduce diarrhea.	Treatment of acute and chronic diarrhea.
Fentanyl Citrate		Highly potent synthetic opioid agonist that binds to mu-opioid receptors, providing rapid and short-acting analgesia.	Used for anesthesia induction and maintenance, postoperative pain management, and management of severe chronic pain.
Methadone Hydrochloride		Synthetic opioid agonist with a long duration of action, acts on mu-opioid receptors, also blocks NMDA receptors.	Used primarily in opioid addiction treatment (maintenance therapy) and for chronic pain management.
Propoxyphene Hydrochloride		Opioid analgesic acting on mu-opioid receptors, used primarily for mild to moderate pain relief.	analgesic

Pentazocine		Partial agonist at kappa-opioid receptors and antagonist at mu-opioid receptors, leading to mixed agonist-antagonist activity.	Used for moderate to severe pain relief.
Levorphanol Tartarate		Synthetic opioid agonist with affinity for mu-opioid receptors, also acts on NMDA receptors.	Used for severe pain management.

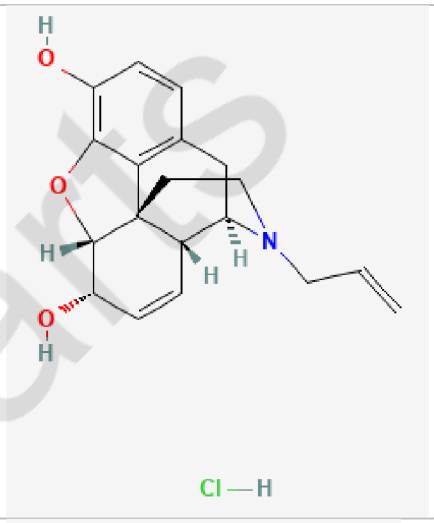
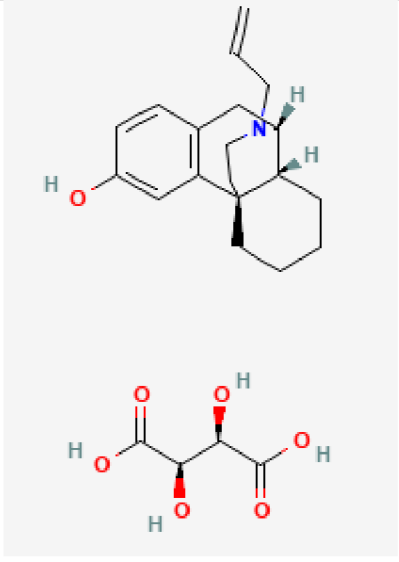
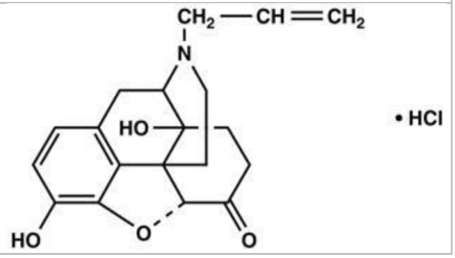
Synthesis of Fentanyl citrate:



Narcotic antagonists:

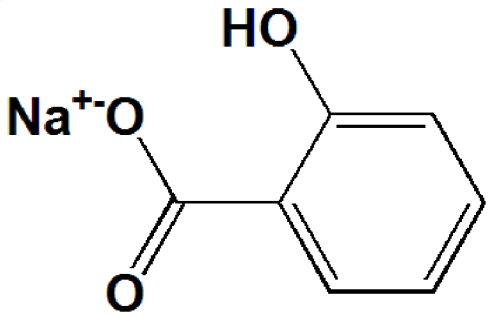
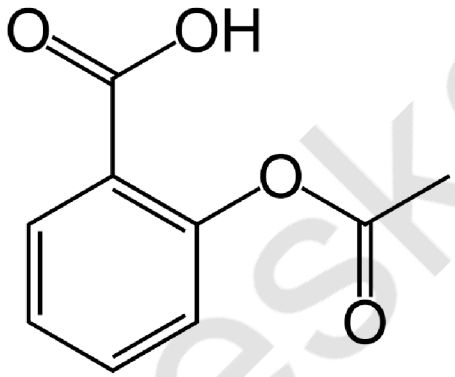
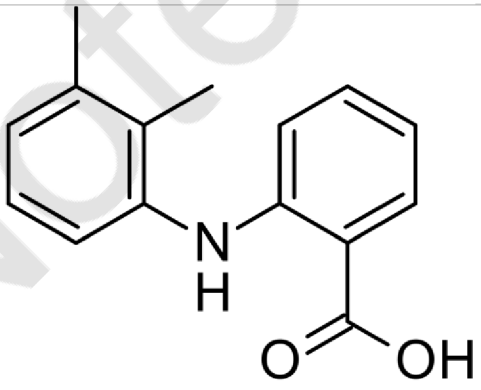
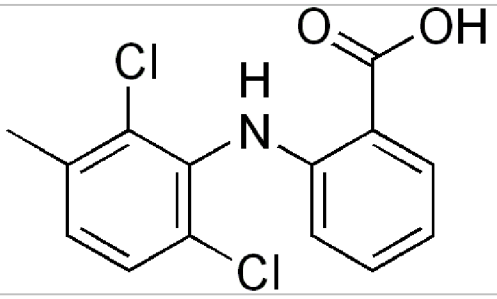
- Narcotic antagonists, also known as opioid antagonists, are a class of medications used to reverse the effects of opioid overdose.
- They work by blocking opioid receptors in the central nervous system (CNS), preventing opioids from binding and exerting their effects.

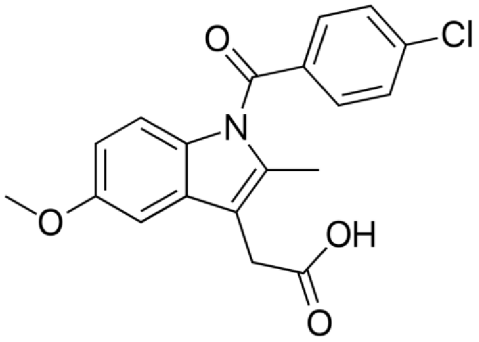
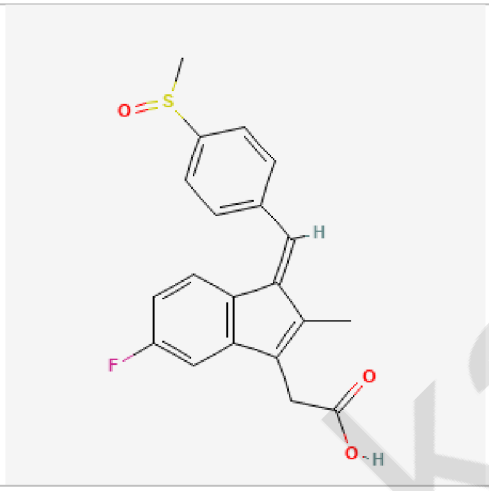
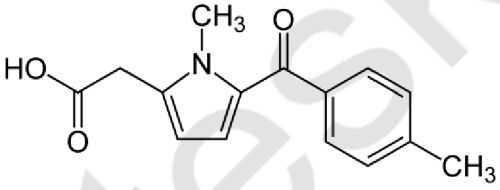
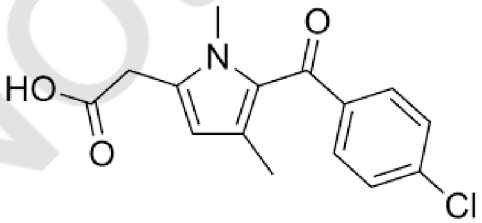
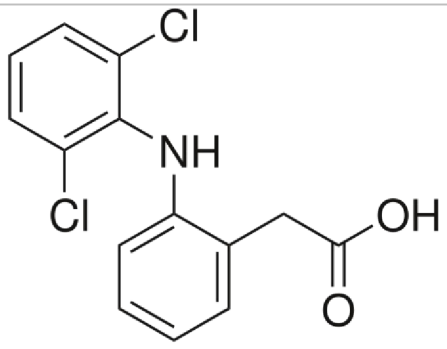
Nalorphine hydrochloride, Levallorphan tartarate, Naloxone hydrochloride.

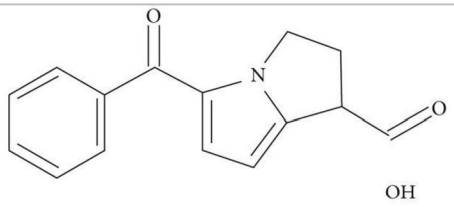
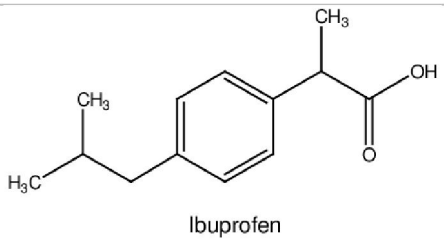
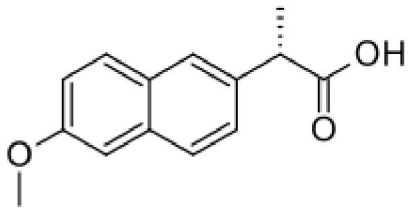
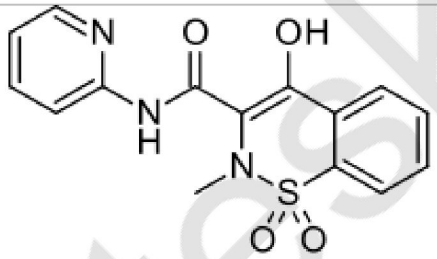
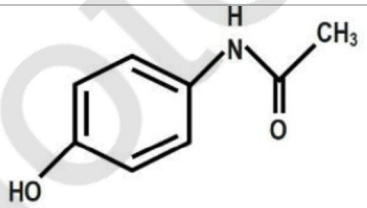
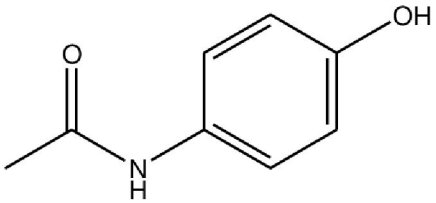
Drug	Mechanism of Action	Uses	Structure
Nalorphine hydrochloride	Partial agonist/antagonist at opioid receptors	Reverses opioid overdose, may cause withdrawal symptoms	
Levallorphan tartrate	Antagonist at mu-opioid receptors, agonist at kappa receptors	Reverses opioid overdose, may cause hallucinations	
Naloxone hydrochloride	Pure antagonist at mu-opioid receptors	Reverses opioid overdose, no agonist effects	

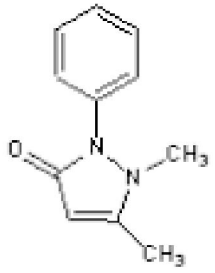
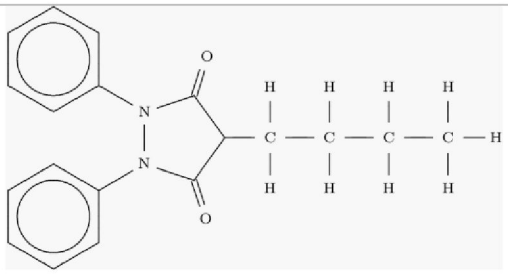
Anti-inflammatory agents:

- Anti-inflammatory agents are medications used to reduce inflammation and pain.

Drug	Structure	Mechanism of Action	Uses
Sodium Salicylate	 sodium salicylate	Derivative of salicylic acid, inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Mild to moderate pain relief, fever reduction, anti-inflammatory effects.
Aspirin		Acetylsalicylic acid, inhibits COX enzymes, irreversibly acetylates COX-1 and COX-2.	Pain relief, fever reduction, anti-inflammatory effects, antiplatelet effects (as low-dose therapy for cardiovascular protection).
Mefenamic Acid		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, including menstrual pain (dysmenorrhea).
Meclofenamate		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, including menstrual pain (dysmenorrhea).

Indomethacin		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of moderate to severe pain, inflammation, and gout.
Sulindac		Prodrug that is metabolized to a COX inhibitor, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, inflammation, and rheumatoid arthritis.
Tolmetin		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, including osteoarthritis and rheumatoid arthritis.
Zomepirac		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Previously used for the treatment of mild to moderate pain, now withdrawn from many markets due to adverse effects.
Diclofenac		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, inflammation, and osteoarthritis.

Ketorolac		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for short-term management of moderate to severe pain, particularly after surgery.
Ibuprofen	 Ibuprofen	Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, inflammation, and fever.
Naproxen		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, inflammation, and fever.
Piroxicam		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Used for the treatment of mild to moderate pain, inflammation, and osteoarthritis.
Phenacetin		Metabolized to paracetamol (acetaminophen), likely through a similar mechanism as paracetamol.	Previously used for pain relief and fever reduction, now withdrawn due to concerns over nephrotoxicity and carcinogenicity.
Acetaminophen		Mechanism not fully understood; may inhibit COX enzymes centrally, but primarily acts on other pathways.	Used for the treatment of mild to moderate pain and fever, considered safer for those who cannot tolerate NSAIDs.

Antipyrine		Mechanism not fully understood, but thought to inhibit prostaglandin synthesis and possibly other pathways.	Used for the treatment of mild to moderate pain and fever, often in combination with other analgesics.
Phenylbutazone		Inhibits COX enzymes, particularly COX-1 and COX-2, reducing prostaglandin synthesis.	Previously used for the treatment of pain and inflammation, now withdrawn from many markets due to safety concerns.